Stereoselective Synthesis of Some Six Membered Oxygen and Nitrogen Heterocyclic Compounds

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Submitted by

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Dedicated
To
My Parents and Grandmother

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**Stereoselective Synthesis of Some Six Membered Oxygen and Nitrogen Heterocyclic Compounds**" is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Anil K. Saikia.

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

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CERTIFICATE

This is to certify that Mr. **Kiran Indukuri** has been working under my supervision since December 2009 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Stereoselective Synthesis of Some Six Membered Oxygen and Nitrogen Heterocyclic Compounds**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

9th October, 2014
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

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Kiran Indukuri

LIST OF ABBREVIATIONS

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

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

s	singlet	t	triplet
d	doublet	q	quartet
dd	doublet of doublet	m	multiplet
ddd	doublet of doublet of doublet	brs	broad signal
dddd	doublet of doublet of doublet of doublet	Hz	Hertz
dt	doublet of triplet	MHz	Mega-Hertz

Abstract

The research work presented in this thesis has been divided into five chapters based on the results of experimental work performed during the complete course of the research period. The chapter **1** of the thesis presents introduction to six membered oxygen and nitrogen heterocyclic compounds, their biological significance and the literature methods for their synthesis. Chapter **2** describes the stereoselective synthesis of 4-aryltetrahydropyrans from epoxides *via* Prins-Friedel-Crafts reaction. Chapter **3** illustrates the diastereoselective synthesis of amido- and phenyl azabicyclic derivatives *via* tandem aza Prins-Ritter/ Friedel-Crafts reaction. In chapter **4** stereoselective synthesis of *O*-tosyl azabicyclic derivatives *via* aza Prins reaction and it's application in the total synthesis of (±)-*epi*-indolizidine **167B** and **209D** has been described. Chapter **5** presents the stereoselective synthesis of 2,3-dihydro-4-pyranones from epoxides *via* hetero-Diels-Alder reaction.

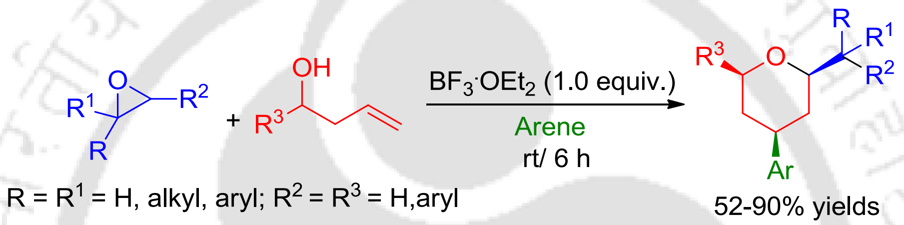
Chapter 1: Introduction to Six Membered Oxygen and Nitrogen Heterocyclic Compounds

Saturated six membered oxygen and nitrogenated heterocyclic compounds play a vital role as commonly occurring substructures found throughout nature in various forms and are the building blocks of numerous natural compounds from antibiotics to vitamins and liposaccharides due to their less ring strain and more abundance.

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

Chapter 2: Stereoselective Synthesis of 4-Aryltetrahydropyrans from Epoxides *via* Prins-Friedel-Crafts reaction

Epoxides are considered as versatile intermediates in organic synthesis due to their high reactivity. The highly strained three membered ring of the epoxide can be opened up by a variety of reagents to give different types of products. One of the most important reactions of epoxides is their rearrangement to a carbonyl equivalent under Lewis acid. Therefore, in this chapter a versatile synthetic methodology for the synthesis of 4-aryltetrahydropyrans using epoxides as carbonyl equivalent and homoallylic alcohols mediated by boron trifluoride etherate is described. The reaction is generalized as shown in *Scheme 1*.



Scheme 1: *Synthesis of 4-aryltetrahydropyrans and the scope of the reaction*

The reaction is highly diastereoselective and all the substituents of the tetrahydropyran ring *cis* to each other. This is evident from the coupling constants of C-2H (*J* = 9.6 and 6.4 Hz), C-4H (*J* = 12.0, 12.0, 3.6 and 3.2 Hz) and C-6H (*J* = 11.2 Hz) of methyl-4-(6-cyclohexyl-tetrahydro-4-phenyl-2*H*-pyran-2yl)-benzoate. The structure and stereochemistry of the compounds were finally confirmed by NOE experiments (*Figure 1*). The strong enhancements between C-2H and C-4H, C-2H and C-6H protons indicate that all three protons are in axial positions.

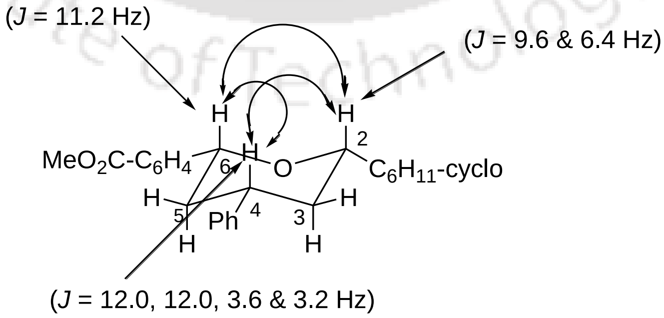
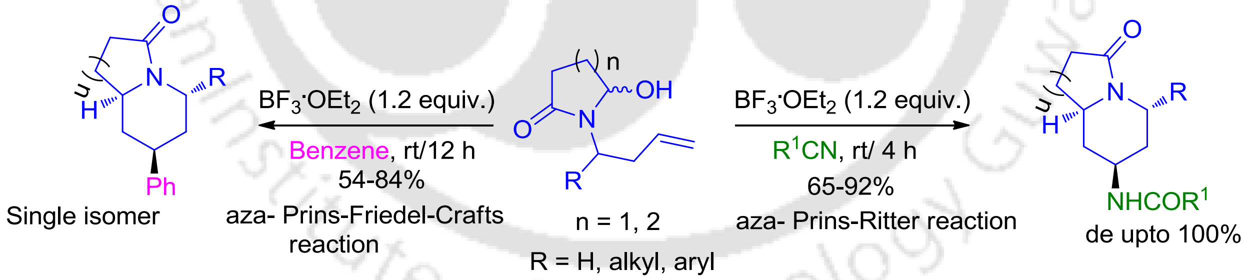


Figure 1: *NOE of methyl-4-(6-cyclohexyl-tetrahydro-4-phenyl-2H-pyran-2yl)-benzoate*

In summary, an efficient highly diastereoselective method for the synthesis of 2, 6-disubstituted-4-aryltetrahydropyrans in good yields has been developed from epoxides *via* Prins cyclization and this method provides an alternative to aldehydes where aldehyde cannot access directly. The good yields, high selectivity, shorter reaction time and activated arene products give more significance to this one-pot synthesis.

Chapter 3: Diastereoselective Synthesis of Amido- and Phenyl Azabicyclic Derivatives *via* Tandem Aza Prins-Ritter / Friedel-Crafts Reaction

Piperidine containing azabicyclic alkaloids are present as core units of several highly significant natural products, which have been shown to exhibit broad biological activity and a diverse pharmacological profile. Especially hexahydroindolizin-3(2*H*)-one, hexahydro-1*H*-quinolizin-4(6*H*)-one and 1,3,4,10*b*tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one units encountered in many biologically active natural alkaloids. In this chapter we describe a simple protocol for the synthesis of amido/phenyl substituted hexahydroindolizin-3(2*H*)-one, hexahydro-1*H*-quinolizin-4(6*H*)-one, and 1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one derivatives *via* boron trifluoride etherate mediated tandem aza-Prins-Ritter/ Friedel−Crafts reactions using *N*-acyliminium ions as key intermediates. The scope of the reaction was carried out with different reduced *N*-homoallyl imides derived from homoallylic alcohols and cyclic imides to give desired products in good yields with high selectivity (*Scheme 2*).



Scheme 2: *Synthesis of amido/phenyl azabicyclic compounds*

The reaction is highly diastereoselective and produced exclusively single diastereomers having a *cis* relationship between the H10 hydrogen at C-10 of the piperidine ring and the H12 hydrogen at C-12 of the ring junction. On the other hand, substituents at C-8 and C-10 are *trans* to each other. A strong NOE between C−H12 and C−H10 and a weak NOE between C−H8 and −NH− were observed in compound *N-((5R*,7S*,8aR*)-5-benzyl-3-oxooctahydroindolizin-7-yl)acetamide*, which was also confirmed from X-ray crystallographic analysis (*Figure 2*).

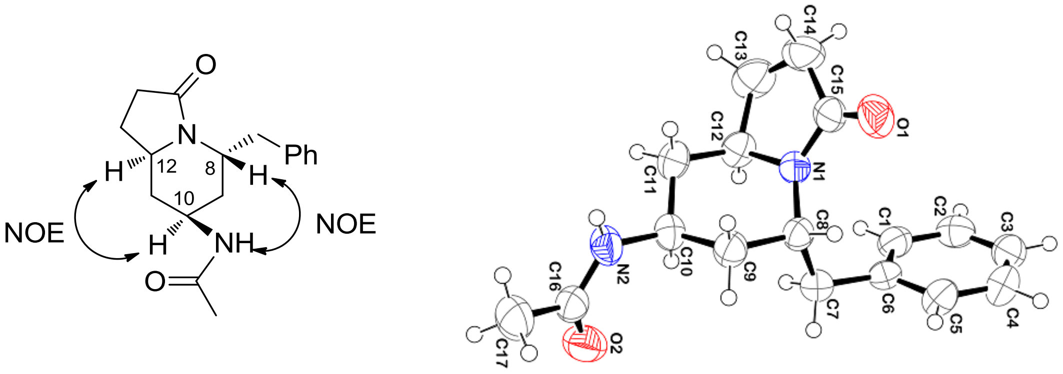
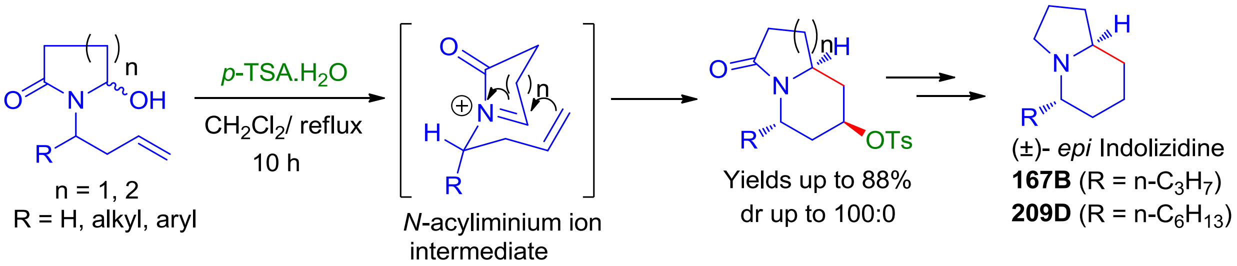


Figure 2. *Correlation between NOE and X-ray crystallographic structure of N-((5R*,7S*,8aR*)-5-benzyl-3-oxooctahydroindolizin-7-yl)acetamide*

In conclusion, the new tandem aza-Prins-Ritter/ Friedel−Crafts approach is experimentally simple, mild, efficient and produced single isomers in most of the cases. Broad scope and high level of functionality present in the end products contributes a great deal of potential towards the synthesis of moderately complex phenyl, amido and amino azabicyclic derivatives. This methodology could be useful for the synthesis of natural and unnatural indolizidine and quinolizide alkaloids.

Chapters 4: Stereoselective Synthesis of *O*-Tosyl Azabicyclic Derivatives *via* Aza Prins Reaction: Application to the Total Synthesis of (±)-*epi*-Indolizidine 167B and 209D

This chapter describes *p*-TSA mediated synthesis of *O*-tosylated azabicyclic compounds from regioselectively reduced homoallyl imides *via* the aza-Prins cyclization, in which the *p*-TSA acts as Brønsted acid as well as a nucleophile. This methodology was utilized for the total synthesis of (±)-*epi*-indolizidine **167B** and **209D**, starting from commercially available succinimide in 5 steps with an overall 28% and 35% yields respectively (*Scheme 3*).



Scheme 3: *Synthesis of O-tosyl azabicyclic compounds via aza-Prins reaction*

The stereochemistry of *O*-tosylated azabicyclic compounds was confirmed by ^{1}H, ^{13}C and NOESY experiments. The NOE results have shown the *trans* relationship of substituent α-to nitrogen with other two substituents at chiral centers. It was further confirmed by X-ray crystallographic analysis (*Figure 3*).

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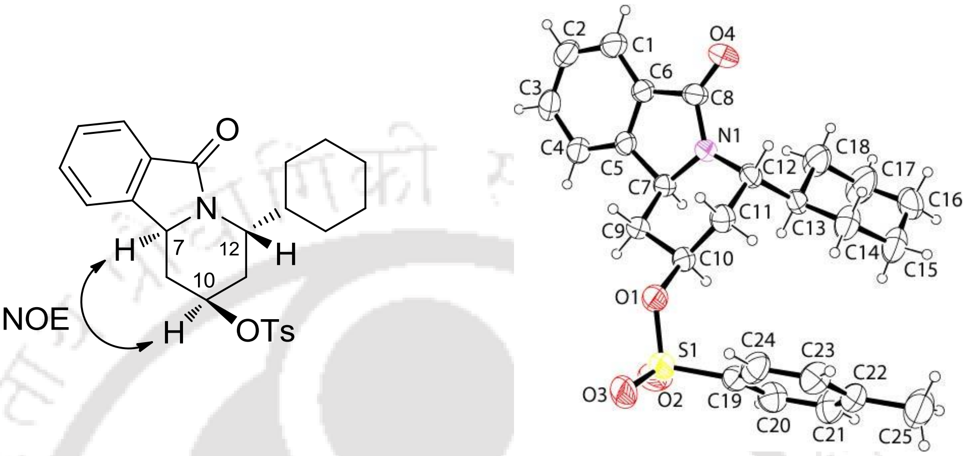
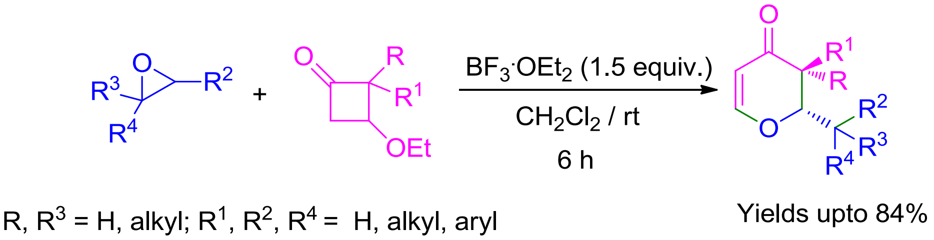


Figure 3: *NOE and crystal structure of (2R*,4S*,10bS*)-4-cyclohexyl-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl-4-methylbenzenesulfonate*

In conclusion, we have demonstrated the dual role of *p*-TSA in *endo*-trig cyclization reaction for the synthesis of 4-*O*-tosyl piperidine containing fused azabicyclic derivatives. This methodology could be useful for accessing other substituted azabicyclic alkaloids by manipulating the tosyl group. This methodology was successfully applied for the total synthesis of indolizidine natural products, (±)-*epi*-indolizidine **167B** and **209D**.

Chapter 5: Synthesis of 2,3-Dihydro-4-pyranones from Epoxides *via* hetero-Diels-Alder Reaction

2,3-Dihydro-4*H*-pyran-4-one is a key synthon for the synthesis of important biologically active molecules. It is also used for the synthesis of carbohydrates and highly functionalized aromatic rings. Thus, the synthesis of 2,3-dihydro-4*H*-pyran-4-one has strongly inspired the synthetic organic community to develop many new strategies. This chapter illustrates a diastereoselective synthesis of 2,3-dihydro-4*H*-pyran-4-one derivatives bearing mono and dialkyl as well as monoaryl groups at the C-3 position starting from 3-alkoxycyclobutanones and epoxides mediated by boron trifluoride etherate. The examination of variously substituted cyclobutanones reveals that the 2,2-disubstituted cyclobutanones gave a single product, whereas, cyclobutanones possessing monosubstitution at the C-2 position gave a mixture of diastereomers with the *trans* isomer as major product (*Scheme 4*).



Scheme 4: *Synthesis of 2,3-dihydro pyran-4-ones via HDA reaction*

In conclusion, we have developed a versatile methodology for the synthesis of 2,3-dihydro-4*H*-pyran-4-ones using epoxides and 3-alkoxycyclobutanones *via* an intermolecular [4+2] cycloaddition reaction in moderate to good yields. The method provides an alternative to Danishefsky's diene and aldehydes for the synthesis of 2,3-dihydro-4*H*-pyran-4-ones where the aldehyde cannot be accessed directly.

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CHAPTER 1

Introduction to Six Membered Oxygen and Nitrogen Heterocyclic Compounds

1.1. Background

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

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

1.2. Importance of Tetrahydropyran, Dihydropyranone and Piperidine Scaffolds in Nature

Saturated six membered cyclic ethers better known as tetrahydropyrans (THPs) are ubiquitious in nature and represent useful precursors for the preparation of many biologically active molecules.[2] For example, pyranicin (**1**), a tetrahydropyran containing natural product from annonaceous acetogenin family, isolated from the stem bark of the *Goniothalamus giganteus* tree, native to Thailand by McLaughlin *et al.* in 1997, acts as antimalarial, antiparasitic, and antitumor drug and it has recently exhibited promising results against Parkinsonism.[3] Neopeltolide (**2**) constitute a novel class of bioactive marine natural products, isolated from a deep-water Caribbean sponge of the family Neopeltidae, collected from the north Jamaican coast by Wright *et al.* It exhibits significantly potent *in vitro* cytotoxicity towards several different cancer cell lines, including A-549 human lung adenocarcinoma, NCI-ADR-RES human ovarian sarcoma, and P388 murine leukemia cell lines with IC_{50} of 1.2, 5.1 and 0.56 nM respectively, and also inhibited the growth of the fungal pathogen *Candida albicans* with a minimum inhibitory concentration of 0.62 μg/ mL.[4] Apicularen A (**3**), isolated from various strains of the myxobacterial genus *Chondromyces* by Kunze *et al.* in 1998, shows antiproliferative properties against a variety of cancer cell lines including drug-resistant line such as ovarian, prostate, lung, kidney, cervix, leukemia, and histiocytic cells with IC_{50} values in the range of 0.23-6.79 nM. It has also proven to be a potential medicine for antiangiogenesis (*Figure 1.2.1*).[5]

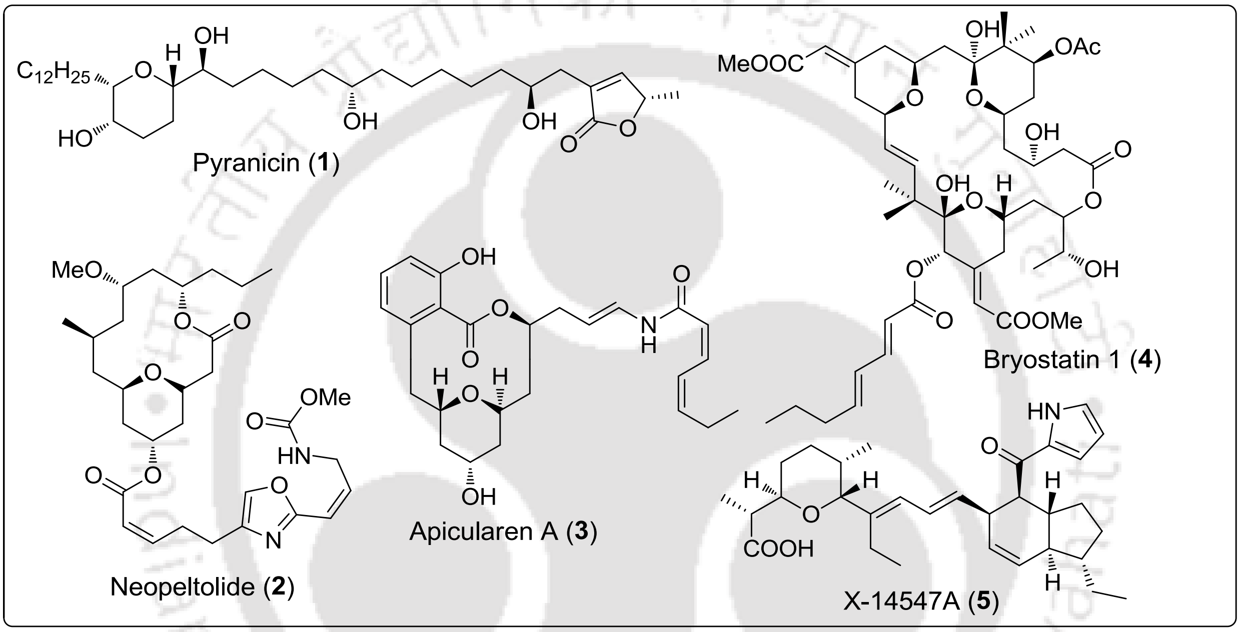


Figure 1.2.1. Some tetrahydropyran containing biological active compounds

Bryostatin 1 (**4**) is an important member of bryostatin family, isolated by Pettit and co-workers from the marine organism *Bugula neritina*.[6] Bryostatin 1 exhibits remarkable *in vitro* and *in vivo* activities relevant to cancer treatment including restoration of apoptotic function, reversal of multidrug resistance, stimulation of the immune system, and synergism with other oncolytics. Currently it is in Phase I and II clinical trials for cancer and is exceptionally potent with only 1.2 milligrams required for a full multi-week treatment cycle. Bryostatin 1 has also shown promising results against Alzheimer's disease in animals. Notably a clinical trial opened in 2008 to test the efficacy of bryostatin 1 against Alzheimer's disease and currently in phase II clinical trails.[7]

A *trans* 2,6-substituted THP containing natural product in ionophore group of antibiotics is X-14547A (**5**) and was isolated from a strain of *Streptomyces antibioticus NRRL 8167*, by Westley *et al*. It has high affinity to transport monovalent cations such as Na^+ and K^+ and divalent cations such as Ca^{2+} and Rb^{2+}. It also shows antibiotic activity against Gram-positive bacteria, antihypertensive and antitumor activities (*Figure 1.2.1*).[8]

Another important class of six membered oxygenated heterocyclic compounds are 2,3-dihydropyran-4-ones, constituting an important core in many natural products and also serves as key synthetic intermediates in natural product synthesis and drug discovery.[9] Polypropionate natural products maurenone (**6**) and vallartanone A-B (**7**) were isolated from specimens of the pulmonate mollusc *Siphonaria maura*, collected from Jaco Beach, Costa Rica and Puerto Vallarta, Mexico respectively, by Manker *et al.*[10] The biological applications of these compounds were not explored yet. In 1998, other polypropionate marine defense natural products, membrenone A-C (**8-9**) were first isolated from a Mediterranean mollusc *Pleurobranchus membranaceus* by Ciavatta *et al*. These compounds were found to protect the mollusk from potential predators in the hostile marine environment.[11] A simple 2,6-substituted 2,3-dihydropyranone hepialone (**10**), is a natural pheromonal component of the male moth, isolated from *Hepialus hecta L.*[12] (+)-Obolactone (**11**), isolated from the trunk bark of a tropical tree (*Cryptocarya obovata* R. Br.) indigenous to northern Vietnam[13] is shown to act against nasopharyngeal carcinoma KB cells (IC_{50} = 3 μM) and against *Trypanosoma brucei brucei*, which causes african sleeping sickness (IC_{50} = 5.3 μM) (*Figure 1.2.2*).[14]

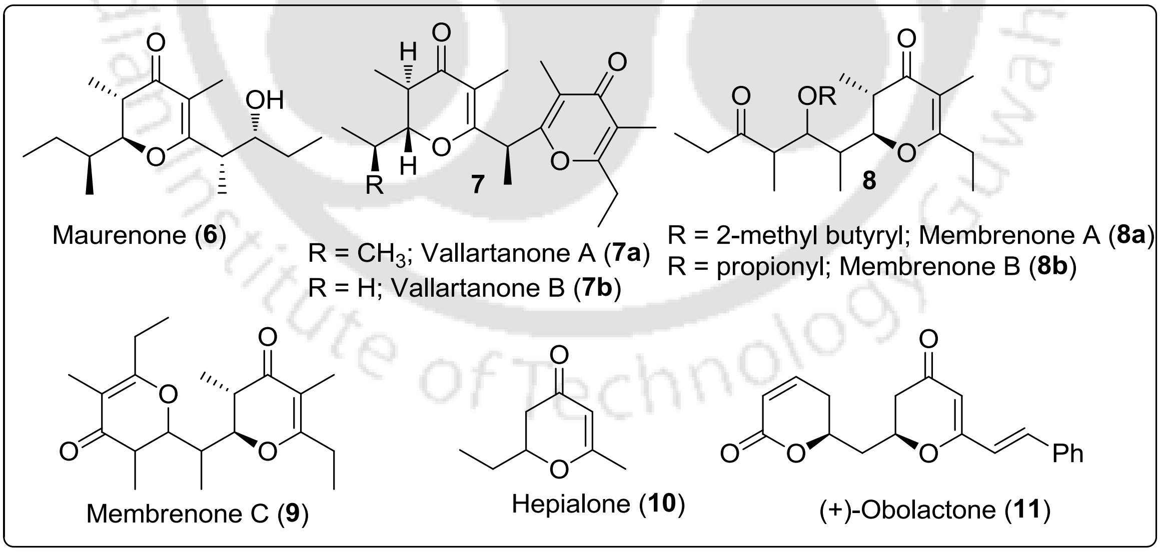


Figure 1.2.2. Some natural products with dihydro-γ-pyrone back bone

Piperidines and their derivatives have become increasingly popular building blocks in a vast array of synthetic protocols and also present in more than half of the alkaloids known today.[15] Top 32 of the 200 brand-name drugs by US retail sales in 2009 contain piperidine fragments and thousands of piperidine compounds have undergone clinical and preclinical studies in last ten years.[16] For example, α-conine (**12**), having a simple piperidine unit is a powerful poison, isolated from hemlock *Conium maculatum*.[17] Similar kind of naturally occurring piperidine alkaloid is (-)-pelletierine (**13**), which was isolated from pomegranate (*Punica granatum*) root bark, and has been found to have anthelmintic properties.[18] Prosophylline (**14**), a hydroxyl piperidine derivative, was isolated from various *Prosopis* species and found to exhibit antibiotic and anaesthetic properties.[19]

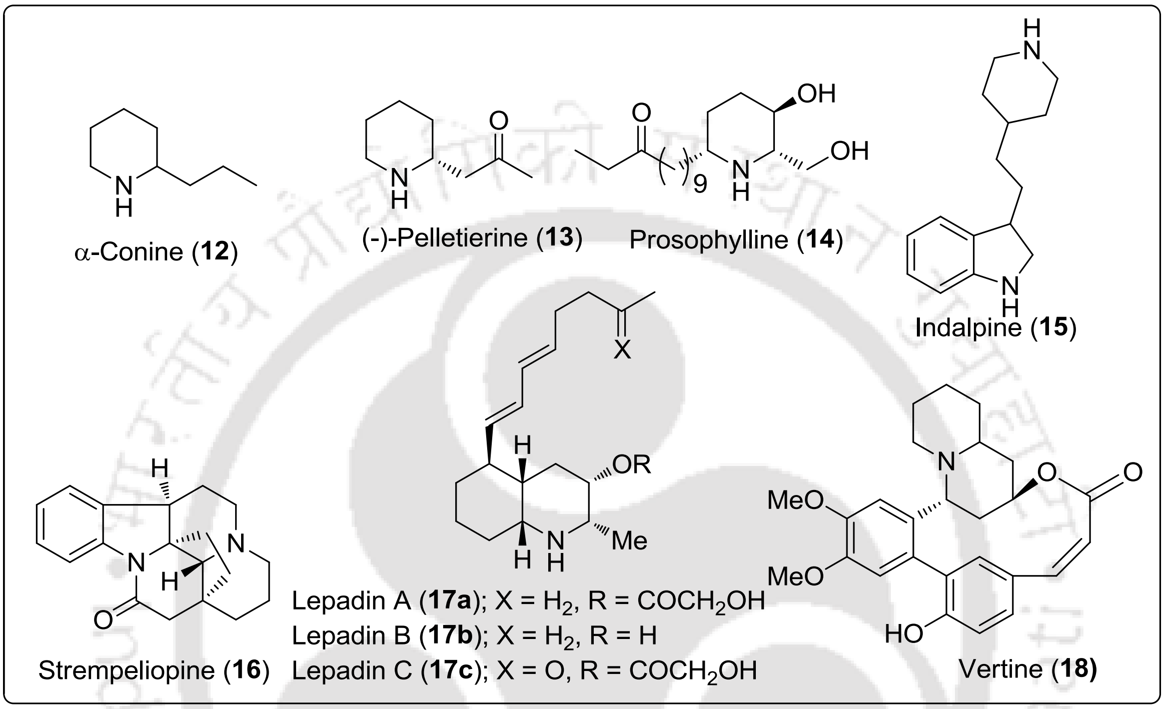


Figure 1.2.3. Some piperidine containing biological active compounds

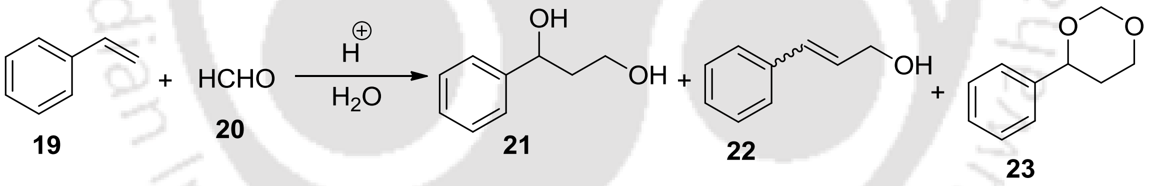
Indalpine (**15**), a selective serotonin reuptake inhibitor (SSRI) class, antidepressant drug was discovered in 1977 by a small Paris based pharmaceutical firm Pharmuka, and got approval for marketing in 1982.[20] Strempeliopine (**16**), an alkaloid of the Cuban species *Strempeliopsis strempelioides* K. Schum, was isolated from the East-African monotypic *shrub Schizozygia coffaeoides* (Boj.) Baill. This plant has been used as a traditional medicine for a variety of skin diseases and also exhibit antifungal and antimicrobial activity.[21] Lepadin A-C (**17**), have been found in the flatworm *Prostheceraeus villatus* and its tunicate prey C. *lepadiformis*. Both lepadins A and B have been shown to exhibit significant *in vitro* cytotoxicity against human cancer cell lines.[22] Similarly, a quinolizidine alkaloid vertine (**18**), isolated from *Decodon verticillatus (L.) Ell* and show anti-inflammatory, sedative, and antispasmodic properties[23] (*Figure 1.2.3*).

1.3. An Overview for the Synthesis of Tetrahydropyran, Piperidine and Dihydro-γ-pyrone Derivatives

To build this class of heterocycles, many strategies have been developed over the years. The most widely used methods are the Prins cyclization, hetero-Diels–Alder (HDA) reaction, oxonium-ene cyclization, intramolecular Michael additions and ring-closing metathesis. Other strategies include electrophile-induced cyclizations of non-activated alkenes and Lewis acid promoted cyclizations of epoxy alcohols/amines. Reported methods used for six membered oxygen and nitrogen ring synthesis have their own advantages and disadvantages. Therefore, development of new and efficient methods is imperative especially to address the issue of diastereoselectivity. Among these methods stated, this thesis mainly discusses Prins, aza-Prins cyclization and HDA reactions in detail for the construction of six membered O- and N-heterocycles.

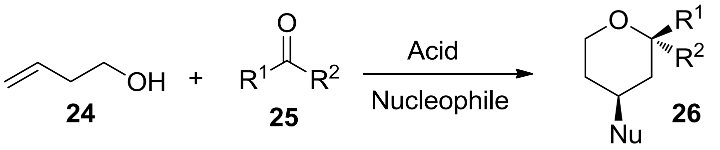
1.3.1. Prins Cyclization Reaction

In 1919 Dutch chemist H. J. Prins first reported a reaction between simple styrene **19** and formaldehyde **20** in aqueous acidic medium, resulting in a mixture of products such as diol **21**, unsaturated alcohol **22** and 1,3-dioxane **23** (*Scheme 1.3.1.1*).[24]



Scheme 1.3.1.1

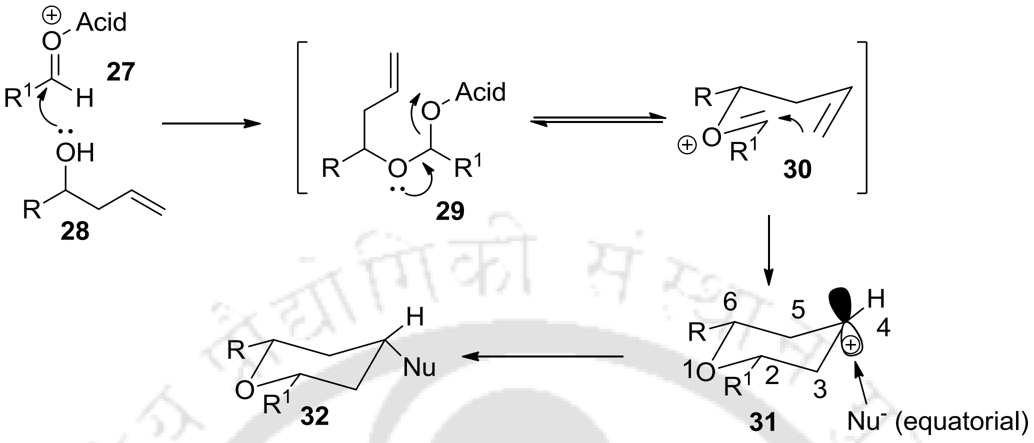
In 1955, Hanschke has further developed Prins reaction for the selective synthesis of tetrahydropyran (THP) rings **26** by combining 3-buten-1-ol **24** with a variety of aldehydes or ketones **25** in the presence of acid, called Prins cyclization reaction (*Scheme 1.3.1.2*).[25]



If acid = H_2SO_4; Nu = OH
If acid = HCl; Nu = Cl

Scheme 1.3.1.2

In most of the cases the Prins cyclization reaction is highly diastereoselective and give 2,4,6-substituted tetrahydropyrans with all equatorial substitutions. The diastereoselectivity was explained as follows.[26]

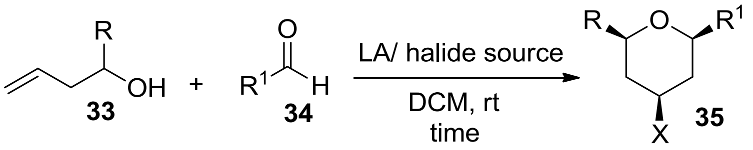


Scheme 1.3.1.3. Mechanism of the Prins cyclization reaction

Homoallylic alcohol **28** reacts with aldehyde **27** in the presence of acid to generate an oxocarbenium ion **30** as a key intermediate, which undergoes 6-*endo*-trig-cyclization to give more stable tetrahydropyranyl cation **31**. According to Alder's DFT calculations, carbocation **31** in its chair conformation is stabilized by stereoelectronic effects. The C2- C3 and C5-C6 σ* and σ orbital overlap both the equatorial lone pair of the oxygen atom and the vacant p orbital at C4. Optimal overlap is reached when the hydrogen atom at C4 is pseudo-axial. This stabilization favors equatorial attack by the nucleophile to give tetrahydropyran **32** (*Scheme 1.3.1.3*).

Since, last five decades a number of modifications were published, that either varied the formation of oxo-carbenium ion from simple homoallyl alcohols and carbonyl compounds or from various substrates such as enol ethers, ene-carbamates, α-acetoxy ethers and allylic/benzylic homoallyl ethers followed by a broad spectrum of nucleophiles to construct various substitutions at 4th position of THP ring *via* formation of C-X, C-O, C-N, C-S and C-C bonds.

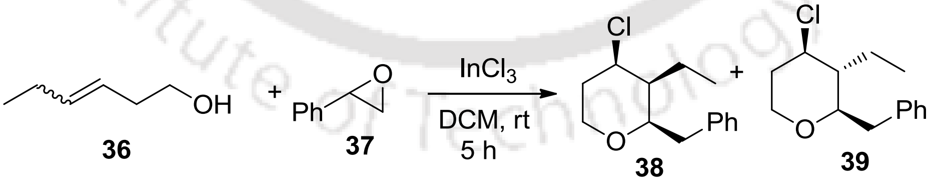
A number of research groups have started to contribute their efforts towards the synthesis of 4-halotetrahydropyrans **35**, using homoallyl alcohols **33** or its precursors with a series of carbonyl compounds **34** in the presence of either halogenated Lewis acids or combination of Lewis acid and halide ion source. It is important to note that, these methodologies affords 2,4,6-*cis*-substituted tetrahydropyrans as major product (*Scheme 1.3.1.4*).[27]



Lewis acid/ halide source	R	R^1	X	time	yield	dr
TiF_4	p-$NO_2C_6H_4$	C_6H_5	F	4 h	80%	100:0
$HBF_4·OEt_2$	H	Cy	F	40 min.	68%	100:0
$BF_3·OEt_2$	H	m-BrC_6H_4	F	2 h	73%	79:21
$InCl_3$	Ph	m-MeC_6H_4	Cl	4 h	76%	100:0
$Fe(acac)_3$/TMSCl	H	$BnO(CH_2)_2$	Cl	12 h	86%	100:0
$InBr_3$	H	o-$OMeC_6H_4$	Br	2 h	86%	80:20
$Fe(acac)_3$/TMSBr	H	i-Bu	Br	12 h	88%	100:0
I_2	H	C_6H_5	I	1 h	89%	100:0

Scheme 1.3.1.4

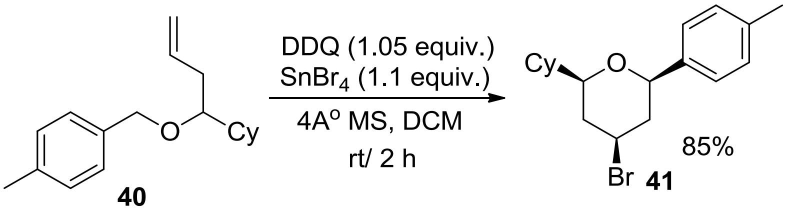
Li and coworkers reported a methodology for the synthesis of 4-chlorotetrahydropyrans **38** and **39** from homoallylic alcohols **36** and epoxides **37** as aldehyde alternates in the presence of $InCl_3$ (*Scheme 1.3.1.5*). The stereochemistry depends upon the geometry of olefin, when *cis* unsaturated alcohol was used 2,3,4-trisubstituted tetrahydropyran **38** with *cis* conformation was obtained as the major product. However, when *trans* unsaturated alcohol, such as *trans*-3-hexene-1-ol was used, 2,3,4-trisubstituted tetrahydropyran **39** with a *trans–trans* conformation was obtained as the dominant product.[28]



Alkene	yield	**38**:**39**
E	87%	0:100
Z	96%	100:0

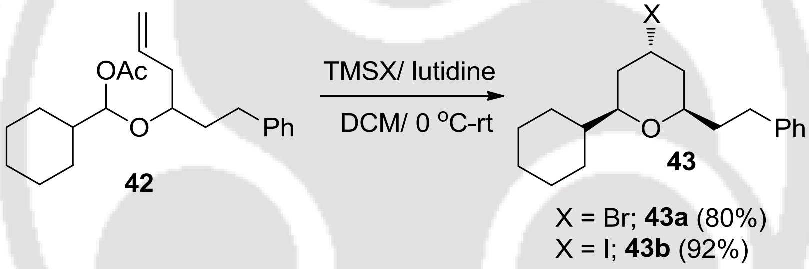
Scheme 1.3.1.5

Recently, Xuegong and coworkers have reported an alternative procedure for the synthesis of 4-bromotetrahydropyran **41**, involving sequential benzylic/allylic C-H bond activation *via* DDQ oxidation and nucleophilic attack of an unactivated olefin **40** at ambient temperature in excellent yield (*Scheme 1.3.1.6*).[29]



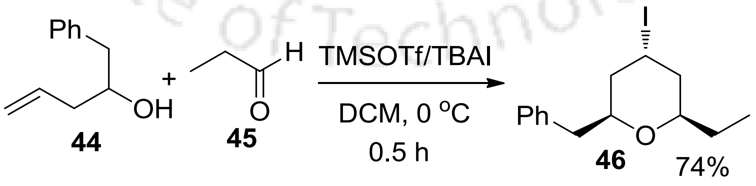
Scheme 1.3.1.6

The halo function in all these reactions is placed in equatorial position in accordance to the Alder model. There are very few methods for the synthesis of 4-axial halotetrahydropyrans. In 2004, Rychnovsky had reported the synthesis of tetrahydropyran **43** with exclusive axial-halide substitution in excellent yields from α-acetoxy ether **42** with TMSX and lutidine as additive in CH_2Cl_2 at 0 °C (*Scheme 1.3.1.7*).[30]



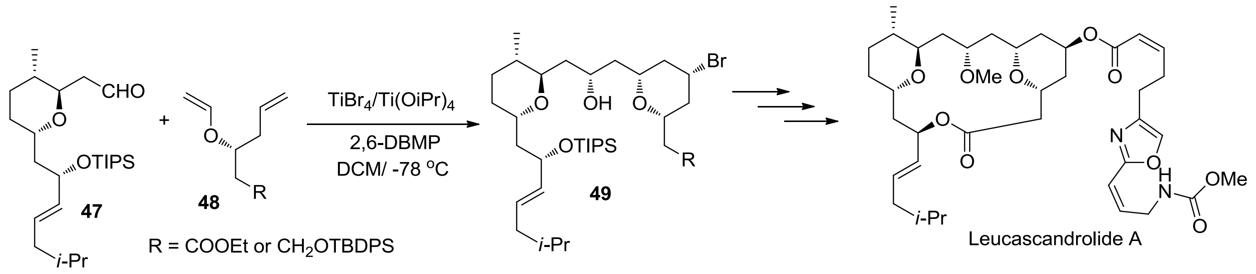
Scheme 1.3.1.7

Saikia and coworkers reported an axial selective Prins cyclization reaction for the synthesis of axial-4-iodotetrahydropyran **46** from simple homoallylic alcohol **44** and aldehyde **45** promoted by TMSOTf and tetrabutylammonium iodide (TBAI) (*Scheme 1.3.1.8*).[31]



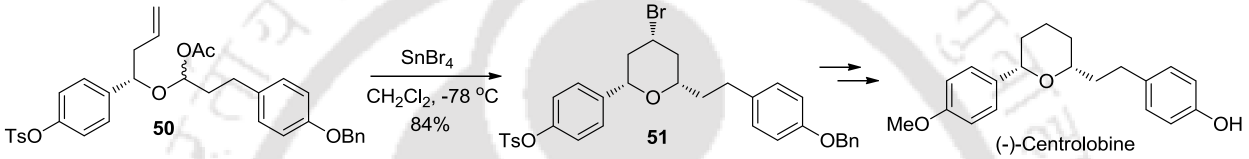
Scheme 1.3.1.8

Rychnovsky and co-workers have utilized halo-Prins cyclization strategy in the total synthesis of a marine natural product Leucascandrolide A. Mukaiyama Aldol-Prins (MAP) reaction between aldehyde **47** and homoallyl vinyl ether **48** in the presence of $TiBr_4$ produces 4-bromotetrahydropyran **49**, which was transformed to Leucascandrolide A after a series of steps (*Scheme 1.3.1.9*).[32]



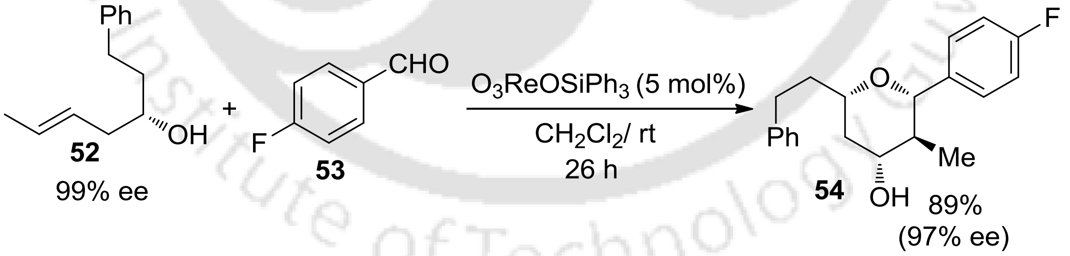
Scheme 1.3.1.9

Similarly, Cyclization of α-acetoxy ether **50** promoted by $SnBr_4$ generated the all equatorial 4-bromo tetrahydropyran **51**. The replacement of tosylate by methyl ether group followed by removal of bromide and benzyl groups give (-)-centrolobine (*Scheme 1.3.1.10*).[33]



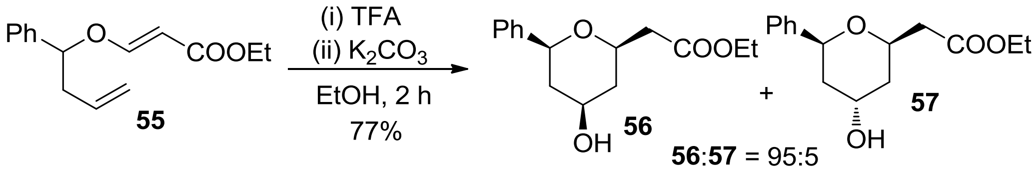
Scheme 1.3.1.10

Trapping the tetrahydropyranyl cation with oxygenated and nitrogenated nucleophiles in inter and intramolecular fashion was developed by several research groups. Tadpetch *et al.* have reported a rhenium(VII) complex catalyzed stereoselective protocol for the synthesis of 4-hydroxytetrahydropyran **54** from homoallylic alcohol **52** and aldehyde **53** (*Scheme 1.3.1.11*).[34]



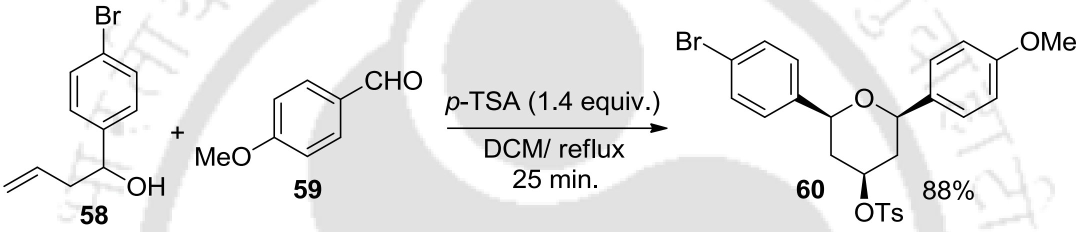
Scheme 1.3.1.11

An alternative and novel methodology for the synthesis of hydroxyl THP derivatives has been described by Hart *et al.* using activated enol-ethers as substrates in Prins cyclization (*Scheme 1.3.1.12*). The enol ether **55** was treated with trifluoroacetic acid (TFA) and subsequent base hydrolysis provides a mixture of alcohols **56** and **57** with a ratio of 95:5 in 77% yield.[35]



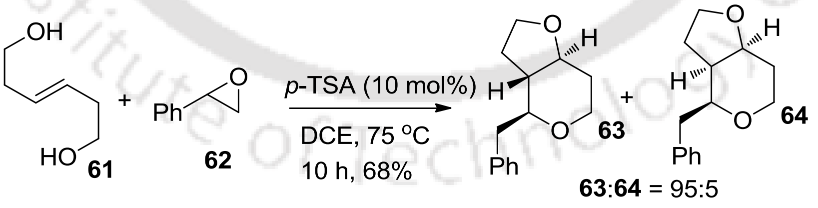
Scheme 1.3.1.12

Ahmed *et al*. have reported a simple, efficient and highly diastereoselective one-pot three-component synthesis of functionalized 2,6-disubstituted-4-tosyloxytetrahydropyrans. *p*-TSA mediated Prins cyclization of homoallyl alcohol **58** and aldehyde **59** in dichloromethane at reflux temperature affords highly *cis*-selective 4-*O*-tosyltetrahydropyran **60** with 88% yield (*Scheme 1.3.1.13*).[36]



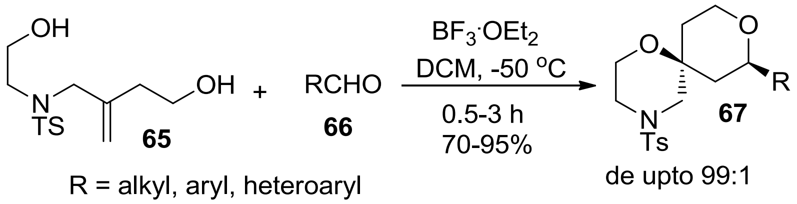
Scheme 1.3.1.13

Yadav *et al*. reported a novel route to access stereoselective bicyclic oxygen heterocycles *via* epoxy-Prins cyclization reaction. The Prins cyclization reaction between styrene oxide **62** and (*E*)-hex-3-ene-1,6-diol **61**, followed by trapping of carbocation with alcohol in intramolecular fashion produced fused bicyclic compounds **63** and **64** (*Scheme 1.3.1.14*).[37]



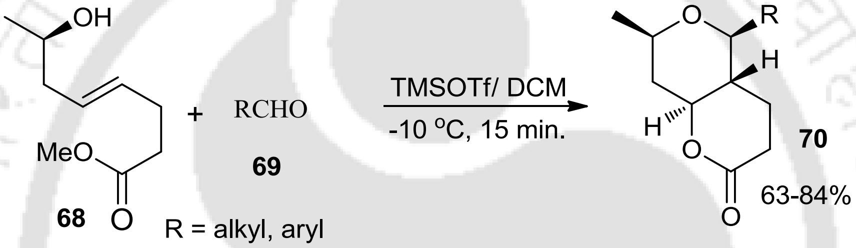
Scheme 1.3.1.14

Reddy and his group showed a novel route for the synthesis of spiromorpholinotetrahydropyran derivatives *via* cascade Prins cyclization and intra molecular C-O bond formation. The coupling of aldehydes **66** with *N*-(4-hydroxy-2-methylenebutyl)-*N*-(2-hydroxyethyl)-4-methylbenzene-sulfonamide **65** mediated by boron trifluoride etherate at low temperature produced 1,9-dioxa-4-azaspiro[5.5]undecane derivatives **67** in good yields and high selectivity (*Scheme 1.3.1.15*).[38]



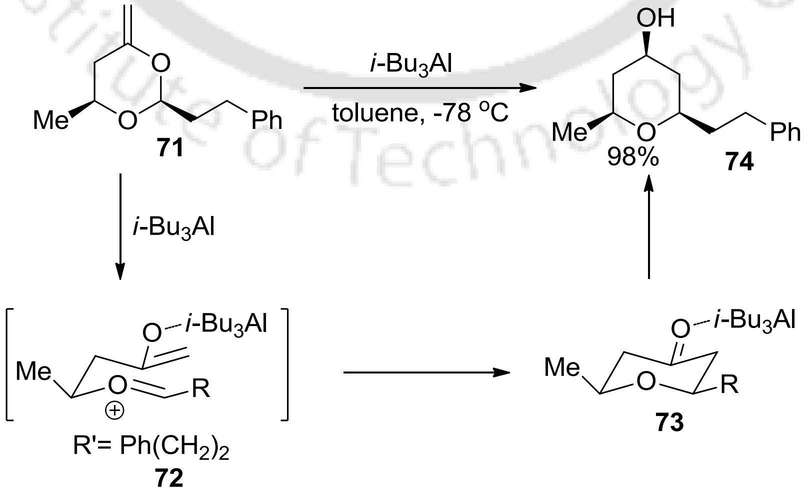
Scheme 1.3.1.15

Recently, Willis and coworkers reported a methodology for bicyclic oxygen heterocycles **70** from the reaction of ethyl (*R*)-3-hydroxybutanoate **68** with a series of aldehydes **69** in the presence of TMSOTf (*Scheme 1.3.1.16*). A single diastereomer had been formed with a *trans* ring junction by the creation of three new stereogenic centres and the two substituents on the tetrahydropyran ring in equatorial position.[39]



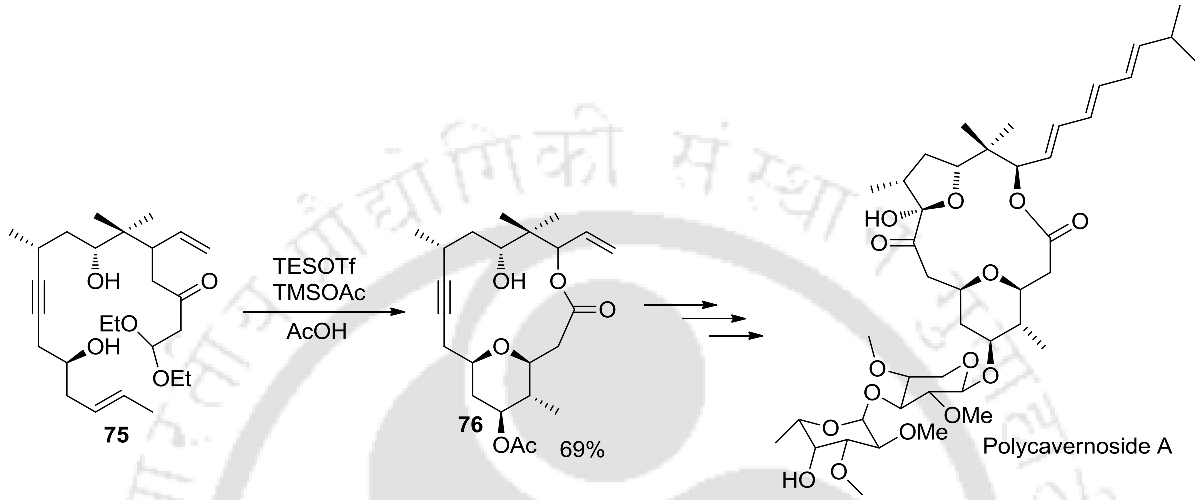
Scheme 1.3.1.16

Petasis *et al*. have reported an efficient protocol for synthesis of tetrahydropyranols. 1,3-Dioxan-4-one **71** was treated with triisobutylaluminum to generate an oxocarbenium intermediate **72**, which on Prins cyclization gives tetrahydropyranone **73**. The subsequent reduction of **73** finally affords tetrahydropyranol **74** in high yield (*Scheme 1.3.1.17*).[40]



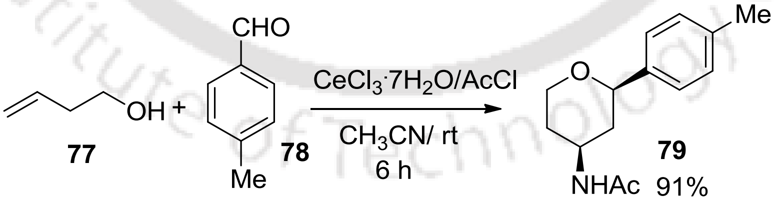
Scheme 1.3.1.17

Woo *et al*. have applied the Prins cyclization in the total synthesis of polycavernoside A. The acyclic precursor, **75** undergoes Prins cyclization in the presence of TESOTf/TMSOAc/AcOH medium to give 4-acetoxytetrahydropyran containing bicyclic macrolactone **76**. The macrolactone **76** is the key intermediate for the synthesis of macrolide, Polycavernoside A (*Scheme 1.3.1.18*).[41]



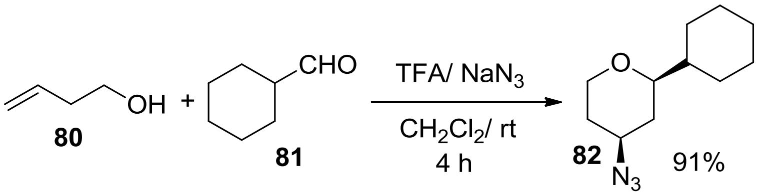
Scheme 1.3.1.18

The construction of C-N bond at 4th position of THPs was successfully demonstrated by Yadav and co-workers *via* Prins-Ritter sequence. The reaction of homoallyl alcohol **77** with aldehyde **78** in the presence of $CeCl_3{\cdot}7H_2O$/AcCl undergoes Prins cyclization to give the 4-tetrahydropyranyl cation, which was trapped by acetonitrile through Ritter reaction to produce the corresponding 4-amidotetrahydropyran **79** with high *cis*-selectivity (*Scheme 1.3.1.19*).[42]



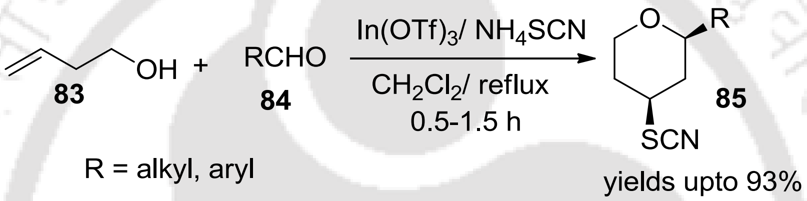
Scheme 1.3.1.19

Yadav *et al.* have reported a novel diastereoselective protocol for the synthesis of 4-azidotetrahydropyran **82** *via* three component reaction of aldehyde **81**, but-3-en-1-ol **80** and sodium azide, using excess amount of trifluoroacetic acid in dichloromethane (*Scheme 1.3.1.20*).[43]



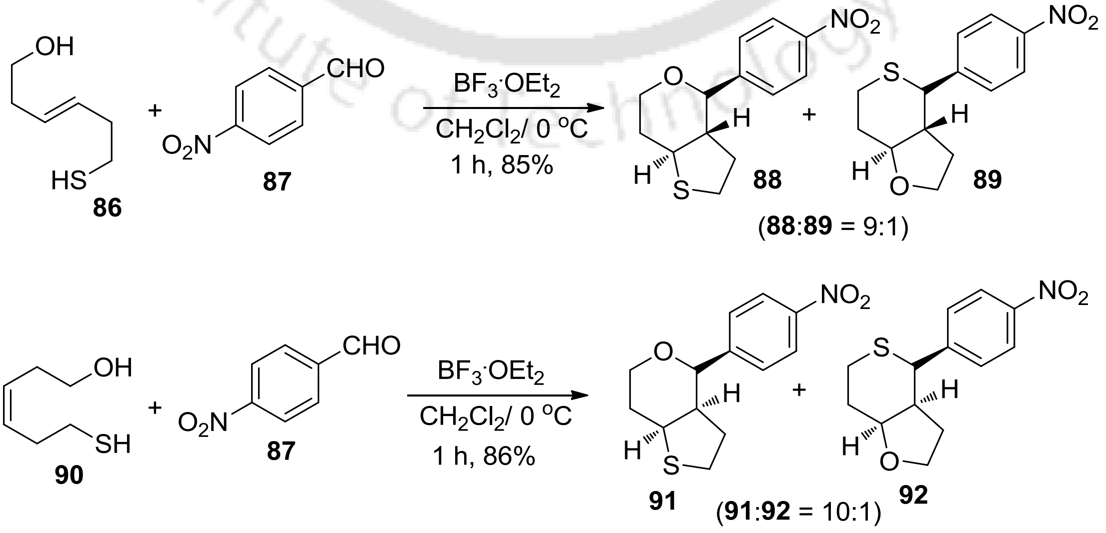
Scheme 1.3.1.20

4-Thiocyanotetrahydropyrans have been synthesized by In(OTf)$_3$ catalyzed simple Prins cyclization reaction of homoallyl alcohol **83**, aldehydes **84** and ammonium thiocyanate as a nucleophilic source (*Scheme 1.3.1.21*). The reaction is highly selective and afforded 2,4-*cis*-4-thiocyano tetrahydropyrans **85** with various alkyl and aryl substitutions at C-2 carbon of THP ring in excellent yields.[44]



Scheme 1.3.1.21

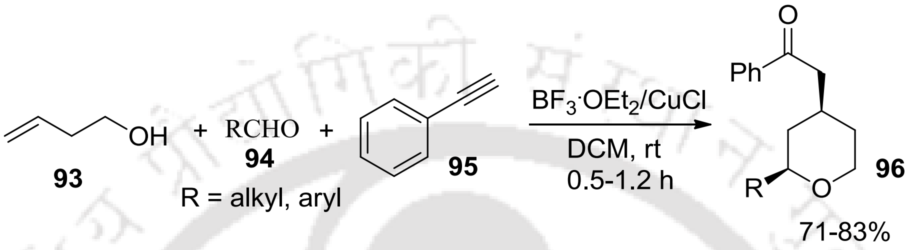
Very recently, intramolecular C-S bond formation at 4th position of THP ring was demonstrated by Reddy *et al.*[45] A smooth coupling of 6-mercaptohex-3-en-1-ol with aldehydes in the presence of $BF_3{\cdot}OEt_2$ afforded fused tetrahydropyrans along with small amounts of fused tetrahydrothiopyrans. The geometry of olefin plays a key role in deciding stereochemistry of the product. Reaction of *trans* and *cis* 6-mercaptohex-3-en-1-ols **86** and **90** with aldehyde **87** give



Scheme 1.3.1.22

the corresponding *trans* and *cis* fused hexahydro-2*H*-thieno[3,2-*c*]pyrans **88** and **91**, respectively (*Scheme 1.3.1.22*).

Yadav and coworkers have reported combined boron trifluoride etherate and cuprous chloride mediated Prins cyclization of homoallyl alcohol **93**, and aldehyde **94** followed by trapppng the carbocation with phenyl acetylene **95** as a nucleophilic source to furnish corresponding ketone **96** at 4th position of tetrahydropyran ring (*Scheme 1.3.1.23*).[46]

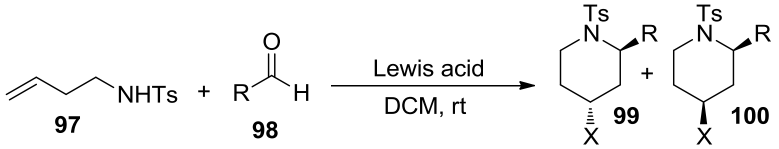


Scheme 1.3.1.23

1.3.2. Aza-Prins Cyclization

In a simplest way, aza-Prins cyclization is the nitrogen verson of Prins cyclization reaction. In principle, the Prins cyclization of homoallylic amines takes place in a fashion similar to that of homoallylic alcohols, whereby the non bonding electrons on the nitrogen initiate the sequence of reaction steps by attacking the electrophilic site of the aldehyde activated by an acid catalyst. The key intermediate of the aza-Prins cyclization is an iminium ion, in analogy to the oxonium ion. Compared to classical Prins cyclization, examples of aza-Prins cyclization using iminium ions leading to nitrogen-containing heterocycles have been less developed in the literature due to less electrophilic nature of iminium ions compared to oxo-carbenium ions. Whereas, aza-Prins cyclization of acyclic/cyclic *N*-acyliminium ion intermediates to achieve piperidine ring containing mono and bicyclic compounds is well explored due to more electrophilic nature of *N*-acyliminium ions.[47]

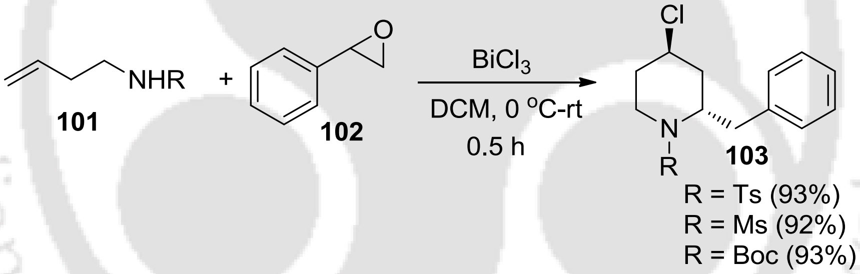
The reaction of *N*-tosyl homoallylamine **97** with aldehydes **98** in the presence of halogenated Lewis acids in dichloromethane afforded the 4-halopiperidines **99** and **100** in good yields. The nature of Lewis acid decides the selectivity of the reaction (*Scheme 1.3.2.1)*.[48]



Lewis acid	R	X	time	yield	**99**:**100**
$HBF_4{\cdot}OEt_2$	*p*-NO_2-C_6H_4	F	4 h	78%	0:100
$BF_3{\cdot}OEt_2$	*p*-Br-C_6H_4	F	2 h	71%	50:50
Et_4NF-5HF	C_7H_{15}	F	1 h	quant.	12:88
$FeCl_3$	*i*-Bu	Cl	10 min.	82%	99:1
$FeBr_3$	$PhCH_2$	Br	10 min.	94%	86:14
GaI_2/I_2	$Ph(CH_2)_2$	I	7 h	91%	98:2

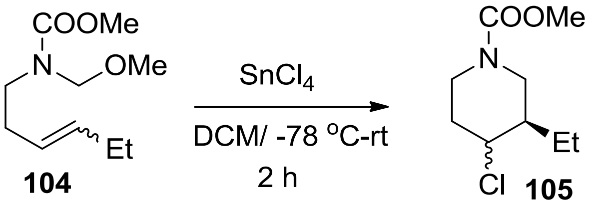
Scheme 1.3.2.1

2-Benzyl substituted piperdines **103** were synthesized from the reaction of styrene oxide **102** with *N*-protected homoallyl amines **101** in the presence of $BiCl_3$. The reaction selectively produces *trans* 2,4-disubstituted piperidine derivatives in good yields (*Scheme 1.3.2.2)*.[49]



Scheme 1.3.2.2

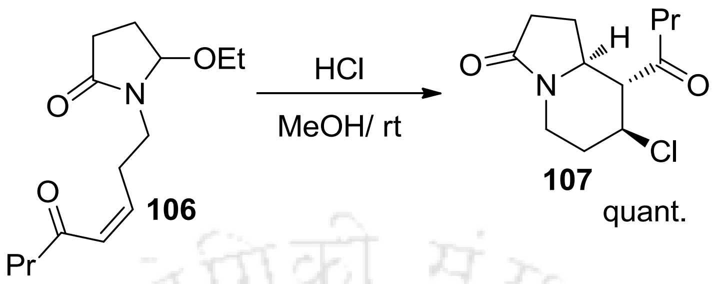
Speckamp and co-workers explored the use of *N*-acyliminium ions in *endo*-trig (aza-Prins type) cyclizations for the synthesis of variously substituted piperidines. The *N*-acyliminium ion precursor **104** undergoes aza-Prins cyclization in the presence of $SnCl_4$ at -78 °C to provide a mixture of 4-chloro piperidines **105** (*Scheme 1.3.2.3).*[50]



Alkene	(α:β)
E	95:5
Z	33:67

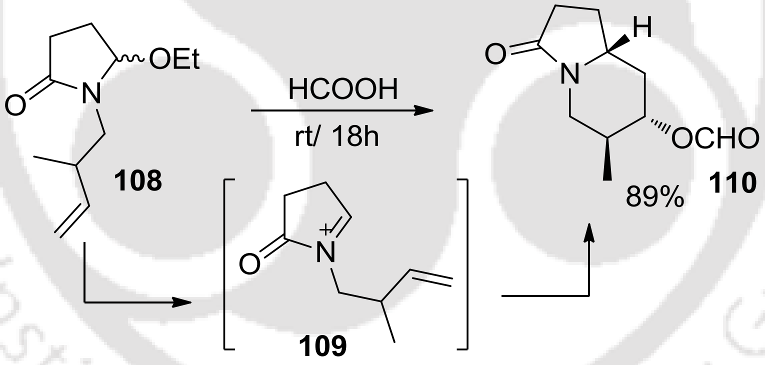
Scheme 1.3.2.3

Speckamp has further extended the above strategy for the synthesis of chloro substituted azabicyclic compounds **107** *via* aza-Prins type cyclization of ethyl ether of reduced homoallyl imide **106**, mediated by anhydrous HCl in MeOH (*Scheme 1.3.2.4)*.[51]



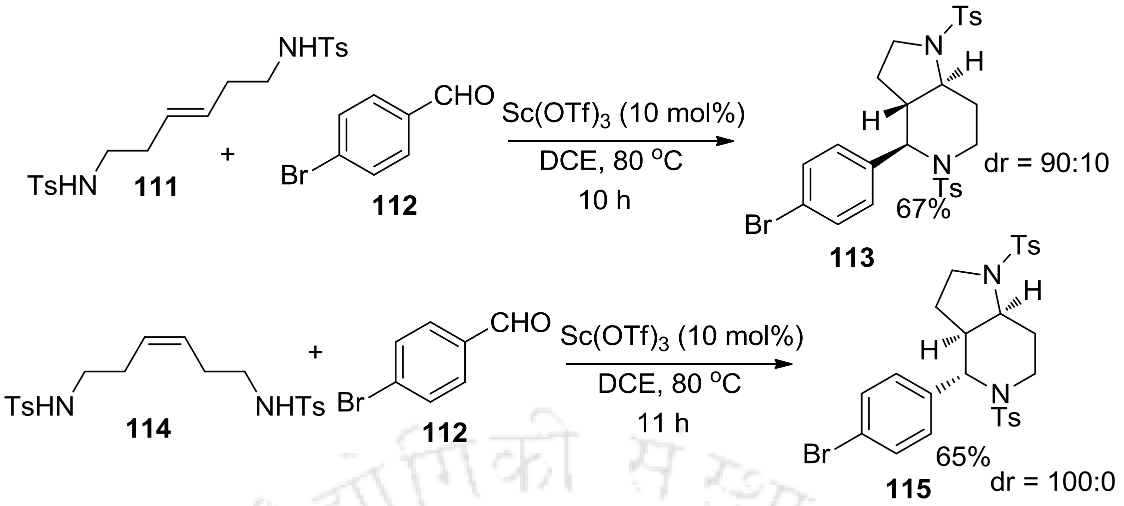
Scheme 1.3.2.4

Speckamp and co-workers also studied the trapping of carbocation generated during aza-Prins cyclization of *N*-acyliminium ions with oxygenated nucleophiles.[52] The treatment of alkoxy ether of reduced homoallyl succinimide **108** with formic acid gives an *N*-acyl iminium ion intermediate **109**, which upon cyclization followed by trapping with formate group gives highly stereoselective azabicycles **110** in good yields (*Scheme 1.3.2.5)*.



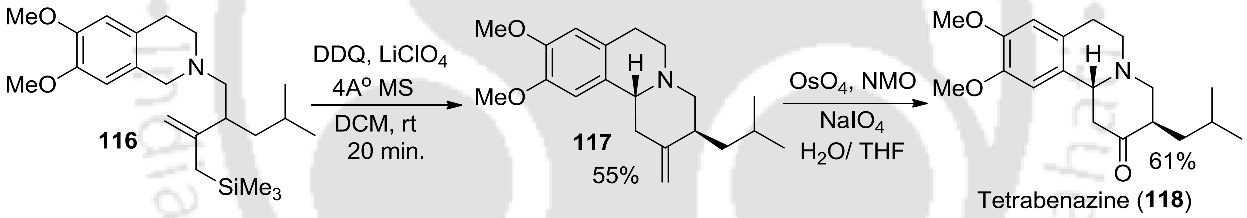
Scheme 1.3.2.5

Aldehyde **112** undergoes smooth coupling with (*E*)-hex-3-ene-1,6-ditosylamide **111** in the presence of 10 mol% Sc(OTf)$_3$ in 1,2-dichloroethane at 80 ^{o}C to produce the corresponding 1,5-ditosyl-octahydro-*1H*-pyrrolidino-[3,2-*c*]pyridines **113** in good yields with high *trans*-selectivity at ring junction, whereas the coupling of (*Z*)-hex-3-ene-1,6-ditosylamide **114** gave *cis*-fused octahydro-1*H*-pyrrolidino[3,2-*c*] pyridines **115** predominantly (*Scheme 1.3.2.6)*.[53]



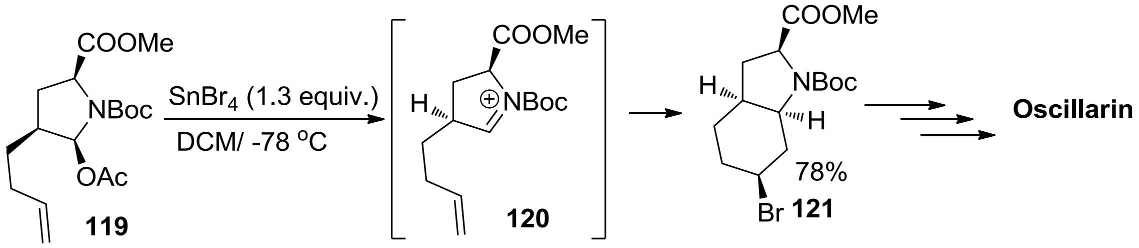
Scheme 1.3.2.6

The DDQ mediated C-H activation of an amino allylsilane **116** gives the corresponding iminium ion, which on ring closure *via* intramolecular aza-Prins-type cyclization gives tricyclic compound **117**. The oxidative cleavage of **117** using OsO_4, NMO, and $NaIO_4$ afforded an antipsychotic drug tetrabenazine **118** in 61% yield (*Scheme 1.3.2.7*).[54]



Scheme 1.3.2.7

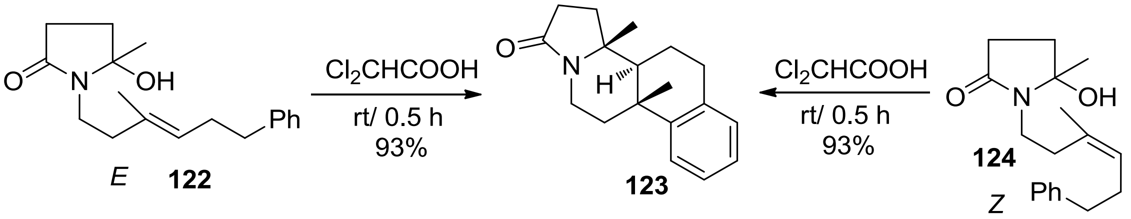
The octahydroindole moiety **121** of oscillarin (a marine natural product exhibiting antithrombotic activity) was prepared by Hanessian and co-workers *via* aza-Prins cyclization. The precursor **119** generates the *N*-acyloxyiminium intermediate **120** by reacting with $SnBr_4$. Cyclization according to the 6-*endo*-trig mode leads to **121** in 78% yield (*Scheme 1.3.2.8*).[55]



Scheme 1.3.2.8

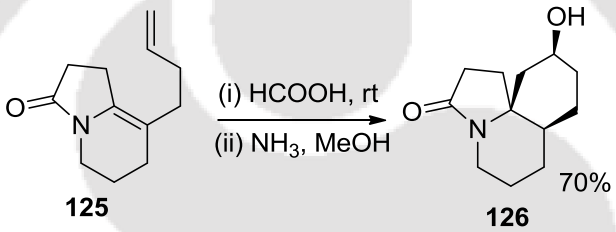
Speckamp and coworkers reported aza-Prins cyclization of phenyl tethered cyclic *N*-acyliminium ions followed by C-C bond formation at 4th position of piperidine *via* intramolecular Friedel-

Crafts reaction.[56] The reaction is highly diastereoselective and both the *E* and *Z* alkene substrates **122** and **124** produced the same cyclized product **123** with high selectivity (*Scheme 1.3.2.9*).



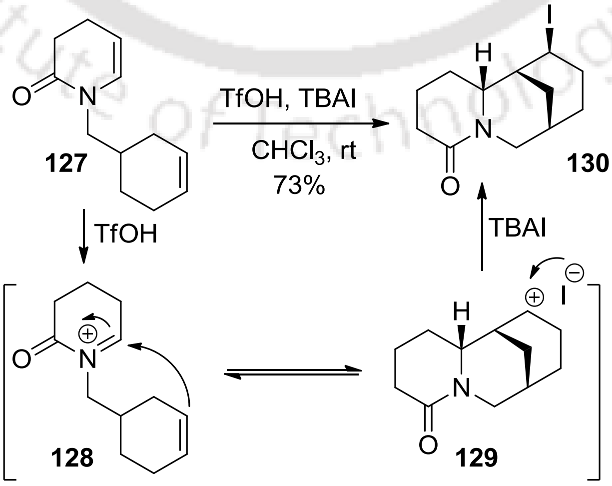
Scheme 1.3.2.9

In 1999, Hiemstra's report featured a highly diastereoselective aza-Prins cyclization of indolizidine substrate **125** to form tricyclic lactam **126** mediated by formic acid and methanolic ammonia (*Scheme 1.3.2.10*).[57]



Scheme 1.3.2.10

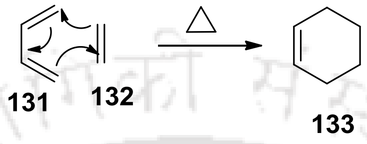
The chloroform solution of **127** was treated with 2.0 equivalents of TfOH and excess of tetrabutylammonium iodide at ambient temperature to provide a single tricyclic iodide **130** in 73% yield. This reaction proceeds *via* cyclization of *N*-acyl iminium ion **128** and further trapping of the carbocation **129** with iodide (*Scheme 1.3.2.11*).[58]



Scheme 1.3.2.11

1.3.3. Diels-Alder Reaction

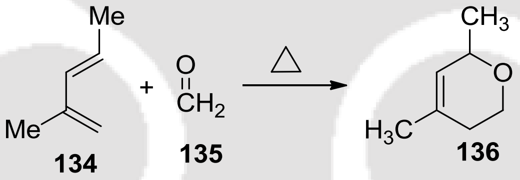
In 1928, Otto Diels and Kurt Alder have reported the cycloaddition reaction between a molecule with double or triple bond (dienophile) **132** and a diene **131** with two conjugated double bonds.[59] The reaction yielded a six membered ring **133** with the rearrangement of the π-bonds to σ-bonds (*Scheme 1.3.3.1*). Relative stereochemistry is usually well defined because of the formation of a cyclic transition state arising from suprafacial-suprafacial interaction, with endo approach.



Scheme 1.3.3.1

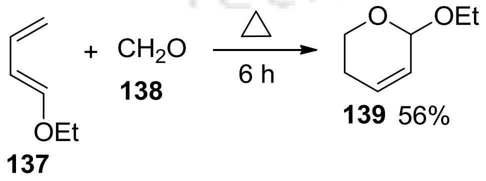
1.3.4. Hetero-Diels-Alder (HDA) Reaction

In 1949, Gresham and Steadman explored the Diels-Alder reaction by replacing dienophile with heterodienophiles such as carbonyls (glyoxalate or formaldehyde) for the synthesis of oxygen heterocycles, called hetero-Diels-Alder (HDA) Reaction (*Scheme 1.3.4.1*).[60]



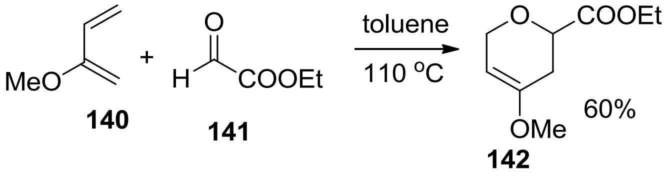
Scheme 1.3.4.1

In 1962, Kubler found that an electron donating group, usually alkoxy group on the 1-position of a diene **137** increases its reactivity in Diels-Alder reaction with paraformaldehyde **138**, to give 2-alkoxy-5,6-dihydro-2*H*-pyran **139** (*Scheme 1.3.4.2*).[61]



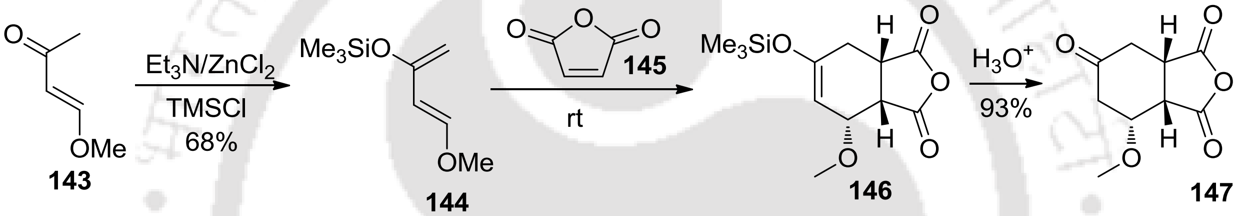
Scheme 1.3.4.2

Wender and co-workers used the above strategy for the synthesis of key dihydropyran unit **142** in the synthesis of phorbol skeleton.[62] The HDA reaction of 2-methoxybutadiene **140** and ethyl glyoxalate **141** in toluene at reflux temperature afforded pyran product **142** in 60% yield (*Scheme 1.3.4.3*).



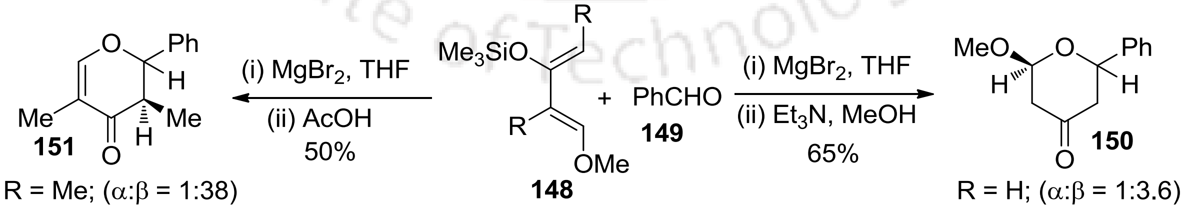
Scheme 1.3.4.3

In 1974, Danishefsky has synthesized a highly activated diene, *trans*-1-methoxy-3-trimethylsilyloxy-l,3-butadiene **144** from commercially available *trans*-4-methoxybutene-2-one **143** using triethylamine-zinc chloride-TMSCl system in 68% yield. The feasibility of this diene towards Diels-Alder reaction was tested by the addition of maleic anhydride **145** at room temperature, resulting in the formation of adduct **146**, which after acidic workup gave 93% of methoxy ketoanhydride **147** (*Scheme 1.3.4.4*).[63]



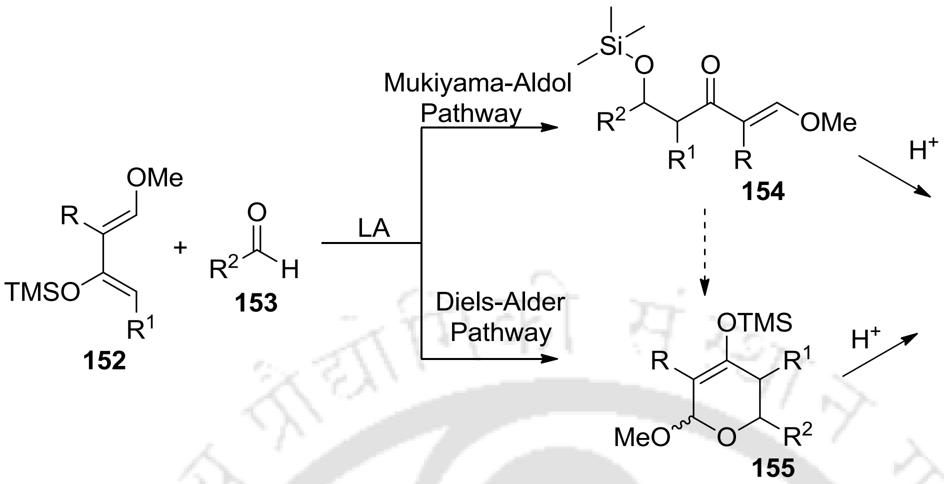
Scheme 1.3.4.4

Ever since, the activated diene (Danishefsky's diene) has received much attention and extended for aldehydes using various Lewis acids.[64] The HDA reaction of aldehyde **149** with Danishefsky's diene **148** in the presence of $MgBr_2$ followed by triethylamine treatment gave tetrahydropyranone **150**, whereas $MgBr_2$ followed by acetic acid treatment produced dihydropyranone **151** (*Scheme 1.3.4.5*).



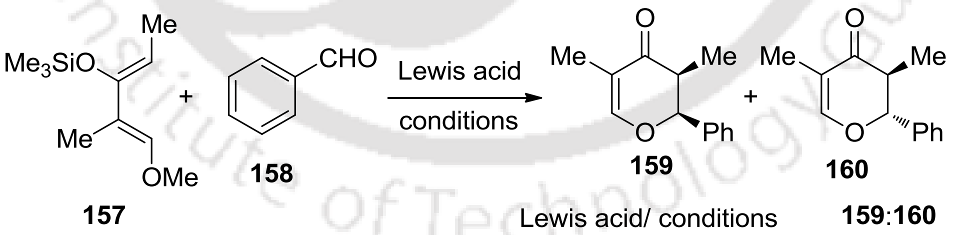
Scheme 1.3.4.5

The mechanism of the Lewis acid catalyzed HDA reaction of aldehydes **153** with activated dienes **152** for the formation of dihydropyranones has been studied by several research groups and reported two possible paths. In the first, the reaction proceeds through a Mukiyama-type Aldol addition step, giving an intermediate **154**, which on subsequent cyclization under acidic conditions gives the HDA product **156**. The second path takes place through a concerted, asynchronous [4+2] cycloaddition giving an adduct **155**, which on acid treatment produces the product **156** (*Scheme 1.3.4.6*).[65]



Scheme 1.3.4.6. Mukiyama-Aldol and Diels-Alder pathways of HDA reaction

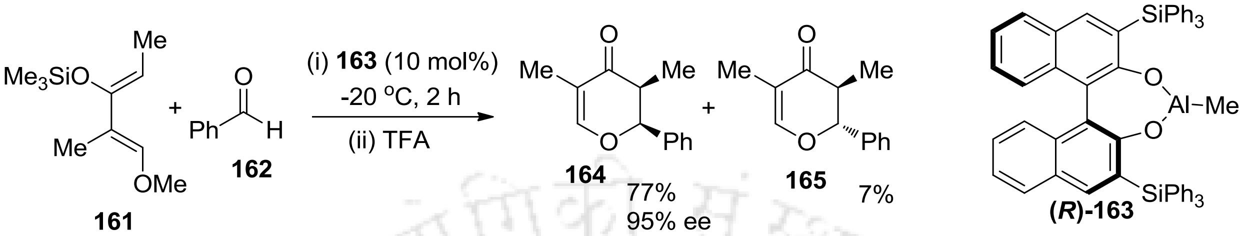
The identity of the Lewis acid plays a crucial role in determining both the mechanism by which the reaction proceeds and the selectivity. Danishefsky *et al.* have developed a stereo controlled methodology for the synthesis of 2,3 dihydropyran-4-ones by Lewis acid catalyzed cycloaddition of Danishefsky's dienes with aldehydes. For example, the HDA reaction of benzaldehyde **158** with *trans*-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene **157** in the presence of BF_3 as the Lewis acid catalyst gave major *trans*-substituted dihydropyranone **160** and a preference for the *cis*-substituted dihydropyranone **159** when $ZnCl_2$ was the catalyst (*Scheme 1.3.4.7*).[66]



Lewis acid/ conditions	**159**:**160**
(i) BF_3/ CH_2Cl_2/ -78^{0}C (ii) TFA	23:68
(i) $ZnCl_2$/ THF (ii) $NaHCO_3$ (iii) TFA	78:2

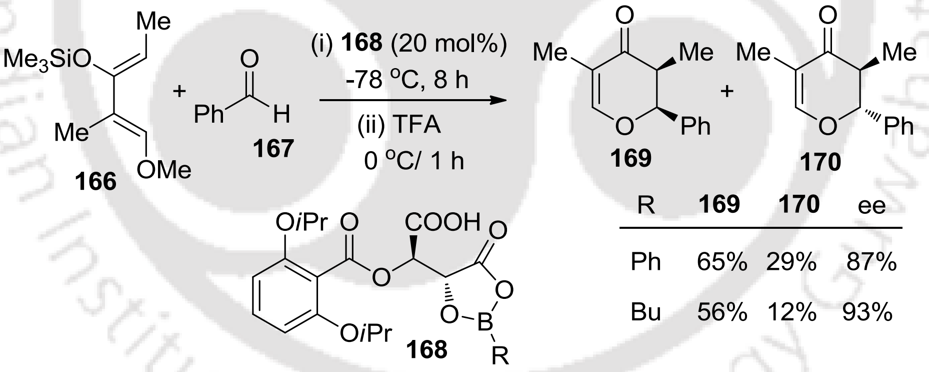
Scheme 1.3.4.7

A wide range of Lewis acids based on Al, B, Ti, Zr, Cu, and Co have been examined for this HDA reaction and in early 1990's Yamamoto and co-workers demonstrated the first example of a catalytic, enantioselective variant of the transformation using an Al-BINOL complex **163** with large substituents at the 3 and 3’ positions of the BINOL backbone.[67] The (*R*)-BINOL **163** catalyzed HDA reaction of Danishefsky’s diene **161** with benzaldehyde **162**, followed by TFA treatment gives *cis* 2,3-substituted dihydropyranone **164** as major isomer with 95% ee (*Scheme 1.3.4.8*).



Scheme 1.3.4.8

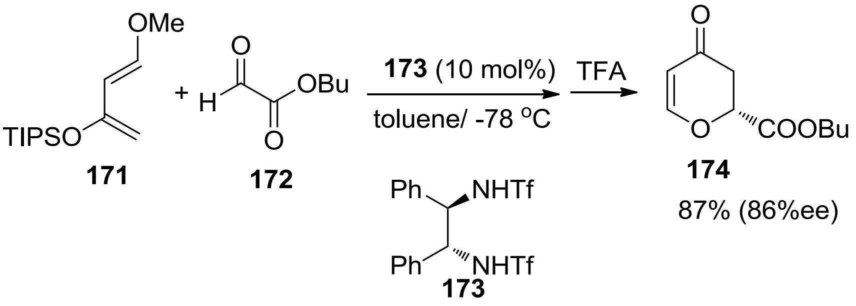
Further investigation by Yamamoto and co-workers led to the development of a stable chiral (acyloxy)borane (CAB) complex for enantioselective HDA reaction. For example, the hetero-Diels-Alder reaction of aldehyde **167** with Danishefsky diene **166** catalyzed by 20 mol% of CAB complex **168** at -78 °C for 8 hours gives an adduct, which was treated with trifluoroacetic acid in dichloromethane to furnish dihydropyranones **169&170** (*Scheme 1.3.4.9*).[68]



R	169	170	ee
Ph	65%	29%	87%
Bu	56%	12%	93%

Scheme 1.3.4.9

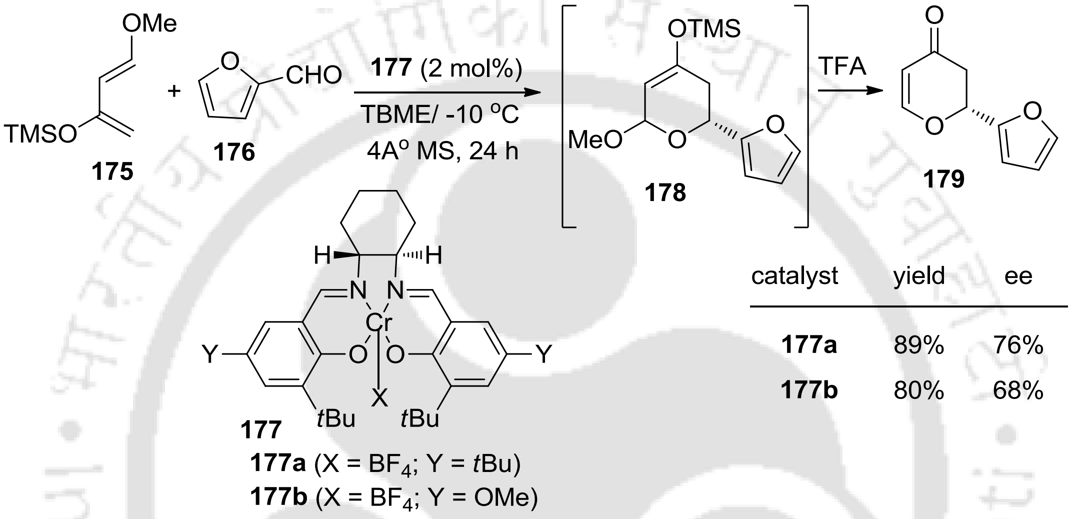
The bis-triflylamide **173** has been used as an efficient chiral Brønsted acid catalyst due to the



Scheme 1.3.4.10

electronegative effect of trifluoromethanesulfonyl substituent for the HDA reaction between Danishefsky's diene **171** and glyoxylate **172** through double hydrogen bonding between catalyst and glyoxalate to furnish 2,3-dihydropyran-4-one product **174** (*Scheme 1.3.4.10*).[69]

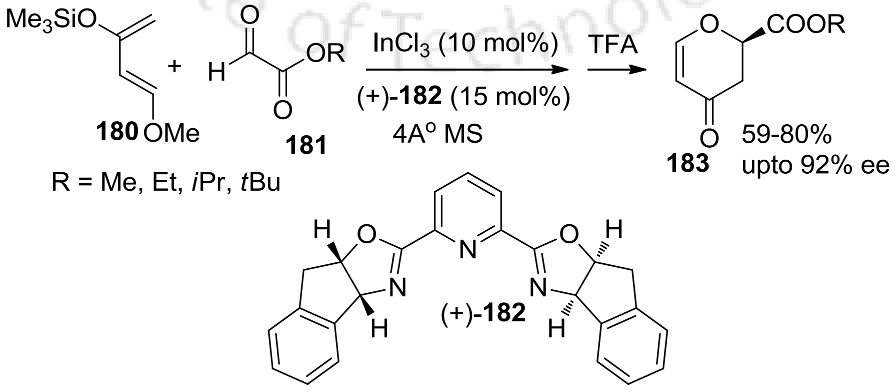
Jacobsen and coworkers investigated the Lewis acid catalyzed HDA reaction between diene **175** and aldehyde **176** with chromium(III) salen complexes **177** for the synthesis of dihydropyranone **179** in good yield with moderate enantioselectivity (*Scheme 1.3.4.11*). The mechanistic studies suggest that the reaction proceeds through a synchronous HDA intermediate **178**.[70]



catalyst	yield	ee
177a	89%	76%
177b	80%	68%

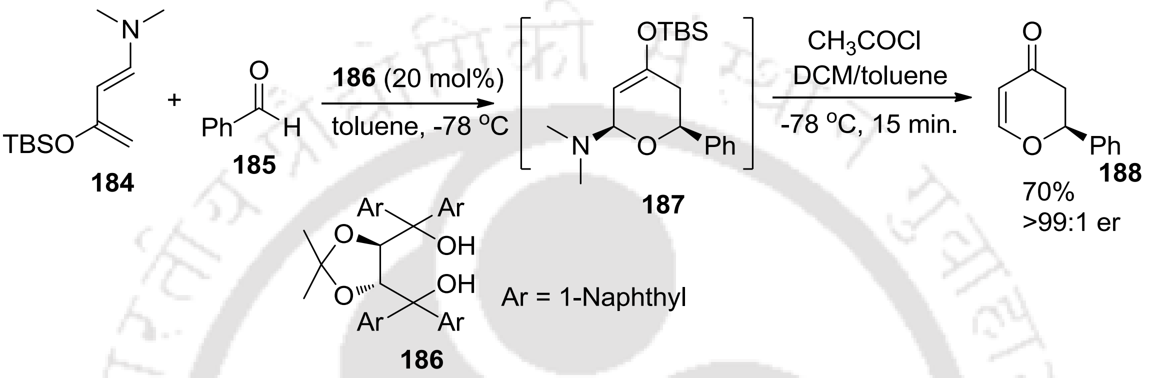
Scheme 1.3.4.11

Zhao *et al.* demonstrated an efficient catalytic enantioselective hetero-Diels-Alder reaction of Danishefsky's diene **180** with glyoxalate esters **181** using a chiral In(III)Pybox complex for the synthesis of (*S*) configurated 2-substituted 2,3-dihyropyran-4-ones **183** in good yields and moderate to high enantioselectivities (*Scheme 1.3.4.12*).[71]



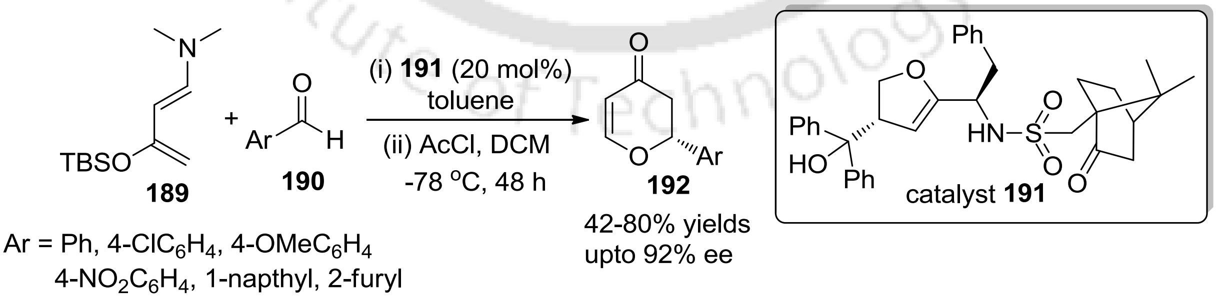
Scheme 1.3.4.12

In order to develope more reactive dienes for the Diels-Alder reaction, Rawal and co-workers introduced a reactive diene **184**, which on participation in HDA reaction with aldehyde **185** in the presence of (*R*,*R*)-1-naphthyl TADDOL **186** gives a Diels-Alder adduct **187** and subsequent unmasking effect by acetyl chloride gave *S*-enantiomeric dihydropyranone **188** preferencially over *R*-enantiomer (>99:1) (*Scheme 1.3.4.13*). This metal free enantioselective HDA reaction accelerates through the formation of hydrogen bonding between carbonyl compound and chiral alcohol.[72]



Scheme 1.3.4.13

Sigman and co-workers have developed an enantioselective HDA reaction for the synthesis of pyranones using a novel chiral oxazoline catalyst **191**, having two hydrogen bond donating arms. The hetero Diels-Alder (HDA) reaction carried out between aldehyde **190** and activated diene **189** in the presence of catalyst **191** gives a Diels-Alder adduct, which followed by decomposition in acetyl chloride yielded the corresponding pyranone **192** in moderate to high yields with an excelent enantiomeric excess (*Scheme 1.3.4.14*).[73]



Scheme 1.3.4.14

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CHAPTER 2

Stereoselective Synthesis of 4-Aryltetrahydropyrans from Epoxides *via* Prins-Friedel-Crafts Reaction

2.1. Biological Importance of 4-Aryltetrahydropyrans

4-Aryltetrahydropyran ring systems are of great interest because of their presence in many natural products, having unique and wide-ranging biological activities.[1] One of the important family in natural products having tetrahydropyran as a key moiety is calyxins, isolated from the plant species *Alpiniablepharocalyx* seeds from south western China, which are used for the treatment of stomach disorders in traditional Chinese medicine.[2] Calyxin L (**1**) is the most potent member of this class, exhibits potent antiproliferative activity against human HT-1080 fibro sarcoma and murine 26-L5 carcinoma.[3] In addition, some of symmetrical 4-aryltetrahydropyrans such as compounds **2** and **3** show olfactory properties[4] and nonredox 5-lipoxygenase inhibiting properties,[5] respectively. Another important 4-aryltetrahydropyran containing natural product (-)-sugiresinol[6] (**4**), isolated from heartwood of *Cryptomeria japonica* by Funaoka *et al.*, has potent antifungal activity and inhibits cyclic AMP phosphodiesterase in addition to the growth of *C. shiitake* hyphae (*Figure 2.1.1*).[7]

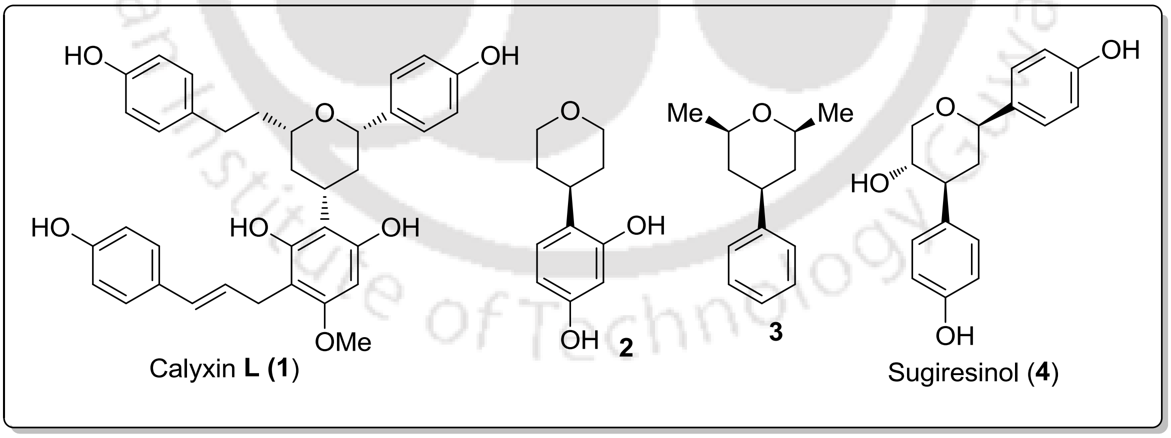
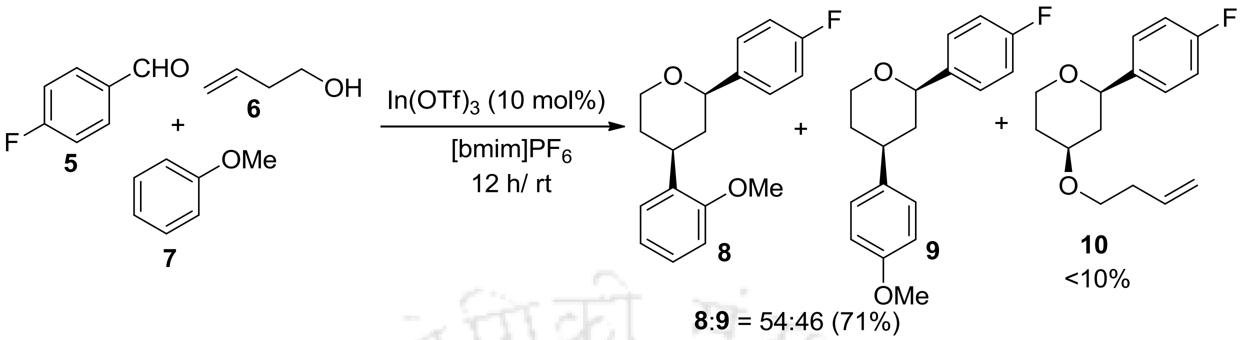


Figure 2.1.1. Some biologically active 4-aryltetrahydropyran derivatives

2.2. Literature Methods

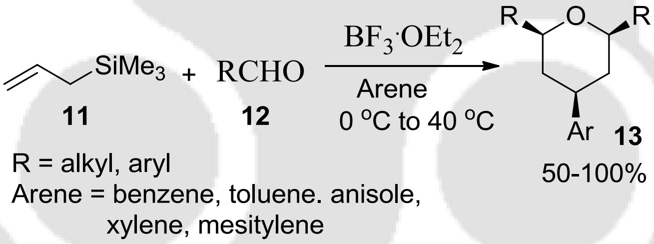
Chao-Jun Li and co-workers reported a three-component cyclization of aldehyde **5**, 3-buten-1-ol **6** and anisole **7** using a catalytic amount of indium(III)triflate in ionic liquid [bmim]PF$_6$ through Prins-Friedel-Crafts cyclization reaction.[8] This reaction ended with a mixture of 4-

aryltetrahydropyrans (**8** & **9**) in 71% overall yield with a ratio of 54:46. Tetrahydropyranyl ether **10** was also a by-product in less than 10% yield (*Scheme 2.2.1*).



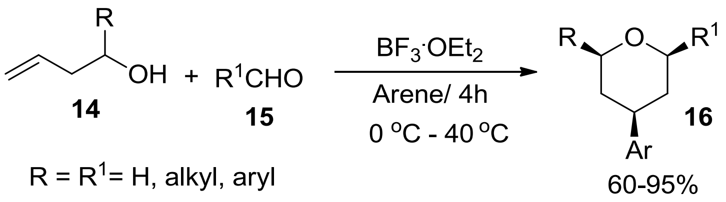
Scheme 2.2.1

Saikia and coworkers have synthesized symmetrical 4-aryltetrahydropyrans **13** through Sakurai-Hosomi-Prins-Friedel-Crafts reaction by the reaction of allyltrimethylsilane **11** with aldehydes **12** and arene, mediated by boron trifluoride etherate.[9] The reaction produced good to excellent yields for both aliphatic and aromatic aldehydes. The reaction is highly diastereoselective having all substituents *cis* to each other (*Scheme 2.2.2*).



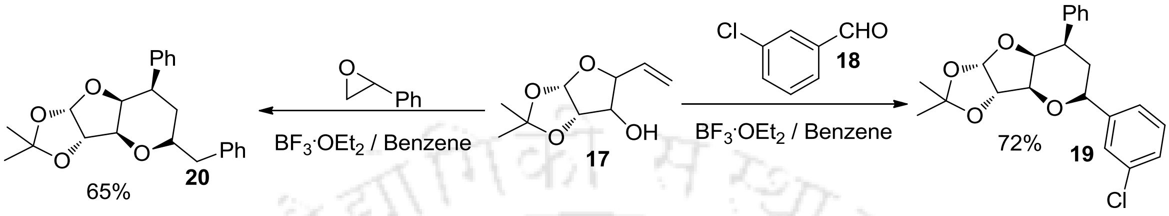
Scheme 2.2.2

Similarly, same group have further developed a diastereoselective one-pot, three-component Prins-Friedel-Crafts reaction for the synthesis of unsymmetrical 4-aryltetrahydropyrans **16** by the reaction of aldehydes **15** with homoallylic alcohols **14** in the presence of arene, promoted by boron trifluoride etherate (*Scheme 2.2.3*).[10] This methodology was successfully applied for both acyclic and cyclic ketones to get corresponding 4-aryltetrahydropyrans.



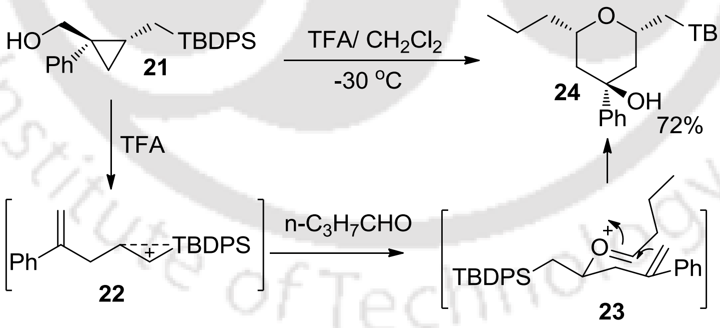
Scheme 2.2.3

Reddy *et al*. have described a method for the synthesis of sugar fused diarylhexahydro-2*H*-furo[3,2-*b*]pyrans **19** through Prins-Friedel-Crafts reaction by treating of D-glucose based homoallyl alcohol **17** with aldehyde **18** using $BF_3{\cdot}OEt_2$ as a catalyst in benzene. Similarly, styrene oxide also worked as carbonyl equivalent and produced corresponding 2-benzyl sugar fused diarylhexahydro-2*H*-furo[3,2-*b*]pyran **20** (*Scheme 2.2.4*).[11]



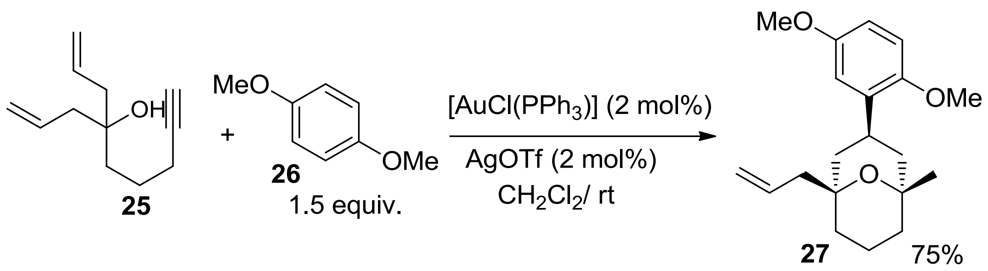
Scheme 2.2.4

V. K. Yadav and co-workers reported a novel methodology for achieving 4-aryl substituted tetrahydropyrans from silylmethyl-substituted cyclopropylcarbinol **21** mediated by trifluoroacetic acid (TFA) (*Scheme 2.2.5*).[12] This method relies on the key formation of the cyclopropyl carbonyl cation. This cation gives stable homoallyl cation **22** through ring cleavage pathway to relieve ring strain. The cation **22** traps the carbonyl function and forms oxocarbenium ion **23**, which further undergoes cyclization followed by hydroxyl attack to give the compound **24** with high diastereoselectivity. This method was explored with a series of aliphatic and aromatic aldehydes to achieve the substituted 4-phenyltetrahydropyrans.



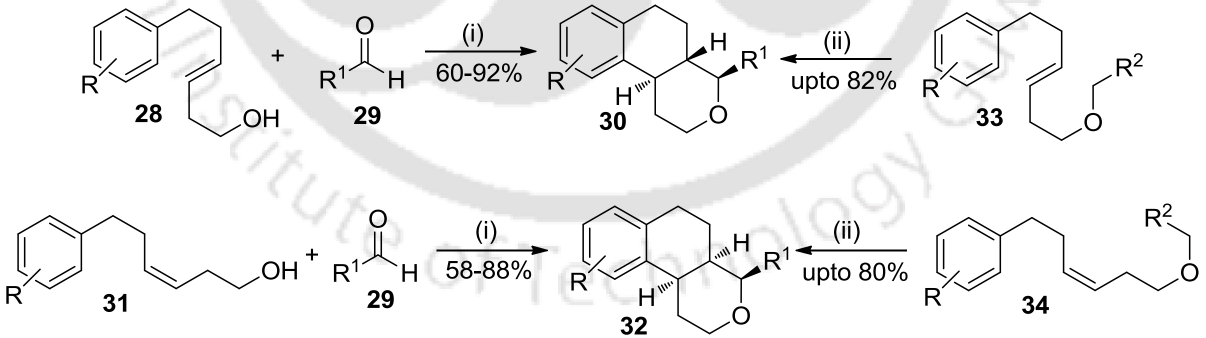
Scheme 2.2.5

Barluenga *et al*. reported a new route for the synthesis of 4-aryltetrahdropyran containing bicyclic compounds *via* the tandem hydroalkoxylation/ Prins type cyclization/ Friedel–Crafts alkylation reaction of alkynol **25** with electron-rich aromatic compound **26** in the presence of 2 mol% of $[AuCl(PPh_3)]/AgOTf$ in dichloromethane. The compound **27** was isolated in 75% yield as single diastereomer (*Scheme 2.2.6*).[13]



Scheme 2.2.6

Subba Reddy and co-workers described a novel tandem Prins-Friedel-Crafts strategy for the synthesis of fused tetrahydropyrans involving 6-arylhex-3-enyl alcohols with aldehyde by using a combination of Lewis and Brønsted acids (*Scheme 2.2.7*), in which, the stereochemistry of the products depends on the double bond geometry of the homoallyl alcohol. In case of (*E*)-6-arylhex-3-enyl alcohols **28** undergo smooth cross coupling with various aldehydes **29** in the presence of 10 mol% Sc(OTf)$_3$ and 30 mol% TsOH to afford the *trans*-fused hexahydro-1*H*-benzo[*f*]isochromenes **30**. Whereas, (*Z*)-6-arylhex-3-enyl alcohols **31**, with aldehydes **29** resulted in *cis*-fused hexahydro-1*H*-benzo[*f*]isochromenes **32** under the same reaction conditions.[14] Similarly, aryl tethered homoallylbenzyl ethers such as benzyl ethers of (*E*)- and (*Z*)-6-arylhex-3-enyl alcohols **33** and **34** also produced the same compounds **30** and **32** *via* the benzylic C–H bond activation followed by tandem Prins/Friedel–Crafts cyclization in the presence of stoichiometric amounts of DDQ and SnCl$_4$ in good yields with complete stereoselectivity (*Scheme 2.2.7*).[15]



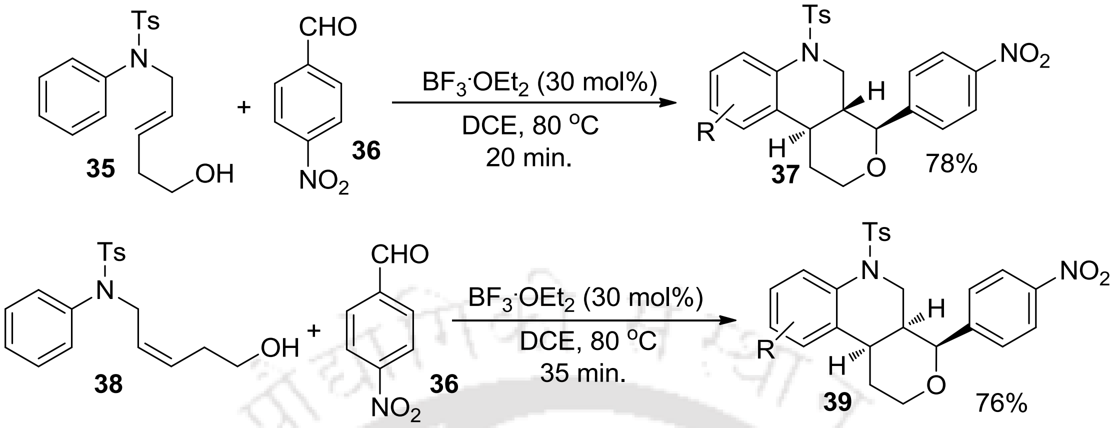
R = H, 3-OMe, 4-Me;
R^1 = *p*-Br, Cy, 2-thiophene, *p*-NO$_2$, styryl, (CH$_3$)$_2$CHCH$_2$

R = H, 3-OMe, 4-Me;
R^2 = Aryl

Reaction Conditions: (i) Sc(OTf)$_3$ (10 mol%) + TsOH (30 mol%), CH$_2$Cl$_2$/ rt
(ii) 1.1 equiv. DDQ +1.1 equiv. SnCl$_4$; 4A^o MS, CH$_2$Cl$_2$; 0 ^{o}C-rt

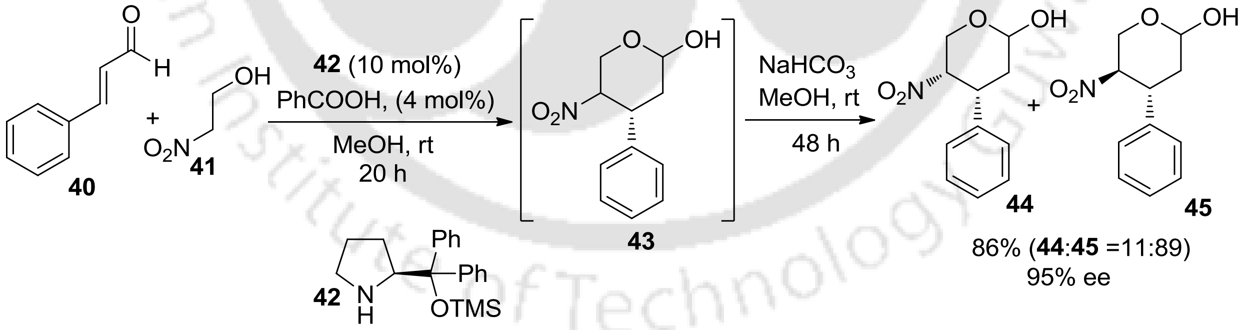
Scheme 2.2.7

They later demonstrated a similar methodology using Prins-Friedel-Crafts reaction between (*E*)-5-(arylamino) pent-3-en-1-ol **35** with aldehyde **36** in the presence of 30 mol% of BF$_3$·OEt$_2$ in 1,2-dichloroethane at 80 °C, which resulted in *trans*-fused hexahydro-1*H*-pyrano[3,4-*c*]quinolone **37** with high diastereoselectivity. Similarly, (*Z*)-5-(arylamino)pent-3-en-1-ol **38** cross coupled with aldehyde **36** to give *cis*-fused hexahydro-1*H*-pyrano[3,4-*c*]quinolone **39** exclusively (*Scheme 2.2.8*).[16]



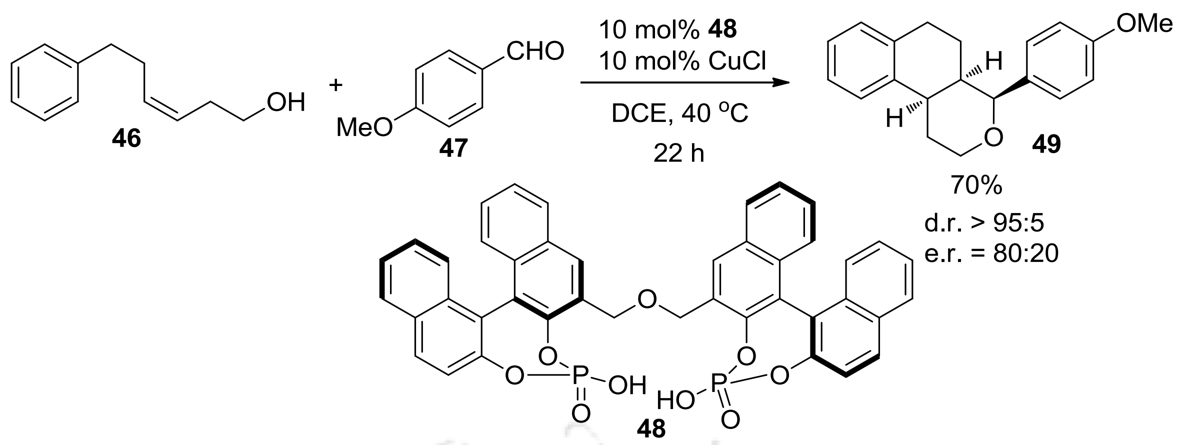
Scheme 2.2.8

A versatile approach for the synthesis of highly substituted tetrahydropyrans *via* asymmetric direct Michael reaction of nitroethanol with α,β-unsaturated aldehydes has been reported by Hayashi (*Scheme 2.2.9*).[17] The reaction of cinnamaldehyde **40** with nitroethanol **41** in the presence of chiral catalyst diphenylprolinolsilylether **42** and benzoic acid generates the Michael adduct γ-nitroaldehyde, which after cyclization gives substituted tetrahydropyrans with low diastereselective *cis*-*trans* isomers **43**. The *cis* isomer **44** undergoes isomerization in the presence of $NaHCO_3$ and converts into more thermodynamically stable *trans*-isomer **45**.



Scheme 2.2.9

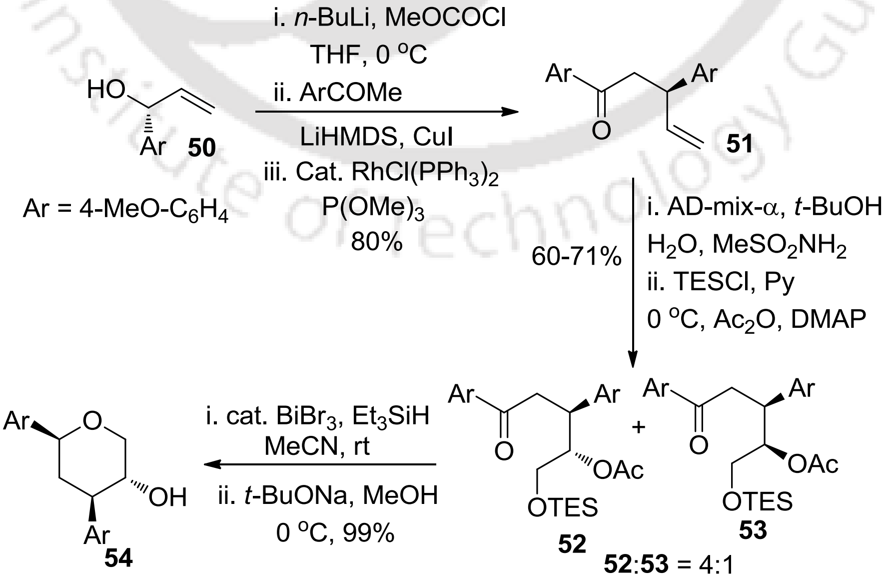
Recently, Weghe and Lalli described the first enantioselective tandem Prins-Friedel-Crafts cyclization of (*Z*)-6-phenylhex-3-en-1-ol **46** with 4-methoxy benzaldehyde **47** using the combination of a chiral BINOL-derived bis-phosphoric acid **48** and CuCl system (*Scheme 2.2.10*). This reaction ended with hexahydro-1*H*-benzo[*f*]isochromene product **49**, by the formation of three new contiguous stereogenic centres with 80% enantioselectivity.[18]



Scheme 2.2.10

2.2.1. 4-Aryltetrahydropyrans in Natural Product Synthesis

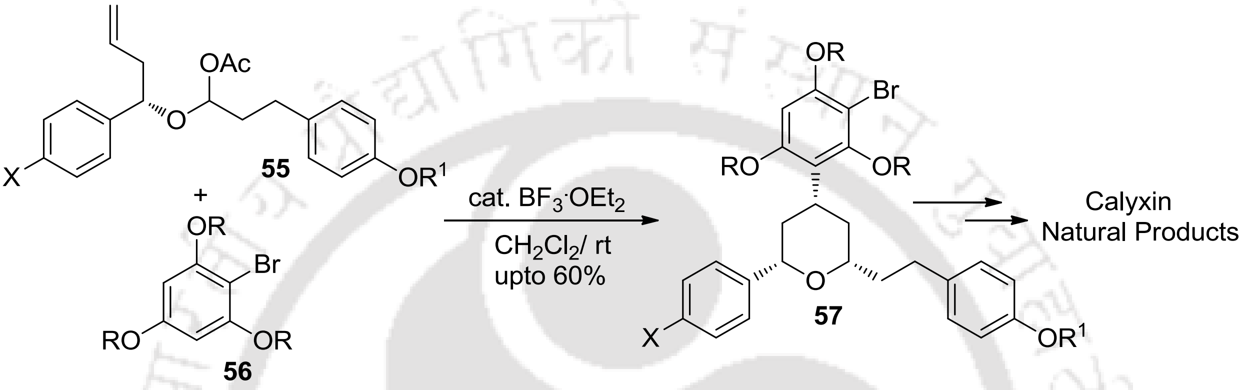
From last few years many research groups have used this Pirns-Friedel-Crafts approach for the synthesis of complex natural products. Evans and co-workers synthesized a 4-aryl THP containing natural product (-)-sugiresinol dimethyl ether (*Scheme 2.2.1.1*). The treatment of chiral allyl alcohol **50** with copper(I) enolates in presence of *n*-butyllithium followed by methyl chloroformate furnished the allylic carbonate, which on further reaction with rhodium catalyst afforded the β-substituted ketone **51** in 80% yield. Sharpless asymmetric dihydroxylation, followed by a one-pot differential protection of **51**, led to the cyclization precursor **52** and **53** in 60-71% yield over two steps, as a 4:1 mixture of diastereoisomers. The mixture was separated, and the desired isomer **52** was then subjected to reductive etherification using bismuth bromide



Scheme 2.2.1.1

and triethylsilane, followed by an in situ deprotection of the acetyl group, to afford (-)-sugiresinol dimethyl ether **54** in 99% yield, with 19:1 diastereoselectivity.[19]

The Prins-Friedel-Crafts cyclization has been applied towards the synthesis of natural product calyxins by Rychnovsky in 2006. In which, the acetal **55** undergoes Prins cyclization followed by trapping of carbocation with aryl bromide **56** gave tetrahydropyran **57** as a single diastereomer with all substituents *cis* to each other in 60% yield (*Scheme 2.2.1.2*).[20] The aryltetrahydropyran moiety **57** thus formed is key unit in Calyxin synthesis.



Scheme 2.2.1.2

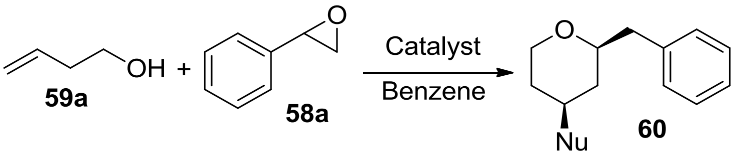
2.3. Results and Discussions

Despite all the excellent examples in literature, the substrate scope is mainly focused on aldehydes as coupling partners in Prins-Friedel-Crafts cyclization by using simple benzene, toluene and xylene as nucleophiles. The alternative use to aldehydes and study of highly activated arenes including phenols as nucleophiles in Prins-Friedel-Crafts reaction remains a challenging task. From earlier results in our group[21] and literature on epoxides, it was evident that epoxides could act as carbonyl equivalents[22] in presence of acids. Prof. D. Seebach stated that “**If carbonyl compounds have been said to be virtually the backbone of organic synthesis, the epoxides correspond to at least one of the main muscles**”. Based on this literature of epoxides and Prins cyclization, we described a versatile one pot synthetic methodology for the synthesis of 4-aryltetrahydropyrans using homoallylic alcohols and epoxides as aldehyde equivalents mediated by boron trifluoride etherate.

Initially, styrene oxide **58a** (0.5 mmol) was reacted with but-3-en-1-ol **59a** (0.6 mmol) in benzene (3.0 mL) using $BF_3·OEt_2$ (0.5 mmol) as Lewis acid. The product (2*R**, 4*S**)-2-benzyl-4-phenyltetrahydro-2*H*-pyran **60a** was obtained in 60% yield with complete *cis* selectivity. The reaction was optimized with other Lewis acids such as $In(OTf)_3$, $Sc(OTf)_3$, $InCl_3$ and $ZrCl_4$ and Brønsted acid TsOH (*Table 2.3.1*). Brønsted acid (TsOH) gave desired product in 28% and 45%

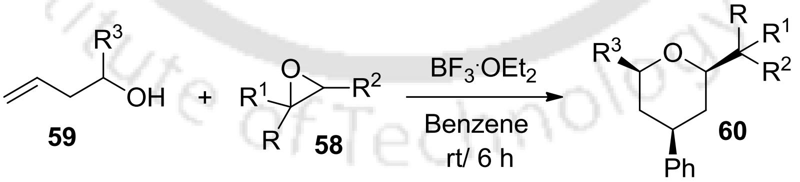
yields at catalytic and stoichiometric loadings, respectively. In a similar manner, Lewis acids $In(OTf)_3$ and $Sc(OTf)_3$ gave desired product with low yields. The chlorinated Lewis acid, $InCl_3$ did not produce any product even after prolonging the reaction for 24h. But, $ZrCl_4$ yielded an inseparable mixture of 4-phenyl and 4-chloro substituted tetrahydropyrans with a ratio of 1:3.5. It was observed that $BF_3{\cdot}Et_2O$ was the most efficient catalyst in terms of yields and diastereoselectivity. The boron trifluoride etherate mediated epoxy Prins-Friedel-Crafts reaction is generalized as shown in *Scheme 2.3.1*.

Table 2.3.1. Optimization of the reaction



Entry	Catalyst (mol%)	Time (h)	Nucleophile (Nu)	Yield (%)[a]
1	**$BF_3{\cdot}OEt_2$ (100)**	**6**	**Ph**	**60**
2	$In(OTf)_3$ (10)	24	Ph	17
3	$Sc(OTf)_3$ (10)	24	Ph	24
4	$InCl_3$ (100)	24	-	-
5	$ZrCl_4$ (100)	2	Ph/Cl (1:3.5)[b]	45[c]
6	*p*-TsOH (10)	5	Ph	28
7	*p*-TsOH (100)	5	Ph	45

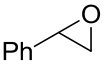
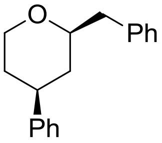
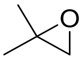
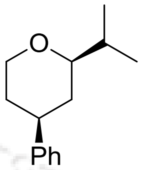
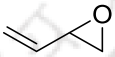
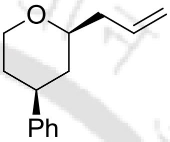
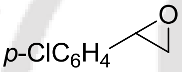
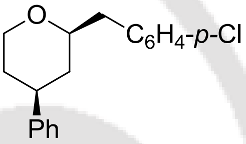
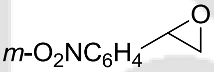
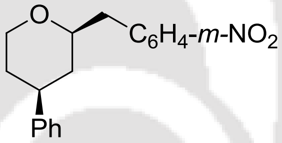
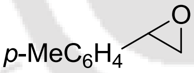
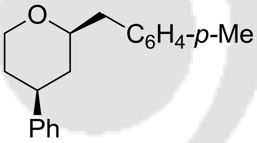
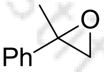
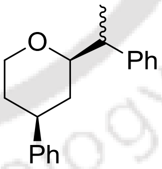
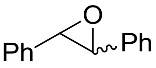
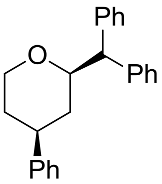
[a] Yield refers to isolated yield. [b] Ratio is determined from the ^1H NMR spectra.
[c] Yield refers to overall yield.



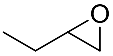
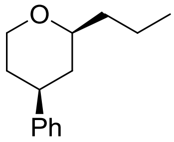
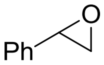
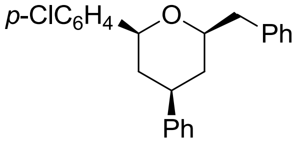
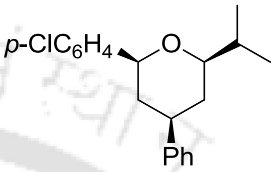
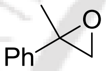
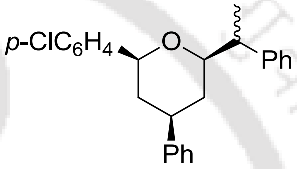
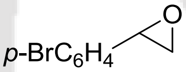
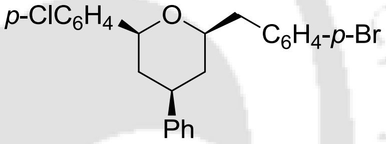
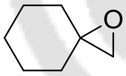
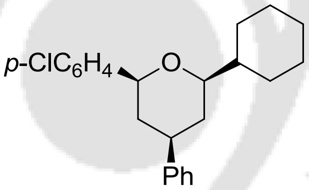
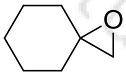
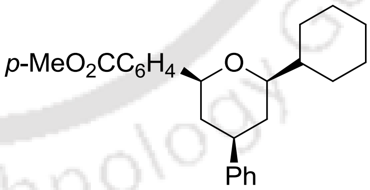
Scheme 2.3.1

The initial success of this methodology prompted us to explore the analogous synthesis of 4-phenyl tetrahydropyrans using alkyl, aryl epoxides and various homoallyl alcohols under the optimized reaction conditions. It was observed that all the reactions produced moderate to good yields with high diastereoselectivity. The results are outlined in the *Table 2.3.2*. In case of epoxides, we observed that monosubstituted terminal alkyl epoxide **58i** did not give the desired product, whereas 2,2-disubstituted alkyl epoxides and aryl epoxides gave good yields. On the other hand, 1,2-epoxybutene **58c** also afforded the desired product in good yield. This is

Table 2.3.2. Synthesis of 2,6-Disubstituted 4-Phenyltetrahydropyrans

Entry	Epoxide **58**	Alcohol **59** R^3 =	Product **60**	Yield (%)^a
a		H		60
b		H		80
c		H		74
d		H		63
e		H		67
f		H		55
g		H		67^b
h		H		65

Continued…………

Entry	Epoxide **58**	Alcohol **59** R^3=	Product **60**	Yield (%)[a]
i		H		0
j		4-ClC$_6$H$_4$		56
k		4-ClC$_6$H$_4$		78
l		4-ClC$_6$H$_4$		63[b]
m		4-ClC$_6$H$_4$		60
n		4-ClC$_6$H$_4$		72
o		4-MeO$_2$CC$_6$H$_4$		74

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

attributed to the lower stability of the carbocation **62**, obtained from monosubstituted terminal alkyl epoxides, compared to 2,2-disubstituted alkyl, aryl and vinylic epoxides, where the carbocation is better stabilized (*Scheme 2.3.3*). In case of α-methyl styrene oxide with primary and secondary homoallyl alcohols produced **60g** and **60l**, respecively as a mixture of diastereomers. This is due to formation of diastereomeric 2-phenylpropanal from α-methyl styrene oxide under Lewis acid conditions. On the other hand, reaction with stillbene oxide **58h** afforded the product **60h** with phenyl migration after epoxide ring opening. The reaction also proceeded smoothly with secondary homoallyl alcohols **59j** and **59o**, giving 2, 6 substituted 4-phenyl tetrahydropyrans **60j-o** in 56-78% yields. The reaction is diastereoselective and all the substituents of the tetrahydropyran ring are *cis* to each other. This is evident from the coupling constants of C-2H (J = 9.6 and 6.4 Hz), C-4H (J = 12.0, 12.0, 3.6 and 3.2 Hz) and C-6H (J = 11.2 Hz) of methyl-4-(6-cyclohexyl-tetrahydro-4-phenyl-2*H*-pyran-2yl)-benzoate **60o**. The structure and stereochemistry of the compounds were finally confirmed by NOE experiments (*Figure 2.3.1*). The strong enhancements between C-2H and C-4H, C-2H and C-6H protons indicate that all three protons are in axial positions.

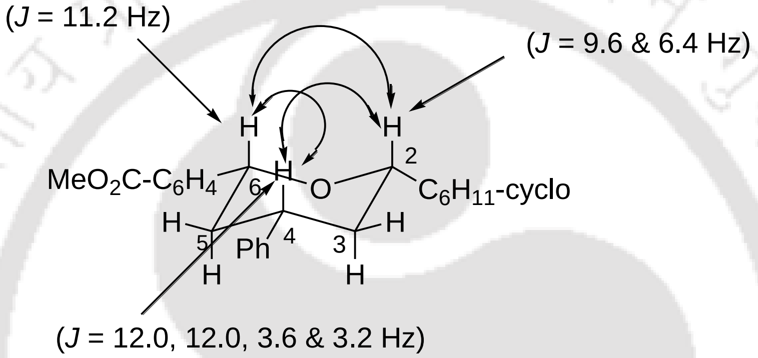
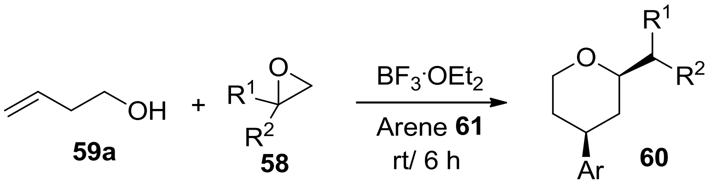


Figure 2.3.1. NOE of Methyl-4-(6-cyclohexyl-tetrahydro-4-phenyl-2H-pyran-2yl)-benzoate

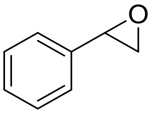
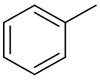
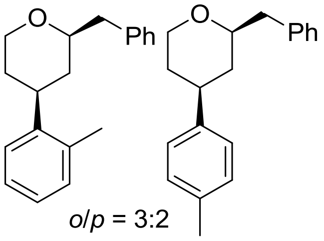
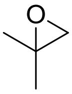
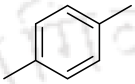
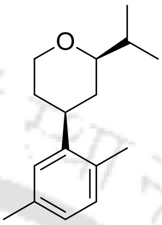
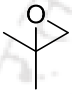
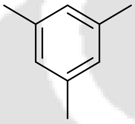
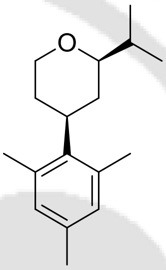
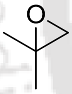
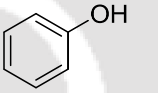
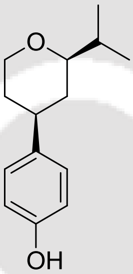
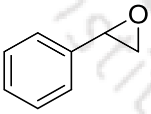
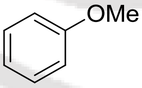
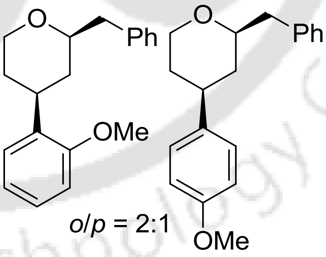
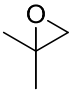
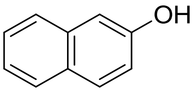
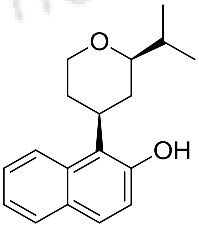
The methodology was further extended to other substituted arenes such as toluene, xylene, mesitylene, phenol, anisole, and β-hydroxynaphthalene as generalized in *Scheme 2.3.2* and the results are depicted in *Table 2.3.3.* The reaction of toluene with styrene oxide gave an inseparable *ortho* and *para* regioisomeric mixture **60p** in 72% yield with a ratio of 3:2. Similarly, reaction of anisole with styrene oxide gave two regioisomeric compounds **60t** with an *ortho*/*para* ratio 2:1, which are separable by chromatography. The reaction with xylene **61q** and mesitylene **61r** gave the corresponding 4-aryltetrahydropyrans **60q** and **60r** as single isomers.



Scheme 2.3.2

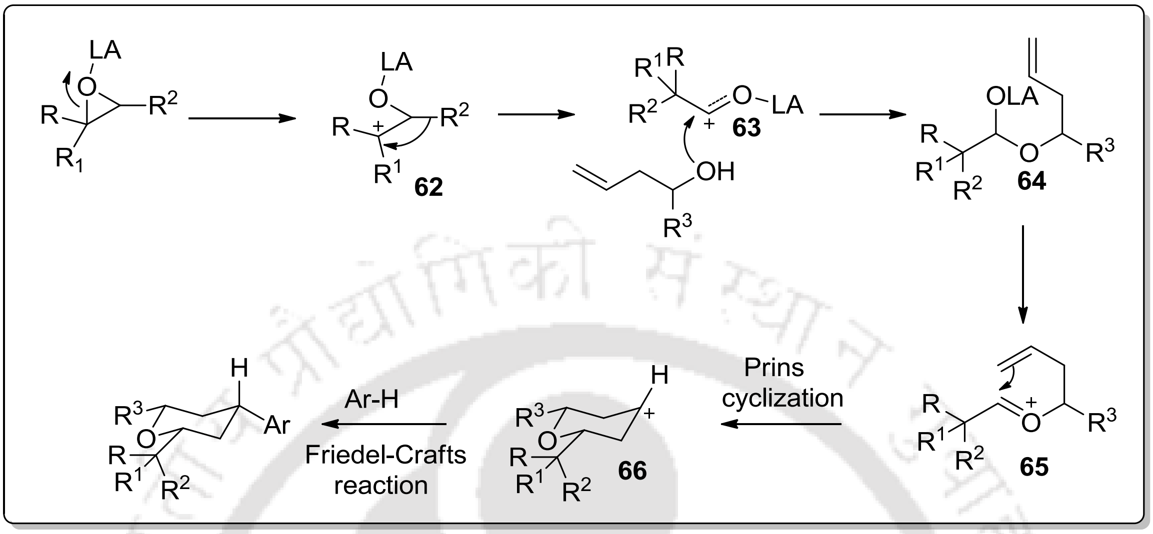
In contrast to this, reaction of phenol with dimethyloxirane gave only a single regioisomer **60s** in 82% yield. The reaction of β-hydroxynaphthalene with dimethyloxirane gave only α-substituted product **60u**. In case of activated arenes, we observed higher yields with excellent diastereoselectivity compared to simple benzene as nucleophile.

Table 2.3.3. Synthesis of 4-Aryltetrahydropyrans

Entry	Epoxide **58**	Arene **61**	Product **60**	Yield (%)[a]
p			 *o*/*p* = 3:2	72[b]
q				77
r				90
s				82
t			 *o*/*p* = 2:1	52[b]
u				80

[a] Yields refer to isolated yield. Products were characterized by IR and NMR spectroscopy and elemental analysis.[b] Ratios are determined from ^{1}H NMR analysis of the crude products.

The mechanism of the reaction can be explained by considering the fact that the epoxide **58**, after ring opening with Lewis acid, gives carbocation **62**, which rearranges to the stable aldehydic intermediate **63**, and reacts with homoallylic alcohol to give acetal **64**. Acetal **64** decomposes to oxocarbenium ion **65**, which gives tetrahydropyranyl cation **66** by Prins cyclization. Trapping of the cation **66** with arenes *via* Friedel–Crafts reaction gives 4-aryltetrahydropyran products **60a-u** (*Scheme 2.3.3*).



Scheme 2.3.3. Plausible mechanism of the reaction

Conclusions

In summary, an efficient and highly diastereoselective method for the synthesis of 2, 6-disubstituted-4-aryltetrahydropyrans in good yields has been developed from epoxides *via* Prins cyclization and this method provides an alternative to aldehyde where aldehyde cannot be accessed directly. The good yields, high selectivity, shorter reaction times and products with activated arenes give more significance to this one-pot synthesis.

2.4. Experimental Section

2.4.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in open capillary tubes using a Büchi B-540 melting point apparatus and are uncorrected. Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Fourier transform-infra red (FT-IR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (400, 600 MHz) or ^{13}C (75, 100, 150 MHz). HRMS spectra were recorded in ESI mode using Agilent Q-TOF mass spectrometer. Crystal Data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromatic Mockα radiation ($\lambda = 0.71073$ Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in different Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

2.4.2. Synthesis of substituted homoallyl alcohols 59j and **59o:** The alcohols **59j** and **59o** were synthesized according to the literature procedures. Both the compounds are known and the analyses were consistent with the literature.[23]

2.4.3. General Procedure for the Synthesis of Compounds 60a-60o:

To a mixture of epoxide **58** (1.0 equiv.) and homoallyl alcohol **59** (1.2 equiv.) in benzene (0.17 M) was added freshly distilled boron trifluoride etherate (1.0 equiv.). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate and then the organic layer was washed with brine. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the title compounds.

Synthesis of (2*R, 4*S**)-2-benzyl-4-phenyltetrahydro-2*H*-pyran (60a, *Table 2.3.2*):** To a mixture of 2-phenyl-oxirane **58a** (60 mg, 0.5 mmol) and but-3-en-1-ol **59a** (44 mg, 0.6 mmol) in benzene (3 mL) was added freshly distilled boron trifluoride etherate (71 mg, 0.5 mmol). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate solution (5 mL) and the product was extracted with ethyl acetate (2x10 mL) and then the organic layer was washed with brine (10 mL). The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product, which was purified by column chromatography over silica gel to give the (2*R**, 4*S**)-2-benzyl-4-phenyl-tetrahydro-2*H*-pyran **60a** in (75mg, 60%) as a pale yellow liquid.

2.4.4. General Procedure for the Synthesis of Compounds 60p-60u:

To a mixture of epoxide **58** (1.0 equiv.), homoallyl alcohol **59** (1.2 equiv.) and arene **61** (5 equiv.**)** in CH_2Cl_2 (0.25 M) was added freshly distilled boron trifluoride etherate (1.0 equiv.). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate and then the organic layer was washed with brine. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the title compounds.

Synthesis of (2*R,4*S**)-2-benzyl-tetrahydro-4-o/p-tolyl-2*H*-pyran (60p, *Table 2.3.3*):** To a mixture of 2-phenyl-oxirane **58a** (60 mg, 0.5 mmol), but-3-en-1-ol **59a** (44 mg, 0.6 mmol) and toluene **61p** (230 mg, 2.5 mmol) in CH_2Cl_2 (2 mL) was added freshly distilled boron trifluoride etherate (71 mg, 0.5 mmol). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate solution (5 mL) and the product was extracted with ethyl acetate (2x10 mL) and then the organic layer was washed with brine (10 mL). The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the (2*R**, 4*S**)-2-benzyl-tetrahydro-4-*o*/*p*-tolyl-2*H*-pyran **60p** in the ratio 3:2 (95 mg, 72%) as a colourless liquid.

2.5. References

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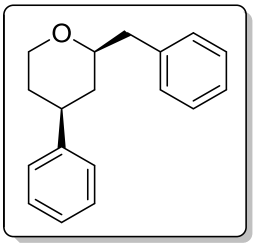
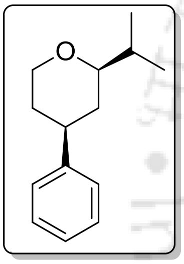
2.6. Characterization Data

(2*R, 4*S**)-2-Benzyl-4-phenyltetrahydro-2*H*-pyran (60a):**



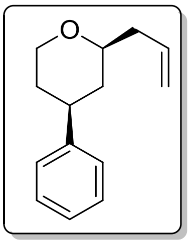
Pale yellow liquid; yield 75 mg, 60%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.47 (ddd, *J* = 12.4, 12.4 and 11.6 Hz, 1 H), 1.68-1.85 (m, 3 H), 2.68-2.76 (m, 2 H), 2.97 (dd, *J* = 13.6 and 6.4 Hz, 1 H), 3.57 (dt, *J* = 11.6 and 2.8 Hz, 1 H), 3.64 (dddd, *J* = 10.8, 4.8, 2.0 and 1.6 Hz, 1 H), 4.12 (dddd, *J* = 11.2, 7.2, 6.0 and 3.6 Hz, 1 H), 7.18-7.23 (m, 5 H), 7.25-7.32 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 33.6, 39.2, 41.9, 43.3, 68.5, 78.9, 126.4, 126.5, 127.0, 128.5, 128.7, 129.6, 138.6, 145.9; **IR** (KBr, Neat): 2934, 2844, 1637, 1379, 1125, 1085, 1026, 750, 698 cm^{-1}; **Anal. Calcd.** for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.52; H, 8.05.

(2*R, 4S*)-2-Isopropyl-4-phenyltetrahydro-2*H*-pyran (60b):**



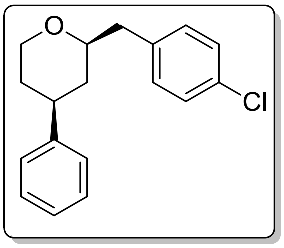
Colourless oil; yield 81 mg, 80%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.42 (ddd, *J* = 12.4, 12.4 and 11.6 Hz, 1 H), 1.65-1.78 (m, 3 H), 1.80-1.86 (m, 1 H), 2.70-2.79 (m, 1 H), 3.12 (dddd, *J* = 11.2, 6.4, 4.8 and 1.6 Hz, 1 H), 3.55 (dddd, *J* = 11.2, 10.8, 4.4 and 2.0 Hz, 1 H), 4.14 (ddd, *J* = 10.4, 3.2, and 2.0 Hz, 1 H), 7.19-7.26 (m, 3 H), 7.30-7.34 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 18.6, 18.9, 33.4, 33.8, 36.4, 42.2, 68.5, 83.1, 126.5, 127.0, 128.7, 146.4; **IR** (KBr, Neat): 2933, 2846, 1637, 1380, 1119, 1089, 905, 756, 698 cm^{-1}; **Anal. Calcd.** for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.55; H, 9.82.

(2*S, 4*S**)-2-Allyl-4-phenyltetrahydro-2*H*-pyran (60c):**



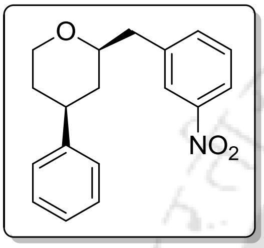
Colourless oil; yield 74 mg, 74%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.45 (ddd, *J* = 12.4, 12.4 and 11.6 Hz, 1 H), 1.76 (m, 2 H), 1.82-1.88 (m, 1 H), 2.25 (dddd, *J* = 12.8, 7.2, 6.8 and 6.0 Hz, 1 H), 2.35 (dddd, *J* = 12.8, 7.2, 6.8 and 6.0 Hz, 1 H), 2.73-2.82 (m, 1 H), 3.48 (dddd, *J* = 11.2, 10.4, 5.6 and 1.6 Hz, 1 H), 3.58 (dddd, *J* = 11.2, 5.6, 4.8 and 1.6 Hz, 1 H), 4.10-4.16 (m, 1 H), 5.06 (d, *J* = 10.0 Hz, 1 H), 5.10 (d, *J* = 10.0 Hz, 1 H), 5.85 (dddd, *J* = 16.8, 10.0, 7.2 and 6.8 Hz, 1 H), 7.19-7.25 (m, 3 H), 7.30-7.34 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 33.6, 39.3, 41.1, 41.9, 68.5, 77.5, 117.2, 126.5, 127.0, 128.7, 134.9, 146.0; **IR** (KBr, Neat): 2933, 2844, 1639, 1380, 1264, 1124, 1086, 1028, 912, 755, 699 cm^{-1}. **Anal. Calcd.** for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.25; H, 8.86.

(2*R**, 4*S**)-2-(4-Chlorobenzyl)-4-phenyltetrahydro-2*H*-pyran (60d):



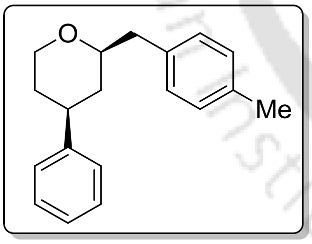
Colourless oil; yield 90 mg, 63%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45 (ddd, *J* = 12.8, 12.0 and 11.6 Hz, 1 H), 1.73-1.81 (m, 3 H), 2.69 (dd, *J* = 13.6 and 6.4 Hz, 1 H), 2.70-2.76 (m, 1 H), 2.89 (dd, *J* = 13.6 and 6.8 Hz, 1 H), 3.50-3.63 (m, 2 H), 4.10-4.13 (m, 1 H), 7.14-7.33 (m, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.5, 39.2, 41.9, 42.5, 68.5, 78.6, 126.6, 127.0, 128.6, 128.7, 130.9, 132.2, 137.2, 145.8; **IR** (KBr, Neat): 2933, 2845, 1637, 1492, 1125, 1086, 756, 699 cm^{-1}; **Anal. Calcd.** for $C_{18}H_{19}ClO$: C, 75.38; H, 6.68. Found: C, 75.32; H, 6.80.

(2*R**, 4*S**)-2-(3-Nitrobenzyl)-4-phenyltetrahydro-2*H*-pyran (60e):



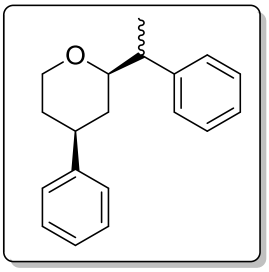
Pale yellow semisolid; yield 99 mg, 67%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.51(ddd, *J* = 12.4, 12.4 and 11.6 Hz, 1 H), 1.77 (m, 2 H), 1.79-1.85 (m, 1 H), 2.73-2.81 (m, 1 H), 2.83 (dd, *J* = 14.0 and 5.2 Hz, 1 H), 2.99 (dd, *J* = 14.0 and 7.6 Hz, 1 H), 3.51-3.57 (m, 1 H), 3.65-3.71 (m, 1 H), 4.10-4.13 (m, 1 H), 7.19-7.24 (m, 3 H), 7.30-7.34 (m, 2 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 8.07-8.12 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.4, 39.3, 41.8, 42.6, 68.5, 78.1, 121.6, 124.4, 126.7, 126.9, 128.8, 129.2, 136.0, 140.9, 145.6, 148.4; **IR** (KBr, Neat): 2932, 2847, 1633, 1529, 1451, 1351, 1126, 1085, 736, 699 cm^{-1}; **Anal. Calcd.** for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.83; H, 6.35; N, 4.85.

(2*R**, 4*S**)-2-(4-Methylbenzyl)-4-phenyltetrahydro-2*H*-pyran (60f):



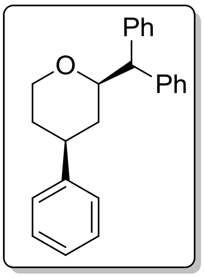
Colourless oil; yield 73 mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45 (ddd, *J* = 12.4, 12.4 and 11.6 Hz, 1 H), 1.67-1.77 (m, 2 H), 1.78-1.84 (m, 1 H), 2.31 (s, 3 H), 2.66 (dd, *J* = 14.0 and 6.8 Hz, 1 H), 2.70-2.74 (m, 1 H), 2.92 (dd, *J* = 14.0 and 6.8 Hz, 1 H), 3.52-3.64 (m, 2 H), 4.10-4.14 (m, 1 H), 7.07-7.13 (m, 4 H), 7.17-7.22 (m, 3 H), 7.27-7.32 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 33.7, 39.2, 42.0, 42.9, 68.5, 79.1, 126.5, 127.0, 128.7, 129.2, 129.5, 135.6, 135.9, 146.0; **IR** (KBr, Neat): 2925, 2846, 1634, 1124, 1084, 699 cm^{-1}; **Anal. Calcd.** for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.75; H, 8.21.

(2*R**, 4*S**)-4-Phenyl-2-(1-phenylethyl)tetrahydro-2*H*-pyran (1:1 ratio diastereomeric mixture) (60g):



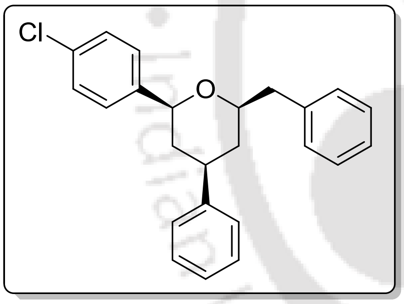
Colourless oil; yield 99 mg, 67%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 7.2 Hz, 3 H), 1.37 (d, *J* = 6.8 Hz, 3 H),1.43 (ddd, *J* = 12.4, 12.4 and 11.2 Hz, 1 H), 1.52-1.57 (m, 1 H), 1.68-1.79 (m, 2 H), 1.82-1.87 (m, 1 H), 2.61-2.67 (m, 1 H), 2.68-2.79 (m, 4 H), 2.86-2.93 (m, 2 H), 3.41-3.62 (m, 4 H), 4.08 (dddd, *J* = 11.2, 4.4, 3.6 and 2.0 Hz, 1 H), 4.18 (dddd, *J* = 11.2, 4.4, 3.2 and 2.0 Hz, 1 H), 7.11-7.33 (m, 20 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.2, 18.6, 33.6, 33.8, 36.3, 37.8, 42.2 (2C), 45.3, 46.3, 68.7 (2C), 82.1, 82.5, 126.3, 126.4, 126.5 (2C), 127.0 (2C), 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 144.6 (2C), 146.1, 146.2; **IR** (KBr, Neat): 2936, 2843, 1633, 1452, 1376, 1127, 1084, 760, 699 cm^{-1}; **Anal. Calcd.** for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.74; H, 8.37.

(2*R,4*S**)-2-Benzhydryl-4-phenyltetrahydro-2*H*-pyran (60h):**



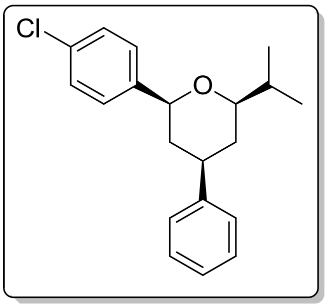
Yellow solid, mp 104-106 °C; yield 106 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 1.47 (ddd, *J* = 12.4, 12.4 and 11.2 Hz, 1 H), 1.67-1.71 (m, 1 H), 2.72-2.81 (m,1 H), 3.59 (ddd, *J* = 11.6, 11.2 and 3.2 Hz, 1 H), 3.95 (d, *J* = 8.8, 1 H), 4.10-4.23 (m, 2 H), 7.10-7.20 (m, 4 H), 7.21-7.31 (m, 9 H), 7.34-7.37 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.7, 38.1, 42.2, 58.1, 68.7, 79.5, 126.4, 126.5, 126.6, 127.0, 128.5, 128.6, 128.8, 142.5, 142.6, 145.9; **IR** (KBr, Neat): 2940, 2845, 1637, 1451, 1376, 1127, 1086, 757, 699 cm^{-1}; **Anal. Calcd.** for $C_{24}H_{24}O$: C, 87.76; H, 7.37. Found: C, 87.88; H, 7.29.

(2*R,4*R**,6*S**)-2-Benzyl-6-(4-chlorophenyl)-4-phenyltetrahydro-2*H*-pyran (60j):**



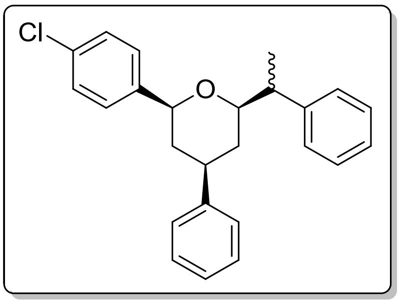
Colourless oil; yield 101 mg, 56%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.50 (ddd, *J* = 12.4, 12.4 and 11.6 Hz, 1 H), 1.63 (ddd, *J* = 12.4, 12.4 and 12.0 Hz, 1 H), 1.84-1.91 (m, 1 H), 2.01-2.08 (m, 1 H), 2.81 (dd, *J* = 13.6 and 6.8 Hz, 1 H), 2.86-2.94 (m, 1 H), 3.09 (dd, *J* = 13.6 and 6.0 Hz, 1 H), 3.82-3.89 (m, 1 H), 4.50-4.55 (m, 1 H), 7.17-7.35 (m, 14 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 38.3, 41.2, 42.2, 43.1, 78.8, 79.1, 126.4, 126.7, 127.0, 127.3, 128.5, 128.6, 128.8, 129.8, 133.1, 138.6, 141.7, 145.4; **IR** (KBr, Neat): 2931, 2846, 1636, 1491, 1377, 1086, 752, 699 cm^{-1}; **Anal. Calcd.** for $C_{24}H_{23}ClO$: C, 79.43; H, 6.39. Found: C, 79.29; H, 6.47.

(2*S,4*R**,6*R**)-2-(4-Chlorophenyl)-6-isopropyl-4-phenyltetrahydro-2*H*-pyran (60k):**



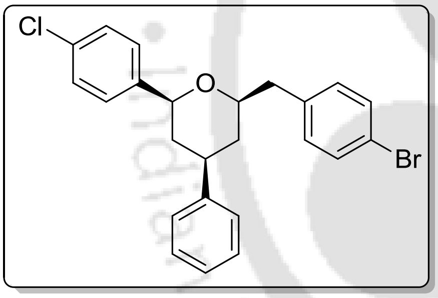
Colourless oil; yield 122 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (d, *J* =6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.47 (ddd, *J* = 12.8,12.0 and 11.6 Hz, 1 H), 1.59 (dd, *J* = 12.8 and 11.2 Hz, 1 H), 1.82-1.91 (m, 2 H), 2.04-2.08 (m, 1 H), 2.94 (dd, *J* = 12.4 and 12.0 Hz, 1 H), 3.37 (dd, *J* =10.8 and 6.0 Hz, 1 H), 4.49 (d, *J* = 11.2 Hz, 1 H), 7.19-7.26 (m, 4 H), 7.28-7.35 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 18.9, 33.4, 35.6, 41.3, 42.3, 78.5, 83.0, 126.6, 127.0, 127.2, 128.5, 128.7, 132.8, 142.1, 145.8; **IR** (KBr, Neat): 2958, 2873, 1638, 1490, 1377, 1086, 827, 758, 699 cm^{-1}; **Anal. Calcd.** for $C_{20}H_{23}ClO$: C, 76.29; H, 7.36. Found: C, 76.40; H, 7.28.

(2*S**,4*R**,6*R**)-2-(4-Chlorophenyl)-4-phenyl-6-(1-phenylethyl)tetrahydro-2*H*-pyran (Diastereomeric mixture: 2:1) (60l):



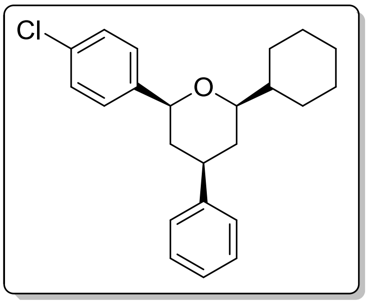
Colourless oil; yield 118 mg, 63%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.39 (d, J = 7.2 Hz, 3 H, 1stisomer), 1.42 (d, J = 6.8 Hz, 3 H, 2nd isomer), 1.44 (ddd, J= 12.0, 12.0 and 11.2 Hz, 1 H), 1.51-1.61 (m, 2 H, 1stisomer), 1.79-1.83 (m, 2 H, 2nd isomer), 2.01-2.10 (m, 1 H), 2.82-2.93 (m, 2 H, 1st isomer), 3.01-3.10 (m, 2 H, 2nd isomer), 3.65-3.70 (m, 1 H, 2nd isomer), 3.74-3.78 (m, 1 H, 1st isomer), 4.48 (d, J = 11.2 Hz, 1 H, 1st isomer), 4.53 (d, J = 11.2 Hz, 1 H, 2nd isomer), 7.12-7.37 (m, 14 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 16.7, 18.5, 35.4, 36.9, 41.2 (2C), 42.2, 42.3, 45.0, 46.2, 78.5, 78.6, 82.1, 82.5, 126,4 (2C), 126.5, 126.6, 127.0 (2C), 127.1, 127.2, 128.1, 128.2, 128.4, 128.5 (2C), 128.6, 128.67, 128.7, 132.8, 132.9, 141.9 (2C), 143.9, 144.5, 145.5 (2C); **IR** (KBr, Neat): 2937, 2846, 1637, 1492, 1381, 1088, 760, 699 cm^{-1}; **Anal. Calcd.** for $C_{25}H_{25}ClO$: C, 79.66; H, 6.69. Found: C, 79.59; H, 6.80.

(2*R**,4*R**,6*S**)-2-(4-Bromobenzyl)-6-(4-chlorophenyl)-4-phenyltetrahydro-2*H*-pyran (60m):



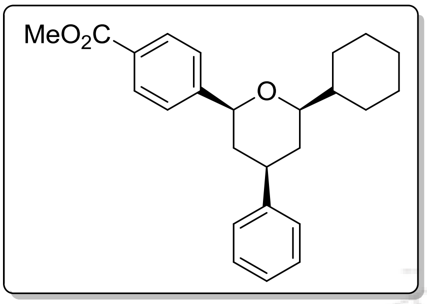
Colourless oil; yield 132 mg, 60%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.49(ddd, J = 12.8, 12.4 and 11.2 Hz, 1 H), 1.62 (ddd, J =12.4, 12.0 and 12.0 Hz, 1 H), 1.85 (ddd, J = 13.2, 3.6 and 1.6 Hz, 1 H), 2.05 (ddd, J = 12.8, 3.6 and 1.6 Hz, 1 H), 2.79 (dd, J = 13.6 and 6.4 Hz, 1 H), 2.92 (tt, J = 12.4 and 3.6 Hz, 1 H), 2.99 (dd, J = 13.6 and 6.4 Hz, 1 H), 3.78-3.85 (m, 1 H), 4.50 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.13 (d, J = 8.4 Hz, 2 H), 7.17-7.22 (m, 4 H), 7.26-7.31 (m, 5 H), 7.40 (d, J = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 38.3, 41.1, 42.1, 42.4, 78.7, 78.8, 120.3, 126.7, 127.0, 127.3, 128.6, 128.8, 131.5, 131.6, 133.1, 137.6, 141.5, 145.2; **IR** (KBr, Neat): 2928, 2846, 1633, 1489, 1072, 1009, 696 cm^{-1}; **Anal. Calcd.** for $C_{24}H_{22}BrClO$: C, 65.25; H, 5.02. Found: C, 65.31; H, 5.12.

(2*S**,4*R**,6*R**)-2-(4-Chlorophenyl)-6-cyclohexyl-4-phenyltetrahydro-2*H*-pyran (60n):



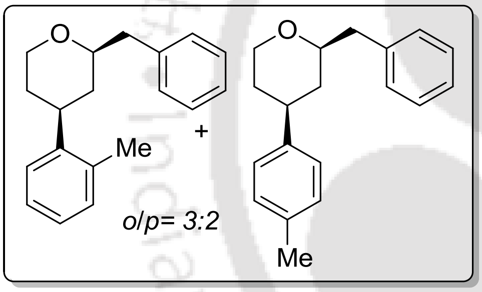
Pale yellow oil; yield 127 mg, 72%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.10 (ddd, J = 12.0, 12.0 and 11.6 Hz, 1 H), 1.16-38 (m, 3 H), 1.39-1.68 (m, 6 H), 1.73-1.80 (m, 2 H), 1.87-2.08 (m, 3 H), 2.89-2.96 (m, 1 H), 3.37-3.41 (m, 1 H), 4.48 (d, J = 11.2 Hz, 1 H), 7.19-7.26 (m, 4 H), 7.28-7.34 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 26.5, 26.9, 28.9, 29.3, 29.9, 35.9, 41.4, 42.4, 43.4, 78.6, 82.4, 126.6, 127.0, 127.3, 128.5, 128.8, 132.9, 142.1, 145.9; **IR** (KBr, Neat): 2931, 2846, 1636, 1491, 1377, 1086, 752, 696 cm^{-1}; **Anal. Calcd.** for $C_{23}H_{27}ClO$: C, 77.83; H, 7.67. Found: C, 77.95; H, 7.56.

Methyl 4-((2*S,4*R**,6*R**)-6-cyclohexyl-4-phenyltetrahydro-2*H*-pyran-2-yl)benzoate (60o):**



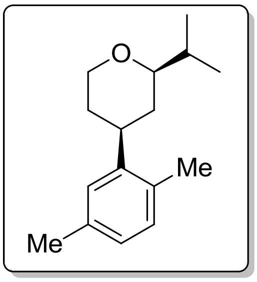
Colourless solid, mp 101-102 °C; yield 139 mg, 74%; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.03-1.17 (m, 2 H), 1.20-1.30 (m, 2 H), 1.47-1.69 (m, 5 H), 1.74-1.77 (m, 3 H), 1.88-2.12 (m, 3 H), 2.95 (tt, *J* = 12.4 and 3.2 Hz, 1 H), 3.40 (dd, *J* = 9.6 and 6.4 Hz, 1 H), 3.90 (s, 3 H), 4.55 (d, *J* = 11.2 Hz, 1 H), 7.18-7.25 (m, 3 H), 7.28-7.33 (m, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.99 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.3, 26.4, 26.8, 28.9, 29.2, 35.7, 41.3, 42.4, 43.3, 52.1, 78.7, 82.3, 125.7, 126.5, 126.9, 128.7, 128.9, 129.7, 145.7, 148.7, 167.1; **IR** (KBr, Neat): 2927, 2852, 1721, 1637, 1434, 1278, 1109, 1017, 732, 700 cm^{-1}; **Anal. Calcd.** for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.28; H, 8.07.

(2*R,4*S**)-2-Benzyl-tetrahydro-4-o/p-tolyl-2*H*-pyran (60p, *o*/*p* = 3:2):**



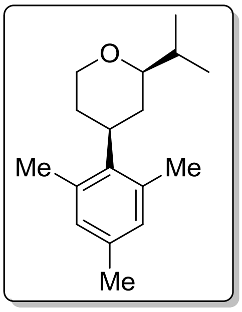
Colourless oil; yield 95 mg, 72%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45 (ddd, *J* = 12.4, 12.4 and 11.2 Hz, 1 H), 1.49 (ddd, *J* = 12.4, 12.4 and 11.6 Hz, 1 H), 1.64-1.82 (m, 3 H), 2.29 (s, 1.8 H), 2.31(s, 1.2 H), 2.64-2.74 (m, 1 H), 2.91-3.00 (m, 1 H), 3.51-3.70 (m, 2 H), 4.08-4.15 (m, 1 H), 6.97-7.02 (m, 1 H), 7.06-7.14 (m, 3 H), 7.17-7.29 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.5, 21.1, 33.0, 33.7, 37.5, 38.3, 39.2, 39.3, 41.9, 43.2, 68.5, 68.7, 78.9, 79.1, 123.9, 125.7, 126.1, 126.3, 126.5, 126.8, 127.2, 127.7, 129.3, 129.5 (2C), 130.5, 135.2, 135.9, 138.6, 143.0, 143.7, 145.9; **IR** (KBr, Neat): 2937, 2842, 1634, 1454, 1378, 1125, 1085, 749, 700 cm^{-1}; **Anal. Calcd.** for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.79; H, 8.25.

(2*R,4*S**)-4-(2,5-Dimethylphenyl)-2-isopropyltetrahydro-2*H*-pyran (60q):**



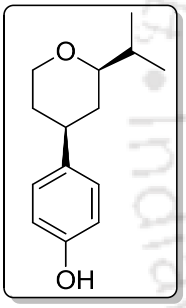
Colourless oil; yield 89 mg, 77%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.41 (ddd, *J* = 12.4, 12.0 and 11.6 Hz, 1 H), 1.63-1.80 (m, 4 H), 2.31 (s, 3 H), 2.32 (s, 3 H), 2.94 (tt, *J* = 12.4 and 3.6 Hz, 1 H), 3.14 (dd, *J* = 10.0 and 6.4 Hz, 1 H), 3.57 (dt, *J* = 12.0 and 2.0 Hz, 1 H), 4.14 (dd, *J* = 11.6 and 3.6 Hz, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 7.03-7.10 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.6, 18.8, 19.1, 21.4, 33.1, 33.4, 35.5, 37.7, 68.7, 83.4, 126.5, 126.8, 130.5, 132.0, 135.8, 143.9; **IR** (KBr, Neat): 2953, 2868, 1637, 1461, 1383, 1120, 1087, 1039, 807 cm^{-1}; **Anal. Calcd.** for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.84; H, 10.52.

(2*R,4*S**)-2-Isopropyl-4-mesityltetrahydro-2*H*-pyran (60r):**



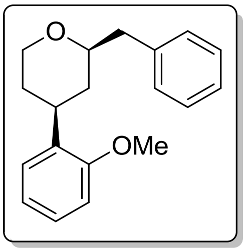
Colourless oil; yield 110 mg, 90%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.47-1.53 (m, 1 H), 1.60-1.66 (m, 1 H), 1.70 (octet, *J* = 6.8 H, 1 H), 1.87 (ddd, *J* = 12.8, 12.4 and 11.2 Hz, 1 H), 2.18-2.28 (m, 1 H), 2.34 (s, 9 H), 3.08 (dddd, *J* = 10.8, 10.4, 2.0 and 2.0 Hz, 1 H), 3.21 (tt, *J* = 12.4 and 3.6 Hz, 1 H), 3.52 (dt, *J* = 14.0 and 2.4 Hz, 1 H), 4.14 (dd, *J* = 11.2 and 4.4 Hz, 1 H), 6.83 (s, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 18.5, 19.0, 20.7, 21.9, 30.1, 32.6, 33.5, 38.5, 69.3, 84.1, 131.2, 135.4, 136.3, 138.2; **IR** (KBr, Neat): 2957, 2873, 1634, 1462, 1384, 1120, 1087, 1038, 850 cm^{-1}; **Anal. Calcd.** for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.79; H, 10.77.

4-((2*R,4*S**)-2-Isopropyltetrahydro-2*H*-pyran-4-yl)phenol (60s):**

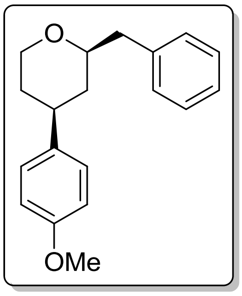


Colourless oil; yield 90 mg, 82%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.92 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 1.40 (ddd, *J* = 11.6, 11.2 and 11.2 Hz, 1 H), 1.66 (dd, *J* = 12.4 and 4.8 Hz, 1 H), 1.72 (octet, *J* = 6.8 Hz, 1 H), 2.09 (dd, *J* = 12.4 and 12.0 Hz, 2 H), 3.09 (dd, *J* = 12.2 and 6.0 Hz, 1 H), 3.46 (dd, *J* = 12.4 and 12.0 Hz, 1 H), 4.08 (dd, *J* = 12.0 and 4.4 Hz, 1 H), 4.34-4.41 (m, 1 H), 6.90-6.97 (m, 3 H), 7.26-7.30 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 18.5, 18.6, 32.8, 33.1, 35.0, 66.0, 74.2, 81.4, 116.4, 121.2, 129.7, 157.4; **IR** (KBr, Neat): 3449, 2959, 2875, 1599, 1494, 1238, 1168, 1088, 1043, 753 cm^{-1}; **Anal. Calcd.** for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.42; H, 9.21.

(2*R,4*S**)-2-Benzyl-4-(*o*/*p* -methoxyphenyl)tetrahydro-2*H*-pyran (60t; *o*/*p* = 2:1): 60t-*o*:**

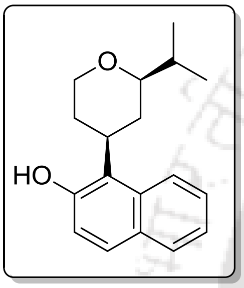


Colourless oil; yield 73 mg, 52%; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.47 (ddd, *J* = 12.4, 12.0 and 11.2 Hz, 1 H), 1.70-1.80 (m, 2 H), 2.71 (dd, *J* = 13.6 and 6.4 Hz, 1 H), 2.94 (dd, *J* = 13.6 and 6.4 Hz, 1 H), 3.16-3.22 (m, 1 H), 3.59 (dt, *J* = 11.6 and 3.6 Hz, 1 H), 3.68 (ddd, *J* = 10.8, 6.4 and 4.4 Hz, 1 H), 3.75-3.84 (m, 1 H), 3.79 (3 H), 4.08-4.12 (m, 1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 6.93 (t, *J* = 6.8 Hz, 1 H), 7.10 (d, *J* = 8.8 Hz, 1 H), 7.15-7.30 (m, 6 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 32.5, 34.5, 37.8, 43.3, 55.4, 68.7, 79.0, 110.6, 120.8, 126.3, 126.8, 127.2, 128.4, 129.6, 134.0, 138.9, 156.9; **IR** (KBr, Neat): 2937, 2837, 1633, 1238, 1085, 1030, 750 cm^{-1}; **Anal. Calcd.** for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.71; H, 7.93.



60t-*p*: Colourless solid, mp 61-63 °C; yield 34 mg, 24%; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.43 (ddd, *J* = 12.4, 12.0 and 11.6 Hz, 1 H), 1.70-1.76 (m, 1 H), 1.77-1.81 (m, 1 H), 2.59-2.67 (m, 1 H), 2.69 (dd, *J* = 13.6 and 6.4 Hz, 1 H), 2.96 (dd, *J* = 13.6 and 6.4 Hz, 1 H), 3.54 (dt, *J* = 11.6 and 3.6 Hz, 1 H), 3.58-3.65 (m, 1 H), 3.73-3.86 (m, 1 H), 3.78 (s, 3 H), 4.08-4.13 (m, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 7.19-7.30 (m, 5 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 33.9, 39.4, 41.0, 43.3, 55.4, 68.5, 79.0, 114.1, 126.4, 127.8, 128.5, 129.6, 138.2, 138.7, 158.2; **IR** (KBr, Neat): 2933, 2836, 1611, 1248, 1126, 1083, 1033, 700 cm^{-1}; **Anal. Calcd.** for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.71; H, 7.93.

1-((2*R,4*S**)-2-Isopropyltetrahydro-2*H*-pyran-4-yl)naphthalen-2-ol (60u):**



Colourless oil; yield 108 mg, 80%; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.92 (d, *J* = 7.2 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 1.46 (ddd, *J* = 12.0, 11.6 and 11.2 Hz, 1 H), 1.55-1.64 (m, 1 H), 1.72 (octet, *J* = 6.8 Hz, 1 H), 2.12-2.23 (m, 2 H), 3.15 (dt, *J* = 11.2 and 2.0 Hz, 1 H), 3.52 (dt, *J* = 12.4 and 2.0 Hz, 1 H), 4.12 (dddd, *J* = 11.6, 4.8, 4.8 and 1.6 Hz, 1 H), 4.49-4.58 (m, 1 H), 7.14 (dd, *J* = 8.0 and 2.4 Hz, 1 H), 7.18 (d, *J* = 2.0 Hz, 1 H), 7.31-7.36 (m, 1 H), 7.42-7.46 (m, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.8 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 18.5, 18.6, 32.7, 33.2, 34.9, 66.1, 74.3, 81.4, 109.1, 119.9, 123.9, 126.6, 126.9, 127.9, 129.3, 129.8, 134.7, 155.3; **IR** (KBr, Neat): 3459, 2958, 2868, 1629, 1468, 1252, 1169, 1087, 1040, 837, 746 cm^{-1}; **Anal. Calcd.** for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.05; H, 8.15.

2.7. Selected Spectra

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

```
ik_11_9

exp1  s2pul

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file            exp   spin            not used
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at            1.998   alfa              20.000
np            25520           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                -186.2
tpwr             57   wp                4525.7
pw            9.850   rfl                759.1
     DECOUPLER        rfp                    0
dn              C13   rp                 120.1
dof               0   lp                -189.8
dm              nnn            PLOT
dmm               c   wc                   250
dpwr             50   sc                     0
dmf           15900   vs                    73
                      th                    20
                      nm   cdc   ph
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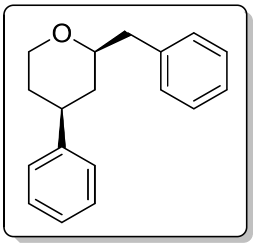

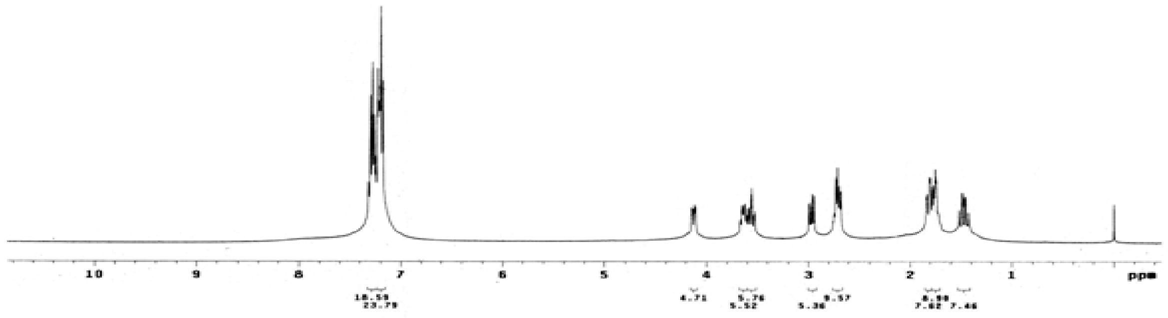

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ik_11_9_13C

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file            exp   spin            not used
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sw          25125.6   pw90              10.000
at            1.199   alfa              20.000
np            60270           FLAGS
fb            13800   il                     n
bs               16   in                     n
d1            1.000   dp                     y
nt             7000   hs                    nn
ct             2112         PROCESSING
    TRANSMITTER       lb                  2.00
tn              C13   fn                 65536
sfrq        100.554          DISPLAY
tof          1536.3   sp               -1377.6
tpwr             61   wp               21493.3
pw            9.300   rfl               9274.4
     DECOUPLER        rfp               7764.9
dn               H1   rp                 -37.6
dof               0   lp                -340.5
dm              yyy            PLOT
dmm               w   wc                   250
dpwr             42   sc                     0
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                      th                     4
                      nm   no   ph
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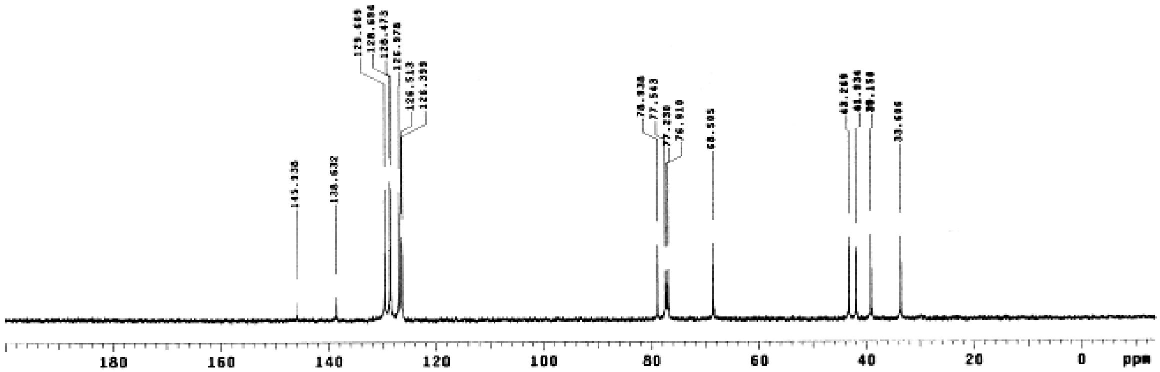
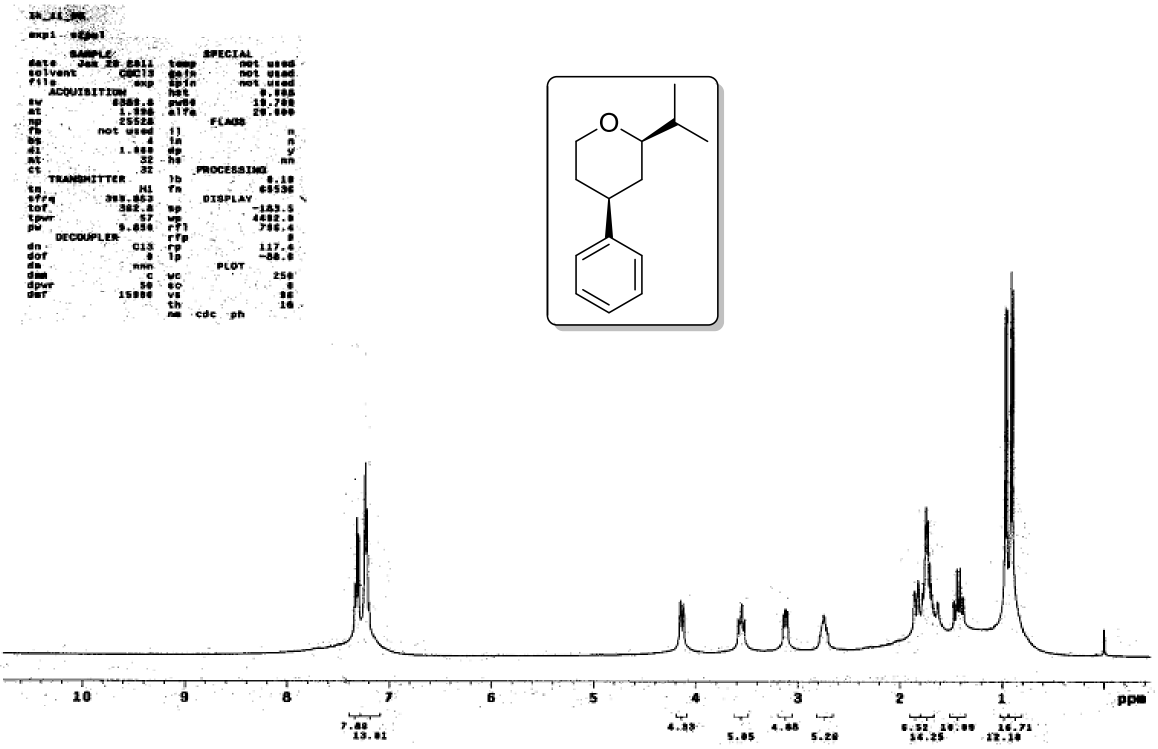


^{1}H and ^{13}C NMR spectra of **(2*R**, 4*S**)-2-Isopropyl-4-phenyltetrahydro-2*H*-pyran**



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tk_11_8H

expl  s2pul

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file            exp   spin        not used
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at            1.996   alfa          20.000
np            25520         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        399.863        DISPLAY
tof           382.8   sp            -183.5
tpwr             57   wp            4482.8
pw            9.850   rfl            786.4
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dn              C13   rp             117.4
dof               0   lp             -88.8
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dmm               c   wc               250
dpwr             50   sc                 0
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                      th                16
                      nm  cdc  ph
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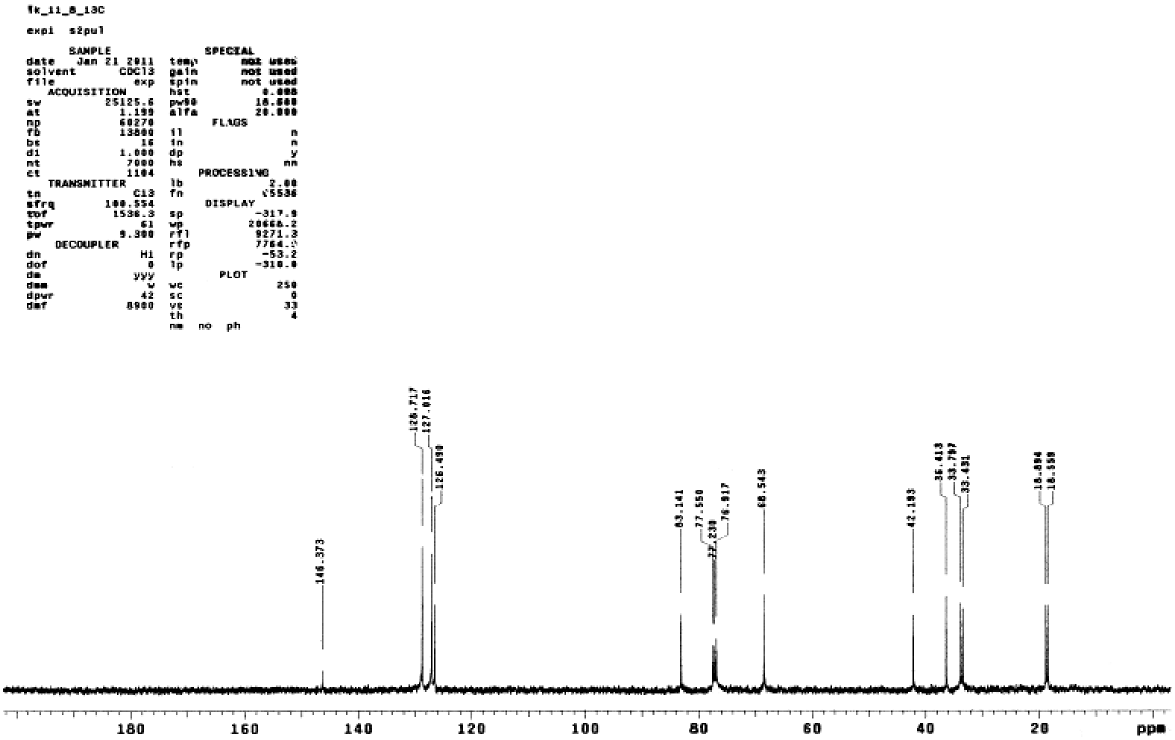

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tk_11_8_13C

expl  s2pul

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solvent       CDCl3   gain        not used
file            exp   spin        not used
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sw          25125.6   pw90          18.000
at            1.199   alfa          20.000
np            60270         FLAGS
fb            13800   il                 n
bs               16   in                 n
d1            1.000   dp                 y
nt             7000   hs                nn
ct             1104       PROCESSING
   TRANSMITTER        lb              2.00
tn              C13   fn             65536
sfrq        100.554        DISPLAY
tof          1536.3   sp            -317.9
tpwr             61   wp           20666.2
pw            9.300   rfl           9271.3
    DECOUPLER         rfp           7764.9
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dof               0   lp            -310.0
dm              yyy          PLOT
dmm               w   wc               250
dpwr             42   sc                 0
dmf            8900   vs                33
                      th                 4
                      nm  no  ph
```
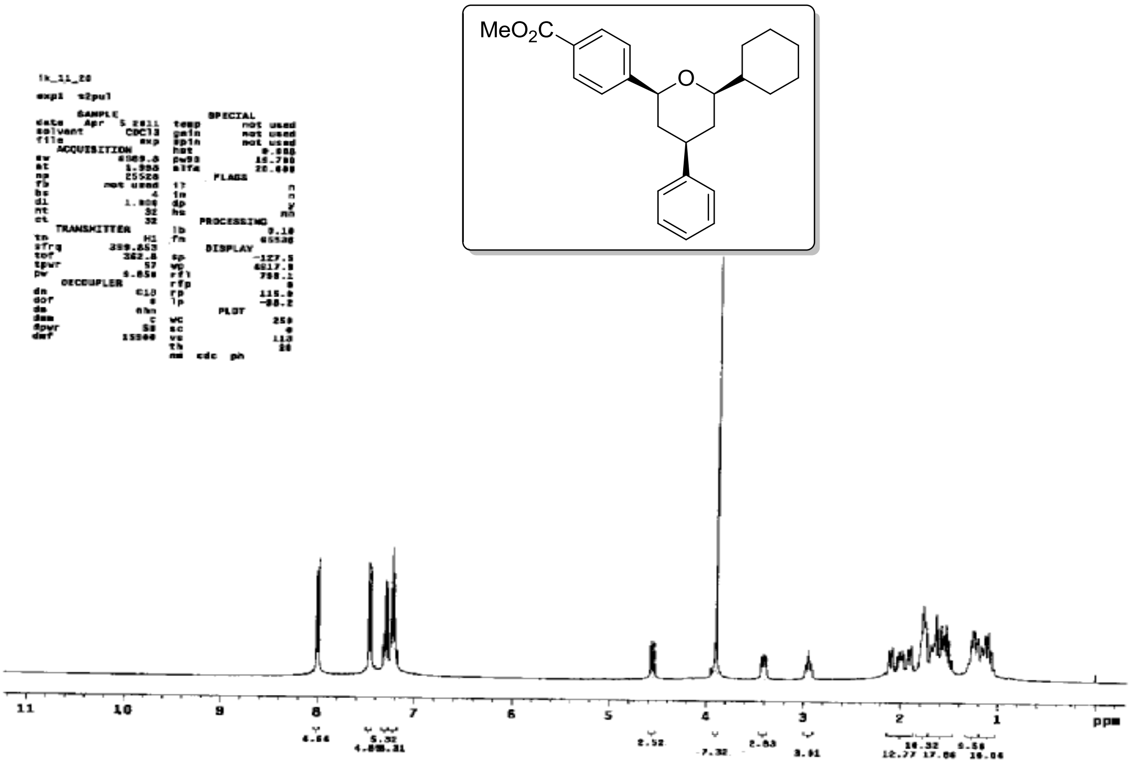
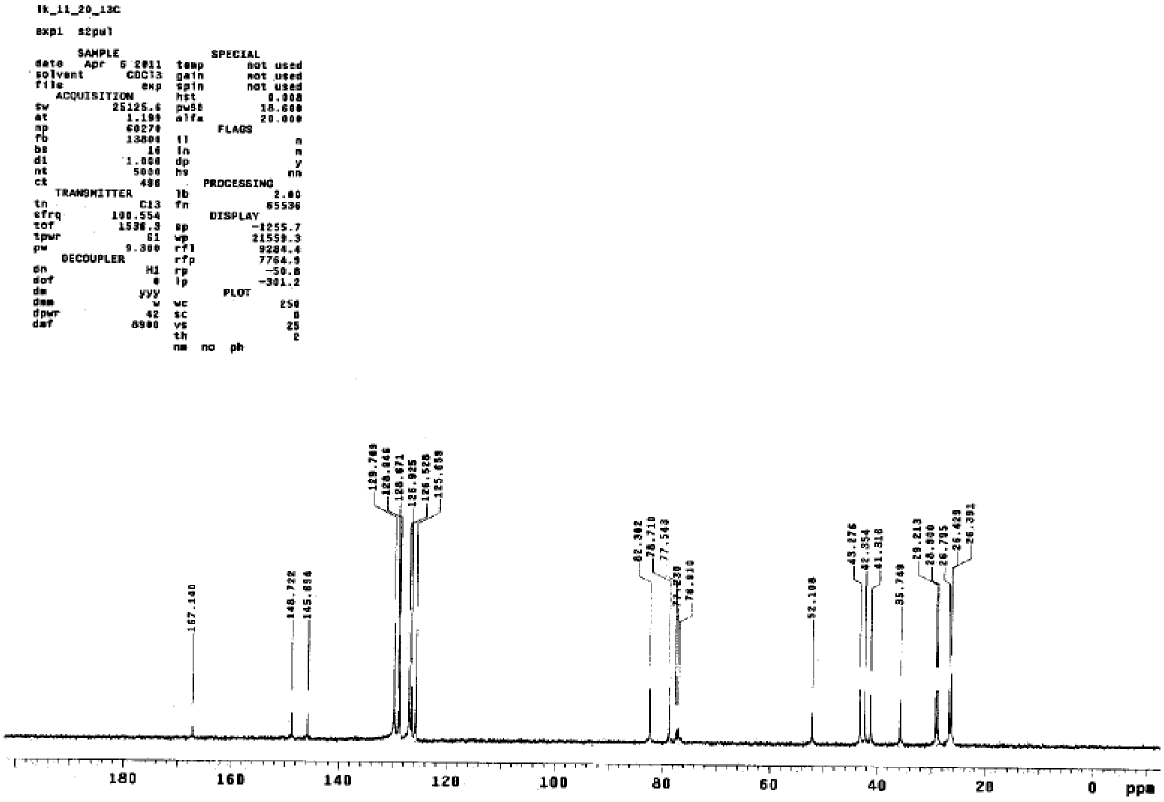
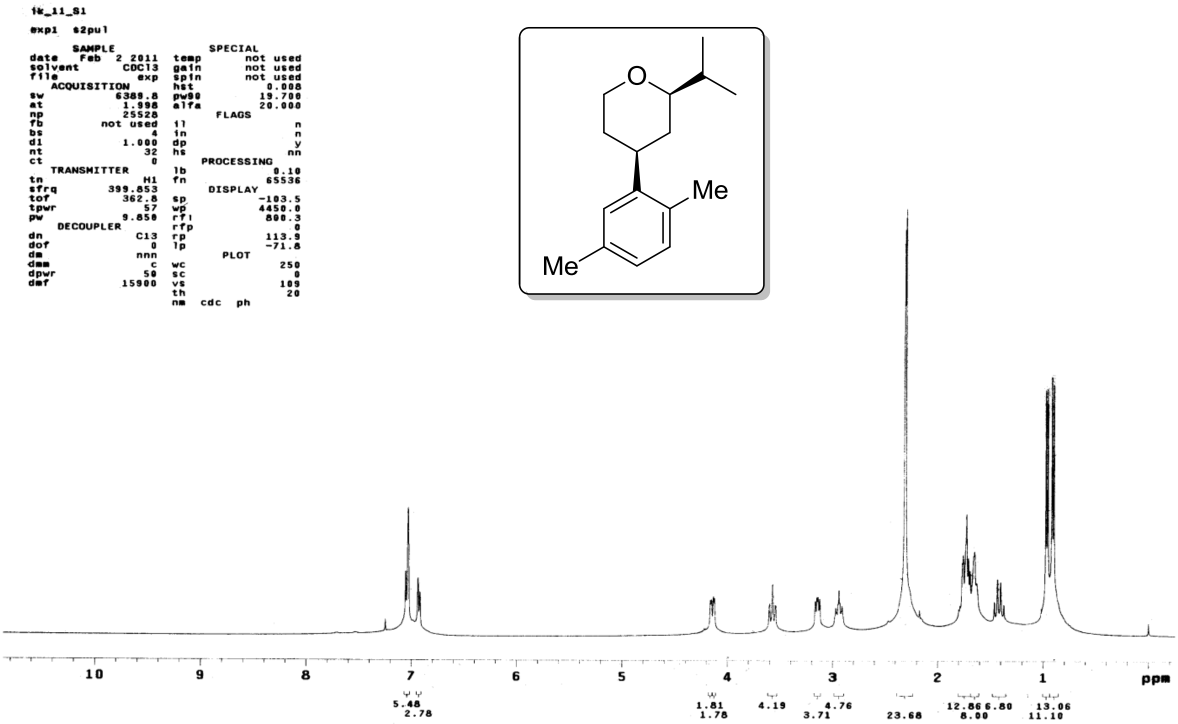

^{1}H and ^{13}C NMR spectra of **Methyl 4-((2*S**,4*R**,6*R**)-6-cyclohexyl-4-phenyltetrahydro-2*H*-pyran-2-yl)benzoate**





^{1}H and ^{13}C NMR spectra of **(2*R**,4*S**)-4-(2,5-Dimethylphenyl)-2-isopropyltetrahydro-2*H*-pyran:**



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d1            1.000   dp                 y
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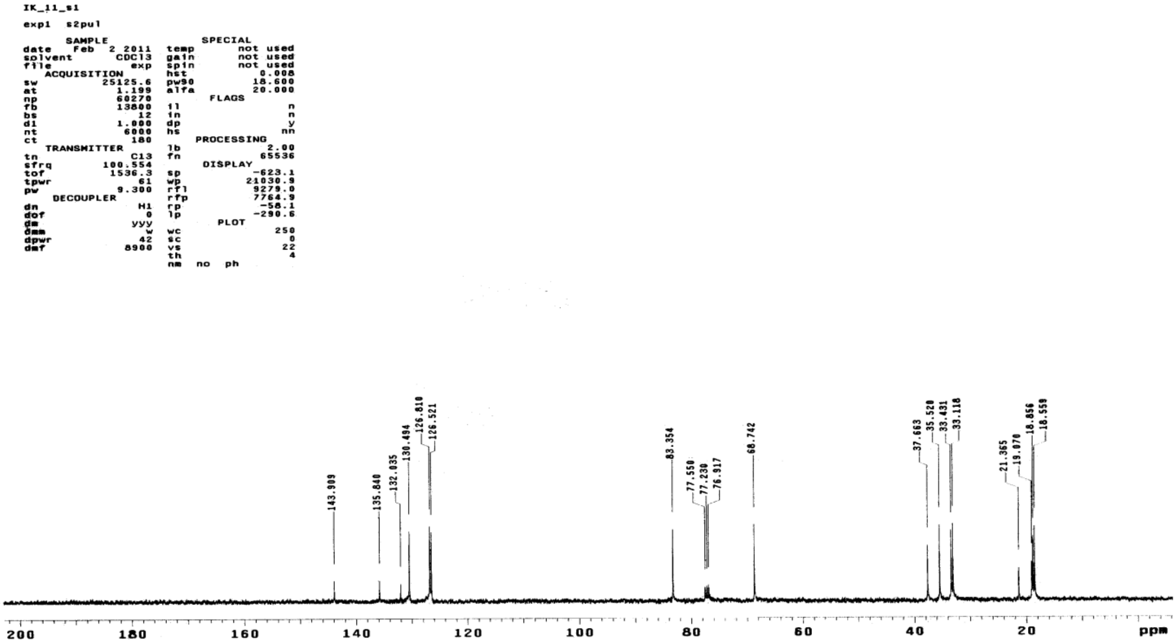

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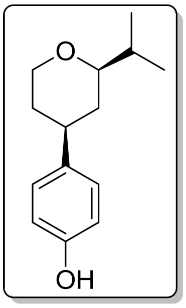
^{1}H and ^{13}C NMR spectra of **4-((2*R**,4*S**)-2-Isopropyltetrahydro-2*H*-pyran-4-yl)phenol**



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bs                4   in                 n
d1            1.000   dp                 y
nt               32   hs                nn
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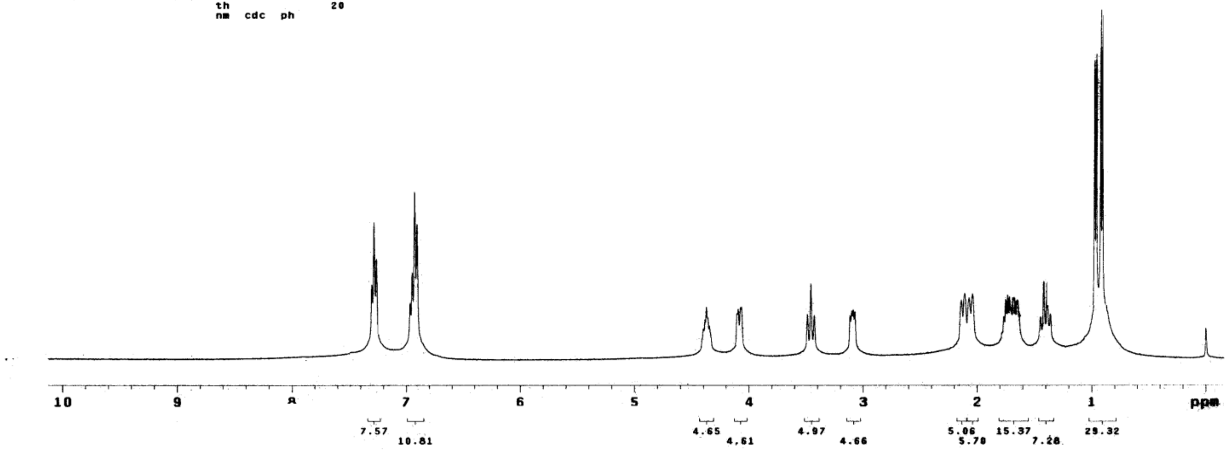

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                      nm   no   ph
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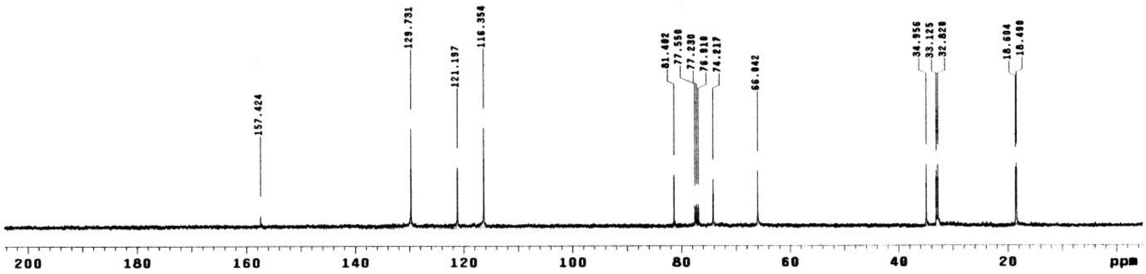


CHAPTER 3

Diastereoselective Synthesis of Amido- and Phenyl Azabicyclic Derivatives *via* Tandem Aza Prins-Ritter/ Friedel-Crafts Reaction

3.1. Importance of Amido, Aryl Piperidine and Azabicyclic Derivatives

The substituted piperidine scaffolds are important units present in many natural products and drug intermediates.[1] 4-Amido piperidine derivative indoramine (**1**) is used as an alpha-1 selective adrenoceptor antagonist.[2] Astemizole (**2**) is a 4-amino piperidine containing second-generation antihistamine drug and marketed under the brand name Hismanal. It acts as histamine H1-receptor antagonist and show anticholinergic and antipruritic effects.[3] The compounds with 4-arylpiperidine backbone such as (-)-paroxetine (**3**), (+)-femoxetine (**4**) and their analogues are significantly important class of serotonin (5-hydroxytryptamine) reuptake inhibitors (*Figure 3.1.1*).[4] Other well-known azabicyclic natural products having either indolizidine or quinolizidine as core structures also shown to exhibit broad biological activity and a diverse pharmacological profile.[5] For example, poly-hydroxylated indolizidine, swainsonine (**5**) exhibits potent glycosidase inhibitory activities and also show activity against carcinogenic cells and Human Immunodeficiency Virus.[6] A marine alkaloid in this class, lepadiformine (**6**) shows moderate cytotoxic activity against various tumor cell lines *in vitro* and shows high *in vivo* and *in*

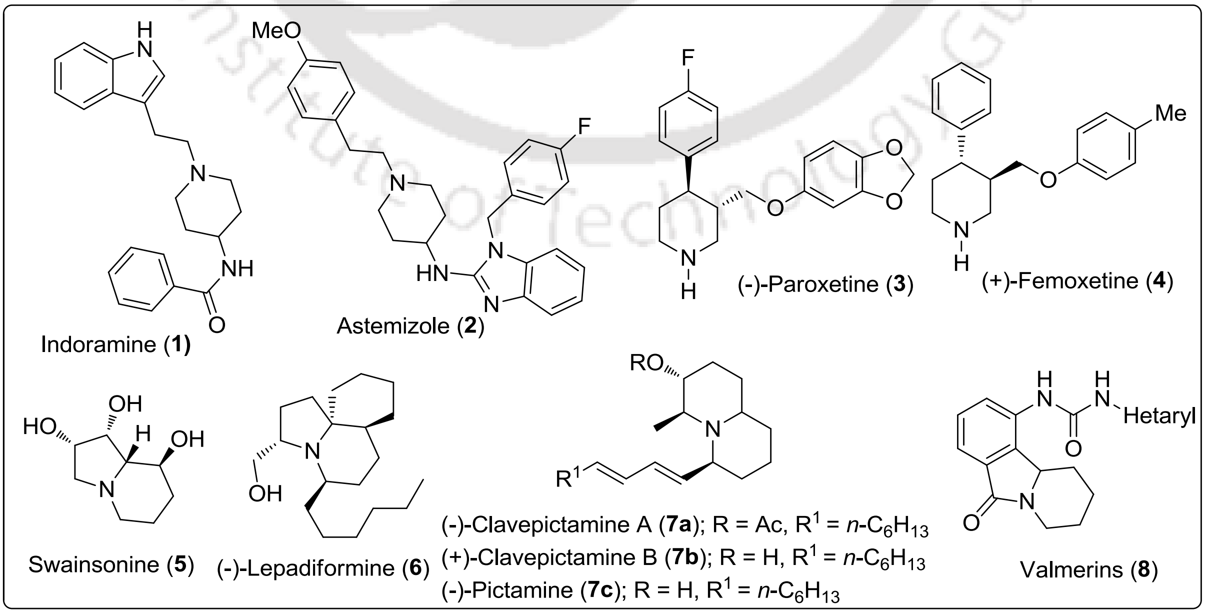


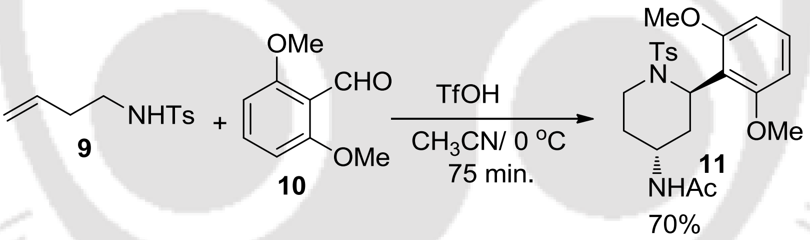
Figure 3.1.1. Some biologically active piperidine derivatives

vitro cardiovascular effects.[7] Similarly, pictamine, clavepictamines A and B (**7**) act as potent blocker for two neuronal nicotinic acetylcholine receptors, possessing significant cytotoxicity against murine leukemia and human solid tumor cell lines (P-388, A-549, U-251, and SN12K1).[8] More recently, tetrahydro-pyrido[1,2-*a*]isoindolone derivatives (valmerins) (**8**) have been reported as a potent Cyclin-Dependent Kinase/Glycogen Synthase Kinase-3 inhibitors and also exhibit anti-tumor properties (*Figure 3.1.1*).[9]

3.2. Literature Methods

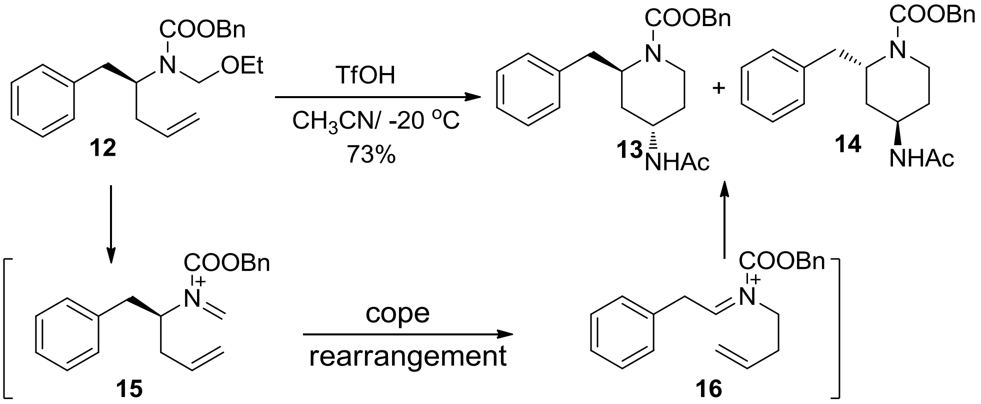
Aza-Prins cyclization reaction is not well explored like simple oxa-Prins cyclization reaction and a few methodologies have been reported for the formation of C-N and C-C bonds at 4th position of piperidine, which mainly includes aza-Prins/ Ritter and Friedel-Crafts reactions by using acyclic or cyclic iminium/ *N*-acyliminium ion intermediates.

Reddy *et al.* proposed a triflic acid promoted aza-Prins-Ritter sequence towards the synthesis of 4-amidopiperidine derivatives.[10] The reaction of *N*-tosyl homoallyl amine **9** with aldehyde **10** in the presence of triflic acid (TfOH) in acetonitrile produced corresponding 4-acetamido-piperidine **11** in 70% yield with exclusive *trans*-selectivity (*Scheme 3.2.1*).



Scheme 3.2.1

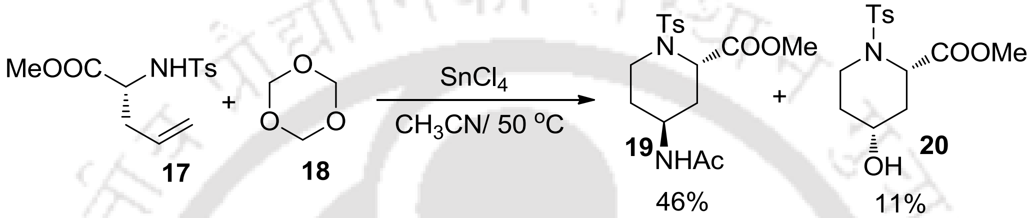
A tandem aza-Cope rearrangement and Ritter reaction was explained by Veenstra *et al.* (*Scheme 3.2.2*). Here, the chiral *N*-acyl iminium precursor **12** was treated with triflic acid in acetonitrile



Scheme 3.2.2

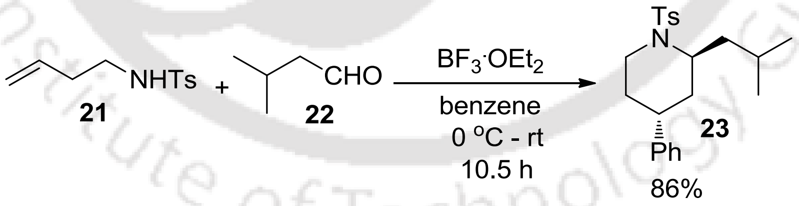
at -20 °C, to give the enantiomeric mixture of *trans*-4-acetamido-piperidines **13** and **14** in 73% yield (*trans*/*cis* ratio 20:1) with only 42% enantioselectivity. The recemization of the reaction is due to aza-cope equilibrium between *N*-acyl iminium ion intermediates **15** and **16.**[11]

Rutjes reported the formation of 4-amidopiperidine derivatives by using allyl substituted *N*-protected amino acid esters as substrates. The enantio pure substrate **17** undergoes cyclization with 1,3,5-trioxane **18** in the presence of $SnCl_4$ to afford enantiopure acetamide **19** with a reasonable yield (46%), without any racemization, together with a small amount of axial alcohol **20** (*Scheme 3.2.3*)**.**[12]



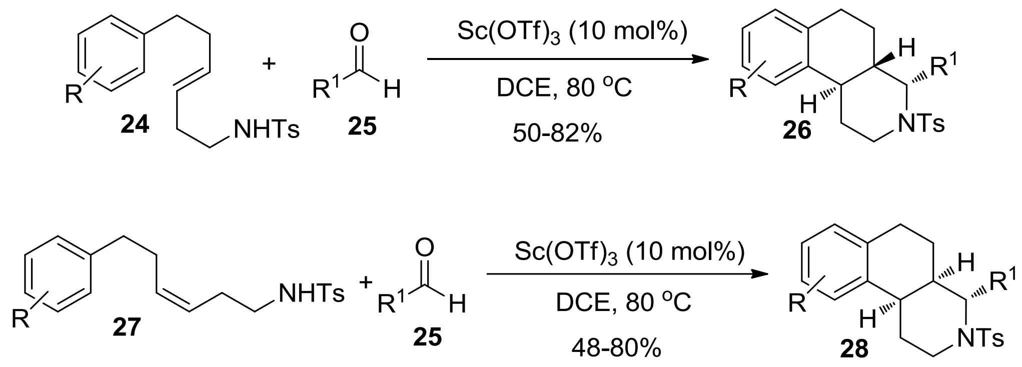
Scheme 3.2.3

Yadav and coworkers have developed a one pot synthesis for 4-arylpiperidines *via* aza-Prins-Friedel-Crafts strategy under mild conditions. It involves coupling between aldehyde **22** and *N*-tosylhomoallylic amine **21** in the presence of boron trifluoride etherate in benzene to give 4-phenyl piperidine **23** with *trans* selectivity (*Scheme 3.2.4*).[13] The reaction was also studied with activated arenes such as, toluene, anisole and diphenyl ether, resulting *ortho*/*para* regio isomeric products.



Scheme 3.2.4

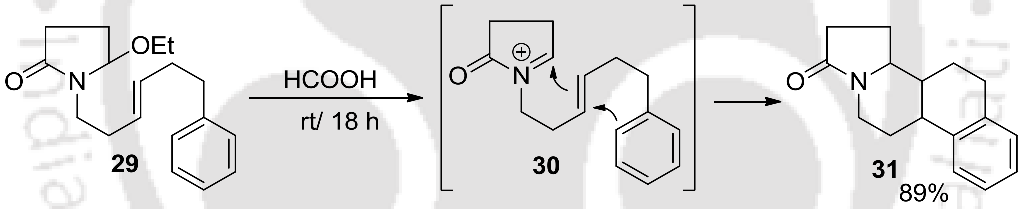
Recent studies by the Reddy group have further emphasised the value of the aza-Prins-Friedel-Crafts reaction for the synthesis of fused piperidine rings with phenyl substitution at 4th position of the piperidine ring (*Scheme 3.2.5*). The reaction of (*E*)-6-arylhex-3-enyl *N*-tosylamides **24** with various aldehydes **25** in the presence of 10 mol% $Sc(OTf)_3$ resulted *trans*-fused *N*-tosyloctahydrobenzo[*f*]isoquinolines **26** in good yields. Similarly, (*Z*)-6-aryl-hex-3-enyl-*N*-tosylamides **27** produced *cis*-fused *N*-tosyloctahydrobenzo[*f*]isoquinolines **28** under the same reaction conditions.[14]



R = H, 3-OMe, 4-Me;
R^1 = *p*-Br, Cy, 2-Thiophene, *p*-NO$_2$, styryl, (CH$_3$)$_2$CHCH$_2$

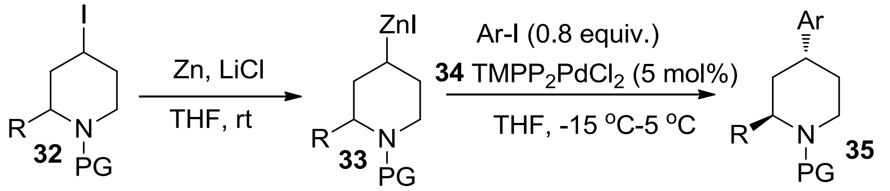
Scheme 3.2.5

The use of *N*-acyliminium ions in Prins cyclization was explored by Specamp and co-workers. They developed the polycyclization reaction of ethoxy lactam **29** in presence of formic acid at ambient temperature, which leads to the stereospecific formation of tetracyclic compound **31** (*Scheme 3.2.6*).[15] This reaction proceeds through the formation of cyclic *N*-acyliminium ion intermediate **30**.



Scheme 3.2.6

Apart from Prins cyclization, a number of methodologies have been developed so far for incorporation of aryl group at 4th position of piperidine moiety. Knochel has reported a highly diastereoselective methodology for the preparation of various substituted piperidines *via* Negishi cross-couplings with (hetero)aryl iodides. The protected 4-iodopiperidine substrates **32** produced corresponding piperidin-4-ylzinc reagents **33** in the presence of Zn/ LiCl. These reagents then



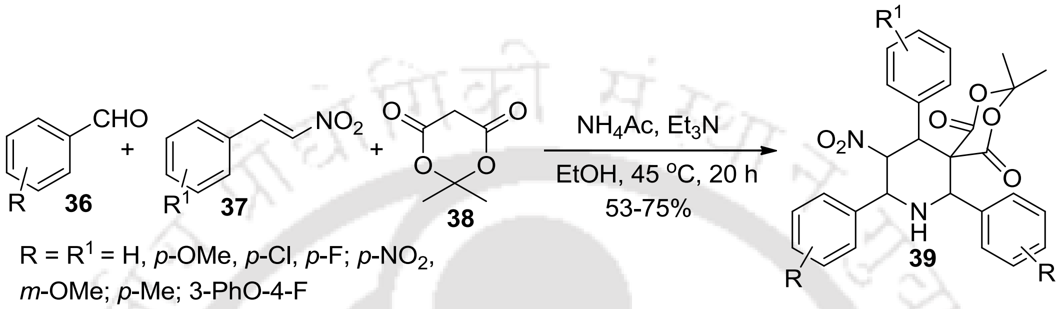
PG = Boc
R = 4-CF$_3$-C$_6$H$_4$

35a (Ar = Ph; 50%; dr = 92:8)
35b (Ar = 4-CN-C$_6$H$_4$; 72%; dr = 91:9)

Scheme 3.2.7

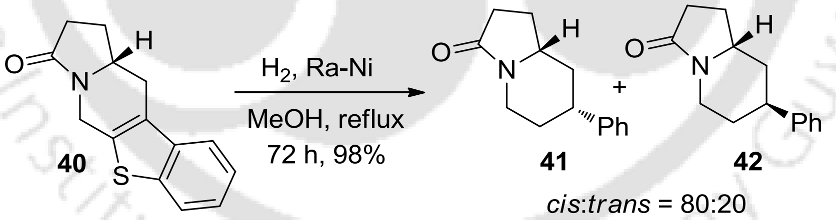
subjected to cross-coupling with aryl iodides, using TMPP$_2$PdCl$_2$ **34** as a catalyst to afford the *trans* coupling products **35** in 50-72% yields (*Scheme 3.2.7*).[16]

Wang and co-workers developed a one pot procedure for the synthesis of highly functionalized piperidines **39**, containing a Meldrum's acid moiety *via* pseudo five-component reaction of aromatic aldehydes **36**, substituted β-nitrostyrenes **37** and Meldrum's acid **38** in the presence of ammonium acetate (*Scheme 3.2.8*).[17]



Scheme 3.2.8

Daich and co-workers demonstrated an alternative route for the synthesis of 4-phenylpiperidine containing azabicyclic compounds through the reductive-desulfurization of the tylophorine analogue **40**. The reaction gave a mixture of *cis-trans* isomers **41** and **42** with a ratio of 80:20 in 98% combined yield (*Scheme 3.2.9*).[18]



Scheme 3.2.9

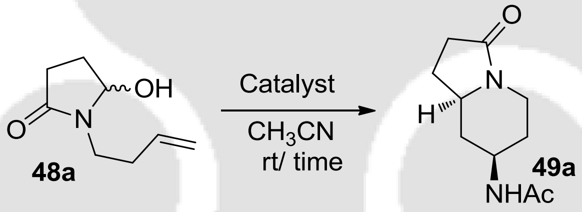
3.3. Results and Discussions

In our previous chapter, we have described the synthesis of 4-aryltetrahydropyrans using Prins cyclization followed by trapping the carbocation with arene nucleophiles *via* Friedel-Crafts reaction. Based on these literature methods and previous reports from our group, we envisioned that the aza-Prins cyclization of cyclic *N*-acyl iminium ions could provide bicyclic ring, which on further trapping with nucleophiles will give a novel class of highly functionalized heterocycles with high diastereoselectivity. In this chapter synthesis of amido/phenyl substituted azabicyclic derivatives *via* boron trifluoride etherate mediated tandem aza Prins-Ritter/

Friedel−Crafts reactions using cyclic *N*-acyliminium ions as key intermediates is described. The DFT calculations were also performed to prove the mechanism.

Initially, we treated, 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one with 1.2 equivalents of boron trifluoride etherate in acetonitrile at ambient temperature and the reaction proceeded smoothly to afford *N*-((7*R**,8a*R**)-3-Oxooctahydroindolizin-7-yl)acetamide **49a** in 81% yield as a single isomer with two hydrogens at stereocenters *cis* to each other. With this result in hand, we started optimization of the reaction as depicted in *Table 3.3.1* with a variety of Lewis acids such as $FeCl_3$, $SnCl_4$, $InCl_3$, $Sc(OTf)_3$, $In(OTf)_3$, TMSOTf, $Zn(OTf)_2$, $Cu(OTf)_2$, AgOTf and montmorillonite K10 and Brønsted acids such as TsOH and camphorsulfonic acid. Among the screened reagents, boron trifluoride etherate was found to be efficient in terms of yields and diastereoselectivity. Chlorinated Lewis acids such as $FeCl_3$, $SnCl_4$, and $InCl_3$ afforded the product in 25%, 17%, and 53% yields, respectively, with 80% de, without producing any halogenated products and starting material was recovered in 60%, 75% and 35% yields, respectively.

***Table 3.3.1*. Optimization of the reaction**

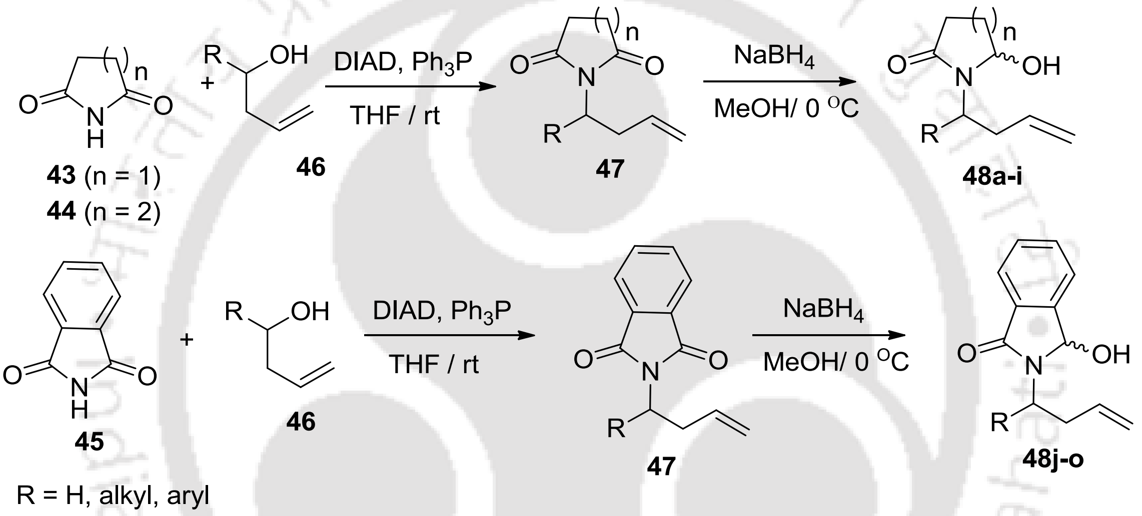


Entry	Catalyst (equiv.)	Time (h)	dr [a]	Yield (%)[b]
1	**$BF_3{\cdot}OEt_2$ (1.2)**	**4**	**100:0**	**81**
2	$FeCl_3$ (1.0)	24	80:20	25
3	$SnCl_4$ (1.0)	24	80:20	17
4	$InCl_3$ (1.2)	24	80:20	53
5	$In(OTf)_3$ (0.2)	4	90:10	<10
6	TMSOTf (1.2)	4	100:0	64
7	$Sc(OTf)_3$ (0.2)	4	90:10	12
8	$Zn(OTf)_2$ (1.0)	24	----	n.d.[c]
9	$Cu(OTf)_2$ (1.2)	24	80:20	38
10	AgOTf (0.2)	24	----	n.d. [c]
11	Mont. K10 (100mg)	24	----	n.d. [c]
12	TsOH (1.2)	4	90:10	48[d]
13	CSA (1.2)	4	90:10	29 [d]

[a]Ratio is determined from ^{1}H NMR. [b]Yield refers to isolated yield. [c]Not detected.
[d]Some decomposed product was also observed.

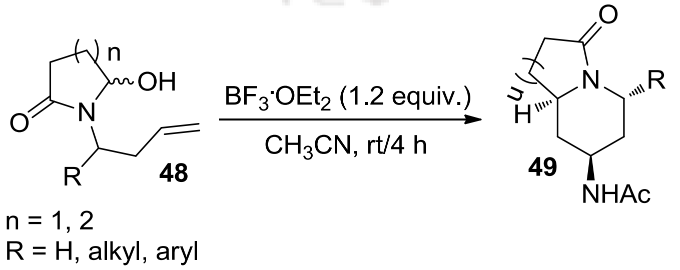
Triflates such as Sc(OTf)$_3$, In(OTf)$_3$, Zn(OTf)$_2$, Cu(OTf)$_2$, AgOTf and TMSOTf proved to be quite less effective, and montmorillonite K10 did not produce the desired product, starting material was recovered from the reaction mixture after 24 h. Similarly, the Brønsted acids TsOH and CSA also gave desired product in 48% and 29% yields, respectively with 90% de respectively. In these cases some decomposed products were also isolated.

With the optimized condition in hand, the scope of the reaction was investigated with a variety of substrates **48a−n**, which were synthesized by Mitsunobu reaction of cyclic imides such as succinimide **43**, glutarimide **44** and pthalimide **45** with homoallyl alcohols **46**,[19] followed by regioselective reduction of imides using NaBH$_4$ (*Scheme 3.3.1*).[20]



Scheme 3.3.1. Synthesis of starting materials

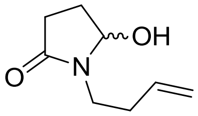
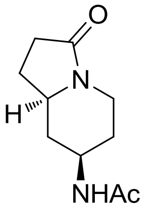
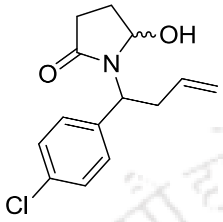
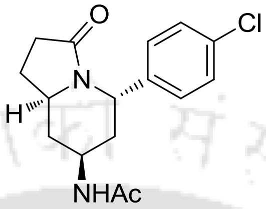
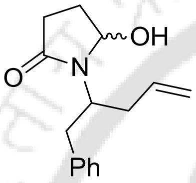
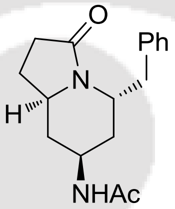
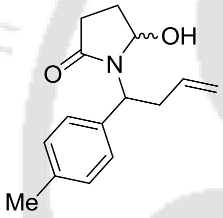
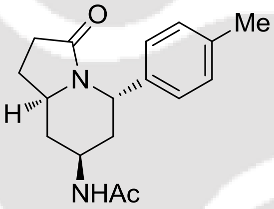
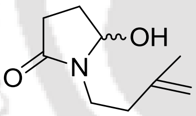
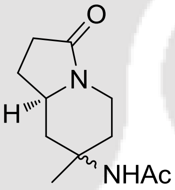
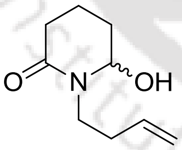
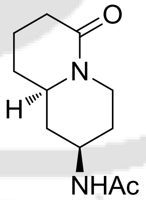
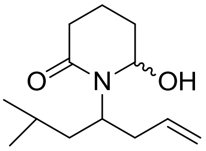
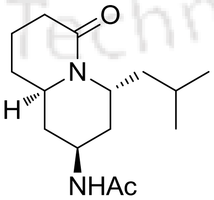
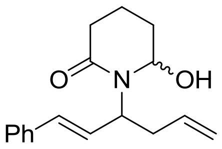
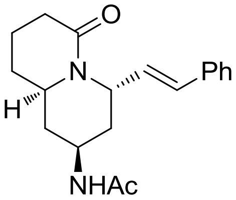
The tandem aza-Prins-Ritter reaction was generalized as shown in *Scheme 3.3.2* and the reduced homoallyl imides **48a−n** produced corresponding amido azabicyclic compounds in moderate to excellent yields having de values ranging from 80 to 100, as determined from ^{1}H and ^{13}C NMR analysis of crude compounds (*Table 3.3.2*).



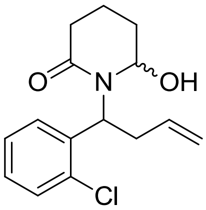
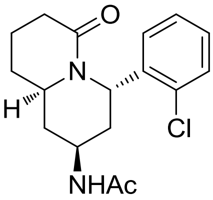
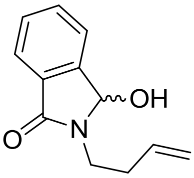
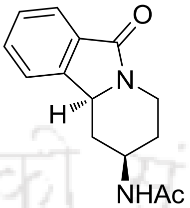
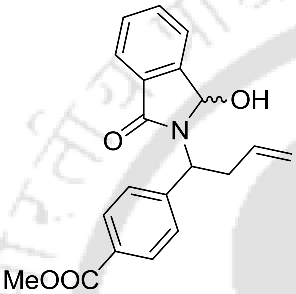
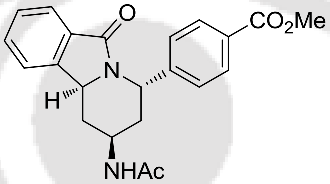
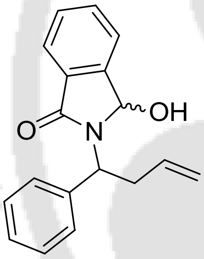
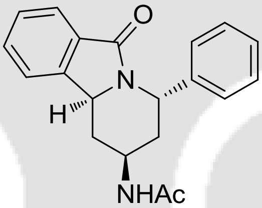
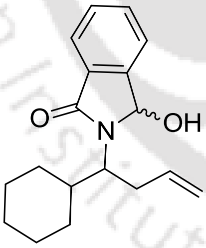
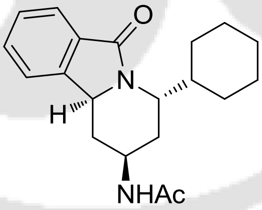
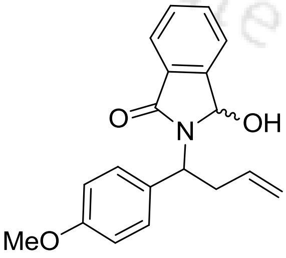
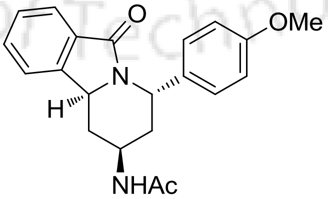
Scheme 3.3.2

It was observed that the yield of the product depends on the nature of the substituent R of homoallylic side chain. In the case of hydrogen- or alkyl-substitution at α–position to nitrogen

Table 3.3.2. Synthesis of Amido Azabicyclic Compounds

Entry	Substrate **48**	Product **49**	dr[a]	Yield (%)[b]
a			100:0	81
b			100:0	72
c			100:0	76
d			100:0	69
e			60:40	86
f			100:0	92
g			100:0	88
h			100:0	71

Continued…………

Entry	Substrate **48**	Product **49**	dr[a]	Yield (%)[b]
i			100:0	80
j			90:10	78
k			90:10	72
l			100:0	70
m			80:20	85
n			90:10	66

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

such as **48a**, **48c**, **48e-g**, **48j** and **48m** (*Table 3.3.2*), the reaction gave higher yields in comparison to aryl-substituted substrates. On the other hand, substrates having electron withdrawing aromatic substituents **48b, 48i**, and **48k** generally gave higher yields in comparison to simple phenyl **48l** and electron donating group containing substrates **48d** and **48n**. This is due to enhanced electrophilic nature of *N*-acyliminium ions **A** (*Scheme 3.3.5*) in the presence of electron-withdrawing aromatic substituents at α–position to nitrogen. 5-Hydroxy-1-(1-phenylpent-4-en-2-yl)-pyrrolidin-2-one **48c** afforded the desired product in 76% yield, without producing any intramolecular Friedel−Crafts product.[21] Similarly, substrates derived from succinimide and glutarimide **48a-i** gave single isomers. On the other hand, 5-hydroxy-1-(3-methylbut-3-en-1-yl)pyrrolidin-2-one **48e** yielded two inseparable diastereomers **49e** with a ratio of 60:40. Notably, the substrates derived from pthalimide, like substituted *N*-homoallyl-3-hydroxyisoindolin-1-ones (substrates **48j**, **48k**, **48m**, and **48n**) gave diastereomeric mixture with dr values of 80:20 to 90:10, but phenylsubstituted *N*-homoallyl-3-hydroxyisoindolin-1-one **48l** produced a single isomer. The reaction is highly diastereoselective and produced exclusively single diastereomers having a *cis* relationship between the H10 hydrogen at C-10 of the piperidine ring and the H12 hydrogen at C-12 of the ring junction. On the other hand, substituents at C-8 and C-10 are *trans* to each other.

The stereochemistry of the compounds was confirmed by observing a strong NOE between C−H12 and C−H10 and a weak NOE between C−H8 and −NH− for compound **49c**, which was further confirmed from X-ray crystallographic analysis (*Figure 3.3.1*).[22]

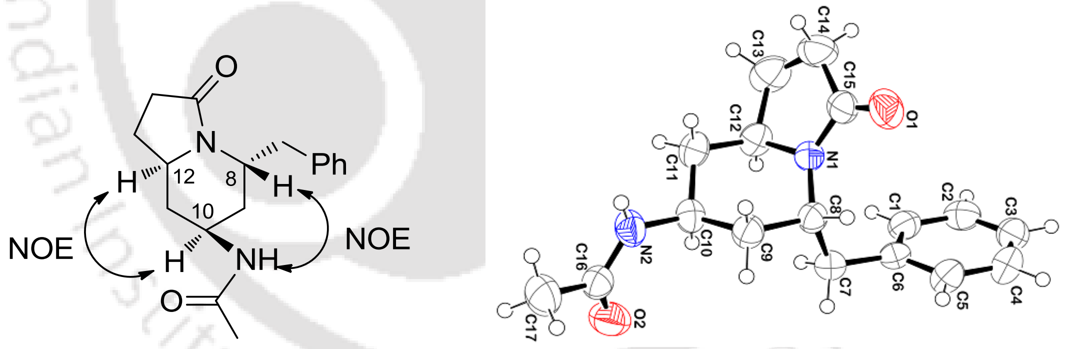
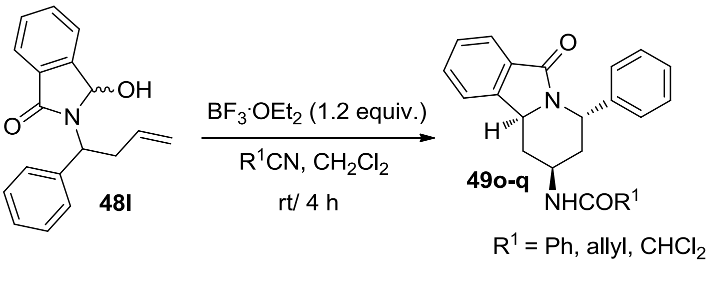


Figure 3.3.1. NOE and X-ray crystallographic structure of **49c**

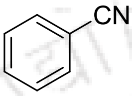
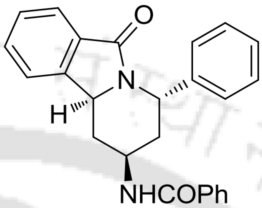
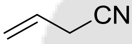
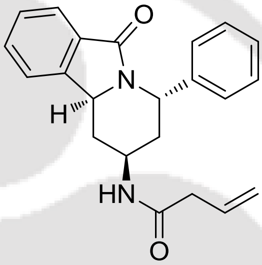
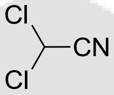
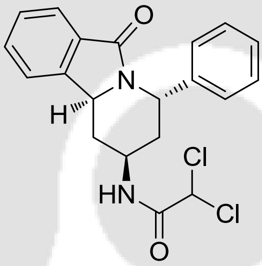
To explore the substrate scope, the reaction was further studied with other nitriles such as benzonitrile **50o**, allylnitrile **50p**, and dichloroacetonitrile **50q** in dichloromethane under the



Scheme 3.3.3

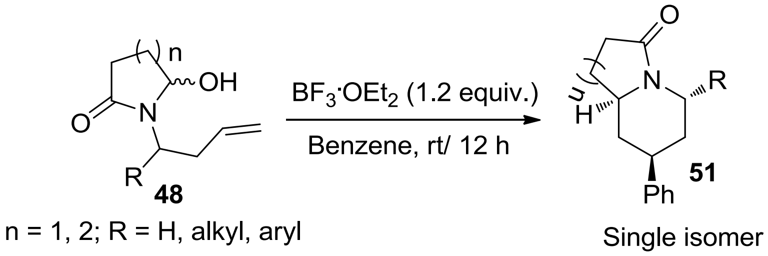
same optimized conditions, as generalized in *Scheme 3.3.3*. The *endo*-trig cyclization followed by Ritter reaction of 3-hydroxy-2-(phenylbut-3-en-1-yl)isoindolin-1-one with benzonitrile **50p** (3 equiv.) produced a single diastereomer of **49o** in 65% yield. Similarly, allylnitrile and dichloroacetonitrile also produced single isomers **49p, q** exclusively in 78% and 73% yields, respectively.

Table 3.3.3. *Endo*-trig Cyclization-Ritter Sequence with Different Nitriles

Entry	Nitrile **50**	Product **49**	Yield (%)[a]
o			65
p			78
q			73

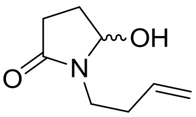
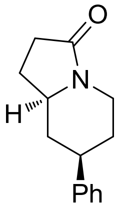
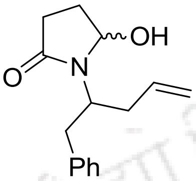
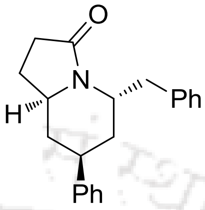
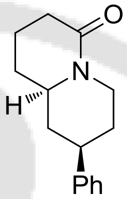
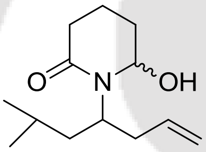
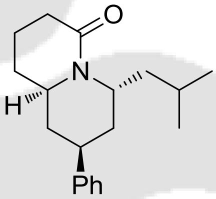
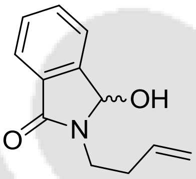
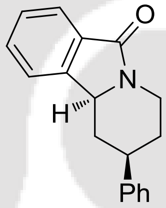
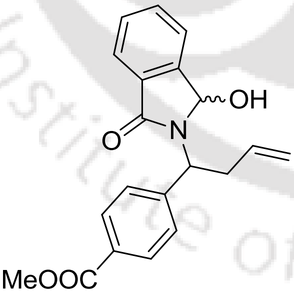
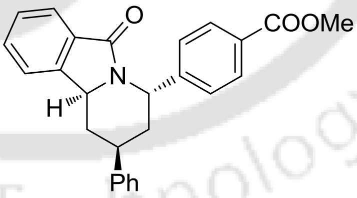
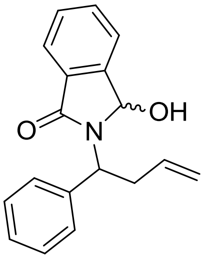
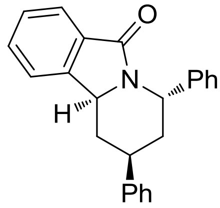
[a]Yield refers to isolated yield. The compounds are characterized by IR, NMR and Mass spectrometry.

The success of the *endo*-trig cyclization−Ritter sequence and previous Prins−Friedel−Crafts reaction protocols from our group[23] prompted us to check the possibility of trapping the carbocation generated during an aza-Prins type cyclization of the endocyclic *N*-acyliminium ion with arene nucleophile (*Scheme 3.3.4)*. To check this hypothesis, 1-(but-3-en-1-yl)-5-hydroxypyrrolidin- 2- one **48a** was treated with 1.2 equivalents of boron trifluoride etherate in

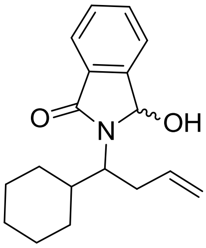
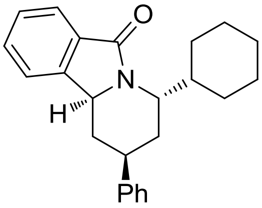
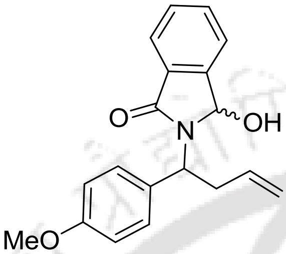
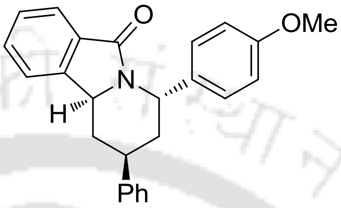


Scheme 3.3.4.

Table 3.3.4. Synthesis of Phenyl Azabicyclic Derivatives

Entry	Substrate **48**	Product **51**	Yield (%)[a]
a			73
b			76
c			84
d			71
e			68
f			72
g			62

Continued…...

Entry	Substrate **48**	Product **51**	Yield (%)[a]
h			71
i			54

[a] Yields refer to isolated yields.

benzene and as expected, the desired product **51a** was obtained as a single isomer in 73% yield (*Table 3.3.4*). The scope of the reaction was studied with various reduced *N*-homoallyl imides, as shown in *Table 3.3.4.* All the substrates worked well and produced the desired Friedel−Crafts products in moderate to good yields. As discussed in the *endo*-trig cyclization−Ritter sequence, substrates having no substitutions or aliphatic substitutions at positions α to *N*-acyliminium ions provided products **51a−e, h** in higher yields than aromatic substitution at the α-position.

The reaction is highly diastereoselective and produced exclusively single diastereomers having a *trans* relationship between the H10 hydrogen at C-10 of the piperidine ring and the H12 hydrogen at C-12 of the ring junction. On the other hand, the H8 hydrogen at C-8 and H10 hydrogen at C-10 are *cis* to each other. This was proved by NOE experiments, where a strong

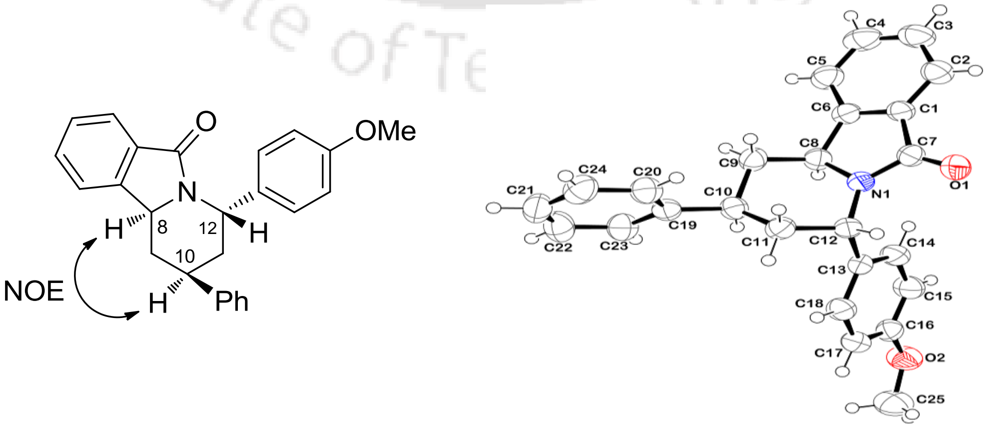
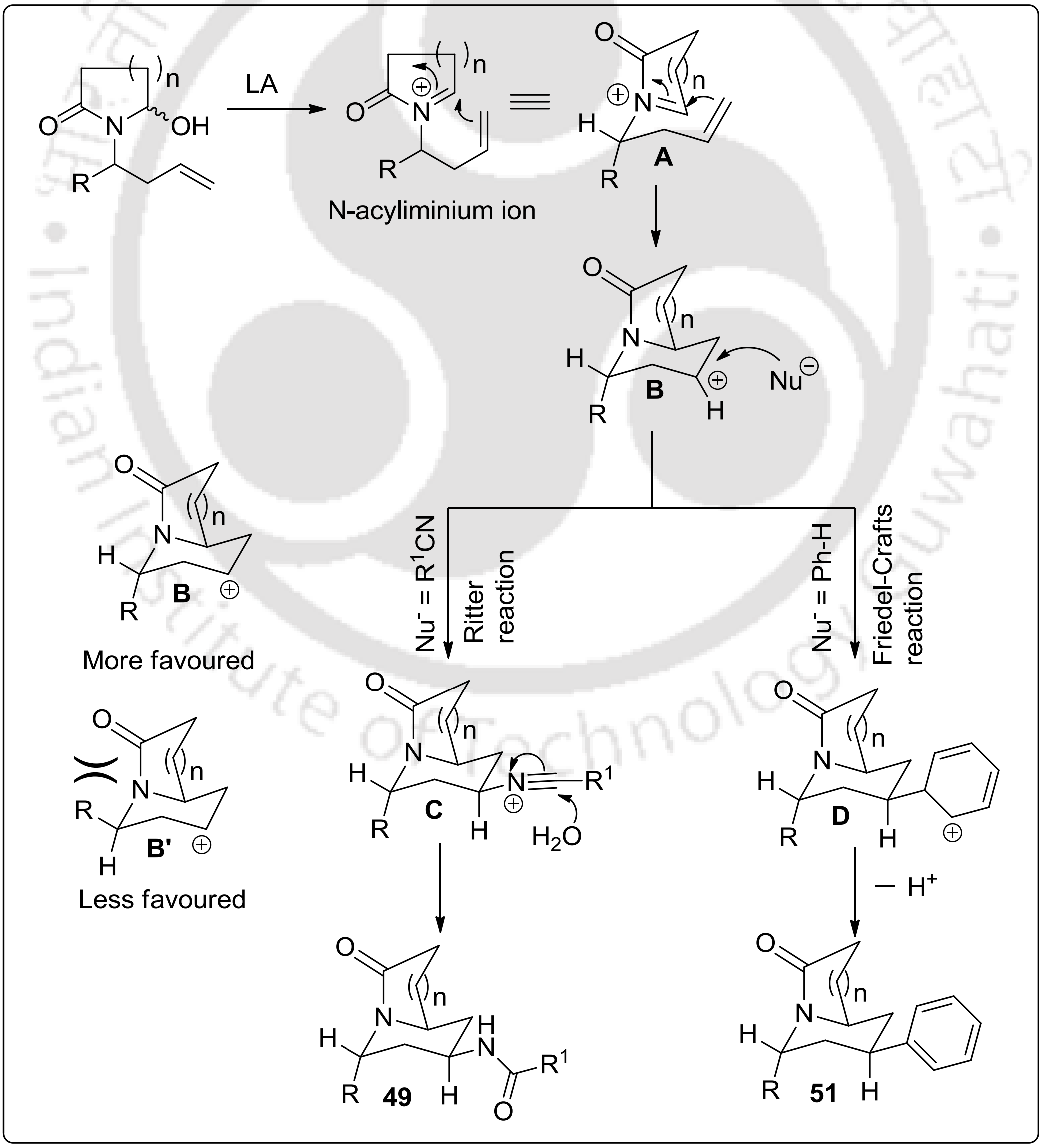


Figure 3.3.2. NOE and X-ray crystallographic structure of **51i**

NOE was observed between H8 and H10 hydrogens. This was further confirmed by X-ray crystallographic analysis of compound **51i** (*Figure 3.3.2*).[24]

The reaction with other activated arenes such as toluene gave an inseparable mixture of *ortho* and *para* isomeric Friedel−Crafts products along with the corresponding eliminated products in 45% overall yield.[25] On the other hand, mesitylene failed to produce the desired products but gave only eliminated products.[25] This might be due to the steric effects of the comparatively bulky nature of toluene and mesitylene.

The diastereoselectivity of the reaction can be explained as follows. The reduced *N*-homoallyl imide under Lewis acidic conditions gives the corresponding *N*-acyliminium ion intermediate **A**, which undergoes 6-*endo*-trig cyclization to give the more favorable chairlike carbocation



Scheme 3.3.5. Plausible mechanism of the reaction

intermediate **B** with axial R substitution, due to strong (1,3) strain and less steric hindrance between the substituent R and the carbonyl group of the *N*-acyliminium ion intermediate (*Scheme 3.3.5*).[26] The carbocation **B** thus formed is trapped by nitrile from an equatorial position to generate intermediate **C**, which after hydrolysis gives the corresponding amido azabicyclic compounds **49**. Similarly, the chair like carbocation **B** undergoes a Friedel−Crafts reaction in the presence of benzene nucleophile to give the intermediate **D**, which after deprotonation gives the corresponding phenyl substituted azabicyclic compounds **51**.

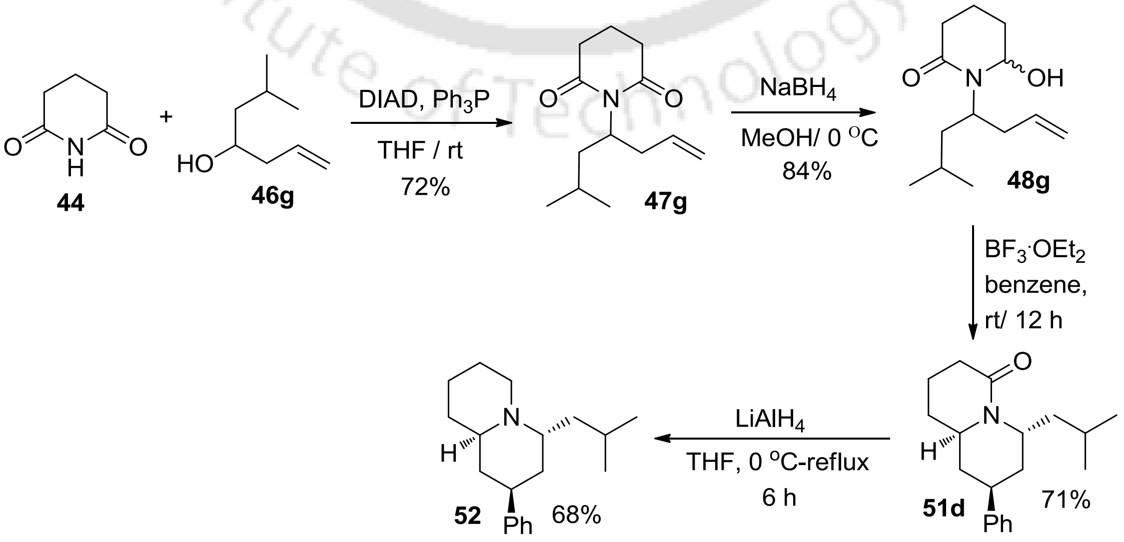
In order to address the observed diastereoselectivity and proposed mechanism of the reaction, the DFT calculations were carried out with the Gaussian 03 program package.[27] Geometry optimizations of **B** and **B'** for compound **49c** were performed at the B3LYP[28] level of theory with the 6-31G(d,p) basis set. The energies of optimized geometries are provided in *Table 3.3.5*. The results showed a preference for formation of **B** over **B′** by energy of 46.304 kJ/mol. This clearly supports the above proposed mechanism.

Table 3.3.5.Computational study of intermediates **B** and **B′** of **49c**

S.No.	Intermediate (R = Bn)	Energy (in eV)
1	**B**	-19379.75810607049
2	**B'**	-19379.27820120443

Energy difference = 0.479904866062 eV = 46.304 kJ/mol.

The importance of this methodology toward the synthesis of corresponding unnatural alkaloid **52** is shown in *Scheme 3.3.6*. The Mitsunobu reaction between glutarimide **44** and homoallyl alcohol **46g** gave corresponding *N*-homoallyl imide, which on further treatment with $NaBH_4$



Scheme 3.3.6. Synthesis of unnatural quinolizidine alkaloid

gave regioselectively reduced *N*-homoallyl carbinol **48g** in 84% yield. The aza-Prins-Friedel-Crafts reaction of **48g** produced cyclized compound **51d**. Finally, the reduction of compound **51d** with $LiAlH_4$ gave an unnatural quinolizidine alkaloid (2*R**,4*S**,9a*S**)-4-isobutyl-2-phenyl-octahydro-1*H*-quinolizine **52** in 68% yield (*Scheme 3.3.6*).[21a]

Conclusions

In conclusion, the new tandem aza-Prins-Ritter/ Friedel−Crafts approach is experimentally simple, mild, efficient and produced single isomers in most of the cases. Broad scope and high level of functionality present in the end products contributes a great deal of potential towards the synthesis of moderately complex phenyl, amido and amino azabicyclic derivatives. This methodology could be useful for the synthesis of natural and unnatural indolizidine and quinolizide alkaloids.

3.4. Experimental section

3.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1.

3.4.2. Synthesis of starting materials

The homoallyl imides and the corresponding carbinol imides were synthesized as per literature procedure and the structure and purity of known compounds **47a**, **47c**, **47f**, **47j**, **48a**, **48c** and **48f** were confirmed by comparison of their spectral data (^{1}H NMR and ^{13}C NMR) with those reported in literature.[19,20]

3.4.3. General Procedure for the Synthesis of Compounds 49a-n:

To 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (1.0 equiv.) in acetonitrile (0.17 M) was added freshly distilled boron trifluoride etherate (1.2 equiv.). The reaction mixture was stirred at room temperature for 4h. The progress of the reaction was monitored by TLC with ethyl acetate as eluent. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with dichloromethane and then the organic layer was washed with brine. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography using ethyl acetate as eluent over silica gel to give the title compounds.

Synthesis of *N*-((7*R**,8a*R**)-3-oxooctahydroindolizin-7-yl)acetamide (49a):

To 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (78 mg, 0.50 mmol) in acetonitrile (3 mL) was added freshly distilled boron trifluoride etherate (86 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for 4h. The progress of the reaction was monitored by TLC with ethyl acetate as eluent. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate solution (5 mL) and the product was extracted with dichloromethane (2x10 mL) and then the organic layer was washed with brine (10 mL). The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography using ethyl acetate as eluent over silica gel to give the *N*-((7*R**,8a*R**)-3-oxooctahydroindolizin-7-yl)acetamide **49a** in (80 mg, 81%) as a colourless liquid.

3.4.4. General Procedure for the Synthesis of Compounds 49o-49q:

To a mixture of 3-hydroxy-2-(1-phenylbut-3-en-1-yl)isoindolin-1-one (1.0 equiv.) and benzonitrile (3.0 equiv.) in dichloromethane (0.17 M) was added freshly distilled boron trifluorideetherate (1.2 equiv.). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with dichloromethane and then the organic layer was washed with brine. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the compounds **49o-49q**.

Synthesis of *N*-((2*R**,4*S**,10b*S**)-6-oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl)benzamide (49*o*):

To a mixture of 3-hydroxy-2-(1-phenylbut-3-en-1-yl)isoindolin-1-one (140 mg, 0.50 m.mol) and benzonitrile (160 mg, 1.50 mmol) in dichloromethane (3 mL) was added freshly distilled boron trifluorideetherate (86 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2x10 mL) and then the organic layer was washed with brine (10 mL). The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the *N*-((2*R**, 4*S**, 10*bS**)-6-oxo-4-phenyl-1,2,3,4,6,10bhexahydropyrido[*2,1-a*]isoindol-2-yl)benzamide (**49o**) in (124 mg, 65%) as a white solid, mp 140-142 °C.

3.4.5. General Procedure for the Synthesis of Compounds 51a-i

To 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (1.0 equiv.) in benzene (0.17 M) was added freshly distilled boron trifluoride etherate (1.2 equiv.). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with dichloromethane and then the organic layer was washed with brine. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the compounds **51a-51i**.

Synthesis of (7*S**,8a*S**)-7-Phenylhexahydroindolizin-3(2*H*)-one (51a):

To 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (78 mg, 0.50 mmol) in benzene (3 mL) was added freshly distilled boron trifluoride etherate (86 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (3:7) as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2x10 mL) and then the organic layer was washed with brine (10 mL). The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the (7*S**,8a*S**)-7-phenylhexahydroindolizin-3(2*H*)-one **51a** (79 mg, 73%) as a pale yellow liquid.

3.4.6. Typical Procedure for the Synthesis of Unnatural Quinolizidine Alkaloid (52):

The compound **51d** (86 mg, 0.3 mmol) in THF (3 mL) was added to a stirred suspension of $LiAlH_4$ (38 mg, 1 mmol) in dry THF (5 mL) at 0 ^{o}C and refluxed for 6 h. The solution was cooled in an ice bath and quenched by the addition of EtOAc (2 mL) at 0 ^{o}C. The precipitate was filtered off through Celite and washed with EtOAc (3x10 mL). The combined filtrate was concentrated and purified by column chromatography using ethyl acetate and hexane (1:4) as eluents giving (2*R**, 4*S**, 9*aS**)-4-Isobutyl-2-phenyloctahydro-1*H*-quinolizine **52** (55 mg, 68%) as colourless liquid.

3.5. References

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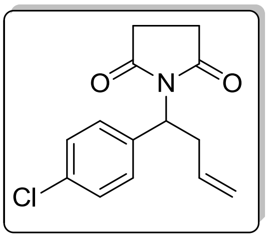
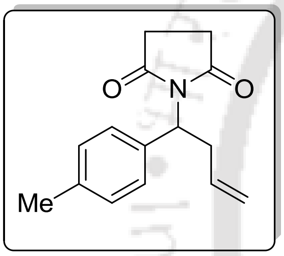
3.6. Characterization Data

1-(1-(4-Chlorophenyl)but-3-en-1-yl)pyrrolidine-2,5-dione (**47b**):



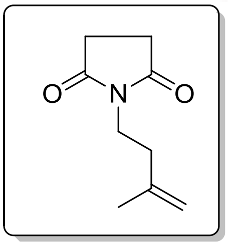
Colourless liquid; yield 1.08 g, 82%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.64 (s, 4 H), 2.81−2.88 (m, 1 H), 3.23−3.31 (m, 1 H), 5.05 (d, *J* = 10.0 Hz, 1 H), 5.14 (d, *J* = 17.2 Hz, 1 H), 5.26 (dd, *J* = 10.4 and 6.0 Hz, 1 H), 5.64−5.74 (m, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.1 (2C), 44.0, 54.3, 118.6, 127.4, 128.6, 128.8 (2C), 129.9 (2C), 134.1, 177.2 (2C); **IR** (KBr, neat) 1702, 1641, 1493, 1386, 1238, 1179, 1104, 828 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{14}NO_2Cl$ $(M + H)^+$ requires 264.0786, found 264.0786.

1-(1-(*p*-Tolyl)but-3-en-1-yl)pyrrolidine-2,5-dione (**47d**):



Pale yellow liquid; yield 0.95 g, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.59 (s, 2 H), 2.60 (s, 2 H), 2.81−2.88 (m, 1 H), 3.25−3.34 (m, 1 H), 5.04 (d, *J* = 10.0 Hz, 1 H), 5.12 (d, *J* = 17.2 Hz, 1 H), 5.26 (dd, *J* = 10.4 and 5.6 Hz, 1 H), 5.65−5.75 (m, 1 H), 7.12 (d, *J* = 7.2 Hz, 2 H), 7.37 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.2, 28.0 (2C), 34.5, 54.6, 118.1, 125.9, 128.3 (2C), 129.2 (2C), 134.6, 135.6, 177.3 (2C); **IR** (KBr, neat) 1724, 1640, 1459, 1377, 1254, 1176, 997, 840 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{17}NO_2$ $(M + H)^+$ requires 244.1332, found 244.1333.

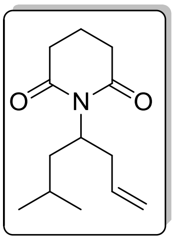
1-(3-Methylbut-3-en-1-yl)pyrrolidine-2,5-dione (**47e**):



Colourless liquid; yield 0.78 g, 93%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.77 (s, 3 H), 2.29 (t, *J* = 7.2 Hz, 2 H), 2.69 (s, 4 H), 3.64 (t, *J* = 7.6 Hz, 2 H), 4.66 (s, 1 H), 4.76 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.5, 27.7 (2C), 35.0, 36.4, 112.1, 141.8, 176.9 (2C); **IR** (KBr, neat) 2914, 1731, 1669, 1450, 1362, 1218, 1110, 925 cm^{-1}; **HRMS** (ESI) calcd for $C_9H_{13}NO_2$ $(M + H)^+$ requires 168.1019, found 168.0981.

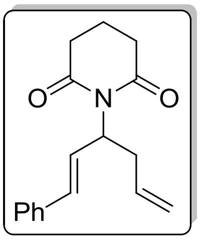
1-(6-Methylhept-1-en-4-yl)piperidine-2,6-dione (47g):

Colourless liquid; yield 0.80 g, 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.4 Hz, 3 H), 0.81 (d, *J* = 6.4 Hz, 3 H), 1.30−1.39 (m, 2 H), 1.76−1.83 (m, 2 H), 1.92 (t, *J* = 8.8 Hz, 1 H), 2.23−2.30 (m, 1 H), 2.52 (t, *J* = 6.0 Hz, 4 H), 2.59−2.67 (m, 1 H), 4.76−4.84 (m, 1 H), 4.86−4.92



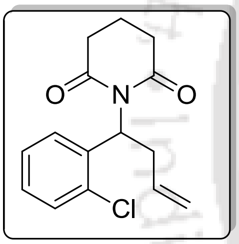
(m, 2 H), 5.53−5.63 (m, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 16.9, 21.8 (2C), 22.8, 25.1 (2C), 36.6, 40.6, 50.0, 116.4, 135.2, 172.7 (2C); **IR** (KBr, neat) 2928, 1724, 1672, 1464, 1384, 1237, 1177, 1125, 918, 738 cm^{-1}; **HRMS** (ESI) calcd for $C_{13}H_{21}NO_2$ $(M + H)^+$ requires 224.1645, found 224.1654.

(*E*)-1-(1-Phenylhexa-1,5-dien-3-yl)piperidine-2,6-dione (47h):



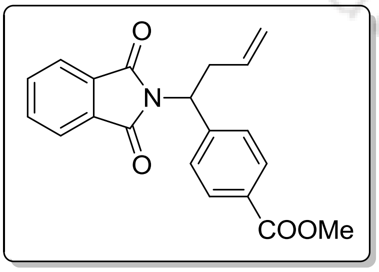
Colourless gum; yield 1.03 g, 76%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 1.85−1.92 (m, 2 H), 2.62 (t, *J* = 6.8 Hz, 4 H), 2.83−2.89 (m, 2 H), 4.94−5.06 (m, 2 H), 5.45−5.65 (m, 1 H), 5.66−5.80 (m, 1 H), 6.27 (d, *J* = 16.0 Hz,1 H), 6.63 (dd, *J* = 16.0 and 8.0 Hz,1 H), 7.19−7.30 (m, 4 H), 7.36−7.38 (m, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 17.0, 33.3 (2C), 36.6, 53.6, 117.4, 126.4 (2C), 127.6, 128.0, 128.5 (2C), 132.8, 134.7, 136.6, 172.7 (2C); **IR** (KBr, neat) 2979, 1725, 1678, 1494, 1384, 1239, 1173, 1108, 971, 918, 754, 695 cm^{-1}; **HRMS** (ESI) calcd for $C_{17}H_{19}NO_2$ $(M + H)^+$ requires 270.1489, found 270.1495.

1-(1-(2-Chlorophenyl)but-3-en-1-yl)piperidine-2,6-dione (47i):



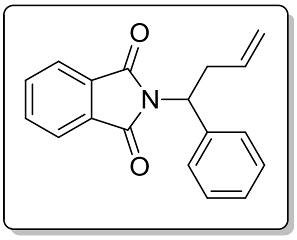
Colourless gum; yield 1.12 g, 81%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 1.82−1.89 (m, 2 H), 2.51−2.63 (m, 4 H), 2.88−2.95 (m, 1 H), 3.08−3.16 (m, 1 H), 5.03−5.12 (m, 2 H), 5.77−5.88 (m, 1 H), 6.03 (dd, *J* = 10.0 and 6.0 Hz,1 H), 7.17−7.38 (m, 3 H), 7.67 (d, *J* = 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 16.9, 33.2 (2C), 34.6, 51.1, 117.6, 125.8, 128.4, 129.3, 131.1, 133.6, 134.7, 135.9, 172.3 (2C); **IR** (KBr, neat) 2979, 1725, 1675, 1466, 1377, 1239, 1173, 1146, 998, 840 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{16}NO_2Cl$ $(M + H)^+$ requires 278.0942, found 278.0949.

Methyl 4-(1-(1,3-dioxoisoindolin-2-yl)but-3-en-1-yl)benzoate (47k):



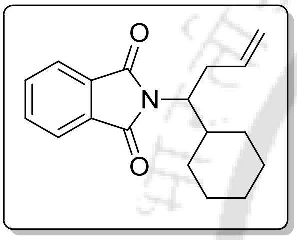
Colourless gum; yield 1.62 g, 89%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 2.95−3.02 (m, 1 H), 3.35−3.44 (m, 1 H), 3.89 (s, 3 H), 5.02 (d, *J* = 10.0 Hz, 1 H), 5.14 (d, *J* = 16.8 Hz, 1 H), 5.49 (dd, *J* = 10.0 and 6.0 Hz, 1 H), 5.71−5.81 (m, 1 H), 7.60 (d, *J* = 7.2 Hz, 2 H), 7.68−7.71 (m, 2 H), 7.79−7.82 (m, 2 H), 8.00 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 35.2, 52.2, 54.0, 118.7, 123.4 (2C), 128.1 (2C), 129.7, 129.9 (2C), 131.7, 134.0 (2C), 134.2 (2C), 144.1, 166.7, 168.2 (2C); **IR** (KBr, neat) 1771, 1707, 1641, 1436, 1384, 1279, 1110, 723 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{17}NO_4$ $(M + H)^+$ requires 336.1230, found 336.1229.

2-(1-Phenylbut-3-en-1-yl)isoindoline-1,3-dione (47l):



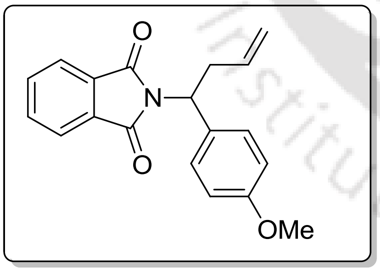
Pale yellow liquid; yield 1.30 g, 94%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 2.93−3.00 (m, 1 H), 3.37−3.46 (m, 1 H), 4.99 (d, *J* = 10.8 Hz, 1 H), 5.13 (d, *J* = 16.0 Hz, 1 H), 5.44 (dd, *J* = 10.8 and 5.6 Hz, 1 H), 5.72−5.83 (m, 1 H), 7.24−7.28 (m, 1 H), 7.31−7.36 (m, 2 H), 7.54 (d, *J* = 7.6 Hz, 2 H), 7.67 (dd, *J* = 5.2 and 2.8 Hz, 2 H), 7.78 (dd, *J* = 5.2 and 3.2 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 35.2, 54.3, 118.1, 123.0 (2C), 127.8, 127.9 (2C), 128.5 (2C), 131.6, 133.8 (2C), 134.3 (2C), 139.2, 168.1 (2C); **IR** (KBr, neat) 1770, 1710, 1641, 1493, 1387, 1335, 1077, 922, 720, 698 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{15}NO_2$ $(M + H)^+$ requires 278.1176, found 278.1178.

2-(1-Cyclohexylbut-3-en-1-yl)isoindoline-1,3-dione (47m):



Colourless liquid; yield 1.00 g, 71%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 0.91−1.37 (m, 6 H), 1.54−1.96 (m, 4 H), 2.06−2.17 (m, 2 H), 2.77−2.85 (m, 1 H), 3.97−4.02 (m, 1 H), 4.88 (d, *J* = 10.4 Hz, 1 H), 4.98 (d, *J* = 16.8 Hz, 1 H), 5.60−5.70 (m, 1 H), 7.68−7.71 (m, 2 H), 7.79−7.82 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 25.8, 25.9, 26.3, 30.3, 30.8, 33.9, 39.3, 56.9, 117.6, 123.1 (2C), 131.7, 133.9 (2C), 135.2 (2C), 168.9 (2C); **IR** (KBr, neat) 2927, 2850, 1770, 1706, 1641, 1449, 1373, 1171, 840, 721 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{21}NO_2$ $(M + H)^+$ requires 284.1645, found 284.1657.

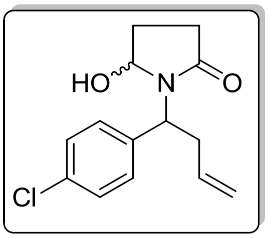
2-(1-(4-Methoxyphenyl)but-3-en-1-yl)isoindoline-1,3-dione (47n):



Colourless liquid; yield 1.06 g, 69%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 2.91−2.98 (m, 1 H), 3.32−3.41 (m, 1 H), 3.77 (s, 3 H), 5.99 (d, *J* = 10.4 Hz, 1 H), 5.13 (d, *J* = 16.8 Hz, 1 H), 5.39 (dd, *J* = 10.4 and 6.0 Hz, 1 H), 5.70−5.83 (m, 1 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.8 Hz, 2 H), 7.65−7.67 (m, 2 H), 7.76−7.79 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 35.6, 54.0, 55.4, 114.0 (2C), 118.3, 123.3 (2C), 127.3, 129.5 (2C), 131.5, 132.0, 134.0 (2C), 134.6 (2C), 168.5 (2C); **IR** (KBr, neat) 2837, 1734, 1638, 1459, 1377, 1253, 1161, 972, 840 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{17}NO_3$ $(M + H)^+$ requires 308.1281, found 308.1294.

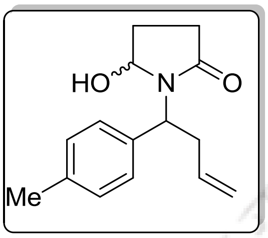
1-(1-(4-Chlorophenyl)but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (48b): (Mixture of isomers with 60:40 ratio)

Pale yellow liquid; yield 0.60 g, 76%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 1.71−1.79 (m, 1 H), 1.99−2.16 (m, 2 H), 2.41−2.55 (m, 1 H), 2.70−2.91 (m, 2 H), 4.84 (d, *J* = 5.2 Hz, 0.6 H), 4.95−5.11 (m, 3 H), 5.25 (d, *J* = 5.6 Hz, 0.4 H), 5.58−5.73 (m, 1 H), 7.18−7.34 (m, 4 H); ^{13}**C**



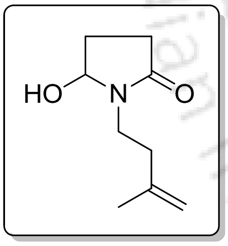
NMR (100 MHz, CDCl$_3$) δ 28.9, 29.0, 29.2, 29.8, 35.3, 36.9, 54.4, 54.9, 82.4, 83.0, 117.9 (2C), 128.8 (2C), 128.9 (2C), 129.5 (2C), 129.9 (2C), 133.6, 133.8, 134.7, 135.1, 137.2, 139.2, 175.0, 175.6; **IR** (KBr, neat) 2925, 1662, 1450, 1376, 1258, 1169, 1091, 996, 838 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{16}NO_2Cl$ $(M + H)^+$ requires 266.0942, found 266.0943.

5-Hydroxy-1-(1-(*p*-tolyl)but-3-en-1-yl)pyrrolidin-2-one (48d): (Mixture of isomers with 50:50 ratio)



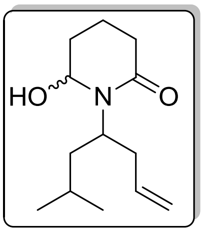
Colourless liquid; yield 0.53 g, 72%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 1.76−1.87 (m, 1 H), 2.06−2.18 (m, 1 H), 2.25−2.32 (m, 1 H), 2.34 (s, 3 H), 2.56−2.67 (m, 1 H), 2.76−2.87 (m, 1 H), 2.87−2.98 (m, 1 H), 4.92 (t, *J* = 6.4 Hz, 0.5 H), 5.07 (d, *J* = 10.4 Hz, 1 H), 5.10−5.17 (m, 1 H), 5.23−5.31 (m, 1 H), 5.34 (t, *J* = 4.8 Hz, 0.5 H), 5.68−5.87 (m, 1 H), 7.16 (dd, *J* = 8.0 and 4.4 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 21.2 (2C), 28.5, 28.9, 29.2 (2C), 35.5, 37.0, 54.5, 55.0, 82.2, 82.6, 117.4, 117.6, 127.9 (2C), 128.3 (2C), 129.3 (2C), 129.5 (2C), 135.0, 135.5, 135.6, 137.2, 137.5, 137.7, 175.0, 175.6; **IR** (KBr, neat) 2923, 1665, 1449, 1279, 1171, 1064, 993, 916, 841 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{19}NO_2$ $(M + H)^+$ requires 246.1489, found 246.1494.

5-Hydroxy-1-(3-methylbut-3-en-1-yl)pyrrolidin-2-one (48e):



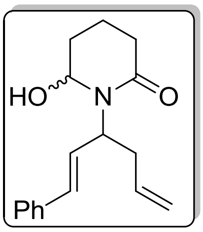
Pale yellow liquid; yield 0.47 g, 92%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 1.77 (s, 3 H), 1.84−1.93 (m, 1 H), 2.25−2.35 (m, 4 H), 2.49−2.57 (m, 1 H), 3.26−3.33 (m, 1 H), 3.59−3.67 (m, 1 H), 3.87 (d, *J* = 7.6 Hz, 1 H), 4.72 (s, 1 H), 4.78 (s, 1 H), 5.21 (t, *J* = 5.2 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 22.0, 27.9, 28.9, 35.3, 37.8, 82.7, 111.7, 142.6, 175.1; **IR** (KBr, neat) 2884, 1631, 1450, 1297, 1158, 1061, 987, 741 cm^{-1}; **HRMS** (ESI) calcd for $C_9H_{15}NO_2$ $(M + H)^+$ requires 170.1176, found 170.1170.

6-Hydroxy-1-(6-methylhept-1-en-4-yl)piperidin-2-one (48g): (Mixture of isomers with 60:40 ratio)



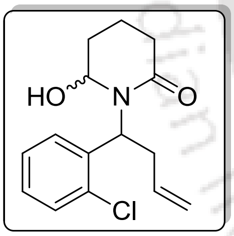
Colourless liquid; yield 0.57 g, 84%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 0.89 (d, *J* = 5.6 Hz, 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 1.31−1.50 (m, 2 H), 1.56−1.76 (m, 3 H), 1.92−1.96 (m, 1 H), 2.09−2.39 (m, 3 H), 2.49 (t, *J* = 8.0 Hz, 2 H), 4.53 (brs, 0.6 H), 4.78 (brs, 0.4 H), 5.01−5.12 (m, 3 H), 5.64−5.77 (m, 1 H), 5.78−5.89 (m, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 22.0, 22.2, 22.7, 23.1, 23.3, 23.4, 24.9, 25.2, 30.9, 31.0, 31.8, 32.3, 37.6 (2C), 38.7, 38.8, 41.4, 41.8, 107.1 (2C), 116.8, 117.0, 136.3, 136.7, 169.8, 171.3; **IR** (KBr, neat) 2955, 1618, 1467, 1330, 1181, 1085, 996, 752 cm^{-1}; **HRMS** (ESI) calcd for $C_{13}H_{23}NO_2$ (M + H)$^+$ requires 226.1802, found 226.1806.

(*E*)-6-Hydroxy-1-(1-phenylhexa-1,5-dien-3-yl)piperidin-2-one (48h): (Mixture of isomers with 60:40 ratio)



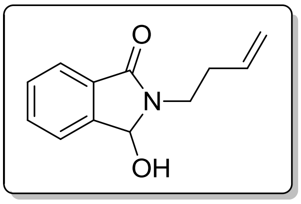
Colourless gum; yield 0.52 g, 64%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 1.60−1.64 (m, 0.8 H), 1.69−1.77 (m, 1.2 H), 1.84−1.93 (m, 1.2 H), 1.98−2.08 (m, 0.8 H), 2.21−2.45 (m, 1 H), 2.45−2.50 (m, 1.2 H), 2.55−2.65 (m, 0.8 H), 2.75−2.83 (m, 0.6 H), 2.85−2.88 (m, 0.4 H), 5.03−5.15 (m, 4 H), 5.71−5.84 (m, 1 H), 6.40−6.59 (m, 2 H), 7.19−7.23 (m, 1 H), 7.26−7.30 (m, 2 H), 7.32−7.37 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 15.2, 15.3, 30.8, 31.2, 32.6, 32.7, 36.5, 37.6, 56.0, 58.0, 77.6,78.9, 117.5 (2C), 126.6 (2C), 126.7 (2C), 127.8, 127.9, 128.6, 128.7 (2C), 128.8 (2C), 129.1, 132.3, 132.6, 135.1, 135.7, 136.7, 136.8, 170.7, 171.0; **IR** (KBr, neat) 2923, 1628, 1459, 1377, 1265, 1182, 971, 840, 749 cm^{-1}; **HRMS** (ESI) calcd for $C_{17}H_{21}NO_2$ (M + H)$^+$ requires 272.1645, found 272.1646.

1-(1-(2-Chlorophenyl)but-3-en-1-yl)-6-hydroxypiperidin-2-one (48i): (Mixture of isomers with 50:50 ratio)



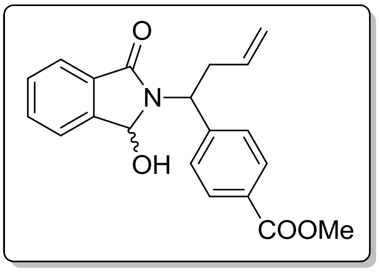
Pale yellow liquid; yield 0.61 g, 73%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 1.92−2.04 (m, 2 H), 2.23−2.28 (m, 2 H), 2.49−2.55 (m, 2 H), 2.64−2.78 (m, 2 H), 5.07−5.15 (m, 3 H), 5.67−5.77 (m, 0.5 H), 5.79−5.95 (m, 1 H), 6.01 (t, *J* = 6.4 Hz, 0.5 H), 7.18−7.45 (m, 4 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 18.1, 20.0, 29.8, 31.9, 35.2, 36.3, 39.2, 43.0, 50.6, 52.3, 106.9 (2C), 118.0, 118.5, 125.9, 126.7, 127.1, 127.8, 128.8, 129.2, 130.2, 130.4, 132.9, 134.0, 134.2, 135.0, 136.6, 139.2, 169.2, 171.5; **IR** (KBr, neat) 2929, 1654, 1441, 1387, 1260, 1194, 917, 754,699 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{18}NO_2Cl$ (M + H)$^+$ requires 280.1099, found 280.1107.

2-(But-3-en-1-yl)-3-hydroxyisoindolin-1-one (48j):



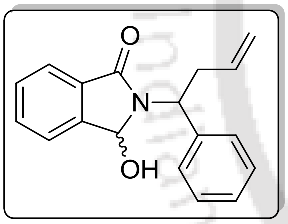
White solid, mp 62-64 °C; yield 0.55 g, 91%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 2.29−2.35 (m, 2 H), 3.23−3.30 (m, 1 H), 3.42−3.50 (m, 1 H), 4.92−5.04 (m, 3 H), 5.68−5.77 (m, 2 H), 7.38 (d, *J* = 7.2 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.50−7.57 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 32.4, 38.3, 81.5, 116.8, 122.7, 123.1, 129.3, 131.2, 131.9, 135.0, 144.0, 167.5; **IR** (KBr, neat) 2902, 1665, 1430, 1215, 1148, 909, 745 cm^{-1}; **HRMS** (ESI) calcd for $C_{12}H_{13}NO_2$ (M + H)$^+$ requires 204.1019, found 204.1009.

Methyl 4-(1-(1-hydroxy-3-oxoisoindolin-2-yl)but-3-en-1-yl)benzoate (48k): (Mixture of isomers with 50:50 ratio)



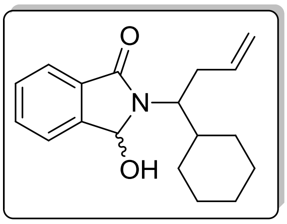
Colourless gum; yield 0.70 g, 69%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.93−3.00 (m, 1 H), 3.15−3.28 (m, 1 H), 3.80 (s, 1.5 H), 3.85 (s, 1.5 H), 4.23 (brs, 1 H), 5.02 (d, *J* = 9.6 Hz, 1 H), 5.10-5.20 (m, 1 H), 5.27 (dd, *J* = 10.0 and 6.4 Hz, 0.5 H), 5.43 (t, *J* = 8.0 Hz, 0.5 H), 5.52 (d, *J* = 11.6 Hz, 0.5 H), 5.72−5.87 (m, 1 H), 5.90 (d, *J* = 11.6 Hz, 0.5 H), 7.41−7.48 (m, 2 H), 7.53 (t, *J* = 8.8 Hz, 3 H), 7.66 (d, *J* = 7.2 Hz, 1 H), 7.81 (d, *J* = 7.2 Hz, 1 H), 7.92 (d, *J* = 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl3) δ 35.6, 36.3, 51.9, 52.0, 55.1, 55.4, 81.5, 82.2, 117.7, 117.8, 123.0 (2C), 123.1 (2C), 127.9 (2C), 128.3 (2C), 128.6 (2C), 129.1 (2C), 129.5 (4C), 129.7 (2C), 131.1, 131.3, 132.2 (2C), 134.6, 134.7, 144.0, 144.3, 166.8, 166.9, 167.3, 167.7; **IR** (KBr, neat) 1721, 1679, 1436, 1282, 1111, 1057, 920, 748 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{19}NO_4$ $(M + H)^+$ requires 338.1387, found 338.1395.

3-Hydroxy-2-(1-phenylbut-3-en-1-yl)isoindolin-1-one (48l): (Mixture of isomers with 60:40 ratio)



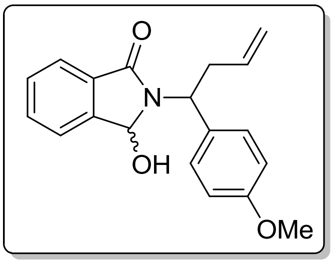
white solid, mp 78-80 °C; yield 0.60 g, 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.92−3.00 (m, 1 H), 3.12−3.17 (m, 0.6 H), 3.24−3.32 (m, 0.4 H), 3.64 (brs, 1 H), 4.99 (d, *J* = 10.0 Hz, 1 H), 5.09- 5.17 (m, 1 H), 5.45−5.53 (m, 1 H), 5.73−5.90 (m, 2 H), 7.26 (t, *J* = 5.2 Hz, 2 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.40−7.52 (m, 5 H), 7.63−7.66 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 36.1, 36.7, 55.3, 56.0, 81.6, 81.7, 117.4, 117.5, 123.0, 123.2, 127.4, 127.8, 127.9 (2C), 128.4 (4C), 128.6 (2C), 129.4 (2C), 131.2, 131.6, 132.1, 132.2, 135.3, 135.4, 138.9 (2C), 141.0 (2C), 143.9, 144.1, 167.4, 167.8; **IR** (KBr, neat) 1665, 1407, 1208, 1104, 1057, 746 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{17}NO_2$ $(M + H)^+$ requires 280.1332, found 280.1334.

2-(1-Cyclohexylbut-3-en-1-yl)-3-hydroxyisoindolin-1-one (48m): (Mixture of isomers with 60:40 ratio)



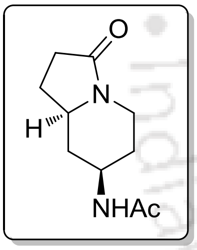
Colourless liquid; yield 0.59 g, 68%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86−1.28 (m, 6 H), 1.49−1.77 (m, 4 H), 1.93−1.95 (m, 1 H), 2.60−2.73 (m, 2 H), 3.73−3.76 (m, 0.4 H), 3.86−3.89 (m, 0.6 H), 4.93 (d, *J* = 8.4 Hz 1 H), 5.01-5.10 (m, 1 H), 5.67−5.85 (m, 2 H), 7.47−7.56 (m, 3 H), 7.57−7.76 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.6, 25.8, 25.9, 26.1, 26.2, 26.5, 28.0 (2C), 29.0 (2C), 33.7, 33.9, 39.1, 39.5, 56.8, 57.6, 82.1, 82.8, 116.6, 116.9, 123.0 (2C), 129.4 (2C), 131.5, 131.7, 131.8 (2C), 133.8 (2C), 135.0, 135.4, 136.3, 136.5, 167.8, 168.1; **IR** (KBr, neat) 2925, 2852, 1672, 1448, 1208, 1161, 914, 747 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{23}NO_2$ $(M + H)^+$ requires 286.1802, found 286.1817.

3-Hydroxy-2-(1-(4-methoxyphenyl)but-3-en-1-yl)isoindolin-1-one (48n): (Mixture of isomers with 60:40 ratio)



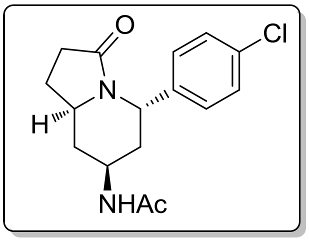
Colourless liquid; yield 0.59 g, 64%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.90–2.96 (m, 1 H), 3.08–3.16 (m, 1 H), 3.77 (s, 1.2 H), 3.79 (s, 1.8 H), 5.00 (d, *J* = 9.6 Hz, 1 H), 5.10–5.24 (m, 2 H), 5.45–5.51 (m, 1 H), 5.72–5.89 (m, 1 H), 6.79–6.89 (m, 2 H), 7.24–7.34 (m, 2 H), 7.39–7.53 (m, 3.5 H), 7.70 (d, *J* = 7.2 Hz, 0.5 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 37.1, 40.7, 52.9, 54.7, 55.3 (2C), 81.5, 81.6, 113.8 (2C), 114.0 (2C), 118.0, 118.2, 123.1, 123.2, 127.2 (2C), 127.7 (2C), 128.2, 129.2, 129.6, 129.7, 130.7, 131.1, 131.2, 131.5, 132.1, 132.2, 134.7, 135.4, 135.6, 135.8, 158.9, 159.1, 169.1 (2C); **IR** (KBr, neat) 1666, 1509, 1405, 1244, 1172, 1031, 745 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{19}NO_3(M + H)^+$ requires 310.1438, found 310.1438.

***N*-((7*R**,8a*R**)-3-Oxooctahydroindolizin-7-yl)acetamide (49a):**



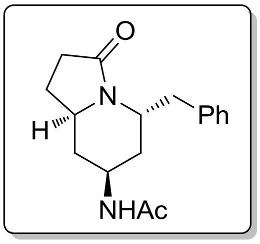
Colourless liquid; yield 80 mg, 81%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.04 (q, *J* = 12.4 Hz, 1 H), 1.23 (dq, *J* = 12.4 and 5.2 Hz, 1 H), 1.55–1.65 (m, 1 H), 1.97 (s, 3 H), 2.19–2.29 (m, 3 H), 2.36–2.43 (m, 2 H), 2.75 (dt, *J* = 13.2 and 2.8 Hz, 1 H), 3.54–3.62 (m, 1 H), 3.94–4.02 (m, 1 H), 4.15 (dd, *J* = 13.2 and 3.2 Hz, 1 H), 6.02 (d, *J* = 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 22.8, 24.3, 30.0, 30.4, 38.1, 39.4, 45.9, 55.7, 169.7, 173.3; **IR** (KBr, neat) 2936, 2887, 1658, 1559, 1451, 1376, 1259, 1150, 738, 609 cm^{-1}; **HRMS** (ESI) calcd for $C_{10}H_{16}N_2O_2$ $(M + H)^+$ requires 197.1285, found 197.1286.

***N*-((5*S**,7*S**,8a*R**)-5-(4-Chlorophenyl)-3-oxooctahydroindolizin-7-yl)acetamide (49b):**



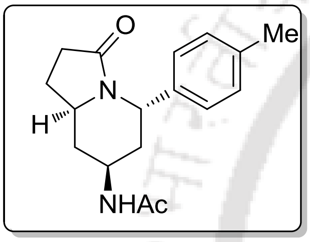
White solid, mp 76-77 °C; yield 110 mg, 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.13 (q, *J* = 12.0 Hz, 1 H), 1.56–1.71 (m, 2 H), 1.97 (s, 3 H), 2.10-2.16 (m, 1 H), 2.22–2.32 (m, 1 H), 2.48-2.54 (m, 2 H), 2.58-2.64 (m, 1 H), 3.59–3.66 (m, 1 H), 3.99–4.08 (m, 1 H), 5.50 (d, *J* = 5.2 Hz, 1 H), 5.68 (d, *J* = 7.2 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.1 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 23.0, 24.4, 29.9, 33.3, 39.5, 42.7, 49.2, 52.8, 127.8 (2C), 128.9 (2C), 133.0, 136.7, 169.8, 174.1; **IR** (KBr, neat) 3066, 2938, 1667, 1550, 1419, 1372, 1288, 1097, 1012, 839, 735, 607 cm^{-1}; **HRMS** (ESI) calcd for $C_{16}H_{19}N_2O_2Cl$ $(M + H)^+$ requires 307.1208, found 307.1208.

N-((5*R**,7*S**,8a*R**)-5-Benzyl-3-oxooctahydroindolizin-7-yl)acetamide (49c):



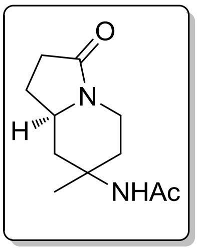
White solid, mp 91-93 °C; yield 109 mg, 76%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.00 (q, *J* = 12.8 Hz, 1 H), 1.24 (dq, *J* = 12.8 and 6.0 Hz, 1 H), 1.52−1.61 (m, 1 H), 1.84 (dd, *J* = 13.2 and 2.0 Hz, 1 H), 1.96 (s, 3 H), 2.17−2.33 (m, 4 H), 2.84 (d, *J* = 8.0 Hz, 2 H), 3.78−3.85 (m, 1 H), 4.27−4.35 (m, 1 H), 4.50 (dd, *J* = 13.6 and 7.6 Hz, 1 H), 5.76 (d, *J* = 7.6 Hz, 1 H), 7.19−7.31 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 22.9, 24.6, 30.1, 32.0, 36.7, 39.8, 42.1, 49.0, 52.4, 126.4, 128.3 (2C), 129.0 (2C), 137.5, 169.7, 173.2; **IR** (KBr, neat) 3064, 2944, 1660, 1552, 1421, 1372, 1284, 1178, 751, 702 cm^{-1}; **HRMS** (ESI) calcd for $C_{17}H_{22}N_2O_2$ $(M + H)^+$ requires 287.1754, found 287.1762.

N-((5S*,7S*,8aR*)-3-Oxo-5-(*p*-tolyl)octahydroindolizin-7-yl)acetamide (49d):



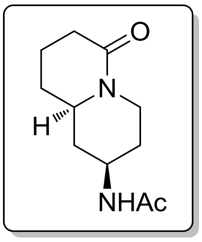
White solid, mp 78-80 °C; yield 99 mg, 69%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (q, *J* = 12.0 Hz, 1 H), 1.55−1.67 (m, 2 H), 1.96 (s, 3 H), 2.11-2.20 (m, 1 H), 2.21−2.28 (m, 1 H), 2.31 (s, 3 H), 2.442−2.53 (m, 2 H), 2.55-2.61 (m, 1 H), 3.62−3.69 (m, 1 H), 4.00−4.11 (m, 1 H), 5.50 (d, *J* = 5.2 Hz, 1 H), 5.92 (d, *J* = 7.2 Hz, 1 H), 7.15 (s, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0, 23.2, 24.5, 30.2, 33.5, 40.0, 42.9, 49.5, 52.8, 126.3 (2C), 129.6 (2C), 135.0, 136.9, 169.8, 174.1; **IR** (KBr, neat) 3058, 2932, 1664, 1550, 1420, 1372, 1288, 1187, 822, 735, 602 cm^{-1}; **HRMS** (ESI) calcd for $C_{17}H_{22}N_2O_2$ $(M + H)^+$ requires 287.1754, found 287.1754.

N-((7*S**,8a*S**)-7-Methyl-3-oxooctahydroindolizin-7-yl)acetamide and N-((7*R**,8a*S**)-7-methyl-3-oxooctahydroindolizin-7-yl)acetamide (49e): (Mixture of isomers with 60:40 ratio)



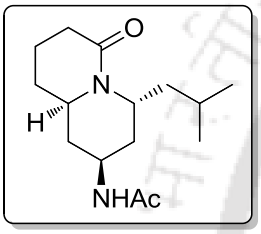
Colourless liquid; yield 90 mg, 86%; **^{1}H NMR** (400 MHz, CDCl3) δ 1.07 (t, *J* = 12.0 Hz, 1 H), 1.19−1.37 (m, 1 H), 1.39 (s, 1.8 H), 1.49 (s, 1.2 H), 1.53−1.63 (m, 1 H), 1.72 (dq, *J* = 13.2 and 5.6 Hz, 1 H), 1.85-1.90 (m, 0.4 H), 1.93 (s, 1.2 H), 1.98 (s, 1.8 H), 2.07-2.12 (m, 0.6 H), 2.16−2.27 (m, 1 H), 2.34−2.39 (m, 2 H), 2.73−2.78 (m, 0.4 H), 2.80−2.91 (m, 0.6 H), 3.58−3.67 (m, 1 H), 3.97 (dd, *J* = 13.6 and 4.0 Hz, 0.6 H), 4.05 (dd, *J* = 13.2 and 3.6 Hz, 0.4 H), 5.90 (brs, 0.4 H), 6.07 (br s, 0.6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.4, 23.5, 23.6, 24.3, 24.6, 26.9, 29.8, 29.9, 34.2, 34.3, 35.1, 35.7, 42.0, 42.7, 51.6, 51.9, 52.2, 52.9, 169.9, 170.6, 173.0, 173.1; **IR** (KBr, neat) 2930, 2875, 1673, 1549, 1455, 1375, 1277, 1170, 751, 606 cm^{-1}; **HRMS** (ESI) calcd for $C_{11}H_{18}N_2O_2$ $(M + H)^+$ requires 211.1441, found 211.1447.

N-((2*R**,9a*R**)-6-Oxooctahydro-1*H*-quinolizin-2-yl)acetamide (49f):



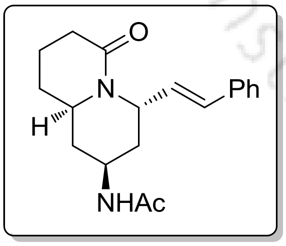
White solid, mp 101-103 °C; yield 97 mg, 92%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.14 (q, *J* = 12.0 Hz, 1 H), 1.24 (dq, *J* = 12.8 and 4.4 Hz, 1 H), 1.45−1.54 (m, 1 H), 1.64−1.74 (m, 1 H), 1.77−1.86 (m, 1 H), 1.92-1.96 (m, 1 H), 1.97 (s, 3 H), 2.00−2.04 (m, 1 H), 2.07-2.12 (m, 1 H), 2.24−2.33 (m, 1 H), 2.41 (dt, *J* = 17.2 and 5.2 Hz, 1 H), 2.53 (dt, *J* = 13.2 and 2.4 Hz, 1 H), 3.33−3.40 (m, 1 H), 3.93−4.04 (m, 1 H), 4.78−4.84 (m, 1 H), 6.18 (d, *J* = 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.8, 22.8, 29.6, 31.1, 32.6, 39.7, 40.6, 46.3, 54.8, 169.2, 169.7; **IR** (KBr, neat) 3079, 2947, 1661, 1451, 1373, 1268, 1162, 1120, 976, 737, 608 cm^{-1}; **HRMS** (ESI) calcd for $C_{11}H_{18}N_2O_2$ $(M + H)^+$ requires 211.1441, found 211.1441.

N-((2*S**,4R*,9a*R**)-4-Isobutyl-6-oxooctahydro-1*H*-quinolizin-2-yl)acetamide (49g):



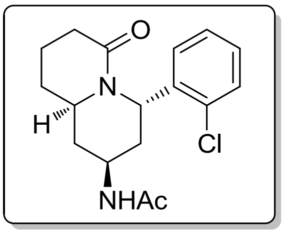
White solid, mp 96-98 °C; yield 117 mg, 88%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.04 (q, *J* = 12.0 Hz, 1 H), 1.31-1.39 (m, 1 H), 1.42-1.50 (m, 1 H), 1.53−1.65 (m, 2 H), 1.74-1.82 (m, 2 H), 1.97 (s, 3 H), 2.08-2.14 (m, 2 H), 2.24−2.33 (m, 2 H), 2.41 (dt, *J* = 17.2 and 4.8 Hz, 2 H), 3.49-3.54 (m, 1 H), 4.15−4.24 (m, 1 H), 5.07-5.12 (m, 1 H), 6.12 (d, *J* = 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.7, 22.7 (2C), 23.2, 25.0, 30.1, 33.3, 34.5, 39.4, 40.8, 42.3, 46.2, 49.6, 169.4, 169.8; **IR** (KBr, neat) 3073, 2952, 2869, 1618, 1554, 1463, 1367, 1273, 1172, 1127, 973, 736, 608 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{26}N_2O_2$ $(M + H)^+$ requires 267.2067, found 267.2073.

N-((2*S**,4*S**,9a*R**)-6-Oxo-4-((*E*)-styryl)octahydro-1*H*-quinolizin-2-yl)acetamide (49h):



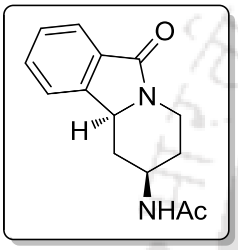
White solid, mp 126-128 °C; yield 111 mg, 71%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.15 (q, *J* = 12.0 Hz, 1 H), 1.42−1.58 (m, 2 H), 1.66-1.72 (m, 1 H), 1.78-1.85 (m, 1 H), 1.98 (s, 3 H), 2.00-2.12 (m, 1 H), 2.16-2.25 (m, 1 H), 2.31−2.40 (m, 1 H), 2.45−2.58 (m, 2 H), 3.56−3.63 (m, 1 H), 4.18−4.25 (m, 1 H), 5.77 (brs, 1 H), 5.90 (d, *J* = 7.6 Hz, 1 H), 6.14 (dd, *J* = 16.0 and 4.4 Hz, 1 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 7.23 (d, *J* = 7.2 Hz, 1 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.37 (d, *J* = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.1, 23.3, 30.3, 33.2, 34.9, 40.5, 43.1, 49.4, 51.1, 126.5 (2C), 127.2, 127.8, 128.6 (2C), 132.2, 136.4, 169.9 (2C); **IR** (KBr, neat) 3058, 2930, 2857,1702, 1619, 1551, 1449, 1370, 1263, 1175, 1124, 970, 757, 700, 608 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{24}N_2O_2$ $(M + H)^+$ requires 313.1911, found 313.1911.

N-((2S^*,4S^*,9aR^*)-4-(2-Chlorophenyl)-6-oxooctahydro-1H-quinolizin-2-yl)acetamide (49i):



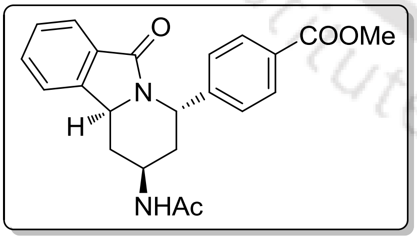
White solid, mp 88-90 °C; yield 128 mg, 80%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.23 (q, J = 12.0 Hz, 1 H), 1.51-1.60 (m, 1 H), 1.69−1.75 (m, 1 H), 1.78-1.82 (m, 1 H), 1.89 (s, 3 H), 2.01-2.08 (m, 1 H), 2.14-2.18 (m, 1 H), 2.38−2.53 (m, 4 H), 3.79−3.84 (m, 1 H), 4.02−4.07 (m, 1 H), 6.14 (d, J = 6.0 Hz 1 H), 6.28 (brs, 1 H), 7.15−7.23 (m, 2 H), 7.29−7.36 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.4, 23.3, 30.7, 33.2, 34.1, 40.0, 43.0, 50.3, 53.9, 127.0, 127.5, 128.5, 130.8, 133.1, 138.5, 170.0, 170.2; **IR** (KBr, neat) 3067, 2947, 2867, 1627, 1552, 1439, 1343, 1309, 1276, 1134, 1038, 974,762, 737, 605 cm^{-1}; **HRMS** (ESI) calcd for $C_{17}H_{21}N_2O_2Cl$ (M + H)$^+$ requires 321.1364, found 321.1364.

N-((2R^*,10bS^*)-6-Oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl)acetamide (49j):



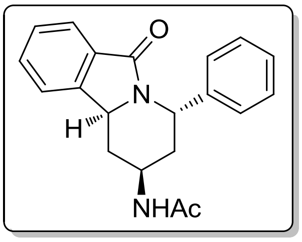
White solid, mp 111−113 °C; yield 95 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.85 (q, J = 12.0 Hz, 1 H), 1.18−1.33 (m, 1 H), 2.03 (s, 3 H), 2.15 (d, J = 7.6 Hz,1 H), 2.61 (d, J = 7.6 Hz,1 H), 3.03-3.10 (m, 1 H), 4.19−4.25 (m, 1 H), 4.37-4.47 (m, 2 H), 6.29 (d, J= 7.6 Hz, 1 H), 7.36 (d, J= 7.2 Hz, 1 H), 7.44 (t, J = 7.2 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.77 (d, J = 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 23.3, 31.4, 37.7, 37.8, 46.1, 57.6, 121.8, 123.5, 128.4, 131.6, 131.7, 144.9, 166.3, 170.0; **IR** (KBr, neat) 3068, 2929, 2863, 1669, 1552,1431, 1371, 1288, 1099, 971, 738, 612 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{16}N_2O_2$ (M + H)$^+$ requires 245.1285, found 245.1285.

Methyl 4-((2R^*,4S^*,10bS^*)-2-acetamido-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-4-yl)benzoate (49k):



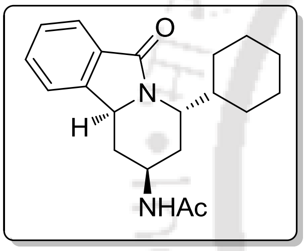
White solid, mp 135-137 °C; yield 136 mg, 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.02 (q, J = 12.0 Hz, 1 H), 1.71 (dq, J = 12.8 and 5.6 Hz, 1 H), 2.02 (s, 3 H), 2.58-2.64 (m, 1 H), 2.74-2.80 (m, 1 H), 3.90 (s, 3 H), 4.25−4.32 (m, 1 H), 4.45 (dd, J = 11.6 and 3.6 Hz, 1 H), 5.82-5.90 (m, 2 H), 7.34−7.41 (m, 3 H), 7.49−7.59 (m, 2 H), 7.91 (d, J = 7.2 Hz, 1 H), 8.01 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 23.4, 33.9, 37.9, 43.4, 49.3, 52.3, 55.1, 122.2, 124.1, 126.7 (2C), 128.7, 129.4, 130.3 (2C), 131.3, 132.1, 144.0, 145.2, 166.8, 167.3, 170.1; **IR** (KBr, neat) 2950, 2723, 1720, 1678, 1549, 1413, 1372, 1282, 1112, 1018, 963, 736, 697, 607 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{22}N_2O_4$ (M + H)$^+$ requires 379.1652, found 379.1659.

N-((2*R**,4*S**,10b*S**)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl)acetamide (49l):



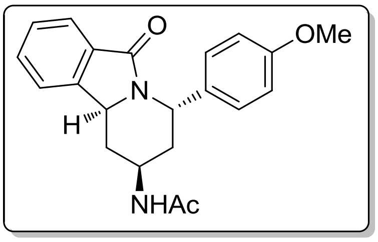
White solid, mp 128-130 °C; yield 112 mg, 70%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 0.99 (q, *J* = 12.0 Hz, 1 H), 1.63-1.72 (m, 1 H), 2.02 (s, 3 H), 2.61 (d, *J* = 12.0 Hz,1 H), 2.75 (d, *J* = 12.0 Hz, 1 H), 4.32−4.39 (m, 1 H), 4.47 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 5.74 (d, *J* = 7.6 Hz, 1 H), 5.87 (d, *J* = 5.6 Hz, 1 H), 7.23−7.26 (m, 1 H), 7.32−7.36 (m, 5 H), 7.48-7.57 (m, 2 H), 7.90 (d, *J* = 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 23.4, 33.8, 38.0, 43.2, 49.2, 55.0, 122.1, 123.9, 126.5 (2C), 127.5, 128.6, 129.0 (2C), 131.4, 132.0, 138.5, 145.3, 167.3, 170.1; **IR** (KBr, neat) 3058, 2930, 1678, 1549, 1413, 1374, 1279, 1116, 962, 738, 699, 606 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{20}N_2O_2$ $(M + H)^+$ requires 321.1598, found 321.1598.

N-((2*R**,4*S**,10b*S**)-4-Cyclohexyl-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl)acetamide (49m):



White solid, mp 89-91 °C; yield 138 mg, 85%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 0.76 (q, *J* = 12.0 Hz, 1 H), 0.96−1.14 (m, 4 H), 1.17-1.27 (m, 1 H), 1.45-1.50 (m, 1 H), 1.65−1.77 (m, 5 H), 1.84-1.89 (m, 1 H), 2.04 (s, 3 H), 2.12-2.17 (m, 1 H), 2.61-2.68 (m, 1 H), 4.19 (dd, *J* = 10.8 and 5.6 Hz, 1 H), 4.32−4.40 (m, 1 H), 4.44 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 5.94 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 7.2 Hz, 1 H), 7.43-7.55 (m, 2 H), 7.78 (d, *J* = 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 23.4, 25.9 (2C), 26.1, 29.7, 30.4, 32.0, 38.0, 38.3, 42.7, 52.7, 54.8, 121.9, 123.7, 128.4, 131.6 (2C), 145.2, 167.1, 170.1; **IR** (KBr, neat) 3068, 2927, 2851, 1671, 1549, 1417, 1370, 1232, 1110, 762, 737, 604 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{26}N_2O_2$ $(M + H)^+$ requires 327.2067, found 327.2067.

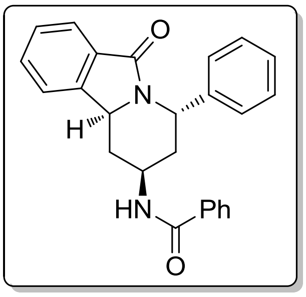
N-((2*R**,4*S**,10b*S**)-4-(4-Methoxyphenyl)-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl)acetamide (49n):



White solid, mp 119-121 °C; yield 115 mg, 66%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 0.95 (q, *J* = 12.0 Hz, 1 H), 1.57-1.66 (m, 1 H), 2.03 (s, 3 H), 2.55-2.60 (m, 1 H), 2.65-2.70 (m, 1 H), 3.77 (s, 3 H), 4.33−4.40 (m, 1 H), 4.42 (dd, *J* = 12.4 and 4.0 Hz, 1 H), 5.79 (d, *J* = 5.6 Hz, 1 H), 6.13 (d, *J* = 8.0 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 7.34 (d, *J* = 7.2 Hz, 1 H), 7.46−7.55 (m, 2 H), 7.87 (d, *J* = 7.2 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 23.3, 33.8, 37.9, 43.2, 48.7, 54.9, 55.3, 114.3 (2C), 122.1, 123.8, 127.7 (2C), 128.5, 130.5, 131.5, 131.9, 145.2, 158.8, 167.1, 170.1; **IR** (KBr, neat)

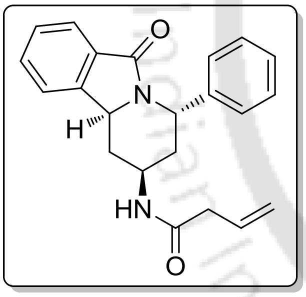
3058, 2932, 2836, 1674, 1512, 1415, 1374, 1252, 1181, 1033, 835, 737, 607 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{22}N_2O_3$ $(M + H)^+$ requires 351.1703, found 351.1703.

N-((2R*,4S*,10bS*)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl)benzamide (49o):



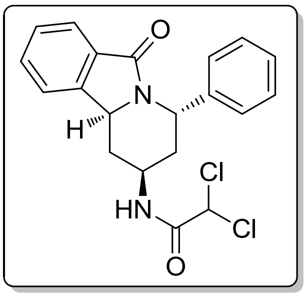
White solid, mp 140-142 °C; yield 124 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.07 (q, *J* = 12.0 Hz, 1 H), 1.71-1.81(m, 1 H), 2.63-2.68 (m, 1 H), 2.81-2.86 (m, 1 H), 4.50 (dd, *J* = 12.0 and 3.6 Hz,1 H), 4.56−4.62 (m, 1 H), 5.88 (d, *J* = 5.6 Hz, 1 H), 6.83 (d, *J* = 7.6 Hz, 1 H), 7.24−7.27 (m, 1 H), 7.31−7.35 (m, 5 H), 7.40-7.47 (m, 3 H), 7.48-7.50 (m, 3 H), 7.81 (d, *J* = 7.6 Hz, 1 H), 7.92 (d, *J* = 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 34.0, 38.2, 44.0, 49.4, 55.1, 122.2, 124.2, 126.7 (2C), 127.3 (2C), 127.6, 128.7, 128.8 (2C), 129.2 (2C), 131.7, 131.9, 132.0, 134.3, 138.7, 145.4, 167.3, 167.4; **IR** (KBr, neat) 2927, 1676, 1536, 1412, 1325, 1226, 1153, 1028, 908, 733, 695, 606 cm^{-1}; **HRMS** (ESI) calcd for $C_{25}H_{22}N_2O_2$ $(M + H)^+$ requires 383.1754, found 383.1757.

N-((2R*,4S*,10bS*)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl)but-3-enamide (49p):



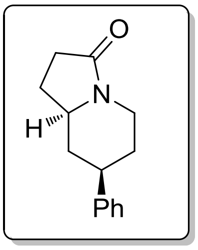
White solid, mp 101-103 °C; yield 135 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.94 (q, *J* = 12.0 Hz, 1 H), 1.60 (dq, *J* = 13.2 and 5.6 Hz,1 H), 2.48-2.53 (m, 1 H), 2.66-2.70 (m, 1 H), 2.97 (d, *J* = 7.2 Hz, 2 H), 4.23−4.31 (m, 1 H), 4.38 (dd, *J* = 12.0 and 2.8 Hz, 1 H), 5.12−5.17 (m, 2 H), 5.79 (d, *J* = 4.8 Hz, 1 H), 5.81−5.92 (m, 2 H), 7.16−7.20 (m, 1 H), 7.24 (brs, 5 H), 7.40-7.49 (m, 2 H), 7.83 (d, *J* = 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 33.8, 37.9, 41.7, 43.5, 49.2, 55.0, 119.7, 122.1, 124.1, 126.6 (2C), 127.5, 128.6, 129.1 (2C), 131.4, 131.6, 131.9, 138.7, 145.3, 167.2, 170.6; **IR** (KBr, neat) 3058, 2925, 2854, 1685, 1546, 1468, 1412, 1347, 1301, 1226, 1096, 1030, 920, 800, 748,696, 610 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{22}N_2O_2$ $(M + H)^+$ requires 347.1754, found 347.1758.

2,2-Dichloro-N-((2R*,4S*,10bS*)-6-oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl)acetamide (49q):



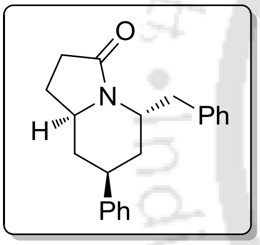
White solid, mp 115-117 °C; yield 142 mg, 73%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.13 (q, *J* = 12.0 Hz, 1 H), 1.77 (dq, *J* = 13.2 and 6.0 Hz,1 H), 2.57-2.61 (m, 1 H), 2.76-2.81 (m, 1 H), 4.28−4.36 (m, 1 H), 4.47 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 5.86 (d, *J* = 5.2 Hz, 1 H), 6.01 (s, 1 H), 7.24 (d, *J* = 7.2 Hz, 1 H), 7.28−7.36 (m, 6 H), 7.46−7.59 (m, 2 H), 7.89 (d, *J* = 7.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 33.4, 37.3, 44.7, 49.2, 54.8, 66.5, 122.2, 124.3, 126.5 (2C), 127.6, 128.8, 129.2 (2C), 131.6, 132.1, 138.3, 145.0, 164.1, 167.3; **IR** (KBr, neat) 2925, 1673, 1412, 1267, 1210, 1090, 1018, 911, 746, 697 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{18}N_2O_2Cl_2$ (M + H)$^+$ requires 398.0818, found 398.0814.

(7*S**,8a*S**)-7-Phenylhexahydroindolizin-3(2*H*)-one (51a):



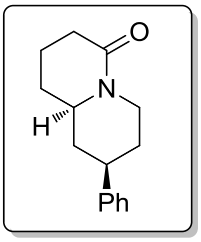
Pale yellow liquid; yield 79 mg, 73%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (q, *J* = 12.0 Hz, 1 H), 1.51−1.70 (m, 2 H), 1.85-1.92 (m, 1 H), 2.04-2.10 (m, 1 H), 2.21−2.30 (m, 1 H), 2.38−2.44 (m, 2 H), 2.70−2.83 (m, 2 H), 3.56−3.63 (m, 1 H), 4.26 (dd, *J* = 13.6 and 4.8 Hz, 1 H), 7.18−7.24 (m, 3 H), 7.27−7.35 (m, 2 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 25.2, 30.4, 32.0, 40.0, 41.0, 42.0, 57.3, 126.6, 126.7 (2C), 128.6 (2C), 145.0, 173.6; **IR** (KBr, neat) 3027, 2930, 2853, 1686, 1452, 1375, 1267, 1188, 759, 701 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{17}NO$ (M + H)$^+$ requires 216.1383, found 216.1383.

(5*S**,7*S**,8a*R**)-5-Benzyl-7-phenylhexahydroindolizin-3(2*H*)-one (51b):



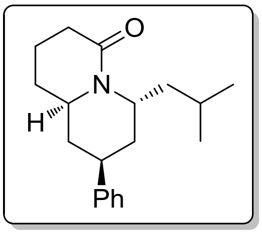
Pale yellow solid, mp 72-74 °C; yield 116 mg, 76%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (q, *J* = 12.0 Hz, 1 H), 1.54−1.69 (m, 2 H), 1.75-1.81 (m, 1 H), 2.08-2.14 (m, 1 H), 2.21−2.30 (m, 1 H), 2.33−2.44 (m, 2 H), 2.87−2.98 (m, 2 H), 3.03-3.10 (m, 1 H), 3.84−3.90 (m, 1 H), 4.56-4.62 (m, 1 H), 7.16−7.23 (m, 4 H), 7.25−7.32 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.5, 30.6, 33.6, 36.7, 36.8, 41.1, 49.6, 53.9, 126.7, 126.8 (2C), 128.7, 128.8 (4C), 129.3 (2C), 138.3, 145.0, 173.7; **IR** (KBr, neat) 2930, 1660, 1492, 1388, 1264, 1103, 753, 695 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{23}NO$ (M + H)$^+$ requires 306.1852, found 306.1853.

(8*R**,9a*R**)-8-Phenylhexahydro-1*H*-quinolizin-4(6*H*)-one (51c):



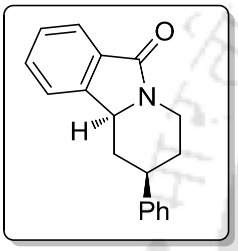
Colourless liquid; yield 96 mg, 84%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.48−1.55 (m, 1 H), 1.56−1.59 (m, 1 H), 1.60−1.65 (m, 1 H), 1.66−1.74 (m, 1 H), 1.81−1.94 (m, 3 H), 1.99−2.04 (m, 1 H), 2.31−2.48 (m, 2 H), 2.58 (dt, *J* = 13.2 and 3.2 Hz, 1 H), 2.72−2.80 (m, 1 H), 3.36−3.43 (m, 1 H), 4.89−4.94 (m, 1 H), 7.18−7.23 (m, 3 H), 7.27−7.32 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.4, 30.4, 32.7, 33.1, 41.7, 42.3, 42.7, 56.7, 126.6, 126.8 (2C), 128.7 (2C), 145.2, 169.5; **IR** (KBr, neat) 2933, 2859, 1629, 1452, 1341, 1268, 1169, 1088, 756 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{19}NO$ (M + H)+ requires 230.1539, found 230.1546.

(6S^*,8R^*,9aS^*)-6-Isobutyl-8-phenylhexahydro-1*H*-quinolizin-4(6*H*)-one (51d):



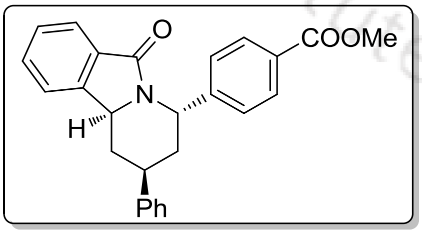
Pale yellow liquid; yield 101 mg, 71%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.94 (q, *J* = 12.0 Hz, 1 H), 0.95 (d, *J* = 6.4 Hz, 3 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 1.39−1.57 (m, 3 H), 1.60−1.69 (m, 2 H), 1.77−1.85 (m, 2 H), 1.86−1.92 (m, 1 H), 1.97−2.04 (m, 1 H), 2.32−2.46 (m, 3 H), 2.96−3.04 (m, 1 H), 3.56−3.63 (m, 1 H), 5.12−5.18 (m, 1 H), 7.19−7.23 (m, 3 H), 7.29−7.33 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.9, 22.8, 23.1, 25.3, 30.5, 33.3, 35.6, 36.8, 39.3, 41.9, 46.6, 51.1, 126.5, 126.8 (2C), 128.6 (2C), 145.3, 169.7; **IR** (KBr, neat) 2952, 2868, 1636, 1459, 1416, 1332, 1274, 1171, 1017, 758, 700 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{27}NO$ $(M + H)^+$ requires 286.2165, found 286.2169.

(2R^*,10bS^*)-2-Phenyl-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one (51e):



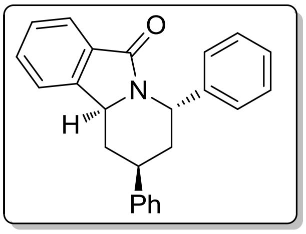
Pale yellow solid, mp 86-88 °C; yield 89 mg, 68%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.35 (q, *J* = 12.0 Hz, 1 H), 1.64 (dq, *J* = 12.4 and 4.8 Hz, 1 H), 1.96-2.06 (m, 1 H), 2.47-2.58 (m, 1 H), 2.96-3.04 (m, 1 H), 3.16 (dt, *J* = 13.2 and 3.2 Hz, 1 H), 4.46 (dd, *J* = 11.6 and 3.2 Hz,1 H), 4.60 (dd, *J* = 13.2 and 3.6 Hz, 1 H), 7.18 (d, *J* = 6.8 Hz, 2 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.39 (d, *J* = 6.8 Hz, 1 H), 7.44−7.54 (m, 2 H), 7.87 (d, *J* = 7.2 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 32.9, 38.9, 39.3, 42.0, 58.8, 121.7, 123.8, 126.8 (2C), 128.3 (2C), 128.7 (2C), 131.2, 132.4, 144.6, 145.3, 166.2; **IR** (KBr, neat) 3026, 2920, 2859, 1688, 1451, 1359, 1289, 1240 1146, 1094, 973, 760, 735, 692 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{17}NO$ $(M + H)^+$ requires 264.1383, found 264.1383.

Methyl 4-((2R^*,4S^*,10bS^*)-6-oxo-2-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-4-yl)benzoate (51f):



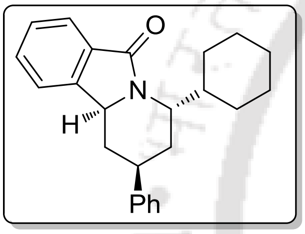
Pale yellow solid, mp 131-133 °C; yield 143 mg, 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (q, *J* = 12.0 Hz, 1 H), 2.12 (dq, *J* = 13.2 and 5.6 Hz, 1 H), 2.44-2.50 (m, 1 H), 2.68-2.74 (m, 1 H), 2.97-3.04 (m, 1 H), 3.91 (s, 3 H), 4.59 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 5.98 (d, *J* = 5.2 Hz, 1 H), 7.17 (d, *J* = 7.2 Hz, 2 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.37−7.45 (m, 3 H), 7.51−7.58 (m, 2 H), 7.97 (d, *J* = 7.2 Hz, 1 H), 8.03 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 35.6, 37.4, 38.8, 49.8, 52.1, 56.1, 121.9, 124.0, 126.5 (2C), 126.6 (2C), 126.8, 128.4, 128.7 (2C), 128.9, 130.0 (2C), 131.5, 131.6, 144.0, 144.8, 145.5, 166.6, 167.2; **IR** (KBr, neat) 3055, 2951, 2924, 1720, 1692, 1612, 1453, 1280, 1111, 1018, 930, 856, 736, 697 cm^{-1}; **HRMS** (ESI) calcd for $C_{26}H_{23}NO_3$ $(M + H)^+$ requires 398.1751, found 398.1752.

(2R^*,4S^*,10bS^*)-2,4-Diphenyl-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one (51g):



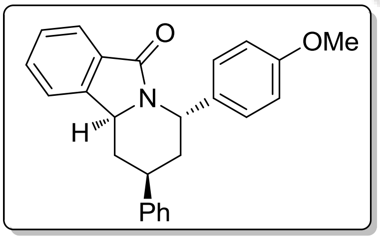
Pale yellow liquid; yield 105 mg, 62%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 1.46 (q, J = 12.0 Hz, 1 H), 2.08 (ddd, J = 5.6, 13.2 and 18.8 Hz, 1 H), 2.44 (d, J = 12.4 Hz, 1 H), 2.69 (d, J = 12.4 Hz, 1 H), 3.06-3.12 (m, 1 H), 4.58 (dd, J = 3.6 and 12.0 Hz,1 H), 5.95 (d, J = 5.2 Hz, 1 H), 7.18 (d, J = 7.6 Hz, 2 H), 7.23−7.43 (m, 8 H), 7.49−7.58(m,3 H), 7.97 (d, J = 7.2 Hz,1 H); **^{13}C NMR** (75 MHz, CDCl$_3$) δ 35.6, 37.4, 39.0, 49.8,56.0, 121.9, 124.1, 126.2, 126.5 (2C), 126.8 (2), 126.9, 127.1, 128.4, 128.8 (2C), 128.9 (2C), 129.0, 131.6, 139.4, 144.5, 167.2; **IR** (KBr, neat) 3057, 3028, 2923, 1699, 1616, 1494, 1468, 1409, 1234, 1161, 1029, 934, 764, 700 cm^{-1}; **HRMS** (ESI) calcd for C$_{24}$H$_{21}$NO (M + H)$^+$ requires 340.1696, found 340.1697.

(2R^*,4S^*,10bS^*)-4-Cyclohexyl-2-phenyl-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one (51h):



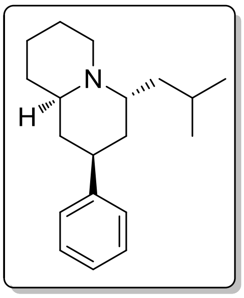
White solid, mp 76-78 °C; yield 122 mg, 71%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 1.05−1.21 (m, 4 H), 1.33 (q, J = 12.0 Hz, 1 H), 1.60−1.91 (m, 8 H), 2.18-2.24 (m, 1 H), 2.45-2.52 (m, 1 H), 3.13-3.21 (m, 1 H), 4.32 (dd, J = 10.0 and 5.2 Hz, 1 H), 4.53 (d, J = 12.0 and 3.6 Hz, 1 H), 7.19−7.24 (m, 3 H), 7.31 (t, J = 7.8 Hz, 1 H), 7.39 (d, J = 7.2 Hz, 1 H), 7.45−7.54 (m, 3 H), 7.88 (d, J = 7.6 Hz, 1 H); **^{13}C NMR** (75 MHz, CDCl$_3$) δ 25.9, 26.1, 29.7, 30.3, 33.3, 37.3, 37.8, 38.8, 39.2, 52.9, 55.8, 121.6, 123.9, 124.1, 126.8 (2C), 128.2, 128.7 (2C), 131.1, 131.5, 144.7, 145.5, 166.8; **IR** (KBr, neat) 3029, 2926, 2851, 1696, 1616, 1449, 1411, 1265, 1164, 1095, 1017, 950, 760, 737, 696 cm^{-1}; **HRMS** (ESI) calcd for C$_{24}$H$_{27}$NO (M + H)$^+$ requires 346.2165, found 346.2164.

(2R^*,4S^*,10bS^*)-4-(4-Methoxyphenyl)-2-phenyl-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one (51i):



White solid, mp 71-73 °C; yield 100 mg, 54%; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 1.43 (q, J = 12.0 Hz, 1 H), 2.02-2.10 (m, 1 H), 2.42-2.47 (m, 1 H), 2.63-2.68 (m, 1 H), 3.08-3.15 (m, 1 H), 3.80 (s, 3 H), 4.56 (dd, J = 12.0 and 4.0 Hz, 1 H), 5.90 (d, J = 4.4 Hz, 1 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.19−7.26 (m, 3 H), 7.33 (t, J = 7.6 Hz, 2 H), 7.40 (t, J = 7.6 Hz, 2 H), 7.49−7.56 (m, 3 H), 7.96 (d, J = 6.8 Hz, 1 H); **^{13}C NMR** (75 MHz, CDCl$_3$) δ 35.5, 37.4, 39.1, 49.3, 55.3, 55.9, 114.2 (2C), 121.8, 124.0, 126.7 (2C), 127.4 (2C), 127.7, 128.3 (2C), 128.7, 131.4, 131.5, 131.9, 144.5, 145.7, 158.5, 167.1; **IR** (KBr, neat) 2931, 2857, 1686, 1612, 1512, 1468, 1410, 1298, 1250, 1179, 1032, 835, 763, 737, 696 cm^{-1}; **HRMS** (ESI) calcd for C$_{25}$H$_{23}$NO$_2$ (M + H)$^+$ requires 370.1802, found 370.1801.

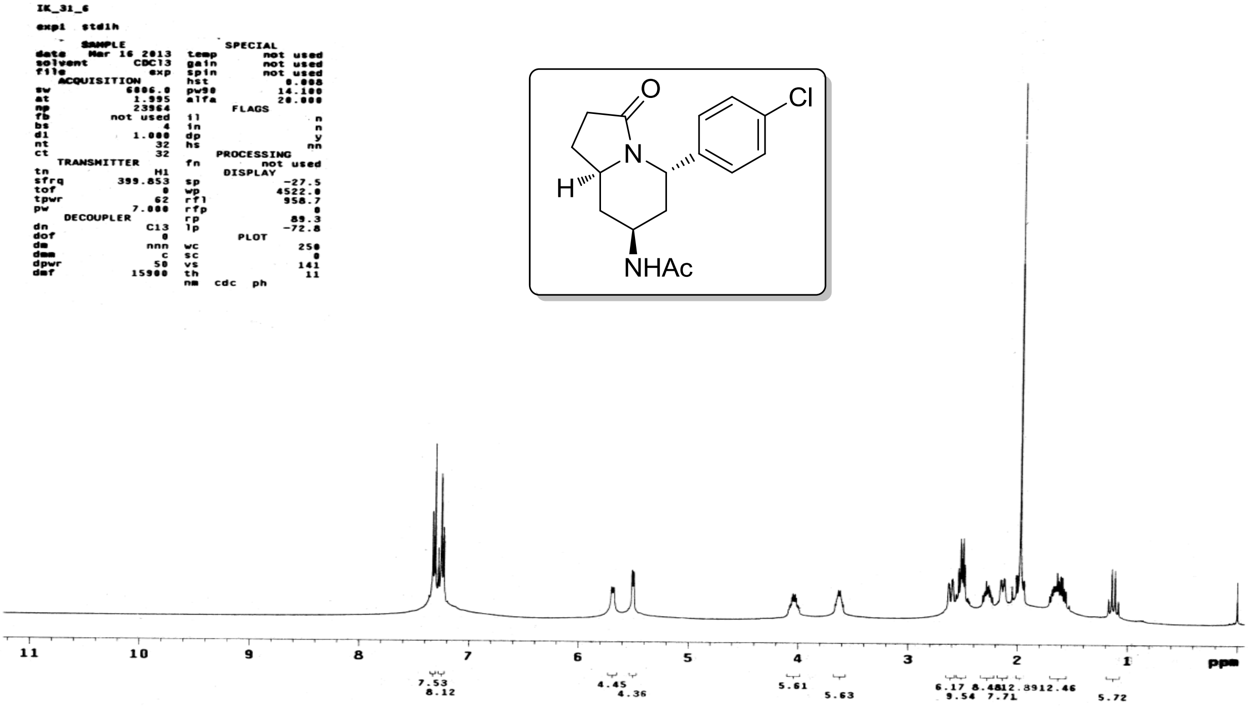
(2*R, 4*S**, 9a*S**)-4-Isobutyl-2-phenyloctahydro-1*H*-quinolizine (52):**



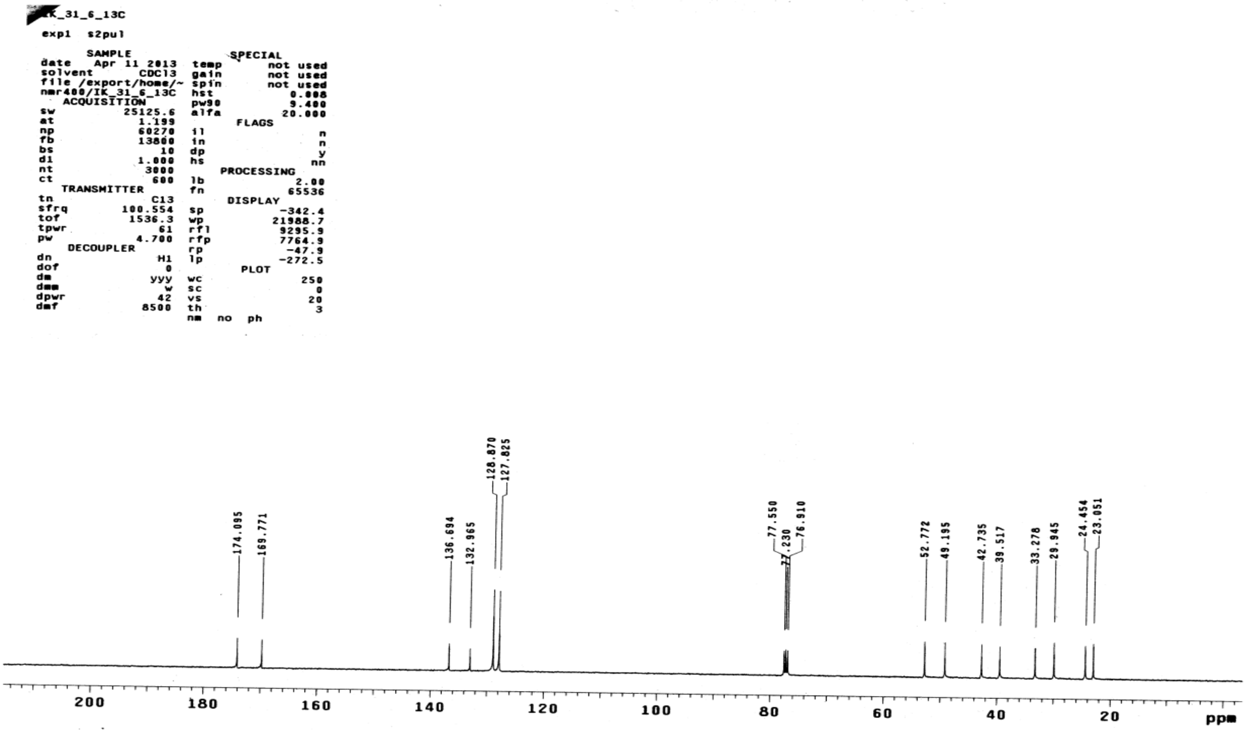
Colourless liquid; yield 55 mg, 68%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.4 Hz, 3 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 1.44-1.50 (m, 2 H), 1.52-1.71 (m, 4 H), 1.73-1.78 (m, 1 H), 1.81-1.86 (m, 1 H), 1.96 (dt, *J* = 12.8 and 4.4 Hz, 1 H), 2.41-2.48 (m, 2 H), 2.53 (dt, *J* = 11.2 and 3.2 Hz, 2 H), 2.63-2.70 (m, 2 H), 2.77-2.85 (m, 2 H), 2.98-3.04 (m, 1 H), 7.15−7.32 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 24.1, 24.5, 26.4, 26.6, 32.1, 32.4, 34.3, 36.4, 36.5, 41.8, 51.8, 54.0, 58.6, 126.3, 127.1 (2C), 128.6 (2C), 146.6; **IR** (KBr, neat) 2924, 2852, 1465, 1261, 1086, 800 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{29}N$ $(M + H)^+$ requires 273.2373, found 273.2371.

3.7. Selected Spectra

^{1}H and ^{13}C Spectra of ***N*-((5*S**,7*S**,8a*R**)-5-(4-Chlorophenyl)-3-oxooctahydroindolizin-7-yl)acetamide**



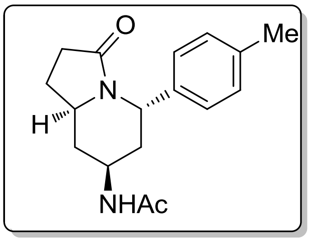
```
IK_31_6

exp1  std1h

        SAMPLE                   SPECIAL
date    Mar 16 2013    temp          not used
solvent       CDCl3    gain          not used
file            exp    spin          not used
   ACQUISITION         hst              0.008
sw           6006.0    pw90            14.100
at            1.995    alfa            20.000
np            23964          FLAGS
fb         not used    il                   n
bs                4    in                   n
d1            1.000    dp                   y
nt               32    hs                  nn
ct               32        PROCESSING
   TRANSMITTER         fn            not used
tn               H1          DISPLAY
sfrq        399.853    sp               -27.5
tof               0    wp              4522.0
tpwr             62    rfl              958.7
pw            7.000    rfp                  0
    DECOUPLER          rp                89.3
dn              C13    lp               -72.8
dof               0            PLOT
dm              nnn    wc                 250
dmm               c    sc                   0
dpwr             50    vs                 141
dmf           15900    th                  11
                       nm   cdc   ph
```

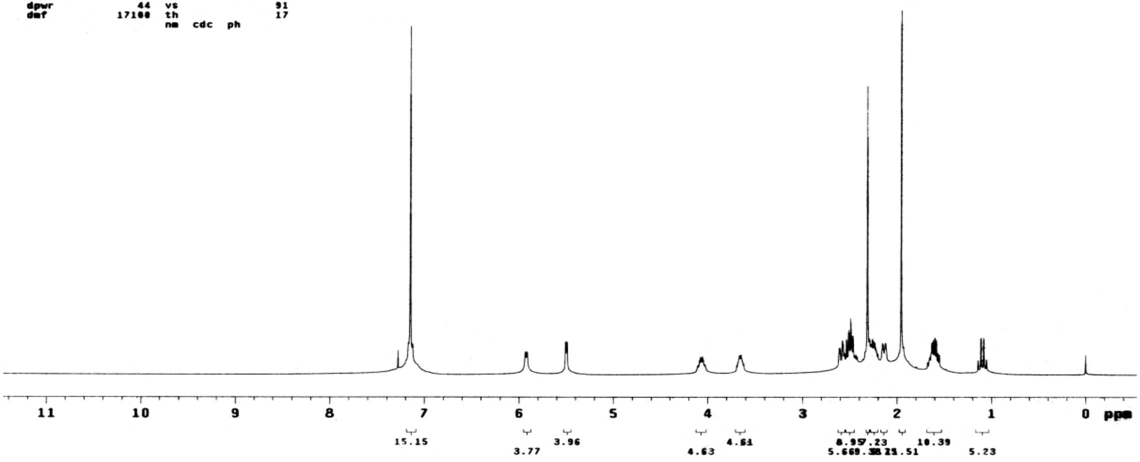


```
IK_31_6_13C

exp1  s2pul

        SAMPLE                   SPECIAL
date    Apr 11 2013    temp          not used
solvent       CDCl3    gain          not used
file /export/home/~   spin          not used
nmr400/IK_31_6_13C     hst              0.008
   ACQUISITION         pw90             9.400
sw          25125.6    alfa            20.000
at            1.199          FLAGS
np            60270    il                   n
fb            13800    in                   n
bs               10    dp                   y
d1            1.000    hs                  nn
nt             3000        PROCESSING
ct              600    lb                2.00
   TRANSMITTER         fn               65536
tn              C13          DISPLAY
sfrq        100.554    sp              -342.4
tof          1536.3    wp             21988.7
tpwr             61    rfl             9295.9
pw            4.700    rfp             7764.9
    DECOUPLER          rp               -47.9
dn               H1    lp              -272.5
dof               0            PLOT
dm              yyy    wc                 250
dmm               w    sc                   0
dpwr             42    vs                  20
dmf            8500    th                   3
                       nm   no   ph
```

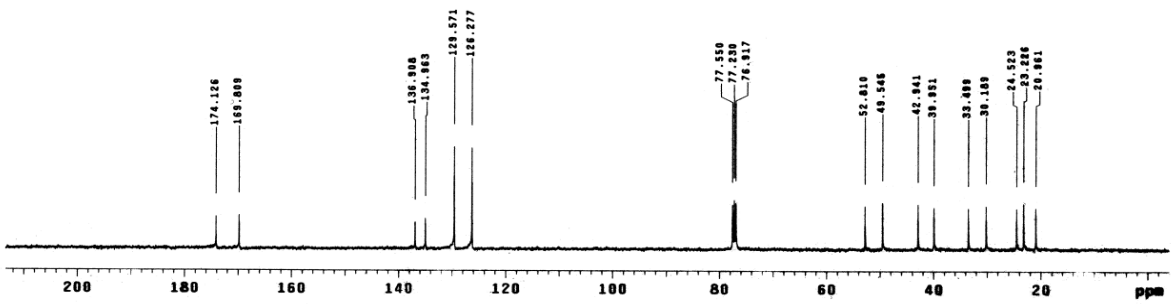
^{1}H and ^{13}C Spectra of ***N*-((5S*,7S*,8aR*)-3-Oxo-5-(*p*-tolyl)octahydroindolizin-7-yl)acetamide**

```
IK_31_8

exp1  std1h

        SAMPLE                      SPECIAL
date   May   3 2013   temp          not used
solvent       CDCl3   gain          not used
file            exp   spin          not used
     ACQUISITION      hst              0.008
sw           6006.0   pw90            15.100
at            1.995   alfa            20.000
np            23064            FLAGS
fb         not used   il                   n
bs                4   in                   n
d1            1.000   dp                   y
nt               32   hs                  nn
ct               32          PROCESSING
     TRANSMITTER      fn            not used
tn               H1            DISPLAY
sfrq        399.853   sp              -217.0
tof               0   wp              4798.4
tpwr             59   rfl              958.7
pw            7.000   rfp                  0
      DECOUPLER       rp               147.9
dn              C13   lp               -65.2
dof               0             PLOT
dm              nnn   wc                 250
dmm               c   sc                   0
dpwr             44   vs                  91
dmf           17100   th                  17
                      nm   cdc   ph
```

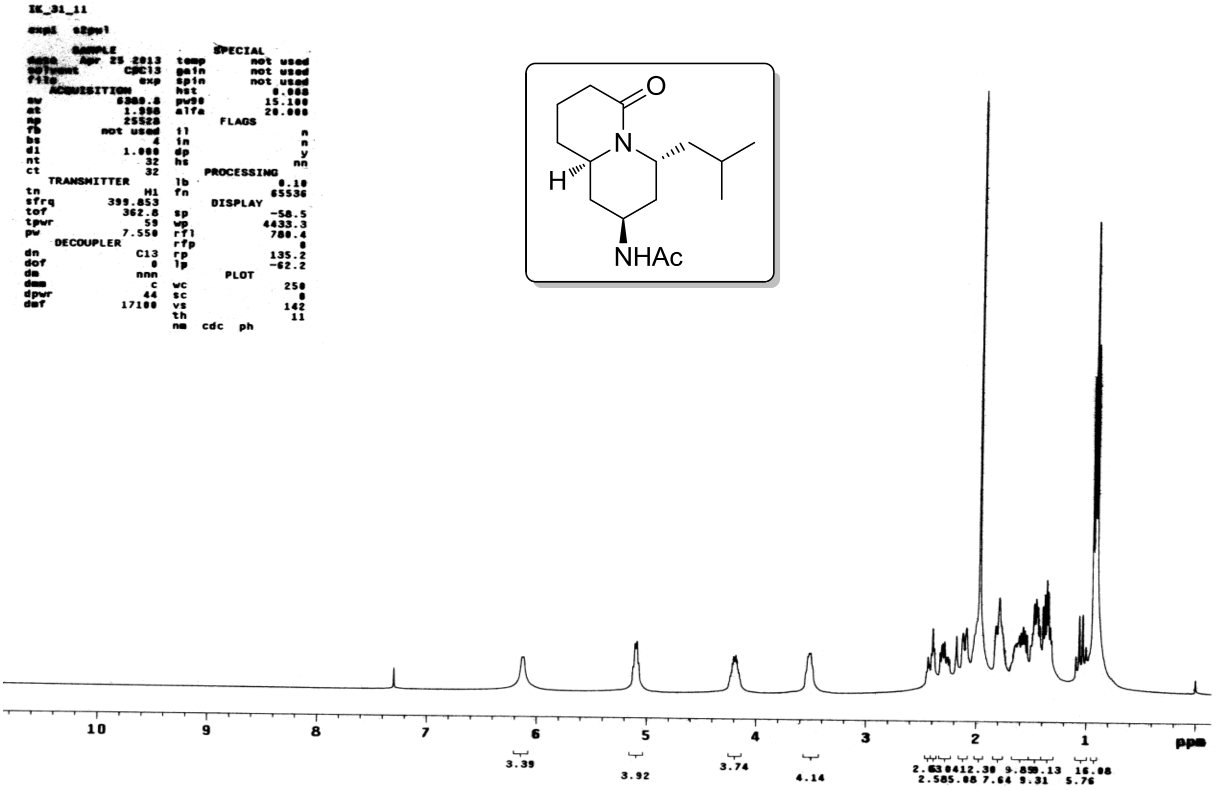




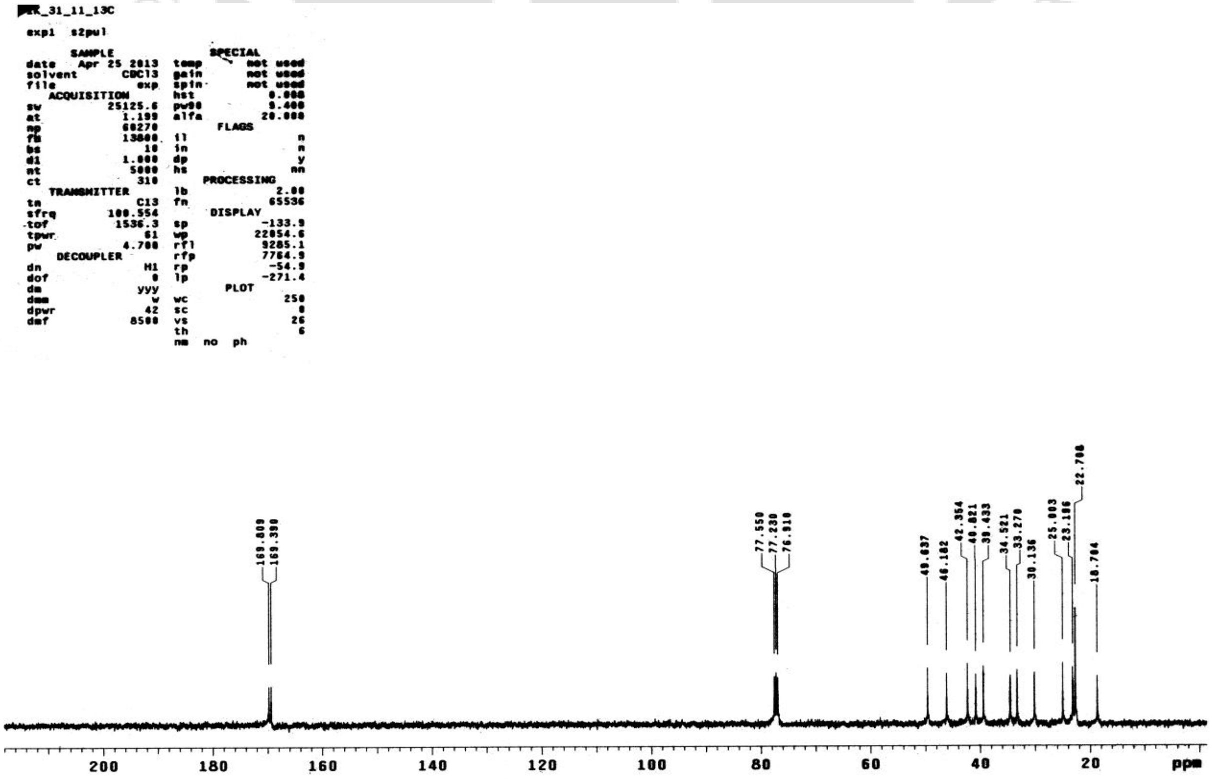
```
IK_31_8_13C

exp1  s2pul

        SAMPLE                      SPECIAL
date   Apr  11 2013   temp          not used
solvent       CDCl3   gain          not used
file /export/home/~   spin          not used
nmr400/IK_31_8_13C    hst              0.008
     ACQUISITION      pw90             9.400
sw          25125.6   alfa            20.000
at            1.199            FLAGS
np            60270   il                   n
fb            13800   in                   n
bs               16   dp                   y
d1            1.000   hs                  nn
nt             2000          PROCESSING
ct              790   lb                2.00
     TRANSMITTER      fn               65536
tn              C13            DISPLAY
sfrq        100.554   sp              -399.2
tof          1536.3   wp             21856.8
tpwr             61   rfl             9285.9
pw            4.700   rfp             7764.9
      DECOUPLER       rp               -74.4
dn               H1   lp              -251.6
dof               0             PLOT
dm              yyy   wc                 250
dmm               w   sc                   0
dpwr             42   vs                  23
dmf            8500   th                   4
                      nm   no   ph
```



^{1}H and ^{13}C Spectra of ***N*-((2*S**,4R*,9a*R**)-4-Isobutyl-6-oxooctahydro-1*H*-quinolizin-2-yl)acetamide**



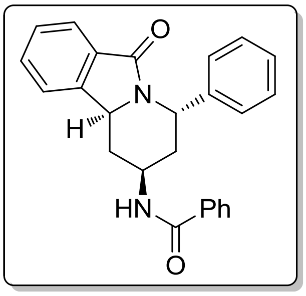
```
IK_31_11

exp1  s2pul

      SAMPLE                     SPECIAL
date    Apr 25 2013      temp          not used
solvent       CDCl3      gain          not used
file            exp      spin          not used
    ACQUISITION          hst              0.008
sw           6389.8      pw90            15.100
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               -58.5
tpwr             59      wp              4433.3
pw            7.550      rfl              780.4
     DECOUPLER           rfp                  0
dn              C13      rp               135.2
dof               0      lp               -62.2
dm              nnn              PLOT
dmm               c      wc                 250
dpwr             44      sc                   0
dmf           17100      vs                 142
                         th                  11
                         nm  cdc   ph
```

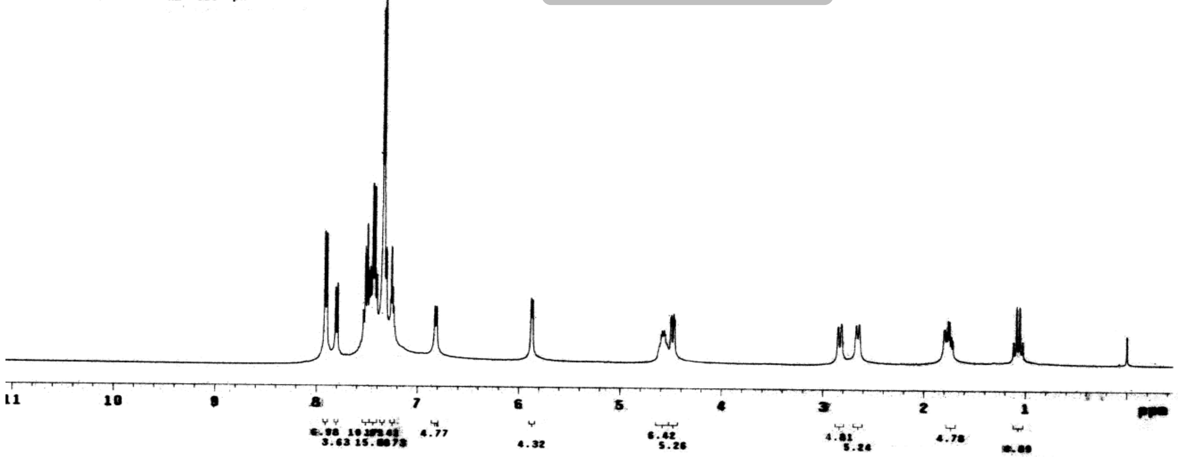


```
IK_31_11_13C

exp1  s2pul

      SAMPLE                     SPECIAL
date    Apr 25 2013      temp          not used
solvent       CDCl3      gain          not used
file            exp      spin          not used
    ACQUISITION          hst              0.008
sw          25125.6      pw90             9.400
at            1.199      alfa            20.000
np            60270              FLAGS
fb            13800      il                   n
bs               10      in                   n
d1            1.000      dp                   y
nt             5000      hs                  nn
ct              310           PROCESSING
    TRANSMITTER          lb                2.00
tn              C13      fn               65536
sfrq        100.554            DISPLAY
tof          1536.3      sp              -133.9
tpwr             61      wp             22054.6
pw            4.700      rfl             9285.1
     DECOUPLER           rfp             7764.9
dn               H1      rp               -54.9
dof               0      lp              -271.4
dm              yyy              PLOT
dmm               w      wc                 250
dpwr             42      sc                   0
dmf            8500      vs                  26
                         th                   6
                         nm  no   ph
```

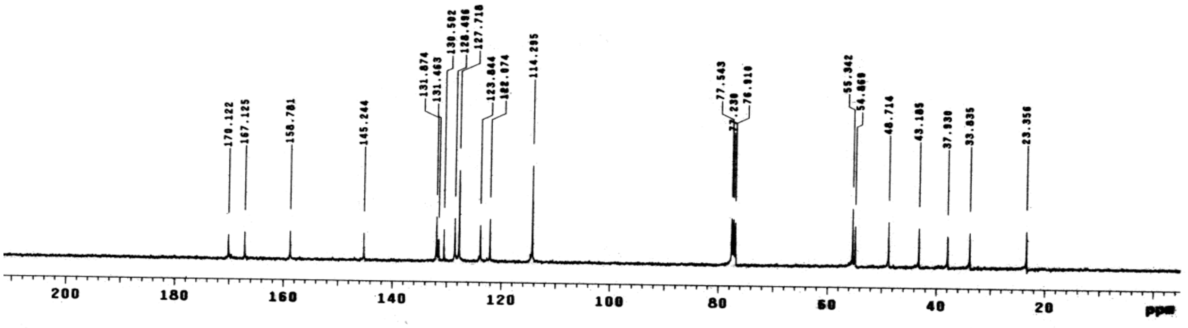
^{1}H and ^{13}C Spectra of ***N*-((2*R**,4*S**,10b*S**)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl)benzamide**

```
IK_31_15

exp1  std1h

      SAMPLE                    SPECIAL
date   Mar 11 2013   temp        not used
solvent       CDCl3  gain        not used
file            exp  spin        not used
   ACQUISITION       hst            0.008
sw           6006.0  pw90          14.100
at            1.995  alfa          20.000
np            23964         FLAGS
fb         not used  il                 n
bs                4  in                 n
d1            1.000  dp                 y
nt               32  hs                nn
ct               32        PROCESSING
   TRANSMITTER       fn          not used
tn               H1         DISPLAY
sfrq        399.853  sp             -45.1
tof               0  wp            4632.7
tpwr             62  rfl            960.5
pw            7.000  rfp                0
    DECOUPLER        rp              87.0
dn              C13  lp             -92.4
dof               0          PLOT
dm              nnn  wc               250
dmm               c  sc                 0
dpwr             50  vs               118
dmf           15900  th                20
                     nm   cdc   ph
```

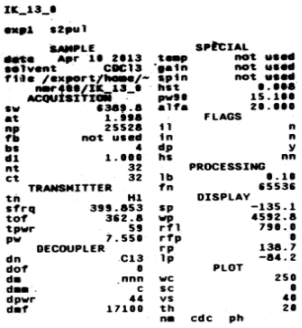




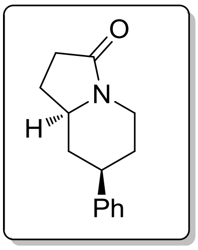
```
IK_31_5_13C

exp1  s2pul

      SAMPLE                    SPECIAL
date   Apr 11 2013   temp        not used
solvent       CDCl3  gain        not used
file /export/home/~  spin        not used
nmr400/IK_31_5_13C   hst            0.008
   ACQUISITION       pw90           9.400
sw          25125.6  alfa          20.000
at            1.190         FLAGS
np            60270  il                 n
fb            13800  in                 n
bs               16  dp                 y
d1            1.000  hs                nn
nt             3000        PROCESSING
ct             1300  lb              2.00
   TRANSMITTER       fn             65536
tn              C13         DISPLAY
sfrq        100.554  sp            -496.6
tof          1536.3  wp           21800.7
tpwr             61  rfl           9284.4
pw            4.700  rfp           7764.9
    DECOUPLER        rp              -6.5
dn               H1  lp            -386.2
dof               0          PLOT
dm              yyy  wc               250
dmm               w  sc                 0
dpwr             42  vs                22
dmf            8500  th                 4
                     nm   no   ph
```

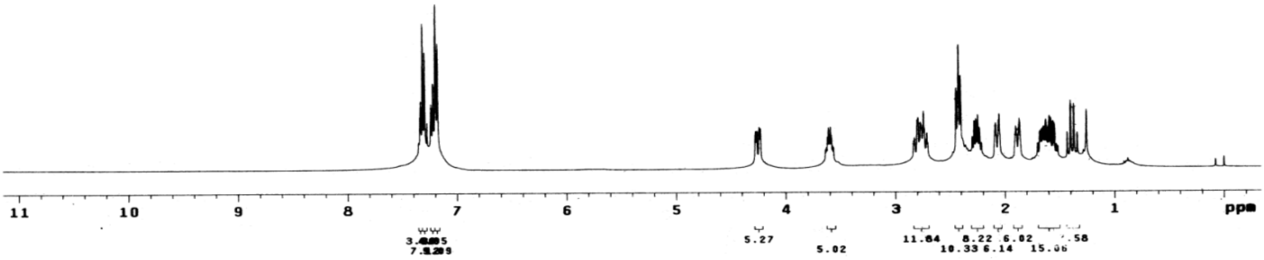


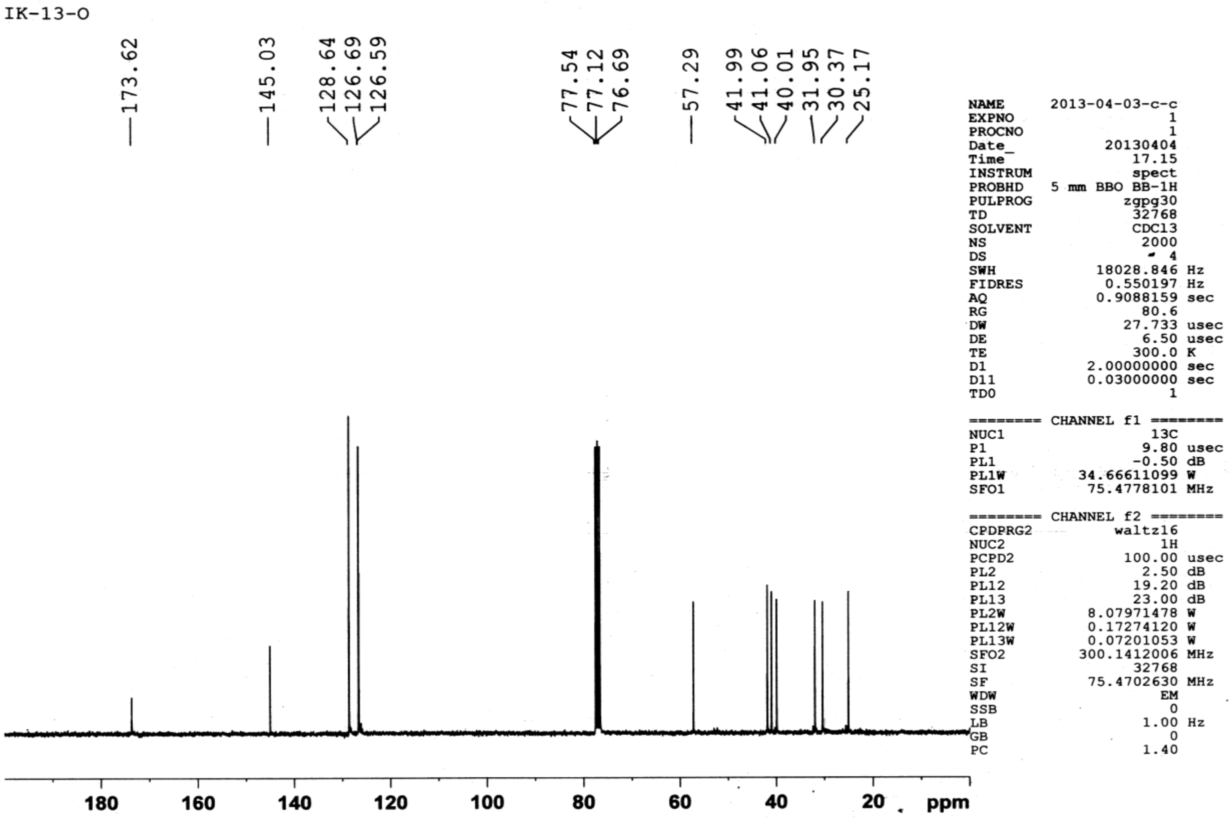
^{1}H and ^{13}C Spectra of **(7*S**,8a*S**)-7-Phenylhexahydroindolizin-3(2*H*)-one**



```
IK_13_0

exp1  s2pul

      SAMPLE                    SPECIAL
date    Apr 10 2013  temp        not used
solvent       CDC13  gain        not used
file /export/home/~  spin        not used
    nmr400/IK_13_0   hst            0.008
   ACQUISITION       pw90          15.100
sw           6389.8  alfa          20.000
at            1.998          FLAGS
np            25528  il                 n
fb         not used  in                 n
bs                4  dp                 y
d1            1.000  hs                nn
nt               32        PROCESSING
ct               32  lb              0.10
   TRANSMITTER       fn             65536
tn               H1          DISPLAY
sfrq        399.853  sp            -135.1
tof           362.8  wp            4592.8
tpwr             59  rfl            790.0
pw            7.550  rfp                0
    DECOUPLER        rp             138.7
dn              C13  lp             -84.2
dof               0           PLOT
dm              nnn  wc               250
dmm               c  sc                 0
dpwr             44  vs                40
dmf           17100  th                20
                     nm   cdc   ph
```



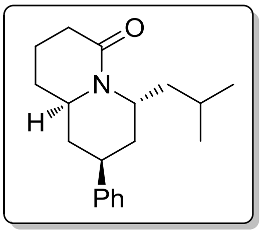


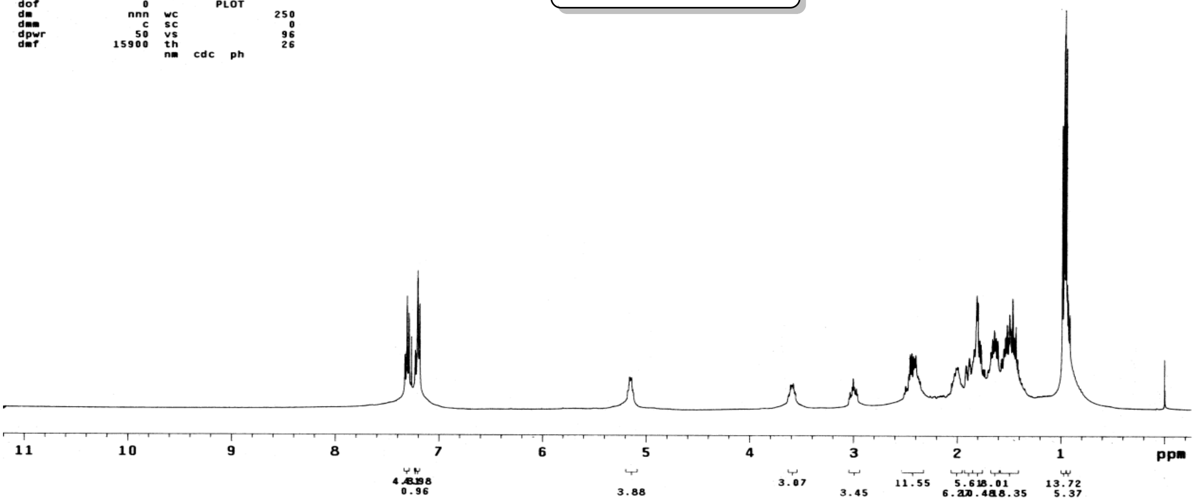


```
NAME       2013-04-03-c-c
EXPNO                   1
PROCNO                  1
Date_            20130404
Time                17.15
INSTRUM             spect
PROBHD     5 mm BBO BB-1H
PULPROG           zgpg30
TD                 32768
SOLVENT            CDC13
NS                  2000
DS                     4
SWH            18028.846 Hz
FIDRES          0.550197 Hz
AQ             0.9088159 sec
RG                  80.6
DW                27.733 usec
DE                  6.50 usec
TE                 300.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.80 usec
PL1                -0.50 dB
PL1W         34.66611099 W
SFO1          75.4778101 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 2.50 dB
PL12               19.20 dB
PL13               23.00 dB
PL2W          8.07971478 W
PL12W         0.17274120 W
PL13W         0.07201053 W
SFO2         300.1412006 MHz
SI                 32768
SF            75.4702630 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

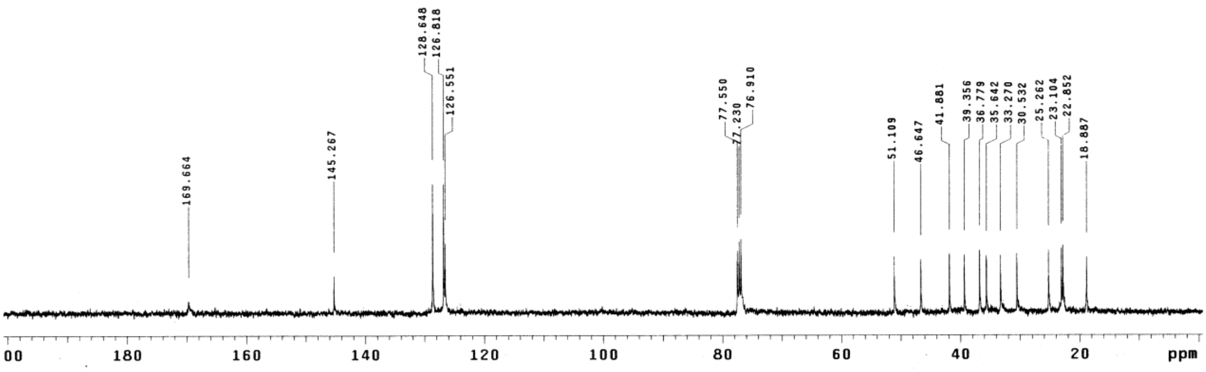
^{1}H and ^{13}C Spectra of **(6*S**,8*R**,9a*S**)-6-Isobutyl-8-phenylhexahydro-1*H*-quinolizin-4(6*H*)-one**

```
IK_13_11

exp1  s2pul

        SAMPLE               SPECIAL
date    Apr 26 2013  temp        not used
solvent       CDCl3  gain        not used
file /export/home/~  spin        not used
   nmr400/IK_13_11   hst            0.008
   ACQUISITION       pw90          19.700
sw           6389.8  alfa          20.000
at            1.998           FLAGS
np            25528  il                 n
fb         not used  in                 n
bs                4  dp                 y
d1            1.000  hs                nn
nt               32         PROCESSING
ct               32  lb              0.10
   TRANSMITTER       fn             65536
tn               H1          DISPLAY
sfrq        399.853  sp            -103.7
tof           362.8  wp            4626.3
tpwr             57  rfl            792.1
pw            9.850  rfp                0
    DECOUPLER        rp             141.5
dn              C13  lp             -66.0
dof               0            PLOT
dm              nnn  wc               250
dmm               c  sc                 0
dpwr             50  vs                96
dmf           15900  th                26
                     nm   cdc   ph
```



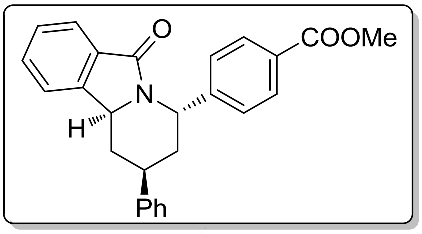


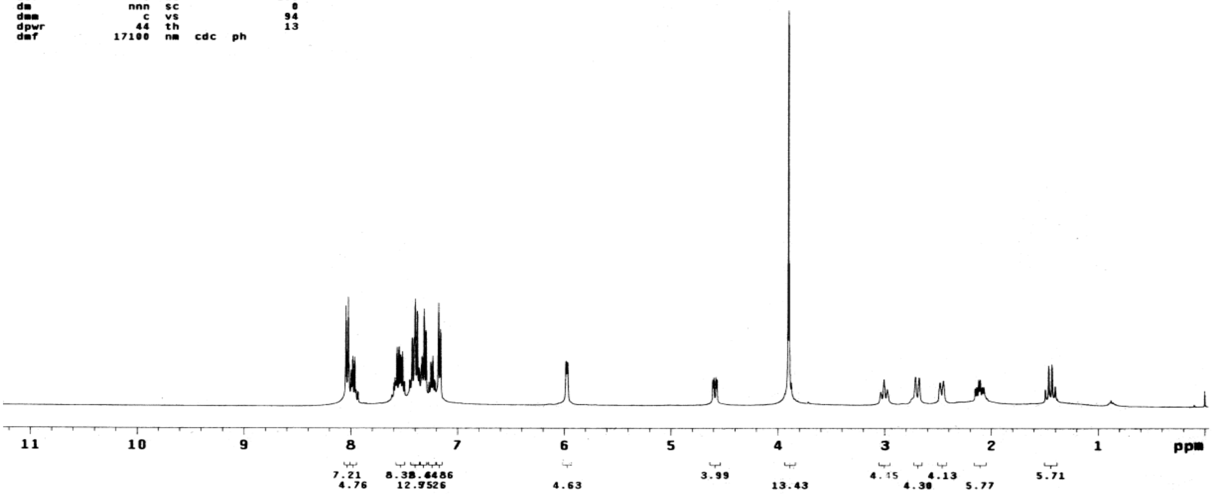
```
13_11U_13C

exp1  s2pul

        SAMPLE               SPECIAL
date    Apr 28 2013  temp        not used
solvent       CDCl3  gain        not used
file /export/home/~  spin        not used
nmr400/IK_13_11U_1~  hst            0.008
                 3C  pw90           9.400
   ACQUISITION       alfa          20.000
sw          25125.6           FLAGS
at            1.199  il                 n
np            60270  in                 n
fb            13800  dp                 y
bs               10  hs                nn
d1            1.000         PROCESSING
nt             8000  lb              2.00
ct             1520  fn             65536
   TRANSMITTER               DISPLAY
tn              C13  sp             -64.9
sfrq        100.554  wp           20469.6
tof          1536.3  rfl           9282.1
tpwr             61  rfp           7764.9
pw            4.700  rp             -55.0
    DECOUPLER        lp            -321.6
dn               H1            PLOT
dof               0  wc               250
dm              yyy  sc                 0
dmm               w  vs                27
dpwr             42  th                 2
dmf            8500  nm   no   ph
```



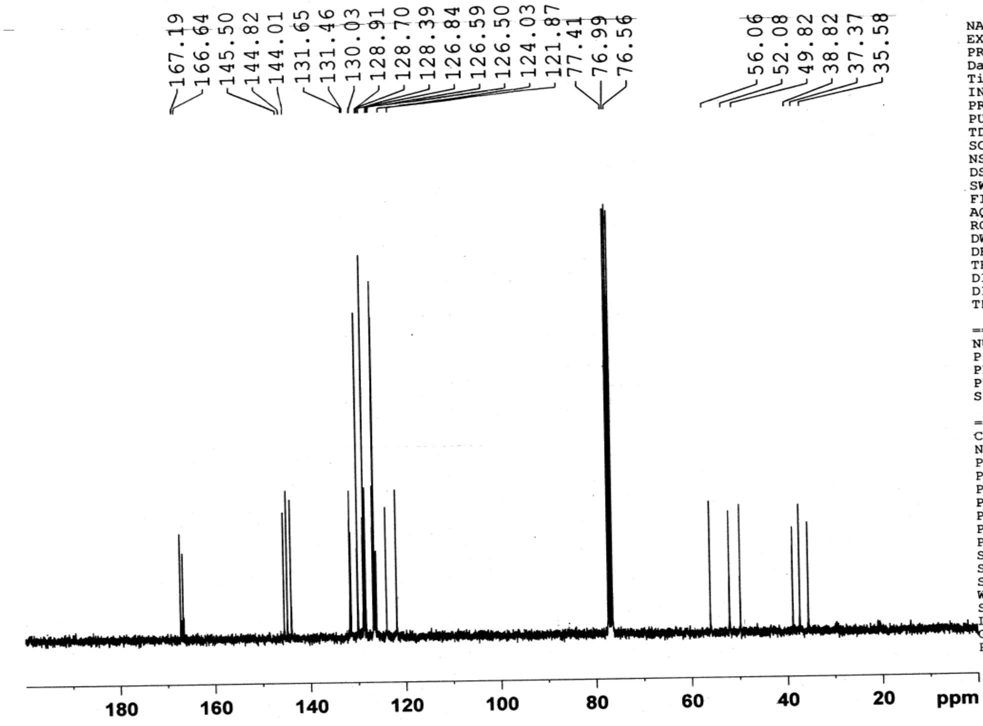
^{1}H and ^{13}C Spectra of **Methyl 4-((2*R**,4*S**,10b*S**)-6-oxo-2-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-4-yl)benzoate**

```
IK_13_2

exp1  std1h

      SAMPLE                  SPECIAL
date    Apr 23 2013  temp        not used
solvent       CDC13  gain        not used
file /export/home/~  spin        not used
   nmr400/IK_13_2    hst            0.008
   ACQUISITION       pw90          15.100
sw           6006.0  alfa          20.000
at            1.995          FLAGS
np            23964  il                 n
fb         not used  in                 n
bs                4  dp                 y
d1            1.000  hs                nn
nt               32       PROCESSING
ct               32  fn          not used
   TRANSMITTER             DISPLAY
tn               H1  sp             -15.4
sfrq        399.853  wp            4561.6
tof               0  rfl            962.3
tpwr             59  rfp                0
pw            7.000  rp             130.4
    DECOUPLER        lp             -70.5
dn              C13          PLOT
dof               0  wc               250
dm              nnn  sc                 0
dmm               c  vs                94
dpwr             44  th                13
dmf           17100  nm   cdc   ph
```





IK-13-2



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Time                 11.38
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PROBHD      5 mm BBO BB-1H
PULPROG            zgpg30
TD                  32768
SOLVENT             CDCl3
NS                   2000
DS                      4
SWH             18028.846 Hz
FIDRES           0.550197 Hz
AQ              0.9088159 sec
RG                   80.6
DW                 27.733 usec
DE                   6.50 usec
TE                  300.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.80 usec
PL1                 -0.50 dB
PL1W          34.66611099 W
SFO1          75.4778101 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  2.50 dB
PL12                19.20 dB
PL13                23.00 dB
PL2W           8.07971478 W
PL12W          0.17274120 W
PL13W          0.07201053 W
SFO2         300.1412006 MHz
SI                  32768
SF            75.4702722 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

3.8. Crystal Parameters

The crystal parameters of compound **49c**

	CCDC 946874
Formula	$C_{17} H_{22} N_2 O_{22}$
Formula weight	286.37
T/K	296(2)
Crystal system	Orthorhombic
Space group	Pbca
a/Å	14.0817(14)
b/Å	9.5974(10)
c/Å	23.030(2)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	3112.5(5)
Z	8
Abs. Coeff./mm^{-1}	0.081
Abs. Correction	Multi-scan
GOF on F^2	1.137
Final R indices [$I > 2\sigma$(I)]	$R1$ = 0.0430 $wR2$ = 0.1363
R indices [all data]	$R1$ = 0.0558 $wR2$ = 0.1489

The crystal parameters of compound **51i**

	CCDC 944753
Formula	$C_{25}H_{23}NO_2$
Formula weight	369.44
T/K	296(2)
Crystal system	Monoclinic
Space group	P 21/c
a/Å	10.493(2)
b/Å	19.484(4)
c/Å	11.334(2)
α/°	90.00
β/°	122.064(14)
γ/°	90.00
V/Å^3	1963.7(7)
Z	4
Abs. Coeff./mm^{-1}	0.079
Abs. Correction	Multi-scan
GOF on F^2	1.695
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0425 $wR2$ = 0.0605
R indices [all data]	$R1$ = 0.0632 $wR2$ = 0.0683

CHAPTER 4

Stereoselective Synthesis of *O*-Tosyl Azabicyclic Derivatives *via* Aza Prins Reaction: Application to the Total Synthesis of (±)-*epi*-Indolizidine 167B and 209D

4.1. Importance of Hydroxy Piperidines, Alkyl Indolizidines and Quinolizidines

Among the piperidine derivatives, 4-Hydroxy piperidine moiety is widely spread in many natural products particularly alkaloids. These motifs are also present in many known drugs and drug intermediates.[1] For example, dienomycin C (**1**) an alkaloid isolated from the *streptomyces* strain MC67-C1, has been found to exhibit antibacterial activity against some strains of mycobacterium tuberculosis.[2] Haloperidol (**2**) a neuroleptic drug, containing 4-hydroxy piperidine moiety is used in the treatment of psychiatry and delirium.[3] Apart from these, some amino- and hydroxylated piperidines show potent antineoplastic and antitumor activities.[4] A new class of alkaloids are the alkyl indolizidines (**3-6**), bicyclic compounds, with fused 6- and 5-membered rings and a bridge head nitrogen, isolated from the skin secretions of certain neotropical frogs of the Dendrobatidae family, represent a class of noncompetitive blockers of neuromuscular transmission.[5] Similarly, another class of piperidine containing alkaloids called quinolizidines (**7-9**), closely related to indolizidines having bicyclic structures with two fused 6-membered rings sharing a bridge head nitrogen, isolated from bacteria, fungi, plants, invertebrates and vertebrates, acts as non-competitive blockers of nicotinic receptors.[6]

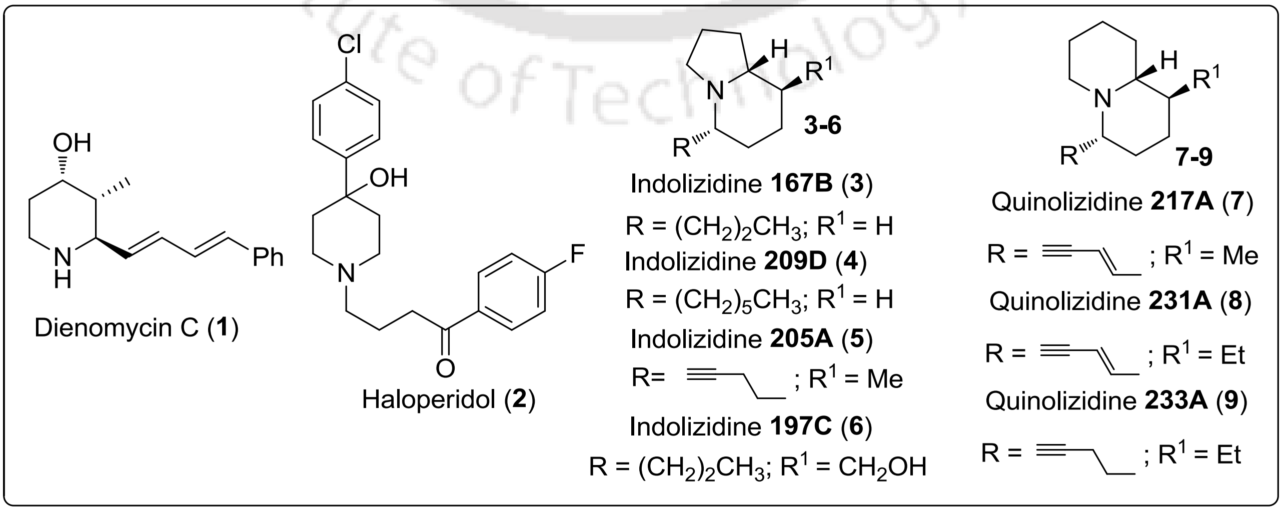
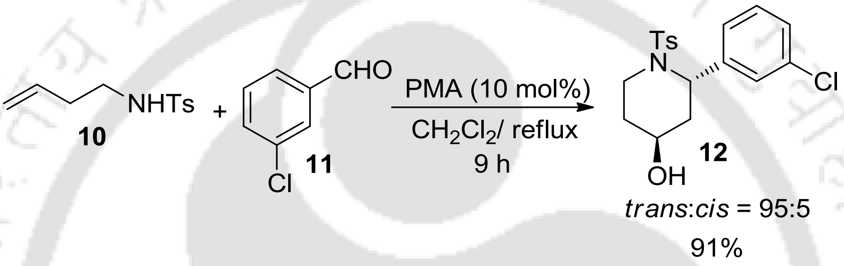


Figure 4.1.1. Some piperidine containing biologically active compounds

4.2. Literature Methods

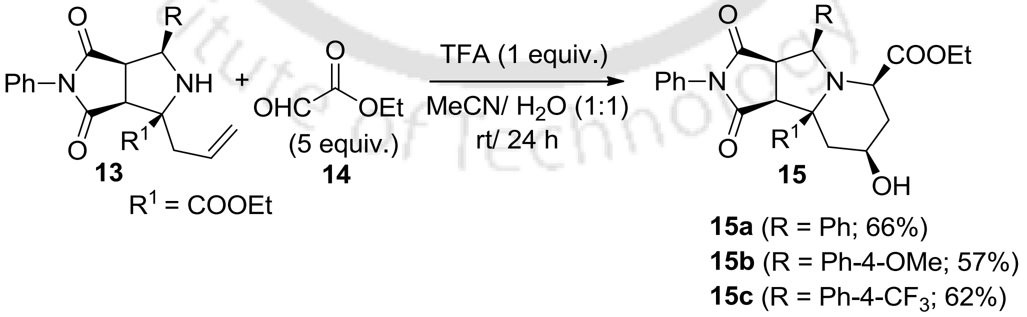
The construction of C-O bond at 4th position of piperidine ring has attracted considerable interest and several reported methodologies offering good results such as, aza-Prins cyclization, carbonyl-ene reactions, tandem Pummerer/Mannich cyclization etc. However, aza-Prins is mostly used, because of its high selectivity.

Yadav *et al.* reported a simple procedure for the synthesis of 4-hydroxy piperidine derivatives **12** *via* phosphomolybdic acid (PMA) catalyzed aza-Prins cyclization of *N*-tosyl homoallylic amine **10** and aldehyde **11**. The reaction is highly stereoselective with the formation of major *trans* isomer (*Scheme 4.2.1*).[7]



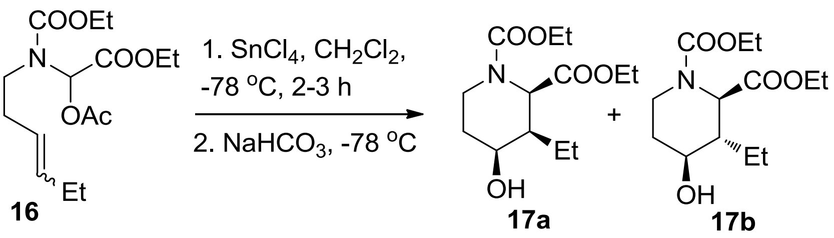
Scheme 4.2.1

Recently, Waters and coworkers proposed a novel route for 4-hydroxy piperidine containing functionalized indolizidine systems through the aza-Prins approach (*Scheme 4.2.2*).[8] In this, the condensation of aldehyde **14** onto 2-allylpyrrolidines **13** yields iminium ions, that undergo highly diastereoselective aza-Prins cyclization to afford indolizidine products **15** with the formation of two new stereogenic centers in one step.



Scheme 4.2.2

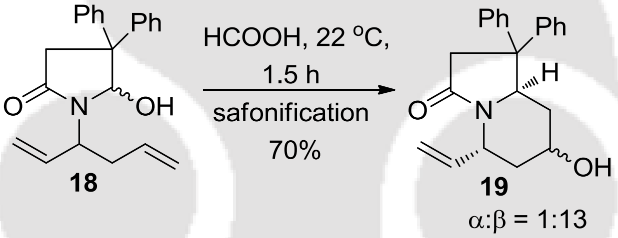
Esch *et al.* have reported a number of methodologies by using *N*-acyliminium ions as electrophiles in *endo*-trig (aza-Prins) cyclization reactions.[9] The intramolecular cyclization of (*E*)-alkene tethered glycine-cation equivalent like ethyl *N*-butenyl carbamate **16**, in the presence of $SnCl_4$ at -78 °C and subsequent quenching with $NaHCO_3$ at -78 °C gave exclusive *cis* substituted piperidine product **17a** (*Scheme 4.2.3*). In case of *Z*-alkene, resulted in a mixture of isomers **17a** and **17b** in a diastereomeric ratio of 90:10.



Alkene geometry	**17a**:**17b**	yield (%)
E	100:0	49
Z	90:10	81

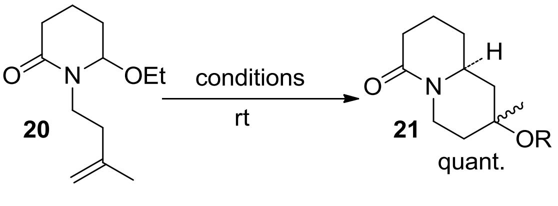
Scheme 4.2.3

Similarly, cyclization of substituted hydroxylactam **18** in HCOOH, followed by saponification provides hydroxy indolizidine **19** in 70% yield, besides some unidentified minor products. This reaction proceeded *via* cyclic *N*-acyliminium ion intermediate (*Scheme 4.2.4*).[10]



Scheme 4.2.4

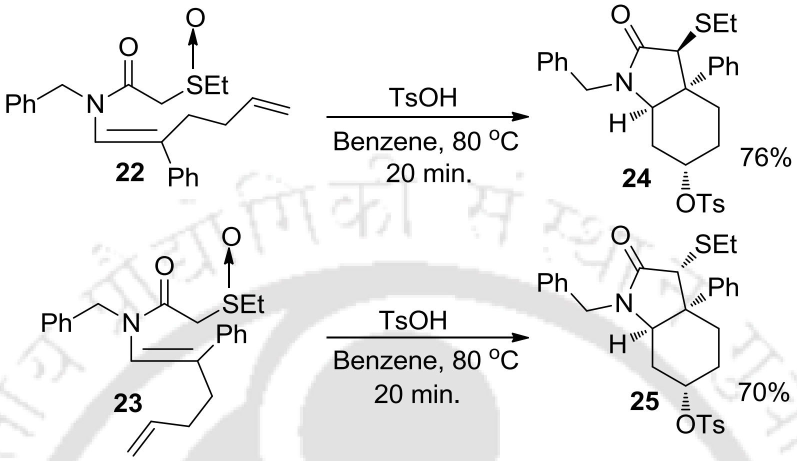
Speckamp and coworkers have further studied the formation of various hydroxy, formate and acetate substituted piperidine emboded azabicycles **21** *via* the 6-*endo*-trig cyclization of ethoxy lactam in quantitative yields (*Scheme 4.2.5*). The nature of C-O bond formation at 4th position of piperidine ring depends upon the reaction conditions used.[11]



Conditions	R	α:β
HCOOH, 1 h	CHO	57:43
AcOH, 23 h	Ac	60:40
AcOH, H_2O, 2 h	H	60:40
$Cl_2CHCOOH$, 2 h	$COCHCl_2$	70:30
HCOOH, Et_2O, 19 h	CHO	57:43
HCOOH, HCOONa, 18 h	CHO	56:44

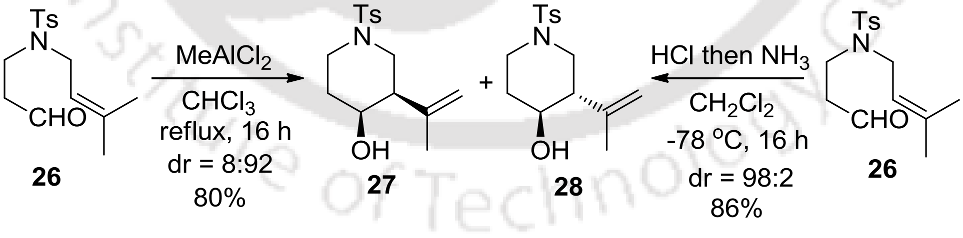
Scheme 4.2.5

Padwa *et al.* reported the dual role of *p*-TSA *via* tandem Pummerer/Mannich cyclization cascade of α-sulfinylamides for the synthesis of tosylated azabicyclic compounds. The stereoselectivity of the reaction depends on the olefin geometry of the sulfoxide tethered enamide heterocycles (*Scheme 4.2.6*). Refluxing of *E*-enamide **22** with *p*-TsOH in benzene at 80 °C afforded tosylate **24** as the major diastereomer in 76% yield. Similarly, *Z*-enamide **23** gave the opposite diastereomer **25** as major one.[12]



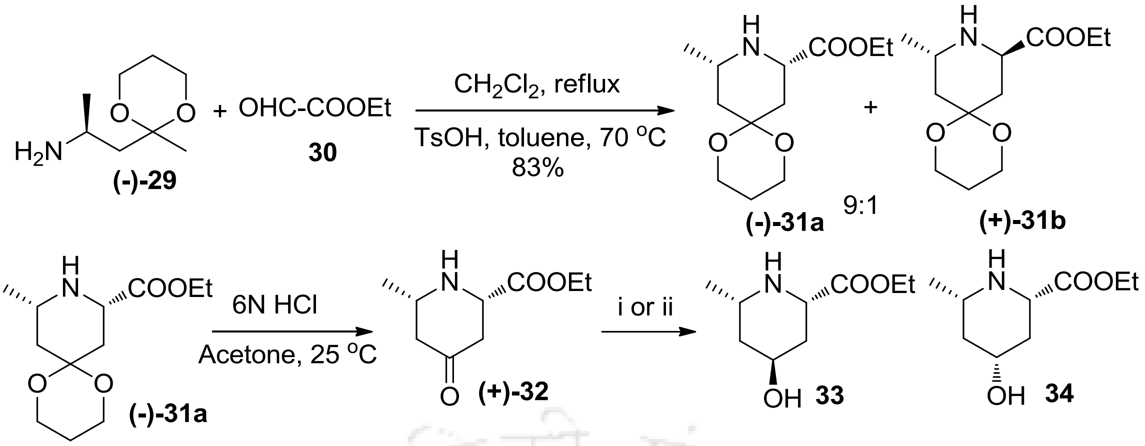
Scheme 4.2.6

In 2005, Snaith described $MeAlCl_2$ catalyzed carbonyl ene cyclization of aldehyde **26,** in refluxing chloroform to afford the *trans* piperidines **28** with a diastereomeric ratio of 92:8. Whereas, aldehyde **26** in the presence of concentrated hydrochloric acid in CH_2Cl_2 at low temperature afforded *cis* chlorine substituted piperidines with a diastereomeric ratio of 98:2. After subsequent elimination of HCl by ammonia gave the eliminated products **27** and **28** without effecting the diastereoselectivity (*Scheme 4.2.7*).[13]



Scheme 4.2.7

Troin and co-workers reported an asymmetric approach for the synthesis of pipecolic acid derivatives from diol protected β-keto amine. The chiral amine **29** with ethyl glyoxylate **30** in refluxing dichloromethane gives the transient imine quantitatively, which when directly treated with *para*- toluenesulfonic acid, produced the cyclic products as *cis-trans* mixture (**31a** & **31b**). The major diastereomer **31a** was separated, cleavage of the dioxane followed by selective reduction, with either L-Selectride® or sodium borohydride, afforded the axial piperidinol **33** and the equatorial piperidinol **34**, respectively (*Scheme 4.2.8*).[14]

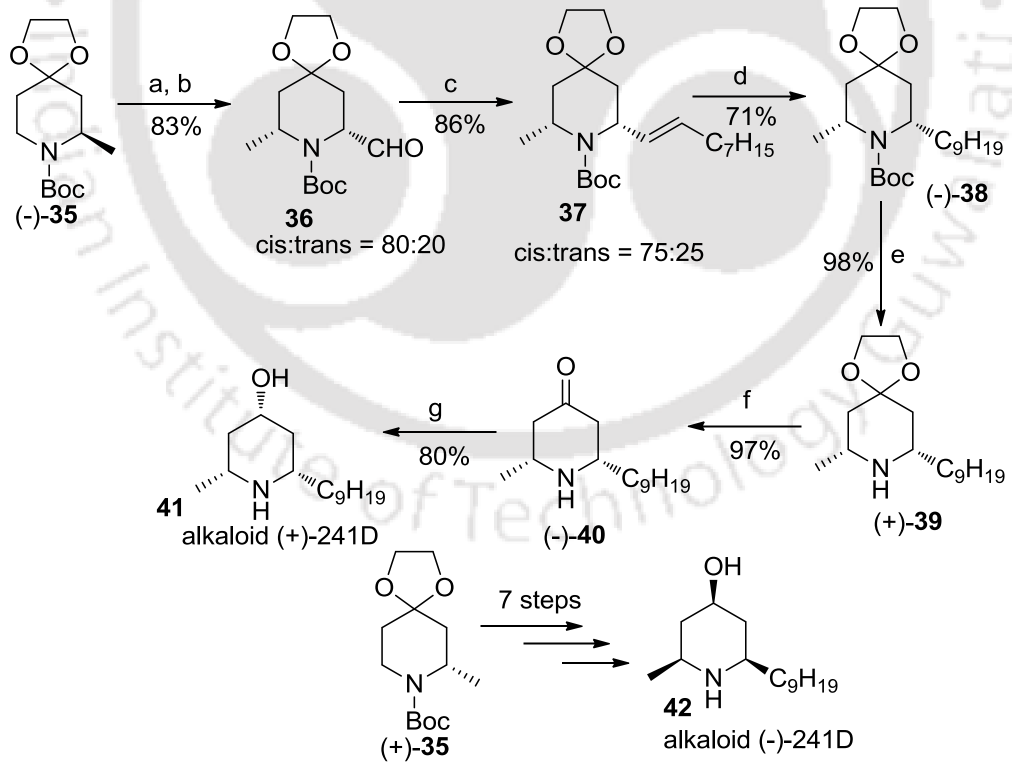


i. L-Selectride, -78 °C, THF, 95%; ii. $NaBH_4$, MeOH, rt, 70%

Scheme 4.2.8

4.2.1. 4-Hydroxy Piperidine Core in Natural Product Synthesis

More recently, Hurvios and coworkers reported the total synthesis of both enantiomers of *cis*-2,4,6-trisubstituted piperidine alkaloid (+)-241D (**41**) by utilizing a chiral *N*-Boc protected 4-piperidone (−)-**35**. The treatment of (−)-**35** with *s*-BuLi/TMEDA in diethyl ether at −80 °C



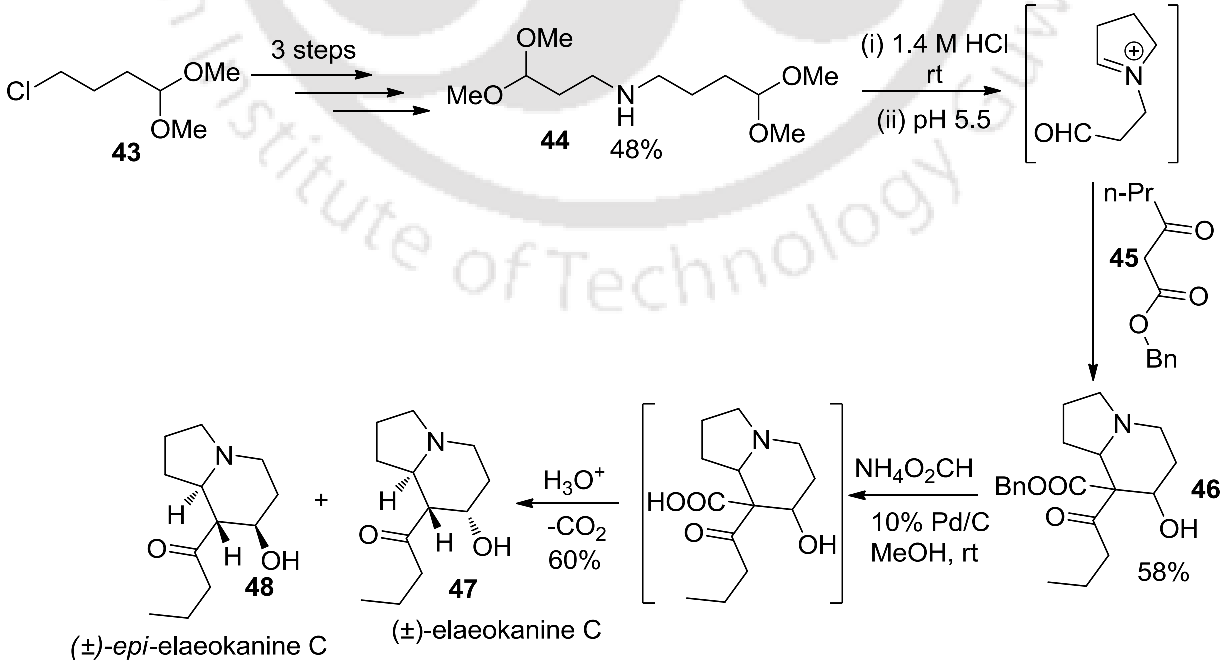
Reagents and conditions: (a) *s*-BuLi (1.5 equiv.), TMEDA (1.5 equiv.), Et_2O, -80 to -65 °C, 3 h; then DMF (2.5 equiv.), -80 °C to rt, 12 h; (b) Et_3N, silica gel, diethyl ether, 60 h, rt; (c) $[nC_8H_{17}(Ph)_3P]^+\cdot Br^-$, *n*-BuLi, THF, -40 to 0 °C, 2 h; then **36**, -70 °C to rt, 3 h; (d) 20% Pd/C, H_2 (3 bar), MeOH, 72 h; (e) $SnCl_4{\cdot}(Et_2O)_2$, 0 °C, Et_2O, 12 h, then 2 M NaOH, 24 h, rt.; (f) 5 M HCl, acetone, 4 h, reflux; (g) $NaBH_4$ (2.0 equiv.), ethanol, 0 °C, 1 h.

Scheme 4.2.1.1

provided the intermediate 2-lithio derivative, which was condensed with an excess of dimethylformamide (DMF) to provide aldehyde **36** as a 75:25 mixture of *trans* and *cis* isomers. Later, the stereochemistry was reversed by stirring **36** in diethyl ether in the presence of silica gel and triethylamine over a 60 h period, to afford aldehyde **36** in 83% yield with predominating *cis* isomer (dr 80:20). After that, Wittig olefination of aldehyde **36** with *n*-octyl-triphenyl-phosphonium bromide yielded an inseparable mixture (75:25 dr) of *Z*-alkenes **37**.

The saturation of the olefinic double bond of **37** was performed by the catalytic hydrogenation in methanol in the presence of 20% Pd/C under hydrogen pressure of 3 bar. In this way *cis*-4-piperidone (−)-**38** was obtained as a sole product in 71% yield. Deprotection of the carbamate moiety was carried out to liberate 4-piperidone (+)-**39**, which was treated with a 5 M HCl to afford the unmasked 4-piperidone (−)-**40** in an overall 95% yield. Finally the hydride reduction of the carbonyl function in (−)-**40** was carried out in ethanol at 0 °C in the presence of $NaBH_4$ for 1 h, to give the expected alkaloid (+)-241D in 80% yield with its C-4 epimer (10%), which was removed easily by chromatography. The same synthetic path was used to synthesize alkaloid (−)-241D (**42**) from 4-piperidone (+)-**35** (*Scheme 4.2.1.1*).[15]

Gribble and coworkers reported a novel route for the synthesis of hydroxy indolizidine alkaloid (±)-elaeokanine from chloro acetal. The amine bisacetal **44**, derived from commercially available chloroacetal **43**, upon treatment with 1.4 M aqueous hydrochloric acid followed by buffering the reaction mixture at pH 5.5 and subsequent addition of the readily available 3-oxohexanoate ester

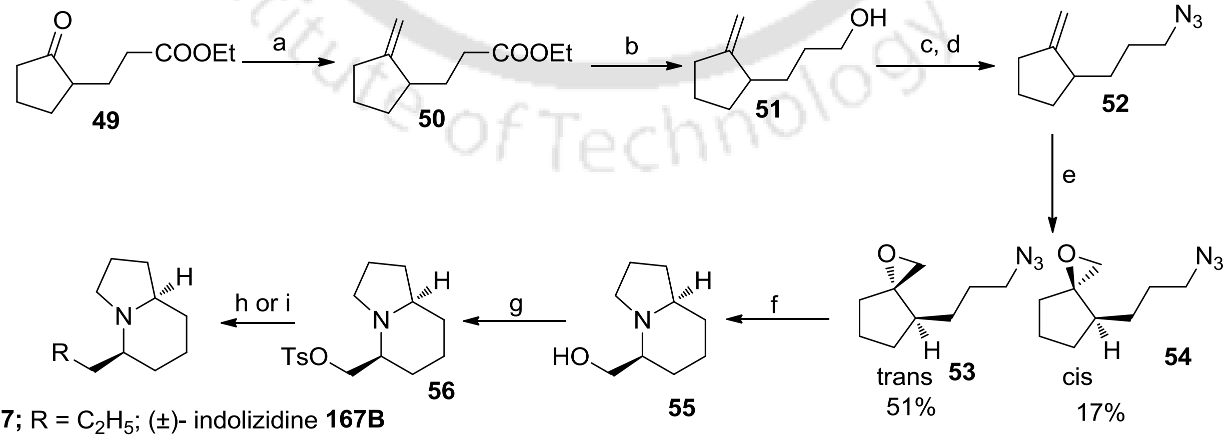


Scheme 4.2.1.2

45, afforded the desired indolizidine **46**. The indolizidine **46**, upon treatment with Pd/C for removal of benzylic group and further removal of acid functionality gave a mixture of (±)-elaeokanine C **47** and (±)-*epi*-elaeokanine C **48** with a ratio of 1:3 in 60% yield, which were separated by preparative TLC technique (*Scheme 4.2.1.2*).[16]

4.2.2. Methods for the Total Synthesis of Indolizidine 167B and 209D Alkaloids

Indolizidine **167B** and **209D** were isolated from the skin secretions of certain neotropical frogs of the Dendrobatidae family along with other indolizidine alkaloids. These compounds act as noncompetitive blockers of neuromuscular transmission. The isolation of trace amounts from natural sources and the pharmacological interest has made it an attractive synthetic subject. A number of protocols have been developed for the total synthesis of indolizidine **167B** and **209D** alkaloids and their epimers.[17] Baskaran and coworkers reported a novel synthetic route for the synthesis of indolizidine **167B** and **209D** *via* epoxide-initiated electrophilic cyclization of azides as a key step. The ketoester **49** was treated with CH_2Br_2/Zn/$TiCl_4$ reagent system to give olefin ester **50** in 71% yield, which was converted to the corresponding azido-alkene **52** in three steps as shown in *Scheme 4.2.2.1*. Azido-alkene **52** upon treatment with *m*-CPBA yielded the epoxyazide as a mixture of *cis* (**54**) and *trans* (**53**) isomers with a ratio of 1:3. Treatment of the major diastereomer **53** with $EtAlCl_2$ at -78 °C followed by reduction with sodium borohydride afforded azabicyclic alcohol **55** in 63% yield. The alcohol was converted to the corresponding tosylate **56** in 93% yield. Treatment of the tosylate **56** with $Et_2CuCNMgBr$ in Et_2O medium at –78 °C afforded indolizidine **167B 57** in 62% yield. Under similar reaction conditions tosylate **56** was converted to indolizidine **209D 58** in 67% yield upon treatment with $(C_5H_{11})_2CuCNMgBr$.[18]

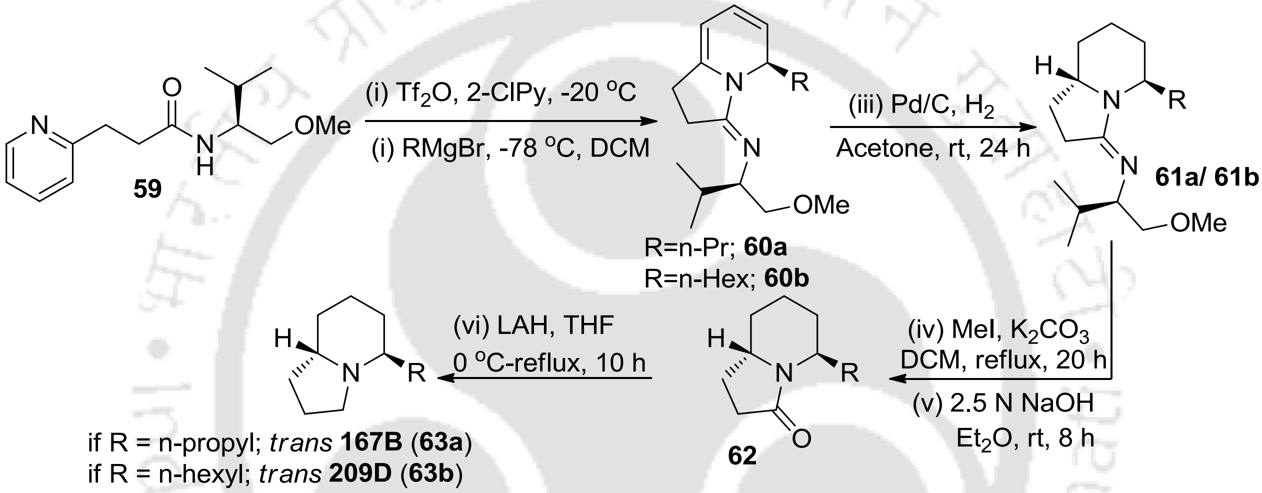


57; R = C_2H_5; (±)- indolizidine **167B**
58; R = C_5H_{11}; (±)-indolizidine **209D**

(a) Zn, CH_2Br_2, $TiCl_4$ (1 M), CH_2Cl_2, 20 °C, 1 h, 71%. (b) $LiAlH_4$, THF, 0 °C, 2 h, 95%. (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 100%. (d) NaN_3, DMF, 55 °C, 4 h, 98%. (e) *m*-CPBA, CH_2Cl_2, 0.5 M $NaHCO_3$, 0 °C, 2.5 h, 68%. (f) $EtAlCl_2$, CH_2Cl_2, -78 °C, 45 min, $NaBH_4$ in 15% aq NaOH, 1 h, 63%. (g) TsCl, Et_3N, DMAP (cat.), 25 °C, 2 h, 93%. (h) EtMgBr, CuCN, Et_2O, - 78 °C, 62%. (i) $C_5H_{11}MgBr$, CuCN, Et_2O, -78 °C, 67%.

Scheme 4.2.2.1

Stereoselective synthesis of polysubstituted indolizidines and quinolizidines and its application in the total synthesis of *trans* indolizidine **167B** and **209D** was accomplished by Barbe *et al*. The amide **59**, upon treatment with *n*-PrMgBr and *n*-HexMgBr as nucleophiles afforded dihydropyridines **60a** and **60b**, respectively. Subsequently, diastereoselective hydrogenation of the alkenes using Pd/C in acetone gave the corresponding saturated bicyclic compounds **61a** and **61b**. These amidines were then regioselectively hydrolyzed *via* the formation of an amidinium salt using MeI as the alkylating reagent, followed by a basic treatment of the amidinium salt in aqueous NaOH resulting in **62**, which upon reduction with LAH gave the corresponding *trans*-indolizidines **63a** and **63b** in 75% overall yield in four steps (*Scheme 4.2.2.2*).[19]

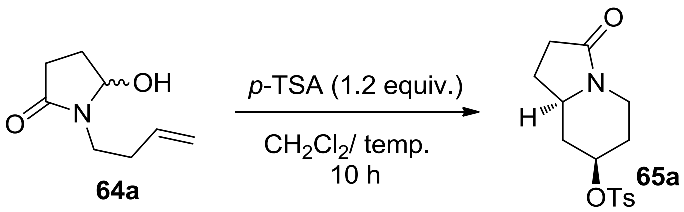


Scheme 4.2.2.2

4.3. Results and Discussions

From the above literature, it was observed that harsh reaction conditions, lack of selectivity, multi-step synthesis and poor yields limit their scope towards the application in natural product synthesis. In chapter 2 and 3, we have demonstrated the use of arene and nitrile nucleophiles in Prins and aza-Prins cyclization reactions. In continuation of our search for the use of other nucleophiles in aza-Prins cyclization reactions and keeping in mind various biomedical applications and with a view to further access the pharmacological profile of azabicyclic compounds, we describe the dual role of *p*-TSA as a Brønsted acid and nucleophile in aza-Prins cyclization approach for the synthesis of *O*-tosylated azabiclic compounds and its application to the total synthesis of (±)-*epi*-indolizidine **167B** and **209D** alkaloids.

Initially, we treated 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one **64a** with 1.2 equivalents of *p*-TSA in dichloromethane at room temperature and the reaction proceeded smoothly to afford (7*R**,8a*R**)-3-oxooctahydroindolizin-7-yl-4-methylbenzenesulfonate **65a** in 79% yield with a diastereomeric ratio of 85:15. Using the same solvent at reflux temperature resulted in 88% yield, without any change in its diastereomeric ratio (*Scheme 4.3.1*).



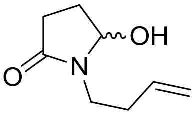
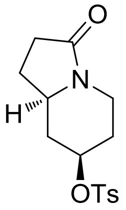
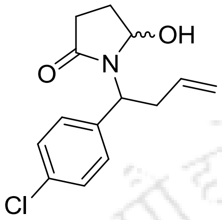
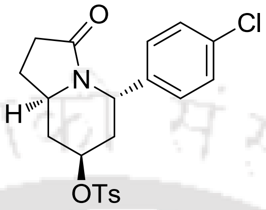
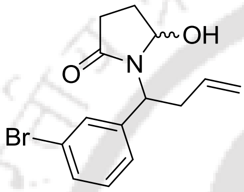
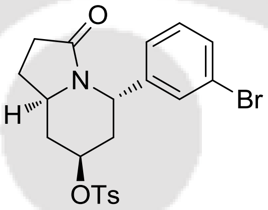
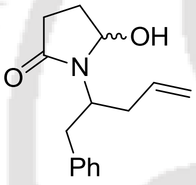
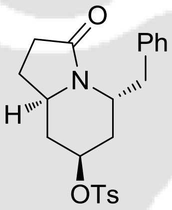
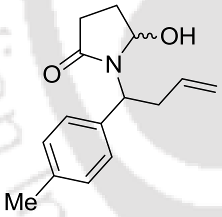
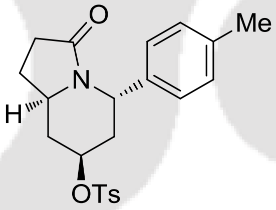
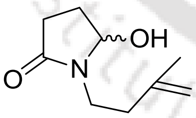
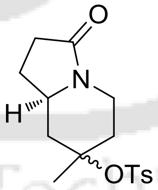
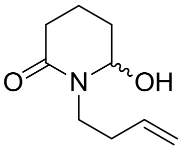
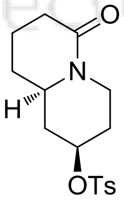
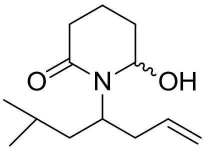
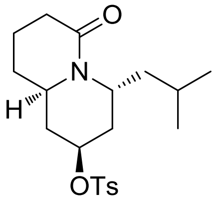
temp.	yield	dr
rt	79%	85:15
40 °C	88%	85:15

Scheme 4.3.1

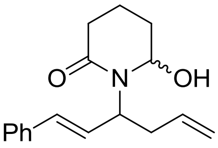
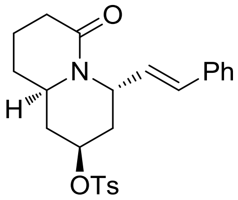
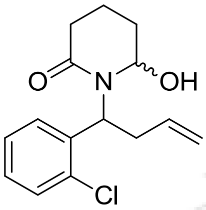
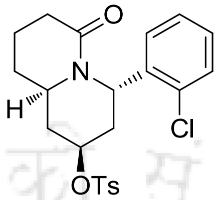
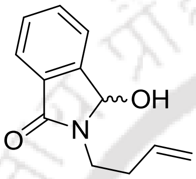
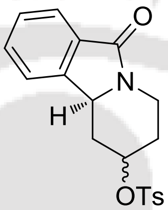
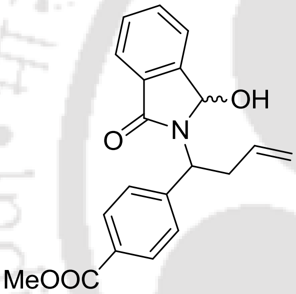
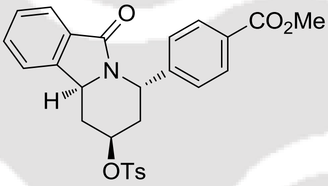
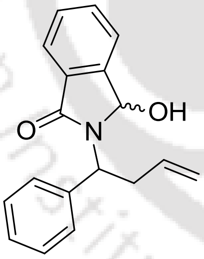
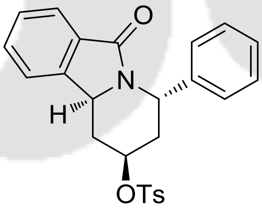
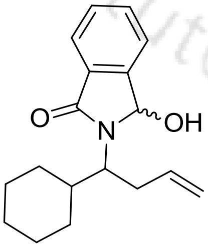
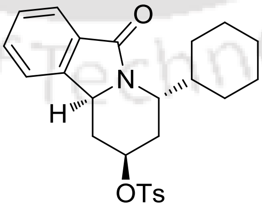
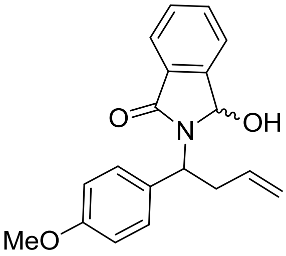
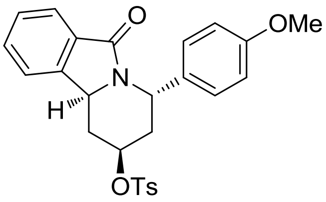
With the established optimal reaction conditions in hand, a variety of regioselectively reduced homoallyl imides **64a-o** derived from cyclic imides and homoallyl alcohols were evaluated and the results are summarized in *Table 4.3.1*. All the substrates produced cyclized products in moderate to high yields without formation of any elimination products. The substrates having no substitution (**64a**, **64g**, and **64k**) at the α-position to nitrogen gave excellent yields with a dr of 50:50 to 90:10. This is due to the absence of a 1,3-diaxial interaction between the axial hydrogen at the α-position to nitrogen of carbocationic intermediate **B** (*Scheme 4.3.2*) and the incoming tosyl group.[20] On the other hand, 5-hydroxy-1-(3-methylbut-3-en-1-yl)pyrrolidin- 2-one **64f** failed to give the desired product, because of steric crowding between the bulky tosyl group and the tertiary carbocation **B** (if H = Me; *Scheme 4.3.2*) formed during the reaction, instead the starting material was recovered in 97%. Reactions of the substrates having alkyl and aryl substitutions at the α-position to nitrogen afforded the desired products with good yields and produced only a single diastereomer. In case of aromatic substitution, the substrates having electron withdrawing aromatic substituents (**64b**, **64c, 64j** and **64l**) gave slightly higher yields, compared to unsubstituted phenyl (**64m**) and electron donating aromatic substituents (**64e** and **64o**). There was no effect of the size of the cyclic imides such as succinimide, glutarimide and phthalimide on yields and diastereoselectivities.

The stereochemistry of compound **65n** was confirmed by ^{1}H, ^{13}C and NOESY experiments. A strong NOE between the H10 hydrogen at C-10 of the piperidine ring and the H7 hydrogen at C-7 of the ring junction of compound **65n** indicates the *cis* relationship between these two hydrogens. Similarly, there was no observation of an NOE between H10 and H12 or between H7 and H12 of the piperidine ring. This clearly supports the *trans* relationship between tosyl and

Table 4.3.1. Synthesis of *O*-Tosyl Azabicyclic Compounds

Entry	Substrate **64**	Product **65**	dr[a]	Yield (%)[b]
a			85:15	88
b			100:0	75
c			100:0	78
d			100:0	81
e			100:0	59
f			----	0
g			90:10	80
h			100:0	86

Continued…………

Entry	Substrate **64**	Product **65**	dr[a]	Yield (%)[b]
i			100:0	68
j			100:0	74
k			50:50	79
l			100:0	83
m			100:0	70
n			100:0	87
o			100:0	54

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

cyclohexyl groups. Finally the stereochemistry of the compound **65n** was confirmed by X-ray crystallographic analysis (*Figure 4.3.1*).[21]

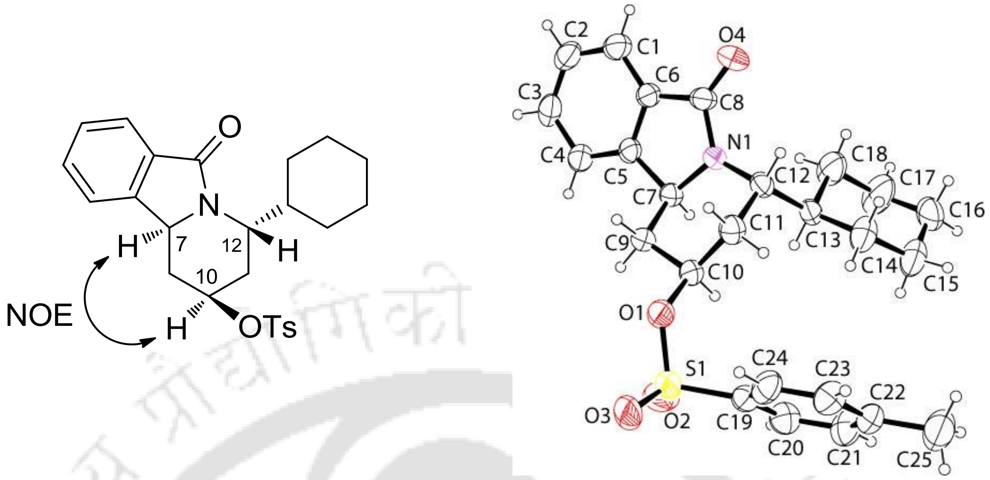
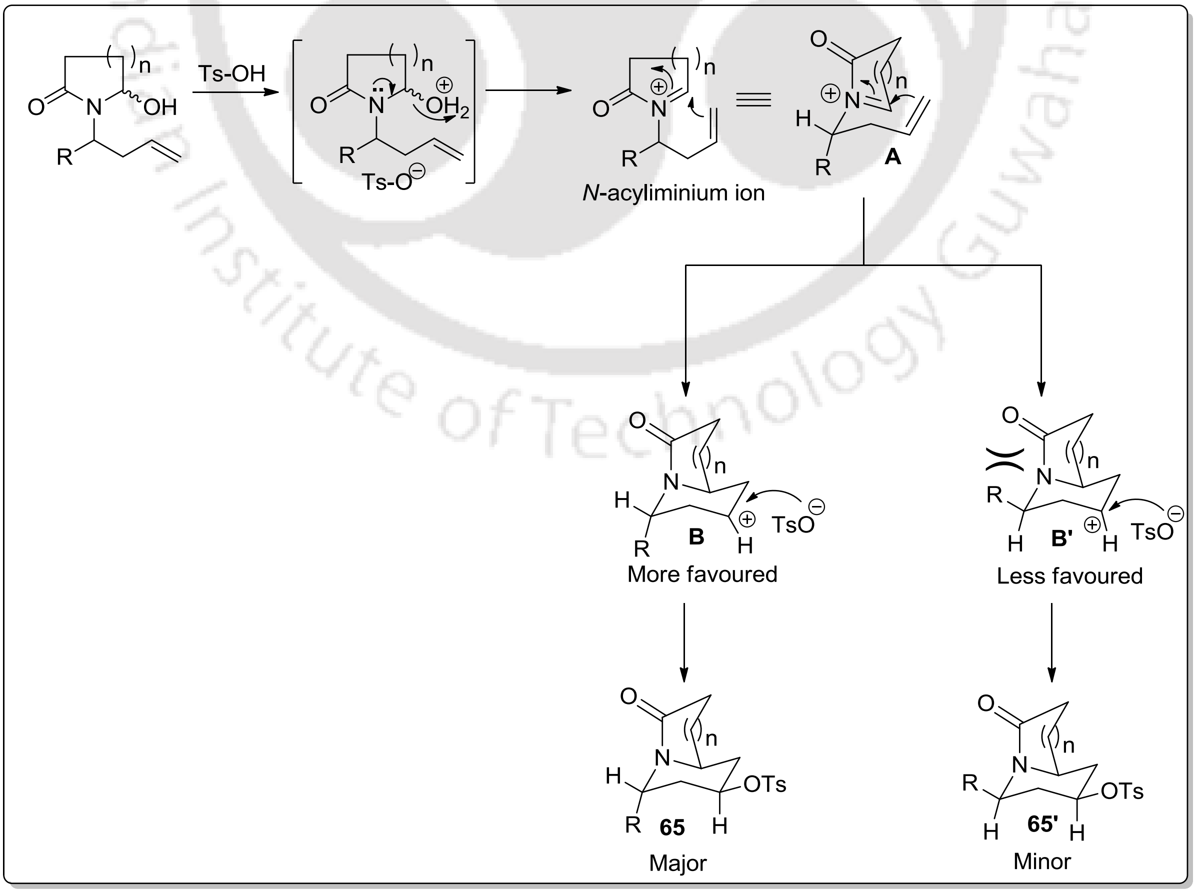


Figure 4.3.1. NOE and crystal structure of (2*R**,4*S**,10b*S**)-4-cyclohexyl-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl 4-methylbenzenesulfonate **65n**

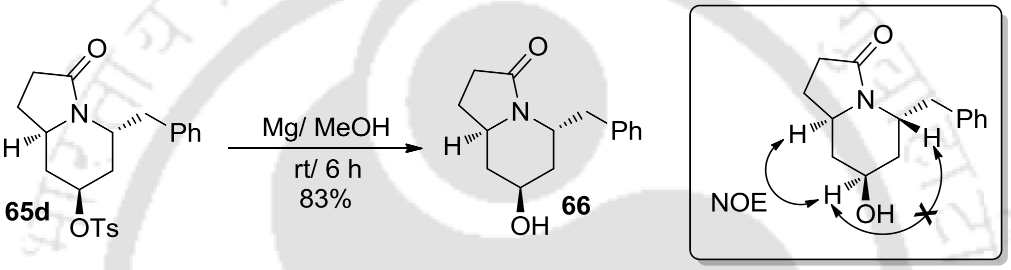
The mechanism of the reaction can be explained as follows. The starting material carbinol in the presence of *p*-TSA gives the corresponding *N*-acyliminium ion intermediate **A**. This intermediate undergoes a 6-*endo*-trig cyclization to give the more stable chair like intermediate **B**, with the R



Scheme 4.3.2. Plausible mechanism of the reaction

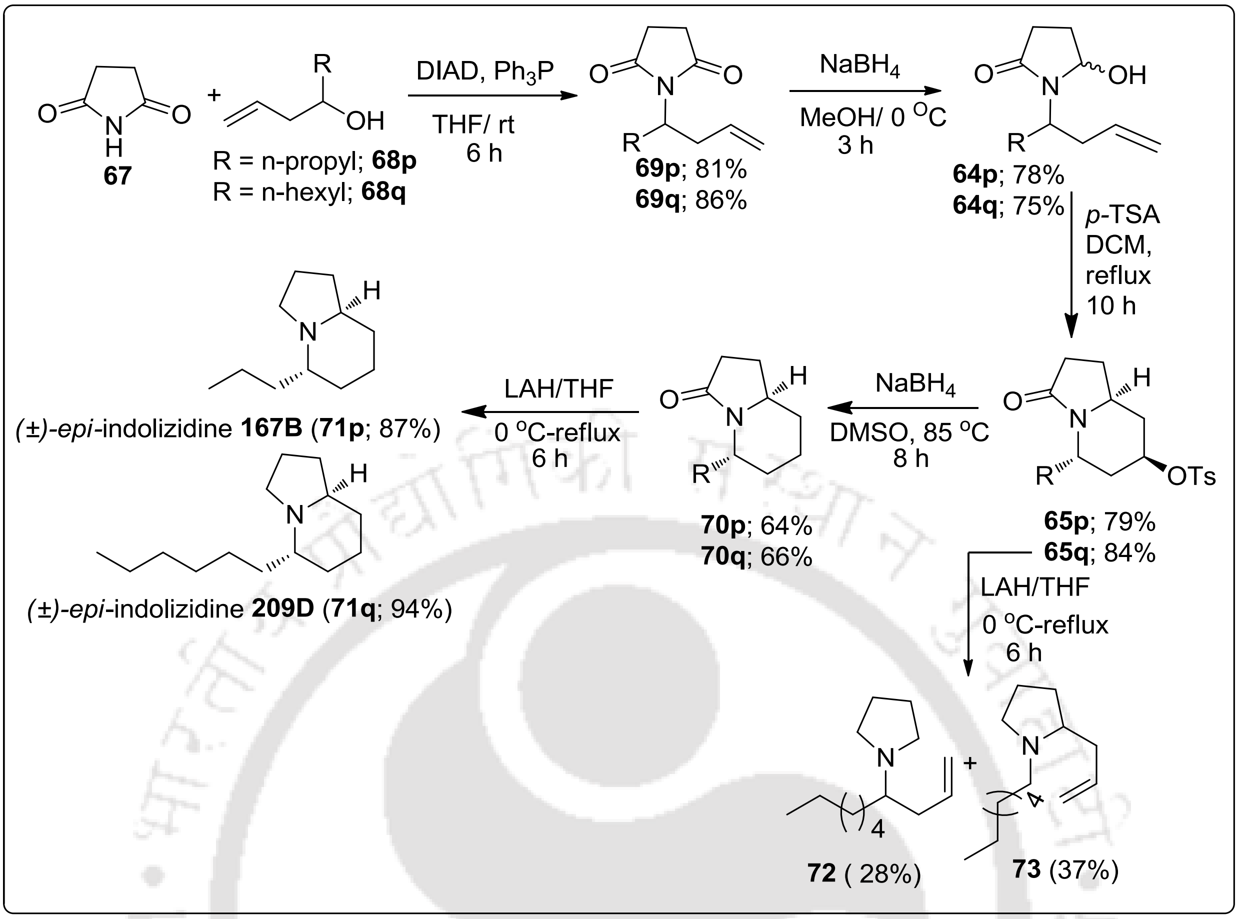
substituent axial, due to more steric crowding and strong angular strain between the substituent R and the lactam carbonyl group.[20] The tosyl nucleophile attacks the carbocation intermediate **B** in an equatorial fashion to give the respective tosyl substituted azabicyclic compounds **65a-o** (*Scheme 4.3.2*).

The conversion of the tosyl group to a hydroxy group was performed for compound (5*R**,7*S**,8a*R**)-5-benzyl-3-oxooctahydroindolizin-7-yl-4-methylbenzenesulfonate **65d** by treating with Mg/MeOH at room temperature to give the corresponding alcohol (5*R**,7*S**,8a*R**)-5-benzyl-7-hydroxyhexahydroindolizin-3(2*H*)-one **66** in 83% yield with retention of configuration. The configuration of the compound **66** was confirmed by the NOESY experiment (*Scheme 4.3.3*).[22]



Scheme 4.3.3. Deprotection of tosyl group and NOE of compound **66**

Synthetic methodology is often limited in value until it can be shown to have some practical applications towards the synthesis of biologically important compounds. The above work has shown that a variety of *O*-tosyl indolizidine and quinolizidine precursors could be accomplished by using *p*-TSA in aza-Prins cyclization. We utilized the above methodology for the synthesis of (±)-*epi*-indolizidine **167B** and **209D**, representative members of the indolizidine alkaloid family (*Scheme 4.3.4*). The secondary homoallyl alcohols **68p–q** were reacted with commercially available succinimide **67** under Mitsunobu reaction conditions[23] to give the corresponding homoallyl imides **69p–q**. The imides **69p–q** were reduced with $NaBH_4$ to the corresponding carbinols **64p–q**.[24] The carbinols **64p–q** were then subjected to the aza-Prins cyclization reaction in the presence of *p*-TSA to give exclusively a single isomer of the tosylated azabicyclic products **65p–q**. To achieve our target, we followed a $LiAlH_4$ reduction procedure for the reduction of lactam and tosyl groups.[25,26] Unfortunately, compound **65q** could not be converted into the desired product and instead ring opening products **72** and **73** were isolated in 28% and 37% yields, respectively. After the failure of this reduction strategy, the tosyl group was first removed using $NaBH_4$ in DMSO at 80 °C to yield the corresponding lactams **70p–q**.[27] The lactams **70p– q** were then finally reduced by LAH in THF at reflux[26] to give the target alkaloids (±)-*epi*-indolizidine **167B** (**71p**) and **209D** (**71q**) in 87% and 94% yields, respectively. The spectral data were in agreement with the literature.[17]



Scheme 4.3.4. Total synthesis of (±)-*epi*-indolizidine **167B** and **209D**

Conclusion:

In conclusion, we have demonstrated the dual role of *p*-TSA in *endo*-trig cyclization reaction for the synthesis of 4-*O*-tosyl piperidine containing hexahydroindolizin-3(2*H*)-one, hexahydro-1*H*-quinolizin-4(6*H*)-one and 1,3,4,10b-tetrahydropyrido [2,1-*a*]isoindol-6(2*H*)-one derivatives. This methodology could be useful for accessing other substituted azabicyclic alkaloids by manipulating the tosyl group. This methodology was successfully applied for the total synthesis of (±)-*epi*-indolizidine **167B** and **209D** in good yields.

4.4. Experimental section

4.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1

4.4.2. Synthesis of Carbinols: The carbinols **64a-o** were synthesized as described in chapter 3 section 3.4.2.

4.4.3. General Procedure for the Synthesis of *O*-Tosyl Azabicyclic Compounds 65a-q:

To a solution of **64** (1.0 equiv.) in dichloromethane (0.17 M) was added *p*-toluenesulfonic acid monohydrate (1.2 equiv.) at once. The reaction mixture was stirred at reflux temperature. The progress of the reaction was monitored by TLC with ethyl acetate as the eluent. The reaction was completed in 10 h and after completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with dichloromethane. The organic layer was washed with brine, dried over (Na_2SO_4) and evaporated to leave the crude product, which was purified by column chromatography using ethyl acetate as the eluent over silica gel to give title compounds **65a-q**.

Typical Procedure for the Synthesis of (7*R**,8a*R**)-3-Oxooctahydroindolizin-7-yl-4-methylbenzenesulfonate (65a):

To a solution of 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one **64a** (78 mg, 0.5 mmol) in dichloromethane (3 mL) was added *p*-toluenesulfonic acid monohydrate (114 mg, 0.6 mmol) at once. The reaction mixture was stirred at reflux temperature. The progress of the reaction was monitored by TLC with ethyl acetate as the eluent. The reaction was completed in 10 h and after completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2x10 mL). The organic layer was washed with brine (5 mL), dried over (Na_2SO_4) and evaporated to leave the crude product, which was purified by column chromatography using ethyl acetate as the eluent over silica gel to give (7*R**,8a*R**)-3-oxooctahydroindolizin-7-yl-4-methylbenzenesulfonate **65a** (136 mg, 88%) as a white solid.

4.4.4. General Procedure for the Reduction of Tosyl Group:

To a stirred solution of **65p-q** (1.0 equiv.) in DMSO (0.2 M), $NaBH_4$ (3.0 equiv.) was added slowly. The reaction mixture was stirred at 85 °C for 8 h. After completion of the reaction, the reaction mixture was washed with brine solution and then extracted with ethylacetate. The combined organic phases were dried over Na_2SO_4 and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluents to give **70p-q**.

4.4.5. General Procedure for the Reduction of Lactams:

Lactams **70p–q** (1.0 equiv.) in THF (0.2 M) were added slowly to a stirred suspension of $LiAlH_4$, (3.0 equiv.) in THF (0.3 M) under a N_2 atmosphere at 0 °C and the reaction mixture was allowed to reflux for 6 h. After completion of the reaction the excess LAH was quenched with ethylacetate at 0 °C. The reaction mixture was filtered through a celite pad. The solvent was removed in a rotary evaporator; the residue was purified by column chromatography on neutral alumina to give the **71p–q**.

4.5. References

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23) (a) Hughes, D. L. *The Mitsunobu Reaction. In Organic Reactions;* Denmark, S., Ed.; Wiley & Sons, 2004; pp 335−656. (b) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1695.

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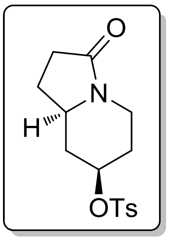
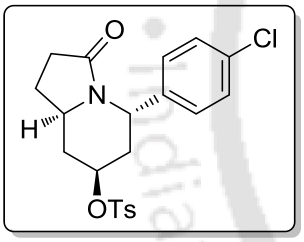
4.6. Characterization Data

(7*R,8a*R**)-3-Oxooctahydroindolizin-7-yl-4-methylbenzenesulfonate (65a):**



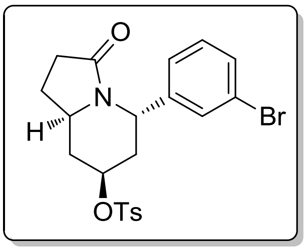
White solid, mp 97–99 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 1.37 (q, *J* = 12.0 Hz, 1 H), 1.51 (dt, *J* = 12.0 and 5.6 Hz, 1 H), 1.56–1.67 (m, 1 H), 1.87–1.92 (m, 1 H), 2.15–2.22 (m, 2 H), 2.32–2.37 (m, 2 H), 2.43 (s, 3 H), 2.59 (dt, *J* = 11.6 and 2.4 Hz, 1 H), 3.42–3.50 (m, 1 H), 4.10 (dd, *J* = 13.6 and 5.2 Hz, 1 H), 4.52 (tt, *J* = 12.0 and 4.4 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) (major diastereomer) δ 21.7, 24.4, 30.0, 30.9, 37.2, 39.7, 55.1, 78.1, 127.7 (2C), 130.1 (2C), 134.2, 145.1, 173.4; **IR** (KBr, neat) 2925, 1685, 1597, 1455, 1358, 1189, 1175, 946, 858, 671, 555 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{19}NO_4S$ $(M + H)^+$ 310.1108, found 310.1100; **ESI-MS**: m/z (relative intensity): 332.2 ($(M + Na)^+$, 100%), 310.2 ($(M + H)^+$, 21%), 242.3 (19), 201.2 (52), 160.1 (58).

(5*S,7*S**,8a*R**)-5-(4-Chlorophenyl)-3-oxooctahydroindolizin-7-yl-4-ethylbenzenesulfonate (65b):**



Colourless gum; yield 157 mg, 75%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.49 (q, *J* = 12.0 Hz, 1 H), 1.66–1.75 (m, 2 H), 1.88 (dt, *J* = 12.0 and 5.6 Hz, 1 H), 2.16 (dd, *J* = 11.6 and 6.0 Hz, 1 H), 2.24 (dd, *J* = 12.4 and 6.0 Hz, 1 H), 2.48 (s, 3 H), 2.49–2.53 (m, 2 H), 3.47–3.54 (m, 1 H), 4.48 (tt, *J* = 11.6 and 4.0 Hz, 1 H), 5.47 (d, *J* = 4.8 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 7.6 Hz, 2 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.9, 24.4, 29.9, 33.5, 39.8, 49.0, 52.2, 75.0 127.7 (2C), 128.0 (2C), 128.8, 129.2 (2C), 130.2 (2C), 133.5, 136.2, 145.3, 174.2; **IR** (KBr, neat) 2924, 1691, 1597, 1492, 1414, 1359, 1189, 1175, 1095, 951, 835, 575, 555 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{22}ClNO_4S$ $(M + H)^+$ 420.1031, found 420.1031; **ESI-MS**: m/z (relative intensity): 442.2 ($(M + Na)^+$, 100%), 420.2 ($(M + H)^+$, 39%), 311.2 (19), 272.1 (24), 270.1 (54), 248.1 (24), 117.1 (33).

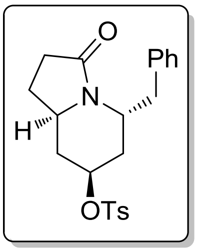
(5*S,7*S**,8aR*)-5-(3-Bromophenyl)-3-oxooctahydroindolizin-7-yl-4-ethylbenzenesulfonate (65c):**



Colourless gum; yield 180 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.50 (q, *J* = 12.0 Hz, 1 H), 1.66–1.76 (m, 1 H), 1.88 (ddd, *J* = 18.0, 12.0 and 6.0 Hz, 1 H), 2.17–2.23 (m, 1 H), 2.25–2.32 (m, 1 H), 2.48 (s, 3 H), 2.50–2.55 (m, 2 H), 3.52–3.61 (m, 1 H), 4.45–4.50 (tt, *J* = 11.6 and 3.6 Hz, 1 H), 5.48 (d, *J* = 5.6 Hz, 1 H), 6.93 (d, *J* = 8.0 Hz, 1 H), 7.14–7.19 (m, 2 H), 7.37–7.41 (m, 3 H), 7.78 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz,

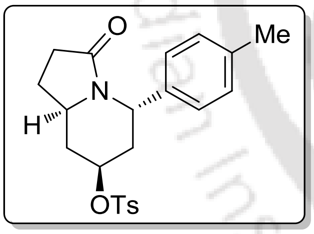
$CDCl_3$) δ 21.9, 24.4, 29.8, 33.5, 39.9, 49.2, 52.3, 75.1, 123.4, 125.0, 127.9 (2C), 129.3, 130.3 (2C), 130.7, 130.9, 133.9, 140.2, 145.3, 174.2; **IR** (KBr, neat) 2924, 1691, 1596, 1419, 1359, 1189, 1176, 949, 855, 671, 554 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{22}BrNO_4S$ $(M + H)^+$ 464.0526, found 464.0529; Found: C, 54.41; H, 4.77; N, 2.99; S, 6.87. **Anal. Calcd.** for $C_{21}H_{22}BrNO_4S$: C, 54.32; H, 4.79; N, 3.02; S, 6.91.

(5*R,7*S**,8a*R**)-5-Benzyl-3-oxooctahydroindolizin-7-yl-4-methylbenzenesulfonate (65d):**



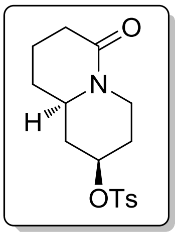
White solid, mp 115–117 °C; yield 162 mg, 81%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.37–1.49 (m, 2 H), 1.57–1.67 (m, 1 H), 1.74 (ddd, *J* = 13.6, 11.2 and 3.2 Hz, 1 H), 2.16–2.27 (m, 1 H), 2.29–2.37 (m, 3 H), 2.47 (s, 3 H), 2.58 (dd, *J* = 12.8 and 10.4 Hz, 1 H), 2.72 (dd, *J* = 13.2 and 6.0 Hz, 1 H), 3.67–3.75 (m, 1 H), 4.45 (pentet, *J* = 5.2 Hz, 1 H), 4.82 (tt, *J* = 12.0 and 4.4 Hz, 1 H), 7.00–7.03 (m, 2 H), 7.21–7.26 (m, 3 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.8, 24.8, 30.2, 31.7, 37.1, 39.9, 48.9, 52.1, 75.6, 126.8, 127.7 (2C), 128.6 (2C), 129.1 (2C), 130.1 (2C), 134.1, 137.2, 145.0, 173.2; **IR** (KBr, neat) 2926, 1682, 1598, 1495, 1417, 1359, 1189, 1174, 1097, 948, 816, 675, 555 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{25}NO_4S$ $(M + H)^+$ 400.1577, found 400.1577; **ESI-MS**: m/z (relative intensity): 422.2 ($(M + Na)^+$, 100%), 400.3 ($(M + H)^+$, 41%), 251.2 (15), 250.2 (55), 228.2 (33), 102.2 (30).

(5*S,7*S**,8a*R**)-3-Oxo-5-(*p*-tolyl)octahydroindolizin-7-yl-4-methylbenzenesulfonate (65e):**



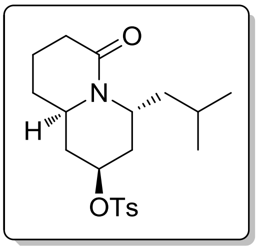
Pale yellow gum; yield 118 mg, 59%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.48 (q, *J* = 12.0 Hz, 1 H), 1.63–1.72 (m, 1 H), 1.85 (ddd, *J* = 18.4, 12.8 and 6.0 Hz, 1 H), 2.13–2.27 (m, 3 H), 2.32 (s, 3 H), 2.49 (s, 3 H), 2.50–2.55 (m, 2 H), 3.49–3.57 (m, 1 H), 4.52–4.56 (tt, *J* = 12.0 and 4.4 Hz, 1 H), 5.46 (d, *J* = 4.8 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 7.6 Hz, 2 H), 7.36 (d, *J* = 7.6 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.1, 21.9, 24.3, 30.0, 33.3, 40.0, 49.2, 52.1, 75.5, 126.1 (2C), 128.0 (2C), 129.3, 129.7 (2C), 130.1 (2C), 134.3, 137.2, 145.2, 174.1; **IR** (KBr, neat) 2923, 1689, 1597, 1416, 1359, 1188, 1176, 948, 856, 680, 556 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{25}NO_4S$ $(M + H)^+$ 400.1577, found 400.1577; **ESI-MS**: m/z (relative intensity): 422.2 ($(M + Na)^+$, 100%), 400.3 ($(M + H)^+$, 60%), 250.2 (84), 228.2 (46), 136.1 (19).

(2*R,9a*R**)-6-Oxooctahydro-1*H*-quinolizin-2-yl-4-methylbenzenesulfonate (65g):**



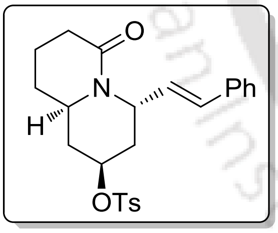
Colorless gum; yield 129 mg, 80%; **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 1.45–1.56 (m, 2 H), 1.60–1.68 (m, 1 H), 1.74–1.82 (m, 2 H), 1.85–2.11 (m, 3 H), 2.23–2.39 (m, 3 H), 2.43 (s, 3 H), 3.21–3.28 (m, 1 H), 4.53 (tt, *J* = 11.6 and 4.4 Hz, 1 H), 4.72–4.79 (m, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) (major diastereomer) δ 19.0, 21.5, 29.6, 31.4, 32.6, 39.6 (2C), 54.0, 78.3, 127.4 (2C), 129.8 (2C), 134.0, 144.8, 169.3; **IR** (KBr, neat) 2948, 1636, 1452, 1356, 1269, 1176, 1093, 941, 849, 817, 670 cm^{-1}; **HRMS** (ESI) calcd for $C_{16}H_{21}NO_4S$ (M + H)$^+$ 324.1264, found 324.1262; **ESI-MS**: m/z (relative intensity): 346.2 ((M + Na)$^+$, 100%), 324.2 ((M + H)$^+$, 66%), 279.2 (28), 215.2 (37), 174.1 (55), 152.1 (41).

(2*S,4*R**,9a*R**)-4-Isobutyl-6-oxooctahydro-1*H*-quinolizin-2-yl- 4-methylbenzenesulfonate (65h):**



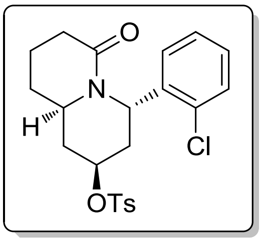
White solid, mp 122–124 °C; yield 163 mg, 86%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.4 Hz, 3 H), 0.85 (d, *J* = 6.4 Hz, 3 H), 1.12–1.31 (m, 2 H), 1.31–1.42 (m, 2 H), 1.44–1.64 (m, 3 H), 1.72–1.82 (m, 2 H), 1.93–2.00 (m, 1 H), 2.07–2.14 (m, 1 H), 2.26–2.39 (m, 2 H), 2.45 (s, 3 H), 3.40–3.47 (m, 1 H), 4.75 (tt, *J* = 11.6 and 4.8 Hz, 1 H), 5.04 (q, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.0, 21.7, 22.5, 22.8, 25.1, 30.1, 33.1, 34.3, 39.3, 40.2, 46.4, 49.4, 76.0, 127.7 (2C), 130.0 (2C), 134.2, 145.0, 169.5; **IR** (KBr, neat) 2954, 1637, 1456, 1360, 1176, 1094, 945, 873, 817, 673 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{29}NO_4S$ (M + H)$^+$ 380.1890, found 380.1890; **ESI-MS**: m/z (relative intensity): 402.3 ((M + Na)$^+$, 100%), 380.3 ((M + H)$^+$, 9%), 271.2 (46), 246.2 (51), 230.2 (84), 208.2 (38).

(2*S,4*S**,9a*R**)-6-Oxo-4-((*E*)-styryl)octahydro-1*H*-quinolizin-2-yl-4-ethylbenzenesulfonate (65i):**



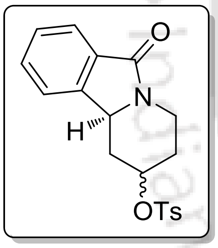
Colorless gum; yield 144 mg, 68%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.52–1.61 (m, 2 H), 1.65–1.75 (m, 1 H), 1.80 (ddd, *J* = 18.6, 13.2 and 6.0 Hz, 2 H), 1.96–2.05 (m, 1 H), 2.07–2.11 (m, 1 H), 2.18–2.22 (m, 1 H), 2.35–2.41 (m, 1 H), 2.46 (s, 3 H), 2.47–2.51 (m, 1 H), 3.48–3.54 (m, 1 H), 4.78 (tt, *J* = 11.4 and 4.2 Hz, 1 H), 5.76 (dd, *J* = 3.6 and 2.4 Hz, 1 H), 5.92 (dd, *J* = 16.2 and 3.6 Hz, 1 H), 6.25 (dd, *J* = 16.2 and 1.8 Hz, 1 H), 7.27 (d, *J* = 7.2 Hz, 3 H), 7.31–7.38 (m, 4 H), 7.81 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.4, 29.9, 30.3, 33.2, 34.4, 40.2, 49.4, 50.7, 75.8, 126.5 (2C), 127.2, 127.9 (2C), 128.1, 128.8 (2C), 130.2 (2C), 132.1, 134.2, 136.3, 145.2, 169.9; **IR** (KBr, neat) 2924, 1635, 1456, 1359, 1176, 1045, 948, 755, 704 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{27}NO_4S$ (M + H)$^+$ 426.1734, found 426.1734; **ESI-MS**: m/z (relative intensity): 448.3 ((M + Na)$^+$, 100%), 426.3 ((M + H)$^+$, 38%), 317.3 (30), 276.2 (65), 150.1 (58), 122.1 (30).

(2*S,4*S**,9a*R**)-4-(2-Chlorophenyl)-6-oxooctahydro-1*H*-quinolizin-2-yl-4-methylbenzenesulfonate (65j):**



Colorless gum; yield 160 mg, 74%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.54–1.65 (m, 2 H), 1.72 (q, *J* = 12.0 Hz, 1 H), 1.76–1.84 (m, 1 H), 1.87–1.97 (m, 2 H), 2.01–2.08 (m, 1 H), 2.10–2.23 (m, 2 H), 2.40–2.48 (m, 4 H), 3.73–3.81 (m, 1 H), 4.67 (tt, *J* = 10.4 and 4.4 Hz, 1 H), 6.05 (dd *J* = 6.8 and 2.8 Hz, 1 H), 7.03–7.07 (m, 1 H), 7.17–7.20 (m, 2 H), 7.24–7.27 (m, 2 H), 7.29–7.33 (m, 1 H), 7.67 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.3, 21.8, 30.3, 32.9, 33.8, 39.6, 50.4, 52.9, 75.6, 126.90, 126.93, 127.7 (2C), 128.5, 130.0 (2C), 130.9, 133.1, 133.9, 137.8, 145.1, 169.9; **IR** (KBr, neat) 2925, 1643, 1443, 1356, 1177, 1039, 950, 846, 759 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{24}ClNO_4S$ $(M + H)^+$ 434.1187, found 434.1189; **ESI-MS**: m/z (relative intensity): 456.2 ($(M + Na)^+$, 100%), 434.2 ($(M + H)^+$, 95%), 334.2 (24), 284.2 (24), 262.2 (52), 118.2 (40).

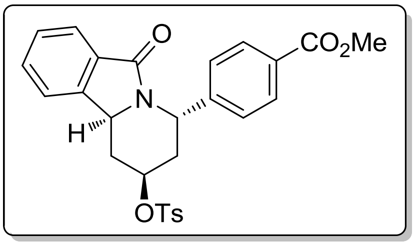
(2*R,10b*S**)-6-Oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl-4-methylbenzenesulfonate and (2*S**,10b*S**)-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl-4-methylbenzenesulfonate (65k, mixture of isomers with 50:50 ratio):**



White solid, mp 129–131 °C; yield 141 mg, 79%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.35 (q, *J* = 12.0 Hz, 1 H), 1.59 (dd, *J* = 12.0 and 5.6 Hz, 1 H), 1.89–2.03 (m, 1 H), 2.47 (s, 3 H), 2.60–2.72 (m, 1 H), 2.98 (t, *J* = 12.8 Hz, 0.5 H), 3.27 (t, *J* = 12.8 Hz, 0.5 H), 4.31–4.38 (m, 1 H), 4.48 (dd, *J* = 13.6 and 4.8 Hz, 0.5 H), 4.62–4.69 (m, 0.5 H), 4.78–4.87 (m, 0.5 H), 5.01 (brs, 0.5 H), 7.34–7.41 (m, 3 H), 7.43–7.49 (m, 1 H), 7.50–7.56 (m, 1 H), 7.82 (d, *J* = 7.2 Hz, 2 H), 7.87 (d, *J* = 8.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.8 (2C), 29.8, 31.5, 33.8, 36.2, 36.5, 37.8, 53.2, 56.7, 75.9, 78.0, 121.8 (2C), 123.9, 124.0, 127.7 (2C), 127.8 (2C), 128.5, 128.7, 130.1 (2C), 130.2 (2C), 131.5, 131.8, 131.9, 132.1, 133.8, 134.0, 144.0, 145.0, 145.2, 145.3, 166.1, 166.2; **IR** (KBr, neat) 2925, 1689, 1597, 1421, 1362, 1290, 1189, 1175, 1097, 989, 947, 899, 851, 761, 734, 689, 671 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{19}NO_4S$ $(M + H)^+$ 358.1108, found 358.1109; **ESI-MS**: m/z (relative intensity): 380.2 ($(M + Na)^+$, 100%), 358.2 ($(M + H)^+$, 78%), 249.2 (27), 208.1 (60), 186.1 (83), 132.1 (12).

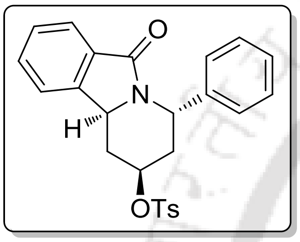
Methyl 4-((2*R,4*S**,10b*S**)-6-oxo-2-(tosyloxy)-1,2,3,4,6,10bhexahydropyrido[2,1-*a*]isoindol-4-yl)benzoate (65l):**

Colorless gum; yield 204 mg, 83%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.48 (q, *J* = 12.0 Hz, 1 H), 1.95–2.32 (m, 1 H), 2.53 (s, 3 H), 2.66 (dd, *J* = 12.0 and 3.0 Hz, 2 H), 3.93 (s, 3 H), 4.37 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 4.72 (tt, *J* = 11.4 and 3.6 Hz, 1 H), 5.86 (d, *J* = 6.0 Hz, 1 H), 7.00 (d, *J* = 7.8 Hz, 2 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 7.58



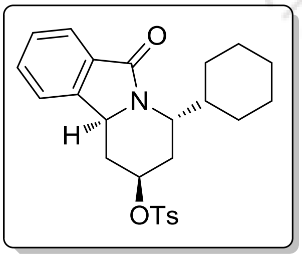
(t, J = 7.8 Hz, 1 H), 7.80 (d, J = 8.4 Hz, 2 H), 7.91–7.94 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.9, 33.8, 38.0, 48.9, 52.4, 54.3, 75.2, 122.1, 124.5, 126.4 (2C), 128.1 (2C), 129.0, 129.6, 130.3 (2C), 130.4 (2C), 131.3, 132.3, 133.7, 143.4, 144.4, 145.5, 166.7, 167.1; **IR** (KBr, neat) 2924, 1721, 1693, 1597, 1467, 1411, 1362, 1280, 1189, 1176, 1112, 964, 853, 754, 665 cm^{-1}; **HRMS** (ESI) calcd for $C_{27}H_{25}NO_6S$ $(M + H)^+$ 492.1475, found 492.1483; **ESI-MS**: m/z (relative intensity): 514.3 ($(M + Na)^+$, 100%), 492.3 ($(M + H)^+$, 80%), 342.3 (71), 320.2 (57), 310.4 (20).

(2*R,4*S**,10b*S**)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl-4-methylbenzenesulfonate (65m):**



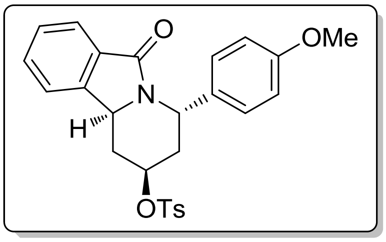
Pale yellow gum; yield 151 mg, 70%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.47 (q, J = 12.0 Hz, 1 H), 1.92–2.00 (m, 1 H), 2.52 (s, 3 H), 2.65 (dd, J = 12.4 and 4.0 Hz, 2 H), 4.38 (dd, J = 12.4 and 3.6 Hz, 1 H), 4.81 (tt, J = 11.2 and 4.0 Hz, 1 H), 5.83 (d, J = 5.6 Hz, 1 H), 6.97–7.01 (m, 2 H), 7.23–7.28 (m, 3 H), 7.36 (d, J = 7.2 Hz, 1 H), 7.41 (d, J = 8.0 Hz, 2 H), 7.50–7.59 (m, 2 H), 7.83 (d, J = 8.0 Hz, 2 H), 7.92 (d, J = 7.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.9, 33.7, 38.1, 48.9, 54.2, 75.5, 122.1, 124.5, 126.3 (2C), 127.7, 128.1 (2C), 128.9, 129.1 (2C), 130.2 (2C), 131.6, 132.1, 133.8, 138.1, 144.5, 145.3, 167.0; **IR** (KBr, neat) 2924, 1692, 1407, 1361, 1177, 1095, 963, 854, 696, 661 cm^{-1}; **HRMS** (ESI) calcd for $C_{25}H_{23}NO_4S$ $(M + H)^+$ 434.1421, found 434.1425; **ESI-MS**: m/z (relative intensity): 456.2 ($(M + Na)^+$, 100%), 300.2 (17), 284.2 (62), 211.3 (18), 168.2 (50).

(2*R,4*S**,10b*S**)-4-Cyclohexyl-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl-4-methylbenzenesulfonate (65n):**



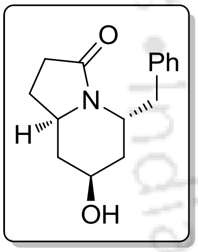
Colorless solid, mp 169–171 °C; yield 191 mg, 87%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86–1.13 (m, 5 H), 1.22–1.28 (m, 1 H), 1.30–1.41 (m, 3 H), 1.42–1.55 (m, 2 H), 1.59–1.71 (m, 2 H), 1.98–2.05 (m, 1 H), 2.47 (s, 3 H), 2.69–2.76 (m, 1 H), 4.16 (dd, J = 10.4 and 5.6 Hz, 1 H), 4.41 (dd, J = 12.4 and 3.2 Hz, 1 H), 4.81–4.91 (m, 1 H), 7.36–7.41 (m, 3 H), 7.47 (t, J = 8.4 Hz, 1 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.81–7.86 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.8, 25.8, 26.0 (2C), 29.7, 30.0, 31.8, 38.0, 38.5, 52.1, 54.1, 75.7, 121.9, 124.1, 128.0 (2C), 128.7, 130.1 (2C), 131.7, 131.8, 133.8, 144.3, 145.3, 166.7; **IR** (KBr, neat) 2928, 1689, 1410, 1361, 1179, 1096, 966, 941, 853, 827, 737, 691 cm^{-1}; **HRMS** (ESI) calcd for $C_{25}H_{29}NO_4S$ (M + H)+ 440.1890, found 440.1893; **ESI-MS**: m/z (relative intensity): 462.3 ($(M + Na)^+$, 100%), 440.3 ($(M + H)^+$, 93%), 331.3 (16), 290.2 (31), 268.2 (45).

(2*R,4*S**,10b*S**)-4-(4-Methoxyphenyl)-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl-4-methylbenzenesulfonate (65o):**



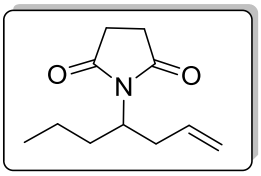
Colorless gum; yield 125 mg, 54%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (q, *J* = 12.0 Hz, 1 H), 1.93 (ddd, *J* = 18.4, 13.2 and 6.0 Hz, 1 H), 2.51 (s, 3 H), 2.63 (dd, *J* = 10.8 and 2.0 Hz, 2 H), 3.78 (s, 3 H), 4.35 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 4.84 (tt, *J* = 11.2 and 4.0 Hz, 1 H), 5.78 (d, *J* = 5.6 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 6.8 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.49–7.58 (m, 2 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.91 (d, *J* = 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.9, 33.7, 38.0, 48.3, 54.1, 55.4, 75.6, 114.4 (2C), 122.1, 124.4, 127.5 (2C), 128.1 (2C), 128.9, 130.0, 130.2 (2C), 131.6, 132.0, 133.9, 144.4, 145.3, 158.9, 166.9; **IR** (KBr, neat) 2924, 1692, 1512, 1467, 1407, 1360, 1249, 1188, 1176, 1033, 964, 854, 738, 693, 665 cm^{-1}; **HRMS** (ESI) calcd for $C_{26}H_{25}NO_5S$ $(M + H)^+$ 464.1526, found 464.1528; **ESI-MS**: m/z (relative intensity): 486.3 ($(M + Na)^+$, 100%), 464.3 ($(M + H)^+$, 14%), 355.2 (11), 314.2 (53), 184.1 (10).

(5*R,7*S**,8a*R**)-5-Benzyl-7-hydroxyhexahydroindolizin-3(2*H*)- one (66):**



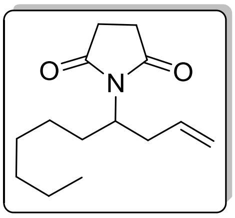
Colorless liquid; yield 51 mg, 83%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.17 (q, *J* = 12.0 Hz, 1 H), 1.30–1.37 (m, 1 H), 1.60–1.69 (m, 1 H), 1.89–1.93 (m, 1 H), 2.18–2.28 (m, 2 H), 2.29–2.37 (m, 2 H), 2.72 (dd, *J* = 13.6 and 10.0 Hz, 1 H), 2.82 (dd, *J* = 13.6 and 6.8 Hz, 1 H), 3.72–3.80 (m, 1 H), 4.11 (tt, *J* = 11.6 and 4.4 Hz, 1 H), 4.51–4.58 (m, 1 H), 7.20–7.32 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.1, 30.6, 35.4, 37.5, 42.9, 49.3, 52.7, 64.9, 126.8, 128.8 (2C), 129.3 (2C), 138.1, 173.6; **IR** (KBr, neat) 2923, 1659, 1453, 1421, 1286, 1081, 1027, 751, 701 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{19}NO_2$ $(M + H)^+$ 246.1489, found 246.1498. **ESI-MS**: m/z (relative intensity): 268.2 ($(M + Na)^+$, 100%), 246.2 ($(M + H)^+$, 25%), 224.2 (8), 202.2 (7), 137.4 (11).

1-(Hept-1-en-4-yl)pyrrolidine-2,5-dione (69p):



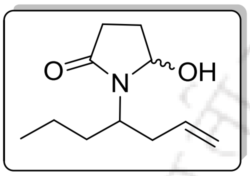
Pale yellow liquid; yield 794 mg, 81%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.6 Hz, 3 H), 1.14–1.26 (m, 2 H), 1.54–1.63 (m, 1 H), 1.91–2.01 (m, 1 H), 2.33–2.40 (m, 1 H), 2.60 (s, 4 H), 2.63–2.73 (m, 1 H), 4.09–4.17 (m, 1 H), 4.93–5.00 (m, 2 H), 5.56–5.66 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 19.9, 28.0 (2C), 33.3, 36.1, 52.0, 117.7, 135.0, 177.8 (2C); **IR** (KBr, neat) 2960, 2873, 1700, 1396, 1371, 1190, 1124, 920, 820 cm^{-1}; **HRMS** (ESI) calcd for $C_{11}H_{17}NO_2$ $(M + H)^+$ 196.1332, found 196.1333; Found: C, 67.73; H, 8.77; N, 7.14. **Anal. Calcd**. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17.

1-(Dec-1-en-4-yl)pyrrolidine-2,5-dione (69q):



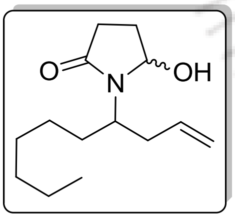
Yellow liquid; yield 1.13 g, 86%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 6.8 Hz, 3 H), 1.11–1.25 (m, 8 H), 1.55–1.65 (m, 1 H), 1.87–1.98 (m, 1 H), 2.30–2.38 (m, 1 H), 2.59 (s, 4 H), 2.60–2.69 (m, 1 H), 4.04–4.13 (m, 1 H), 4.90–4.99 (m, 2 H), 5.53–5.65 (m, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 14.1, 22.6, 26.6, 28.0 (2C), 28.9, 31.2, 31.7, 36.1, 52.3, 117.6, 134.9, 177.7 (2C); **IR** (KBr, neat) 2928, 2857, 1704, 1397, 1372, 1177, 1143, 994, 918, 820 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{23}NO_2$ $(M + H)^+$ 238.1802, found 238.1799; Found: C, 70.79; H, 9.79; N, 5.95. **Anal. Calcd**. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90.

1-(Hept-1-en-4-yl)-5-hydroxypyrrolidin-2-one (64p, mixture of isomers with 50:50 ratio):



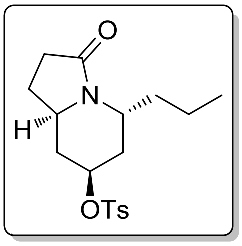
Pale yellow gum; yield 614 mg, 78%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3 H), 1.16–1.28 (m, 2 H), 1.30–1.41 (m, 1 H), 1.49–1.70 (m, 2 H), 1.75–1.93 (m, 1 H), 2.19–2.37 (m, 2 H), 2.41–2.52 (m, 1 H), 2.57–2.68 (m, 1 H), 3.94–4.01 (m, 0.5 H), 4.02–4.09 (m, 0.5 H), 5.01–5.11 (m, 2 H), 5.23 (t, *J* = 4.8 Hz, 1 H), 5.65–5.75 (m, 0.5 H), 5.78–5.88 (m, 0.5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 13.9, 14.0, 19.8, 20.0, 29.0 (2C), 29.3, 29.4, 33.3, 36.4, 36.5, 39.1, 52.2, 52.3, 82.5, 82.6, 116.9, 117.0, 135.6, 136.1, 176.0, 176.1; **IR** (KBr, neat) 2958, 1664, 1449, 1281, 1182, 1064, 989, 915, 787 cm^{-1}; **HRMS** (ESI) calcd for $C_{11}H_{19}NO_2$ $(M + H)^+$ 198.1489, found 198.1492; Found: C, 67.04; H, 9.69; N, 7.06. **Anal. Calcd**. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10.

1-(Dec-1-en-4-yl)-5-hydroxypyrrolidin-2-one (64q, mixture of isomers with 60:40 ratio):



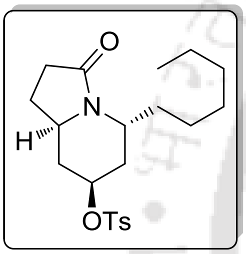
Pale yellow gum; yield 717 mg, 75%; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.8 Hz, 3 H), 1.20–1.35 (m, 7 H), 1.50–1.58 (m, 0.6 H), 1.62–1.70 (m, 1 H), 1.74–1.80 (m, 0.4 H), 1.86–1.94 (m, 1 H), 2.15–2.35 (m, 3 H), 2.43 (t, *J* = 7.2 Hz, 1 H), 2.49–2.68 (m, 2 H), 3.89–4.00 (m, 1 H), 4.75 (brs, 1 H), 4.98–5.10 (m, 2 H), 5.23 (brs, 1 H), 5.63–5.74 (m, 0.4 H), 5.75–5.86 (m, 0.6 H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 13.93, 13.95, 22.50, 22.55, 26.5, 26.6, 28.9, 29.0, 29.20, 29.22, 29.28, 29.32, 31.0, 31.6, 31.7, 34.1, 36.4, 39.0, 52.2, 52.4, 82.3, 82.4, 116.5, 116.7, 135.6, 136.0, 175.5, 175.6; **IR** (KBr, neat) 2957, 1669, 1458, 1281, 1166, 1065, 990, 915, 786 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{25}NO_2$ $(M + H)^+$ 240.1958, found 240.1957; **ESI-MS**: m/z (relative intensity): 262.2 ($(M + Na)^+$, 61%), 240.2 ($(M + H)^+$, 66%), 222.2 (100), 210.3 (61), 185.2 (27), 130.2 (79).

(5*S,7*S**,8a*S**)-3-Oxo-5-propyloctahydroindolizin-7-yl-4-methylbenzenesulfonate (65p):**



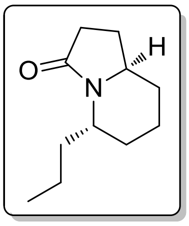
Colorless liquid; yield 834 mg, 79%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3 H), 1.12–1.20 (m, 2 H), 1.24–1.33 (m, 2 H), 1.39–1.46 (m, 1 H), 1.54–1.65 (m, 2 H), 1.77–1.82 (m, 1 H), 2.17–2.25 (m, 2 H), 2.37 (dd, *J* = 9.2 and 7.6 Hz, 2 H), 2.46 (s, 3 H), 3.58–3.66 (m, 1 H), 4.26 (q, *J* = 6.8 Hz, 1 H), 4.73 (tt, *J* = 12.0 and 4.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.7, 19.5, 21.7, 24.4, 30.1, 33.1, 34.0, 40.0, 47.2, 51.6, 75.7, 127.7 (2C), 130.0 (2C), 134.2, 145.0, 173.5; **IR** (KBr, neat) 2926, 1684, 1599, 1458, 1420, 1360, 1177, 1096, 946, 848, 816, 678 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{25}NO_4S$ $(M + H)^+$ 352.1577, found 352.1579; **ESI-MS**: m/z (relative intensity): 374.2 ($(M + Na)^+$, 100%), 352.2 ($(M + H)^+$, 46%), 243.2 (55), 202.2 (32), 180.2 (37).

(5*S,7*S**,8a*S**)-5-Hexyl-3-oxooctahydroindolizin-7-yl-4-methylbenzenesulfonate (65q):**



Pale yellow liquid; yield 990 mg, 84%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3 H), 1.07–1.15 (m, 1 H), 1.16–1.46 (m, 10 H), 1.52–1.65 (m, 2 H), 1.76–1.83 (m, 1 H), 2.15–2.26 (m, 2 H), 2.36 (dd, *J* = 9.6 and 8.0 Hz, 2 H), 2.45 (s, 3 H), 3.58–3.65 (m, 1 H), 4.22 (q, *J* = 7.2 Hz, 1 H), 4.72 (tt, *J* = 11.6 and 4.4 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.1, 21.6, 22.5, 24.3, 26.1, 28.9, 30.1, 30.9, 31.6, 33.8, 40.0, 47.3, 51.5, 75.7, 127.6 (2C), 129.9 (2C), 134.1, 145.0, 173.3; **IR** (KBr, neat) 2928, 1688, 1417, 1361, 1288, 1177, 1095, 946, 851, 678 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{31}NO_4S$ $(M + H)^+$ 394.2047, found 394.2047; Found: C, 64.19; H, 7.93; N, 3.52; S, 8.09. **Anal. Calcd.** for $C_{21}H_{31}NO_4S$: C, 64.08; H, 7.94; N, 3.56; S, 8.15.

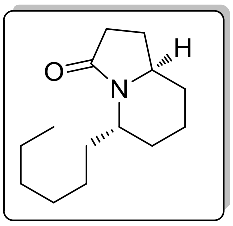
(5*S,8a*R**)-5-Propylhexahydroindolizin-3(2*H*)-one (70p):**



Colorless liquid; yield 231 mg, 64%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.6 Hz, 3 H), 1.07–1.44 (m, 5 H), 1.46–1.64 (m, 5 H), 1.80–1.87 (m, 1 H), 2.09–2.21 (m, 1 H), 2.31–2.39 (m, 2 H), 3.52–3.60 (m, 1 H), 4.20 (q, *J* = 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.1, 19.0, 19.7, 25.3, 27.5, 30.4, 32.3, 33.9, 48.0, 53.3, 173.8; **IR** (KBr, neat) 2933, 1682, 1418, 1371, 1306, 1271, 1155, 1078, 749 cm^{-1}; **HRMS** (ESI) calcd for $C_{11}H_{19}NO$ $(M + H)^+$ 182.1539, found 182.1533; **ESI-MS**: m/z (relative intensity): 204.2 ($(M + Na)^+$, 100%), 182.2 ((M + H)+, 61%), 168.2 (44), 166.2 (15).

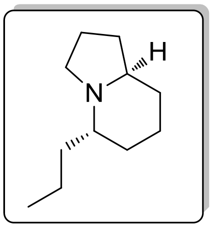
(5*S,8a*R**)-5-Hexylhexahydroindolizin-3(2*H*)-one (70q):**

Colorless liquid; yield 294 mg, 66%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.8 Hz, 3 H), 1.06–1.26 (m, 9 H), 1.36–1.62 (m, 7 H), 1.78–1.86 (m, 1 H), 2.11–2.20 (m, 1 H), 2.33 (dd, *J* = 9.2 and 7.6 Hz, 2 H), 3.51–3.59 (m, 1 H), 4.17 (q, *J* = 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz,



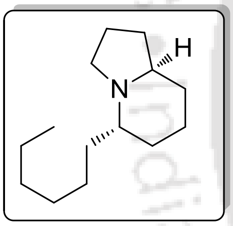
$CDCl_3$) δ 14.1, 19.0, 22.6, 25.3, 26.3, 27.4, 29.2, 30.1, 30.3, 31.8, 33.9, 48.1, 53.2, 173.5; **IR** (KBr, neat) 2928, 1684, 1416, 1306, 1269, 1020, 738 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{25}NO$ (M + H)$^+$ 224.2009, found 224.2009; **ESI-MS**: m/z (relative intensity): 246.2 ((M + Na)$^+$, 95%), 224.2 ((M + H)$^+$, 52%), 210.2 (100), 204.2 (48), 168.2 (43).

(5*S,8a*R**)-5-Propyloctahydroindolizine (71p):**



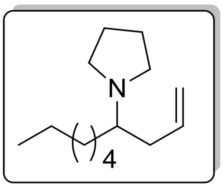
Colorless liquid; yield 145 mg, 87%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.2 Hz, 3 H), 1.03–1.15 (m, 2 H), 1.21–1.33 (m, 3 H), 1.35–1.49 (m, 3 H), 1.52–1.59 (m, 3 H), 1.65–1.76 (m, 3 H), 2.33–2.41 (m, 1 H), 2.55 (q, *J* = 9.2 Hz, 1 H), 2.74 (ddd, *J* = 11.6, 8.4 and 3.2 Hz, 1 H), 2.86 (ddd, *J* = 12.8, 6.8 and 3.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.5, 19.5, 20.9, 21.0, 25.8, 27.7, 30.8, 31.4, 48.8, 55.1, 55.3; **IR** (KBr, neat) 2868, 2802, 1459, 1378, 1263, 1142, 1091, 896, 740 cm^{-1}; **HRMS** (ESI) calcd for $C_{11}H_{21}N$ (M + H)$^+$ 168.1747, found 168.1756; **ESI-MS**: m/z (relative intensity): 168.2 ((M + H)$^+$, 100%), 144.2 (23), 130.2 (45), 126.2 (44).

(5*S,8a*R**)-5-Hexyloctahydroindolizine (71q):**



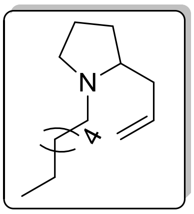
Colorless liquid; yield 196 mg, 94%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.13–1.18 (m, 2 H), 1.24–1.38 (m, 9 H), 1.41–1.55 (m, 3 H), 1.56–1.66 (m, 3 H), 1.71–1.82 (m, 3 H), 2.43–2.48 (m, 1 H), 2.63 (dd, *J* = 17.4 and 9.6 Hz, 1 H), 2.81 (ddd, *J* = 12.0, 9.0 and 3.0 Hz, 1 H), 2.90 (ddd, *J* = 13.2, 6.0 and 2.4 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.3, 19.6, 21.1, 22.9, 23.8, 27.8, 27.9, 29.9, 30.9, 31.4, 32.1, 49.0, 55.4, 55.7; **IR** (KBr, neat) 2927, 2857, 2802, 1460, 1378, 1262, 1148, 1088, 749 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{27}N$ (M + H)$^+$ 210.2216, found 210.2222; **ESI-MS**: m/z (relative intensity): 210.3 ((M + H)$^+$, 50%), 204.2 (100), 202.2 (15), 182.2 (22), 145.0 (9).

1-(Dec-1-en-4-yl)pyrrolidine (72):



Pale yellow liquid; yield 58 mg, 28%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.25–1.37 (m, 7 H), 1.40–1.46 (m, 1 H), 1.65–1.71 (m, 2 H), 1.95–2.02 (m, 4 H), 2.42–2.48 (m, 1 H), 2.51–2.57 (m, 1 H), 2.79 (brs, 1 H), 3.02 (brs, 4 H), 5.13–5.19 (m, 2 H), 5.80–5.88 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.3, 22.8, 23.7 (2C), 25.9, 29.7, 31.3, 31.9, 35.8, 51.5 (2C), 63.9, 117.4, 135.3; **IR** (KBr, neat) 2923, 2856, 1632, 1457, 1030, 738, 610 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{27}N$ (M + H)$^+$ 210.2216, found 210.2218; **ESI-MS**: m/z (relative intensity): 210.2 ((M + H)$^+$, 100%), 168.2 (77), 97.1 (17), 83.1 (21).

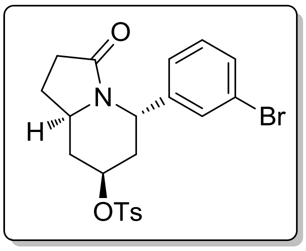
2-Allyl-1-heptylpyrrolidine (73):

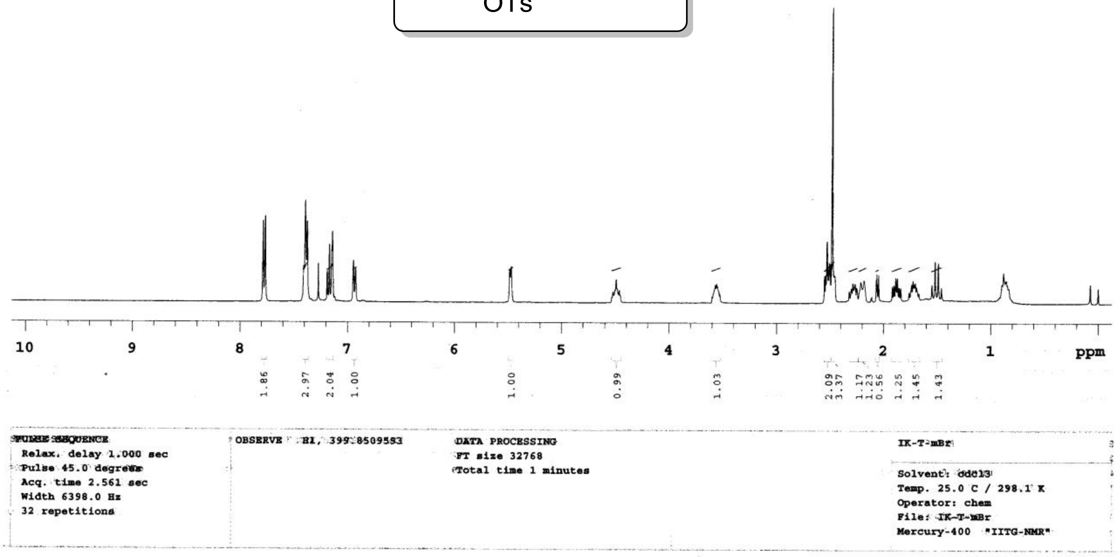


Pale yellow liquid; yield 77 mg, 37%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.23–1.35 (m, 10 H), 1.96–2.06 (m, 4 H), 2.16–2.30 (m, 2 H), 2.70–2.90 (m, 3 H), 3.20–3.35 (m, 2 H), 5.18 (d, *J* = 10.0 Hz, 1 H), 5.27 (d, *J* = 17.2 Hz, 1 H), 5.67–5.79 (m, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.2, 21.9, 22.8, 27.0, 27.6, 29.2, 30.0, 31.9, 36.8, 53.8, 54.4, 65.9, 117.9, 134.6; **IR** (KBr, neat) 2924, 2854, 1628, 1465, 1018, 734, 611 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{27}N$ $(M + H)^+$ 210.2216, found 210.2221; **ESI-MS**: m/z (relative intensity): 210.2 ($(M + H)^+$, 100%), 168.2 (24).

4.7. Selected Spectra

^{1}H and ^{13}C NMR spectra of **(5*S**,7*S**,8a*R**)-5-(3-Bromophenyl)-3-oxooctahydroindolizin-7-yl-4-ethylbenzenesulfonate**





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PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions
OBSERVE   H1, 399.8509583
DATA PROCESSING
FT size 32768
Total time 1 minutes
IK-T-mBr

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: IK-T-mBr
Mercury-400  "IITG-NMR"
```

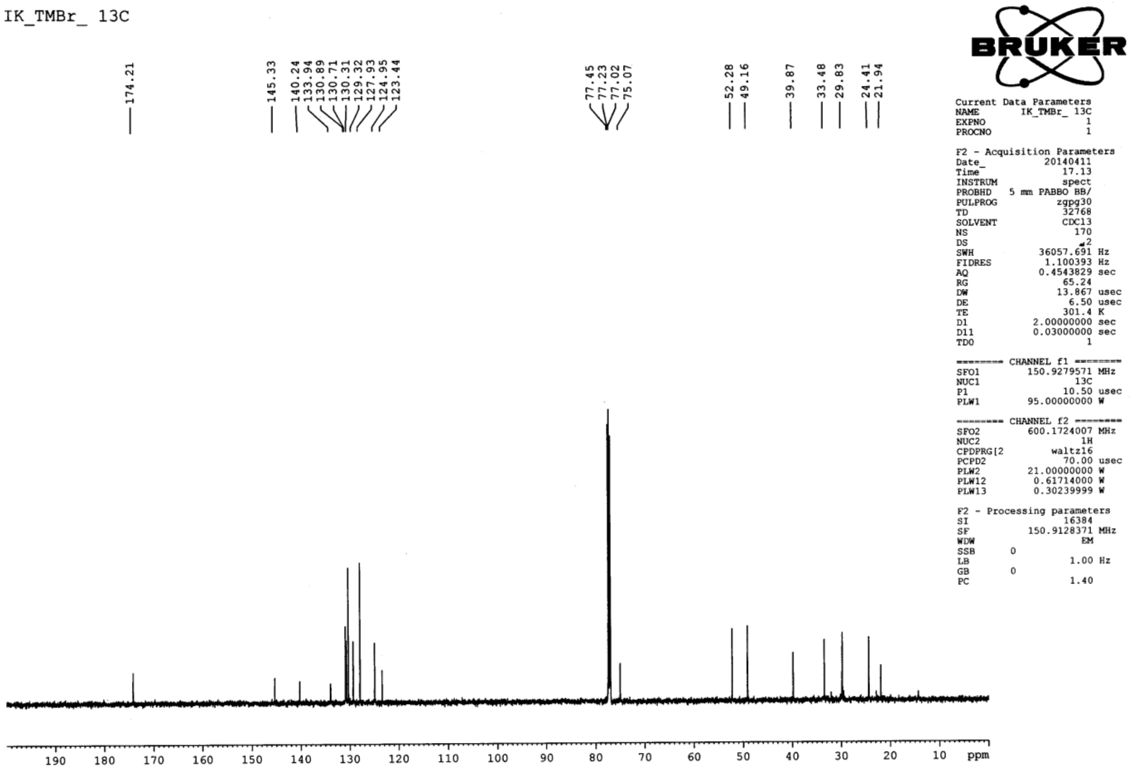

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Current Data Parameters
NAME          IK_TMBr_ 13C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
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Time                 17.13
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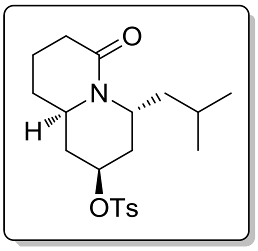
PULPROG            zgpg30
TD                   32768
SOLVENT              CDC13
NS                     170
DS                       2
SWH              36057.691 Hz
FIDRES            1.100393 Hz
AQ               0.4543829 sec
RG                   65.24
DW                  13.867 usec
DE                    6.50 usec
TE                   301.4 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

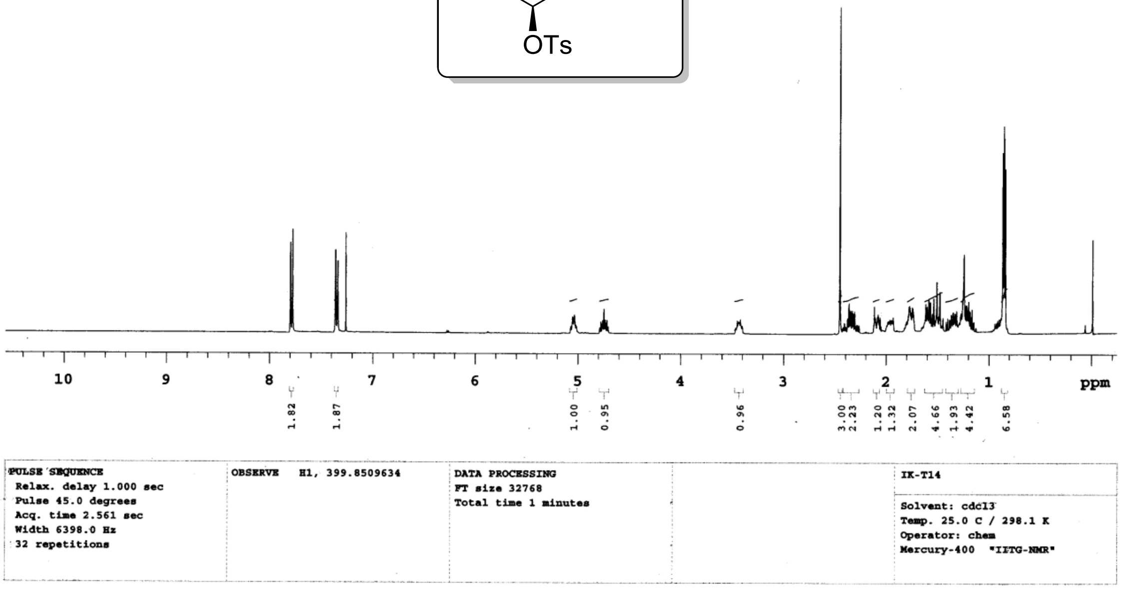
======== CHANNEL f1 ========
SFO1           150.9279571 MHz
NUC1                   13C
P1                   10.50 usec
PLW1           95.00000000 W

======== CHANNEL f2 ========
SFO2           600.1724007 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                70.00 usec
PLW2           21.00000000 W
PLW12           0.61714000 W
PLW13           0.30239999 W

F2 - Processing parameters
SI                   16384
SF             150.9128371 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

^{1}H and ^{13}C NMR spectra of **(2*S**,4*R**,9a*R**)-4-Isobutyl-6-oxooctahydro-1*H*-quinolizin-2-yl-4-methylbenzenesulfonate**





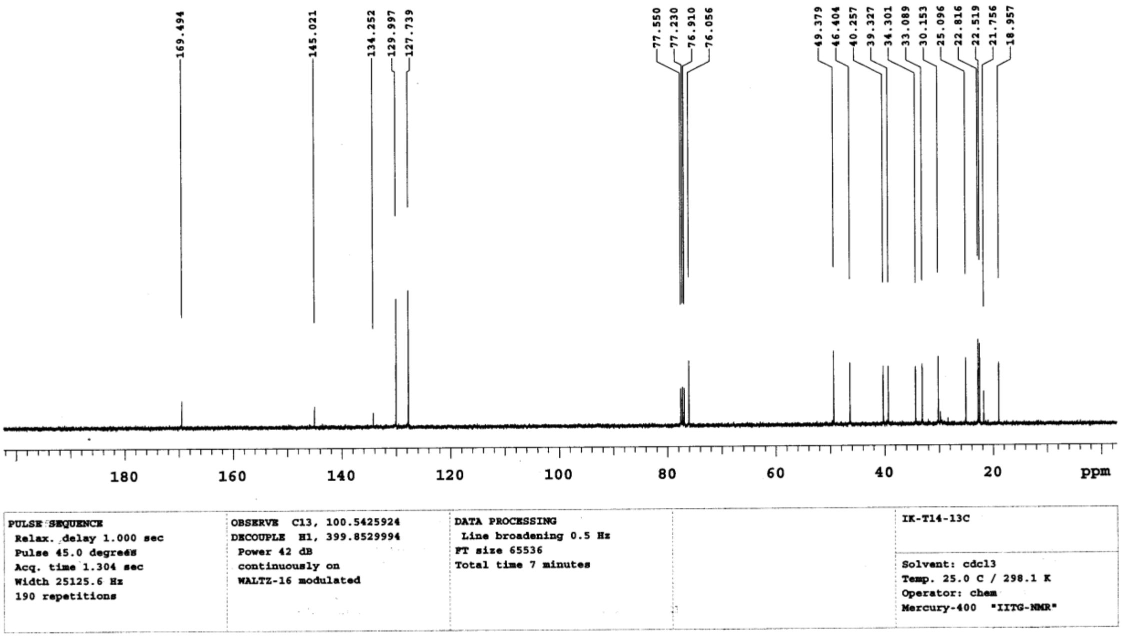
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions

OBSERVE H1, 399.8509634

DATA PROCESSING
FT size 32768
Total time 1 minutes

IK-T14

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400 "IITG-NMR"



PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
190 repetitions

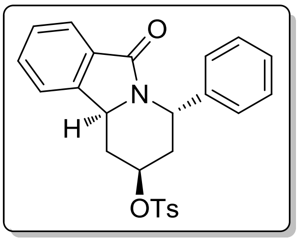
OBSERVE C13, 100.5425924
DECOUPLE H1, 399.8529994
Power 42 dB
continuously on
WALTZ-16 modulated

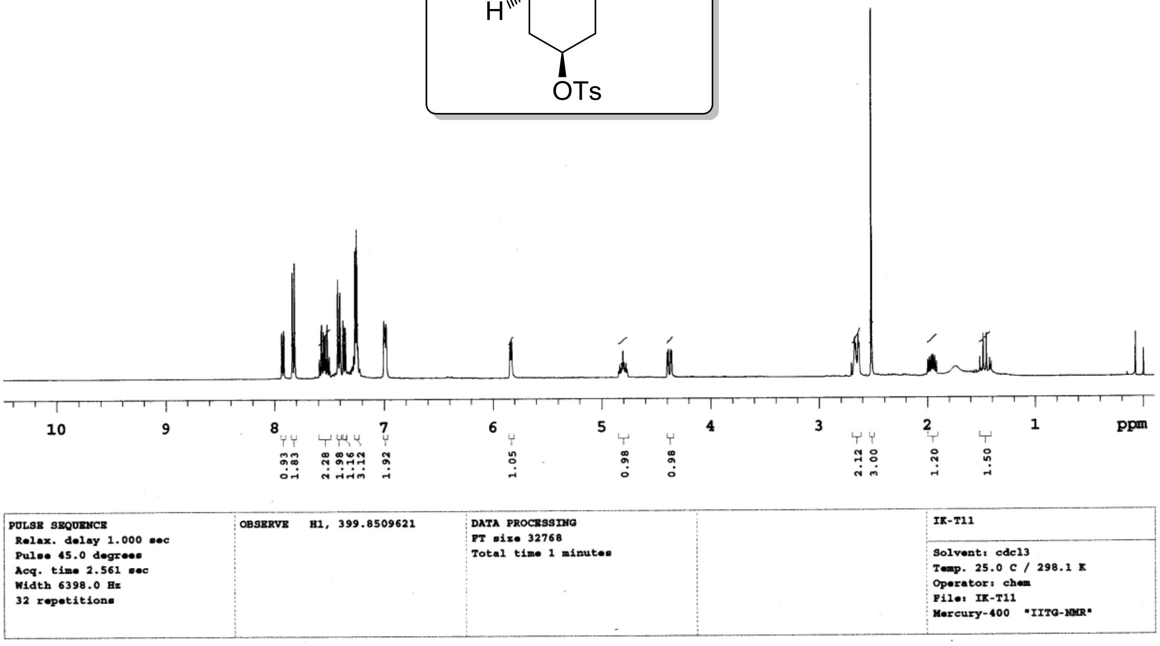
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 minutes

IK-T14-13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400 "IITG-NMR"

^{1}H and ^{13}C Spectra of **(2*R***,4*S***,10b*S***)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl-4-methylbenzenesulfonate**





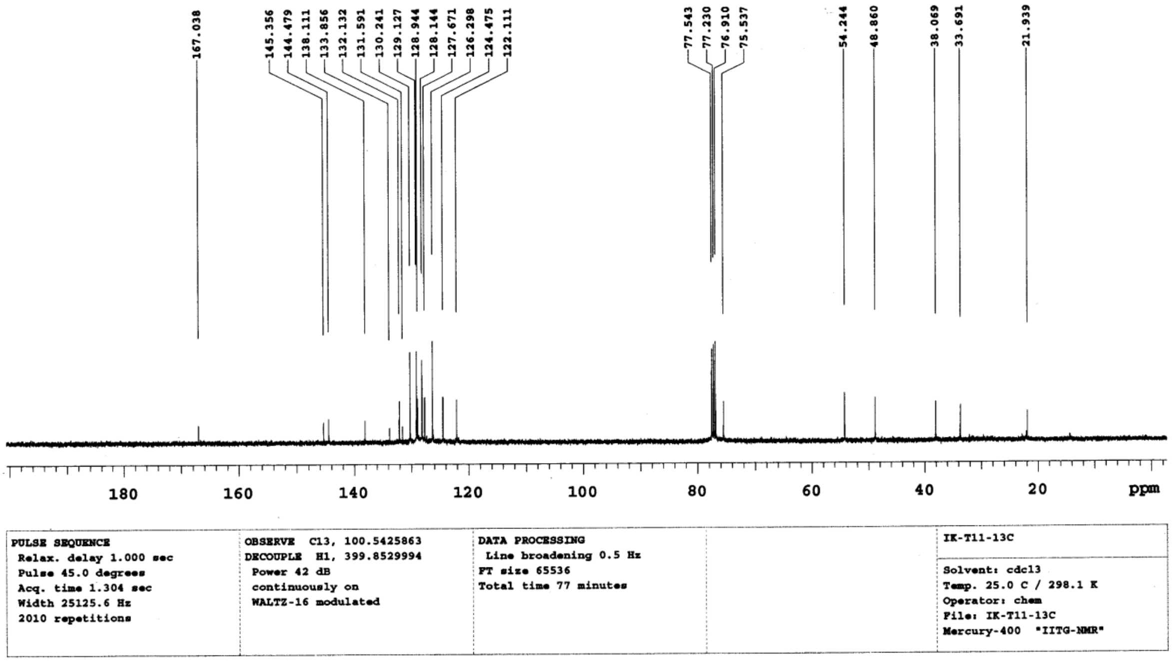
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions

OBSERVE H1, 399.8509621

DATA PROCESSING
FT size 32768
Total time 1 minutes

IK-T11

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: IK-T11
Mercury-400 "IITG-NMR"



PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
2010 repetitions

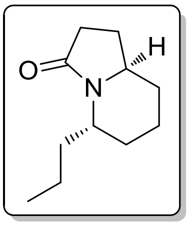
OBSERVE C13, 100.5425863
DECOUPLE H1, 399.8529994
Power 42 dB
continuously on
WALTZ-16 modulated

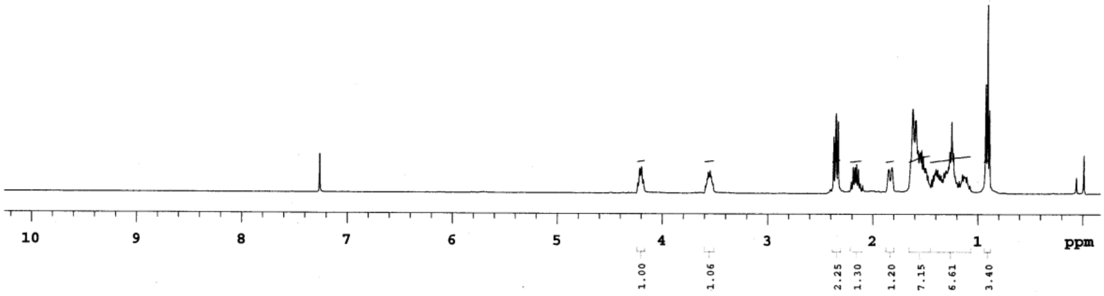
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 77 minutes

IK-T11-13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: IK-T11-13C
Mercury-400 "IITG-NMR"

^{1}H and ^{13}C Spectra of **(5*S**,8a*R**)-5-Propylhexahydroindolizin-3(2*H*)-one**





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PULSE SEQUENCE                OBSERVE   H1, 399.8509634       DATA PROCESSING           IK-R-PRO
 Relax. delay 1.000 sec                                      FT size 32768
 Pulse 45.0 degrees                                          Total time 1 minutes      Solvent: cdcl3
 Acq. time 2.561 sec                                                                   Temp. 25.0 C / 298.1 K
 Width 6398.0 Hz                                                                       Operator: chem
 32 repetitions                                                                        Mercury-400  "IITG-NMR"
```

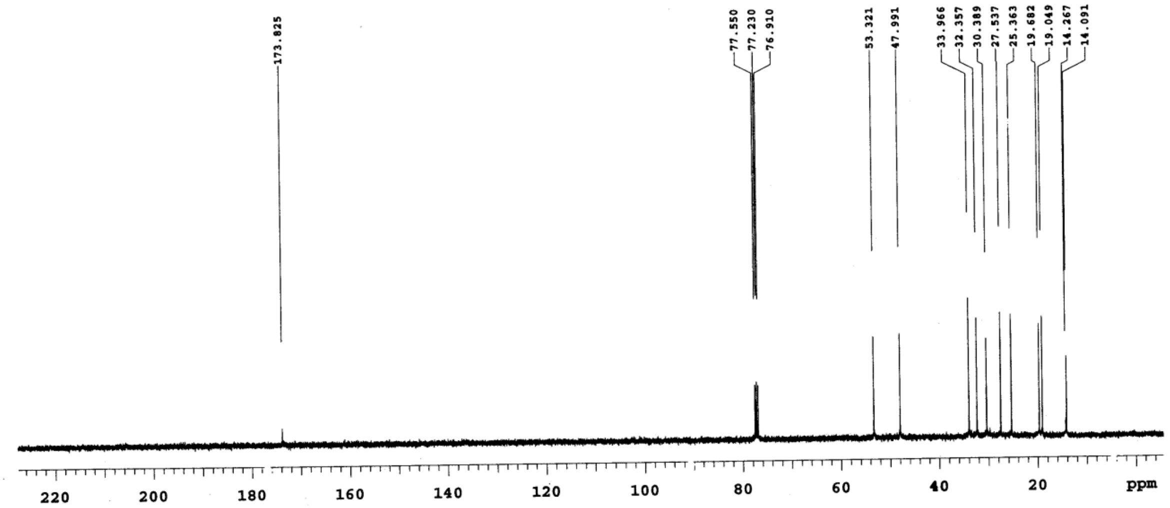

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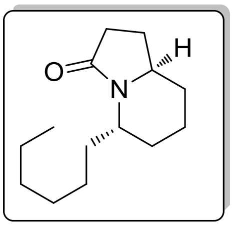
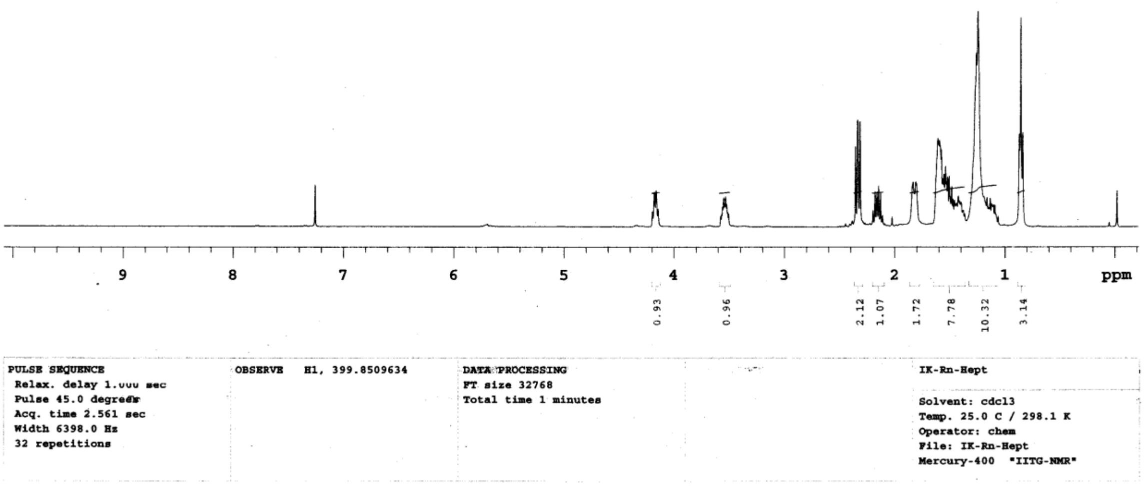
PULSE SEQUENCE                OBSERVE  C13, 100.5425909       DATA PROCESSING                IK-R-PRO-13C
 Relax. delay 1.000 sec       DECOUPLE  H1, 399.8529994        Line broadening 0.5 Hz
 Pulse 45.0 degrees            Power 42 dB                    FT size 65536                  Solvent: cdcl3
 Acq. time 1.304 sec           contiruously on                Total time 14 minutes          Temp. 25.0 C / 298.1 K
 Width 25125.6 Hz              WALTZ-16 modulated                                            Operator: chem
 370 repetitions                                                                             Mercury-400  "IITG-NMR"
```

^{1}H and ^{13}C Spectra of **(5*S***,8a*R***)-5-Hexylhexahydroindolizin-3(2*H*)-one**





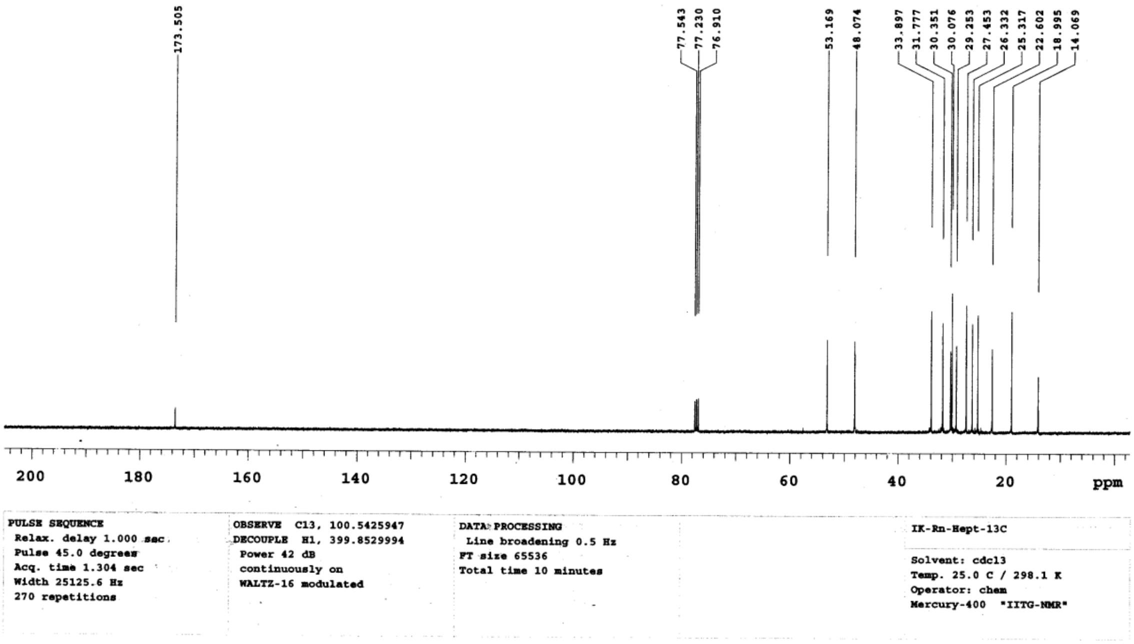
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions

OBSERVE H1, 399.8509634

DATA PROCESSING
FT size 32768
Total time 1 minutes

IK-Rn-Hept

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: IK-Rn-Hept
Mercury-400 "IITG-NMR"



PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
270 repetitions

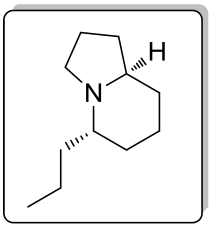
OBSERVE C13, 100.5425947
DECOUPLE H1, 399.8529994
Power 42 dB
continuously on
WALTZ-16 modulated

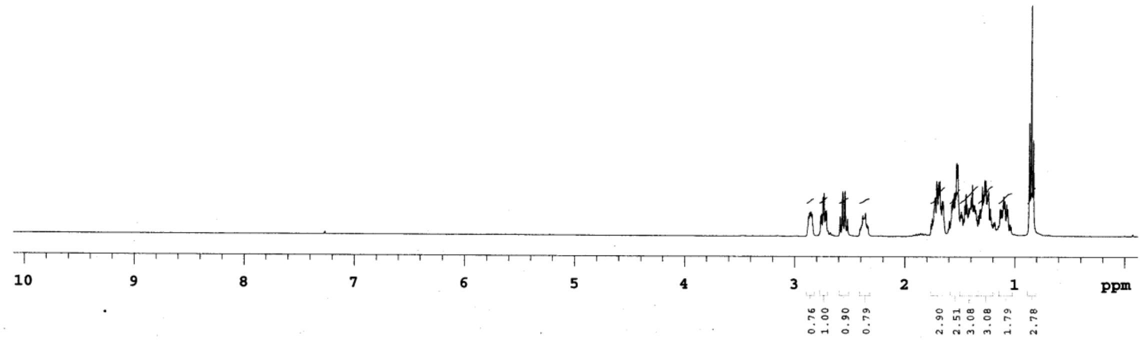
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 10 minutes

IK-Rn-Hept-13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400 "IITG-NMR"

^{1}H and ^{13}C Spectra of **(5*S**,8a*R**)-5-Propyloctahydroindolizine**





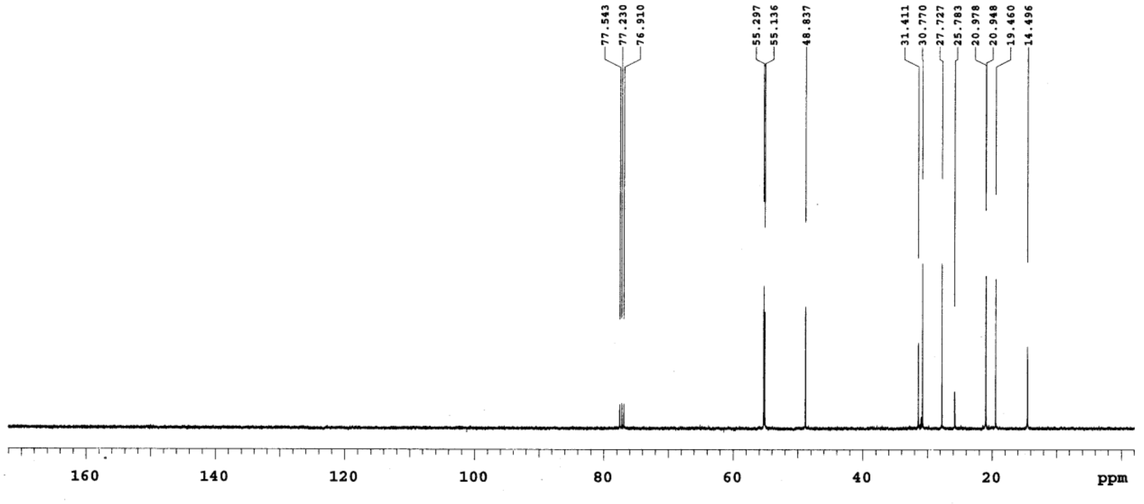
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions

OBSERVE H1, 399.8509615

DATA PROCESSING
FT size 32768
Total time 1 minutes

IK-TNP-Pro

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400 "IITG-NMR"



PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
10 repetitions

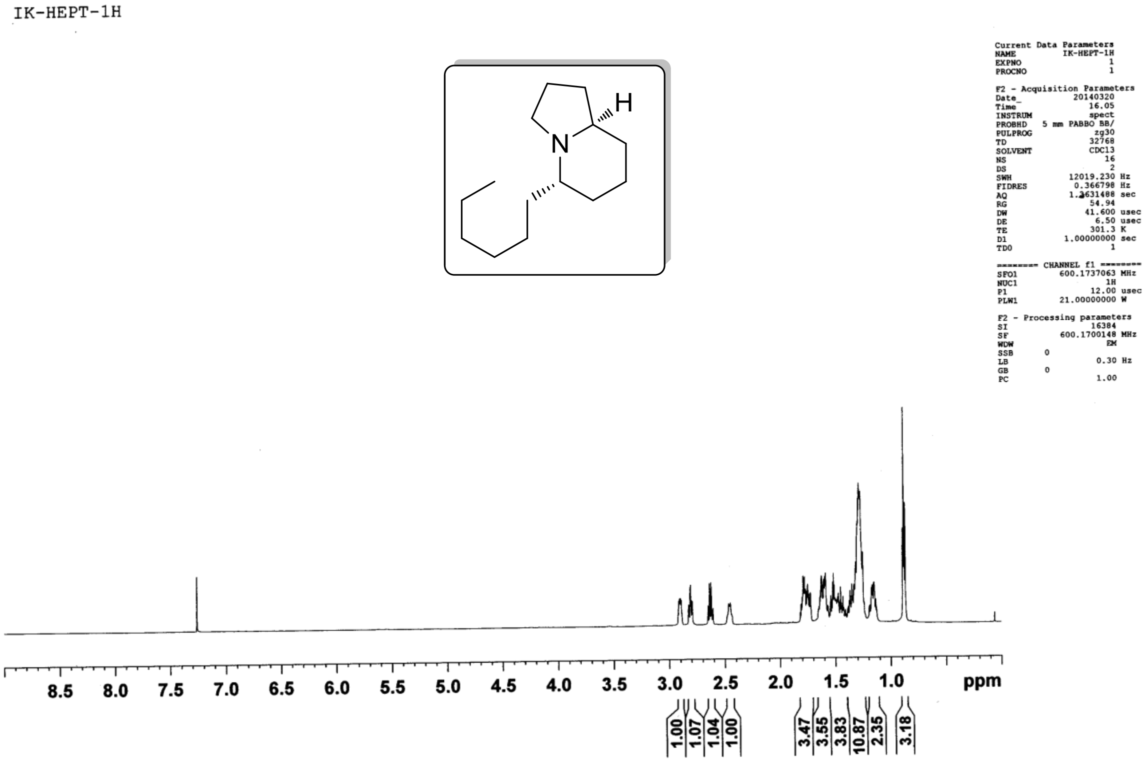
OBSERVE C13, 100.5425878
DECOUPLE H1, 399.8529994
Power 42 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 minute

IK-TNP-Pro-13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400 "IITG-NMR"

^{1}H and ^{13}C Spectra of **(5*S**,8a*R**)-5-Hexyloctahydroindolizine**



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PROCNO                    1

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PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               12019.230 Hz
FIDRES             0.366798 Hz
AQ                1.3631488 sec
RG                    54.94
DW                   41.600 usec
DE                     6.50 usec
TE                    301.3 K
D1               1.00000000 sec
TD0                       1

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

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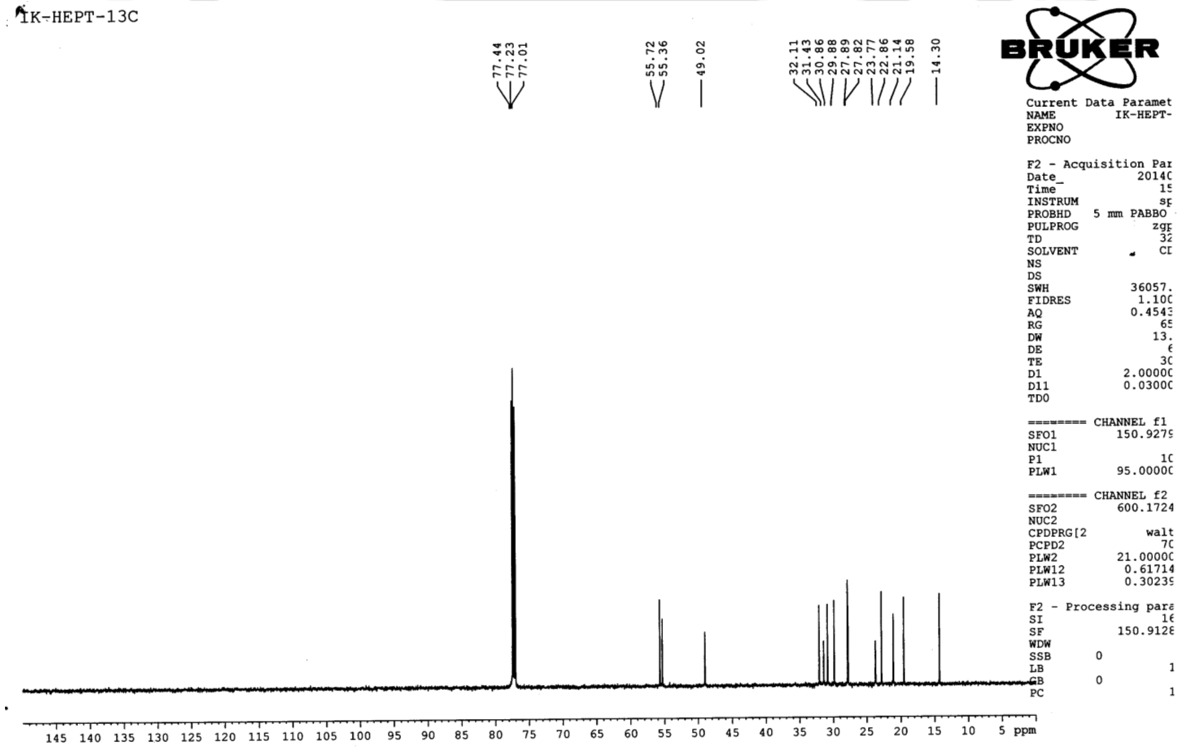

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Current Data Paramet
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EXPNO
PROCNO

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PULPROG            zgp
TD                  32
SOLVENT             CI
NS
DS
SWH            36057.
FIDRES          1.10C
AQ             0.4543
RG                  65
DW                 13.
DE                   6
TE                  3C
D1            2.0000C
D11           0.0300C
TD0

======== CHANNEL f1
SFO1          150.9279
NUC1
P1                  1C
PLW1          95.0000C

======== CHANNEL f2
SFO2          600.1724
NUC2
CPDPRG[2          walt
PCPD2               7C
PLW2          21.0000C
PLW12          0.61714
PLW13          0.30239

F2 - Processing para
SI                  16
SF            150.9128
WDW
SSB        0
LB                   1
GB         0
PC                   1
```

4.8. Crystal Parameters

The crystal parameters of compound **65c**

	CCDC 1000260
Formula	$C_{25} H_{29} N O_4 S$
Formula weight	439.56
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)/c
a/Å	10.812(3)
b/Å	11.923(3)
c/Å	18.961(5)
α/º	90.00
β/º	93.50
γ/º	90.00
V/Å^3	2439.7(11)
Z	4
Abs. Coeff./mm^{-1}	0.162
Abs. Correction	Multi-scan
GOF on F^2	0.949
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0467 $wR2$ = 0.1265
R indices [all data]	$R1$ = 0.0674 $wR2$ = 0.1433

CHAPTER 5

Synthesis of 2,3-Dihydro-4-pyranones from Epoxides *via* Hetero-Diels-Alder Reaction

5.1. Importance of 2,3-Dihydro-4-pyranones

2,3-Dihydro-4*H*-pyran-4-ones are ubiquitous functionalities found in many natural products and used for the synthesis of important biologically active molecules.[1] It is also used for the synthesis of carbohydrates[2] and highly functionalized aromatic rings.[3] Stegobiol (**1**) and stegobinone (**2**) are labile pheromone of the drugstore beetle *Stegobium paniceum* and the furniture beetle, *Anobium punctatum*.[4] On the other hand, 2,3-dihydro pyran-4-one containing compound **3**, an important intermediate in the total synthesis of natural product pederin, originally isolated from the terrestrial beetle, *Paederus fuscipes* act as potent cytotoxins that showed efficacy *in vivo* against leukemia and solid tumor models (*Figure 5.1.1*).[5]

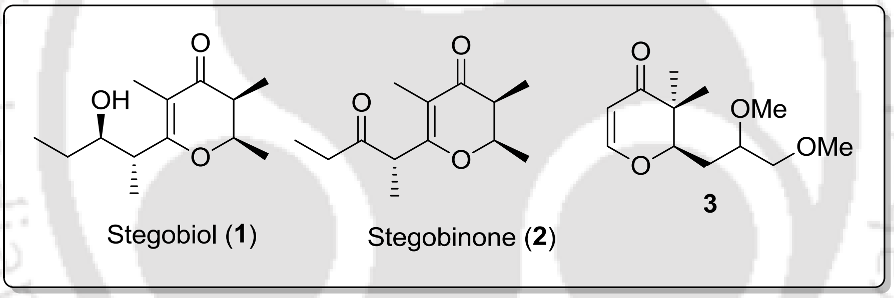
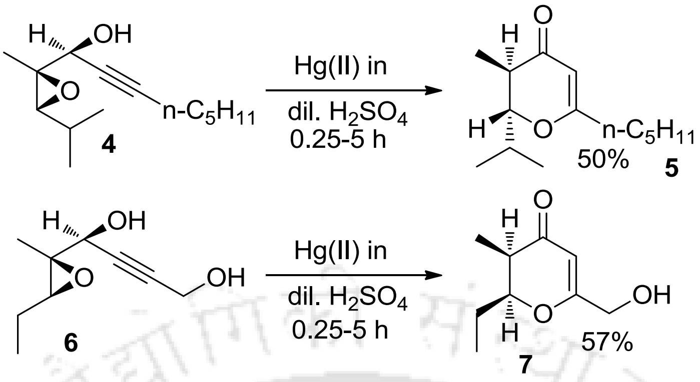


Figure 5.1.1: Some important 2,3-dihydro-4-pyranone containing products

5.2. Literature Methods

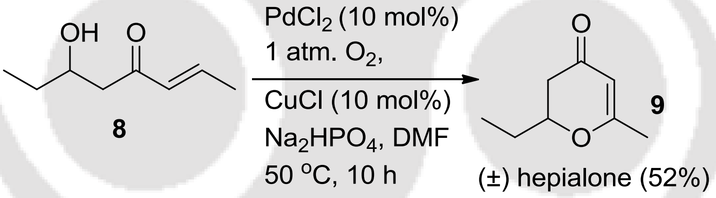
Over the years several methods have been developed for the syntheis of 2,3-dihydro-4-pyranones, which includes hetero-Diels-Alder reaction, cyclization of 5-hydroxy-1,3-diketones, oxidative cyclization of β-hydroxyenones with palladium(II), addition of different nucleophiles to unsaturated lactones and others. In introductory chapter (Section 1.3.4), we have already discussed about the HDA reaction of Danishefsky's diene. Some of the other methodologies for the synthesis of 2,3-dihydro-4-pyranones are discussed below.

Marson *et al.* have reported a stereospecific protocol for the synthesis of 2,3-dihydropyran-4-one derivatives by Hg(II)- catalyzed rearrangement of 1-alkynyl-2,3-epoxy alcohols (*Scheme 5.2.1*). The relative configuration of the 2,3-disubstituted dihydropyranones is determined solely by the configuration of the epoxide. The epoxide **4** derived from (*Z*)-alkene leads to the exclusive formation of *trans* product **5**. The alternative stereochemistry of epoxide **6** leads to the dihydropyranone **7** with only *cis* 2,3-disubstitution.[6]



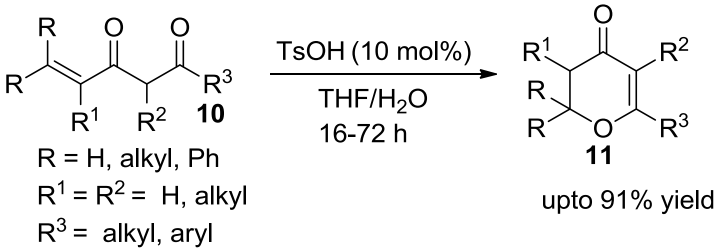
Scheme 5.2.1

Gouverneur and co-workers reported a palladium(II) mediated oxidative cyclization of β-hydroxyenones **8** for the synthesis of 2,6-disubstituted 2,3-dihydro-4*H*-pyran-4-ones **9**. The reaction scope is viable for a variety of alkyl and aryl substituents at the α-position to alcohol in β-hydroxyenones and applied for the preparation of (±)-hepialone **9**, a natural pheromonal component of the male moth, isolated from *Hepialus hecta L* (*Scheme 5.2.2*).[7]



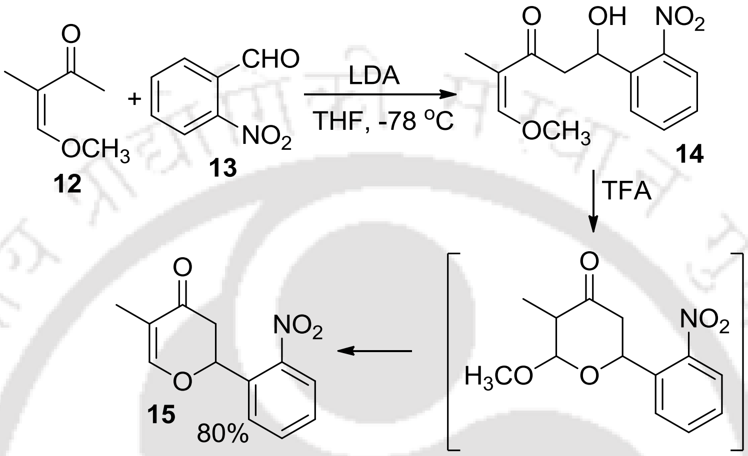
Scheme 5.2.2

Burnell and co-workers have disclosed a very efficient approach to the synthesis of 2,3-dihydro-4*H*-pyran-4-ones based on cyclization reaction of α,β-unsaturated 1,3-diketones in an acidic aqueous medium. In this strategy α,β-unsaturated 1,3-diketones **10** were treated with catalytic *p*-TSA in THF/H_2O mixture to afford the corresponding 2,3-dihydro-4*H*-pyran-4-ones **11** in excellent yields (*Scheme 5.2.3*).[8]



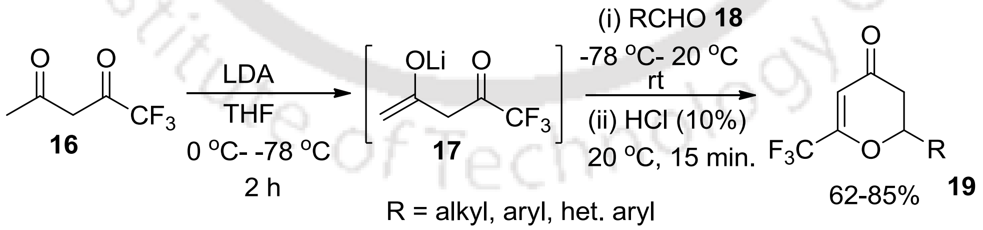
Scheme 5.2.3

Feng and coworkers have reported a versatile tandem Aldol reaction-conjugate addition approach for the synthesis of 2,3-dihydro-4*H*-pyran-4-ones, in which the enone **12** was added to a solution of LDA to form the lithium enolate. The lithium enolate forms aldol product **14** with aldehyde **13**, which was cyclized to corresponding dihydropyranone **15** in the presence of trifluoro acetic acid. The scope of the reaction was explored with a series of alkyl, aryl and heteroaryl aldehydes, which gave good to excellent yields (*Scheme 5.2.4*).[9]



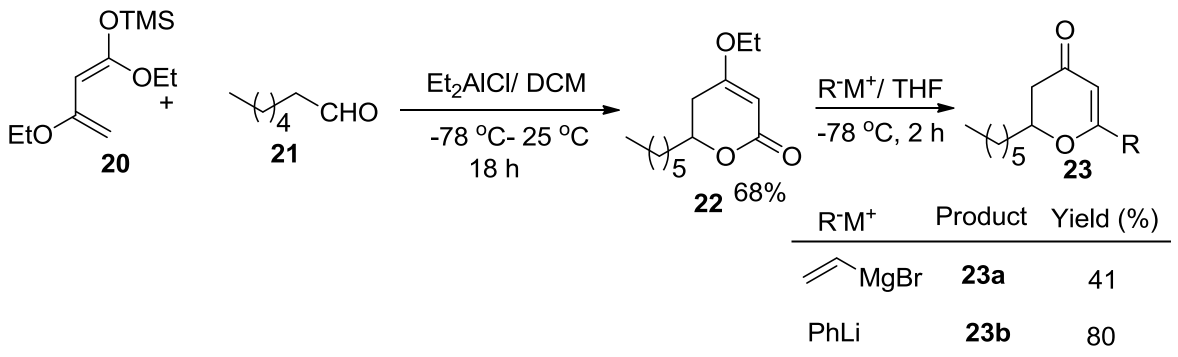
Scheme 5.2.4

Fluorinated 2,3-dihydropyran-4-ones were achieved by simple cyclocondensation between 1,3-dicarbonyl dianions and aldehydes, by Langer *et al*. First commercially available 1,1,1- trifluoro-pentan-2,4-dione **16** was treated with LDA, to generate the lithium enolate **17**, which was cyclized with aldehydes **18** and subsequent addition of hydrochloric acid afforded the 2,3-dihydro-6-trifluoromethyl-pyran-4-ones **19** in 62-85% yields (*Scheme 5.2.5*).[10]



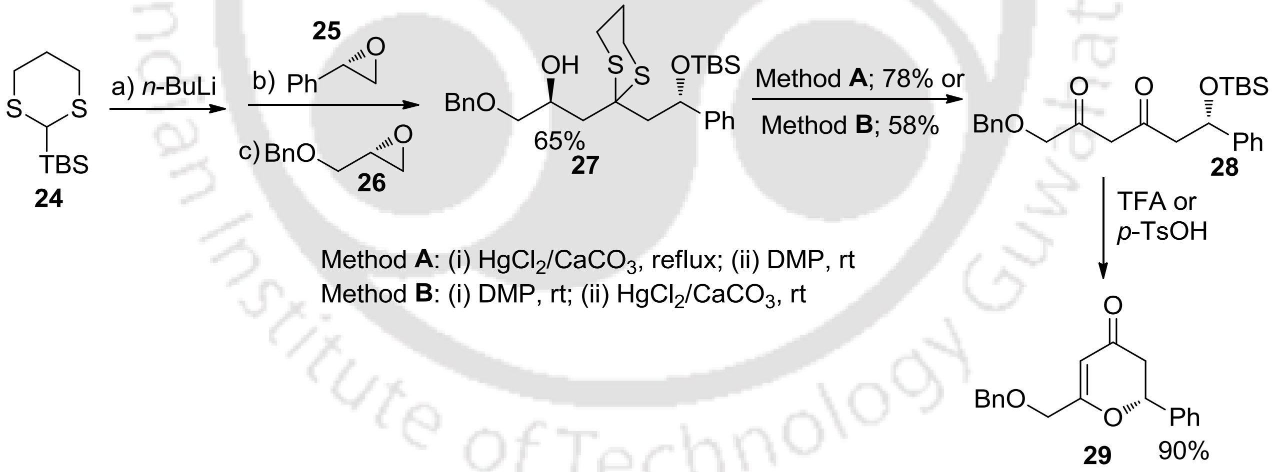
Scheme 5.2.5

Winkler and coworkers showed a novel route for the synthesis of 2,3-dihydro-4-pyranones by using HDA product of Brassard's diene with aldehydes. The Diels-Alder reaction of Brassard's diene **20** with aldehyde **21** in the presence of diethyl aluminium chloride affords 3-ethoxy α-β unsaturated lactone **22**. The vinylogous carbonate **22** was further reacted with excess of Grignard reagent or alkyl lithium reagent, leading to ring opened double addition products **23** at low temperature (*Scheme 5.2.6*).[11]



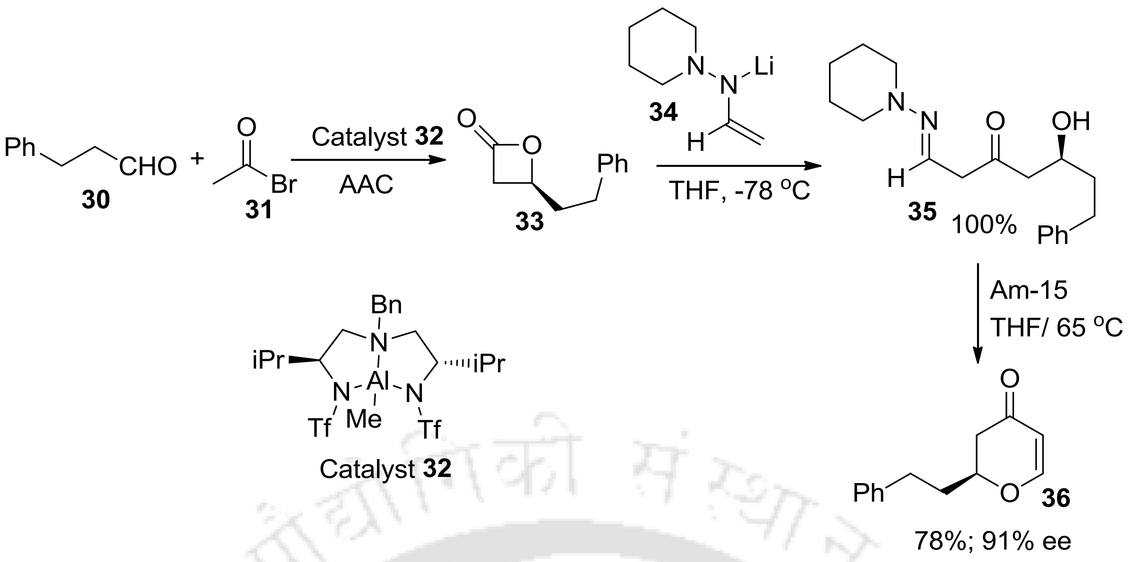
Scheme 5.2.6

Work published by Xian and coworkers in 2007 provided a versatile strategy for the synthesis of 2,6-disubstituted dihydropyranones, using Smith three-component dithiane linchpin coupling strategy (*Scheme 5.2.7*).[12] The three-component linchpin coupling of silyl dithiane **24** with two epoxides **25** and **26** gave the corresponding diol derivative **27** in 65% yield, which was converted to 1,3 dicarbonyl compound **28** by either removal of the dithiane group followed by oxidation of the unprotected hydroxyl group or vice-versa. The 1,3-dicarbonyl compound **28** cyclizes in acidic medium to afford 2,6-disubstituted 2,3-dihydropyranone **29**. This protocol allows for the synthesis of various 2,6-substituted dihydropyranones by using different sets of epoxides.



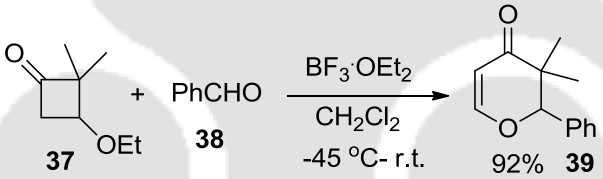
Scheme 5.2.7

Nelson *et al.* discussed a novel method for the synthesis of enantioenriched dihydropyranones from chiral 4-substituted 2-oxetanones. The chiral oxetanone **33** was prepared from asymmetric acyl halide-aldehyde cyclocondensation (AAC) reaction using chiral Al(III)-triamine complex **32**. Reaction of this chiral lactone **33** with lithiated hydrazone **34** at -78 °C provided β-keto hydrazone **35** *via* regioselective carbonyl addition and ensuing ring opening, which upon cyclization in the presence of amberlyst-15 acidic resin (Am-15) gave dihydro pyranone derivative **36** (*Scheme 5.2.8*).[13]



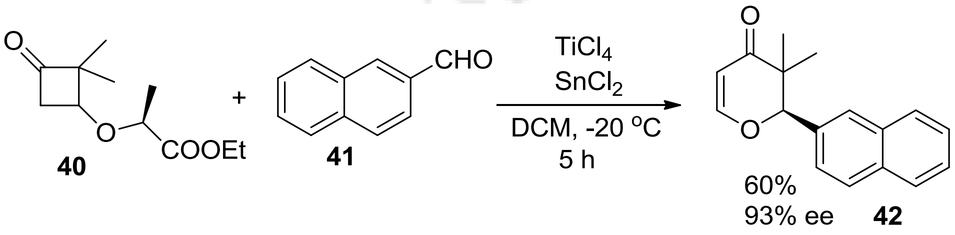
Scheme 5.2.8

Recently, Matsuo and coworkers have proposed an alternative procedure for the synthesis of 2,3-dihydro-4-pyranones **39** from 3-alkoxy cyclobutanone **37** and aldehyde **38** mediated by $BF_3{\cdot}OEt_2$ in dichloromethane (*Scheme 5.2.9*).[14]



Scheme 5.2.9

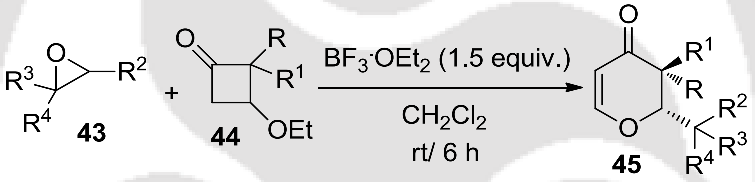
Later the asymmetric version of this methodology was reported, using chiral ethoxy cyclobutanone. The treatment of cyclobutanone **40** having L-ethyl lactate as a chiral auxiliary with aldehyde **41** in the presence of combined titanium(IV) chloride and tin(II) chloride produced 2,3-dihydro-4-pyranone **42** in 93% ee (*Scheme 5.2.10*).[15]



Scheme 5.2.10

5.3. Results and Discussions

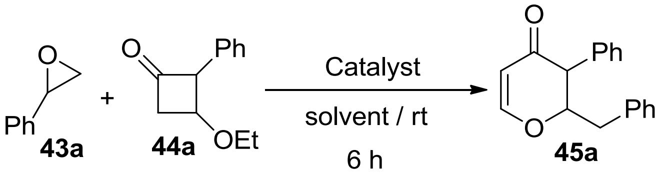
The literature survey reveals that the hetero-Diels–Alder reaction of Danishefsky's dienes provide one of the most convenient approaches for the formation of 2,3-dihydro-4-pyranone ring system among all other methods, but the preparation and purification of Danishefsky's dienes and formation of diastereomers are found to be troublesome. In addition, the alternative methods to the Danishefsky's diene also suffers from poor selectivity and limited scope for the synthesis 3-alkyl substituted of 2,3-dihydro-4*H*-pyran-4-ones. While searching for efficient starting material for dihydropyranone synthesis, we found Matsuo's protocol of using 3-alkoxy cyclobutanone as an alternative for Danshefsky's diene. Taking clues from the literature and the experience of epoxides as carbonyl equivalents from chapter 1, we have developed a methodology for diastereoselective synthesis of *trans* 2,3-dihydro-4*H*-pyran-4-one bearing mono and dialkyl as well as monoaryl groups at C-3 position starting from 3-alkoxycyclobutanones and epoxides mediated by boron trifluoride etherate as shown in *scheme 5.3.1*.



Scheme 5.3.1

In an initial investigation, styrene oxide **43a** was treated with 3-ethoxy-2-phenylcyclobutanone **44a** in the presence of boron trifluoride etherate at room temperature and 2-benzyl-2,3- dihydro-3-phenylpyran-4-one **45a** was obtained in 76% yield, with a *cis-trans* ratio of 11:89. In order to improve the yield and diastereosectivity, the reaction was screened with other Lewis acids such as $TiCl_4$, $In(OTf)_3$, TMSOTf and Brønsted acid TsOH as shown in *Table 5.3.1*. These results showed that $BF_3{\cdot}Et_2O$ was the efficient Lewis acid. No desired product was observed when $TiCl_4$ or TMSOTf was used. Brønsted acid TsOH was also found to be ineffective. On the other hand $In(OTf)_3$ produced only 28% of product with 17:83 mixture of *cis-trans* isomers. The reaction in toluene and THF, gave desired products with a mixture of isomers in the ratio of 17:83 and 14:86 respectively. The yield and the diastereoselectivity were found to be same even after continuing the reacton for 12 h. Therefore, $BF_3{\cdot}Et_2O$ in CH_2Cl_2 was considered as the best combination for both the yields and stereoselectivity.

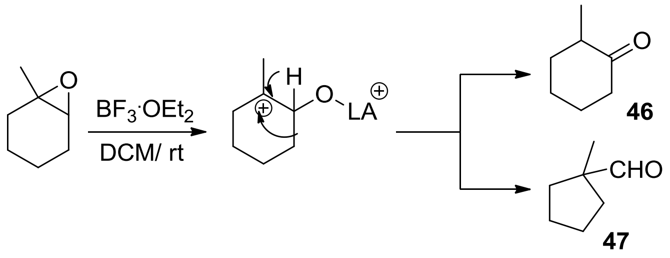
Table 5.3.1. Optimization of the reaction



Entry	Catalyst (equiv.)	Solvent	*cis*:*trans*[a]	Yield (%)[b]
1	**$BF_3{\cdot}OEt_2$ (1.5)**	**CH_2Cl_2**	**11:89**	**76**
2	$TiCl_4$ (1.0)	CH_2Cl_2	---	n.d.[c]
3	$In(OTf)_3$ (0.2)	CH_2Cl_2	17:83	28
4	TMSOTf (1.0)	CH_2Cl_2	---	n.d.[c]
5	*p*-TsOH (1.0)	CH_2Cl_2	---	n.d.[c]
6	$BF_3{\cdot}OEt_2$ (1.5)	Toluene	17:83	42
7	$BF_3{\cdot}OEt_2$ (1.5)	THF	14:86	35
8	$BF_3{\cdot}OEt_2$ (1.5)	CH_2Cl_2	11:89	76[d]

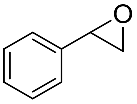
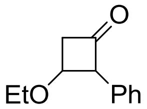
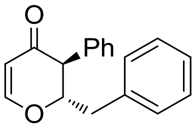
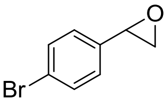
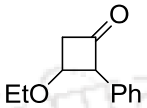
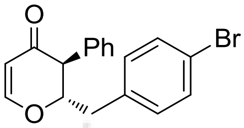
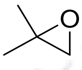
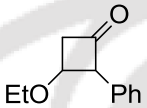
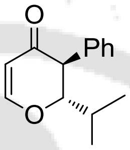
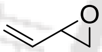
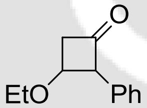
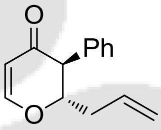
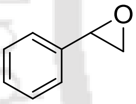
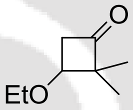
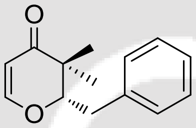
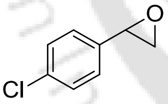
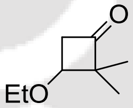
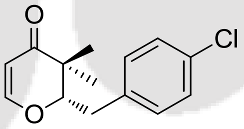
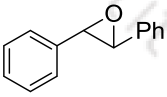
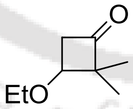
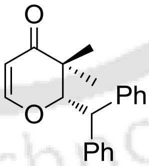
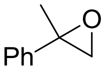
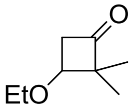
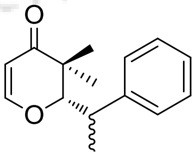
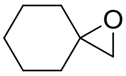
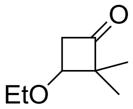
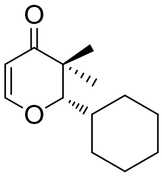
[a]Ratio is determined from ^1H NMR. [b]Yield refers to isolated yield. [c]n.d. = Not detected. [d]Reaction is continued for 12h.

With the optimal conditions in hand, we examined the scope of the reaction by using variety of ethoxy cyclobutanones and epoxides (*Table 5.3.2*). As shown in *Table 5.3.2*, both alkyl and aryl epoxides worked well. In general, good yields were obtained when using 1,1-disubstituted alkyl epoxides, whereas unsaturated alkyl epoxide **43d** gave the desired product in good yield. On the other hand, monosubstituted alkyl epoxide **43k** failed to produce the desired product. This is attributed to the lower stability of the carbocation **48** (*Scheme 5.3.3*), formed from monosubstituted epoxides compared to 1,1-disubstituted, vinylic epoxides and styrene oxides, where carbocation **48** is better stabilized due to the tertiary, allylic and benzylic centres, respectively. The epoxide, 1-methyl-7-oxabicyclo[4.1.0]heptane **43j** gave the product **45j** with a ring contraction in cyclohexyl ring in 35% yield. This is due to the fact that after ring opening, 1-methyl-7-oxabicyclo[4.1.0]heptane **43j** produces two products, ketone **46** and aldehyde **47** with a ratio of 1:1 (*Scheme 5.3.2*).[16] The aldehyde **47** only takes part in the reaction to form the dihydropyranone **45j**.

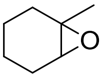
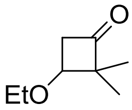
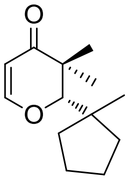
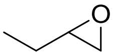
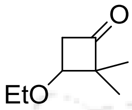
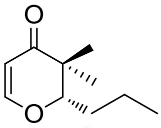
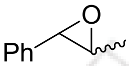
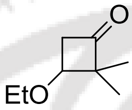
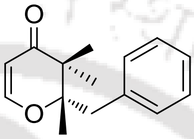
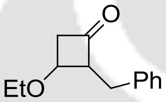
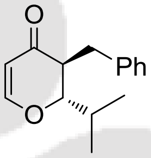
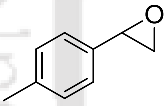
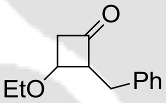
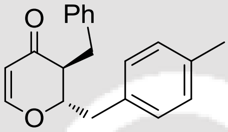
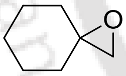
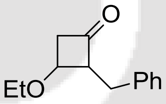
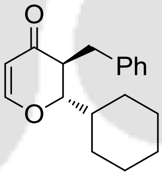
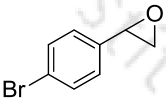
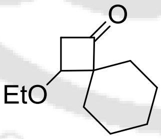
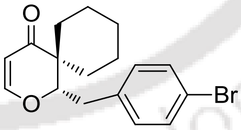
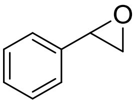
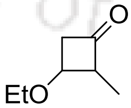
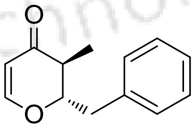
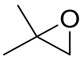
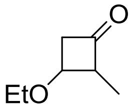
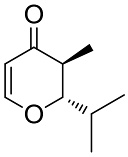


Scheme 5.3.2. Rearrangement of epoxide **43j** into carbonyl compounds

Table 5.3.2. Synthesis of 2,3-dihydro-4-pyranones

Entry	Epoxide **43**	Cyclobutanone **44**	Product **45**	*cis*:*trans*[a]	Yield (%)[b]
a				11:89	76
b				11:89	68
c				10:90	84
d				11:89	60
e				---	81
f				---	65
g				---	71
h				---	63[c]
i				---	78

Continued…………..

Entry	Epoxide **43**	Cyclobutanone **44**	Product **45**	*cis*:*trans*[a]	Yield (%)[b]
j				---	35
k				---	0
l				---	0
m				6:94	72
n				8:92	64
o				11:89	80
p				---	58
q				17:83	68
r				12:88	79

[a] Ratios are determined from crude ^{1}H NMR. [b] Yields refer to isolated yield. [c] The compound is obtained as an inseparable diastereomeric mixture at the benzylic position.

Similarly, 2-methyl-3-phenyloxirane **43l** was also not effective for this reaction. In this case, the epoxide after rearrangement produces 1-phenylpropan-2-one, which being a ketone does not take part in the reaction. In case of styrene oxides, simple styrene oxide gave good yields, where as styrene oxides with electron withdrawing and donating substitutions afforded the products **45b, f, n, p** in moderate yields. The α-methyl styrene oxide **43h** afforded an inseperable mixture of diastereomers at benzylic position with a ratio of 1:2 in 63% yield. On the other hand, *trans* stillbene oxide **43g** gave the corresponding rearranged product **45g** in 71% yield, due to the formation of 2,2-diphenylacetaldehyde, after the migration of phenyl group from the carbocation **48**.

Simultaneously, we explored the reaction with various cyclobutanone derivatives such as 3-ethoxy-2-phenylcyclobutanone, 3-ethoxy-2,2-dimethylcyclobutanone, 2-benzyl-3-ethoxy cyclobutanone, 3-ethoxyspiro[3.5]nonan-1-one and 3-ethoxy-2-methylcyclobutanone. It was observed that the reaction furnished moderate to good yields in all the cases as outlined in the *Table 5.3.2*. The 2,2-disubstituted cyclobutanones gave single product, whereas, the cyclobutanones possessing monosubstitution at C-2 position gave a mixture of 2,3-substituted dihydro pyranones with *trans* isomer as major product, which was determined from the coupling constants of ^{1}H NMR spectroscopy. Thus, the coupling constants of C-3H for compounds *cis* and *trans* 2-benzyl-2,3-dihydro-3-phenylpyran-4-one were found to be 4.4 and 11.6 Hz, respectively (*Figure 5.3.1*).

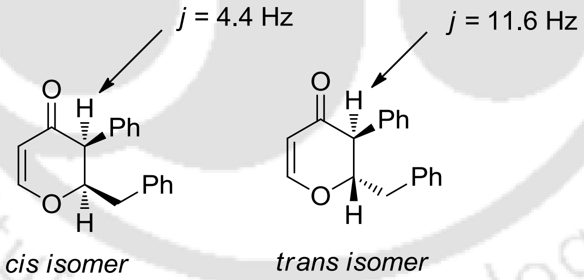
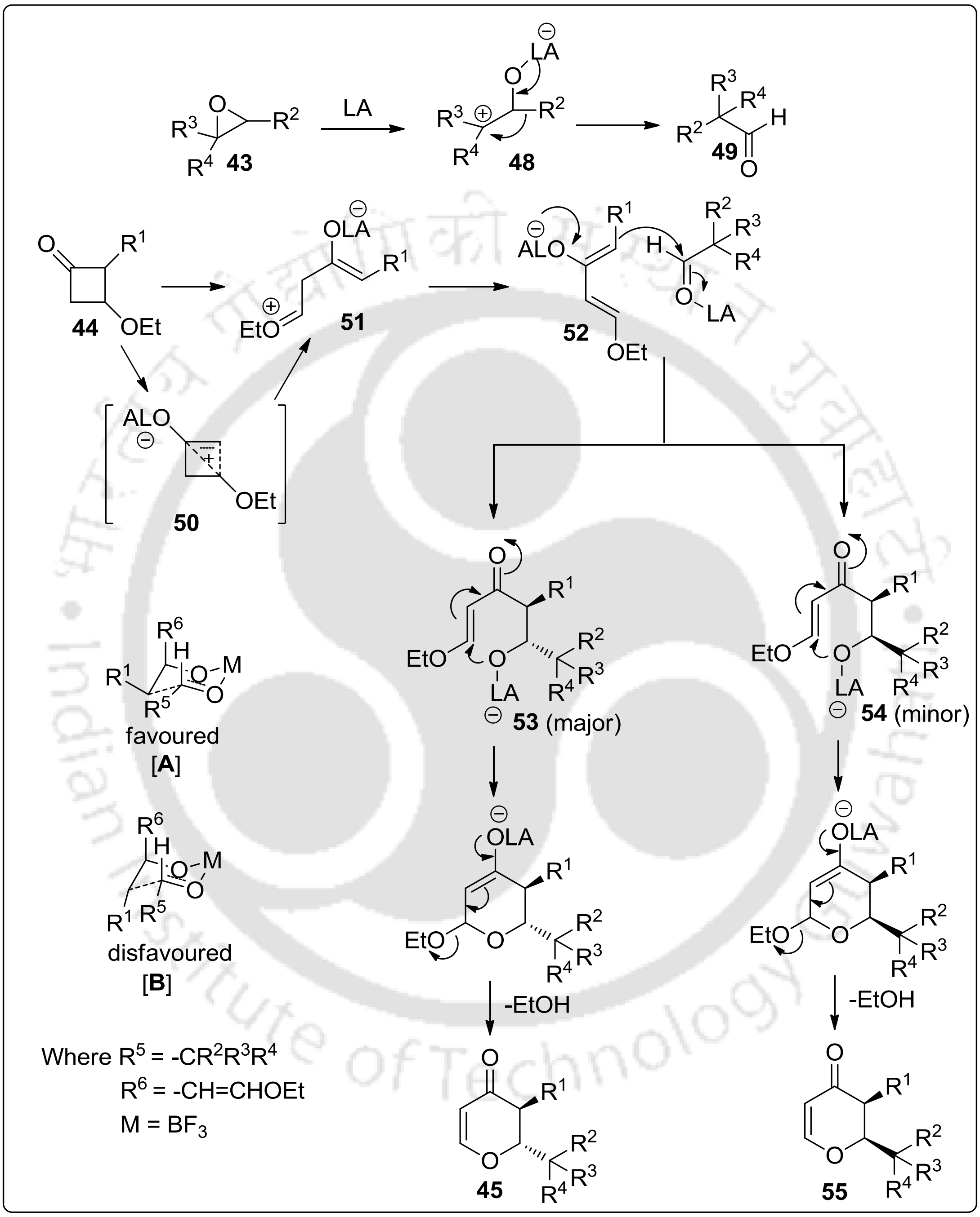


Figure 5.3.1: Coupling constants of *cis* and *trans* isomers for 2-benzyl-2,3-dihydro-3-phenylpyran-4-one

The mechanism of the reaction can be explained as follows. The epoxide **43** under Lewis acidic condition opens up to a carbocation **48**, which rearranges to the corresponding aldehyde **49**. Similarly in presence of Lewis acid, 3-alkoxycyclobutanone **44** undergoes regioselective cleavage of highly substituted C2-C3 bond *via* bicyclobutonium ion **50** to give more stable enolate, which exists as a zwitterionic intermediate **51**. The intermediate **51** eliminates a proton to generate diene **52**, similar to Danishefsky's diene, which reacts with aldehyde **49** in a step wise fashion to give *trans* intermediate **53** as a major and *cis* **54** as a minor one *via* six membered more favoured chair transition state [**A**] and a less favoured [**B**], respectively. The intermediates **53** and **54** after cyclization and subsequent elimination of ethanol affords the desired 2,3-

dihydropyranones **45** and **55**, respectively (*Scheme 5.3.3*). This stepwise mechanism is in accordance with the mechanism proposed by Danishefsky group,[17] which supports the formation of *trans* product as a major one.



Scheme 5.3.3: Mechanism for the synthesis of 2, 3-dihydro-4-pyranones

Conclusions

In conclusion, we have developed a versatile methodology for the synthesis of 2,3-dihydro-4*H*-pyran-4-ones using epoxides and 3-alkoxycyclobutanones *via* an intermolecular [4+2] cycloaddition reaction in moderate to good yields. One of the important features of the reaction is that 2,3-dihydro-4*H*-pyran-4-ones with a benzylic group in 2-position can be obtained. The method provides an alternative to aldehydes for the synthesis of 2,3-dihydro-4*H*-pyran-4-ones where aldehyde cannot be accessed directly.

5.4. Experimental Section

5.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1

5.4.2. Synthesis of Starting Materials: The 3-ethoxy cyclobutanones **44** were synthesized by the literature procedures.[14, 18]

5.4.3. General Procedure for the Synthesis of 2,3-Dihydro-4-pyranones (45a-r):

To a mixture of epoxide **43** (1.0 equiv.) and 3-ethoxy cyclobutanone **44** (1.2 equiv.) in dichloromethane (0.17 M) was added freshly distilled boron trifluoride etherate (1.5 equiv). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with dichloromethane and then the organic layer was washed with brine. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the title compounds.

Synthesis of (2*S**,3*S**)-2-Benzyl-3-phenyl-2*H*-pyran-4(3*H*)-one (45a):

To a mixture of 2-phenyl-oxirane **43a** (60 mg, 0.5 mmol) and 3-ethoxy-2-phenyl cyclobutanone **44a** (57 mg, 0.6 mmol) in dichloromethane (3 mL) was added freshly distilled boron trifluoride etherate (107 mg, 0.75 mmol). The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2x10 mL) and then the organic layer was washed with brine (5 mL). The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel to give the (2*S**,3*S**)-2-benzyl-3-phenyl-2*H*-pyran-4(3*H*)-one **45a** in (100mg, 76%) as a pale yellow liquid.

5.5. References

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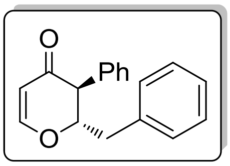
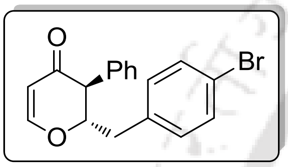
5.6. Characterization Data

(2*S,3*S**)-2-Benzyl-3-phenyl-2*H*-pyran-4(3*H*)-one (45a):**



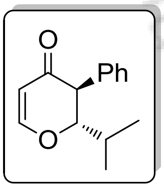
Pale yellow liquid; yield 100 mg, 76%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.89 (d, *J* = 6.0 Hz, 2 H), 3.65 (d, *J* = 11.6 Hz, 1 H), 4.85 (ddd, *J* = 11.6, 6.4 and 6.0 Hz, 1 H), 5.55 (d, *J* = 6.0 Hz, 1 H), 7.11-7.18 (m, 4 H), 7.24-7.35 (m, 5 H), 7.36-7.41 (m, 2 H); **^{13}C NMR** (100 MHz, CDCl3) δ 38.9, 56.3, 84.0, 107.2, 127.0, 128.0, 128.6, 129.2, 129.3, 129.8, 135.8, 136.7, 162.5, 193.0; **IR** (KBr, Neat) 3030, 2924, 1675, 1600, 1495, 1277, 1181, 1037, 751, 670 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{16}O_2$ $(M+H)^+$ 265.1223. Found 265.1234.

(2*S,3*S**)-2-(4-Bromobenzyl)-3-phenyl-2*H*-pyran-4(3*H*)-one (45b):**



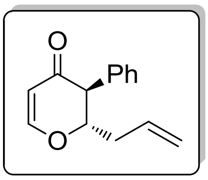
Pale yellow liquid; yield 116 mg, 68%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.83 (d, *J* = 6.0 Hz, 2 H), 3.65 (d, *J* = 12.0 Hz, 1 H), 4.85 (ddd, *J* = 12.0, 6.4 and 5.6 Hz, 1 H), 5.56 (d, *J* = 6.0 Hz, 1 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.30-7.43 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 38.4, 56.3, 83.6, 107.4, 121.0, 128.1, 129.2, 129.3, 131.5, 131.6, 135.5, 135.6, 162.4, 192.8; **IR** (KBr, Neat) 2924, 1676, 1600, 1489, 1405, 1275, 1037, 1012, 802, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{15}BrO_2$ $(M+H)^+$ 343.0328. Found 343.0334.

(2*S,3*S**)-2-Isopropyl-3-phenyl-2*H*-pyran-4(3*H*)-one (45c):**



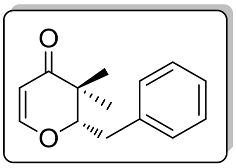
Pale yellow liquid; yield 90 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.8 Hz, 3 H), 1.01(d, *J* = 6.8 Hz, 3 H), 1.56-1.65 (m, 1 H), 3.75 (d, *J* = 12.4 Hz, 1 H), 4.43 (dd, *J* = 12.4 and 2.8 Hz, 1 H), 5.55 (d, *J* = 6.0 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.28-7.38 (m, 3 H), 7.47 (d, *J* = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 19.8, 28.9, 54.7, 87.6, 107.0, 127.7, 129.1, 129.3, 135.7, 163.3, 194.1; IR (KBr, Neat) 2966, 2875, 1675, 1600, 1466, 1406, 1276, 1035, 748, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}O_2$ $(M+H)^+$ 217.1223. Found 217.1226.

(2*S,3*S**)-2-Allyl-3-phenyl-2*H*-pyran-4(3*H*)-one (45d):**



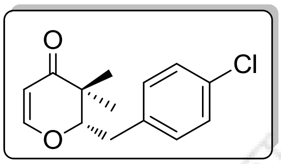
Pale yellow liquid; yield 64 mg, 60%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.25-2.40 (m, 2 H), 3.69 (d, *J* = 12.0 Hz, 3 H), 4.66 (ddd, *J* = 12.0, 6.8 and 4.0 Hz, 1 H,), 5.05 (dd, *J* = 15.6 and 4.8 Hz, 1 H), 5.15 (dd, *J* = 10.4 and 4.4 Hz, 1 H), 5.57 (d, *J* = 6.0 Hz, 1 H), 5.77-5.88 (m, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.27-7.38 (m, 3 H), 7.44 (d, *J* = 6.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 36.8, 56.0, 82.7, 107.2, 119.0, 127.8, 129.0, 129.3, 132.4, 135.5, 162.5, 193.1; **IR** (KBr, Neat) 2926, 1676, 1601, 1496, 1406, 1281, 1034, 801, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{14}O_2$ $(M+H)^+$ 215.1067. Found 215.1077.

(S*)-2-Benzyl-3,3-dimethyl-2*H*-pyran-4(3*H*)-one (45e):



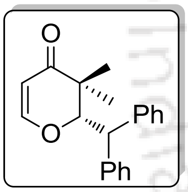
Colourless liquid; yield 86 mg, 81%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.23 (s, 3 H), 2.91-3.02 (m, 2 H), 4.24 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 5.34 (d, *J* = 6.0 Hz, 1 H), 7.23-7.28 (m, 3 H), 7.31-7.36 (m, 3 H); **^{13}C NMR** (100 MHz, CDCl3) δ 18.2, 20.1, 35.0, 44.6, 87.5, 105.4, 126.8, 128.6, 129.4, 138.0, 161.8, 198.4; **IR** (KBr, Neat) 2971, 2873, 1673, 1602, 1496, 1403, 1270, 1058, 1040, 751 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{16}O_2$ $(M+H)^+$ 217.1223. Found 217.1232.

(S*)-2-(4-Chlorobenzyl)-3,3-dimethyl-2*H*-pyran-4(3*H*)-one (45f):



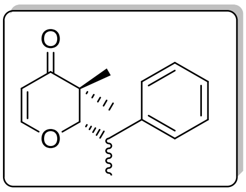
Colourless liquid; yield 81 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.22 (s, 3 H), 2.87-3.00 (m, 2 H), 4.19 (dd, *J* = 10.0 and 2.8 Hz,1 H), 5.35 (d, *J* = 5.6 Hz, 1 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 6.0 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.2, 20.1, 34.3, 44.5, 87.2, 105.5, 128.8, 130.8, 132.7, 136.4, 161.6, 198.1; **IR** (KBr, Neat) 2971, 2873, 1673, 1603, 1493, 1401, 1270, 1095, 1041, 815, 796 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{15}ClO_2$ $(M+H)^+$ 251.0833. Found 251.0845.

(S*)-2-Benzhydryl-3,3-dimethyl-2*H*-pyran-4(3*H*)-one (45g):



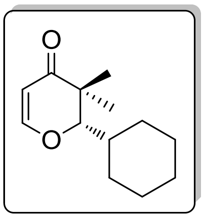
Pale yellow liquid; yield 103 mg, 71%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.81 (s, 3 H,), 1.06 (s, 3 H), 4.38 (d, *J* = 6.0 Hz, 1 H), 4.83 (d, *J* = 6.0 Hz, 1 H), 5.34 (d, *J* = 5.2 Hz, 1 H), 7.19-7.32 (m, 7 H), 7.36 (d, *J* = 7.2 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.2, 20.6, 45.7, 51.9, 88.0, 105.5, 126.9, 127.9, 128.6, 128.8, 129.3, 129.6, 141.0, 142.6, 161.9, 198.6; **IR** (KBr, Neat) 2967, 2926, 1673, 1601, 1495, 1452, 1276, 1058, 1040, 816, 704 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{20}O_2$ $(M+H)^+$ 293.1536. Found 293.1549.

(S*)-3,3-Dimethyl-2-(1-phenylethyl)-2*H*-pyran-4(3*H*)-one (diastereomeric mixture with a ratio: 1:2) (45h):



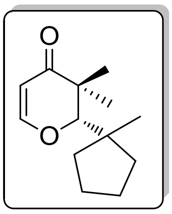
Colourless liquid; yield 72 mg, 63%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.92 (s, 3 H, minor), 0.99 (s, 3 H, major), 1.08 (s, 3 H, minor), 1.12 (s, 3 H, major), 1.41 (d, *J* = 6.8 Hz, 3 H, major), 1.47 (d, *J* = 7.2 Hz, 3 H, minor), 3.13-3.17 (m, 1 H, minor), 3.18-3.26 (m, 1 H, major), 4.15 (d, *J* = 2.8 Hz, 1 H, minor), 4.28 (d, *J* = 4.8 Hz, 1 H, major), 5.30 (d, *J* = 6.0 Hz, 1 H,minor), 5.35 (d, *J* = 5.6 Hz, 1 H, major), 7.20-7.42 (m, 5 H), 7.48-7.51 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.9, 18.7, 19.1, 19.3, 21.2, 22.0, 40.2, 40.4, 45.4, 45.6, 89.9, 90.2, 104.6, 105.3, 126.8, 126.9, 127.6, 127.8, 128.5, 128.8, 143.0, 145.8, 159.3, 162.0, 198.6, 198.8; **IR** (KBr, Neat) 2979, 2933, 1675, 1603, 1454, 1404, 1271, 1158, 1034, 814, 702 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{18}O_2$ $(M+H)^+$ 231.1380. Found 231.1389.

(*S**)-2-Cyclohexyl-3,3-dimethyl-2*H*-pyran-4(3*H*)-one (45i):



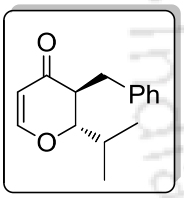
Colourless liquid; yield 81 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.09 (s, 3 H), 1.18 (s, 3 H), 1.20-1.50 (m, 4 H), 1.55-1.70 (m, 3 H), 1.71-1.80 (m, 4 H), 3.88 (d, *J* = 2.8 Hz, 1 H), 5.28 (d, *J* = 6.0 Hz, 1 H), 7.31 (d, *J* = 6.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.1, 22.3, 26.2, 26.5, 26.7, 28.2, 32.6, 39.0, 44.7, 91.1, 104.9, 162.2, 198.9; **IR** (KBr, Neat) 2930, 2854, 1675, 1603, 1450, 1408, 1276, 1159, 1041, 814 cm^{-1}; **HRMS** (ESI) calcd. For $C_{13}H_{20}O_2$ $(M+H)^+$ 209.1536. Found 209.1546.

(*S**)-3,3-Dimethyl-2-(1-methylcyclopentyl)-2*H*-pyran-4(3*H*)-one (45j):



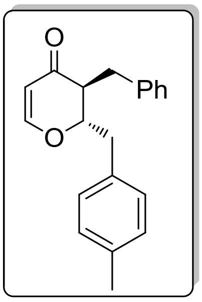
Pale yellow liquid; yield 37 mg, 35%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.07 (s, 3 H), 1.16 (s, 3 H), 1.24 (s, 3H), 1.49-1.53 (m, 2 H), 1.58-1.70 (m, 6 H), 3.82 (s, 1 H), 5.31 (d, *J* = 5.6 Hz, 1 H,), 7.35 (d, *J* = 5.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.3, 21.9, 22.5, 22.6, 24.6, 39.0, 40.4, 46.0, 48.7, 95.0, 104.8, 162.6, 199.5; **IR** (KBr, Neat) 2929, 2873, 1676, 1604, 1460, 1407, 1271, 1239, 1157, 1037, 814 cm^{-1}; **Anal. Calcd** for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found C, 75.05; H, 9.51.

(2*S**,3*S**)-3-Benzyl-2-isopropyl-2*H*-pyran-4(3*H*)-one (45m):



Pale yellow liquid; yield 83 mg, 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H,), 2.07-2.17 (m, 1H), 2.68-2.75 (m, 1 H), 2.90 (dd, *J* = 13.6 and 8.8 Hz, 1 H), 3.04 (dd, *J* = 13.6 and 5.2 Hz, 1 H), 3.89 (t, *J* = 7.2 Hz, 1 H), 5.39 (d, *J* = 5.6 Hz, 1 H), 7.16-7.24 (m, 3 H), 7.25-7.32 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.7, 18.9, 28.2, 34.7, 49.1, 85.8, 105.9, 126.7, 128.6, 129.3, 138.4, 161.5, 194.4; **IR** (KBr, Neat) 2965, 2931, 1673, 1602, 1496, 1409, 1278, 1033, 800, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{18}O_2$ $(M+H)^+$ 231.1380. Found 231.1390.

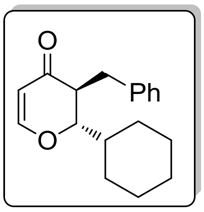
(2*S**,3*S**)-3-Benzyl-2-(4-methylbenzyl)-2*H*-pyran-4(3*H*)-one (45n):



Pale yellow liquid; yield 93 mg, 64%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 2.60 (dd, *J* = 13.2 and 6.0 Hz, 1 H), 2.86 (dd, *J* = 13.2 and 5.2 Hz, 1 H), 2.98-3.04 (m, 3 H), 4.45 (ddd, *J* = 13.6, 8.4 and 5.2 Hz, 1 H), 5.45 (d, *J* = 5.6 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.20-7.30 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.2, 34.9, 37.0, 50.4, 81.4, 106.0, 126.8, 128.8, 129.2, 129.3, 129.4, 133.4, 136.6, 137.9, 161.0, 194.1; **IR** (KBr, Neat) 2924, 2855, 1673, 1600, 1495, 1407, 1269, 1039, 810, 717 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{20}O_2$ $(M+H)^+$ 293.1536. Found 293.1546.

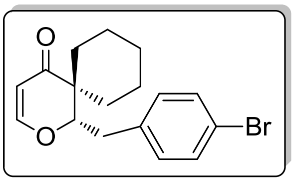
(2*S**,3*S**)-3-Benzyl-2-cyclohexyl-2*H*-pyran-4(3*H*)-one (45o):

Pale yellow liquid; yield 108 mg, 80%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.83-1.25 (m, 6 H), 1.42-1.80 (m, 5 H), 2.73 (ddd, *J* = 13.6, 9.2 and 4.8 Hz, 1 H), 2.83 (dd, *J* = 13.6 and 9.6 Hz, 1 H), 3.07



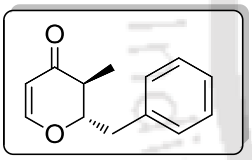
(dd, *J* = 13.6 and 4.4 Hz, 1 H), 3.95 (dd, *J* = 7.2 and 4.8 Hz, 1 H), 5.39 (d, *J* = 6.0 Hz, 1 H), 7.18-7.24 (m, 3 H), 7.25-7.32 (m, 3 H); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 25.6, 25.8, 26.1, 28.2, 28.9, 34.9, 37.5, 48.6, 85.1, 105.7, 126.6, 128.6, 129.2, 138.3, 161.5, 194.6; **IR** (KBr, Neat) 2929, 2853, 1672, 1600, 1452, 1410, 1274, 1033, 797, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{22}O_2$ $(M+H)^+$ 271.1693. Found 271.1703.

(*S)-1-(4-Bromobenzyl)-2-oxaspiro[5.5]undec-3-en-5-one (45p):**



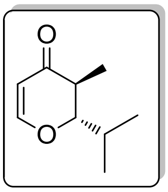
Colourless solid, mp 106-108°C; yield 97mg, 58%; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 1.38-1.52 (m, 4 H), 1.58-1.64 (m, 2 H), 1.68-1.78 (m, 2 H), 1.98-2.05 (m, 2 H), 2.79 (dd, *J* = 14.4 and 2.8 Hz, 1 H), 2.96 (dd, *J* = 14.4 and 11.2 Hz, 1 H), 4.61 (dd, *J* = 11.2 and 3.2 Hz, 1 H), 5.34 (d, *J* = 6.0 Hz, 1 H), 7.03 (d, *J* = 6.0 Hz, 1 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 21.7, 22.0, 25.9, 27.6, 32.2, 32.6, 47.5, 85.4, 105.9, 120.7, 131.0, 131.8, 137.3, 158.5, 198.4; **IR** (KBr, Neat) 2928, 2856, 1672, 1604, 1490, 1402, 1254, 1011, 792 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{19}BrO_2$ $(M+H)^+$ 335.0641. Found 335.0654.

(2*S,3*S**)-2-Benzyl-3-methyl-2*H*-pyran-4(3*H*)-one (45q):**



Pale yellow liquid; yield 69 mg, 68%; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 1.22 (d, *J* = 7.2 Hz, 3 H), 2.39-2.50 (m, 1 H), 2.98 (dd, *J* = 14.4 and 8.0 Hz, 1 H), 3.16 (dd, *J* = 14.4 and 4.0 Hz, 1 H), 4.34 (ddd, *J* = 11.6, 8.0 and 4.0 Hz, 1 H), 5.37 (d, *J* = 6.0 Hz, 1 H), 7.19-7.35 (m, 6 H); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 11.4, 38.5, 43.6, 84.4, 106.0, 126.9, 128.5, 129.7, 136.5, 162.1, 194.8; **IR** (KBr, Neat) 2924, 1675, 1599, 1405, 1254, 1025, 750, 699 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{14}O_2$ $(M+H)^+$ 203.1067. Found 203.1062.

(2*S,3*S**)-2-Isopropyl-3-methyl-2*H*-pyran-4(3*H*)-one (45r):**



Colourless liquid; yield 60 mg, 79%; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 0.97 (d, *J* = 6.8 Hz, 3 H), 1.09 (d, *J* = 6.4 Hz, 3 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.89-2.03 (m, 1 H), 2.50-2.58 (m, 1 H), 2.92 (dd, *J* = 12.0 and 3.2 Hz, 1 H), 5.37 (d, *J* = 6.0 Hz, 1 H), 7.35 (d, *J* = 6.0 Hz, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 10.2, 14.8, 19.6, 28.7, 41.9, 88.10, 105.9, 162.7, 195.6; **IR** (KBr, Neat) 2969, 2878, 1676, 1602, 1407, 1298, 1048, 1025, 815 cm^{-1}; **HRMS** (ESI) calcd. for $C_9H_{14}O_2$ $(M+H)^+$ 155.1067. Found 155.1070.

5.7. Selected Spectra

^{1}H and ^{13}C NMR spectra of **(2*S**,3*S**)-2-Benzyl-3-phenyl-2*H*-pyran-4(3*H*)-one**

```
IK_2_01

expl  s2pul

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file /export/home/~  spin        not used
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sw           6389.8  alfa          20.000
at            1.998         FLAGS
np            25528  il                n
fb         not used  in                n
bs                4  dp                y
d1            1.000  hs               nn
nt               32       PROCESSING
ct               32  lb             0.10
   TRANSMITTER       fn            65536
tn               H1        DISPLAY
sfrq        399.853  sp            -66.3
tof           362.8  wp           4567.6
tpwr             57  rfl           796.8
pw            9.850  rfp               0
    DECOUPLER        rp             91.4
dn              C13  lp            -69.8
dof               0          PLOT
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dmm               c  sc                0
dpwr             50  vs               41
dmf           15900  th                7
                     nm   cdc   ph
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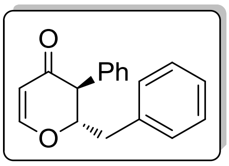

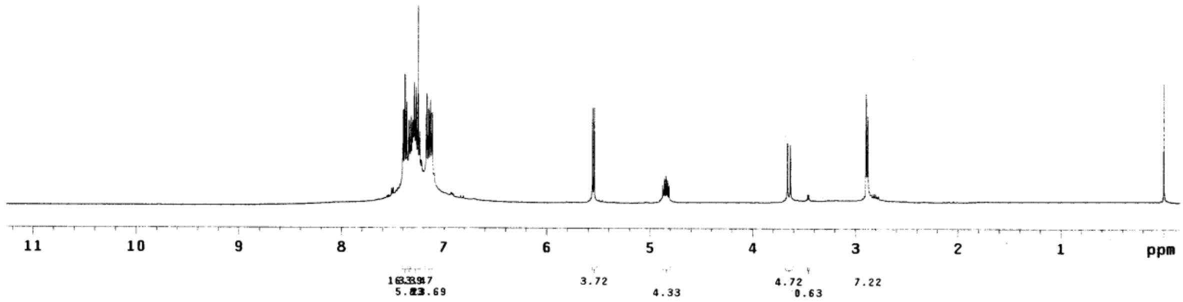

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file            exp  spin        not used
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at            1.199  alfa          20.000
np            60270         FLAGS
fb            13800  il                n
bs               10  in                n
d1            1.000  dp                y
nt             5000  hs               nn
ct             1810       PROCESSING
   TRANSMITTER       lb             2.00
tn              C13  fn            65536
sfrq        100.554        DISPLAY
tof          1536.3  sp           -192.1
tpwr             61  wp          22847.5
pw            9.300  rfl          9277.5
    DECOUPLER        rfp          7764.9
dn               H1  rp            -29.5
dof               0  lp           -352.2
dm              yyy          PLOT
dmm               w  wc              250
dpwr             42  sc                0
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                     th                2
                     nm   no   ph
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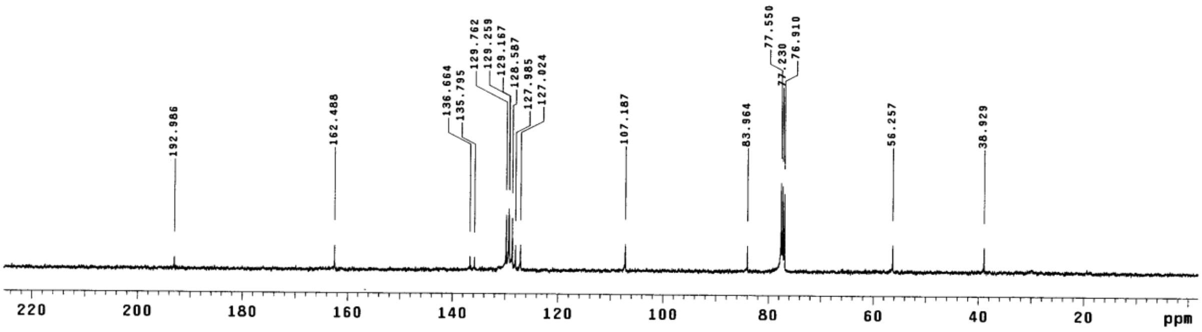

^{1}H and ^{13}C NMR spectra of **(2*S**,3*S**)-2-Isopropyl-3-phenyl-2*H*-pyran-4(3*H*)-one**

```
IK_2_02

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file /export/home/~   spin        not used
   ciftemp/IK_2_02    hst            0.008
   ACQUISITION        pw90          19.700
sw           6389.8   alfa          20.000
at            1.998         FLAGS
np            25528   il                 n
fb         not used   in                 n
bs                4   dp                 y
d1            1.000   hs                nn
nt               32       PROCESSING
ct               32   lb              0.10
   TRANSMITTER        fn             65536
tn               H1         DISPLAY
sfrq        399.853   sp             -80.7
tof           362.8   wp            4542.5
tpwr             57   rfl            794.3
pw            9.850   rfp                0
    DECOUPLER         rp              95.4
dn              C13   lp             -92.4
dof               0           PLOT
dm              nnn   wc               250
dmm               c   sc                 0
dpwr             50   vs                61
dmf           15900   th                14
                      nm  cdc  ph
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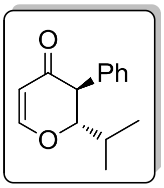

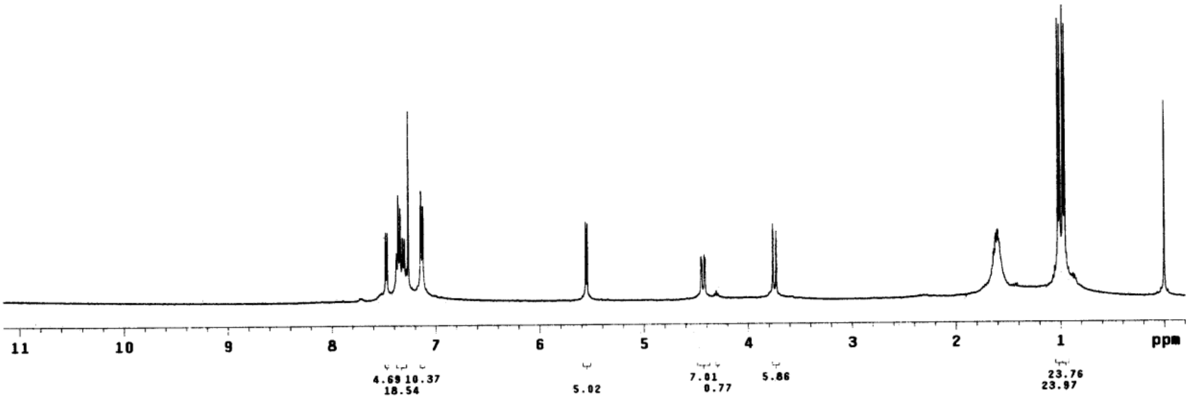

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IK_2_02_13C

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solvent       CDCl3   gain        not used
file            exp   spin        not used
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sw          25125.6   pw90          18.600
at            1.199   alfa          20.000
np            60270         FLAGS
fb            13800   il                 n
bs               16   in                 n
d1            1.000   dp                 y
nt             5000   hs                nn
ct             1376       PROCESSING
   TRANSMITTER        lb              2.00
tn              C13   fn             65536
sfrq        100.554         DISPLAY
tof          1536.3   sp             -92.5
tpwr             61   wp           22648.9
pw            9.300   rfl           9276.7
    DECOUPLER         rfp           7764.9
dn               H1   rp             -50.1
dof               0   lp            -318.4
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dmm               w   wc               250
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dmf            8900   vs                15
                      th                 3
                      nm  no  ph
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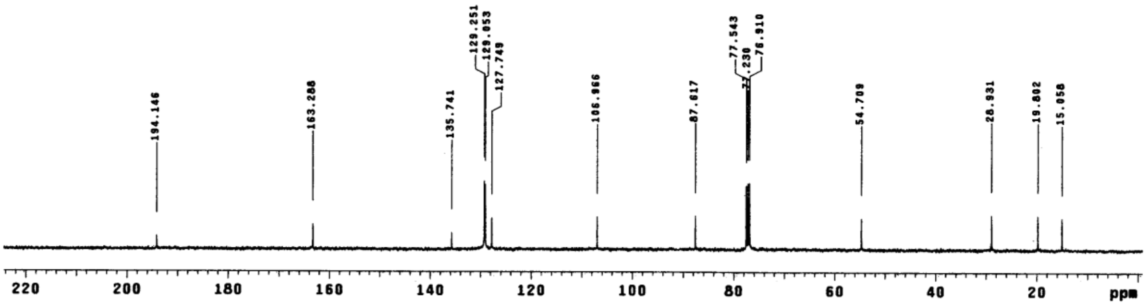

^{1}H and ^{13}C NMR spectra of **(*S**)-2-(4-Chlorobenzyl)-3,3-dimethyl-2*H*-pyran-4(3*H*)-one**

```
IK_2_06

exp1  s2pul

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solvent       CDCl3    gain          not used
file            exp    spin          not used
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sw           6389.8    pw90            19.700
at            1.998    alfa            20.000
np            25528           FLAGS
fb         not used    il                   n
bs                4    in                   n
d1            1.000    dp                   y
nt               32    hs                  nn
ct               32          PROCESSING
   TRANSMITTER         lb                0.10
tn               H1    fn               65536
sfrq        399.853           DISPLAY
tof           362.8    sp               -72.3
tpwr             47    wp              4769.1
pw            9.850    rfl              794.3
     DECOUPLER         rfp                  0
dn              C13    rp                96.1
dof               0    lp               -69.8
dm              nnn            PLOT
dmm               c    wc                 250
dpwr             50    sc                   0
dmf           15900    vs                  78
                       th                  17
                       nm   cdc   ph
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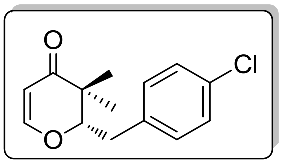

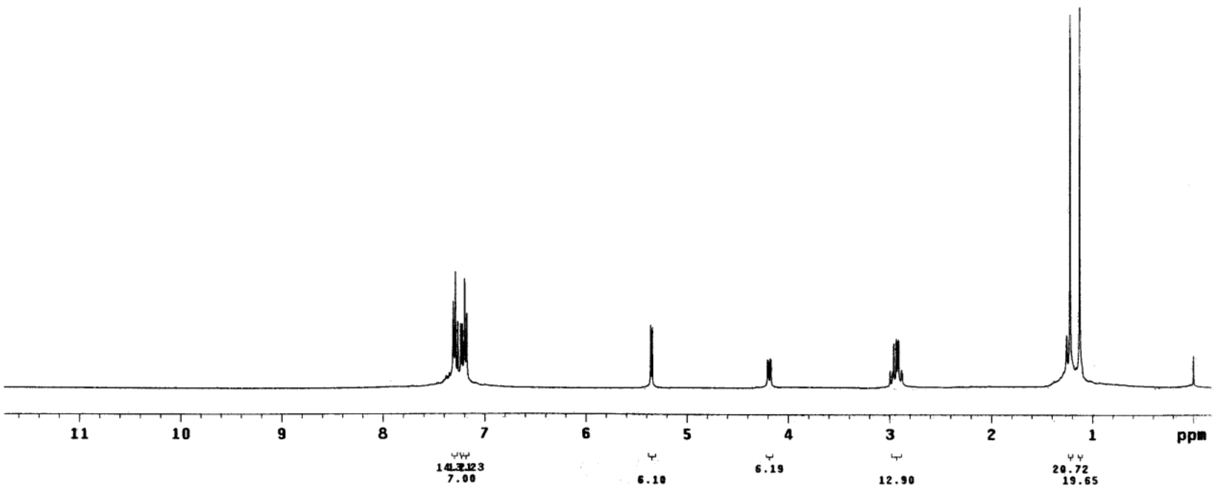

```
[illegible]_2_06_13C

exp1  s2pul

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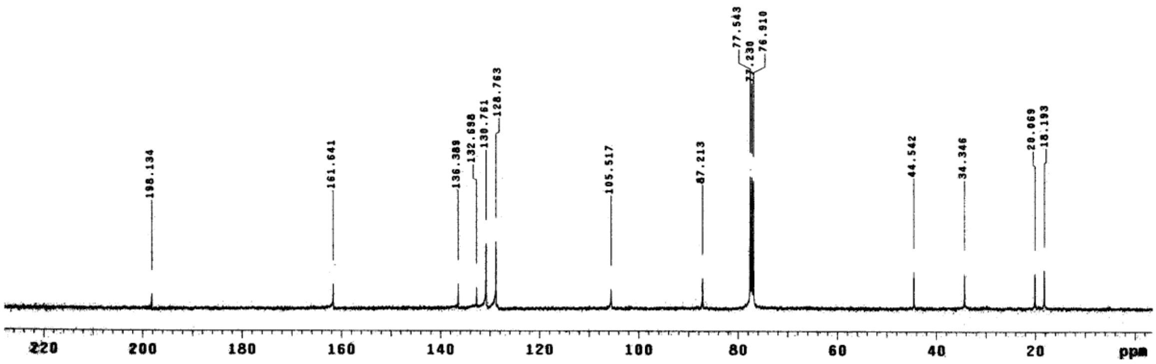
solvent       CDCl3    gain          not used
file /export/home/~    spin          not used
ciftemp/IK_2_06_13~    hst              0.008
                  C    pw90            18.600
   ACQUISITION         alfa            20.000
sw          25125.6           FLAGS
at            1.199    il                   n
np            60270    in                   n
fb            13800    dp                   y
bs               16    hs                  nn
d1            1.000          PROCESSING
nt            12000    lb                2.00
ct            12000    fn               65536
   TRANSMITTER               DISPLAY
tn              C13    sp              -355.5
sfrq        100.554    wp             23276.1
tof          1536.3    rfl             9275.9
tpwr             61    rfp             7764.9
pw            9.300    rp               -83.0
     DECOUPLER         lp              -271.4
dn               H1            PLOT
dof               0    wc                 250
dm              yyy    sc                   0
dmm               w    vs                  28
dpwr             42    th                   3
dmf            8900    nm   no   ph
```



^{1}H and ^{13}C NMR spectra of **(2*S***,3*S***)-3-Benzyl-2-isopropyl-2*H*-pyran-4(3*H*)-one**

```
IK_2_13

exp1  s2pul

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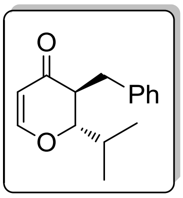
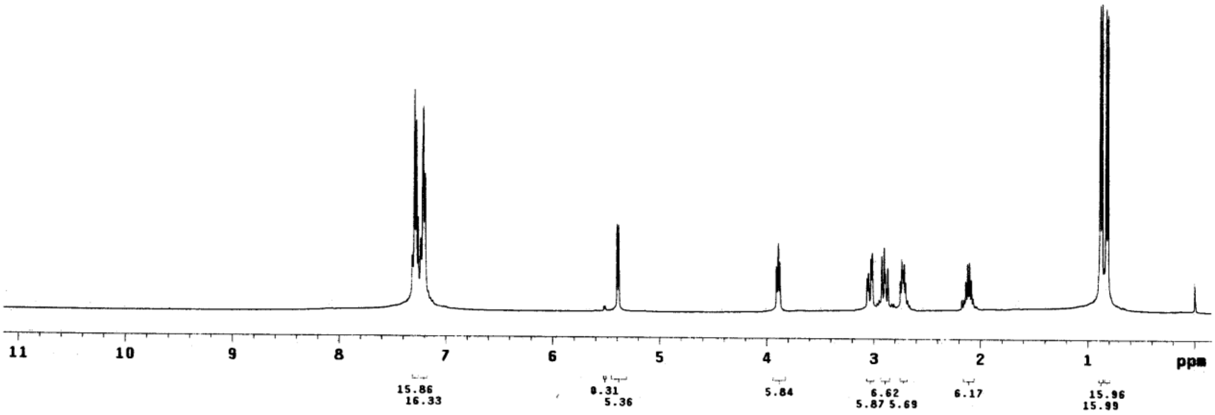
solvent       CDCl3   gain          not used
file /export/home/~   spin          not used
   ciftemp/IK_2_13   hst              0.008
   ACQUISITION        pw90            19.700
sw           6389.8   alfa            20.000
at            1.998          FLAGS
np            25528   il                   n
fb        not used,   in                   n
bs                4   dp                   y
d1            1.000   hs                  nn
nt               32        PROCESSING
ct               32   lb                0.10
   TRANSMITTER        fn               65536
tn               H1          DISPLAY
sfrq        399.853   sp               -63.6
tof           362.8   wp              4517.3
tpwr             57   rfl              794.1
pw            9.850   rfp                  0
    DECOUPLER         rp               112.8
dn              C13   lp               -91.5
dof               0           PLOT
dm              nnn   wc                 250
dmm               c   sc                   0
dpwr             50   vs                  64
dmf           15900   th                   9
                      nm   cdc   ph
```





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exp1  s2pul

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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             3000   hs                  nn
ct             1136        PROCESSING
   TRANSMITTER        lb                2.00
tn              C13   fn               65536
sfrq        100.554          DISPLAY
tof          1536.3   sp              -350.9
tpwr             61   wp             22668.0
pw            9.300   rfl             9279.8
    DECOUPLER         rfp             7764.9
dn               H1   rp               -52.8
dof               0   lp              -361.2
dm              yyy           PLOT
dmm               w   wc                 250
dpwr             42   sc                   0
dmf            8900   vs                  17
                      th                   3
                      nm   no   ph
```

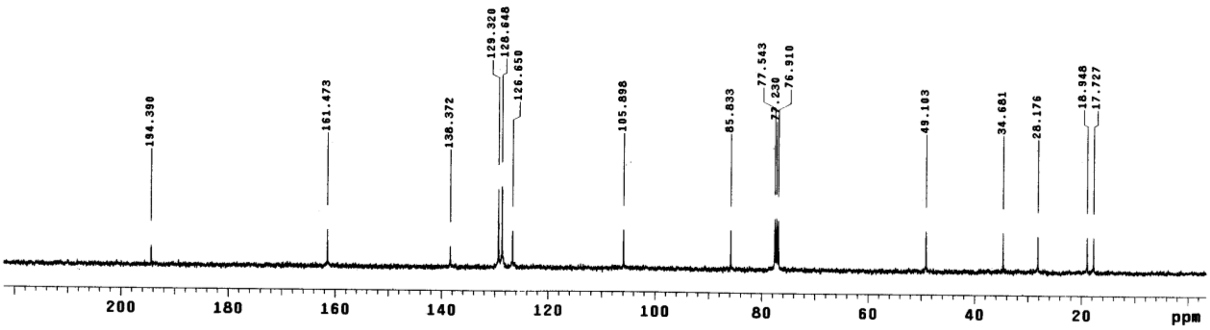

^{1}H and ^{13}C NMR spectra of **(*S**)-1-(4-Bromobenzyl)-2-oxaspiro[5.5]undec-3-en-5-one**

```
IK_2_09

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               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             -71.0
tpwr            57  wp            4473.6
pw           9.850  rfl            794.7
    DECOUPLER       rfp                0
dn             C13  rp              90.8
dof              0  lp             -81.6
dm             nnn           PLOT
dmm              c  wc               250
dpwr            50  sc                 0
dmf          15900  vs                79
                    th                18
                    nm  cdc  ph
```

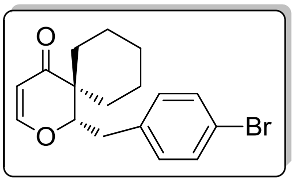

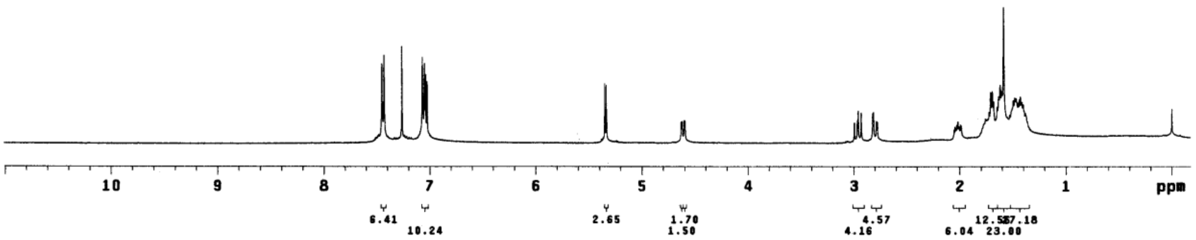

```
IK_2_09P_13C

exp1  s2pul

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solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/IK_2_09P_1~ hst            0.008
                3C  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            6592  fn             65536
   TRANSMITTER             DISPLAY
tn             C13  sp            -351.6
sfrq       100.554  wp           23144.2
tof         1536.3  rfl           9272.1
tpwr            61  rfp           7764.9
pw           9.300  rp             -29.8
    DECOUPLER       lp            -416.3
dn              H1           PLOT
dof              0  wc               250
dm             yyy  sc                 0
dmm              w  vs                25
dpwr            42  th                 2
dmf           8900  nm  no  ph
```

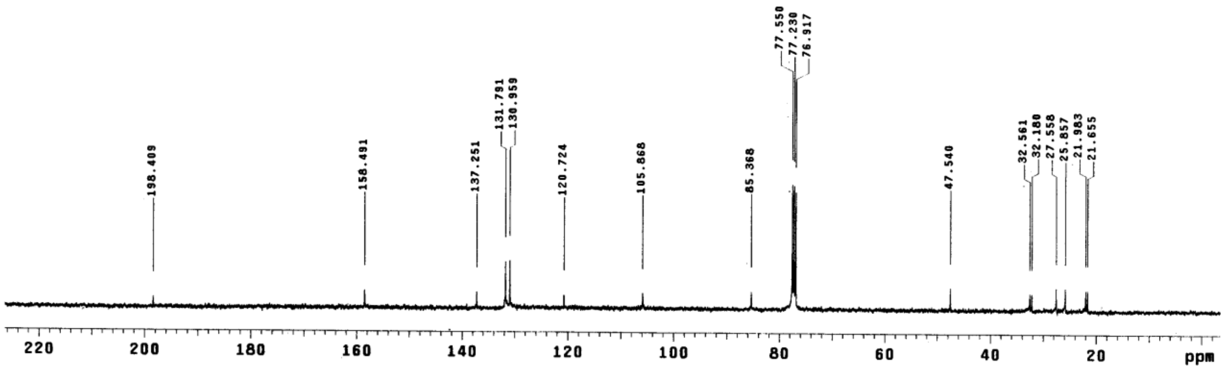

List of Publications

1. "Stereoselective, One-Pot, Three-Component Synthesis of 4-Aryltetrahydropyrans from Epoxides *via* Prins Cyclization Reaction" **Indukuri, K.**; Bondalapati, S.; Kotipalli, T.; Gogoi, P.; Saikia, A. K. *Synlett* **2011**, 233.
2. "Synthesis of 2, 3-Dihydro-4-pyranones from Epoxides *via* Intermolecular [4+ 2] Cycloaddition Reaction" **Indukuri, K.**; Bondalapati, S.; Sultana, S.; Saikia, A. K. *RSC Adv*. **2012**, *2*, 9398.
3. "Stereoselective Synthesis of Amido and Phenyl Azabicyclic Derivatives *via* a Tandem Aza Prins-Ritter/Friedel–Crafts Type Reaction of Endocyclic *N*-Acyliminium Ions" **Indukuri, K.**; Unnava, R.; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013**, *78*, 10629.
4. "Stereoselective Synthesis of *O*-Tosyl Azabicyclic Derivatives *via* Aza Prins Reaction of Endocyclic *N*-Acyliminium Ions: Application to the Total Synthesis of (±)-*epi*-Indolizidine **167B** and **209D**" Saikia, A. K.; **Indukuri, K.**; Das, J. *Org. Biomol. Chem.* **2014**, *12*, 7026.
5. "Axial-selectivity in Prins Cyclization Reaction: Synthesis of 4-Iodotetrahydropyrans" Saikia, A. K.; Bondalapati, S.; **Indukuri, K.**; Gogoi, P. *Chem. Lett*. **2011**, 1176.
6. "Diastereoselective Synthesis of Substituted Tetrahydrothiopyrans *via* (3, 5)-Thionium–Ene Cyclization Reaction" Bondalapati, S.; Gogoi, P.; **Indukuri, K.**; Saikia, A. K. *J. Org. Chem*. **2012**, *77*, 2508.
7. "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.
8. "Stereoselective Synthesis of Tetrahydroquinolines Through an Imino-Ene Cyclization Reaction" Bondalapati, S.; **Indukuri, K.**; Ghosh, P.; Saikia, A. K. *Eur. J. Org. Chem.* **2013**, 952.
9. "Scandium (III) triflate Catalyzed Synthesis of Primary Homoallylic Alcohols *via* Carbonyl-Ene Reaction" Sultana, S.; Bondalapati, S.; **Indukuri, K.**; Gogoi, P.; Saha, P.; Saikia, A. K. *Tetrahedron Lett.* **2013**, *54*, 1576.
10. "Unveiling the Mode of Action of Antibacterial Labdane Diterpenes from *Alpinia nigra* (Gaertn.) B. L. Burtt Seeds" Ghosh, S.; **Indukuri, K.**; Bondalapati, S.; Saikia, A. K.; Rangan, L. *Eur. J. Med. Chem.* **2013**, *66*, 101.
11. "Diastereoselective Synthesis of Dihydropyrans *via* Prins Cyclization of Enol Ethers: Total Asymmetric Synthesis of (+)-Civet Cat Compound" Sultana, S.; **Indukuri, K.**; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013**, *78*, 12182.

12. "Lewis Acid Mediated Intramolecular C-C bond formation of Alkyne-Epoxide Leading to Six Membered Nitrogen and Oxygen Heterocycles" Ghosh, P.; Saha, P.; Bondalapati, S.; **Indukuri, K.**; Saikia, A. K. *J. Org. Chem.* **2014**, *79*, 4119.
13. "Regioselective One-Pot, Three-Component Synthesis of Substituted 2*H*-Indazoles from Nitroarylaldehyde, Alkyne and Amine Catalyzed by CuBr/Zn(OTf)$_2$ System" Saikia, A. K.; Unnava, R.; **Indukuri, K.**; Sarkar, S. *RSC Adv*. **2014**, *4*, 55296.
14. "Diastereoselective Synthesis of Substituted Tetrahydrothiophenes and –thiopyrans *via* Thia-Prins Cyclization Reaction" Borah, M.; Gogoi, P.; **Indukuri, K.**; Saikia, A. K. *J. Org. Chem.* **2015**, *80*, 2641.
15. "Synthesis of 5, 6 and 7-Membered 1, 3- and 1, 4-Heterocyclic Compounds *via* Intramolecular Hydroalkoxylation/ Hydrothio-alkoxylation of Alkenols/ Thioalkenols" Deka, M. J.; **Indukuri, K.**; Sultana, S.; Borah, M.; Saikia, A. K. (Communicated).