Asymmetric Synthesis of Bioactive Molecules and new Synthetic Methodologies to γ-Butyrolactones, Epoxy Esters and Chromanes

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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 ***"Asymmetric Synthesis of Bioactive Molecules and new Synthetic Methodologies to γ-Butyrolactones, Epoxy Esters and Chromanes"*** which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Dattatray Ambadas Devalankar*** 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.

February 2014
Pune

Dr. A. Sudalai
(Research Guide)

NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Asymmetric Synthesis of Bioactive Molecules and new Synthetic Methodologies to γ-Butyrolactones, Epoxy Esters and Chromanes"*** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

February 2014
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CONTENTS

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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 "**Asymmetric Synthesis of Bioactive Molecules and new Synthetic Methodologies to γ-Butyrolactones, Epoxy Esters and Chromanes**" is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and to develop useful synthetic methodologies. **Chapter 1** describes the synthesis of optically pure γ-butyrolactones and epoxy esters *via* two-stereocentered hydrolytic kinetic resolution of 3-substitued epoxy esters and their application in the formal synthesis of (-)-paroxetine and (+)-eldanolide. **Chapter 2** presents the total synthesis of (+)-deoxoprosophylline and (*S*, *S*)-3-hydroxypipecolic acid *via* HKR of azido epoxides. **Chapter 3** deals with enantioselective synthesis of (+)-sertraline and eupomatilione-6 using HKR and SmI_2-mediated reductive coupling of aldehydes with chiral crotonates respectively. **Chapter 4** describes synthetic methodologies involving enantioselective synthesis of γ-butenolides *via* sequential α-aminoxylation followed by *cis*-Wittig olefination of aldehydes and its application in the synthesis of *trans*-(+)-cognac lactone and synthesis of 4-substituted chromanes *via* Au(III)-catalyzed intramolecular Friedel-Crafts reaction of 3-aryoxy benzyl alcohols.

CHAPTER 1

Synthesis of Optically Pure γ-Butyrolactones and Epoxy Esters *via* Two-Stereocentered HKR of 3-Substituted Epoxy Esters: A Formal Synthesis of (-)-Paroxetine and (+)-Eldanolide

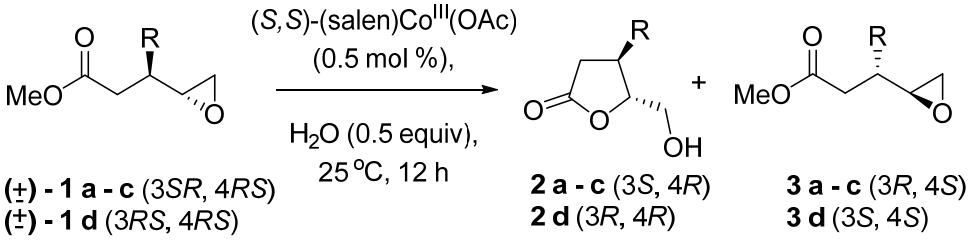
Hydrolytic kinetic resolution (HKR) developed by Jacobsen *et al.* has emerged as a powerful tool to obtain terminal epoxides as well as their corresponding diols in enantiomerically pure form.[1] These compounds are important intermediates in the synthesis of various bioactive molecules.[2] The enantiomerically pure γ-butyrolactone and epoxy esters are also valuable 'building blocks' for the asymmetric synthesis of bioactive natural products.[3,4] This chapter deals with the development of a novel method in which HKR of 3-substituted epoxides catalyzed by chiral Co(III)(salen)-OAc complex was employed, for the first time to produce chiral substituted γ-butyrolactones and epoxy esters, followed by its application in the asymmetric

synthesis of (-)-paroxetine and (+)-eldanolide. This chapter is divided into two sections. **Section I** deals with the synthesis of optically pure γ-butyrolactones and epoxy esters *via* two-stereocentered HKR of 3-substituted epoxy esters while **Section II** describes the formal synthesis of (-)-paroxetine **14** and (+)-eldanolide **15**.

<u>SECTION I:</u> Synthesis of Optically Pure γ-Butyrolactones and Epoxy Esters *via* Two-Stereocentered HKR of 3-Substitued Epoxy Esters

For the first time, HKR of racemic *anti*- or *syn*- 3-substituted aryl or alkyl epoxy esters derivative was carried out. In this strategy, the relative stereochemistry between aryl/alkyl epoxide functions is established prior to the HKR step and thus a single asymmetric reaction is employed to form compounds with two asymmetric centers. The racemic *anti*- and *syn*- 3-substituted epoxy esters (**1** & **4**), the substrates for HKR, were efficiently prepared in a highly diastereoselective manner from the corresponding allylic alcohol by essentially following a three-step procedure:[5] (i) Johnson-Claisen rearrangement (ii) diastereoselective iodolactonization; (iii) methanolysis reaction to form the corresponding racemic epoxides. In this section, we have described a flexible, novel method that employs HKR of racemic 3-substituted (aryl or alkyl) epoxy esters **1** with two stereocentres to produce substituted γ-butyrolactones **2** and epoxy esters **3** in high optical purities (**Table 1**) in a single step.

Table 1. Co-catalyzed HKR of racemic 3-substituted *anti*-epoxy esters



(±) - 1 a - c (3*SR*, 4*RS*)
(±) - 1 d (3*RS*, 4*RS*)

2 a - c (3*S*, 4*R*)
2 d (3*R*, 4*R*)

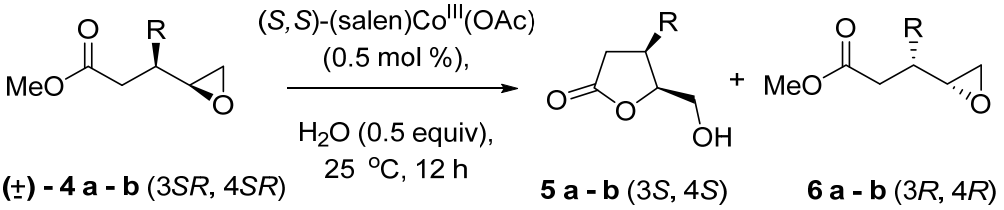
3 a - c (3*R*, 4*S*)
3 d (3*S*, 4*S*)

Entry	Substrates (R) (±) - **1** (**a - d**)	Lactones **2** (**a - d**)		Epoxides **3** (**a - d**)	
		yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
a	phenyl	45	99	48	97
b	4-fluorophenyl	46	99	49	99
c	4-methoxyphenyl	48	97	47	96
d	methyl	46	97	48	96

[a] Isolated yield after column chromatographic purification; [b] ee determined by chiral HPLC.

When HKR of racemic *anti*-3-substituted epoxy ester **1a** was carried out with (*S, S*)-(salen)Co(III)OAc complex (0.5 mol %) and H_2O (0.5 equiv), the corresponding *trans*- 3,4-disubstituted γ-butyrolactone **2a** (45%) and 3-substituted epoxy ester **3a** (48%) were isolated in high yields and optical purity [**2a** (99% ee) and **3a** (97% ee)]. We have examined its scope by subjecting several racemic *anti*-3-substituted epoxy esters **1b - d** to HKR, which proceeded smoothly, with complete regiocontrol, to give the respective enantioenriched *trans*-3,4-disubstituted γ-butyrolactones **2b - d** and *anti*-epoxy esters **3b - d** in excellent ees (96 to 99% ee) and high yields (45 to 49%). Similarly, when *syn*-3-substituted epoxy esters **4a - b** were subjected to HKR under identical reaction conditions, the corresponding chiral *cis*-3,4-disubstituted γ-butyrolactones **5a - b** and *syn*-epoxy esters **6a - b** were obtained in high yields and ees upto 99%. The results of this study are presented in Table 2.

Table 2. Co-catalyzed HKR of racemic 3-substituted *syn*-epoxy esters



(±) - 4 a - b (3*SR*, 4*SR*) **5 a - b** (3*S*, 4*S*) **6 a - b** (3*R*, 4*R*)

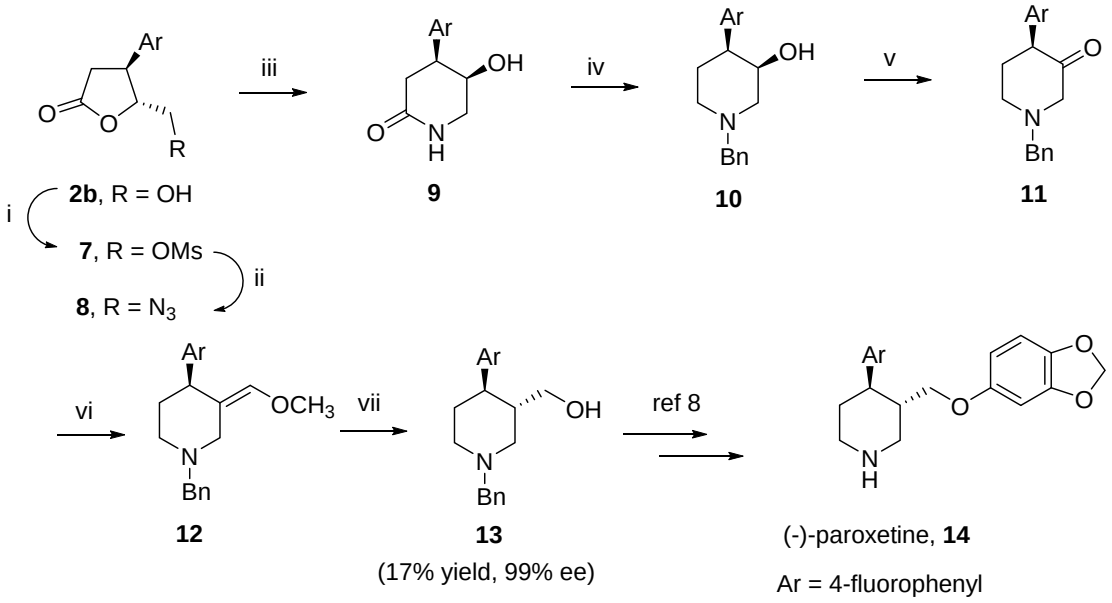
Entry	Substrates (R) (±) - **4** (**a - b**)	Lactones **5**(**a - b**)		epoxides **6** (**a - b**)	
		yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
a	Phenyl	47	98	48	97
d	4-bromophenyl	46	98	48	97

[a] Isolated yield after column chromatographic purification; [b] ee determined by chiral HPLC.

SECTION II: Formal Synthesis (-)-Paroxetine and (+)-Eldanolide

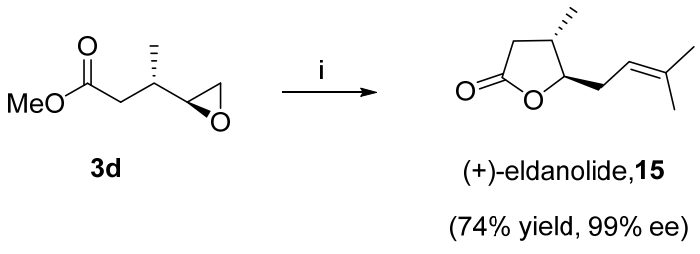
(-)-Paroxetine **14**, a *trans*-3,4-disubstitued piperidine derivative, is used in the treatment of depression, panic disorder[6] and natural product (+)-eldanolide **15** is a long range sex attractant isolated from the male wing gland of African sugarcane stem borer *Eldana sacharina*.[7] This section describes a concise enantioselective synthesis of (-)-paroxetine **14** and (+)-eldanolide **15** using HKR of 3-substituted epoxides. Our synthesis of (-)-paroxetine **14** commences from γ-butyrolactone **2b**. Mesylation of **2b** gave the mesylate **7**, which was converted to the corresponding azide **8** (NaN_3, DMF, 80 °C) in 95% yield. Azide **8** was then subjected to intramolecular reductive

cyclization over $Pd(OH)_2/H_2$ (1 atm) to afford *cis*-3,4-disubstituted piperidinone core **9** in 98% yield. Reduction of amide carbonyl **9** with $BH_3{\cdot}SMe_2$ followed by *in situ* *N*-benzyl protection gave *cis*-piperidine derivative **10** in 85% yield. Swern oxidation of alcohol **10** gave ketone **11**, which on Wittig olefination with $Ph_3P{=}CHOMe$ produced enol ether **12** in 60% yield. Acid hydrolysis of **12** followed by $NaBH_4$ reduction of the resulting aldehyde provided the known intermediate *N*-benzyl amino alcohol **13**,[8] (overall yield 17% from **2b**) thus constituting a formal synthesis of (-)-paroxetine **14** (**Scheme 1**).



Scheme 1: (i) MsCl, Et_3N, CH_2Cl_2, 0 ^oC,1 h, 92%; (ii) NaN_3, DMF, 80 ^oC, 3 h, 95%; (iii) $Pd(OH)_2$, H_2 (1 atm), MeOH, 12 h, 25 ^oC, 98%; (iv) $BH_3.SMe_2$, THF, reflux,12 h, then BnBr, Na_2CO_3, CH_2Cl_2 /H_2O (1:1), reflux, 12 h, 85%; (v) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78 ^oC, 1 h, 80%; (vi) $PPh_3^+CH_2OCH_3Cl^-$, *n*-BnLi, THF, 0 to 25 ^oC, 48 h, 60%; (vii) (a) 1. 0.1 M H_2SO_4, THF, 50 ^oC, 2 h; (b) $NaBH_4$, MeOH, 25 ^oC, 1 h, 72% (for two steps).

Also, synthesis of natural product (+)-eldanolide **15** was achieved by the regioselective ring opening of chiral epoxide **3d** with $(Me)_2C{=}CHMgBr$ followed by intramolecular lactonization, all in a single step with 74% yield (**Scheme 2**).



Scheme 2: (i) $(CH_3)_2C{=}CHMgBr$, $CuBr.SMe_2$, THF, -30 to 0 ^oC, 5 h, 74%.

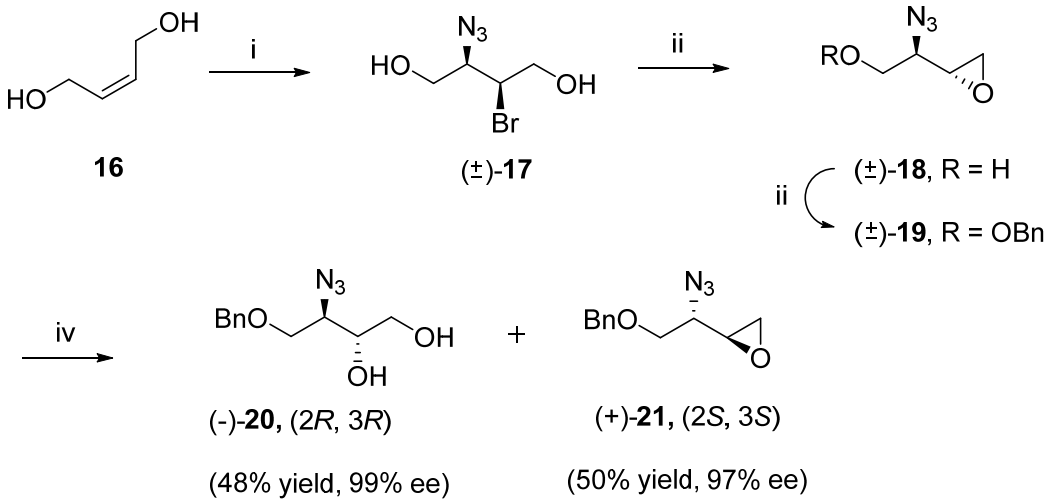
CHAPTER 2

Enantioselective Synthesis of (+)-Deoxoprosophylline and (*S*, *S*)-3-Hydroxypipecolic Acid *via* Hydrolytic Kinetic Resolution of Azido Epoxides

Chapter II is divided into two sections. **Section I** presents the enantioselective synthesis of (+)-deoxoprosophylline **29** *via* HKR of azido epoxide **19** while **Section II** describes the asymmetric synthesis of (*S*, *S*)-3-hydroxypipecolic acid **34** from the key intermediate azido aldehyde **24**.

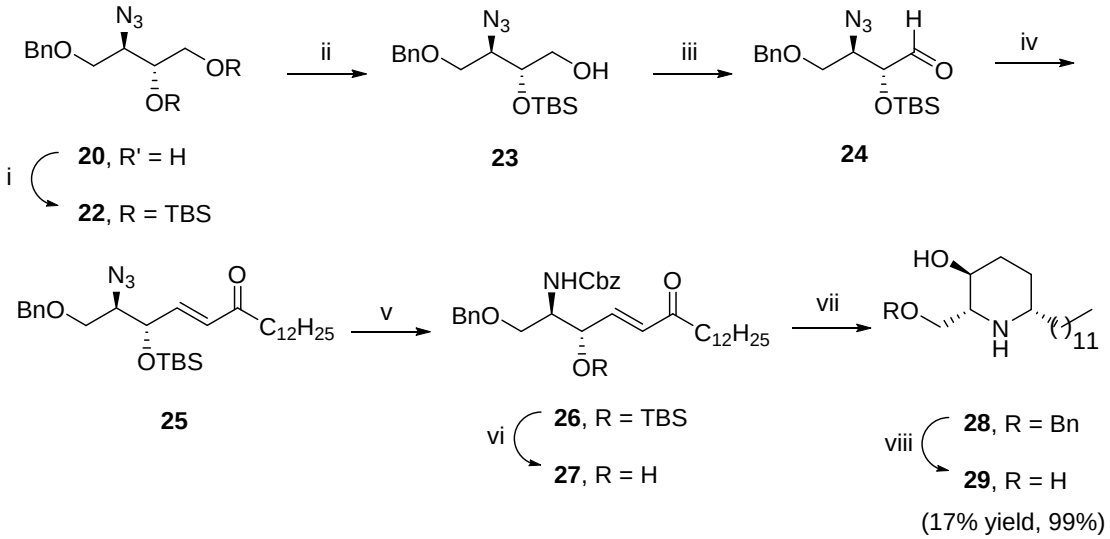
SECTION I: A Concise Synthesis of (+)-Deoxoprosophylline *via* Co(III)(salen)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxides

(+)-Deoxoprosophylline **29** belongs to prosopis alkaloids containing 2,6-disubstituted piperidine-3-ols has been isolated from the leaves of an African plant, *Prosopis africana* Taub[9] and is found to exhibit anaesthetic, analgesic and antibiotic properties.[9,10] Our synthesis of (+)-deoxoprosophylline **29** commenced with commercially available *cis*-2-butene-1,4-diol **16**, which on treatment with NBS in the presence of NaN_3, gave bromo azide **17** in 89% yield. The bromo azide **17** was readily transformed into racemic *anti*-azido epoxide (NaOH, dry THF, 0 ^oC, 84%). The protection of primary hydroxyl group in **18** as benzyl ether (BnBr, NaH, DMF, - 40 ^oC) produced protected racemic azido epoxide **19** in 94% yield.



Scheme 3: (i) NBS (1.2 equiv), NaN_3 (2 equiv), CH_3CN/H_2O (3:1), 0 ^oC, 3 h, 89%; (ii) NaOH, THF, 0 ^oC, 3 h, 84%; (iii) BnBr, NaH, DMF, -40 ^oC, 2 h, 94%; (iv) (*S*,*S*)-Co^{III} (salen) (0.5 mol %), H_2O (0.49 equiv), 0 to 25 ^oC, 12 h.

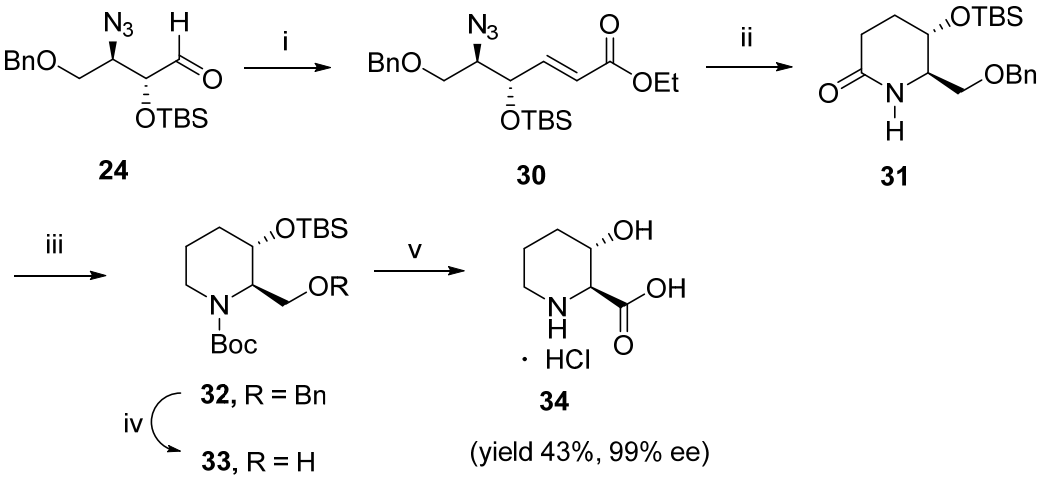
Compound **19** was then subjected to HKR with (*S*, *S*)- (salen)Co(III)(OAc) complex (0.5 mol %) and H_2O (0.49 equiv), which produced the corresponding diol **20** (48%, 99% ee) and chiral epoxide **21** (50%, 97% ee) in high optical purity (**Scheme 3**).[11] We then protected both the free hydroxyl groups in diol **20** as its disilyl ether derivative **22** (TBSCl, imid., DMF), followed by selective deprotection (CSA, MeOH, 0 ^oC) of primary silyl ether that afforded monosilyl ether **23** in 92% yield. Further, the primary hydroxyl group in **23** was oxidized using IBX to produce the corresponding crude aldehyde **24** in 91% yield. The crude aldehyde **24** was then subjected to Wittig reaction [$(EtO)_2POCH_2COC_{12}H_{25}$, prepared from diethyl-2-oxopropylphosphonate and 1-iodoundecane, $^iPr_2NEt$, MeCN, 0 ^oC] to give the corresponding (*E*)-unsaturated keto azide **25** in 87% yield with exclusive *trans* selectivity. Then azide in **25** was reduced to amino group using Staudinger conditions (PPh_3, THF/H_2O) followed by *in situ* protection of the corresponding amine as its carbamate derivative **26**. Deprotection of silyl group in **26** was achieved (TBAF, THF, 0 to 25 ^oC) to give amino ketone **27** in 95% yield. Further, amino compound **27** was subjected to intramolecular diastereoselective cyclization under catalytic hydrogenation conditions [$Pd(OH)_2$, MeOH, H_2 (60 psig)] that gave **28** as a single diastereomer, without affecting the OBn group. Finally, *O*-debenzylation in **28** was carried out by Birch reduction (Na, liquid NH_3, THF, -78 ^oC), which furnished (+)-deoxoprosophylline **29** in quantitative yield (**Scheme 4**).



Scheme 4: (i) TBSCl, imid., DMF, 24 h, 98% (ii) CSA, MeOH, 0 ^oC, 5 h, 92%; (iii) IBX, EtOAc, reflux, 3 h, 91%; (iv) $(EtO)_2POCH_2COC_{12}H_{25}$, *i*-$Pr_2NEt$, CH_3CN, 25 ^oC, 12 h, 87%; (v) PPh_3, THF/H_2O, 25 ^oC, 12 h, then aq. Na_2CO_3, CbzCl, 0 to 25 ^oC, 12 h, 88%; (vi) TBAF, THF, 0 ^oC, 2 h, 95%; (vii) 20% $Pd(OH)_2$, MeOH, H_2 (60 psig), 24 h, 94%; (viii) Na, liquid NH_3, THF, -78 ^oC, 1 h, 97%.

<u>SECTION II</u>: Asymmetric Synthesis of (2*S*, 3*S*)-3-Hydroxy Pipecolic Acid *via* Co(III)(salen)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxides

The piperidine unit of 3-hydroxypipecolic acid **34** is found in a number of biologically important products.[12] For example, the *trans* isomer of 3-hydroxypipecolic acid is a precursor of (-)-swainsonine, which has shown potent and specific α-D-mannosidase inhibitory activity,[13] and found in the structure of febrifugine, a potent antimalarial agent.[14] The synthesis of (2*S*, 3*S*)-3-hydroxypipecolic acid **34** commenced from *cis*-2-butene-1,4-diol. The azido aldehyde **24** was prepared from *cis*-2-butene-1,4-diol by following, a simple procedure described in previous section (**Schemes 3 & 4**). Thus, the key intermediate **32** was readily synthesized in 3 steps starting from **24**. The crude aldehyde **24** was treated with $(EtO)_2POCH_2CO_2Et$ under Wittig-Horner conditions to give the corresponding (*E*)-azidoester **30** in 93% yield. Further, azide function in **30** was subjected to intramolecular reductive cyclization over catalytic 10% Pd/C, H_2 (1 atm) that afforded *trans*-2,3-disubstituted piperidinone core **31** in 90% yield with the OBn group intact. Reduction of **31** with $BH_3{\cdot}SMe_2$ followed by *in situ N*-Boc protection gave *trans*-piperidine derivative **32** in 80% yield, which was hydrogenated over Pd/C in MeOH at 70 psig H_2 pressure to furnish alcohol **33** in 96% yield. Finally oxidation of alcohol **33** to carboxylic acid was achieved with $RuCl_3/NaIO_4$ combination, followed by successful removal of both protecting groups under acidic condition gave (2*S*, 3*S*)-3-hydroxypipecolic acid **34** with an overall yield 43% from **24** in 6 steps.



<u>Scheme 5:</u> (i) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0-25 ^oC, 1 h, 93%; (ii) 10% Pd/C, H_2 (1 atm), MeOH, 25 ^oC, 24 h, 90%; (iii) $BH_3.SMe_2$, THF, reflux, 6 h, then CH_2Cl_2/H_2O (1:1), Na_2CO_3, $(Boc)_2O$, 25 ^oC, 12 h, 80%; (iv) 10% Pd/C, H_2 (70 psig), MeOH, 25 ^oC, 24 h, 96%; (v) (a) $RuCl_3$ (2 mol%), $NaIO_4$ (4 equiv), $CH_3CN/CCl_4/H_2O$ (1:1:3), 25 ^oC, 30 min; (b) 6 N HCl, reflux, 2 h, for two steps 68%.

CHAPTER 3

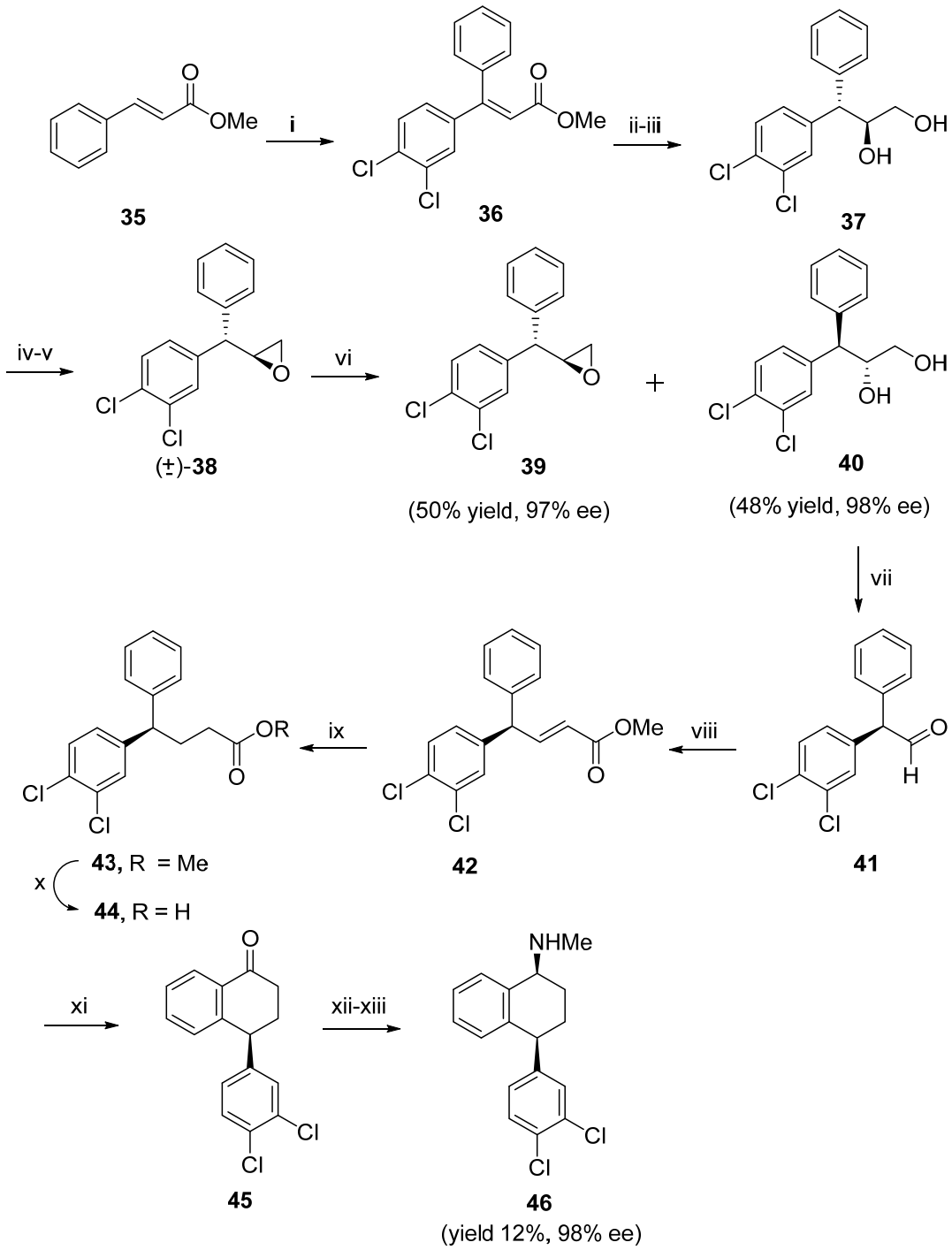
Enantioselective Synthesis of (+)-Sertraline *via* Hydrolytic Kinetic Resolution of 3-Diarylsubstituted Epoxide and Synthesis of Eupomatilone-6 *via* SmI_2-Mediated Reductive Coupling of Aldehyde with Crotonate Ester

Chapter III is divided into two sections. **Section I** presents the synthesis of (+)-sertraline **46**, an antidepressant drug *via* hydrolytic kinetic resolution of 3-diarylsubstituted epoxide while **Section II** describes the total synthesis of eupomatilone-6 **51** *via* SmI_2-mediated reductive coupling of aldehyde with crotonate ester.

SECTION I: A Short Enantioselective Synthesis of (+)-Sertraline *via* Hydrolytic Kinetic Resolution of 3-Diarylsubstituted Epoxide

(+)-Sertraline **46**, a selective competitive inhibitor of synaptosomal serotonin uptake, is an important antidepressant[15] drug discovered by Pfizer, USA in 1970. This section describes an enantioselective synthesis of (+)-sertraline **46** *via* hydrolytic kinetic resolution of 3-diarylsubstituted epoxide. Our strategy to the synthesis of (+)-sertraline **46**, commenced with methyl cinnamate **35,** which was reacted with 3,4-dichlorobenzenediazonium tetrafluoroborate to produce unsaturated ester **36** in 82% yield (**Scheme 6**). Ester group of **36** was reduced using DIBAL-H followed by its regioselective hydroboration/oxidation of in gave diol **37** in 84% yield. The primary hydroxyl group of **37** was selectively tosyled followed by its conversion to epoxide **38** under basic condition (K_2CO_3, MeOH).

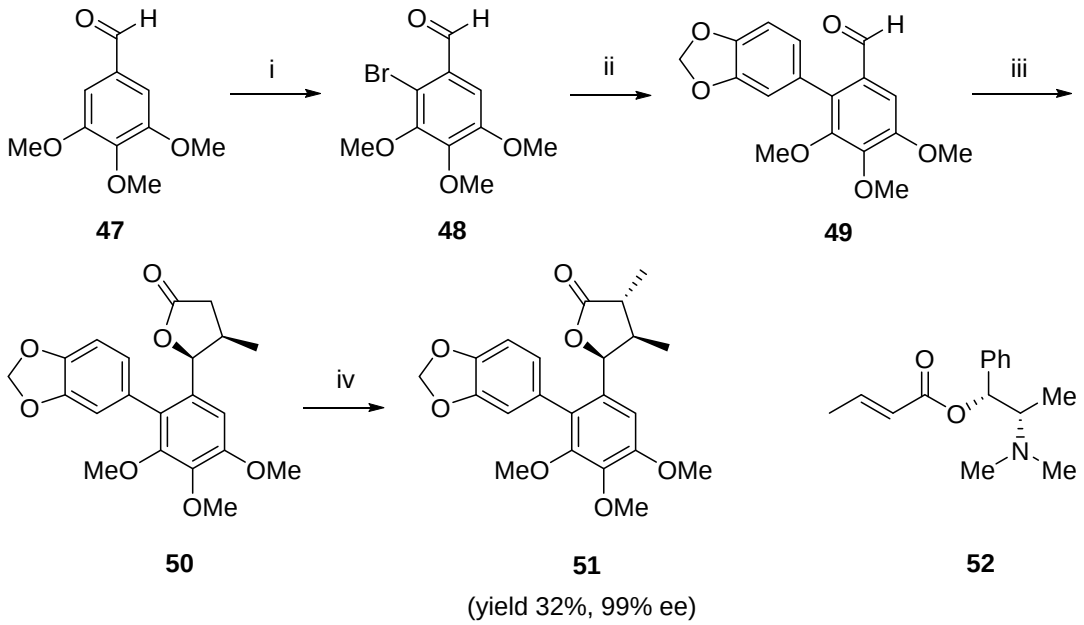
Epoxide **38** was then subjected to HKR with (*S*, *S*)-(salen)Co(III)(OAc) complex (0.5 mol %) and H_2O (0.49 equiv), which produced the corresponding diol **40** (48%, 98% ee) and chiral epoxide **39** (50%, 97% ee) in high optical purities. Diol **40,** on oxidation with $NaIO_4$ gave corresponding the aldehyde **41** in 82% yield, which was then subjected to Wittig olefination to give the α,β-unsaturated ester **42**, which on hydrogenolysis (10% Pd/C, H_2 (20 psig), MeOH) gave saturated ester **43** in 90% yield. Ester **43** was subsequently hydrolysed to obtained carboxylic acid **44**, which was cyclised under acidic conditions to give tetralone **45** in 82% yield. Finally, reductive amination of **45** ($TiCl_4$, excess $MeNH_2$, then Raney Ni (cat.), H_2 (1 atm) afforded (+)-sertraline **46** with an overall yield 12% and 98% ee (**Scheme 6**).



Scheme 6: (i) 3,4-dichlorobenzenediazonium tetrafluoroborate, $Pd(OAc)_2$, MeOH, 4 h, 82%; (ii) DIBAL-H, CH_2Cl_2, 0 ^oC, 1 h, 95%; (iii) BH_3.DMS, THF, 4 h, 30% aq. H_2O_2, NaOH, 5 h, 84%; (iv) TsCl, Et_3N, Bu_2SnO, DMAP, CH_2Cl_2, 0 ^oC, 3 h, 95%; (v) K_2CO_3, MeOH, 25 ^oC, 85%, (vi) (*S*,*S*)-Co^{III} (salen) (0.5 mol %), H_2O (0.49 equiv), 0 to 25 ^oC, 12 h; (vii) $NaIO_4$, CH_2Cl_2, 25 ^oC, 30 min, 82%; (viii) $Ph_3P{=}CHCO_2Et$, dry benzene, 25 ^oC, 12 h, 92%; (ix) 10% Pd/C, H_2 (20 psig), MeOH, 25 ^oC, 94%; (x) 6 N HCl, reflux, 23 h, 89%; (xi) $ClSO_3H$, CH_2Cl_2, 25 ^oC, 2 h, 82%; (xii) $TiCl_4$, excess $MeNH_2$ in THF, 0 ^oC, 1 h, then Raney Ni (cat.), MeOH, H_2 (1 atm), 12 h, 88%.

<u>SECTION II</u>: Total Synthesis of Eupomatilone-6 *via* SmI_2-Mediated Reductive Coupling of Aldehyde with Crotonate

The Australian shrub *Eupomatia Bennettii* F. Muell is a source[16] of rich variety of lignans like eupomatenoids, eupodienones, eupobennettin, bennettinone and eupomatilones. Eupomatilones-6 **51** possesses biological activity like antitumor, anti-HIV, antiviral, ability to influence nucleic acid metabolism.[17,18] This section deals with the synthesis of eupomatilones-6 **51**, starting from trimethoxy benzaldehyde **47**, which on bromination with NBS gave bromo aldehyde **48**. The Suzuki coupling of bromo aldehyde **48** with 3,4-(methylenedioxy)phenylboronic acid in the presence of catalytic amount of Pd(0) catalyst afforded biaryl aldehyde **49** in 75% yield. The reaction of biaryl aldehyde **49** with chiral crotonate **52** (derived from esterification of *trans*-crotonyl chloride with (1*S*, 2*R*)-*N*-methylephedrine) in presence of SmI_2 gave butyrolactone **50** in 98% ee.[19] Finally, diastereoselective methylation at C-3 position in **50** was carried out using LiHMDS-MeI to give eupomatilone-6 **51** in 32% overall yield and 98% ee (**Scheme 7**).



<u>Scheme 7:</u> (i) NBS, $CHCl_3$, 3 h, 25 ^oC, 90%; (ii) $Pd[PPh_3]_4$, 3,4-(methylenedioxy) phenylboronic acid, 2 M Na_2CO_3, C_2H_5OH, benzene, reflux, 8 h, 75 %; (iii) SmI_2, chiral crotonate **52**, THF/*t*-BuOH, -10 ^oC, 68%; (iv) LiHMDS, MeI, THF, -78 to 0 ^oC, 70%.

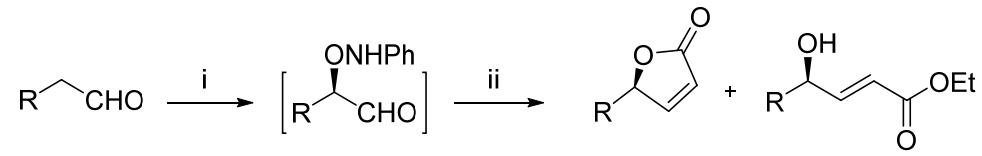
CHAPTER 4

γ-Butenolides *via* Sequential α-Aminoxylation and *cis*-Wittig Olefination of Aldehydes and its Application for the Synthesis of *trans*-(+)-Cognac Lactone and Synthesis of 4-Substituted Chromanes *via* Au(III)-Catalyzed Intramolecular Friedel-Crafts Reaction

Chapter **IV** is divided into two sections. **Section 1** deals with synthetic methodologies involving enantioselective synthesis of γ-butenolides **55** *via* sequential α-aminoxylation and *cis*-Wittig olefination of aldehydes and its application for the synthesis of *trans*-(+)-cognac lactone **57** while **Section 2** describes synthesis of 4-substituted chromanes **59** *via* Au-catalyzed intramolecular Friedel-Crafts reaction of 3-aryloxy benzyl alcohols.

SECTION I: Synthesis of γ-Butenolides *via* Sequential α-Aminoxylation and *cis*-Wittig Olefination of Aldehydes and its Application in the Synthesis of *trans*-(+)-Cognac Lactone

The γ - butenolide skeleton is widely found in over 13,000 biologically active natural products,[20] like pheromones[21] and other aroma components of many fruits;[22] and are also valuable 'building blocks' for the asymmetric synthesis of bioactive natural products. In this section, we describe an efficient sequential α-hydroxylation followed by *cis*-Wittig olefination of aldehydes that leads to enantioselective synthesis of γ-butenolides **55** up to 99% ee as the major product along with minor amounts of γ-hydroxy α,β-unsaturated esters **56** (**Scheme 8**).



53 R = alkyl, Bn

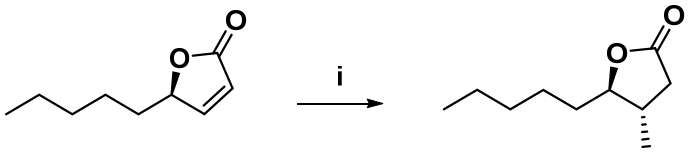
54

55 Yield: 62-70% 98-99% ee

56 Yield: 16-21% 98-99% ee

Scheme 8: (i) L-proline (10 mol%), PhNO (1 equiv), DMSO, 25 ^{o}C, 15 min; (ii) ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (1.5 equiv), DBU (2 equiv), LiCl (2 equiv), THF, -20 ^{o}C, 3 h then $Cu(OAc)_2.H_2O$ (30 mol%), MeOH, 25 ^{o}C, 12 h.

To demonstrate the utility of this methodology, a short asymmetric synthesis of cognac lactone **57** has been achieved. The synthesis involved a stereoselective conjugate addition of Me_2CuLi onto γ-butenolide **55a** in ether that afforded (+)-*trans*-cognac lactone **57**, in 78% yield (**Scheme 9**).



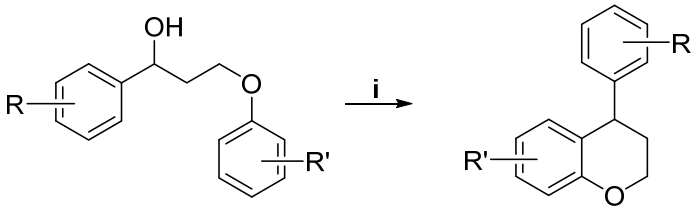
55a **57**

78%, 99% ee

Scheme 9: (i) CuI (1.6 equiv), MeLi (3.3 equiv), ether, -78 to -20 °C.

SECTION II: Synthesis of 4-Substituted Chromanes *via* Au(III)-Catalyzed Intramolecular Friedel-Crafts Reaction of 3-Aryloxy Benzyl Alcohols

The chromane and benzopyran structures are abundant in natural products that possess a broad array of biological activities such as antimicrobial, antiviral, mutagenicity, antiproliferative, sex pheromone, antitumor, and central nervous system activity.[23] Organic transformations catalyzed by Au have been the focus of attention recently.[24] Such processes could provide efficient ways to construct C-C bonds from simple arene substrates. Alkylation of aromatic groups is typically achieved with Friedel-Crafts reactions.[25] This section presents an efficient method for the synthesis of 4-substituted chromanes **59** directly from alcohol **58**. 3-Aryloxy benzyl alcohols **58** when subjected to intramolecular Friedel-Crafts reaction using $AuCl_3$ as catalyst, gave 4-aryl substituted chromanes **59** in 90-98% yields (**Scheme 10**).



58 **59**

R, R' = H, alkyl, halo, alkoxy

yield = 90-98%

Scheme 10 : (i) $AuCl_3$ (1 mol%), CH_2Cl_2 (5 mL) 25 °C, 8 h.

References

1. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science*, **1997**, *277*, 936.
2. (a) Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron*, **2007**, *63*, 2745; (b) Kumar, P.; Gupta, P. *Synlett*, **2009**, 1367; (c) Yu, Q.; Wu, Y.; Xia, L.-J.; Tang, M.-H.; Wu, Y.-L. *Chem. Commun.,*

1999, 129; (d) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. Eur. J*., **2006**, *12*, 1397; (e) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.,* **2004**, *126*, 2495; (f) Kumar, P.; Naidu, S. V. *J. Org. Chem*., **2006**, *71*, 3935.

3. (a) Bandichhor, R.; Nosse, B; Reiser, O. *Top. Curr. Chem.,* **2005**, *243*, 43; (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem. Int. Ed.,* **2009**, *48*, 9426.
4. (a) Ha, H.-J.; Yim, Y.-G. *Synth. Commun.,* **2000**, *30*, 581; (b) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.,* **1980**, *102*, 2118; (c) Bartlett P. A.; Myerson, J. *J. Am. Chem. Soc*., **1978**, *100*, 3950; (d) Yadav, J. S.; Reddy, P. S. R. *Synthesis,* **2007**, 1070; (e) Bartlett, P. A.; Myerson, J. *J. Org. Chem*., 1979, *44*, 1625; (f) Mori, K.; Umemura, T. *Tetrahedron Lett*., 1982, *23*, 3391.
5. (a) Gonzalez, F. B.; Bartlett, P. A. *Org. Synth.,* **1986**, *64*, 175; (*b*) Chamberlin, A. R. ; Dezube, M.; Dussault, P. *Tetrahedron Lett*., **1981**, *22*, 4611.
6. Gunasekara, N. S.; Noble, S.; Benfield, P. *Drugs,* **1988**, *55*, 85.
7. (a) Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem. Eur. J*., **2003**, *9*, 1566; (b) Suzuki, Y.; Mori, W.; Ishizone, H.; Naito, K.; Honda, T. *Tetrahedron Lett.,* **1992**, *33*, 4931; (c) Kong, L.; Zhuang, Z.; Chen, Q.; Deng, H.; Tang, Z.; Jia, X.; Zhai, H. *Tetrahedron: Asymmetry,* **2007**, *18*, 451.
8. Bower, J. F.; Riis-Johannessen, T.; Szeto, P.; Whitehead, A. J.; Gallagher, T. *Chem. Commun.,* **2007**, 728.
9. (a) Ratle, G.; Monseur, X.; Das, B.; Yassi, J.; Khuong-Huu, Q.; Goutrarel, R. *Bull. Soc. Chim. Fr*. **1996**, 2945; (b) Khuong-Huu, Q.; Rutle, G.; Monseur, X.; Goutrarel, R. *Bull. Soc. Chim. Belg*. **1972**, *81*, 425.
10. (a) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, pp 89; (b) Bourinet, P.; Quevauviller, A. *Compt. Rend. Soc. Biol*. **1968**, *162*, 1138; (c) Bourinet, P.; Quevauviller, A. *Ann. Pharm. Fr*. **1968**, *26*, 787.
11. (a) Reddy, R. S.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun*. **2010**, *46*, 5012.
12. (a) Schneider, M. J. Pyridine and Piperidine Alkaloids: An Update. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155; (b) Fodor, G. B.; Colasanti, B. The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology. In *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1985; Vol. 3, p 1; (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.(d) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781; (d) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693; (e) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.
13. Ferreira, F.; Greck, C.; Genet, J. P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 615.
14. McLaughlin, N. P.; Evans, P. *J. Org. Chem.* **2009**, *75*, 518.
15. (a) Welch, W. M.; Harbert, C. A.; Koe, B. K.; Kraska, A. R. European Patent 30081, **1981**; *Chem. Abstr.* **1981**, *95*, 209648; (b) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, *27*, 1508.

16. (a) Carroll. A. R.; Taylor. W. C. *Aust. J. Chem.* **1991**, 44, 1615; (b) Carroll. A. R.; Taylor. W. C. *Aust. J. Chem.* **1991**, 44, 1705.

17. Torssell. K. G. B. *Natural Product Chemistry*, Wiley, Chichester, **1983**; for a review on the synthesis of biaryls, see: Stanforth, S. P. *Tetrahedron*, **1998**, 54, 263.

18. Thomson. R. H., *The Chemistry of Natural Products*, Blackie and Son., Glasgow, **1985**.

19. (a) Zhang, Y.; Wang, Y.; Dai, W.-M. *J. Org. Chem*., **2006**, 71, 2445; (b) Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc*., **1997**, 119, 1482.

20. (a) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem*. **2005**, *243*, 43; (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem*., *Int. Ed*. **2009**, *48*, 9426.

21. (a) Kunesch, G.; Zagatti, P.; Lallemand, J. Y.; Debal, A.; Vigneron, J. P. *Tetrahedron Lett*. **1981**, *22*, 5271–5274; (b) Vigneron, J. P.; Meric, R.; Larcheveque, M.; Debal, A.; Lallemand, J. Y.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521.

22. (a) Rao, Y. S. *Chem. Rev*. **1976**, *76*, 625; (b) Rao, Y. S. *Chem. Rev*. **1964**, *64*, 353.

23. (a) Ellis, G. P.; Lockhart, I. M. *The Chemistry of Heterocyclic Compounds, Chromenes, Chromanones, and Chromones*; Ellis,G. P., Ed.;Wiley-VCH: New York, **2007**; Vol. *31*, pp 1. (b) Horton, D. A.; Bourne, G. T.; Smythe,M. L. *Chem. Rev*. **2003**, *103*, 893; (c) Kumar, S.; Malachowski, W. P.; DuHadaway, J. B.; LaLonde, J. M.; Carroll, P. J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem*. **2008**, *51*, 1706.

24. (a) Hashmi, A. S. K. *Gold Bull*. **2004**, *37*, 51; (b) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem*. **2004**, *8*, 795; (b) Hashmi, A. S. K. *Chem. Rev*. **2007**, *107*, 3180.

25. (a) Olah, G. A. *Friedel-Crafts and Related Reactions*; Wiley: New York, **1973**; (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

Chapter I

Synthesis of Optically Pure γ-Butyrolactones and Epoxy Esters via Two-Stereocentered HKR of 3-Substituted Epoxy Esters: A Formal Synthesis of (-)-Paroxetine and (+)-Eldanolide

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1. "Optically pure γ-butyrolactones and epoxy esters *via* two stereocentered HKR of 3-substituted epoxy este" **Devalankar, D. A.;** Kalabhor, P. U.; Sudalai, A. *Org. Biomol. Chem.*, **2013**, *11*, 1280.

Section I

Synthesis of Optically Pure γ-Butyrolactones and Epoxy Esters *via* Two-Stereocentered HKR of 3-Substitued Epoxy Esters

1.1.1 Introduction

The γ-butyrolactone skeleton represents an important core structure in many biologically active natural products.[1] In particular, certain functionalized chiral γ-butyrolactones are sex attractant pheromones[2] and some utilized as flavoring components.[3] The enantiomerically pure epoxy esters are also valuable 'building blocks' for the asymmetric synthesis of bioactive natural products.[4] Due to their interesting biological activity in medicinal chemistry, an efficient catalytic method for the synthesis of substituted γ-butyrolactones and epoxy esters from commercially available materials is of current interest.[5]

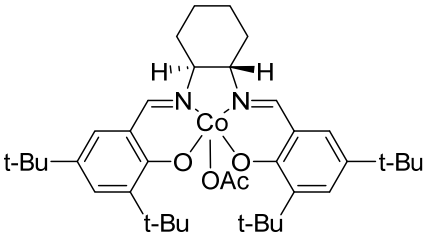
Jacobsen's Hydrolytic Kinetic Resolution (HKR) that uses readily accessible Co(III)-based chiral salen complexes as catalyst and water as the only reagent to afford chiral epoxides and diols of high ee in excellent yields, has been comprehensively studied in recent years to reveal its mechanistic and synthetic aspects.[6] In the present section, we have described a flexible, novel single-step method that employs Co-catalyzed HKR of racemic 3-substituted (aryl or alkyl) epoxy esters with two stereocentres to produce substituted γ-butyrolactones and epoxy esters in high optical purities.

1.1.2 Hydrolytic kinetic resolution (HKR)

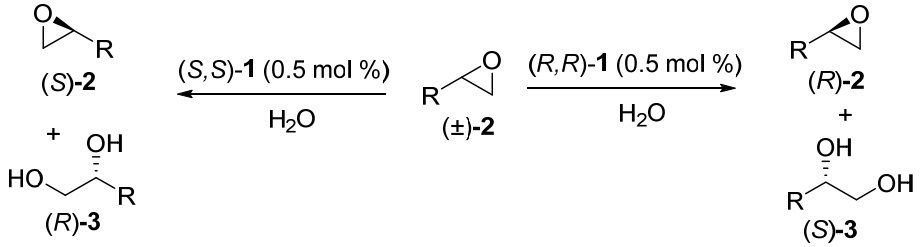
The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[7] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents,

oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[8] Thus epoxides are versatile building blocks for organic synthesis. However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomerically pure form. Terminal epoxides are available very inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, given an economical and operationally simple method. Readily accessible synthetic catalysts (chiral cobalt-salen complexes)[9] have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent, no added solvent, and low loadings of a recyclable catalyst (0.5 mol%), and it affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric enrichment. One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions. This is an important consideration in the present case, since low-molecular weight terminal epoxides are typically liquids at room temperature and are not readily derivatized as salts, and therefore it is not a straightforward matter to upgrade their enantiomeric composition by crystallization. However, in the absence of straightforward substrate racemization protocols, kinetic resolutions have the significant disadvantage of a 50% maximum yield of substrate recovery. With a specific interest in devising a practical method for obtaining highly enantioenriched terminal epoxides, the following criteria must be met in order for a kinetic resolution approach to be viable.[10] (1) The racemic epoxides must be inexpensive or easily accessible from inexpensive commercial starting materials. (2) The catalyst for the resolution must be readily available in both

enantiomeric forms. In the optimal case, the catalyst would be used in small quantities in the resolution and would be recyclable. (3) The nucleophile used for the ring opening should be inexpensive and easily handled. (4) The resolved epoxides must be obtained in good yield and very high enantiopurity and must be easily separated from the ring-opened products. (5) Ideally, although not necessarily, the ring-opened byproducts should also be valuable chiral building blocks and be obtainable in high enantiomeric excess.



1, (*S*,*S*)-(salen)Co(III)(OAc) complex



Scheme 1: Hydrolytic kinetic resolution (HKR) of racemic epoxide

The (salen)Co complex **1** catalyzes the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 1**).[11] This new method appears to hold considerable promise with regard to meeting all of the criteria outlined above. First, racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive

than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[12]

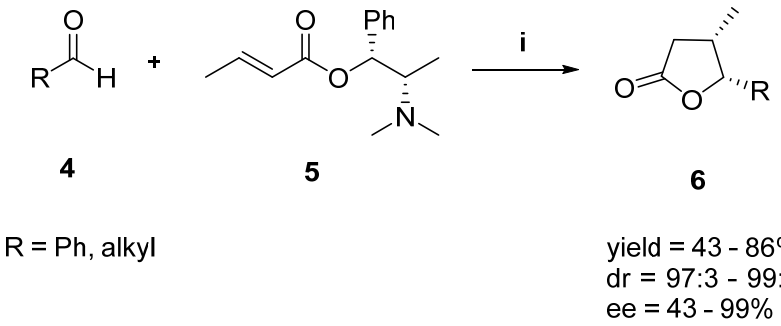
The cobalt analogues (*R*,*R*)-**1** and (*S*,*S*)-**1** proved equally accessible, and these are also now available in bulk. Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture. Fourth, for those examples that were described in the preliminary report, highly enantioenriched epoxides were recovered from the HKR. Finally, the HKR provides useful enantioenriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[13] Two useful methods for the generation of complex **1.**OAc have been developed. Method A involves isolation of **1.**OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate ~ 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed *in vacuo*, affording **1.**OAc as a brown solid residue that can be used without further purification. Method B involves *in situ* generation of **1.**OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere.

1.1.3. Review of Literature

Various syntheses of enantiomerically pure *syn*- or *anti*- 3,4-disubstituted γ-butyrolactones and epoxy esters have been documented in the literature. Some of the interesting and important synthetic routes are described below.

Fukuzawa's approach (1997)[14]

Fukuzawa, *et al.* have reported samarium(II) iodide-mediated asymmetric synthesis of *cis*-3,4-disubstituted-*γ*-butyrolactones **6** by reductive coupling of aldehydes **4** with crotonates **5** possessing *N*-methylephedrine as chiral auxiliary. The *cis* isomer of the 3,4-disubstituted-γ-butyrolactone **6** was produced predominantly (97:3 to 99:1) with enantioselectivity 43 to 99% ee and chemical yield up to 86%. The mechanism of the reaction includes the ketyl radical and alkene coupling reaction where chelation control by samarium atom would play an important role in the asymmetric induction and diastereoselectivity (**Scheme 2**).

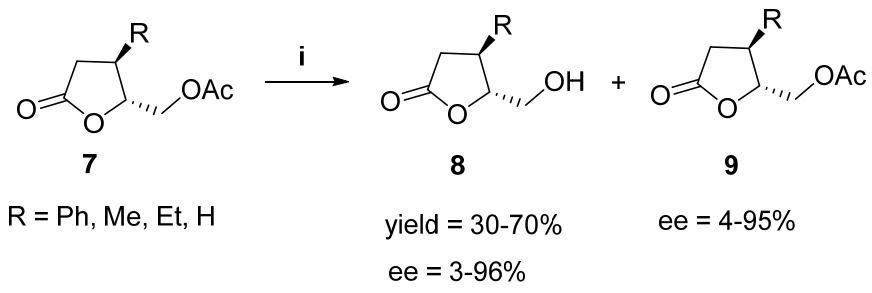


4 **5** **6**

Scheme 2: (i) SmI_2, *t*-BuOH, THF, -78 to 0 ^oC, 5-6 h.

Hyun-Joon Ha's approach (1998)[15]

Hyun-Joon Ha *et al.* have described a new method of synthesis of chiral *γ*-butyrolactones by resolution of the *β*-substituted *γ*-((acetyloxy)methyl)-*γ*-butyrolactones **7** by using lipase PS (LPS). A mixed solvent system made up of buffer



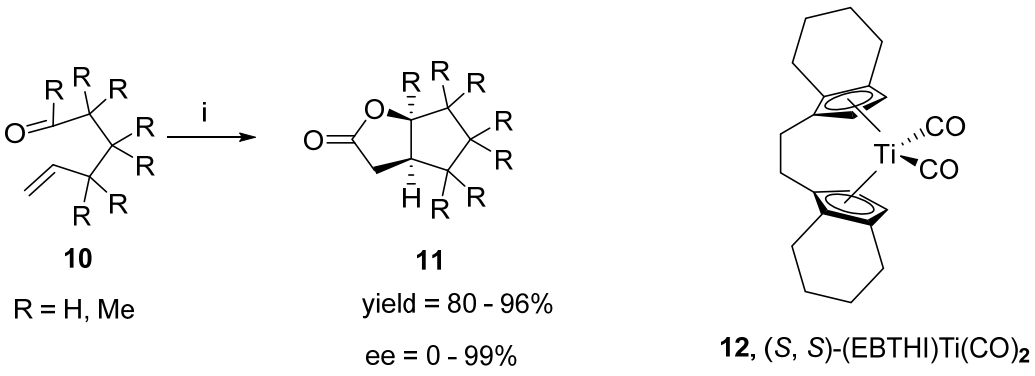
7 **8** **9**

Scheme 3: (i) Lipase PS (3.0 mass equiv), pH 7.2, acetone, 35 ^oC,. 0.5 to 58 h.

and acetone (97:3) was used as the reaction medium. Under this reaction medium, resolution of *trans*- and *cis*-*β*- substituted-*γ*-((acetyloxy)methyl)-*γ*-butyrolactones **7** was achieved up to 70% conversion to give lactone **8** along with unreacted ester **9** (**Scheme 3**).

Crowe's approach (2001)[16]

Crowe *et al*. have reported a new route for the synthesis of *γ*-butyrolactones by intramolecular Hetero-Pauson-Khand cyclization. In this method, intramolecular cyclocarbonylation between enals and enones of substrate **10** was achived using a chiral titanocene catalyst **12** in toluene at 100 °C, which gave fused γ-butyrolactones **11** with yield up to 96% **(Scheme 4)**.



10

R = H, Me

11

yield = 80 - 96%

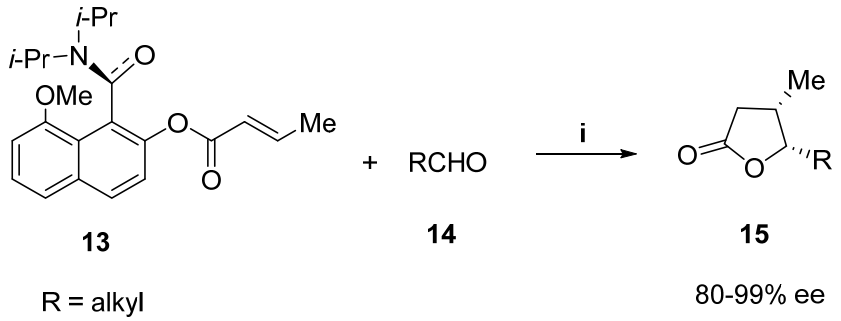
ee = 0 - 99%

12, (*S*, *S*)-(EBTHI)Ti(CO)$_2$

Scheme 4: (i) **12** (10-20 mol%), PMe_3 (30 - 80 mol%), CO (50 psi), toluene, 36-40 h, 100 ^oC.

Dai's approach (2005)[17]

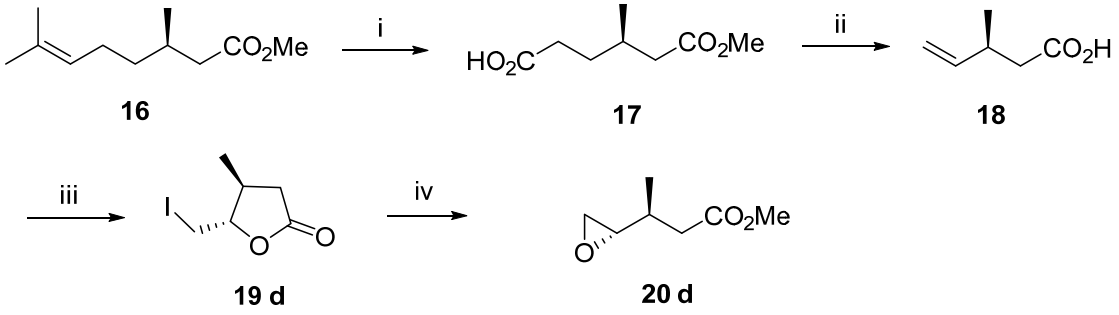
Dai *et al*. have reported reductive coupling of aldehydes **14** with chiral crotonates possessing 2- hydroxy-8 methoxy-1-naphthamide **13** as chiral auxiliary that afforded the *cis*-*γ*- butyrolactones **15** in 90% yield and up to 99% ee with a *cis*/*trans* ratio of 90:10 (**Scheme 5**).



Scheme 5: (i) SmI_2 (3 equiv), *t*-BuOH (1.3 equiv), THF, -20 to -15 ^oC, 6 h, 58 -90%.

Umemura's approach (1982)[4f]

Umemura *et al.* have synthesized *anti* 3-substituted epoxy esters **20d** by using chiral pool staring material namely methyl (*R*)-(+)-citronellate **16**. Ozonolysis of **16**, followed by its oxidative work up gave half ester **17**. Compound **17** was oxidatively



Scheme 6: (i) (a) O_3, CH_2Cl_2, -78 ^oC, 1h, 80%; (b) CrO_3, aq. H_2SO_4, acetone, 1 h, 25 ^oC, 90 %; (ii) (a) $Pb(OAc)_4$, $Cu(OAc)_2$, benzene, refluxed, 6 h, 85%; (b) aq. 10% KOH, H_2O, refluxed, 2 h, 82%; (iii) I_2, CH_3CN, 0 ^oC, 24 h, 80%; (iv) K_2CO_3, MeOH, reflux, 1 h, 93%.

decarboxylated and the resulting ester was hydrolyzed to give olefinic acid **18**. Thermodynamic iodolactonization of **18** yielded iodolactone product **19d**. Finally, iodolactone **19d** was converted into epoxy ester **20d** by methanolysis reaction with an overall yield of 37% (**Scheme 6**).

1.1.4 Present Work

1.1.4.1 Objective

As can be seen from the above discussion, the literature methods for the synthesis of enantiomerically pure 3,4-disubstituted γ-butyrolactones (**8** & **25**) and 3-substituted epoxy esters (**20** & **24**) suffer from certain limitations such as use of expensive catalysts, chiral pool resources, multiple steps or products obtained in low optical purity. Despite enormous applications, HKR has only been applied to the resolution of simple terminal epoxides with one stereocentre.[18] To the best our knowledge, study related to HKR of functionalized epoxides with two stereocentres is rather rare.[19]

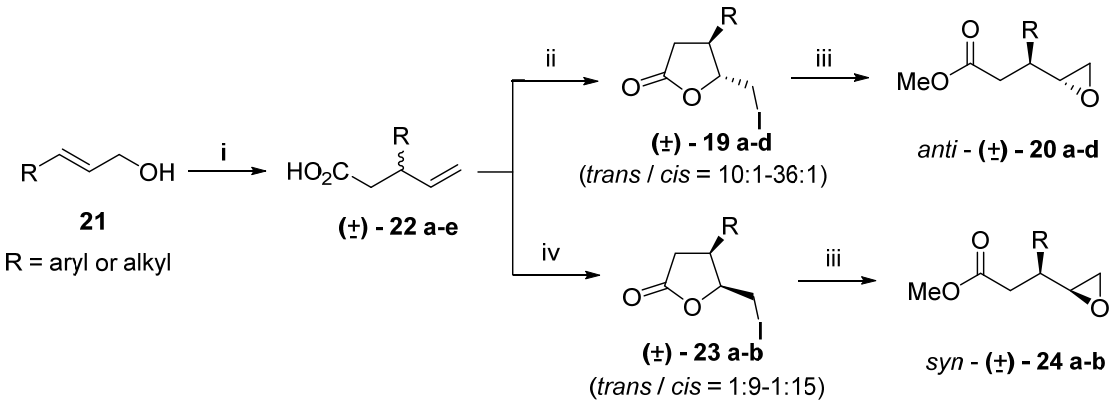
1.1.4.2 Results and Discussion

In the present work, we have extended the scope of the applicable substrates for HKR to cover multi-functionalized molecules with two stereocentres. The aim of such an investigation is to access enantiomerically enriched 3,4-disubstituted γ-butyrolactones (**8** & **25**) and 3-substituted epoxy esters (**20** & **24**) by a direct and simple method from the respective racemic materials; thus complementing the other tedious routes. Due to its importance as 'building-blocks' for the synthesis of highly functionalized molecules, racemic 3-substituted epoxy esters **(±)-20** & **(±)-24** were chosen for the study and subjected to HKR with chiral Co-catalysts. In this section, we have described a flexible, novel method that employs HKR of racemic 3-substituted epoxy esters **(±)-20** & **(±)-24** to generate 3,4-disubstituted γ-butyrolactones (**8** & **25**) and 3-substituted epoxy ester (**20** & **24**) with two stereocentres of high optical purities in a single step has been described (**Table 1**).

Preparation of racemic *anti*- and *syn*-3-substituted epoxy esters

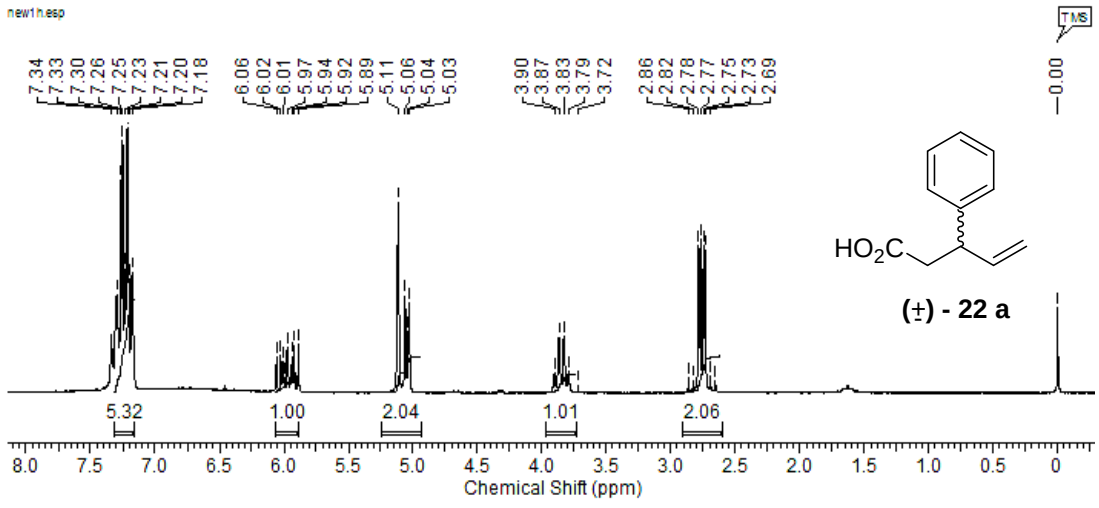
The racemic *anti*- and *syn*-3-substituted epoxy esters (**20** & **24**), the substrates for HKR, were efficiently prepared[20] in a highly diastereoselective manner from the

corresponding allylic alcohols **21.** Thus, allylic alcohols **21a-e** were subjected to Johnson-Claisen rearrangement in presence of $MeC(OEt)_3$, hexanoic acid (catalytic) to give acyclic olefinic acids **22** in 78-92% yields (**Scheme 7**).



Scheme 7: (i) $MeC(OEt)_3$, hexanoic acid, 80-150 ^oC, 3 h, 78-92%; (ii) I_2, CH_3CN, 0 ^oC, 24 h, 80-89%; (iii) MeOH, Na_2CO_3, reflux, 3 h, 88-95%; (iv) I_2, $NaHCO_3$, $CHCl_3$, 0 ^oC, 6 h, 71-80%.

The formation of olefinic acids, (±)-**22a-e** was confirmed by ^1H and ^{13}C-NMR spectroscopy. For example, the ^1H-NMR spectrum of (±)-**22a** showed typical signals at δ 5.03-5.11 (m, 2H) and δ 5.89-6.06 (m, 1H) due to olefinic protons and at δ 3.83 (q, 1H) due to benzylic protons. Its ^{13}C-NMR spectrum showed a typical carbon signal at δ 178.3 due to carbonyl carbon group **(Fig. 1).**



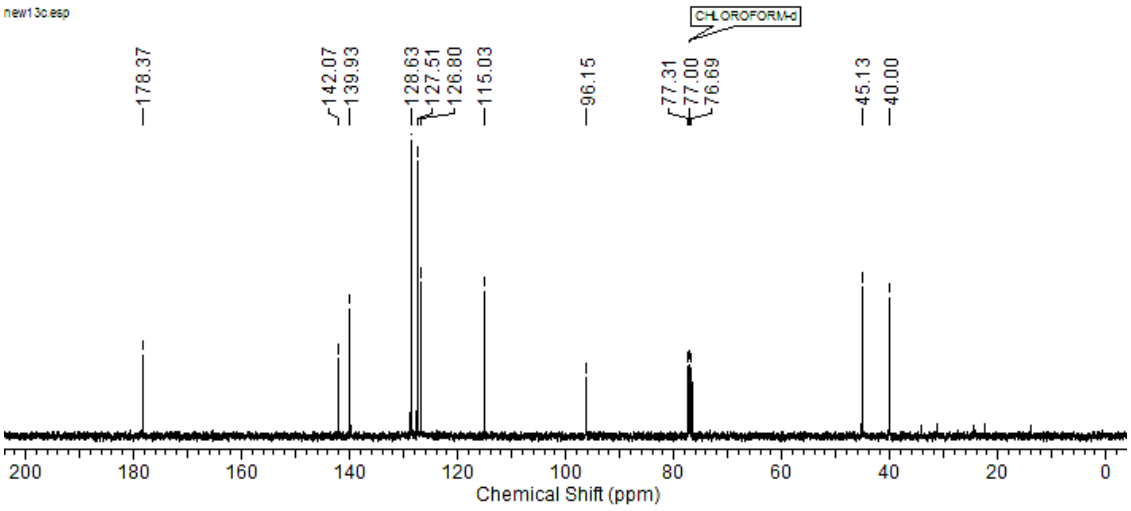
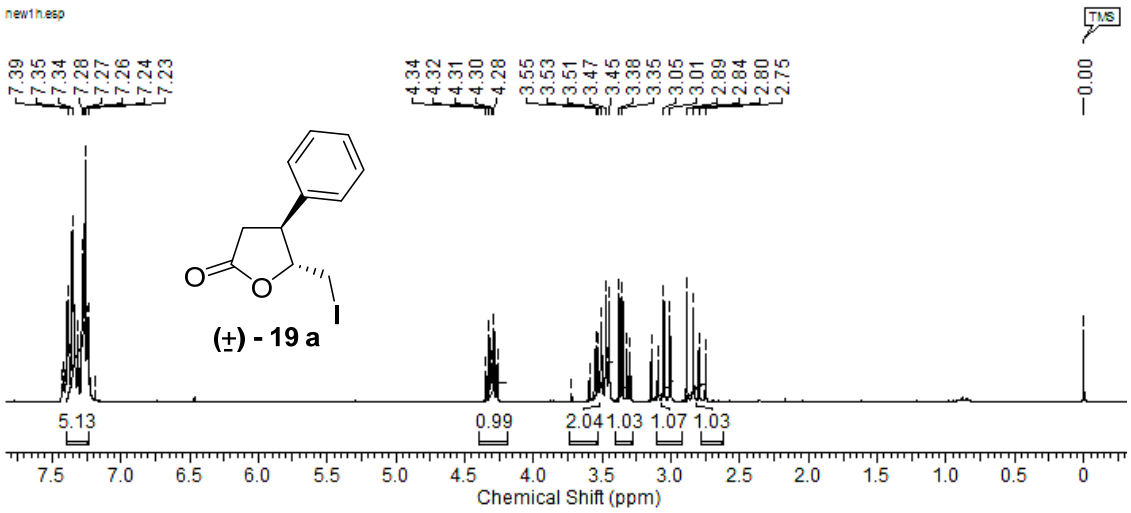


Fig. 1: ^{1}H and ^{13}C NMR spectra of **(±)-22a**

Acyclic olefinic acids **22** were then subjected to diastereoselective iodolactonization (for *trans*: I_2, CH_3CN, 0 ^{o}C, 24 h; for *cis*: I_2, $NaHCO_3$, $CHCl_3$, 0 ^{o}C, 6 h) to give *trans* or *cis*-iodolactones (**19** or **23**) in 71-89% yields.

The formation of *trans*-iodolactone **(±)-19** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. For example, compound (±)-**19a** showed two doublets of doublet at δ 2. 80 (dd, J = 9.6, 17.9 Hz, 1H) and δ 3.05 (dd, J = 9.0, 17.8 Hz, 1H) for the protons attached to α-carbon atom. Its ^{13}C-NMR spectrum showed a typical carbon signal at δ 6.3 due to carbon attached to iodo group and a characteristic signal at δ 174.0 for carbonyl carbon group **(Fig. 2)**.



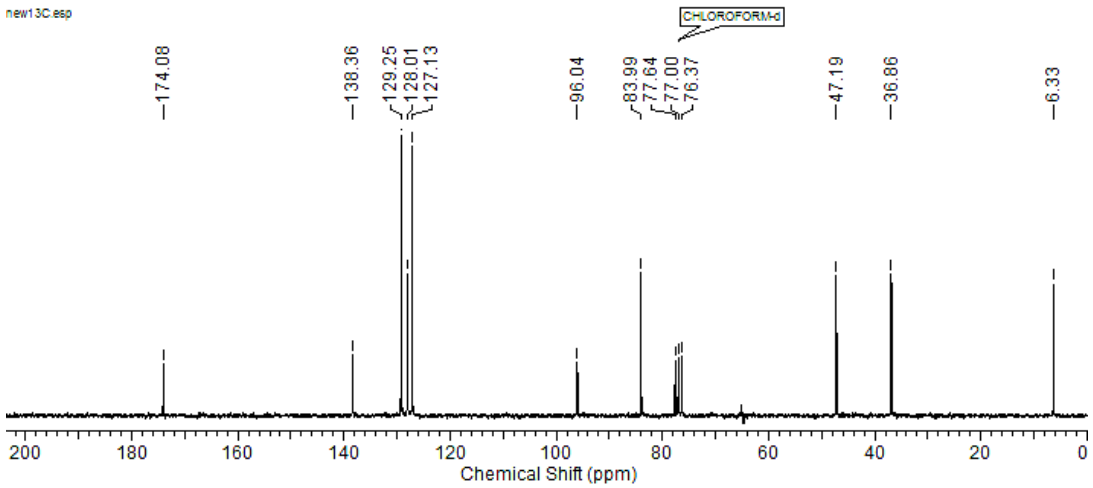
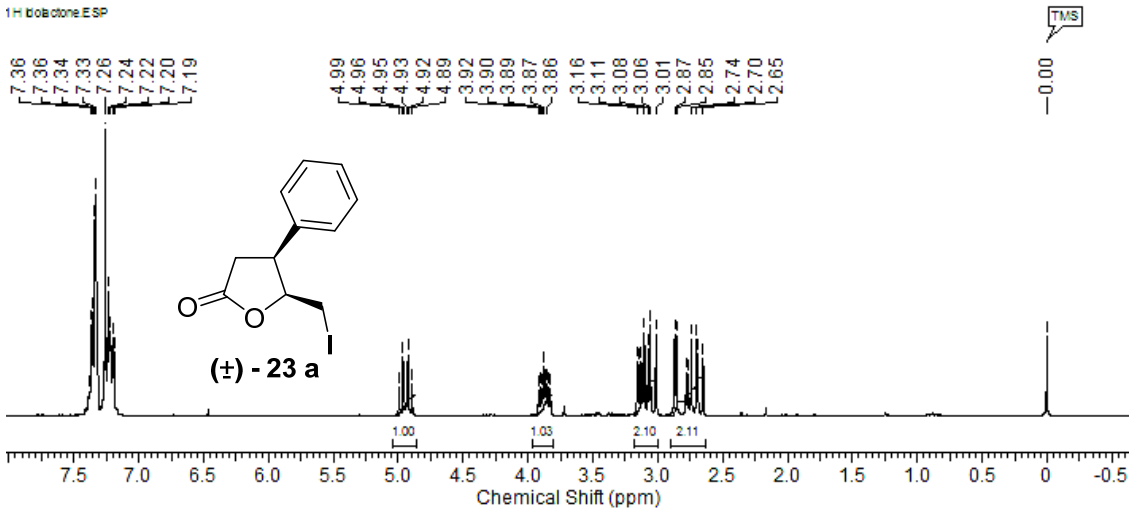


Fig. 2: ^{1}H and ^{13}C NMR spectra of **(±)-19a**

Similarly, the formation of *cis*-iodolactone **(±)-23** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy **(Fig. 3)**. The ^{1}H-NMR spectrum of *syn*-iodolactone **(±)-23a** showed



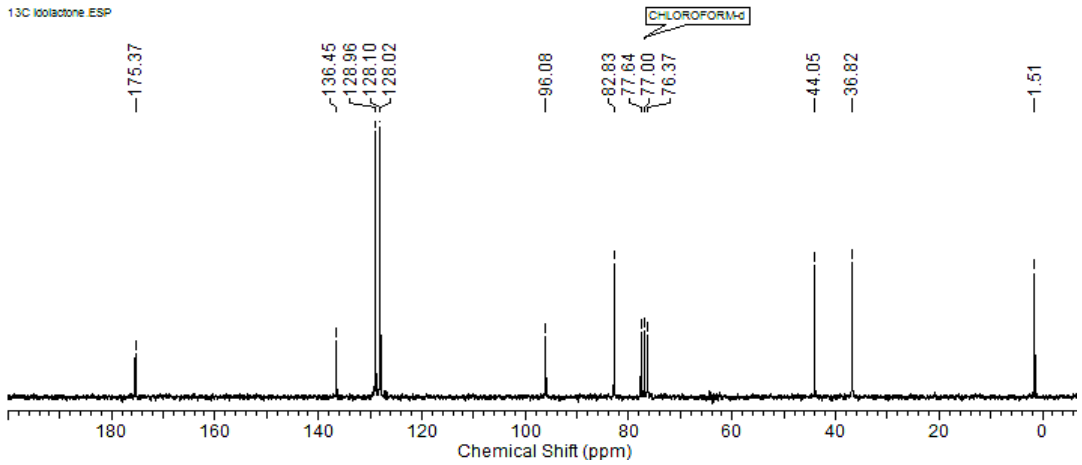


Fig. 3: ^{1}H and ^{13}C NMR spectra of **(±)-23 a**

typical signal at δ 3.89 (m, 1H) for methine protons at benzylic position and multiplet δ 4.95 (1H) for methine protons attached to adjacent oxygen atom. Its ^{13}C-NMR showed characteristic signals at δ 1.5 due to carbon attached to iodo group and δ 175.3 for carbonyl carbon group **(Fig. 3)**.

Methanolysis of iodolactones **(±)-19** or **(±)-23** under basic conditions produced the required racemic *anti*- or *syn*- 3- substituted epoxy esters **(±)-20** or **(±)-24 (Scheme 7)**. For example, the ^{1}H-NMR spectrum of *anti*-3-substituted epoxy ester **(±)-20a** showed a typical signal at δ 3.60 (s, 3H) corresponding to methoxy protons. Its ^{13}C-NMR spectrum showed characteristic signals at δ 46.9 and δ 55.2 due to carbons of the epoxide moiety and δ 171.8 for carbonyl carbon group **(Fig. 4)**.

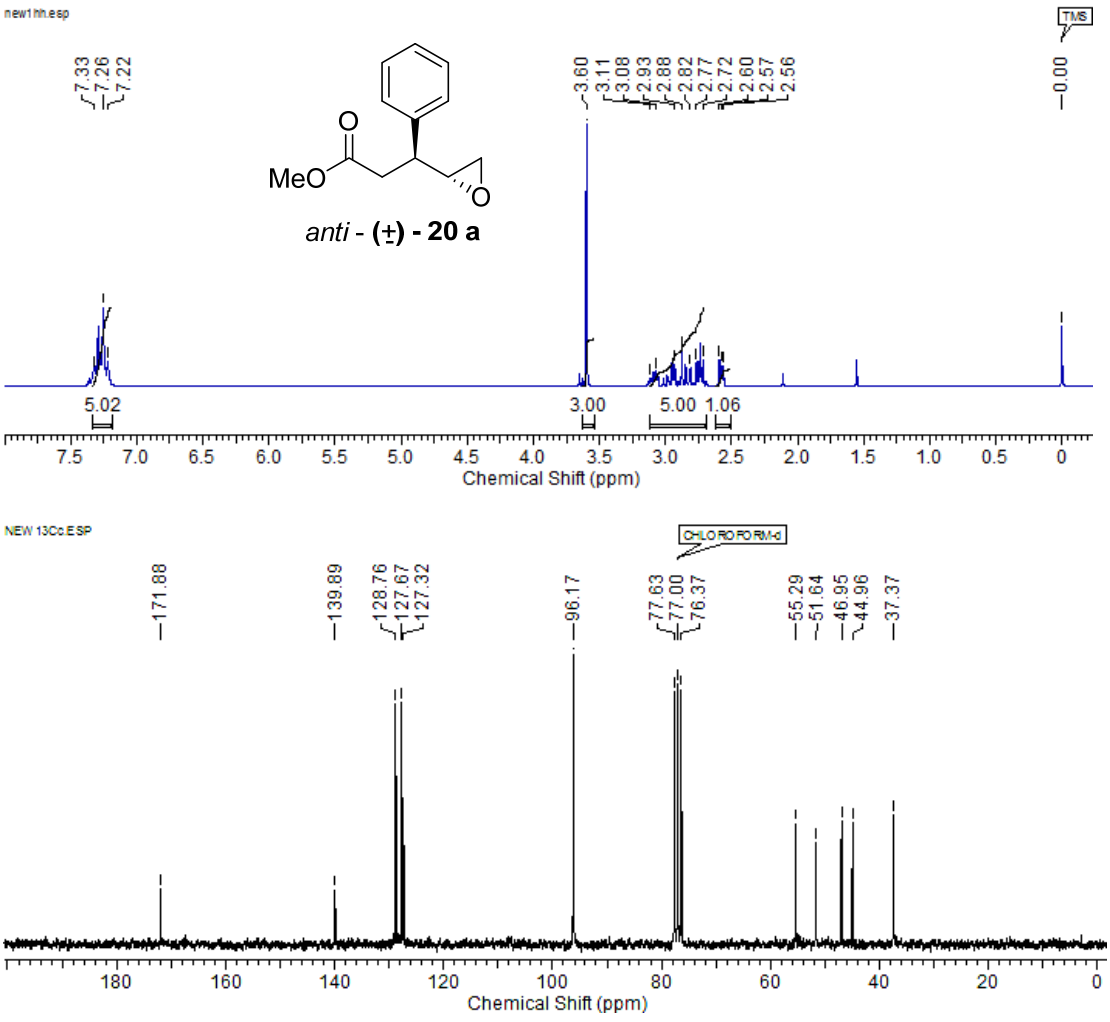


Fig. 4: ^{1}H and ^{13}C NMR spectra of **(±)-20 a**

Similarly, the formation of *syn*-3- substituted epoxy esters **(±)-24** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. The ^{1}H-NMR spectrum of **(±)-24a** showed a typical signal at δ 3.63 (s, 3H) for methoxy protons. Its ^{13}C-NMR showed characteristic signals at δ 45.67 and δ 54.43 due to carbons of the epoxide ring and δ 171.80 for carbonyl carbon group **(Fig. 5)**.

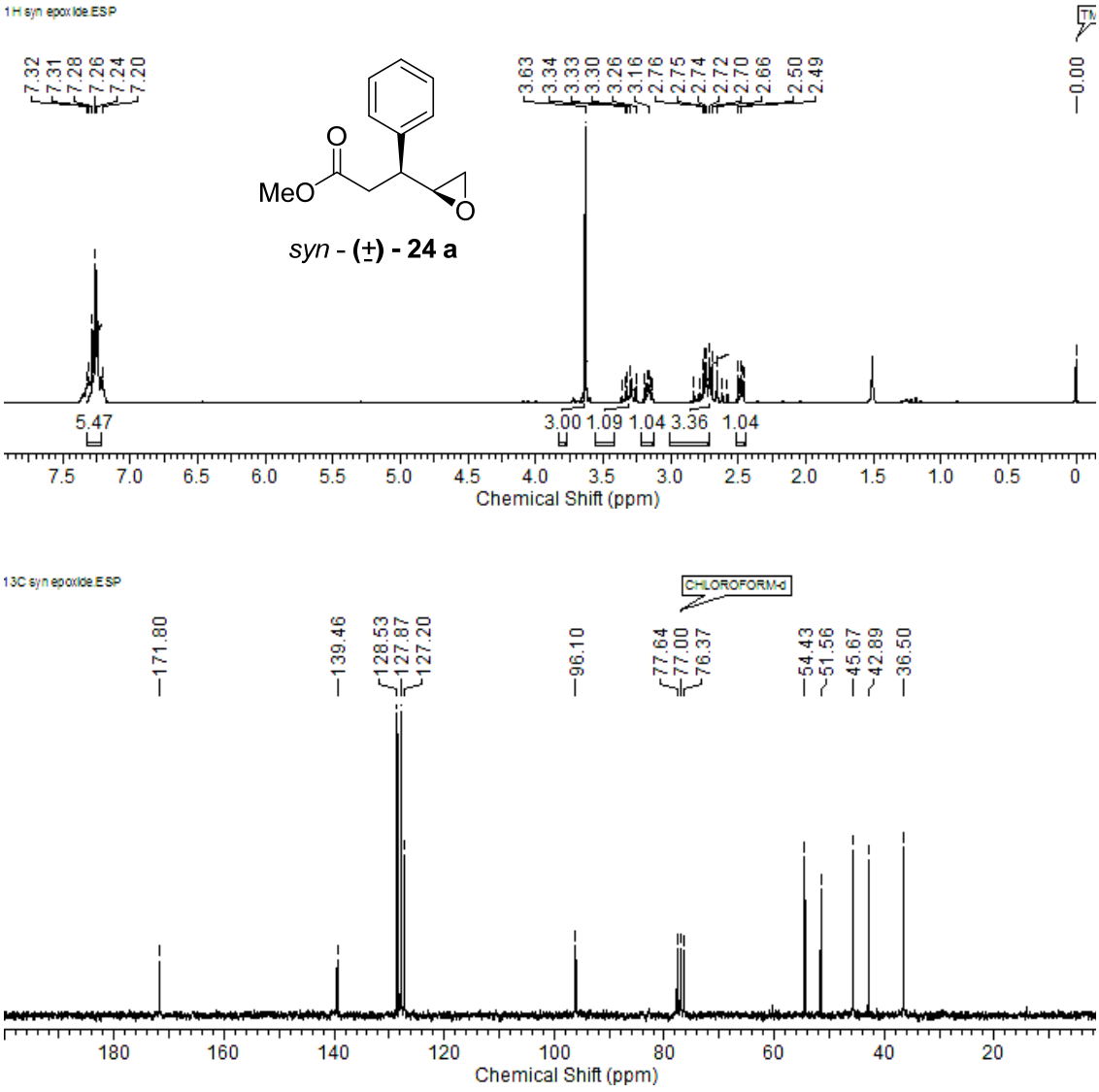


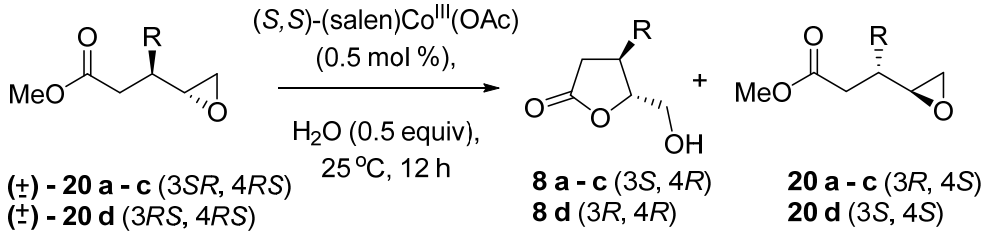
Fig. 5: ^{1}H and ^{13}C NMR spectra of **(±)-24 a**

HKR of racemic azido epoxides

Initially, when HKR of racemic *anti*- 3-substituted epoxy ester **20a** was carried out with (*S, S*)-(salen)Co(OAc) complex **1** (0.5 mol %) and H_2O (0.5 equiv), the

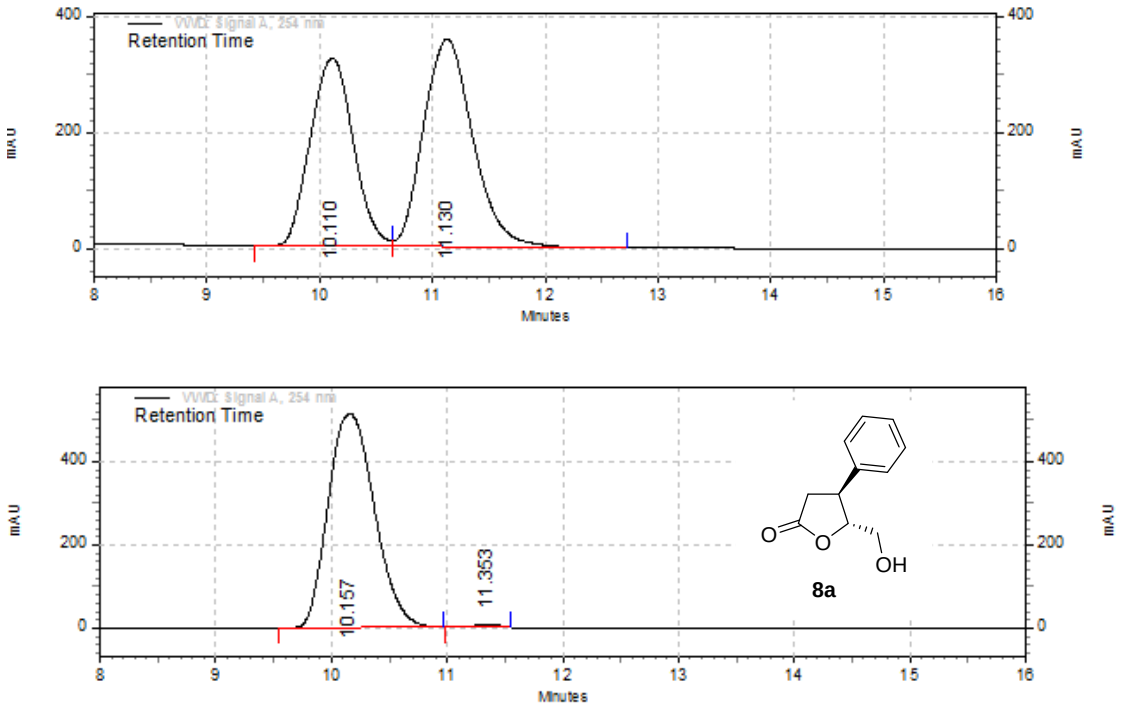
corresponding *trans*-3,4-disubstituted γ-butyrolactone **8a** (45%) and 3-substituted epoxy ester **20a** (48%) were isolated in high yields and optical purity [**8a** (99% ee) and **20a** (97% ee)]. The formation of γ-butyrolactone **8a** can be explained on the basis of intramolecular cyclization of the chiral diol formed *in situ* with ester carbonyl functionality. Encouraged by this result, we have examined its scope by subjecting several racemic *anti*-3-substituted epoxy esters **20a-d** to HKR, which proceeded smoothly, with complete regiocontrol, to give the respective enantioenriched *trans*-3,4-disubstituted γ-butyrolactones **8a-d** and *anti*- epoxy esters **20a-d** in excellent ees (96 to 99% ee) and high yields (45 to 49%). The enantiomeric excess of *trans*-3,4-disubstituted γ-butyrolactone **8a-d** and *anti*- epoxy esters **20a-d** were determined from chiral HPLC analysis **(Fig. 6)**. The results of such a study are shown in Table 1. The reaction thus exhibited good generality with respect to the degree of functionalization of epoxides.

Table 1. Co-catalyzed HKR of racemic 3-substituted *anti*-epoxy esters



entry	substrates (R)	lactones **8** (**a - d**)		epoxides **20** (**a - d**)	
	(±) - **20** (**a - d**)	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
a	phenyl	45	99	48	97
b	4-fluorophenyl	46	99	49	99
c	4-methoxyphenyl	48	97	47	96
d	methyl	46	97	48	96

[a] Isolated yield after column chromatographic purification; [b] ee determined by chiral HPLC.



Retention Time	Area	Area %	Height	Height %
10.157	239861276	99.56	8617320	99.39
11.353	1070458	0.44	52774	0.61
Totals	240931734	100.00	8670094	100.00

Column :Chiracel OD-H (4.6X250 nm), Mobile Phase :IPA:n-Hexane (50:50) Wavelength :254 nm, Flow rate :0.5ml/min

Fig. 6: HPLC chromatogram of **8a**

The formation of *trans*-3,4-disubstituted γ-butyrolactone **8a** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. For example, the ^{1}H NMR spectrum of **8a** exhibited characteristic doublet of doublets at δ 2.80 (dd, J = 9.9, 17.8 Hz, 1H) and δ 3.09 (dd, J = 9.1, 17.8 Hz, 1H) due to the protons attached to α-carbon atom. Its ^{13}C-NMR spectrum also showed typical carbon signals at δ 61.73 due to carbon attached to hydroxyl group and δ 176.30 for carbonyl carbon group **(Fig.7)**.

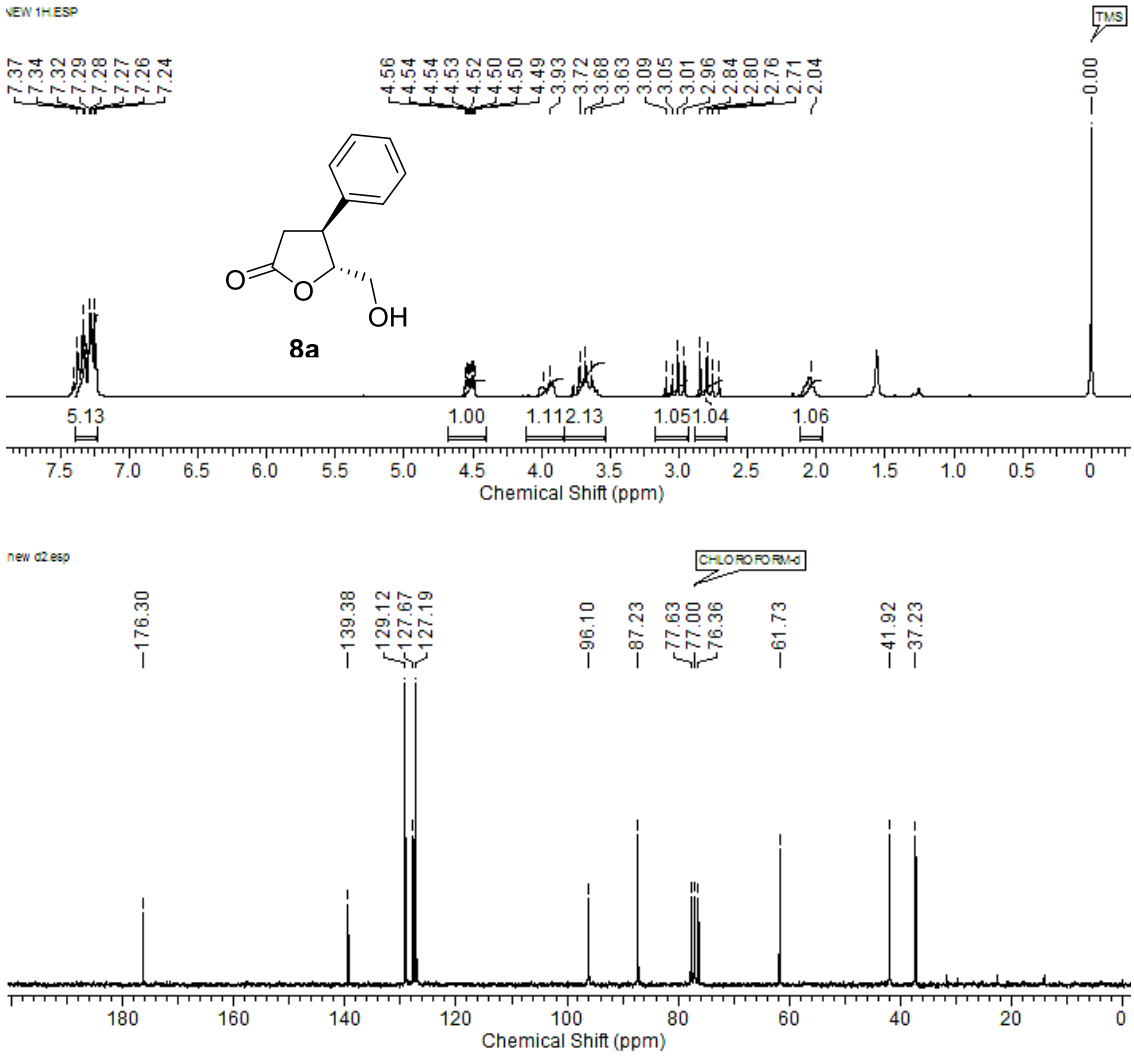


Fig. 7: ^{1}H and ^{13}C NMR spectra of **8a**

Lactone functionality in **8a** was further confirmed from its IR spectrum, which showed a characteristic strong absorption band at υ_{max} 1778 cm^{-1}. The *trans*-stereochemistry of γ-butyrolactone **8a** was further confirmed by single crystal X-ray crystallographic study **(Fig. 8)**.

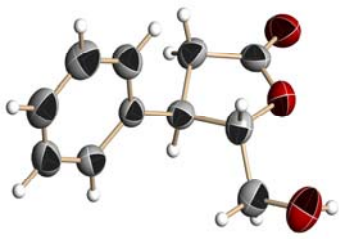
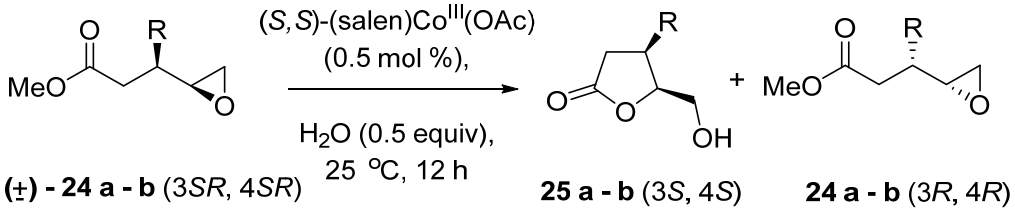


Fig. 8: ORTEP diagram for **8a**

Similarly, when *syn*- 3-substituted epoxy esters **24a-b** were subjected to HKR under identical reaction conditions, the corresponding chiral *cis*-3,4-disubstituted γ-butyrolactones **25a-b** and *syn*-epoxy esters **24a-b** were obtained in high yields and ees upto 99%. The enantiomeric excess of *cis*-3,4-disubstituted γ-butyrolactones **25a-b** was determined from chiral HPLC analysis. The results of this study are presented in Table 2.

Table 2. Co-catalyzed HKR of racemic 3-substituted *syn*-epoxy esters



(±) - 24 a - b (3*SR*, 4*SR*) **25 a - b** (3*S*, 4*S*) **24 a - b** (3*R*, 4*R*)

entry	substrates (R)	lactones **25** (**a - b**)		epoxides **24** (**a - b**)	
	(±) - **24** (**a - b**)	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
A	phenyl	47	98	48	97
D	4-bromophenyl	46	98	48	97

[a] Isolated yield after column chromatographic purification; [b] ee determined by chiral HPLC chromatogram.

The formation of *cis*-3,4-disubstituted γ-butyrolactone **25a-b** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. For example the ^{1}H NMR spectrum of *anti*-azido diol **25a** showed a typical signal at δ 3.90 (q , J = 8.2 Hz, 1H) for methine protons at benzylic position and δ 4.79 (m, 1H) for methine protons adjacent to oxygen atom. Its ^{13}C- NMR showed characteristic signals at δ 62.10 and 176.72 due to carbon attached to hydroxy group and carbonyl carbon group respectively **(Fig. 9)**. The absolute configuration of both 3,4-disubstituted γ-butyrolactones (**8** & **25**) and 3-substituted epoxy esters (**20** & **24**) was further ascertained by comparing their optical rotations

with those reported in the literature.[4d, 15]

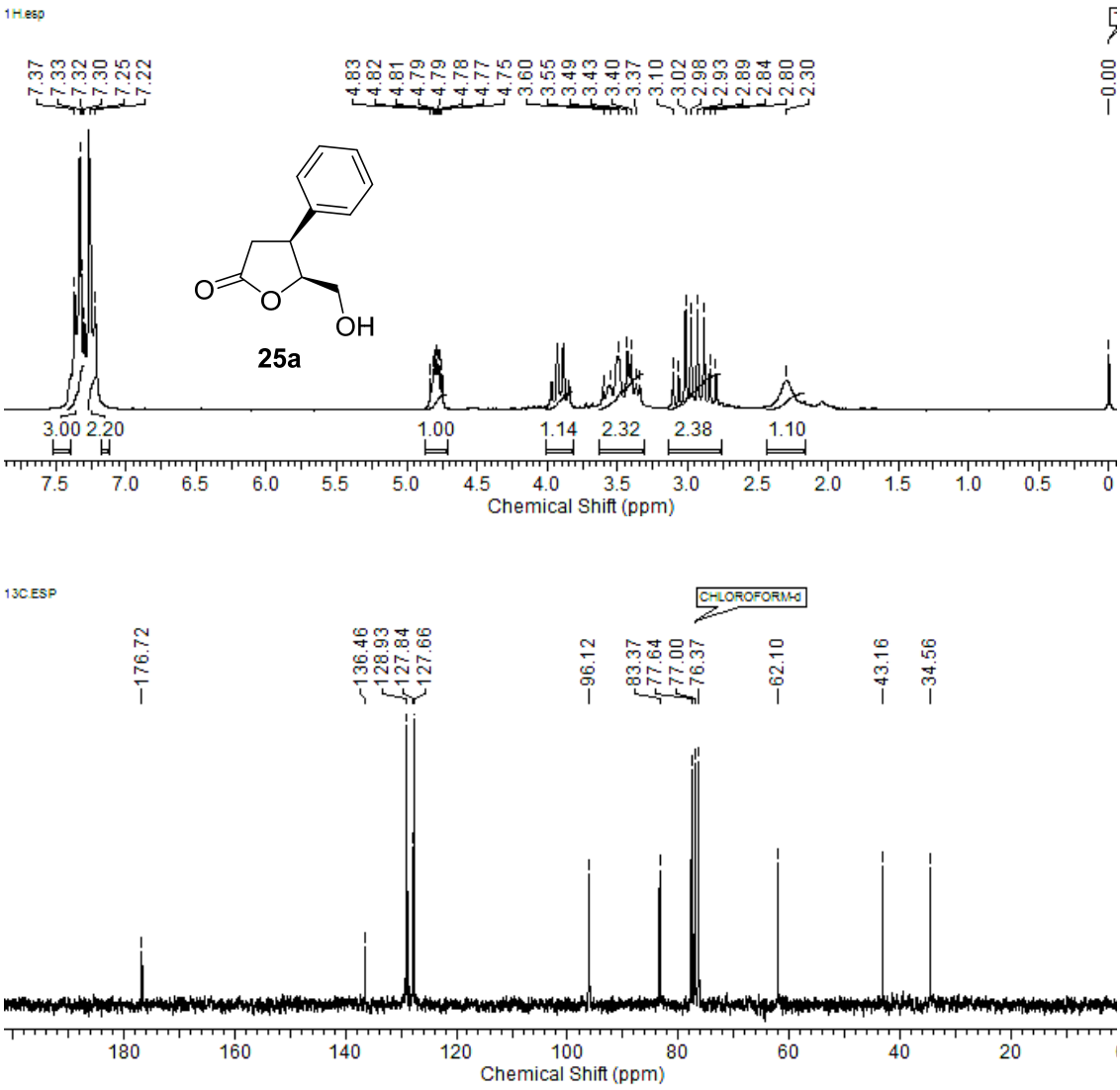


Fig. 9: ^{1}H and ^{13}C NMR spectra of **25a**

1.1.5 Conclusion

In conclusion, the (salen)Co(III)-catalyzed HKR of racemic *anti*- or *syn*- 3-substituted epoxy esters provides a highly practical route to the synthesis of substituted enantioenriched γ-butyrolactones **8a-d/ 25a-b** and 3-substituted epoxy esters **20a-d/ 24a-b** in a single step. The reaction is convenient to carry out under mild conditions. We believe that this HKR strategy will find applications in the field of asymmetric

synthesis of bioactive molecules owing to the flexible nature of synthesis of racemic 3-substituted epoxy ester and the commercial availability of Co-salen catalysts in both enantiomeric forms.

1.1.6 Experimental section

General procedure for the synthesis of acyclic olefinic acid (22a-e)

A mixture of allylic alcohol **21** (37.31 mmol), triethyl orthoacetate (37.31 mmol) and hexanoic acid (0.23 mL, 1.85 mmol) was placed in a round-bottomed flask equipped with thermometer, Claisen head and condenser. The solution was heated with distillation of ethanol (upto 70-150 ^{o}C). After 3 h distillation of ethanol slows and another 0.1-mL portion of hexanoic acid was added. Additional portions (0.1 mL) of hexanoic acid were added again after at 3 and 4 h followed by continued heating for the next 6 h. After which it was allowed to cool and aq. solution of KOH (2.9 g, 52.2 mmol, 20 ml) in MeOH (60 mL) was added. The resulting mixture was refluxed for 4 h and then allowed to cool to room temperature. After that the resulting solution washed with diethyl ether and acidified with dil HCl. The acidic solution was extracted with diethyl ether and the organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **22.** The crude material was used as such for the next reaction without any further purification.

3-Phenylpent-4-enoic acid (22a)

Yield: 90%, colorless solid, **mp** 48 ^{o}C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 732, 1026, 1638, 1708, 3028; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.69 (dd, *J* = 7.5, 15.7 Hz, 1H), 2.82 (dd, *J* = 7.9, 15.7 Hz, 1H), 3.83 (q, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 5.5 Hz, 1H), 5.11 (s, 1H), 5.89-6.06 (m, 1H), 7.18-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.00, 45.13, 115.03, 126.80, 127.51, 128.63, 139.93, 142.07, 178.37; **Anal**. Calcd for $C_{11}H_{12}O_2$ requires C, 74.98; H, 6.86; found C, 74.70; H, 6.80%.

3-(4-Fluorophenyl)pent-4-enoic acid (22b)

Yield: 88%, colorless solid, **mp** 82 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1124, 1420, 1509, 1710, 2912, 2987, 3035, 3076; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.66 (dd, *J* = 7.7, 15.7 Hz, 1H), 2.81 (dd, *J* = 7.7, 15.7 Hz, 1H), 3.83 (q, *J* = 7.4 Hz, 1H), 5.01-5.12 (m, 2H), 5.86-6.03 (m, 1H), 6.94-7.02 (m, 2H), 7.13-7.20 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.06, 44.34, 115.18 (d, *J* = 4.7 Hz) , 129.13 (d, *J* = 7.7 Hz), 137.72 (d, *J* = 3.3 Hz), 139.81, 164.16 (d, *J* = 245.0 Hz), 178.23; **Anal**. Calcd for $C_{11}H_{11}O_2F$ requires C, 68.03; H, 5.71; found C, 68.11; H, 5.75%.

3-(4-Methoxyphenyl)pent-4-enoic acid (22c)

Yield: 88%, colorless solid, **mp** 78 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1037, 1125, 1512, 1610, 1708, 2836, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.69 (dd, *J* = 7.5, 15.5 Hz, 1H), 2.75 (dd, *J* = 7.7, 15.4 Hz, 1H), 3.78 (s, 3H), 3.81 (m, 1H), 5.00-5.09 (m, 2H), 5.86-6.03 (m, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.13, 44.31, 55.13, 114.02, 114.68, 128.49, 134.10, 140.29, 158.38, 178.37; **Anal**. Calcd for $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84; found C, 69.74; H, 6.94%.

3-Methylpent-4-enoic acid (22d)

Yield: 78%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1011, 1260, 1711, 2967, 3083; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.7 Hz, 3H), 2.31 (dd, *J* = 7.6, 15.0 Hz, 1H), 2.39 (dd, *J* = 6.8, 15.2 Hz, 1H), 2.62-2.76 (m, 1H), 4.95-5.09 (m, 2H), 5.70-5.87 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.68, 34.09, 41.11, 113.66, 142.08, 179.24; **Anal**. Calcd for $C_6H_{10}O_2$ requires C, 63.14; H, 8.83; found C, 63.20; H, 8.75%.

3-(4-Bromophenyl)pent-4-enoic acid (22e)

Yield: 84%, colorless solid, **mp** 108 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 856, 1044, 1132. 1706, 3044; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.70 (dd, *J* = 7.7, 15.8 Hz, 1H), 2.81 (dd,

J = 7.6, 15.8 Hz, 1H), 3.79 (q, *J* = 7.6 Hz, 1H), 5.02-5.13 (m, 2H), 5.84- 6.01 (m, 1H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.75, 44.51, 115.52, 120.78, 129.34, 131.78, 139.41, 140.99, 178.03; **Anal**. Calcd for $C_{11}H_{11}O_2Br$ requires C, 51.79; H, 4.35; found C, 51.68; H, 4.32%.

General procedure for the synthesis of *trans*-iodolatone product (19)

To a solution of olefinic acid **22** (5.68 mmol) in acetonitrile (20 mL), solid I_2 (4.6 g, 18.17 mmol) was added at 0 ^oC under nitrogen atmosphere. The reaction mixture was protected from light and stirred for 24 h. After the completion of the reaction (monitored by TLC), it was quenched by the addition of saturated solution of aq. $NaHCO_3$ followed by extraction with diethyl ether. Organic layer was separated and washed with 20% aq. $Na_2S_2O_3$ until colorless, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **19**. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave **19** in pure form as given below..

5-(Iodomethyl)-4-phenyldihydrofuran-2(3*H*)-one (19a)

Yield: 89%, colorless thick liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1420, 1506, 1780, 2839, 2913; **^{1}H NMR** (200 MHz, $CDCl_3$) 2. 80 (dd, *J* = 9.6, 17.9 Hz, 1H), 3.05 (dd, *J* = 9.01, 17.8 Hz, 1H), 3.34 (dd, *J* = 4.4, 11.2 Hz, 1H), 3.45-3.59 (m, 2H), 4.31 (m, 1H), 7.24-7.42 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 6.33, 36.86, 47.19, 83.99, 127.13, 128.01, 129.25, 138.36, 174.08; **Anal**. Calcd for $C_{11}H_{11}O_2I$ requires C, 43.73; H, 3.67; found C, 43.72; H, 3.70%.

4-(4-Fluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (19b)

Yield: 82%, colorless thick liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1056, 1230, 1781, 2833, 2963; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.76 (dd, *J* = 9.2, 17.8 Hz, 1H), 3.07 (dd, *J* = 9.1, 17.9 Hz, 1H), 3.29-3.60 (m, 3H), 4.27 (m, 1H), 7.03-7.12 (m, 2H), 7.21-7.28 (m,

2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 1.14, 37.10, 43.36, 82.62, 116.17 (d, *J* = 21.6 Hz), 129.78 (d, *J* = 8.1 Hz), 132.28 (d, *J* = 3.3 Hz), 162.0 (d, *J* = 248.1 Hz), 175.19; **Anal**. Calcd for $C_{11}H_{10}O_2FI$ requires C, 41.27; H, 3.15; found C, 41.30; H, 3.12%.

5-(Iodomethyl)-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (19c)

Yield: 85%, colorless thick liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 945, 1126, 1783, 2812; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.64-2.84 (m, 1H), 2.97-3.10 (m, 1H), 3.28-3.54 (m, 3H), 3.81 (s, 3H), 4.24 (m, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 6.25, 36.93, 46.55, 55.16, 84.13, 114.55, 128.16, 130.00, 159.21, 174.07; **Anal**. Calcd for $C_{12}H_{13}O_3I$ requires C, 43.39; H, 3.95; found C, 43.45; H, 3.88%.

5-(Iodomethyl)-4-methyldihydrofuran-2(3*H*)-one (19d)

Yield: 80%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 749, 826, 1778, 2913; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.6 Hz, 3H), 2.24 (dd, *J* = 7.8, 17.2 Hz, 1H), 2.34-2.55 (m, 1H), 2.81 (dd, *J* = 8.3, 17.1 Hz, 1H), 3.37 (m, 2H), 4.04 (q, *J* = 5.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 6.00, 18.19, 35.75, 36.55, 84.45, 174.70; **Anal**. Calcd for $C_6H_9O_2I$ requires C, 30.02; H, 3.78; found C, 30.10; H, 3.82%.

General procedure for the synthesis of *cis*-iodolatone product (23)

To a stirred solution of olefinic acid **22** (5.68 mmol) in chloroform (20 mL), aq. $NaHCO_3$ (0.95 g, 11.36 mmol) in 20 mL of water, solid I_2 (2.88 g, 11.36 mmol) was added at 0 ^oC under nitrogen atmosphere, the reaction mixture protected from light and stirring continued for 6 h. After the completion of the reaction (monitored by TLC), organic layer was separated and washed with 20% aq. $Na_2S_2O_3$ until colorless, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **23**. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (9:1) as eluent gave **23** in pure form.

5-(Iodomethyl)-4-phenyldihydrofuran-2(3*H*)-one (23a)

Yield: 80%, colorless solid, **mp** 104 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1052, 1131,1782, 2906; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.65-2.87 (m, 2H), 3.01-3.16 (m, 2H), 3.83-3.92 (m, 1H), 4.95 (m, 1H), 7.19-7.24 (m, 2H), 7.33-7.38 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 1.51, 36.82, 44.05, 82.83, 128.02, 128.10, 128.96, 136.45, 175.37; **Anal**. Calcd for $C_{11}H_{11}O_2I$ requires C, 43.73; H, 3.67; found C, 43.82; H, 3.75%.

4-(4-Bromophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (23b)

Yield: 71%, colorless thick liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1207, 1420, 1782; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.60-2.81 (m, 2H), 3.02-3.21 (m, 2H), 3.85 (m, 1H), 4.92 (m, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 1.19, 36.79, 43.51, 82.34, 122.12, 129.68, 132.05, 135.43, 175.07; **Anal**. Calcd for $C_{11}H_{10}BrO_2I$ requires C, 34.68; H, 2.65; found C, 3.58; H, 2.74%.

General procedure for the synthesis of *anti* and *syn* epoxy esters (20a-d & 24a-b)

To a solution of iodolactone **19** or **23** (3.3 mmol) in methanol (15 mL) finely powdered anhydrous Na_2CO_3 (0.38 g, 3.63 mmol) was added and the reaction mixture refluxed for 8 h under nitrogen atmosphere. After the completion of the reaction (monitored by TLC), the resulting reaction mixture was concentrated under reduced pressure and partitioned between 50 mL water and 50 mL diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the corresponding crude product **20** or **24**. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (9:1) as eluent gave **20** or **24** pure in form.

Methyl 3-(oxiran-2-yl)-3-phenylpropanoate (20a)

Yield: 88%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1044, 1426, 1736; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.55 (dd, J = 2.6, 4.8 Hz, 1H), 2.72-3.12 (m, 5H), 3.60 (s, 3H), 7.20-

7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.37, 44.96, 46.95, 51.64, 55.29, 127.32, 127.67, 128.76, 139.89, 171.88; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{12}H_{15}O_3$: 207.1016 found: 207.1014.

Methyl 3-(4-fluorophenyl)-3-(oxiran-2-yl)propanoate (20b)

Yield: 90%, colorless thick liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1520, 1736, 2851, 2940; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.56 (dd, *J* = 2.8, 4.8 Hz, 1H), 2.68-2.75 (m, 2H), 2.86 (dd, *J* = 5.5, 15.6 Hz, 1H), 3.01 (m, 2H), 3.60 (s, 3H), 7.01 (m, 2H), 7.21 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.20, 43.97, 46.74, 51.66, 55.11, 115.81 (d, *J* = 21.2 Hz), 129.27 (d, *J* = 8.1 Hz), 135.51 (d, *J* = 3.3 Hz), 162.00 (d, *J* = 245.9 Hz), 171.74; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{12}H_{14}FO_3$: 225.0921 found: 225.0921.

Methyl 3-(4-methoxyphenyl)-3-(oxiran-2-yl)propano- ate (20c)

Yield: 95%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 760, 823, 1224, 1735; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.56 (dd, *J* = 2.5, 4.8 Hz, 1H), 2.70-3.08 (m, 5H), 3.6 (s, 3H), 3.79 (s, 3H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.41, 44.04, 46.82, 51.48, 55.00, 55.30, 114.03, 128.54, 131.70, 158.68, 171.86; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{13}H_{17}O_4$: 237.1121 found: 237.1119.

(*S*)-Methyl 3-(oxiran-2-yl)butanoate (20d)

Yield: 91%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1220, 1523, 1737, 2840; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.9 Hz, 3H), 1.86 (m, 1H), 2.27 (dd, *J* = 8.2, 15.2 Hz, 1H), 2.50-2.60 (m, 2H), 2.73-2.84 (m, 2H), 3.69 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.66, 33.24, 38.05, 46.11, 51.33, 55.43, 172.35; **Anal**. Calcd for $C_7H_{12}O_3$ requires C, 58.32; H, 8.39; found C, 58.28; H, 8.42%.

Methyl 3-(oxiran-2-yl)-3-phenylpropanoate (24a)

Yield: 90%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 732, 950, 1022, 1736; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.47 (dd, *J* = 2.6, 4.9 Hz, 1H), 2.58-2.83 (m, 3H), 3.14 (m, 1H),

3.26-3.36 (m, 1H), 3.63 (s, 3H), 7.20-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.50, 42.89, 45.67, 51.56, 54.43, 127.20, 127.87, 128.53, 139.46, 171.80; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{12}H_{15}O_3$: 207.1016 found: 207.1028.

Methyl 3-(4-bromophenyl)-3-(oxiran-2-yl)propanoate (24b)

Yield: 93%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 842, 1039, 1207, 1735; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.44 (dd, *J* = 2.6, 4.9 Hz, 1H), 2.56-2.82 (m, 3H), 3.10-3.16 (m, 1H), 3.21-3.31 (m, 1H), 3.63 (s, 3H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.50, 42.47, 45.74, 51.69, 54.17, 121.24, 129.68, 131.67, 138.34, 171.52; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{12}H_{14}BrO_3$: 285.0121 found: 285.0121.

A general experimental procedure for Hydrolytic Kinetic Resolution (HKR) of 3-substituted epoxy esters (20a-d & 24a-b):

To a solution of (*R*,*R*)- or (*S*,*S*)-(salen)Co(II)complex (0.024 mmol, 0.5 mol %) in toluene (1 mL), acetic acid (0.014 g, 0.24 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min during which time the color changed from orange-red to a dark brown and it was then concentrated under reduced pressure to get the Co(III)-salen complex-**1** as brown colored solid. To this, racemic 3-substituted epoxy esters (±)-**20/24** (4.85 mmol) and H_2O (0.043 g, 2.42 mmol) was added at 0 °C. The reaction was allowed to warm to 25 °C and stirred for 12 h. After completion of reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral epoxy esters **20a-d** and **24a-b** [solvent system; petroleum ether: ethyl acetate (9:1)] and chiral γ-butyrolactones **8a-d** and **25a-b** [solvent system; petroleum ether: ethyl acetate (1:1)] in pure form.

(4*S*, 5*R*)-5-(Hydroxymethyl)-4-phenyldihydrofuran-2(3*H*)-one (8a)

Yield: 45%, colorless solid, **mp** 82 °C; **$[\alpha]_D^{25}$** = -25.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}):

υ_{max} 1015, 1778, 3443; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.04 (br s, 1H), 2.80 (dd, *J* = 9.9, 17.8 Hz, 1H), 3.09 (dd, *J* = 9.1, 17.8 Hz, 1H), 3.63-3.77 (m, 2H), 3.93-3.99 (m, 1H), 4.53 (m, 1H), 7.24-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.23, 41.92, 61.73, 87.23, 127.19, 127.67, 129.12, 139.38, 176.30; **HRMS (*m/z*):** calculated $[M+H]^+$ for $C_{11}H_{13}O_3$: 193.0859 found: 193.0859; **Optical purity**: 99% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{major} = 10.15 and t_{minor} = 11.35 min.

(*R*)-Methyl 3-((*S*)-oxiran-2-yl)-3-phenylpropanoate (20a)

Yield: 48%, colorless oil; **$[\alpha]_D^{25}$** = -12.7 (*c* 1, $CHCl_3$); **Optical purity**: 97% ee determined from HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 10.28 and t_{major} = 11.24 min.

(4*S*, 5*R*)-4-(4-Fluorophenyl)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (8b)

Yield: 46%, colorless solid, **mp** 90 °C; **$[\alpha]_D^{25}$** = -23.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1777, 3439; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.21 (dd, *J* = 5.8, 7.3 Hz, 1H), 2.72 (dd, *J* = 9.7, 17.7 Hz, 1H), 3.03 (dd, *J* = 9.1, 17.7 Hz, 1H), 3.58-3.78 (m, 2H), 3.91-4.01 (m, 1H), 4.48 (m, 1H), 7.01-7.10 (m, 2H), 7.21-7.28 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.30, 41.22, 61.56, 87.21, 116.24 (d, *J* = 21.6 Hz), 128.89 (d, *J* = 8.1 Hz), 135.01 (d, *J* =2.9 Hz), 162.10 (d, *J* = 246.6 Hz), 176.15; **HRMS (*m/z*):** calculated $[M+H]^+$ for $C_{11}H_{12}FO_3$: 211.0765 found: 211.0766; **Optical purity**: 99% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 10.72 and t_{major} = 11.28 min.

(*R*)-Methyl 3-(4-fluorophenyl)-3-((*S*)-oxiran-2-yl)propanoate (20b)

Yield: 49%, colorless thick liquid; **$[\alpha]_D^{25}$** = -7.47 (*c* 1, $CHCl_3$); **Optical purity**: 99% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{major} = 23.61 and t_{minor} = 29.29 min.

(4*S*, 5*R*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)dihydro- furan-2(3*H*)-one (8c)

Yield: 48%, colorless solid, **mp** 93 °C; **$[\alpha]_D^{25}$** = -26.6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1764, 3449; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.17-2.32 (m, 1H), 2.73 (dd, *J* = 10.2, 17.8 Hz, 1H), 2.98 (dd, *J* = 8.9, 17.7 Hz, 1H), 3.58-3.71 (m, 2H), 3.80 (s, 3H), 3.89-3.97 (m, 1H), 4.47 (m, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.33, 41.25, 55.19, 61.67, 87.33, 114.51, 128.23, 131.06, 159.05, 176.15; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{12}H_{15}O_4$: 223.0965 found: 223.0964; **Optical purity**: 97% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 13.27 and t_{major} = 14.03 min.

(*R*)-Methyl 3-(4-methoxyphenyl)-3-((*S*)-oxiran-2-yl)propano- ate (20c)

Yield: 47%, colorless oil; **$[\alpha]_D^{25}$** = -25.0 (*c* 1, $CHCl_3$); **Optical purity**: 96% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor}= 14.90 and t_{major} = 15.54 min.

(4*R*, 5*R*)-5-(Hydroxymethyl)-4-methyldihydrofuran-2(3*H*)-one (8d)

Yield: 46%, colorless oil; **$[\alpha]_D^{25}$** = -51.0 (*c* 1, $CHCl_3$) {lit.[15] $[\alpha]_D$ +49.4 for its antipode }; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1770, 3419; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.6 Hz, 3H), 2.16 (br s, 1H), 2.21 (dd, *J* = 8.6, 16.8 Hz, 1H), 2.43-2.65 (m, 1H), 2.76 (dd, *J* = 8.5, 16.8 Hz, 1H), 3.61-3.72 (m, 1H), 3.87-3.97 (m, 1H), 4.13 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 17.67, 30.88, 36.80, 62.10, 87.46, 177.07; **Anal.** Calcd for $C_6H_{10}O_3$ requires C, 55.37; H, 7.74; found C, 55.39; H, 7.80%. **Optical purity**: 97% determined from Mosher's ester.

Synthesis of Mosher's Ester

(2*R*)-((2*R*,3*R*)-Tetrahydro-3-methyl-5-oxofuran-2-yl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (8d1):

To a stirred solution of **8d** (50 mg, 0.38 mmol), DCC (95 mg, 0.46 mmol) and catalytic N,N-diaminopyridine (5 mg, 10 mol%), Mosher's acid [(R)-(+)-α-Methoxy-α-trifluoro-methylphenyl acetic acid] (108 mg, 0.46mmol) in CH_2Cl_2 (2 mL) was added at 0 ^oC and allowed to stir for 2 h at same tempreture. After the completion of reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product corresponding Mosher's ester. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (7:3) as eluent gave to give pure corresponding Mosher's ester **(8d1)**.

Yield: 68%, colorless liquid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.8 Hz, 3H), 2.16 (dd, *J* = 8.3, 17.3 Hz, 1H), 2.34 (m, 1H), 2.64 (dd, *J* = 8.5, 17.6 Hz, 1H), 3.53 (s, 3H), 4.25 (m, 1H), 4.39 (dd, *J* = 5.3, 12.3 Hz, 1H), 4.57 (dd, *J* = 2.8, 12.1 Hz, 1H), 7.41 (m, 3H), 7.51 (m, 2H); **^{19} F NMR** (400 MHz, $CDCl_3$+CF_3COOH) δ -72.17 (minor diasteromer, integral = 1%), -72.27 (major diastereomer, integral = 58.46%) [Ratio of diasteromer major : minor, 98.32 : 1.68]

(*S*)-Methyl 3-((*S*)-oxiran-2-yl)butanoate (20d)

Yield: 48%, colorless liquid; **$[\alpha]_D^{25}$** = +3.5 (*c* 1, $CHCl_3$) {lit.[4d] $[\alpha]_D^{25}$ +3.8 (*c* 2, $CHCl_3$)}; **Optical purity**: 96% determine from Mosher's ester (Note: epoxide **20d** was opened with water using non-chiral way then corresponning lactone is used for the preparation of corresponding Mosher's ester **20d1**, Synthesis of **20d1** was carried out using same procedure as described for **8d1**).

(2*R*)-((2*S*,3*S*)-Tetrahydro-3-methyl-5-oxofuran-2-yl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate:

Yield: 56%, colorless liquid,**^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.8 Hz, 3H),

2.13 (dd, *J* = 7.8, 17.6 Hz, 1H), 2.30 (m, 1H), 2.57 (dd, *J* = 8.5, 17.3 Hz, 1H), 3.54 (s, 3H), 4.27 (m, 1H), 4.34 (dd, *J* = 4.3, 12.3 Hz, 1H), 4.61 (dd, *J* = 2.5, 12.1 Hz, 1H), 7.41 (m, 3H), 7.50 (m, 2H); **^{19}F NMR** (400 MHz, $CDCl_3$+CF_3COOH) δ -72.26 (major diastereomer, integral = 51.56%), -72.36 (minor diasteromer, integral = 1%) [Ratio of diasteromer major : minor , 98.10 : 1.90].

(4*S*, 5*S*)-5-(Hydroxymethyl)-4-phenyldihydrofuran-2(3*H*)-one (25a)

Yield: 47%, colorless thick liquide; **$[\alpha]_D^{25}$** = -76.56 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1780, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.30 (br s, 1H), 2.87 (dd, *J* = 8.9, 17.4 Hz, 1H), 3.04 (dd, *J* = 8.3, 17.4 Hz, 1H), 3.34-3.60 (m, 2H), 3.90 (q , *J* = 8.2 Hz, 1H), 4.79 (m, 1H), 7.22-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.56, 43.16, 62.10, 86.37, 127.66, 127.84, 128.93, 136.46, 176.72; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{11}H_{13}O_3$: 193.0859 found: 193.0859; **Optical purity**: 98% ee determined by HPLC analysis (OJ-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{major} = 10.51 and t_{minor} = 13.84 min.

(4*S*, 5*S*)-4-(4-Bromophenyl)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (25b)

Yield: 46%, colorless thick liquid; **$[\alpha]_D^{25}$** = -108.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1773, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.13 (br s, 1H), 2.83 (dd, *J* = 9.0, 17.2 Hz, 1H), 3.01 (dd, *J* = 8.7, 17.3 Hz, 1H), 3.40 (m, 1H), 3.57 (m, 1H), 3.86 (q, *J* = 8.6 Hz, 1H), 4.74 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.54, 43.03, 61.85, 82.92, 121.88, 129.54, 132.08, 135.48, 176.27; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{11}H_{12}BrO_3$: 270.9964 found: 270.9965; **Optical purity**: 98% ee determined by HPLC analysis (OJ-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{major} = 12.33 and t_{minor} = 13.41 min.

(*R*)-Methyl 3-((*R*)-oxiran-2-yl)-3-phenylpropanoate (24a)

Yield: 48%, colorless oil; $[\alpha]_D^{25}$ = +17.3 (*c* 1, $CHCl_3$); **Optical purity:** 97% ee determined from HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 13.68 and t_{major} = 14.93 min.

(*R*)-Methyl 3-(4-bromophenyl)-3-((*R*)-oxiran-2-yl)propanoate (24b)

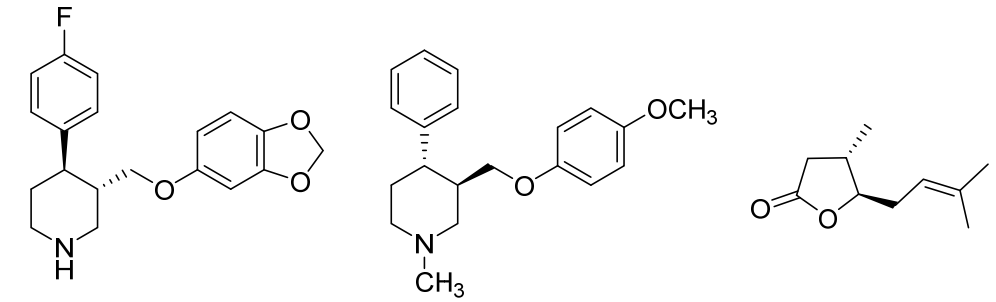
Yield: 48%, colorless oil; $[\alpha]_D^{25}$ = +8.8 (*c* 1, $CHCl_3$); **Optical purity:** 97% ee determined from HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 14.36 and t_{major} = 15.09 min.

Section II

Formal Synthesis (-)-Paroxetine and (+)-Eldanolide

1.2.1 Introduction and Pharmacology

The class of compounds containing 3, 4-disubstituted piperidine ring as a core structure is of substantial medicinal use. Many biological compounds, which consist of the piperidine core have wide range of biological activities.[21] The biological activity of these classes of compounds depends on the position and substitution at the piperidine ring. The two important molecules belonging to the 3, 4-disubstituted piperidine class are paroxetine **(26)**[22] and femoxetine **(27) (Fig. 10)**, both are the well known anti-depressant drugs. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) introduced in the market by a pharmaceutical company, GlaxoSmithKline in 1992. It is mainly used for the treatment of major depression, obsessive-compulsive disorder (OCD), panic disorder, social anxiety and generalized anxiety disorder in adult outpatients.[23] It is marketed under the trade names Paxil, Seroxat and Aropax.



(-)-paroxetine **26** (+)-femoxetine **27** (+)-eldanolide **28**

Fig. 10: Structures of some of the anti-depressants drugs (-)-paroxetine **26,** (+)-femoxetine **27** and pheromone (+)-eldanolide **28**

The naturally occurring compound i.e. (+)-eldanolide **28 (Fig. 10)**, is a long range sex attractant isolated from the male wing gland of African sugarcane stem borer *Eldana sacharina*,[24] in 1981. Due to its attractive biological activities, the monoterpenoid

pheromone has aroused enormous attention from the synthetic community.

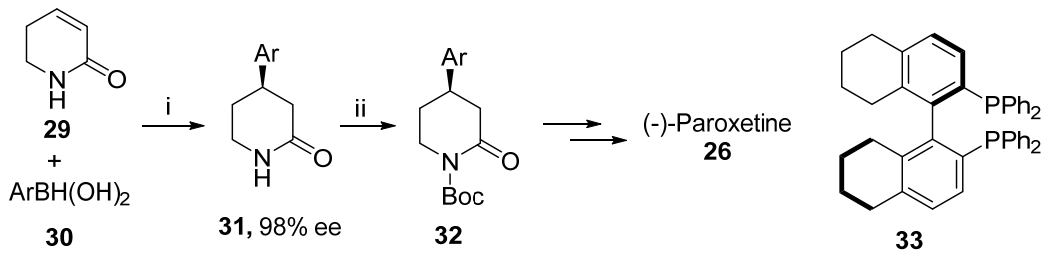
1.2.2 Review of Literature

Various syntheses of (-)-paroxetine **26** and (+)-eldanolide **28** have been documented in the literature. Some of the recent interesting and important synthetic routes are described below.

(a) Review of literature for (-)-Paroxetine 26

Hayashi's approach (2001)[25]

Hayashi *et al.* have reported the formal synthesis of (-)-paroxetine **26** *via* Rh-catalyzed Michael addition of aryl boronic acid **30** to 5,6-dihydro-2(1*H*)-pyridinone **29** to give 4-aryl-2-piperidinone **31** using chiral bisphosphine ligand **33** in 70% yield and 98% ee. The amide moiety in 4-aryl-2-piperidinone **31** was protected as Boc group to give **32,** the key intermediate for the synthesis of (-)-paroxetine **26** (**Scheme 8**).

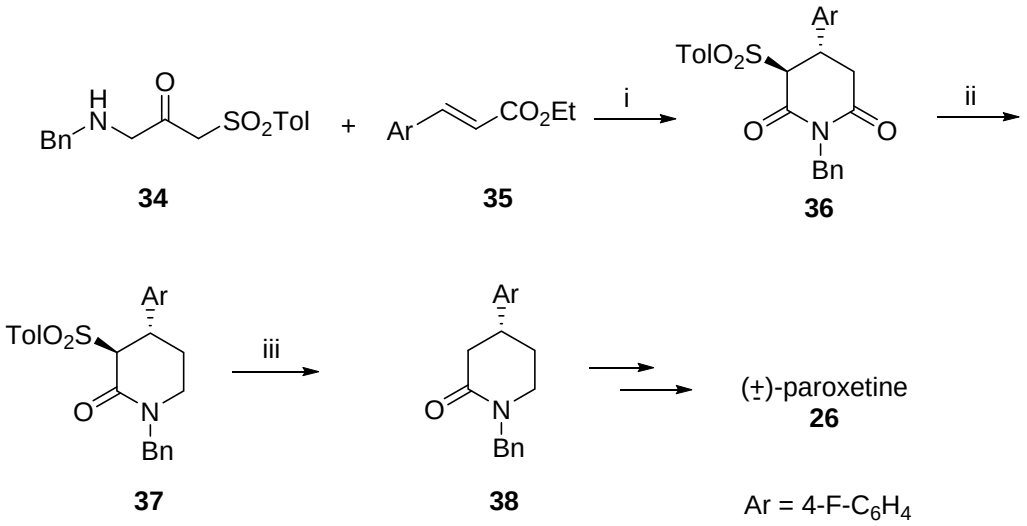


Scheme 8: (i) $Rh(acac)(C_2H_4)_2$ (3 mol %), ligand **33** (3.3 mol %), dioxane:H_2O (10:1), 40 °C, 3 h, 70%, 98% ee; (ii) $(Boc)_2O$, DMAP, CH_3CN, reflux, 82%.

Chang's approach (2003)[26]

Chang *et al.* have used conjugated addition of **34** onto the unsaturated ester **35** to prepare *N*-alkyl-3-sulfonyl glutarimide **36.** This was then subjected to selective reduction of amide moiety in **36** to give 4-substituted 3-sulfonyl-δ-lactam **37.** Further,

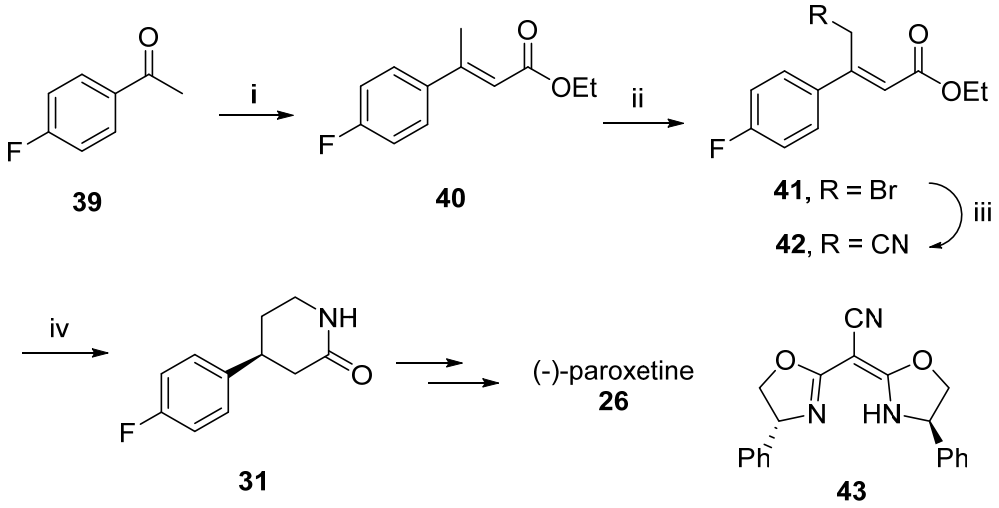
desulfurization with Na-Hg and Na_3PO_4 led to **38**, an important intermediate in the synthesis of (±)- paroxetine **26** (**Scheme 9**).



Scheme 9: (i) NaH, THF, 80 ºC, 1 h, 75%; (ii) Et_3N, $LiAlH_4$, THF, 80 ºC, 3 h, 76%; (iii) Na-Hg, Na_3PO_4, MeOH, 25 ºC, 2 h, 90%.

Sudalai's approach (2006)[27]

Quit recently, we have reported $CoCl_2$-catalyzed asymmetric reduction of *γ*-cyano-*α*, *β*-unsaturated ester **42** to afford the key lactam **31** leading to the formal synthesis of (-)- paroxetine **26**. The unsaturated ester **40,** prepared from 4-fluoroacetophenone (**39**), was subjected to allylic bromination (catalytic AIBN, NBS) to give bromo



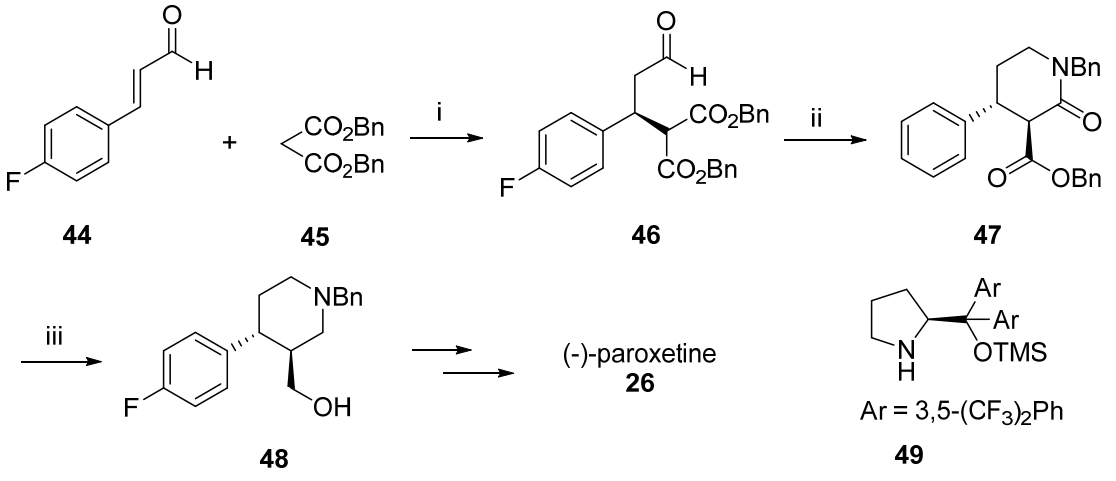
Scheme 10: (i) (a) ethyl bromoacetate (12 mmol), $ArCOCH_3$ (10 mmol), Zn dust

(12 mmol), dry benzene, 80 ºC, 6 h; (b) *p*-TSA (10 mol %), benzene, Dean-Stark, 80 ºC, 12 h, 80 %; (ii) AIBN (10 mol %), NBS, CCl_4, reflux, 12 h, 84 %; (iii) NaCN, dry DMF, 25 ºC, 81%; (iv) cyano ester (1 mmol), $CoCl_2$ (1 mol %), ligand **43** (1.1 mol %), $NaBH_4$ (4 mmol), DMF: EtOH (1:1), 25 ºC, 24 h, 99 %, 86 % ee.

derivative **41**. Displacement of the bromide group in **41** with cyanide (NaCN in DMF) gave nitrile **42**. Asymmetric reduction of **42** with catalytic amount of $CoCl_2$ using chiral ligand **43** provided the key intermediate **31** in 99% yield and 86% ee (**Scheme 10**).

Jørgensen's Approach (2006)[28]

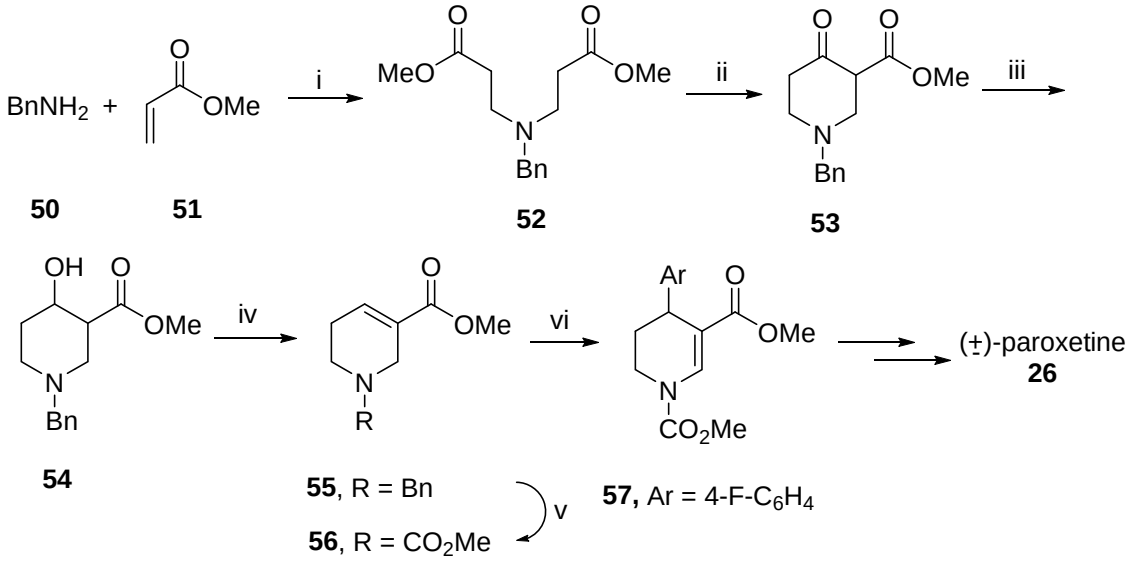
Jørgensen *et al.* have used organocatalytic route for the synthesis of paroxetine **26** which involved Michael addition of dibenzyl malonate **45** onto (*E*)-3-(4-fluorophenyl) acrylaldehyde (**44**) to give dibenzyl 2-[(*S*)-1-(4-fluorophenyl)-2-formylethyl]malonate (**46**). Reductive amination of aldehyde **46** with benzyl amine followed by intramolecular cyclization gave lactam **47**. Further, simultaneous reduction of ester and amide carbonyl groups in **47** was achieved with $LiAlH_4$ to produce the known key intermediate **48** (**Scheme 11**).



Scheme 11: (i) 10% catalyst **49**, EtOH, 0 ºC (ii) $PhCH_2NH_2$, $NaBH(OAc)_3$, dioxane, 70%; (iii) $LiAlH_4$, THF, 85%.

Chavan's approach (2007)[29]

Chavan *et al.* have reported *racemic* formal synthesis of paroxetine **26**. In this approach, amino diester **52** was prepared by double Michael addition of benzyl amine onto methyl acrylate. It was then subjected to Dieckmann condensation to give ketoester **53**, which was reduced to *β*- hydroxy ester **54.** This hydroxyester underwent elimination during mesylation to afford olefin **55**. Benzyl group in **55** was then exchanged with methyl carbamate **56**, followed by Heck arylation of **56** furnished the known intermediate **57** in moderate yields (**Scheme 12**).

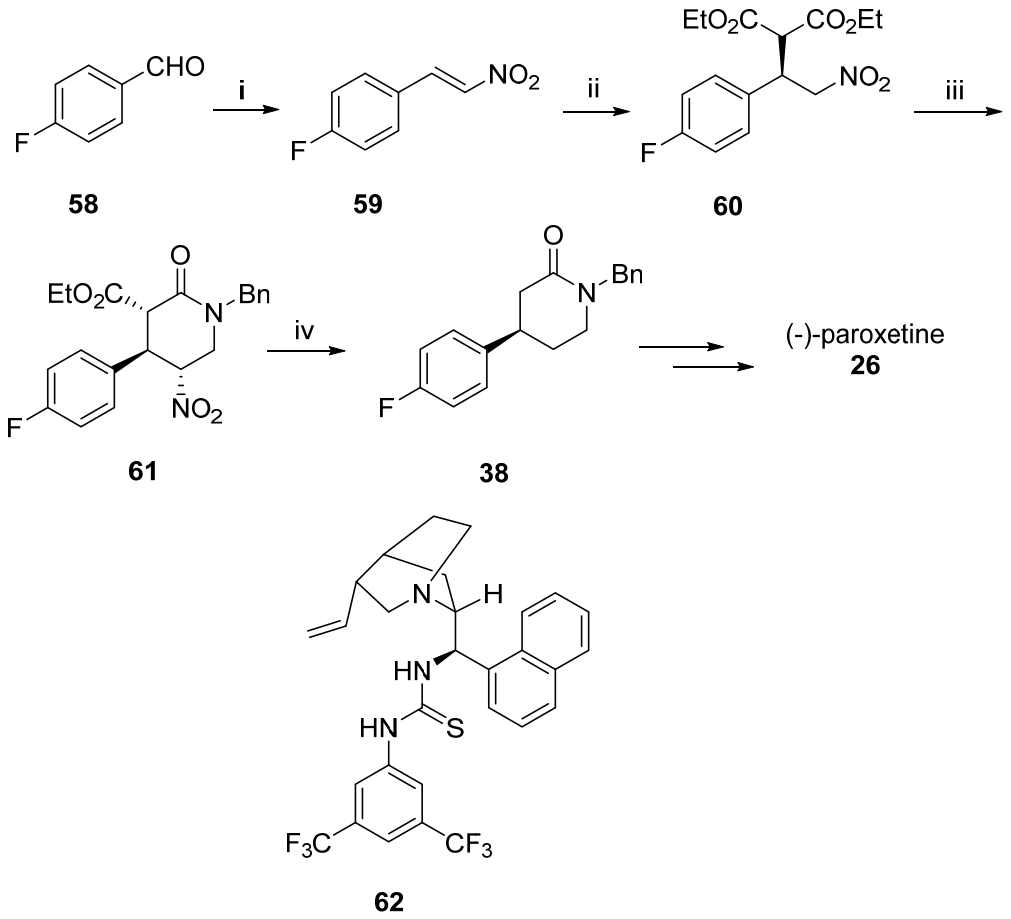


Scheme 12: (i) Et_3N, reflux (neat), overnight, 90%; (ii) NaH, PhH, reflux, 3 h, 82%; (iii) $NaBH_4$, MeOH, 0-25 °C, 2 h; (iv) MsCl, Et_3N, CH_2Cl_2, 0-25 °C, overnight, 75% (for two steps); (v) $ClCO_2Me$, $NaHCO_3$, CH_2Cl_2, 25 °C, 24 h, 80%; (vi) 1-bromo-4-fluorobenzene, $Pd(PPh_3)_4$, K_2CO_3, Bu_4NBr, 120 °C, 48 h.

Dixon's approach (2008)[30]

Dixon *et al.* have used Michael addition of malonate nucleophile onto nitro olefin **59** catalyzed by a bifunctional organocatalyst **62** for obtaining nitro diester **60** in 92 % yield and 99% ee. Nitro derivative **60** was then subjected to nitro-Mannich lactamization (HCHO, $BnNH_2$ in MeOH) to give lactam **61.** Further decarboxylation

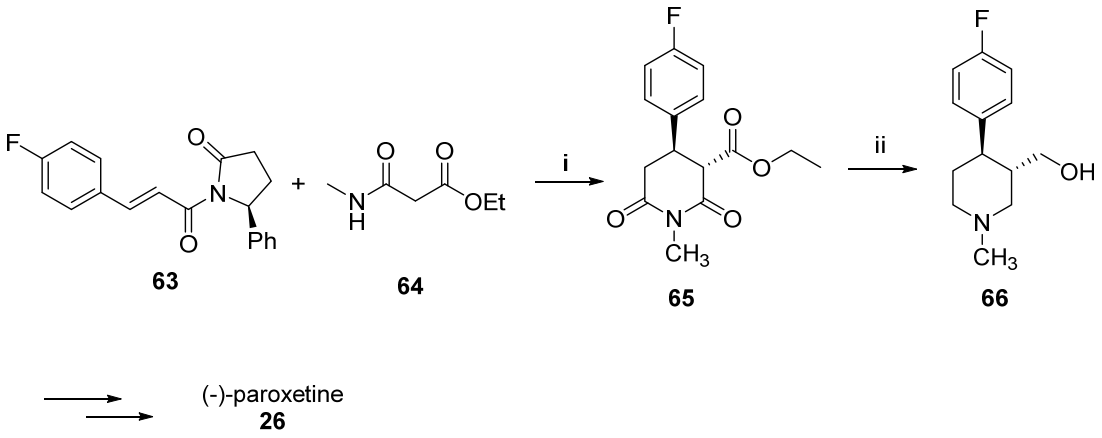
and reductive removal of nitro group was achieved with tributyltin hydride and AIBN to afford the known lactam **38** (**Scheme 13**).



Scheme 13: (i) CH_3NO_2, NH_4OAc, reflux, 24 h, 92%; (ii) catalyst **62**, dimethyl malonate, CH_2Cl_2, -20 °C, 72 h, 92%, 99% ee.(iii) HCHO (37% solution in water), benzylamine, MeOH , reflux, 16 h, 68%; (iv) Bu_3SnH, AIBN, toluene, 110 °C, 78%.

Reddy's approach (2011)[31]

Reddy *et al*. recently used the asymmetric conjugate addition reaction between a chiral α,β-unsaturated amido ester **63** and ethyl-*N*-methylmalonamide **64**, for the formal synthesis of (–)-paroxetine **26**. The conjugate addition of **63** and **64** in the presence of NaH and DMSO furnished imide **65.** The subsequent reduction of imide **65** furnished alcohol **66** which is a crucial intermediate for the synthesis of paroxetine **26** (**Scheme 14**).

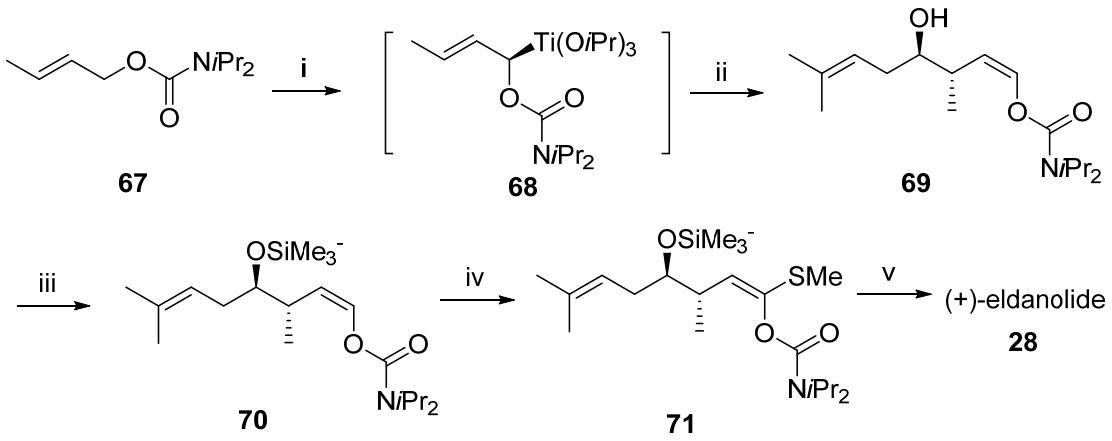


Scheme 14: (i) NaH, DMSO, 25 ^{o}C, 4 h, 80%; (ii) $LiAlH_4$, THF, 0-60 ^{o}C, 2 h, 80%.

(b) Review of literature for (+)-eldanolide 28

Hoppe's approach (1992)[32]

Hoppe *et al* have reported the synthesis of (+)-eldanolide **28** from (*E*)-2-butenyl *N,N*-diisopropylcarbamate **67** *via* homoaldol reaction. The chirality-inducing step consists of the (-)-sparteine-assisted enantioselective deprotonation. The (-)-sparteine-induced lithiation of the (*E*)-crotyl carbamate **67**, followed by treatment with excess titanium tetraisopropoxide and addition of 4-methylpent-3-enal yielded the homoaldol product **69** with > 98 % ds and 92 % ee (**Scheme 15**).

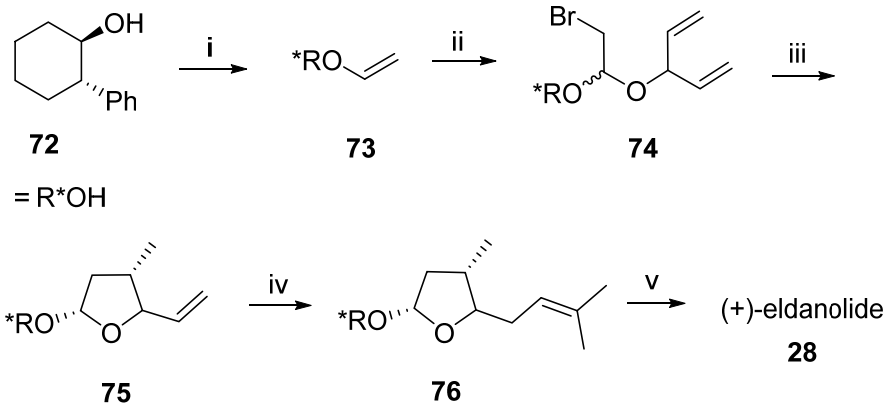


Scheme 15: (i) (a) *n*-BuLi/(-)-sparteine/cyclohexane, crystallization; (b) $Ti(OiPr)_4$; (ii) 4-methylpent-3-enal; aq. HCl;(iii) Me_3SiCl/NEt_3, CH_2Cl_2; (iv) (a) *n*-BuLi/TMEDA; (b) MeSSMe; (v) $MeSO_3H$, MeOH.

Alcohol **69** was protected as its trimethyl silyl derivative to give **70**. Methylsulfenylation of the silyl ether **70** to yield the ketene monothioacetal **71**. Finally desilylated, solvolyzed and lactonized furnished (+)-eldanolide **28.**

Villar's approach (2000)[33]

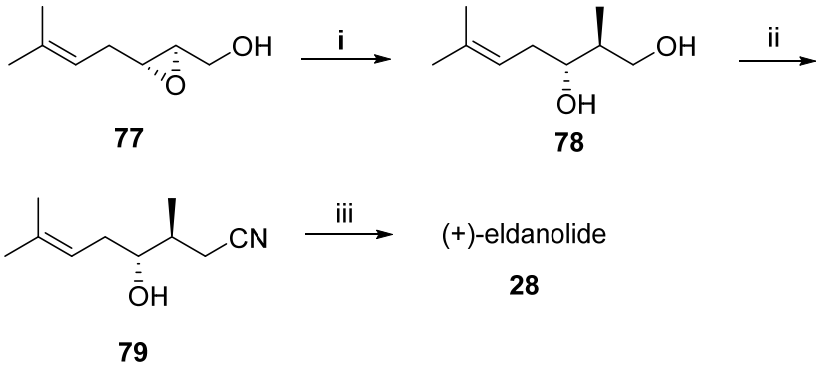
Villar *et al* have reported the synthesis of (+)-eldanolide **28** using Ueno-Stork radical cyclizationprotocol. Bromoacetal **74** was thus prepared from (1*R*, 2*S*)-2-phenylcyclohexanol **72** *via* mercury(II)-catalyzed transetherification followed by bromoacetalization with 1,4-pentadien-3-ol. The bromoacetal **74** was then submitted to Ueno-Stork radical cyclization intramolecularly to afford **75.** The *γ*-chain of **75** was modified in a straightforward manner by hydroboration, Swern oxidation, and Wittig reaction to give **76**. Finally, hydrolysis of the acetal **76** furnished the lactol together with recovered (1*R*, 2*S*)-2- phenylcyclohexanol (62%). Oxidation of the lactol with PCC gave enantiomerically pure (+)-eldanolide **28** (**Scheme 16**).



Scheme 16: (i) ethyl vinyl ether, $Hg(OAc)_2$, 70%; (ii) 1,4-pentadien- 3-ol, NBS, 75% (1:1 mixture of diastereomer); (iii) (a) Bu_3SnH, Et_3B, O_2, 85%, ds >98%; (iv) (a) 9-BBN then H_2O_2, NaOH, 93%; (b) $(COCl)_2$, DMSO, 95%; (c) $Ph_3PC(CH_3)_2$, 51%; (v) (a) HCl, H_2O, 68% [(1*R*,2*S*)-2-phenylcyclohexanol recovered in 62%]; (b) PCC, Al_2O_3, 73%.

Kong's approach (2007)[34]

Kong *et al* have reported the synthesis of (+)-eldanolide **28** in four steps from chiral 2,3-epoxy alcohol **77,** an intermediate easily available from Sharpless asymmetric epoxidation. Ring opening of **77** with Me_2CuLi produced 1,3-diol **78.** Selective tosylation of diol **78** at the primary hydroxyl gave a monotosylate, which was subjected to SN_2 displacement using NaCN to furnish nitrile **79.** Finally, its saponification followed by lactonization in an acidic media gave (+)-eldanolide **28** (**Scheme 17**).



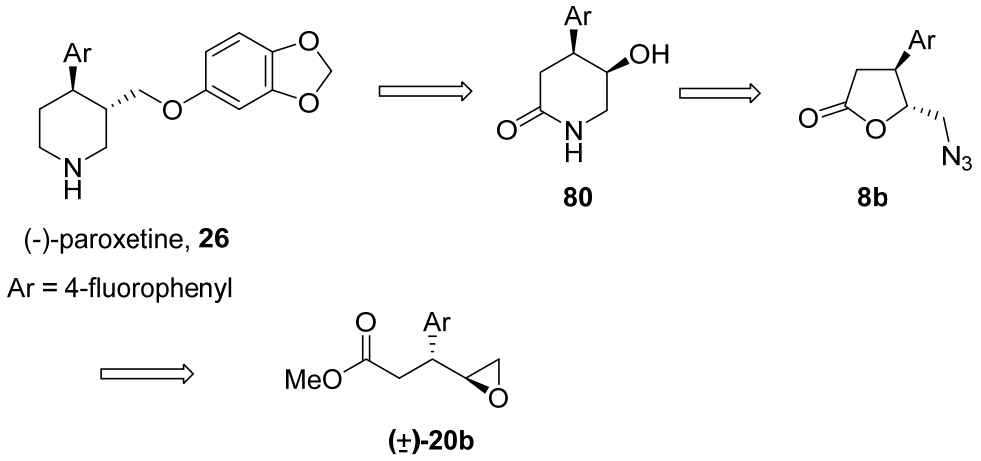
Scheme 17: (i) MeLi, CuI, THF, 0 ^oC, 1 h; (ii) TsCl, Et_3N, DMAP, NaCN, NaI, 75%; (iii) NaOH, H_2SO_4, 86%.

1.2.3 Present Work

1.2.3.1 Objective

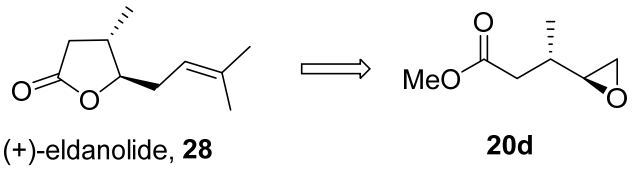
Literature search revealed that several strategies such as classical resolution, chemoenzymatic and metal-catalyzed chemical synthesis have been reported for the synthesis of (-)-paroxetine **26** and (+)-eldanolide **28**. However, these methods suffer broadly from disadvantages such as low overall yields, the need for separation of diastereomers and use of expensive reagents. In this section, a concise enantioselective synthesis of (-)-paroxetine **26** and (+)-eldanolide **28** using HKR of 3-substituted epoxides as the chiral inducing step is described.

Retrosynthetic analysis of (-)-paroxetine **26** reveals that *cis*-3,4-disubstituted piperidinone core **80** could be visualized as the key intermediate for the synthesis of (-)-paroxetine **26**. The *cis*-isomer **80** could be prepared from γ-butyrolactone **8b** to be obtained by the cobalt-catalyzed hydrolytic kinetic resolution of *racemic* 3-substituted epoxy ester (±)**-20b (see Section I**) (**Scheme 18**).



Scheme 18: Retrosynthetic analysis of (-)-paroxetine **26**

Similarly, we visualized that 3-substituted epoxide **20d** as the key intermediate for the synthesis of (+)-eldanolide **28**. Chiral 3-substituted epoxide **20d** will be prepared by the cobalt-catalyzed hydrolytic kinetic resolution of *racemic* 3-substituted epoxy ester (±)**-20d (see Section I) (Scheme 19).**

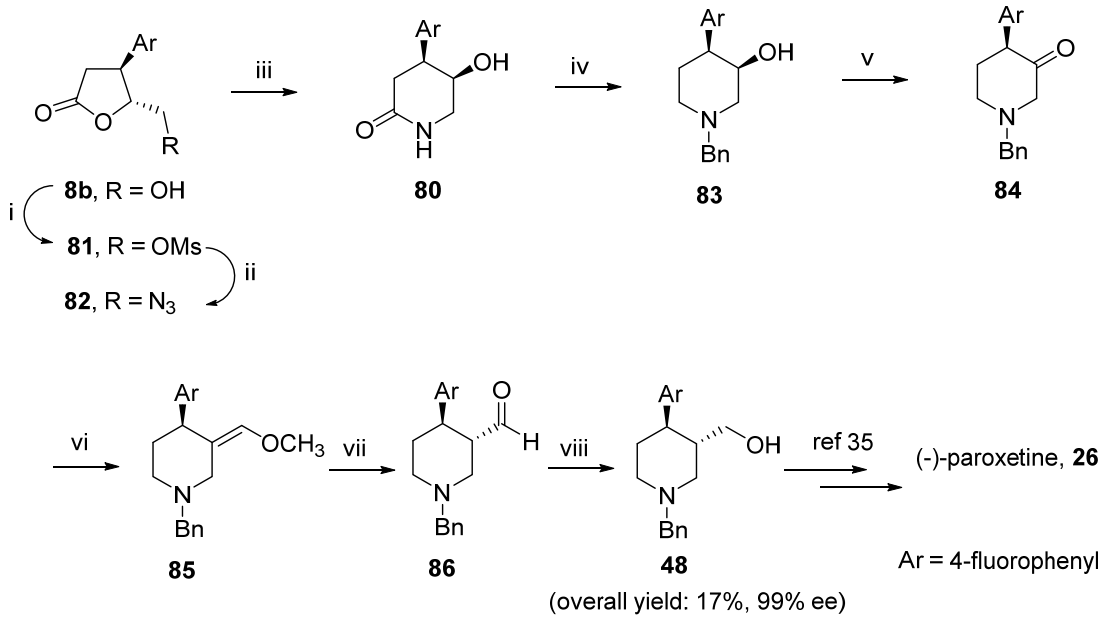


Scheme 19: Retrosynthetic analysis of (+)-eldanolide **28**

1.2.3.2 Results and Discussion

(a) Formal synthesis of (-)-paroxetine (26)

The synthesis of (-)-paroxetine **26** commences from γ-butyrolactone **8b**, obtained by Co-catalyzed hydrolytic kinetic resolution of *racemic* 3-substituted epoxy ester (±)-**20b** as described in previous section **(Section I, Table 1)**. Thus, mesylation of **8b** gave the mesylate **81** in 92% yield **(Scheme 20)**. The formation of mesylate **81** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **81** showed a strong signal at δ 3.08 (s, 3H) for methyl protons. Its ^{13}C NMR showed a typical carbon signal at δ 37.7 for methyl carbon, which confirmed the formation of mesylate **81 (Fig. 11).**



Scheme 20: (i) MsCl, Et_3N, CH_2Cl_2, 0 ^{o}C, 1 h, 92%; (ii) NaN_3, DMF, 80 ^{o}C, 3 h, 95%; (iii) $Pd(OH)_2$, H_2 (1 atm), MeOH, 12 h, 25 ^{o}C, 98%; (iv) $BH_3.SMe_2$, THF, reflux, 12 h, then BnBr, Na_2CO_3, CH_2Cl_2 /H_2O (1:1), reflux, 12 h, 85%; (v) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78 ^{o}C, 1 h, 80%; (vi) $PPh_3^{+}CH_2OCH_3Cl^{-}$, *n*-BnLi, THF, 0 to 25 ^{o}C, 48 h, 60%; (vii) 0.1 M H_2SO_4, THF, 50 ^{o}C, 2 h, 82%; (viii) $NaBH_4$, MeOH, 25 ^{o}C, 1 h, 72% (for two steps).

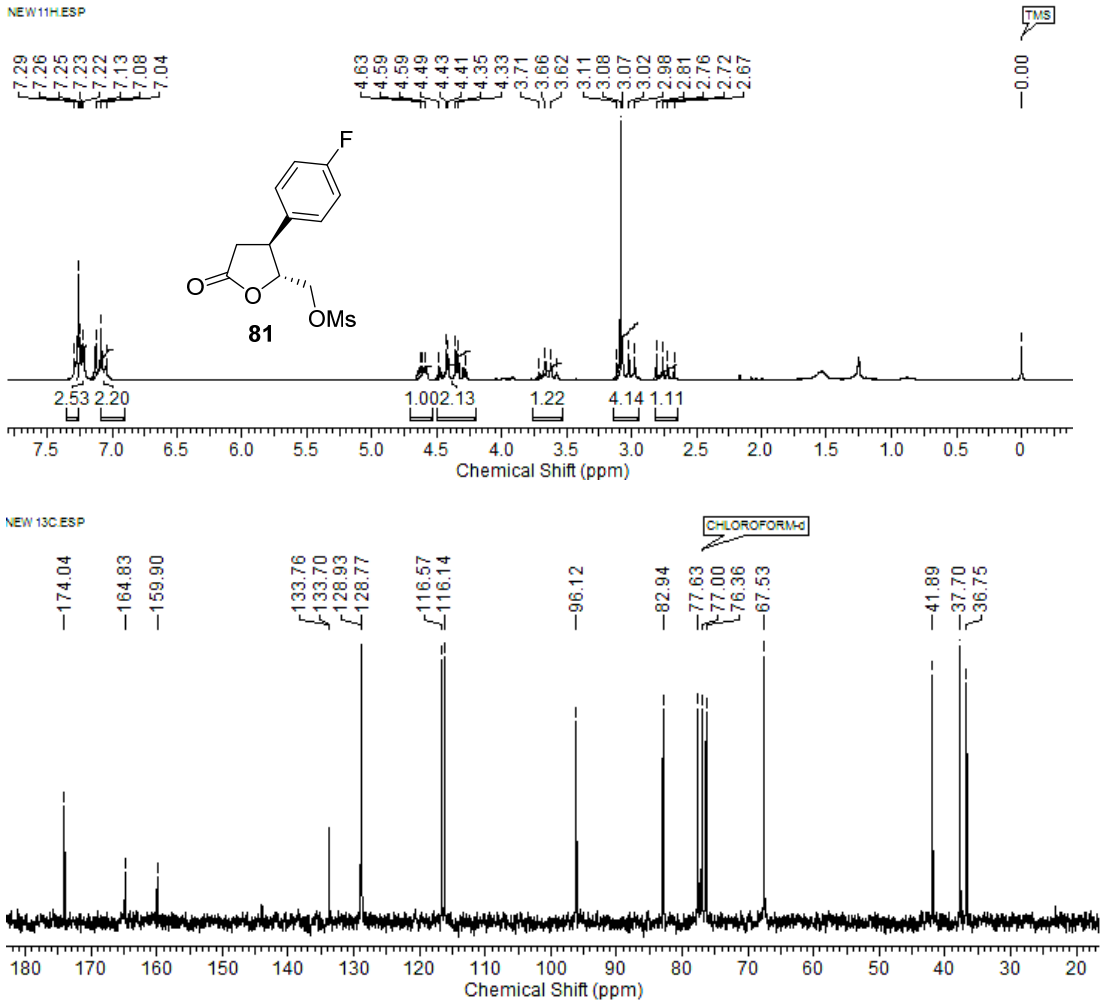


Fig. 11: ^{1}H and ^{13}C NMR spectra of **81**

Mesylate **81** was converted into the corresponding azide **82** (NaN_3, DMF, 80 ^{o}C) in 95% yield. The formation of azido derivative **82** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 2105 cm^{-1} typically for azide functionality. Its ^{1}H NMR spectrum showed the appearance of a multiplet at δ 4.47-4.55 (1H) corresponding to methine proton (-**CH**-O). Its structure was further confirmed by its ^{13}C NMR spectrum, which showed a typical methine carbon (-**CH**-O) appearing at δ 84.3 (**Fig. 12**).

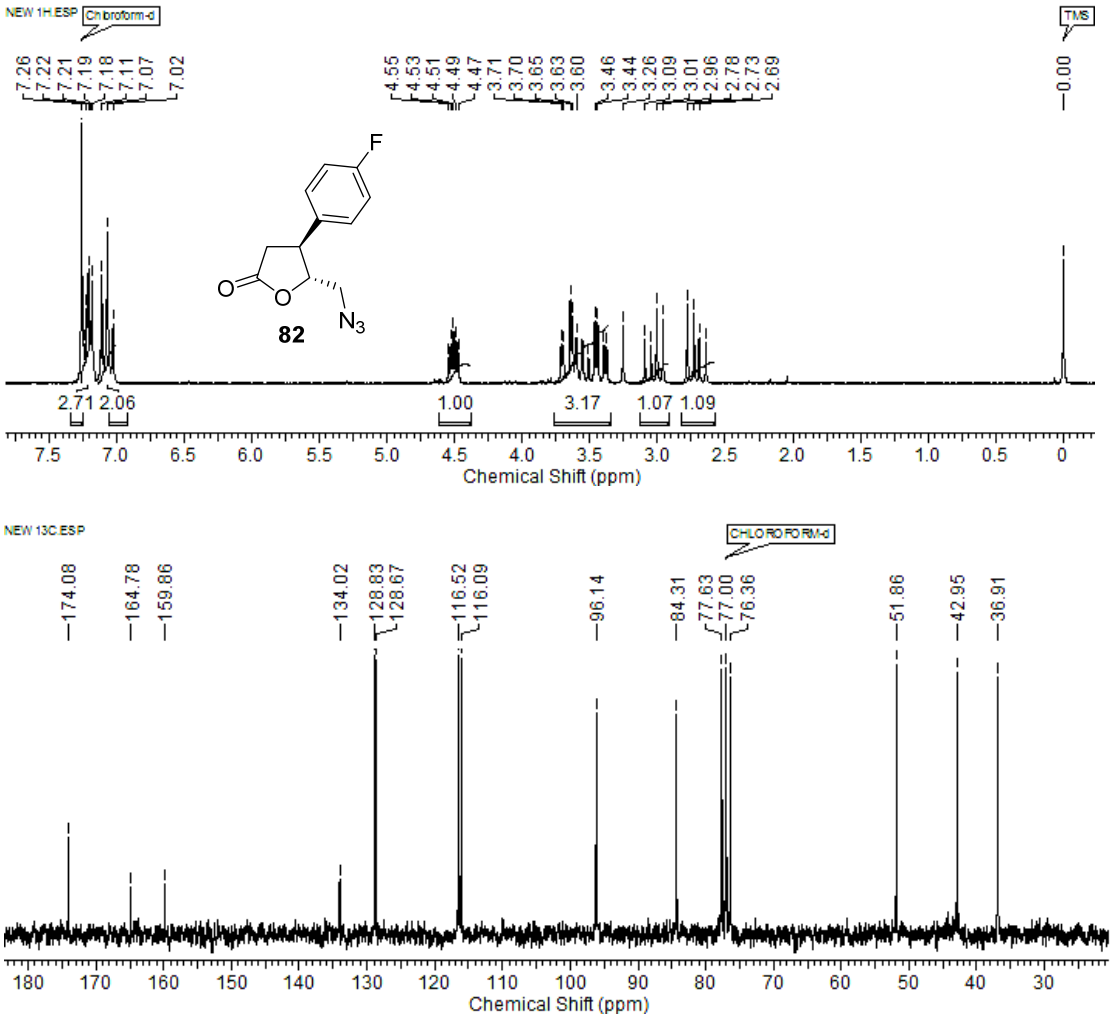


Fig. 12: ^{1}H and ^{13}C NMR spectra of **82**

Azide **82** was then subjected to intramolecular reductive cyclization over $Pd(OH)_2/H_2$ (1 atm) to afford *cis*-3,4-disubstituted piperidinone core **80** in 98% yield. The ^{1}H-NMR spectrum of the lactam **80** showed a typical signal at δ 4.01 (m, 1H) corresponding to the methine protons attached C**H**-OH and other signals at δ 2.36 (dd, 1H) and 2.82 (dd, 1H) corresponding to methylene protons attached to C**H$_2$**-CO. Its ^{13}C-NMR spectrum showed a typical carbon signal at δ 174.5 for amide carbonyl carbon. The formation of cylclic lactam was further confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1652 cm^{-1} typically for amide carbonyl functionality (**Fig. 13**).

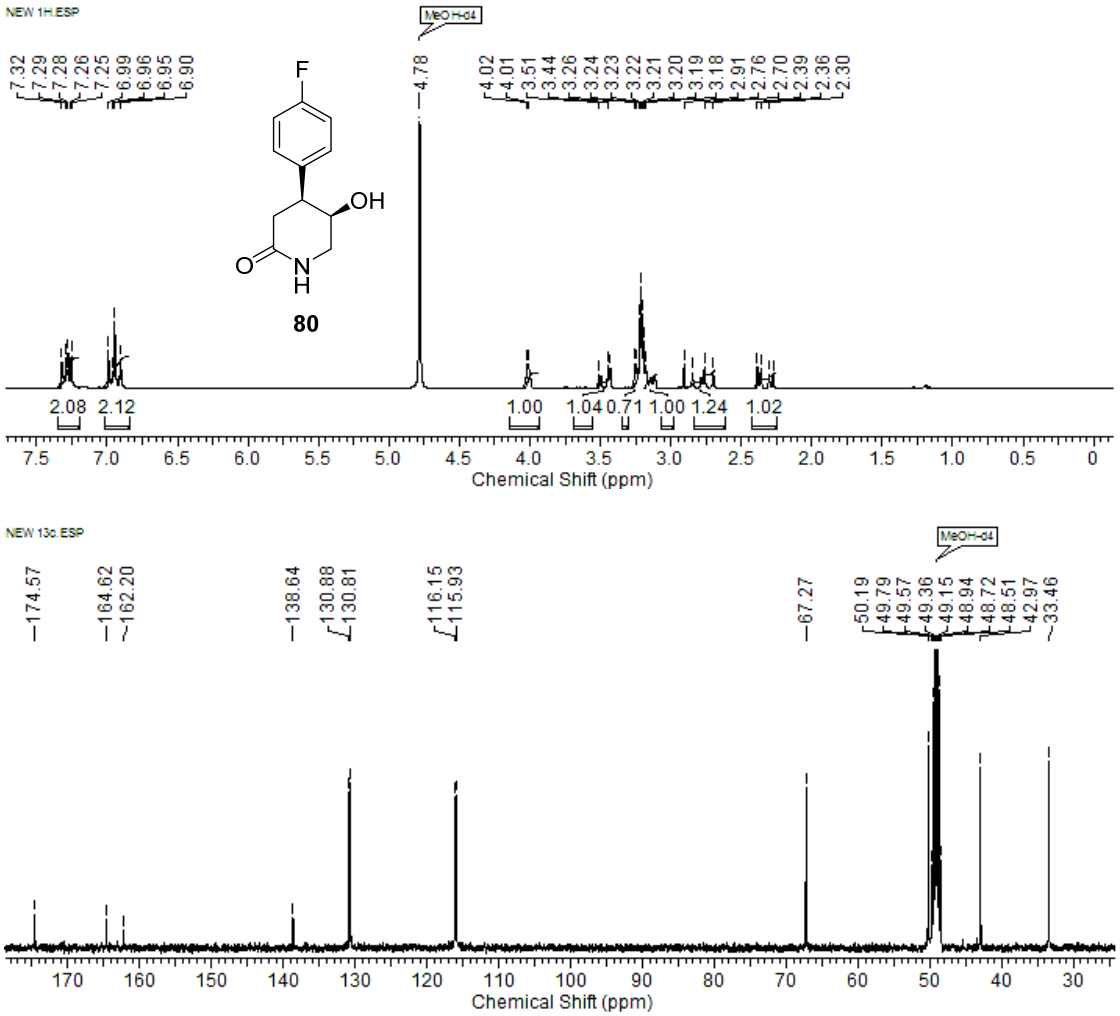


Fig. 13: ^{1}H and ^{13}C NMR spectra of **80**

Reduction of amide carbonyl in **80** with $BH_3{\cdot}SMe_2$ followed by *in situ* *N*-benzyl protection gave *cis*-piperidine derivative **83** in 85% yield. The formation of **83** was confirmed by its ^{1}H NMR spectrum, which showed typical signals at δ 3.61 (2H) corresponding to benzylic protons and δ 3.86 (1H) for methine proton (-**CH**-O). This was further confirmed by its ^{13}C NMR spectrum, which showed characteristic carbon signals at δ 68.9 and δ 62.6 for methine carbon attached to hydroxyl group and benzylic methylene carbons respectively (**Fig. 14**).

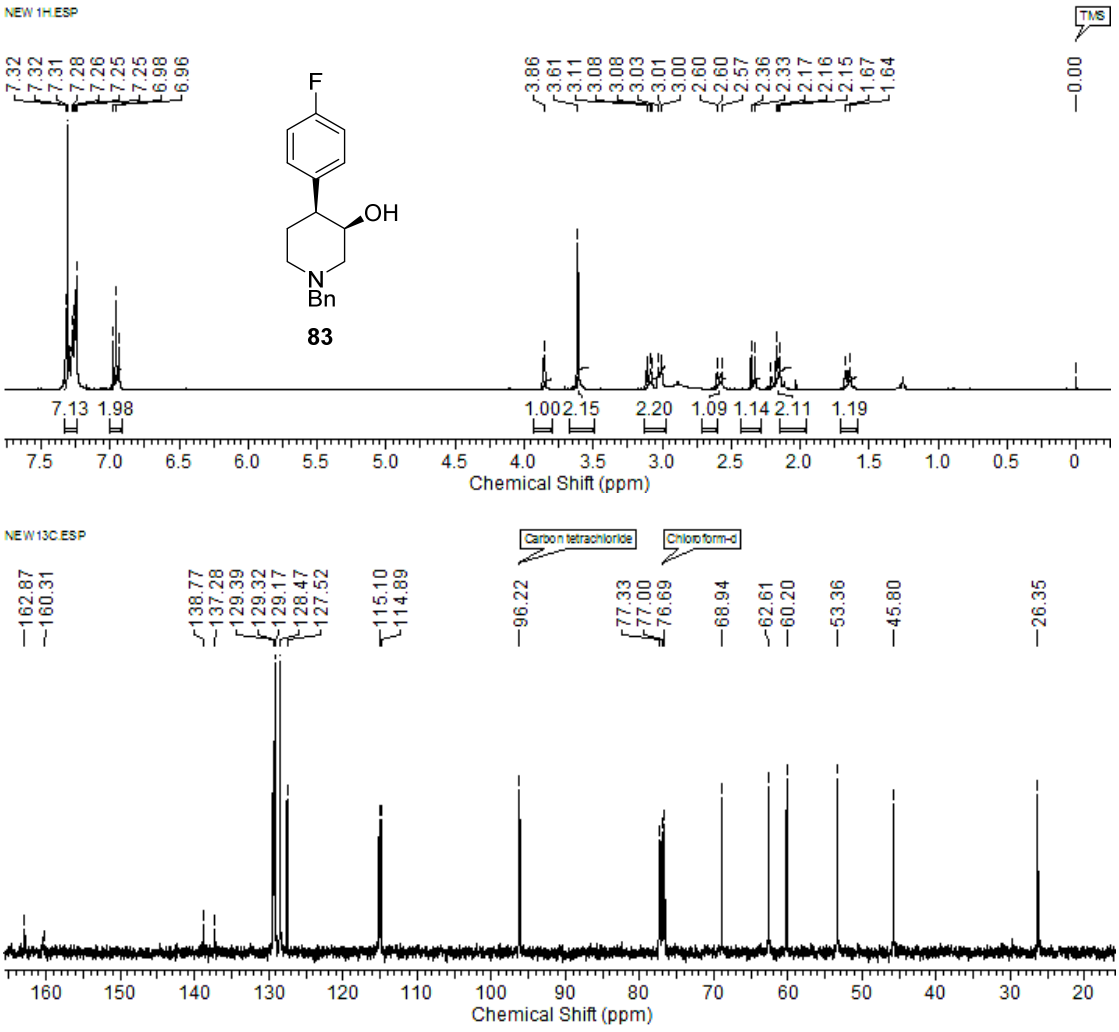


Fig. 14: ^{1}H and ^{13}C NMR spectra of **83**

Next, oxidation of alcohol **83** was carried out using Swern oxidation conditions (DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78 ^{o}C) to give the corresponding ketone **84** in 80% yield. The formation of ketone **84** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1722 cm^{-1} typically for ketone functionality. Its ^{1}H NMR spectrum showed the appearance of a triplet signal at δ 3.51 (1H) corresponding to methine proton at benzylic position and other peaks at δ 2.89 (d, J = 13. 9 Hz, 1H), δ 3.34 (dd, J = 1.5, 13.9 Hz, 1H) due to methylene protons (N-**C**$\mathbf{H_2}$-CO). Its ^{13}C NMR spectrum showed a typical signal at δ 205.1 for carbonyl carbon of ketone (**Fig. 15**).

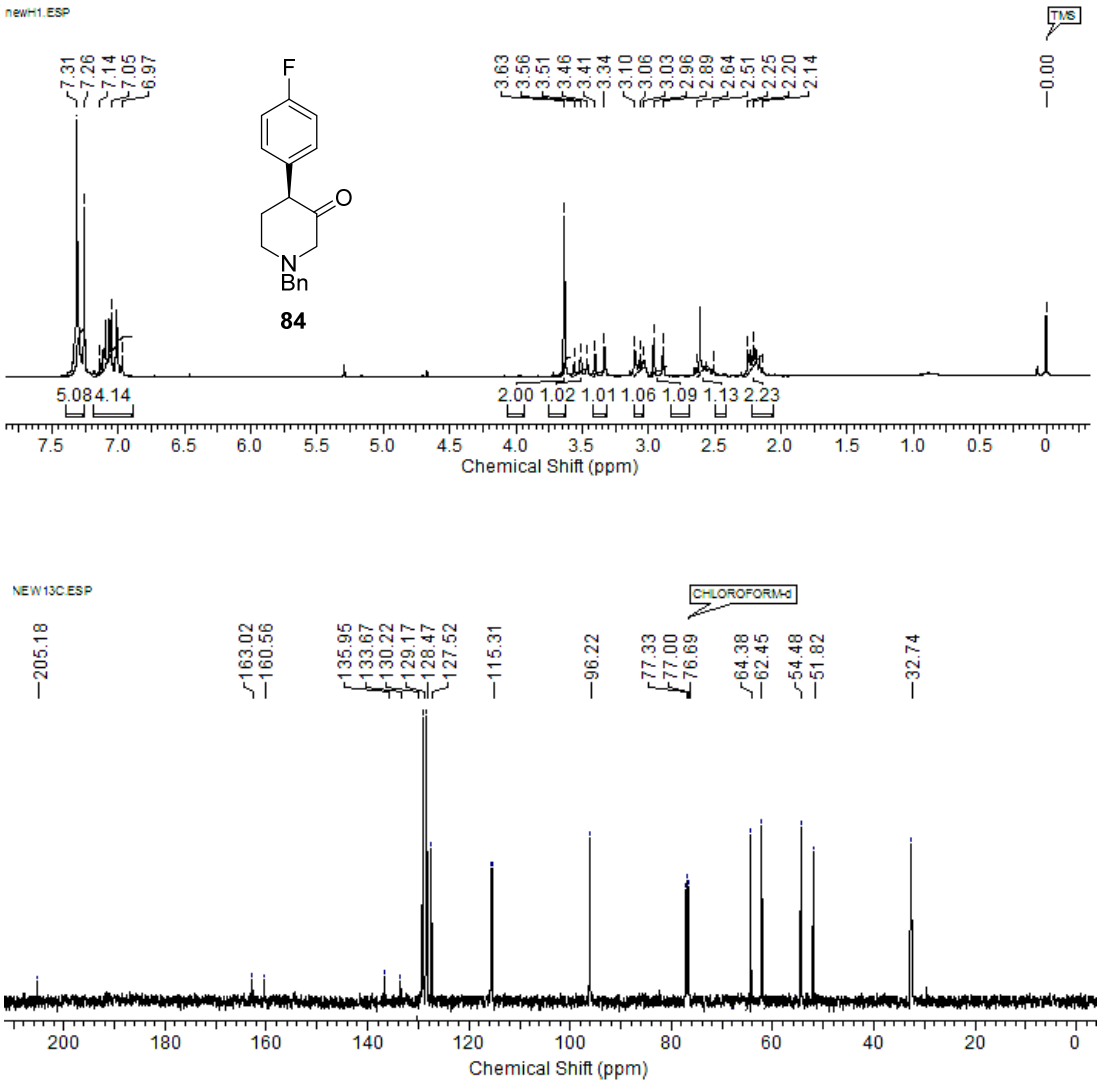


Fig. 15: ^{1}H and ^{13}C NMR spectra of **84**

Cyclic ketone **84** on Wittig olefination with Ph_3P=CHOMe produced enol ether **85** as a single diastereomer in 60% yield.[35] The formation of enol ether **85** was confirmed by its ^{1}H NMR spectrum which showed typical signals at δ 5.14 (1H) and δ 3.42 (3H) corresponding to olefinic and methoxy (O-**C**$\mathbf{H_3}$) protons respectively. This was further confirmed by its ^{13}C NMR spectrum, which showed carbon signals at δ 114.9 and δ 143.3 due to olefinic carbons and δ 59.4 due to methyl carbon attached to hydroxyl group (**Fig. 16**).

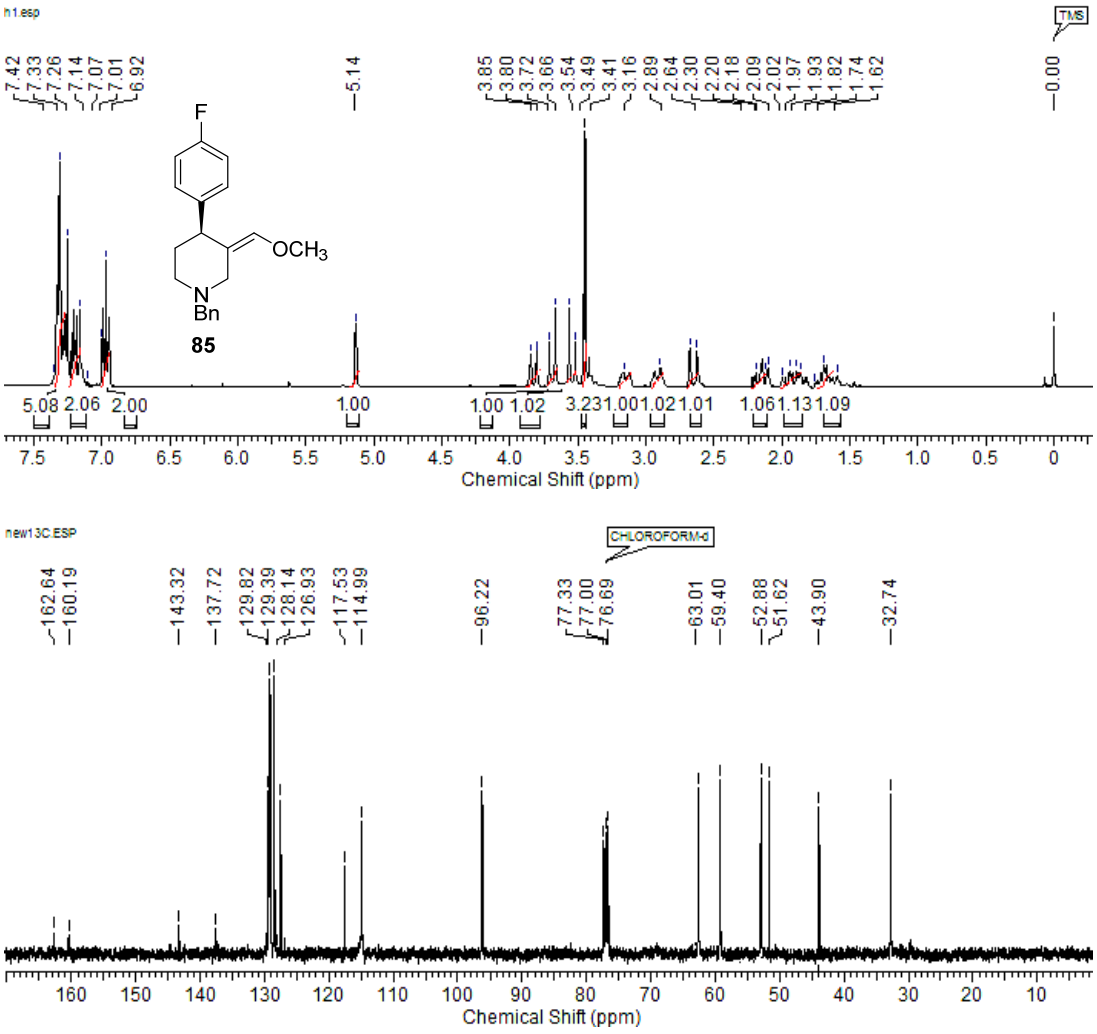


Fig. 16: ^{1}H and ^{13}C NMR spectra of **85**

Acid hydrolysis of enol ether **85** gave aldehyde **86** in 82% yield. Newly generated stereocenter at 3rd position is α- due to the β-aryl ring present at 4th position. The formation of aldehyde **86** was confirmed by its ^{1}H NMR spectrum, which showed a typical proton signal at δ 9.46 (1H) corresponding to aldehydic proton. The disappearance of signal for methyl protons and olefinic protons further confirmed the formation of **86**. Its ^{13}C NMR spectrum, which showed a typical signal at δ 203.0 for carbonyl carbon of aldehyde group (**Fig. 17**).

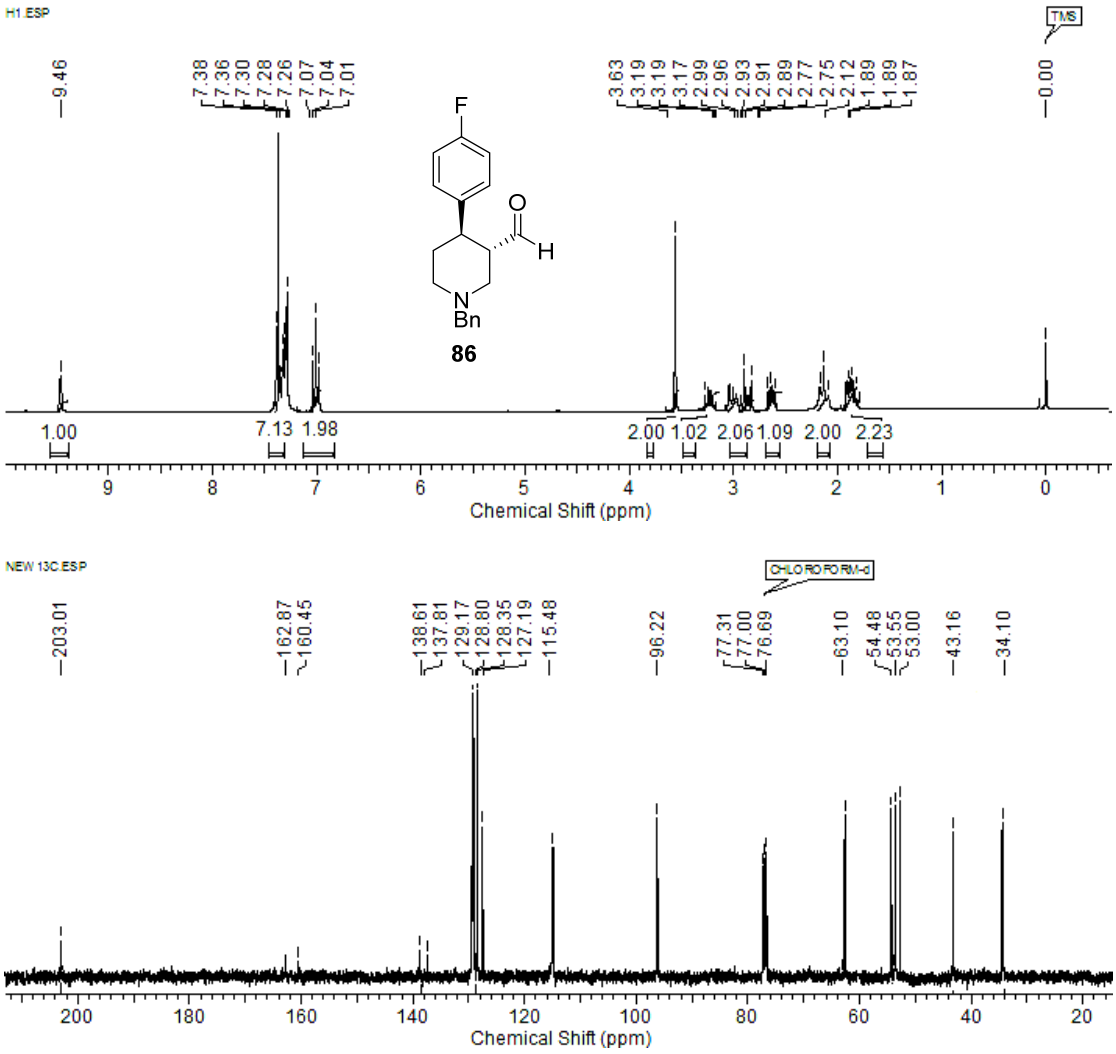


Fig. 17: ^{1}H and ^{13}C NMR spectra of **86**

Finally, reduction of aldehyde **86** was carried out using $NaBH_4$ that provided the known intermediate *N*-benzyl amino alcohol **48** (overall yield 17% from **8b**), thus constituting a formal synthesis of (-)-paroxetine **26** (**Scheme 20**). The ^{1}H NMR spectrum of **48** showed signals at δ 3.54 (d, J = 13.2 Hz, 1H) and δ 3.63 (d, J = 13.2 Hz, 1H) due to the corresponding benzylic protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 63.4 and δ 64.3 due to methylene carbons attached to hydroxyl and benzylic postion respectvily (**Fig. 18**).

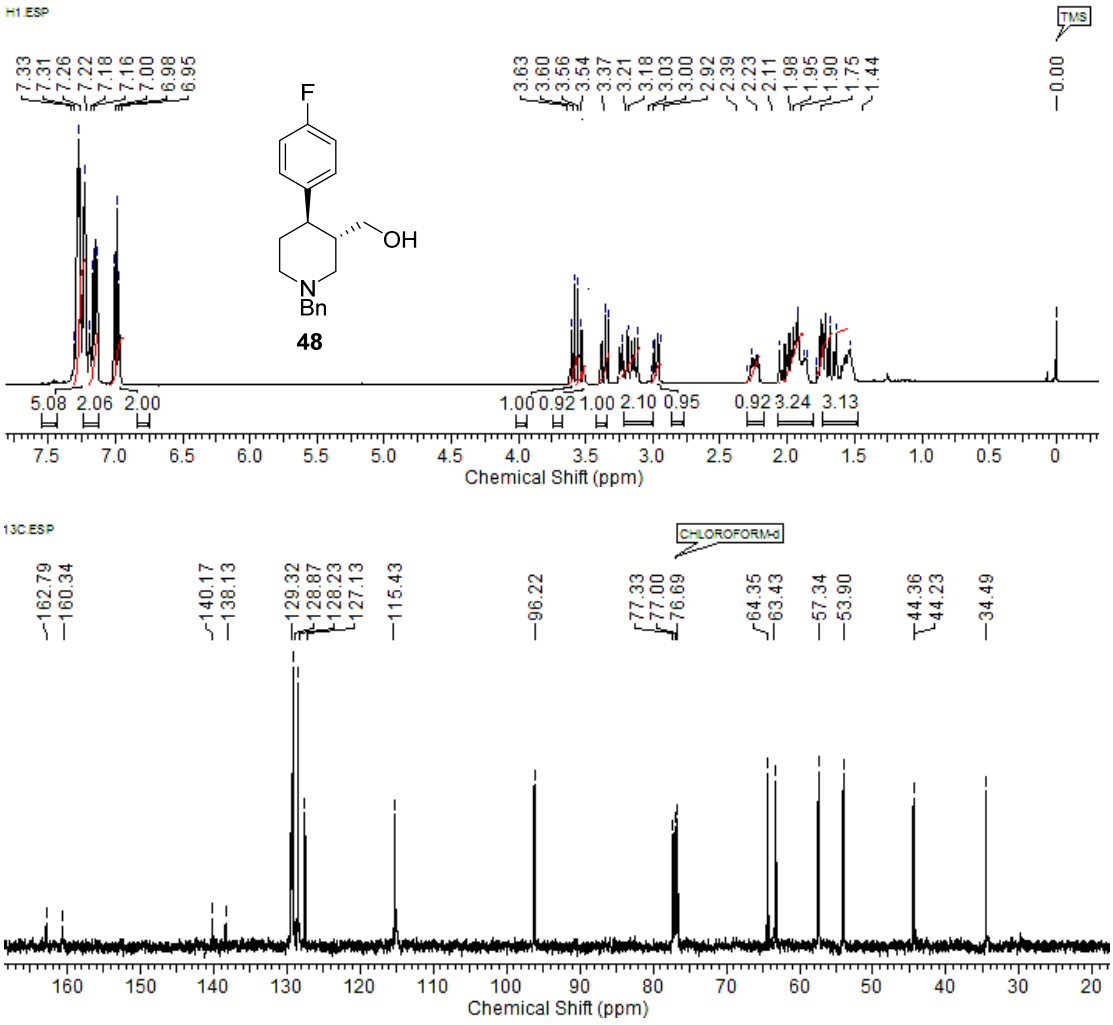
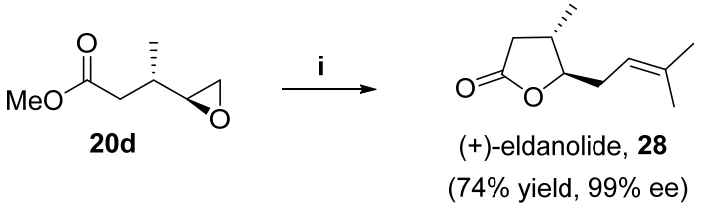


Fig. 18: ^{1}H and ^{13}C NMR spectra of **48**

(b) Synthesis of (+)-eldanolide (28)

Synthesis of natural product, (+)-eldanolide, **28** was achieved by the regioselective ring opening of chiral epoxide **20d** with $(Me)_2C{=}CHMgBr$ followed by intramolecular lactonization, all in a single step with 74% yield (**Scheme 21**).



Scheme 21: (i) $(CH_3)_2C{=}CHMgBr$, $CuBr.SMe_2$, THF, -30 to 0 °C, 5 h, 74%.

The formation of (+)-eldanolide **28** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1781 cm^{-1} typical for lactone carbonyl group. Its ^{1}H NMR spectrum showed two singlets at δ 1.64 (3H) and δ 1.73 (3H) for the corresponding methyl protons (-C-**C**$\mathbf{H_3}$) and a typically proton signal at δ 5.17 (m, 1H) for olefinic proton. This was further confirmed by its ^{13}C NMR spectrum, which showed typical carbons signals at δ 118.0 and δ 135.4 due to olefinic carbon and δ 176.1 for carbonyl carbon of lactone moiety (**Fig. 19**). The absolute configuration of both *N*-benzyl amino alcohol **48** and (+)-eldanolide **28** was further ascertained by comparing their optical rotations with those reported in the literature.[29, 33]

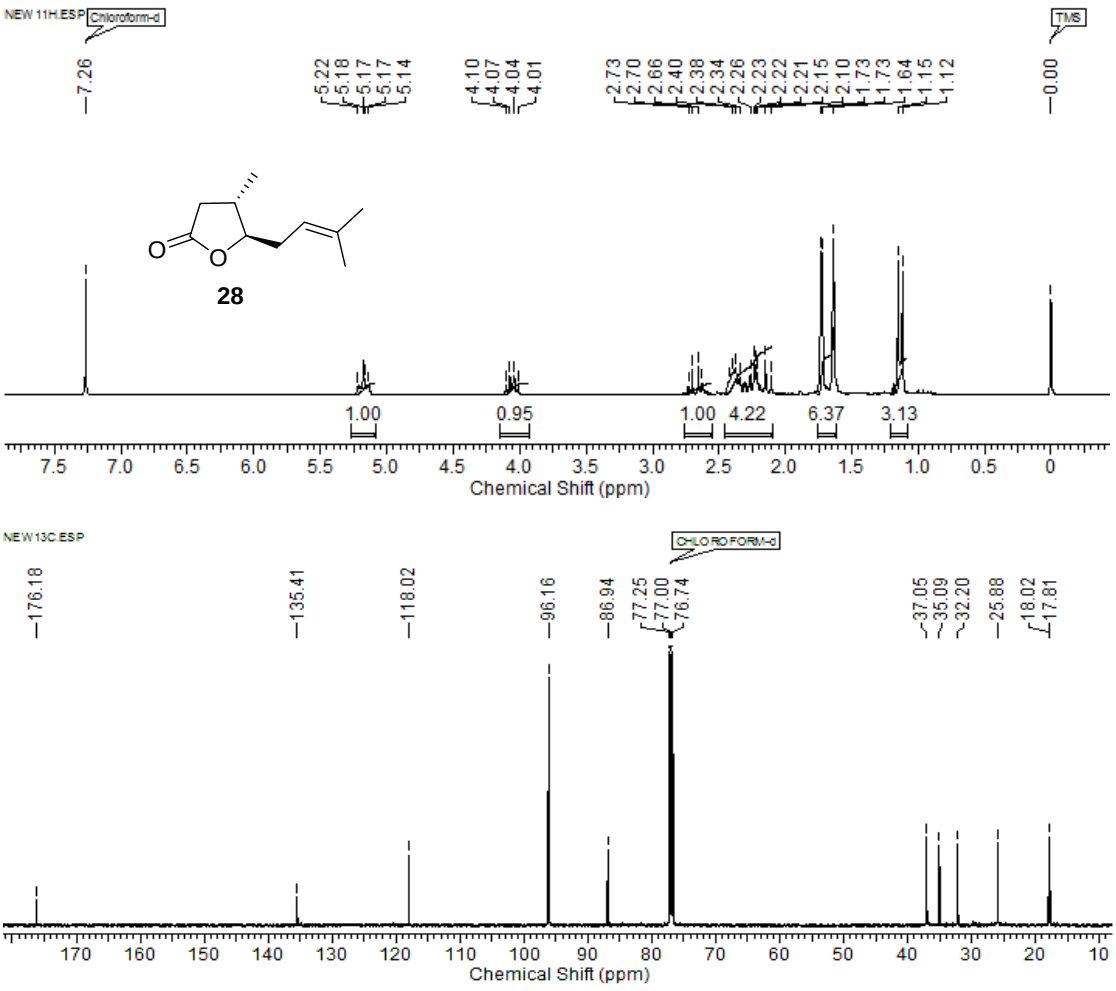


Fig. 19: ^{1}H and ^{13}C NMR spectra of **28**

1.2.4 Conclusion

In conclusion, we have successfully demonstrated an efficient, formal synthesis of (-)-paroxetine **26** and (+)-eldanolide **28** *via* two-stereocentred HKR of *racemic* 3-substituted epoxy esters as a key step. The high enantiomeric excess obtained in this method render the present protocol a good alternative to the known methods.

1.2.5 Experimental section

((2*R*, 3*S*)-3-(4-Fluorophenyl)-5-oxotetrahydrofuran-2-yl)methyl methanesulfonate (81)

To a stirred solution of lactone **8b** (4.76 mmol) in CH_2Cl_2 (15 mL) and triethylamine (0.86 mL, 6.19 mmol), mesyl chloride (0.44 mL, 5.71 mmol) was added at 0 ^oC under nitrogen atmosphere. The resulting solution was stirred at the same temperature for 1 h. After the completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **81**. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (7:3) as eluent gave **81** in pure form.

Yield: 92%, yellow oil; $[\alpha]_D^{25}$ = -31.9 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1150, 1420, 1789, 2836; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.74 (dd, *J* = 9.7, 17.8 Hz, 1H), 3.05 (dd, *J* = 9.1, 18.1 Hz, 1H), 3.08 (s, 3H), 3.64 (q, *J* = 9.1 Hz, 1H), 4.27-4.49 (m, 2H), 4.61 (m, 1H), 7.04-7.13 (m, 2H), 7.22-7.29 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.75, 37.70, 41.89, 67.53, 82.94, 116.14 (d, *J* = 21.6 Hz), 128.93 (d, *J* = 8.1 Hz), 133.76 (d, *J* = 3.3 Hz), 162.36 (d, *J* = 248.1 Hz), 174.04; **HRMS (*m/z*):** calculated $[M+H]^+$ for $C_{12}H_{14}FO_5S$: 289.0540 found: 289.0536.

(4*S*, 5*R*)-5-(Azidomethyl)-4-(4-fluorophenyl)dihydrofuran-2(3*H*)-one (82)

To a stirred mixture of crude **81** (3.47 mmol) in DMF (10 mL), sodium azide (0.27 g,

4.16 mmol) was added. Reaction mixture was stirred for 8 h at 80 ^{o}C. After the completion of the reaction (monitored by TLC), it was extracted with EtOAc (3 x 10 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 **77**, which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (8:2) as eluent to give pure **82** as colorless oil.

Yield: 95%, colorless oil; $[\alpha]_D^{25}$ = -89.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1065, 1217, 1789, 2105; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.71 (dd, *J* = 9.9, 17.8 Hz, 1H), 3.03 (dd, *J* = 8.9, 17.7 Hz, 1H), 3.26-3.71 (m, 3H), 4.51 (m, 1H), 7.02-7.11 (m, 2H), 7.18-7.26 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.91, 42.95, 51.86, 84.31, 116.52 (d, *J* = 21.6 Hz), 128.83 (d, *J* = 8.1 Hz), 134.02 (d, *J* = 3.3 Hz), 162.32 (d, *J* = 247.7 Hz), 174.08; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{11}H_{11}FN_3O_2$: 236.0830 found: 236.0829.

(4*S*, 5*R*)-4-(4-Fluorophenyl)-5-hydroxypiperidin-2-one (80)

To a solution of **82** (4.25 mmol) in dry methanol $Pd(OH)_2$ (0.05 g) was added and the reaction mixture was stirred under an atmosphere of H_2 (1 atm) for 24 h at 25 ^{o}C. After the completion of the reaction (monitored by TLC), it was filtered over Celite and the filtrate was concentrated under reduced pressure to provide amide **80**, which was purified by column chromatography using ethyl acetate: methanol (9:1) to obtain pure **80**.

Yield: 98%, colorless solid; **mp** 176 °C; $[\alpha]_D^{25}$ = +74.7 (*c* 1, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1130, 1636, 1652, 2912, 3439; **^{1}H NMR** (200 MHz, MeOH-d_4) δ 2.33 (dd, *J* = 5.6, 17.3 Hz, 1H), 2.82 (dd, *J* = 12.2, 29.5 Hz, 1H), 3.11 (m, 1H), 3.25 (m, 1H), 3.48 (dd, *J* = 2.9, 13.0 Hz, 1H), 4.01 (m, 1H), 6.90-6.99 (m, 2H), 7.25-7.32 (m, 2H); **^{13}C NMR** (50 MHz, $MeOD_4$): δ 33.46, 42.97, 50.19, 67.27, 115.93 (d, *J* = 21.6 Hz),

130.81 (d, *J* = 7.7 Hz), 138.64, 163.41 (d, *J* = 243.5 Hz), 174.57; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{11}H_{13}FNO_2$: 210.0925 found: 210.0925.

(3*R*, 4*S*)-1-Benzyl-4-(4-fluorophenyl)piperidin-3-ol (83)

To a solution of lactam **80** (0.5 g, 2.39 mmol) in dry THF (10 mL), $BH_3{\cdot}SMe_2$ (0.45 mL, 4.78 mmol) was added dropwise at 0 ^oC under N_2 atmosphere and the mixture was then refluxed for 6 h. After the completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. Without purification, the crude amino alcohol was then dissolved in CH_2Cl_2/H_2O (1:1, 10 mL) and Na_2CO_3 (0.75 g, 7.71 mmol) was added, followed by dropwise addition of benzyl bromide (0.34 mL, 2.87 mmol). The reaction mixture was refluxed for 8 h. After the completion of the reaction (monitored by TLC), it was extracted with CH_2Cl_2 (3 x 5 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 **83**, which was purified by column chromatographic purification with silica gel using petroleum ether: ethyl acetate (7:3) as eluent gave **83** in pure form.

Yield: 85%, colorless solid, **mp** 114 °C; $\mathbf{[\alpha]_D^{25}}$ = +37.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1134, 1509, 2856, 2936, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.66 (m, 1H), 2.15-2.36 (m, 2H), 2.35 (d, *J* = 11.3 Hz, 1H), 2.59 (d, *J* = 12.3 Hz, 1H), 3.06 (dd, *J* = 7.0, 30.4 Hz, 2H), 3.61 (s, 2H), 3.86 (s, 1H), 6.94-6.98 (m, 2H), 7.24-7.32 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.35, 45.80, 53.36, 60.20, 62.61, 68.94, 115.10 (d, *J* = 20.8 Hz), 127.52, 128.47, 129.17, 129.39 (d, *J* = 6.9 Hz), 137.28, 138.77, 161.59 (d, *J* = 243.5 Hz); **Anal. Calcd** for $C_{18}H_{20}FNO$ requires C, 75.76; H, 7.06; N, 4.91; found C, 75.78; H, 7.01; N, 4.82%.

(*S*)-1-Benzyl-4-(4-fluorophenyl)piperidin-3-one (84)

To a stirred solution of oxalyl chloride (0.15 mL, 1.75 mmol) in dry CH_2Cl_2 (3 mL),

DMSO (0.2 mL, 2.63 mmol) was added at -78 ^{o}C under N_2 atmosphere. The reaction mixture was stirred for 20 min followed by the addition of a solution of alcohol **83** (0.25 g, 0.88 mmol) in CH_2Cl_2 (1 mL). After stirring for 1 h at -78 ^{o}C, triethylamine (0.5 mL, 3.5 mmol) was added and it was stirred at room temperature for additional 15 min, after which it was quenched with H_2O (5 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 3 mL), the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the corresponding crude ketone **84**, which was used for next reaction without purification.

Yield: 80%, colorless oil; $[\alpha]_D^{25}$ = +11.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 846, 1117, 1244, 1722, 2840; **^{1}H NMR** (200 MHz, $CDCl_3$) 2.14-2.25 (m, 2H), 2.51-2.64 (m, 1H), 2.89 (d, *J* = 13. 9 Hz, 1H), 3.03-3.10 (m, 1H), 3.34 (dd, *J* = 1.5, 13.9 Hz, 1H), 3.51 (t, *J* = 9.2 Hz, 1H), 3.63 (s, 2H), 6.97-7.14 (m, 4H), 7.31 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 32.74, 51.97, 54.36, 62.45, 64.46, 115.31 (d, *J* = 11.5 Hz), 127.52, 128.47, 129.17, 130.22 (d, *J* = 8.4 Hz), 133.67, 136.91, 161.79 (d, *J* = 247.4 Hz), 205.18; **Anal. Calcd** for $C_{18}H_{18}FNO$ requires C, 76.30; H, 6.40; N, 4.94; found C, 76.58; H, 6.32; N, 4.88%.

(*S*)-1-Benzyl-4-(4-fluorophenyl)-3-(methoxymethylene)piperidine (85)

To a stirred solution of methoxymethyltriphenylphosphonium chloride (0.48 g, 1.41 mmol) in dry THF (3 mL), *n*-butyl lithium (1.6 M in hexane, 0.5 mL, 0.84 mmol) was added dropwise at 0 ^{o}C under N_2 atmosphere. The resulting red solution was stirred at this temperature for 1 h, after which solution of **84** (0.2 g, 0.7 mmol) in THF (1.5 mL) was added dropwise and the reaction mixture was allowed to stirred for another 48 h at 0 ^{o}C After the completion of the reaction (monitored by TLC), it was extracted with CH_2Cl_2 (3 x 5 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 enol ether **85**, which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave pure enol ether **85** as colorless oil.

Yield: 60%, colorless oil; $[\alpha]_D^{25}$ = +7.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1129, 1222, 1603, 1675, 2933; **^{1}H NMR** (200 MHz, $CDCl_3$) 1.62-1.74 (m, 1H), 1.93 (m, 1H), 2.09 (m, 1H), 2.64 (d, *J* = 12.3 Hz, 1H), 2.89 (d, *J* = 11.6 Hz, 1H), 3.16 (d, *J* = 10.3 Hz, 1H), 3.41 (s, 3H), 3.54 (d, *J* = 13.0 Hz, 1H), 3.72 (d, *J* = 13.0 Hz, 1H), 3.80 (d, *J* = 12.3 Hz, 1H), 5.14 (s, 1H), 6.92 (m, 2H), 7.14-7.42 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 32.71, 43.90, 51.62, 52.88, 59.40, 63.01, 114.99 (d, *J* = 21.2 Hz), 117.53, 126.93, 128.14, 129.39, 129.82 (d, *J* = 7.6 Hz), 137.75, 137.93, 143.32, 161.41 (d, *J* = 245.0 Hz); **Anal. Calcd** for $C_{20}H_{22}FNO$ requires C, 77.14; H, 7.12; N, 4.50; found C, 77.24; H, 7.15; N, 4.41%.

(3*S*, 4*R*)-1-Benzyl-4-(4-fluorophenyl)piperidine-3-carbaldehyde (86)

To a solution of enol ether **85** (0.06 g, 0.19 mmol) in THF (3 mL), 0.1 M aqueous H_2SO_4 (2.8 mL, 0.28 mmol) was added. The solution was refluxed for 12 h, after which it was allowed to cool to room temperature and a saturated solution of $NaHCO_3$ (10 mL) was added. The resulting mixture was extracted with diethyl ether (3 x 5 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the corresponding crude aldehyde **86**, which was used for next reaction without further purification.

Yield: 82%, yellow oil; $[\alpha]_D^{25}$ = -19.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 833, 1160, 1224, 1721, 2938; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.89 (m, 2H), 2.12 (t, *J* = 11.1 Hz, 2H), 2.77 (m, 1H), 2.89-2.99 (m, 2H), 3.17-3.19 (m, 1H), 3.63 (m, 2H), 7.01-7.07 (m, 2H), 7.26-7.38 (m, 7H), 9.46 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR** (100 MHz,

$CDCl_3$): δ 34.10, 43.16, 53.00, 53.55, 54.48, 63.10, 115.48 (d, *J* = 21.4 Hz), 127.19, 128.35, 128.80, 129.17, 137.81, 138.61, 161.66 (d, *J* = 242.0 Hz), 203.01; **Anal. Calcd** for $C_{19}H_{20}FNO$ requires C, 76.74; H, 6.78; N, 4.71; found C, 76.70; H, 6.82; N, 4.66%.

((3*S*, 4*R*)-1-Benzyl-4-(4-fluorophenyl)piperidin-3-yl)methanol (48)

To a solution of this crude aldehyde **86** in MeOH (2 mL), $NaBH_4$ (0.01 g, 0.21 mmol) was added at 0 ^oC and the stirred reaction mixture stirred for 1 h at 25 ^oC. After the completion of the reaction (monitored by TLC), it was treated with 2 N aq. NaOH (5 mL) and extracted with CH_2Cl_2 (3 x 5 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 intermediate **48**, which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave pure **48** as colorless oil.

Yield: 72%, colorless oil; $\mathbf{[\alpha]_D^{25}}$ = -15.2 (*c* 1, $CHCl_3$) {lit.[35] $[\alpha]_D^{20}$ -16.0 (*c* 0.8, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 739, 836, 1130, 1510, 2934, 3424; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44-1.90 (m, 3H), 1.95-2.11 (m, 3H), 2.23-2.39 (m, 1H), 2.92 (m, 1H), 3.18-3.21 (m, 2H), 3.37 (dd, *J* = 2.5, 11.2 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 6.95-7.00 (m, 2H), 7.18-7.22(m, 2H), 7.26-7.33 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 34.49, 44.23, 44.36, 53.90, 57.34, 63.43, 64.35, 115.43 (d, *J* = 21.2 Hz), 127.13, 128.23, 128.87, 129.32, 138.13, 140.17 (d, *J* = 3.0 Hz), 162.06 (d, *J* = 245.0 Hz); **Anal. Calcd** for $C_{19}H_{22}FNO$ requires C, 76.22; H, 7.41; N, 4.68; found C, 76.23; H, 7.35; N, 4.61%.

(+)-Eldanolide (28)

To a stirred solution of $CuBr.SMe_2$ (0.128 g, 0.62 mmol, 30 mol %) in THF (5 mL), 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 10 mL, 5.2 mmol) was

added at -20 ^{o}C under nitrogen atmosphere and stirring was continued for 30 min. A solution of epoxide **20d** (0.39 g, 2.08 mmol) in THF (5 mL) was added dropwise and the stirring continued for 3 h at -20 ^{o}C to 0 ^{o}C. Then the mixture was quenched with saturated aq. NH_4Cl solution (5 mL) and the product extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product **28** which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (9:1) as eluent gave pure **28** as colorless oil.

Yield: 74%, colorless oil; $\mathbf{[\alpha]_D^{25}}$ = +48.5 (*c* 1, MeOH) {lit.[34] $[\alpha]_D^{20}$ +48.2 (*c* 1.15, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1155, 1230, 1420, 1781, 2822, 2931; **^{1}H NMR** (200 MHz, $CDCl_3$) 1.12 (d, *J* = 6.6 Hz, 3H), 1.64 (s, 3H), 1.73 (s, 3H), 2.10-2.42 (m, 4H), 2.66 (m, 1H), 4.07 (q, *J* = 6.2 Hz, 1H), 5.17 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.81, 18.02, 25.88, 32.20, 35.09, 37.05, 86.94, 118.02, 135.41, 176.18; **Anal. Calcd** for $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59; found C, 71.20; H, 9.42%.

1.2.6 References

1. (a) Bandichhor, R.; Nosse, B; Reiser, O. *Top. Curr. Chem.,* **2005**, *243*, 43; (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem. Int. Ed.,* **2009**, *48*, 9426.
2. (a) Masuda, M.; Nishimura, K. *Phytochemistry,* **1971**, *10*, 1401; (b) Rao, Y. S. *Chem. Rev*., **1976**, *76*, 625; (c) Rao, Y. S. *Chem.Rev*., **1964**, *64*, 353.
3. (a) Stephens, B. E.; Liu, F. *J. Org. Chem*., **2009**, *74*, 254; (b) Venkataiah, M.; Reddipalli, G.; Jasti, L. S.; Fadnavis, N. W. *Tetrahedron: Asymmetry,* **2011**, *22*, 1855; (c) Risi, C. D.; Fanton, G.; Pollini, G. P.; Trapella, C.; Valente, F.; Zanirato, V. *Tetrahedron: Asymmetry,* **2008**, *19*, 131; (d) Pelletier, S. W.; in *Alkaloids: Chemical and Biological Perspectives*, ed. Wiley: New York, 1985, vol. 3; (e) M. G. P. Buffat, *Tetrahedron,* 2004, **60**, 1701.
4. (a) Ha, H.-J.; Yim, Y.-G. *Synth. Commun.,* **2000**, *30*, 581; (b) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.,* **1980**, *102*, 2118; (c) Bartlett P. A.; Myerson, J. *J. Am. Chem. Soc*., **1978**, *100*, 3950; (d) Yadav, J. S.; Reddy, P. S. R. *Synthesis,* **2007**, 1070; (e) Bartlett, P. A.; Myerson, J. *J. Org. Chem*., **1979**, *44*, 1625; (f) Mori, K.; Umemura, T. *Tetrahedron Lett*., **1982**, *23*, 3391.
5. (a) Toullec, P. Y.; Genin, E.; Antoniotti, S.; Genet, J.-P.; Michelet, V.; *Synlett,* **2008**, 707; (b) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genet, J.-P.; Michelet, V. *J. Am. Chem.*

Soc., **2006**, *128*, 3112; (c) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.,* **1999**, *121*, 669; (d) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol*., **2005**, *9*, 285; (e) Ferrie, L.; Bouyssi, D.; Balme, G. *Org. Lett*., **2005**, *7*, 3143; (f) Peng, Z.-H.; Woerpel, K. A.; *Org. Lett*., **2001**, *3*, 675; (g) Okada, T.; Sakaguchi, Shinada, K.; T.; Ohfune, Y. *Tetrahedron Lett.,* **2011**, *52*, 5740; (h) Mao, B.; Ji, Y.; Fananas-Mastral, M.; Caroli, G.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed*., **2012**, *51*, 3168; (i) Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J.-x. *J. Org. Chem*., **2002**, *67*, 1738.

6. Tokunaga, M.; larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science,* **1997**, *277*, 936.
7. (a) Wilkinson, R. G.; Shepherd, R. G.; Thomas, J. P.; Baughn, C. *J. Am. Chem. Soc*. **1961**, *83*, 2212; (b) Shepherd, R. G.; Wilkinson, R. G. *J. Med. Chem*. **1962**, *5*, 823; (c) Wilkinson, R. G.; Cantrall, M. B.; Shepherd, R. G. *J. Med. Chem*. **1962**, *5*, 835.
8. Some, among many, notable examples: (a) Fumagillin: Tarbell, D. S.; Carman, R. M.; Chapman, D. D.; Cremer, S. E.; Cross, A. D.; Huffman, K. R.; Kuntsmann, M.; McCorkindale, N. J.; McNally, J. G.; Rosowsky, A.; Varino, F. H. L.; West, R. L. *J. Am. Chem. Soc.* **1961**, *83*, 3096. (b) Ovalicin: Sigg, H. P.; Weber, H. P. *Hel*v. *Chim. Acta* **1968**, *51*, 1395. (c) Coriolin: Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215. (d) Disparlure: Bierl, B. A.; Beroza, M.; Collier, C. W. *Science* **1970**, *170*, 87.
9. For reviews and lead references, see: (a) Winstein, S.; Henderson, R. B. *Heterocyclic Compounds*, Vol. 1; Elderfield, R. C., Ed.; Wiley: New York, 1950; Chapter 1; (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737; (c) Barto´k, M.; La´ng, K. L. *Small Ring Heterocycles In The Chemistry of Heterocyclic Compounds*, Vol. *42*, Part 3; Hassner, A., Ed.; Wiley: New York, **1985**; Chapter 1.
10. Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 6776.
11. For an in depth discussion of practical considerations in kinetic resolution reactions, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth., Catal.* **2001**, *343*, 5.
12. (a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939; (b) Larrow, J. F.; Jacobsen, E. N. *Org. Synth*. **1997**, *75*, 1.
13. For the most effective catalyst developed thus far for the asymmetric dihydroxylation of terminal olefins, see: (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448. For a general review of the AD reaction, see: (b) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
14. Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc*., **1997**, *119*, 1482.
15. Ha, H.-J.; Yoon, K.-N.; Lee, S.-Y.; Park, Y.-S.; Lim, M.-S.; Yim, Y.-G. *J. Org. Chem*., **1998**, *63*, 8062.
16. Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc*., **2001**, *123*, 6457.
17. Zhang, Y.; Wang, Y.; Dai, W.-M. *J. Org. Chem*., **2006**, *71*, 2445.
18. (a) Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron*, **2007**, *63*, 2745; (b) Kumar, P.; Gupta, P. *Synlett*, **2009**, 1367; (c) Yu, Q.; Wu, Y.; Xia, L.-J.; Tang, M.-H.; Wu, Y.-L. *Chem. Commun.,* **1999**, 129; (d) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. Eur. J*., **2006**, *12*, 1397; (e) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.,* **2004**, *126*, 2495; (f) Kumar, P.; Naidu, S. V. *J. Org.*

Chem., **2006**, *71*, 3935.

19. (a) Reddy, R. S.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun*., **2010**, *46*, 5012; (b) Devalankar, D. A.; Sudalai, A. *Tetrahedron Lett.,* **2012**, *53*, 3213; (c) Kim, Y.-J.; Tae, J. *Synlett*, **2006**, 61.
20. (a) Gonzalez, F. B.; Bartlett, P. A. *Org. Synth.,* **1986**, *64*, 175; (b) Chamberlin, A. R.; Dezube, M.; Dussault, P. *Tetrahedron Lett*., **1981**, *22*, 4611.
21. (a) Strunz, G. M.; Findlay, J. A. The Alkaloids; Academic: New York, **1985**; Vol. 26, p 89. (b) Viera, E.; Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Güller, R.; Hirth, G.; Märki, H. P.; Müller, M.; Oefner, C.; Stadler, H.; Wilhelm, M.; Wostl, W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1397. (c) Güller, R.; Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Hirth, G.; Jenny, C.; Kansy, M.; Montavon, F.; Muller, M.; Oefner, C.; Stadler, H.; Vieira, E.; Wilhelm, M.; Wostl, W.; Marki, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1403. (d) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (e) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.
22. De Risi, C.; Fanton, G.; Pollini, G. P.; Trapella, C.; Valente, F.; Zanirato, V. *Tetrahedron: Asymmetry* **2008**, *19*, 131.
23. Gunasekara, N. S.; Noble, S.; Benfield, P. *Drugs* **1998**, *55*, 85.
24. Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem. Eur. J*., **2003**, *9*, 1566.
25. Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852.
26. Chen, C. Y.; Chang, B. R.; Tsai, M. R.; Chang, M. Y.; Chang, N. C. *Tetrahedron* **2003**, *59*, 9383.
27. Paraskar, A. S. Sudalai A. *Tetrahedron* **2006**, *62*, 4907.
28. Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4305.
29. Chavan, S. P.; Khobragade,D.A.; Pathak, A.B.; Kalkote, U. R. *Synth. Commun.* **2007**, *37*, 3143.
30. Hynes, P. S.; Stupple, P. A.; Dixon, D.J.; *Org. Lett.* **2008**, *10*, 1389.
31. Somaiah, S.; Sashikanth, S.; Raju, V.; Reddy, K. V. *Tetrahedron: Asymmetry* **2011**, *22*, 1.
32. Paulsen, H.; Hoppe, D. *Tetrahedron,* **1992**, *48*, 5667.
33. Villar, F.; Equey, O.; Renaud, P. *Org. Lett*., **2000**, *2*, 1061
34. Kong, L.; Zhuang, Z.; Chen, Q.; Deng, H.; Tang, Z.; Jia, X.; Li, Y.; Zhai, H. *Tetrahedron: Asymmetry,* **2007**, *18*, 451.
35. Bower, J. F.; Riis-Johannessen, T.; Szeto, P.; Whitehead, A. J.; Gallagher, T. *Chem. Commun.,* **2007**, 728.

Chapter II

Enantioselective Synthesis of (+)-Deoxoprosophylline and (S, S)-3-Hydroxypipecolic Acid via Hydrolytic Kinetic Resolution of Azido Epoxides

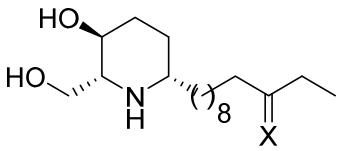
1. "A concise synthesis of (+)-deoxoprosophylline via Co(III)(salen)-catalyzed two stereocentered HKR of racemic azido epoxides" **Devalankar, D. A**.; Sudalai, A. *Tetrahedron Lett*. **2012**, *53*, 3213.
2. "Concise enantioselective syntheses of (+)-L-733,060 and (2*S*, 3*S*)-3-hydroxypipecolic acid by Co(III)(salen)-catalyzed two-stereocenter hydrolytic kinetic resolution of racemic azido epoxides" **Devalankar, D. A.**; Chouthaiwale, P. V.; Sudalai. A. *Synlett*, **2014**, *25*, 102.

Section I

A Concise Synthesis of (+)-Deoxoprosophylline *via* Co(III)(salen)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxides

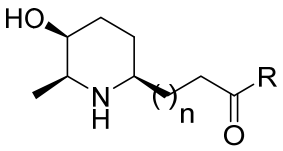
2.1.1 Introduction and Pharmacology

Alkaloids with multifunctionalized piperidine rings are found abundantly in nature.[1] In particular, prosopis alkaloids containing 2,6-disubstituted piperidin-3-ols have been isolated from the leaves of an African plant, *Prosopis africana* Taub.[2] Typical representatives include prosophylline (**1**), deoxoprosophylline (**2**) and Cassia alkaloids such as (+)-cassine (**3**) and carpamic acid (**4**) **(Fig. 1)**. These naturally occurring piperidine alkaloids and their derivatives are medicinally important as they possess anaesthetic, analgesic and antibiotic properties.[2,3]



1, (+)-prosophylline (X = O)

2, (+)-deoxoprosophylline (X = H, H)



3, (+)-cassine (n = 9, R = CH_3)

4, (+)-carpamic acid (n = 6, R = OH)

Fig. 1: Some bioactive 2,6-*cis*-disubstituted piperidin-3-ols

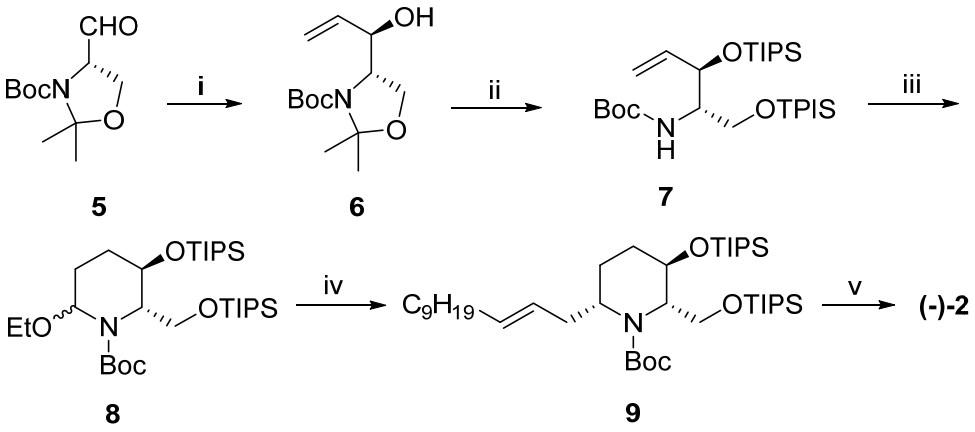
Structurally, these compounds possess a polar head group essentially required for the inhibition of various glycosidases and lipophilic aliphatic tail that serves to facilitate transfer across lipid membranes.[4,5] These interesting structural features and therapeutic potential make them attractive synthetic targets.

2.1.2 Review of Literature

Various syntheses of (+)-deoxoprosophylline **2** have been documented in the literature , most of which are based on chiral pool strategies. Some of the interesting and important synthetic routes to (+)/(-)-deoxoprosophylline (**2**) are described below.

Ojima's approach (1998)[6]

Ojima *et al.* have achieved the synthesis of (-)-deoxoprosophylline (**2**) using (*S*)-Garner's aldehyde **5**, which on reaction with vinylmagnesium bromide afforded allyl alcohol **6**. Removal of the acetonide group of **6**, followed by protection of hydroxyl groups as TIPS ether gave compound **7**. Rh-BIPHEPHOS complex catalyzed cyclohydrocarbonylation of **7** at 65 ^{o}C and 4 atm of CO and H_2 (1:1) in ethanol afforded the key cyclic intermediate **8**, which on reaction with allyl silane in the presence of $BF_3.OEt_2$ at -78 ^{o}C gave the compound **9**. Compound **9** on sequential hydroxyl group deprotection, hydrogenation and *N*-Boc deprotection delivered (-)-deoxoprosophylline **2 (Scheme 1)**.

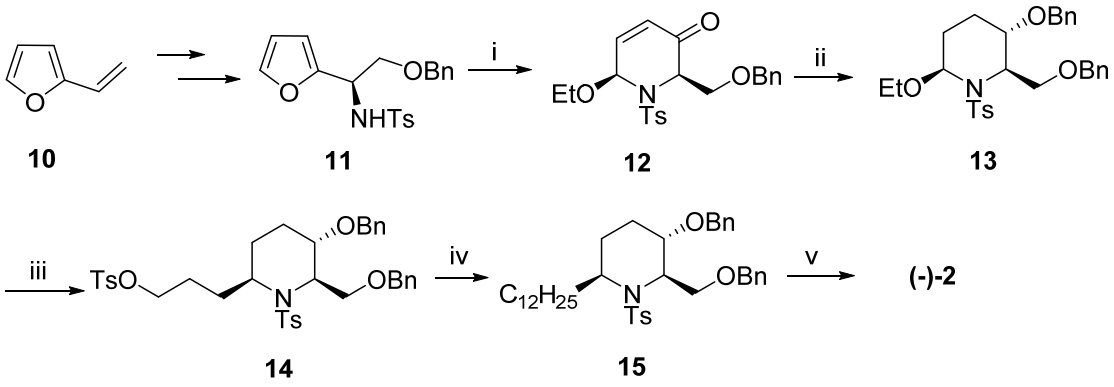


Scheme 1: (i) CH_2=CHMgBr, THF, -30 ^{o}C to 0 ^{o}C, 1 h, 77%; (ii) (a) *p*-TSA, MeOH, 1 h, 25 ^{o}C, 95%; (b) TIPSCl, imid., DMF, 0 ^{o}C, 2 h, 72%; (iii) Rh(acac)$(CO)_2$ (1 mol%), BIPHEPHOS (2 mol%), H_2/CO (1/1, 4 atm), EtOH, 65 ^{o}C, 14 h, 96%; (iv) $C_9H_{19}CH(SiMe_3)CH{=}CH_2$, $BF_3.Et_2O$, -78 ^{o}C, 4 h, 90%; (v) (a) Bu_4NF, THF, 25 ^{o}C, 12 h, 38%,; (b) Pd/C, H_2, C_2H_5OH, 2 h, 25 ^{o}C; (c) TFA, CH_2Cl_2, 25 ^{o}C, 4 h (77%, 2 steps).

Zhou's approach (1998)[7]

Zhou and co-workers have reported the synthesis of (-)-deoxoprosophylline **2** from α-furyl ethylene **10**. Compound **10** was converted into α-furyl amine derivative **11** in five steps. Treatment of **11** with *m*-CPBA and the resultant dihydropyridone hydroxyl

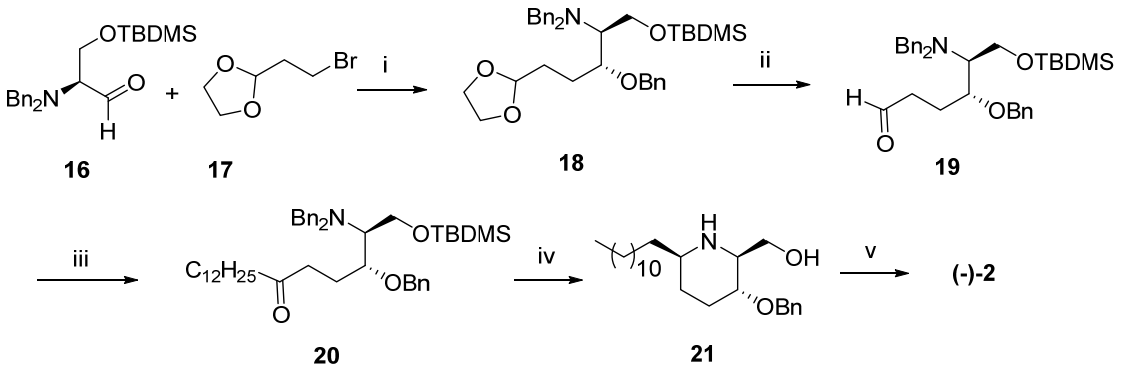
group was protected to give the compound **12**. Reduction of keto group of **12** followed by protection of the hydroxyl group as benzyl ether gave compound **13**. Treatment of **13** with allyl trimethyl silane followed by hydroboration and tosylation delivered **14**. Treatment of **14** with Grignard reagent afforded compound **15**. Finally deprotection of hydroxyl and amino groups gave (+)-deoxoprosophylline **2 (Scheme 2)**.



Scheme 2: (i) (a) *m*-CPBA, CH_2Cl_2, 25 ^oC, 82%; (b) $CH(OEt)_3$, $BF_3.OEt_2$, 4 A^o M.S., THF, 0 ^oC, 97%; (ii) (a) $NaBH_4$, MeOH, 0 ^oC, 88%; (b) BnBr, NaH, THF, 25 ^oC, 85%; (iii) (a) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78 ^oC, 67%; (b) $BH_3.SMe_2$, THF, NaOH, H_2O_2, 45%; (c) Ts-Im, NaH, THF, 0 ^oC, 87%; (iv) $C_9H_{19}MgBr$, Li_2CuCl_4, THF, 0 ^oC, 68%; (v) (a) 10% Pd/C, H_2, EtOH, 84%; (b) Na/NH_3, -78 ^oC, 46%.

Zhu's approach (2001)[8]

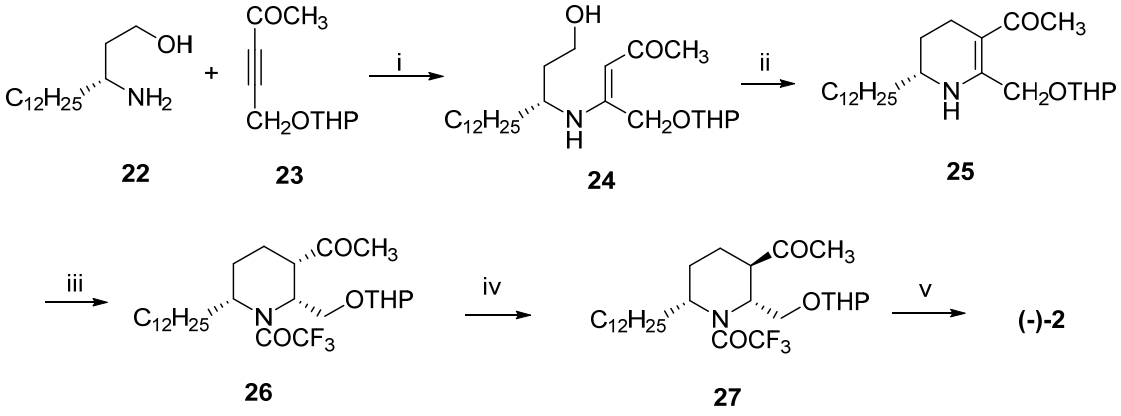
Zhu *et al.* have synthesized (-)-deoxoprosophylline **2** from serine as chiral pool source. Nucleophilic addition of Grignard reagent **17** (Buchi Grignard reagent) with serine aldehyde **16** followed by protection of the secondary alcohol as its benzyl ether gave **18**. Acidic hydrolysis of dioxolane **18** gave the aldehyde **19**. Reaction of aldehyde **19** with dodecyl magnesium bromide and subsequent oxidation of alcohol gave ketone **20**. Catalytic hydrogenation of **20** under acidic conditions furnished the (-)-deoxoprosophylline **2** in 19% overall yield **(Scheme 3)**.



Scheme 3: (i) (a) Mg, THF, 25 °C, 86%; (b) NaH, BnBr, Bu_4NI, THF, 0°C to 25 °C, 85%; (ii) (a) 3N HCl–THF, (b) TBDMSCl, imidazole, DMF, 25 °C, 90%; (iii) (a) $C_{12}H_{25}Br$, Mg, dibromoethane, THF, 70°C, 80%; (b) DMSO, $(COCl_2)$ then Et_3N, 84%; (iv) $Pd(OH)_2$, cyclohexene, EtOH, reflux; (v) Pd/C, MeOH, 73%.

Dawei 's approach (2003)[9]

Dawei *et al.* have reporeted the synthesis of (-)-deoxoprosophylline **2** from chiral amino alcohol **22**, which was prepared by Davies procedure.[10] Michael addition of **22** to the alkynone **23** gave the enamine **24**, which on treatment with PPh_3 and CCl_4 followed by refluxing in acetonitrile afforded cyclic enamine **25**. Hydrogenation of **25** anhydride to provide the amide **26**. Epimerization of the 3-acetyl group of **26** was

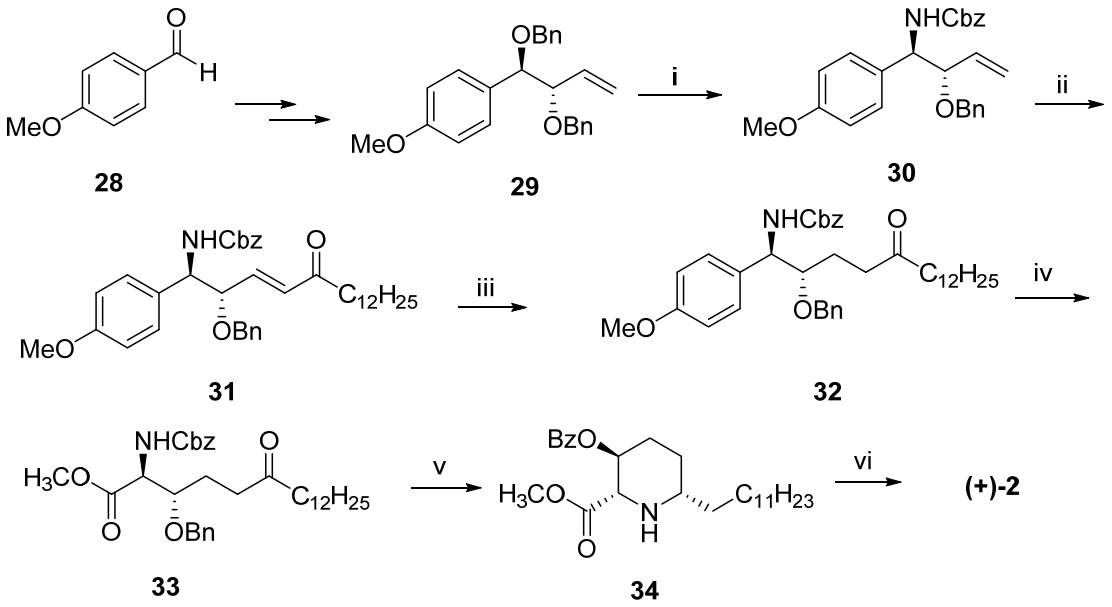


Scheme 4: (i) DMF, 25 °C, 82%; (ii) (a) PPh_3, CBr_4, Et_3N,CH_2Cl_2; (b) Et_3N, CH_3CN, reflux, 76%; (iii) (a) PtO_2, H_2, AcOH; (b) $(CF_3CO)_2O$, Et_3N, DMAP; (iv) DBU, THF, 25 °C, 87%; (v) (a) 95% H_2O_2, $(CF_3CO)_2O$, NaH_2PO_4, CH_2Cl_2; (b) HCl-MeOH, 45%.

achieved by treating with DBU to give **27**. Treatment of **27** with trifluoroperacetic acid afforded the Baeyer-Villiger product, which was hydrolysed to deliver the (-)-deoxoprosophylline **2 (Scheme 4)**.

Jung's approach (2007)[11]

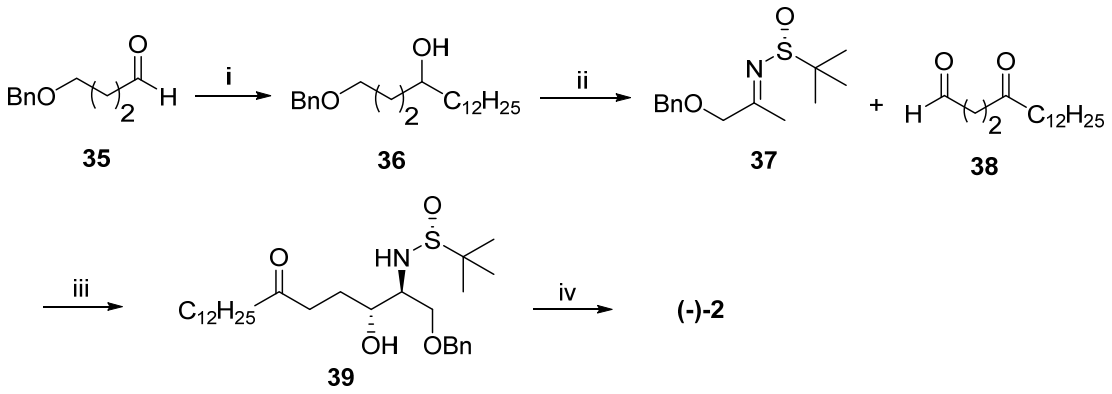
Jung *et al.* have described the synthesis of (+)-deoxoprosophylline **2** *via* the stereoselective amination of *anti*-1,2-dibenzyl ether using chlorosulfonyl isocyanate (CSI) as key step. Synthesis began with *anti*-1,2-dibenzyl ether **29** obtained from *p*-anisaldehyde **28**. The regioselective and diastereoselective amination of *anti*-1,2-dibenzyl ether **29** using chlorosulfonyl isocyanate gave *anti*-1,2-amino alcohol **30**. Further *anti*-1,2-amino alcohol **30** was then converted into (+)-deoxoprosophylline **2** using cross-metathesis and Pd-catalyzed intramolecular cyclization **(Scheme 5)**.



Scheme 5: (i) (a) CSI, Na_2CO_3, toluene, -78 ^oC, 24 h; (b) 25% Na_2SO_3, 24 h; (ii) pentadec-1-en-3-one, Hoveyda 2nd Grubbs catalyst, toluene, 80 ^oC, 48 h; (iii) PtO_2, H_2, EtOAc, 2 h; (iv) (a) cat. $RuCl_3$, $NaIO_4$, H_2O/CH_3CN/EtOAc (2:1:1), 4 h; (b) CH_2N_2, Et_2O, 0 ^oC, 1 h; (v) 10% Pd/C, H_2, MeOH, 24 h; (vi) (a) $LiAlH_4$, THF, 12 h; (b) 8 N KOH, MeOH, reflux, 10 h.

Liu's approach (2008)[12]

Liu *et al.* have reported the synthesis of (-)-deoxoprosophylline **2** using SmI_2-mediated cross-coupling of chiral *N-tert*-butanesulfinyl imine **37** with 4-oxohexadecanal **38**. Removal of the chiral auxiliary in **39** followed by acidic hydrogenation gave (-)-deoxoprosophylline **2 (Scheme 6)**.

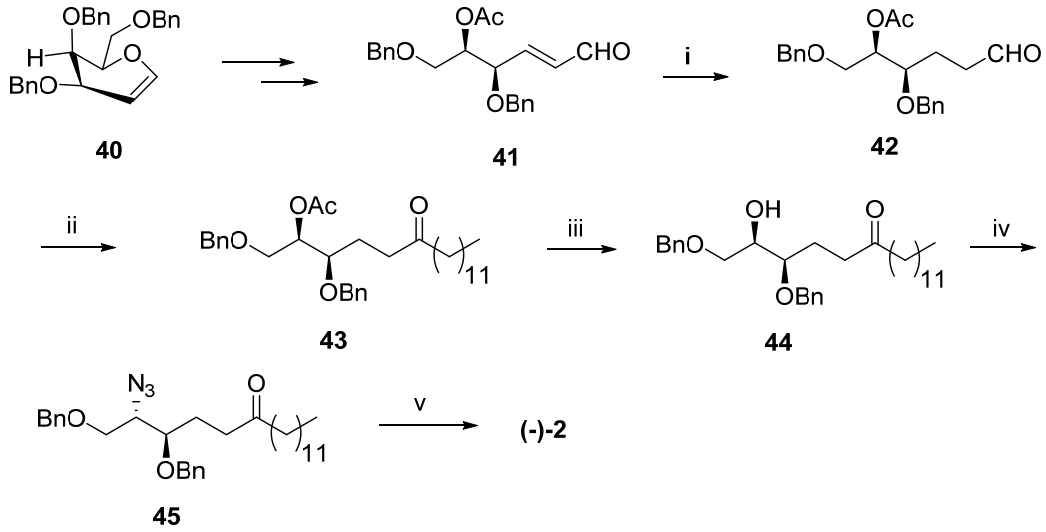


Scheme 6: (i) $C_{12}H_{25}MgBr$, THF, 88%; (ii) (b) Pd/C, H_2, MeOH, 25 ^oC, 12 h; (b) PCC, CH_2Cl_2, 5 h, two steps 81%; (iii) SmI_2, *t*-BuOH, THF, 83%; (iv) (a) HCl/MeOH, MeOH; (b) $Pd(OH)_2/C$, H_2, EtOH, 4 h, then conc. HCl, 33 h, two steps 58%.

Vankar's approach (2010)[13a]

Vankar *et al.* have described the synthesis of (-)-deoxoprosophylline starting from chiral staring material, 3,4,6-*tri*-*O*-benzyl glycol **40**. Thus, 3,4,6-*tri*-O-benzylated glycals **40** was subjected to Perlin hydrolysis followed by acetylation to afford *trans*-enals **41**. Chemoselective saturation of double bond in **41** was carried out under H_2/Pd-C conditions to give **42**. The obtained aldehyde **42** was subjected to Grignard reaction using dodecylmagnesium bromide and further oxidation of the free hydroxyl gave ketones **43**. Methanolysis of acetate **43** gave the hydroxy ketone **44**. Conversion of the hydroxyl group of **44** as mesylate followed by an SN_2 displacement with sodium azide gave the azido derivative **45**. These azido ketone **45** underwent

reductive ring closure followed by debenzylation gave single isomer of (-)-deoxoprosophylline **2 (Scheme 7)**.



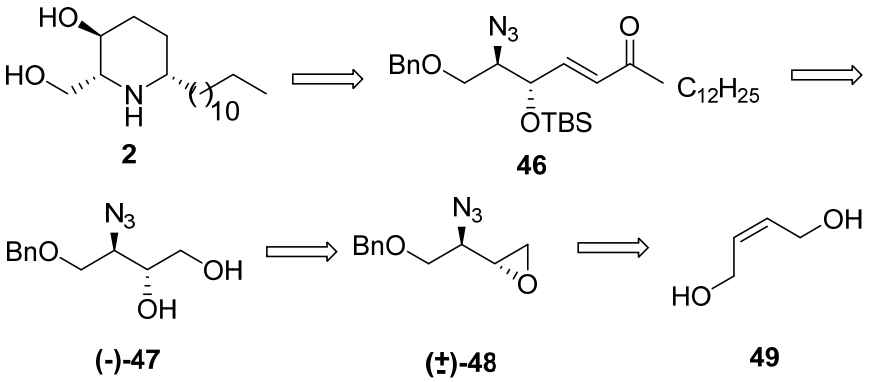
Scheme 7: (i) H_2/Pd-C, EtOAc, 30 min, 92%; (ii) (a) $C_{12}H_{25}MgBr$, Et_2O, -78 ^oC; (b) CrO_3, Py, Ac_2O, CH_2Cl_2, 0 ^oC, 71% for two steps; (iii) NaOMe (cat.), MeOH, 2 h, 86%; (iv) (a) MsCl, Et_3N, 0 ^oC, CH_2Cl_2, 20 min, 96%; (b) NaN_3, DMF, 110 ^oC, 6 h, 85%; (v) H_2/$Pd(OH)_2$.C, MeOH, 82%.

2.1.3. Present Work

2.1.3.1 Objective

As can be seen from the above discussion, the reported methods of synthesis (+)-deoxoprosophylline **2** suffer from certain limitations such as the use of chiral building blocks, exotic reagents, involvement of longer reaction sequences, low overall yields, etc. We have recently reported a flexible method that employs Co-catalyzed Hydrolytic Kinetic Resolution (HKR) of racemic *anti*-azido epoxides with two-stereocenters to generate the corresponding diols and epoxides in high optical purity (97-99% ee) in a single step.[14] This section describes an enantioselective synthesis of (+)-deoxoprosophylline (**2**) by employing two-stereocentered HKR of racemic azido epoxides. From the retrosynthetic analysis as shown in (**Scheme 8**), the *anti*-azido diol **47** could be visualized as an important precursor for the synthesis of target

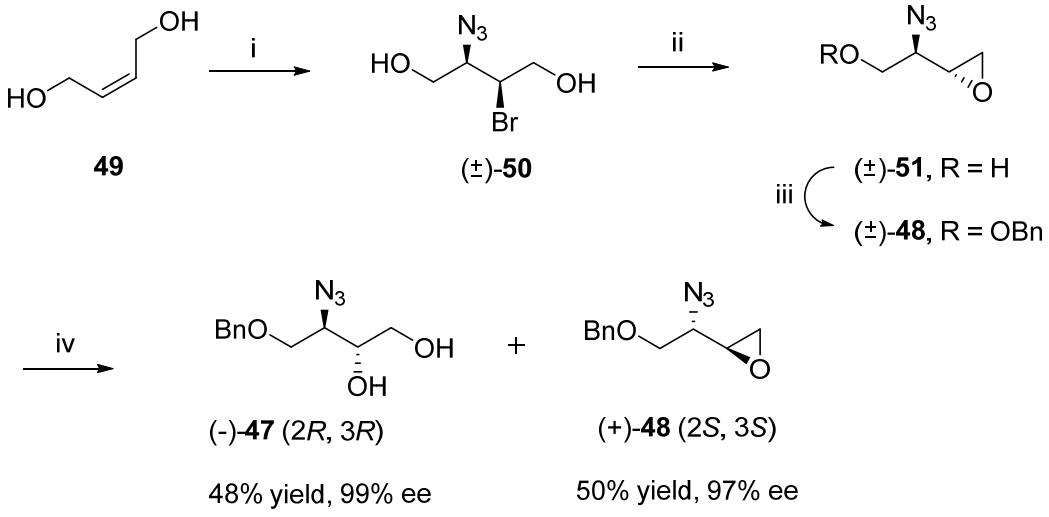
molecule **2**. The synthesis of **47** could then be achieved by means of Co-catalyzed Hydrolytic Kinetic Resolution of racemic azido epoxide **48**. The racemic azido epoxide **48** can readily prepared in three steps from *cis*-butenediol **(49)**.



Scheme 8: Retrosynthetic analysis of (+)-deoxoprosophylline **2**

2.1.3.2 Results and Discussion

Accordingly, the synthesis of (+)-deoxoprosophylline (**2**) has commenced with commercially available *cis*-2-butene-1,4-diol (**49**), which on treatment with NBS in the presence of NaN_3, gave bromo azide **50** in 89% yield (**Scheme 9**).



Scheme 9: Reaction conditions: (i) NBS (1.2 equiv), NaN_3 (2 equiv), CH_3CN/H_2O (3:1), 0 ^oC, 3 h, 89%; (ii) NaOH, THF, 0 ^oC, 3 h, 84%; (iii) BnBr, NaH, DMF, -40 ^oC, 2 h, 94%; (iv) (*S*,*S*)-Co^{III} (salen) (0.5 mol %), H_2O (0.49 equiv), 0 to 25 ^oC, 12 h.

The formation of azido bromide, (±)-**50** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **50** showed a typical signal at δ 4.12-4.20 (m, 1H) for methine (-CH-N_3) proton. Its ^{13}C NMR showed a typical carbon signal at δ 54.3 due to carbon attached to bromo group (**Fig. 2**).

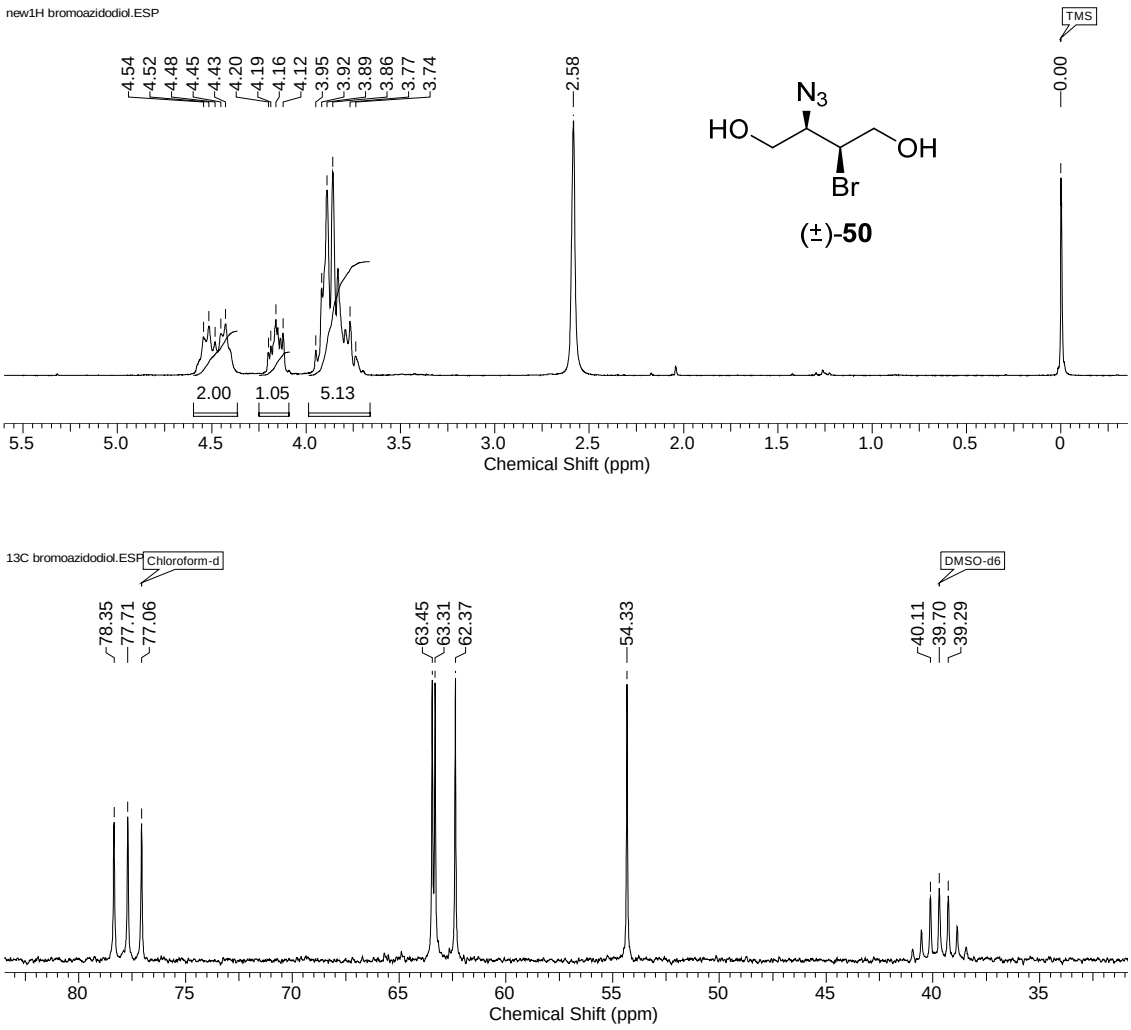


Fig. 2: ^{1}H and ^{13}C NMR spectra of **(±)-50**

The bromo azide **50** was readily transformed into racemic *anti*-azido epoxide **51** (84% yield) under base treatment (NaOH, dry THF, 0 ^{o}C). The formation of epoxide was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **51** showed proton signals at δ 2.82-2.90 (m, 2H) and δ 3.47-3.49 (m, 1H) for methylene and

methine protons of epoxide ring respectively. Its ^{13}C NMR showed typical carbon signals at δ 44.8 and δ 50.61 due to carbons of epoxide ring **(Fig. 3).**

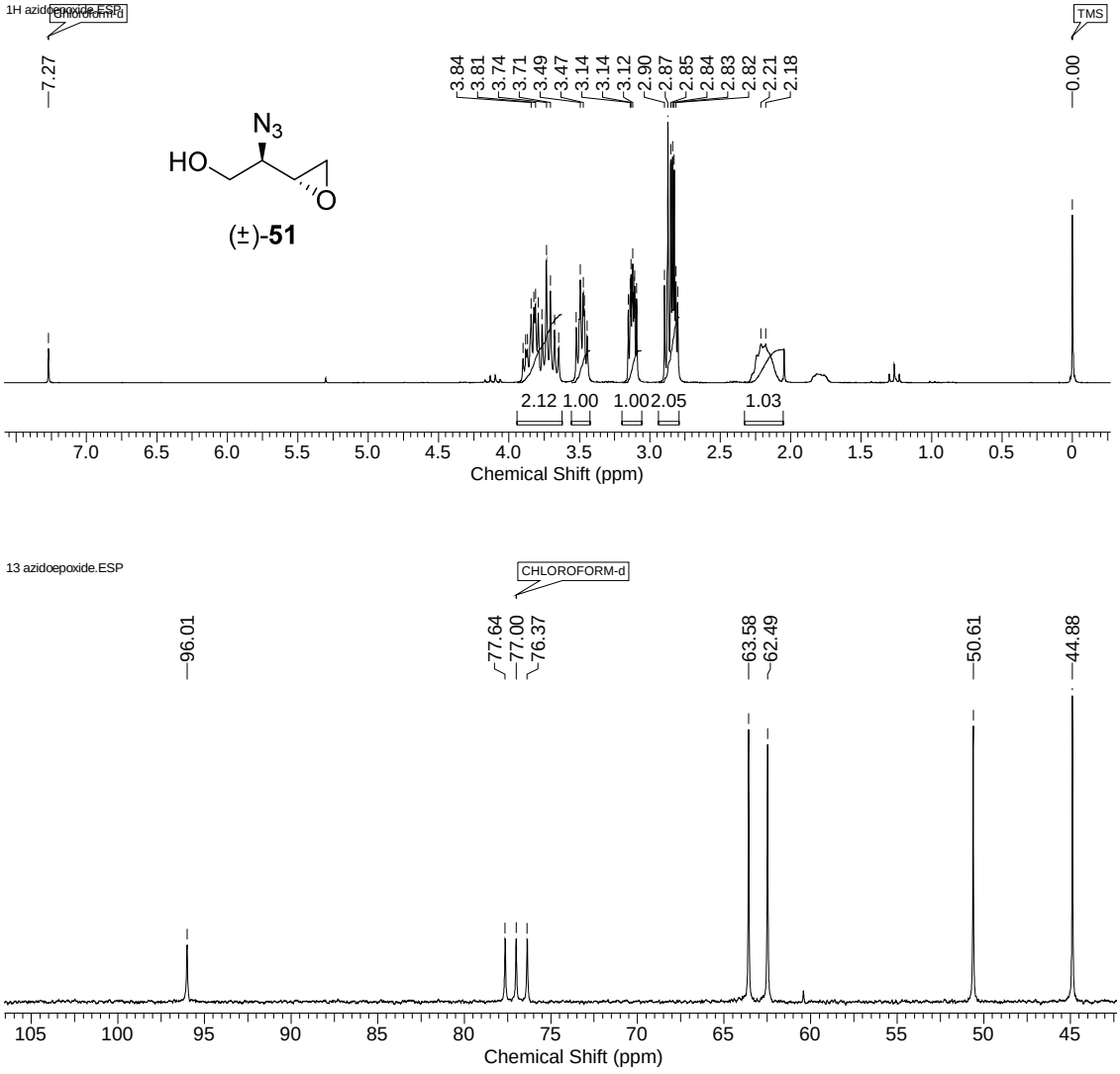


Fig. 3: ^{1}H and ^{13}C NMR spectra of **(±)-51**

The protection of primary hydroxyl group in azido epoxide **51** as benzyl ether (BnBr, NaH, DMF, -40 ^{o}C) was achieved to give protected racemic azido epoxide (±)-**48** in 94% yield. The formation of compound **48** was confirmed by the appearance of proton signals, in its ^{1}H NMR spectrum, at δ 7.33 (m, 5H) for aromatic protons of benzyl group. Its ^{13}C NMR spectrum showed a typical signal at δ 73.4 for benzylic carbon confirming benzyl protected azido epoxide **48 (Fig. 4)**.

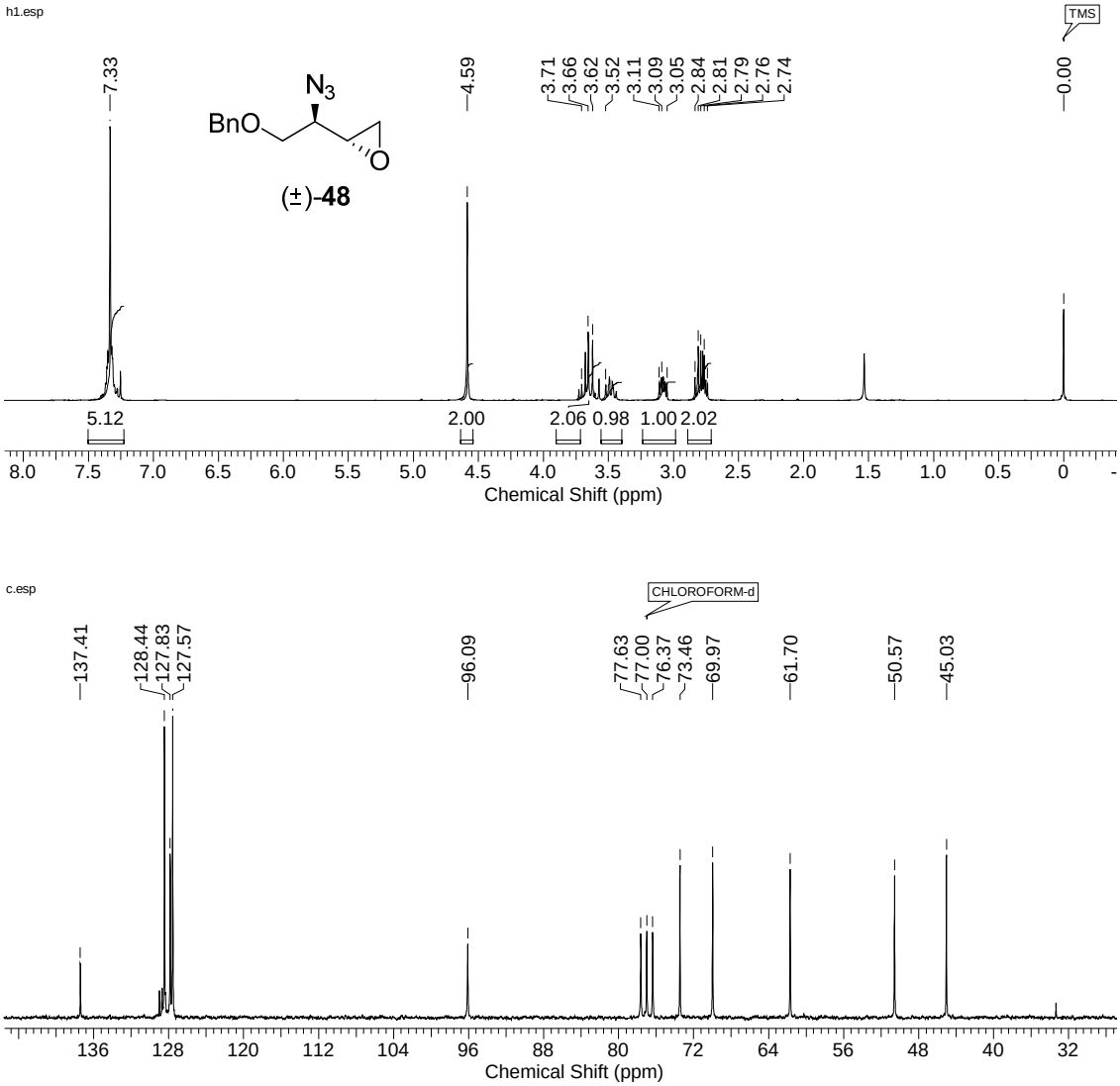


Fig. 4: ^{1}H and ^{13}C NMR spectra of **(±)-48**

Compound **48** was then subjected to HKR with (*S*, *S*)-salen Co(III)OAc complex (0.5 mol %) and H_2O (0.49 equiv), which produced the corresponding diol **47** (48%, 99% ee) and chiral epoxide **48** (50%, 97% ee) in high optical purity (**Scheme 9**). The diol (-)-**47** was, however, readily separated from epoxide (+)-**48** by a simple flash column chromatographic purification over silica gel. The enantiomeric excess of azido diol (-)-**47** was determined from chiral HPLC analysis; Chiralpak OD-H **(Fig. 5)**.

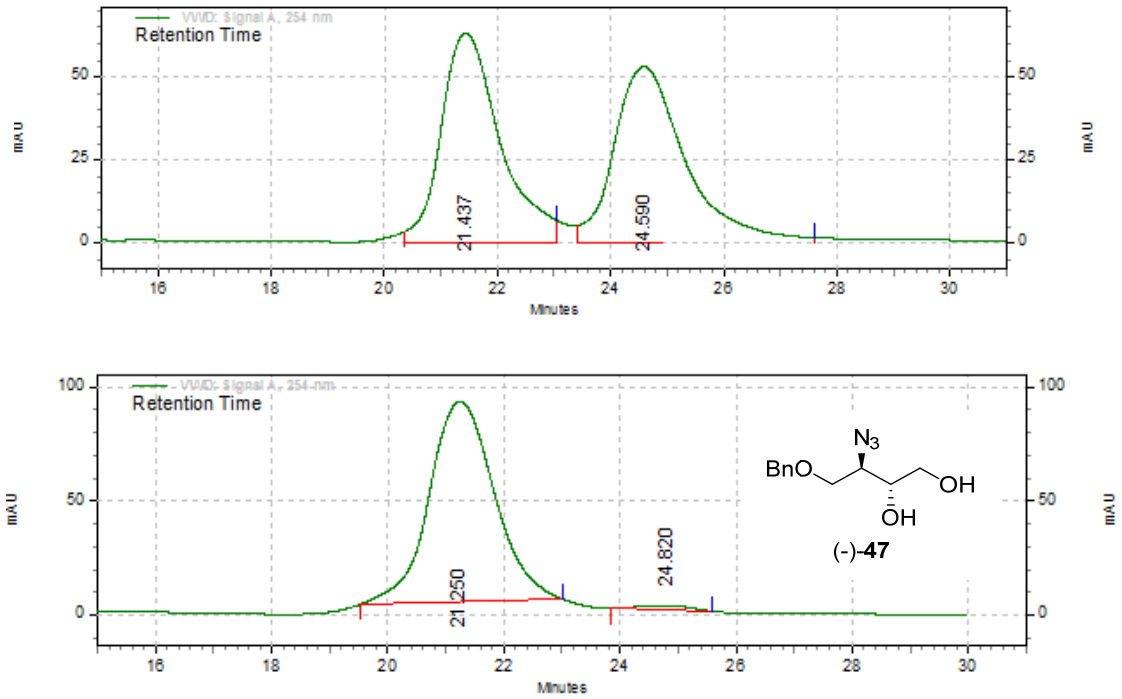
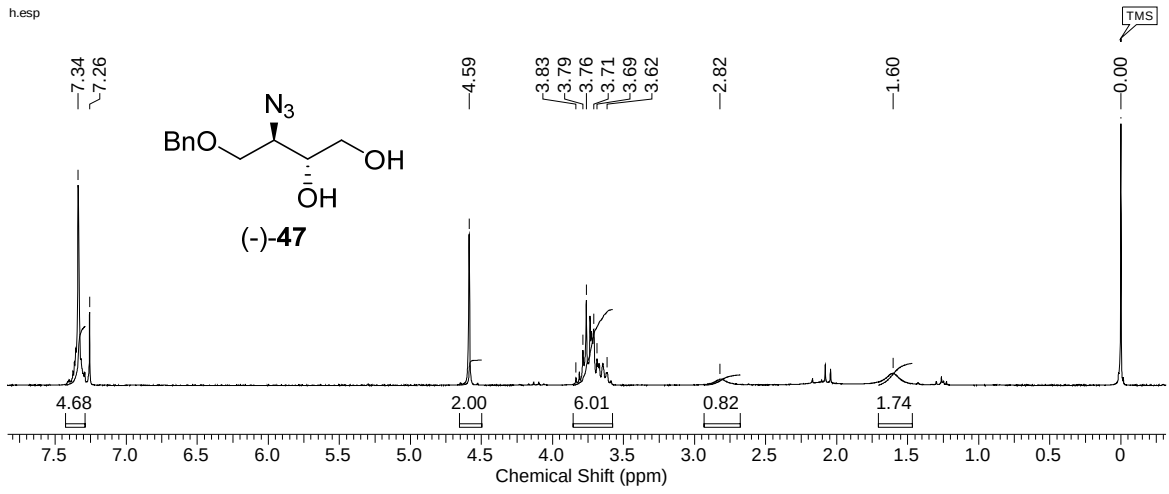


Fig. 5: HPLC chromatogram of (-)-**47,** 99% ee (Chiral OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm); Retention time: t_{major} = 21.50 (99.55%) and t_{minor} = 24.82 min. (0.45%)

The formation of azido diol (-)-**47** was confirmed by the appearence of a broad singlets, in its ^{1}H NMR spectrum, at δ 2.82 and δ 1.60 due to the hydroxy protons and a singlet at δ 4.56 due to benzylic protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 63.3 and δ 71.3 for the methine and methylene carbons attached to hydroxyl groups respectively (**Fig. 6**).



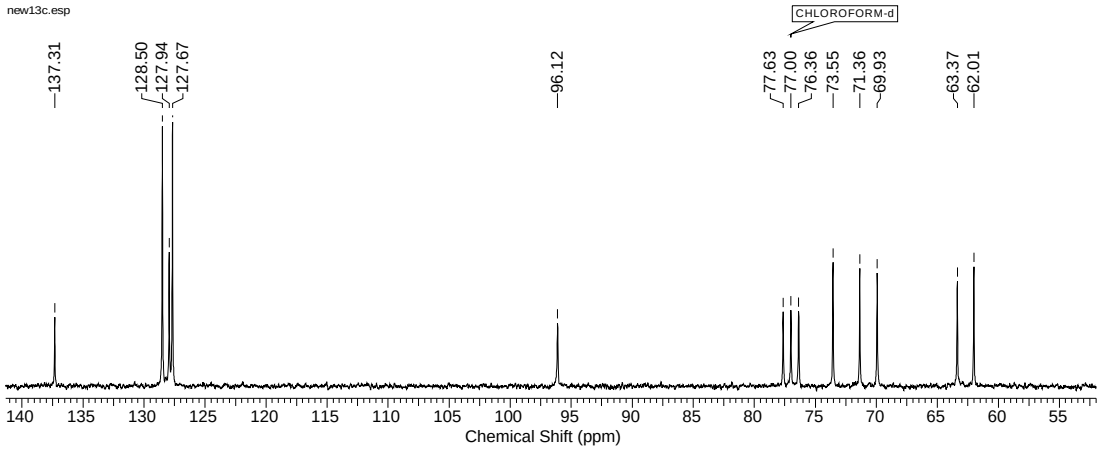
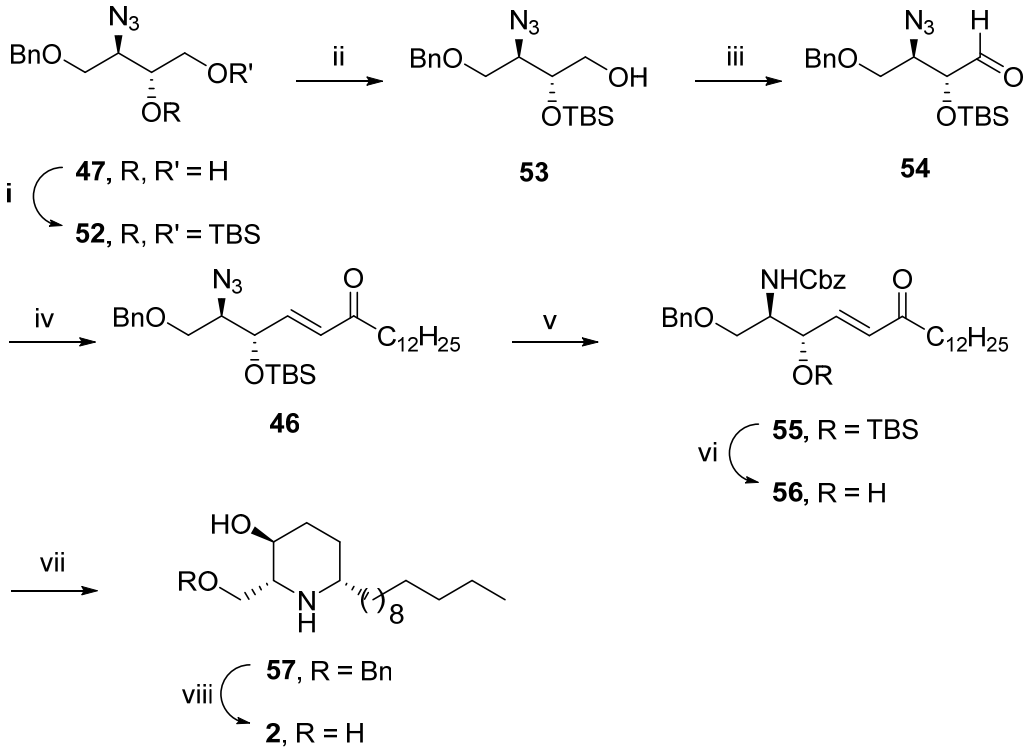


Fig. 6: ^{1}H and ^{13}C NMR spectra of (-)-**47**

We then protected both the free hydroxyl groups in diol (-)-**47** as its disilyl ether derivative **52**, followed by selective deprotection (CSA, MeOH, 0 ^{o}C) of primary silyl ether that afforded monosilyl ether **53** in 88% yield **(Scheme 10)**.



Scheme 10. Reaction conditions: (i) TBSCl, imid., DMF, 24 h, 98% (ii) CSA, MeOH, 0 ^{o}C, 5 h, 88%; (iii) IBX, EtOAc, reflux, 3 h, 91%; (iv) $(EtO)_2POCH_2COC_{12}H_{25}$, *i*-$Pr_2NEt$, CH_3CN, 25 ^{o}C, 12 h, 87%; (v) PPh_3, THF/H_2O, 25 ^{o}C, 12 h, then aq. Na_2CO_3, CbzCl, 0 to 25 ^{o}C, 12 h, 88%; (vi) TBAF, THF, 0 ^{o}C, 2 h, 95%; (vii) $Pd(OH)_2$, MeOH, H_2 (60 psig), 24 h, 94%; (viii) Na, liquid NH_3, THF, -78 ^{o}C, 1 h, 97%.

The formation of compound **52** was confirmed by its ^{1}H NMR spectrum, which showed the appearance of two singlets at δ 0.80 and δ 0.82 due to *tert*-butyl protons. The other proton signals at δ -0.06 and δ -0.02 are assigned to methyl protons attached to silicon atom. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 25.8 and δ 25.9 due to methyl carbons attached to silicon atom (**Fig. 7**).

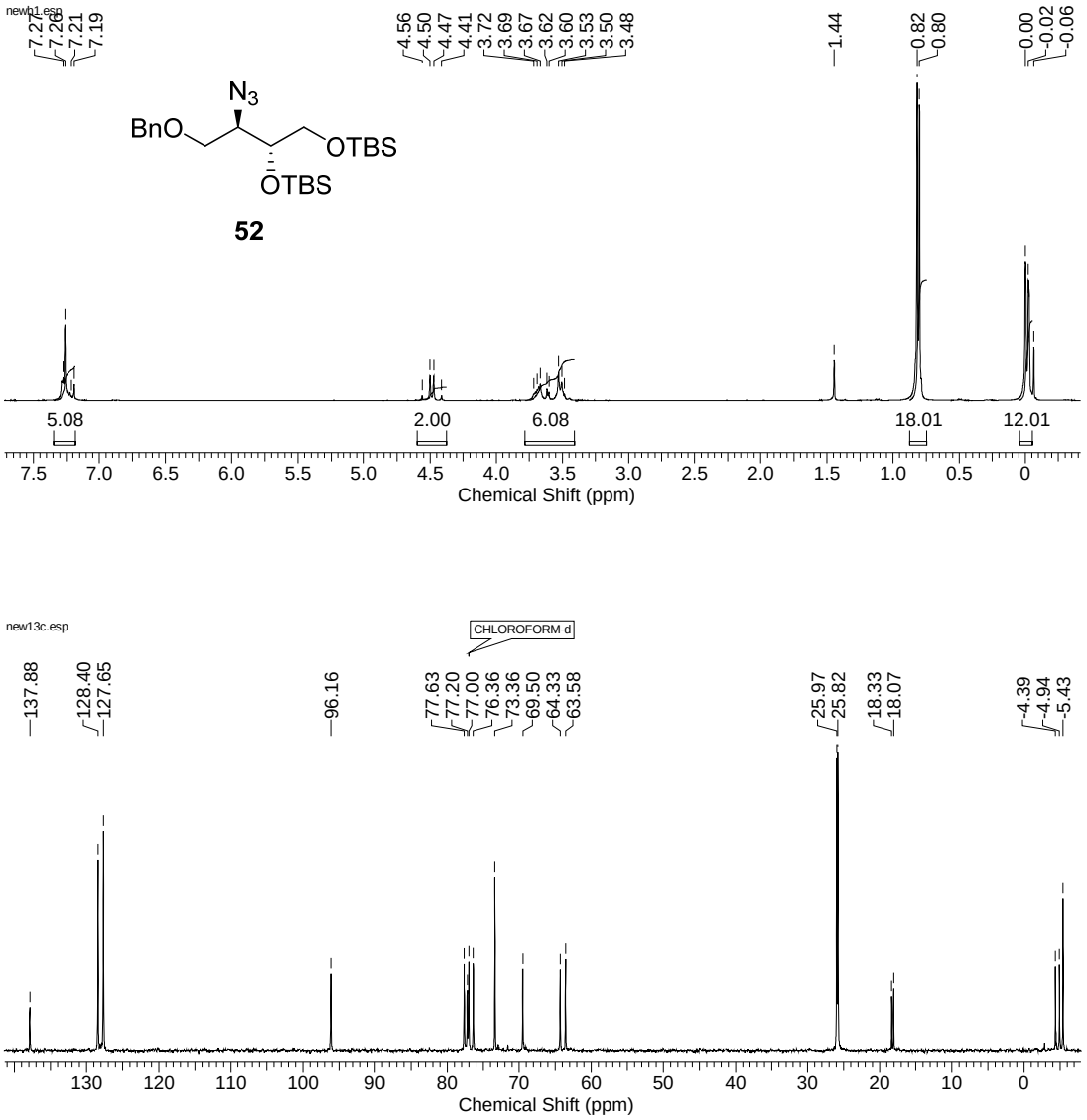


Fig. 7: ^{1}H and ^{13}C NMR spectra of **52**

The formation of alcohol **53** was confirmed by the appearance of characteristic proton signals at δ 0.07 and δ 0.08 integrating for 6 protons (Si-(C**H**$_3$)$_2$) in its ^{1}H NMR

spectrum. It wasfurther confirmed by ^{13}C NMR spectrum, which showed only one carbon signal at δ 25.7 for methyl carbon attached to silicon atom **(Fig. 8)**.

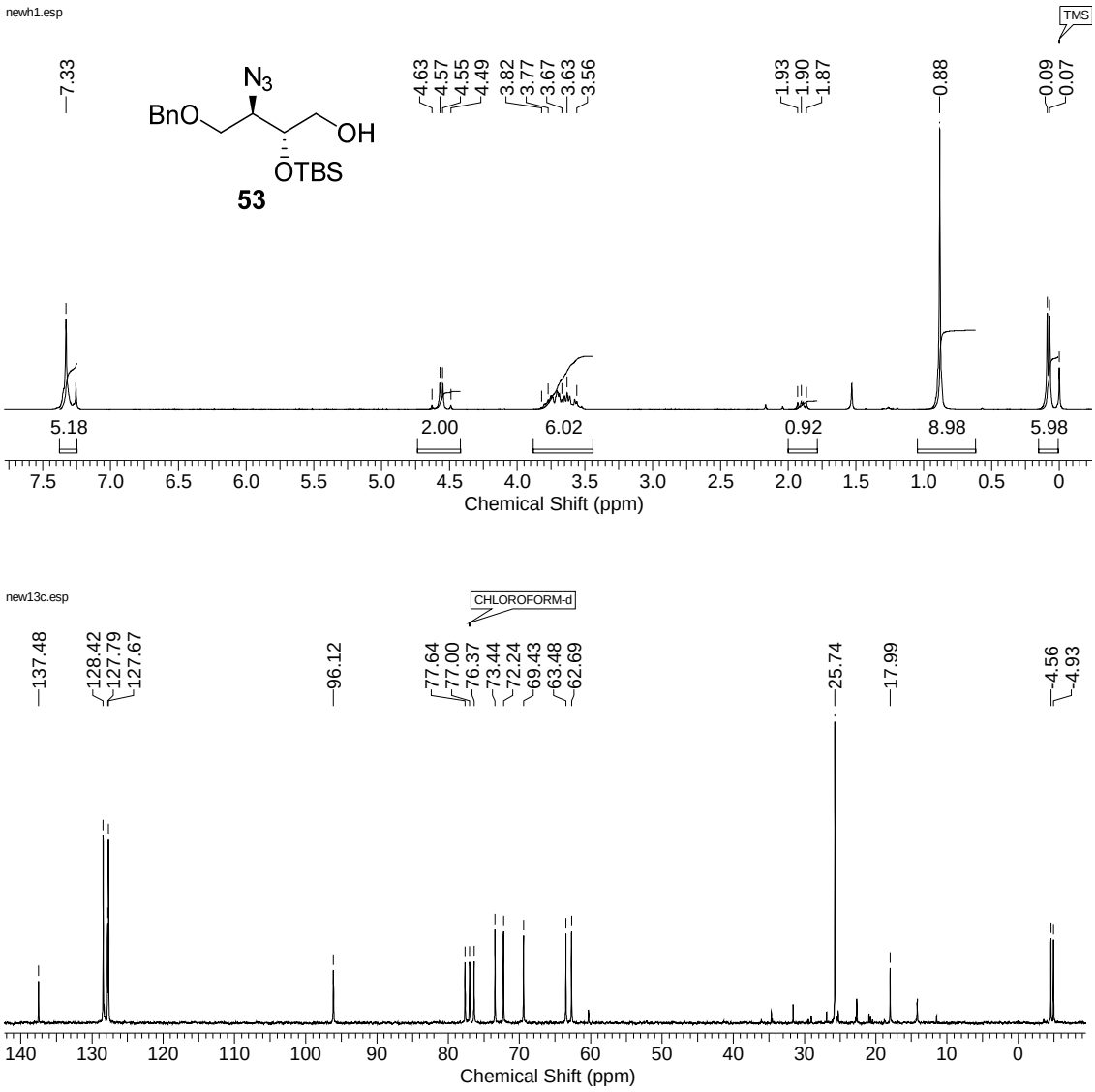


Fig. 8: ^{1}H and ^{13}C NMR spectra of **53**

Further, the primary hydroxyl group in **53** was oxidized using IBX to produce the corresponding crude aldehyde **54** in 91% yield. The aldehyde **54** was confirmed by the appearance of its characteristic signal at δ 9.55 for aldehydic proton in its ^{1}H NMR spectrum. Finally, a characteristic signal at δ 201.0, in its ^{13}C NMR spectrum, confirms the presence of aldehyde group in **54 (Fig. 9)**.

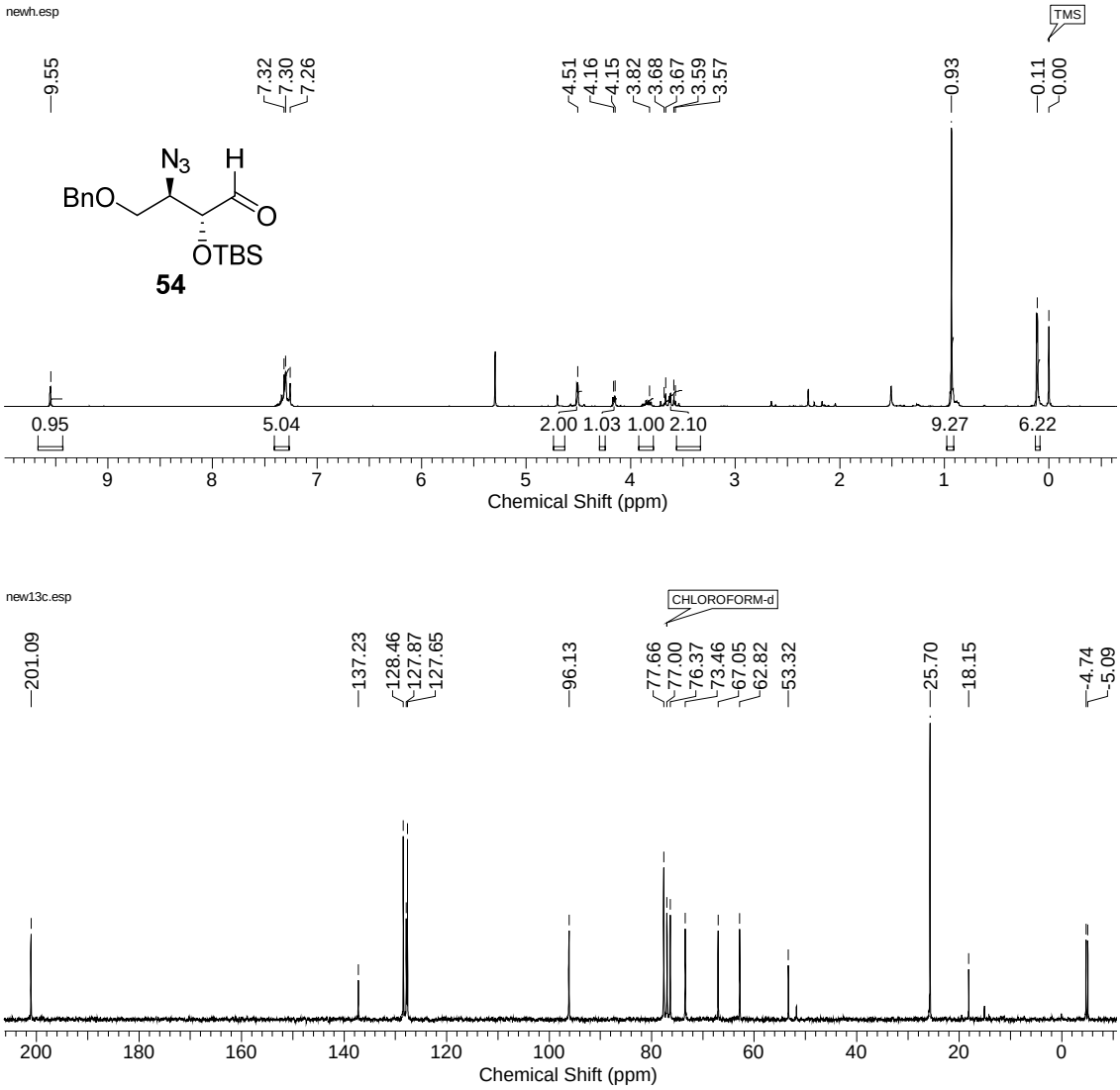


Fig. 9: ^{1}H and ^{13}C NMR spectra of **54**

The crude aldehyde **54** was then subjected to Wittig reaction [$(EtO)_2POCH_2COC_{12}H_{25}$, prepared from diethyl-2-oxopropylphosphonate and 1-iodoundecane, *i*-Pr_2NEt, CH_3CN, 0 ^{o}C] to give the corresponding (*E*)-unsaturated keto azide **46** in 87% yield with exclusive *trans* selectivity (J = 15.9 Hz). Its characteristic IR frequencies at1717 and 2101 cm^{-1} due to ketone and azide functions, respectively establish its structure. The formation of *trans*-α,β-unsaturated azidoester **46** was confirmed from its ^{1}H NMR spectrum, which showed the appearance of doublets of doublets at δ 6.25 (dd, J = 1.0, 15.6 Hz, 1H) and δ 6.70 (dd, J = 4.3, 15.9 Hz, 1H) due

to olefinic protons. Its ^{13}C NMR spectrum showed typical carbon signals at δ 130.6 and δ 143.4 due to the olefinic carbons (**Fig. 10**).

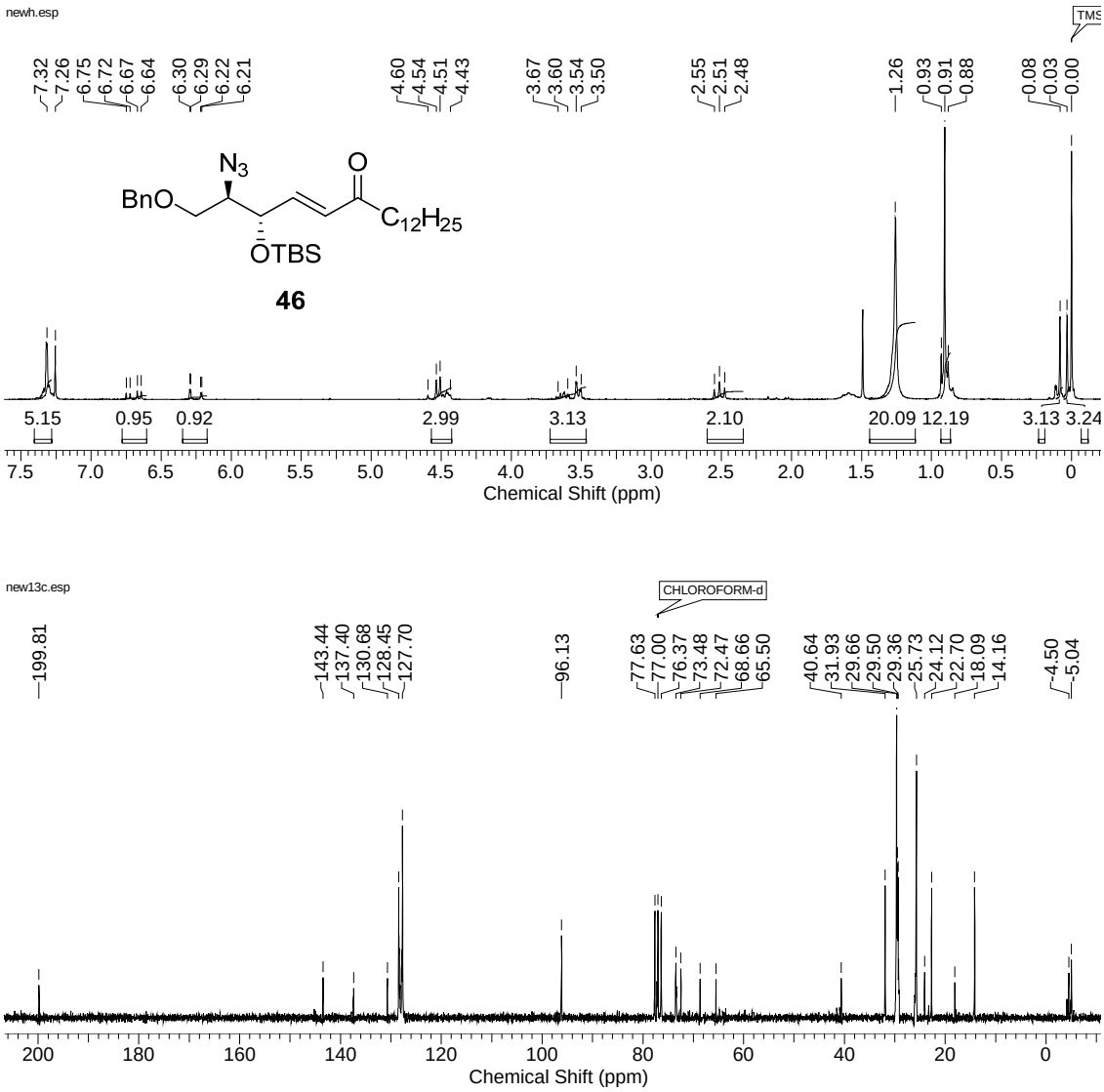


Fig. 10: ^{1}H and ^{13}C NMR spectra of **46**

When we attempted a one-pot catalytic hydrogenation of **46** [1N HCl, MeOH, $Pd(OH)_2$, H_2 (60 psig)] with the hope of obtaining (+)-deoxoprosophylline **2** (azide reduction, hydroxy deprotection and reductive cyclization; all occurring in a single step), complex mixtures of products were obtained. Alternatively, we designed a new route, wherein we first reduced azide functionality in **46** to amino group using

Staudinger conditions (PPh_3, THF/H_2O) followed by *in situ* protection of the corresponding amine as its carbamate derivative **55**. The formation **55** was confirmed by its ^1H NMR spectrum, which showed the appearance of typical proton signals at δ 4.47 and δ 5.04 due to benzylic protons. Its ^{13}C NMR spectrum showed a typical signal at δ 155.9 for amide carbonyl carbon group (**Fig. 11**).

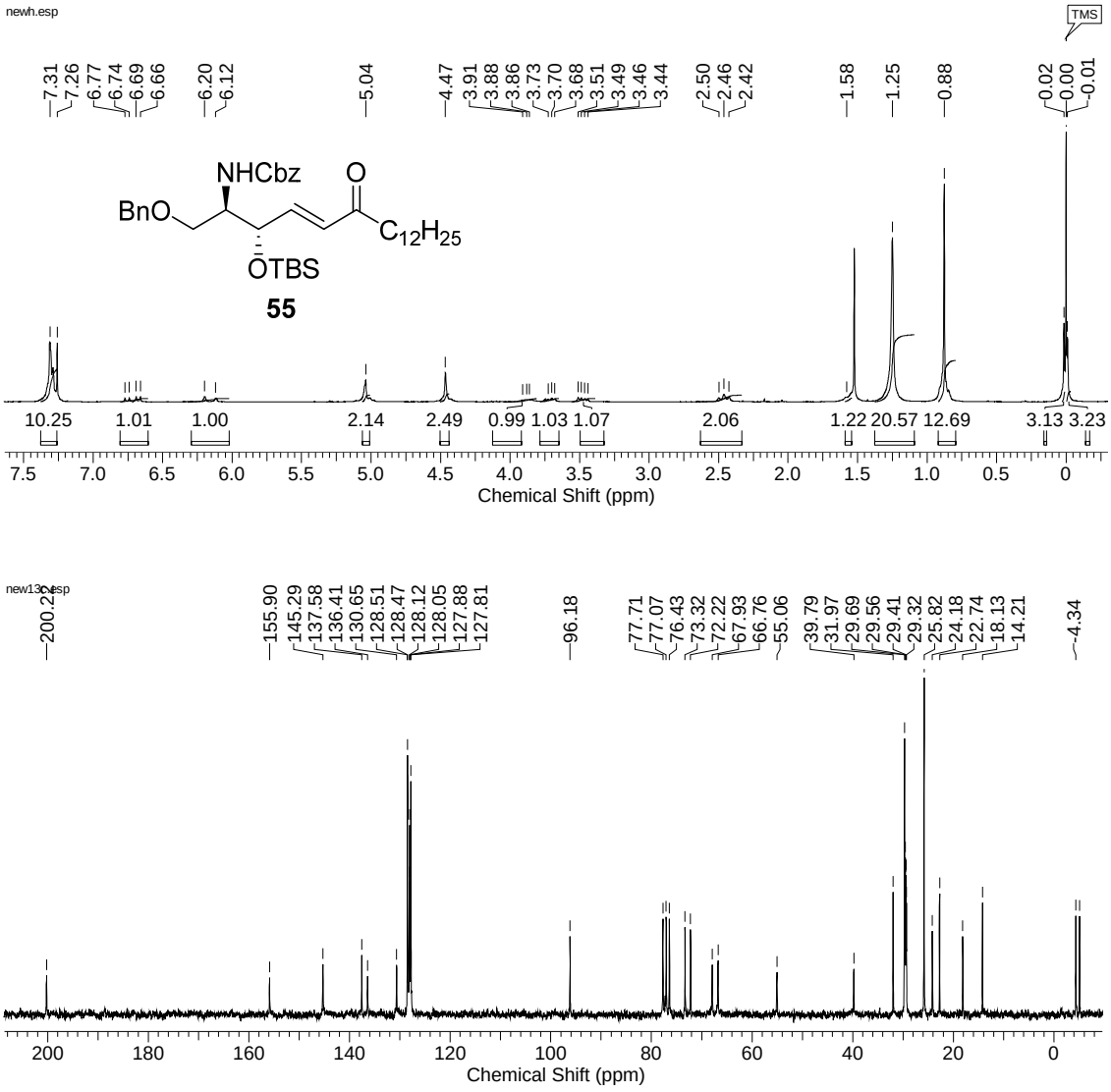


Fig. 11: ^1H and ^{13}C NMR spectra of **55**

Deprotection of silyl group in **55** was achieved (TBAF, THF, 0 to 25 ^oC) to give amino ketone **56** in 95% yield. The formation of **56** was confirmed by its ^1H NMR

spectrum, which showed two proton signals at δ 6.36 and δ 6.77 for olefinic protons. The disappearance of proton signals corresponding to TBS group confirmed the formation of **56**. Its ^{13}C NMR spectrum showed typical carbon signals at δ 156.2 and δ 200.0 due to the carbonyl carbons of amide and ketone functions respectively (**Fig. 12**).

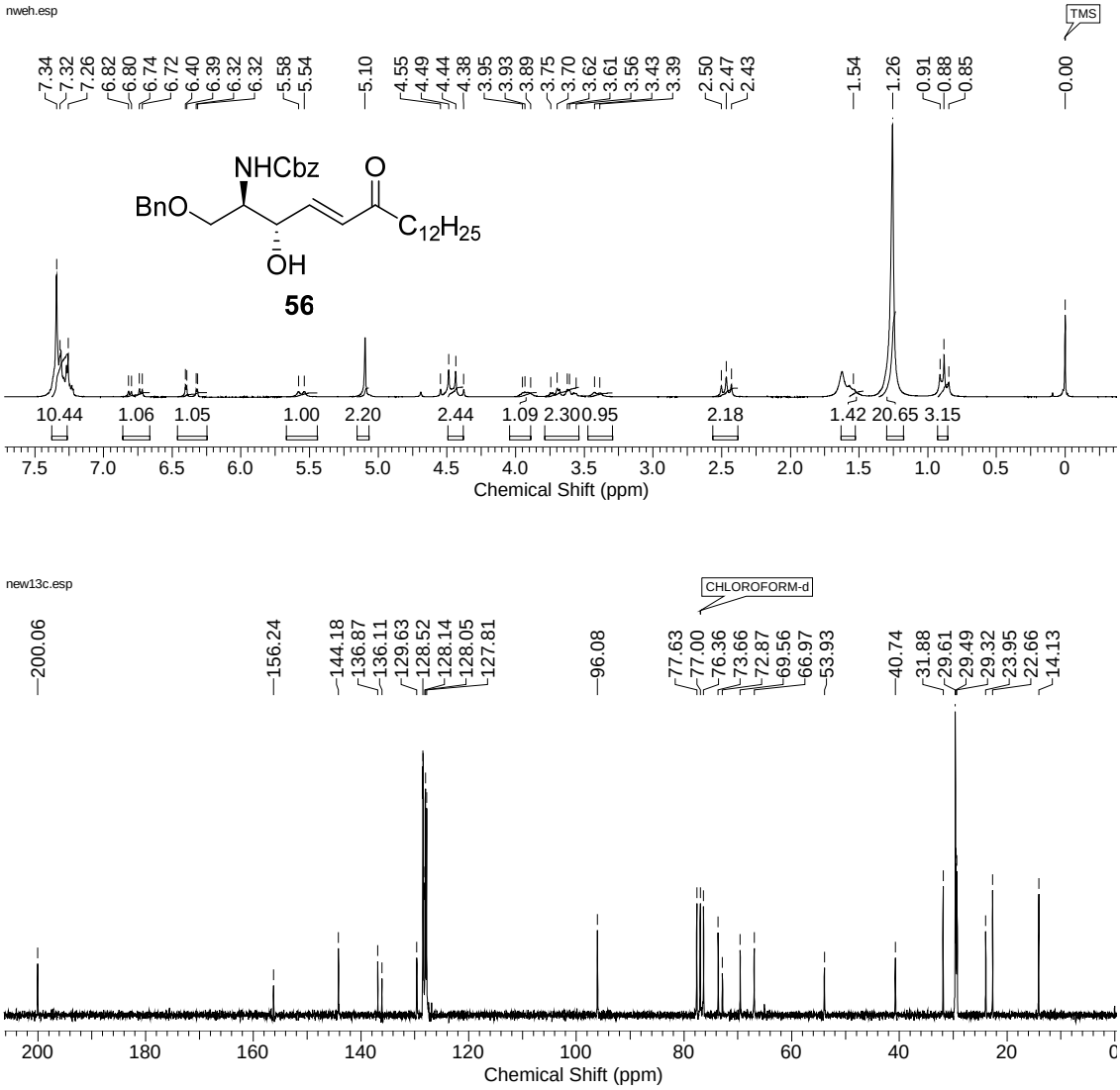


Fig. 12: ^{1}H and ^{13}C NMR spectra of **56**

Further, compound **56** was subjected to intramolecular diastereoselective cyclization under catalytic hydrogenation conditions [$Pd(OH)_2$, MeOH, H_2 (60 psig)] that gave **57** as a single diastereomer, without affecting the OBn group. The ^{1}H NMR spectrum of

57 showed signals at δ 4.54 for benzylic protons and a multiple at δ 7.32 for aromatic protons. Its ^{13}C NMR spectrum showed typical carbon signals at δ 127.7, 128.4 and 137.8 for aromatic carbones which established that OBn group was intact in hydrogenation reaction (**Fig. 13**).

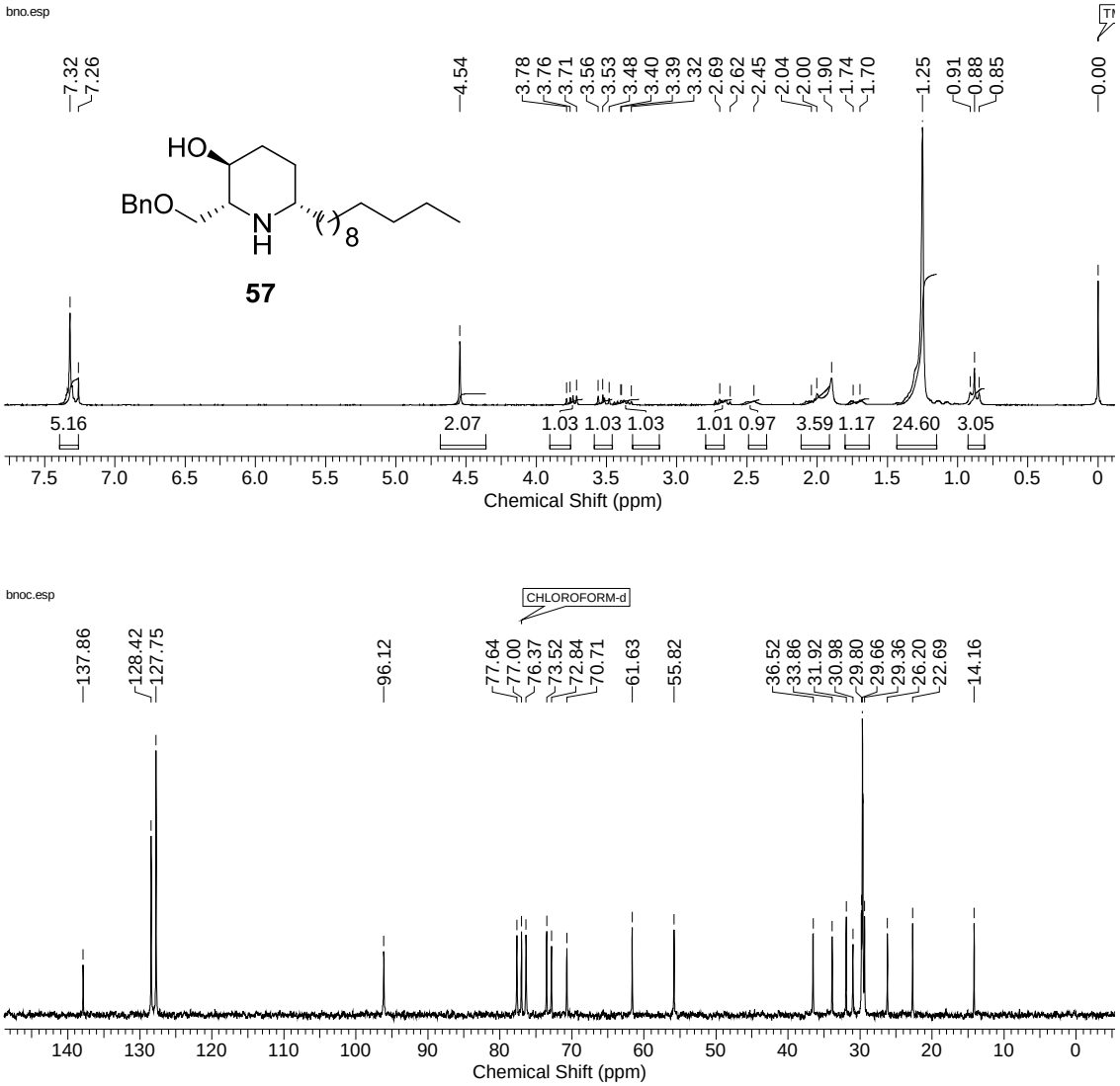


Fig. 13: ^{1}H and ^{13}C NMR spectra of **57**

Finally, *O*-debenzylation in **57** was carried out by Birch reduction (Na, liquid NH_3, THF, -78 ^{o}C), which furnished (+) deoxoprosophylline **2** in quantitative yield. The spectral data and optical rotation of the synthesized (+)-deoxoprosophylline **2** are in good agreement with the reported values.[13] The formation of (+)-deoxoprosophylline

2 was confirmed by the disappearance of aromatic signals from its ^{1}H and ^{13}C NMR spectra. The multiplets at δ 3.41 and δ 3.65 correspond to methylene (-**C**$\mathbf{H_2}$-O) protons and a signal at 3.83 (1H) is due to methine (-**C**$\mathbf{H}$-O) protons. This was further ascertained by the appearance of signals in its ^{13}C NMR spectrum at δ 63.4 and 69.3 due to methylene (-**C**$\mathbf{H_2}$-O) and methine (-**C**$\mathbf{H}$-O) carbons respectively (**Fig. 14**).

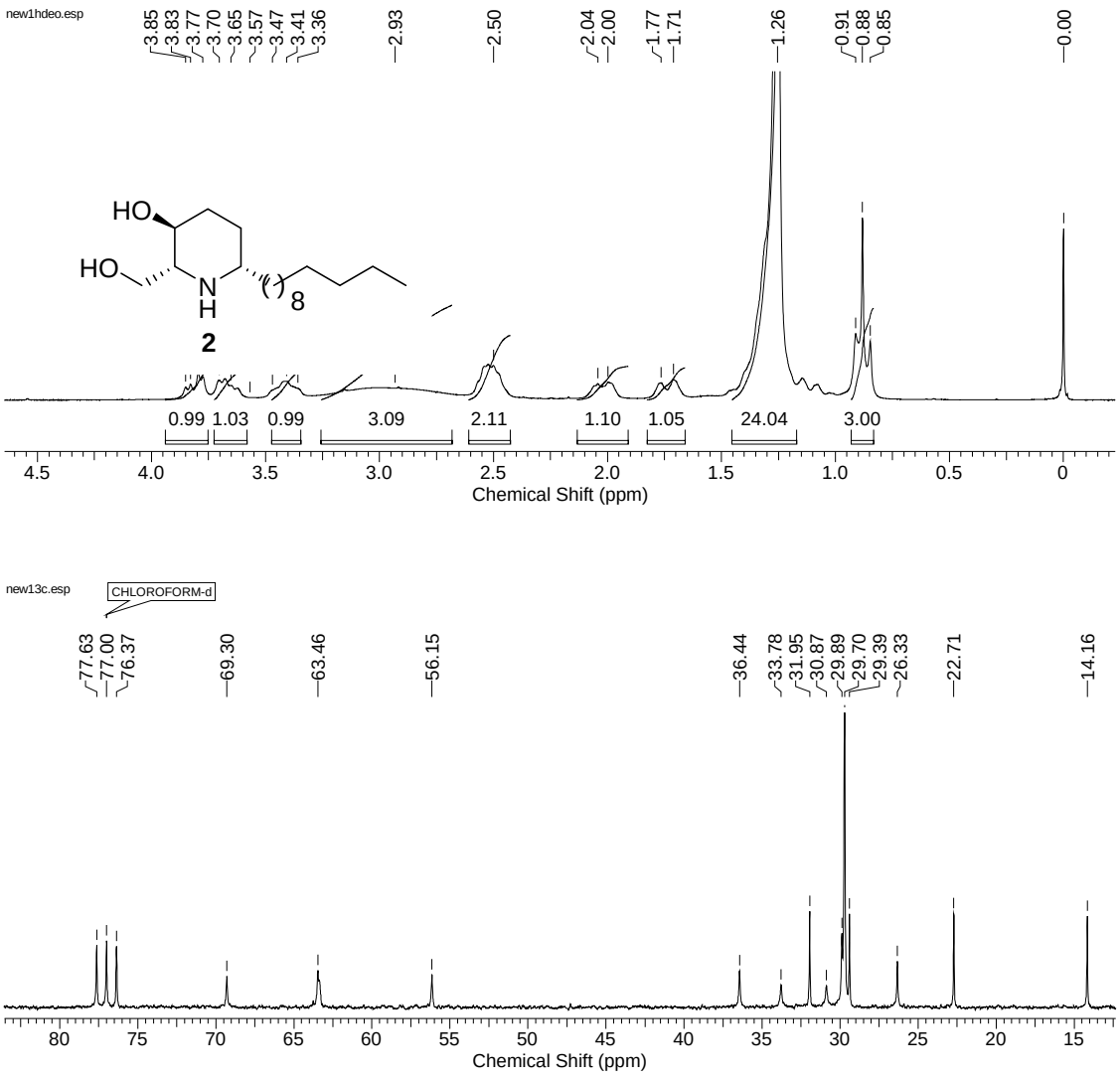


Fig. 14: ^{1}H and ^{13}C NMR spectra of **2**

2.1.4 Conclusion

In conclusion, we have described a short and efficient enantioselective synthesis of (+)-deoxoprosophylline **2** with an overall yield of 17.5% and high optical purity, that are achieved using two-stereocentered Co-catalyzed HKR of racemic azido epoxides. The other operationally simple reaction sequences include Wittig reaction and diastereoselective intramolecular reductive cyclization. This strategy is expected to find wide scope for the synthesis of other similar multifunctionalized piperidine alkaloids.

2.1.5 Experimental section

2-Azido-3-bromobutane-1,4-diol (50)

A mixture of *cis*-2-butene-1,4-diol **49** (10 g, 113.63 mmol), NaN_3 (14.77 g, 227.27 mmol) was taken in CH_3CN/H_2O (180:60 mL) and NBS (24.13 g, 136.36 mmol) was added slowly *via* solid addition funnel, with stirring at 0 °C and progress of reaction was monitored by TLC. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with EtOAc (80 mL), and the aq. layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography using petroleum ether: ethyl acetate (50:50) to afford pure product **50** as white solid.

Yield: 89%, colorless solid, **mp** 52 °C; **IR0** (neat, cm^{-1}): υ_{max} 1035, 1267, 2104, 3361; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 3.74-3.95 (m, 5H), 4.12-4.20 (m, 1H), 4.43-4.54 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6): δ 54.33, 62.37, 63.31, 63.45; **Anal**. Calcd for $C_4H_8BrN_3O_2$ requires C, 22.87; H, 3.84; N, 20.01; found C, 22.80; H, 3.82; N, 20.06%.

2-Azido-2-(oxiran-2-yl)ethanol (51)

Azido bromide **50** (8 g, 38.27 mmol) was taken in THF (50 mL) and NaOH powder (1.83 g, 45.93 mmol) was added slowly with stirring at 0 °C for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with EtOAc (60 mL) and water (50 mL). The organic layer was further separated and the aq. layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography using petroleum ether: ethyl acetate (8:2) as eluents to afford **51** as colourless oil.

Yield: 84%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 2104, 2931, 3383; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.18 (br s, 1H), 2.80-2.90 (m, 2H), 3.09-3.15 (m, 1H), 3.44-3.52 (m, 1H), 3.65-3.90 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.24, 49.97, 61.85, 62.94; **Anal**. Calcd for $C_4H_7N_3O_2$ requires C, 37.21; H, 5.46; N, 32.54; found C, 37.28; H, 5.56; N, 32.46%.

2-(1-Azido-2-(benzyloxy)ethyl)oxirane (48)

To suspension of sodium hydride (1.7 gm, 42.63 mmol) in DMF (80 mL), a solution of epoxy alcohol **51** (5 g, 38.75 mmol) in DMF (10 mL) was added. To this, BnBr (5 mL, 42.63 mmol) was added slowly and the stirring was continued for 2 h at -40 ^oC. After completion of reaction (monitored by TLC), it was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 50 mL). The combined organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude product was purified by column chromatography over silica gel using petroleum ether: ethyl acetate (95:5) to give product **48.**

Yield: 94%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 1453, 2102, 2864; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.74-2.83 (m, 2H), 3.05-3.11 (m, 1H), 3.44-3.52 (m, 1H), 3.57-

3.73 (m, 2H), 4.59 (s, 2H), 7.28-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 45.03, 50.53, 61.70, 69.97, 73.46, 127.57, 127.83, 128.44, 137.41; **Anal.** Calcd for $C_{11}H_{13}N_3O_2$ requires C, 60.26; H, 5.98; N, 19.17; found C, 60.24; H, 5.90; N, 19.20%.

HKR of 3-Azido-4-(benzyloxy)butane-1,2-diol (±)-47

To a solution of (*S*,*S*)-Co-salen (0.027g, 0.5 mol%) in toluene (2 mL), AcOH (0.02 g, 0.36 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min. During this time the color changed from orange-red to a dark brown, it was then dried under vacuum. To this racemic azido epoxide (2 g, 9.13 mmol) and H_2O (0.08 mL, 4.47 mmol) was added at 0 °C. Then the reaction was allowed to stir for 12 h at 25 °C. After completion of reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral azido epoxide **(+)-48,** [solvent system; petroleum ether: ethyl acetate (95:5)] and chiral azido diol **(-)-47** [solvent system; petroleum ether: ethyl acetate (6:4)] in pure form.

(2*R*, 3*R*)-3-Azido-4-(benzyloxy)butane-1,2-diol (-)-47

Yield: 48%, colorless oil; **$[\alpha]_D^{25}$** = -37.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1271, 1453, 2099, 2870, 2929, 3384; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.60 (br s, 1H), 2.81 (br s, 1H), 3.59-3.83 (m, 6H), 4.59 (s, 2H), 7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.02, 63.37, 69.94, 71.36, 73.55, 127.67, 127.94, 128.50, 137.31; **Anal**. Calcd for $C_{11}H_{15}N_3O_3$ requires C, 55.69; H, 6.37; N, 17.71; found C, 55.70; H, 6.48; N, 17.65%; **Optical purity**: 99% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{major} = 21.25 and t_{minor} = 24.82 min.

(*S*)-2-((*S*)-1-Azido-2-(benzyloxy)ethyl)oxirane (+)-48

Yield: 50%, colorless oil; **$[\alpha]_D^{25}$** = +29.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 1453, 2102, 2864; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.74-2.83 (m, 2H), 3.05-3.11 (m,

1H), 3.44-3.52 (m, 1H), 3.57-3.73 (m, 2H), 4.59 (s, 2H), 7.28-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 45.03, 50.53, 61.70, 69.97, 73.46, 127.57, 127.83, 128.44, 137.41; **Anal**. Calcd for $C_{11}H_{13}N_3O_2$ requires C, 60.26; H, 5.98; N, 19.17; found C, 60.24; H, 5.90; N, 19.20%; **Optical purity**: 99% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 13.51 and t_{major} = 16.20 min.

***bis*-Silyl ether (52)**

To a solution of azido diol **47** (4 g, 16.87 mmol) in DMF (25 mL) at 25 ºC, TBSCl (5.59 g, 37.13 mmol) and imidazole (3.44 g, 50.63 mmol) was added. The resulting solution was stirred at 25 ºC for 24 h, then quenched with water and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated reduced pressure to give the crude product. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (95:5) as eluent gave pure *bis*-TBS ether **52** as colorless oil.

Yield: 98%, colorless oil; **$[\alpha]_D^{25}$** = -5.1 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1255, 1470, 2099, 2857, 2929; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.06 (s, 6H), 0.86 (s, 9H), 0.88 (s, 9H), 3.55-3.80 (m, 6H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.43, -4.94, -4.39, 18.07, 18.33, 25.82, 25.97, 63.58, 64.33, 69.50, 73.36, 77.20, 127.65, 128.40, 137.88; **Anal.** Calcd for $C_{23}H_{43}N_3O_3Si_2$ requires C, 59.31; H, 9.31; N, 9.02; found C, 59.43; H, 9.38; N, 9.10%.

(2*R*,3*R*)-3-Azido-4-(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)butan-1-ol (53)

To a solution of *bis*-TBS ether **52** (4 g, 8.60 mmol) in MeOH (60 mL) was added camphorsulfonic acid (0.099 g, 0.43 mmol) at 0 °C and the mixture stirred for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was

neutralized with $NaHCO_3$ and concentrated under reduced pressure to give the crude product, which upon purification by column chromatography using petroleum ether: ethyl acetate (7:3) as eluent to furnish mono-TBS-protected azido alcohol **53** as colorless oil.

Yield: 88%, colorless oil; $[\alpha]_D^{25}$ = -27.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1256, 1471, 2100, 2884, 3454; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.90 (m, 1H), 3.53-3.82 (m, 6H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.93, -4.56, 17.99, 25.74, 62.69, 63.48, 69.43, 72.24, 73.44, 127.67, 127.79, 128.42, 137.48; **Anal.** Calcd for $C_{17}H_{29}N_3O_3Si$ requires C, 58.09; H, 8.32; N, 11.95; found C, 58.12; H, 8.40; N, 12.01%.

(2*R*,3*R*)-3-Azido-4-(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)butanal (54)

To a stirred solution of TBS-protected azido alcohol **53** (2 g, 5.69 mmol) in EtOAc, 2-iodoxybenzoic acid (4.76 g, 17.09 mmol) was added under nitrogen atmosphere and reaction mixture was refluxed for 3 h. After the completion of the reaction (monitored by TLC), and it was filtered through a sintered funnel and the filtrate was concentrated under reduced pressure to afford the crude product **54**, which was used for next reaction without purification.

Yield: 91%, colorless oil; $[\alpha]_D^{25}$ = -10.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1217, 1471, 1735, 2103, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 3.54-3.71 (m, 2H), 3.80-3.89 (m, 1H), 4.15 (dd, *J* = 1.2, 3.2 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 7.28-7.34 (m, 5H), 9.55 (d, *J* = 1.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.09, -4.74, 18.15, 25.70, 53.32, 62.82, 67.05, 73.46, 77.68, 127.65, 127.87, 128.46, 137.23, 201.09; **Anal.** Calcd for

$C_{17}H_{27}N_3O_3Si$ requires C, 58.42; H, 7.79; N, 12.02; found C, 58.40; H, 7.80; N, 12.06%.

(2*R*,3*S*,*E*)-2-Azido-1-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)octadec-4-en-6-one (46)

To a well stirred solution of $(EtO)_2POCH_2COC_{12}H_{25}$ (1.14 g, 3.43 mmol), LiCl (0.24 g, 5.73 mmol) in acetonitrile *i*-Pr_2NEt (0.44 g, 3.43 mmol) was added at 0 ^oC. Then a solution of azido aldehyde **54** (1 g, 2.86 mmol) in acetonitrile (10 mL), was added at 0 ^oC and reaction mixture was stirred at 25 ^oC for 12 h. After completion of reaction (monitored by TLC), it was quenched with water (5 mL). The product was extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using petroleum ether: ethyl acetate (9:1) as eluent to give (*E*)-α, β-unsaturated azido ketone **46** as colorless oil.

Yield: 87%, colorless oil; $[\alpha]_D^{25}$ = +21.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1463, 1681, 1717, 2101, 2855, 2925; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.08 (s, 3H), 0.91 (s, 12H), 1.26 (br s, 20H), 2.51 (t, *J* = 7.5 Hz, 2H), 3.50-3.68 (m, 3H), 4.44-4.60 (m, 3H), 6.25 (dd, *J* = 1.3, 15.9 Hz, 1H), 6.70 (dd, *J* = 5.5, 15.7 Hz, 1H), 7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.04, -4.50, 14.16, 18.09, 22.70, 24.12, 25.73, 29.36, 29.50, 29.66, 31.92, 40.63, 65.50, 68.65, 72.46, 73.33, 73.48, 127.70, 127.86, 128.45, 130.67, 137.40, 143.44, 199.81; **Anal.** Calcd for $C_{31}H_{53}N_3O_3Si$ requires C, 68.46; H, 9.82; N, 7.73; found C, 68.55; H, 9.86; N, 7.67%.

Synthesis of Diethyl 2-oxotetradecylphosphonate [$(EtO)_2POCH_2COC_{12}H_{25}$**]**

To a stirred suspension of activated NaH (0.24 g, 6.18 mmol) in dry THF (5 mL) under nitrogen atmosphere at 25 ^oC, a solution of diethyl-2-oxopropylphosphonate (1 g, 5.15 mmol) in THF (2 mL) was added. The stirring was continued for 1.5 h, to this

n-butyl lithium (3.8 mL, 6.18 mmol, 1.6 M solution in hexane) was added drop wise and reaction mixture was stirred for another 20 min at 0 ^{o}C. To this reaction mixture a solution of 1-iodoundecane (1.74 g, 6.18 mmol) in THF (3 mL) was added at 0 ^{o}C and stirring was continued for 30 min. After completion of reaction (monitored by TLC) the reaction was quenched by addition of saturated aqueous ammonium chloride solution (5 mL) and the product extracted with ethyl acetate (3 x 10 mL). The combined organic layer were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography using ethyl acetate and petroleum ether (1:1) to give diethyl 2-oxotetradecylphosphonate.

Yield: 86%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1466, 1716, 2854, 2924; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.25 (s, 18H), 1.34 (t, *J* = 7.0 Hz, 6H), 1.57 (m, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.99 (s, 1H), 3.10 (s, 1H), 4.14 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.20, 16.33, 16.45, 22.74, 23.48, 29.04, 29.41, 29.45, 29.53, 29.69, 31.97, 41.16, 43.69, 44.10, 62.38, 62.51, 201.82; **Anal**. Calcd for $C_{18}H_{37}O_4P$ requires C, 62.04; H, 10.70; found C, 62.10; H, 10.72%.

Benzyl (2*R*,3*S*,*E*)-1-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-6-oxooctadec-4-en-2-ylcarbamate (55)

To a solution of azide **46** (2 g, 3.68 mmol) in THF/water (20:1 mL) was added PPh_3 (1.44 g, 5.52 mmol) and the mixture was stirred at 25 ^{o}C for 12 h. To this solution, aqueous Na_2CO_3 (0.77 g, 7.36 mmol in 5 mL water) was added and stirred for another 10 min at 0 ^{o}C. To this ice cold solution, CbzCl (0.62 mL, 4.41 mmol) was added and stirring was continued for further 12 h at 25 ^{o}C. After completion of reaction (monitored by TLC), solvent was removed under reduced pressure and the residue extracted with ethyl acetate (2 x 20 mL). The combined organic phase was dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product which was subjected to column chromatographic purification using petroleum ether: ethyl acetate (7:3) to give **55**.

Yield: 88%, colorless oil; $[\alpha]_D^{25}$ = -9.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1504, 1676, 1724, 2926; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.01 (s, 3H), 0.02 (s, 3H), 0.88 (s, 12H), 1.25 (s, 20H), 1.58 (m, 1H), 2.46 (t, *J* = 7.3 Hz, 2H), 3.49 (dd, *J* = 4.4, 9.4 Hz, 1H), 3.73 (dd, *J* = 4.4, 9.3 Hz, 1H), 3.87 (m, 1H), 4.47 (s, 2H), 5.04 (s, 2H), 6.12 (d, *J* = 16.0 Hz, 1H), 6.74 (dd, *J* = 6.0, 15.9 Hz, 1H), 7.31 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.15, -4.40, 14.15, 18.06, 22.68, 24.11, 25.75, 29.26, 29.34, 29.46, 29.50, 29.62, 31.90, 39.73, 54.99, 66.69, 67.86, 72.15, 73.25, 127.75, 127.81, 127.98, 128.05, 128.40, 128.45, 130.58, 136.34, 137.51, 145.22, 155.84, 200.16; **Anal**. Calcd for $C_{39}H_{61}NO_5Si$ requires C, 71.84; H, 9.43; N, 2.15; found C, 71.78; H, 9.50; N, 2.10%.

Benzyl (2*R*,3*S*,*E*)-1-(benzyloxy)-3-hydroxy-6-oxooctadec-4-en-2-ylcarbamate (56)

To a stirred solution of the silyl ether **55** (1.5 g, 2.30 mmol) in THF (5 mL), TBAF (4.6 mL of 1 M solution in THF) was added at 0 ^oC. The reaction mixture was stirred for 2 h at the same temperature. After completion of reaction (monitored by TLC), it was quenched with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which was then purified by column chromatography using petroleum ether: ethyl acetate (7:3) to obtain pure **56**.

Yield: 95%, yellow thick liquid; $[\alpha]_D^{25}$ = +27.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1216, 1701, 2853, 2925, 3426; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.26 (s, 20H), 1.57 (br, 1H), 2.47 (t, *J* = 7.4 Hz, 2H), 3.41 (d, *J* = 8.3 Hz, 1H),

3.60 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.71 (dd, *J* = 3.0, 9.4 Hz, 1H), 3.91 (m, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 5.10 (s, 2H), 5.56 (d, *J* = 8.3 Hz, 1H), 6.36 (dd, *J* = 15.7, 1.7 Hz, 1H), 6.77 (dd, *J* = 4.0, 15.7 Hz, 1H), 7.34 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.13, 22.66, 23.95, 29.26, 29.32, 29.45, 29.49, 29.61, 31.88, 40.74, 53.93, 66.97, 69.56, 72.87, 73.66, 127.82, 128.05, 128.14, 128.47, 128.52, 129.63, 136.11, 136.87, 144.18, 156.24, 200.07; **Anal.** Calcd for $C_{33}H_{47}NO_5$ requires C, 73.71; H, 8.81; N, 2.60; found C, 73.79; H, 8.86; N, 2.56%.

(2*R*,3*S*,6*S*)-2-(Benzyloxymethyl)-6-dodecylpiperidin-3-ol (57)

To a solution of **56** (0.8 g, 1.48 mmol) in dry MeOH was added $Pd(OH)_2$ (0.05 g) and the reaction mixture was stirred under an atmosphere of H_2 (60 psig) for 24 h at 25 ^oC. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered over celite and the filtrate was concentrated under reduced pressure to provide the **57**, which was purified by column chromatography using petroleum ether: ethyl acetate (50:50) to obtain pure **57**.

Yield: 94%, colorless oil; **$[\alpha]_D^{25}$** = +9.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1095, 1454, 2853, 2923, 3030, 3331; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.25 (s, 24H), 1.68-1.77 (m, 1H), 1.90-2.08 (m, 3H), 2.48 (m, 1H), 2.62-2.72 (m, 1H), 3.32-3.44 (m, 1H), 3.52 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.75 (dd, *J* = 9.0, 5.3 Hz, 1H), 4.54 (s, 2H), 7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.16, 22.69, 26.20, 29.36, 29.60, 29.66, 29.80, 30.98, 31.92, 33.86, 36.52, 55.82, 61.63, 70.71, 72.84, 73.52, 127.75, 128.42, 137.86; **Anal.** Calcd for $C_{25}H_{43}NO_2$ requires C, 77.07; H, 11.12; N, 3.60; found C, 77.02; H, 11.06; N, 3.69%.

(+)-deoxoprosophylline (2)

To a stirred solution of ammonia (5 mL) at -78 ^oC, freshly cut pieces of sodium (0.5 g) was added under nitrogen atmosphere. To this, a solution of **57** (0.6 g, 2.06 mmol)

in dry THF (2 ml) was added drop wise and the stirring continued for 1 h at -78 ^{o}C. The mixture was then quenched with dry solid ammonium chloride and ammonia gas was allowed to evaporate by keeping reaction mixture at room temperature for 1 h. The residue was diluted with H_2O (5 mL), brine (2 mL) and extracted with chloroform (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography using MeOH:$CHCl_3$ (1:9) to as eluents to afford **2** as colorless solid.

Yield: 97%, colorless solid, **mp** 85^{o}C {lit.[13b] mp. 89-90 ^{o}C}; **$[\alpha]_D^{25}$** = +13.5 (*c* 1, $CHCl_3$) {lit.[13b] $[\alpha]_D^{24}$ = +13.5 (*c* 0.3, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1059, 1467, 2851, 2922, 3169, 3266; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.26 (br s, 24H), 1.71-1.80 (m, 1H), 1.98-2.06 (m, 1H), 2.43-2.60 (m, 2H), 2.77-3.20 (br, 3H), 3.31-3.51 (t, *J* = 10.6 Hz, 1H), 3.68 (dd, *J* = 10.9, 5 Hz, 1H), 3.83 (dd, *J* = 10.9, 4.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.16, 22.71, 26.33, 29.39, 29.70, 29.89, 30.87, 31.95, 33.78, 36.44, 56.15, 63.37, 63.46, 69.30; **Anal.** Calcd for $C_{18}H_{37}NO_2$ requires C, 72.19; H, 12.45, N, 4.68%; found C, 72.26, H, 12.36, N, 4.70%.

Section II

Asymmetric Synthesis of (2*S*, 3*S*)-3-Hydroxypipecolic Acid *via* Co(III)(salen)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxides

2.2.1 Introduction and Pharmacology

Chiral 2,3-disubstituted piperidines with the β-hydroxy function are widespread in numerous natural products and are common subunits found in drugs and drug candidates.[1] Further, hydroxylated piperidine alkaloids are frequently found in living systems and display a wide range of biological activities due to their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[15] 3-Hydroxypipecolic acids **58** and **59**, six-membered cyclic α-amino-β-hydroxy acids, constitute non-natural variants of a structural motif often encountered in a variety of functional molecules and may be regarded as expanded hydroxylated proline or a conformationally restricted serine derivative, which may affect the physiological and pathological processes **(Fig. 15)**.[16] Additionally, piperidine unit of 3-hydroxypipecolic acid is found in a number of biologically important products.

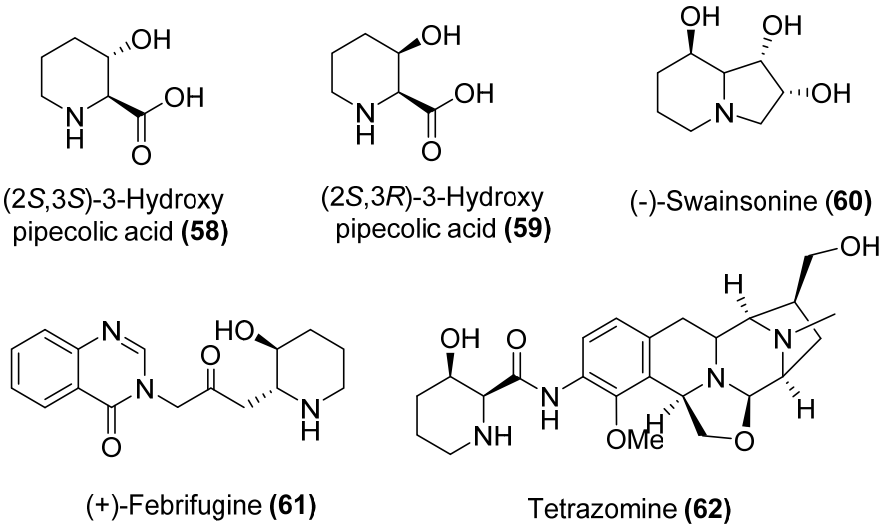


Fig. 15: 3-Hydroxypipecolic acid analogues

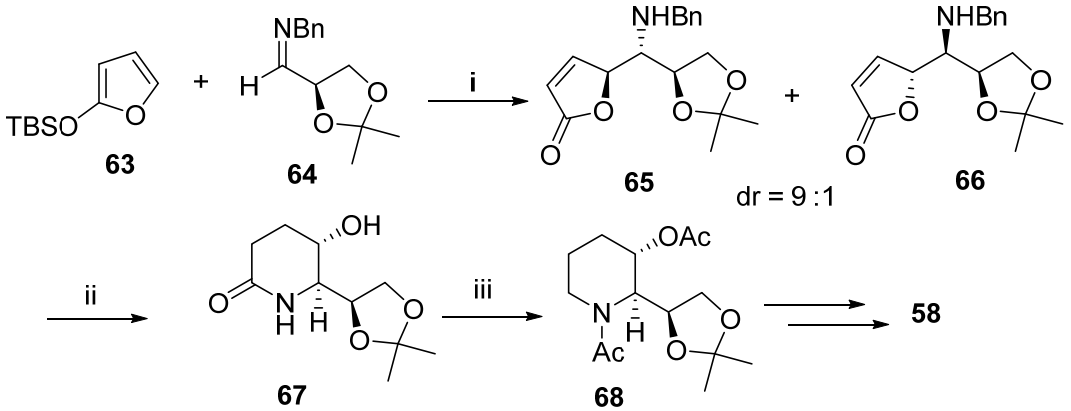
For example, the *trans* isomer **58** is a precursor of (-)-swainsonine **60**, which has shown potent and specific α-D-mannosidase inhibitory activity,[17] and it is also found in the structure of febrifugine **61**, a potent antimalarial agent,[18] while the *cis*-isomer **59** forms a part of the structure of tetrazomine **62**,[19] an antitumor antibiotic. These interesting structural features and therapeutic potential make them attractive synthetic targets.

2.2.2 Review of Literature

The wide applicability and occurrence of this scaffold attracted attention of many organic chemists towards its synthesis. Some of the interesting and important synthetic routes to 3-hydroxypipecolic acid are described below

Casiraghi's approach (1997)[20]

Casiraghi *et al*. developed a novel diastereoselective addition of silyloxy furan (TBSOF) and imines derived from L and D glyceraldehydes and exploited it for the synthesis of 3-hydroxypipecolic acid **58 (Scheme 11)**. Thus, the 2-silyloxyfuran **63** and imine **64** were coupled to provide butenolide amines **65** and **66** in the ratio 9:1.

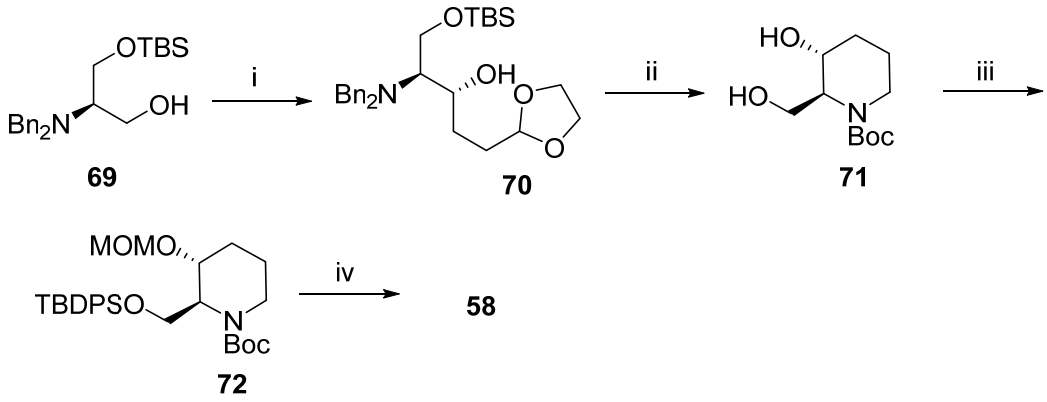


Scheme 11: (i) (a) TBSOTF, - 80 °C, DCM, 90%; (b) H_2, Pd/C, NaOAc, 75%; (ii) DBU, 80 °C, 82%; (iii) (a) $LiAlH_4$, $AlCl_3$, THF, -80 °C, -20 °C; (b) Ac_2O, pyridine, DMAP, DCM, 90%.

Butenolide amine **66** was subjected to hydrogenation followed by treatment with DBU to provide amide **67**. Amide **67** was reduced using $LiAlH_4$, $AlCl_3$ to provide aminol acetate **68,** which on subsequent transformations gave 3-hydroxypipecolic acid **58**.

Zhu's Approach (2000)[21]

Zhu *et al*. have reported the synthesis of 3-hydroxypipecolic acid **58** starting from amino alcohol **69** derived from serine **(Scheme 12)**. Amino alcohol **69** was oxidized to aldehyde which was subjected to reaction with Grignard reagent to obtain *anti*-amino alcohol **70** as a major Product. Protected amino alcohol **70** was subjected to hydrogenation and subsequently underwent Boc protection to give diol **71**. The primary alcohol in diol **71** was protected selectively as -OTBDPS and secondary hydroxyl as -OMOM to give **72**. Then the TBDPS group of **72** was deprotected, and the resulting alcohol was subjected to oxidation followed by MOM group was deprotection gave (2*R*, 3*R*)- 3-hydroxypipecolic acid **(58)**.

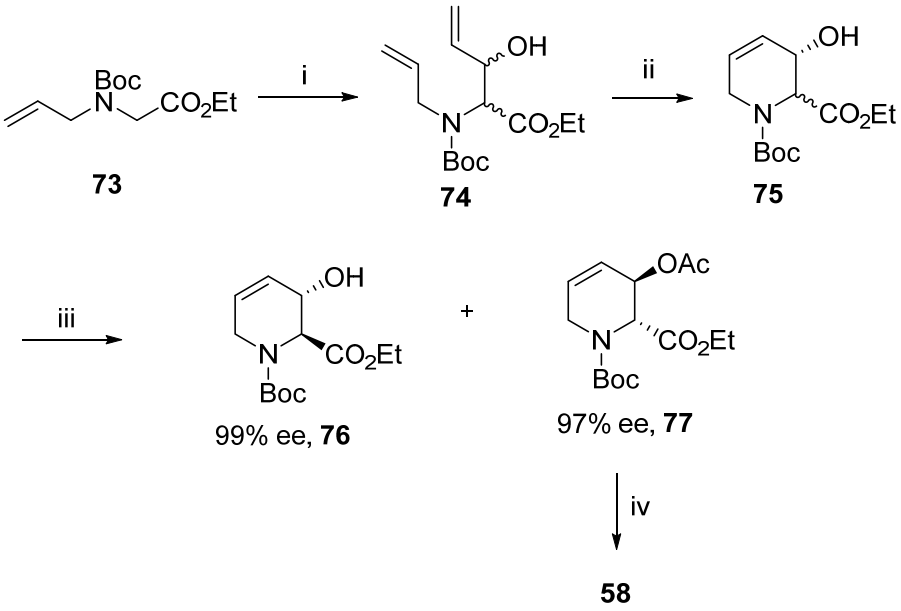


69 **70** **71** **72**

Scheme 12: (i) (a) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ^oC, then Et_3N; (b) 2-(2-bromethyl)-1,3-dioxolane, Mg, THF, 86%; (ii) (a) H_2, 10% Pd/C, 3 N HCl, THF:*t*-BuOH (1:1); (b) Boc_2O, H_2O, dioxane, 1 N NaOH, 80%; (iii) (a) TBDPSCl, DMF, imidazole; (b) MOMCl, Hunig's base, CH_2Cl_2, reflux, 90%; (iv) (a) HF (48%), pyridine, THF, 85%; (b) CrO_3/H_2SO_4, 2.67 M, acetone, 0 ^oC; (c) 6 N HCl, 80 ^oC, 2 h, 75%.

Takahata's Approach (2008)[22]

Takahata *et al*. have reported a new method for synthesis of 3-hydroxypipecolic acid **58** using RCM and enzymatic resolution as the key steps **(Scheme 13)**. Ester **73** was treated with LiHMDS and acrolein to provide di-allyl compound **74**, which was subsequently subjected to RCM reaction to furnish piperidine **75**. The piperidine derivative **75** on enzymatic resolution gave alcohol **76** and acetate **77**. The acetate ester **77** on hydrogenation followed by acidic hydrolysis provided 3-hydroxypipecolic acid (**58**).



73 **74** **75**

99% ee, **76** 97% ee, **77**

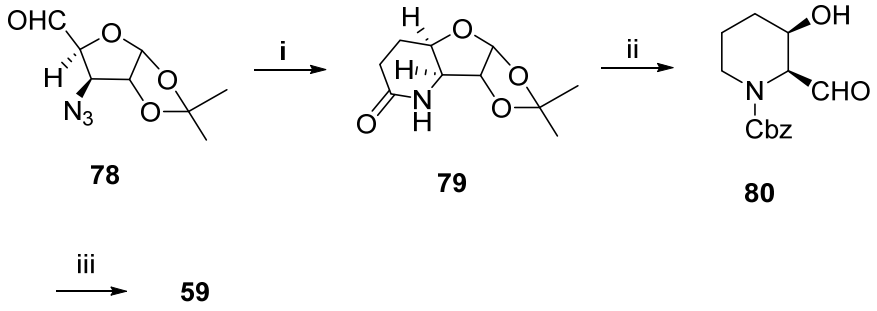
58

Scheme 13: (i) LiHMDS, acrolein, THF; (ii) Grubbs 1st gen. cat., CH_2Cl_2; (iii) Lipase PS-C, vinyl acetate, *i*-Pr_2O; (iv) (a) H_2, Pd/C; (b) 5N HCl.

Dhavale's approach (2008)[23]

Dhavale *et al*. utilized D-glucose as a starting material for the synthesis of *cis*-3-hydroxypipecolic acid **59**. The azido aldehyde **78** obtained from D-glucose by literature reported method. Compound **78** was subjected to Wittig reaction followed by azide reduction to furnish amide **79**. Amide **79** was reduced using $LiAlH_4$ followed by Cbz protection, acetonide deprotection and cleavage of generated diol to give

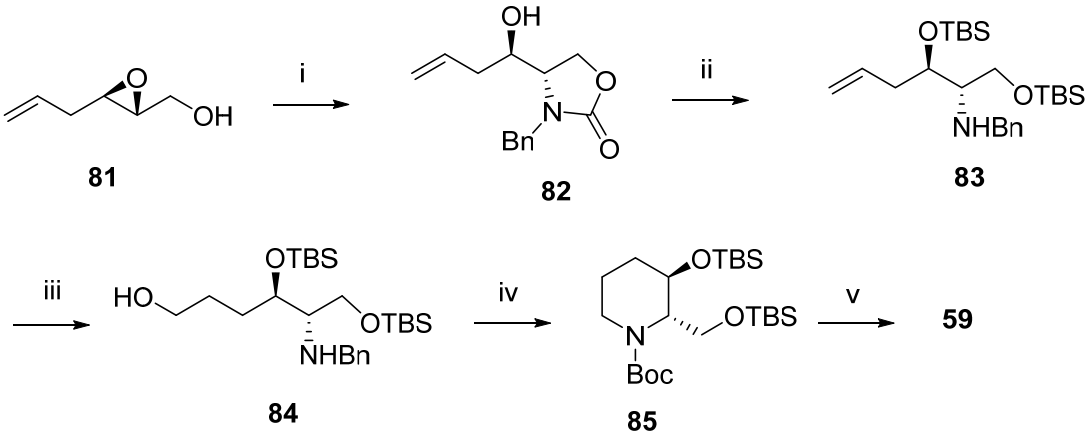
aldehyde **80**. Finally, aldehyde **80** was converted to 3-hydroxypipecolic acid **59** by oxidation and Cbz deprotection (**Scheme 14**).



Scheme 14: (i) (a) $Ph_3P{=}CHCO_2Et$; (b) H_2, Pd/C; (ii) (a) $LiAlH_4$, THF; (b) CbzCl, $NaHCO_3$; (c) TFA, H_2O; (d) $NaIO_4$, acetone/H_2O; (iii) (a) $NaClO_2$, 30% H_2O_2, CH_3CN/H_2O; (b) H_2, Pd/C.

Riera's Approach (2008)[24]

This method of synthesis of (2*R*, 3*R*)- 3-hydroxypipecolic acid **59** have commenced from epoxy alcohol **81** which was prepared by Sharpless asymmetric epoxidation **(Scheme 15)**. Epoxide **81** was intramolecularly opened using benzyl isocyanate to provide cyclic carbamate **82**. Cyclic carbamate **82** was deprotected under basic

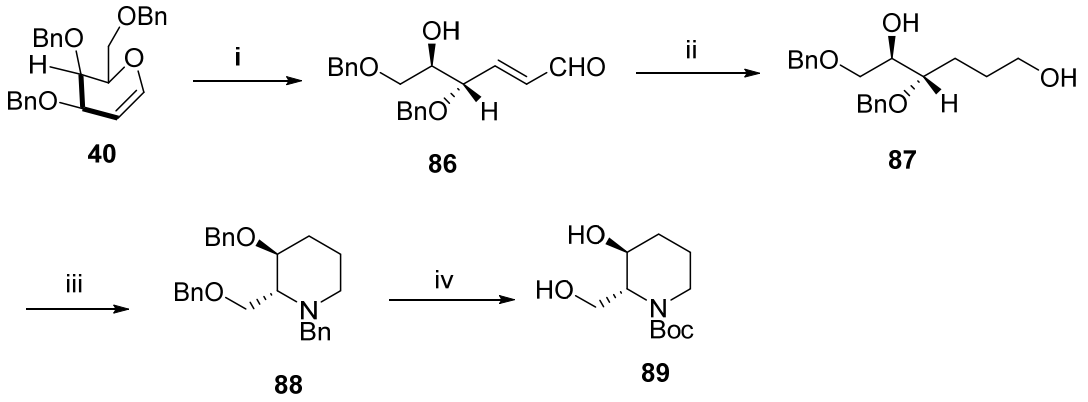


Scheme 15: (i) (a) BnNCO, THF; (b) $NaN(TMS)_2$, 86%; (ii) (a) MeOH/H_2O, 6M NaOH; (b) TBSOTf, lutidine, DCM, 0 °C, 2 h, 96%; (iii) (a) 9-BBN, THF/Hexane, -78 °C; (b) NaOH, H_2O_2, 81%; (iv) (a) H_2, Pd(OH)/C, $(Boc)_2O$; (b) MsCl, py; (c) *t*-BuOK, THF, 72% over two steps; (v) (a) *p*-TsOH, MeOH, 2 h, 74%; (b) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$; (c) 6M, HCl, 63% over two steps.

condition and the resulting diol was protected as its TBS derivative **83**. The olefin **83** was subjected to hydroboration-oxidation to give alcohol **84**. The *N*-benzyl in **84** was deprotected under catalytic hydrogenation conditions followed by its protection with Boc group. Subsequently, the primary alcohol was mesylated followed by its treatment with base furnished piperidine derivative **85**. Primary TBS ether in **85** was selectively deprotected using PTSA followed by oxidation using ruthenium catalyst and acidification gave hydrochloride salt of (2*R*, 3*R*)-3-hydroxypipecolic acid (**58**).

Vankar's Approach (2010)[13a]

Vankar *et al*. have completed a formal synthesis of pipecolic acid along with deoxoprosophylline starting from D-glycal by taking advantage of Perlin hydrolysis, chemoselective saturation of olefins and reductive amination as the key steps **(Scheme 16)**. D-Glycol **40** was subjected to Perlin hydrolysis to provide unsaturated aldehyde **86**, which was subjected to reduction followed by hydrogenation to furnish diol **87**. Diol **87** on mesylation and subsequent treatment with benzyl amine provided piperidine **88**, which on hydrogenation and Boc protection gave diol **89**, which is the key intermediate for 3-hydroxypipecolic acid **(58)**.



40 86 87 88 89

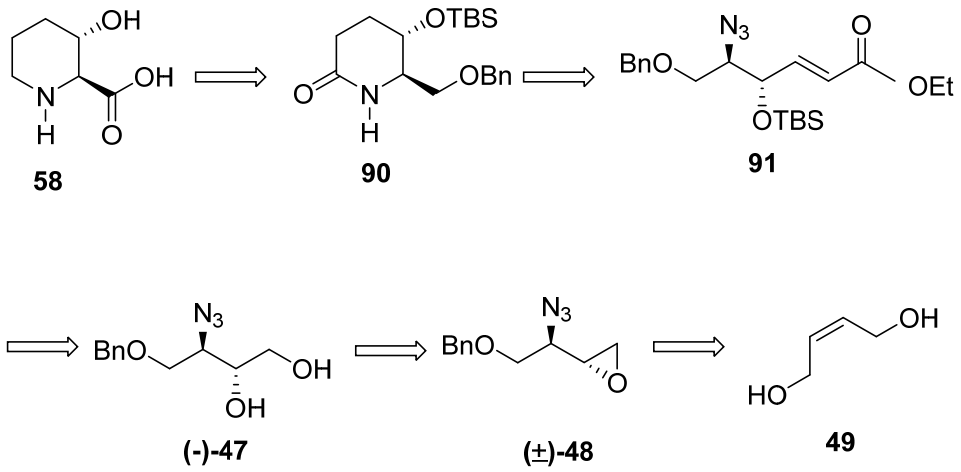
Scheme 16: (i) Perlin hydrolysis; (ii) (a) $NaBH_4$, $CeCl_3$.$7H_2O$, MeOH, rt, 1 h, (b) H_2, Pd/C, EtOAc, 30 min; (iii) (a) MsCl, Et_3N, CH_2Cl_2, 20 min; (b) $BnNH_2$, 90 ^oC, 2 h; (iv) (i) H_2, $Pd(OH)_2$/C, (b) $(Boc)_2O$, Na_2CO_3, MeOH.

2.2.3. Present Work

2.2.3.1 Objective

Even though several methods of enantioselective synthesis of **58** or its isomers have been reported, majority of them employ chiral pool as starting material, enzymatic resolution, a lengthy number of steps and are not sufficiently flexible to allow stereoselective access to different stereoisomeric structures. 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 (2*S*, 3*S*)-3-hydroxypipecolic acid **58**. This section presents a highly enantioslective synthesis of (2*S*, 3*S*)-3-hydroxypipecolic acid **58** using HKR of azido epoxide[14] as key step.

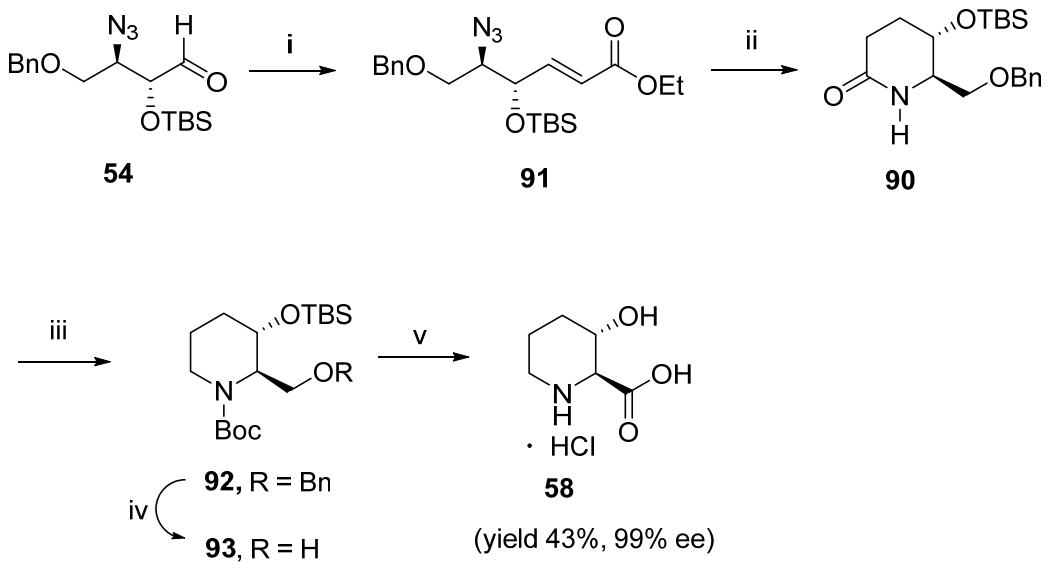
As can be seen from the retrosynthetic analysis **(Scheme 17)**, the *anti*-azido diol **47** could be visualized as an important precursor for the synthesis of target molecule **58.** The synthesis of *anti*-azido diol **47** could be achieved by means of Co-catalyzed Hydrolytic Kinetic Resolution of racemic azido epoxide **48**. The racemic azido epoxide can be readily prepared in three steps from *cis*-butenediol **49.**



Scheme 17: Retrosynthetic analysis of (2*S*, 3*S*)-3-hydroxypipecolic acid **(58)**

2.2.3.2 Results and Discussion

The synthesis of (2*S*, 3*S*)-3-hydroxypipecolic acid **(58)** commenced from *cis*-2-butene-1,4-diol. The azido aldehyde **54** was prepared from *cis*-2-butene-1,4-diol by following a simple procedure described in the previous section as shown in **Schemes 9 & 10**. Thus, the crude aldehyde **54** was treated with $(EtO)_2POCH_2CO_2Et$ under Wittig-Horner conditions to give the corresponding (*E*)-azidoester **91** in 93% yield **(Scheme 18)**.



Scheme 18: (i) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0-25 °C, 1 h, 93%; (ii) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 90%; (iii) $BH_3.SMe_2$, THF, reflux, 6 h, then CH_2Cl_2/H_2O (1:1), Na_2CO_3, $(Boc)_2O$, 25 °C, 12 h, 80%; (iv) 10% Pd/C, H_2 (70 psig), MeOH, 25 °C, 24 h, 96%; (v) (a) $RuCl_3$ (2 mol%), $NaIO_4$ (4 equiv), $CH_3CN/CCl_4/H_2O$ (1:1:3), 25 °C, 30 min; (b) 6 N HCl, reflux, 2 h, for two steps 68%.

The formation of (*E*)-azidoester **91** was confirmed by the appearance of proton signals at δ 6.01 (dd, *J* = 15.5, 1H) and δ 6.86 (dd, *J* = 15.5, 1H) due to olefinic protons in its ^1H NMR spectrum. Its ^{13}C NMR spectrum showed a characteristic ester carbonyl carbon signal at δ 165.7, which confirmed ester **91 (Fig. 16)**.

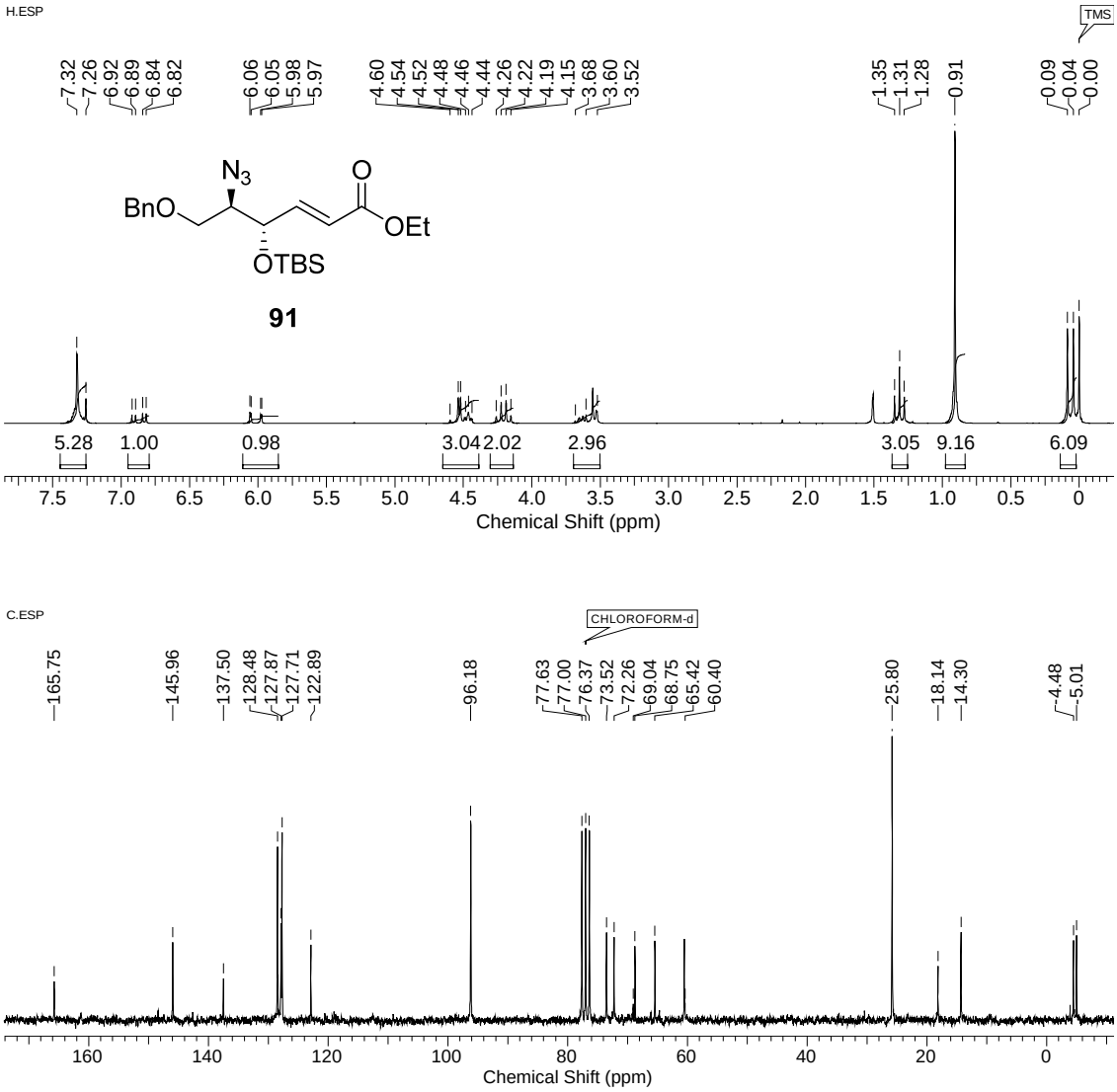


Fig. 16: ^{1}H and ^{13}C NMR spectra of **91**

Further, the azide function in **91** was subjected to intramolecular reductive cyclization over catalytic 10% Pd/C, H_2 (1 atm) that afforded *trans*-2,3-disubstituted piperidinone core **90** in 90% yield with the OBn group intact. The formation of lactam **90** was confirmed by its ^{1}H NMR spectrum, which showed the appearance of multiplets at δ 1.72-2.58 due to methylene protons of lactam ring. The other signals at δ 4.52 and δ 7.31 are due to the presence of -OBn group. Its ^{13}C NMR spectrum showed a typical signal at δ 170.89corresponding to amide carbonyl carbon group **(Fig. 17)**.

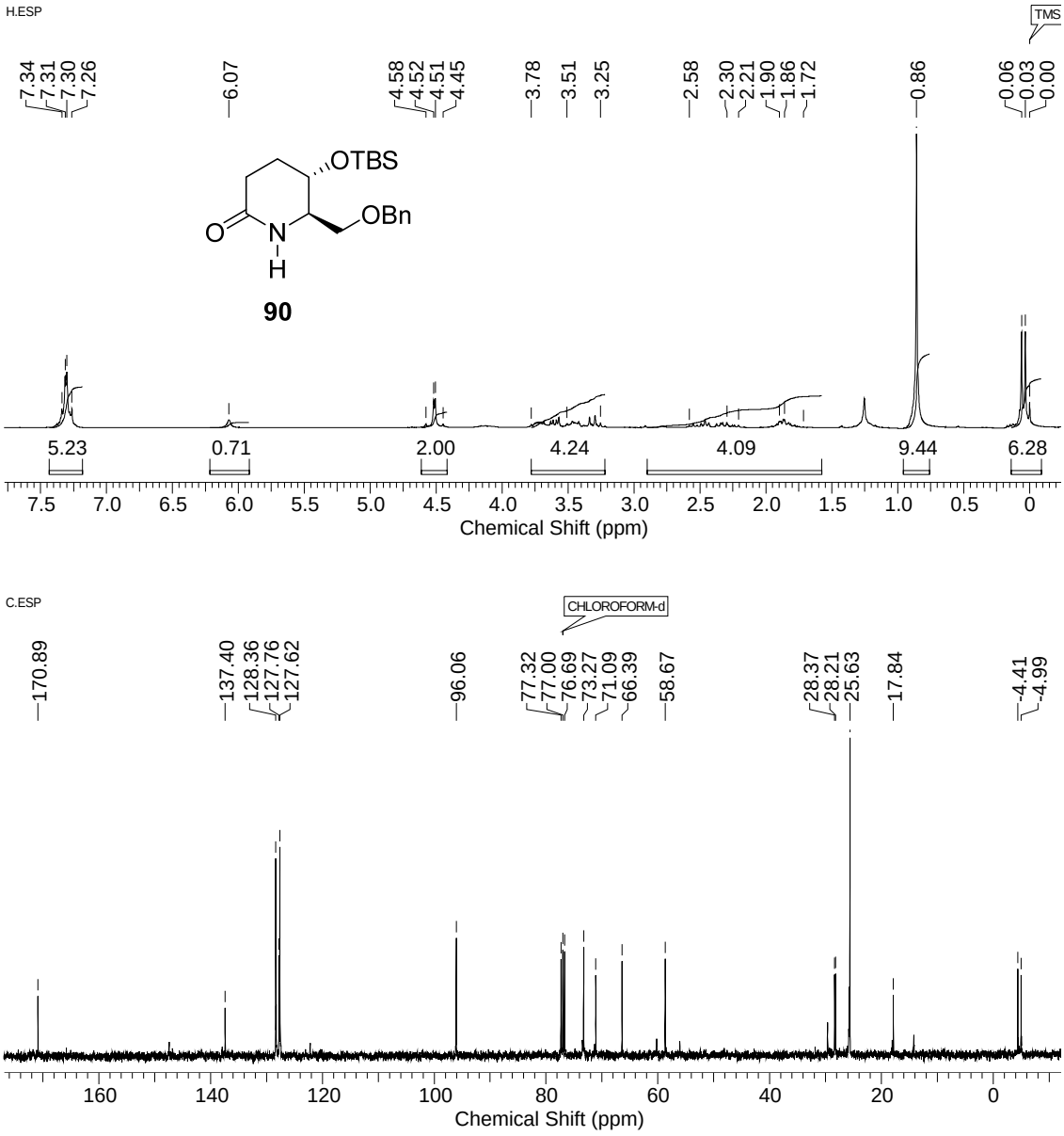


Fig. 17: ^{1}H and ^{13}C NMR spectra of **90**

Reduction of **90** with $BH_3 \cdot SMe_2$ followed by *in situ* *N*-Boc protection gave *trans*-piperidine derivative **92** in 80% yield. The ^{1}H NMR spectrum of **92** displayed a typical proton signal at δ 1.45 for methyl protons of *N*-Boc group. Its ^{13}C NMR spectrum showed a characteristic signal at δ 79.0 for quaternary carbon of *N*-Boc group **(Fig. 18)**.

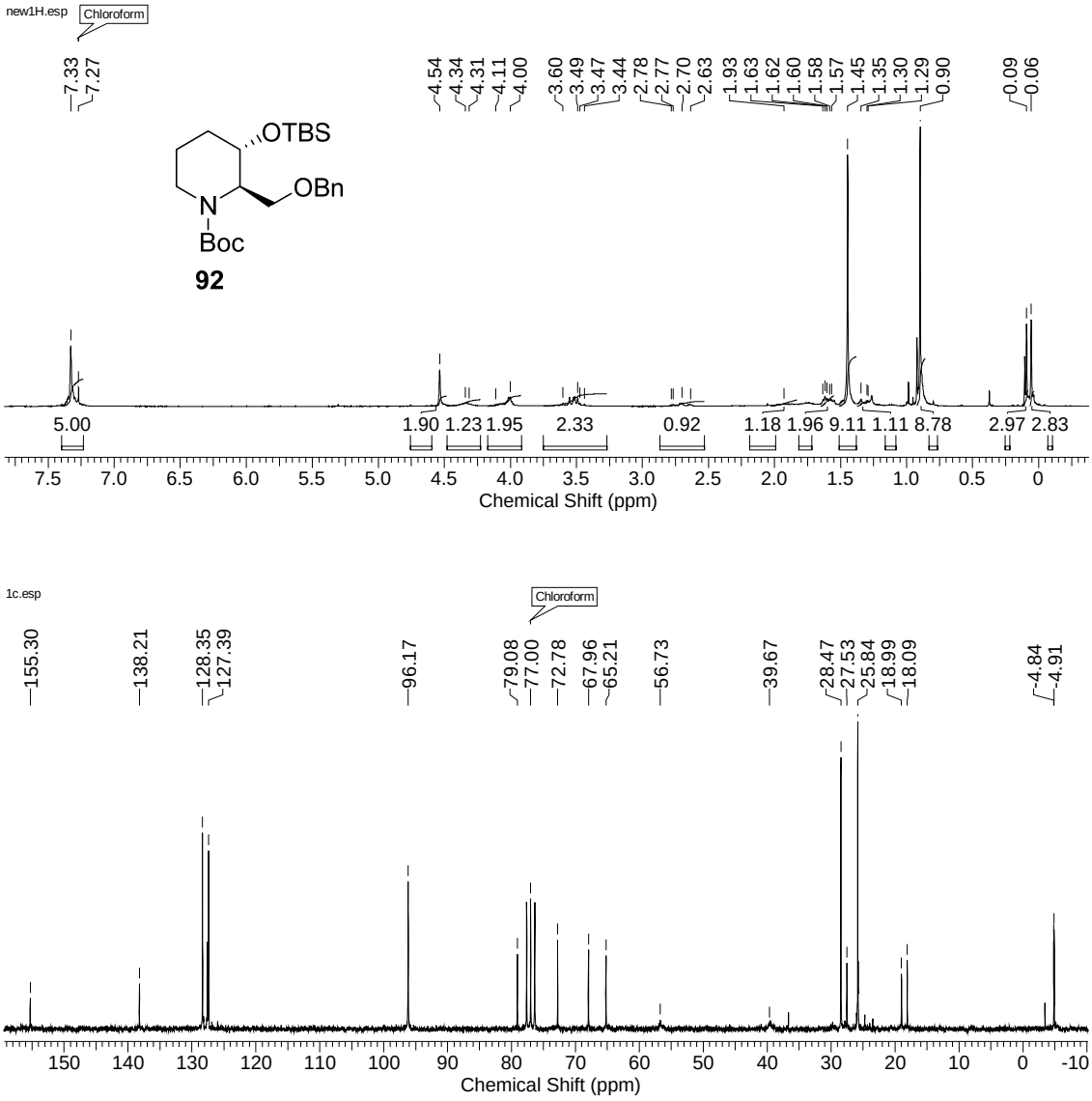


Fig. 18: ^{1}H and ^{13}C NMR spectra of **92**

Cyclic amine **92** was hydrogenated over Pd/C in MeOH at 70 psig of H_2 pressure to furnish alcohol **93** in 96% yield. The ^{1}H NMR spectrum of **93** displayed characteristic signals at δ 0.05, 0.08 and 0.88 for methyl protons of TBS group. The disappearance of proton signals in the aromatic region confirmed the deprotection of benzyl group. Its ^{13}C NMR showed characteristic signal at δ 156.0 due to amide carbonyl carbon group **(Fig. 19)**.

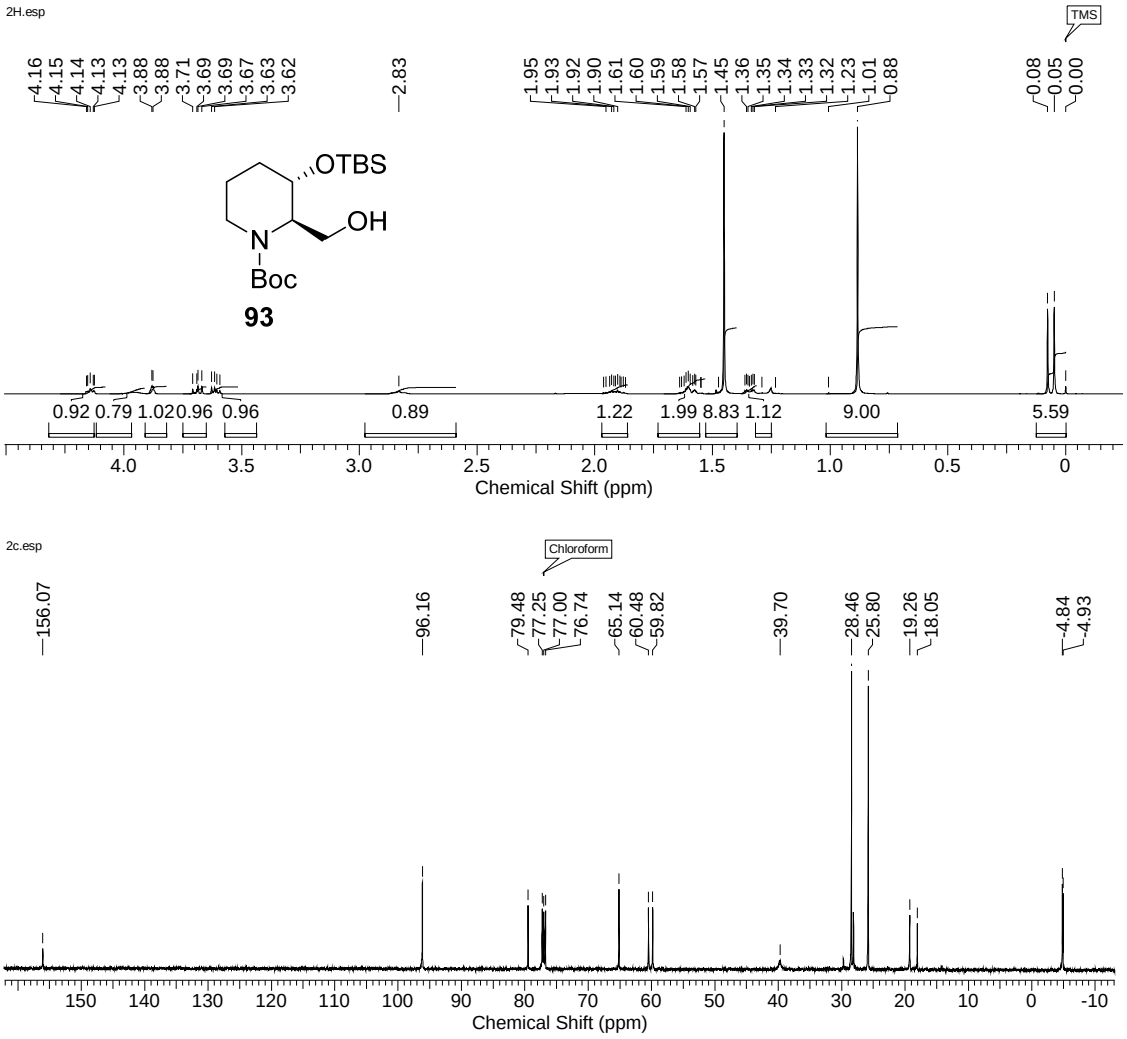


Fig. 19: ^{1}H and ^{13}C NMR spectra of **93**

Finally, the oxidation of alcohol **93** to carboxylic acid was achieved with $RuCl_3/NaIO_4$ combination, followed by successful removal of both the protecting groups under acidic conditions (6N HCl) gave (2*S*, 3*S*)-3-hydroxypipecolic acid **(58)** with an overall yield of 43% from **54** in 6 steps. The formation of (2*S*, 3*S*)-3-hydroxypipecolic acid **58** was confirmed by its ^{1}H and ^{13}C NMR spectra. Its ^{1}H NMR spectrum showed multiplets at δ 3.84 (1H) and δ 4.16 (1H) due to methine (-**C**H-O) protons. This was further ascertained by ^{13}C NMR spectrum, which showed signals at δ 61.1 and δ 65.9 for methine (-**C**H-O) carbons. A typical carbon signal at δ 171.3 is due to carbonyl carbon group (**Fig. 20**).

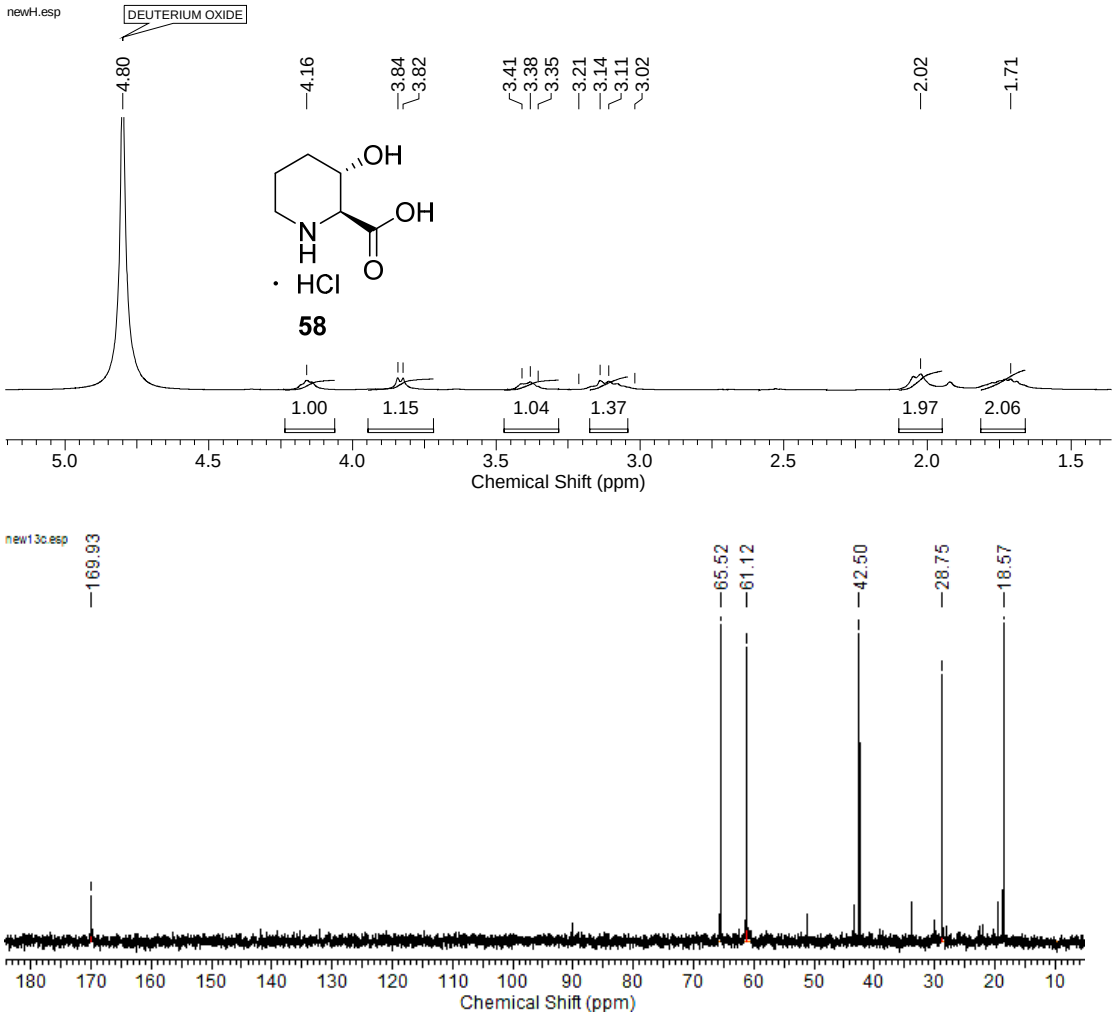


Fig. 20: ^{1}H and ^{13}C NMR spectra of **58**

2.2.4 Conclusion

In conclusion, this section has presented a short and practical enantioselective synthesis of *trans* (2*S*, 3*S*)-3-hydroxypipecolic acid (**58**) with good overall yield and high optical purity (ee up to 99%). The key reaction employed was a two-stereocentered Co-catalyzed HKR of racemic azido epoxides. The other operationally simple reaction sequences include Wittig reaction and intramolecular reductive cyclization. The synthetic strategy described herein has significant potential for further extension to other stereoisomers and related analogues of multifunctionalized piperidine alkaloids owing to its flexible nature of the synthesis of racemic azido

epoxides with different stereochemical combinations and with different substituents.

2.2.5 Experimental section

(4*S*, 5*R*, E)-Ethyl 5-azido-6-(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate (91)

To a stirred solution of NaH (0.24 g, 6 mmol) in dry THF (10 mL), triethyl phosphonoacetate (1.7 g, 7.5 mmol) was added at 0 ^{o}C. After 5 min, a solution of crude aldehyde **54** (1.5 g, 5 mmol) in THF (5 mL) was added drop wise. The reaction mixture was stirred at 25 ^{o}C for 3 h, and then quenched with saturated solution of NH_4Cl (5 mL). The product was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **91**, which was purified by column chromatography using petroleum ether: ethyl acetate (20:1) as eluent to give (*E*)-α,β-unsaturated azidoester **91** as a yellow oil.

Yield: 93%, colorless oil; $[\alpha]_D^{25}$ = +10.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1610, 1740, 2101, 2935; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.31 (t, *J* = 7.0 Hz, 3H), 3.52-3.68 (m, 3H), 4.22 (q, *J* = 14.2, 7.0 Hz, 2H), 4.44-4.60 (m, 3H), 6.01 (dd, *J* = 15.5, 1.6 Hz, 1H), 6.86 (dd, *J* = 15.5, 5.3 Hz, 1H), 7.28-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): -5.0, -4.4, 14.2, 18.1, 25.8, 60.4, 65.4, 68.7, 72.2, 73.5, 122.8, 127.7, 127.8, 128.4, 137.3, 145.9, 165.7; **Anal.** Calcd for $C_{21}H_{33}N_3O_4Si$ requires C, 60.11; H, 7.93; N, 10.01; found C, 60.08; H, 7.80; N, 10.18%.

(5*S*,6*R*)-6-((Benzyloxy)methyl)-5-((*tert*-butyldimethylsilyl)oxy)piperidin-2-one (90)

To a solution of (*E*)-α,β-unsaturated azidoester **91** (1.0 g, 2.66 mmol) in methanol (10 mL), 10% Pd/C (60 mg) was added and the slurry stirred under H_2 atmosphere (1 atm)

at 25 ^{o}C for 12 h. The progress was monitored by TLC. After completion of reaction, it was filtered through a Celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under *vacuum*. The crude product thus obtained was refluxed in ethanol (20 mL) for 1 h. Ethanol was then concentrated under *vacuum*. The crude product was purified by column chromatography on silica gel using petroleum ether: ethyl acetate (6:4) as eluent to give TBS protected lactam **90** in pure form.

Yield: 90%, colorless oil; $\mathbf{[\alpha]_D^{25}}$ = +38.6 (*c* 1, $CHCl_3$) {lit.[25] $[\alpha]_D^{25}$ -39.7 for its antipode (*c* 0.6, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1150, 1670, 2915, 3256; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.72-2.58 (m, 4H), 3.25-3.78 (m, 4H), 4.52 (d, *J* = 2.2 Hz, 2H), 6.07 (brs, 1H), 7.26-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.0, -4.4, 17.8, 25.6, 28.2, 28.3, 58.6, 66.3, 71.1, 73.2, 127.6, 127.7, 128.3, 137.4, 170.8; **Anal.** Calcd for $C_{19}H_{31}NO_3Si$ requires C, 65.29; H, 8.94; N, 4.01; found C, 65.18; H, 8.80; N, 4.15%.

(2*R*, 3*S*)-*tert*-Butyl 2-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate (92)

To a stirred solution of lactum **90** (0.2 g, 0.57 mmol) in dry THF (10 mL), $BH_3{\cdot}SMe_2$ (0.11 mL, 1.14 mmol) was added dropwise at 0 °C under N_2 atmosphere and the mixture was then refluxed for 6 h. After the completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. The crude amino alcohol was then dissolved in CH_2Cl_2/H_2O (1:1) (10 mL) followed by the addition of Na_2CO_3 (0.16 gm, 1.58 mmol) and $(Boc)_2O$ (0.208 mL, 0.9 mmol). The reaction mixture was stirred for 12 h. After the completion of the reaction (monitored by TLC), it was extracted with CH_2Cl_2 (3 x 5 mL), washed with brine and dried over anhydrous

Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude **92**, which was purified by column chromatography with silica gel using pet. ether : ethyl acetate (7:3) as eluent to give **92** in pure form.

Yield: 80%, colorless oil; $[\alpha]_D^{25}$ = -15 (*c* 1, $CHCl_3$); {lit.[26] $[\alpha]_D^{25}$ -14 (*c* 0.9, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1290, 1452, 2930, 1691; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.9 (s, 9H), 1.29-1.34 (m, 1H), 1.45 (s, 9H), 1.57-1.63 (m, 2H), 1.80-1.93(m, 1H), 2.77 (m, 1H), 3.44-3.60 (m, 2H), 4.00 (m, 2H), 4.31 (m, 1H), 4.54 (s, 2H), 7.33 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.8, 18.0, 18.9, 25.8, 27.5, 28.4, 39.6, 56.7, 65.2, 67.9, 72.7, 79.0, 127.3, 127.5, 128.3, 138.2, 155.3; **Anal.** Calcd for $C_{24}H_{41}NO_4Si$ requires C, 66.16; H, 9.49; N, 3.21; found C, 66.18; H, 9.45; N, 3.17%.

(2*R*, 3*S*)-*tert*-Butyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)piperidine-1-carboxylate (93)

To a solution of **92** (0.43 g, 1 mmol) in dry methanol was added Pd/C (0.05 g) and the reaction mixture was stirred under an atmosphere of H_2 (70 psig) for 24 h at 25 ^oC. After the completion of the reaction (monitored by TLC), it was filtered over Celite and the filtrate was concentrated under reduced pressure to provide the crude product **93**, which was purified by column chromatography using petroleum ether: ethyl acetate (8:2) to obtain pure **93.**

Yield: 96%, colorless oil; $[\alpha]_D^{25}$ = -16 (*c* 1, $CHCl_3$) {lit.[26] $[\alpha]_D^{23}$ -16 (*c* 0.74, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 870, 1190, 3435, 1669; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.23-1.36 (m, 1H), 1.45 (s, 9H), 1.57-1.61 (m, 2H), 1.90-1.95 (m, 1H), 2.83 (m, 1H), 3.62-3.63 (m, 1H), 3.69-3 .71 (m, 1H), 3.88 (m, 1H), 3.96 (m, 1H) 4.13-4.16 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.8, 18.0, 19.2,

25.8, 28.1, 28.4, 39.7, 59.8, 60.4, 65.1, 79.4, 156.0; **Anal.** Calcd for $C_{17}H_{35}NO_4Si$: C, 59.09; H, 10.21; N, 4.05. Found: C, 59.01; H, 10.20, N, 4.10.

(2*S*, 3*S*)-3-hydroxypipecolic acid (58)

To a stirred solution of **93** (70 mg, 0.2 mmol) and $NaIO_4$ (170 mg, 1.0 mmol) in $CH_3CN/CCl_4/H_2O$ (1:1:3) (3 mL) was added $RuCl_3 \cdot 3H_2O$ (2 mg, 5 mol %) in one portion, and the reaction mixture was stirred for 30 min at 25 ^oC. After the completion of the reaction (monitored by TLC), it was filtered through Celite and concentrated under reduced pressure and the residue was taken in 6N HCl (5 ml) and refluxed for 2 h. The reaction mixture was cooled to room temperature and extracted once with CH_2Cl_2 (20 ml) to remove any organic impurities. The aqueous layer was concentrated under vacuum, residue dried under high vacuum to afford the desired compound (2*S*, 3*S*)-3-hydroxypipecolic acid **(58)**.

Yield: 68%, colorless solid, **mp** 232 ^oC; $[\alpha]_D^{25} = +14.2$ (*c* 1, H_2O) {lit.[26] $[\alpha]_D^{23}$ +14.5 (*c* 0.4, H_2O)}; **IR** (neat, cm^{-1}): υ_{max} 1085, 1420, 1685, 3420; **^{1}H-NMR** (200 MHz, D_2O): δ 1.71 (m, 2H), 2.02 (m, 2H), 3.02-3.21 (s, 1H), 3.35-3.41 (m, 1H), 3.84 (d, *J* = 7.6 Hz, 1H), 4.16 (m, 1H); **^{13}C-NMR** (50 MHz, D_2O): δ 18.5, 28.7, 42.5, 61.1, 65.5, 169.9; **Anal.** calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.74; N, 9.65; found: C, 49.60; H, 7.69; N, 9.70.

2.2.6 References

1. (a) Schneider, M. J. Pyridine and Piperidine Alkaloids: An Update. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155; (b) Fodor, G. B.; Colasanti, B. The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology. In *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S.W., Ed.; Wiley-Interscience: New York, 1985; Vol. 3, p 1.

2. (a) Ratle, G.; Monseur, X.; Das, B.; Yassi, J.; Khuong-Huu, Q.; Goutrarel, R. *Bull. Soc. Chim. Fr*. **1996**, 2945; (b) Khuong-Huu, Q.; Rutle, G.; Monseur, X.; Goutrarel, R. *Bull. Soc. Chim. Belg*. **1972**, *81*, 425.

3. (a) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, pp 89; (b) Bourinet, P.; Quevauviller, A. *Compt. Rend. Soc. Biol*. **1968**, *162*, 1138; (c) Bourinet, P.; Quevauviller, A. *Ann. Pharm. Fr*. **1968**, *26*, 787.

4. (a) Asano, N. *Glycobiology* **2003**, *13*, 93. (b) Junge, B.; Matzke, M.; Stoltefuss, J. In *Handbook of Experimental Pharmacology*; Kuhlmann, J., Puls, W., Eds.; Springer: Berlin, Heidelberg, New York, 1996; Vol. 119, p 411.

5. Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed*. **1999**, *38*, 1532.

6. Ojima, I.; Vidal, E. S. *J. Org. Chem.* **1998**, *63*, 7999.

7. Yang, C.; Liao, L.; Xu, Y.; Zhang, H.; Xia, P.; Zhou, W. *Tetrahedron: Asymmetry* **1999**, *10*, 2311.

8. Jourdant, A.; Zhu, J. *Heterocycles* **2004,** *64*, 249.

9. Ma, N.; Ma, D. *Tetrahedron: Asymmetry* **2003**, *14*, 1403.

10. Davies, S. G.; Ichihara, O. *Tetrahedron*: *Asymmetry* **1991**, *2*, 183.

11. Kim, I. S.; Ryu, C. B.; Li, Q. R.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett*. **2007**, *48*, 6258.

12. Liu, R.-C.; Wei, J.-H.; Wei, B.-G.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2008**, *19*, 2731.

13. (a) Kokatla, H. P.; Lahiri, R.; Kancharla, P. K.; Doddi, V. R.; Vankar, Y. D. *J. Org. Chem*. **2010**, *75*, 4608; (b) Chavan, S. P.; Praveen, C. *Tetrahedron Lett*. **2004**, *45*, 421.

14. Reddy, R. S.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun*. **2010**, *46*, 5012.

15. (a) Pinder, A. R. *Nat. Prod. Rep*. **1989**, *6*, 67. (b) Pinder, A. R. *Nat. Prod. Rep*. **1992**, *9*, 17. (c) Pinder, A. R. *Nat. Prod. Rep*. **1992**, *9*, 491. (d) Nadin, A. *Contemp. Org. Synth.* **1997**, *4*, 387. (e) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun*. **1998**, 633. (f) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1. (g) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553

16. (a) Sugisaki, C. H.; Caroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* **1998**, *39*, 3413. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

17. Scott, J. D.; Tippie, T. N.; Williams, R. M. *Tetrahedron Lett.* **1998**, *39*, 3659.

18. Ferreira, F.; Greck, C.; Genet, J. P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 615.

19. Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7033.

20. Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2975.

21. Jourdant, A.; Zhu, J. P. *Tetrahedron Lett*. **2000**, *41*, 7033.

22. Ohara, C.; Takahashi, R.; Miyagawa, T.; Yoshimura, Y.; Kato, A.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem.* **2008**, *16*, 8273.

23. Kalamkar, N. B.; Kasture, V. M.; Dhavale, D. D. *J. Org. Chem.* **2008**, *73*, 3619.

24. Alegret, C.; Ginesta, X.; Riera, A. *Eur. J. Org. Chem.* **2008**, 1789.

25. Liu, R.-C.; Wei, J.-H.; Wei, B.-G.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2008**, *19*, 2731.

26. Wang, B.; Run-Hua, L. *Eur. J. Org. Chem*. **2009**, 2845.

Chapter III

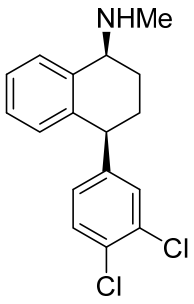
Enantioselective Synthesis of (+)-Sertraline via Hydrolytic Kinetic Resolution of 3-Diarylsubstituted Epoxide and Synthesis of Eupomatilone-6 via SmI_2-Mediated Reductive Coupling of Aldehyde with Crotonate Ester

Section I

A Short Enantioselective Synthesis of (+)-Sertraline *via* Hydrolytic Kinetic Resolution of 3-diarylsubstituted Epoxide

3.1.1 Introduction and Pharmacology

Selective serotonin reuptake inhibitors are a class of antidepressants used for the treatment of depression.[1] Drugs are designed to allow serotonin, the neurotransmitter to be utilized more effectively. Low-level serotonin is currently seen as one of numerous neurochemical symptoms of depression. These low levels of serotonin can be caused by an anxiety disorder, because serotonin is necessary to metabolize stress hormones. A depressive disorder is believed to be caused by a chemical imbalance in the brain. Messages are passed between two nerve cells *via* a small gap between the cells. The nerve cells sending the information release neurotransmitters into that gap.



(*S*)-(+)-1

Fig. 1: Structure of (*S*)-(+)-sertraline **1**

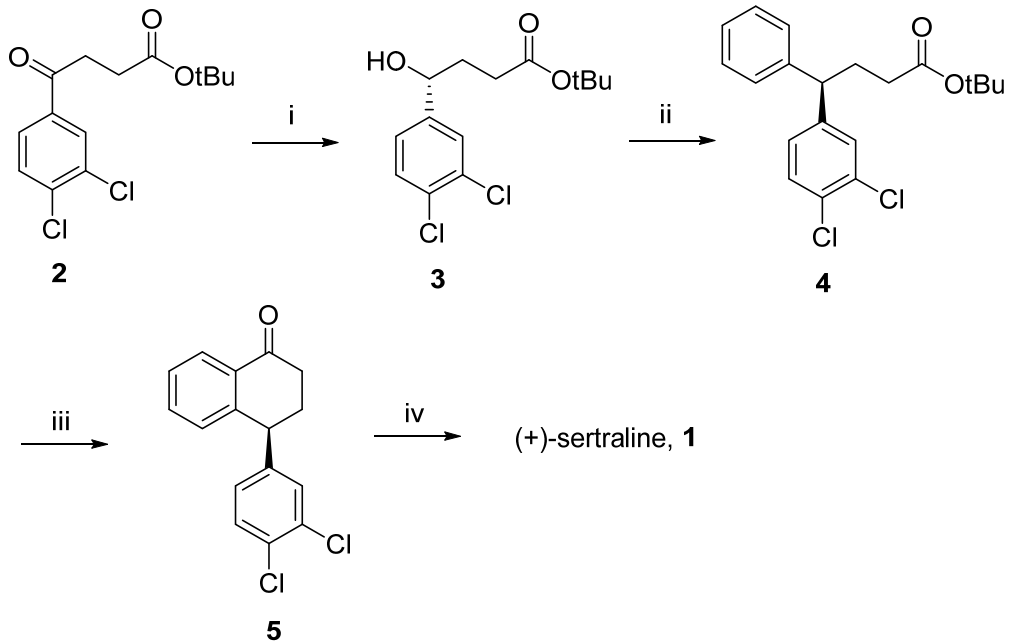
These neurotransmitters are recognized by receptors on the surface of the recipient cell, which relays the signal. Approximately, 10% of the neurotransmitters are lost in this process, with the other 90% released from the receptors and taken up again by monoamine transporters. Depression has been associated with a lack of stimulation of the recipient neuron at the synapse. To stimulate this cell, selective serotonin reuptake inhibitor (SSRI) block the reuptake of serotonin. (+)-Sertraline **1**, a selective serotonin

reuptake inhibitor (SSRI), is an important antidepressant drug discovered by Pfizer chemist Reinhard Sarges in 1970. It is one of the highest selling drugs, sold under the trade name Zoloft®.[2] Medically, sertraline (**1**) is also prescribed for the treatment of post-traumatic stress disorder and panic disorder. Administration of sertraline comes with side effects such as gastrointestinal complaints, nervousness and sexual dysfunction on long-term users.

3.1.2 Review of literature

Quallich's approach (1992)[3]

Quallich *et al*. have reported the first asymmetric synthesis of (+)-sertraline **1** using asymmetric CBS reduction reaction as key step (**Scheme 1**). Synthesis began with asymmetric reduction of γ-keto ester **2** with CBS catalyst, which gave the hydroxy ester **3** in quantitative yield and 88% ee. Alcohol **3** was mesylated and coupled with

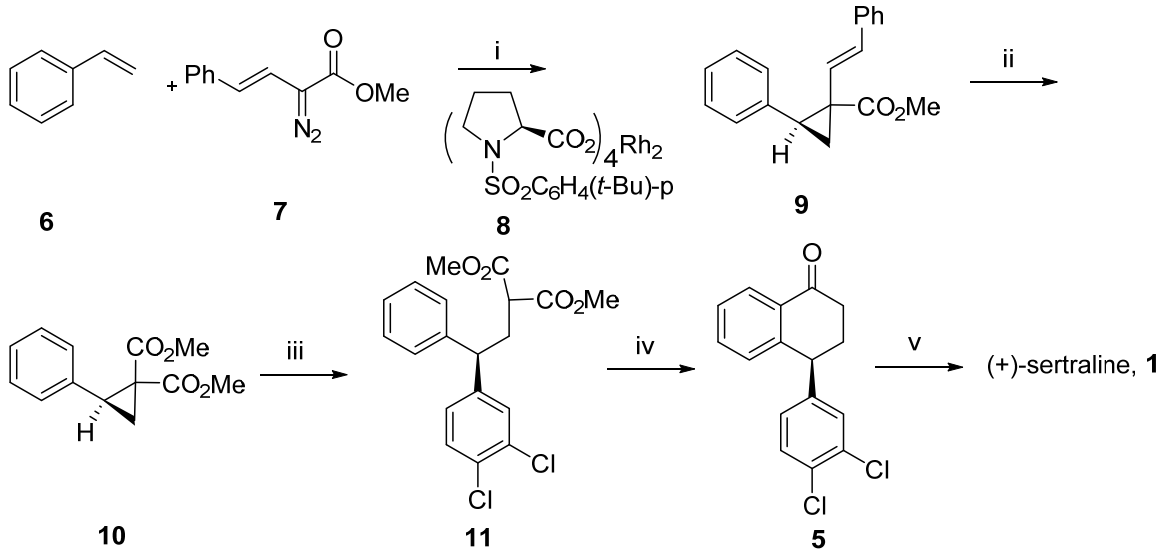


Scheme 1: (i) BH_3, (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrollo [1,2-C][1,3,2] oxazaborole (CBS), THF, 0 °C, 100%; (ii) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min; (b) CuCN, PhLi, Et_2O, -45 °C, (iii) CF_3CO_2H, benzene, 70 °C, 2 h; (iv) $TiCl_4$, $MeNH_2$ then Raney Ni, H_2, MeOH.

higher order phenyl cuprate to give butyrate **4** in 70% yield. The butyl ester **4** was directly cyclized to form tertralone **5** in the presence of triflic acid. Finally, transformation of **5** to (+)-sertraline **1** was achieved by reductive amination.

Corey's approach (1994)[4]

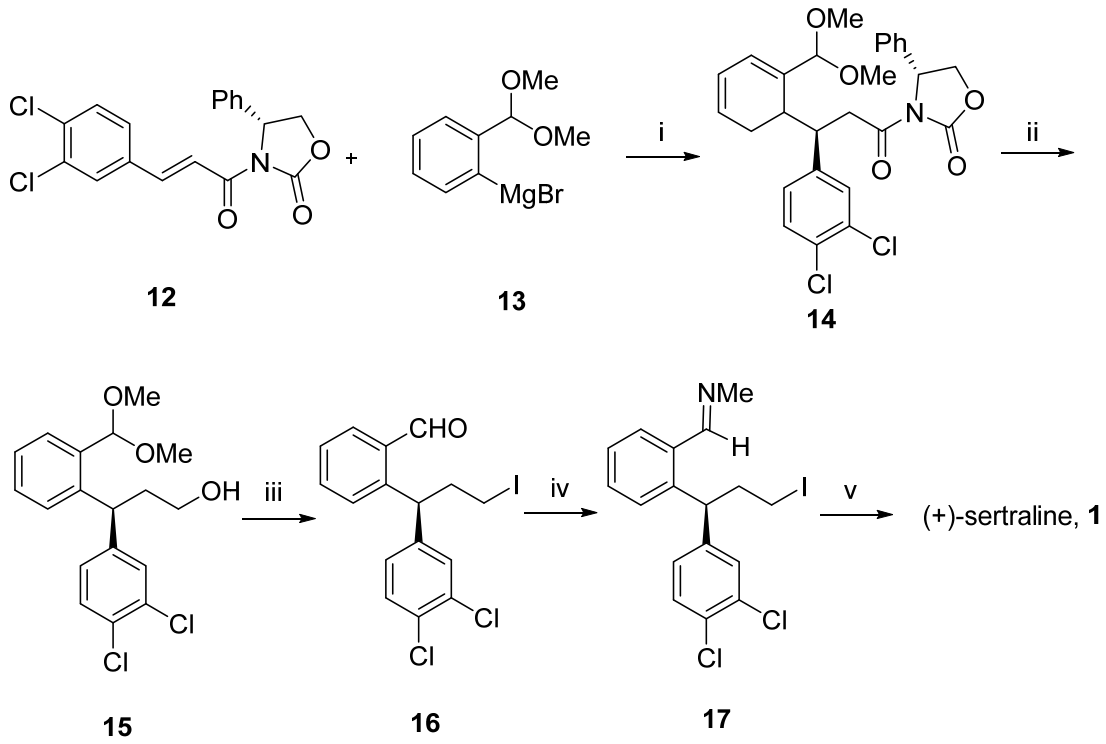
Corey *et al*. have reported the synthesis of (+)-sertraline **1** by employing Rh-catalyzed asymmetric cyclopropanation as key step. Thus, diazo butanoate **7** was subjected to asymmetric cyclopropanation with styrene **6** using proline derived catalyst **8** to afford cyclopropane ester **9** in 79% yield and 94% ee. The oxidation of styrenic C=C of **9** with $KMnO_4/NaIO_4$ followed by esterification afforded malonyl ester **10**. Treatment of **10** with Ar_2CuLi_2CN (prepared from 3,4-dichlorophenyl iodide) led to ring opening of cyclopropane ring to give diester **11** in 82% yield. Hydrolysis of diester **11** with 6N HCl followed by cyclization with chlorosulfonic acid gave tetralone **5**; reductive amination of which resulted in the formation of (+)-sertraline **1** (**Scheme 2**).



Scheme 2: (i) 10 mol% of catalyst **8**, pentane, 25 ^oC, 12 h, 79%; (ii) (a) $KMnO_4$, $NaIO_4$, K_2CO_3, ^tBuOH, 0.5 h, 25 ^oC, 83%; (b) K_2CO_3, Me_2SO_4, acetone, 3 h, 97%; (iii) BuLi, 3,4-dichlorophenyl iodide, CuCN, Et_2O, 15 min, 82%; (iv) (a) 6N HCl, reflux, 20 h then 1N NaOH; (b) $ClSO_3H$, CH_2Cl_2, 30 min, 84%; (v) reductive amination using $MeNH_2$.

Chen's approach (1999)[5]

Chen *et al*. have achieved the synthesis of (+)-sertraline **1** by the addition of Grignard reagent **13** onto α,β-unsaturated chiral oxazolidinone **12** to prvide **14** in 90% yield. Reductive removal of chiral auxiliary in **14** using $NaBH_4$ in THF-H_2O gave alcohol **15**. Alcohol **15** was transformed into iodoaldehyde **16** in 85% yield, which on treatment with methylamine, gave the corresponding imine **17.** Finally, compound **17** was subjected to BuLi-mediated intramolecular ring closing to give a single diastereomer of (+)-sertraline **1** (**Scheme 3**).

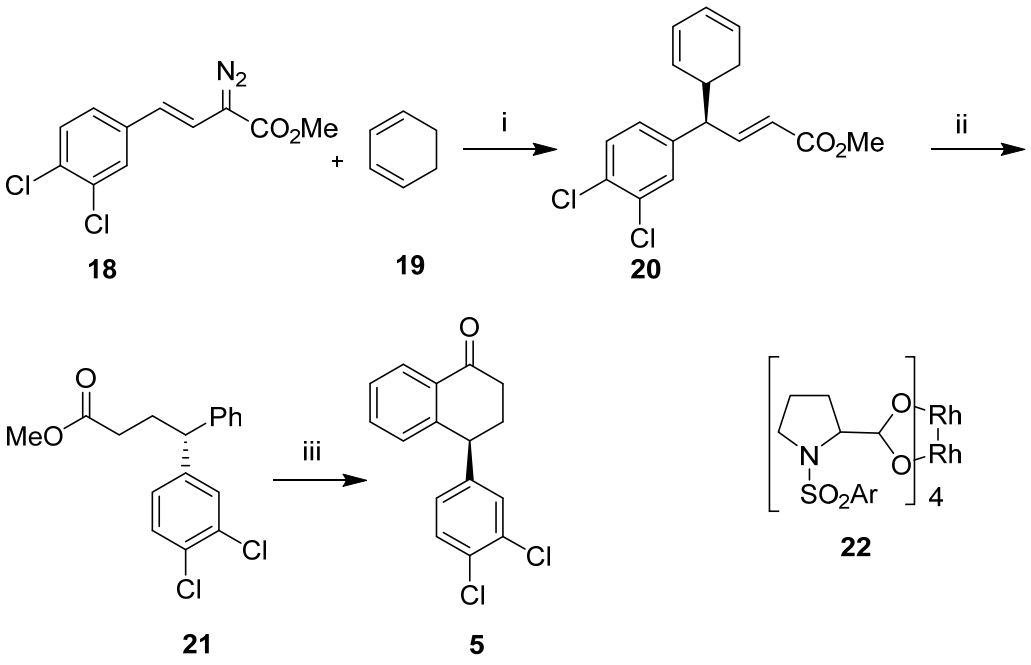


Scheme 3: (i) $CuBr{\cdot}SMe_2$ (20 mol%), THF, -30 °C, 90%; (ii) $NaBH_4$, THF-H_2O; (iii) (a) PPh_3, I_2, imid., CH_2Cl_2; (b) 2N HCl, 85%; (iv) 2.0 M $MeNH_2$ in THF, (v) *t*-BuLi, THF, toluene, -78 °C, 69%.

Davies's approach (1999)[6]

Davies *et al*. have reported a formal synthesis of (+)-sertraline **1** using Rh-catalyzed C-H insertion as the key step. The α-diazo ester **18** and cyclohexadiene **19** were

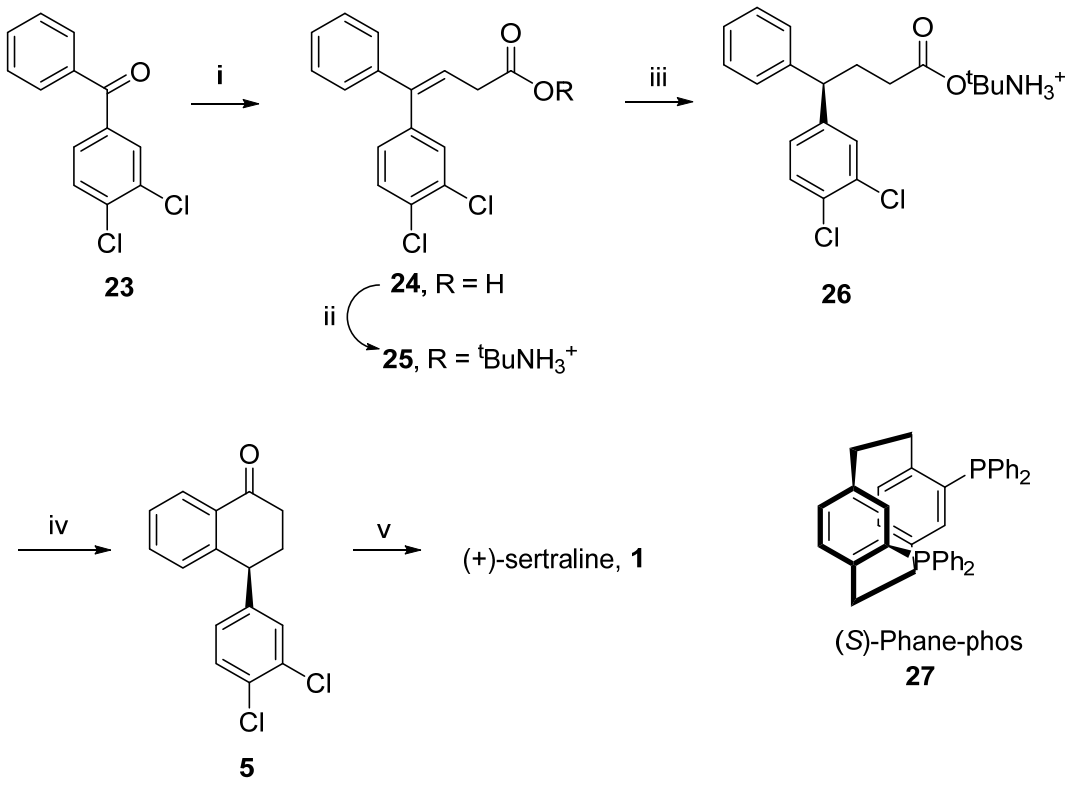
exposed to intramolecular C-H insertion using Rh-catalyst **22** that resulted in the formation of α,β-unsaturated ester **20**. Aromatization of **20** using DDQ followed by catalytic hydrogenation afforded saturated ester **21** in 52% yield. Ester **21** was hydrolyzed and cyclized intramolecularly to produce tetralone **5** in 79% yield and 96% ee, which is key intermediate for the synthesis of sertraline **1** (**Scheme 4**).



Scheme 4 (i) Rh_2(S-DOSP)$_4$, hexane, 23 ^oC, 59%; (ii) (a) DDQ, toluene; (b) Pd/C, H_2 (20 psi), EtOH, 52%; (iii) 6N HCl, then $ClSO_3H$, 25 ^oC, 2 h, 79%.

Boultan's approach (2003)[7]

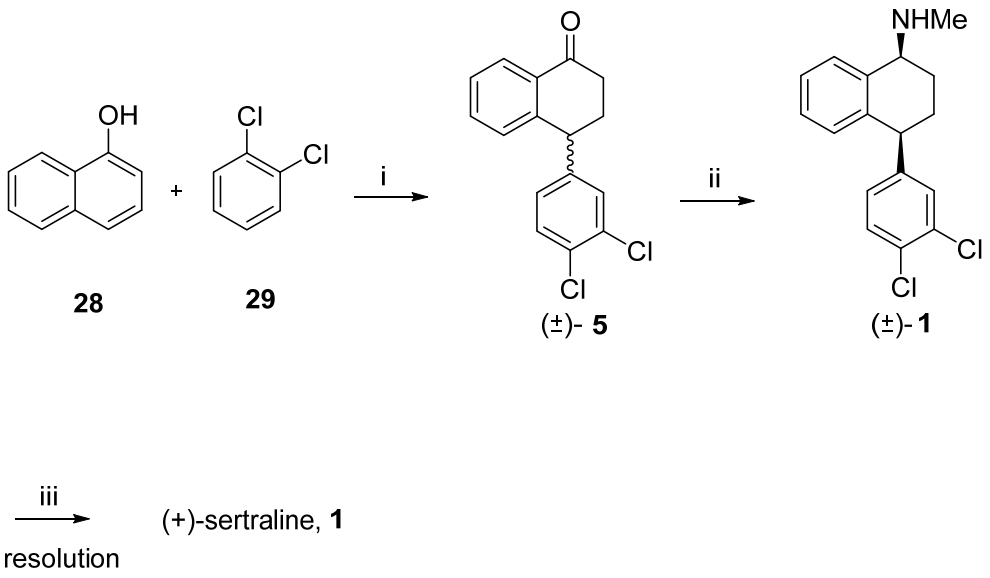
Boultan *et al*. have employed asymmetric hydrogenation as the key reaction. Diarylbutanoate salt **25** was prepared from 3,4-dichlorobenzophenone **23** by Wittig olefination. The compound **25** was subjected to asymmetric catalytic hydrogenation using Rh-phane-phos catalyst **27** and H_2 (120 psi) to afford enantioenriched saturated ester **26** in quantitative yield and 90% ee. Further, the synthesis of (+)-sertraline **1** was completed from **26** by following the three-step reaction sequences of hydrolysis, cyclization and reductive amination (**Scheme 5**).



Scheme 5: (i) $KOBu^t$, diethyl succinate, ^tBuOH; then 48% HBr, AcOH, 32%; (ii) $^tBuNH_2$, EtOAc, 99%; (iii) $[RhCOD]BF_4$, ligand **27**, H_2 (120 psi), MeOH; (iv) 2M H_2SO_4, EtOAc; then $ClSO_3H$, CH_2Cl_2, 91%; (v) $MeNH_2$, H_2, MeOH.

Colberg's approach (2004)[8]

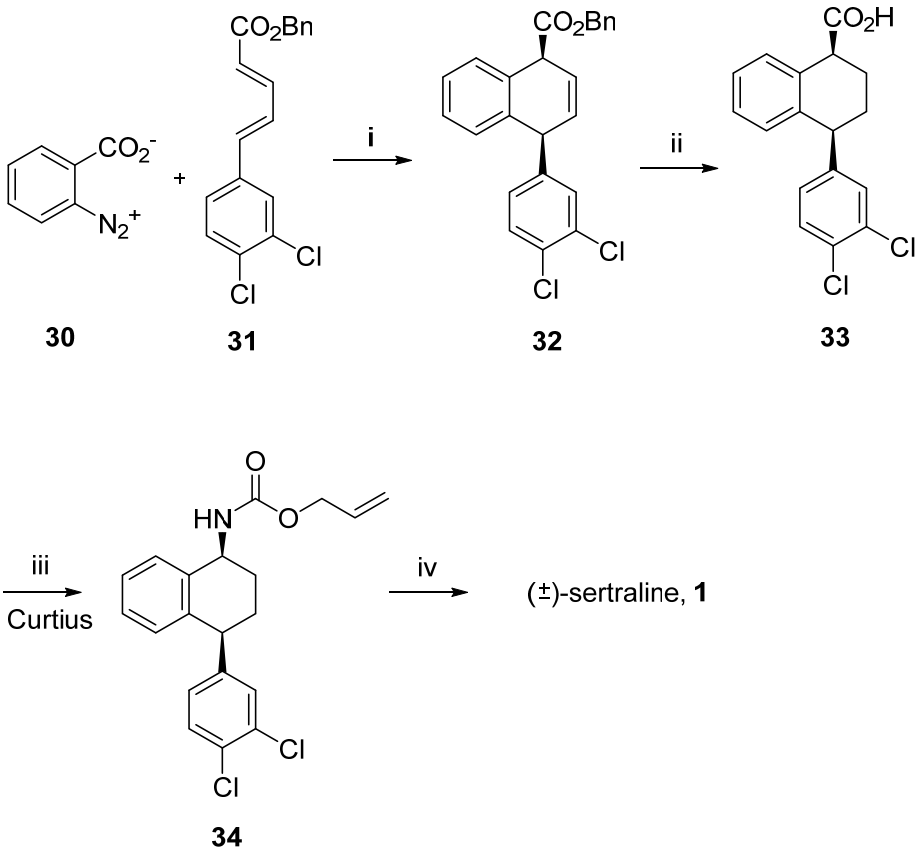
Colberg *et al*. have reported a short method of synthesis of (+)-sertraline **1** by employing kinetic resolution of recemic (±)-sertraline **1** as the key step. α-Napthol **28** and 1,2-dichlorobenzene **29** were reacted in the presence of anhyd. $AlCl_3$ under Friedel-Crafts alkylation conditions to give recemic (±)-tetralone **5** in 95% yield. Treatment of (±)-tetralone **5** with excess of methyl amine in ethanol furnished the corresponding imine, which was then subjected to reductive amination [$Pd/CaCO_3$, H_2 (50 psi)] to yield (±)-sertraline, **1** (*cis:trans* 20:1) with *cis* as the major isomer. The racemic sertraline, was then treated with D-mandelic acid so that the *cis* isomer is resolved selectively in solid form (**Scheme 6**).



Scheme 6: (i) $AlCl_3$; (ii) $MeNH_2$, EtOH, 95%; then $Pd/CaCO_3$ (1% w/w), H_2 (50 psi), 40%; (iii) (D)-mandelic acid, EtOH, reflux then -5 ^oC, 36%.

Lautens's approach (2005)[9]

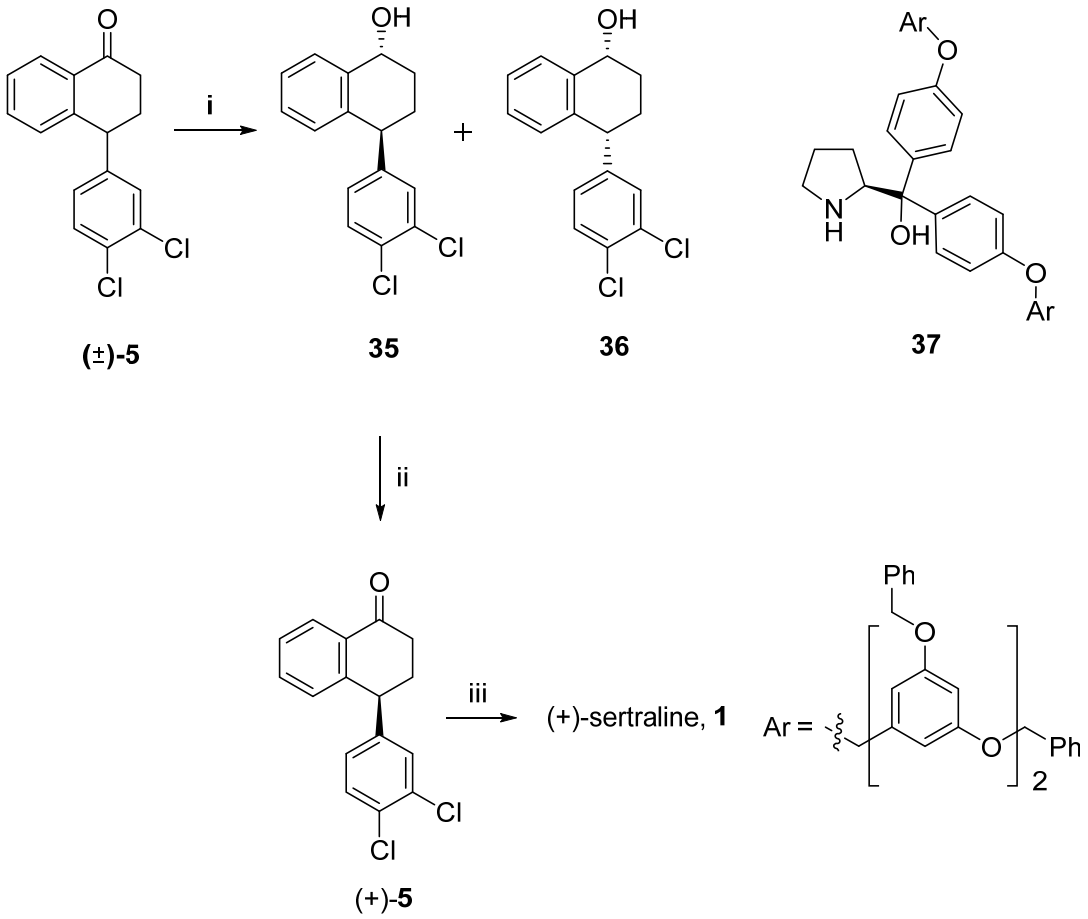
Lautens *et al*. have reported the synthesis of (±)-sertraline **1** by employing Diels-Alder reaction between benzenediazonium-2-carboxylate **30**, a benzyne-equivalent and dienyl ester **31** in 1,2-dichloroethane as solvent at 60 ^oC, to give the cycloadduct **32** in 78% yield. Cycloadduct **32** was hydrogenated and the benzyl group deprotected in one-pot with 10% Pd/C and H_2 (4 atm) to give carboxylic acid **33** in 94% yield. The compound **33** was then subjected to Curtius rearrangement *via* the initial formation of acylazide ($ClCO_2Et$, then NaN_3) followed by the addition of allyl alcohol at 90 ^oC, which afforded allyl carbamate **34** in 65% yield. *N*-Methylation and deprotection of allyl group in **34** resulted in the formation of (±)-sertraline **1** (**Scheme 7**).



Scheme 7: (i) 1,2-dichloroethane, 60 °C, 78%; (ii) 10% Pd/C, H_2 (4 atm), MeOH, 94%; (iii) (a) $ClCO_2Et$, NaN_3, Et_3N, toluene, 25 °C; (b) allyl alcohol (10 equiv.), toluene, 90 °C, 65%; (iv) (a) NaH, MeI, THF, 91%; (b) $Pd(OAc)_2$, $HNEt_2$, H_2O:CH_3CN, 75%.

Zhao's approach (2006)[10]

Zhao *et al.* reported a short synthesis of (+)-sertraline **1,** starting from recemic (±)-tetralone **5**. Compound **5** was subjected to reduction with L-proline derived catalyst **37** and $Me_2S{\cdot}BH_3$ to give diastereomers **35** and **36,** which were readily separated (in 94% yield and 97% ee). The oxidation of *trans* isomer **35** with PCC give the optically active (+)-tetralone **5**, which was transformed to (+)-sertraline **1** *via* reductive amination ($MeNH_2$, $TiCl_4$, Raney-Ni) (**Scheme 8**).

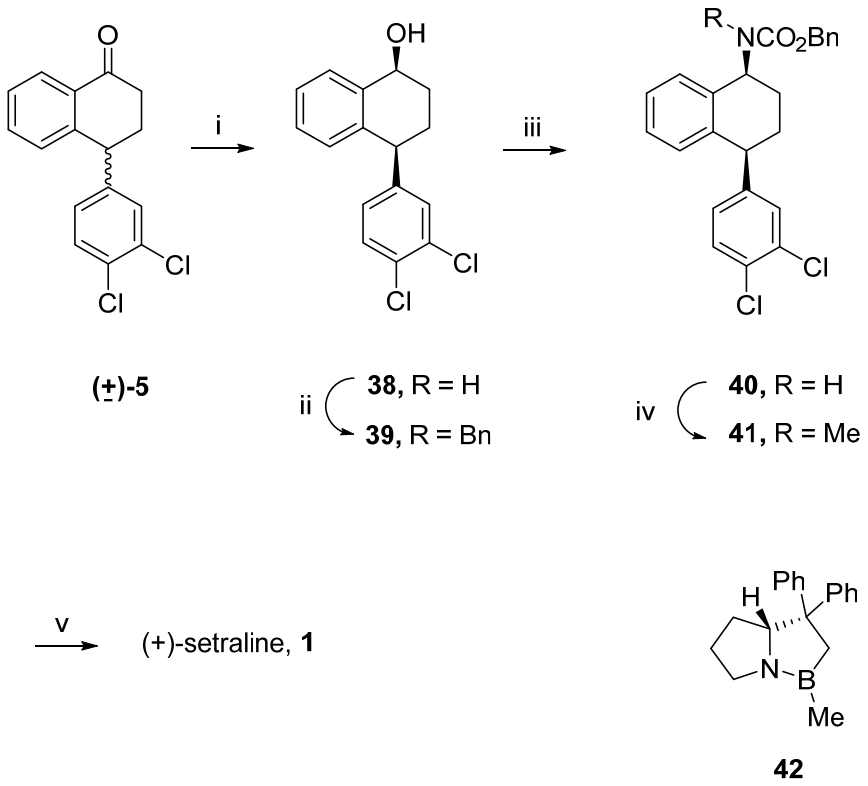


Scheme 8: (i) $Me_2S{\cdot}BH_3$, **37** (5 mol%) , THF, reflux, 42%; (ii) PCC, CH_2Cl_2, 25 ^oC; (iii) $TiCl_4$, $MeNH_2$, Et_2O, -78 ^oC; then Raney Ni, H_2, MeOH.

Jung's approach (2011)[11]

Jung *et al*. have reported synthesis of (+)-sertraline **1** using stereoselective amination of chiral benzylic ethers using chlorosulfonyl isocyanate. Thus, recemic (±)-tetralone **5** was diastereoselectively converted to the chiral alcohol **38** by employing (*R*)-(+)-2-methyl-CBS-oxazaborolidine as catalyst **(42)** and *N*,*N*-diethylaniline borane as reducing agent. Benzylation of alcohol **38** afforded the ether **39**. Treatment of the benzyl ether **39** with chlorosulfonyl isocyanate and sodium carbonate in anhydrous *n*-hexane at -40 °C for 40 h, followed by reduction of the *N*-chlorosulfonyl group with an aqueous sodium sulfite solution furnished the carbamate **40**. Finally, methylation

of the carbamate **40** and subsequent deprotection of the Cbz group gave (+)-sertraline **1 (Scheme 9)**.



Scheme 9: (i) **42**, *N*,*N*-diethylaniline borane, toluene, 25 ^{o}C, 485; (ii) BnBr, NaH, THF/DMF (4:1), 25 ^{o}C, 82%; (iii) (a) CSI, Na_2CO_3, *n*-hexane, -40 ^{o}C; (b) sat. Na_2SO_3, 25 ^{o}C, 80%; (iv) MeI, NaH, THF/DMF (4:1), 25 ^{o}C, 99%; (v) (a) Raney Ni, H_2, CH_2Cl_2/MeOH (1:4), 25 ^{o}C; (b) HCl, ether, 25 ^{o}C, 75%.

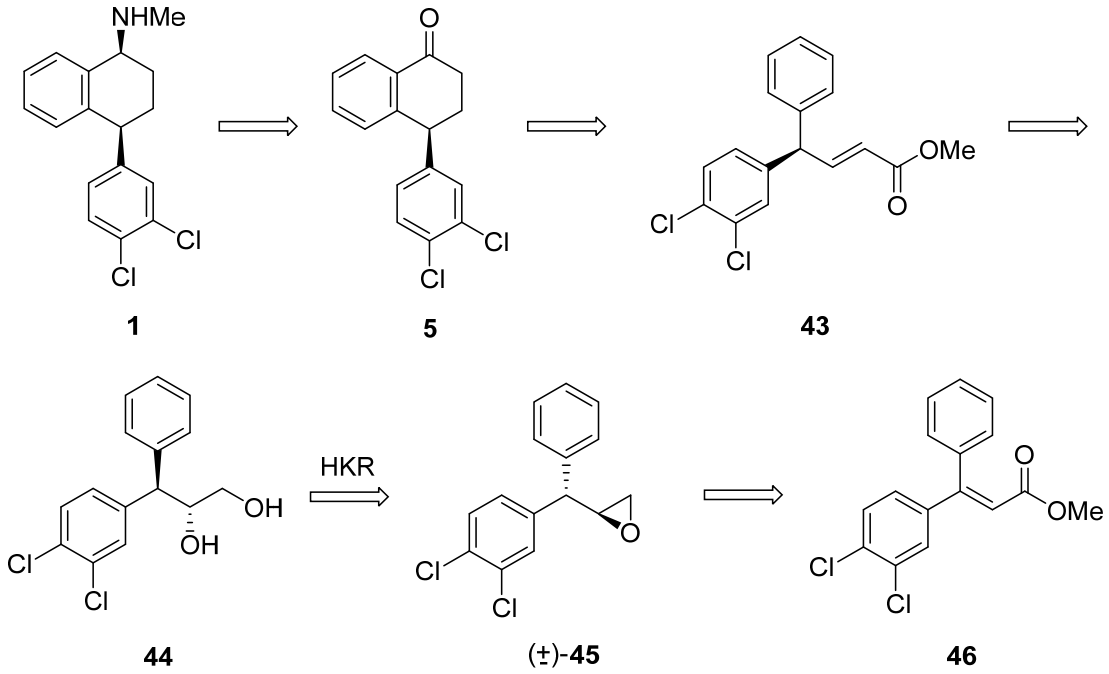
3.1.3 Present Work

3.1.3.1 Objective

As can be seen from the above synthetic studies, the literature methods in the synthesis of (+)-sertraline **1** employ either chiral starting materials or expensive reagents involving longer reaction sequences, often resulting in poor product selectivities. The enantioselective synthesis of (+)-sertraline **1** is thus undertaken to overcome some of the disadvantages associated with the reported methods. This section describes an enantioselective synthesis of (+)-sertraline **1** *via* hydrolytic

kinetic resolution of 3-diarylsubstituted epoxide.[12]

The retrosynthetic analysis of (+)-sertraline **1** is shown in **Scheme 10**. We envisaged that tetralone **5** could serve as a valuable intermediate for the asymmetric synthesis of (+)-sertraline **1**. The tetralone moiety **5** could be constructed by intramolecular cyclization of unsaturated ester **43** after reduction of the C=C bond. The α,β-unsaturated ester **43** can be thought to be obtained from diol **44**, which could be achieved by means of Co-catalyzed Hydrolytic Kinetic Resolution of racemic *anti*-3-diarylsubstituted epoxide **45**. The racemic *anti*-3-diarylsubstituted **45** can be easily prepared from the corresponding *E*-cinnamate esters **46**.

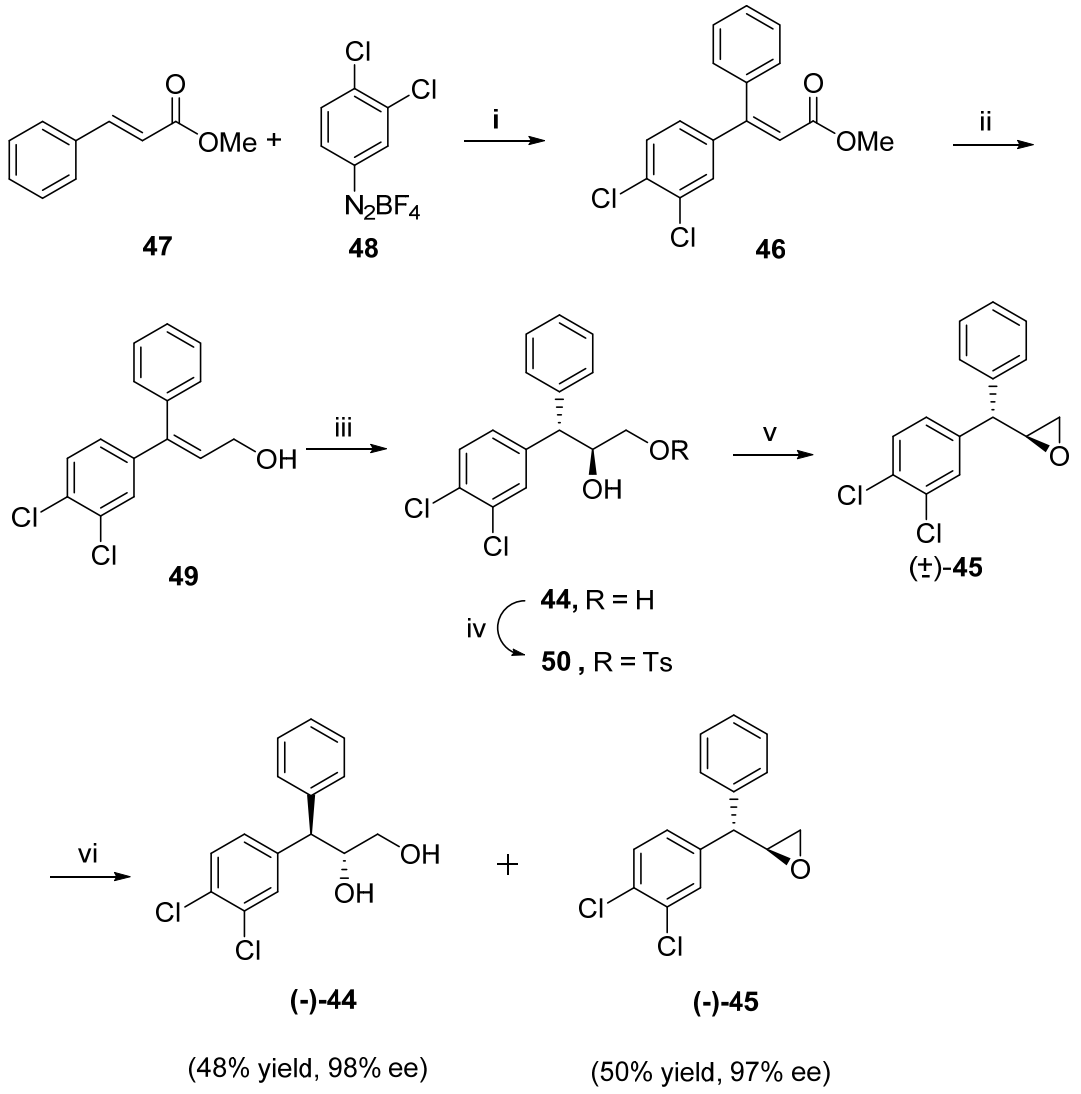


Scheme 10: Retrosynthetic analysis of (+)-sertraline **1**

3.1.3.2 Results and Discussion

The synthetic scheme for the synthesis of (+)-sertraline **1** is shown in **Scheme 11.** It commenced with methyl cinnamate **47,** which was reacted with 3,4-

dichlorobenzenediazonium tetrafluoroborate **48** to produce unsaturated ester **46** in 82% yield.[13]



Scheme 11: (i) $Pd(OAc)_2$, MeOH, 4 h, 82%; (ii) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 95%; (iii) BH_3.DMS, THF, 4 h, 30% aq. H_2O_2, NaOH, 5 h, 84%; (iv) TsCl, Et_3N, Bu_2SnO, DMAP, CH_2Cl_2, 0 °C, 3 h, 95%; (v) K_2CO_3, MeOH, 25 °C, 85%, (vi) (*S, S*)-Co^{III} (salen) (0.5 mol %), H_2O (0.49 equiv), 0 to 25 °C, 12 h.

The formation of **46** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1727 cm^{-1} due to the presence of α, β-unsaturated ester functionality. The ^1H NMR spectrum of **46** showed singlets at δ 3.61 (3H) and 6.32 (s 1H) corresponding to methoxy and olefinic protons respectively. Its ^{13}C NMR

spectrum showed a typical carbon signal at δ 165.7 due to carbonyl carbon of ester moiety (**Fig. 2**).

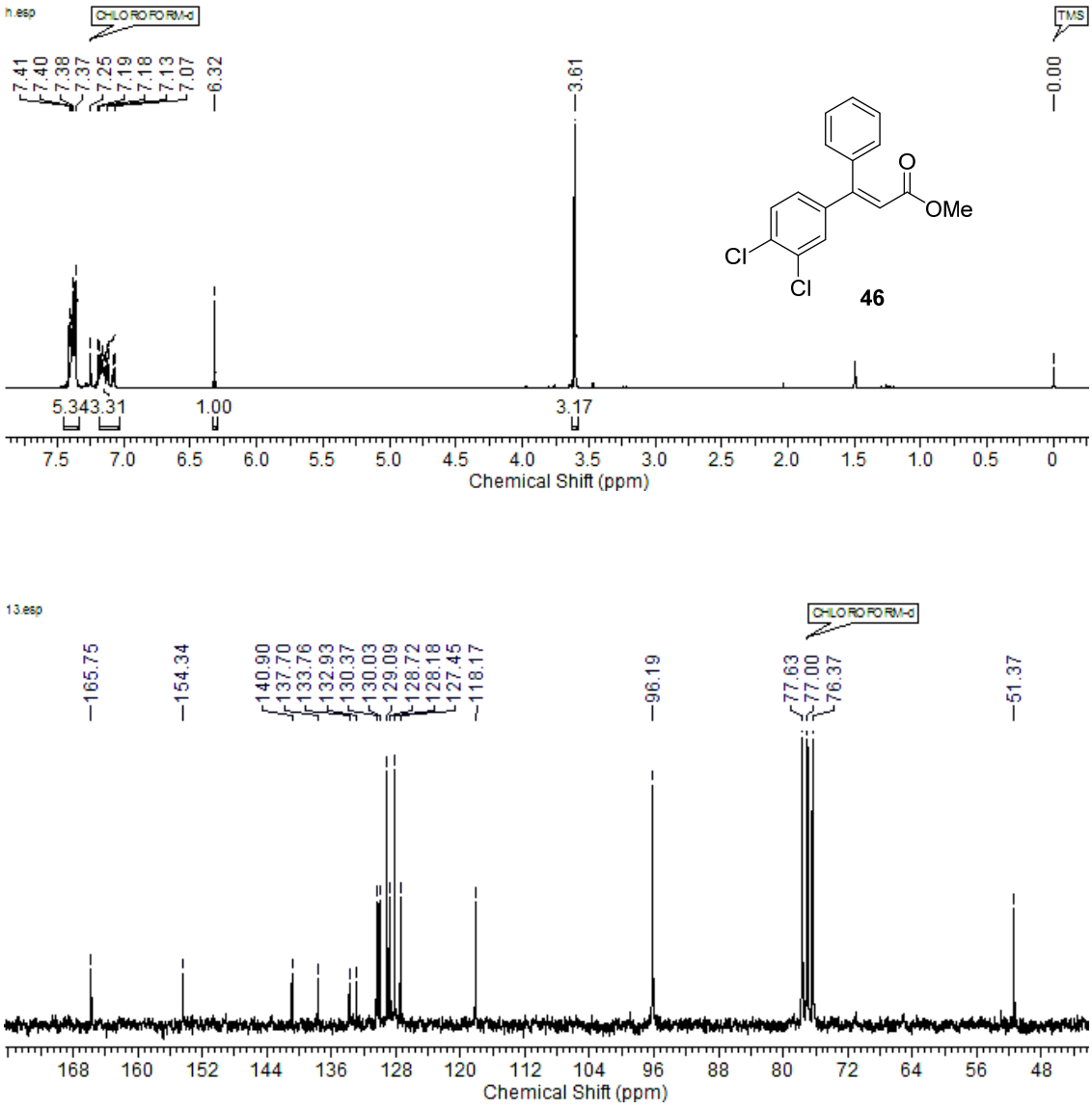


Fig. 2: ^{1}H and ^{13}C NMR spectra of **46**

Reduction of ester carbonyl in **46** was achieved with DIBAL-H at 0 ^{o}C to give allylic alcohol **49** in 95% yield**.** The ^{1}H NMR spectrum of **49** showed the appearance of a doublet at δ 4.22 (2H) corresponding to methylene protons (-**CH$_2$**-OH) and a triplet at δ 6.22 (t, *J* = 6.6 Hz, 1H), due to olefinic proton. Its ^{13}C NMR spectrum showed a typical signal at δ 60.4 due to methylene carbon attached to hydroxyl group (**Fig. 3**).

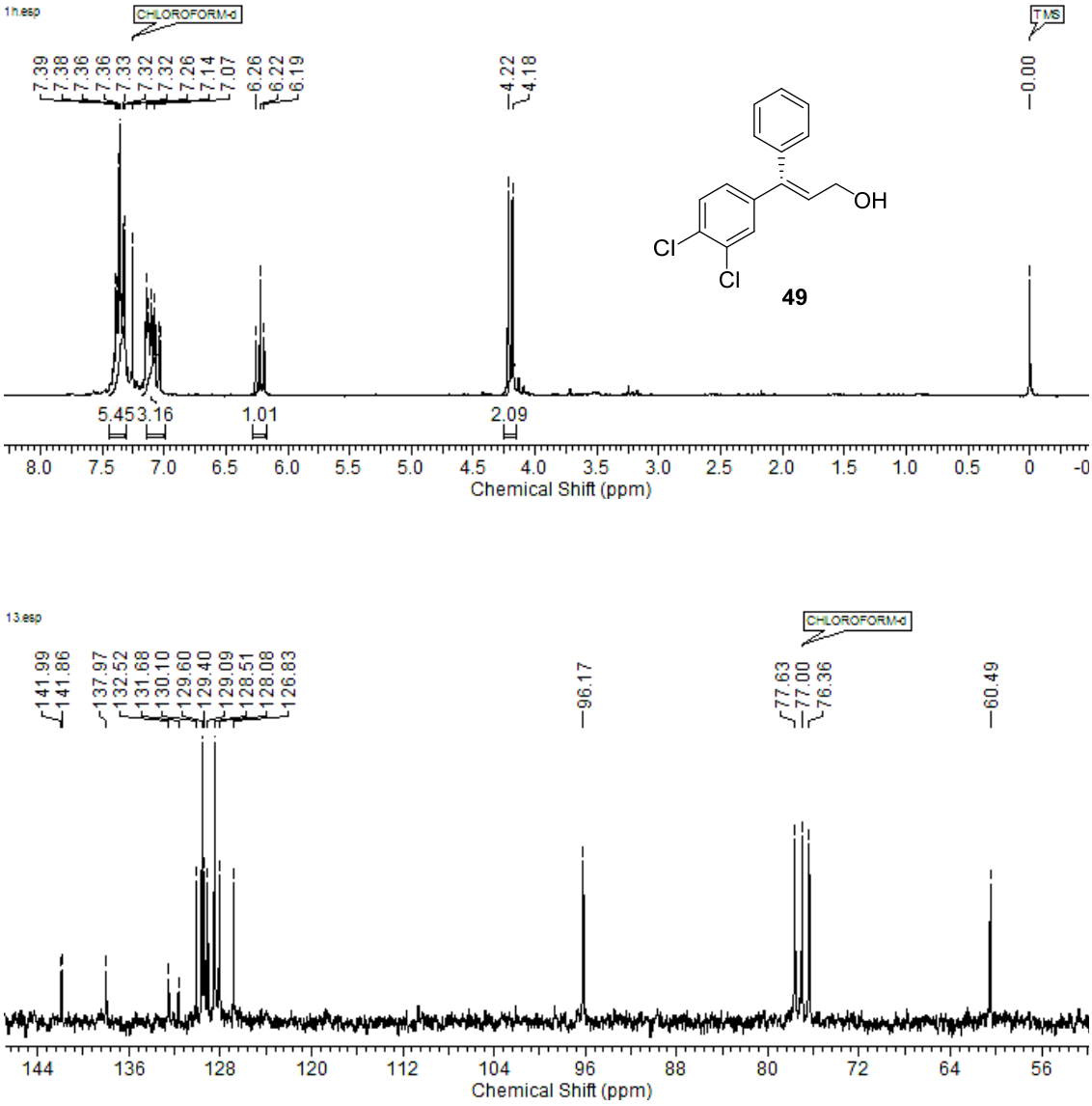


Fig. 3: ^{1}H and ^{13}C NMR spectra of **49**

Allylic alcohol **49** was then converted into (±)-diol **44** *via* regioselective hydroboration-oxidation protocol. The formation of diol **44** was confirmed by its ^{1}H NMR spectrum, which showed a doublet at δ 4.00 (1H) corresponding to benzylic proton and a multiplet at δ 4.40 (1H) due to methine proton (-**CH**-OH). This was further confirmed from its ^{13}C NMR spectrum, which showed characteristic signals at δ 64.3 and 73.3 corresponding to methylene and methine carbons attached to hydroxyl group respectively (**Fig. 4**).

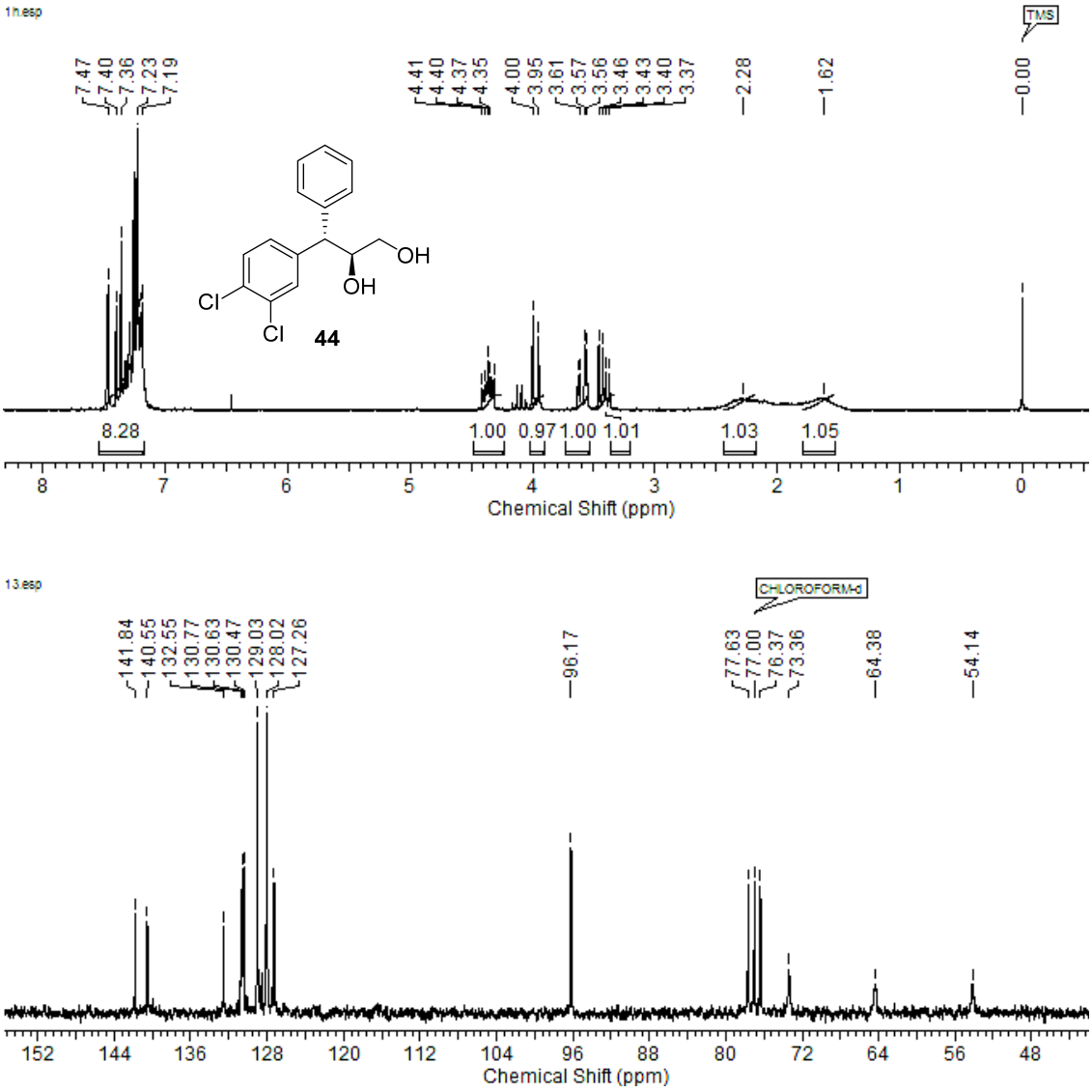


Fig. 4: ^{1}H and ^{13}C NMR spectra of **(±)-44**

Selective tosylation of primary hydroxyl group in diol **44** (TsCl, Et_3N, Bu_2SnO) was carried out to give the mono tosylate **50** in 95% yield. The formation of tosylate **50** was confirmed by its ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **50** showed the appearance of a singlet at δ 2.45 (3H) corresponding to methyl protons of tosyl group. This was futher confirmed by its ^{13}C NMR spectrum, which showed a typical carbon signal at δ 21.7 due to methyl carbon of tosyl group (**Fig. 5**).

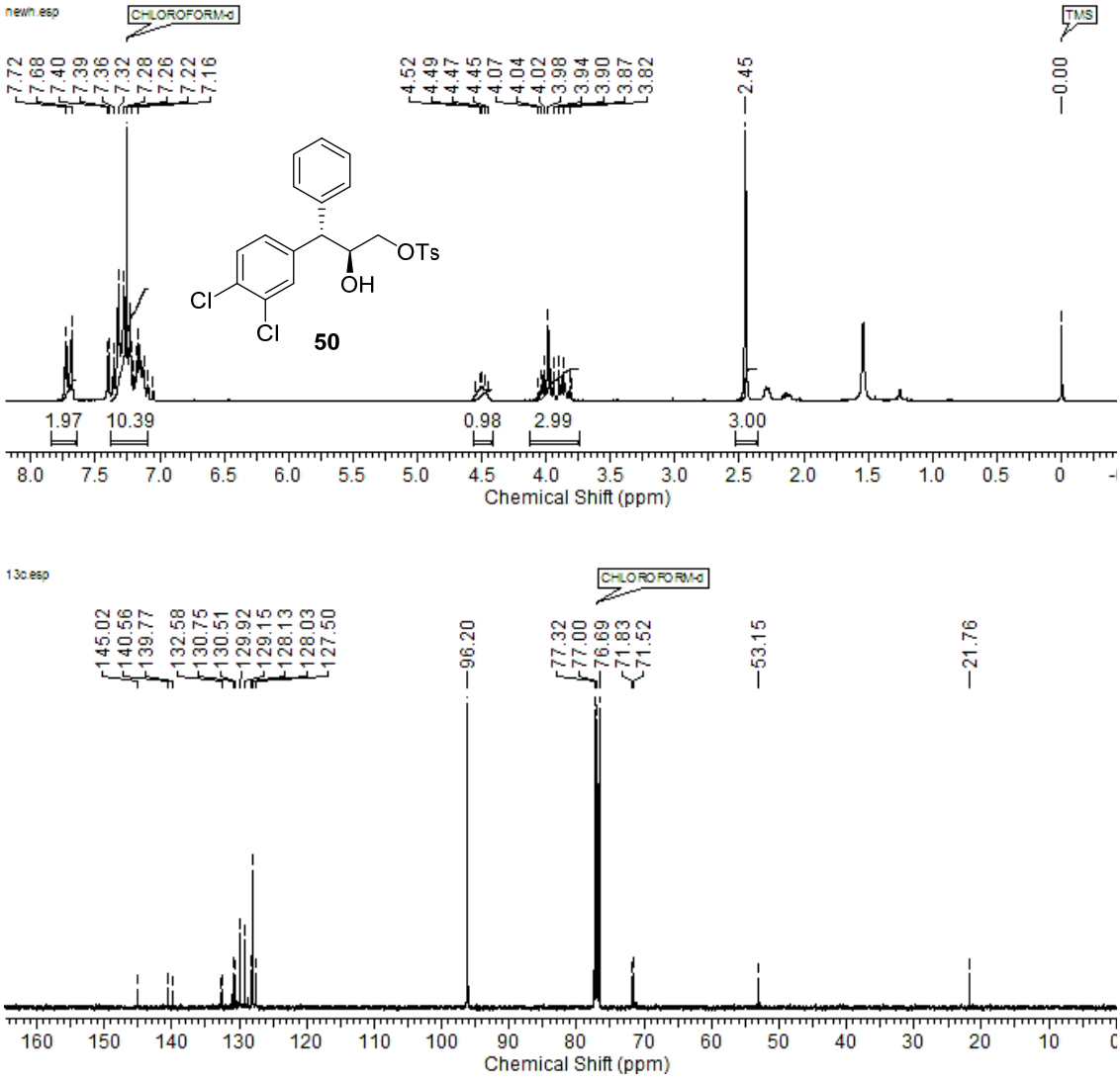


Fig. 5: ^{1}H and ^{13}C NMR spectra of **(±)-50**

Mono tosylate **50**, on treatment with K_2CO_3 in MeOH, gave the *anti*-3-diarylsubstituted epoxide **45** in 85% yield. The formation of epoxide **45** was confirmed by the presence of multiplets at δ 2.51, 2.85 and 3.44 attributed to the presence of epoxide protons. Its ^{13}C NMR spectrum displayed carbon signals at δ 46.3 and δ 54.4, due to epoxide carbons attached to oxygen atom (**Fig. 6**). In this strategy, the relative stereochemistry is established prior to the HKR step.

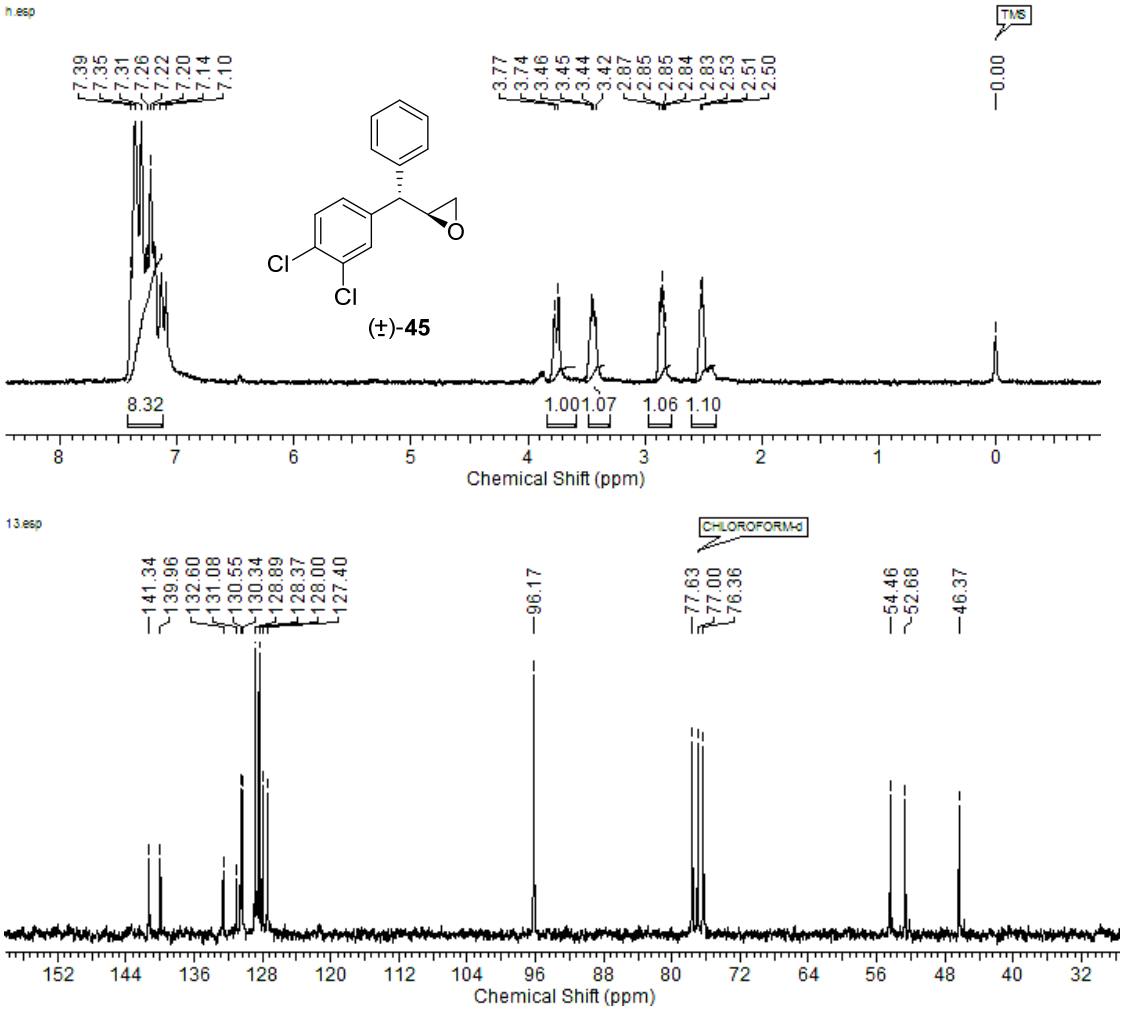
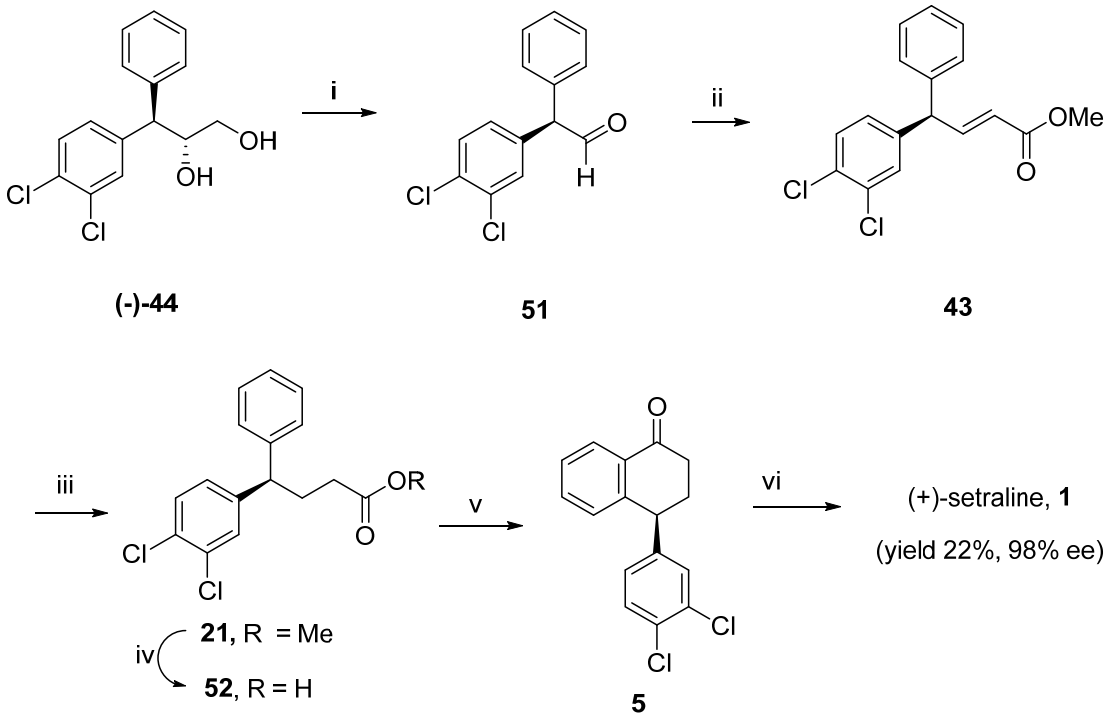


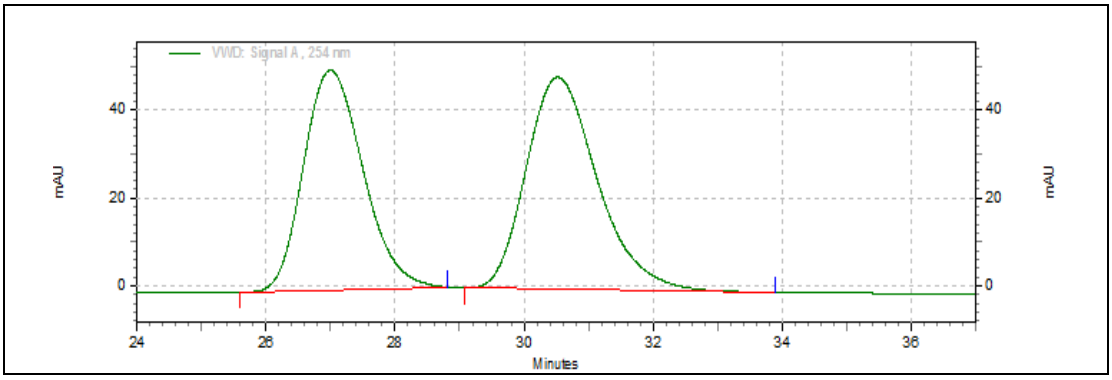
Fig. 6: ^{1}H and ^{13}C NMR spectra of **(±)-45**

Thus, when, racemic epoxide **45** was subjected to HKR with (*S*, *S*)-(salen)Co(III)(OAc) complex (0.5 mol %) and H_2O (0.49 equiv), it produced the corresponding diol (-)-**44** (48%, 98% ee) and chiral epoxide **(-)-45** (50%, 97% ee) in high optical purities (**Scheme 11**).[12] The ^{1}H NMR spectrum of diol (-)-**44** and epoxide **(-)-45** are the same as the racemic compounds (see **Fig**. **5** and **Fig**. **6**). The enantiomeric excess of 3-diarylsubstituted diol **(-)-44** and 3-diarylsubstituted epoxide **(-)-45** was determined from chiral HPLC analysis; Chiralpak OD-H **(Fig. 7)**. Diol (-)-**44** was separated readily from epoxide **(-)-45** and taken up for the synthesis of (+)-setraline **1**. Thus, diol **(-)-44**, on oxidation with $NaIO_4$ gave the corresponding

aldehyde **51** in 82% yield (**Scheme 12**). The formation of aldehyde **51** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1720 cm^{-1} for the presence of carbonyl functionality. The ^{1}H NMR spectrum of **51** showed the appearance of a doublet at δ 9.92 (d, J = 1.2 Hz, 1H) corresponding to aldehydic proton and further confirmed by its ^{13}C NMR spectrum, which showed a typical signal at δ 197.2 due to carbonyl carbon of aldehydic function (**Fig. 8**).



Scheme 12: (i) $NaIO_4$, CH_2Cl_2, 25 °C, 30 min, 82%; (ii) $Ph_3P{=}CHCO_2Et$, dry benzene, 25 °C, 12 h, 92%; (iii) 10% Pd/C, H_2 (20 psig), MeOH, 25 °C, 94%; (iv) 6 N HCl, reflux, 23 h, 89%; (v) $ClSO_3H$, CH_2Cl_2, 25 °C, 2 h, 82%; (vi) $TiCl_4$, excess $MeNH_2$ in THF, 0 °C, 1 h then Raney Ni (cat.), MeOH, H_2 (1 atm), 12 h, 88%.



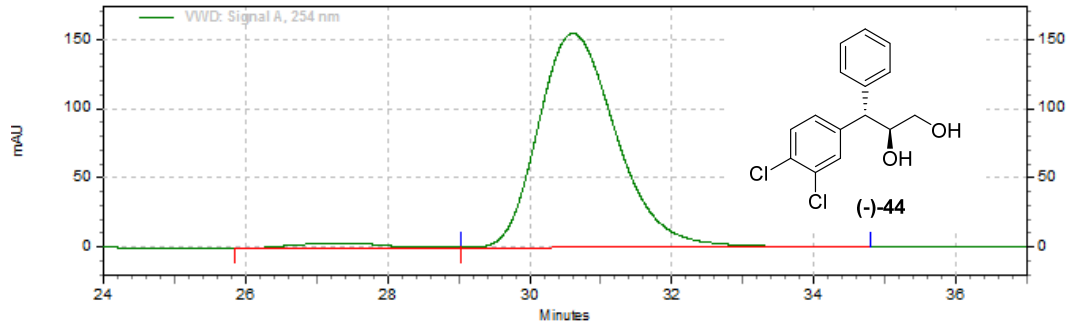


Fig. 7: HPLC chromatogram of 43 (98% ee, Chiral OD-H column, *n*-hexane/ 2-propanol (90:10),0.5 mL/min, 254 nm Retention time: t_{minor} = 27.00 (0.92%) and t_{major} = 30.59 min. (99.08%))

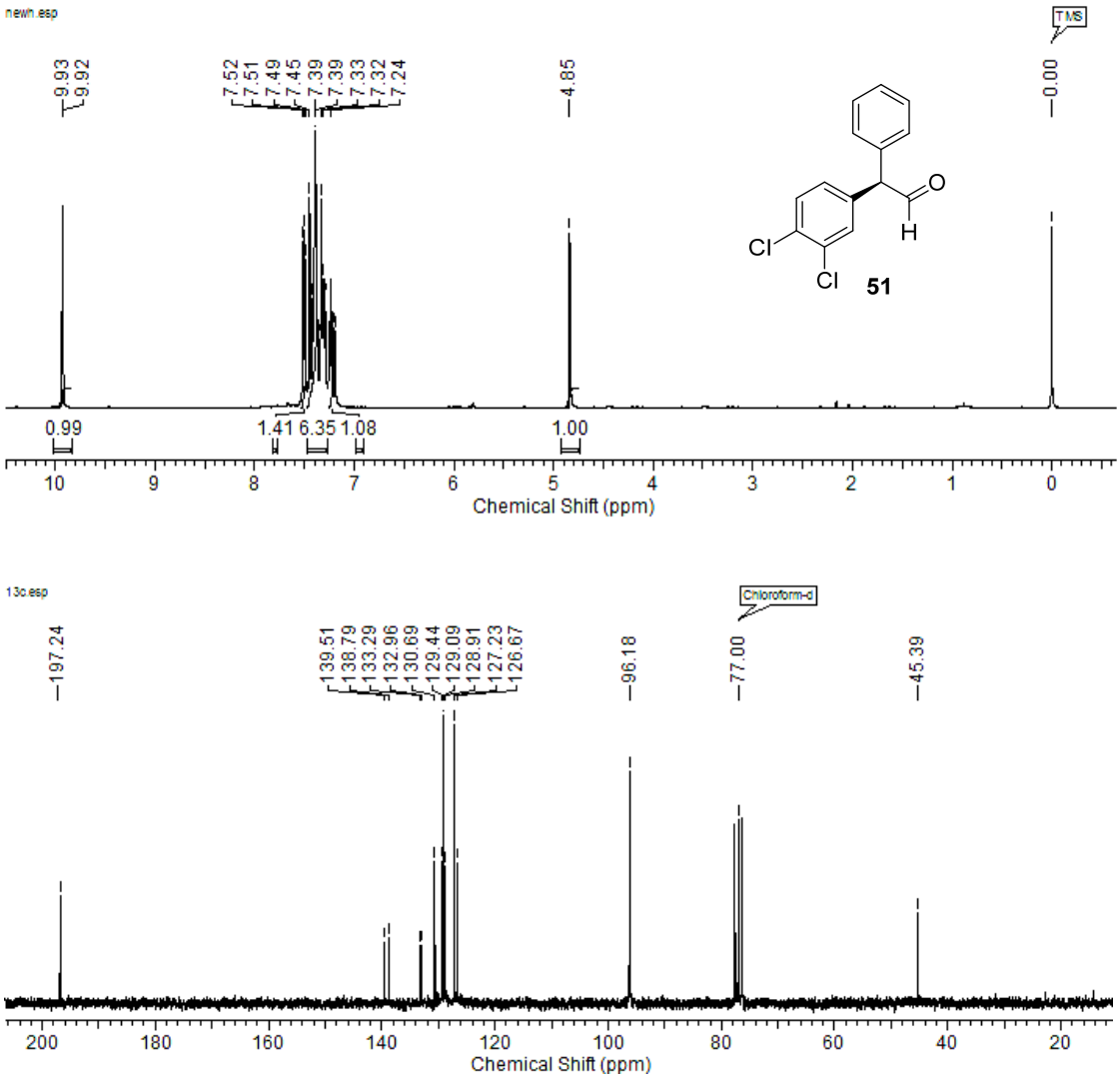


Fig. 8: ^{1}H and ^{13}C NMR spectra of **51**

Aldehyde **51** was then subjected to Wittig olefination to give the corresponding α, β-unsaturated ester **43**. The ^{1}H NMR spectrum of **43** showed typical signals at δ 4.83 (1H) and 5.75 (1H) corresponding to olefinic protons and other signal at δ 3.75 (3H) due to methoxy protons. Its ^{13}C NMR spectrum showed a typical signal at δ 165.2 for carbonyl carbon of ester group (**Fig. 9**).

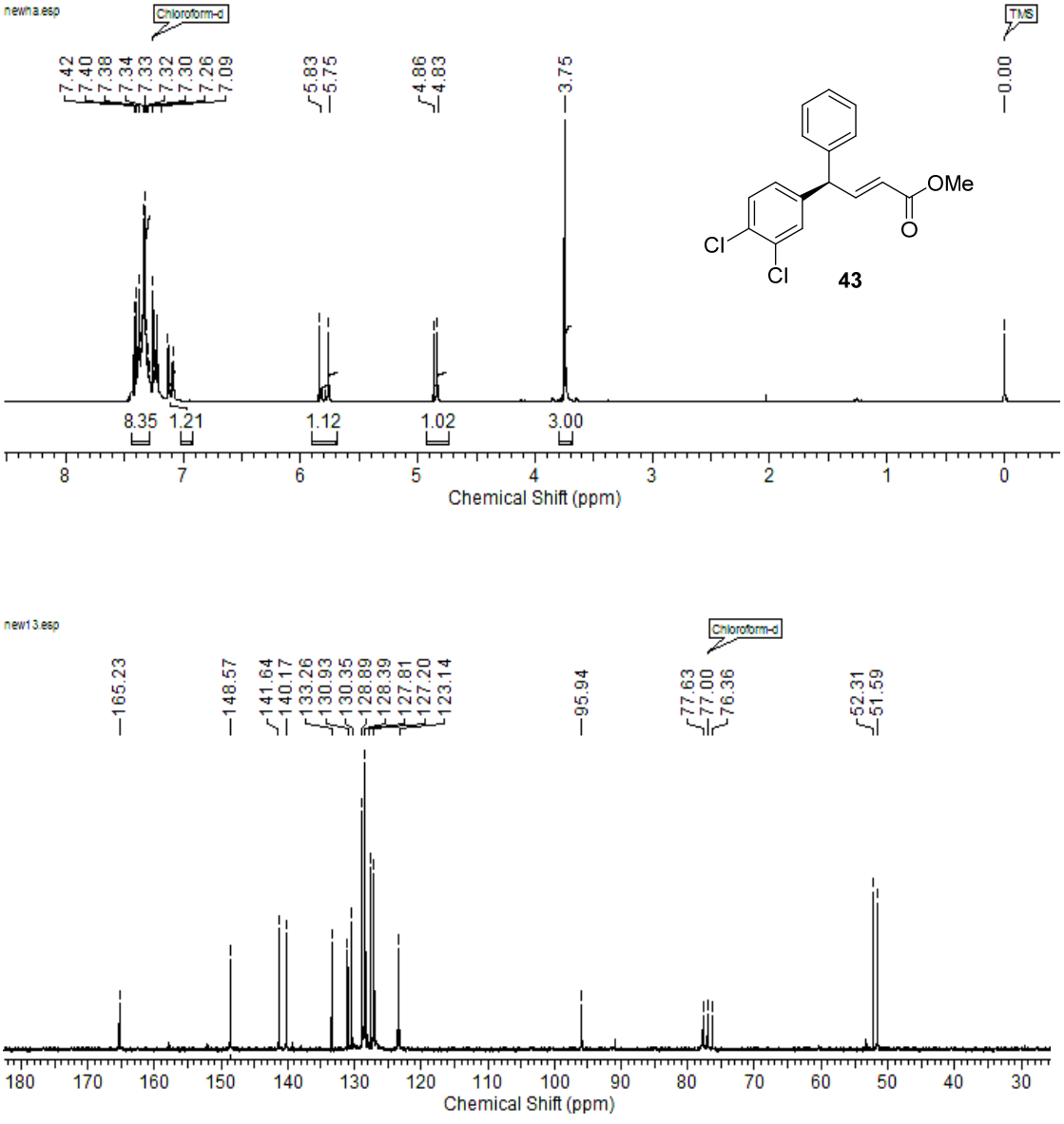


Fig. 9: ^{1}H and ^{13}C NMR spectra of **43**

The α, β-unsaturated ester **43** on catalytic hydrogenation (10% Pd/C, H_2 (20 psig), MeOH) gave the saturated ester **21** in 90% yield. The ^{1}H NMR spectrum of **21**

showed the appearance of multiplets at δ 2.28 (4H) and δ 3.88 (1H) corresponding to methylene protons and methine proton respectively. Its ^{13}C NMR spectrum showed a typical signal at δ 173.0 for carbonyl carbon of ester group (**Fig. 10**).

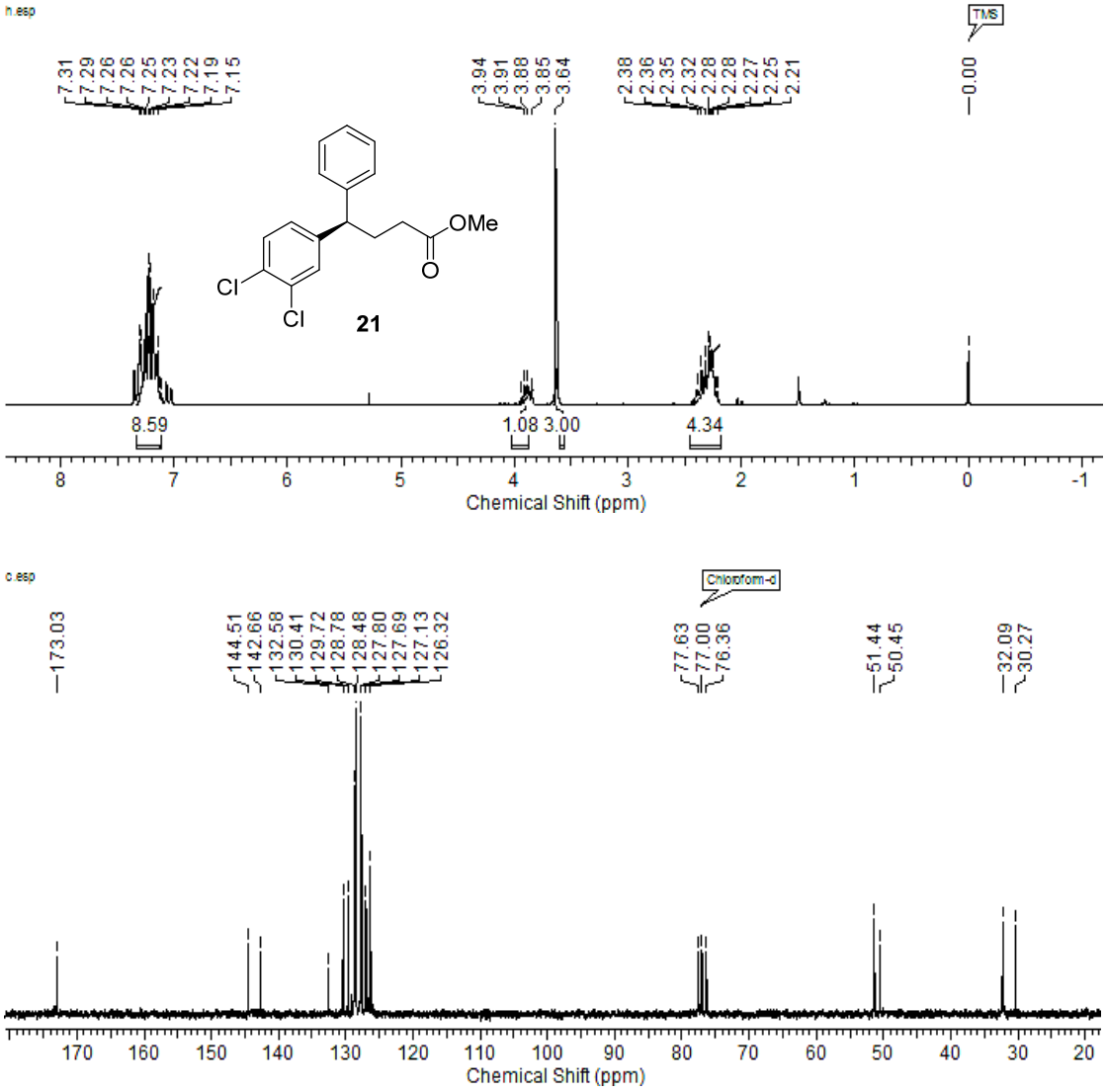


Fig. 10: ^{1}H and ^{13}C NMR spectra of **21**

Ester **21** was subsequently hydrolysed to obtain carboxylic acid **52.** The formation of acid **52** was confirmed by the disappearance of methoxy signals from ^{1}H and ^{13}C NMR spectra. Its ^{13}C NMR spectrum showed a typical signal at δ 178.6 due to carbonyl carbon of acid functionality (**Fig. 11**).

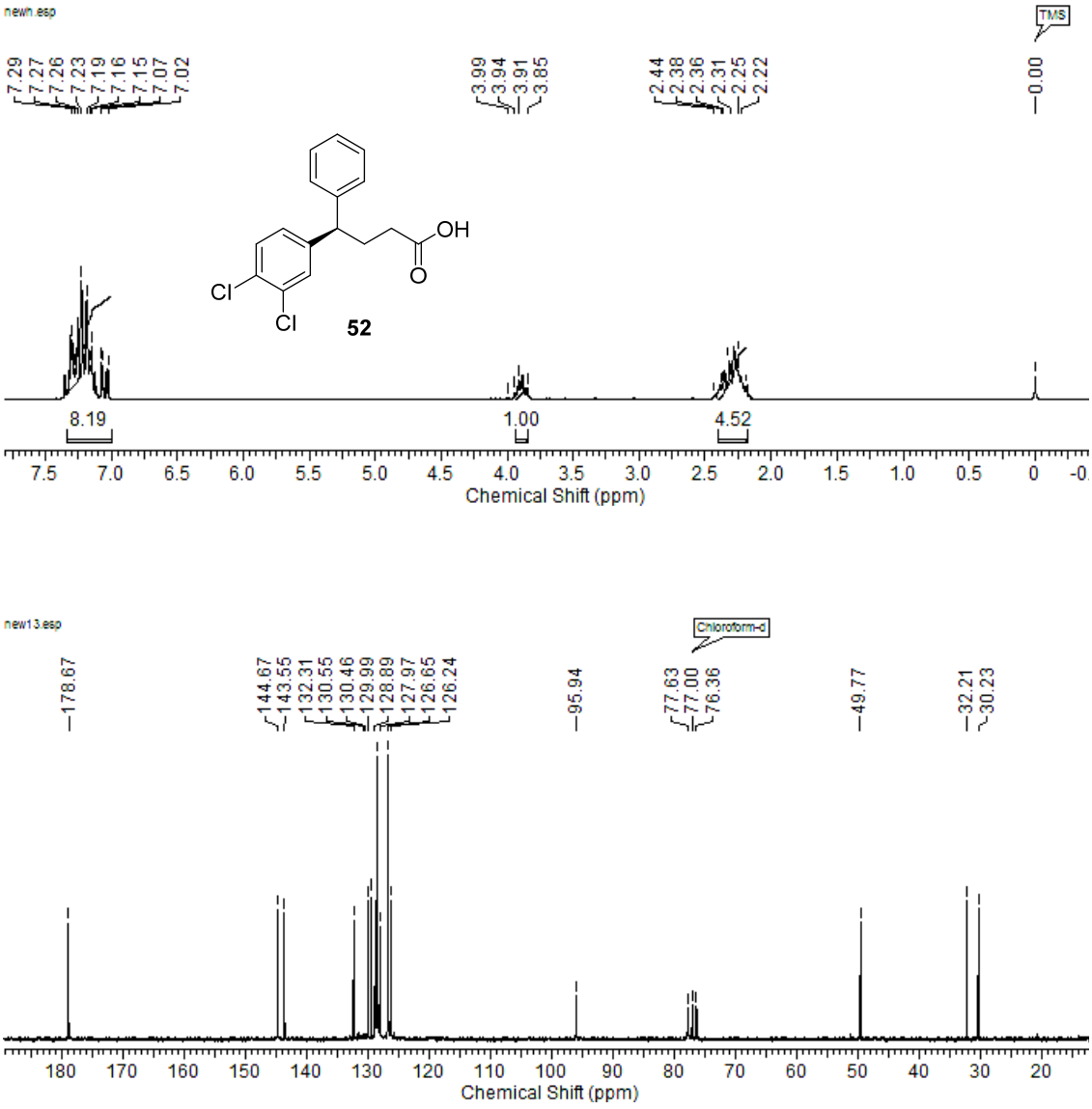


Fig. 11: ^{1}H and ^{13}C NMR spectra of **52**

Acid **52** was further cyclized under acidic conditions to give tetralone **5** in 82% yield. The formation of ketone **5** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1715 cm^{-1} typically for aromatic ketone functionality. The ^{1}H NMR spectrum of **5** showed the appearance of multiplet at δ 4.29 (1H) corresponding to methine proton at benzylic position. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 196.9 due to carbonyl carbon of tetralone moiety (**Fig. 12**).

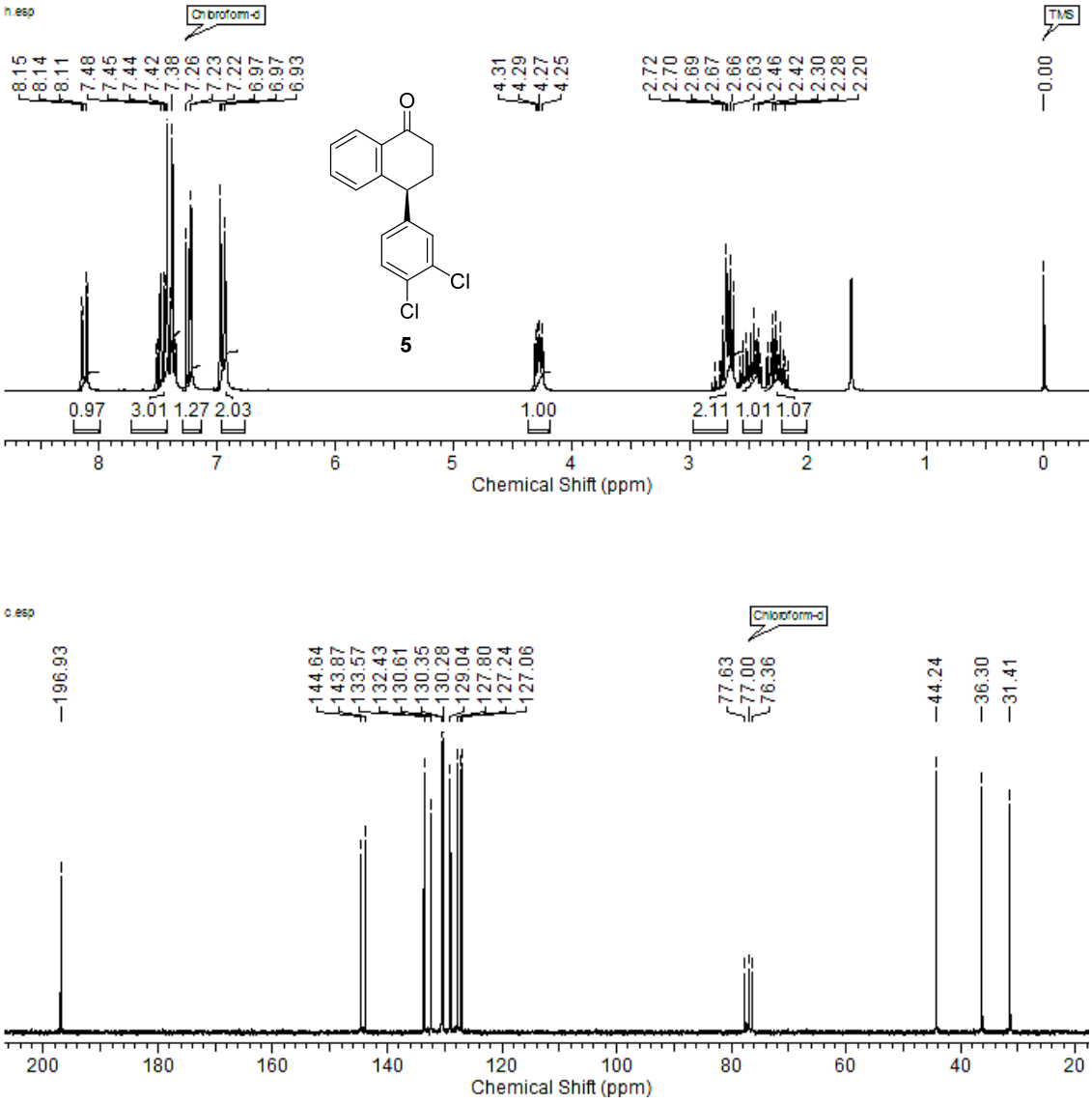


Fig. 12: ^{1}H and ^{13}C NMR spectra of **5**

Finally, reductive amination of tetralone **5** ($TiCl_4$, excess $MeNH_2$, then Raney-Ni, H_2 (1 atm) afforded (+)-sertraline **1** with an overall yield 12% and 98% ee (**Scheme 12**). The formation of (+)-sertraline **1** was confirmed by its ^{1}H NMR spectrum, which showed a typical signal at δ 2.53 (3H) corresponding to methyl protons attached to nitrogen (-HN-**CH_3**) and other signals at δ 3.71 and δ 3.97 due to methine protons at benzylic position. This was further confirmed by its ^{13}C NMR spectrum, which showed typical carbon signal at δ 34.4 for methyl carbon attached nitrogen atom and

another carbon signal at δ 57.4 due to methine carbon attached to nitrogen atom (**Fig. 13**). Stereochemistry of the synthesized sertraline **1** was confirmed unambiguously by comparing with its specific rotation reported in the literature.[10]

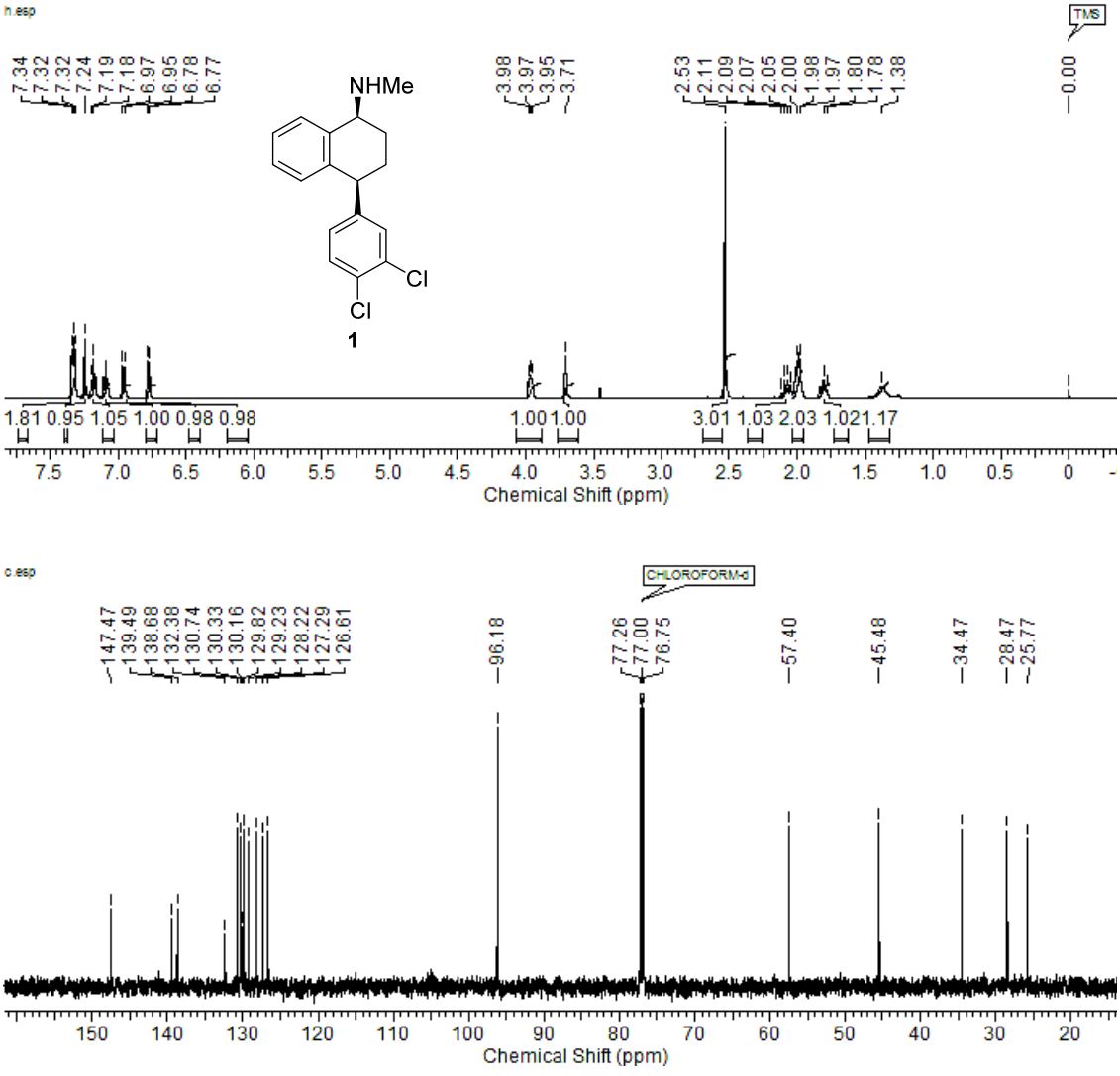


Fig. 13: ^{1}H and ^{13}C NMR spectra of (±)-sertraline **1**

3.1.4 Conclusion

In conclusion, we have described a short and efficient enantioselective synthesis of (+)-sertraline **1** with an overall yield of 12% and 98% ee, that are achieved using two-stereocentered Co-catalyzed HKR of racemic 3-diarylsubstituted epoxide as key reaction.

3.1.5 Experimental section

Methyl (*E*)-3-(3,4-dichlorophenyl)-3-phenylacrylate (46)

To a solution of methyl cinnamate **47** (1.6 g, 10 mmol) in methanol (60 mL), $Pd(OAc)_2$ (240 mg, 10 mol%) and 3,4-dichlorobenzenediazonium tetrafluoroborate **48** (3.12 g, 12 mmol) was added. The reaction mixture was stirred at 25 ^oC for 4 h. After completion of reaction (monitored by TLC), it was filtered through a pad of Celite and washed with methanol (3 x 15 mL). The combined filtrates were concentrated to give crude product, **46** which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (3:7) as eluent gave pure **46** as colorless oil.

Yield: 82%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 823, 874, 1190, 1275, 1549, 1620, 1727, 2948; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.61 (s, 3H), 6.32 (s, 1H), 7.07-7.19 (m, 3H), 7.37-7.41 (5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.3, 118.1, 127.4, 128.1, 128.7, 129.0, 130.0, 130.3, 132.9, 133.7, 137.7, 140.9, 154.3, 165.7; **Anal. Calcd** for $C_{16}H_{12}O_2Cl_2$ requires C, 62.56; H, 3.94; found C, 62.50; H, 3.95%.

(*E*)-3-(3,4-Dichlorophenyl)-3-phenylprop-2-en-1-ol (49)

To a stirred solution of the ester **46** (1 g, 3.26 mmol), in dry CH_2Cl_2 (50 mL), a solution of diisobutylaluminium hydride (1 M solution in toluene, 7.1 mL, 7.18 mmol)) was added dropwise at 0 ^oC and the reaction mixture was stirred at this temperature for 2 h. After completion of reaction (monitored by TLC), it was diluted with a saturated solution of Rochelle salt and stirred for further 3 h. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product **49**, which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave pure **49** as colorless oil.

Yield: 95%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1055, 1130, 1430, 1520, 2847, 2956, 3430; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.22 (d, *J* = 6.8 Hz, 2H), 6.22 (t, *J* = 6.6 Hz, 1H), 7.04 (m, 3H), 7.32-73.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 60.4, 126.8, 128.0, 128.5, 129.0, 129.4, 129.6, 130.1, 132.5, 137.9, 141.8, 141.9; **Anal. Calcd** for $C_{15}H_{12}OCl_2$ requires C, 64.54; H, 4.33; found C, 64.66; H, 4.38%.

3-(3,4-Dichlorophenyl)-3-phenylpropane-1,2-diol (44)

To a stirred solution of homoallyl alcohol **49** (2.6 g, 9.4 mmol) in THF (5 mL) at 0 °C, $BH_3.SMe_2$ (5.8 mL, 4.5 mmol) was added and the reaction mixture was stirred at 25 °C for 2 h. After dilution with THF/MeOH (14 mL, 1:1) followed by the addition of 3 M solution of NaOH (4 mL) and an aq. solution 30% H_2O_2 (4 mL), the reaction was stirred for 1 h and quenched with a saturated solution of Na_2SO_3 (20 mL). The reaction mixture was then cooled to 0 °C, diluted with sat. $NaHCO_3$ (35 mL) and Et_2O (35 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (5:5) as eluent gave pure **44** as colorless oil.

Yield: 84%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 749, 850, 1011, 1236, 1462, 1620, 2844, 3456; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.62 (br s, 1H), 2.28 (br s, 1H), 3.43 (dd, *J* = 6.3, 11.1 Hz, 1H), 3.61 (dd, *J* = 3.0, 11.1 Hz, 1H), 4.00 (d, *J* = 9.2 Hz, 1H), 4.40 (m, 1H), 7.19-7.47 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.1, 64.3, 73.3, 127.2, 128.0, 129.0, 130.4, 130.6, 130.7, 132.5, 140.5, 141.8; **Anal. Calcd** for $C_{15}H_{14}O_2Cl_2$ requires C, 60.63; H, 4.75; found C, 60.75; H, 4.70%.

3-(3,4-Dichlorophenyl)-2-hydroxy-3-phenylpropyl-4-methylbenzenesulfonate (50)

A solution of diol **44** (3.5 g, 11.8 mmol) in CH_2Cl_2 (50 mL) was treated with TsCl (2.25 g, 11.8 mmol), Bu_2SnO (883.8 mg, 30 mol%), Et_3N (4.21 mL, 30 mmol) and DMAP (cat.) at 0 °C and stirred for 1 h. After the reaction was complete (monitored by TLC), it was quenched with water (10 mL) and product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product **50**, which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (7:3) as eluent gave pure **50** as colorless oil.

Yield: 95%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3407, 3019, 2927, 1518, 1454, 1364, 1215, 1176, 1047, 928; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.80-4.07 (m, 3H), 4.45-4.56 (m, 1H), 7.06-7.40 (m, 10H), 7.68-7.72 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.7, 53.1, 71.5, 71.8, 127.5, 128.0, 128.1, 129.1, 129.9, 130.5, 130.7, 132.5, 132.6, 139.7, 140.5, 145.0; **Anal. Calcd** for $C_{22}H_{20}O_4Cl_2S$ requires C, 58.54; H, 4.47; found C, 58.60; H, 4.50%.

(3,4-dichlorophenyl)(phenyl)methyl)oxirane (45)

To a solution of tosylate **50** (5.3 g, 11.8 mmol) in MeOH (50 mL) was added K_2CO_3 (1.79 g, 13 mmol) and the mixture was stirred at 0 °C for 30 min. After the reaction was complete (monitored by TLC), solvent was evaporated and the residue was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave pure **45** as colorless oil.

Yield: 85%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 810, 904, 1081, 1209, 1371, 1443, 3062, 3390, 756,; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.50-2.53 (m, 1H), 2.83-2.87, (m, 1H), 3.42-3.46 (m, 1H), 3.74-3.77 (m, 1H), 7.10-7.39 (m, 8H) ; **^{13}C NMR** (50

MHz, $CDCl_3$): δ 46.3, 52.6, 54.4, 127.4, 128.0, 128.3, 128.8, 130.3, 130.5, 131.0, 132.6, 139.9, 141.3; **Anal. Calcd** for $C_{15}H_{12}OCl_2$ requires C, 64.54; H, 4.33; found C, 64.55; H, 4.35%.

HKR of (3,4-Dichlorophenyl)(phenyl)methyl)oxirane (45)

To a solution of (*S*, *S*)-Co-salen (0.027g, 0.5 mol%) in toluene (2 mL), acetic acid (0.02 g, 0.36 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min. During this time the color of the solution changed from orange-red to a dark brown, it was then dried under vacuum. To this, racemic epoxide (±)-**45** (2.5 g, 9.13 mmol) and H_2O (0.08 mL, 4.47 mmol) were added at 0 °C. Then the reaction was allowed to stirred for 12 h at 25 °C. After completion of reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral epoxide **(-)-45,** [solvent system; petroleum ether: ethyl acetate (95:5)] and chiral diol **(-)-44** [solvent system; petroleum ether: ethyl acetate (2:8)] in pure form.

(2*R*,3*R*)-3-(3,4-dichlorophenyl)-3-phenylpropane-1,2-diol [(-)-44]

Yield: 48%, colorless oil; $[\alpha]_D^{25}$ = -28.5 (*c* 1, $CHCl_3$); **Optical purity**: 98% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm); Retention time: t_{minor} = 27.00 and t_{major} = 30.59 min.

(*S*)-2-((*S*)-(3,4-Dichlorophenyl)(phenyl)methyl)oxirane [(-)-45]

Yield: 50%, colorless oil; $[\alpha]_D^{25}$ = -23.6 (*c* 1, $CHCl_3$); **Optical purity**: 97% ee determined from HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 254 nm); Retention time: t_{minor} = 13.70 and t_{major} = 14.95 min.

(*R*)-2-(3,4-Dichlorophenyl)-2-phenylacetaldehyde (51)

To stirred solution of diol **(-)-44** (1 g, 3.3 mmol) in ethanol/H_2O (15 mL, 2:1) at 20 ^oC, $NaIO_4$ (0.863 g, 4.0 mmol) was added and the reaction mixture was stirred for 4 hour. After completion of reaction (monitored by TLC), it was quenched with water

(10 mL) and product was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product **51** which was taken up for further reaction without purification.

Yield: 82%, colorless oil; $[\alpha]_D^{25}$ = +4.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 1030, 1136, 1178, 1380, 1448, 1466, 1720, 2853, 2929 ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.85 (d, *J* = 1.3 Hz, 1H), 7.24 -7.52 (m, 8H), 9.92 (d, *J* = 1.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 45.4, 126.7, 127.2, 128.9, 129.1, 129.4, 130.7, 132.9, 133.3, 138.8, 139.5, 197.2; **Anal. Calcd** for $C_{14}H_{10}OCl_2$ requires C, 63.42; H, 3.80; found C, 63.45; H, 3.81%.

Methyl (*R*, *E*)-4-(3,4-dichlorophenyl)-4-phenylbut-2-enoate (43)

To a solution of aldehyde **51** (0.9 g, 3.55 mmol) in dry benzene (25 mL), was added $Ph_3P{=}CHCO_2Me$ (1.42 g, 4.26 mmol) at 25 ^oC. The reaction mixture was refluxed for 10 h, and then quenched with water (5 mL). The product was extracted with EtOAc (3 x 20 mL) and washed with water (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave pure **43** as colorless oil.

Yield: 92%, colorless oil; $[\alpha]_D^{25}$ = +1.2 (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{20}$ +1.0 (*c* 1.12, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 636, 700, 818, 918, 983, 1030, 1130, 1170, 1377, 1652, 1713, 2946; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.75 (s, 3H), 4.84 (d, *J* = 7.3 Hz, 1H), 5.75 (d, *J* = 15.6 Hz, 1H), 7.09 (m, 1H), 7.26-7.42 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.6, 52.3, 123.1, 127.2, 127.8, 128.4, 128.9, 130.3, 130.9, 133.3, 140.2, 141.6, 148.6, 165.2; **Anal. Calcd** for $C_{17}H_{14}O_2Cl_2$ requires C, 63.57; H, 4.39; found C, 63.60; H, 4.40%.

Methyl (*R*)-4-(3,4-dichlorophenyl)-4-phenylbutanoate (21)

To a solution of ester **43** (0.85 g, 2.66 mmol) in methanol (20 mL), was added 10% Pd/C (60 mg) and stirred under hydrogen atmosphere (1 atm) at 25 ^{o}C. The reaction mixture was further stirred at 25 ^{o}C for 6 h, and the progress monitored by TLC. After completion of reaction, it was filtered through a Celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under vacuum. The crude product thus obtained was purified by column chromatography on silica gel using using petroleum ether: ethyl acetate (8:2) as eluent to give pure **21** as colorless oil.

Yield: 94%, colorless oil; $\mathbf{[\alpha]_D^{25}}$ = -6.0 (*c* 1, $CHCl_3$) {lit.[6] $[\alpha]_D^{20}$ -6.1 (*c* 1.12, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 680, 2970, 1202, 1365, 1494, 1600, 1722, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.21-2.38 (m, 4H), 3.64 (s, 3H), 3.85-3.94 (m, 1H), 7.15-7.31 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.2, 32.0, 50.4, 51.4, 126.3, 127.1, 127.6, 127.8, 128.4, 128.7, 129.7, 130.4, 132.5, 142.6, 144.5, 173.0; **Anal. Calcd** for $C_{17}H_{16}O_2Cl_2$ requires C, 63.17; H, 4.99; found C, 63.21; H, 4.87 %.

(*R*)-4-(3,4-Dichlorophenyl)-4-phenylbutanoic acid (52)

To a solution of the ester **21** (0.3 g, 0.92 mmol) in ethanol/ H_2O (5 mL, 5:1), sodium hydroxide (0.07 g, 1.85 mmol) was added and the solution was heated at reflux for 24 h. After completion of reaction (monitored by TLC), it was cooled and the resulting solution was neutralized by adding with dil HCl and the acidified solution extracted with EtOAc (3 x 10 mL). The combined organics were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give corresponding acid **52**, which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (6:4) as eluent gave pure **52** as colorless solid.

Yield: 89%, colorless solid, **mp** 117 ^{o}C; $\mathbf{[\alpha]_D^{25}}$ = -4.5 (*c* 1, $CHCl_3$) {lit.[15] $[\alpha]_D^{25}$ -4.9 (*c* 1.02, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1406, 1470, 1715, 2664, 2975; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.22-2.44 (m, 4H), 3.85-3.99 (m, 1H), 7.02- 7.29 (m, 8H); **^{13}C NMR**

(50 MHz, $CDCl_3$): δ 30.2, 32.2, 49.7 , 126.4, 126.6, 127.9, 128.8, 129.9, 130.4, 130.5, 132.5, 132.3, 143.3, 144.6, 178.6; **Anal. Calcd** for $C_{16}H_{14}O_2Cl_2$ requires C, 62.16; H, 4.56; found C, 62.15; H, 4.60 %.

(*S*)-4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (5)

To a solution of the carboxylic acid **52** (0.184 g, 0.60 mmol) in CH_2Cl_2 (11 mL) was added $ClSO_3H$ (0.20 mL; 3.0 mmol; 5.0 equiv.) and the reaction mixture was stirred at 25 ^oC for 2 h. After 2 h, the reaction mixture was added to a saturated $NaHCO_3$ solution (75 mL) and extracted with CH_2Cl_2 (2 x 30 mL) followed by diethyl ether (2 x 30 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give tetralone **5**, which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (6:4) as eluent gave pure **5** as colorless solid.

Yield: 82%, colorless solid, **mp** 84 ^oC; $\mathbf{[\alpha]_D^{25}}$ = +65.0 (*c* 1, benzene) {lit.[10] $[\alpha]_D^{24}$ +65.8 (*c* 1.2, benzene)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 676, 730, 756, 823, 1030, 1132, 1284, 1329, 1469, 1599, 1683, 1715, 2984, 3019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.20-2.34 (m, 1H), 2.42 (m, 1H), 2.63-2.72 (m, 2H), 4.25-4.31 (m, 1H), 6.93 (dd, *J* = 2.1, 8.4 Hz, 2H), 7.22-7.26 (m, 1H), 7.38-7.48 (m, 3H), 8.14 (dd, *J* = 1.7, 7.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.4, 36.3, 44.2, 127.0, 127.2, 127.8, 129.0, 130.3, 130.6, 132.4, 133.6, 143.6, 144.6, 196.9; **Anal. Calcd** for $C_{16}H_{12}OCl_2$ requires C, 66.00; H, 4.15; found C, 66.10; H, 4.17 %.

(+)-Sertraline 1

A stirred solution of tetralone **5** (0.6 g, 2.06 mmol) in a dry diethyl ether (10 mL) was cooled to -78 ^oC. Then, methylamine in THF (1.5 mL, excess) was introduced dropwise *via* syringe, followed by the addition of $TiCl_4$ (1 M in CH_2Cl_2, 3 mL, 3.09 mmol). The reaction mixture was allowed to warm to 25 ^oC slowly and stirred

overnight. After the reaction was complete, it was filtered through a pad of Celite and washed with ether (3 x 15 mL). The combined filtrates were concentrated to give imine, which was taken up for further reaction without purification. Formed Imine (0.109 g, 0.35 mmol) was dissolved in methanol (5 mL) and hydrogenated (1 atm) over Raney-Ni. After completion of the reaction (monitored by TLC), it was filtered over Celite and the filtrate was concentrated under reduced pressure to provide **1**, which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (5:5) as eluent gave pure **1** as colorless oil.

Yield: 88%, colorless oil; $\mathbf{[\alpha]_D^{25}}$ = +36.7 (*c* 1, MeOH) {lit.[10] $[\alpha]_D^{26}$ +36.5 (*c* 1, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 1028, 1134, 1215, 1401, 1468, 1589, 2749, 2926, 3019, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.38 (m, 1H), 1.80 (m, 1H), 1.98 (m, 2H), 2.07 (m, 1H), 2.53 (s, 3H), 3.71 (m, 1H), 3.97 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 7.09 (m, 1H), 7.19 (m, 1H), 7.24 (m, 1H), 7.32 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.7, 28.4, 34.4, 45.4, 57.4, 126.6, 127.2, 128.2, 129.2, 129.8, 130.1, 130.3, 130.7, 132.3, 138.6, 139.4, 147.4; **Anal. Calcd** for $C_{17}H_{17}NCl_2$ requires C, 66.68; H, 5.60; N, 4.57; found C, 66.70; H, 5.65; N, 4.59%.

Section II

Total Synthesis of Eupomatilone-6 *via* SmI_2-Mediated Reductive Coupling of Aldehyde with Crotonate

3.2.1 Introduction and Pharmacology

Lignans are a widely distributed class of dimeric phenyl propanoid derivatives, found abundantly throughout the plant kingdom.[16] These naturally occurring lignans and their derivatives are medicinally important[17] as they possess antitumor, anti-HIV, antiviral, antimocrobial properties and their ability to influence nucleic acid metabolism.[18] Particularly, lignans possessing antitumor activity have common features such as: (i) five membered lactone ring; (ii) 3,4,5-trimethoxyphenyl group; (iii) methylenedioxy group and (iv) two substituted phenyl groups. The Australian shrub *Eupomatia bennettii* F. Muell is the source[19] of a variety of lignans such as eupodienones, eupobennettin, bennettinone and seven closely related substances termed as eupomatilones (**Fig. 14**). These species are characterized by highly oxygenated biaryl systems connected to a trisubstituted γ-lactone core. These interesting structural features and therapeutic potential make them attractive synthetic targets. Typical representative is eupomatilone-6 **54**.

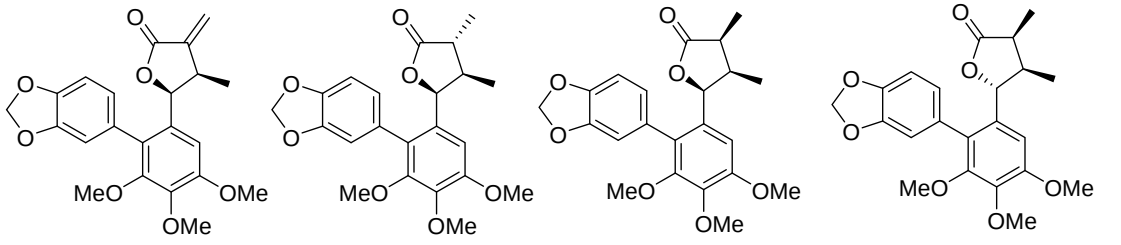


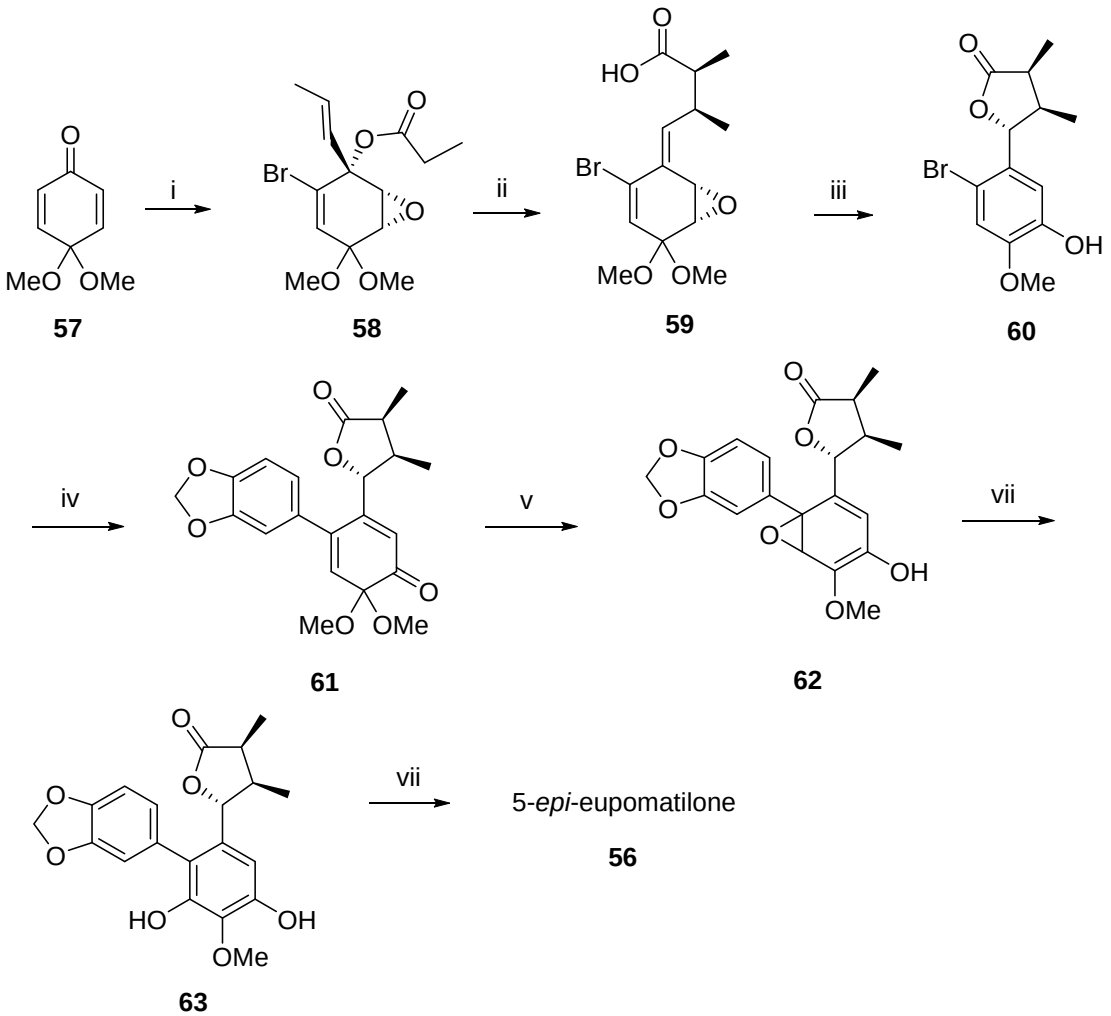
Fig. 14: Structures of eupomatilones

3.2.2 Review of Literature

Very few syntheses of eupomatilone-6 have been documented in the literature. Some of the interesting and important synthetic routes to eupomatilone-6 are described below.

McIntosh's approach (2002)[20]

McIntosh *et al.* have reported the synthesis of 5-*epi*-eupomatilone-6 **56** *via* Ireland-Claisen rearrangement as the key step (**Scheme 13**).

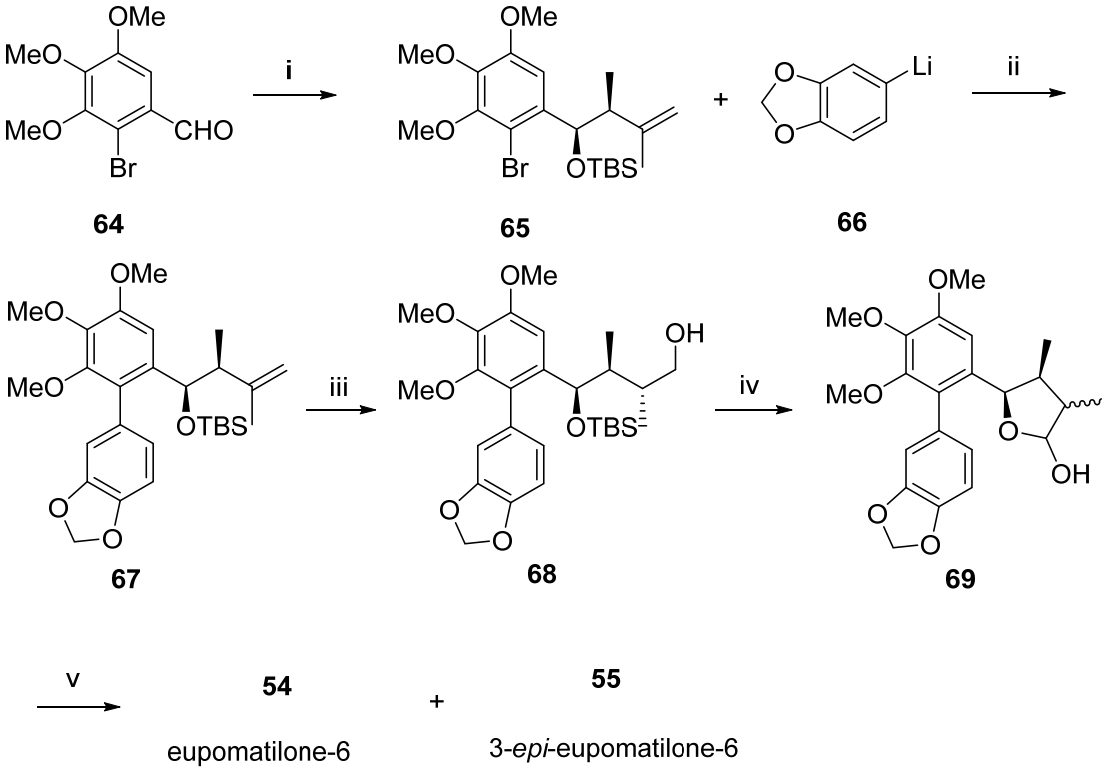


Scheme 13: (i) (a) H_2O_2, K_2CO_3, THF/H_2O; (b) Br_2, Et_3N, hexanae/Et_2O; (c) (*E*)-propenyl lithium, THF, $(EtCO)_2O$.; (ii) KHMDS, TMSCl, Et_2O, -78 ^oC, 60 %; (iii) AcOH, 80 ^oC; (iv) (a) $PhI(OAc)_2$, MeOH; (b) $Pd_2(dba)_3$, $CHCl_3$, PPh_3, CuI, THF, 80 ^oC, piperonyl tributylstannane; (v) DMDO, acetone, CH_2Cl_2, 25 ^oC; (vi) Mg, AcOH, 25 ^oC to 80 ^oC; (vii) K_2CO_3, MeI, acetone.

The synthesis involved conversion of the *p*-quinone monoketal **57** to the bromo epoxide derivative followed by the addition of (*E*)-propenyl lithium and *in situ* esterificiation to afford **58**. Then ester **58** was converted to **59** by Ireland-Claisen rearrangement. Acid **59** on treatment with AcOH underwent SN_2' lactonization and *in situ* aromatization to give **60**. Oxidation of phenol **60** using $PhI(OAc)_2$ followed by Stille coupling with piperonyl tributylstannane gave **61**. Regioselective epoxidation of **61** using DMDO gave epoxide **62**. Reductive ring opening of the epoxide **62** produced biaryl compound **63**. Finally, methylation of the phenolic hydroxyl group of **63** gave 5-*epi*-eupomatilone-6 **56**.

Coleman's approach (2004)[21]

Coleman *et al.* have reported the synthesis of isomers of eupomatilone-6 **54** using Lipshutz biarylcuprate cross-coupling reaction **(Scheme 14)**.



64 65 66 67 68 69

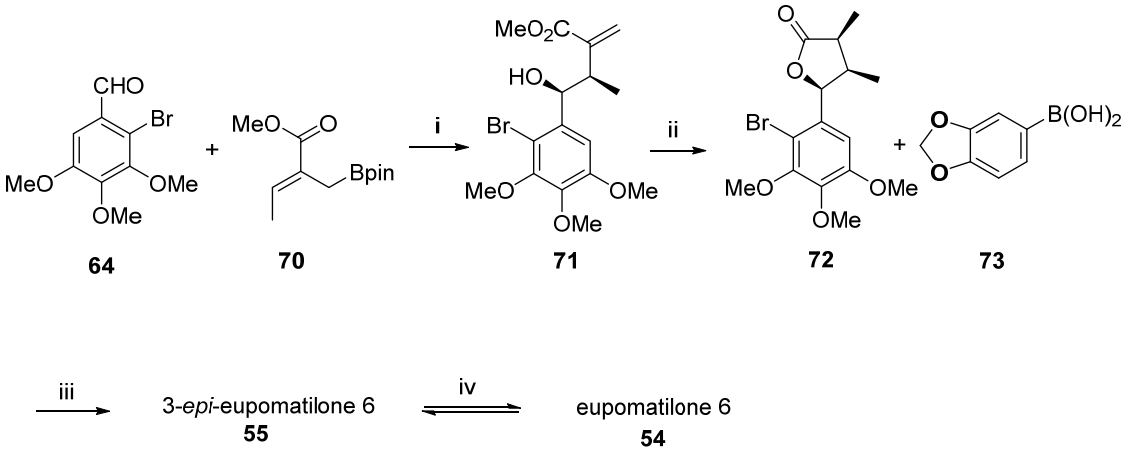
Scheme 14: (i) (a) (*E*)-(2-methylbut-2-en-1-yl)magnesium bromide, THF, -78 °C; (b) 2,6-lutidine, *t*-$BuMe_2SiOTf$, CH_2Cl_2, -78 °C; (ii) *n*-BuLi, CuCN, THF, -78 °C

then **42**; (iii) 9-BBN, THF, NaOH, H_2O_2; (iv) (a) PDC, CH_2Cl_2, 25 ^oC, 2 h; (b) *n*-Bu_4NF, THF, 25 ^oC; (v) PDC, CH_2Cl_2, 25 ^oC.

Its synthesis began with the addition of (*E*)-2-methyl-2-buten-1-ylmagnesium bromide to aldehyde **64**, which provided bromoderivative **65.** Cuprate coupling of aryl bromide **65** with aryllithium **66** afforded biphenyl derivative **67**. Hydroboration/oxidation of alkene **67** gave the corresponding primary alcohol **68**. Oxidation of **68** with PDC followed by silyl deprotection gave lactol **69**. Finally, lactol **69** on oxidation afforded a eupomatilone-6 **54** along with its isomer 3-*epi*-eupomatilone-6 **55** as 1:3 mixture, which could be separated by column chromatography.

Hall's approach (2005)[22]

Hall *et al* have reported the synthesis of eupomatilone-6 **54** from 2-bromo-3,4,5-trimethoxybenzaldehyde **64**. The key step in this synthesis was the thermal allylboration of aldehyde **64** with allylboronates **70**, which proceeded without isomerization to give *syn*-hydroxy ester **71**. The ester **71** was lactonized under mildly

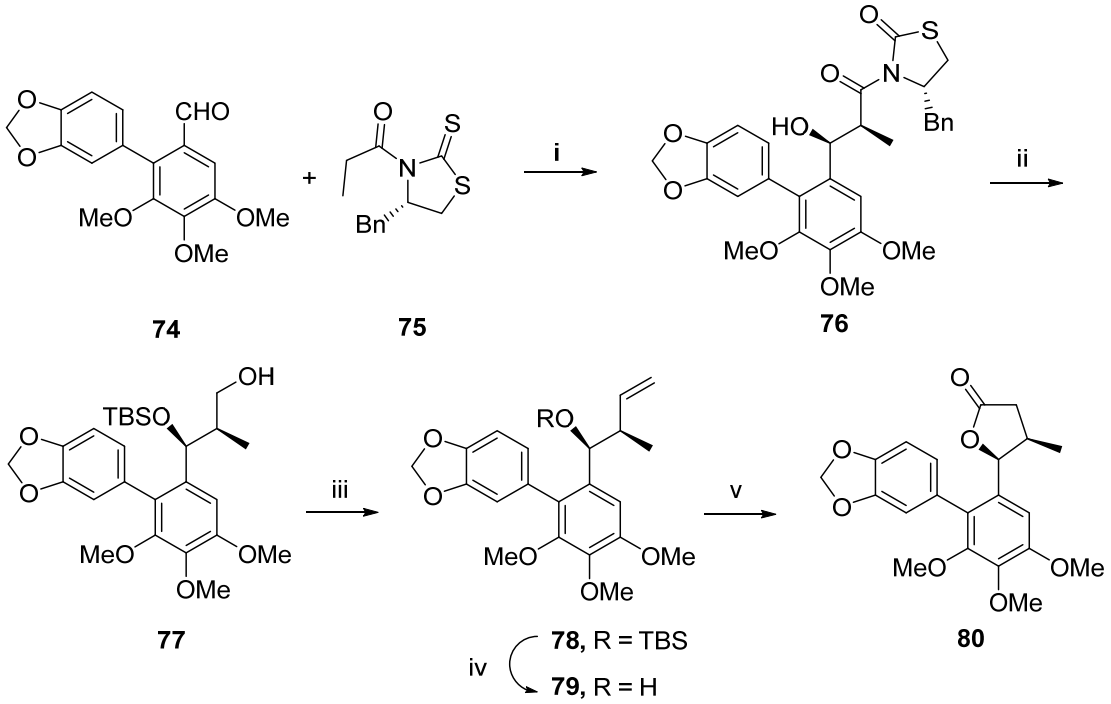


Scheme 15: (i) toluene, 110 ^oC, 48 h; (ii) (a) p-TSA, toluene, 25 ^oC, 6 h; (b) H_2, $ClRh(PPh_3)_3$, toluene, 25 ^oC, 3 h; (iii) $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), K_2CO_3 (2 equiv), toluene, 110 ^oC, 12 h; (iv) DBU, MeOH/toluene (1:1), 80 ^oC, 48 h.

acidic conditions, followed by hydrogenation produce **72**. Lactone **72** was subjected to the Suzuki coupling with aryl boronic acid **73** to give 3-*epi*-eupomatilone-6 **55.** The isomerization of **56** with DBU in methanol, gave an equilibrium ratio of the two separable epimers of eupomatilone-6 **(Scheme 15)**.

Gurjar's approach (2005)[23]

Gurjar *et al.* have reported the asymmetric synthesis of eupomatilone-6 **54** which began with aldol condensation of *N*-propionyl thiazolidinethione **75** with aldehyde **74** to give aldol adduct **76**. After having an access for the key aldol adduct **76**, the free hydroxyl group in **76** was protected as its TBS-ether followed by reductive removal of

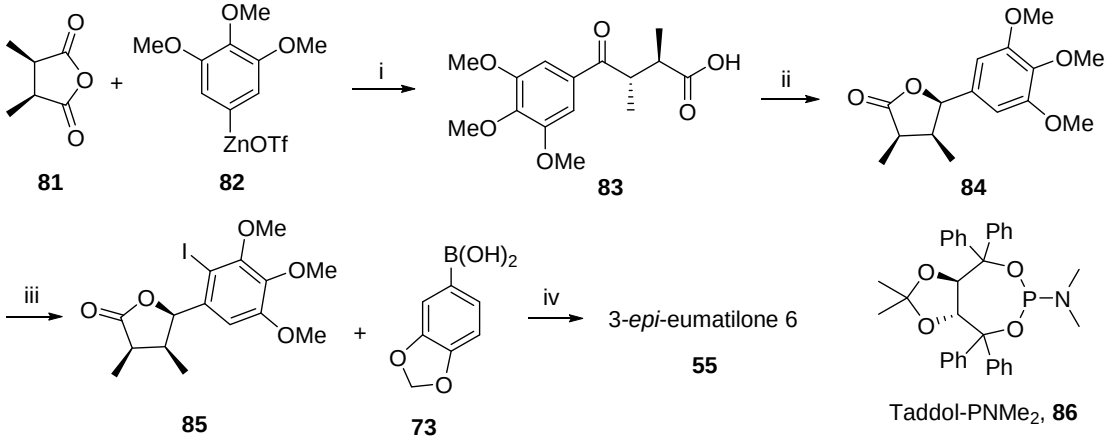


Scheme 16: (i) $TiCl_4$, TMEDA, 0 °C, CH_2Cl_2, 2.5 h, 65%; (ii) (a) TBSOTf, 2,6-lutidine, 79%; (b) $NaBH_4$, THF-EtOH, 25 °C, 5 h, 82%; (iii) (a) Dess-Martin periodinane, CH_2Cl_2, 25 °C; (b) CH_3PPh_3I, *n*-BuLi, THF, 0 °C; (iv) TBAF, THF, 0 °C, 4 h, 85%; (v) (a) $BH_3{\cdot}Me_2S$, 66%; (b) TEMPO, NCS, 65%; (vi) LiHMDS, THF, -78 to 0 °C, MeI.

the thiazolidinethione auxiliary with $NaBH_4$ gave **77**. Primary hydroxy group in **77** was oxidized to aldehyde using Dess-Martin periodinane followed by Wittig reaction of the generated aldehyde with $PPh_3{=}CH_2$ gave the olefin **78**. The TBS group of **78** was removed using TBAF to afford **79**. The olefin **79** was subjected to successive hydroboration/oxidation reaction followed by lactonization gave the lactone derivative **80**. The alkylation of lactone **80** at C-3 position was executed by using LiHMDS-MeI to give eupomatilone-6 **54 (Scheme 16)**.

Rovis's approach (2007)[24]

Rovis *et al.* have achieved the synthesis of 3-*epi*-eupomatilone-6 **55** using rhodium catalyzed cross-coupling of arylzinc triflate **82** with *cis*-dimethylsuccinic anhydride **81** as the key step which produced keto acid **83**. Diastereoselective reduction and cyclization of **83** provide lactone **84** in 91% yield with 98:2 diastereomeric ratios. Iodination of **84** was accomplished by treatment with I_2 in the presence of a silver salt, providing aryl iodide **85** in 89% yield. Suzuki coupling of **85** with aryl boronic acid **73** using Pd catalyst gave 3-*epi*-eupomatilone 6 **55**, in four steps from **81** with 60% overall yield **(Scheme 17)**.



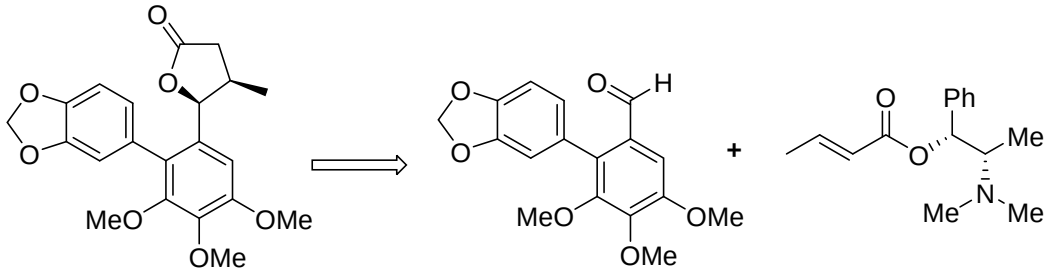
Scheme 17: (i) [{Rh(cod)Cl}$_2$], ligand **59**, DMF, 50 ^oC, 85%; (ii) DIBAL-H, THF/toluene (5:1), -78 ^oC, then TFA (0.02%), CH_2Cl_2, 91%; (iii) $Ag(OCOCF_3)$, I_2, $CHCl_3$, 23 ^oC, 89%; (iv) $Pd(PPh_3)_4$ (6 mol%), $NaHCO_3$, DME/H_2O, 87%.

3.2.3. Present Work

3.2.3.1 Objective

As can be seen from the above discussion, the reported methods of synthesis of eupomatilone-6 **54**, have certain limitations such as the use of chiral building blocks, exotic reagents, involvement of longer reaction sequences, low overall yields and the need for separation of diastereoisomers, etc. In this section, a short and effective synthesis of eupomatilone-6 **54**, using diastereoselective SmI_2-mediated coupling of aldehyde and chiral crotonate as the key step is descriebed.[25]

As can be seen from the retrosynthetic analysis (**Scheme 18**), the γ-butyrolactone **80** unit could be visualized as an important precursor for the synthesis of the target molecule **54**. Thus, the synthesis of γ-butyrolactone **80** could be achieved by means of SmI_2-mediated coupling of aldehyde **74** with chiral crotonate **87**. The aldehyde **74** can be readily prepared from Suzuki coupling reaction of 2-bromo-3,4,5-trimethoxybenzyaldehyde and the corresponding aryl boronic acid.

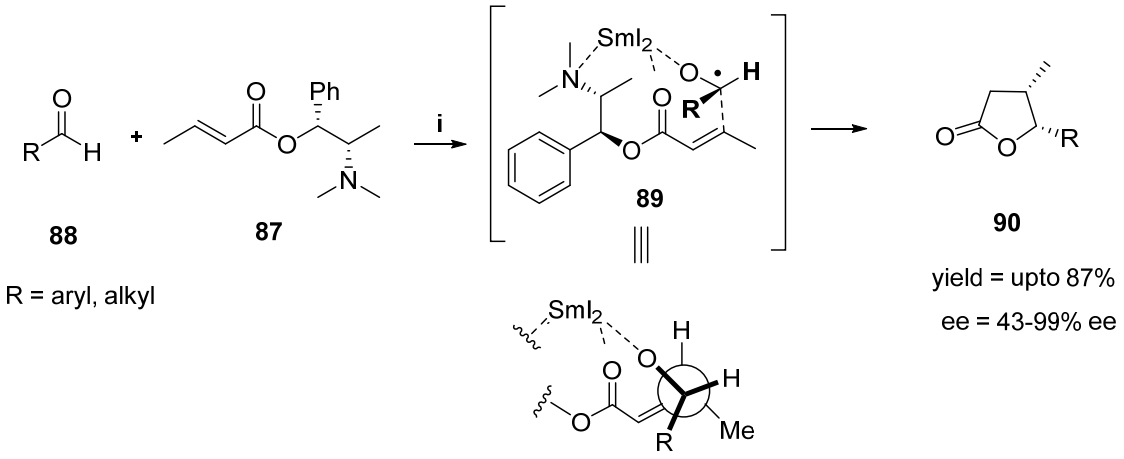


Scheme 18: Retrosynthetic analysis of eupomatilone-6 **(54)**

Stereoselective synthesis of lactone *via* SmI_2 mediated reductive coupling of aldehydes and crotonates

Fukuzawa, *et al.*[25] have reported SmI_2 mediated asymmetric synthesis of *cis*-3,4-disubstituted-*γ*-butyrolactones by reductive coupling of aldehydes with α, *β*-unsaturated esters. An interesting feature of the reaction is the formation of *cis*-isomer

(dr = 70:30 to 99:1) predominantly. These reactions often produce high stereoselectivity due to chelation control of the samarium atom with the oxygen or nitrogen moiety present in starting materials. Fukuzawa, *et al.* also achieved the chiral version of this reaction by using reductive coupling of aldehydes **88** with chiral crotonates **87** possessing *N*-methylephedrine as chiral auxiliary, in which the *cis* isomer of the 3,4-disubstituted-γ-butyrolactone **90** was produced predominantly (dr = 97:3 to 99:1) with 43 to 99% ee and chemical yield up to 86% (**Scheme 19**). The mechanism of the reaction involves coupling of ketyl radical with alkene part wherein chelation control by samarium atom plays an important role in the asymmetric induction and diastereoselectivity



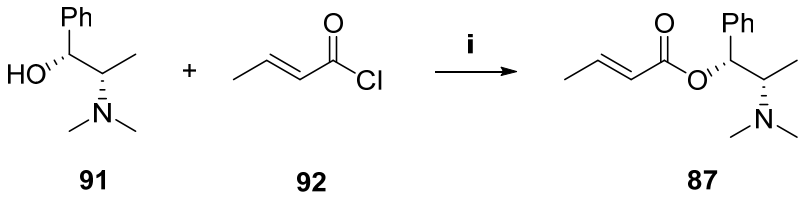
Scheme 19: (i) SmI_2, *t*-BuOH, THF, -78 to 0 ^oC, 5-6 h.

3.2.3.2 Results and Discussion

(a) Synthesis of (1*R*, 2*S*)-*N*-methylephedrinyl crotonate (87)

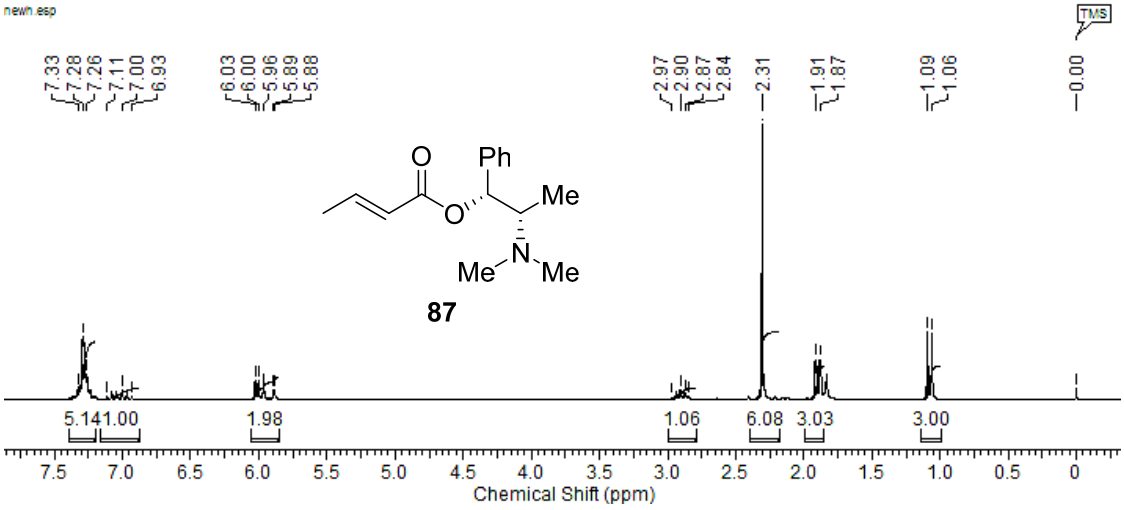
N-Methylephedrinyl crotonate **87** was prepared by the esterification of commercially available (1*S*, 2*R*)-*N*-methylephedrine **91** with *trans*-crotonyl chloride **92** in presence of triethylamine in 82% yield (**Scheme 20**). The formation of crotonate **87** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1722 cm^{-1} typically for ester functionality. The ^1H NMR spectrum of **87** showed the

appearance of a signal at δ 1.06 (d, J = 6.7 Hz, 1H) for methyl protons (CH-**CH_3**) and a multiplet at δ 2.90 for methine proton (N-**CH**). It was further confirmed by ^{13}C NMR spectrum, which showed characteristic carbon signals at δ 122.6 and δ 144.7 for olefinic carbons (**Fig. 15**).



91 **92** **87**

Scheme 20: Reaction conditions: (i) Et_3N, ether, 0 °C, 3 h, 82%.



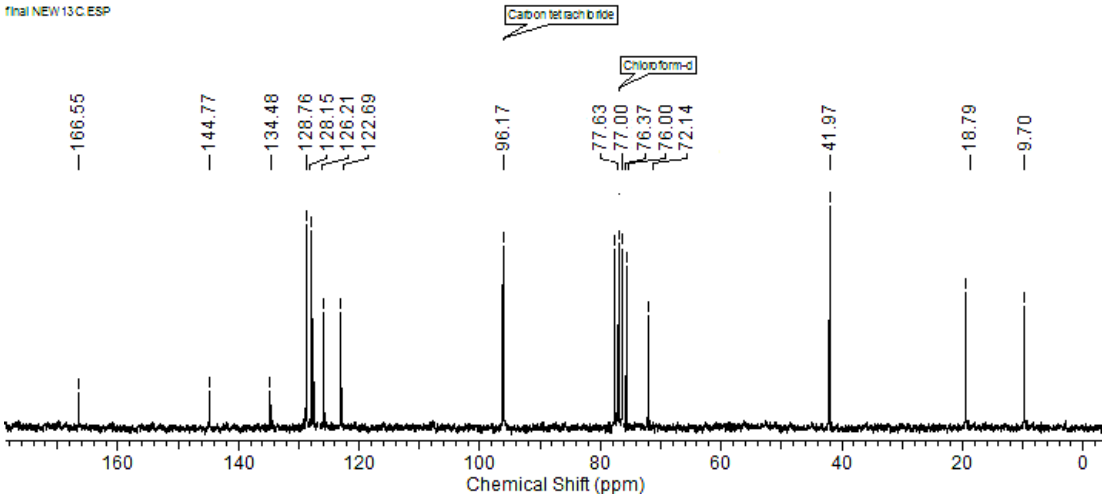
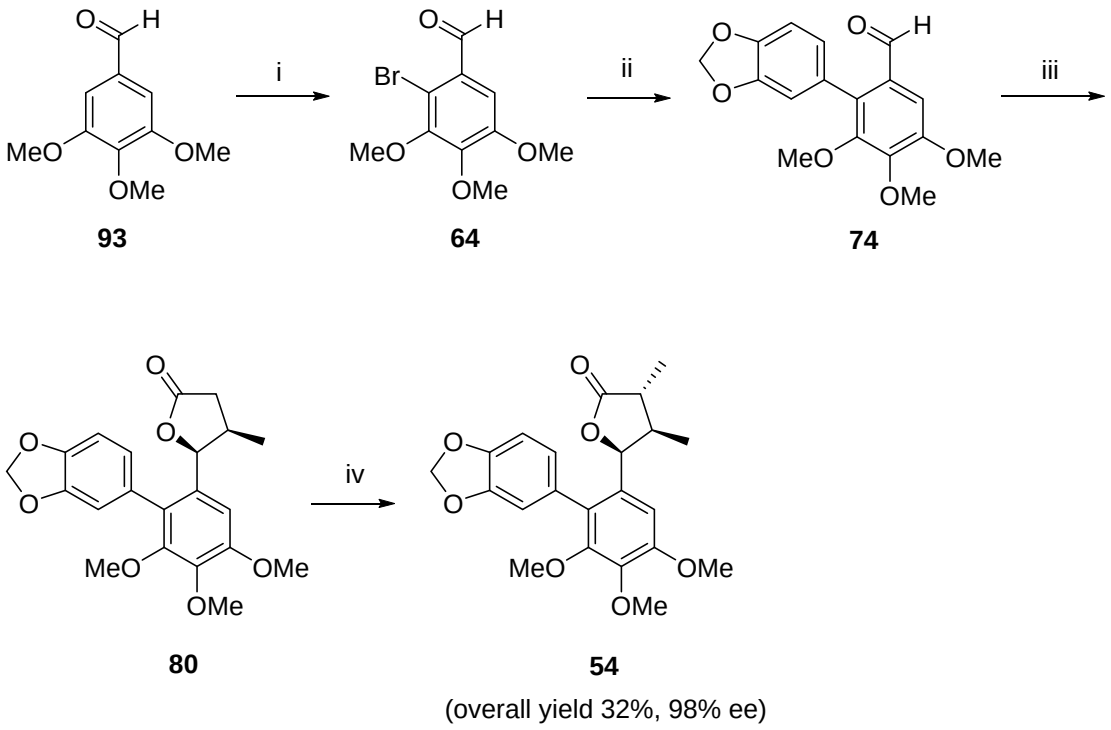


Fig. 15: ^1H and ^{13}C NMR spectra of **87**

(b) Synthesis of eupomatilones-6 (54)

Scheme 21 shows the synthetic scheme for eupomatilones-6 **54**, starting from trimethoxybenzaldehyde **93**, which on bromination with NBS produced 2-bromo-3,4,5-trimethoxy benzaldehyde **64** in 90% yield.



Scheme 21: Reaction conditions: (i) NBS, CH_3CN/H_2O (4:1), 3 h, 0 ^oC, 90%; (ii) $Pd(PPh_3)_4$, 3,4-(methylenedioxy) phenylboronic acid, 2 M Na_2CO_3, C_2H_5OH, benzene, reflux, 8 h, 75 %; (iii) SmI_2, chiral crotonate **87**, THF/*t*-BuOH, -10 ^oC, 68%; (iv) LiHMDS, MeI, THF, -78 to 0 ^oC, 70%.

The formation of **64** was confirmed by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **64** showed a typical singlet at δ 10.30 (s, 1H) for aldehydic proton and signals at δ 3.92 (6H) and 3.99 (3H) due to methoxy protons. This was further confirmed by its ^{13}C NMR spectrum which showed a typical carbon signal at δ 107.4 for aromatic methine carbon and carbon signal at 190.6 due to carbonyl carbon of aldehyde group (**Fig. 16**).

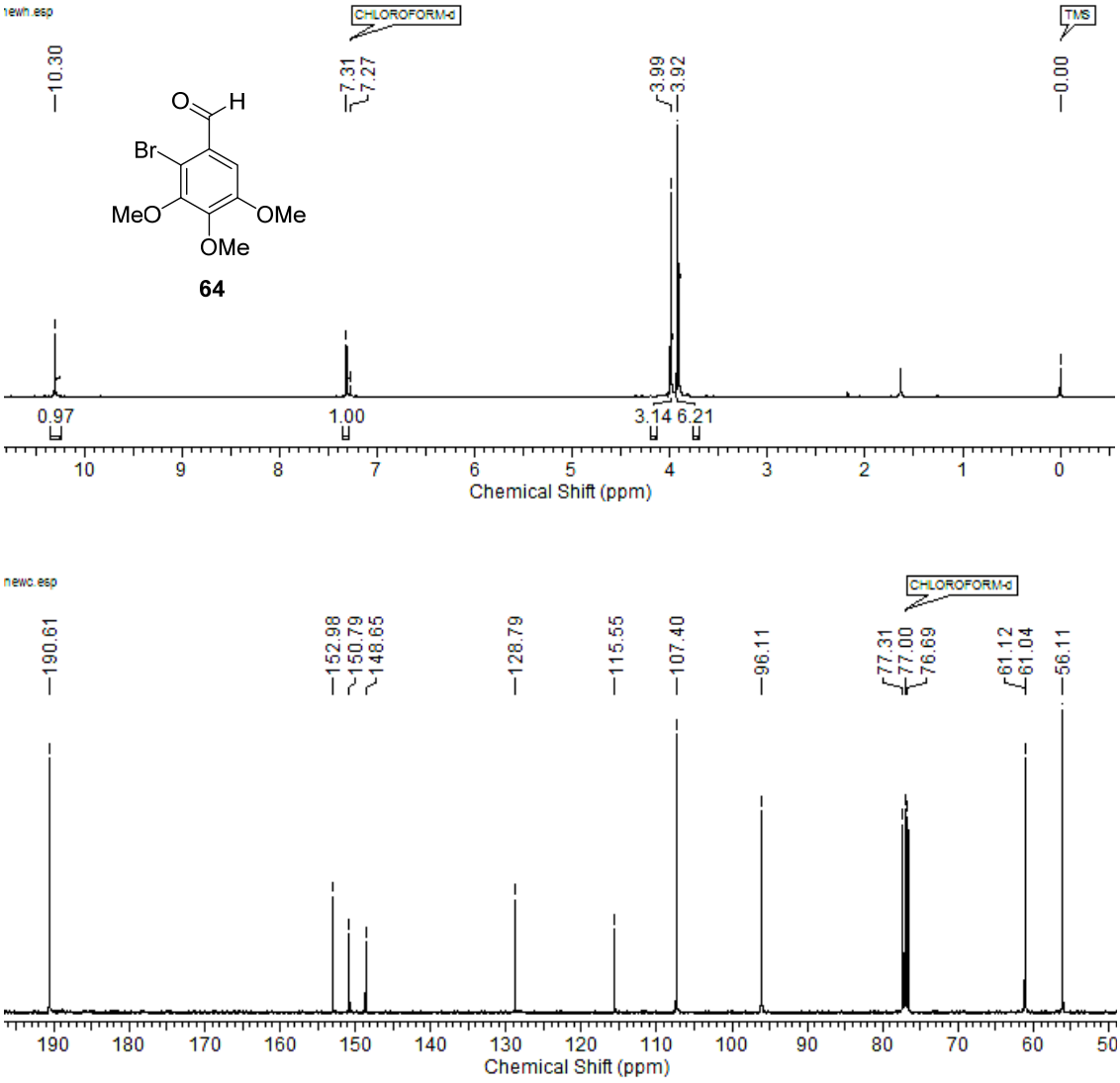


Fig. 16: ^{1}H and ^{13}C NMR spectra of **64**

The Suzuki coupling of aldehyde **64** with 3,4-(methylenedioxy)phenylboronic acid in the presence of $Pd(PPh_3)_4$ as catalyst afforded biaryl aldehyde **74** in 75% yield.[23] The formation of compound **74** was confirmed from its IR spectrum, which showed a strong absorption band at υ_{max} 1679 cm^{-1} typically for aromatic aldehyde functionality. Its ^{1}H NMR spectrum showed the appearance of a signal at δ 6.05 (s, 2H) due to methine proton (O-**CH**-O). Its ^{13}C NMR showed a typical carbon signal at δ 190.9 due to carbonyl carbons of aldehyde and signal at δ 101.2 due to methylene carbon **(O-CH_2-O) (Fig. 17).**

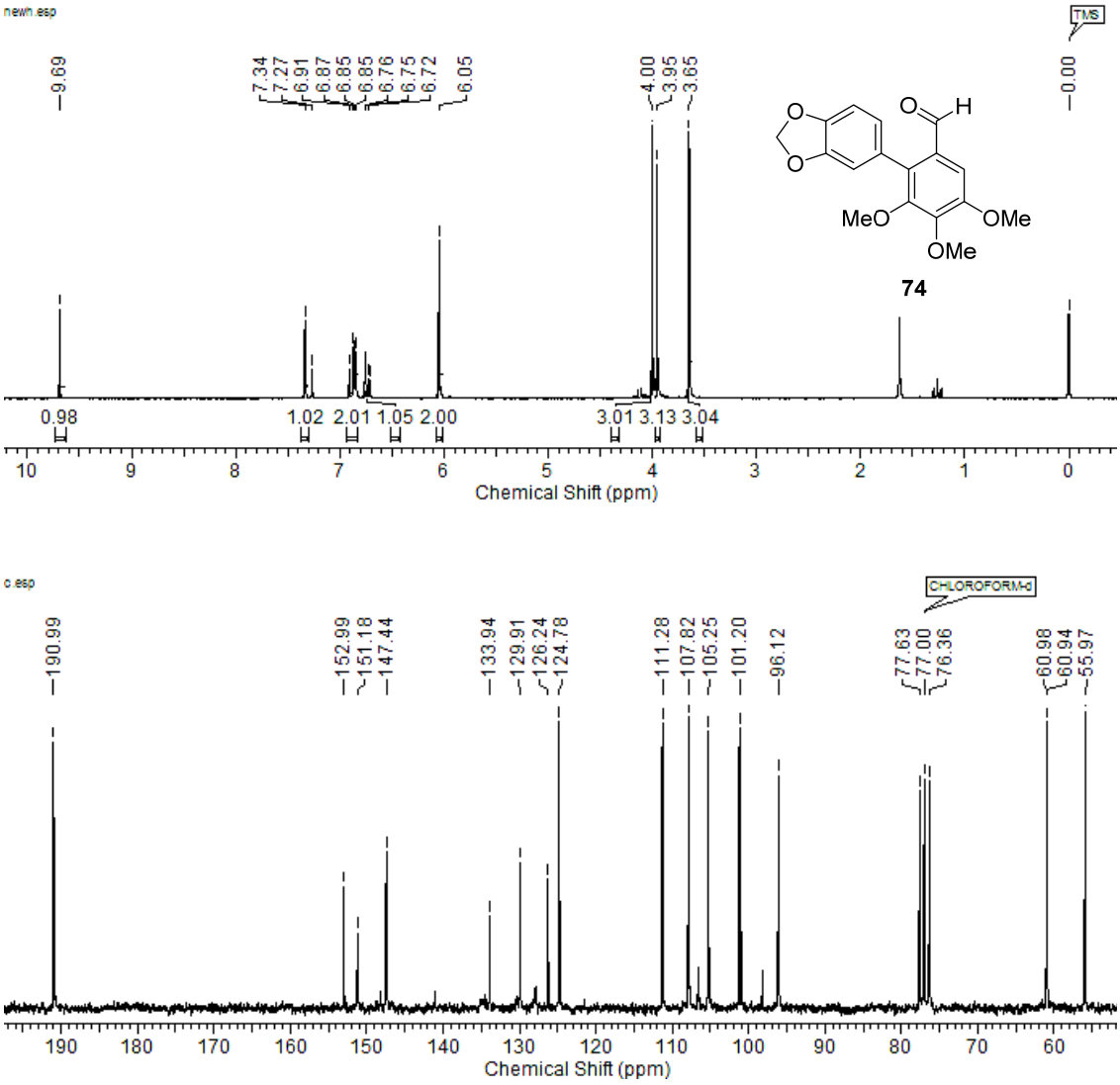


Fig. 17: ^{1}H and ^{13}C NMR spectra of **74**

Next, the reaction of biaryl aldehyde **74** with chiral crotonate **87** in presence of SmI_2 produced *cis*-3,4-disubstituted butyrolactone **80** in 98% ee. The enantiomeric excess of lactone **80** was determined from chiral HPLC analysis; Chiralpak OD-H **(Fig. 19)**. The formation of lactone derivative **80** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1777 cm^{-1} typically for cyclic carbonyl ester functionality. The ^{1}H NMR spectrum of **80** showed the appearance of a multiplet at δ 0.66 (1H) corresponding to methyl protons (CH-$\mathbf{CH_3}$). This was further confirmed by its ^{13}C NMR spectrum, which showed a typical carbon signal at δ 176.1 for carbonyl

carbon of ester moiety (**Fig. 18**). Absolute configuration of *cis*-3,4-disubstituted γ-butyrolactone **80** was confirmed by comparing its specific optical rotation with the values reported in the literature.[23]

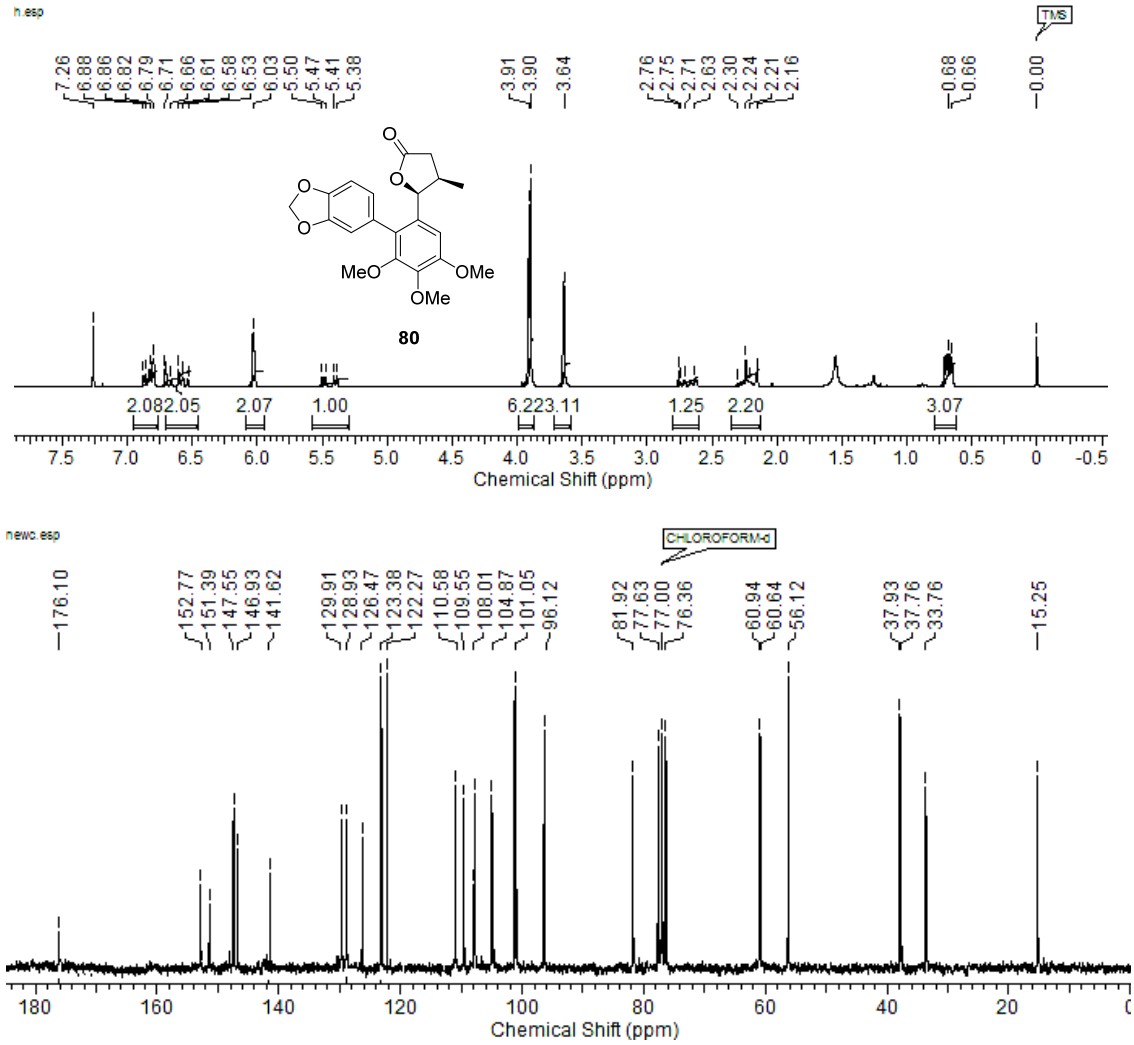
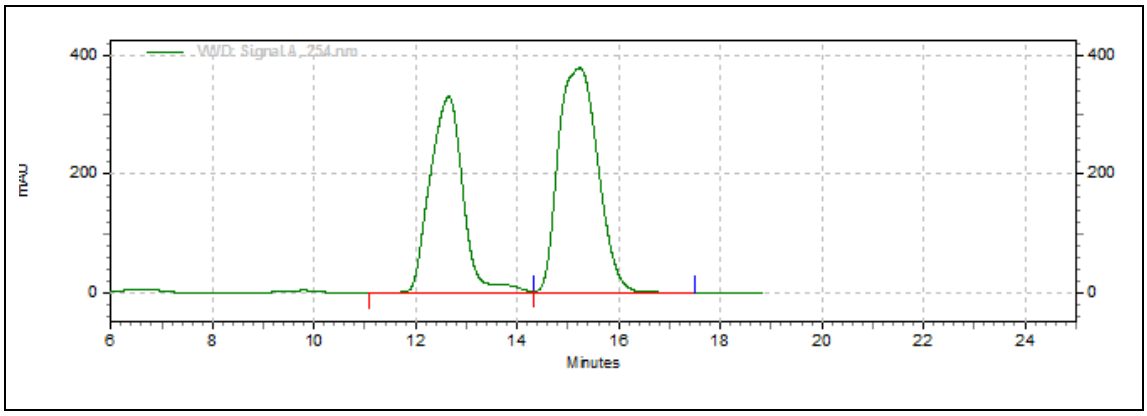


Fig. 18: ^{1}H and ^{13}C NMR spectra of **80**



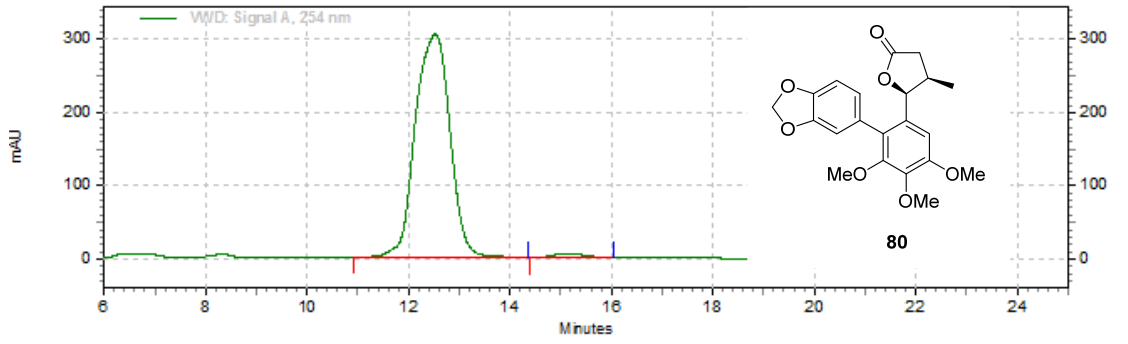
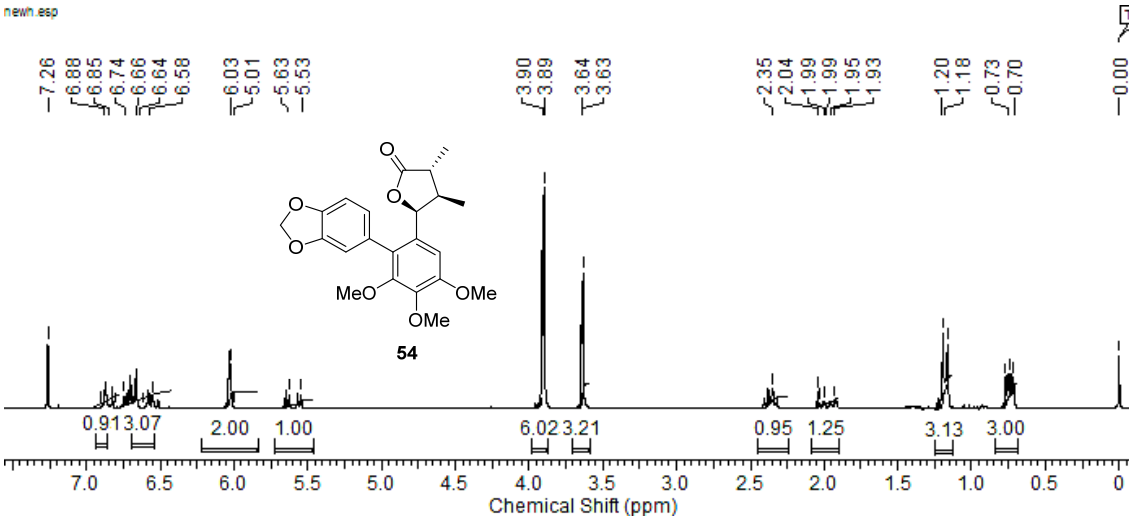


Fig. 19: HPLC chromatogram of **80** [Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min, 254 nm; retention time 12.80 (99.17%) and 15.43 (0.83%)]

Finally, diastereoselective methylation at C-3 position in **80** was carried out by using LiHMDS-MeI combination to give eupomatilone-6 **54** in 32% overall yield and 98% ee (**Scheme 21**). Stereochemistry of methyl group at C-3 position was controlled by the chiral center already present in the molecule. The formation of eupomatilone-6 **54** was confirmed by its ^{1}H NMR spectrum which showed the appearence of signals at δ 1.18 (m, 3H) due to methyl proton (α-CH-**CH$_3$**) and at δ 5.53 (1H) due to methine proton (O-**CH**). This was further confirmed by ^{13}C NMR spectrum, which showed carbon signals at δ 79.86 and 179.6 due to methine carbon (O-**CH**) and carbonyl carbon of lactone moiety respectively (**Fig. 20**).



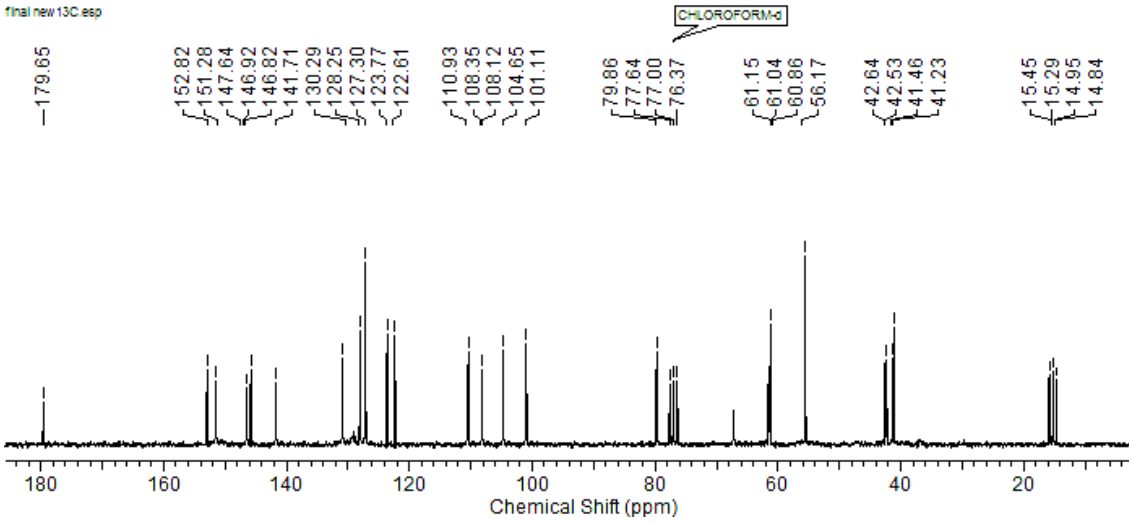


Fig. 20: ^{1}H and ^{13}C NMR spectra of **54**

3.2.4 Conclusion

In conclusion, a short synthetic route to eupomatilone-6 **54** incorporating a successful application of diastereoselective SmI_2-mediated coupling of aldehyde with crotonate has been developed. Eupomatilone-6 **54** was obtained with an overall yield of 32% and 98% ee. The operationally simple reactions with less number of steps and high overall yield make this approach an attractive and a good alternative to the known methods.

3.2.5 Experimental section

(1*R*, 2*S*)-*N*-Methylephedrinyl crotonate (87)

To a solution of (1*R*, 2*S*)-(-)-*N*-methylephedrine **91** (3.58 g, 20 mmol) in dry diethyl ether (100 ml) at 0 ^{o}C, triethylamine (2.42g, 24.0 mmol) and crotonyl chloride **92** (2.51g, 24.0 mmol) was added. It was allowed to stir at 0 °C for 2 h. After completion of reaction (monitored by TLC), it was quenched with saturated solution of NH_4Cl (10 mL) and water (40 mL). The organic layer was further separated and the aq. layer was extracted with diethyl ether (3 x 20 mL). The combined organic phase was dried

over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using petroleum ether: ethyl acetate (9:1) as eluent to give **(**1*R*, 2*S*)-*N*-Methylephedrinyl crotonate **87** as colorless liquid.

Yield: 82%, colorless oil; $\mathbf{[\alpha]_D^{25}}$ = + 0.6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1009, 1102, 1175, 1264, 1452, 1657, 1722; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.7 Hz, 3H), 1.87 (dd, *J* = 1.6, 7.0 Hz, 3H), 2.31 (s, 6H), 2.90 (m, 1H), 5.88 (m, 1H), 6.93 (d, *J* = 4.8 Hz, 1H), 7.00 (m, 1H), 7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.7, 18.8, 41.9, 72.1, 76.0, 122.6, 126.2, 128.1, 128.7, 134.4, 144.7, 166.5; **Anal.** Calcd for $C_{15}H_{21}NO_2$ requires C, 72.84; H, 8.56; N, 5.66; found C, 72.80; H, 8.60; N, 5.70%.

2-Bromo-3,4,5-trimethoxybenzaldehyde (64)

A mixture of trimethoxybezylaldehyde **93** (2 g, 10.2 mmol) in CH_3CN/H_2O (4:1, 50 mL), NBS (2.17 g, 12.24 mmol) was added slowly *via* solid addition funnel, with stirring at 0 °C and progress of reaction was monitored by TLC. After completion of the reaction (monitored by TLC), it was diluted with EtOAc (60 mL) and water (50 mL). The organic layer was further separated and the aq. layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography using petroleum ether: ethyl acetate (8:2) as eluents to afford pure product **64** as colorless solid.

Yield: 90%, colorless solid, **mp** 77 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 726, 774, 817 1002, 1165, 1285, 1426, 1686, 2866, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.92 (s, 6H), 3.99 (s, 3H), 7.31 (s, 1H), 10.30 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.1, 61.0, 61.2, 107.4, 115.5, 128.7, 148.6, 150.7, 152.9, 190.6; **Anal.** Calcd for $C_{10}H_{11}BrO_4$

requires C, 43.66; H, 4.03; found C, 43.60; H, 4.06%.

2-(Benzo[d][1,3]dioxol-5-yl)-3,4,5-trimethoxybenzaldehyde (74)

To a stirred solution of aldehyde **64** (1.2 g, 4.3 mmol) in benzene/EtOH (9 mL:2 mL) mixture at 25 ^{o}C, $Pd(PPh_3)_4$ (150 mg, 0.13 mmol), Na_2CO_3 (4.3 mL, 8.6 mmol) and 3,4-(methylenedioxy)phenylboronic acid (800 mg,4.8 mmol) were added and the reaction mixture was refluxed under N_2 for 24 h. After completion of the reaction (monitored by TLC), it was diluted with EtOAc (20 mL) and water (20 mL). The organic layer was further separated and the aq. layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography using petroleum ether: ethyl acetate (19:1) as eluents to afford pure product **74**.

Yield: 75%, gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1187, 1233, 1436, 1679, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 6.05 (s, 2H), 6.75 (dd, *J* = 1.6, 7.8 Hz, 1H), 6.87 (m, 2H), 7.34 (s, 1H), 9.69 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.9, 60.9, 61.0, 101.2, 105.2, 107.8, 111.2, 124.7, 126.2, 129.9, 133.9, 147.4, 151.1, 152.9, 190.9; **Anal.** Calcd for $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.10; found C, 64.65; H, 5.17%.

***syn*-Lactone (80)**

To a stirred solution of the chiral crotonate **87** (59 mg, 0.24 mmol) and aldehyde **74** (60 mg, 0.20 mmol) in THF/ *t*-BuOH (2 mL: 0.2 mL) at -10 ^{o}C, SmI_2 (0.1 M in THF, 6 mL, 0.60 mmol) was added dropwise under N_2 atmosphere. The resulting solution was stirred at this temperature for 3 h. After completion of the reaction (monitored by TLC), it was diluted with EtOAc (20 mL) and water (10 mL). The organic layer was further separated and the aq. layer was extracted with EtOAc (3 x 5 mL). The

combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography using petroleum ether: ethyl acetate (7:3) as eluents to afford pure product **80** as colorless thick oil.

Yield: 68%, colorless oil; $\mathbf{[\alpha]_D^{25}}$ = -26.0 (*c* 1, $CHCl_3$) {lit.[23] $[\alpha]_D^{25}$ -26.3 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3020, 1777, 1599, 1483, 1215, 1042, 757; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.68 (m, 3H), 2.24 (m, 2H), 2.75 (m, 1H), 3.64 (d, *J* = 1.6 Hz, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 5.41 (m, 1H), 6.03 (m, 2H), 6.53-6.71 (m, 2H) 6.79-6.88 (m, 2H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.2, 33.7, 37.7, 37.9, 56.12, 60.6, 60.9, 81.9, 101.0, 104.8, 108.0, 109.5, 110.5, 122.2, 123.3, 126.4, 128.9, 129.9, 141.6, 146.9, 147.5, 151.3, 152.7, 176.1; **Optical purity**: 98% ee determined from HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm); Retention time: t_{major} = 12.80 and t_{minor} = 15.43 min; **Anal.** Calcd for $C_{21}H_{22}O_7$ requires C, 65.28; H, 5.74; found C, 65.30; H, 5.80%.

Eupomatilone-6 (54)

To a stirred solution of **80** (0.1 g, 0.258 mmol) in anhydrous THF (1 mL) at -78 °C, LiHMDS (1 M in THF, 0.3 mL, 0.3 mmol) was added and the stirring was continued for 1h. A solution of MeI (0.02 mL, 0.32 mmol) in THF (0.5 mL) was then added dropwise to the reaction mixture and the stirring continued for 1 h at -78 ^oC and the temperature brought to 0 ^oC. After completion of the reaction (monitored by TLC), it was diluted with EtOAc (20 mL) and water (10 mL). The organic layer was further separated and the aq. layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography using petroleum ether: ethyl acetate (8:2) as eluents to

afford pure product **54** as colorless oil.

Yield: 70%, colorless oil; $[\alpha]_D^{25}$ = +24.5 (*c* 1, $CHCl_3$) {lit.[23] $[\alpha]_D^{25}$ +24.7 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1197, 1326, 1457, 1596, 1773, 2932; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.70 (m, 3H), 1.18 (m, 3H), 1.93-2.04 (m , 1H), 2.35 (m, 1H), 3.63 (d, *J* = 1.6 Hz, 3H) 3.89 (s, 3H), 3.90 (s, 3H), 5.53 (dd, *J* = 1.6, 6.9 Hz, 1H), 6.03 (m, 2H), 6.58-6.74 (m, 3H), 6.85 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.8, 14.9, 15.2, 15.4, 41.2, 41.4, 42.5, 42.6, 56.1, 60.8, 61.0, 61.1, 79.8, 101.1, 104.6, 108.1, 110.9, 122.6, 123.7, 127.3, 128.2, 130.2, 141.7, 146.8, 146.9, 147.6, 151.2, 152.8, 179.6; **Anal.** Calcd for $C_{22}H_{24}O_7$ requires C, 65.99; H, 6.04; found C, 65.95; H, 6.08%.

3.2.6 References

1. (a) Pinder. R. M.; Bropden, R. N.; Speight. T. M.; Avery, G. S. *Drugs*, **1977**, *13*, 321; (b) Salama, A. I.; Insalaco, J. R.; Maxwell, R. A. *J. Pharmacal. Exp. Ther.* **1971**, *178,* 474; (c) Coppen, A.; Shaw, D. M.; Herzberg, B.; Maggs, R. *Lancet II*, **1967**, 1178; (d) Carlsson, A.; Corrodi, H.; Fuxe, K.; Hokfelt, T. *Eur. J. Pharmacal.* **1969**, *5*, 357.

2. (a) Welch, W. M.; *Adv. Med. Chem*. **1995**, *3*, 113; (b) Sarges, R.; Tretter, J. R.; Tenen, S. S.; Weissman, A. *J. Med. Chem.* **1973**, *16*, 1003.

3. Quallich, G. J.; Woodwall, T. M. *Tetrahedron*, **1992**, *48*, 10239.

4. Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5537.

5. Chen, C-Y.; Reamer, R. A. *Org. Lett*. **1999**, *1*, 293.

6. Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett*. **1999**, *1*, 233.

7. Boulton, L. T.; Lennon, I. C.; McCague, R. *Org. Biomol. Chem*. **2003**, *1*, 1094.

8. Taber, G. P.; Pfisterer, D. M.; Colberg, J. C. *Org. Process. Res. Dev*. **2004**, *8*, 385.

9. Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028.

10. Wang, G.; Zheng, C.; Zhao, G. *Tetrahedron: Asymmetry*, **2006**, *17*, 2074.

11. Lee, S. H.; Kim, I.S.; Qing, L. R.; Dong, G. R.; Jeong, L. S.; Jung, Y. H. *J. Org. Chem.* **2011**, *76*, 10011.

12. Tokunaga, M.; larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science,* **1997**, *277*, 936.

13. Pastre, J. C.; Correia, C. R. D. *Adv. Synth. Catal.* **2009**, *351*, 1217.

14. Alexakis, A.; Hajjaji, S. E.; Polet, D.; Rathgeb, X. *Org. Lett.* **2007**, *9*, 3393.

15. Roesner, S.; Casatejada, J. M.; Elford, T. G.; Sonawane, R. P.; Aggarwal. V. K. *Org. Lett.*

2011*, 13,* 5740.

16. Cole, J. R.; Weidhopf, R. M. Chemistry of Lignans, (Rao C. B. S., ed), p. 307, Andhra University Press, India.

17. (a) *Comprehensive Natural Product Chemistry*, Vol. 1; (b) *Studies in Natural Product Chemistry*, Vol 26, Elsvier Science.

18. (a) MacRae , W. D.; Towers, G. H. N. *Phytochemistry*, **1984**, *23*, 1207; (b) Ward, R. S. *Nat. Prod. Rep*., **1997**, *14*, 43.

19. Carroll, A. R.; Taylor, W. C. *Aust. J. Chem*., **1991**, *44*, 1705.

20. Hong. S.-p.; McIntosh. M. C. *Org. Lett*. **2002**, *4*, 19.

21. Coleman. R. S.; Gurrala. S. R. *Org. Lett.* **2004**, 6, 4025.

22. Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc*. **2005**, *127*, 12808.

23. Gurjar, M. K.; Karumudi, B.; Ramana, C. V. *J. Org. Chem.* **2005**, *70*, 9658.

24. Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4514.

25. Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc*., **1997**, *119*, 1482.

Chapter IV

γ-Butenolides via Sequential α-Aminoxylation and cis-Wittig Olefination of Aldehydes and its Application for the Synthesis of trans-(+)-Cognac Lactone and Synthesis of 4-Substituted Chromanes via Au(III)-Catalyzed Intramolecular Friedel-Crafts Reaction

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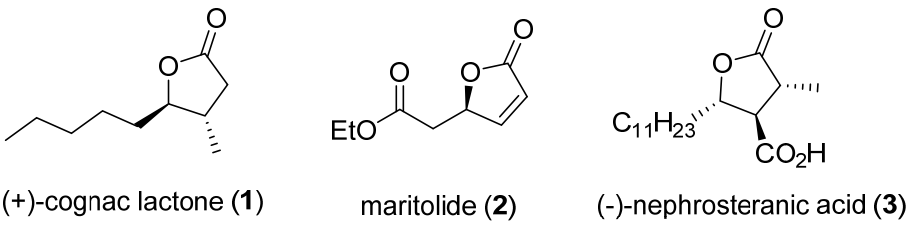
1. "Organocatalytic sequential α-aminoxylation and *cis*-Wittig olefination of aldehydes: synthesis of enantiopure γ-butenolides" **Devalankar, D. A.**; Chouthaiwale, P. V.; Sudalai, A. *Tetrahedron: Asymmetry*, **2012**, *23*, 240.
2. "Process For The Production of 4-Subtituted Chromanes *via* Gold Catalysis" Chouthaiwale, P. V.; **Devalankar, D. A.;** Sudalai, A. **2013, WO2013088455 (A1)** (Patent).

Section I

Synthesis of γ-Butenolides *via* Sequential α-Aminoxylation and *cis*-Wittig Olefination of Aldehydes and its Application in the Synthesis of *trans*-(+)-Cognac Lactone

4.1.1 Introduction

The γ-butenolides skeleton is widely found in over 13,000 biologically active natural products,[1] synthetic pheromones[2] and other aroma components of many fruits.[3] Chiral γ-butenolides are also valuable 'building blocks' for the asymmetric synthesis of substituted bioactive γ-butyrolactones such as **1-3** (**Fig. 1**). For example, (+)-cognac lactone **1**, which is an aroma producing compound, is found in many liquors such as whisky, brandy and wine stored in oak barrels. As a result of their interesting biological activities such as antibiotic and anti-tumor properties, several methods of preparation of optically active γ-butenolides have been reported from both chiral and non-chiral sources.[4]



(+)-cognac lactone (**1**) maritolide (**2**) (-)-nephrosteranic acid (**3**)

Fig. 1: Structures of some naturally-occurring γ-butyrolactones

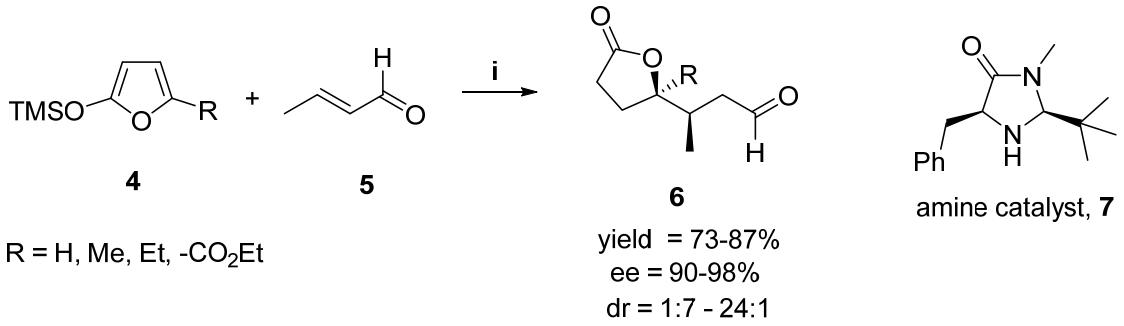
4.1.2 Review of Literature

Literature search revealed that several reports are available for the synthesis of γ-butenolides derivatives; some of which are described below.

MacMillan's approach (2003)[5]

MacMillan *et al*. have reported the asymmetric synthesis of γ-butenolides using

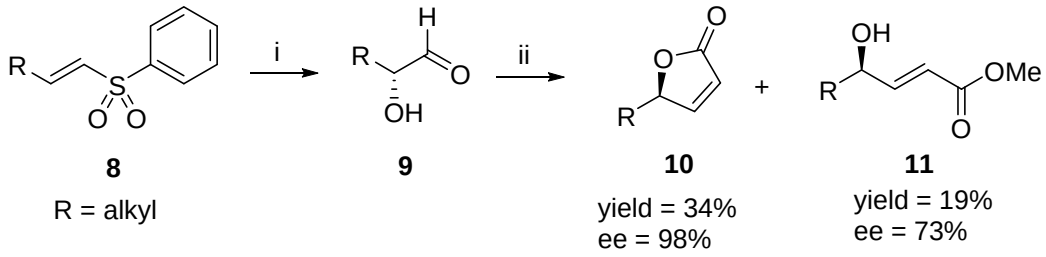
Mukaiyama-Michael reaction as key step. Enantioselective organocatalytic synthesis of γ-butenolide **6** was achieved by the addition of silyloxy furan **4** on crotonaldehyde **5** in presence of chiral imidazolidinone catalyst **7 (Scheme 1)**.



Scheme 1: (i) 20 mol% **11**.DNBA, CH_2Cl_2/H_2O, -70 °C to -20 °C.

Evans's approach (2003)[6]

Evans *et al*. have developed a new method for the synthesis of enantioenriched γ-butenolides from the corresponding vinyl sulfones. The asymmetric dihydroxylation of α,β-unsaturated sulfones **8** under Sharpless conditions affords enantioenriched α-hydroxyaldehydes **9**, which on Still olefination gave the corresponding γ-butenolides **10** along with α,β-unsaturated esters **11 (Scheme 2)**.

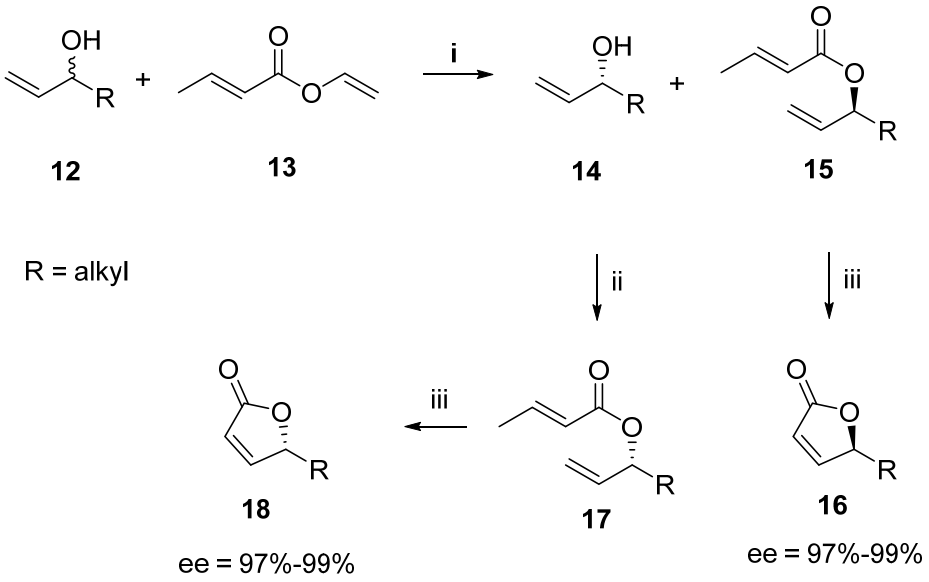


Scheme 2: (i) AD-mix-β, *t*-BuOH/H_2O (1:1), 15 °C, 24 h; (ii) NaH, THF, $(F_3CH_2CO)_2POCH_2CO_2Me$, -78 °C to 25 °C, 24 h.

Fujii's approach (2006)[7]

Fujii *et al.* have described a useful chemoenzymatic synthesis of chiral γ-butenolides. 1-Alkylallyl alcohol **12** was subjected to enantioselective esterification in the presence of Novozyme 435 and vinyl crotonate **13** to give crotonic ester **15** in >99% ee. Then

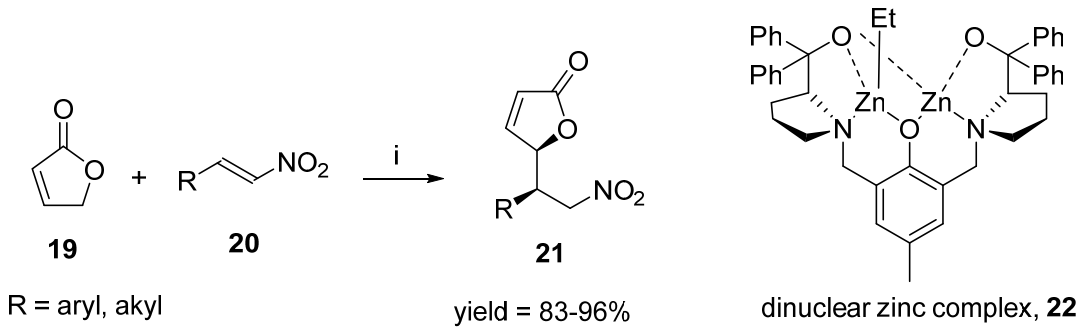
crotonic ester **15** was converted to γ-butenolide **16** by using ring-closing metathesis strategy (RCM) **(Scheme 3)**.



Scheme 3: (i) Novozyme 435, 38 °C, 24 h to 72 h (ii) acyloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 86%; (iii) Grubb's catalyst II, CH_2Cl_2, refluxed, 24 h.

Trost's approach (2009)[8]

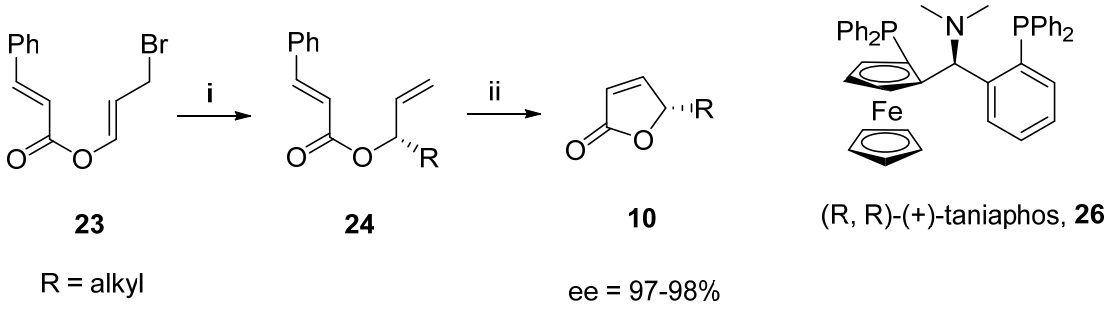
Trost et al. have developed an elegant method for the synthesis of γ-substituted butenolides **21** using Zn catalysed asymmetric Michael addition of 2(5*H*)-furanone **19** to nitroalkenes **20**. Reaction with ee upto 96% and diastereomeric ratio up to 20:1 (**Scheme 4**).



Scheme 4: (i) **22** (10 mol%), 4 A° MS, THF, 25 °C.

Feringa's approach (2011)[9]

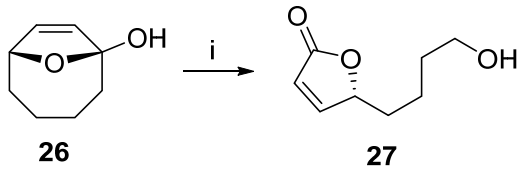
Feringa *et al.* have reported asymmetric synthesis of γ-butenolides **10** from cinnamyl ester **23** using Cu-catalyzed *hetero*-allylic asymmetric alkylation (*h*-AAA), which gave compound **24** bearing two olefinic moieties. The olefinic substrates **24** was directly converted to γ-butenolides **10** *via* ring closing metathesis (RCM) strategy **(Scheme 5)**.



Scheme 5: (i) **26** (3.6 mol%), $CuBr.SMe_2$ (3 mol%), RMgBr, CH_2Cl_2, -78 ^oC; (ii) Hoveyda Grubb's II (3 mol%), CH_2Cl_2, 40 ^oC, 82-83%.

Iwabuchi's approach (2013)[10a]

Iwabuchi *et al*. have developed a single-step method for the synthesis of 5-(4-hydroxybutyl)-2(5*H*)furanone **27** from 9-oxabicyclo[4.2.1]non-7-en-1-ol **26** using HTIB [PhI(OH)OTs, Koser's reagent]-mediated oxidative fragmentation reaction **(Scheme 6)**.

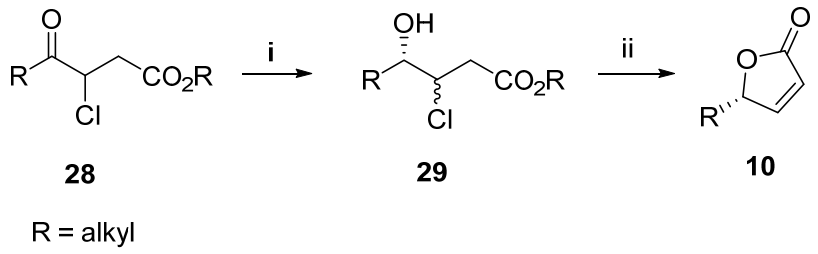


Scheme 6: (i) PhI(OH)OTs, $NaH_2PO_4.2H_2O$, CH_3CN, 50 ^oC, 54%.

Tsuboi's approach (1998)[10b]

Tsuboi *et al*. have reported the synthesis of optically active γ-butenolides **10** starting from 3-chloro-4-oxoalkanoates **28** *via* reduction with Bakers' yeast. Reduction of **28**

with industrial Bakers' yeast was carried out in tap water at 35 °C, giving (4*S*)-3-chloro-4-hydroxyalkanoates **29** in 22-75% yields. Hydrolysis of (4*S*)-**29** with 19% hydrochloric acid and the subsequent dehydrochlorination with an excess amount of triethylamine gave optically pure γ-butenolides **10** in good yields **(Scheme 7)**.

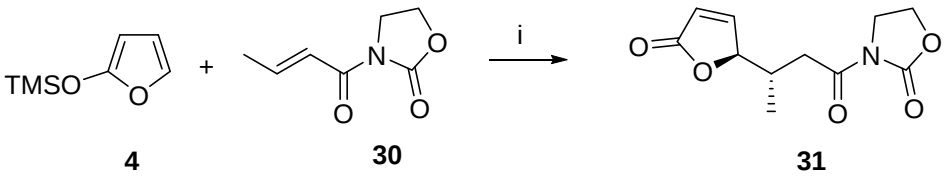


28 **29** **10**

Scheme 7: (i) Baker's yeast; (ii) (a) 19% HCl, 25 °C, 24 h; (b) Et_3N, 25 °C, 48 h.

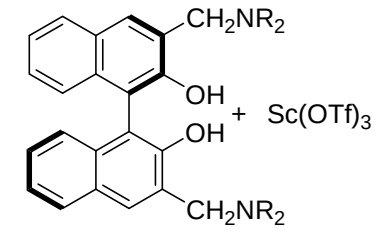
Katsuki's s approach (1998)[10c]

Katsuki *et al*. have described a new method of synthesis of γ-butenolides **31** from readily available 2-trimethylsilyloxyfurans **4** and 3-crotonoyl-1,3-oxazolidin-2-one **31** using an asymmetric Michael reaction as the key with catalysts such as **32** or **33** **(Scheme 8)**.

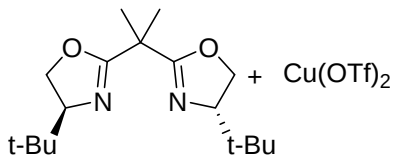


4 **30** **31**

32, 68% ee (*anti:syn* = > 50:1)
33, 95% ee (*anti:syn* = 8.5:1)



scandium–BINOL, **32**



copper–bis(oxazoline) complex, **33**

Scheme 8: (i) catalyst **32** or **33**, MS 4 A°, $(CF_3)_2CHOH$.

4.1.3 Present Work

4.1.3.1 Objective

Literature search reveals that although a number of powerful methods have been reported, several of them employ expensive catalysts, chiral pool resources or involve multisteps and thus there is a genuine need to develop efficient catalytic asymmetric protocols toward construction of γ-butenolides.

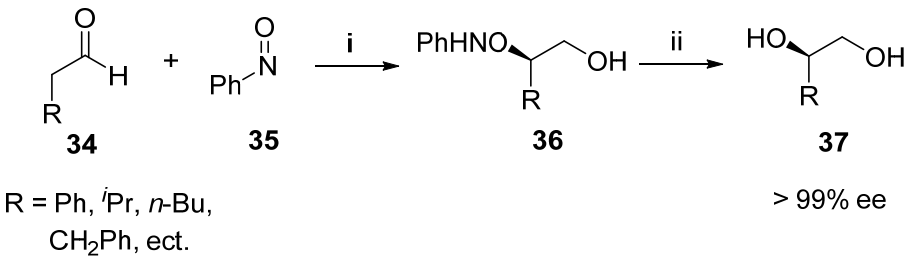
Organocatalysis is a rapidly growing research field in organic synthesis and has the advantage of being highly selective and reducing synthetic manipulations.[11] In particular, proline-catalyzed direct α-functionalization of aldehydes has emerged as a reliable method for the enantioselective synthesis of α-hydroxy or α-amino acid derivatives.[12] Proline-catalyzed α-functionalization and its sequential reactions are arguably one of the most extensively studied and developed asymmetric catalytic reaction.[13,14] In this section, a sequential protocol involving proline-catalyzed α-aminoxylation followed by *cis*-Wittig olefination of aldehydes that provides easy access to chiral γ-butenolides has been described.

Since this section deals with a highly important and attractive asymmetric reaction i.e., proline-catalyzed α-aminoxylation, which introduces stereogenicity into the prochiral molecule, a brief account of the same is described below.

4.1.3.2 Proline-catalyzed α-aminoxylation

Optically active α-hydroxy aldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[15] Sharpless dihydroxylation of enol ethers,[16] manganese-salen epoxidation of enol ethers,[17] and Shi epoxidation of enol ethers.[18] It is only rather

recently that direct catalytic, asymmetric variants have been reported.[19] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde. Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur and phosphorus and does not contain any metals. The advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Asymmetric organocatalysis has begun to catch up with the spectacular advancements of enantioselective transition metal catalysis. In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms has emerged as a practical and versatile organocatalyst.[12] Proline is equally efficient for α-functionalization[12,13] of aldehydes and ketones. When an aldehyde **34** without substitution at α-position was reacted with nitrosobenzene **35** in presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at α-position. The aminoxyl moiety undergoes hydrogenolysis with either Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **37** in very high enantioselectivities (**Scheme 9**).



Scheme 9: (i) (a) L-proline (20 mol%), DMSO, 25 °C; (b) $NaBH_4$, MeOH, 0 °C to 25 °C, 1h; (ii) Pd/C, H_2, MeOH, 24 h or $CuSO_4$ (30 mol%), MeOH, 25 °C, 24 h.

The mechanism of the α-aminoxylation reaction is shown in **Fig. 2**. The observed enantioselectivitiy of the catalytic α -aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state **39** wherein the *Si* face of an *E*-enamine **41** formed from the aldehyde **34** and L-proline **38** approaches the less

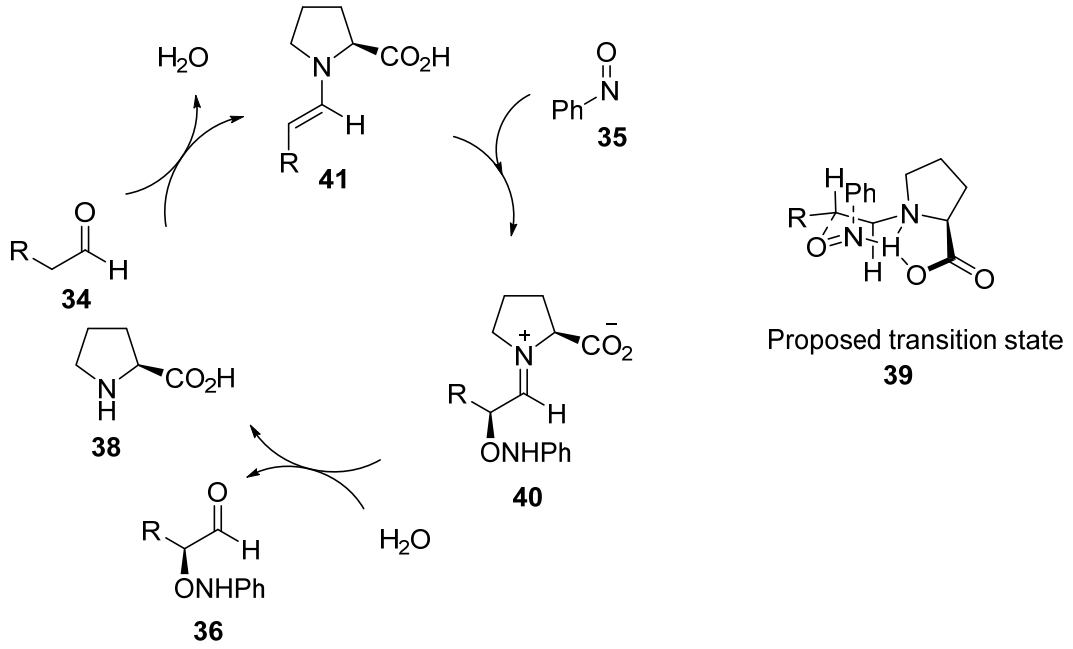
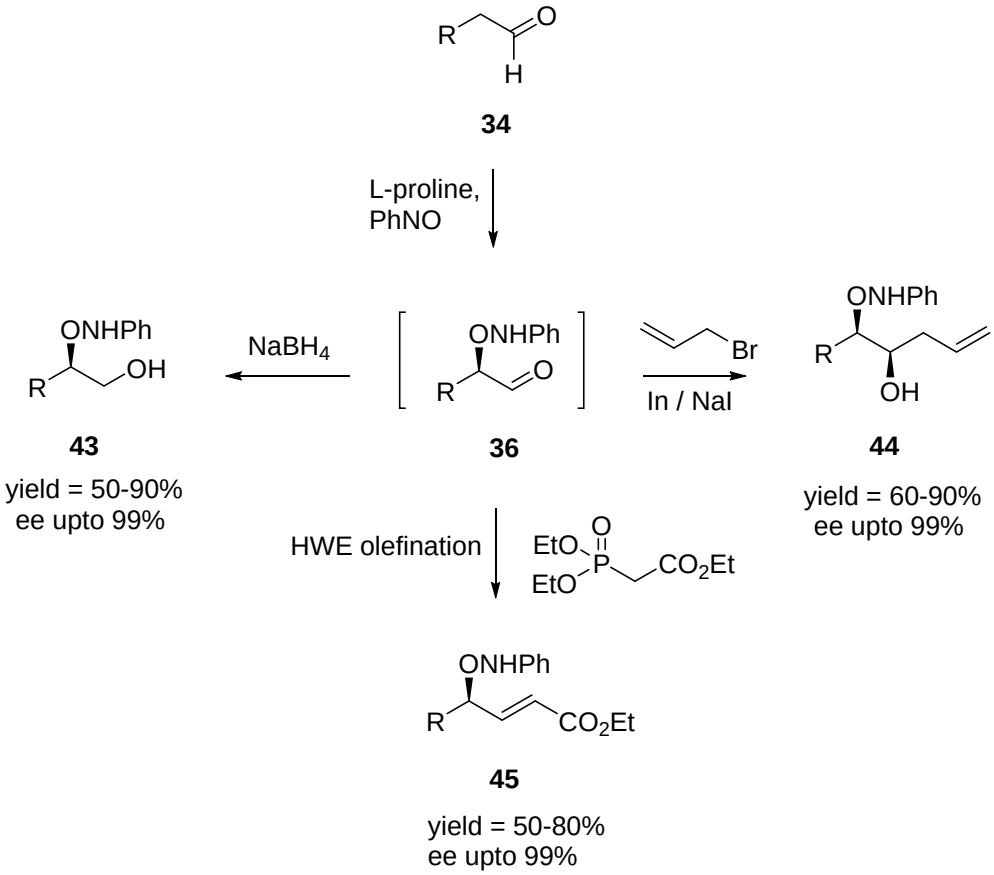


Fig. 2: Proposed mechanism of the α-aminoxylation reaction

hindered oxygen atom of nitrosobenzene **35** to provide a chiral α -aminoxyaldehyde **36**. Since proline is commercially available in both enantiopure forms, a one-pot sequential catalytic α -aminoxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

In proline-catalyzed direct α-aminoxylation of aldehydes, the reactive intermediate **36**, generated *in situ* can be transformed into several functionalized organic derivatives: for instance it can be reduced to 1,2-aminoxy alcohol **43**,[12c] it can undergo

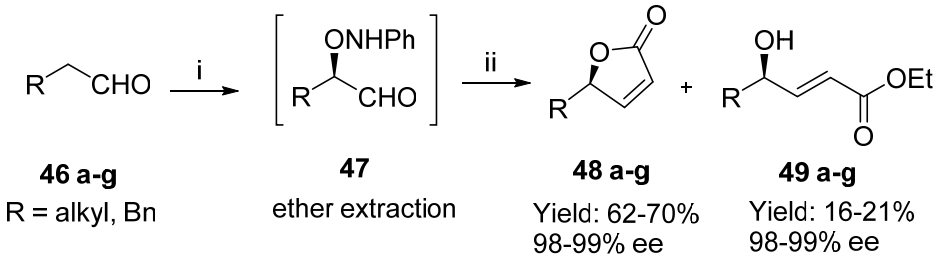
diastereoselective In-mediated allylation to give diol **44**,[14h] or can be converted to γ-aminoxy α,β-unsaturated esters and ketones **45** (**Scheme 10**).[12b] In this connection, it is of interest to design experiments in trapping the intermediate **36** with other reagents.



Scheme 10: Sequential trapping of α-aminoxy aldehyde **36**

4.1.3.3 Results and Discussion

In continuation of our work on the utilization and application of enantiomerically-enriched α-functionalized aldehydes,[20] a new procedure for obtaining highly enantioselective γ-butenolides **48** has been developed using L-proline-catalyzed tandem α-aminoxylation-Still olefination of aldehydes **46 (Scheme 11).**



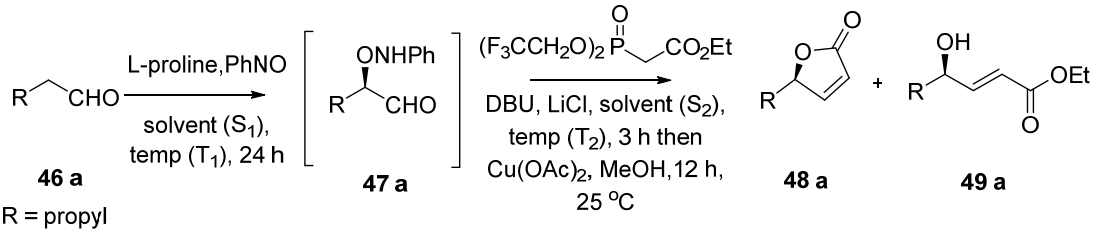
Scheme 11: Reaction conditions: (i) L-Proline (10 mol%), PhNO (1equiv), DMSO, 25 ^{o}C, 15 min; (ii) $(F_3CH_2CO)_2POCH_2CO_2Et$ (1.5 equiv) , DBU (2 equiv), LiCl (2 equiv), THF, -20 ^{o}C, 3 h then Cu(OAc)2 (30 mol%), MeOH,12 h, 25 ^{o}C.

In a preliminary study, the α-aminoxylation reaction between *n*-valeraldehyde **46a** with nitrosobenzene as oxygen source was carried out in the presence of L-proline (20 mol%) in CH_3CN at -20 ^{o}C to obtain α-aminoxy aldehydes **47** *in situ*. Since these aminoxy aldehydes are prone to racemization under basic conditions, we performed several experiments to identify the most effective and suitable reaction conditions such as variation of solvents, bases, temperature, etc for the subsequent sequential *cis*-Wittig reaction (Table 1). First, *in situ* olefination of **47** was carried out by the addition of *cis*-selective ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (Still reagent)[21] (1.5 equiv) and DBU (2 equiv) in presence of LiCl (Masamune-Roush protocol)[22] in CH_3CN at -20 ^{o}C. After Wittig olefination, its treatment with $Cu(OAc)_2$ at 25 ^{o}C in excess methanol resulted in deprotection of anilinoxy group[23] giving a mixture of γ-butenolide **48a** and γ-hydroxy α, β-unsaturated ester **49a** in the ratio 3:2 respectively, with an overall yield of 85%. When $CHCl_3$ was employed as solvent for both the reactions, a reduced yield (60%) was obtained with an improved product selectivity 2:1. Further, when solvent was changed to THF, a drastic reduction in yield (20%) has occurred due to poor solubility of L-proline in THF, although the selectivity in favor of γ-butenolide was increased to 3:1. Finally, the best result for **48a** was obtained when aminoxylation was carried out in DMSO and Wittig reaction

in THF, a higher yield (84%) could be realized with the selectivity ratio of **48a : 49a** being 3:1. The results of the optimization study are summarized in **Table 1**.

Reactions carried out at low temperatures (-20 °, -40 ° or -78 °C) did not significantly improve either the yield or product selectivity. However, for all the cases studied, the enantioselectivity of the reaction consistently remained in 98-99% ee range. Several other bases (NaH, NaOH and Cs_2CO_3) were indeed examined to improve the product selectivity ratio; but only complex mixtures of products were obtained in all the cases studied.

Table 1: L-Proline-catalyzed sequential α-aminoxylation and *cis*-olefination of *n*-valeraldehyde[a]

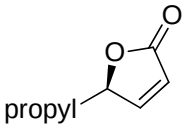
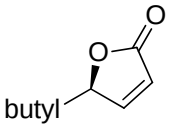
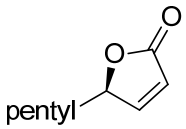
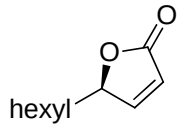
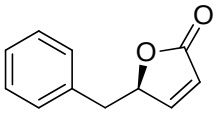
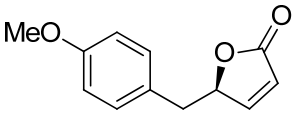
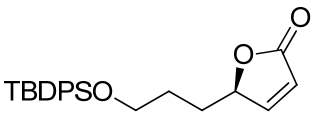


entry	solvent		temp (°C)		yield (%)[d]	ratio of (48a : 49a)	% ee[e]	
	S_1[b]	S_2[c]	T_1[b]	T_2[c]			48a	49a
1.	CH_3CN	CH_3CN	-20	-20 or -78	85	3 : 2	99	99
2.	$CHCl_3$	$CHCl_3$	-20	-20	60	2 : 1	98	98
3.	THF	THF	-20	-20	20	3 : 1	99	99
4.	DMSO	THF	25	-20 or -78	84	3 : 1	99	99

Reaction conditions: [a] aldehyde (1 equiv), PhNO (1 equiv), L-proline (10 mol %), 15 min. -24 h, ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (1.5 equiv), DBU (2 equiv), LiCl (2 equiv) 3 h, followed by $Cu(OAc)_2$ (30 mol%) , MeOH 12 h. [b] S_1 & T_1 refer to solvent and temperature for aminoxylation reaction. [c] S_2 &T_2 refer to solvent and temperature for Wittig reaction. [d] combined yield after column chromatographic purification.[e] %ee determined from chiral HPLC analysis.

Next, we have examined the scope of the reaction by subjecting several aliphatic and aromatic aldehydes under the optimized reaction conditions and the results are presented in **Table 2**.

Table 2: L-Proline-catalyzed asymmetric sequential α- aminoxylation and *cis*-olefination of aldehydes [a]

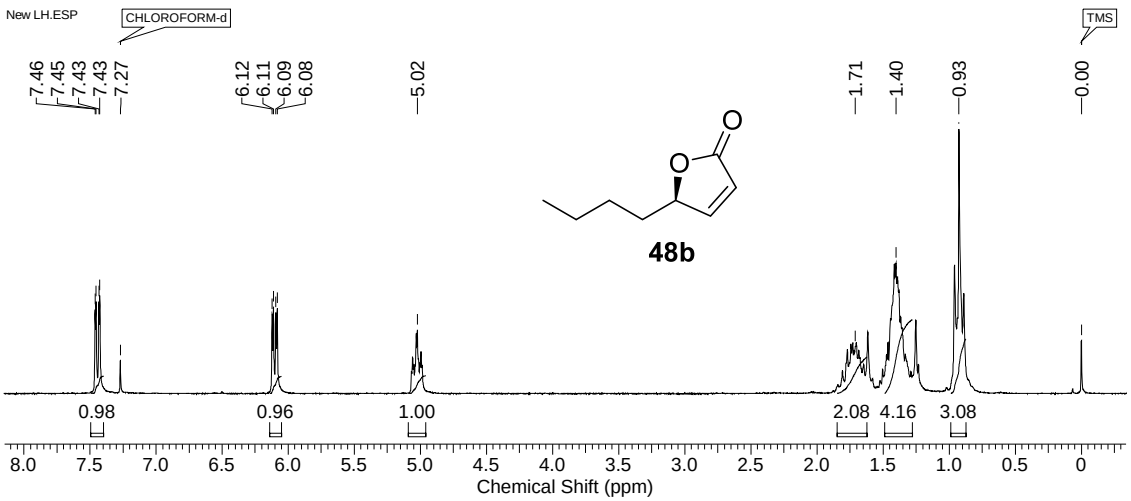
entry	substrates **46**	products **48**	ratio of **48:49 (a-g)**	**48 (a-g)** % yield [b]	% ee [c]
1	pentanal	 **48a**	3:1	63	99
2	hexanal	 **48b**	3:1	66	99
3	heptanal	 **48c**	7:2	68	99
4	octanal	 **48d**	7:2	65	98
5	dihydrocinnaldehyde	 **48e**	4:1	64	99
6	4-methoxydihydro-cinnaldehyde	 **48f**	4:1	70	98
7.	5-((*tert*-butyldipheny-silyl)oxy)pentanal	 **48g**	4:1	62	99

Reaction conditions: [a] aldehyde (1 equiv), PhNO (1 equiv), L-proline (10 mol %), ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (1.5 equiv), DBU (2 equiv), LiCl (2 equiv), $Cu(OAc)_2$ (30 mol%) were used. [b] yield of isolated product after column chromatography. [c] %ee was calculated by chiral HPLC analysis.

In the case of aliphatic aldehydes (entries 1-4), the ratio of **48 : 49** ranged from 3-3.5 : 1, while for aromatic and functionalized aldehydes, it was found to be 4:1. The excellent enantioselectivity (98-99% ee) exhibited by both the products is quite remarkable, although the isolated yields of γ-butenolides **48** were only moderate to good (62-70%). The absolute configuration of the newly generated hydroxyl centre was assigned based on the basis of the previously established configuration of α-hydroxy aldehydes and γ-butyrolactones.[12, 24, 27]

The formation of γ-butenolides **48** and γ-hydroxy α,β-unsaturated esters **49** was established unambiguously from their ^{1}H & ^{13}C NMR and IR spectral data. Their optical purity was established from chiral HPLC analysis.

Example 1: The formation of γ-butenolide **48b** was confirmed from its IR spectrum, which showed a strong absorption band at υ_{max} 1755 cm^{-1} typically for lactone carbonyl functionality. The ^{1}H NMR spectrum of **48b** showed the appearance of a multiplet at δ 5.02 (1H) corresponding to methine proton (-C**H**-O). This was further confirmed by other doublets at δ 6.10 (dd, *J* = 5.6, 2.0 Hz, 1H) and 7.42 (dd, *J* = 5.6, 1.3 Hz, 1H) due to *cis*-olefinic protons. Its ^{13}C NMR spectrum showed a carbonyl signal peak at δ 172.69 for carbonyl carbon of lactone function (**Fig. 3**).



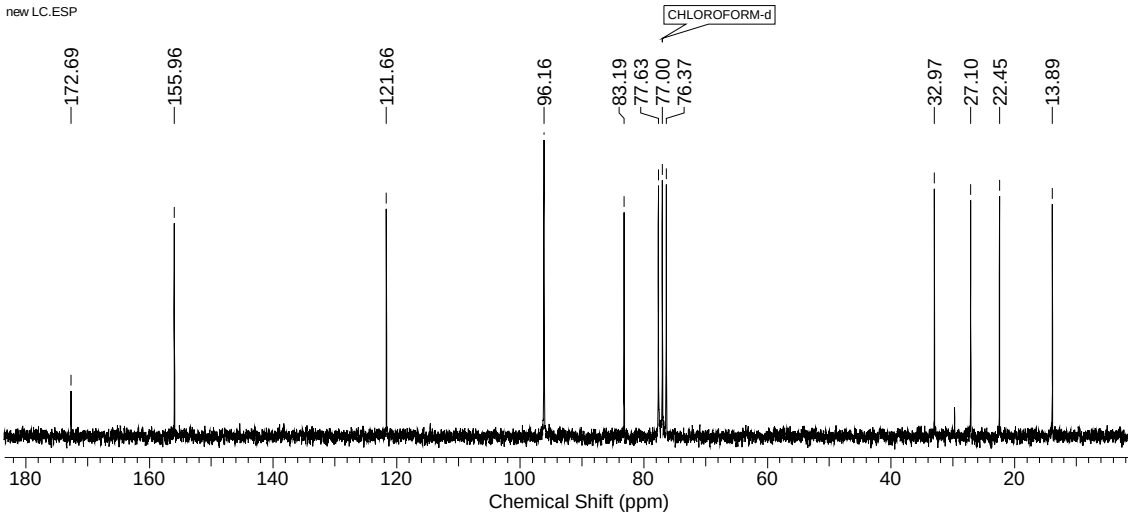


Fig. 3: ^{1}H and ^{13}C NMR spectra of **48b**

Its enantiomeric excess (>99% ee) was determined from chiral HPLC analysis (ChiracelOD-H). The chiral HPLC chromatogram is shown in **Fig. 4**.

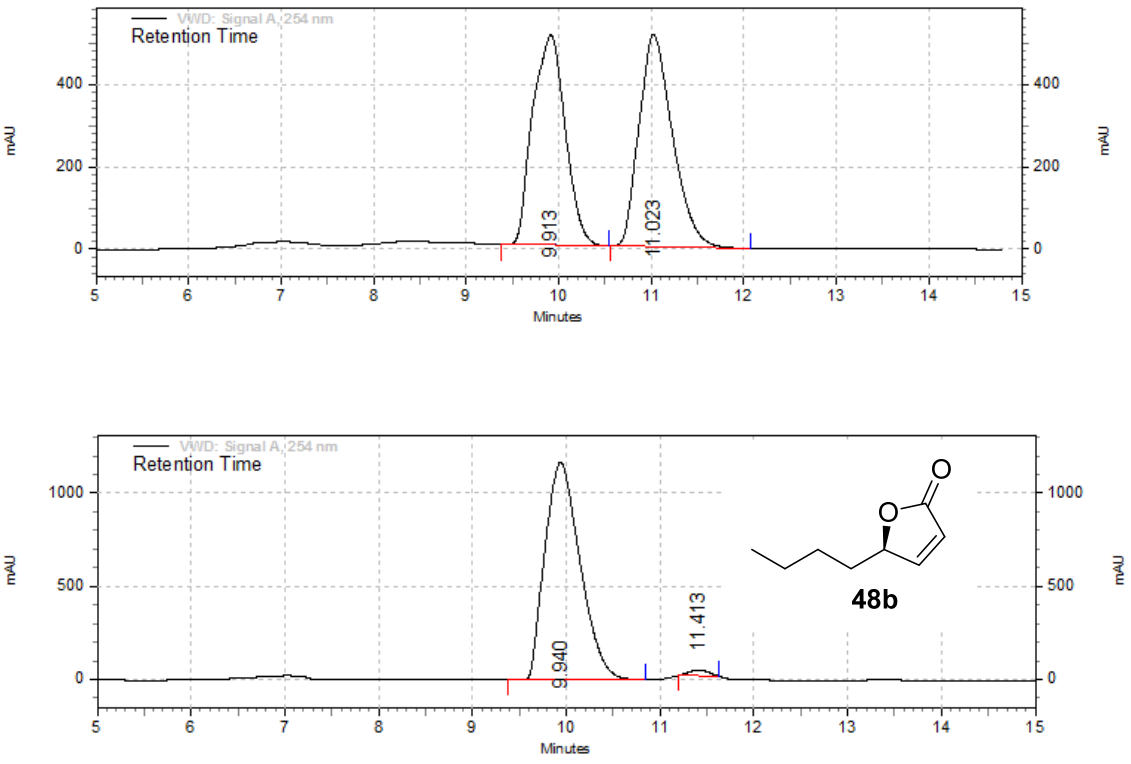


Figure. 4: HPLC chromatogram of **48b** [Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min, 210 nm; retention time 09.94 (99.47%) and 11.41 (0.53%)]

Example 2: Similarly the formation of γ-hydroxy α, β-unsaturated ester **49b** was confirmed from its IR spectrum, which showed a strong absorption band at υ_{max} 1717 cm^{-1} typically for ester carbonyl functionality. The ^{1}H NMR spectrum of **49b** showed the appearance of a multiplet at δ 4.34 (m, 1H), corresponding to methine proton (-**CH**-O). This was further confirmed by signals at δ 6.02 (dd, *J* = 15.6, 1.6 Hz, 1H) and δ 6.93 (dd, *J* = 15.6, 4.9 Hz, 1H) due to *trans*-olefinic protons. Its ^{13}C NMR spectrum displayed a typical carbon signal at δ 166.5 for carbonyl carbon of ester group (**Fig. 5**).

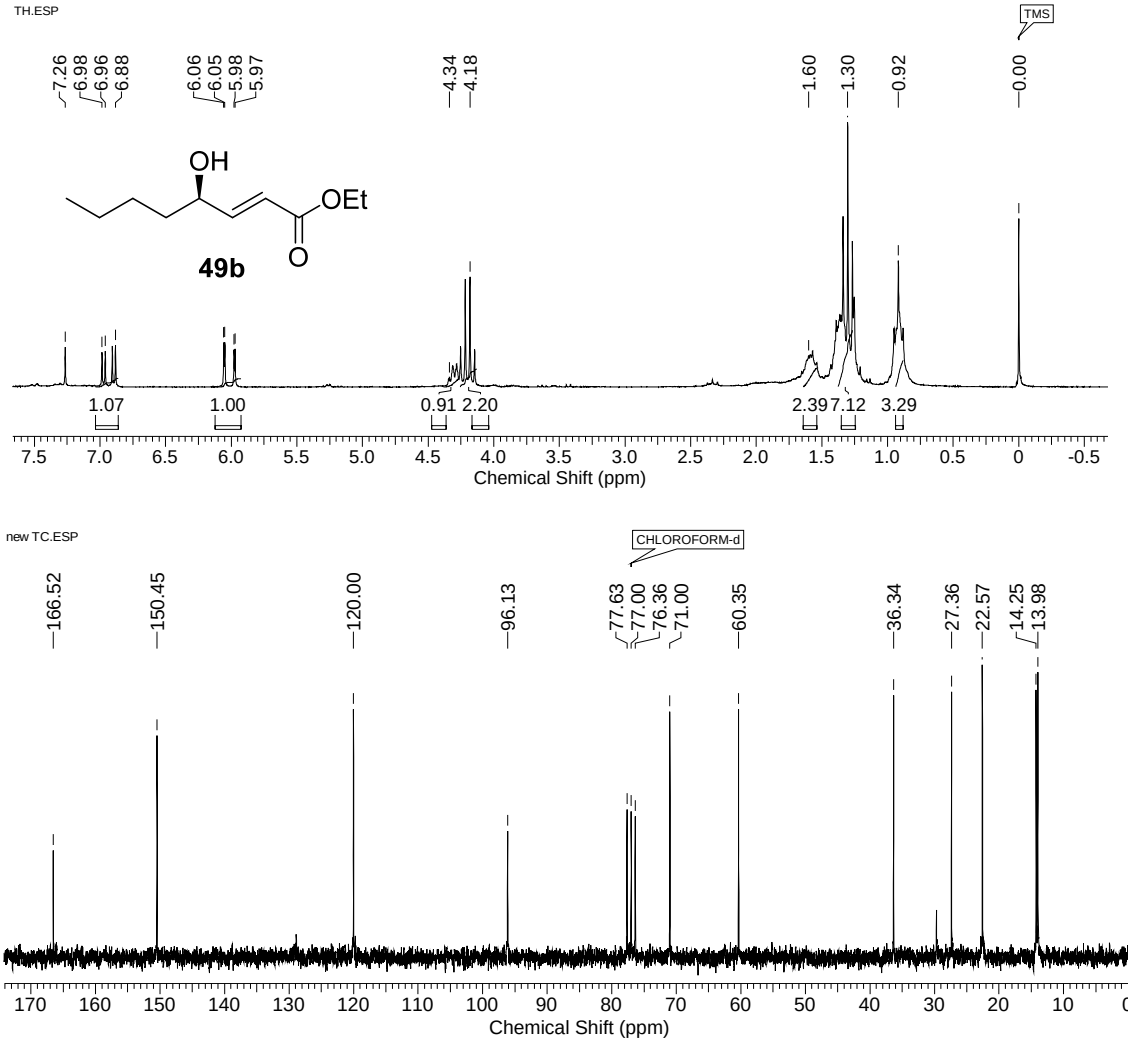
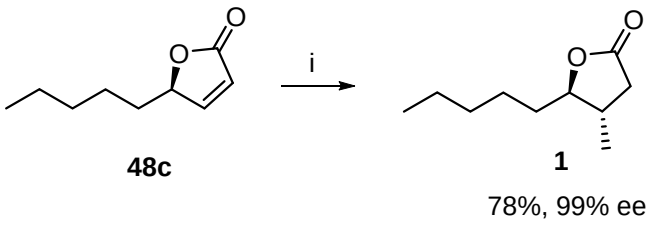


Fig. 5: ^{1}H and ^{13}C NMR spectra of **49b**

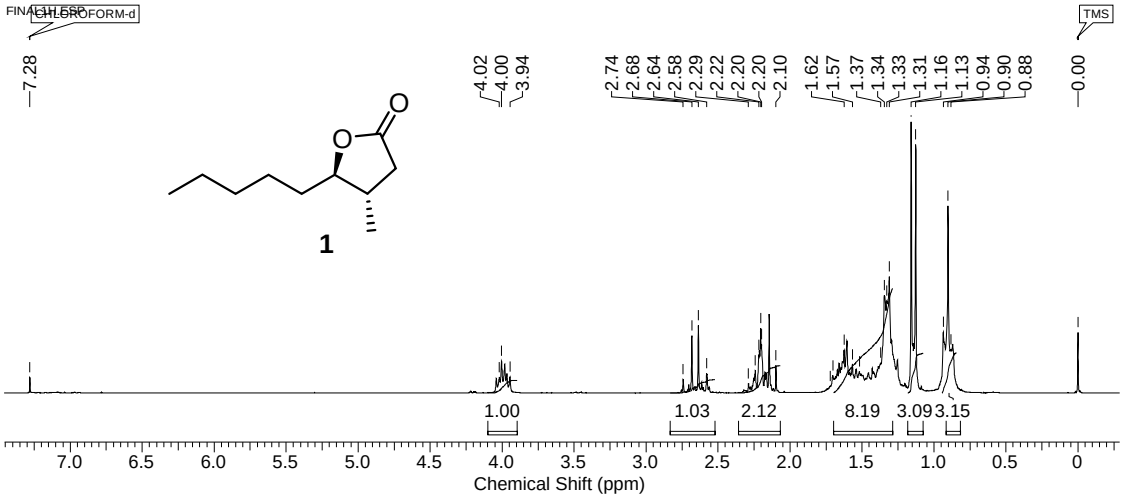
4.1.3.4 Application: asymmetric synthesis of *trans*-(+)-cognac lactone

To demonstrate the utility of this methodology, a short asymmetric synthesis of cognac lactone **1** has been achieved (**Scheme 12**). The synthesis involved a stereoselective conjugate addition of Me_2CuLi onto γ-butenolide **48c** in ether that afforded (+)-*trans*-cognac lactone **1** in 78% yield. The spectral data and the specific rotation of **1** were in excellent agreement with those previously reported.[9]



Scheme 12: Reaction conditions: (i) CuI (1.6 equiv), MeLi (3.3 equiv), ether,-78 to -20°C

The ^{1}H NMR spectrum of **1** showed the appearance of a doublet at δ 1.13 (d, J = 6.3 Hz, 2H) for methyl protons (CH-**CH_3**) and a multiplet at δ 4.0 (1H) corresponding to methine proton (-**CH**-O). This was further confirmed by its ^{13}C NMR spectrum, which showed a typical carbon signal at δ 176.1 due to carbonyl carbon of lactone group (**Fig. 6**). The IR spectrum of **1** showed a strong absorption band at υ_{max} 1780 cm^{-1} typically for lactone carbonyl functionality.



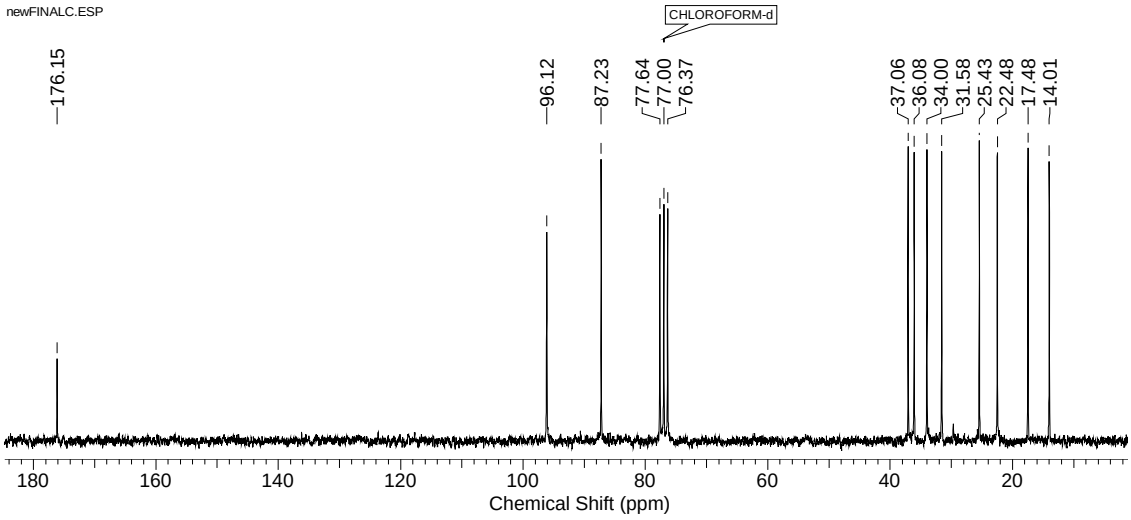


Fig. 6: ^{1}H and ^{13}C NMR spectra of **1**

4.1.4 Conclusion

In summary, this section presents a simple procedure of sequential α-hydroxylation-*cis*-Wittig olefination of aldehydes that leads to enantioselective synthesis of γ-butenolides **48** up to 99% ee as the major product along with minor amounts of γ-hydroxy α,β-unsaturated esters **49**. The potential of this reaction has been demonstrated by its easy and shortest synthesis of cognac lactone **1** in high enantiomeric excess.

4.1.5 Experimental Section

General procedure for the synthesis of γ-butenolide

To a solution of aldehyde **46** (2.0 mmol) and nitrosobenzene (214 mg, 2.0 mmol) in dry DMSO (2 mL), L-proline (23 mg, 10 mol%) was added. The mixture was stirred vigorously at 25 ^{o}C for about 10 to 20 min. The progress of the reaction was monitored by its color change from green to orange. After completion of reaction, ice (5 g) was added, followed by water (10 mL). The aqueous mixture was extracted with ether (3 X 15 mL). The combined organic phase was washed with water (2 X 20 mL), dried over anhyd. Na_2SO_4, and concentrated at under reduced pressure. The resulting

yellow oil (α-aminoxylated aldehyde, **47**) was dried under vacuum and dissolved in THF which is directly used for next sequential olefination reaction as follows.

Anhydrous lithium chloride (168 mg, 4 mmol) was suspended, under nitrogen atmosphere, in dry THF (5 mL) and ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (0.7 mL, 3 mmol) was added. The entire mixture was stirred for 15 min at 25 ^{o}C and then cooled to 0 ^{o}C. DBU (0.6 mL, 4 mmol) was added to it and the mixture was stirred for another 30 min. To this mixture, a solution of previously made α-aminoxylated aldehyde **47** (5 mL in THF) was added dropwise through a septum at -20 ^{o}C. After 3 h, the olefination reaction was complete (TLC). To this, $Cu(OAc)_2$ (120 mg, 30 mol%) and excess of methanol were added and the mixture stirred at room temperature for 12 h. After completion (TCL), solvents were concentrated under reduced pressure. Then, the mixture was diluted with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 X 30 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography (packed with silica gel 60-120 mesh) using dichloromethane and petroleum ether (7:3) as eluents to afford the products **48** and **49** in pure form.

(*R*)-5-Propylfuran-2(5*H*)-one (48a)

Yield: 63%; Colorless oil; $[\alpha]_D^{25}$ -102.6 (*c* 1, $CHCl_3$) {lit.[7] $[\alpha]_D^{25}$ +110 for its antipode (*c* 1.16, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1164, 1265, 1465, 1603, 1755, 2926; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.40-1.81 (m, 4H), 5.04 (m, 1H), 6.10 (dd, *J* = 5.8, 2.0 Hz, 1H), 7.44 (dd, *J* = 5.8, 1.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 18.4, 35.2, 83.1, 121.5, 156.1, 172.9; **Analysis**: $C_7H_{10}O_2$ required C, 66.65; H, 7.99; found C, 66.50; H, 7.81%; **Optical purity**: 99% ee determined from

HPLC analysis (Chiral OJ-H column, Hex/*i*-PrOH 95:5, 0.5 mL/min, 210 nm). Retention time: t_{minor} = 25.29 and t_{major} = 26.83 min.

(*R*)-5-Butylfuran-2(5*H*)-one (48b)

Yield: 66%; Colorless oil; $[\alpha]_D^{25}$ -101.2 (*c* 1, $CHCl_3$) {lit.[9] $[\alpha]_D^{25}$ +103.5 for its antipode (*c* 0.7, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1162, 1463, 1495, 1603, 1755, 2861, 2929; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.8 Hz, 3H), 1.29-1. 52 (m, 4H), 1.65-1.84 (m, 2H), 5.02 (m, 1H), 6.10 (dd, *J* = 5.6, 2.0 Hz, 1H), 7.42 (dd, *J* = 5.6, 1.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 22.4, 27.0, 32.9, 83.1, 121.6, 155.9, 172.6; **Analysis**: $C_8H_{12}O_2$ required C, 68.54; H, 8.63; found C, 68.42; H, 8.70%; **Optical purity**: 99% ee determined from HPLC analysis (Chiral OD-H column, Hex/*i*-PrOH 90:10, 0.5 mL/min, 210 nm). Retention time: t_{minor} = 9.94 and t_{major} = 11.41 min.

(*R*)-5-Pentylfuran-2(5*H*)-one (48c)

Yield: 68%; Colorless oil; $[\alpha]_D^{25}$ -96.8 (*c* 1, $CHCl_3$) {lit.[9] $[\alpha]_D^{25}$ +97 for its antipode (*c* 0.6, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1162, 1602, 1752, 2861, 2929; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.5 Hz, 3H), 1.21-1. 48(m, 6H), 1.61-1.79 (m, 2H), 5.03(m, 1H), 6.10 (dd, *J* = 5.6, 2.0 Hz, 1H), 7.42 (dd, *J* = 5.6, 1.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 22.4, 24.7, 31.5, 33.2, 83.2, 121.6, 155.9, 172.7; **Analysis**: $C_9H_{14}O_2$ required C, 70.10; H, 9.15; found C, 70.22; H, 9.17%; **Optical purity**: 99%ee determined from HPLC analysis (Chiral OJ-H column, Hex/*i*-PrOH 95:5, 0.5 mL/min, 210 nm). Retention time: t_{minor} = 19.50 and t_{major} = 20.35 min.

(*R*)-5-Hexylfuran-2(5*H*)-one (48d)

Yield: 65%; Colorless oil; $[\alpha]_D^{25}$ -91.8 (*c* 1, $CHCl_3$) {lit.[7] $[\alpha]_D^{25}$ +89.4 for its antipode (*c* 1.01, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1163, 1464, 1603, 1756, 2854, 2925; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.25-1.45(m, 8H), 1.61-1.83 (m,

2H), 5.02 (m, 1H), 6.10 (dd, *J* = 5.6, 1.8 Hz, 1H), 7.43 (dd, *J* = 5.6, 1.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.5, 24.9, 29.0, 31.5, 33.2, 83.2, 121.6, 155.9, 172.7; **Analysis**: $C_{10}H_{16}O_2$ required C, 71.39; H, 9.59; found C, 71.22; H, 9.68%; **Optical purity**: 98% ee determined from HPLC analysis (Chiral OJ-H column, Hex/*i*-PrOH 95:5, 0.5 mL/min, 210 nm). Retention time: t_{minor} = 18.60 and t_{major} = 19.44 min.

(*R*)-5-Benzylfuran-2(5*H*)-one (48e)

Yield: 64%; yellow oil; **$[\alpha]_D^{25}$** -112.0 (*c* 1, $CHCl_3$) {lit.[25] $[\alpha]_D^{25}$ +117 for its antipode (*c* 2.19, 1,4-dioxane)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1496, 1600, 1755, 2928; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.89-2.99 (dd, *J* = 13.7, 7.2 Hz, 1H), 3.12-3.22 (dd, *J* = 13.7, 6.3 Hz, 1H), 5.22 (m, 1H), 6.08 (dd, *J* = 5.6, 1.9 Hz, 1H), 7.17-7.33 (m, 5H), 7.39 (dd, *J* = 5.68, 1.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.7, 83.2, 122.1, 127.3, 128.7, 129.3, 134.7, 155.3, 172.4; **Analysis:** $C_{11}H_{10}O_2$ required C, 75.84; H, 5.79; found C, 76.60; H, 5.88%; **Optical purity:** 99% ee determined from HPLC analysis ((*R,R*)-whelk column, Hex/EtOH 90:10, 0.5 mL/min, 210 nm). Retention time: t_{major} = 16.45 and t_{minor} = 17.40 min.

(*R*)-5-(4-Methoxybenzyl)furan-2(5*H*)-one (48f)

Yield: 70%; colorless solid, **mp** 62 °C; **$[\alpha]_D^{25}$** -159.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1514, 1613, 1755, 2924; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.84-2.95 (dd, *J* = 13.9, 7.0 Hz, 1H), 3.06-3.16 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.79 (s, 3H), 5.17 (m, 1H), 6.06 (dd, *J* = 5.8, 2.0 Hz, 1H), 6.81(d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.37 (dd, *J* = 5.6, 1.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.7, 55.1, 83.5, 114.1, 122.1, 126.6, 130.4, 155.4, 158.8, 172.5; **Analysis**: $C_{12}H_{12}O_3$ required C, 70.57; H, 5.92; found C, 70.50; H, 5.80%; **Optical purity**: 98% ee determined from HPLC analysis

((*R,R*)-whelk column, Hex/*i*-PrOH 90:10, 0.5 mL/min, 254 nm). Retention time: t_{major} = 35.35 and t_{minor} = 46.28 min

(*R*)-5-(3-((*tert*-Butyldiphenylsilyl)oxy)propyl)furan-2(5*H*)-one (48g)

Yield: 62%; colorless oil; **$[\alpha]_D^{25}$** -38.9 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1110, 1427, 1755, 2856, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.68-1.80 (m, 3H), 1.90-1.96 (m, 1H), 3.71 (m, 2H), 5.05 (m, 1H), 6.11 (dd, *J* = 5.7, 1.8 Hz, 1H),7.39 (m, 7H), 7.64 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.2, 26.9, 27.8, 29.9, 63.0, 83.0, 121.7, 127.7, 129.7, 133.6, 135.5, 156.0, 172.8; **Analysis:** $C_{23}H_{28}O_3Si$ required C, 72.59; H, 7.42; found C, 72.63; H, 7.38%; **Optical purity:** 99% ee determined from HPLC analysis (Chiral OJ-H column, Hex/ *i*-PrOH 95:5, 0.5 mL/min, 210 nm). Retention time: t_{minor} = 45.30 and t_{major} = 46.86 min.

(*R*)-(*E*)-Ethyl 4-hydroxyhept-2-enoate (49a)

Yield: 21%; colorless oil; **$[\alpha]_D^{25}$** -21.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1277, 1659, 1714, 2931, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 6.9 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.35-1.65 (m, 4H), 1.79 (br s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.31 (m, 1H), 6.01 (dd, *J* = 15.6, 1.6 Hz, 1H), 6.93 (dd, *J* = 15.8, 5.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 14.2, 18.4, 38.7, 60.3, 70.8, 120.0, 150.3, 166.4 ; **Analysis:** $C_9H_{16}O_3$ required C, 62.77; H, 9.36; Found: C, 62.79; H, 9.50%; **Optical purity:** 99% ee determined from HPLC analysis ((*R,R*)-whelk column, Hex/ EtOH 95:5, 0.5 mL/min, 210 nm). Retention time: t_{minor}= 10.56 and t_{major} = 11.07 min

(*R*)-(*E*)-Ethyl 4-hydroxyoct-2-enoate (49b)

Yield: 20%; colorless oil; **$[\alpha]_D^{25}$** -19.5 (*c* 1, $CHCl_3$) {lit.[26] $[\alpha]_D^{24}$ -19.3 (*c* 0.36, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1267, 1372, 1658, 1719, 2960, 3456; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.37 (m, 4H), 1.60 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.34 (m, 1H), 6.01 (dd, *J* = 15.6, 1.6 Hz, 1H), 6.94

(dd, *J* = 15.6, 4.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 14.2, 22.5, 27.3, 36.3, 60.3, 70.9, 120.0, 150.4, 166.5; **Analysis**: $C_{10}H_{18}O_3$ required C, 64.49; H, 9.74; Found: C, 64.32; H, 9.88%.

(*R*)-(*E*)-Ethyl 4-hydroxynon-2-enoate (49c)

Yield: 19%; colorless oil; **$[\alpha]_D^{25}$** -21.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1248, 1513, 1656, 1717, 2926, 3421; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.5 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.35 (m, 6H), 1.60 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.30 (m, 1H), 6.02 (dd, *J* = 15.6, 1.6 Hz, 1H), 6.93 (dd, *J* = 15.6, 4.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 14.2, 22.5, 24.9, 31.7, 36.6, 60.3, 71.0, 120.0, 150.3, 166.4; **Analysis**: $C_{11}H_{20}O_3$ required C, 65.97; H, 10.07; Found: C, 65.80; H, 10.12%.

(*R*)-(*E*)-Ethyl 4-hydroxydec-2-enoate (49d)

Yield: 19%; colorless oil; **$[\alpha]_D^{25}$** -21.9 (*c* 1, $CHCl_3$) {lit.[6] $[\alpha]_D^{20}$ -22.4 (*c* 1.03, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1177, 1658, 1722, 2929, 3439; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.21-1.41 (m, 11H), 1.56 (m, 2H), 1.99 (br s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.30 (m, 1H), 6.01 (dd, *J* = 15.6, 1.5 Hz, 1H), 6.93 (dd, *J* = 15.6, 4.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 14.2, 22.6, 25.2, 29.1, 31.7, 36.6, 60.3, 71.0, 120.0, 150.3, 166.4; **Analysis**: $C_{12}H_{22}O_3$ required C, 67.26; H, 10.35; Found: C, 67.18; H, 10.46%.

(*R*)-(*E*)-Ethyl 4-hydroxy-5-phenylpent-2-enoate (49e)

Yield: 17%; colorless oil; **$[\alpha]_D^{25}$** +6.0 (*c* 1, $CHCl_3$) {lit.[26] $[\alpha]_D^{22}$ +6.5 (*c* 0.15, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1454, 1656, 1717, 2925, 3447; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.67 (br s, 1H), 2.76 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.95 (dd, *J* = 13.6, 4.8Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.52 (m, 1H), 6.05 (dd, *J* = 15.5, 1.7 Hz, 1H), 7.00 (dd, *J* = 15.5, 4.4 Hz, 1H), 7.15-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 43.2, 60.4, 71.7, 120.5, 126.8, 128.6, 129.5, 137.0, 149.2, 166.4; **Analysis**:

$C_{13}H_{16}O_3$ required C, 70.89; H, 7.32; Found: C, 70.92; H, 7.28%.

(*R*)-(*E*)-Ethyl 4-hydroxy-5-(4-methoxyphenyl)pent-2-enoate (49f)

Yield: 17%; yellow oil; **$[\alpha]_D^{25}$** +10.2 (*c* 1, $CHCl_3$) {lit.[27] $[\alpha]_D^{25}$ -10.27 for its antipode (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1513, 1659, 1714, 2928, 3462; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.30 (t, *J* = 7.2 Hz, 3H), 1.63 (br s, 1H), 2.72 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.90 (dd, *J* = 13.7, 4.9 Hz, 1H), 3.79 (s, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.46 (m, 1H), 6.03 (dd, *J* = 15.6, 1.7 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.99 (dd, *J* = 15.5, 4.4 Hz, 1H), 7.12 (d, *J* = 8.7, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 42.3, 55.1, 60.3, 71.8, 114.1, 120.5, 128.6, 130.4, 149.0, 158.6, 166.3; **Analysis**: $C_{14}H_{18}O_4$ required C, 67.18; H, 7.25; Found: C, 67.30; H, 7.32%.

(*R*)-(*E*)-Ethyl 7-((*tert*-butyldiphenylsilyl)oxy)-4-hydroxyhept-2-enoate (49g)

Yield: 16%; colorless oil; **$[\alpha]_D^{25}$** -8.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1427, 1719, 2931, 3433; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.65-1.79 (m, 4H), 3.73 (m, 2H), 4.23 (q, *J* = 7.0 Hz, 2H), 4.38 (m, 1H), 6.11 (dd, *J* = 15.8, 1.8 Hz, 1H), 6.98 (dd, *J* = 15.8, 4.5 Hz, 1H), 7.42 (m, 6H), 7.69 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 19.1, 26.8, 28.2, 33.7, 60.3, 64.0, 70.6, 120.2, 127.6, 129.7, 133.2, 135.5, 150.2, 166.5; **Analysis**: $C_{25}H_{34}O_4Si$ required C, 70.38; H, 8.03; Found: C, 70.42; H, 8.12%.

Procedure for synthesis of (+)-*trans*-cognac lactone (1)

A slurry of CuI (223 mg, 1.17 mmol, 1.6 equiv) in dry ether (5 mL) was treated with 1.6 M MeLi in dry hexane (1.22 mL, 2.48 mmol, 3.3 equiv) at -78 ^oC under nitrogen atmosphere and the stirring was continued for 1h. A solution of γ-butenolide **48c** (115 mg, 0.75 mmol, 1 equiv) in dry ether (2 mL) was added dropwise and the stirring continued for 2 h at -78 ^oC to -20 ^oC. Then, the mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and the product extracted with ethyl

acetate (3 X 20 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography (packed with silica gel 60-120 mesh) using ethyl acetate and petroleum ether (1:3) as eluents to afford cognac lactone **1** in optically pure form.

(+)-(4*S*, 5*R*)-4-Methyl-5-pentyldihydrofuran-2(3*H*)-one or (+)-*trans*-cognac lactone (1)

Yield: 78%; Colorless oil; $\mathbf{[\alpha]_D^{25}}$ +72.3 (*c* 1, $CHCl_3$, cm^{-1}) {lit.[9] $[\alpha]_D^{20}$ -73.4 for its antipode (*c* 0.22, $CHCl_3$)}; **IR** ($CHCl_3$): υ_{max} 1459, 1780, 2932; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.9 (t, *J* = 6.5 Hz, 3H), 1.13 (d, *J* = 6.3 Hz, 2H), 1.25-1.70 (m, 9H), 2.10-1.29 (m, 2H), 2.56-2.74 (m, 1H), 4.00 (td, *J* = 7.3, 4.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 17.4, 22.4, 25.4, 31.5, 34.0, 36.0, 37.0, 87.2, 176.1; **Analysis**: $C_{10}H_{18}O_2$ required C, 70.55; H, 10.66; found C, 70.47; H, 10.60%.

Section II

Synthesis of 4-substituted chromanes *via* Au(III)-catalyzed intramolecular Friedel-Crafts type reaction of 3-aryloxy benzyl alcohols

4.2.1 Introduction

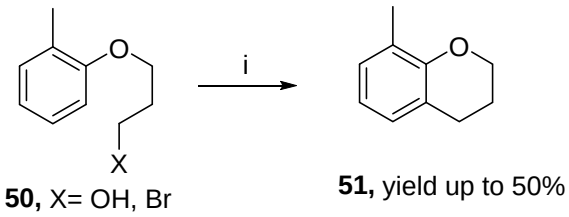
The structures of chromane and benzopyrane are abundantly present in natural products that possess a broad array of biological activities such as antimicrobial, antiviral, mutagenicity, antiproliferative, sex pheromone, antitumor, and central nervous system activity.[28] Organic transformations catalyzed by gold have been the focus of attention recently.[29] Generally Au(I) and Au (III) show unique activity in mediating reactions involving alkynes. In contrast, Au-catalyzed arene functionalization has been given scant attention. Such processes could provide efficient ways to construct C-C bonds from simple arene substrates. Alkylation of aromatic groups is typically achieved with Friedel-Crafts reactions.[30] In this section, a new method of synthesis of 4-aryl substituted chromanes has been described that employs Au (III) chloride-catalyzed intramolecular Friedel-Crafts type reaction of 3-aryloxy benzyl alcohol.

4.2.2 Review of Literature

Literature search reveals that there are several reports available for the synthesis of chromane derivatives. Some of these methods are briefly discussed below.

Rindfusz's approach (1920)[31]

Rindfusz *et al*. have reported dehydration of hydroxyl or bromo -alkyl-aryl ether **50** with $ZnCl_2$ or P_2O_5 to give chromane **51** in 10-50% yields. This method requires high temperature and stoichiometric amount of Lewis acids (**Scheme 13**).



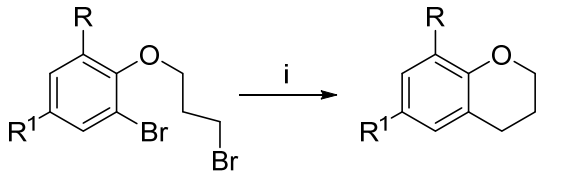
50, X= OH, Br

51, yield up to 50%

Scheme 13: (i) $ZnCl_2$ or P_2O_5, 235 °C, 10-50%.

Bradsher's approach (1981)[32]

Bradsher *et al.* have found that addition of butyl lithium at -100 °C to 3-(o-bromophenoxy) propyl bromides **52** led to preferential exchange of aryl bromine at the ortho position. The resulting organolithium reagent, under suitable conditions, cyclized to afford 3,4-dihydro-2*H*-l-benzopyrans **53** in 79-80% yields (**Scheme 14**).



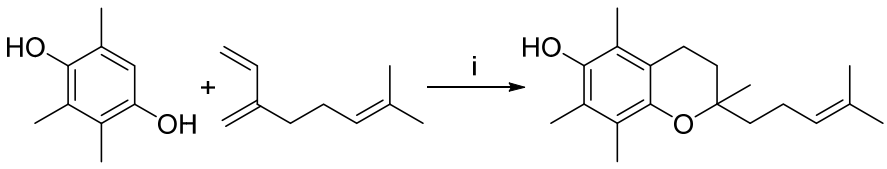
52, R = H, Br
R^1= H, Me, OMe, Cl

53, yield = 79-80%

Scheme14: (i) BuLi (2 equiv), THF, -100 °C, 2 h, 79-80%.

Yamamoto's approach (1995)[33]

Yamamoto *et al.* have reported an elegant method that employs $AlCl_3$–tetralkylammonium halide complex as catalyst in Friedel-Crafts alkylation for substrates such as trimethylhydroquinone **54** and myrcene **55** to give the chromane



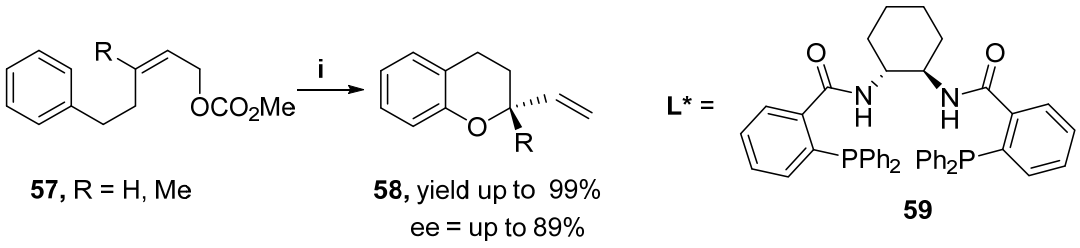
54 **55** **56,** yield = 94%

Scheme 15: (i) $AlCl_3$, Bu_4NBr, 25 °C, 94%.

compound **56** as a major product (**Scheme 15**). This reagent system may expand the use of Lewis acid catalyst in a non-polar solvent system and may be applicable to a wide range of reaction.

Trost's approach (2003)[34]

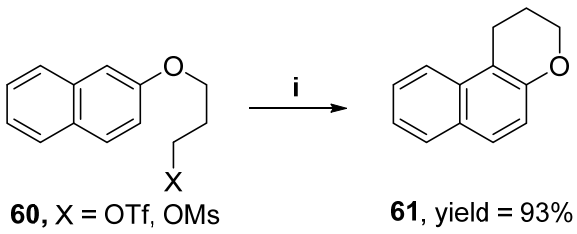
Trost *et al.* have described the application of Pd-catalyzed asymmetric allylic alkylation reaction of phenol allylic carbonates **57** with ligand **59** to the synthesis of chiral chromans **58**. The authors have observed the remarkable influence on enantioselectivity by the use of acetic acid as an additive and the proper olefin geometry of the substrates (**Scheme 16**).



Scheme 16:(i) Pd_2dba_3 (2 mol%), L* **59** (6 mol%), AcOH, CH_2Cl_2.

He's approach (2004)[35]

He *et al.* have found that chromanes **61** can be synthesized in good yields with the use of Au(III)-catalyzed functionalization of aromatic C-H with primary alcohol triflate or methanesulfonate esters **60** to construct C-C bonds (**Scheme 17**). The mechanistic studies have indicated the involvement of the aryl gold(III) species as the reaction

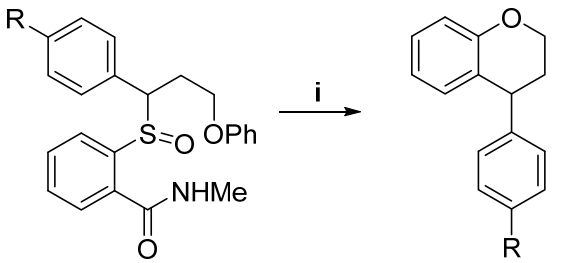


Scheme 17: (i) $AuCl_3$/3Ag(OTf) (5 mol%), $ClCH_2CH_2Cl$, 128 ^oC, 48 h, 15-93%.

intermediate. This intermediate then reacts with the sulfonate ester to give the chromane.

Zanda's approach (2005)[36]

Zanda *et al.* have developed a two-step approach for synthesis of 4-arylbenzopyrans **63**, exploiting the synthetic potential of ortho-*N*-methylformamidophenylsulfoxides **62**. The authors have observed that the synthesis of *ortho-N*-methylformamidophenylsulfoxides requires more number of steps (**Scheme 18**).

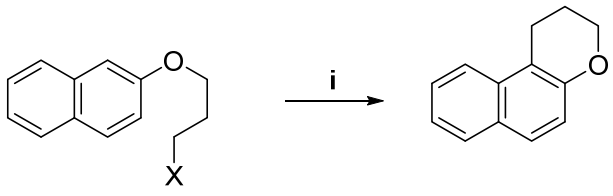


62, R = H, OMe **63,** 63-99%

Scheme 18: (i) Tf_2O, 2,2,6,6-tetramethyl piperidine, CH_2Cl_2, -78 ^oC.

Kim's approach (2010)[37]

Recently Kim *et al.* have described new method for the ring-closure cyclization of primary and secondary halo- and alkanesulfonyloxyalkyl aromatic systems **64** which led to the synthesis of corresponding chromanes **65,** in ILs such as [bmim][PF_6] **(Scheme 19**).



64, X = OTs,OMs, I, Br **65**, upto 85%

Scheme 19: (i) [bmim][BF_4], 150 ^oC, 24-48 h.

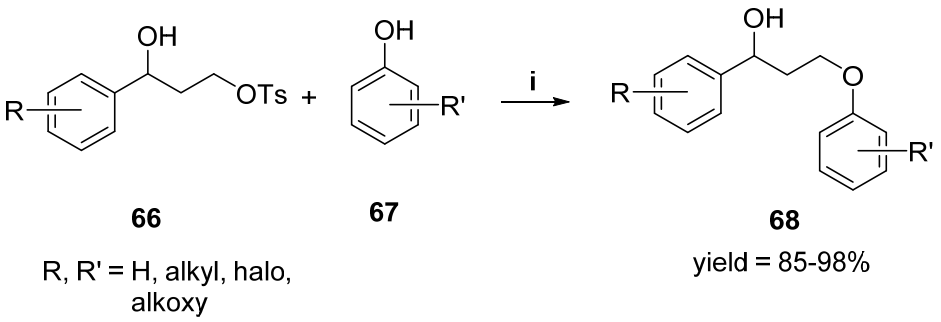
4.2.3 Present Work

4.2.3.1 Objective

From the above discussion, it is clear that most of the reported methods are run under harsh conditions with high concentration of Lewis acids, which can hardly be tolerated by many functional groups. Given the importance of these valuable chromanes as well as the lack of efficient methods for the preparation of these important active agents, development of a new catalytic synthesis of these compounds appears to be of great importance. In this section, we describe a novel $AuCl_3$-catalyzed synthesis of 4-substituted chromanes from 3-aryloxy benzyl alcohol by the Friedel-Crafts type intramolecular cyclization of 3-aryloxy benzyl alcohols.

4.2.3.2 Results and Discussion

3-Aryloxy benzyl alcohols **68a-i,** precursors for the synthesis of 4-substituted chromanes, were readily prepared by the nucleophilic displacement of 3-hydroxy-3-aryl propyl tosylate **66** with phenols **67** in the presence of sodium hydride as base (**Scheme 20**).[38]



Scheme 20: (i) NaH , DMF, 80 °C, 2 h.

A variety of phenols underwent the nucleophilic substitution with tosylates **66a-i** to give the corresponding 3-aryloxy benzyl alcohols **68a-i** in excellent yields. The formation of 3-aryloxy benzyl alcohols **68a-i** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. **Example:** The ^{1}H NMR spectrum of **68a** showed multiplets at δ 4.03

(m, 1H) and 4.21 (m, 1H), due to methylene (-CH_2-OAr) protons and δ 5.08 (1H) due to benzylic proton. Its ^{13}C NMR showed a typical signals at δ 29.9 and 71.8 due to methyl carbon of *tert*-butyl group and benzylic carbon attached to oxygen atom respectively (**Fig.7**).

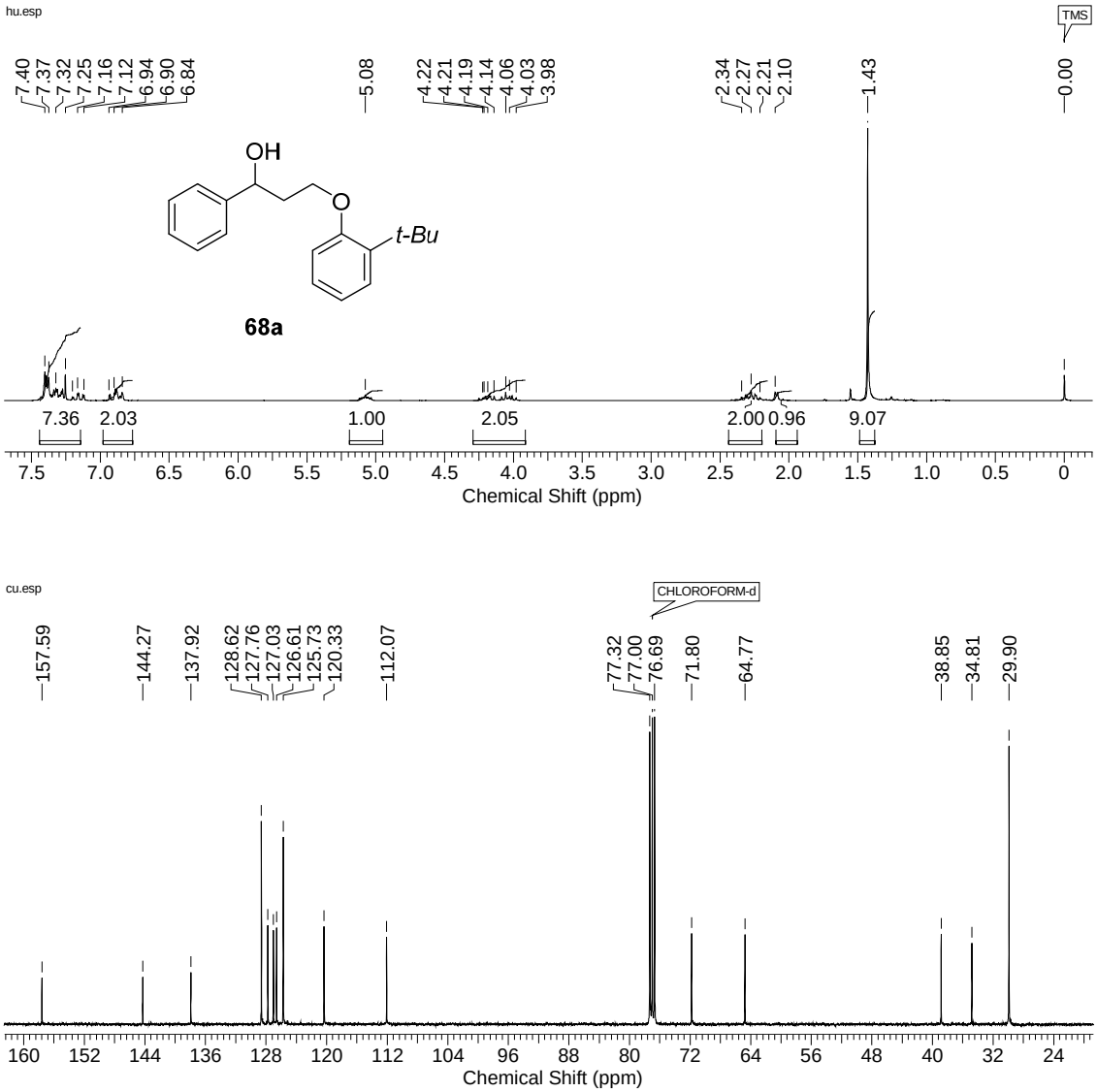
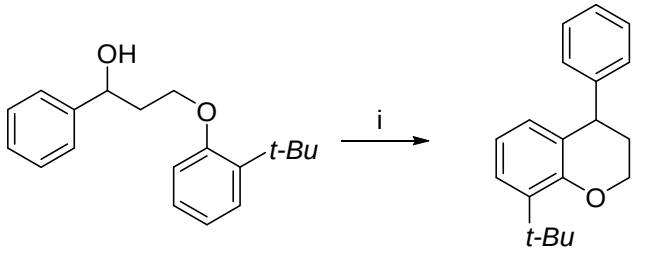


Fig. 7: ^{1}H and ^{13}C NMR spectra of **68a**

When 3-aryloxy benzyl alcohol **68a** was subjected to Au(III) chloride-catalyzed Friedel-Crafts type intramolecular cyclization in dichloromethane as a solvent at 25 ^{o}C, it proceeded to give 4-aryl substituted chromanes **69a** in 98% yields (**Scheme 21**).

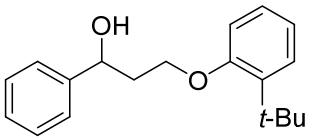
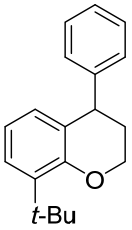
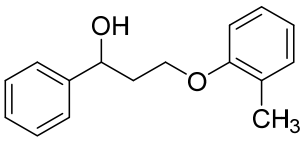
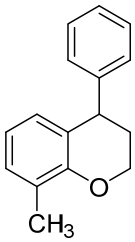
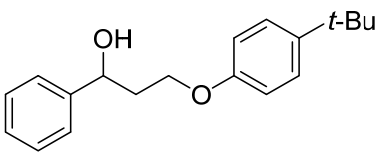
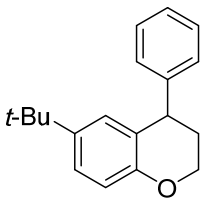


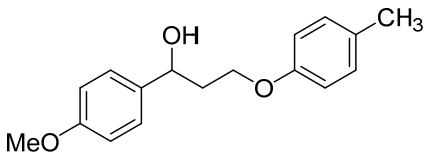
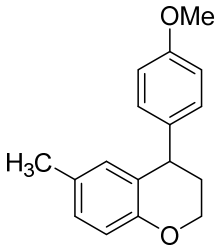
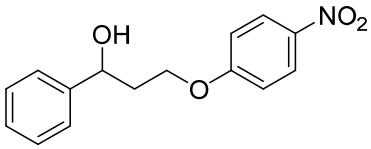
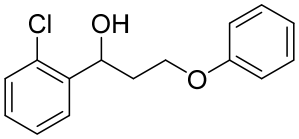
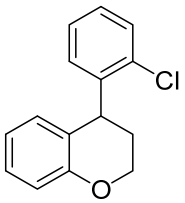
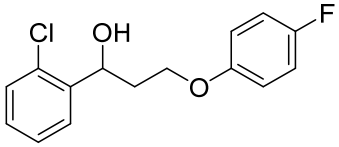
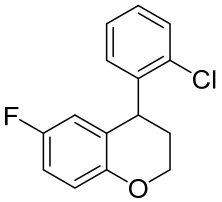
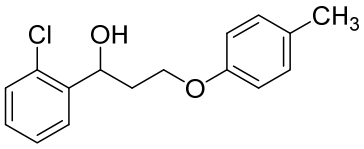
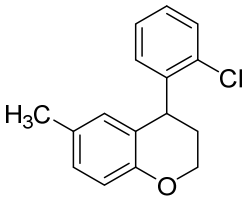
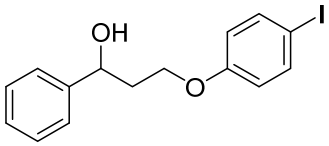
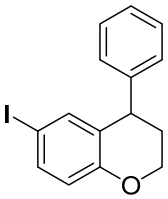
68a **69a**, 98%

Scheme 21: (i) $AuCl_3$ (1 mol%), CH_2Cl_2, 25 °C, 6 h.

To study the generality of the reaction, several 3-aryloxy benzyl alcohols **68a-i** were subjected to $AuCl_3$-catalyzed Friedel-Crafts type intramolecular cyclization; the results of which are presented in **Table 3**. 3-Aryloxy benzyl alcohols having electron-donating groups (**68a-d)** gave good yields of chromanes **69a-d**, while reaction failed in the case of electron-withdrawing group like nitro **(68e)**. Also, when chiral 1-phenyl-3-(o-tolyloxy)propan-1-ol [38] was employed as substrate, no optical induction took place.

Table 3: Synthesis of 4-aryl substituted chromanes (**69**) [a]

Entry	Substrates (68) Ar	Products (69)	Yield (%)[b]
a			98
b			95[c]
c			90

d			92
e		--	No reaction
f			90
g			90
h			91
i			90

Reaction conditions: [a] 3-aryloxy benzyl alcohols (1 mmol), $AuCl_3$ (1 mol%), CH_2Cl_2 (5 mL) 25 °C, 5h; [b] yields refer to isolated yields after column chromatography. Also reaction was carried out with chiral 1-phenyl-3-(o-tolyloxy)propan-1-ol, however no chiral induction was observed.

The formation of chromanes **69a-i** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. **Example:** The ^{1}H NMR spectrum of **69a** showed multiplet at δ 4.19 (m, 3H) due to methylene protons (O-**CH_2**-) attached to oxygen atom and methine proton at benzylic postion and a singlet at δ 1.40 (9H) for methyl protons of *tert*-butyl group. Its ^{13}C

NMR spectrum showed typical signals at δ 63.0 due to methylene carbon attached to oxygen atom and at δ 41.6 due to carbon attached to benzylic position **(Fig. 8).**

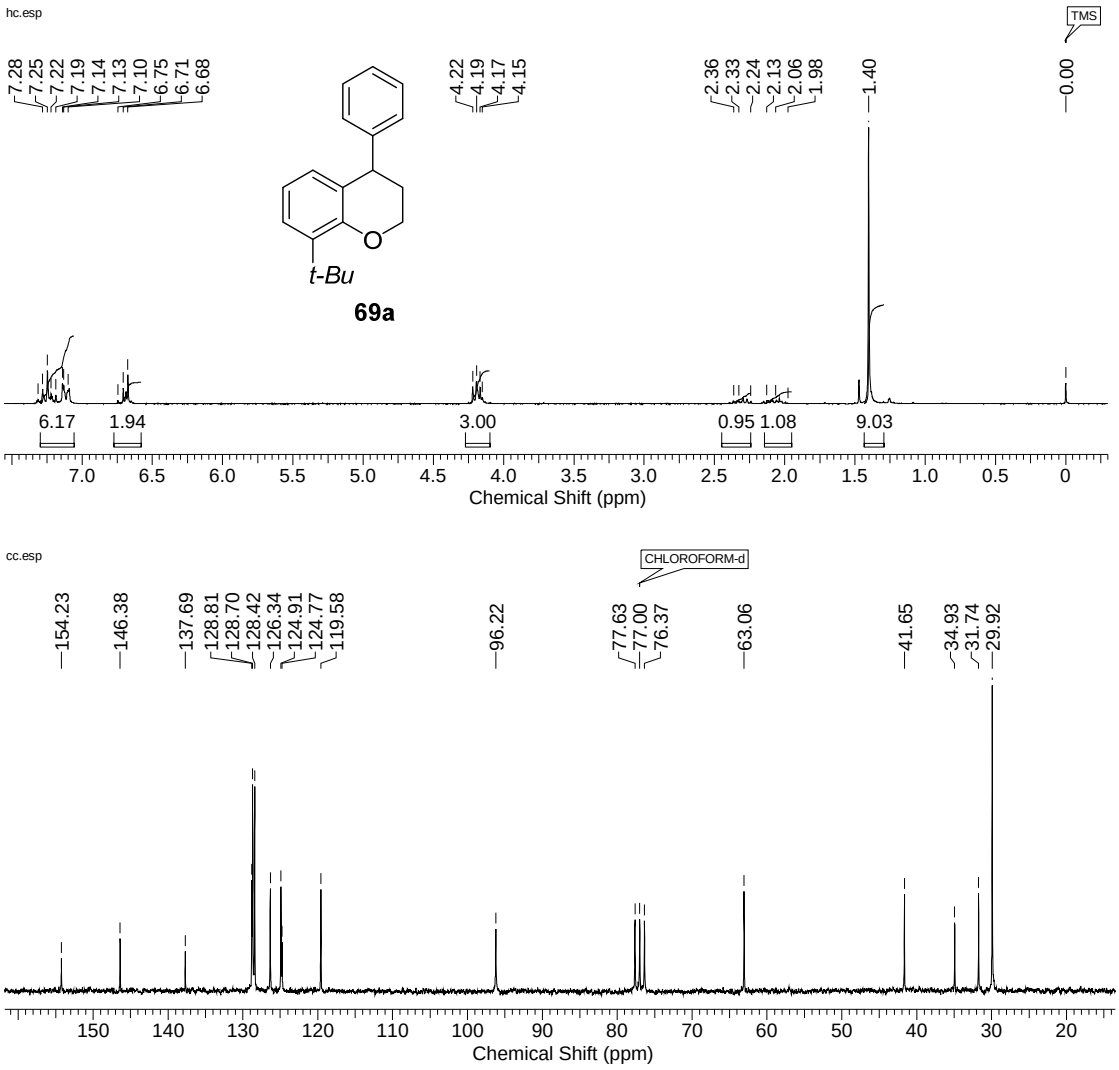
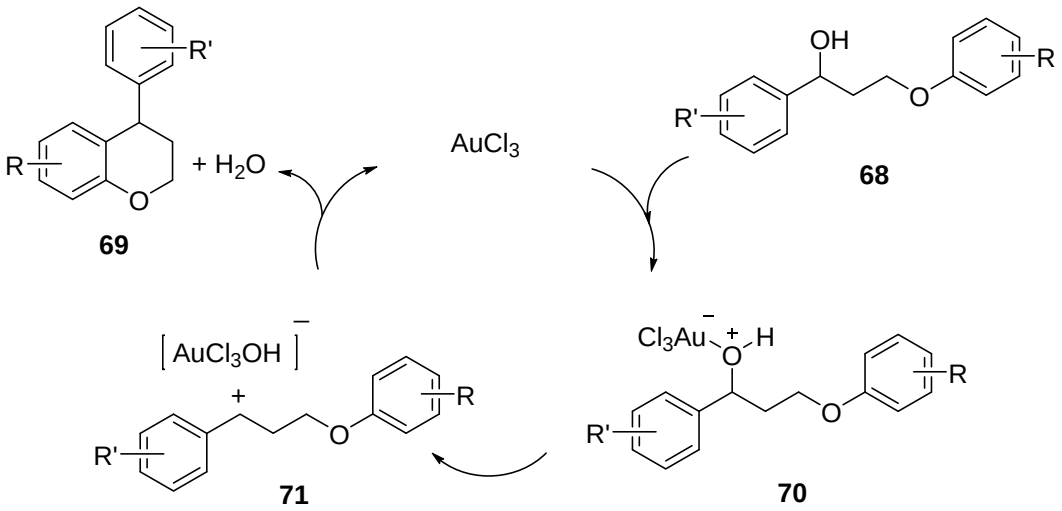


Fig. 8: ^{1}H and ^{13}C NMR spectra of **69a**

4.2.4 Mechanism

A simplified catalytic cycle consisting of the following three steps is shown in **Scheme 22**: (1) coordination of oxygen atom of the benzyl alcohol **68** to Au-catalyst; (2) transfer of the hydroxyl group to the metal with concomitant generation of the intermediate carbocation **71**;[39] (3) trapping of the carbocation by the electron-rich aryloxy ring to produce cyclized product **69** with the generation of 1 mole of water.



Scheme 22: Proposed catalytic cycle for Au(III)-catalyzed cyclization of 3-aryloxy benzylalcohols.

4.2.5 Conclusion

In conclusion, it has been shown that Au(III) chloride is highly effective catalyst for the intramolecular Friedel-Crafts type cyclization of 3-aryloxy benzyl alcohols at mild reaction condition to give 4-aryl substituted chromanes in 90-98% yields.

4.2.6 Experimental Section

General experimental procedure for the preparation of 3-aryloxy benzyl alcohols (68a-i)

To a solution of phenolic substrates **67a-i** (1.0 mmol) in DMF (5 mL) was added 60% of sodium hydride (0.04 g, 1.0 mmol) dispersed in mineral oil at 25 °C. After five minutes of stirring, 3-hydroxy-3-arylpropyltosylate **66** (0.309 g 1.0 mmol) in DMF (2 mL) was added via syringe. The reaction mixture was warmed to 70 °C and stirred at the same temperature for 2 h. After completion of reaction (monitored by TLC), it was quenched with aq. NH_4Cl (5 mL) and extracted with EtOAc (3×10 ml)). The combined organic layers were washed with saturated solution of brine (10 ml), dried over anhyd. Na_2SO_4, concentrated under reduced pressure to give the crude product

which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (8:2) as eluents to afford the pure benzylic alcohols **68a-i**.

3-(2-(*tert*-Butyl)phenoxy)-1-phenylpropan-1-ol (68a)

Yield: 92%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1100, 1216, 1459, 1508, 2849, 2950, 3500; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.10 (d, *J* = 3.2 Hz, 1H), 2.27 (m, 2H), 3.98-4.14 (m, 1H), 4.19-4.22 (m, 1H), 5.08 (m, 1H), 6.64-6.94 (m, 2H), 7.12-7.40 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.9, 34.8, 38.8, 64.7, 71.8, 112.0, 120.3, 125.7, 126.6, 127.0, 127.7, 128.6, 137.9, 144.2, 157.6; **Anal. Calcd** for $C_{19}H_{24}O_2$ requires C, 80.24; H, 8.51; found C, 80.25; H, 8.56%.

1-Phenyl-3-(o-tolyloxy)propan-1-ol (68b)

Yield: 90%, colorless oil; I**R** ($CHCl_3$, cm^{-1}): υ_{max} 827, 1036, 1175, 1230, 1520, 2855, 2913, 3415; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.16-2.24 (m, 2H), 2.26 (s, 3H), 2.57 (d, *J* = 3.0 Hz, 1H), 4.03-4.19 (m, 2H), 5.03 (m, 1H), 6.76-6.88 (m, 2H), 7.08-7.15 (m, 2H), 7.25-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.7, 39.8, 65.3, 72.2, 112.0, 120.5, 126.4, 128.5, 129.9, 131.0, 144.5, 156.5; **Anal. Calcd** for $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49; found C, 79.35; H, 7.50%.

3-(4-(*tert*-Butyl)phenoxy)-1-phenylpropan-1-ol (68c)

Yield: 88%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 735, 1165, 1260, 1510, 2833, 3520; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.29 (d, *J* = 2.6 Hz, 1H), 2.00-2.13 (m, 1H), 2.24-2.39 (m, 1H), 4.10-4.19 (m, 3H), 6.75-6.83 (m, 2H), 7.10-7.29 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.6, 34.0, 38.5, 65.4, 72.0, 96.1, 114.0, 125.8, 126.2, 127.5, 128.4, 143.5, 144.4, 156.4 ; **Anal. Calcd** for $C_{19}H_{24}O_2$ requires C, 80.24; H, 8.51; found C, 80.29; H, 8.55%.

1-(4-Methoxyphenyl)-3-(p-tolyloxy)propan-1-ol (68d)

Yield: 90%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1420, 1610, 2940, 3460; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.09-2.17 (m, 1H), 2.20-2.27 (m, 1H), 2.29 (s, 3H), 2.45 (d, *J* = 3.2 Hz, 1H), 3.81 (s, 3H), 3.98-4.04 (m, 1H), 4.10-4.15 (m, 1H), 4.94-4.97 (m, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.0, 41.5, 56.8, 63.3, 72.4, 114.6, 114.9, 122.8, 129.6, 130.1, 136.5, 156.7, 157.9; **Anal. Calcd** for $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40; found C, 74.98; H, 7.45%.

3-(4-Nitrophenoxy)-1-phenylpropan-1-ol (68e)

Yield: 89%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1380, 1550, 2810, 3550; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.25 (m, 2H), 4.13-4.20 (m, 1H), 4.27-4.38 (m, 1H), 5.08 (m, 1H), 7.00-7.09 (m, 2H), 7.26-7.57 (m, 5H), 7.88-8.01 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.2, 66.8, 71.4, 114.3, 124.7, 125.8, 127.5, 128.5, 139.5, 144.8, 162.6; **Anal. Calcd** for $C_{15}H_{15}O_4N$ requires C, 65.92; H, 5.53; N, 5.13 found C, 65.88; H, 5.60; N, 5.16%.

1-(2-Chlorophenyl)-3-phenoxypropan-1-ol (68f)

Yield: 98%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1024, 1133, 1514, 2822, 2944, 3460; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.21-2.32 (m, 2H), 2.77 (br s, 1H), 4.05-4.29 (m, 2H), 5.08 (m, 1H), 6.86-6.93 (m, 2H), 7.15-7.41 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.4, 66.7, 72.1, 113.2, 121.6, 125.7, 127.5, 127.7, 128.5, 130.3, 144.2, 154.2; **Anal. Calcd** for $C_{15}H_{15}O_2Cl$ requires C, 68.57; H, 5.75; found C, 68.60; H, 5.80%.

1-(2-Chlorophenyl)-3-(4-fluorophenoxy)propan-1-ol (68g)

Yield: 95%, Yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1067, 1234, 1510, 2843, 3520; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.09-2.16 (m, 1H), 2.27-2.32 (m, 1H), 2.70 (d, *J* = 3.3 Hz, 1H), 4.11-4.18 (m, 2H), 5.37 (m, 1H), 6.83-6.97 (m, 4H), 7.19-7.33 (m, 3H), 7.61

(m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.6, 66.5, 69.2, 115.6, 115.8, 116.0, 127.2, 128.6, 129.5, 131.7, 141.5, 157.0 (d, *J* = 240 Hz); **Anal. Calcd** for $C_{15}H_{14}O_2FCl$ requires C, 64.18; H, 5.03; found C, 64.20; H, 5.10%.

1-(2-Chlorophenyl)-3-(p-tolyloxy)propan-1-ol (68h)

Yield: 95%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1216, 1517, 1622, 2870, 2913, 3530; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.04-2.24 (m, 2H), 2.29 (s, 3H), 2.94 (d, *J* = 3.5 Hz, 1H), 4.15 (m, 2H), 5.33-5.41 (m, 1H), 6.77 (m, 2H), 6.97 (m, 2H), 7.34-7.60 (m, 3H), 7.60 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.6, 36.6, 66.3, 69.6, 114.5, 127.1, 127.2, 128.4, 129.4, 130.0, 130.3, 131.6, 141.6, 156.4; **Anal. Calcd** for $C_{16}H_{17}O_2Cl$ requires C, 69.44; H, 6.19; found C, 69.48; H, 6.22%.

3-(4-Iodophenoxy)-1-phenylpropan-1-ol (69i)

Yield: 93%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1236, 1520, 1611, 2853, 3480; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.13-2.27 (m, 3H), 3.92-4.03 (m, 1H), 4.10-4.18 (m, 1H), 4.97 (m, 1H), 6.64 (d, *J* = 9.0 Hz, 2H), 7.25-7.36 (m, 5H), 7.51 (d, *J* = 9.0 Hz, 2H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.3, 65.3, 71.8, 83.0, 116.9, 125.7, 127.7, 128.6, 138.2, 144.0, 158.6; **Anal. Calcd** for $C_{15}H_{15}O_2I$ requires C, 50.87; H, 4.27; found C, 50.90; H, 4.31%.

General experimental procedure for the preparation of chromanes (69a-i)

To a solution of Au(III) chloride (3 mg, 1 mol%), in CH_2Cl_2 (5 mL) was added 3-aryloxy benzyl alcohols **68a-i** (1.0 mmol) in (2 mL, CH_2Cl_2) at room temperature. The resulting mixture was stirred at 25 ^oC for 6 h. After the completion of the reaction (monitored by TLC), it was then quenched with water and extracted with CH_2Cl_2 (10 mL× 2). The combined organic layer was concentrated under reduced pressure to give the crude product, which was purified by column chromatography with silica gel

using petroleum ether: ethyl acetate (9:1) as eluents to afford the pure chromanes **69a-i**.

8-(*tert*-Butyl)-4-phenylchromane (69a)

Yield: 98%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 766, 1030, 1218, 1403, 1491, 2884, 2952,; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.98-2.13 (m, 1H), 2.24-2.36 (m, 1H), 4.15-4.22 (m, 3H), 6.68-6.75 (m, 2H), 7.10-7.31 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.9, 31.7, 34.9, 41.6, 63.0, 119.6, 124.7, 124.9, 126.3, 128.4, 128.7, 128.8, 137.7, 146.4, 154.2; **Anal. Calcd** for $C_{19}H_{22}O$ requires C, 85.67; H, 8.32; found C, 85.62; H, 8.36%.

8-Methyl-4-phenylchromane (69b)

Yield: 95%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1100, 1260, 1404, 1491, 2840, 2961,; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.02-2.15 (m, 1H), 2.22 (s, 3H), 2.26-2.38 (m, 1H), 4.13-4.23 (m, 3H), 6.65 (m, 2H), 6.95-7.31 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 16.2, 31.8, 41.2, 63.7, 119.6, 123.7, 125.7, 128.2, 128.6, 128.9, 145.9, 153.3; **Anal. Calcd** for $C_{16}H_{16}O$ requires C, 85.68; H, 7.19; found C, 85.66; H, 7.20%.

8-(*tert*-Butyl)-4-phenylchromane (69c)

Yield: 90%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1041, 1137, 1255, 1521, 2820, 2933; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.98-2.13 (m, 1H), 2.26-2.37 (m, 1H), 4.13 (m, 3H), 6.75-6.83 (m, 2H), 7.10-7.30 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.5, 31.9, 34.0, 41.1, 63.4, 116.2, 123.2, 124.8, 126.3, 127.3, 128.3, 128.6, 142.7, 145.8, 152.9; **Anal. Calcd** for $C_{19}H_{22}O$ requires C, 85.67; H, 8.32; found C, 85.68; H, 8.35%.

4-(4-Methoxyphenyl)-6-methylchromane (69d)

Yield: 92%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 852, 1043, 1222, 1612, 2851, 2933; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.95-2.10 (m, 1H), 2.16 (s, 3H), 2.19-2.34 (m, 1H), 3.80

(s, 3H), 4.06-4.17 (m, 3H), 6.64-6.95 (m, 5), 7.03 (d, *J* = 6.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.4, 31.8, 40.0, 55.1, 63.6, 113.7, 116.4, 124.6, 128.4, 129.3, 129.5, 130.7, 137.8, 152.8, 158.0; **Anal. Calcd** for $C_{17}H_{18}O_2$ requires C, 80.28; H, 7.13; found C, 80.29; H, 7.15%.

4-(2-Chlorophenyl)chromane (69f)

Yield: 90%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1132, 1209, 1513, 2836, 2944; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.04-2.19 (m, 1H), 2.26-2.41 (m, 1H), 4.15-4.21 (m, 1H), 4.27-4.32 (m, 2H), 6.74 (m, 2H), 7.08 (m, 2H), 7.19-7.32 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.4, 41.2, 64.5, 120.3, 121.8, 126.2, 126.7, 128.6, 129.0, 145.0, 150.9; **Anal. Calcd** for $C_{15}H_{13}OCl$ requires C, 73.62; H, 5.35; found C, 73.69; H, 5.40%.

4-(2-Chlorophenyl)-6-fluorochromane (69g)

Yield: 90%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 755, 836, 1027, 1230, 1611, 2823, 2944; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.99-2.14 (m, 1H), 2.24-2.40 (m, 1H), 4.05-4.23 (m, 2H), 4.64 (t, *J* = 6 Hz, 1H), 6.55 (m, 1H), 6.82-6.93 (m, 3H), 7.13-7.22 (m, 2H), 7.39-7.43 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.6, 41.8, 66.9, 112.8, 115.7, 120.8, 127.6, 127.8, 129.5, 130.1, 132.8, 133.6, 135.8, 150.4, 155.2 (d, *J* = 259 Hz); **Anal. Calcd** for $C_{15}H_{12}OClF$ requires C, 68.58; H, 4.60; found C, 68.62; H, 4.65%.

4-(2-Chlorophenyl)-6-methylchromane (69h)

Yield: 91%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1139, 1208, 1532, 2875, 2966; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.97-2.11 (m, 1H), 2.18 (s, 3H), 2.25-2.41 (m, 1H), 4.03-4.22 (m, 2H), 4.62 (t, *J* = 5.7 Hz, 1H), 6.64-6.98 (m, 4H), 7.13-7.18 (m, 2H), 7.38-7.41 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.5, 35.8, 40.7, 64.7, 112.6, 127.3, 127.4, 129.5, 130.1, 131.2, 131.5, 133.1, 133.7, 136.1, 152.3; **Anal. Calcd** for $C_{16}H_{15}OCl$ requires C, 74.27; H, 5.84; found C, 74.30; H, 5.88%.

6-Iodo-4-phenylchromane (69i)

Yield: 90%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 836, 1035, 1105, 1618, 2849, 2931; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.97-2.12 (m, 1H), 2.20-2.36 (m, 1H), 4.09-4.18 (m, 3H), 6.60 (d, *J* = 8.6 Hz, 1H), 7.07-7.40 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.2, 40.6, 63.6, 82.4, 116.8, 119.2, 126.7, 127.0, 128.5, 128.6, 136.6, 138.9, 144.7, 155.0; **Anal. Calcd** for $C_{15}H_{13}OI$ requires C, 53.59; H, 3.90; found C, 53.62; H, 3.93%.

4.2.7 References

1. (a) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem*. **2005**, *243*, 43; (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem*., *Int. Ed*. **2009**, *48*, 9426.

2. (a) Kunesch, G.; Zagatti, P.; Lallemand, J. Y.; Debal, A.; Vigneron, J. P. *Tetrahedron Lett*. **1981**, *22*, 5271; (b) Vigneron, J. P.; Meric, R.; Larcheveque, M.; Debal, A.; Lallemand, J. Y.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521.

3. (a) Rao, Y. S. *Chem. Rev*. **1976**, *76*, 625–694; (b) Rao, Y. S. *Chem. Rev*. **1964**, *64*, 353.

4. (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc*. **1999**, *121*, 669; (b) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed*. **2006**, *45*, 7230; (c) Ube, H.; Shimada, N.; Terada, M. *Angew. Chem*., *Int. Ed*. **2010**, *49*, 1858; (d) Suzuki, K.; Inomata, K. *Tetrahedron Lett*. **2003**, *44*, 745; (e) Suzuki, K.; Shoji, M.; Kobayashi, E.; Inomata, K. *Tetrahedron*: *Asymmetry* **2001**, *12*, 2789.

5. Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 1192.

6. Evans, P.; Leffray, M.; *Tetrahedron* **2003**, 59, 7973.

7. Fujii, M.; Fukumura, M.; Hori, Y.; Hirai, Y.; Akita, H.; Nakamura, K.; Toriizukaa, K.; Idaa, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 2292.

8. Trost, B. M.; Hitce, J. *J. Am. Chem. Soc*. **2009**, *131*, 4572.

9. Mao. B.; Geurts, K.; Fananas-Mastral, M; van Zijl, A. W.; Fletcher, S. P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett*. **2011**, *13*, 948.

10. (a) Kawasumi, M.; Iwabuchi, Y. *Org. Lett*. **2013**, *15*, 1788; (b) Tsuboi, S.; Sakamoto, J.; Yamashita, H.; Sakai, T.; Utaka, M. *J. Org. Chem*. **1998**, *63*, 1102; (c) Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165.

11. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3726; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138; (c) Houk, K. N.; List, B. *Acc. Chem. Res*. **2004**, *37*, 487; (d) List, B. *Adv. Synth. Catal*. **2004**, *346*, 1021; (e) Bolm, C. *Adv. Synth. Catal*. **2004**, *346*, 1022; (f) Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.

12. (a) List, B. *J. Am. Chem. Soc*. **2002**, *124*, 5656; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (d) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293.

13. For a review of proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573.

14. (a) Oelke, A. J.; Kumarn, S.; Longbottom, D. A.; Ley, S. V. *Synlett* **2006**, 2548; (b) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F. III *Org. Lett.* **2003**, *5*, 1685; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2003**, *43*, 1112; (d) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J*. **2004**, *10*, 3673; (e) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F. III *Org. Lett.* **2003**, *5*, 1685; (f) Zhao, G. –L.; Liao, W, -W.; Cordova, A. *Tetrahedron Lett* **2006**, *47*, 4929; (g) Liao, W. –W.; Ibrahem I.; Cordova A. *Chem. Commun.* **2006**, 674; (h) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637; (i) Zhong, G. Chem. Commun. **2004**, 606.

15. Davis, F. A.; Bang-Chi, C. *Chem. Rev*. **1992**, *92*, 919.

16. Morikawa, K.; Park, J.; Andersson, P.G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1993**, *115*, 8463.

17. Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512.

18. Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819.

19. Merino, P.; Tejero, T.*; Angew. Chem. Int. Ed.* **2004**, *43*, 2995.

20. Kotkar, S. P.; Chavan, V. B.; Sudalai, A. *Org. Lett.* **2007**, *9*, 1001.

21. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

22. (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett*. **1984**, *25*, 2183; (b) Rubsam, F.; Evers, A. M.; Michel, C.; Giannis, A. *Tetrahedron* **1997**, *53*, 1707.

23. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2003**, *125*, 6038.

24. (a) Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron Lett*. **1994**, *35*, 4123; (b) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem*. **1995**, *60*, 5628; (c) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, *52*, 3905.

25. Tanikaga, R.; Hosoya, K.; Kaji, A. *Synthesis* **1987**, *4*, 389.

26. Petersen, K. S.; Posner, G. H.. *Org. Lett*. **2008**, *10*, 4685.

27. Chouthaiwale, P. V.; Kotkar, S. P.; Sudalai, A, *ARKIVOC* **2009**, 88.

28. (a) Ellis, G. P.; Lockhart, I. M. *The Chemistry of Heterocyclic Compounds, Chromenes, Chromanones, and Chromones*; Ellis,G. P., Ed.;Wiley-VCH: New York, **2007**; Vol. *31*, pp 1. (b) Horton, D. A.; Bourne, G. T.; Smythe,M. L. *Chem. Rev*. **2003**, *103*, 893. (c) Geen, G. R.; Evans, J. M.; Vong, A. K. *Comprehensive Heterocyclic Chemistry II: Pyrans and their Benzo Derivatives: Applications*; Katritzky, A. R., Rees, C.W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, **1996**; Vol. *5*, pp 469. (d) Neugebauer, R. C.; Uchiechowska, U.; Meier, R.; Hruby, H.; Valkov, V.; Verdin, E.; Sippl, W.; Jung, M. *J. Med. Chem.* **2008**, *51*, 1203–1213. (e) Posakony, J.; Hirao, M.; Stevens, S.; Simon, J. A.;

Bedalov, A. *J. Med. Chem.* **2004**, *47*, 2635–2644. (f) Wilkinson, J.; Foretia, D.; Rossington, S.; Heagerty, A.; Leonard, J.; Hussain, N.; Austin, C. *Eur. J. Pharmmacol*. **2007**, *561*, 160. (g) Maloney, D. J.; Deng, J. Z.; Starck, S. R.; Gao, Z.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 4140. (h) Kumar, S.; Malachowski, W. P.; DuHadaway, J. B.; LaLonde, J. M.; Carroll, P. J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem*. **2008**, *51*, 1706.

29. (a) Hashmi, A. S. K. *Gold Bull*. **2004**, *37*, 51; (b) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem*. **2004**, *8*, 795; (c) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271; (d) Bond, G. C.; Louis, C.; Thompson, D. T. *Catalysis*; Gold Imperial College Press: London, **2006**; (e) Fu¨rstner, A.; Davies, P. W. *Angew. Chem., Int. Ed*. **2007**, *46*, 3410; (f) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395; (g) Hashmi, A. S. K. *Chem. Rev*. **2007**, *107*, 3180.

30. (a) Olah, G. A. *Friedel-Crafts and Related Reactions*; Wiley: New York, **1973**; (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

31. Rindfusz, R. E.; Ginnings, P. M.; Harnack, V. L. *J. Am. Chem. Soc.* **1920**, *42*, 157.

32. Bradsher, C. K.; Reames, D**.** C. *J. Org. Chem.* **1981,** 46**,** 1384.

33. Matsui, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2663.

34. Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276.

35. Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596.

36. Volonterio, A.; Zanda, M. *Tetrahedron Lett*. **2005**, *46*, 8723.

37. Hong , D. J.; Kim, D. W.; Chi, D. Y. *Tetrahedron Lett*. **2010**, *51*, 54.

38. Ali, I. S.; Sudalai, A. *Tetrahedron Letters*, **2002**, *43*, 5435.

39. Cuenca, A. B.; Mancha, G.; Asensio, G.; Medio-Sim, M. *Chem. Eur. J.* **2008**, *14*, 1518.

LIST OF PUBLICATIONS

1. "Concise enantioselective syntheses of (+)-L-733,060 and (2*S*, 3*S*)-3-hydroxypipecolic acid by Co(III)(salen)-catalyzed two-stereocenter hydrolytic kinetic resolution of racemic azido epoxides" **Devalankar, D. A.**; Chouthaiwale, P. V.; Sudalai. A. *Synlett*, **2014**, *25*, 102.
2. "Optically pure γ-butyrolactones and epoxy esters *via* two stereocentered HKR of 3-substituted epoxy este" **Devalankar, D. A.;** Kalabhor, P. U.; Sudalai, A. *Org. Biomol. Chem.*, **2013**, *11*, 1280.
3. "A concise synthesis of (+)-deoxoprosophylline via Co(III)(salen)-catalyzed two stereocentered HKR of racemic azido epoxides" **Devalankar, D. A**.; Sudalai, A. *Tetrahedron Lett*. **2012**, *53*, 3213.
4. "Organocatalytic sequential α-aminoxylation and *cis*-Wittig olefination of aldehydes: synthesis of enantiopure γ-butenolides" **Devalankar, D. A.**; Chouthaiwale, P. V.; Sudalai, A. *Tetrahedron: Asymmetry*, **2012**, *23*, 240.
5. "Process For The Production of 4-Subtituted Chromanes *via* Gold Catalysis" Chouthaiwale, P. V.; **Devalankar, D. A.;** Sudalai, A. **2013, WO2013088455 (A1)** (Patent).
6. "Total synthesis of eupomatilone-6 *via* SmI_2-mediated reductive coupling of aldehyde with crotonate" **Devalankar, D. A**.; Sudalai, A. (Manuscript under preparation).
7. **"**A short enantioselective synthesis of (+)-sertraline *via* hydrolytic kinetic resolution of 3-diarylsubstituted epoxide**" Devalankar, D. A**.; Sudalai, A. (Manuscript under preparation).
8. "Synthesis of 4-substituted chromanes *via* Au(III)-catalyzed intramolecular Friedel-Crafts reaction of 3-aryloxy benzyl alcohols" **Devalankar, D. A**.; Sudalai, A. (Manuscript under preparation).