Enantioselective Synthesis of Bioactive Molecules *via* Metal-Catalysed Kinetic Resolution of Benzylic Alcohols and Azido Epoxides, α-Aminoxylation of Aldehydes and Methodology involving Diazidation of Alkenes

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IN

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By

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UNDER THE GUIDANCE OF

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules via Metal-Catalysed Kinetic Resolution of Benzylic Alcohols and Azido Epoxides, α-Aminoxylation of Aldehydes and Methodology involving Diazidation of Alkenes"*** which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Dayanand Ambadas Kamble*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

April 2014
Pune

Dr. A. Sudalai
(Research Guide)

NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules via Metal-Catalysed Kinetic Resolution of Benzylic Alcohols and Azido Epoxides, α-Aminoxylation of Aldehydes and Methodology involving Diazidation of Alkenes"*** 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 CSIR-National Chemical Laboratory, Pune, India.

April 2014

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Dedicated to my Beloved

Parents & Teachers

CONTENTS

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Dayanand A. Kamble

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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
t-Bu	*tert*-Butyl
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
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
dr	Diastereomeric ratio
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
HNO_3	Nitric acid
IR	Infra red
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
M+	Molecular ion
Me	Methyl

MeOH	Methyl alcohol
MOM	Methoxymethyl
min	Minutes
mg	Miligram
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
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromatel
$Pd(OH)_2$	Palladium hydroxide
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
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
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 (230-400 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 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.
8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.
9. Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a chiral column.
10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.
11. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
12. Elemental analysis was done on Carlo ERBA EA 110B instrument.
13. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

ABSTRACT

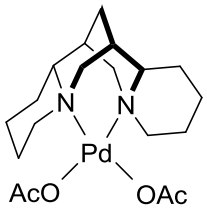
The thesis entitled "**Enantioselective Synthesis of Bioactive Molecules *via* Metal-Catalysed Kinetic Resolution of Benzylic Alcohols and Azido Epoxides, α-Aminoxylation of Aldehydes and Methodology involving Diazidation of Alkenes**" is divided into four chapters. The title of the thesis clearly indicates the objective that is to synthesize enantiomerically pure drugs and to interface synthetic organic chemistry for the development of new methodologies. **Chapter 1** deals with (–)-sparteine/Pd(II) (**1**)- catalyzed oxidative kinetic resolution of α-bromo benzylic alcohols **2a-f** and their application in the asymmetric synthesis of (*S*)-duloxetine **12** and (–)-chloramphenicol **20**. **Chapter 2** describes an enantioselective synthesis of (*R*)-rugulactone **33** *via* D-proline- catalyzed α-aminoxylation of aldehyde, and asymmetric synthesis of (*R*)-coniine **42** and formal synthesis of (+)-febrifugine **52** employing Sharpless asymmetric dihydroxylation of dienic ester. **Chapter 3** describes the (salen)Co[$OC(CF_3)_3$].H_2O (**53**)-catalyzed phenolytic kinetic resolution of benzyloxy epoxides **55a & b** to chiral α-aryloxy-α'-benzyloxy alcohols **57a-g** and asymmetric synthesis of D-*erythro*-sphinganine **71** *via* (salen) Co(III)($OCOCH_3$) (**54**)-catalyzed hydrolytic kinetic resolution of azido epoxide **62**. **Chapter 4** deals with the $NaIO_4$–NaN_3–mediated diazidation of alkenes **72a-i** to 1,2-diazido alkanes **73a-i** and Cu(I) catalyzed synthesis of phenyl substituted *gem*-ditriazoles **75a-f** from, α,α-diazido aromatic ketones **74a-f**.

CHAPTER 1

Pd-Catalyzed Oxidative Kinetic Resolution of α-Bromobenzylic Alcohols Using (–)-Sparteine as Chiral Auxiliary: A Practical Synthesis of (*S*)-Duloxetine and (–)-Chloramphenicol

Oxidative Kinetic Resolution (OKR) of racemic benzylic alcohols to obtain enantiomerically pure benzylic alcohols has been comprehensively studied in recent years to reveal its mechanistic and synthetic aspects. The enantiomerically pure benzylic alcohols are valuable 'building blocks' for the asymmetric synthesis of bioactive pharmaceuticals and ligands. This chapter is divided into 3 sections. **Section I** describes a flexible method of Pd-sparteine complex (**1**) catalyzed OKR of racemic α-bromobenzylic alcohols **2a-f** to produce the corresponding chiral α-bromobenzylic

alcohols **4a-f** while **Sections II** and **III** demonstrate the application of this methodology in the asymmetric synthesis of (–)-chloramphenicol **12** and (*S*)-duloxetine **20**. The chiral Pd-catalyst **1** (**Fig. 1**) was readily prepared in *situ* from $Pd(OAc)_2$ and (–)-sparteine.

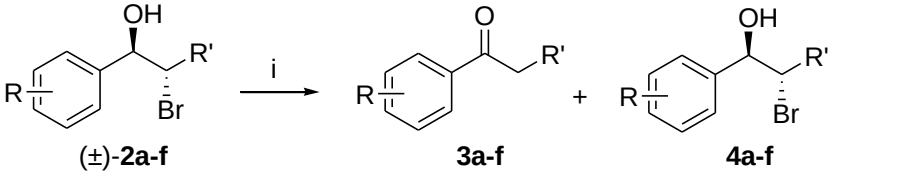


1

Fig. 1: (—)-Sparteine-Pd(II) complex

SECTION I: Oxidative Kinetic Resolution of *anti*-α-Bromobenzylic Alcohols using Pd-Sparteine as Chiral Catalyst

Pd-catalyzed kinetic resolution of secondary benzylic alcohols that uses moleculer oxygen as the terminal oxidant and naturally occurring (–)-sparteine as a chiral ligand has been reported to afford chiral secondary benzylic alcohols (ee up to 99%).[1] This section deals with the extension of this methodology for the resolution of racemic α-bromobenzylic alcohols **2a-f** containing two adjacent stereocenters. The relative stereochemistry of the α-bromobenzylic alcohols **2a-f** was established prior to the kinetic resolution step as follows. The racemic compounds **2a-f** were readily prepared from the corresponding styrenes with NBS-H_2O system in a single step with dr > 99%. Several *anti*-bromobenzylic alcohols with various substituents on the aromatic ring were subjected to the Pd-sparteine-catalyzed OKR, which resulted in the production of aromatic ketones **3a-f** and the enantiomerically pure *anti*-α-bromobenzylic alcohols **4a-f** (**Scheme 1**).



(±)-**2a-f**

R = H, Me, F, etc.
R' = OBn, Me

3a-f

(38-41% yield)

4a-f

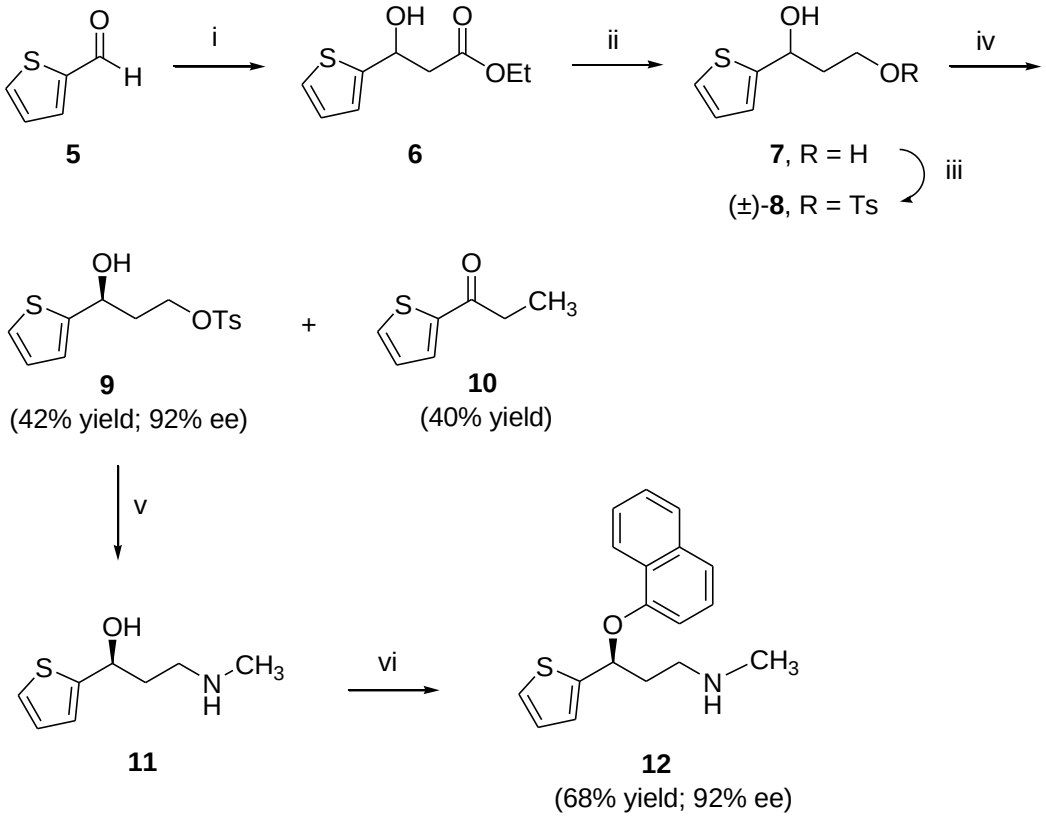
(36-42% yield; 90-92% ee)

6 examples

Scheme 1: (i) $Pd(OAc)_2$ (5 mol %), (–)-sparteine (20 mol %) /O_2 (1 atm), 3 A^o MS, dry toluene, 80 ^oC, 36 h.

SECTION II: Asymmetric Synthesis of (*S*)-Duloxetine *via* Pd-Catalyzed Oxidative Kinetic Resolution of Racemic Thiophenic Alcohol

(*S*)-Duloxetine **12**, marketed as Cymbalta, functions as an antidepressant drug.[2] This section presents the application of the OKR methodology in the concise enantioselective synthesis of (*S*)-duloxetine **12**. Thus, when thiophene-2-carboxaldehyde **5** was reacted with ethyl bromoacetate under Reformatsky condition, β-hydroxy thiophene ester **6** was obtained in 97% yield. The ester functionality in **6** was reduced with $LiAlH_4$ to give 1,3-diol **7** in 93% yield. Selective protection of primary alcohol in **7** as its tosylate **8** (TsCl, Et_3N, 95%) was carried out. The racemic thiophene alcohol (±)-**8** was then subjected to Pd-sparteine-catalyzed oxidative kinetic resolution under O_2 (1 atm) which produced the enantiomerically pure alcohol **9** in 42% yield and 92% ee along with reductive detosylated ketone **10** in 40% yield.

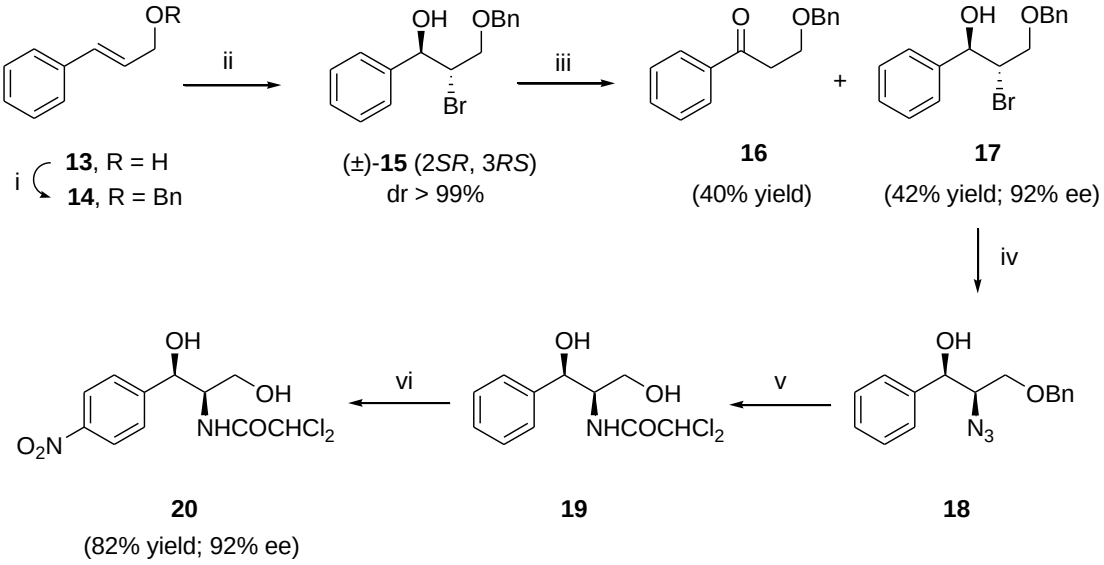


Scheme 2: (i) $BrCH_2CO_2Et$ (1 mmol), Zn (1.2 mmol), 10% aq. NH_4Cl, 0-60 °C, benzene, 4 h, 97 %; (ii) $LiAlH_4$ (1.2 mmol), dry THF, reflux, 6 h, 95%; (iii) Et_3N, TsCl, CH_2Cl_2, 0 °C, 2 h, 95%; (iv) $Pd(OAc)_2$ (5 mol %), (–)-sparteine (20 mol%), O_2 (1 atm), toluene, 3 A° MS, 80 °C 32 h; (v) 40% aq. $MeNH_2$ (1.2 mmol), 60 °C, 8 h, 86%; (vi) 1-fluoronaphthalene, NaH, DMSO, 50 °C, 2 h, 68%.

The S_N2 displacement of tosyl group in **9** with 40% aq. $MeNH_2$ gave the corresponding 1,3-aminoalcohol **11** in 86% yield. Finally the *ipso* substitution of *N*-methyl-γ-amino alcohol **11** with 1-fluoronaphthalene afforded (*S*)-duloxetine **12** in 22% overall yield and 92% ee. (**Scheme 2**).

SECTION III: Enantioselective Synthesis of (–)-Chloramphenicol *via* Pd-Catalyzed Oxidative Kinetic Resolution of Racemic *anti*-α-Bromobenzylic Alcohol

(–)-Chloramphenicol **20** is an antibiotic, active only in its D-*threo* configuration and specially effective in the treatment of typhus, dysentery and ocular bacterial infections.[3] This section deals with the asymmetric synthesis of (–)-chloramphenicol **20** employing Pd-sparteine (**1**)- catalyzed two-stereocentered OKR as the chirality inducing step. Its synthesis commenced with the protection of cinnamyl alcohol **13** as its benzyl ether **14** (BnBr, NaH, DMF, 0 ^oC).



Scheme 3: (i) BnBr, NaH, THF, 0 ^oC, 1 h, 96%; (ii) NBS, CH_3CN/H_2O (2:1), 25 ^oC, 8 h, 91%; (iii) $Pd(OAc)_2$ (5 mol%), (-)-sparteine (20 mol%), O_2, toluene, 3 A^o MS, 80 ^oC, 32 h; (iv) NaN_3, DMSO, 80 ^oC, 2 h, 99%; (v) 10% Pd/C, H_2 (1 atm), MeOH, $Cl_2CHCOCl$ (1 equiv), 25 ^oC, 18 h, 72%; (vi) conc. HNO_3-conc. H_2SO_4, – 20-25 ^oC, 1.5 h, 82%.

The compound **14** was bromohydroxylated in a highly regio- and diastereoselective manner [NBS, CH_3CN/H_2O (2:1, v/v), 25 ^oC] to give *anti*-α-bromoalcohol **15** in 91% yield and > 99% dr. The racemic bromoalcohol **15** was then subjected to Pd-sparteine-catalyzed OKR to furnish the chiral bromoalcohol **17** in 42% yield and 92% ee (HPLC analysis) along with aromatic ketone **16** in 40% yield. The bromide function

in **17** was then subjected to S_N2 displacement with azide ion [NaN_3, DMSO, 80 ^oC] to give *syn*-α-azidoalcohol **18** in quantitative yield. The catalytic hydrogenation of azide function followed by its dichloroacetylation furnished amidodiol **19** in 72% yield. Finally, regioselective *p*-nitration of **19** was achieved with mixed acids (conc. HNO_3 and conc. H_2SO_4) to give (–)-chloramphenicol **20** with an overall yield of 21% and 92% ee (**Scheme 3**).

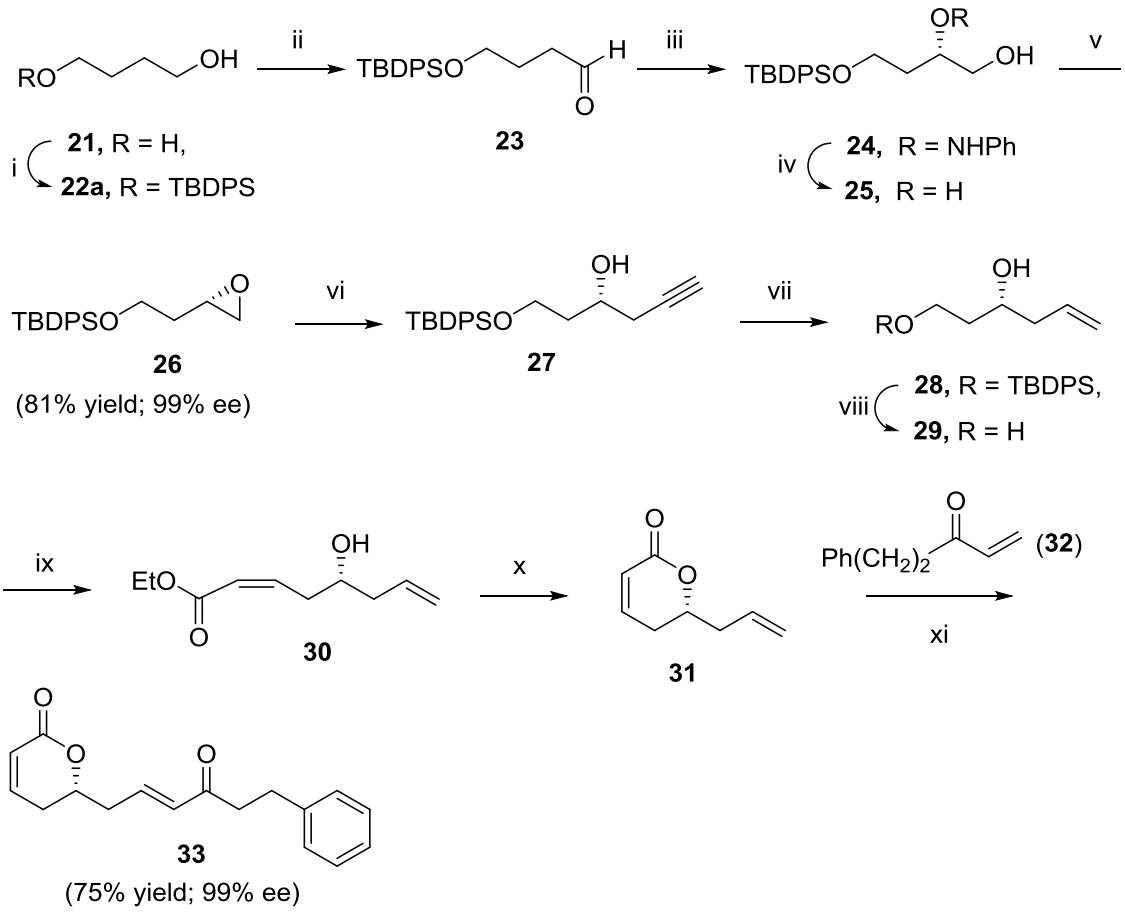
CHAPTER 2

Asymmetric Synthesis of (*R*)-Rugulactone, (*R*)-Coniine and Formal Synthesis of (+)-Febrifugine

Asymmetric organocatalysis has provided several new methods in organic synthesis for obtaining chiral compounds in an environmentally benign manner. In particular proline is efficient for α-funtionalization of aldehydes and ketones. In addition, Sharpless Asymmetric Dihydroxylation (ADH) is one of the most effective methods for the preparation of chiral diols, key intermediates in the synthesis of various bioactive molecules. This chapter is divided into 3 sections. **Section I** deals with asymmetric synthesis of (*R*)-rugulactone **33** *via* proline-catalyzed asymmetric α-aminoxylation of aldehyde whereas **Sections II** and **III** describe enantioselective synthesis of (*R*)-coniine **42** and (+)-febrifugine **52** *via* asymmetric dihydroxylation of *trans*-alkenic esters **36** & **44**.

SECTION I: Asymmetric Synthesis of (*R*)-Rugulactone *via* Proline-Catalyzed Asymmetric α-Aminoxylation of Aldehyde

(*R*)-Rugulactone **33** has been found to inhibit the nuclear factor (NF-kB) activation pathway occurring in different types of cancers.[4] Its enantioselective synthesis, as outlined in (**Scheme 4)**, commenced with monosilyl protection of 1,4-butanediol **21** followed by the oxidation of primary alcohol **22a** to give aldehyde **23**.



Scheme 4: (i) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC, 8 h, 86%; (ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 ^oC, 2 h, 96%; (iii) PhNO, D-proline (10 mol %), DMSO, 25 ^oC, 30 min. then $NaBH_4$, MeOH; (iv) 10% Pd/C, H_2 (1atm), MeOH, 12 h, 87% (over two steps); (v) (a) *p*-TsCl, cat. Bu_2SnO, Et_3N, DMAP, CH_2Cl_2, 0-25 ^oC, 1.5 h; (b) K_2CO_3, MeOH 81%; (vi) LiC≡CH.EDA, DMSO, 25 ^oC, 24 h, 90%; (vii) H_2 (1 atm), Lindlar's catalyst, toluene, 2 h, 93%; (viii) TBAF, THF, 25 ^oC, 6 h, 79%; (ix) (a) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 4 h, 75%; (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78 ^oC, 2 h, 78%; (x) *p*-TSA, benzene, 80 ^oC, 1 h, 91%; (xi) Grubb's-II (5 mol %), dry CH_2Cl_2, 40 ^oC, 12 h, 75%.

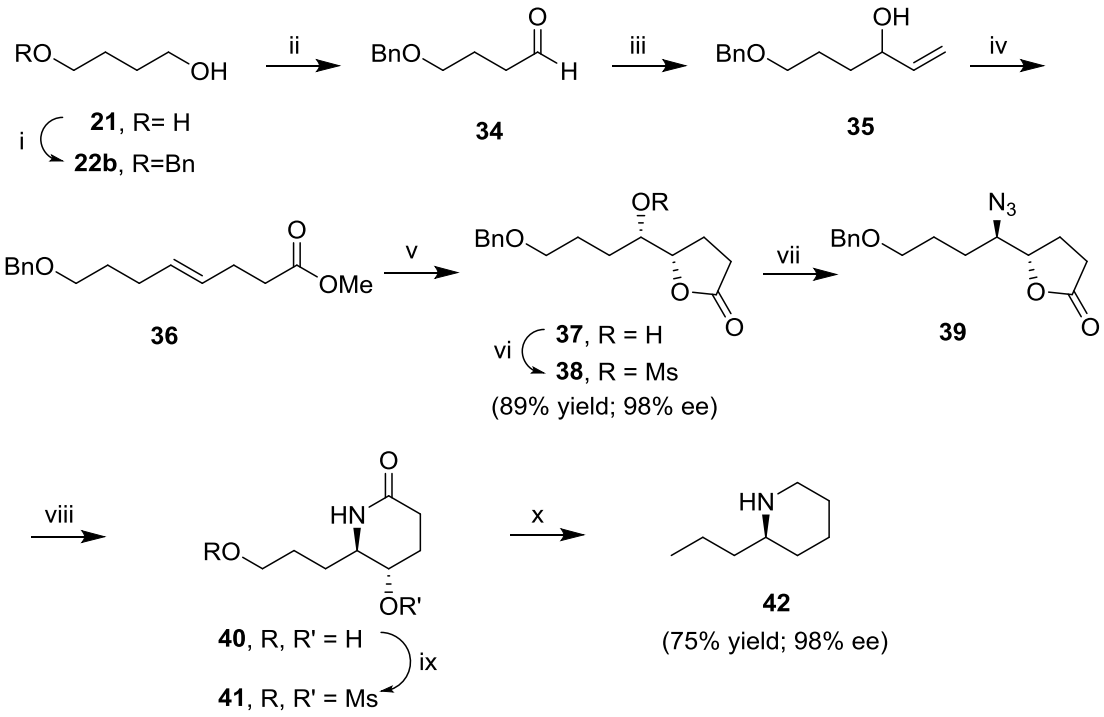
Aldehyde **23** was then subjected to D-proline-catalyzed asymmetric α-aminoxylation followed by in *situ* reduction of aminoxy aldehyde with $NaBH_4$ in methanol gave the aminoxy alcohol **24**, which was subsequently subjected to hydrogenolysis without purification [10% Pd/C, H_2 (1 atm), MeOH] to furnish the chiral diol **25** in 87% yield (for two steps) and 99% ee (HPLC analysis). Diol **25** was smoothly converted to the corresponding epoxide **26** in 81% yield *via* two- step reaction sequence: (i) selective monotosylation and (ii) base-induced epoxide formation. Regioselective ring opening of epoxide **26** with lithium acetylide gave the homopropargylic alcohol **27** in 90%

yield. The partial catalytic hydrogenation of alkyne **27** [Lindlar's catalyst, H_2 (1 atm), toluene] of alkyne **27** produced the corresponding alkene **28** in 93% yield.

The silyl group was then deprotected to give alcohol **29** (TBAF, THF, 25 ^oC), which was subjected to oxidation under TEMPO/BAIB condition to give the corresponding aldehyde. The crude aldehyde was immediately treated with Stille-Gennari reagent [$EtO_2CCH_2P(O)(OCH_2CF_3)_2$] to afford *cis*-α, β-unsaturated ester **30** in 78% yield (with E/Z ratio = 5:95). The α, β-unsaturated ester **30** was then subjected to intramolecular lactonization [*p*-TSA, benzene, 80 ^oC] to obtain lactone **31** in 91% yield, which was further subjected to Ru-catalyzed cross metathesis with unsaturated ketone **32** to produce the target molecule **33** as a colorless oil in 15 % overall yield and with 99% ee.

Synthesis of (*R*)-Coniine *via* Sharpless Asymmetric Dihydroxylation of SECTION II: Enantioslective Homoallylic Ester

Coniine **42** is an alkaloid found in the poisonous hemlock plant *Conium maculatum L.* It has been considered as an excellent target for its anaesthetic property.[5] Our synthesis of (*R*)-coniine **42** commenced with monobenzyl protected 1,4-butanediol **22b**. The free hydroxyl group in **22b** was oxidised (IBX, DMSO, 25 ^oC) to give the corresponding aldehyde **34**, which was immediately treated with vinyl magnesium bromide in THF to give allylic alcohol **35** in 83% yield. The allylic alcohol **35** was then subjected to Johnson - Claisen [3,3]-sigmatropic rearrangement [$CH_3C(OMe)_3$, cat. $CH_3CH_2CO_2H$, xylene, 135 ^oC] to give γ, δ- (*E*)-alkenic ester **36** in 85% yield. Os-catalyzed asymmetric dihydroxylation of **36** [OsO_4, $(DHQ)_2$-AQN, $K_3[Fe(CN)_6]$, K_2CO_3, *tert*-BuOH:H_2O (1:1)], furnished δ-hydroxy γ-lactone **37** in 89% yield and 98% ee (HPLC analysis). The free hydroxyl group in **37** was protected as its mesylate **38** (MsCl, Et_3N, CH_2Cl_2, 0 °C), which was subjected to S_N2 nucleophilic displacement with azide anion to give azido lactone **39** with complete stereochemical inversion. The catalytic hydrogenation of azide in **39** [10% Pd/C, H_2 (1 atm)] gave the six- membered lactam **40** in 98% yield, presumably formed by the intramolecular lactamization of the free amine generated *in situ* releasing the free alcohol. Deoxygenation of hydroxy function and reduction of amide carbonyl were carried out simultaneously *via* a "one-pot" two-step reaction sequence: [selective mesylation of free -OH function followed by its reduction with $LiAlH_4$] to afford coniine **42** in 32% overall yield and 98% ee (**Scheme 5**).



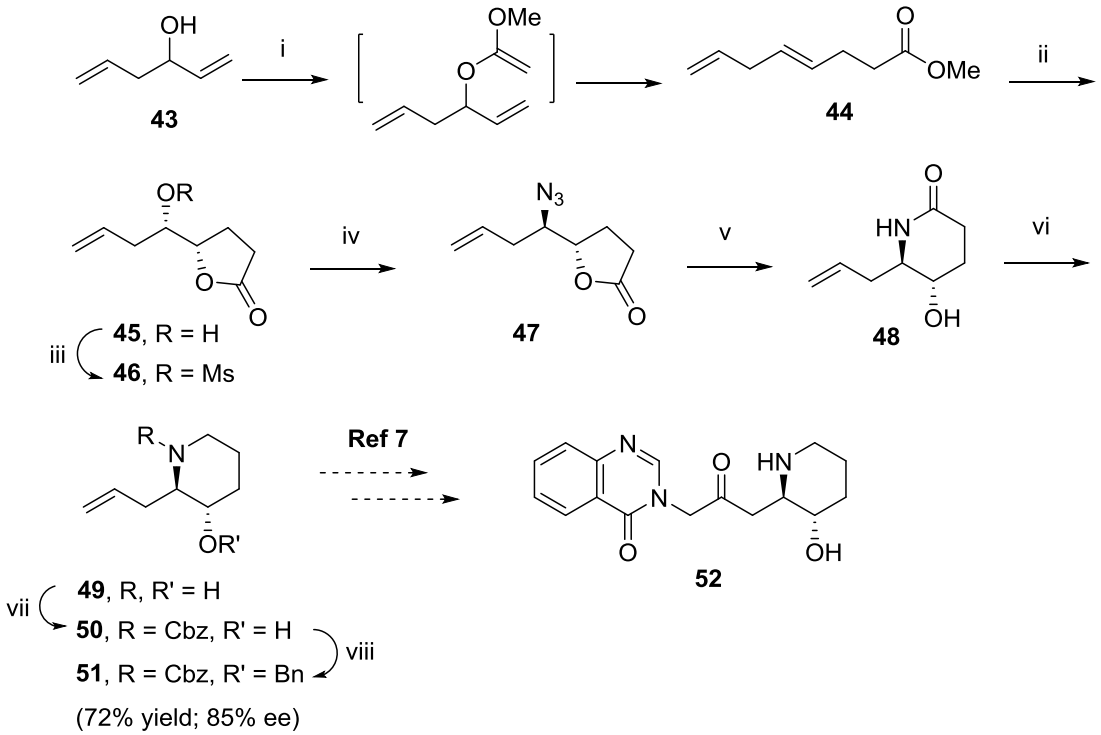
Scheme 5: (i) BnBr, NaH, DMF, 0 ^{o}C, 1 h, 84%; (ii) IBX, DMSO, 25 ^{o}C, 1 h, 98%; (iii) CH_2=CHMgBr, dry THF, 0 ^{o}C 3 h, 83%; (iv) $CH_3C(OMe)_3$, cat. $CH_3CH_2CO_2H$, xylene, 135 ^{o}C, 4 h, 85%; (v) OsO_4 (0.1 mol%), $(DHQ)_2$-AQN (0.5 mol%), $K_3[(Fe(CN)_6)]$ (3 equiv), K_2CO_3 (3 equiv), *tert*-BuOH:H_2O (1:1), 24 h, 89%, 98% ee; (vi) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^{o}C, 1 h, 98%; (vii) NaN_3, DMF, 60 ^{o}C, 5 h, 87%; (viii) (10%) Pd/C, H_2 (1 atm), MeOH, 25 ^{o}C, 24 h, 98%; (ix) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^{o}C, 1 h; (x) $LiAlH_4$, dry THF, 12 h, reflux, 75%.

SECTION III: A Short Enantioselective Formal Synthesis of (+)-Febrifugine, a Potent Antimalarial Drug

Febrifugine **52**, was isolated from the Chinese medicinal plant, *Dichroa febrifuga Lour*. It has been found to be effective against avian malaria.[6] This section describes a short enantioselective synthesis of febrifugine **52** *via* Os-catalyzed asymmetric dihydroxylation of (*E*)-dienic ester **44**. The synthetic approach to febrifugine started with commercially available 1,5-hexadiene-3-ol **43**, which was subjected to Johnson - Claisen [3,3]-sigmatropic rearrangement [$CH_3C(OMe)_3$, cat. $CH_3CH_2CO_2H$, xylene, 135 ^{o}C], which produced (*E*)-dienic ester **44** exclusively as a single isomer in 88% yield.

Regioselective asymmetric dihydroxylation of dienic ester **44** was achieved using α-AD mix [cat. OsO_4, $(DHQ)_2$-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3, *tert*-BuOH:H_2O (1:1), 0 °C, 2 h] to produce the hydroxylactone **45** in 73% yield. Mesylation of the free alcohol (MsCl, Et_3N,

CH_2Cl_2, 0 °C) in **45** followed by its S_N2 displacement with NaN_3 in DMF at 80 °C resulted in the formation of azidolactone **47**.



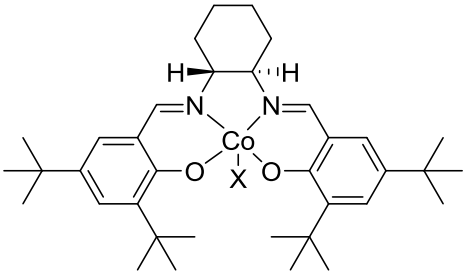
Scheme 6: (i) $CH_3C(OMe)_3$, cat. $CH_3CH_2CO_2H$, xylene, 135 °C, 8 h, 88%; (ii) OsO_4, $(DHQ)_2$-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3, *tert*-BuOH:H_2O (1:1), 0 °C, 24 h, 73%; (iii) MsCl, CH_2Cl_2, 0 °C, 1 h; (iv) NaN_3, DMF, 80 °C, 4 h, 82% over two steps; (v) PPh_3, THF/H_2O (19:1), 25 °C then reflux, 8 h, 93%; (vi) $LiAlH_4$, dry THF, reflux, 12 h, 85%; (vii) CbzCl, K_2CO_3, THF:H_2O (1:1), 0-25 °C, 8 h,; (viii) BnBr, NaH, dry DMF, 0 °C, 1 h, 84%.

Reduction of azide function under Staudinger conditions (PPh_3, THF/H_2O, 60 °C) furnished the 6-membered lactam **48** in 93% yield. Chemoselective reduction of carbonyl function in lactam **48** was achieved with $LiAlH_4$ to give hydroxy piperidine **49**. The free amino and alcoholic groups were subsequently protected with Cbz and BnBr respectively in that order to afford the key intermediate **51** in 72% yield over three steps in 85% ee (**Scheme 6**). The transformation of key intermediate **51** to (+)-febrifugine **52** has already been reported in the literature.[7]

CHAPTER 3

Phenolytic Kinetic Resolution of Benzyloxy Epoxides and Asymmetric Synthesis of D-*erythro*-Sphinganine *via* Co(III)(salen)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxides

The kinetic resolution of terminal epoxides with phenols as nucleophiles known as Phenolytic Kinetic Resolution, (PKR) provides a highly practical route to optically pure 1-aryloxy-2-alcohols with readily accessible Co(III)-catalyst **53**, prepared from the commercially available (salen)Co(II) complex.[8]



53, X = O-C$(CF_3)_3$.H_2O
54, X = OAc

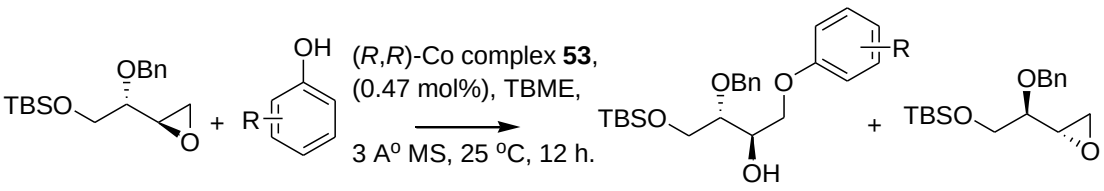
Fig 2: (*R*,*R*)-(salen)Co(III) complex

This chapter is divided into 2 sections. **Section I** deals with the (salen)Co[OC$(CF_3)_3$].H_2O (**53**)- catalyzed PKR of α-benzyloxy epoxides **55a** & **b** to afford chiral α-aryloxy-α'-benzyloxy alcohols **57a-g**. While **Section II** presents the application of HKR of azido epoxide **62** in asymmetric synthesis of D-*erythro*-sphinganine **71** using (salen)Co(III)($OCOCH_3$) catalyst **54**.

SECTION I: Phenolytic Kinetic Resolution of Benzyloxy Epoxides: A New synthesis of Enantiomerically Pure α-Aryloxy-α'-Benzyloxy Alcohols

The enantiomerically pure α-aryloxy alcohols are valuable targets for asymmetric synthesis as a result of their role as key synthetic intermediates in a variety of pharmaceutically important compounds.[9] The racemic *anti*- and *syn*- alkoxy epoxides **55a & b**, substrates for PKR, were efficiently prepared in highly diastereoselective fashion from *cis*-2-butenediol and *trans*-cinnamyl alcohol respectively, essentially involving a two-step reaction sequence of NBS-bromination in the presence of benzylic alcohol, followed by its treatment with base.[10]

Table 1: Co-catalyzed PKR of *anti*-benzyloxy epoxide with phenols

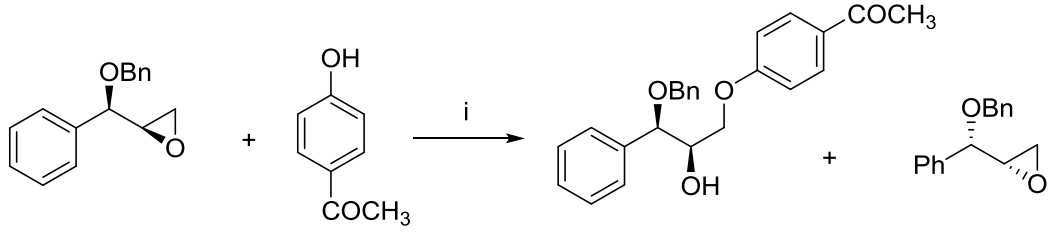


55a, (2*SR*, 3*RS*) (±)-(2.2 equiv) | **56a-f,** (1 equiv) | **57a-f**, (2*R*, *3S*) (75-96% yield; 96-99% ee) | **58** (excess)

		anti-benzyloxy alcohols (**57a-f)**	
entry	R	yield (%)[a]	ee (%)[b]
a	4-CN	96	98
b	4-NO_2	89	96
c	4-$COCH_3$	87	99
d	4-CHO	75	96
e	4-CO_2Me	81	97
f	2,3,5-Cl_3	79	97

[a]Isolated yield after column chromatographic purification *w.r.t.* nucleophile; [b] determined by chiral HPLC analysis.

Racemic *anti*-benzyloxy epoxide **55a** was then subjected to PKR with several differently substituted phenols **56a-f** using (salen)Co[$OC(CF_3)_3$].H_2O (**53**) as catalyst, which produced optically pure *anti*-α-aryloxy-α'-benzyloxy alcohols **57a-f** with complete regiocontrol in excellent yields (75-96%) and ee (96-99%). The results of such a study are shown in **Table 1**.



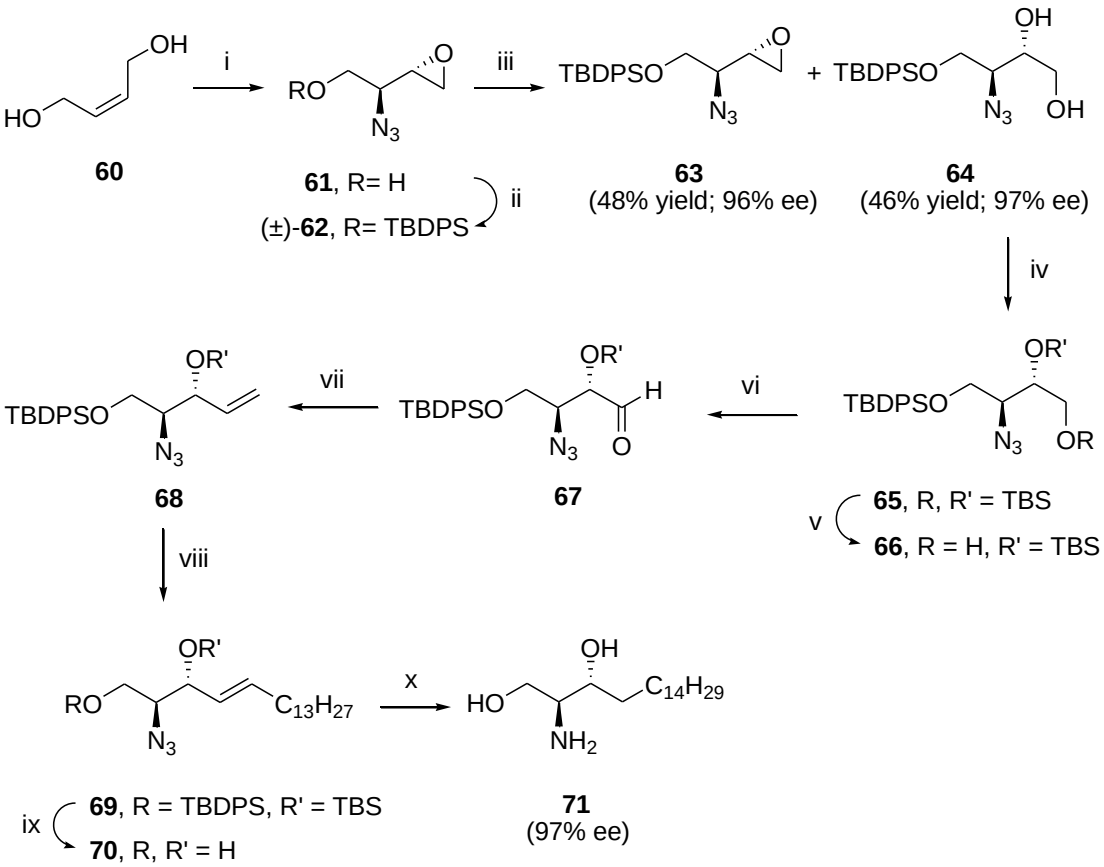
55b, (2*RS*, 3*RS*) (±)-(2.2 equiv) | **56c** (1 equiv) | **57g**, (2*R*, 3*R*) (89% yield; 97% ee) | **59** (excess)

Scheme 7: (i) (*R*,*R*)-Co complex **53** (0.47 mol%); *tert*-butyl methyl ether, 3 A° MS, 25 °C, 12 h.

Similarly, racemic *syn*-benzyloxy epoxide **55b**, when subjected to (salen)Co[$OC(CF_3)_3$].H_2O, (**53**) -catalyzed PKR, afforded the corresponding enantiomerrically pure *syn*-α-aryloxy-α'-benzyloxy alcohol **57g** in 89% yield and 97% ee (**Scheme 7**).

SECTION II: Asymmetric Synthesis of D-*erythro*-Sphinganine *via* (salen)Co(III)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxide

D-erythro-Sphinganine **71** strongly inhibits protein kinase C.5.[11] The biological significance and the complicated isolation of sphingolipids from natural sources justifies the efforts towards their synthesis.



Scheme 8: (i) (a) NBS, NaN_3, CH_3CN:H_2O (4:1), 0 ^oC, 3 h, 89%; (b) NaOH, THF, 0 ^oC, 3 h, 84%. (ii) TBDPSCl, imid., CH_2Cl_2, 0 ^oC, 4 h, 97%; (iii) (*R,R*)-(-)-N,N'–bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamiocobalt(III) **54** (0.5 mol%), H_2O (0.48 equiv), 25 ^oC, 24 h; (iv) TBSCl, imid., dry DMF, 0 ^oC, 6 h, 87%; (v) CSA, MeOH, 25 ^oC, 30 min, 75%; (vi) IBX, EtOAc, reflux, 3 h, 80%; (vii) $Ph_3P^+CH_3I^-$, *n*-BuLi, dry THF, 0 ^oC, 8 h, 65%; (viii) 1-pentadecene, Grubbs' II generation catalyst (10 mol %), CH_2Cl_2, 40 ^oC, 32 h; (ix) TBAF, THF, 25 ^oC, 6 h, 79% (over two steps); (x) (10%) Pd/C, H_2 (1 atm), MeOH/AcOH (5:1), 25 ^oC, 12 h, 90%.

This section describes the asymmetric synthesis of D-*erythro*-sphinganine **71** using Co-catalyzed Hydrolytic Kinetic Resolution (HKR) of azido epoxide **62** as the key reaction for the introduction of chirality The synthesis commenced with bromoazidation of commercially available *cis*-1,4-butenediol **60** in presence of NBS and NaN_3 followed by its base treatment gave racemic *anti*-azido epoxy alcohol **61** in 84% yield and > 99% dr. The primary hydroxyl group in **61** was protected as its silyl

ether **62** (TBDPSCl, imid., CH_2Cl_2). The azido epoxide **62** was then subjected to HKR using (*R,R*)-(salen) Co(III)($OCOCH_3$) (**54**) as the catalyst that produced azido diol **64** in 46% yield and 97% ee along with the unreacted *anti*-azido epoxide **63** in 48% yield and 96% ee. Both **64** and **63** were readily separated by column chromatography. The diol **64** was protected as TBS ether **65**, followed by the selective deprotection of the primary alcoholic silyl ether group in **65** (using 10 mol% camphor sulfonic acid) that gave the primary alcohol **66** in 75% yield, which was oxidized to the corresponding aldehyde **67** (IBX, EtOAc).

The crude aldehyde **67** on Wittig reaction ($PPh_3^+CH_3I^-$, *n*-BuLi, THF) gave the terminal alkene **68** in 65% yield over two steps. The terminal alkene **68** was subjected to Ru-catalyzed cross metathesis with 1-pentadecene in the presence of Grubbs'-II generation catalyst to obtain the long chain azido alkene **69** in 71% yield. The synthesis of D-*erythro*-azidosphingosine **70** was achieved by the removal of silyl groups in **69** (TBAF in THF, 79% yield). Both the azido group and the alkene functionality in **70** were hydrogenated [H_2 (1 atm), 10% Pd/C, MeOH/AcOH] to give D-*erythro*-sphinganine **71** in 6% overall yield and 97% ee (**Scheme 8**).

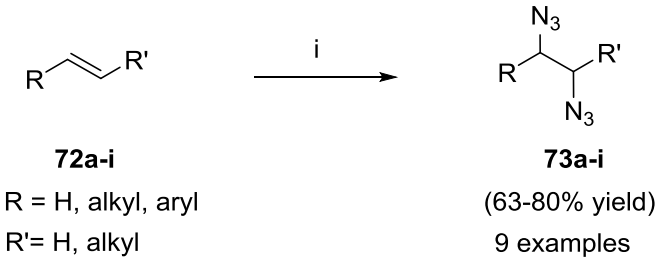
CHAPTER 4

$NaIO_4$–NaN_3–Mediated Diazidation of Alkenes and Cu(I)-Catalyzed Synthesis of *gem*-Ditriazoles

This chapter is divided into 2 sections. **Section I** deals with the $NaIO_4$–NaN_3–mediated *vicinal* diazidation of alkenes giving 1, 2-diazidoalkanes **73a-i** while **Section II** presents Cu(I)-catalyzed [3+2]-cycloaddition of α,α-diazido aromatic ketones **74a-f** with phenyl acetylene leading to the synthesis of novel phenyl substituted *geminal* ditriazoles **75a-f**.

SECTION I: $NaIO_4$–NaN_3–Mediated Diazidation of Alkenes

Vicinal diazides are important precursors to 1,2-diamines, which are useful functional groups present in a variety of natural products, pharmaceutical substances (e.g. D-(+)-biotin).[12] In addition, 1,2-diamines find increasing utilization in organic synthesis either as chiral auxiliaries or as metallic ligands especially in the field of catalytic asymmetric synthesis.

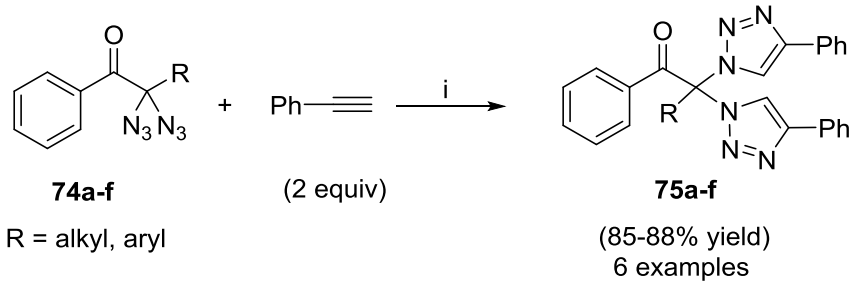


Scheme 9: (i) alkene (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), DMSO:AcOH (4:1), 75 ^oC, 4 h.

This section presents a simple, effective methodology for the direct transformation of alkenes **72a-i** to the corresponding diazidoalkanes **73a-i** in high yields (63-80%) under mild reaction condition. The reagent system employed was ($NaIO_4$/NaN_3/DMSO-AcOH) (**Scheme 9**).

SECTION II: Synthesis of *gem*-Ditriazoles from α, α-Diazido Ketones

1,4-Disubstituted 1,2,3-triazoles are known to possess remarkable cytotoxic activity against the various human cell lines.[13] One of the most attractive ways to prepare these compounds involve the thermal 1,3-dipolar cycloaddition of azides with alkynes, pioneered by Huisgen.[14] This section deals with the reaction of different α,α-diazidoketones, prepared from the respective aromatic ketones *via* $NaIO_4$–NaN_3 mediated α,α-diazidation, with phenylacetylene (2 equiv) in the presence of Cu(I) as the catalyst in toluene at 80 ^oC that provided *gem*-α,α-ditriazole aryl ketones **75a-f** in high yields (85-88%) (**Scheme 10**).



Scheme 10: (i) CuI (5 mol%), toluene, 80 ^oC, 8 h.

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Chapter I

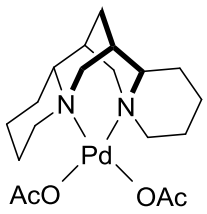
Pd-Catalyzed Oxidative Kinetic Resolution of α-Bromobenzylic Alcohols Using (–)-Sparteine as Chiral Auxiliary: A Practical Synthesis of (S)-Duloxetine and (–)-Chloramphenicol

SECTION I:

Pd-Catalyzed Oxidative Kinetic Resolution of α-Bromobenzylic Alcohols Using (–)-Sparteine as Chiral Auxiliary

1.1.1 Introduction:

Kinetic resolution is a comprehensively studied and widely applied reaction.[1] Despite these achievements the kinetic resolution has only been applied to the resolution of simple benzylic alcohols with one stereocentre.[2] Recently the Hydrolytic Kinetic Resolution HKR has been applied to the resolution of α-functionalised epoxides to generate two stereocentres.[3] This invention prompted us to apply the oxidative kinetic resolution (OKR) to the α-functionalised benzylic alcohols, to generate two stereocentres of high optical purities in a single step. To the best of our knowledge, study related to the OKR of functionalised alcohols has not been reported. Previously, Tsuji *et al* have reported the Pd(II)- catalyzed oxidation of α-bromobenzylic alcohols to produce unfunctionalized ketones[4] while Stoltz and Sigman *et al.* independantly have reported the Pd(II)-sparteine (**1**) (**Fig. 1**) resolution of the unfunctionalised benzylic alcohols.[4] The enantiomerically pure *anti*-α-bromobenzylicalcohols are valuable building blocks for asymmetric synthesis of bioactive pharmaceuticals, dyes, flame retardants and agrochemicals.[5]



1

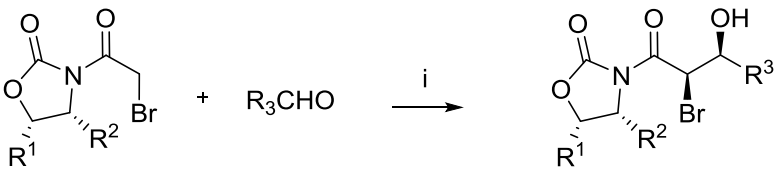
Fig. 1: Pd(II)-(–)-sparteine complex (**1**)

1.1.2 Review of literature:

Literature search revealed that there are only few reports[6-9] available for the asymmetric bromohydroxylation, which involve the use of metal salts (Ag, Yb) and stoichiometric amounts of Br_2/*N*-halosuccinimides, as described below.

Evans' approach (1987)[6]

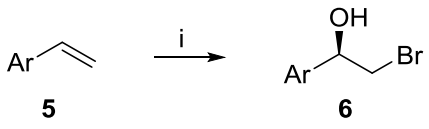
Evans *et al*. have reported the asymmetric bromohydroxylation using aldol reaction of chiral bromoacetate enolates **2** with aromatic or aliphatic aldehydes **3** in presence of Bu_2BOTf and Et_3N yielding bromohydroxylated products **4** with diastereomeric ratio >94:6 and 63-94% yields (**Scheme 1**).



Scheme 1: (i) Bu_2BOTf, Et_3N, CH_2Cl_2, -78 °C, 63-94%.

Sudalai's approach (2003)[7]

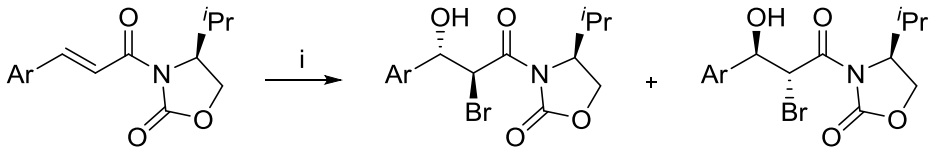
Asymmetric bromohydroxylation of β-cyclodextrin complexes of styrenic substrates **5** has been described with $NaIO_4$ and LiBr in aqueous acetonitrile under acidic conditions to provide bromohydrins **6** with good yield (78-90%) and moderate enantiomeric excess (20-55%) (**Scheme 2**).



Scheme 2: (i) β-cyclodextrin complex of styrene, LiBr (1.2 equiv), $NaIO_4$ (25 mol%), aq. H_2SO_4, CH_3CN/H_2O (3:1), 25 ºC, 12 h, 78-90%, 20-55% ee.

Hajra's approach (2005)[8]

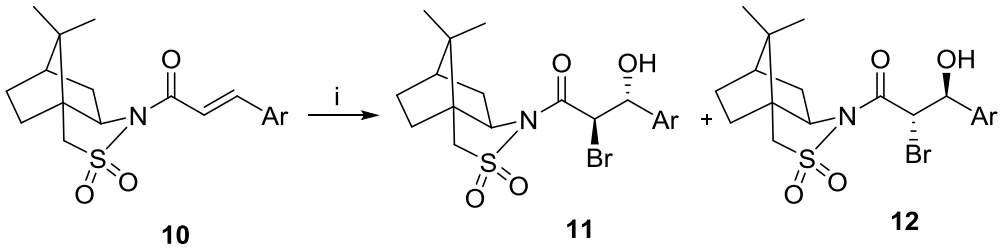
The halohydrin formation of chiral *N*-enoyl-2-oxazolidinones **7** by bromine and water has been reported in presence of silver (I) salt to give the product bromohydrins **8** and **9** with moderate diastereoselectivity (upto 4:1) (**Scheme 3**).



7 **8** **9**

Scheme 3: (i) $AgOAc/Ag_2O/AgNO_3$, Br_2, aqueous acetone, 0 to 25 °C, 88-97%.

The same authors have developed Lewis acid-catalyzed asymmetric bromohydroxylation of chiral α, β-unsaturated carboxylic acid derivatives **10** with NBS and aqueous CH_3CN giving bromohydrins **11** and **12** with diastereoselectivity upto 4:1 (**Scheme 4**).

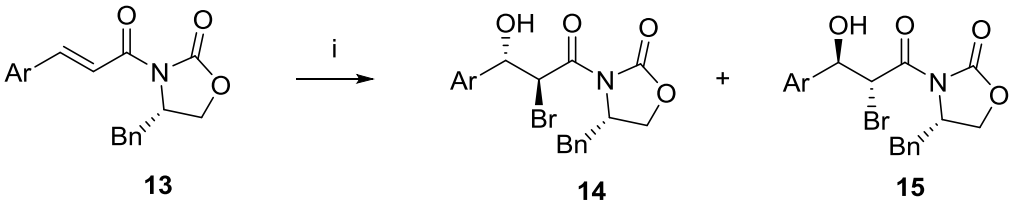


10 **11** **12**

Scheme 4: (i) $Yb(OTf)_3$, NBS, aqueous CH_3CN, 25 °C.

Sudalai's approach (2007)[9]

(4*S*)-*N*-Cinnamoyl-4-benzyl-2-oxazolidinone **13**, readily derived from Evans's chiral auxillary obtainable from (*S*)-phenylalanine, was subjected to oxidative bromination in the presence of 30 mol% $NaIO_4$ in a 2:1 mixture of CH_3CN and water using LiBr (1.2 equiv) as the bromine source under acidic conditions (aq. HCl), to obtain the corresponding bromohydrins **14** and **15** in 81% combined yield and high diastereoselectivity (dr = 5.5:1).



13 **14** **15**

Scheme 5: (i) carboxamide (5 mmol), $NaIO_4$ (30 mol%), LiBr (6 mmol), 35% aq. HCl (0.5 ml), CH_3CN/H_2O (2:1), 25 ºC, 3 h, (de 5-10:1), 81%.

Several (4*S*)-*N*-cinnamoyl-4-benzyl-2-oxazolidinones with electron- donating as well aswithdrawing substituents on the aromatic nucleus were subjected to bromohydroxylation to produce the corresponding bromohydrins **14** and **15** in excellent yields and high diastereoselectivity (**Scheme 5**).

1.1.3 Present work

1.1.3.1 Objective:

In principle, access to chiral bromohydrins may be provided by few methods such as asymmetric aldol reactions and asymmetric bromohydroxylation.[10a-c] However, these asymmetric halohydrin reactions suffer from several disadvantages such as low diastereoselectivities, use of expensive metal salts (Ag, Yb) and stoichiometric amounts of organic and inorganic wastes.[10d-e] We envisioned that application of Pd(II)-sparteine complex- catalysed OKR to the racemic α-bromobenzylic alcohols would enable us to obtain one of the enantiomer of *anti*-α-bromobenzylic alcohol depending upon the chiral ligand chosen. In this context, a more practical method for chiral bromohydrin is highly desirable. Since Oxidative kinetic resolution has been figured the prominent reaction for introducing chirality in to the molecules, it is apt to give a brief account of it.

1.1.3.2 Kinetic Resolution: Resolution strategies have always played a central role in the preparation of optically active compounds.[11] Resolutions fall broadly into three

classes: (i) *Classical resolutions* involve the use of stoichiometric amount of chiral resolving agent.[12]

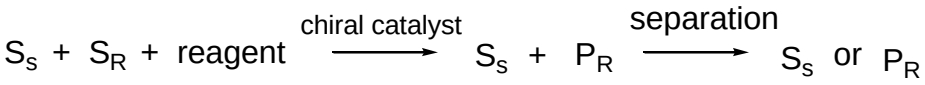


Fig.2: Catalytic kinetic resolution

(ii) *Chiral chromatography* generally relies on the use of chiral stationary phases to resolve enantiomers contained in a mobile phase, and in principal it can be carried out on analytical or preparative scale. (iii) *Kinetic resolution* involves the use of a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantioenriched starting material and product, the desired component is then isolated (**Fig.2**).[13] If the undesired resolution byproduct can be racemized or otherwise converted back to the desired enantiomer, then this can improve the yield, and therefore the practicality of the resolution process. In some special circumstances, it is possible to induce substrate racemization under the conditions of resolution. It then becomes possible in principle to convert essentially 100 % of the racemate to the desired product. Such process constitutes a very special subclass of kinetic resolution known as *dynamic kinetic resolutions*. Catalytic kinetic resolutions are particularly attractive, because of the need for only small amounts of chiral "resolving agent". In kinetic resolutions, enantiomers of a racemic substrate (S) react at different rates to form a product (P) that may or may not be a chiral.

Theoretical Considerations

Standard kinetic Resolutions

In kinetic resolution, enantiomers of a racemic (S) react at different rates to form a product (P) that may or may not be a chiral. In a catalytic kinetic resolution , the relative rates of reaction for the substrate enantiomers, typically expressed as s or k_{rel}

$= k_{fast} / K_{slow}$, are dictated by the magnitude of $\Delta\Delta G^{\#}$ thus corresponds to the difference in energies

$$K_{rel} = S = K_{fast} / K_{slow} = {}_{e}\Delta\Delta G^{\#}/RT$$

Between the diastereomeric transition states in the selectivity determining step of the catalytic reaction . Thus K_{rel} in a kinetic resolution is related to $\Delta\Delta G\#$ in the same manner as it is an enatioselective reaction of a prochiral substrate. Although the selectivities observed for both kinetic resolution and enantioselective reactions of prochiral substrates reflect the magnitude of $\Delta\Delta G\#$ there is also an important practical difference between the two. While under normal conditions, enantioselective reactions of prochiral substrates yield product of constant ee, the ee obtained in a kinetic resolution changes as a function of conversion

$S_R \xrightarrow[\text{Chiral catalysts}]{K_R = K_{fast}} P_R$

$S_S \xrightarrow[\text{Chiral catalyst}]{K_S = k_{slow}} P_S$

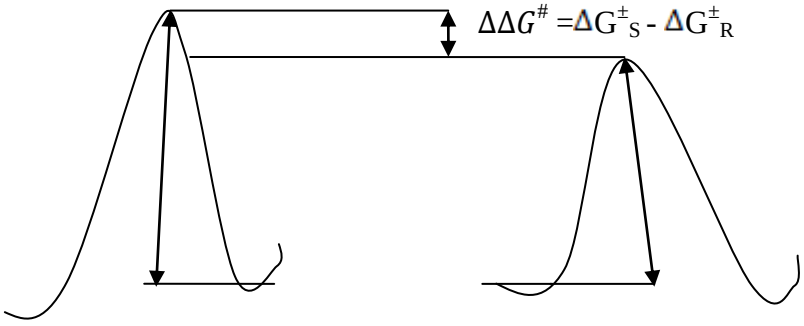


Fig. 3: The difference in energies observed in kinetic resolutions

Dynamic and parallel kinetic Resolution

Dynamic and parallel kinetic resolution rely on differential reactivity of substrate enantiomer toward a chiral catalyst; however they are also quite different from standard kinetic resolutions because in principle the catalyst is always encountering a racemization at a rate greater than that of its transformation to the product. Under such circumstances, the product of the resolution reaction can theoretically be isolated in 100% yield with an ee determined by the magnitude of k_{rel}. In a parallel kinetic resolution, both enantiomers undergo reaction at comparable rates to give different products. In this case , as with standard kinetic resolutions, the maximum yield is 50% for each product. However, the ee the product is much less depending on the degree of conversion.

Oxidative Kinetic Resolution of Alcohols (OKR)

Although excellennt catalytic enantioselective methods exist for a variety of oxidation processes such as epoxidation, dihydroxylation, and aziridination, there are relatively few catalytic enantioselective examples of ubiquitous alcohol oxidation.

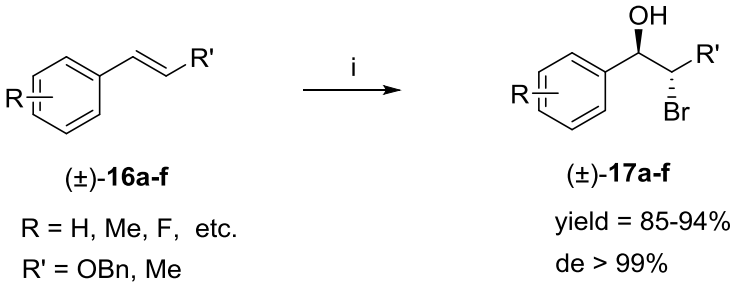
In 1981, Sharpless has reported asymmetric epoxidation of allylic alcohols. The same catalytic system ($Ti(OPr^i)_4$/diisopropyl tartarate) was used for the kinetic resolution of secondary allylic alcohol to afford the corresponding optically pure alcohol and epoxides depending on the ligand used. Acetone was used as hydrogen acceptor in the oxidative reaction. More recently, Uemura and Hidai have reported the successful kinetic resolution of benzylic alcohols catalysed by (oxazolinylferrocenylphosphine) Ru complex to yield optically pure alcohol and the corresponding ketone.

A recent advance in this regard is the catalytic oxidative kinetic resolution of secondary alcohols using molecular oxygen as the terminal stoichiometric reoxidant. The use of molecular oxygen in combination with a catalytic metal complex has

exceptional advantages for application in organic synthesis. This is partly due to the favorable economy associated with molecular oxygen and the formation of environmentally benign byproducts in the oxidation manifold (water and H_2O_2). In this connection, Pd-catalyzed kinetic resolution of secondary alcohols that uses molecular oxygen as the terminal oxidant and naturally occuring (-)-sparteine as a chiral ligand has been reported affording chiral alcohols (ee upto 99%) and the corresponding ketones.[2]

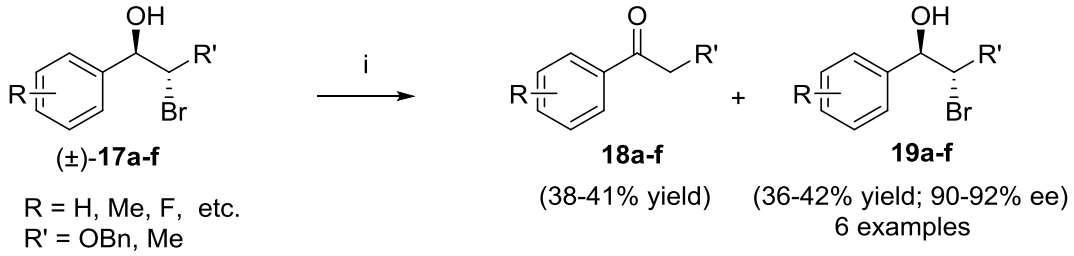
1.1.3.3 Result and Discussion

Our initial experiments involving Pd(II)-(-)-sparteine-catalyzed OKR of benzylic α-hydroxyesters and benzylic hydroxyepoxides resulted in the mixture of complex products, which were difficult to separate and analyse. We decided then to try the same OKR reaction on racemic *anti*-1,2- bromohydrins. Thus the racemic *anti*-α-bromobenzylic alcohols (**17a-f**), the substrates for OKR, were efficiently prepared in a highly diastereoselective manner from the corresponding (*E*)-alkenes[14] (**16a-f**) in a single-step involving NBS-bromination in the presence of water[3] (**Scheme 6**).



Scheme 6: (i) NBS, CH_3CN/H_2O (3:1), 25 ^oC, 8 h.

The relative stereochemistry between the hydroxy group and bromine atom is established prior to the OKR step itself[15] and in this way a simple asymmetric reaction can be used to form the enantiomerically pure bromohydrin with two stereocenters as given below.



Scheme 7: (i) $Pd(OAc)_2$ 5 mol%, O_2 (1 atm), (-)- Sparteine (20 mol %), 4 Å, 10-12 h

Initially, when OKR of racemic *anti*-2-bromo-1-phenylpropan-1-ol **(17a)** was performed with *in-situ* generated Pd(II)-(-)-sparteine complex (**1**) from $Pd(OAc)_2$ (5 mol%) and (-)-sparteine (20 mol%) under oxygen atmosphere in toluene as solvent, the corresponding chiral bromohydrin (**19a**) (**Table 1**) (40% yield and 90% *ee*) and the dehalogenated, oxidized ketone (**18a**) (41% yield) were isolated (**Scheme 7**).

Table 1: Oxidative Kinetic Resolution (OKR) of *anti*-α-bromo benzylic alcohols[a]

entry	*anti*-α-Bromo alcohol [**(±)17a-f**]		Ketones Yield (%) (**18a-f**)	*anti*-α-Bromo alcohol (**19a-f**)	
	R	R'		Yield[b] (%)	*ee*[c] (%)
a	H	CH_3	41	40	90
b	4-CH_3	CH_3	38	41	92
c	4-CF_3	CH_3	40	36	90
d	4-F	CH_3	40	38	91
e	2,4-F_2	CH_3	41	38	91
f	H	OBn	40	42	92

Reaction conditions: [a]bromohydrin (5 mmol), $Pd(OAc)_2$ (5 mol%), O_2, (-)-sparteine (20 mol%), 4 Å, 10-12 h; [b]yields refer to isolated yield after column chromatography; [c]ees based on the chiral HPLC analysis.

Encouraged by the observation of high yield and enantioselectivity, we examined its scope by subjecting several racemic *anti*-α-bromobenzylic alcohols (**17a-f**) to OKR, which indeed proceeded smoothly to give the respective enantiopure bromohydrins **19a-f** in excellent yields and enantiomeric excess. **Table 1** shows the results of such a study.

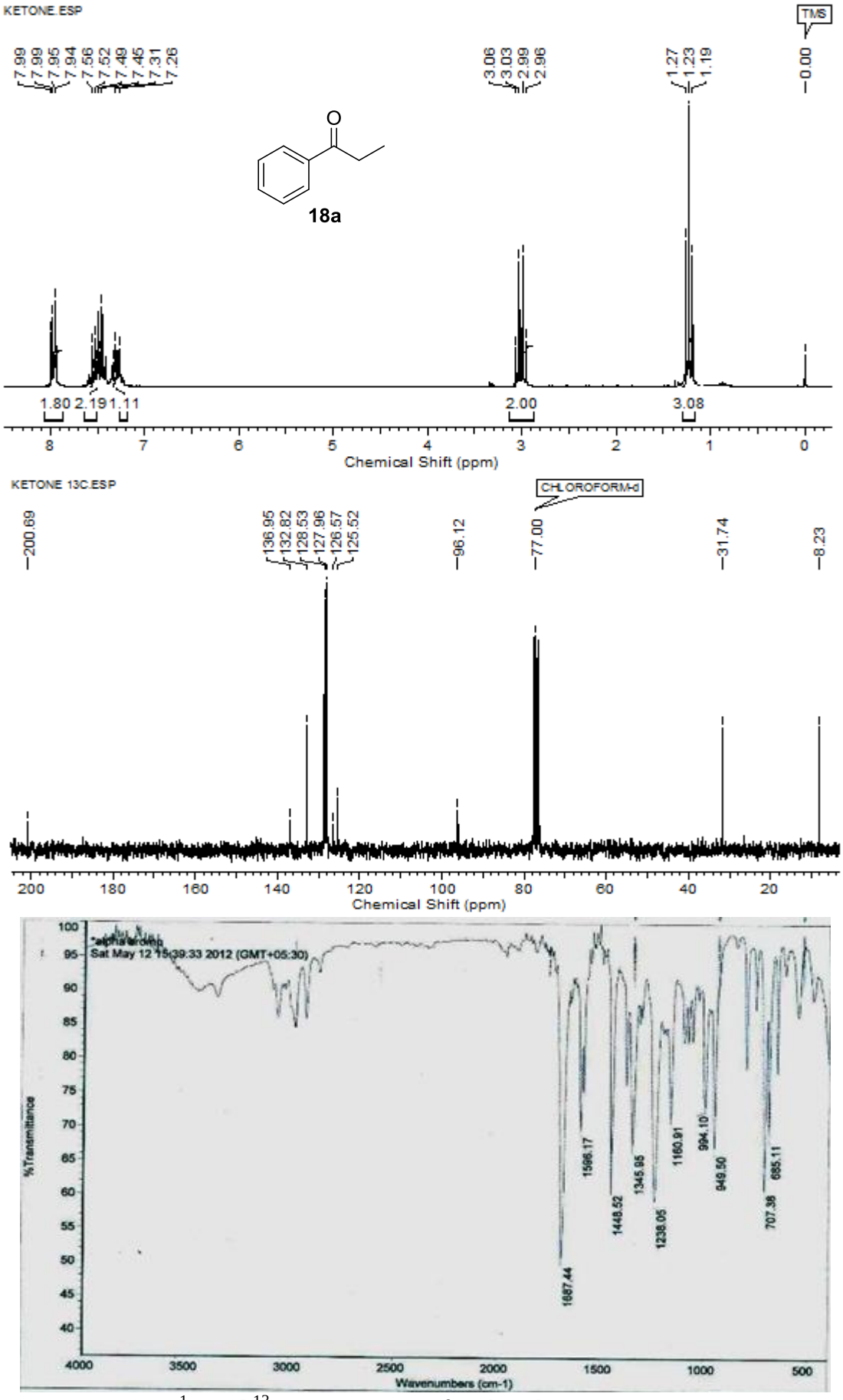


Fig. 4: ^{1}H and ^{13}C NMR spectra of 1-phenyl propan-1-one **(18a)**

The reaction was then carried out with several bromohydrins; thereby exhibiting the generality with respect to the degree of functionalization of bromohydrins and the range of substituents on aromatic nucleus (see **17a-f)**. Further, bromohydrins bearing strong-electron donating substituents like methoxy on the aromatic ring gave the inseparable mixture of diastereomers. The formation of products **18a-f** and **19a-f** was confirmed by ^{1}H and ^{13}C NMR spectroscopy as given below. The compounds **18a** and **19a** were readily separated by silica gel column chromatography.

Example 1: The ^{1}H NMR spectrum of **18a** showed typical signals at δ 6.85-6.95 and at δ 2.96-3.06 for the α- methylenic (-COC**H**$_2$) protons. The disappearance of a signal at δ 5.00 for the benzylic proton (-C**H**OH) confirmed the formation of ketone **18a**. Its ^{13}C NMR spectrum showed a typical signal at δ 200.69 while its IR spectrum exhibited a charachterisic absorption at 1687 cm^{-1} due to the carbonyl carbon confirming the formation of ketone (**Fig. 4**).

The ^{1}H NMR of **19a** showed a typical signal at δ 5.00 for the benzylic proton (-C**H**OH) and a doublet of quartet at δ 4.35-4.45 due to (-C**H**Br) proton. Its ^{13}C NMR spectrum showed two typical signals at δ 77.3 and 56.1 due to the benzylic carbon (-**C**HOH) and the carbon attached to bromine atom (-**C**HBr) respectively; thus confirming the formation of **19a** The enantiomeric purity of **19a** was determined as 90% ee from its chiral HPLC analysis (**Fig. 5**).

The compounds **18b** and **19b** were readily separated by silica gel column chromatography.

Example 2: The ^{1}H NMR spectrum of **18b** showed typical signal at δ 6.85-6.95 and at δ 2.91-3.02 for the α- methylenic (-COC**H**$_2$) protons. The disappearance of a signal at δ 4.95 for the benzylic proton (-C**H**OH) confirmed the formation of ketone **18b**. Its

^{13}C NMR spectrum showed a typical signal at δ 199.9 for the carbonyl carbon, which confirmed the formation of aromatic ketone **18b** (**Fig. 6**).

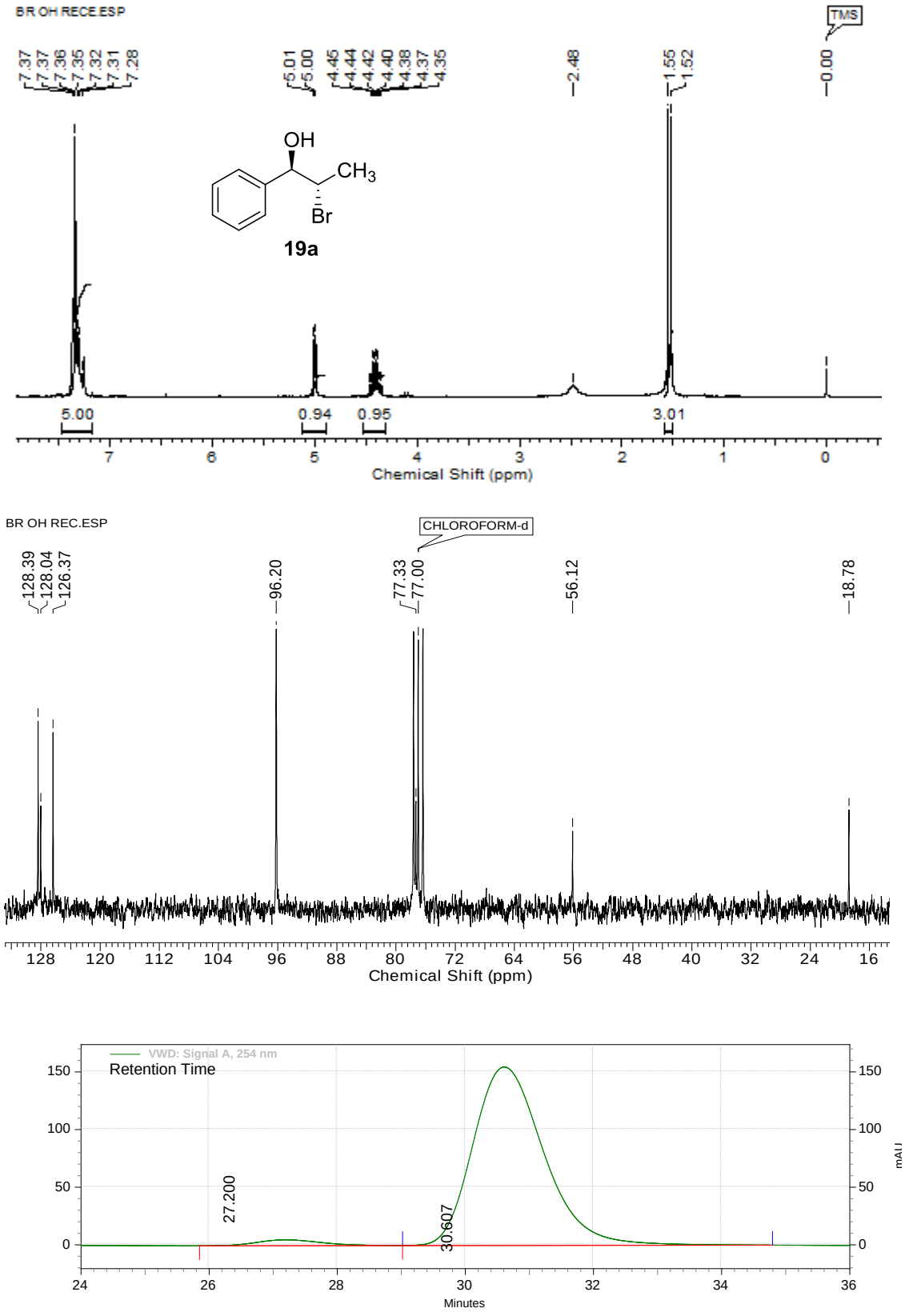


Fig. 5: ^{1}H, ^{13}C NMR spectra and HPLC chromatogram of bromoalcohol **(19a)**

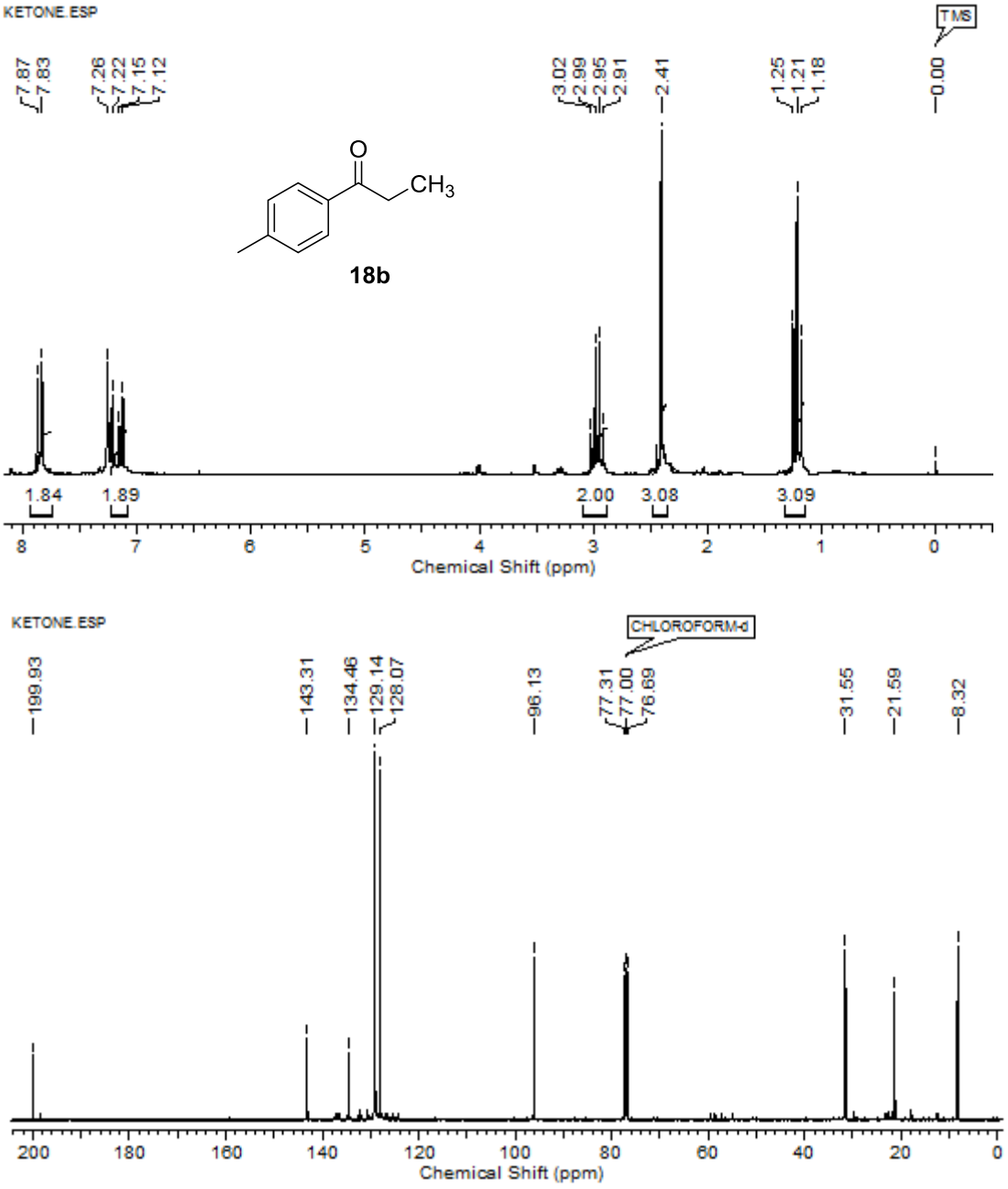


Fig. 6: ^{1}H and ^{13}C NMR spectra of 1-(*p*-tolyl)propan-1-one **(18b)**

The ^{1}H NMR spectrum of **19a** showed two typical signals at δ 4.95-4.96 for the benzylic proton (-C**H**OH) and a doublet of quartet at δ 4.37-4.41 for the methine proton (-C**H**Br). Its ^{13}C NMR spectrum showed two typical signals at δ 77.2 and 56.3 due to the benzylic carbon (-**C**HOH) and the carbon attached to bromine atom (-**C**HBr) respectively, thus confirming the formation of **19a (Fig. 7)**.

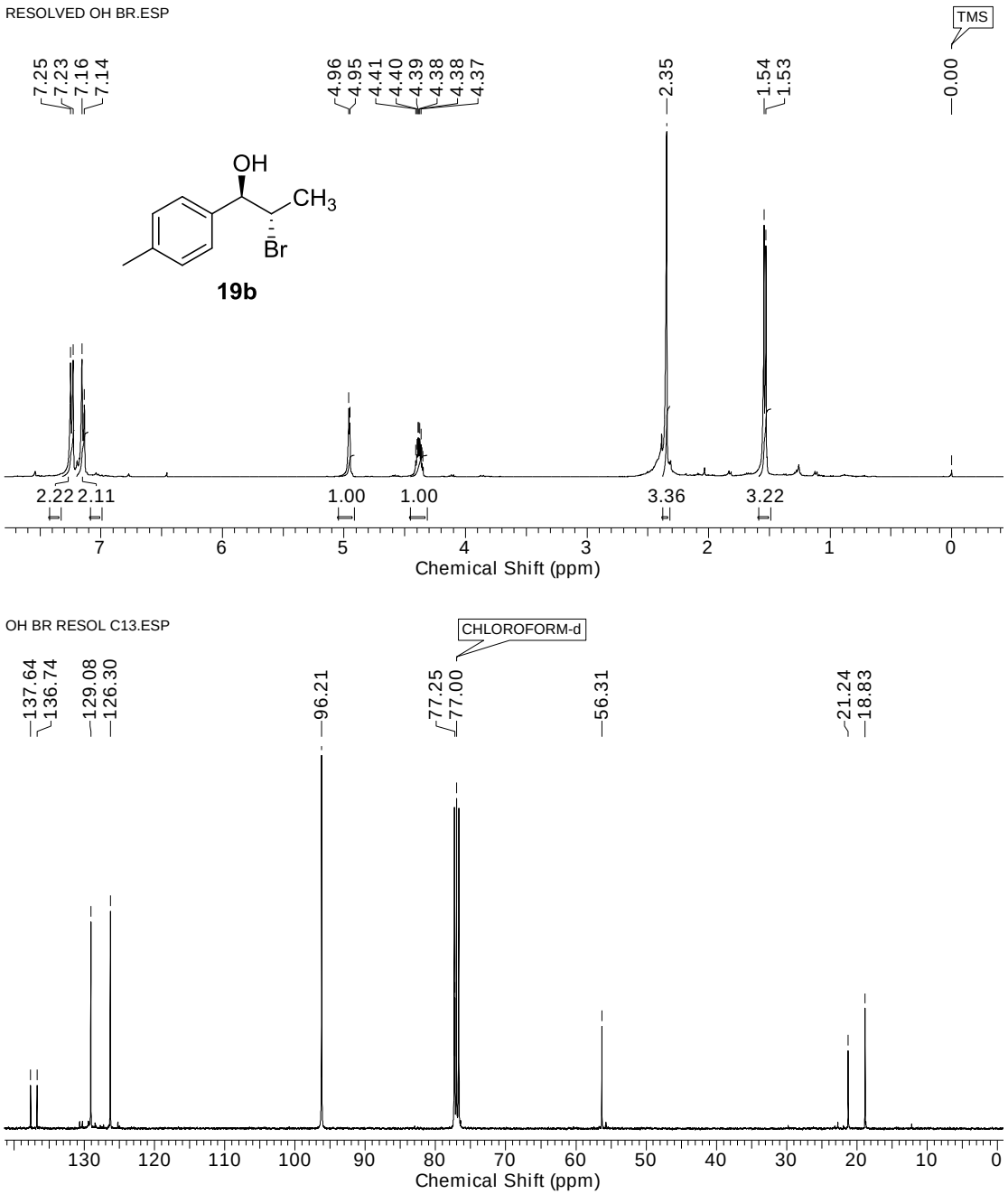


Fig. 7: ^{1}H and ^{13}C NMR spectra of 1-(*p*-tolyl)propan-1-one (**19b**)

1.1.4 Conclusion

In summary, Pd(II)-(-)-sparteine-catalyzed OKR of racemic-α-bromobenzylic alcohols provides for a highly practical route to the corresponding enantiomerically pure *anti*-α-bromobenzylic alcohols in a single step. The reaction is convenient to carry out. The methodology displays a wide range of substrate scope. We believe that

this OKR stratergy will find application in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of the synthesis of racemic α-bromobenzylic alcohols and the readily avaibilability of the sparteine ligands in both enantiomeric forms.

1.1.5 Experimental Procedure:

(a) General procedure for the synthesis of racemic *anti*-α-bromo benzylic alcohols:

To a solution of (*E*)-β-methyl styrene (**16a-f**) (5 mmol) in acetonitrile/water (20:10) was added *N*-bromosuccinimide (1.062 g, 6 mmol) slowly *via* addition funnel, with stirring at 25 ^{o}C. The reaction was stirred overnight at this temperature. The progress of reaction was monitored by TLC. After completion of reaction , it was diluted with EtOAc and washed with water and brine. The organic layer was separated and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified by column chromatography (packed with silica gel 100-200 mesh) using petroleum ether and ethyl acetate as eluents to afford the products (**17a-f**) in 85-94% yield and > 99% de.

b) General procedure for the oxidative kinetic resolution of Racemic *anti*-α-bromo benzylic alcohols:

To a 100 mL side arm flask 0.042 g (0.185 mmol) of $Pd(OAc)_2$ was placed followed by the addition 40 mL of dry toluene, 100 mg of 3Å sieves and 0.16 mL (0.174 g, 0.74 mmol) of (-)-sparteine. A balloon filled with O_2 was then attached to the flask fitted with a condenser. The whole system was evacuvated and refilled with O_2 (1 atm) from the balloon three to four times. The contents were heated to 80 ^{o}C in an oil bath. After 30 min, 3.7 mmol of *anti*- bromohydrins (**17a-f)** in toluene was added dropwise as the case may be. After 10-12 h of refluxed temperature, the reaction mixture was cooled to room temperature. It was quenched with 2% TFA in methanol.

The solvent was concentrated under vaccuo, to give the mixture of crude products which were purified by column chromatography (packed with silica gel 100-200 mesh) using pet. ether and ethyl acetate (95:5) to give ketones **18a-f** in 38-41% yield, while chiral *anti*-α-bromohydrins **19a-f** were isolated in 36-42% yield (90-92% ee) using pet. ether/ethyl acetate (80:20) ratio.

1-Phenylpropan-1-one (18a)

Yield: 41%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3063, 2978, 1682, 1583, 1464, 1301, 1225, 1105, 937; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.07-7.94 (m, 2H), 7.53-7.41 (m, 2H), 7.35-7.24 (m, 1H), 3.06-2.96 (q, *J* = 8 Hz, 2H), 1.27-1.19 (t, *J* = 6 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 200.7, 136.9, 132.8, 128.5, 128.0, 31.7, 8.2; **Analysis:** $C_9H_{10}O$ requires C, 80.56; H, 7.51; found: C, 80.52; H, 7.43%.

1-(*p*-Tolyl)propan-1-one (18b)

Yield: 38%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3031, 2938, 1685, 1573, 1454, 1371, 1225,1111, 952; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.87-7.83 (d, *J* = 6 Hz, 2H), 7.26-7.22 (d, *J* = 8Hz, 2H,), 3.02-2.91 (q, *J* = 8 Hz, 2H,), 2.41 (s, 3H), 1.25-1.18 (t, *J* = 8 Hz, 3H,); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 199.9, 143.3, 134.5, 129.1, 128.1, 31.5, 21.6, 8.3; **Analysis:** $C_{10}H_{12}O$ requires C, 81.04; H, 8.16; found: C, 81.00; H, 8.11%.

1-(4-(Trifluoromethyl)phenyl)propan-1-one (18c)

Yield: 40%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2967, 2928, 1682, 1599, 1460, 1327, 1260, 1174, 1030, 955; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 2H,), 7.73 (d, *J* = 8 Hz, 2H,), 3.04 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 199.7, 139.6, 134.2 128.3, 125.6 123.6 32.1, 8.0; **Analysis:** $C_{10}H_9F_3O$ requires C, 59.41; H, 4.41; found: C, 59.38; H, 4.48%.

1-(4-Fluorophenyl)propan-1-one (18d)

Yield: 40%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2925, 1693,1601, 1507, 1463, 1357, 1227, 1160, 960, 855, 805; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.07-7.6 (m, 2H), 7.13-7.09 (m, 2H), 2.99-2.93, (dd, *J* = 4Hz, 2H), 1.24-1.20 (t, *J* = 4 Hz, 3H,); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 199.2, 165.6 (d, *J* = 252.8 Hz), 133.7 (d, *J* = 3Hz), 130.6 (d, *J* = 9 Hz), 115.6 (d, *J* = 21.8 Hz), 31.7, 8.2; **Analysis:** C_9H_9FO requires C, 71.04; H, 5.96; found: C, 70.98; H, 5.87 %.

1-(2,4-difluorophenyl)propan-1-one (18e)

Yield: 41%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3057, 2989, 1696, 1612, 1515, 1429, 1283, 1171, 791; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.61-7.50 (m, 1H), 6.96-6.74(m, 2H), 5.22 (d, *J* = 4 Hz, 1H), 4.53-4.41 (dq, *J* = 4 Hz, 1H), 1.53 (d, *J* = 6 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.5, 36.4, 105.7, 112.0, 122.2, 133.0, 161.9, 169.9, 201.2; **Analysis:** $C_9H_8F_2O$ requires C, 63.53; H, 4.74; found: C, 63.48; H, 4.79%.

3-(benzyloxy)-1-phenylpropan-1-one (18f)

Yield: 40%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3086, 2975, 1682, 1590, 1513, 1457, 1265, 1160, 1030, 871; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.91-3.95 (dd, *J* = 4.8, 9.7 Hz, 1H), 4.18-4.22 (dd, *J* = 8.2, 10.0 Hz, 1H), 4.57-4.64 (dd, *J* = 11.8, 17.8, Hz, 2H), 5.19-5.23 (dd, *J* = 5.9 and 7.3 Hz 1H), 7.26-7.34 (m, 5H), 7.48 (t, *J* = 8.2 Hz, 2H); 7.59 (t, *J* = 6.8 Hz, 1H), 7.99-8.01 (d, *J* = 7.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 42.4, 70.2, 73.8, 127.8, 128.4, 128.7, 128.9, 133.7, 134.5, 137.5, 192.0; **Analysis**: $C_{16}H_{16}O_2$ requires: C, 79.57; H, 6.71; found: C, 79.55; H, 6.68 %.

(2*S*,3*R*)-(+)-2-Bromo-1-phenylpropan-1-ol (19a)

Yield: 40%, pale yellow oil; **$[\alpha]_D^{25}$** +19.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3483, 3019, 2923, 1952, 1600, 1496, 1015, 757; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.30-7.39

(m, 5H), 5.03-5.01 (d, *J* = 4 Hz, 1H,), 4.49-4.37 (dq, *J* = 4.0 and 6.0 Hz, 1H,), 2.50 (bs, 1H), 1.54-1.57 (d, *J* = 6 Hz, 3H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 139.6, 128.4, 128.0, 126.4 , 56.1, 18.78; **Optical purity**: 90% ee determined from HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 254 nm); Retention time: t_{minor} = 27.200 and t_{major} = 30.607 min.; **Analysis:** $C_9H_{11}BrO$ requires C, 50.26; H, 5.15; found: C, 50.32; H, 5.18%.

(2*S*,3*R*)-2-Bromo-1-(*p*-tolyl)propan-1-ol (19b)

Yield: 41%; pale yellow oil; **$[\alpha]_D^{25}$** +51.72 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3502, 2926, 1384, 1111, 1029, 757; **^{1}H NMR** (200 MHz, $CDCl_3$)- 7.25-7.23 (d, *J* = 4 Hz, 2H,), 7.16-7.14 (d, *J* = 4 Hz, 2H,), 4.96-4.95 (d, *J* = 2 Hz, 1H,), 4.41-4.35 (m, 1H), 2.35 (s, 3H), 1.54-1.53 (d, *J* = 4Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 137.4, 136.7, 129.1, 126.3, 77.2, 56.3, 21.2, 18.8; **Optical purity**: 92% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (85:15), 0.5 mL/min, 214 nm) Retention time: t_{minor} = 13.21 and t_{major} = 15.64 min.; **Analysis:** $C_{10}H_{13}BrO$ requires C, 52.42; H, 5.72; found: C, 52.36; H, 5.68%.

(2*S*,3*R*)-2-bromo-1-[4-(trifluoromethyl)phenyl]propan-1-ol (19c)

Yield: 36%; pale yellow oil; **$[\alpha]_D^{25}$** +9.8 (*c* 0.8, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3598, 2977, 1604, 1455, 1109, 928; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.65-7.48 (dd, *J* = 8 and 18Hz, 4 H), 5.05-5.06 (d, *J* = 2 Hz, 1H,), 4.47-4.35 (dq, *J* = 4 Hz, 1H,), 2.81 (bs, 1H) 1.54-1.51 (d, *J* = 6Hz, 3H,); **^{13}C NMR** (50 MHz, $CDCl_3$) 18.6, 55.3, 76.7, 125.3-125.5 (q, *J* = 3.29 Hz), 126.7, 127.1; **Optical purity**: 90% ee determined by HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (99:1), 0.5 mL/min, 254 nm); Retention time: t_{minor} = 44.350 and t_{major} = 51.250 min; **Analysis:** $C_{10}H_{10}BrF_3O$ requires C, 42.43; H, 3.56; found: C, 42.47; H, 3.61%.

(2*S*,3*R*)-2-Bromo-1-(4-fluorophenyl)propan-1-ol (19d)

Yield: 38%; pale yellow oil; $[\alpha]_D^{25}$ +7.76 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 3582, 2989, 1242, 1043; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.38-7.30 (m, 2H), 7.09-7.00 (m, 2H), 4.99-4.97 (d, *J* = 4 Hz, 1H), 4.43-4.31 (dq, *J* = 4.0 and 6.9 Hz, 1H), 2.48 (bs, 1H), 1.51-1.54 (d, *J* = 9 Hz, 3H,): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 160, 135.3, 128.1, 128, 115.5 (d, *J* = 20.6 Hz), 76.6, 55.9, 18.7; **Optical purity**: 91% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (92:8), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 17.56 and t_{major} = 19.31 min.; **Analysis:** $C_9H_{10}BrFO$ requires C, 46.38; H, 4.32; found: C, 46.37; H, 4.29%.

2-bromo-1-(2,4-difluorophenyl)propan-1-ol (19e)

Yield: 38%; pale yellow oil; $[\alpha]_D^{25}$ +22.45 (*c* 2.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3502, 2926, 1497, 1216, 1019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.61-7.50 (m, 1H), 6.96-6.74 (m, 2H), 5.22 (d, , *J* = 4 Hz, 1H), 4.53-4.41 (dq, *J* = 4 and 7.1 Hz, 1H), 1.53 (d, *J* = 6 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.9, 54.1, 71.1, 103.6 (t, *J* = 28.88 Hz), 111.2-111.5 (dd, *J* = 2.8 and 21.1 Hz), 122.5-122.7 (dd, *J* = 3.8 and 13.4 Hz), 129.1-129.2 (dd, *J* = 5.8 and 9.8 Hz), 158.2-160.7 (dd, *J* = 12.5 and 249.2 Hz), 161.2-163.8 (dd, *J* = 11.5 and 249.2 Hz); **Optical purity**: 91% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (90:10), 0.4 mL/min, 254 nm); Retention time: t_{major} = 10.92 and t_{minor} = 12.39 min.; **Analysis:** $C_9H_9BrF_2O$ requires C, 43.05; H, 3.61; found: C, 43.04; H, 3.64%.

(1*R*, 2*S*)-3-(Benzyloxy)-2-bromo-1-phenylpropan-1-ol (19f)

Yield: 42%; pale yellow oil; $[\alpha]_D^{25}$ +52.75 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3602, 2927, 1604, 1021, 757; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.30 (d, *J* = 4.5, 1H), 3.66-3.74 (dd, *J* = 5.8 and 10.6, Hz 1H), 3.82-3.90 (dd, *J* = 5.3 and 10.7, Hz, 1H), 4.30-4.38 (q, *J* = 5.4 and 10.4 Hz 1H), 4.55 (s, 2H), 5.01 (t, *J* = 5.0 and 10.0 Hz, 1H);

7.33 (s, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.8; 71.3, 73.4, 76.1, 126.6, 127.7, 127.9, 128.0, 128.2, 128.4, 137.1, 140.2; **Optical purity**: 92% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol 60:40), 0.6 mL/min, 254 nm); Retention time: t_{major} = 13.51 and t_{minor} = 15.84 min.; **Analysis**: $C_{16}H_{17}BrO_2$ requires: C, 59.83, ; H, 5.33; found: C, 59.81; H, 5.32 %.

SECTION II:

Asymmetric Synthesis of (*S*)-Duloxetine *via* Pd-Catalyzed Oxidative Kinetic Resolution of Racemic Thiophenic Alcohol

1.2.1 Introduction and pharmacology

The thiophene ring can be recognized in various biologically active compounds with applications in medicine[16] or agrochemistry,[17] which often reveal higher activity compared to analogous phenyl-type substituents.[18] Structures containing thiophenes are also useful in the synthesis of new materials[19] and catalysts.[20] Quite stabile S-metal bonds create the possibility of using thiophene derivatives as ligands for catalysis.[20] Moreover, oligothiophenes are interesting materials in organic electronics[21] and in the preparation of fluorescent biosensors.[22]

Being a potent dual inhibitor of serotonin and noradrenalin reuptake, (*S*)-duloxetine **(20)** has therapeutic potency to treat stress urinary incontinence as well as major depressive disorder.[23] In contrast, its ancestor, fluoxetine (**21**),[24] which represents a selective serotonin reuptake inhibitor (SSRI), is prescribed only as an antidepressant (**Fig. 8**). In addition, contrary to **21** that was approved as a racemate,[25] duloxetine (**20)** was supposed to reach the therapeutic market as a single enantiomer from the outset of its development.

(S)-Duloxetine (**20**) Fluoxetine (**21**)

Fig. 8: Structures of (S)-duloxetine (**20**) and fluoxetine (**21**)

Thus, a wide range of chiral technologies has been explored to-date for scalable processes that should provide **1** of high stereochemical purity;[26] This section describes a short enantioselective synthesis of (*S*)-duloxetine (**20**) *via*- Pd-sparteine complex catalyzed oxidative kinetic resolution of benzylic alcohol strategy.

Duloxetine [(S)-N-Methyl-3-(1-naphthalenyloxy)-2-thiophenepropanamine, **20**], marketed as Cymbalta, functions as a dual serotonin and norepinephrine reuptake inhibitor in presynaptic cells (**Fig. 8**).[27] It was approved by the U.S. Food and Drug Administration in August 2004 and is prescribed for the treatment of major depressive disorders as well as stress urinary incontinence. In contrast to the preceding drug fluoxetine (**21**) (Prozac), which is an approved racemate, **20** is marketed in enantiomerically pure form,[28] and the development of its scalable and enantioselective synthesis is of broad interest. Commonly explored synthetic approaches are optical resolution,[29] dynamic kinetic resolution,[30] catalytic asymmetric reduction,[31] and catalytic asymmetric hydrogenation.[32] The catalytic Pd-sparteine complex catalysed oxidative kinetic resolution strategy has not been explored.[33] The design of an efficient and catalytic route to duloxetine therefore continues to be important. In this section, we envisioned that Pd-sparteine complex- catalyzed oxidative kinetic resolution of benzylic alcohols as a viable approach for concise enantioselective synthesis of duloxetine **20**.

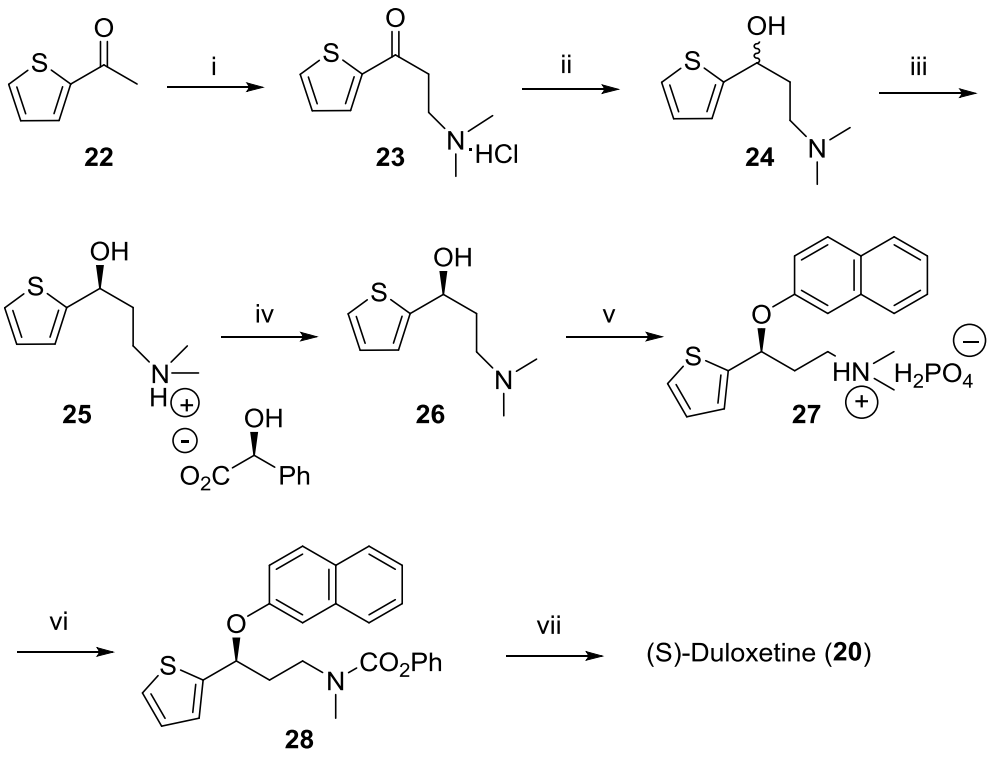
1.2.2 Review of Literature

Literature search revealed that there are few reports available on the synthesis of (*S*)-duloxetine (**20**), which are described below.

Ikunaka's approach (2006)[34]

The resolution-racemization-recycle (RRR) synthesis of **20** developed at Eli Lilly starts with the Mannich reaction of 2-acetylthiophene **22**. The *β*-aminoketone **23** freed

from Mannich product by base treatment was subjected to $NaBH_4$-mediated reduction. After acidic workup cleaving both B-O and B-N linkages, basification afforded ((S)-(*N*,*N*-dimethyl)aminoalcohol **24** as a free base, which was extracted into *t*-BuOMe (MTBE). To the MTBE solution was added (*S*)-mandelic acid (0.45 equiv) dissolved in EtOH. The resulting slurry [MTBE/EtOH (9.8:1)] was heated to reflux and then cooled to ambient temperature to form a diastereomeric salt with (*S*)-**25**. The precipitated salt **25** was collected by filtration and treated with aqueous NaOH solution to liberate **26**. Compound **26** was is treated with NaH (1.0 equiv) in the presence of $PhCO_2K$ (0.1 equiv) in DMSO, and allowed to participate in aromatic nucleophilic substitution on 1-fluoronaphthalene (1.2 equiv).

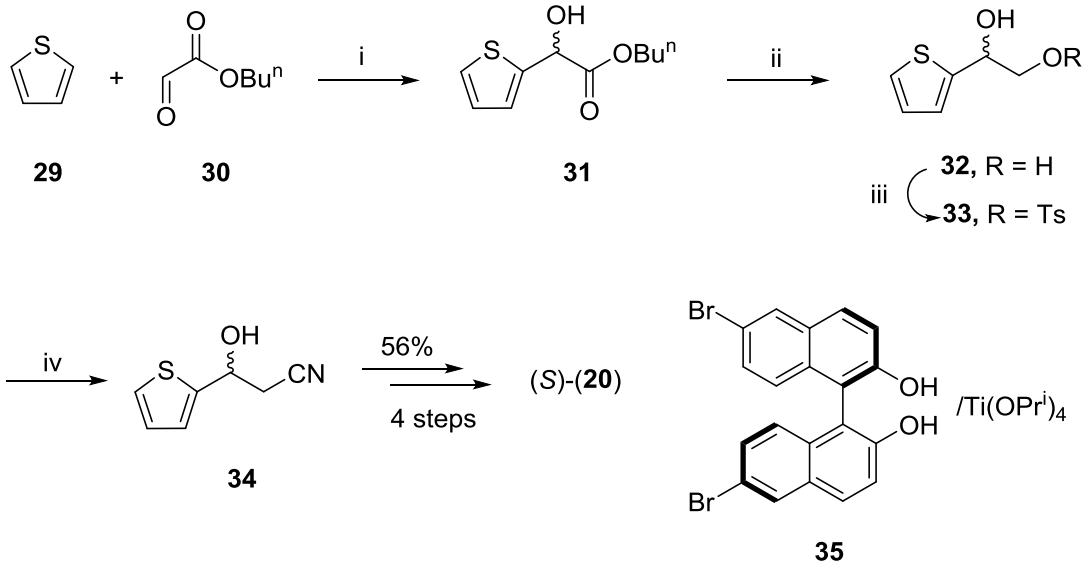


Scheme 8: (i) Me_2NH/HCl, CH_2O, HCl, *i*-PrOH; (ii) (a) EtOH, NaOH (pH 11-12); (b) $NaBH_4$, MeOH, 0 ^oC; (c) *tert*-BuOMe, HCl (pH 1-1.5); (d) NaOH (pH 12); (iii) (*S*)-Mandelic acid (0.45 equiv) *tert*-BuOMe/EtOH (9.8:1); (iv) NaOH, H_2O; (v) (a) 1-fluoronaphthalene, NaH, DMSO, $PhCO_2K$; (b) H_3PO_4, AcOEt; (vi) (a) NH_3, H_2O, toluene; (b) PhOCOCl, toluene, *i*-Pr_2NEt; (vii) (a) NaOH, H_2O, DMSO; (b) HCl, AcOEt.

The coupled product was then isolated as its phosphate salt **27** of 91% ee in 79.6% yield from **26**. On basification under the biphasic conditions (NH_3, H_2O, PhMe), the free amine liberated from **27** was taken up into PhMe. To the PhMe solution was added *i*-Pr_2EtN (0.10 equiv) followed by PhOCOCl (1.25 equiv), and the resulting homogeneous mixture was heated to 55 °C to implement *N*-demethylation. The resulting phenyl carbamate **28** was finally subjected to alkaline hydrolysis (NaOH, H_2O, DMSO) without isolation. Aqueous workup with AcOH, washing with *n*-hexane, basification to pH 10.5 with 50% aqueous NaOH solution, extraction with AcOEt followed by salt formation with HCl eventually provided duloxetine hydrochloride (**20.**HCl) as a colorless solid with an overall yield of 32% from **26** (**Scheme 8**).

Jurcjak's approach (2009)[33]

The reaction of simple thiophene with *n*-butyl glyoxylate in presence of 1 mol % of catalyst (*R*)-6, 6'- Br_2-BINOL / $Ti(OPr)_4$ (**35**) provided product **31** with moderate yield (42%) and 92% enantioselectivity.

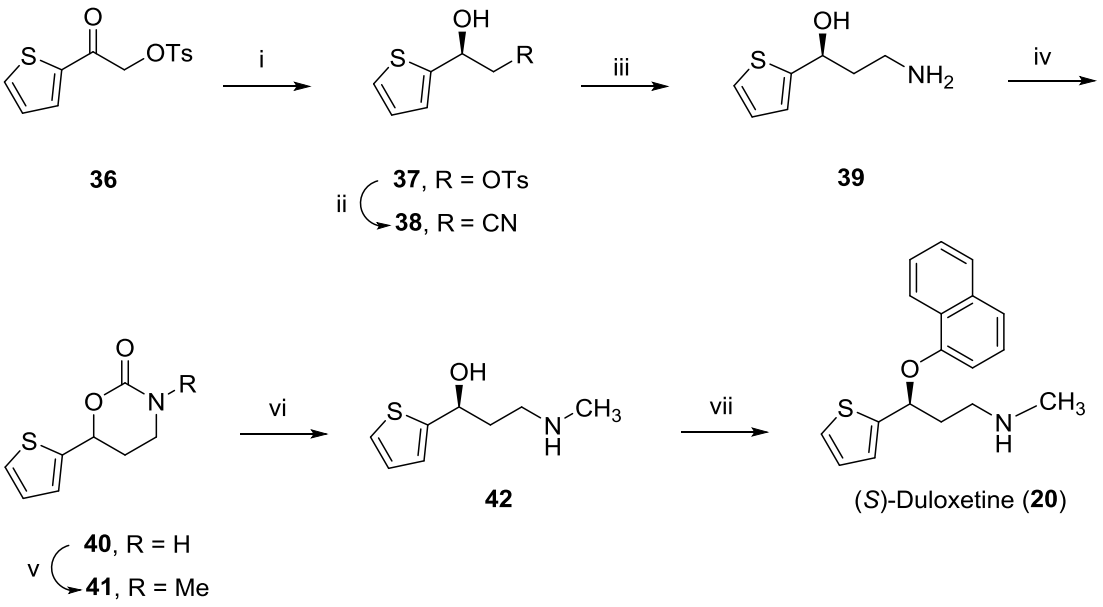


Scheme 9: (i) (*R*)-6, 6'- Br_2-BINOL / $Ti(OPr)_4$ (2:1) **35** (1 mol%) 0-20 ^oC, 24 h, 42%; (ii) $LiAlH_4$, 97%; (iii) *p*-TsCl, Et_3N, Bu_2SnO, 98%; (iv) KCN, 93%.

The product **31** was reduced to the diol **32**, and the primary hydroxy group was protected with tosyl group **33**, which was subsequently displaced with cyanide **34**. The nitrile **34** was obtained in three steps from **31** with 88% yield. The nitrile **34** was transformed in a four-step sequence to duloxetine (**20**) in 56% yield by following reported procedures (**Scheme 9**).

Lee's approach (2010)[32c]

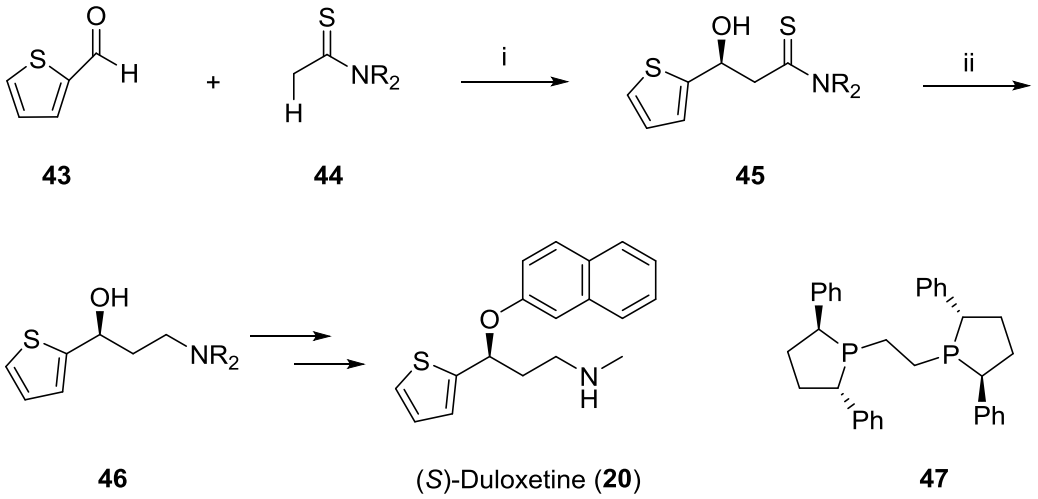
The approach involved the asymmetric-transfer hydrogenation of 2-tosyloxy-1-(2-thiophenyl)ethanone **36**. The catalytic reduction of **36** (substrate/catalyst molar ratio 500) with Cp*RhCl[(S,S)-TsDPEN], effectively was performed with an azeotropic mixture of formic acid/triethylamine (molar ratio 5/2) in ethyl acetate to produce (S)-2-tosyloxy-1-(2-thiophenyl)ethanol **37**, $[\alpha]_D^{27}$= -31.3 (*c* 1.08, $CHCl_3$), in 95% yield with 95% ee. The tosylate (*S*)-**37** was readily converted into nitrile **38** without loss of chirality on treatment with sodium cyanide in DMSO. Subsequently, the nitrile **38** was reduced with borane-dimethyl sulfide in refluxing THF to give the γ-aminoalcohol **39**, which was directly cyclized using *N*,*N*-carbonyldiimidazole (CDI) in the presence of catalytic amount of DMAP to obtain the corresponding cyclic carbamate **40** in 71% yield over two steps. Indeed, this allowed for a facile introduction of *N*-methyl group, by the treatment of methyl iodide with sodium hydride in THF to give the *N*-methyl oxazinanone **41**. Hydrolysis of the oxazinanone **41** on reflux with lithium hydroxide in aqueous methanol afforded aminoalcohol **42**. The final installation was then carried out by nucleophilic aromatic substitution with 1-fluoronaphthalene by means of sodium hydride in DMSO to afford (*S*)-duloxetine **(20)** in 78% yield with 95% *ee* (**Scheme 10**).



Scheme 10. (i) 10 mmol of catalyst (S/C = 500), Cp*RhCl[(*S*,*S*)-TsDPEN], HCO_2H/Et_3N (molar ratio 5/2, 2 mL), EtOAc, 3 h, 95%, 95% *ee*; ii) NaCN, DMSO, 20 h, 88%; iii) $BH_3 \cdot SMe_2$, THF, reflux, 2 h; iv) CDI, cat. DMAP, CH_2Cl_2, 8 h, 71% (for 2 steps); v) MeI, NaH, THF, ice-bath, 6 h, 89%; vi) LiOH, MeOH-H_2O, reflux, 8 h, 84%; vii) 1-fluoronaphthalene, NaH, DMSO, 8 h, 78%.

Shibasaki's approach (2012)[28]

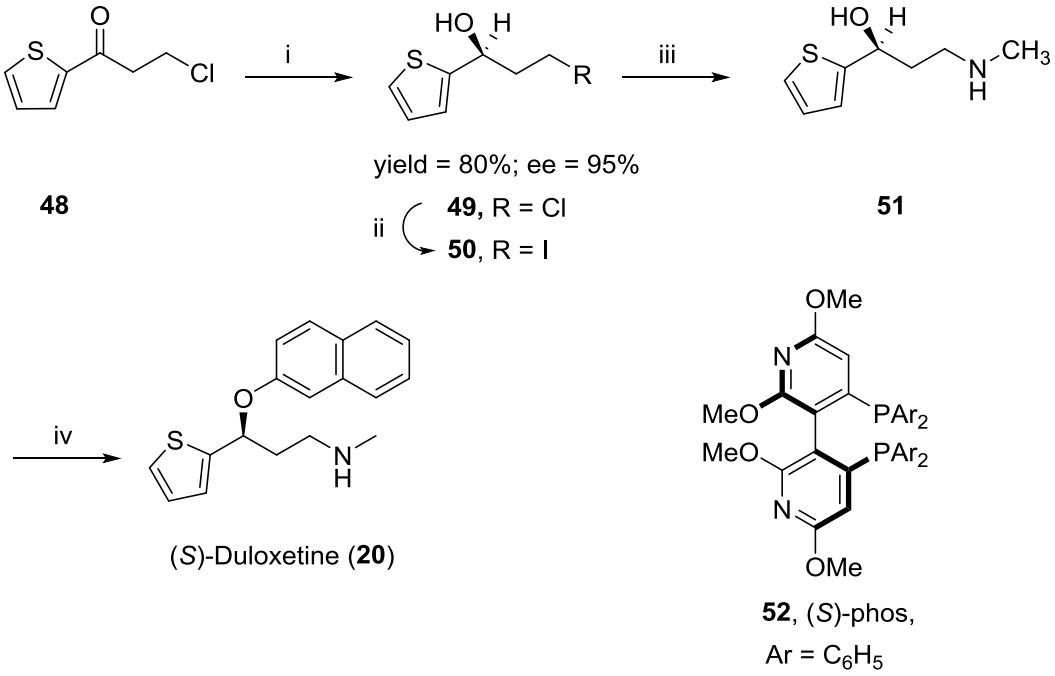
Yuta Suzuki and his co-workers have achieved the formal synthesis of (S)-duloxetine (**20)** from γ-diallyl amino alcohol **45.** The direct catalytic asymmetric aldol reaction of thioamide **44** with aldehyde **43** proceeded with very good β- stereoselectivity to give β-hydroxy thioamide **45** in 73% yield and 93% ee. Reduction of thioamide was achieved using $LiAlH_4$ in THF at -78 ^oC to give γ-diallyl amino alcohol **46** in 56% yield. Removal of allyl groups on nitrogen under Pd catalysis followed by its treatment with methyl chloroformate gave carbamate, which upon reduction with $LiAlH_4$ under reflux conditions in THF afforded N-methylated γ-aminoalcohol. The ether formation by *ipso* substitution with 1-fluoronaphthalene furnished duloxetine (**20**) in 19.66% overall yield (**Scheme 11**).



Scheme 11: (i) (*S*,*S*)-Ph-BPE (**47**) $[Cu(CH_3CN)_4]PF_6$ $Li[OC_6H_4$-P-OMe] 7.5 mol% DMF / THF = 4.4/1 -70^0 C, 48 h; (ii) $LiAlH_4$ -70 ^{0} C , THF, 56%, (2 steps); (iii) $Pd(ph_3P)_4$ 5 mol%, N,N- dimethylbarbituric acid, CH_2Cl_2, 50 ^{o}C, methyl chloroformate, K_2CO_3 , CH_2Cl_2/ H_2O, 25 ^{o}C.

Li's approach (2013)[35]

In this approach hydrosilylation of ketone **48** in the presence of chiral ligand **52** furnished the corresponding chloro-substituted chiral alcohol **49** with 95% ee, respectively. Then, reaction of enantioenriched alcohol **49** with saturated sodium iodide in acetone at reflux cleanly provided iodo alcohol **50** (>99% yield). Next, the mixture of iodo alcohol **50** and 40% aqueous methylamine in THF was stirred at room temperature to afford amine intermediate **51** (80% yield). Finally, alcohol **51** was reacted with sodium hydride in N,N-dimethylacetamide (DMA) at 70 °C for 0.5–1 h followed by its treatment with 1-fluoronaphthalene afforded the target molecule i.e. (S)-duloxetine (**20**) in 62% yield (**Scheme 12**).



Scheme 12: (i) a) 3 mol% $Cu(OAc)_2.H_2O$, 1 mol%, (*S*)-**52**, 1.2 equiv, $PhSiH_3$, toluene, -20 ^oC, 48 h, in air; b) aq. HCl, 80%; (ii) NaI, acetone, reflux, 16 h, >99% yield; (iii) $MeNH_2$, THF, 25 ^oC, 12 h 80%; (iv) DMA, NaH, 70 ^oC, 1 h, 1-fluoronaphthalene, 90 ^oC, 48 h, 62%.

1.2.3 Present Work

1.2.3.1 Objective

Different methods of synthesis have been reported for duloxetine (**20**) where in asymmetric reduction[36] and kinetic resolution[34] as the key steps are the most commonly employed. Surprisingly, the asymmetric synthesis of duloxetine **(20**) has not been reported *via* Pd-sparteine complex- catalyzed oxidative kinetic resolution of benzylic alcohols, which is commonly used for other *anti*-depressant drugs like fluoxetine (**21**). An efficient, catalytic route to duloxetine (**20**) is therefore highly desirable. Generally, the use of oxidative conditions in presence of sulphur atom in the molecule is not feasible. This synthesis proves that this oxidative kinetic resolution strategy can also be used in presence of aromatic sulphur- containing compounds. The reported synthetic methodologies for the target molecule **20**, mostly

suffer either from poor enantioselectivity, low overall yields, and/or a large number of steps involved. As a part of our research program aimed at developing enantioselective syntheses of bioactive molecules, we became interested in developing a simple and reliable route to duloxetine (**20**). This section presents the enantioslective synthesis of duloxetine (**20**) using Pd-sparteine complex catalysed oxidative kinetic resolution strategy as a key step in the synthesis.

1.2.3.2 Results and Discussion

As can be seen from the retrosynthetic analysis, the chiral β-hydroxy tosylate **57** could be visualized as an important precursor for the synthesis of target molecule **20**, wherein the synthesis of **20** could be achieved by the tosylate displacement with methyl amine followed by *ipso* substitution of 1-fluoronaphthalene on chiral β-hydroxy tosylate **57**. The β-hydroxy tosylate **57** could be achieved by means of Pd-sparteine complex-catalyzed oxidative kinetic resolution (OKR) of racemic β-hydroxy tosylate. The racemic β-hydroxy tosylate could be easily prepared in three steps from thiophene-2-carboxaldehyde (**53**) (**Fig. 9**).

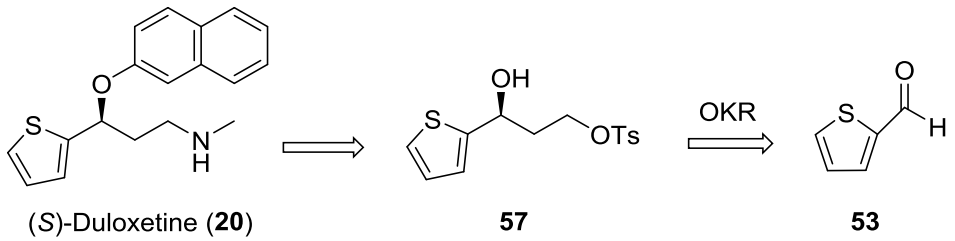
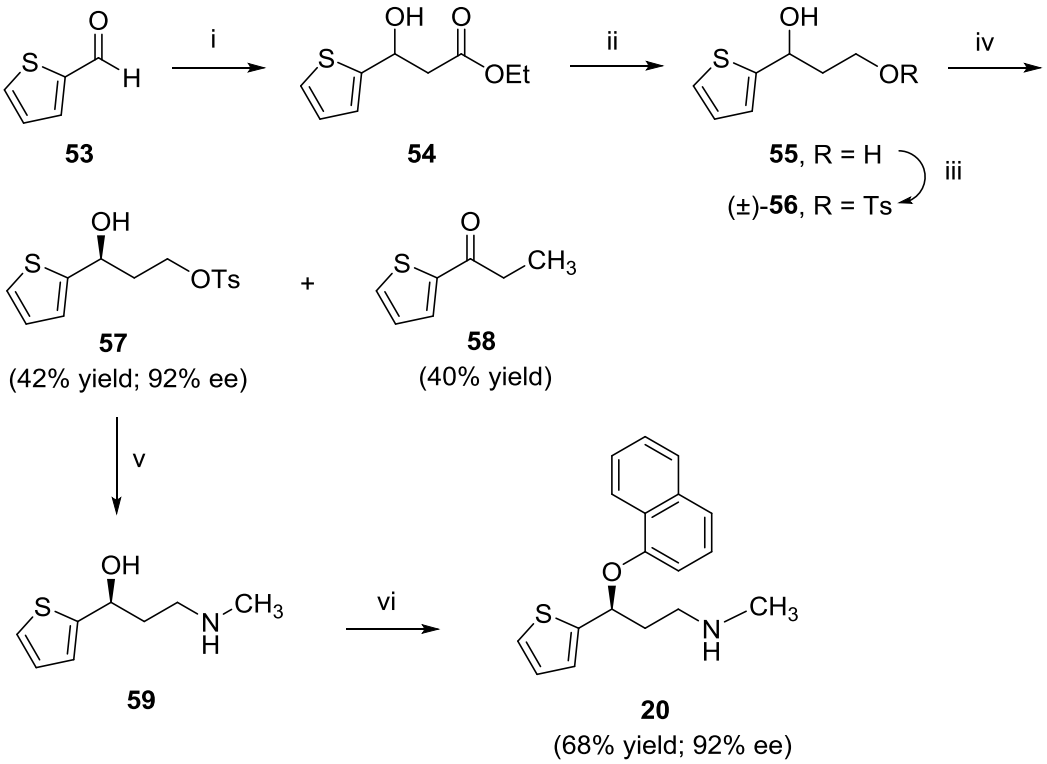


Fig. 9: Retrosynthetic analysis of (*S*)-duloxetine (**20**)

The synthesis of (S)-duloxetine (**20**) commenced from thiophene-2-carboxaldehyde (**53**), which on reaction with ethyl bromoacetate under Reformatsky condition gave β-hydroxy thiophene ester **54** in 97% yield (**Scheme 13**). It was confirmed by the ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **54** showed a characteristic

quartet at δ 4.13-4.24 due to methylenic protons attached to oxygen (-OC**H**$_2$CH$_3$) and a triplet at δ 1.27 for three methyl protons (-OCH$_2$C**H**$_3$). The characteristic carbon signals at δ 60.7 and 14.0 in its ^{13}C NMR spectrum were due to methylenic carbon attached to oxygen atom (-O**C**H$_2$CH$_3$) and methyl carbon (-OCH$_2$**C**H$_3$) respectively (**Fig. 10**).



Scheme 13: (i) BrCH$_2$CO$_2$Et (1 mmol), Zn (1.2 mmol), 10% aq. NH$_4$Cl, 0-60 ^{o}C, benzene, 4 h, 97 %; (ii) LiAlH$_4$ (1.2 mmol), dry THF, reflux, 6 h, 95%; (iii) Et$_3$N, TsCl, CH$_2$Cl$_2$, 0 ^{o}C, 2 h, 95%; (iv) Pd(OAc)$_2$ (5 mol %), (–)-sparteine (20 mol%), O$_2$ (1 atm), toluene, 3 A^o MS, 80 ^{o}C 32 h; (v) 40% aq. MeNH$_2$ (1.2 mmol), 60 ^{o}C, 8 h, 86%; (vi) 1-fluoronaphthalene, NaH, DMSO, 50 ^{o}C, 2 h, 68%.

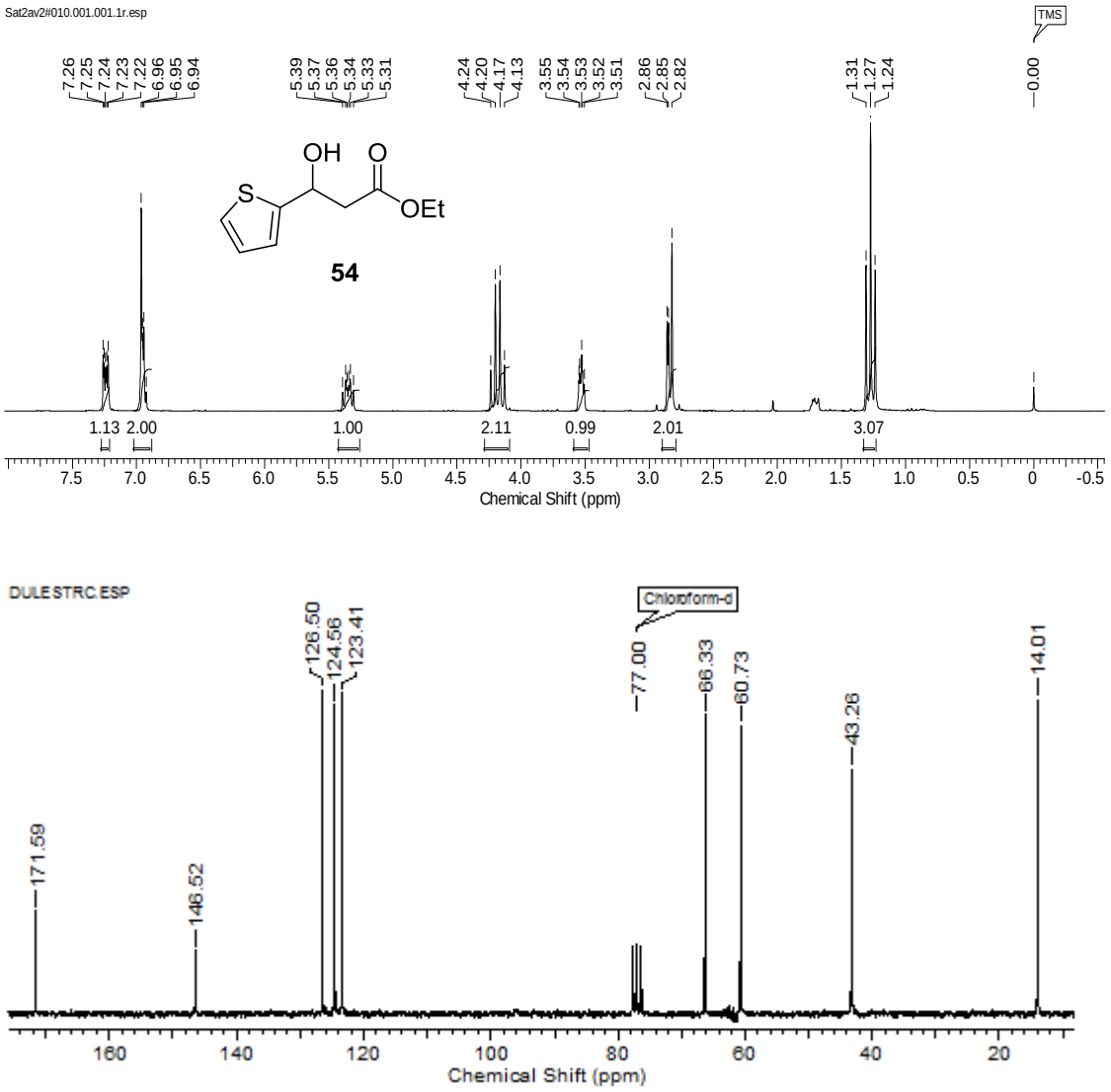


Fig. 10. ^{1}H and ^{13}C NMR spectra of 3-hydroxy-3-(thiophen-2-yl)propanoate (**54**)

The ester functionality in β-hydroxy ester **54** was then reduced using $LiAlH_4$ in THF at reflux condition to give 1,3-diol **55** in 93% yield after purification over silica gel column chromatoghraphy. The ^{1}H NMR spectrum of **55** showed a broad singlet at δ 3.81 due to methylenic (-C**H**$_2$OH) and hydroxyl (-O**H**) protons attached to oxygen confirming the formation of diol. The reduction of ester group was also substantiated by the disappearance of methylenic proton signal (-OC**H**$_2$CH$_3$) at δ 4.13-4.24 and three methyl protons (-OCH$_2$C**H**$_3$) at δ 1.27 in its ^{1}H NMR spectrum. The characteristic carbon signals at δ 68.9 and 60.2 in its ^{13}C NMR spectrum were due to

methinic (-**C**HOH) and methylenic carbons (-C**H**$_2$OH) attached to oxygen atom (**Fig. 11**).

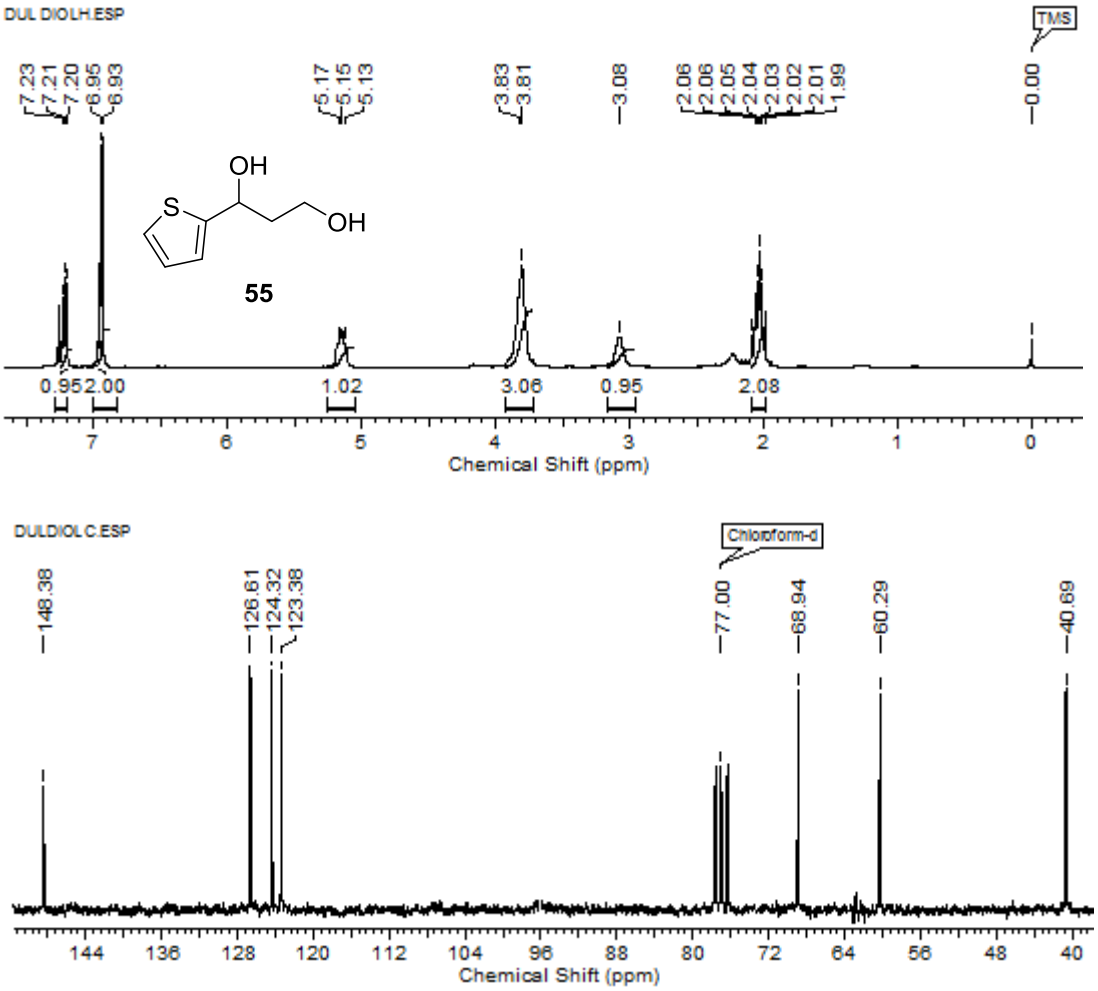


Fig. 11. ^{1}H and ^{13}C NMR of 1-(thiophen-2-yl) propane-1,3-diol **(55)**

The primary hydroxyl group of 1,3- diol **55** was protected selectively (*p*-toluene sulfonyl chloride, Et_3N in CH_2Cl_2 as a solvent at 0 ^{o}C) to deliver racemic monotosyl protected 1,3-diol **56** in 95% yield after column purification over silica gel. The ^{1}H NMR spectrum of **56** showed characteristic multiplets at δ 7.22-7.36 and δ 7.76-7.80 for the aromatic protons and the display of a typical singlet at δ 2.18 due to CH_3 group confirmed the formation of sulfonate ester **56**. The two characteristic carbon signals at δ 144.0 and 144.9 in its ^{13}C NMR spectrum were due to quaternary carbons

of tosylate group and a signal at δ 132.8 was due to the quatarnery carbons of thiophene ring. The other signals at δ 129.9 and 127.8 were due to the aromatic carbons of tosylate group. The presence of a typical signal at δ 29.7 due to the tosylate methyl carbon (**C**H_3Ar) confirmed the formation of monotosylate **56** (**Fig. 12**).

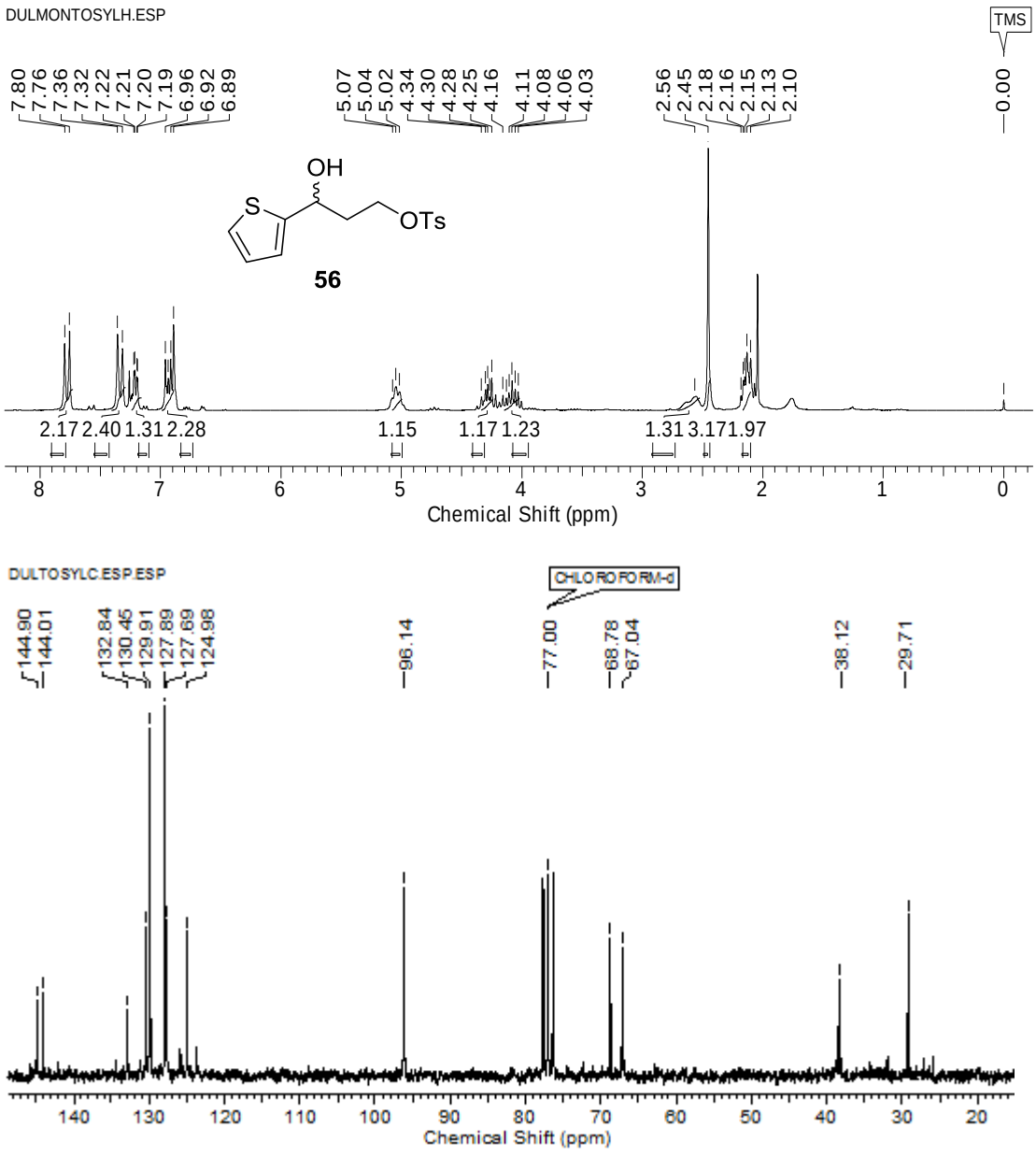


Fig. 12. ^{1}H NMR and ^{13}C NMR spectra of 3-hydroxy-3-(thiophen-2-yl)propyl-4-methylbenzenesulfonate (**56**)

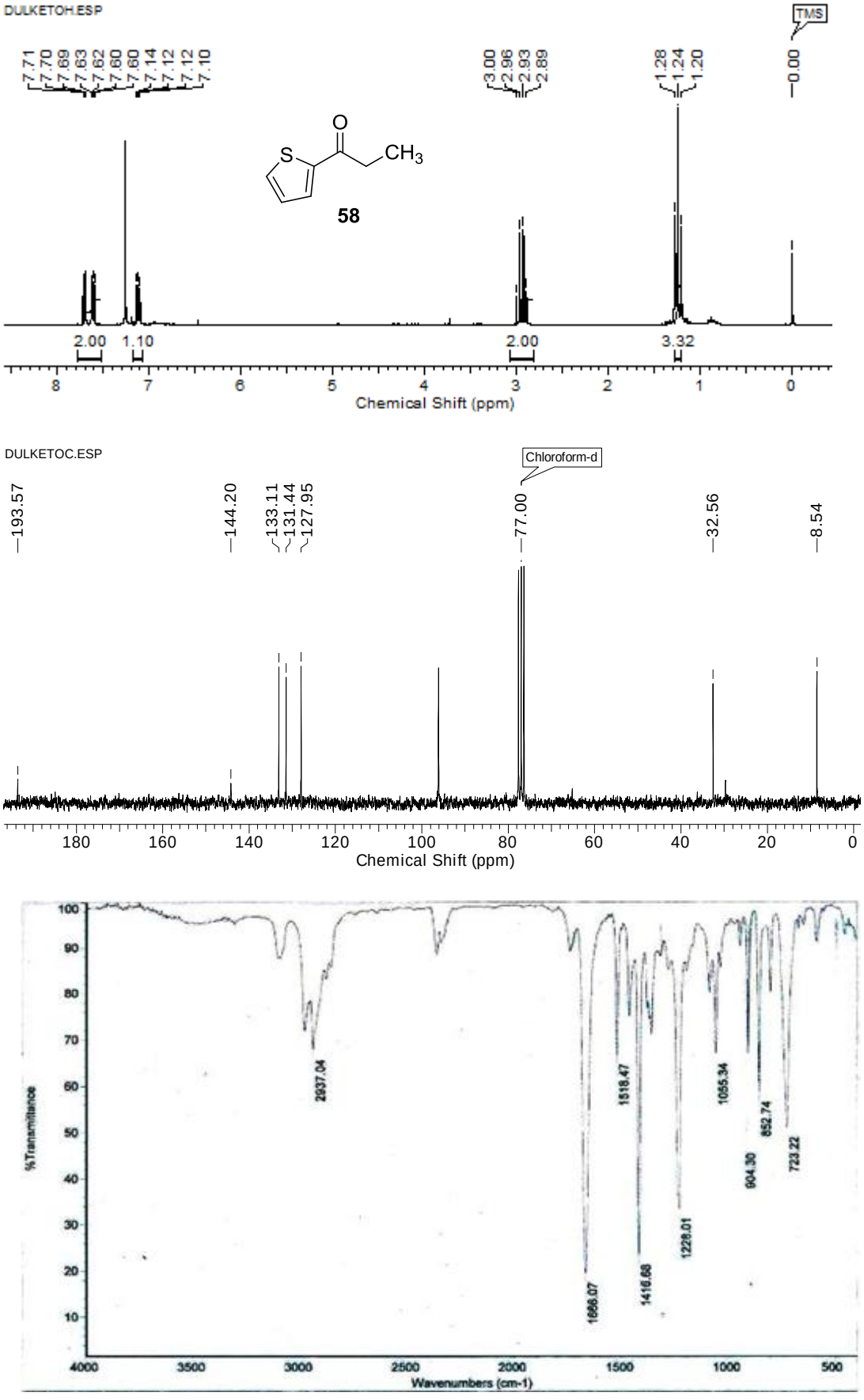


Fig. 13. ^{1}H and ^{13}C NMR of 1-(thiophen-2-yl)propan-1-one (**58**)

The racemic thiophene alcohol (±)-**56** was then subjected to Pd-sparteine-catalyzed oxidative kinetic resolution under O_2 (1 atm) in dry toluene under reflux, which produced the enantiomerically pure alcohol **57** in 42% yield and 92% ee; interestingly, along with reductive detosylated ketone **58** in 40% yield. The reductive process of formation of **58** is not clearly understood and the mechanistic study is under progress. The formation of ketone **58** was confirmed by the ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **58** showed a characteristic quartet at δ 2.95 due to methylenic protons (-C**H**$_2$CH$_3$) and a triplet at δ 1.24 for three methyl protons (-CH$_2$C**H**$_3$) confirming the oxidation of secondary alcohol (-C**H**OH) and the reductive detosylation of primary alcohol (C**H**$_2$OH). The disappearance of methine carbon signal and the appearance of methine and methyl carbon signals δ 32.5 and 8.5 in its ^{13}C NMR spectrum and the display of a typical absorption at 1666 cm^{-1} for the carbonyl carbon in its IR spectrum confirmed the formation of **58** (**Fig. 13**).

The ketone **58** and the chiral alcohol **57** were readily separated over silica gel column chromatography.

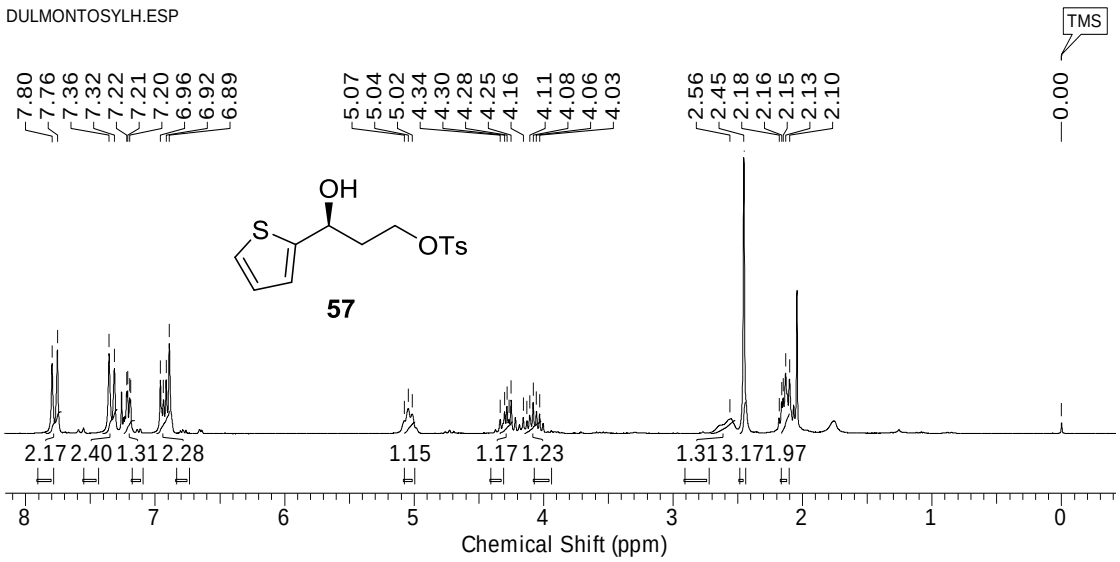


Fig. 14. ^{1}H NMR spectra of (*S*)-3-hydroxy-3-(thiophen-2-yl)propyl-4-methylbenzenesulfonate (**57**)

The formation of alcohol **57** was confirmed by ^{1}H and ^{13} C NMR spectroscopy. The ^{1}H NMR spectrum of **57** showed characteristic multiplets at δ 5.02-5.07 for the methine protons (-C**H**OH) and a broad singlet at δ 2.56 also confirmed the formation of chiral alcohol **57.** Its specific rotation was found to be $[\alpha]_D^{25}$ -29.2 (*c* 1.0, $CHCl_3$) (**Fig. 14**).

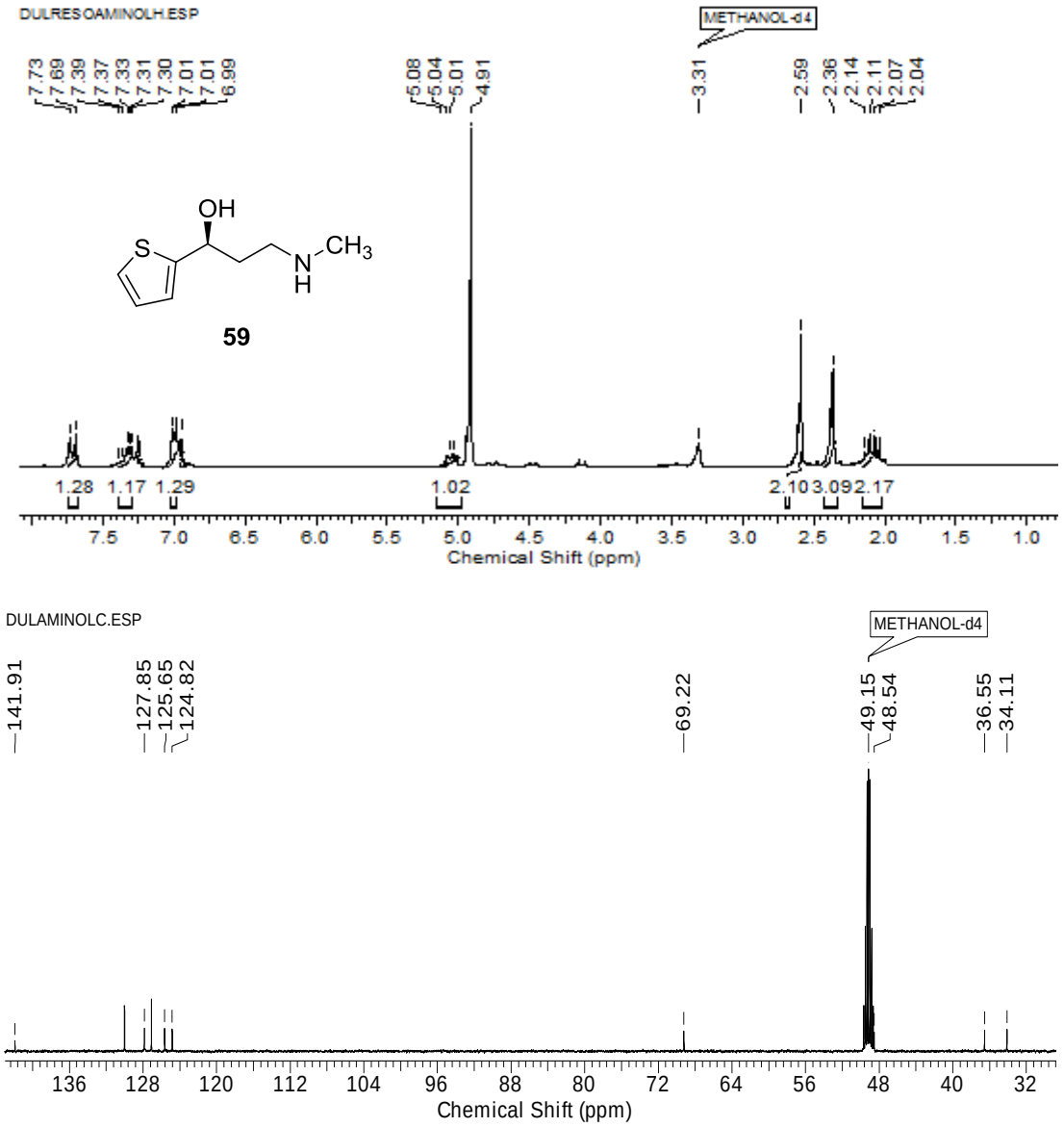
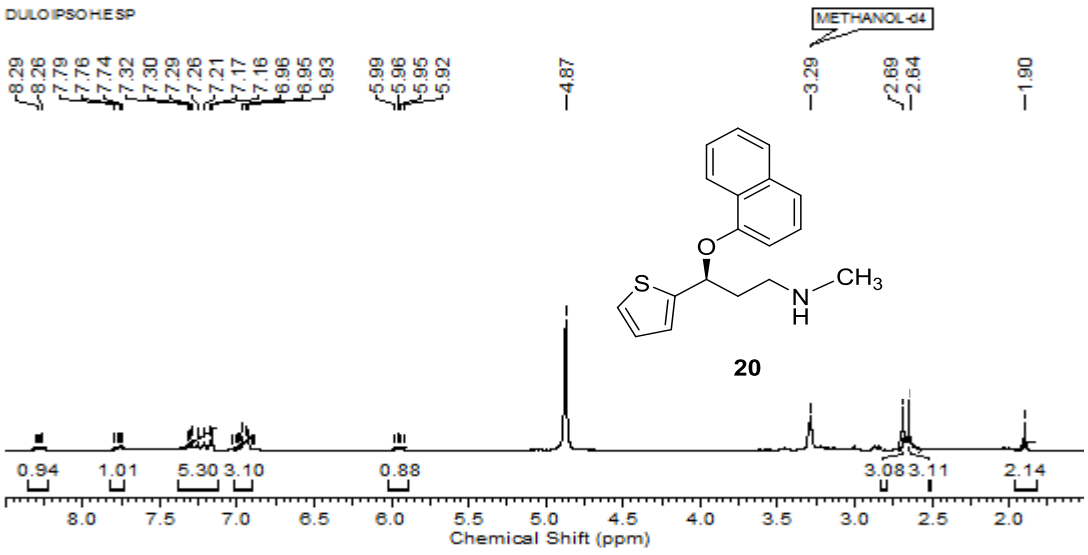


Fig. 15. ^{1}H and ^{13}C NMR spectra of (S)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol (**59**)

The S_N2 displacement of tosyl group in **57** with 40% aq. $MeNH_2$ gave the corresponding 1,3-aminoalcohol **59 {**$[\alpha]^{25}_D$ -9.4 (*c* 1, $CHCl_3$); lit.[28] $[\alpha]_D^{24}$ −9.1 (*c* 0.55, $CHCl_3$, 92% ee)} in 86% yield.

The ^1H NMR spectrum of **59** showed a characteristic singlet at δ 2.36 due to methy protons and the disappearance of aromatic proton signals at δ 7.32-7.80 for the toluene ring further confirmed the displacement of tosylate group. A typical carbon signal at δ 36.5 in its ^{13}C NMR spectrum was due to methyl carbon attached to nitrogen atom (-HN**C**H_3) confirming the formation of aminoalcohol **59** (**Fig. 15**).

Finally, the *ipso* substitution of *N*-methyl-γ-amino alcohol **59** with 1-fluoronaphthalene (NaH, DMSO) afforded (*S*)-duloxetine **20 {**$[\alpha]_D^{25}$ +108.4 (*c* 1.0, MeOH); lit.[37] $[\alpha]_D^{30}$ +114 (*c* 1, MeOH)} in 22 % overall yield and 92% ee (**Scheme 13**).



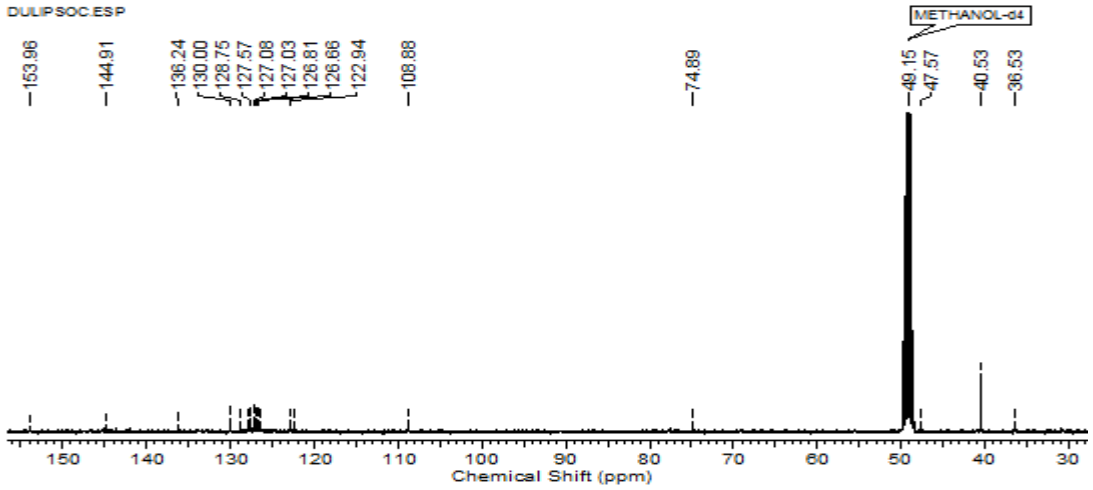


Fig. 16. ^{1}H, ^{13}C NMR spectra of (*S*)-duloxetine (**20**)

The formation of (*S*)-duloxetine **20** was confirmed by the appearance of three typical signals in the aromatic region at δ 8.26-8.29 (m, 1H), 7.76 (dd, *J* = 3.5, 6.1 Hz, 1H) and 7.17-7.32 (m, 5H) due to naphthalenic protons in its ^{1}HNMR spectrum. Its ^{13}C NMR spectrum showed typical signals at δ 153.9 (-O**C**=C-) and δ 136.2 for the naphthalenic quaternary carbons which confirmed the formation of **20 (Fig. 16)**.

1.2.4 Conclusion

In conclusion, a short and efficient synthesis of (S)-duloxetine (**20**) has been achieved in 31% overall yield and 92% ee. The Pd-sparteine-complex- catalyzed oxidative kinetic resolution of benzylic alcohol has been used as key step to introduce chirality in the molecule.

1.2.5 Experimental Section

3-Hydroxy-3-(thiophen-2-yl)propanoate (54)

A 100 mL two necked flask equipped with water condenser and septum was charged with activated zinc (3.67 g, 0.056 mol) and kept under N_2 atmosphere. Dry benzene (25 ml) was introduced in the flask and the reaction flask was heated up to 80 ^{o}C (oil bath temp.) A solution of ethyl bromoacetate (8.63 g, 51 mmol) and thiophene- 2-

carboxaldehyde **53** (5 g, 47 mmol) in dry benzene were added dropwise to the reaction mixture. After completion of addition, the reaction mixture was refluxed for 5 h cooled to25 ^{o}C and then quenched by adding ice cold 4 N H_2SO_4 (5 mL) extracted with diethyl ether. After evaporation of solvent under reduced pressure, the crude hydroxy ester was purified over column chromatography packed with silica gel, eluting with Pet ether : ethyl acetate (9:1) to give pure ethyl 3-hydroxy-3-(thiophen-2-yl)propanoate **54** (10.39 g; 97%).

Yield: 97%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3453, 2982, 1727, 1373, 1032, 703; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.07 Hz, 3H), 2.82-2.86 (m, 2H), 3.51-3.55 (s, 1H), 4.13-4.24 (q, *J* = 7.20 Hz, 2H), 5.31-5.39 (s, 1H), 6.92-6.96 (m, 2H), 7.22-7.26 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.01, 43.26, 60.73, 66.33,, 77.00, 123.41, 124.56, 126.50, 146.52, 171.59; **Analysis**: $C_9H_{12}O_2S$ requires: C, 53.98; H, 6.04; found: C, 53.90; H, 6.09%.

1-(Thiophen-2-yl) propane-1,3-diol (55)

β-Hydroxy ester **54** (2 g, 10 mmol) dissolved in THF was added slowly into the stirred solution of $LiAlH_4$ (0.74 g, 20 mmol) in THF at 0 ^{o}C. After completion addition, the reaction mixture was refluxed till all the starting material gets consumed monitored by using TLC. The reaction mixture was then cooled to 0 ^{o}C and quenched with saturated aq. solution of NaOH, filtered and the organic layer was concentrated under reduced pressure. The obtained crude β-hydroxy ester was purified using column chromatography packed with silica gel, eluting with Pet ether: ethyl acetate (6:4) to give pure 1-(thiophen-2-yl) propane-1,3-diol **55** (1.58 g; 95%).

Yield: 95%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3381, 2923, 1048, 701; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.99-2.06 (m, 2H), 3.08 (bs, 1H), 3.81-3.83 (m, 3H), 5.13-5.17 (t, *J* = 4.5 Hz, 1H), 6.03 (d, *J* = 3.8 Hz, 2H), 7.20-7.23 (dd, *J* = 6.1, 9.1 Hz,

1H), **^{13}C NMR** (50 MHz, $CDCl^3$): δ 40.6, 60.2, 68.9, 77.0, 123.9, 124.38, 124.3, 126.6, 148.3. **Analysis**: $C_7H_{10}O_2S$ requires: C, 53.14; H, 6.37; found: C, 53.11; H, 6.36%.

3-Hydroxy-3-(thiophen-2-yl)propyl-4-methylbenzenesulfonate (56)

Triethylamine (1.77 mL, 12.658 mmol) was added dropwise in the solution of 1-(thiophen-2-yl)propane-1,3-diol **55** (1 g, 6.329 mmol) in CH_2Cl_2 at 0 ^oC followed by the slow addition of *p*-TsCl (1.326 g, 6.96 mmol) in fractions. When the starting material got consumed completely the reaction mixture was concentrated under reduced pressure. The crude β-hydroxy tosylate **56** purified using column chromatography packed with silica gel eluting with Pet ether : ethyl acetate (8:2) to give of 3-hydroxy-3-(thiophen-2-yl)propyl-4-methylbenzenesulfonate **56** (1.87 g; 95%).

Yield: 95%; colorless solid (decomposed in dry condition); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3420, 2939, 1736, 1598, 1175, 957; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.10-2.16 (d, 2H), 2.45 (t, *J* = 4.7 Hz, 3H), 2.56 (s, 1H), 4.16-4.11 (m, 1H), 4.25-4.34 (s, 1H), 5.02-5.07 (s, 1H), 6.89-6.92 (d, *J* = 4.1 Hz, 2H), 7.22 (s, 1H), 7.34 (d, *J* = 3.7 Hz, 2H), 7.78 (d, *J* = 3.9 Hz, 2H); **Analysis**: $C_{14}H_{16}O_4S_2$ requires: C, 53.82; H, 5.16 found: C, 53.76; H, 5.11 %.

Kinetic resolution of racemic *β*-hydroxy tosylate (56)

$Pd(OAc)_2$ (175.7 mg, 0.783 mmol) was taken in to a dry two neck round bottom flask then dry tolune was added in to the flask followed by the addition of Molecular sieves 3 A^o. After addition of (-)-Sparteine ligand (734.0 mg, 3.312 mmol) the reaction mixture was evacuvated completely and charged with O_2 gas and heated up to 80 ^oC for 30 min. then the racemic 3-hydroxy-3-(thiophen-2-yl)propyl 4-methylbenzenesulfonate **56** (4.9 g, 15.66 mmol) dissolved in dry Tolune was added

dropwise and refluxed at 110 ^{o}C for 32 h. Then the reaction mixure was cooled to rt and 15 ml of 2% TFA / methanol was added to quench the reaction, the solvent was removed under reduced pressure and the residue was taken in minimal amount of CH_2Cl_2 The crude residue was then purified by column chroamatography eluting with pet ether/Ethyl acetate (95:5) to get ketone **58** in 40% (1.97 g) and pet. ether/ethyl acetate (80:20) to get 3-Hydroxy-3-(thiophen-2-yl)propyl-4-methylbenzenesulfonate **57** in 42% (2.05 g, 92% ee).

1-(thiophen-2-yl)propan-1-one 58

Yield: 40%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2937, 1666, 1518, 1416, 1228, 904; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.3 Hz, 3H), 3.00-2.89 (q, *J* = 7.3 Hz, 2H), 7.14-7.10 (s, 1H), 7.60-7.63 (dd, *J* = 1.0 and 4.9 Hz, 1H), 7.69-7.72 (dd, J = 1.1 and 3.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 8.54, 32.56, 77.0, 127.95, 131.44, 133.11, 144.20, 193.57; **Analysis**: $C_{14}H_{16}O_4S_2$ requires: C, 53.83; H, 5.16 found: C, 53.90; H, 5.09 %.

(*S*)-3-Hydroxy-3-(thiophen-2-yl)propyl 4-methylbenzenesulfonate (57)

Yield: 92%; colorless solid (decomposed in dry condition); $[\alpha]_D^{25}$ -29.2 (*c* 1.0, $CHCl_3$) lit.[18] $[\alpha]_D^{27}$-31.3 (*c* 1.08, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3422, 2940, 1737, 1598, 1175, 957; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.08-2.17 (dd, *J* = 6.44 and 12.51 Hz, 2H), 2.46 (s, 3H), 2.39 (s, 1H), 4.04-4.12 (m, 1H), 4.22-4.34 (m, 1H), 5.01-5.10 (dt, *J* = 4.3 and 6.6 Hz, 1H), 6.89-6.92 (m, 2H), 7.20-7.23 (dd, *J* = 1.5 and 4.6 Hz, 1H), 7.32-7.36 (d, *J* = 8.1 Hz, 2H), 7.76-7.80 (d, *J* = 8.3 Hz, 2H); **Analysis**: $C_{14}H_{16}O_4S_2$ requires: C, 53.82; H, 5.16 found: C, 53.76; H, 5.10 %.

(S)-3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol (59)

$MeNH_2$ (aq. 40%) was added to the stirred solution of 3-hydroxy-3-(thiophen-2-yl)propyl 4-methylbenzenesulfonate (**57**) (1 g, 3.205 mmol) in CCl_4 and the mixture

refluxed for 3 h. The reaction mixture was then concentrated and purified over silica gel column chromatography to afford γ-amino alcohol **59** (0.471 g; 86%).

Yield: 86%; colorless liquid; $[\alpha]_D^{25}$ -9.5 (*c* 0.8, MeOH); lit.[13] $[\alpha]_D^{22}$ = +9.74 (*c* 3.8, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3298, 2851, 2360, 1074, 701 cm^{-1}; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 2.04-2.17 (q, *J* = 6.8 Hz, 2H), 2.65 (s, 3H), 2.94-3.07 (m, 2H), 5.01-5.08 (t, *J* = 6.0 Hz, 1H), 6.99-7.01 (m, 1H), 7.30-7.39 (m, 1H), 7.69-7.73 (dd, *J* = 1.3 and 4.8 Hz, 1H); **^{13}C NMR** (50 MHz, MeOH-d_4): δ 34.11, 36.55, 48.54, 49.15, 69.22, 124.82, 125.65, 127.85, 141.92; **Analysis**: $C_8H_{13}NOS$ requires: C, 56.11; H, 7.65; N, 8.18 found: C, 56.04; H, 7.63; N, 8.11 %.

(S)-Duloxetine (20)

Both sodium hydride (36 mg, 1.5 mmol) and 1-fluoronaphthalene (190 mg, 1.3mmol) were added to a stirred solution of alcohol **59** (171 mg, 1 mmol) in DMSO (5 ml). After stirring for 8 h, the reaction mixture was partitioned with ethyl acetate and water. After an extractive workup, the combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography eluting with ethyl acetate/methanol (85:15) to yield (S)-duloxetine **20** in 22 % overall yield and 92% ee.

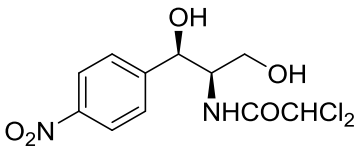
Yield: 68%; coloreless viscous liquid; $[\alpha]_D^{25}$ = +108.4 (*c* 1.0, MeOH); lit.[22] $[\alpha]_D^{30}$ = +114 (*c* 1, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3050, 2925, 2851, 1396, 1094; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 1.90 (s, 2H), 2.64 (s, 3H), 2.69 (s, 3H), 5.92-5.99 (dd, *J* = 4.93 and 7.71 Hz, 1H) 6.93-6.96 (m, 3H), 7.16-7.32 (m, 5H), 7.74-7.79 (m, 1H), 8.26-8.29 (m, 1H); **^{13}C NMR** (50 MHz, MeOH-d_4): δ 36.5, 40.5, 47.5, 74.8, 108.8, 122.9, 126.6, 126.8, 127.0, 127.5, 128.7, 130.0, 136.2, 144.9, 153.9; **Analysis**: $C_{18}H_{19}NOS$ requires: C, 72.69; H, 6.44; N, 4.71 found: C, 72.60; H, 6.48; N, 4.77 %.

Section III:

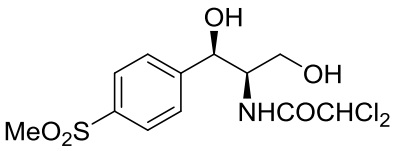
Enantioselective Synthesis of (–)-Chloramphenicol *via* Pd-Catalyzed Oxidative Kinetic Resolution of Racemic *anti*-α-Bromobenzylic Alcohol

1.3.1 Introduction and pharmacology

Optically active amino alcohols with vicinal stereocenters are important as drugs and natural products such as amino sugars,[38] peptides and peptide analogs,[39] enzyme inhibitors, such as glycosphingolipids, antibiotics and alkaloids. (-)-Chloramphenicol (**60**) and (+)-thiamphenicol (**61**) (**Fig. 17**) are broad-spectrum antibiotics with a range of biological activities.[40] The antibiotic chloramphenicol is active only in its D-*threo* configuration and is effective in the treatment of typhus, dysentery and ocular bacterial infections.[41] (+)-Thiamphenicol (**61**), a synthetic analogue of chloramphenicol (**60**), is bacteriostatic for both gram-positive and gram-negative aerobes and for some anaerobes.[42] Owing to their potential biological activity, a number of syntheses have been described.[43-71]



60



61

Fig. 17: Structures of (-)-chloramphenicol (**60**) and (+)-thiamphenicol (**61**)

Chloramphenicol (**60**) is a lipid-soluble compound consisting of an aromatic nitro moiety and an aliphatic side chain {(1*R*,2*R*)-2-(dichloroacetamido)-1-[(4-nitro)phenyl]-1,3-propanediol}. Considerable modification can be performed at the *para* position without a marked loss in its antimicrobial activity. For example, the

nitro group can be substituted by a methyl sulfonyl (which is thiamphenicol (**61**)). In the parent compound, substitution at the 3-hydroxy position causes total loss of biological activity and the L(+) isomer lacks antibacterial activity. The simple structure and inherent stability of the intramolecular bonds in chloramphenicol yield a compound that is remarkably resistant to acid or alkaline degradation, autoclaving, oxidation by light, and decomposition by extremes of temperature. Chloramphenicol works by binding to the 50S subunit of the bacterial ribosome. It then prevents attachment of amino acyl tRNA to the ribosome. At this time, it is not known if it prevents attachment of the tRNA to the A-site or the P-site. It prevents peptide formation and elongation, and is therefore bacteriostatic. An important aspect of chloramphenicol's distribution is that it is able to penetrate the CSF, lymph, and ganglions, making it a treatment option for paratyphoid, typhoid fever, and meningitis. Thiamphenicol (**61**) possesses high *in vivo* activity for having a good property of unbinding with glucuronic acid in liver and has been used clinically.

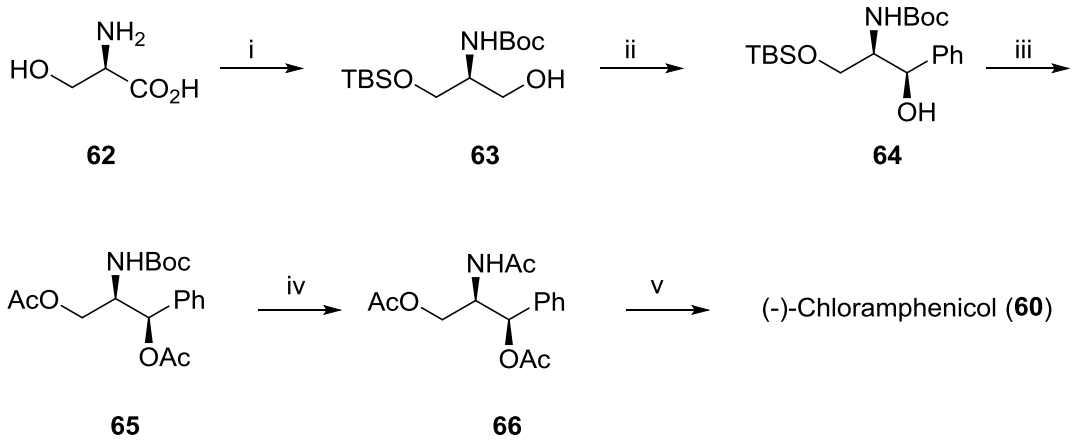
1.3.2 Review of literature

Literature search revealed that there are several reports available for the synthesis of (-)-chloramphenicol (**60**) involving chiral pool, chemo-enzymatic approach or enantioselective syntheses, which are described below.

Datta's approach (1998)[54]

Datta *et al.* have achieved the synthesis of (-)-chloramphenicol (**60**) using a chiral pool approach starting with D-serine **62**, which was converted into the amino diol derivative **63** in four steps. Swern oxidation of the alcohol **63** followed by Grignard addition with phenyl magnesium bromide afforded the *syn*-amino alcohol **64** with diastereoselectivity >19:1. A stepwise deprotection, acylation sequence of **64** gave the desired product **65**, which on nitration with conc. HNO_3- conc. H_2SO_4 (1:1) followed

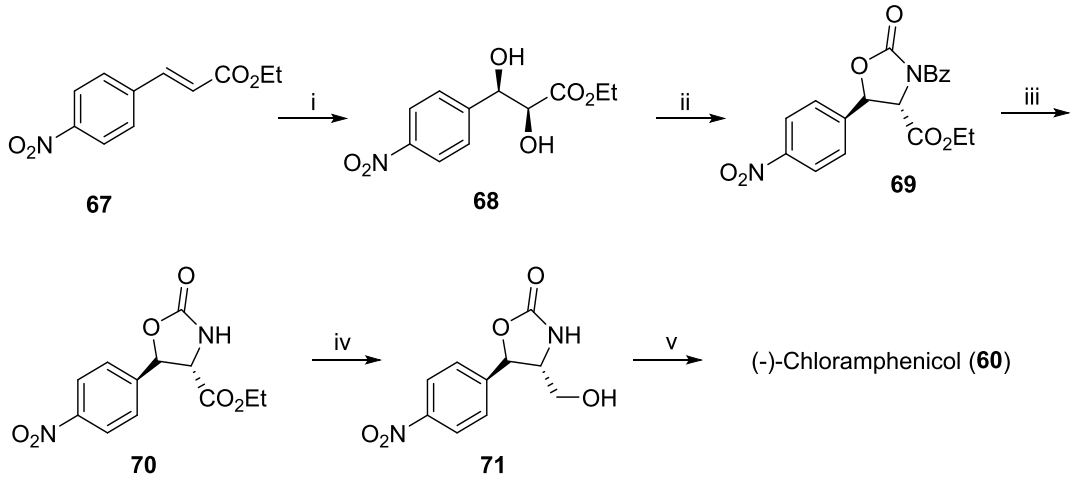
by treatment with methyl dichloroacetate gave (-)-chloramphenicol (**60**) in 73% yield (**Scheme 14**).



Scheme 14: (i) (a) MeOH, HCl; (b) $(Boc)_2O$, Et_3N, THF; (c) TBSCl, imidazole, CH_2Cl_2; (d) $LiBH_4$, THF, 80%; (ii) $(COCl)_2$, DMSO, $^iPr_2NEt$, CH_2Cl_2, -78 °C then PhMgBr, THF, 25 °C, 69%; (iii) (a) Bu_4NF, THF, 0°C to 25°C; (b) Ac_2O, DMAP, pyridine, 92%; (iv) (a) CF_3CO_2H, 0 °C; (b) Ac_2O, DMAP, pyridine, 85%; (v) (a) Conc. HNO_3-conc. H_2SO_4 (1:1), -20 °C to 25 °C; (b) aq. 5% HCl, 90 °C, 66%; (c) Cl_2CHCO_2Me, 90 °C, 73%.

Koh's approach (2000)[55]

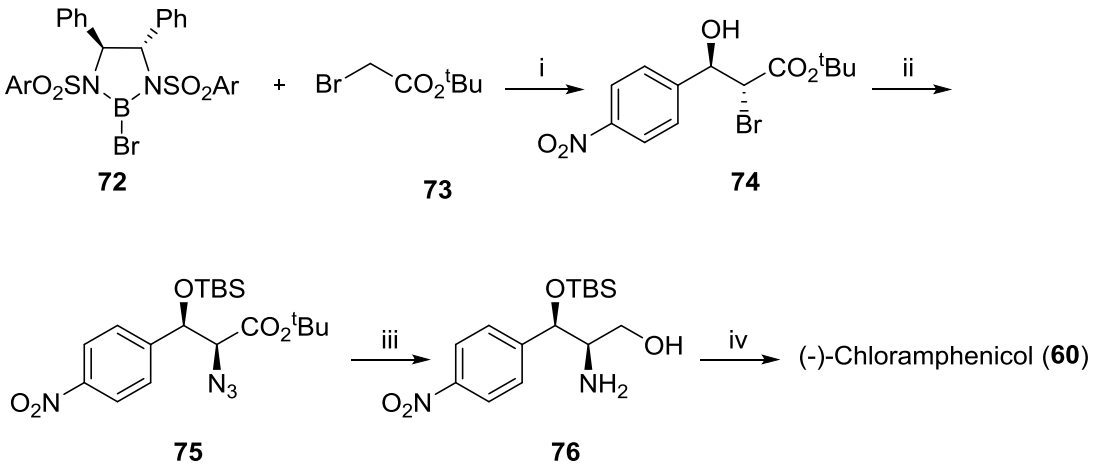
Koh *et al.* have synthesized (-)-chloramphenicol (**60**) by employing Sharpless asymmetric dihydroxylation as the key reaction. Thus the ester **67** was subjected to asymmetric dihydroxylation to give the diol **68** in 98% yield which was successively treated with Bu_2SnO, BzNCS and Bu_4NBr to give the protected *syn* amino alcohol **69**. Debenzoylation of **69** with $Ti(O^iPr)_4$ and ethanol afforded **70,** which was then treated with $NaBH_4$ to give the alcohol **71** in 92%yield. Hydrolysis of **71** with 1 N NaOH followed by amidation with methyl dichloroacetate gave (-)-chloramphenicol (**60**) in 74% yield and 99% ee (**Scheme 15**).



Scheme 15: (i) AD-mix-β, *t*-BuOH:H_2O (1:1), 25 °C, 98%, >99% ee; (ii) (a) Bu_2SnO; (b) BzNCS; (c) Bu_4NBr; (iii) $Ti(O^iPr)_4$, ethanol, 81%; (iv) $NaBH_4$, 92%; (v) (a) 1N NaOH, 92%; (b) Cl_2CHCO_2Me, 74%.

Corey's approach (2000)[56]

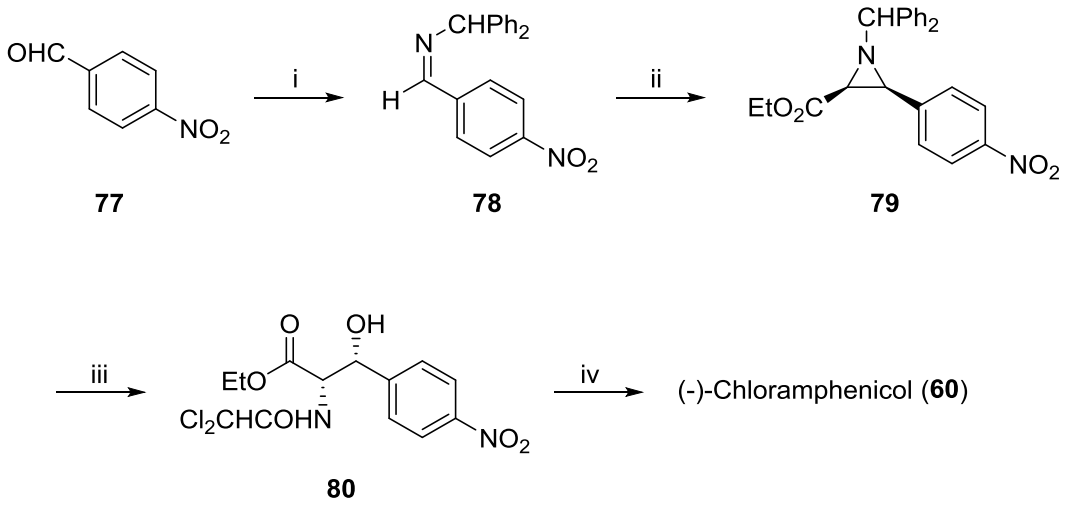
(-)-Chloramphenicol (**60**) was also synthesized by Corey *et al. via* aldol reaction of *p*-nitrobenzaldehyde and *t*-butyl bromoacetate in the presence of (*S*,*S*)-bromoborane **72** to give the bromohydrin **74** in 99% yield and 93% ee.



Scheme 16: (i) (a) toluene, -78 °C, Et_3N; (b) *p*-nitrobenzaldehyde, -78 °C, 99%, d.r. = 96:4, 93% ee; (ii) (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 96%; (b) NaN_3, DMF, 40 °C, 73%; (iii) (a) $LiBH_4$, Et_2O, 0 °C, 80%; (b) PPh_3, THF-H_2O, 80%; (iv) (a) Cl_2CHCO_2Me, CH_2Cl_2, 0 °C; (b) Bu_4NF, THF.

Wulff's approach (2001)[57]

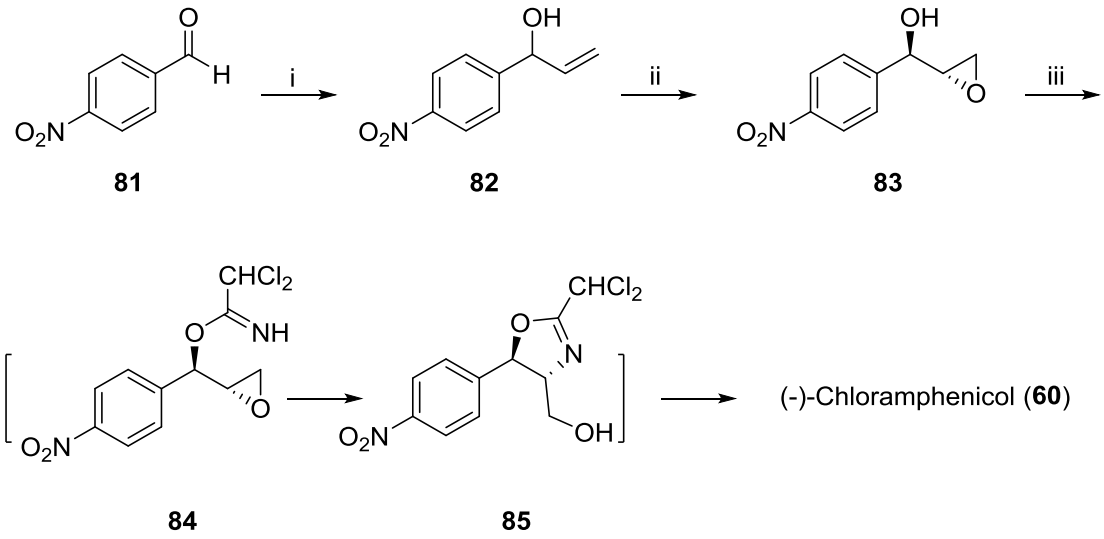
Wulff *et al.* have synthesized (-)-chloramphenicol (**60**) *via* catalytic aziridination of *p*-nitrobenzaldimine **78** in presence of 10 mol% of a catalyst prepared from triphenylborate and (*S*)-VAPOL to give the aziridine **79** in 80% yield and 96% ee. Treatment of aziridine **79** with 10 equivalents of dichloroacetic acid gave the hydroxyl acetamide **80**, which on subsequent reduction with $NaBH_4$ in MeOH afforded (-)-chloramphenicol (**60**) in 74% yield and 96% ee (**Scheme 17**).



Scheme 17: (i) Ph_2CHNH_2, $MgSO_4$, CH_2Cl_2, 25 °C, 10 h, 80%; (ii) N_2CHCO_2Et, triphenylborate and (*S*)-VAPOL (10 mol%), toluene, 0 °C, 20 h, 80%, *cis* : *trans* = 30:1, 96% ee; (iii) Cl_2CHCO_2H, 1,2-$C_2H_4Cl_2$, reflux, 1 h, 80%; (iv) $NaBH_4$, MeOH, 0 °C, 0.5 h, 74%.

Rao's approach (2004)[58]

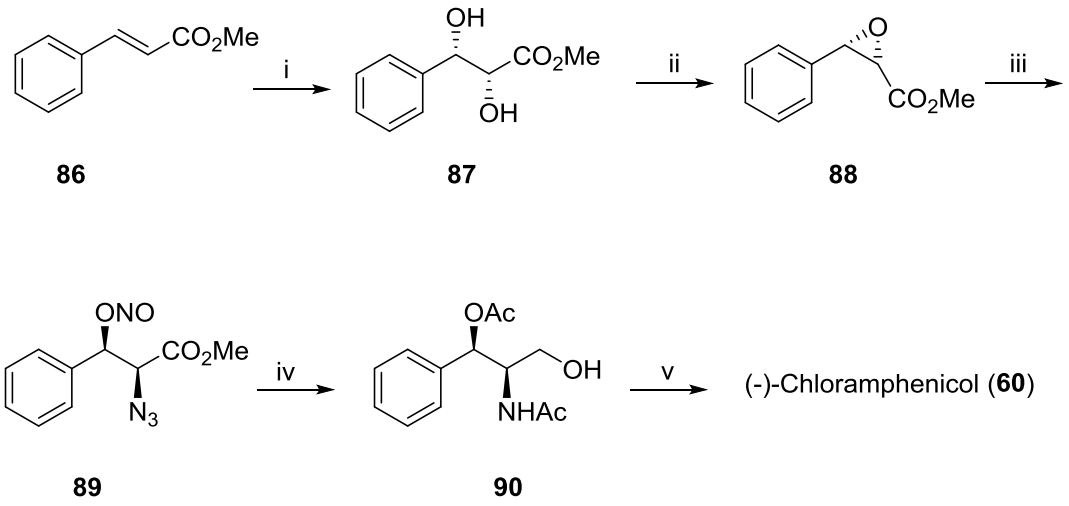
Rao *et al*. have achieved the synthesis of (-)-chloramphenicol (**60)** by employing Sharpless asymmetric epoxidation of the allylic alcohol **82** using (-)-DIPT to afford the chiral epoxyalcohol **83** with 95% ee. Epoxyalcohol **83** was then converted into (-)-chloramphenicol (**60)** by treatment with dichloroacetonitrile in the presence of NaH followed by an *in situ* opening of the product **85** with $BF_3.Et_2O$ (**Scheme 18**).



Scheme 18: (i) divinyl zinc, THF, Et_2O, -78 ^{0}C to 25 ^{0}C, 10 h, 72%; (ii) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 ^{o}C, 14 h, 45%; (iii) NaH, dichloroacetonitrile, CH_2Cl_2, 0 ^{0}C to 25 ^{0}C, 1 h, then $BF_3.OEt_2$, -78 ^{0}C to 25 ^{0}C, 3 h, 71%.

Barua's approach (2005)[59]

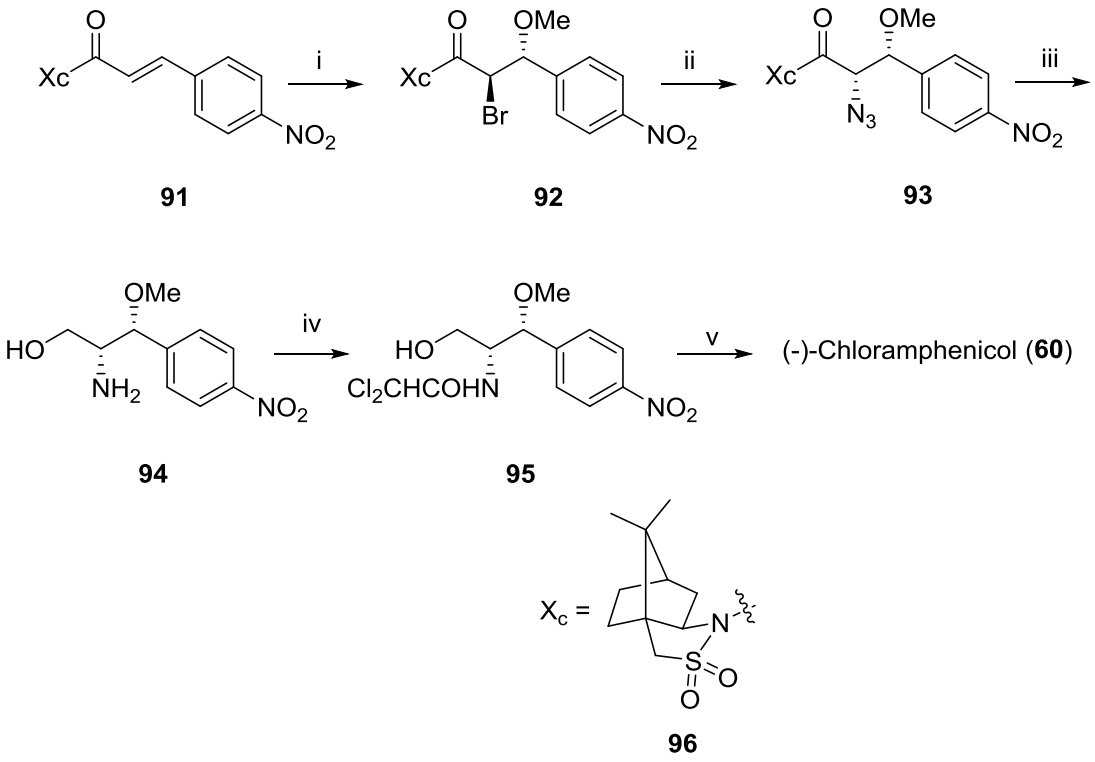
(-)-Chloramphenicol (**60**) was also synthesized by Barua *et al.* using regioselective ring opening of epoxide **88,** which was prepared from methyl cinnamate **86** by Sharpless asymmetric dihydroxylation. The epoxide **88** was exposed to $NaNO_2$ and acetic acid in water followed by treatment with diphenyl phosphorylazide (DPPA), DEAD and PPh_3 to afford the azide **89**. Catalytic hydrogenation of **89** [10% Pd/C, MeOH, H_2 (1 atm)] followed by acylation with Ac_2O gave the amino alcohol **90**. The synthesis of (-)-chloramphenicol (**60)** was completed by following the three-step standard reaction sequences: nitration, hydrolysis and *N*-acylation in 98% ee (**Scheme 19**).



Scheme 19: (i) OsO_4 (cat.), NMO, DHQ-*p*ClBz, acetone, H_2O, 98% ee; (ii) (a) TsCl, pyridine, CH_2Cl_2; (b) K_2CO_3, H_2O, DMF, 86%; (iii) (a) $NaNO_2$, AcOH, H_2O, 0 °C to 25 °C, 2 h, 89%; (b) DPPA, DEAD, PPh_3, THF, 0 °C to 25 °C, 1.5 h, 82%; (iv) (a) 10% Pd/C, MeOH, H_2 (1 atm), 25 °C, 12 h, 97%; (b) Ac_2O, DMAP, pyridine; (v) (a) Conc. HNO_3-conc. H_2SO_4, -20 °C to 25 °C; (b) aq. 5% HCI, 90 °C, 69%; (c) Cl_2CHCO_2Me, 90 °C, 1 h, 80%.

Hajra's approach (2006)[60]

Hajra *et al.* have synthesized (-)-chloramphenicol (**60**) using silver (I)-promoted asymmetric bromomethoxylation of camphor-based carboxamide **91**. Thus, the $AgNO_3$-promoted bromomethoxylation of α, β- unsaturated carboxamide **91** provided the desired product **92** in 72% yield. Reaction of **92** with NaN_3 in DMF gave the azido product **93,** which was subjected to a two-step reduction process with $LiBH_4$ followed by PPh_3 in THF-H_2O to furnish the amino alcohol **94**. *N*-Acylation of **94** gave **95**, which on subsequent demethylation with BBr_3 gave the target molecule **60** in 80% yield (**Scheme 20**).



Scheme 20: (i) $AgNO_3$, Br_2, MeOH, 0 ^oC, 30 min, 72%, d.r. = 3:1; (ii) NaN_3, DMF, 60 ^oC, 4 h, 92%; (iii) (a) $LiBH_4$, THF, MeOH; (b) PPh_3, THF-H_2O, 25 ^oC, 5 h, 82%; (iv) Cl_2CHCO_2Me, 90 ^oC, 1 h, 87%; (v) BBr_3, CH_2Cl_2, -78 ^oC to -20 ^oC, 10 h, 80%.

1.3.3 Present work

1.3.3.1 Objective

Even though several methods are reported for the synthesis of (-)-chloramphenicol (**60**),[43-71] most of these methods suffer from the fact that they make use of chiral starting materials, expensive and hazardous reagents, low overall yields, low diastereomeric ratios and also the use of unnatural ligands for the introduction of chirality. In this context, a more practical method for the synthesis of (-)-chloramphenicol (**60**) is highly desirable.

Retrosynthetic analysis

Retrosynthetic analysis for (-)-chloramphenicol (**60**) reveals that *syn*-amidodiol **103** could be visualized as the key intermediate. (-)-Chloramphenicol (**60**) could be achieved by *para*- nitration of amidodiol **103**. The amidodiol **103** could be prepared from bromoalcohol **101** by performing simple S_N2 displacement of Br function with azide followed by its reduction to amidodiol. The chiral *anti*-bromoalcohol **101** can be obtained by the Pd(II)-(-)sparteine catalyzed oxidative kinetic resolution of (±) *anti*-bromoalcohol **99**. The requisite racemic *anti*-bromoalcohol **99** could be readily prepared from the protected cinnamylalcohol **98** *via* bromohydroxylation reaction (**Fig. 18**).

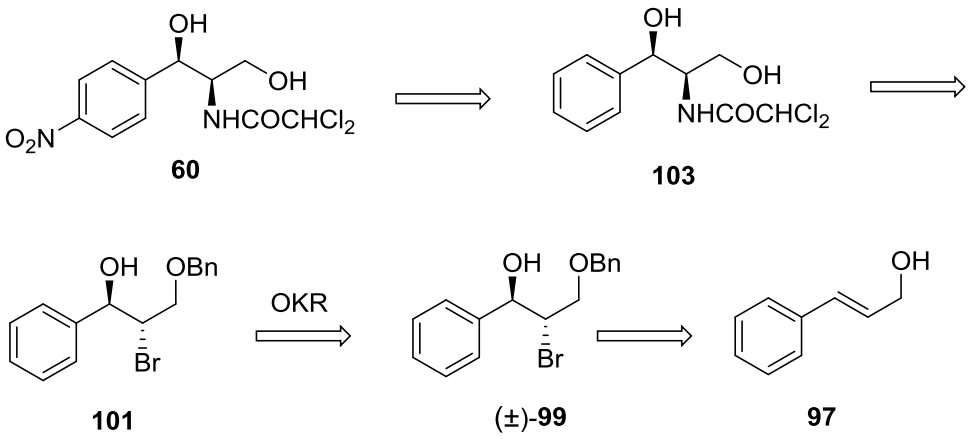
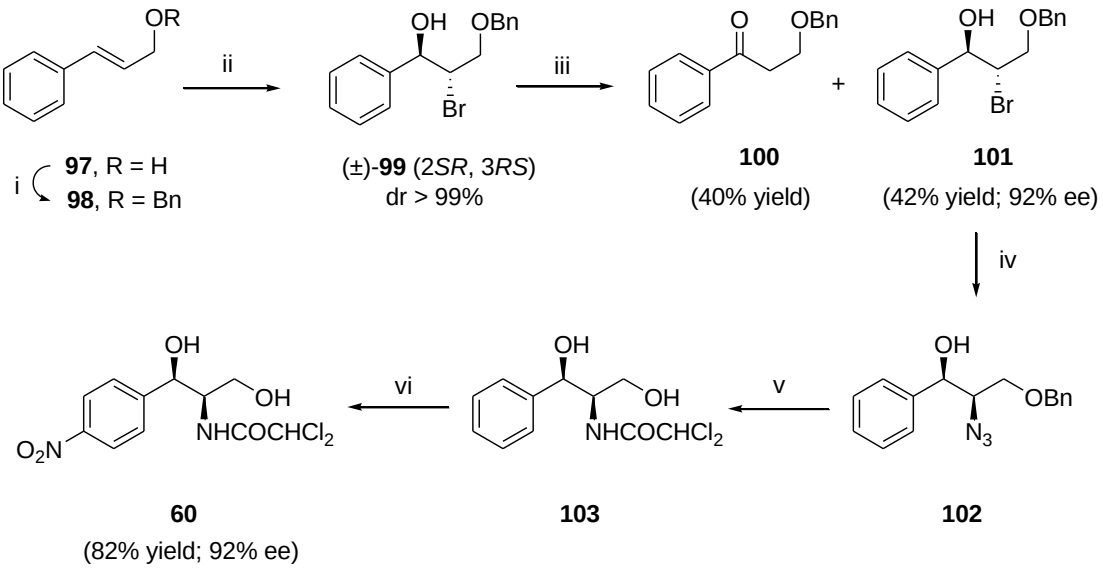


Fig. 18: Retrosynthetic analysis of (-)-chloramphenicol (**60**)

1.3.3.2 Result and discussion

This section deals with the asymmetric synthesis of (–)-chloramphenicol **60** employing Pd-sparteine- catalyzed two-stereocentered OKR as the chirality inducing step. The sequence of reactions for (-)- chloramphenicol synthesis is outlined in **Scheme 21**.



Scheme 21: (i) BnBr, NaH, THF, 0 ^{o}C, 1 h, 96%; (ii) NBS, CH_3CN/H_2O (2:1), 25 ^{o}C, 8 h, 91%; (iii) $Pd(OAc)_2$ (5 mol%), (-)-sparteine (20 mol%), O_2, toluene, 3 A^{o} MS, 80 ^{o}C, 32 h; (iv) NaN_3, DMSO, 80 ^{o}C, 2 h, 99%; (v) 10% Pd/C, H_2 (1 atm), MeOH, $Cl_2CHCOCl$ (1 equiv), 25 ^{o}C, 18 h, 72%; (vi) conc. HNO_3-conc. H_2SO_4, – 20-25 ^{o}C, 1.5 h, 82%.

As can be seen, the synthesis of (–)-chloramphenicol **60** commenced with the protection of cinnamyl alcohol **97** as its benzyl ether **98** (BnBr, NaH, DMF, 0 ^{o}C). The ether **98** was bromohydroxylated in a highly regio- and diastereoselective manner [NBS, CH_3CN/H_2O (2:1, v/v), 25 ^{o}C] to give *anti*-α-bromoalcohol **99** in 91% yield and > 99% dr. The ^{1}H NMR spectrum of **99** showed a typical triplet at δ 5.01 for the benzylic proton (-C**H**OH) and a quartet at δ 4.30-4.35 for the methine proton (-C**H**Br) attached to bromine atom. This was substantiated by the absence of olefinic proton signals. Its ^{13}C NMR spectrum showed two typical signals at δ 76.1 and 55.8 due to the benzylic carbon (-**C**HOH) and the carbon attached to bromine atom (-**C**HBr) respectively confirming the formation of **99** (**Fig. 19**).

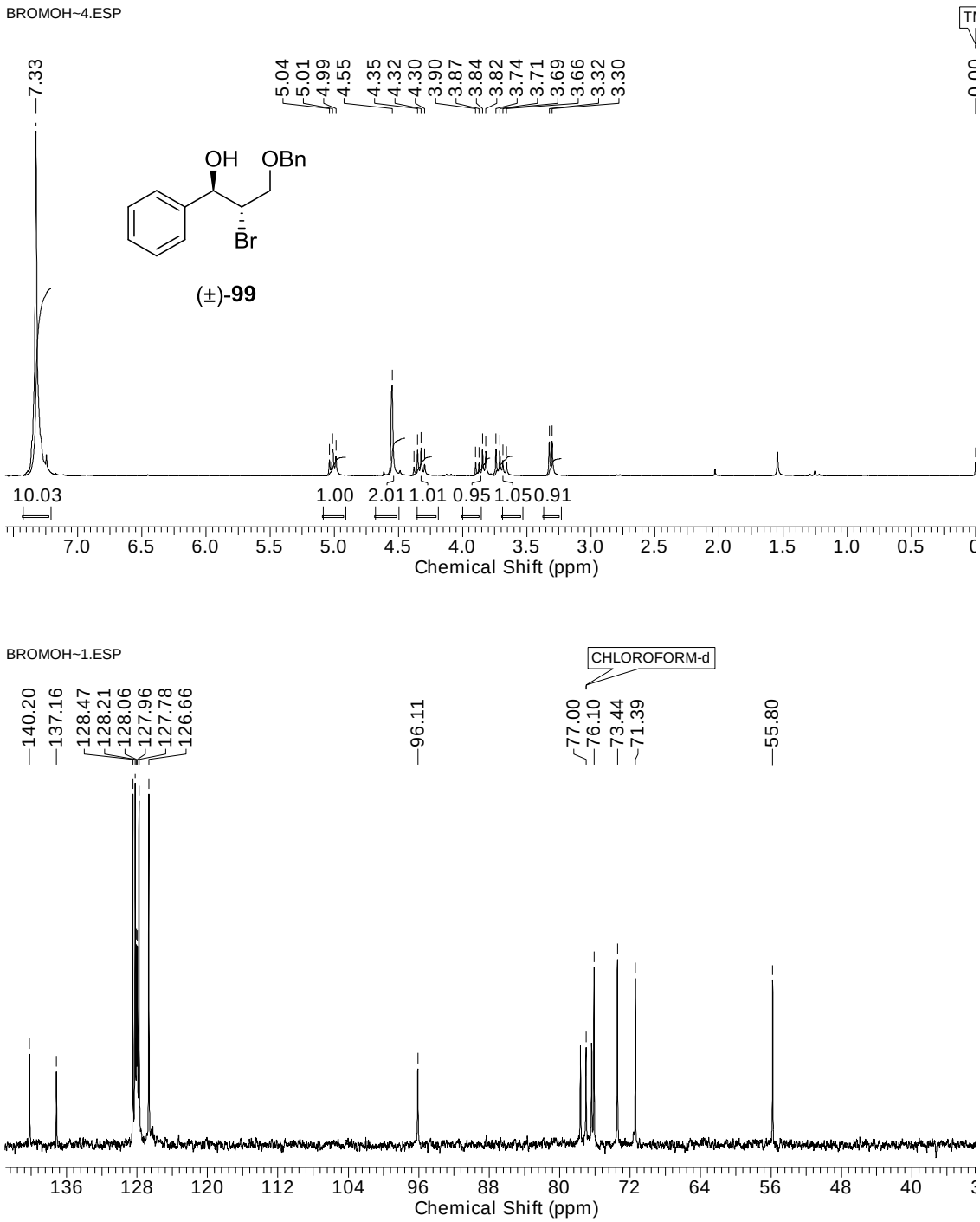


Fig. 19: ^{1}H and ^{13}C NMR spectra of racemic 3-(benzyloxy)-2-bromo-1-phenylpropan-1-ol **((±)-99)**

The racemic bromoalcohol **99** was then subjected to Pd-sparteine-catalyzed OKR which furnished the chiral bromoalcohol **101** in 42% yield and 92% ee (HPLC analysis) along with aromatic ketone **100** in 40% yield. The aromatic ketone **100** and

chiral bromoalcohol **101** then were readily separated using column chromatography. The ^{1}H NMR spectrum of **100** showed a typical signal at δ 5.19-5.23 for the α-methylenic (-COC**H**$_2$) protons.

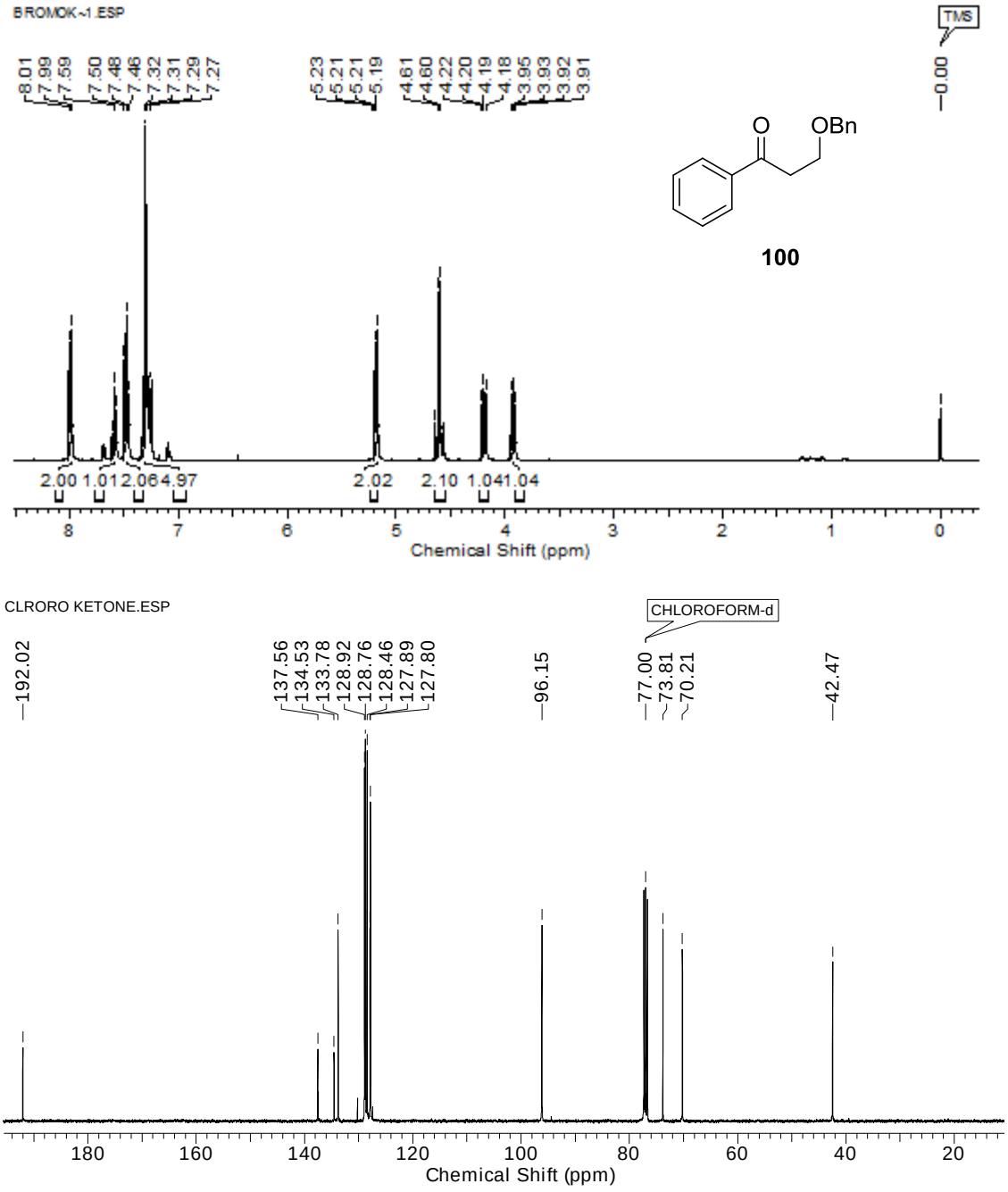


Fig. 20: ^{1}H and ^{13}C NMR spectra of 3-(benzyloxy)-1-phenylpropan-1-one (**100**)

The disappearance of a signals at δ 5.00 due to the benzylic proton (-C**H**OH) and δ 4.30-4.35 for the methinic proton (-C**H**Br) attached to bromine confirmed the formation of ketone **100**. Its ^{13}C NMR spectrum showed a typical signal at δ 192.0 for the carbonyl carbon, which further confirmed the formation of ketone **100** (**Fig. 20**).

The ^{1}H NMR spectrum of **101** showed a typical signal at δ 4.99-5.04 for the benzylic proton (-C**H**OH) and a triplet at δ 4.30-4.35 for the methine proton (-C**H**Br) attached to bromine atom.

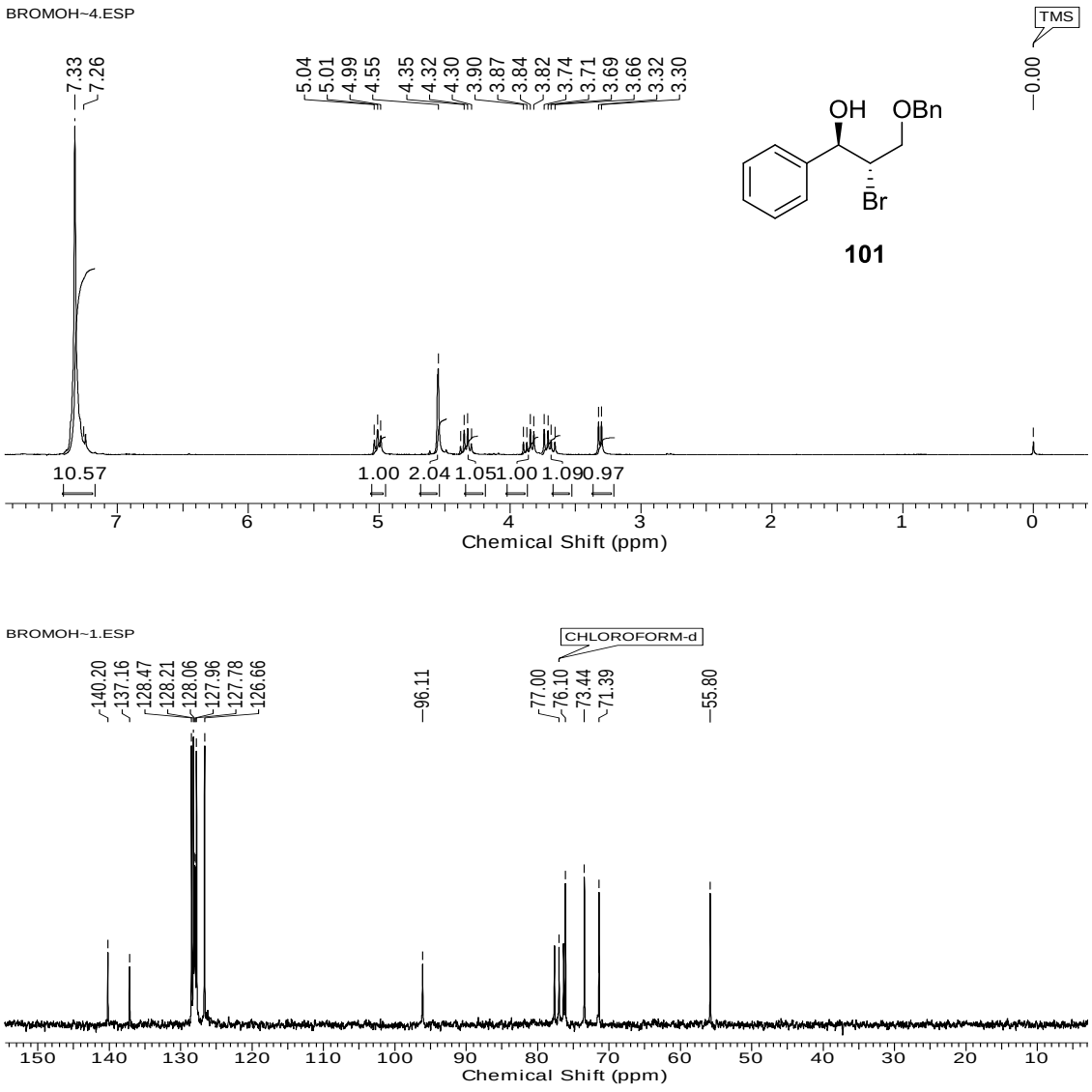


Fig. 21: ^{1}H and ^{13}C NMR spectra of bromohydrin (**101**)

Its ^{13}C NMR spectrum showed two typical signals at δ 76.1 and 55.8 due to the benzylic carbon (-**C**HOH) and the carbon attached to bromine atom (-**C**HBr) respectively confirming the formation of **101 (Fig. 21)**.

The bromide function in **101** was then subjected to S_N2 displacement with azide ion [NaN_3, DMSO, 80 ^oC] to give *syn*-α-azidoalcohol **102** in quantitative yield.

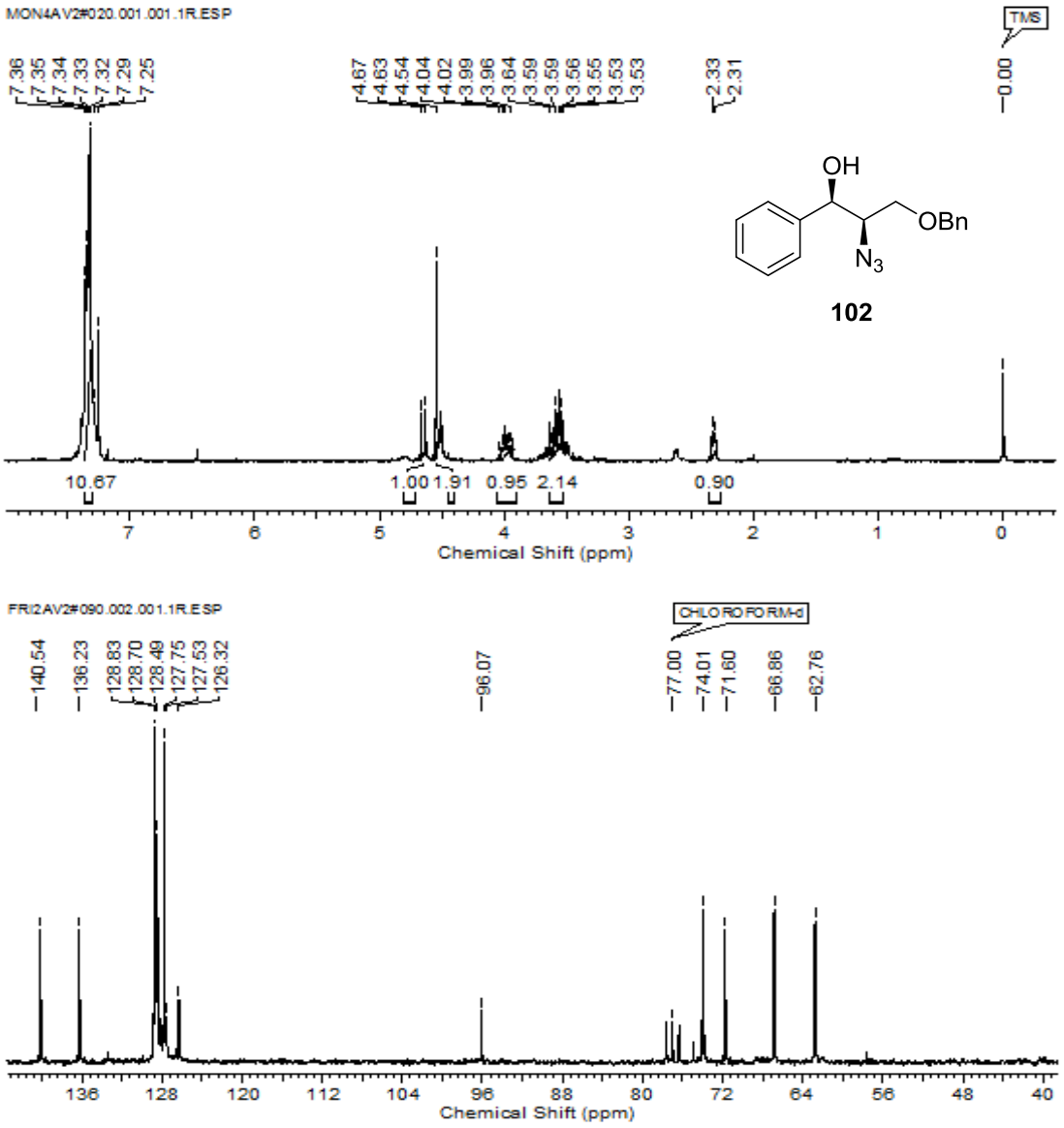


Fig. 22: ^1H and ^{13}C NMR spectra of (1*R*,2*R*)-2-azido-3-(benzyloxy)-1-phenylpropan-1-ol (**102**)

The ^1H-NMR spectrum of azide **102** showed a typical signal at δ 3.96-4.04 (m, 1H) for methine (-**CH**- N_3) proton. Its ^{13}C NMR spectrum displayed a typical peak at δ

62.7 corresponding to methine (-**CH**-N_3) carbon. The appearance of a strong absorption at 2101 cm^{-1} in its IR spectrum also confirmed the formation of **102** (**Fig. 22).**

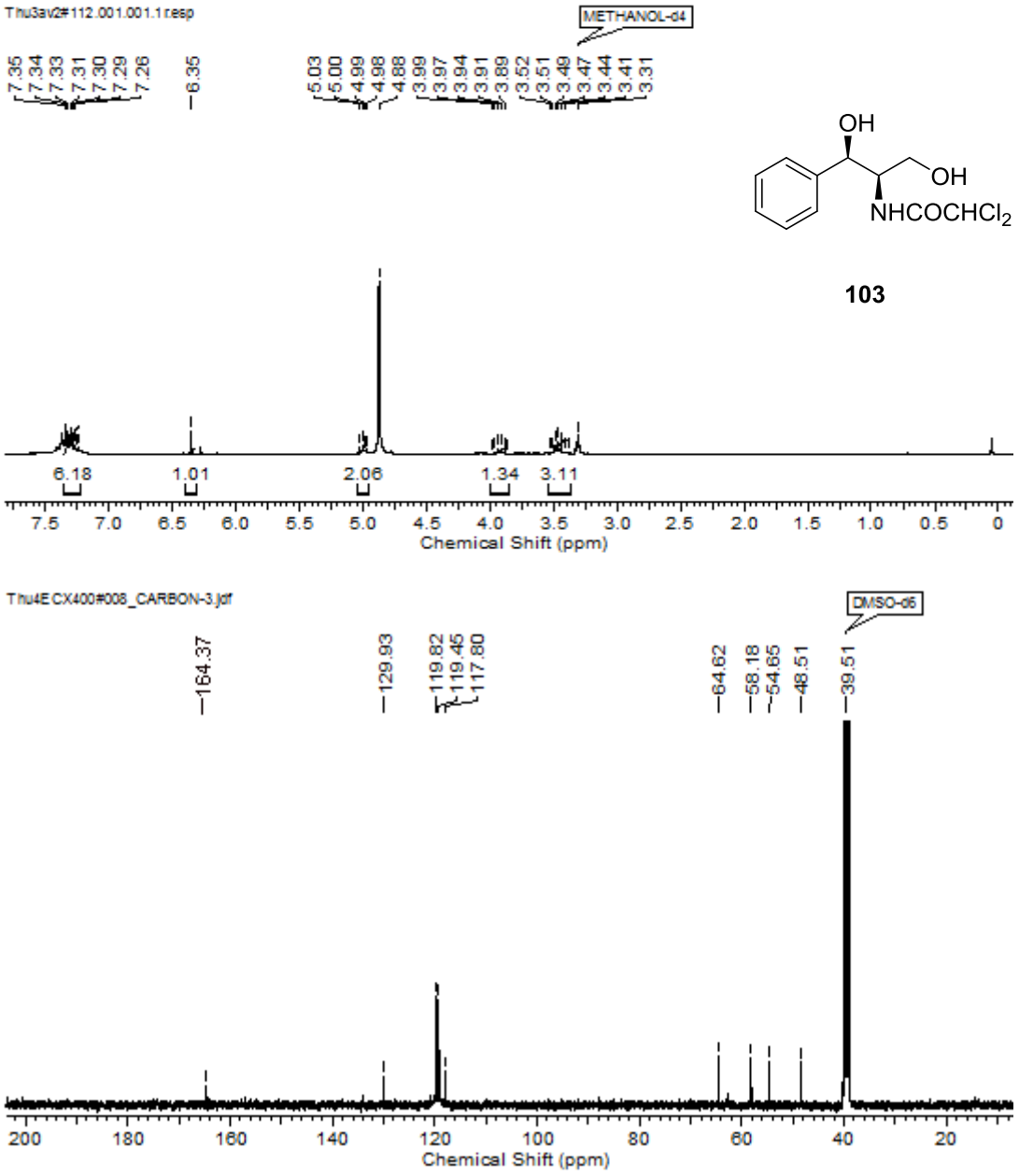
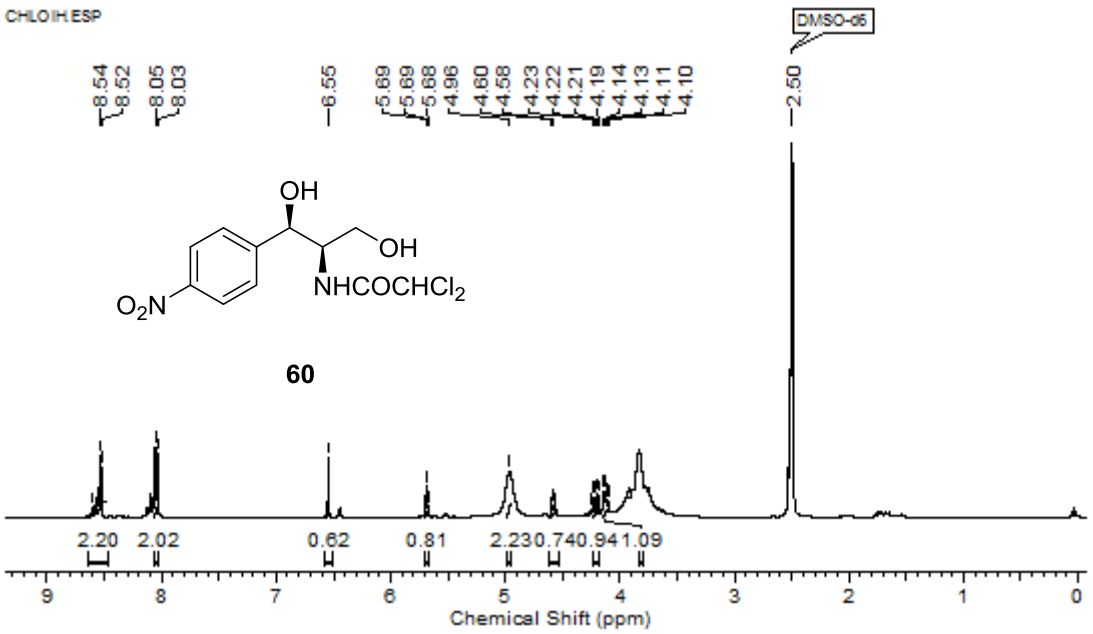


Fig. 23: ^{1}H and ^{13}C NMR spectra of 2,2-dichloro-N-((1*R*,2*R*)-1,3-dihydroxy-1-phenylpropan-2-yl)acetamide (**103**)

The catalytic hydrogenation [10% Pd/C, H_2 (1 atm) and $COClCHCl_2$] of azide function in **102** followed by its dichloroacetylation furnished amidodiol **103** in 72%

yield in a single step. A singlet at δ 6.35 integrating for one proton indicated the presence of CH proton (NHCO**CH**Cl_2) in its ^{1}H NMR spectrum. The formation of **103** was further supported by the appearance of typical carbon signals at δ 48.5 (-**C**HNH-), 54.6 (-**C**H_2OH), 58.1 64.6 (-CO**C**HCl_2), 64.6 (-**C**HOH-) and 164.37 (NH**C**OCHCl_2) in its ^{13}C-NMR spectrum (**Fig. 23).**

Finally, regioselective *p*-nitration of **103** was achieved with mixed acids (conc. HNO_3 and conc. H_2SO_4) to give (–)-chloramphenicol **60** {$[\alpha]^{25}_D$ −24.2 (*c* 1, EtOAc); [lit.[72] $[\alpha]^{23}_D$ −25.5 (*c* 1, EtOAc)]}; with an overall yield of 21.44% and 92% ee (**Scheme 21**). Two doublets at δ 8.52-8.54 and 8.03-8.05 for the aromatic protons *ortho*- and *meta*- respectively to the nitro substituent on aromatic ring with downfield shift from δ 7.29 to7.35 clearly indicated the presence of a nitro group at the *para*- position. This was further ascertained by the presence of a typical carbon signal at δ 146.3 for the quaternary carbon attached to the nitro group (-**C**NO_2). The IR spectrum of **103** displayed a characteristic broad absorption at 3425 cm^{-1} indicating the presence of –OH and –NH groups (**Fig. 24**).



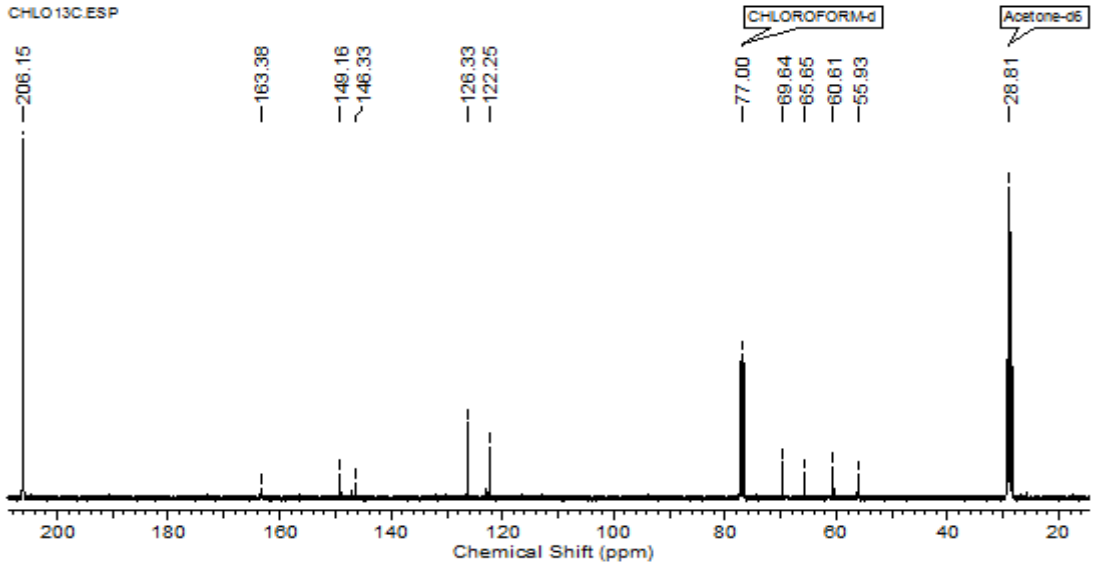


Fig. 24: ^{1}H and ^{13}C NMR spectra of (-)-Choramphenicol (**60**)

1.3.4 Conclusion

In conclusion, we have achieved an efficient synthesis of (-)-chloramphenicol (**60**) with an overall yield of 21.44%; 92% ee. The synthesis involved oxidative kinetic resolution as the key chirality inducing reaction. The major advantages of this synthesis is the use of naturally-occurring ligand i.e. (-)-sparteine for the kinetic resolution step and the achievement of two chiral centres in a single step.

1.3.5 Experimental section

3-(Benzyloxy)-2-bromo-1-phenylpropan-1-ol (99)

See experimental section of chapter I section I for the experimental procedure.

2-Bromo-3-benzyloxy-1-phenylpropan-1-one (100)

To a 100 mL side arm flask 0.057 g (0.25 mmol) of $Pd(OAc)_2$ was placed followed by the addition 40 mL of dry toluene, 100 mg of 3Å sieves and 0.21 mL (0.235 g, 0.99 mmol) of (-)-sparteine. A balloon filled with O_2 was then attached to the flask fitted with a condenser. The whole system was evacuvated and refilled with O_2 (1 atm) from the balloon three to four times. The contents were heated to 80 ^{o}C in an oil bath.

After 30 min, (1.6 g, 5 mmol) of *anti*- bromohydrin **99** in toluene was added dropwise. After 10-12 h of refluxed temperature, the reaction mixture was cooled to room temperature. It was quenched with 2% TFA in methanol. The solvent was concentrated under vaccuo, to give the mixture of crude products which were purified by column chromatography (packed with silica gel 100-200 mesh) using pet. ether and ethyl acetate (95:5) to give ketone **100** in 40% yield, while chiral *anti*-α-bromohydrin **101** was isolated in 42% yield (92% ee) using pet. ether/ethyl acetate (80:20) ratio.

Yield: 40%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3086, 2975, 1682, 1590, 1513, 1457, 1265, 1160, 1030, 871; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.91-3.95 (dd, *J* = 4.9 and 9.8 Hz, 1H), 4.18-4.22 (dd, *J* = 8.2 and 10.1 Hz, 1H), 4.57-4.64 (dd, *J* = 11.8 and 17.8 Hz, 2H), 5.19-5.23 (dd, *J* = 5.9 and 7.3 Hz, 1H), 7.26-7.34 (m, 5H), 7.48 (t, *J* = 8.21 Hz, 2H); 7.59 (t, *J* = 6.81 Hz, 1H), 7.99-8.01 (d, *J* = 7.74 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 42.4, 70.2, 73.8, 127.8, 128.4, 128.7, 128.9, 133.7, 134.5, 137.5, 192.0; **Analysis**: $C_{16}H_{15}BrO_2$ requires: C, 60.21; H, 4.74; found: C, 60.28; H, 4.69 %.

(1*R*, 2*S*)-3-(Benzyloxy)-2-bromo-1-phenylpropan-1-ol (101)

Yield: 42%; pale yellow oil; **$[\alpha]_D^{25}$** +52.75 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3602, 2927, 1604, 1021, 757; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.30 (d, *J* = 4.5, 1H), 3.66-3.74 (dd, *J* = 5.8 and 10.6 Hz 1H), 3.82-3.90 (dd, *J* = 5.2 and 10.7 Hz, 1H), 4.30-4.38 (q, *J* = 5.4 Hz, 1H), 4.55 (s, 2H), 5.01 (t, *J* = 5.01 Hz, 1H); 7.33 (s, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.8; 71.3, 73.4, 76.1, 126.6, 127.7, 127.9, 128.0, 128.2, 128.4, 137.1, 140.2; **Analysis**: $C_{16}H_{17}BrO_2$ requires: C, 59.83, ; H, 5.33; found: C, 59.77; H, 5.29 %.

(1*R*,2*R*)-2-Azido-3-(benzyloxy)-1-phenylpropan-1-ol (102)

To a stirred solution of bromohydrin **101** (0.77 g, 2.43 mmol) in DMSO (5 mL) was

added sodium azide (455 mg, 7 mmol) and the reaction mixture was heated at 60 ^{o}C for 12 h. After the completion of the reaction as monitored by TLC, it was extracted with EtOAc (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 (8:2) to obtain pure dibenzyloxy azide **102** as colorless oil.

Yield: 99%; colorless oil.; **[α]$^{25}_{D}$** −30.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) ν_{max} 3029, 2101, 1450, 1264, 789, 699; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.31-2.33 (d, *J* = 4.4 Hz, 1H), 3.53-3.64 (m, 2H), 3.96-4.04 (m, 1H), 4.54 (s, 2H), 4.63-4.67 (d, *J* = 6.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.7, 66.8, 71.6, 74.0, 126.3, 127.5, 127.7, 128.4, 128.7, 128.8, 136.2, 140.5; **Analysis**: $C_{16}H_{17}H_3O_2$ requires: C, 67.83; H, 6.05; N 14.83; found: C, 67.90; H, 6.11; N 14.75%.

2,2-Dichloro-*N*-((1*R*,2*R*)-1,3-dihydroxy-1-phenylpropan-2-yl)acetamide (103)

To a stirred solution of azide **102** (0.45 g, 1.6 mmol) and dichloroacetylchloride in methanol (10 mL) was added 20% $Pd(OH)_2/C$ (265 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 crude material it was then purified by column chromatography on silica gel using petroleum ether/EtOAc (3:7) to give triacetate acetamidodiol **103** as a pale yellow liquid.

Yield: 72%; pale yellow liquid. **[α]$^{25}_{D}$** −19.5 (*c* 1, EtOAc); **IR** ($CHCl_3$, cm^{-1}) ν_{max} 3425, 3021, 2935, 1687, 1403, 1348, 1216; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 3.31-3.52 (m, 3H), 3.89-3.99 (m, 1H), 4.98-5.03 (m, 2H), 6.35 (s, 1H) 7.26-7.35 (m, 6H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 48.5, 54.6, 58.1, 64.6, 117.8, 119.4, 119.8, 129.9, 200.6; **Analysis**: $C_{11}H_{13}Cl_2NO_3$ requires: C, 47.50; H, 4.71; N 5.04; found: C, 47.43;

H, 4.66; N 4.98 %.

(-)-Choramphenicol 60

To a stirred solution of conc. HNO_3: conc. H_2SO_4 (1:1) (2 mL) was added acetamide **103** (150 mg, 1.02 mmol) at -20 ^oC, the resulting solution was stirred for 1.5 h at 25 °C. After the completion of the reaction as monitored by TLC, it was poured into water (5 mL) and extracted with diethyl ether (3 x 10 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/ EtOAc (3:7) to give the product **60** as a colorless solid.,

Yield: 82%; colorless solid. **mp:** 150-152 ^oC [lit.[35] 149.7-150.7 ^oC]; $\mathbf{[\alpha]^{25}_D}$ −24.2 (*c* 1, EtOAc) [lit.[11] $[\alpha]^{23}_D$ −25.5 (*c* 1, EtOAc)]; **IR** ($CHCl_3$, cm^{-1}) ν_{max} 3420, 3020, 2929, 1686, 1604, 1523, 1454, 1403, 1348, 1216, 1049, 850; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.61-3.65 (m, 1H), 3.70-3.75 (m, 1H), 4.09-4.12 (m, 1H), 5.20 (d, *J* = 2.24 Hz, 1H), 6.06 (s, 1H); **^{13}C NMR** (50 MHz, acetone-d_6): δ 56.92, 61.6, 66.6, 70.6, 123.2, 127.3, 147.3, 150.1, 164.3, 207.1; **Analysis**: $C_{11}H_{12}Cl_2N_2O_5$ requires: C, 40.89; H, 3.74; N 8.67; found: C, 40.81; H, 3.80; N 8.60 %.

1.3.6 Reference

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Chapter II

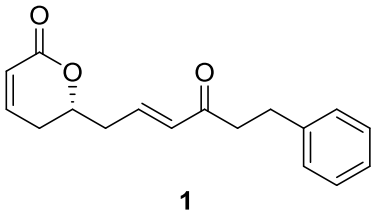
Asymmetric Synthesis of (R)-Rugulactone, (R)-Coniine and Formal Synthesis of (+)-Febrifugine

SECTION I:

Asymmetric Synthesis of (*R*)-Rugulactone *via* Proline-Catalyzed Asymmetric α-Aminoxylation of Aldehyde

2.1.1 Introduction and Pharmacology

The alkyl and aryl substitueted α, β-unsaturated α-pyrones (6-arylalkyl-5,6-dihydro-2*H*-pyran-2-ones) possess important biological properties such as antitumor, antiviral, antifungal, *anti*-inflammatory, etc. These properties arise as a result of Michael acceptor property of α-pyrones towards the amino acid residues of the receptors. The biological assays of 6-arylalkyl-5,6-dihydro-2*H*-pyran-2-one, (*R*)-rugulactone **1**, which has been extracted from the evergreen tree *Cryptocarya rugulosa*[1] of Lauraceae family has been found to inhibit the nuclear factor (NF-kB) activation pathway occurring in different types of cancers.[2]



1

Fig. 1: Structure of (*R*)-rugulactone (**1**)

On account of its interesting biological properties and scare availability, it has attracted considerable attention from organic and medicinal chemistry community alike.

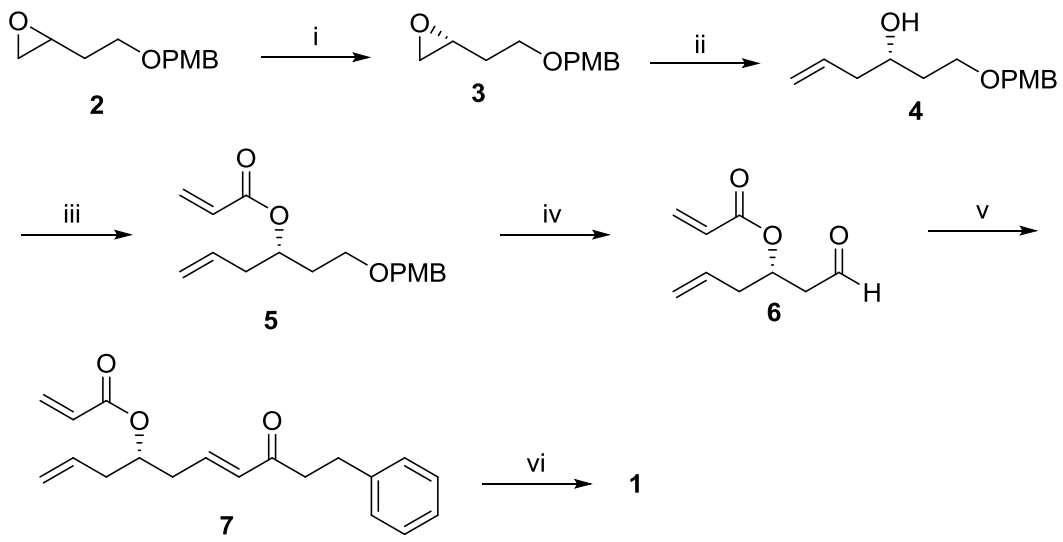
2.1.2 Review of literature

Till date seven synthetic routes have been documented in the literature, which are described below.

Yadav's approach (2009)[3]

J. S. Yadav *et al*. were the first to report the synthesis of (*R*)-rugulactone **1**. The synthesis began with the Jacobsen's hydrolytic kinetic resolution of epoxide **2** to

obtain the (*R*)-MPM-ethyl oxirane **3**, which was treated with vinyl magnesium bromide in the presence of CuI to afford the homoallyl alcohol **4** in excellent yield (87% ee). Acylation of the secondary alcohol followed by PMB deprotection (DDQ, CH_2Cl_2, H_2O), and alcohol oxidation (DMP) led to the corresponding aldehyde **6** (78% over three steps). Horner–Wadsworth–Emmons homologation of **6** with dimethyl (2-oxo-4-phenylbutyl) phosphonate in presence of sodium *bis*-(trimethylsilyl)amide gave the α,β-unsaturated ketone **7** in 87% yield. Finally, exposure of **7** to Grubbs' first generation catalyst (10 mol%) in refluxing CH_2Cl_2 afforded rugulactone (**1**) in 82% yield (**Scheme1**).

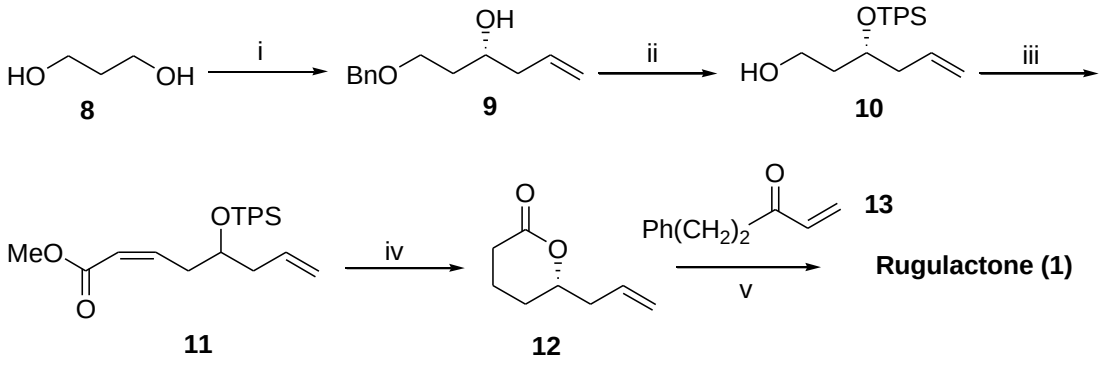


Scheme 1. (i) (*R*,*R*)-(salen) CoIII(OAc).H_2O (0.5 equiv) 25 ^oC., 12 h, 47%; (ii) Vinylmagnesium bromide, CuI, THF, 0 ^oC, 2 h, 91%; (iii) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 12 h, 92%; (iv) (a) DDQ, CH_2Cl_2, H_2O, 25 ^oC, 1 h, 89%; (b) DMP, CH_2Cl_2, 0 ^oC, 2 h, 96%; (v) NaHMDS, dimethyl(2-oxo-4-phenylbutyl) phosphonate, 0 ^oC, 12 h, 87% and 84%; (vi) Grubbs' Ist generation catalyst, CH_2Cl_2, reflux, 12 h, 82% and 80%.

Venkateswarlu's approach (2009)[4]

Venkateswarlu *et al* have developed a simple and highly efficient stereoselective synthetic route for the synthesis of (*R*)-rugulactone (**1**). As outlined in **Scheme 2**, the

free alcohol in mono benzyl ether was oxidized using iodoxybenzoic acid (IBX) in DMSO to afford the corresponding aldehyde, which was subjected to the catalytic asymmetric allyl stannation to furnish the homoallylic alcohol **9** in 80% yield with an excellent enantioselectivity of 97.5% ee. The secondary hydroxyl group in **9** was protected as TPS ether, the protected primary hydroxyl group on reduction using lithium naphthalenide gave alcohol **10** in 81% yield. Alcohol **10** was oxidized to aldehyde (IBX in DMSO), which was further subjected to Still–Gennari modification of the Horner–Emmons olefination to afford unsaturated ester **11** with a *Z*/*E* ratio of 95:05 in 80% yield.

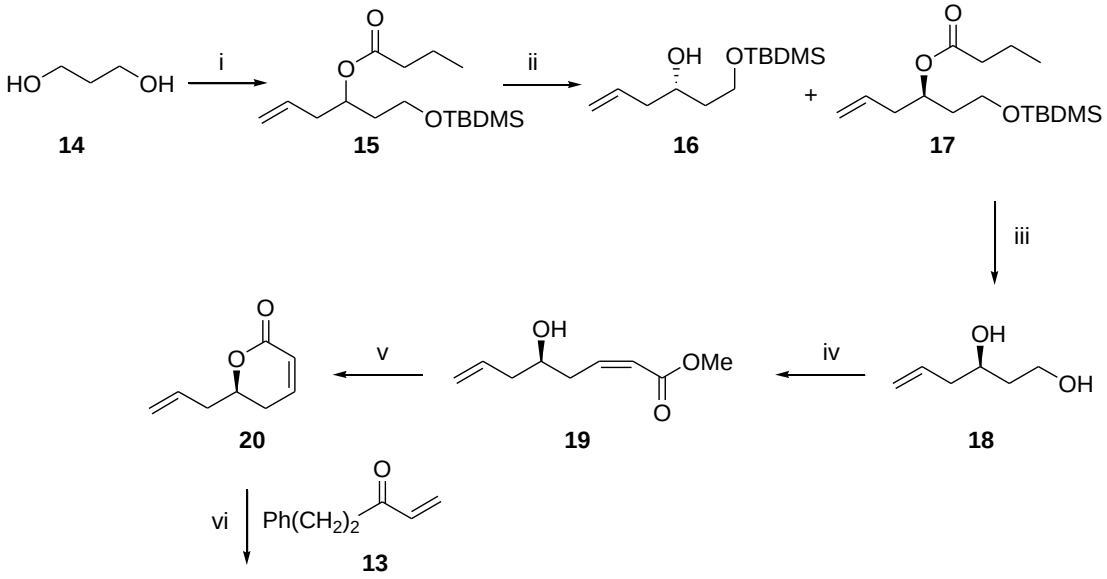


Scheme 2. (i) (a) BnBr, NaH, TBAI, THF. 0 ^{o}C to rt, 2 h, 85%; (ii) (b) IBX, dry DMSO; dry CH_2Cl_2, 5 h, 88%, (c) (*R*)-BINOL, 4 Å MS, $Ti(OiPr)_4$, allyltributylstannane, CH_2Cl_2, -78 ^{o}C to 20 ^{o}C, 80%; (ii) (a) TBDPSCl, imidazole, dry CH_2Cl_2, 4 h, 95%; (b) Li in naphthalene, -20 ^{o}C, 3 h, 81%; (iii) (a) IBX, dry DMSO, dry CH_2Cl_2, 5 h, 85%, (b) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78 ^{o}C, 2 h, 76%; (iv) 3% HCl in MeOH 30 min, 78%. (v) Grubbs, 2nd generation catalyst (5 mol %), dry CH_2Cl_2, 40 ^{o}C, 12 h, 74%.

Compound **11** upon treatment with 3% HCl in MeOH afforded 6-allyl-5,6-dihydro-pyrone **12** in 78% yield. Finally, compounds **12** and **13** (1:3) ratio were subjected to cross metathesis using second generation Grubbs' catalyst (5 mol %) in dichloromethane under reflux conditions to yield the desired (*R*)-rugulactone **(1)** in 74% yield, $[\alpha]^{25}{}_{D}$ -61.9 (*c* 0.5, $CHCl_3$) (**Scheme 2**).

Fadnavis's approach (2010)[5]

Fadnavis *et al* have described the synthesis of (*R*)-rugulactone **(1)** using enzymatic kinetic resolution of the racemic butyrate ester **15** (Scheme 4) in excellent yield and enantiomeric purity. The chiral esters so obtained were converted to the (*R*)- and (*S*)-enantiomers of rugulactone **1**.



(*R*)-Rugulactone **1**

Scheme 3. Reagents and conditions: (I) a) NaH, TBDMSCl, DME, 25 ^{o}C overnight; b) $(COCl)_2$, DMSO, DCM, -78 ^{o}C 1 h; (c) Zn, allyl bromide, NH_4Cl in THF 3 h; (d) DCC, DMAP, butyric acid in DCM, 2 h; (ii) Tris–HCl buffer, 0.05 M, pH 7.5; Candida rugosa lipase, 48 h; (iii) a) PTSA, MeOH, 1 h; b) K_2CO_3, MeOH, 4 h; (iv) a) BAIB, TEMPO, DCM, 4 h; b) Methyl *P*,*P*-bis(2,2,2-trifluoroethyl)phosphonoacetate, NaH, THF, -78^{o}C; (v) PTSA, benzene reflux, 1 h; (vi) $ArCH_2CH_2COCHCH_2$, Grubbs's IInd-generation catalyst, CH_2Cl_2, 50 ^{o}C, 5 h.

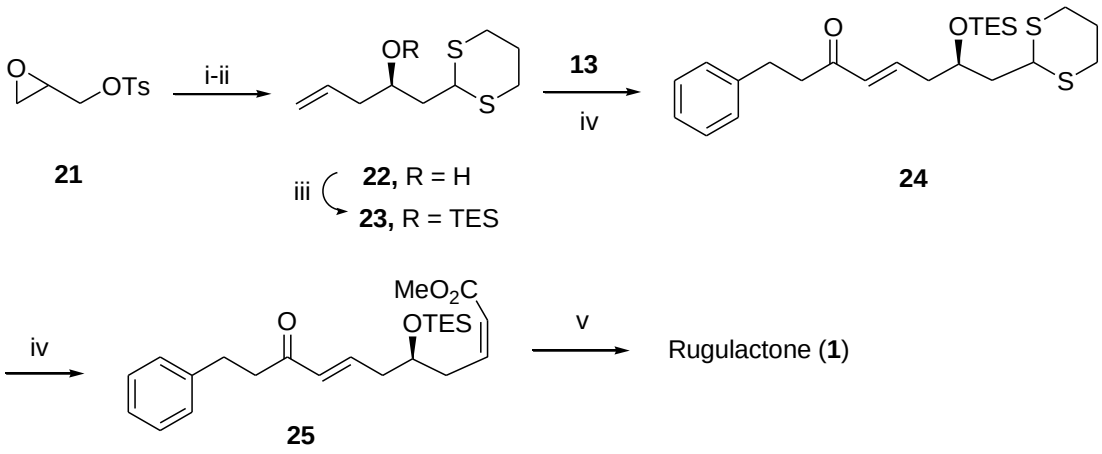
The monosilyl ether (85%) prepared from 1,3-propanediol **14** was oxidized to the corresponding aldehyde and allylated by Barbier's procedure to racemic homoallylic alcohol (92% over two steps). This was esterified with butyric acid to obtain racemic **15**. The enantioselective hydrolysis of **15** was carried out using lipase from *Candida*

rugosa (E = 244) provided the (*S*)-alcohol namely (*S*)-**16** with ee 98% at approximately 50% conversion and the unreacted ester (*R*)-**17** with ee >99%. Ester **17** was hydrolyzed to alcohol which after desilylation with PTSA afforded diol (*R*)-**18**. The diol (*R*)-**18** was selectively oxidized with TEMPO and BAIB to give the crude aldehyde, which was converted to unsaturated ester (*R*)-**19**, *via* the Still–Gennari modification of the Horner–Emmons olefination reaction (*Z*/*E* ratio of 95:5). The pure *Z*-isomer (71% over two steps) upon treatment with PTSA was cyclized to give the lactone (*R*)-**20** (95%). The cross-metathesis reaction of the lactone (*R*)-**20** with 5-phenyl-pent-1-en-3-one **13** in the presence of a Grubbs' IInd generation catalyst gave enantiomerically pure (*R*)-rugulactone **1** (75%) (**Scheme 3**).

Ducrot's approach (2010)[6]

Ducrot *et al* have described the synthesis of rugulactone (**1**) from commercially available (2*S*)-glycidyl tosylate **21** and 3-phenylpropanal. First, the tosylate moiety in **21** was displaced by using lithiated 1,3-dithiane (*n*-BuLi, 1,3-dithiane, THF, –78 °C) to give the corresponding thioacetal. The epoxide ring was then opened by Cu-catalyzed Grignard vinylation (vinylMgBr, CuI, THF, –60 °C; 65% from **21**), which gave the secondary homoallylic alcohol **22.** It was protected as its triethylsilyl ether (TESCl, imidazole, DMAP, DMF; 98%) to give the cross-metathesis precursor **23**. The cross-metathesis coupling reaction of **23** and **13** (5 mol% Grubbs IInd catalyst, CH_2Cl_2, reflux) gave the desired intermediate **24** in 72% yield. Removal of the thioacetal group from dithiane **24** was then performed cleanly (methyl iodide, calcium carbonate, aqueous acetonitrile) to give the crude aldehyde which was immediately subjected to Still–Gennari olefination [methyl *P*,*P*-bis(2,2,2-trifluoroethyl)phosphono acetate, potassium hexamethyldisilazide, 18-Crown-6, THF, –78 °C) to give the (*Z*)-α,β-unsaturated ethyl ester **25** in 52% overall yield from **23**, with a *Z*/*E* ratio of 97:3.

Finally, one-pot deprotection and intramolecular lactonization of **25** (80% AcOH) gave rugulactone **1** in 86% yield (30% overall yield from **21**) (**Scheme 4**).

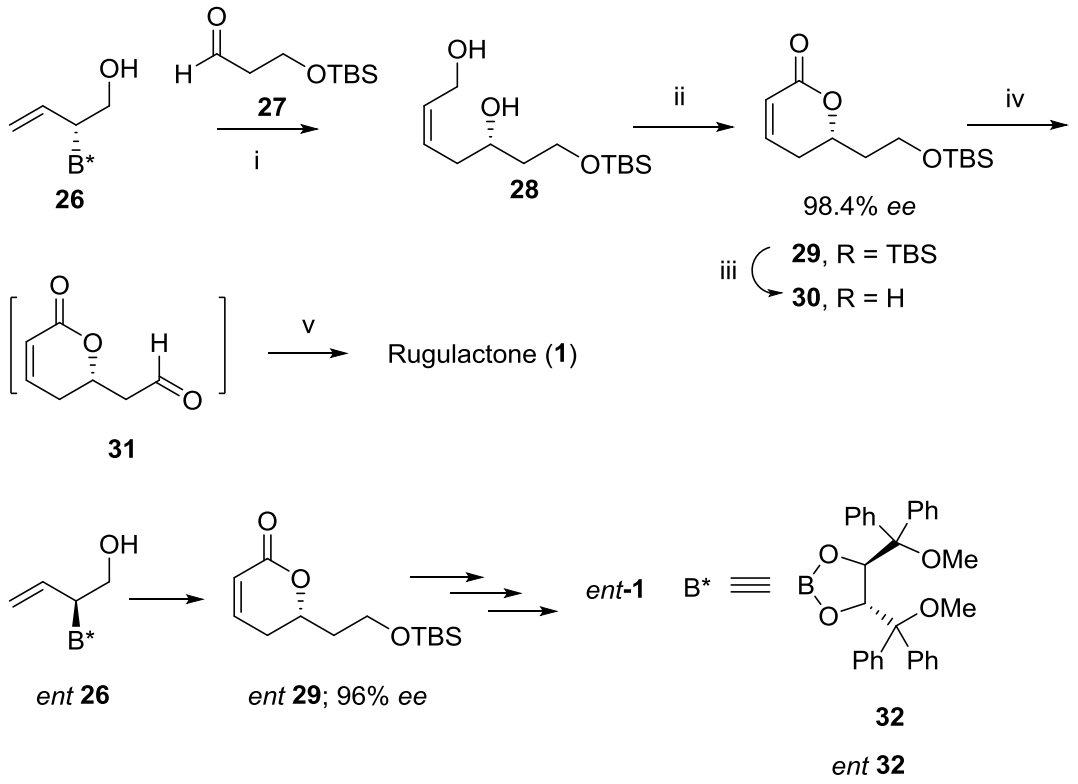


Scheme 4. (i) *n*-BuLi, 1,3-dithiane, THF, -78 ^{o}C; (ii) H_2C=CHMgBr, CuI, THF, -40 ^{o}C, 65% (over two steps) (iii) TESCl, imidazole, DMAP, DMF, 0 ^{o}C 98%; (iv) $PhCH_2CH_2COCH=CH_2$, Grubbs' IInd (5 mol%), CH_2Cl_2, reflux 72%; (v) $CaCO_3$, MeI, CH_3CN/H_2O (9:1); (vi) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, KHMDS, 18-Crown-6, THF, -78 ^{o}C, (52% over two steps). (vii) AcOH, 60 ^{o}C, 24 h, 86%.

Pietruszka's approach (2011)[7]

Pietruszka *et al*. have described the stereoselective total synthesis of both enantiomers of rugulactone **1** by applying enantioselective allyl additions as key steps. Two different strategies based on highly stable and enantiomerically pure α-substituted allylboronic esters **26** and ent **26** were performed starting from boronic ester **32**. The subsequent addition of reagent **26** to aldehyde **27** gave 1,5-ene-diol **28** in 93% yield, with almost complete *Z*-selectivity (dr >20:1) and in excellent enantioselectivity (98.4%). The regioselective oxidation of diol **28** with $PhI(OAc)_2$ (BAIB) and TEMPO in CH_2Cl_2 produced lactone **29** (92%); the TBS-group was deprotected with $BF_3.OEt_2$ to obtain lactone **30** in 92% yield. The oxidation of lactone **30** with BAIB led to aldehyde **31** *in situ* which was directly subjected to HWE-olefination giving

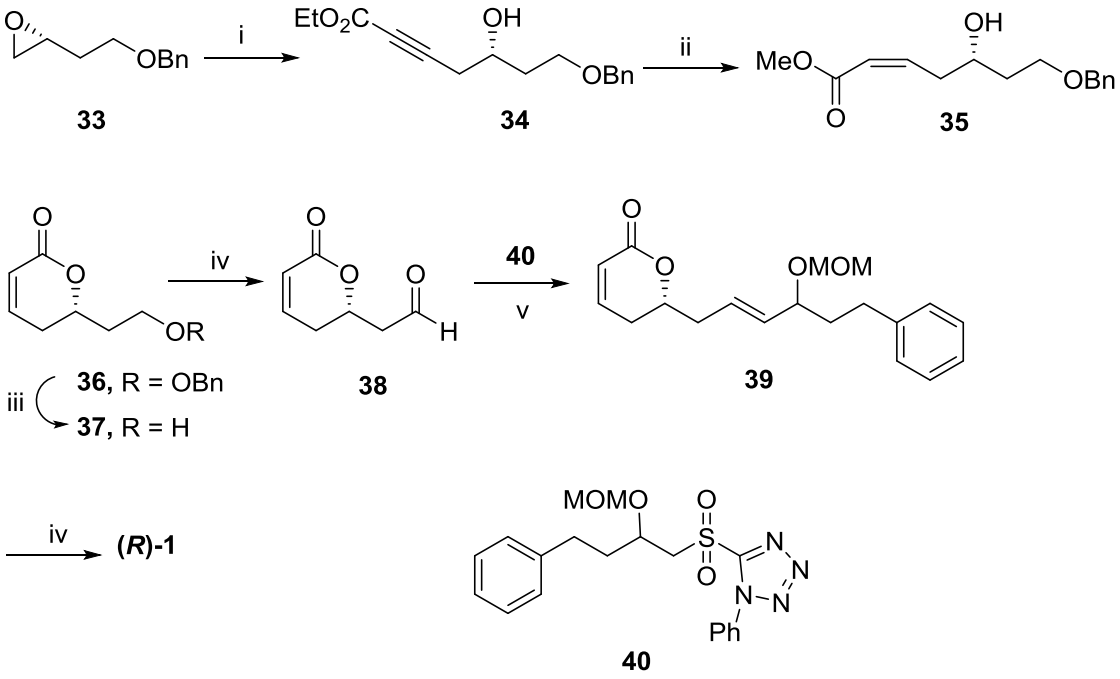
rugulactone (**1**) in 48% yield after two steps (38% yield after 5 steps starting from **26**). In a similar manner, (*S*)-rugulactone was obtained from *ent*-**26** (**Scheme 5**).



Scheme 5: (i) CH_2Cl_2, 0 ^oC, to 25 ^oC., 92% 98.4% ee; (ii) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 92% yield; (iii) $BF_3.OEt_2$, CH_2Cl_2, 0 ^oC, 92%; (iv) $PhI(OAc)_2$, TEMPO, CH_2Cl_2; (v) NaHMDS, -78 ^oC to rt 48% over two steps.

Barua's approach (2011)[8]

Barua *et al* have described a novel route for stereoselective total synthesis of (*R*)-rugulactone **1** starting from a substituted epoxide **33** and 3-benzylpropionaldehyde employing Julia-Kocienski olefination as a key step to construct (*E*)-configured *α,β*-unsaturated keto-group. The synthesis commenced by the Yamaguchi coupling of the known epoxide **33** with ethyl propionate affording the corresponding propargylic alcohol **34** in 93% yield.



Scheme 6: (i) Ethyl propionate, *n*-BuLi, $BF_3.OEt_2$, -78 ^oC, THF, 93%; ii) H_2, Lindlar catalyst, quinoline, EtOAc, 91%; iii) 3% HCl in methanol, 90%; iv) DDQ, CH_2Cl_2-H_20, 80%; v) DMP, dry CH_2Cl_2, 0 ^oC-25 ^oC.

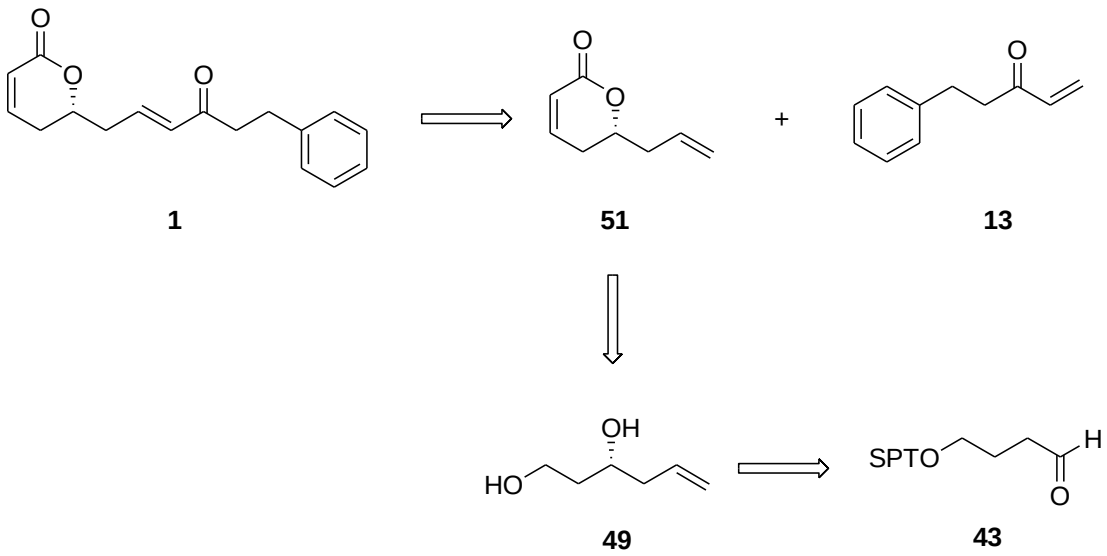
Subsequent selective hydrogenation of acetylenic compound **34** over Lindlar catalyst furnished the unsaturated ester **35**. Hydrolysis of the ester group of compound **35** proceeded with *in situ* lactonization to deliver the lactone **36**. Removal of the benzyl protecting group of compound **36** with 3% HCl furnished the -pyrone subunit **37**. The aldehyde **38** was prepared by oxidation of alcohol using Dess-Martin periodinane. The Julia-Kocienski olefination of crude aldehyde **38** with the the sulfone **40** under basic (KHMDS) conditions afforded intermediate compound in 65% yield. The MOM group deprotection of **39** and subsequent oxidation of the resulting crude alcohol with IBX furnished the target molecule **1** in 92% yield (**Scheme 6**).

2.1.3 Present Work

2.1.3.1 Objective

Reported methods for the synthesis of (*R*)-Rugulactone **1**, employ the use of stoichiometric amount of chiral auxillary, for the generation of chirality, longer reaction sequences and are not atom-economical.

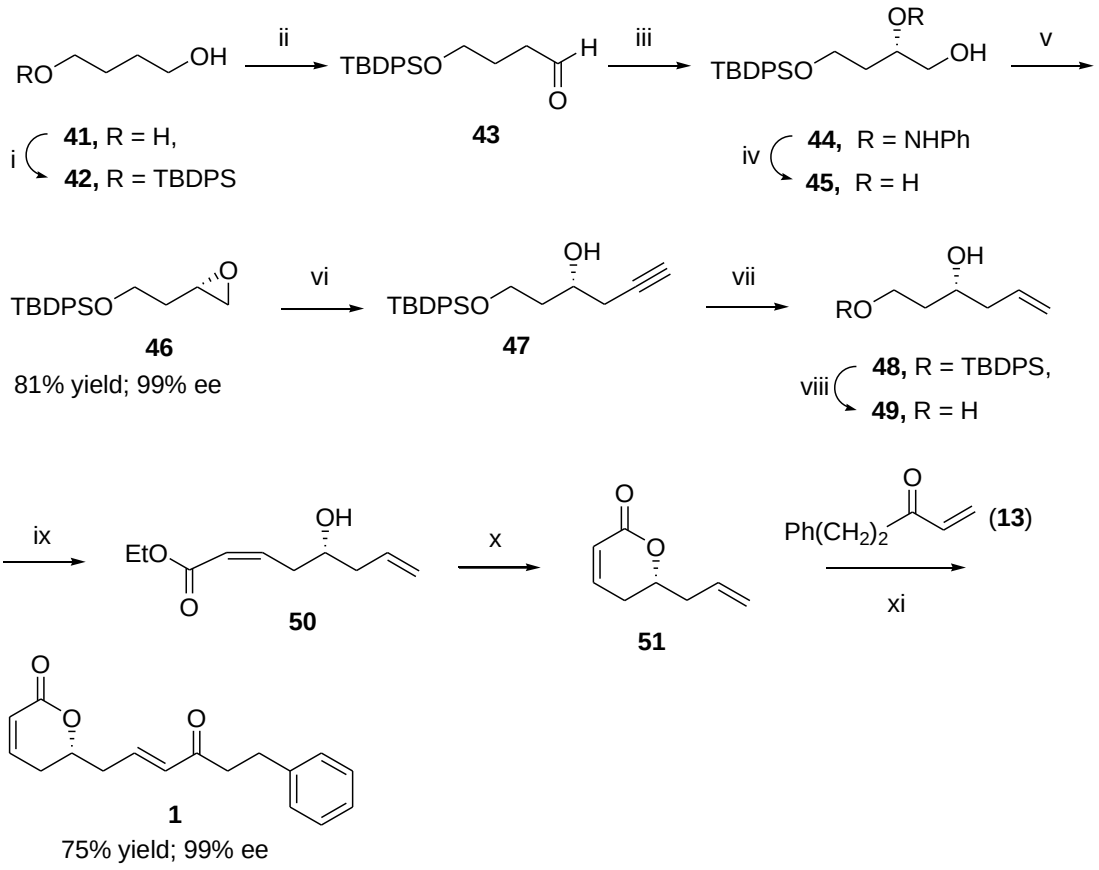
Organocatalytic asymmetric synthesis has provided several new methods for obtaining chiral compounds.[9] In particular, proline, an abundant, inexpensive amino acid available in both enantiomeric forms has emerged arguably as the most practical and versatile organocatalyst.[10] In continuation of our work on proline-catalyzed synthesis of bioactive molecules, in this section, a facile synthesis of **1**, whose activity makes it an attractive synthetic target is described. The retrosynthetic analysis of **1**, wherein proline-catalyzed α-aminoxylation[11] reaction constitutes the key step for the introduction of chirality, is presented in **Scheme 8**. Evidently, 1,3-diol **49** has emerged as the key intermediate in the synthesis of **1 (Scheme 7)**.



Scheme 7: Retrosynthetic analysis of (*R*)-Rugulactone (**1**)

2.1.3.2 Results and Discussion

Our synthesis of (*R*)-rugulactone **1**, as outlined in **Scheme 8**, commenced with selective monosilyl protection of 1,4-butanediol **41** to give alcohol **42**, followed by its oxidation with Swern reagent giving aldehyde **43** in 96 % yield.



Scheme 8: (i) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC, 8 h, 86%; (ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 ^oC, 2 h, 96%; (iii) PhNO, D-proline (10 mol %), DMSO, 25 ^oC, 30 min. then $NaBH_4$, MeOH; (iv) 10% Pd/C, H_2 (1 atm), MeOH, 12 h, 87% (over two steps); (v) (a) *p*-TsCl, cat. Bu_2SnO, Et_3N, DMAP, CH_2Cl_2, 0-25 ^oC, 1.5 h; (b) K_2CO_3, MeOH 81%; (vi) LiC≡CH.EDA, DMSO, 25 ^oC, 24 h, 90%; (vii) H_2 (1 atm), Lindlar's Pd- catalyst, toluene, 2 h, 93%; (viii) TBAF, THF, 25 ^oC, 6 h, 79%; (ix) (a) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 4 h, 75%; (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78 ^oC, 2 h, 78%; (x) *p*-TSA, benzene, 80 ^oC, 1 h, 91%; (xi) Grubb's-II generation Ru-catalyst (5 mol %), dry CH_2Cl_2, 40 ^oC, 12 h, 75%.

The ^{1}H NMR spectrum displayed a characteristic signal at δ 9.78 for aldehydic proton (-C**H**O) while its ^{13}C NMR spectrum showed a characteristic signal at δ 202.6 corresponding to the aldehydic carbonyl carbon (H-**C**=O) (**Fig. 2**).

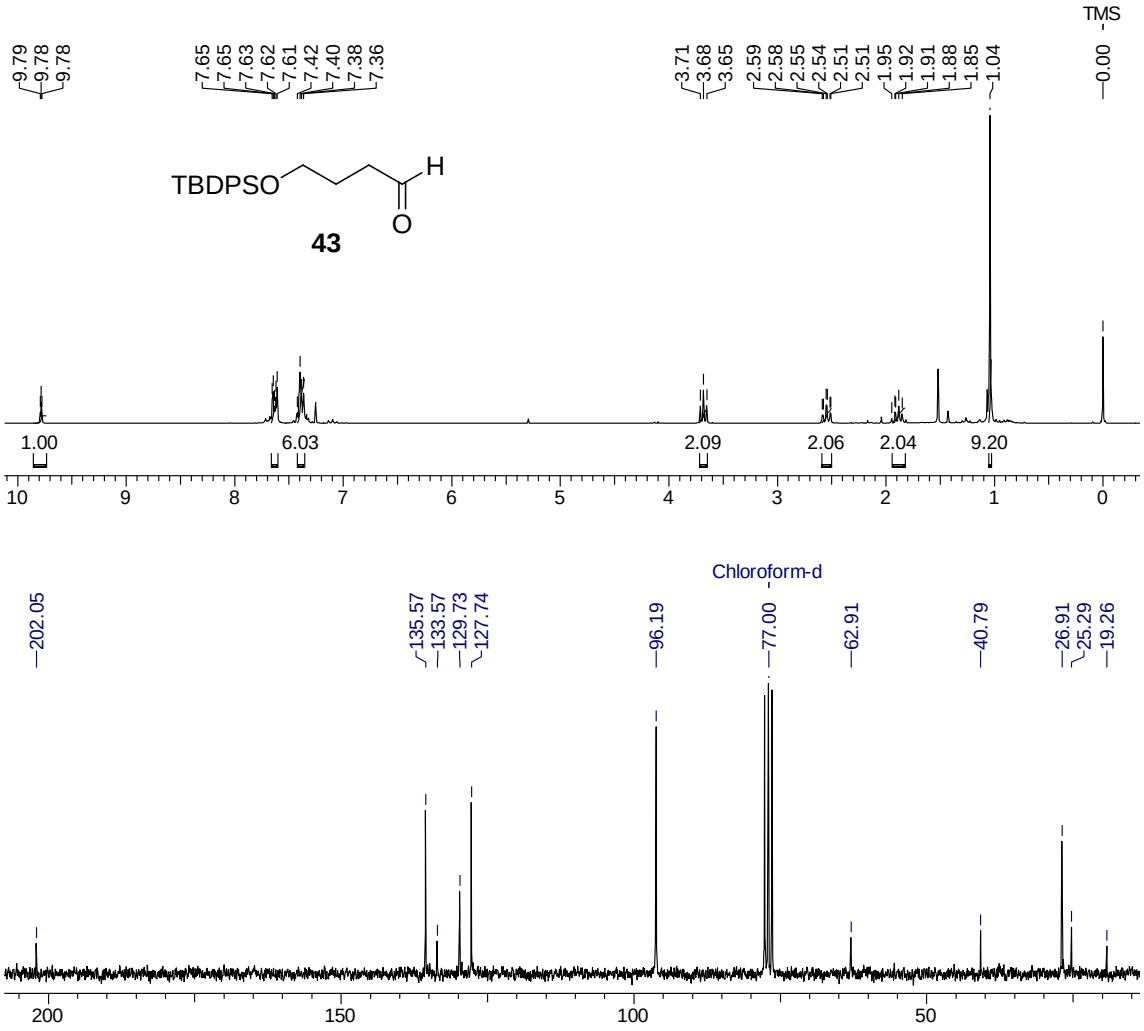


Fig. 2: ^{1}H and ^{13}C NMR spectra of 4-(*tert*-Butyldiphenylsilanyloxy)-butan-1-al **43**

Aldehyde **43** was then subjected to D-proline-catalyzed asymmetric α-aminoxylation followed by *in situ* reduction of aminoxy aldehyde with $NaBH_4$ in methanol gave the aminoxy alcohol **44**, which was subsequently subjected to hydrogenolysis without purification [10% Pd/C, H_2 (1 atm), MeOH] to furnish the chiral diol **45** in 87% yield (for two steps) and 99% ee (HPLC analysis). The formation of diol **45** was confirmed by its ^{1}H NMR spectrum, which showed a multiplet at δ 3.84-4.02 (3H)

corresponding to methylene (-C**H**$_2$-OH) and methine (-C**H**-OH) protons respectively. This was further ascertained by its ^{13}C NMR spectrum, which displayed two characteristic carbon signals at δ 62.1 and 66.6 corresponding to methylene (-**C**H$_2$-OH) and methine (-**CH**-OH) carbons attached to the oxygen atom respectively (**Fig 3**).

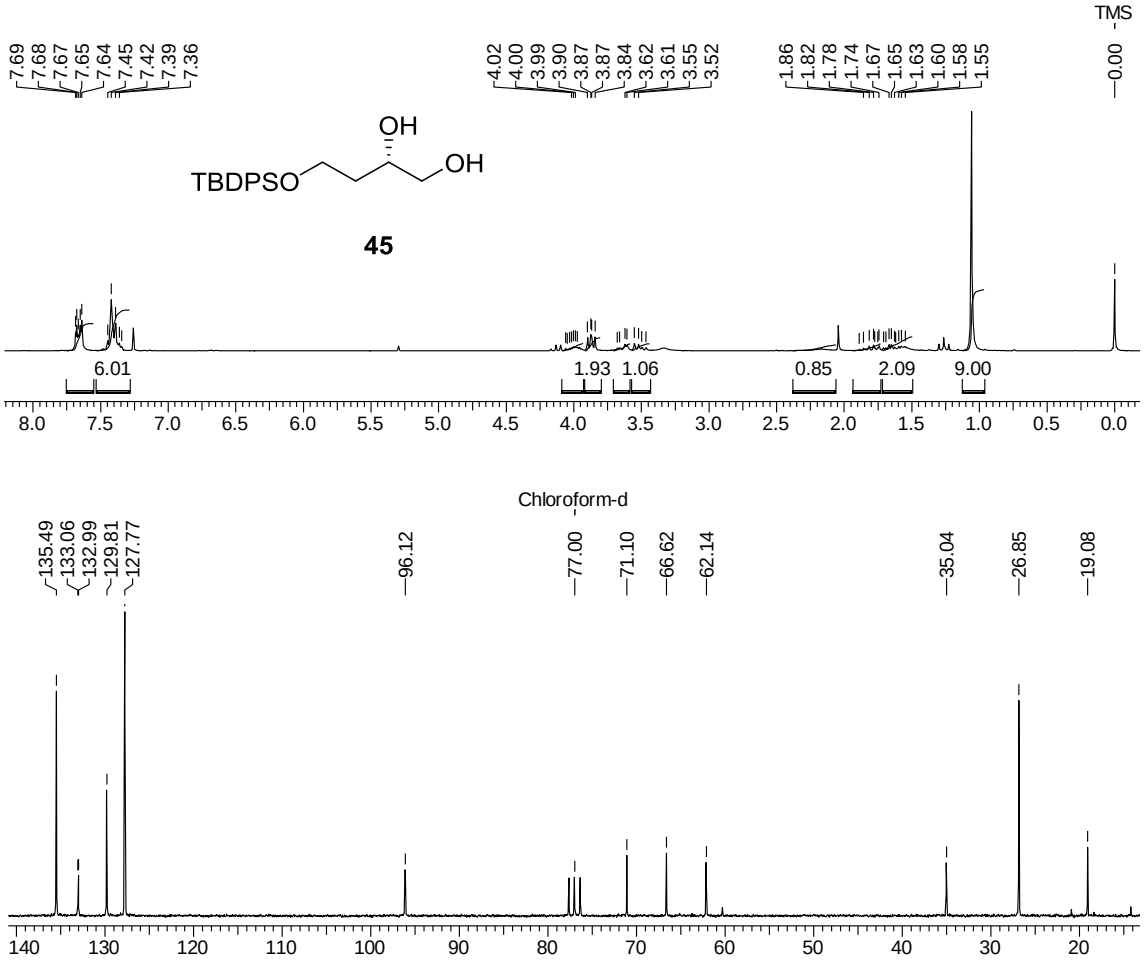
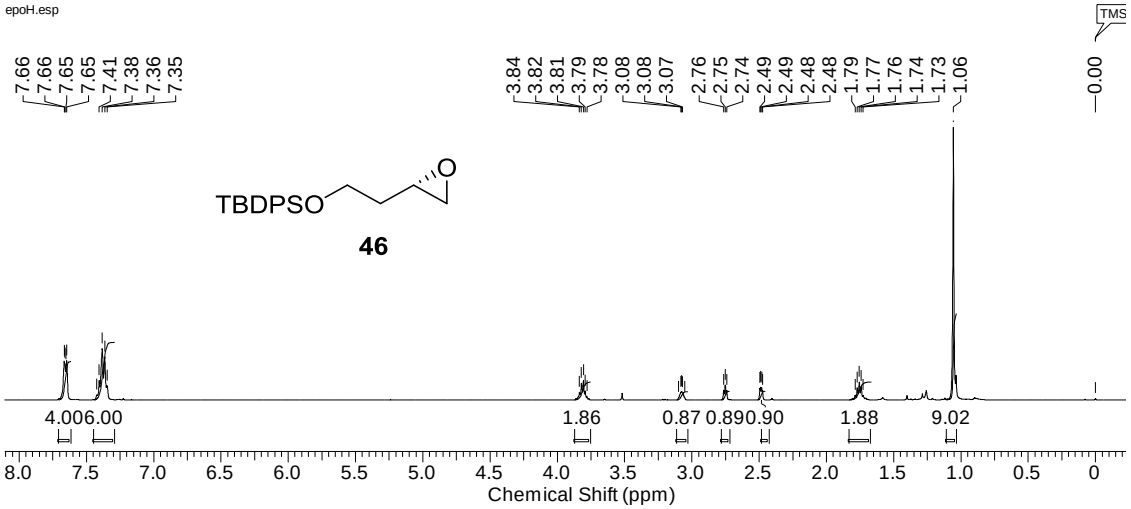
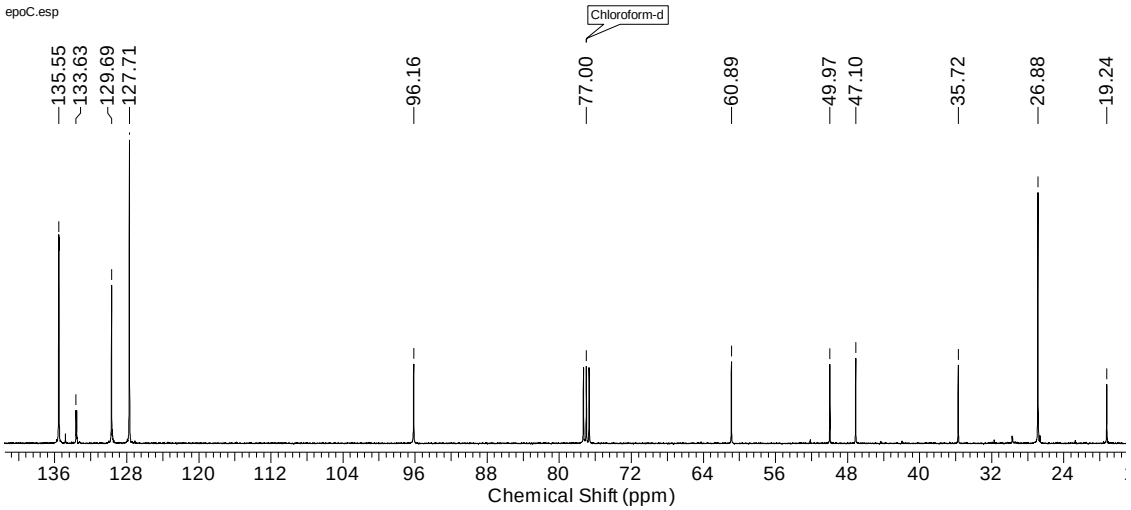


Fig. 3: ^{1}H and ^{13}C NMR spectra of 4-(*tert*-Butyldiphenylsilanyloxy)-butan-1,2-diol **(45)**

Diol **45** was smoothly converted to the corresponding epoxide[12] **46** in 81% yield *via* two- step reaction sequence: (i) selective monotosylation and (ii) base-induced epoxide formation. The formation of epoxide **46 {**$[\alpha]_D^{25}$ -8.8 (*c* 3.0, $CHCl_3$)} was confirmed by the presence of multiplets at δ 2.48-2.49 (m, 1H); 2.74-2.76 (t, *J* = 3.9





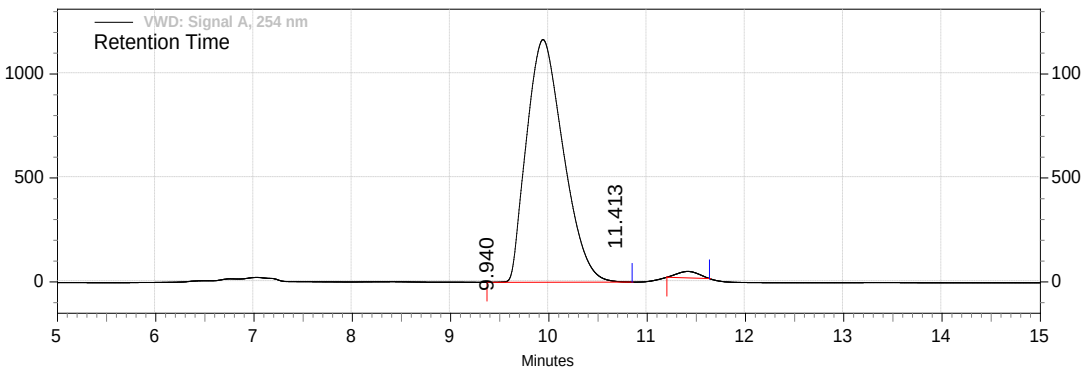


Fig. 4: ^{1}H, ^{13}C NMR and HPLC chromatogram of (2-(oxiran-2-yl) ethoxy) (*tert*-butyl) diphenylsilane **(46)**

Hz, 1H) and 2.87-2.90 (m, 1H) for the oxirane methylene (-C**H**$_2$O-) and methine (-C**H**O-) protons respectively. Its ^{13}C NMR displayed two characteristic carbon signals at δ 47.1 and 49.9, due to carbons attached to oxygen atom. The HPLC chromatogram showed ee > 98% for the epoxide **46** (**Fig. 4**).

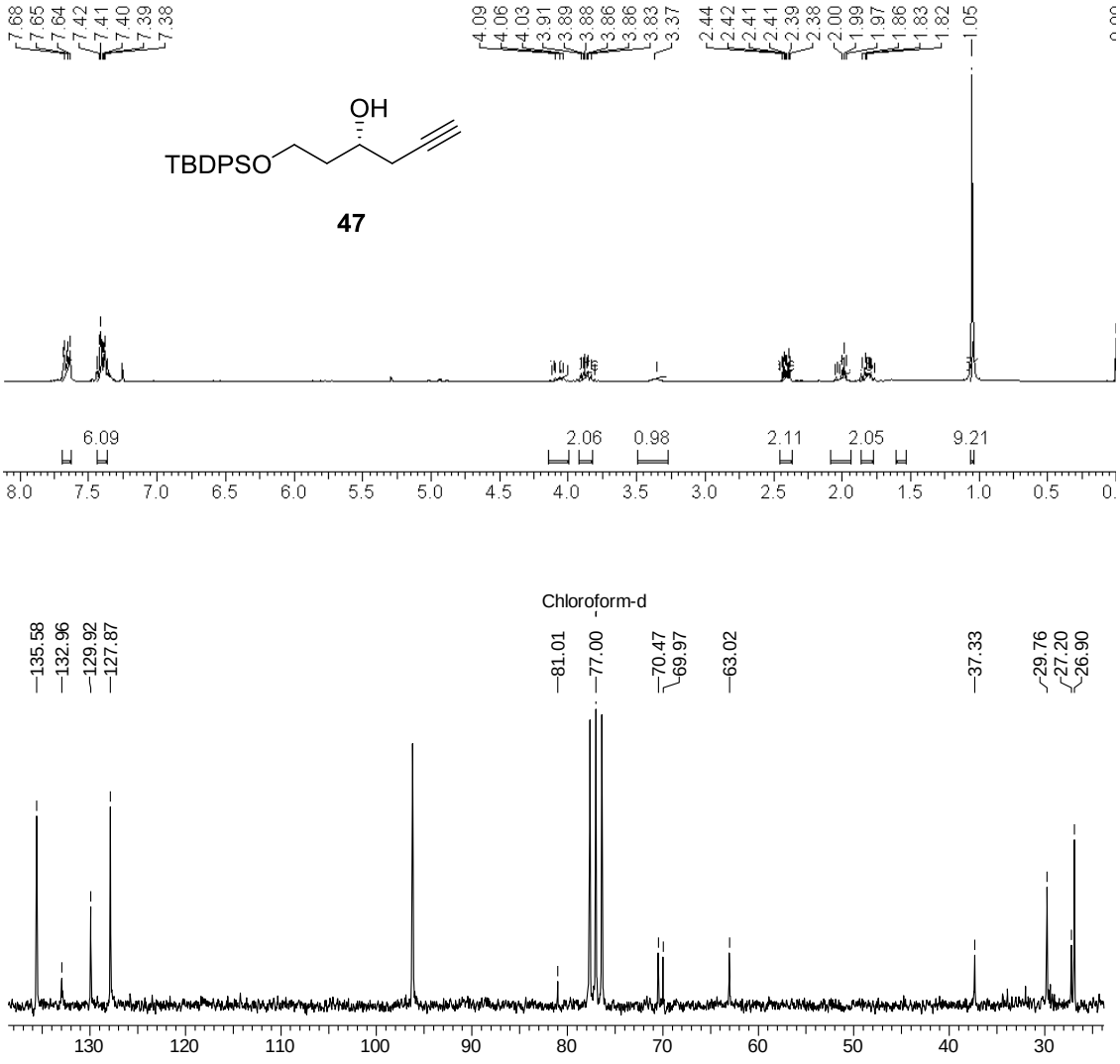


Fig. 5: ^{1}H and ^{13}C NMR spectra of 3-hydroxy-1(-*tert*-butyldiphenylsililoxy) hex-1-yne **(47)**

Regioselective ring opening of epoxide **46** with lithium acetylide[13] gave the homopropargylic alcohol **47** in 90% yield. The ^{1}H NMR spectrum of **47** showed characteristic alkyne proton signal at δ 1.99 (m, 1H) and 2.38-2.44 (m, 2H) for the propargylic methylenic protons. The carbon signals at δ 69.9, 81.0 and 70.4 in its ^{13}C

NMR spectrum were due to alkynic carbons and carbon attached to oxygen atom respectively (**Fig. 5**).

The partial catalytic hydrogenation[14] [Lindlar's catalyst, H_2 (1 atm), toluene] of alkyne **47** produced the corresponding alkene **48** in 93% yield. The characteristic proton peaks at δ 5.02 (s 1H), 5.10-5.13 (d, J = 4.2 Hz, 1H) and 5.72-5.93 (m, 1H) were due to the primary and secondary olefinic protons. Further, the disapperance of alkyne proton signal at δ 1.99 confirmed the alkene formation. The carbon signals at δ 117.4 and 135.5 in its ^{13}C NMR spectrum were due to primary and secondary alkenic carbons respectively (**Fig. 6**).

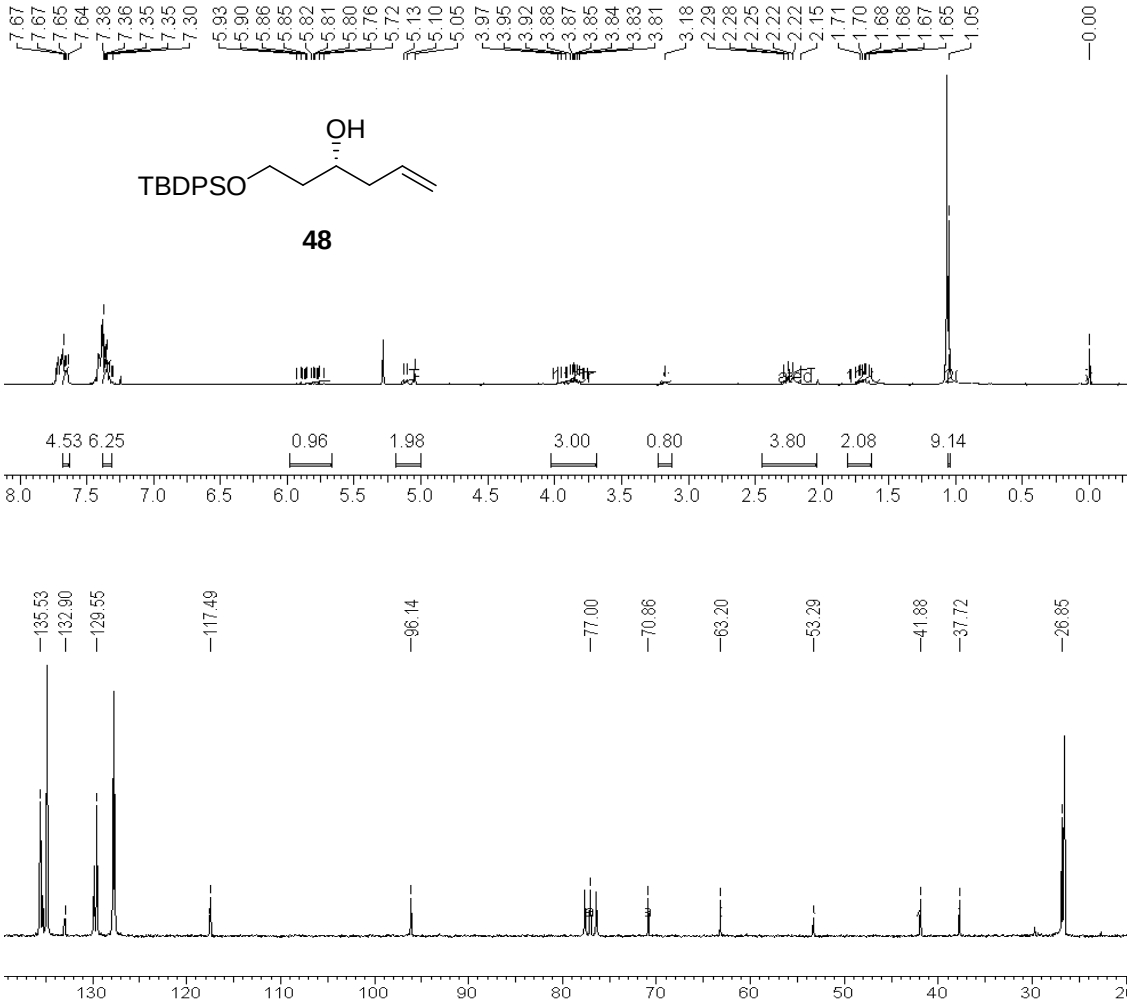


Fig. 6: ^{1}H and ^{13}C NMR spectra of alcohol **48**

The silyl group was then deprotected to give the diol **49** in 79% yield (TBAF, THF, 25 ^{o}C). The diol **49** was confirmed by the appearance of a characteristic peaks at δ 3.18 and 2.15 for the alcoholic (-O**H**) protons. Further, it was substantiated by the disappearance of *tert*-butyl and aromatic protons at δ 1.05 and δ 7.30-7.67 respectively (**Fig. 7**).

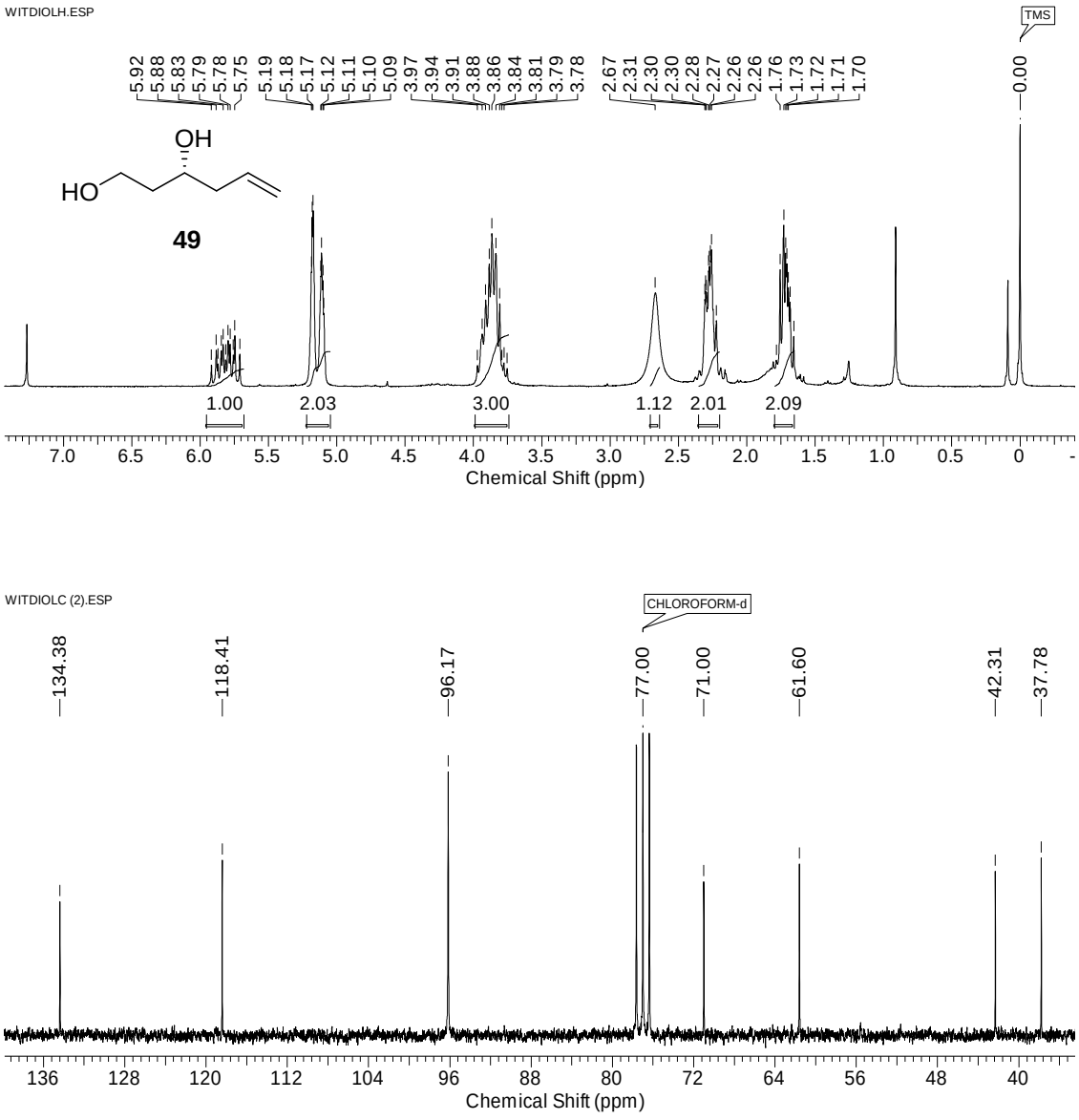


Fig. 7: ^{1}H and ^{13}C NMR spectra of 1,3-dihydroxy hex-5-ene **49**

The primary alcohol **49** was subjected to oxidation under TEMPO/BAIB condition to give the corresponding aldehyde in 75% yield. The crude less stable aldehyde was immediately treated with Stille-Gennari[15] reagent [$EtO_2CCH_2P(O)(OCH_2CF_3)_2$] to afford *cis*- α, β-unsaturated ester **50** in 78% yield (with *E*/*Z* ratio = 5:95). The formation of ester **50** was confirmed by its ^{1}H NMR spectrum, which showed proton resonance signals at δ 6.32-6.41 (dt, *J* = 3.8 and 8.3 Hz, 1H), 5.87 (d, *J* = 11.3 Hz, 1H) for the β- and α- alkenic protons respectively.

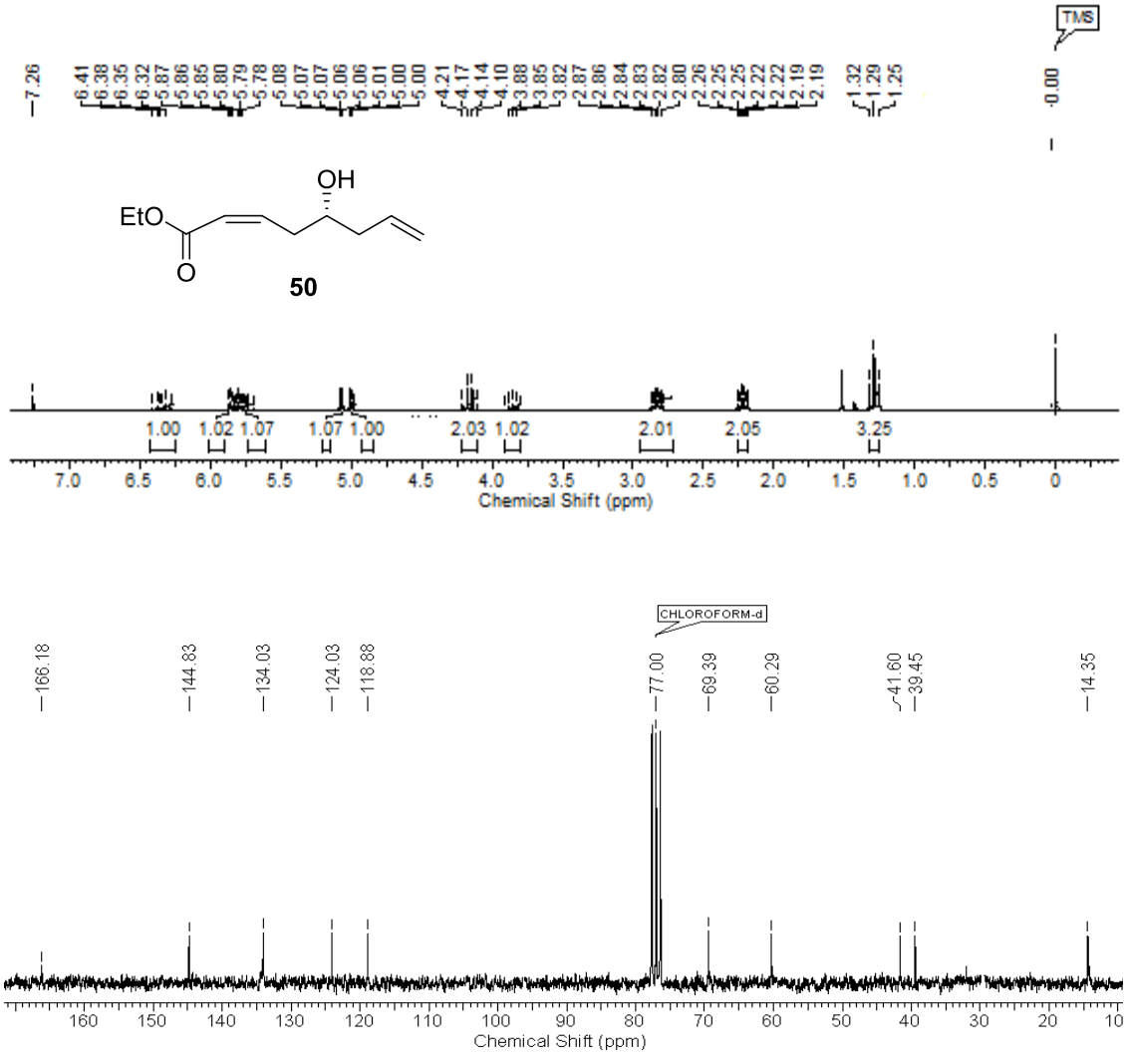
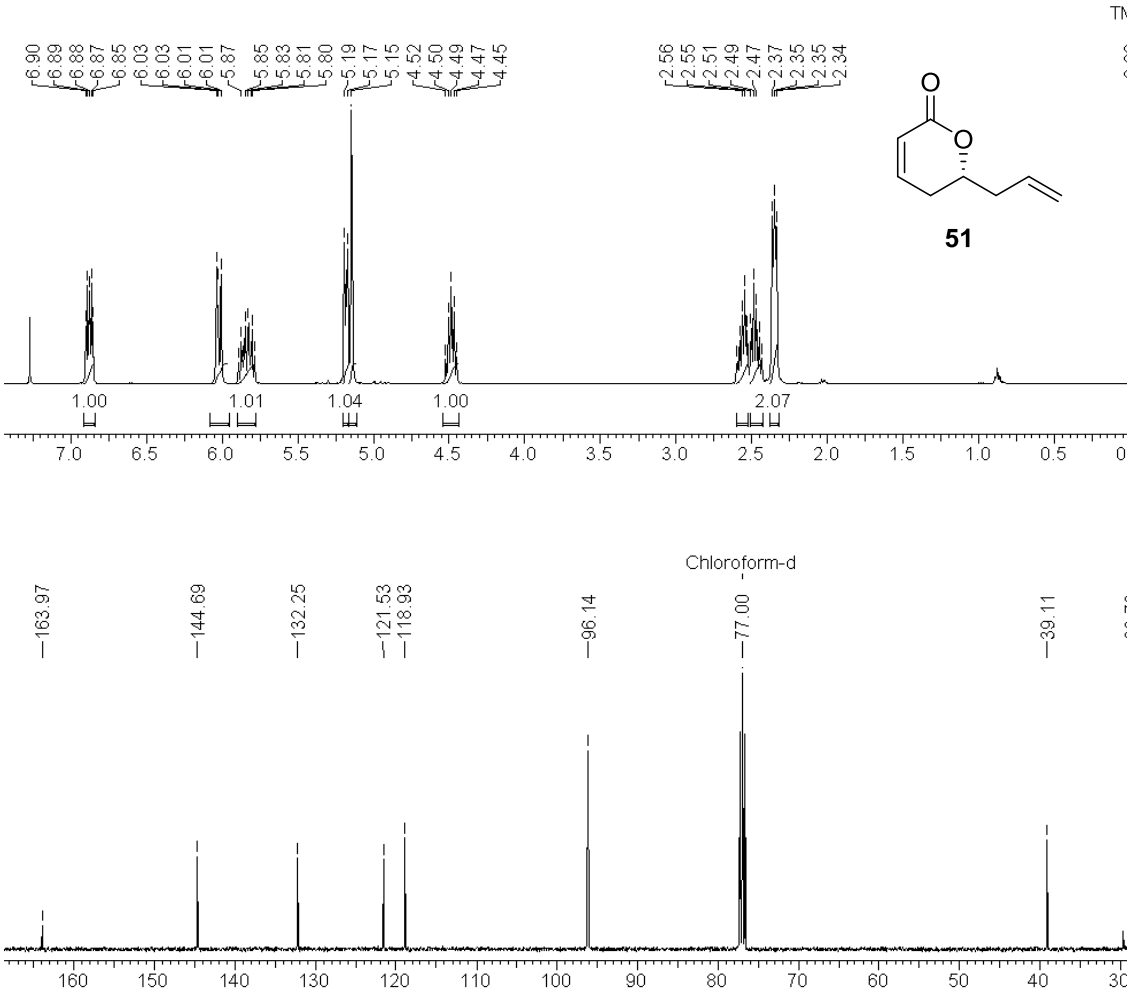


Fig. 8: ^{1}H and ^{13}C NMR spectra of (*R*,*Z*)-Ethyl 5-hydroxyocta-2,7-dienoate (*R*)-**(50)**

It was further confirmed by the appearance of signals at 4.16 (q, J = 7.8 Hz, 2H) and 1.29 (t, J = 7.5 Hz, 3H) corresponding to methylene and methyl protons respectively of the ester. Its ^{13}C NMR spectrum showed two carbon signals at δ 144.8 and 124.0 due to the carbons β- and α- to the ester group (**Fig. 8**). Its IR spectrum also displayed a characteristic vibrational frequency at 1724 cm^{-1} due to C=O group.

The α,β-unsaturated ester **50** was then subjected to intramolecular lactonization (*p*-TSA, benzene, 80 ^{o}C) to obtain lactone **51** in 91% yield. The disappearance of ethyl signal in the ^{1}H NMR spectrum of **51** confirmed the formation of lactone. The other two characteristic signals at δ 6.01-6.03 and 6.85-6.90 in its ^{1}H NMR spectrum indicated the presence of alkenic (-C**H**=C**H**-) protons present in conjugation with carbonyl group.



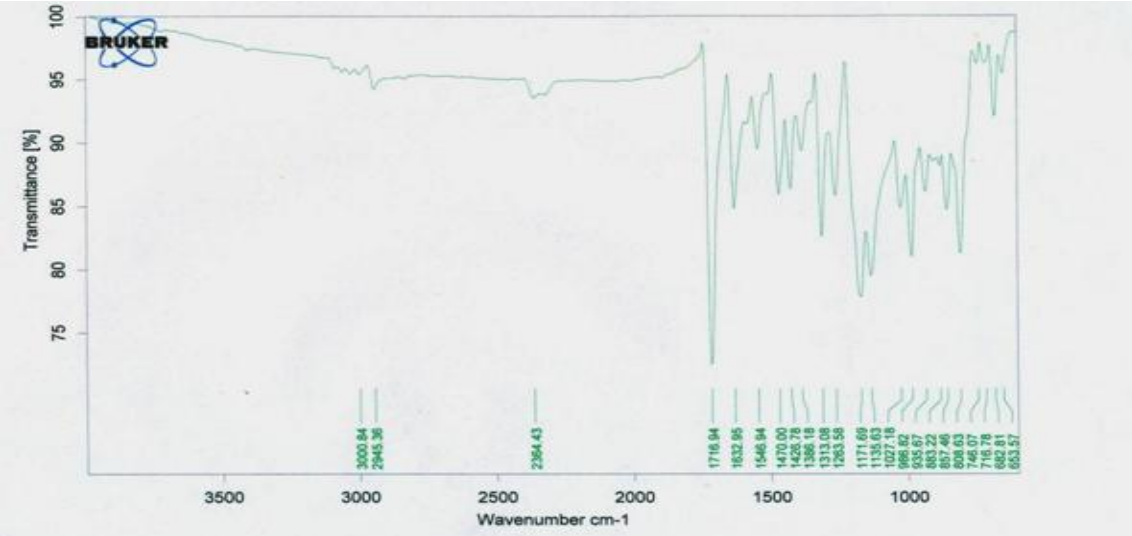
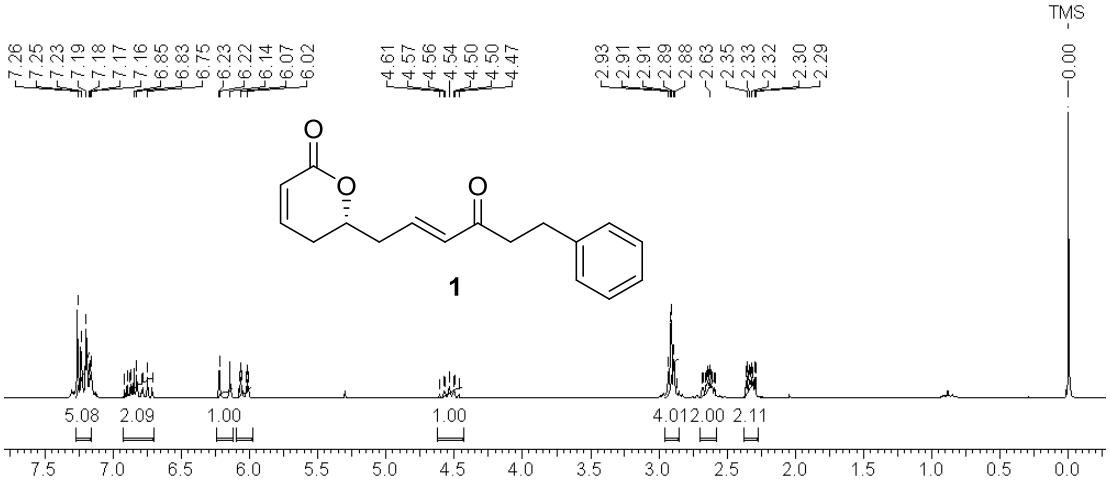
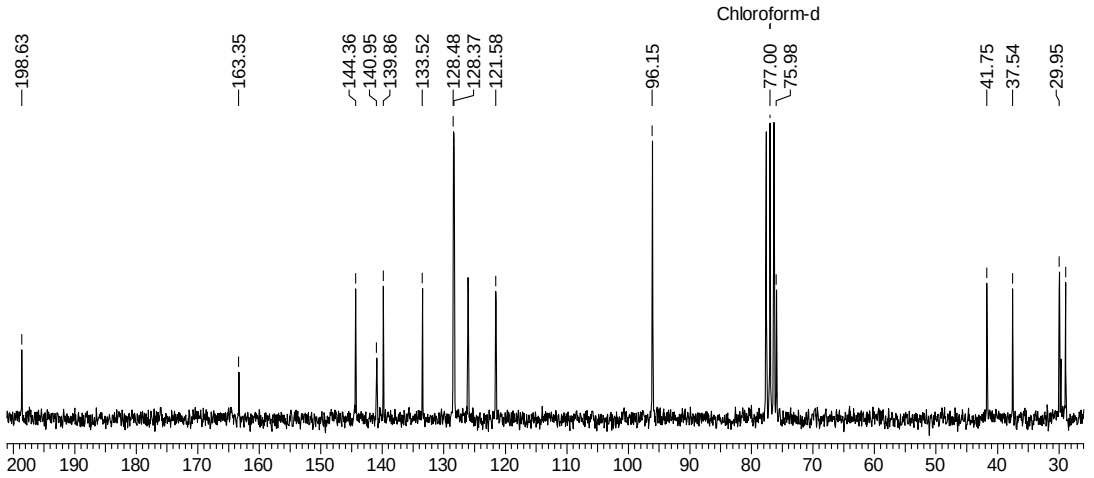


Fig. 9: ^{1}H ^{13}C NMR and IR spectra of (*R*)-6-Allyl-5,6-dihydro-2*H*-pyran-2-one (*R*)-**(51)**

In the ^{13}C NMR spectrum of **51**, the carbonyl carbon signal has shown upfield shift *i.e.* from δ 166.18 to 163.97 due to the transformation of ester to lactone. Its IR spectrum showed an absorption band at 1717 cm^{-1} that corresponds to the presence of five-membered lactone carbonyl moiety (**Fig. 9**). It was further subjected to Ru-catalyzed cross metathesis[16] with unsaturated ketone **13**[4] to produce the target molecule **1** as a colorless oil in 15 % overall yield and with 99% ee. {$[\alpha]^{25}_{D}$ -46.7 (*c* 1, $CHCl_3$); lit[5] $[\alpha]^{25}_{D}$ -46.9 (*c* 1, $CHCl_3$)}. The disappearance of terminal olefinic protons (-C**H**=C**H**$_2$-) at δ 4.49, 5.17 and 5.85 and the appearance of two new characeteristic signals at δ 6.02-6.23 in its ^{1}H NMR spectrum with the upfield shift confirmed the formation of alkenic protons (-C**H**=C**H**-COO-) in conjugation with the carbonyl group. The ^{1}H NMR spectrum of **1** displayed signals in the range δ 2.88-2.93 (m, 4H) and 6.75-7.26 (m, 5H) corresponding to the two new methylene (-C**H**$_2$C**H**$_2$-) unit along with aromatic protons respectively.





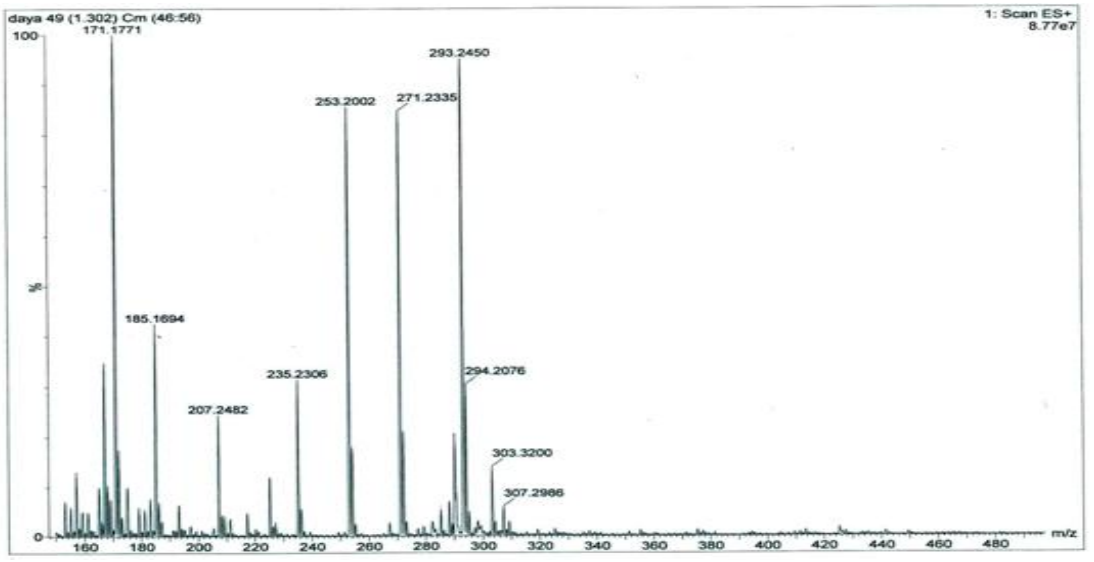


Fig. 10: ^{1}H, ^{13}C NMR and LCMS spectra of (*R*)-rugulactone (**1**)

Its ^{13}C NMR spectrum showed typical carbon resonance signals at δ 133.5, 144.3 and 198.6 corresponding to the new alkenic carbons (-C**H**=C**H**-COO-) and carbonyl carbon (C=O) functionality (**Fig. 10**).

2.1.4. Conclusion

In conclusion, an alternative, concise method has been developed successfully by the application of proline-catalyzed α-aminoxylation strategy for the synthesis of (*R*)-rugulactone **1**. The operationally simple reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline-catalyst that is available in both enantiomeric forms. The high overall yield (*via* α-aminoxylation; 15 %) and less number of steps render our approach a good alternative to the known methods.

2.1.5. Experimental

4-(*tert*-Butyldiphenylsilanyloxy) butan-1-ol (42):

To the stirred solution of 1,4-butane diol **41** (3 g, 33.33 mmol) in dry CH_2Cl_2 (80 ml), Et_3N (10.09g, 99.99 mmol) and DMAP (0.2 g 1.66 mmol) were added and the reaction mixture was cooled in ice bath, *tert*-Butyldiphenylsilyl chloride (9.149 g, 33.33 mmol) was added dropwise at 0 ^oC. After complete addition, the reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (monitored by TLC) it was diluted with CH_2Cl_2 (40 ml) and washed with water (2x10 ml). Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 2:8) yielding **42** as a colorless oil.

Yield: 86 %; colorless liquid; **IR** (neat, cm^{-1}): υ_{max} 703, 916, 1051, 2929, 3077, 3373; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.64-1.71(m, 4H), 3.62-3.72 (m, 4H), 7.36-7.40 (m, 6H), 7.63-7.68 (m, 4H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.26, 26.93,

29.34, 29.83, 62.64, 64.02, 127.72, 129.70, 133.63, 135.60; **Analysis:** $C_{20}H_{28}O_2Si$ required C, 73.12; H, 8.59; found C, 73.18; H, 8.27 %.

4-(*tert*-Butyldiphenylsilanyloxy)-butan-1-al (43)

DMSO (7.135g, 91.47 mmol) was added dropwise to the stirred solution of oxalyl chloride (7.007 g, 60.98 mmol) in CH_2Cl_2 (150 ml) at -78 ^oC. After stirring for 15 min., monoprotected alcohol **42** (10 g, 30.49 mmol) was added and stirring continued for additional 45 min. The reaction mixture was finally quenched by addition of triethylamine (12.31 g, 121.96 mmol) at -78 ^oC and stirred mixture for further 15 min. at same temperature and 30 min at the room temperature. The reaction mixture was then diluted by adding CH_2Cl_2 (100 ml) and washed with water (3x25 ml). Organic layer was separated and dried over anhydrous Na_2SO_4, evaporated under reduced pressure and chromatographed over silica gel (60-120 mesh) yielding pure aldehyde **43**.

Yield: 99%; pale yellow liquid; **IR** (neat, cm^{-1}): υ_{max} 822, 1467, 1725, 2859, 3003; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.82-1.95 (m, *J* = 6.9 Hz, 2H), 2.51-2.59 (dt, *J* = 5.5 Hz, 2H), 3.65-3.71 (t, *J* = 5.9 Hz, 2H), 7.36-7.65 (m, 10 H), 9.78-9.79 (d, *J* = 1.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.24, 25.26, 26.88, 40.76, 62.89, 127.71, 133.54, 135.54, 202.02; Analysis: $C_{20}H_{26}O_2Si$ required C, 73.57; H, 8.03; found: C, 73.15; H, 8.05%.

4-(*tert*-Butyldiphenylsilanyloxy) butan-1,2-diol (45)

To the solution of **43** (9.7 g, 29.75 mmol) in dry DMSO (60 ml) was added nitrosobenzene (2.9 g, 26.78 mmol) followed by D-proline (343 mg, 2.975 mmol) at 25 ^oC. and stirred for 30 min. Then $NaBH_4$ (2.5 equiv.) gradually added stirred for 1 h. In the end the reaction mixture was quenched with the sat. solution of NH_4Cl in water (4 ml) at 0 ^oC and extracted with EtOAc (3x25 ml), washed with brine (2X20

ml); organic layer was concentrated under vaccuo. The obtained residue was dissolved in MeOH to which Pd/C (60 mg) was added and stirred under H_2 (1 atm) at 25 ^oC, after complete reduction of aminoxy group (checked by TLC), the reaction mixture was filtered through celite, washed with MeOH, concentrated under vacuum and the residue was chromatographed on silica gel (60-120 mesh), pure diol **45** was obtained as colorless gum. **Yield** 78%; colorless gum; **IR** (neat, cm^{-1}): υ_{max} 701, 1107, 1466, 2360, 2859, 2930, 3415; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.58-1.84 (m, 2H), 3.46-3.64 (m, 2H), 3.81-3.87 (t, J = 8.1 Hz, 2H), 3.94-3.98 (m, 1H), 7.36-7.67 (m, 10H), **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.14, 26.91, 35.01, 62.20, 66.68, 71.15, 127.83, 129.87, 133.05, 135.55. **Analysis:** $C_{20}H_{28}O_3Si$ required C, 69.72; H, 8.19; found: C, 69.78; H, 8.13 %.

(2-(oxiran-2-yl) ethoxy) (*tert*- butyl) diphenylsilane (46)

Bu_2SnO (0.0075g, 0.03 mmol) and *P*-TSCl (4.753 g, 25.014 mmol) were added to the solution of diol **4**5 (7.8 gm, 45.48 mmol) in CH_2Cl_2, followed by the addition of Et_3N (4.6 g, 45.48 mmol) and DMAP (5 mol%) at 0 ^oC. The reaction mixture was slowly warmed to 25 ^oC and stirred for 1.5 h. After complete conversion (monitored by TLC), reaction mixture was diluted with CH_2Cl_2 (80 ml), washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Crude tosylate (7.6 g) was dissolved in MeOH (100 ml) and stirred with anhydrous K_2CO_3 (3.510 g, 21.39 mmol) for 30 min. at 0 ^oC. After the reaction was complete, it concentrated and the dissolved crude in EtOAc was washed with water and brine, dried over anhydrous Na_2SO_4, concentrated and chromatographed over silica gel (60-120 mesh). Pure epoxide **46** was obtained as a colorless oil (5.10 g,).

Yield: 81 %; colorless liquid; $[\alpha]_D^{25}$ -8.8 (*c* 3.0, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 789, 1158, 1274, 1442, 1626, 2937; **^{1}H NMR** (200 MHz, $CDCl_3$): δ (s, 9H), 1.73-1.79 (m,

2H), 2.48-2.49 (dd, *J* = 2.5 and 5.0 Hz, 1H), 2.74-2.76 (t, *J* = 4.7 Hz, 1H), 3.05-3.10 (quint, *J* = 6.2 and 8.78 Hz, 1H), 3.78-3.84 (m, 2H), 7.35-7.42 (m, 6H), 7.65-7.66 (m, 4H), **^{13}C NMR** (50 MHz): δ 19.24, 26.88, 35.72, 47.10, 49.17, 60.99, 127.71, 129.69, 133.63, 135.55. Optical purity: 99% ee from **HPLC analysis**: Column: Chiracel OD-H (4.6 X 250 nm), mobile phase: hexane/isopropyl alcohol (4/96), flow rate: 0.5 mL/min, retention time: 9.940 min (-)-isomer, 11.413 min (+)-isomer; **Analysis:** $C_{20}H_{26}O_2Si$ required C, 73.57; H, 8.03; found: C, 73.68; H, 8.15%.

3-Hydroxy-1(-*tert*-butyldiphenylsililoxy)hex-1-yne (47)

Lithium acetylide.EDA complex (2.82 g, 30.67 mmol) in dry DMSO (15 ml) was stirred with epoxide **46** (5 g, 15.34 mmol) for 1 h. at 25 ^{o}C. After completion of the reaction, it was quenched with ice and extracted with EtOAc (2x50 ml) washed with brine, organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography of crude product using EtOAc/hexane (1:9) as eluent yielded the homopropargylic alcohol **47** (4.58 g).

Yield: 89%; colorless liquid; **IR** (neat, cm^{-1}): υ_{max} 850, 1145, 1430, 2867, 3075, 3125; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.76-1.86 (m, 2H), 1.97-2.00 (t, J = 2.65 Hz, 1H), 2.38-2.44 (m, 2H), 3.78-3.96 (m, 2H), 4.0-4.13 (quint, *J* = 6.32 and 12.38 Hz, 1H), 7.34-7.44 (m, 6H), 7.64-7.71 (m, 4H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.1, 26.87, 29.74, 37.30, 62.99, 69.94, 70.44, 80.98, 127.84, 129.90, 132.93, 135.55. **Analysis:** $C_{22}H_{28}O_2Si$ required C, 74.95; H, 8.01; found: C, 75.01; H, 8.14 %.

1,3-dihydroxy hex-5-ene (49)

A solution of **47** (4.5 g, 12.78 mmol) in tolune was stirred under the H_2 (1 atm) in presense of Lindlar catalyst (150 mg) catalyst for 2.5 h. When no alkyne observed on TLC, reaction mixture was filtered through celite, washed with MeOH, collected organic layer was evaporated under vaccum. The obtained crude monoprotected diol

48 was dissolved in dry THF (30 ml), to which 1 molar solution of TBAF (3.150 g, 14.06 mmol) in THF was added at 25 ^{o}C and the mixture stirred for 8 h. After complete conversion of the substrate (checked by TLC), reaction mixture was quenched with water (2 ml) at 0 ^{o}C and concentrated. The residue was dissolved in EtOAc and washed with brine, concentrated under vacuum and purified using silica gel (60-120 mesh) to five 1,3-diol (*R*)-**49** as a colorless oil (1.29 g, 88%).

Yield: 88%; colorless liquid; **IR** (neat, cm^{-1}): υ_{max} 742, 1214, 2927, 3018, 3404; **^{1}H NMR** (200 MHz, $CDCl_3$) : δ 1.66-1.78 (m, 2H), 2.22-2.31 (m, 2H), 2.67 (br s, 1H), 3.75-3.97 (m, 3H), 5.09-5.19 (m, 2H), 5.71-5.92 (m, 1H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 37.77, 42.29, 61.59, 70.99, 118.40, 134.37; **Analysis:** $C_6H_{12}O_2$ required C, 62.04; H, 10.41; found: C, 62.07; H, 10.18%.

(*R*, *Z*)-Ethyl 5-hydroxyocta-2,7-dienoate [(*R*)-50]

BAIB (4.99 g, 15.51 mmol) and TEMPO (162 mg, 1.04 mmol) were added to a stirred solution of **49** (1.2 g, 10.34 mmol) in CH_2Cl_2 at 25 ^{o}C and the mixture stirred for 4 h; The reaction was quenched with saturated solution of $Na_2S_2O_3$ in water (0.5 ml). The reaction mixture was diluted with CH_2Cl_2 (30 ml), washed with water, concentrated under vacuum to get crude aldehyde, which was used for the next reaction without purification. 60 % dispersion of NaH (448 mg, 13.30 mmol) in mineral oil was added to the stirred solution of ethyl P,P-*bis*-(2,2,2-trifluoroethyl)phosphonoacetate (3.496 g, 10.52 mmol) in dry THF (50 ml) at 0 ^{o}C; The resulting ylide solution was stirred for 45 min. at same temperature, and cooled to -78 ^{o}C. The crude aldehyde dissolved in dry THF (10 ml) was added dropwise and the stirring was continued for next 3 h. After completion of the reaction as per TLC, it was quenched with saturated NH_4Cl solution (2 ml) at 0 ^{o}C, concentrated under reduced pressure. Residue obtained was dissolved in EtOAc washed with water and brine, organic layer was evaporated under

vaccuo and purified using silica gel column chromatography (100-200 mesh, EtOAc/hexane 2:8) to obtain (*R*)-**50** as a oily colorless compound.

Yield: 78%; colorless liquid; **IR** (neat, cm^{-1}): υ_{max} 748, 1042, 1273, 1708, 2854, 2926; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.26–2.37 (m, 2H), 2.80–2.89 (m, 2H), 3.75 (s, 3H), 3.82 (br s, 1H), 4.44–4.53 (m, 1H), 5.12–5.19 (m, 2H), 5.78–5.86 (m, 1H), 5.87 (d, *J* = 11.2 Hz, 1H), 6.32 (dt, *J* = 3.41, 1H), **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.9, 41.8, 51.6, 70.4, 118.8, 121.7, 134.9, 146.3. **Analysis:** $C_{10}H_{16}O_3$ required C, 65.19; H, 8.75; found: C, 65.05; H, 8.68%.

(*R*)-6-Allyl-5,6-dihydro-2*H*-pyran-2-one [(*R*)-51]

A solution of hydroxy ester (*R*)-**50** (1.2 g, 6.63 mmol) in benzene was refluxed with *P*-TsA (57 mg, 0.331 mmol) with stirring for 1 h. When the starting material was consumed, reaction mixture was concentrated under reduced pressure, extracted in EtOAc and washed with the solution of Na_2CO_3 (0.5 ml, 10%). The organic layer was then dried over anhydrous Na_2SO_4, concentrated and the residue was chromatographed over silica gel (100-200 mesh, CH_2Cl_2/hexane 5:5) yielding (*R*)-**51** as a colorless oil. **Yield:** 91%; colorless liquid; **IR** (neat, cm^{-1}): υ_{max} 883, 1171, 1632, 1717, 2364, 2945, 3000; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34-2.37 (m, 2H), 2.44-2.60 (m, 2H), 4.45-4.52 (quint, *J* = 6.32 and 14.02 Hz, 1H), 5.15 (s, 1H), 5.17-5.19 (d, *J* = 6.02 Hz, 1H), 5.79-5.89 (m, 1H), 6.1-6.03 (dd, *J* = 6.1, and 9.03 Hz, 1H), 6.85-6.90 (m, 1H). **^{13}C NMR** (200 MHz, $CDCl_3$): δ 28.7, 39.1, 118.9, 121.5, 132.2, 144.6, 163.9; **Analysis:** $C_8H_{10}O_2$ required C, 69.54; H, 7.30; found: C, 69.48; H, 7.19%.

2.1.6.9 (*R,E*)-6-(4-Oxo-6-phenylhex-2-enyl)-5,6-dihydro-2*H*-pyran- 2-one (*R*)-Rugulactone (*R*)-1

Grubbs' IInd catalyst (123.1 mg, 0.145 mmol) was added to a stirred solution of lactone (*R*)-**51** (200 mg, 1.45 mmol) and 5-phenylpent-1-ene-3-one **13** (693.173 mg,

4.347 mmol). Stirring was continued for 12 h at 45 ^{o}C, when complete starting material was consumed (checked by TLC). The reaction mixture was concentrated and purified by silica gel (100-200 mesh) chromatography (EtOAc/hexane 3:7) to yield (*R*)-**1** (293 mg,) as a colorless oil.

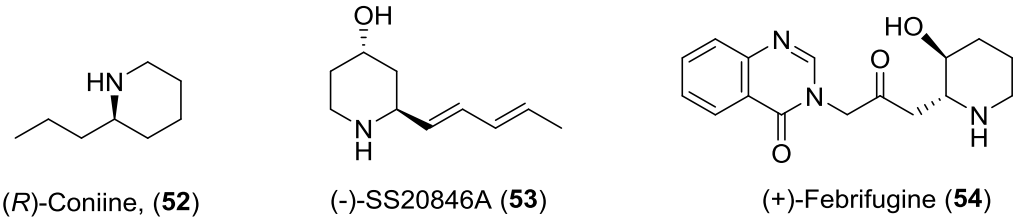
Yield: 75%; colorless oil; **IR** (neat, cm^{-1}): υ_{max} 746, 1040, 1245, 1494, 1717, 2856, 2925, 3020; $[\alpha]^{25}_{D}$ -46.7 (*c* 1, $CHCl_3$), lit[5] $[\alpha]^{25}_{D}$ -46.9 (*c* 1, $CHCl_3$). **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.29-2.36 (m, 2H), 2.59-2.68 (m, 2H), 2.87-2.93 (m, 4H), 4.47-4.61 (m, 1H), 6.01-6.07 (dt, *J* = 1.77, 3.66 and 9.73 Hz, 1H), 6.13-6.23(dt, *J* = 1.39, 2.78 and 15.92 Hz, 1H), 6.71-6.92 (m, 2H), 7.16-7.26 (m, 5H); **^{13}C NMR** (50 MHz): δ 28.9, 29.9, 37.5, 41.7, 121.6, 128.3, 128.4, 133.5, 139.8, 140.9, 144.3, 163.3, 198.6; **Analysis**: $C_{17}H_{18}O_3$ required C, 75.53; H, 6.71; found: C, 75.46; H, 6.69%; **LCMS (ESI):** m/z Calcd for $C_{17}H_{18}O_3Na$ $[M + Na]^+$, 293.1256; found, 293.2450.

SECTION II:

Enantioslective Synthesis of (*R*)-Coniine *via* Sharpless Asymmetric Dihydroxylation of Homoallylic Ester

2.2.1. Introduction and pharmacology

The substituted piperidines and ring-fused piperidines such as indolizidines are among the most ubiquitous heterocyclic building blocks in both natural products and synthetic compounds for their anaesthetic properties[17] and various other important biological activities.[18] Some of the important piperidine containing natural products and bioactive molecules include (*R*)-Coniine (**52**), (-)-SS20846A (**53**) and (+)-Febrifugine (**54**) (**fig. 11**). The interest in the piperidine alkaloids is well displayed by the wealth of published material detailing their sources and biological activities and their structure diversity makes them interesting targets for organic chemists.



(*R*)-Coniine, (**52**) (-)-SS20846A (**53**) (+)-Febrifugine (**54**)

Fig. **11**. Some of the important piperidine containing natural products and bioactive molecules.

(*R*)-(-)-Coniine (**52**), is a popular target for the demonstration of chiral methodology in the piperidine and indolizidine field. It is a poisonous hemlock alkaloid extracted from the plant *Conium maculatum L.* and from other tropical subspecies. Therefore, considerable efforts have been directed towards synthesizing them[19] in stereo- and enantioselective manner[20] and the interest in their chemistry remains unabated. (*R*)-coniine (**52**), the simplest members of piperidine alkaloids has attracted great interest from chemists as a representative target demonstrating the viability of the synthetic routes to piperidine derivaties.

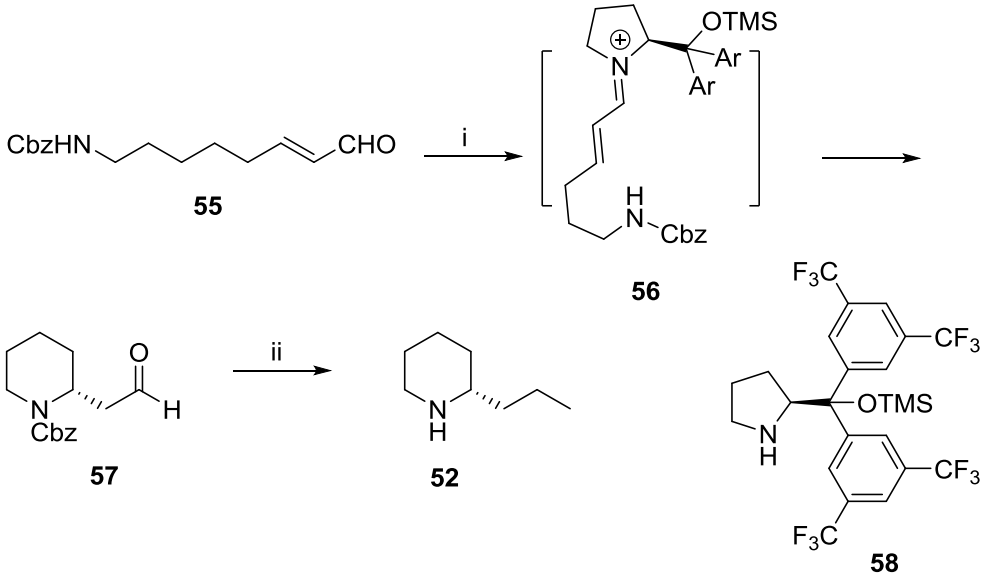
2.2.2. Review of Literature

Several approaches have been reported in the literature for the synthesis of racemic as well as optically active coniine. A few interesting and recent syntheses of coniine ((*R*)-(-)-**52**, and (*S*)-(+)-***ent*-52**), are described below.

Approches towards synthesis of (*R*)-/(*S*)-coniine

Fustero's approach (2007)[21]

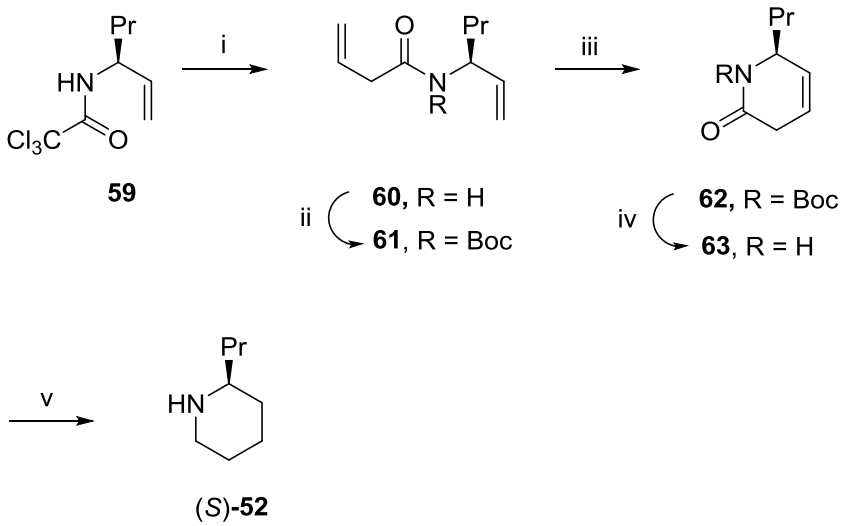
Fustero et al. have reported an intramolecular aza-Michael reaction as the key reaction for the synthesis of (S)-coniine (**52**). Thus, intramolecular aza-Michael reaction of carbamate **56** obtained from aldehyde **55** bearing remote α, β-unsaturated aldehydes as Michael acceptors in presence of catalyst **58** and phenyl acetic acid as additive furnished aldehyde **57,** which was subsequently transformed into (+)-coiniine (**52**) by Wittig homologation followed by hydrogenation of the double bond (**Scheme 9**).



Scheme 9: (i) Catalyst **19**, $PhCO_2H$, $CHCl_3$, -50 °C to -30 °C, 80%; (ii) PPh_3MeBr, ^tBuOK, THF; (iii) H_2 (1 atm), 10% Pd/C, EtOH, 25 ^oC, 12 h.

Richard's approach (2009)[22]

Richard *et al*. have reported the synthesis of (*S*)-coniine from hydrolysis of trichloroacetamide **59,** followed by DCC-mediated acylation with but-3-enoic acid giving **60** in 81% yield. The protection of amine **60** as NBoc gave **61**, followed by its RCM with 2.7 mol% Ru-catalyst, and subsequent TFA-mediated deprotection gave **63** in 52% overall yield. Alkene hydrogenation and reduction of amide group with $LiAlH_4$ gave (*S*)-coniine (**52**) (**Scheme 10**).

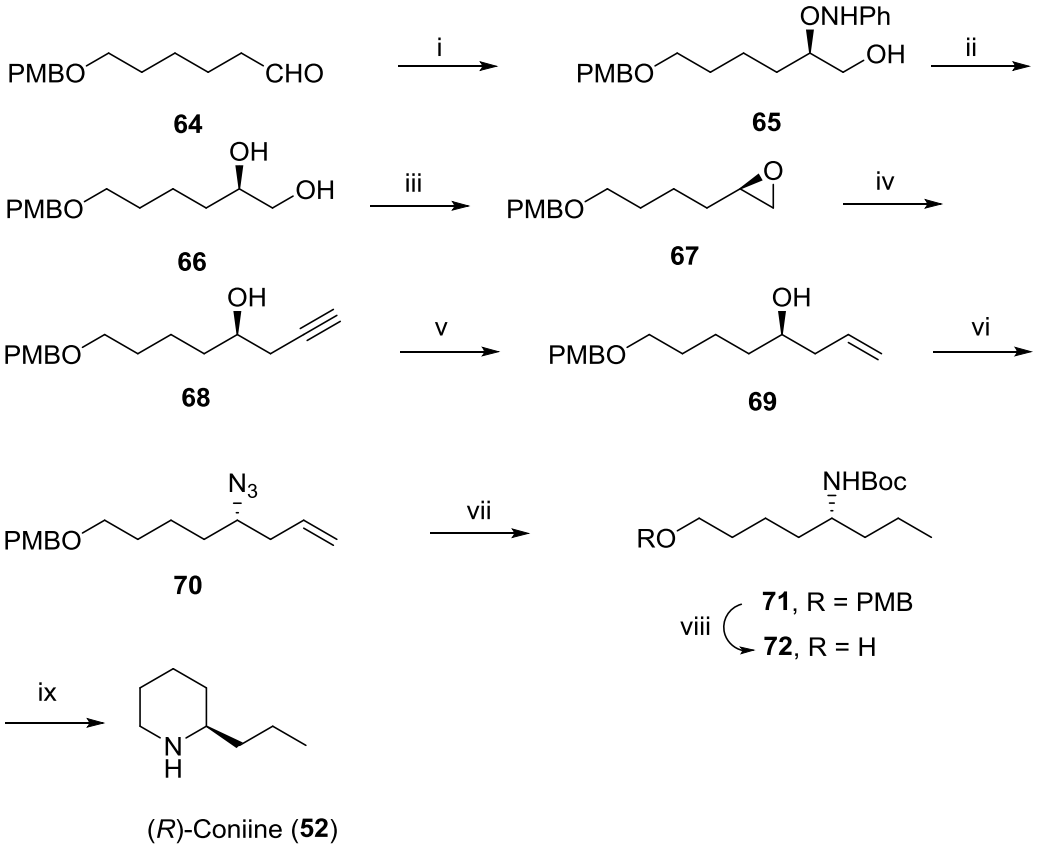


Scheme 10: (i) (a) NaOH, MeOH, 50 ^oC, 12 h; (b) but-3-enoic acid, DCC, CH_2Cl_2, 25 ^oC, 12 h, 81%; (ii) (a) NaH, THF; (b) $(Boc)_2O$, 50 ^oC, 20h, 56%; (iii) Grubbs' II cat. CH_2Cl_2, 25 ^oC, 12, 81%; (iv) TFA, CH_2Cl_2, -5 ^oC, 12 h, 74%; (v) (a) H_2 (1 atm), Pd/C (5%), MeOH, 25 ^oC, 12 h; (b) $LiAlH_4$, Et_2O, reflux, 16 h, (c) HCl, 80%.

Kumar's approach (2010)[23]

Kumar *et al*. have developed an organocatalytic approach for the synthesis of coniine **52** starting from aldehyde **64**, which on aminoxylation, $NaBH_4$ reduction and reductive hydrogenation gave the diol **66** in 71% yield and >95% ee. It was monotosylated selectively followed by its treatment with base gave epoxide **67** in 79% yield. Epoxide **67** on opening with lithium acetylide followed by partial

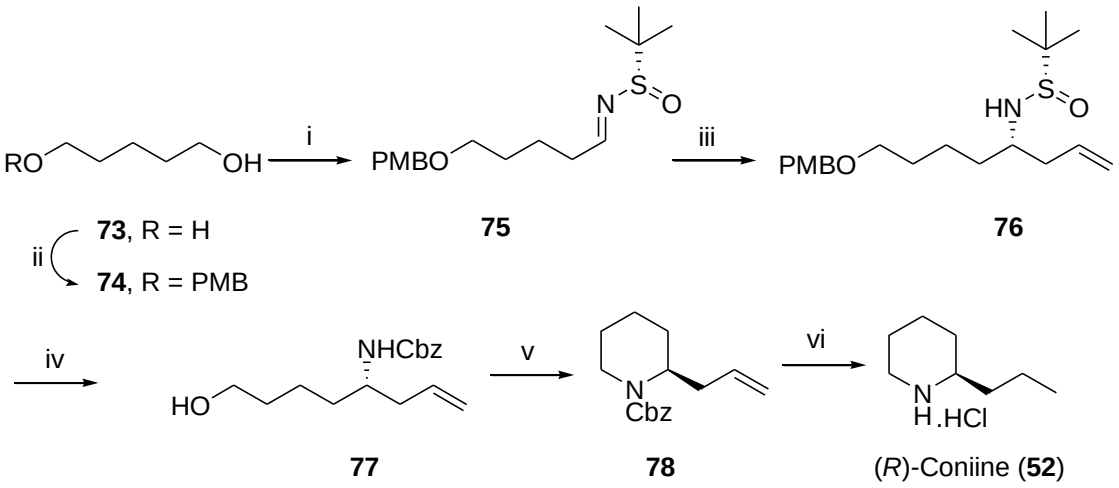
catalytic hydrogenation gave the homoallylic alcohol **69**. Alcohol **69** was then transformed to azide **70** *via* treatment with MsCl, and sodium azide in a sequential manner. It was converted into amine followed by its *in situ* protection as *tert*-butyl carbamate **71**. Finally the target molecule was achieved *via* PMB deprotection, mesylation and base treatement (**Scheme 11**).



Scheme 11: (i) (a) L-proline, nitrosobenzene, DMSO; (b) $NaBH_4$, MeOH, 71% (over two steps); (ii) H_2/Pd-C, EtOAc, 85%; (iii) (a) TsCl, Bu_2SnO, Et_3N; (b) K_2CO_3, MeOH, 79% (over two steps); (iv) Li. acetylide, DMSO, 82%; (v) H_2 (1 atm), Lindlar's catalyst, EtOAc, 90%; (vi) (a) MsCl, Et_3N, CH_2Cl_2; (b) NaN_3, DMF, 68% (over two steps); (vii) (a) H_2/Pd-C, $(Boc)_2O$, EtOAc; (b) DDQ, $NaHCO_3$, CH_2Cl_2: H_2O, 80% (over two steps); (viii) MsCl, Et_3N, 85%; (ix) NaH, -78 °C, HCl in methanol, 90%.

Das's approach (2011)[24]

Das *et al*. have reported an elegant method of stereoselective synthetic route to piperidine alkaloid i.e. (*R*)-coniine (**52**). Its synthesis was initiated by converting pentane-1,5-diol **73** into its PMB ether **74.** The alcohol **74** was oxidized with pyridinium chlorochromate (PCC) to give crude aldehyde which was condensed with (*S*)-*N*-*tert*-butanesulfinamide in the presence of (anhydrous $CuSO_4$) to give the corresponding (*S*)-(*N*-*tert*-butanesulfinyl)imine **75** in 88% yield. The sulfinimine **75** was then subjected to indium-mediated allylation under Barbier conditions to give corresponding *N*-*tert*-butanesulfinyl homoallylamine **76** was obtained in 85% yield with excellent diastereoselectivity.



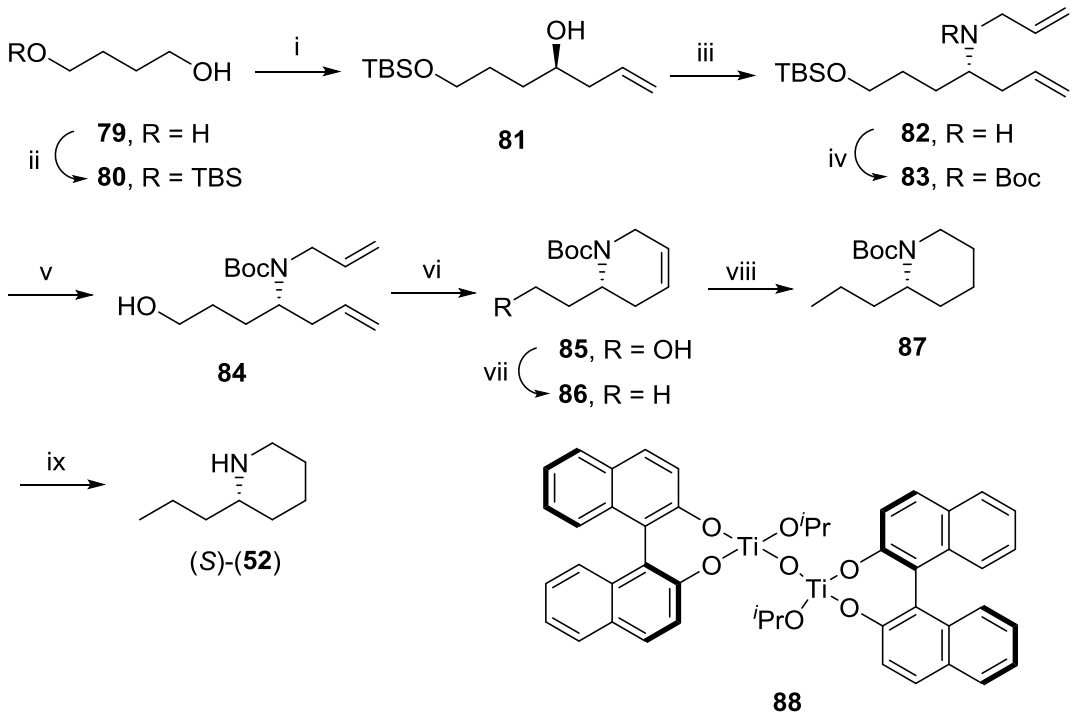
Scheme 12: (i) PMBBr, NaH, THF, 0 °C to 25 °C., 8 h, 79%; (ii) (a) PCC, CH_2Cl_2, 25 °C, 2 h, 90%; b) (*S*)-*t*-$BuSONH_2$, $CuSO_4$(anhyd), CH_2Cl_2, 25 °C, 24 h, 88%; (iii) CH_2=$CHCH_2Br$, In, THF, 66 °C, 4 h, 85%; (iv) (a) 4 M HCl/dioxane, MeOH, 25 °C, 45 min; (b) CbzCl, K_2CO_3, THF–H_2O (1:1), 24 h, 64% (two steps); (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (b) *t*-BuOK, THF, 0 °C to 25 °C, 3 h, 93% (two steps); (vi) (a) H_2 (1 atm), 10% Pd/C, EtOAc, 25 °C., 24 h; (b) HCl, Et_2O, 25 °C, 10 min, 80% (two steps).

Removal of the sulfinyl and PMB group and selective *N*-protection with benzyloxycarbonyl chloride gave the hydroxyhomoallylamine **77** in moderate yield.

Hydroxyl group was then mesylated and the crude product was subjected to ring closer by the treatment with base to give 2-allylpiperidine **78** in 93% yield over the two steps. Compound **78** was subjected to olefinic double bond reduction and deprotection of the benzyloxycarbonyl group to give a 2-propylpiperidine whose hydrochloride salt showed identical analytical data to those reported for (*R*)-(–)-coniine (**Scheme 12**).

Das's approach (2011)[25]

In yet another approach, Das *et al*. have reported the synthesis of (+)-coniine from butane-1,4-diol **79** which was converted into mono-silylated ether **80** on treatment with TBSCl and imidazole. The silylated ether on oxidation with PCC followed by Maruoka allylation[24] with allyltributylstannane in the presence of the (*S*)-BINOL. Titanium complex (*S*,*S*)-**88** to produce the chiral homoallylic alcohol **81** (96% ee). Mesylation followed by nucleophilic displacement by a S_N2 process with allylamine in DMF at 50 ^oC afforded the amine derivative **82** (92% ee) which was protected with $(Boc)_2O$ and the deprotection of TBS ether was achieved to give primary alcohol **84** in 89% yield. Diene **84** was subjected to a ring-closing metathesis (RCM) reaction using a Grubbs' second generation catalyst to give the cyclic tetrahydropyridine derivative **85**. The alcohol in **85** was treated with I_2 and imidazole to form the corresponding iodide derivative, which was reduced with Zn/AcOH to produce (+)-coniine derivative **86**. The reduction of the olefinic double bond in **86** with H_2/Pd–C followed by treatment with aqueous HCl and washing with NaOH solution afforded (+)- coniine **52** (**Scheme 13**).



Scheme 13: (i) TBSCl, imidazole, CH_2Cl_2, 0 °C to 25 °C, 0.5 h, 90%; (ii) (a) PCC, CH_2Cl_2, 0 °C to 25 °C, 0.5 h, 90%, (b) (*S*,*S*)-Ti catalyst **88**, CH_2=$CHCH_2SnBu_3$, CH_2Cl_2, -15 to 0 °C, 72 h, 85%; (iii) (a) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 25 °C, 1 h, (b) allylamine, DMF, H_2O, 50 °C, 30 h, 78% (over two steps); (iv) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 3 h, 92%; (v) *p*-TSA, THF/H_2O (3:1), 25 °C, 0.5 h; 89%; (vi) Grubbs' II catalyst (10 mol %), CH_2Cl_2, reflux at 50 °C, 4 h, 90%; (vii) (a) I_2, TPP, imidazole, CH_3CN/ether (1:3), 0 °C to 25 °C, 15 min; (b) Zn, CH_2Cl_2, 25 °C, 30 min, then AcOH, 0 °C to rt, 0.5 h, 80% (over two steps); (viii) H_2 (1 atm), 10% Pd–C, EtOAc, 25 °C, 2 h, 91%; (ix) 5 M HCl, THF, 25 °C, 89%.

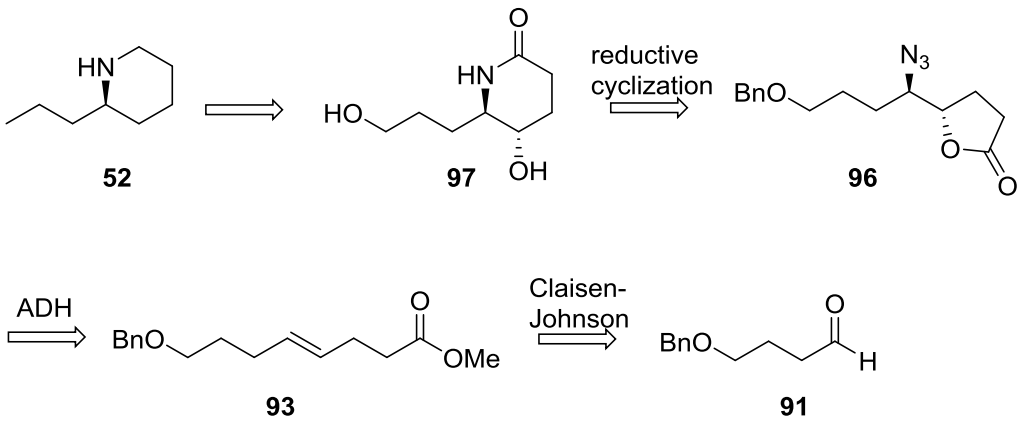
2.2.3. Present work

2.2.3.1 Objective

Given the vast chemistry, structural modifications and biological activities associated with the piperidine molecules, interest in the synthesis of these class of compounds remains unabated. Although a few syntheses are reviewed above, several more are documented in the literature. This explains the importance of research work in this area. With the exploration of Sharpless asymmetric dihydroxylation for the

application towards the synthesis of substituted piperidines, our attention was focused to extrapolate the above knowledge to the synthesis of (*R*)-coniine **52**.

The retrosynthetic analysis of (*R*)-Coniine (**52**) is shown in **Scheme 14.** We envisaged that lactam **97** could serve as a valuable intermediate for the asymmetric synthesis of (*R*)-Coniine (**52**). We further anticipated that the lactam moiety in **97** could be constructed by the reductive *N*- to *O*- ring expansion of azidolactone **96,** which in turn could be obtained readily *via* regioselective asymmetric dihydroxylation (ADH) of alkenic ester **93**. We also thought that the vinyl Grignard addition on the aldehyde **6** to produce allylic alcohol and its chemoselective [3,3]-sigmatropic Claisen-Johnson rearrangement would result in the formation of alkenic ester **93**.

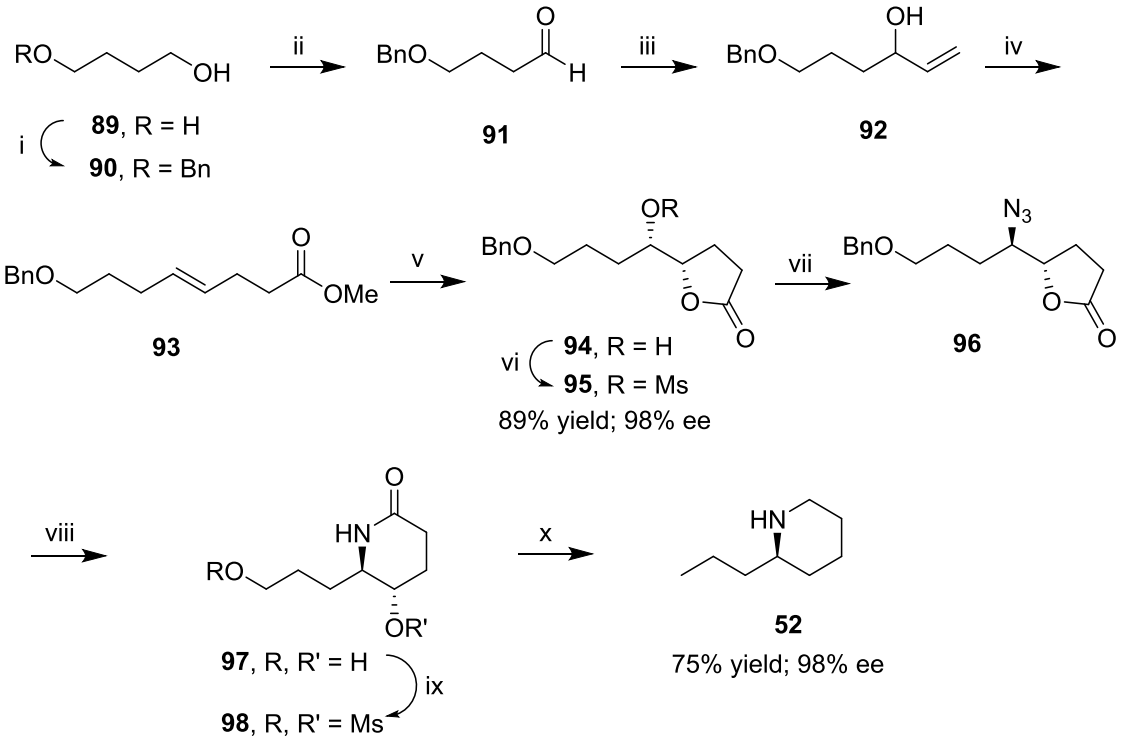


Scheme 14. Retrosynthetic route for the syntheses of (*R*)-coniine (**52**)

2.2.3.2 Results and discussion

In continuation of our interest in transition metal-catalyzed and asymmetric synthesis of piperidine,[26] we have undertaken the synthesis of (*R*)-coniine, employing Johnson-Claisen rearrangement followed by Sharpless asymmetric dihydroxylation as key steps. Our synthesis of (*R*)-coniine **52** commenced with monobenzyl protected 1,4-butanediol **89** (**Scheme 15**).

The free hydroxyl group in **90** was oxidized (IBX, DMSO, 25 ^{o}C) to give the corresponding aldehyde **91**, which was immediately treated with vinyl magnesium bromide in THF to give allylic alcohol **92** in 83% yield. The characteristic proton signals at δ 5.75-5.84 and 5.04-5.24 were due to the secondary and primary olefinic protons. Further the absence of aldehyde proton signal confirmed the allylic alcohol formation. The carbon signals at δ 114.3 and 141.0 in its ^{13}C NMR spectrum were due to secondary and primary alkenic carbons respectively. The formation of allylic alcohol **92** was also confirmed by the absence of carbonyl carbon signal in its ^{13}C NMR spectrum (**Fig. 12**).



Scheme 15: (i) BnBr, NaH, DMF, 0 ^{o}C, 1 h, 84%; (ii) IBX, DMSO, 25 ^{o}C, 1 h, 98%; (iii) CH_2=CHMgBr, dry THF, 0 ^{o}C 3 h, 83%; (iv) $CH_3C(OMe)_3$, cat. $CH_3CH_2CO_2H$, xylene, 135 ^{o}C, 4 h, 85%; (v) OsO_4 (0.1 mol%), $(DHQ)_2$-AQN (0.5 mol%), $K_3[(Fe(CN)_6)]$ (3 equiv), K_2CO_3 (3 equiv), *tert*-BuOH:H_2O (1:1), 24 h, 89%, 98% ee; (vi) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^{o}C, 1 h, 98%; (vii) NaN_3, DMF, 60 ^{o}C, 5 h, 87%; (viii) 10% Pd/C, H_2 (1 atm), MeOH, 25 ^{o}C, 24 h, 98%; (ix) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^{o}C, 1 h; (x) $LiAlH_4$, dry THF, 12 h, reflux, 75%.

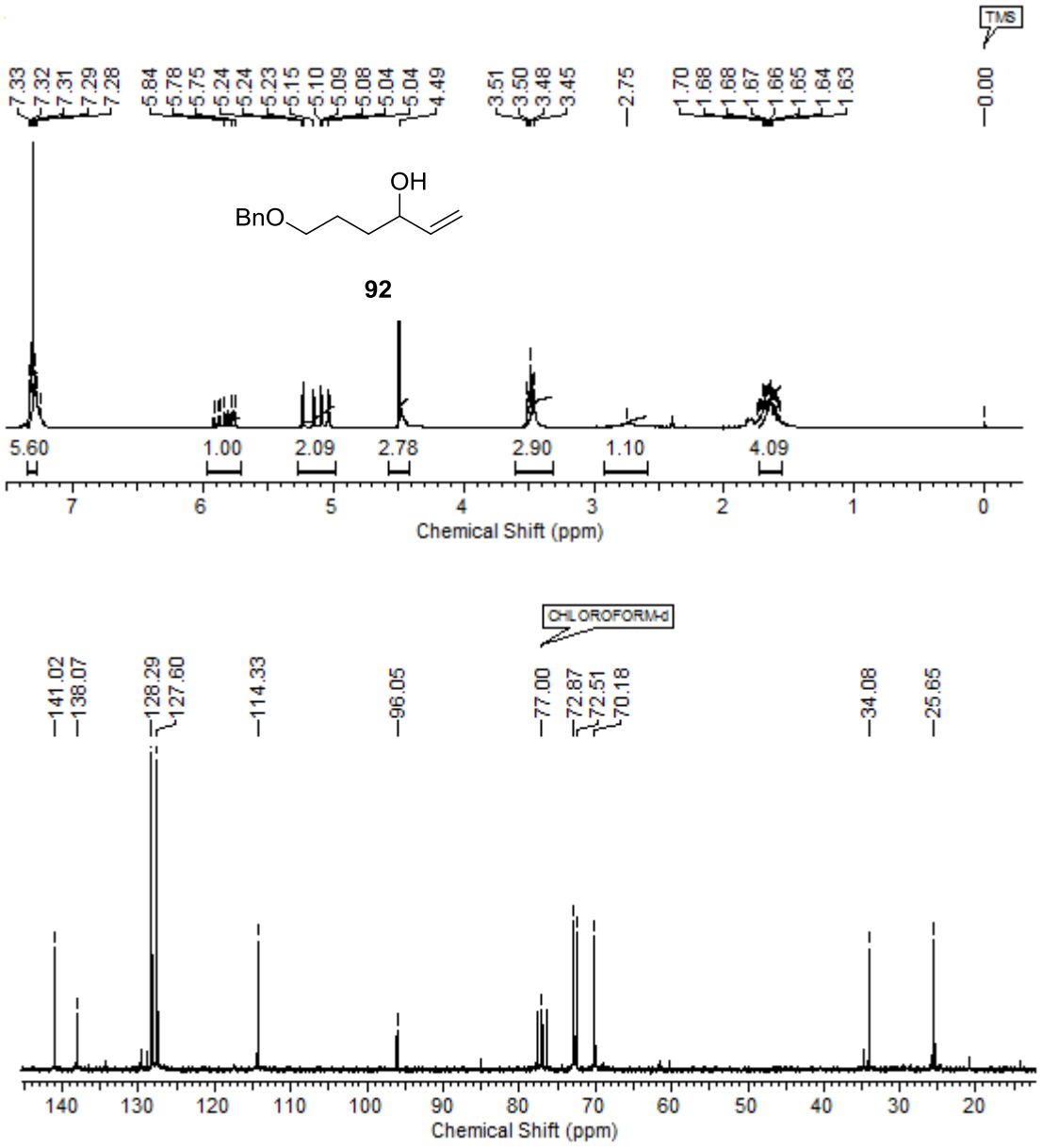


Fig. 12: ^{1}H and ^{13}C NMR of 6-(benzyloxy)hex-1-en-3-ol **(92)**

The allylic alcohol **92** was then subjected to Johnson-Claisen [3,3]-sigmatropic rearrangement [$CH_3C(OMe)_3$, cat. $CH_3CH_2CO_2H$, xylene, 135 ^{o}C] to give γ, δ- (*E*)-alkenic ester **93** in 85% yield. The formation of alkenic ester **93** was confirmed by the appearance of a singlet at δ 3.66 (s) in the ^{1}H NMR spectrum of alkenic ester **93** due to the presence of OMe of ester proton (-$CO_2C\mathbf{H_3}$). The display of signals at the olefinic region (δ 5.22-5.51, 2H) further confirmed the presence of internal alkenic

protons. Its ^{13}C NMR spectrum displayed characteristic carbon signal at δ 173.5 due to the carbonyl carbon (-**C**=O) and other signals at δ 127.5 and 128.3 corresponding to the alkenic carbons **(Fig. 13)**.

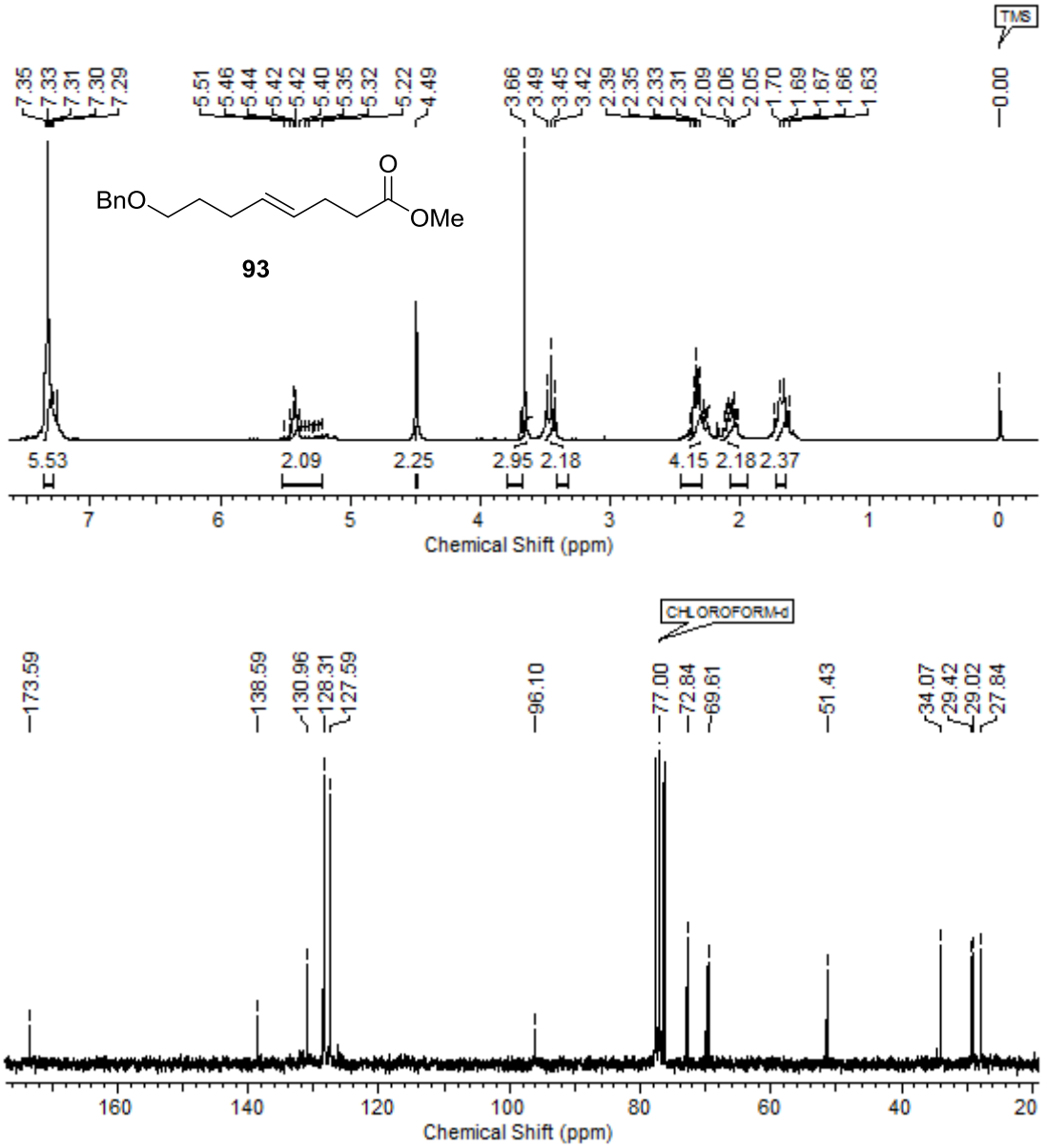


Fig. 13: ^{1}H and ^{13}C NMR of methyl (*E*)-8-(benzyloxy)oct-4-enoate **(93)**

The Os-catalyzed asymmetric dihydroxylation of **93** [OsO_4, $(DHQ)_2$-AQN, $K_3[Fe(CN)_6]$, K_2CO_3, *tert*-BuOH:H_2O (1:1)], furnished δ-hydroxy γ-lactone **94** in 89% yield and 98% ee (HPLC analysis). The IR spectrum of lactone **94** showed a strong absorption band at 1769 cm^{-1} that corresponds to the presence of five-

membered lactone carbonyl moiety. The disappearance of methyl (C**H**$_3$) and alkene (-C**H**=C**H**-) signals in the ^{1}H NMR spectrum of **94** confirmed the formation of lactone.

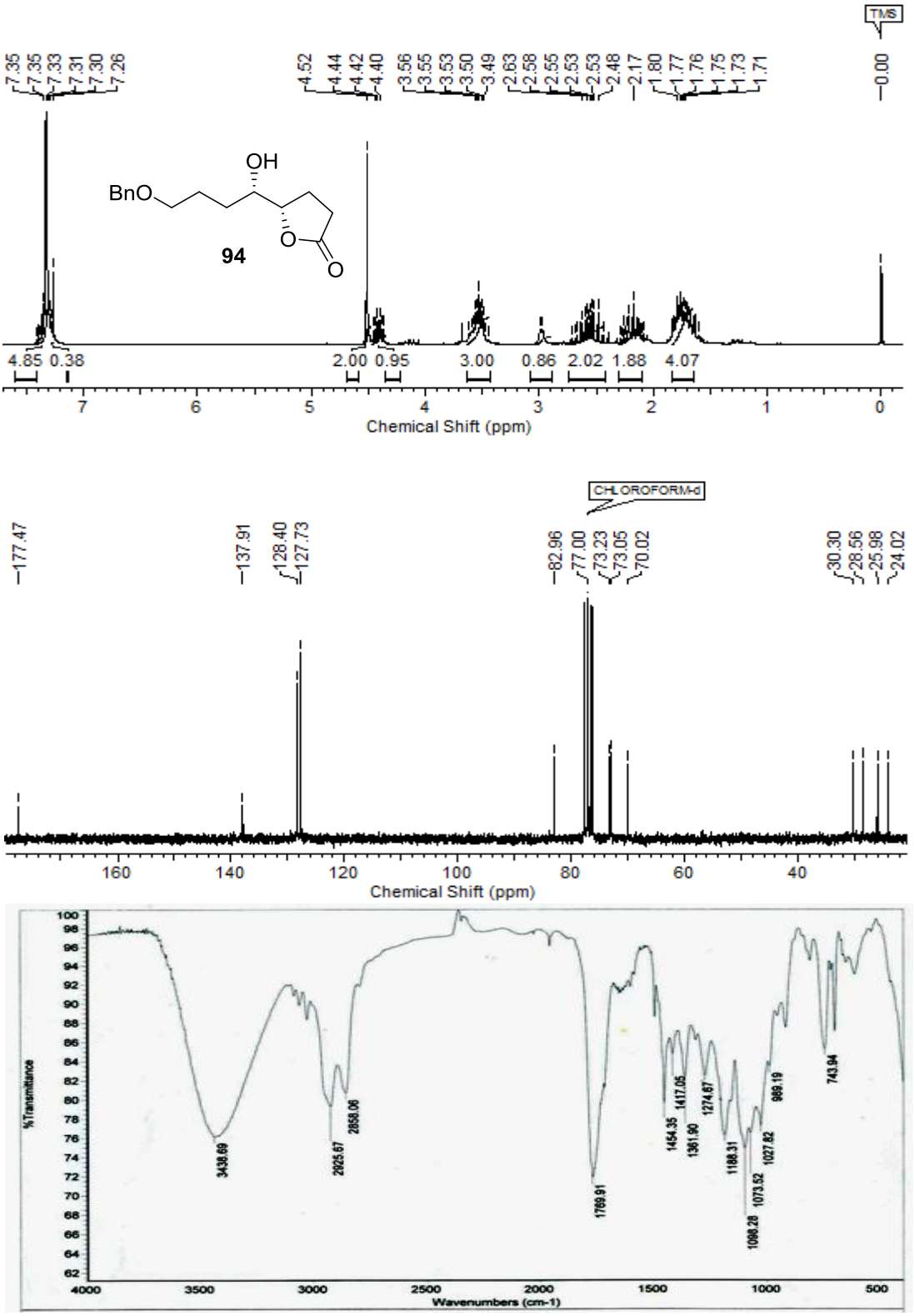


Fig. 14: ^{1}H and ^{13}C NMR of hydroxyl lactone **(94)**

The two newly formed methine protons (-C**H**O- and -C**H**OH-) have displayed proton signals as multiplets at δ 4.42 and 3.53 respectively. In its ^{13}C NMR spectrum, the carbonyl carbon signal has shown a downfield shift *i.e.* at δ 177.4 from δ 173.5 to due to the formation of five-membered lactone **(Fig. 14)**.

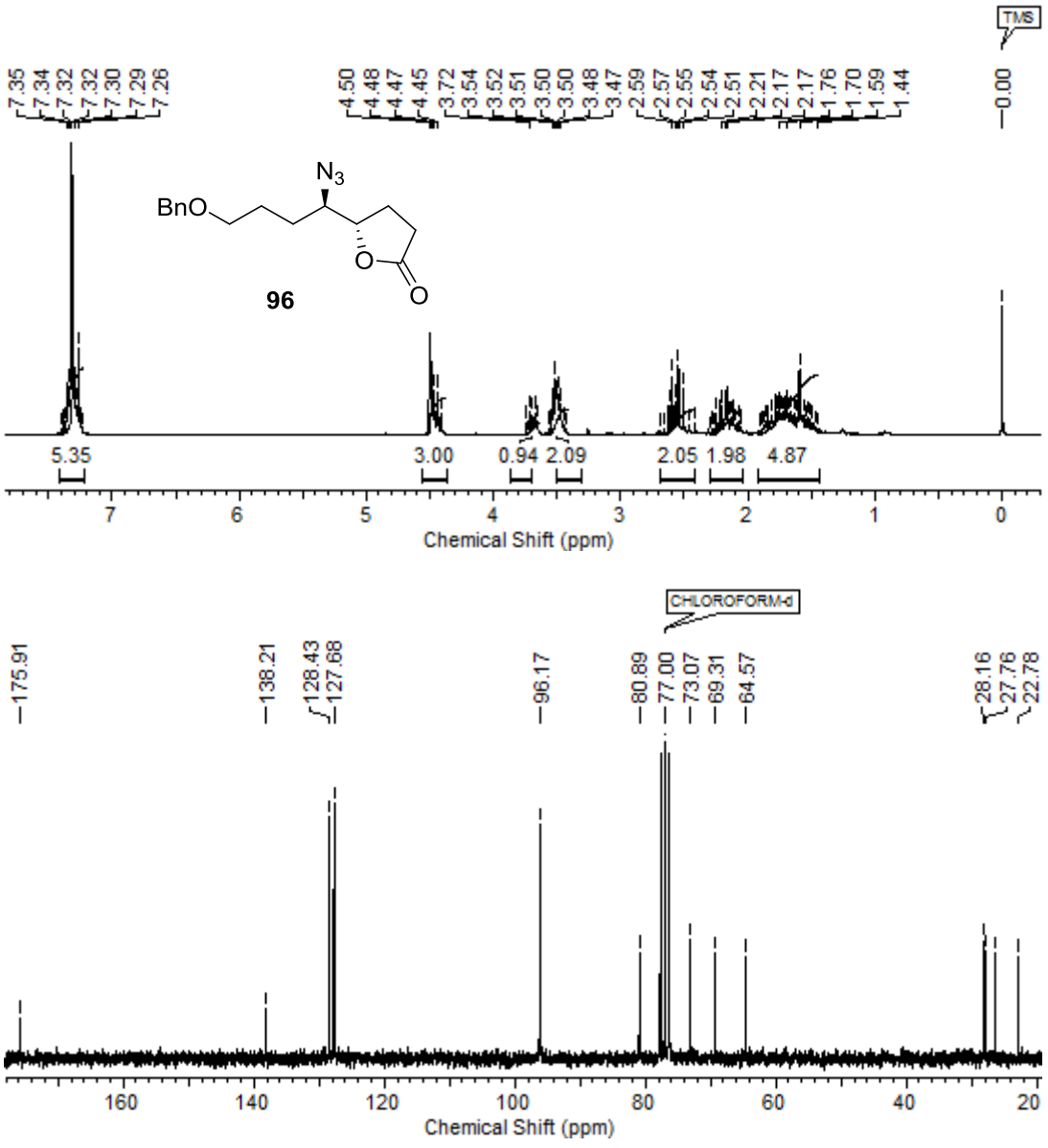


Fig. 15: ^{1}H and ^{13}C NMR spectra of azido lactone **(96)**

The free hydroxyl group in **94** was then protected as its mesylate **95** (MsCl, Et_3N, CH_2Cl_2, 0 °C), which was subjected to S_N2 nucleophilic displacement with azide anion to give azido lactone **96** with complete stereochemical inversion. The ^{1}H NMR spectrum of **96** showed typical signals at δ 3.52 and 4.47 due to the methine protons

of -C**H**N_3- and -C**H**O- groups respectively. Its ^{13}C NMR displayed signals at δ 80.8 and 64.5 due to -**C**HN_3- and -**C**HO- carbons respectively. Further, the appearance of a typical carbon signal at δ 175.9 indicated the presence of lactone carbonyl function (**Fig. 15**).

The catalytic hydrogenation of azide in **96** [10% Pd/C, H_2 (1 atm)] gave the six-membered hydroxyl lactam **97** in 98% yield, presumably formed by the intramolecular lactamization of the free amine generated *in situ* releasing the free alcohol.

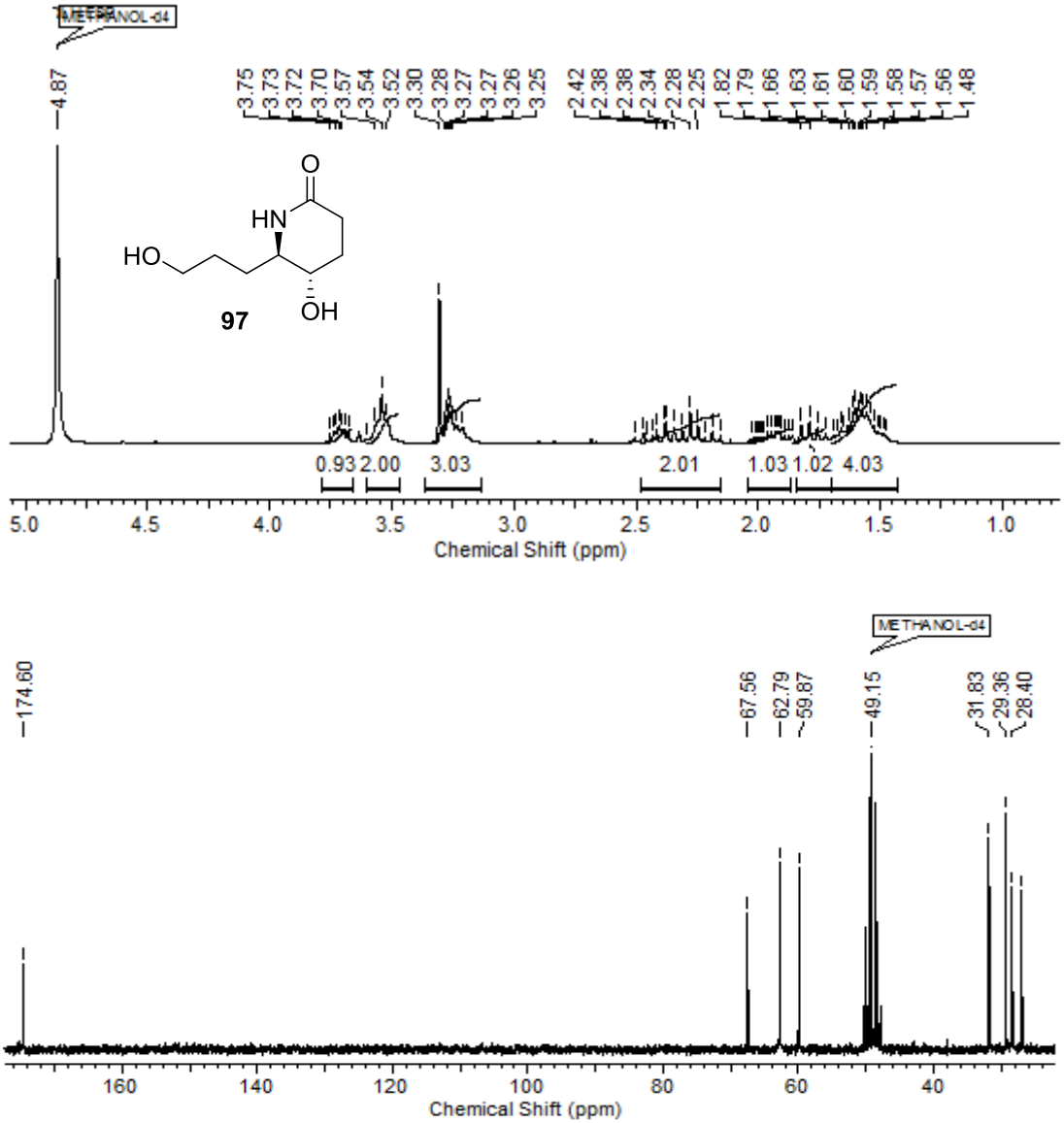
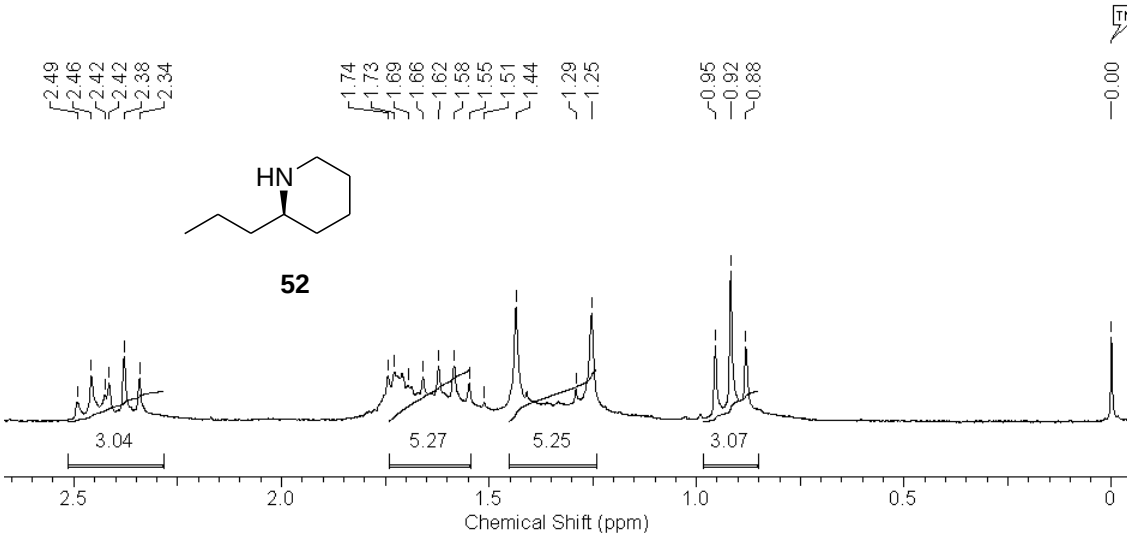


Fig. 16: ^{1}H and ^{13}C NMR of hydroxy lactam **(97)**

The disappearance of aromatic ($C_6\mathbf{H}_5$) and benzylic ($C_6H_5C\mathbf{H}_2$-) protons from the ^{1}H NMR spectrum of **97** indicated the reduction of -OBn group. The ^{1}H NMR spectral signals for methine protons (-C**H**NH- and -C**H**OH-) have appeared as multiplets at δ 3.27 and 3.72 respectively which confirmed the formation of lactam ring. The formation of hydroxy lactam **97** was further substantiated from its ^{13}C NMR spectrum, which showed a typical signal at δ 174.6 for the amide carbonyl (-**C**ONH) function (**Fig.16**).

The simultaneous deoxygenation of hydroxy function and reduction of amide carbonyl in **97** were achieved *via* a "one-pot" two-step reaction sequence: [selective mesylation of free -OH function followed by its reduction with $LiAlH_4$] to afford coniine **52** in 32% overall yield and 98% ee (**Scheme 15**). The ^{1}H NMR spectrum of **52** showed the appearance of four new proton signals at δ 1.25-1.74 and 2.34-2.49; thus confirming the reduction of amide carbonyl (-NHC**O**-) to methylene (-NHC$\mathbf{H}_2$-) group. The appearance of a triplet at δ 0.92 (C$\mathbf{H}_3$) in its ^{1}H NMR spectrum has proven the reduction of primary mesylate group. Further, the reduction of amide carbonyl was confirmed from its ^{13}C NMR spectrum, which showed the absence of carbonyl carbon (-NH**C**O-) signal (**Fig. 17**).



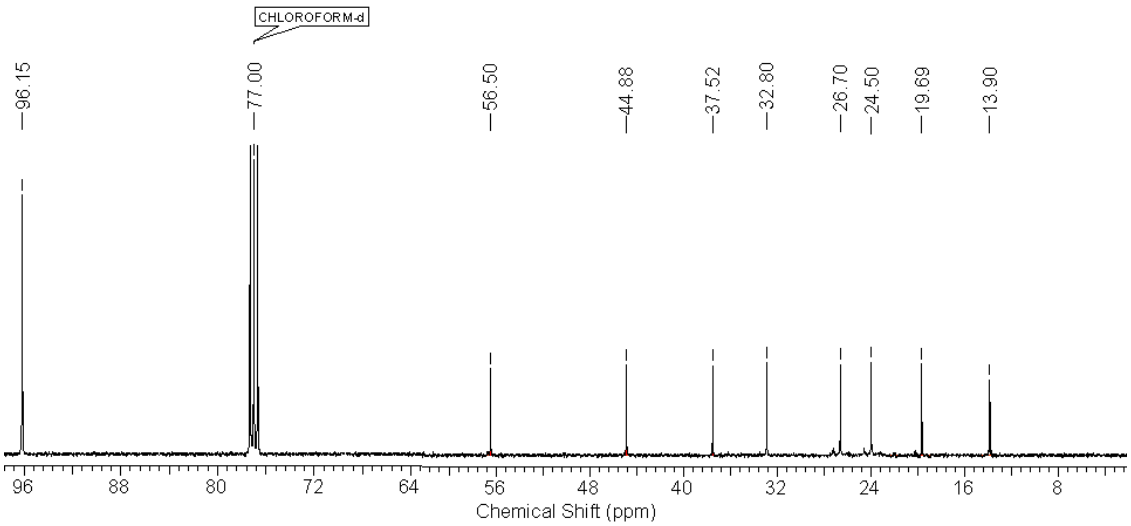


Fig. 17: ^{1}H NMR and ^{13}C NMR spectra of (*R*)-Coniine (**52**)

2.2.4 Conclusion

In conclusion, we were able to establish an alternative, short enantioselective synthesis of (+)-coniine (**52)** *via* asymmetric dihydroxylation of γ,δ-unsaturated ester in 10 linear steps with 98% ee. The carbon backbone of (R)-coniine was synthesized through Claisen-Johnson rearrangement of 1-hexen-3,6-diol while the piperidine ring was constructed using reductive ring expansion of azido lactone. This synthesis is practical and seems generally applicable for the synthesis of substituted piperidines.

2.2.5 Experimental

6-(Benzyloxy)hex-1-en-3-ol (92)

To a stirred solution of 1,3-prpanediol **89** (13.5 g, 150 mmol) in DMF (100 mL) was added 60% sodium hydride (5.54 g, 165 mmol) dispersed in mineral oil at 0 ^{o}C. After 5 min of stirring, benzyl bromide (25.65 g, 150 mmol) was added dropwise *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 **90**, which was purified by column chromatography using petroleum ether:ethyl acetate (4:1) to afford **90** as colorless liquid in (22.68 g, 84% yield). It was used directely in the next reaction.

To a solution of monoprotected alcohol **90** (22 g, 122.2 mmol) in DMSO (150 mL) was added iodoxybenzoic acid (IBX) (40.38 g, 144 mmol) and the reaction mixture was allowed to stir at 25 °C for 1 h. It was then quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were concentrated to give crude product, which was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to give aldehyde **91** (21.32g, 98% yield), which was immediately used in the next reaction, due to its lability.

A two-necked round bottomed flask was charged with Mg metal (3.11 g, 129.8 mmol), a pinch of iodine and THF (300 mL). To this stirred mixture, vinyl bromide (16.41 g, 153.4 mmol) in THF (164 mL) was added dropwise 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, aldehyde **91** (21 g, 118 mmol) in THF (10 mL) was added slowly over a period of 10 min at 0 ^oC and the mixture 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 **92**, which was

purified by column chromatography using petroleum ether: ethyl acetate (4:1) to obtain pure allylic alcohol **92** as colorless oil.

Yield: 83%; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 3423, 2922, 2852, 1583; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.60-1.70 (m, 4H), 2.75 (bs, 1H), 3.45-3.51 (m, 3H), 4.49 (s, 3H), 5.03-5.10 (m, 1H), 5.14-5.24 (m, 1H), 5.75-5.92 (m, 1H); 7.27-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.6, 34.0, 70.1, 72.5, 72.8, 114.3, 127.6, 128.2, 138.0, 141.0**; Anal.** Calcd. for $C_{13}H_{18}O_2$ C, 75.69; H, 8.80%; Found: C, 75.65; H, 8.81%.

Methyl (*E*)-8-(benzyloxy)oct-4-enoate (93)

An oven dried 500 mL round bottomed flask was charged with 6-(benzyloxy)hex-1-en-3-ol **92** (20.6 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 ^oC 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 **93**, which was purified by column chromatography using petroleum ether: ethyl acetate (9:1) to obtain pure **93** as colorless oil.

Yield: 85%; colorless liquid; **IR** (neat, cm^{-1}): ν_{max} 2936, 2861, 2332, 1735, 1520, 1442, 1251, 956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.63-1.76 (m, 3H), 2.06-2.09 (m, 2H), 2.10-2.35 (m, 3H), 3.45 (t, J = 6.4 Hz, 2H), 3.66 (s, 3H), 4.49 (s, 2H), 5.40-5.54 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.8, 29.0, 29.4, 34.0, 69.6, 70.0, 72.8, 127.4, 127.5, 128.3, 128.5, 130.9, 138.5, 173.5; **Anal.** Calcd for. $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; Found: C, 73.23; H, 8.44%.

(*S*)-5-((*S*)-4-(benzyloxy)-1-hydroxybutyl)dihydrofuran-2(3*H*)-one (94)

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), $(DHQ)_2$-AQN (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 alkenic ester **93** (10.48 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 **94**, which was purified by column chromatography using petroleum ether: ethyl acetate (1:1) to give **94** as a viscous gum.

Yield: 89%; colorless liquid; $[\alpha]^{25}_D$ +11.2 (*c* 0.6, $CHCl_3$); **IR** (neat, cm^{-1}): ν_{max} 1454, 1769, 2858, 2925, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.67-1.87 (m, 4H), 2.10-2.32 (m, 2H), 2.40-2.72 (m, 2H), 2.97 (d, *J* = 4.27 Hz, 1H), 3.44-3.63 (m, 3H), 4.36-4.46 (m, 1H), 4.51 (s, 2H) 7.28-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.0, 25.9, 28.5, 30.3, 70.0, 73.0, 73.2, 82.9, 127.7, 128.4, 137.9, 177.4; **Anal.** Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; Found: C, 68.11; H, 7.58; %.

(*S*)-5-((*S*)-1-Azido-4-(Benzyloxy)butyl)dihydrofuran-2(3*H*)-one (96)

To a stirred solution of hydroxy lactone **94** (10.032 g, 38 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 dropwise. 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 **95** in 96% yield as a viscous liquid, which was taken up directly for the next reaction

To a stirred mixture of crude methane sulfonate ester **95** (12.654g, 37 mmol) in DMF (30 mL) was added sodium azide (87 g, 475 mmol) and the reaction mixture was heated at 80 ^{o}C 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 **96**, which was purified by column chromatography using petroleum ether: ethyl acetate (9:1);

Yield: 87%; colorless viscous liquid; $[\alpha]^{25}_{D}$ -19 (*c* 1.0, $CHCl_3$); **IR** (neat, cm^{-1}): ν_{max} 1101, 1454, 1781, 2111, 2860, 2933; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44-1.86 (m, 5H), 2.08-2.25(m, 2H), 2.51-2.63 (m, 2H), 4.41-4.48 (dt, *J* = 4.40, 7.10 Hz, 1H), 4.50 (s, 2H), 7.27-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.7, 26.3, 27.7, 28.1, 64.5, 69.3, 73.0, 80.8, 127.6, 128.4, 138.2, 175.9; **Anal.** Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52; Found: C, 62.19; H, 6.55; N, 14.59%.

(5S)-5-Hydroxy-6-(3-hydroxypropyl)piperidin-2-one (97)

To a stirred solution of azidolactone **96** (3.5 g, 19.3 mmol) in dry MeOH (50 mL) was added 10% Pd/C under hydrogen environment (1 atm) at room temperature. The reaction mixture was stirred at that temperature till the starting material gets consumed (monitored by TLC). After the completion of the reaction, solvent was removed under reduced pressure to give the crude lactam **97**, which was purified by column chromatography using ethyl acetate to provide the pure lactam **97**.

Yield: 98%; colorless liquid; **$[\alpha]_D^{25}$** -29.4 (*c* 1.0, $CHCl_3$); **IR** (neat, cm^{-1}): ν_{max} 3546, 3445, 2939, 2895, 1657, 965; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.52-1.71 (m, 4H), 1.76-1.86 (m, 1H), 1.95-2.07 (m, 1H), 2.20-2.51 (m, 2H), 3.25 (m, 1H), 3.34 (s, 1H), 3.52-

3.61 (m, 2H), 3.72-3.79 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.0, 28.4, 29.3, 31.8, 59.8, 62.7, 67.5, 79.6, 174.6; **Anal.** Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; Found: C, 55.39; H, 8.78; N, 8.08%.

Coniine (52)

To a stirred solution of lactum **97** (173 mg, 1 mmol) in CH_2Cl_2 (60 mL) was added Et_3N (606 mg, 6 mmol) at 0 ^oC. After 5 min, methane sulfonyl chloride (342 mg, 3 mmol) was added dropwise. The reaction mixture was then stirred for another 3 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 **98** as a viscous liquid. It was directly employed in the next step.

An oven dried two-necked round bottomed flask was charged with lithium aluminium hydride (136 mg, 4 mmol) and dry THF (20 mL) was added *via* syringe. The suspension was cooled to 0 ^oC and a solution of mesylate **98** (329 mg, 1 mmol) in THF (10 mL) was added dropwise 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 8 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 target molecule i.e. coniine **52,** which was purified by neutral alumina column chromatography using petroleum ether:ethyl acetate (1:1) to get coniine **52** as colorless solid.

Yield: 0.032 g, 90%; gum; $[\alpha]_D^{25}$ -8.23 (*c* 0.25, EtOH), {Lit[13] $[[a]_D^{25}$: -7.3 (*c* 0.33, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2962, 1215. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.0 Hz, 3H), 1.46 (bs, 4H), 1.93 (bs, 5H), 2.85-2.92 (m, 2H), 3.45-3.50 (m, 1H), 9.14-9.39 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 18.7, 22.3, 22.4, 28.2, 35.4, 45.0, 57.3; **Anal.** Calcd. for $C_8H_{17}N$ C, 75.52; H, 13.47; N, 11.01%; Found: C, 75.65; H, 13.34; N, 11.15%.

SECTION III:

A Short Enantioselective Formal Synthesis of (+)-Febrifugine, a Potent *anti*-Malarial Drug

2.3.1 Introduction and pharmacology:

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.[27] 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.[28]

(+)-Febrifugine (**99**) and isofebrifugine (**100**) both isolated in 1947 from the Chinese medicinal plant and related plants are well-known antimalarial agents.[29] (+)-Febrifugine (**99**) is found to be effective against avian malaria, *Plasmodiuna cynomolgi* in monkey and *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 (**99**) and isofebrifugine (**100**) are epimerizable *via* ω–aminoenone under acidic condition.[30] These alkaloids were approximately 100 times as effective as quinine against *Plasmodia lophurae* in ducks.

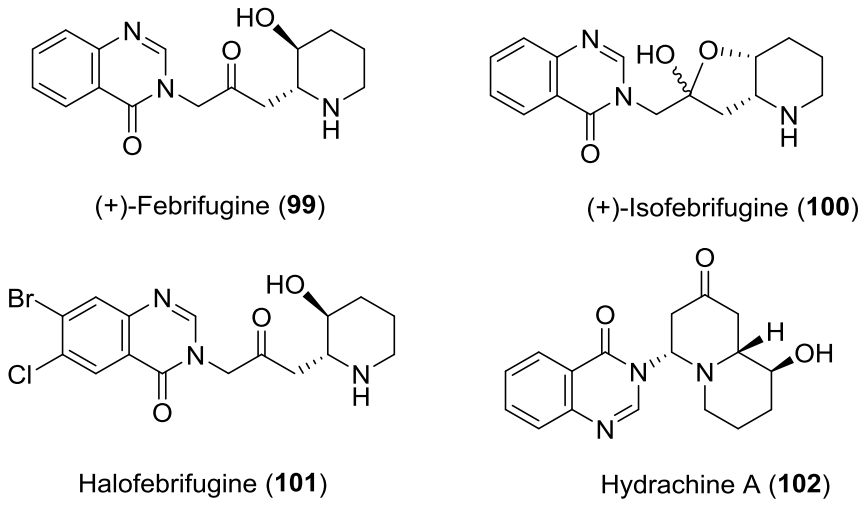


Fig. 18: Febrifugine and its structurally related compounds

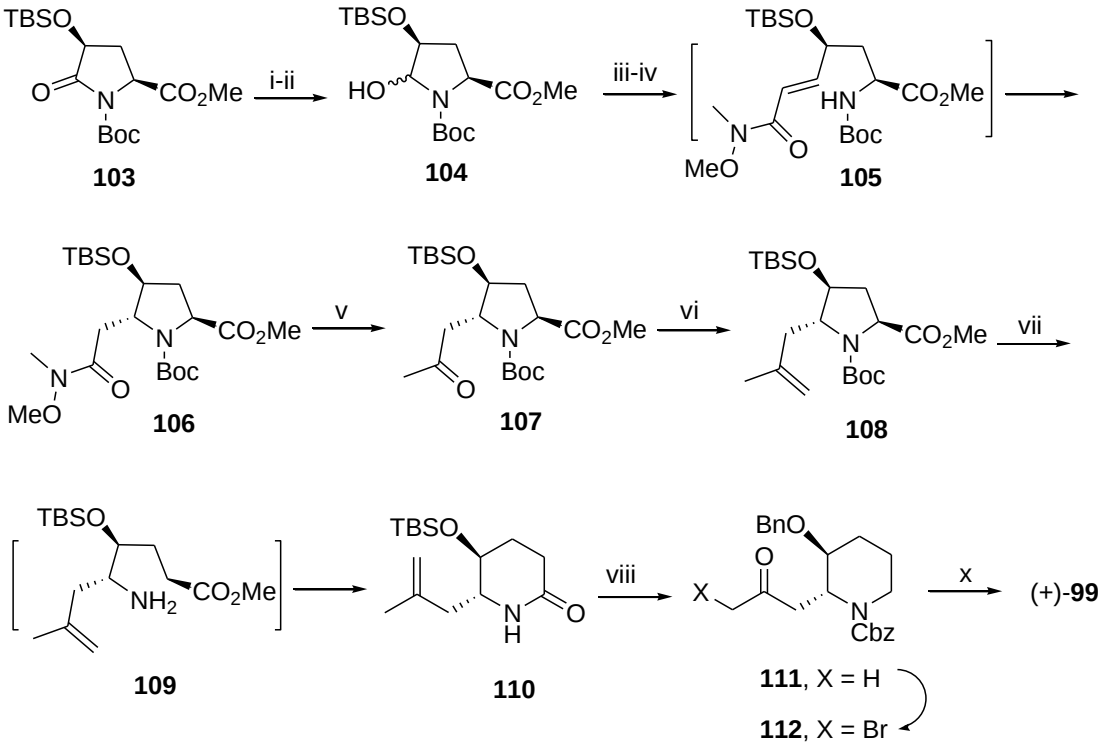
The planer structures of **99** and **100** were first proposed in 1950. Subsequently, their relative and absolute structures were proposed, based on Baker's synthetic work.[31] The relative configuration of **99** was corrected in 1973 and then the absolute structures of **99** and **100** were corrected in 1999, as shown in **Fig. 18**. 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 (**101**) 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.[32] Recent studies also led to the isolation of hydrachine A (**102**) as a novel alkaloid and the discovery of several febrifugine analogues,[33] which show potent antimalarial activity **(Fig. 18)**.

2.3.2 Review of Literature

Literature search reveals that there are several reports available for the asymmetric as well as racemic syntheses of febrifugine (**99**); some of the recent methods of synthesis are described below.

Honda's approach (2004)[34]

In this approach, protected (4*R*)-hydroxy-L-proline ester (**103**) was oxidized with RuO_4 to give the corresponding lactam, which upon reduction with lithium triethylborohydride gave aminal **104.**

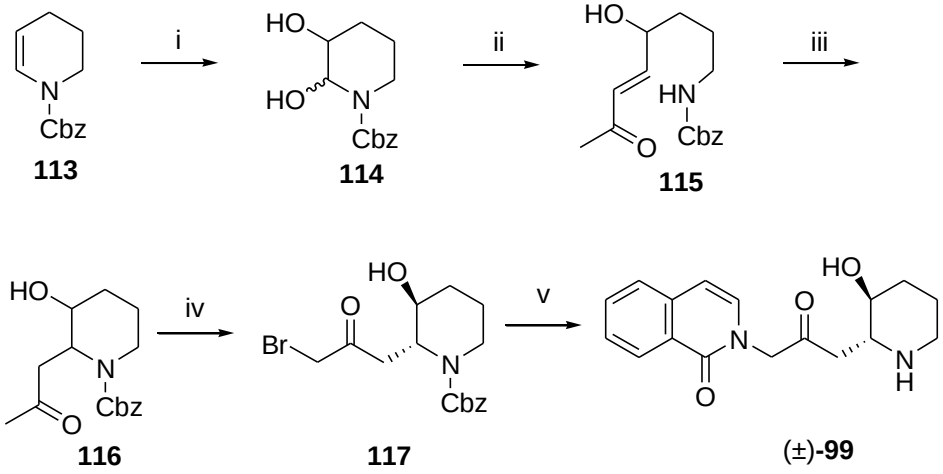


Scheme 16: (i) cat. RuO_4, $NaIO_4$, AcOEt/H_2O, 25 ºC, 86%; (ii) $LiEt_3BH$, THF, -78 ºC; (iii) $(EtO)_2P(O)CH_2CON(Me)OMe$, NaH, THF, 25 ºC, 83%; (iv) $BF_3.Et_2O$, CH_2Cl_2; (v) MeMgBr, THF, 0 ºC, 88%; (vi) Tebbe's reagent, THF, 40 ºC to 25 ºC, 81% (vii) a) $ZnBr_2$, CH_2Cl_2,25 ºC; b) SmI_2, THF:HMPA, 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%.

Wittig olefination of aminal **104** gave the Weinreb amide **106** formed *via* Michael addition of *α,β*-unsaturated amide **105**. Grignard addition of MeMgBr to the amide **106** afforded the ketone **107**, which on reaction with Wittig reagent gave the olefin **108** in 43% yield. Selective removal of the Boc group in **108** was achieved using $ZnBr_2$ to afford amine, which was subjected to SmI_2-promoted reductive deamination to furnish the lactam **110**. Reduction of lactam **110** with $LiAlH_4$ followed by protection of the resulting amine and alcohol functionalities and ozonolysis of the resulting olefin gave ketone **111**. Finally, ketone **111** was converted to (+)-febrifugine (**99**) *via* *α*-bromination (**112**) and coupling with 4-hydroxyquinazoline **(Scheme 16)**.

Harayama's approach (2005)[35]

Harayama *et al.* have described the synthesis of *dl*-febrifugine using intramolecular Michael addition of *ω*-amidoenone **115** as the key step. 2,3-Piperidinediol **114**, prepared from tetrahydropyridine **113** by oxone-acetone oxidation, was subjected to Wittig olefination to afford *ω*–amidoenone **115** with (*E*)-selectivity.

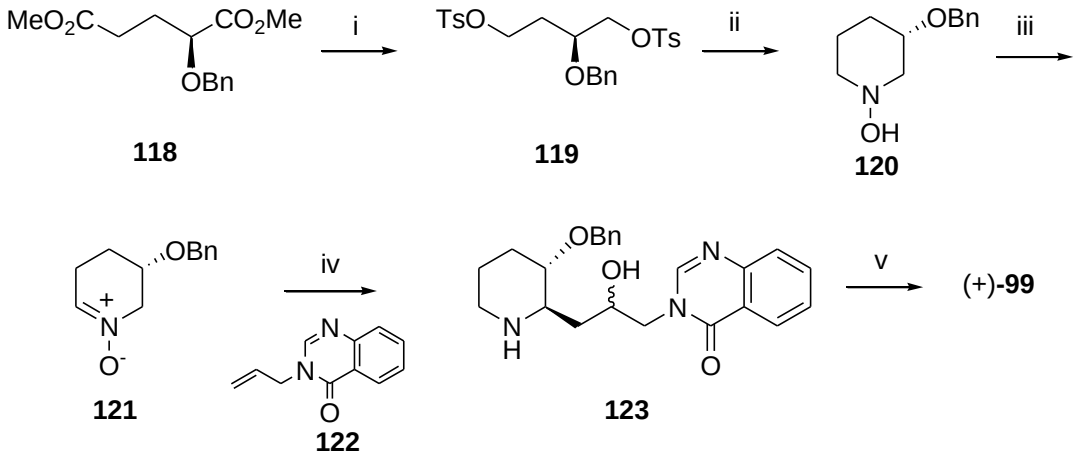


Scheme 17: i) Oxone, K_2CO_3, acetone, H_2O, 25 ºC, 2 h, 84%; ii) $CH_3COCH{=}PPh_3$, CH_3CN, reflux, 1 h, 76%; iii) $BF_3{\cdot}OEt_2$, CH_3CN, 25 ºC, 75%; iv) (a)TMS·OTf, *i*-Pr_2EtN, CH_2Cl_2, 25 ºC, 20 min; (b) NBS, 25 ºC, 2 h; v) (a) 4(*3H*)-quinazolinone, 25 ºC, 4.5 h, 51%; (b) H_2 (1 atm), $Pd(OH)_2$/C, MeOH/THF, 25 ºC, 3.5 h, 88%.

The *trans* olefin **115** was subjected to Michael addition in the presence of $BF_3 \cdot OEt_2$ to afford the Michael adduct **116**. Methyl ketone **116** was converted to (±)-febrifiugine (**99**) *via* standard reaction sequences involving α-bromination followed by coupling with 4(3*H*)-quinazolinone **(Scheme 17)**.

Caprio's approach (2005)[36]

Caprio *et al.* have employed 1,3-dipolar cycloaddition of nitrone **121** with *N*-allylquinazolone **122** as the key step to give febrifugine. Reduction of diester **118** using $LiAlH_4$ followed by di-tosylation of the resulting diol with tosyl chloride in the presence of DMAP gave 1,5-ditosylate **119**. Cyclization of **119** was achieved on reacting with hydroxylamine hydrochloride to give piperidine **120,** which was then oxidized using manganese dioxide to give a mixture of readily separable regioisomeric nitrones **121**.



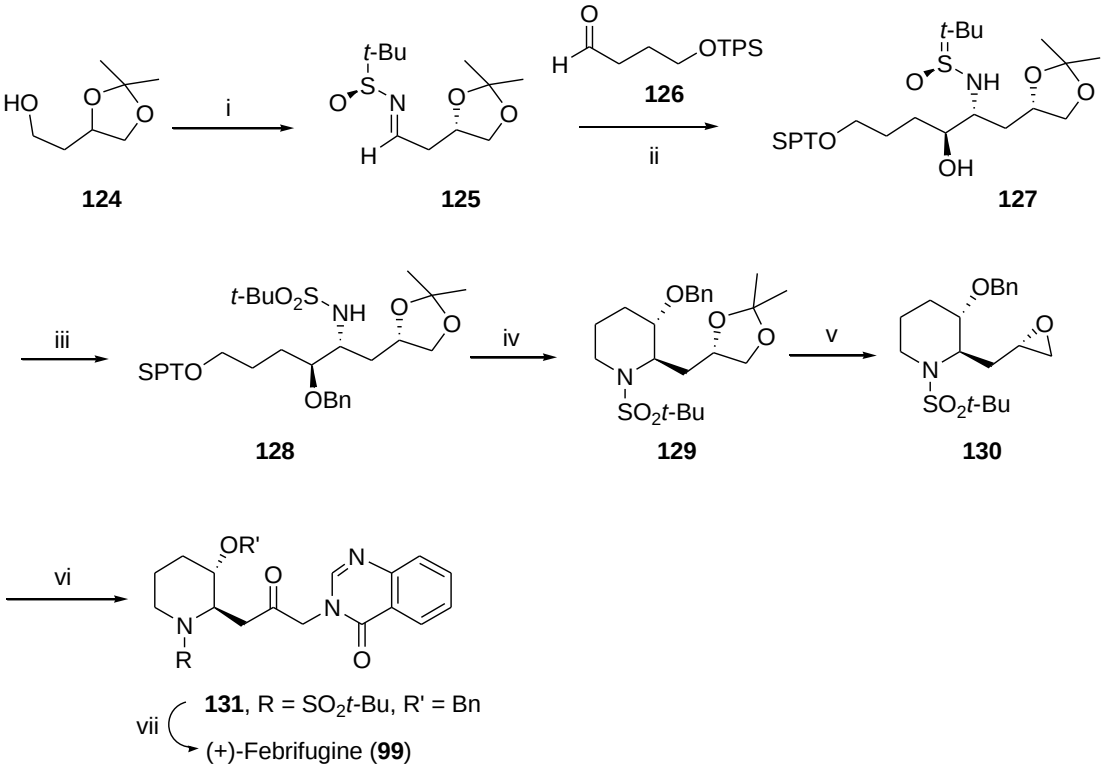
Scheme 18: (i) a) $LiAlH_4$, Et_2O, 24 h, 88%; b) TsCl, DMAP, Et_3N, CH_2Cl_2, 12 h, 86%; (ii) $NH_2OH \cdot HCl$, Et_3N, reflux, 4 h, 74%; (iii) MnO_2, CH_2Cl_2, 0 °C, 12 h, 88% overall yield; (iv) a) **122**, PhMe, reflux, 24 h, 48%; b) Zn, HOAc, reflux; (v) a) Boc_2O, Et_3N, CH_2Cl_2; b) Dess–Martin periodinane, pyridine, CH_2Cl_2, quant.; c) 6M HCl, reflux, 67%.

The 1,3-dipolar cycloaddition of nitrone **121** with dipolarophile **122** produced the corresponding adduct, whose *N-O* bond was reductively cleaved using Zn/acetic acid

to give the crude **123**. Amino alcohol **123** was converted to febrifugine by standard sequence of reactions *i.e.* Boc protection, oxidation and deprotection **(Scheme 18)**.

Lin's approach (2009)[37]

Alcohol **124** was subjected to oxidation under Swern's conditions to afford crude aldehyde which, without further purification, was treated with Ellman's reagent to afford imine **125** in 85% overall yield. Aldehyde **126** was readily obtained by Swern oxidation of monoprotected butane-1,4-diol**.**



Scheme 19: (i) a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 ^oC, 97%; b) Ellman's reagent $CuSO_4$ (anhyd) 85% (two steps); (ii) SmI_2, *t*-BuOH, THF, -78 ^oC, 85%; (iii) a) NaH, BnBr, THF, 50 ^oC, 83% b) MCPBA, CH_2Cl_2, 96%; (iv) a) TBAF, THF, 0 ^oC b) MsCl, Et_3N, CH_2Cl_2 -78 ^oC; c) NaH, THF, 89% (three steps); (v) a) TsOH, MeOH, 88%; b) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2; c) DBU, CH_2Cl_2, 91%; (vi) a) 4-quinazolone, KH, DMF, reflux 84%; b) Dess–Martin periodinane, pyridine, CH_2Cl_2, 84%.; vii) 6M HCl, reflux, 79%.

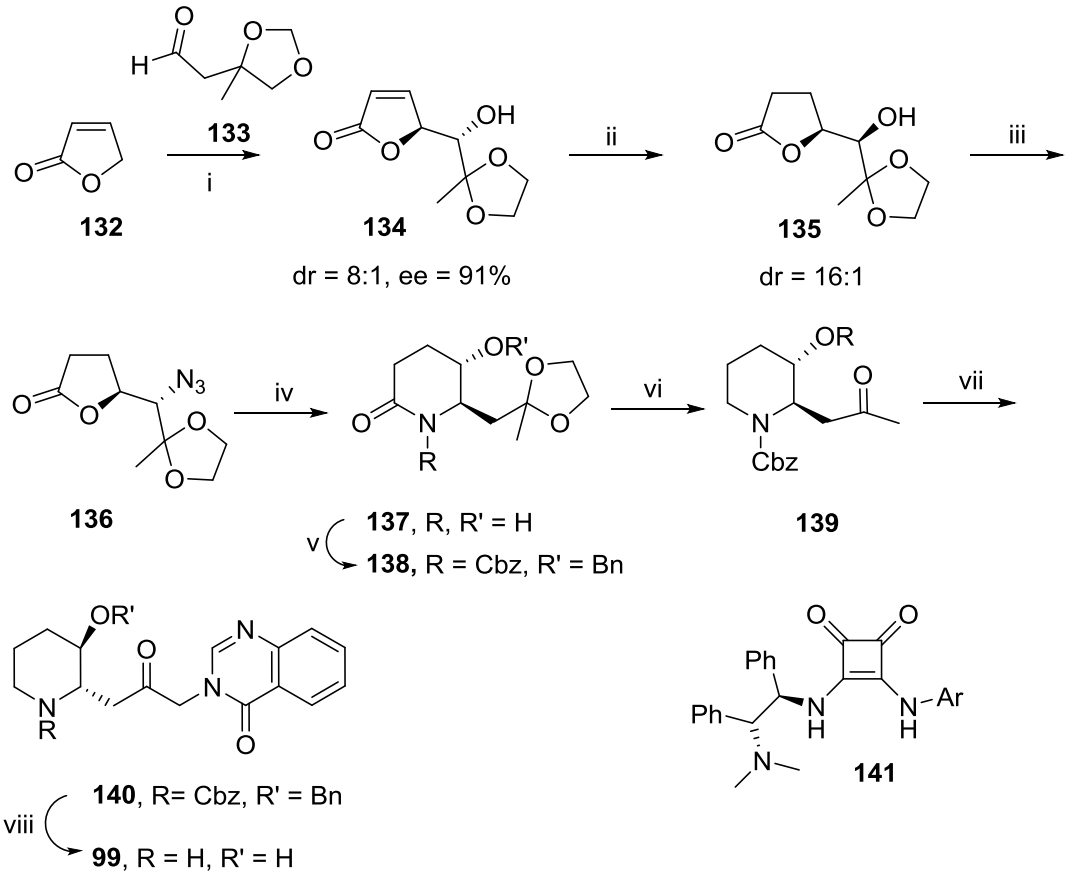
Imine **125** was subjected to crucial SmI_2-mediated reductive cross-coupling reaction to furnish **127** in 85% yield with typical 93.5:4.0:2.0:0.5 diastereoselectivity**.** The

newly formed hydroxyl group in amido alcohol **127** was first converted into benzyl ether subsequent exposure to MCPBA delivered sulfonamide **128** in 96% yield. Removal of the silyl group with TBAF, mesylation of the resulting free hydroxyl group with $MeSO_2Cl/Et_3N$ followed by treatment with NaH in THF provided *N*-sulfonylpiperidine **129** in 89%yield over 3 steps. Acetonide **129** was then exposed to *p*-toluene sulfonic acid in methanol to give diol, which was converted to epoxide **130** in 91% yield. Epoxide **130** was opened with 4-quinazolone potassium salt; the resulting alcohol was treated with Dess–Martin periodinane to furnish **131** in 86% yield. Finally, **131** was subjected to global deprotection in refluxing 6 N hydrochloric acid to produce (+)-febrifugine (**99**) in 79% yield (**Scheme 19**).

Pansare's approach (2013)[38]

The direct vinylogous aldol reaction of γ-crotonolactone **132** with the aldehyde **133** using **141** as the catalyst provided the butenolide **134** in good yield and diastereoselectivity (74%, *anti*/*syn* = 8:1) and excellent enantiomeric excess (er = 19:1 for the *anti*-diastereomer) **(Scheme 20)**. For this, **134** was first hydrogenated and the alcohol was first oxidized to provide the ketolactone, which on reduction with K-Selectride gave *syn*-**135** (70%) (*syn*/*anti* = 16:1). The lactone **135** was readily converted into the azido lactone **136** (mesylation and azidation with inversion) with the required *anti* stereochemistry (*anti*/*syn* = 16:1). Reduction of the azide (H_2, Pd/C) produced the required piperidone **137**, (80%) obtained from the intramolecular *N*-acylation of the amino lactone. Reduction of the lactam in **137** provided the corresponding piperidine, which was isolated as a single diastereomer. *N*-Protection and subsequent benzylation of OH provided key intermediate **138**. The ketone in **138** was unmasked by treatment of the ketal with iodine in acetone to provide **139**. Bromination of the ketone in **139** was achieved (TMSOTf, DBU then NBS) and the

crude bromoketone was reacted with 4- hydrazoquinazoline to provide the protected febrifugine derivative **140**. Deprotection of **140** (aq 6 M HCl) and subsequent neutralization provided (+)-febrifugine (**99**).



Scheme 20: (i) a) catalyst **141**, CH_2Cl_2, 24 h, 74%; (ii) a) H_2 (1 atm), Pd/C (5%), MeOH, 25 ^oC, b) Dess–Martin periodinane, pyridine, CH_2Cl_2, 84%. c) K-selectride, THF, -78 ^oC (70%) (iii) a) MsCl, Et_3N, CH_2Cl_2 0 ^oC b) NaN_3, DMF, 80 ^oC 8 h; (iv) H_2, Pd/C, MeOH, 25 ^oC, K_2CO_3, (80% 3 steps) (v) a) $LiAlH_4$, THF, 24 h, 88%; b) CbzCl, Et_3N, DMAP, CH_2Cl_2, 25 ^oC; c) KH, BnBr, THF, 0 ^oC, (71% three steps) (vi) I_2, axetone 84% (vii) a) TMSOTf, DIPEA, then NBS; b) 4-OH quinazoline K_2CO_3 (47% 2 steps); (viii) 6M HCl, reflux, then K_2CO_3 75%.

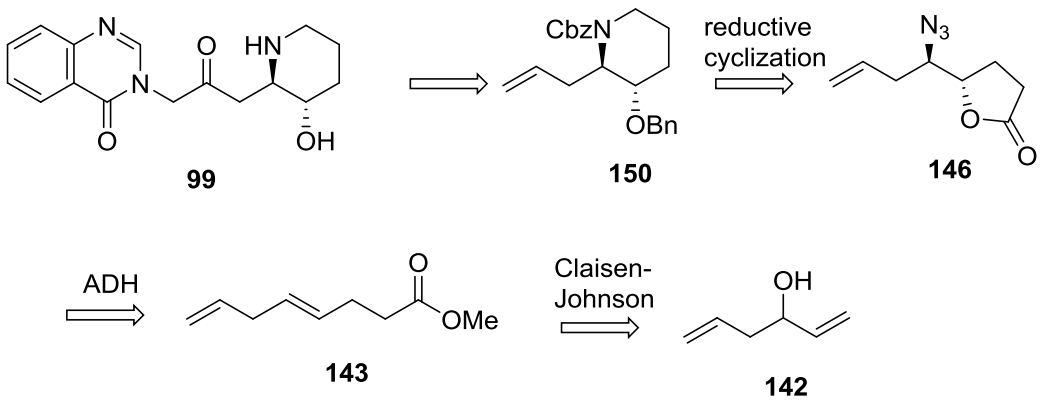
2.3.3 Present Work

2.3.3.1 Objective

As can be seen from the above discussion, the literature methods for the synthesis of (+)-febrifugine (**99**) employ either chiral starting materials or expensive reagents involving longer reaction sequences, often resulting in poor product selectivities. The catalytic synthesis of (+)-febrifugine (**99**) is thus undertaken by employing the asymmetric dihydroxylation of homoallylic ester as the key reaction.

Retrosynthetic analysis

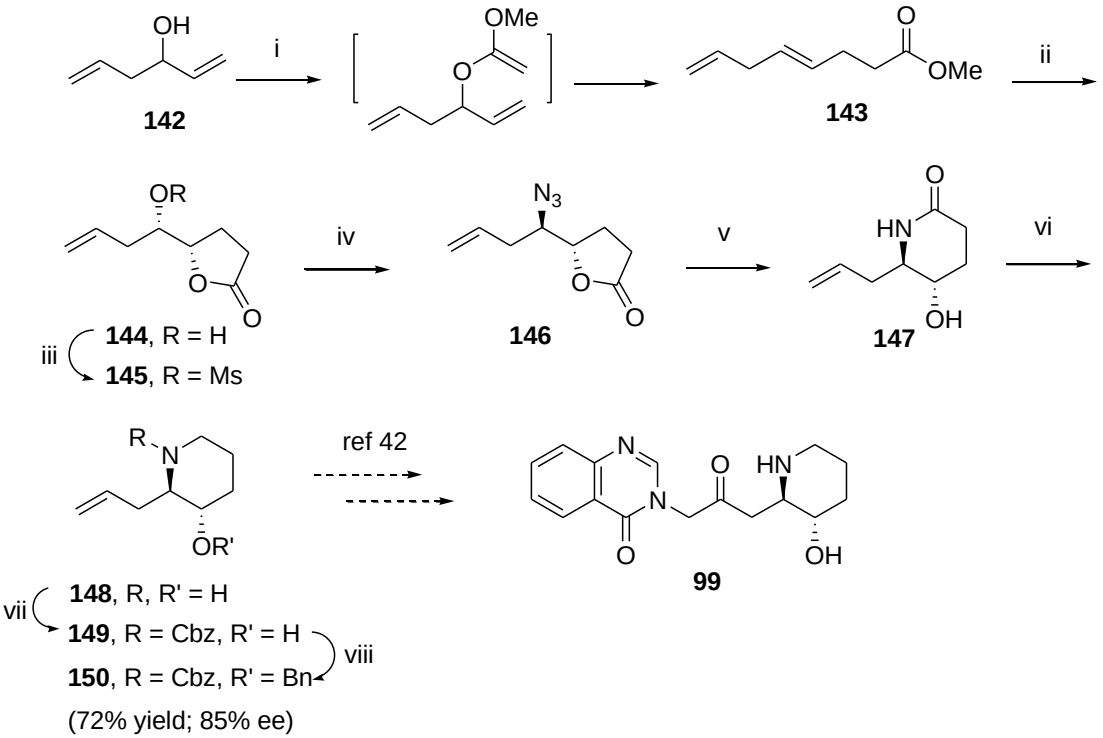
The retrosynthetic analysis of (+)-febrifugine (**99**) is shown in **Scheme 21.** We envisaged that 2-allyl-3-hydroxypiperidine **150** could serve as a valuable intermediate for the asymmetric synthesis of (+)-febrifugine **99**. We further anticipated that the piperidine moiety in **150** could be constructed by the reductive *N*- to *O*- ring expansion of azidolactone **146**, which in turn could be obtained readily *via* regioselective asymmetric dihydroxylation (ADH) of 1,4-dienic ester **143**. We also thought that the chemoselective [3,3]-sigmatropic Claisen-Johnson rearrangement of 1,5-hexadiene-3-ol (**142)** would result in the formation of dienic ester **143**.



Scheme 21: Retrosynthetic analysis of (+)-febrifugine (**99**)

2.3.3.2. Results and Discussion

Our synthesis of (+)-febrifugine (**99)** commenced with the commercially available 1,5-hexadien-3-ol (**142**), which was subjected to Claisen-Johnson [3,3]-sigmatropic rearrangement[39] (trimethyl orthoacetate, cat. propionic acid, xylene, 135 ^{o}C) to give (*E*)-1,4-dienic ester **143** exclusively in 86% yield **(Scheme 22).**



Scheme 22: (i) $CH_3C(OMe)_3$, cat. $CH_3CH_2CO_2H$, xylene, 135 °C, 8 h, 88%; (ii) OsO_4, $(DHQ)_2$-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3, *tert*-BuOH:H_2O (1:1), 0 ^{o}C, 24 h, 73%; (iii) MsCl, CH_2Cl_2, 0 °C, 1 h; (iv) NaN_3, DMF, 80 °C, 4 h, 82% over two steps; (v) PPh_3, THF/H_2O (19:1), 25 °C then reflux, 8 h, 93%; (vi) $LiAlH_4$, dry THF, reflux, 12 h, 85%; (vii) CbzCl, K_2CO_3, THF:H_2O (1:1), 0-25 ^{o}C, 8 h,; (viii) BnBr, NaH, dry DMF, 0 °C, 1 h, 84% (two steps).

Surprisingly, we observed that the reaction conditions exclusively favored the Claisen-Johnson rearrangement to give the desired dienic ester **143** over a possible oxy-Cope rearrangement; no trace of 5-hexenal, an oxy-Cope product was formed. The appearance of a singlet at δ 3.67 (s) in the ^{1}H NMR spectrum of dienic ester **143**

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 δ 115.6, 129.6, 129.7 and 137.7 corresponding to the olefinic carbons **(Fig. 19)**.

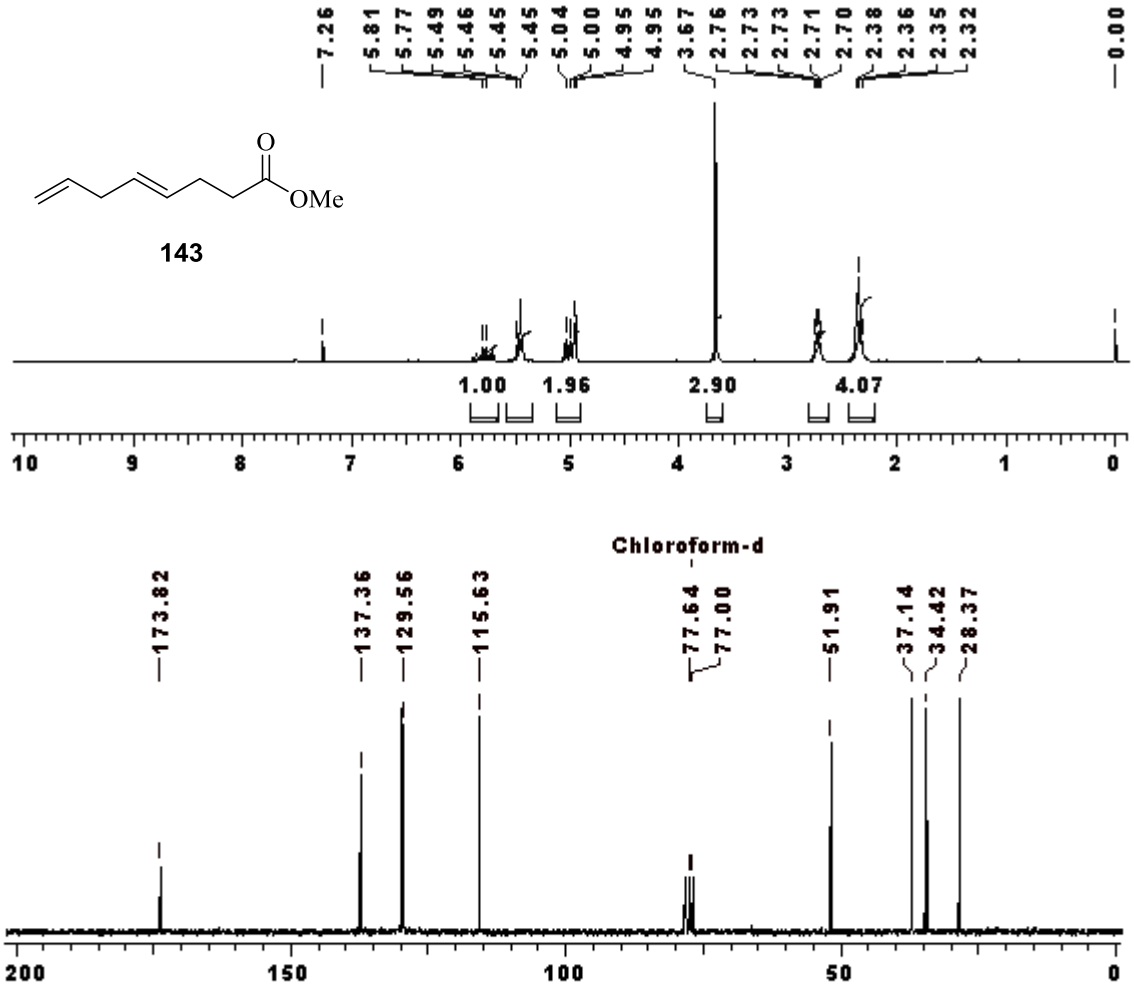


Fig. 19 : ^{1}H and ^{13}C NMR spectra of dienic ester **143**

The regioselective asymmetric dihydroxylation of internal olefin **143** was achieved [$(DHQ)_2$-PHAL, cat. OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, *t*-BuOH:H_2O (1:1) at 0 °C] to give the hydroxylactone **144** 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 **144**. No trace of six- membered lactone was found.

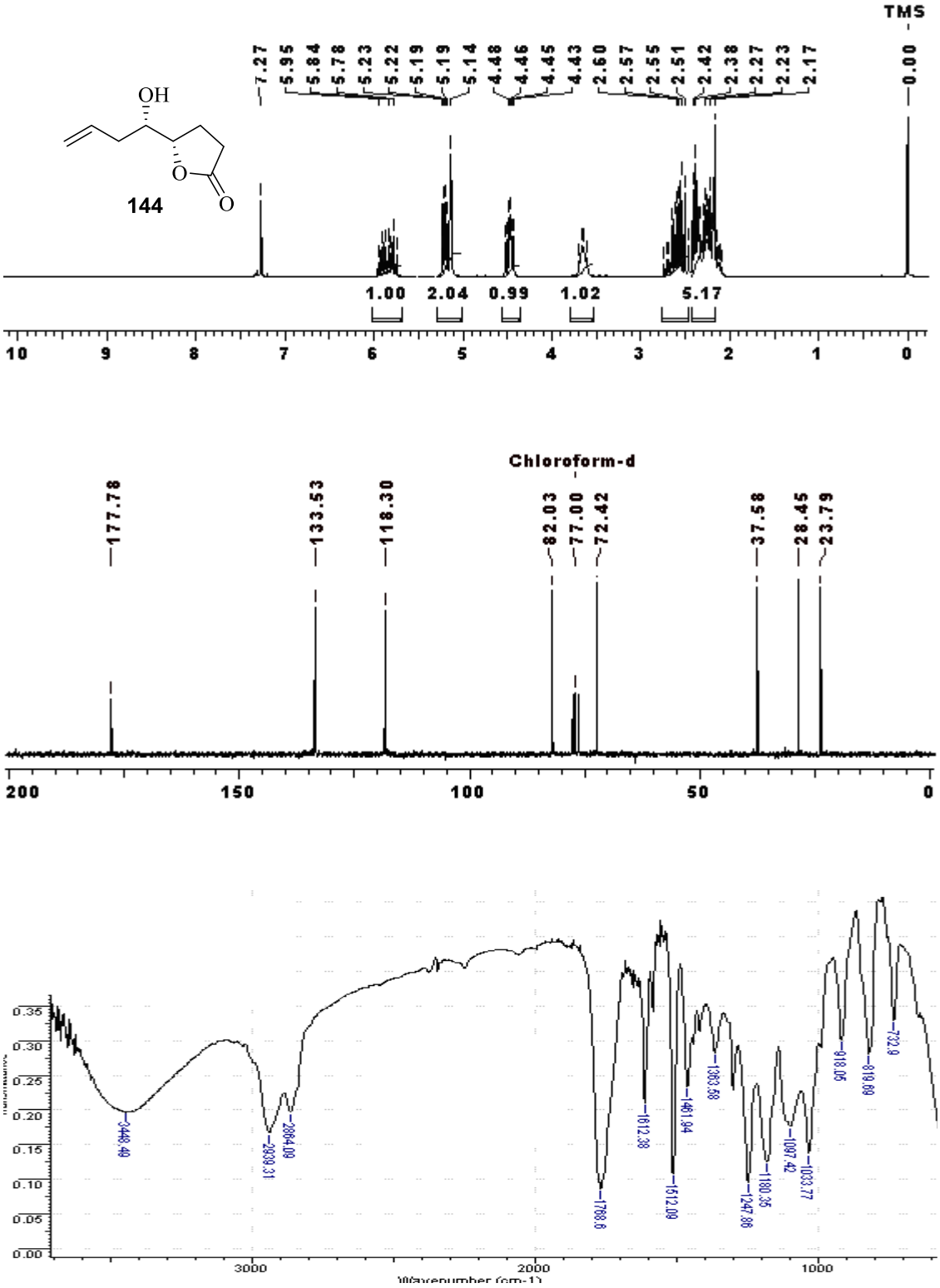


Fig. 20: ^{1}H ,^{13}C NMR and IR spectra of hydroxyl lactone **144**

The IR spectrum of lactone **144** showed a strong absorption band at 1768 cm^{-1} that corresponds to the presence of five-membered lactone carbonyl moiety. The disappearance of methyl signal in the ^{1}H NMR spectrum of **144** confirmed the formation of lactone. The two characteristic signals at δ 5.19 and 5.84 in its ^{1}H 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 **144**, 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. 20)**. Carrying out the reaction for longer reaction time has produced the desired 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 ^{o}C.

Mesylation of the free alcohol group in **144** (MsCl, Et_3N, CH_2Cl_2, 0 °C) produced the corresponding methane sulfonate ester **145** in quantitative yield. Without purification, mesylate **145** was subjected to S_N2 displacement with NaN_3 in DMF at 80 °C to furnish the azidolactone **146** with complete 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 ^{1}H NMR spectrum of **146**. The signals at δ 3.74 and 4.48 were due to the methine protons (-C**H**N_3- and -C**H**O-) respectively. Its ^{13}C NMR spectrum displayed a typical signal at δ 173.1 for the lactone carbonyl and other signals at δ 132.4 and 119.4 due to the terminal olefinic carbons. Reduction of azide **146** under Staudinger condition[40] (PPh_3, H_2O, heat) gave lactam **147** {$[\alpha]^{25}_{D}$ +10 (*c* 0.8, $CHCl_3$);

presumably formed by the intramolecular lactamization of the free amine generated *in situ* by the reduction of azide.[41]

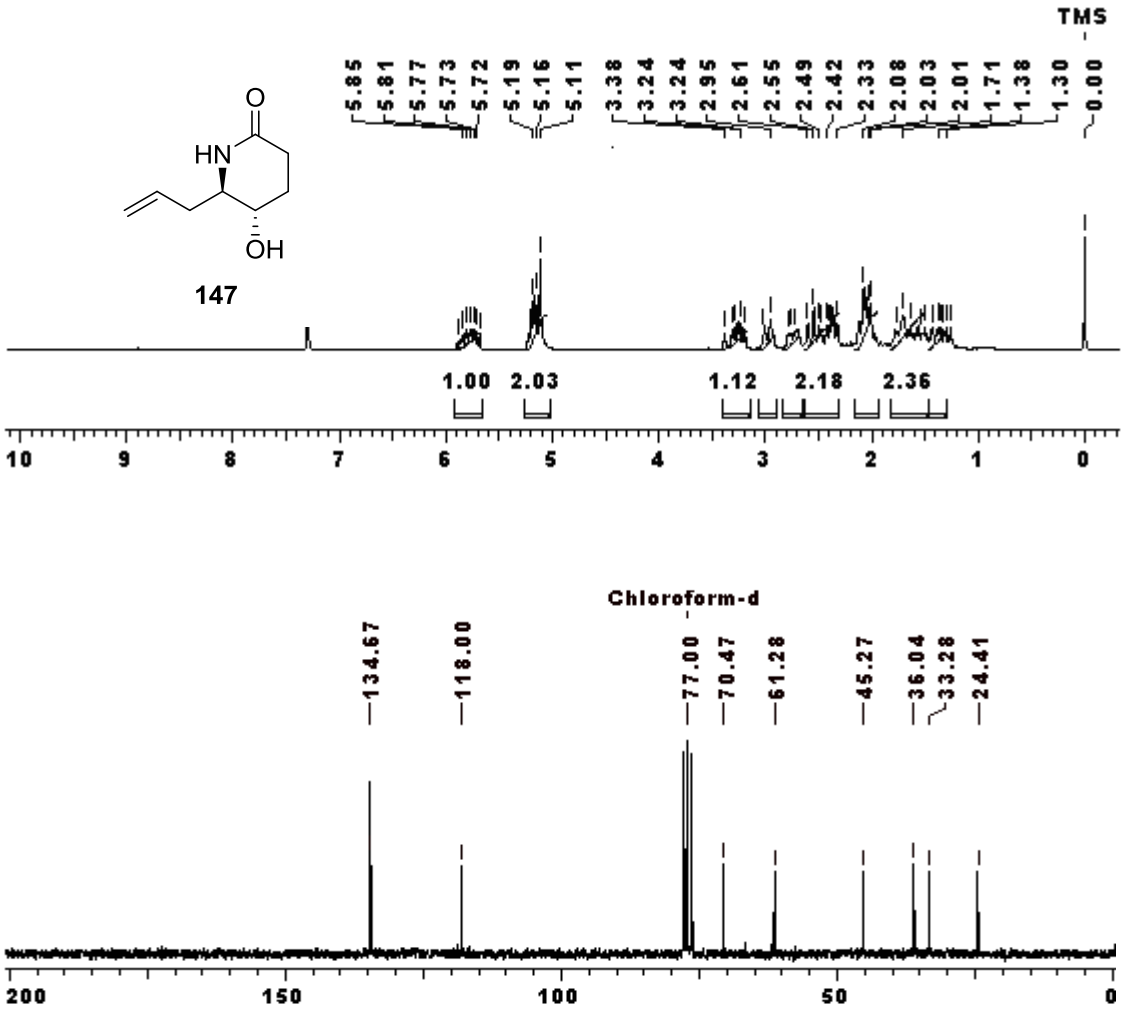


Fig. 21: ^{1}H and ^{13}C NMR spectra of **147**

The ^{1}H NMR spectrum of **147** 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 **147** was further confirmed from its ^{13}C NMR spectrum, which showed a typical signal at δ 172.0 due to the amide carbonyl (-**C**ONH) function (**Fig.21**).

The chemoselective reduction of lactam **147** was achieved with lithium aluminium hydride to afford 2-allyl-3-hydroxypiperidine (**148)**. The ^{1}H NMR spectrum of **148** showed that the terminal olefin was unaffected during $LiAlH_4$ reduction and displayed signals at δ 5.81 and 5.16 due to the secondary (**H**C=CH_2) and primary (HC=C**H**$_2$) olefinic protons rspectively. Further, the reduction of amide carbonyl was confirmed from its ^{13}C NMR spectrum, which showed the absence of carbonyl carbon signal. The free amine and alcohol groups were subsequently protected with Cbz and Bn groups respectively to obtain the intermediate **150** 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, $CHCl_3$)}.

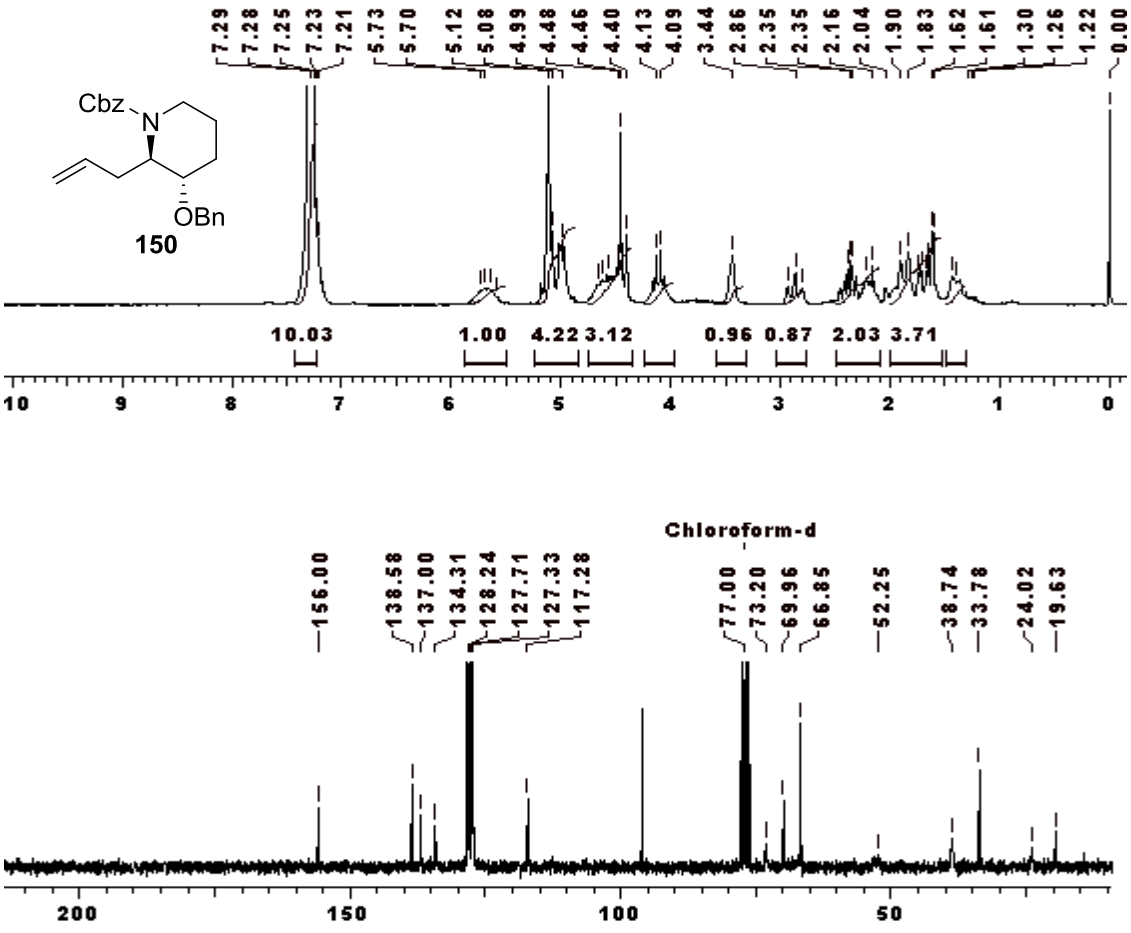


Fig. 22: ^{1}H and ^{13}C NMR spectra of substituted piperidine **150**

The ^{1}H NMR spectrum of **150** 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 –$OC\mathbf{H_2}$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) remained 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 of Cbz protection **(Fig. 22)**.

The transformation of key intermediate **150** to (+)-febrifugine **99** has already been reported in the literature.[42]

2.3.4. Conclusion

In summary, we were able to establish an alternative, short enantioselective synthesis of (+)-febrifugine (**99)** *via* asymmetric dihydroxylation of 1,4-dienic ester in 12 linear steps with 82% ee. The carbon backbone 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.

2.3.5. Experimental Section

(*E*)-Methyl octa-4,7-dienoate (143)

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 **143**, which was purified

by column chromatography using petroleum ether: ethyl acetate (9:1) to obtain pure **143** as colorless liquid.

Yield: 88% (13.55 g); colorless liquid; **IR** (neat, cm^{-1}): 2936, 2861, 2355, 2332, 1735, 1520, 1442, 1251, 1176, 956, 852; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.36 (m, 6H), 2.73 (dt, *J* = 4.8 and 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; **Analysis:** $C_9H_{14}O_2$: 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 (144)

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 **143** (6.16 g, 40 mmol) was added dropwise 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 **144**, which was purified by column chromatography using petroleum ether: ethyl acetate (1:1) to give **144** as a gum.

Yield: 73% (4.55 g); gum; $[\alpha]^{25}_D$ +42 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3445, 2936, 2866, 1769, 1519, 1247, 1185, 1035, 963; **^{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 and 3.5 Hz, 1H), 4.43-4.52 (ddd, *J* =10.9, 7.3, 3.7 Hz, 1H), 5.14 (dd, *J* = 2.3 and 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; **Analysis:** $C_8H_{12}O_3$: 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 (145)

To a stirred solution of hydroxyl lactone **144** (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 dropwise. 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 **145,** which was purified by column chromatography using petroleum ether: ethyl acetate (1:1) to give pure mesylate **145** as a viscous liquid.

Yield: 94% (5.63 g); viscous liquid; $[\alpha]^{25}_D$ + 28 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2939, 2868, 1775, 1735, 1512, 1355, 1250, 1185, 1011, 815; **^{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 and 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; **Analysis:** $C_9H_{14}O_5S$: C, 46.14; H, 6.02; Found: C, 46.19; H, 6.14%.

(*S*)-5-((*R*)-1-Azidobut-3-enyl)-dihydrofuran-2(3*H*)-one (146)

To a stirred mixture of crude methane sulfonate ester **145** (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 **146,** 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, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2935, 2865, 2110, 1775, 1514, 1247, 1031, 819; **^{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; **Analysis:** $C_8H_{11}N_3O_2$: 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 (147)

To a stirred solution of azidolactone **146** (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 **147**, which was purified by column chromatography using petroleum ether: ethyl acetate (1:1) to provide the pure lactam **147**.

Yield: 93% (2.8 g); $[\alpha]^{25}_{D}$ +10 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3445, 2939, 2895, 1657, 1132, 965; **^{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 and 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; **Analysis:** $C_8H_{13}NO_2$: 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 (148)

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 ^{o}C and a solution of lactam **147** (2.5 g, 16 mmol) in THF (20 mL) was added dropwise maintaining the temperature of the reaction mixture below 10 ^{o}C. 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 **148,** which was purified by column chromatography using petroleum ether:ethyl acetate (1:1) to get amino alcohol **148** as colorless solid.

Yield: 85% (2.1 g); **mp**: 112-114 °C (recrystallized from $CHCl_3$); $[\alpha]^{25}_{D}$ -46 (*c* 1, MeOH); **IR** (KBr, cm^{-1}): 3412, 2942, 2893, 1672, 1395; **^{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 and 3.1 Hz, 1H), 2.46-2.59 (dt, *J* = 12.0 and 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 and 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; **Analysis:** $C_8H_{15}NO$: 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 (149)

To a mixture of amino alcohol **148** (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 ^{o}C. 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 **149**, which was purified by column chromatography using petroleum ether:ethyl acetate (8:2) to give **149** as a viscous brown oil.

viscous liquid; $[\alpha]^{25}_{D}$ -37 (*c* 1, $CHCl_3$); **IR** (neat, cm^{-1}): 3412, 2935, 2889, 1723, 1685, 1352, 1163, 1025, 982; **^{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 and 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; **Analysis:** $C_{16}H_{21}NO_3$: 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 (150)

To a stirred solution of crude amino alcohol **149** (3.5 g) in DMF (40 mL) was added 60% sodium hydride (550 mg, 16.2 mmol) dispersed in mineral oil at 0 ^oC. 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 **150**, which was purified by column chromatography using petroleum ether:ethyl acetate (4:1) to afford **150** 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, $CHCl_3$); **IR** (neat, cm^{-1}): 2939, 2887, 1727, 1680, 1625, 1352, 1163; **^{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 and 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; **Analysis:** $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.63; H, 7.52; N, 3.92%.

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Chapter III

Phenolytic Kinetic Resolution of Benzyloxy Epoxides and Asymmetric Synthesis of D-erythro-Sphinganine via Co(III)(salen)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxides

SECTION I:

Co(III)(salen)-catalyzed PKR of two stereocentered benzyloxy epoxides

3.1.1 Introduction

Enantiomerically pure *anti*- or *syn*-1-aryloxy-3-benzyloxy-2-alcohols (**1** and **2**) are valuable 'building blocks' for asymmetric synthesis of bioactive pharmaceuticals.[1] These structural units are present in numerous bioactive compounds such as erythritol,[2] an antidiabetic C4 polyol, *β*-adrenolytic drugs,[3] and broussonetine family of naturally- occurring iminosugars,[4] which show potent glucosidase inhibitory activities with enormous therapeutic potential as *anti*-tumor and *anti*-HIV agents. In addition, these aryloxy benzyloxy alcohols (**1a-f** and **2)** can be used as precursors of 1,2 diols and simple oxiranes, which are versatile intermediates in the synthesis of bioactive molecules (**Fig. 1**).

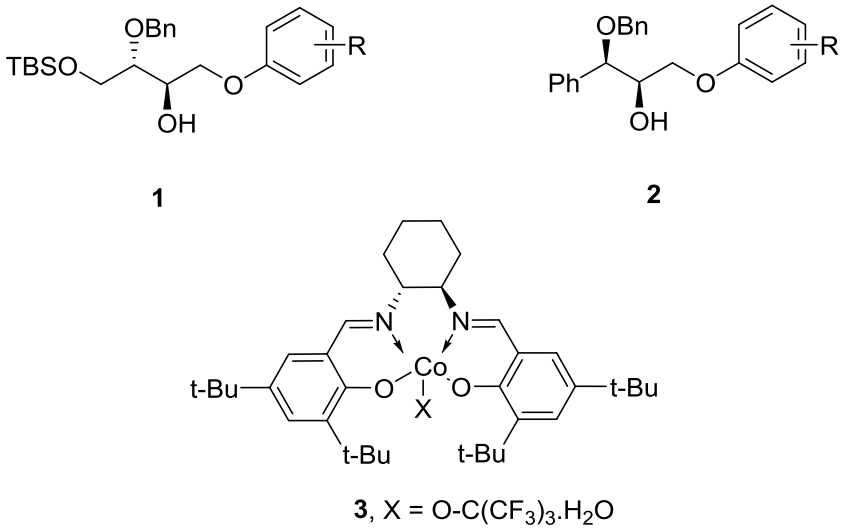


Fig. 1: Structures of *anti*- and *syn*-1-aryloxy-3-benzyloxy-2-alcohols (**1** & **2**) and Co(III)-salen complex (**3**)

The Jacobsen's hydrolytic and phenolic kinetic resolutions (HKR & PKR) of terminal epoxides with one stereocenter, catalyzed by Co(III)-salen complex **3** employ water

and phenol as nucleophiles, respectively.[5] While HKR of epoxides has been comprehensively studied in recent years to understand its mechanistic and synthetic aspects that includes a recent study[6] relating to HKR of functionalized epoxides with two stereocentres, its phenolic version (PKR) has been less explored. In the present work, we have extended the scope of the applicable substrates to cover multi-functionalized epoxides with two stereocenteres and employing functionalized phenols (**5a-f** and **5c**) as the nucleophiles.

3.1.2 Review of literature

Literature search reveals that there are no reports available for the syntheses of enantiomerically pure *anti*- or *syn*-1-aryloxy-3-benzyloxy-2-alcohols.

3.1.3 Present Work

3.1.3.1 Objective

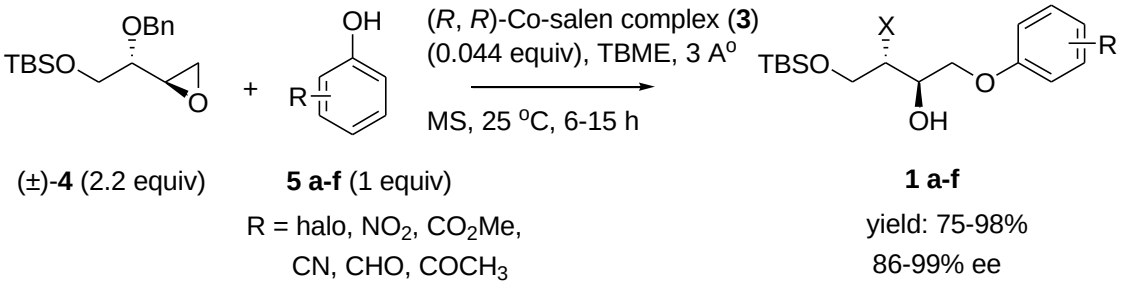
The aim of such an investigation is to obtain enantioenriched 1-aryloxy-3-benzyloxy-2-alcohols (**1** and **2**) by a direct method from the respective racemic materials, thus complementing the other tedious routes.[7] In this section we have described a flexible, novel method that employs PKR of racemic benzyloxy epoxides **4** and **6** to generate benzyloxy alcohols **1** and **2** respectively, with two stereocenters of high optical purities in a single step (**Schemes 1 and 2**).

3.1.4 Results and Discussion

We envisioned that the extension of PKR to the two- stereocentered racemic epoxides would enable us to obtain both the enantiomers of *anti*- or *syn*- aryloxy alcohols depending upon the chiral ligands chosen. Thus, the racemic *anti*- and *syn*-benzyloxy epoxides (**4** and **6**), the substrates for PKR, were efficiently prepared in a highly diastereoselective manner from the corresponding (*Z*)- and (*E*)- allylic alcohols respectively, by following a reported procedure.[6] In this strategy, the relative

stereochemistry between the benzyloxy and epoxide groups is established prior to the PKR step itself and in this way a simple asymmetric reaction can be used to obtain the key enantiomerically pure 1-aryloxy-3-benzyloxy-2-alcohols (**1** and **2)**.

Thus, when PKR of racemic *anti*-benzyloxy epoxide **4** was performed with (*R*, *R*)-Co(III)-salen complex **3** (0.044 equiv) and 4-acetylphenol (1 equiv) (**5c**) in *tert*-butyl methyl ether (TBME), the corresponding *anti*-1-aryloxy-3-benzyloxy-2-alcohol **1c** was isolated in 98% yield and 86% ee (entry c table 1). The PKR can be conducted at low temperatures (-20 ^{o}C), although yields obtained were found to be low. Further, the stereoselectivities in the PKR displayed strong epoxide concentration dependence, requiring at least 2.2 equivalents of epoxides to realize excellent enantioselectivity (**Scheme 1**).



Scheme 1. PKR of *anti*-benzyloxy epoxides.

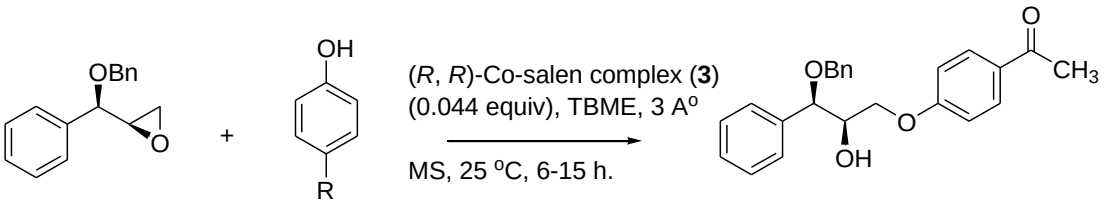
A variety of phenolic substrates were then screened for the PKR process that led to the isolated yields of **1a-f**, with complete regiocontrol. The benzyloxy epoxides underwent the reaction only with electron-deficient phenols (**Table 1**). Unfortunately, simple phenolic substrates like 1-naphthol and electron-rich phenols failed to undergo reaction.

Table 1. PKR of *anti*-benzyloxy epoxide[a]

entry	phenols (R) (**5a-f**)	*anti*-benzyloxy alcohol (**1a-f**) yield (%)[b]	ee (%)[c]
a	4-CN	87	98
b	4-NO_2	89	97
c	4-$COCH_3$	98	86
d	4-CHO	75	99
e	4-CO_2Me	81	97
f	2,3,5-Cl_3	78	97

[a] racemic azido or benzyloxy epoxide **5** (5 mmol), (*R,R*)-Co(III)-salen complex **3** (86 mg, 0.1 mmol), TBME, 3 A^o MS, or phenol (**6**) (2.25 mmol); [b] isolated yield after column chromatographic purification with respect to nucleophile; [c] ee determined by chiral HPLC analysis (see the experimental section for details).

Similarly, the racemic *syn*-benzyloxy epoxide **6**, prepared readily from the corresponding cinnamyl alcohol,[6] was subjected to PKR under identical reaction condition that produced the corresponding enantiopure *syn*- product **2** in high isolated yield and ee (**Scheme 2**).



(±)-**6** (2.2 equiv) **5c** (1 equiv) R = $COCH_3$ **2** yield: 89% 98% ee

Scheme 2. PKR of *syn*-benzyloxy epoxides.

Interestingly, only electron-deficient phenols reacted efficiently with the *syn*-benzyloxy epoxides also, with good yields and ees. The formation of 1-aryloxy-3-

benzyloxy-2-alcohols **1** and **2** was confirmed by ^{1}H and ^{13}C NMR and IR spectroscopy.

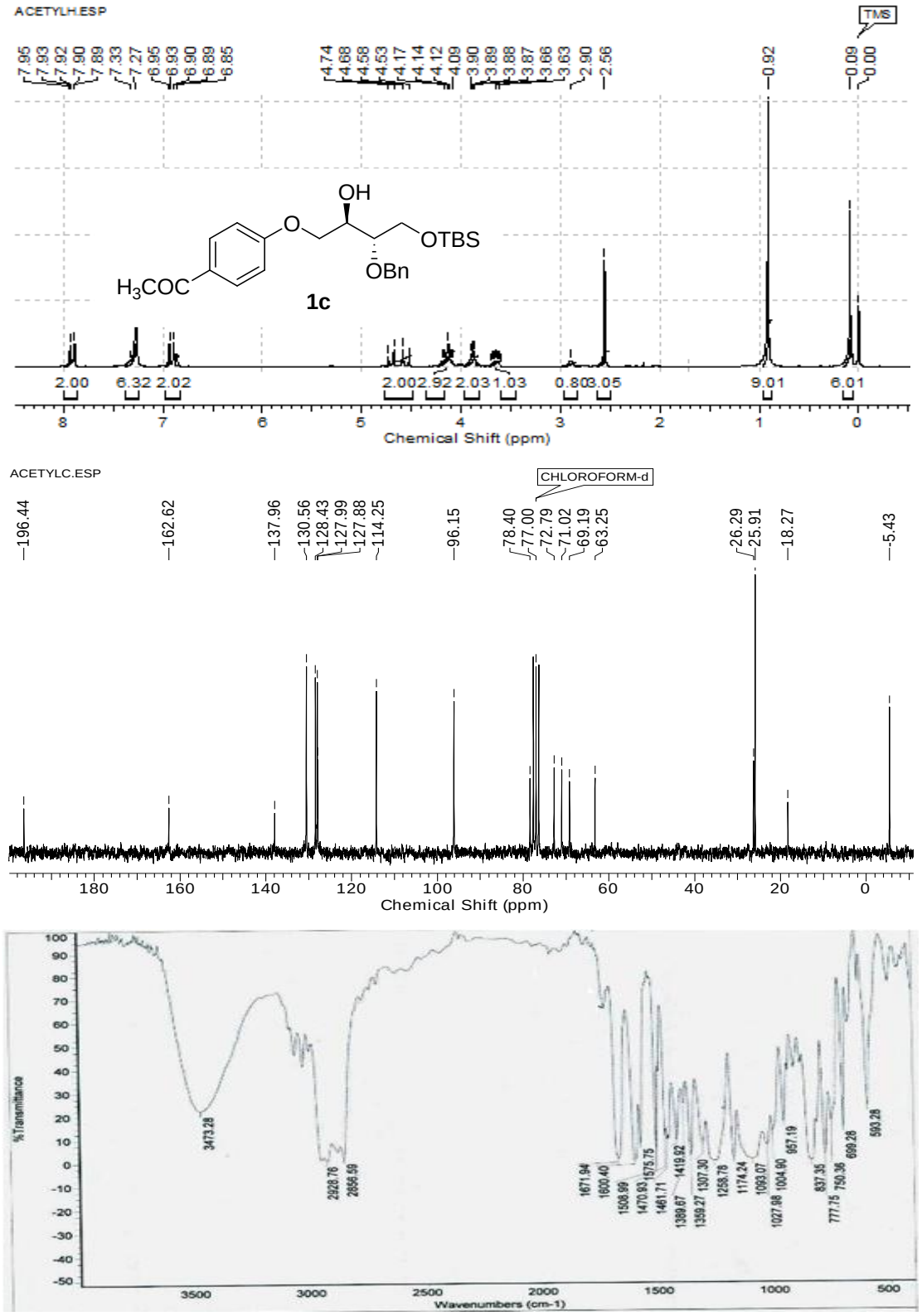
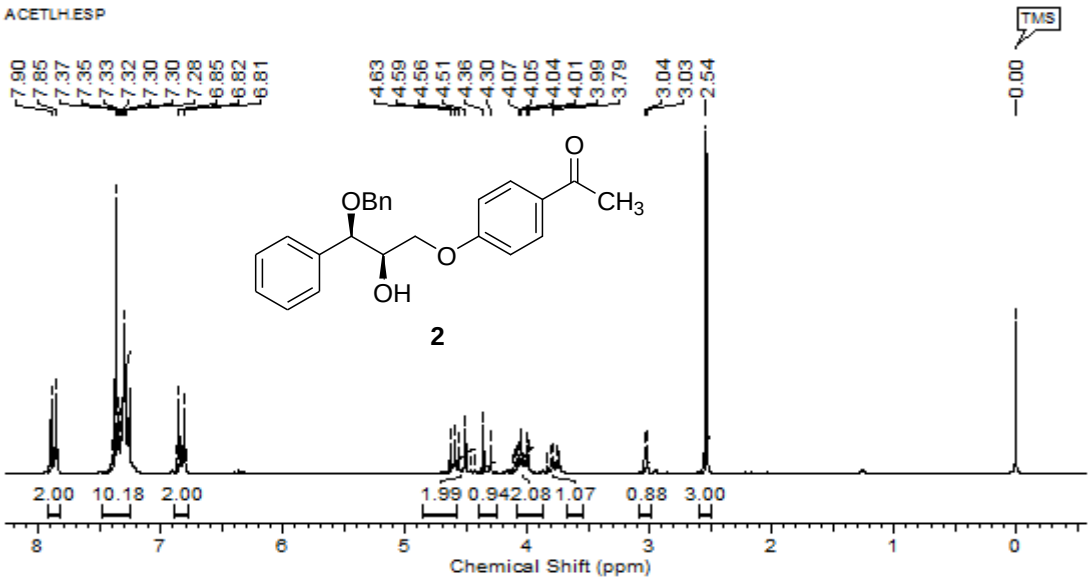


Fig. 2: ^{1}H and ^{13}C of 4-((2*R*,3*S*)-4-(*tert*-butyl dimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)benzonitrile (**1c**)

Example 1: The ^{1}H NMR spectrum of **1c** showed typical signals in the aromatic region at δ 6.85-6.95 and at δ 7.89-7.95 for the aromatic protons. The disappearance of signals in the epoxide region at δ 2.70-3.06 confirmed the opening of epoxide with phenol (**5c**). Its ^{13}C NMR spectrum showed two typical signals at δ 69.1 and 71.0 due to the methylenic (-**C**H_2O) and methinic (-**C**HO-) carbons respectively. A typical signal at δ 196.4 for the carbonyl carbon (-**C**O-) confirmed the opening of epoxide. The disappearance of signals at δ 45.4 and 50.9 in its ^{13}C spectrum and an absorption band at 1671 cm^{-1} in its IR spectrum further substantiated the opening of epoxide with 4-acetylphenol (**Fig. 2**).

Example 2: The ^{1}H NMR spectrum of **2** showed typical signals in the aromatic region at δ 6.81-6.82 and at δ 7.85-7.90 for the protons of acetyl substituted phenolic part and signals at δ 6.85-7.37 for another two aromatic rings. The disappearance of signals in the epoxide region at δ 2.46-3.21 confirmed the opening of epoxide with phenol (**5c**). Its ^{13}C NMR spectrum showed two typical signals at δ 26.2 for the acetyl



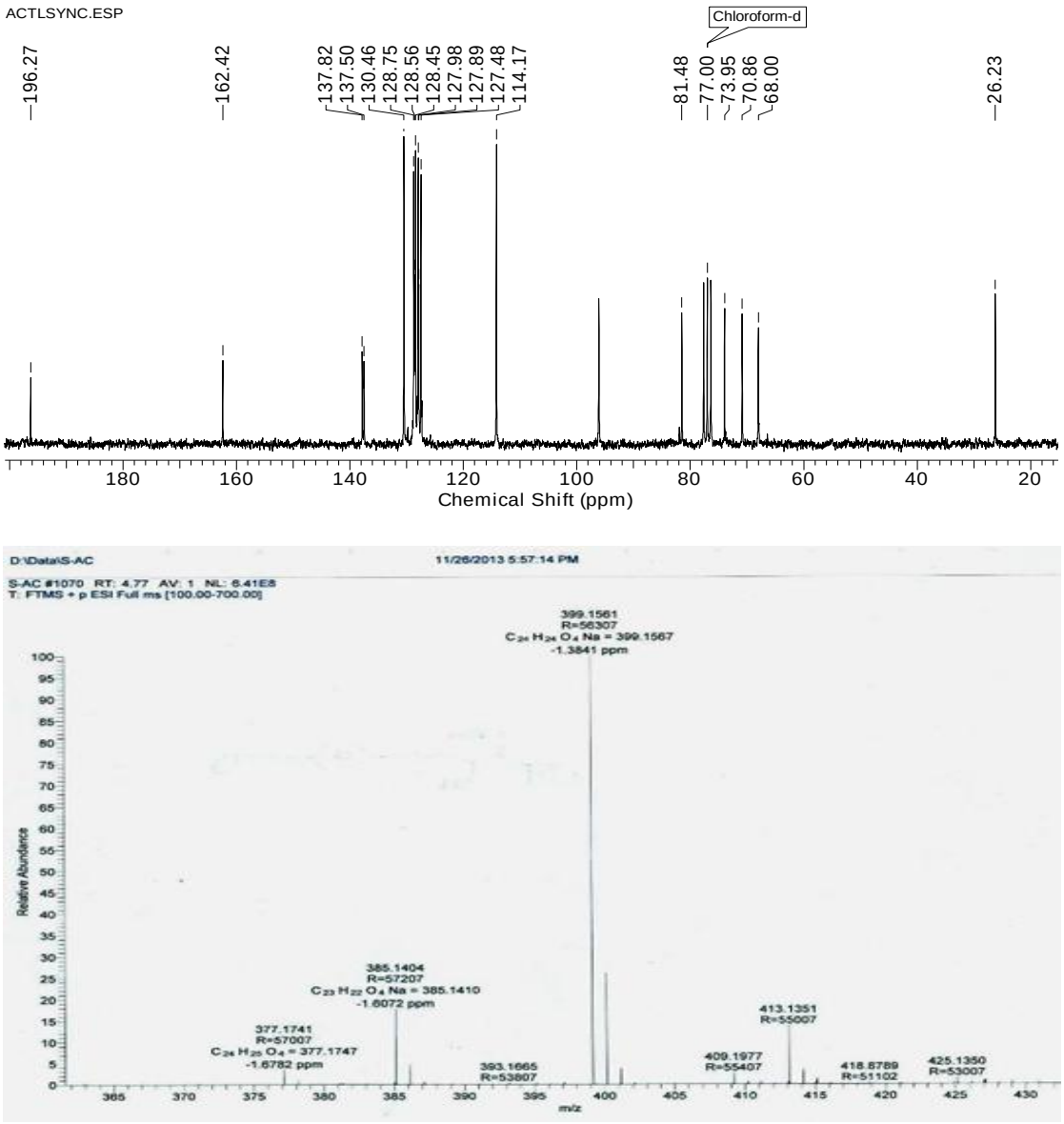


Fig. 3: ^{1}H, ^{13}C and HRMS of (2*R*, 3*S*)-4-(*tert*-Butyldimethylsiloxy)-1-(4-nitrophenoxy)-3-(benzyloxy)butan-2-ol (**2**)

protons (-COC**H**$_3$) and other signals at 68.0, 70.8 and 81.4 due to the methinic (-**C**HOH), methylenic (-**C**H$_2$O-) and benzylic methine (-**C**HOH) carbons respectively. A typical signal at δ 196.2 for the carbonyl carbon (-**C**O-) confirmed the opening of epoxide. The formation of **2** was also substantiated by the presence of molecular ion peak at m/z 399.1567 in its HRMS spectrum (**Fig. 3**).

The relative and absolute stereochemistry of the products **1** and **2** were confirmed by the X-ray crystallographic analysis (see **Fig. 4** for **1c**).

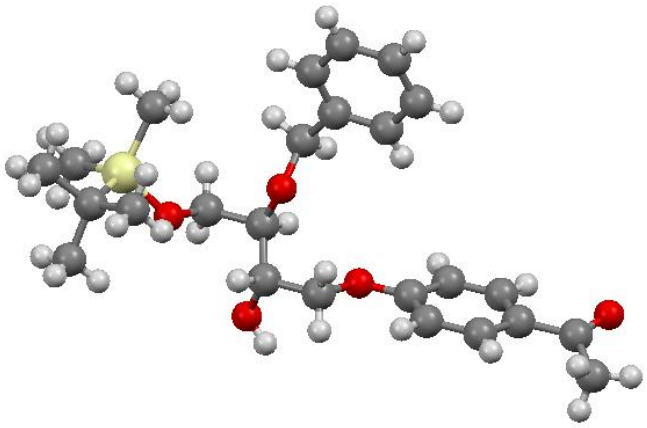


Fig. 4: ORTEP diagram of **1c**

3.1.4 Conclusion

In conclusion, the (salen) Co(III)-catalysed PKR of racemic benzyloxy epoxides provided a highly practical route to enantiopure *anti*- or *syn*-benzyloxy alcohols **1** and **2** in a single step. The reaction is convenient to carry out under mild conditions displaying a wide range of substrate scope. We believe that this PKR strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of the synthesis of racemic benzyloxy epoxides and the readily accessible catalyst in both enantiomeric forms.

3.1.5. Experimental

General procedure for the phenolic kinetic resolutions of *anti*- and *syn*- aryloxy benzyloxy alcohols: (see **Schemes 1 and 2)**

To a stirred solution of (*R*, *R*)-(salen) Co[$OC(CF_3)_3$](H_2O) (**3**) (86 mg, 0.1 mmol), molecular sieve (100 mg, 3 A^o) and racemic *anti*- or *syn*-benzyloxy epoxides (**4** or **6**) (5 mmol), in *tert*-butyl methyl ether (0.15 mL), phenol (2.25 mmol) (**5a-f**) was added at 25 ^oC. The reaction was stirred for 6-15 h till all the phenol gets converted (as monitored by TLC). Solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (eluting with pet.

ether/EtOAc) to give optically pure *anti*- or *syn*-1-aryloxy-3-benzyloxy-2-alcohols in pure form. The enantiomeric purity was determined by chiral HPLC analysis.

(2*R*, 3*S*)-4-(4-(*tert*-Butyldimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)benzo-nitrile (1a)

Yield: 87%; colorless solid, **mp:** 62-63 ^{o}C; **$[\alpha]_D^{25}$** -7.74 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 835, 1096, 1172, 1258, 1302, 1454, 1508, 1605, 2224, 2856, 2883, 2929, 2953, 3474; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.91 (s, 9H), 2.90-2.92 (m, 1H), 3.64 (q, *J* = 5.4 Hz, 1H), 3.86-3.89 (m, 2H), 4.10-4.18 (m, 3H), 4.51-4.73 (dd, *J* = 11.5 and 11.7 Hz, 2H), 6.90-6.96 (m, 2H), 7.27 (m, 5H), 7.53-7.61 (m, 2H); **^{13}C NMR** (50 Hz, $CDCl_3$): -5.5, 18.1, 25.7, 62.9, 69.3, 70.6, 72.5, 78.2, 104.0, 115.1, 118.8, 127.7, 127.8, 128.2, 133.7, 137.7, 161.9; **Optical purity**: 98% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (80:20), 0.5 mL/min, 210 nm) Retention time: t_{major} = 10.15 and t_{minor} = 11.35 min.; HRMS (ESI) m/z Calcd for $C_{24}H_{33}NO_4NaSi$ $[M + Na]^+$, 450.2071; found, 450.2070.

(2*R*, 3*S*)-4-(*tert*-Butyldimethylsiloxy)-1-(4-nitrophenoxy)-3-(benzyloxy)butan-2-ol (1b)

Yield: 89%; colorless liquid; **$[\alpha]_D^{25}$** -16.52 (*c* 1, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 752, 778, 1111, 1263, 1340, 1517, 1593, 2856, 2928, 3472; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.92 (s, 9H), 2.97 (br s, 1H), 3.58-3.67 (m, 1H), 3.87-3.90 (m, 2H), 4.10-4.21 (m, 3H), 4.51-4.73 (dd, *J* = 11.6 and 11.8 Hz, 2H), 6.89-6.97 (m, 2H), 7.24-7.32 (m, 5H), 8.14-8.22 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.2, 25.8, 63.0, 69.8, 71.0, 72.6, 78.1, 114.4, 125.7, 127.9, 128.4, 137.7, 141.6, 163.7; **Optical purity:** 97% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (80:20), 0.5 mL/min, 210 nm) Retention time: t_{major} = 12.53 and t_{minor} = 15.12 min.; **HRMS** (ESI): m/z Calcd for $C_{23}H_{33}NO_6NaSi$ $[M + Na]^+$, 470.1969; found, 470.1975.

1-(4-((2*R*,3*S*)-4-(*tert*-butyl dimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)phenyl)ethanone (1c)

Yield: 98%, colorless solid; **mp:** 91-92 ^{o}C; **[α]$_D^{25}$** -19.89 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 775, 957, 1093, 1258, 1359, 1470, 1575, 1600, 1671, 2856, 2928, 3473; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.92 (s, 9H), 2.56 (s, 3H), 2.90 (br s 1H), 3.61-3.69 (m, 1H), 3.87-3.90 (dd, *J* = 3.0 and 5.4 Hz, 2H), 4.09-4.19 (m, 3H), 4.53-4.74 (dd, *J* = 11.6 Hz, 2H), 6.85-6.95 (m, 2H), 7.27 (s, 5H), 7.89-7.95 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.43, 18.29, 25.91, 26.29, 63.25, 69.19, 71.02, 72.79, 78.40, 114.25, 127.88, 127.99, 128.43, 130.56, 137.96, 162.62, 196.42; **Optical purity:** 86% ee determined by HPLC analysis (OJ-H column, *n*-hexane/ 2-propanol (80:20), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 14.38 and t_{major} = 15.07 min. **HRMS** (ESI): m/z Calcd for $C_{25}H_{36}O_5NaSi$ $[M + Na]^+$, 467.2224; found, 467.2220

(2*R*, 3*S*)-4-(4-(*tert*-Butyldimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)benz-aldehyde (1d)

Yield: 75%; gum; **[α]$_D^{25}$** +14.02 (*c* 1, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 755, 834, 1097, 1256, 1462, 1509, 1600, 1693, 2928, 3454; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.92 (s, 9H), 2.95 (br s, 1H), 3.63-3.69 (m, 1H) 3.87-3.91 (m, 2H), 4.11-4.21 (m, 3H), 4.62 (dd, *J* = 11.6 and 11.8 Hz, 2H), 6.96-7.00 (m, 2H), 7.24-7.35 (m, 5H), 7.80-7.85 (m, 2H), 9.88 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.2, 25.9, 63.2, 69.3, 71.0, 72.7, 78.3, 114.8, 128, 128.4, 130.1, 131.9, 137.9, 163.7, 190.4; **Optical purity:** 99% ee determined by HPLC analysis (OJ-H column, *n*-hexane/ 2-propanol (80:20), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 14.38 and t_{major} = 15.07 min.; **HRMS** (ESI): m/z Calcd for $C_{24}H_{34}O_5NaSi$ $[M + Na]^+$, 453.2068; found, 453.2062

(2*R*, 3*S*)-Methyl 4-(4-(*tert*-butyldimethylsiloxy)-3-(benzyloxy)-2-hydroxybutoxy)-benzoate (1e)

Yield: 81%, colorless liquid; **[α]$_D^{25}$** -20.04 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 771, 837, 1169, 1255, 1435, 1511, 1605, 1718, 2928, 3478; **^{1}H NMR** (200 MHz, $CDCl_3$) δ

0.09 (s, 6H), 0.91 (s, 9H), 2.94 (br s, 1H), 3.63- 3.68 (m, 1H), 3.81-3.96 (m, 5H), 4.07-4.17 (m, 3H), 4.53-4.74 (dd, *J* = 11.6 and 11.8 Hz, 2H), 6.85-6.92 (m, 2H), 7.27 (m, 5H), 7.93-8.00 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.2, 25.8, 51.7, 63.2, 69.0, 70.8, 72.7, 78.4, 114.1, 122.7, 127.8, 127.9, 128.3, 131.5, 137.9, 162.4, 166.6; **Optical purity:** 97% ee determined by HPLC analysis (OJ-H column, *n*-hexane/ 2-propanol (80:20), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 14.38 and t_{major} = 15.07 min. **HRMS** (ESI): m/z Calcd for $C_{25}H_{36}O_6NaSi$ $[M + Na]^+$, 483.2173; found, 483.2169.

(2*R*,3*S*)-1-(2,4,5-trichlorophenoxy)-4-(*tert*-butyldimethylsiloxy)-3-(benzyloxy)butan-2-ol (1f)

Yield: 78%; gum; **$[\alpha]_D^{25}$** +5.9 (*c* 1.0, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 701, 763, 1050, 1261, 1454, 1492, 2104, 2935, 3034, 3416; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.92 (s, 9H), 2.88-2.95 (m, 1H), 3.64-3.71 (m, 1H) 3.84-3.91 (m, 2H), 4.06-4.13 (m, 3H), 4.52-4.75 (dd, *J* = 11.7, 2H), 6.93 (s, 1H), 7.28-7.30 (m, 5H), 7.43 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.3, 25.9, 63.4, 70.6, 70.9, 72.9, 78.2, 115.0, 122.1, 124.4, 127.9, 127.9, 128.1, 128.4, 130.8, 131.2, 137.9, 153.3; **Optical purity:** 97% ee determined by HPLC analysis (OJ-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 14.38 and t_{major} = 15.07 min.; **HRMS** (ESI): m/z Calcd for $C_{23}H_{31}Cl_3O_4NaSi$ $[M + Na]^+$, 527.0949; found, 527.0953.

(2*R*,3*R*)-1-[4-(3-(Benzyloxy)-2-hydroxy-3-phenylpropoxy)phenyl]ethanone (2)

Yield: 89%; gum; **$[\alpha]_D^{25}$** +21.56 (*c* 1, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 701, 755, 1065, 1255, 1358, 1454, 1599, 1673, 3453; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.54 (s, 3H), 3.04 (br s, 1H), 3.74-3.80 (m, 1H), 3.97-4.16 (m, 2H), 4.30-4.56 (dd, *J* = 11.2 and 11.3 Hz, 2H), 4.61 (d, *J* = 6.8 Hz, 1H), 6.79-6.86 (m, 2H), 7.30-7.42 (m, 10H), 7.86 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.2, 68.0, 70.8, 73.9, 81.4, 114.1, 127.4, 127.8, 127.9, 128.4, 128.5, 128.7, 130.4, 137.5, 137.8, 162.4, 196.2; **Optical purity:**

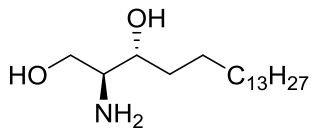
98% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (70:30), 0.5 mL/min, 254 nm) Retention time: minor = 10.72 and t_{major} = 11.28 min.; **HRMS** (ESI) m/z Calcd for $C_{24}H_{24}O_4Na$ $[M + Na]^+$, 399.1567; found, 399.1567.

SECTION II:

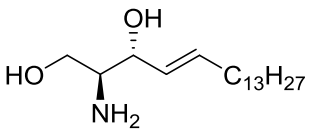
Asymmetric Synthesis of D-*erythro*-Sphinganine *via* Co(III)-(salen) Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxide

3.2.1 Introduction and pharmacology

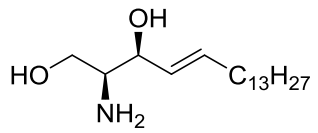
Sphingolipids such as ceramides, cerebrosides and gangliosides are ubiquitous components of cell membranes.[8] They play critical roles in many physiological processes including cell growth, differentiation, neuronal repair, cell recognition, adhesion, and signalling.[9] Over the past decade, significant 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.[10] 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 or without a 4,5-*trans* double bond as in sphingosines (**8 and 9)** and sphinganine **(7)** or 2-amino-1,3,4 triol head group without unsaturation as in phytosphingosine (**10**).[10]



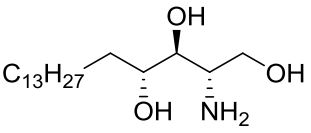
7, *D-erythro*-sphinganine



8, D-*erythro*- sphingosine



9, *threo*- sphingosine



10, *D-ribo*-phytosphingosine

Fig. 5: Structures of some 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*-sphinganine (**7**) and *erythro*-sphingosine (**8**) **(Fig. 5**).

ribo-Phytosphingosine is readily obtained on an industrial scale from yeast fermentation process. But the complicated isolation of other sphingolipids from natural sources, and 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.[11-12] The most commonly employed strategies are those which make use of carbohydrates[13] and serine[14] as a source of chirality; many approaches are also based on asymmetric reactions, such as aldol condensation[15] as well as Sharpless asymmetric dihydroxylation[16] and asymmetric epoxidation (using Shi's catalyst or Sharpless protocol[17]). The design of an efficient and catalytic route to *D-erythro*-sphinganine therefore continues to be important as it strongly inhibits protein kinase C.5.[18] Thus the biological significance and the complicated isolation of sphingolipids from natural sources justifies the efforts towards their synthesis.

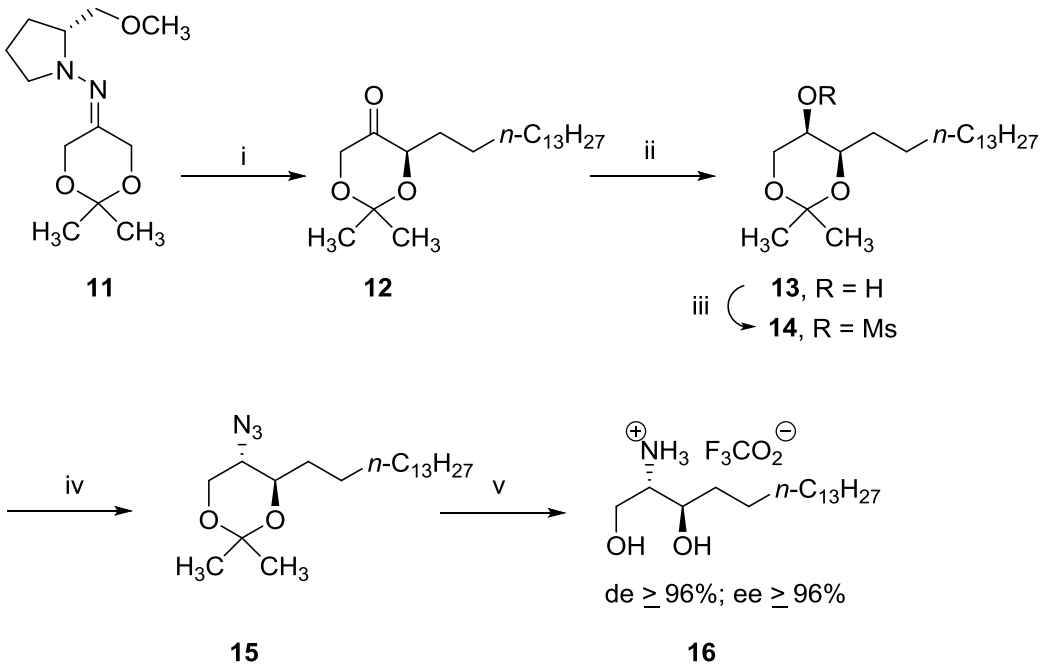
3.2.2 Review of Literature

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

Ender's approach (2004)[19]

The stereogenic centres are generated by α-alkylation using the RAMP hydrazone methodology and diastereoselective reduction of the ketone **12** with L-selectride. In the first step hydrazone **11** was alkylated with pentadecyl bromide. Subsequently, hydrazone was cleaved with a saturated aqueous solution of oxalic acid to produce the

ketone **12** in excellent yield (96%) and enantiomeric excess (ee 96%). The ketone **12** was reduced with L-Selectride to give alcohol **13** in practically quantitative yield (98%) and very high diastereomeric excess (de 96%). Treatment of alcohol **13** with methanesulfonyl chloride yielded the corresponding mesylate **14** which was then converted into the azide **15** by nucleophilic substitution with sodium azide in DMF in the presence of 18-Crown-6. Reduction of the azide **15** with lithium aluminium hydride followed by hydrolytic cleavage of the acetonide group with trifluoroacetic acid in THF and water afforded the ammonium salt **16** with an overall yield of 47%, a diastereomeric excess of greater than 96% and an enantiomeric excess of greater than 96% (**Scheme 3**).

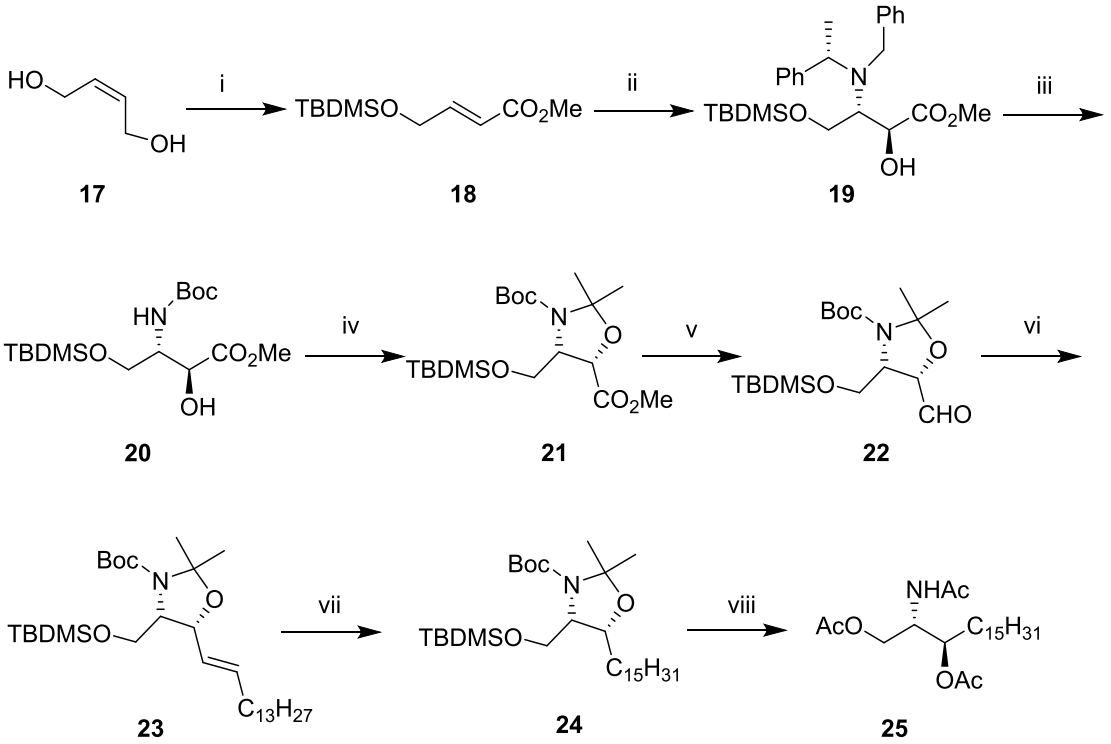


Scheme 3: i) a) *t*-BuLi, THF, -78 °C, then pentadecyl bromide, -100 °C; b) aq. oxalic acid; ii) L-Selectride, THF, -78 °C; iii) MsCl, CH_2Cl_2, Et_3N, 0 °C,; iv) NaN_3, 18-Crown-6, DMF, 100 °C; v) a) $LiAlH_4$, THF, 25 °C.; b) TFA, THF/H_2O, 25 °C.

Davies *et al.* (2008)[20]

The synthesis of spinganine started with γ-silyloxy-α, β-unsaturated ester **18**, which

was subjected to conjugate addition of lithium (*S*)-*N*-benzyl-N-(α-methylbenzyl) amide followed by enolate oxidation with (+)-CSO proceeded to generate the corresponding (2S,3S,αS)-α-hydroxy-β-amino-γ-silyloxy ester **19**, which was isolated in good yield (91%), and >98% de. Reductive debenzylation of **19** and insitu boc protection afforded compound **20**.



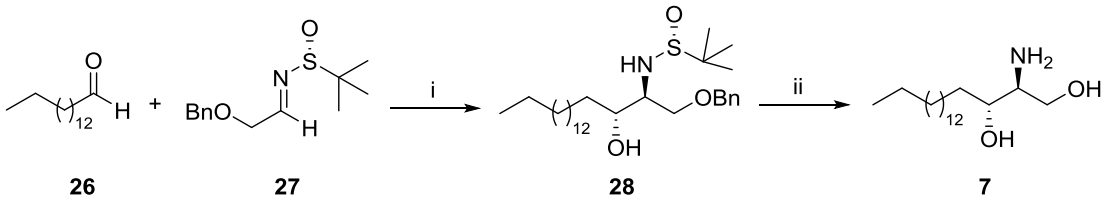
Scheme 4: (i) a) TBDMSCl, imidazole, DMAP, DCM, 25 °C, 12 h; b) O_3, CH_2Cl_2, −78 °C, 30 min, then DMS, 25 °C, 12 h; c) $(EtO)_2P(O)CH_2CO_2R$, $^iPr_2NEt$, LiCl, MeCN, 48 h; (ii) lithium (*S*)-*N*-*benzyl*-*N*-(α-methylbenzyl)amide, THF,−78 °C, 2 h, then (+)-CSO, −78 °C to 25 °C, 12 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, Boc_2O, EtOAc, 25 °C, 12 h; (iv) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, 50 °C, 12 h. (v) a) $LiAlH_4$, THF, 0 °C, 6 h; b) IBX, DMSO, rt, 12 h; (vi) $C_{14}H_{29}PPh_3^+Br^-$, BuLi, THF–hexane (1 : 1), −78 °C to 25 °C, 12 h; (vii) H_2 (1 atm), Pd/C, EtOAc, 25 °C, 6 h; (viii) a) HCl (3M, aq),MeOH, 50 °C, 3 h; b) Ac_2O,DMAP, pyridine, 25 °C, 12 h.

Amino alcohol **20** was acetonide protected gave ester **21** followed by reduction with $LiAlH_4$ and subsequent oxidation with IBX to give aldehyde **22.** Compound **22** on Wittig olefination gave olefin **23**, which was subjected to hydrogenation conditions

and acetate protection to give *N, O, O*-triacetyl sphinganine **25** (**Scheme 4**).

Lin's approach (2008)[21]

This approach involves the SmI_2-mediated cross-coupling of *N-tert*-butanesulfinyl imines and aldehydes, which provides ready access to enantiopure *anti*-1,2-amino alcohols. When palmitaldehyde **26** (4 equiv) was treated with imine **27** at -78 ^oC in THF, amino alcohol **28** was obtained as a single diastereomer in 64% yield. Removal of the benzyl and sulfinyl groups gave D-*erythro*-sphinganine (**7**) in 90% yield with 97% ee. This approach represents one of the most convenient synthesis of **7** reported to date (**Scheme 5**).

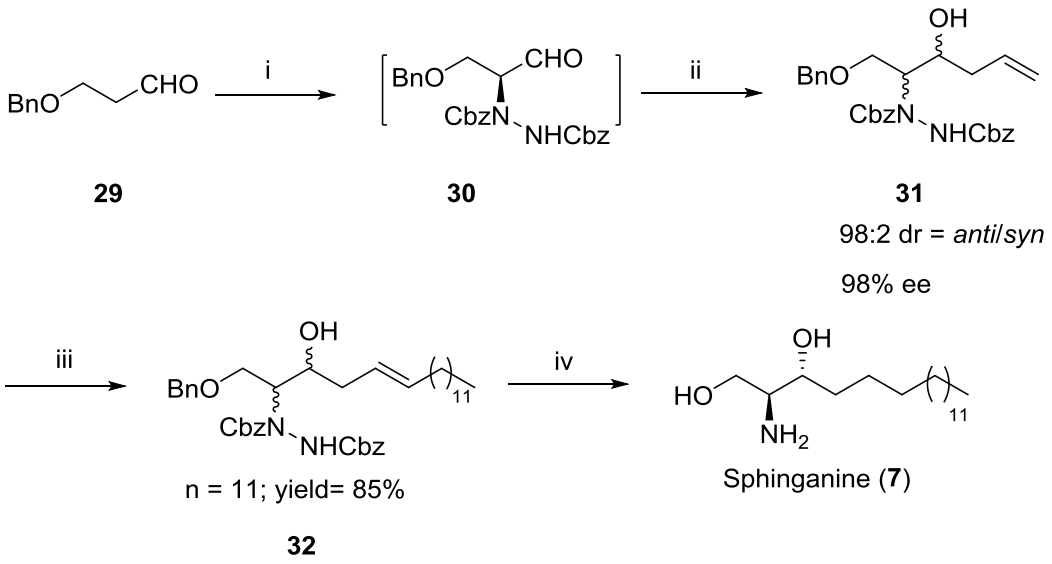


Scheme 5: (i) SmI_2, *t*-BuOH, 64%; (ii) a) Li/naphthalide, b) HCl, 90%

Kumar's approach (2013)[22]

The synthesis of sphinganine (**7)** started by treating commercially available 3-(benzyloxy) propanal **29** with 10 mol % of D-proline followed by the addition of dibenzyl azodicarboxylate (DBAD) in acetonitrile at 0 ^oC for 3 h. The reaction mixture having **30** in situ was diluted with THF/H_2O (3:1) and then reacted with indium powder and allyl bromide at room temperature for 12 h that produced homoallylic alcohol **31** in 72% yield. *anti* Diastereomer was formed as a major product. Eantioselectivity was found to be 95% (chiral HPLC). The cross metathesis reaction between homoallylic alcohol **31** and tetradec-1-ene proceeded smoothly using 5 mol% of Grubbs' second–generation catalyst in CH_2Cl_2 producing **32** in 85% yield. And finally the N-N bond in **32** was successfuly cleaved and the double bond

was reduced simultaneously under hydrogenation conditions (Raney-Ni in MeOH and AcOH at 60 psi) to afford sphinganine (**7**) ([α]$^{25}_{D}$ +9.8 (*c* 0.04, MeOH)] in 99% yield (**Scheme 6**).

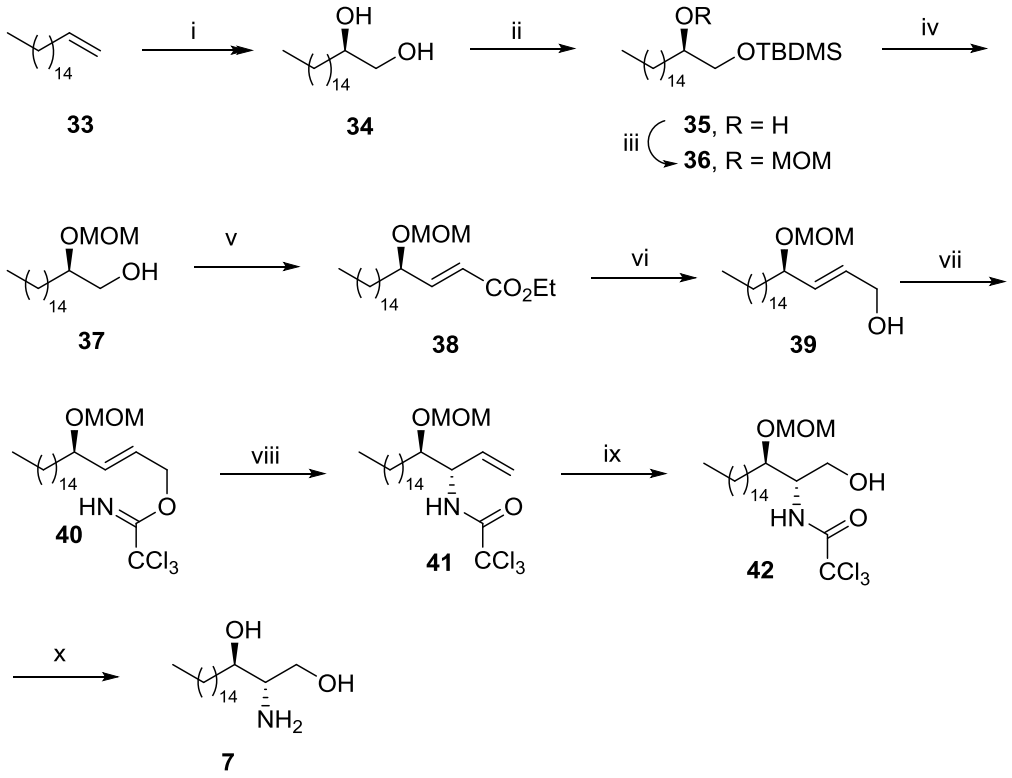


Scheme 6: DBAD (1.2 equiv), D-proline (10 mol %), CH_3CN (0.1 M), 0 ºC, 3 h; In (2 equiv), 1-bromo-2-propene (2 equiv), CH_3CN-THF-H_2O (4:3:1) 25 ^{o}C, 12 h, 72%; tetradec-1-ene, Grubb's 2nd generation, 6 h, CH_2Cl_2 85%; H_2 (60 psi), Raney Ni, MeOH, AcOH, 8 h, 99%.

Sutherland's approach (2013)[23]

The synthesis began with the preparation of a suitable allylic alcohol substrate for the ether-directed Overman rearrangement. Initially, a chiral diol was prepared by the Sharpless asymmetric dihydroxylation of 1-heptadecene. Thus dihydroxylation of **33** gave diol **34** in >99% enantiomeric excess and in 87% yield. The primary and secondary hydroxyl groups of **34** were then selectively protected as TBDMS and MOM ethers, respectively, under standard conditions, giving **36** in quantitative yield. Removal of the TBDMS protecting group was followed by a one-pot Swern oxidation/Horner−Wadsworth−Emmons reaction of **37** with triethyl phosphonoacetate under Masamune-Roush conditions gave exclusively (*E*)-α,β-unsaturated ester **38**.

DIBAL-H reduction of **38** gave allylic alcohol **39**. Allylic alcohol **39** was transformed into the corresponding allylic trichloroacetimidate **40** using trichloroacetonitrile and DBU, and this was treated with *bis*(acetonitrile)palladium(II) chloride (10 mol %) to effect the key Overmann rearrangement. Analysis of the ^{1}H NMR spectrum showed the presence of the *erythro*- **41** and *threo*-allylic trichloroacetamides in a 28:1 diastereomeric ratio, respectively, which was purified by column chromatography (major *erythro* diastereomer **41** in 78% yield from allylic alcohol **39**).



Scheme 7: (i) AD-mix-*β*, *t*-BuOH/H_2O, 87%; (ii) TBDMSCl, imidazole, THF; (iii) MOMBr, EtN*i*-Pr_2, CH_2Cl_2, 100%; (iv) TBAF, THF, 91%; (v) DMSO, $(COCl)_2$ Et_3N, CH_2Cl_2, -78 ^oC; (v) triethylphosphonoacetate, LiCl, DBU, MeCN, 100%; (vi) DIBAL-H, Et_2O, -78 ^oC, 86%; (vii) CCl_3CCN, DBU, CH_2Cl_2; (viii) $PdCl_2(MeCN)_2$, *p*-benzoquinone, tolune, 45 ^oC, dr = 28:1, 78%; (ix) O_3, MeOH, CH_2Cl_2, -78 ^oC, then $NaBH_4$ 78%; (x) 6M HCl, 60 ^oC, 100%.

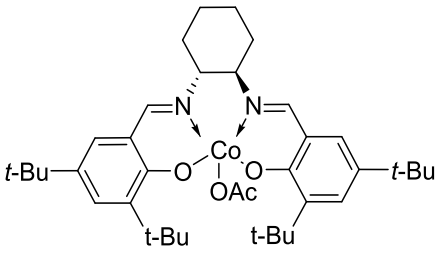
To complete the synthesis of D-*erythro*-sphinganine, alkene **41** was subjected to ozonolysis followed by a reductive workup, gave alcohol **42** in 78% yield. Removal

of both protecting groups under acid-mediated conditions completed the 11-step synthesis of D-*erythro*-sphinganine **7** in 41% overall yield (**Scheme 7**).

3.2.3 Present Work

3.2.3.1 Objective

As can be seen from the above discussion, several methods for enantioselective synthesis of **7** or its isomers have been reported. Unfortunately, most of the reported methods for the synthesis of sphinganine (**7**), either employ chiral starting materials, expensive reagents or involve longer reaction sequences coupled with poor product selectivity. Despite recent improvements in the synthetic methodology for the control of the two stereo centers in the target molecule **7**, most of them suffer either from poor diastereoselectivity, low overall yields, and/or a large number of steps involved. The development of an efficient and catalytic route to sphinganine therefore continues to attract the attention of chemists. As a part of our research program aimed at developing enantioselective syntheses of bioactive molecules, we became interested in developing a simple and feasible route to *anti*-amino alcohol **7**. The section describes an enantioslective synthesis of D-*erythro*-sphinganine (**7**) *via*- Co(III)-salen (**Fig. 6**) catalyzed hydrolytic kinetic resolution (HKR) of azido epoxide as a key step for the introduction of chirality in the molecule (**Scheme 9**).

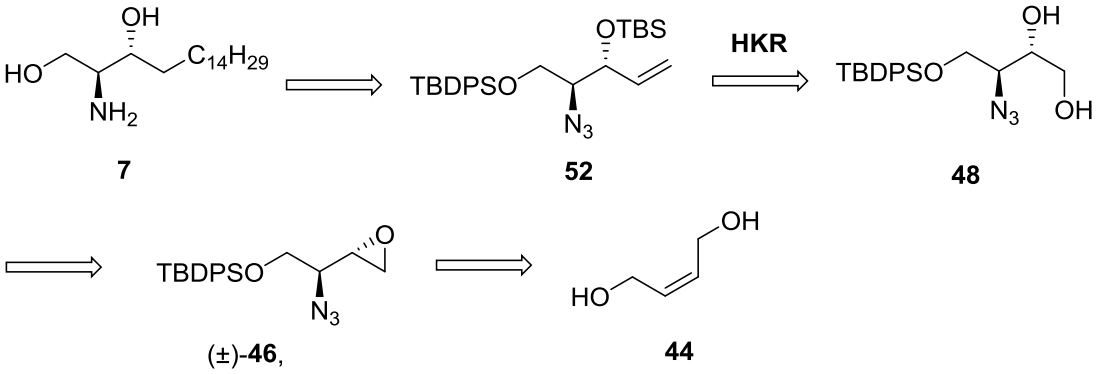


43

Fig. 6: (*R*,*R*)-Co(III)-salen complex (**43**)

3.2.3.2 Results and Discussion

Retrosynthetic analysis reveals that, for the synthesis of *D-erythro*-sphinganine **1**, alkene **52** was envisaged as the key intermediate, which could be easily prepared from (2S, 3S)-3-azido diol **48**. We further visualized that diol **48** could be prepared from Co(III)salen-catalyzed HKR of racemic azido epoxide **46**. The precursor epoxide **46** could be readily prepared from *cis*-butene-1,4-diol **44** (**Scheme 8**).

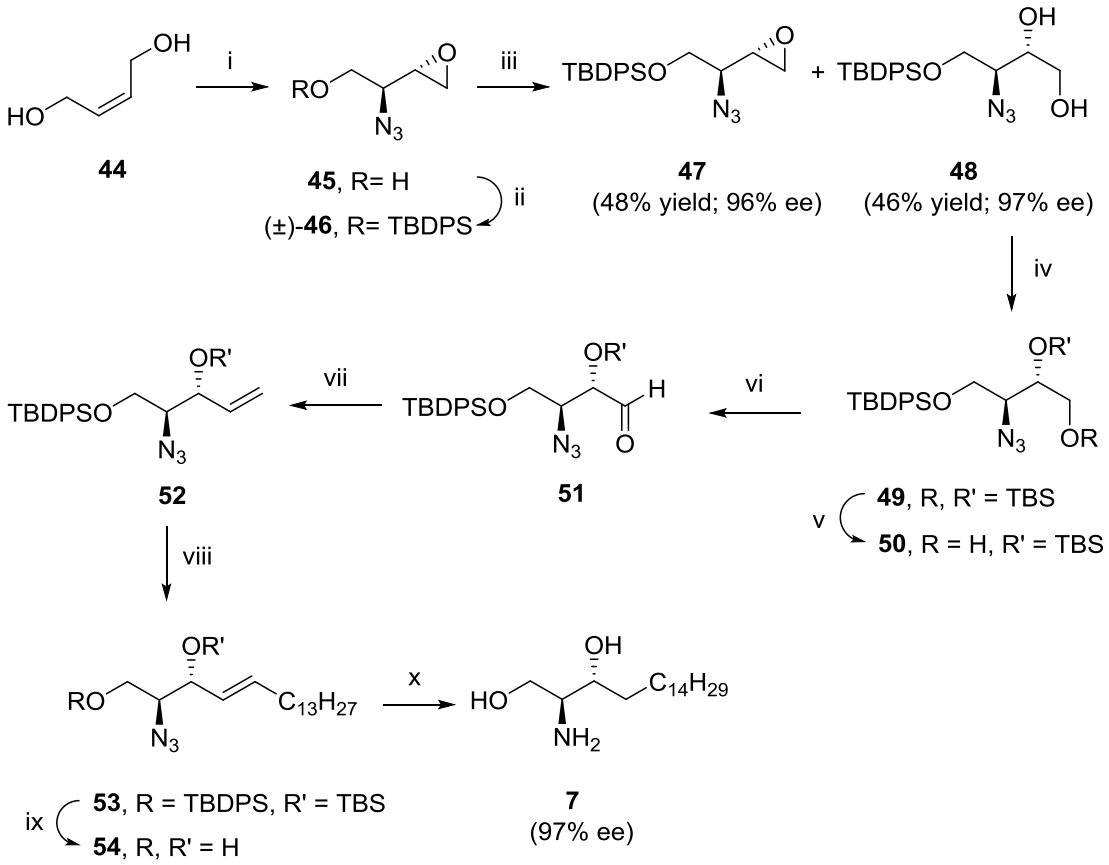


Scheme 8: Retrosynthetic analysis of *D-erythro*-sphinganine (**7)**

The synthesis of **7** commenced with bromoazidation of commercially available *cis*-1,4-butenediol **44** in presence of NBS and NaN_3 followed by its base treatment (powdered NaOH, THF) gave racemic *anti*-azido epoxy alcohol **45** in 84% yield and > 99% dr (**Scheme 9**). The epoxide formation was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **45** showed two typical multiplets at δ 2.82-2.90 (m, 2H) and δ 3.09-3.12 (m, 1H) for methylene (-C**H**$_2$O) and methane (-C**H**O-) protons respectively. Its ^{13}C NMR spectrum showed typical signals at δ 45.0 and 50.3 due to primary and secondary carbons of epoxide ring respectively **(Fig. 7).**

The primary hydroxyl group in **45** was protected as its silyl ether **46** (TBDPSCl, imid., CH_2Cl_2). The formation of racemic silyl protected *anti*-azido epoxide **46** was confirmed by ^{1}H NMR spectrum, which displayed signals at δ 7.39-7.69 (m, 10H) for aromatic protons of diphenyl group and a typical singlet at δ 1.08 (s, 9H) for the *tert*-butyl group. Its ^{13}C-NMR showed typical signals at δ 127.8-135.5 for diphenyl ring

carbons and δ 26.7 for *tert*-butyl group in the aliphatic region, which confirmed the formation of TBDPS protected azido epoxide **46** (**Fig. 8**).



Scheme 9: (i) (a) NBS, NaN_3, CH_3CN:H_2O (4:1), 0 ^oC, 3 h,; (b) NaOH, THF, 0 ^oC, 3 h, 84%. (ii) TBDPSCl, imid., CH_2Cl_2, 0 ^oC, 4 h, 97%; (iii) (*R*,*R*)-(-)-N,N'–*bis*(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamiocobalt(III) **43** (0.5 mol%), H_2O (0.48 equiv), 25 ^oC, 24 h; (iv) TBSCl, imid., dry DMF, 0 ^oC, 6 h, 87%; (v) CSA, MeOH, 25 ^oC, 30 min, 75%; (vi) IBX, EtOAc, reflux, 3 h, 80%; (vii) $Ph_3P^+CH_3I^-$, *n*-BuLi, dry THF, 0 ^oC, 8 h, 65%; (viii) 1-pentadecene, Grubbs' II generation catalyst (10 mol %), CH_2Cl_2, 40 ^oC, 32 h, (ix) TBAF, THF, 25 ^oC, 6 h, 79% (over two steps); (x) (10%) Pd/C, H_2 (1 atm), MeOH/AcOH (5:1), 25 ^oC, 12 h, 90%.

The azido epoxide **46** was then subjected to HKR using (*R*,*R*)-(salen) Co(III)($OCOCH_3$) (**43**) as the catalyst that produced azido diol **48** in 46% yield and 97% ee along with the unreacted *anti*-azido epoxide **47** in 48% yield and 96% ee. Both **48** and **47** were however readily separated by column chromatography. The formation of *anti*-azidodiol **48** was confirmed by ^1H and ^{13}C NMR spectroscopy.

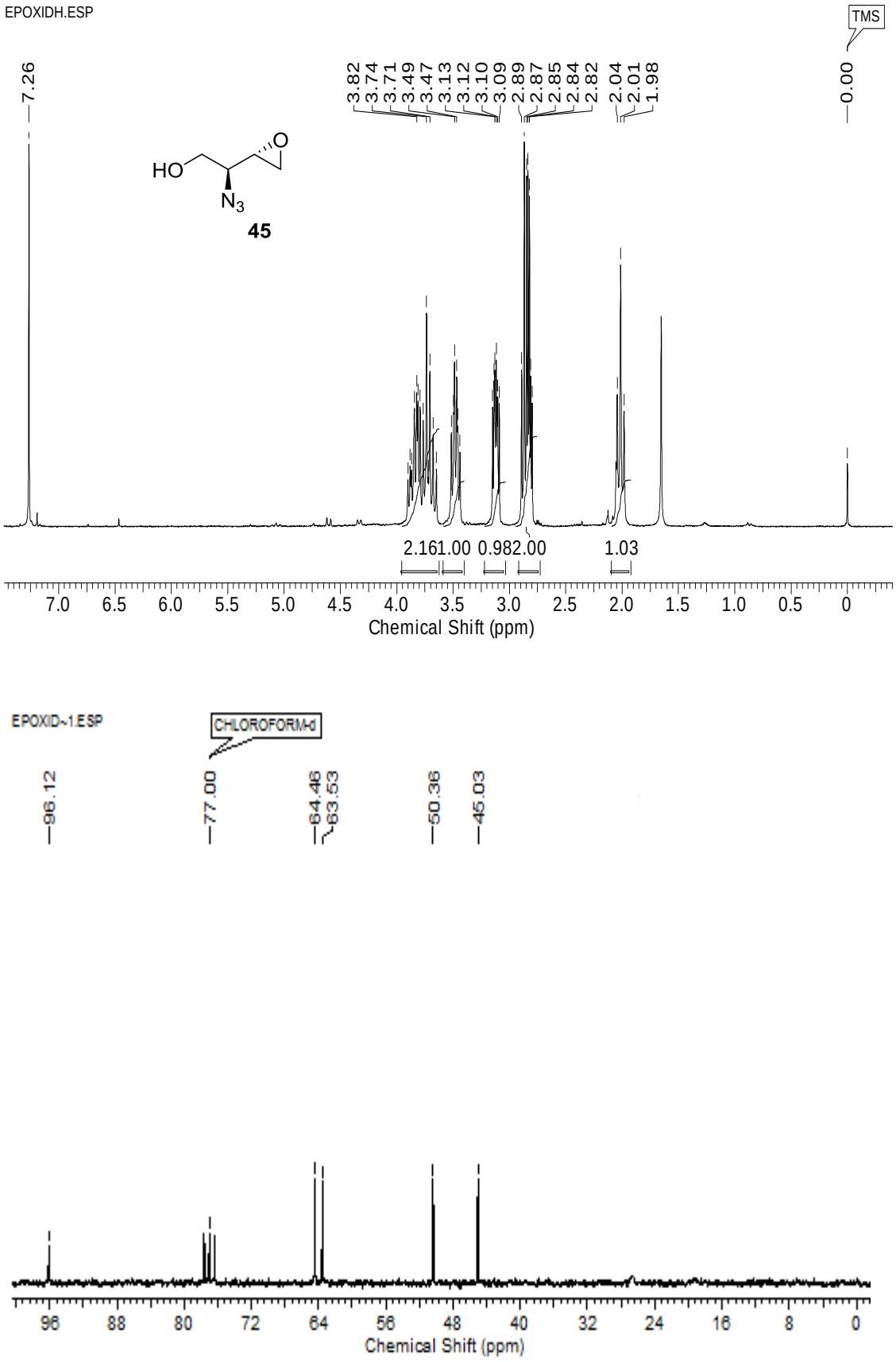


Fig. 7: ^{1}H and ^{13}C NMR spectra of Azido epoxide **(45)**

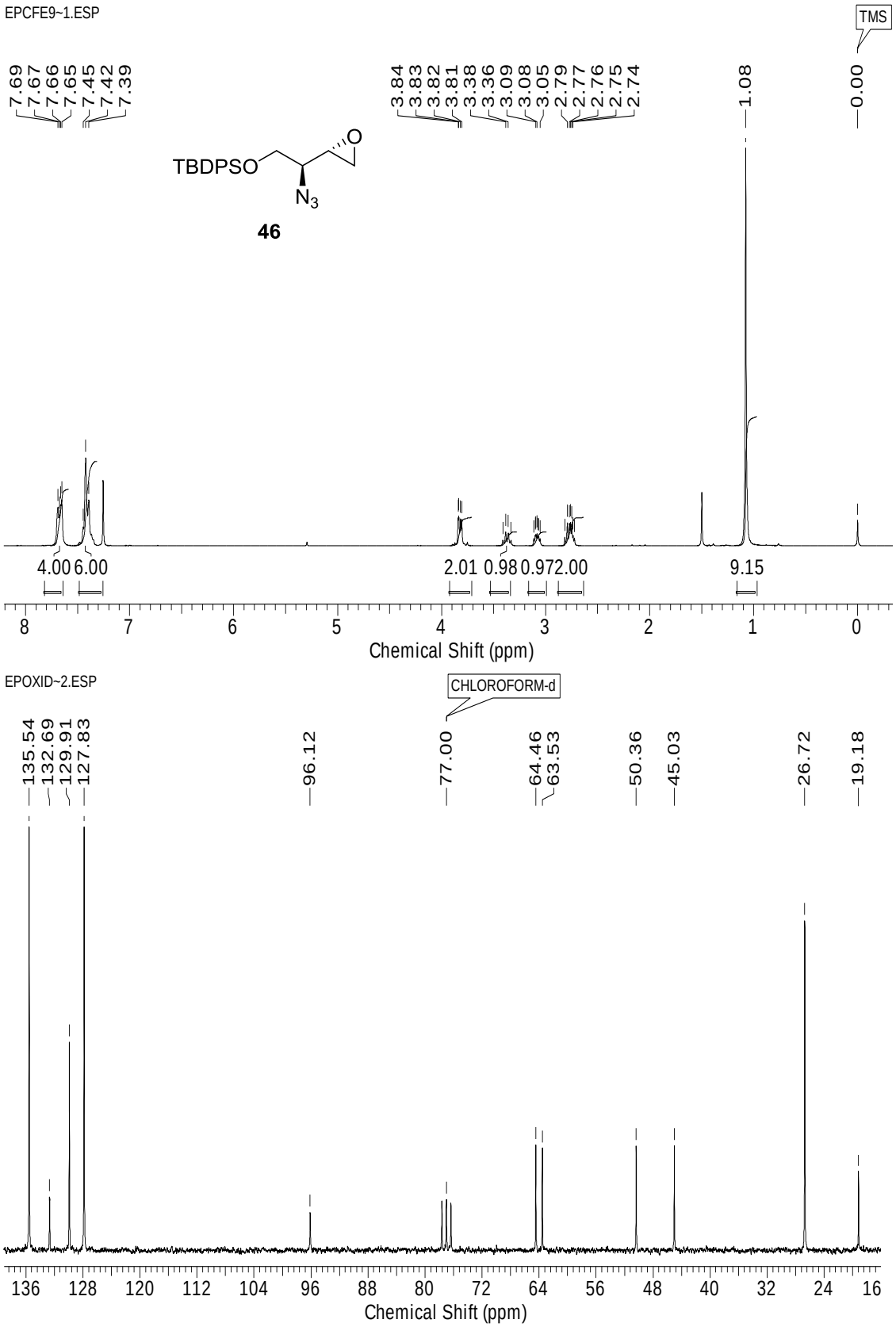


Fig. 8: ^{1}H and ^{13}C NMR spectra of ((S)-2-azido-2-((S)-oxiran-2-yl)ethoxy)(*tert*-butyl)diphenylsilane **(46)**

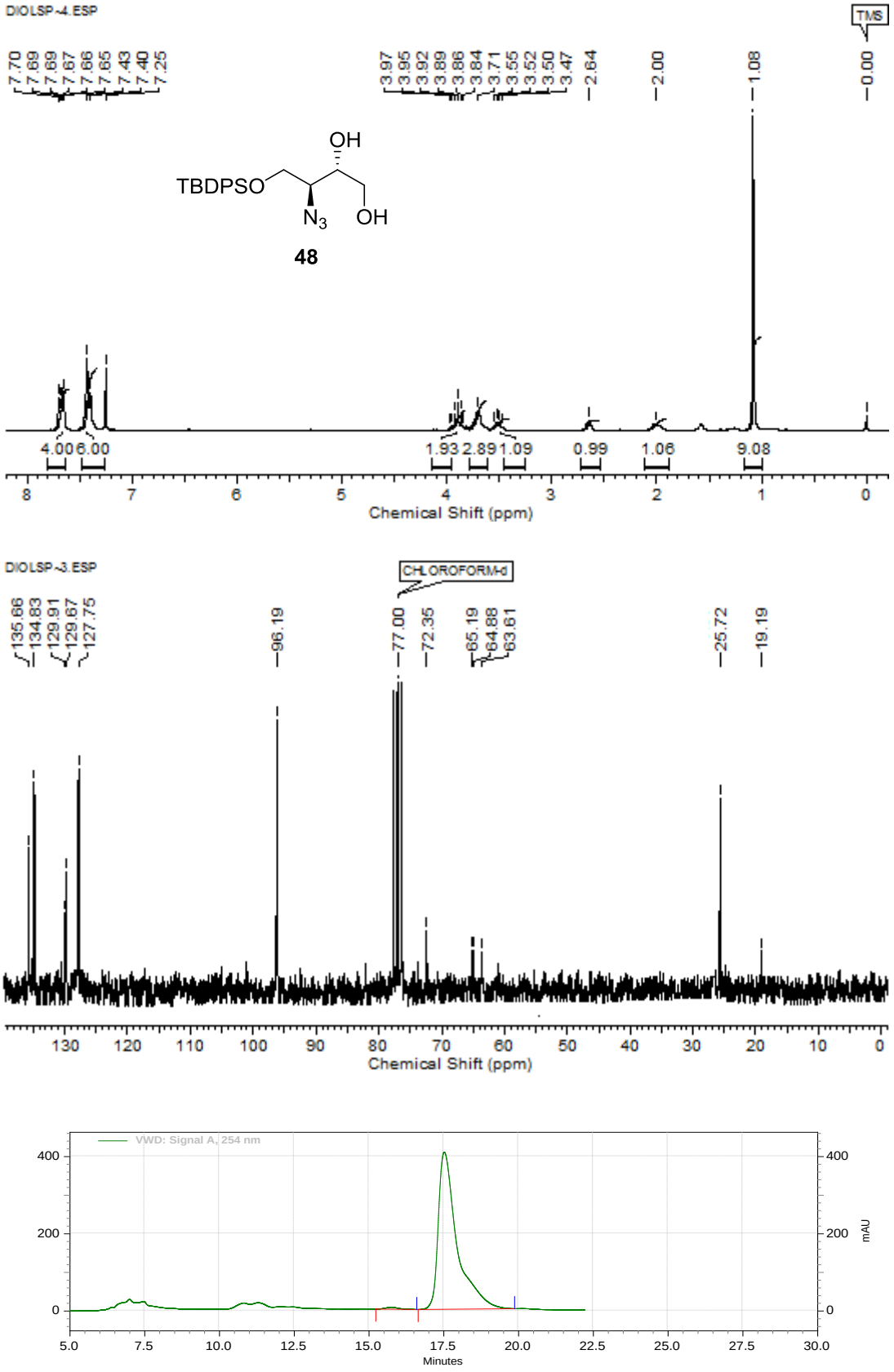


Fig. 9: ^{1}H and ^{13}C NMR spectra of (2S,3S)-3-Azido-(4-((*tert*-butyldiphenylsilyl)oxy) butan-1,2-diol **(48)**

The ^{1}H NMR spectrum of *anti*- azidodiol **48** showed a typical signal at δ 3.89-3.97 (m, 2H) for methylene (-C**H**$_2$OH) protons and δ 2.0 and 2.64 for the two -O**H** protons of the diol. Its ^{13}C NMR spectrum showed a characteristic carbon signal at δ 72.3 due to methine carbon (-**C**HOH) attached to hydroxyl group. Its HPLC chromatogram showed 97% ee (**Fig. 9**).

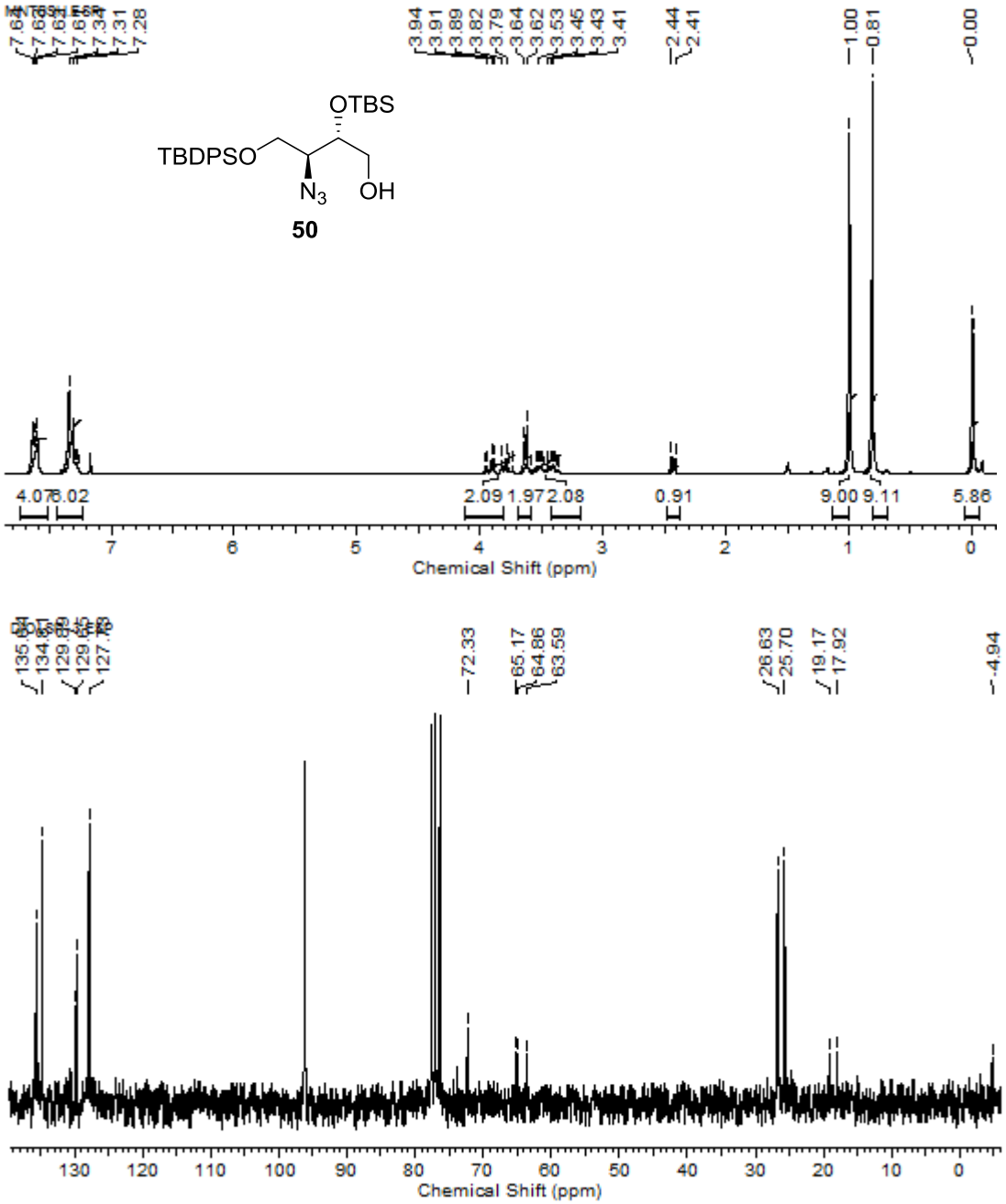


Fig. 10: ^{1}H and ^{13}C NMR spectra of (2S,3S)-3-azido-2-(*tert*-butyldimethylsiloxy-(4-((*tert*-butyldiphenylsilyl)oxy)butan-1-ol **(50)**

The diol **48** was protected as di-TBS ether **49**, followed by the selective deprotection of the primary alcoholic silyl ether group in **49** with 10 mol% camphor sulfonic acid gave the primary alcohol **50** in 75% yield.

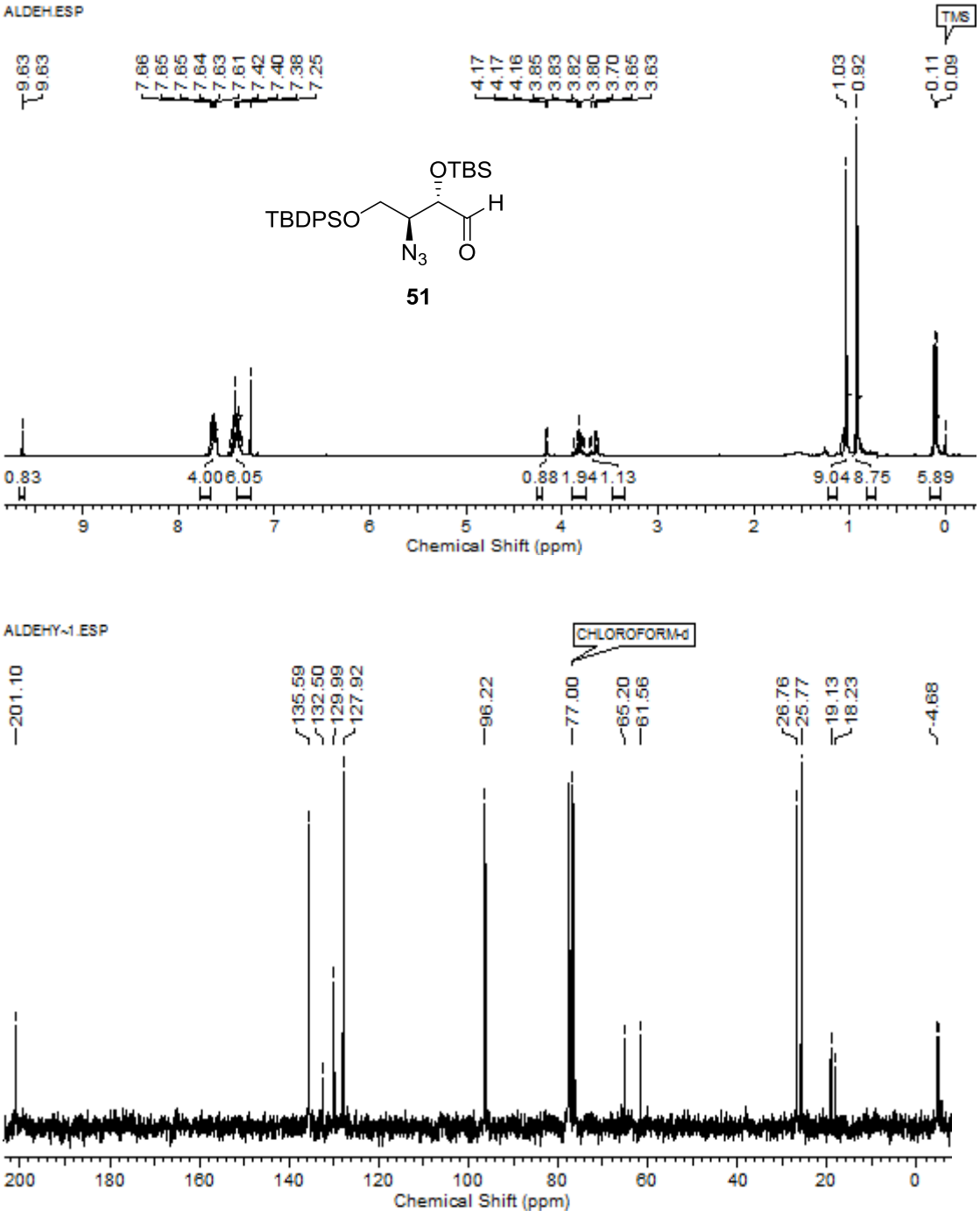


Fig. 11: ^{1}H and ^{13}C NMR spectra of (2S,3S)-3-azido-2-(*tert*-butyldimethylsiloxy-(4-((*tert*-butyldiphenylsilyl)oxy)butan-1-al **(51)**

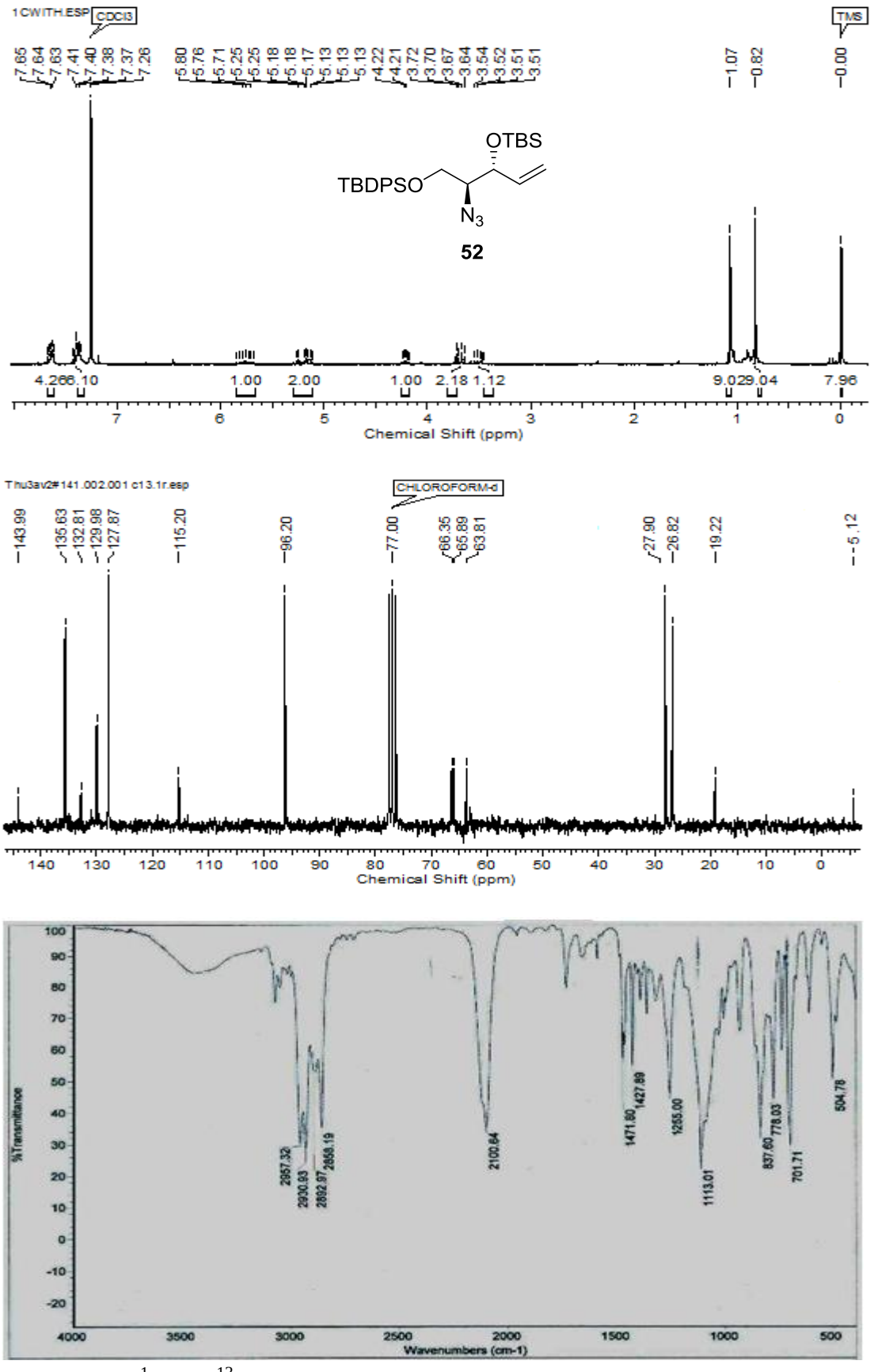


Fig. 12: ^{1}H and ^{13}C NMR and IR spectra of ((2S,3R)-2-azido-pent-4-en-1,3-yloxy)(tert-butyl)diphenyldimethylsilane **(52)**

The formation of **50** was confirmed by the display of characteristic signals at δ 0.00 integrating for 6 protons of dimethyl protons and two typical signals at δ 0.81 integrating for 9 protons of *tert*-butyl group in its ^{1}H NMR spectrum, thus establishing the presence of only one TBS group. Its ^{13}C NMR spectrum showed typical signal at δ 72.3 for methylenic carbon having free hydroxyl group (-C**H**$_2$OH) (**Fig. 10**).

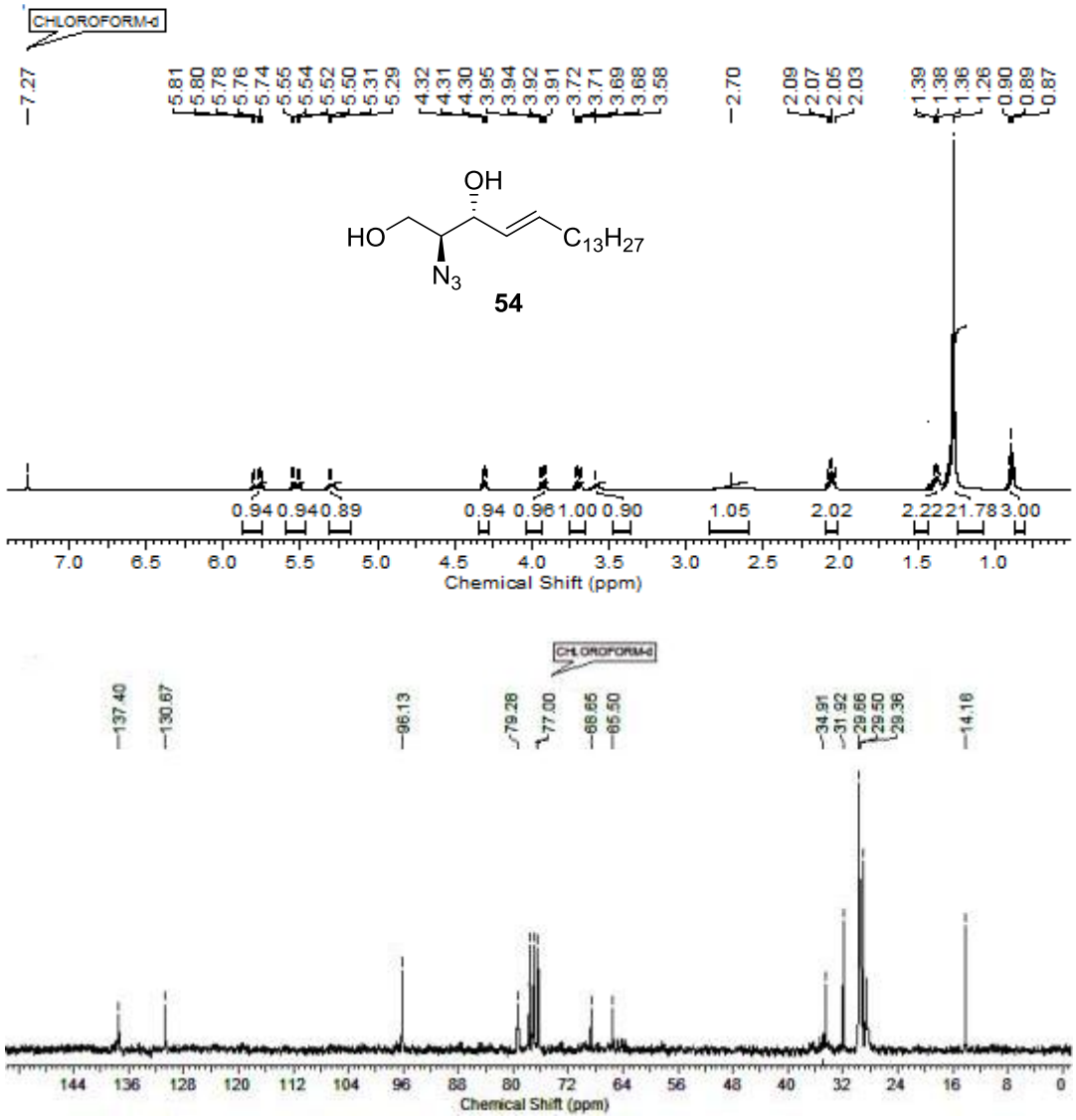


Fig. 13: ^{1}H and ^{13}C NMR of ((*E*,2S,3R)-2-azido-octadec-4-en-1,3-yloxy)(*tert*-butyl)diphenyldimethylsilane (**54**)

The alcohol **50** was then oxidized to the corresponding aldehyde **51** in 80% yield (IBX, EtOAc). The aldehyde **51** was confirmed from its characteristic singlet at δ 9.6

(s, 1H) for aldehyde (-C**H**O) proton in its ^{1}H NMR spectrum. A characteristic carbon signal at δ 201.1 due to -C=O group in its ^{13}C NMR spectrum confirmed the formation of aldehyde **51** (**Fig. 11**).

The crude aldehyde **51** on Wittig reaction ($PPh_3^+CH_3I^-$, *n*-BuLi, THF) gave the terminal alkene **52** in 65% yield over two steps. The formation of **52** was confirmed by the appearance of characteristic multiplets at δ 5.13-5.25 (m, 2H) for terminal alkenic protons (HC=C**H**$_2$) and δ 5.13-5.25 (m, 1H) for alkenic protons at secondary carbon in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed signals at δ 115.2 and 143.9 due to methylene (HC=**C**H$_2$) and methine (H**C**=CH$_2$) alkenic carbons respectively (**Fig. 12**).

The terminal alkene **52** was subjected to Ru-catalyzed cross metathesis with 1-pentadecene in the presence of Grubbs' IInd generation catalyst to obtain the crude long chain azido alkene **53**. The synthesis of D-*erythro*-azidosphingosine **54** was achieved by the removal of silyl groups in crude long chain azido alkene **53** (TBAF in THF, 79% yield). The display of characteristic multiplets at δ 5.81 (m, 1H) and δ 5.74 (m, 1H) for alkenic protons confirmed the formation of long chain alkene. The disappearance of signals in the aromatic and aliphatic protons for the phenyl and *tert*-butyl groups in its ^{1}H NMR spectrum confirmed the deprotection of both TBDPS and TBS groups. Its ^{13}C NMR spectrum showed typical signals at δ 130.6 and 137 for the two alkenic carbons (-H**C**=**C**H-) and two characteristic signals at δ 79.2 and δ 68.8 corresponding to the (-**C**H$_2$OH) methylenic and methine (-**C**HOH) carbons respectively, having free hydroxyl group confirmed the formation of long chain alkene and deprotection of silyl ethers (**Fig. 13**).

Both the azido group and the alkene functionality in **54** were hydrogenated [H_2 (1 atm), 10% Pd/C, MeOH/AcOH] to give D-*erythro*-sphinganine **7** ($[\alpha]^{25}_D$ +8.9 (*c* 0.04,

MeOH)]; lit.[25] ($[\alpha]^{25}_{D}$ +8.1 (*c* 1.0, MeOH)] in 6% overall yield and 97% ee (**Scheme 9**). The formation of **7** was confirmed by the disappearance of characteristic multiplets at δ 5.81 (m, 1H) and δ 5.74 (m, 1H) for alkenic protons (**H**C=C**H**) in its ^{1}H NMR spectrum. Further the reduction of alkene in **54** was confirmed by the disappearance of signals for alkenic carbons (H**C**=**C**H) at δ 130.6 and 137 in its ^{13}C NMR spectrum (**Fig. 14**).

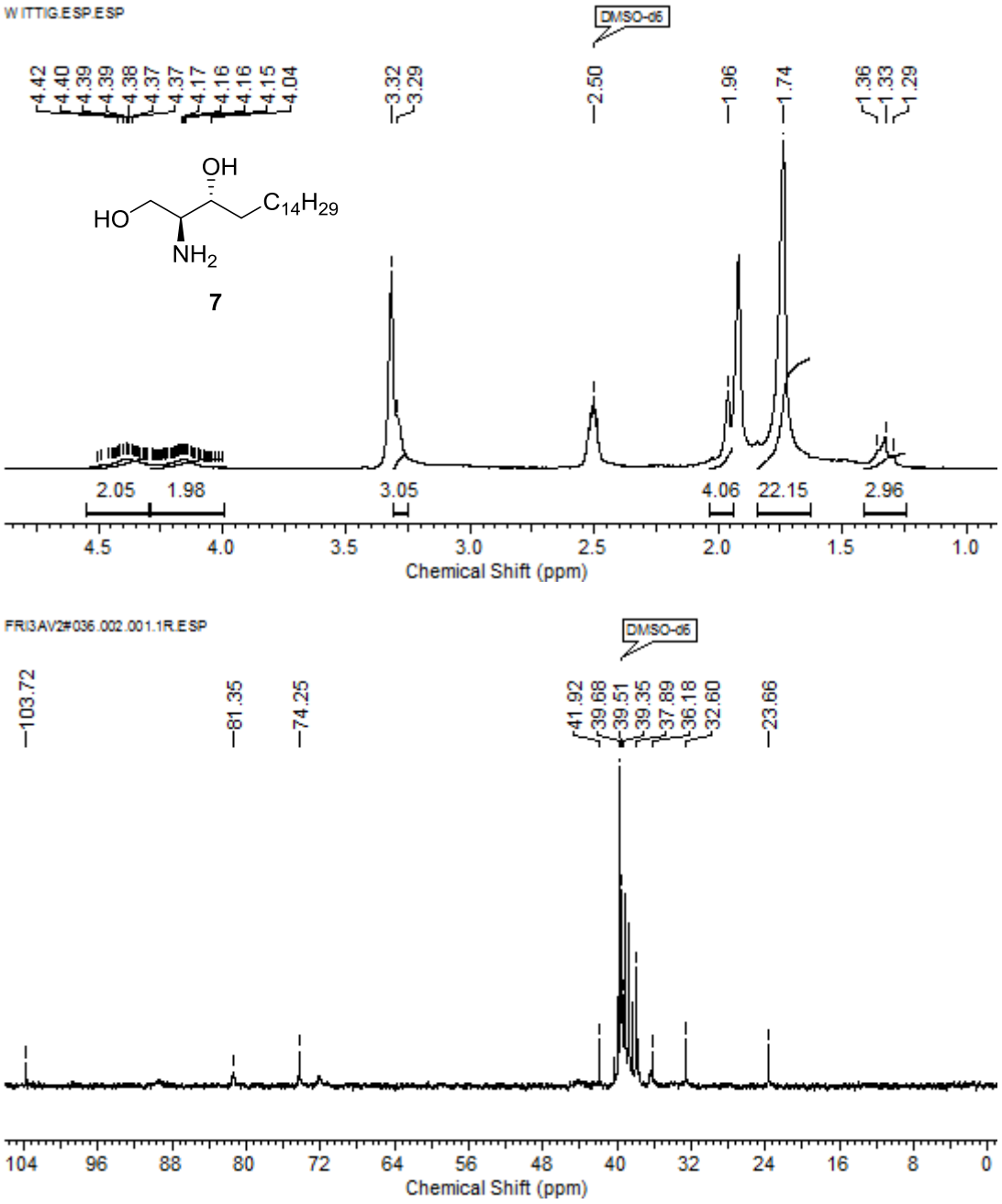


Fig. 14: ^{1}H and ^{13}C NMR spectra of D-*erythro*-sphinganine (**7**)

3.2.4 Conclusion

In conclusion, we have achieved the synthesis of D-*erythro*-sphinganine (**7**) in 6% overall yield and 97% ee. The key intermediate, aldehyde **52** obtained *via*- Jacobsen Hydrolytic Kinetic Resolution of two- stereo centered azido epoxide **46** has been used as key step to introduce chirality.

3.2.5 Experimental

(S)-2-Azido-2-((S)-oxiran-2-yl)ethanol (45)

cis-Butenediol **44** (5 g, 56.81 mmol) was taken up in CH_3CN and H_2O mixture (30:10), and NaN_3 (7.38 g, 113.63 mmol) was added to it followed by the addition of *N*-bromosucciniimide (12.06 g, 68.18 mmol) slowly at 0 ^oC. After addition, the content was stirred for 4 h at 0 ^oC. To the reaction mixture water was added and the reaction mixture was extracted with EtOAc. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was used for next step without purification.

The crude product azido bromide (5 g, 25.90 mmol) was taken in dry THF and powdered NaOH (1.243 g, 31.08 mmol) was added slowly with stirring at 0 ^oC for 3 h. The reaction mixture was diluted with EtOAc (2 X 25 mL) followed by addition of water (30 mL). The organic layer separated and the aq. layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography over silica gel using CH_2Cl_2: Pet. ether: EtOAc (80:20:10) as an eluent to give pure azido epoxide **45.**

Yield: 84%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 702, 1427, 2105, 2837, 2961, 3472; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.18-2.21 (bs, 1H), 2.82-2.90 (m, 2H), 3.11-3.15 (m,

1H), 3.47-3.49 (m, 1H), 3.71-3.84 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.24, 49.97, 61.85, 62.94; **Analysis**: $C_4H_7N_3O_2$ requires: C, 37.21; H, 5.46; N, 32.54 found: C, 37.20; H, 5.45, N, 32.55 %.

((S)-2-Azido-2-((S)-oxiran-2-yl)ethoxy)(*tert*-butyl)diphenylsilane (46)

To a stirred solution of epoxide **45** (12 g, 133.32 mmol) in dry CH_2Cl_2 (200 ml), imidazole (13.59 g, 199.98 mmol) was added and the reaction mixture was cooled in ice-bath. *tert*-Butyldiphenyl silyl chloride (36.59 g, 133.32 mmol) was added slowly at 0 ^oC. After complete addition, the reaction mixture was stirred at room temperature for 6 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2 (40 ml) and washed with water (2x10 ml) Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 19:1) yielding **46** as a colorless viscous oil.

Yield: 97%; viscous colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 702, 1113, 1427, 2105, 2858, 2931; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 2.72-2.81 (m 2H), 3.05-3.11 (m, 1H), 3.33-3.41 (q, *J* = 3.4 Hz, 1H), 3.81-3.84 (dd, *J* = 3.1 and 7.8 Hz, 2H), 7.35-7.45 (m, 6H); 7.65-7.69 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.1, 26.2, 45.0, 50.3, 63.5, 64.4, 127.8, 129.9, 132.6, 135.5; **Analysis**: $C_{20}H_{25}N_3O_3Si$ requires: C, 65.36; H, 6.86; N, 11.43 found: C, 65.34; H, 6.83, N, 11.42 %.

(2S,3S)-3-Azido-(4-((tert-butyldiphenylsilyl)oxy)butane-1,2-diol (48)

To a solution of (*R,R*)-cobalt salen (**43**) ((0.055 g, 0.09 mmol) in toluene (10 mL) was added glacial acetic acid. The solution was allowed to stir at 25 ^oC in open air for 30 min over which time color changed from orange-red to a dark brown and it was then concentrated in vaccuo to get the Co-salen complex (**Fig. 2**) as a brown solid.To a solution of Co-salen complex (**43**) (0.055 g, 0.5 mol %) and azido epoxide **46** (6.70

g, 18.26 mmol) in THF (2 mL) at 0 ^{o}C was added H_2O (0.12 g, 7.3 mmol) dropwise over 5 min. The reaction was allowed to warm to 25 ^{o}C and stirred for 14 h. After completion of reaction (monitored by TLC), solvent was removed *in vacuo*. The crude product was purified by column chromatography over silica gel using Pet.Ether: EtOAc (60:40) as eluent to give pure chiral *anti*-azidodiol **48** in 3.22 g.

Yield: 46%; $[\alpha]^{25}_{D}$: -59.30 (*c* 1, $CHCl_3$); Optical purity 97% ee from **HPLC analysis**: Column: Chiracel OJ-H (4.6 X 250 nm), mobile phase: hexane/isopropyl alcohol (95/15), flow rate: 0.5 mL/min, retention time: 15.747 min (+)-isomer, 17.517 min (-)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 741, 1047, 1270, 1427, 2099, 2858, 2931, 3384; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 2.00 (s, 1H), 2.64 (bs, 1H), 3.50-3.55 (m, 1H), 3.71 (bs, 3H), 3.81-3.97 (m, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.1, 25.7, 63.6, 64.8, 65.1, 72.3, 127.7, 129.6, 129.9, 134.8, 135.6. **Analysis**: $C_{20}H_{27}N_3O_3Si$ requires: C, 62.31; H, 7.06; N, 10.90 found: C, 62.31; H, 7.07; N, 10.90 %.

(2S,3S)-3-Azido-2-(*tert*-butyldimethylsiloxy-(4-((*tert*-butyldiphenylsilyl)oxy)butan-1-ol (50)

A mixture of chiral diol **48** (3.98 g, 10.36 mmol), was taken in dry DMF (10 mL) to which imidazole (2.82 g, 41.45 mmol) was added followed by slow addition of TBS-Cl (6.24 g, 41.45 mmol) at 25 ^{o}C. The reaction mixture was stirred for 14 h at room temperature. Water was added to the reaction mixture and the product was extracted with EtOAc. The organic layer was concentrated under pressure. The crude compound was purified by column chromatography over silica gel using pet.ether: EtOAc (95:5) as eluent to give pure di-*tert*-butylsilyl ether **49** in 87% yield.

Pure di-TBS product **49** obtained (di-TBS) (4 g, 8.60 mmol) was taken up in 50 mL MeOH. To this, CSA (0.099 g, 0.43 mmol) was added at -25 ^{o}C. Reaction content was stirred for 30 min. After completion of reaction (monitored by TLC) to reaction saturated solution of ammonium chloride was added and the product was extracted

with CH_2Cl_2. The organic layer was separated and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using pet.ether : EtOAc (95:5) as eluent to give pure monoTBS **50** in 75% yield.

Yield: 75%; $[\alpha]^{25}_D$: -22.20 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 837, 1112, 1256, 2101, 2857, 2930, 3420; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 3.52-3.82 (m, 6H), 4.49-4.63 (dd, *J* = 4.1 and 7.2 Hz, 2H), 7.26-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.94, -4.57, 25.76, 62.69, 63.48, 69.43, 72.24, 73.44, 96.12, 127.67, 127.97, 128.43, 137.49; **Analysis**: $C_{26}H_{41}N_3O_3Si_2$ requires: C, 62.48; H, 8.27; N, 8.41 found: C, 62.42; H, 8.19; N, 8.37 %.

(2S,3S)-3-Azido-2-(*tert*-butyldimethylsiloxy-(4-((*tert*-butyldiphenylsilyl)oxy)butan -1-al (51)

To a stirred solution of oxalyl chloride i.e. $(COCl)_2$ (1.09 g, 4.27 mmol) in CH_2Cl_2 (30 mL) at -78 ^oC, was added a solution of DMSO (0.90 mL, 12.82 mmol). The reaction mixture was stirred for 20 min followed by the addition of alcohol **50** (1.5 gm, 4.27 mmol) in CH_2Cl_2 (20 mL). After stirring for 1 h the reaction was quenched by the addition of Et_3N (2.39 mL, 17.09 mmol). The reaction mixture was stirred for 30 min followed by the addition of water (10 mL). The organic phase was separated and aqueous phase extracted with CH_2Cl_2. Combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude aldehyde **51.** The obtained product was sufficiently pure for characterization.

Yield: 80%; $[\alpha]^{25}_D$ = -8.52 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 838, 1112, 1391, 1428, 1738, 2098, 2858, 2931; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.42 (s, 6H), 0.93 (s, 9H), 3.54-3.71 (m, 3H), 4.15 (bs, 1H), 4.51 (d, *J* = 6.7 Hz, 2H), 7.26-7.30 (m, 5H), 9.55 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.74, -5.09, 18.15, 25.70, 53.32, 62.82,

67.05, 73.46, 96.13, 127.65, 128.26, 137.37, 205.32; **Analysis**: $C_{26}H_{39}N_3O_3Si_2$ requires: C, 62.73; H, 7.90; N, 8.44; found: C, 62.68; H, 7.89; N, 8.41 %.

((2S,3R)-2-Azido-pent-4-en-1,3-yloxy)(*tert*-butyl)dimethyl-diphenylsilane (52)

To a stirred slurry of methylphosphonium bromide (1.1 g, 3.13 mmol) in THF (60 ml) at 0 ^oC was added *n*-BuLi (1.435 ml, 2.87 mmol, 2.07 M in Et_20) and the resultant solution was stirred at 0 ^oC for 10 min, followed by dropwise addition of the crude aldehyde **51** (1.3 g, 2.61 mmol) in THF (3 ml). After stirring at 0 ^oC for 1 h, reaction mixture was quenched by adding H_2O (3 ml). After allowing the reaction mixture to warm to room temperature, it was diluted with water (10 mL) and extracted with Et_2O (2 x 70 mL). The collected organic layer was washed with brine, dried over anhyd. Na_2SO_4 and concentrated. The crude product was purified by column chromatography over silica gel (100-200 mesh) (hexane/EtOAc, 95:5) to give olefin **52** (0.84 g, 65%) as yellowish liquid.

Yield: 65%; yellowish liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 701, 837, 1113, 1255, 1471, 2100, 2858, 2957; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.83 (s, 9H), 1.08 (s, 9H), 3.59-3.76 (m, 3H), 4.22 (m, 1H); 5.13-5.30 (m, 2H); 5.68-5.85 (m, 1H); 7.35-7.43 (m, 6H); 7.62-7.69 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ -4.9, 19.2, 25.8, 26.8, 63.6, 68.2, 74.0, 117.1, 127.8, 129.8, 135.6, 137.1; **Analysis**: $C_{27}H_{41}N_3O_2Si_2$ requires: C, 65.41; H, 8.34; N, 8.48 found: C, 65.38; H, 8.37; N, 8.38 %.

(*E*)-(2*S*,3*R*)-2-Azidooctadec-4-ene-1,3-diol (54)

Grubbs' second-generation catalyst (123.1 mg, 0.145 mmol) was added to a stirred solution of ((2S,3R)-2-azido-pent-4-en-1,3-yloxy)(*tert*-butyl)dimethyl-diphenylsilane **52** (0.717 g, 1.45 mmol) and pentadec-1-ene (0.912 g, 4.347 mmol) in CH_2Cl_2 and stirring was continued for 12 h at 45 ^oC. When starting material was consumed completely, (checked by TLC), reaction mixture was concentrated and purified over

silica gel (100-200 mesh) chromatography (EtOAc/hexane 3:7) to yield alkene **53** (0.840 g) as a colorless oil, which was used directly for the next step.

The above crude silylprotected azidosphingosine **53** (0.800 g, 1.240 mmol) was dissolved in dry THF (30 ml), in which 1 molar solution of TBAF (0.806 g, 3.10 mmol) in THF was added at 25 ^{o}C and stirred for 8 h. After complete conversion of substrate into diol (monitored by TLC), reaction mixture was quenched with water (2 ml) at 0 ^{o}C and concentrated. The residue was dissolved in EtOAc and washed with brine, concentrated under reduced pressure and purified over silica gel (100-200 mesh) and pet ether/ethyl acetae (85:15) to give *D-erythro*-azidosphinganine **54** as a gummy solid (0.371 g, 79% over two steps).

Yield: 79%; gummy solid; $[\alpha]^{D}_{25}$ -31.4 (*c* 0.8, $CHCl_3$); lit.[24] $[\alpha]^{D}_{25}$ -32.9 (*c* 4, $CHC1_3$)]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3400, 2921, 2100, 1612; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.74-5.81 (dt, *J* = 14.5, 6.5 Hz, 1H), 5.50-5.65 (dd, *J* = 15.5, 6.2 Hz, lH), 5.29 (d, *J* = 7.03 Hz, lH), 4.31 (t, *J* = 4.7 Hz, 1H), 3.91-3.95 (dd, *J* = 11.2, 3.51 Hz, 1H), 3.68-3.72 (dd, *J* = 11.2, 3.51 Hz, lH), 3.58 (s, 1H), 2.70 (s, 1H), 2.03-2.09 (q, *J* = 7.03 Hz, 2H) 1.35-1.39 (m, 2H), 1.26 (s, 22H), 0.89 (t, *J* = 6.53 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 29.3, 29.5, 29.6, 31.9, 34.9, 65.5, 68.8, 79.2, 130.6, 137.4; **Analysis**: $C_{18}H_{35}N_3O_2$ requires: C, 66.42; H, 10.84; N, 12.91 found: C, 66.38; H, 10.80; N, 12.89 %.

***D-erythro*-Sphinganine (7)**

To a stirred solution of *D-erythro*-azidosphingosine **54** (0.350 g, 1.07 mmol) in methanol (5 ml) was added 10% Pd/C (5 wt%). The reaction mixture was then stirred under H_2 atmosphere (1 atm) at rt for 10 h. After completion of the reaction (monitored by TLC), the catalyst was filtered over Celite. The filtrate was concentrated under reduced pressure to give *D-erythro*-sphinganine **7** (0.316 g, 90%)

as a gum.

Yield: 90%; gum; $[\alpha]^{D}_{25}$ +8.9 (*c* 0.8, MeOH); {lit.[25] ($[\alpha]^{25}_{D}$ +8.1 (*c* 1.0, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3349, 2921, 1602, 1465, 1051; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 6.3 Hz, 3H), 1.74 (s, 22H), 1.96 (s, 4H), 3.29 (bs, 3H), 4.04-4.17 (m, 2H); 4.37-4.42 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.6, 32.6, 36.1, 37.8, 39.3, 39.6, 41.9, 74.2, 81.3, 103.7; **Analysis**: $C_{18}H_{39}NO_2$ requires: C, 71.70; H, 13.04; N, 4.65 found: C, 71.67; H, 13.01; N, 4.63 %.

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Chapter IV

$NaIO_4$–NaN_3–Mediated Diazidation of Alkenes and Cu(I)-Catalyzed Synthesis of gem-Ditriazoles

Section I:

$NaIO_4$–NaN_3–mediated diazidation of Alkenes

4.1.1 Introduction

Vicinal diazides are important precursors to 1, 2-diamines,[1] which are useful functional groups present in a variety of natural products, pharmaceutical substances (e.g. D-(+)-biotin),[2] etc. In addition, 1, 2-diamines find increasing utilization in organic synthesis either as chiral auxiliaries or as metallic ligands especially in the field of catalytic asymmetric synthesis.[3] Despite their extensive utility, the development of new method allowing for efficient preparation of 1, 2-diamine remains a stimulating challenge. The general methods of diamine synthesis usually involves the synthesis of vicinal diazides as intermediates *via* azidation of epoxides[4] or 1,2 diols[5] *via* dimesylation. In contrast, the direct oxidative diazidation of alkenes to diazides presents an attractive and useful strategy.

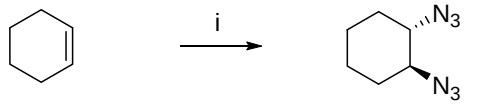
4.1.2 Review of literature

There are only six methods available in the literature for the direct diazidation of alkenes. Quite recently, few useful methods of introducing vicinal diazide functionality onto alkenes have been reported.[6] Some of the methods reported in the recent times have been briefly discussed below.

Fristad's approach (1985)[7]

Fristad *et al.* have reported the 1, 2-diazidation of some of the alkenes with stoichiometric amounts of $Mn(OAc)_2$ and NaN_3 to give the corresponding mixture of *syn*- and *anti*-diazide products **2** in 51-68% yields. Mechanistically, it was proposed that the alkene is intimately involved in Mn(III)- reduction ligand-transfer oxidation, rather than the intermediacy of free azide radicals. The *β*-azidoalkyl radical intermediate reacts with a second Mn(III)-N_3 species in a typical ligand-transfer fashion to complete the double addition. The yield of 1, 2-diazide was highly

dependent on the reactant concentrations. The major side product in the reaction was the 1-azidoalkane. Higher reactant concentrations, however, allowed good selectivity for the 1, 2-diazidoalkanes over 1-azidoalkanes (**Scheme 1**).



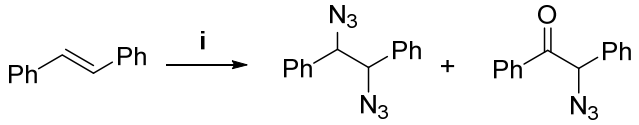
1 **2**

syn: anti = 1: 6

Scheme 1: (i) $Mn(OAc)_2$ (4.80 mmol), NaN_3 (72 mmol), AcOH (25 mL), 85-110 °C, 10-30 min, 51-68%.

Moriarty's approach (1986)[8]

Moriarty *et al.* have reported 1, 2-diazidation of a variety of alkenes such as **3** with PhIO-AcOH-NaN_3 reagent system to give vicinal diazides **4** in 34-85% yields, along with *α*-azidoketone **5** in 14% yields. This approach involves initial electrophilic attack of the hypervalent iodine (PhIO) species upon the C=C double bond to yield cationic intermediate, which is attacked by azide anion. Subsequent reductive elimination of iodobenzene with attack by a second azide anion produced the vicinal diazides. This pathway accounts for the lack of stereoselectivity (**Scheme 2**).



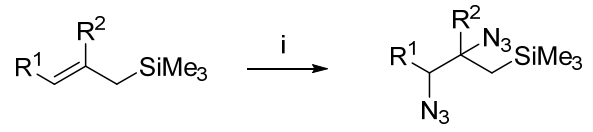
3 **4,** 34-85% **5**, 14%

syn: anti = 3:7

Scheme 2: (i) PhIO (0.01 mol), NaN_3 (0.04 mol), AcOH (25 mL), 50 °C, 3 h, 34-85%.

Arimoto's approach (1989)[9]

In this approach, *β*-substituted allyltrimethylsilane **6** were converted into the corresponding *vic*-diazides **7** with (PhIO) and $TMSN_3$ in moderate yields (**Scheme 3**).



6 **7**

R^1 = H, 52-86%

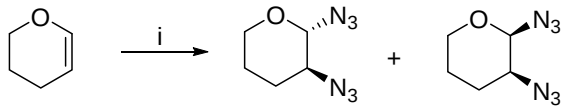
R^2 = n-$C_7H_{15}CH(OAc)(CH_2)_2$-,

$C_6H_5(CH_2)CH(OAc)CH_2$-

Scheme 3: (i) (PhIO)n, $TMSN_3$, CH_2Cl_2, -78 -25 °C, 52-86%.

Snider's approach (1998)[10]

Snider *et al* have described that alkenes and glycals react with $Mn(OAc)_3.2H_2O$ and NaN_3 in 9:1 acetonitrile/trifluoroacetic acid to give 1, 2-diazides in >80% yields. Glycals could not undergo *vic*-diazidation under Fristad's condition. The salient feature of this method is that, the 1, 2-diazidation of glycols **8** has been achieved simply by changing AcOH used in Fristads method by CF_3CO_2H at (-20 ^oC) and the reaction proceeding within comparatively less reaction time (3 min). The extensive synthetic utility of glycopyranosyl azides (**9** & **10**) for the preparation of glycosylated asparagine derivatives,[11] renders this method more attractive (**Scheme 4**).



8 **9-*anti*** **10-*syn***

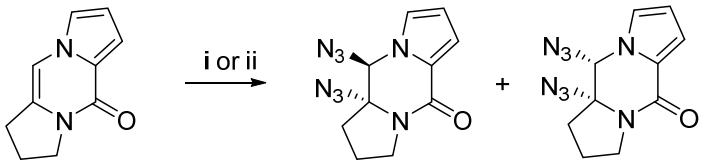
anti:*syn* = (94:6)

Scheme 4: (i) $Mn(OAc)_2$ (1.5 mmol), NaN_3 (2.5 mmol), CH_3CN:TFA (9:1), -20 °C, 3 min, 86%.

Austin's approach (2004)[12]

Austin *et al*. have studied the diazidation of pyrazinone **11** to give the corresponding *syn*- and *anti*-diazidopyrazinone **12** in upto 62% yield. The bimolecular nucleophilic substitution by excess azide, under the solution-phase conditions, resulted in *syn*-diazide **13** product, whereas the second azide displacement reaction was expected to

proceed through addition from the less sterically hindered face, under solid-phase conditions, to produce the *anti*-diazide product **12**. *syn*-Diazidopyrazinone **13** was used as an intermediate in the total synthesis of (±)-dibromophakellstatin. Another interesting feature is that, this methodology has been extensively applied in the *syn* azidation of various additional alkene substrates and their use in the synthesis of guanidine-containing natural products (**Scheme 5**).



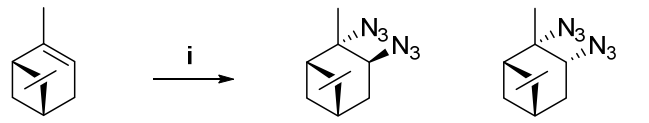
i = *anti;syn* = 62:0%

ii = *anti*:*syn* = 7:41%

Scheme 5: (i) ICl (5.09 mmol), NaN_3 (17.4 mmol), MeCN (6 ml), -10 °C, 3 h; (ii) $PhI(OAc)_2$ (4.38 mmol), $TMSN_3$ (9.04 mmol), -10 °C, 10 h.

Ohba's approach (2005)[13]

In this approach, the authors have described direct a *vic*-diazidation of *α*-pinene **14** to give the corresponding mixtures of diazides **15** and **16** by using $Mn(OAc)_2$ and NaN_3 in acetic acid. This was the first example of conversion of *α*-pinene to 2,3-pinane diazide. The absolute configuration of *anti*- and *syn*-pinane diazides were determined



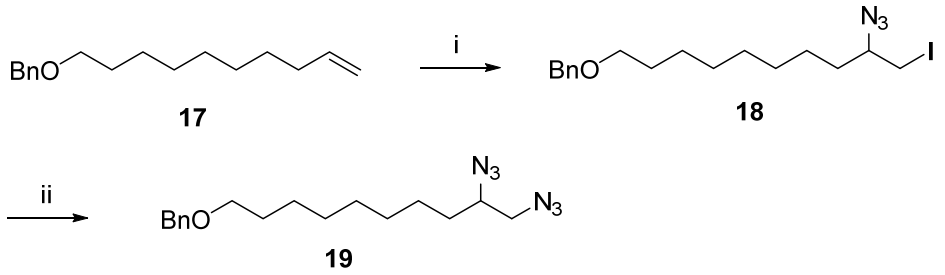
14 **15,** *anti* = 20% **16,** *syn* = 22%

Scheme 6: (i) $Mn(OAc)_2$ (66 mmol), NaN_3 (330 mmol), AcOH (56 mL), 50 °C, 2 h.

by 2D ^{1}HNMR and X-ray crystallography. Easy availability of *α*-pinene as an enantiomeric pure sample and ease of chemical modification rendered this method more practical (**Scheme 6**).

Pfaendler's approach (2004)[14]

Pfaendler *et al.* have reported a mild and two-step sequence for the *vic*-diazidation of olefins that produced diazides **19** in 78% yields. The sequence included azidoiodination of alkenes **17** followed by substitution with azide ion to give 1,2-diazido product **19**. The use of DMSO as solvent rather than DMF enhanced the reaction rate, and reduced the temperature from 100 ^{o}C to 25 ^{o}C. (**Scheme 7**).



Scheme 7: (i) ICl (1.30 mmol), NaN_3 (3.25 mmol), CH_3CN (1 mL) 2.5 h, 99%; ii) NaN_3 (1.5 mmol), DMSO (1 mL), 20 h, 78%.

4.1.3 Present Work

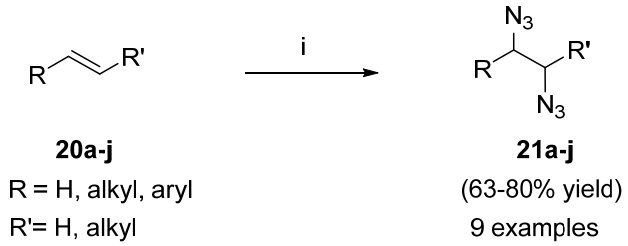
4.1.3.1 Objective

In recent years, as can be seen from the above discussions, a considerable progress has been made in diazidation of various types of alkenes. It has become a major tool of synthetic organic chemistry, thus providing an efficient and versatile access to new diazido compounds. The reported methods include combinations like Mn^{3+} -NaN_3 (large excess)- AcOH[7] or TFA,[10] Fe^{2+}-H_2O_2-NaN_3,[15] PhIO-NaN_3-AcOH[8] and S_N2 displacements involving multi-steps.[14] However, some of them suffer from certain drawbacks like low yields, multi-step reaction sequences, expensive metal salts and oxidants. In this context, a more practical and efficient synthesis of 1,2-diazidoalkanes is highly desirable. Moreover, combination such as $NaIO_4$-NaN_3-AcOH has not been reported for the diazidation of alkenes. In this section we describe a new $NaIO_4$-

NaN_3-AcOH- mediated procedure for the direct diazidation of various aromatic as well as aliphatic alkenes that affords the corresponding vicinal diazides (**2**) in excellent yields (**Table 1**).

4.1.3.2 Results and Discussion

During the course of this study of $NaIO_4$-mediated oxidative functionalization of alkenes, we observed that the treatment of alkenes **20a-j** with stoichiometric amounts of $NaIO_4$ and sodium azide in DMSO:AcOH (4:1) as solvent at 75 °C, produced diazides **21a-j** in good yields. In particular, when styrene **20a** was subjected to oxidative functionalization with $NaIO_4$ (1 equiv) in the presence of NaN_3 (3 equiv) in DMSO:AcOH (4:1) as solvent at 75 °C, gave diazide **21a** in 75% yield (**Scheme 8**).



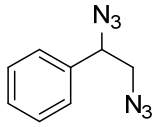
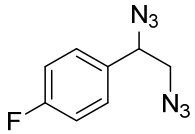
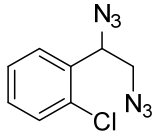
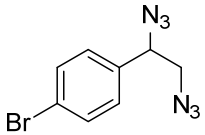
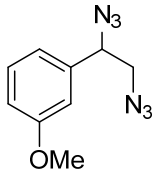
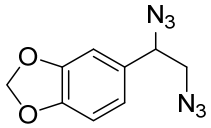
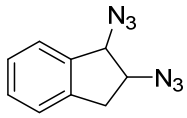
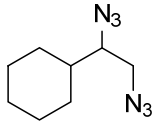
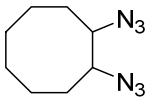
20a-j
R = H, alkyl, aryl
R'= H, alkyl

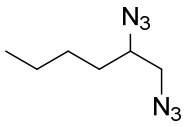
21a-j
(63-80% yield)
9 examples

Scheme 8: (i) alkene (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), DMSO:AcOH (4:1), 75 ^oC, 4 h.

To study the generality of the reaction, a variety of alkenes were subjected to diazidation with $NaIO_4$-NaN_3 reagent combination, and the results are presented in (**Table 1**). Aromatic olefins as well as aliphatic olefins gave good yields of the corresponding 1,2-diazides. Internal olefins such as indene and cyclooctene have proceeded to give products in excellent yields with 1:1 diastereoselectivity (**20g** and **20i**) as confirmed by their ^1H NMR spectra. However, no reaction took place in the case of α, β–unsaturated carbonyl compounds, which may be a limitation of this method.

Table 1: $NaIO_4$-mediated diazidation of alkenes[a]

Entry	Substrate (20a-j)	Products (21a-j)	Yield (%)[b]	*anti : syn*
a	styrene		75	-
b	4-fluorostyrene		89	-
c	2-clorostyrene		85	-
d	4-bromostyrene		90	-
e	3-methoxystyrene		90	-
f	methylenedioxyvinylbenzene		90	-
g	indene		75	1:1
h	vinylcyclohexane		80	-
i	cyclooctene		60	1:1

j	1-hexene		70	-

Reaction conditions: [a]alkenes (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), 20ml DMSO: AcOH (4:1), 75 °C, 2 h; [b] yields refer to isolated yield after column chromatography.

The formation of diazides **21a-j** was confirmed by ^{1}H and ^{13}CNMR and IR spectroscopy.

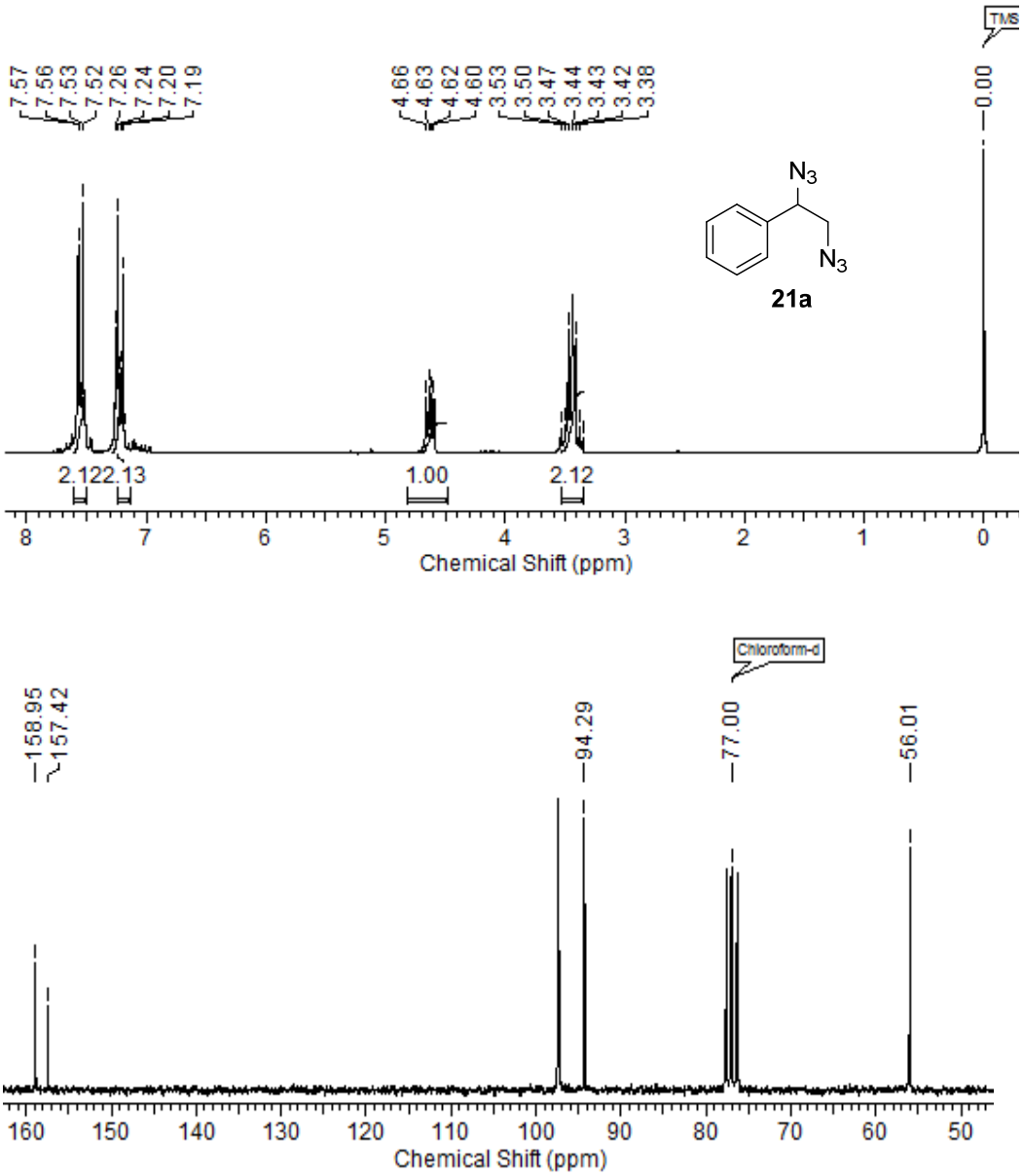


Fig. 1: ^{1}H and ^{13}C NMR of styrene diazide **21a**

Example 1: The ^{1}H NMR spectrum of **21a** showed a doublet of doublet at δ 4.65 (1H) for benzylic proton and a typical multiplet at δ 3.37-3.55 (m, 2H) for homobenzylic protons. Its ^{13}C NMR spectrum displayed typical signals at δ 65.4 and 55.8 for the benzylic and homobenzylic carbons respectively (**Fig. 1**). Its IR spectrum displayed a strong absorption band at 2103 cm^{-1} confirming the formation of azide function. The diasteromeric ratios (*anti: syn*) for internal olefins were determined from ^{1}H NMR spectroscopic studies (dr = 1:1).

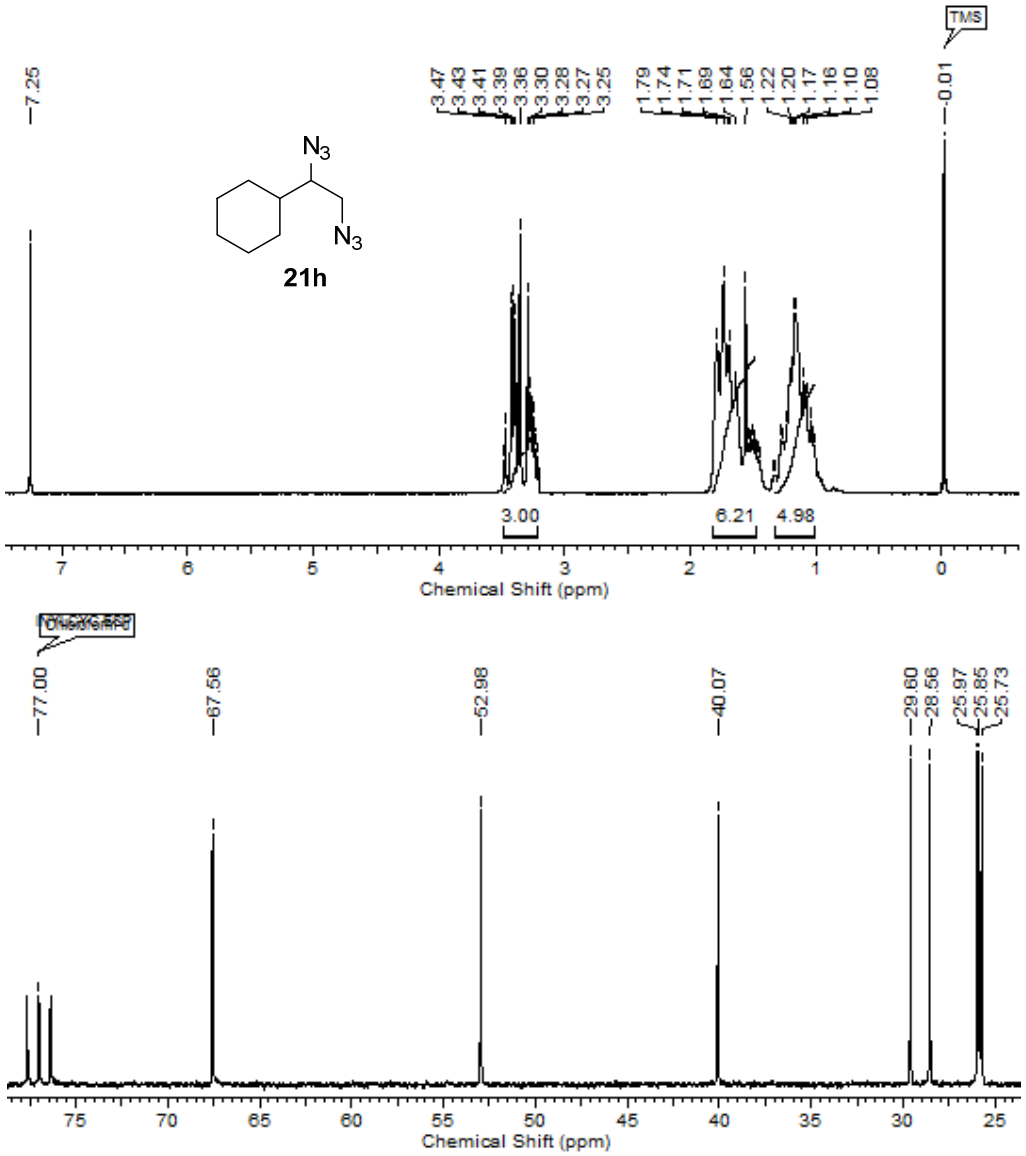
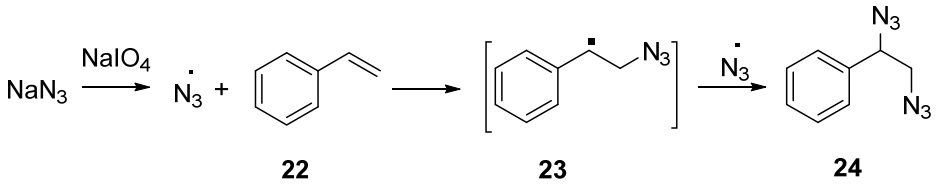


Fig. 2: ^{1}H and ^{13}C NMR of styrene diazide **21h**

Example 2: The ^{1}H NMR spectrum of **21h** showed a multiplets at δ 3.25-3.47 (3H) for protons attached to azidocarabons ($N_3C\mathbf{H}_2$ & $N_3C\mathbf{H}$) and multiplets in the range δ 1.08-1.79 for cyclohexane ring protons. The disappearance of signals in the olefinic region substantiated the formation of diazide **21h**. Its ^{13}C NMR spectrum displayed typical two signals at δ 67.5 and 52.9 for the azidocarabons ($N_3\mathbf{C}H_2$ & $N_3\mathbf{C}H$) respectively (**Fig. 2**).

4.1.4 Mechanism

The probable mechanism for the direct diazidation of alkenes to the corresponding diazides is proposed, that involves a radical pathway. Accordingly, the $NaIO_4$ is able to oxidize NaN_3 to give the corresponding azide radical,[16] which is then added onto alkene to give the secondary radical **23**. Subsequently, the secondary radical is further believed to be trapped with another azide radical to give diazides (**Scheme 9**).



Scheme 9: Proposed mechanism for the 1,2-diazidation of alkenes

4.1.5. Conclusion

In conclusion, we have developed a new reagent system consisting of $NaIO_4$-NaN_3 as a new efficient system suitable for direct diazidation of alkenes into their corresponding vicinal diazides. The procedure is simple and high yielding. The reaction is believed to proceed *via* radical pathway.

4.1.6. Experimental

General experimental procedure for 1,2-diazidation of alkenes:

To a suspension of NaN_3 (0.975 g, 15 mmol) and $NaIO_4$ (1.069 g, 5 mmol) in 20 mL of DMSO: glacial AcOH (4: 1) was added alkenes **20a-j** (5 mmol) and the reaction mixture was stirred at 75 °C for 2 h until the mixture became dark brown in color. After the reaction was complete (monitored by TLC) it was poured into water (100 ml) and extracted with EtOAc (3 × 50 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 ml) followed by aqueous $Na_2S_2O_3$ (5%, 50 ml), dried over anhyd. Na_2SO_4. Distillation of the organic layer under reduced pressure gave the crude diazides, which was subjected to column purification using hexane/ethyl acetate (19:1) as eluent to obtain pure 1,2-diazides **21a-j**.

1, 2-Diazido-1-phenylethane (21a)

Yield: 75%; pale yellow liquid; **IR** (neat, cm^{-1}): ν_{max} 700, 759, 1257, 1454, 2100, 2926; **^{1}H-NMR** (200 MHz, $CDCl_3$,): δ 3.37-3.55 (m, 2H), 4.65 (dd, *J* = 5.4, 7.8 Hz, 1H), 7.29-7.55 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$,): δ 55.8, 65.4, 126.8, 128.9, 129.0, 136.3; **Anal.** Calcd for $C_8H_8N_6$: C, 51.06; H, 4.28; N, 44.66; Found: C, 51.30; H, 4.08; N, 44.50%.

1-Fluoro-4-(1,2-diazidoethyl) benzene (21b)

Yield: 89%; pale yellow liquid; **IR** (neat, cm^{-1}): ν_{max} 1254, 2103, 2940; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.44 (dd, *J* = 7.7, 12.7 Hz, 2H), 4.65 (dd, *J* = 5.6, 7.7 Hz, 1H), 7.10 (m, 2H), 7.32 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.9, 64.8, 115.9, 116.3, 128.7, 128.8, 32.2, 132.3, 160.4, 165.4; **Anal.** Calcd for $C_8H_7FN_6$: C, 46.60; H, 3.42; N, 40.70; Found: C, 46.60; H, 3.42; N, 40.76%.

1-Chloro-2-(1,2-diazidoethyl)benzene (21c)

Yield: 85%; pale yellow liquid; **IR** (neat, cm^{-1}): ν_{max} 665, 756, 1037, 1255, 1336, 1437,

1474, 2100, 2936, 3063; **^{1}HNMR** (200 MHz, $CDCl_3$): δ 3.40 (dd, *J* = 4.04, 12.58 Hz, 1H), 3.53 (dd, *J* = 8.1, 12.8 Hz, 1H), 5.22 (dd, *J* = 3.81, 8.54 Hz, 1H), 7.32 (m, 2H); 7.40 (m, 1H), 7.47 (m, 1H); **^{13}CNMR** (50 MHz, $CDCl_3$): δ 54.8, 62.1, 127.5, 128.1, 129.9, 132.6, 134.1; **Anal.** Calcd for $C_8H_7ClN_6$: C, 43.16; H, 3.17; N, 37.75; Found: C, 43.15; H, 3.17; N, 37.76%.

1-Bromo-4-(1,2-diazidoethyl)benzene (21d)

Yield: 90%; pale yellow liquid; **IR** (neat, cm^{-1}): ν_{max} 719, 856, 1073, 1267, 1489, 1590, 2076, 2929; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.44 (dd, *J* = 7.75, 12.68 Hz, 2H), 4.62 (dd, J = 5.36, 7.62 Hz, 1H), 7.24 (m, 2H), 7.55 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56, 94.2, 157.4, 158.9; **Anal.** Calcd for $C_8H_7BrN_6$: C, 35.98; H, 2.64; N, 31.47; Found: C, 35.96; H, 2.64; N, 31.48%.

1-(1,2-Diazidoethyl)-3-methoxybenzene (21e)

Yield: 90%; pale yellow liquid; **IR** (neat, cm^{-1}): ν_{max} 783, 1153, 1267, 1437, 1601, 2099, 2937; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.45 (dd, *J* = 7.9, 12.7 Hz, 2H), 3.83 (s, 3H), 4.64 (dd, *J* = 5.5, 7.9 Hz, 1H) 6.88 (m, 3H), 7.32 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 55.8, 65.3, 112.5, 114.2, 118.9, 130, 137.7, 159.9; **Anal.** Calcd for $C_9H_{10}N_6O$: C, 49.54; H, 4.62; N, 38.51; Found: C, 49.55; H, 4.61; N, 38.51%.

5-(1, 2-Diazidoethyl)benzo[1,3]dioxole (21f)

Yield: 90%; pale yellow viscous liquid; **IR** (neat, cm^{-1}): ν_{max} 730, 933, 1102, 1247, 1444, 1504, 2100, 2902; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.40 (dd, *J* = 8.09, 12.81 Hz, 2H), 4.56 (dd, J = 5.39, 7.79 Hz, 1H), 6.00 (s, 2H), 6.80 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.9, 65.3, 101.4, 107, 108.5, 120.8, 130.1, 148.3; **Anal.** Calcd for $C_9H_8N_6O_2$: C, 46.55; H, 3.47; N, 36.19; Found: C, 46.53; H, 3.47; N, 36.20%.

1, 2-Diazidoindane (21g)

Yield: 70%; pale yellow viscous liquid; mixture of *anti* : *syn* (1:1); **IR** (neat, cm^{-1}): ν_{max}

704, 738, 1265, 2104, 2926; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 2.94 (dd, *J* = 6.7, 16 Hz, 1H), 3.17 (d, *J* = 6.7 Hz, 2H), 3.35 (dd, *J* = 6.8, 16 Hz, 1H), 4.16 (dd, *J* = 6.7, 12 Hz, 1H), 4.29 (dd, *J* = 6.7, 12 Hz, 1H), 4.76 (d, *J* = 5.6 Hz, 1H), 4.82 (d, *J* = 5.7 Hz, 1H), 7.23-7.42 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$,): δ 35.4, 35.9, 63.9, 66.8, 67.5, 124.41, 124.7, 125.0, 125.2, 127.5, 127.6, 129.3, 129.5, 137.4, 137.6, 138.9, 139.6; **Anal.** Calcd for $C_{10}H_{10}N_6$: C, 56.07; H, 4.71; N, 39.23; Found: C, 55.60; H, 4.88; N, 39.50%.

1, 2-Diazido-1-cyclohexylethane (21h)

Yield: 80%; pale yellow liquid; **IR** (neat, cm^{-1}): ν_{max} 1252, 2102, 2937; **^{1}H-NMR** (200 MHz, $CDCl_3$,): δ 0.96-1.35 (m, 5H), 1.45-1.17 (m, 6H), 3.21-3.30 (m, 1H), 3.36-3.49 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$,): δ 25.7, 25.8, 28.5, 29.6, 40.0, 52.9, 67.5; **Anal** Calcd for $C_8H_{14}N_6$: C, 49.47; H, 7.26; N, 43.27; Found: C, 49.25; H, 7.50; N, 43.20%.

1, 2-Diazidocyclooctane (21i)

Yield: 60%; pale yellow viscous liquid; **IR** (neat, cm^{-1}): ν_{max} 1252, 2094; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.56 (m, 6H), 1.81 (m, 6H), 3.55 (m, 1H), 3.73 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.50, 26.5, 27.0, 27.3, 28.1, 29.3 61.5, 63.3; **Anal.** Calcd for $C_8H_{14}N_6$: C, 49.47; H, 7.26; N, 43.27; Found: C, 49.45; H, 7.28; N, 43.29%.

1, 2-Diazidohexane (21j)

Yield: 70%; pale yellow viscous liquid; **IR** (neat, cm^{-1}): ν_{max} 1253, 2103, 2930; **^{1}HNMR** (200 MHz, $CDCl_3$,): δ 0.93 (t, *J* = 6.7, 3H), 1.25-1.41 (m, 4H), 1.51-1.58 (m, 2H), 3.25-3.53 (m, 3H); **^{13}CNMR** (50 MHz, $CDCl_3$,): δ 13.7, 22.2, 27.8, 31.3, 54.7, 61.9; **Anal.** Calcd for. $C_6H_{12}N_6$: C, 42.84; H, 7.19; N, 49.96; Found: C, 42.50; H, 7.31; N, 49.90%.

SECTION II:

Synthesis of *gem*-Ditriazoles from α,α-Diazido Ketones

4.2.1 Introduction and Pharmacology

Triazoles, like many other five membered heterocyclic compounds are used very often in the pharmacological and medicinal applications. 1,2,3–Triazole and its derivatives enhanced considerable attention for the past few decades due to their chemotherapeutical value. Many 1,2,3–triazole derivatives are found to be more potent *anti*-microbial,[18] *anti* inflammatory,[19] analgesic,[20] local anesthetic,[21] *anti*-allergic, *anti*-convulsant,[22] *anti*-neoplastic,[23] *anti*-malarial,[24] *anti*-HIV[25] and *anti*-cancer activities.[26] Some of the 1,2,3-triazoles are also used as deoxyribose nucleic acid (DNA) cleaving agents[27] and potassium channel activators.[28] These moieties have been widely used in the synthetic intermediates and industrial applications, such as dyes, anti corrosive agents, photo stabilizers, photographic materials and agrochemicals.[29] Thus, 1,2,3-triazoles are useful building blocks in chemistry and are stable to moisture, oxygen, light and also metabolism in the body. Moreover, these moieties can be turned to form powerful pharmacophores and also play an important role in bio-conjugation. 1,2,3-Triazole moieties are attractive connecting units, since they are stable to metabolic degradation and capable of hydrogen bonding which can be favorable in binding of biomolecular targets.

4.2.2 Review of Literature

Literature search reveals that there are no reports available for the syntheses of *gem*-ditriazoles.

4.2.3 Present Work

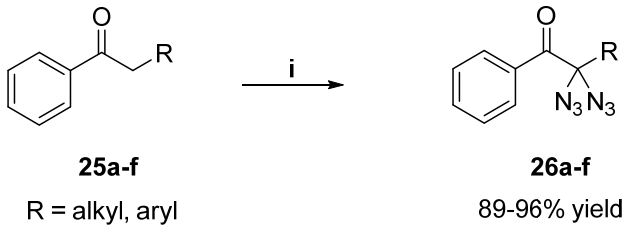
4.2.3.1 Objective

One of the most attractive ways to prepare these compounds involve the thermal 1,3-dipolar cycloaddition of azides with alkynes, pioneered by Huisgen.[17] This section

deals with the synthesis of some novel *gem*-ditriazoles from several α,α-diazidoketones, prepared from the respective aromatic ketones *via* $NaIO_4$–NaN_3 mediated α,α-diazidation, in view of pharmacological significance of triazole derivatives.

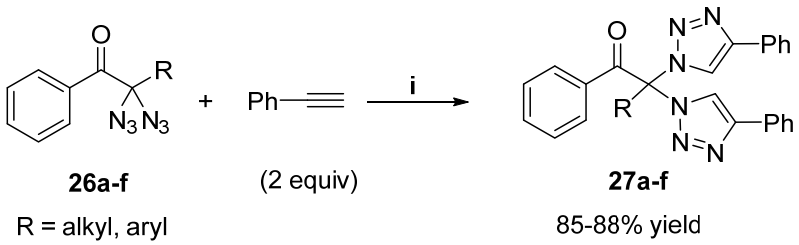
4.2.3.2 Results and Discussion

During the course of this study of $NaIO_4$-mediated oxidative α,α-diazidation of arylketones, we found that treatment of α,α-diazidoketones **26a-f** with phenylacetylene (2 equiv) in the presence of Cu(I) as the catalyst in toluene at 80 ^oC, provided *gem*-α,α-ditriazole aryl ketones **27a-f** in high yields (85-88%) (**Scheme 11**). The starting material i.e. α, α- diazidoketones **26a-f** were prepared by the $NaIO_4$-NaN_3 mediated diazidation of corresponding aromatic ketones **25a-f** in excellent yields (**Scheme 10**).[30]



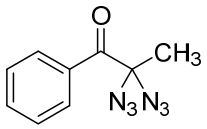
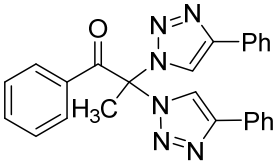
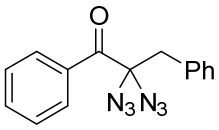
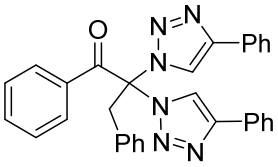
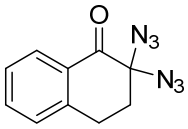
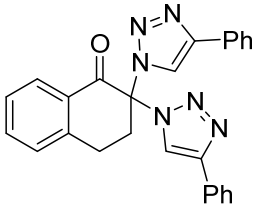
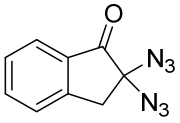
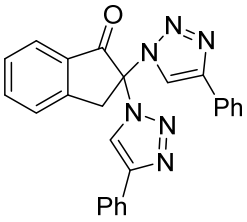
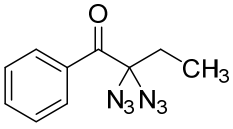
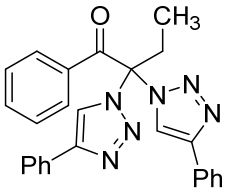
Scheme 10: (i) ketone (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), DMSO:AcOH (4:1), 75 ^oC, 4 h.

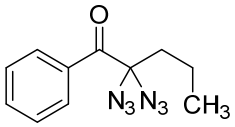
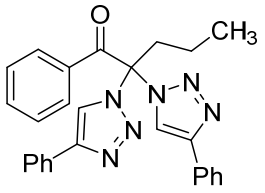
In particular when 2,2-diazido-1-phenylpropan-1-one **26a** was subjected to 1,3-cycloaddition reaction with phenylacetylene (2 equiv) in the presence Cu(I) as the catalyst gave diatriazole **27a** in 88% yield. Range of substrates have been screened including open chain as well as cyclic aromatic ketones. The sterically hindered diazidoketones like **26c** and **26d** also were converted in to α,α-geminal ditriazole **27c** and **27d** in very good yield 85% each. Continuation of reaction more than 8 h did not improve the yields (**Table 2**).



Scheme 11: (i) CuI (5 mol%), toluene, 80 ^{o}C, 8 h.

Table 2: CuI-mediated synthesis of *gem*-α,α-ditriazole aryl ketones[a]

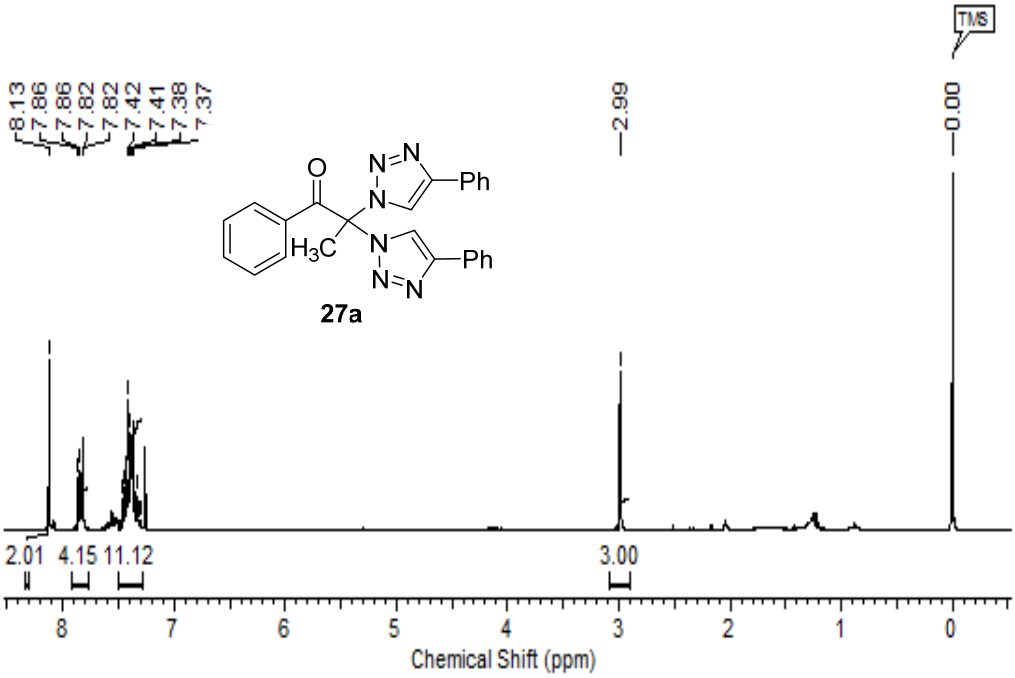
Entry	Substrate (26a-f)	Products (27a-f)	Yield (%)[b]
a			88
b			87
c			85
d			85
e			87

f			86

Reaction conditions: [a] α,α-diazidoketones (5 mmol), phenyl acetylene (10 mmol), CuI (0.25 mmol), 20 ml, toluene 80 °C, 8 h; [b] yields refer to isolated yield after column chromatography.

The formation of *gem*-α,α-ditriazole **27a-f** was confirmed by ^{1}H and ^{13}C NMR and IR spectroscopy.

Example 1: The ^{1}H NMR spectrum of **27a** showed a typical singlet at δ 8.13 for alkene protons in the triazole ring and multiplets at δ 7.30-7.45 and 7.82-7.86 for aromatic protons. Its ^{13}C NMR spectrum showed two typical signals at δ 148.5 and 191.8 for the alkenic carbon in the triazole ring and carbonyl carbon respectively. The disappearance of signal at 2108 cm^{-1} in its IR spectrum further substantiated the formation of triazole ring (**Fig. 3**).



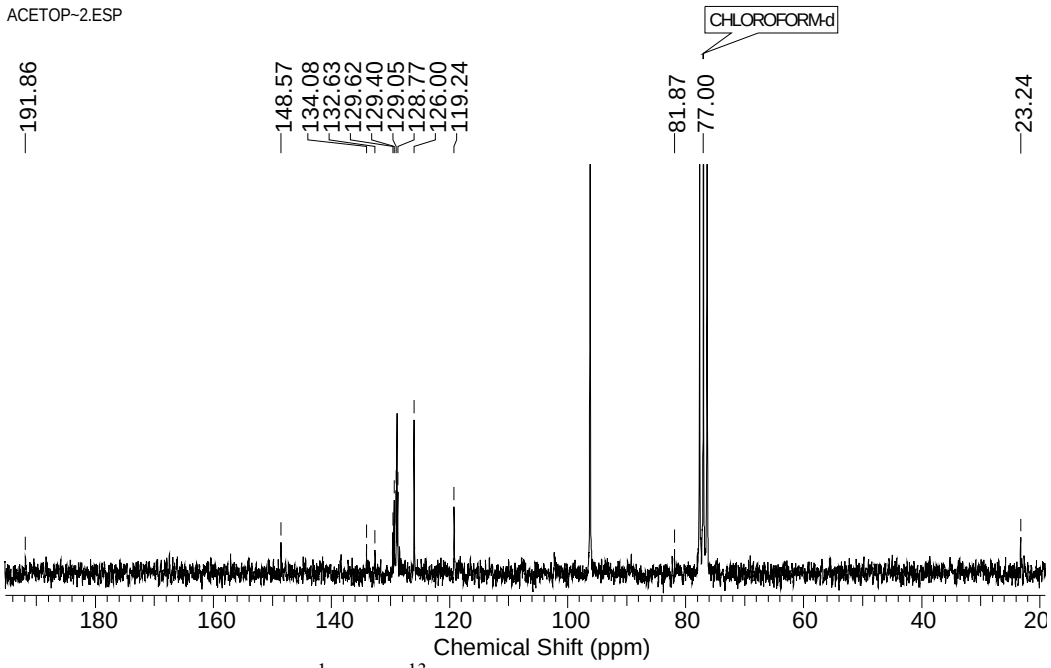
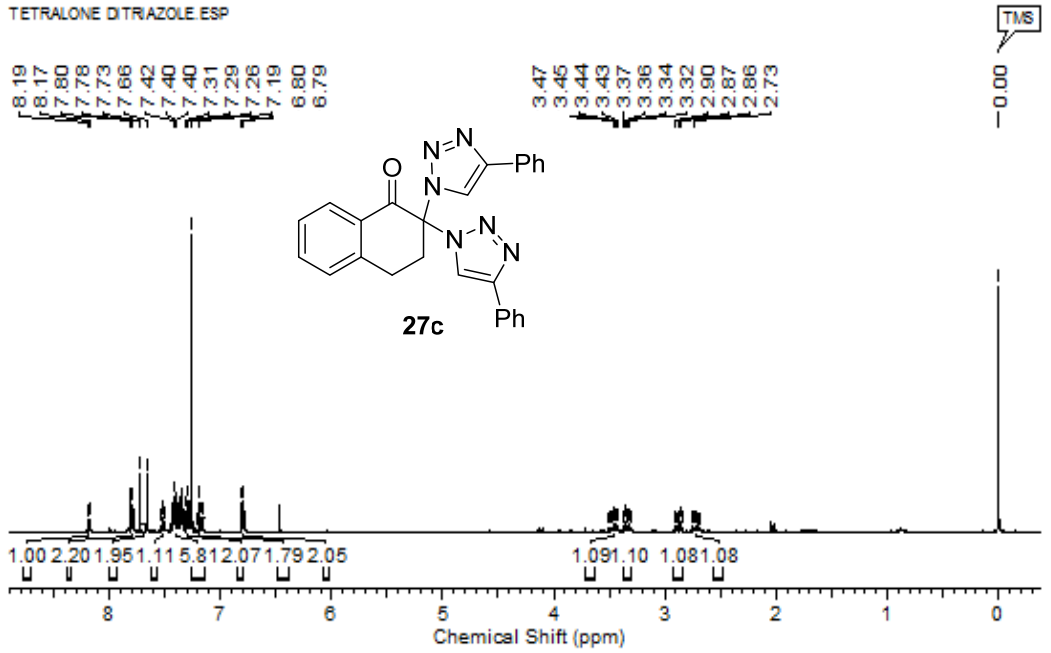


Fig. 3: ^{1}H and ^{13}C NMR spectra of ditriazole **27a**

Example 2: The ^{1}H NMR spectrums showed a typical signals at δ 2.68-2.91 and 3.31-3.50 for the four aliphatic protons of **27c** whereas typical singlets at δ 7.66 and 7.33 for alkenic protons in the triazole ring and multiplets at δ 6.78-7.42 and 7.78-7.81for aromatic protons.



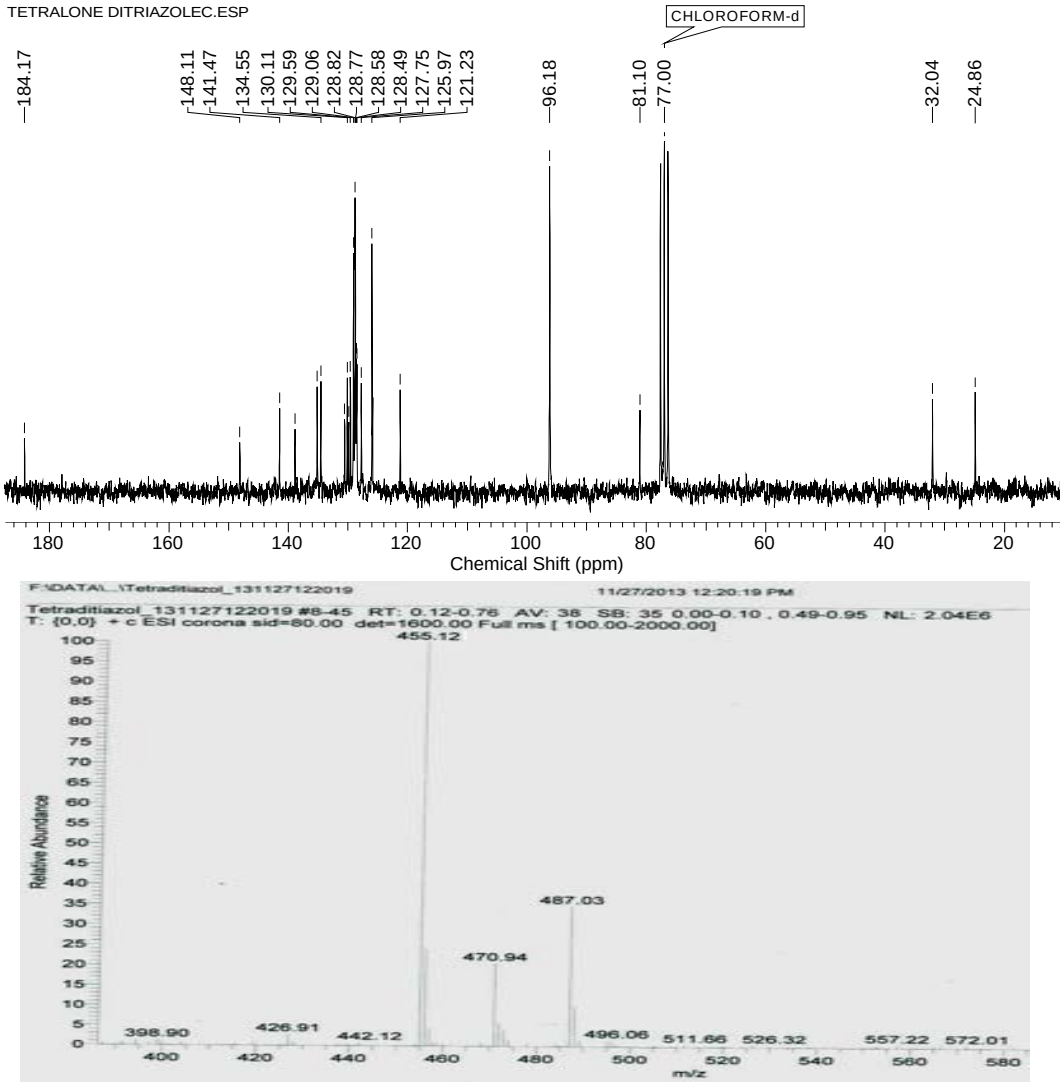


Fig. 4: ^{1}H, ^{13}C NMR and LCMS spectra of ditriazole **27c**

Its ^{13}C NMR spectrum displayed two typical signals at δ 24.8 and 32.0 for the β- and α-aliphatic carbons respectively. The signals at δ 148 and 191.8 for the quaternary carbons in the triazole ring and carbonyl carbon respectively. Its LCMS chromatogram showed the molecular ion peak at m/z for $[M + Na]^{+}$, 455.12 (**Fig. 4**).

4.2.4. Conclusion

In conclusion, we have provided an efficient method for the synthesis of *gem*-α,α-ditriazole aryl ketones *via* the CuI catalyzed 1,3-dipolar cycloaddition reaction

between α,α-diazidoketones and phenylacetylene. The compounds are believed to be important owing to the various significant properties of triazoles. The procedure is simple and high yielding.

4.2.5. Experimental

General experimental procedure for the synthesis of *gem*-ditriazoles from α,α-diazido ketones:

To a suspension of CuI (0.25 mmol) and phenyl acetylene (10 mmol) in 20 mL of toluene was added α,α-diazidoketones **26a-f** (5 mmol), as the case may be, and the reaction mixture was stirred at 80 °C for 8 h. It was monitored by TLC and then the reaction mixture was poured into water (100 ml) and extracted with EtOAc (3 × 20 ml). The combined organic layers were washed with a saturated solution of aqueous $Na_2S_2O_3$ (5%, 50 ml), dried over anhyd. Na_2SO_4. Concentration of the organic layer under reduced pressure gave crude ditriazoles, which was subjected to column purification using hexane/ethyl acetate (9:1) as eluent to obtain pure *gem*-α,α-ditriazole aryl ketones **27a-f**.

1-Phenyl-2,2-*bis*(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-1-one (27a)

Yield: 88%; pale yellow solid; **mp:** 195-200 ^oC; **IR** (neat, cm^{-1}): ν_{max} 691, 764, 1070, 1452, 1697, 1741, 2921; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.99 (s, 3H), 7.42 (m, 11H), 7.82 (dd, *J* = 7.6 and 12.2 Hz, 4H), 8.13 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.2, 81.8, 119.2, 126, 128.7, 129, 129.4, 129.6, 132.6, 134, 148.5; **Anal.** Calcd for $C_{25}H_{20}N_6O$: C, 71.41; H, 4.79; N, 19.99; Found: C, 71.39; H, 4.77; N, 20.00 %.

1,3-Diphenyl-2,2-*bis*(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-1-one (27b)

Yield: 87%; pale yellow solid; **mp:** 144-149 ^oC; **IR** (neat, cm^{-1}):, ν_{max} 752, 1162, 1434, 1692, 1738, 2937; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.95 (d, *J* = 3.2 Hz, 2H), 6.84-6.88 (m, 2H), 7.18-7.75 (m, 20H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 42.3, 83.7, 118.6, 125.8, 127.9, 128.5, 128.7, 128.8, 129.0, 129.2, 130.3, 131.1, 133.7, 135.0,

147.6, 189.5; **Anal.** Calcd for $C_{31}H_{24}N_6O$: C, 74.98; H, 4.87; N, 16.92; Found: C, 74.96; H, 4.87; N, 16.91 %.

3,4-Dihydro-2,2-*bis*(4-phenyl-1*H*-1,2,3-triazol-1-yl)naphthalen-1(2*H*)-one (27c)

Yield: 85%; pale yellow solid; **mp:** 166-168 ^oC; **IR** (neat, cm^{-1}): ν_{max} 685, 783, 1058, 1441, 1695, 1745, 2931; **^{1}H NMR** (200 MHz, $CDCl_3$): □ 2.68-2.76 (m, 1H), 2.85-2.91 (dt, *J* = 5.04, 4.58 and 17.86 Hz 1H), 3.31-3.37 (m, 1H), 3.43-3.50 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): □ 24.8, 32.0, 81.1, 121.2, 125.8, 125.9, 127.7, 128.8, 129.0, 129.5, 130.1, 130.5, 134.5, 135.1, 138.8, 141.4, 148.1, 184.1; **Anal.** Calcd for. $C_{26}H_{20}N_6O$: C, 72.21; H, 4.66; N, 19.43; Found C, 72.20; H, 4.65; N, 19.44 %; **LCMS** (ESI) m/z Calcd for $C_{26}H_{20}N_6Na$ $[M + Na]^+$, 455.1699; found, 455.12.

3,4-Dihydro-2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)naphthalen-1(2*H*)-one (27d)

Yield: 85%; pale yellow solid; **mp:** 152-154 ^oC; **IR** (neat, cm^{-1}): ν_{max} 691, 764, 1070, 1452, 1689, 1735, 2940; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.71 (s, 1H), 7.18-7.51 (m, 13H), 7.77 (s, 2H), 7.85 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.1, 99.2, 126.1, 127.8, 134.2, 136.9, 147.3, 155.8, 198.4; **Anal.** Calcd for $C_{25}H_{18}N_6O$: C, 71.76; H, 4.34; N, 20.08; Found: C, 71.75; H, 4.32; N, 20.06 %.

1-Phenyl-2,2-*bis*(4-phenyl-1*H*-1,2,3-triazol-1-yl)butan-1-one (27e)

Yield: 87%; pale yellow solid; **mp**: 169-171 ^oC; **IR** (neat, cm^{-1}): ν_{max} 751, 1120, 1469, 1698, 1745, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.1 Hz, 3H), 2.40 (q, *J* = 7.2 Hz 2H), 7.22-7.34 (m, 14H), 7.63 (s, 2H), 8.02 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.8, 20.5, 93.9, 127.8, 129.2, 129.6, 130.3, 132.6, 133.7, 134.0 148.4; **Anal.** Calcd for $C_{26}H_{22}N_6O$: C, 71.87; H, 5.10; N, 19.34; Found: C, 71.85; H, 5.11; N, 19.31 %.

1-Phenyl-2,2-*bis*(4-phenyl-1*H*-1,2,3-triazol-1-yl)pentan-1-one (27f)

Yield: 86%; pale yellow solid; **mp:** 175-178 ^oC; **IR** (neat, cm^{-1}): ν_{max} 675, 1254,

1478, 1694, 1742, 2967; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.0 Hz, 3H), 1.42 (m, 2H), 2.41 (m, 2H), 7.22-7.48 (m, 13H), 7.65 (s, 2H), 8.87 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.8, 20.5, 93.9, 127.8, 129.2, 129.6, 130.3, 132.6, 133.7, 134.0 148.4; **Anal.** Calcd for $C_{27}H_{24}N_6O$: C, 72.30; H, 5.39; N, 18.74; Found: C, 72.32; H, 5.38; N, 18.72%.

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2. "$NaIO_4$-NaN_3-mediated diazidation of styrenes, alkenes, benzylic alcohols, and aryl ketones" **Kamble, D. A**.; Karabal, P. U.; Chouthaiwale, P. V.; Sudalai, A. *Tetrahedron Lett.,* **2012**, *53*, 4195..
3. "Co(III)(salen)-catalyzed phenolic kinetic resolution of two stereocentered benzyloxy and azido epoxides: its application in the synthesis of ICI-118,551, and anti-hypertensive agent" Karabal, P. U.; **Kamble, D. A**.; Sudalai, A. *Org. Biomol. Chem*., **2014,** *12*, 2349.
4. "Phenolytic kinetic resolution of azido and alkoxy epoxides" Karabal, P. U.; **Kamble, D. A.**; Sudalai, A. US patent: WO2013093943A9.
5. "Pd-Catalyzed Oxidative Kinetic Resolution of α-Bromobenzylic Alcohols Using (–)-Sparteine as Chiral Auxiliary: A Practical Synthesis of (–)-Chloramphenicol" **Kamble, D. A**.; Kamble, R.; Suryavanshi G.; Sudalai, A. (Manuscript under preparation).