TOTAL SYNTHESES OF SIPHONARIENAL, SIPHONARIENONE, (–)-SEDRIDINE AND DEVELOPMENT OF NOVEL METHODOLOGIES

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CERTIFICATE

This is to certify that the thesis entitled **"TOTAL SYNTHESES OF SIPHONARIENAL, SIPHONARIENONE, (–)-SEDRIDINE AND DEVELOPMENT OF NOVEL METHODOLOGIES"** submitted by **Mr. SUPRIYA GHANTY** bearing Reg. No. **09CHPH22** in partial fulfillment of the requirements for the award of Doctor of Philosophy in **CHEMISTRY** is a bonafide work carried out by him under my supervision and guidance at Indian Institute of Chemical Technology, Hyderabad.

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I **Mr. SUPRIYA GHANTY** hereby declare that this thesis entitled **"TOTAL SYNTHESES OF SIPHONARIENAL, SIPHONARIENONE, (–)-SEDRIDINE AND DEVELOPMENT OF NOVEL METHODOLOGIES"** submitted by me under the guidance and supervision of **Dr. B. V. SUBBA REDDY, FNASc** Indian Institute of Chemical Technology, CSIR, Hyderabad-500 007, India is a bonafide research work which is also free from plagiarism. I also declare that it has not been submitted previously in part or full to this University or any other University or Institution for the award of any degree or diploma. I hereby agree that my thesis can be deposited in Shodganga/INFLIBNET.

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*Finally, I thank the **Director- IICT** for allowing me to submit this work in the form of thesis.*

Mr. SUPRIYA GHANTY

GENERAL REMARKS

- Boiling points and melting points are uncorrected. Melting points were recorded on a Buchi-510 instrument.

- Infrared spectra were recorded on Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. Spectra were calibrated against the standard polystyrene absorption at 1601 cm^{-1}.

- NMR spectra were recorded in $CDCl_3$ on Bruker NMR instrument operating at ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz). Chemical shifts (δ) are quoted in parts per million and are internally referenced (0.0 ppm for TMS for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). Coupling constants (J) are quoted in Hertz. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, dd= doublet of doublet, t = triplet, q = quartet, m = multiplet and br = broad.

- Mass spectra were recorded on Micromass VG-7070H for EI and VG Autospec M for FABMS.

- Optical rotations of the products were recorded on Digipol-781 M6U Polarimeter.

- Column chromatography was performed over silica gel (BDH 60-120, 100-200 mesh) and TLC with silica gel GF$_{254}$.

- All the reactions were monitored by thin-layer chromatography (TLC) using UV light as visualizing agent and/or by exposure to Iodine vapors and/or by spraying with p-anisaldehyde/H_2SO_4 reagent followed by heating at $ca.$ 60 ^{o}C.

- Moisture sensitive reactions were carried out by using standard syringe septum techniques.

- All solvents used for silica gel column chromatography were distilled prior to use and dry solvents were prepared following the standard protocols for individual solvents.

List of Abbreviations

Units

°C	Degree centigrade
mg	Milligram
h	Hour
Hz	Hertz
ml	Millilitre
MHz	Megahertz
mmol	Millimol
nm	nanometre
ppm	Parts per million

Chemical Groups

Aq.	Aqueous
Ac	Acetyl
BH	Brønsted acid
Bn	Benzyl
Bu	Butyl
cm^{-1}	Wave no
COSY	Correlation spectroscopy
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethyl amino pyridine
DMF	Dimethylformamide
DMSO-d_6	Deuterated dimethyl sulphoxide
EIMS	Electron impact mass spectroscopy
ESIMS	Electron Spray Ionisation
eV	Electronvolt
h	Hour

hz	Hertz
IBX	Iodoxy benzoic acid
LAH	Lithium aluminium hydride
m.p	Melting point
Me	Methyl
Mg	Miligram
NMR	Nuclear magnetic resonance
NMO	*N*-Methylmorpholine *N*-oxide
OBS	*o*-Benzenedisulfonimide
PCC	Pyridium chloro chromate
TPP	Triphenyl phosphine
TPAP	Tetrapropylammonium Perruthenate
TBAF	Tetrabutyl ammonium fluoride
TFA	Trifluoro acetic acid
Tert	Tertiary
Tf	Trifluromethanesulfonyl
Ph	Phenyl
p-TSA	*p*-Toluensulphonic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
UV	Ultra Violet

Other Notations

Cat.	Catalytic
calcd	Calculated
d	Doublet
δ	Chemical shift
eq	Equation
equiv	Equivalent
e.g.	Example
HRMS	High resolution mass spectrometry
IR	Infrared

J	Coupling constant in NMR
m.p.	Melting point
MS	Mass spectrometry
M.S.	Molecular sieves
M.W.	Molecular weight
NMR	Nuclear magnetic resonance
%	Percentage
rt	Room temperature
TLC	Thin layer chromatography
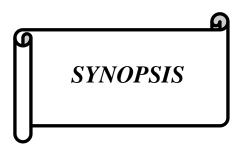
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SYNOPSIS

SYNOPSIS

The thesis entitled **"TOTAL SYNTHESES OF SIPHONARIENAL, SIPHONARIENONE, (–)-SEDRIDINE AND DEVELOPMENT OF NOVEL METHODOLOGIES''** is divided into three chapters.

CHAPTER I: This chapter is further divided into three sections.

Section A: Introduction on Prins cyclisation.

Section B: Synthesis of hexahydro-1*H*-furo[3,4-c]pyranylamide derivatives *via* Prins/Ritter reaction.

Section C: Synthesis of 4-amidotetrahydropyran derivatives *via* Prins/Ritter reaction.

CHAPTER II: This chapter is further divided into two sections.

Section A: Introduction and previous approaches for the synthesis of Sedridine

Section B: Stereoselective Synthesis of (–)-Sedridine.

CHAPTER III: This chapter is further divided into two sections.

Section A: Introduction and previous approaches for the syntheses of Siphonarienal and Siphonarienone

Section B: Stereoselective Syntheses of Siphonarienal and Siphonarienone

CHAPTER I: Section A: Introduction on Prins Cyclization

CHAPTER I: Section B: This section describes the synthesis of hexahydro-1*H*-furo[3,4-c]pyranylamide derivatives *via* Prins/Ritter reaction

　　　Oxygen containing bicycles such as furo[3,2-c]pyrans are often found in various biologically active natural products such as cordigol, triFA1, flavonoids, catechins, and pterocarpans (Fig.1). Prins cyclization is one of the most elegant strategies for the synthesis of substituted tetrahydropyran scaffolds. A few acid catalysts are reported for the synthesis of tetrahydropyranyl amide derivatives through a Prins/Ritter cascade process. Herein we wish to report on the synthesis of furo[3,4-c]pyran scaffolds *via* Prins cyclization promoted by B(C$_6$F$_5$)$_3$

Figure 1. Representative examples of cordigol and triFA1

　　　Following our interest on Prins/Ritter reaction, Herein we wish to report a simple and efficient strategy for the synthesis of a novel class of *cis*-fused 7a,3,6-trisubstituted hexahydro-1*H*-furo[3,4-*c*]pyranyl amide derivatives through a sequential Prins and Ritter reactions. At first, we have attempted the coupling of (2-(4-methoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methanol (**1**) with benzaldehyde (**2**) using catalytic amount of B(C$_6$F$_5$)$_3$ in acetonitrile at room temperature. The reaction was complete within 20 min affording the corresponding *cis*-fused 6-(phenyl)-3-(4-methoxyphenyl)hexahydro-1*H*-furo[3,4-*c*]pyran-7-yl)acetamide **4a** in 80% yield (Scheme 1).

Scheme 1. A sequential Prins/Ritter reaction

This result provided the incentive for further study of reaction with various aldehydes and ketones in presence of different nitriles. The reaction of aliphatic aldehydes such as propanal and butanal with [2-aryl-4-methylene-tetrahydrofuran-3-yl]methanol **1** in acetonitrile gave the corresponding bicyclic acetamide derivatives in good yields (entries **b** and **c**, Table **1**). Our next attempt was made to explore the feasibility of this protocol with ketones. Interestingly, the cyclic ketones such as cyclohexanone and cyclopentanone participated well in this reaction to provide the corresponding spirotricyclic amides (entries **d** and **g**, Table **1**). The reaction proceeded efficiently not only with cyclic ketones but also with acetone (entry **h**, Table **1**). Other aromatic aldehydes such as *p*-chloro-, and *p*-nitrobenzaldehydes also reacted well with *exo*-cyclic hydroxy olefin **1** in the presence of nitriles to yield the corresponding bicyclic amide derivatives (entries **f** and **i**, Table **1**). Next, we examined the reactivity of different nitriles. Remarkably, the reaction was successful with different nitriles such as acrylonitrile, propionitrile and benzonitrile to afford the corresponding acrylamide, propionamide and benzamide derivatives respectively (entries **e**-**j**, Table **1**). The scope of $B(C_6F_5)_3$ catalyzed Prins/Ritter reaction is illustrated with various aldehydes and ketones in the presence of different nitriles and the results are presented in Table **1**.

Table 1. B(C$_6$F$_5$)$_3$-catalyzed synthesis of hexahydro-1*H*-furo[3,4-*c*]pyran-7a-yl amide derivatives

Entry	Carbonyl compounds	Nitrile	Product (**4**)[b]	Time (min)	Yield %)[c]
a	PhCHO	MeCN		20	80
b		MeCN		20	85
c		MeCN		20	85
d		MeCN		25	80
e		CN		20	85
f		CN		20	90
g		CN		25	80
h		CN		25	85
i		PhCN		25	90
j		PhCN		20	85

[a]Reaction was performed with 0.5 mmol olefin, 0.75 mmol aldehyde/ ketone using 5 mol% of B(C$_6$F$_5$)$_3$ in nitrile solvent. [b]All products were characterized by NMR, IR and mass spectroscopy. [c]Yield refers to pure products after chromatography.

In all cases the products were obtained in good yields with *cis*-selectivity. A single product was formed in each reaction. The relative stereochemistry of **4f** was established by using detailed 1D and 2D NMR experiments.

In summary, we have developed a novel and efficient protocol for the synthesis of *cis*-fused hexahydro-1*H*-furo[3,4-*c*]pyranylamide derivatives using $B(C_6F_5)_3$ as a mild Lewis acid catalyst. This method offers significant advantages such as mild conditions, short reaction times and absence of side products.

Section C: This section describes the synthesis of 4-amidotetrahydropyran derivatives *via* Prins/Ritter reaction.

In recent years, *o*-benzenedisulfonimide (**1**, 1,3,2-benzodithiazole-1,1,3,3-tetraoxide; Figure **1**) has received a great attention due to its versatility in organic synthesis. It has been used for various organic transformations such as etherification, esterification, Hosomi-Sakurai reaction, Ritter reaction, Nazarov electro-cyclisation, disproportionations of dialkyl diarylmethyl ethers and Strecker reaction.

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Figure 1. *o*-Benzenedisulfonimide (OBS) (**1**)

4-Aminotetrahydropyran ring is a core structure in several natural products such as ambruticin VS3 and dysiherbaine (Figure **2**).

Ambruticin VS3

Dysiherbaine

Figure 2. Representative examples of 4-aminotetrahydropyrans

Following our interest on Prins cyclization, a highly diastereoselective synthesis of 4-amidotetrahydropyran derivatives is achieved using *o*-benzenedisulfonimide as catalyst under mild conditions. The synthesis involves sequential allylation followed by Prins-Ritter amidation. For instance, treatment of 2.1 equiv. of *p*-chlorobenzaldehyde with 1 equiv. of allyltrimethylsilane in acetonitrile in the presence of 10 mol% catalyst (**1**) at room temperature gave the corresponding 4-acetamido-2,6-diphenyl-

tetrahydropyran **3a** in 85% yield with *cis*-selectivity. The reaction was completed within 1 h (Scheme **1**).

Scheme 1. A sequential allylation and Prins/Ritter amidation

This result provided the incentive for further study of reaction with various aldehydes in presence of different nitriles. Interestingly, aromatic aldehydes such as *p*-chlorobenzaldehyde and *p*-bromobenzaldehyde underwent a smooth reaction with allyltrimethylsilane in acetonitrile to give the corresponding 4-acetamido-2,6-diaryl-tetrahydropyrans in good yields (entries **a** and **b** Table **1**). This method is effective even for sterically hindered substrate, for example, 2-naphthaldehyde (entry **c**, Table **1**). Similarly, benzaldehyde also reacted well with allyltrimethylsilane in benzyl cyanide to yield the corresponding 2,6-diaryl-4-phenylacetamido-tetrahydropyrans (entry **d**, Table **1**). Next, we studied the reactivity of aromatic and aliphatic aldehydes in benzonitrile. Interestingly, *p*-chlorobenzaldehyde and *n*-butanal participated well in the Hosomi–Sakurai-Prins/Ritter amidation in benzonitrile to yield the respective 2,6-disubstituted-4-benzamidotetrahydropyrans (entries **e** and **f**, Table **1**). The scope of the catalyst **1** is illustrated with respect to various aldehydes and the results are presented in Table **1**.

Table 1. *o*-Benzenedisulfonimide catalyzed Prins/Ritter reaction

Entry	Aldehyde	Nitriles	Product (**3**)[a]	Time (h)	Yield (%)[b]
a	4-Cl-C₆H₄-CHO	CH₃CN		1.0	85
b	4-Br-C₆H₄-CHO	CH₃CN		1.0	86
c	2-naphthyl-CHO	CH₃CN		1.5	82
d	C₆H₅-CHO	PhCH₂CN		1.0	80
e	4-Cl-C₆H₄-CHO	PhCN		1.5	91
f	CH₃CH₂CH₂CHO	PhCN		1.5	80

[a]All products were characterized by ^{1}H NMR, IR and mass spectrometry.
[b]Yield refers to pure products after chromatography.

The simplicity of this procedure encouraged us to further extend it to the preparation of unsymmetrical 4-amidotetrahydropyran derivatives by means of Prins/Ritter reaction. In a typical experiment, 1.2 eq of *p*-chlorobenzaldehyde was treated with 1.0 eq of 3-buten-1-ol in presence of 10 mol% of catalyst **1** in acetonitrile. Interestingly, the reaction was completed within 1 h at room temperature and the

corresponding 2-phenyl-4-acetamidotetrahydropyran **4a** was obtained in 87% yield with *cis*-selectivity (Scheme **2**).

Scheme 2. Preparation of 2-phenyl-4-amidotetrahydropyran **4a**

This result provided the incentive for further study of reaction with various aldehydes and ketones in presence of different nitriles. The scope and generality of this process is illustrated in Table **2**.

Table 2. *o*-Benzenedisulfonimide catalyzed Prins/Ritter reaction

Entry	Aldehyde/ Ketone	Nitriles	Homoallyl alcohol	Product (**4**)[a]	Time (h)	Yield (%)[b]
a		CH$_3$CN			1.0	87
b		CH$_3$CN			1.0	80
c					1.2	80
d					1.2	82
e		CH$_3$CN			1.0	90
f					1.2	83
g		CH$_3$CN			1.0	80

[a]All products were characterized by ^{1}H NMR, IR and mass spectrometry.

[b]Yield refers to pure products after chromatography.

The catalyst can easily be recovered and reused in further reactions with only a slight loss of catalytic activity. The use of recyclable catalyst **1** in this transformation makes this method economically viable process for the synthesis of 4-amidotetrahydropyran derivatives.

In summary, a direct one-pot method has been developed for the synthesis of 4-amidotetrahydropyran derivatives by means of Prins/Ritter cyclisation using a recyclable

Brönsted acid catalyst (**1**). This method provides easy access to the synthesis of a wide range of symmetrical, unsymmetrical and spiro-cyclic 4-amidotetrahydropyran derivatives with excellent yield.

CHAPTER II:

Section A: Introduction and previous approaches for the synthesis of Sedridine.

Section B: This section describes stereoselective synthesis of (–)-Sedridine.

Piperidine alkaloids are widely distributed in nature and found to display a broad spectrum of biological activities. In particular, 2-substituted piperidine alkaloids have attracted considerable attention due to their potent biological activities such as memory enhancing properties. Beyerman's and Schöpf's groups have independently reported the isolation of (–)-sedridine **1**, an alkaloid consisting of a piperidine core from *Sedum acre*, they have also determined its absolute configuration. Sedridines are alkaloids that were isolated from *sedum acre* and later it was obtained from other species also.

(–)-Sedridine (**1**)

Figure 1

In continuation of our work on Prins cyclization and its utilization in the total synthesis of natural products, we herein report an elegant approach for the synthesis of (–)-sedridine *via* Prins/Ritter amidation sequence. As per our retrosynthetic analysis, (–)-sedridine, could be synthesized from the intermediate **7**, which in turn could easily be prepared through Prins/Ritter amidation followed by reductive opening of the 2-iodomethyl-4-amidotetrahydropyran **6** (Scheme 1).

Scheme1. Retrosynthetic analysis of (−)-sedridine **1**

Accordingly, we started the synthesis of (−)-sedridine (**1**) from the chiral homoallylic alcohol **3**. As shown in Scheme 2, the chiral (*R*)-homoallylic diol **3** was prepared from commercially available epichlorohydrin by using literature procedure. Chemoselective tosylation of the primary alcohol of **3** with TsCl in presence of dibutyltin oxide and Et$_3$N gave the homoallylic alcohol **4** in 98% yield. Three-component, one-pot coupling of homoallyl alcohol **4** with acetaldehyde and acrylonitrile in the presence of 10 mol% BF$_3$.Et$_2$O under Prins/Ritter reaction conditions gave the 4-amidotetrahydropyran **5** in 54% yield with high diastereoselectivity. After establishing the structure of the tosylate **5**, it was converted into the corresponding iodomethyl tetrahydropyran **6** in 90% yield using NaI in acetone under reflux conditions. Reductive ring-opening of **6** with Zn dust in refluxing EtOH gave the corresponding *anti*-1,3-amino alcohol **7** in 90% yield, which is a key intermediate for the synthesis of (−)-sedridine. After establishing the structure of compound **7**, the free hydroxyl group was protected as its TBS ether **8** using TBSCl in presence of imidazole in 95% yield. Ring-closing metathesis of **8** using Grubb's I catalyst in dichloromethane gave the α,β-unsaturated-δ-lactam **9** in 90% yield. Reduction of **9** using Pd/C in methanol gave the δ-lactam **10** in 90% yield. Removal of the silyl ether of **10** using TBAF in THF gave the desilylated δ-lactam **11** in 95% yield.

Finally, the reduction of **11** with LiAlH$_4$ in Et$_2$O gave the target molecule (–)-sedridine (**1**) in 76% yield.

Scheme 2*:* Total synthesis of (–)-sedridine **1**

Reagents and conditions: (i) Et$_3$N, dibutyltin oxide, TsCl, CH$_2$Cl$_2$, rt, 1 h, 98%; (ii) Acetaldehyde, acrylonitrile, BF$_3$.OEt$_2$ (10 mol%), rt, 2 h, 54%; (iii) NaI, acetone, reflux, 8 h, 90%; (iv) Zn dust, EtOH, reflux, 8 h, 90%; (v) TBSCl, Imidazole, DMAP(catalytic), CH$_2$Cl$_2$, 1 h, 95%; (vi) Grubb's I (10 mol%), CH$_2$Cl$_2$, rt, 12 h, 90%; (vii) Pd/C, MeOH, Et$_3$N, H$_2$ (1 atm), 90%; (viii) TBAF, THF, rt, 5 h, 95%; (ix) LiAlH$_4$, Et$_2$O, reflux, 2 h, 76%.

In conclusion, a simple and efficient approach has been developed for the total synthesis of piperidine alkaloid, (–)-sedridine (**1**) in a highly stereoselective manner. Our approach involves mainly the use of Prins/Ritter amidation reaction followed by reductive ring opening sequence.

CHAPTER III: This chapter is divided into two sections.

Section A: Introduction and previous approaches for the syntheses of Siphonarienal and Siphonarienone

Section B: Stereoselective syntheses of Siphonarienal and Siphonarienone

Polypropionate containing natural products are an important class of biologically active molecules and the efforts for the discovery of new strategies are still continuing. In particular, siphonarienal (**1**), siphonarienone (**2**) and pectinatone were isolated from the marine mollusks genus *Siponaria* such as *Siphonariea grisea* and *S. pectinata* respectively. These compounds are active against Gram-positive bacteria, yeast, and various human cancer cell lines. The structures of **1** and **2** were characterized by X-ray diffraction analysis and chemical correlations. The members of this class consists of (2*S*),(4*S*),(6*S*)-trimethylnonane segment which is connected through an olefinic linker to a more polar oxygen containing group (Figure **1**).

Siphonarienal 1   Siphonarienone 2

Figure 1. Representative structures of Siphonarienal (1) and Siphonarienone (2)

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Our retrosynthetic plan for the synthesis of siphonarienal (**1**) and siphonarienone (**2**) is depicted in Scheme 1. Synthesis of **1** and **2** could be achieved by the functional group transformation of a key intermediate **3**. The compound **3** can be accessed from the alcohol **13** by a simple oxidation and Wittig olefination. The intermediate **13** was expected to be synthesized from **6** in a stereoselective manner involving Wittig reaction, Evans asymmetric alkylation and Grignard reaction. Compound **6** can in turn be synthesized from the commercially available (*R*)-methyl 3-hydroxy-2-methyl propionate involving simple protection, oxidation and Wittig olefination, reduction and diastereoselective oxidative kinetic resolution using Glucose oxidase from *Aspergillus niger.*

Scheme1. Retrosynthetic analysis of Siphonarienal (**1**) and Siphonarienone (**2**)

Our synthesis of siphonarienal (**1**) and siphonarienone (**2**) started from the known precursor **4** which is available in three steps from the commercially available (*R*)-methyl 3-hydroxy-2-methylpropanoate. The ester **4** was transformed into the alcohol **5** (as 1:1 diastereomeric mixture) in 88% yield (Scheme 2). We have performed the oxidation of the alcohol **5** with commercially available glucose oxidase derived from *Aspergillus niger*. The oxidation proceeded selectively to give the aldehyde, which spontaneously oxidized to carboxylic acid **7** during the reaction. At the end of the reaction, the desired alcohol **6** was obtained in 48% yield.

Scheme 2. Kinetic resolution of alcohol **5**

Reagents and conditions: (i) (a) Mg, MeOH, rt, 12 h; (b) LAH, Et$_2$O, 0-25 $^{\circ}$C, 2 h, 88% (two steps); (ii) Glucose oxidase, Phosphate buffer pH= 8, DCM, 25 °C, 2 h, 48%.

Subsequent oxidation of the alcohol **6** followed by chain elongation by C2 Wittig olefination with (ethoxycarbonylmethylene)-triphenylphosphorane gave the *α,β*-unsaturated ester **8** in 86% yield over two steps. Chemoselective reduction of the olefinic bond with Pd/C in EtOAc afforded the saturated ester **9** in 96% yield, which was then

hydrolyzed under basic conditions to furnish the corresponding carboxylic acid **10** in 93% yield. The coupling of **10** with Evans chiral oxazolidinone using pivaloyl chloride in presence of Et$_3$N and LiCl gave the required compound **11** in 93% yield. Methylation of the Na-enolate of **11** with MeI gave the desired compound **12** with high diastereoselectivity. Treatment of compound **12** with NaBH$_4$ in MeOH gave the chiral alcohol **13** in 92% yield with three stereogenic centers. The primary alcohol **13** was converted into tosylate using TsCl, Et$_3$N followed by Grignard reaction with EtMgBr in THF at -20 °C in presence of a catalytic amount of Li$_2$CuCl$_4$ furnished the product **14** in 85% yield. Deprotection of the silyl group in compound **14** using TBAF in THF gave the primary alcohol **15** in 95% yield. Oxidation of the alcohol **15** provided the required aldehyde, which was then subjected to C3 Wittig olefination with (1-carbethoxyethylidene)-triphenylphosphorane gave the *α,β*-unsaturated ester **3** ((*E*)-isomer), as a major product in 88% yield over two steps, which is a common precursor for the synthesis of two natural products **1** and **2**. Partial reduction of unsaturated ester **3** with DIBAL-H at -78 °C provided directly the target molecule siphonarienal (**1**). For the synthesis of siphonarienone (**2**), the *α,β*-unsaturated ester **3** was directly converted into the corresponding Weinreb amide using MeNHOMe.HCl and *i*-PrMgCl, which upon treatment with EtMgBr in THF provided the siphonarienone (**2**) in 80% yield over two steps (Scheme 3).

Scheme 3. Synthesis of siphonarienal (**1**) and siphonarienone (**2**)

Reagents and conditions: (i) (a) TPAP, NMO, CH_2Cl_2, 0.5 h; (b) Ph_3PCHCO_2Et, C_6H_6, 80 ^{o}C, 12 h, 86% (two steps); (ii) Pd/C, H_2, AcOEt, 2 h, 96%; (iii) $LiOH.H_2O$, MeOH:H_2O (4:1), 2 h, 93%; (iv) (*R*)-4-benzyl-oxazolidin-2-one, Piv-Cl, Et_3N, LiCl, THF, -20-0 ^{o}C, 3 h, 93%; (v) NaHMDS, MeI, -78 ^{o}C, THF, 93%; (vi) $NaBH_4$, MeOH, 0-25 ^{o}C, 92%; (vii) (a) TsCl, DCM, Et_3N, DMAP; (b) EtMgBr, Li_2CuCl_4, THF, -20 ^{o}C, 85%, (two steps); (viii) TBAF, THF, 2 h, 95%; (ix) (a) TPAP, NMO, CH_2Cl_2, 0.5 h; (b) $Ph_3PC(Me)CO_2Et$, C_6H_6, 80 ^{o}C, 88% (two steps); (x) DIBAL-H, CH_2Cl_2, -78 ^{o}C; (xi) (a) MeNHOMe.HCl, i-PrMgCl, THF, -20 ^{o}C, 1.5 h (b) EtMgBr, THF, rt, 45 min, 80% (two steps).

In conclusion, we have demonstrated the asymmetric total syntheses of siphonarienal and siphonarienone from commercially available starting materials. The key transformations of these syntheses are the Wittig olefination, diastereoselective oxidative kinetic resolution using Glucose oxidase derived from *Aspergillus niger*, Evans asymmetric alkylation, and Grignard reaction.

CHAPTER I: SECTION A

Prins cyclisation: a versatile method in organic synthesis for construction of tetrahydropyran scaffolds

1.1 SECTION A

Prins cyclisation: a versatile method in organic synthesis for the construction of tetrahydropyran scaffolds

1.1.1 INTRODUCTION

In organic synthesis, the development of novel strategies for heterocyclic compounds is an important goal as many of such compounds display valuable properties. Six-membered oxygen, nitrogen and sulfur containing heterocycles are widely recognized as very important scaffolds in many areas of bio-organic and medicinal chemistry. In particular, mono-, bi- and tricyclic tetrahydropyran and tetrahydrofuran constitute as core structures in many biologically active natural products such as (−)-Dactylolide, Laulimalide, Leucascandrolide A, (−)-Kendomycin, (+)-Neopeltolide, (+)-Spirolaxine methyl ether, (−)-Centrolobine, Clavosolide D, (−)-diospongin, epi Apicularen A, Calyxin L and Bryostatines I etc (**1**-**12**, Figure **1**). Therefore it is important to design new and efficient strategies towards such active target molecules. Several methods have been devised for the construction of tetrahydropyran and piperidine rings. These methods mainly include Prins cyclization,[1] hetero-Diels-Alder cycloaddition,[2] heterocyclization of epoxides and aziridines,[3] Pictet-Spengler cyclization,[4] Petasis-Ferrier rearrangement,[5] oxa- and aza-Micheal addition,[6] cyclization through oxidative carbon-hydrogen bond fuctionalization[7] and ring closing methathesis[8] etc. During past decades, a rapid advancement has been made in this area by various research groups. In this chapter, we present a brief review of the Prins cyclization reaction, focusing on new methodologies development and applications to natural product synthesis, as a background that led us to choose this reaction as a key topic for our research.

(–)-Dactylolide (1) Laulimalide (2) Leucascandrolide A (3)

(–)-Kendomycin (4) (+)-Neopeltolide (5) (+)-Spirolaxine methyl ether (6)

(–)-Centrolobine (7) Clavosolide D (8) (–)-diospongin A (9)

epi Apicularen A (10) Calyxin L (11) Bryostatine-I (12)

Figure 1. Examples of biologically active tetrahydropyrans

1.1.2 Prins Reaction:

From historical background, the concept of Prins cyclisation comes from Prins reaction which was studied by H. J Prins.[9] The Prins reaction is an organic reaction consisting of an electrophilic addition of an aldehyde or ketone **13** to an alkene **14** followed by capture of an external nucleophile. The Prins reaction is one of the fundamental methods for C–C bond formation. The outcome of the reaction depends on the substrate structure and the reaction conditions, resulting in mixture of products, such as 1,3-diol **15**, 1,3-dioxan **16** or unsaturated alcohol **17** from mechanistic perspective (Scheme 1).

Scheme 1. Prins reaction of olefins with aldehydes

Mechanistically the reaction proceeds *via* the formation of oxocarbenium ion **20**, which is generated *in situ* from the hemiacetal **19**, which formed by the reaction of homoallylic alcohol **18** with aldehyde mediated by acid catalyst. Six-membered oxocarbenium adopts a chair like conformation and undergoes rapid 6-*endo* cyclization with terminal olefin to give selectively a secondary tetrahydropyranyl carbocation **21**, which can be trapped by different external nucleophiles to form tetrahydropyran scaffolds **22** (Scheme 2).

Scheme 2. Prins cyclization of homoallylic alcohol with aldehydes

The analogous reaction, the so-called carbonyl-ene reaction,[10] exclusively generates homoallyl alcohols from carbonyl compounds and either mono- or di-substituted olefins mediated by Lewis acids (Scheme 3).

Scheme 3

In 1960, Stapp[11] reported direct synthesis of tetrahydropyran derivatives *via* the Prins cyclization (Scheme 4).

Scheme 4

1.1.3 Mechanism of Prins Cyclisation:

According to a common reaction mechanism the high stereoselectivity was observed in Prins cyclization (Scheme 5). The intermediate oxonium ion **20** formed from homoallylic alcohol **18** and aldehyde attains the more favorable chair-like transition state **23** in which the substituents at 2nd and 6th positions were oriented at equatorial side which is the most

stable conformation and thus avoiding the disfavored transition state **24** in which a severe 1,3-diaxial interactions between the groups at 2nd and 6th positions were present. Hence, the nucleophile attacks from the equatorial position forming *cis* products **25** as a main stereoisomer.

Scheme 5. Prins Cyclization mechanism

1.1.4 Development of Prins cyclization methodologies

Many research groups including work from our group have broadened the scope of Prins cyclization to synthesize a wide range of functionalized tetrahydropyran scaffolds *via* the development of novel methodologies. Several two/three component protocols have been invented to introduce different functionalities at C4 position of THP subunit by trapping a secondary tetrahydropyranyl carbocation **23** with different nucleophiles (Scheme 6). These mainly include trapping by halogen, acetate, hydroxyl,

aryl, thiophenol, azide, thiocyano, cyano, and alkyne nucleophiles. 4-Halotetrahydropyrans **27** are produced *via* trapping of secondary tetrahydropyranyl carbocation intermediate in Prins cyclization by halide nucleophiles. Synthesis of 4-chloro- and 4-bromotetrahydropyrans has been extensively achieved by the reaction of substituted or simple homoallylic alcohols with aldehydes or ketones using stoichiometric amount of halogenated Lewis acids such as $InCl_3$, $InBr_3$, $FeCl_3$, $TiCl_4$, $TiBr_4$, $SnBr_4$, $ZrCl_4$, TMSCl, TMSBr, $NbCl_5$, $AlCl_3$ etc. or ionic liquid [bmim]$Cl.2AlCl_3$.[12] 4-Fluorotetrahydropyrans have been produced by using acid catalyst like $HBF_4.Et_2O$ and $BF_3.Et_2O$ or ionic liquid HF salt i.e. $Et_4NF.5HF$ in Prins cyclization.[13] Similarly, the synthesis of 4-iodotetrahydropyrans was reported using I_2, LiI or NaI as a source of iodo nucleophile in combination with catalytic amount of Lewis or Brønsted acid.[14] Iodine itself can do this transformation without the use of an acid catalyst.[15] Formation of THP bearing an oxygen atom in position 4 is conditioned by the replacement of halide in the Lewis acid by ligands of lower nucleophilicity, most often triflates. These methods lead to 4-hydroxy, 4-alkoxy, and 4-alkoxycarbonyl substituted THP derivatives **28**. Most examples in this field concern the synthesis of 4-hydroxytetrahydropyrans.[16] 4-Azido- and 4-thiocyanato-THP **29**, **30** derivatives are produced *via* In(III) catalyzed reaction of homoallylic alcohol with aldehyde in the presence of NaN_3 and NH_4SCN respectively.[17] Subsequently, tandem Prins cyclization sequences such as Prins-Friedel-Crafts,[18] Prins-Ritter,[19] Prins-alkynylation[20] and Prins-thioarylation[21] have also been well established for stereoselective synthesis of 4-aryl, 4-amide, 4-phenacyl and 4-arylthio THPs **31**-**34** respectively and are discussed separately. In general, all these methods provide *cis*-2,4-disubstituted or *cis*-2,4,6-trisubstituted THP derivatives in a stereoselective manner. The schematic representation of the all above mentioned methodologies for the synthesis of a wide range of tetrahydropyran subunits is shown in scheme **6**.

Scheme 6. Scope of Prins cyclization for synthesis of THP scaffolds

Syntheses of 4-fluoro-tetrahydropyrans: Trapping by fluoride anion is not frequently encountered in literature. Willis and co-workers[22] reported the synthesis of 2,6-disubstituted 4-fluorotetrahydropyrans using $BF_3.Et_2O$ as the Lewis acid. The product was obtained as a single stereoisomer from acetal in 55% yield with an excellent control of the diastereoselectivity (Scheme 7).

Scheme 7

Recently, our group[23] has developed direct one-pot method for the synthesis of 4-fluorotetrahydropyrans by means of Prins-cyclization using $HBF_4.OEt_2$. We have attempted the coupling of 1 equiv. of benzaldehyde with 1.2 equiv. of 3-buten-1-ol promoted by $HBF_4.OEt_2$. Interestingly, the reaction was completed within 20 min and the corresponding 2-phenyl-4-fluoro-tetrahydropyran was isolated in 77% yield with *cis*-selectivity (Scheme 8).

Scheme 8

Nicholas *et al.*[24] reported the synthesis of 2-alkynyl-4-fluoro-tetrahydropyrans from dicobalt hexacarbonyl complexes of propargylic acetals. Yields ranging from 52 to 85% were obtained using either $HBF_4.Et_2O$ or $BF_3·OEt_2$ as acid catalyst with lower diastereoselectivity (Scheme 9).

Scheme 9

Fugichami and co-workers[25] reported the synthesis of 4-fluoro-THPs using ionic liquid hydrogen fluoride salts (Scheme 10). No cyclisation could be observed with ketone. This method is applicable for the synthesis of fluorinated thiacyclohexanes and piperidines.

Scheme 10

Syntheses of 4-Chloro-tetrahydropyrans: Chan *et al.*[26] reported the coupling between allylsilanes and aldehydes to prepare symmetrical *cis*-2,6-disubstituted-4-chlorotetrahydropyrans (Scheme 11).

Lewis Acid = TiCl$_4$, AlCl$_3$, SnCl$_4$

Scheme 11

Loh group[27] reported the similar reaction catalyzed by Indium trichloride with chloroallylsilane. The unsymmetrical THPs were also prepared *via* the successive addition of two different aldehydes. No cyclization could be observed with conjugated aldehydes like cinnamaldehyde or trans-2-pentenal (Scheme 12).

Scheme 12

Coppi and co-workers[28] found an analogous condensation by directly mixing aldehydes and unsaturated alcohols at 0 °C in the presence of Lewis acid (Scheme 13).

Scheme 13

Metzger *et al.*[29] achieved AlCl$_3$-mediated enantioselective synthesis of tetra-hydropyrans from methyl ricinoleate and various aldehydes (Scheme 14).

Scheme 14

Gross and co-workers[30] reported the synthesis of bis-(2-tetrahydropyranyl)-methanes using $TiCl_4$ (Scheme 15).

Scheme 15

The use of $TiCl_4$ and $AlCl_3$ often generates experimental difficulties owing to their highly hygroscopic in nature. Indium trichloride avoids the use of an inert atmosphere and anhydrous solvents. It was an alternative choice for the synthesis of 4-chloro-tetrahydropyrans *via* Prins cyclization. The synthesis of symmetrical 2,6-dialkyl-4-chloro-tetrahydropyrans was achieved, in the presence of 1.2 eq. of indium trichloride.[31]

Our group used ionic liquids as solvents in Prins cyclization.[32] Imidazolium chloroaluminates, formed *via* the reaction of *n*-butyl-3-methylimidazolinium chloride with $AlCl_3$, play at the same time as the role of solvent and the reactant to produce 4-chloro-THPs (Scheme 16).

Scheme 16

Indium triflate can also be used in catalytic amount in the presence of TMSCl as the source of chloride anion.[33]

Syntheses of 4-Bromo-tetrahydropyrans: Wang and co-workers[34] used allyl halides in ionic liquids generated from imidazolium or pyridinium halides and the corresponding Sn(II) halides. The method associates in a tandem process Barbier reaction and subsequent Prins cyclization. Both aromatic and aliphatic aldehydes led to the formation of 4-bromotetrahydropyrans in good yield (Scheme 17).

Scheme 17

Rychnovsky *et al.*[35] used Titanium tetrabromide to introduce 4-bromo-THP units. The tandem reaction between diene, where the masked acetaldehyde is introduced as an enol ether and acetone led to the formation of product in 79% yield with a high diastereomeric ratio in favour of the all *cis*-isomer (Scheme 18).

Scheme 18

Syntheses of 4-iodo-tetrahydropyrans: Our group[36] has synthesized the 4-iodo-tetrahydropyrans *via* Prins cyclization in the presence of TMSCl/NaI (Scheme 19).

Scheme 19

Syntheses of 4-arylthio-tetrahydropyrans: Recently, our group[37] has highlighted the synthesis of 4-arylthiotetrahydropyrans *via* Prins cyclization in presence of aryl thiol (Scheme 20).

Scheme 20

1.1.5 Cascade/tandem sequences in Prins cyclization

Sakurai/Prins cyclization: A number of examples have been reported where homoallylic substrates were generated *in situ* through Sakurai allylation of aldehydes with allylsilane mediated by Lewis acids.[38] Thus *in situ* generated homoallylic alcohol undergoes Prins cyclization to give the 2,6-symmetrically substituted THPs. For instance, the reaction of 2 equiv. of benzaldeyde with allyl dimethylsilyl chloride catalyzed by $InCl_3$ affords the tetrahydropyran derivative (Scheme 21).

Scheme 21. Synthesis of THP derivative by Sakurai/Prins cylization

Prins/Friedel-Crafts cyclization: Saikia group[18] highlighted three-component Prins-Friedel-Crafts cyclization for the synthesis of 4-aryl-THP scaffolds from the reaction of carbonyl compounds with homoallyl alcohol in the presence of arene nucleophilic solvents catalyzed by borontrifluoride etherate. In the same way, Sakurai/Hosomi/Prins/Friedel–Crafts reaction is also available for creation of 2,6-symmetrically substituted 4-aryl-THPs (Scheme 22).

Scheme 22. Synthesis of THP derivative by Prins/Friedel-Crafts cylization

Ene/Prins cyclization: In our group few tandem Ene-Prins reactions were developed. Our strategy involves prenylic group and aldehyde within the same molecule i.e. (*R*)-citronellal which first undergo Ene reaction in the presence of Sc(OTf)$_3$ to produce the homoallylic alcohol followed by Prins cyclization with aldehyde to generate bicyclic tetrahydropyrans (Scheme 21).[39]

Scheme 21. Tandem Ene/Prins reaction of (*R*)-citronellal

13

Mukaiyama Aldol/Prins (MAP) cascade: Rychnovsky and co-workers[40] first reported the Mukaiyama aldol-Prins (MAP) cascade cyclization in which unsaturated enol ether undergoes a rapid Prins cyclization promoted by allylsilane as the internal nucleophile followed by aldol reaction to afford *cis*-2,6-disubstituted tetrahydropyran derivatives (Scheme 22).

Scheme 22. The first examples of a Mukaiyama aldol-Prins cascade cyclization

Prins/Alkynylation cascade: Our group developed a simple Prins/Alkynylation reaction for the first time.[41] It is a three component reaction of aldehyde, homoallylic alcohol and phenyl acetylene in the presence of $BF_3.OEt_2$/CuCl (10 mol%) in dichloromethane to produce 4-phenacyl tetrahydropyran derivative in 80% yield (Scheme 23).

Scheme 23. Prins/Alkynylation cascade

Prins/Ritter sequence: Prins-Ritter Reaction:

4-Aminotetrahydropyran skeleton is a core structure in several natural products[42] such as ambruticin VS3 and dysiherbaine, oligomers of glucoamino acids acid, sialic acid (Figure **2**). The compound **A** is a heat generating photosensitive material used in photographic films. Compound **B,** a non-macrocyclic supramolecule showed appreciable binding with alkali metals (Li$^+$, Na$^+$ and K$^+$) with association constants (K_a) greater than 107-108 and compound **C** is a melanocortin receptor agonist.[43]

Figure 2: Examples of some biologically active 4-amino-tetrahydropyran derivatives

Prins–Ritter reaction: amide formation:

Using Prins cyclization 'N' hetero-atom can be selectively incorporated at 4th-position of tetrahydropyranyl cation. There are rather few examples of 4-tetrahydropyranyl carbocation trapping by nitrogen-centered nucleophiles in literature. Owing to their basicity, most of them are incompatible with strong Lewis acids. The most frequently encountered examples of C–N bond formation involve the Ritter reaction.

Perron and Albizati developed Prins cyclization and Ritter sequence for the first time.[44] They had prepared diastreoselective 4-acetamidopyranoside from the reaction of trimethoxy-methane with 3-methylbut-3-en-1-ol in acetonitrile promoted by $SnCl_4$ in 77% yield (Scheme 24).

Scheme 24

Willis and co-workers[45] developed 4-amidotetrahydropyrans *via* Prins-Ritter reaction. They had treated homoallylic acetal with triflic acid in acetonitrile to give the 4-amido derivative in 95% yield with total control of diastereoselectivity (Scheme 25).

Scheme 25

Our group[19] described a Prins/Ritter reaction sequence for the synthesis of 4-amido tetrahydropyrans from homoallylic alcohols with various carbonyls in nitrile solvent in presence of $CeCl_3.7H_2O/AcCl$ at ambient temperature. The reaction of 2-naphthaldehyde with but-3-en-1-ol in acetonitrile in presence of 10 mol% of $CeCl_3.7H_2O$ and 1.5 equiv of acetyl chloride at ambient temperature afforded 4-acetamido tetrahydropyran in 88% yield with all *cis*-selectivity (Scheme 26).

Scheme 26

Recently, Prins-Ritter reaction was explored with efficient catalysts such as Phosphomolybdic acid, $Bi(OTf)_3$ and $Ce(SO_4)_2$.[46] An efficient protocol for the synthesis of 4–amidotetrahydropyrans by using PMA as solid acid catalyst has also been reported (Scheme 27).

Scheme 27

Rovis and Epstein[47] developed a one-pot, three component reaction for the synthesis of 4-amidotetrahydropyran derivative from the reaction of 4-acetoxy-1,3-dioxane with allyltrimethyl silane in the presence of TMSOTf, TfOH and acetonitrile in 80% yield with high diastereoselectivity (Scheme 28).

Scheme 28

Saikia group highlighted the synthesis of 2,6-disubtituted 4-amidotetrahydropyran mediated by $BF_3.Et_2O$.[48] As illustrated in Scheme 29, treatment of two equivalents of 4-chloro benzaldehyde with allyltrimethylsilane in acetonitrile using $BF_3.Et_2O$ as catalyst at room temperature, gave 4-Acetamido-2,6-di(4-chlorophenyl)-tetrahydropyran in 75% yield with *cis*-selectivity

Scheme 29

Sabitha *et al.*[49] reported the multicomponent Sakurai–Prins–Ritter reaction using $Bi(OTf)_3$ catalyst. As illustrated in Scheme 30, treatment of two equivalents of benzaldehyde with allyltrimethylsilane in acetonitrile in presence of 10 mol% $Bi(OTf)_3.4H_2O$ at room temperature, gave 4-acetamido-2,6-diphenyl tetrahydropyran in 85% yield with high diastereoselectivity.

Scheme 30

Barluenga *et al.*[50] first reported the Prins-Ritter reaction on alkynols in acetonitrile with H_2O in presence of 2 mol% of $PtCl_4$ under reflux conditions, product amide derivatives were isolated in high yield and as single diastereoisomer. The similar reaction was also carried out with 2 mol% of $AuCl_3$ as the catalyst.

Scheme 31

Herein, the following section of this chapter describes the recent development of our novel methodologies on Prins/Ritter reaction.

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CHAPTER I: SECTION B

B(C$_6$F$_5$)$_3$-catalyzed Prins/Ritter reaction: a novel synthesis of hexahydro-1H-furo[3,4-c] pyranylamide derivatives

1.2 SECTION B

B(C$_6$F$_5$)$_3$-catalyzed Prins/Ritter reaction: a novel synthesis of hexahydro-1*H*-furo[3,4-c]pyranylamide derivatives

1.2.1 INTRODUCTION

Oxygen containing bicycles such as furo[3,4-c]furans and furo[3,2-c]pyrans are often found in various biologically active natural products such as cordigol, triFA1, sesamin, flavonoids, catechins, and pterocarpans (Fig.**1**).[1] Prins cyclization is one of the most elegant strategies for the synthesis of substituted tetrahydropyran scaffolds.[2] A few acid catalysts are reported for the synthesis of tetrahydropyranyl amide derivatives through a Prins/Ritter cascade process. However, the generation of *tert*-amide functionality into a bicyclic system through a Prins/Ritter cascade process is still unexplored. Herein we wish to report on the synthesis of furo[3,4-c]pyran scaffolds *via* Prins cyclization promoted by B(C$_6$F$_5$)$_3$.

Cordigol   **triFA1**

R,R^1 = -OCH$_2$O- (methylenedioxyl)
    for Sesamin and Asarinin
R = OH, R1 = OMe for Pinoresinol
R,R^1 = -OCH$_3$ for Eudesamin

Figure 1. Representative examples of cordigol, triFA1, sesamin and related compounds.

Commercially available tris(pentafluorophenyl)borane is referred to as "BCF". The three pentafluorophenyl groups are attached to the central boron atom in a "paddle-wheel" manner; the BC_3 core is planar. It has been described as the "ideal Lewis acid" because of its versatility and the relative inertness of the B-C bonds. It is a non-conventional acid catalyst and its Lewis acidity is comparable to $BF_3.OEt_2$ but without the problems associated with reactive B–F bonds. Recently, $B(C_6F_5)_3$ has attracted considerable attention because of its high reactivity, stability, non-toxicity and ability to tolerate moisture or water.[3] Consequently, various research groups were engaged in exploring the potential utility of $B(C_6F_5)_3$ for various organic transformations.[4] To the best of our knowledge, there are no reports on the use of $B(C_6F_5)_3$ for Prins type cyclisation.

1.2.2 PRESENT WORK

In continuation of our research on Prins/Ritter reaction,[5] we herein report a simple and efficient strategy for the synthesis of a novel class of *cis*-fused 7a,3,6-trisubstituted hexahydro-1*H*-furo[3,4-*c*]pyranyl amide derivatives through a sequential Prins and Ritter reactions.

1.2.2.1 *Results and Discussion*

The desired starting material, (2-(4-methoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methanol (**1**) was prepared from anisaldehyde in four steps. Reduction of the ester (**1c**) with LAH afforded the desired alcohol (**1**) in good yield (Scheme 1).

Scheme 1. Preparation of *exo*-cyclic hydroxyl olefin (**1**)

Reagents and conditions: (i) Ph$_3$P=CHCO$_2$Et, Benzene, reflux, 85%; (ii) Prop-2-yn-1-ol, LiBr, CAN, MeCN, 70%; (iii) Cp$_2$TiCl$_2$, Zn, THF, 80%; (iv) LAH, THF, 0°C - r.t. 80%.

At first, we attempted the coupling of an *exo*-cyclic hydroxy olefin (**1**) with benzaldehyde (**2**) using a catalytic amount of B(C$_6$F$_5$)$_3$ in acetonitrile at room temperature. The reaction was complete within 20 min affording the corresponding *cis*-fused 6-(phenyl)-3-(4-methoxyphenyl)hexahydro-1*H*-furo[3,4-*c*]pyran-7-yl)acetamide **4a** in 80% yield (Scheme 2).

Scheme 2. A sequential Prins/Ritter reaction

Unlike classical Prins/Ritter reaction, the formation of undesired side products such as 4-halo- or 4-hydroxy tetrahydropyrans was not observed when a catalytic amount tris(pentafluorophenyl)borane was employed. Inspired by the unique catalytic properties of [B(C$_6$F$_5$)$_3$], we extended this protocol for other substrates. Interestingly, the coupling

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of aliphatic aldehydes such as propanal and butanal with [2-aryl-4-methylene-tetrahydrofuran-3-yl]methanol in acetonitrile gave the corresponding bicyclic acetamide derivatives in good yields (entries **b** and **c**, Table **1**). Our next attempt was made to explore the feasibility of this protocol with ketones. Interestingly, the cyclic ketones such as cyclohexanone and cyclopentanone participated well in this reaction to provide the corresponding spirotricyclic amides (entries **d** and **g**, Table **1**). For instance, the reaction of (2-(4-methoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methanol with cyclohexanone in acetonitrile under the influence of 5 mol% [B(C$_6$F$_5$)$_3$] furnished the spiro-3-(4-methoxyphenyl)hexahydro-1*H*-furo[3,4-*c*]pyran-7a-yl)acetamide in 80% yield (entry **d**, Table **1**). The reaction proceeded efficiently not only with cyclic ketones but also with acetone (entry **h**, Table **1**).

Other aromatic aldehydes such as *p*-chloro-, and *p*-nitrobenzaldehydes also reacted well with *exo*-cyclic hydroxy olefin **1** in the presence of nitriles to yield the corresponding bicyclic amide derivatives (entries **f** and **i**, Table **1**). Next, we examined the reactivity of different nitriles. Remarkably, the reaction was successful with different nitriles such as acrylonitrile, propionitrile and benzonitrile to afford the corresponding acrylamide, propionamide and benzamide derivatives (entries **e-j**, Table **1**). In all cases, the products were obtained in good yield with *cis*-selectivity. A single product was formed in each reaction, the structure of which was confirmed by the NMR spectrum. The scope of the tris(pentafluorophenyl)borane catalyzed Prins/Ritter reaction is illustrated with various aldehydes and ketones in the presence of different nitriles and the results are presented in Table **1**.

Table 1. B(C$_6$F$_5$)$_3$-catalyzed synthesis of hexahydro-1*H*-furo[3,4-*c*]pyran-7a-yl amide derivatives

Entry	Carbonyl compounds	Nitrile	Product (**4**)[b]	Time (min)	Yield %)[c]
a	PhCHO	MeCN		20	80
b	propionaldehyde	MeCN		20	85
c	butyraldehyde	MeCN		20	85
d	cyclohexanone	MeCN		25	80
e	propionaldehyde	CN (acrylonitrile)		20	85
f	4-Cl-C$_6$H$_4$CHO	CN (acrylonitrile)		20	90
g	cyclopentanone	CN (acrylonitrile)		25	80
h	acetone	CN (propionitrile)		25	85
i	4-O$_2$N-C$_6$H$_4$CHO	PhCN		25	90
j	PhCHO	PhCN		20	85

[a]Reaction was performed with 0.5 mmol olefin, 0.75 mmol aldehyde/ ketone using 5 mol% of B(C$_6$F$_5$)$_3$ in nitrile solvent. [b]All products were characterized by NMR, IR and mass spectroscopy. [c]Yield refers to pure products after chromatography.

The relative stereochemistry of **4f** was established by using detailed 1D and 2D NMR experiments.[6] The scalar coupling constants $^3J_{\text{H2-H3(ax)}}$ = 11.4 Hz, $^3J_{\text{H2-H3'(eq)}}$ = 3.5 Hz, $^3J_{\text{H5(ax)-H6(ax)}}$ = 9.9 Hz along with the appearance of NOE cross peaks between H2-H6(ax), H3(ax)-H5(ax) support the existence of six membered ring in $^4C_1$ chair conformation, while the chlorophenyl substitution at C2 occupies equatorial position. The stereochemistry at the fusion of two rings was determined by the observation of NOE cross peaks H9-H2, NH-H5, H7-H6(ax), H7-H6(eq) as *cis* fusion at C4-C5 bond as represented in Fig. 2. The double-edged arrows show characteristic NOE correlations. Furthermore the structure of **4e** was established by single crystal X-ray crystallography (Fig. 3).[7]
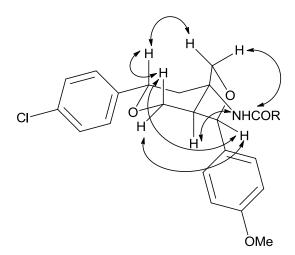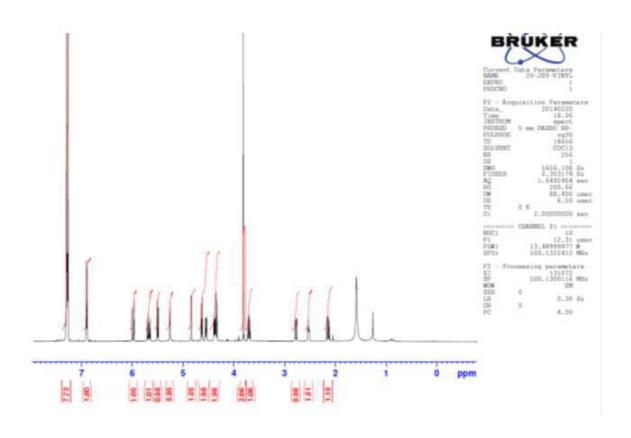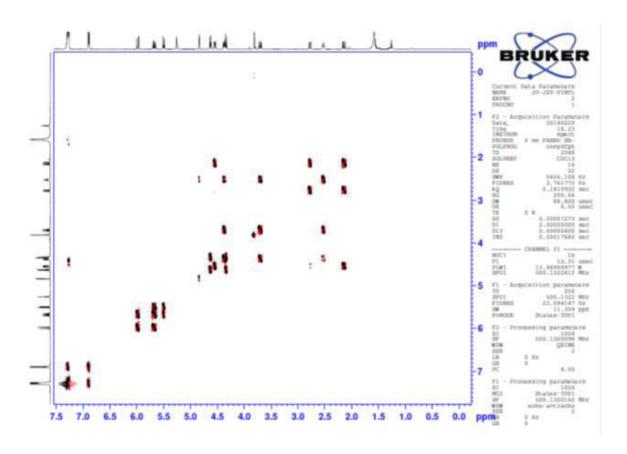
Figure 2. Characteristic nOes of **4f**
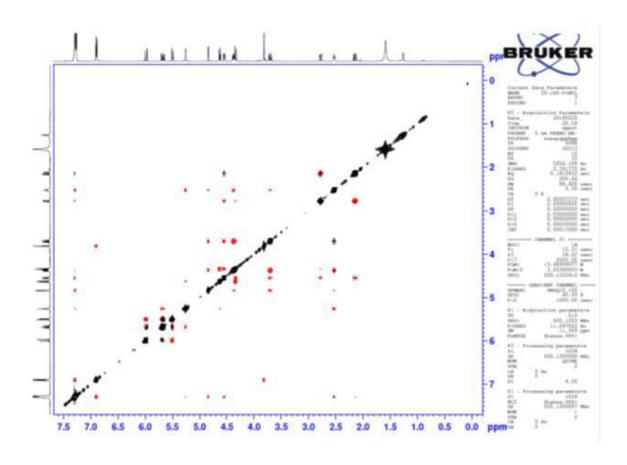
NMR spectrum of compound **4f**

2D DQFCOSY (Double Quantum Filtered Correlation spectroscopy) spectrum of compound 4f

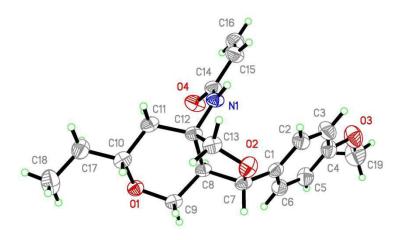**2D NOESY (Nuclear Overhauser effect spectroscopy) spectrum of compound 4f**

Figure 3. ORTEP diagram of **4e**

1.2.2.2 *Mechanistic study*

The reaction was proposed to proceed *via* the formation of oxocarbenium ion from hemi-acetal which is formed *in situ* from *exo*-cyclic hydroxy olefin **1** and aldehyde **2**. Thus formed oxocarbenium ion may undergo smooth cyclization with an internal olefin to generate the carbocation which is subsequently trapped with a nitrile leading to the formation of hexahydro-1*H*-furo[3,4-*c*]pyranyl amide **4** as depicted in Scheme 3.

Scheme 3. A plausible reaction pathway

Table 2. Screening of catalysts in the formation of **4a**

Entry	Acid catalyst[a]	Amide (**4a**) (%)[b]
a	$BF_3.OEt_2$ (0.1 eq)	60
b	$InBr_3$ (1 eq)	<35
c	$CeCl_3.7H_2O$ (1 eq)	15
d	TFA (1 eq)	<30
e	$InCl_3$ (1 eq)	20
f	TMS(OTf) (1 eq)	35
g	$GaCl_3$ (1 eq)	<25
h	$B(C_6F_5)_3$ (0.05 eq)	80
i	$Sc(OTf)_3$ (0.1 eq)	<45

[a]The reactions were performed in 20 min.
[b]Yield refers to products after chromatography.

However, no reaction was observed in the absence of the catalyst. To compare the efficiency of $B(C_6F_5)_3$, we have performed the reaction with commonly used acid catalysts. As shown in Table **2**, in most cases, the Prins/Ritter amidation was associated with other side products such as hydroxy or halo adducts along with the desired amide derivatives. For instance, the reaction of **1** with benzaldehyde in acetonitrile in the presence of MX_3 gave the halo substituted tetrahydropyran along with the required 4-acetamidotetrahydropyran derivative **4a**. In case of metal triflates, the formation of hydroxytetrahydropyran was observed together with the desired amide **4a**. Unlike $BF_3.OEt_2$ catalyst, $B(C_6F_5)_3$ is a stable and highly reactive due to the presence of strong electron-withdrawing pentafluorophenyl groups. Furthermore, the counter ion $C_6F_5^{(-)}$ is non-nucleophilic. Therefore, $B(C_6F_5)_3$ is a much superior catalyst for the Prins/Ritter reaction than a commonly used $BF_3.OEt_2$.

1.2.2.3 *Conclusion:*

In summary, we have developed a novel and efficient protocol for the synthesis of *cis*-fused hexahydro-1*H*-furo[3,4-c]pyranyl amide derivatives using $B(C_6F_5)_3$ as a mild Lewis acid catalyst. This method offers significant advantages such as mild conditions, short reaction times, absence of side products, operational simplicity and not requiring inert atmosphere. This method provides an easy access for the synthesis of a new class of *cis*-fused hexahydro-1*H*-furo[3,4-c]pyranyl amide derivatives which may be useful for the screening of biological activity.

1.2.3 EXPERIMENTAL

1.2.3.1 *Preparation of starting materials*

The synthetic route for the preparation of starting material is depicted in scheme **1**. To a stirred solution of anisaldehyde (5 g, 36.70 mmol) in benzene (40 mL) was added the stabilized ylide $Ph_3P=CHCO_2CH_2CH_3$ (19.0 g, 55.10 mmol) and resulting mixture was stirred for overnight at 80 ^{o}C temperature. The reaction mixture was then concentrated under reduced pressure and purified on silica gel chromatography

(EtOAc/Hexane, 1:19) to afford the unsaturated ester **1a** (6.51 g, 86% yield) as a pale yellow oily liquid.

To a stirred solution of the unsaturated ester **1a** (6.5 g, 31.6 mmol), anhydrous LiBr (3.3 g, 38.0 mmol) and propargyl alcohol (22.0 g, 380 mmol) in dry acetonitrile (50 ml), a solution of ceric(IV) ammonium nitrate (26.0 g, 47.42 mmol) in acetonitrile (50 ml) was added slowly at room temperature under nitrogen atmosphere. The reaction mixture was further stirred for 3 h, and then diluted with ether (50 ml). The organic layer was separated, washed with brine (3 x 20 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After evaporating the solvent, the crude product was purified by column chromatography (EtOAc/Hexane, 1:19) afforded the pure bromoether compound **1b** (7.5 g, 70% yield).

To a stirred solution of titanocene dichloride (10.95 g, 44 mmol) in dry THF (100 mL), activated zinc dust (10 g, 154 mmol) was added at room temperature under nitrogen atmosphere. The reaction mixture was further stirred for 1 h. The resulting green solution was then added slowly to a stirred solution of bromo-alkyne **1b** (7.48 g, 22.0 mmol) in dry THF (75 mL) at room temperature.[8] The reaction mixture was stirred for overnight and was quenched with 10% H_2SO_4 (100 mL). Most of the solvent was removed under reduced pressure and the residue was extracted with diethyl ether (3 x 100 mL). The combined ether extracts were washed with saturated $NaHCO_3$ (2 x 35 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography (EtOAc/Hexane, 1:9) to afford the tri-substituted tetrahydrofuran derivative **1c**.

First, LAH (1.02 g, 26.92 mmol) was dissolved in anhydrous THF (50 mL). Compound **1c** (4.6 g, 17.6 mmol) in anhydrous THF (40 mL) was added to it under nitrogen atmosphere at 0°C. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C, the excess LAH was quenched by addition of sat. aq Na_2SO_4 (6 mL). After completely quenching of LAH, the reaction mixture was filtered through a pad of Celite and washed with hot EtOAc (2 x 25 mL). The filtrate was

evaporated under vacuum and the residue was purified by column chromatography (EtOAc/hexane, 1:4) to furnish compound **1**.

1.2.3.2 *General experimental procedure for Prins/Ritter reaction:*

To a mixture of aldehyde/ketone (0.75 mmol) and $B(C_6F_5)_3$ (5 mmol%) in nitrile (4 mL) was added exo-cyclic hydroxy olefin (0.5 mmol). The resulting mixture was stirred at room temperature (27 ^{o}C) for the specified time. After completion, as indicated by TLC, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine followed by water, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The resulting crude mass was subjected to flash column chromatography using 1:3 mixture of n-hexane and ethyl acetate as eluent to afford the pure compound. The products thus obtained were characterized by IR, NMR and mass spectroscopy.

1.2.3.3 *Spectral data of Compounds:*

(2-(4-Methoxyphenyl)-4-methylene-tetrahydro-furan-3-carboxylic acid ethyl ester (1c):

Yield	:	4.6 g, 80%
Molecular formula	:	$C_{15}H_{18}O_4$
Physical State	:	Yellow oil
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.31 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.20-5.16 (m, 2H), 5.10 (dd, J = 2.1, 4.6 Hz, 1H), 4.66-4.60 (m, 1H), 4.52-4.46 (m, 1H), 4.28-4.20 (m, 1H), 4.19-4.12 (m, 1H), 3.8 (s, 3H), 3.50-3.45 (m, 1H), 1.27 (t, J = 7.3 Hz, 2H).

^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 170.7, 159.5, 146.7, 131.9, 127.5, 113.9, 106.2, 83.2, 71.5, 61.08, 57.07, 55.3, 14.2.
IR (Neat)	:	ν$_{max}$ 2924, 1734, 1516, 1249, 1173, 1034, 829, 773 cm^{-1}
HRMS (ESI)	:	Calculated for C$_{15}$H$_{18}$O$_4$Na 285.17507, found: 285.17496

[2-(4-Methoxyphenyl)-4-methylene-tetrahydro-furan-3-yl]-methanol (1):

Yield	:	3.09 g, 80%
Molecular formula	:	C$_{13}$H$_{16}$O$_3$
Physical State	:	Yellow liquid
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.31 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.11 (dd, J = 2.3, 4.4 Hz, 1H), 5.07 (dd, J = 2.3, 4.7 Hz, 1H), 4.80 (d, J = 7.3 Hz, 1H), 4.63-4.58 (m, 1H), 4.44-4.39 (m, 1H), 3.89-3.83 (m, 1H), 3.8 (s, 3H), 3.76--3.69 (m, 1H), 2.80-2.75 (m, 1H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 159.3, 148.9, 133.0, 127.7, 113.9, 104.9, 83.2, 71.3, 61.9, 55.3, 53.9.
IR (Neat)	:	ν$_{max}$ 3413, 2921, 2852, 1612, 1514, 1463, 1377, 1220, 1176, 1036, 772, 686 cm^{-1}
HRMS (ESI)	:	Calculated for C$_{13}$H$_{16}$O$_3$Na 243.13555, found: 243.13578.

***N*-(3-(4-Methoxy-phenyl)-6-phenyl-tetrahydro-furo[3,4-c]pyran-7a-yl)-acetamide (4a):**

Yield	:	80%
Molecular formula	:	$C_{22}H_{25}NO_4$
Physical State	:	White solid, m.p. 175-177 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.39-7.21 (m, 7H), 6.9 (d, *J* = 8.5 Hz, 2H), 5.28 (br, 1H), 4.82 (d, *J* = 2.4 Hz, 1H), 4.6-4.5 (m, 2H), 4.39-4.27 (m, 2H), 3.8 (s, 3H), 3.68 (dd, *J* = 10.0, 12.1 Hz, 1H), 2.64 (dd, *J* = 3.2, 14.3 Hz, 1H), 2.57-2.47 (m, 1H), 2.22 (dd, *J* = 11.1, 14.1 Hz, 1H), 1.64 (s, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 169.7, 158.8, 141.5, 134.2, 128.3, 127.5, 126.0, 125.6, 113.9, 81.6, 75.7, 73.8, 66.9, 61.3, 55.3, 50.7, 35.9, 23.7.
IR (Neat)	:	ν$_{max}$ 2926, 1653, 1513, 1220, 1033, 773, 686 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{22}H_{26}NO_4$ 368.18563, found: 368.18600.

***N*-[6-Ethyl-3-(4-methoxy-phenyl)-tetrahydro-furo[3,4-c]pyran-7a-yl]-acetamide (4b):**

Yield	:	85%
Molecular formula	:	$C_{18}H_{25}NO_4$
Physical State	:	White solid, m.p. 112-114 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.26 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.11 (br, 1H), 4.74 (br, 1H), 4.53 (d, *J* = 9.6 Hz, 1H), 4.24-4.11 (m, 2H), 3.80 (s, 3H), 3.47 (dd, *J* = 10.6, 11.9 Hz, 1H), 3.40-3.28 (m, 1H), 2.52-2.34 (m, 2H), 1.76 (dd, *J* = 11.3, 14.0 Hz, 1H), 1.68 (s, 3H), 1.66-1.50 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 169.7, 158.8, 134.6, 125.9, 113.9, 81.5, 75.6, 73.6, 67.4, 61.6, 55.4, 51.1, 34.4, 28.8, 24.0, 9.9.
IR (Neat)	:	ν$_{max}$ 3301, 2926, 1660, 1536, 1464, 1378, 1248, 1175, 1076, 761 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{18}H_{25}NO_4Na$ 342.16758, found: 342.16721
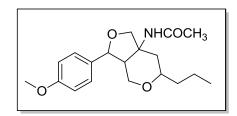
_N_-[3-(4-Methoxy-phenyl)-6-propyl-tetrahydro-furo[3,4-c]pyran-7a-yl]-acetamide (4c)

Yield	:	85%
Molecular formula	:	$C_{19}H_{27}NO_4$
Physical State	:	Yellowish solid, m.p. 120-122 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.18 (br, 1H), 4.73 (br, 1H), 4.52 (d, *J* = 9.8 Hz, 1H), 4.25-4.10 (m, 2H), 3.80 (s, 3H), 3.52-3.37 (m, 2H),

2.50-2.35 (m, 1H), 2.10-2.0 (m, 1H), 1.77 (dd, *J* = 11.5, 14.0 Hz, 1H), 1.68 (s, 3H), 1.58-1.21 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 169.7, 158.7, 134.5, 125.9, 113.9, 81.5, 73.9, 73.5, 67.2, 61.4, 55.3, 50.9, 37.9, 34.7, 23.9, 18.6, 13.9.
IR (Neat)	:	ν_{max} 2930, 2866, 1617, 1512, 1459, 1383, 1246, 1158, 1037, 750 cm^{-1}
HRMS (ESI)	:	Calculated for C$_{19}$H$_{28}$NO$_4$ 334.20128, found: 334.20130.
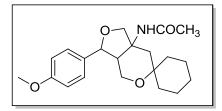
N-(3'-(4-methoxyphenyl)hexahydrospiro[cyclohexane-1,6'-furo[3,4-c]pyran]-7a'-yl)acetamide (4d):

Yield	:	80%
Molecular formula	:	C$_{21}$H$_{29}$NO$_4$
Physical State	:	Greenish solid, 178-180 $^{\text{o}}$C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.30 (d, *J* = 7.2 Hz, 2H), 6.88 (d, *J* = 7.7 Hz, 2H), 6.04 (br, 1H), 4.94 (d, *J* = 9.1 Hz, 1H), 4.26 (d, *J* = 8.7 Hz, 1H), 4.10-4.03 (m, 1H), 3.84 (dd, *J* = 3.4, 12.9 Hz, 1H), 3.80 (s, 3H), 3.57 (d, *J* = 12.9 Hz, 1H), 2.46 (d, *J* = 14.9 Hz, 1H), 2.11-2.04 (m, 1H), 2.01-1.93 (m, 4H), 1.7-1.21 (m, 10H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 170.0, 159.2, 133.9, 127.4, 113.9, 80.7, 79.5, 71.9, 58.0, 55.4, 55.1, 51.1, 39.7, 37.2, 31.5, 29.5, 25.6, 23.4, 21.7.

IR (Neat)	:	ν_{max} 3307, 2929, 1643, 1551, 1444, 1371, 1250, 1178, 1050, 883 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{21}H_{30}NO_4$ 360.21693, found: 360.21652.

N-[6-Ethyl-3-(4-methoxy-phenyl)-tetrahydro-furo[3,4-c]pyran-7a-yl]acrylamide (4e):

Yield	:	85%
Molecular formula	:	$C_{19}H_{25}NO_4$
Physical State	:	White solid, m.p 114-116 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.25 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 6.02 (d, J = 15.8 Hz, 1H), 5.72 (dd, J = 10.6, 17.4 Hz, 1H), 5.5 (d, J = 11.3 Hz, 1H), 5.4 (br, 1H), 4.75 (d, J = 2.3 Hz, 1H), 4.58 (d, J = 9.8 Hz, 1H), 4.25-4.14 (m, 2H), 3.80 (s, 3H), 3.5 (dd, J = 10.6, 12.1 Hz, 1H), 3.43-3.30 (m, 1H), 2.54 (dd, J = 2.3, 14.3 Hz, 1H), 2.45-2.35 (m, 1H), 1.77 (dd, J = 11.3, 14.4Hz, 1H), 1.64-1.40 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 164.8, 158.8, 134.4, 131.1, 126.0, 113.9, 81.6, 75.6, 73.5, 67.3, 61.7, 55.3, 51.4, 34.4, 28.8, 9.9.
IR (Neat)	:	ν_{max} 3303, 2926, 2855, 1661, 1537, 1514, 1406, 1248, 1110, 1076, 1038, 832, 761, 665 cm^{-1}

40

HRMS (ESI)	:	Calculated for $C_{19}H_{26}NO_4$ 332.18563, found: 332.18522.

N-(6-(4-Chloro-phenyl)-3-(4-methoxy-phenyl)-tetrahydro-furo[3,4-c]pyran-7a-yl)-acrylamide (4f):

Yield	:	90%
Molecular formula	:	$C_{23}H_{24}ClNO_4$
Physical State	:	White solid, m.p. 211-213 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.32-7.25 (m, 6H), 6.89 (d, J = 8.71 Hz, 2H), 5.98 (d, J = 16.9 Hz, 1H), 5.68 (dd, J = 10.4, 16.9 Hz, 1H), 5.50 (d, J = 10.4 Hz, 1H), 5.25 (br, 1H), 4.83 (br, 1H), 4.63 (d, J = 9.8 Hz, 1H), 4.54 (dd, J = 3.1, 11.4 Hz, 1H), 4.40-4.30 (m, 2H), 3.80 (s, 3H), 3.69 (dd, J = 10.0, 12.1 Hz, 1H), 2.77 (dd, J = 3.1, 14.5 Hz, 1H), 2.56-2.50 (m, 1H), 2.14 (dd, J = 11.4, 14.5 Hz, 1H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 164.8, 158.9, 140.0, 133.9, 133.2, 130.8, 128.5, 126.9, 126.4, 126.1, 113.9, 81.6, 75.0, 73.6, 67.0, 61.5, 55.3, 50.8, 35.9.
IR (Neat)	:	v_{max} 3313, 2925, 2854, 1675, 1512, 1408, 1245, 1103, 1080, 1031, 833, 633 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{23}H_{24}ClNO_4Na$ 436.12861, found: 436.12891

N-(3'-(4-methoxyphenyl)hexahydrospiro[cyclopentane-1,6'-furo[3,4-c]pyran]-7a'-yl)acrylamide (4g):

Yield	:	80%
Molecular formula	:	$C_{21}H_{27}NO_4$
Physical State	:	Pale yellow solid, m.p.193-195 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.22 (d, *J* = 16.8 Hz, 1H), 6.03 (dd, *J* = 10.2, 17.0 Hz, 1H), 5.87 (br, 1H), 5.6 (d, *J* = 10.1 Hz, 1H), 4.9 (d, *J* = 9.4 Hz, 1H), 4.26 (d, *J* = 8.5 Hz 1H), 4.12-3.94 (m, 2H), 3.72 (s, 3H), 3.52 (d, *J* = 12.1 Hz, 1H), 3.09-2.91 (m, 1H), 2.3 (dd, *J* = 8.8, 14.5 Hz, 1H), 2.12-2.02 (m, 1H), 1.85-1.4 (m, 8H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 165.2, 159.3, 133.7, 130.5, 127.5, 113.9, 82.4, 80.8, 78.4, 58.7, 56.8, 55.2, 51.2, 41.2, 36.8, 33.3, 24.5, 22.2.
IR (Neat)	:	ν_{max} 3291, 2925, 2855, 1658, 1513, 1463, 1246, 1220, 1116, 1037, 830, 772, 682 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{21}H_{28}NO_4$ 358.20128, found: 358.20130

N-[3-(4-Methoxy-phenyl)-6,6-dimethyl-tetrahydro-furo[3,4-c]pyran-7a-yl]-propoinamide (4h):

Yield	:	85%
Molecular formula	:	$C_{19}H_{27}NO_4$
Physical State	:	Yellowish white solid, m.p 124-126 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.57 (br, 1H), 4.88 (d, *J* = 9.3 Hz, 1H), 4.19 (d, *J* = 8.5 Hz, 1H), 4.03 (d, *J* = 8.7 Hz, 1H), 3.80 (dd, *J* = 3.7, 13.3 Hz, 1H), 3.73 (s, 3H), 3.54 (d, *J* = 13.1 Hz, 1H), 2.29 (d, *J* = 14.8 Hz, 1H), 2.14 (q, *J* = 7.5 Hz, 2H), 2.05 (d, *J* = 9.1 Hz, 1H), 1.77 (d, *J* = 14.9 Hz, 1H), 1.22 (s, 3H), 1.21 (s, 3H), 1.08 (t, *J* =7.5 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 173.7, 159.3, 133.8, 127.5, 113.9, 80.8, 79.16, 71.04, 58.4, 56.6, 55.2, 50.9, 38.5, 31.6, 23.6, 9.8.
IR (Neat)	:	ν$_{max}$ 2927, 1645, 1514, 1462, 1369, 1247, 1176, 1037, 830, 685 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{19}H_{28}NO_4$ 334.20119, found: 334.20121.

N-(3-(4-Methoxy-phenyl)-6-(4-nitro-phenyl)-tetrahydro-furo[3,4-c]pyran-7a-yl)-benzamide (4i)

43

Yield	:	90%
Molecular formula	:	$C_{27}H_{26}N_2O_6$
Physical State	:	Yellow solid, 198-200 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 8.10 (d, *J* = 8.8 Hz, 2H), 7.50-7.15 (m, 7H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5. 76 (br, 1H), 4.84 (br, 1H), 4.69 (d, *J* = 9.9 Hz, 1H), 4.62 (dd, *J* = 3.05, 11.4 Hz, 1H), 4.43-4.34 (m, 2H), 3.73 (s, 3H), 3.69 (dd, *J* = 10.5, 12.36 Hz, 1H), 2.92 (dd, *J* = 3.05, 14.4 Hz, 1H), 2.67-2.60 (m, 1H), 2.06 (dd, *J* = 11.6, 14.4 Hz, 1H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 166.6, 159.0, 148.9, 147.2, 134.0, 133.9, 131.6, 128.3, 126.5, 126.4, 126.0, 123.7, 114.2, 81.25, 75.1, 73.7, 67.6, 61.7, 55.3, 50.9, 36.6.
IR (Neat)	:	ν$_{max}$ 3366, 2925, 1650, 1516, 1486, 1247, 1176, 1035, 852, 713 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{27}H_{26}N_2O_6$ Na 497.16831 found: 497.16834.

N-(3-(4-Methoxy-phenyl)-6-phenyl-tetrahydro-furo[3,4-c]pyran-7a-yl)-benzamide (4j):

Yield	:	85%
Molecular formula	:	$C_{27}H_{27}NO_4$
Physical State	:	White solid, m.p. 184-186 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.36-7.23 (m, 5H), 7.22-7.15 (m, 5H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.73 (br, 1H), 4.84 (br, 1H), 4.71 (d, *J* = 9.9 Hz, 1H), 4.53 (dd, *J* =

3.0, 11.4 Hz, 1H), 4.40-4.34 (m, 2H), 3.72 (s, 3H), 3.68 (dd, J = 10.4, 12.4 Hz, 1H), 2.9 (dd, J = 3.2, 14.5 Hz, 1H), 2.64-2.58 (m, 1H), 2.1(dd, J = 11.4, 14.5 Hz, 1H).

^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 166.5, 158.9, 141.4, 134.5, 134.2, 131.4, 128.5, 128.2, 127.6, 126.5, 126.1, 125.6, 114.2, 81.2, 76.2, 73.6, 67.7, 61.9, 55.3, 51.1, 36.9.
IR (Neat)	:	ν_{max} 3285, 2956, 1628, 1532, 1489, 1255, 1157, 1083, 988, 817, 692 cm^{-1}
HRMS (ESI)	:	Calculated for C$_{27}$H$_{27}$NO$_4$Na 452.18323 found: 452.18291

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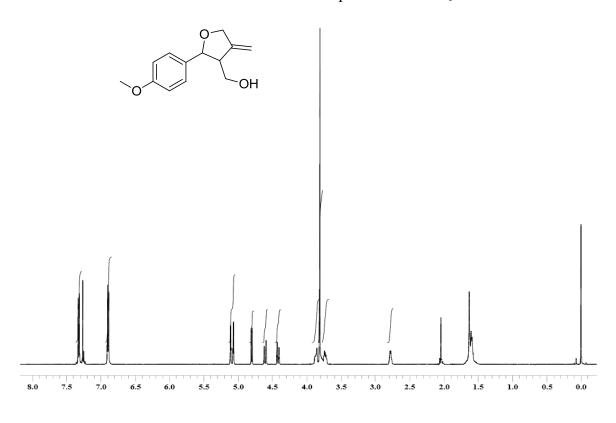
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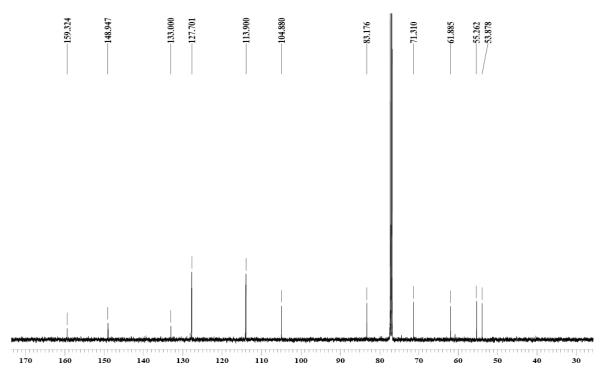
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7. CCDC 1002541 contains supplementary crystallographic data for compound **4e**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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SPECTRA
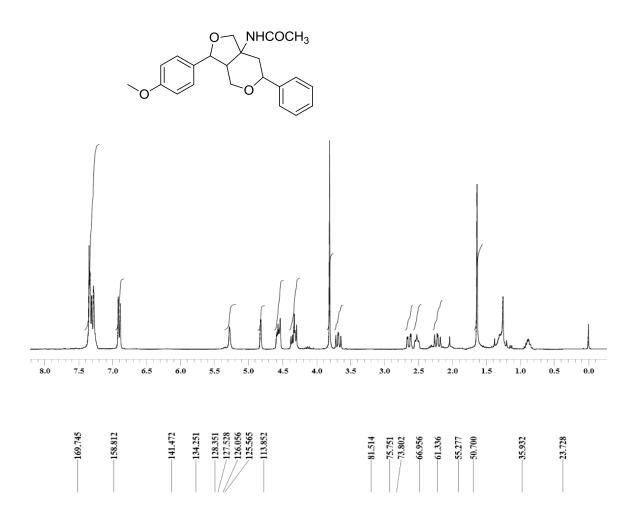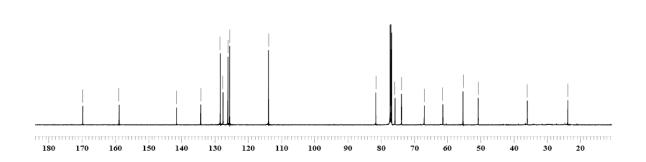
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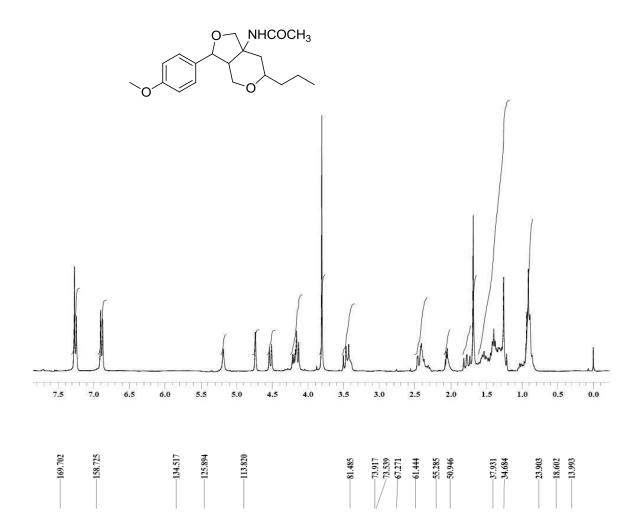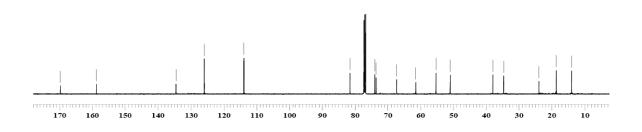
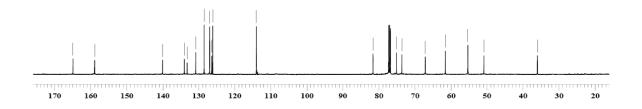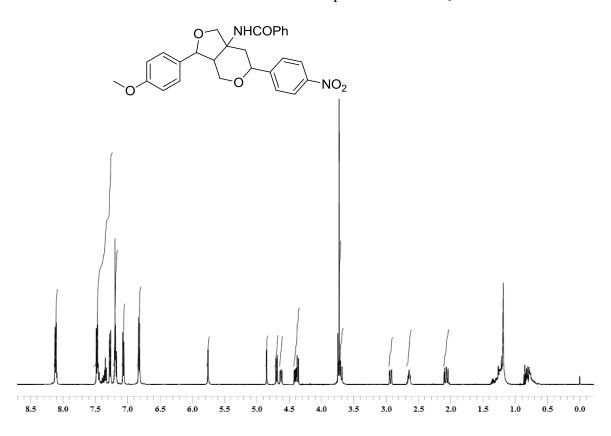# ^{1}H-NMR and ^{13}C-NMR of compound **4a** in CDCl$_3$
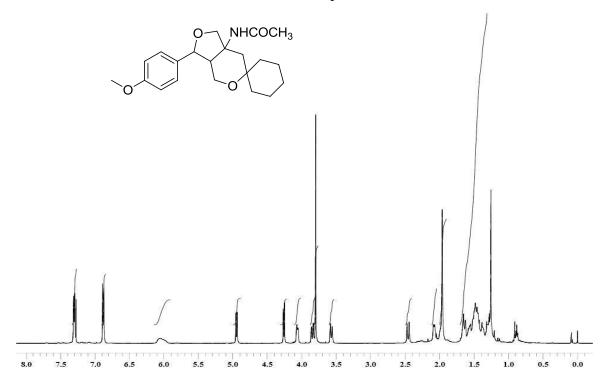
^{1}H-NMR and ^{13}C-NMR of compound **4c** in CDCl$_3$

^{1}H-NMR spectrum with peaks from 7.5 to 0.0 ppm.

^{13}C-NMR peaks: 169.702, 158.725, 134.517, 125.894, 113.820, 81.485, 73.917, 73.539, 67.271, 61.444, 55.285, 50.946, 37.931, 34.684, 23.903, 18.602, 13.993

^{1}H-NMR and ^{13}C-NMR of compound **4d** in CDCl$_3$

^{1}H-NMR spectrum with peaks labeled across 8.0–0.0 ppm.

^{13}C-NMR peaks:
170.003, 159.193, 133.874, 127.418, 113.835, 80.763, 79.446, 71.866, 58.043, 55.436, 55.134, 51.076, 39.709, 37.217, 31.506, 25.611, 23.359, 21.618

^{1}H-NMR and ^{13}C-NMR of compound **4e** in CDCl$_3$

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

164.815
158.837
134.409
131.108
126.028
113.957
81.559
75.563
73.528
67.296
61.711
55.332
51.425
34.361
28.798
9.868

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

^{1}H-NMR and ^{13}C-NMR of compound **4f** in CDCl$_3$

^{1}H-NMR spectrum with x-axis from 8.0 to 0.0 ppm.

^{13}C-NMR peak labels:
164.892, 158.877, 140.007, 133.956, 133.198, 130.800, 128.474, 126.965, 126.359, 126.113, 113.931, 81.592, 75.051, 73.585, 67.064, 61.482, 55.272, 50.806, 35.926

^{13}C-NMR spectrum with x-axis from 170 to 20 ppm.

^{1}H-NMR and ^{13}C-NMR of compound **4h** in CDCl$_3$
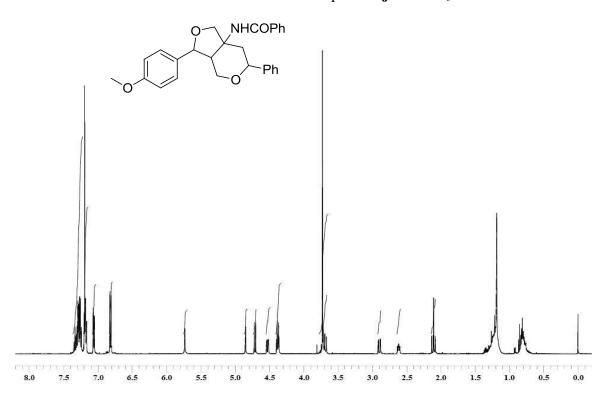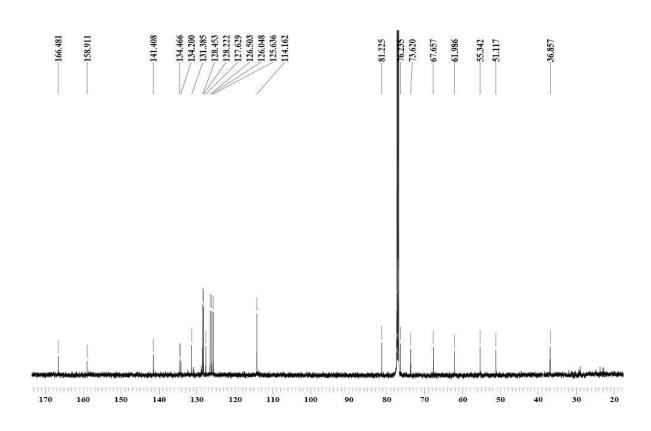
^{1}H-NMR and ^{13}C-NMR of compound **4i** in CDCl$_3$

^{1}H-NMR and ^{13}C-NMR of compound 4j in CDCl$_3$

CHAPTER I: SECTION C

Synthesis of 4-amidotetrahydropyran derivatives via Prins/Ritter reaction

1.3 SECTION C

o-Benzenedisulfonimide as a recyclable homogeneous organocatalyst for an efficient and facile synthesis of 4-amidotetrahydropyran derivatives through Prins-Ritter reaction

1.3.1 INTRODUCTION

o-Benzenedisulfonimide (**1**, 1,3,2-benzodithiazole-1,1,3,3-tetraoxide; Fig. **1**) was a very well known and thoroughly investigated Brönsted acid catalyst. Disulfonimides are sulfonamide derivatives that contain two sulfone groups attached to the nitrogen atom. The two sulfonyl groups flanking nitrogen provide substantial anionic charge stabilization. The free imide was completely ionized in (not in extractable form) water and its acidity is comparable to that of hydrochloric acid.[1] In recent years, catalyst **1** has received a great attention due to its versatility in organic synthesis. It has been used for various organic transformations such as etherification/acetalization,[2] esterification,[3] Hosomi-Sakurai reaction,[4] Ritter reaction,[5] Nazarov electro-cyclisation,[6] disproportionations of dialkyl diarylmethyl ethers,[7] Strecker reaction,[8] Synthesis of triaryl and trisindolylmethanes,[9] Hetero-Micheal Reaction,[10] Pictet-Spengler reaction,[11] Friedländer annulation reaction[12] and Mukaiyama aldol reaction.[13] The catalyst is a non-toxic, non-volatile and non-corrosive homogeneous Brönsted acid.

Figure 1. *o*-Benzenedisulfonimide (OBS) (**1**)

1.3.2 PRESENT WORK

In literature, a few one-pot approaches have been reported for the synthesis of 4-amidotetrahydropyrans. Typically, these methods combine three reactions such as (i) Sakurai-Hosomi, (ii) Prins cyclization and (iii) Ritter amidation in a one-pot operation. However, most of these methods require activators such as acetyl chloride and stoichiometric amount of catalysts. Hence, there is still a scope to develop catalytic methods with low catalytic loading and high efficiency for the synthesis of 4-amidotetrahydropyran derivatives.[14] A highly diastereoselective synthesis of 4-amidotetrahydropyran derivatives is achieved using *o*-benzenedisulfonimide as catalyst under mild conditions. The synthesis involves sequential allylation followed by Prins-Ritter amidation.

1.3.2.1 *Results and Discussion*

Following our interest on Prins cyclization,[15] we herein report an efficient and rapid approach for the synthesis of symmetrical 2,6-disubstituted 4-amidotetrahydropyrans through a sequential Sakurai–Hosomi–Prins/Ritter reaction. The Hosomi–Sakurai allylation of both aromatic and aliphatic aldehydes proceeds rapidly under the influence of the catalyst (**1**). Thus *in situ* formed homoallylic alcohol underwent a smooth Prins cyclization with another equiv. of aldehyde in presence of nitrile to afford the corresponding 4-amidotetrahydropyran. For instance, treatment of 2.1 equiv. of *p*-chlorobenzaldehyde with 1 equiv. of allyltrimethylsilane in acetonitrile in the presence of 10 mol% catalyst (**1**) at room temperature gave the corresponding 4-acetamido-2,6-diphenyl-tetrahydropyran **3a** in 85% yield with *cis*-selectivity. The reaction was completed within 1 h with an excellent diastereoselectivity (Table **1**, Scheme **1**).

Scheme 1. A sequential allylation and Prins/Ritter amidation

Unlike classical Prins cyclization, no formation of undesired 4-hydroxytetrahydropyrans was observed when a catalytic amount of catalyst **1** was employed. These results encouraged us to extend this protocol for various aldehydes and nitriles. Interestingly, aromatic aldehydes such as *p*-chlorobenzaldehyde and *p*-bromobenzaldehyde underwent a smooth reaction with allyltrimethylsilane in acetonitrile to give the corresponding 4-acetamido-2,6-diaryl-tetrahydropyrans in good yields (entries **a** and **b** Table **1**). This method is effective even for sterically hindered substrate, for example, 2-naphthaldehyde (entry **c**, Table **1**). Similarly, benzaldehyde also reacted well with allyltrimethylsilane in benzyl cyanide to yield the corresponding 2,6-diaryl-4-phenylacetamido-tetrahydropyrans (entry **d**, Table **1**). Next, we studied the reactivity of aromatic and aliphatic aldehydes in benzonitrile. Interestingly, *p*-chlorobenzaldehyde and *n*-butanal participated well in the Hosomi–Sakurai-Prins/Ritter amidation in benzonitrile to yield the respective 2,6-disubstituted-4-benzamidotetrahydropyrans (entries **e** and **f**, Table **1**). Thus, it is very useful for the preparation of a diverse range of 2,6-diaryl- or 2,6-dialkyl-4-amidotetrahydropyrans. The structures of the products were established by NMR, IR and mass spectroscopy. It is noteworthy to mention that the reaction was not successful in the absence of acid catalyst (**1**) even after an extended reaction time (12 h). The scope of the catalyst **1** is illustrated with respect to various aldehydes and the results are presented in Table **1**. As shown in Table **1**, this method works well with both electron-donating as well as electron-withdrawing aldehydes.

Table 1. *o*-Benzenedisulfonimide catalyzed Prins/Ritter reaction

Entry	Aldehyde	Nitriles	Product (**3**)[a]	Time (h)	Yield (%)[b]
a	4-Cl-C6H4-CHO	CH3CN		1.0	85
b	4-Br-C6H4-CHO	CH3CN		1.0	86
c	2-naphthyl-CHO	CH3CN		1.5	82
d	C6H5-CHO	PhCH2CN		1.0	80
e	4-Cl-C6H4-CHO	C6H5CN		1.5	91
f	CH3CH2CH2CHO	C6H5CN		1.5	80

[a]All products were characterized by ^{1}H NMR, IR and mass spectrometry.
[b]Yield refers to pure products after chromatography.

The simplicity of this procedure encouraged us to further extend it to the preparation of unsymmetrical 4-amidotetrahydropyran derivatives by means of Prins/Ritter reaction (entries **4a-g**, Table **2**). In a typical experiment, 1.2 eq of *p*-chlorobenzaldehyde was treated with 1.0 eq of 3-buten-1-ol in presence of 10 mol% of catalyst **1** in acetonitrile. Interestingly, the reaction was completed within 1 h at room

temperature and the corresponding 2-phenyl-4-acetamidotetrahydropyran **4a** was obtained in 87% yield with *cis*-selectivity (Table **2**, Scheme **2**).

Scheme 2. Preparation of 2-phenyl-4-amidotetrahydropyran **4a**

Table 2. *o*-Benzenedisulfonimide catalyzed Prins/Ritter reaction

Entry	Aldehyde/ Ketone	Nitriles	Homoallyl alcohol	Product (4)[a]	Time (h)	Yield (%)[b]
a	4-Cl-C$_6$H$_4$-CHO	CH$_3$CN	(homoallyl alcohol)	(product)	1.0	87
b	CH$_3$CH$_2$CH$_2$-CHO	CH$_3$CN	(homoallyl alcohol)	(product)	1.0	80
c	C$_6$H$_5$-CHO	C$_6$H$_5$CH$_2$CN	(homoallyl alcohol)	(product)	1.2	80
d	C$_6$H$_5$-CHO	C$_6$H$_5$CN	(homoallyl alcohol)	(product)	1.2	82
e	4-Cl-C$_6$H$_4$-CHO	CH$_3$CN	(homoallyl alcohol, Ph)	(product)	1.0	90
f	4-Br-C$_6$H$_4$-CHO	C$_6$H$_5$CN	(homoallyl alcohol, Ph)	(product)	1.2	83
g	(N-methylisatin)	CH$_3$CN	(homoallyl alcohol)	(product)	1.0	80

[a]All products were characterized by ^{1}H NMR, IR and mass spectrometry.
[b]Yield refers to pure products after chromatography.

Subsequently, we have found that this method works not only with aldehydes but also with ketones. For instance, *N*-methylisatin (1-methylindoline-2,3-dione) reacted smoothly with 3-buten-1-ol in the presence of catalyst **1** (10 mol %) in acetonitrile to furnish the corresponding spiro-tetrahydropyranyl amide[16] **4g** in 80% yield (Scheme **3**, entry **g**, Table **2**).

Scheme 3. Spiro-4-amidotetrahydropyran **4g**

Next, we tested the efficiency of *o*-benzenedisulfonimide with known acid catalysts for the condensation of homoallylic alcohol with *N*-methylisatin in acetonitrile at 25 °C and the results are presented in Table **3**.

Table 3. Screening of various acid catalysts in the formation of **4g**

Entry	Catalyst(10 mol%)	Reaction Time	Yield (%)[a]
a	HCOOH	12 h	Trace
b	$BF_3.OEt_2$	10 h	50
c	Phosphomolybdic acid	12 h	40
d	TFA	12 h	45
e	$4\text{-MeC}_6\text{H}_4\text{SO}_3\text{H}$	10 h	60
f	$MeSO_3H$	10 h	63
g	NH_2SO_3H	10 h	40
h	*o*-Benzenedisulfonimide	1.0 h	80

[a]Yield refers to pure product after chromatography

As seen from Table **3**, the product **4g** was obtained in 80% yield in a short reaction time (1 h) with *o*-benzenedisulfonimide compared to other acid catalysts. Thus, the catalyst **1** was found to be superior catalyst in promoting Prins/Ritter amidation. It is a first example on Prins/Ritter amidation of *N*-methylisatin, which may find a useful application in medicinal chemistry to generate spiro-cyclic oxindole scaffolds.

The catalyst **1** is a strong acid[8] which is soluble in both water and organic solvents. One of the most remarkable aspects in the use of **1** is its ease of recovery in good yields from the reaction mixture owing to its complete solubility in water and its reuse in further reactions without significant loss of catalytic activity. The use of recyclable Brönsted acid (**1**) in this transformation makes this method economically viable process for the synthesis of 4-amidotetrahydropyran derivatives. The recovered catalyst **1** was recycled in several consecutive runs and the results are presented in Table 4. The yields of **4a** and the recovery of **1** are always excellent throughout the course of different runs.

Table 4. Reusability of the catalyst (**1**) in the preparation of **4a**[a]

Entry	Yield[a] (%) (**4a**)[b]	Recovery (%) (**1**)[c]
1	87	85 (18.6 mg)
2	82	81 (15.06 mg)
3	80	78 (11.75 mg)
4	78	75 (8.23 mg)

[a]All the reaction were performed in 1 h. [b]Yield refers to the pure product.
[c]The reaction was performed in 1 mmol scale using 0.1 mmol of the catalyst (**1**).

The products were obtained in good yields with *cis*-selectivity as confirmed from the NMR spectrum of the crude product. Only a single diastereoisomer was formed in each reaction, the structure of which was confirmed by coupling constants (*J* values) and nOe experiments.[17] The relative stereochemistry of the compound **3a** was determined by detailed NMR studies. Compound **3a** possess a C_2 symmetry that was further confirmed by ^{1}H NMR spectrum, which showed double intensity for H2 and H3 protons. The stereochemistry at C2 and C4 was established by the observation of large coupling constant for H2 $^3J_{\text{H2-H3(ax)}} = 11.0$ Hz and the presence of nOe cross peak between H2-H4

to support the six membered ring in $^1C_4$ chair conformation with substitutions at C2 and C4 in the equatorial positions as depicted in figure **2**.
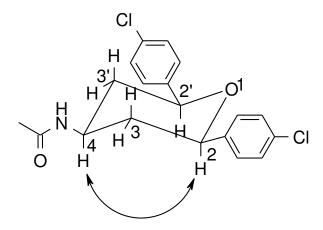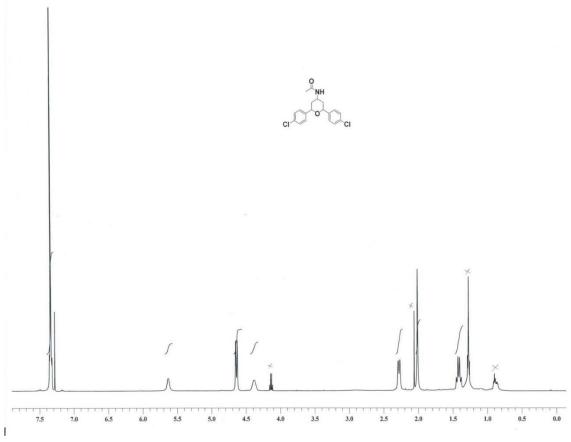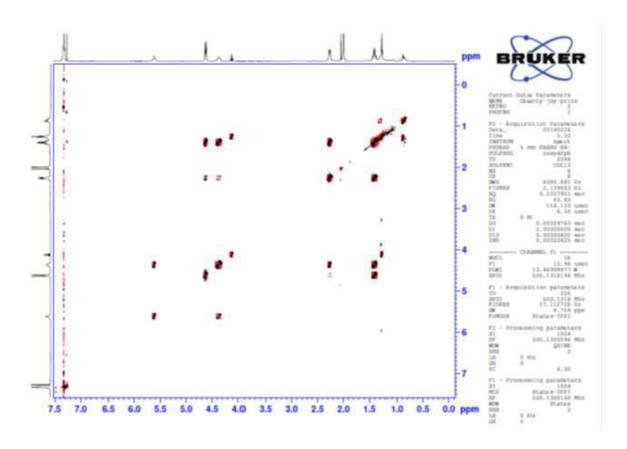
Figure 2. Schematic nOe diagram of **3a**
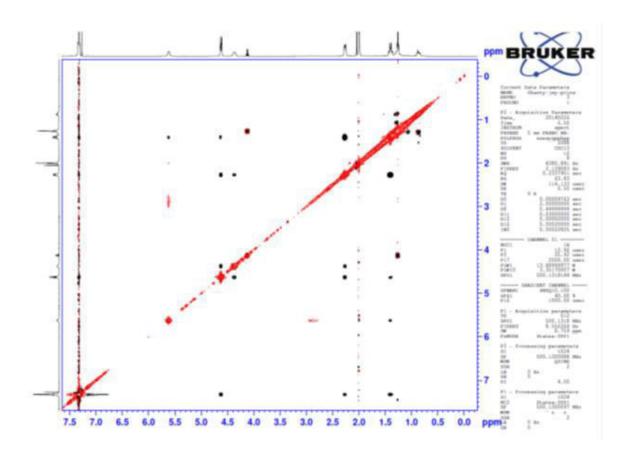
^{1}H-NMR spectrum of compound **3a**.

2D DQFCOSY (Double Quantum Filtered Correlation spectroscopy) spectrum of compound 3a

2D NOESY (Nuclear Overhauser effect spectroscopy) spectrum of compound 3a

1.3.2.2 *Mechanistic study*

The *cis*-selectivity of the Prins/Ritter amidation reaction can be explained by the formation of oxo-carbenium ion in the presence of an acid catalyst. Attack of the alkene to oxo-carbenium ion through a chair like transition state generates a tetrahydropyranyl cation. In the ring closure step, the C2 substituent occupies favorably in equatorial position to produce (*E*)-oxo-carbenium ion over the (*Z*)-oxo-carbenium ion. Therefore, the stereochemistry of the C2 substituent is transferred to the newly formed carbon-carbon bond. The stereochemistry at C4 is controlled by the extensive delocalization of the tetrahydropyranyl cation. The optimal geometry for this delocalization places hydrogen at C4 in a pseudoaxial position. So, the nucleophilic attack occurs from equatorial side to deliver *cis*-tetrahydropyran skeleton.[18]

Scheme 4. A plausible reaction pathway

1.3.2.3 *Conclusion:*

In summary, a direct one-pot method has been developed for the synthesis of 4-amidotetrahydropyran derivatives by means of Prins cyclisation using a recyclable Brönsted acid catalyst (**1**). The synthetic usefulness of *o*-benzenedisulfonimide (**1**) as an organocatalyst in Prins/Ritter reaction has been demonstrated. This strong bench-stable Brönsted acid has been shown to catalyze the three-component Prins/Ritter amidation under mild conditions. This method provides an easy access to the synthesis of a wide

range of symmetrical, unsymmetrical and spiro-cyclic 4-amidotetrahydropyran derivatives with excellent yields.

1.3.3. EXPERIMENTAL

1.3.3.1 *General experimental procedures*

A solution of allyltrimethylsilane (0.5 mmol) was added to a mixture of aldehyde (1.05 mmol) and *o*-benzenedisulfonimide (**1**) (10 mmol %) in nitrile (4 mL). The resulting mixture was stirred at room temperature for the specified time. After completion, as indicated by TLC, the reaction mixture was poured into dichloromethane/water (20 mL, 1:1). The aqueous layer was separated and extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with water (3 x 4 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The resulting crude mass was then subjected to flash column chromatography using 7:3 mixture of *n*-hexane and ethyl acetate as eluent to afford the pure 4-amidotetrahydropyran. The product thus obtained were characterised by IR, NMR and mass spectroscopy.

The aqueous layer and aqueous washings were collected and evaporated under reduced pressure. The residue was passed through a column of Dowex AG 50W-X8 ion-exchange resin (acidic in nature, 100-200 mesh, 160 mg resin/100 mg product) with water as eluent. After removal of the water under reduced pressure, virtually the pure catalyst **1** was recovered as a white solid; mp 190–192 °C (toluene) (Lit.[18] 192-194 °C). The recovered catalyst **1** was employed in further catalytic cycles under the conditions described above.

1.3.3.2 *Spectral data of products*

N-(2,6-Bis(4-chlorophenyl)-tetrahydro-2*H*-pyran-4-yl)acetamide (3a):

Yield	:	85%
Molecular formula	:	$C_{19}H_{19}Cl_2NO_2$
Physical State	:	White solid; m.p. 177-179 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.37-7.24 (m, 8H), 5.35 (brd, 1H), 4.62 (d, *J* = 10.9 Hz, 2H), 4.40-4.24 (m, 1H), 2.33-2.21 (m, 2H), 1.95 (s, 3H), 1.33 (dd, *J* = 11.3, 23.4 Hz, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 169.4, 140.2, 133.3, 128.5, 127.0, 77.7, 46.5, 40.2, 23.4.
IR (Neat)	:	ν_{max} 3194, 2960, 1699, 1463, 1368, 1262, 1168, 791 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{19}H_{19}NO_2NaCl_2$: 386.070, found: 386.069.
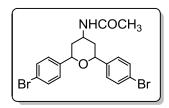
N-(2,6-Bis(4-bromophenyl)-tetrahydro-2H-pyran-4-yl)acetamide (3b):

Yield	:	86%
Molecular formula	:	$C_{19}H_{19}Br_2NO_2$
Physical State	:	White solid; m.p. 230-232 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.45 (d, *J* = 7.9 Hz, 4H), 7.25 (d, *J* = 7.9 Hz, 4H), 5.24 (brd, 1H), 4.60 (d, *J* = 10.9 Hz, 2H), 4.39-4.27 (m, 1H), 2.31-2.22 (m, 2H), 1.95 (s, 3H), 1.4-1.23 (m, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 169.4, 140.7, 131.5, 127.3, 121.4, 77.7, 46.5, 40.1, 23.4.
HRMS (ESI)	:	Calculated for $C_{19}H_{19}NO_2NaBr_2$ 473.9678, found: 473.9680.

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N-(Tetrahydro-2-(naphthalen-2-yl)-6-naphthalen-3-yl)-2H-pyran-4-yl)acetamide (3c):

Yield	:	82%
Molecular formula	:	$C_{27}H_{25}NO_2$
Physical State	:	Pale yellow solid; m.p. 220-222 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.90 (brs, 1H), 7.88-7.70 (m, 8H), 7.63-7.57 (m, 2H), 7.50-7.40 (m, 4H), 4.87 (d, J = 10.9 Hz, 2H), 4.39-4.22 (m, 1H), 2.34-2.23 (m, 2H), 1.86 (s, 3H), 1.58 (dd, J = 12.0, 24.1 Hz, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 169.2, 139.1, 132.6, 132.2, 131.7, 127.4, 127.0, 125.5, 125.2, 123.8, 123.7, 78.0, 46.0, 40.1, 22.6.
IR (Neat)	:	ν$_{max}$ 3280, 2924, 1737, 1639, 1547, 1463, 1306, 1082, 823, 747 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{27}H_{25}NO_2Na$: 418.1793; found: 418.1782.
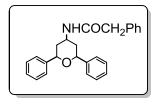
N-(Tetrahydro-2,6-diphenyl-2H-pyran-4-yl)-2-phenylacetamide (3d):

Yield	:	80%
Molecular formula	:	$C_{25}H_{25}NO_2$
Physical State	:	White solid; m.p. 178-180 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.40-7.13 (m, 15H), 5.12 (brd, 1H), 4.62 (d, J = 10.7 Hz, 2H), 4.42-4.26 (m, 1H), 3.53 (s, 2H), 2.27-

	2.15 (m, 2H), 1.34-1.18 (m, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	: δ 170.3, 141.9, 134.6, 129.3, 129.0, 128.3, 127.5, 125.6, 78.2, 46.7, 43.8, 40.3.
IR (Neat)	: ν_{max} 3307, 2924, 1737, 1639, 1537, 1494, 1320, 1066, 750, 669 cm^{-1}
HRMS (ESI)	: Calculated for C$_{25}$H$_{25}$NO$_2$Na: 394.1773; found: 394.1782.
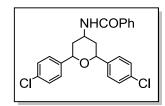
N-(2,6-Bis(4-chlorophenyl)–tetrahydro-2*H*-Pyran-4-yl)benzamide (3e)

Yield	: 91%
Molecular formula	: C$_{25}$H$_{25}$NO$_2$
Physical State	: White solid; m.p. 197-199 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	: δ 7.74-7.67 (m, 2H), 7.52-7.28 (m, 11H), 5.96 (brd, 1H), 4.68 (d, *J* = 9.8 Hz, 1H), 4.60-4.48 (m, 1H), 2.44-2.34 (m, 2H), 1.46 (dd, *J* = 12.0, 24.1 Hz, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	: δ 166.9, 140.2, 134.2, 133.3, 131.7, 128.6, 128.5, 127.0, 126.8, 77.7, 46.9, 40.2.
IR (Neat)	: ν_{max} 3285, 2926, 1628, 1532, 1489, 1306, 1083, 817, 692 cm^{-1}
HRMS (ESI)	: Calculated for C$_{24}$H$_{21}$NO$_2$NaCl$_{2:}$ 448.0847, found: 448.0847.
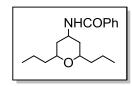
N-(Tetrahydro-2,6-dipropyl-2H-pyran-4-yl)benzamide (3f)

Yield   :   80 %

Molecular formula   : $C_{18}H_{27}NO_2$

Physical State   :   White solid; m.p. 103-105 °C

^{1}H-NMR (CDCl$_3$, 300 MHz)   :   δ 7.75-7.68 (m, 2H), 7.51-7.35 (m, 3H), 5.84 (brd, 1H), 4.26-4.10 (m, 1H), 3.44-3.33 (m, 2H), 2.02 (dd, $J = 4.5$, 12.0 Hz, 2H), 1.59-1.30 (m, 10H), 1.06 (dd, $J = 11.3$, 23.4 Hz, 2H), 0.93 (t, $J = 6.8$ Hz, 6H).

^{13}C-NMR (CDCl$_3$, 75 MHz)   :   δ 166.7, 134.6, 131.4, 128.5, 126.8, 75.8, 46.8, 38.6, 38.2, 18.8, 13.9.
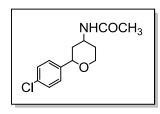
IR (Neat)   :   ν$_{max}$ 3280, 2926, 1628, 1543, 1494, 1378, 1153, 1076, 965, 695 cm^{-1}

HRMS (ESI)   :   Calculated for $C_{18}H_{27}NO_2Na$: 312.1926, found: 312.1939.

N-(2-(4-Chlorophenyl)-tetrahydro-2*H*-4-yl)acetamide (4a):

Yield   :   87%

Molecular formula   : $C_{18}H_{27}NO_2$

Physical State   :   White solid; m.p 153-155 °C

^{1}H-NMR (CDCl$_3$, 300 MHz)   :   δ 7.30-7.20 (m, 4H), 5.31 (brd, 1H), 4.36 (d, $J =$ 11.1 Hz, 1H), 4.22-4.05 (m, 2H), 3.64 (t, $J =$ 12.0

Hz, 1H), 2.25-2.14 (m, 2H), 1.95 (s, 3H), 1.24 (dd, *J*

= 11.7, 23.8 Hz, 2H).

¹³C-NMR (CDCl₃, 75 MHz) : δ 169.5, 140.5, 133.2, 128.4, 126.9, 77.8, 66.9, 46.2,

40.6, 32.5, 23.4.

IR (Neat) : ν_{max} 3288, 2926, 1647, 1552, 1492, 1368, 1148,

1086, 825, 772 cm⁻¹

HRMS (ESI) : Calculated for $C_{13}H_{16}NO_2NaCl$ 276.0779, found:

276.0767.

N-(2-Propyl-tetrahydro-2H-pyran-4-yl)acetamide (4b)

Yield : 80%

Molecular formula : $C_{18}H_{27}NO_2$

Physical State : White solid; m.p. 72-73 °C

¹H-NMR (CDCl₃, 300 MHz) : δ 5.38 (brd, 1H), 4.07-3.93 (m, 2H), 3.46 (t, *J* = 12.0

Hz, 1H), 3.40-3.28 (m, 1H), 1.98 (s, 3H), 1.58-1.23

(m, 6H), 1.06 (dd, *J* = 11.07, 23.2 Hz, 2H), 0.90 (t, *J*

= 7.0 Hz, 3H).
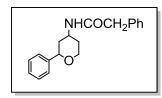
¹³C-NMR (CDCl₃, 75 MHz) : δ 169.4, 76.2, 66.4, 46.2, 38.6, 38.2, 32.8, 23.2, 18.4,

13.9.

HRMS (ESI) : Calculated for $C_{10}H_{19}NO_2Na$ 208.1315, found:

208.1313.

2-Phenyl-N-(2-phenyltetrahydro-2H-pyran-4-yl)acetamide (4c):

Yield	:	80%
Molecular formula	:	$C_{19}H_{21}NO_2$
Physical State	:	White solid; m.p. 131-133 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.37-7.15 (m, 10H), 5.16 (brd, 1H), 4.35 (d, J = 10.9 Hz, 1H), 4.19-4.05 (m, 2H), 3.62 (t, J = 11.7 Hz, 1H), 3.50 (s, 2H), 2.10 (d, J = 12.8 Hz, 1H), 1.90 (d, J = 12.1 Hz, 1H), 1.44-1.20 (m, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 170.2, 141.8, 134.7, 129.2, 128.9, 128.3, 127.5, 127.2, 125.5, 78.5, 66.8, 46.4, 43.7, 40.5, 32.4.
IR (Neat)	:	ν_{max} 3287, 2925, 1645, 1544, 1369, 1147, 1084, 1032, 757, 698 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{19}H_{21}NO_2Na$ 318.1483, found: 318.1469.
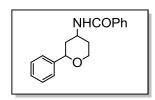
N-(2-Phenyl-tetrahydro-2*H*-pyran-4-yl)benzamide (4d)

Yield	:	82%
Molecular formula	:	$C_{18}H_{19}NO_2$
Physical State	:	White solid; m.p 149-150 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.72 (d, J = 6.9 Hz, 2H), 7.50-7.19 (m, 8H), 6.12 (brd, 1H), 4.48-4.28 (m, 2H), 4.19 (dd, J = 3.4, 11.9 Hz, 1H), 3.70 (t, J = 12.2 Hz, 1H), 2.35-2.25 (m, 1H), 2.10-2.0 (m, 1H), 1.46 (dd, J = 11.7, 23.8 Hz, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 166.8, 141.8, 134.4, 131.4, 128.5, 128.3, 127.5, 126.8, 125.5, 78.6, 66.9, 46.8, 40.6, 32.7.

66
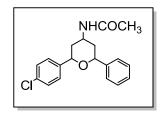
IR (Neat)	:	ν_{max} 3286, 2924, 1636, 1538, 1318, 1146, 1084, 1028, 757, 689 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{18}H_{19}NO_2Na$ 304.1320, found: 304.1313.

N-(2-(4-Chlorophenyl)-6-phenyl-tetrahydro-2H-pyran-4-yl)acetamide (4e):

Yield	:	90%
Molecular formula	:	$C_{19}H_{20}ClNO_2$
Physical State	:	White solid; m.p. 148-150 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.47-7.23 (m, 9H), 5.45 (brd, 1H), 4.69-4.60 (m, 2H), 4.46-4.30 (m, 1H), 2.34-2.21 (m, 2H), 1.97 (s, 3H), 1.50-1.32 (m, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 169.4, 141.7, 140.5, 128.5, 128.4, 127.6, 127.0, 125.6, 78.3, 77.6, 46.6, 40.3, 40.2, 23.4.
IR (Neat)	:	ν_{max} 3285, 2924, 1644, 1544, 1372, 1286, 1084, 816, 750 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{19}H_{20}NO_2NaCl$ 352.1077, found: 352.1080.
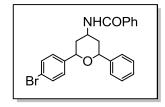
N-(2-(4-Bromophenyl)-6-phenyl-tetrahydro-2H-pyran-4-yl)benzamide (4f)

67

Yield	:	83%
Molecular formula	:	$C_{24}H_{22}BrNO_2$
Physical State	:	White solid; m.p. 176-178 ^oC
^1H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.70 (d, J = 6.9 Hz, 2H), 7.50-7.20 (m, 12H), 5.94 (brd, 1H), 4.74-4.63 (m, 2H), 4.60-4.48 (m, 1H), 2.45-2.35 (m, 2H), 1.56-1.40 (m, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 166.9, 141.7, 141.0, 134.4, 131.4, 128.6, 127.4, 126.8, 125.6, 121.2, 78.4, 77.7, 47.1, 40.2.
IR (Neat)	:	ν$_{max}$ 3294, 2926, 1633, 1539, 1348, 1307, 1076, 812, 697 cm^{-1}
HRMS (ESI)	:	Calculated for $C_{24}H_{22}NO_2NaBr$ 458.0729, found: 458.0731.

N-(1-methyl-2-oxo-3',4',5',6'-tetrahydrospiro[indoline-3,2'-pyran]-4'-yl)acetamide (4g)

Yield	:	80%
Molecular formula	:	$C_{15}H_{18}N_2O_3$
Physical State	:	White solid; m.p 158-160 ^oC
^1H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.34-7.18 (m, 2H), 7.00 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 5.44 (brd, 1H), 4.88-4.70 (m, 2H), 3.83 (dd, J = 4.5, 11.9 Hz, 1H), 3.15 (s, 3H), 2.16-2.0 (m, 2H), 1.92 (s, 3H), 1.66 (dd, J = 12.6, 24.9 Hz, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 175.4, 169.2, 143.1, 129.9, 123.2, 122.9, 108.2,

75.7, 62.2, 41.5, 37.9, 32.2, 30.9, 23.4.

| IR (Neat) | : | ν_{max} 3267, 2924, 1720, 1644, 1570, 1465, 1372, 1253, 1130, 748 cm^{-1} |
| HRMS (ESI) | : | Calculated for $C_{15}H_{18}N_2O_3Na$ 297.1205, found: 297.1215. |
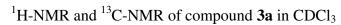
1.3.4 REFERENCES:
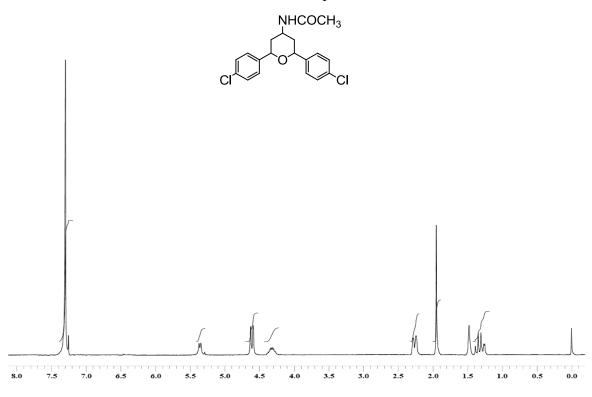
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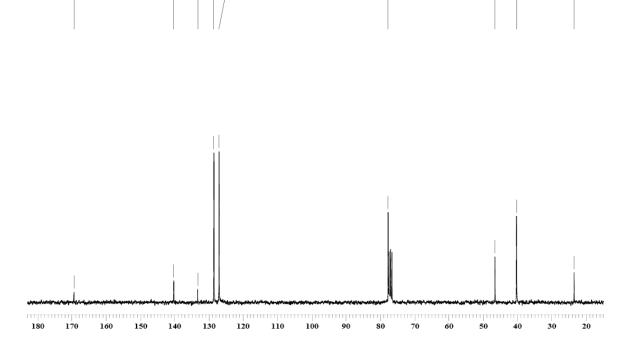
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SPECTRA

^{1}H-NMR and ^{13}C-NMR of compound **3a** in CDCl$_3$

NHCOCH$_3$

^{1}H-NMR spectrum with peaks at approximately 7.5, 5.5, 4.5, 2.2, 2.0, 1.5, and 0.0 ppm.

^{13}C-NMR: 169.371, 140.253, 133.272, 128.529, 127.023, 77.701, 46.513, 40.206, 23.423
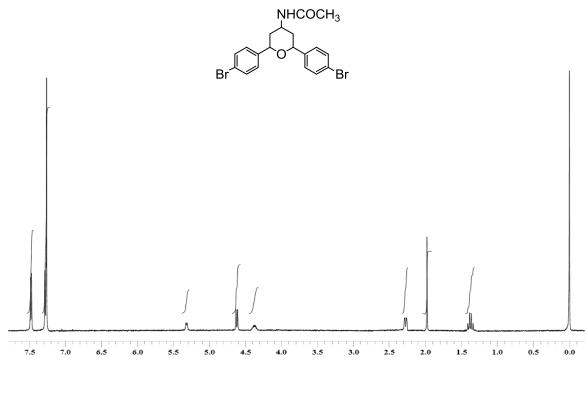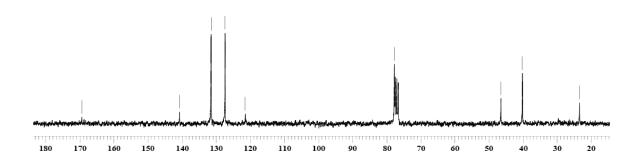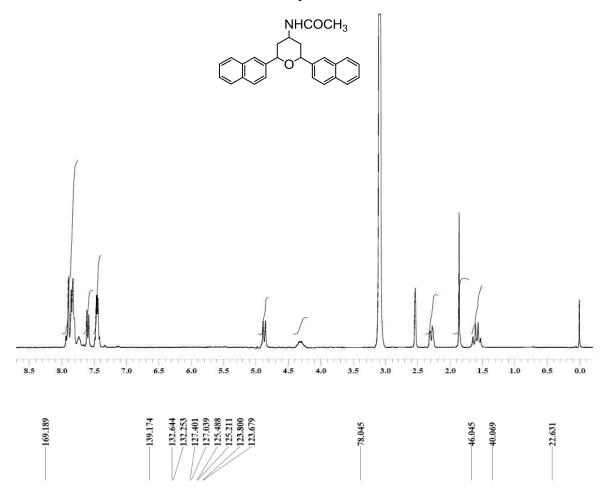
^{1}H-NMR and ^{13}C-NMR of compound **3b** in CDCl$_3$
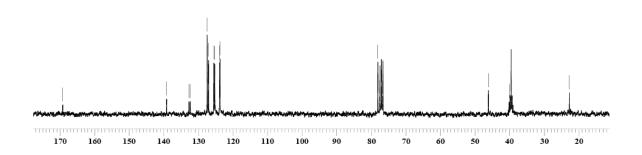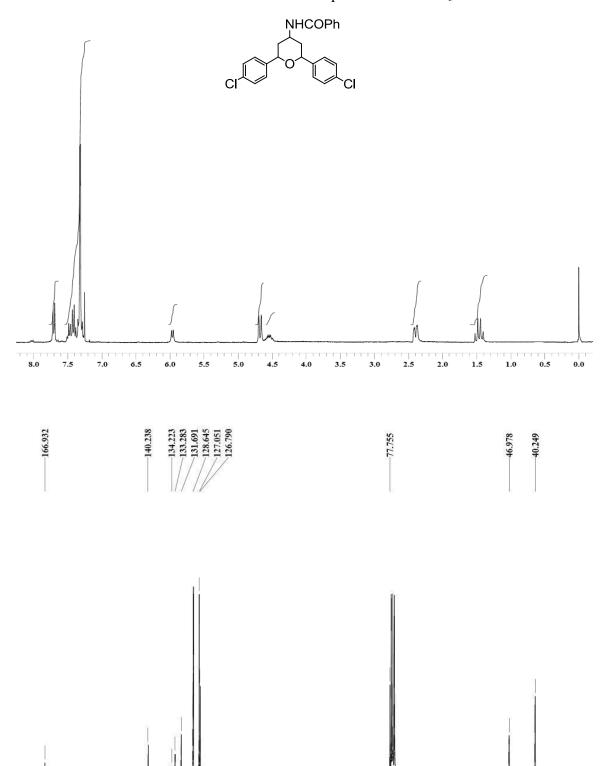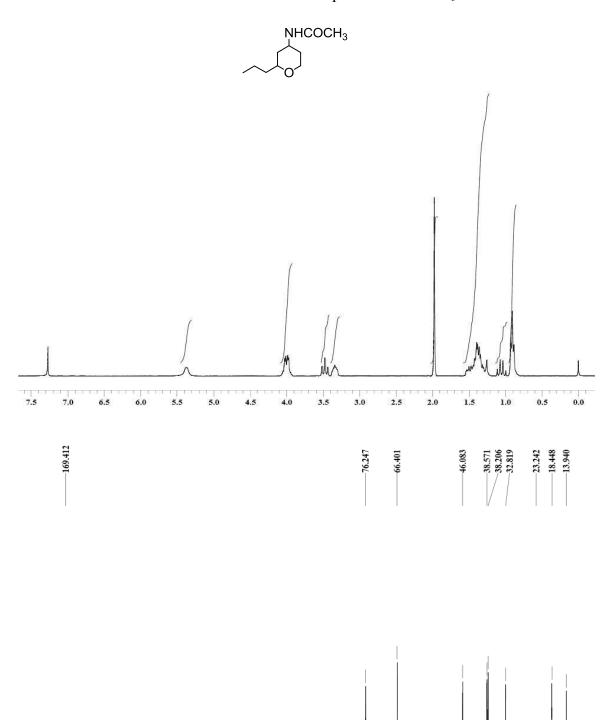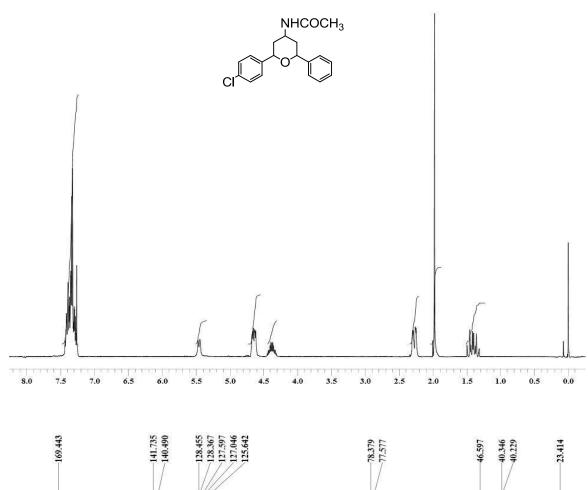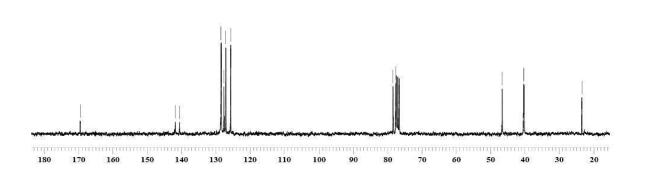
^{1}H-NMR and ^{13}C-NMR of compound **3c** in CDCl$_3$ + DMSO
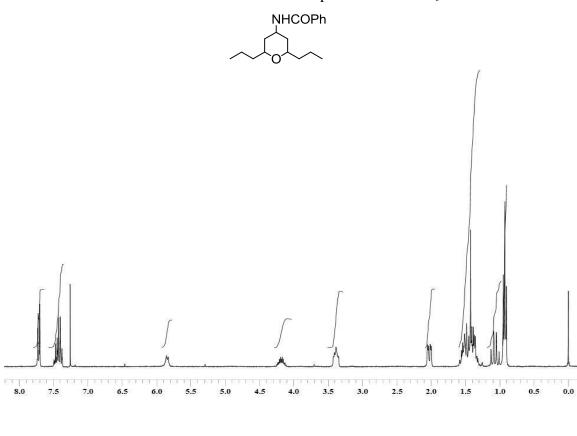
^{1}H-NMR and ^{13}C-NMR of compound 3e in CDCl$_3$

NHCOPh

Cl — Cl

166.932

140.238
134.223
133.283
131.691
128.645
127.051
126.790

77.755

46.978
40.249
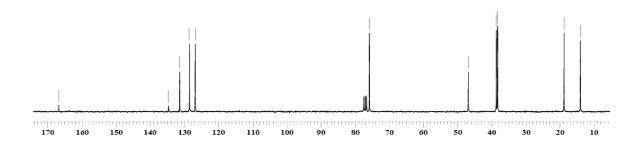
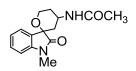# ^{1}H-NMR and ^{13}C-NMR of compound **3f** in CDCl$_3$

NHCOPh
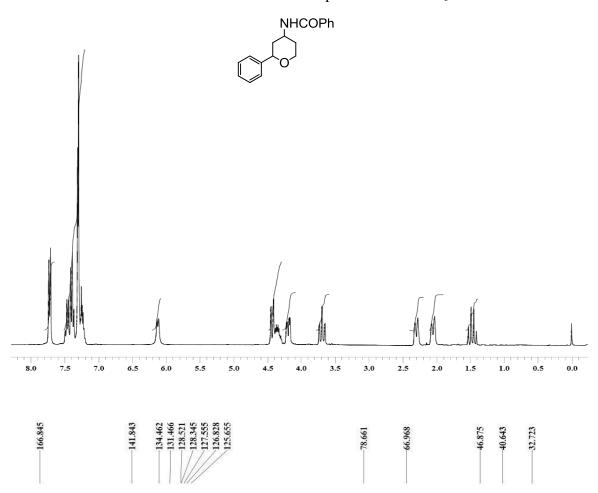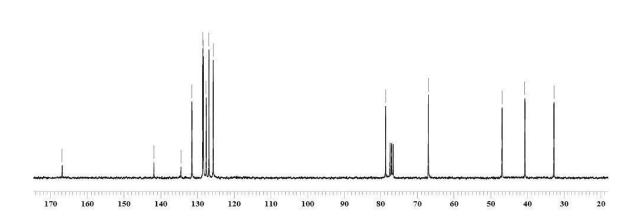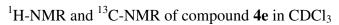
^{1}H-NMR and ^{13}C-NMR of compound **4b** in CDCl$_3$

NHCOCH$_3$

^{13}C peaks: 169.412, 76.247, 66.401, 46.083, 38.571, 38.206, 32.819, 23.242, 18.448, 13.940

^{1}H-NMR and ^{13}C-NMR of compound 4d in CDCl$_3$

NHCOPh

^{1}H-NMR and ^{13}C-NMR of compound 4e in CDCl$_3$

^{1}H-NMR spectrum with peaks at 8.0, 7.5, 7.0, 6.5, 6.0, 5.5, 5.0, 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5, 0.0

^{13}C-NMR peaks: 169.443, 141.735, 140.490, 128.455, 128.367, 127.597, 127.046, 125.642, 78.379, 77.577, 46.597, 40.346, 40.229, 23.414

^{1}H-NMR and ^{13}C-NMR of compound 4f in CDCl$_3$

NHCOPh

Br

^{1}H-NMR and ^{13}C-NMR of compound **4g** in CDCl$_3$

^{1}H-NMR spectrum peaks at approximately 7.5, 7.0, 6.5, 5.5, 4.5, 3.5, 3.0, 2.0, 1.5, 0.0 ppm

^{13}C-NMR signals:
175.376
169.201
143.083
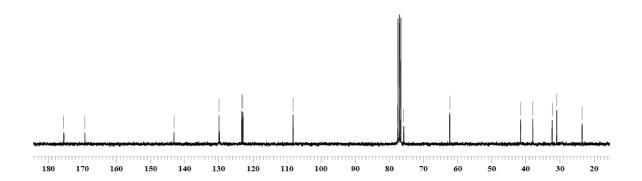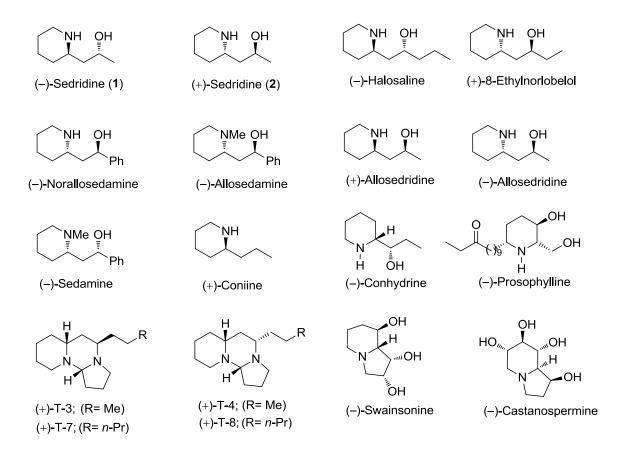129.901
123.225
122.876
108.164
75.723
62.245
41.490
37.876
32.220
30.879
23.435

CHAPTER II: SECTION A

Introduction and previous approaches for the synthesis of Sedridine

2.1 INTRODUCTION

Piperidine alkaloids are widely distributed in nature and found to display a broad spectrum of biological activities.[1] In particular; 2-substituted piperidine alkaloids (Fig. **1**) have attracted considerable attention because of their potent biological activities such as memory enhancing properties. They can also be used in the treatment for cognitive disorder,[2] neurological disorders such as Alzheimer's, Parkinson's, asthma, bronchitis and pneumonia.[3] Several synthetic approaches have been developed for the synthesis of these piperidine alkaloids because of their scarcity from natural sources.[4] In this context, during the past few years, several methods were developed for the synthesis of 2-substituted piperidine alkaloids, as well as for the synthesis of 2,6-disubstituted piperidine alkaloids.[5] Few representative piperidine alkaloids are listed in Fig. **1**.

(−)-Sedridine (**1**)	(+)-Sedridine (**2**)

(−)-Halosaline   (+)-8-Ethylnorlobelol

(−)-Norallosedamine   (−)-Allosedamine

(+)-Allosedridine   (−)-Allosedridine

(−)-Sedamine   (+)-Coniine   (−)-Conhydrine   (−)-Prosophylline

(+)-T-3; (R= Me)
(+)-T-7; (R= *n*-Pr)

(+)-T-4; (R= Me)
(+)-T-8; (R= *n*-Pr)

(−)-Swainsonine   (−)-Castanospermine

Figure 1: Representative examples of 2-substituted piperidine alkaloids.

A large numbers of alkaloids have been isolated from various sources such as *Sedum* and *Lobelia* species. All the members of this alkaloid contain functional group like C=O or CHOH, *cis/trans* geometry, side chain with different terminal R group and occasionally bearing extra OH in the region of 3,4,5-carbons. The group includes both -*N*H and -*N*Me analogues (Fig. **2**). All These compounds contain either 1,3-aminoalcohol or 1,3-diamine scaffolds. Even though they are not biochemically related but synthetically very close to each other. Several of these alkaloids have been isolated from the herb *Lobelia inflata*, commonly referred to as Indian tobacco.

3   **4**

Sedum acre plant   *Lobelia inflate* (Indian Tobacco)
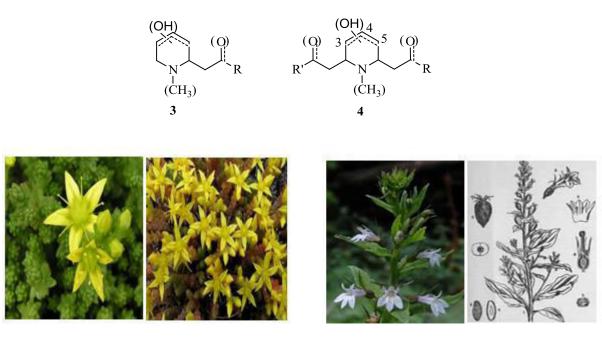
Figure 2: Summary of various types of alkaloids found in *Sedum* and *Lobelia species*

Interest in the synthesis of these alkaloids has been ongoing for nearly half a century. They have become a testing ground for methodology, especially in terms of the control of relative and, absolute stereochemistry of the 1,3-amino alcohol frameworks.

2.2 Previous approaches for the synthesis of sedridine:

1. Hiroki Takahata's approach:[6]

In 1999, Hiroki *et al*. described the synthesis of naturally occurring piperidine-related alkaloids from 5-hexenyl azide **5**. Sharpless asymmetric dihydroxylation (AD) of **5** provided the diol **6** which was converted into epoxide **7** by Sharpless's one-pot procedure in 85% yield. The regioselective cleavage of the epoxide **7** with vinylmagnesium bromide in combination with CuBr.Me$_2$S complex gave the alcohol **8** in 90% yield. Treatment of **8** with MsCl in the presence of pyridine provided the mesylated compound **9** in 82% yields. The Staudinger reaction of azide **9** in aqueous THF at 50 °C produced the free amine, which immediately cyclized into the desired 2-propenylpiperidines **10** in 86% yield. Next, Cbz-protection of NH in compound **10** gave the *N*-CBZ compound **11** in 96% yield. Sharpless asymmetric dihydroxylation (AD) of **11** followed by epoxidation gave **13**. Reduction of **13** with LAH in THF at room temperature afforded secondary alcohol **14**. Compound **14** was then subjected to hydrogenation in the presence of palladium hydroxide in methanol to furnish the title compound **1**.

Scheme 1. Total synthesis of (−)-sedridine (**1**)

Reagents and conditions: (i) AD-mix-*β*, *t*-BuOH:H$_2$O (1:1), 70%; (ii) (a) (MeO)$_3$CCH$_3$/PPTS; (b) MeCOBr; (c) K$_2$CO$_3$/MeOH, 85%; (iii) Vinylmagnesium bromide/CuBr.Me$_2$S, 90%; (iv) MsCl, Pyridine, 82%; (v) PPh$_3$, H$_2$O/THF, 86%; (vi) CbzCl, K$_2$CO$_3$, 96%; (vii) AD-mix-*β*, *t*-BuOH:H$_2$O (1:1), 70%; (viii) (a) (MeO)$_3$CCH$_3$/PPTS; (b) MeCOBr; (c) K$_2$CO$_3$/MeOH, 85%; (ix) LAH, THF, 90%; (x) H$_2$/Pd(OH)$_2$, MeOH, 90%.

2. Takashi Itoh's approach:[7]

In 2006, Takashi and co-workers reported the synthesis of (–)-sedridine using Proline-catalyzed asymmetric addition. Reaction of 4-hydroxybutanal with *p*-anisidine generates an imine, which was treated with an enamine derived from L-proline and acetone afforded the Compound **15** in 76 % yield. Compound **15** was then reduced using LAH to give the diol **16** as a mixture of epimers. Compound **16** was then cyclized to compound **17** under Mitsunobu condition in 88% total yield. Compound **17** was then transformed to compound **18** by deprotection of PMP group followed by protection with a Cbz group in 54 % (two steps) yield. Compound **18** was then readily transformed to (-)-sedridine **1** by reductive cleavage of the Cbz group.

Scheme 2. Total synthesis of (–)-sedridine (**1**)

Reagents and conditions: (i) L-Proline (30 mol%), *i*-PrOH, -10 $^{\circ}$C, 185 h, 76%; (ii) LAH, THF, 0°C, 30 min, 72%; (iii) DEAD, PPh$_3$, CH$_2$Cl$_2$, rt, 2 h, 88%; (iv) (a) CAN, MeCN:H$_2$O=1:1, 0 $^{\circ}$C, 3 h, (b) Cbz-Cl, 5N NaOH, 54% (two steps); (v) H$_2$, Pd(OH)$_2$, MeOH, rt, 90%.

3. Saroja Nuguri's approach:[8]

In 2006, Nuguri and co-workers accomplished the stereoselective synthesis of (–)-sedridine from commercially available (*S*)-malic acid. Alcohol **19** has been synthesized from (*S*)-malic acid using literature procedure.[9] The primary alcohol **19** was converted to aldehyde, followed by Maruoka Keck allylation to provide the homoallyl alcohol **20** in 92% yield. This secondary alcohol was converted to the corresponding tosylate **21** in good yield (87%) by using *p*-toluenesulfonyl chloride in pyridine. The tosylate **21** was then treated with NaN$_3$ in dry DMF at 60 ºC to furnish the corresponding azide **22** in 86% yield. Primary acetonide group in compound **22** was removed by using *p*TSA in MeOH to afford the diol **23** in good yield. Chemoselective tosylation of the diol **23** gave the mono-tosylated compound. This was taken up for the oxirane formation using K$_2$CO$_3$ in methanol to afford the epoxide **24**. Reduction of the epoxide as well as azide in Compound **24** with LAH in dry THF afforded the corresponding amino alcohol, which was further protected with (Boc)$_2$O to give *N*-Boc derivative **25** in 88% yield. The treatment of compound **25** with allyl bromide and NaH in dry THF gave the N-allyl compound **26**. Ring-closing metathesis of **26** using Grubb's-I catalyst (5 mol%) in dry CH$_2$Cl$_2$ at room temperature gave the lactam **27**. Reduction of **27** using Pd-C/H$_2$ in EtOAc gave the compound **28** in quantitative yield. Finally, Boc protecting group in **28** was then deprotected by treatment with aq. phosphoric acid to give the target molecule (–)-sedridine **1**.

Scheme 3: Total synthesis of (–)-sedridine **1**

Reagents and conditions: (i) (a) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, -78 ^{o}C, 1 h; (b) Allyltributyl tin, (*S*)-BINOL, Ti(O^{i}Pr)$_4$, CH$_2$Cl$_2$, -20 ^{o}C, 92%, (two steps); (ii) TsCl, pyridine, 0 ^{o}C to rt, 16 h, 87%; (iii) NaN$_3$, DMF, 60 ^{o}C, 14 h, 86%; (iv) *p*TSA, MeOH, rt, 5 h, 96%; (v) TsCl, dibutyltin oxide, Et$_3$N, CH$_2$Cl$_2$, 0 ^{o}C to rt, 4 h, then K$_2$CO$_3$, MeOH, rt, 3 h; (vi) (a) LAH, THF, 0 ^{o}C to rt, 1 h; (b) 10% NaOH, (Boc)$_2$O, 0 ^{o}C to rt, 4 h, 88%; (vii) NaH, allyl bromide, THF, saturated aq. NH$_4$Cl, 0 ^{o}C to rt, 18 h, 92%; (viii) Grubb's-I catalyst, dry CH$_2$Cl$_2$, rt, 85%; (ix) 10% Pd-C/H$_2$, EtOAc, rt, 6 h, 84%; (x) aq. phosphoric acid, CH$_2$Cl$_2$, rt, 4 h, 86%.

4. Timothy Gallagher's approach:[10]

In 1996, Gallagher's *et al*. reported the synthesis of (+)-sedridine. Regiospecific alkylation of methyl acetoacetate with the *N*-protected 3-bromopropylamine **29** gave the **30** in 49% yield. Asymmetric reduction of *β*-ketoester **30** was achieved using King's method to give the (3*R*)-hydroxyester **31** in 92% yield. After removal of the *p*-methoxybenzyl (PMB) moiety from **31** followed by conversion of the methyl ester to the corresponding *β*-hydroxy ketone **32** was achieved in 3 steps with 63% overall yield. *Syn-*

selective reduction of ketone **32** gave the 1,3-diol **33**, which was converted to 1,3- cyclic sulfate **34** in usual way. Compound **34** was then treated with NaH followed by acidic hydrolysis and subsequent reductive cleavage of sulfonamide with Na/liquid NH$_3$, gave (+)-sedridine.

Scheme 4: Total synthesis of (+)-sedridine (**2**)

Reagents and conditions: (i) MeCOCH$_2$CO$_2$Me, NaH followed by *n*-BuLi, then **29**, 49%; (ii) [(*R*)-(BINAP)RuCl$_2$]$_2$.Et$_3$N, H$_2$ (200 psi), aq. HCl (cat), MeOH, 92%; (iii) CAN, CH$_3$CN/H$_2$O; (iv) LiCH$_2$SO$_2$Ph, THF; (v) *n*Bu$_3$SnH, AIBN, Toluene, 63% (three steps); (vi) Et$_2$BOMe, NaBH$_4$; (vii) SOCl$_2$, then RuCl$_3$, NaIO$_4$, 87%; (viii) NaH, THF then H$^+$; (ix) Na, liq. NH$_3$, 77% (two steps).

5. F A Davis's Approach:[11]

In 2003, Franklin A. Davis and co-workers reported the concise enantioselective synthesis of (+)-sedridine starting from enantiopure *N*-sulfinyl *β*-amino Weinreb amide. The requisite sulfinimine, (*S*)-(+)-*N*-(6-chloropentylidine)-*p*-toluene-sulfinamide **36**, was prepared by condensation of 5-chlorovaleroaldeyde with commercially available (*S*)-(+)-*p*-toluenesulfinamide **35** using Ti(OEt)$_4$ in 54% yield. Treatment of (+)-**36** with potassium enolate of *N*-methoxy-*N*-methylacetamide gave the corresponding *β*-amino Weinreb amide (*S*)-(+)-**37** in 76% yield. Reaction of the amide **37** with 5 equiv. of

MeMgBr in dry ether gave the methyl ketone (*S*)-(+)-**38** in 77% yield. Stereoselective reduction of amino ketone **38** with Super Hydride (LiEt₃BH) in DCM gave only the *anti-*product (2*R*,3*S*)-(+)-**39** in 71% yield. The acyclic 1,3-amino alcohol was then cyclized to hydroxy piperidines *anti*-(2*S*,3*S*)-(+)-**40** by stirring with NaH/THF in the presence of 30 mol% 18-crown-6 for 1 h. The *N*-sulfinyl group in **40a** was then oxidized to tosylate **40b** with *m*-CPBA. Reductive cleavage of the sulfonamides with Na/liquid NH₃, afforded the pure alkaloid in 70-84% yield.

Scheme 5: Total synthesis of (+)-sedridine

Reagents and conditions: (i) Cl-(CH₂)₄CHO, Ti(OEt)₄, 54%; (ii) Potassium enolate of *N*-methoxy-*N*-methyl acetamide, THF, 76%; (iii) CH₃MgBr, THF, 77%; (iv) LiEt₃BH, THF, 71%; (v) NaH, THF, 71%; (vi) *m*-CPBA, 75%; (vii) Na/Liq NH₃, 70-84%.

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CHAPTER II: SECTION B

Stereoselective Synthesis of (–)-Sedridine via Prins-Ritter reaction

2.2 SECTION B

Stereoselective synthesis of (–)-sedridine *via* Prins-Ritter reaction

Beyerman's and Schöpf's groups have independently reported the isolation of (–)-sedridine (**1**), an alkaloid consisting of a piperidine core from *Sedum acre* and they have also determined its absolute configuration.[1] Sedridine alkaloids were isolated from *sedum acre* and later it was obtained from other species also.[2] *Sedum acre* is a perennial flowering plant in the family Crassulaceae. It is a native of Europe, but also naturalized in North America, Japan and New Zealand. The juice of the leaves of this plant was found to be biologically potent with predominantly antibacterial and it was recommended in malarial fevers, and even in epilepsy.[3] As an ongoing project on the synthesis of biologically active natural products, we have initiated a programme on the stereoselective synthesis of (–)-sedridine.

(–)-Sedridine (**1**)

Figure 1

2.2.1 PRESENT WORK

In this context, we would like to report an efficient and stereoselective synthesis of optically active piperidine alkaloid (–)-sedridine (**1**) *via* Prins/Ritter amidation sequence. Our group has established a general route for the stereoselective synthesis of *anti*-1,3-aminoalcohol frameworks [4] attention was turned to prove its practicality and thus extended the method for the synthesis of a piperidine alkaloid, (–)-sedridine **1** as this alkaloid possesses *anti*-1,3-aminoalcohol core. We herein wish to report an elegant approach for the synthesis of (–)-sedridine *via* Prins/Ritter amidation sequence.

2.2.1.1 Retrosynthesis of 1

The retrosynthetic strategy followed in the present work for the synthesis of (–)-sedridine **1** is summarized in Scheme 1. As per our retrosynthetic analysis, (–)-sedridine could be synthesized from the intermediate **11**, which in turn could easily be prepared

through Prins/Ritter amidation followed by reductive opening of the 2-iodomethyl-4-amidotetrahydropyran **10**.

Scheme 1

2.2.1.2 Results and Discussion

The synthesis of chiral homoallylic alcohol **7** began with Jacobsen's hydrolytic kinetic resolution (HKR) of **3** epoxide.[5] The synthesis started from benzyl glycidyl ether **3** (Scheme 2). Jacobson resolution of **3** using (*S,S*)-(salen)Co(II) precatalyst, AcOH and H_2O (0.51 equiv) for 22 hours resulted in (*R*)-benzyl glycidyl ether **4**. Regioselective opening of epoxide **4** with vinylmagnesium bromide (formed by addition of vinyl bromide to Mg in THF) in the presence of CuCN gave homoallylic alcohol **5**. ^{1}H NMR spectrum of the compound **5** exhibited two multiplets due to olefinic protons at δ 5.91-5.75 and δ 5.17-5.05 integrating one and two protons respectively. Oxygen attached C-H signals were integrated for five protons confirming that the regioselection was in anticipated line. In addition, IR spectrum showed hydroxyl absorbtion at 3360 cm^{-1} and ESIMS showed (M+H) signal at *m/z* 193, further confirming the structure. Substrate **5** on treatment with lithium in liquid NH_3 underwent debenzylation to produce diol **6**. In ^{1}H NMR spectrum of **6**, disappearance of peaks due to benzyl group and presence of broad singlet due to hydroxyl protons at δ 2.92 integrating two protons confirmed the conversion. Chemoselective tosylation of the primary hydroxyl group in **6** with TsCl in the presence of dibutyltin oxide and triethyl amine gave the desired homoallylic alcohol

7.[6] In ^{1}H NMR spectrum of **7**, appearance of aromatic peaks at δ 7.78 and 7.34 as doublets and a singlet peak at δ 2.4, integrating for three protons confirmed the tosylation, furthermore HRMS showed the exact mass as 279.0659 confirmed the product.

Scheme 2

As shown in Scheme 3, Three-component, one-pot coupling of homoallyl alcohol **7** with acetaldehyde and acrylonitrile in presence of 10 mol% $BF_3.Et_2O$ under Prins/Ritter reaction conditions gave the 4-amidotetrahydropyran **8** with high diastereoselectivity.[7] In ^{1}H NMR spectrum of **8**, appearance of peak at 5.55 as broad doublet corresponds to amide –NH and 2.47 as singlet corresponds to methyl group in tosyl functionality confirmed the product, in IR spectrum weak absorbance at 3389 cm^{-1} due to –NH, further more HRMS spectrum gave the exact mass as 376.11826 confirmed the product **8** formation.

Scheme 3

Energy minimized structure of 9 along with the characteristic NOEs

Furthermore the structure and stereochemistry of compound **9** was derived by extensive NMR experiments including 2-D Nuclear Overhauser Effect spectroscopy (NOESY) and Double Quantum Filtered Correlation Spectroscopy (DQFCOSY). From

the one dimensional ^{1}H NMR experiments, the coupling constants involving the six membered ring, $^3J_{\text{H2-H3(}pro\text{-}S)} = 2.0$, $^3J_{\text{H2-H3(}pro\text{-}R)} = 11.5$, $^3J_{\text{H3(}pro\text{-}S)\text{-H4}} = 4.0$, $^3J_{\text{H3(}pro\text{-}S)\text{-H3(}pro\text{-}R)} = 12.0$, $^3J_{\text{H3(}pro\text{-}R)\text{-H4}} = 12.0$, $^3J_{\text{H4-H5(}pro\text{-}S)} = 12.0$, $^3J_{\text{H4-H5(}pro\text{-}R)} = 4.0$, $^3J_{\text{H5(}pro\text{-}S)\text{-H5(}pro\text{-}R)} = 12.0$, $^3J_{\text{H5(}pro\text{-}S)\text{-H6}} = 11.2$, $^3J_{\text{H5(}pro\text{-}R)\text{-H6}} = 2.0$Hz were obtained. The large values of $^3J_{\text{H2-H3(}pro\text{-}R)}$, $^3J_{\text{H3(}pro\text{-}R)\text{-H4,}}$ $^3J_{\text{H4-H5(}pro\text{-}S}$and $^3J_{\text{H5(}pro\text{-}S)\text{-H6}}$ clearly indicate their diaxial disposition. The characteristic NOE correlations H2/H4, H2/H6, H4/H6 and H3(*pro-R*)/H5(*pro-S*) strongly the above findings and are consistent with $^4C_1$ chair conformation of the six-membered ring. In addition $^3J_{\text{H4-H7}} = 8.2$Hz and NOE correlations, H3(*pro-R*)/H7 and H5(*pro-S*)/H7 support an *anti-* conformation of H4 and H7. The energy minimized structure (Figure 2 and 3) adequately supports the proposed structure.

Figure 2: Energy minimized structure of compound **9**
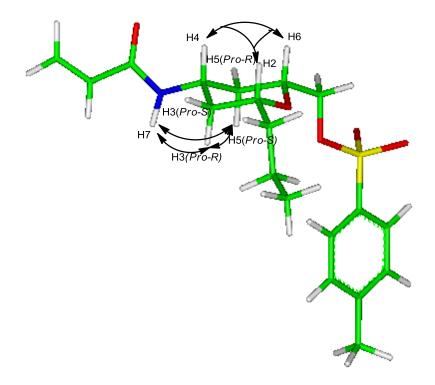
Figure 3: Energy minimized structure of **9** along with the characteristic NOEs.

As shown in Scheme 4, compound **8** was then converted into the corresponding iodomethyl tetrahydropyran **10** using NaI in acetone under reflux conditions. Disappearance of tosyl group signals and presence of other required signals in ^{1}H NMR spectrum characterized the compound **10**. It was further supported by HRMS, which showed (M+H) peak at *m/z* 310.02985. Reductive ring opening of **10** with Zn dust in refluxing EtOH furnished open chain intermediate **11** with the required *anti*-1,3-aminoalcohol system.[4] Appearance of characteristic terminal olefinic proton signals at δ 5.78-5.66 and δ 5.10- 5.02 integrating for one and two protons respectively along with other required signals in ^{1}H NMR spectrum and a strong absorption at 3280 cm^{-1} in IR spectrum confirmed the structure of **11**.

Scheme 4

Having succeeded in achieving the key intermediate **11** with required stereochemistry for the synthesis of (−)-sedridine, the free hydroxyl group of **11** was then protected as its *tert*-butyldimethylsilyl (TBS) ether **12** using TBS chloride, imidazole and DMAP in CH_2Cl_2 (Scheme 5). Appearance of peaks in ^1H NMR spectrum at δ 0.08 integrating to 6 protons and ^{13}C NMR spectrum showed peaks at δ -4.7, -4.2 confirmed the TBS protection, further more HRMS gave the exact mass as $C_{16}H_{31}O_2NNaSi$: 320.18535 confirmed the formation of compound **12**. Compound **12** was then subjected to ring closing metathesis using Grubb's-I catalyst (10 mol%) in DCM to furnish the *α,β*-unsaturated-*δ*-lactam **13**.[8] ^1H NMR spectrum of the compound **13** gave peaks at δ 6.59-6.50 integrated to one proton as multiplet and a doublet peak at δ 5.87 with a coupling constant *J* = 9.6 Hz, confirmed the ring closing and formation of compound **13**. Furthermore HRMS for compound **13** gave exact mass as $C_{14}H_{28}O_2NSi$: 270.18838, found: 270.18781, confirmed the product formation.

Scheme 5

As shown in Scheme 6, the RCM Product **13** was subjected to hydrogenation to reduce the olefinic unsaturation using palladium on carbon in methanol gave the *δ*-lactam **14**. In ^1H NMR spectrum of the compound **14** disappearance of peaks corresponds to olefin confirmed the formation of **14.** Furthermore the HRMS spectrum of compound **14** gave the exact mass as $C_{14}H_{20}O_2NSi$: 272.20403, found: 272.20339. After establishing compound **14** formation, deprotection of silyl ether in compound **14** with TBAF in THF gave the desilylated *δ*-lactam **15**. Disappearance of peaks corresponds to silyl group in ^1H NMR spectrum of the compound **15** confirmed the formation. Furthermore, HRMS spectrum of compound **15** gave the exact mass as $C_8H_{16}NO_2$: 158.11756, found: 158.11710 confirms its formation.

Scheme 6

Finally, the reduction of δ-lactam **15** with LAH in refluxing Et_2O gave the target molecule, (–)-sedridine **1** (Scheme 12). The data of synthetic (–)-sedridine **1** was in good agreement with the data reported in literature.[9]

Scheme 12

2.2.2 Conclusion:

In conclusion, a simple and efficient strategy has been developed for the total synthesis of piperidine alkaloid, (–)-sedridine (**1**) in a highly stereoselective manner. Our approach involves mainly the use of Prins/Ritter amidation reaction followed by reductive ring opening sequence. It is a modular approach, which can be employed for the synthesis of other piperidine alkaloids.

2.3 EXPERIMENTAL SECTION

(2*R*)-2-[(benzyloxy)methyl]oxirane (4).

To the (*S*,*S*)-(salen)Co(II) precatalyst (101 mg, 0.167 mmol, 0.5 mol%) in a flask was charged sequentially with (±)-benzyl glycidyl ether **3** (5.50 g, 33.50 mmol) and AcOH (38 μL, 0.67 mmol). After the reaction mixture turned from a red suspension to a dark brown solution, the flask was cooled to 0 °C and THF (0.25 mL) followed by H_2O (330 μL, 18.42 mmol, 0.55 equiv) were added. The reaction mixture was allowed to warm to room temperature over 2 h and stir for an additional 20 h. Distillation of the

reaction mixture under *vacuo* (75 °C, 11 mm Hg) gave unreacted (*R*)-benzyl glycidyl ether **4** R_f = 0.6 (SiO$_2$, 20% EtOAc in hexane).

Yield	:	2.5 g, 45%
Molecular formula	:	$C_{10}H_{12}O_2$
Physical State	:	colorless oil
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.38-7.27 (m, 5H), 4.59 (dd, *J* = 11.9, 27.9 Hz, 2H), 3.77 (dd, *J* = 11.4, 3.05 Hz, 1H), 3.44 (dd, *J* = 5.8, 11.2 Hz, 1H), 3.19 (m, 1H), 2.80 (t, *J* = 4.6 Hz, 1H), 2.62 (dd, *J* = 4.9, 2.6 Hz, 1H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 137.8, 128.4, 127.7, 73.3, 70.8, 50.8, 44.3.
$[\alpha]_D^{25}$	:	−5.2 (*c* 2.0, CHCl$_3$).
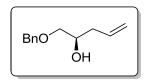
(2*R*)-1-benzyloxy)pent-4-en-2-ol (5):

To the magnesium (360 mg, 15.0 mmol) in dry THF (10 mL) at room temperature was sequentially added 1,2-dibromoethane (2 drops) and freshly prepared vinyl bromide (1.05 mL, 15.0 mmol) in a drop wise manner. CuCN (67 mg, 5 mol%) was added after allowing the reaction mixture to stir for 0.5 h. Then the mixture was cooled to –78 °C and added epoxide **4** (2.46 g, 15.0 mmol) in THF (15 mL) and warmed the mixture to –40 °C and stirred for 4 h. Quenched with saturated NH$_4$Cl solution (15 mL) and extracted with EtOAc (3 x 15 mL). Combined organic layers were washed with brine (20 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by column chromatography afforded **5** as a colorless liquid. R_f = 0.45 (SiO$_2$, 20% EtOAc in hexane).

Yield	:	2.65 g, 92%

Molecular formula	:	$C_{12}H_{16}O_2$
Physical State	:	colorless liquid
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.40-7.27 (m, 5H), 5.91-5.75 (m, 1H), 5.17-5.05 (m, 2H), 4.56 (s, 2H), 3.94-3.83 (m, 1H), 3.52 (dd, J = 9.4, 3.4 Hz, 1H), 3.38 (dd, J = 7.36, 9.4 Hz, 1H), 2.27 (t, J = 6.7 Hz, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 137.8, 134.1, 128.4, 127.6, 117.5, 73.8, 73.3, 69.6, 37.8.
IR (KBr)	:	v_{max} 3360, 3021, 1637, 1494, 1450 cm^{-1}
$[\alpha]_D^{25}$	:	− 2.32 (c = 1.2, CHCl$_3$)
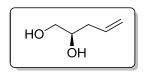
(*R*)-pent-4-ene-1,2-diol (6):

To a solution of lithium (474 mg, 67.5 mmol) in liquid NH$_3$ (25 ml) was added compound **5** (2.60 g, 13.5 mmol) in dry THF (8 ml). The mixture was stirred for 20 min and quenched with solid NH$_4$Cl (4.0 g) was added. Ammonia was allowed to evaporate and to the residual mixture was added ether and filtered through Celite. The filtrate was dried over Na$_2$SO$_4$. Removal of the solvent and purification by column chromatography of the crude product afforded alcohol **6**. R_f = 0.25 (SiO$_2$, 80% EtOAc in hexane).

Yield	:	1.10 g, 80 %
Molecular formula	:	$C_5H_{10}O_2$
Physical State	:	Colorless oil
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 5.91-5.75 (m, 1H), 5.20-5.09 (m, 2H), 3.83-3.60 (m, 2H), 3.47 (dd, J = 11.3, 7.4 Hz, 1H), 2.92 (brs, 2H), 2.28-2.20 (m, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 157.7, 134.6, 134.0, 129.2, 118.1, 113.7, 69.8, 55.1, 42.0, 38.6, 31.0.
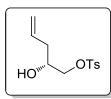
IR (KBr)   : ν_{max} 3388, 2927, 1645, 1440, 1075 cm^{-1}

$[\alpha]_D^{25}$:   + 3.6 (c = 2.8, CHCl$_3$)

(*R*)-2-Hydroxypent-4-enyl-4-methylbenzenesulfonate (7):

      To a stirred solution of **6** (1.08 g, 10.6 mmol) in CH$_2$Cl$_2$ (50 mL) were added triethylamine (2.23 mL, 16 mmol) and dibutyltinoxide (54 mg, 0.21 mmol). After 15 min continuous stirring, tosyl chloride (2.02 g, 10.6 mmol) was added to this mixture, and the resulting solution was stirred at 25 ^{o}C for 50 min. After completion, the reaction was quenched with water (15 mL) and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water (2 × 20 mL) followed by brine solution (2 × 20 mL). The organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in *vacuo*. The resulting crude product was purified by silica gel column chromatography using hexane:EtOAc (9:1) as eluent to give the monotosylated homoallyl alcohol **7**.

Yield   :   2.66 gm, 98%

Molecular formula   :   C$_{12}$H$_{16}$O$_4$S

Physical State   :   Pale yellow oil

^{1}H-NMR (CDCl$_3$, 300 MHz)   :   δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.79-5.70 (m, 1H), 5.13-5.07 (m, 2H), 4.01 (dd, *J* = 3.0, 9.8 Hz, 1H), 3.93-3.83 (m, 2H), 2.47 (s, 3H), 2.30-2.20 (m, 2H).

^{13}C-NMR (CDCl$_3$, 75 MHz)   :   δ 144.9, 132.8, 129.8, 127.8, 118.6, 72.9, 68.4, 37.3, 21.5.

HRMS (ESI)   Calculated for C$_{12}$H$_{16}$O$_4$NaS: 279.0661, found: 279.0659.
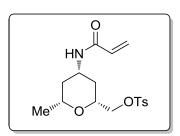
IR (KBr)	:	ν_{max} 3449, 3072, 2928, 1642, 1598, 1494, 1451, 1400, 1355, 1173, 1097, 983, 817, 669 cm^{-1}
$[\alpha]_D^{25}$	:	-7.2 (c = 1.0, CHCl$_3$)

((2*R*,4*S*,6*R*)-4-Acrylamido-6-methyl-tetrahydro-2H-pyran-2-yl)methyl-4-methylbenzenesulfonate (8):

To a mixture of acetaldehyde (0.66 ml, 11.7 mmol) and homoallyl alcohol **7** (2.0 g, 7.8 mmol) in acrylonitrile (20.0 mL) was added boron trifluoride etherate (0.02 mL, 0.12 mmol) slowly at 0°C. The resulting mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with sat. NaHCO$_3$ solution and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography to afford the compound **8** R$_f$ = 0.3 (SiO$_2$, 30% EtOAc in hexane) as brown solid.

Yield	:	1.5 g, 54%
Molecular formula	:	C$_{12}$H$_{16}$O$_4$S
Physical State	:	Brown solid, m.p 82-84 °C
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.3-6.22 (m, 1H), 6.08-5.95 (m, 1H), 5.68-5.60 (m, 1H), 5.55 (d, *J* = 7.9 Hz, 1H), 4.15-3.9 (m, 3H), 3.67-3.43 (m, 2H), 2.47 (s, 3H), 2.0-1.88 (m, 2H), 1.32-1.21 (dd, *J* = 7.1, 10.4 Hz, 2H), 1.14 (d, *J* = 6.0 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 164.9, 144.8, 132.7, 130.6, 129.7, 127.9, 126.6,

73.1, 72.4, 71.9, 45.6, 39.2, 33.3, 21.5, 21.3.

HRMS (ESI)	Calculated for $C_{17}H_{23}O_5NNaS$: 376.11891, found: 376.11826.
IR (KBr)	: ν_{max} 3449, 3072, 2928, 1642, 1598, 1494, 1451, 1400, 1355, 1173, 1097, 983, 817, 669 cm^{-1}
$[\alpha]_D^{25}$	: -7.2 (c = 1.0, CHCl$_3$)

N-((2R,4S,6R)-2-(Iodomethyl)-6-methyl-tetrahydro-2H-pyran-4-yl)acrylamide (10):

A mixture of **8** (1.5 g, 4.25 mmol) and NaI (3.2 g, 21.25 mmol) in 30 mL of acetone was stirred under reflux for 24 h. After completion, the solvent was removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate and dried over Na$_2$SO$_4$. Removal of the solvent followed by purification on silica gel column chromatography gave the compound **10** as a white solid. R$_f$ = 0.3 (SiO$_2$, 30% EtOAc in hexane).

Yield	: 1.17 g, 90%
Molecular formula	: $C_{10}H_{16}INO_2$
Physical State	: White solid. m.p. 87-89 ^{o}C
^{1}H-NMR (CDCl$_3$, 300 MHz)	: δ 6.34-6.22 (m, 1H), 6.08-5.92 (m, 1H), 5.70-5.60 (m, 1H), 5.33 (d, J = 6.8 Hz, 1H), 4.21-4.04 (m, 1H), 3.67-3.57 (m, 1H), 3.44-3.34 (m, 1H), 3.18 (d, J = 5.3 Hz, 2H), 2.23-2.15 (m, 1H), 2.0-1.90 (m, 1H), 1.24 (d, J = 6.0 Hz, 3H), 1.07 (dd, J = 2.6, 12.1 Hz, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	: δ 164.7, 130.7, 126.7, 74.9, 72.6, 45.8, 39.4, 37.7, 21.5, 9.0.

HRMS (ESI)	Calculated for $C_{10}H_{17}O_2NI$ 310.02894, found: 310.02985.
IR (KBr)	: ν_{max} 3352, 2925, 2855, 1642, 1598, 1494, 1451, 1355, 1240, 1173, 1097, 950, 817, 669 cm^{-1}
$[\alpha]_D^{25}$	: $- 25.5$ (c = 1.5, CHCl$_3$)
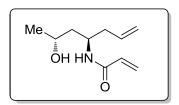
N-((4*R*,6*R*)-6-Hydroxyhept-1-en-4-yl)acrylamide (11):

A mixture of iodide **10** (1.5 g, 3.72 mmol) and zinc dust (3.65 g, 55.8 mmol) in ethanol (30 mL) was stirred under reflux for 8 h. After completion, it was quenched with solid ammonium chloride (6 g) and diluted with ether (90 mL). The resulting mixture was stirred for 15 min to form a gray suspension which was then filtered through Celite. The filtrate was concentrated in vacuo and then purified by flash chromatography to give the compound **11** as a colorless liquid. R$_f$ = 0.4 (SiO$_2$, 30% EtOAc in hexane).

Yield	: 612 mg, 90%
Molecular formula	: $C_{10}H_{17}NO_2$
Physical State	: colorless liquid
^{1}H-NMR (CDCl$_3$, 300 MHz)	: δ 6.26-6.20 (m, 1H), 6.08-6.0 (m, 1H), 5.78-5.66 (m, 2H), 5.64-5.59 (m, 1H), 5.10-5.02 (m, 2H), 4.21 (brd, 1H), 3.70-3.63 (m, 1H), 3.54-3.44 (m, 1H), 2.30-2.18 (m, 2H), 1.56-1.50 (m, 1H), 1.39-1.32 (m, 1H), 1.11 (d, J = 6.2 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	: δ 166.5, 133.9, 130.2, 127.3, 118.4, 63.4, 46.0, 45.0, 39.4, 22.6.
HRMS (ESI)	: Calculated for $C_{10}H_{18}O_2N$: 184.13321, found: 184.13344.

93
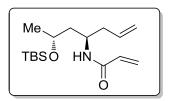
IR (KBr)	:	ν_{max} 3280, 2924, 2853, 1657, 1545, 1440, 1409, 1317, 1149, 1067, 987, 802, 707 cm^{-1}
$[\alpha]_D^{25}$	:	$-$ 12.9 (c = 1.1, CHCl$_3$)

N-((4*R*,6*R*)-6-(tert-Butyldimethylsilyloxy)hept-1-en-4-yl)acrylamide (12):

To a stirred solution of **11** (625 mg, 3.4 mmol) in DCM (15 mL) were added imidazole (0.65 g, 9.4 mmol), TBSCl (1.06 g, 7.0 mmol) and catalytic amount of DMAP at 0 °C. The resulting solution was stirred at room temperature for 1 h. After completion, the mixture was quenched with sat. NH$_4$Cl (10 mL) and the organic layer was extracted with DCM, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane:EtOAc 7:3) to afford the compound **12** as a pale yellow oil. R$_f$ = 0.7 (EtOAc:hexane, 30%).

Yield	:	960 mg, 95%
Molecular formula	:	C$_{16}$H$_{31}$NO$_2$Si
Physical State	:	pale yellow oil
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 6.30-6.19 (m, 1H), 6.09-5.92 (m, 2H), 5.83-5.67 (m, 2H), 5.62-5.54 (m, 1H), 5.11-5.01 (m, 2H), 4.18-3.98 (m, 2H), 2.46-2.21 (m, 2H), 1.72-1.53 (m, 2H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.92 (s, 9H), 0.08 (d, *J* = 3.7 Hz, 6H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 164.8, 134.5, 131.2, 125.9, 117.5, 66.6, 46.8, 41.8, 38.7, 25.9, 23.6, 17.9, -4.7, -4.2.
HRMS (ESI)	:	Calculated for C$_{16}$H$_{31}$O$_2$NNaSi: 320.18598, found: 320.18535.
IR (KBr)	:	ν_{max} 3275, 3078, 2955, 1625, 1549, 1460, 1317,
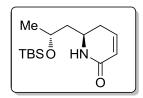
1247, 1061, 911, 842, 665 cm^{-1}

$[\alpha]_D^{25}$: -8.5 (c = 1.1, CHCl$_3$)

(*R*)-6-((*R*)-2-(tert-Butyldimethylsilyloxy)propyl)-5,6-dihydropyridin-2(1*H*)-one (13):

To a stirred solution of **12** (0.950 g, 3.2 mmol) in degassed CH$_2$Cl$_2$ (500 mL) was added bis(tricyclohexylphosphine)benzylideneruthenium dichloride (250 mg, 0.3 mmol) at room temperature under argon atmosphere. The resulting mixture was stirred for 12 h at room temperature and then the solvent was evaporated under reduced pressure. Thus residue was purified by silica gel column chromatography (EtOAc/Hexane = 3.5:6.5) to afford the compound **13** as a colorless semi-solid.

Yield	:	775 mg, 90%
Molecular formula	:	C$_{14}$H$_{27}$NO$_2$Si
Physical State	:	colorless semi-solid
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 6.59-6.50 (m, 1H), 6.34 (brs, 1H), 5.87 (d, *J* = 9.6 Hz, 1H), 4.13-4.06 (m, 1H), 3.90-3.80 (m, 1H), 2.31-2.10 (m, 2H), 1.83-1.71 (m, 1H), 1.56-1.49 (m, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.09 (d, *J* = 3.4 Hz, 6H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 165.9, 140.3, 124.6, 66.3, 47.5, 43.3, 30.8, 25.7, 22.7, 17.9, -5.0, -4.5.
HRMS (ESI)	:	Calculated for C$_{14}$H$_{28}$O$_2$NSi: 270.18838, found: 270.18781.
IR (KBr)	:	ν$_{max}$ 3338, 2965, 2928, 1669, 1604, 1456, 1372, 1304, 1140, 950, 810, 640 cm^{-1}
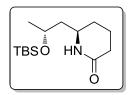
$[\alpha]_D^{25}$: -19.8 (c = 0.97, $CHCl_3$)

(*R*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)propyl)piperidin-2-one (14):

To a stirred solution of **13** (0.8 g, 2.97 mmol) in MeOH (15 mL) at room temperature were added a catalytic amount of Pd/C and triethylamine (0.008 mL, 0.06 mmol). The resulting mixture was stirred under H_2 atmosphere. The progress of the reaction was monitored by TLC. After completion, the mixture was filtered through a pad of celite and the solvent was evaporated to give the product **14** as a pale yellow liquid. R_f = 0.3 (SiO_2, 40% EtOAc in hexane).

Yield	:	760 mg, 95%
Molecular formula	:	$C_{14}H_{29}NO_2Si$
Physical State	:	pale yellow liquid
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 6.58 (brd, 1H), 4.13-4.05 (m, H), 3.67-3.58 (m, 1H), 2.40-2.30 (m, 1H), 2.28-2.19 (m, 1H), 1.93-1.34 (m, 6H), 1.20 (d, J = 5.9 Hz, 3H), 0.9 (s, 9H), 0.09 (d, J = 3.9 Hz, 6H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 172.0, 66.2, 49.5, 45.0, 30.9, 29.5, 25.7, 23.0, 19.9, -4.9, -4.5.
HRMS (ESI)	:	Calculated for $C_{14}H_{20}O_2NSi$: 272.20403, found: 272.20339.
IR (KBr)	:	ν_{max} 3210, 2935, 1669, 1558, 1413, 1261, 1082, 841 cm^{-1}
$[\alpha]_D^{25}$	:	-13.6 (c = 1.0, $CHCl_3$)

(*R*)-6-((*R*)-2-Hydroxypropyl)piperidin-2-one (15):

To a stirred solution of **14** (0.75 g, 2.76 mmol) in anhydrous THF (25 mL) was added TBAF (4.15 mL, 1.0 M in THF) at 0 °C. After 15 min, the mixture was brought to room temperature and then stirred it for another 5 h. After completion of the reaction, it was quenched by addition of sat. NH_4Cl (6 mL) solution, extracted with ethyl acetate (2 x 40 mL), washed with brine and dried over anhydrous Na_2SO_4. After removing the solvent, the product was purified by column chromatography to afford the pure lactam **15** as a pale yellow liquid. R_f = 0.7 (SiO_2, 5% MeOH in DCM).

Yield	:	410 mg, 95%
Molecular formula	:	$C_{14}H_{29}NO_2Si$
Physical State	:	pale yellow liquid
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 4.14-4.04 (m, 1H), 3.75- 3.67 (m, 1H), 2.39-2.20 (m, 2H), 1.95-1.35 (m, 6H), 1.24 (d, *J* = 5.9 Hz, 2H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 172.7, 64.2, 49.2, 44.2, 31.0, 29.0, 23.9, 23.3
IR (Neat)	:	v_{max} 3450, 3385, 2952, 1657, 1456, 1304, 1093, 1025, 764 cm^{-1}.
HRMS (ESI)	:	Calculated for $C_8H_{16}NO_2$: 158.11756, found: 158.11710.
$[\alpha]_D^{25}$	:	− 15.0 (c = 0.25, CHCl$_3$)

(–)-Sedridine (1)

To a stirred solution of lactam **15** (0.4 g, 2.54 mmol) in 15 mL of anhydrous ether was added lithium aluminum hydride (0.115 g, 3.0 mmol) slowly and the stirring was continued under reflux for 2 h. After completion, the reaction was quenched with 14 mL of 10% NaOH solution and then extracted with ethyl acetate (3 x 40 mL). The combined

organic layers were dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (91% CH_2Cl_2, 7.6% MeOH, 1.4% NH_4OH) to afford the (−)-sedridine (**1**).

Yield	:	0.27 g, 76%
Molecular formula	:	$C_8H_{17}ON$
Physical State	:	White solid; m.p 78-80 ^{o}C.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 5.68 (brd, 1H), 4.2-4.07 (m, 1H), 3.38-3.06 (m, 2H), 2.70 (td, J = 3.7, 12.8 Hz, 1H), 1.80-1.55 (m, 6H), 1.53-1.40 (m, 2H), 1.2 (d, J = 6.0 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 63.4, 54.3, 44.9, 41.9, 29.6 (2C), 23.3 (2C).
IR (Neat)	:	ν_{max} 3270, 2926, 2854, 1569, 1458, 1406, 1378, 1053, 940, 770, 652 cm^{-1}
HRMS (ESI)	:	Calculated for $C_8H_{18}ON$: 144.13829, found: 144.13798.
$[\alpha]_D^{25}$	:	−24.2 (c = 1.0, EtOH); reported $[\alpha]_D^{25}$ = −25.6 (c = 0.95, EtOH).

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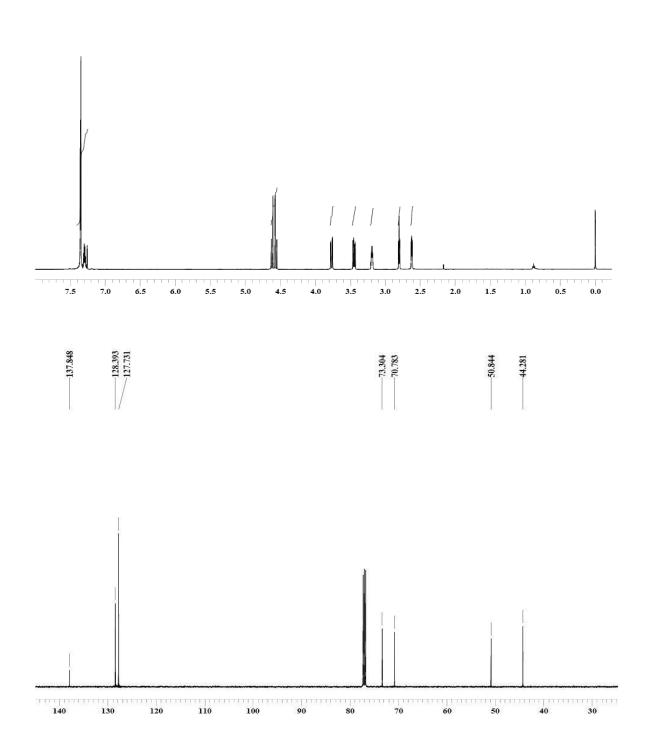
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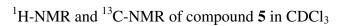
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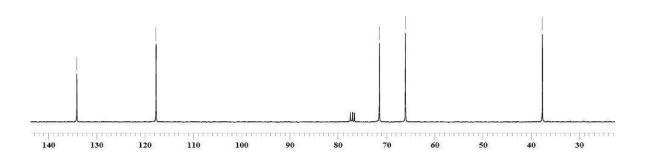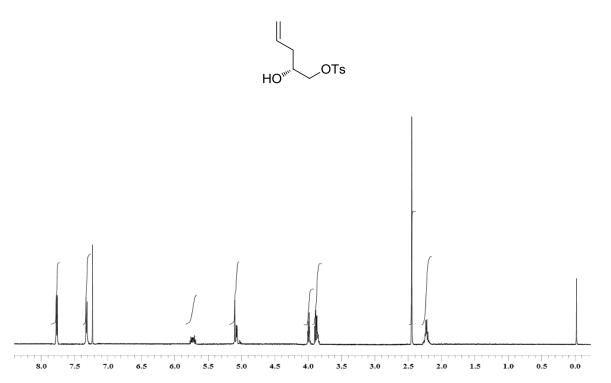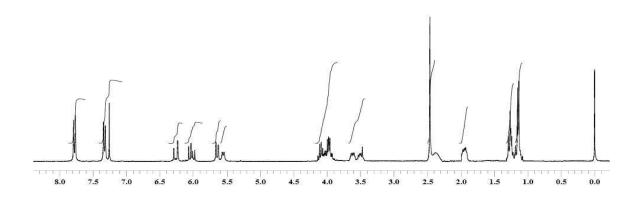
SPECTRA
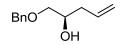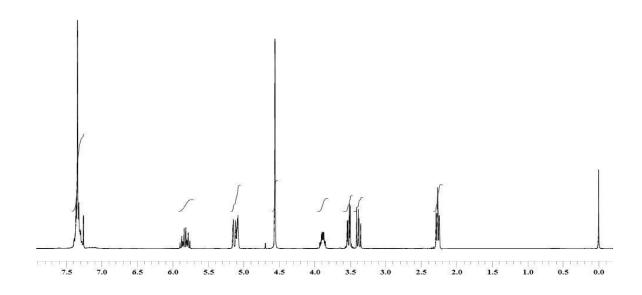
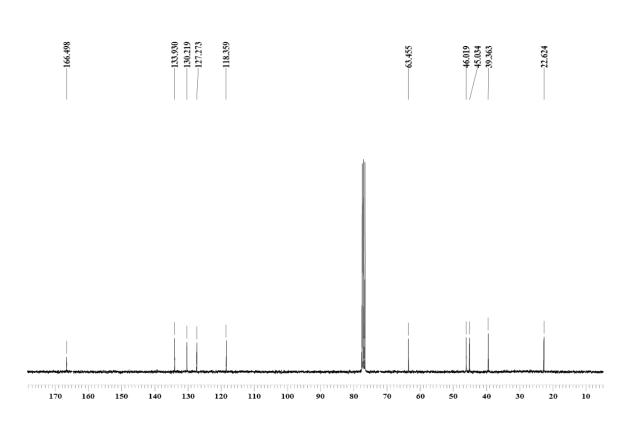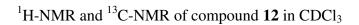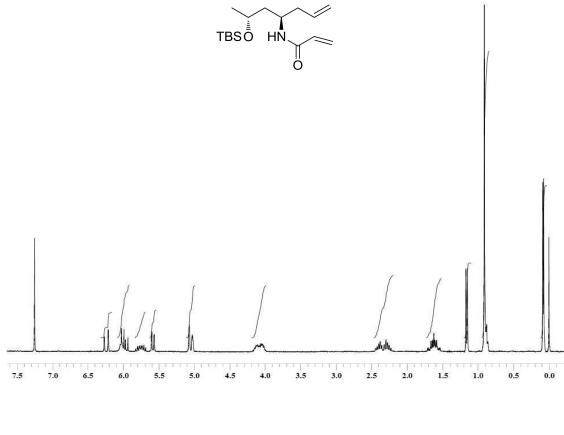# ^{1}H-NMR and ^{13}C-NMR of compound **4** in CDCl$_3$

BnO⌃◁O

^{1}H-NMR spectrum with axis labeled from 7.5 to 0.0 ppm

13C-NMR peak labels: 137.848, 128.393, 127.731, 73.304, 70.783, 50.844, 44.281
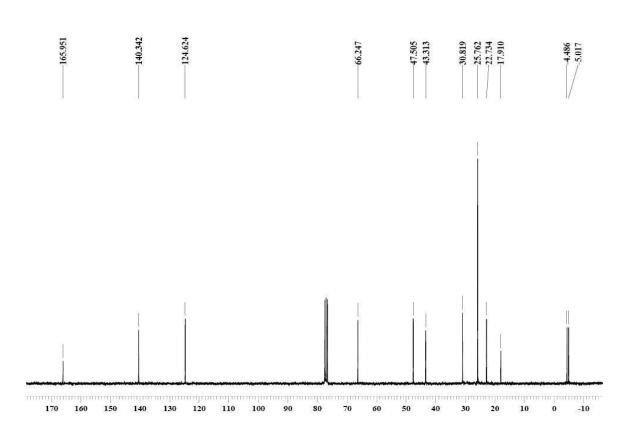

^{13}C-NMR spectrum with axis labeled from 140 to 30 ppm

^{1}H-NMR and ^{13}C-NMR of compound **5** in CDCl$_3$

BnO

OH

^{1}H-NMR and ^{13}C-NMR of compound **6** in CDCl$_3$

134.084

117.685

71.425
66.023

37.660
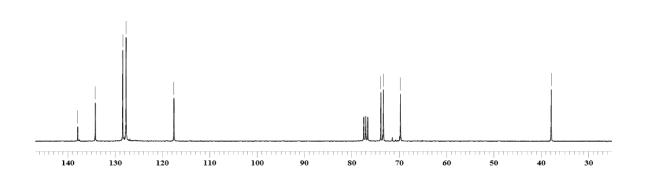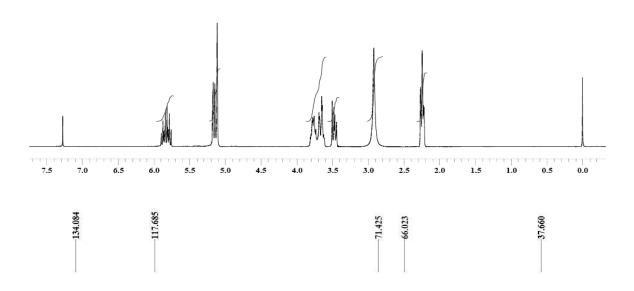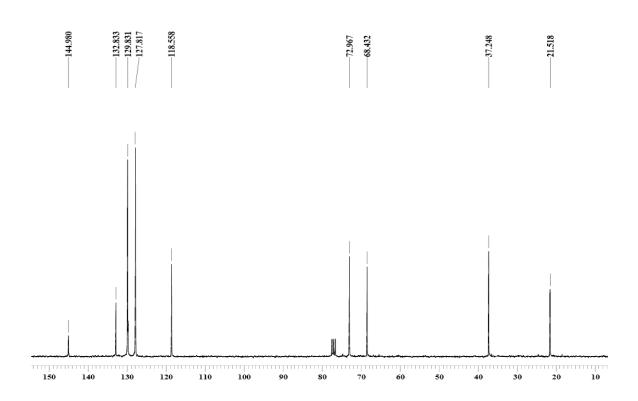
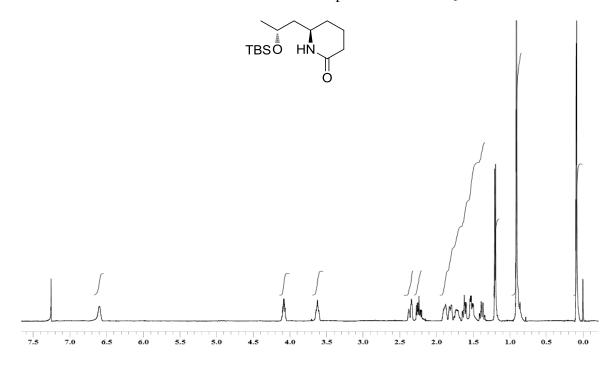# ^{1}H-NMR and ^{13}C-NMR of compound 7 in CDCl$_3$
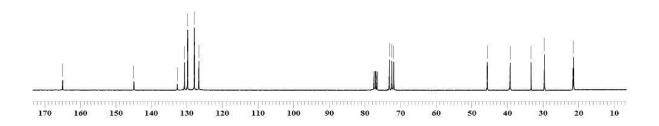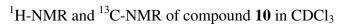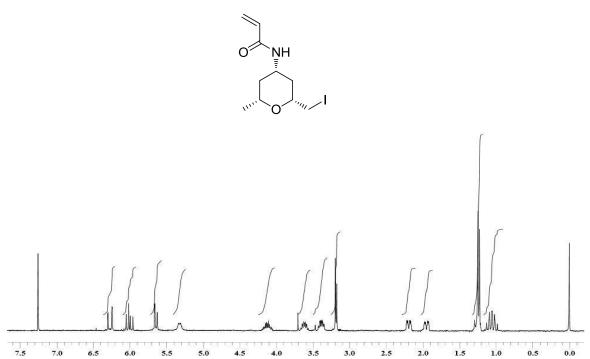
^{1}H-NMR and ^{13}C-NMR of compound **8** in CDCl$_3$

164.860

144.849

132.638
130.675
129.756
127.875
126.615

73.129
72.429
71.877

45.615

39.195

33.321
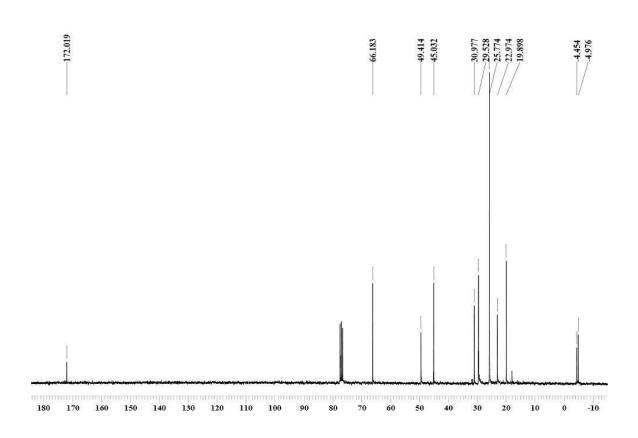29.589

21.350

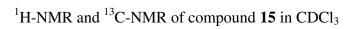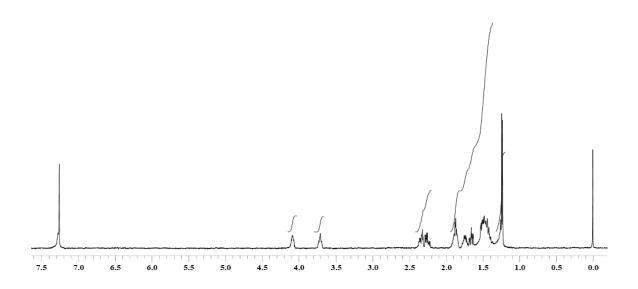# ^{1}H-NMR and ^{13}C-NMR of compound **10** in CDCl$_3$
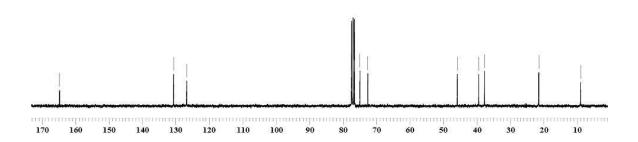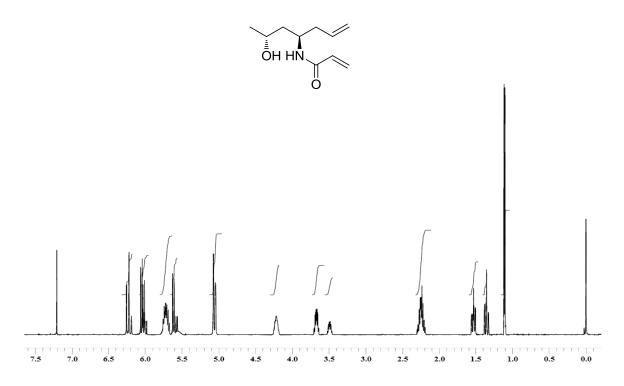
¹H-NMR and ¹³C-NMR of compound **11** in CDCl₃
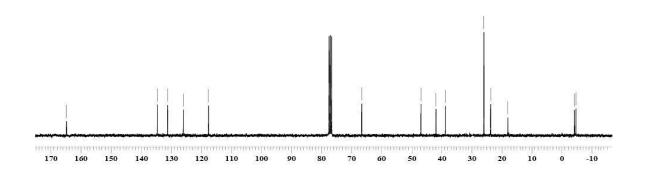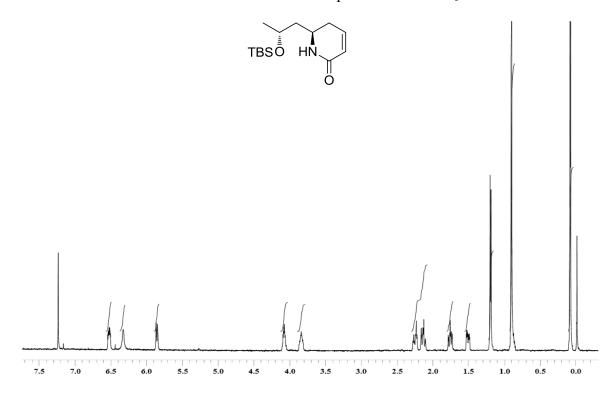
^{1}H-NMR and ^{13}C-NMR of compound 12 in CDCl$_3$

^{1}H-NMR spectrum with chemical shift axis from 7.5 to 0.0 ppm.

^{13}C-NMR peaks: 164.811, 134.575, 131.186, 125.920, 117.508, 66.576, 46.871, 41.864, 38.756, 25.905, 23.677, 17.961, -4.229, -4.711

^{13}C-NMR spectrum with chemical shift axis from 170 to -10 ppm.

^{1}H-NMR and ^{13}C-NMR of compound **13** in CDCl$_3$

^{1}H-NMR and ^{13}C-NMR of compound **14** in CDCl$_3$

^{1}H-NMR spectrum

^{13}C-NMR spectrum

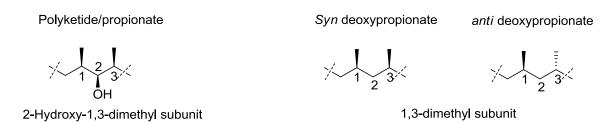# ^{1}H-NMR and ^{13}C-NMR of compound **1** in CDCl$_3$

(–)-Sedridine **1**
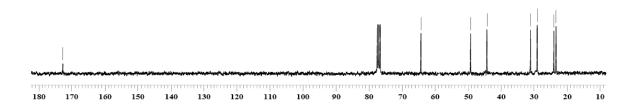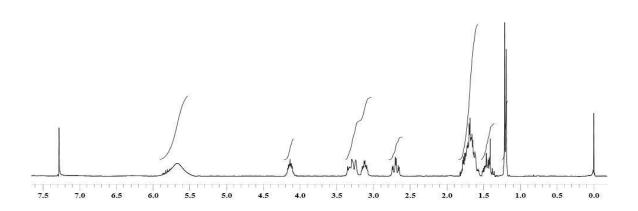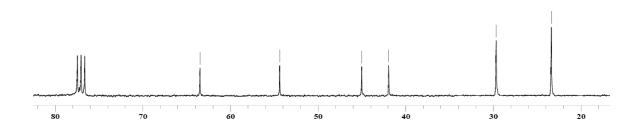
CHAPTER III: SECTION A

Introduction and previous approaches for the syntheses of Siphonarienal and Siphonarienone

3.1 INTRODUCTION:

Marine natural products derived from polyketides and polypropionates have attracted a considerable attention during the last 50 years and a great deal of research has concerned itself with their isolation, biological activity, biogenesis and total synthesis.[1] Polypropionate subunits are aliphatic chains bearing alternating hydroxyl and methyl groups with distinct stereochemistry. Nature sometimes deviates from the polypropionate pattern by removing the hydroxyl group from its structure resulting *syn* or *anti* 1,3,5,..... *n*-polymethyl alkyl chains (Figure **1**). They are termed as deoxypropionates which are basically enzymatically dehydrated, reduced products of polypropionates and are widely distributed as individual and combined structures in natural products.

Polyketide/propionate   *Syn* deoxypropionate   *anti* deoxypropionate

2-Hydroxy-1,3-dimethyl subunit   1,3-dimethyl subunit

Figure1: The polyketide/propionate structure compared to the related deoxypropionate structure

Polyketides containing deoxypropionate units are synthesized by bacteria, fungi, and plants (Figure **2**).[2] Many naturally occurring deoxypolypropionates have been isolated and a broad range of fascinating biological activities are associated with these deoxypropionates. Different structural deoxypropionates have been reported so far e.g.; siphonarienal (**1**), siphonarienone (**2**), pectinatone, lardolure,[3] waxes: 4,6,10,16,18-hexamethyldocosane,[4] borrelidin,[5] doliculide,[6] calcium ionophores: ionomycin,[7] siphonarienolone,[8] TMC-151A,[9] (+)-Vittatalactone, 10-Norvittatalactone and virulent markers: PDIM A.[10]

Figure 2: Example of naturally occurring deoxypropionates

A wide variety of synthetic methods for the construction of polypropionates has been described over last decades, especially the aldol condensation based on chiral auxiliary, developed by Evans and others. This strategy contributed to a large extent to the synthesis of polypropionates. Many synthetic strategies have also been developed for deoxypropionate units because of its abundant presence in natural products.[11] These strategies are often based on the selective introduction of methyl subunits in a consecutive (iterative) fashion, either *syn* or *anti*, and can be divided into two catagories: non-catalytic and catalytic pathways.

Marine molluscs of the genus *Siphonaria* is the rich source of polypropionates,[12] polyether antibiotics[13] and macrolides.[14] Natural products derived from marine mollusks gained interest for their bio-active secondary metabolites[15] and unusual structures. Siphanarienes **1**, **2** and Pectinatone are marine polypropionate natural products.

3.2 Previous synthetic approaches of polypropionates 1 and 2

1. Teck-Peng Loh's approach:[16]

Teck-Peng Loh *et al*. developed a general method for the synthesis of deoxy-propionate *via* the iterative application of CuI-Tol-BINAP-catalyzed asymmetric conjugate addition to *α,β*-unsaturated ester. Synthesis of siphonarieal and siphonarienone began from commercially available methyl *trans*-2-hexenoate (**3**), the first methyl stereogenic centre was introduced by using (*S*)-Tol-BINAP to give the methyl ester (**4**) in 68% yield (Scheme 1).

After one-pot DIBAL-H reduction, followed by Wittig olefination protocol furnished the (*E*)-enoate (**5**). The similar elongation protocol furnished the *syn*-enoate **7**. The third stage conjugate addition was modified by using (*S*)-Tol-BINAP followed by bromination to result the *α*-bromomethyl ester. The *α*-bromomethyl ester (**8**) was reduced to alcohol using DIBAL-H. This alcohol was then treated with zinc dust and glacial acetic acid in THF to afford the terminal olefin (**9**). One-pot ozonolysis and Wittig olefination protocol gave the *α,β*-unsaturated ester (**10**). From this *α,β*-unsaturated ester (**10**), a two-step DIBAL-H reduction and IBX oxidation furnished the siphonarieal (**1**). For the synthesis of siphonarienone (**2**), the *α,β*-unsaturated ester (**10)** was directly

converted into the corresponding Weinreb amide using MeNHOMe.HCl and *i*-PrMgCl, which upon treatment with EtMgBr in dry THF provided the Siphonarienone (**2**).

Scheme 1

Reagent and condition: (i) CH_3MgBr, CuI, *S*-Tol-BINAP, *t*-BuOMe, -20 °C, 68%; (ii) (a) DIBAL-H, hexane, -78 °C, 1.5 h; (b) $Ph_3P=CHCO_2Me$, THF, reflux, 7 h, 64%; (iii) (a) CH_3MgBr, CuI, *S*-Tol-BINAP, *t*-BuOMe, -20 °C, 66%; (iv) (a) DIBAL-H, hexane, -78 °C, 1.5 h; (b) $Ph_3P=CHCO_2Me$, THF, reflux, 7 h, 58%; (v) (a) CH_3MgBr, CuI, *S*-Tol-BINAP, *t*-BuOMe, -20 °C, 68%; (b) Br_2; (vi) (a) DIBAL-H, hexane, -40 °C, 2 h; (b) Zn, AcOH, THF, reflux, 16 h, 44%; (vii) (a) O_3, CH_2Cl_2, -78 °C, 30 min, then Me_2S; (b) $Ph_3P=C(Me)CO_2Me$, DCE, reflux, 14 h, 42%; (viii) (a) DIBAL-H, hexane, 0 °C, 1.5 h; (b) IBX, DMSO, rt, 4 h, 63%; (ix) (a) MeNHOMe.HCl, ^{i}PrMgBr, THF, -20 °C 1.5 h; (b) EtMgBr, THF, rt, 16 h, 67%.

2. Ei-ichi Negishi's approach:[17]

      Ei-ichi Negishi *et al*. developed a general method for the synthesis of polypropionates *via* Zr-catalyzed asymmetric carboalumination for the synthesis of siphonarienal (**1**) and siphonarienone (**2**).

      (3*S*)-3-Methyl-1-hexanol (**11**) was prepared from commercially available 3-buten-1-ol by using Zr-catalyzed asymmetric carboalumination method in one step. The alcohol **11** was converted to olefin **12** which was again subjected to Zr-catalyzed protocol

to obtain the alcohol (2*S*,4*S*)-2,4-dimethyl-1-heptanol (**13**). A three-step protocol on compound **13** consisting of iodination, Pd-catalyzed vinylation, and Zr-catalyzed asymmetric carboalumination-oxidation furnished the alcohol **14** in 46% yield (three steps). Swern oxidation of **14** produced the corresponding aldehyde (**15**) which was treated with $Et_3SiCH(Me)CHNCy$ and *s*-BuLi in THF at -78 °C followed by quenching with TFA furnished siphonarienal (**1**) in 85% yield over two steps (Scheme 3). Conversion of siphonarienal (**1**) to siphonarienone (**2**) was achieved by the reaction of **1** with EtMgBr in 88% yield, followed by oxidation with Dess-Martin periodinane in 90% yield.

Scheme 2

Reagents and conditions: (i) (a) $^{n}Pr_3Al$ (2.5 eq), IBAO, 5% (+)-$(NMI)_2ZrCl_2$; (b) H^{+}, 88%; (ii) (a) Swern oxidation; (b) $Ph_3P=CH_2$, 84%; (iii) (a) Me_3Al (1.5 eq), MAO (0.3 eq), % (+)-$(NMI)_2ZrCl_2$, then O_2, 79%; (iv) (a) Iodination; (b) Pd-cat. Vinylation; (v) Swern oxidation; (vi) *s*-BuLi, THF, -78 °C to -20 °C, 1 h, and then TFA, 0 °C, 85%; (vii) (a) EtMgBr, THF; (b) Dess-Martin periodinane, 90% .

4. Michael A. Calter's approach:[18]

Calter *et al.* reported the synthesis of marine polypropionate siphonarienal (**1**). The key step of this synthesis is an aldol reaction which constructs all three stereocenters of the target molecule. They have already reported a convenient procedure for the synthesis of propionic anhydride to methyl ketene dimer. Opening of the dimer with lithium amide of *N,O*-dimethyl hydroxylamine, followed by reduction yielded *β*-

hydroxyamide **17**. Compound **17** was then converted to aldehyde **20** by Barton–McCombie deoxygenation method followed by amide reduction. Now this aldehyde **20** underwent aldol reaction and afforded the aldol adduct **21** with high diastereoselectivity. Compound **21** was reduced to *syn*-diol **22** by using $Zn(BH_4)_2$ in dry Et_2O at -78 ^{o}C. Diol **22** was converted to bis-methanesulfonate **23**. Reduction of mesylates **23** with excess LAH in THF at room temperature followed by oxidation with iodobenzene diacetate/TEMPO afforded the aldehyde **24**. Wittig homologation of **24**, followed by reduction, effectively yielded the allylic alcohol. Finally, oxidation of allylic alcohol with MnO_2 in hexanes yielded siphonarienal **1**.

Scheme 3

Reagents and conditions: (i) (a) NH(OMe)Me.HCl, 5 mol% pyridone, THF, 0 ^{o}C; (b) $Zn(OTf)_2$, $NaBH_4$, THF, -20 ^{o}C; (ii) (a) CS_2, MeI, NaH, THF, 0 ^{o}C; (iii) *n*-Bu_3SnH, AIBN, Toluene, 110 ^{o}C; (iv) DIBAL-H. Et_2O, -78 ^{o}C; (v) **17**, NH(OMe)Me.HCl, *i*-PrMgCl, Et_2O,-78 ^{o}C; (vi) $Zn(BH_4)_2$, Et_2O, -78 ^{o}C; (vii) MsCl, CH_2Cl_2, Pyridine, DMAP; (viii) (a) LAH, anhydrous Et_2O, -78 ^{o}C to 0 ^{o}C; (b) BAIB, TEMPO, CH_2Cl_2, 0 ^{o}C; (x) Ph_3P=C(Me)CO_2Et, Toluene, Reflux; (x) DIBAL-H, CH_2Cl_2, -78 °C; (b) MnO_2, Hexane.

5. Gowravaram Sabitha's approach:[19]

Sabitha *et al*. reported the total synthesis of the marine natural product, siphonarienal and siphonarienone by using desymmetrization method. Synthesis started with the known precursor **26**[20] accordingly; allylation of the lactone **26** with allyl bromide in the presence of LiHMDS in dry THF at -78 °C afforded compound **27**. The bicyclic lactone **27** was reductively opened by using excess LAH in anhydrous THF resulted the triol **28**. The adjacent dihydroxy groups of the triol **28** were protected with acetonide by using 2,2-DMP in 9:1 mixture of CH_2Cl_2 and Et_2O in presence of catalytic amount of CSA. The primary hydroxyl group of compound **28** was protected as its benzyl ether using NaH and BnBr in anhydrous THF under reflux to afford **29** in 92% yield. The cleavage of acetonide protection in compound **29** using aqueous 2N HCl in THF afforded diol in 90% yield. The primary hydroxyl group in diol was tosylated using tosyl chloride, Et_3N, and catalytic amount of DMAP in anhydrous CH_2Cl_2 at 0 °C, followed by reductive cleavage (LAH, THF) of the sulfonate leading to the formation of alkane **31**. The secondary hydroxyl group in **31** was deoxygenated using Barton–McCombie method to give the compound **33**. Oxidative removal of the PMB ether in compound **33** with DDQ in buffered CH_2Cl_2 gave **34** which was deoxygenated using Barton–McCombie method to provide the compound **36**. Hydrogenolysis and hydrogenation of benzyl ether **36** at one pot synthesis using Pd/C in EtOAc afforded the alcohol which on oxidation with IBX provided the corresponding aldehyde **37**. The aldehyde **37** was then subjected to Wittig olefination to give the siphonarienone **2**. To prepare target compounds **1**, aldehyde **37** was subjected to a Wittig reaction using the stabilized ylide $Ph_3PC(Me)CO_2CH_2CH_3$ in refluxing dry benzene to give ester **25**. The ester was reduced to allylic alcohol, and further oxidized to afford siphonarienal **1**.

Scheme 5

*Reagents and conditions***:** (i) LiHMDS, allyl bromide, THF, -78 °C, 94%; (ii) LAH, THF, 0 °C-25 °C; (iii) (a) 2,2 DMP, CSA, CH$_2$Cl$_2$, Et$_2$O, 93%; (b) NaH, BnBr, THF, reflux, 92%; (iv) (a) 2M HCl, THF/H$_2$O, 25 °C, 90%; (b) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 92%; (v) (a) LAH, THF, 0 °C–25 °C, 80%; (vi) CS$_2$, MeI, NaH, 0 °C-25 °C, 89%; (vii) *n*-Bu$_3$SnH, AIBN, toluene, reflux, 91%; (viii) (a) DDQ, CH$_2$Cl$_2$, pH 7 buffer, 0 °C -25 °C, 89%; (ix) CS$_2$, MeI, NaH, 0 °C - 25 °C, 91% anhydrous THF; (x) *n*-Bu$_3$SnH, AIBN, Toluene, reflux; (xi) (a) Pd/C, H$_2$, 88%; (b) IBX/DMSO, 81%; (xii) (a) Dry benzene, reflux, 81%; (b) DIBAL-H, CH$_2$Cl$_2$ -78 °C - rt, 72%; (c) IBX/DMSO, 72%; (xiv) Dry benzene, reflux, 56%.

6. Yana Galeyeva's approach:[21]

　　　　Galeyeva *et al*. reported the synthesis of naturally occurring marine polypropoinate from methyl (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoate **38**. Enantiomerically pure compound **38** was available from preen-gland wax of the musk duck *Cairina moschata* and the domestic goose *Anser a. f. domesticus*.[22] Compound **38** was then *α*-hydroxylated to give the corresponding hydroxyl ester **39** as a diastereomeric mixture (dr 67:33) using literature procedure.[23] The secondary alcohol was then converted into mesylate **40** using MsCl and Et$_3$N in dichloromethane. Treatment of the crude mesylate **40** with DBU in toluene at reflux condition afforded a mixture of unreacted compound **40** (5%), regioisomer **41** (27%) and desired *α,β*-unsaturated ester **42** (32%). Reduction of ester **43** with DIBAL-H in dichloromethane afforded exclusively the allylic alcohol **44**. Subsequent Swern oxidation of **44** provided the siphonarienal **1**. The *α,β*-unsaturated ester **43**　was reacted with Me(OMe)NH·HCl and *i*-PrMgCl at　-40 °C to give the Weinreb amide **45** in 84% yield, which was then treated with EtMgBr in THF to yield the desired ketone **2**.

Scheme 6

Reagents and conditions: (i) LDA, MoOPH, THF, -78°C, 80%; (ii) MsCl, Et$_3$N, CH$_2$Cl$_2$; (iii) DBU, Toluene; (iv) DIBAL-H, CH$_2$Cl$_2$, 93%; (v) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, Et$_3$N, -78°C, 89%; (vi) Me(OMe)NH·HCl, *i*-PrMgCl , THF, -40 °C, 84%; (vii) EtMgBr, THF, 83%.

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CHAPTER III: SECTION B

Stereoselective Syntheses of Siphonarienal and Siphonarienone

3.2 SECTION B

Stereoselective syntheses of siphonarienal and siphonarienone

Polypropionate containing natural products are an important class of biologically active molecules and efforts for the discovery of new strategies are still continuing. Siphonarienal **1**, siphonarienone **2**, and pectinatone can be isolated from the marine mollusks genus *Siphonaria*, such as *Siphonaria grisea* and *Siphonaria pectinate*, respectively collected from intertidal region of the Mediterranean sea and Atlantic ocean (Fig. **1**).[1] These compounds are active against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), yeast (*Candida albicans* and *Saccharomyces cervisiae*), and various human cancer cell lines.[2] The structures of **1** and **2** were characterized by X-ray diffraction analysis and chemical correlations.[3] The members of this class of natural products contain a (2*S*,4*S*,6*S*)-trimethylnonane segment that is connected through an olefinic linker to a more polar oxygen containing group (Fig. **1**). This structural motif offers a challenging work in asymmetric synthesis. As an ongoing project on the synthesis of biologically active natural products, we have initiated a programme on stereoselective syntheses of siphonarienal and siphonarienone.

Siphonarienal 1   **Siphonarienone 2**

Figure 1

3.2.1 PRESENT WORK

In this context, we would like to report an asymmetric synthesis of marine Polypropionates siphonarienal (**1**) and siphonarienone (**2**) *via* diastereoselective oxidative kinetic resolution. We have synthesized a general route for an attractive method for stereoselective synthesis of *syn*-1,3 dimethyl arrays, attention was turned to prove its practicality and thus extended the method for the synthesis of marine Polypropionates siphonarienal (**1**) and siphonarienone (**2**), as these Polypropionates possess *syn*-1,3 dimethyl arrays.

3.2.1.1 Retrosynthesis of 1 and 2

Our retrosynthetic plan for the synthesis of siphonarienal (**1**) and siphonarienone (**2**) is depicted in Scheme 1. Synthesis of **1** and **2** could be achieved by the functional group transformation of a key intermediate **3**. The compound **3** can be accessed from the alcohol **17** *via* simple oxidation and Wittig olefination. The intermediate **17** was expected to be synthesized from **10** in a stereoselective manner involving Wittig reaction, Evans asymmetric alkylation and Grignard reaction. Compound **6** can in turn be synthesized from the commercially available (*R*)-methyl 3-hydroxy-2-methyl propionate involving simple protection, oxidation and Wittig olefination, reduction and diastereoselective oxidative kinetic resolution using Glucose oxidase from *Aspergillus niger.*

Scheme1. Retrosynthetic analysis of Siphonarienal (**1**) and Siphonarienone (**2**)

Scheme 1

3.2.1.2 Results and Discussion

The Scheme 2 depicts the synthesis of **1** and **2** started from the known precursor **7** which is available in three steps from the commercially available (*R*)-methyl 3-hydroxy-2-methylpropanoate.[4] We have started from commercially available (*R*)-methyl 3-hydroxy-2-methylpropanoate **4** which was protected as its *tert*-butyldiphenylsilyl (TBDPS) ether **5** with *tert*-butylchlorodiphenylsilane and imidazole in anhydrous CH_2Cl_2 at 0 ^{o}C in 95% yield. In ^{1}H NMR spectrum, the two phenyl group of TBDPS resonated as a set of two multiplets at δ 7.68-7.62 ppm integarting for four protons and δ 7.45-7.35 ppm integrating for six protons where as the nine protons of *t*-butyl group resonated as a

singlet at δ 1.03 ppm. In ^{13}C NMR spectrum signals were also in full accord with the incorporation of TBDPS group. The IR absorbance peak at 1741 cm^{-1} corresponding to the ester carbonyl group and the ESI-HRMS peak at *m/z* [M + Na]$^+$ 379.17004 further confirmed the formation of compound **5**. The methyl ester in compound **5** was reduced to corresponding alcohol **6** using DIBAL-H in anhydrous CH_2Cl_2 at -78 ^{o}C (Scheme **2**). The formation of alcohol **6** was confirmed by ^{1}H NMR analysis which showed the absence of the singlet at δ 3.68 ppm for -OMe methyl group protons. ^{13}C NMR spectrum also showed the absence of carbonyl peak. In IR spectroscopy a broad peak at 3435 cm^{-1} for hydroxyl functional group and a peak at *m/z* 351.1755 [M + Na]$^+$ in ESI-HRMS spectrum provided an additional proof in the favor of formation of alcohol **6**. The Dess-Martin periodinane[5] oxidation of alcohol **6** was carried out in CH_2Cl_2 in presence of $NaHCO_3$ to afford aldehyde in 91% yield. The aldehyde was used immediately for the next reaction without any characterization. The aldehyde was subjected to Wittig olefination using (1-carbethoxyethylidene)-triphenylphosphorane in anhydrous benzene at 80 ^{o}C furnished olefin **7**. In ^{1}H NMR the proton resonance at δ 6.52 (dd, *J* = 1.4, 9.9 Hz) ppm for one olefinic proton and multiplet at δ 4.11, shows –CH$_2$ protons of the ester (-CH$_2$-CH$_3$), and the presence of carbonyl functionality was also confirmed by IR strong absorption band at 1680 cm^{-1} suggested the formation of **7**. Along with above data, a peak at *m/z* 433 [M + Na]$^+$ in ESI-MS spectrum gave additional support in favor of compound **7** (Scheme **2**). The unsaturated ester **7** was reduced with Mg in MeOH to provide saturated ester of diastereomeric mixture of (4*S*)-ethyl and methyl 5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylpentanoate **8**. The saturated ester **8** was used for the next reaction without any characterization. The reduction of the ester functionality of **8** with LAH in anhydrous ether afforded alcohol **9** (as diastereomeric mixtures; 1:1).[6] Now we have explored diastereoselective oxidative kinetic resolution by Glucose oxidase from *Aspergillus niger* with this alcohol **9**. In earlier report, the selective oxidation of alcohol was performed using whole cells *Gluconobacter Oxydans*.[7] This procedure was cumbersome and need a microbiologist to grow the cells, which are not commercially available. Since the reaction is apparently catalyzed by glucose oxidase, we have performed the oxidation with commercially available glucose oxidase derived from *Aspergillus niger*. The oxidation proceeds selectively to give the aldehyde, which spontaneously oxidizes to carboxylic

acid **11** during the reaction. At the end of the reaction, the desired alcohol **10** was obtained in 48% yield. Compound **10** was characterized by the appearance of the proton signal at the region of δ 3.56-3.30 (m, 4H) ppm corresponding to the four –CH$_2$OH protons and no characteristic signal for carbonyl group in ^{13}C NMR. By IR spectrum showed absorption peak at 3455 cm^{-1} which indicated the hydroxyl functional group. Compound **10** was also characterized by HRMS [ESI] data which showed the [M+Na]$^+$ peak at *m/z* 393.22189. The chiral alcohol **10** is known in the literature and its absolute stereochemistry was confirmed by comparing its Specific rotation [α]$_D^{25}$: +1.75 (*c*= 0.25, CHCl$_3$) with authentic sample.[7a, 8]

Scheme 2

Reagents and conditions: (i) TBDPSCl, Imidazole, CH$_2$Cl$_2$, 0 ^{o}C, 95%; (ii) DIBAL-H, CH$_2$Cl$_2$, -78 ^{o}C; (iii) (a) DMP, NaHCO$_3$, CH$_2$Cl$_2$; (b) Ph$_3$P=C(CH$_3$)CO$_2$CH$_2$CH$_3$, C$_6$H$_6$, reflux, 86% (two steps); (iv) (a) Mg, MeOH, rt, 12 h; (b) LAH, Et$_2$O, 0-25 ^{o}C, 2 h; (ii) Glucose oxidase enzyme, Phosphate buffer pH= 8, DCM, 25 °C. 2 h, 48%.

For our synthetic exercise we need a chiral precursor **10**. Therefore, the oxidation was stopped after 2 h interval. The undesired acid **11** can be converted back into the alcohol **10** by a two-step epimerization reaction.[7a] The acid **11** was treated with DBU in THF at 70 ^{o}C it afforded the epimerized acid, which was reduced to the alcohol **9** (88% in two steps). The alcohol **9** can again be used in the initial oxidation step.

Table 1
Product distribution in the Oxidative Kinetic Resolution of Alcohol **10** by Glucose Oxidase enzyme

Time (h)	Yield of Alcohol **10** (%)[a]	Yield of acid **11** (%)	Yield of Aldehyde (%)
1.0	35	30	10
2.0	48	46	<5
3.0	70	20	<5
5.0	80	17	Traces

[a] Yields are obtained as isolated yield after purification

Subsequent oxidation of the alcohol **10** followed by chain elongation by C2 Wittig olefination with (ethoxycarbonylmethylene)-triphenylphosphorane gave the α,β-unsaturated ester **12** in 86% yield over two steps. The formation of the product was confirmed by appearance of signals of the two olefinic protons at δ 6.80 (dd, $J = 15.7, 8.3$ Hz, 1H) and 5.78 (d, $J = 15.7$ Hz, 1H) ppm in ^{1}H NMR spectrum confirmed product as *trans*-olefin, also showed characteristic resonances as a quartet at δ 4.19 (q, $J = 7.2$ Hz, 2H) and triplet at δ 1.29 (t, $J = 7.2$ Hz, 3H) ppm in ^{1}H NMR spectrum which corresponds to the presence of α,β-unsaturated ethyl ester. Compound **12** was also characterized by HRMS [ESI] data which showed the [M+Na]$^+$ peak at *m/z* 461.24742. Chemoselective reduction of the olefinic bond in compound **12** with Pd/C in AcOEt afforded the saturated ester **13** in 96% yield. This transformation was confirmed from ^{1}H NMR spectroscopy which showed no characteristic resonance at the region of δ 6.80 (dd, $J = 15.7, 8.3$ Hz, 1H) and 5.78 (d, $J = 15.7$ Hz, 1H) ppm correspond to olefinic protons. Further confirmation was obtained from HRMS [ESI] data which showed the [M+Na]$^+$ peak at *m/z* 463.26295. Saturated ester **13** was then hydrolyzed under basic conditions to furnish the corresponding carboxylic acid **14** in 93% yields. This hydrolysis was confirmed by ^{1}H NMR spectroscopy which showed disappearances of the proton signals at the region of δ 4.19 (q, $J = 7.2$ Hz, 2H) and 1.29 (t, $J = 7.2$ Hz, 3H) ppm corresponding to the ethyl ester group. Further confirmation was obtained from the HRMS[ESI] data which showed [M+Na]+ peak at *m/z* 435.23238 and from IR spectrum which showed an absorption band at 1710 cm^{-1} due to C=O stretching frequency of acid group.

Coupling of carboxylic acid **14** with the Evan's chiral oxazolidinone using pivaloyl chloride in presence of triethylamine and LiCl furnished the required compound

15 in 93% yield. Compound **15** was characterized by the resonance of fifteen aromatic protons as multiplet between δ 7.71-7.63 (m, 4H) and 7.45-7.16 (m, 11H) ppm and appearance of peak at the region of δ 3.04-2.78 (m, 2H) ppm corresponding to benzyl group. Further confirmation was obtained from IR spectrum which showed disappearances of absorption band at 1698 cm^{-1} due to C=O stretching frequency of acid group and appearances of absorption band at 1783 cm^{-1} due to C=O stretching frequency of keto group and from HRMS[ESI] data which showed the [M+Na]$^{+}$ peak at *m/z* 594.29941.

Diastereoselective methylation of Na-enolate of compound **15** with MeI in anhydrous THF furnished the desired compound **16** in 93% yield and in >97:3[9] diastereoselectivity (confirmed by ^{1}H NMR). Compound **16** was characterized by ^{1}H-NMR spectroscopy which showed peak at δ 1.20 (d, *J* = 6.7 Hz, 3H) ppm for the newly formed methyl center and from HRMS [ESI] data which showed the [M+Na]$^{+}$ peak at *m/z* 608.31370. Compound **16** was then reduced under NaBH$_4$ in MeOH to obtain the desired primary alcohol **17** having three stereogenic centers in place with 92% yield (Scheme 9). The formation of product was confirmed by ^{1}H NMR spectroscopy which showed characteristic proton signals at the aromatic protons as multiplet δ 7.70-7.63 (m, 4H), 7.45-7.34 (m, 6H), and from the IR spectroscopy which showed absorption band at 3019 cm^{-1} due to OH stretching frequency. Further evidence was obtained by the appearance of peak at *m/z* 435.27008 for [M+Na]$^{+}$ in HRMS[ESI] data.

Scheme 3

Reagents and conditions: (i) (a) TPAP, NMO, CH_2Cl_2, 0.5 h; (b) $Ph_3P=CHCO_2Et$, C_6H_6, 80 °C, 12 h, 86% ; (ii) Pd/C, H_2, AcOEt, 2 h, 96 %; (iii) $LiOH.H_2O$, $MeOH:H_2O$(4:1), 2 h, 93 %; (iv) (*R*)-4-benzyl-oxazolidin-2-one, PiV-Cl, Et_3N, LiCl, THF, -20- 0 °C, 3 h, 93%; (v) NaHMDS, MeI, -78 °C, THF, 93%; (vi) $NaBH_4$, MeOH, 0-25 °C, 92%.

       The primary alcohol **17** was converted into tosylate using TsCl, Et_3N in presence of catalytic amount of DMAP followed by Grignard reaction with EtMgBr in THF at -20 °C in presence of a catalytic amount of Li_2CuCl_4 furnished the product **18** in 85% yield.[10] Grignard compound **18** was characterized by the disappearance of two proton signals as a multiplet at the region of δ 3.55-3.45 (m, 2H) ppm corresponding to the $-CH_2OH$ protons in ^1H NMR spectroscopy and disappearance of OH stretching absorption at 3418 cm^{-1} in IR spectroscopy. Compound **18** was treated with TBAF in THF yielded desilylated primary alcohol **19** in 95%. Compound **19** was confirmed by the disappearance of proton signals at δ 7.68-7.54 (m, 4H), 7.40-7.25 (m, 6H) and 0.98 (s, 9H) ppm corresponding to TBDPS group and from the IR spectroscopy which showed strong absorption band at the region of 3449 cm^{-1} confirmed the presence of hydroxyl group. The primary alcohol group in **19** was oxidized with TPAP and NMO to the corresponding aldehyde, followed by three-carbon homologation using $Ph_3P=C(CH_3)CO_2Et$ in benzene to furnish the (*E*)-*α,β*-unsaturated ester **3** in 86% overall yield.[11] The ^1H NMR spectrum of **3** showed resonances at δ 6.45 (d, *J* = 10.2 Hz, 1H) for one olefin proton and δ 4.28-4.11 (m, 2H) shows $-CH_2$ protons of the ester ($-CH_2-CH_3$), and the presence of carbonyl functionality was also confirmed by IR spectroscopy, it shows a strong absorption band at 1648 cm^{-1}. Further evidence was obtained by the appearance of peak at *m/z* 268.23968 for [M+Na]$^+$ in HRMS [ESI] data.

Scheme 4: Synthesis of siphonarienal (**1**) and siphonarienone (**2**)

Reagents and conditions: (i) (a) TsCl, DCM, Et$_3$N, DMAP; (b) EtMgBr, Li$_2$CuCl$_4$ THF, -20 ^{o}C, 85%; (ii) TBAF, THF, 2 h, 95%; (iii) (a) TPAP, NMO, CH$_2$Cl$_2$, 0.5 h; (b) Ph$_3$PC(Me)CO$_2$Et, C$_6$H$_6$, 80 ^{o}C, 86%; (iv) DIBAL-H, CH$_2$Cl$_2$, -78 ^{o}C, 88%; (v) (a) MeNHOMe.HCl, *i*-PrMgCl, THF, -20 ^{o}C, 1.5 h (b) EtMgBr, THF, rt, 45 min, 80%.

The target molecule, siphonarienal **1** was readily achieved in 88% yield by reduction of **3** with DIBAL-H at -78 $^°$C. Final product **1** was confirmed by ^{1}H NMR spectroscopy which showed a peak as singlet at the region of δ 9.39 (s, 1H) ppm, corresponding to aldehyde proton, the proton adjacent to the aldehyde group resonated at δ 2.92–2.75 as a multiplet and from ^{13}C NMR spectroscopy which showed characteristic peak at δ 195.5 ppm corresponding to carbon resonance of aldehyde group. Further evidence was obtained from IR spectrum which showed absorption band of C=O stretching frequency of aldehyde at 1691 cm^{-1}.

For the synthesis of siphonarienone (**2**), the *α,β* -unsaturated ester **3** was directly converted into the corresponding Weinreb amide using NMeHOMe**.**HCl and *i*-PrMgCl, which upon treatment with EtMgBr in THF provided the siphonarienone (**2**) in 80% yield over two steps. The compound **2** was well characterized by its ^{1}H NMR, ^{13}C NMR, IR and mass spectral properties. In the ^{1}H NMR spectrum the vinylic proton resonated at δ 6.34 (dd, *J* = 9.6, 1.2 Hz, 1H), methyl attached to sp^2 carbon resonated as singlet at δ 1.80, and from ^{13}C NMR spectroscopy which showed characteristic peak at δ 202.8 ppm corresponding to carbon resonance of conjugated keto group. The mass spectrum

ESI(MS) showed $[M+H]^+$ peak at *m/z* 253 and an absorption band at 1700 cm^{-1} in the IR spectrum further confirmed the *α,β*-unsaturated ketone **2** (Scheme 4).

The ^{1}H and ^{13}C NMR spectral data of our synthetic compounds (**1** and **2**) were in good agreement with the data previously reported in the literature.[12]

3.2.2 Conclusion

In conclusion we have demonstrated the asymmetric total syntheses of siphonarienal and siphonarienone from commercially available starting materials. The key transformations of these syntheses are the Wittig olefination, diastereoselective oxidative kinetic resolution using Glucose oxidase from *Aspergillus niger*, Evans asymmetric alkylation, and Grignard reaction. This approach further illustrates the application of oxidative kinetic resolution for the synthesis of deoxypolypropionate units. Further work is under progress to synthesize the other members of this family.

3.3 EXPERIMENTAL SECTION

(*R*)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate (5):

To an ice cooled solution of (*R*)-methyl 3-hydroxy-2-methylpropanoate (2.0 g, 16.95 mmol) and imidazole (2.88 g, 42.37 mmol) was added TBDPSCl (4.84 ml, 18.6 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at 0 ^{o}C for 1 h and quenched with aqueous NH_4Cl solution (15 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography utilizing ethyl acetate and hexane (1:24) as mobile phase to afford silyl ether **5** as a colorless liquid.

Yield	:	5.73 g, 95%
Molecular formula	:	$C_{21}H_{28}O_3Si$
Physical State	:	colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.68-7.62 (m, 4H), 7.45-7.35 (m, 6H), 3.38 (dd, *J* = 9.8, 6.8 Hz, 1H), 3.73 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.68 (s, 3H), 2.72 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 9H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 175.2, 135.5, 133.4, 129.6, 127.6, 65.9, 51.4, 42.3, 26.7, 19.2, 13.4.
HRMS (ESI)	:	Calculated for $C_{21}H_{28}O_3NaSi$: 379.16999, found: 379.17004.
IR (KBr)	:	ν_{max} 3070, 2935, 2859, 1741, 1466, 1429, 1255, 1199, 1109, 1027 cm^{-1}
$[\alpha]_D^{25}$		-13.6 (*c* = 1.16, CHCl$_3$);
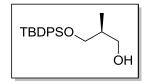
(*R*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropan-1-ol (6):

A stirred solution of ester **5** (5.7 g, 16.01 mmol) in anhydrous CH_2Cl_2 (30 mL) was treated with DIBAL-H (25.17 mL of 1.4 M solution in toluene, 35.24 mmol) at −78 °C and stirred for 2 h. The reaction was quenched with MeOH (3 mL) and saturated aqueous sodium potassium tartrate solution (30 mL). The reaction mixture was warmed to room temperature and stirred for 5 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 40 mL). Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:9) as mobile phase to afford alcohol **6** as a colorless liquid.

Yield	:	4.73 g, 90%

Molecular formula	:	$C_{20}H_{28}O_2Si$
Physical State	:	colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.74-7.63 (m, 4H), 7.49-7.34 (m, 6H), 3.73 (dd, J = 10.5, 4.5 Hz, 1H), 3.70-3.65 (m, 2H), 3.59 (dd, J = 9.8, 7.5 Hz, 1H), 2.00 (m, 1H), 1.06 (s, 9H), 0.83 (d, J = 7.5 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 135.5, 133.2, 129.7, 127.7, 68.5, 67.4, 37.3, 26.8, 19.1, 13.1.
HRMS (ESI)	:	Calculated for $C_{20}H_{28}O_2NaSi$: 351.17508, found: 351.17551.
IR (KBr)	:	ν_{max} 3435, 3056, 2956, 2861, 1466, 1426, 1389, 1107, 1037, 701 cm^{-1}
$[\alpha]_D^{25}$		-5.1 (c = 1.0, CHCl$_3$)

(*S*,*E*)-ethyl-5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylpent-2-enoate (7):

Alcohol **6** (4.7 g, 14.33 mmol) was dissolved under nitrogen atmosphere in dry CH_2Cl_2 (30 ml) and cooled to 0 °C. NaHCO$_3$ (3.61 g, 43 mmol) and Dess-Martin-periodinane (9.12 g, 21.5 mmol) were added and the suspension stirred for 1 hour. Afterwards, saturated aqueous NaHCO$_3$ (20 ml) and saturated aqueous Na$_2$S$_2$O$_3$ (30 ml) were added and the mixture was stirred for another 20 min. The organic phase was extracted with CH_2Cl_2 (3 x 30 mL), dried over Na$_2$SO$_4$ and the solvent removed under reduced pressure to give crude aldehyde. The aldehyde was used immediately for the next reaction without any characterization. The aldehyde was subjected to Wittig olefination using (1-carbethoxyethylidene)-triphenylphosphorane (6.9 g, 19.05 mmol) in anhydrous benzene at 80 °C furnished olefin **7** as a pale yellow liquid.

Yield	:	5.05 g, 86%
Molecular formula	:	$C_{25}H_{34}O_3Si$

Physical State	:	Colorless liquid.

^{1}H-NMR (CDCl$_3$, 300 MHz)   :   δ 7.61-7.55 (m, 4H), 7.38-7.28 (m, 6H), 6.52 (dd, *J* = 1.4, 9.9 Hz, 1H), 4.15-4.07 (m, 2H), 3.50-3.45 (m, 2H), 2.71-2.63 (m, 1H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.97 (s, 9H), 0.96 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (CDCl$_3$, 75 MHz)   :   δ 168.2, 144.4, 135.6, 133.6, 129.6, 127.6, 67.7, 60.4, 36.1, 26.8, 19.2, 16.3, 14.3, 12.6.

HRMS (ESI)   :   Calculated for C$_{25}$H$_{34}$O$_3$NaSi: 433.21694, found: 433.21747.
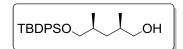
IR (KBr)   :   ν$_{max}$ 3050, 2859, 2858, 1716, 1680, 1509, 1465, 1428, 1267, 1083, 740, 701 cm^{-1}

$[α]_D^{25}$:   -2.6 (*c* = 1.1, CHCl$_3$)

(2*R*,4*S*)-5-(*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethylpental-1-ol (10):

Mg turnings (2.92 gm, 122.0 mmol) were added to the unsaturated ester **7** (5 gm, 12.2 mmol) in anhydrous MeOH (100 mL). Gas evolution was observed after 25 min of stirring and after four hours all magnesium turnings were dissolved and a white precipitate had formed. After that the reaction mixture was cooled to 0°C and dilute HCl (200 mL, 2.5M) was added to dissolve the solid, followed by the extraction with diethyl ether (3 x 150 mL), the combined ethereal extracts was washed with sat. NaHCO$_3$ (50 mL) and brine (50 mL), followed by drying (MgSO$_4$) and concentrated in *vacuo* and purified on silica gel chromatography (EtOAc/Hexane, 1:19) of the crude product afforded a mixture of methyl and ethyl esters **8**, which were taken up in anhydrous diethyl ether (30 mL) and reduced immediately with LAH (1.4 gm, 36.6 mmol) in anhydrous ether (30 mL) at 0 ^{o}C. After 2 hours of stirring, the mixture was diluted with ether (50 mL) and quenched by slow addition of saturated aq. Na$_2$SO$_4$ solution (15 mL). When the effervescence subsided, the reaction mixture was filtered

through a pad of celite and washed with hot ethyl acetate (60 mL). The filtrate was evaporated in *vacuo* the residue was purified by column chromatography (EtOAc/Hexane, 1:3) to furnish the compound **9** (2 isomer, 3.97 gm, 88% over 2 steps) as colourless liquid. To a stirred solution of alcohol **9** (3.97 gm, 10.74 mmol) in DCM (30 mL), Phosphate buffer (25 ml, pH = 8, 0.1M) and 800 mg of glucose oxidase enzyme were added subsequently at 25 °C. The biotransformations were monitored periodically by TLC analysis. After two hours the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatographic separation on silica gel (Hexane/EtOAc, 3:1) afforded pure compound **10**.

Yield	:	1.91 g, 48%
Molecular formula	:	$C_{23}H_{34}O_2Si$
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.71-7.60 (m, 4H), 7.48-7.34 (m, 6H), 3.56-3.30 (m, 4H), 1.80-1.56 (m, 2H), 1.51-1.39 (m, 2H), 1.06 (s, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 135.5, 133.8, 129.4, 127.5, 68.6, 67.9, 37.1, 32.9, 26.8, 17.8, 17.3.
HRMS (ESI)	:	Calculated for $C_{23}H_{34}O_2NaSi$: 393.22203, found: 393.22189.
IR (KBr)	:	v_{max} 3455, 2931, 2856, 1110, 1091, 702 cm^{-1}
$[\alpha]_D^{25}$	:	+1.75 (*c*= 0.25, CHCl$_3$)

(4*R*,6*S*,*E*)-Ethyl 7-((*tert*-butyldiphenyl silyl)oxy)-4,6-dimethylhept-2-enoate (12):

To a stirred solution of the alcohol **10** (1.50 gm, 4.05 mmol) and activated powder 4Å molecular sieves (2 gm) in anhydrous CH_2Cl_2 (40 ml) at 0 °C were added tetrapropyl

ammonium perruthenate (VII), (70 mg, 0.2 mmol) and 4-methylmorpholine-N-oxide (700 mg, 6 mmol). The reaction mixture was stirred under argon for 30 min and filtered through a short pad of silica eluting with ethyl acetate to yield the aldehyde. To this crude aldehyde in benzene (20 mL) was added the stabilized ylide $Ph_3P=CHCO_2CH_2CH_3$ (2.10 gm, 6.0 mmol) and reaction mixture was stirred for overnight at 80 ^{o}C temperature. The reaction mixture was then concentrated under reduced pressure and purified on silica gel chromatography (EtOAc/Hexane, 1:19) to afford the unsaturated ester **12** as a colorless liquid.

Yield	:	1.51 gm, 86% (over two steps)
Molecular formula	:	$C_{27}H_{38}O_3Si$
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.70-7.62 (m, 4H), 7.46-7.32 (m, 6H), 6.80 (dd, *J* = 15.7, 8.3 Hz, 1H), 5.78 (d, *J* = 15.7 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.50-3.40 (m, 2H), 2.46-2.30 (m, 1H), 1.74-1.48 (m, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 166.8, 154.4, 135.6, 133.9, 129.5, 119.7, 68.9, 60.1, 39.8, 34.1, 33.3, 26.8, 20.4, 19.2, 16.7, 14.2.
HRMS (ESI)	:	Calculated for $C_{27}H_{38}O_3NaSi$: 461.24824, found: 461.24742.
IR (KBr)	:	ν_{max} 2928, 2856, 1725, 1664, 1464, 1374, 1264, 1108, 1047, 821, 704, 506 cm^{-1}
$[\alpha]_D^{25}$	:	+25.5 (*c* = 1.0 in CHCl$_3$)
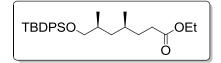
(4*S*,6*S*)-Ethyl 7-((*tert*-butyldiphenylsilyl)oxy)-4,6-dimethylheptanoate (13):

To a stirred solution of compound **12** (1.50 gm, 3.42 mmol) in AcOEt (10 mL) was added Pd/C (10%, 20 mg) and subjected to hydrogenation under atmospheric pressure using H_2-filled balloon. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated in *vacuo* and purified on silica gel chromatography (EtOAc/Hexane, 1:19) to afford the saturated ester **13** as colorless liquid.

Yield	:	1.44 gm, 96%
Molecular formula	:	$C_{27}H_{40}O_3Si$
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.70-7.62 (m, 4H), 7.46-7.34 (m, 6H), 4.11 (q, J = 7.2 Hz, 2H), 3.55-3.37 (m, 2H), 2.36-2.18 (m, 2H), 1.80-1.62 (m, 2H), 1.53-1.32 (m, 4H), 1.24 (t, J = 7.2 Hz, 3H), 1.05 (s, 9H), 0.92 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 174.0, 135.6, 129.4, 127.5, 68.8, 60.1, 40.7, 33.0, 31.8, 31.5, 29.6, 26.8, 19.9, 17.5, 14.2.
HRMS (ESI)	:	Calculated for $C_{27}H_{40}O_3NaSi$: 463.26389, found: 463.26295.
IR (KBr)	:	v_{max} 2928, 2856, 1738, 1464, 1430, 1372, 1254, 1107, 1054, 703, 612, 507cm^{-1}
$[\alpha]_D^{25}$	:	+5.4 (c = 1.0 in CHCl$_3$)

(4*S*,6*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-4,6-dimethylheptanoic acid (14):

To a stirred solution of ester **13** (1.40 gm, 3.18 mmol) in 25 mL of CH$_3$OH:H$_2$O (4:1) was added portion wise LiOH.H$_2$O (400 mg, 9.60 mmol) at 0 °C and the stirring was continued for 2 h at room temperature. The reaction mixture was then concentrated in *vacuo* and the residue was diluted with EtOAc (20 mL) and washed with saturated aq.

NH$_4$Cl solution and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Removal of solvent followed by column chromatography (EtOAc/hexane, 1:5) afforded the acid **14** as a colorless liquid.

Yield	:	1.23 gm, 93%
Molecular formula	:	C$_{25}$H$_{36}$O$_3$Si
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.71-7.62 (m, 4H), 7.45-7.34 (m, 6H), 3.53-3.37 (m, 2H), 2.41-2.22 (m, 2H), 1.80-1.30 (m, 6H), 1.05 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 180.4, 135.6, 134.0, 129.8, 127.5, 68.8, 40.7, 33.1, 31.6, 31.3, 29.6, 26.9, 19.8, 19.3.
HRMS (ESI)	:	Calculated for C$_{25}$H$_{36}$O$_3$NaSi: 435.23314; found 435.23238.
IR (KBr)	:	ν$_{max}$ 2956, 2926, 2860, 1710, 1495, 1246, 1101, 912, 830, 768cm^{-1}
[α]$_D^{25}$	:	+8.0 (c = 1.0 in CHCl$_3$)

(*R*)-4-Benzyl-3-((4*S*,6*S*)-7-((*tert*-butyldiphenylsilyl)oxy)-4,6-dimethyl heptanoyl)oxazolidin-2-one (15):

To a stirred solution of acid **14** (1.20 gm, 2.91 mmol) in dry THF (15 mL) at –20 °C was added Et$_3$N (0.9 mL, 7.3 mmol) followed by PivCl (0.4 mL, 2.91 mmol) under nitrogen atmosphere. After stirring for 1 h at –20 °C, LiCl (183 mg, 4.37 mmol) followed by (*R*)-1,3-oxazolidin-2-one (560 g, 3.2 mmol) were added to it at the same temperature. The stirring was continued for 1 h at –20 °C and then 2 h at 0 °C. It was then quenched with saturated NH$_4$Cl solution (10 mL) and extracted with ethyl acetate (3 × 25 mL). The

combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:16) to give **15** as a pale yellow liquid.

Yield	:	1.54 g, 93 %
Molecular formula	:	$C_{35}H_{45}NO_4Si$
Physical State	:	pale yellow liquid
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.71-7.63 (m, 4H), 7.45-7.16 (m, 11H), 4.72-4.60 (m, 1H), 4.24-4.11 (m, 2H), 3.91-3.83 (m, 1H), 3.52 (dd, J = 5.3, 9.6 Hz, 1H), 3.41 (dd, J = 6.6, 9.8 Hz, 1H), 3.29 (dd, J = 3.2, 13.4 Hz, 1H), 304-2.78 (m, 2H), 2.72 (dd, J = 9.6, 13.2 Hz, 1H), 1.86-1.33 (m, 4H), 1.30-1.21(m, 2H), 1.05 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 173.6, 153.3, 135.6, 133.9, 129.4, 128.9, 127.5, 127.3, 68.8, 66.0, 55.1, 40.9, 37.8, 33.2, 33.0, 30.9, 29.6, 26.8, 19.9, 19.3, 17.6.
HRMS (ESI)	:	Calculated for $C_{35}H_{45}NO_4SiNa$: 594.30101; found 594.29941.
IR (KBr)	:	ν_{max} 2925, 2855, 1783, 1698, 1457, 1385, 1352, 1273, 1195, 1106, 770, 702 cm^{-1}
$[\alpha]_D^{25}$	:	+40.0 (c = 1.0 in CHCl$_3$)
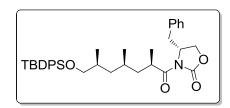
(*R*)-4-Benzyl-3-((2*R*,4*R*,6*S*)-7-((*tert*-butyldiphenylsilyl)oxy)-2,4,6-trimethyl heptanoyl)oxazolidin-2-one (16):

A flame dried 100 mL round bottom flask was charged with **15** (1.5 gm, 2.63 mmol) and 25 mL anhydrous THF. The solution was cooled to −78 °C, NaHMDS (1M solution in THF, 4.0 mL, 4.0 mmol) was added dropwise with stirring under nitrogen atmosphere. After 30 min stirring, MeI (0.33 mL, 5.26 mmol) was added dropwise to the reaction mixture and then stirring was continued for another 2 h at −78 °C. Then the mixture was quenched with saturated NH_4Cl (15 mL) and warmed to room temperature and then extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:19) to afford the product **16** as colorless liquid.

Yield	:	1.43 g, 93%
Molecular formula	:	$C_{36}H_{47}NO_4Si$
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.71-7.62 (m, 4H), 7.45-7.18 (m, 11H), 4.67-4.60 (m, 1H), 4.14 (d, J = 5.3 Hz, 2H), 3.91-3.83 (m, 1H), 3.50 (dd, J = 5.3, 9.7 Hz, 1H), 3.41 (dd, J = 6.6, 9.6 Hz, 1H), 3.24 (dd, J = 3.2, 13.3 Hz, 1H), 2.75 (dd, J = 9.6, 13.5 Hz, 1H), 1.95-1.77 (m, 3H), 1.50-1.32 (m, 3H), 1.20 (d, J = 6.7 Hz, 3H), 1.05 (s, 9H), 0.93 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 177.2, 152.9, 135.6, 134.0, 129.4, 128.8, 127.5, 127.3, 69.1, 65.9, 55.2, 41.5, 40.5, 37.8, 35.3, 33.0, 29.7, 28.1, 26.8, 20.5, 19.3, 18.7, 17.6.
HRMS (ESI)	:	Calculated for $C_{36}H_{47}NO_4SiNa$: 608.31666; found 608.31370.
IR (KBr)	:	v_{max} 2957, 2923, 2853, 1783, 1699, 1460, 1385, 1351, 1218, 1109, 772, 703, 613 cm^{-1}
$[\alpha]_D^{25}$	:	+42.8 (c = 1.0 in CHCl$_3$)
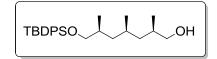
(2*R*,4*S*,6*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-2,4,6-trimethylheptan-1-ol (17):

To a stirred solution of **16** (1.4 g, 2.4 mmol) in MeOH (10 mL) was added NaBH$_4$ portion wise (274 mg, 7.2 mmol) at 0 °C. The reaction mixture was allowed to stir for 1 hour at same temperature and then quenched with saturated aqueous NH$_4$Cl. The solvent was removed under reduced pressure and the resulting residue was diluted with water and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/hexane, 1:9) to afford the pure product **17** as a viscous liquid.

Yield	:	910 mg, 92%
Molecular formula	:	C$_{26}$H$_{40}$O$_2$Si
Physical State	:	viscous liquid
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.70-7.63 (m, 4H), 7.45-7.34 (m, 6H), 3.54-3.45 (m, 2H), 3.44-3.30 (m, 2H), 1.79-1.64 (m, 2H), 1.41-1.18 (m, 5H), 1.05 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 135.6, 134.0, 129.5, 127.6, 68.7, 68.2, 41.8, 41.2, 33.2, 27.7, 26.9, 21.0, 18.1, 17.6, 16.5.
HRMS (ESI)	:	Calculated for C$_{26}$H$_{40}$O$_2$SiNa: 435.26898; found 435.27008.
IR (KBr)	:	ν$_{max}$ 3019, 2957, 2928, 2857, 1466, 1428, 1364, 1216, 1109, 1033, 823, 771, 667 cm^{-1}
[α]$_D^{25}$	:	−5.98 (*c* = 1.0 in CHCl$_3$)
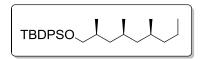
tert-Butyldiphenyl (((2*S*,4*S*,6*S*)-2,4,6-trimethylnonyl)oxy)silane (18):

A solution of alcohol **17** (0.9 g, 2.18 mmol) in dry CH_2Cl_2(15 mL) and dry triethylamine (0.4 mL, 2.6 mmol) was cooled at 0 ^{o}C and then was added *p*-toluenesulfonyl chloride (414 mg, 2.18 mmol). The resulting mixture was stirred at room temperature for 3 h. After complete conversion as confirmed by TLC, the mixture was quenched with NH_4Cl solution and then extracted with EtOAc (3 × 15 mL). Removal of the solvent followed by purification on silica gel column chromatography (Ethyl acetate/hexane, 1:19) gave the pure tosyl derivative. To a stirred solution of activated Mg-turnings (178 mg, 7.4 mmol) in anhydrous diethyl ether (6 mL), Ethyl bromide (0.6 mL, 7.63 mmol) was added slowly. After complete addition, the mixture was then heated to reflux (~30 min) until initiation of the reaction. After disappearance of the metal, this solution was transferred via a cannula to a solution containing tosylate (1.166 g, 2.06 mmol) in dry diethyl ether (20 mL) at -20 ^{o}C under nitrogen atmosphere. To this mixture, solution of Li_2CuCl_4 (0.1M in tetrahydrofuran, 0.2 mL, 0.2 mmol) was slowly added. The resulting mixture was stirred vigorously overnight at room temperature and then quenched with saturated aqueous NH_4Cl (10 mL) at 0°C and then extracted with diethyl ether (3 × 20 mL). Removal of the solvent under reduced pressure followed by column chromatography (Pentane: Et_2O, 5:1) gave the product **18** as a colorless liquid.

Yield	:	786 mg, 85%
Molecular formula	:	$C_{28}H_{44}OSi$
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 7.70-7.64 (m, 4H), 7.45-7.34 (m, 6H), 3.55-3.45 (m, 2H), 1.80-1.65 (m, 1H), 1.64-1.46 (m, 2H), 1.42-1.18 (m, 6H), 1.06 (s, 9H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.92-0.87 (m, 8H), 0.84 (d, *J* = 6.6 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 135.6, 134.0, 129.5, 127.5, 69.4, 43.2, 41.3, 40.4, 33.1, 32.4, 32.2, 27.5, 27.3, 26.9, 20.6, 19.9, 19.7, 19.3, 17.8, 16.6.
HRMS (ESI)	:	Calculated for $C_{28}H_{45}OSi$: 425.32396; found 425.32340**.**
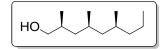
| IR (KBr) | : | ν_{max} 2958, 2928, 2857, 1464, 1428, 1380, 1363, 1219, 1110, 824, 772, 703, 614 cm^{-1} |
| $[\alpha]_D^{25}$ | : | -7.0 (c = 1.07, CHCl$_3$) |

(2*S*,4*S*,6*S*)-2,4,6-Trimethylnonan-1-ol (19):

To a stirred solution of **18** (750 mg, 1.77 mmol) in dry THF (15 mL), was added TBAF (1M solution in THF, 5.3 mL, 5.3 mmol) under nitrogen atmosphere. The resulting reaction mixture was stirred for 5 h and subsequently concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane mixture (1:9) to yield the compound **19** as colorless oil.

Yield	:	313 mg, 95% yield
Molecular formula	:	C$_{12}$H$_{26}$O
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 3.50 (dd, *J* = 5.3, 10.6 Hz, 1H), 3.34 (dd, *J* = 6.8, 10.6 Hz, 1H), 1.78-1.64 (m, 2H), 1.62-1.43 (m, 2H), 1.40-1.10 (m, 6H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90-0.82 (m, 10H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 68.2, 45.1, 41.2, 38.8, 33.0, 29.7, 27.5, 20.9, 20.4, 19.9, 17.5, 14.4**.**
HRMS (ESI)	:	Calculated for C$_{12}$H$_{26}$ONa: 209.18813; found 209.18890**.**
IR (KBr)	:	ν_{max} 3449, 2955, 2919, 2857, 1637, 1457, 1371, 1101, 760 cm^{-1}
$[\alpha]_D^{25}$	:	-12.0 (c = 1.0, CHCl$_3$)
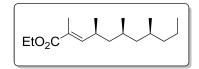
(4*S*,6*S*,8*S*,*E*)-Ethyl 2,4,6,8-trtramethyl undec-2-enoate (3):

To a stirred solution of the alcohol **19** (300 mg, 1.61 mmol) and activated powder 4Å molecular sieves (800 mg) in anhydrous CH_2Cl_2 (15 ml) at 0 °C were added tetrapropyl ammonium perruthenate (VII), (28 mg, 0.08 mmol) and 4-methylmorpholine-N-oxide (283 mg, 2.4 mmol).The mixture was stirred under argon for 30 min and filtered through a short pad of silica eluting with ethyl acetate to yield the aldehyde. To this crude aldehyde in benzene (10 mL) was added the stabilized ylide $Ph_3P=C(Me)CO_2CH_2CH_3$ [(1-carbethoxyethylidene)-triphenylphosphorane]   (875 mg, 2.14 mmol) and resulting mixture was stirred for overnight at 80 °C temperature. The reaction mixture was concentrated under reduced pressure and purified on silica gel chromatography (3% EtOAc/hexane) to afford the unsaturated ester **3** (378 mg, 88% over two steps) as a colorless liquid.

Yield	:	378 mg, 88% (over two steps)
Molecular formula	:	$C_{17}H_{32}O_2$
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 6.45 (d, *J* = 10.2 Hz, 1H) 4.28-4.11 (m, 2H), 2.68-2.53 (m, 1H), 1.84 (s, 3H), 1.54-1.14 (m, 10H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.86-0.76 (m, 9H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 168.3, 148.0, 126.2, 60.2, 45.5, 44.3, 39.3, 30.8, 29.6, 28.1, 20.5, 20.4, 19.9, 14.3, 14.2, 12.4**.**
HRMS (ESI)	:	Calculated for $C_{17}H_{32}O_2$ 268.23968; found 268.23968.
IR (KBr)	:	ν_{max} 3453, 2958, 2925,1711, 1648, 1460, 1378, 1102, 1035, 760, 667 cm^{-1}
$[\alpha]_D^{25}$	:	+18.12 (*c* = 0.9 in CHCl$_3$)
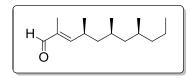
(4*S*,6*S*,8*S*,*E*)-2,4,6,8-Tetramethyl-2-undecenal (Siphonarienal) (1):

To a cooled (-78 ^{o}C) solution of **3** (185 mg, 0.69 mmol) in dry CH_2Cl_2 (5 mL), DIBAL-H (0.75 mL, 0.75 mmol, 20% solution in toluene) was added slowly. The resulting mixture was allowed to stir for 30 min at -78 ^{o}C. The reaction was quenched with sat. solution of sodium potassium tartarate (5 mL). The reaction mixture was then stirred vigorously at room temperature till a clear biphasic separation was observed. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were concentrated in *vacuo*. Purification of the residue by column chromatography (EtOAc/hexane, 1:30) gave the siphonarienal (**1**) (247 mg, 80%) as a colorless liquid.

Yield	:	247 mg, 80%
Molecular formula	:	$C_{15}H_{28}O$
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 9.39 (s, 1H), 6.23 (d, *J* = 9.8 Hz, 1H), 2.92-2.75 (m, 1H), 1.77 (s, 3H), 1.55-1.10 (m, 7H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.95-0.77 (m, 12H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 195.5, 160.7, 137.9, 45.6, 44.2, 39.2, 32.2, 29.6, 28.2, 20.5, 20.3, 20.0, 19.9, 14.3, 9.3**.**
MS(ESI)	:	*m/z* = 225 (M+H)$^+$
IR (KBr)	:	ν$_{max}$ 2956, 2925, 2910, 2871, 2705, 1691, 1644, 1457, 1378, 1008, 807 cm^{-1}
[α]$_D$^{25}	:	+16.1 (*c* = 1.1, CHCl$_3$). Lit. [α]$_D$^{30} +16.5 (*c* = 1.0, CHCl$_3$)
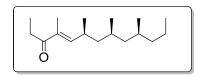
[(6*S*,8*S*,10*S*,*E*)-4,6,8,10-Tetramethyl tridec-4-3-one] (Siphonarienone) (2):

To stirred solution of **3** (185 mg, 0.69 mmol) and *N,O*-dimethylhydroxylamine-hydrochloride (MeONHMe.HCl) (202 mg, 2.07 mmol) in dry THF (5 mL) at -20 ^{o}C was added ^{i}PrMgCl solution (2M solution in THF, 1.15 mL, 3.0 mmol) slowly. After 1.5h, the reaction was quenched sat. NH_4Cl solution and the aqueous layer were extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. Without further purification the solution of weinreb amide containing residue was used for the next step. To a stirred solution of this in dry THF (5mL) was added EtMgBr (3M solution in Et_2O, 1.15 mL, 3.45 mmol) at 0°C under nitrogen atmosphere. The reaction mixture was stirred for 45 min at room temperature. After completion of the reaction, it was quenched with sat. NH_4Cl solution. The aqueous layer was extracted with Et_2O (3×10 mL), and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The resulting residue was purified by column chromatography (ethyl acetate/hexane, 1:30) gave the siphonarienone (**2**) (139 mg, 80%) as a colorless oil.

Yield	:	139 mg, 80%
Molecular formula	:	$C_{17}H_{32}O$
Physical State	:	Colorless liquid.
^{1}H-NMR (CDCl$_3$, 300 MHz)	:	δ 6.34 (dd, *J* = 9.6, 1.2 Hz, 1H), 2.75-2.64 (m, 3H), 1.80 (s, 3H), 1.54-1.15 (m, 10H), 1.10 (t, *J* = 7.3 Hz, 3H), 1.0 (d, *J* = 6.6 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).
^{13}C-NMR (CDCl$_3$, 75 MHz)	:	δ 202.8, 148.2, 135.3, 45.5, 44.5, 39.3, 31.2, 30.3, 29.6, 28.2, 20.7, 20.4, 19.9, 14.4, 11.5, 8.9.
MS(ESI)	:	*m/z* = 253 (M+H)$^+$.

| IR (KBr) | : | ν_{max} 3451, 2960, 2940, 2871, 2844, 1700, 1650, 1450, 1360, 1250, 1050, 790 cm^{-1} |
| $[\alpha]_D^{25}$ | : | +22.4 (*c* = 1.0, CHCl$_3$). Lit $[\alpha]_D^{30}$ +26.4 (*c* = 1.5, CHCl$_3$) |

3.5 REFERENCES:
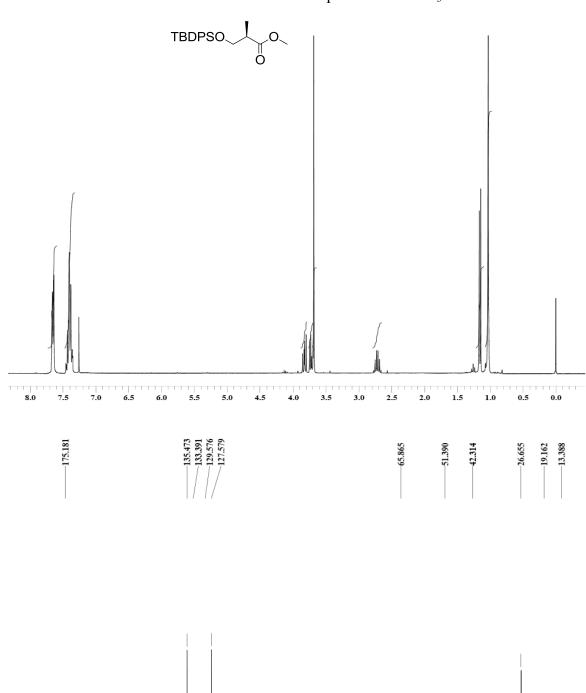
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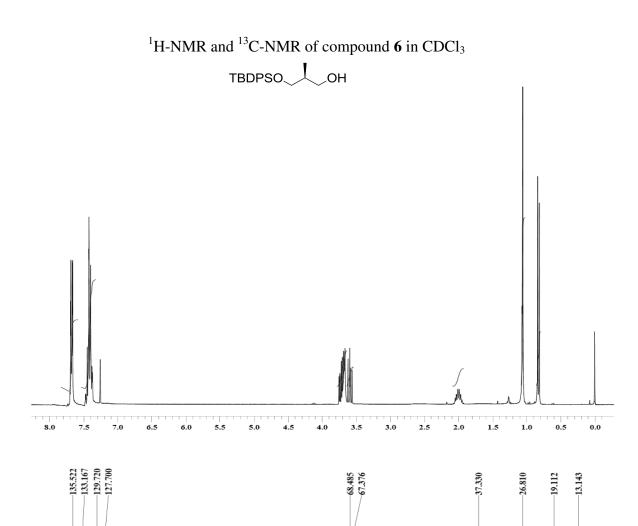
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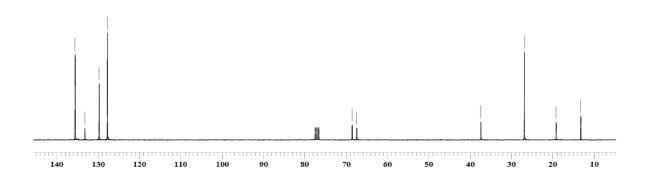
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¹H-NMR and ¹³C-NMR of compound 5 in CDCl₃

^{1}H-NMR and ^{13}C-NMR of compound **5** in CDCl$_3$

^{1}H-NMR and ^{13}C-NMR of compound **6** in CDCl$_3$

TBDPSO ⟍⟍ OH

135.522
133.167
129.720
127.700

68.485
67.376

37.330

26.810

19.112
13.143

^{1}H-NMR and ^{13}C-NMR of compound 7 in CDCl$_3$

TBDPSO CO$_2$Et

^{1}H-NMR and ^{13}C-NMR of compound **10** in CDCl$_3$

^{1}H-NMR and ^{13}C-NMR of compound **12** in CDCl$_3$

^{1}H-NMR and ^{13}C-NMR of compound **13** in CDCl$_3$

^{1}H-NMR spectrum with peaks from ~0.0 to ~8.0 ppm.

^{13}C-NMR chemical shifts:
174.015
135.569
133.955
129.451
127.531
68.809
60.126
40.709
33.035
31.859
31.546
29.641
26.846
19.875
17.532
14.207

^{1}H-NMR and ^{13}C-NMR of compound **14** in CDCl$_3$

^{1}H-NMR and ^{13}C-NMR of compound **15** in CDCl$_3$

^{1}H-NMR and ^{13}C-NMR of compound **16** in CDCl$_3$

^{1}H-NMR spectrum with peaks at 8.0, 7.5, 7.0, 6.5, 6.0, 5.5, 5.0, 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5, 0.0 ppm

^{13}C-NMR spectrum peaks: 177.190, 152.963, 135.609, 134.041, 129.442, 128.877, 127.540, 127.296, 69.106, 65.899, 55.226, 41.486, 40.495, 37.794, 35.261, 32.999, 29.686, 28.154, 26.855, 20.550, 19.279, 18.696, 17.583

^{1}H-NMR and ^{13}C-NMR of compound **17** in CDCl$_3$

TBDPSO~~~~OH

135.601
134.038
129.448
127.522

68.684
68.130

41.726
41.207

33.150

27.696
26.862

20.955
18.041
17.612
16.478

^{1}H-NMR and ^{13}C-NMR of compound 18 in CDCl$_3$

TBDPSO

^{1}H-NMR and ^{13}C-NMR of compound **19** in CDCl$_3$

^{13}C peaks: 68.248, 45.130, 41.230, 38.788, 33.059, 29.711, 27.488, 20.892, 20.418, 19.923, 17.516, 14.413

^{1}H-NMR and ^{13}C-NMR of compound **3** in CDCl$_3$

^{1}H-NMR and ^{13}C-NMR of compound **1** in CDCl$_3$

^{1}H-NMR spectrum with peaks at approximately 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 ppm.

^{13}C-NMR chemical shifts:
195.494, 160.671, 137.939, 45.560, 44.225, 39.225, 31.216, 29.622, 28.236, 20.492, 20.320, 20.017, 19.959, 14.342, 9.328

^{1}H-NMR and ^{13}C-NMR of compound **2** in CDCl$_3$

Chemical shift labels on ^{13}C-NMR:
202.844
148.236
135.318
45.530
44.436
39.289
31.213
30.345
29.616
28.239
20.688
20.431
19.959
14.368
11.508

LIST OF PUBLICATIONS

The research work described in this thesis has been published in the following journals.

1. *The Stereoselective Synthesis of 2-(2-hydroxyalkyl)piperidine alkaloids through Prins-Ritter reaction.* B. V. Subba Reddy, **Supriya Ghanty**, N. Siva Senkar Reddy, Y. Jayasudhan Reddy, J. S. Yadav. **Synth. Commun. 2014, 44, 1658.**

2. *o-Benzenedisulfonimide as a recyclable homogeneous organocatalyst for an efficient and facile synthesis of 4-amidotetrahydropyran derivatives through Prins-Ritter reaction.* B. V. Subba Reddy, **Supriya Ghanty**. **Synth. Commun. 2014, 44, 2545.**

3. *B(C_6F_5)$_3$-catalyzed Prins/Ritter reaction: a novel synthesis of hexahydro-1H-furo[3,4-c]pyranyl amide derivatives.* B. V. Subba Reddy, **Supriya Ghanty**, Ch. Kishore, B. Sridhar. **Tetrahedron Lett. 2014, 55, 4298.**

4. *Stereoselective Syntheses of Siphonarienal and Siphonarienone.* **Supriya Ghanty**, Chinta Krinda Suresh Kumar, B. V. Subba Reddy. **Tetrahedron: Asymmetry 2015, 26, 885.**

LIST OF CONFERRENCE AND SYMPOSIUM

The Candidate attended the following Conferences and Symposium during his tenure.

1.   Participated in the National Conference on **"Recent Advances in Chemical Research"** held at Department of Chemistry, Osmania University, Hyderabad, India (February 6-7, 2009).

2.   Participated in the International Symposium on **"12th CRSI National Symposium in Chemistry & 4th CRSI-RSC Symposium in Chemistry"** held at IICT, Hyderabad, India (February 4-7, 2010).

3.   Participated in the International symposium on **"Chemistry and Chemical Biology of Natural Products"** held at IICT, Hyderabad, India (August 2-4, 2012).