Asymmetric Synthesis of Bioactive 1, 2-Aminoalcohols and Methodologies involving Dihydroxylation of Olefins, Esterification and Iodination of Aromatics

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

To

UNIVERSITY OF PUNE

By

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UNDER THE GUIDANCE OF

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October 2008

DEDICATED TO

MY BELOVED FAMILY

MEMBERS

AND

FRIENDS

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Asymmetric Synthesis of Bioactive 1, 2-Aminoalcohols and Methodologies involving Dihydroxylation of Olefins, Esterification and Iodination of Aromatics**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

October 2008 **(Dr. A. Sudalai)**

Pune Research Supervisor

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled **"Asymmetric Synthesis of Bioactive 1, 2-Aminoalcohols and Methodologies involving Dihydroxylation of Olefins, Esterification and Iodination of Aromatics"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

October 2008
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L. Emmanuvel

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl Lithium
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DIBAL-H	Diisobutyl alulinum hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
ee	Enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
IR	Infra red
IBX	2-Iodoxybenzoic acid
Imid.	Imidazole
KHMDS	potassium hexamethyl disilazide

K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyl disilazide
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
Red-Al	Bis(2-methoxyethoxy)aluminum hydride
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
TMSCN	Trimethylsilyl cyanide
Ts	Tosyl

GENERAL REMARKS

1. All solvents were distilled and dried before use.

2. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.

3. Organic layers after every extraction were dried over anhydrous sodium sulfate.

4. Column Chromatography was performed over silica gel (60-120 mesh).

5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.

6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.

7. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 and MSL-300 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.

8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.

9. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.

10. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

11. Elemental analysis was done on Carlo ERBA EA 110B instrument.

12. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

ABSTRACT

The thesis entitled "**Asymmetric Synthesis of Bioactive 1, 2-Aminoalcohols and Methodologies involving Dihydroxylation of Olefins, Esterification and Iodination of Aromatics**" is divided into four chapters.

The title of the thesis clearly reflects the objective, which involes the synthesis of enantiomerically pure bioactive molecules and also the development of useful synthetic methodologies. **Chapter 1** describes the synthesis of two *trans* hydroxypiperidine-based bioactive amino alcohols, *namely* Febrifugine, a potent antimalarial alkaloid and the formal synthesis of (-)-epiquinamide, a quinazolizidine alkaloid, using OsO_4 catalyzed asymmetric dihydroxylation of homoallylic esters. **Chapter 2** deals with the synthesis of (+)-L-733,060 *via* Shi epoxidation of homoallylic carboxylate and sphingosine *via* kinetic resolution of allylic alcohol. **Chapter 3** deals with $NaIO_4$-mediated synthetic transformations involving catalytic modification of the Prevost and Woodward reactions for *syn* and *anti* dihydroxylation of olefins and aromatic electrophilic iodination of activated arenes using $NaIO_4$/KI/NaCl in acetic acid and direct esterification of aldehydes *via* radical pathway. **Chapter 4** presents synthetic transformations involving a titanium superoxide-catalyzed one pot dioxy functionalization of olefins under truly heterogeneous conditions to afford diols as well as vicinal methoxy alcohols and Pd- catalyzed ligand and base-free Suzuki type coupling of boronic acids with arylmercuric acetates.

CHAPTER I

A short and enantioselective synthesis of (+)-febrifugine, an antimalarial alkaloid and formal synthesis of (-)-epiquinamide *via* Sharpless asymmetric dihydroxylation of homoallylic esters

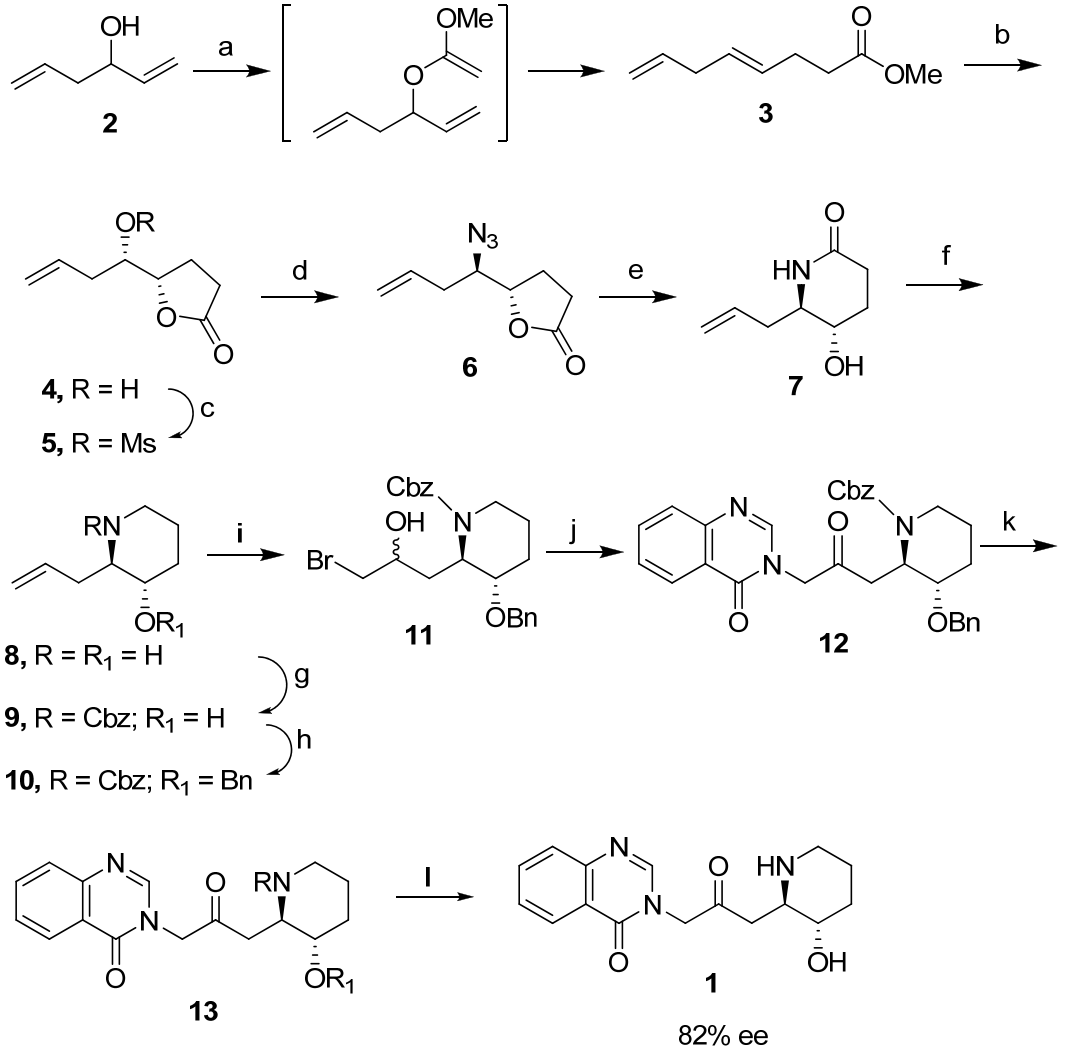
Sharpless Asymmetric dihydroxylation (ADH) is one of the most effective methods for the preparation of chiral diols, which are important intermediates for the synthesis of various bioactive molecules.[1] This chapter deals with enantioselective synthesis of febrifugine and (-)-epiquinamide using ADH of homoallylic esters.

Section 1: A short, enantioselective synthesis of (+)-Febrifugine, a potent antimalarial alkaloid

Febrifugine (**1**), isolated from the Chinese medicinal plant *Dichroa febrifuga Lour*, has been found to be effective against avian malaria, *Plasmodiuna cynomolgi* in monkey, *Plasnaoclium berghei* in mice.[2] Interestingly, Febrifugine (**1**) was also found to exhibit excellent therapeutic activity than its enantiomer, racemate and isofebrifugine against malarial parasite plasmodium. This section describes a short enantioseletive synthesis of febrifugine *via* aymmetric dihydroxylation of 1,4-diene.

The synthetic approach towards febrifugine started with commercially available 1,5-hexadien-3-ol (**2**), which was subjected to Johnson-Claisen [3,3]-sigmatropic rearrangement (trimethyl orthoacetate, catalytic amount of propionic acid, xylene, 135 ^{o}C) to give exclusively *E*-diene ester **3** as a single product in 86% yield (**Scheme 1**).[3] Regioselective asymmetric dihydroxylation of internal olefin in **3** was achieved using α-AD mix {cat. OsO_4, $(DHQ)_2$-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3, ^{t}BuOH: H_2O (1:1), 0 °C, 2 h} to produce the hydroxylactone **4** in 73% yield. Mesylation of the free alcohol (MsCl, Et_3N, CH_2Cl_2, 0 °C) in **4** followed by S_N2 displacement with NaN_3 in DMF at 80 °C resulted in the formation of azidolactone **6.** Reduction of azide under Staudinger conditions (PPh_3, H_2O)[4] furnished the lactam **7**; presumably formed by the intramolecular lactamization of the free amine generated *in situ* releasing the free alcohol.[5] Chemoselective reduction of lactam **7** was achieved with lithium aluminium hydride (LAH) to give hydroxy piperidine

8. The free amine and alcohol groups were subsequently protected with Cbz and BnBr respectively to afford the intermediate **10** in 72% yield over three steps.



Scheme 1: Reagents and conditions: a) $CH_3C(OMe)_3$, cat. propanoic acid, xylene, 135 °C, 88%; b) OsO_4, $(DHQ)_2PHAL$, $K_3[Fe(CN)_6]$, K_2CO_3, *t*-BuOH:H_2O (1:1), 73%; c) MsCl, CH_2Cl_2, 0 °C; d) NaN_3, DMF, 80 °C, 82% over two steps; e) PPh_3, THF, 25 °C then H_2O reflux, 93%; f) LAH, THF, reflux, 85%; g) CbzCl, K_2CO_3, THF:H_2O (1:1); h) BnBr, NaH, DMF, 0 °C, 84%; i) NBS, CH_3CN/H_2O; j) 4-quinazolinone, KOH, MeOH, 25 °C; k) Dess-Martin periodinane, CH_2Cl_2, 78% over two steps; l) 6 N HCl, reflux, 78% over two steps.

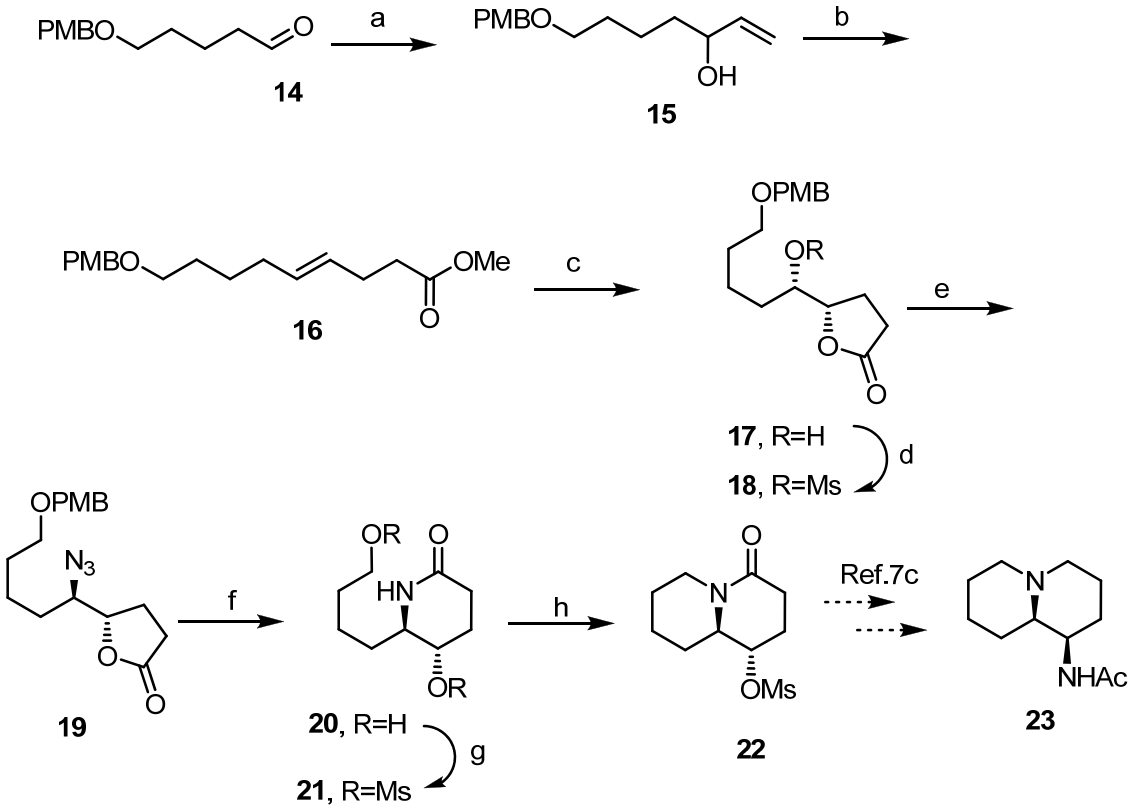
Regioselective bromohydroxylation (NBS, CH_3CN: H_2O) of terminal olefin in **10** gave the separable diastereomeric terminal halide **11** in the ratio 1:1 (^{1}H NMR spectral analysis). Without separation of the isomers, halohydrin **11** was coupled with 4-quinazolinone to afford the corresponding coupled product **12**, which was subjected to oxidation with Dess-Martin periodinane (DMP)[6] to obtain protected febrifugine **13** in 83% yiled. Finally, removal of protecting groups was successfully achieved using 6N HCl to afford febrifugine **1.** Thus, a practical asymmetric synthesis of febrifugine alkaloid **1** is achieved using Sharpless asymmetric dihydroxylation of homoallylic carboxylate as the key step.

Section 2: Enantioselective formal synthesis of (-)-Epiquinamide *via* asymmetric dihydroxylation

(-)-Epiquinamide (**23**), a quinazolizidine alkaloid, was recently isolated from the skin extracts of the Ecuadorian poison dart frog *Epipedobates tricolor*.[7] It has modest activity in cells expressing various nAChR subtypes, with highest activity in SH-sy5y cells and k-177 cells expressing human α4β2-nAChR. It represents a new structural class of nicotinic agonists and is also proven to function as a potential lead compound for the development of new therapeutics for neuronal receptors.

Our synthesis of quiazolizidinone intermediate **22** commenced with Grignard addition of vinylmagnesium bromide to the aldehyde **14** to afford allylic alcohol **15** , which was subjected to Johnson-Claisen [3,3] sigmatropic rearrangement (trimethyl orthoacetate, catalytic amount of propionic acid, xylene, 135 ºC) to give *E*-homoallylic ester **16** exclusively in 75% yileld (**Scheme 2**). Having the required carbon backbone with olefin functionality at *γ, δ* position, asymmetric dihydroxylation {$OsO_4(DHQ)_2$-AQN, $K_3[Fe(CN)_6]$, K_2CO_3, ^{t}BuOH:H_2O} was performed to yield hydroxylactone **17** in 79% yield and 85% ee (HPLC analysis). Mesylation (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ºC) of free

alcohol group in **17** gave its mesylate **18**, which was subjected to S_N2 displacement with NaN_3 (DMF, 80 ºC) to furnish azidolactone **19** with complete inversion of configuration.



Scheme 2: Reagents and conditions: a) CH_2=CHMgBr, THF, 0 ^oC, 3 h, 83%; b) $CH_3C(OMe)_3$, cat. $CH_3CH_2CO_2H$, xylene, 135 ^oC, 4 h, 85%; c) OsO_4 (0.1 mol%), $(DHQ)_2AQN$ (0.5 mol%), $K_3[Fe(CN)_6]$ (3 equiv.), K_2CO_3 (3 equiv.), *t*-BuOH:H_2O (1:1), 24 h, 89%; d) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^oC, 1 h, 98%; e) NaN_3, DMF, 60 ^oC, 5 h, 87%; f) Pd/C, H_2, MeOH, 25 ^oC, 24 h, 99%; g) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^oC, 1 h, 98%; h) NaH, THF, reflux, 97%.

Reduction of azide group and PMB deprotection in **19** under hydrogenation conditions {H_2 (1 atm.), 10%Pd/C} at 25 ^oC produced lactam **20** in 98% yield, presumably *via* intramolecular *O*-to-*N* ring expansion of amine generated *in situ*. Mesylation (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ºC) of both the hydroxyl groups in **20** gave dimesylate **21,** which was subjected to *N*-alkylation (NaH, THF, reflux) to form the known intermediate

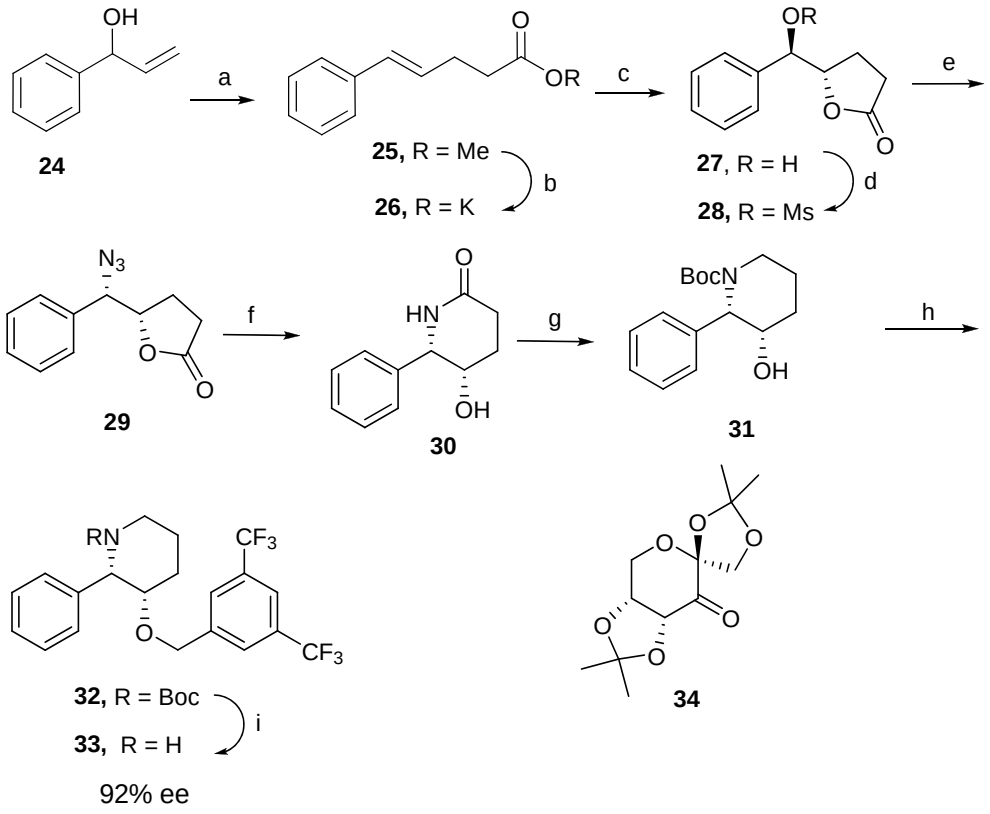
quinazolizidine **22** in 97% yiled. The conversion of quinazolizidinone **22** to epiquinamide **23** has been reported in the literature.[7c]

CHAPTER II

Section 1: A short enantioselective synthesis of (+)-L-733,060 *via* Shi epoxidation of a homoallylic carboxylate

(+)-L-733,060 (**33**) possessing 2-alkyl-3-hydroxypiperidine structural unit has proven to be selective and potent non-peptide neurokinin substance P receptor antagonist.[8] Also, it has been implicated in a variety of disorders including migraine, rheumatoid arthritis and pain. Recent studies have shown that (+)-L-733,060 (**33**) can act both as an antitumor agent and as a promising new target for the treatment of retinoblastoma. This section illustrates the practical, enantioselective synthesis of (+)-L-733,060 (**33**) *via* Shi epoxidation of homoallylic carboxylate 2**6** using ketone **34,** derived from D-fructose, as the chiral catalyst. Our approach to the synthesis of L-733,060 (**33**) commenced with allylic alcohol 2**4,** which was subjected to Johnson–Claisen [3,3]- sigmatropic rearrangement to give *E*-homoallylic ester **25** exclusively in 82% yield (**Scheme 3**). Alkaline hydrolysis of ester **25** using aq. KOH furnished potassium alkenoate **26,** which was subjected to Shi epoxidation[9] using D-fructose-derived ketone **34** as the chiral catalyst (30 mol%) and Oxone as the stoichiometric oxidant to afford hydroxylactone **27** in 62% yield and 92% ee [%ee was determined from ^{1}H NMR of the corresponding Mosher's ester]. Mesylation (MsCl, Et_3N) of alcohol **27** gave the mesylate **28,** which was subjected to S_N2 displacement with NaN_3 (DMF, 60 ^oC) to afford azidolactone **29**. Reduction of azide **29** under Staudinger conditions (PPh_3, THF, 25 ^oC then H_2O, reflux) produced lactam **30** in 91% yield, *via* intramolecular *O*-to-*N*- ring expansion of the amine generated *in situ*. Reduction of lactam **30** with $BH_3.SMe_2$ in THF followed by the protection of the secondary amine with $(Boc)_2O$ gave the *syn*

aminoalcohol **31** in 73% yield over two steps. *O*-alkylation of **31** with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH furnished **32,** which upon deprotection of the Boc group under acidic conditions afforded L-733,060 (**33).**

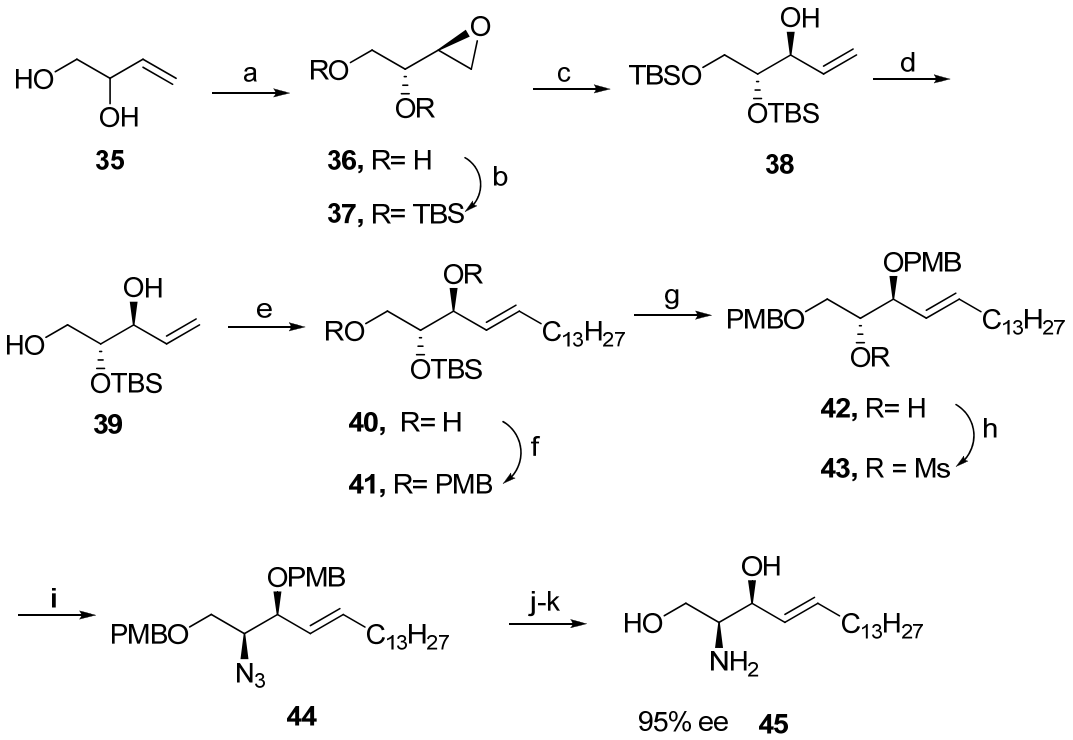


Scheme 3: Reagents and conditions: a) $CH_3C(OMe)_3$, propanoic acid, 135 °C, 6 h, 82%; b) aq. KOH, reflux; c) *p*H 10-11, Oxone, chiral ketone **34**, KOH, CH_3CN, -5 °C, 1 h then 15 °C, 5 h, 62%; d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 96%; e) NaN_3, DMF, 60 °C, 12 h, 94%; f) PPh_3, THF, 25 °C , 2 h then H_2O reflux 3 h, 91%; g) i) $Me_2S{\cdot}BH_3$, THF, reflux, 6 h; ii) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 0 – 25°C, 73% over two steps; h) 3, 5-bis (trifluoromethyl)benzyl bromide, NaH, DMF:THF (3:1), 0 °C, 6 h; i) TFA, CH_2Cl_2, 18 h, 81% over two steps.

Thus, an efficient organocatalytic asymmetric synthesis of (+)-L-733,060 (**33**) has been achieved using Shi epoxidation of homoallylic carboxylate as the key step.

Section II: Enantioselective synthesis of sphingosine *via* Sharpless kinetic resolution

Sphingolipids[10] are derived from the common base structure, *i.e.* sphingosine (**45**). As important messengers for controlling cell growth, maturity, survival, and death, sphingolipids show promising efficacy for the control of cancer and other proliferative diseases. The related *N*-acylsphingosines are widely used in the cosmetic industry as active ingredients to improve skin cell cohesion. This section describes the synthesis of sphingosine **45** *via* Sharpless kinetic resolution of allylic alcohol.[11]



Scheme 4 : Reagents and conditions: a)TBHP, D-(-)-DET, Ti(O*i*Pr)$_4$, CH_2Cl_2, 4 Aº MS, -20 °C, 18 h, 43%; b) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 93%; c) $(CH_3)_3S^+I^-$, *n*BuLi, THF, -20 °C- 0 °C, 2 h, 82%; d) CSA, MeOH:CH_2Cl_2 (1:1), 0 °C, 2 h, 85%; e) Grubbs' catalyst (10 mol%), Pentdec-1-ene, CH_2Cl_2, reflux, 10 h, 62%; f) PMB-Cl, NaH, DMF:THF, 2 h, 0 °C; g) TBAF, CH_2Cl_2, 0 °C; 83% over two steps; h) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 1 h; i) NaN_3, DMF, 80 °C, 6 h, 79% over two steps; j) DDQ, CH_2Cl_2:H_2O, 0 ºC; k) $LiAlH_4$, THF, 0 °C 1 h then reflux 2 h, 82%.

The synthesis of sphingosine **45** was started with the kinetic resolution of racemic diol **35** *via* Sharpless epoxidation using (-)-DET and Ti(O*i*Pr)$_4$ to furnish epoxyalcohol **36**

followed by silyl protection of the diol with TBSCl (**Scheme 4**). The chiral epoxide **37** was regioselectively opened with sulfonium ylide[12] to get the allyl alcohol **38** with one carbon homologation. Selective deprotection of the primary silyl ether in **38** was achieved using camphor sulfonic acid to result in the formation of diol **39**, which was cross-coupled with pentadec-1-ene in the presence of Grubbs catalyst[13] to get the long chain diol **40** in 62% yield. The free alcohol groups were then protected as PMB ethers and the secondary silyl protection was cleaved using TBAF to furnish the free alcohol **42** in 83% yield over two steps. Mesylation (MsCl, Et_3N) of OH followed by S_N2 displacement with NaN_3 resulted in azide **44** with complete inversion of configuration. Deprotection of PMB ether followed by reduction of azide function using $LiAlH_4$ furnished sphingosine **45** in 82% yield and 95% ee.

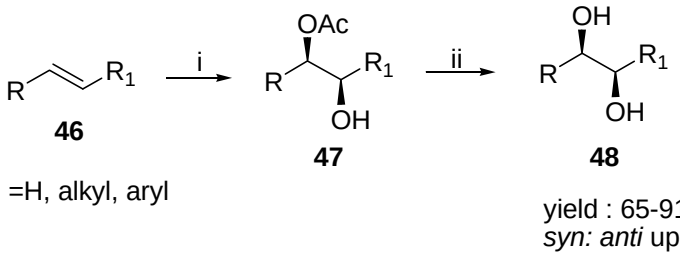
CHAPTER III

Section 1: $NaIO_4$/LiBr-mediated diastereoselective dihydroxyaltion of olefins: a catalytic approach to Prevost-Woodward reaction

The catalytic dihydroxylation of alkenes represents a unique method for the preparation of 1,2-diols with defined relative configuration and several oxidants are now used for this purpose both in the laboratory and industry. This section deals with, a new "transition metal-free" procedure for the dihydroxylation of alkenes catalyzed by LiBr and mediated by either $NaIO_4$ or (diacetoxyiodo)benzene [$PhI(OAc)_2$], which are quite stable at the reaction temperature.

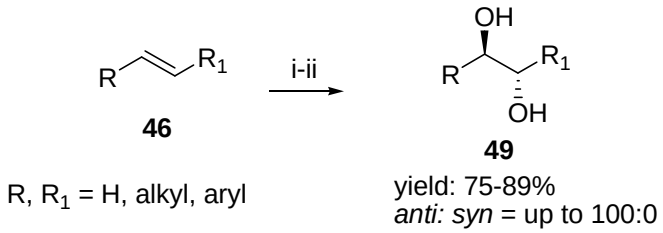
During the course of our investigation on $NaIO_4$-mediated organic transformations, we observed that treatment of olefin **46** with catalytic amount of $NaIO_4$, LiBr and acetic acid resulted in *syn* diol derivative **47,** which upon hydrolysis under basic conditions furnished

syn diol **48** (**Scheme 5**). The *syn* selectivity is controlled by water, formed *in situ* from $NaIO_4$ and AcOH. This reaction is a simple catalytic modification of Woodward reaction.[14]



Scheme 5: Reagents and conditions: i) olefin (3 mmol), $NaIO_4$ (30 mol%), KI (20 mol%), AcOH (5 mL), 95 ºC, 18 h; ii) K_2CO_3 (4.5 mmol), MeOH (15 mL), 25 °C, 24 h.

Attempts to obtain *anti* diols, by removing water formed *in situ* using either molecular sieves (4A°) or anhydrous $MgSO_4$ were not successful. Interestingly, a*nti* diols **49** were obtained when $PhI(OAc)_2$ was employed as the oxidant in stoichiometric amounts under the same reaction conditions (**Scheme 6**). The absence of water in the reaction mixture led to the formation of *anti* diol, a Prevost product.[15]

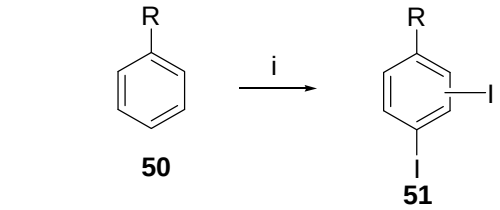


Scheme 6: Reagents and conditions: i) olefin (3 mmol), LiBr (20 mol%), $PhI(OAc)_2$ (3 mmol), AcOH (5 mL), 95 °C, 18 h; ii) K_2CO_3 (9 mmol), MeOH (20 mL), 25 °C, 24 h.

Several alkenes (aliphatic, styrenic, allylic, di-substituted alkenes, α, β-unsaturated alkenes, etc) with electron-donating and -withdrawing groups underwent dihydroxylation and produced the corresponding *syn* and *anti* diols in excellent yields.

Section 2: $NaIO_4$/KI/NaCl: A new reagent system for iodination of activated aromatics through *in situ* generation of iodine monochloride

Aromatic iodo compounds are versatile building blocks for the preparation of organometallic reagents and some are potential intermediates for the synthesis of pharmaceutical and bioactive molecules. They are also useful in metal-catalyzed (e.g. Heck, Stille and Negishi) cross-coupling reactions, which are widely employed in the preparation of C-C, C-N, etc. bond- forming reactions.[16] Aryl iodides are usually more difficult to prepare than the corresponding other aryl halides due to the low electrophilic strength of iodine. This section deals with an efficient, new and milder procedure for the iodination of activated aromatics using $NaIO_4$/ KI/NaCl/aq.AcOH reagent (**Scheme 7**). Iodination of activated aromatics had been achieved with alkali metal iodides (KI or NaI) as iodine source and $NaIO_4$ as oxidant in aq. AcOH acting both as solvent and an acid source in the presence of NaCl (2 equiv.) as additive to obtain iodoaromatics **51** in excellent yields.



50 **51**

R = NH_2,OH, OMe

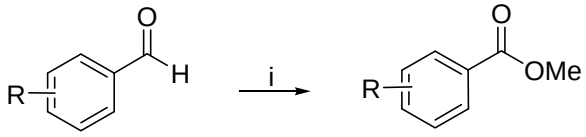
without NaCl = only 55%
with NaCl = up to 98%

Scheme 7: Reagents and conditions: i) arene (3 mmol), KI (3 mmol), $NaIO_4$ (3 mmol), NaCl (6 mmol), 10 mL of AcOH:H_2O (9:1), 25 $^{\circ}$C.

The addition of NaCl as additive increases the yield considerably. Other oxidizing agents like KIO_3, Oxone also gave excellent yields with KI as well as I_2 as iodine source.

Section 3: $NaIO_4$/LiBr-mediated direct esterification of aromatic aldehydes to esters

The direct conversion of aldehydes or alcohols to the corresponding carboxylic esters is often required in organic synthesis particularly in the synthesis of natural products. The conventional method for the synthesis of carboxylic esters involves oxidation of aldehydes to carboxylic acids followed by esterification with alcohols catalyzed by either acid or base.[17] Thus the direct esterification of alcohols or aldehydes to esters minimizes the number of steps in the organic syntheses. This section describes a new cost-effective procedure for the direct esterification of aromatic aldehydes **52** to the corresponding esters **53** mediated by $NaIO_4/LiBr/H^+$ combination (**Scheme 8**).



52 **53**

R=Me, NO_2, Cl, etc yield: 78-98%

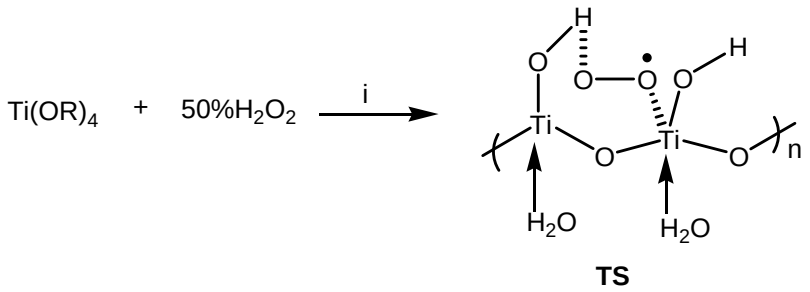
Scheme 8: Reagents and conditions: (i) aldehyde (3 mmol), $NaIO_4$ (3 mmol), mmol), conc. H_2SO_4 (1 mL), methanol (9 mL), 25 °C, 18 h.

CHAPTER 4

Section 1: Titanium superoxide: A stable and reusable catalyst for one-pot oxyfunctionalization of olefins via epoxide opening

Direct introduction of two oxygen atoms across the olefin with either *syn* or *anti* selectivity is one of the most important reactions since the resulted diols or diol derivatives are the important building blocks in organic chemistry. Generally, diol derivatives are prepared *via* a two-step process of epoxidation followed by its opening in the presence of acid catalysts. This section describes the one-pot synthesis of diols and alkoxyalcohols from olefins using *m*CPBA as oxidant and catalyzed by titanium superoxide (**TS**) as catalyst.

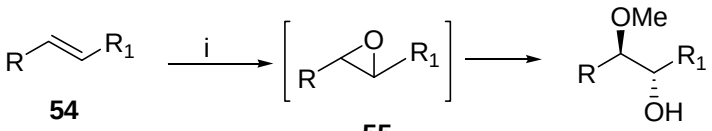
Titanium superoxide (**TS**) was prepared by the addition of H_2O_2 to titanium tetraisopropoxide[18] in methanol to produce a yellow solid and has been proposed to have the polymeric structure as shown in (**Scheme 9**).



TS

Scheme 9: Reagents and conditions: (i) MeOH, 25 ºC, 1 h.

We observed that when olefin **54** was reacted with mCPBA in the presence of titanium superoxide and methanol furnished alkoxy alcohols **56** in excellent yields probably *via* opening of *in situ* generated epoxides **55** with alcohols as nucleophiles. Both aliphatic as well as aromatic olefins regioselectively produced the alkoxy alcohols in excellent yields (**Scheme 10**).



54 **55** **56**

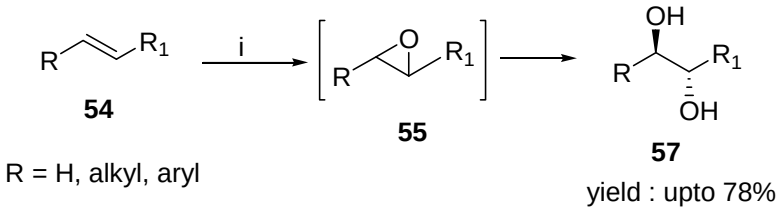
R, R1 = alkyl, aryl, H

yield upto 95%

Scheme 10: Reagents and conditions: (i) alkene, *m*CPBA, titanium superoxide (20 wt%), $CHCl_3$:MeOH (9:1), 25 ºC, 5 h.

We also observed that when methanol was replaced with water, *anti* diols **57** were produced in good yields **(Scheme 11)**. However, vigorous stirring was required to achieve good yields of diol. After the completion of the reaction, the reaction mixture was filtered

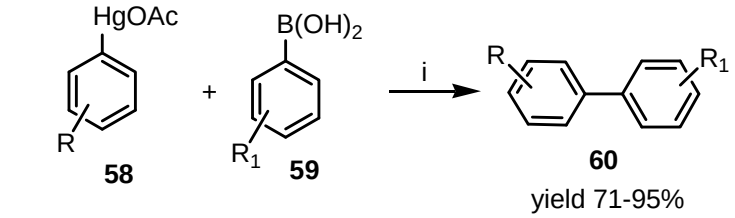
and the residue containing titanium superoxide was tested for reusability and found to be active for oxyfunctionalization of olefins.



Scheme 11: Reagents and conditions: (i) alkene, *m*CPBA, titanium superoxide (20 wt%), $CHCl_3$:H_2O (9:1), 25 ºC, 5 h.

Section 2: Phosphine ligand and base-free, Pd- catalyzed Suzuki type cross-coupling reaction of arylboronic acids with arylmercuric acetates

The palladium-catalyzed Suzuki-Miyaura coupling of aryl halides with arylboronic acids or esters is one of the most powerful and versatile methods for the formation of C-C bonds, in particular for the preparation of biaryl compounds. In recent years this reaction has been successfully applied for the synthesis of natural products, drugs and conducting polymers. This section describes the Suzuki type cross-coupling reaction of arylboronic acids with arylmercuric acetates.



Scheme 12: Reagents and conditions: i) arylmercuric acetate (3 mmol), aryl boronic acid (3 mmol) $Pd(dba)_2$ (5 mol%), toluene (5 mL), 25 °C , 3 h.

It has been reported that the reaction of arylboronic acids **59** with aryl mercuric salts **58** in polar solvent such as methanol led to the isolation of diarylmercury.[19] We found that when the same reaction was carried out in non-polar solvents like toluene in the presence of palladium salts as catalyst it took different course to give the cross-coupled biaryls **60** in good yield (**Scheme 12).** Among the several metal salts and solvents screened, palladium catalysts were found to be extremely active and gave excellent yields of biphenyls over other metal complexes. Among the solvents, toluene gave excellent yield while the more polar solvents like MeOH, CH_3CN, H_2O and dioxane resulted in diphenyl mercury as the major product. A remarkable feature of this system is that neither base nor phosphine ligand was required.

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CHAPTER 1

A short and enantioselective synthesis of (+)-febrifugine and formal synthesis of (-)-epiquinamide via Sharpless asymmetric dihydroxylation of homoallylic esters

Section I:

A short enantioselective synthesis of (+)-Febrifugine, a potent antimalarial alkaloid

1.1.1 Introduction

Malaria is by far the most important tropical parasitic disease that kills more people than any other communicable diseases except for tuberculosis. In many developing countries, especially in Africa, malaria exacts an enormous toll in lives, in medical costs, and in days of labor lost. *Plasmodium falciparum* accounts for the majority of infections and is found to be the most lethal.[1] However, malaria is a curable disease if promptly diagnosed and adequately treated. Currently, a number of drugs such as chloroquine and quinine are available for the treatment of malaria, but the rapid development of drug resistance is a serious problem. Medicinal agents based on novel mechanisms of action are, therefore, required to overcome the emergence of resistance and to control an ever-increasing number of epidemics caused by the malarial parasite. For centuries in China, the roots of *Dichroa febrifuga* Lour (Chinese name: Cháng Shan), a saxifragaceous plant, have been employed against malarial fevers, and no parasite resistant to *D. febrifuga* has been reported.[2]

(+)-Febrifugine (**1**) and isofebrifugine (**2**) both isolated in 1947 from the Chinese medicinal plant and related plants are well-known antimalarial agents.[3] (+)-Febrifugine (**1**) is found to be effective against avian malaria, *Plasmodiuna cynomolgi* in monkey, *Plasnaoclium berghei* in mice, has powerful emetic index and has been found to exhibit excellent therapeutic activity than its enantiomer, racemate or isofebrifugine against malarial parasite plasmodium. Interestingly, febrifugine and isofebrifugine are

epimerizable *via* ω–aminoenone under acidic condition.[4] These alkaloids were approximately 100 times as effective as quinine against Plasmodia lophurae in ducks.

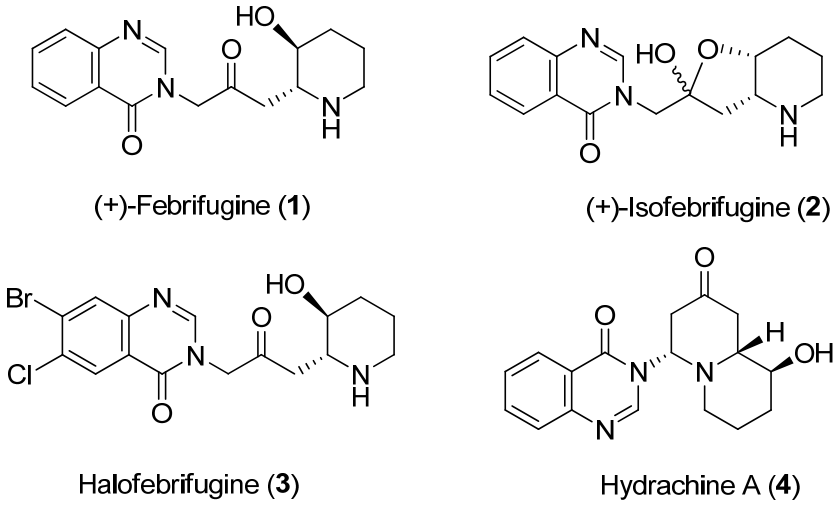


Fig. 1: Febrifugine and its structurally related compounds

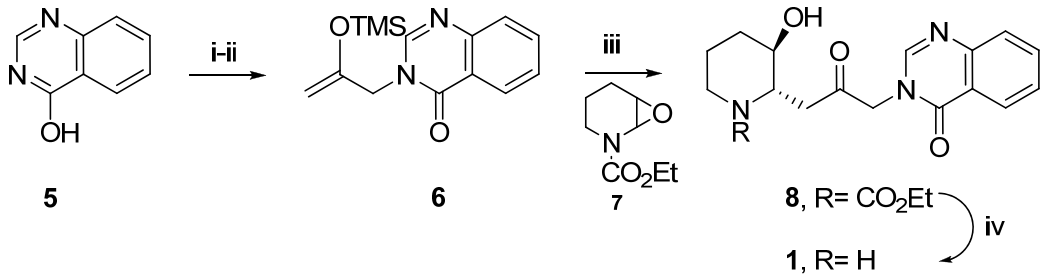
The planar structures of **1** and **2** were first proposed in 1950. Subsequently, their relative and absolute structures were proposed, based on Baker's synthetic work.[5] The relative configuration of **1** was corrected in 1973 and then the absolute structures of **1** and **2** were corrected in 1999, as shown in Fig. 1. These repeated errors and corrections have caused much confusion in the study of the relationship between the structure and antimalarial activity of febrifugine derivatives. The antimalarial activity exhibited by these two compounds have stimulated intensive chemical and biological studies, which have led to the development of halofebrifugine (**3**) as an antiparasitic feed additive, which has recently been shown to inhibit collagen production and is currently under clinical trials for treatment of scleroderma in human.[6] Recent studies also led to the isolation of hydrachine A (**4**) as a novel alkaloid and led to the discovery of several febrifugine analogues,[7] which show potent antimalarial activity **(Fig. 1)**.

1.1.2 Review of Literature

Literature search reveals that there are several reports available for the asymmetric as well as racemic syntheses of febrifugine (**1**); some of the recent ones are described below.

Burgess' approach (1996)[8]

This approach deals with opening of epoxide **7**, generated from cyclic ene carbamate, with silyl enol ether **6** in the presence of a Lewis acid as the key step. Accordingly, silyl enol ether **6,** the necessary nucleophilic partner, was readily prepared from 4-hydroxyquinazoline (**5**) by *N*-alkylation with chloroacetone followed by enolisation and its protection as trimethylsilyl ether. Reaction of **6** with epoxide **7** was then accomplished in the presence of titanium tetrachloride to generate a mixture of separable diastereomers of **8**. After chromatography purification, hydrolysis of the carbamate ester with potassium hydroxide yielded the natural product, febrifugine (**1**) **(Scheme 1)**.

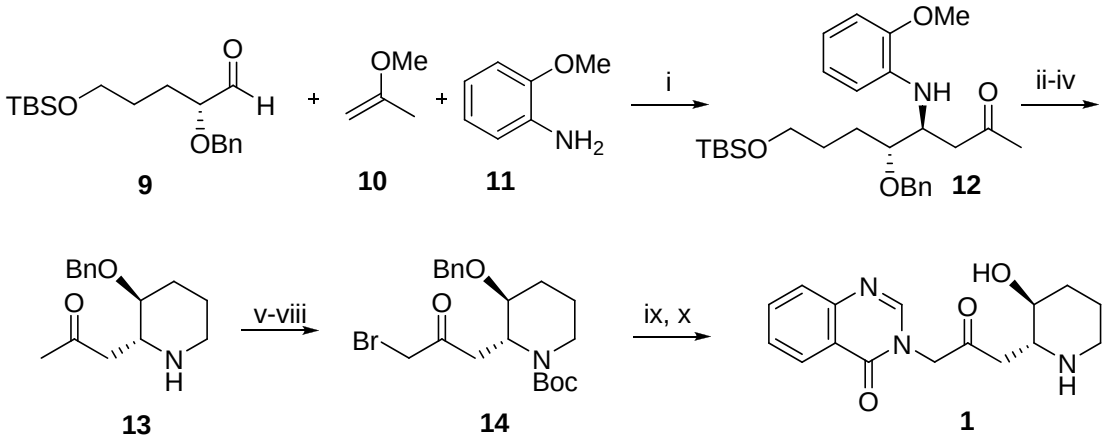


Scheme 1: i) NaH, DMF, 0 ºC then chloroacetone 0 ºC to 25 ºC, 62%; ii) TMSOTf, Hunig base, CH_2Cl_2, 25 ºC, 82%; iii) **7**, cat. $TiCl_4$, CH_2Cl_2, 0 ºC, 40%; iv) separation by flash chromatography, then KOH, diethylene glycol, H_2O, reflux, 10%.

Kobayashi's approach (1999)[9]

Kobayashi *et al.* have described the synthesis of febrifugine using lanthanide-catalyzed three-component reaction between aldehyde **9**, 2-methoxypropene (**10**) and 2-methoxyaniline (**11**), which furnished the protected 1,2-amino alcohol **12** in 92% yield. The *anti*-adduct was then treated with HF to deprotect the silyl (TBS) group. Bromination

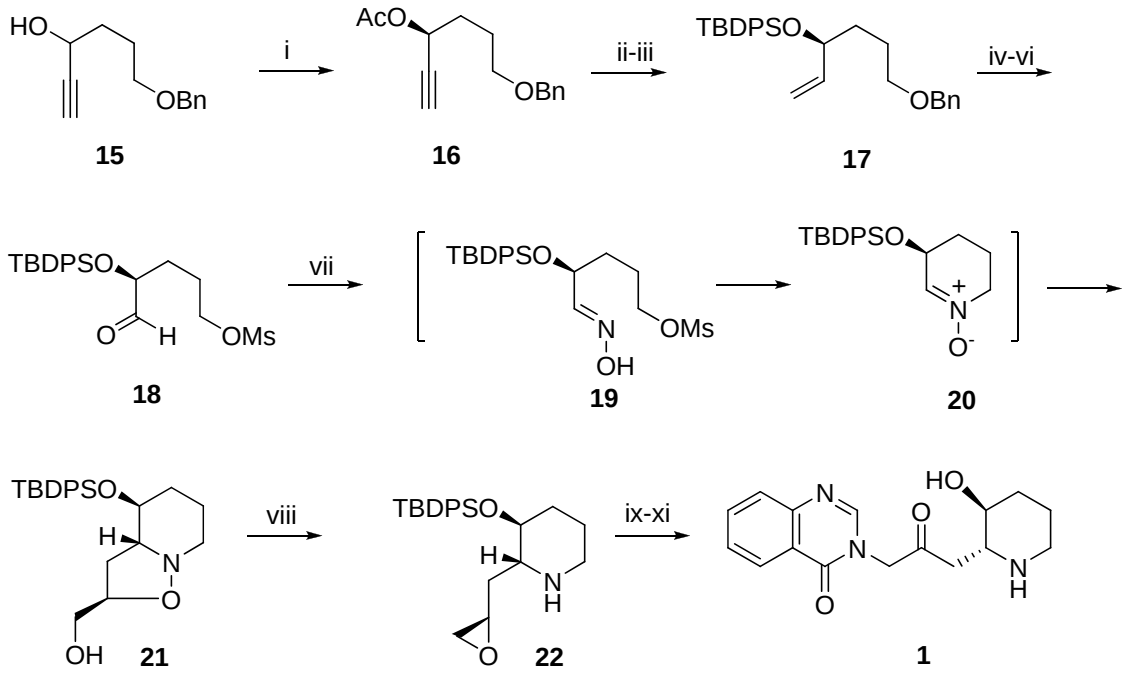
of the resulting free hydroxyl group gave a cyclized adduct, whose *N*-protecting group was removed using ceric ammonium nitrate (CAN) to afford **13** in excellent yield. Piperidine **13** was protected as its *N*-Boc group and was treated with lithium hexamethyldisilazide (LHMDS) and then trimethylsilyl chloride (TMSCl) to obtain silyl enol ether. The resulting silyl enol ether was oxidized with *m*-CPBA and then brominated to give bromoketone **14**. The coupling of bromoacetone **14** with 4-hydroxyquinazoline using potassium hydroxide (KOH) followed by removal of protecting groups using 6N HCl afforded febrifugine (**1**) **(Scheme 2)**.



Scheme 2: i) $Yb(OTf)_3$ (10 mol%), THF:H_2O, 5 ºC, 92%; ii) HF, THF, 99%; iii) PPh_3, CBr_4, CH_2Cl_2, 96%; iv) CAN, CH_3CN, H_2O, 0 ºC, 70%; v) Boc_2O; vi) LHMDS, THF, TMSCl; vii) *m*-CPBA, CH_2Cl_2, 52%; viii) PPh_3, CBr_4, CH_2Cl_2, 79%; ix) 4-hydroxyquinazoline, KOH, 75%; x) 6N HCl, reflux, quant.

Hatakeyama's approach (2001)[10]

Hatakeyama *et al.* have employed the 1,3-dipolar addition of nitrone **20** with allyl alcohol as the key step. This synthesis started with enzyme mediated kinetic resolution of racemic propargylic alcohol **15** on acetylation with vinyl acetate in the presence of Novozym 435 to afford (*S*)-acetate **16** with 91% ee and 43% yield. Selective hydrogenation of **16** with

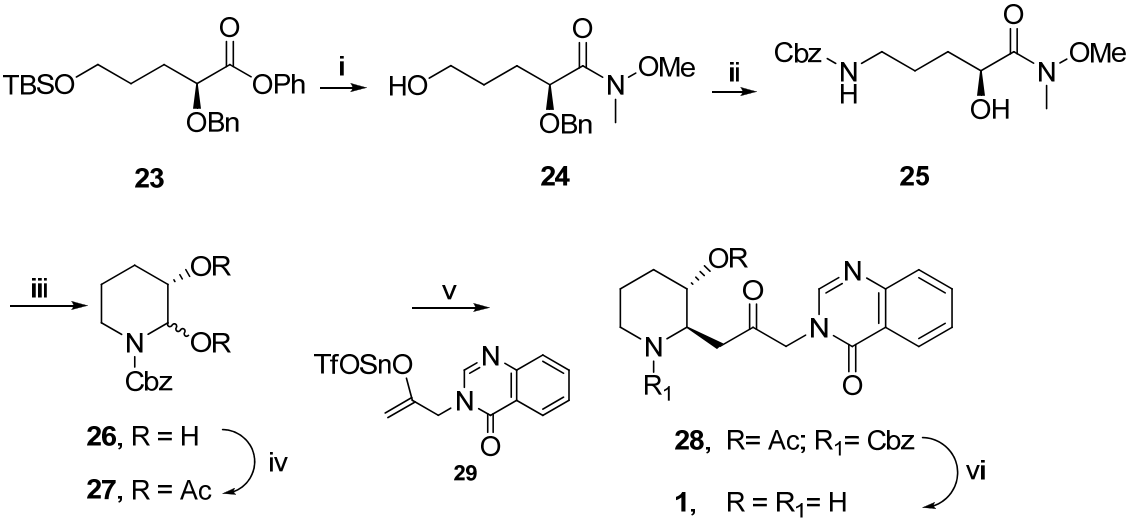


Scheme 3: i) CH_2=CHOAc, Novozym 435, *i*-Pr_2O, 43%, 91% ee; ii) Lindlar catalyst, H_2, MeOH then K_2CO_3; iii) TBDPSCl, imid, DMF, 80%; iv) lithium naphthalenide, THF, -25 ºC; v) MsCl, Et_3N, CH_2Cl_2, 93%; vi) O_3 then Me_2S, CH_2Cl_2, -78 ºC; vii) $NH_2OH{\cdot}HCl$, Et_3N, allyl alcohol, 74% diastereomeric mixtures; viii) (a) H_2, $PdCl_2$, MeOH; (b) Boc_2O, Et_3N, CH_2Cl_2, 94%; (c) tosyl imidazole, NaH, THF, 92%; ix) 4-quinazolone, KH, DMF, 77%; x) Dess-Martin periodinane, CH_2Cl_2, 98%; xi) 6N HCl, reflux.

Lindlar catalyst followed by *in situ* methanolysis of ester and silyl protection gave olefin **17** in 80% yield. Upon reductive removal of the benzyl ether using lithium naphthalenide, mesylation followed by ozonolysis of the olefin gave aldehyde **18**. Treatment of aldehyde **18** with $NH_2OH.HCl$ in the presence of Et_3N in allyl alcohol generated nitrone **20** *in situ* which underwent simultaneous 1,3-dipolar cycloaddition with allyl alcohol to give **21** as diastereomers. Hydrogenolytic *N-O* bond fission and Boc protection gave the corresponding diol, which was converted into epoxide **22** by reaction with *N*-tosyl imidazole. Regioselective opening of epoxide with potassium salt of 4-quinazolone followed by oxidation with Dess-Martin periodinane produced protected febrifugine, which upon acid treatment furnished (+)-febrifugine (**1**) (**Scheme 3**).

Kobayashi's approach (2001)[11]

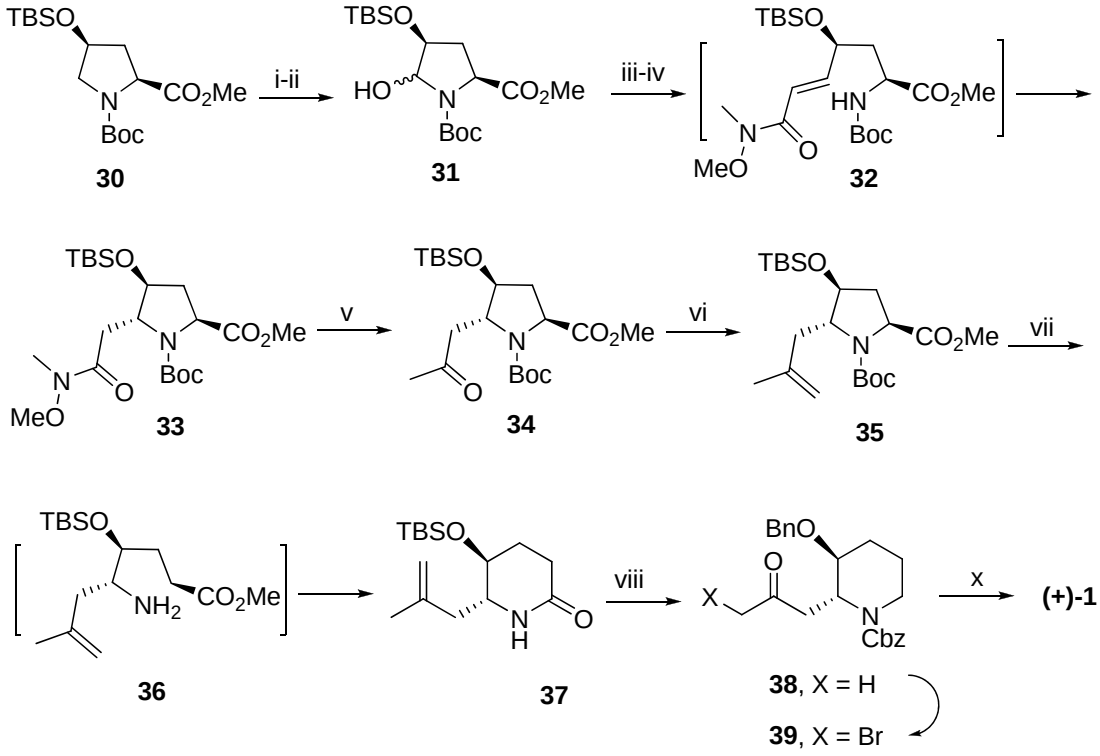
Kobayashi *et al.* have described the synthesis of febrifugine (**1**) from 2,3-diacetoxy-*N*-benzyloxycarbonylpiperidine (**27**) employing diastereoselective nucleophilic addition of tin enolate. Accordingly, ester **23** was converted into its Weinreb amide **24** on treatment with methoxy methyl amine followed by silyl deprotection. Mitsunobu reaction of **24** using diphenylphosporic azide (DPPA) converted the hydroxyl group at the 5-position into an azide group, which upon palladium-catalyzed hydrogenolysis followed by Cbz protection of the resulting amine yielded Weinreb amide **25** in 42% yield. Lithium aluminium hydride reduction of **25** provided a high yield of (3*S*)-*N*-benzyloxycarbonyl-2,3-dihydroxypiperidine (**26**). Diacetylation and coupling with the tin (II) enolate **29** followed by deprotection afforded febrifugine (**1**) **(Scheme 4)**.



Scheme 4: i) a) Me_3Al, MeNH(OMe); b) 1N HCl, 65%, two steps; ii) (a) DEAD, PPh_3, DPPA; (b) H_2 (10 atm), 10% Pd/C; (c) CbzCl, 42%, three steps; iii) $LiAlH_4$ in Et_2O, 91%; iv) Ac_2O, DMAP, Et_3N, quant.; v) **29**, $Sn(OTf)_2$, *i*-$PrEt_2N$, 0□25 °C, 70%; vi) (a) 30% HBr/AcOH, (b) MeONa/MeOH, 25%, two steps.

Honda's approach (2004)[12]

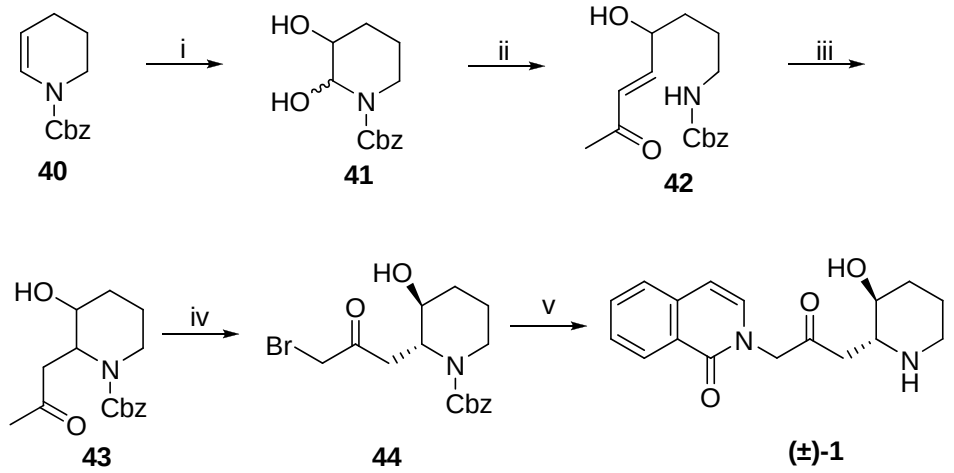
In this approach, protected (4*R*)-hydroxy-L-proline ester (**30**) was oxidized with RuO_4 to give the corresponding lactam, which upon reduction with lithium triethylborohydride gave aminal **31.** Wittig olefination of aminal **31** gave the Weinreb amide **33** formed *via* Michael addition of *α,β*-unsaturated amide **32**. Grignard addition of MeMgBr to the amide **32** afforded the ketone **34**, which on reaction with Wittig reagent gave the olefin **35** in 43% yield. Selective removal of the Boc group in **35** was achieved using $ZnBr_2$ to afford amine, which was subjected to SmI_2-promoted reductive deamination to furnish the lactam **37**. Reduction of lactam **37** with $LiAlH_4$ followed by protection of the resulting amine and alcohol functionalities and ozonolysis of the resulting olefin gave ketone **38**. Finally, ketone **38** was converted to (+)-febrifugine (**1**) *via* *α*-bromination (**39**) and coupling with 4-hydroxyquinazoline **(Scheme 5)**.



Scheme 5: i) cat. RuO_4, $NaIO_4$, AcOEt/H_2O, 25 ºC, 86%; ii) $LiEt_3BH$, THF, -78 ºC; iii) $(EtO)_2P(O)CH_2CON(Me)OMe$, NaH, THF, 25 ºC, 83%; iv) $BF_3.Et_2O$, CH_2Cl_2; v) MeMgBr, THF, 0 ºC, 88%; (vi) Tebbe's reagent, THF, 40 ºC to 25 ºC, 81% (vii) a) $ZnBr_2$, CH_2Cl_2,25 ºC; b) SmI_2, THF:HMPA, MeOH, 0 ºC to 25 ºC, 90%; viii) (a) $LiAlH_4$, THF, 65 ºC; (b) CbzCl, Et_3N, DMAP, CH_2Cl_2, 25 ºC, 95%; (c) BnBr, NaH, DMF, 0 ºC, 90%; (d) O_3, MeOH, -78 ºC then Me_2S, 92%; ix) (a) TMSOTf, DIPEA, CH_2Cl_2, 25 ºC; (b) NBS, 25 ºC; x) (a) 4-hydroxyquinazoline, KH, DMF, 70 ºC, 57%; (b) 6N HCl, reflux 92%.

Harayama's approach (2005)[13]

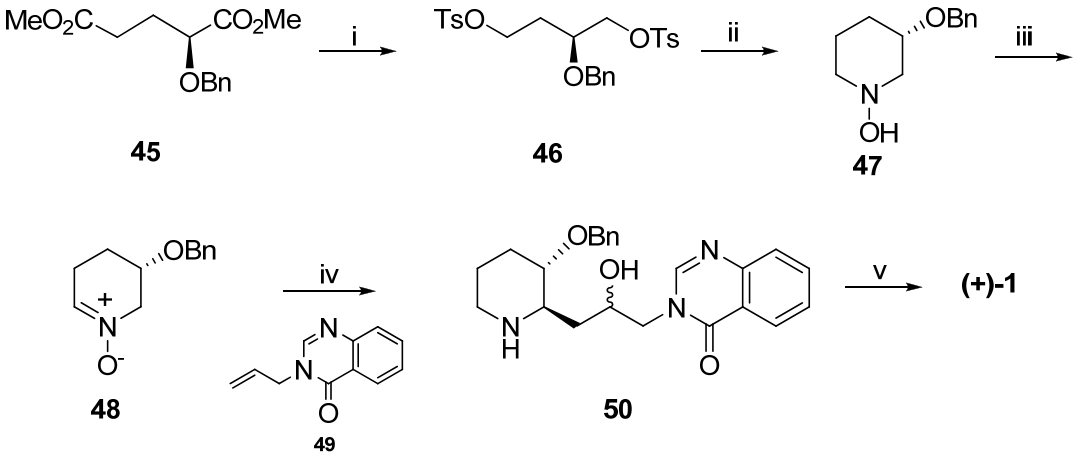
Harayama *et al.* have described the synthesis of *dl*-febrifugine using intramolecular Michael addition of *ω*-amidoenone **42** as the key step. 2,3-Piperidinediol **41**, prepared from tetrahydropyridine **40** by oxone-acetone oxidation, was subjected to Wittig olefination to afford *ω*–amidoenone **42** with *E*-selectivity. The *trans* olefin **42** was subjected to Michael addition in the presence of $BF_3{\cdot}OEt_2$ to afford the Michael adduct **43**. Methyl ketone **43** was converted to febrifiugine (**1**) *via* standard reaction sequences involving α-bromination followed by coupling with 4(3*H*)-quinazolinone **(Scheme 6).**



Scheme 6: i) Oxone, K_2CO_3, acetone, H_2O, 25 ºC, 2 h, 84%; ii) $CH_3COCH{=}PPh_3$, CH_3CN, reflux, 1 h, 76%; iii) $BF_3{\cdot}OEt_2$, CH_3CN, 25 ºC, 75%; iv) (a)TMS·OTf, *i*-Pr_2EtN, CH_2Cl_2, 25 ºC, 20 min; (b) NBS, 25 ºC, 2 h; v) (a) 4(*3H*)-quinazolinone, 25 ºC, 4.5 h, 51%; (b) H_2, $Pd(OH)_2/C$, MeOH/THF, 25 ºC, 3.5 h, 88%.

Caprio's approach (2005)[14]

Caprio *et al.* employed 1,3-dipolar cycloaddition of nitrone **48** with *N*-allylquinazolone **49** as the key step to give febrifugine. Reduction of diester **45** using $LiAlH_4$ followed by di-tosylation of the resulting diol with tosyl chloride in the presence of DMAP gave 1,5-ditosylate **46**. Cyclization of **46** was achieved on reacting with hydroxylamine hydrochloride to give piperidine **47,** which was then oxidized using manganese dioxide to give a mixture of readily separable regioisomeric nitrones **48**. The 1,3-dipolar cycloaddition of nitrone **48** with dipolarophile **49** produced the corresponding adduct, whose *N-O* bond was reductively cleaved using Zn/acetic acid to give the crude **50**. Amino alcohol **50** was converted to febrifugine by standard reactions *i.e.* Boc protection, oxidation and deprotection **(Scheme 7)**.



Scheme 7: (i) a) $LiAlH_4$, Et_2O, 24 h, 88%; b) TsCl, DMAP, Et_3N, CH_2Cl_2, 12 h, 86%; (ii) $NH_2OH{\cdot}HCl$, Et_3N, reflux, 4 h, 74%; (iii) MnO_2, CH_2Cl_2, 0 °C, 12 h, 88% overall yield; (iv) a) **49**, PhMe, reflux, 24 h, 48%; b) Zn, HOAc, reflux; (v) a) Boc_2O, Et_3N, CH_2Cl_2; b) Dess–Martin periodinane, pyridine, CH_2Cl_2, quant.; c) 6M HCl, reflux, 67%.

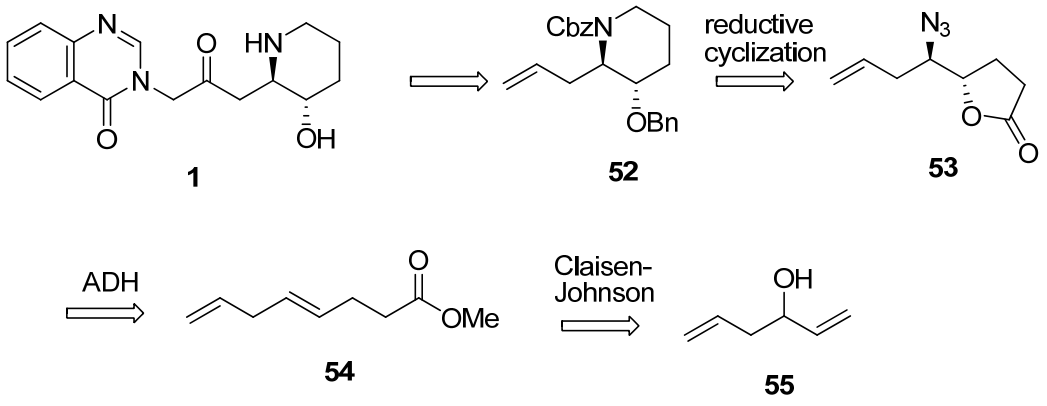
1.1.3 Present Work

1.1.3.1 Objective

As can be seen from the above discussions, the literature methods for the synthesis of (+)-febrifugine (**1**) employ either chiral starting materials or expensive reagents involving longer reaction sequences, often resulting in poor product selectivities. The catalytic synthesis of (+)-febrifugine (**1**) is thus undertaken by employing the asymmetric dihydroxylation of homoallylic ester as the key reaction.

Retrosynthetic analysis

The retrosynthetic analysis of (+)-febrifugine (**1**) is shown in **Scheme 8.** We envisaged that 2-allyl-3-hydroxypiperidine **52** could serve as a valuable intermediate for the asymmetric synthesis of (+)-febrifugine **1**. We further anticipated that the piperidine moiety in **52** could be constructed by the reductive *N*- to *O*- ring expansion of azidolactone **53,** which in turn could be obtained readily *via* regioselective asymmetric dihydroxylation (ADH) of 1,4-dienic ester **54**. We also thought that the chemoselective [3,3]-sigmatropic Claisen-Johnson rearrangement of 1,5-hexadiene-3-ol (**55)** would result in the formation of dienic ester **54**. Since the synthetic strategy involves asymmetric dihydroxylation as the key reaction, a brief account of ADH is described below.

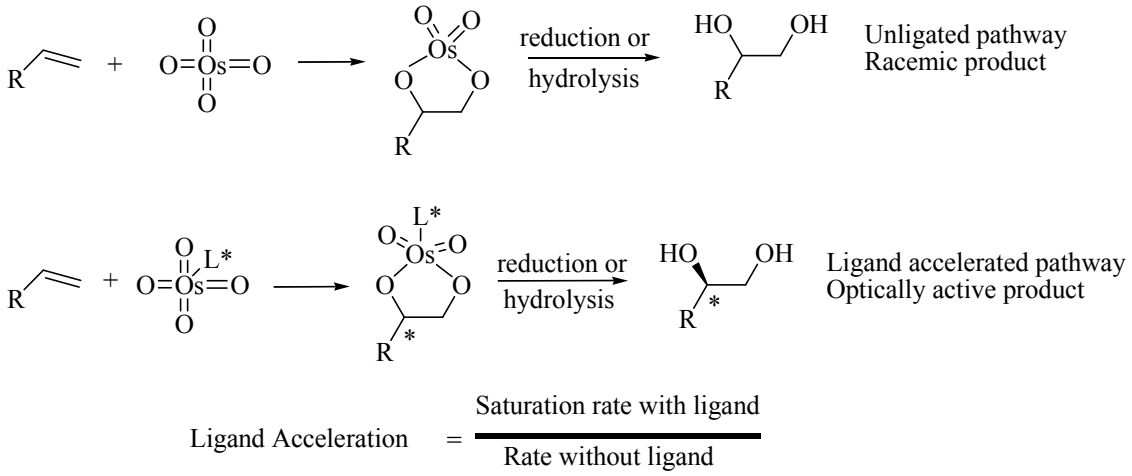


Scheme 8: Retrosynthetic analysis of (+)-febrifugine (**1**)

1.1.3.2 Asymmetric Dihydroxylation

In recent years much attention has been focused on the catalytic asymmetric synthesis. There are several methods to obtain enantiomerically pure compounds that include classical optical resolution, chromatographic separation of enantiomers, enzymatic resolution and asymmetric synthesis.[15] It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[16] Among all these reactions, Sharpless Catalytic Asymmetric Dihydroxylation (AD) is one of the most important practical and widely used reactions in organic synthesis. It has become the most general method for the preparation of optically active vicinal *cis*-diols from activated as well as inactivated olefins.[17]

In 1936, Criegee *et al.*[18] have found that addition of pyridine or any other tertiary amine to osmylation of olefins accelerates the rate of reaction considerably. A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless[17b] *et al.* demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ).[19] A number of recent methods employ chiral diamine ligands for the asymmetric osmylation of olefins. The simplified mechanism of achiral and chiral dihydroxylation is given in **Scheme 9.**



Scheme 9: Simplified mechanism of achiral and chiral dihydroxylation

Mechanism of OsO_4-catalyzed dihydroxylation of olefin

In order to develop a catalytic method, several co-oxidants such as sodium or potassium chlorate,[20] hydrogen peroxide,[21] *tert*-butyl hydroperoxide[22] and *N*-methylmorpholine *N*-oxide (NMO) [23] were introduced .

The idea to use these co-oxidants was to minimize the amount of toxic and costly osmium so as to make the process more economical. Sharpless *et al* [24] have established that the most practical and suitable catalytic method is with NMO as co-oxidant but the ee's of the diol was less than those produced by the stoichiometric reactions (primary catalytic cycle) The reason was thought to be the involvement of second catalytic cycle (secondary catalytic cycle), which results in low or no ee at all. To improve the %ee of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3[Fe(CN)_6]$ as reoxidant and using biphasic conditions **(Fig. 2)**.[25]

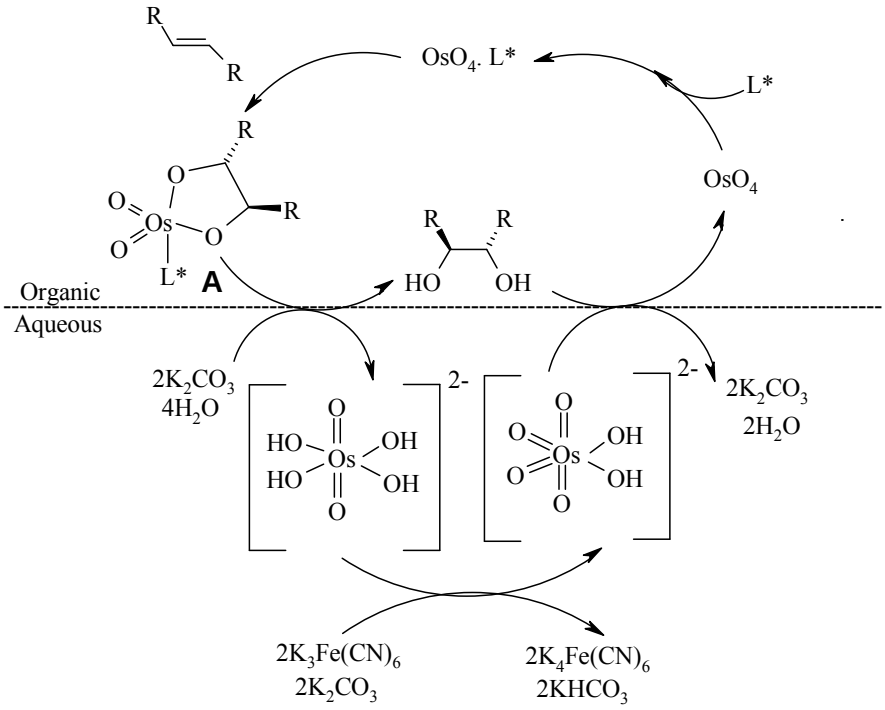
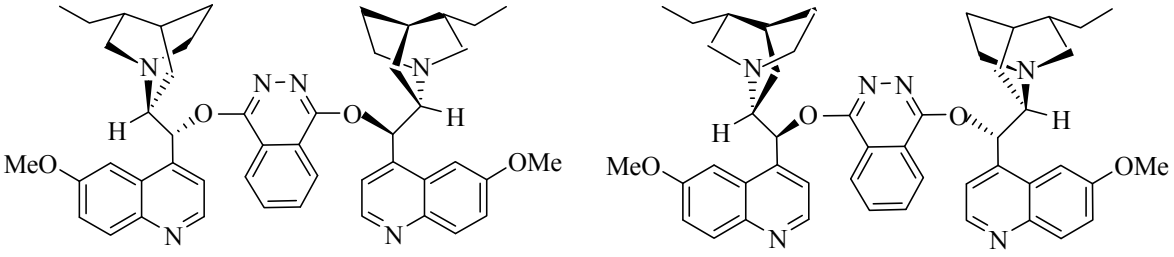


Fig. 2: Catalytic cycle for AD using $K_3[Fe(CN)_6]$ as co-oxidant.

These conditions helped in protecting the organic osmate-(VI) monoglycolate ester (species **A**, **Fig. 2**) from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) gets reoxidized and recycled into the catalytic cycle. Further improvement in the AD was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species **A**, thus facilitating the dihydroxylation smoothly. Addition of methyl sulfonamide also allowed carrying out the reactions of 1, 2-ditri- and tetra- substituted olefins at 0 ^{0}C, which improved the selectivity as well as %ee. In order to develop the asymmetric version of the Os-catalyzed AD reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the *bis*-DHQ (**56**)

or DHQD (**57**) ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselectivities of the chiral diols (Fig. 3).[26]



$(DHQ)_2$-PHAL (**56**) $(DHQD)_2$-PHAL (**57**)

Fig. 3: Ligands for asymmetric dihydroxylation reaction

The recent studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[26,27] Sharpless *et al* have shown that the facial selectivity for both ligands **56** and **57** is different, based on their ability to induce the ee into the diols.

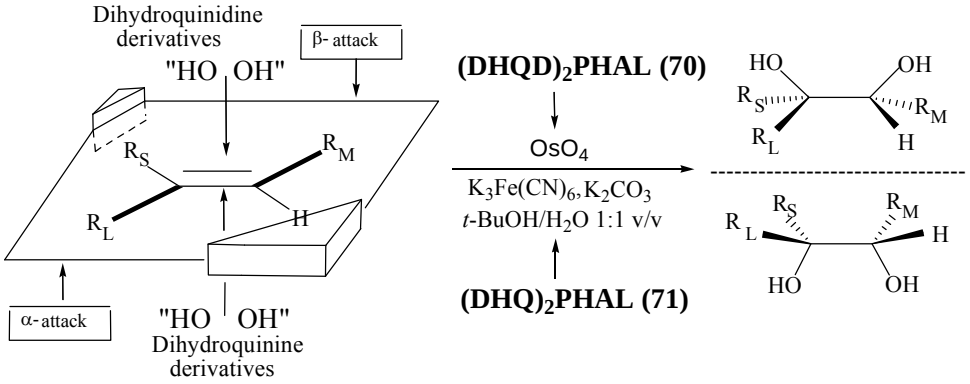
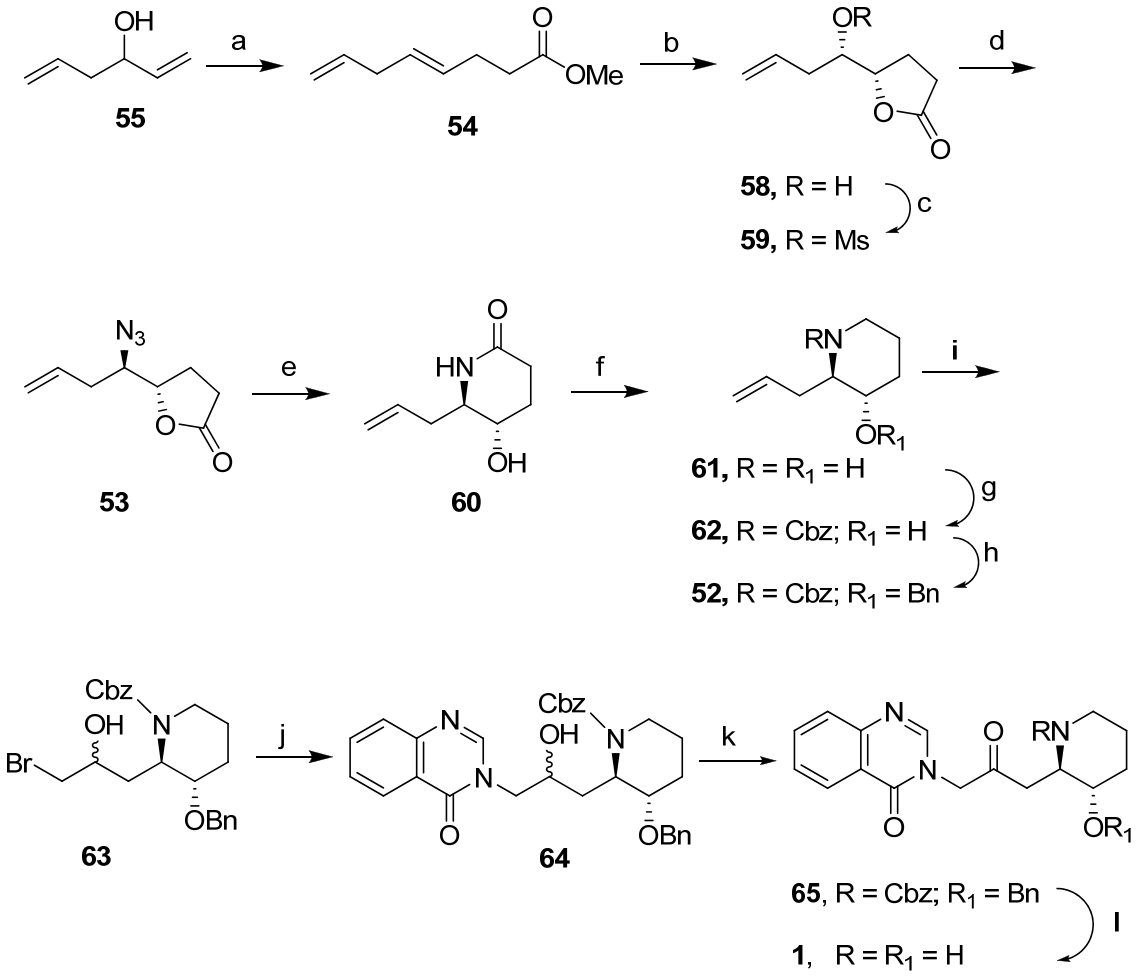


Fig. 4: Enantioselectivity in ADH

This observation has led to the development of mnemonic model **(Fig. 4)** in which olefin with the constraints will be attacked either from the top (i.e. β) face in the presence of dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

1.1.4. Results and Discussion

Our synthesis of (+)-febrifugine (**1)** commenced with the commercially available 1,5-hexadien-3-ol (**55**), which was subjected to Claisen-Johnson [3,3]-sigmatropic rearrangement (trimethyl orthoacetate, cat. propionic acid, xylene, 135 ^{o}C) to give (*E*)-1,4-dienic ester **54** exclusively in 86% yield **(Scheme 10).**[28] Surprisingly, we observed that the reaction conditions exclusively favored the Claisen-Johnson rearrangement to give the desired dienic ester **54** over a possible oxy-Cope rearrangement; no trace of 5-hexenal, an oxy-Cope product was formed. The appearance of a signal at δ 3.67 (s) in the ^{1}H NMR spectrum of dienic ester **54** confirmed the presence of ester methyl proton (-$CO_2C\mathbf{H_3}$). The display of four signals at the olefinic region (δ 4.95-5.81, 5H) further confirmed the presence of both terminal as well as internal olefins. Its ^{13}C NMR spectrum displayed characteristic signals at δ 173.8 due to the carbonyl carbon (-**C**=O) and at δ 115.6, 129.6, 129.7 and 137.7 corresponding to the olefinic carbons **(Fig. 5)**.



Scheme 10: Reagents and conditions: (a) $CH_3C(OMe)_3$, cat. propanoic acid, xylene, 135 °C, 88%; (b) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3, *t*-BuOH: H_2O (1:1) 73%; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C; (d) NaN_3, DMF, 80 °C, 82% over two steps; (e) PPh_3, THF, 25 °C then H_2O reflux, 93%; (f) $LiAlH_4$, THF, reflux; 85%; (g) CbzCl, K_2CO_3, THF:H_2O (1:1); (h) BnBr, NaH, DMF, 0 °C, 84%; (i) NBS, CH_3CN/H_2O, 88%; (j) 4-quinazolinone, KOH, MeOH, 25 °C; (k) Dess-Martin periodinane, CH_2Cl_2, 78% over two steps; (l) 6 N HCl, reflux, 63%.

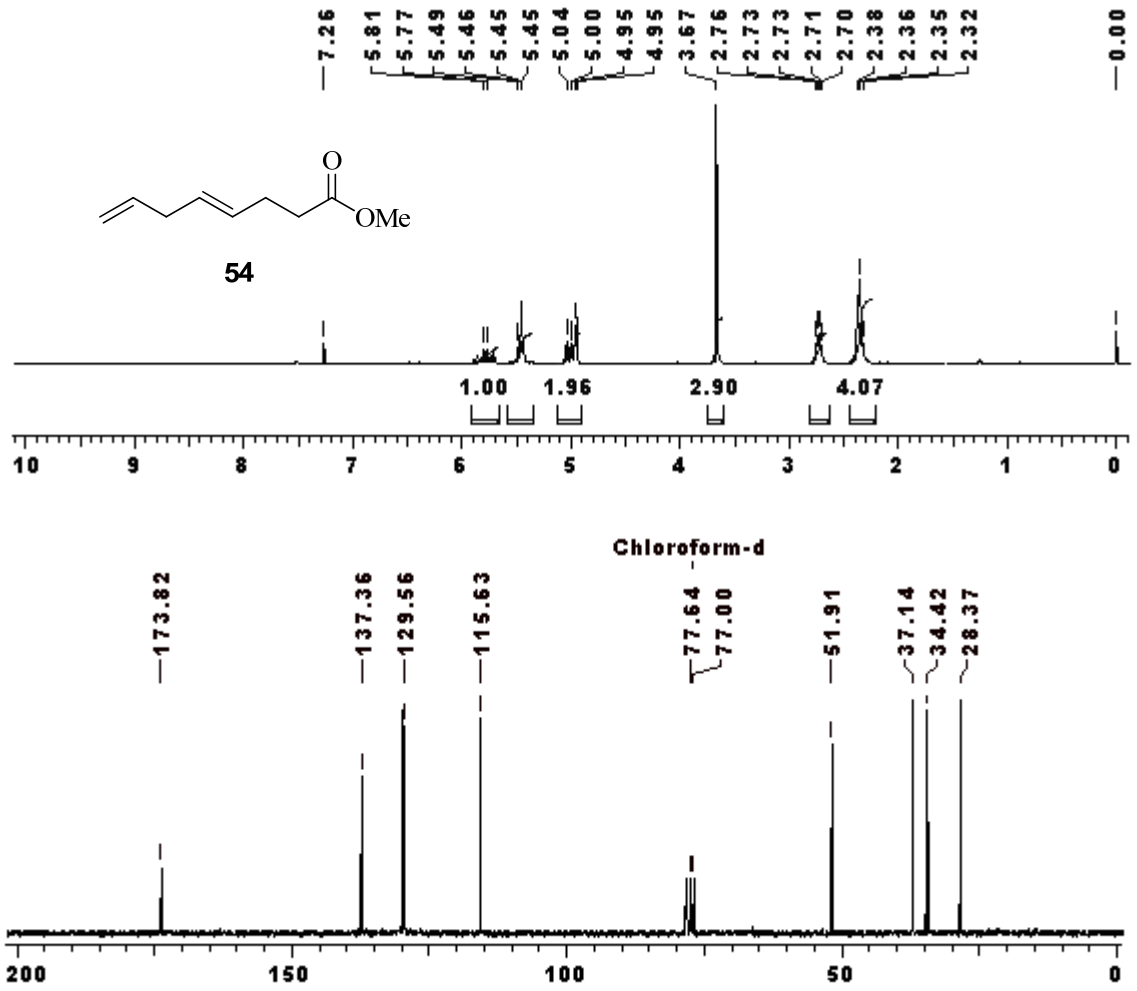


Fig. 5 : ^{1}H and ^{13}C NMR spectra of **54**

Regioselective asymmetric dihydroxylation of internal olefin of **54** was achieved using $(DHQ)_2$-PHAL, cat. OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, $^{t}BuOH:H_2O$ (1:1) at 0 °C to get the hydroxylactone **58** in 73% isolated yield and 82% ee (determined from its Mosher's ester). Under the basic condition, the resulting diol simultaneously underwent lactonization to form exclusively the five-membered lactone **58**. No trace of six-membered lactone was found.

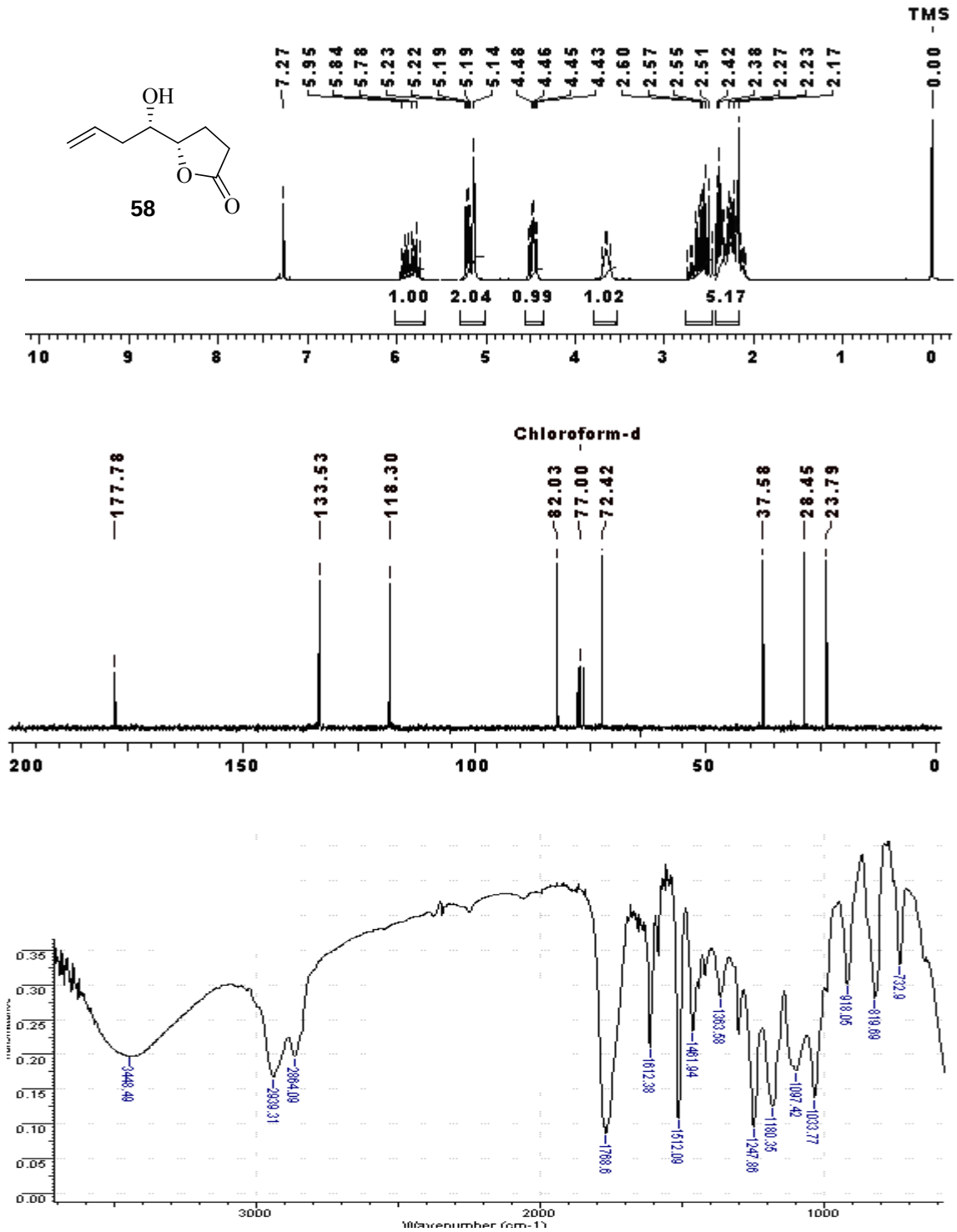


Fig. 6: ^{1}H , ^{13}C NMR and IR spectra of **58**

The IR spectrum of ester **58** showed an absorption band at 1768 cm^{-1} that corresponds to the presence of five-membered lactone carbonyl moiety. The disappearance of methyl signal in the ^1H NMR spectrum of **58** confirmed the formation of lactone. The two characteristic signals at δ 5.19 and 5.84 in its ^1H NMR spectrum indicated that only internal olefin in the molecule underwent dihydroxylation leaving the terminal olefin (-C**H**=C**H$_2$**) unaffected. The two newly formed methine protons (-C**H**O- and -C**H**OH-) have displayed signals at δ 4.46 and 3.62 respectively. In the ^{13}C NMR spectrum of **58**, the carbonyl carbon signal has shown downfield shift *i.e.* from δ 173.8 to 177.8 due to the formation of strained five-membered lactone **(Fig. 6)**. Carrying out the reaction for longer reaction time has produced the crude product in diminished crude yield, presumably due to the dihydroxylation of both the C=C double bonds. It may also be noted that replacing OsO_4 with potassium osmate, resulted in poor selectivity, leading to dihydroxylation of both the C=C bonds even at 0 ^oC.

Mesylation of the free alcohol group in **58** (MsCl, Et_3N, CH_2Cl_2, 0 °C) produced the corresponding methane sulfonate ester **59** in quantitative yield. Without purification, mesylate **59** was subjected to S_N2 displacement with NaN_3 in DMF at 80 °C to furnish the azidolactone **53** with inversion of configuration. The signals for the terminal olefins (C**H$_2$**=C- and R-C**H**=C) have appeared as multiplets at δ 5.23 and 5.85 respectively in the ^1H NMR spectrum of **53**. The signals at δ 3.74 and 4.48 are due to the methine protons (-C**H**N_3- and -C**H**O-) respectively. Its ^{13}C NMR displayed a typical signal at δ 173.1 for the lactone carbonyl and at δ 132.4 and 119.4 due to the terminal olefinic carbons.

Reduction of azide **53** under Staudinger condition[29] (PPh_3, H_2O, heat) gave lactam **60** {$[\alpha]^{25}_D$ +10 (*c* 0.8, $CHCl_3$)}; presumably formed by the intramolecular lactamization of

the free amine generated *in situ* by the reduction of azide.[30] The ^{1}H NMR spectrum of **60** showed a broad singlet at δ 6.08 due to the amide proton (-N**H**CO-), while the olefinic protons (C**H**$_2$=C- and R-C**H**=C) have shown peaks at δ 5.22 and 5.76 respectively. The signals for methine protons (-C**H**NH- and -C**H**OH-) have appeared as multiplets at δ 3.68 and 3.26 respectively. The formation of lactam **60** was further confirmed from its ^{13}C NMR spectrum, which showed a typical signal at δ 172.0 for the amide carbonyl (-**C**ONH) function.

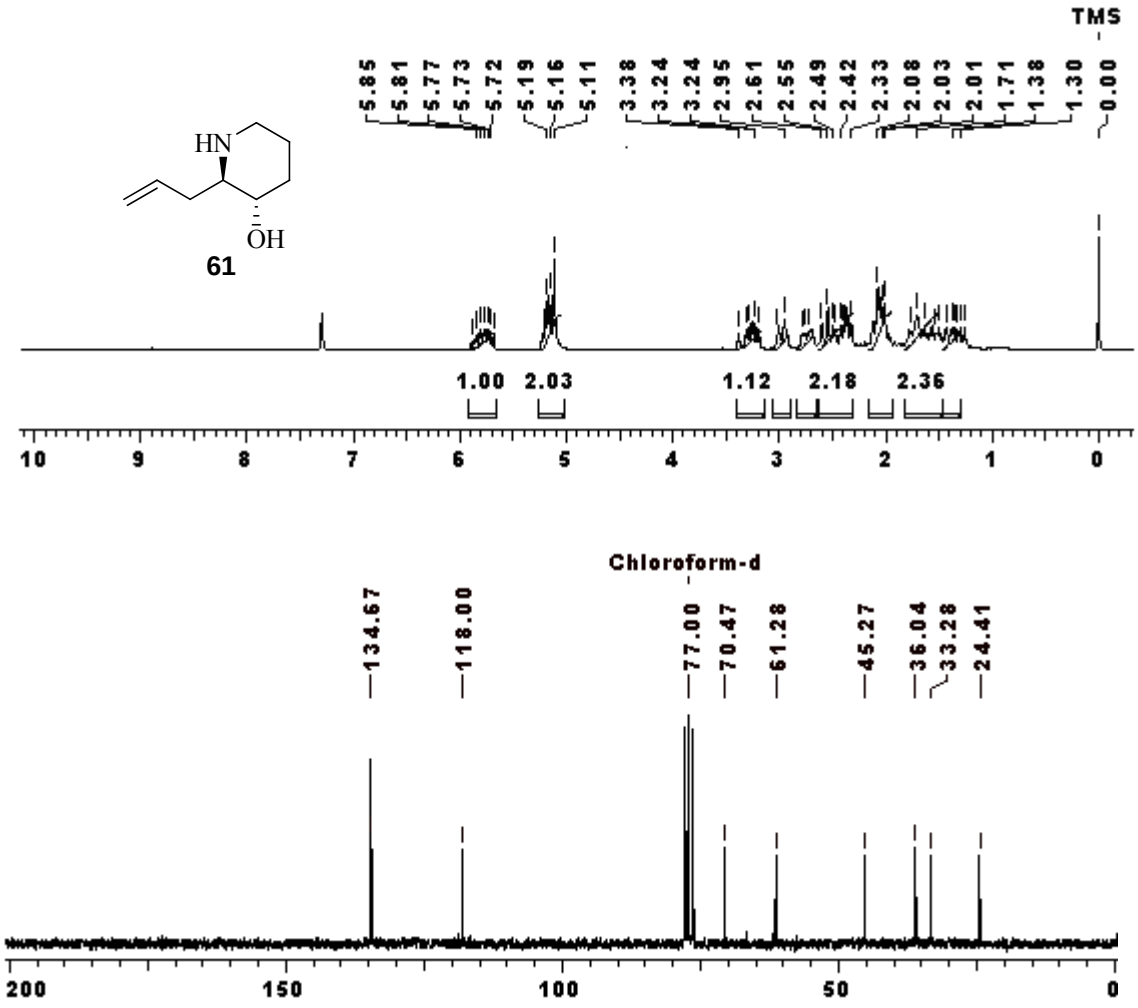


Fig. 7: ^{1}H and ^{13}C NMR spectra of **61**

The chemoselective reduction of lactam **60** was achieved with lithium aluminium hydride to afford 2-allyl-3-hydroxypiperidine (**61)**. The ^{1}H NMR spectrum of **61** showed that the terminal olefin was unaffected during $LiAlH_4$ reduction and displayed signals at δ 5.81 and 5.16. Further, the reduction of amide carbonyl was confirmed from its ^{13}C NMR spectrum, which showed the absence of carbonyl carbon signal **(Fig. 7)**.

The free amine and alcohol groups were subsequently protected with Cbz and Bn groups respectively to obtain the intermediate **52** in 72% yield in that order over two steps {$[\alpha]^{25}_{D}$ -37 (*c* 0.8, $CHCl_3$); lit.[5h] $[\alpha]^{25}_{D}$ -45 (*c* 1.55, $CHCl_3$)}.

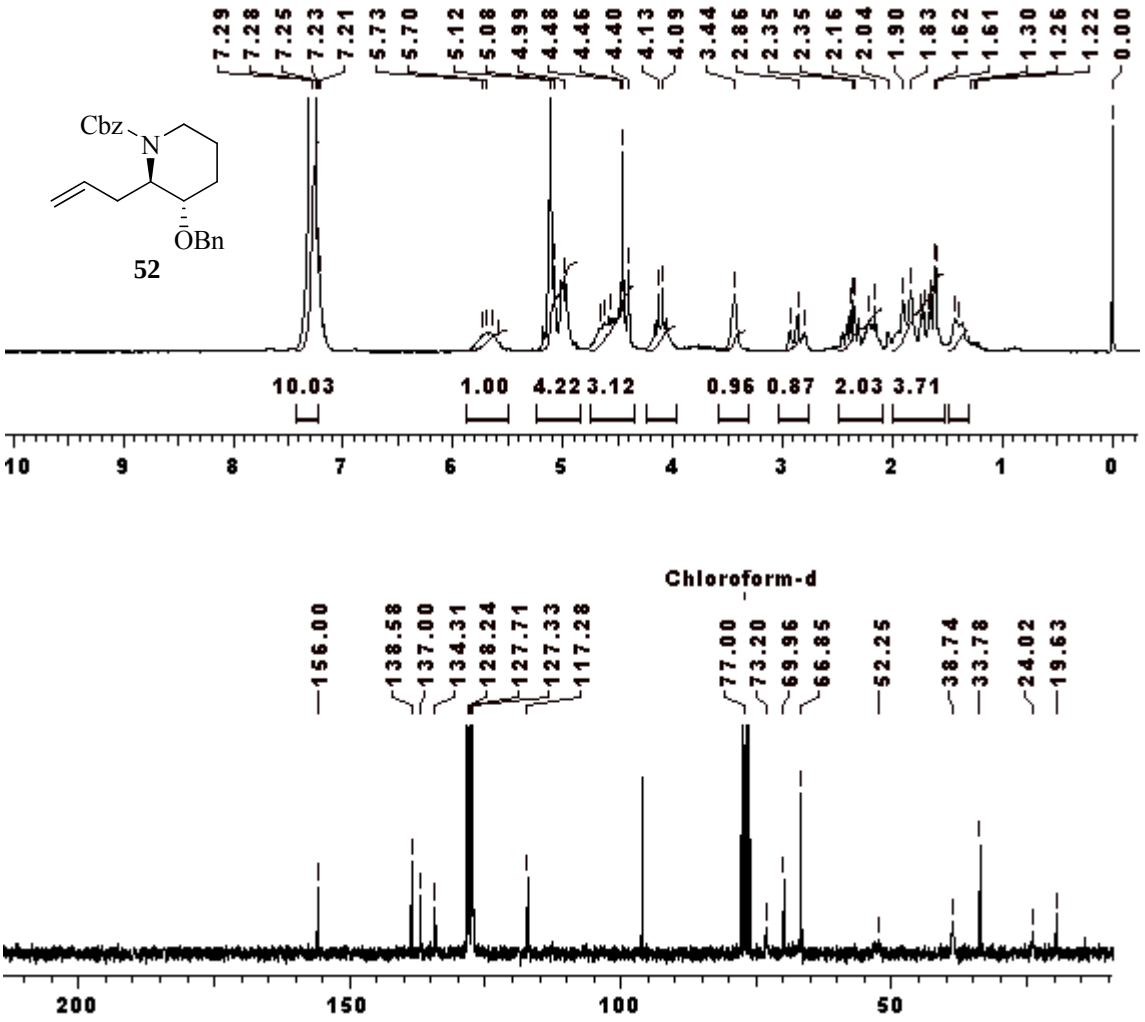


Fig. 8: ^{1}H and ^{13}C NMR spectra of **52**

The ^{1}H NMR spectrum of **52** displayed a multiplet at δ 7.23 for two phenyl rings ($C_6\mathbf{H_5}$-) while the signals for benzylic protons (-$NCO_2C\mathbf{H_2}$-Ph and –O$C\mathbf{H_2}$Ph) have appeared at δ 5.12 and 4.49 respectively. As expected, the olefinic protons ($C\mathbf{H_2}$=C- and R-C**H**=C) remain unaffected displaying signals at δ 5.73 and 5.12. Its ^{13}C NMR spectrum exhibited a typical signal at δ 156 corresponding to the carbonyl carbon in Cbz protection **(Fig. 8)**. With the intermediate **52** in hand, we began bromohydroxylation (NBS, CH_3CN:H_2O) of terminal olefin in **52** to obtain the corresponding halohydrin. Thus, bromohydroxylation of **52** took place regioselectively to give a separable diastereomeric terminal halide **63** in the ratio 1.5:1 (determined from the ^{1}H NMR spectrum). The disappearance of the signals corresponding to the olefinic protons in the ^{1}H NMR spectrum of **63** confirmed that the functionalization of olefin has occured. The IR spectrum of halohydrin **63** exhibited a broad absorption at 3348 cm^{-1} indicating the presence of hydroxyl group whereas the dibromo derivative, a minor product formed, had no IR absorption. After separating the dibromide, the diastereomers of halohydrin **12** mixture was coupled with 4-hydroxyquinazoline in the presence of KH to afford the diastereiosmers of *N*-alkylated product **64** as the inseparable mixture. The free alcohol group in **64** was then oxidized using Dess- Martin periodinane[31] to furnish the protected febrifugine **65** {$[\alpha]^{25}_{D}$ -25.0 (c 0.5, $CHCl_3$); lit.[5h] $[\alpha]^{25}_{D}$ -22.0 (c 1.0, $CHCl_3$)}. The ^{1}H NMR spectrum of **65** displayed signals in the range δ 7.5-8.2 corresponding to the quinazolinone unit along with aromatic protons. Its ^{13}C NMR spectrum showed a typical signal at δ 200.1 corresponding to the carbonyl carbon (C=O) functionality.

Finally, treatment of **65** with 6N HCl produced (+)-febrifugine (**1)** in 63% yield. After recrystallization from ethanol, its ^{1}H and ^{13}C NMR spectra and melting point were found to be completely identical with the reported values **(Fig. 9)**.

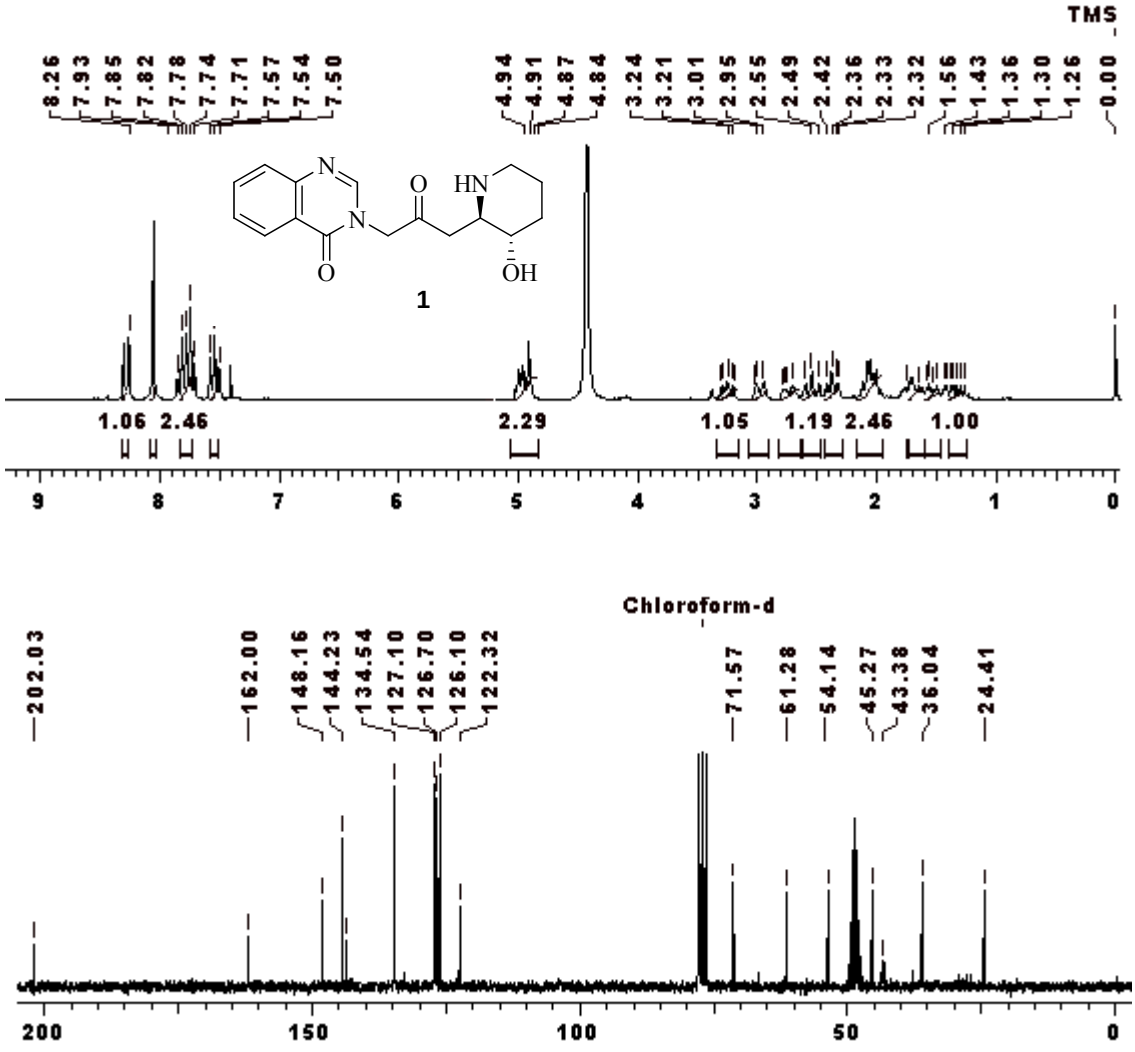


Fig. 9: ^{1}H and ^{13}C NMR spectra of (+)-febrifugine (**1)**

1.1.5. Conclusion

In summary, we were able to establish an alternative, short enantioselective synthesis of (+)-febrifugine (**1)** *via* asymmetric dihydroxylation of 1,4-dienic ester in 12 linear steps

with 82% ee. The carbon back-bone of (+)-febrifugine was synthesized through Claisen-Johnson rearrangement of 1,5-hexadien-3-ol while the piperidine ring was constructed using reductive ring expansion of azido lactone. This synthesis is practical and seems obviously applicable for the synthesis of substituted hydroxyl piperidines.

1.1.6. Experimental section

(*E*)-Methyl octa-4,7-dienoate (54)

An oven dried 500 mL round bottomed flask was charged with 1,5-hexadien-3-ol (**55**) (9.8 g, 100 mmol), propanoic acid (390 mg, 5 mol%), trimethyl orthoacetate (72.0 g, 600 mmol) and xylene (300 mL). The mixture was refluxed at 135 ^{o}C for 18 h. After the completion of the reaction, as monitored by TLC, it was cooled to room temperature and the excess trimethyl orthoacetate and xylene were removed under reduced pressure. It was then extracted with ethyl acetate (3 x 25 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude ester **54**, which was purified by column chromatography using petroleum ether: ethyl acetate (9:1) to obtain pure **54** as colorless oil. **Yield**: 88% (13.55 g); **^{1}H- NMR** (200 MHz, $CDCl_3$): δ 2.36 (m, 6H), 2.73 (dt, *J* = 4.8, 1.2 Hz, 2H), 3.67 (s, 3H), 4.95 (t, *J* = 1.5 Hz, 1H), 5.02 (m, 1H), 5.46 (m, 2H), 579 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 27.8, 33.9, 36.6, 51.4, 115.1, 129.0, 129.3, 136.8, 173.3; **IR** (neat, cm^{-1}): 2936, 2861, 2355, 2332, 1735, 1520, 1442, 1251, 1176, 956, 852; Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.21 %.

(*S*)-Dihydro-5-((*S*)-1-hydroxybut-3-enyl)furan-2(3*H*)-one (58)

A 500 mL two-necked round bottomed flask was charged with potassium ferricyanide (8. 39 g, 120 mmol), potassium carbonate (39.48 g, 120 mmol), $(DHQ)_2$-PHAL (311 mg, 1

mol%) and *t*-BuOH:H_2O (1:1, 300 mL). The reaction mixture was cooled to 0 ^oC on an ice bath and OsO_4 (10. 8 mg in toluene, 0.22 mL, 0.5 mol%) was added *via* syringe. After 10 min. of stirring at 0 ^oC dienic ester **54** (6.16 g, 40 mmol) was added drop-wise and allowed to stir for 2 h at 0 ^oC. After the completion of the reaction as monitored by TLC, it was quenched with saturated sodium sulfite and extracted with ethyl acetate (3 x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude hydroxy lactone **58**, which was purified by column chromatography using petroleum ether: ethyl acetate (1:1) to give **58** as a viscous gum. **Yield**: 73% (4.55 g); $[\alpha]^{25}_D$ +42 (*c* 0.6, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.13-2.42 (m, 5H), 2.5-2.65 (m, 2H), 3.61-3.69 (ddd, *J* = 10.3, 6.7, 3.5 Hz, 1H), 4.43-4.52 (ddd, *J* =10.9, 7.3, 3.7 Hz, 1H), 5.14 (dd, *J* = 2.3, 1.2 Hz, 1H), 5.17-5.23 (m, 1H), 5.75-5.95 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 24.0, 28.6, 37.8, 72.6, 82.2, 118.5, 133.7, 178.0; **IR** ($CHCl_3$, cm^{-1}): 3445, 2936, 2866, 1769, 1519, 1247, 1185, 1035, 963; Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.61; H, 7.79%.

(*S*)-1-((*S*)-Tetrahydro-5-oxofuran-2-yl)but-3-enyl methanesulfonate (59)

To a stirred solution of hydroxyl lactone **58** (4 g, 25.6 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (3.87 g, 38 mmol) at 0 ^oC. After 5 min. methane sulfonyl chloride (3.5 g, 30.7 mmol) was added drop-wise. The reaction mixture was then stirred for another 1 h at 0 ^oC and brought to room temperature. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 50 mL) washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to obtain crude mesylate **59,** which was purified by column chromatography using petroleum ether: ethyl acetate (1:1) to give pure mesylate **59** as a viscous liquid**. Yield**:

94% (5.63 g); $[\alpha]^{25}_{D}$ + 28 (*c* 1.4, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.29-2.40 (m, 4H), 2.45-2.65 (m, 2H), 3.07 (s, 3H), 4.16-4.37 (m, 1H), 4.61-4.78 (m, 1H), 5.20 (dd, *J* = 2.1, 1.0 Hz, 1H), 5.22-5.29 (m, 1H), 5.57-5.87(m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.9, 27.9, 35.8, 39.1, 78.9, 82.0, 118.0, 133.1, 176.1; **IR** ($CHCl_3$, cm^{-1}): 2939, 2868, 1775, 1735, 1512, 1355, 1250, 1185, 1011, 815; Anal. Calcd for $C_9H_{14}O_5S$: C, 46.14; H, 6.02; S, 13.69. Found: C, 46.19; H, 6.14%.

(*S*)-5-((*R*)-1-Azidobut-3-enyl)-dihydrofuran-2(3*H*)-one (53)

To a stirred mixture of crude methane sulfonate ester **59** (5.95 g) in DMF (30 mL) was added sodium azide (87 g, 475 mmol) and the reaction mixture was heated at 80 ^oC for 7 h. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude azido lactone **53,** which was purified by column chromatography using petroleum ether: ethyl acetate (7:3). **Yield**: 87% (3.8 g); $[\alpha]^{25}_{D}$ -21 (*c* 0.5, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.1-2.43 (m, 4H), 2.51-2.63 (m, 2H), 3.70 -3.80 (ddd, *J* = 11.2, 6.3, 5.1 Hz, 1H), 4.42-4.51 (ddd, *J* = 11.8, 7.4, 5.0 Hz, 1H), 5.18 (dd, *J* = 2.1, 1.0 Hz, 1H), 5.21-5.29 (m, 1H), 5.73-5.94 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 22.7, 28.1, 35.2, 63.8, 80.1, 119.4, 132.4, 176.1; **IR** ($CHCl_3$, cm^{-1}): 2935, 2865, 2110, 1775, 1514, 1247, 1031, 819; Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.10; H, 6.18; N, 23.24%.

(5*S*, 6*R*)-6-Allyl-5-hydroxypiperidin-2-one (60)

To a stirred solution of azidolactone **53** (3.5 g, 19.3 mmol) in dry THF (50 mL) was added triphenyl phosphine (5.06 g, 21.23 mmol) at room temperature. The reaction mixture was stirred at room temperature till the evolution of nitrogen gas is ceased.

Water (720 mg, 40 mmol) was added and the reaction mixture was refluxed for 3 h. After the completion of the reaction, solvent and traces of water were removed under reduced pressure to give the crude lactam **60**, which was purified by column chromatography using petroleum ether: ethyl acetate (1:1) to provide the pure lactam **60**. **Yield**: 93% (2.8 g); $[\alpha]^{25}_{D}$ +10 (*c* 0.8, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.79-2.28 (m, 4H), 2.40-2.63 (m, 2H), 3.25 (m, 1H), 3.67 (m, 1H), 5.13-5.17 (dd, *J* = 8.5, 1.1 Hz, 1H), 5.22 (m, 1H), 5.64-5.84 (m, 1H), 6.08 (br s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 27.5, 28.4, 38.5, 57.7, 67.5, 119.4, 133.4, 172.0, 122.2, 138.9; IR ($CHCl_3$, cm^{-1}): 3445, 2939, 2895, 1657, 1132, 965; Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.02; H, 8.41; N, 9.11%.

(2*R*, 3*S*)-2-Allylpiperidin-3-ol (61)

An oven dried two-necked round bottomed flask was charged with lithium aluminium hydride (648 mg, 24 mmol) and dry THF (50 mL) was added *via* syringe. The suspension was cooled to 0 ^oC and a solution of lactam **60** (2.5 g, 16 mmol) in THF (20 mL) was added drop-wise maintaining the temperature of the reaction mixture below 10 ^oC. After the addition was complete, the reaction mixture was stirred at the same temperature for 1 h and then refluxed for 5 h to ensure the completion of the reaction. It was then quenched with ethyl acetate and filtered through celite. The filtrate was washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get the crude amino alcohol **61,** which was purified by column chromatography using petroleum ether:ethyl acetate (1:1) to get amino alcohol **61** as colorless solid. **Yield**: 85% (2.1 g); **mp**: 112-114 °C (recrystallized from $CHCl_3$); $[\alpha]^{25}_{D}$ -46 (*c* 1, MeOH); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.21-1.35 (m, 1H), 1.45-1.57 (m, 1H),

1.63-1.74 (m, 1H), 1.98- 2.14 (m, 2H), 2.11 (brs, 2H), 2.30-2.41 (dt, *J* = 9.6, 3.1 Hz, 1H), 2.46-2.59 (dt, *J* = 12.0, 3.8 Hz, 1H), 2.62-2.75 (m, 1H), 2.92-3.02 (m, 1H), 3.21-3.33 (ddd, *J* = 13.9, 9.68, 4.18 Hz, 1H), 5.10 (t, *J* = 1.0 Hz, 1H), 5.13-5.24 (m, 1H), 5.71-5.94 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.6, 37.5, 40.2, 49.5, 65.5, 74.7, 122.2, 138.9; **IR** (KBr, cm^{-1}): 3412, 2942, 2893, 1672, 1395; Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.09; H, 10.65; N, 9.85%.

4.8. (2*R*, 3*S*)-Benzyl 2-allyl-3-hydroxypiperidine-1-carboxylate (62)

To a mixture of amino alcohol **61** (1.9 g, 13.5 mmol) in THF: H_2O (20 mL, 1:1) was added K_2CO_3 (3.73 g, 27 mmol) followed by benzyl chloroformate (2.754 g, 16.2 mmol) drop-wise at 0 ^oC. After stirring for 5 h, the reaction mixture was extracted with ethyl acetate, washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get the crude *N*-protected amino alcohol **62**, which was purified by column chromatography using petroleum ether:ethyl acetate (8:2) to give **62** as a viscous brown oil. $[\alpha]^{25}_D$ -37 (*c* 1, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.39-1.50 (m, 1H), 1.65-2.05 (m, 4H), 2.17-2.46 (m, 2H), 2.85 (dt, *J* = 10.24, 2.33 Hz, 1H), 3.83 (brs, 1H), 4.03-4.12 (m, 1H), 4.30-4.38 (m, 1H), 4.98-5.02 (m, 2H), 5.13 (s, 2H), 5.59-5.79 (m, 1H), 7.33 (s, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.0, 25.8, 33.8, 38.9, 57.1, 66.7, 72.8, 117.3, 127.8, 127.9, 128.5, 134.4, 136.8, 156.7; **IR** (neat, cm^{-1}): 3412, 2935, 2889, 1723, 1685, 1352, 1163, 1025, 982; Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.98; H, 7.58; N, 5.11%.

(2*R*, 3*S*)-Benzyl 2-allyl-3-(benzyloxy)piperidine-1-carboxylate (52)

To a stirred solution of crude amino alcohol **62** (3.5 g) in DMF (40 mL) was added 60% sodium hydride (550 mg, 16.2 mmol) dispersed in mineral oil at 0 ^{o}C. After 5 min. of stirring, benzyl bromide (2.6 g, 15 mmol) was added drop-wise *via* syringe and allowed to stir for another 4 h. After completion of the reaction, as monitored by TLC, it was quenched with sat. NH_4Cl solution. It was then extracted with ethyl acetate (3 x 200 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude product **52**, which was purified by column chromatography using petroleum ether:ethyl acetate (4:1) to afford **52** as colorless liquid. **Yield**: 84% (4.14 g, two steps); $[\alpha]^{25}_{D}$ -37 (*c* 0.8, $CHCl_3$); lit.[5h] $[\alpha]^{25}_{D}$ -45 (*c* 1.55, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36-1.43 (m, 1H), 1.61-1.95 (m, 3H), 2.11-2.25 (m, 1H), 2.31-2.46 (m, 1H), 2.82-2.93 (dt, *J* = 13.4, 2.4 Hz, 1H), 3.44 (br s, 1H), 3.99-4.17 (m, 1H), 4.4-4.67 (m, 3H), 4.97-5.18 (m, 4H), 5.59-5.73 (m, 1H), 7.21-7.29 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.7, 24.1, 33.9, 38.8, 52.3, 66.9, 70.0, 73.3, 117.4, 127.4, 127.7, 127.8, 128.3, 128.4, 134.5, 137.0, 138.7, 156.1; **IR** (neat, cm^{-1}): 2939, 2887, 1727, 1680, 1625, 1352, 1163; Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.63; H, 7.52; N, 3.92%.

4.10. Diastereomers of halohydrin (63)

To a stirred solution of **52** (2 g, 5.48 mmol) in CH_3CN: H_2O (2:1, 20 mL) was added *N*-bromosuccinimide (1.67 g, 6 mmol) at room temperature. After completion of the reaction, it was quenched with aq. sodium thiosulphate solution and extracted with ethyl acetate, washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude halohydrin **63**, which was purified by column chromatography using petroleum ether:ethyl acetate (4:1)

to give **63** as a gum. **Yield**: 87% (2.2 g); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.39- 1.44 (d, *J* = 8.60, 1H), 1.53- 1.72 (m, 3H), 1.82- 1.98 (m, 2H), 2.25 (1H), 2.67-2.74 & 2.80-2.93 (t, *J* = 13 Hz, 1H), 3.33 & 3.4 (s, 1H), 3.52-3.64 (m, 1H), 3.70-3.90 (m, 1H), 3.99-4.21 (m, 2H), 4.44 & 4.50 (s, 2H), 5.11 & 5.15 (s, 2H), 7.21-7.35 (m, 10H); **IR** ($CHCl_3$, cm^{-1}): 3456, 2912, 2872, 1728, 1683, 1031, 819.

4.11. *O*-Benzyl-*N*-benzyloxycarbonyl febrifugine (65)

To a stirred solution of **63** (668 mg, 1.8 mmol**)** in dry methanol (10 mL) was added KOH (0.5 g, 3.6 mmol) and 4-hydroxyquinazoline (263 mg, 1.8 mmol) and the mixture was stirred at room temperature for 24 h. Then, solvent was removed under reduced pressure and the residue was extracted with ethyl acetate, washed with brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give inseparable mixture of **64** as viscous liquid, which was subjected to oxidation as described below. To a stirred solution of crude alcohol **64** in dry CH_2Cl_2 was added Dess-Martin periodinane (848 mg, 2 mmol) at room temperature. After the completion of the reaction, it was quenched with water. The precipitate formed was filtered through a sintered funnel and the filtrate was concentrated and subjected to column chromatographic purification to give the protected febrifugine **65** as a pale yellow oil. **Yield**: 78%; $[\alpha]^{25}_D$ -25.0 (c 0.5, $CHCl_3$); lit.[5h] $[\alpha]^{25}_D$ -22.0 (c 1.0, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.40 (d, *J* = 10.5 Hz, 1H), 1.60-1.66 (m, 1H), 1.86-1.93 (m, 2H), 2.74-2.95 (m, 3H), 3.50 (s, 1H), 4.05 (br, 1H), 4.50-5.25 (m, 7H), 7.24-7.31 (m, 10H), 7.46-7.49 (m, 1H), 7.70-7.90 (m, 4H), 8.24-8.26 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.3, 24.1, 39.4, 40.7, 50.5, 50.6, 53.8, 67.2, 70.3, 73.5, 121.7, 126.5, 127.2, 127.4, 127.5, 127.6, 127.9, 128.2, 128.4, 134.3, 136.4, 138.2, 146.4, 148.1, 160.8, 200.0; **IR** (neat):

2932, 2895, 1730, 1680, 1620, 1352, 1163 cm^{-1}; Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75. 63; H, 7.52; N, 3.92%.

4.12. Febrifugine (1)

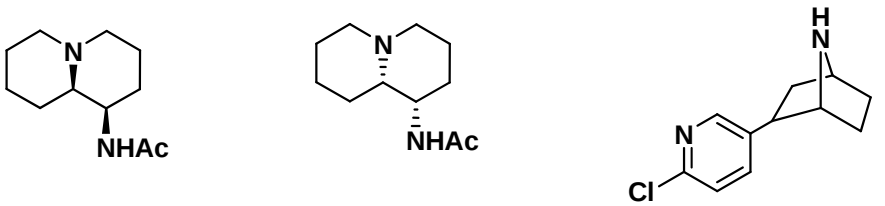
A mixture of protected febrifugine **65** (116 mg, 0.30 mmol) and 6N aqueous HCl solution was heated at reflux for 4 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated. The residue was subjected to column chromatographic purification (neutral Al_2O_3; ethyl acetate: petroleum ether 2:1) to give **1** as colorless needle. **Yield**: 63% (57 mg); mp: 138-140 °C (lit.[5m] mp 139-140 °C); $[\alpha]^{25}_D$ +25.0 (*c* 0.1, EtOH) {lit.[5j] $[\alpha]^{25}_D$ +28 (*c* 0.5, EtOH)}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30-1.38 (m, 1H), 1.48-1.57 (m, 1H), 1.72-1.74 (m, 1H), 2.07-2.10 (m, 1H), 2.58 (dt, *J* = 2.4, 12.2 Hz, 1H), 2.65 (dd, *J* = 7.3, 15.8 Hz, 1H), 2.88 (dd, *J* = 4.6, 7.7 Hz, 1H), 2.97 (d, *J* = 12.2 Hz, 1H), 3.12 (dd, *J* = 4.8, 15.8 Hz, 1H), 3.29 (m, 1H), 4.83 (d, *J* = 17.4 Hz, 1H), 4.89 (d, *J* = 17.4 Hz, 1H), 7.51 (dt, *J* = 8.1, 1.2 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.78 (dt, *J* = 8.1, 1.2 Hz, 1H), 7.90 (s, 1H), 8.28 (dd, *J* = 0.9, 7.9 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 25.7, 35.3, 44.0, 45.9, 54.7, 60.1, 72.2, 121.9, 126.8, 127.4, 127.6, 134.5, 146.4, 148.2, 161.0, 202.7; **IR** (KBr, cm^{-1}): 2928, 2856, 1722, 1675, 1616; Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63. 79; H, 6.39; N, 13.96%.

Section II

Enantioselective Formal Synthesis of (-)-Epiquinamide *via* Asymmetric Dihydroxyaltion

1.2.1 Introduction

Agonists and partial agonists acting at nicotinic acetylcoline receptors (nAChR) are currently of much interest.[32] Epiquinamides (**66a-b**), unprecedented quinolizidine alkaloids, were isolated[35] by Daly and co-workers in 2003 from the skin extract of the Ecuadorian poison dart frog *Epipedobates tricolor*, which also serves as source of epibatidine (**Fig. 10**). They have modest activity in cells expressing various nAChR subtypes, with highest activity noted in SH-sy5y cells and k-177 cells expressing human α4β2-nAChR.[36] Epiquinamide represents the first example of a new class of nicotinic ligand and has been found to be highly selective for b2 nicotinic acetylcholine receptors (nAChRs), as such, representing a new structural class of nicotinic agonists and could be considered a lead compound for the development of nAChR therapeutic agents.



(-)- epiquinamide (66a) **(+)- epiquinamide (66b)** **Epibatidine (67)**

Fig. 10

The minute amount (~240 μg) of **66** isolated from the skin extracts was enough to determine the structure and the relative stereochemistry of the natural product as (1*R*, 10*R*)-1-acetamidoquinolizidine. Due to the fact that epiquinamides (**66a-b)** could be a novel nicotinic agonist it was decided to synthesize epiquinamide (**66)** with the aim of developing new nicotinic agents. During the course of this work, the structure and

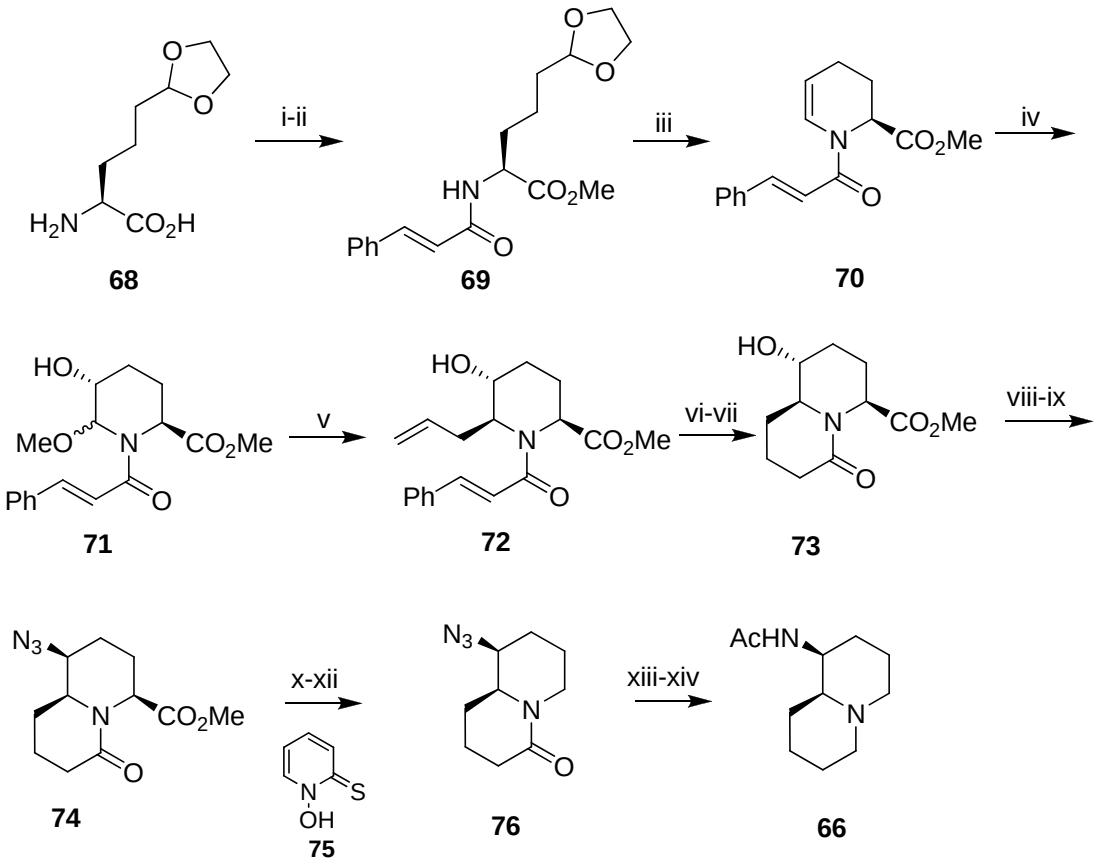
relative stereochemistry of epiquinamides (**66a-b**) were confirmed by two independent asymmetric syntheses.

1.2.2 Review of literature

Literature search reveals that there are only three reports on the asymmetric synthesis of either (-) or (+)-epiquinamide and one for the racemic synthesis using pipecolic acid. A short description of all the four reported methods is presented below.

Blaauw's approach (2005)[37]

Blaauw *et al.* have employed a strategy in which the addition of allyl silane to the *N*-acyliminium ion became the key step. This synthesis commenced with treatment of cinnamoyl chloride with amino acid **68** followed by esterification of acid functionality with methyl iodide to furnish amido ester **69** in quantitative yield. Deprotection of acetal moiety in **69** with TFA furnished the piperidine **70,** which upon selective oxidation of the enamide double bond with Oxone in methanol furnished *N*, *O*-acetal **71**. In the presence of $BF_3.OEt_2$, allyltrimethylsilane was added to the *N*-acyliminium ion formed from **71** stereoselectively to yield diene **72**. Ring closing metathesis followed by reduction of double bond gave the bicyclic ring **73**. Mesylation of free alcohol group in **73** followed by nucleophilic displacement with NaN_3 resulted in azide **74**. The decarboxylation was achieved in three step procedure i.e. ester hydrolysis, mixed anhydride formation with Boc-Cl and elimination by coupling with 2-mercaptopyridine-*N*-oxide (**75**) to obtain bicyclic azido amide **76**. Reduction of azide functionality in **76** using $LiAlH_4$ and then acetylation of the resulting amine produced (-)-epiquinamide (**66a**) (**Scheme 11**).

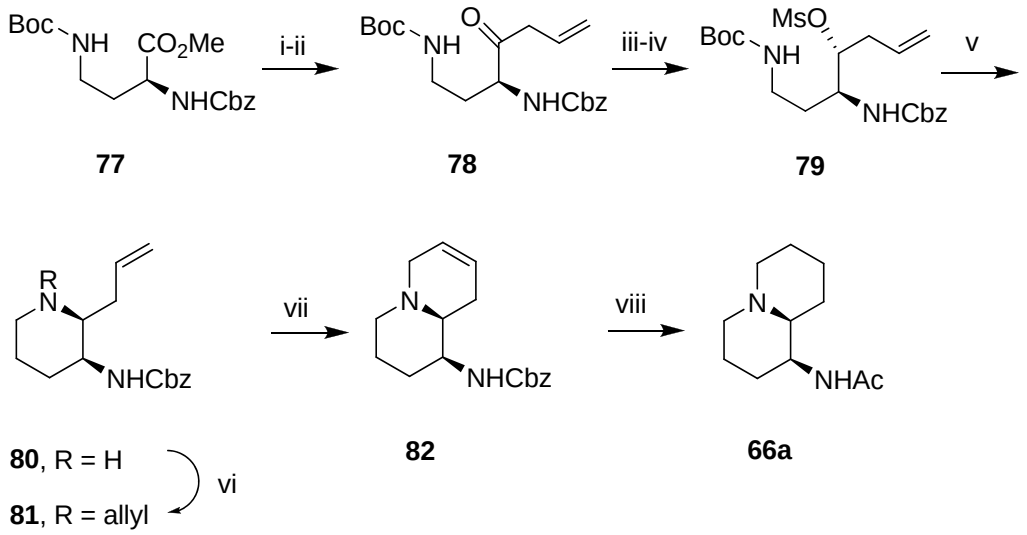


Scheme 11: i) cinnamoyl chloride, NaOH, $NaHCO_3$, H_2O, 0 ºC; ii) MeI, K_2CO_3, DMF, 0 ºC, 97%; iii) TFA, 25 ºC; iv) Oxone, $NaHCO_3$, MeOH; v) allyl trimethylsilane, $BF_3.OEt_2$, CH_2Cl_2, -30 ºC; vi) Grubbs' II generation catalyst, CH_2Cl_2, reflux; vii) H_2, Pd/C, MeOH, 25 ºC; viii) MsCl, Et_3N, CH_2Cl_2, 25 ºC; ix) NaN_3, DMF, 80 ºC; x) NaOH, THF, H_2O, 25 ºC; xi) (a) Boc-Cl, NMM, THF, -15 ºC; xii) **75**, ^tBuSH, THF, 25 ºC; xiii) $LiAlH_4$, THF, 60 ºC; xiv) Ac_2O, NaOH, 1,4-dioxane, H_2O.

Gerwick's approach (2006)[38]

In this chiral pool approach, ornithine is used as the starting material. Treatment of ornithine derived amino ester **77** with methoxy methyl amine gave Weinreb amide which on reaction with allyl Grignard reagent furnished the ketone **78**. Chelation-controlled hydride reduction of ketone **78** employing $LiAl(O^tBu)_3H$ produced alcohol, which was subsequently converted to methane sulfonate ester **79** in the presence of triethyl amine. Removal of the Boc protection in TFA/CH_2Cl_2 and then intramolecular S_N2 cyclization

induced by K_2CO_3 yielded substituted piperidine intermediate **80**. *N*-Allylation of the free amine with allyl bromide gave diallyl piperidine **81**. The bicyclic ring was constructed by the ring closing metathesis using Grubbs' second generation catalyst to yield **82**, which was converted to (-) epiquinamide (**66a**) *via* hydrogenation followed by acetylation (**Scheme 12**).

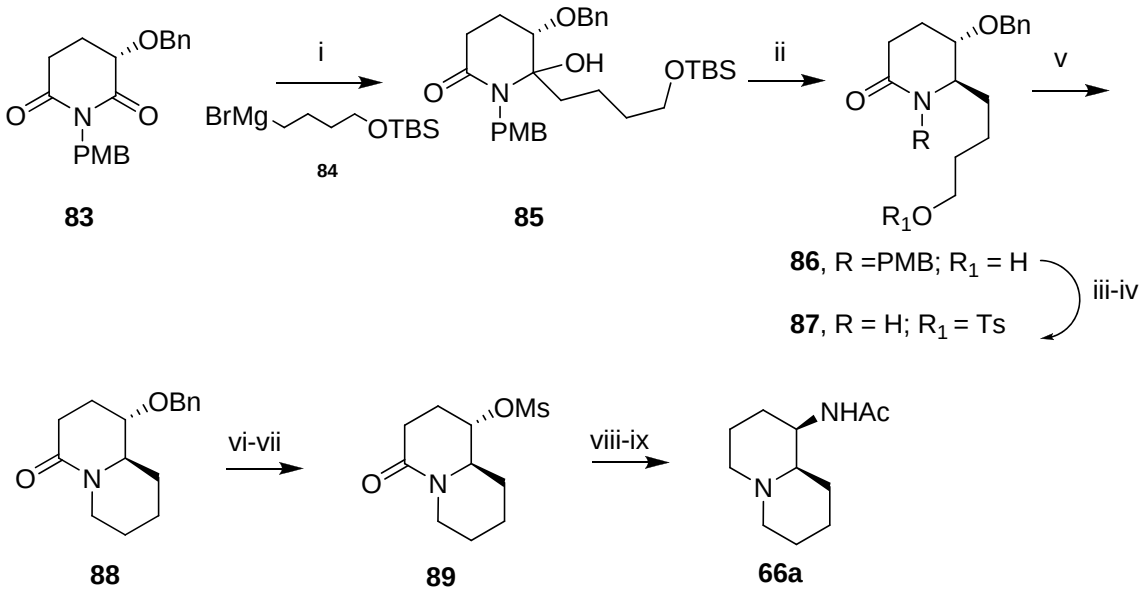


Scheme 12: i) MeONH(Me).HCl, EDCI, DMAP, Et_3N, CH_2Cl_2, 93%; ii) CH_2=CH-CH_2Br, Et_2O, -78 ^oC-25 ^oC, 86%; iii) $LiAl(O^iBu)_3H$, -78 ^oC, 93%; iv) MsCl, Et_3N, CH_2Cl_2, 97%; v) TFA, CH_2Cl_2, 0 ^oC-25 ^oC then K_2CO_3; vi) K_2CO_3, CH_3CN then allyl bromide, 73% over two steps; vii) Grubbs' II generation catalyst, CH_2Cl_2, reflux, 5 h, 83%; viii) Pd/C, H_2, MeOH, Ac_2O, 2 days, 63%.

Huang's approach (2006)[39]

Huang *et al.* have described the synthesis of (-)-epiquinamide using Grignard addition to glutarimide derivative as the key step. Alkyl magnesium bromide **84** was added to the glutarimide derivative **83** to obtain a separable diastereomeric mixture of **85**. Treatment of **85** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ as acid catalyst gave desilylated piperidinone **86** in 96:4 diastereomeric ratio. Tosylation of **86** led to the corresponding sulfonate ester in 92% yield, which after oxidative *N*-deprotection using ceric ammonium

nitrate (CAN) provided tosylate **87.** Intramolecular *N*-alkylation was achieved with sodium hydride to afford the bicyclic lactam **88** in quantitative yield. Catalytic hydrogenation of **88** led to benzyl deprotection to give the free alcohol, which upon mesylation gave the mesylate **89** in 100% yield. Mesylate **89** was finallyconverted to (-) epiquinamide (**66a**) by displacing Ms group with NaN_3 followed by reduction and acetylation (**Scheme 13**).

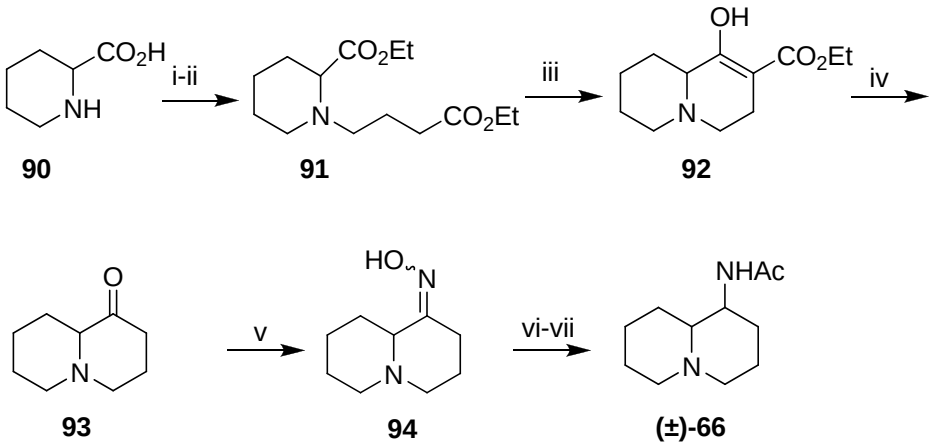


Scheme 13: i) **84**, CH_2Cl_2, -78 ^oC, 93%; ii) $BF_3.OEt_2$, Et_3SiH, CH_2Cl_2, -78 ^oC, 60%; iii) TsCl, Pyridine, CH_2Cl_2, 25 ^oC; iv) CAN, CH_3CN:H_2O, 70%; v) NaH, THF, 100%; vi) 10% Pd/C, H_2, MeOH, 98%; vii) MsCl, Et_3N, CH_2Cl_2, 100%; viii) NaN_3, DMF, 80 ^oC, 53%; ix) $LiAlH_4$, THF then Ac_2O, 78%.

Barker's approach (2006)[40]

Barker *et al.* have employed the Diekmann condensation as the key step to construct the bicyclic ring. The synthesis started with racemic pipecolinic acid (**90**), which was converted into its ethyl ester using thionyl chloride in ethanol and then *N*-alkylated with ethyl 4-bromobutyrate to give diester **91** in 85% yield. Dieckmann cyclisation of diester **91** was achieved using potassium *tert*-butoxide in THF at room temperature to give keto-

ester **92**. Hydrolysis and decarboxylation of **92** by heating in 4M HCl furnished ketone **93** in 89% yield. Ketone **93** was converted into oxime **94** using $NH_2OH{\cdot}HCl$. Reduction of oxime **94** using $LiAlH_4$ followed by acetylation furnished the diastereoisomers of epiquinamide (**66**) in excellent yields (**Scheme 14**).



Scheme 14: (i) $SOCl_2$, EtOH, reflux, 2 h, 99%; (ii) 1.05 equiv ethyl 4-bromobutyrate, K_2CO_3, acetone, reflux, 22 h, 85%; (iii) 2 equiv KO^{t}Bu, THF, 0 ^oC to 25 ^oC, 2 h, 95%; (iv) 4M HCl, 90–100 ^oC, 12 h, 89%; (v) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux, 1 h, 82%; (vi) $LiAlH_4$, THF, 0 ^oC to 25 ^oC, 1 h, 84%; (vii) AcCl, NEt_3, DMF, 25 ^oC, 20 h.

1.2.3 Present work

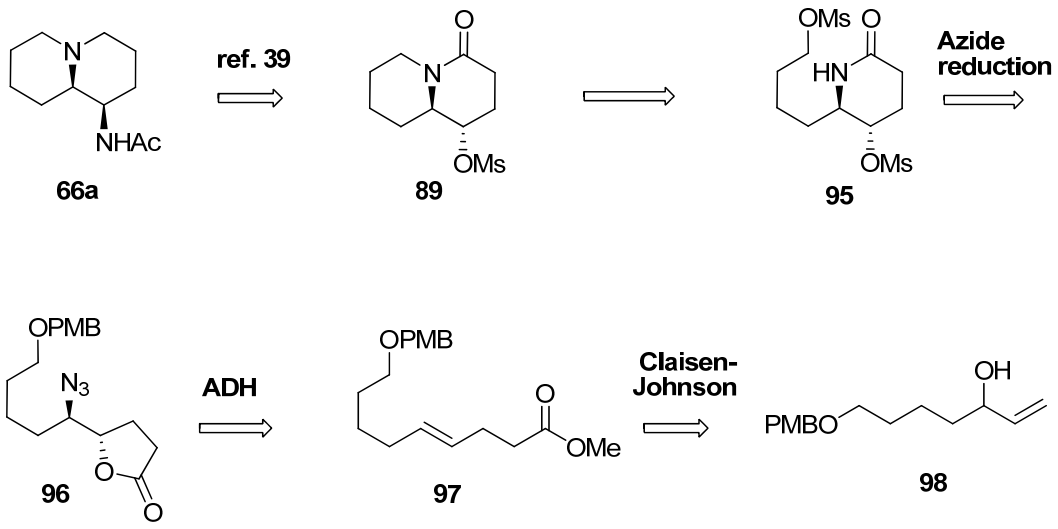
1.2.3.1 Objective

From the above discussions, it is obvious that only a few reports are available for the synthesis of (-)-epiquinamide and all the reported methods employ the chiral pool strategy. Hence, a catalytic method to introduce chirality into the molecule along with a flexibility to obtain all the four diastereoisomers is desirable.

Retrosynthetic analysis

The retrosynthetic analysis of (-)-epiquinamide is shown in **Scheme 15.** We envisioned that (-)-epiquinamide (**66a**) could be easily prepared by the displacement of mesylate with amide function as in **95** to provide the bicyclic ring. The amide **95** in turn can be

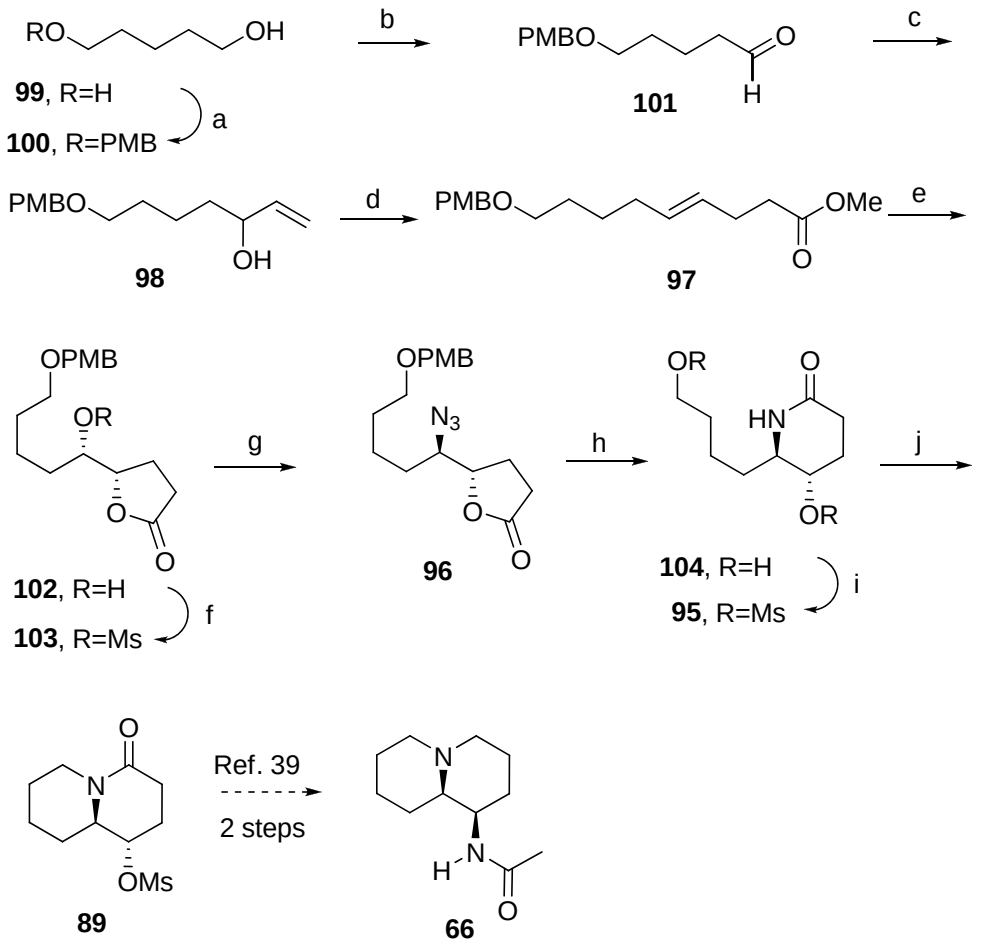
prepared by the reduction of azide **96** using catalytic hydrogenation in excess. The azide **96** could be prepared by asymmetric dihydroxylation of olefin **97,** which would be easily prepared by the Claisen-Johnson rearrangement of allylic alcohol **98**.



Scheme 15: Retrosynthetic analysis of (-) epiquinamide

1.2.4 Results and discussion

The synthetic route employed for the asymmetric synthesis of (-)-epiquinamide (**66**) is shown in **Scheme 16**. The synthesis started with mono protection of commercially available 1,5-pentanediol (**99**) using *p*-methoxy benzyl chloride and NaH in DMF: THF at 0 ^{o}C to get the primary alcohol **100** with good yield (82%) along with the diprotected product (8%). The formation of mono protection was confirmed from the ^{1}H NMR spectrum of **99**, which showed typical signals at δ 6.87 (d) and 7.26 (d) corresponding to aromatic protons. The methoxy protons (-OC**H**$_3$) and the benzylic protons have appeared as singlets at δ 3.8 and 4.43 respectively. Its ^{13}C NMR spectrum exhibited a typical pattern for the 1,4-substituted aromatic ring, which appeared at δ 159, 130, 129 and 113. Further, the free –OH group showed an absorption band (broad) at 3498 cm^{-1} whereas the diprotected compound had no absorption in this region.



Scheme 16: (a) NaH, PMB-Cl, DMF: THF (1:1), 0 ^{o}C-25 ^{o}C, 2 h, 82%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 ^{o}C, 97%. (c) CH_2=CHMgBr, THF, 3 h, 83%; (d) $CH_3C(OMe)_3$, $CH_3CH_2CO_2H$, 135 ^{o}C, 4 h, 85%; (e) $K_3[Fe(CN)_6]$, K_2CO_3, $(DHQ)_2$-AQN, OsO_4, ^{t}BuOH:H_2O (1:1), 89%; (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^{o}C, 98%; (g) NaN_3, DMF, 60 ^{o}C, 5 h, 87%; (h) Pd/C(10%), H_2 (1atm), MeOH, 25 ^{o}C, 99%; (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^{o}C, 1 h, 98%; (j) NaH, THF, reflux, 97%.

Under Swern oxidation[8] conditions (oxalyl chloride, DMSO, Et_3N, -78 ^{o}C), the primary alcohol **100** was quantitatively oxidized to aldehyde **101** without any over oxidation. Its ^{1}H NMR spectrum displayed a characteristic signal for aldehydic proton (-C**H**O) at δ 9.75 while the ^{13}C NMR spectrum showed a characteristic signal at δ 202.5 corresponding to the aldehydic carbonyl carbon (-H**C**=O) (**Fig. 11)**.

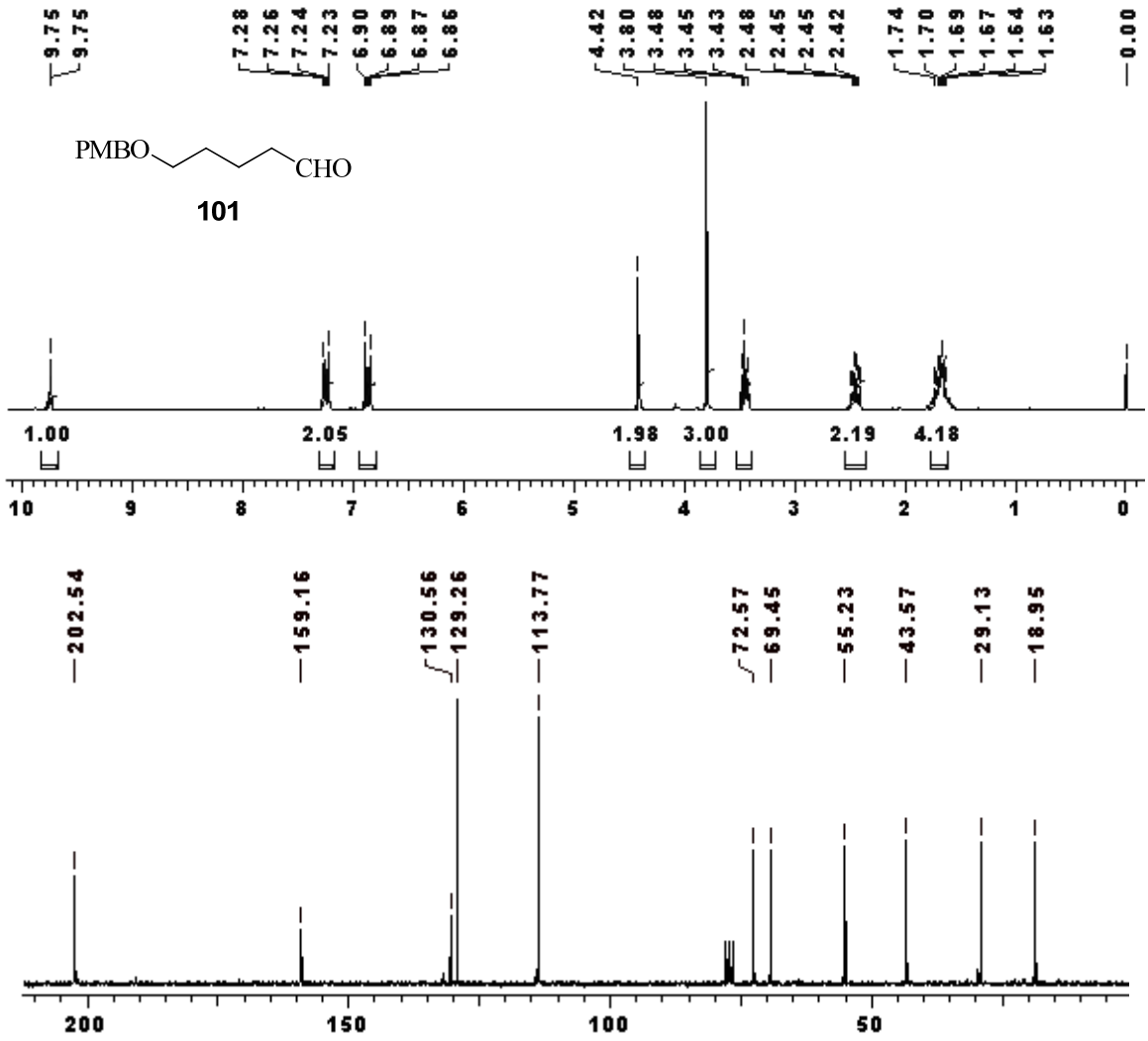


Fig. 11: ^{1}H and ^{13}C NMR spectra of **101**

Also, the IR spectrum of **101** showed a sharp absorption band at 1710 cm^{-1} corresponding to the carbonyl (-C=O) stretching frequency. Grignard addition of vinyl magnesium bromide (prepared from vinyl bromide and magnesium metal in the presence of a pinch of iodine) to aldehyde **101** at 0 ^{o}C in THF as the solvent resulted in the formation of allylic alcohol **98**. Its ^{1}H NMR spectrum showed characteristic signals in the olefinic region *i.e.* δ 5.18 and 5.78 corresponding to the terminal olefin. Its ^{13}C NMR spectrum displayed two typical signals at δ 116.5 and 136.5 in addition to the aromatic carbon

signals for the olefinic function. The broad absorption band at 3448 cm^{-1} in the IR spectrum of **98** further confirmed the presence of alcohol group (-OH).

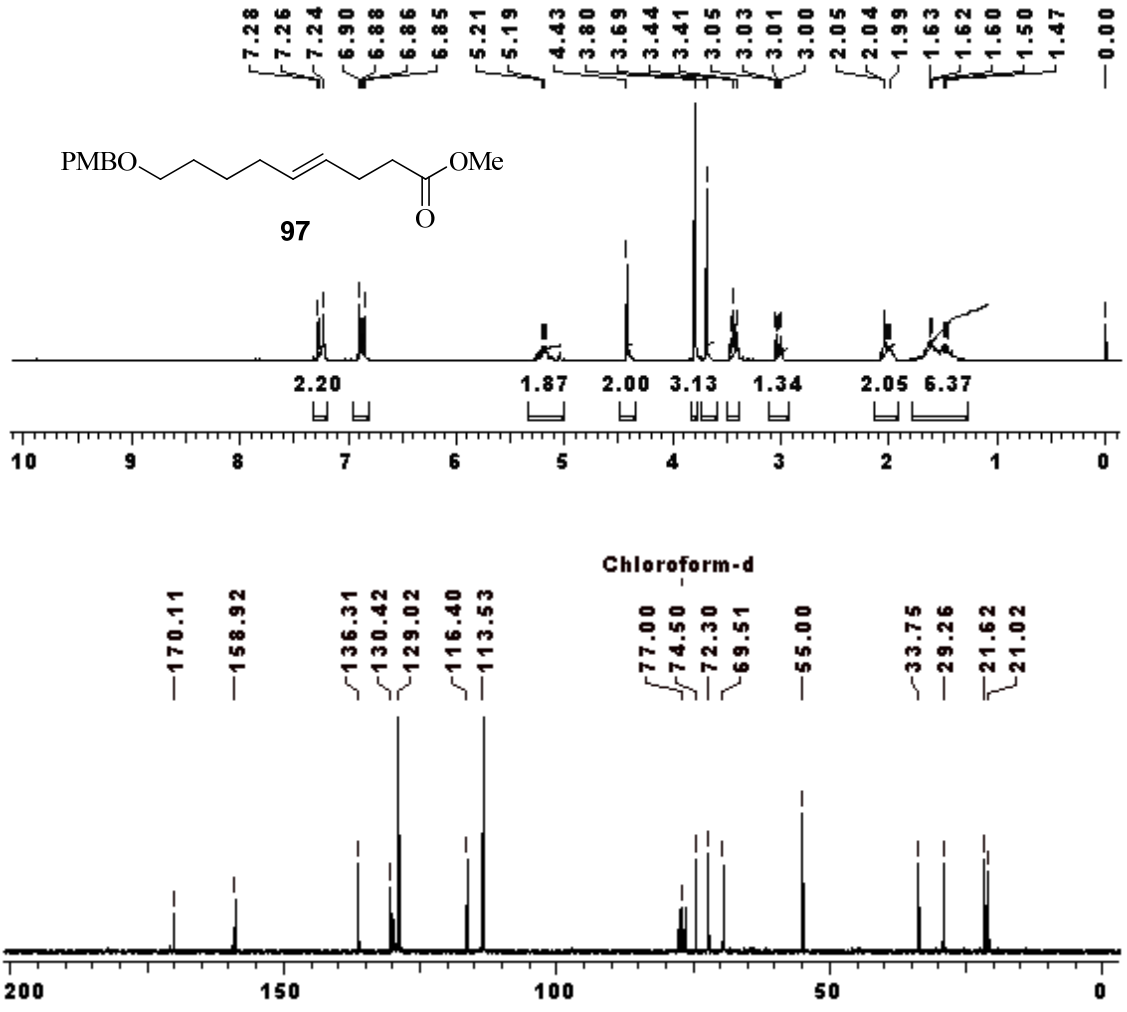


Fig. 12: ^{1}H and ^{13}C NMR spectra of **97**

Allylic alcohol **98** was then subjected to Claisen-Johnson rearrangement[28] with trimethyl orthoacetate in the presence of catalytic amount of propionic acid at 135 ^{o}C to get γ, δ-olefinic ester **97.** This reaction was found to be highly stereospecific and produced only *E*-isomer. The ^{1}H NMR spectrum of **97** showed a typical multiplet at δ 5.21 corresponding to the internal olefin while the methyl ester (-CO_2**Me**) exhibited a singlet (3H) at δ 3.69. The carbonyl group (**C**=O) of ester appeared at δ 170 in its ^{13}C NMR

spectrum (**Fig. 12**). Further, its IR spectrum displayed a sharp absorption band at 1737 cm^{-1} corresponding to the ester carbonyl group in **97**.

With the required carbon backbone for epiquinamide in hand, we focused our attention on introducing the hetero atoms across the olefinic bond. The olefin **97** was then subjected to the asymmetric dihydroxylation (ADH) using cat. OsO_4 and $(DHQ)_2$-PHAL as ligand and $K_3[Fe(CN)_6]$ as the reoxidant. Under basic condition (K_2CO_3) of ADH, the resulting diol underwent lactonization with the ester moiety regioselectively to form a stable five-membered lactone **102**; $[\alpha]_D^{25}$ +8.12 (*c* 0.1, $CHCl_3$). The formation of lactone **102** enabled us to differentiate the two hydroxyl groups thereby facilitating stepwise introduction of hetero atoms into the molecule. The formation of lactone was confirmed by the ^1H NMR spectrum, which exhibited two new signals at δ 4.46 and 3.65 corresponding to the methine protons (-C**H**-O). The carbonyl carbon showed a downfield chemical shift *i.e.* from δ 170.1 to 176.2 in its ^{13}C NMR spectrum of **102** due to the formation of five-membered lactone ring strain (**Fig. 13**). Its IR spectrum showed strong absorption bands at 3448 and 1769 cm^{-1} due to the presence of –OH and lactone carbonyl (-C=O) groups respectively. Its optical purity was determined from the chiral HPLC analysis, which accounts for 90% ee (**Fig. 14**).

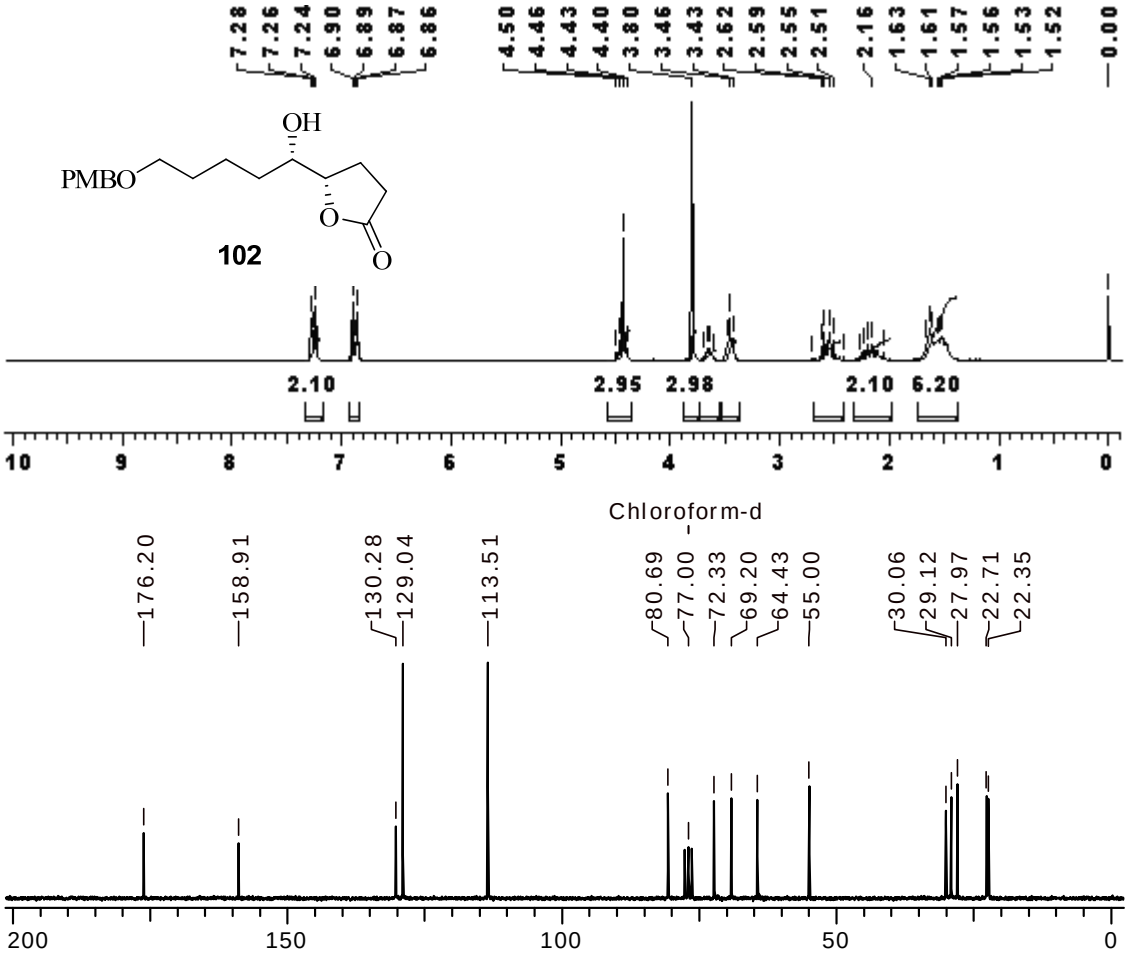
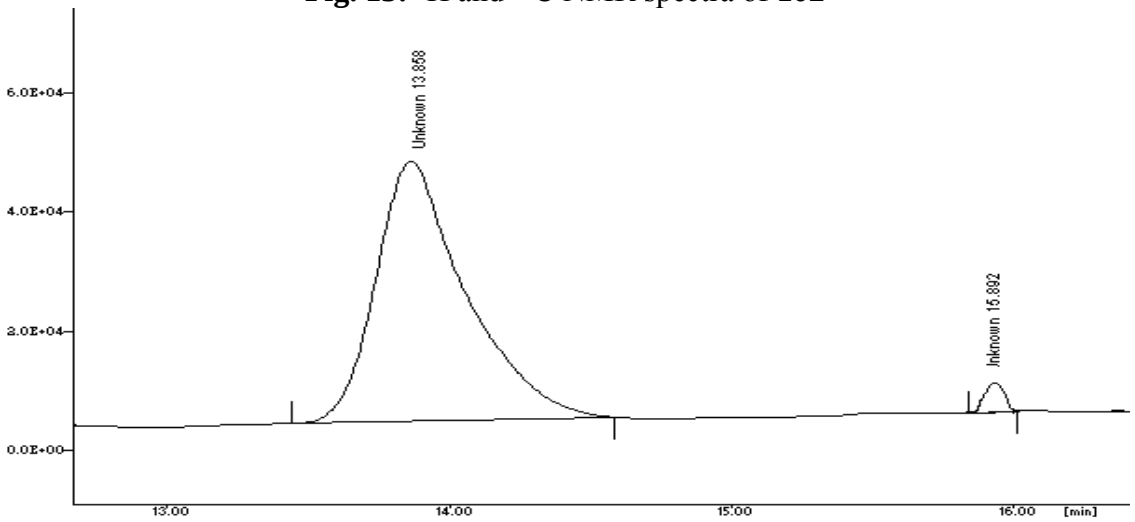


Fig. 13: ^{1}H and ^{13}C NMR spectra of **102**



#	Name	RT (min)	Area[μV.Sec]	%Area
1	E_1	13.858	2830483.324	95.264
2	E_2	15.892	140716.000	4.736

Fig. 14: Chiral HPLC of hydroxyl lactone **102**

The free alcohol group was then converted into its methane sulfonate ester **103** on treatment with methane sulfonyl chloride in CH_2Cl_2 at 0 ^oC in the presence of Et_3N. Without further purification, mesylate **103** was subjected to S_N2 displacement with NaN_3 in DMF to afford the azido lactone **96** in excellent yield. There was no appreciable change in the ^1H NMR spectra of azidolactone **96** and hydroxylactone **102**. However, its ^{13}C NMR spectrum showed a slight upfield shift for **C**-N_3 carbon *i.e.* from δ 73.1 to 64.7. Further, a characteristic sharp absorption at 2108 cm^{-1} in its IR spectrum confirmed the presence of azide (-N_3) group (**Fig. 15**).

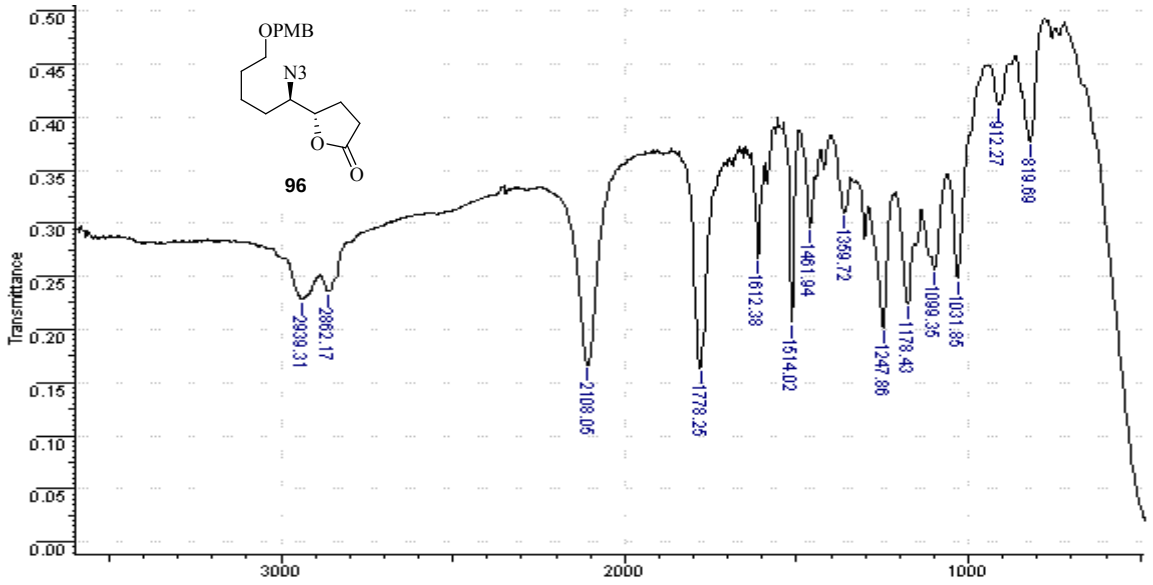


Fig.15: IR spectrum of azidolactone **96**

The reduction of azide group as well as the PMB deprotection were achieved using Pd catalyst (5% Pd/C, H_2) to obtain the lactam **104** as the single product in quantitative yield: the azide **96** underwent reduction to give the corresponding amine, which further underwent intramolecular opening with the lactone forming a stable six-membered amide; thus releasing the free alcohol. It was also observed that the use of lesser amount

of Pd/C (5 wt%) resulted in the reduction of azide group only while the PMB group remained unaffected.

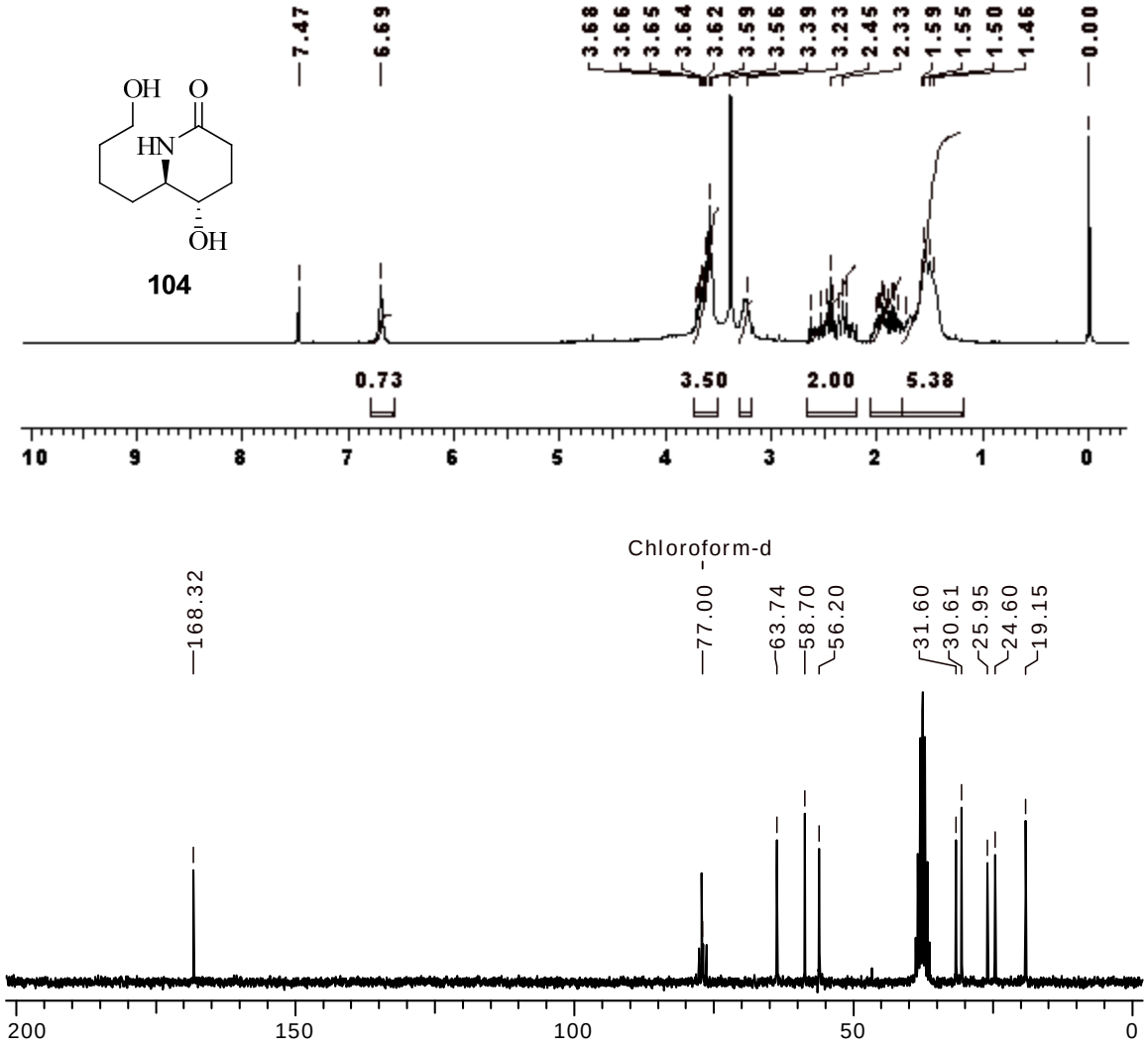


Fig. 16: ^{1}H and ^{13}C NMR spectra of **104**

The ^{1}H NMR spectrum of lactam **104** had no signals in the aromatic region, which confirmed the deprotection of the PMB ether. A broad peak at δ 6.69 (s) is due to the amide proton (-NHCO-) and peaks at δ 3.6 and 3.2 correspond to methine protons (CH-O and CH-N) respectively. Its ^{13}C NMR spectrum showed a typical signal at δ 168.3 corresponding to amide carbonyl (-CO-NH) group (**Fig. 16**). The presence of amide

group was further evidenced by the two characteristic absorption band at 1346 and 1664 cm^{-1} in its IR spectrum. The diol groups in lactam **104** were mesylated completely with two equivalent of CH_3SO_2Cl in the presence of Et_3N in THF to give dimesylate **95**; $[\alpha]_D^{25}$ + 4.41 (*c* 0.6, $CHCl_3$)**.** Surprisingly, this reaction failed when CH_2Cl_2 was used probably due to the insolubility of the diol **104**. The appearance of two singlets each integrating to three protons at δ 3.03 and 3.10 in the ^1H NMR of **94** confirmed the formation of dimesylate.

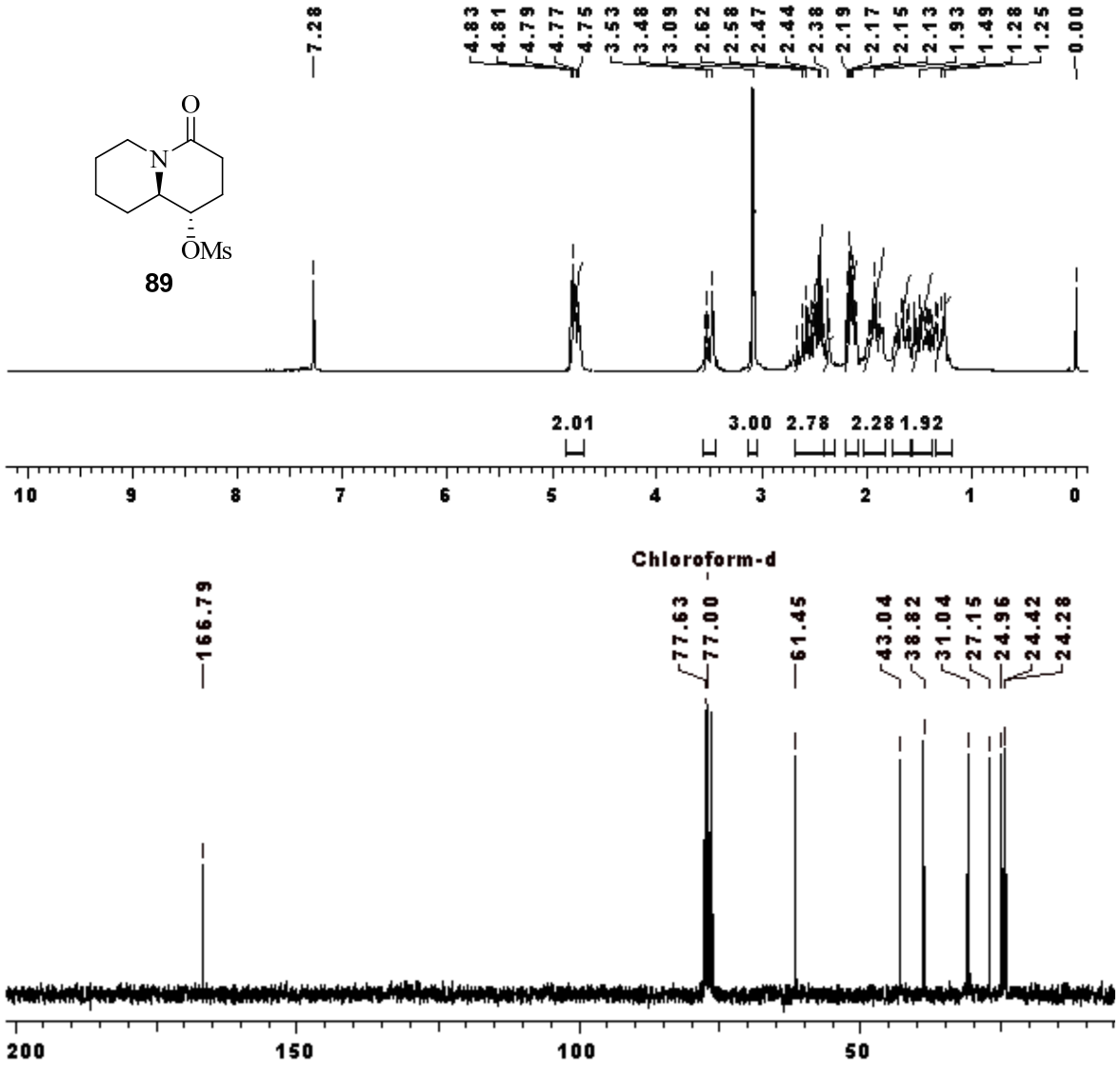


Fig. 17: ^1H and ^{13}C NMR spectra of **89**

Finally, the bicyclic ring was constructed by the *N*-alkylation of the amide using sodium hydride in THF to obtain quinolizidine **89**; $[\alpha]_D$ + 2.25 (*c* 0.5, $CHCl_3$). The other possible three-membered ring was not formed probably due to the ring strain. The formation of bicyclic ring was confirmed by the disappearance of the amide proton (NHCO) in the ^1H NMR of **89**. Further, a peak at δ 3.09 (s, 3H) in its proton spectrum indicated that one of the methane sulfonate esters (CH_3SO_2-) remained unaffected during the intramalocular *N*-alkylation. Its ^{13}C NMR showed signals at δ 77.63 and 61.5 due to the methine carbons (**Fig. 17**). Further, the synthesis of (-)-epiquinamide (**66a**) from intermediate **89** has been reported in the literature.[39]

1.2.6 Conclusion

In conclusion, a concise enantioselective formal synthesis of (-)-epiquinamide (**66a**) has been achieved with 90% ee in ten steps from commercially available 1,5- pentane diol using asymmetric dihydroxyaltion of homoallylic ester **97** as the chiral inducing step. Intramolecular reductive cyclization and *N*-alkylation was employed to construct the quinolizidine ring while Claisen-Johnson rearrangement was used to generate the required carbon backbone. The synthetic strategy described herein has significant potential for further extension to quinazolizidine-based bioactive molecules and has the flexibility to synthesize all the four stereoisomers of epiquinamide by changing either the ligand or olefin geometry in ADH step.

1.2.7 Experimental section

5-(4-Methoxybenzyloxy)pentan-1-ol (100)

To a stirred solution of 1,5-pentane diol **99** (10.4 g, 100 mmol) in THF:DMF (1:1, 240 mL) was added 60% sodium hydride (4 g, 100 mmol) at 0 ^oC. After 5 min of stirring, *p*-

methoxy benzyl chloride (15.6 g, 13.5 mL, 100 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred for additional 1 h at the same temperature. After the completion of the reaction as monitored by TLC, it was quenched with saturated NH_4Cl solution and the solvent was then evaporated under reduced pressure. The residue was extracted with ethyl acetate (3 X 200 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure and purified by column chromatography using petroleum ether: ethyl acetate (4:1) to get mono protected ether **100** as a colorless oil. **Yield**: 82% (18.368 g); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 3.8 (s, 3H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.45 (t, *J* = 6.3 Hz, 2H), 1.43-1.67 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 159.1, 130.5, 129.2, 113.7, 72.5, 70.0, 62.5, 55.2, 32.4, 29.4, 22.4; **IR** ($CHCl_3$, cm^{-1}): 3498, 2935, 2860, 1733, 1612, 1533, 1461, 1365, 1301, 1247, 1172, 1097, 1035, 819; Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.52; H, 9.01%.

5-(4-Methoxybenzyloxy)pentan-1-al (101)

To a stirred solution of oxalyl chloride (12.1 g, 8.22 mL, 98 mmol) in CH_2Cl_2 (25 mL) at -78 ^oC was added dimethyl sulfoxide (11.232 g, 10.2mL, 144 mmol) in CH_2Cl_2 (25 mL) drop-wise. The reaction was highly exothermic and care was taken to maintain the temperature at -78 ºC. After stirring for 10 min, a solution of alcohol **100** (10.72 g, 48 mmol) in CH_2Cl_2 (250 mL) was added slowly so that the temperature is maintained less than -70 ^oC. It was stirred for 1 h at the same temperature and triethylamine (19.372 g, 26.7 mL, 192 mmol) was added drop-wise. The reaction mixture was then slowly brought to room temperature and stirred for another 1 h. After the completion of the reaction, it was quenched with water and extracted with CH_2Cl_2 (3 x 100 mL), washed with water,

brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to afford the crude aldehyde **101**, which was purified by column chromatography using petroleum ether: ethyl acetate (9:1) to obtain pure aldehyde **101** as a colorless oil. **Yield**: 97% (10.3 g); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.45 (t, *J* = 5.8 Hz, 2H), 2.45 (dt, *J* = 7.1, 1.7 Hz, 2H), 1.69 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 202.5, 159.1, 130.5, 129.2, 113.7, 69.4, 55.2, 43.5, 29.1, 18.9; **IR** ($CHCl_3$, cm^{-1}): 2933, 2858, 2360, 1733, 1710, 1604, 1514, 1456, 1247, 1163, 1101, 1033, 821; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.23; H, 9.17%.

7-(4-Methoxybenzyloxy)hept-1-en-3-ol (98)

A two-necked round bottomed flask was charged with Mg metal (1.2 g, 50 mmol), a pinch of iodine and THF (200 mL). To this stirred mixture, vinyl bromide (6.42 g, 60 mmol) in THF was added drop-wise at room temperature. During the addition, it was gently heated on water bath (45 ^oC) to initiate the Grignard reagent formation. The initiation of the reaction was observed visually and the light brown color of iodine disappeared. After the Mg metal have dissolved completely, the aldehyde **101** (10.2 g, 46 mmol) in THF (10 mL) was added slowly over a period of 10 min at 0 ^oC and stirred for another 3 h. After the completion of the reaction, it was cooled to -10 ^oC and a saturated solution of aq. NH_4Cl was added to quench the excess Grignard reagent. Solvent was then evaporated under reduced pressure and the residue was extracted with ethyl acetate (3 x 100 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure and the crude allylic alcohol **98** was purified by column chromatography using petroleum ether: ethyl acetate (4:1) to

obtain pure allylic alcohol **98** as colorless oil. **Yield**: 83% (9.545 g); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.77 (m, 1H), 5.20 (m, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.43 (t, *J* = 6.4 Hz), 1.61 (m, 4H), 1.43 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 158.9, 136.3, 130.3, 129.0, 116.4, 113.5, 74.5, 72.3, 69.5, 55.0, 33.7, 29.2, 21.6; **IR** ($CHCl_3$, cm^{-1}) 3448, 2939, 2862, 2360, 2331, 1733, 1612, 1591, 1514, 1461, 1363, 1301, 1247, 1174, 1097, 1033, 821; Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.34; H, 8.92%.

(*E*)-Methyl 9-(4-methoxybenzyloxy)non-4-enoate (97):

A oven dried 100 mL round bottomed flask was charged with allylic alcohol **98** (3. 49 g, 14 mmol), propionic acid (208 mg, 20 mol%) and trimethyl orthoacetate (13.44 g, 14 mL, 112 mmol). The mixture was refluxed at 135 ^oC for 5 h. After the completion of the reaction as monitored by TLC, it was cooled to room temperature and the excess trimethyl orthoacetate was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 25 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to obtain the crude olefinic ester **97**, which was purified by column chromatography using petroleum ether:ethyl acetate (9: 1) to obtain pure olefinic ester **97** as a colorless oil. **Yield**: 85% (3.64 g); Colorless oil; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.19 (m, 2H), 4.43 (s, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.44 (t, *J* = 6. 5 Hz, 2H), 3.03 (dd, *J* = 6.8, 3.15 Hz, 2H), 2.02 (m, 2H), 1.55 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 172.0, 159.1, 130.7, 129.2, 113.9, 92.0, 84.1, 72.5, 69.8, 55.2, 51.8, 34.7, 29.1, 28.3, 25.6; **IR** ($CHCl_3$, cm^{-1}): 3444, 2937, 2856, 2360, 2331, 1737,

1612, 1514, 1460, 1438, 1363, 1301, 1247, 1220, 1172, 1099, 1035, 821; Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 69.46; H, 9.12%.

(*S*)-5((*S*)-5-(4-Methoxybenzyloxy)-1-hydroxypentyl)dihydrofuran-2(3*H*)-one (102)

A 250 mL two-necked flask was charged with potassium ferricyanide (8.39 g, 25.5 mmol), potassium carbonate (3.519 g, 25.5 mmol), $(DHQ)_2$-PHAL (72.5 mg, 1 mol%) and *t*-BuOH:H_2O (1:1, 150 mL). The reaction mixture was cooled to 0 ^oC on an ice bath and OsO_4 (0.5 mol%, 10.8 mg in toluene) was added *via* syringe. After 10 min. of stirring at 0 ^oC olefin **97** (2.397 g, 8.5 mmol) was added drop-wise. The reaction mixture was brought to room temperature and stirred for 24 h. After the completion of the reaction as monitored by TLC, it was quenched with saturated sodium sulfite solution and extracted with ethyl acetate (3x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to obtain the crude lactone **102**, which was purified by column chromatography using petroleum ether: ethyl acetate (1:1). **Yield**: 89% (2.33 g); mp: 78 ^oC ; $[\alpha]_D^{25}$ + 8.12 (*c* 0.1, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H),3.38 (m, 1H), 3.80 (s, 3H), 3.56 (m, 1H), 3.46 (t, *J* = 5.9 Hz, 2H), 2.55 (m, 2H), 2.23 (m, 3H), 1.58 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 177.8, 159.1, 130.55, 129.3, 113.7, 83.1, 73.1, 72.5, 69.8, 55.2, 32.5, 29.4, 28.6, 23.9, 22.3; **IR** ($CHCl_3$, cm^{-1}): 3448, 2939, 2864, 1768, 1612, 1512, 1461, 1363, 1247, 1180, 1097, 1033, 918, 819, 732; Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 65.12; H, 7.32%.

(*S*)-5-(4-Methoxybenzyloxy)-1-((*S*)-tetrahydro-5-oxofuran-2-yl)pentyl methane sulfonate (103)

To a stirred solution of hydroxyl lactone **102** (830 mg, 2.6 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (530 mg, 5.2 mmol) at 0 ^oC. After 5 min of stirring, methane sulfonyl chloride (355 mg, 3.1 mmol) was added drop-wise at the same temperature. The reaction mixture was stirred for another 1 h at 0 ^oC and brought to room temperature. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get crude mesylate **103**, which was purified by column chromatography using petroleum ether: ethyl acetate (1:1). **Yield**: 98% (1.172 g); $[\alpha]_D^{25}$ + 12.1 (*c* 0.7, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.69 (m, 1H), 4.56 (m, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.46 (t, *J* = 6.1 Hz, 2H),3.10 (s, 3H), 2.57 (m, 2H), 2.32 (m, 1H), 2.08 (m, 1H), 1.65 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 176.2, 159.2, 130.5, 129.3, 113.8, 83.3, 79.6, 72.6, 69.5, 55.3, 38.9, 30.5, 29.1, 28.0, 24.1, 21.7; **IR** ($CHCl_3$, cm^{-1}): 2941, 2869, 1782, 1731, 1612, 1512, 1352, 1247, 1174, 1118, 1033, 923, 821; Anal. Calcd for $C_{18}H_{26}O_7S$: C, 55.94; H, 6.78; S 8.30. Found: C, 55.24; H, 7.0%.

(*S*)-5-((*R*)-5-(4-Methoxybenzyloxy)-1-azidopentyl)dihydrofuran-2(3*H*)-one (96)

To a stirred solution of methane sulfonate ester **103** (900 mg, 2.25 mmol) in DMF (5 mL) was added sodium azide (455 mg, 7 mmol) and the reaction mixture was heated at 60 ^oC for 8 h. After the completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure and the residue was purified by column chromatography using petroleum ether: ethyl acetate (7:3) to obtain pure azido lactone **95** as colorless oil. **Yield**: 87% (651 mg); $[\alpha]_D^{25}$ -15.16 (*c* 0.5, $CHCl_3$);

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.46 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.64 (m, 1H), 3.46 (t, *J* = 5.8 Hz, 1H), 2.55 (m, 2H), 2.16 (m, 1H), 1.52-1.66 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 176.2, 158.9, 130.3, 129.0, 113.5, 80.7, 72.3, 69.2, 64.4, 55.0, 30.1, 29.1, 27.9, 22.7, 22.3; **IR** ($CHCl_3$, cm^{-1}): 2939, 2862, 2108, 1778, 1612, 1514, 1461, 1359, 1247, 1178, 1099, 1031, 912, 819; Anal. Calcd. for $C_{17}H_{23}N_3O_4$: C, 61.25; H, 6.95; N, 12.60. Found: C, 60.42; H, 6.27; N, 12.55%.

(5*S*, 6*R*)-5-Hydroxy-6-(4-hydroxybutyl)piperidin-2-one (104)

To a stirred solution of azide **95** (400 mg, 1. 2mmol) in methanol (10 mL) was added 5% Pd/C (200 mg, 50 wt %) carefully at room temperature and a hydrogen balloon was kept to provide hydrogen atmosphere. After the completion of the reaction as monitored by TLC, it was filtered over celite and the filtrate was concentrated under reduced pressure to provide the diol **103**, which was purified by column chromatography using methanol: ethyl acetate (1:9) to give pure diol **103** as colorless solid**. Yield**: 99% (222 mg); mp: 85 ^{o}C; $[\alpha]_D^{25}$ + 3.56 (*c* 0.5, MeOH); **^{1}H-NMR** (200 MHz, CD_3OD): δ 6.69 (s, 1H), 3.66 (m, 1H), 3.59 (t, *J* = 5.7, 2H), 3.23 (m, 1H), 2.29-2.63 (m, 2H), 1.79-2.0 (m, 2H), 1.55 (m, 6H); **^{13}C-NMR** (50 MHz, CD_3OD): δ 168.3, 63.7, 58.7, 56.2, 31.6, 30.6, 25.9, 24.6, 19.2; **IR** (KBr, cm^{-1}) 3445, 2995, 2992, 1662, 1342, 1170, 927; Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 56.89; H, 9.89; N, 7.55%.

Dimesylated amide 95

To a stirred solution of diol **104** (830 mg, 2.6 mmol) in THF (200 mL) was added Et_3N (530 mg, 5.2 mmol) at 0 ^{o}C. After 5 min of stirring, methane sulfonyl chloride (710 mg, 6.2 mmol) was added drop-wise over a period of 10 min. The reaction mixture was

stirred for another 1 h at 0 ^{o}C and brought to room temperature. After the completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get the crude dimesylate **95,** which was purified by column chromatography using petroleum ether: ethyl acetate (1:1) to get pure dimesylate **95** as a viscous gum. **Yield**: 98% (873 mg); $[\alpha]_D^{25}$ + 4.41 (*c* 0.6, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.02 (s, 1H), 4.85 (q, *J* = 8.5, 4.30 Hz), 4.25 (t, *J* = 6.1 Hz), 3.61 (m, 1H), 3.10 (s, 3H), 3.03 (s, 3H), 2.48 (m, 2H), 2.18 (m, 2H), 1.80 (m, 3H), 1.57 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 169.4, 75.2, 69.1, 58.1, 55.1, 37.7, 36.1, 32.8, 27.6, 25.6, 22.6, 20.1; **IR** ($CHCl_3$, cm^{-1}): 3020, 2941, 1664, 1346, 1215, 1174, 927, 757; Anal. Calcd for $C_{11}H_{21}NO_7S_2$: C, 38.47; H, 6.16; N, 4.08. Found: C, 37.46; H, 6.99; N, 4.01%.

(1*S*, 9*R*)-Octahydro-4-oxo-1H-quinolizin-1-yl methanesulfonate (89)

To a cooled solution of **95** (121 mg, 0.29 mmol) at −40 °C in THF (25 mL) was added a suspension of NaH (13.92 mg, 0.58 mmol) in THF (5 mL) over a period of 10 min. After stirring for 1 h at that temperature, the mixture was warmed to 40 °C and stirred for another 1 h. It was then quenched by addition of saturated aq. NH_4Cl (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (4×5 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate: petroleum ether = 1/1) on silica gel to give bicyclic lactam **89** as a viscous gum. **Yield**: 97% (69 mg); $[\alpha]_D$ + 2.25 (*c* 0.5, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.77 (dt, *J* = 11.5, 4.4 Hz, 2H), 3.5 (dt, *J* = 9.6, 2.78 Hz, 1H), 3.09 (s, 3H), 2.53 (m, 2H), 2.15 (m, 2H), 1.93 (m, 2H), 1.25-1.73 (m, 5H);

^{13}C-NMR (50 MHz, $CDCl_3$): δ 24.3, 24.4, 25.0, 27.2, 31.0, 38.8, 43.0, 61.5, 77.6, 166.8; **IR** ($CHCl_3$, cm^{-1}): 2934, 2857, 1610, 1445, 1215.5, 1048; Anal. Calcd for $C_{10}H17NO_4S$: C, 48.57; H, 6.93; N, 5.66; S, 12.97. Found: C, 48.50; H, 6.99; N, 5.60%.

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CHAPTER 2

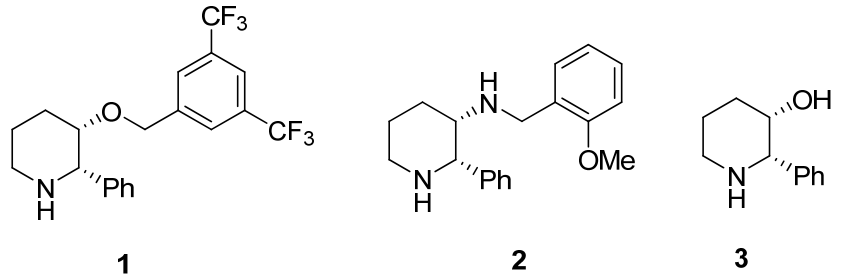
A short and enantioselective synthesis of (+)-L-733,060 and threo-sphingosine via asymmetric epoxidations

Section I

A short enantioselective synthesis of (+)-L-733,060 *via* Shi' epoxidation of homoallylic carboxylate

2.1.1. Introduction

Substance P (SP), a peptide neurotransmitter, is a member of the tochynin family of peptides, which include neurokinins A and B (NKA, NKB). These peptides bind to a series of three neurokinin receptors, NK_1, NK_2, and NK_3, which have selective affinity for SP, NKA, and NKB respectively.[1] For example SP has been shown to elicit a IL-I production in macrophages, sensitize neutrophils and enhance dopamine release in the *substantia nigra* region in cat brain. The neurokinin substance P has also been associated with a variety of biological effects including smooth muscle contraction, neurogenic inflammation and pain transmission. Recently, (+)-L-733,060 (**1**)[2] and (+)-CP-99,994 (**2**),[3] possessing 2-alkyl-3-hydroxypiperidine and 2-alkyl-3-aminopiperidine structural units respectively, have proven to be selective and potent non-peptide neurokinin substance P receptor antagonists (**Fig. 1**). Also, they have been implicated in a variety of disorders including migraine, rheumatoid arthritis and pain.[4] Recent studies[5] have further shown that (+)-L-733,060 (**1**) can act both as an antitumor agent and as a promising new target for the treatment of retinoblastoma. In view of these potential pharmacological applications, several reports on the synthesis of **1** and **2**, both in racemic and optically active forms, have been published.[6]



1 **2** **3**

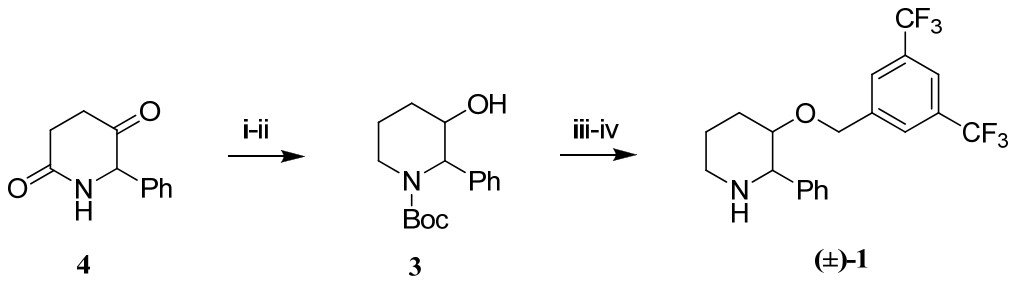
Fig. 1

2.1.2. Review of Literature

Various asymmetric syntheses of non-peptidic neurokinin NK1 receptor antagonist namely (+)-L-733,060 (**1)** and (2*S*,3*S*)-3-hydroxy-2-phenyl piperidine (**3**) have been documented in the literature.[2] Some of the interesting and important synthetic routes to (+)-L-733,060 (**1**) are described below.

Harrison's approach (1994)[2]

Harrison and co workers have accomplished the first synthesis of (±)-L-733,060 (**1**) and explored its NK_1 receptor antagonist property. This approach employs the reduction of keto lactam **4** to give the corresponding hydroxy piperidine in 72% yield, which was protected with $(Boc)_2O$ to obtain the intermediate **3**. Etherification of alcohol group in **3** with 3,5-bis(trifluromethyl)benzyl bromide followed by removal of the Boc protection afforded (±)-L-733,060 (**1**) in good yield (**Scheme 1**).

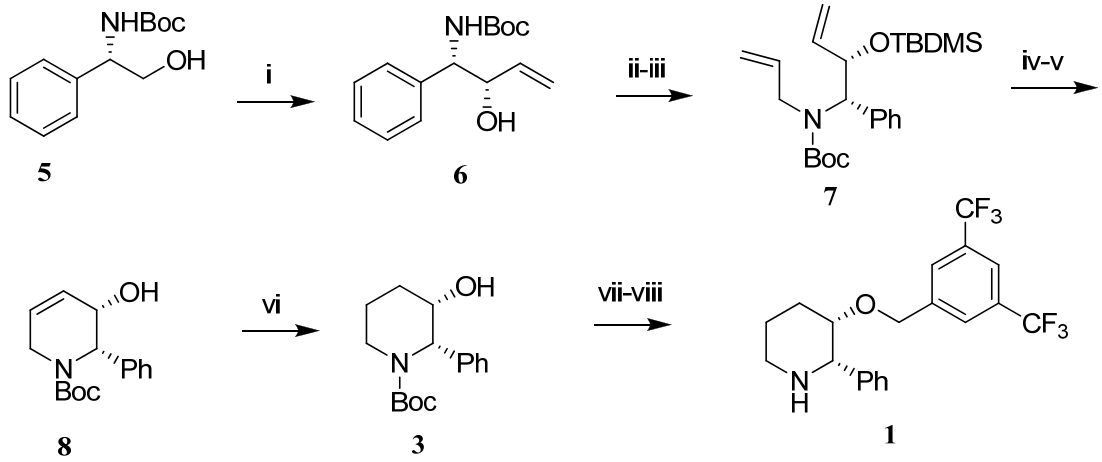


4 **3** **(±)-1**

Scheme 1: (i) $LiAlH_4$, THF, reflux, 72%; (ii) di-*t*-butyl dicarbonate, CH_2Cl_2, 98%; (iii) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 47%; (iv) TFA, CH_2Cl_2, 81%.

Rao's approach (2003)[7]

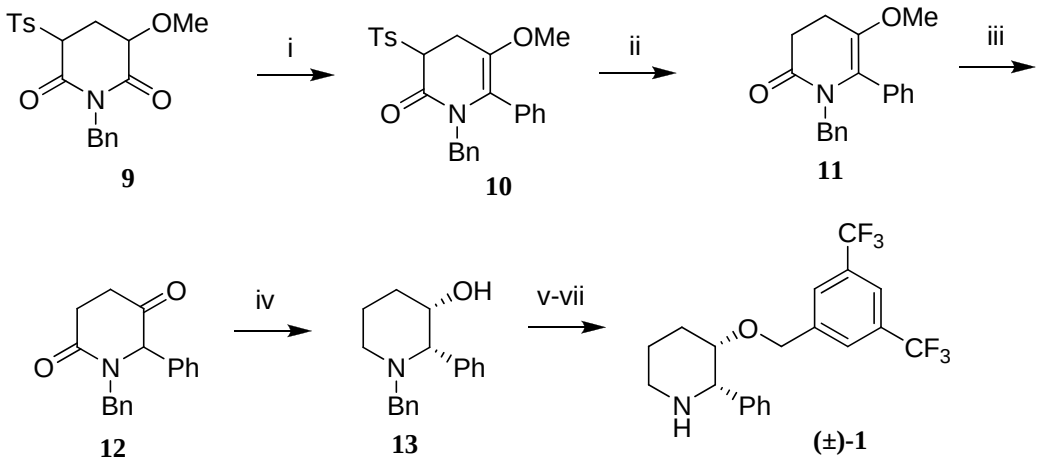
This approach describes the synthesis of (+)-L-733,060 (**1**) starting from *N*-Boc protected amino alcohol **5.** Oxidation of the primary alcohol **5** under Swern oxidation condition {$(COCl)_2$, DMSO, Et_3N} followed by addition of vinyl magnesium bromide to it produced allylic alcohol **6**. Protection of allylic alcohol as silyl ether followed by *N*-allylation of the amine resulted in diene **7**, which upon ring closing metathesis using Grubbs' catalyst gave the unsaturated piperidine moiety **8**. The catalytic hydrogenation of olefin **8** furnished the intermediate **3** in 65% yield. Etherification of alcohol group in **3** with 3,5-bis(trifluromethyl)benzyl bromide followed by deprotection of the Boc-group provided (+)-L-733,060 (**1**) (**Scheme 2**).



Scheme 2: (i) DMSO, $(COCl)_2$, *i*-Pr_2NEt, CH_2Cl_2 then CH_2=CHMgBr, THF, 2 h, 90%; (ii) TBDMS-Cl, imid., CH_2Cl_2, 24 h, 90%; (iii) Allyl bromide, NaH, DMF, 0 ºC- 25 ºC, 24 h, 90%; (iv) TBAF-AcOH, THF, 0 ºC- 25 ºC, 24 h, 85%; (v) Grubbs' catalyst, CH_2Cl_2, 25 ºC, 6 h, 82%; (vi) Pd/C, H_2, EtOH, 4 h, 65%; (vii) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 80%; (viii) TFA, CH_2Cl_2, 79%.

Chang's approach (2005)[8]

Chang *et al.* have employed a new method of addition of Grignard reagent onto glutarimide **9** for the synthesis of (±)-L-733,060 (**1**). Accordingly, addition of phenyl magnesium bromide to glutarimide **9** followed by trapping the resulted –OH group with Ac_2O proceeded regioselectively to provide the enol ether **10** in 82% yield. Removal of the sulfonate ester group was achieved using Na/Hg to obtain enol ether **11.** Hydrolysis of enol ether **11** using BBr_3 afforded ketolactam **12,** which was reduced with $LiAlH_4$ to give piperidine **13**. Etherification of alcohol group in **13** with 3,5-bis(trifluromethyl)benzyl bromide followed by deprotection of benzyl group produced (±)-L-733,060 (**1**) (**Scheme 3**).

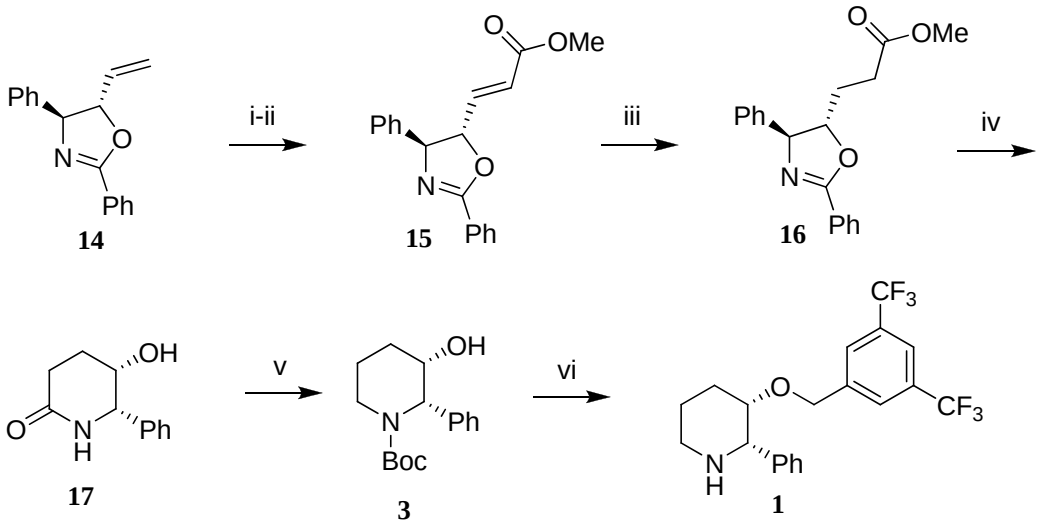


Scheme 3: (i) NaH, PhMgBr, THF, 25 ºC, 1 h, 82%; (ii) Na-Hg, MeOH, 25 ºC, 90%; (iii) BBr_3, CH_2Cl_2, -78 ºC, 90%; (iv) $LiAlH_4$, THF, reflux, 87%; (v) $Pd(OH)_2$, H_2, MeOH, 25 ºC, 90%; (vi) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 47%; (vii) TFA, CH_2Cl_2, 81%.

Ham's approach (2005)[9]

This approach describes the synthesis of (+)-L-733,060 starting from chiral oxazoline **14** prepared from the corresponding amino alcohol. Ozonolysis of double bond in **14**

followed by Horner-Wittig reaction of the resulting aldehyde furnished α, β-unsaturated ester **15** in 87% yield. 1,4-Reduction of **15** with copper bromide, Red-Al and 2-butanol gave the saturated methyl ester **16** in 83% yield. Reduction of oxazoline was achieved using $Pd(OH)_2/H_2$ during which process intramolecular lactamization took place to give lactam **17**. Reduction of lactam **17** with $LiAlH_4$ and protection of amine gave the required intermediate **3**. Etherification of alcohol **3** with 3,5-bis(trifluromethyl)benzyl bromide followed by deprotection afforded (+)-L-733060 (**1**) (**Scheme 4**).

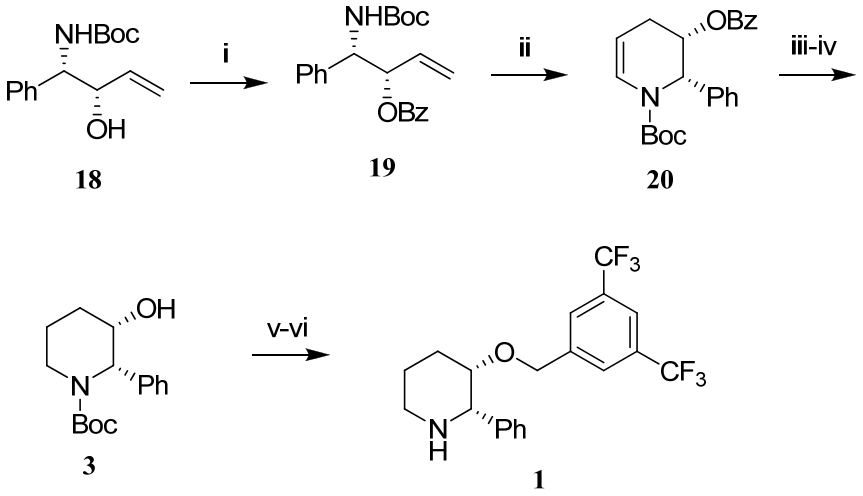


Scheme 4: (i) O_3, MeOH, -78 ^oC, then $(CH_3)_2S$; (ii) $(MeO)_2POCH_2COOMe$, LiCl. $^iPr_2NEt$, CH_3CN, 87% ; (iii) CuBr, Red-Al, 2-butanol, THF, 83% ; (iv) 20% $Pd(OH)_2/C$, H_2, (70 psi), MeOH:AcOH (10:1), 76% ; (v) (a) $BH_3{\cdot}SMe_2$, MeOH, THF ; (b) $(Boc)_2O$, CH_2Cl_2, 62%; (vi) (a) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 76%; (b) trifluoroacetic acid, 93%.

Oshitari's approach (2006)[10]

Oshitari *et al.* have achieved the synthesis of (+)-L-733,060 starting from optically active amino alcohol **18**. Protection of amine functionality in **18** with $(Boc)_2O$ followed by esterification of the free alcohol group with benzoyl chloride gave the protected amino alcohol **19**. One carbon extension and ring closure to obtain enamine **20** was achieved in one-pot *via* $Rh(acac)(CO)_2$ catalyzed hydroformylation of olefin **19**. Hydrogenation of

C=C bond in **20** followed by hydrolysis gave the intermediate **3** which was converted to (+)-L-733,060 (**1**) *via* standard reaction sequences (**Scheme 5**).

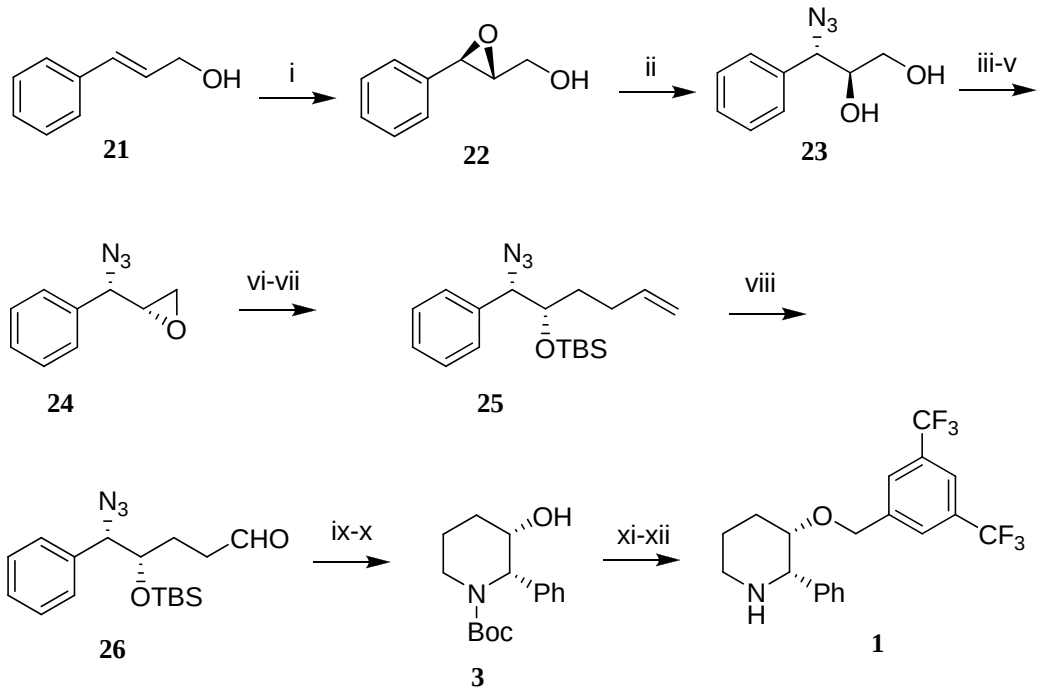


Scheme 5: (i) BzCl, pyridine, 25 ^{o}C, 10 h; (ii) Rh(acac)$(CO)_2$ (3 mol%), biphephos (6 mol%), CO/H_2 (5 atm), THF, 65 °C, 5 h; (iii) 10% Pd/C, H_2 (1 atm), EtOH, 25 ^{o}C, 20 h; (iv) 1 M NaOH:MeOH:1,4-dioxane, (2:3:6), 25 ^{o}C, 1 h; (v) 3,5-$(CF_3)_2C_6H_3CH_2Br$, NaH, THF:DMF (1:3), 0 °C, 6 h; (vi) TFA, 25 ^{o}C, 1.5 h, $NaHCO_3$.

Kumar's approch (2007)[11]

This approach employs opening of chiral azido epoxide **24** with allyltrimethyl silane in the presence of $TiCl_4$ as Lewis acid. Accordingly, the synthesis started with Sharpless asymmetric epoxidation of cinnamyl alcohol (**21**) to get epoxy alcohol **22** in 99%ee. Regioselective opening of epoxide with NaN_3 resulted in *trans* azido diol **23**, which was converted to the *cis* azido epoxide **24** *via* standard reaction sequences. Among the several reagents screened, allyltrimethyl silane opened azido epoxide **24** regioselctively to give the azido alcohol in moderate yield, which was protected as silyl ether **25**. One carbon degradation was achieved *via* one-pot dihydroxylation followed by diol cleavage to get the crucial azido aldehyde **26**. Azido aldehyde **26** underwent aza-Wittig reaction in the presence of PPh_3 to provide six-membered imine, which upon reduction with $NaBH_4$

gave piperidine moiety **3**. Etherification of alcohol with 3,5-bis(trifluromethyl)benzyl bromide followed by deprotection afforded (+)-L-733,060 (**1**) (**Scheme 6**).

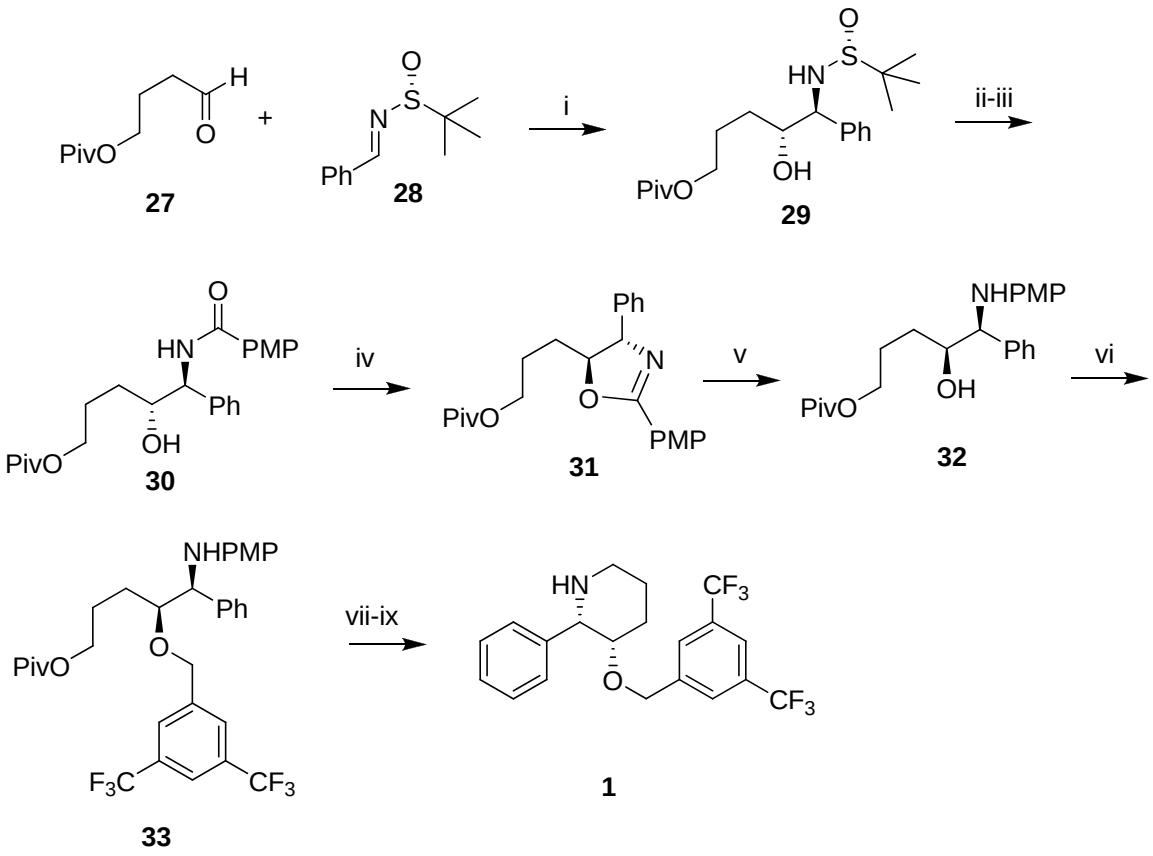


Scheme 6: (i) (*S*,*S*)-(−)-DET, Ti(OPr-*i*)$_4$, TBHP, MS 4 Å, CH_2Cl_2, −20 °C, 3 h, 89%; (ii) NaN_3, NH_4Cl, MeOH:H_2O (8:1), 65 °C, 5 h, 98%; (iii) PivCl, Pyridine, CH_2Cl_2 (1:1), 0 °C–25 °C, 5 h; (iv) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C–25 °C, 1 h; (v) K_2CO_3, MeOH, 25 °C, 10 h, 80% (3 steps); (vi) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78 °C, 1 h, 65%. (vii) TBSOTf, 2,6-lutidine, 0 °C, 1 h, 95%; (viii) OsO_4, $NaIO_4$, 1,4-dioxane:H_2O (3:1), 0 °C, 3 h; (ix) PPh_3, THF, 25 °C, 16 h; (x) $NaBH_4$, MeOH, 0 °C, 30 min., 65%; (xi) Boc_2O, Et_3N, CH_2Cl_2, 2 h, 95%; (xii) TBAF, THF, 0 °C–25 °C, 10 h, 90%; (xiii) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 80 °C, 12 h, 78%; (xiv) TFA, MeOH, 25 °C, 12 h, 70%.

Wang's approach (2008)[12]

Wang *et al*. employed the reductive coupling of 4-pivaloxybutanal (**27**) with (*R*)-phenyl *N-tert*-butanesulfinyl imine (**28**) in the presence of SmI_2 to afford amino alcohol **29** with required stereochemistry. Removal of the chiral auxiliary followed by selective *N*-acylation with 4-methoxybenzoic anhydride afforded amide **30**. Mesylation of free alcohol group in **30** furnished oxazoline **31** in 85% yield, with complete inversion of

configuration at C-2. Reductive ring-opening of oxazoline **31** ($NaBH_3CN$, HOAc, 40 °C) gave *syn*-1,2-amino alcohol **32** in excellent yield. Selective *O*-alkylation with 3, 5-bis(trifluromethyl)benzyl bromide provided **33** in 82% yield. The intermediate **33** was converted to (+)-L-733,060 (**1**) by standard reaction sequences (**Scheme 7**).



Scheme 7: i) SmI_2, ^tBuOH, -78 ^oC, 78%; (ii) HCl, MeOH; (iii) $(PMPCO)_2O$, Et_3N, CH_2Cl_2, 88%; (iv) MsCl, Et_3N, CH_2Cl_2, 85%; (v) $NaCNBH_3$, AcOH, 90%; (vi) NaH, 3,5-bis(trifluromethyl)benzyl bromide, TBAI, DMF, 82%; (vii) NaOMe, MeOH; (viii) MsCl, Et_3N, CH_2Cl_2, 78%; (ix) DDQ, CH_2Cl_2, 0 ^oC.

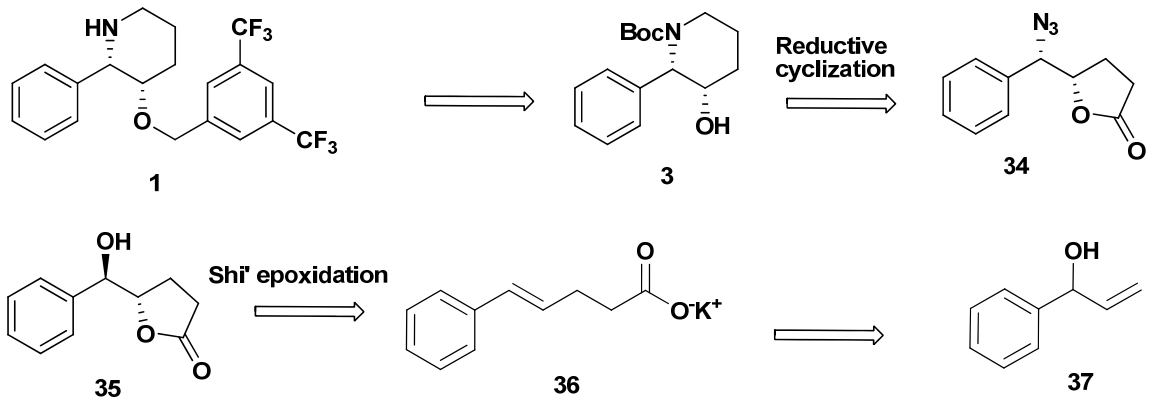
2.1.3. Present Work

2.1.3.1. Objective

As can be seen from the above discussion, the literature methods for the synthesis of (+)-L-733,060 (**1**), either employ chiral starting material, expensive reagents, involve longer

reaction sequences or lack of selectivity. Hence, the synthesis of (+)-L-733,060 using catalytic enantioselective reactions is desirable. This section describes a short synthesis of (+)-L-733,060 (**1**), using Shi' epoxidation[13] of homoallylic carboxylate **36** as the key step to induce chirality in the molecule. The retrosythetic analysis for the synthesis of (+)-L-733,060 (**1**) is shown in **Scheme 8**.

The retrosynthetic analysis of **1** reveals that *syn* amino alcohol **3** could be considered as a key intermediate. We thus planned to employ intramolecular reductive cyclization of azidolactone **34** under Staudinger reduction conditions for the construction of the 6-membered heterocyclic ring in **3**. The azidolactone **34** can be readily made from the corresponding hydroxy lactone **35** by S_N2 displacement with azide ion. We envisaged further that introduction of chirality in **35** with *trans* stereochemistry could be realized *via* Shi epoxidation of potassium 5-phenylpent-4-enoate (**36**), which in turn could be prepared from allylic alcohol **37** through [3,3]-sigmatropic rearrangement.



Scheme 8: Retrosynthesis of (+)-L-733, 060 (**1**)

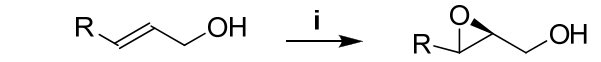
Since this synthetic strategy involves asymmetric epoxidation of unfunctionalized olefin using chiral ketone (Shi' epoxidation) as the key reaction, a brief account on this epoxidation method is described below.

2.1.3.2. Asymmetric epoxidation of olefins

Chiral epoxides are versatile building blocks for the synthesis of enantiomerically pure complex molecules. Also, regioselective opening of epoxides with nucleophiles such as alcohol, azide, amine, water, etc could result in valuable intermediates in organic synthesis. Asymmetric epoxidation of olefins, which are abundant in nature, presents a powerful strategy for the synthesis of enantiomerically enriched epoxides.

Sharpless asymmetric epoxidation

Asymmetric epoxidation remained a daunting task till Sharpless and Katsuki reported the use of titanium tetraisopropoxide for epoxidation in 1980.[14] The enantiomeric excesses greater than 90% were reported in the titanium tartarate-based epoxidation of a variety of allylic alcohols **38**. Subsequent development of this system led to a catalytic system for the asymmetric epoxidation of allylic alchohols. The discovery and development of the reaction, now known as 'Sharpless epoxidation', was a significant factor in awarding 2001 Nobel Prize in Chemistry to Professor Sharpless for his work on asymmetric oxidations (**Scheme 9**).



38
R = alkyl, aryl, H, etc

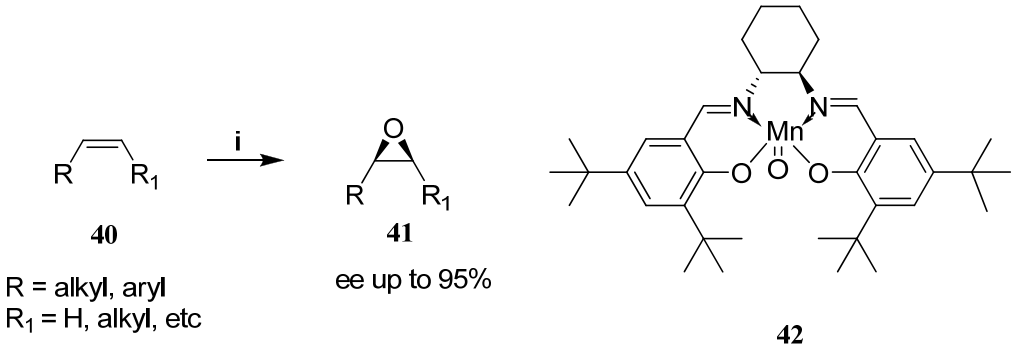
39
yield up to 95%
ee up to 99%

Scheme 9: i) (*S*,*S*)-(−)-DET, Ti(OPr-*i*)$_4$, TBHP, MS 4 Å, CH_2Cl_2, −20 °C, 3 h.

Jacobsen asymmetric epoxidation

In 1990, Eric Jacobsen and Tsutomu Katsuki announced their independently developed systems for the catalytic AE of unfunctionalized alkenes **40** to obtain the corresponding chiral epoxides **41** using manganese salen complex **42.**[15] The use of only nonbonding

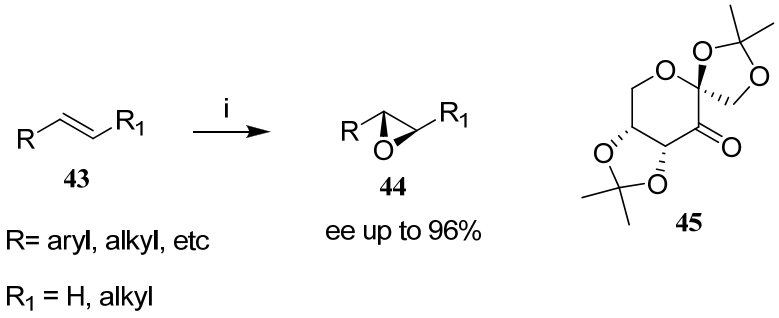
interactions between the substrate and catalyst broadens the potential scope of this catalyst. The greater enantioselectivity (ee's > 90%) obtained in this method represented a major breakthrough in catalytic AE. Unfortunately, these Mn(salen) complexes were successful only for the epoxidation of *cis*-olefins and failed with *trans*-olefins (**Scheme 10**).



Scheme 10: NaOCl, cat. **42**, CH_2Cl_2.

Shi' asymmetric epoxidation

Asymmetric epoxidation of unfunctionalized *trans*-olefin was a challenge until Shi reported the use of fructose-derived ketone **45** as the chiral inducing source. He explained that dioxiranes generated *in situ* from chiral ketone **45** could be used for a highly enantioselective asymmetric epoxidation of *trans*-olefins **43** to obtain the corresponding epoxides **44** with excellent enantioselectivity (**Scheme 11**).[16]



Scheme 11: i) oxone, 45, aq. KOH, CH_3CN, 0 ^oC.

Mechanism of Shi' epoxidation

The mechanism proposed by Shi for the enantioselective epoxidation of unfunctionalized olefins using chiral ketone is shown in **Scheme 12**. The chiral ketone **45** derived from fructose is attacked by the $KHSO_5$ under basic condition to give peroxy compound **46**.

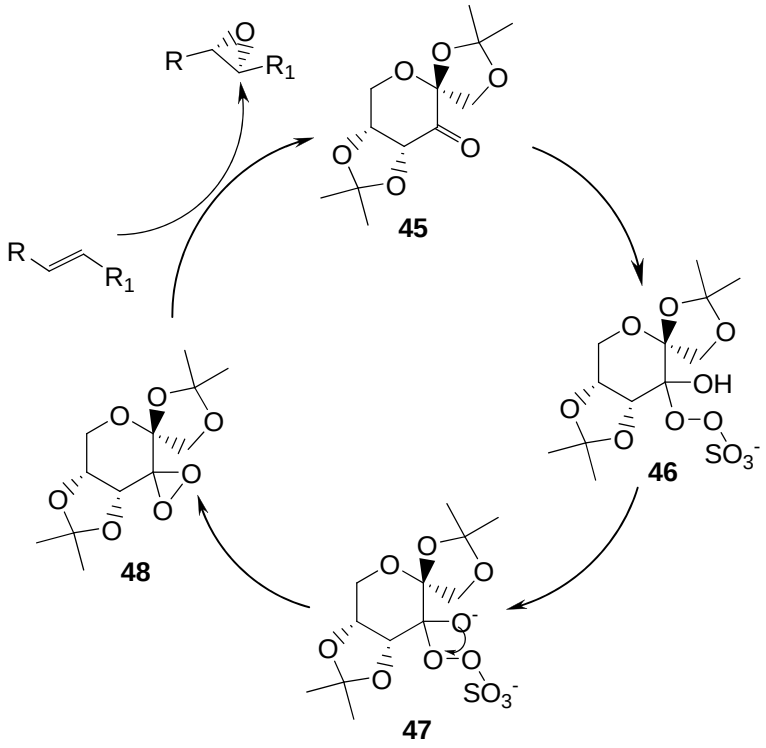


Fig. 2: Mechanism of Shi' epoxidation

The peroxy compound eliminates the sulphate ion under basic condition to produce the dioxirane **48**. The olefin then adds to the dioxirane **48** in such a way that the least steric hindrance is encountered by olefin. Finally, dioxirane decomposes to liberate the catalyst namely chiral ketone with the production of chiral epoxides (**Fig. 2**).

The pH is a very important factor for the epoxidation of olefins with dioxiranes generated *in situ*. Generally, higher pH results in more rapid auto decomposition of oxone, which

leads to decrease of epoxidation efficiency. For this reason, epoxidations are usually carried out at the optimal pH within a narrow window of 7.8-8. The Baeyer-Villiger oxidation is one of the major decomposition pathways for the catalyst, although no direct evidence has been obtained thus far. Further analysis of the reaction suggests that the competing Baeyer-Villiger reaction may be reduced at a higher pH, which leads to a more efficient formation of dioxirane **48**.

Enantioselectivity in Shi' epoxidation

Understanding the reaction mode of the dioxirane-mediated epoxidation is critical for developing a reliable model to predict the stereochemical outcome of the reaction and for designing a more effective ketone catalyst. Two mechanistic extremes namely spiro (**I**) and planar (**II**) are presented in **Fig. 3**.

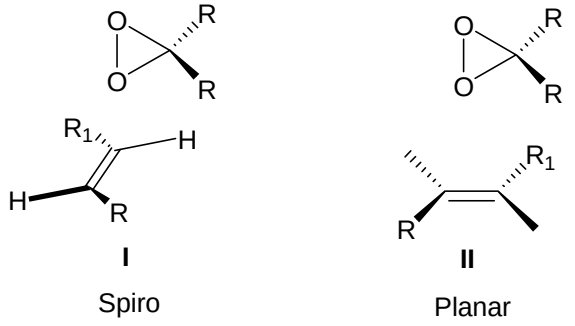


Fig. 3: Spiro and planar transition states for the dioxirane epoxidation of olefins

Based on the experimental observation of higher reactivity of *cis*-olefin than the corresponding *trans*-olefin, a spiro transition (**IV**) state was proposed by Baumstark *et al.*[17] This proposal came from the analysis of steric effects in both transition states. The lower reactivity of *trans*- hexenes can be attributed to the fact that there is a unfavorable steric interaction between the alkyl group of the *trans*-olefin and methyl group of

dioxirane in the spiro-*trans* transition state (**III**), while such interaction does not exist in the spiro-*cis* transition state (**IV) (Fig. 4**).

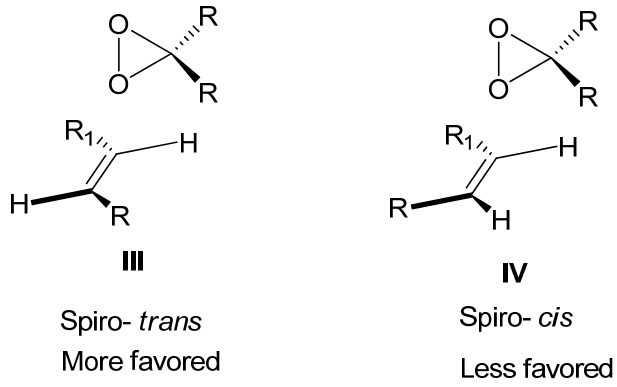


Fig. 4: Spiro and planar transition states for the epoxidation of *trans* and *cis*-olefins with dimethyldioxirane.

Stereochemical analysis provides another valuable way to address this issue. **Figure 5** lists a few of the possible reaction transition states for the epoxidation of the olefin using dioxirane of ketone **45**. Due to the steric repulsion, transition states **B** and **D** are disfavored (for *trans*-disubstituted olefins). The favored transition states spiro **A** and planar **D** result in the opposite stereochemistry for the epoxide product. Therefore, analyzing the stereochemistry of resulting epoxides will allow us to determine which of these two transition states is favored. For *trans*-disubstituted and trisubstitued olefins, all the examples with known epoxide configurations show that epoxide **49** is formed predominantly, which supports a spiro transition state. This analysis provides us with a model to predict the stereochemistry of the formed epoxide (**Fig. 5**).[18]

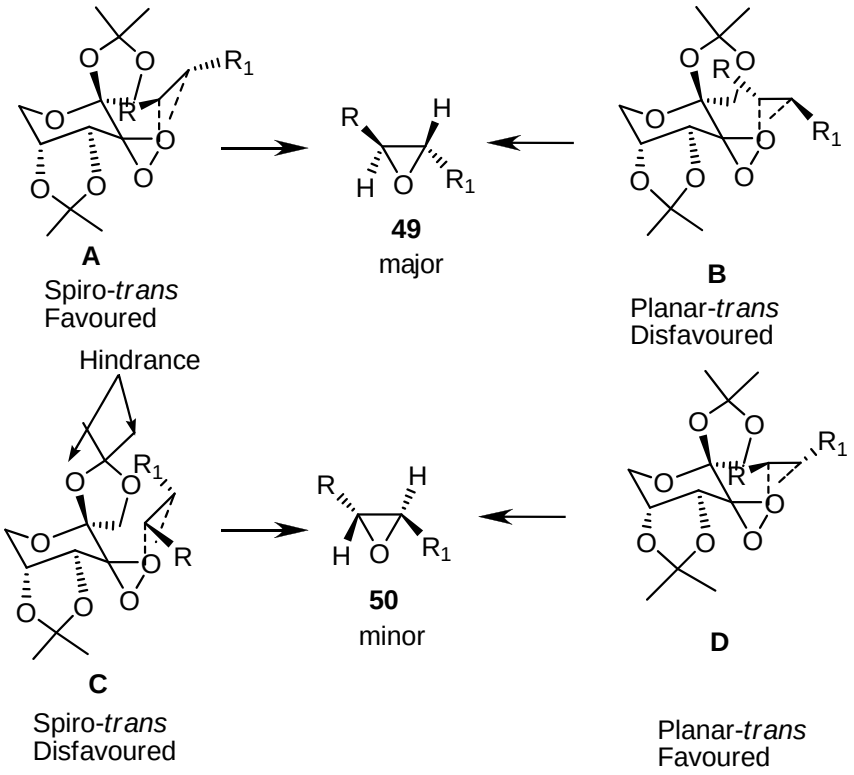
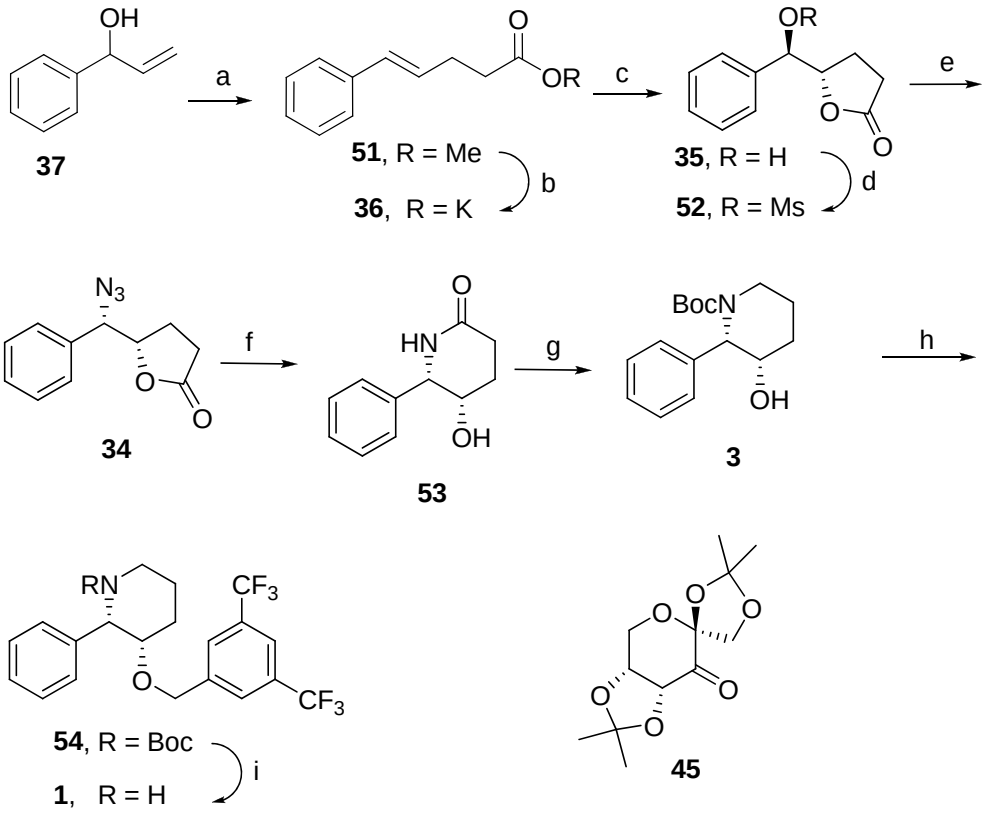


Fig. 5: Possible transition states in Shi' epoxidation of olefin

2.1.4. Results and discussion

Our synthesis of L-733,060 (**1**) commenced with the preparation of allylic alcohol **37** by the Grignard addition of vinyl magnesium bromide onto benzaldehyde. The reaction proceeded smoothly at 0 ^{o}C to give allylic alcohol **37** in 86% yield (**Scheme 12**). The formation of allylic alcohol **37** was confirmed from its ^{1}H NMR spectrum, which showed characteristic signals at δ 6.07 (m, 1H) and 5.26 (m, 2H) corresponding to the terminal olefin. The benzylic methine proton signal (-C**H**-OH) has appeared as doublet at δ 5.36. Its ^{13}C NMR spectrum showed a signal at δ 75.0 corresponding to the methine carbon (-**C**HOH) and at δ 114.8 and 127.5 due to the olefinic carbons. Allylic alcohol **37** was then subjected to Claisen-Johnson [3,3]-sigmatropic rearrangement[19] on reaction with

trimethyl orthoacetate in the presence of catalytic amount of $CH_3CH_2CO_2H$ at 135 °C to obtain exclusively *E*-homoallylic ester **51** in 82% yield.



Scheme 12: a) $CH_3C(OMe)_3$, propanoic acid, 135 °C, 6 h, 82%; b) aq. KOH, reflux; c) pH 10-11, Oxone, chiral ketone **45**, KOH, CH_3CN, -5 °C, 1 h then 15 °C, 5 h, 62%; d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 96%; e) NaN_3, DMF, 60 °C, 12 h, 94%; f) PPh_3, THF, 25 °C , 2 h then H_2O reflux 3 h, 91% ; g) i) $Me_2S\cdot BH_3$, THF, reflux, 6 h; ii) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 0–25°C, 73% over two steps; h) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF: THF (3:1), 0 °C, 6 h; i) TFA, CH_2Cl_2, 18 h, 81% over two steps.

The ^{1}H NMR spectrum of homoallylic ester **51** displayed a singlet at δ 3.68 corresponding to the methoxy protons (-OC**H**$_3$). The signals for olefinic protons (PhC**H**=C- and C=C**H**-) have appeared at δ 6.4 and 6.2 respectively. Its ^{13}C NMR spectrum showed a characteristic signal at δ 173.1 corresponding to the ester carbonyl carbon (**C**=O) (**Fig. 6**).

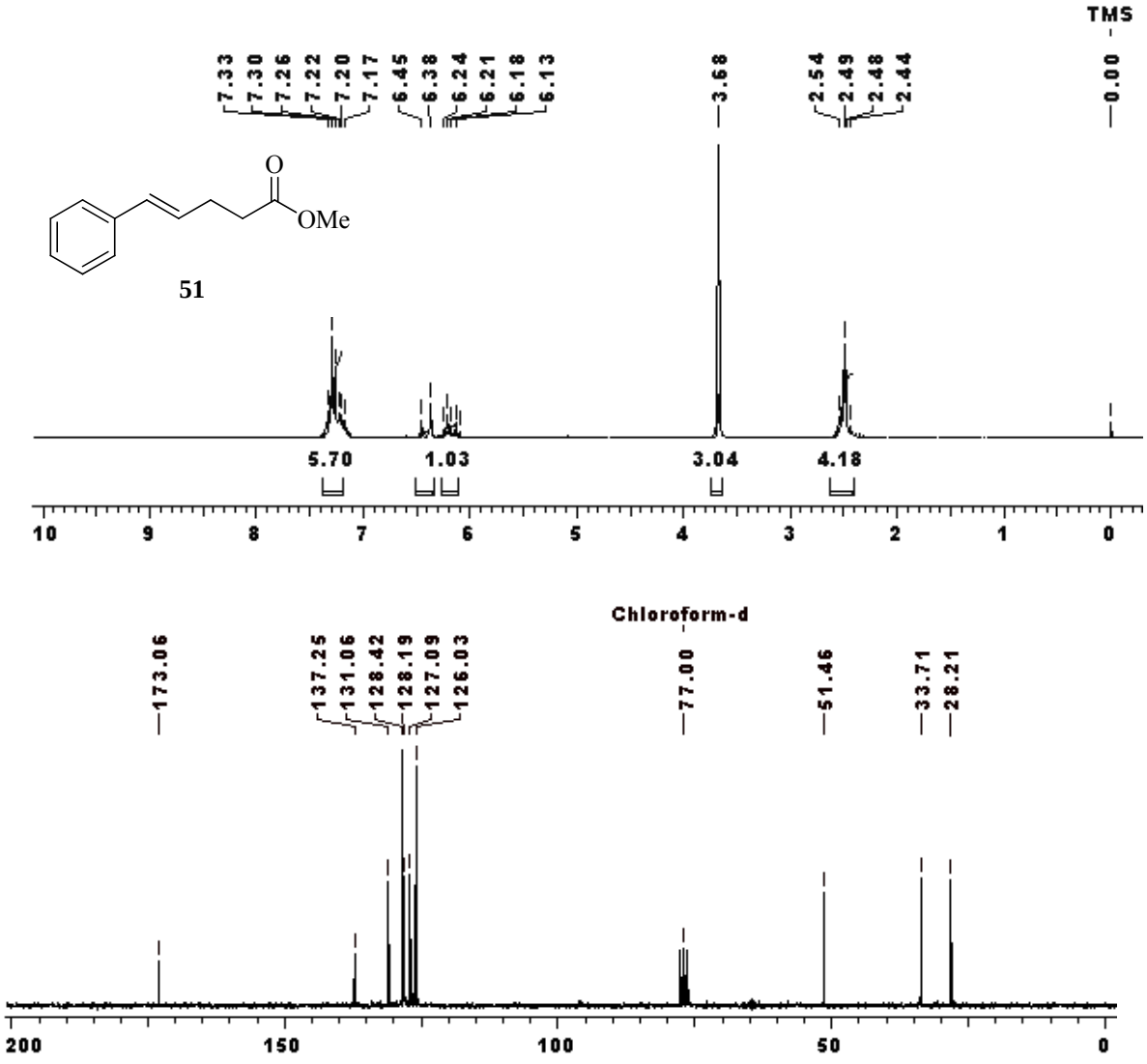


Fig. 6: ^{1}H and ^{13}C NMR spectra of **51**

Alkaline hydrolysis of ester **51** using aq. KOH furnished potassium alkenoate **36**, which was subjected to Shi' epoxidation using D-fructose-derived ketone **45** as the chiral catalyst (30 mol%) and Oxone as the stoichiometric oxidant to afford hydroxylactone **35** in 62% yield and 92% ee [%ee was determined from the ^{1}H NMR of the corresponding Mosher's ester and $[\alpha]^{25}_{D}$ -53.3 (*c* 0.22, $CHCl_3$)].[8]

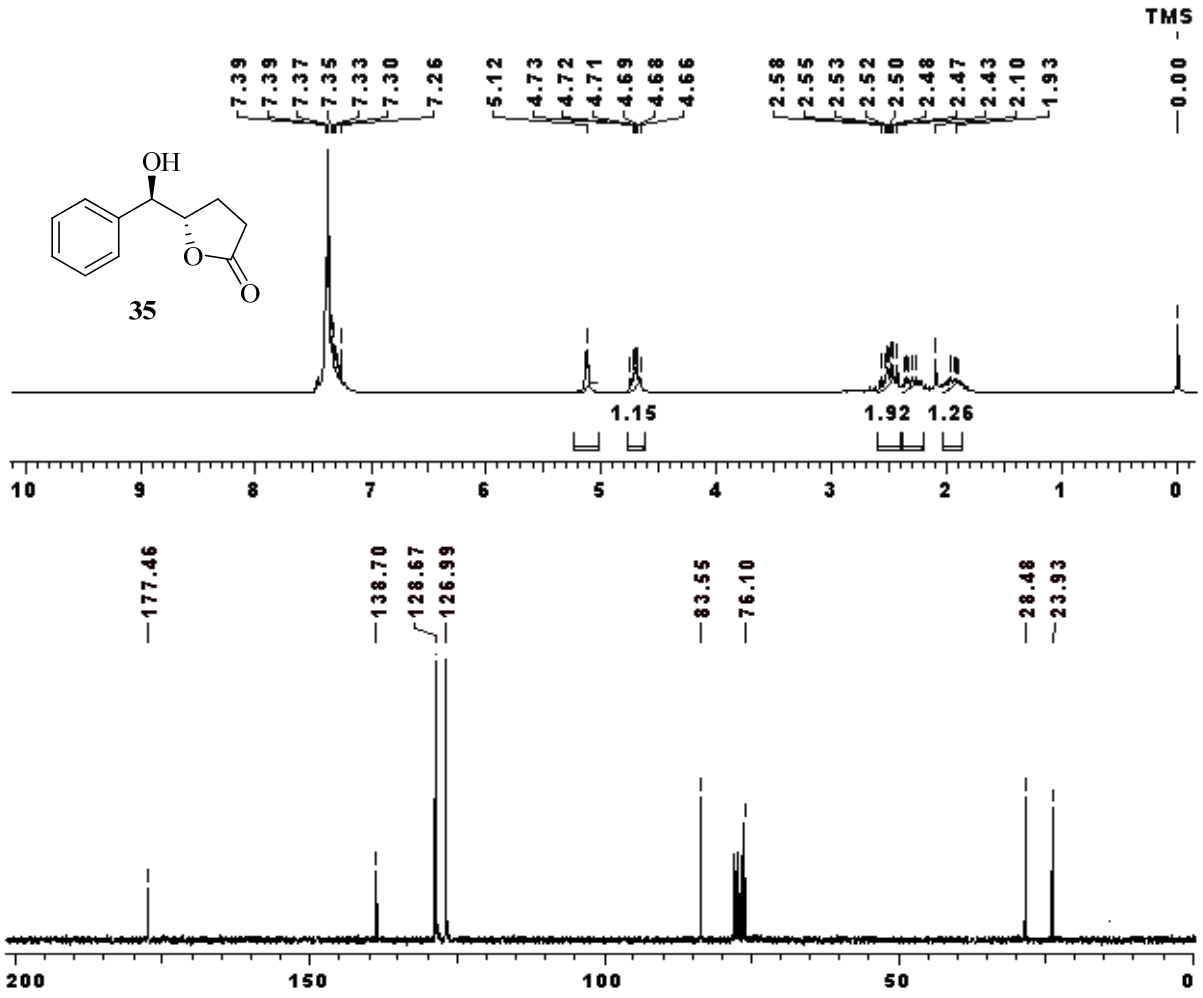


Fig. 7: ^{1}H and ^{13}C NMR spectra of **35**

The disappearance of signals corresponding to the methoxy proton (-OC**H**$_3$) in the ^{1}H NMR spectrum of **35** confirmed the formation of lactone. The functionalization of C=C was confirmed by the appearance of signals at at δ 4.69 and 5.2 (d) due to the newly formed methine protons of **35** (-C**H**-O and -C**H**-OH) respectively. Its ^{13}C NMR spectrum displayed signals for the methine carbons of **35** (-**C**HOH and –**C**HO) at δ 76.1 and 83.55 respectively while the methylene carbon signals (-**C**H$_2$- and **C**H$_2$-CO) have appeared at δ 23.93 and 28.48. Further, the presence of lactone group was confirmed by the appearance of a typical signal at δ 177.46 corresponding to the lactone carbonyl carbon (**C**=O) group

(**Fig. 7**). The IR spectrum of the lactone **35** showed a strong absorption band at 1768 cm^{-1} indicating the presence of five-membered lactone.

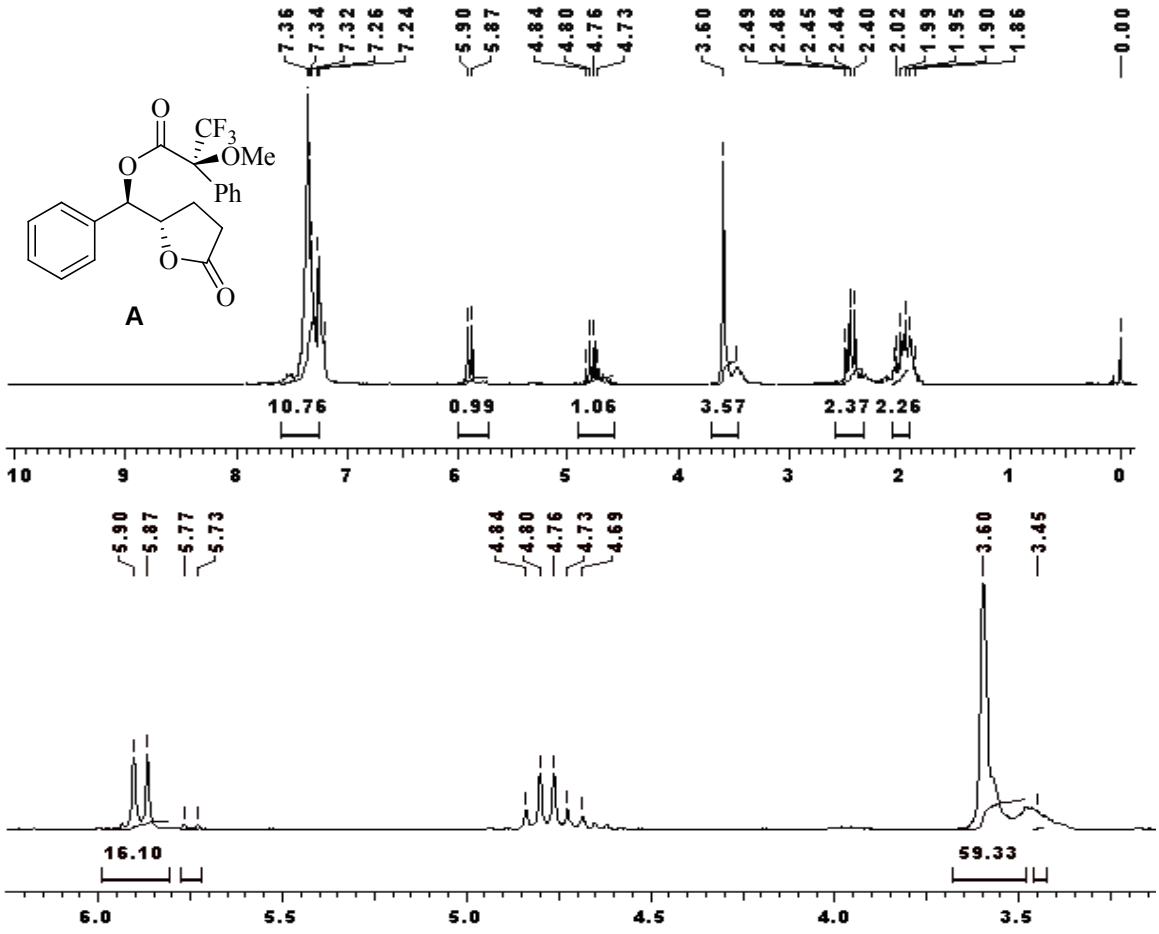


Fig. 8: Mosher's ester of hydroxy lactone **35**

The free alcohol group was then esterified with Mosher's acid in the presence of diethyl azodicarboxylate to get the corresponding Mosher ester **A**. From the ^1H NMR spectrum of the Mosher's ester of alcohol **35**, the ee was found to be 92%. It displayed two signals at δ 5.89(d) and 5.75(d) in the ratio (16.1:1) due to the benzylic protons and singlets at δ 3.60 and 3.45 corresponding to the methoxy protons (OC**H**$_3$) (**Fig. 8**).

Mesylation of free alcohol group in **35** using MsCl in Et_3N gave the corresponding methane sulfonate ester, which was subjected to S_N2 displacement with NaN_3 (DMF, 60

^{o}C) to afford azidolactone **34** {$[\alpha]^{25}_{D}$ +163.49 (*c* 0.7, $CHCl_3$)} with complete inversion of configuration.

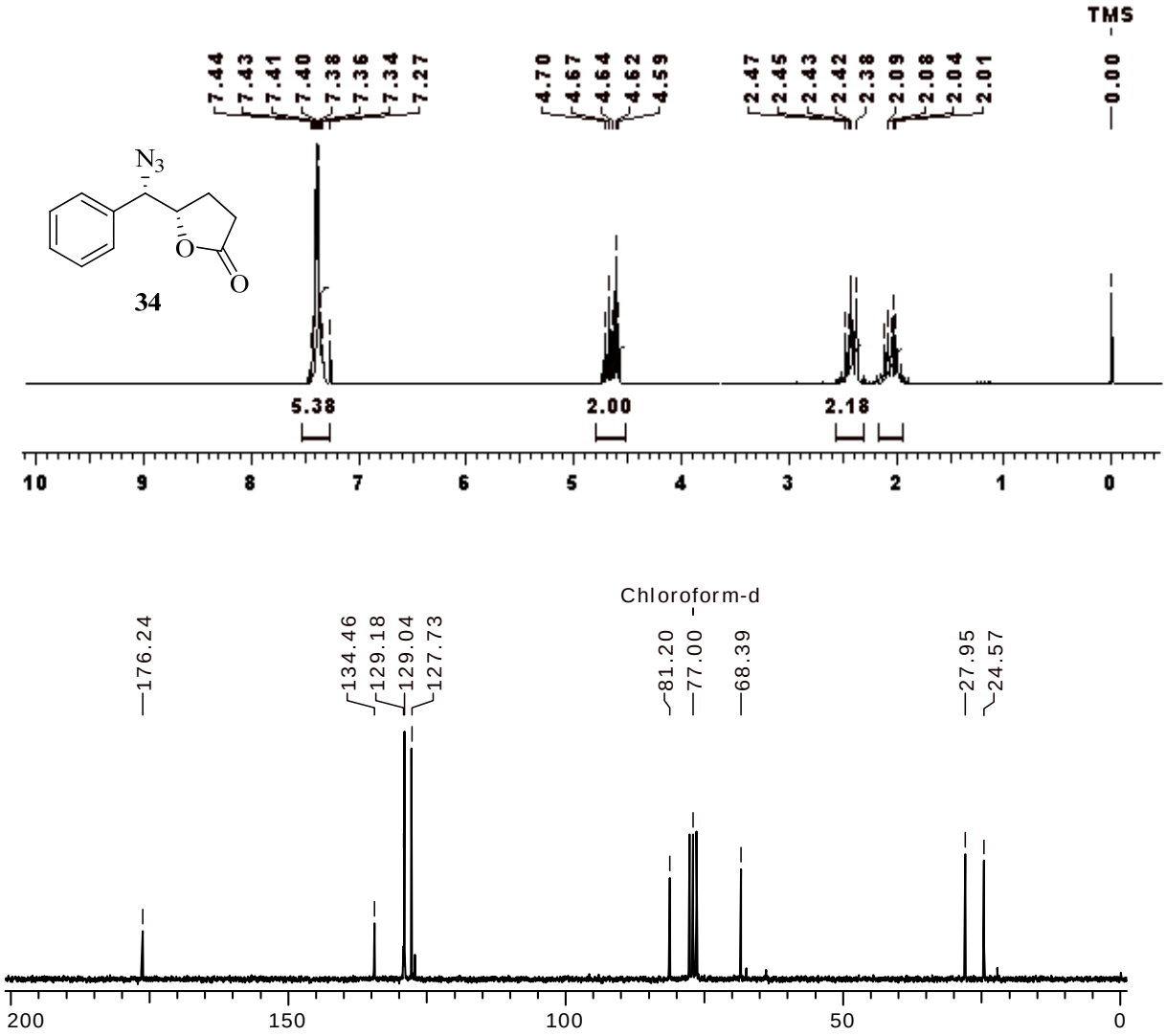
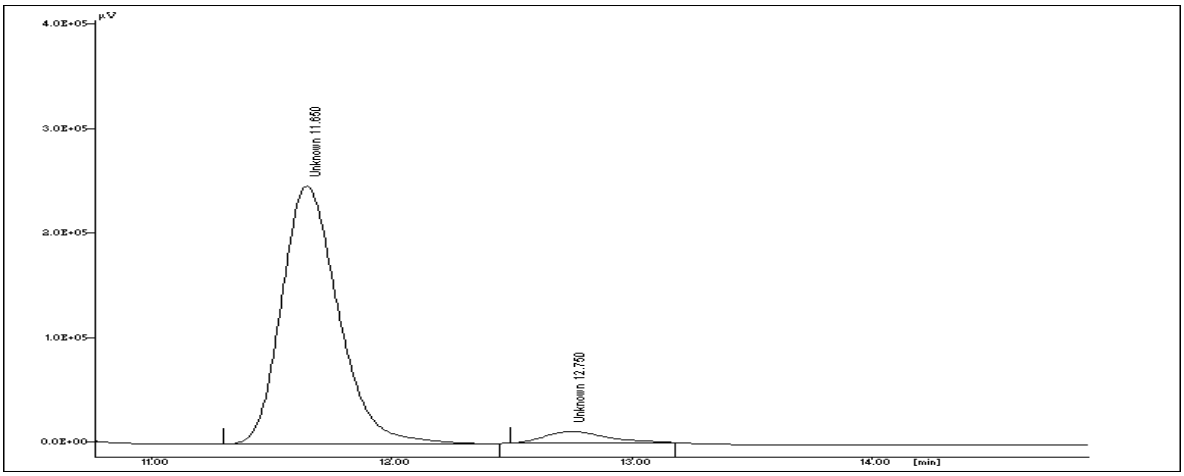


Fig. 9: ^{1}H and ^{13}C NMR spectra of **34**

The ^{1}H NMR spectrum of **34** displayed a multiplet at δ 4.64 corresponding to the methine protons (C**H**N_3 and –C**H**O) and signals at δ 2.04 and 2.47 are due to the methylene protons (-C$\mathbf{H_2}$-C and -C$\mathbf{H_2}$CO) respectively. Its ^{13}C NMR spectrum showed a characteristic peak shifted to upfield at δ 68.39, which corresponds to the **C**-N_3 group (**Fig. 9**). The chiral HPLC of azidolactone shows that the enantiomers have formed in the

ratio (96:4), which corresponds to 92% ee (**Fig. 10**). The IR spectrum of azidolactone **34** displayed strong absorption bands at 2108 cm^{-1} and 1778 cm^{-1} corresponding to the azide and carbonyl **C**=O group of lactone respectively.



#	Name	RT (min)	Area[µV.Sec]	%Area
1	**E_1**	11.650	4440217.538	95.786
2	**E_2**	12.750	195342.500	4.214

Fig. 10: HPLC chromatogram of azido lactone **34**

Reduction of azide **34** under either Staudinger protocol (PPh_3, THF, 25 ^oC then H_2O, reflux) or catalytic hydrogenation [H_2 (1 atm), 10% Pd/C] at ambient conditions produced lactam **53** in 91% yield, presumably *via* intramolecular *O*-to-*N*- ring expansion[20] of the amine generated *in situ*. The formation of lactam **53** was confirmed from its ^1H NMR spectrum, which displayed signals at δ 4.48 and 3.85 corresponding to the methine protons (-C**H**-NHCO and -C**H**OH). Its ^{13}C NMR spectrum showed signals at δ 73 and 67.1 corresponding to the methine carbons (-**C**H-NHCO and -**C**HOH). The other signal at δ 177.4 corresponds to amide carbonyl carbon (-**C**ONH-) and signals at δ 30.99 and 28.65 are due to methylene carbons (-**C**H_2- and –**C**H_2CO-) respectively.

Reduction of lactam **53** was achieved using $BH_3 \cdot SMe_2$ in THF to give the amino alcohol whose protection of the secondary amine with $(Boc)_2O$ gave the *syn*- amino alcohol **3** in 73% yield over two steps. The ^1H NMR spectrum of **3** indicated the presence of Boc methyl protons at δ 1.43 as a singlet (**Fig. 11**). The signals at δ 5.30 and 4.44 correspond to the methine protons (C**H**-N and C**H**-O) of the substituted piperidine moiety **3**. Its ^{13}C NMR spectrum displayed signals at δ 156.72 and 80.12 indicating the presence of Boc carbonyl (-N**C**O-) and tertiary butyl carbon (Me_3**C**-O) groups respectively.

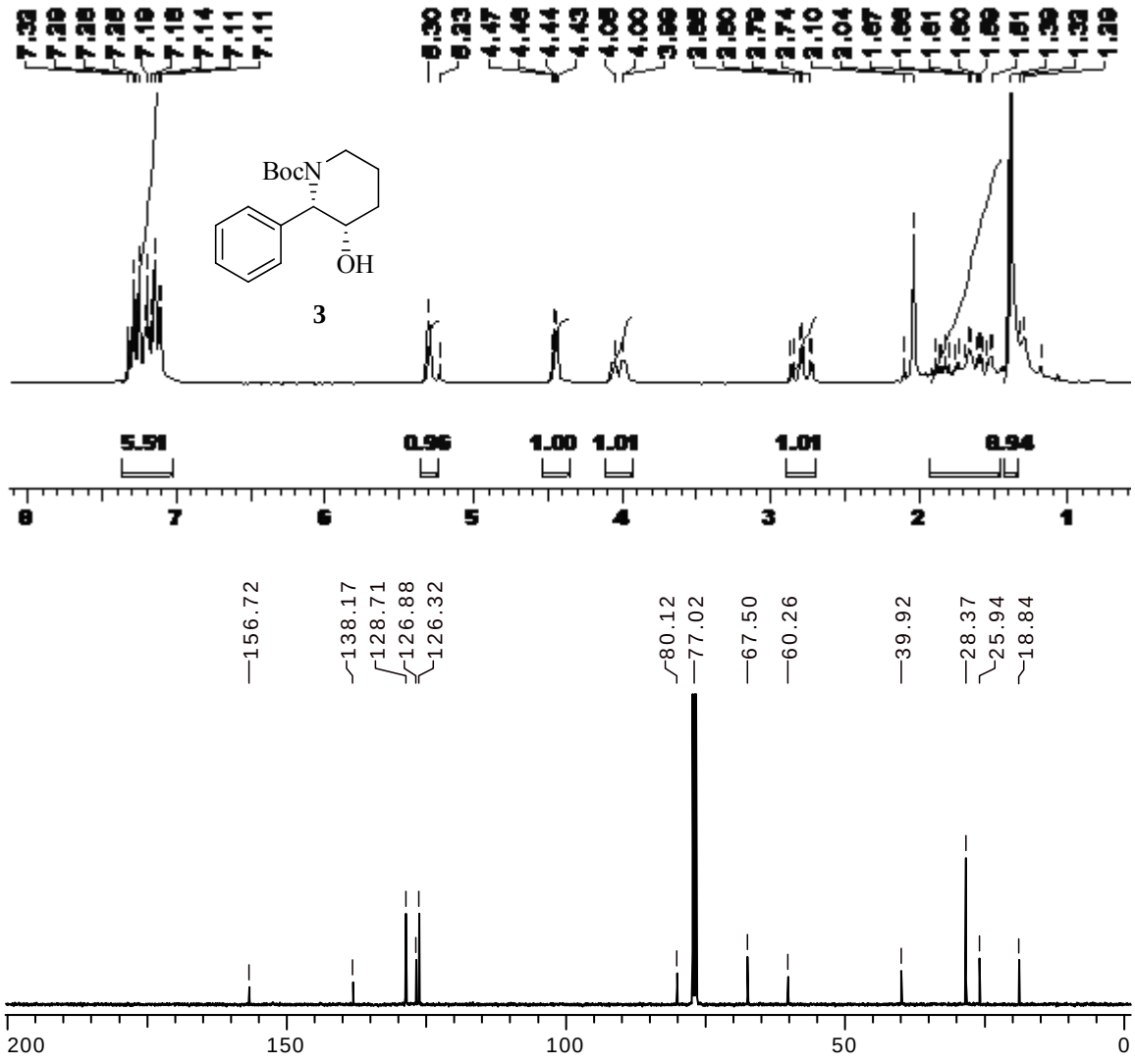


Fig. 11: ^1H and ^{13}C NMR spectra of **3**

Having constructed the piperidine ring with the desired *syn*-stereochemistry, *O*-alkylation of **3** with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH was performed to give **54** {$[\alpha]^{25}_{D}$ +27.9 (*c* 0.8, $CHCl_3$); lit.[5h] $[\alpha]^{25}_{D}$ +30.38 (*c* 1.55, $CHCl_3$)}. Finally, deprotection of the Boc group under acidic conditions afforded (+)-L-733,060 (**1**) {$[\alpha]^{25}_{D}$ +31.7 (*c* 0.5, $CHCl_3$); [lit.[5h] $[\alpha]^{25}_{D}$ +34.29 (*c* 1.32, $CHCl_3$]}. The ^{1}H, ^{13}C NMR and other spectral data were in complete agreement with the reported values (**Fig. 12**).

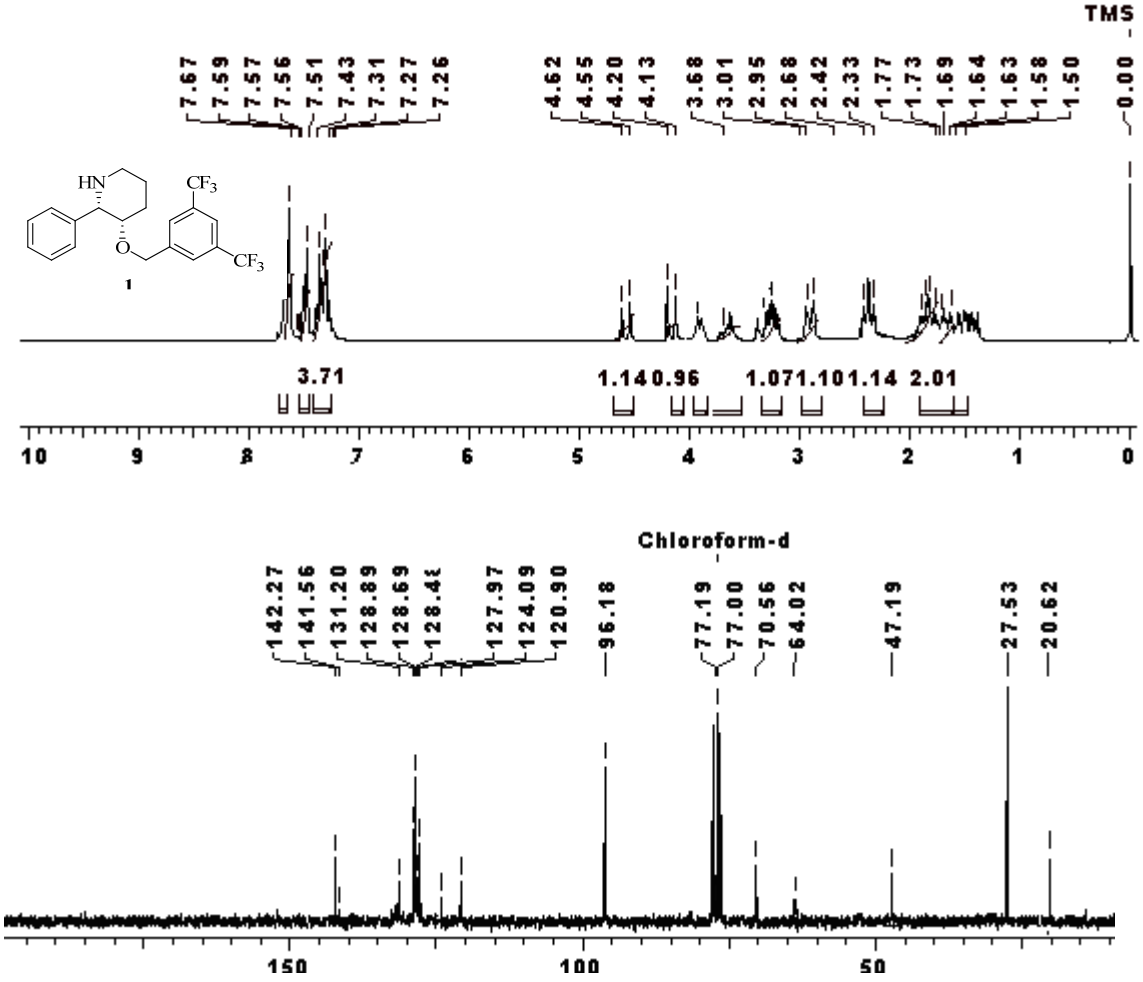


Fig. 12: ^{1}H and ^{13}C NMR spectra of **1**

2.1.5. Conclusion

In summary, the enantioselective synthesis of (+)-L-733, 060 (**1**) has been achieved in 92% ee using Shi' epoxidation of homoallylic carboxylate **36** as the chiral inducing step. The intramolecular reductive cyclization of azidolactone **34** was used in the construction of piperidine ring while Claisen-Johnson rearrangement was employed for the construction of the required carbon backbone. The synthetic strategy described herein has significant potential for further extension to piperidine-based bioactive molecules as well as other NK_1 receptor antagonists.

2.1.6. Experimental Section

Phenylprop-2-en-1-ol (37)

A two-necked round bottomed flask was charged with Mg metal (1.44 g, 60 mmol), a pinch of iodine and dry THF (300 mL). To this mixture, vinyl bromide (5.35 g, 50 mmol) in dry THF was added drop-wise. The reaction mixture was gently heated on water bath (45 ^{o}C) to initiate the Grignard reagent formation. The initiation of the reaction was observed visually and the iodine color disappeared. After the Mg metal dissolved completely, benzaldehyde (5.3 g, 50 mmol) in THF (10 mL) was added slowly at 0 ^{o}C. After the completion of the reaction, it was cooled to -10 ^{o}C and a saturated solution of NH_4Cl was added to quench the excess Grignard reagent. Solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate (3 x 100 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude product, which was purified by column chromatography using petroleum ether: ethyl acetate (4:1) to get pure allylic alcohol **37** as colorless oil. **Yield**: 82% (5.494 g); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.31

(m, 5H), 6.01 (m, 1H), 5.32 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.18 (dt, *J* = 5.7, 1.4 Hz, 1H), 5.14 (m, 1H), 2.14 (brs, 1H); **^{13}C- NMR** (50 MHz**,** $CDCl_3$): δ 142.5, 140.2, 128.3, 127.5, 126.3, 114.8, 75.0; **IR** ($CHCl_3$, cm^{-1}): 3448, 2939, 2862, 2360, 2331, 1733, 1612, 1591, 1514, 1461, 1363, 1301, 1247, 1174, 1097, 1033, 821; Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 79.38; H, 8.02%.

(*E*)-Methyl 5-phenypent-4-enoate (51)

An oven dried 100 mL round bottomed flask was charged with allylic alcohol **37** (5 g, 37 mmol) and propanoic acid (259 mg, 10 mol%) followed by trimethyl orthoacetate (22.2 g, 185 mmol). The mixture was refluxed at 135 ^oC for 5 h. After the completion of the reaction as monitored by the TLC, it was cooled to room temperature and the excess trimethyl orthoacetate was removed under reduced pressure. The reaction mixture was extracted with ethyl acetate (3 x 25 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was then concentrated under reduced pressure to obtain the crude olefinic ester **51,** which was subjected to column chromatographic purification using petroleum ether: ethyl acetate (9:1) to obtain pure ester **51** as colorless oil. **Yield**: 73% (5.53 g); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.26 (m, 5H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.18 (m, 1H), 3.68 (s, 3H), 2.49 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 173.1, 137.2, 131.0, 128.4, 128.2, 127.1, 84.2, 72.5, 69.8, 55.2, 51.8, 34.8, 29.1, 28.3, 25.6; **IR** ($CHCl_3$, cm^{-1}): 3444, 2937, 2856, 2360, 2331, 1737, 1612, 1514, 1460, 1438, 1363, 1301, 1247, 1220, 1172, 1099, 1035, 821; Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.69; H, 7.51%.

(*S*)-5-((*R*)-Hydroxy(phenyl)methyl)dihydrofuran-2(3*H*)-one (35)

A mixture of homoallylic ester **51** (5 g, 27 mmol) and 20% aq. KOH (25 mL) was refluxed on an oil bath for 3 h. After the completion of the reaction, water was removed under educed pressure to get colorless solid of potassium salt of homoallylic carboxylate **36** along with excess potassium hydroxide. Without further purification it was subjected to Shi' epoxidation as follows.

The potassium salt **36** was dissolved in CH_3CN:H_2O (1:1, 50 mL) and the pH of the solution was adjusted to 10-11 by adding 25% aq. sulphuric acid. The reaction mixture was cooled to 0 ^oC and the chiral ketone **45** (2.064 g, 8 mmol, 30 mol%) was added as a solution in acetonitrile. Aqueous solutions of oxone (13.8 g, 30 mmol) and 20% aq. KOH (1.68 g, 30 mmol) were added simultaneously over approximately 4 h such that the reaction pH was maintained at 10-11 and the temperature at -5 to 5 °C. Upon completion of the oxone charge, the resultant white slurry was warmed to 10-15 °C and held for 2 h. The lactone **35** is formed spontaneously under the reaction conditions after the epoxidation has occurred. To isolate the lactone **35**, the epoxidation reaction mixture was acidified to pH 2 with 25% sulphuric acid and extracted with CH_2Cl_2. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under vacuum, cooled to 20-30 °C, and crystallized in hexane to get lactone **35** as colorless solid. **Yield**: 62% (3.21 g); **mp**: 102 °C; $[\alpha]^{25}_D$ -53.3 (c 0.22, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.37 (m, 5H), 5.12 (d, *J* = 2.9 Hz, 1H), 4.7 (m, 1H), 2.50 (m, 2H), 2.30 (m, 1H), 1.94 (m, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 177.92, 138.52, 128.71, 128.50, 125.98, 83.37, 73.23, 28.54, 20.54; **IR** ($CHCl_3$, cm^{-1}): 3448, 2939, 2864, 1768, 1612, 1512, 1461, 1363, 1247, 1180, 1097, 1033, 918, 819, 732; Anal. Calcd for $C_{11}H_{12}O_3$: C 68.74; H 6.29; Found: C 68. 26; H, 6.62%.

(*R*)-5-((*S*) Azido(phenyl)methyl)-dihydrofuran-2(3*H*)one (34)

To a solution of alcohol **35** (4 g, 20.8 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (4.07 g, 40 mmol) at 0 ^oC. After 5 min of stirring, methane sulfonyl chloride (2.28 g, 20 mmol) was added drop-wise over a period of 5 min. The reaction mixture was then stirred for another 1 h at 0 ^oC and brought to room temperature. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3x 50 ml) washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get crude methane sulfonate ester **52** in almost quantitative yield.

To a solution of mesylate **52** (5 g, 18.5 mmol) in DMF (50 mL) was added sodium azide (3.25g, 50mmol) and the reaction mixture was heated at 60 ^oC for 7 h. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3x 50 mL) washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude azido lactone **34**, which was purified by column chromatography using petroleum ether: ethyl acetate (8:2) to produce **34** as pale yellow oil. **Yield**: 89% (3.47 g); $[\alpha]^{25}_D$ +163.49 (*c* 0.7, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.0-2.12 (m, 2H), 2.40 (dd, *J* = 8.8, 1.8 Hz, 1H), 2.45 (dd, *J* = 9.0, 3.9 Hz), 4.62 (t, *J* = 6.3 Hz, 1H), 4.69 (dd, *J* = 6.6, 0.5 Hz, 1H), 7.40 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 24.6, 27.9, 68.4, 81.2, 127.7, 129.0, 129.1, 134.5, 176.2; **IR** ($CHCl_3$, cm^{-1}): 2939, 2862, 2108, 1778, 1612, 1514, 1461, 1359, 1247, 1178, 1099, 1031, 912, 819; Anal. Calcd for $C_{11}H_{11}N_3O_2$: C 60.82; H 5.10; N 19.34. Found: C 60.42; H 5.96; N 18.78%.

5-Hydroxy-6-phenylpiperidin-2-one (53)

To a solution of azide **34** (3 g, 14.2 mmol) in dry THF (100 mL) was added PPh_3 (5.24 g, 20 mmol) carefully at room temperature and stirred for 2 h. After that H_2O (5 mL) was added and the reaction mixture was refluxed for 5 h. After the completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3x 50 mL) washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude lactam **53**, which was purified by column chromatography using petroleum ether: ethyl acetate (8:2) to obtain **53** as gum. **Yield**: 91%; $[\alpha]_D$ +51.4 (*c* 0.8, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.73-1.86 (m, 2H), 2.2-2.34 (m, 1H), 2.43-2.59 (dd, *J* = 16.0, 6.9 Hz, 1H), 3.81-3.85 (m, 1H), 4.48 (d, *J* = 4.4 Hz), 7.33 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 30.0, 30.1, 65.4, 69.8, 131.3, 132.2, 132.6, 141.9, 177.6; **IR** (neat, cm^{-1}): 3020, 2941, 1664, 1346.22, 1215, 1174, 927; Anal. Calcd for $C_{11}H_{13}NO_2$: C 69.09; H 6.85; N 7.32. Found: C 69.98; H 6.02; N 7.55%.

(2S, 3S)-1-(3-Hydroxy-2-phenyl piperidin-1-yl)-2,2-dimethyl propan-1-one (3)

To a solution of the lactam **53** in dry THF (30 mL) at 25 ^oC was added $BH_3.SMe_2$ drop-wise and the mixture was then refluxed for 6 h. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate to give the corresponding amino alcohol. Without purification, amino alcohol was dissolved in CH_2Cl_2 and Et_3N followed by catalytic amount of DMAP were added. After stirring for 5 min at 0 ^oC, $(Boc)_2O$ was added drop-wise and the reaction mixture was allowed to stir for another three hours. After the completion of the reaction, it was extracted with ethyl acetate, washed with water, brine and dried over anhydrous Na_2SO_4 to get crude product. Chromatographic purification of the crude product using petroleum

ether: ethyl acetate gave the pure **3** as viscous liquid. **Yield**: 73% (over two steps); $[\alpha]^{25}_{D}$ +33.0 (*c* 1.0, $CHCl_3$) {lit.[11] $[\alpha]_D^{25}$ +37.5 (*c* 1.0, $CHCl_3$)}; **^{1}H- NMR** (200 MHz, $CDCl_3$): δ 7.13–7.35 (m, 5H), 5.32 (m, 1H), 4.45–4.49 (m, 1H), 4.0–4.09 (m, 1H), 2.74–2.89 (ddd, *J* = 3.2, 9.7, 12.9 Hz, 1H), 1.55–2.01 (m, 5H), 1.40 (s, 9H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.98, 25.92, 28.36, 39.90, 60.24, 67.48, 80.11, 126.86, 126.89, 138.15, 156.70; **IR** ($CHCl_3$, $cm^{-}1$): 3447, 3018, 2979, 2955, 1676, 1602, 1495, 1418, 1367, 1327, 1168, 1137, 984, 876, 851, 756; Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.43; H, 8.13; N, 4.92%.

(2*S*, 3*S*)-1-(*tert*-Butyoxycarbonyl)-2-phenyl-3-[(3,5-bis(trifluoromethyl)benzyloxy] piperidine (54)

To a stirred solution of **3** in dry DMF (1 mL) at 0 ^oC was added sodium hydride (10 mg, 60% dispersion in mineral oil, 0.43 mmol) in one portion. After 5 min of stirring at the same temperature 3,5-bis(trifluoromethyl)benzyl bromide (110 mg, 0.36 mmol) in dry DMF (1 mL) was added *via* syringe. The reaction mixture was stirred for 12 h at 80 ^oC and it was then quenched with water (3 mL) and extracted with Et_2O (5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel column using petroleum ether: ethyl acetate (7:3) to provide **54** (0.14 g) as a colorless oil. **Yield**: 78%; $[\alpha]_D^{25}$ +30.45 (*c* 1.0, $CHCl_3$) {lit.[7] $[\alpha]_D^{25}$ +30.4 (*c* 1.55, $CHCl_3$)}; **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ 1.42 (s, 9H), 1.32-1.66 (m, 2H), 1.78-2.12 (m, 2H), 2.76 (ddd, *J* = 11.2, 9.8, 4.6 Hz, 1H), 3.79-3.98 (m, 2H), 4.66 (d, *J* = 11.4 Hz, 1H), 4.74 (d, *J* = 12.2 Hz, 1H), 5.67 (d, *J* = 4.6 Hz, 1H), 7.22-7.38 (m, 3H), 7.42-7.52 (m, 2H), 7.66 (s, 2H), 7.78 (s, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz): δ 20.2, 25.3, 26.3, 27.2, 44.4, 63.2, 71.2, 77.0, 120.2,

123.1, 126.7, 127.3, 127.8, 132.4, 141.2, 142.4, 159.0; **IR** (neat, cm^{-1}): 2945, 1644, 1381, 1345, 1253, 1172, 875, 665; Anal. Calcd for $C_{25}H_{27}F_6NO_3$: C, 59.64; H, 5.41; F, 22.64; N, 2.78; Found. C, 59.61; H, 5.38; N, 2.76%.

Preparation of (+)-L-733,060 (1)

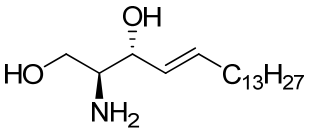
To an ice-cooled solution of **54** (100 mg, 0.2 mmol) in dry CH_2Cl_2 (4 mL) was added trifluoroacetic acid (228 mg, 2 mmol). The reaction mixture was stirred at room temperature for 12 h and then quenched with saturated $NaHCO_3$ and extracted with dichloromethane (3x5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using CH_3OH:$CHCl_3$ (1:9) as eluent to give pure **1** as colorless viscous liquid. **Yield:** 89% (79 mg); $[\alpha]_D^{25}$ +31.2 (*c* 0.66, $CHCl_3$) {lit.[11] $[\alpha]_D^{25}$ +34.3 (*c* 1.32, $CHCl_3$)}; **^{1}H-NMR** ($CDCl_3$, 200 MHz) : d 1.42-204 (m, 3H), 2.22 (br d, *J* = 13 Hz, 1H), 2.62 (s, H), 2.76-2.81 (m,1H), 3.23-3.38 (m, 1H), 3.66 (s, 1H), 3.84 (brs, 1H), 4.12 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 7.20-7.50 (m, 7H), 7.78 (s, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz): 20.6, 27.5, 47.1, 64.0, 70.5, 77.2, 120.9, 124.1, 127.7, 128.5, 128.7, 131.2, 141.6, 142.3; Anal. Calcd for $C_{20}H19F_6NO_3$: C, 59.55; H, 4.75; N, 3.47; Found. C, 59.52; H, 4.81; N, 3.56%.

Section II

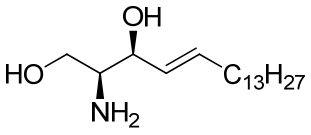
Enantioselective synthesis of *threo*-sphingosine using kinetic resolution *via* Sharpless epoxidation

2.2.1. Introduction

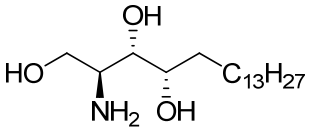
Sphingolipids such as ceramides, cerebrosides and gangliosides are ubiquitous components of cell membranes.[21] They play critical roles in many physiological processes including cell growth, differentiation, neuronal repair, cell recognition, adhesion, and signalling.[22] Over the past decade, significant strides have been made in the elucidation of biological function of sphingolipids. One of the remarkable findings is the identification of sphingolipid metabolites as second messengers, which provides the basis for the emerging concept of sphingolipid metabolites as therapeutics with clinical potential.[23] Common to this diverse group of natural products is a sphingoid base scaffold with a polar 2-amino alcohol head and a long aliphatic chain with a 4,5-*trans* double bond as in sphingosines (**55 & 56)** or an 2-amino-1,3,4 triol head group without unsaturation as in phytosphingosines (**57 & 58**).[3]



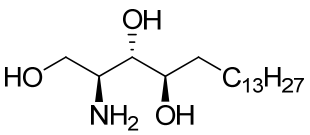
55, *erythro*- sphingosine



56, *threo*- sphingosine



57, *lyxo*-phytosphingosine



58, *ribo*-phytosphingosine

Fig. 13: Structures of sphingolipids

The hydrophilic moiety, located on the external surface of the membrane, determines the specificity of interactions, whereas the lipophilic portion, anchored on the outer-

leaflet, contributes primarily to the structural rigidity of the membrane. The most common naturally occurring sphingoid bases of animal and plant tissues are *erythro*-sphingosine (**55**) and *ribo*-phytosphingosine (**57**) **(Fig. 13**).

ribo-Phytosphingosine is readily obtained on an industrial scale from yeast fermentation process while *erythro*-sphingosine is available only by chemical synthesis or laborious animal tissue extraction. The wide spectrum of the biological activity of these molecules justifies the efforts towards the synthesis of them as well as of their stereoisomers and various analogues.[24] The most commonly employed strategies are those which make use of carbohydrates[25] and serine[26] as a source of chirality; many approaches are also based on asymmetric reactions, such as aldol condensation[27] as well as Sharpless asymmetric dihydroxylation[28] and asymmetric epoxidation (using Shi's catalyst or Sharpless protocol[29]). The design of an efficient and catalytic route to sphingosines therefore continues to be important.

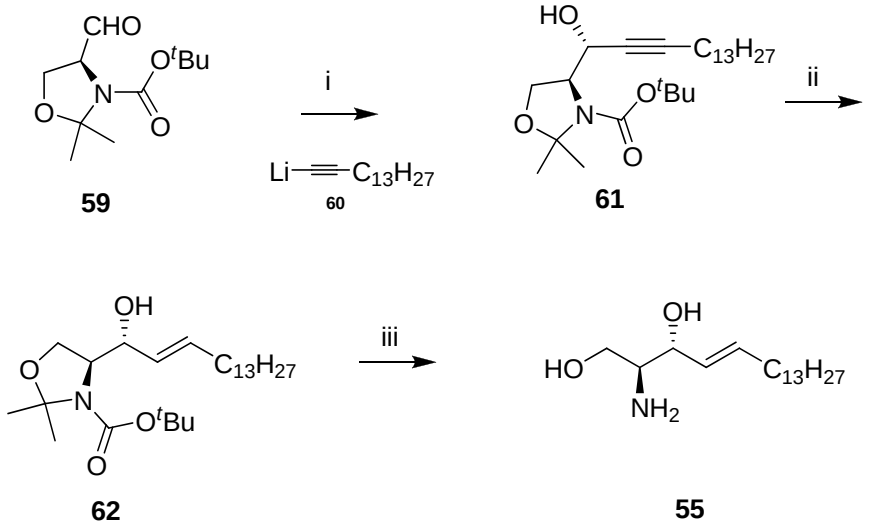
2.2.2. Review of literature

Literature search revealed that there are more than hundred reports on the synthesis of the diastereomers of sphingosines. Many synthetic efforts have utilized starting materials derived from the chiral pool, in particular, carbohydrate, serine, and tartaric acid precursors.

Garner's approach (1988)[30]

Garner and his co-workers have achieved the synthesis of *erythro*-sphingosine (**55**) from the known oxazolidine aldehyde **59**, available from *N*-Boc-L-serine in just 3 steps. The addition of lithium 1-pentadecyne (**60**) to the aldehyde **59** proceeded with very good *erythro* stereoselectivity to give a diastereomeric mixture of propargylic alcohols **61** in the ratio 8:1. Partial reduction of alkyne was achieved using Benkeser's conditions (lithium in ethylamine) at -78 ^{o}C to obtain the protected sphingosine derivative **62.**

Deprotection of acetonide group in **62** with hot aqueous HC1 afforded sphingosine (**55**) in 65% overall yield after basic workup (**Scheme 13**).

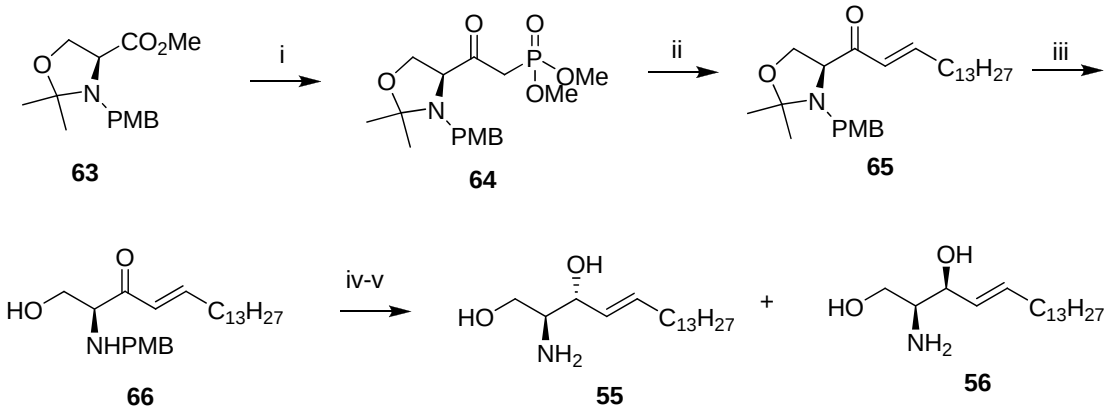


59 **60** **61** **62** **55**

Scheme 13: i) THF, 23 ^{o}C, quant.; ii) Li, EtNH$_2$, -78 ^{o}C; iii) 1N HCl.

Chung's approach (1999)[31]

Chung *et al.* have employed the chiral oxazolidine **63**, derived from serine in three steps, as the starting material. The ester group in **63** was converted to the β-keto phosphonate **64** by treating with dimethyl methylphosphonate. Phosphonate ester **64** was then subjected to Horner–Wadsworth–Emmons olefination with tetradecylaldehyde



63 **64** **65** **66** **55** **56**

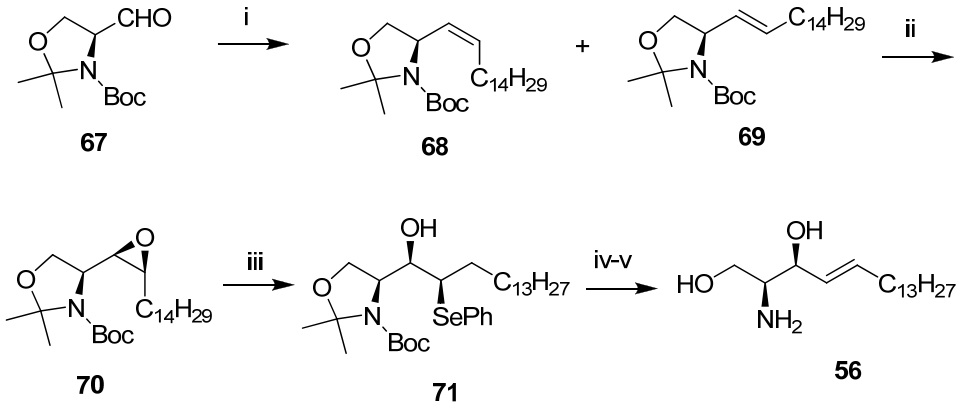
Scheme 14: i) $CH_3PO(OMe)_2$, *n*-BuLi, THF; (ii) $C_{13}H_{27}CHO$, DBU, LiCl, THF; (iii) 10% HCl, THF; iv) $NaBH_4$, MeOH; vi) DDQ, CH_2Cl_2.

to provide *O*, *N*-protected enone **65**, whose acetonide group was deprotected to generate the *N*-protected amino enones **66** in 65% yield. Reduction of ketone group with

$Zn(BH_4)_2$ in THF produced *erythro*-sphingosine (**55**) while use of $NaBH_4$ in MeOH furnished *threo*-sphingosine (**56**) as the major product (**Scheme 14**).

Ogino's approach (1999)[32]

Garner's aldehyde **67** has been used as the starting material in this synthesis. Wittig olefination of serine-derived aldehyde **67** with $C_{15}H_{31}PPh_3^+Br^-$ using lithium hexamethyldisilazide (LHMDS) as the base produced a separable mixture of (*Z*)- and (*E*)-olfins **68** and **69** in 80-84% combined yield. The epoxidation of *Z*-olefin (**70**) was achieved using 2 equiv. of *m*-CPBA with good enantioslectivity. Treatment of **70** with diphenyl diselenide (PhSeSePh) and sodium borohydride gave the hydroxy selenide **71**. The subsequent oxidation of the crude hydroxyselenide **71** with 30% hydrogen peroxide resulted in elimination to give allylic alcohol, which upon deprotection of the oxazolidine ring under acidic condition furnished sphingosine (**56**) (**Scheme 15**).

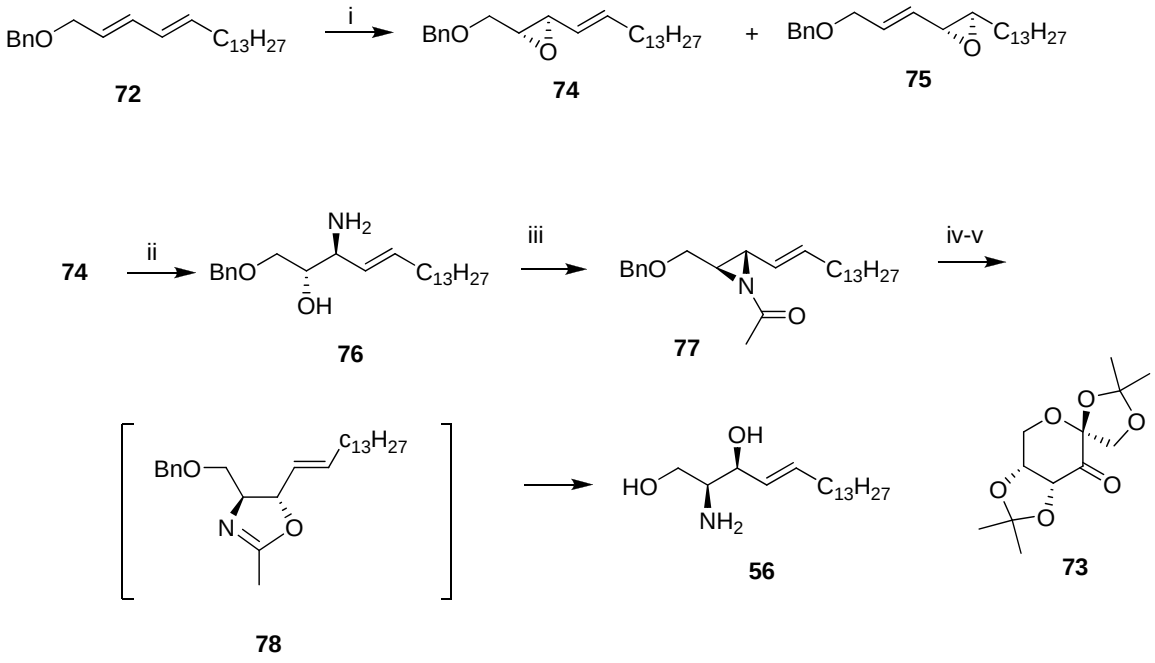


Scheme 15: i) $C_{15}H_{31}PPh_3Br$, LHMDS, -78 °C; ii) *m*CPBA, 25 °C; iii) PhSeSePh, $NaBH_4$, reflux; iv) 30% H_2O_2, 25 °C; v) CF_3CO_2H, 25 °C.

Somfai's approach (2003)[33]

Somfai *et al.* have accomplished the synthesis of *threo*-sphingosine (**56**) using Shi' epoxidation of olefin **72** as the chiral inducing step. Accordingly, treatment of diene **72** with chiral catalyst **73** and oxone as oxidant produced the separable regioisomeric mixtures of epoxides **74** and **75**. Regioselective opening of the epoxide **74** with NH_4OH gave *trans* amino alcohol **76** at 125 °C. Under Mitsunobu reaction condition the amino

alcohol was converted to the corresponding aziridine, which was subsequently protected as its acetate **77**. Treatment of the protected aziridine **77** with Lewis acid ($BF_3{\cdot}OEt_2$) followed by hydrolysis under acidic condition furnished sphingosine (**56**) (**Scheme 16**).

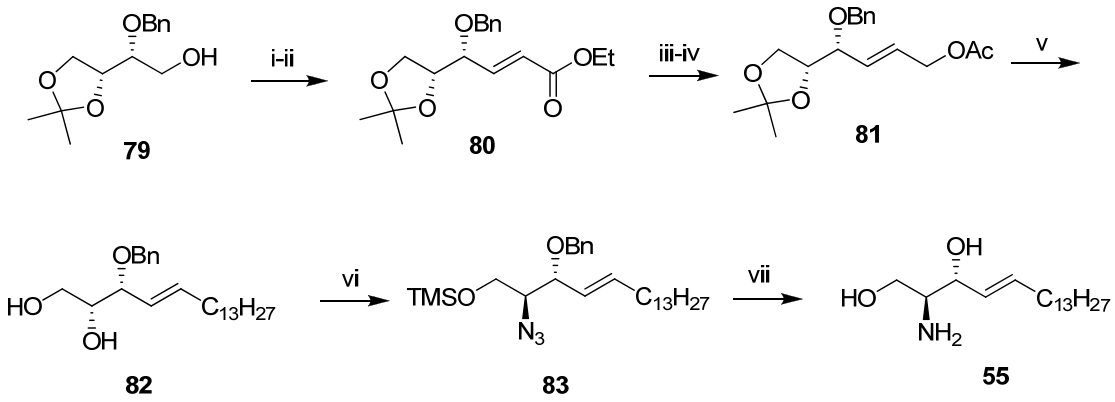


Scheme 16: i) cat. **73**, Oxone; ii) NH_4OH, 125 ^oC, 1 h; iii) Ac_2O, CH_2Cl_2, 0 ^oC; iv) $BF_3{\cdot}OEt_2$, H_2O; v) H_2SO_4.

Bittman's approach (2005)[34]

Scheme **17** illustrates the synthesis of *erythro*-sphingosine **55** from protected D-threitol derivative, which was achieved by Bittman *et al*. Alcohol **79** was oxidized with PCC to afford the corresponding aldehyde, which was subjected to Horner-Wittig reaction to afford α, β-unsaturated ester **80**. Reduction of the ester group in **80** with DIBAL-H followed by protection of the resulting alcohol with AcCl gave the acetate **81**. Coupling of acetate **81** with freshly prepared $C_{12}H_{25}MgBr$ in the presence of catalytic Li_2CuCl_4 in Et_2O at -78 ^oC followed by deprotection of acetal group with 5% H_2SO_4 provided diol **82**. Treatment of diol **82** with a mixture of diisopropylazodicarboxylate (DIAD) and Ph_3P at 0 ^oC and then adding $TMSN_3$ resulted the azide substituted product **83** with concomitant transfer of the silyl group to the primary hydroxyl group. Azido silyl ether

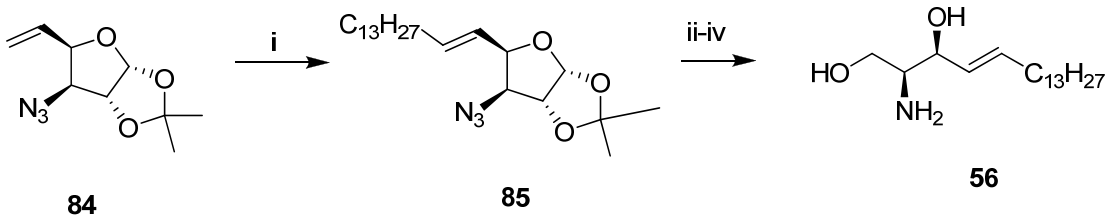
83 was converted to *erythro*-sphingosine (**55)** following standard reaction sequences (**Scheme 17**).



Scheme 17: i) PCC, NaOAc, CH_2Cl_2, MS; ii) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, NEt_3, LiBr, THF, 25 ^oC; iii) DIBAL-H, -78 ^oC, CH_2Cl_2; iv) AcCl, $i\text{-Pr}_2NEt$, CH_2Cl_2, -40 ^oC; v) (a) $C_{12}H_{25}MgBr$, Li_2CuCl_4, Et_2O, -78 ^oC; (b) 5% H_2SO_4, MeOH; vi) (a) PPh_3, DIAD, CH_2Cl_2, 0 ^oC; (b) $TMSN_3$, 0 ^oC; (c) TBAF, THF; vii) (a) PPh_3, THF:H_2O (9:1); (b) Na, NH_3, THF, -78 ^oC, 30 min.

Dhavale's approach (2005)[35]

In this approach, the olefin **84**, obtained from D-glucose in five steps, was subjected to cross-metathesis reaction with pentadec-1-ene to get the corresponding cross-coupled product **85** with exclusively *E*-selectivity at the olefinic bond. Removal of the acetonide protection under acidic conditions followed by cleavage of the resulting diol using $NaIO_4$ and then reduction gave *threo*-sphingosine **56** in excellent yield (**Scheme 18**).

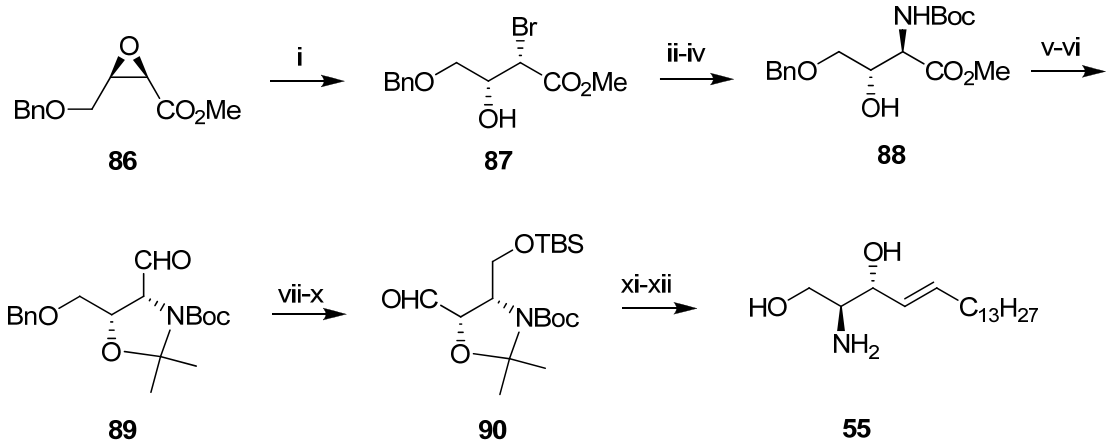


Scheme 18: i) Pentadec-1-ene, Grubbs' catalyst, CH_2Cl_2, 30 ^oC; ii) TFA, 30 ^oC; iii) $NaIO_4$, acetone/water, 30 ^oC; iv) $LiAlH_4$, THF

Bonini's approach (2006)[36]

Bonini *et al.* have described the synthesis of *erythro*-sphingosine (**55**) *via* the regioselective opening of the epoxide **86**, prepared from *cis*-butene 1,4-diol *via*

asymmetric epoxidation, with NaBr in the presence of amberlyst-15 to obtain the bromohydrin **87** in almost quantitative yield. Displacement of the bromide in **87** with azide followed by its hydrogenation and protection of the amine group resulted in *trans*-amino alcohol **88**. Protection of the amino alcohol with dimethoxy propane and controlled reduction of the ester with DIBAL-H gave the aldehyde **89**. Reduction of aldehyde with $NaBH_4$ and TBS protection of the resulting alcohol proceeded smoothly to give the corresponding silyl ether in 95% yield. The benzyl protection was removed under catalytic hydrogenation and the resulting alcohol was oxidized with Py/SO_3 to get the corresponding aldehyde **90**. Finally, aldehyde **90** was transformed into the D-*erythro*-sphingosine (**55**) following standard synthetic sequences (**Scheme 19**).



Scheme 19: i) NaBr, Amberlyst-15, -20 ^oC; ii) NaN_3, DMF, 25 ^oC; iii) H_2/Pd; iv) Boc_2O, EtOAc, 25 ^oC; v) 2,2-DMP, *p*-TsOH, CH_2Cl_2, 25 ^oC; vi) DIBAL, -78 ^oC, 95%; vii) $NaBH_4$, *i*-PrOH/THF, 25 ^oC, 95%; viii) TBDPSCl, Et_3N, DMAP, 25 ^oC, 93%; ix) H_2/Pd, MeOH, 25 ^oC, 93%; x) Py/SO_3, DMSO, 0 ^oC, 85%. xi) $nC_{14}H_{29}PPh_3Br$, *n*BuLi, THF, -78 ^oC-25 ^oC, 95% (Z/E, 30/70); xii) TFA:H_2O (1:1), 25 ^oC, 75%.

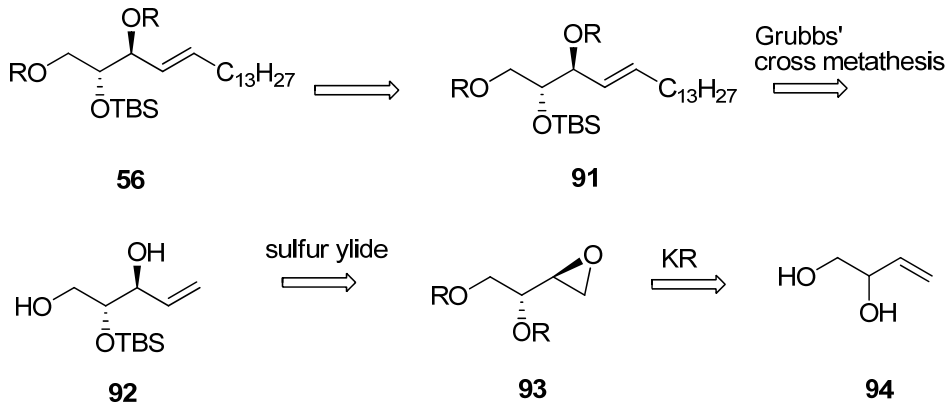
2.2.3 Present Work

2.2.3.1 Objective

As can be seen from the above discussion, there are only a few reports on the synthesis of *threo*-sphingosine (**56**). Unfortunately, most of the reported methods for the synthesis of sphingosines (**55-56**), either employ chiral starting materials, expensive reagents or

involve longer reaction sequences coupled with poor product selectivity. The development of an efficient and catalytic route to sphingosines therefore continues to attract the attention of chemists. Hence, we thought to synthesize *threo*-sphingosine (**56**), using kinetic resolution *via* Sharplesss asymmetric epoxidation of allylic alcohol. The retrosynthetic analysis for the synthesis of *threo*-sphingosine (**56**) is shown in **Scheme 20.**

We envisaged that the protected triol **91** could serve as a valuable intermediate for the asymmetric synthesis of *threo*-sphingosine (**56**). We anticipated that the long aliphatic chain could be attached by cross-metathesis of pentadec-1-ene and the allyl alcohol **92**, which in turn could be prepared readily *via* regioselective opening of epoxide **93** with sulfur ylide. We presumed that the kinetic resolution of allyl alcohol **94** *via* epoxidation would result in the desired epoxide **93 (Scheme 20)**. Since the present strategy involves the regioselective ring opening of epoxide **93** with sulphur ylide as one of the key steps a brief account of it is discussed below.

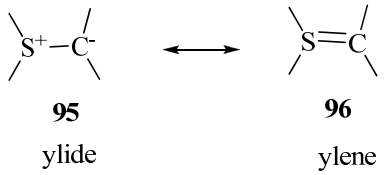


Scheme 20: Retrosynthetic analysis of *threo*-sphingosine (**56**)

2.2.3.2 Chemistry of sulfur ylides

The chemistry of ylides attracted considerable interest in the early 1950s after Wittig has discovered the reaction of phosphonium ylides with carbonyl compounds giving rise to alkenes. Investigations carried out by Corey and Franzen extended the Wittig reaction

to sulfur ylides and initiated extensive studies of sulfonium ylides.[37] The further development of the chemistry of these compounds demonstrated that they could be widely used in organic synthesis. Sulfur ylides contain a negatively charged carbon atom directly bound to a positively charged sulfur atom. In the general form, these compounds can be represented by two resonance structures, viz., ylide **95** and ylene **96** (**Scheme 21**).



Scheme 21: Resonance structures of sulfonium ylides

Sulfonium (**95**) and sulfoxonium (**97**) ylides containing two organic substituents at the sulfur atoms are most often used in organic synthesis. Sulfinyl ylides (**98**), sulfonyl ylides (**99**), thiocarbonyl ylides (**100**) and iminosulfuranes (**101**) are also well known. Sulfur ylides act as nucleophilic reagents; their reactivities being inversely proportional to their stability (**Fig. 14**).

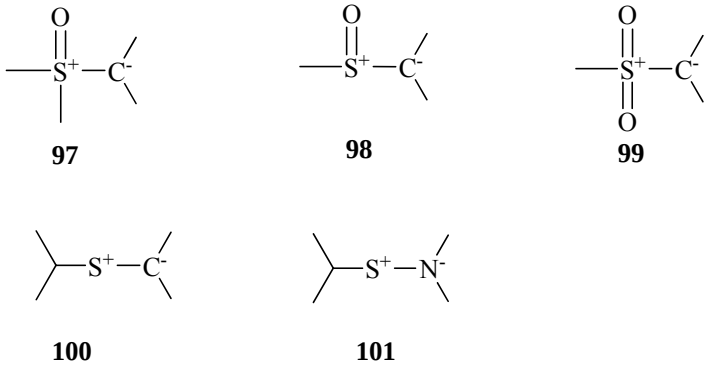
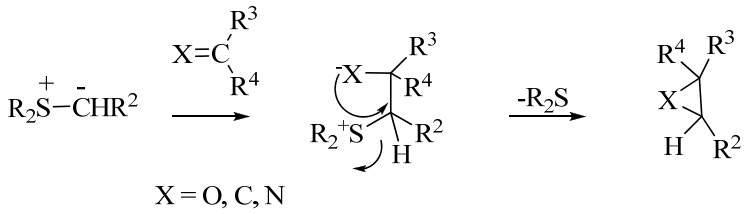


Fig. 14: Commonly used sulfur ylides

Ylides are stabilized through the electron density delocalisation under the action of electron-withdrawing substituents at the carbanionic centre. The reactions of sulfur ylides with compounds containing C=X bonds (X=O, C or N) gained wide acceptance in organic synthesis. These reactions proceed as the nucleophilic addition followed by

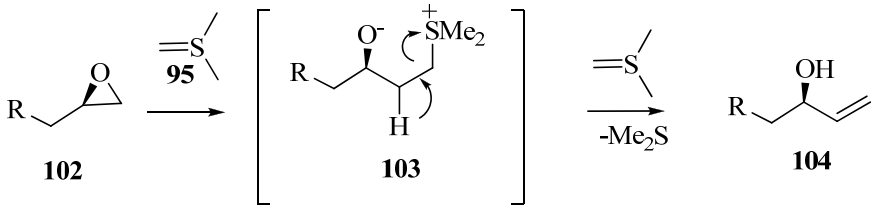
1,3-elimination of a sulfur-containing group to form epoxide, cyclopropane or aziridine, respectively (**Scheme 22**).[38]



Scheme 22: Nucleophilic addition of sulfur ylides

Due to their zwitterionic character, sulfonium ylides are also widely used in rearrangements generating new C-C bonds (often with high stereo- and regioselectivity).

Terminal, allylic and benzylic epoxides are smoothly converted directly to one carbon homologated allylic alcohols in good yields when treated with excess of dimethylsulfonium methylide.[39] In these cases, reaction appears as an interesting stereochemical alternative to the less selective addition of vinyl Grignard to a carbonyl (**Scheme 23**).



Scheme 23: Stereoselective opening of epoxide with dimethylsulfonium methylide

In the last decade, interest in sulfur ylides was quickened owing to their successful use in asymmetric synthesis. A one-stage procedure, which has been developed recently for the synthesis of optically active epoxides and aziridines, represent a considerable achievement in this field.

2.2.4 Results and discussion

Our synthesis of *threo*-sphingosine (**56**) started with the opening of commercially available epoxy butene (**105**) with water in the presence of titanium superoxide as the reusable acidic catalyst (**Scheme 24**). For an elaborate discussion on these reactions, refer the present work under Section I, Chapter IV. The hydrolysis proceeded smoothly to produce the but-3-ene-1,2-diol (**94**) in excellent yields. The ^{1}H NMR spectrum of **94** showed characteristic signals at δ 5.81(m) and 5.25 (m) corresponding to the terminal olefins. The signals for allylic methine proton and the methylene protons (CH_2=CH-C**H**- and-C**H**$_2$-OH) have appeared as multiplets at δ 4.12 and 3.51 respectively. Its ^{13}C NMR spectrum displayed typical signals at δ 136.7 and 116.4 for the olefinic carbons and at δ 73.1 and 66.0 corresponding to the methine and methylene carbons respectively (**Fig. 15**). The formation of diol was also confirmed from the IR spectrum of **94**, which showed a broad signal at 3320 cm^{-1} due to the hydroxyl groups.

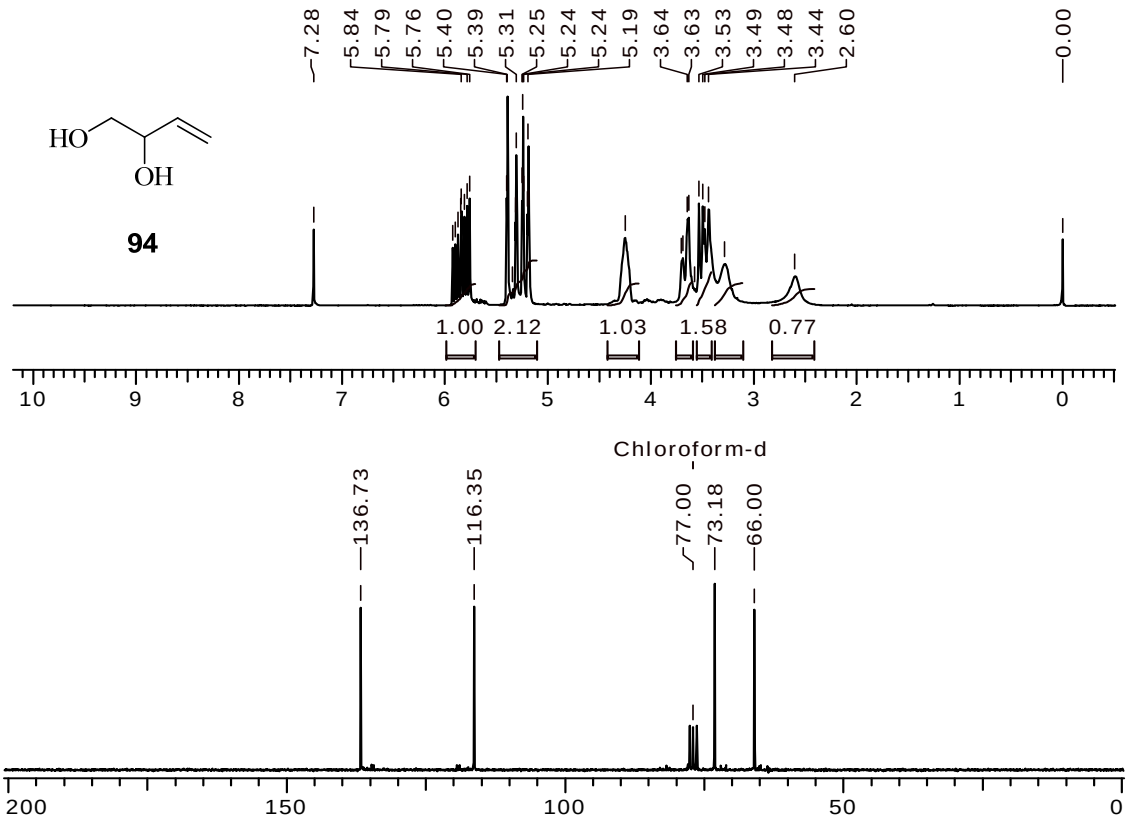
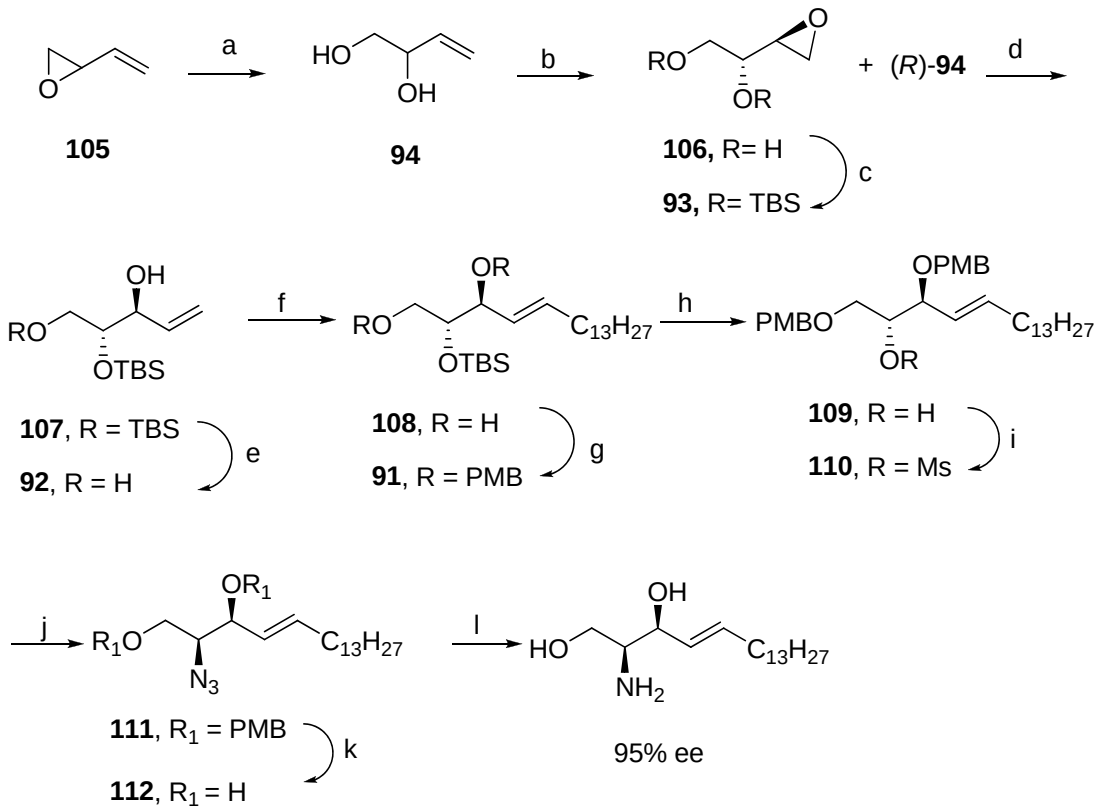


Fig. 15: ^{1}H and ^{13}C NMR spectra of **94**



Scheme 24: (a) H_2O, Titanium superoxide (20 wt%), 25 ºC, quant.; (b) TBHP, D-(-)-diethyl tartarate, Ti(O*i*Pr)$_4$, CH_2Cl_2, 4 Aº MS, -20 °C, 18 h, 43% (c) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 93%; (d) $(CH_3)_3S^+I^-$, *n*BuLi, THF, -20 °C- 0 °C, 2 h, 82%; (e) CSA, MeOH:CH_2Cl_2 (1:1), 0 °C, 2 h, 85%; (f) Grubbs' catalyst (10 mol%), Pentdec-1-ene, CH_2Cl_2, reflux, 10 h, 62%; (g) PMB-Cl, NaH, DMF:THF (1:1), 2 h, 0 °C; (h) TBAF, CH_2Cl_2, 0 °C; 83% over two steps; (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (j) NaN_3, DMF, 80 °C, 6 h, 79% over two steps; (k) DDQ, CH_2Cl_2: H_2O, 0 ºC; (l) $LiAlH_4$, THF, 0 °C 1 h then reflux 2 h, 82% over two steps.

The kinetic resolution of racemic diol **94** *via* Sharpless epoxidation[40] was achieved using (-)-diethyl tartarate as the ligand and Ti(O*i*Pr)$_4$ as the catalyst to produce chiral epoxy alcohol **106** $[\alpha]_D^{25}$ +21 (*c* 0.8, $CHCl_3$) in 43% yield along with the diol (*R*)-**94** $[\alpha]_D^{25}$ +32 (*c* 1.0, $CHCl_3$); {lit.[41] $[\alpha]_D^{25}$ +35.5 (*c* 1.2, $CHCl_3$) }. The disappearance of the olefinic protons in the region of δ 5-7 in the ^{1}H NMR spectrum of **106** confirmed the formation epoxide. Further, characteristic three signals at δ 2.61 (dd), 2.72 (dd) and 2.92 (dd) correspond to the presence of terminal epoxide. Its ^{13}C NMR spectrum has shown four signals in the region δ 40-75 indicating the formation of epoxide moiety.

The diol groups were protected as silyl ethers using TBS-Cl in the presence of imidazole at 0 ^{o}C to give **93** in 93% yield {$[\alpha]_D^{25}$ -18.5 (*c* 1.0, $CHCl_3$)}. The ^{1}H NMR spectrum of disilyl ether **93** showed signals at δ 0.87 and 0.05 due to ^{t}Bu (($C\mathbf{H_3})_3C$-) and methyl (Si-$C\mathbf{H_3}$) groups respectively. Its ^{13}C NMR spectrum displayed characteristic signals at δ 25.8, 18.02 and -4.24 corresponding to the TBS group (**Fig. 16**).

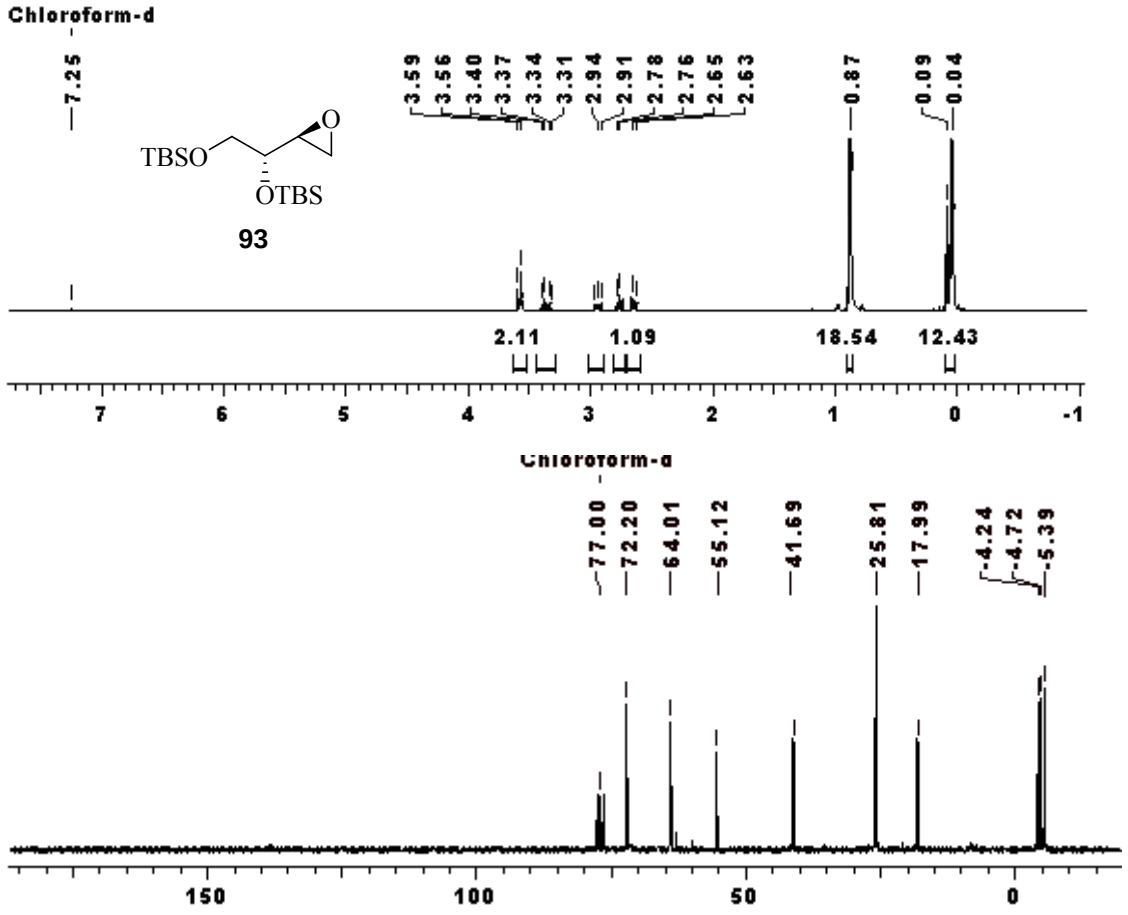


Fig. 16: ^{1}H and ^{13}C NMR spectra of **93**

Silyl ether protected epoxide **93** was subjected to regioselective ring opening with trimethylsulfonium ylide at -20 ^{o}C to furnish the allylic alcohol **107** in 82% yield {$[\alpha]_D^{25}$ -12 (*c* 1.2, $CHCl_3$)}. Surprisingly, this reaction failed when the TBS protection was replaced with *p*-methoxy benzyl ether and the starting material was recovered. The ^{1}H NMR of allylic alcohol **107** displayed characteristic signals for the terminal olefin at δ 5.88 and 5.19, which confirmed the formation of allylic alcohol. The allylic methine

proton and alkoxy protons have displayed signals at δ 4.28 and δ 3.61 respectively. Its ^{13}C NMR spectrum displayed signals at δ 138.2 and 115.7 corresponding to the olefinic carbons and at δ 74.5 due to the allylic carbon respectively (**Fig. 17**). Further, a strong absorption at 3372 cm^{-1} in the IR spectrum of **107** confirmed the presence of hydroxyl group.

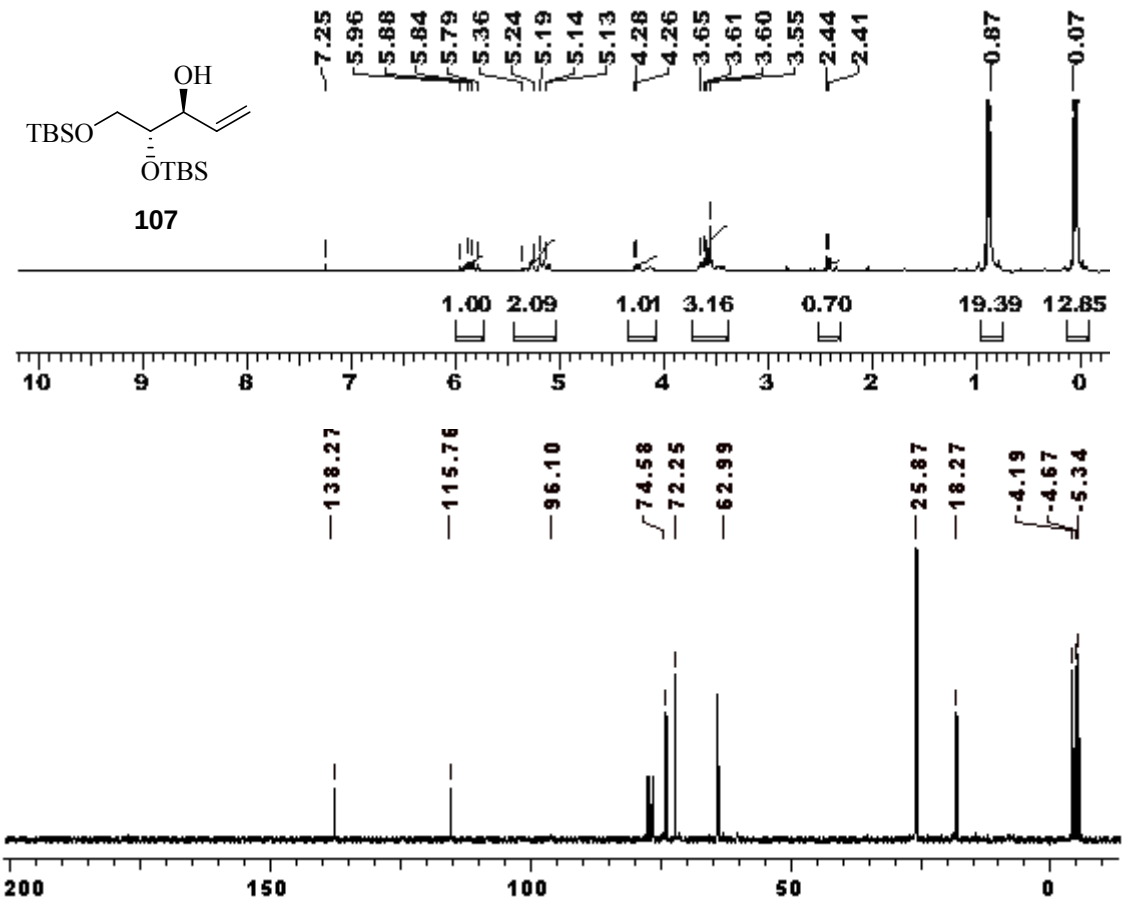


Fig. 17: ^{1}H and ^{13}C NMR spectra of **107**

Selective deprotection of the primary alcoholic silyl ether group in **107** was achieved at 0 ^{o}C using 10 mol% camphor sulfonic acid (CSA) to give diol **92** $\{[\alpha]_D^{25}$ -25 (*c* 0.7, $CHCl_3)\}$. This reaction was found to be very fast. However, deprotection of both the silyl groups was observed if the reaction was carried out either at 25 ^{o}C or for a prolonged reaction time. The ^{1}H NMR spectrum of diol **92** showed signals at δ 0.83 and -0.02 corresponding to the silyl protection, which account for only one TBS group. Its ^{13}C

NMR displayed characteristic signal at δ 137.6 and 117 due the olefinic carbons and at δ 25.7, 18.0, and - 4.3 corresponding to the TBS group respectively (**Fig. 18**).

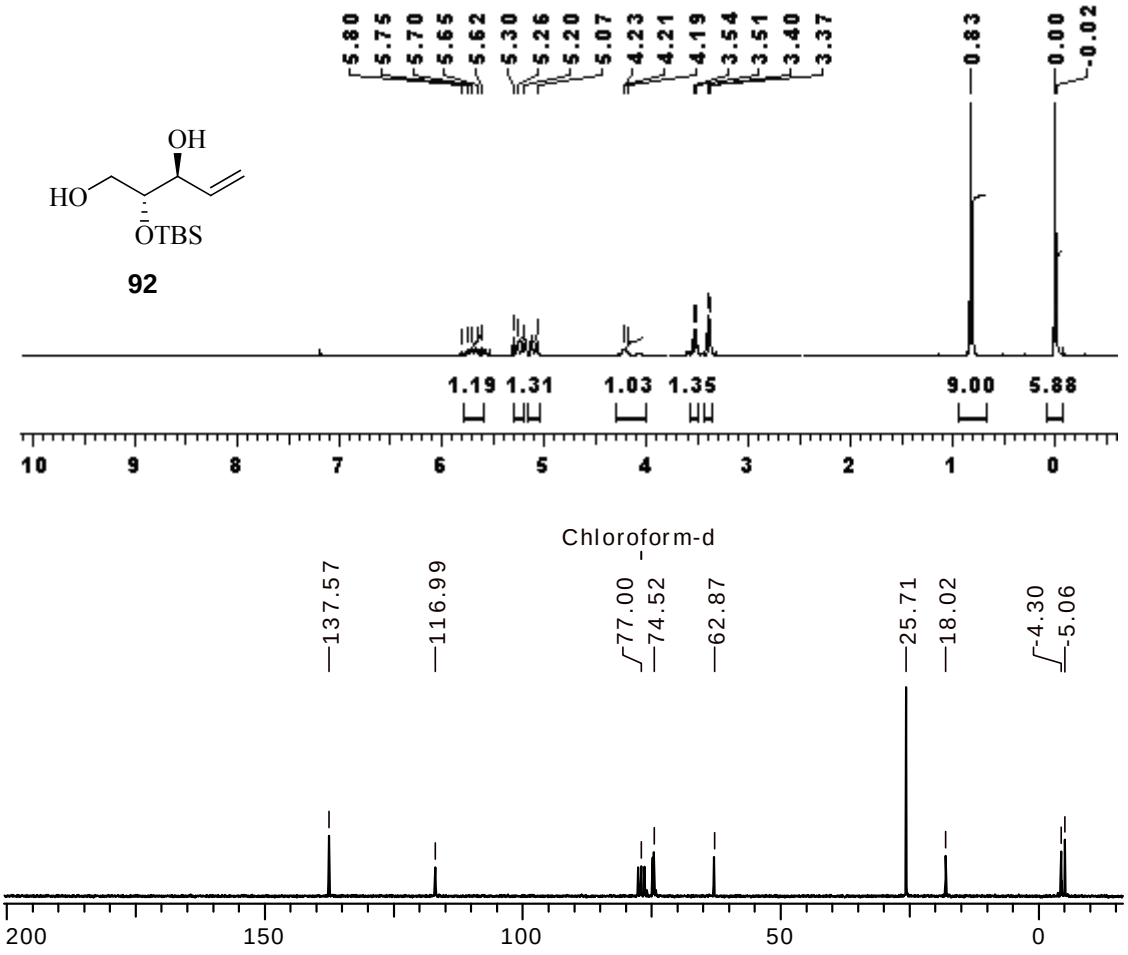


Fig. 18: ^{1}H and ^{13}C NMR spectra of **92**

The terminal olefin in **92** was subjected to cross-metathesis with pentadec-1-ene in the presence of Grubbs' second generation catalyst[42] to obtain the long chain diol **108** in 62% yield $\{[\alpha]_D^{25}$ +6.5 (*c* 0.8, $CHCl_3$)$\}$. The cross-metathesis furnished exclusively the *E*-isomer and no trace of *Z*-isomer was observed. However, we observed that disilyl protected olefin **107** failed to furnish the cross-metathesis product even after 2 days {Grubb's cat. 10 mol%, CH_2Cl_2, 45 ^{o}C, 2 days); probably due to the steric hindrance offered by the bulky *t*-Bu groups in the molecule. The ^{1}H NMR spectrum of the cross-coupled product **108** displayed characteristic signals at δ 5.6 and 5.4 due to the internal olefin, which accounted for only two protons. The methylene protons of the long

aliphatic chain have appeared as multiplets in the region δ 1.15-1.30, while the signal for methyl proton (C**H**$_3$-C) has merged with ^{t}Bu group signal {$(CH_3)_3$C-Si)} at δ 0.80 (**Fig. 19**).

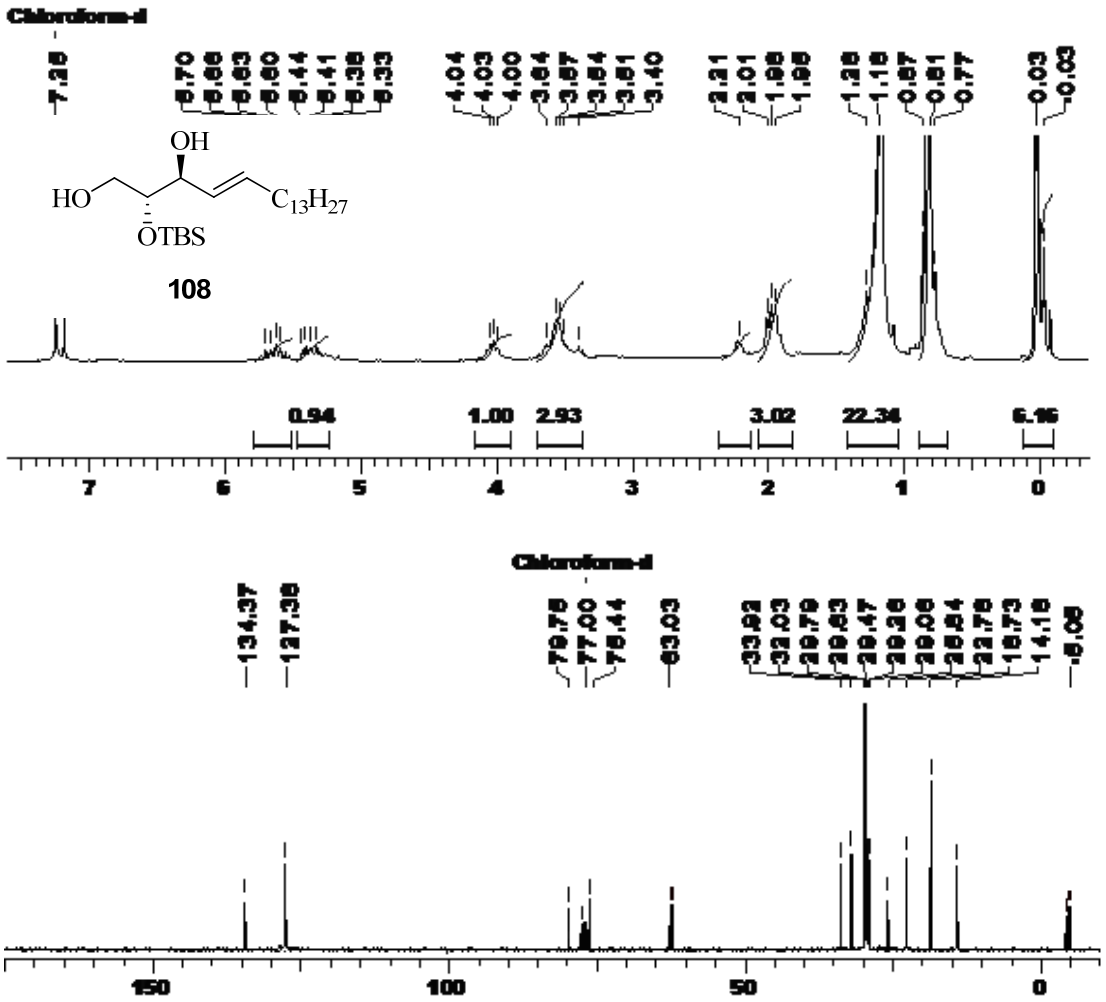


Fig. 19: ^{1}H and ^{13}C NMR spectra of **108**

The free alcoholic groups in **108** were then protected as PMB ether in the presence of NaH at 0 ^{o}C to give the corresponding PMB protected ether **91**. Its ^{1}H NMR spectrum which showed characteristic two doublets at δ 6.84 and 7.2 corresponding to 1,4-disubstituted aromatic ring and a singlet at δ 3.65 due to the methoxy protons (-OC**H**$_3$). The deprotection of silyl group in **91** was achieved using tetrabutylammonium fluoride (TBAF) in THF at 0 ^{o}C to give the corresponding alcohol **109**. The disappearance of the signals at δ 0.83 and -0.02 corresponding to the TBS group in the ^{1}H NMR spectrum of

109 confirmed the deprotection of silyl ether. The alkoxy protons (-C**H**$_2$-O and (-C**H**-O) have shown signals at δ 4.22, 3.61 and 3.48 while the internal olefinic protons have displayed at δ 5.7 and 5.39 respectively (**Fig. 20**).

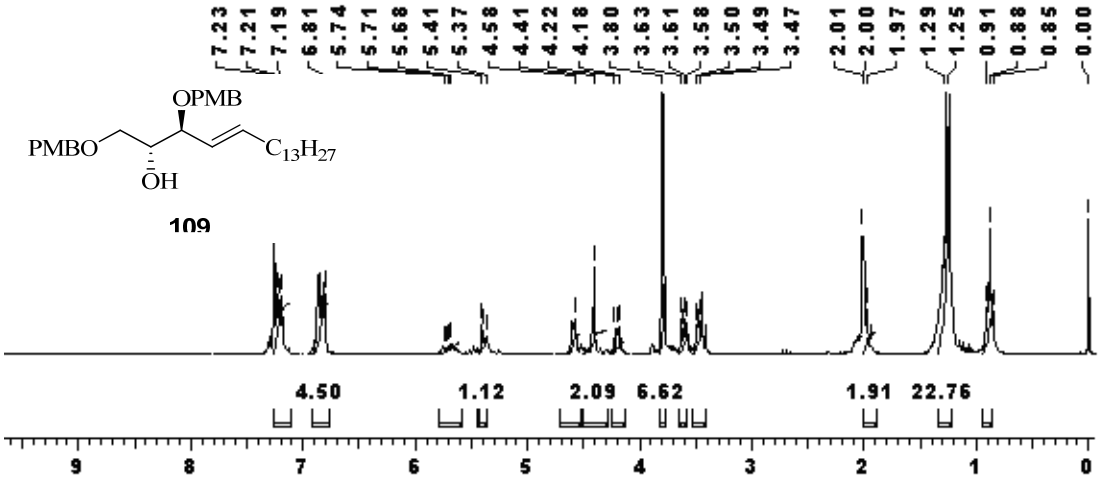


Fig. 20: ^{1}H NMR spectrum of **109**

Mesylation (MsCl, Et_3N) of the free OH group in **109** gave the mesylate **110**, which was subjected to S_N2 displacement with NaN_3 to give azide **111** with complete inversion of configuration. Although there was not much difference between the ^{1}H NMR spectra of alcohol **109** and azide **111**, the **C**-N_3 carbon of **111** showed an upfield shift in the ^{13}C NMR spectrum. The IR spectrum of azide **111** had a strong absorption at 2110 cm^{-1} indicating the presence of azide group.

Oxidative deprotection of the PMB ethers in **111** using DDQ in CH_2Cl_2 at 0 ^{o}C gave the azido diol **112**, which was subjected to reduction with $LiAlH_4$ to furnish *threo*-sphingosine **56** in 82% yield and 95% ee (determined by comparing the $[\alpha]_D$ value) $[\alpha]_D^{25}$ -2.7 (*c* 1.0, $CHCl_3$), {lit.[27] $[\alpha]_D^{25}$-2.83 (*c* 1.2, $CHCl_3$)}. The ^{1}H, ^{13}C NMR and other spectral data were in complete agreement with the reported values. The ^{1}H NMR spectrum of *threo*-sphingosine (**56**) showed signals at δ 5.74 and 5.39 due to the internal olefinic protons and at δ 2.87 corresponding to the methine proton attached to amine functionality (-CH-NH_2). The signals for alkoxy protons (-CH_2-O, -CH-O) have

appeared at δ 3.62 and 4.05 respectively. Its ^{13}C NMR spectrum displayed characteristic signals in the range δ 14- 32 corresponding to the long chain carbons and three signals at δ 56.5, 63.4 and 75.0 due to the carbons attached to heteroatoms respectively (**Fig. 21**).

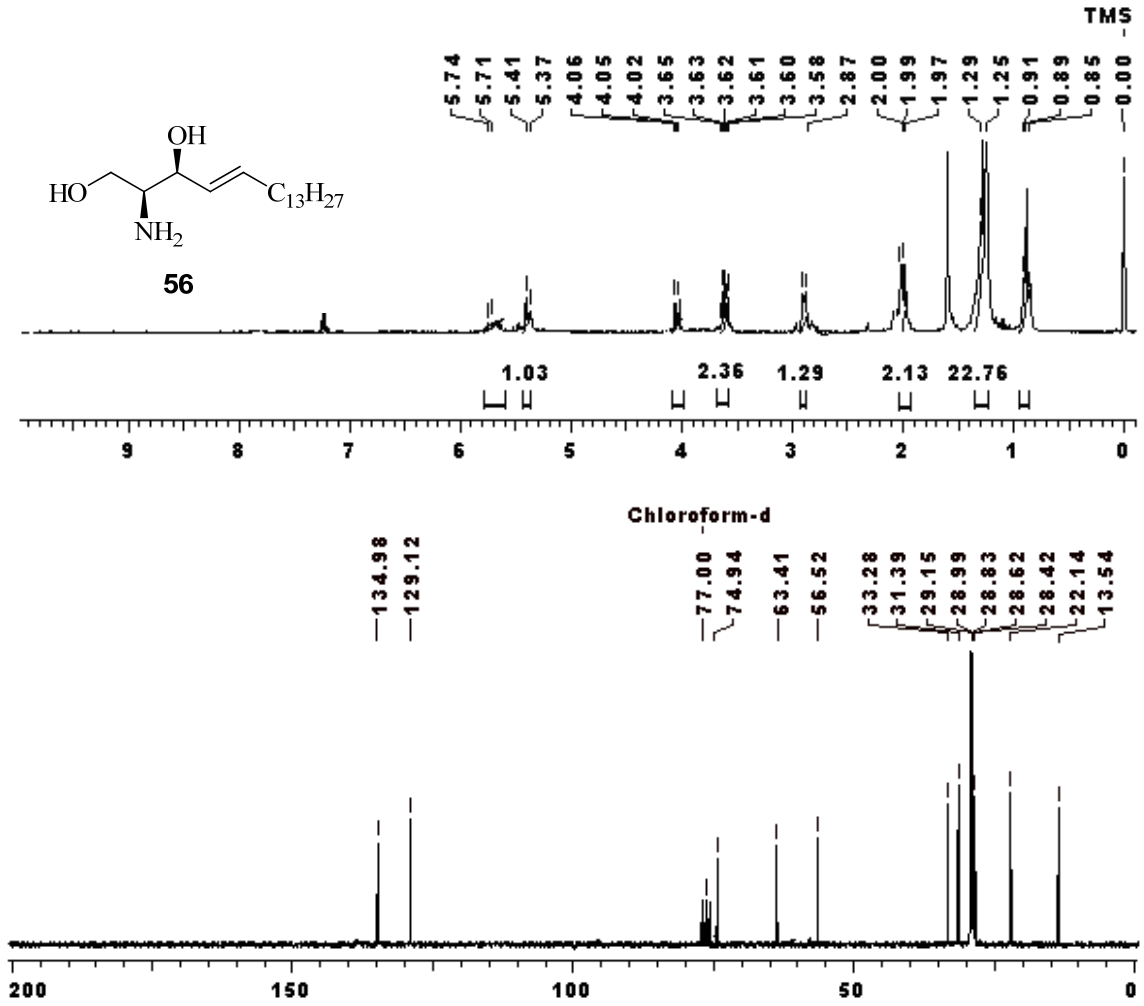


Fig. 21: ^{1}H and ^{13} C NMR spectrum of **56**

2.2.5 Conclusion:

The enantioselective synthesis of *threo*-sphingosine (**56**) has been achieved in 95% ee using kinetic resolution *via* Sharpless asymmetric epoxidation of but-3-ene-1,2-diol (**94**). The synthesis involves eleven steps and makes use of readily available reagents. This synthetic route has the potential to extend for the synthesis of other sphingolipids.

2.2.6 Experimental Section

But-3-ene-1,2-diol (94)

A 100 mL round bottomed flask was charged with epoxy butane (**105**) (7 g, 100 mmol) and H_2O (1.8 g, 100 mmol). To this mixture was added titanium superoxide (1.4 g, 20 wt%) at room temperature (For an elaborate discussion on these reactions, refer the present work under Section I, Chapter IV). The reaction was exothermic while addition of Ti-superoxide so that the mixture was cooled externally with cold water to keep the temperature below 40 ^oC. After stirring for 5 h at room temperature, ethyl acetate was added to the reaction mixture and filtered. The filtrate was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give the crude diol, which was purified by column chromatography to give **94** as colourless liquid. **Yield**: 99%; **^{1}H-NMR** ($CDCl_3$, 200 MHz) δ 2.60 (brs, 1H), 3.29 (brs, 1H), 3.49 (dd, *J* = 8.1, 10.5 Hz, 1H), 3.64 (dd, *J* = 6.2, 1.5 Hz, 1H), 4.25 (m, 1H), 5.25 (m, 2H), 5.79 (m, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz) δ 66.0, 73.2, 116.4, 136.7; **IR** ($CHCl_3$, cm^{-1}): 3320, 2912, 1213, 1130, Anal. Calcd for $C_4H_8O_2$: C, 54.53; H, 9.15. Found: 54.48, 9.19%.

(*R*)-1-((*R*)-Oxiran-2-yl)ethane-1,2-diol (106)

To a two-necked round bottomed flask charged with 4A^o molecular sieves in CH_2Cl_2 at -23 ^oC were added (-)-diethyl tartarate and $Ti(OiPr)_4$. The resulting mixture was stirred at -23 ^oC for 5 min and then TBHP was added drop-wise. The mixture was stirred at -23 ^oC for 30 min. Allylic alcohol **94** (8.8 g, 100 mmol) was then added drop-wise and the resulting mixture was kept at -23 ^oC for 20 h. It was then quenched with 15% aqueous NaOH solution and was brought to 0 ^oC and stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to obtain

pure **106** as colourless liquid. **Yield**: 43%; $[\alpha]_D^{25}$ +21 (*c* 0.8, $CHCl_3$); **^{1}H-NMR** ($CDCl_3$, 200 MHz) δ 2.62 (dd, *J* = 4.1, 2.1 Hz, 1H), 2.72 (dd, *J* = 4.1, 2.5 Hz, 1H), 2.93 (dd, *J* = 5.5, 3.1 Hz, 1H), 3.46 (dd, *J* = 8.5, 10.2 Hz, 1H), 3.66 (dd, *J* = 6.2, 1.5 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz) δ 41.2, 55.1, 66.2, 73.1; **IR** ($CHCl_3$, cm^{-1}): 3315, 2915, 1152, 1130, 984; Anal. Calcd for $C_4H_8O_3$: C, 46.15; H, 7.75. Found: 46.21, 7.59%.

Disilyl ether 93

To a solution of the diol **106** (4.16 g, 40 mmol) in CH_2Cl_2 at 0 ^oC was added imidazole (5.44 g, 80 mmol) followed by *tert*-butyldimethyl silyl chloride (12 g, 80 mmol) and stirred for 1 h at 0 ^oC. After the completion of the reaction it was extracted with CH_2Cl_2. The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using petroleum ether: ethyl acetate (9:1) to obtain pure disilyl protected silyl ether **93** as colourless liquid. **Yield**: 93%; $[\alpha]_D^{25}$ -18.5 (*c* 1.0, $CHCl_3$); **^{1}H-NMR** ($CDCl_3$, 200 MHz) δ 0.04 (s, 6H), 0.09 (s, 6H), 2.65 (dd, *J* = 4.2, 2.3 Hz, 1H), 2.77 (dd, *J* = 4.3, 2.4 Hz, 1H), 2.92 (dd, *J* = 5.2, 2.9 Hz, 1H), 3.32 (m, 1H), 3.58 (d, *J* = 6 Hz, 2H); **^{13}C-NMR** ($CDCl_3$, 50 MHz) δ -5.4, -4.7, -4.3, 18.0, 25.8, 41.7, 55.1, 64.0, 72.2; **IR** ($CHCl_3$, cm^{-1}): 2915, 1175, 1152, 1132, 915; Anal. Calcd for $C_{16}H_{36}O_3Si_2$: C, 54.53; H, 9.15. Found: 54.48, 9.19%.

(3*R*, 4*R*)-4,5-bis(*tert*-Butyldimethylsilyloxy)pent-1-en-3-ol (107)

To a stirred suspension of trimethylsulfonium iodide (8.568 g, 42 mmol) in dry THF (150 mL) was added *n*-BuLi (5.736 g, 1.6 M hexane solution, 84 mmol) at -10 ^oC. After 30 min, epoxide **106** (11.6 g, 35 mmol) in dry THF (30 mL) was introduced drop-wise and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water and extracted with diethyl ether (3 x 100 mL). The combined extracts were

washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography using petroleum ether: ethyl acetate (90:10) to give allyl alcohol **107** as colorless oil. **Yield**: 82%; $[\alpha]_D^{25}$ -12 (*c* 1.2, $CHCl_3$); **^{1}H-NMR** ($CDCl_3$, 200 MHz) δ 0.07 (m, 12H), 0.87 (m, 18H), 2.42 (d, *J* = 6.1 Hz, 1H), 3.61 (m, 3H), 4.28 (m, 1H), 5.19 (m, 2H), 5.88 (m, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz) δ -5.3, -4.7, -4.2, 18.3, 25.9, 63.0, 72.3 74.6, 96.1, 115.8, 138.3; **IR** ($CHCl_3$, cm^{-1}): 3291, 2912, 1612, 1132, 1092; Anal. Calcd for $C_{17}H_{38}O_3Si_2$: C, 58.90; H, 11.05. Found: C, 58.88; H, 11.23%.

(2*R*, 3*R*)-2-((*tert*-Butyldimethylsilyloxy)pent-4-ene-1,3-diol (92)

To a stirred solution of disilyl ether **107** (8.65 g, 25 mmol,) in MeOH:CH_2Cl_2 at -20 ^oC was added camphor sulfonic acid (10 mol%) and stirred for 2 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography using petroleum ether: ethyl acetate (6:4) to give 1,3-diol **92**. **Yield**: 85%; $[\alpha]_D^{25}$ -25 (*c* 0.7, $CHCl_3$); **^{1}H-NMR** ($CDCl_3$, 200 MHz) δ -0.02 (s, 6H), 0.83 (s, 9H), 3.38 (d, *J* = 6.2 Hz, 2H), 3.53 (m, 1H), 4.22 (m, 1H), 5.09 (dd, *J* = 11.2, 7.4 Hz, 1H), 5.27 (dd, *J* = 11.6, 6.9 Hz, 1H), 5.70 (m, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz) δ -5.1, -4.3, 18.0, 25.7, 62.9, 74.5, 117.0, 137.6; **IR** ($CHCl_3$, cm^{-1}): 3312, 3291, 2962, 1612, 1132, 1092; Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41; Si, 12.09. Found: C, 56.88; H, 10.43%.

(2*R*, 3*R*, *E*)-2-((*tert*-Butyldimethylsilyloxy)octadec-4-ene-1,3-diol (108)

To a solution of allylic alcohol **92** (2.32 g, 10 mmol) in dry CH_2Cl_2 (100 mL) was added pentadec-1-ene (8.4 g, 40 mmol) followed by Grubbs' second generation catalyst (10 mol%, 1 mmol). The reaction mixture was refluxed at 45 ^oC for 18 h. After the completion of the reaction, as monitored by TLC, it was concentrated under reduced

pressure to obtain the residue, which was then purified by column chromatography using petroleum ether: ethyl acetate (7:3) to obtain pure cross-metathesis product **108**.

Yield: 62%; $[\alpha]_D^{25}$ +6.5 (*c* 0.8, $CHCl_3$); **^{1}H-NMR** ($CDCl_3$, 200 MHz) δ 0.03 (s, 6H), 0.81 (m, 12H), 1.18 (s, 22H), 1.98 (m, 3H), 2.21 (brs, 1H), 3.57 (m, 3H), 4.03 (m, 1H), 5.42 (m, 1H), 5.83 (m, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz) δ -5.1, -4.9, 14.2, 18.7, 22.8, 25.8, 29.1, 29.3, 29.5, 29.6, 29.8, 32.0, 33.9, 63.0, 76.4, 79.8, 127.4, 134.4; **IR** ($CHCl_3$, cm^{-1}): 3311, 2922, 2912, 1612, 1141, 1132, 1092; Anal. Calcd for $C_{24}H_{50}O_3Si$: C, 69.50; H, 12.15. Found: C, 69.45; H, 12.11%.

(2*R*, 3*R*, *E*)-1,3-bis(4-methoxybenzyloxy)octadec-4-en-2-ol (109)

An oven dried round bottomed flask was charged with diol **108** (2.085 g, 5 mmol) and THF:DMF (1:1, 40 mL). The reaction mixture was cooled to 0 ^oC followed by addition of 60% NaH in mineral oil (240 mg, 6 mmol) in one portion. After stirring for 5 min at the same temperature, *p*-methoxy benzyl chloride (1.884 g, 12 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred for another 1 h at 0 ^oC and 30 minutes at room temperature. After the completion of the reaction, as monitored by TLC, THF was removed under reduced pressure and extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude protected triol **91**.

Without further purification, the silyl ether **91** was dissolved in THF (20 mL) and to this mixture added TBAF (10 mL of 1 M solution in THF) was added at 0 ^oC. The reaction mixture was stirred for 1 h at the same temperature and then quenched with water. It was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which was then purified by column chromatography using petroleum ether: ethyl acetate (90:10) to obtain pure **109**. **Yield**: 83%; $[\alpha]_D^{25}$ +8.4 (*c* 1.0, $CHCl_3$);

^{1}H-NMR ($CDCl_3$, 200 MHz) δ **^{1}H-NMR** ($CDCl_3$, 200 MHz) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.29 (m, 22H), 1.98 (m, 2H), 2.0 (brs, 1H), 3.50 (m, 1H), 3.46 (dd, *J* = 8.2, 31 Hz, 2H), 3.80 (s, 6H), 4.19 (dd, *J* = 8.2, 3.1 Hz, 1H), , 4.41 (s, 2H), 4.58 (s, 2H), 5.73 (m, 1H), 5.39 (m, 1H), 6.81 (m, 4H), 7.22 (m, 4H); **^{13}C-NMR** ($CDCl_3$, 50 MHz) δ 14.0, 22.6, 28.9, 29.2, 29.3, 29.4, 29.55, 29.59, 29.61, 31.9, 32.3, 55.3, 55.2, 61.3, 65.3, 72.6, 72.7, 73.4, 113.2, 113.5, 129.1, 129.2, 129.3, 128.0, 130.3, 135.8, 158.9, 158.1; **IR** ($CHCl_3$, cm^{-1}): 3325, 2937, 2856, 2360, 2331, 1737, 1612, 1514, 1460, 1438, 1363, 1301, 1247, 1220, 1172, 1099, 1035, 821; Anal. Calcd for $C_{34}H_{52}O_5$: C, 75.51; H, 9.69. Found: C, 75.45; H, 9.56%.

(2*R*, 3*R*, *E*)-1, 3-bis(4-Methoxybenzyloxy)-2-azido octadec-4-ene (111)

To a solution of alcohol **109** (1.62 g, 3 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (407 g, 4 mmol) at 0 ^oC. After 5 minutes methane sulfonyl chloride (448 mg, 4 mmol) was added drop-wise over a period of 5 min. The reaction mixture was stirred for another 1 h at 0 ^oC and brought to room temperature. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get crude methane sulfonate ester **110** in almost quantitative yield.

To a solution of crude mesylate **110** (1.94 g) in DMF was added sodium azide (650 mg, 10 mmol) and the reaction mixture was heated at 80 ^oC for 7 h. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 50 ml), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to obtain the crude azido sphingosine **111**, which was purified by column chromatography using petroleum ether: ethyl acetate (8:2). **Yield**: 79%; $[\alpha]_D^{25}$ -5.4 (*c* 1.0, $CHCl_3$) **^{1}H-NMR** ($CDCl_3$, 200 MHz) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.29 (m, 22H), 1.98 (m, 2H), 2.0 (brs, 1H), 3.46 (dd, *J* = 8.2, 31 Hz, 2H), 3.50

(m, 1H), 3.80 (s, 6H), 4.19 (dd, *J* = 8.2, 3.1 Hz, 1H) 4.43 (s, 2H), 4.52 (s, 2H), 5.73 (m, 1H), 5.39 (m, 1H), 6.81 (m, 4H), 7.22 (m, 4H); **^{13}C-NMR** ($CDCl_3$, 50 MHz) δ 14.0, 22.6, 28.9, 29.2, 29.3, 29.4, 29.55, 29.59, 29.61, 31.9, 32.3, 55.3, 55.2, 61.3, 65.3, 67.3, 72.6, 72.7, 113.2, 113.5, 129.1, 129.2, 129.3, 128.0, 130.3, 135.8, 158.9, 158.1; **IR** ($CHCl_3$, cm^{-1}): 2937, 2856, 2360, 2331, 2119, 1737, 1612, 1514, 1460, 1438, 1363, 1301, 1247, 1220, 1172, 1099, 1035, 821; Anal. Calcd for $C_{34}H_{51}N_3O_4$: C, 72.18; H, 9.09; N, 7.43. Found: C, 72.21; H, 9.36; N, 7.26%.

***Threo*-Sphingosine (56)**

To a solution of PMB ether (565 mg, 1 mmol) in CH_2Cl_2:H_2O (9:1, 10 mL) at 0 ^oC was added DDQ (900 mg, 4 mmol) in one portion and the reaction mixture was stirred for 1 h at the same temperature. After the completion of the reaction, as monitored by TLC, it was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the azido sphingosine **112,** whose azide group was reduced using $LiAlH_4$ as follows. An oven dried two neck RB was charged with $LiAlH_4$ (110 mg, 3 mmol) and dry THF (20 mL) was added *via* syringe. The suspension was cooled to 0 ^oC and a solution of crude azide **112** (355 mg) in dry THF (2 mL) was added drop-wise maintaining the temperature below 10 ^oC. After the addition was complete, the reaction mixture was stirred at the same temperature for 1 h and then refluxed for 5 h to ensure the completion of the reaction. The reaction mixture was then quenched with ethyl acetate and filtered through cealite. The filtrate was concentrated under reduced pressure to get the crude sphingosine. The crude residue was purified by flash chromatography using ethyl acetate: methanol (9:1) to yield **56** as a white solid. **Yield**: 82%; **mp**: 84–85 ^oC; (lit.[27] 86–87 ^oC); $[\alpha]_D^{25}$ -2.7 (*c* 1.0, $CHCl_3$), {lit.[27] $[\alpha]_D^{25}$ -2.83 (*c* 1.2, $CHCl_3$)}; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.0 Hz,

3H), 1.23 (m, 22H), 2.02 (q, *J* = 7.0 Hz, 2H), 2.84 (q, *J* = 5.2 Hz, 1H), 3.64 (m, 2H), 4.04 (t, *J* = 6.0 Hz, 1H), 5.44 (dd, *J* = 15.4, 7.2 Hz, 1H), 5.71 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 13.5, 22.1, 28.4, 28.6, 28.8, 29.0, 29.2, 31.4, 33.3, 56.5, 63.4, 74.9, 129.1, 135.0; **IR** ($CHCl_3$, cm^{-1}): 3325, 3292, 2912, 2895, 1642, 1123, 1112; Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.22; H, 12.37; N, 4.53%.

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CHAPTER 3

$NaIO_4$-mediated dihydroxylation of olefins, iodination of aromatics and direct esterification of aldehydes

Section I

$NaIO_4$/LiBr-mediated diastereoselective dihydroxylation of olefins: A catalytic approach to the Prevost-Woodward reaction

3.1.1 Introduction

Vicinal diols with *syn* and *anti* configurations are potential intermediates in the synthesis of several natural products, drugs and fine chemicals.[1] The catalytic dihydroxylation of alkenes represents a unique method for the preparation of these 1,2-diols with defined relative configuration. Several oxidants are now used for this purpose both in the laboratory and industry. For example, the *syn* dihydroxylation of alkenes is most often achieved using OsO_4 or RuO_4 as catalysts, which add from the less hindered diastereotopic face of alkene.[2] Despite the synthetic utility, the toxicity and high cost of OsO_4 and poor product-selectivity exhibited by $KMnO_4$ and RuO_4/H_2O_2 systems have prevented a successful application of these reagents on industrial scale. The *syn* dihydroxylation from the more hindered face can be effected using Woodward's procedure in which alkenes are treated with I_2-AgOAc in AcOH containing water.[3] On the other hand, *anti* dihydroxylation of an alkene is generally achieved using certain peroxy acids as well as I_2-silver benzoate *in the absence of water* (Prevost reaction).[4]

3.1.2. Review of literature

Literature search reveals that there are several reports available for the preparation of racemic as well as chiral 1,2-diols. Based on the reagents used, the dihydroxylation mehtods can be divided into the following three categories.

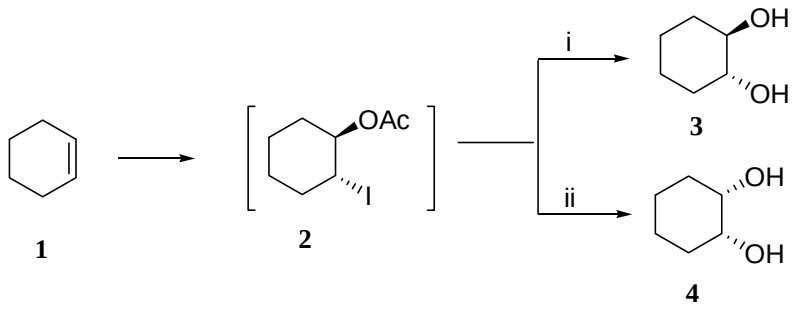
1. Prevost-Woodward type reaction
2. Metal oxide addition to olefin
3. Epoxide opening with oxygen nucleophiles

The above three types of dihydroxylation are briefly discussed below.

Prevost-Woodward type reaction

Prevost-Woodward reaction

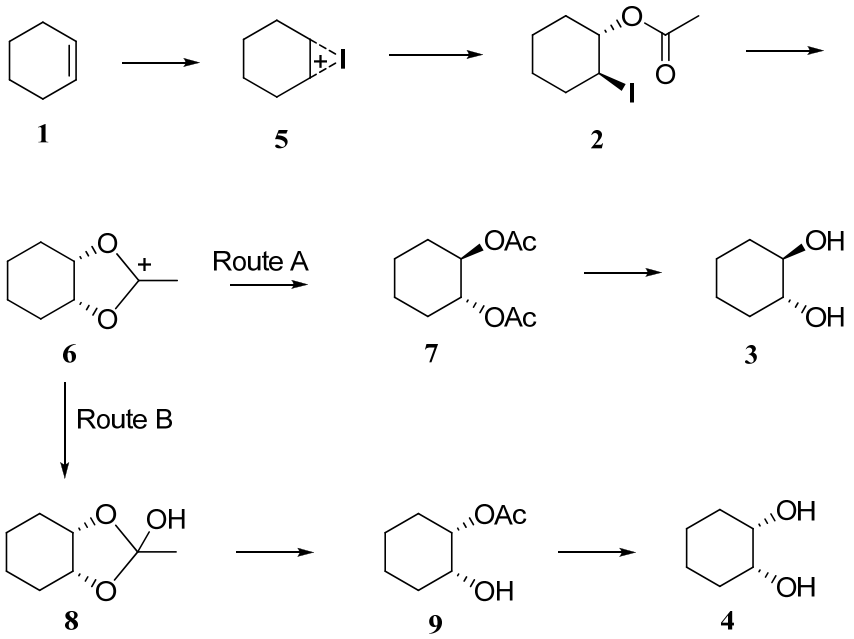
The Prevost reaction[4b] and its Woodward modification[3a] are important methods for the preparation of *trans* and *cis* 1,2-diols respectively with excellent yields. These reactions involve the treatment of an alkene with iodine and silver (I) carboxylate. Both reactions are considered to proceed through *trans* iodocarboxylate **2**, which by interaction of neighbouring acyloxy group and displacement with water or acetoxy group results in the formation of *syn* or *anti* diol derivatives depending upon the reaction conditions (**Scheme 1**). The alkaline hydrolysis of these diol derivatives gives the corresponding *trans* and *cis* diols **3** and **4** respectively.



Scheme 1: i) a) I_2, $PhCO_2Ag$ (2 equiv.), AcOH, 85 ºC; b) K_2CO_3, MeOH, 25 ºC. ii) a) I_2, $PhCO_2Ag$ (1 equiv.), AcOH, H_2O, 85 ºC; b) K_2CO_3, MeOH, 25 ºC.

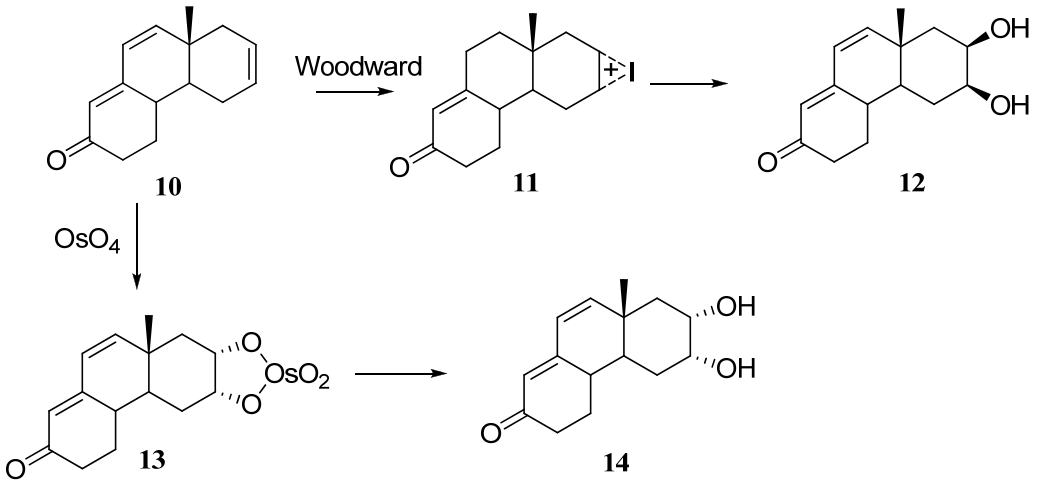
Mechanistically, in the first step of the reaction iodine adds to cyclohexene (**1)** to form iodonium ion **5**, which is opened with nucleophilic silver (I) carboxylate to give *trans* 2-iodocyclohexyl acetate (**2, Scheme 2**). Iodo acetate **2** can be isolated in quantitative yield from the reaction by conducting the reaction at lower temperature and lesser equivalent of metal carboxylate. Neighboring group participation of the acetate group displaces the iodine to produce 1,3-dioxolan-2-ylium intermediate **6**. Under anhydrous condition

(Prevost condition), acetate ion attacks the cyclic intermediate at C-4 position to furnish *trans* diacetate (**7**, route **A**). On the other hand, in the presence of water (Woodward condition), the intermediate is attacked by the water molecule at C-2 position to produce hydroxy acetate (**9**) with *syn* stereochemistry (route **B**).



Scheme 2: Mechanism of Prevost-Woodward reaction

Woodward noted[5] that his modification of the Prevost reaction offers the opposite facial selectivity as compared to oxidation with OsO_4 in the dihydroxylation of synthetic steroid intermediate **10**. Here, the steric approach factors first direct the stereochemistry of the iodination which is followed by hydroxylation from the opposite face to furnish *cis* diol **12** whereas oxidation with OsO_4 leads to the isomeric *cis* diol **14** by direct attack of OsO_4 from the most accessible face *via* osmate ester **13** (**Scheme 3**).



Scheme 3: Comparison of facial selectivity between Woodward and OsO_4 dihydroxylations

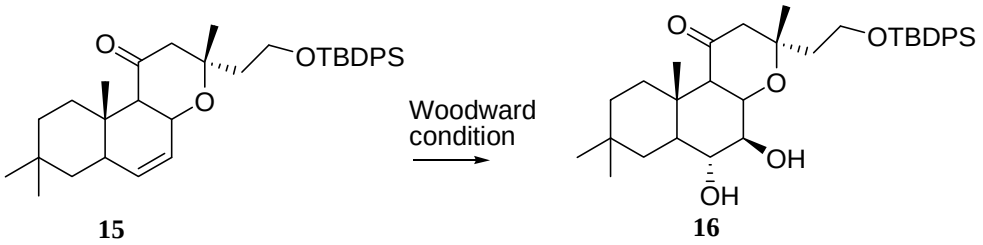
However, Prevost-Woodward reaction suffers from the following disadvantages

i) Woodward reaction affords only low yields of *cis* diols with tri- or tetra substituted olefins.

ii) Highly activated aromatic rings like 1-allyl phenol undergo aromatic iodination to give 2-allyl 6-iodophenol.

iii) The deactivated olefins like alkyl cinnamates are less reactive or unreactive under this reaction condition.

iv) Often sterically hindered olefins fail to produce the desired diol derivatives. For example, the olefin **15** gave the corresponding *trans* 1,2-diol **16** even in the presence of water (Woodward condition). The reason for non-participation of water was discussed in terms of sterical hindrance that prevents nucleophilic attack of water to the acetoxonium ion (**Scheme 4**).[6]



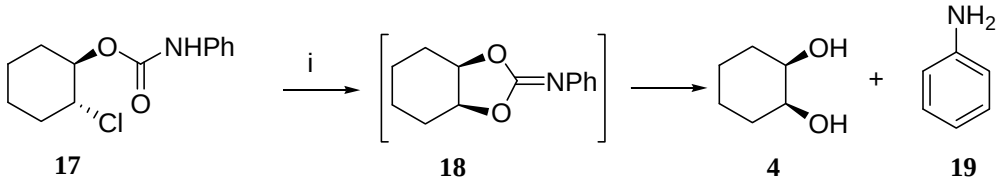
15 **16**

Scheme 4: Unprecedented Prevost reaction under Woodward condition

Since Prevost-Woodward reaction serves as a mild and efficient method to prepare diols, several modifications in the reagent system have been attempted. Several metal carboxylates like Cu, Bi, Hg (II) were employed as acetate sources and *N*-bromoacetamide, I_2, Br_2, *N*-bromosuccinamide were screened as halogen sources. Some of the modifications are briefly discussed below.

Fenton's approach (1970)[7]

Fenton *et al.* found that when *trans* 2-*N*-phenylurethane cyclohexyl chloride (**17**) was heated in aqueous ethanol for 70 h in a sealed tube, *cis*-1,2-cyclohexane diol (**4**) was formed in 95% *via* dioxane intermediate **18**. Aniline (**19**) was also separated as the by product (**Scheme 5**).

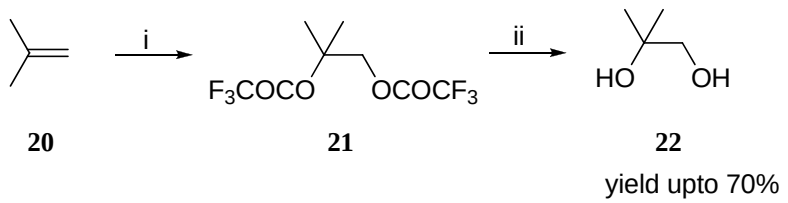


17 **18** **4** **19**

Scheme 5: i) aq. EtOH, 90 ^{o}C, sealed tube, 70 h, 95%.

Buddrus' approach (1973)[8]

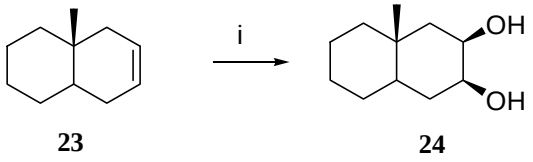
Iodine tris(trifluoroacete) was also found to oxidize olefins to diols. Thus, addition of olefin **20** to a solution of iodine tris(trifluoroacete) in pentane followed by hydrolysis resulted in the formation of *vic*-diol **22** in 50-70% yields *via* diacetate **21** (**Scheme 6**).



Scheme 6: i) $I(OCOCF_3)$, pentane, 25 ^oC; ii) K_2CO_3, MeOH, 25 ^oC.

Granger's approach (1976)[9]

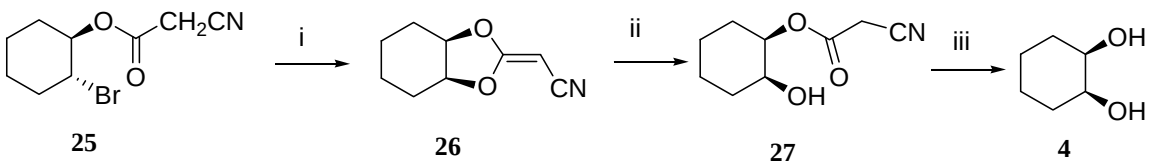
N-Bromoacetamide (NBA) had also been employed as the halogen source to obtain bromoacetoxy derivative. When deccalin derivative **23** was treated with *N*-bromoacetamide (NBA) and silver (I) benzoate in wet acetic acid produced *syn* diol derivatives, which on hydrolysis produced *cis*-diol **24** (**Scheme 7**).



Scheme 7: (i) a) NBS, $PhCO_2Ag$ (1 equiv.), AcOH, H_2O, 85 ºC; b) K_2CO_3, MeOH, 25 ^oC.

Corey's approach (1976)[10]

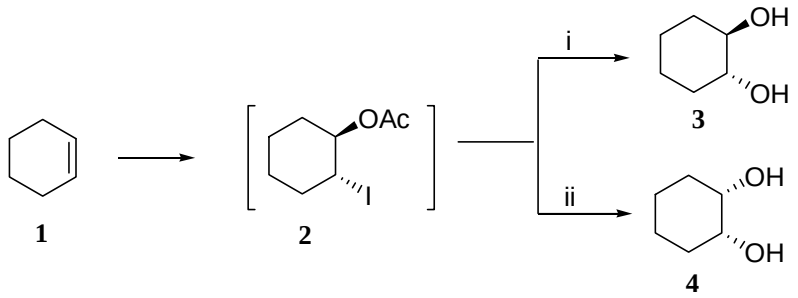
Corey *et al.* reported an efficient method for the synthesis of *syn* diols that involves cyano acetic ester as the intermediate. Accordingly, reaction of the cyanoacetate ester **25** with excess of NaH generated the corresponding enolate, which underwent intramolecular nucleophilic displacement to form cyanoketone acetal **26**. Hydrolysis using 1N HCl produced the mono cyanoacetate **27**, which upon alkaline ester hydrolysis afforded *cis* diol **4** (**Scheme 8**).



Scheme 8: i) NaH (excess), THF, 0 ^oC; ii) 1N HCl, 25 ^oC; iii) aq. KOH, 80 ^oC, 79%.

Trainor's approach (1992)[11]

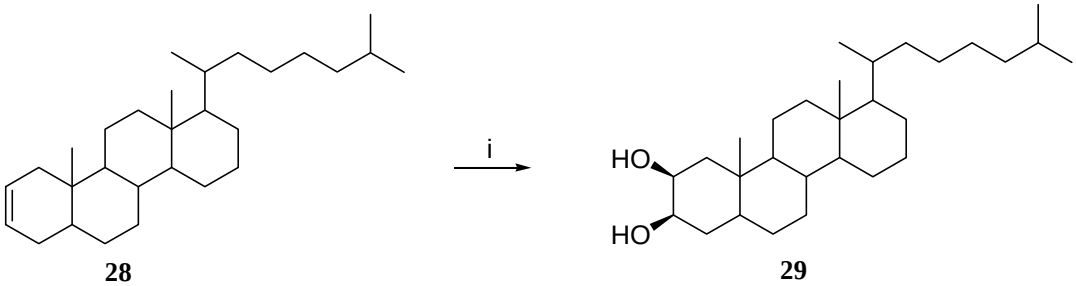
cis and *trans* Cyclohexane 1,2-diols (**4** & **3**) were prepared from cyclohexene (**1**) by reaction with I_2 and bismuth (III) acetate in wet and dry acetic acid respectively. Reaction using lesser amounts of $Bi(OAc)_3$ under dry conditions gave the intermediate *i.e trans* 2-iodocyclohexyl acetate (**2**) (**Scheme 9**).



Scheme 9: i) a) I_2, $Bi(OAc)_3$ (2 equiv.), AcOH, 85 ºC; b) K_2CO_3, MeOH, 25 ^oC. ii) a) I_2, $Bi(OAc)_3$ (1 equiv.), AcOH, H_2O, 85 ºC; b) K_2CO_3, MeOH, 25 ^oC.

Welzel's approach (2000)[12]

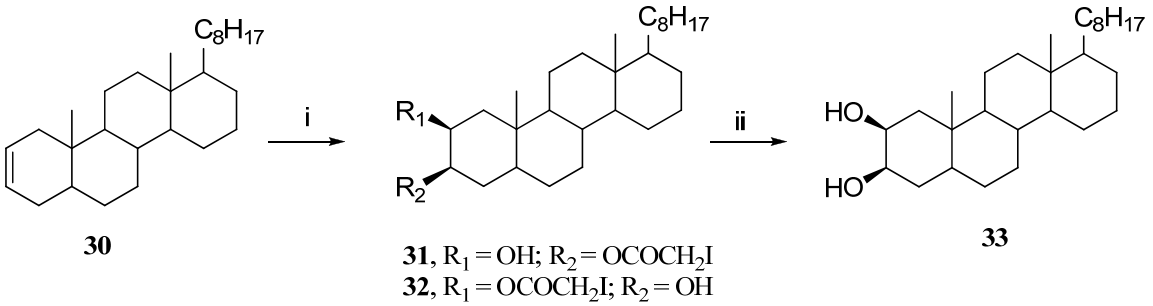
Welzel *et al.* replaced silver (I) benzoate or acetate with mercuric (II) acetate to get diol derivatives even in hindered cholestane. Cholestane **28** was treated with mercuric (II) acetate and iodine in wet acetic acid at 85 ^oC to get *syn* diol derivatives. The diol derivatives are further hydrolyzed under basic conditions to obtain the diol **29** (**Scheme 10**).



Scheme 10: i) a) I_2, $Hg(OAc)_2$ (1 equiv.), AcOH, H_2O, 85 ºC; b) aq. KOH, 50 ^oC.

Horiuch's approach (2006)[13]

Horiuch *et al.* used copper (II) acetate as a better alternative to silver (I) benzoate. The reaction of cholest-2-ene (**30**) with iodine and copper (II) acetate in acetic acid under refluxing conditions yielded diol derivatives **31** and **32** which upon hydrolysis furnished diol **33** (**Scheme 11**).



30

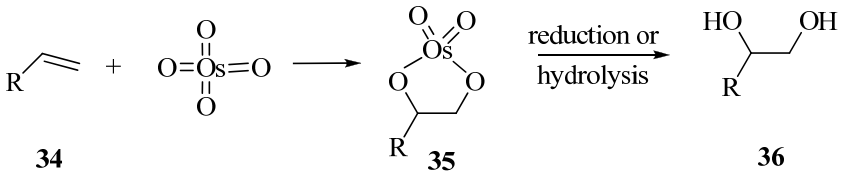
31, R_1 = OH; R_2 = $OCOCH_2I$
32, R_1 = $OCOCH_2I$; R_2 = OH

33

Scheme 11: i) a) I_2, $Cu(OAc)_2$ (1 equiv.), AcOH, H_2O, 85 ºC; ii) K_2CO_3, MeOH, 25 ºC.

3.1.2.2 Metal oxide addition to olefin

OsO_4 catalyzes the *cis*-dihydroxylation of alkenes by hydrogen peroxide or related sources of oxygen atoms in the presence of water. In terms of mechanism, OsO_4 adds to alkenes to afford cyclic osmate esters **35** which undergo hydrolysis to give the *vic* diol **36** (**Scheme 12**).[2c]



34 **35** **36**

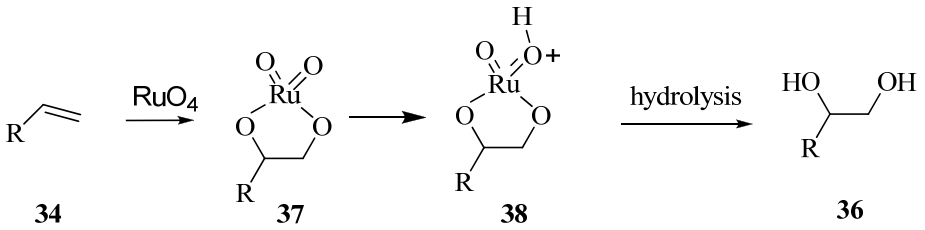
Scheme 12: OsO_4-catalyzed dihydroxylation of olefins

Lewis bases such as tertiary amines and pyridines were found to increase the rate of the reaction. This "ligand-acceleration" arises *via* the formation of adduct OsO_4-L, which

adds more rapidly to the alkene. If the amine is chiral, then the dihydroxylation can proceed with enantioselectivity (see Sharpless asymmetric dihydroxylation).

Since OsO_4 is toxic and expensive, it is used in catalytic amounts. The osmium catalyst is regenerated by oxidizing agents, such as H_2O_2, N-methylmorpholine N-oxide (NMO) and $K_3Fe(CN)_6$. These oxidizing reagents do not react with the alkenes on their own. Other sources of osmium tetroxide include potassium osmate(VI) dihydrate ($K_2OsO_4 \cdot 2H_2O$) and osmium (III) chloride hydrate ($OsCl_3.xH_2O$) which oxidize osmium (VI) to osmium (VIII) in the presence of above mentioned oxidants.

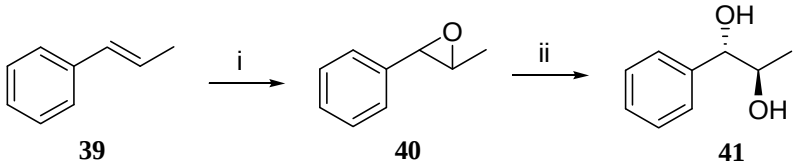
Despite its success, some problems still need to be solved. The oxidation is limited to electron-rich or mono-, di-, and in some cases, trisubstituted olefins. Furthermore, the osmium catalyst is toxic and very expensive. RuO_4, as a dihydroxylation catalyst, is most promising. In 1954, Djerassi introduced RuO_4 in organic chemistry. Since then, it has mainly been used for the degradation of unsaturated organic compounds. However, in ethyl acetate/acetonitrile/water a very fast dihydroxylation of olefins using 7mol % of RuO_4 was observed (**Scheme 13**). Longer reaction times resulted in the formation of fission products. Thus, treatment of olefin **34** with catalytic $RuCl_3$, $NaIO_4$ as reoxidant in ethyl acetate/acetonitrile/water solvent system in the presence of acid produced the corresponding diols **36** in excellent yields. The reaction proceeds *via* the cyclic ruthenium ester **37**.[2j]



Scheme 13: RuO_4-catalyzed dihydroxylation of olefins

3.1.2.3 Epoxide opening with oxygen nucleophile

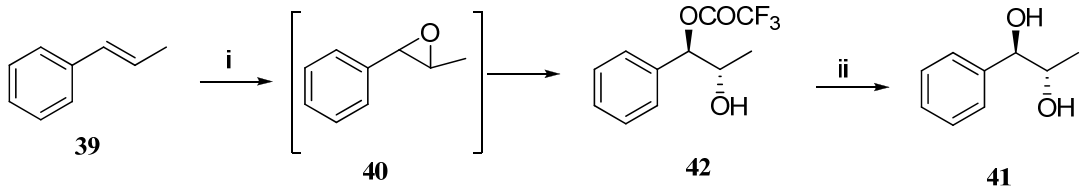
One of the simple and efficient methods to afford *trans* diols involves the epoxidation of olefin followed by regioselective ring opening of epoxides in the presence of Lewis acids such as $FeCl_3$, $BF_3.OEt_2$, $SnCl_4$ (**Scheme 14**). Recently, organic molecules like CBr_4 were also found to promote epoxide opening with water to afford *trans* diol.[4a]



Scheme 14: i) *m*CPBA, $CHCl_3$, 25 ^oC; ii) Lewis acid, H_2O.

Freeman's approach (1954)[14]

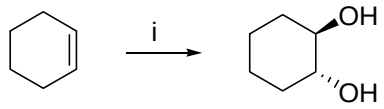
Freeman *et al.* observed that when peroxy trifluoroacetic acid (CF_3CO_3H) was used for the epoxidation of olefin **39**, the epoxide was opened with *in situ* liberated trifluoroacetic acid to produce acetoxy alcohol **42**. Further, hydrolysis of **42** under basic condition produced *trans*- diol **41** (**Scheme 15**).



Scheme 15: i) CF_3CO_3H, $CHCl_3$, 25 ^oC; ii) K_2CO_3, MeOH.

Stock's approach (1960)[15]

Olefins were directly converted to *trans* diols with excellent yields by treating with a mixture of potassium peroxymonosulfate ($KHSO_5$), potassium hydrogen sulfate ($KHSO_4$) and potassium sulfate (K_2SO_4). This reaction proceeds through epoxidation followed by opening with water under acidic condition (**Scheme 16**).



1 **3**

Scheme 16: i) $KHSO_5$. $KHSO_4$. K_2SO_4, H_2O, 25 ^oC.

3.1.3. Present work

3.1.3.1 Objective

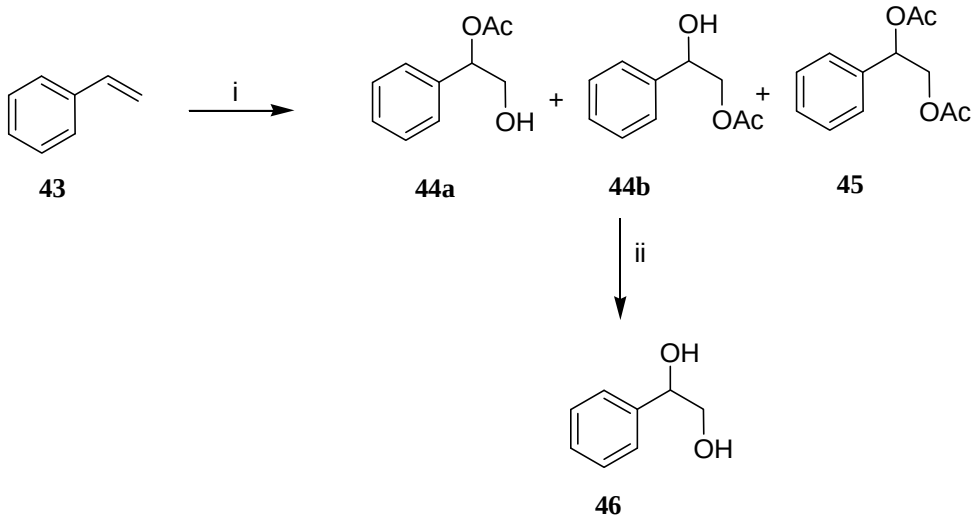
As can be seen from the above discussion, several methods exit in the literature for the preparation of *vic* diols. Although Prevost-Woodward reaction promises excellent yields, it suffers from drawbacks such as use of expensive metal carboxylates, stoichiometric amount of molecular halogen, and formation of large amount of organic and inorganic wastes. The OsO_4-catalyzed dihydroxylation is expensive including its toxicity and volatility while epoxide opening with water involves two purification steps. Hence, a new alternative, reagent system for the Prevost-Woodward, which produces 1,2-diols is desirable.

3.1.4 Results and Discussion

In our lab, we have quite recently reported that the $NaIO_4$/LiBr combination oxidizes toluene under acidic conditions to benzyl acetate in excellent yield.[16] During the study on mechanistic investigation, we further observed that the reaction proceeded through benzyl bromide and that its rate of solvolysis was enhanced by the addition of a catalytic amount

of $NaIO_4$. Surprisingly, when (1,2-dibromoethyl)benzene was subjected to this solvolysis, bromides at benzylic as well as homobenzylic positions underwent solvolysis to give regioisomers of diol derivatives **44a, 44b** and **45** in excellent yield.

Encouraged by this result, we envisioned to prepare styrene diol directly from styrene (**43**) using a catalytic amount of LiBr (20 mol %) and $NaIO_4$ (30 mol %) in AcOH at 95 °C and indeed obtained regioisomers of styrene mono- (**44a**, **44b**) and diacetates (**45**) with the ratio 87:5 in 92% combined yield. This mixture was subjected to basic hydrolysis (K_2CO_3, MeOH, 25 °C) without separation to furnish 1-phenyl-1,2-ethanediol (**46**) in 87% yield (**Scheme 16**). Control experiments indicated that no dihydroxylation occurred in the absence of either LiBr or $NaIO_4$.



Scheme 16: (i) styrene (3 mmol), $NaIO_4$ (30 mol %), LiBr (20 mol %), AcOH (5 mL), 95 °C, 18 h; (ii) K_2CO_3 (4.5 mmol), MeOH (15 mL), 25 °C, 24 h.

Among other oxidants screened (entries 8-14), KIO_3, $Na_2S_2O_8$, and $PhI(OAc)_2$ have exhibited comparable activity as that of $NaIO_4$. Lowering the amount of LiBr below 20 mol % led to a sharp decline in the yield of the diol (**entry 4**, **Table 1**). We determined that 30 mol % of $NaIO_4$, acting both as oxidant and as a source of water (thus providing

"wet" Woodward condition), is sufficient to convert 1 equiv. of styrene (**43**) to the corresponding diol **46**.

Table 1: Effect of oxidant and halogen sources on catalytic dihydroxylation of styrene[a]

entry	oxidant[b]	halogen source[c]	yield of diol (%)[d]
1	$NaIO_4$	NaCl	22
2	$NaIO_4$	KI	65
3	$NaIO_4$	NaBr	84
4	$NaIO_4$	LiBr	87 (53)[f]
5	$NaIO_4$	NBS	79
6	$NaIO_4$	Br_2	82
7	$NaIO_4$	$PyHBr_3$	78
8	KIO_3	LiBr	84
9	V_2O_5	LiBr	42
10	WO_3	LiBr	36
11	$Na_2S_2O_8$	LiBr	85
12	oxone	LiBr	77
13	*m*CPBA[e]	LiBr	trace
14	$PhI(OAc)_2$	LiBr	85

[a] Reaction conditions: (i) styrene (3 mmol), oxidant (30 mol % to 1 equiv.), halogen source (20 mol %), AcOH (5 mL), 95 °C, 18 h; (ii) K_2CO_3 (4.5 mmol), MeOH (15 mL), 25 °C, 24 h; [b] $NaIO_4$ (30 mol %); KIO_3 or V_2O_5 or WO_3 or $Na_2S_2O_8$ (50 mol %); oxone or *m*CPBA or $PhI(OAc)_2$ (1 equiv.); [c] Halogen source (20 mol %); [d] Isolated yield; [e] *m*-Chloroperbenzoic acid; [f] 10 mol % LiBr employed.

Several alkenes (aliphatic, styrenic, allylic, disubstituted alkenes, *α,β*-unsaturated alkenes, etc.) with electron-donating and -withdrawing groups underwent dihydroxylation (**Table 2**) and produced the corresponding diols in excellent yields with *syn* diastereoselectivity. All the prepared diols were thoroughly characterized by comparing the melting points, IR, ^{1}H NMR and ^{13}C NMR spectra.

For example, the ^{1}H NMR spectrum of **48a** showed signals at δ 4.57 and 3.47 corresponding to the methine (-C**H**-OH) and methylene (-C**H**$_2$OH) protons respectively,

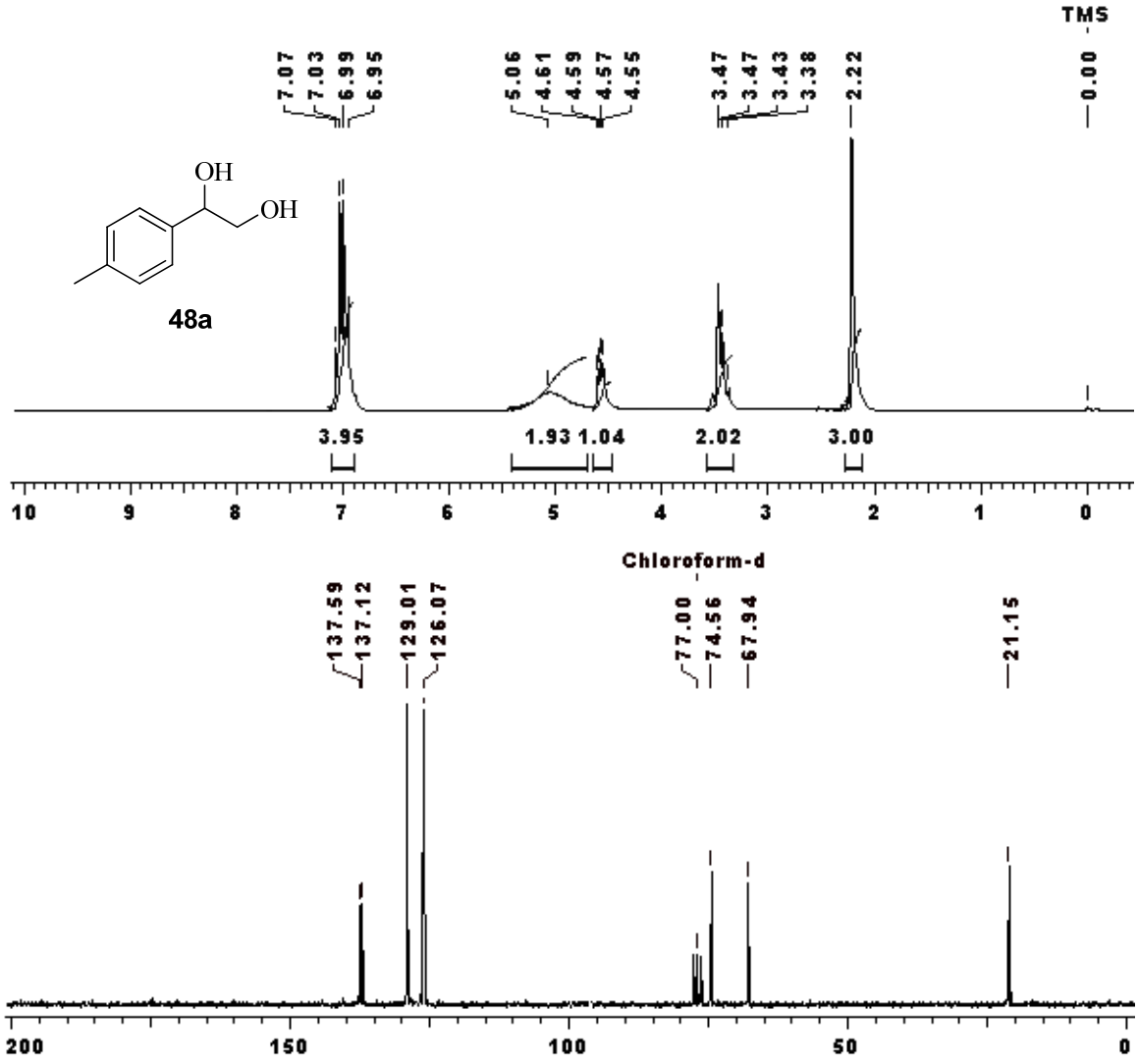
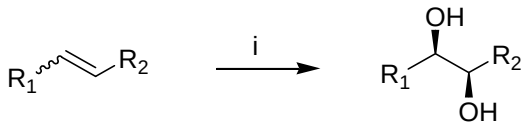


Fig. 1: ^{1}H and ^{13}C NMR spectra of **48a**

Table 2: LiBr-Catalyzed Dihydroxylation of Olefins Using $NaIO_4$[a]



47a- t **48a-t**

no.	olefin (**47a-t**)	product (**48a-t**)	dr[b] *syn:anti*	diol yield (%)[c]
1	4-methylstyrene	**48a**		89
2	4-bromostyrene	**48b**		90
3	4-acetoxystyrene	**48c**		78[d]
4	*β* - methylstyrene	**48d**	88 : 12	84
5	*cis*-stilbene	**48e**	99 : 1	87[j]
6	*trans*-stilbene	**48f**	100 : 0	79
7	indene	**48g**	98 : 2	87
8	1,2-dihydronaphthalene	**48h**	98 : 2	79
9	cinnamyl alcohol	**48i**	85 :15[i]	77
10	allyl phenyl ether	**48j**		80
11	methyl *trans*-cinnamate	**48k**	80 : 20	65[e]
12	4-Cl-α-methylstyrene	**48l**		82[g]
13	vinylcyclohexane	**48m**		85
14	3-buten-1-ol	**48n**		91[d]
15	*cis*-2-butene-1,4-diol	**48o**	92 : 8	83[d,j]
16	allyl alcohol	**48p**		86[d]
17	allyl bromide	**48q**		79[d,h]
18	cyclohexene	**48r**	90 : 10	86[f]
19	cyclooctene	**48s**	85 : 15	83
20	1-octene	**48t**		84

[a] Reactions were carried out following the experimental procedure; [b] Diastereomeric ratios were determined from ^{1}H NMR and GC; [c] Isolated yield after chromatographic purification; [d] Product was isolated as acetate after acetylation (Ac_2O, py); [e] Time 36 h; [f] At 80 °C for 36 h; [g] Hydrolyzed using KOH, MeOH; [h] 50 mol % of $NaIO_4$ employed; [i] 1 equiv of water was used (diastereoselectivity in the absence of water was *syn:anti*) 77:23); [j] Corresponding *syn*-diol was formed.

while the signals for the methyl protons appeared at δ 2.2 as singlet (**Fig. 1**). Its ^{13}C NMR displayed signals at δ 74.6 and 67.9 for the methine carbons (-**C**H-OH). The *syn* selectivity is controlled by water, formed *in situ* from $NaIO_4$ and AcOH, which attacks 1,3-dioxolon-2-ylium ion (**C**) at C-2 position (**Scheme 18**).

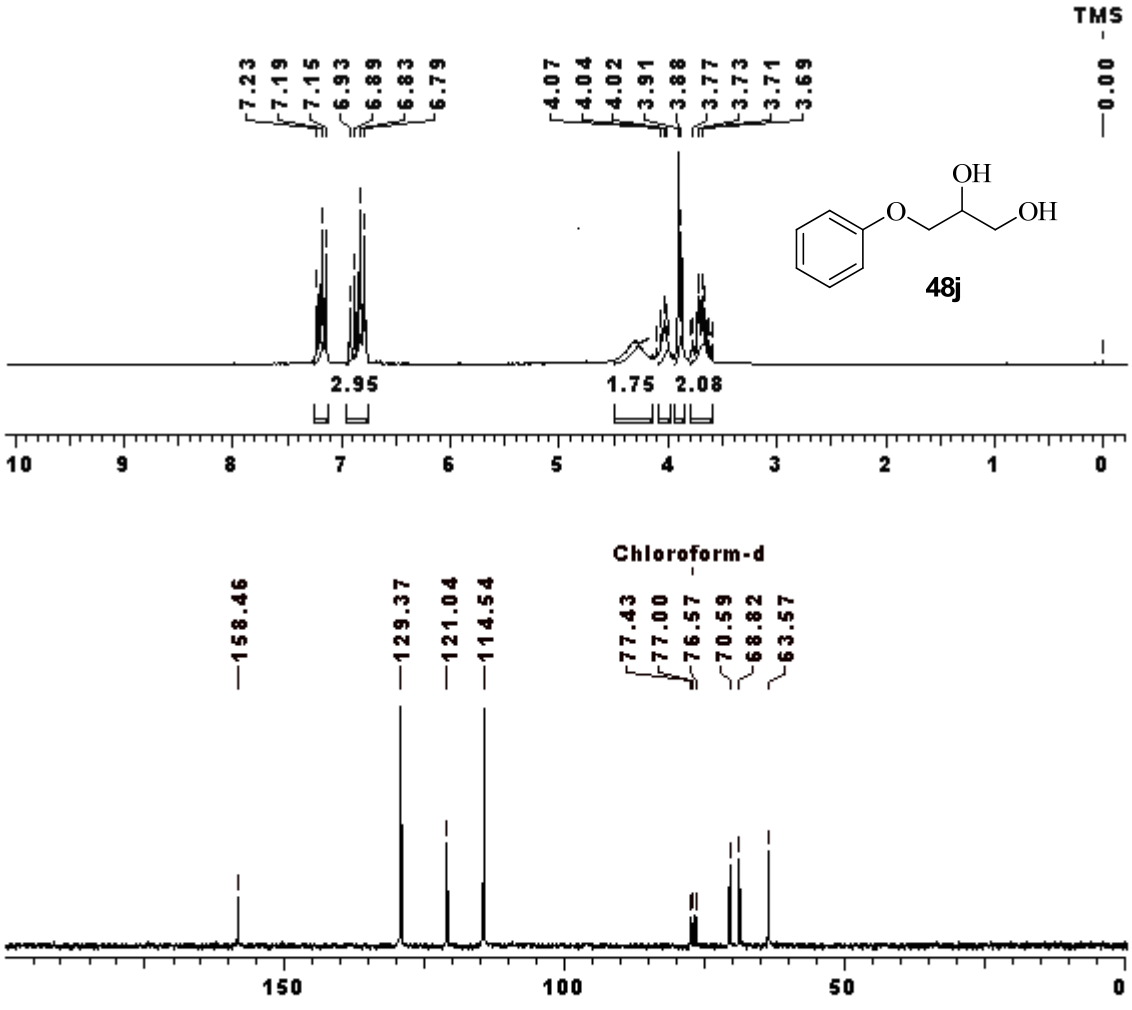
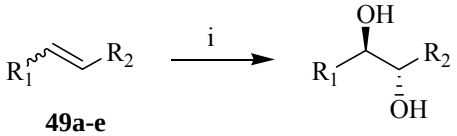


Fig. 2: ^{1}H and ^{13}C NMR spectra of **48j**

As expected, allyl bromide gave the triol due to successive solvolysis of 1,3-dibromide. Lower yield in the case of α, β-unsaturated ester may be ascribed to the slower rate of bromoacetoxylation. In the case of allyl alcohol, 3-butene-1-ol, cinnamyl alcohol and 4-acetoxystyrene acylation was carried out instead of basic hydrolysis to get corresponding

triacetates. In another example, the ^{1}H NMR spectrum of **48j** showed signals at δ 3.89 and 3.73 due to the methylene protons (PhOC**H$_2$**- and –C**H$_2$**OH) whereas the signals for the methine protons (-C**H**OH) appeared at δ 4.02. The ^{13}C NMR spectrum of **48j** displayed typical signals at 63.6, 68.8 and 70.6 for the aliphatic carbons (**C**-O) with oxygen substituents (**Fig. 2**). However, attempts to obtain *anti* diols, by removing water formed *in situ* using either molecular sieves (4 Å) or anhydrous $MgSO_4$ were not successful. Interestingly, *anti* diols were indeed obtained when $PhI(OAc)_2$ was employed as the oxidant in stoichiometric amounts under the same reaction condition. Since no water is formed, acetic acid acts as the nucleophile and opens up the intermediate **C** at C-4 position to result in *trans*-diastereoselectivity (**Scheme 18**).

Table 3: LiBr-Catalyzed dihydroxylation of olefins using $NaIO_4$[a]



49a-e **50a-e**

No.	olefin (**4**)	product (**6**)	yield of diol (%)[b]	dr[c] (*anti:syn*)
1	indene	**50a**	79	100 : 0
2	*cis*-stilbene	**50b**	84	100 : 0[d]
3	*trans*-stilbene	**50c**	87	100 : 0
4	cyclohexene	**50d**	82	77 : 23
5	*β*-methylstyrene	**50e**	85	33 : 67

[a] Reactions were carried out following the general procedurebut with 1 equiv of $PhI(OAc)_2$; [b] Isolated yield after chromatographic purification; [c] Diastereomeric ratios were determined from GC; [d] The corresponding *anti*-diol was formed.

The lower selectivity observed in the case of cyclohexene and α-methylstyrene can be explained in terms of S_N2 displacement of bromide in **B** by LiOAc (**Table 3**).

All the anti diols were systematically characterized from their ^{1}H, ^{13}C NMR spectra and comparing the melting points.

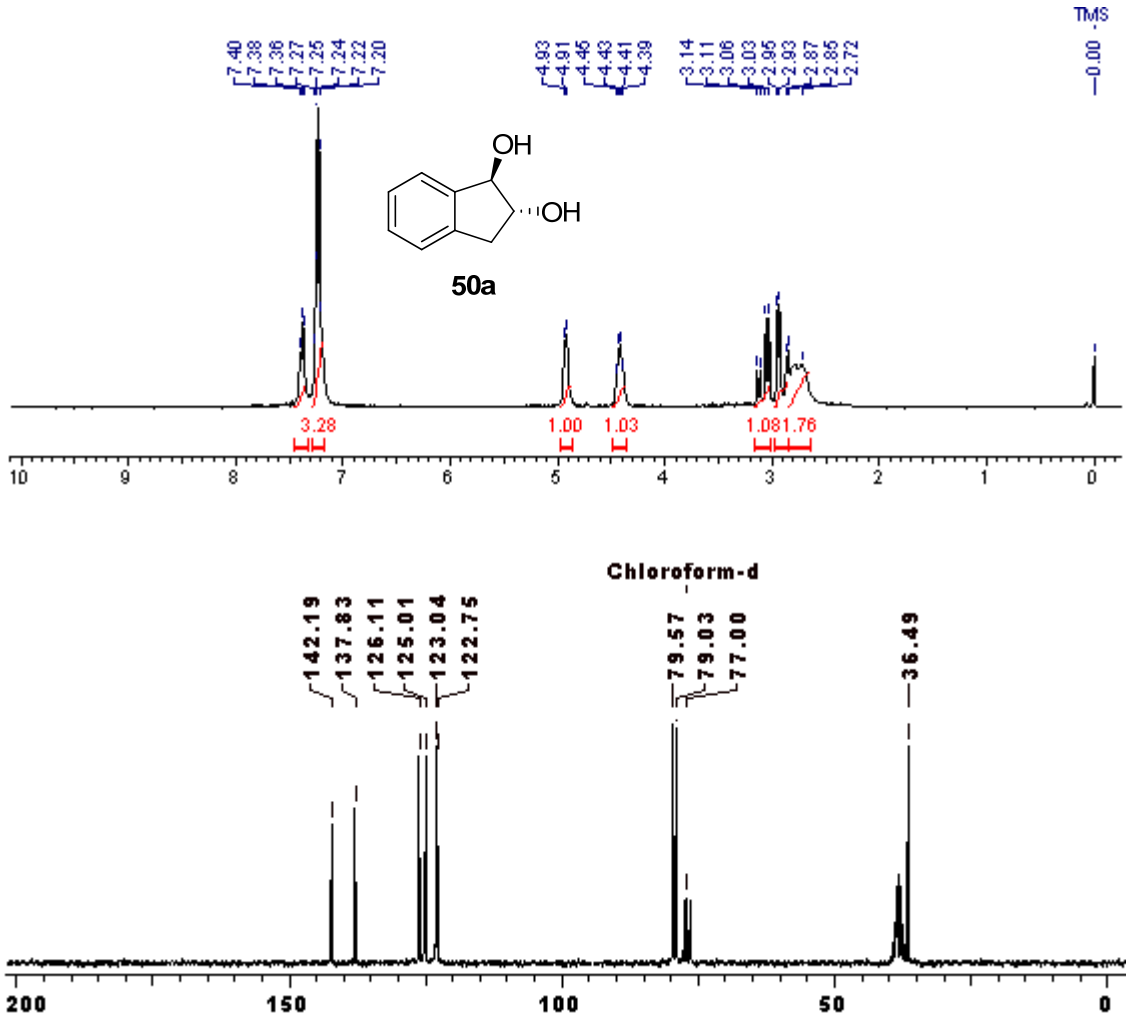


Fig. 3: ^{1}H and ^{13}C NMR spectra of **50a**

For example, the ^{1}H NMR spectrum of **50a** displayed signals at δ 4.91(d) and 4.43(m) corresponding to the methine protons (-C**H**-OH). It also indicated that the bezylic protons (Ar-CH_2-) remained unaffected displaying signals at δ 3.08 and 2.87(dd). Its ^{13}C NMR

spectrum exhibited signals at δ 79.7 and 79.0 due to the methine carbons (-**C**H-OH) whereas the signal for benzylic methylene carbon (Ar-**C**H_2-) appeared at δ 36.5 (**Fig. 3**).

3.1.6. Mechanism

Our earlier studies[16] had shown that 1 equiv. of $NaIO_4$ was sufficient to oxidize 8 equiv of Br^- ions, as can be seen from **Scheme 17**..

$$8\ LiBr + NaIO_4 + 8H^+ \longrightarrow 4\ Br_2 + 4H_2O$$

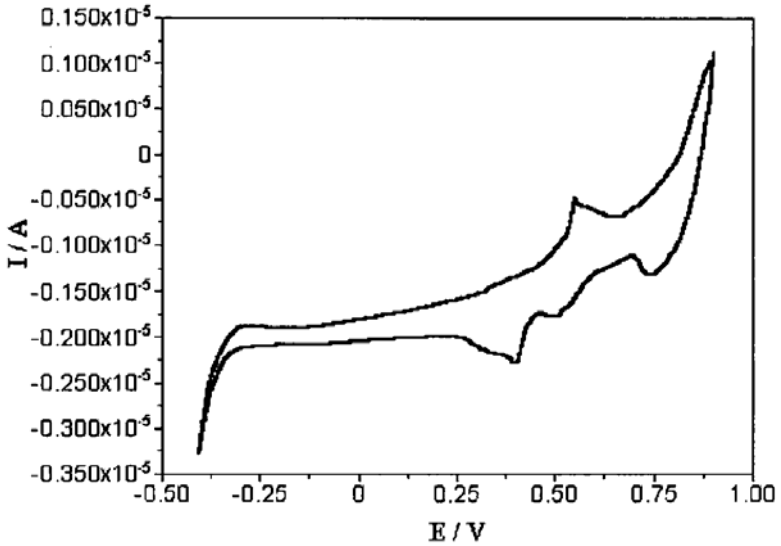
$$2\ Br^- \longrightarrow Br_2 + 2e$$

$$IO_4^- + 2H + 2e^- \longrightarrow IO_3^- + H_2O$$

$$IO_3^- + 6H + 6e^- \longrightarrow I^- + 3H_2O$$

$$I_2 + 2\ e \xrightarrow{\text{fast}} 2I$$

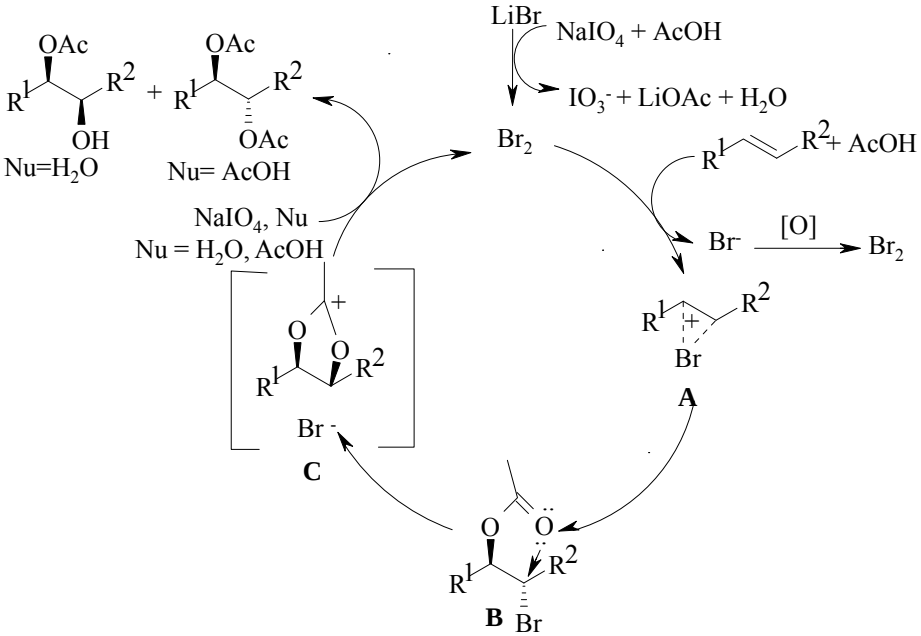
Scheme 17: Steps involving in LiBr oxidation with $NaIO_4$



Voltage vs. Ag/AgCl reference

Fig. 4: Cyclic voltagram of LiBr oxidation with $NaIO_4$

The cyclic voltagram (**Fig. 4**) of LiBr oxidation with $NaIO_4$ shows one oxidation peak at Ep_a = 0.565 V and three reduction peaks at Ep_c = 0.720 V, 0.490 V and 0.390 V. The comparison of this value with the literature values revealed that the reaction involves four steps. Hence, only 30 mol % of $NaIO_4$ was required to bring about 100% conversion. From the above facts and the evidence provided by the cyclic voltammetry study, the proposed catalytic cycle for the LiBr catalyzed dihydroxylation is shown in **Scheme 18**. The halogens (X = I, Br, Cl), generated *in situ* from alkali metal halides by oxidation with $NaIO_4$ or $PhI(OAc)_2$ rapidly undergo bromoacetoxylation with alkenes *via* bromonium ion **A** to produce *trans*-1,2-bromoacetate derivative **B**, which was isolated and characterized. The intermediate species **C**, formed from **B** in the presence of $NaIO_4$, assisted anchimerically by the acetate group, is opened either by water to give *cis*-hydroxy acetate or by acetic acid to give the *trans* diacetate with concomitant liberation of Br_2 (**Scheme 18**).



Scheme 18: Proposed mechanistic pathway

Only organic halides with acetyl groups at the 2-positions were oxidized by $NaIO_4$ or $PhI(OAc)_2$. Octyl bromide failed to undergo oxidation under the same reaction condition. Hence, we believe that neighboring group participation by the acetate group makes the C-Br bond more polar and thus facilitating the oxidation process.

3.1.7. Conclusion

Here, we have developed, for the first time, a new, practical and "metal-free" procedure for the dihydroxylation of alkenes catalyzed by LiBr using commercially available $NaIO_4$ or $PhI(OAc)_2$ as oxidants in acetic acid to produce *syn* as well as *anti* diols respectively. The simplicity, environmental friendliness and readily accessible reagents make this system superior to other expensive and toxic Tl(I), Ag(I), Bi(III) and Hg(II) reagents.

3.1.8. Experimental section

General experimental procedure:

A mixture of olefin (3 mmol), $NaIO_4$ (30 mol%), LiBr (20 mol%) was taken in 25 mL round bottomed flask and glacial acetic acid (5 mL) was added. The reaction mixture was heated at 95 °C (using oil bath) for 18 h. The light yellow colored reaction mixture became purple in color after the completion of the reaction. The reaction mixture was then extracted with ethyl acetate (30 mL x 3) and the combined organic phase was washed with saturated aq. sodium thiosulfate solution, water and aq. $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was subjected to basic hydrolysis without purification.

The crude product as obtained above was stirred with K_2CO_3 (1.5 equiv.) in methanol (20 mL) at 25 °C for 24 h. After completion of the reaction, methanol was removed under

reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with water and brine. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude diol, which was purified by column chromatography packed with silica gel using petroleum ether: ethyl acetate (7:3) as eluent to afford pure diol.

General procedure for the acetylation of polyols: (48d and 48o-r)

To the crude polyol was added acetic anhydride (1 mL) and pyridine (3 mL) and stirred at 90 °C for 10 h. After completion of the reaction it was extracted with ethyl acetate and thoroughly washed with water and brine successively. Then the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude poly acetate, which was purified by column chromatography packed with silica gel using petroleum ether: ethyl acetate (9:1) as eluents to afford pure acetate derivatives.

1-Phenyl-1,2-ethanediol (46)

Yield: 87%; **mp**: 64-65 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.57 (m, 2H), 4.51 (brs, 2H), 4.69 (dd, *J* = 3.8, 8.2 Hz, 1H), 7.24 (s, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 59.0, 73.3, 125.5, 126.8, 126.9, 140.9; **IR** ($CHCl_3$, cm^{-1}): 3412, 2942, 2896, 1324, 1156, 992; Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.31. Found: C, 69.53; H, 7.29%.

1-(4-Methylphenyl)-1, 2-ethanediol (48a):

Yield: 89%; **mp**: 76-77 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.46 (m, 2H), 4.58 (dd, *J* = 4.1, 8.0 Hz, 1H), 5.05 (brs, 2H), 6.97 (d, *J* = 7.9, 2H), 7.05 (d, *J* = 8.1, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.1, 67.9, 74.5, 126.1, 129.0, 137.1, 137.6; **IR** ($CHCl_3$,

cm^{-1}): 3423, 2931, 2897, 1329, 1141, 1002; Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.96. Found: C, 70.96; H, 8.09%.

1-(4-Bromophenyl)-1, 2-ethanediol (48b):

Yield: 90%; **mp**: 81 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$ and DMSO-d_6): δ 3.60 (m, 2H), 4.72 (dd, *J* = 3.8, 8.2 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$ and DMSO-d_6): δ 82.6, 88.5, 135.2, 143.8, 146.0, 157.9; **IR** ($CHCl_3$, cm^{-1}): 3323, 2935, 2891, 1299, 1155, 982; Anal. Calcd for $C_8H_9O_2Br$: C, 44.27; H, 4.19; Br, 36.81. Found: C, 44.26; H, 4.16; Br, 36.79%.

1-(4-Acetoxyphenyl)-1, 2- diacetoxyethane (48c)

Yield: 78%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.10 (s, 3H), 2.28 (s, 3H) 4.27 (m, 2H), 6.0 (dd, *J* = 4.0, 8.0 Hz); **^{13}C-NMR** (50 MHz, $CDCl_3$): 19.0, 19.3, 64.3, 71.1, 120.3, 126.4, 132.6, 149.3, 167.3, 168.1, 168.7; **IR** ($CHCl_3$, cm^{-1}): 3383, 2912, 2895, 1745, 1496, 1298, 1150, 971; Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.94; Found: C, 60.58; H, 5.79%.

1-Phenyl-1, 2-propane-*cis*-diol (48d):

Yield: 84%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.3 Hz, 3H), 3.74 (m, 1H), 4.10 (brs, 2H), 4.2 (d, *J* = 7.9 Hz, 1H), 7.25 (s, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.8, 72.1, 79.5, 127.1, 127.9, 128.3, 141.3; **IR** ($CHCl_3$, cm^{-1}): 3392, 2922, 2897, 1496, 1352, 1150; Anal. Calcd for $C_9H_{11}O_2$: C, 71.50; H, 7.33. Found: C, 71.32; H, 7.41%.

***meso*-1,2-Diphenyl-1, 2-ethanediol (48e & 50c)**

Yield: 87%; **mp**: 98 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.04 (s, 2H), 4.61 (s, 2H), 7.050 (m, 4H), 7.19 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 78.6, 126.9, 127.3, 140.7; **IR** ($CHCl_3$, cm^{-1}): 3392, 2922, 2912, 1456, 1272, 1150; Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found: C, 78.40; H, 6.60%.

1,2-Diphenyl-1, 2-ethanediol (48f & 50b)

Yield: 79%; **mp**: 116-117 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.79 (brs, 2H), 4.61 (s, 2H), 7.06 (m, 4H), 7.21 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$ and DMSO-d_6): δ 78.35, 126.61, 127.02, 140.47; **IR** ($CHCl_3$, cm^{-1}): 3392, 2922, 2912, 1456, 1372, 1150; Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found: C, 78.56; H, 6.71%.

Indane-1, 2-*cis*-diol (48g)

Yield: 87%; **mp**: 108-109 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.72 (br, s, 1H), 2.79 (brs, 1H), 2.90 (dd, J = 3.6, 16.42 Hz, 1H), 3.08 (dd, J = 5.7, 16.3 Hz, 1H), 4.41 (m, 1H), 4.91 (d, J = 4.1 Hz, 1H), 7.24 (m, 3H), 7.38 (m, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6 and $CDCl_3$): δ 38.5, 73.0, 75.3, 124.9, 126.4, 127.8, 140.7, 144.0; **IR** ($CHCl_3$, cm^{-1}): 3412, 2942, 2896, 1324, 1156, 992; Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.73. Found: C, 71.79; H, 6.65%.

Tetrahydronaphthalene 1, 2-*cis*-diol (48h)

Yield: 79%; **mp**: 100-102 °C; **^{1}H-NMR** (200 MHz, MeOH- d_4): δ 1.85 (m, 1H), 2.13 (m, 1H), 2.90 (m, 2H,), 3.82 (m, 1H), 4.50 (d, J = 7.1 Hz, 1H,), 7.13 (m, 3H), 7.55 (m, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6 and $CDCl_3$): δ 38.5, 73.0, 75.2, 124.9, 126.4, 127.7, 140.7, 144.0; **IR** ($CHCl_3$, cm^{-1}): 3372, 2941, 2893, 1323, 1151, 992; Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.36. Found: C, 73.24; H, 7.33%.

1-(Phenyl)-1, 2, 3-triacetoxy propane (48i)

Yield: 77%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.05 (s, 6H), 2.06 (s, 3H), 3.76 (dd, *J* = 4.2, 12.0 Hz, 1H), 4.25 (dd, *J* = 4.0, 12.1 Hz, 1H), 5.4 (m, 1H), 5.94 (d, *J* = 7.9 Hz, 1H), 7.34 (s, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.5, 20.6, 20.8, 62.0, 72.2, 73.7, 127.1, 128.6, 128.8**,** 169. 8, 170.1, 170.8 136.4; **IR** ($CHCl_3$, cm^{-1}): 2912, 2895, 1745, 1496, 1213, 1150, 971; Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.35; H, 6.01%.

3-(Phenoxy)-1, 2-propane diol (48j)

Yield: 80%; **mp**: 50-52 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.70 (m, 2H), 3.90 (d, *J* = 5.3 Hz, 2H), 4.05 (m, 1H), 4.31 (brs 2H), 6.85 (m, 3H), 7.19 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 63.6, 68.8, 70.6, 114.5, 121.0, 129.3, 158.5; **IR** ($CHCl_3$, cm^{-1}): 3423, 2931, 2897, 2132, 1329, 1141, 1002; Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.21. Found: C, 64.20; H, 7.09%.

3-Phenyl-3-acetoxy-2-hydroxy methyl propionate (48k)

Yield: 65%; gum; **^{1}H-NMR** (200Hz, $CDCl_3$): δ 2.10 (s, 3H), 3.77 (s, 3H), 4.35 (d, *J* = 2.6 Hz, 1H), 6.03 (d, *J* = 2.9 Hz, 1H), 7.33 (m, 5H); **^{13}C-NMR** (50Hz, $CDCl_3$): δ 20.7, 52.6, 73.5, 75.5, 126.2, 127.0, 128.4, 136.4, 169.4, 172.3; **IR** ($CHCl_3$, cm^{-1}): 3372, 2912, 2895, 1745,1738, 1496, 1312, 1213, 1150, 975; Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.49; H, 5.92. Found: C, 60.31; H, 5.77%.

2-(4-Chlorophenyl)-propane-1, 2-diol (48l)

Yield: 82%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 3H), 2.69 (brs, 1H), 3.07 (brs, 1H), 3.42 (dd, *J* = 1.4, 11.0 Hz, 1H) 3.66 (dd, *J* = 1.8, 11.8 Hz, 1H), 3.66 (d, *J* = 11.2 Hz),

7.3 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 36.2, 80.7, 84.7, 106.4, 137.0, 138.43, 142.8, 154.5; **IR** ($CHCl_3$, cm^{-1}): 3332, 2932, 2893, 1393, 1299, 1155, 981; Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.91; H, 5.90; Cl, 18.99. Found: C, 57.98; H, 5.81; Cl, 18.91%.

1-Cyclohexyl-1, 2-ethane diol (48m)

Yield: 85%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.91-1.45 (m, 6H); 1.59-1.87, (m, 5H); 3.27 (brs, 2H), 3.33-3.51 (m, 2H); 3.64 (dd, *J* = 2.0, 10.3 Hz, 1H). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 26.1, 26.4, 28.6, 29.0, 40.7, 64.6, 76.3; Anal. Calcd for $C_8H_{16}O_2$: C, 66.61; H, 11.18. Found: C, 66.78; H, 11.29%.

1, 2, 4-Triacetoxybutane (48n)

Yield: 91%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.94 (m, 2H), 2.05 (s, 3H), 2.07 (s, 6H), 4.09 (m, 3H), 4.28 (dd, *J* = 3.5, 11.5 Hz, 1H), 5.17 (m, 1H) ; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.5, 20.7, 29.8, 60.0, 64.6, 68.4, 169.9, 170.2, 170.4; **IR** ($CHCl_3$, cm^{-1}): 2912, 2895, 1745, 1496, 1150, 971; Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.66; H, 6.93%.

1, 2, 3, 4-Tetraacetoxybutane (48o)

Yield: 83%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.07-2.11 (m, 9H), 2.13 (s, 3H), 4.21 (m, 2H), 4.32 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.2, 20.36, 2.2, 65.0, 65.3, 68.6, 169.1, 169.3, 169.4, 169.6; **IR** ($CHCl_3$, cm^{-1}): 2911, 2892, 2868, 1745, 1496, 1324, 1210, 1150, 971; Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found C, 49.78; H, 6.14%.

1, 2, 3-Triacetoxy propane (48p & 48q)

Yield: (48q = 86; 48r = 79 %); gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.07 (s, 6H), 2.09 (s, 3H), 4.13 (dd, *J* = 6.0, 10.0 Hz, 2H) 4.28 (dd, *J* = 4.0, 12.0 Hz, 2H), 5.19 (m, 1H); **^{13}C- NMR** (50 MHz, $CDCl_3$): δ 20.0, 20.3, 61.7, 68.6, 169.2, 169.6; **IR** ($CHCl_3$, cm^{-1}): 2912, 2896, 2867, 1743, 1495, 1323, 1213, 1158, 971, 891; Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.46. Found: C, 49.69; H, 6.32%.

Cyclohexane-1, 2-*cis*-diol (48r)

Yield: 86%; **mp**: 92-93 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (m, 2H), 1.61 (m, 6H), 3.73 (m, 2H), 4.05 (brs, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.5, 29.7, 70.6; **IR** ($CHCl_3$, cm^{-1}): 3343, 2992, 2918, 2896, 2867, 1495, 1323, 1213; Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found C, 61.92; H, 10.36%.

Cyclooctane-1, 2-*cis*-diol (48s)

Yield: 83%; **mp**: 75 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.52-1.91 (m, 14H), 2.76 (brs, 2H), 3.87 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.7, 26.3, 29.9, 72.9; **IR** ($CHCl_3$, cm^{-1}): 3321, 2985, 2918, 2896, 1463, 1323, 1213, 1120; Anal. Calcd for $C_8H_{16}O_2$: C, 66.62; H, 11.18. Found: C, 66.78; H, 11.03%.

***n*-Oct-1, 2-diol (48t)**

Yield: 84%; **mp**: 30 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.89 (m, 3H), 1.25-1.41 (m, 10H), 3.02 (brs, 2H), 3.39 (m, 1H), 3.62 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.5, 25.6, 29.4, 31.8, 33.0, 66.5, 72.2; **IR** ($CHCl_3$, cm^{-1}): 3323, 2981, 2912, 2893, 1464, 1324, 1213, 1120, 993; Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.40. Found: C, 65.78; H, 12.31%.

Indane-1, 2- *cis*-diol (50a)

Yield: 79%; **mp**: 182-183 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.76 (dd, *J* = 8.1, 15.4 Hz, 1H), 3.17 (dd, *J* = 7.4, 15.4 Hz, 1H), 4.28 (m, 1H), 4.92 (d, *J* = 6.0 Hz, 1H), 7.20 (m, 3H), 7.36 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ and DMSO-d_6): δ 36.4, 79.0, 79.5, 122.7, 123.0, 125.0, 126.1, 137.8, 142.1; **IR** ($CHCl_3$, cm^{-1}): 3412, 2942, 2896, 1324, 1156, 992; Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.73. Found: C, 71.82; H, 6.78%.

Section I

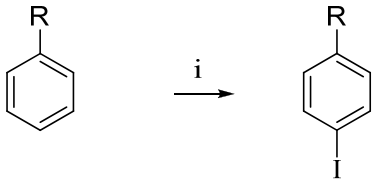
$NaIO_4$/KI/NaCl: A new reagent system for iodination of activated aromatics through *in situ* generation of iodine monochloride

3.2.1 Introduction

Aromatic iodo compounds are important intermediates for the synthesis of various pharmaceutical and bioactive compounds.[17] They are also useful in metal-catalyzed cross coupling reactions, such as Heck, Stille and Negishi reactions, which are utilized in C–C and C–N bond formation.[18] Iodo compounds are more expensive, less stable and their reactivity by one order of magnitude higher than that of the corresponding bromide compounds. However, direct iodination of aromatic compounds is difficult due to the low electrophilicity of molecular iodine compared to that of molecular chlorine and bromine. Further, iodination is reversible, hydrogen iodide (HI) generated in reaction tends to reduce the iodo compound to the starting material. It must, therefore, be removed from the reaction mixture as soon as it formed. This can be achieved by its neutralization with $NaHCO_3$, $CaCO_3$ or HgO. In the ideal situation, HI can be reoxidized to iodine by fuming sulfuric acid (oleum), nitric acid, iodic acid, H_2O_2, alkali persulphate, organic peroxyacids and other oxidizing agents.[19]

The most common oxidizing agents are iodine, hydrogen iodide, iodine monochloride, iodine monobromide, hypoiodous acid (HOI) alkalihypoiodite (KOI), alkylhypoiodite (ROI) and acylhypoiodites (RCOI). Phosphorous-based iodine reagents like phosphorous triiodide (PI_3), triphenyl phosphate diiodie $(PhO)_3PI_2$, triphenoxyphosphonium iodide $(PhO)_3P^+MeI^-$ prepared from their components also act as iodinating agents. The important iodinating agents are *N*-iodosuccinimide and 1,3-diiodo-5,5-dimethyl hydantoin, which are prepared by iodination of N-H bond.

Almost all types of aromatic nuclei with electron withdrawing as well as donating substituents can be iodinated using molecular iodine in the presence of strong acid or oxidizing agents. For example, iodination of aromatic nucleus **51** is shown in the **Scheme 19**. In some cases, the iodinating agent is not iodine but acetyl hypoiodite, formed from iodine and acetic acid in the presence of an oxidizing agent.



51
R = OH, OMe, NMe_2, Me

52
yield: 40-90%

Scheme 19: i) Reagents and conditions

1. I_2, H_2SO_4, Ag_2SO_4, 75-80%
2. I_2, HNO_3, 86%
3. I_2, $Na_2S_2O_8$, AcOH, 70%
4. I_2, CH_3CO_3H, H_2SO_4, 77%
5. I_2, CF_3SO_3Ag, 100%
6. I_2, $Tl(OCOCF_3)_3$, 89%.

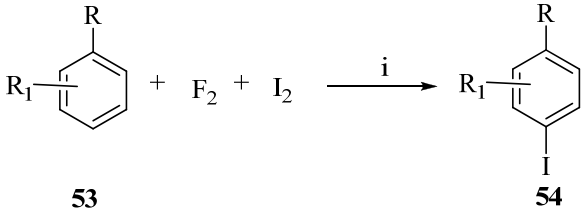
The reaction conditions shown in **Scheme 19** are applicable to most of the aromatic compounds having alkyl groups or substituents attached to the benzene rings. Depending on the nature of such substituents, milder or harsher conditions must be applied.

3.2.2 Review of literature

Literature search revealed that in addition to the above methods, there are also several other reagents for the efficient iodination of aromatic nucleus. Some of these methods are briefly discussed below.

Rozen's approach (1990)[20]

Rozen *et al.* have reported iodination of aromatic compounds **53** using *in situ* generated iodine monofluoride from I_2 and F_2 to form the corresponding iodoarenes **54.** Even aromatic compounds with electron-withdrawing groups like NO_2, CN, CO_2Et, etc underwent iodination with excellent yields (**Scheme 20**).



53 **54**

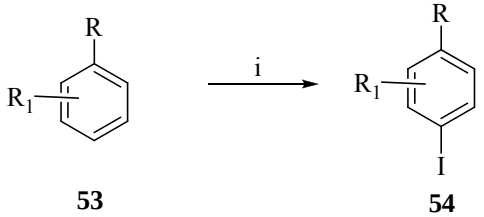
R = H, alkyl, OAc, OPh
NO_2, CN, Br, CO_2Et

yield upto 98%

Scheme 20: i) I_2, F_2, $CFCl_3$, -78 ^oC.

Ellervik's approach (1994)[21]

Ellervik *et al.* have employed iodine monochloride (ICl) for an efficient iodination of aromatics in the presence of Lewis acids like indium triflate or mercuric triflate to furnish iodo compounds with excellent yields (**Scheme 21**).



53 **54**

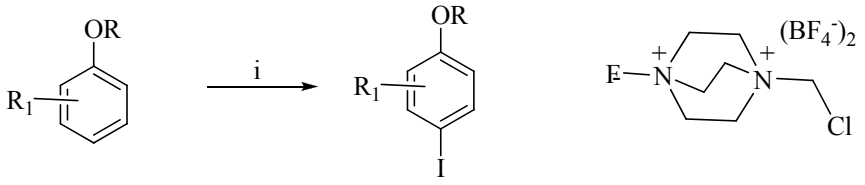
R = OMe, NMe_2, NH_2, OH, Me
R_1 = NO_2, CN, Br, alkyl

yield upto 98%

Scheme 21: ICl, $In(OTf)_3$, 1 h, 25 ^oC.

Zupan's approach (1996)[22]

Regioselective iodination of aromatic ethers have been carried out by Zupan and his co-workers using selectfluor (**57**) as oxidant and molecular iodine as iodine source at ambient conditions (**Scheme 22**).



55 — R= H, F, Cl, Br, I, COMe, CHO, tBu; R_1 = H, alkyl, alkoxy, aryloxy, halogen

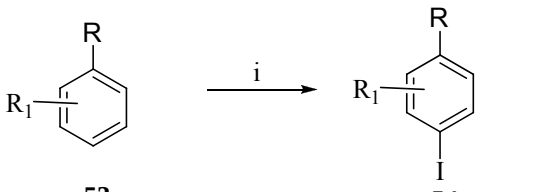
56 — yield upto 95%

57 — selectfluor

Scheme 22: I_2, selectfluor, CH_3CN, 22 ^oC.

Kashima's approach (1997)[23]

Kashima *et al*. have developed an efficient method for the regioselective aromatic iodination using iodine and nitrogen dioxide in the presence of catalytic sulfuric acid (**Scheme 23**).



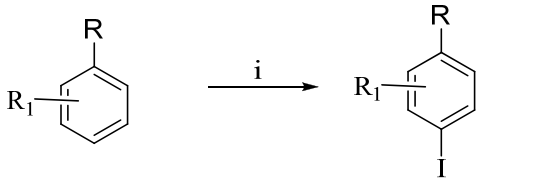
53 — R, R_1 = H, alkyl, alkoxy, aryloxy, halogen

54 — yield upto 95%

Scheme 23: I_2, NO_2 (excess), H_2SO_4, $CHCl_3$, 40-90 ^oC, 10 h.

Kim's approach (1999)[24]

A practical method for the iodination of aromatic compounds has been described by Kim *et al.* using a mixture of iodine and tetrabutyl ammonium peroxydisulfate as the oxidant under ambient conditions (**Scheme 24**).



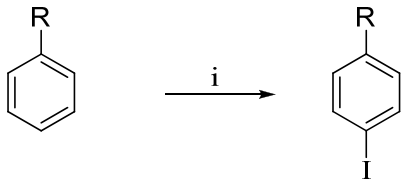
53
R, R_1 = H, alkyl, alkoxy, aryloxy, halogen

54
yield 87- 95%

Scheme 24: $(n\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$, I_2, CH_3CN, 25 °C.

Mukaiyama's approach (2000)[25]

Mukaiyama *et al*. have reported iodination of activated aromatics using a combination of iodine monochloride (ICl) and catalytic zinc oxide as the acid scavenger (**Scheme 25**).



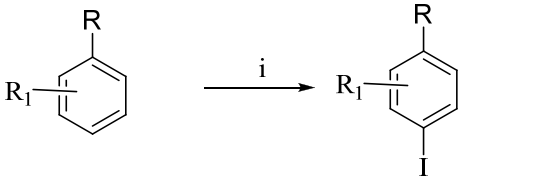
51
R, R_1 = H, alkyl, alkoxy, OH, NH_2

52
yield 70- 95%

Scheme 25: ICl, ZnO (1 equiv.), CH_2Cl_2, 25 °C.

Ruoho's approach (2002)[26]

Tetramethyl ammonium dichloro iodate $[(Me_4)N^+ICl_2^-]$ has been employed by Ruoho *et al.* as an efficient and environmentally friendly reagent for the iodination of aromatic compounds under mild and solvent-free conditions (**Scheme 26**).



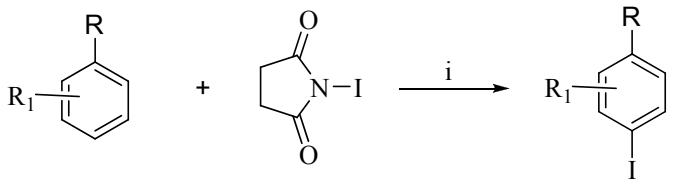
53
R = OMe, NH_2, Me, Cl, CHO, CO_2H, etc

54
yield upto 100%

Scheme 26: $Me_4N^+ICl_2^-$, CH_2Cl_2, 5-45 min, 25 °C.

Broutin's approach (2002)[27]

N-Iodosuccinimide (**58**) as the iodine source along with catalytic trifluoroacetic acid has been employed for the mild and regioselective iodination of electron-rich aromatic compounds (**Scheme 28**).



53 R, R_1 = H, alkyl, alkoxy, aryloxy, halogen

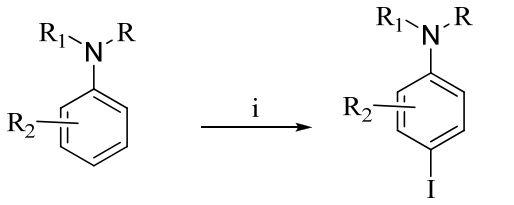
58

54 yield 60- 99%

Scheme 28: cat. CF_3CO_2H, CH_3CN, reflux.

Skulski's approach (2002)[28]

Skulski *et al.* have described iodination of aniline derivatives **59** using urea-hydrogen peroxide addition complex (UHP) as the oxidant and molecular I_2 as the halogen source under microwave irradiation (**Scheme 29**).



59 R, R_1 = H, Me

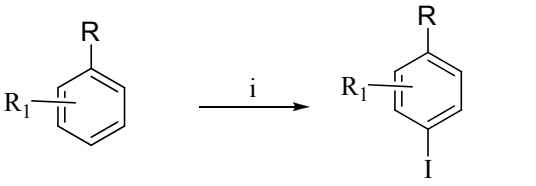
R_2 = Me, Cl, Br

60 yield 40-80%

Scheme 29: Urea·H_2O_2 complex, I_2, $CHCl_3$, microwave, 10 min.

Shiri's approach (2003)[29]

Direct and regioselective iodination of benzene, naphthalene and other activated aromatic compounds using iodine or sodium iodide in the presence of $Fe(NO_3)_3$. 1.5 N_2O/ charcoal system has been achieved by Shiri *et al.* (**Scheme 30**).



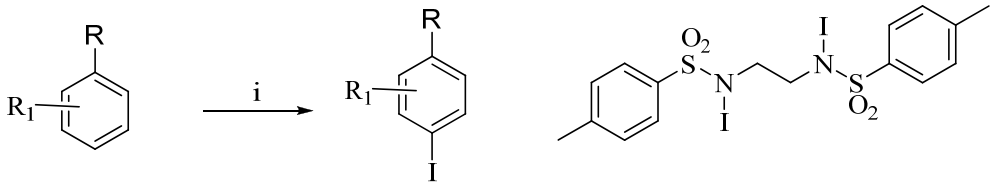
53
R = OMe, H, OPh
R1 = Me

54
yield upto 94%

Scheme 30: I_2 or NaI, $Fe(NO_3)_3$. 1.5 N_2O_4, CH_2Cl_2, 25 ^oC, 2-24 hrs

Vaghei's approach (2003)[30]

Iodination of activated aromatics have been carried out using *N*,*N*'-diiodo-*N*,*N*'-1,2-ethane *bis*(*p*-toluene sulfonamide) (**61**) as the iodine source in the presence of trifluoroacetic acid (**Scheme 31**).



53
R, R_1 = NMe_2, NHCOMe, OMe, Me, H

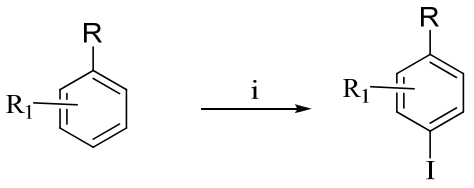
54
yield upto 93%

61

Scheme 31: Reagent **61**, cat. CF_3CO_2H, CH_3CN, 25 ^oC.

Kulkarni's approach (2004)[31]

The mixture of ammonium iodide (NH_4I) and oxone ($KHSO_5$ $KHSO_4$ K_2SO_4) was found to iodinate activated aromatics with high regioselectivity at ambient conditions. Mechanistically, it was proposed that oxone oxidized ammonium iodide to liberate electrophilic iodine (I^+) species (**Scheme 33**).



53 **54**

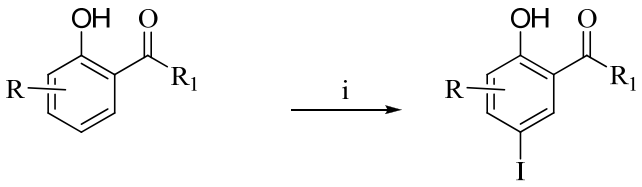
R = OMe, OH, Me, H yield up to 99%

R1 = NO_2, Cl, Me

Scheme 33: NH_4I, Oxone, MeOH, 25 ^oC.

Vibhute's approach (2005)[32]

Vibhute *et al*. have studied the iodination of different aryl hydroxy ketones **62** using iodine and iodic acid (HIO_3) at ambient conditions. Iodic acid acts as oxidant as well as acid source (**Scheme 34**).



62 **63**

R = Br, Cl, Me, H yield: 81-87%

R1 = CH_2Cl, Et, Propyl, Ph, etc.

Scheme 34: I_2, HIO_3, 30-40 ^oC, EtOH: H_2O.

3.2.3. Present Work

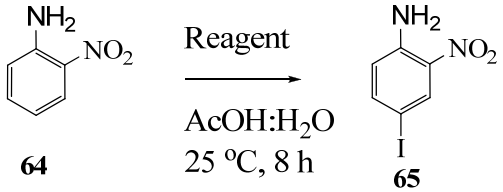
3.2.3.1 Objective

From the above discussion, it is clear that most of the reported methods for iodinations employ either toxic molecular iodine as the iodine source or expensive metal salts as oxidant. Some reports even mention new and commercially non-available reagents. Hence, a practical method, which should involve less toxic metal halide as the iodine source or the process is metal-free, will be of paramount importance. This section describes one such process which involves the iodination of activated aromatics using

$NaIO_4$ as the oxidizing agent and potassium iodide as the iodine source in acetic acid as solvent.

3.2.4. Results and discussion

In connection with our interest on $NaIO_4$ mediated oxidations,[33] we thought of providing a cheaper method for producing 4-iodo-2-nitroaniline (**65**) using $NaIO_4$/KI combination. It may be noted that 4-iodo-2-nitroaniline (**65**) is the starting material for 3,3',4,4'-tetraaminobiphenyl (TAB), a monomer for fuel cell applications.[34] When iodination of 2-nitroaniline (**64**) was carried out with alkali metal iodides (KI or NaI) as the iodine source and $NaIO_4$ as the oxidant in aq. AcOH, acting both as solvent and acid source, iodination occurred to give **65** in 55% yield. Surprisingly, when NaCl (2 equiv) was added to the reaction mixture, both the reactivity as well as the yield of **65** (98%) increased significantly (**Scheme 36**). Comparable yield of **65** (95%) was also achieved with molecular iodine as the iodine source. The ^{1}H NMR spectrum of 4-iodo-2-nitroaniline (**65**) displayed a singlet at δ 3.83 for the N**H$_2$** protons and three signals at δ 6.66(d), 7.55(d) and 8.38(s) corresponding to the aromatic protons. Its ^{13}C NMR spectrum showed a characteristic peak shifted to upfield at δ 74.96 corresponding to the **C**-I bond (**Fig. 5**).



64 **65**

Reagent: $NaIO_4$-KI 55%
$NaIO_4$-I_2-NaCl 95%
$NaIO_4$-KI-NaCl 98%

Scheme 36: Iodination using $NaIO_4$-KI- NaCl system

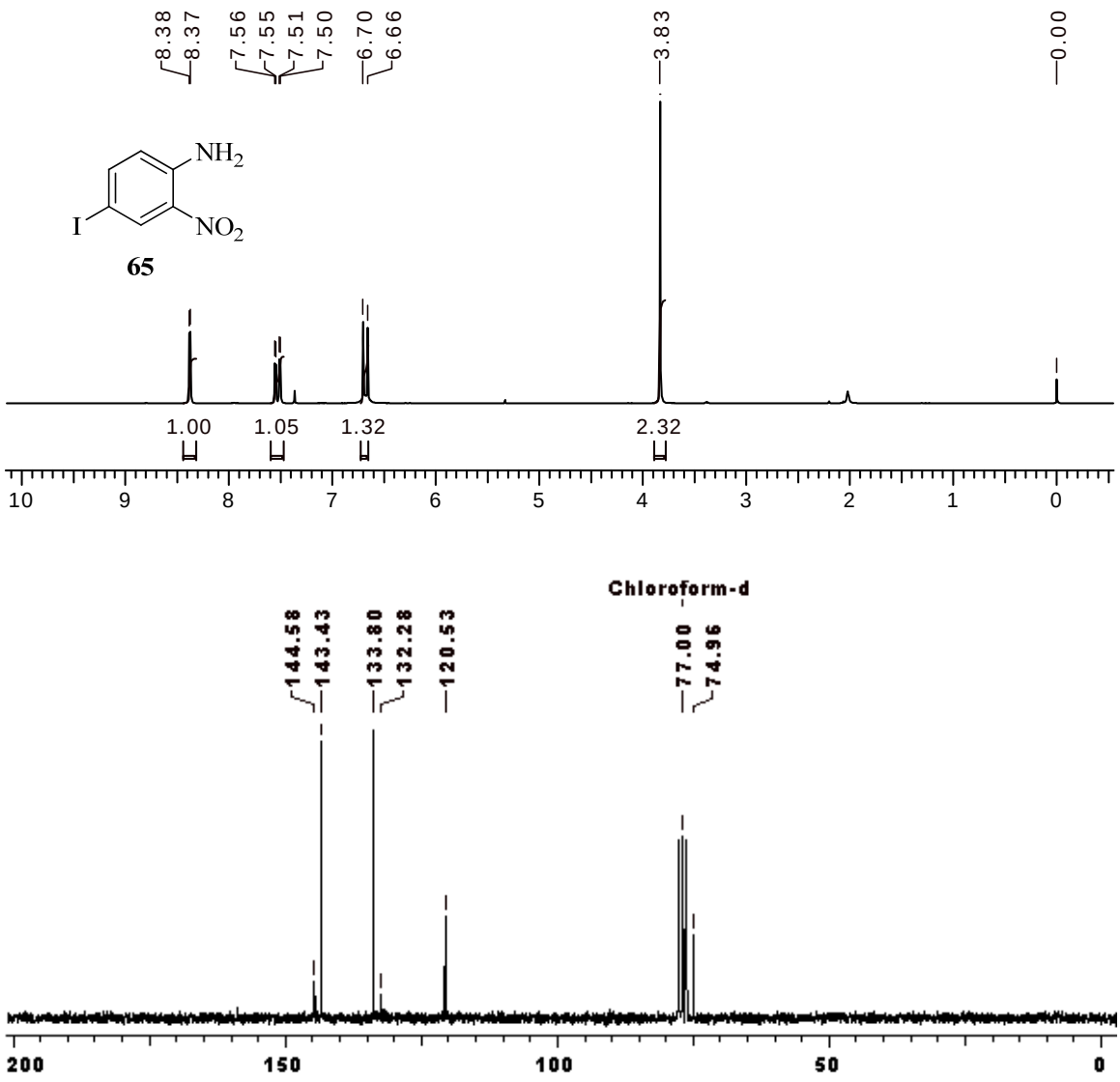


Fig. 5: ^{1}H and ^{13}C NMR spectra of **65**

Encouraged by this result, we screened several other oxidants which are known to oxidize alkali metal halides that liberate iodine and the results are shown in **Table 4**. The use of a catalytic amount of $NaIO_4$ (30 mol%) and NaCl (30 mol%) was not fruitful in terms of yield. Also, when LiBr was employed as the additive, nuclear bromination was a competitive reaction resulting in the formation of 4-iodo-2-nitroaniline and 4-bromo-2-nitroaniline in the ratio of 1:6.

Table 4: Iodination of 2-nitroaniline (**64**)[a]

No.	Oxidant[a]	iodine source	additive	Yield[b] (%) of **65**
1	$NaIO_4$	KI	-	55
2	$NaIO_4$	KI	NaCl	98
3	KIO_3	KI	NaCl	98
4	$KBrO_3$	KI	NaCl	71
5	Oxone	KI	NaCl	47
6	HIO_4	KI	NaCl	87
7	mCPBA[g]	KI	NaCl	56
8	V_2O_5	KI	NaCl	32[c]
9	$NaIO_4$	NaI	NaCl	84
10	$NaIO_4$	NBu_4NI	NaCl	82
11	$NaIO_4$	I_2	NaCl	95[d]
12	$NaIO_4$	KI	NaF	58
13	$NaIO_4$	KI	LiBr	100[f] (16: 84)[e]
14	$NaIO_4$	KI	NCS[g]	73

[a] Reaction conditions: Molar equivalents of oxidant: iodine source: additive = 1:1:2 unless otherwise stated, 10 mL of AcOH: H_2O (9:1), 25 °C, 8 h; [b] Isolated yield by column chromatography; [c] Reaction was done at 60 °C. Yield at 25 °C was 5%; [d] 0.5 equivalent of molecular iodine was used; [e] 4-iodo-2-niroaniline: 4-bromo-2-niroaniline in the ratio 1:6 were formed. Conversion was found by GC-MS; [f] *m*CPBA = m-chloroperbenzoic acid. NCS=N-chloro succinimide.

To establish the scope of the methodology, we subjected a variety of activated aromatic compounds to nuclear iodination and the results are shown in **Table 5**. As can be seen, activated aromatic compounds were converted to mono or poly-iodoaromatics in quantitative yields within a short period of time at 25 °C. The reaction of phenol with one molar equivalent of KI led to a mixture of mono and poly-iodinated products. The degree of poly-iodination is temperature dependent, but attempts to control iodination of phenol by conducting the reaction at 0 °C resulted in low conversion probably due to the fact

that NaCl was not oxidized at 0 °C. Similarly, aniline and substituted anilines were extremely active and gave excellent yields of iodoaromatics. The formation of iodo compounds were systematically confirmed from ^{1}H, ^{13}C NMR and IR spectra. For example, the ^{1}H NMR of 4-iodoanisole (**67d**) displayed a singlet at δ 3.77 due to –OC**H**$_3$ protons and other characteristic signals at δ 6.68(d) and 7.55(d) corresponding to 1,4-substituted aromatic protons. Its ^{13}C NMR showed typical signals at δ 55.2 and 82.6 for the –O**C**H$_3$ and **C**-I carbons respectively (**Fig. 6)**.

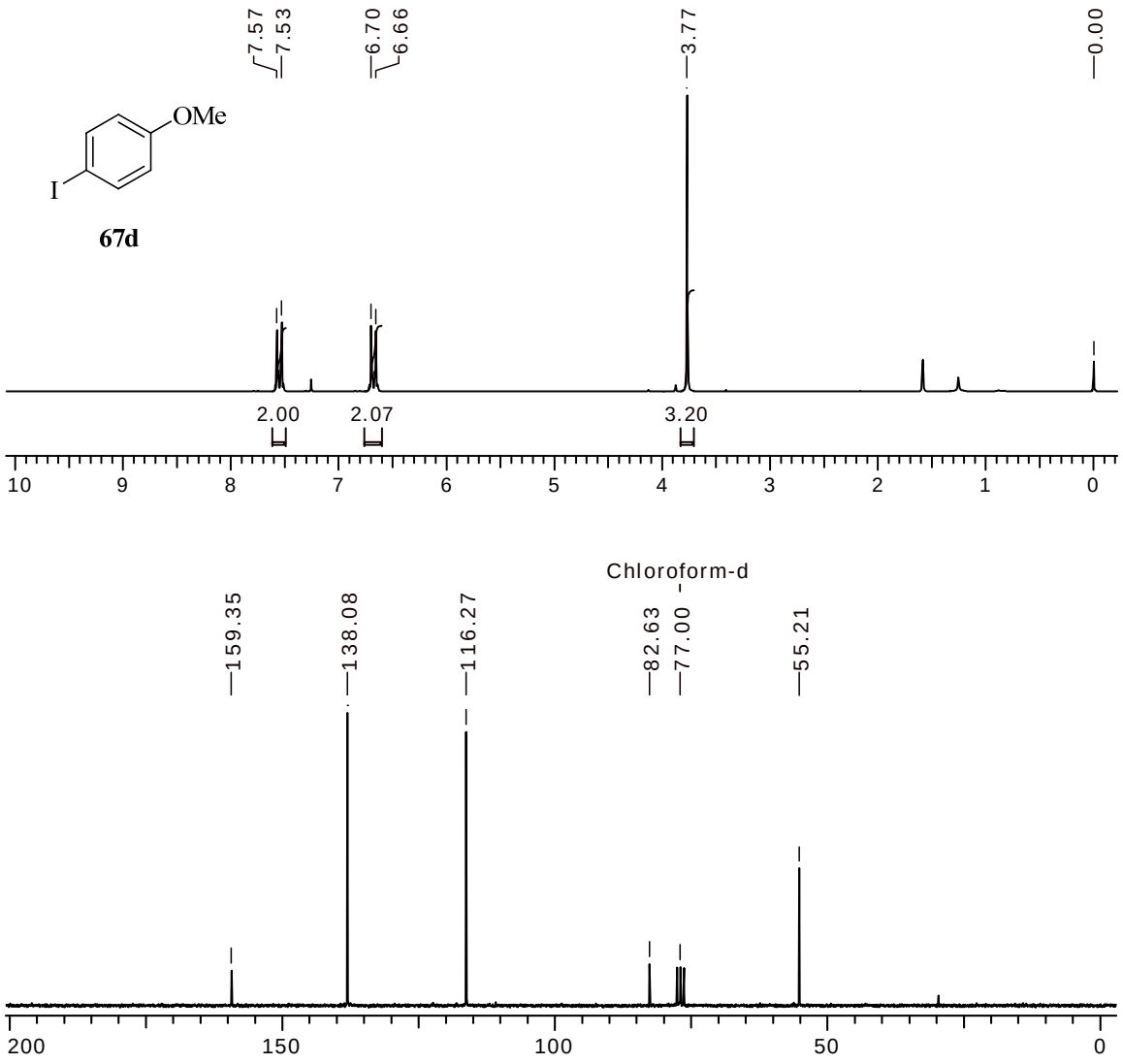
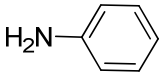
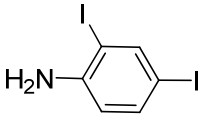
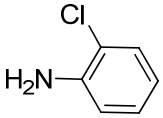
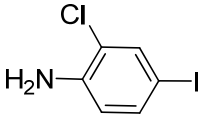
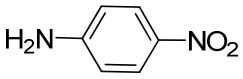
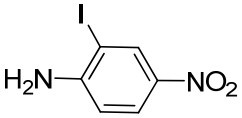
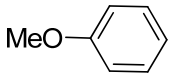
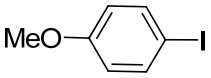
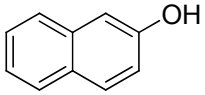
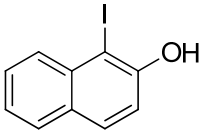
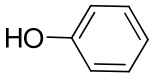
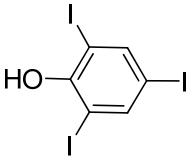
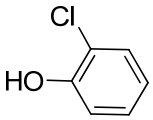
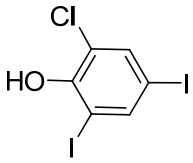
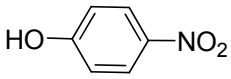
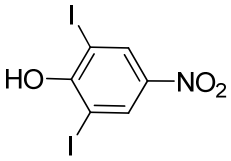
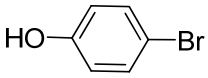
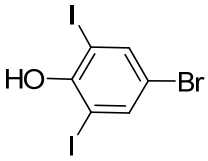
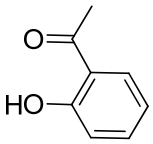
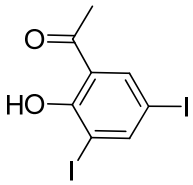


Fig. 6: ^{1}H and ^{13}C NMR spectra of **67d**

When anilines with deactivating groups such as NO_2, CO_2H, Cl and I were subjected to the iodination, only mono-iodination took place. The reaction was exothermic; often the temperature of the reaction reached 50–55 °C during the addition of KI. Easily oxidizable groups such as hydroxy, aldehyde or amine were not affected, but sulfides and o-phenylenediamine, when subjected to the oxidation, gave sulfoxides and ring opened product, respectively. Also the method failed in the case of deactivated and weakly activated aromatic systems such as arenes and alkyl arenes.

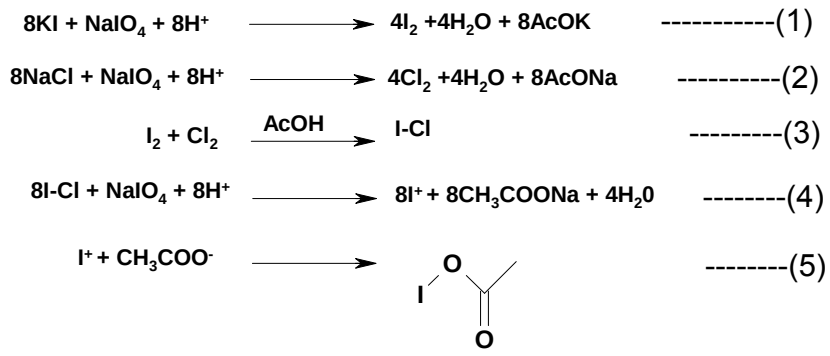
Table 5: $NaIO_4$/KI/NaCl-mediated iodination of activated arenes[a]

No.	Substrate (**66**)	KI (equiv.)	Product (**67**)	Time (hrs)	Yield[b] (%)
a		1		2	97
b		1		3	95
c		1		3	96
d		1		12	87[c]
e		1		8	95
f		3		0.5	99[d]

g		2		6	97
h		1		6	95
i		2		0.5	95
j		2		1	97

[a] Reaction condition for monoiodination: Substrate (3 mmol), KI (3 mmol), $NaIO_4$ (3 mmol), NaCl (6 mmol), 10 mL of AcOH: H_2O (9:1), 25 °C; [b] Isolated yield by column chromatographic purification; [c] Diiodination was not observed even with 1.2 equiv. of KI. [d] KI was added in portion to maintain the temperature around 50 °C.

The proposed reaction pathway for the iodination is shown in **Scheme 37**. It has been established in our earlier studies[33] that $NaIO_4$ oxidizes metal halides (*e.g.* KI, NaCl) in the presence of acid to liberate halogens (I_2, Cl_2) (eqns. **1** and **2**). Iodine monochloride,[35] presumably formed from the liberated halogens, acts as the electrophile (eqns. **3-5**). The formation of I-Cl was confirmed by the fact that styrene under the same reaction conditions yielded a mixture of 1-(1-chloro-2-iodoethyl)benzene (23%) and 2-iodo-1-phenylethylacetate (35%).



Scheme 37: Proposed mechanistic pathway for the iodination

3.2.5. Conclusion

In conclusion, we have developed a simple protocol for the iodination of activated aromatic compounds using $NaIO_4$/KI/NaCl as a mild, inexpensive and selective iodinating agent. The methodology involves *in situ* generation of I-Cl acting as electrophile for iodination. A remarkable feature of this system is that even acid sensitive functionalities like anilines could be iodinated quantitatively.

3.2.6. Experimental section

General procedure for the mono iodination

To a mixture of aromatic compound (3 mmol), $NaIO_4$ (3 mmol), NaCl (6 mmol) in 10 mL of AcOH:H_2O (9:1) was added KI (3 mmol) slowly so that the temperature of the reaction mixture does not exceed 50 °C. The reaction mixture was stirred at 25 °C for a period mentioned in **Table 5** and poured over ice cold water. The solid was extracted with dichloromethane, washed twice with water, dried over anhydrous sodium sulfate and

concentrated under reduced pressure. The crude product obtained was purified by column chromatography.

2-Iodo-4-nitroaniline (65)

Orange powder; **mp**: 105 ºC; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.7 Hz, 1H,), 8.04 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.54 (d, *J* = 2.4 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 80.2, 113.5, 127.0, 137.1, 139.6, 156.5; **IR** ($CHCl_3$, cm^{-1}): 3390, 2940, 1640, 1600, 1515, 1470, 1330; Anal. Calcd for $C_6H_5IN_2O_2$: C, 27.29; H, 1.91; I, 48.97; N, 10.61. Found: C, 27.22; H, 1.95; I, 48.93; N, 10.67%.

2,4-Diiodoaniline (67a)

Dark powder; **mp**: 94-96 ºC; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 6.57 (d, *J* = 8.2 Hz, 1H), 7.33 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 78.6, 85.2, 117.9, 139.3, 147.2, 149.8; **IR** ($CHCl_3$, cm^{-1}): 3480, 3393, 1610, 1470, 1380; Anal. Calcd for $C_6H_5I_2N$: C 20.89; H 1.46; I 73.58; N 4.06. Found: C 20.83; H 1.41; I 73.58; N 4.12%.

2-Chloro 4-iodoaniline (67b)

Dark powder; **mp**: 82-84 ºC; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 4.07 (br, 2H), 6.51 (d, *J* = 8.9 Hz, 1H), 7.31 (dd, *J* = 8.3, 2.05 Hz), 7.52 (d, *J* = 2.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 78.05, 117.5, 120.25, 136.37, 137.17, 142.78; **IR** ($CHCl_3$, cm^{-1}): 3440, 3391, 2912, 1612, 1473, 1380; Anal. Calcd for C_6H_5ClIN: C, 28.43; H, 1.99; Cl, 13.99; I, 50.07. Found: C, 28.34; H, 1.89; Cl, 14.05; I, 50.17%.

4-Iodoanisole (67d)

Colorless solid; **mp**: 46-48 ºC; **^{1}H-NMR** (200 MHz, $CDCl_3$) 7.93 (s, 1H); δ 7.55 (d, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 55.4,

82.8, 116.4, 138.2, 159.5; Anal. Calcd for C_7H_7IO: C, 35.92, H, 3.01, I 54.22. Found: C, 35.97, H, 3.06, I, 54.26%.

1-Iodo-2-naphthol (67e)

Brown oil; **^{1}H-NMR** (200 MHz, acetone-d_6) δ 7.29 (d, *J* = 9.0 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 9.52 (s, 1H); **^{13}C-NMR** (50 MHz, acetone-d_6) δ 94.3, 117.4, 123.0, 124.9, 128.2, 128.6, 129.9, 130.5, 137.7, 152.36; **IR** (neat, cm$^-$1): 3500, 3380, 2940, 1620, 1600, 1470, 1380, 1220, 1170, 1150; Anal. Calcd for $C_{10}H_7IO$: C, 44.47; H, 2.61; I, 46.99. Found: C, 44.41; H, 2.65; I, 46.92%.

2, 4, 6-Triiodophenol (67f)

Light brown solid; **mp**: 156-159 ºC; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.95 (s, 2H); **^{13}C-NMR** (50MHz, $CDCl_3$) δ 83.1, 84.6 146.2, 154.5; **IR** ($CHCl_3$, cm$^-$1): 3440, 2970, 1430, 1080; Anal. Calcd for $C_6H_3I_3O$: C, 15.27; H, 0.64; I, 80.69. Found: C, 15.21; H, 0.69; I, 80.63%.

2-Chloro-4,6-diiodo phenol (67g)

Colorless solid; **mp**: 145-146 ºC; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 5.97 (brs, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.89 (d, *J* = 2.6 Hz, 1H); **^{13}C-NMR** (50 MHz , $CDCl_3$); δ 82.2, 84.7, 120.0, 137.6, 145.1, 151.1; **IR** ($CHCl_3$, cm^{-1}): 3452, 2912, 1612, 1473, 1380; Anal. Calcd for $C_6H_3ClI_2O$: C, 18.95; H, 0.80; Cl, 9.32; I, 66.73. Found: C, 18.91; H, 0.89; Cl, 9.38; I 66.81%.

2, 6-Diiodo-4-nitrophenol (67h)

Yellow crystals; **mp**: 154-157 ºC; **^{1}H-NMR** (200 MHz, acetone-d_6) δ 8.62 (s, 2H); **^{13}C-NMR** (50 MHz, acetone-d_6) δ 81.9, 130.4, 135.1, 161.4; **IR** ($CHCl_3$, cm$^-$1): 3460, 3085,

1595, 1525, 1446, 1341, 1327; Anal. Calcd for $C_6H_3I_2NO_3$: C, 18.44; H, 0.77; I, 64.93; N, 3.58. Found: C, 18.41; H, 0.71; I, 64.93; N, 3.55%.

4-Bromo-2, 6-diiodophenol (67i)

Colorless solid; **mp**: 125-126 ºC; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 5.76 (s, 1H), 7.79 (s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 82.5, 113.6, 140.9, 153.1; **IR** ($CHCl_3$, cm^-1): 3520, 3085, 1595, 1446, 1327, 1123; Anal. Calcd for $C_6H_3BrI_2O$: C, 16.96; H, 0.71; Br, 18.81; I, 59.75. Found: C, 16.91; H, 0.74; Br, 18.81; I 59.72%.

1-(2-Hydroxy-3,5-diiodophenyl)ethanone (67j)

Colorless solid; **mp**: 85 ºC; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.65 (s, 3H), 8.0 (s, 1H), 8.2 (s, 1H), 13.1 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 26.6, 80.5, 88.3, 121.2, 139.2, 152.6, 160.8, 203.1; **IR** ($CHCl_3$, cm^-1): 3565, 2997, 1723, 1595, 1327, 1123; Anal. Calcd for $C_6H_3BrI_2O$: C, 16.96; H, 0.71; Br, 18.81; I, 59.75. Found: C, 16.91; H, 0.74; Br, 18.81; I 59.72%.

Section III

$NaIO_4$/LiBr-mediated direct conversion of aromatic aldehydes to aromatic esters

3.3.1 Introduction

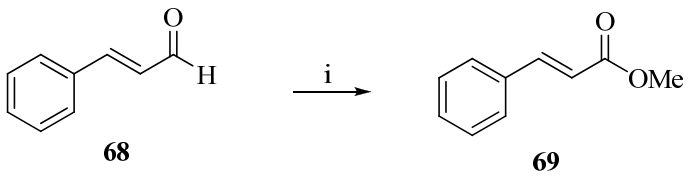
The direct transformation of aldehydes into the corresponding esters[36] under mild conditions is often required in organic synthesis especially in the synthesis of natural products.[37] Esterification processes are widespread in the industrial synthesis of a variety of end-products such as fragrances, monomers, plasticizers etc, many of which are classed as high production volume (HPV) chemicals. In addition, applications to lower volume, high-value pharmaceutical and fine chemicals targets are prominent, and often require more stringent coupling protocols to achieve the desired chemo- and stereoselectivity. The conventional method for the synthesis of carboxylic esters involves oxidation of aldehydes to carboxylic acids followed by esterification with alcohols catalyzed by either acid or base. In contrast, the direct method of conversion of alcohols or aldehydes to carboxylic esters holds promise in organic synthesis as it minimizes the number of steps.

3.3.2 Review of literature

Literature survey revealed that there are various methods available for the direct transformation of aldehydes into the corresponding esters. Direct transformation of aldehydes into esters has been achieved using a variety of reagents such as V_2O_5/H_2O_2, oxone®, $DMSO/Ac_2O$, $Br_2/NaHCO_3$, O_3/KOH, pyridinium hydrobromide perbromide, pyridinium dichromate, electrochemical method, TMSOTf/NBS/AIBN, $S.SnO_2$/SBA-1-H_2O_2 and more recently acetone cyanohydrin. Some of the recent developments on this reaction are discussed below.

Gopinath's approach (2000)[38]

In Gopinath's approach, aldehydes, in the presence of methanol, undergo oxidative transformation to the corresponding esters upon treatment with catalytic amounts of vanadium pentoxide in combination with oxidant 30% hydrogen peroxide (**Scheme 38**).

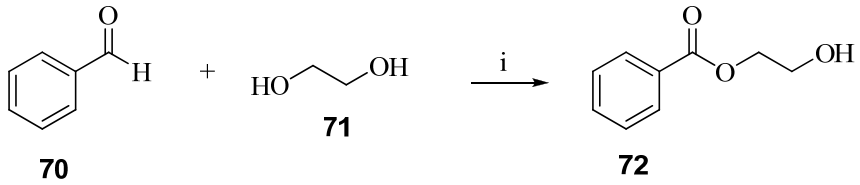


68 **69**

Scheme 38: (i) V_2O_5 (cat.), MeOH, H_2O_2, 80 °C, 100%.

Sarvari's approach (2003)[39]

Sarvari *et al.* have found $Al_2O_3/MeSO_3H$ (AMA) as an extremely efficient reagent for the conversion of aromatic aldehydes and diols to the corresponding glycol monoesters **72**. The reaction has shown direct excellent selectivity, which is an attractive feature of this method (**Scheme 39**).



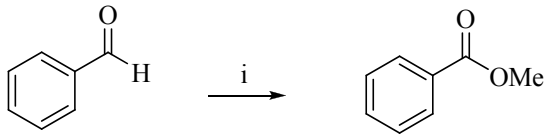
70 **71** **72**

Scheme 39: (i) Al_2O_3, $MeSO_3H$, 80 °C, 4 h, 80%.

Traivs's approach (2003)[40]

Travis *et al*. have developed a highly efficient, mild, and simple protocol for the oxidation of aldehydes to carboxylic acids utilizing oxone as the sole oxidant. Direct conversion of aldehydes in alcoholic solvents to their corresponding ester products has also been reported. These reactions may prove to be valuable alternatives to traditional

metal-mediated oxidations but it uses more than stoichiometric amounts of oxone (**Scheme 40**).

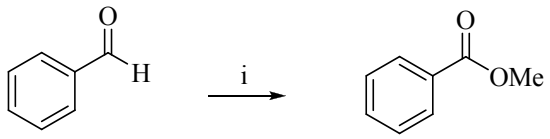


70 **73**

Scheme 40: (i) Oxone, MeOH, 18 h, 25 °C, 96%.

Onami's approach (2004)[41]

In this approach, the direct esterification of aldehydes and alcohols was carried out with pyridinium hydrobromide perbromide (PHPB) in water at room temperature. A variety of aldehydes were converted to their respective ester derivatives with alcohols such as methanol, 1,2-ethanediol and 1,3-propanediol. Further, a variety of aliphatic alcohols were also converted to the corresponding Tishchenko-like dimeric esters in good yields under the same reaction conditions (**Scheme 41)**.

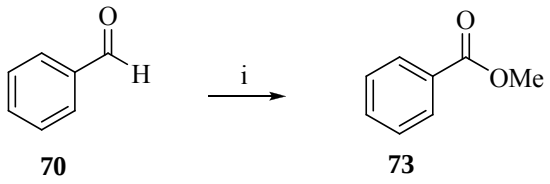


70 **73**

Scheme 41: PHPB, MeOH, H_2O, 25 °C, 87 h, 94%.

Budhewar's approach (2006)[42]

Budhewar *et al.* have developed a simple and mild procedure for the facile direct oxidative methyl esterification of aldehydes using molecular iodine in combination with (diacetoxyiodo)benzene in methanol. Oxidative esterification is induced by iodonium ion generated *in situ* by the chemical oxidation of molecular iodine with (diacetoxyiodo)benzene (**Scheme 42**).

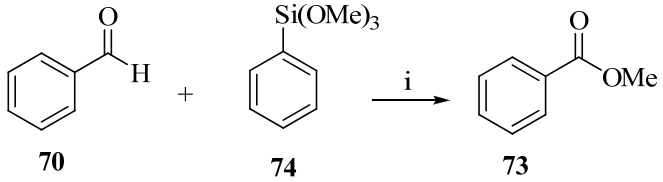


70 **73**

Scheme 42: (i) I_2, $PhI(OAc)_2$, MeOH, 25 °C, 87%.

Wolf's approach (2006)[43]

In this approach, aldehydes and siloxanes **74** form methyl esters in a single step through mild oxidative esterification in the presence of a palladium catalyst or afford secondary alcohols *via* TBAF-promoted arylation (**Scheme 43**).

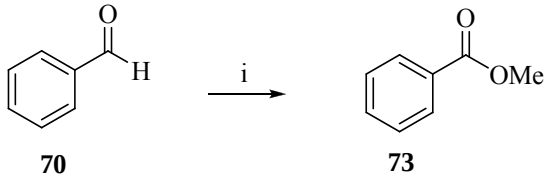


70 **74** **73**

Scheme 43: (i) $PdCl_2$ (cat.), TBAF, CH_3CN, 25 °C, 97%.

Sudalai's approach (2007)[44]

Sudalai *et al.* have described a simple procedure for the single-step conversion of electron-deficient aldehydes into the corresponding esters on reaction with alcohols in excellent yields mediated by acetone cyanohydrin or NaCN and base (**Scheme 44**).

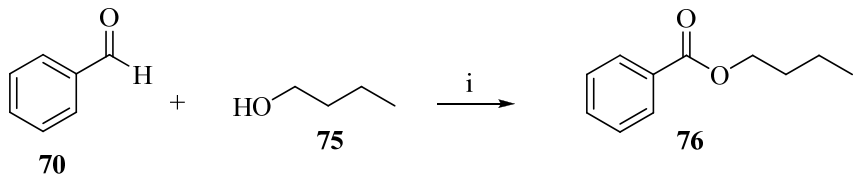


70 **73**

Scheme 44: (i) acetone cyanohydrin (5 mmol), Et_3N (7.5 mmol), alcohol (5 mL), 25 ^oC, 2 h.

Li's approach (2007)[45]

Li *et al.* have developed an oxidative esterification reaction between aldehydes and alcohols **38** catalyzed by a combination of $Cu(ClO_4)_2.6H_2O$ and $InBr_3$ using TBHP as an oxidant (**Scheme 45**).



70 **75** **76**

Scheme 45: (i) $Cu(ClO_4)_2$ $6H_2O$, $InBr_3$, TBHP, 100 ^oC, 16 h, 91%.

3.3.3 Present Work

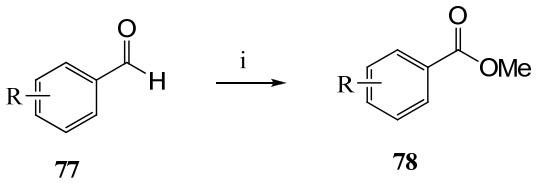
3.3.3.1 Objective

Although several reports of transformation of aldehydes directly into esters in the presence of alcohols has been reported, these methods usually require harsh conditions and are effective for a limited range of substrates (electron-rich aldehydes and primary alcohols). In addition, these transformations generally involve an oxidative pathway and require more than stoichiometric amount of oxidants coupled with long reaction times. Also these reagents are unsatisfactory for aldehydes containing electron-withdrawing groups. Since formation of minor amounts of acids often complicates the oxidative process. This section describes a facile method for the direct conversion of electron-deficient aldehydes to esters mediated by $NaIO_4$ and LiBr.

3.3.4 Results and discussion

Recently, we reported[33] that $NaIO_4$-mediated oxidation of alkylarenes led to the high yield preparation of benzoic acids, formed *via* the oxidation of their respective benzyl alcohols and aldehydes when the reaction was carried out in water. In this regard, we envisioned that replacing water with alcohol should result in the formation of esters.

During this investigation, we found that $NaIO_4$-LiBr-H^+ combination oxidatively transforms aromatic aldehydes directly to the corresponding aromatic esters in high yields (**Scheme 46**).

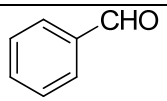
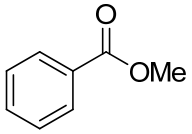
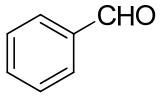
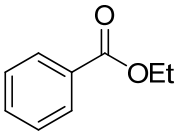
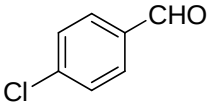
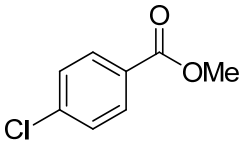
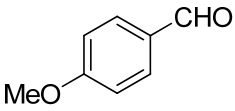
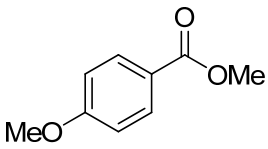
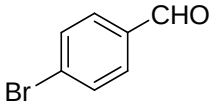
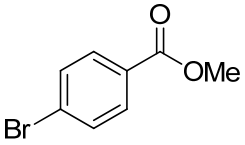
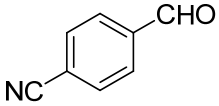
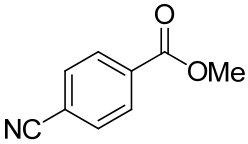
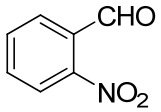
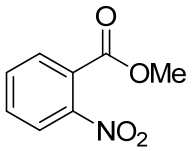
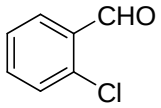
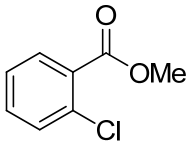
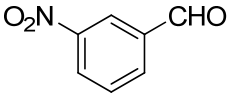
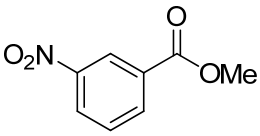
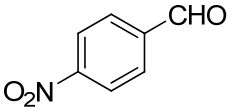
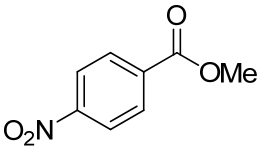


77 **78**

Scheme 46: (i) $NaIO_4$ (3 mmol), LiBr (3 mmol), conc. H_2SO_4 (1 mL), MeOH (9 mL), 25 °C, 18 h.

In order to establish the scope of this reaction, a number of aromatic aldehydes were subjected to oxidation and the results are presented in the **Table 6**. As can be seen from **Table 6**, aromatic aldehydes with electron-donating as well as electron-withdrawing substituents on the nucleus underwent oxidative esterification smoothly to give their corresponding aromatic esters in 71-95% yields. In the case of substrates with electron-donating groups, the reaction proceeded at 25 °C while the substrates with electron-withdrawing groups, except 4-chloro aromatics, required higher temperature (65 °C) to achieve excellent conversions. For 4-methoxy-benzyl alcohol, the oxidative esterification occurred along with nuclear bromination when 2 molar equivalents of LiBr was used (entry d). We also observed that use of sub-stoichiometric amount of $NaIO_4$ (25-40 mol%) resulted in poor yields of esters (< 40%). All the aromatic esters synthesized were systematically characterized from the IR, ^1H and ^{13}C NMR spectra of the esters. For example, the ^1H NMR spectrum of **78d** displayed two typical signals at δ 3.86 and 3.88 for the two –OC**H$_3$** protons while the aromatic protons have appeared at δ 6.91 and 7.99. Its ^{13}C NMR spectrum showed characteristic signals at δ 51.7 and 55.3 for the methyl carbons (-O**C**H_3) and δ 189.5 corresponding to the ester carbonyl group (C=O) (**Fig. 7**).

Table 6: Direct conversion of benzylic alcohols or aldehydes to aromatic esters[a]

Entry	Substrate	Product (**78a-k**)	Yield (%)[b]
a			98
b			82[c]
c			91
d			85[d]
e			87
f			85
g			80
h			78[e]
i			79[e]
j			82[e]

[a]Aldehyde (3 mmol), $NaIO_4$ (3 mmol), LiBr (3 mmol), conc. H_2SO_4 (1 mL), methanol (9 mL), 25 °C, 18 h; [b]After purification by column chromatography; [c] ethanol was used as the solvent; [d] Yield of the methyl 3-bromo-4-methoxybenzoate when 2 equiv. of LiBr used; [e] at 65 °C with aq. H_2SO_4 (0.85 N, 1 mL).

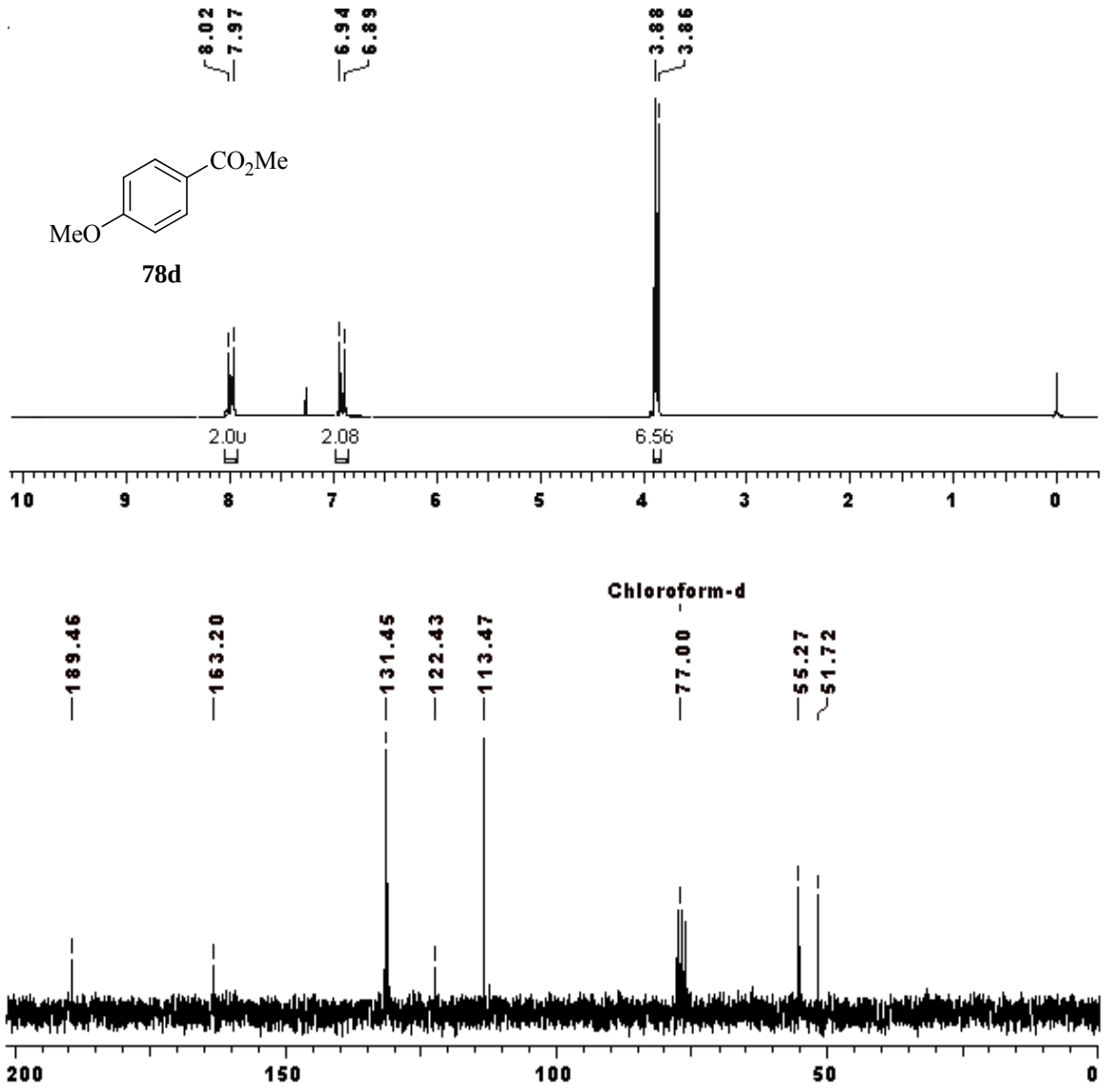


Fig. 7: ^{1}H and ^{13}C NMR spectra of **78d**

In another example, the ^{1}H NMR spectrum of **78h** showed a signal at δ 4.0 (s) for the methoxy protons (-OC**H**$_3$) and three signals at δ 7.67, 8.41 and 8.87 for the aromatic protons. In its ^{13}C NMR spectrum, the carbonyl group (-C=O) has appeared at δ 164.7 while the methoxy carbon (-O**C**H$_3$) appeared at δ 52.6 (**Fig. 8**).

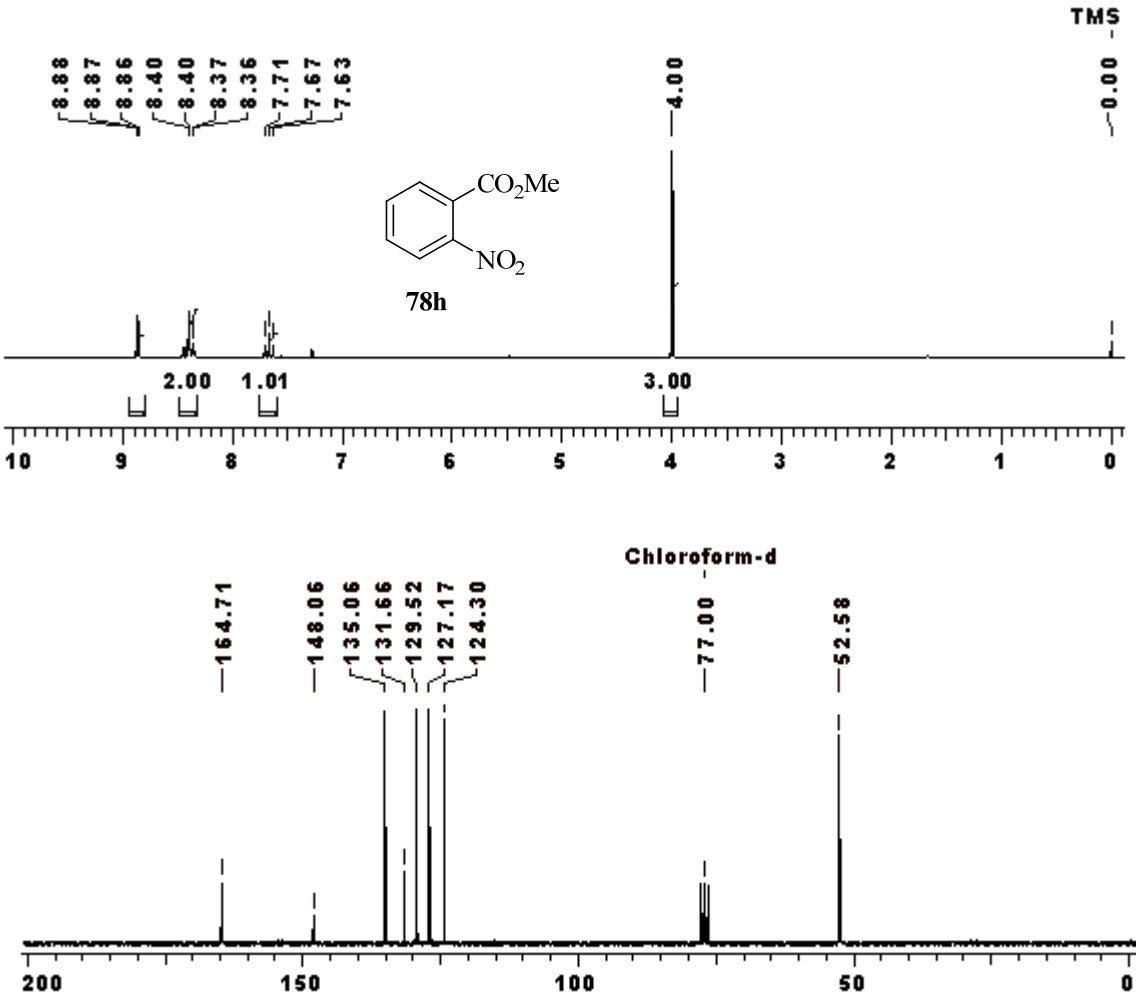
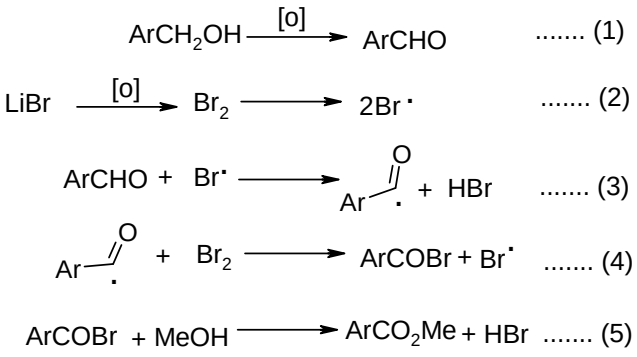


Fig. 8: ^{1}H and ^{13}C NMR spectra of **78h**

Among the several solvent combinations screened, a mixture of MeOH:H_2O (9:1, 10 mL) gave the highest yield of esters. Control experiments have proved that both $NaIO_4$ and LiBr are needed to produce esters. Ethanol was also found to give ethyl esters (entry b) while other alcohols such as 2-propanol and benzyl alcohol have failed to give their respective esters probably due to steric hindrance. Aliphatic alcohols or aldehydes were found to be inactive under the reaction conditions, which may be a limitation of this process. Replacing LiBr with other halide sources like tetrabutylammonium bromide or NaBr also brought about this conversion with comparable yield while KI and NaCl failed.



Scheme 47: proposed radical pathway for the direct esterification of aromatic aldehydes and benzylic alcohols.

Based on the observations that no traces of acetal or carboxylic acid was identified in the present study as well as from our earlier work on $NaIO_4$/LiBr mediated reactions,[33] a probable mechanism[46] for the oxidative esterification of aromatic aldehydes and benzylic alcohols has been given in **Scheme 47**. Initially, LiBr is oxidized by $NaIO_4$ in the presence of acetic acid to liberate bromine. Thus, the liberated bromine probably generates bromine radical which then initiates the propagation step by adding to the aldehyde to produce acyl radical. This acyl radical further reacts with bromine to form acylbromide, which upon hydrolysis furnish the corresponding esters.

3.2.4. Conclusion

In conclusion we have developed a new reagent system comprising $NaIO_4$/ LiBr and H_2SO_4 for the direct conversion of aldehydes and alcohols to their corresponding methyl and ethyl esters. The reaction is believed to proceed *via* radical pathway.

3.3.5. Experimental

Typical Experimental Procedure

To a 50 mL round bottom flask charged with aromatic aldehyde (3 mmol), lithium bromide (3 mmol) sodium metaperiodate (3 mmol), conc. H_2SO_4 (1 mL) in methanol (9 mL) was added at 25 ^oC. The reaction mixture was stirred for 18 h and then excess solvent was removed under reduced pressure. The residue was extracted with ethyl acetate, and the organic phase was washed with water, saturated $Na_2S_2O_3$, brine and dried over anhydrous sodium sulphate. Concentration of the organic layer gave crude ester, which was subjected to column purification using hexane/ethyl acette (19:1) as eluent to obtain pure aromatic esters.

Methyl benzoate (78a)

Yield: 98%; colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 7.35-7.41 (t, *J* = 6.2 Hz, 2H), 7.52 (m, 1H), 8.03 (d, *J* = 8.1 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 51.2, 128.3, 129.2, 130.7, 133.1, 148.1, 165.6; **IR** (neat, cm^{-1}): 715, 750, 1140, 134, 1510, 1600, 1732, 2940, 3060; Anal. Calcd for. $C_8H_8O_2$: C, 70.57; H, 5.92. Found C, 70.52; H, 5.97%.

Ethyl benzoate (78b)

Yield: 82%; colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 8.5 Hz, 3H), 4.13 (q, J = 7.5 Hz), 7.32-7.42 (t, *J* = 6.5 Hz, 2H), 7.53 (m, 1H), 8.03 (d, *J* = 7.2 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 14.1, 60.7, 128.1, 128.9, 129.5, 133.3, 166.4; **IR** (neat, cm^{-1}): 715, 755, 1040, 1314, 1520, 1600, 1730, 2942, 3055; Anal. Calcd for. $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.52; H, 6.57%.

Methyl 4-chlorobenzoate (78c)

Yield: 91%; colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.80-7.85 (d, *J* = 8.6 Hz, 2H), 7.91-7.96 (d, *J* = 8.6 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.9, 128.6,

129.5, 130.9, 139.2, 165.6; **IR** ($CHCl_3$, cm^{-1}): 1127, 1265, 1146, 1510, 1510, 1733, 2304, 2971, 3049; Anal. Calcd for. $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.28; H, 4.19%.

Methyl 4-methoxybenzoate (78d)

Yield: 85%; colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.88 (s, 3H), 6.91 (d, *J* =10.2 Hz , 2H), 8.01 (d, *J* = 10.3 Hz , 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.7, 55.3, 113.5, 122.4, 131.5, 163.2, 189.5; **IR** ($CHCl_3$, cm^{-1}): 1145, 133, 1510, 1603, 1723, 2940, 3060; Anal. Calcd for. $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.12; H, 6.01%.

Methyl 4-bromobenzoate (78e)

Yield: 87%; colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$,): δ 3.91 (s, 3H), 7.55-7.59 (d, *J*= 8.6 Hz, 2H), 7.87-7.91 (d, *J* =8.6 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$,): δ 52.1, 127.9, 129.0, 131.0, 131.6, 165.9; **IR** (Neat, cm^{-1}): 712, 1236, 1413, 1651, 1739, 2118, 2876, 3062; Anal. Calcd for. $C_8H_7BrO_2$: C, 44.68; H, 3.28; Found C, 44.62; H, 3.24%.

Methyl 4-cyanobenzoate (78f)

Y**ield**: 85%; colorless solid; **mp**: 82 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.97 (s, 3H), 7.74-7.77 (d, *J* = 6.0 Hz, 2H), 8.16-8.13 (d, *J* = 6.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 52.4, 116.5, 117.4, 129.9, 132.0, 133.7, 164.8; **IR** ($CHCl_3$, cm^{-1}): 1108, 1281, 439, 1605, 1729, 1951, 2229, 2957; Anal. Calcd for. $C_9H_7NO_2$: C, 67.06; H, 4.38; N, 8.69; Found: C, 67.29; H, 4.66 ; N, 8.31%.

Methyl 4-fluorobenzoate (78g)

Yield: 80%; colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.06-7.15 (d, *J* = 8.1 Hz, 2H), 8.05-8.09 (d, *J* = 8.1 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 52.1, 116.2, 129.8, 131.7, 165.2, 163.9; **IR** ($CHCl_3$, cm^{-1}): 720, 937, 1172, 1270, 1431, 1619, 1737, 2989, 3079; Anal. Calcd for. $C_8H_7FO_2$: C, 62.34; H, 4.58. Found: C,62.39; H, 4.55%.

Methyl 2-nitrobenzoate (78h)

Yield: 78%; yellow solid; **mp**: 121 ^{o}C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.0 (s, 3H), 7.64-7.67 (t, *J* = 8.2 Hz, 1H), 8.40-8.43 (m, 2H), 8.87 (d, *J* = 2.1 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 52.6, 124.3, 127.2, 129.52, 131.7, 135.1, 148.1, 164.7; **IR** ($CHCl_3$, cm^{-1}): 715, 750, 1140, 134, 1510, 1600, 1732, 2940, 3060; Anal. Calcd for. $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.03; H, 3.93; N, 7.78%.

Methyl 3-nitrobenzoate (78j)

Yield: 79%; yellow solid; **mp**: 121 ^{o}C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 7.48-7.56 (t, *J* = 8.6 Hz, 1H), 8.19-8.30 (m, 2H), 8.75 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 52.3, 124.3, 127.7, 129.7, 129.9, 131.9, 133.1, 164.9; **IR** ($CHCl_3$, cm^{-1}): 715, 750, 1140, 134, 1510, 1600, 1735, 2940, 3060; Anal. Calcd for. $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.03; H, 3.93; N, 7.78%.

Methyl 4-nitrobenzoate (78k)

Yield: 82%**;** yellow solid; **mp:** 93 ^{o}C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.97 (s, 3H), 8.16-8.30 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 52.5, 123.4, 130.6, 135.4, 150.8, 164.8; **IR** ($CHCl_3$, cm^{-1}): 1112, 1253, 1440, 1612, 1728, 3038; Anal. Calcd for. $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73; Found: C, 53.09; H, 3.83; N, 7.71%.

3.3.7 References

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CHAPTER 4

Ti-Superoxide catalyzed one-pot oxyfunctionalization of olefins and Pd-catalyzed Suzuki-type coupling reaction of arylmercuric acetate with arylboronic acid

Section I

Titanium superoxide: An efficient, reusable catalyst for one pot oxyfunctionalization of olefin *via* epoxide opening

4.1.1. Introduction

Alkoxy alcohols are the important intermediates in organic synthesis and also present in some naturally occurring compounds such as fugimycin (**1**), rapamycin (**2**), etc **(Fig. 1)**.[1] Further, oxidation of the alcohol group is a common method for the preparation of α-alkoxy ketones or aldehydes. The simple and straight forward method for the synthesis of alkoxy alcohols and diols is the ring opening of epoxides with alcohol or water in the presence of Lewis acid catalysts.[2] The common Lewis acids used for this purpose include $BF_3.OEt_2$, $SnCl_4$, anhydrous $FeCl_3$ etc.[3] However, standard methods for the nucleophilic opening of epoxides are not always satisfactory and suffer from disadvantages such as high acidity, lack of regioselectivity, longer reaction time, non-catalytic reagent and difficulty in handling.

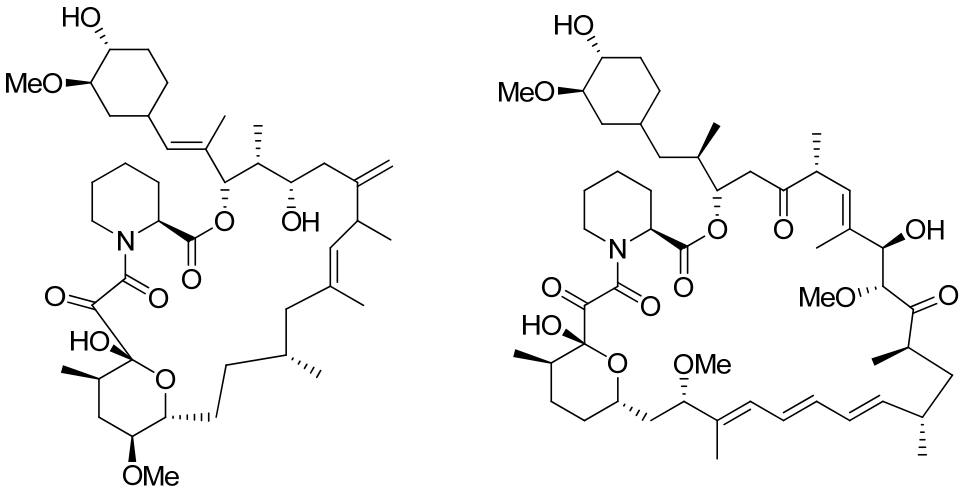


Fig. 1: Naturally occurring 1,2-methoxy alcohols

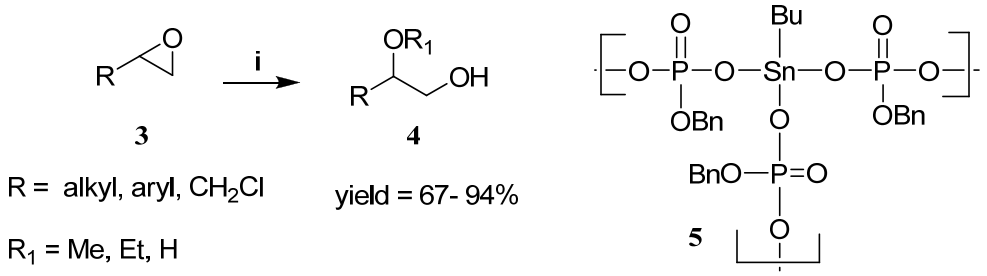
The epoxide opening with water leads to the formation of diols, which are widely used in organic synthesis as intermediates and fine chemicals. In addition to epoxide opening, diols are readily obtained through Prevost-Woodward reaction or dihydroxylation of olefins using OsO_4, RuO_4 or RuO_4 reaction (see chapter III).

4.1.2. Review of Literature

Literature search revealed that several methods exit for the preparation of β-alkoxy alcohols and 1,2-diols. Most of the methods describe the opening of epoxides in the presence of acid catalysts or organic molecule. Some of the methods reported in the recent time have been briefly discussed below.

Otera's approach (1988)[4]

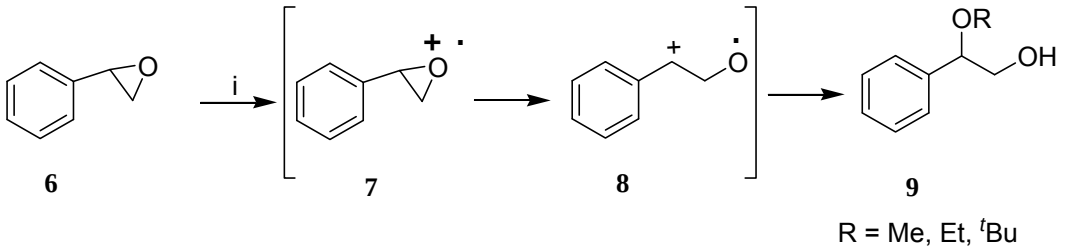
Otera *et al.* have reported highly regioselective alcoholysis of epoxides **3** catalyzed by organotin phosphate condensates (**5**, Sn-P) to provide a variety of β-alkoxy alcohols **4** in good yields. The *anti* stereoisomers are solely produced in all the cases, indicating the coordinative pathway of the catalyst. The salient feature of this method is the recyclability of the catalyst without any appreciable decrease in the activity and the selectivities (**Scheme 1**).



Scheme 1: cat. **5**, MeOH, hexane, reflux, 24 h.

Iranpoor's approach (1990)[5]

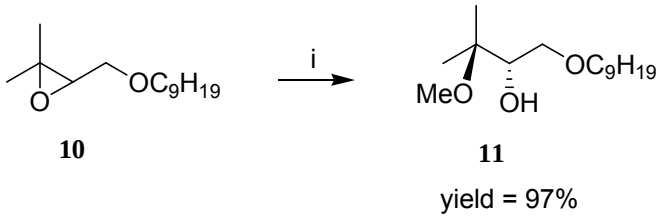
Iranpoor *et al.* have achieved the ring opening of epoxides with nucleophiles to obtain the corresponding β-alkoxy alcohols in excellent regioselctivity using catalytic amount of 2,3-dichloro-5,6-dicyano *p*-benzoquinone (DDQ) under neutral conditions in primary, secondary and tertiary alcohols as solvents. Thus, styrene oxide (**6**) furnished the corresponding alkoxy alcohol (**9**) with excellent yield and selectivity. The reaction is believed to proceed through single electron-transfer mechanism as shown in **Scheme 2**.



Scheme 2: DDQ (1 equiv.), MeOH, 25 °C, 5-12 h.

Masaki's approach (1993)[6]

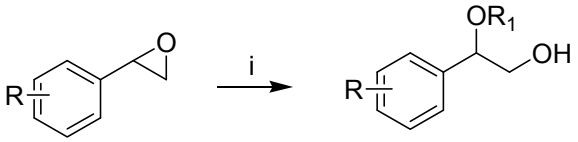
In this approach, tetracycanoethylene, a π-acid, has been employed to catalyze alcoholysis of epoxide **10** under ambient conditions. The stereospecific *anti* opening and favorable chemoselectivity without affecting the acid sensitive groups like tetrahydropyran ether and ethylene acetal are the major advantages of this protocol (**Scheme 3**).



Scheme 3: Tetracycnoethylene, MeOH, 0-40 °C.

Iranpoor's approach (1994)[7]

Iranpoor *et al.* have described a catalytic, simple and mild method for the conversion of epoxides into their corresponding β-alkoxy alcohols in the presence of ferric chloride ($FeCl_3$) as the catalyst. The β-alkoxy alcohols were obtained with high stereo- and regioselectivity and in good to excellent yields (**Scheme 4**).



12

R = Me, Cl, H
R_1 = Me, Et

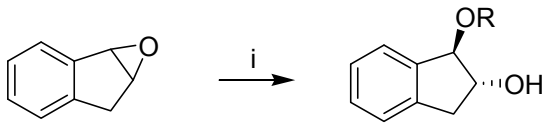
13

yield 63-98%

Scheme 4: cat. $FeCl_3$. $6H_2O$, R_1OH, 25 ^oC.

Iranpoor's approach (1996)[8]

Iranpoor *et al.* have observed that $FeCl_3$. $6H_2O$ absorbed on chromatographic silica gel could act as an efficient catalyst for alcoholysis, hydrolysis of epoxide. Accordingly, methanolysis of indene oxide (**14**) proceeded with high regioselectivity and excellent yield. They found that this protocol could also convert epoxides to their corresponding halohydrins in the presence of chloride and bromide ions (**Scheme 5**).



14

15

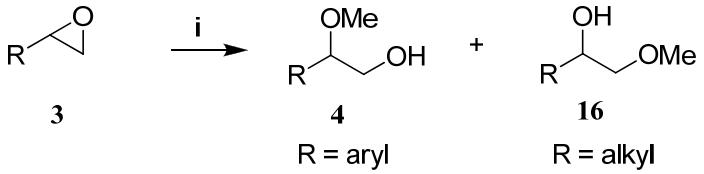
R = Me, Et, H

yield upto 95%

Scheme 5: $FeCl_3$. $6H_2O$. SiO_2, 25 ^oC or heat.

Kim's approach (2004)[9]

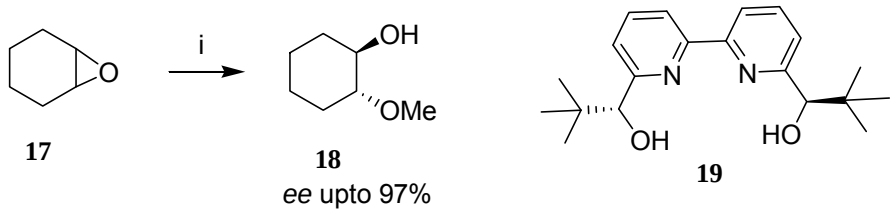
Kim *et al.* have achieved regioselective ring opening of epoxides to obtain β-alkoxy alcohols with good yields in the presence of indium trichloride ($InCl_3$) as catalyst. While the alcoholysis of styrene oxides produced S_N1 type product, the alcoholysis of epoxides with heteroatom in the proximity predominantly produced S_N2 type product (**Scheme 6**).



Scheme 6: cat. $InCl_3$, MeOH, 25 °C.

Schneider's approach (2004)[10]

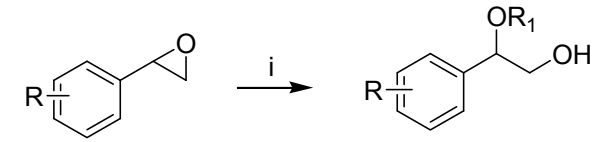
The catalytic desymmetrization of meso epoxides **17** *via* ring opening with methanol to obtain chiral β-methoxy alcohols **18** was achieved by Schneider *et al.* in the presence of $Sc(OTf)_3$ and bipyridyl based chiral ligand **19** (**Scheme 7**).



Scheme 7: $Sc(OTf)_3$, MeOH, CH_2Cl_2, 25 °C, 12-24 h.

Yadav's approach (2005)[11]

In this approach, epoxides **12** underwent rapid ring opening with a range of alcohols and water in the presence of catalytic carbon tetrabromide (CBr_4) under mild and convenient conditions to produce the corresponding β-alkoxy alcohols **13** and 1,2-diols in high yields with high regioselectivity (**Scheme 8**).



12 **13**

R = H, Me, Cl

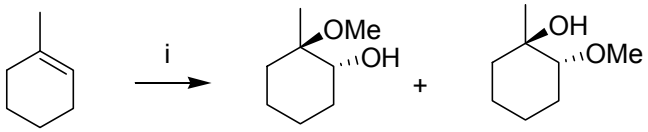
R_1 = H, Me, Et, Bn

yield = 63-98%

Scheme 8: CBr_4, R_1OH, 60 °C.

Bras' approach (2005)[12]

Bras *et al.* have described a simple method to obtain methoxy alcohols from the one-pot reaction of alkenes with oxone in methanol, in the absence of any additive or catalyst (**Scheme 9**). The use of other alcohols as solvents had shown that the efficiency of the process decreases with the steric hindrance of the alcohol. This is the only method available in the literature for the one-pot synthesis of alkoxy alcohols from olefin.



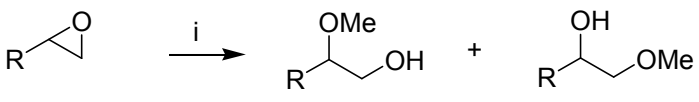
20 **21** **22**

regioselectivity = 91:9

Scheme 9: Oxone, MeOH, 25 °C.

Moghadam's approach (2007)[13]

Moghadam *et al.* have employed a new electron-deficient tin(IV)tetraphenyl phorphyrinato tetrafluoroborate [Sn^{IV}(tpp)(BF_4)] as an efficient catalyst for the alcoholysis, hydrolysis of epoxides. The results showed that replacing of BF_4^- with Cl- converts the tin(IV) phorphyrin to an efficient Lewis acid (**Scheme 10**).



3 **4** **16**

Scheme 10: [Sn^{IV}(tpp)(BF_4)], MeOH, 25 °C.

Dihydroxylation of olefins to obtain vicinal 1,2 diols had been extensively studied and several methods are available in the literature. The most often used method includes OsO_4 catalyzed dihydroxylation,[14] Prevost-Woodward reaction[15] and hydroxy acetoxylation followed by hydrolysis.[16] For an elaborate discussion on these reactions, refer the review of literature under Section I, Chapter III.

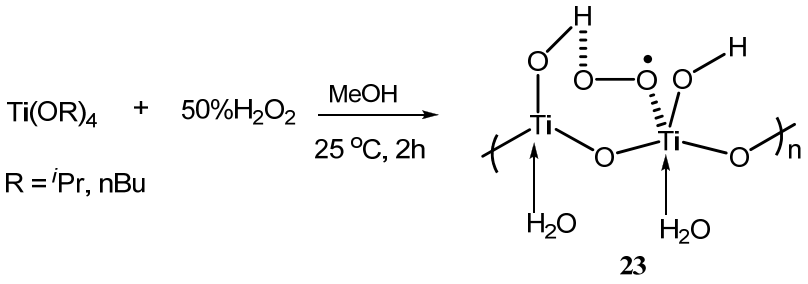
4.1.3. Present work

4.1.3.1 Objective

From the above discussion, it is clear that the synthesis of 1,2-alkoxy alcohols are generally achieved *via* opening of epoxides. However, a one-pot synthesis from olefin is rare probably due to the intolerance of the catalyst under oxidation condition. Hence, a stable metal catalyst, which can withstand oxidation conditions yet catalyzes the epoxide opening with nucleophiles, would have great relevance in the synthesis of fine chemicals.

4.1.4 Results and discussion

Recently, in our laboratory, we have reported the preparation of titanium superoxide (**23**) by treating H_2O_2 with titanium tetraisopropoxide ($Ti(O^iPr)_4$ in dry methanol.[17] Titanium superoxide was filtered as yellow colored solid and its structure was proposed to have polymeric Ti oxide as shown in **Fig. 2**.



23

Fig. 2: Preparation of Titanium superoxide

We have thoroughly characterized the generation of superoxide species **23** on the hydrated titanium matrix by various spectroscopic techniques such as FTIR, Raman spectroscopy, XRD, ESR, TG/DTA, and chemical analysis as follows. Its IR spectrum showed characteristic absorption bands at 3720 (w), 3665 (w), and 3450 (s) cm^{-1} indicating the presence of vibrational modes of coordinated water molecules at Ti^{4+} site and of surface Ti-OH groups. The other IR absorption bands at 1027 (s) and 1157 (m) indicates the presence of superoxide radical ion in the solid material. It also has IR absorption bands in the range of 900-538 (m) cm^{-1} corresponding to the presence of Ti-O-Ti linkages. An intense line at 900 cm^{-1} in the Raman spectrum of the catalyst **23** further confirmed the presence of Ti-O-Ti linkages. The other weak Raman lines observed in the range of 1025-1119 cm^{-1} assigned for the $O_2^{\cdot}$.

A sample of **23** dried at 25 ^oC (3 mm Hg) showed characteristic ESR signals at g_1 = 2.024, g_2 = 2.009 and g_3 = 2.003 (**Fig. 3**), which strongly suggest the presence of unpaired electrons of the stable superoxide radical anion generated by the decomposition of H_2O_2 over Ti-matrix. However, the characteristic ESR signals disappeared when its ESR was recorded at 90 ^oC.

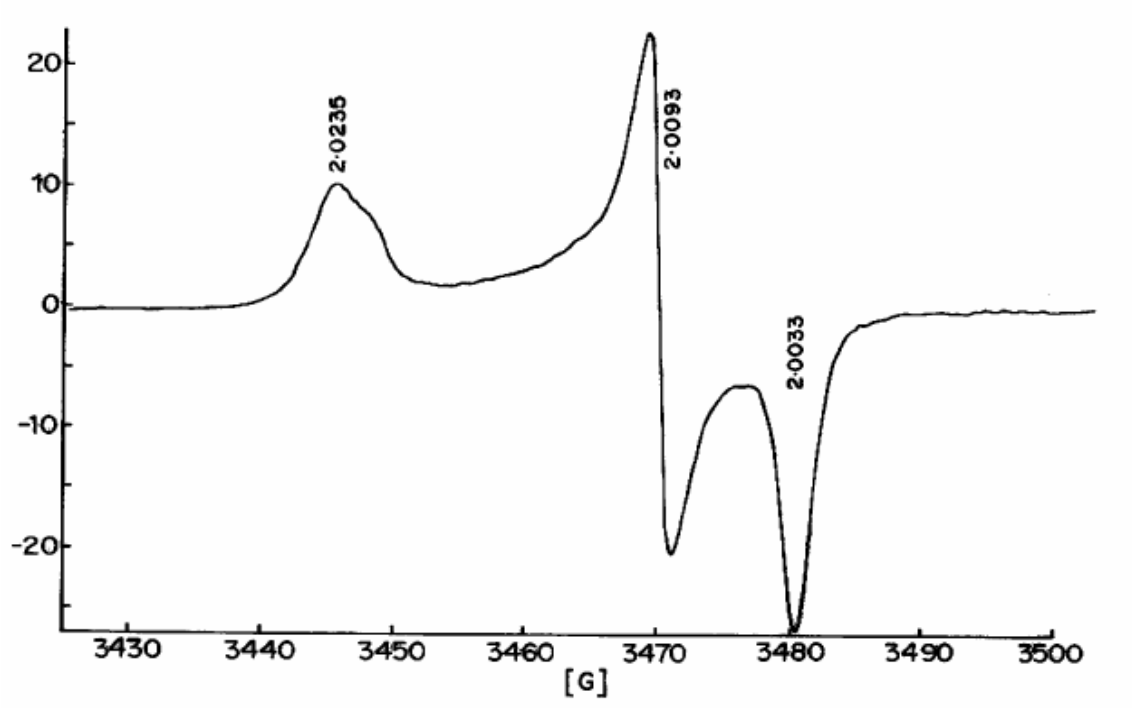
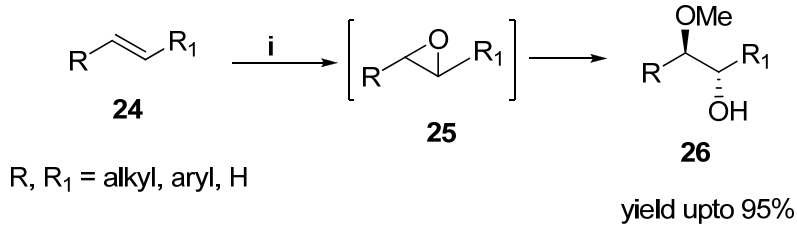


Fig. 3: ESR spectrum of **23** at 298 K.

During the study of its application in organic synthesis, we found that olefins can be oxyfunctionalized in one-pot *via* epoxide opening. Thus, treatment of olefin **24** with *m*-chloroperbenzoic acid (*m*CPBA) in the presence of MeOH at ambient conditions produced alkoxy alcohols **26** *via* epoxide **25** in good to excellent yields (**Scheme 11**).



Scheme 11: Titanium superoxide (**23**, 20wt%), *m*CPBA, $CHCl_3$: MeOH (9:1), 25 ^oC, 5 h.

Encouraged by this result, we subjected styrene to oxyfunctionalization with *m*CPBA in the presence of several alcohols like methanol, ethanol, isopropanol, etc. It was observed that sterically less hindered methanol produced the corresponding alkoxy alcohol in excellent yield while isopropanol gave poor yield (**Table 1**). The other titanium catalysts

screened for this transformation were found to be unsatisfactory in catalyzing the reaction.

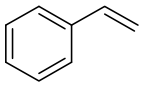
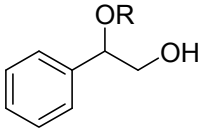
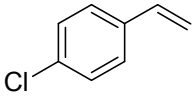
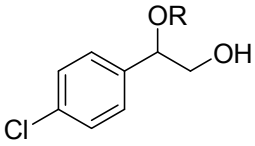
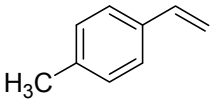
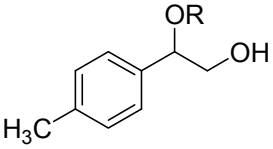
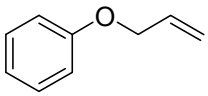
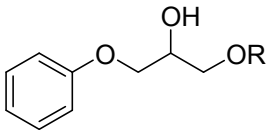
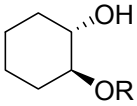
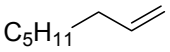
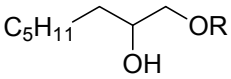
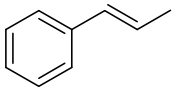
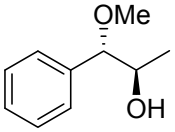
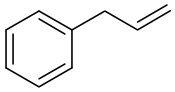
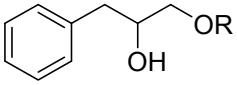
Table 1: Screening of nucleophiles and catalysts[a]

S.No	Nucleophile[b]	Catalyst	Yield (%)[c]
1	MeOH	Ti-superoxide	95%
2	EtOH	Ti-superoxide	89%
3	^{i}PrOH	Ti-superoxide	32
4	^{t}BuOH	Ti-superoxide	0
5	MeOH	TiO_2	24[d]
6	MeOH	$TiCl_4$	16[d]
7	MeOH	$Ti(O^{i}Pr)_4$	35[d]

[a]Reaction condition: styrene (3 mmol), catalyst, *m*CPBA (1 equiv.), $CHCl_3$: nucleophile (9:1), 25 ^{o}C, 5 h; [b]1 ml of alcohol was employed in all the cases; [c]Isolated yield after column chromatographic purification; [d]20 mol% of catalyst was employed.

In order to study the scope of this reaction, we screened several styrenes with electron-donating as well as electron-withdrawing groups and the results are presented in **Table 2**. Methanolysis proceeded smoothly at 25 ^{o}C to give alkoxy alcohols in excellent yields. In styrene derivatives nucleophilic methanol adds at the benzylic position due to its more electropositive nature. No trace of epoxide was isolated in the workup. This observation led to the conclusion that the epoxides formed *in situ* completely underwent regioselective opening with alcohol. Not only styrenes but also aliphatic olefins like cyclohexene and 1-octene underwent this reaction to produce the corresponding alkoxy alcohols (**27**-**34**).

Table 2: Oxyfunctionalization of olefins[a]

S. No	Substrate	product	Yield (%)[b]
1	 **27**	 R = H, Me, Et	**27a**, R = Me; 89 **27b**, R = Et; 82 **27c**, R = H; 65
2	 **28**	 R = H, Me, Et	**28a**, R = Me; 85 **28b**, R = Et; 79 **28c**, R = H; 66
3	 **29**	 R = H, Me, Et	**29a**, R = Me; 92 **29b**, R = Et; 83 **29c**, R = H; 69
4	 **30**	 R = H, Me, Et	**30a**, R = Me; 89 **30b**, R = Et; 81 **30c**, R = H; 65
5	 **31**	 R = H, Me, Et	**31a**, R = Me; 89 **31b**, R = Et; 83 **31c**, R = H; 59
6	 **32**	 R = H, Me, Et	**32a**, R = Me; 85 **32b**, R = H; 62
7	 **33**	 R = H, Me	**33a**, R = Me; 95 **33b**, R = H; 72
8	 **34**	 R = H, Me, Et	**34a**, R = Me; 92 **34b**, R = Et; 85 **34c**, R = H; 72

[a]Reaction condition: olefin (3 mmol), titanium superoxide (20 wt%), *m*CPBA (1.5 equiv.), $CHCl_3$: nucleophile (9:1), 25 ^oC, 5 h; [b]Isolated yield after column chromatographic purification.

All the alkoxy alcohols were systematically characterized from their ^{1}H, ^{13}C NMR and IR spectra. For example, the ^{1}H NMR spectrum of **27a** showed a singlet at δ 3.31(s) corresponding to the methoxy protons (-OC**H**$_3$) and two signals at δ 4.3 and 3.6 for the methine (-C**H**-O) and methylene (-C**H**$_2$OH) protons respectively. Its ^{13}C NMR spectrum displayed signals at δ 84.7 due to the benzylic carbon and at δ 66.9 and 56.5 for the methylene (-**C**H$_2$OH) and methoxyl (**C**H$_3$O-) carbons respectively (**Fig.4**). The IR spectrum of all the compounds showed a strong absorption band in the region of 3200-3500 cm^{-1} due to the presence of hydroxyl group.

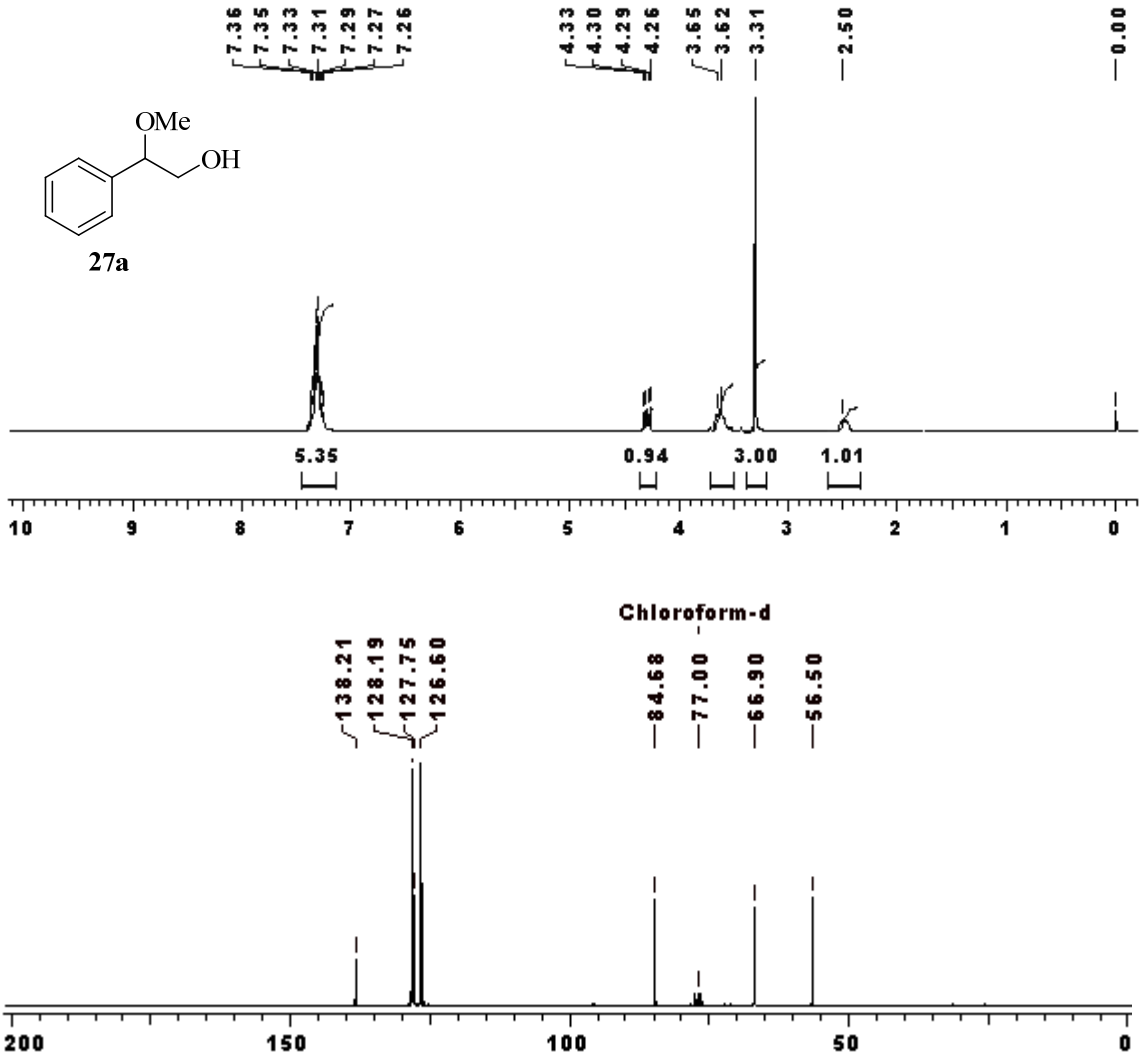


Fig. 4: ^{1}H and ^{13}C NMR spectra of **27a**

Interestingly, the internal olefins with aromatic rings like indene and β-methyl styrene produced exclusively one regioisomer with *anti*-selectivity. The formation of *trans*-β-alkoxy alcohol **33a** was confirmed from its ^{1}H NMR spectrum, which displayed characteristic peaks at δ 1.09(d) and δ 3.28(s) corresponding to the C–C**H$_3$** and OC**H$_3$** protons respectively. Its ^{13}C NMR spectrum showed signals at δ 17.7 for C-**C**H$_3$ carbon and at δ 56.9, 70.5 and 87.5 for the other aliphatic carbons respectively (**Fig.5**).

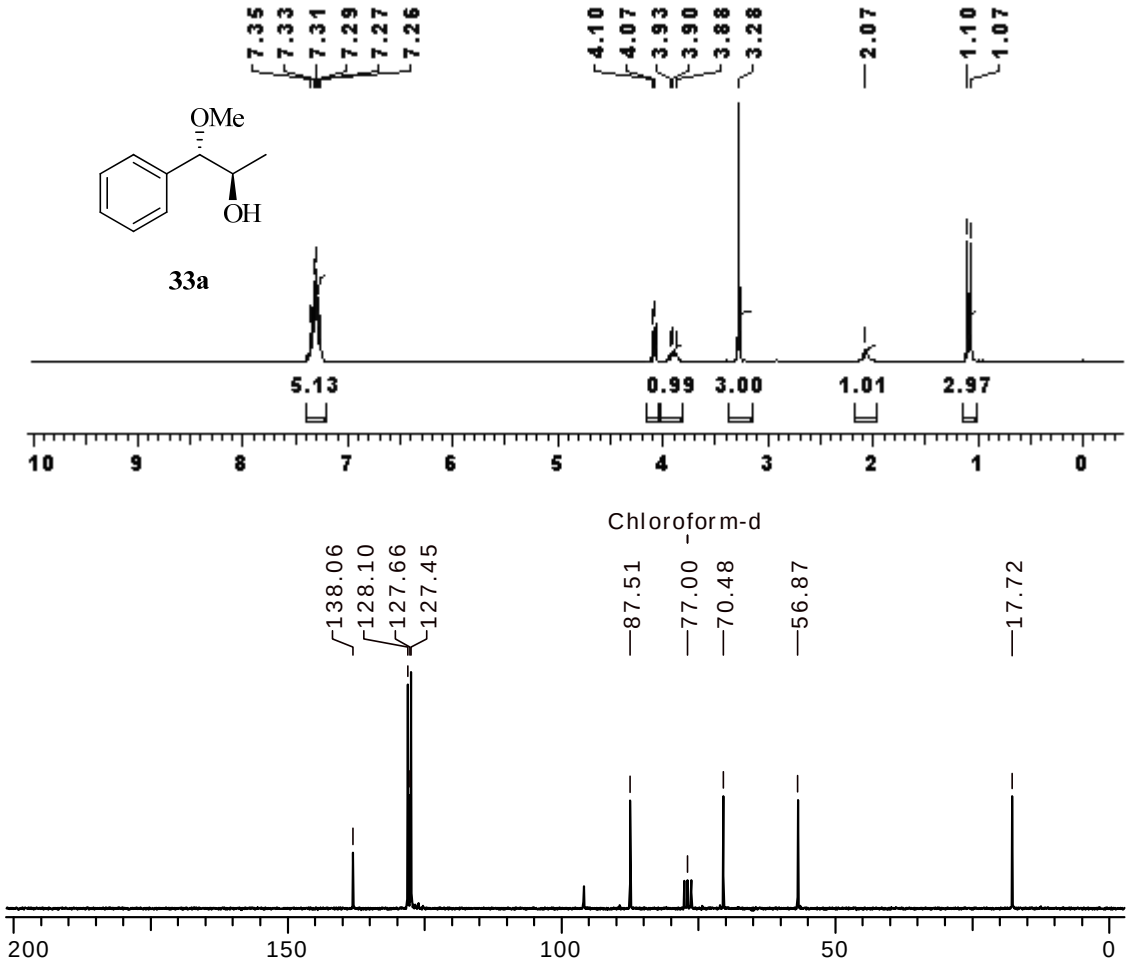


Fig. 5: ^{1}H, ^{13}C NMR spectra of **33a**

After the successful preparation of several alkoxy alcohols, we anticipated that the replacement of alcohols with water would result in the formation of diols. Indeed, diols

were obtained in moderate yield due to the immiscibility of water. However, vigorous stirring required to obtain good yield of the diols. Our attempts to make the solvents miscible by adding phase transfer catalysts like $nBu_4N^+Br^-$ resulted in the formation of halohydrin. Here, the oxidant *m*CPBA liberates Br_2 from $nBu_4N^+Br^-$, which underwent bromohydroxylation in the presence of water.

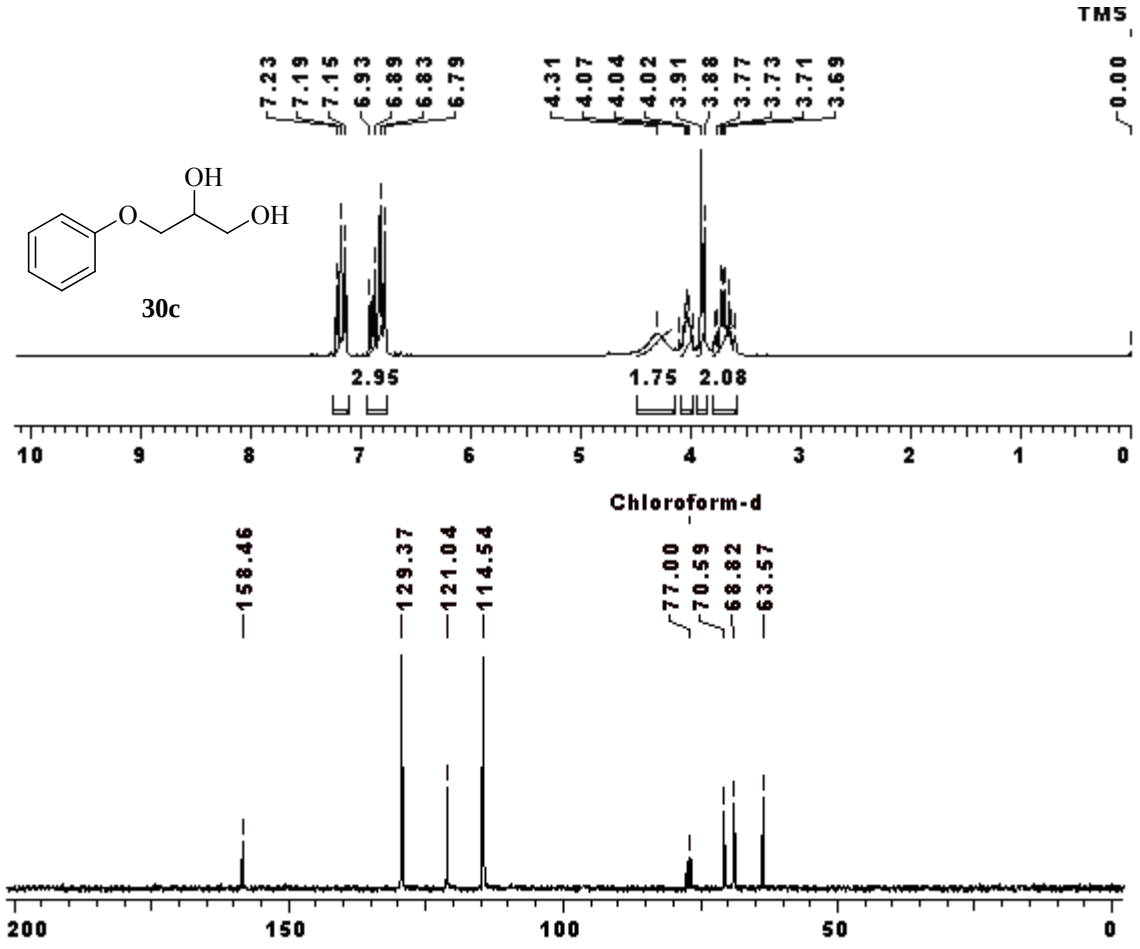


Fig. 6: ^{1}H and ^{13}C NMR spectra of **30c**

All the diols were systematically characterized from their ^{1}H, ^{13}C NMR spectra and comparing their melting points. For example, the ^{1}H NMR spectrum of **30c** showed signal at δ 3.89(m) and 3.73(m) for the methylene protons (PhOC**H**$_2$- and –C**H**$_2$OH) respectively while the signal for methine proton (-C**H**OH) appeared at δ 4.02. Its ^{13}C

NMR spectrum showed signals at δ 63.6, 68.8 and 70.6 for the aliphatic carbons (**C**-O) having oxygen substituents (**Fig.6**).

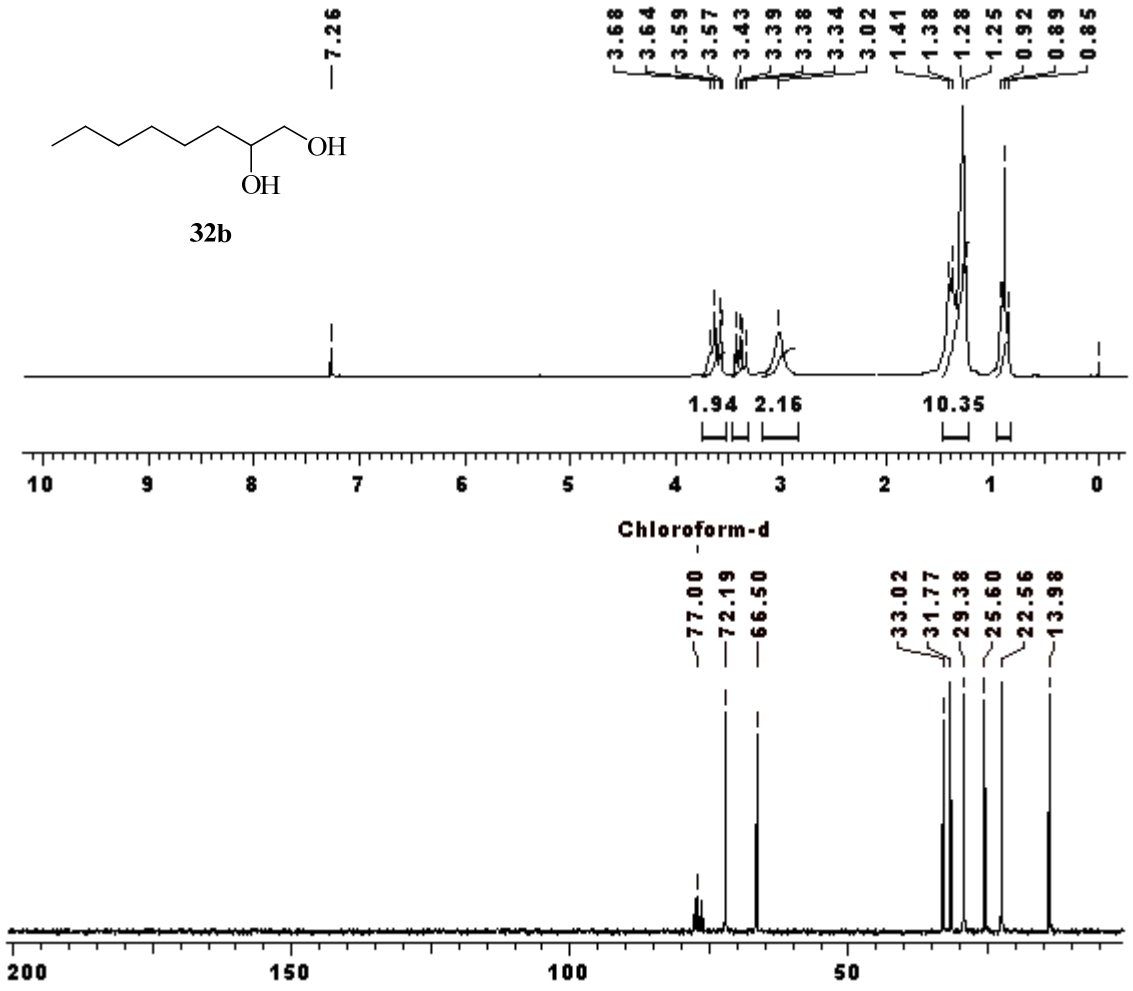


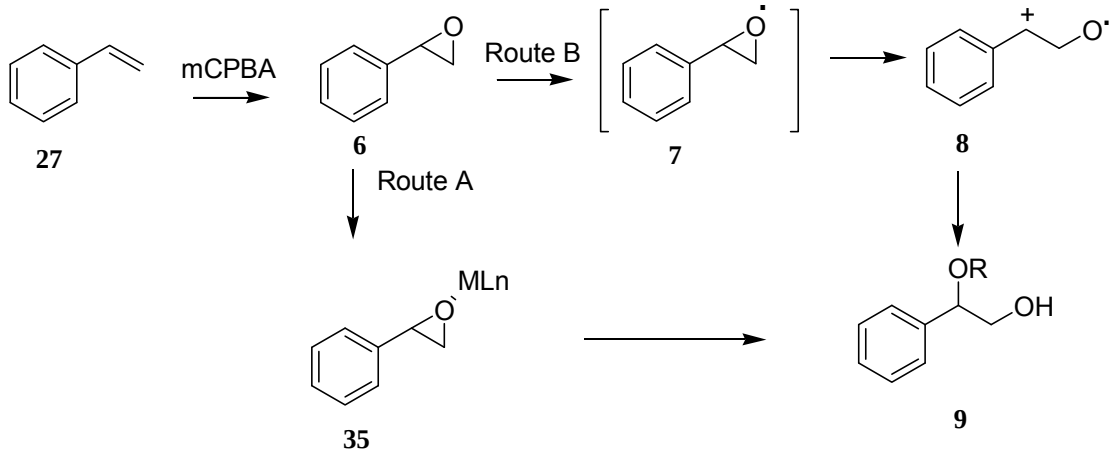
Fig. 7: ^{1}H and ^{13}C NMR spectra of **32b**

In another example, the ^{1}H NMR spectrum of **32b** displayed signals at δ 3.64 and 3.39 (m) corresponding to the C**H**O and C**H**$_2$O protons respectively, whereas a multiplet at δ 1.28 corresponds to the long chain proton. Its ^{13}C NMR showed two signals at δ 72.2 and 66.5 due to the two carbons having oxygen atoms and six signals in the region of δ 14.0-33.5 due to long chain carbons (**Fig.7**).

As expected, the internal olefins produced the corresponding *trans*-diols in moderate yields. Even trace of *cis*-diols were not observed in their ^{1}H NMR spectrum. After the completion of the reaction, the reaction mixture was dissolved with excess chloroform and the solid metal catalyst was separated by simple filtration. After drying at room temperature it was tested for its ability to catalyze oxyfuntionalization. The reaction proceeded smoothly with the recovered titanium superoxide without appreciable loss of activity and selectivity.

4.1.3.2 Mechanism

Mechanistically, the reaction may be expected to proceed through the following two routes; i) Lewis acid-coordination (route A) and ii) Single electron-transfer (route B). Since, the structure of the metal catalyst is believed to contain a radical, one may propose the electron-transfer mechanism as shown in route B. Theoretically, route B proceeds through carbocation **8** so that it should lead to the formation of both *cis*- and *trans*-alkoxy alcohols for internal olefins. In contrast, it has been experimentally found that cyclohexene produced the corresponding *trans*-alkoxy alcohols or diols exclusively. Further, route B requires stoichiometric amount of metal catalyst, which cannot be recycled. Because of the above reasons, we believe that the catalyst acts as a stable Lewis acid (**35**) than a single electron-transfer agent (**Scheme 11**).



Scheme 11: Possible mechanistic pathways

4.1.4. Conclusion

In summary, we have developed a novel one-pot procedure for the preparation of 1,2-alkoxy alcohols and diols from olefin *via* titanium superoxide catalyzed ring opening of *in situ* generated epoxides. The metal catalyst was found to be stable under the reaction condition and can be recycled without any appreciable loss of activity. Excellent regioselectivity and stereoselectivity was achieved.

4.1.5. Experimental section

4.1.5.1. Preparation of titanium superoxide[17]

50% H_2O_2 (5.98 g, 0.175 mol) was added slowly to a solution of $Ti(OiPr)_4$ (5.0 g, 0.0175 mol) in anhydrous MeOH (50 mL) over 40 min. under N_2 with stirring at room temperature. The yellow precipitate that formed was collected by filtration on a sintered funnel, washed with anhydrous methanol, and dried under reduced pressure (3 mmHg) at 258 ^oC for 1 h. Yield: 3.94 g

4.1.5.2. General experimental procedure for the preparation of alkoxy alcohols

To a solution of alkene (3 mmol) in $CHCl_3$: ROH (9:1) at 25 ^oC was added *m*-chloroperbenzoic acid (*m*CPBA) (4.5 mmol) and titanium superoxide (20 wt% based on the substrate). The reaction mixture was stirred at the same temperature for 12 h. After the completion of the reaction, the solid 3-chlorobenzoic acid was dissolved in excess $CHCl_3$ and filtered to get back the metal catalyst. The filtrate was washed with $NaHCO_3$, water, brine and dried over anhydrous Na_2SO_4 to obtain the crude alkoxy alcohols. Chromatographic purification of the crude product using silica gel and ethyl acetate:petroleum ether (1:9) as eluent gave the pure alkoxy alcohols.

4.1.5.3. General experimental procedure for the preparation of diols

To a solution of alkene (3 mmol) in $CHCl_3$:H_2O (9:1) at 25 ^oC was added *m*-chloroperbenzoic acid (*m*CPBA) (4.5 mmol) and titanium superoxide (20 wt% based on the substrate). The reaction mixture was stirred at the same temperature for 12 h. After the completion of the reaction, the solid 3-chlorobenzoic acid was dissolved in excess $CHCl_3$ and filtered to get back the metal catalyst. The filtrate was washed with $NaHCO_3$, water, brine and dried over anhydrous Na_2SO_4 to obtain the crude alkoxy alcohols. Chromatographic purification of the crude product using silica gel and ethyl acetate: petroleum ether (1:9) as eluent gave the pure diols.

2-Methoxy-2-phenylethanol (27a)

Yield: 89%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 7.26-7.41 (m, 5H), 4.32 (dd, *J* = 4.0, 8.3 Hz, 1H), 3.58-3.72 (m, 2H), 3.31 (s, 3H), 2.37 (s, 1H); **^{13}C-NMR** (300 MHz, $CDCl_3$) δ 138.2, 128.5, 128.1, 126.8, 84.6, 67.4, 56.9; **IR** ($CHCl_3$, cm^{-1}): 3420, 3030, 2982, 2933, 1454, 1355, 1112; **GC-MS** m/z (rel. intensity) 152 (1, M+), 121 (100),

105 (16), 91 (41), 77 (44); Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.12; H, 8.01%.

2-Ethoxy-2-phenylethanol (27b)

Yield: 82%; Colorless liquid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.27-7.39 (m, 5H), 4.42 (dd, *J* = 4.2 Hz, 8.2 Hz, 1H), 3.56-3.70 (m, 2H), 3.36-3.53 (m, 2H), 2.35 (dd, *J* = 3.8 Hz, 9.2 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 138.9, 128.3, 127.8, 126.6, 82.7, 67.2, 64.3, 15.1; **IR** ($CHCl_3$, cm^{-1}): 3428, 3033, 2979, 2873, 1452, 1347, 1105; **GC-MS** m/z (rel. intensity) 166 (1, M+), 135 (100), 121 (3), 107 (63), 91 (12), 79 (54); Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.12; H, 8.31%.

1-Phenyl-1,2-ethanediol (27c)

Yield: 65%; Colorless solid; **mp**: 64-65 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.57 (m, 2H), 4.51 (brs, 2H), 4.69 (dd, *J* = 3.8, 8.2 Hz, 1H), 7.24 (s, 5H). **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 59.02, 73.33, 125.15, 126.08, 126.96, 140.93; **IR** ($CHCl_3$, cm^{-1}): 3426, 2993, 2954, 1453, 1380, 1099, 985; **GC-MS** m/z (rel. intensity) 166 (1, M+), 135 (100), 121 (3), 107 (63), 91 (12), 79 (54); Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.31. Found: C, 69.53; H, 7.29%.

2-(1-Methylethoxy)-2-phenylethanol (27d)

Yield: 80%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.26-7.37 (m, 5H), 4.53 (dd, *J* = 4.6, 7.9 Hz, 1H), 3.54-3.64 (m, 3H), 2.55 (dd, *J* = 4.2, 8.6 Hz, 1H), 1.19 (d, *J* = 5.9 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 139.6, 128.3, 127.8, 126.7, 79.9, 69.4, 67.4, 23.4, 21.2; **IR** ($CHCl_3$, cm^{-1}): 3426, 3033, 2973, 2924, 1453, 1380, 1099; **GC-MS** m/z (rel. intensity) 180 (1, M+), 149 (50), 121 (8), 107 (100),

91 (15), 79 (35); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.22; H, 8.81%.

2-(4-Chlorophenyl)-2-methoxyethanol (28a)

Yield: 85%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$); δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.26 (dd, *J* = 4.3, 7.8 Hz, 1H), 3.51-3.65 (m, 2H), 3.28 (s, 3H), 2.36 (br s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 136.8, 133.8, 128.7, 128.2, 84.0, 67.1, 56.9; **IR** (neat, cm^{-1}): 3436, 3004, 2937, 2913, 1454, 1112, 829; **GC-MS** m/z (rel. intensity) 186 (8, M+), 151 (11), 141 (100), 125 (6), 113 (29), 77 (66); Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.92; H, 5.94. Found: C, 57.95; H, 5.99%.

2-(4-Chlorophenyl)-2-ethoxyethanol (28b)

Yield: 79%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.39 (dd, *J* = 4.4, 7.9 Hz, 1H), 3.57-3.65 (m, 2H), 3.35-3.52 (m, 2H), 2.57 (dd, *J* = 4.2, 8.4 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 137.6, 133.7, 128.7, 128.1, 82.0, 67.2, 64.6, 15.2; **IR** ($CHCl_3$, cm^{-1}): 3435, 3031, 2976, 2874, 1491, 1091, 825; **GC-MS** m/z (rel. intensity) 200 (1, M+), 169 (100), 155 (3), 141 (84), 125 (13), 113 (20), 77 (41); Anal. Calcd for $C_{10}H_{13}ClO_2$: C, 59.86; H, 6.53. Found: C, 59.88; H, 6.61%.

1-(4-Chlorophenyl)-1,2ethanediol (28c)

Yield: 66%; Colorless solid; mp: 81 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$ and DMSO-d_6): δ 3.60 (m, 2H), 4.72 (dd, *J* = 3.8, 8.2 Hz, 1H), 7.25 (d, *J* = 8.34 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H). **^{13}C-NMR** (50 MHz, $CDCl_3$ and DMSO-d_6): δ 82.67, 88.59, 135.29, 143.83, 146.0, 157.93; Anal. Calcd for $C_8H_9O_2Br$: C, 44.27; H, 4.19; Br, 36.81. Found: C, 44.26; H, 4.16; Br, 36.79 %.

2-Methoxy-2-(4-methylphenyl)ethanol (29a)

Yield: 92%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 7.16-7.26 (m, 4H), 4.28 (dd, *J* = 3.9, 8.4 Hz, 1H), 3.53-3.71 (m, 2H), 3.29 (s, 3H), 2.52 (dd, *J* = 3.7, 9.2 Hz, 1H), 2.35 (s, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 137.7, 135.1, 129.1, 126.7, 84.5, 67.2, 56.6, 21.0; **IR** (KBr, cm^{-1}): 3426, 3022, 2929, 2871, 1447, 1351, 1115, 815; **GC-MS** m/z (rel. intensity) 166 (1, M+), 135 (100), 119 (14), 105 (12), 91 (30), 77 (4); Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.33%.

2-Ethoxy-2-(4-methylphenyl)ethanol (29b)

Yield: 83%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 4.43 (dd, *J* = 3.8, 8.4 Hz, 1H), 3.59-3.74 (m, 2H), 3.39-3.56 (m, 2H), 2.66 (br s, 1H), 2.39 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 137.7, 136.0, 129.2, 126.7, 82.7, 67.4, 64.3, 21.1, 15.3; **IR** ($CHCl_3$, cm^{-1}): 3438, 3025, 2977, 2929, 1448, 1339, 1098, 815; **GC-MS** m/z (rel. intensity) 180 (1, M+), 149 (100), 134 (9), 121 (57), 105 (31), 93 (39), 77 (18); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.22; H, 9.00%.

1-(4-Methylphenyl)-1,2 ethanediol (29c):

Yield: 69%; Colorless gum; **mp**: 76-77 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.46 (m, 2H), 4.58 (dd, *J* = 4.1, 8.0 Hz, 1H), 5.05(br, s, 2H), 6.97 (d, *J* = 7.9, 2H), 7.05 (d, *J* = 8.1, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.2, 67.9, 74.6, 126.1, 129.1, 137.2, 137.6; **IR** ($CHCl_3$, cm^{-1}): 3438, 3015, 2972, 2923, 1448, 1339, 1018, 928; Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.96. Found C, 70.96; H, 8.09 %.

1-Methoxy-3-phenoxy-2-propanol (30a)

Yield: 89%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.24-7.30 (m, 2H), 6.89-6.97 (m, 3H), 4.12-4.18 (m, 1H), 3.99-4.01 (m, 2H), 3.50-3.59 (m, 2H), 3.39 (s, 3H), 3.00 (br s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 158.5, 129.5, 121.0, 114.5, 73.6, 69.0, 68.9, 59.2; **IR** ($CHCl_3$, cm^{-1}): 3424, 3039, 2932, 2886, 1598, 1501, 1458, 1374, 1250, 1113, 1040; **GC-MS** m/z (rel. intensity) 182 (35, M+), 136 (2), 119 (11), 108 (13), 94 (100), 77 (25); Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.98; H, 7.65%.

1-Ethoxy-3-phenoxy-2-propanol (30b)

Yield: 81%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.20-7.27 (m, 2H), 6.88-6.94 (m, 3H), 4.12-4.21 (m, 1H), 3.93-4.02 (m, 2H), 3.44-3.61 (m, 4H), 3.37-3.39 (m, 1H), 1.18 (t, J = 7.0 Hz, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 158.6, 129.8, 129.5, 121.0, 114.6, 71.6, 69.0, 66.9, 15.1; **IR** ($CHCl_3$, cm^{-1}): 3428, 3040, 2978, 2933, 1597, 1498, 1458, 1381, 1247, 1115, 1044; **GC-MS** m/z (rel. intensity) 196 (41, M+), 136 (3), 119 (11), 103 (19), 94 (100), 77 (25); Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.35; H, 8.32%.

3-(Phenoxy)-1,2-propanediol (30c)

Yield: 65%; **mp**: 50-52 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.70 (m, 2H), 3.90 (d, J = 5.31 Hz, 2H), 4.05 (m, 1H), 4.31 (br, s 2H), 6.85 (m, 3H), 7.19 (m, 2H). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 63.57, 68.82, 70.59, 114.54, 121.04, 129.37, 158.46; **IR** ($CHCl_3$, cm^{-1}): 3424, 2915, 2889, 1598, 1501, 1458, 1374, 1295, 1250, 1117, 1044; Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.21. found C, 64.20; H, 7.09 %.

***trans*-2-Methoxycyclohexanol (31a)**

Yield: 89%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.40 (s, 3H), 3.37-3.44 (m, 1H), 2.90-2.98 (m, 1H), 2.57 (brs, 1H), 1.99-2.15 (m, 2H), 1.69-1.76 (m, 2H), 1.06-1.31

(m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 85.0, 73.8, 56.3, 32.0, 28.3, 24.1, 23.9; **IR** ($CHCl_3$, cm^{-1}): 3440, 2934, 2862, 1453, 1102; **GC-MS** m/z (rel.intensity) 130 (50, M+), 112 (13), 98 (32), 84 (46), 71 (100), 58 (23); Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.64; H, 10.72%.

***trans*-2-Ethoxycyclohexanol (31b)**

Yield: 83%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.72 (ddd, *J* = 7.1, 9.3, 14.0 Hz, 1H), 3.42 (m, 2H), 3.02 (ddd, *J* = 4.3, 8.5, 10.7 Hz, 1H), 1.99-2.10 (m, 2H), 1.70-1.73 (m, 2H), 1.10-1.30 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 83.5, 73.7, 64.0, 32.0, 29.2, 24.2, 23.9, 15.6; **IR** ($CHCl_3$, cm^{-1}): 3441, 2974, 2934, 2865, 1451, 1107; **GC-MS** m/z (rel. intensity) 144 (16, M+), 126 (2), 115 (8), 98 (32), 85 (100), 70 (68), 57 (80); Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.72; H, 11.34%.

Cyclohexane-1, 2-*trans*-diol (31c)

Yield: 59%; Colorless solid; mp: 92-93 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (m, 2H), 1.61 (m, 6H), 3.73 (m, 2H), 4.05 (br, s, 2H). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.58, 29.75, 70.64. **IR** ($CHCl_3$, cm^{-1}): 3359, 2995, 2967, 1445, 1167, 992; Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found C, 61.92; H, 10.36 %.

1-Methoxy-1-phenylpropan-2-ol (33a)

Yield: 95%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.09 (d, *J* = 6.2 Hz, 3H), 2.07 (brs, 1H), 3.28 (s, 3H), 3.90 (m, 1H), 4.09 (d, *J* = 6.6 Hz, 1H), 7.29 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 17.7, 56.9, 70.5, 87.5, 127.5, 127.7, 128.1, 138.1; **IR** ($CHCl_3$, cm^{-1}): 3420, 3030, 2982, 2933, 1454, 1355, 1112; Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.19; H, 8.31%.

1-Phenyl propan-1, 2diol (33b)

Yield: 72%; Colorless gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.92 (d, *J* = 8.7 Hz, 3H), 3.74 (m, 1H), 4.1 (brs, 2H), 4.22 (d, *J* = 8.2 Hz, 1H), 7.29 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.8, 72.2, 79.6, 127.1, 127.7, 128.1, 141.3; **IR** ($CHCl_3$, cm^{-1}): 3352, 3015, 2995, 2923, 1454, 1355, 986; Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.19; H, 8.31%.

1-Methoxyoctan-2-ol (32a)

Yield: 85%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.0 Hz, 3H), 1.12–1.52 (m, 10 H), 2.95 (brs, 1H), 3.25–3.38 (m, 2H), 3.45 (s, 3H), 3.65– 4.00 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.6, 25.64, 29.4, 31.8, 33.1, 59.2, 72.2, 80.1; **EI-MS**: *m*/*z* (%) = 160 (M+, 23), 145 (10), 129 (35), 111 (100), 70(41), 42 (21); **IR** ($CHCl_3$, cm^{-1}) 3441, 2974, 2934, 2865, 1451, 1107; Anal. Calcd for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.55; H, 12.64%.

n-Oct-1, 2-diol (32b)

Yield: 62%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.89 (m, 3H), 1.25-1.41 (m, 10H), 3.02 (br, s, 2H), 3.39 (m, 1H), 3.62 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.02, 22.59, 25.64, 29.42, 31.81, 33.06, 66.54, 72.23; **IR** (neat, cm^{-1}): 3421, 3012, 2975, 1397, 1152, 962; Anal. Calcd for $C_8H_{18}O_2$ C, 65.71; H, 12.40. Found C, 65.78; H, 12.31%.

1-Methoxy-3-phenyl-2-propanol (34a)

Yield: 92%; Colorless liquid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.20-7.32 (m, 5H), 3.94-4.03 (m, 1H), 3.25-3.40 (m, 2H), 3.35 (s, 3H), 2.71-2.84 (m, 2H), 2.61 (d, *J* = 3.7 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 137.9, 129.2, 128.3, 126.3, 75.9, 71.1, 58.9, 39.7; **IR** (KBr, cm^{-1}): 3429, 3033, 2922, 2898, 1450, 1125, 1085; **GC-MS** m/z (rel. intensity) 166

(1, M+), 148 (45), 121 (29), 103 (40),92 (100), 75 (24); Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.22; H, 8.40%.

1-Ethoxy-3-phenyl-2-propanol (34b)

Yield: 85%; Pale-yellow liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.20-7.31 (m, 5H), 3.95-4.04 (m, 1H), 3.27-3.56 (m, 4H), 2.72-2.84 (m, 2H), 2.68 (s, 1H), 1.19 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 138.1, 129.4, 128.4, 126.4, 73.8, 71.3, 66.7, 39.9, 15.1; **IR** ($CHCl_3$, cm^{-1}): 3436, 3032, 2977, 2929, 1450, 1118; **GC-MS** m/z (rel. intensity) 162 (35, M+-H_2O), 133 (35), 121 (26), 103 (35), 92 (100), 77 (12), 61 (42); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.25; H, 9.01%.

3-Phenyl propane-1,2-diol (34c)

Yield: 72%; Colorless solid; **mp**: 64-65 ^oC; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 2.56 (brs, 2H), 2.76 (d, *J* = 7.4 Hz, 2H), 3.45-3.50 (s, 1H), 3.65 (d, *J* = 11.1 Hz, 1H), 3.65 (d, *J* =11.1 Hz, 1H), 3.91 (d, *J* = 7.2 Hz, 1H), 7.20-7.33 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 39.8, 66.0, 73.0, 126.5, 128.6, 129.3, 137.8**; IR** (neat, cm^{-1}): 3230, 3029, 2923, 2862, 1495, 1456; Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.96. Found C, 71.06; H, 8.01 %.

Section II

Phosphine ligand and base-free Pd-catalyzed Suzuki type cross-coupling reaction of arylboronic acids with aryl mercuric acetates

4.2.1. Introduction

The palladium-catalyzed Suzuki-Miyaura coupling of aryl halides with arylboronic acids or esters is one of the most powerful and versatile methods for the formation of C-C bonds, in particular for the preparation of biaryl compounds.[18] In recent years this reaction has been successfully applied in the synthesis of natural products (**36-40) (Fig. 8**), [19] drugs[20] and conducting polymers.[21]

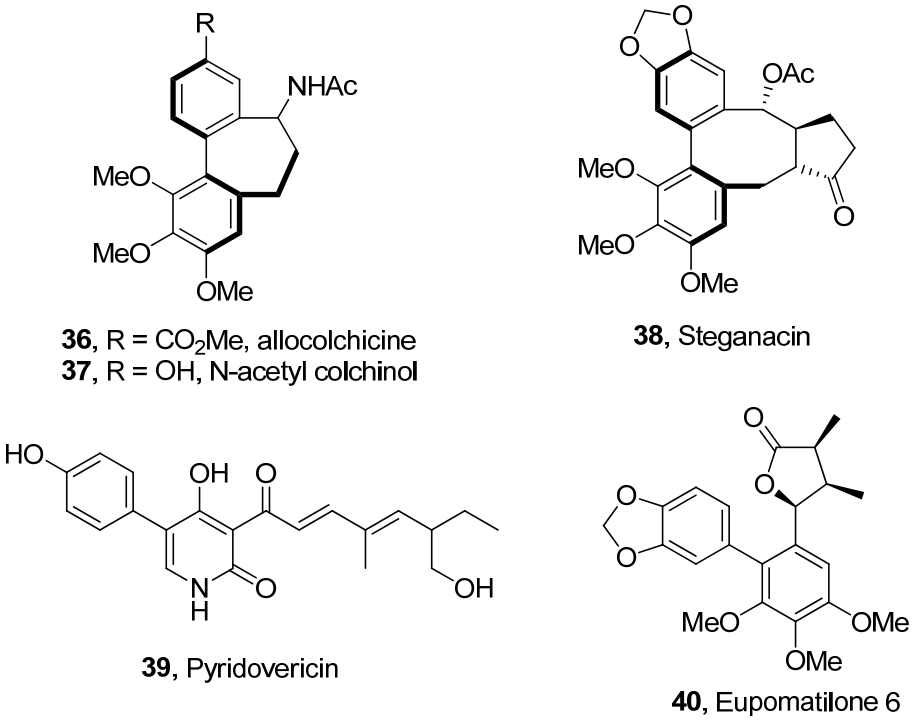


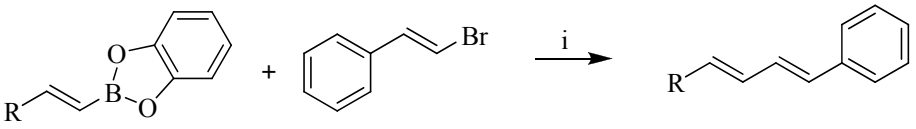
Fig. 8: Naturally-occurring biaryls

The massive interest for the Suzuki reaction can be explained by the impressively wide range of substrates' tolerance, relatively higher stability and less toxicity of boronic acids. The development of improved conditions for the Suzuki reaction has received much

recent attention due to the importance of biaryls that find applications in a range of pharmaceuticals, herbicides, as well as in conducting polymers and liquid crystalline materials.

Suzuki coupling

Initially, Akira Suzuki and co-workers reported[22] in 1979 that reaction of an equimolar amount of (*E*)- 1-hexenyldisiamyl borane (**41**) in THF with (*E*)-1-bromo-2-phenylethene (**43**) in presence of base such as sodium methoxide, ethoxide, acetate and hydroxide and 1 mol% of *tetrakis*(triphenylphosphine) palladium gave (*E*,*E*)-1-phenyl-1,3-octadiene (**44**) in good yields (**Scheme 12**). They also applied the same reaction for the synthesis of (*E*, *Z*)-dienes. Although the reactions proceeded smoothly, the results were unsatisfactory because the initially formed (*E*, *Z*) isomer underwent isomerization to the more stable (*E*, *E*) isomer.



41, R = C_4H_9

42, R = C_6H_{13}

43

44

Scheme 12: $Pd(PPh_3)_4$, Na_2CO_3, THF.

Reaction mechanism:

By analogy to the other cross-coupling reactions, the catalytic cycle of Suzuki coupling reaction involves the following three basic steps: 1) Oxidative addition, 2) Transmetallation and 3) Reductive elimination.[23] A general catalytic cycle for the Suzuki coupling reaction is given in **Fig. 9.**

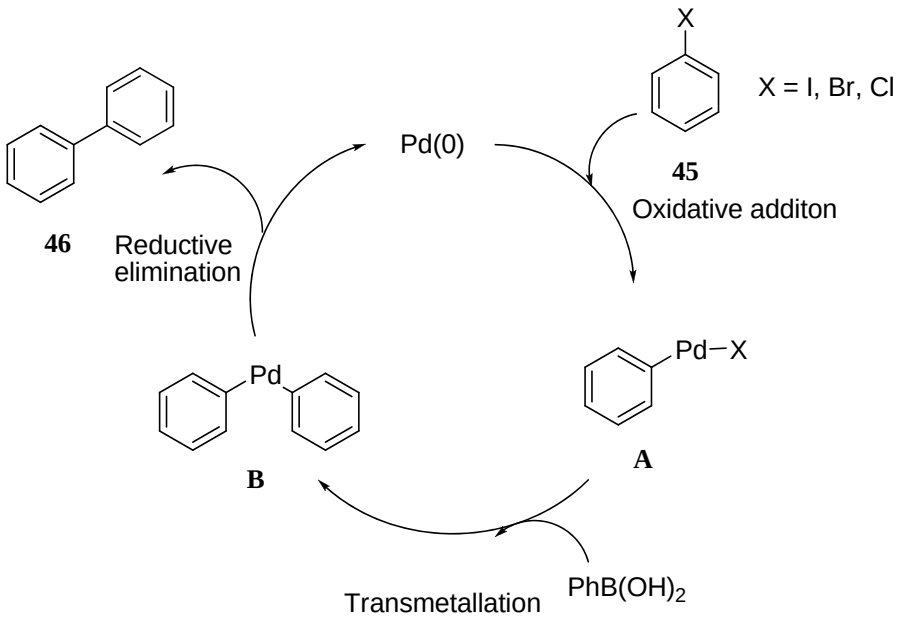


Fig. 9: Catalytic cycle for Suzuki coupling

The efficiency of palladium originates from its ability, when it is zerovalent, to activate C-X bonds (X = I, Cl, Br, O) in **45** by an oxidative addition which provides an organopalladium (II) complex **A** prone to react with nucleophiles.[24] A large variety of palladium(0) catalysts or precursors can be used for this reaction. $Pd(0)L_4$ where L = phosphine is most commonly used since they are air stable. Palladium (II) complexes along with a reducer are also used. Oxidative addition of 1-alkenyl, 1-alkynyl, allyl, benzyl and aryl halides to a Pd(0) complex gives a stable palladium (II) complex. The reaction proceeds with complete retention of stereochemistry for alkenyl halide and with inversion for allylic and benzylic halides. Oxidative addition is often the rate determining step in the catalytic cycle. The mechanism of the oxidative addition step is characterized by means of electrochemical techniques (as the metal is oxidized) such as steady state voltametry, transient voltametry, cyclic voltametry and reaction kinetics.

The transmetallation step between organopalladium (II) complex and organoboron compound does not usually proceed in the absence of base due to low nucleophilicity of

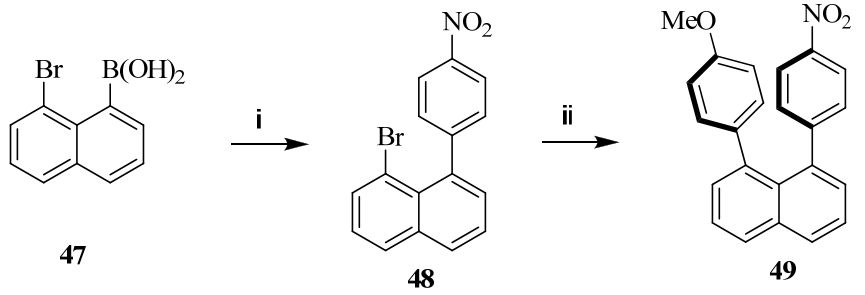
organic group on boron atom. However, the nucleophilicity can be enhanced by quarternization of boron with negatively charged bases giving the corresponding "borate" complex. It is reported that such "borate" complexes undergo clean coupling reaction with organic halide to give species **B**.[25] The transmetallation of primary alkyl borane to Pd occurs with retention of stereochemistry.

As the name implies reductive elimination involves the elimination or expulsion of a molecule from a transition metal complex. In the process of this elimination, the metal center is reduced by two electrons and a coordinatively unsaturated metal center is obtained. Reductive elimination takes place directly in the complex to expel biaryls **46** and palladium (0) species.

Applications of Suzuki coupling reaction:

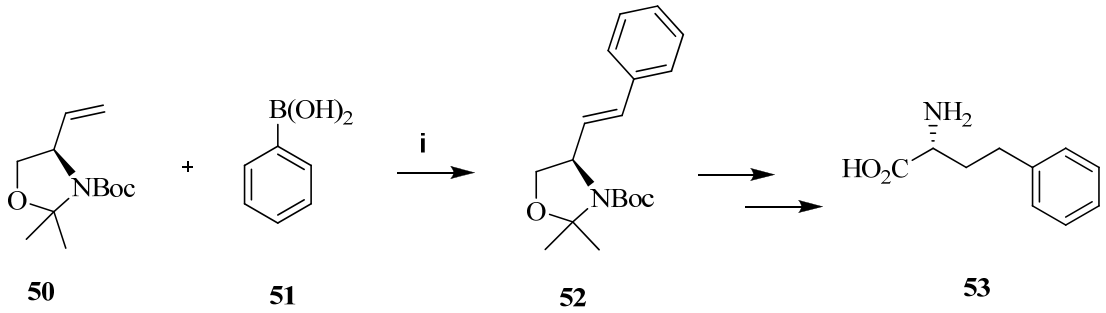
Suzuki coupling reaction has huge applications in various fields of chemistry and few examples are outlined here to represent the diversity of this reaction.

Nonlinear optics (NLO) is the branch of optics that describes the behavior of light in nonlinear media. This branch of optics has become much more important in the context that one day photonics will replace electronics. In this connection, Suzuki reaction has been employed to synthesize the molecules, which have both electron donor and electron acceptor groups. Synthesis of one such molecule namely 1,8-di(hetero)arylnapthalene derivative **49** was achieved by Grahn *et al*. from boronic acid **47** using sequential Suzuki cross-coupling reaction (**Scheme 13**).[26]



Scheme 13: i) 4-nirto phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, EtOH:toluene:H_2O, 74%; ii) 4-methoxy phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, EtOH:toluene:H_2O, 49%.

Unnatural amino acids are gaining importance in the field of biochemistry as building blocks in designing peptide-based biologically active molecules. They are also used as conformational constraints, molecular scaffolds and pharmacologically active products.[27] Analogues of homophenylalanines, such as 4-methoxyhomophenylalanine (**53**) have received particular attention as constituents of potential pharmaceuticals. **Scheme 14** represents the synthesis of homophenylalanines from amino alcohol **50** *via* Suzuki coupling with phenyl boronic acid **51**.



Scheme 14: i) 9-BBN, $PdCl_2$, NaOH, bromobenzene, 80 ^oC.

Recent advances and modifications in Suzuki coupling

Other than investigating synthetic application of Suzuki coupling reaction, scientists have also investigated various ligands and medium in which the reactions can be carried out. With the increasing interest in Green Chemistry processing research groups have recently

focused on the development of new polymeric support materials for catalysis in water. Uozumi and co-worker reported for the first time on the successful use of amphiphilic PEG-PS(poly(ethylene glycol) modified poly(styrene)) resin supported triphenyl phosphine palladium complexes in Suzuki coupling reactions in aqueous media under mild reaction conditions.[28]

Ionic liquids also play important role as liquid support in designing more mild and efficient protocol for Suzuki coupling, which gives stability and recyclability of the catalyst. A recent paper describes this reaction in 50% ethanol catalyzed by immobilized $Pd(OAc)_2$ on reversed phase alumina with the aid of an ionic liquid (Pd-SILC). The Suzuki-Miyaura cross-coupling of 4-iodophenol immobilized on polystyrene-Wang resin with various arylboronic acids was significantly accelerated by the ionic liquid namely 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4^-]).[29]

One of the most challenging field is to design a " ligand free" catalytic system for this reaction as most of the ligands used are not only sensitive to air and/or moisture but also difficult to prepare. This goal is recently achieved by Liu and his group. They reported an aerobic ligand free Suzuki coupling reaction catalyzed by the in situ generated palladium nanoparticles in PEG-400 at 45 ^oC.[30] The research work is being carried out continuously to modify the reaction conditions as well as to analyze the scope of different ligands in the Suzuki coupling.

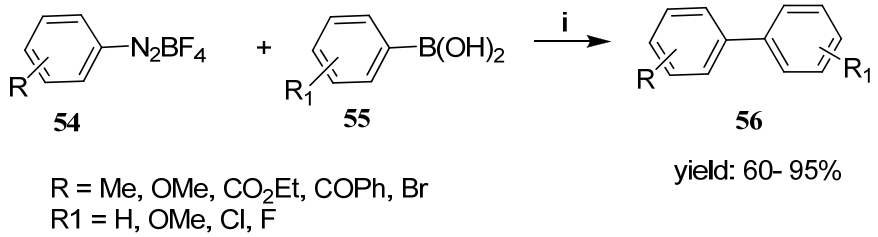
4.2.2. Review of literature

From its report in 1979, the Suzuki coupling reaction is the most investigated cross-coupling reaction. The amount of work done in this area is enormous. In Sci-finder the search for Suzuki coupling reaction, yields over 4000 papers. Research groups are still

working on the various aspects of this reaction and its applications. Few, interesting recent examples are briefly described below.

Genet's approach (1996)[31]

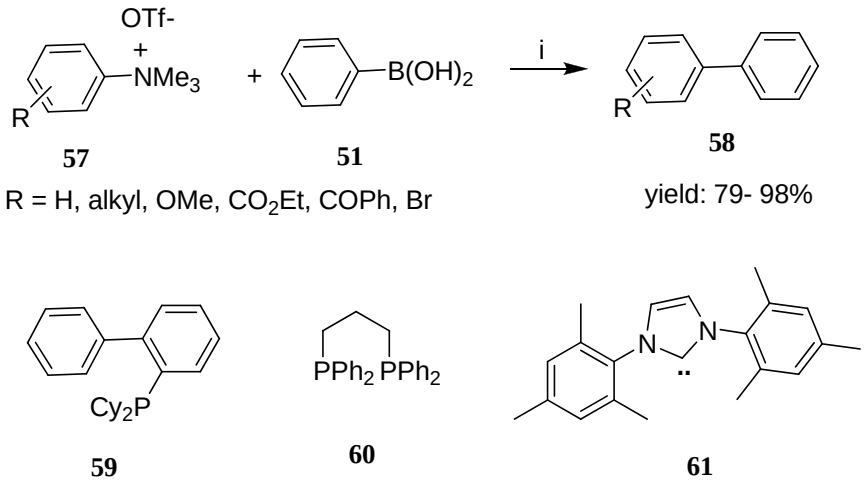
An efficient Suzuki cross-coupling between various arene diazonium tetrafluoroborates **54** and arylboronic acids **55** in the presence of catalytic amount of $Pd(OAc)_2$ has been described by Genet *et al.* This reaction proceeded smoothly at ambient conditions and produced biaryls in excellent yields (**Scheme 15**).



Scheme 15: i) 5 mol% $Pd(OAc)_2$, dioxane, 20 ^oC.

Macmillan's approach (2003)[32]

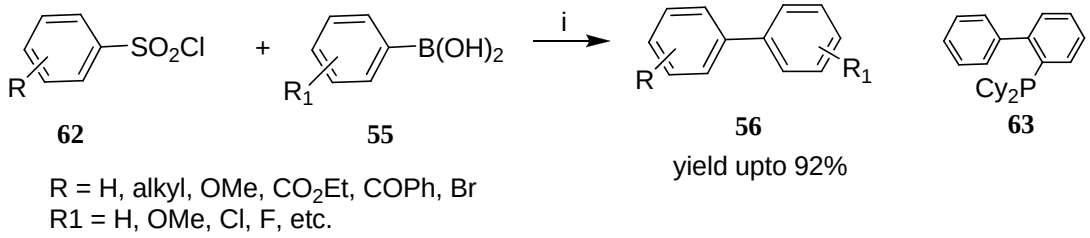
Macmillan *et al*. have achieved the preparation of biaryls **58** through the Suzuki-type cross-coupling reaction between aryl trimethyl ammonium triflates **57** and arylboronic acids **51**. The authors have described the use of Ni catalysts with various phosphine ligands (**59-61**) for this conversion (**Scheme 16**).



Scheme 16: i) Ni(0), ligand (**59-61**), CsF, dioxane, 80 ^{o}C, 12 h.

Vogel's approach (2004)[33]

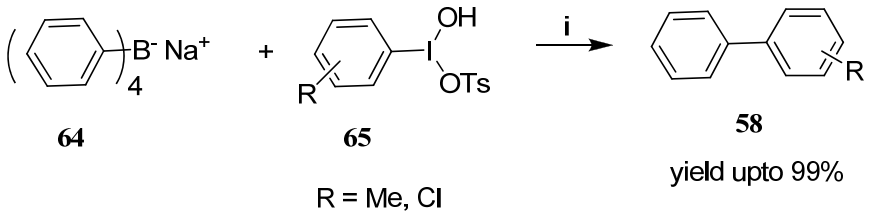
Vogel *et al.* have used aryl or alkenyl sulfonyl chloride **62** as new coupling partners for the Suzuki-Miyaura cross-coupling reactions with arylboronic acids **55** to obtain the corresponding biaryls **56** in excellent yields (**Scheme 17**). The authors also found that the reactivity of this reaction was little lower than iodoarene but higher than bromoarene.



Scheme 17: 1.5 mol% $Pd_2(dba)_3$, ligand **63**, Na_2CO_3, THF, 15 h.

Yan's approach (2005)[34]

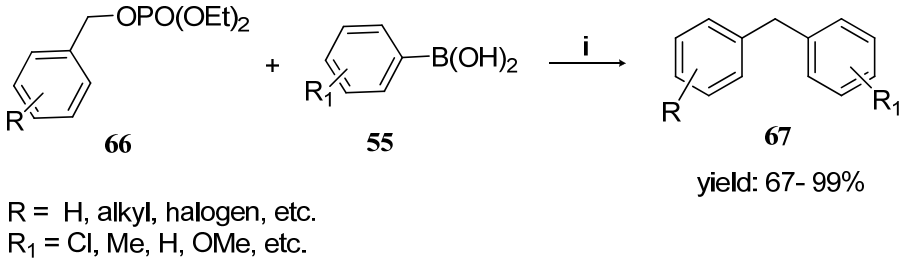
Yan *et al*. have reported the preparation of biaryls **58** in good yields *via* a fast and efficient Suzuki-type coupling reaction of sodium tetraphenyl borate **64** with iodanes **65**. This reaction was carried out in water as the solvent and at ambient conditions. Interestingly, this reaction does n't require any metal catalyst or base (**Scheme 18**).



Scheme 18: H_2O, 25 °C, 0.5 h.

Mclaughlin's approach (2005)[35]

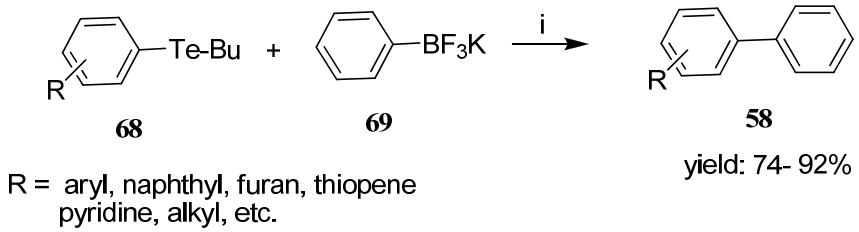
Suzuki-Miyaura cross-coupling between benzylic phosphates **66** and aryl boronic acids **55** to produce diarylmethane **67** has been studied by Mclaughlin *et al.* employing a simple catalytic system comprising $Pd(OAc)_2$ and PPh_3 in the presence of potassium phosphate or potassium carbonate as the base (**Scheme 19**).



Scheme 19: $Pd(OAc)_2$ (1 mol%), PPh_3 (4 mol%), K_3PO_4, toluene, 90 °C.

Stefani's approach (2006)[36]

Potassium aryl trifluoroborate salts **69** and aryl tellurides **68** containing a variety of functional groups underwent Pd(0) catalyzed cross-coupling reaction to afford the corresponding biaryls **58** in good to excellent yields (**Scheme 20**).



Scheme 20: $Pd(PPh_3)_4$, Ag_2O, MeOH:Et_3N, 12 h.

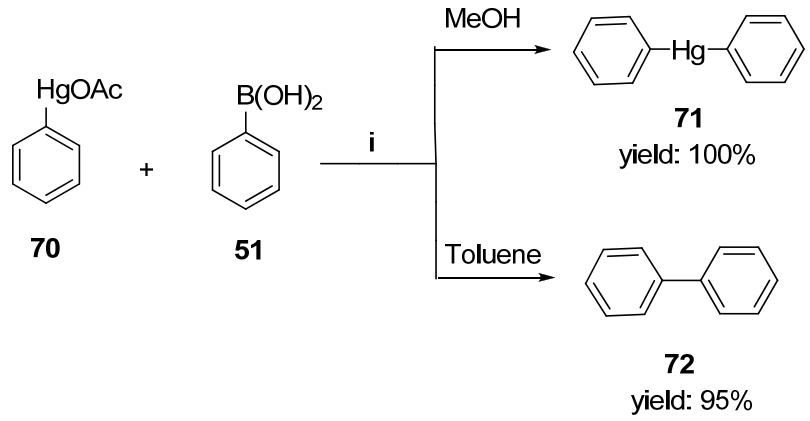
4.2.3. Present work

4.2.3.1 Objective

From the above discussion, it is clear that several reports exit for the Suzuki cross-coupling reaction in the presence of various palladium salts or complexes under different reaction conditions. Yet, the search for a new and readily available coupling partner is desirable. This section describes the use of arylmercuric acetates as the coupling partner with the boronic acid in non-polar solvents to get biaryl compounds under ambient temperature.

4.2.4. Results and discussions

It has been reported in the literature that the reaction of arylboronic acid (**51)** with mercuric salt (**70)** in polar solvent such as methanol led to the isolation of diarylmercury (**71**).[37] We found that when the same reaction was carried out in *non-polar solvents* like toluene in the presence of palladium salts as catalyst it took different course to give the cross coupled biphenyl (**72)** in good yield (**Scheme 21**).



Scheme 21: i) Phenylmercuric acetate (3 mmol), phenylboronic acid (3 mmol), catalyst (5 mol %), solvent (5 mL), 25 ºC, 3 h.

In order to study this catalytic system in a systematic manner, several metal salts and solvents have been screened and the results are shown in the **Table 3**. Remarkably,

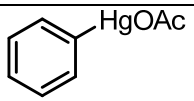
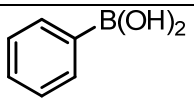
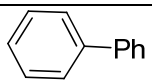
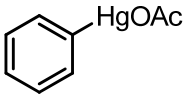
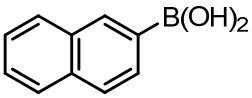
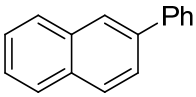
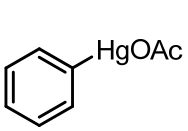
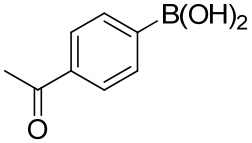
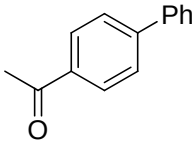
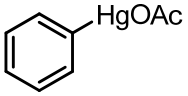
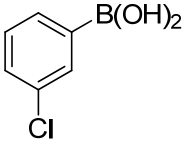
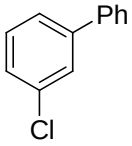
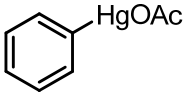
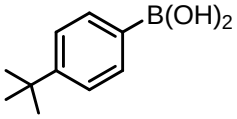
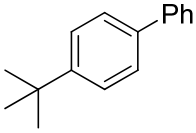
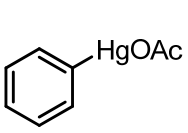
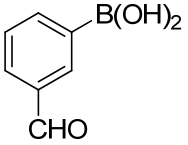
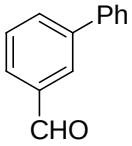
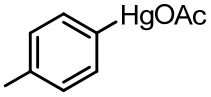
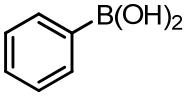
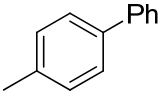
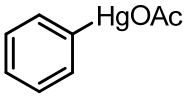
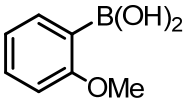
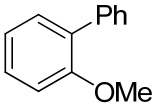
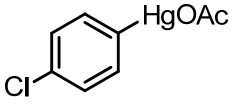
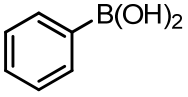
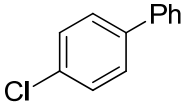
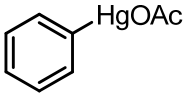
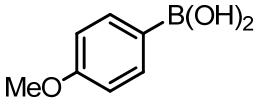
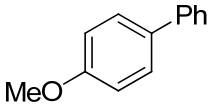
palladium salts were found to be extremely active and gave excellent yield of biphenyl over other metal complexes. The maximum yield of biphenyl was obtained with $Pd(dba)_2$ whereas Pd/C gave poor yield. Other metals like Cu, Ni and Ru were found to be inactive. Among the solvents screened, toluene gave excellent yield while the more polar solvents like MeOH, CH_3CN, H_2O and dioxane resulted in diphenyl mercury as the major product. Another interesting feature of this reaction is that the base, which is typically an important requirement in palladium-catalyzed coupling reactions, was not required. In contrast, addition of organic bases increases the polarity of the system and thus resulted in the formation of diphenyl mercury in considerable amounts.

Table 3. Effect of catalyst and solvent on coupling reaction of phenylboronic acid with phenyl mercuric acetate[a]

Entry	Catalyst	Solvent	Yield of **72** (%)[b]
1	$PdCl_2$	toluene	82
2	$Pd(OAc)_2$	toluene	90
3	$Pd(dba)_2$	toluene	95
4	$Pd(PPh_3)_4$	toluene	93
5	$RuCl_3.3H_2O$	toluene	trace
6	$RuH_2CO(PPh_3)_3$	toluene	0
7	5% Pd/C	toluene	11[c]
8	$Pd(dba)_2$	DMF	14
9	$Pd(dba)_2$	CH_2Cl_2	87
10	$Pd(dba)_2$	$CHCl_3$	78
11	$Pd(dba)_2$	CCl_4	53
12	$Pd(dba)_2$	dioxane	20
13	$Pd(dba)_2$	CH_3CN	trace

[a]Reaction conditions. Phenylmercuric acetate (3 mmol), phenylboronic acid (3 mmol), catalyst (5 mol %), solvent (5 mL), 25 ºC, 3 h; [b]Isolated yield by column chromatography.

Table 4: Pd- Catalyzed Suzuki-type cross-coupling reaction[a] between arylmercuric acetate and arylboronic acid

Entry	Substrate	Boronic acid	Product (**72a-j)**	Yield (%)
a				95
b				92
c				71
d				77
e				89
f				75
g				85
h				82
i				74
j				78

[a] Reaction conditions: arylmercuric acetate (3 mmol), aryl boronic acid (3 mmol) $Pd(dba)_2$ (5 mol%), toluene (5 mL), 25 °C , 3 h; [b] 5 mol% $Pd_2(dba)_3$ has been employed; [c] isolated yield by column chromatography.

With the optimized conditions in hand we subjected a variety of boronic acids with phenylmercuric acetate and the results are given in the **Table 4**. Substituted phenyl mercuric acetates were prepared following the known electrophilic mercuration methods.[37] In all the cases a <5% of homo-coupled product was also isolated. The biaryls were purified using column chromatography and systematically characterized by the ^{1}H, ^{13}C NMR and IR spectroscopy techniques. For example, the ^{1}H NMR spectrum of 4-methoxy biphenyl showed a characteristic singlet at δ 3.72 for the OC**H**$_3$ proton. Its ^{13}C NMR spectrum showed signal at δ 55.1 due to the O**C**H$_3$ carbon (**Fig. 10**).

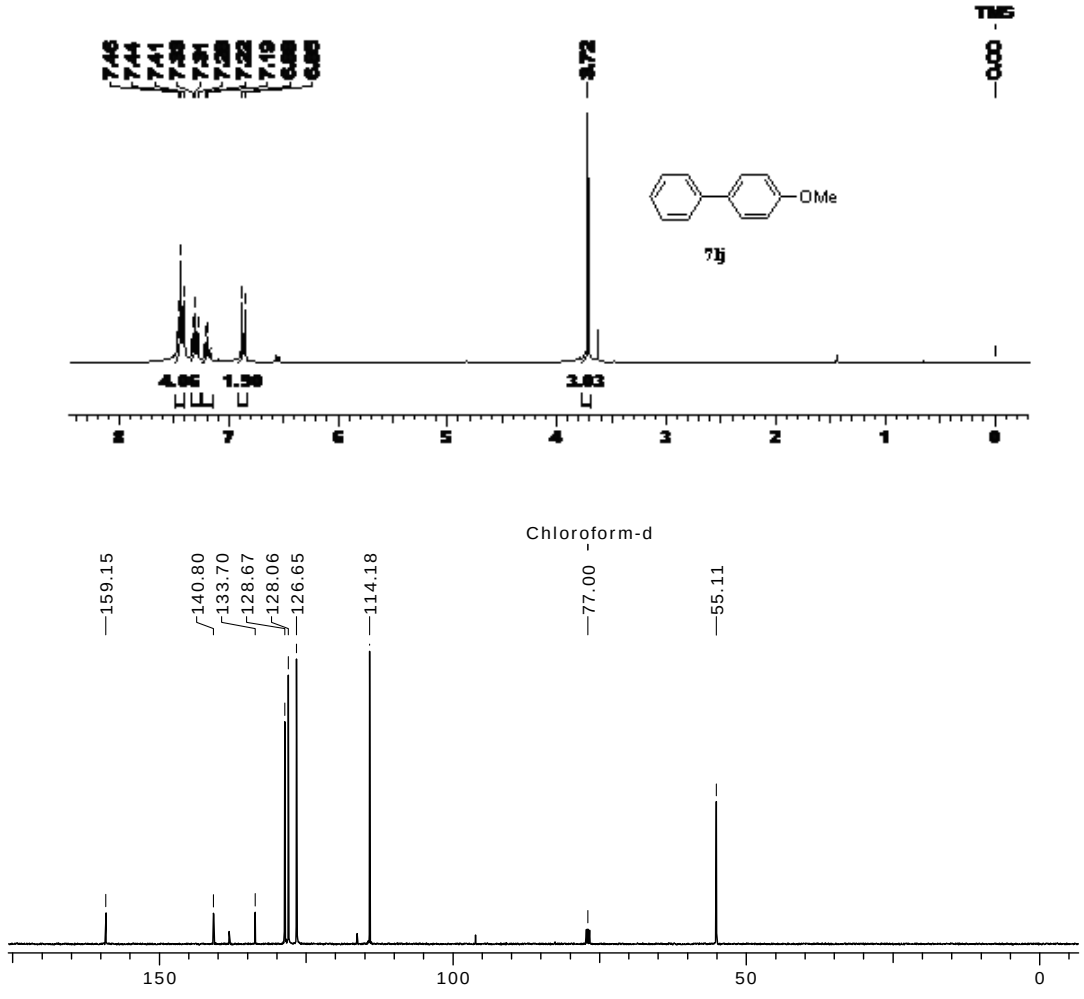


Fig. 10: ^{1}H and ^{13}C NMR spectra of **72j**

Attempts to avoid the homo-coupled product by reducing the reaction temperature up to (15 ºC) had no considerable effect. The cross-coupling reaction was successful only in the case of arylmercuric acetate and failed in the case of arylmercuric bromide or chloride. In the case of 4-chlorophenylmercuric acetate the boronic acid replaced only the mercuric acetate while the chlorine was unaffected. Easily oxidizable aldehyde group was found to be unaffected in this reaction condition. After the reaction the Pd-catalyst was deposited as black colored particle and mercury (II) as mercury metal.

One may expect the reaction to proceed through two different routes, *i.e.* i) normal Suzuki coupling mechanism of oxidative addition followed by aryl transfer and reductive elimination; ii) initial formation of diarylmercury followed by its dimerization[37] catalyzed by palladium. Since dimerization requires high temperatures as well as highly polar solvents like HMPA, MeOH, CH_3CN, etc, we presume that the reaction might follow the Suzuki coupling pathway. The non-requirement of base may be ascribed to the acetate anion liberated from the phenylmercuric acetate, which acts as base and increases the nucleophilicity of the neutral boronic acid thus facilitating the transmetallation from boron to organopalladium. This assumption also explains the inactivity of arylmercuric halides towards arylboronic acid under the reaction conditions (**Fig. 11**).

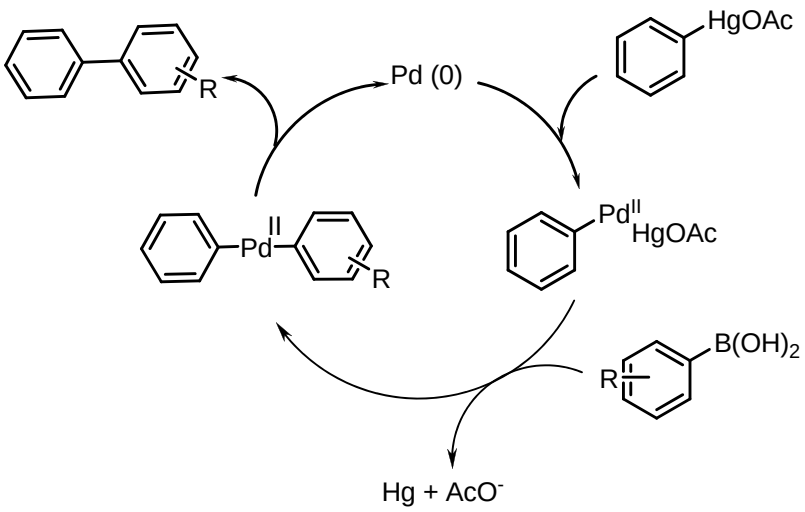


Fig. 11: Proposed mechanistic pathway

4.2.5. Conclusion

In summary, we have described that arylmercuric acetates underwent smooth coupling with arylboronic acids in a non-polar solvent in the presence of palladium as catalyst under ambient conditions to give the corresponding biaryl compound. A remarkable feature of this system is that neither a base nor a phosphine ligand was required.

4.2.6. Experimental Section:

General procedure for the Pd- catalyzed coupling of arylmercuric acetates with boronic acids:

To a mixture of arylmercuric acetate (3 mmol) and $Pd_2(dba)_3$ (5 mol%) in toluene (10 mL) was added arylboronic acid (3 mmol) and the reaction mixture was stirred at 25 $^{\circ}$C. The reaction was monitored by TLC periodically. After the completion of the reaction it was extracted with ethyl acetate washed twice with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography.

Biphenyl (72a):

Yield: 78%; Colorless solid; mp: 68–70 °C {lit.[38] 69 °C}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.18–7.65 (m, 10H); **^{13}C-NMR** ($CDCl_3$) δ 127.2, 127.3, 128.8, 141.3; **IR** ($CHCl_3$, cm^{-1}): 3008, 2986, 1602, 1424; Anal Calcd for $C_{12}H_{10}$: C, 93.46; H, 6.54. Found: C, 93.51; H, 6.60%.

2-Phenylnaphthalene (72b):

Yield: 89%; Colorless solid; **mp**: 105 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.40-8.27 (m, 12H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 125.3, 125.7, 125.9, 126.0, 126.9, 127.2, 127.6, 128.2, 130.0, 131.6, 133.8, 140.2, 140.8; **IR** ($CHCl_3$, cm^{-1}): 668, 688, 758, 770, 820, 860, 892, 1076, 1216, 1452, 1496, 1598, 1948, 3106, 3058; Anal calcd for $C_{16}H_{12}$: C, 94.08; H, 5.92. Found: C, 94.29; H, 5.70%.

1-Biphenyl-4-yl-ethanone (72c):

Yield: 78%; Colorless solid; **mp**: 119 °C {lit.[38] 120 °C};; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.40-7.47 (m, 3H), 7.56-7.65 (m, 4H), 7.97-8.01 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 26.3, 127.0, 128.0, 128.7, 135.6, 139.6, 145.4, 196.8; **IR** ($CHCl_3$, cm^{-1}): 595, 668, 697, 756, 1007, 1216, 1267, 1358, 1604, 1680, 3019; **MS** (m/z, % relative intensity): 196 (M^+**,** 51), 181 (100), 153 (33), 152 (51), 76 (13), 43 (4); Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.59; H 6.42%.

3-Chlorobiphenyl (72d):

Yield: 86%; Colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.16-7.44 (m, 9H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 125.2, 127.1, 127.2,127.3, 127.8, 128.8, 129.9, 134.7, 139.8, 143.1; **IR** ($CHCl_3$, cm^{-1}): 523, 624, 766, 803, 892, 1014, 1061, 1114, 1420, 1604, 1694,

1766, 1810, 1884, 1957, 3033, 3086; Anal. Calcd for $C_{12}H_9Cl$: C, 76.4; H, 4.81; Cl, 18.79. Found: C, 76.12; H, 4.95; Cl, 18.54%.

4-^{t}Butyl biphenyl (72e):

Yield: 89%; Colorless solid; **mp**: 48 ^oC; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 1.41 (s, 9H), 7.3-7.64 (m, 9H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 150.5, 141.3, 138.6, 129, 127.3, 127.2, 127, 126, 34.8, 31.7; **IR** ($CHCl_3$) 2962, 1486, 1179, 836, 766; Anal. Calcd for $C_{16}H_{18}$: C, 91.38; H, 8.62. Found: C, 90.23; H, 9.5%.

Biphenyl-3-carbaldehyde (72f):

Yield: 75%; Colorless solid; **mp:** 53–54 °C; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 9.9 (s, 1H), 8.01 (m, 1H) 7.78 (m, 2H), 7.49 (m, 3H), 7.32 (m, 2H), 7.21(m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 191.2, 137.2, 137.1, 136.6, 133.34, 129.8, 129.3, 129.2, 128.5, 127.9, 127.8, 127.3; **IR** ($CHCl_3$, cm^{-1}) 2982, 2832, 1690, 1592, 1200, 720; Anal. Calcd for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.72; H, 5.55.

4-Methylbiphenyl (72g):

Yield: 95%; Gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), δ 7.20-7.57 (m, 9H); **^{13}C-NMR** (50MHz, $CDCl_3$): δ 21.15, 126.82, 126.99, 127.17, 128.70, 129.47, 136.80, 138.43, 141.21; **IR** ($CHCl_3$, cm^{-1}): 546, 667, 760, 822, 1038, 1352, 1598, 1907, 2589, 2583, 3065; **MS** (m/z, % relative intensity): 168 (M^+**,** 100), 167 (68), 165 (22), 152 (20), 115 (6); Anal. Calcd for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.64; H, 7.40%.

2-Methoxybiphenyl (72h):

Yield: 82%; Gum; **^{1}H- NMR** (200 MHz, $CDCl_3$): δ 3.71 (s, 3H), 6.75-7.49 (m, 9H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.3, 111.3, 120.8, 121.62, 126.6, 127.7, 128.4, 128.5, 129.4, 130.7, 133.2, 138.6, 156.5; **IR** ($CHCl_3$, cm^{-1}): 565, 612, 667, 698, 732, 753, 800, 1028,

1055, 1122, 1236, 1259, 1463, 1504, 1597, 2834, 2956, 3011, 3061; Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.85; H, 6.49%.

4-Chlorobiphenyl (72i):

Yield: 74%; Colorless gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.52 (m, 4H), 7.4 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 140, 139.6, 133.3, 129, 128.9, 128.4, 127.6, 127.1; **IR** ($CHCl_3$, cm^{-1}): 803, 892, 1061, 1114, 1420, 1604, 1694, 1766, 1810, 1884, 1957, 2983, 3033; Anal. Calcd for $C_{12}H_9Cl$: C, 76.4; H, 4.81; Cl, 18.79. Found: C, 76.01; H, 4.23; Cl, 17.93%.

4-Methoxybiphenyl (72j):

Yield: 81%; Colorless solid; **mp**: 87 °C {lit.[38] 89 °C}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.72 (s, 3H), 6.85-7.46 (m, 9H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.1, 114.2, 126.6, 128.1, 128.6, 133.7, 140.8, 159.1; **IR** ($CHCl_3$, cm^{-1}): 566, 703, 776, 845, 1051, 1130, 1198, 1304, 1414, 1462, 1530, 1615, 2917, 2970, 3065; **MS** (m/z, % relative intensity): 184 (M^+**,** 100), 169 (44), 141 (38), 115 (26), 63 (4); Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.56. Found: C, 84.55; H, 6.81%.

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List of Publications

1. $NaIO_4$/LiBr-mediated Diastereoselective Dihydroxylation of Olefins: A Catalytic Approach to the Prevost-Woodward Reaction. **Emmanuvel, L**; Shaikh, T. M.; Sudalai, A. *Org. Lett.,* **2005**, *7,* 5071.
2. $NaIO_4$-mediated selective oxidation of alkylarenes and benzylic bromides/alcohols to carbonyl derivatives using water as solvent. Shaikh, T. M.; **Emmanuvel, L**; Sudalai, A. *J. Org. Chem.* **2006**, 71, 5043.
3. $NaIO_4$/KI/NaCl: a new reagent system for iodination of activated aromatics through in situ generation of iodine monochloride. **Emmanuvel, L**; Shukla, R. K.; Sudalai, A. Gurunath, S.; Sivaram, S. *Tetrahedron Lett.* **2006**, 47, 4793.
4. $NaIO_4$/LiBr-mediated direct conversion of benzylic alcohols and aromatic aldehydes to aromatic esters. Shaikh, T. M.; **Emmanuvel, L**; Sudalai, A. *Synth. Comm.* **2006**, *37*, 2641.
5. Phosphine ligand and base-free, Pd- catalyzed oxidative cross-coupling reaction of arylboronic acids with arylmercuric acetates. **Emmanuvel, L**; Sudalai, A. *Arkivoc* **2007**, 14, 126.

6 A short enantioselective synthesis of (+) -L-733,060 *via* Shi epoxidation of a homoallylic carboxylate. **Emmanuvel, L**; Sudalai, A. *Tetrahedron Lett.* **2008**, *49*, 5736.

7 A concise synthesis of (+)-febrifugine. **Emmanuvel, L**; Kamble, D. A.; Sudalai, A. (communicated to *Tetrahedron: Asymmetry*).

8 A new catalytic process for the preparation of high quality 3, 3'-diaminobenzidine and their analogues. Shukla, R. K.; **Emmanuvel, L**; Sudalai, A. Gurunath, S.; Sivaram, S. US patent Filed

9 Enantioselective formal synthesis of (-)-epiquinamide. **Emmanuvel, L**; Sudalai, A. (Manuscript under preparation)

10 Oxyhalogens in Organic Chemistry (Review, Manuscript under preparation)