Enantioselective Synthesis of Bioactive Molecules *via* Proline Catalyzed α-Functionalization, Asymmetric Epoxidation and Synthetic Methodologies Involving Pd-Catalyzed Reductive Cyclization, Selective Hydrosilylation of Carbonyl Compounds

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BY

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UNDER THE GUIDANCE OF

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September 2012

DEDICATED TO

MY BELOVED PARENTS

The two greatest people I have ever known
You have been everything as parents that a son could ever want or need

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules via Proline Catalyzed α-Functionalization, Asymmetric Epoxidation and Synthetic Methodologies Involving Pd-Catalyzed Reductive Cyclization, Selective Hydrosilylation of Carbonyl Compounds"*** which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Varun Rawat*** 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.

September 2012
Pune

Dr. A. Sudalai
(Research Guide)

NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules via Proline Catalyzed α-Functionalization, Asymmetric Epoxidation and Synthetic Methodologies Involving Pd-Catalyzed Reductive Cyclization, Selective Hydrosilylation of Carbonyl Compounds"*** 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.

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CONTENTS

		Page No.
Acknowledgements		i
Abbreviations		iv
General Remarks		vi
Abstract		vii
Chapter I	**Total Synthesis of (-)-Oseltamivir Free Base, (-)-Methyl 3-*epi*-shikimate and 3-*epi*-Jaspine B**	
Section I	**Synthesis of the *anti*-influenza agent (-)-Oseltamivir free base and (-)-Methyl 3-*epi*-shikimate**	
1.1.1	Introduction and Pharmacology	1
1.1.2	Review of Literature	2
1.1.3	Present Work	6
1.1.3.1	Objective	6
1.1.3.2	Sharpless Asymmetric Epoxidation	7
1.1.3.3	Results and Discussion	8
1.1.4	Conclusion	32
1.1.5	Experimental Section	32
Section II	**A tandem desilylation-oxa Michael addition reaction for the synthesis of 3-*epi*-Jaspine B**	
1.2.1	Introduction and Pharmacology	50
1.2.2	Review of Literature	51
1.2.3	Present Work	54
1.2.3.1	Objective	54
1.2.3.2	Results and Discussion	55
1.2.4	Conclusion	63
1.2.5	Experimental Section	64
1.2.6	References	69
Chapter II	**Enantioselective Synthesis of (-)-Aspinolide A, *anti*-Alzheimer's Agent (*S*)-*N*-(5-Chlorothiophene-2-sulfonyl)-β,β-diethylalaninol and Cholesterol Biosynthesis Inhibitor Metabolite, (+)-Decarestrictine L**	

Section I	**Asymmetric synthesis of (-)-Aspinolide A**	
2.1.1	Introduction and Pharmacology	71
2.1.2	Review of Literature	71
2.1.3	Present Work	73
2.1.3.1	Objective	73
2.1.3.2	Results and Discussion	74
2.1.4	Conclusion	86
2.1.5	Experimental Section	86
Section II	**A facile enantioselective synthesis of (*S*)-*N*-(5-Chlorothiophene-2-sulfonyl)-β,β-diethylalaniol (7.b.2) *via* proline catalyzed asymmetric α-aminooxylation and α-amination of aldehyde**	
2.2.1	Introduction and Pharmacology	96
2.2.2	Review of Literature	97
2.2.3.	Present Work	98
2.2.3.1	Objective	98
2.2.3.2	Results and Discussion	99
2.2.4	Conclusion	110
2.2.5	Experimental Section	110
Section III	**A concise enantioselective synthesis of (+)-Decarestrictine L *via* proline-catalyzed sequential α-aminooxylation and Horner-Wadsworth-Emmons olefination**	
2.3.1	Introduction and Pharmacology	118
2.3.2	Review of Literature	118
2.3.3	Present Work	122
2.3.3.1	Objective	122
2.3.3.2	Results and Discussion	123
2.3.4	Conclusion	138
2.3.5	Experimental Section	139
2.3.6	References	150
Chapter III	**A New Concise Method for the Synthesis of Chiral Tetrahydroquinolin-3-ols, (-)-Sumanirole (PNU-95666E) and 1-[(*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propanone, (*S*)-903**	

Section I	**Organocatalytic sequential α-aminooxylation/reductive cyclization of *o*-nitrohydrocinnamaldehydes: A high yield synthesis of chiral Tetrahydroquinolin-3-ols**	
3.1.1	Introduction	153
3.1.2	Review of Literature	154
3.1.3	Present Work	161
3.1.3.1	Objective	161
3.1.3.2	Results and Discussion	163
3.1.4	Conclusion	171
3.1.5	Experimental Section	171
Section II	**Asymmetric synthesis of (-)-Sumanirole (PNU-95666E) and 1-[(*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl] propanone [(*S*)-903]**	
3.2.1	Introduction and Pharmacology	179
3.2.2	Review of Literature	180
3.2.3	Present Work	185
3.2.3.1	Objective	185
3.2.3.2	Results and Discussion	185
3.2.4	Conclusion	200
3.2.5	Experimental Section	201
3.2.6	References	208
Chapter IV	**Pd-catalyzed Hydrosilylation of Aryl Aldehydes and Chemoselective Reduction of aryl α,β-Unsaturated Carbonyls**	
Section I	**Pd-catalyzed hydrosilylation of aryl aldehydes with triethylsilane**	
4.1.1	Introduction	211
4.1.2	Review of Literature	211
4.1.3	Present Work	217
4.1.3.1	Objective	217
4.1.3.2	Results and Discussion	218
4.1.3.3	Mechanism	227
4.1.4	Conclusion	227
4.1.5	Experimental Section	227
Section II	**Pd-catalyzed chemoselective reduction of aryl α,β-unsaturated**	

	carbonyls with triethylsilane	
4.2.1	Introduction	233
4.2.2	Review of Literature	233
4.2.3	Present Work	240
4.2.3.1	Objective	240
4.2.3.2	Results and Discussions	240
4.2.4	Conclusion	248
4.2.5	Experimental Section	248
4.2.6	References	252
	List of Publications	

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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
CAN	Cerric ammonium nitrate
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
DET	Diethyl Tartarate
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
DBAD	Dibenzyl azodicarboxylate
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
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
MOM	Methoxymethyl
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
Pd/C	Palladium on activated charcoal
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
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, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.

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

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

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

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

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

ABSTRACT

The thesis entitled "**Enantioselective Synthesis of Bioactive Molecules *via* Proline Catalyzed α-Functionalization, Asymmetric Epoxidation and Synthetic Methodologies Involving Pd-Catalyzed Reductive Cyclization, Selective Hydrosilylation of Carbonyl Compounds**" 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** presents the total synthesis of the *anti*-influenza agent oseltamivir, methyl 3-*epi*-shikimate and *anti*-cancer agent 3-*epi*-jaspine B. **Chapter 2** describes the enantioselective synthesis of (-)-aspinolide A, *anti*-Alzheimer's agent (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaniol (7.b.2) and fungal metabolite (+)-decarestrictine L *via* proline-catalyzed α-functionalization. **Chapter 3** deals with a new protocol involving sequential proline-catalyzed α-aminooxylation and Pd-catalyzed reductive cyclization of *o*-nitrohydrocinnamaldehydes that leads to facile synthesis of chiral tetrahydroquinolin-3-ols and its application in the enantioselective synthesis of *anti*-parkinson's agent PNU-95666E and inotropic agent 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propanone (*S*-903). **Chapter 4** presents synthetic transformations involving a Pd-catalyzed hydrosilylation of aryl aldehydes and chemoselective reduction of aryl α,β-unsaturated carbonyls.

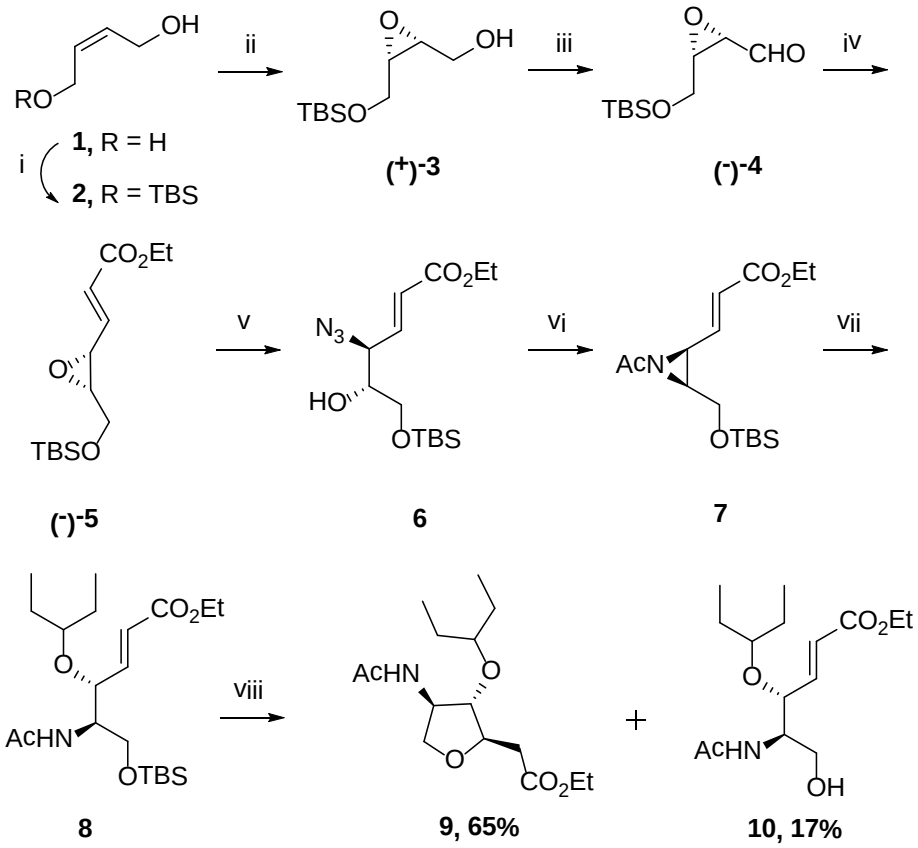
CHAPTER 1

Total Synthesis of (-)-Oseltamivir Free Base, (-)-Methyl 3-*epi*-shikimate and 3-*epi*-Jaspine B

Chapter I is divided into two sections. **Section I** presents the enantioselective synthesis of *anti*-influenza agent oseltamivir **22** and methyl 3-*epi*-shikimate **24** while **Section II** describes the asymmetric synthesis of *anti*-cancer agent 3-*epi*-jaspine B **29** *via* Sharpless asymmetric epoxidation.

SECTION I: Synthesis of the *anti*-influenza agent (-)-Oseltamivir free base and (-)-Methyl 3-*epi*-shikimate [1]

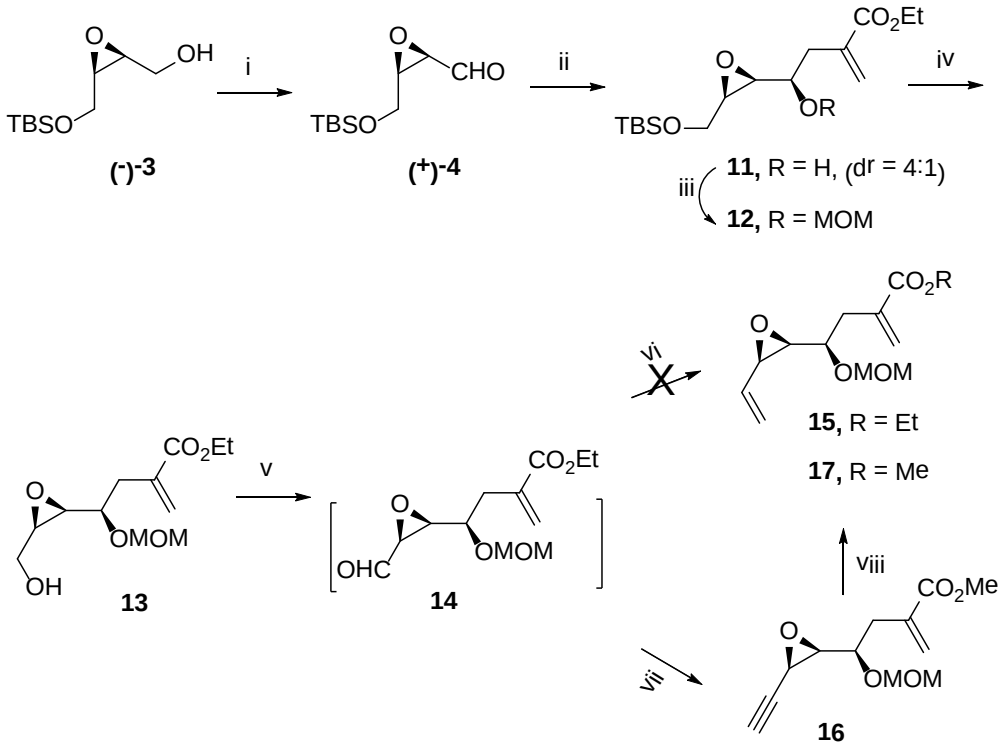
Oseltamivir **22** (Tamiflu) is an orally effective neuraminidase inhibitor,[2] widely used for the treatment and prevention of human influenza (H1N1) and avian influenza (H5N1) infections.[3] The key steps in the synthesis of **22** include Sharpless asymmetric epoxidation (AE), disatereoselective Barbier allylation and ring closing metathesis (RCM).



Scheme 1: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (-)-DET, $Ti(O^iPr)_4$, anhydrous TBHP (5-6 M in decane), 4 Å molecular sieves, dry CH_2Cl_2, -10 ºC, 12 h, 93%; (iii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (iv) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, 25 ºC, 2 h, 92%; (v) NaN_3, NH_4Cl, DMF/EtOH/H_2O (4:4:1), 0-25 ºC, 10 h, 85%; (vi) (a) Ph_3P, PhMe, reflux, 3 h; (b) Ac_2O, DMAP, Et_3N, dry CH_2Cl_2, 0-25 ºC, 45 min, 81% (over two steps); (vii) 3-pentanol, $BF_3{\cdot}OEt_2$, -10 ºC, 30 min, 75%; (viii) TBAF, THF, 0 ºC, 2 h.

Initially, epoxy aldehyde **(-)-4** was prepared from *cis*-2-butene-1,4-diol **1** in three steps: (i) monosilylation of diol **1** (TBSCl, imid., 73%), (ii) AE of allylic alcohol **2** [$Ti(OiPr)_4$, (-)-DET, anhydrous TBHP, 93%], (iii) oxidation of epoxy alcohol **(+)-3** (TEMPO, BAIB, 95%). Wittig olefination of **(-)-4** with $Ph_3P{=}CHCO_2Et$ gave α,β-unsaturated

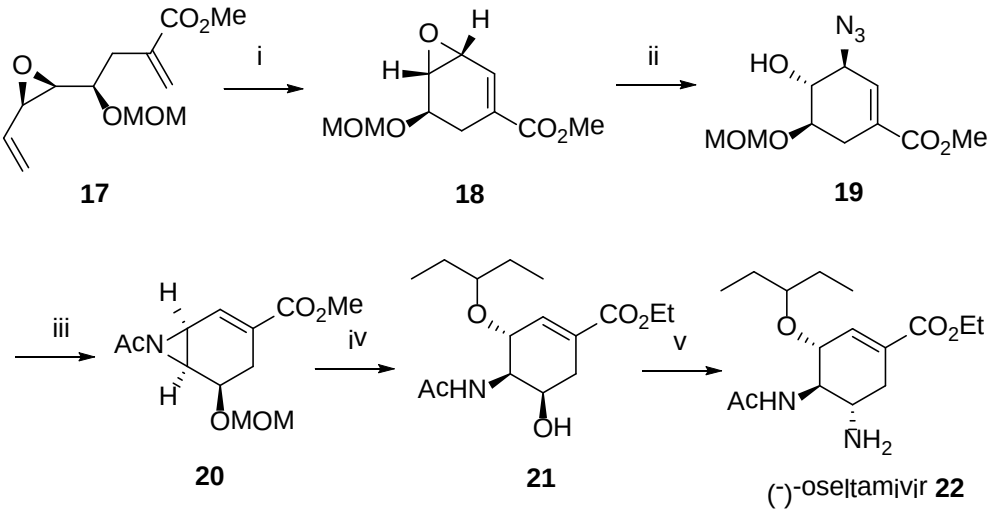
epoxy ester **(-)-5** in 92% yield. Regioselective ring opening of **5** with azide ion was accomplished in 85% yield to give azido alcohol **6**. Staudinger reaction (Ph_3P, toluene) followed by *N*-acetylation (Ac_2O, DMAP, Et_3N) afforded protected aziridine **7** in 81% yield (over two steps). Regioselective ring opening of **7** with 3-pentanol in presence of 1.5 equivalent of $BF_3{\cdot}OEt_2$ furnished α,β-unsaturated ester **8** as the exclusive product in 75% yield. On desilylation with TBAF, unsaturated ester **8** unexpectedly gave the furan derivative **9**, a Michael adduct, as the major product (65%) along with the desired alcohol **10** in minor amounts (17% yield) (**Scheme 1**). Since the yield of **10** was miserably low, an alternate route to **22** was undertaken as shown in **Scheme 2**.



Scheme 2: (i) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (ii) ethyl 2-(bromomethyl)acrylate, Zn dust, NH_4Cl, THF/H_2O (4:1), 0-25 ºC, 10 h, 64% (for *syn*-selectivity); (iii) MOMCl, DIPEA, dry CH_2Cl_2, 0-25 ºC, 10 h, 90%; (iv) TBAF, THF, 0 ºC, 2 h, 88%; (v) IBX, dry DMSO, 25 ºC, 1 h; (vi) *n*-BuLi, $Ph_3P^+CH_3I^-$, dry THF, -10 ºC to 25 ºC, 3 h; (vii) diethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 25 ºC, 2 h, 82% (over two steps); (viii) H_2, Lindlar's catalyst, pyridine/1-octene/EtOAc (1:1:10), 6 h, 95% yield of **17**.

Alternatively, antipode epoxy alcohol **(-)-3** was readily prepared in two steps as described above: (i) monosilylation, (ii) AE using (+)-DET as chiral source. Oxidation of **(-)-3** (TEMPO, BAIB) gave the aldehyde **(+)-4**, which was subjected to Barbier allylation with

ethyl 2-(bromomethyl)acrylate to afford the homoallylic alcohol **11** in 64% yield (dr = 4:1). The hydroxyl group in **11** was then protected (MOMCl, DIPEA, 90%) and TBS group in **12** deprotected (TBAF, THF) to produce **13**, which was then subjected to oxidation (IBX/DMSO) to give the labile aldehyde **14**. Several attempts to perform Wittig olefination (*n*-BuLi, $PPh_3^+CH_3I^-$, THF) of **14** to produce diene **15** were quite unsuccessful, due to its rapid decomposition under the strongly basic condition. Alternately, the crude aldehyde **14** was subjected to Seyferth-Gilbert homologation using Bestman-Ohira reagent in presence of K_2CO_3 and MeOH, which gave the terminal alkyne **16** in 82% yield with completely transesterified methyl ester in 2 h. Selective catalytic hydrogenation [H_2 (1 atm), Lindlar's catalyst, pyridine/1-octene, EtOAc] of alkyne **16** gave alkene **17** (**Scheme 2**).

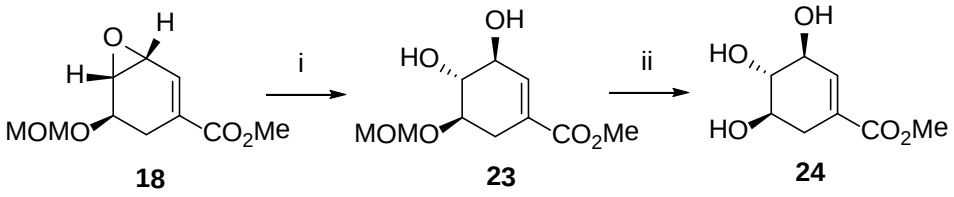


Scheme 3: (i) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 14 h, 90%; (ii) NaN_3, NH_4Cl, DMF/EtOH/H_2O (4:4:1), 0-25 ºC, 10 h, 83%; (iii) (a) Ph_3P, PhMe, reflux, 3 h; (b) Ac_2O, DMAP, Et_3N, dry CH_2Cl_2, 0-25 ºC, 45 min, 81% (over two steps); (iv) (a) 3-pentanol, $BF_3{\cdot}OEt_2$, -10 ºC, 30 min, (b) 2 N HCl, EtOH, 25 ºC, 12 h, 64% (over two steps); (v) (a) MsCl, Et_3N, dry CH_2Cl_2, 0 ºC, 1 h; (b) NaN_3, DMF, 80 ºC, 3 h; (c) H_2, Lindlar's cat, EtOH, 72% (over three steps).

The RCM of **17** using Grubbs II catalyst gave the cyclohexene core **18.** Conversion of **18** to aziridine **20** was achieved in three steps as before (**see Scheme 1**) with an overall yield of 67%: (i) epoxide opening with azide, (ii) formation of aziridine and (iii) its N-acetylation. Regioselective ring opening of aziridine **20** with 3-pentanol followed by simultaneous MOM deprotection and transesterification using 2 N HCl in EtOH afforded

the key amino alcohol **21**. Amino alcohol **21** was then converted to oseltamivir free base **22** in three steps by following the reported procedures:[4] (i) mesylation of alcohol **21**, (ii) displacement of mesylate with azide ion, (iii) reduction of azide with Lindlar's catalyst (**Scheme 3**).

The cyclic epoxide **18** was also considered as an important precursor for the synthesis of (-)-methyl 3-*epi*-shikimate **24**. Thus, **18** was readily converted into the desired triol **24** through a two step reaction sequence: (i) epoxide opening (H_2SO_4, THF/H_2O); (ii) MOM deprotection of **23** (2N HCl, MeOH) (**Scheme 4**). The comparison of spectral data of **24** with the reported values[5] further establishes the absolute configuration of cyclic epoxide **18**.

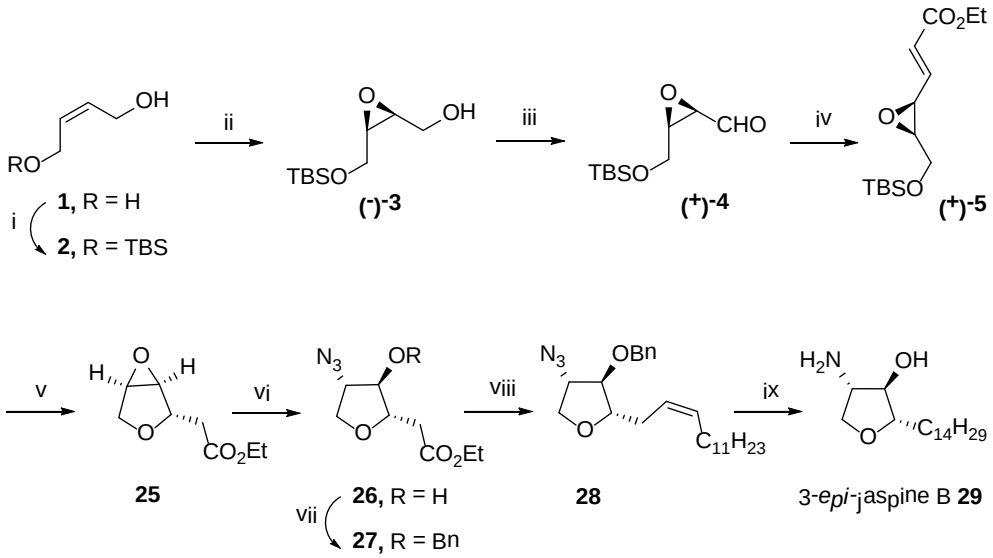


Scheme 4: (i) H_2SO_4, THF/H_2O (3:1), 0-25 °C, 2 h, 96%; (ii) 2 N HCl, MeOH, 25 °C, 6 h, 74%.

SECTION II: A tandem desilylation-oxa Michael addition reaction for the synthesis of 3-*epi*-Jaspine B

3-*epi*-Jaspine B **29** and its stereoisomers have been found to have excellent anti-cancer activity.[6] Initially, α,β-unsaturated epoxy ester **(+)-5** was prepared in 59.3% yield from commercially available *cis*-2-butene-1,4-diol **1** in four steps; (i) monosilylation of diol **1** (TBSCl, imid., 73%), (ii) AE of allylic alcohol **2** [$Ti(OiPr)_4$, (+)-DET, anhydrous TBHP, 93%], (iii) oxidation of epoxy alcohol (-)-**3** (TEMPO, BAIB, 95%), (iv) Wittig olefination of (+)-**4** with $Ph_3P{=}CHCO_2Et$ (Scheme 1). The THF core **25** was then constructed smoothly in 93% yield *via* a diastereoselective tandem desilylation-oxa Michael addition reaction of **(+)-5** mediated by TBAF. Regioselective epoxide opening of **25**, with azide ion in presence of NH_4Cl was accomplished in 91% yield to give azido alcohol **26**. The hydroxyl group in **26** was then protected (BnBr, Ag_2O, 95%) and ester group in **27** selectively reduced (DIBAL-H, toluene, -78 °C) to produce the corresponding aldehyde, which was then subjected to Wittig olefination (*n*-BuLi, $PPh_3{}^+C_{12}H_{25}Br^-$, THF) to give the olefin **28**. Global reduction was afforded under

catalytic hydrogenation condition [10% Pd/C, H_2 (1 atm.)] which gave 3-*epi*-jaspine B **29** with an overall yield of 34.7% (**Scheme 5**).



Scheme 5: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (+)-DET, $Ti(O^iPr)_4$, anhydrous TBHP (5-6 M in decane), 4 Å molecular sieves, dry CH_2Cl_2, -10 ºC, 12 h, 93%; (iii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (iv) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, 25 ºC , 2 h, 92%; (v) TBAF, THF, 25 ºC, 2 h, 93%, de > 99%; (vi) NaN_3, NH_4Cl, EtOH/H_2O (4:1), 80 ºC, 12 h, 91%; (vii) BnBr, Ag_2O, dry CH_2Cl_2, 0-25 ºC, 6 h, 95%; (viii) (a) DIBAL-H, toluene, -78 ºC, 1 h; (b) *n*-BuLi, $PPh_3{}^+C_{12}H_{25}Br^-$, THF, -78-0 ºC, 3 h, 75%; (ix) H_2 (1 atm), 10% Pd/C, MeOH, 25 ºC, 12 h, 97%.

CHAPTER 2

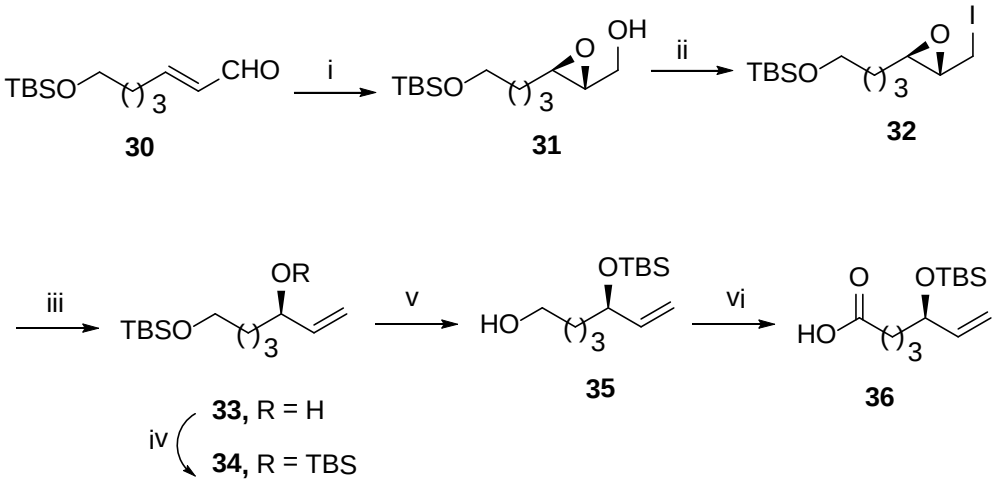
Enantioselective Synthesis of (-)-Aspinolide A, *anti*-Alzheimer's Agent (*S*)-*N*-(5-Chlorothiophene-2-sulfonyl)-β,β-diethylalaninol and Cholesterol Biosynthesis Inhibitor Metabolite, (+)-Decarestrictine L

Asymmetric organocatalysis in organic chemistry has provided several new methods for obtaining chiral compounds in an environmentally benign manner. In this connection, proline, an abundant, inexpensive aminoacid available in both enantiomeric forms has emerged as a practical and versatile organocatalyst. Proline is equally efficient for α-functionalization of aldehydes and ketones. This chapter is divided into three sections. **Section I** deals with the asymmetric synthesis of (-)-aspinolide A **41** while **Section II** describes an organocatalytic route to *anti*-Alzheimer's agent (*S*)-*N*-(5-chlorothiophene-2-

sulfonyl)-β,β-diethylalaniol **51**; **Section III** presents the enantioselective synthesis of (+)-decarestrictine L **66** using proline-catalyzed sequential reactions.

SECTION I: Asymmetric synthesis of (-)-Aspinolide A

Aspinolide A **41**, isolated from cultures of *Aspergillus ochraceus* has attracted considerable attention due to its interesting biological properties and scare availability.[7] Based on retrosynthetic analysis, we visualized homoallylic alcohol **40** and carboxylic acid **36** as key intermediates for the synthesis of **41**. Fragment **40** can be obtained by Brown allylation.[8] The carboxylic acid fragment **36** can be obtained *via* two routes: (i) Jorgensen's asymmetric epoxidation[9] of unsaturated aldehdye **30**; (ii) asymmetric α-aminooxylation[10] of aldehyde **37**.

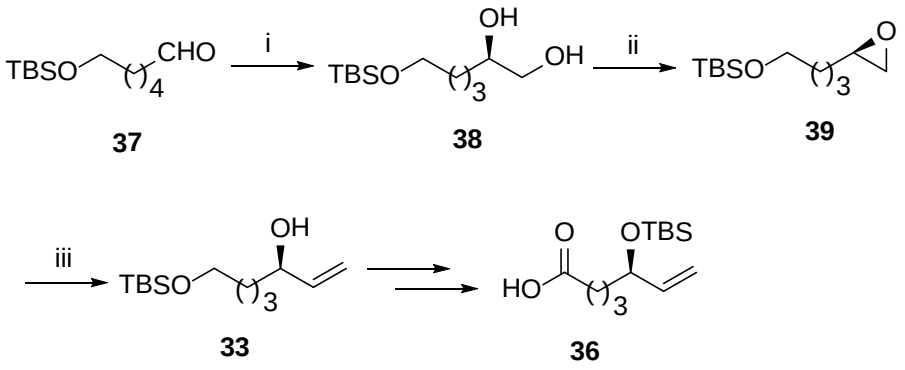


Scheme 6: (i) H_2O_2, CH_2Cl_2, (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol tri-methylsilyl ether (**A**), 25 ºC, 4 h then $NaBH_4$, MeOH, 0 ºC, 1 h, 43%; (ii) I_2, PPh_3, imid., Et_2O/CH_3CN (3:1), 0-25 ºC, 2 h, 90%; (iii) Zn, NaI, MeOH, reflux, 3 h, 90%; (iv) TBSCl, imid., CH_2Cl_2, 0-25 ºC, 6 h, 86%; (v) (+)-camphor-10-sulfonic acid, MeOH, 25 ºC, 5 min, 63%; (vi) TEMPO, $PhI(OAc)_2$, $CH_3CN:H_2O$ (4:1), 25 ºC, 4 h, 80%.

Scheme 6 shows the synthetic route to (-)-aspinolide A **41**, which employs Jorgensen's asymmetric epoxidation as the key chiral inducing step. Thus, α-epoxidation of α,β-unsaturated aldehyde **30** was carried out using H_2O_2 as the oxygen source in the presence of 10 mol% of (*S*)-prolinol-based catalyst **A**[9] in CH_2Cl_2 at 25 ºC followed by its reduction with $NaBH_4$ in MeOH to give the crude α-epoxy alcohol **41** *in situ*. A two-step conversion of **31** to allylic alcohol **33** was then achieved by: (i) I_2, PPh_3, imid., Et_2O/CH_3CN (3:1), 0-25 ºC; (ii) Zn, NaI, MeOH, reflux, 3 h. Conversion of allylic

alcohol **33** to carboxylic acid **36** was then accomplished in three simple steps as described below: (i) silylation of secondary alcohol functionality in **33**; (ii) chemoselective desilylation of primary alcohol **34** [camphor sulphonic acid (CSA), MeOH, 63%]; (iii) Complete oxidation of **35** to carboxylic acid **36** [TEMPO, $PhI(OAc)_2$, CH_3CN/H_2O (4:1)].

Our second approach for the synthesis of carboxylic acid fragment **36** commences from aldehyde **37**, which was subjected to L-Proline Catalyzed *α*-aminooxylation in a two step reaction sequence: (i) reaction of aldehyde **37** with nitrosobenzene as the oxygen source in the presence of 20 mol% L-Proline in CH_3CN at -20 ºC followed by its treatment with $NaBH_4$ in MeOH gave the crude *α*-aminoxy alcohol *in-situ* and (ii) subsequent reduction of the crude *α*-aminoxy alcohol using 10 % Pd/C over H_2 (1 atm) furnished chiral diol **38** in **77**% yield over two steps (**Scheme 7**).

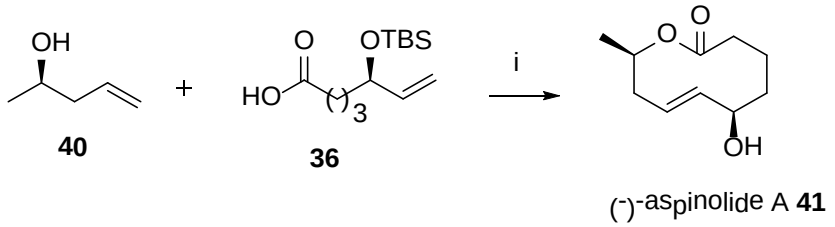


Scheme 7: (i) (a) PhNO (1 equiv.), L-proline (20 mol %), CH_3CN, -20 ºC, 24 h then $NaBH_4$, MeOH, 0 ºC, 10 min; (b) 10% Pd/C, H_2, MeOH, 24 h, 77% (over two steps); (ii) (a) TsCl, Et_3N, Bu_2SnO, DMAP; (b) K_2CO_3, MeOH, 30 min., 92% (over two steps); (iii) $S^+Me_3I^-$, NaH, DMSO, 0 ºC, 2 h, 89%.

Selective tosylation of diol **38** (TsCl, Et_3N, Bu_2SnO) followed by treatment with K_2CO_3 in MeOH gave the optically pure terminal epoxide **39** in 92% yield. Regioselective opening of epoxide **39** into the corresponding allylic alcohol **33** was readily achieved by using Corey-Chaykovsky reagent (SMe_3I, NaH, DMSO) in 89% yield. Conversion of **33** to carboxylic acid **36** was achieved in three steps with an overall yield of 27.3% and 98% ee as described before (**see Scheme 6**).

With both the fragments readily available, we carried out the coupling of the two fragments using stiglich esterification (EDCI, Et_3N) followed by desilylation (TBAF,

THF) and RCM (Grubbs II, CH_2Cl_2) (**Scheme 8**).



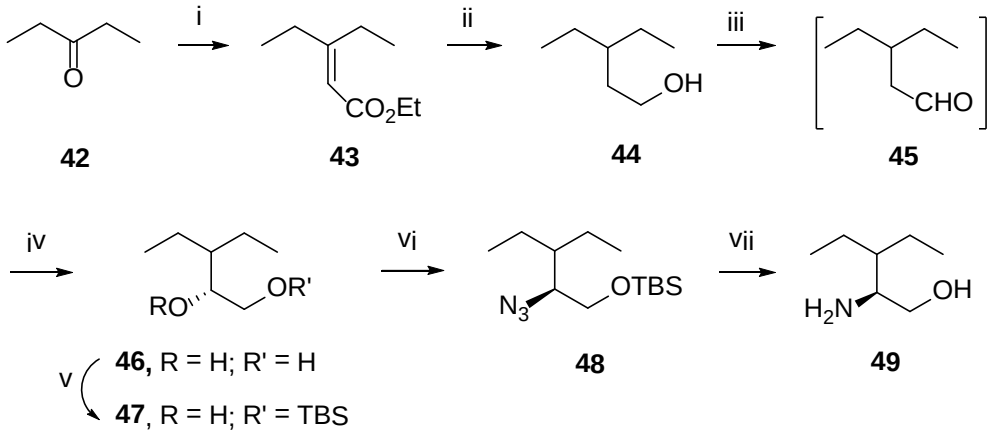
Scheme 8: (a) EDCI·HCl, Et_3N, CH_2Cl_2, 25 °C, 6 h; (b) TBAF, THF, 0 °C, 2 h; (c) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 24 h, 53.3% (over three steps).

SECTION II: A facile enantioselective synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaniol *via* proline catalyzed asymmetric α-aminooxylation and α-amination of aldehyde[11]

(*S*)-*N*-(5-Chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **51** (**7.b.2**), a Notch-1-sparing γ-secretase inhibitor (with EC_{50}= 28 nM), has been found to be effective in the treatment of Alzheimer's desease.[12] Our synthesis of **51** commenced from 3-pentanone **42**, which on Horner-Wardworth-Emmons olefination (triethyl phosphonoacetate, NaH, THF), gave the corresponding α,β-unsaturated ester **43** in 93% yield. Its hydrogenation [10% Pd/C, H_2 (1 atm), MeOH] and reduction with $LiAlH_4$ in THF at 25 °C afforded the saturated primary alcohol **44** in 83% yield (over two steps). Oxidation of primary alcohol **44** with IBX/DMSO mixture gave the key precursor aldehyde **45**, which was immediately subjected to proline-catalyzed α-aminooxylation[10] and α-amination[13] respectively (**Schemes 9** and **10**).

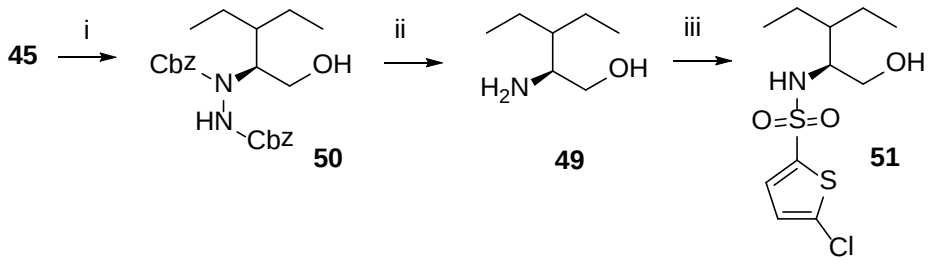
Firstly, the L-proline-catalyzed α-aminooxylation of aldehyde **45** was carried out in a two-step reaction sequence: (i) reaction of aldehyde **45** with nitrosobenzene as the oxygen source in the presence of 20 mol% L-proline followed by its treatment with $NaBH_4$ in MeOH gave the crude α-aminooxy alcohol *in situ* and (ii) subsequent reduction of the crude α-aminooxy alcohol with 10% Pd/C over H_2 (1 atm) furnished chiral diol **46** in 77% yield over two steps. Selective protection of primary hydroxyl group in diol **46** followed by mesylation of the secondary alcohol **47** and displacement of mesylate with sodium azide gave the corresponding azide **48** in 78% yield. The $LiAlH_4$ reduction of TBS azide **48** in THF at 50 °C afforded the key intermediate (*S*)-2-amino-3-ethylpentan-1-ol **49** in 75% yield with 99% ee that was accomplished with the

simultaneous removal of TBS group (**Scheme 9**). Since the number of steps involved in the α-aminooxylation process are relatively too many thereby limiting the overall yield (25.5%), we have explored alternative chemistry that involved a direct α-amination approach.



Scheme 9: (i) triethyl phosphonoacetate, NaH, dry THF, 0-25 ºC, 8 h, 93%; (ii) (a) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 25 ºC; (b) $LiAlH_4$, dry THF, 0-25 ºC, 12 h, 83% (over two steps); (iii) IBX, dry DMSO, 25 ºC, 1 h; (iv) (a) PhNO, L-proline (20 mol %), CH_3CN, -20 ºC, 24 h then MeOH, $NaBH_4$, 10 min; (b) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 25 ºC, 77% (over two steps); (v) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 2 h, 81%; (vi) (a) MsCl, Et_3N, 45 min; (b) NaN_3, dry DMF, 60 ºC, 30 h, 78%; (vii) $LiAlH_4$, dry THF, 50 ºC, 12 h, 75%.

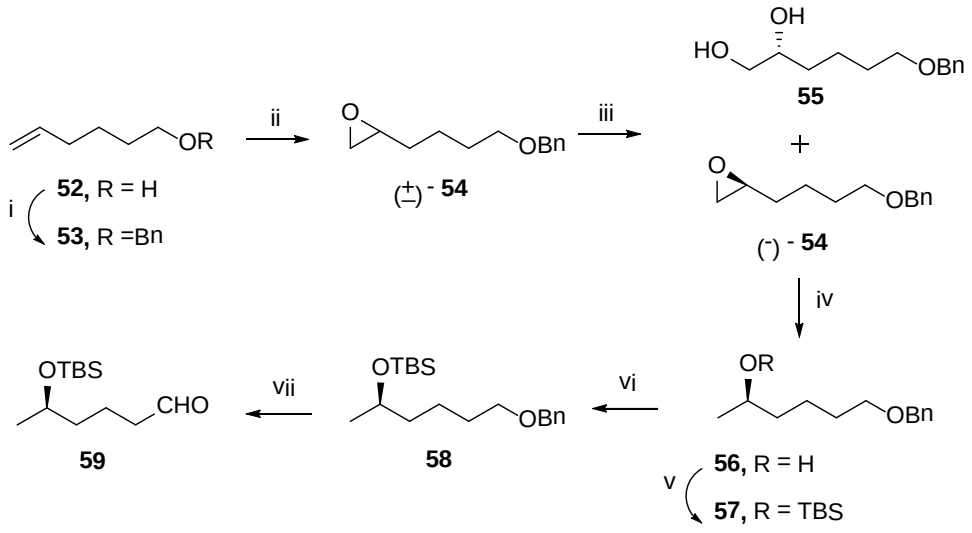
Accordingly, aldehyde **45** was subjected to α-amination with dibenzyl azodicarboxylate in the presence of D-proline (10 mol%) to produce the α-amino aldehyde, which upon *in situ* reduction with $NaBH_4$ afforded the protected amino alcohol **50** in 92% yield and 98% ee (determined by chiral HPLC). The amino alcohol **50** was then hydrogenated [Raney Ni, H_2 (11.8 atm), MeOH, AcOH (5 drops)] to give (*S*)-2-amino-3-ethylpentan-1-ol **49** in 70% yield (**Scheme 10**). Finally, the amino alcohol **49** was condensed with 5-chlorothiophene-2-sulfonyl chloride in the presence of Et_3N to afford the target molecule **51** in 91% yield and 98% ee.



Scheme 10: (i) dibenzyl azodicarboxylate, D-proline (10 mol%), CH_3CN, 0-25 °C, 3 h then MeOH, $NaBH_4$, 92%; (ii) H_2 (11.8 atm), Raney Ni, MeOH, AcOH, 70%; (iii) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, dry CH_2Cl_2, 0-25 °C, 30 min, 91%.

SECTION III: A concise enantioselective synthesis of (+)-decarestrictine L *via* proline-catalyzed sequential α-aminooxylation and Horner-Wadsworth-Emmons olefination[14]

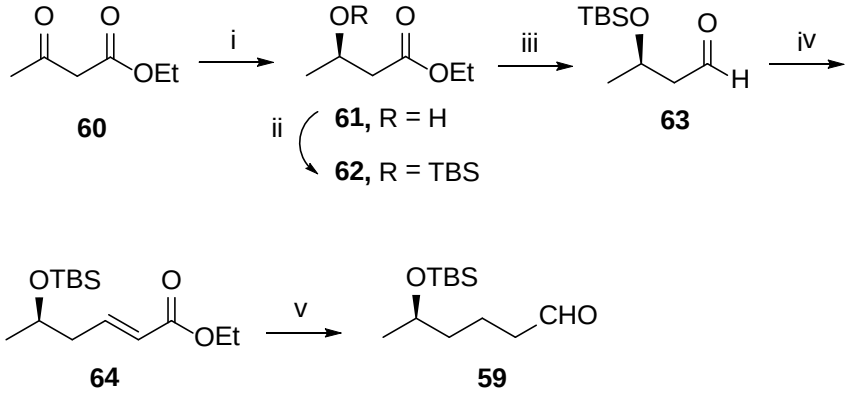
The decarestrictines are secondary metabolites that were isolated from various *Penicillium* strains.[15] In this section we have described the synthesis of (+)-decarestrictine L. **Scheme 11** presents the synthesis of intermediate aldehyde **59** which commences with 5-hexene-1-ol **52**, protected as its benzyl ether **53**. The olefinic function in **53** was epoxidized smoothly {*m*CPBA, $CHCl_3$} to give racemic epoxide **(±)-54**, which was subjected to Jacobsen's HKR {(*S,S*)-cobalt salen, H_2O}[17] to give the corresponding enantiomerically pure epoxide **(-)-54** in 43% yield and 99% ee. The chiral epoxide **(-)-54**, was then subjected to regioselective reductive ring opening with $LiAlH_4$ in THF at 0 °C to afford the secondary alcohol **56**. The alcohol **56** was protected as its TBS ether and the benzyl ether **57** was subsequently deprotected under hydrogenolysis condition to give the primary alcohol **58** in 97% yield. The oxidation of alcohol **58** (IBX, DMSO) produced the key intermediate aldehyde **59** in 98% yield. Since the overall yield for intermediate aldehyde **59** that could be realized in HKR route was considerably lower (30%), we envisioned an alternate route for its synthesis (**Scheme 11**).



Scheme 11: (i) BnBr, NaH, THF, 0-25 °C, 6 h, 97%; (ii) *m*CPBA, $CHCl_3$, 25 °C, 6 h, 85%; (iii) (*S*,*S*)-(–)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-

cyclohexanediaminocobalt (0.5 mol %), H_2O (0.55 equiv), 24 h, 43%, 99% ee; (iv) $LiAlH_4$, THF, 0 ºC, 30 min, 92%, 99% ee; (v) TBSCl, imid., CH_2Cl_2, 0-25 ºC, 2 h, 98%; (vi) H_2 (1 atm), 10% Pd/C, Et_3N, MeOH, 12 h, 25 ºC, 97%; (vii) IBX, DMSO, 25 ºC 2 h, 98%.

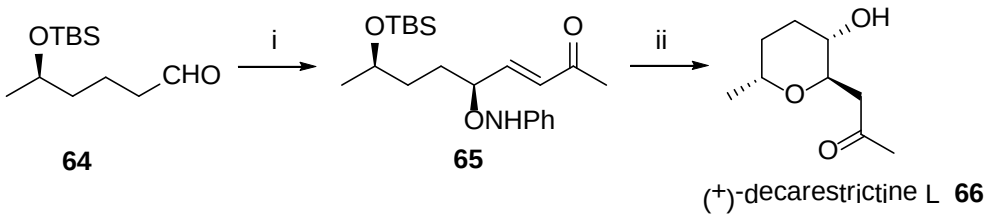
Our second approach towards the synthesis of intermediate aldehyde **59** involves Ru-catalyzed asymmetric reduction[18] {[(*R*)-Ru(BINAP)Cl_2]$_2$·NEt_3, 2N HCl, H_2 (100 psi)} of ethylacetoacetate **60** that produced (*R*)-ethyl 3-hydroxybutyrate **61** in 95% yield with high enantiopurity (98% ee, Mosher ester). After protecting as its TBS ether, the resulting ester **62** was subjected to selective reduction with DIBAL-H at -78 °C that afforded the corresponding aldehyde **63** in 85% yield which was immediately reacted with stabilized Wittig salt to give α,β-unsaturated ester **64** in 93% yield. Exposure of the ester **64** to 10% Pd/C under H_2 (1 atm.) followed by its selective reduction with DIBAL-H at -78 ^oC furnished aldehyde **59** in 60% overall yield **(Scheme 12**).



Scheme 12: (i) [(R)-Ru(BINAP)Cl_2]$_2$· NEt_3 (0.1 mol%), 2N HCl (0.1 mol%), MeOH, H_2(100 psig), 50 ºC, 16 h, 95%, 98% ee; (ii) TBSCl, imid., CH_2Cl_2, 0-25 ºC, 2 h, 97%; (iii) DIBAL-H, toluene, -78 ºC, 1 h, 85%; (iv) Ph_3P=$CHCO_2Et$, THF, 25 ºC, 12 h, 93%; (v) a) H_2 (1 atm), 10% Pd/C,Et_3N, MeOH, 12 h; b) DIBAL-H, toluene, -78 ºC, 1 h, 82% (over two steps).

With the intermediate aldehyde **59** made available, we carried out the sequential aminoxylation-olefination on aldehyde **59** catalyzed by D-proline at -20 ^oC, that resulted in the formation of the precursor aminooxy olefinic ketone **65** in 60% yield (**Scheme 13**). The removal of anilinoxy group in **65,** {$Cu(OAc)_2$, EtOH}, followed by desilylation of

the crude product induced an instantaneous intramolecular 1,4-conjugate addition to afford (+)-decarestrictine L **66** in 98% ee and with de > 99%.



Scheme 13: (i) PhNO, D-proline (20 mol %), -20 ºC, 24 h then diethyl(2-oxopropyl)phosphonate, Cs_2CO_3, -20-0 ºC, 2 h, 60%; (ii) (a) $Cu(OAc)_2$, EtOH, 25 ºC, 6 h; (b) TBAF, THF, 25 ºC, 6 h, 60% (over two steps).

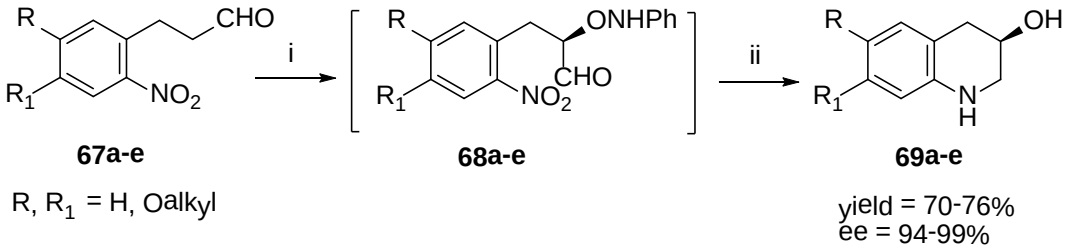
Chapter III

A New Concise Method for the Synthesis of Chiral Tetrahydroquinolin-3-ols, (-)-Sumanirole (PNU 95666-E) and 1-((*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl)propan-1-one, (*S*)-903

SECTION I: Organocatalytic sequential α-aminooxylation/reductive cyclization of *o*-nitrohydrocinnamaldehydes: A high yield synthesis of chiral tetrahydroquinolin-3-ols

The 1,2,3,4-tetrahydroquinoline (THQ) is a very common structural motiff found in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[19] Only a few methods exist in the literature for the asymmetric synthesis of tetrahydroquinilin-3-ols, most of which are based on chiral pool resources. In this regard, an organocatalytic protocol that provides for the efficient synthesis of chiral 3-substituted THQs is highly desirable.[20]

In this section, we wish to disclose, for the first time, a sequential protocol involving α-aminooxylation of *o*-nitrohydrocinnamaldehydes **67a-e** and Pd-catalyzed intramolecular reductive cyclization that provides easy access to chiral 3-hydroxy THQs **69a-e** in high yields (**Scheme 14**).



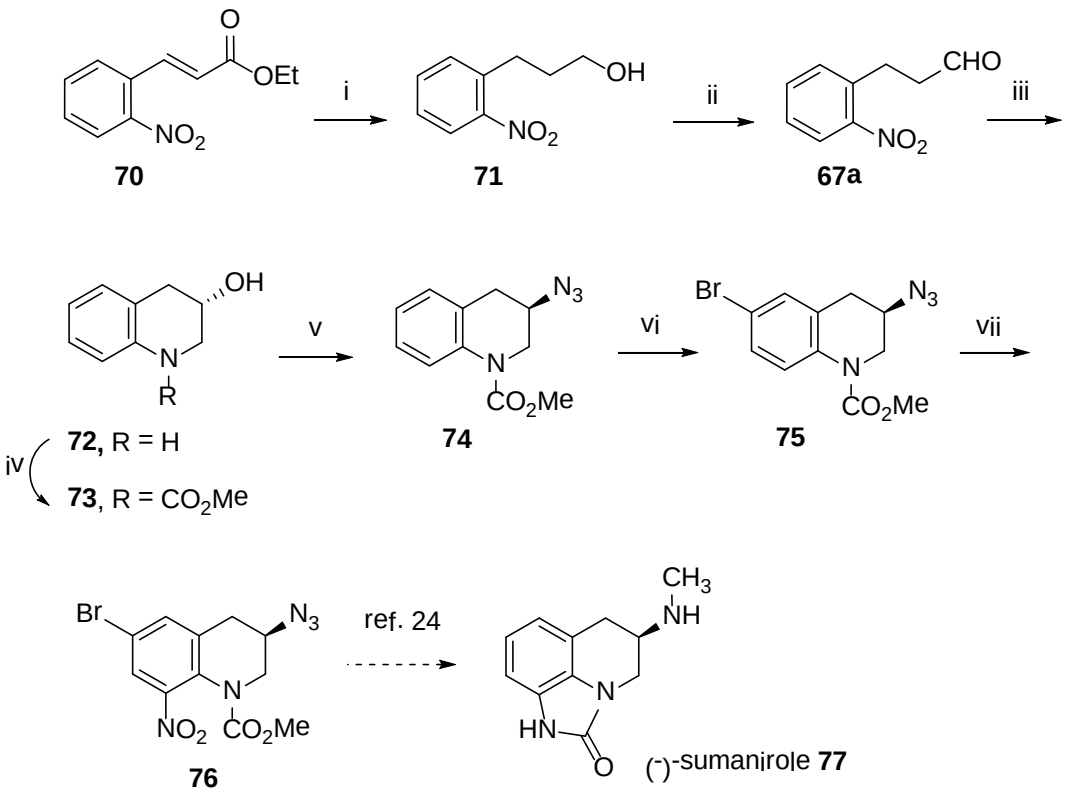
Scheme 14: (i) L-proline (20 mol%), PhNO (1 equiv), DMSO, 15 min; (ii) 10% Pd/C, H_2 (1 atm), 25 ^oC, 6 h.

When subjected to L-proline catalyzed α-aminooxylation with 1 equiv of PhNO followed by Pd-catalyzed reductive cyclization several *o*-nitrohydrocinnamaldehydes **67a-e** gave the corresponding (*R*)-3-hydroxytetrahydroquinoline **69a-e** (70-76%) derivatives respectively with excellent enantioselectivities (upto 99% ee).

SECTION II: Asymmetric synthesis of (-)-Sumanirole (PNU-95666-E) and 1-[(*S*)-3-(Dimethyl-amino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]propanone [(*S*)-903]

Among the various applications of this sequential protocol, an enantioselective synthesis of (-)-sumanirole **77** and (*S*)-903 (**81**) seemed attractive to us due to their pharmacological importance.[21,22]

A) Synthesis of (-)-sumanirole 77: (-)-Sumanirole **77** (PNU-95666E) is a selective and high affinity agonist at the dopamine D_2 receptor subtype and has proven as a potential agent for the treatment of Parkinson's disease and restless leg syndrome.[21] For the synthesis of (-)-sumanirole **77**, intermediate **72** was prepared readily in three steps by following the present protocol starting from α,β-unsaturated ester **70**: (i) Co-catalyzed chemoselective reduction of **70** gave hydrocinnamyl alcohol **71** ($CoCl_2.6H_2O$, iPr_2NH, $NaBH_4$, 85%); (ii) PCC mediated oxidation of **71** smoothly afforded **67a** in 85%; (iii) sequential protocol involving D-proline catalyzed α-aminooxylation of o-nitrohydrocinnamaldehyde **67a** followed by Pd/C catalyzed reductive cyclization under H_2 (1 atm) gave the corresponding annulated (*3S*)-hydroxy THQ **72**. Amine functionality in **72** was then converted to its carbamate **73** ($ClCO_2Me$, K_2CO_3, 98%). **73** was readily transformed to the corresponding azide **74** in two steps: mesylation (MsCl, Et_3N) and treatment of mesylate with azide anion (NaN_3, DMF, 93%). Regioselective nitration of **74** at C-8 position was carried out successfully in two steps: (i) bromination (Br_2, AcOH, 95%) of azido carbamate **74**; (ii) subsequent regiospecific nitration of **75** ($NaNO_3$, TFA, 95%) gave the key intermediate **76** with an overall yield of 42.2% and 96% ee (**Scheme 15**).[23]

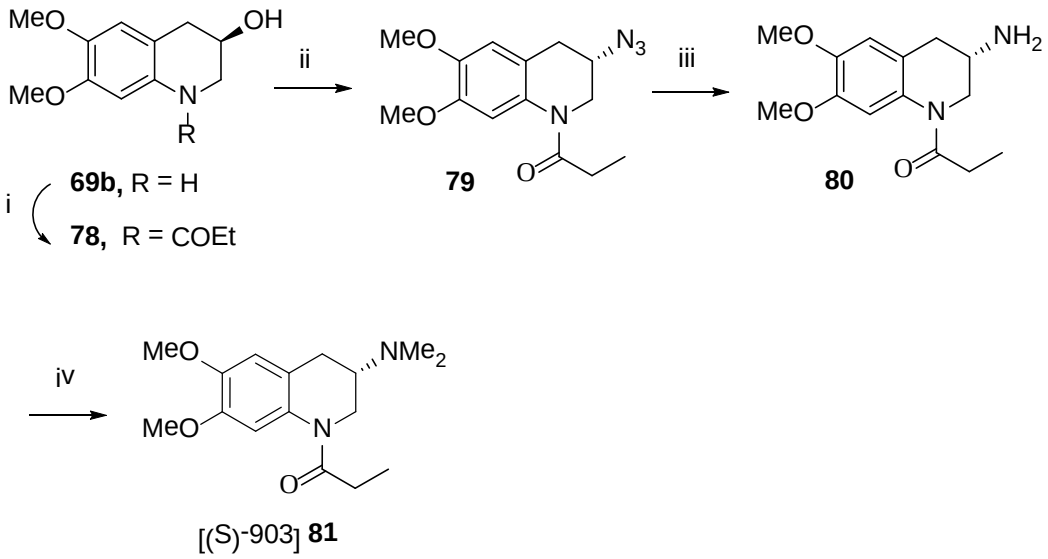


Scheme 15: (i) $CoCl_2 \cdot 6H_2O$, $^{i}Pr_2NH$, $NaBH_4$, EtOH, 25-60 ^{o}C, 85%; (ii) PCC, CH_2Cl_2, 25 ^{o}C, 6 h, 85%; (iii) (a) PhNO, D-proline, DMSO, 25 °C, 15 min; (b) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 6 h, 71%; (iv) $ClCO_2Et$, K_2CO_3, CH_2Cl_2 / H_2O (4:1), 0-25 °C, 6 h, 98% ; (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min; (b) NaN_3, DMF, 80 °C, 4 h, 93% (over two steps); (vi) Br_2, AcOH, NaOAc, 25 °C, 1h, 95%; (vii) $NaNO_3$, TFA, 25 °C, 30 min, 95%.

B) Synthesis of (S)-903:

1-[(*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propanone **81** [(*S*)-903] has recently been identified as a potentially interesting positive inotropic agent.[22] Asymmetric synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one **81**, is described in this section.

Thus, the synthesis of **81** commenced with THQ **69b** (**Scheme 16**), which was prepared in 98% ee using L-proline as catalyst and PhNO as oxygen source by following the optimized condition described in **Section I**. Tetrahydroquinolinol **69b,** was treated with propionic anhydride to give amido alcohol **78** in 98% yield. Alcohol **78** on mesylation (MsCl, Et_3N in CH_2Cl_2) followed by its displacement with azide ion (NaN_3 in DMF) gave azide **79** in 94% yield**.** Finally, azide **79** was reduced to amine [H_2 (1 atm), 10% Pd/C]. The *N*, *N'*- dimethylation of amine **80** was achieved by treating it with formic acid and formaldehyde solution under reflux condition to afford **81** in 71.6% yield.



Scheme 16: (i) $(EtCO)_2O$, K_2CO_3, CH_2Cl_2/H_2O (4:1), 25 °C, 98%; (ii) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min; (b) NaN_3, DMF, 80 °C, 12 h, 94% (over two steps); (iii) H_2 (1atm), 10% Pd/C, MeOH, 25 °C, 12 h, 96%; (iv) HCHO, HCO_2H, 80 °C, 3 h, 91%.

CHAPTER IV

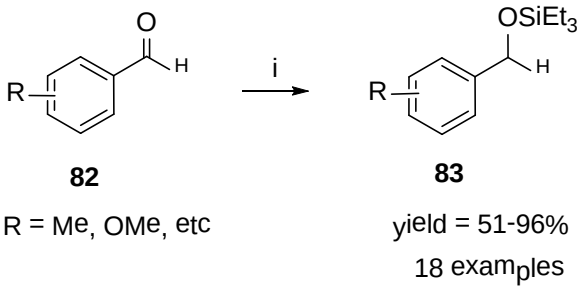
Pd-catalyzed Hydrosilylation of Aryl Aldehydes and Chemoselective Reduction of aryl α,β-Unsaturated Carbonyls[24]

Chapter **IV** is divided into two sections. **Section 1** deals with Pd-catalyzed hydrosilylation of aryl aldehydes using triethylsilane while **Section 2** describes an chemoselective reduction of aryl α,β-Unsaturated Carbonyls.

Section: 1 Palladium catalyzed hydrosilylation of aryl aldehydes with triethylsilane

In recent years hydrosilylation of various organic carbonyl compounds has made considerable progress and became a major tool of synthetic organic chemistry and organosilicon chemistry as well as providing efficient and versatile access to new organo silicon compounds.[25] There are many methods available in the literature for hydrosilylation of carbonyl compounds using a variety of metal catalysts and hydrosilanes. Moreover, metals such as palladium have not been studied extensively for the hydrosilylation of aldehydes.[26] In this section, we describe an efficient and selective method for the hydrosilylation of various aryl aldehydes catalyzed by palladium using triethylsilane as hydride source. We found that palladium catalysts were more effective for hydrosilylation of aldehydes **82** in DMF at room temperature using triethylsilane as a

hydride source to produce silyl ethers **83** in 51-96% yield **(Scheme 17**). All the palladium catalysts gave excellent yield of hydrosilylated products **83**. The maximum yield of silylether obtained was with $Pd(OAc)_2$ (98%) whereas $Pd(dba)_2$ (60%) gave the lowest yield.



Scheme 17: aryl aldehyde (1 mmol), 10% $Pd(OAc)_2$ (0.5 mol%), Et_3SiH (1.2 mmol), DMF (2 ml), 25 ^oC, 1 h.

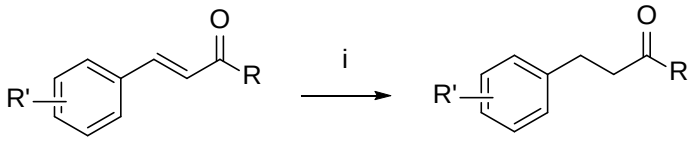
A noteworthy feature of this protocol is that when the reaction was carried out in DMF-water (4:1) solvent system, the corresponding alcohols were produced in high yields. Thus, both hydrosilylation and deprotection of the silyl ether were achieved in a single step by using a simple modification of solvent systems.

Section II

Pd-catalyzed chemoselective reduction of aryl α,β-unsaturated carbonyls with triethylsilane

The hydrogenation of α,β-unsaturated carbonyl compounds is a useful but challenging transformation. As both 1,2- and 1,4-conjugate reductions readily occur, low selectivity for either of the two pathways is common. Further, catalytic hydrogenations of α,β-unsaturated carbonyls are possible, yet the chemoselectivity is often found to be low.[27] Further, additional functional groups that are sensitive to hydrogenation conditions such as the benzyloxy, nitro, and nitrile groups are usually not tolerated.[28] Undoubtedly, an ecofriendly, safe and economically viable protocol would be a welcome addition to the repertoire of existing methodologies.

In this section we describe a efficient chemoselective method for the 1,4-reduction of aryl α,β-unsaturated carbonyls **84**. The best yields of saturated product **85** was obtained with 1 mol% $Pd(OAc)_2$ and 2 equiv of Et_3SiH in DMF as Solvent (yield upto 89%) (**Scheme 18**).



84 **85**

R = H, alkyl, aryl, -OEt yield = 74-89%

R' = Me, OMe, etc 15 examples

Scheme 18: (i) aryl α,β-unsaturated carbonyls (1 mmol), $Pd(OAc)_2$ (1 mol%) Et_3SiH (2 mmol), DMF (2 mL), 25 °C, 4h

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Chapter I

Total Synthesis of (-)-Oseltamivir Free Base, (-)-Methyl 3-epi-shikimate and 3-epi-Jaspine B

"Synthesis of the *anti*-influenza agent (-)-oseltamivir free base and (-)-methyl 3-*epi*-shikimate" Varun Rawat, Soumen Dey, Arumugam Sudalai *Org. Biomol. Chem.*, **2012**, *10*, 3988. {**This work is highlighted in Synfacts 2012, 8, 0001; DOI: 10.1055/s-0032-1316977**}

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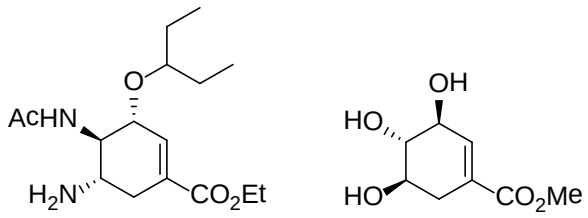
Section I

Synthesis of the *anti*-influenza agent (-)-Oseltamivir free base and (-)-Methyl 3-*epi*-shikimate

1.1.1 Introduction and Pharmacology

Oseltamivir phosphate, marketed as Tamiflu (**1**·H_3PO_4, **Figure 1**) is an orally effective neuraminidase inhibitor,[1] widely used for the treatment and prevention of human influenza (H1N1) and avian influenza (H5N1) infections.[2] The Neuraminidase inhibitors interact with a unique target in the viral replicative cycle, which is the release of the progeny virus particles from the cells.[3] Release of the virus particles from the cells requires the action of the virus-associated neuraminidase which cleaves off the terminal sialic acid (linked with galactose in the influenza H1N1 and H5N1 receptor). This cleavage is needed for the virus particles to be released from the infected cells and allows the virus to spread to other cells. Neuraminidase inhibitors prevent this release and thus ‘‘trap’’ the newly formed virus particles at the cell surface, thereby inhibiting further virus spread.[4] The *anti*-influenza drug **1**·H_3PO_4 was initially discovered by Gilead Sciences and subsequently licensed to Roche for production. Roche’s manufacturing process of tamiflu employs (-)-shikimic acid. Shikimic acid and several of its epimers (e.g. methyl 3-*epi*-shikimate **2**) form the constituents of various natural products of biological importance and their syntheses have thus attracted considerable attention.[5]



1 **2**

Figure 1: Structures of oseltamivir (**1**) and methyl 3-*epi*-shikimate (**2**)

1.1.2 Review of Literature

Various syntheses of (-)-oseltamivir **1** are known in literature by several routes, which include chiral pool and asymmetric induction. Since the syntheses have been excessively reviewed before[6] only the latest developments will be documented in the following section.

Table 1 summarizes some of the key approaches in the synthesis of (-)-oseltamivir **1**. The academic or industrial group, the year of publication, starting material(s), number of steps and overall yield of the synthetic route are highlighted.[6a,b]

Table 1: Summary of synthetic approaches to (-)-oseltamivir **1**

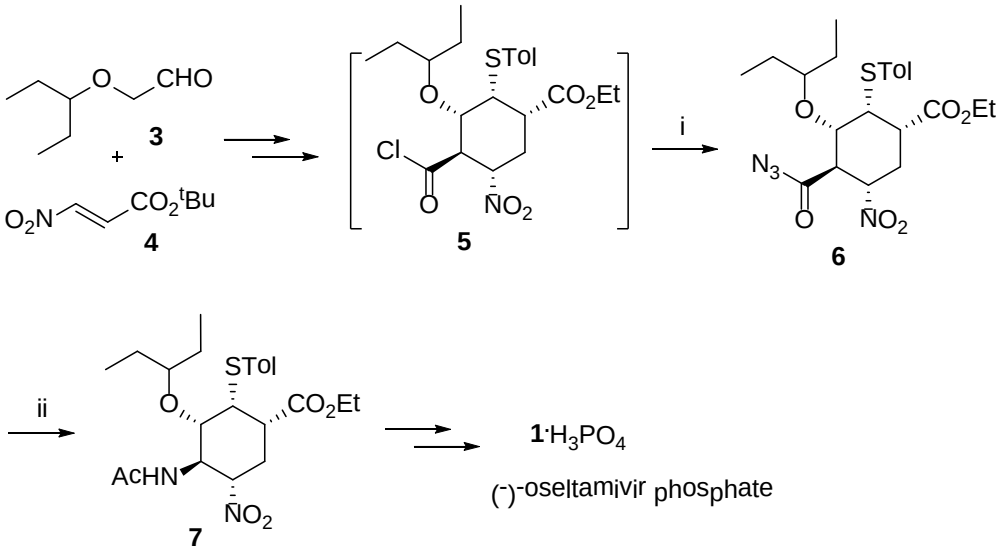
Sources	Starting material	Steps	Overall yield (%)
Gilead Sciences (1997)	(-)-shikimic acid	14	15
F. Hoffmann-La Roche Ltd. (1999)	(-)-quinic acid	8	35
F. Hoffmann-La Roche Ltd. (2004)	furan and ethyl acrylate	9	3.2
F. Hoffmann-La Roche Ltd. (2004)	1,6-dimethoxy phenol	14	28
Corey (2006)	1,3-butadiene and 2,2,2-trifluoroethyl acrylate	11	27
Shibasaki (2006)	*N*-3,5-dinitrobenzoylaziridine	17	1.4
Yao (2006)	L-serine	25	8
Shibasaki (2007)	*N*-3,5-dinitrobenzoylaziridine	20	16
Shibasaki (2007)	tert-butyl (1S,6S)-6-azidocyclohex-3-enylcarbamate	12	7.4
Fukuyama (2007)	pyridine	14	5.6
Fang (2007)	D-xylose	16	14
Kann (2007)	ethyl ester and cyclohexadienoic acid	14	5

Okamura (2008)	*N*-nosyl-3-hydroxy-2-pyridone and ethyl acrylate	7	11
Shibasaki (2009)	1-(trimethylsiloxy)-1,3-butadiene and dimethyl fumarate	12	16
Hayashi (2009)	(E)-*tert*-butyl 3-nitroacrylate and 2-(pentan-3-yloxy)acetaldehyde	9	57
Shi (2009)	(-)-shikimic acid	13	40
Shi (2009)	(-)-shikimic acid	9	47
Mandai (2009)	D-mannitol	18	7.5
Mandai (2009)	L-methionine	18	8
Hudlicky (2010)	ethyl benzoate	13	7
Liu (2010)	D-glucal	22	2.6
Chai (2010)	D-ribose	12	9
Kongkathip (2010)	D-ribose	14	5
Ko (2010)	D-mannitol	16	7
Ma (2010)	(E)-N-(2-nitrovinyl)acetamide and 2-(pentan-3-yloxy) -acetaldehyde	5	46
Lu (2010)	diethyl D-tartrate	11	21
Kamimura (2010)	tert-butyl 1H-pyrrole-1-carboxylate and ethyl 3-bromopropiolate	16	2
Raghavan (2011)	(R)-3-Cyclohexene carboxylic acid	16	4.3
Trost (2011)	6-Oxabicyclo[3.2.1]oct-3-en-7-one	8	30
Hayashi (2011)	1,2-epoxycyclohex-4-ene	21	0.05

Hayashi's approach (2011)[7]

Hayashi *et al.* have used a microflow reaction of the Curtius rearrangement as a key step. In a

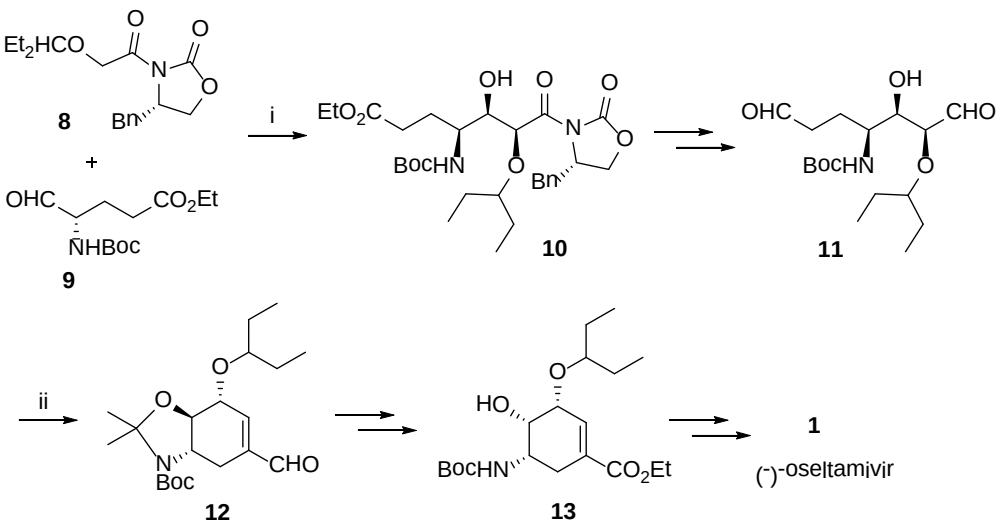
one-pot reaction sequence starting from aldehdye **3** and nitroalkene **4** functionalized cyclohexane **5** was prepared. By using trimethylsilyl azide as an azide source, **5** was converted to **6** followed by Curtius rearrangement and *in situ* trapping of the generated isocyanate with a nucleophile to give acetamide **7**. Purification of **7** by recystallization followed by another one-pot reaction sequence furnished tamiflu. This synthesis requires nine reactions, a total of three separate one-pot operations, and one recrystalization. The total yield of (-)-oseltamivir phosphate from nitroalkene **4** is 57% (**Scheme 1**).



Scheme 1: (i) $TMSN_3$, py, toluene, 20 min; (ii) AcOH, Ac_2O, 25 ^oC.

Saicic's approach (2011)[8]

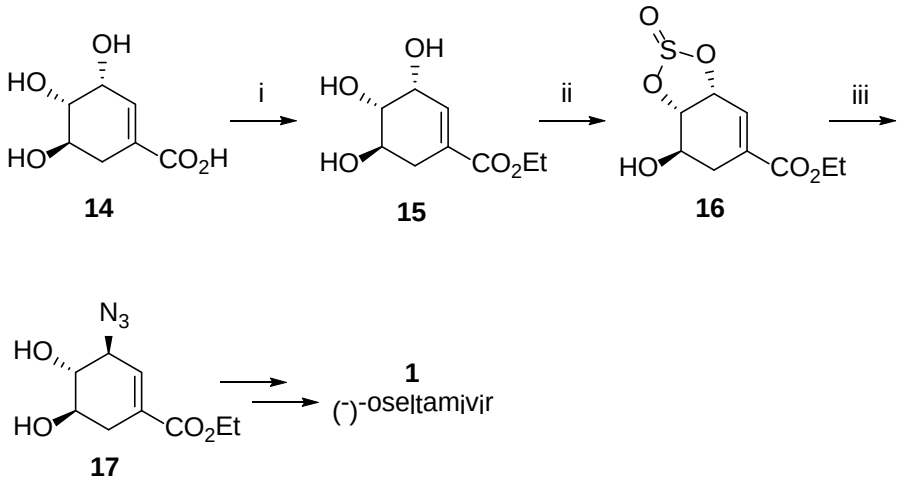
In Saicic's approach, formation of all carbon–carbon bonds and stereocenters, was achieved using two aldol reactions: three stereocenters in the acyclic intermediate **10** were installed in the reaction of the Evans oxazolidinone derived boron enolate of **8** with glutaraldehyde **9**, while the cyclization was achieved *via* enamine catalyzed intramolecular condensation of **11**. Enal **12** was then converted to known intermediate **13**, thus constituting a formal synthesis of oseltamivir free base **1** (**Scheme 2**).



Scheme 2: (i) (a) n-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 ^oC, 30 min then **10**; (b) H_2O_2, MeOH, 45%; (ii) $Bn_2NH{\cdot}TFA$, toluene, 25 ^oC, 3 h.

Lu's approach (2011)[9]

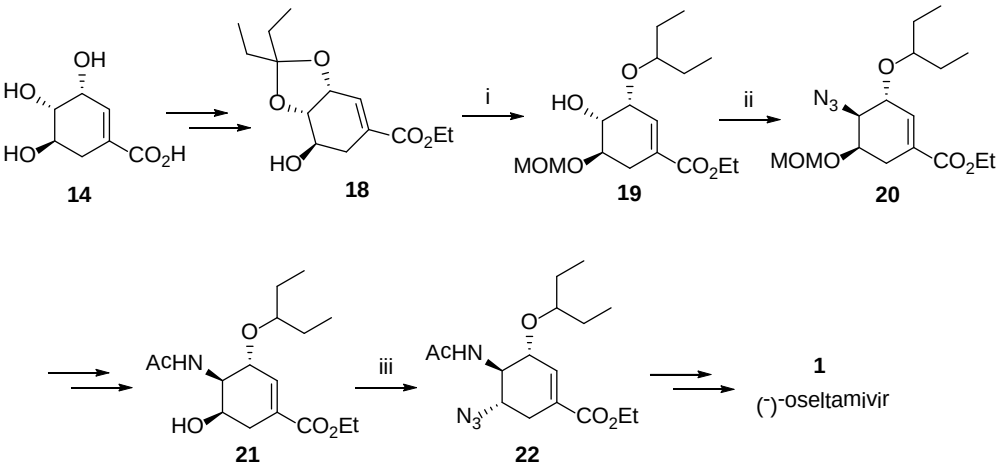
Lu *et al.* have described asymmetric synthesis of oseltamivir **1** from (-)-shikimic acid **14**. Esterification of **14** gave ethyl shikimate **15**, which was then converted into cyclic sulfite **16**. The characteristic step of the synthesis is the regio- and stereospecific nucleophilic substitution with sodium azide at the allylic (C-3) position of 3,4-cyclic sulfite **16**. Target compound **1** was obtained from **17** in 39% overall yield from a six-step reaction sequence (**Scheme 3**).



Scheme 3: (i) EtOH, $SOCl_2$, reflux, 3 h, 97%; (ii) $SOCl_2$ (2.5 equiv), Et_3N, 5 ^oC, 2h then 25 ^oC for 12 h, 98%; (iii) NaN_3, EtOH, reflux, 12 h, 93%.

Park's approach (2012)[10]

Park *et al.* have reported the synthesis of oseltamivir **1** in 9 steps with a 27% overall yield from commercially available (-)-shikimic acid **14**. Selective ring opening reaction of ketal **18** and azide Mitsunobu reaction for facile replacement of a hydroxyl group by the N_3 group at the C-3 position of **19** and at the C-4 position of alcohol **21** successfully served as the key steps giving cyclic azides **20** and **22** respectively (**Scheme 4**).



Scheme 4: (i) Et_3SiH, $TiCl_4$, CH_2Cl_2, 3 h, 70%; (ii) PPh_3, DEAD, HN_3, THF, 82%; (iii) PPh_3, DEAD, HN_3, THF, 84%.

1.1.3 Present Work

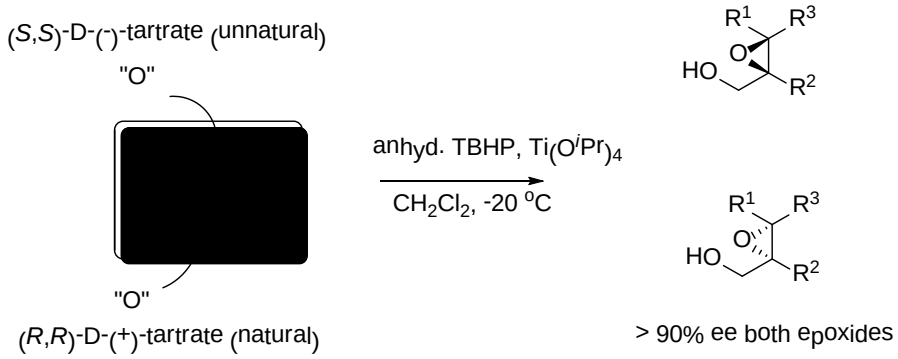
1.1.3.1 Objective

The present commercial manufacturing process of Tamiflu **1**·H_3PO_4 employs (-)-shikimic acid **14**,[11] a natural product isolated from the Chinese star anise plant, as the raw material. The production of (-)-shikimic acid **14** with consistent purity, however, requires a lot of time and is costly. Therefore, there is an urgent demand for the development of alternative practical synthesis of Tamiflu **1**·H_3PO_4, starting from readily available and less expensive starting materials. This section describes an efficient synthesis of (-)-oseltamivir free base **1** and (-)-methyl 3-*epi*-shikimate **2**, a unnatural methyl ester of shikimic acid **14**, starting from *cis*-2-

butene-1,4-diol **27** by employing Sharpless asymmetric epoxidation (AE), diastereoselective Barbier allylation and Ring Closing Metathesis (RCM) as the key reactions.

1.1.3.2 Sharpless asymmetric epoxidation (AE)[12]

Asymmetric epoxidation of allylic alcohols is one of the leading areas of investigation in synthetic organic chemistry, mainly due to the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents. The Sharpless epoxidation is a popular laboratory and industrial process due to its both enantioselective and catalytic nature. The reaction mixture includes a titanium tetraalkoxide, a chiral tartrate diester, an allylic alcohol substrate, and an alkyl hydroperoxide as the oxidant. The consistency of the reaction is remarkable, excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. In addition to being able to asymmetrically oxidize prochiral substrates to products of predictable absolute configuration, the reaction is extremely sensitive to pre-existing chirality in selected positions of the allylic alcohols. For example, kinetic resolution of racemic secondary allylic alcohols is very efficient since it can be used for generating chiral allylic alcohols as well as *anti*-epoxyalcohols in high enantiomeric excess. Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product (**Scheme 5**). Since its discovery in 1980, the Sharpless epoxidation of allylic alcohols has become a benchmark classic method in asymmetric synthesis. One factor that simplifies the standard epoxidation reaction is that the active chiral catalyst is generated *in situ*, which means that the pre-preparation of the active catalyst is not required. It is believed that the species containing equal moles of Ti and tartrate is the most active catalyst. It promotes the reaction much faster than Ti(IV) tetraalkoxide alone and exhibits selective ligand-accelerated reaction.[13]



Scheme 5: The Sharpless epoxidation reaction

Sharpless suggested that epoxidation was catalyzed by a single Ti center in a dimeric complex with a C_2 symmetric axis (**Figure 2**).[14]

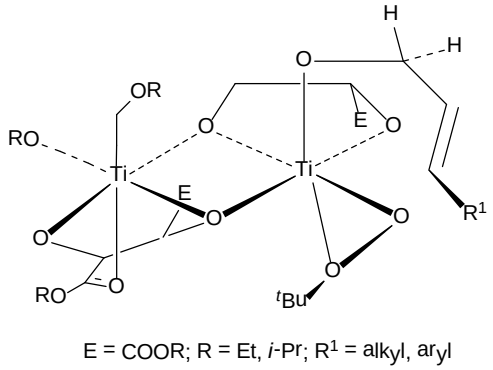
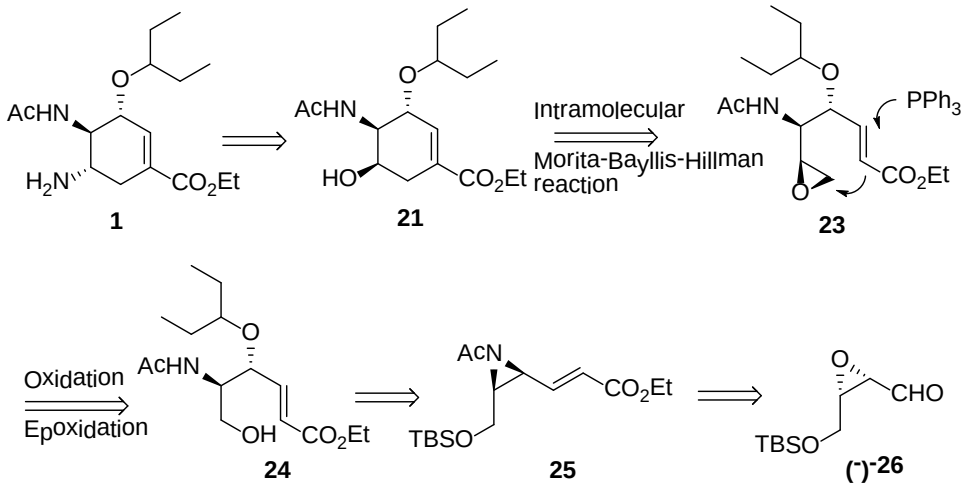


Figure 2: Structure of dinuclear Ti-tartrate complex

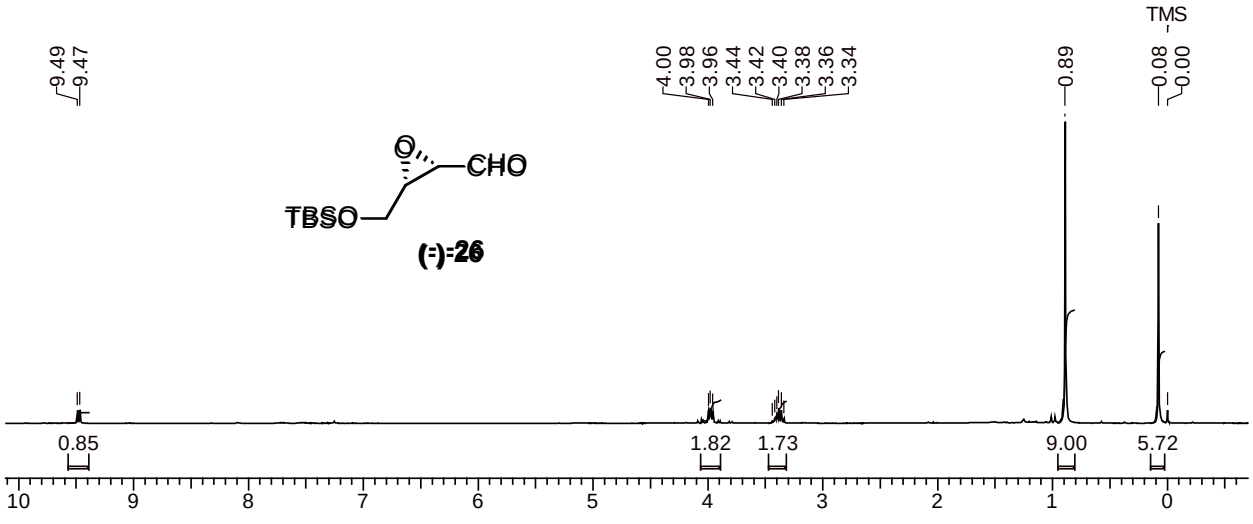
1.1.3.3 Results and Discussion

Our initial retrosynthetic scheme for the construction of functionalized cyclohexene core **21**, the key intermediate in the synthesis of oseltamivir **1**, is depicted in **Scheme 6**. It was envisioned that cyclic alcohol **21** could be obtained *via* an intramolecular Morita-Bayllis-Hillman cyclization of epoxide **23**.[15] The epoxide **23** could in turn be obtained by a sequence of reactions such as oxidation, olefination and diastereoselective epoxidation of alcohol **24**. Ester **24** was envisaged from acetamidate **25** by the regioselective aziridine opening with 3-pentanol. Protected aziridine **25** could in turn be obtained from epoxy aldehyde **(-)-26**.



Scheme 6: Initial attempt towards the synthesis of oseltamivir **1**

To start with, epoxy aldehyde **(-)-26** was prepared in 64.5% yield from commercially available *cis*-2-butene-1,4-diol **27** in three steps: (i) monosilylation of diol **27** (TBSCl, imid., 73%); (ii) AE of allylic alcohol **28** [$Ti(OiPr)_4$, (-)-DET, anhydrous TBHP, 93%]; (iii) oxidation of epoxy alcohol **(+)-29** (TEMPO, BAIB, 95%) (**Scheme 7**). The ^{1}H NMR spectrum of **(-)-26** showed a characteristic signal for aldehydic proton at δ 9.47. Other signals at δ 3.34-3.44 (m, 2H) and 3.96-4.00 (m, 2H) were due to methine (-**CH**-O-**CH**-) and methylene (-**CH_2**-OTBS) protons. Its ^{13}C NMR spectrum showed a typical signal at δ 197.2 due to aldehyde carbon while other carbon signals at δ 57.3, 59.6 and 59.7 were indicative of carbons attached to oxygen atom (**Figure 3**).



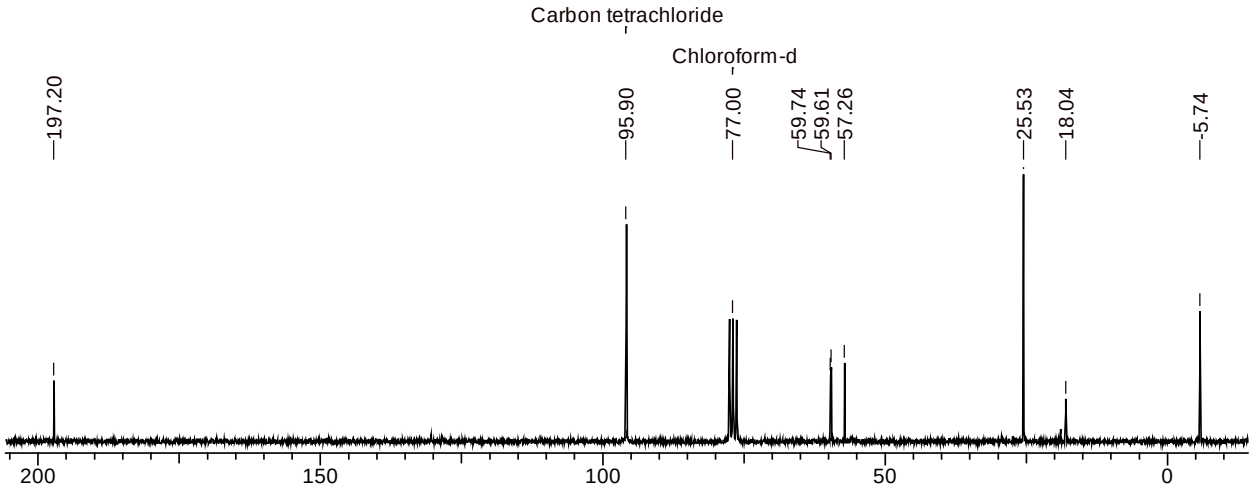
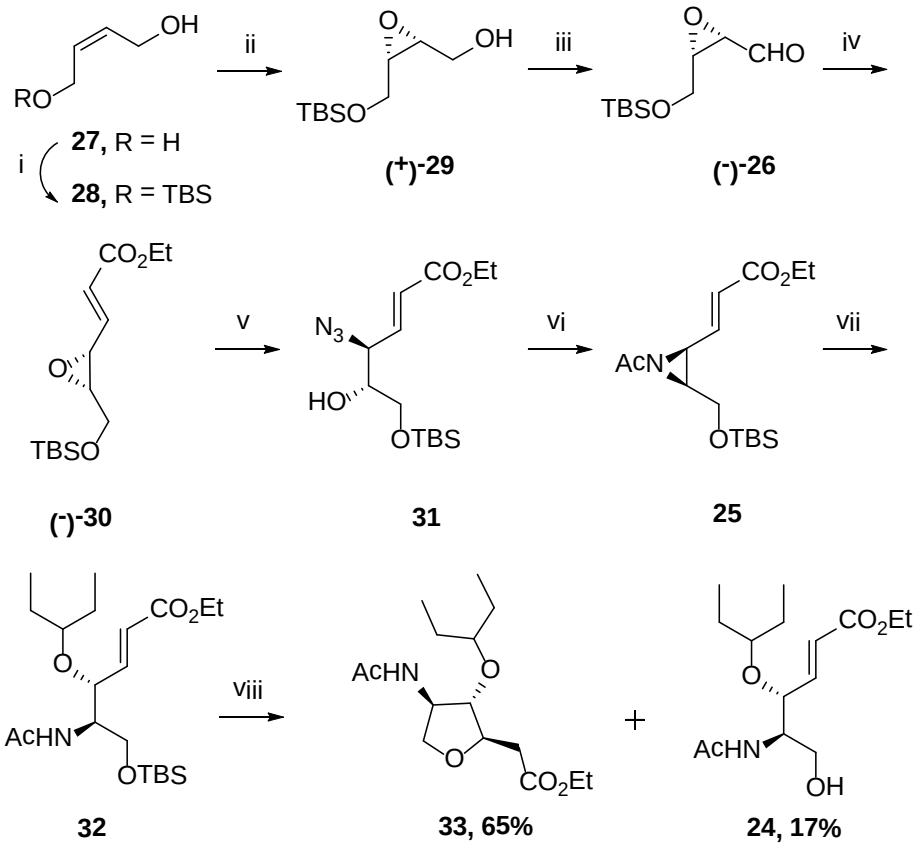


Figure 3: ^{1}H and ^{13}C NMR spectra of epoxy aldehyde **(-)-26**



Scheme 7: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (-)-DET, $Ti(O^iPr)_4$, anhydrous TBHP (5-6 M in decane), 4 Å molecular sieves, dry CH_2Cl_2, -10 ºC, 12 h, 93%; (iii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (iv) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, 0-25 ºC, 2 h, 92%; (v) NaN_3, NH_4Cl, DMF/EtOH/H_2O (4:4:1), 25 ºC, 10 h, 85%; (vi) (a) Ph_3P, PhMe, reflux, 3 h; (b) Ac_2O, DMAP, Et_3N, dry CH_2Cl_2, 0-25 ºC, 45 min, 81% (over two steps); (vii) 3-pentanol, $BF_3{\cdot}OEt_2$, -10 ºC, 30 min, 75%; (viii) TBAF, THF, 0 ºC, 2 h.

Wittig olefination of **(-)-26** with $Ph_3P{=}CHCO_2Et$ gave the α,β-unsaturated epoxy ester **(-)-30** in 92% yield. Regioselective ring opening of **(-)-30** at the allylic position with azide ion in presence of NH_4Cl was accomplished in 85% yield to give azido alcohol **31**. Staudinger reaction (Ph_3P, toluene) followed by *N*-acetylation (Ac_2O, DMAP, Et_3N) afforded protected aziridine **25**; $[\alpha]_D^{25}$ +60 (*c* 2.0, $CHCl_3$). The ^1H NMR spectrum of **25** showed multiplets at δ 2.82-2.91 and 3.15-3.22 for methine protons attached to aziridine nitrogen. Its ^{13}C NMR spectrum showed typical carbon signals at δ 39.8 and 44.2 corresponding to methine carbons of the aziridine ring (**Figure 4**).

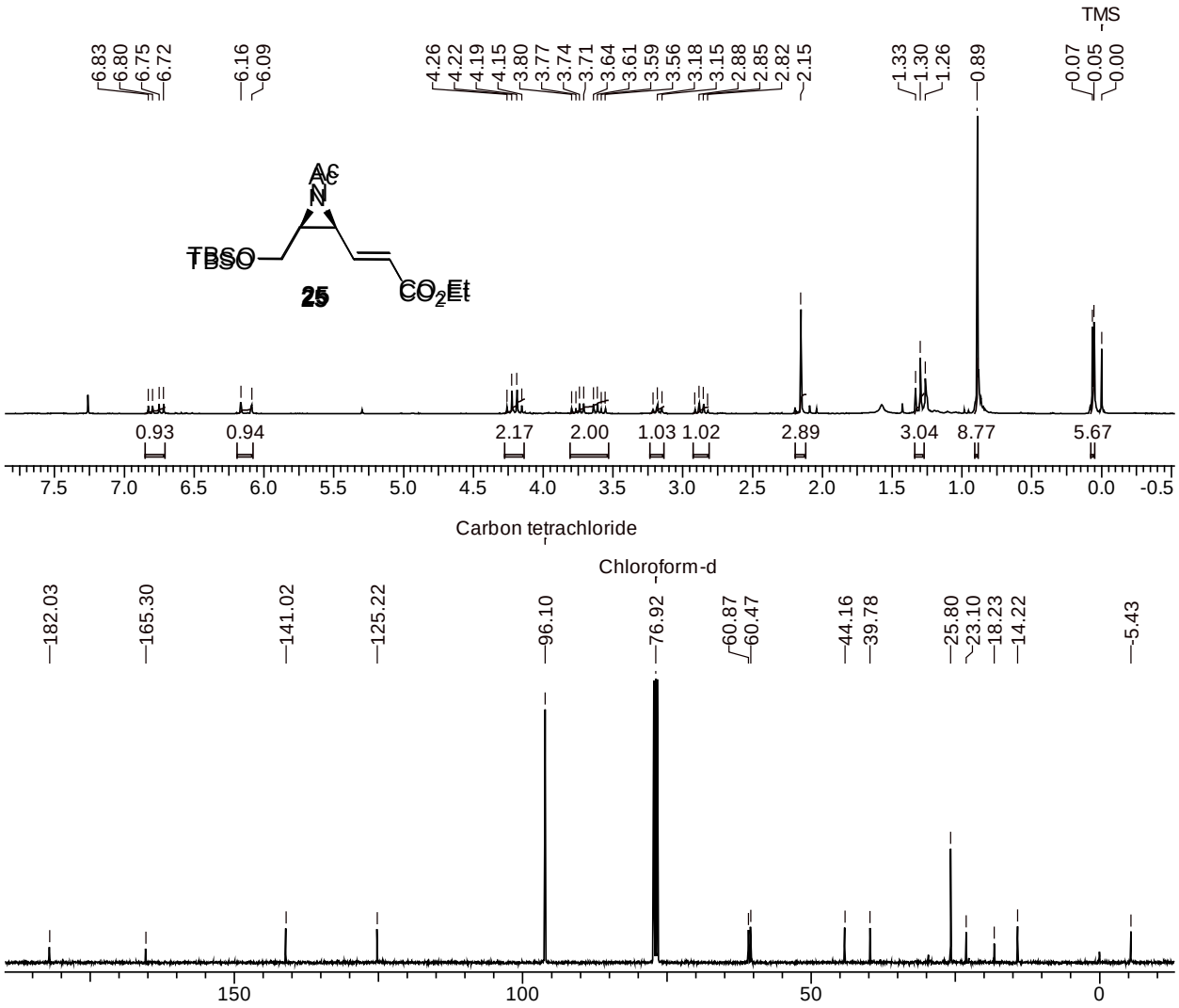


Figure 4: ^1H and ^{13}C NMR spectra of aziridine **25**

Regioselective ring opening of **25** with 3-pentanol in presence of $BF_3{\cdot}OEt_2$ proceeded smoothly to furnish α,β-unsaturated ester **32** as the exclusive product in 75% yield. The formation of **32** was confirmed from its ^1H and ^{13}C NMR spectra, which displayed multiplets at δ 3.96-4.04 & 4.34-4.37 for methine protons and δ 80.6 & 73.2 for methine carbons attached to oxygen (**Figure 5**). The proton signals at δ 0.06 & 0.85 in its ^1H NMR spectrum and carbon signals at δ -5.5, -5.3, 18.1 & 25.8 in its ^{13}C NMR spectrum were attributed to the TBS ether functionality.

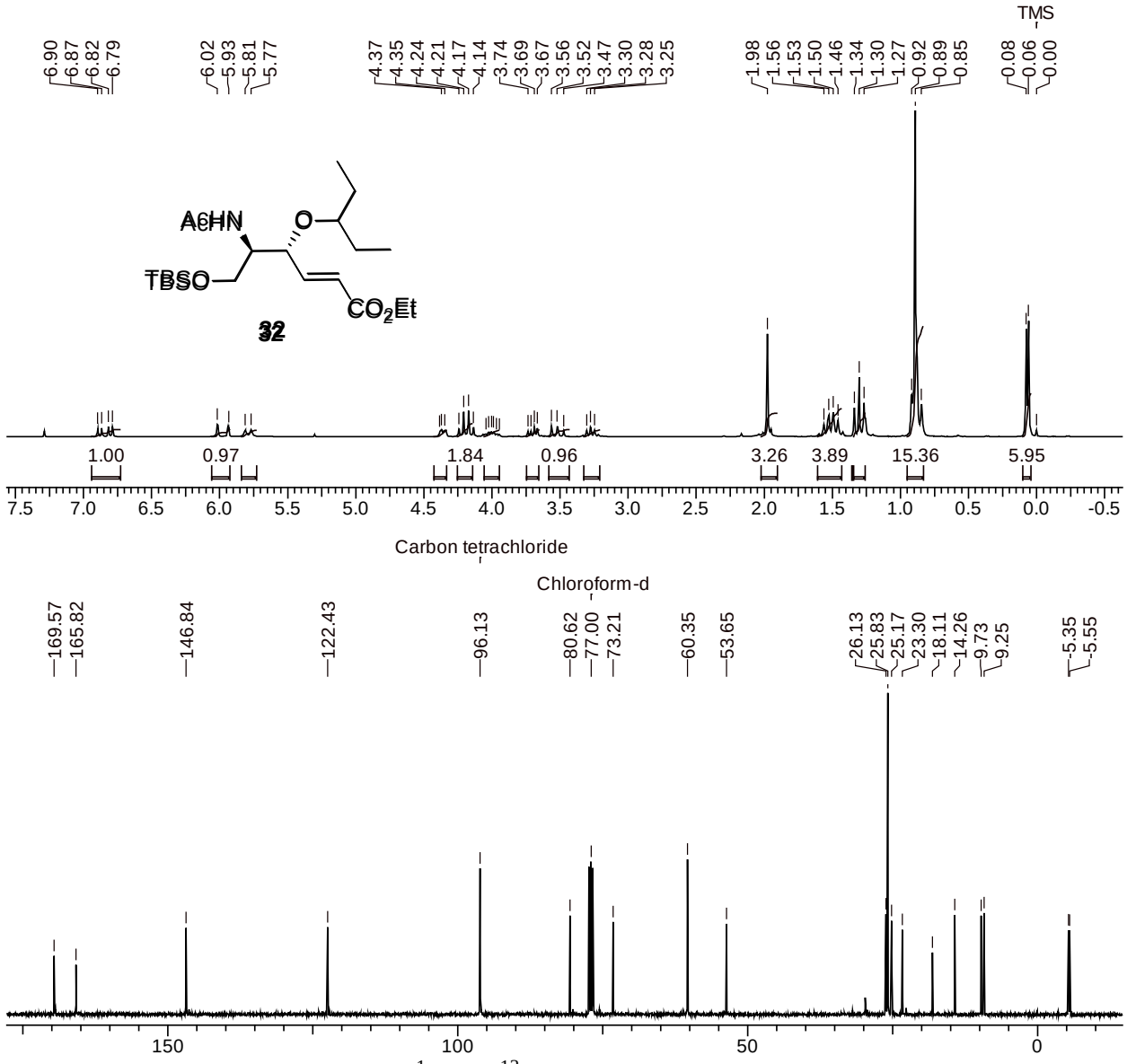


Figure 5: ^1H and ^{13}C NMR spectra of ester **32**

On desilylation with TBAF, **32** unexpectedly gave the furan derivative **33**, a Michael adduct, as the major product (65% yield) along with the desired alcohol **24** in minor amounts (17% yield). The formation of the desired alcohol **24** was confirmed from its ^{1}H and ^{13}C NMR spectra, which showed the disappearance of typical signals for TBS ether. The multiplets at δ 5.98-6.06 (1H) and 6.77-6.88 (1H) were attributed to the olefinic protons. The carbon signals at δ 170.5 and 165.7 were due to amide and ester carbonyl functionalities, while the carbon signal at δ 145.8 and 123.1 accounted for olefinic function (**Figure 6**).

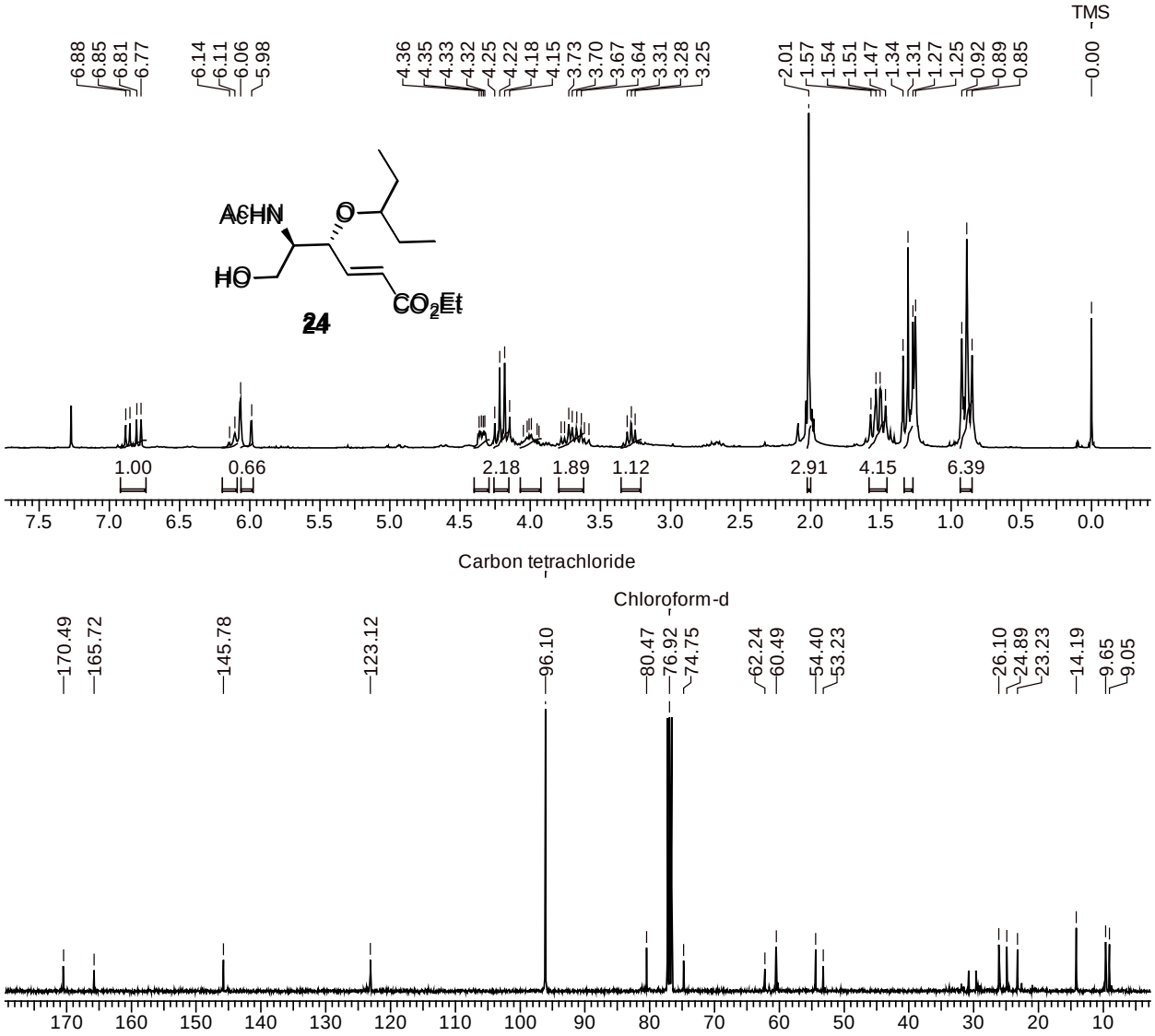


Figure 6: ^{1}H and ^{13}C NMR spectra of alcohol **24**

The formation of intramolecular Michael addition product **33** was confirmed by its ^{1}H and ^{13}C NMR spectral analysis, which showed the disappearance of typical signals for olefin functionality. Its ^{1}H NMR spectrum showed multiplets at δ 3.36-3.52 (1H), 3.81-3.92 (3H) and 4.12-4.29 (3H) which were due to protons of methine and methylene group attached to oxygen. The singlet at δ 2.0 (3H) was attributed to methyl protons of acetyl group. The signals at δ 169.4 and 171.0 in its ^{13}C NMR spectrum accounted for the amide and ester carbonyls (**Figure 7**).

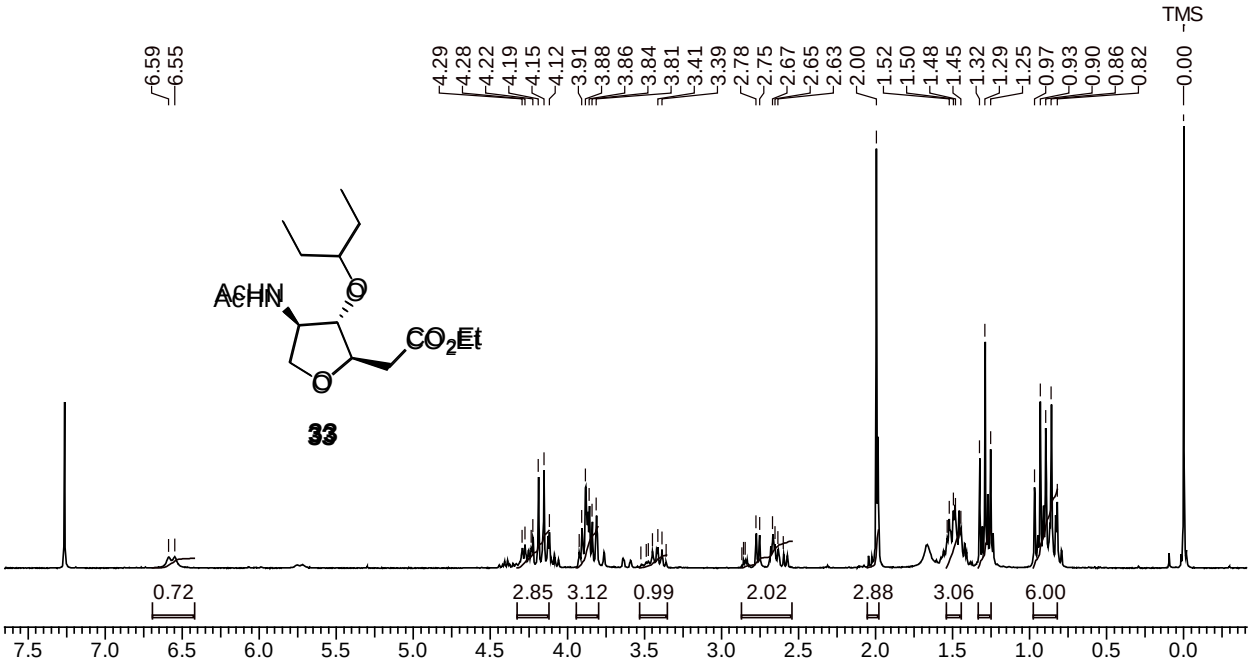
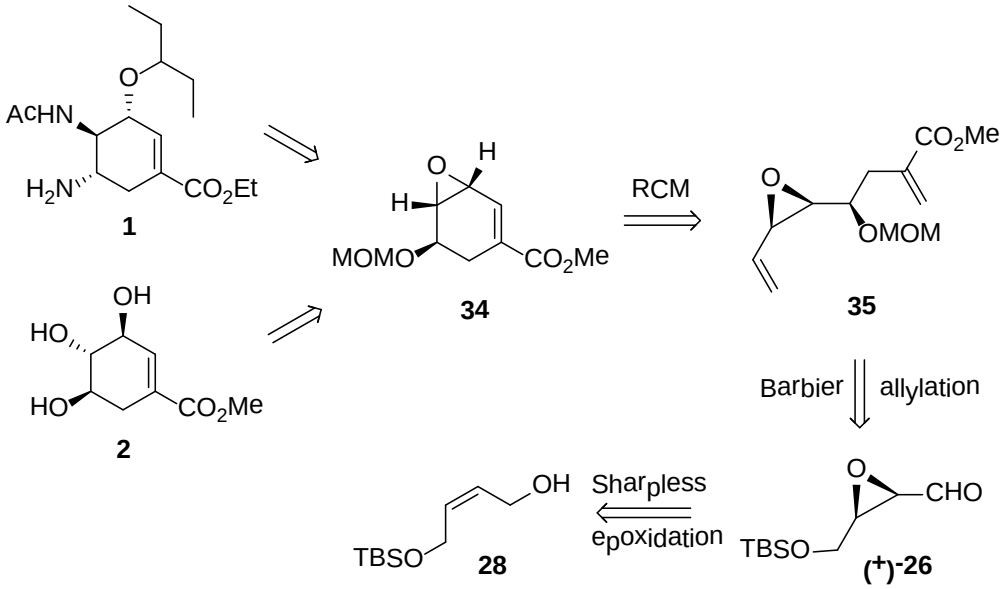


Figure 7: ^{1}H NMR spectrum of tetrahydrofuran **33**

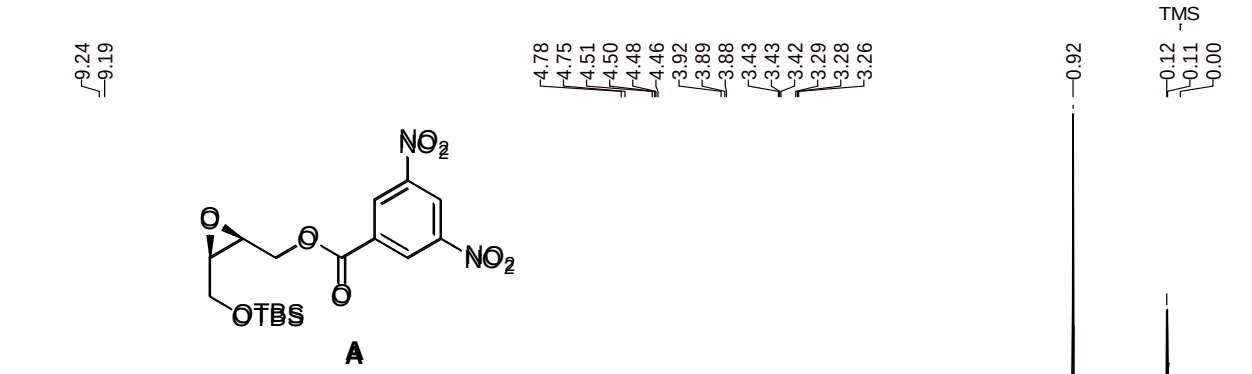
Since the yield of **24** was miserably low, an alternate route to oseltamivir **1** was undertaken. Based on retrosynthetic analysis, we visualized that epoxide **34** can be considered as the key precursor in the synthesis of (-)-oseltamivir free base **1** and (-)-methyl 3-*epi*-shikimate **2** (**Scheme 8**). Cyclic epoxide **34** was envisaged from ring closing metathesis (RCM) of diene **35**. Epoxy alcohol **35** was in turn obtained from diastereoselective Barbier allylation of chiral epoxy aldehyde **(+)-26**. Sharpless asymmetric epoxidation of allylic alcohol **28** was employed for the introduction of chirality.



Scheme 8: Retrosynthetic analysis of oseltamivir free base (**1**) and methyl 3-*epi*-shikimate (**2**)

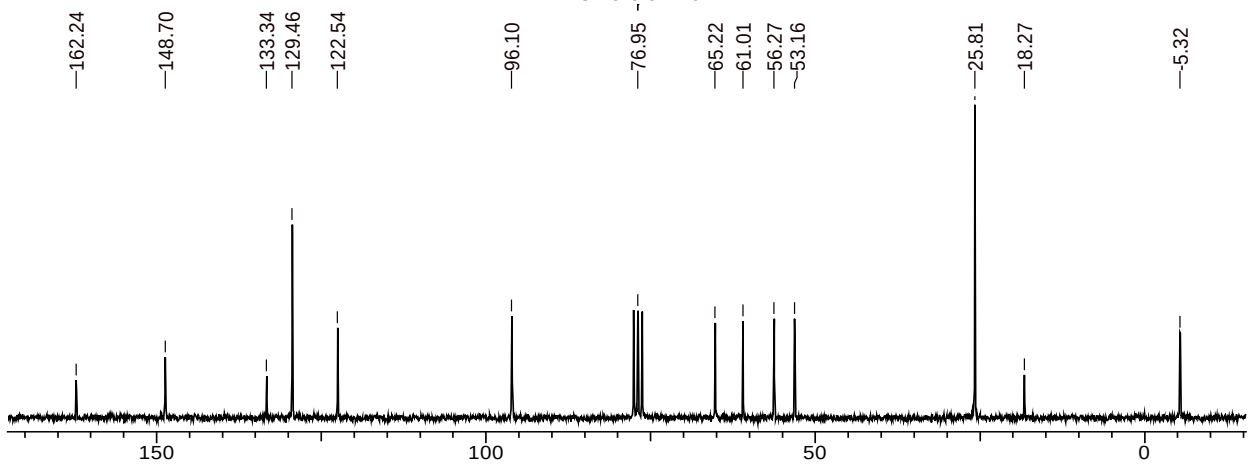
Accordingly, in the second approach, antipode epoxy alcohol **(-)-29** was readily prepared (97% ee confirmed by HPLC analysis of the corresponding 3,5-dinitro benzoate **A**) in two steps as described earlier in **Scheme 7**: (i) monosilylation, (ii) AE with (+)-DET as chiral source. The ^{1}H NMR spectrum of the 3,5-dinitro benzoate derivative of alcohol **(-)-29** (**A**) showed signals at δ 9.19 (s, 2H) and 9.24 (s, 1H) which accounted for the three aromatic protons. Its ^{13}C NMR spectrum showed carbon signal at δ 162.2 which was attributed to ester carbonyl, while other peaks at δ 122.5, 129.5, 133.3 and 148.7 were indicative of the aromatic carbons. Its IR spectrum showed a typical carbonyl stretching frequency band at υ_{max} 1737 cm^{-1} (**Figure 8**). The multiplets at δ 3.26-3.29 (1H) and 3.24-3.44 (1H) in its ^{1}H NMR spectrum indicated the presence of epoxide protons. Methine and methylene carbons attached to the oxygen atom gave signals at δ 53.2, 56.3, 61.0 and 66.2 in its ^{13}C NMR spectrum. Its chiral HPLC gave an enantiomeric

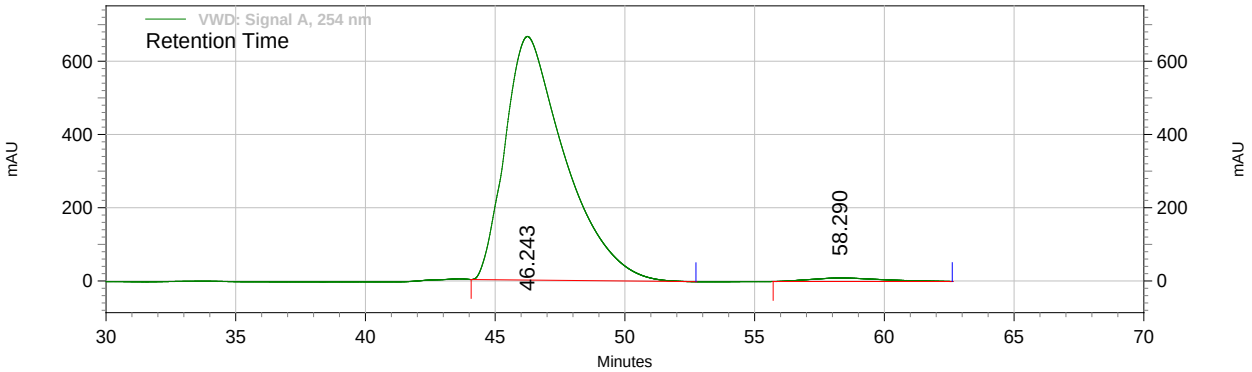
excess of 97% (Column: Chiracel OD-H retention time: 46.24 min (-)-isomer, 58.29 min (+)-isomer).



Carbon tetrachloride

Chloroform-d



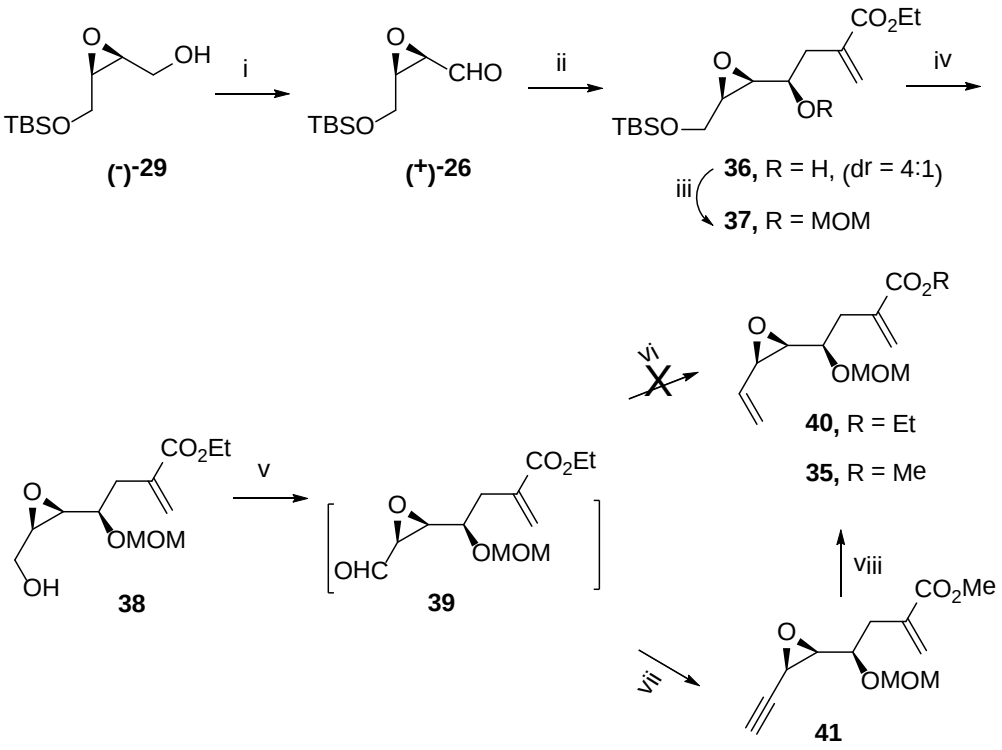


Retention Time	Area	Area %	Height	Height %

46.243	1792753436	98.31	11156727	98.56
58.290	30806312	1.69	162754	1.44
Totals	1823559748	100.00	11319481	100.00

Figure 8: ^{1}H & ^{13}C NMR spectra and chiral HPLC chromatogram of benzoate **A**

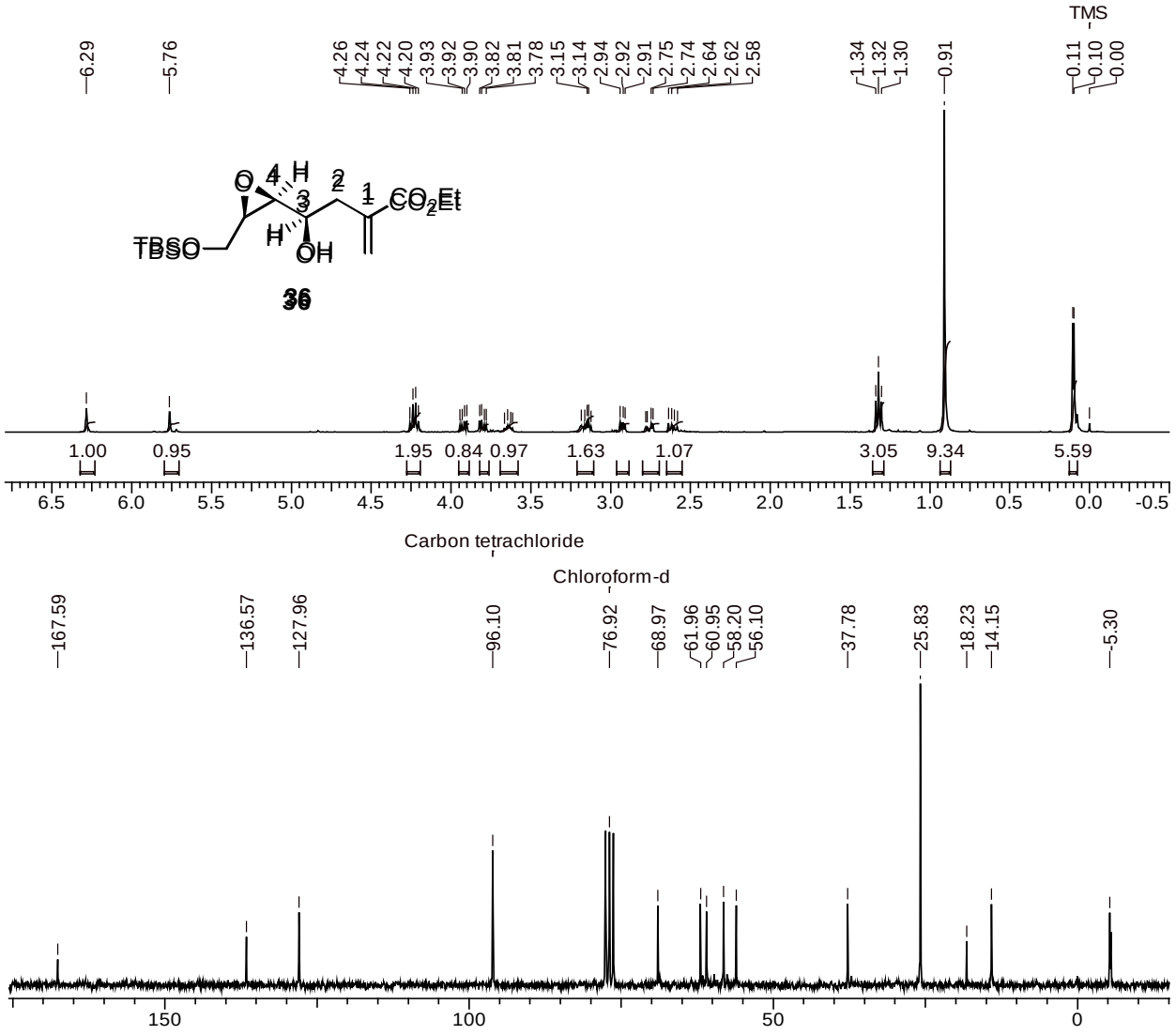
Oxidation of **(-)-29** (TEMPO, BAIB) gave the aldehyde **(+)-26**, which upon purification was subjected to Barbier allylation with ethyl 2-(bromomethyl)acrylate to afford the homoallylic alcohol **36** in 64% yield (dr = 4:1) (**Scheme 9**).

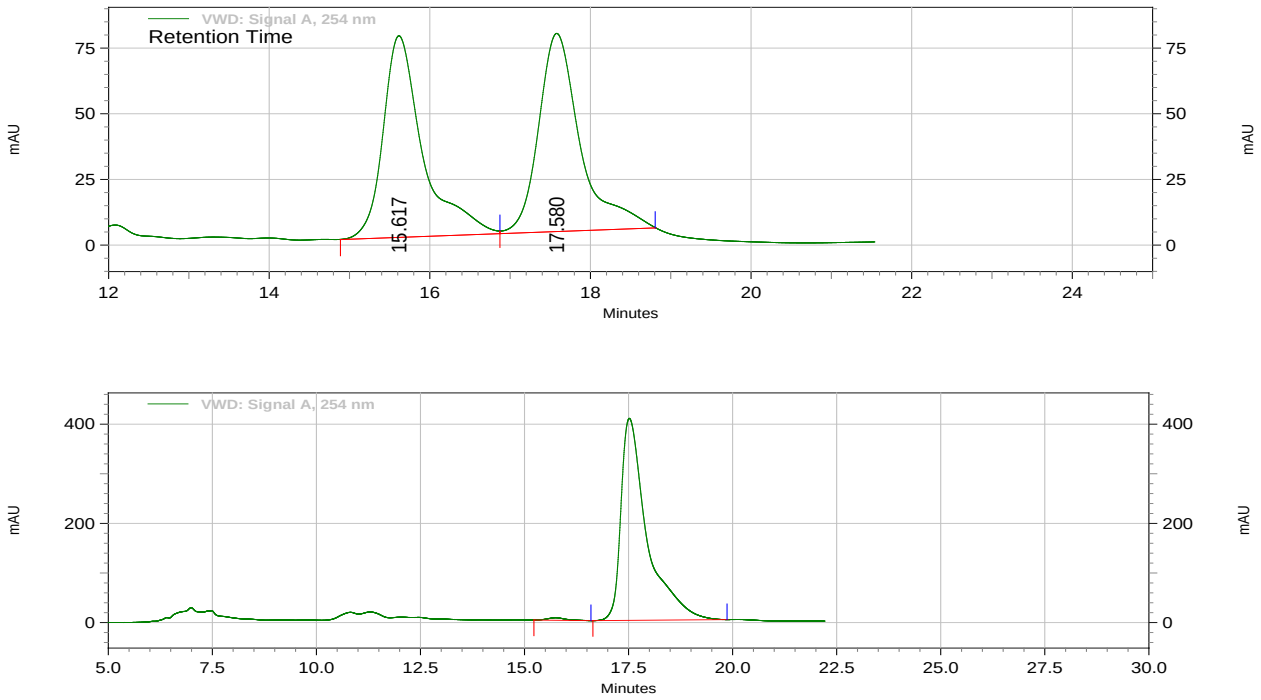


Scheme 9: (i) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (ii) ethyl 2-(bromomethyl)acrylate, Zn dust, NH_4Cl, THF/H_2O (4:1), 0-25 ºC, 10 h, 64% (for *syn*-selectivity); (iii) MOMCl, DIPEA, dry CH_2Cl_2, 0-25 ºC, 10 h, 90%; (iv) TBAF, THF, 0 ºC, 2 h, 88%; (v) IBX, dry DMSO, 25 ºC, 1 h; (vi) *n*-BuLi, $Ph_3P^+CH_3I^-$, dry THF, -10 ºC to 25 ºC, 3 h; (vii) diethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 25 ºC, 2 h, 82% (over two steps); (viii) H_2, Lindlar's catalyst, pyridine/1-octene/EtOAc (1:1:10), 6 h, 95% yield of **35**.

The ^{1}H NMR spectrum of *syn*-epoxy alcohol **36** showed singlets at δ 5.76 (1H) and 6.29 (1H) which accounted for the two olefinic protons. The other signals at δ 3.78 (dd, J = 5.8, 11.8 Hz, 1H) and 3.90 (dd, J = 5.8, 11.5 Hz, 1H) were attributed to methylene attached to silyl ether group. The multiplet at δ 3.61 was due to the methine attached to hydroxyl group. Its ^{13}C NMR

spectrum showed a characteristic carbonyl ester resonance at δ 167.6. The two olefinic carbons displayed signal at δ 136.5 and 127.9, while the other signals at 56.1, 58.2, 60.9, 61.9 and 68.9 were indicative of the carbons attached to oxygen atom. A significant COSY and NOESY correlation was observed between H_4 and H_3 in **36** (**Figure 9**).





Retention Time	Area	Area %	Height	Height %
15.747	2578055	0.86	86067	1.24
17.517	297132318	99.14	6829082	98.76
Totals	299710373	100.00	6915149	100.00

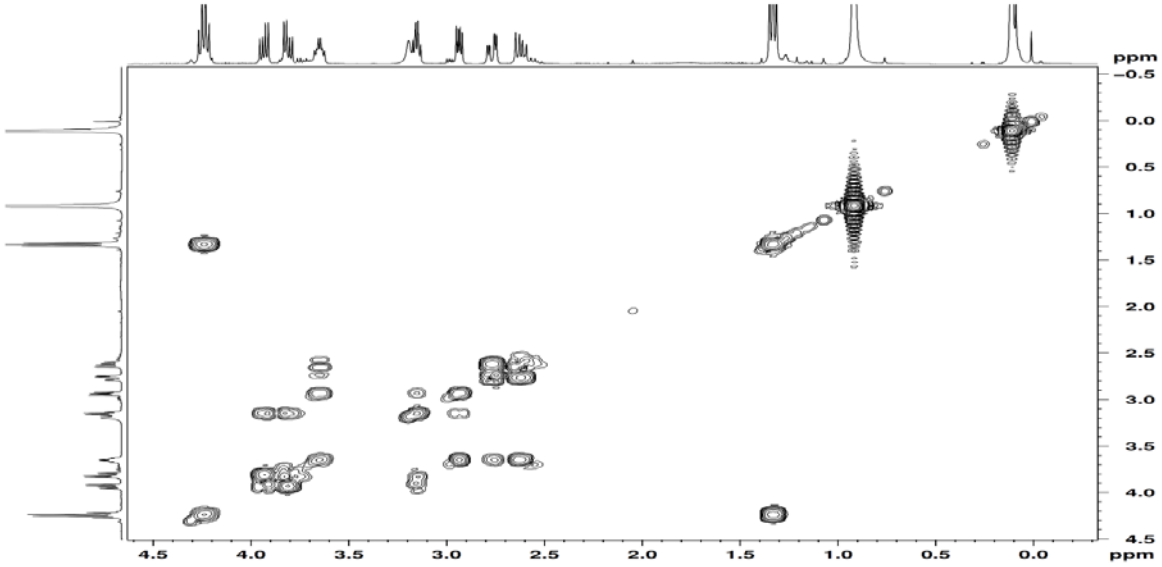
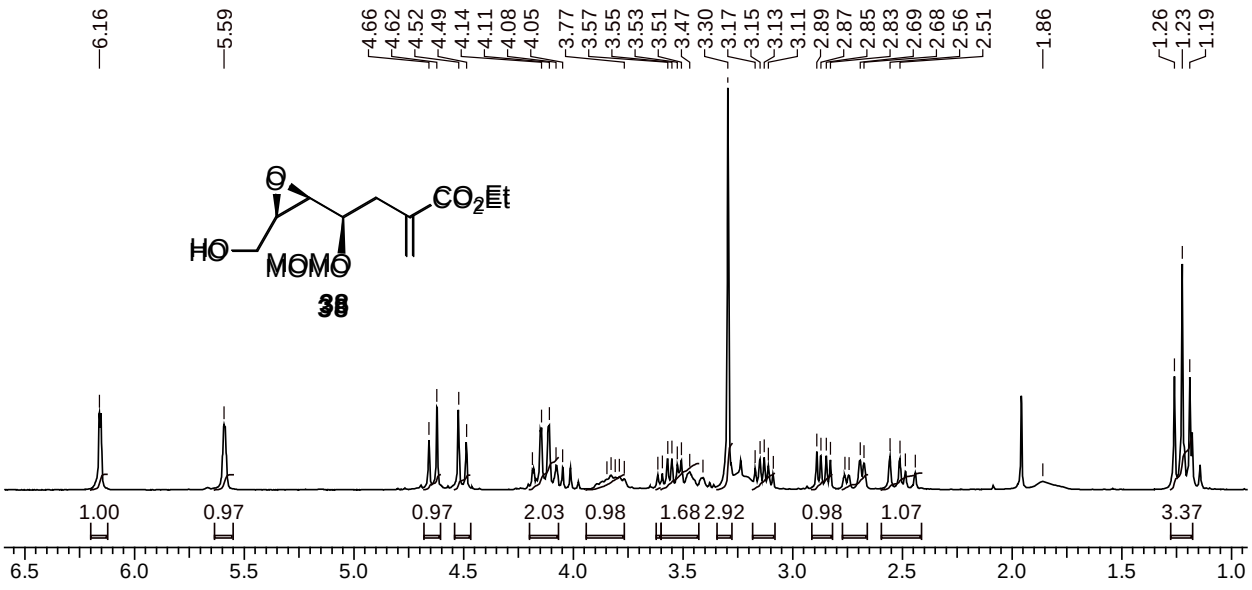


Figure 9: ^{1}H, ^{13}C & COSY NMR spectra and HPLC chromatogram of epoxy alcohol **36**

The hydroxyl group in **36** was then protected as its MOM ether (MOMCl, DIPEA, 90%) and TBS group in **37** deprotected with 1 M TBAF solution in THF to produce alcohol **38**; $[\alpha]_D^{25}$ +4.1 (*c* 0.6, $CHCl_3$). This transformation was confirmed by analyzing the ^1H and ^{13}C NMR spectra of compound **38**. The disappearance of signals corresponding to TBS ether confirmed the deprotection. Its ^1H NMR spectrum showed typical signals at δ 5.59 (s, 1H) and 6.16 (s, 1H) corresponding to olefinic protons, while the carbon signals at δ 96.0 and 72.7 in its ^{13}C NMR spectrum accounted for the MOM ether group (**Figure 10**).



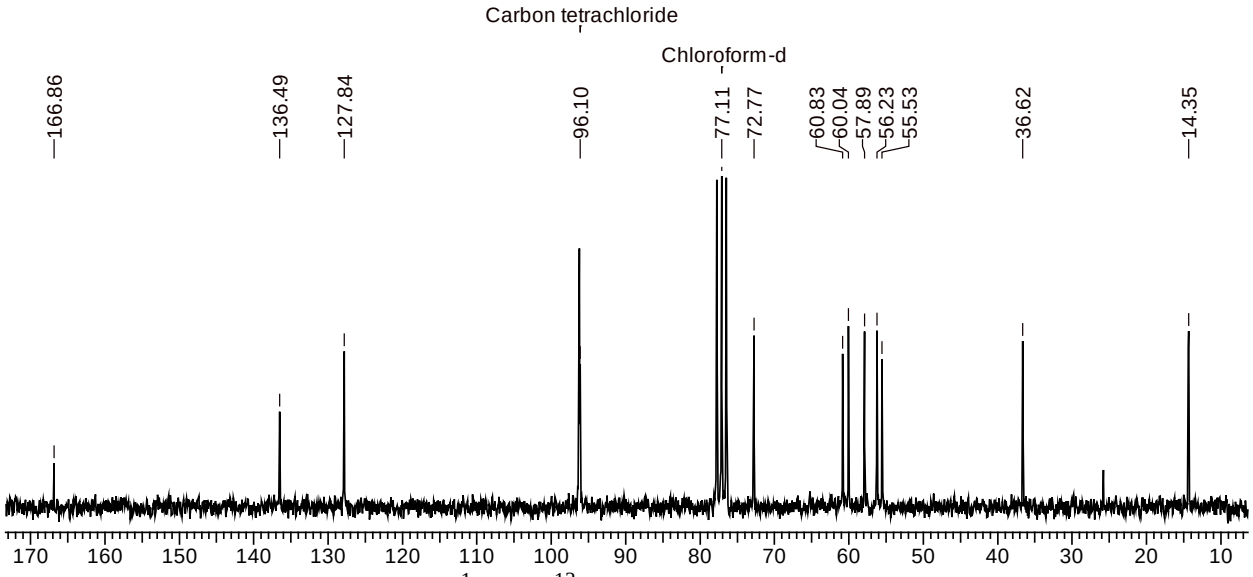


Figure 10: ^{1}H and ^{13}C NMR spectra of alcohol **38**

Primary alcohol **38** was then subjected to oxidation (IBX/DMSO) to give the labile aldehyde **39**. Several attempts to perform Wittig olefination (n-BuLi, $PPh_3{}^{+}CH_3I^{-}$, THF) of **39** to produce diene **40** were quite unsuccessful, due to its rapid decomposition under the strongly basic condition. Alternately, the crude aldehyde **39** was subjected to Seyferth-Gilbert homologation using Bestman-Ohira reagent[16] in presence of K_2CO_3 and MeOH, which gave the terminal alkyne **41** in 82% yield with completely transesterified methyl ester in 2 h. To prevent the transesterification process, the Seyferth-Gilbert homologation was carried out in EtOH; however no reaction took place even after 6 h. The acetylenic functionality in **41** was confirmed from its IR spectrum which showed a characteristic strong absorption band at υ_{max} 2226 cm^{-1}. Its ^{1}H and ^{13}C NMR spectra showed a signal at δ 2.45 (d, J = 1.6 Hz, 1H) indicative of acetylenic proton and at δ 75.1 and 78.2 corresponding to acetylenic carbons (**Figure 11**). A singlet at δ 3.76 (s, 3H) in its ^{1}H NMR confirmed the presence of methyl ester.

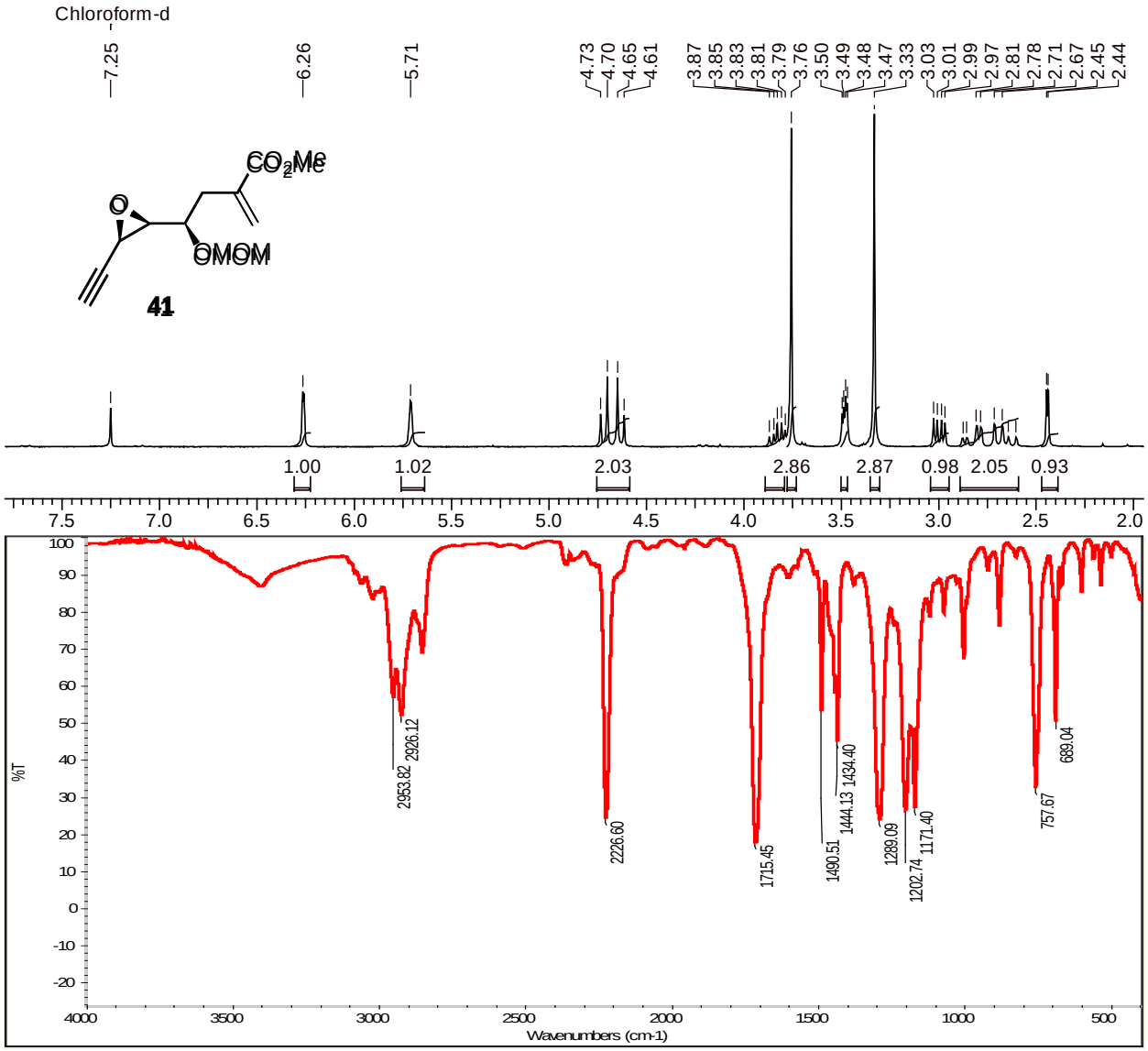


Figure 11: ^{1}H NMR and IR spectra of alkyne **41**

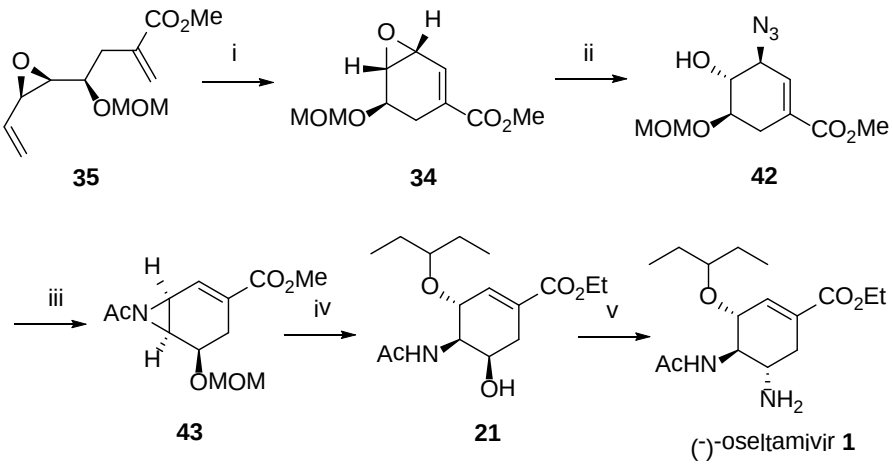
Next, a systematic study of selective catalytic hydrogenation [H_2 (1 atm), Lindlar's catalyst, additives, solvents] of alkyne **41** to alkene **35** was undertaken and the results are summarized in **Table 2**. As can be seen, ethyl acetate and pyridine combination gave good yields (64%) of diene **35**; $[\alpha]_D^{25}$ -5.4 (*c* 0.5, $CHCl_3$), while the lowest yield was realized when 1,10-phenanthroline was used as additive with DMF as solvent; however higher selectivity (95%) to **35** could be achieved when pyridine/1-octene was used in combination with EtOAc as solvent.

Table 2: Optimization studies for selective catalytic hydrogenation of alkyne **41**: role of additives[a]

Entry	Solvent	Additives[b]	Yield of 29 (%)[d]
1	MeOH	Quinoline[c]	26
2		Quinoline	23
3		Pyridine	34
4	DMF	Quinoline	22
5		Pyridine	16
6		1,10-phenanthroline	14
7	EtOAc	Quinoline	57
8		Pyridine	64
9[e]		Pyridine/1-octene	95
10	Benzene	Pyridine	33

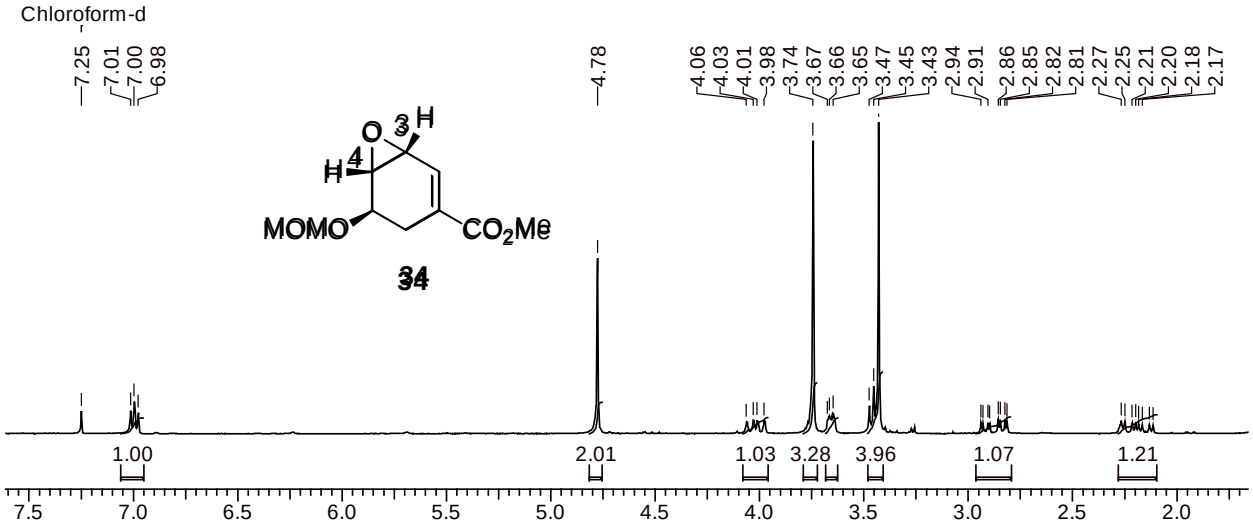
[a] H_2 (1 atm), Lindlar's catalyst (5 wt%), dry solvent, 25 °C, 6 h; [b] 1.2 equiv; [c] 10 mol%; [d] isolated yield; [e] py/1-octene/EtOAc (1:1:10).

The formation of diene **35** was confirmed by the appearance of signals in its ^{1}H NMR spectrum at δ 5.33 (m, 1H), 5.52 (d, *J* = 1.7 Hz, 1H) and 5.67-5.71 (m, 2H) corresponding to the olefinic protons. This was further substantiated by its ^{13}C NMR spectrum analysis which showed the presence of typical carbon signals at δ 120.5, 127.7, 132.1 and 136.4 due to olefin functionality. The cyclohexene core **34** was then constructed smoothly in 90% yield *via* a RCM strategy using Grubbs II catalyst under high dilution (**Scheme 10**).



Scheme 10: (i) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 14 h, 90%; (ii) NaN_3, NH_4Cl, DMF/EtOH/H_2O (4:4:1), 0-25 ºC, 10 h, 83%; (iii) (a) Ph_3P, PhMe, reflux, 3 h; (b) Ac_2O, DMAP, Et_3N, dry CH_2Cl_2, 0-25 ºC, 45 min, 81% (over two steps); (iv) (a) 3-pentanol, $BF_3.OEt_2$, -10 ºC, 30 min, (b) 2 N HCl, EtOH, 25 ºC, 12 h, 64% (over two steps); (v) (a) MsCl, Et_3N, dry CH_2Cl_2, 0 ºC, 1 h; (b) NaN_3, DMF, 80 ºC, 3 h; (c) H_2, Lindlar's cat, EtOH, 72% (over three steps).

The formation of desired cyclohexene core **34** was confirmed by its ^{1}H NMR spectrum which showed a characteristic olefinic proton at δ 6.98 (t, J = 3.4 Hz, 1H), thus confirming the annulation. This was further evidenced by the appearence of carbon signals at δ 128.3 and 131.1 of the olefinic carbons in its ^{13}C NMR spectrum (**Figure 12**). A significant COSY and NOESY correlation was observed between H_4 and H_3 in cyclic epoxide **34**.



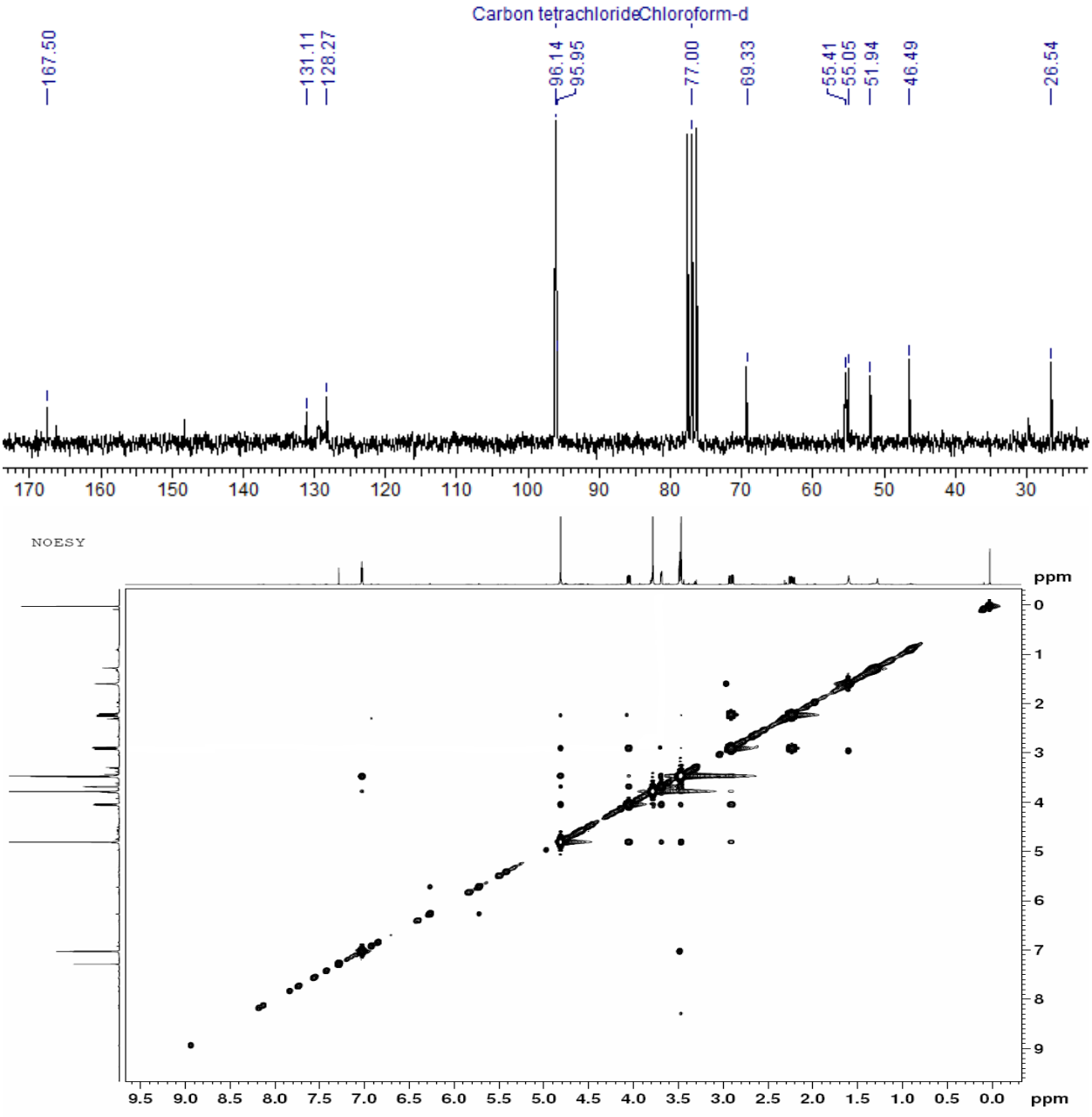


Figure 12: ^{1}H, ^{13}C and NOESY NMR spectra of cyclic epoxide **34**

The Conversion of **34** to aziridine **43** was achieved using a sequence of reactions similar to the one described in **Scheme 7**. Consequently, the regioselective epoxide opening of **34** was achieved in 83% yield with azide anion [NaN_3, NH_4Cl, DMF/EtOH/H_2O (4:4:1)]. The structure of azido alcohol **42** was confirmed by its IR, ^{1}H and ^{13}C NMR spectra as shown in **Figure 13**: Its ^{1}H NMR showed a triplet at δ 6.59 (J = 2.5 Hz, 1H) which indicated the presence of olefinic

proton, while a singlet at δ 3.77 (3H) accounted for methyl ester. Its IR spectrum showed an intense absorption band at υ_{max} 2099 cm^{-1} typical for azide bond stretching vibrations.

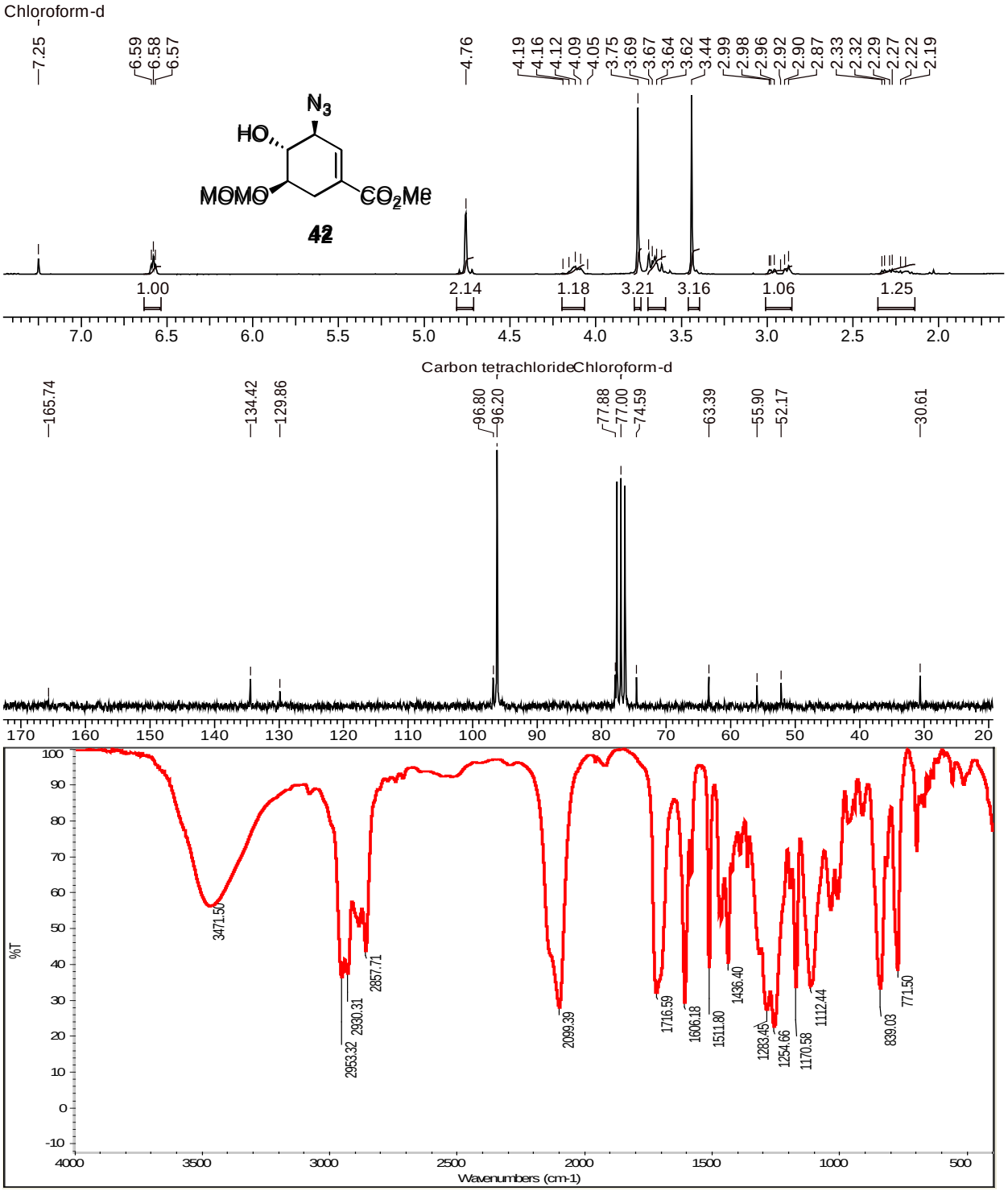


Figure 13: ^{1}H & ^{13}C NMR and IR spectra of azido alcohol **42**

Compound **42** was treated with 1 equiv of triphenylphosphine and the resulting mixture refluxed in toluene to afford the corresponding aziridine. It was found that aziridine was hard to separate by chromatography from the triphenylphosphine oxide, formed during the reaction. Fortunately, the unprotected aziridine could be purified by washing the reaction mixture with cold diethyl ether (Et_2O). The precipitated triphenylphosphine oxide was removed by filtration and the filtrate evaporated. Aziridine was then immediately exposed to 2 equiv of acetic anhydride and 3 equiv of triethylamine in dry CH_2Cl_2 to produce *N*-acetyl aziridine **43** in 81% yield; $[\alpha]_D^{25}$ -57.8 (*c* 0.5, $CHCl_3$). The formation of acetamide **43** was confirmed by the appearance of a typical singlet at δ 2.10 (3H) in its ^{1}H NMR spectrum, which indicated the presence of methyl protons of acetyl group. This was acertained by its ^{13}C NMR spectrum which showed the presence of acetamide carbonyl at δ 184.9. Its IR spectrum showed an intense absorption band at υ_{max} 1732 cm^{-1} typical for ester carbonyl stretching vibrations. Its ^{1}H NMR spectrum showed singlets at δ 3.34 and 3.76 which was attributed to the methyl protons of MOM ether and ester group respectively.

Regioselective ring opening of aziridine **43** with 3-pentanol in presence of 1.5 equiv $BF_3{\cdot}OEt_2$ followed by simultaneous MOM deprotection and transesterification using 2 N HCl in EtOH afforded the key amino alcohol **21**, whose spectral data were in complete agreement with reported values.[10] The ^{1}H NMR spectrum of **21** showed a singlet at δ 6.84 (1H) indicating the presence of olefinic proton. The multiplet at δ 4.41 (1H), were due to methine proton attached to oxygen of 3-pentyl ether. Its ^{13}C NMR spectrum showed characteristic signals at δ 166.8 and 171.8 indicating the presence of carbonyl of ester and acetamide respectively. The signals at δ 0.90 (t, *J* = 6.7 Hz, 6H) and 1.42 (m, 4H) in its ^{1}H NMR spectrum accounted for methylene and

methyl protons of 3-pentyl ether. Its IR spectrum showed a strong absorption band at υ_{max} 3396 cm^{-1} attributed to the hydroxyl stretching vibrations (**Figure 14**).

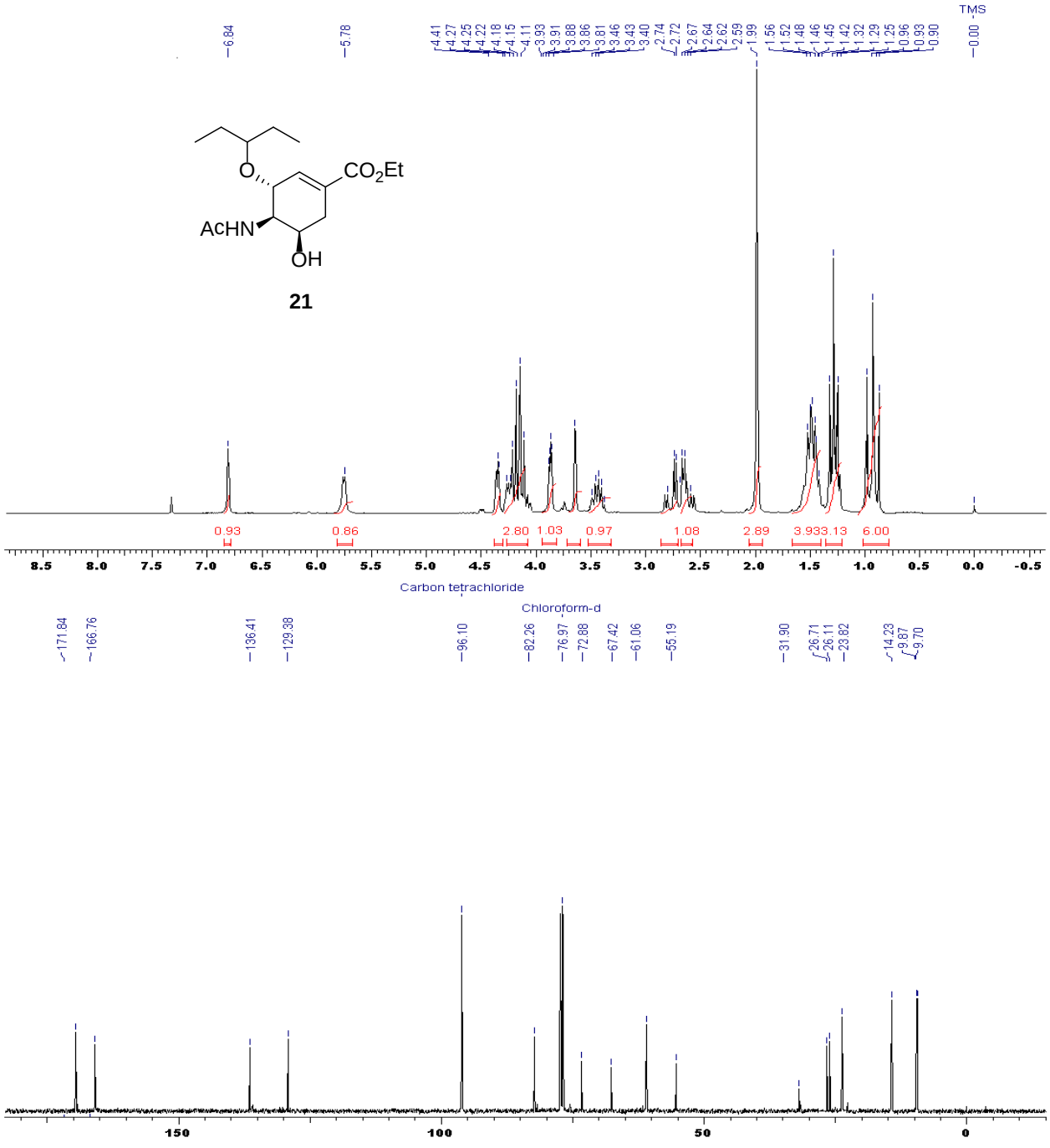
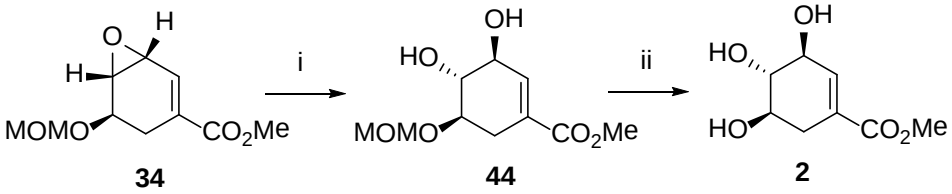


Figure 14: ^{1}H and ^{13}C NMR spectra of alcohol **21**

Amino alcohol **21** was then converted to oseltamivir free base in three steps; by following the reported procedures:[10] (i) mesylation of alcohol **21**, (ii) displacement of mesylate with azide ion, (iii) reduction of azide with Lindlar's catalyst. The sample of (-)-oseltamivir free base **1** obtained from the synthesis described herein has been found to be identical in all respects with the values reported in the literature.[10]

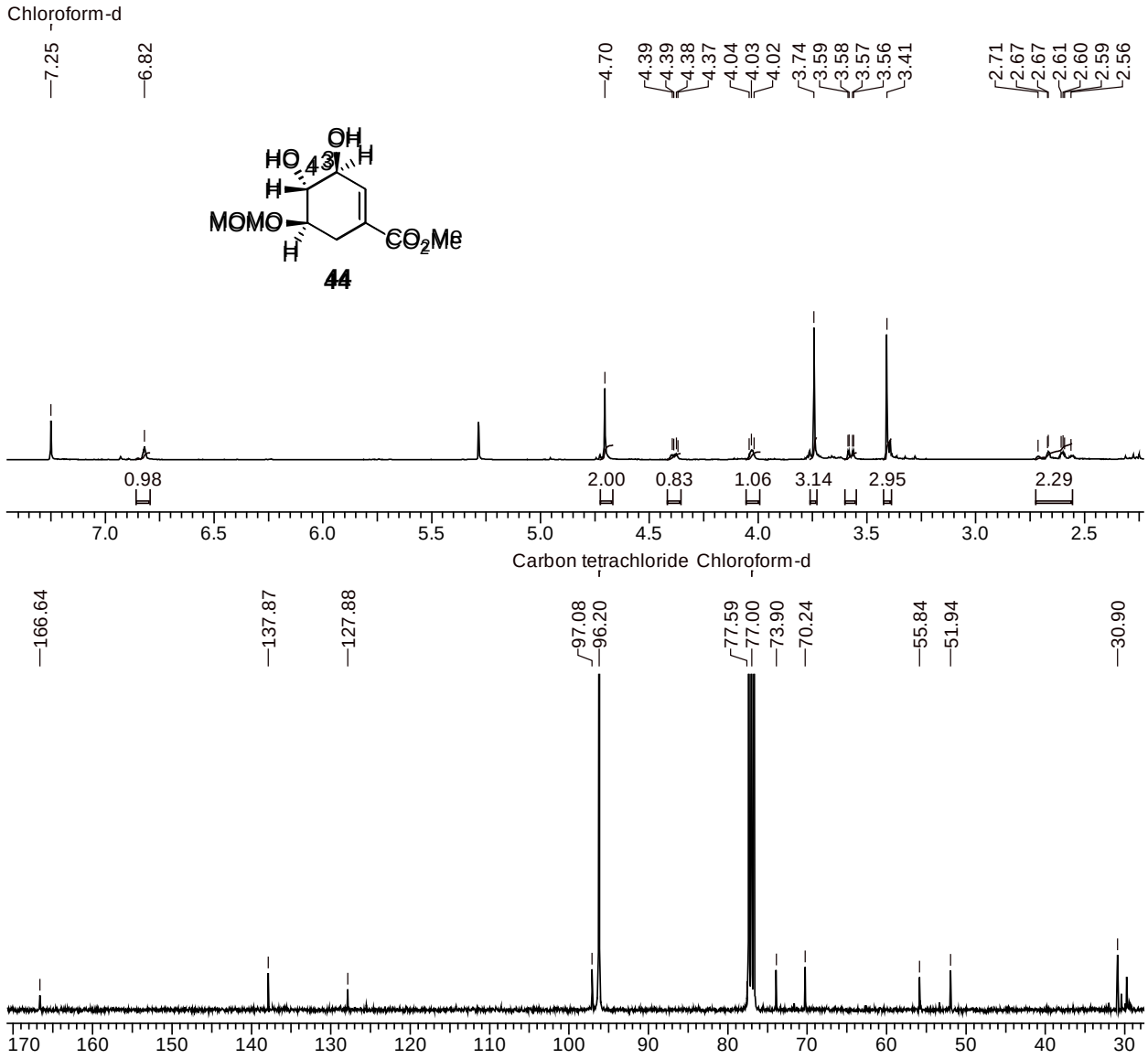
Additionally, a concise enantioselective synthesis of 3-*epi*-shikimate **2** was undertaken to demonstrate the direct application of cyclic epoxide **34**, an important precursor for the synthesis of 3-*epi*-shikimate **2**. Thus, cyclic epoxide **34** was readily converted into the desired triol **2** through a two step reaction sequence: (i) epoxide opening in presence of H_2SO_4 with THF/H_2O as solvent combination; (ii) MOM deprotection of **44** with 2N HCl in MeOH (**Scheme 11**). The comparison of spectral data of **2** with the reported values[5b,c] further establishes the absolute configuration of cyclic epoxide **34**.

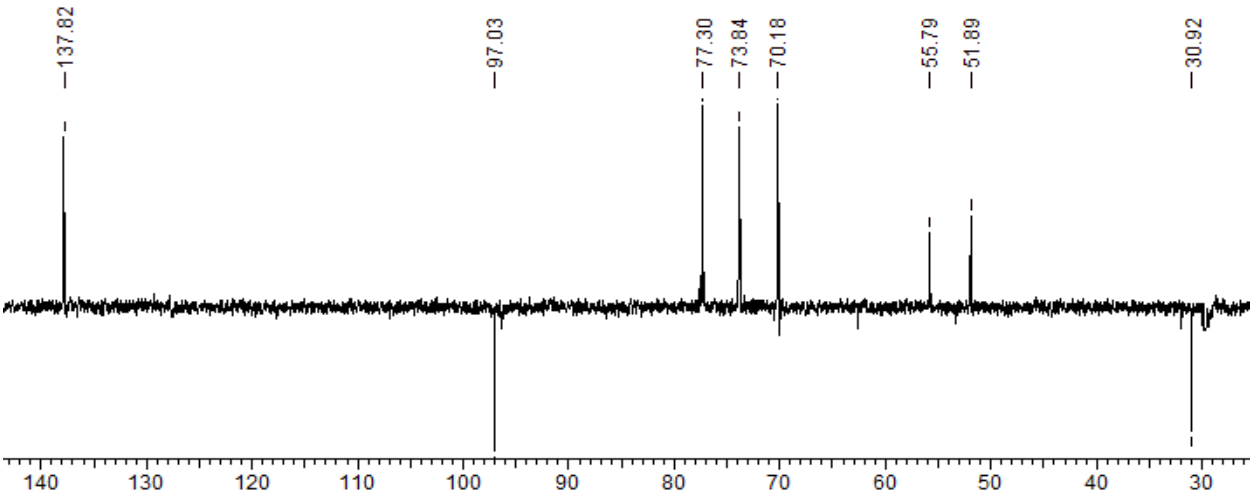


Scheme 11: (i) H_2SO_4, THF/H_2O (3:1), 0-25 °C, 2 h, 96%; (ii) 2 N HCl, MeOH, 25 °C, 6 h, 74%.

The ^{1}H NMR spectrum of **44** showed a characteristic olefinic proton signal at δ 6.82 (s). A singlet at δ 4.70 accounted for methylene protons of MOM ether, while the singlets at δ 3.74 and 3.41 were due to methyl protons of ester and MOM ether respectively. The multiplets at δ 3.56-3.59, 4.03-4.04 and 4.37-4.39 were attributed to the methine attached to oxygen atom. Its ^{13}C NMR spectrum showed signals at δ 127.9 and 137.9 corresponding to olefinic carbons, while a resonance peak appearing at δ 166.6 accounted for ester carbonyl. The signal at δ 97.1 indicated the presence of methylene carbon of MOM ether. The other carbon signals at δ 70.2, 73.9 and

77.6 were due to carbons attached to oxygen atom. The 2D NMR studies of compound **44** showed *anti*-relationship between proton H_3 and H_4 (**Figure 15**). The disappearance of signals due to MOM ether in the ^{1}H and ^{13}C NMR spectra of triol **2** confirmed the deprotection reaction.

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73.84
70.18
55.79
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100
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80
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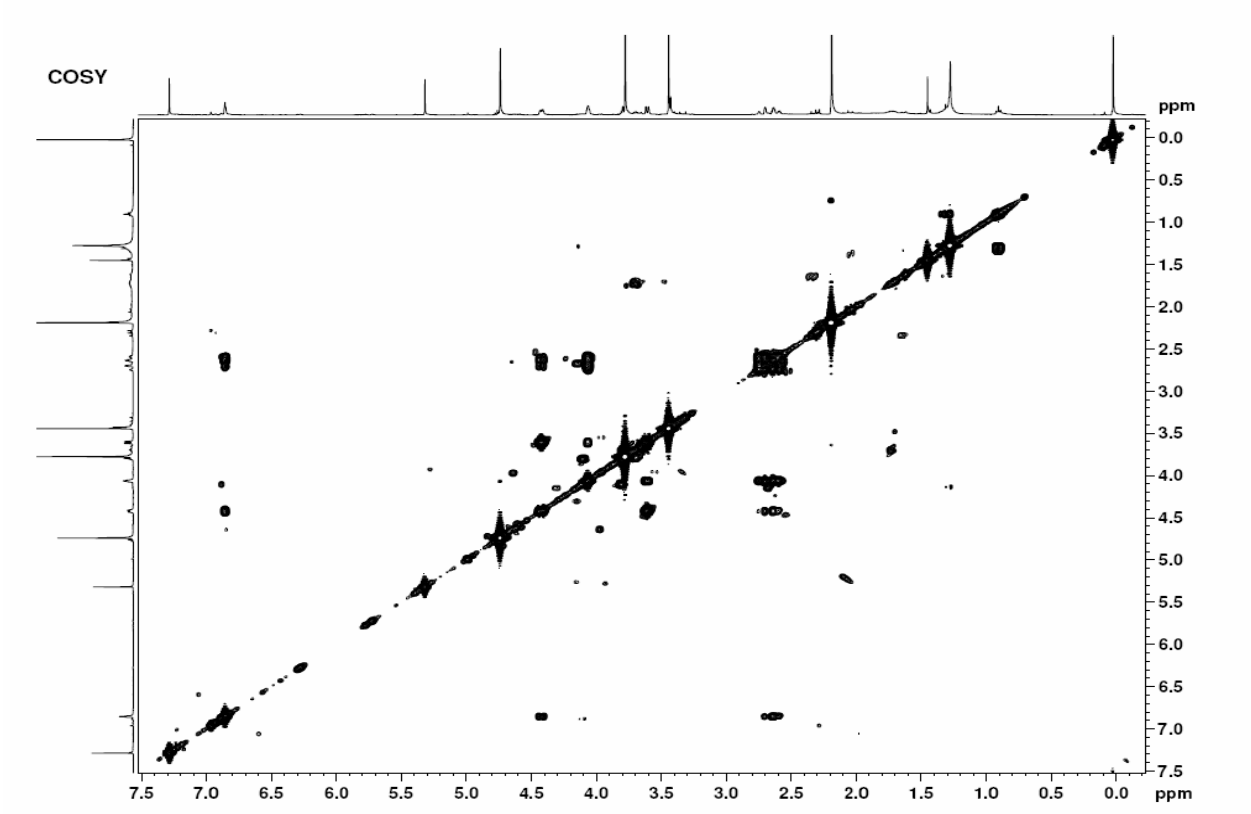
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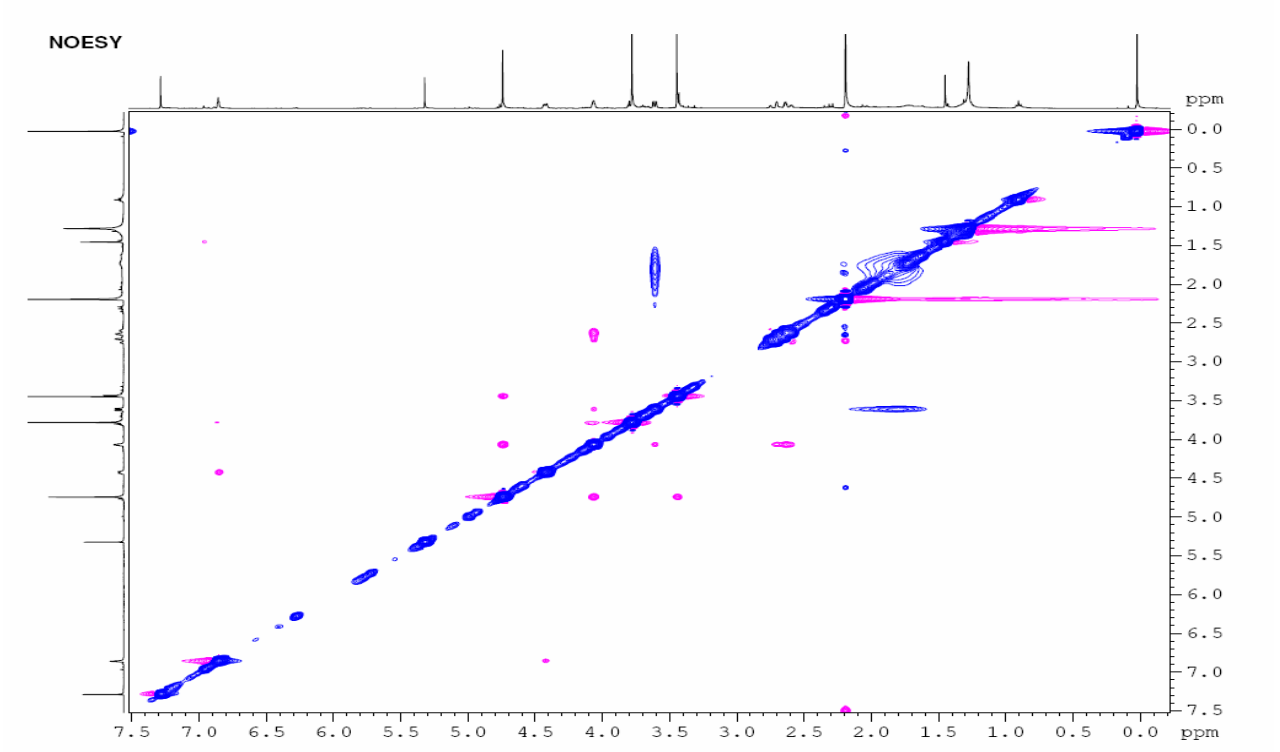
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3.5
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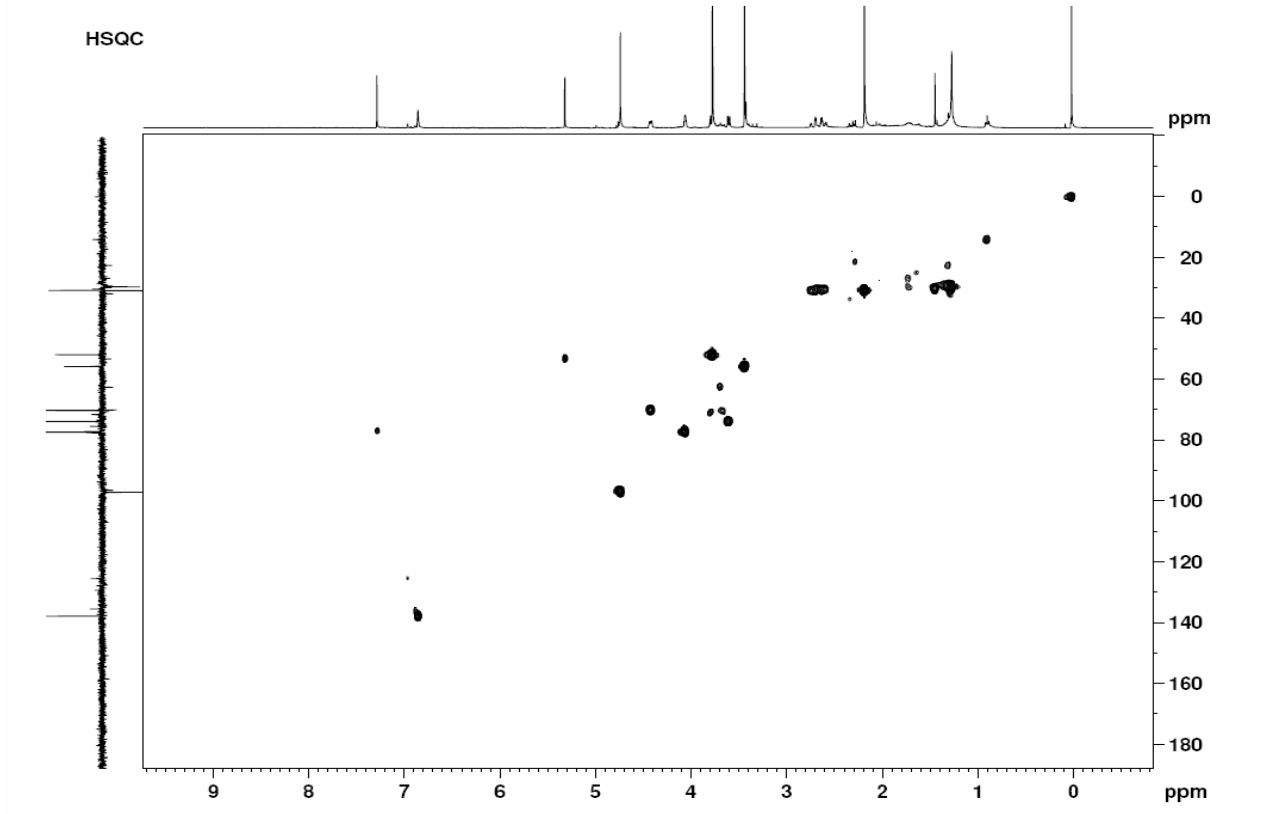
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140
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9 8 7 6 5 4 3 2 1 0 ppm

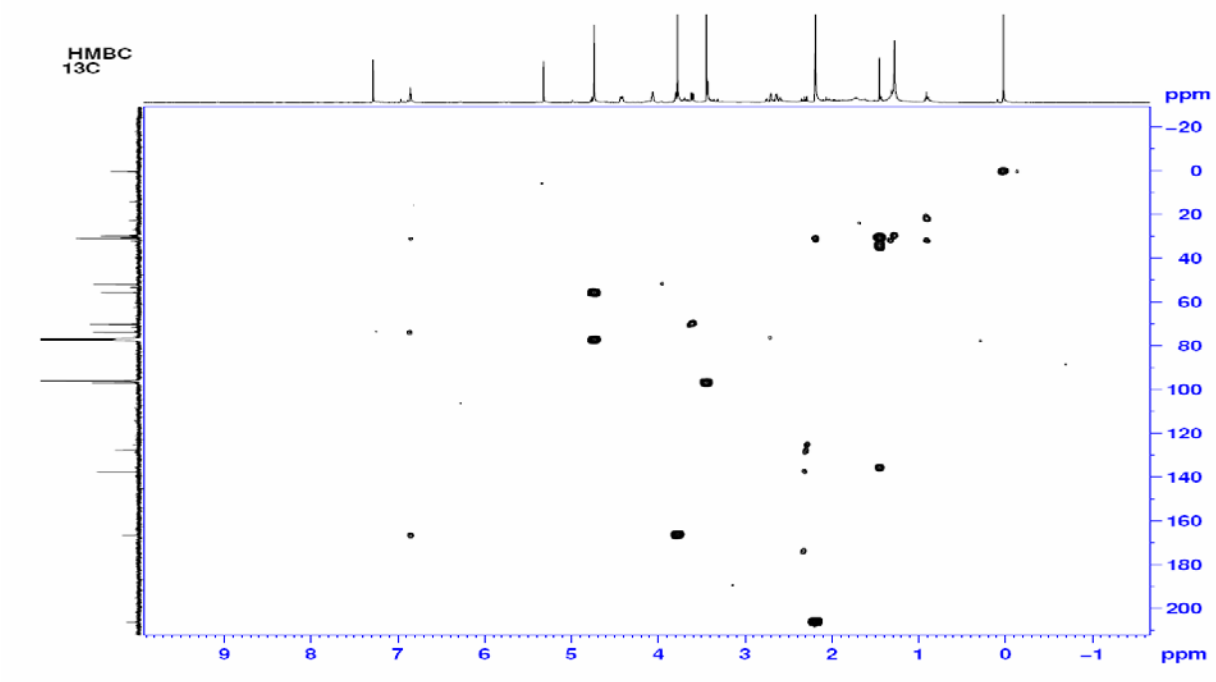


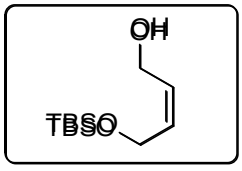
Figure 15: $^{1}H,^{13}C$, DEPT, COSY, NOESY, HSQC and HMBC NMR spectra of *anti*-diol **44**

1.1.4 Conclusion

In conclusion, we have described a new enantioselective synthesis of the *anti*-influenza agent (-)-oseltamivir **1** (7.1% overall yield; 98% ee) and (-)-methyl 3-*epi*-shikimate **2** (16% overall yield; 98% ee) starting from cheap and readily available *cis*-1,4-butene diol **27**. The key steps employed in the synthesis are the Sharpless asymmetric epoxidation, diastereoselective Barbier allylation and Ring Closing Metathesis. This method comprises of operationally simple yet efficient reactions with the use of inexpensive and non-toxic reagents, amenable for commercial exploitation.

1.1.5 Experimental section

(*Z*)-4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol (28)



To a solution of alcohol **27** (20 g, 227.27 mmol) in dry CH_2Cl_2 (700 mL) at 0 ^oC was added imidazole (23.21 g, 340.91 mmol) and *tert*-butyldimethylsilyl chloride (37.68 g, 250 mmol). The reaction mixture was then stirred at 0 ^oC for 6 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2, washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product which was then purified by column chromatography with petroleum ether/EtOAc (9:1 v/v) to give **28** (33.57 g) as a colorless liquid.

Yield: 73%; **IR** ($CHCl_3$): υ_{max} 777, 837, 1033, 1088, 1255, 1471, 2857, 2929, 3354 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.86 (s, 9H), 2.9 (br s, 1H), 4.10-4.20 (m, 4H), 5.57-5.61 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 25.9, 58.6, 59.5, 130.1, 131.1; **Anal.** Calcd for $C_{10}H_{22}O_2Si$ requires C, 59.35; H, 10.96; Found: C, 59.38; H, 10.99%.

((2*R*,3*S*)-3-((*tert*-Butyldimethylsilyloxy)methyl) oxiran-2-yl)methanol [(+)-29]: To a stirred suspension of powdered 4 Å molecular sieves (10.0 g) in dry CH_2Cl_2 (700 mL), titanium tetraisopropoxide (5.68 g, 20 mol%) was added under nitrogen atmosphere. The reaction mixture was cooled to -10 ºC and (-)-diethyl tartrate (6.11 g, 30 mol%) added and stirred for 10 min. To the above solution, *tert*-butyl hydroperoxide 5-6 M solution in decane (39.5 mL, 2 equiv) was added and stirred at -10 ºC for further 30 min, after which allylic alcohol **28** (20 g, 98.83 mmol) dissolved in dry CH_2Cl_2 (150 mL) was added and stirred at ⁻10 ºC for 12 h. After completion of the reaction (monitored by TLC), it was quenched with 1M NaOH (25 mL) with further stirring for 1 h at -10 ºC. The organic layer was then separated, washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column

chromatography using petroleum ether/EtOAc (7:3 v/v) to afford the allylic alcohol **(+)-29** (20.07 g) as a colorless liquid.

Yield: 93%; $[\alpha]_D^{25}$ +11.7 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 777, 837, 1047, 1257, 1472, 2858, 2955, 3441 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.86 (s, 9H), 2.9 (br s, 1H), 3.13-3.20 (m, 2H), 3.65-3.73 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -5.3, 18.3, 25.8, 56.2, 56.5, 60.6, 61.6; **Anal.** Calcd for $C_{10}H_{22}O_3Si$ requires C, 55.00; H, 10.15; Found: C, 55.07; H, 10.18%.

(2*S*,3*S*)-3-((*tert*-Butyldimethylsilyloxy)methyl)oxirane-2-carbaldehyde [(-)-26]

To a solution of alcohol **(+)-29** (15.02 g, 69.44 mmol) in dry CH_2Cl_2 was added in one portion (diacetoxyiodo)benzene (24.34, 75.62 mmol) and TEMPO (1.08 g, 6.91 mmol). The reaction mixture was then allowed to stir at 25 ^oC for 1 h. After completion of reaction (monitored by TLC), it was quenched by addition of saturated solution of aq. sodium thiosulphate. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, evaporated and the residue subjected to column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) to afford the epoxy aldehyde **(-)-26** (14.27 g) as yellow colored liquid.

Yield: 95%; $[\alpha]_D^{25}$ -41.7 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 778, 838, 1099, 1256, 1472, 1720, 2858, 2930 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.89 (s, 9H), 3.34-3.44 (m, 2H), 3.96-4.00 (m, 2H), 9.47 (d, *J* = 4.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.7, 18.0, 25.5, 57.3, 59.6, 59.7, 197.2; **Anal.** Calcd for $C_{10}H_{20}O_3Si$ requires C, 55.52; H, 9.32; Found: C, 55.60; H, 9.43%.

(*E*)-Ethyl-(2*R*,3*S*)-3-((*tert*-butyl dimethyl silyloxy)methyl(oxiran-2-yl)acrylate [(-)-30]

To a stirred solution of aldehyde **(-)-26** (10.0 g, 46.22 mmol) in dry CH_2Cl_2 (250 mL) at 25 ^oC was added $Ph_3P{=}CHCO_2Et$ (24.0 g, 70.0 mmol) and the reaction mixture was stirred for 2 h. After completion of reaction (monitored by TLC), solvent was distilled off under reduced pressure and the crude mass on column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) gave the α,β-unsaturated ester **(-)-30** (12.18 g) as a slightly yellow colored liquid.

Yield: 92%; $[\alpha]_D^{25}$ -13.7 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 778, 838, 1035, 1260, 1722, 2858, 2930 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 3.32-3.35 (m, 1H), 3.56-3.58 (m, 1H), 3.72-3.75 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.11 (d, *J* = 15.8 Hz, 1H), 6.77-6.82 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -5.3, 14.1, 18.2, 25.8, 54.6, 59.1, 60.5, 60.8, 125.3, 141.2, 165.1; **Anal.** Calcd for $C_{14}H_{26}O_4Si$ requires C, 58.70; H, 9.15; Found: C, 58.78; H, 9.13%.

(4*S*,5*R*,*E*)-Ethyl 4-azido-6-(*tert*-butyldimethylsilyloxy)-5-hydroxyhex-2-enoate (31)

To a solution of epoxy ester **(-)-30** (9 g, 31.44 mmol) in DMF/EtOH/ H_2O (80:80:20 mL) were added NH_4Cl (10.2 g, 189 mmol) and NaN_3 (12.6 g, 189 mmol) at 0 ^oC. The mixture was then stirred at 25 ^oC for 10 h. After completion of reaction (monitored by TLC), EtOH was removed by rotary evaporation. The remaining solution was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (20 mL x 3) and dried (anhydrous Na_2SO_4). After evaporation of the solvent, the residue was purified using coulumn chromatography with petroleum ether/EtOAc (7:3 v/v) to give the azido alcohol **31** (8.79 g) as yellow colored liquid.

Yield: 85%; $[\alpha]_D^{25}$ +15.1 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 668, 765, 835, 1110, 1250, 1515, 1585, 1610, 1740, 2106, 2955, 3320 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.91 (s,

9H), 1.31 (t, *J* = 7.1 Hz, 3H), 2.46 (br s, 1H), 3.60-3.73 (m, 3H), 4.17-4.28 (m, 3H), 6.07 (d, *J* = 15.7 Hz, 1H), 6.82-6.93 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 14.2, 18.2, 25.8, 60.7, 63.2, 64.2, 73.3, 124.8, 141.2, 165.4; **Anal.** Calcd for $C_{14}H_{27}N_3O_4Si$ requires C, 51.04; H, 8.26; N, 12.75; Found: C, 51.10; H, 8.23, N, 12.89%.

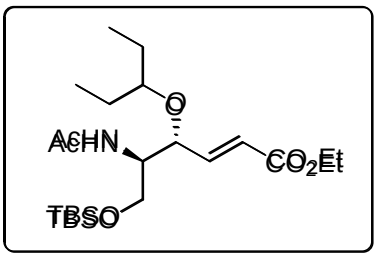
(*E*)-Ethyl 3-((2*S*,3*S*)-1-acetyl-3-((*tert*-butyl di-methyl silyloxy)methyl)aziridin-2-yl)acrylate (25)

To a solution of azido alcohol **31** (5 g, 15.18 mmol) in toluene (30 mL) was added triphenyl phosphine (4.38 g, 16.70 mmol) and the reaction mixture was refluxed for 3 h. After removal of the solvent under reduced pressure, diethylether (10 mL) was added, and the mixture cooled with ice-bath. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate evaporated. This procedure was repeated to remove any traces of triphenylphosphine oxide. The residue obtained was then dissolved in dry CH_2Cl_2 cooled at 0 ^oC. To this solution was added Et_3N (3.10 g, 30.36 mmol), DMAP (5 mg) and acetic anhydride (2.32, 22.77 mmol) and the mixture stirred at 25 ^oC for further 45 minutes. After completion of reaction (monitored by TLC), the reaction mixture was quenched by addition of H_2O. The organic layer was separated, washed with brine, dried (anhydrous Na_2SO_4) and subjected to column chromatographic purification with petroleum ether/EtOAc (7:3 v/v) to afford the acetamide **25** (4.02 g) as a yellow liquid.

Yield: 81%; $[\alpha]_D^{25}$ +60.0 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 973, 1187, 1256, 1356, 1472, 1643, 1715, 2858, 2930 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 2.15 (s, 3H), 2.82-2.91 (m, 1H), 3.15-3.22 (m, 1H), 3.56-3.80 (m, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 6.09 (d, *J* = 15.7 Hz, 1H), 6.72-6.83 (m, 1H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ -5.4, 14.2, 18.2, 23.1, 25.8, 39.8, 44.2, 60.5, 60.9, 125.2, 141.0, 165.3, 182.0; **Anal.** Calcd for $C_{16}H_{29}NO_4Si$ requires C, 58.68; H, 8.93; N, 4.28; Found: C, 58.73; H, 8.86, N, 4.35%.

(4*R*,5*R*,*E*)-Ethyl 5-acetamido-6-(*tert*-butyldimethylsilyloxy)-4-(pentan-3-yloxy)hex-2-enoate (32)



To a well stirred solution of acetamide **25** (4 g, 12.21 mmol) in 3-pentanol (30 mL), a solution of 1.5 equiv $BF_3{\cdot}Et_2O$ in 3-pentanol was added at -10 ^oC, followed by stirring at this temperature for additional 30 minutes. After the completion of reaction (monitored by TLC), it was quenched with a saturated aq. solution of K_2CO_3. The organic layer is then washed with H_2O, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic separation with petroleum ether/EtOAc (6:4 v/v) gave the title compound **32** (3.81 g) as a light yellow colored liquid.

Yield: 75%; $[\alpha]_D^{25}$ +23.6 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 768, 838, 1199, 1345, 1472, 1645, 1720, 2959, 2930, 3320 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.85-0.92 (m, 15H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.46-1.56 (m, 4H), 1.98 (s, 3H), 3.25-3.30 (m, 1H), 3.47-3.56 (m, 1H), 3.67-3.74 (m, 1H), 3.96-4.04 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.34-4.37 (m, 1H), 5.77 (d, *J* = 8.7 Hz, 1H), 5.93 (d, *J* = 15.8 Hz, 1H), 6.79 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, -5.3, 9.2, 9.7, 14.3, 18.1, 23.3, 25.2, 25.8, 26.1, 53.6, 60.3, 73.2, 80.6, 122.4, 146.8, 165.8, 169.6; **Anal.** Calcd for $C_{21}H_{41}NO_5Si$ requires C, 60.68; H, 9.94; N, 3.37; Found: C, 60.76; H, 10.06, N, 3.35%.

Ethyl 2-((2*R*,3*S*,4*R*)-4-acetamido-3-(pentan-3-yloxy)tetrahydrofuran-2-yl)acetate (33) and (4*R*,5*R*,*E*)-Ethyl 5-acetamido-6-hydroxy-4-(pentan-3-yloxy)hex-2-enoate (24)

To a well stirred solution of silyl ether **32** (200 mg, 0.48 mmol) was added 1 M solution of tetrabutylammonium fluoride (1 mL, 1 mmol) at 0 ^{o}C. The reaction mixture was stirred at this temperature for 2 h after which the solvent was removed under reduced pressure and the residue was subjected to column chromatography with petroleum ether/EtOAc (5:5 v/v) to afford furan derivative **33** (94 mg) as major product (65%) and free alcohol **24** (25 mg) as minor product (17%).

Compound 33: Yield: 65%; viscous liquid; $[\alpha]_D^{25}$ +41.7 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1085, 1218, 1231, 1346, 1373, 1545, 1643, 1710, 2978, 3320, 3416 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.82-0.97 (m, 6H), 1.29 (t, *J* = 8.0 Hz, 3H), 1.45-1.52 (m, 4H), 2.00 (s, 3H), 2.63-2.78 (m, 2H), 3.36-3.52 (m, 1H), 3.81-3.92 (m, 3H), 4.12-4.29 (m, 3H), 6.55 (d, *J* = 6.5, Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.0, 9.9, 14.0, 23.0, 25.4, 26.2, 37.4, 56.3, 60.6, 72.3, 80.5, 81.3, 85.5, 169.4, 171.0; **Anal.** Calcd for $C_{15}H_{27}NO_5$ requires C, 59.78; H, 9.03; N, 4.65; Found: C, 59.83; H, 9.08, N, 4.70%.

Compound 24: Yield: 17%; viscous liquid; $[\alpha]_D^{25}$ +34.8 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1165, 1274, 1266, 1306, 1455, 1485, 1659, 1710, 2968, 3311, 3377 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.89 (t, *J* = 7.5 Hz, 6H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.47-1.57 (m, 4H), 2.01 (s, 3H), 3.25-3.34 (m, 1H), 3.64-3.73 (m, 2H), 3.94-4.04 (m, 1H), 4.18 (q, *J* = 7.2, Hz, 2H), 4.32-4.36 (m, 1H), 5.98-6.14 (m, 2H), 6.77-6.88 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.0, 9.7, 14.2, 23.2, 24.9, 26.1, 54.4, 60.5, 62.2, 74.7, 80.5, 123.1, 145.8, 165.7, 170.5; **Anal.** Calcd for $C_{15}H_{27}NO_5$ requires C, 59.78; H, 9.03; N, 4.65; Found: C, 59.91; H, 9.16, N, 4.79%.

((2*S*,3*R*)-3-((*tert*-Butyldimethylsilyloxy)methyl)oxiran-2-yl)methanol [(-)-29]

To a stirred suspension of powdered 4 Å molecular sieves (10.0 g) in dry CH_2Cl_2 (700 mL), titanium tetraisopropoxide (5.68 g, 20 mol %) was added under nitrogen atmosphere. The reaction mixture was cooled to -10 ºC and (+)-diethyl tartrate (6.11 g, 30 mol %) added and stirred for 10 min. To the above solution, *tert*-butyl hydroperoxide 5-6 M solution in decane (39.5 mL, 2 equiv.) was added and stirred at -10 ºC for further 30 min, after which allylic alcohol **28** (20 g, 98.83 mmol) dissolved in dry CH_2Cl_2 (150 mL) was added and stirred at ⁻10 ºC for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with 1M NaOH (25 mL) with further stirring at -10 ºC for 1 h. The organic layer was then separated, washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (7:3 v/v) to afford the allylic alcohol **(-)-29** as a colorless liquid. $[\alpha]_D^{25}$ -11.1 (*c* 2.0, $CHCl_3$).

3,5-Dinitrobenzoate of alcohol (-)-29 (A)

To a stirred solution of 3,5-dinitro benzoylchloride (230 mg, 1 mmol) in dry CH_2Cl_2 was added Et_3N (303 mg, 3 mmol) at 0 ^oC. To the cooled solution was added epoxy alcohol **(-)-29** (218.4 mg, 1 mmol) in CH_2Cl_2 and DMAP (2 mg). The reaction is then stirred at 25 ^oC for further 2 h. After completion of the reaction (monitored by TLC), it was diluted with CH_2Cl_2 and quenched with H_2O. The organic layer is further washed with brine, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure. The crude product is then purified by column chromatography using petroleum ether/EtOAc (7:3 v/v) to afford the title compound **A** (395 mg) as a pale yellow liquid.

Yield: 96%; $[\alpha]_D^{25}$ -8.8 (*c* 3.0, $CHCl_3$); Optical purity 97% ee from **HPLC analysis**: Column: Chiracel OD-H (4.6 X 250 nm), mobile phase: hexane/isopropyl alcohol (80/20), flow rate: 0.5 mL/min, retention time: 46.24 min (-)-isomer, 58.29 min (+)-isomer; **IR** ($CHCl_3$): υ_{max} 721, 888, 1099, 1276, 1462, 1737, 2857, 2929, 3103 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 3.26-3.29, (m, 1H), 3.42-3.43 (m, 1H), 3.88-3.92 (m, 2H), 4.46-4.51 (m, 1H), 4.75-4.78 (m, 1H), 9.19 (s, 2H), 9.24 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 25.8, 53.2, 56.3, 61.0, 65.2, 122.5, 129.5, 133.3, 148.7, 162.2; **Anal.** Calcd for $C_{17}H_{24}N_2O_8Si$ requires C, 49.50; H, 5.86; N, 6.79; Found: C, 49.53; H, 5.88; N, 6.80%.

(2*R*,3*R*)-3-((*tert*-Butyldimethylsilyloxy)methyl)oxirane-2-carbaldehyde [(+)-26]

To a solution of alcohol **(-)-29** (15.02 g, 69.44) in dry CH_2Cl_2 was added in one portion (diacetoxyiodo)benzene (24.34, 75.62 mmol) and TEMPO (1.08 g, 6.91 mmol). The reaction mixture was then allowed to stir at 25 ^oC for 1 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched by addition of saturated solution of aq. sodium thiosulphate. The organic layer was separated, washed with brine and subjected to column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) to afford the epoxy aldehyde **(+)-26**. $[\alpha]_D^{25}$ +43.0 (*c* 3.0, $CHCl_3$).

(*R*)-Ethyl 4-((2*S*,3*R*)-3-((*tert*-butyldimethylsilyloxy)methyl) oxiran-2-yl)-4-hydroxyl-2-methylenebutanoate (36): To a pre-cooled (0 ^oC), well stirred mixture of **(+)-26** (4 g, 18.51 mmol), Zn dust (3.02 g, 45 mmol) and ethyl 2-(bromomethyl)acrylate (8.10 g, 41 mmol) in 80 mL of THF was added a saturated solution of NH_4Cl (8 mL). The mixture was stirred for 10 h at ambient temperature until the aldehyde was totally consumed (monitored by TLC). The mixture was filtered and the precipitate was thoroughly washed with THF (3 x 10 mL). THF was then

removed under vaccum and the remaining solution extracted with EtOAc. The organic layer is then washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic separation with petroleum ether/EtOAc (7:3 v/v) gave title compound *syn*-epoxy alcohol **36** (3.91 g) along with minor amount of its corresponding diastereomer (977 mg) as a yellow colored liquid in 4:1 ratio.

Yield: 64%; $[\alpha]_D^{25}$ -19.2 (*c* 2.0, $CHCl_3$); Optical purity 98% ee from **HPLC analysis**: Column: Chiracel OJ-H (4.6 X 250 nm), mobile phase: hexane/isopropyl alcohol (90/10), flow rate: 0.5 mL/min, retention time: 15.747 min (+)-isomer, 17.517 min (-)-isomer; **IR** ($CHCl_3$): υ_{max} 778, 838, 1097, 1256, 1472, 1715, 2857, 2956, 3471 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.32 (t, *J* = 7.0 Hz, 3H), 2.58 (dd, *J* = 7.8, 14.1 Hz, 1H), 2.74 (dd, *J* = 3.8, 14.1 Hz, 1H), 2.91-2.94 (m, 1H), 3.12-3.14 (m, 1H), 3.15 (br s, 1H), 3.63-3.65 (m, 1H), 3.78 (dd, *J* = 5.8, 11.8 Hz, 1H), 3.90 (dd, *J* = 5.8, 11.5 Hz, 1H), 4.24 (q, *J* = 7.3 Hz, 2H), 5.76 (s, 1H), 6.29 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -5.3, 14.1, 18.2, 25.8, 37.8, 56.1, 58.2, 60.9, 62.0, 69.0, 128.0, 136.6, 167.6; **Anal.** Calcd for $C_{16}H_{30}O_5Si$: C, 58.15; H, 9.15; Found: C, 58.20; H, 9.12%.

Yield: 16%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (d, *J* = 3.0 Hz, 6H), 0.90 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H), 2.54-2.60 (m, 2H), 2.99 (dd, *J* = 4.2, 7.3 Hz, 1H), 3.14 (dd, *J* = 4.7, 10.5 Hz, 1H), 3.68-3.81 (m, 2H), 4.20 (q, *J* = 7.1, 14.3 Hz, 2H), 5.72 (s, 1H), 6.27 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, -5.2, 14.2, 18.3, 25.9, 37.1, 57.7, 59.8, 60.9, 61.7, 68.7, 128.1, 136.2, 166.9.

(*R*)-Ethyl 4-((2*S*,3*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)-4-methoxymethoxy) -2-methylenebutanoate (37)

To a solution of compound **36** (3 g, 9.09 mmol) in dry CH_2Cl_2 (50 mL) was added *N*,*N*-diisopropylethylamine (DIPEA) (1.3 g, 29.7 mmol), followed by addition of MOMCl (1 mL, 19.8 mmol) at 0 ^oC. The mixture was stirred for 10 h and H_2O (10 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (petroleum ether/ EtOAc = 9/1) to give MOM protected compound **37** (3.39 g) as a colorless oil.

Yield: 90%; $[\alpha]_D^{25}$ +2.9 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 778, 838, 1150, 1257, 1716, 2857, 2955 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H), 2.53-2.57 (m, 2H), 2.96-3.09 (m, 2H), 3.32 (s, 3H), 3.62-3.87 (m, 3H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.56 (dd, *J* = 6.7 Hz, 1H), 4.84 (dd, *J* = 6.8 Hz, 1H), 5.68 (s, 1H), 6.25 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -5.2, 14.2, 18.3, 25.9, 35.4, 55.5, 55.6, 59.1, 60.7, 61.8, 73.3, 95.3, 127.7, 136.2, 166.4; **Anal.** Calcd for $C_{18}H_{34}O_6Si$: C, 57.72; H, 9.15; Found: C, 57.78; H, 9.12%.

(*R*)-Ethyl 4-((2*S*,3*R*)-3-(hydroxymethyl)oxiran-2-yl)-4-(methoxy methoxy)-2-methylene butanoate (38): To a well stirred solution of silyl ether **37** (1.1 g, 2.94 mmol) was added 1 M solution of tetrabutylammonium fluoride (6.2 mL, 5.87 mmol) at 0 ^oC. The reaction mixture was stirred at this temperature for 2 h after which the solvent was removed under reduced pressure and the residue was subjected to column chromatography with petroleum ether/EtOAc (6:4 v/v) to afford free alcohol **38** (673 mg) oily liquid.

Yield: 88%; $[\alpha]_D^{25}$ +4.1 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 919, 1048, 1305, 1410, 1632, 1716, 2983.3, 3453 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.23 (t, *J* = 7.1 Hz, 3H), 2.51 (dd, *J* = 9.0, 14.0

Hz, 1H), 2.68 (dd, *J* = 3.4, 13.6 Hz, 1H), 2.83-2.89 (m, 1H), 3.11-3.17 (m, 1H), 3.24 (br s, 1H), 3.30 (s, 3H), 3.51-3.57 (m, 2H), 3.77-4.08 (m, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.52 (d, *J* = 7.2 Hz, 1H), 4.66 (d, *J* = 7.2 Hz, 1H), 5.59 (s, 1H), 6.16 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 36.6, 55.5, 56.2, 57.9, 60.0, 60.8, 72.8, 96.0, 127.8, 136.5, 166.9; **Anal.** Calcd for $C_{12}H_{20}O_6$ requires C, 55.37; H, 7.74; Found: C, 55.43; H, 7.90%.

(*R*)-Methyl 4-((2*S*,3*R*)-3-ethynyloxiran-2-yl)-4-(methoxymethoxy)-2-methylenebutanoate (41)

To a solution of epoxy alcohol **38** (1.4 g, 5.34 mmol) in DMSO (5 mL) in a round-bottomed flask was added IBX (1.68 g, 6 mmol) in one portion and the reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was quenched with diethylether (5 mL), H_2O (0.5 mL) and filtered through a pad of celite. The residue was repeatedly washed with diethyl ether. The filtrate was then washed with H_2O, brine, dried ($Na_2SO_{4)}$ and concentrated to give the crude aldehyde **39**, which was pure enough and used in the next step without further purification. To a solution of crude aldehyde **39** and K_2CO_3 (900 mg, 8 mmol) in 20 mL dry MeOH are added diethyl-1-diazo-2-oxopropylphosphonate (1.26 g, 6 mmol) and stirring is continued until the reaction is complete as indicated by TLC (2 h). The reaction mixture is diluted with diethylether (100 mL), washed with an aq. solution of $NaHCO_3$ and dried over Na_2SO_4. Evaporation of solvent yielded analytically pure terminal alkyne **41** (1.05 g) as a colorless liquid.

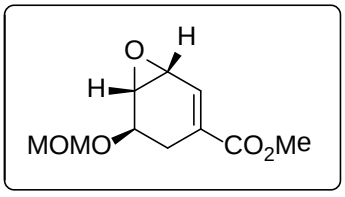
Yield: 82%; $[\alpha]_D^{25}$ -9.4 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 757, 1171, 1289, 1441, 1409, 1715, 2226, 2953 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.44 (d, *J* = 1.6 Hz, 1H), 2.67 (dd, *J* = 7.4, 14.3 Hz, 1H), 2.78 (dd, *J* = 5.4, 15.3 Hz, 1H), 2.99 (dd, *J* = 3.7, 8.1 Hz, 1H), 3.33 (s, 3H), 3.48-3.50

(m, 1H), 3.76 (s, 3H), 3.79-3.87 (m, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 5.71 (d, *J* = 1.0 Hz, 1H), 6.26 (d, *J* = 1.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.4, 45.2, 51.8, 55.7, 58.5, 73.6, 75.1, 78.2, 95.7, 127.7, 136.2, 167.4; **Anal.** Calcd for $C_{12}H_{16}O_5$ requires C, 59.99; H, 6.71; Found: C, 60.02; H, 6.78%.

(*R*)-Methyl 4-(methoxymethoxy)-2-methylene-4-((2*S*,3*R*)-3-vinyl oxiran-2-yl)butanoate (35)

To a solution of **41** (240 mg, 1 mmol) in 5 mL of ethyl acetate/pyridine/1-octene (10:1:1) was added Lindlar's catalyst (12 mg). The reaction mixture was stirred for 6 h under a balloon of H_2 at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (7:3 v/v) as eluent to give olefin **35** (230 mg) as colorless liquid.

Yield: 95%; $[\alpha]_D^{25}$ -5.4 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 878, 1169, 1204, 1341, 1514, 1711, 2924, 3034 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.51 (d, *J* = 7.0 Hz, 2H), 3.05-3.11 (m, 1H), 3.34 (s, 3H), 3.38-3.41 (m, 1H), 3.67-3.74 (m, 1H), 3.76 (s, 3H), 4.58 (d, *J* = 6.7 Hz, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 5.33 (m, 1H), 5.52 (d, *J* = 1.7 Hz, 1H), 5.67-5.71 (m, 2H), 6.23 (d, *J* = 1.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.1, 51.8, 55.3, 57.4, 59.3, 71.1, 94.9, 120.5, 127.7, 132.1, 136.4, 167.1; **Anal.** Calcd for $C_{12}H_{18}O_5$ requires C, 59.49; H, 7.49; Found: C, 59.71; H, 7.61%.



(1*R*,5*R*,6*S*)-Methyl 5-(methoxymethoxy)-7-oxabicyclo[4.1.0]hept-2-ene-3-carboxylate (34): A mixture of diene **35** (400 mg, 1.65 mmol) and Grubbs' second-generation catalyst (70 mg, 5 mol%) in dry CH_2Cl_2 (50 mL) was stirred under reflux for 14 h. The reaction mixture was evaporated and the residue purified on silica gel chromatography by eluting with petroleum ether/ EtOAc (7:3 v/v) to afford **34** (318 mg) as gum.

Yield: 90%; $[\alpha]_D^{25}$ -32.7 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1091, 1139, 1235, 1387, 1497, 1579, 1719, 2986 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.17-2.27 (m, 1H), 2.81-2.86 (m, 1H), 3.43 (s, 3H), 3.45-3.47 (m, 1H), 3.65-3.67 (m, 1H), 3.74 (s, 3H), 3.98-4.06 (m, 1H), 4.78 (s, 2H), 6.98 (t, *J* = 3.4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.5, 46.5, 51.9, 55.0, 55.4, 69.3, 95.9, 128.3, 131.1, 167.5; **Anal.** Calcd for $C_{10}H_{14}O_5$ requires C, 56.07; H, 6.59; Found: C, 56.01; H, 6.53%.

(3*S*,4*R*,5*R*)-Methyl 3- azido-4-hydroxy-5-(methoxymethoxy)cyclo hex-1-enecarboxylate (42)

To a solution of cyclic epoxy ester **34** (107 mg, 0.5 mmol) in DMF/EtOH/ H_2O (4:4:1 mL) were added NH_4Cl (160 mg, 3 mmol) and NaN_3 (197 mg, 3 mmol) at 0 ^oC. The mixture was then stirred at 25 ^oC for 10 h. After completion of reaction (monitored by TLC), EtOH was removed by rotary evaporation. The remaining solution was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with, brine (20 mL x 6) and dried (anhydrous Na_2SO_4). After evaporation of the solvent, the residue was purified by chromatography (petroleum ether/ EtOAc (6/4 v/v).

Yield: 83% (106 mg); yellow liquid; $[\alpha]_D^{25}$ +17.3 (*c* 0.7, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1073, 1176, 1235, 1365, 1448, 1489, 1561, 1714, 2106, 2994, 3345 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.19-2.33 (m, 1H), 2.87-3.00 (m, 1H), 3.44 (s, 3H), 3.62-3.67 (m, 2H), 3.75 (s, 3H), 4.05-4.19 (m, 1H), 4.76 (s, 2H), 6.59 (t, *J* = 2.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.6, 52.2, 55.9, 63.4, 74.6, 77.9, 96.8, 129.9, 134.4, 165.7; **Anal. Calcd** for $C_{10}H_{15}N_3O_5$ requires C, 46.69; H, 5.88; N,

16.33; Found: C, 46.61; H, 5.85; N, 16.38%.

(1*S*,5*R*,6*S*)-Methyl 7-acetyl-5-(methoxymethoxy)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (43)

To a solution of azido alcohol **42** (150 mg, 0.58 mmol) in toluene (5 mL) was added triphenylphosphine (152 mg, 0.58 mmol) and the reaction mixture was refluxed for 3 h. After removal of the solvent under reduced pressure, diethylether (1 mL) was added, and the mixture cooled with ice-bath. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate evaporated. This procedure was repeated to remove any trace of triphenylphosphine oxide. The residue obtained was then dissolved in dry CH_2Cl_2 cooled at 0 ^oC. To this solution was added Et_3N (175.74 mg, 1.74 mmol), DMAP (5 mg) and acetic anhydride (118.32 mg, 1.16 mmol) and the mixture stirred at 25 ^oC for further 45 min. After completion of reaction (monitored by TLC), it was quenched by the addition of H_2O. The organic layer was separated, washed with brine, dried (anhydrous Na_2SO_4) and subjected to column chromatographic purification with petroleum ether/ EtOAc (7:3 v/v) to afford the cyclic acetamide **43** (120 mg) as colorless viscous liquid.

Yield: 81%; $[\alpha]_D^{25}$ -57.8 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1073, 1195, 1255, 1324, 1369, 1448, 1708, 1732, 2987, 3115 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.10 (s, 3H), 2.20-2.27 (m, 1H), 2.86-2.96 (m, 2H), 3.16 (m, 1H), 3.36 (s, 3H), 3.76 (s, 3H), 4.41-4.46 (m, 1H), 5.61-5.73 (m, 2H), 7.11 (t, *J* = 1.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 23.8, 46.4, 51.9, 55.0, 55.4, 69.3, 95.9, 133.2, 148.3, 166.2, 184.9; **Anal.** Calcd for $C_{12}H_{17}NO_5$ requires C, 56.46; H, 6.71; N, 5.49; Found: C, 56.51; H, 6.85; N, 5.48%.

(3*R*,4*R*,5*R*)-Ethyl 4-acetamido-5-hydroxy-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (21):

To a well stirred solution of cyclic acetamide **43** (160 mg, 0.64 mmol) in 3-pentanol (10 mL), a solution of 1.5 equiv. of $BF_3{\cdot}Et_2O$ (0.96 mmol) in 3-pentanol (2 mL) was added at -10 ^oC, followed by stirring at this

temperature for additional 30 min. After the completion of reaction (monitored by TLC), it was quenched with a saturated aq. solution of K_2CO_3. The organic layer was then washed with H_2O, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude amino alcohol product of sufficient purity as a gum, which was used for further reaction. To a well stirred solution of crude amino alcohol in EtOH (10 mL), a 2 N solution of HCl (2 mL) was added. The reaction was stirred for an additional 12 h at 25 ^oC. After the completion of reaction (monitored by TLC), it was quenched by adding aqueous K_2CO_3. The reaction mixture was then partitioned between EtOAc and brine. The organic layer was further washed with brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic purification with petroleum ether/ EtOAc (3:7 v/v) gave title compound **21** (128 mg) as colorless solid.

Yield: 64%; m.p. 129-131 ^oC {lit.[10] m.p. 131.9-132.2 ^oC}; $[\alpha]_D^{25}$ -84.8 (*c* 1.0, EtOAc) {lit.[10] $[\alpha]_D^{25}$ -104 (*c* 3, EtOAc)}; **IR** ($CHCl_3$): υ_{max} 1085, 1274, 1266, 1306, 1373, 1455, 1585, 1649, 1707, 2963, 3311, 3396 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.90 (t, *J* = 6.7 Hz, 6H), 1.25 (t, *J* = 7.9 Hz, 3H), 1.42 (m, 4H), 1.99 (s, 3H), 2.59 (m, 2H), 3.40 (m, 1H), 3.46 (s, 1H), 3.86 (m, 1H), 3.91 (t, *J* = 6.7 Hz, 1H), 4.15 (m, 3H), 4.41 (m, 1H), 5.78 (m, 1H), 6.84 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.7, 9.8, 14.2, 23.8, 26.1, 26.7, 31.9, 55.2, 61.1, 67.4, 72.9, 82.3, 129.4, 136.4, 166.8, 171.8; **Anal.** Calcd for $C_{16}H_{27}NO_5$ requires C, 59.46 requires C, 61.32; H, 8.68; N, 4.47; Found: C, 61.47; H, 8.71; N, 4.56%.

(-)-Oseltamivir free base (1)

Compound **21** (312 mg, 1 mmol) and triethylamine (303 mg, 3 mmol) were dissolved in dry CH_2Cl_2 (15 mL), and the solution cooled to 0 ^oC. Methanesulfonyl chloride (229.2 mg, 2 mmol) was added, and then the resulting solution was stirred at 0 ^oC for 1 h. After TLC showed that the reaction was complete, excess CH_2Cl_2 (20 mL) was added. The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After the solvent was removed under vaccum, the crude product was dissolved in DMF and NaN_3 (390 mg, 6 mmol) was added. The reaction mixture was then stirred at 80 ^oC for 3 h. After the completion of reaction (monitored by TLC), it was then partitioned between EtOAc and brine. The organic layer was further washed with brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic purification with petroleum ether/EtOAc (4:6 v/v) gave the corresponding cyclic azide. The cyclic azide was then dissolved in EtOH and Lindlar's catalyst (20 mg) added. The reaction mixture was stirred for 6 h under a balloon of H_2 at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using MeOH/EtOAc (5:5 v/v) as eluent to give (-)-oseltamivir free base **1** (224 mg).

Yield: 72%; $[\alpha]_D^{25}$ -37.8 (*c* 1, EtOH) {lit.[10] $[\alpha]_D^{25}$ -49.2 (*c* 9.33, EtOH)}; **IR** ($CHCl_3$): υ_{max} 1068, 1127, 1255, 1374, 1456, 1568, 1644, 1714, 2977, 3289 cm-1; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.90 (m, 6H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.42 (m, 4H), 2.03 (s, 3H), 2.23 (m, 1H), 2.76 (m, 1H), 3.30 (m, 1H), 3.46 (m, 1H), 4.15 (m, 3H), 5.78 (m, 1H), 6.79 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.1, 10.2, 14.8, 24.5, 26.3, 26.7, 34.3, 49.8, 59.5, 61.3, 75.7, 82.3, 129.9, 138.0, 167.1, 171.8; **Anal.** Calcd for $C_{16}H_{28}N_2O_4$ requires C, 61.51; H, 9.03; N, 8.97; Found: C, 61.47; H, 8.98; N,

8.88%.

(3*R*,4*S*,5*R*)-Methyl 3,4-dihydroxy-5-(methoxymethoxy)cyclohex-1-enecarboxylate (44)

To a well stirred solution of epoxide **34** (107 mg, 0.5 mmol) in THF/H_2O (3:1), concentrated H_2SO_4 (5 drops) was added. The reaction was stirred for an additional 2 h at 25 ^oC. After the completion of reaction (monitored by TLC), it was diluted with excess of EtOAc. The organic layer is further washed with H_2O, brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic purification with petroleum ether/EtOAc (2:8 v/v) gave diol **44** (111 mg) as viscous liquid.

Yield: 96%; $[\alpha]_D^{25}$ -45.1 (*c* 0.5, EtOH); **IR** ($CHCl_3$): υ_{max} 1088, 1300, 1373, 1717, 2878, 2967, 3387, 3468 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.56-2.71 (m, 2H), 3.41 (s, 3H), 3.56-3.59 (m, 1H), 3.74 (s, 3H), 4.02-4.04 (m, 1H), 4.37-4.39 (m, 1H), 4.70 (s, 2H), 6.82 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.9, 51.9, 55.8, 70.2, 73.9, 77.6, 97.1, 127.9, 137.8, 166.6; **Anal.** Calcd for $C_{10}H_{16}O_6$ requires C, 51.72; H, 6.94; Found C, 51.82; H, 6.98.

Methyl 3-*epi* shikimate (2)

To a well stirred solution of diol **44** (95 mg, 0.41 mmol) in MeOH was added 2N solution of HCL. The reaction was stirred for an additional 6 h at 25 ^oC. After the completion of reaction (monitored by TLC), it was diluted with excess of EtOAc. The organic layer is further washed with H_2O, brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic purification with MeOH/EtOAc (3:7 v/v) gave title compound **2** (57 mg) in 74% yield as colorless solid.

Yield: 74%; m.p. 131-133 ^oC {lit.[5] m.p. 132 ^oC}; $[\alpha]_D^{25}$ -13.1 (*c* 0.5, MeOH) {lit.[5] $[\alpha]_D^{25}$ -13.4 (*c*

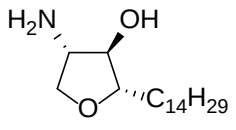
0.5, MeOH)}; **IR** ($CHCl_3$): υ_{max} 1089, 1176, 1245, 1378, 1489, 1661, 1714, 2106, 2994, 3456 cm^{-1}; **^{1}H NMR** (200 MHz, D_2O): 2.23 (m, 1H), 2.81 (m, 1H), 3.47 (dd, *J* = 8.5, 10 Hz, 1H), 3.76 (s, 3H), 3.77 (m, 1H), 4.24 (m, 1H), 6.68 (m, 1H); **^{13}C NMR** (50 MHz, D_2O): 168.6, 138.4, 127.2, 76.4, 71.9, 68.6, 52.8, 31.7; **Anal.** Calcd for $C_8H_{12}O_5$ requires C, 51.06; H, 6.43; O, 42.51; Found C, 51.11; H, 6.54.

Section II

A tandem desilylation-oxa Michael addition reaction for the synthesis of 3-*epi*- Jaspine B

1.2.1 Introduction and Pharmacology

Poly-substituted tetrahydrofurans (THFs) represents an important class of five-membered heterocycles that can be found as structural elements of many natural products and pharmaceutically important substances.[17] Tri-substituted THFs like 3-*epi*-jaspine B **45** (**Figure 16**) and its stereoisomers have shown remarkable cytotoxic activity against A549 human lung carcinoma cell lines (LD_{50} = 1.50 ±0.03 µM) and MCF7 primary breast cancer cells (IC_{50} = 1.50 ±0.03 µM).[18] It was initially believed that 3-*epi*-jaspine B **45** and its stereoisomers inhibit sphingomyelin synthase and thus increases the intracellular ceramide level, inducing apoptotic cell death by a caspase dependent pathway.[18] Toxic effects of **45** were investigated by flow cytometry analysis after double labelling with annexin V (AV) and propidium iodide (PI). The results on A549 cells cultured in the presence of **45** at different concentrations as well as control experiments indicated that the percentage of AV-stained cells (2%) was not significantly increased. Finally, a concentration-dependent increase in the percentage of PI positive cells were observed in all cases.[18,19] These results demonstrate that apoptosis only accounts for a minor percentage of cell death and, therefore, a different cell death mechanism must be implicated.[19]



45

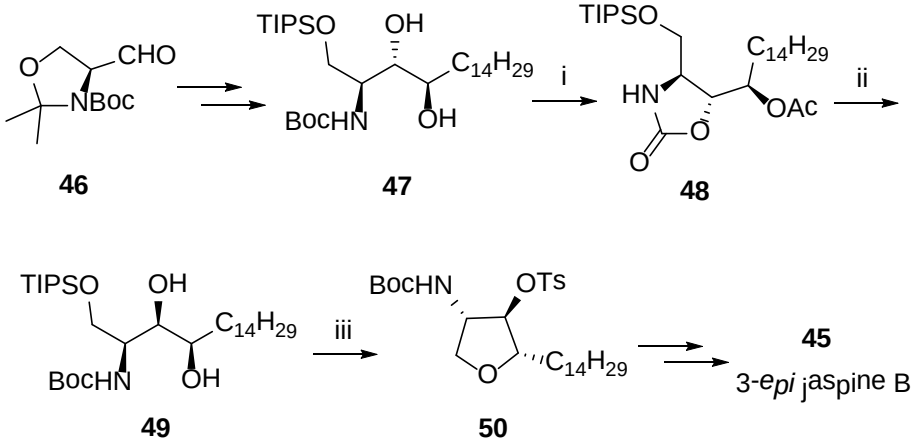
Figure 16: Structure of 3-*epi*-jaspine B (**45**)

1.2.2 Review of literature

Various syntheses of 3-*epi* jaspine B **45** have been documented in the literature, most of which are based on chiral pool strategies. Some of the interesting and important synthetic routes are described below.

Yoshimitsu's approach (2009)[20]

Yoshimitsu *et al*. have employed a stereoselective synthesis of 3-*epi* jaspine B **45** by use of regio- and stereospecific ring-opening reaction of the oxazolidin-2-one **48** assisted by a Boc group. This key step gave *syn*-diol **49**. Reaction of **47** with $MeC(OMe)_3$ in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ directly afforded the desired oxazolidinone **48** in excellent yield, *via* orthoester formation, followed by regioselective nucleophilic attack of the Boc oxygen toward C-3. The three stereogenic centers were constructed starting from Garner's aldehyde **46** as the sole chiral source; the title compound **45** was obtained in 11 steps with an overall yield of 23.4% (**Scheme 12**).

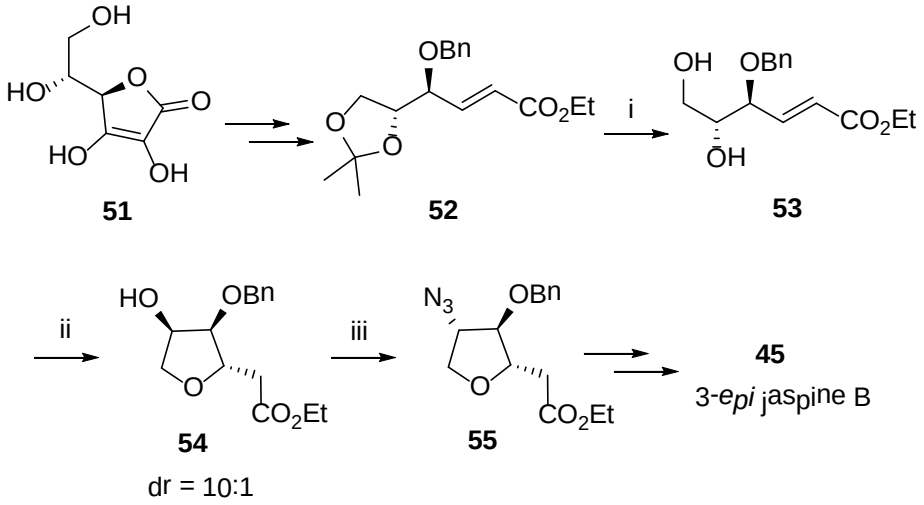


Scheme 12: (i) $MeC(OMe)_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25 °C, 96%; (ii) (a) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C; (b) NaOMe, MeOH, 25 °C, 75% (over two steps); (iii) (a) TsCl, Et_3N, CH_2Cl_2, 25 °C; (b) TBAF, THF, 25 °C, 70% (over two steps).

Basha's approach (2010)[21]

Basha *et al*. have described a stereoselective synthesis of 3-*epi* jaspine B **45** from D-(-)-

isoascorbic acid **51** as the starting material. The key reaction of the synthesis is the base catalyzed intramolecular oxa-Michael addition of diol **53**, which afforded the tetrahydrofuran derivative **54** in dr = 10:1. Conversion of alcohol **54** to **55** was done in two steps: (i) Mesylation and (ii) Azidation. The seven-step conversion from isoascorbic acid **51** to intermediate **55** was achieved with an overall yield of 55.5% (**Scheme 13**).

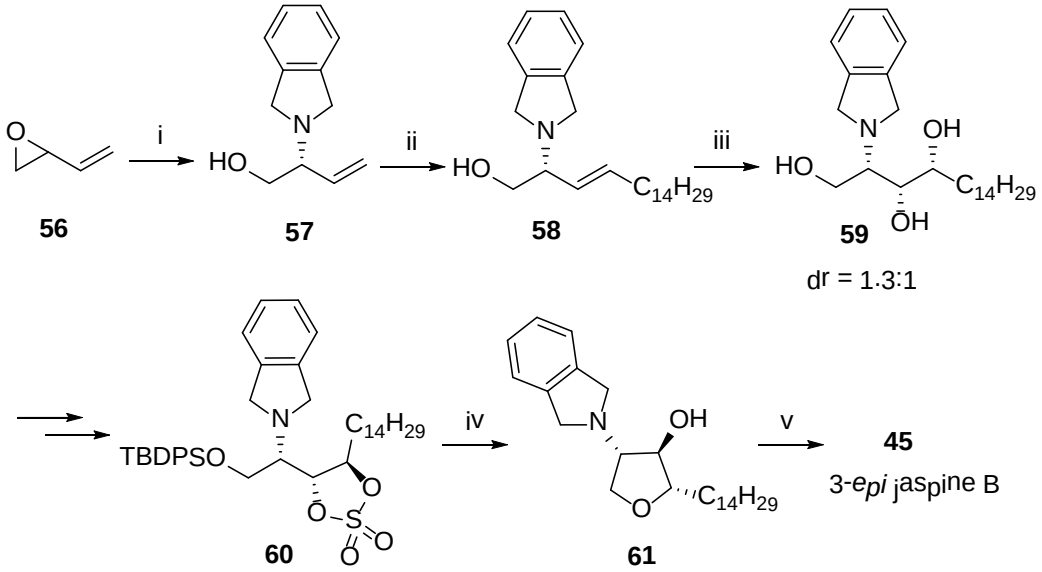


Scheme 13: (i) 80% aq. AcOH, 0°C, 8 h, 98%; (ii) NaH, THF, 0.5 h, -40 °C, 96%; (iii) (a) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h; (b) NaN_3, DMF, 120°C, 8 h, 90% (over two steps).

Castillon's approach (2011)[22]

In Castillon's approach, butadiene monoepoxide **56** was treated with phthalimide in the presence of Pd/(*S*,*S*)-DACH-naphthyl to afford 2-*N*-phthalimido-3-buten-1-ol **57** *via* a Pd-catalyzed DYKAT process. Compound **57** was treated with an excess amount of 1-hexadecene in the presence of the second generation Grubbs catalyst to afford compound **58**. Substrate-controlled dihydroxylation of olefine **58** by using osmium catalysis provided diol **59**. Diol **59** was converted to cyclic sulfite **60** by a series of known reactions. Compound **60** was treated with TBAF in THF at room temperature to afford protected tetrahydrofuran **61** *via* desilylative cyclization and sulfate

hydrolysis in 93% yield over two steps. Finally, removal of the phthalimido group with methylamine afforded **45** with an overall yield of 24% (**Scheme 14**).

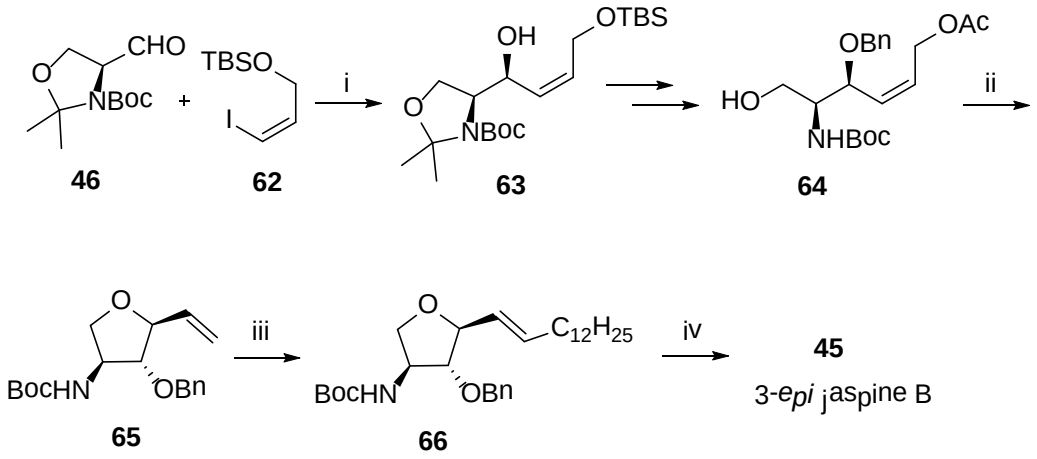


Scheme 14: (i) Pd/(*S*,*S*)-DACH-naphthyl, Na_2CO_3, CH_2Cl_2, 25 °C, 8 h, 94%, 98%ee; (ii) Grubbs' II,1-hexadecene, CH_2Cl_2, 12 h, reflux, 99%; (iii) K_2OsO_4, $(DHQD)_2$-PYR, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *tert*-BuOH:H_2O (1:1), 25 °C, 24 h, 98%;(iv) (a) TBAF, THF, 25 °C, 2 h; (b) H_2SO_4, THF, H_2O, 25°C,2 h, 93% (over two steps); (v) $MeNH_2$, 1h, 50 °C, 85%.

Koskinen's approach (2011)[23]

This route consists of nine steps from the commercially available Garner's aldehyde **46**. Iodide **62**, prepared from propargyl alcohol, was coupled with Garner's aldehyde **46** using *n*-BuLi as base and $ZnCl_2$ as additive giving alcohol **63** (*syn*/*anti* = 5.7:1). The furan framework **65** was obtained from alcohol **64** *via* an η^3-allylpalladium intermediate using $Pd(PPh_3)_4$ as catalyst. Cross metathesis between **65** and 1-tetradecene using Grubbs' second generation catalyst was used for the introduction of aliphatic side chain. The final hydrogenation and global deprotection was performed on olefine **66**. Firstly, the double bond and benzyl ether were hydrogenated over Pd/C at an atmospheric pressure of

H_2 gas. Next the *t*-butyl carbamatewas cleaved off with HCl in MeOH at 0 ◦C and after basic work up **45** was obtained in an overall yield of 2% only (**Scheme 15**).



46 **62** **63** **64** **65** **66**

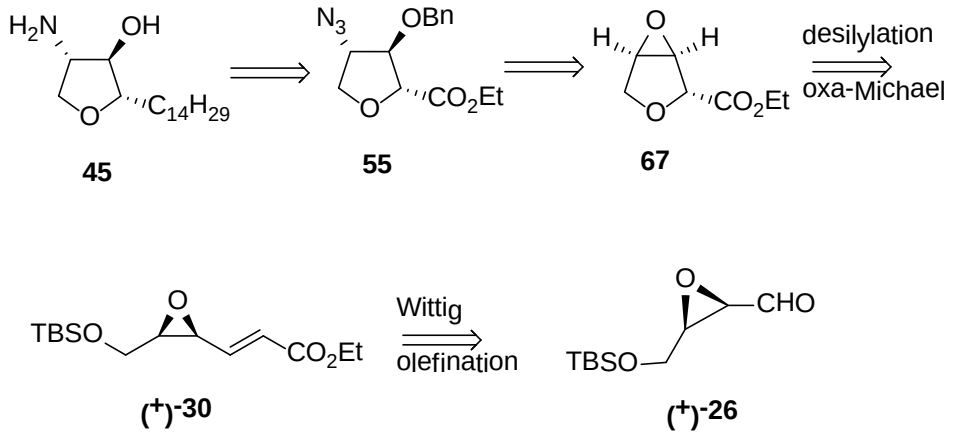
Scheme 15: (i) *n*-BuLi, $ZnCl_2$, toluene/Et_2O, -95 °C, 72%; (ii) $Pd(PPh_3)_4$, PPh_3, THF, 1h, 55°C, 8%; (iii) Grubbs' 2nd gen., 1-tetradecene, CH_2Cl_2, 45 °C, 78%; (iv) (a) 10% Pd/C, H_2 (1 atm.),MeOH, 25°C; (b) HCl, MeOH, 0 °C

1.2.3 Present Work

1.2.3.1 Objective

As can be seen from the review section, several methods of synthesis for 3-*epi* jaspine B **45** have been reported. However, many of them suffer from one or more disadvantages, which include use of chiral pool strategy and low yields. With a view to elucidate the effect of stereochemistry and substitution on the biological activity as well as study of mode of action of various jaspines, a useful synthetic route with high flexibility in yields and stereoselectivity is required. During our initial attempt at the synthesis of (-)-oseltamivir **1**, we came across unexpectedly a one-pot tandem desilylation-oxa Michael addition reaction for the facile construction of optically and diastereomerically pure tetrahydrofurans (**see Section I**). This section describes the application of the desilylation-oxa Michael addition strategy in the synthesis of 3-*epi* jaspine B **45**.

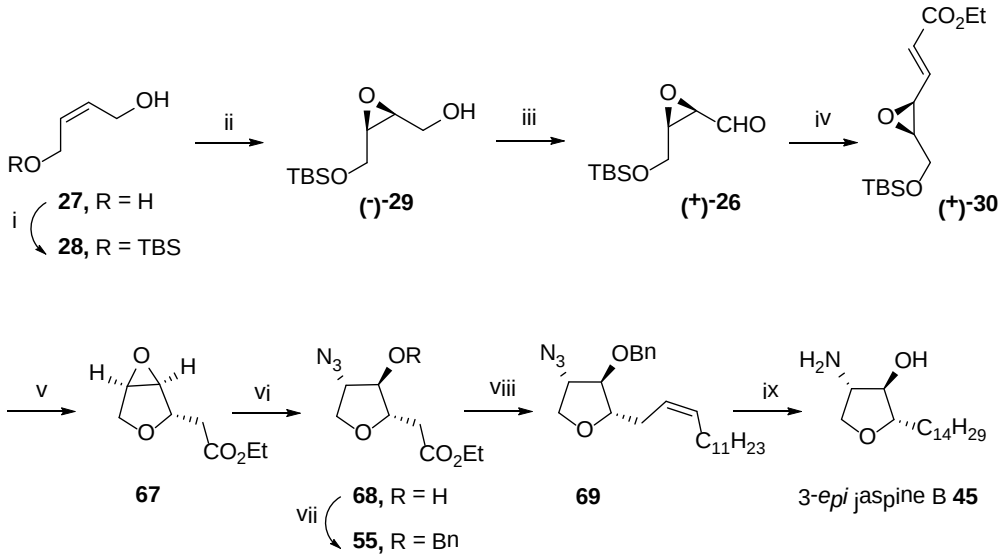
Based on retrosynthetic analysis, we visualized that 3-*epi* jaspine B **45** could be obtained from benzyl ether **55**, which in turn could be envisaged from epoxide **67** (**Scheme 16**). Cyclic epoxide **67** was envisioned *via* a one-pot tandem desilylation-oxa Michael addition reaction of epoxy ester **(+)-30**. α,β-Unsaturated ester **(+)-30** was envisaged from chiral epoxide **(+)-26**.



Scheme 16: Retrosynthetic analysis of 3-*epi* jaspine B **45**

1.2.3.2 Results and Discussion

The present synthetic route to 3-*epi* jaspine B **45** is shown in **Scheme 17**.



Scheme 17: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (+)-DET,

$Ti(O^iPr)_4$, anhydrous TBHP (5-6 M in decane), 4 Å molecular sieves, dry CH_2Cl_2, -10 ºC, 12 h, 93%; (iii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (iv) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, 25 ºC, 2 h, 92%; (v) TBAF, THF, 25 ºC, 2 h, 93%, de > 99%; (vi) NaN_3, NH_4Cl, $EtOH/H_2O$ (4:1), 80 ºC, 12 h, 91%; (vii) BnBr, Ag_2O, dry CH_2Cl_2, 0-25 ºC, 6 h, 95%; (viii) (a) DIBAL-H, toluene, -78 ºC, 1 h; (b) *n*-BuLi, $PPh_3{}^+C_{12}H_{25}Br^-$, THF, -78-0 ºC, 3 h, 75%; (ix) H_2 (1 atm), 10% Pd/C, MeOH, 25 ºC, 12 h, 97%.

Initially, α,β-unsaturated epoxy ester **(+)-30** was prepared in an overall yield of 59.3% from commercially available *cis*-2-butene-1,4-diol **27** in four steps by following the procedure described in **Section I**: (i) selective monosilylation of diol **27** (TBSCl, imid, 73%); (ii) Sharpless asymmetric epoxidation of allylic alcohol **28** [$Ti(O^iPr)_4$, (+)-DET, anhydrous TBHP, 93%]; (iii) oxidation of epoxy alcohol **(-)-29** (TEMPO, BAIB, 95%); (iv) Wittig olefination of **(+)-26** with $Ph_3P{=}CHCO_2Et$. The formation of α,β-unsaturated ester **(-)-30** was confirmed by its ^1H, ^{13}C NMR and IR spectral analysis. Its ^1H NMR spectrum of **(+)-30** showed signals at δ 3.32-3.35 (m) and 3.56-3.58 (m) due to methine protons attached to epoxide group. The signals at δ 3.72-3.75 (m) and 4.19 (q, J = 7.1 Hz, 2H) were attributed to methylene protons attached to silyl ether (-$\mathbf{CH_2}$-OTBS) and ester (-OCO$\mathbf{CH_2}CH_3$) groups respectively. Its ^{13}C NMR spectrum showed typical signals at δ 54.6 and 59.1 due to epoxide carbons, while the signals appearing at δ 60.5 and 60.8 were due to methylene carbons attached to oxygen (**Figure 17)**. The characteristic carbon signal at δ 165.1 accounted for ester carbonyl function. The IR spectrum of epoxy ester **(+)-30** showed a strong absorption band at υ_{max} 1722 cm^{-1} for ester carbonyl frequency.

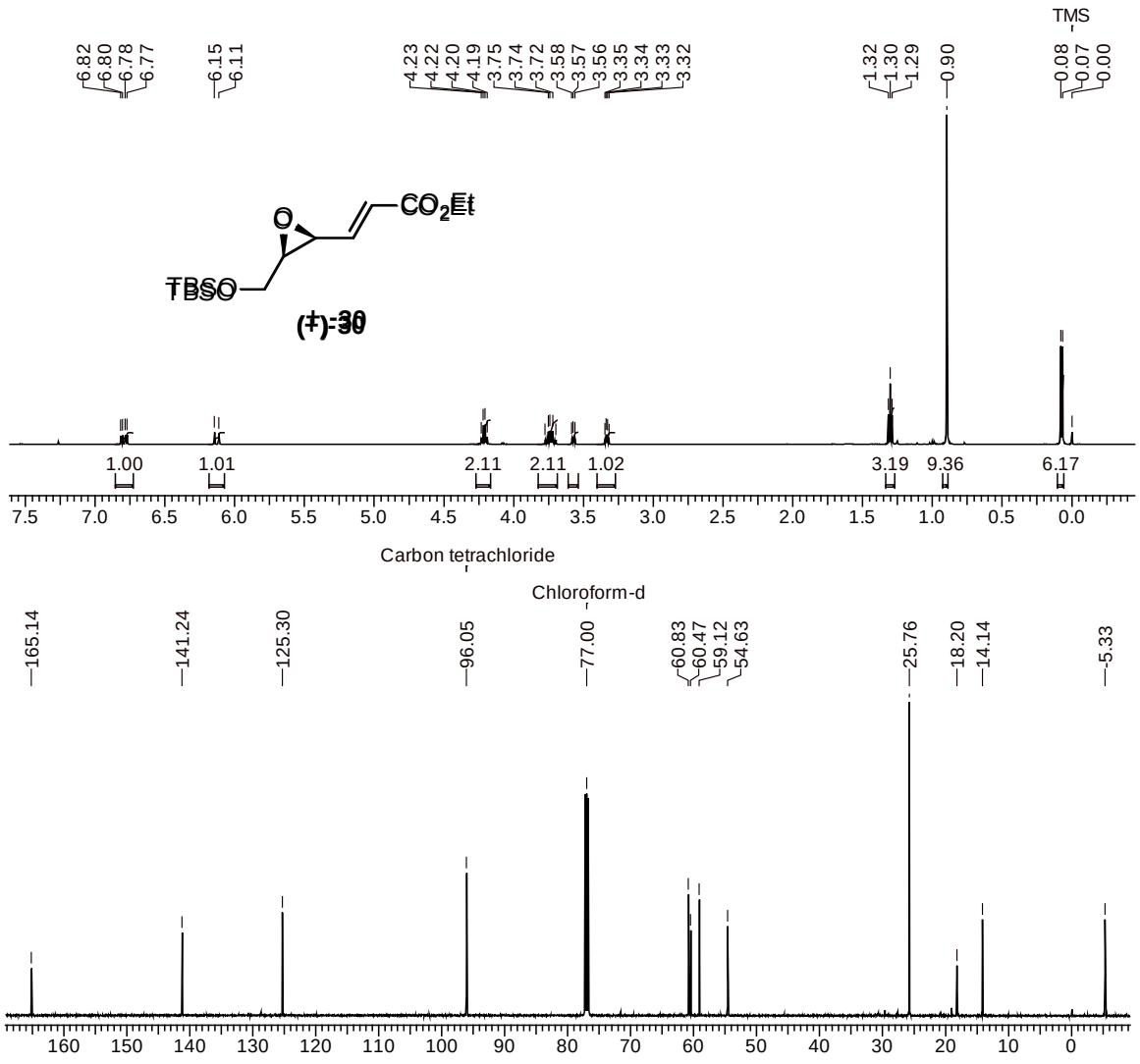
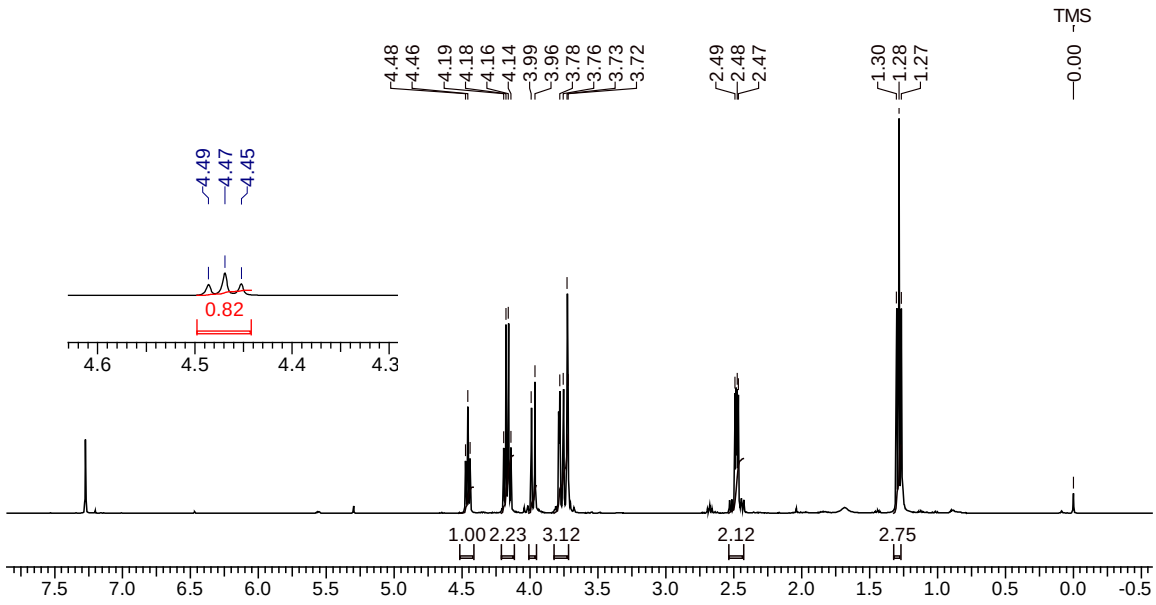
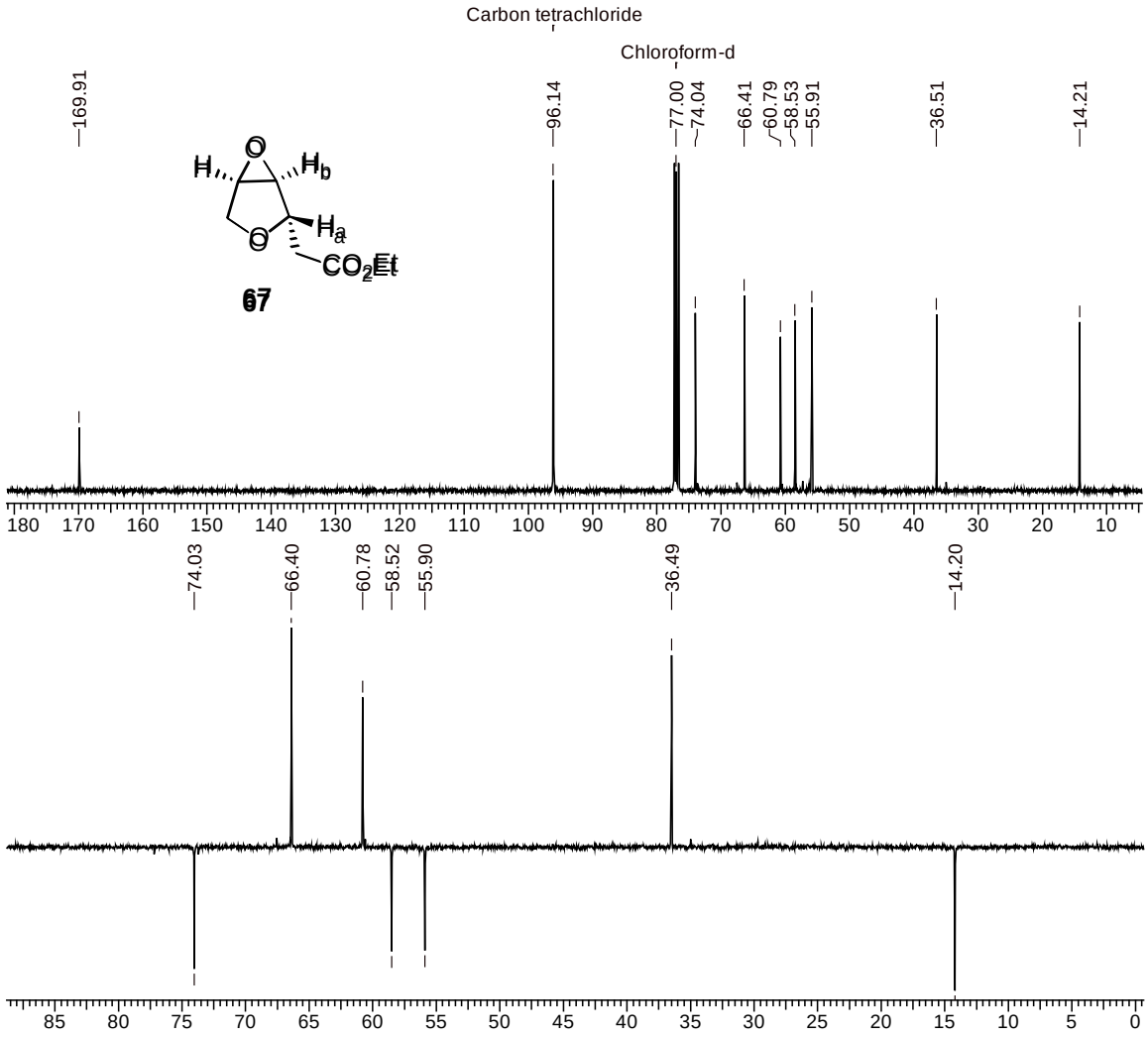


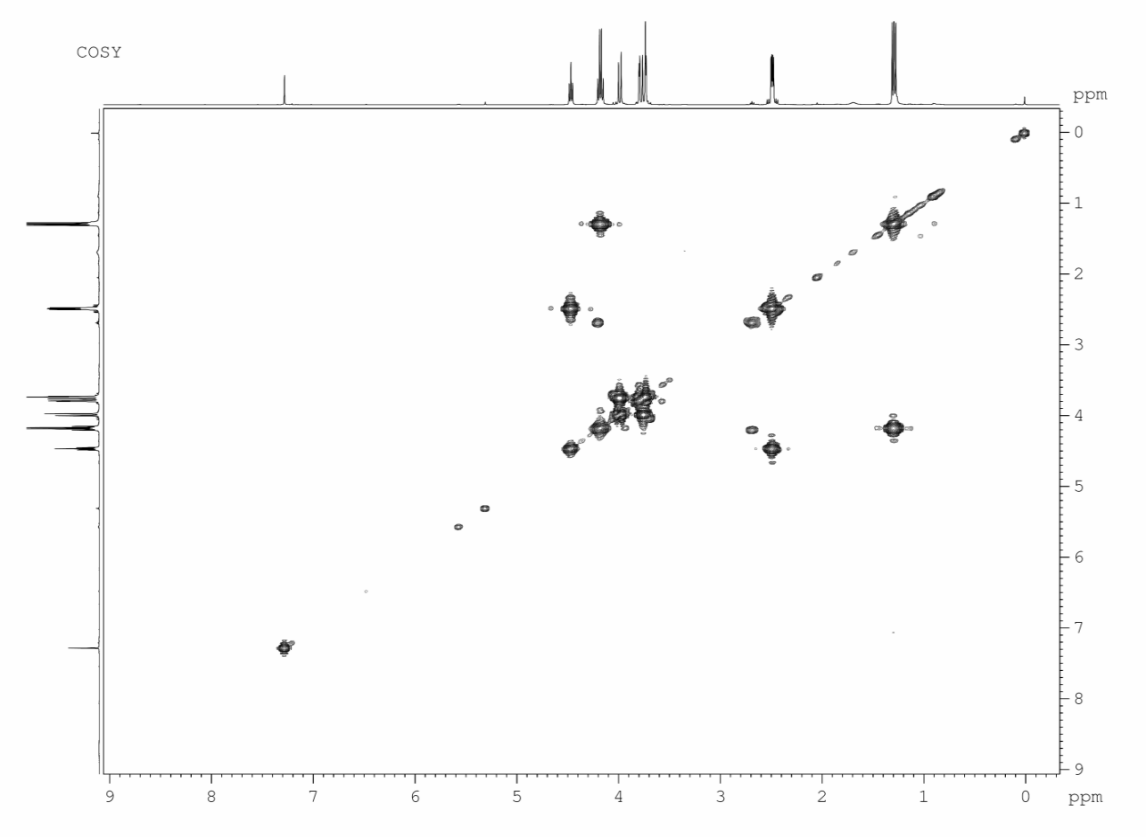
Figure 17: ^{1}H and ^{13}C NMR of epoxy ester **(+)-30**

The THF core **67** was then constructed as a single diastereomer in 93% yield *via* a diastereoselective tandem desilylation-oxa Michael addition reaction of silyl ether **(+)-30** mediated by tetrabutylammonium fluoride (TBAF). The stereoselectivity and diastereoslectivity (dr > 99) of cyclic epoxide **67** was confirmed by ^{1}H NMR and 2D NMR spectra analysis. The disappearance of signals corresponding to olefinic functionality from its ^{1}H NMR and ^{13}C NMR spectra provided evidence for a successful Michael addition reaction. The ^{1}H NMR spectrum of **67** showed a triplet at δ 4.46 for

methine proton attached to furanyl oxygen. This indicated *anti*-relationship between the two adjacent methine protons attached to oxygen of furan ($\mathbf{H_a}$) and epoxide ($\mathbf{H_b}$). This was further confirmed by its 2D NMR studies, which did not show any correlation between the two adjacent protons ($\mathbf{H_a}$ and $\mathbf{H_b}$). The proton signals at δ 3.72-3.78 (m, 3H), 3.96 (d, J = 10.5 Hz, 1H) and 4.18 (q, J = 7.0 Hz, 2H) were indicative of methine and methylene groups attached to oxygen atom. Its ^{13}C NMR spectrum showed a typical signal at δ 74.0 corresponding to methine carbon attached to furanyl oxygen, while a peak at δ 169 was due to ester carbonyl function (**Figure 18**).




Carbon tetrachloride
Chloroform-d
169.91
96.14
77.00
74.04
66.41
60.79
58.53
55.91
36.51
14.21
Ha
Hb
CO2Et
67
74.03
66.40
60.78
58.52
55.90
36.49
14.20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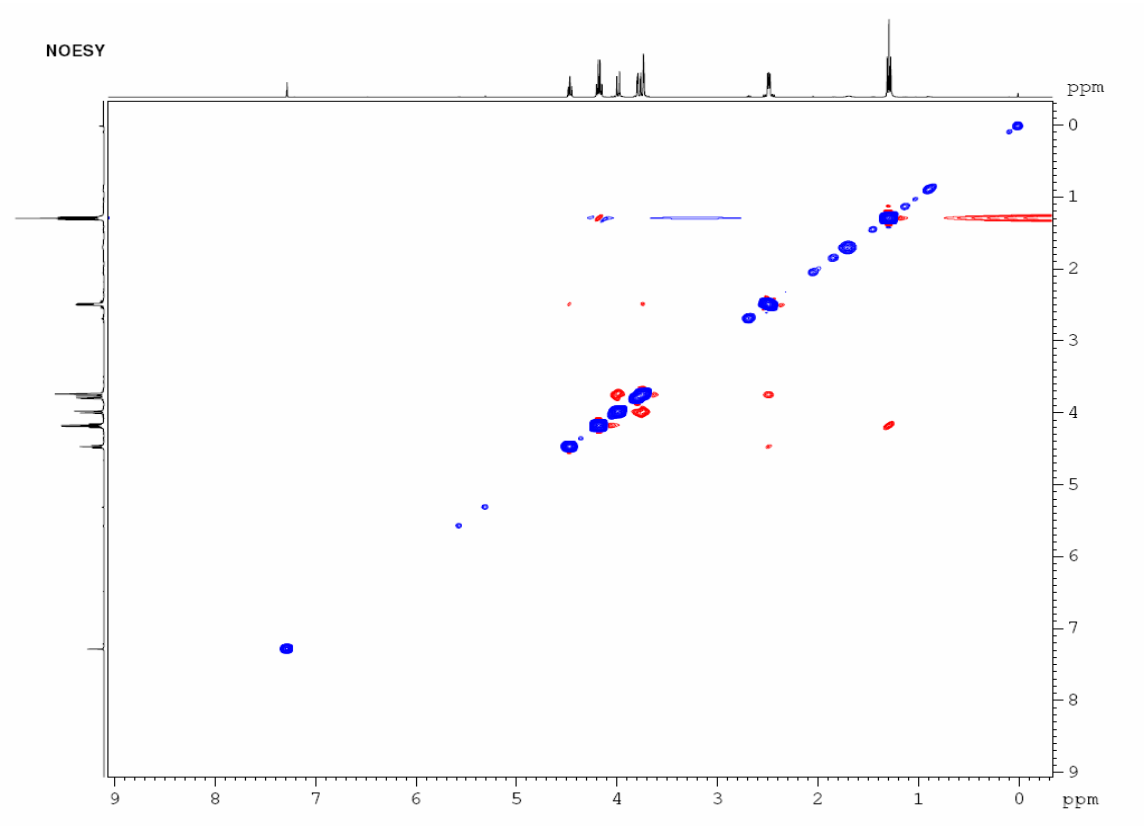
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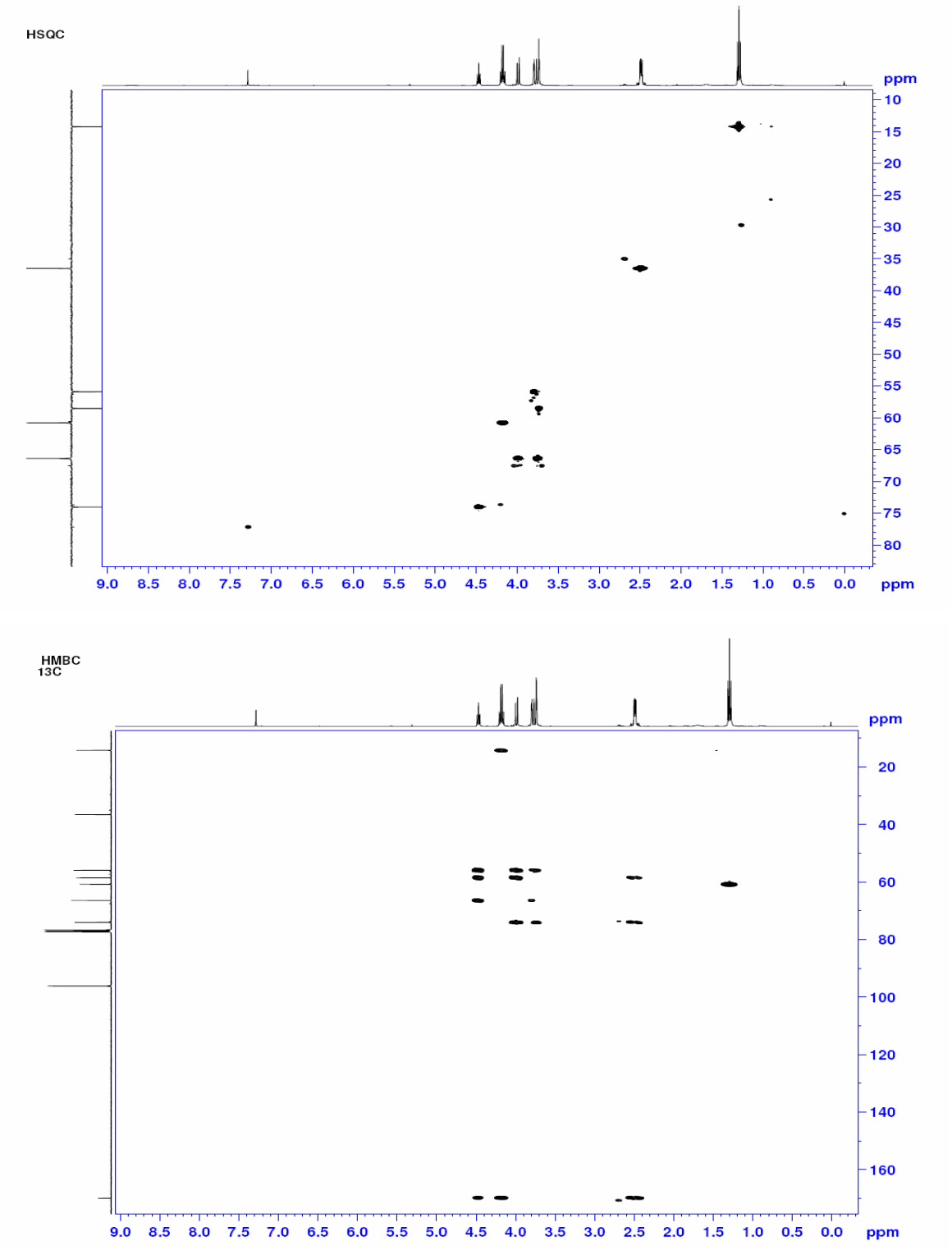
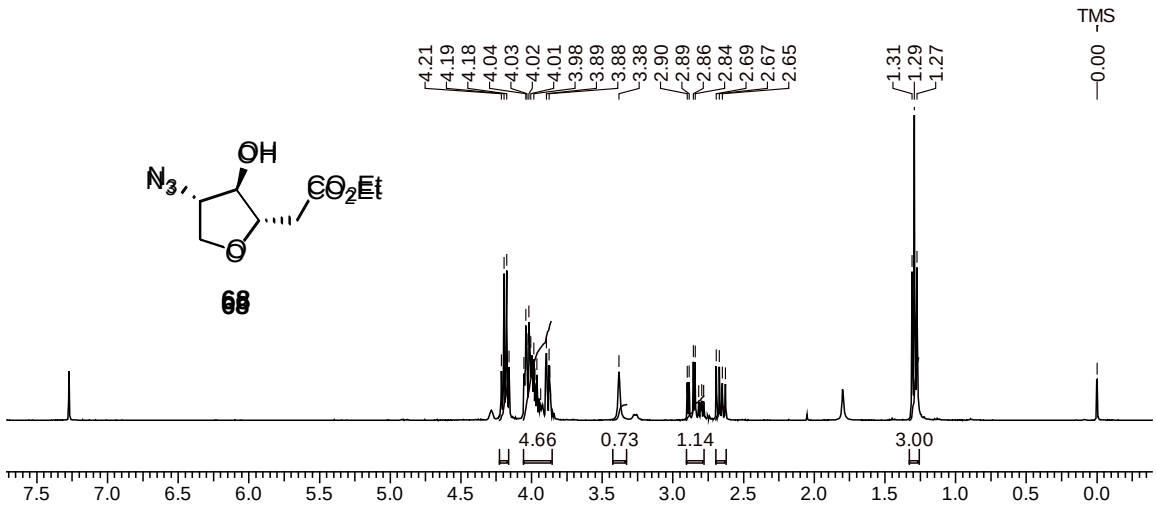


Figure 18: ^{1}H, ^{13}C NMR, DEPT, COSY, NOESY, HSQC and HMBC NMR spectra of epoxy THF **67**

Regioselective opening of epoxide **67** with NaN_3 in presence of NH_4Cl was accomplished

smoothly in a solvent mixture of $EtOH/H_2O$ (4:1) giving the azido alcohol **68** in 91% yield; $[\alpha]_D^{25}$ +10.2 (*c* 0.4, $CHCl_3$). The formation of azido alcohol **68** was proved by its IR spectrum analysis, which showed the appearance of absorption peaks at υ_{max} 2105 and 3439 cm^{-1} corresponding to azide and alcohol functionalities. The multiplet at δ 3.88-4.03 (m, 5H) was indicative of methine and methylene protons attached to furanyl oxygen while a broad singlet at δ 3.38 (1H) was due to alcohol functionality, thus confirming the presence of hydroxyl group. Its ^{13}C NMR spectrum showed typical signals at δ 61.2, 67.5, 70.5, 81.2 and 81.5 which was attributed to the presence of carbons attached to oxygen atom (**Figure 19**).



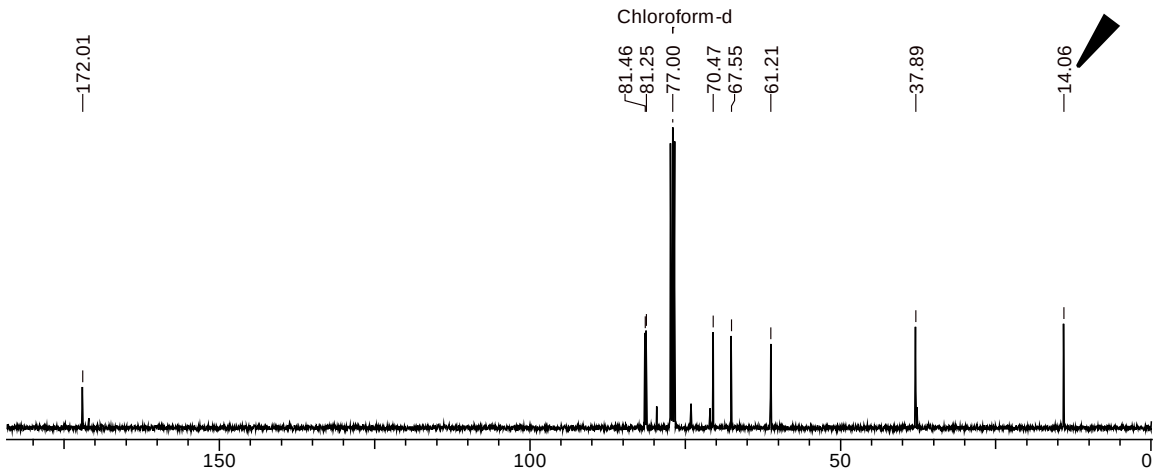
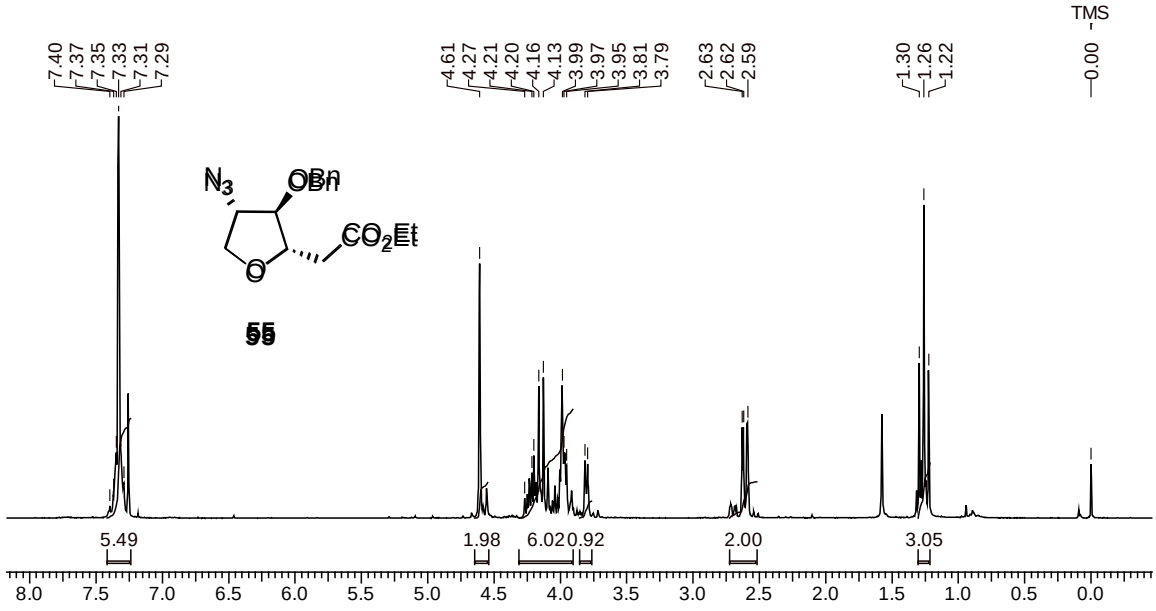


Figure 19: ^{1}H and ^{13}C NMR of azido alcohol **68**

The hydroxyl group in **68** was then protected (BnBr, Ag_2O) to give the benzyl ether **55** in 95% yield. Benzyl protection was confirmed by the presence of a multiplet at δ 7.29-7.40 corresponding to five aromatic protons. The benzylic protons appeared at δ 4.61 (s, 2H) in its ^{1}H NMR spectrum. Its ^{13}C NMR showed the characteristic ester carbonyl signal at δ 170.3 while the other resonance absorptions at δ 14.2 and 38.2 were due to methyl ($-CO_2\mathbf{CH_2}CH_3$) and methylene ($-\mathbf{CH_2}CO_2Et$) carbons respectively (**Figure 20**).



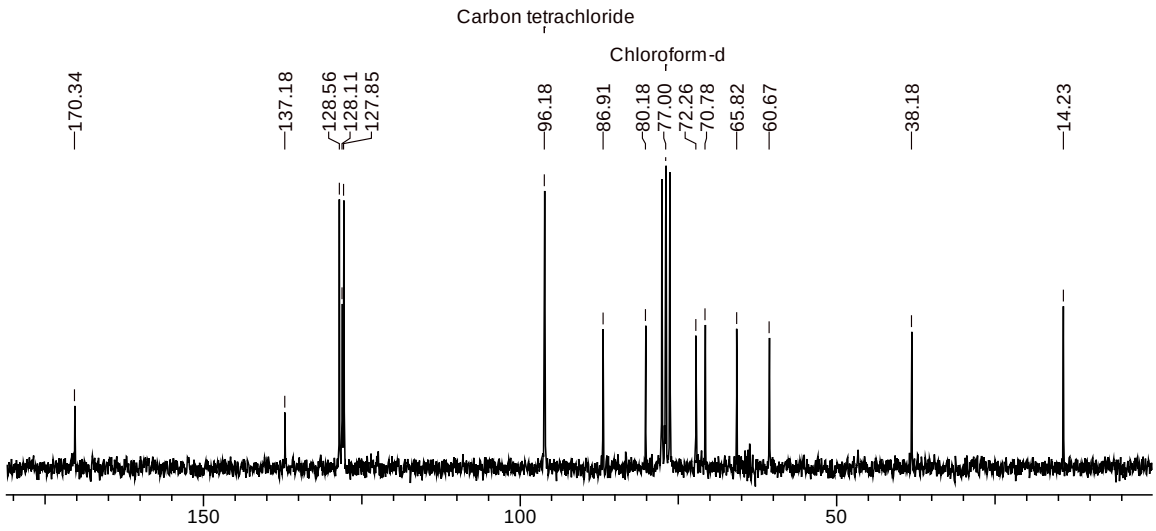


Figure 20: ^{1}H and ^{13}C NMR of benzyl ether **55**

The ester functionality in **55** was selectively reduced with DIBAL-H in dry toluene at -78 ^{o}C to produce the corresponding aldehyde, which was used as such without purification due to its instability on silica gel column. Thus, the crude aldehyde upon Wittig olefination (*n*-BuLi, $PPh_3^{+}C_{12}H_{25}Br^{-}$, THF) gave olefin **69** in 75% yield $[\alpha]_D^{25}$ +7.4 (*c* 1.0, $CHCl_3$). The formation of olefin **69** was confirmed by the presence of multiplets at δ 5.33-5.35 (1H) and 5.42-5.45 (1H) corresponding to olefinic protons. This was further substantiated by the appearance of carbon signals at δ 127.9 and 133.0 in its ^{13}C NMR spectrum. The final step in the synthesis was the global reduction which included the reduction of azide and olefin functions along with benzyl deprotection. Accordingly, compound **69** was subjected to reduction under catalytic hydrogenation condition [10% Pd/C, H_2 (1 atm.), 97%] which gave the title compound 3-*epi* jaspine B **45** with an overall yield of 34.7%. The formation of **45** was confirmed by the appearance of broad absorption band at υ_{max} 3359 cm^{-1} and the disappearance of sharp absorption band for azide functionality in its IR spectrum. This was further evidenced by the disappearance of signals corresponding to benzyl and olefin functionality from its ^{1}H and ^{13}C NMR

spectra. The spectroscopic data along with physical properties like specific rotation and melting point of the final product thus obtained were in agreement with the literature values.[23]

1.2.4 Conclusion

In conclusion, we have described an elegant and concise synthetic route to 3-*epi* jaspine B **45** (10 steps, 34.7% overall yield). Our strategy is based on two key reactions i.e. Sharpless asymmetric epoxidation and diastereoselective tandem desilylation-oxa Michael addition. The protocol is facile, flexible and hence can be applied to the synthesis of other THF based bioactive molecules as well.

1.2.5 Experimental section

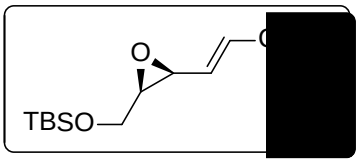
(2*S*,3*S*)-3-((*tert*-Butyldimethylsilyloxy)methyl)oxirane-2-carbaldehyde [(+)-26]

To a solution of alcohol **(-)-29** (15.02 g, 69.44 mmol) in dry CH_2Cl_2 was added in one portion (diacetoxyiodo)benzene (24.34, 75.62 mmol) and TEMPO (1.07 g, 6.91 mmol). The reaction mixture was then allowed to stir at 25 ^oC for 1 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched by the addition of saturated solution of aq. sodium thiosulphate. The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified using coulumn chromatography with petroleum ether/EtOAc (9:1 v/v) as eluent to afford the epoxy aldehyde **(+)-26** (14.27 g) as yellow colored liquid.

Yield: Yield: 95%; $[\alpha]_D^{25}$ +41.9 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 778, 838, 1099, 1256, 1472, 1720, 2858, 2930 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.89 (s, 9H), 3.34-3.44 (m, 2H), 3.96-4.00 (m, 2H), 9.47 (d, *J* = 4.2 Hz, 1H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ -5.7, 18.0, 25.5, 57.3, 59.6, 59.7, 197.2; **Anal.** Calcd for $C_{10}H_{20}O_3Si$ requires C, 55.52; H, 9.32; Found: C, 55.60; H, 9.43%.

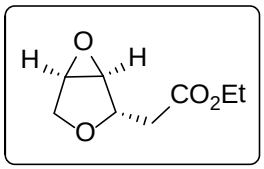
(E)-Ethyl ((2*R*,3*S*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)acrylate [(+)30]



To a stirred solution of aldehyde **(+)-26** (10.0 g, 46.22 mmol) in dry CH_2Cl_2 (250 mL) at 25 ^oC was added $Ph_3P{=}CHCO_2Et$ (24.0 g, 70.0 mmol) and the reaction mixture was stirred for 2 h. After completion of reaction (monitored by TLC), solvent was distilled off under reduced pressure and the crude mass on column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) gave the α,β-unsaturated ester **(+)-30** (12.18 g) as a slightly yellow colored liquid.

Yield: 92%; $[\alpha]_D^{25}$ +13.5 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 778, 838, 1035, 1260, 1722, 2858, 2930 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 3.33-3.35 (m, 1H), 3.56-3.58 (m, 1H), 3.72-3.75 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.11 (d, *J* = 15.8 Hz, 1H), 6.77-6.82 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -5.3, 14.1, 18.2, 25.8, 54.6, 59.1, 60.5, 60.8, 125.3, 141.2, 165.1; **Anal.** Calcd for $C_{14}H_{26}O_4Si$ requires C, 58.70; H, 9.15; Found: C, 58.78; H, 9.13%.

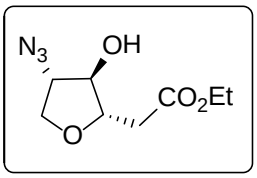
Ethyl 2-((1*S*,2*S*,5*R*)-3,6-dioxabicyclo[3.1.0]hexan-2-yl)acetate (67)



To a well stirred solution of silyl ether **(+)-30** (200 mg, 0.5 mmol) was added 1 M solution of tetrabutylammonium fluoride (1 mL, 1 mmol) at 25 ^oC. The reaction mixture was stirred at this temperature for 2 h after which the solvent was removed under reduced pressure and the residue was subjected to column chromatography purification with petroleum ether/EtOAc (5:5 v/v) to afford furan derivative **67** (80 mg) as a single diastereomer.

Yield: 93%; colorless liquid; $[\alpha]_D^{25}$ +5.4 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$): ν_{max} 838, 1256, 1719, 2876 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 2.47 (m, 2H), 3.72-3.78 (m, 3H), 3.96 (d, *J* = 10.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.46 (t, *J* = 6.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 36.5, 55.9, 58.5, 60.8, 66.4, 74.0, 169.9; **Anal.** Calcd for $C_8H_{12}O_4$ requires C, 55.81; H, 7.02; Found: C, 55.85; H, 6.94%.

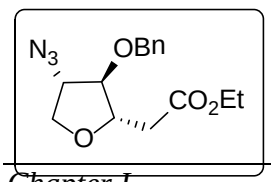
Ethyl 2-((2*S*,3*R*,4*S*)-4-azido-3-hydroxytetrahydrofuran-2-yl)acetate (68)



To a solution of epoxide **67** (3 g, 17.43 mmol) in EtOH/ H_2O (80:20 mL) was added NaN_3 (6.83 g, 104.59 mmol) and NH_4Cl (5.6, 104.59 mmol) at 25°C. The mixture was then stirred at 80°C for 12 h. After completion of reaction (monitored by TLC), EtOH was removed by rotary evaporation. The reaction mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with H_2O (20 mL x 3), brine (20 mL x 3) and dried (anhydrous Na_2SO_4). After evaporation of the solvent, the residue was purified using coulumn chromatography with petroleum ether/EtOAc (6:4 v/v) to give the azido alcohol **68** (3.41 g) as yellow colored liquid.

Yield: 91%; $[\alpha]_D^{25}$ +10.2 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$): ν_{max} 1073, 1725, 2105, 3439 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, d, *J* = 7.0 Hz, 3H), 2.65 (dd, *J* = 8.9, 16.8 Hz, 1H), 2.84 (dd, *J* = 5.3, 16.8 Hz, 1H), 3.38 (br s, 1H), 3.88-4.03 (m, 5H), 4.18 (q, *J* = 7.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 37.9, 61.2, 67.5, 70.5, 81.2, 81.5, 172.0; **Anal.** Calcd for $C_8H_{13}N_3O_4$ requires C, 44.65; H, 6.09; N, 19.53; Found: C, 44.71; H, 6.19; N, 19.59%.

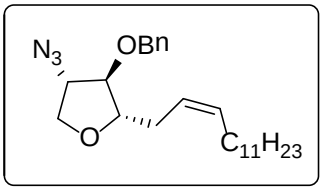
Ethyl 2-((2*S*,3*R*,4*S*)-4-azido-3-(benzyloxy)tetrahydrofuran-2-yl)acetate (55)



To a solution of azido alcohol **68** (2.1 g, 9.76 mmol) in dry CH_2Cl_2 (60 mL) was added Ag_2O (3.39 g, 14.64 mmol) followed by BnBr (2.0 g, 11.71 mmol) at 0 ^oC. The reaction mixture was stirred for 6 h at 25 ^oC and then filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was purified by column chromatography with petroleum ether/EtOAc (8:2 v/v) to give **55** (2.82 g) as yellow colored liquid.

Yield: 95%; $[\alpha]_D^{25}$ +15.8 (*c*1.0, $CHCl_3$) {lit.[21] $[\alpha]_D^{25}$ +15.4 (c 1.1, $CHCl_3$)}; **IR** ($CHCl_3$): ν_{max} 747, 1020, 1171, 1436,1497,1737, 2105, 3031 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.59 (dd, *J* = 1.9, 7.1 Hz, 2H), 3.79 (d, *J* = 2.1 Hz, 1H), 3.95-4.27 (m, 6H), 4.61 (s, 2H), 7.29-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.2, 60.7, 65.8, 70.8, 72.3, 80.2, 86.9, 127.8, 128.1, 128.6, 137.2, 170.3; **Anal.** Calcd for $C_{15}H_{19}N_3O_4$ requires C, 59.01; H, 6.27; N, 13.76; Found: C, 59.21; H, 6.31; N, 13.8%.

(2*S*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((*Z*)-tetradec-2-enyl)tetrahydrofuran (69)



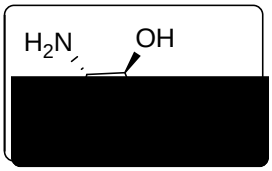
To a stirred solution of ester **55 (**1.0 g, 3.27 mmol) in dry toluene (50 mL), a solution of diisobutylaluminium hydride (3.6 mL, 3.6 mmol, 1M in cyclohexane) was added dropwise at -78 ^oC and stirred at this temperature for 1 h. After completion of reaction (monitored by TLC), it was diluted with a saturated solution of potassium sodium tartrate (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 phase was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude aldehyde which was used as such for the next reaction.

To a stirred solution of dodecyl triphenylphosphonium bromide (2.05 g, 4.0 mmol) in 20 mL of dry THF at -78 ^oC was added *n*-BuLi (1.6 M solution in hexane 2.5 mL, 3.8 mmol)

dropwise and the resulting solution was stirred for 30 min. The crude aldehyde obtained above was dissolved in dry THF (5 mL) and added dropwise with stirring to the ylide solution at -78 ^{o}C. The reaction mixture was then brought to 0 ^{o}C and stirred for 3 h. The reaction was quenched with 6 mL of saturated NH_4Cl solution at 0 ^{o}C, the solvent was evaporated under reduced pressure; the residue was extracted with EtOAc (2 x15 mL), and dried with anhydrous Na_2SO_4. After evaporation of ethyl acetate the residue was chromatographed (silica gel, 230-400 mesh, petroleum ether/EtOAc (9.5:0.5 v/v) to obtain **69** (1.02 g) as viscous liquid.

Yield: 75%; $[\alpha]_D^{25}$ +7.4 (*c* 1.0, $CHCl_3$) {lit.[21] $[\alpha]_D^{25}$ +6.7 (c 2.8, $CHCl_3$)}; **IR** ($CHCl_3$): ν_{max} 747, 1081, 1460, 1729, 2853, 2937 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.1 Hz, 3H), 1.31-1.34 (m, 18H), 2.01-2.02 (m, 2H), 2.45-2.47 (m, 2H), 3.63 (dd, *J* = 3.2, 9.8 Hz, 1H), 3.83-3.85 (m, 2H), 3.97-4.01 (m, 1H), 4.14 (dd, *J* = 5.7, 9.5 Hz, 1H), 4.52 (d, *J* = 12.3 Hz, 1H), 4.62 (d, *J* = 11.1 Hz, 1H), 5.33-5.35 (m, 1H), 5.42-5.45 (m, 1H), 7.29-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.8, 22.7, 27.3, 29.3, 29.5, 29.6, 30.9, 31.9, 65.9, 70.6, 72.2, 84.0, 87.1, 123.9, 127.7, 127.9, 128.4, 133.0, 137.2; **Anal.** Calcd for $C_{25}H_{39}N_3O_2$ requires C, 72.60; H, 9.50; N, 10.16; Found C, C, 72.56; H, 9.47; N, 10.21%.

3-*epi* Jaspine B (45)



To a stirred ethanolic solution of olefin **69** (50 mg, 0.12 mmol, 5 mL) was added Pd/C (10% on carbon, 5 mg) and the reaction mixture stirred under an H_2 atmosphere at room temperature for about 12 h. After the completion of reaction it was filtered over celite plug (EtOH eluent)

and solvent evaporated under reduced pressure to give 3-*epi* jaspine B **45** (35 mg) as colorless solid.

Yield: 97%; m.p. 75-77 ^{o}C {lit.[20] m.p. 75-76 ^{o}C}; $[\alpha]_D^{25}$ -3.7 (*c* 0.5, $CHCl_3$) {lit.[20] $[\alpha]_D^{25}$ -1.8 (c 0.8, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3359, 2924, 2857, 1637, 1435 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25 (m, 24H), 1.55-1.67 (m, 2H), 2.12 (br s, 3H), 3.32 (dd, *J* = 4.9, 6.6Hz, 1H,), 3.60 (dd, *J* = 4.8, 9.4 Hz, 1H), 3.62-3.64 (m, 2H), 4.01 (dd, *J* = 5.9, 9.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.7, 26.0, 29.3, 29.57, 29.60, 29.65, 29.67, 31.9, 34.0, 60.5, 73.6, 84.1, 85.2; **Anal.** Calcd for $C_{18}H_{37}NO_2$ requires C, 72.19; H, 12.45; N, 4.68; Found: C, 72.34; H, 12.52; N, 4.71%.

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Chapter II

Enantioselective Synthesis of (-)-Aspinolide A, (S)-N-(5-Chlorothiophene-2-sulfonyl)-β,β-diethylalaninol and (+)-Decarestrictine L

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1. "A concise enantioselective synthesis of (+)-decarestrictine L via proline-catalyzed sequential alpha-aminooxylation and Horner-Wadsworth-Emmons olefination" Varun Rawat, Pandurang V. Chouthaiwale, Gurunath Suryavanshi, Arumugam Sudalai; *Tetrahedron Asymmetry* **2009**, *20*, 2173.

2. "A facile enantioselective synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol via proline-catalyzed asymmetric α-aminooxylation and α-amination of aldehyde" Varun Rawat, Pandurang V. Chouthaiwale, Vilas B. Chavan, Gurunath Suryavanshi, Arumugam Sudalai *Tetrahedron Letters* **2010**, *51,* 6565.

Section I

Asymmetric synthesis of (-)-Aspinolide A

2.1.1 Introduction and Pharmacology

Macrolides, isolated from various fungal metabolites have attracted considerable attention due to their interesting biological properties and scarce availability.[1] (-)-Aspinolide A **1**, a decanolide, was isolated in 1997 from the cultures of *Aspergillus ochraceus* along with other members of aspinolide family (**Figure 1**).[2] Various aspinolides have been tested for their antibacterial and antifungal activity and it was observed that most aspinolides show potent activity against all the tested bacterial and fungal strains. Evaluation of their biosynthesis revealed a carbon-skeleton rearrangement leading to branched pentaketides. Surprisingly, the pathways could be directed by using increased dissolved oxygen concentrations during fermentation. The analysis of the extracts of *Aspergillus ochruceus* grown under different culture conditions by chemical screening method resulted in the isolation of seven new pentaketide metabolites.[2]

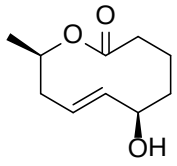

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Figure 1: Structure of (-)-aspinolide A **(1)**

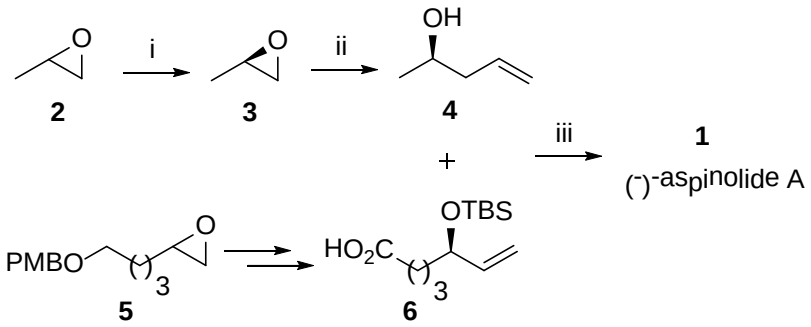
On account of their interesting biological properties and scare availability, they have attracted considerable attention from organic and medicinal chemistry community alike.

2.1.2 Review of Literature

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

Kumar's approach (2009)[3]

The total synthesis of (-)-aspinolide A **1** described by Kumar *et al.* is based on hydrolytic kinetic resolution of terminal epoxides (**2** and **5**) for the introduction of chirality. (*R*)-Propylene oxide **3** was treated with vinylmagnesium bromide in the presence of cuprous iodide to give the required homoallylic alcohol **4** in 88% yield. The synthesis of acid fragment **6** involves a Jacobsen's hydrolytic kinetic resolution of racemic terminal epoxide **5** using (*R,R*)-salen-Co-OAc catalyst. Alcohol fragment **4** and carboxylic acid fragment **6** were coupled using 3-(ethyliminomethyleneamino)-*N*,*N*-dimethyl-propan-1-amine (EDCI) followed by desilylation and Ring Closing Metathesis (RCM) (**Scheme 1**).

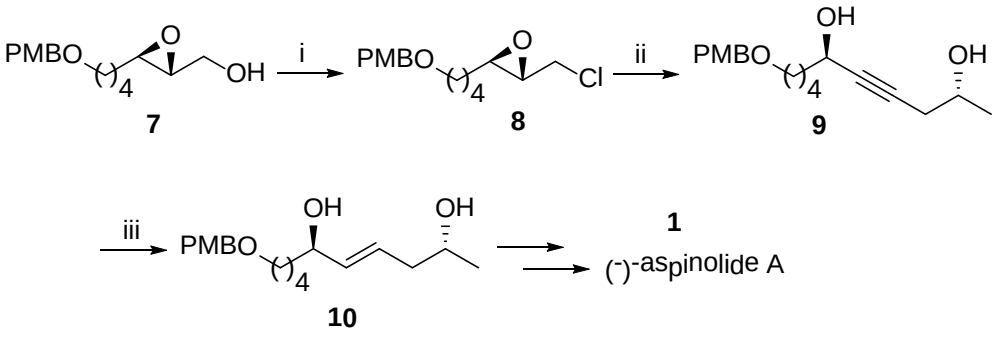


Scheme 1: (i) (*R,R*)-salen-Co-(OAc) (0.5 mol %), H_2O (0.55 equiv), 0 ^oC, 45%, 14 h; (ii) vinylmagnesium bromide, THF, CuI, -20 ^oC, 88%, 12 h; (iii) (a) EDCl·HCl, DMAP, CH_2Cl_2, 0 ^oC, 5 h, 86%; (b) TBAF, THF, 7 h, 80%; (c) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, reflux, 42 h, 60%.

Yadav's approach (2011)[4]

Yadav *et al.* have achieved the synthesis of (-)-aspinolide A **1** by an iterative acetylene-epoxide coupling strategy. The epoxy alcohol **7** was converted to the corresponding epoxy chloride **8** using Appel reaction condition. Compound **8** was treated with $LiNH_2$ in liquid NH_3 to furnish the corresponding terminal acetylene, which was subsequently coupled *in situ* with (2*R*)-2-methyloxirane to get the chiral propargyl alcohol **9**. The triple bond in **9** was reduced with $LiAlH_4$ in THF providing alcohol **10** (**Scheme 2**). The

completion of synthesis was achieved in five steps: (i) TBS protection of allylic alcohol **10**; (ii) PMB deprotection (DDQ, CH_2Cl_2/H_2O); (iii) pinnick oxidation of primary alcohol; (iv) Yamaguchi laconization and (v) silyl deprotection.



Scheme 2: (i) Ph_3P, $NaHCO_3$, reflux, CCl_4, 4 h; 87%; (ii) (*R*)-methyl oxirane, Li, liq. NH_3 , $Fe(NO_3)_3$, dry THF, 8 h, 80%; (iii) $LiAlH_4$, dry THF, 4 h; 85%.

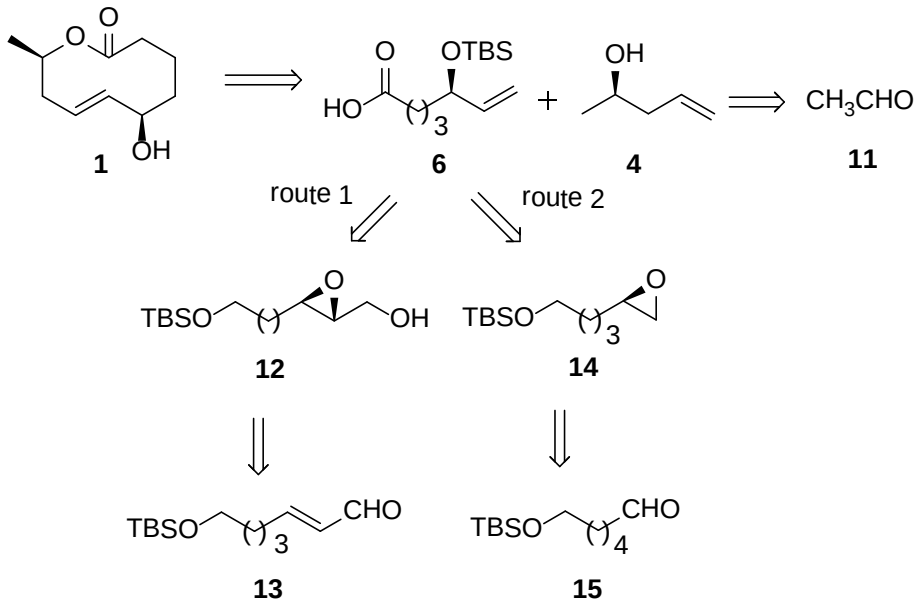
2.1.3. Present Work

2.1.3.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of (-)-aspinolide A **1**, either employ chiral starting materials or use kinetic resolution protocol for the induction of chirality, apart from employing expensive reagents and longer reaction sequences. As part of our continuing interest aimed at developing enantioselective synthesis of biologically active natural product based on asymmetric organocatalysis,[5] we became interested in devising a simple concise and flexible route for the synthesis of (-)-aspinolide A **1**. This section describes an enantioselective synthesis of (-)-aspinolide A **1**, using organocatalytic asymmetric α-epoxidation and -aminooxylation as the key steps for the introduction of chirality in the molecule.

Based on retrosynthetic analysis, we visualized homoallylic alcohol **4** and carboxylic acid **6** as key intermediates for the synthesis of **1**. Fragment **4** can be obtained by Brown

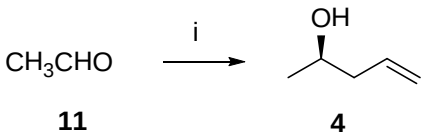
allylation.[6] The carboxylic acid fragment **6** was in turn envisioned *via* two routes: (i) Jorgensen's asymmetric epoxidation[7] of unsaturated aldehdye **13** and (ii) asymmetric α-aminooxylation[8] of aldehyde **15** (**Scheme 3**).



Scheme 3: Retrosynthetic analysis of (-)-aspinolide A **1**

2.1.3.2 Results and Discussion

The synthesis of homoallylic alcohol **4** began with a known protocol involving Brown allylation of acetaldehyde **11**, which gave the homoallylic alcohol **4** in 77% yield. The optical purity of **4** was determined as 95% enantiomeric excess (ee) by comparing its optical rotation with the reported values $[\alpha]_D^{25}$ -9.67 (*c* 3.0, Et_2O) {lit.[3,6] $[\alpha]_D^{25}$ -9.84 (*c* 3.1, Et_2O)} (**Scheme 4**).



Scheme 4: (i) (-)-*B*-allyldiisopinocamphenylborane, Et_2O-pentane, -78 °C, 1 h, NaOH, aq. 35% H_2O_2, 77%.

The synthesis of intermediate carboxylic acid fragment **6** commences with (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**A**) catalyzed epoxidation[7] of α,β-unsaturated aldehyde **13** in a "one-pot" reaction sequence: thus, treatment of aldehyde **13** with 35% H_2O_2 as the oxygen source in the presence of 10 mol% pyrrolidine catalyst **A** with CH_2Cl_2 as solvent at 25 ºC followed by its reduction with $NaBH_4$ in MeOH gave the crude α-epoxy alcohol **12** *in situ* (**Scheme 5**). The ^1H NMR spectrum of **12** showed characteristic epoxy proton signals at δ 2.89-2.97 (m, 2H). The signals at δ 55.9, 58.5, 61.7 and 62.8 in its ^{13}C NMR spectrum were due to carbons attached to oxygen atom (**Figure 2**).

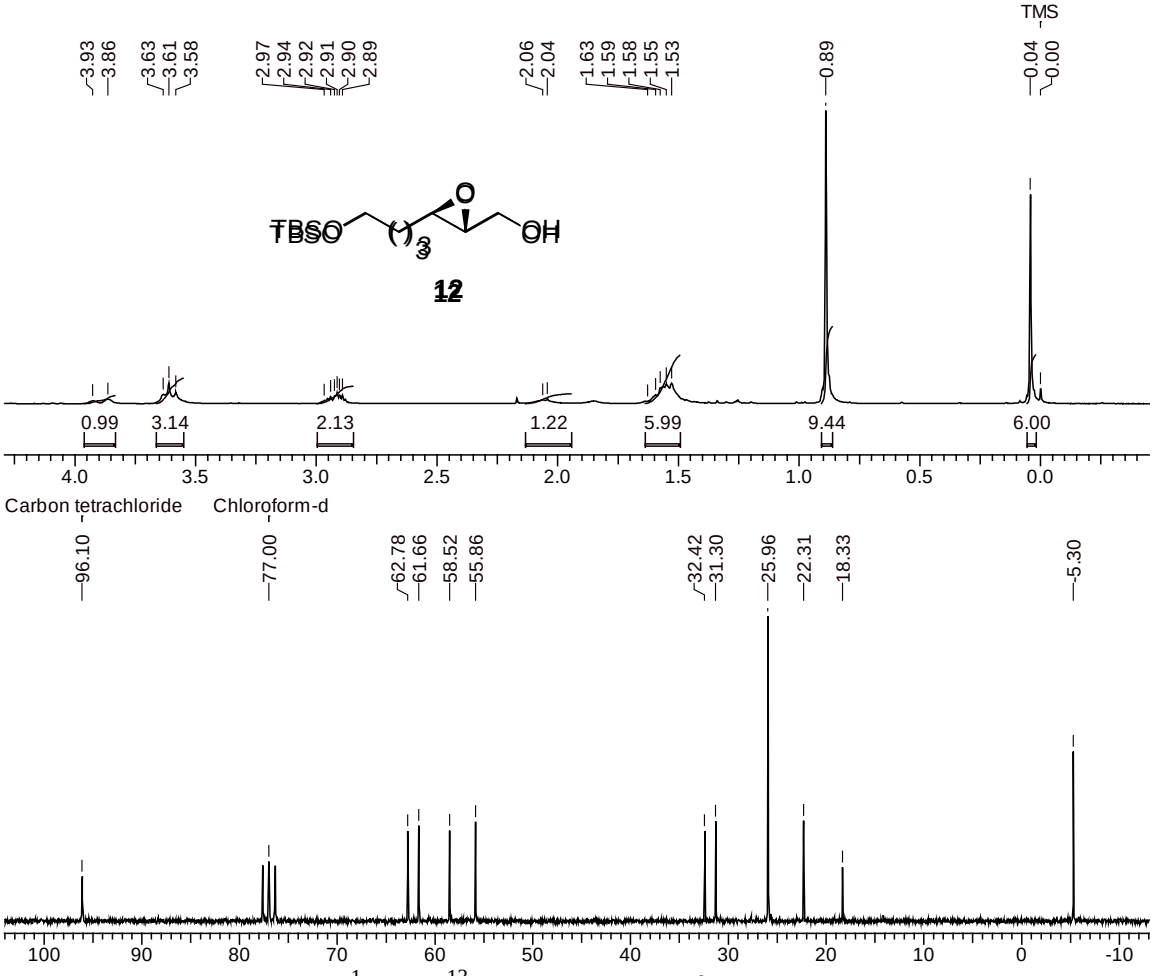
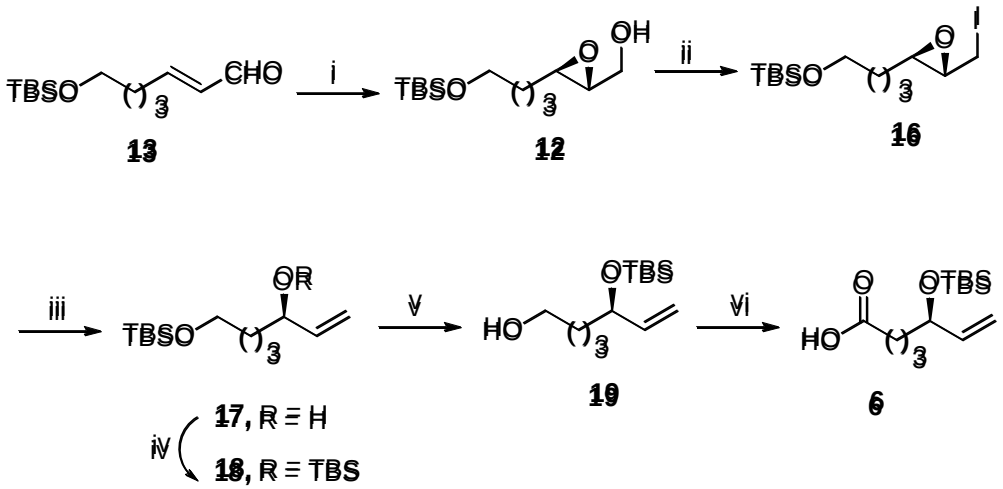
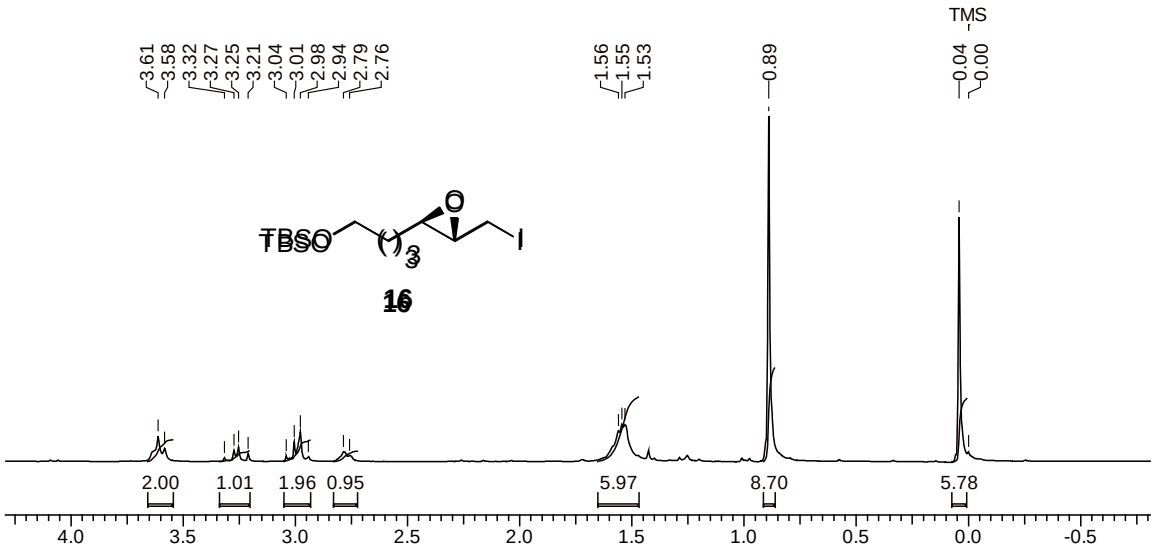


Figure 2: ^1H and ^{13}C NMR spectra of epoxy alcohol **12**



Scheme 5: (i) H_2O_2, CH_2Cl_2, (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol tri-methylsilyl ether (**A**), 25 ºC, 4 h then $NaBH_4$, MeOH, 0 ºC, 10 min, 43%; (ii) I_2, PPh_3, imid., Et_2O/CH_3CN (3:1), 0-25 ºC, 2 h, 90%; (iii) Zn, NaI, MeOH, reflux, 3 h, 90%; (iv) TBSCl, imid., CH_2Cl_2, 0-25 ºC, 6 h, 86%; (v) (+)-camphor-10-sulfonic acid, MeOH, 25 ºC, 5 min, 63%; (vi) TEMPO, $PhI(OAc)_2$, CH_3CN:H_2O (4:1), 25 ºC, 4 h, 80%.

Conversion of epoxy alcohol **12** to epoxy iodide **16** was achieved using Appel reaction condition: I_2, PPh_3 and imid.; $[\alpha]_D^{25}$ +8.0 (*c* 2.0, $CHCl_3$). Its ^{1}H NMR spectrum showed multiplets at δ 2.76-2.79 (1H), 2.94-3.04 (m, 2H) and 3.21-3.32 (1H) corresponding to -**CH$_2$**I and -**CH**-O-**CH**- protons. The typical carbon signals at δ 58.4, 62.3 and 62.7 in its ^{13}C-NMR spectrum were attributed to carbons attached to oxygen atom (**Figure 3**).



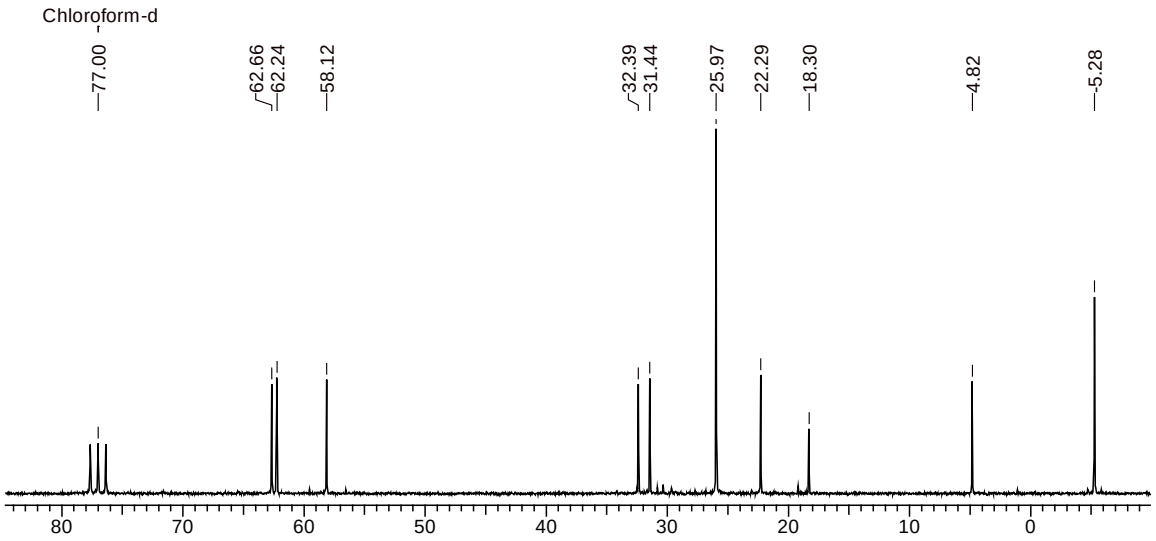
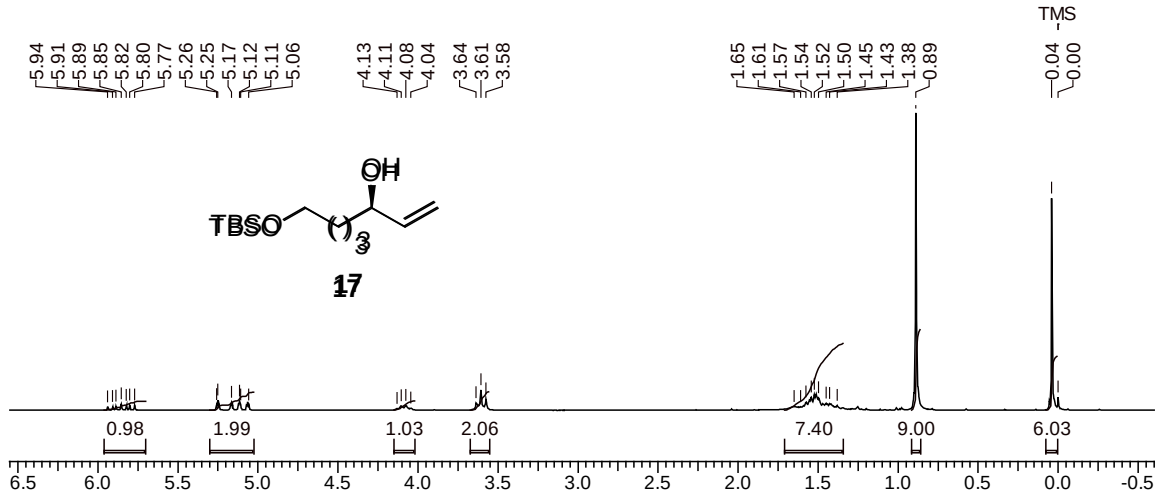


Figure 3: ^{1}H and ^{13}C NMR spectra of epoxy iodide **16**

Next step in the synthesis of carboxylic acid **6** was the reductive ring opening of epoxide **16** in the presence of Zn powder, which was accomplished smoothly to give allylic alcohol **17** in 90% yield. The formation of **17** was confirmed by the analysis of its ^{1}H and ^{13}C NMR spectra. The multiplets at δ 5.06-5.26 (2H) and 5.77-5.94 (1H) in its ^{1}H NMR spectrum indicated the formation of olefinic protons. The presence of olefin functionality in **17** was further substantiated by the presence of carbon signals at δ 114.5 and 141.3 in its ^{13}C NMR spectrum (**Figure 4**).



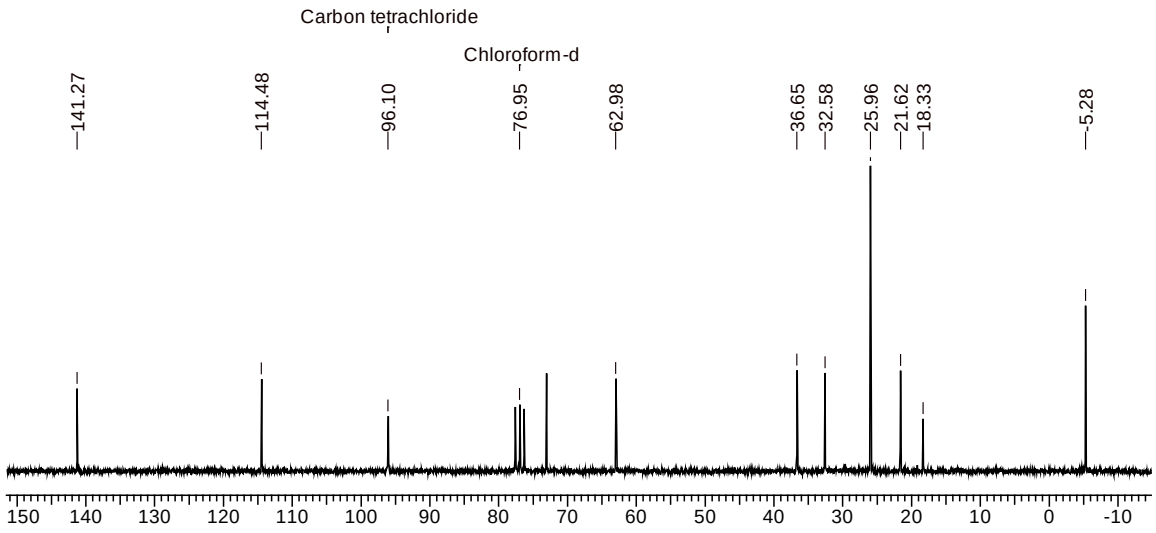


Figure 4: ^{1}H and ^{13}C NMR spectra of allylic alcohol **17**

Conversion of allylic alcohol **17** to carboxylic acid **6** was achieved in three steps as described here: (i) silylation of secondary alcohol functionality in **17**, (ii) chemoselective desilylation in **18** with (+)-camphor-10-sulfonic acid (CSA, MeOH, 63%), (iii) oxidation of **19** to carboxylic acid **6** using TEMPO/BAIB mixture in CH_3CN/H_2O (3:1) solvent combination. Carboxylic acid fragment **6** was obtained with an overall yield of 15.1% in 98% ee, determined by comparing its optical rotation with the reported values $[\alpha]_D^{25}$ -6.5 (*c* 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ -6.6 (*c* 1.15, $CHCl_3$)} (**Scheme 5**). The formation of primary alcohol **19** was confirmed by its IR spectrum which showed a strong absorbtion band at υ_{max} 3441 cm^{-1} corresponding to alcohol functionality. Its ^{1}H NMR spectrum showed signals at δ 3.60 (t, *J* = 6.3 Hz, 2H) and 4.05 (q, *J* = 6.1 Hz, 1H) indicative of methylene (-**CH_2**-OH) and methine (-**CH**-OTBS) protons respectively. The signals at δ -4.7, -4.3, 18.3 and 25.9 in its ^{13}C NMR spectrum were attributed to carbons of TBS ether functionality, while the resonance peaks at δ 62.8 and 73.8 accounted for methylene (-**CH_2**-OH) and methine (-**CH**-OTBS) carbons respectively (**Figure 5**).

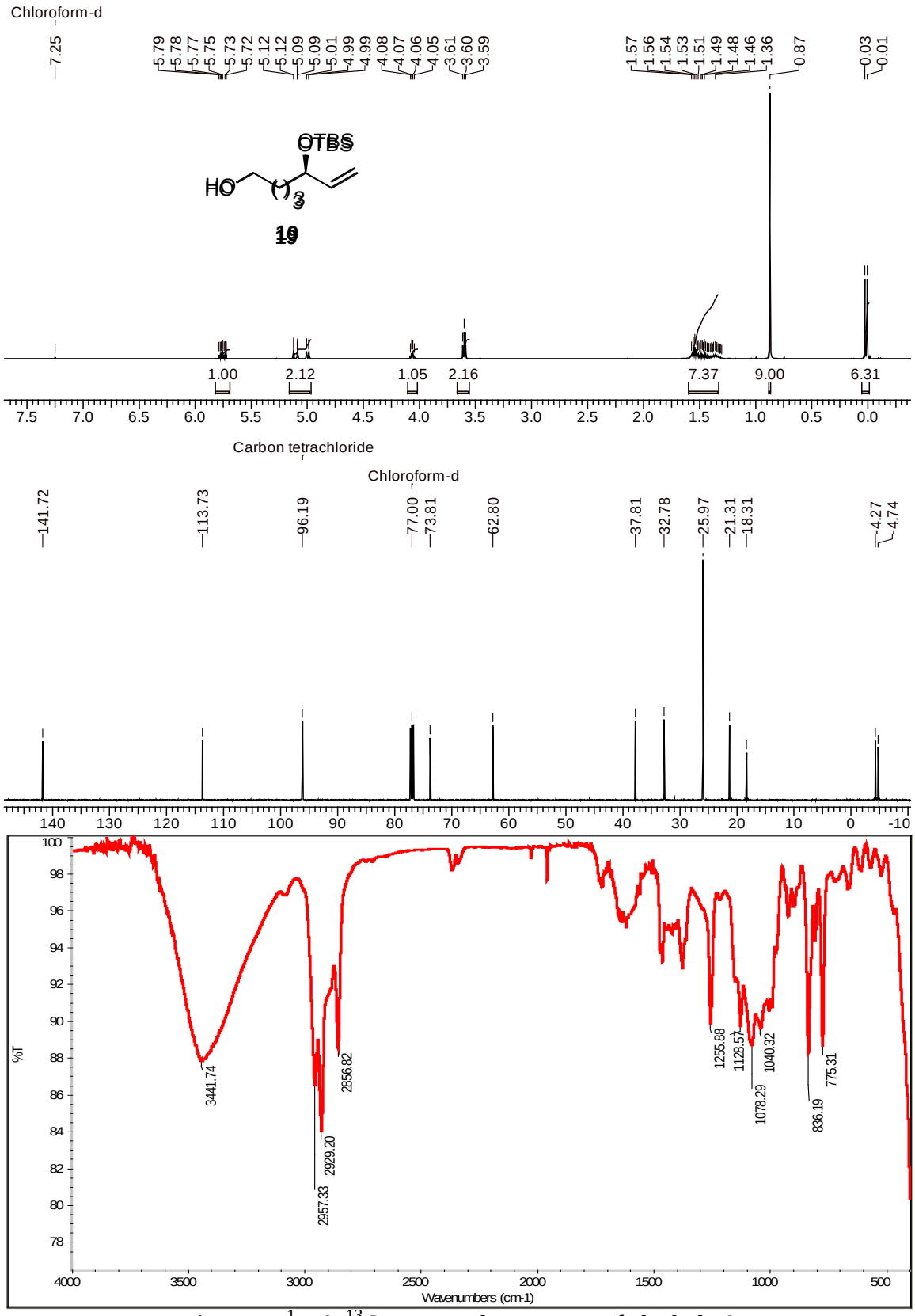
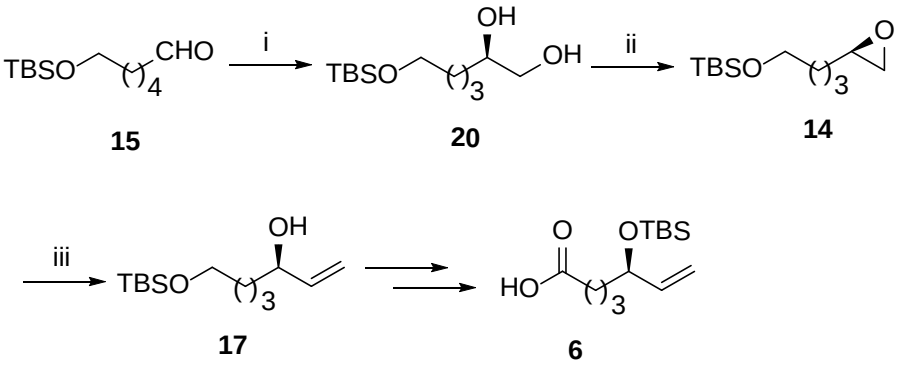


Figure 5: ^{1}H & ^{13}C NMR and IR spectra of alcohol **19**

Our second approach for the synthesis of acid fragment **6** commenced from aldehyde **15**, which was subjected to L-proline catalyzed *α*-aminooxylation in a two-step reaction sequence: (i) reaction of aldehyde **15** with nitrosobenzene as the oxygen source in the presence of 20 mol% L-proline in CH_3CN at -20 ºC followed by its reduction with $NaBH_4$ in MeOH gave the crude *α*-aminoxy alcohol *in-situ*; (ii) subsequent reduction of the crude *α*-aminoxy alcohol using 10 % Pd/C over H_2 (1 atm) furnished chiral diol **20** in **77**% yield over two steps (**Scheme 6**).



Scheme 6: (i) (a) PhNO (1 equiv.), L-proline (20 mol %), CH_3CN, -20 ºC, 24 h then $NaBH_4$, MeOH, 0 ºC, 10 min; (b) 10% Pd/C, H_2, MeOH, 24 h, 77% (over two steps); (ii) (a) TsCl, Et_3N, Bu_2SnO, DMAP; (b) K_2CO_3, MeOH, 30 min., 92% (over two steps); (iii) $S^+Me_3I^-$, NaH, DMSO, 0 ºC, 2 h, 89%.

The formation of diol **20** was confirmed by the presence of a broad singlet (br s) at δ 2.92 in its ^{1}H NMR spectrum, corresponding to hydroxyl protons. The multilplets at δ 3.35-3.44 (1H) and 3.58-3.69 (4H) in its ^{1}H NMR spectrum was assigned to methine (-**CH**-OH) and methylene (-**CH_2**-OH, -**CH_2**-OTBS) protons attached to oxygen atoms. Another multiplet at δ 1.42-1.57 was due to the six internal methylene protons (-**CH_2**-**CH_2**-**CH_2**-). Its ^{13}C NMR spectrum showed signals at δ 63.0, 66.6 and 72.1 corresponding to methylene and methine carbons attached to oxygen atoms respectively (**Figure 6**).

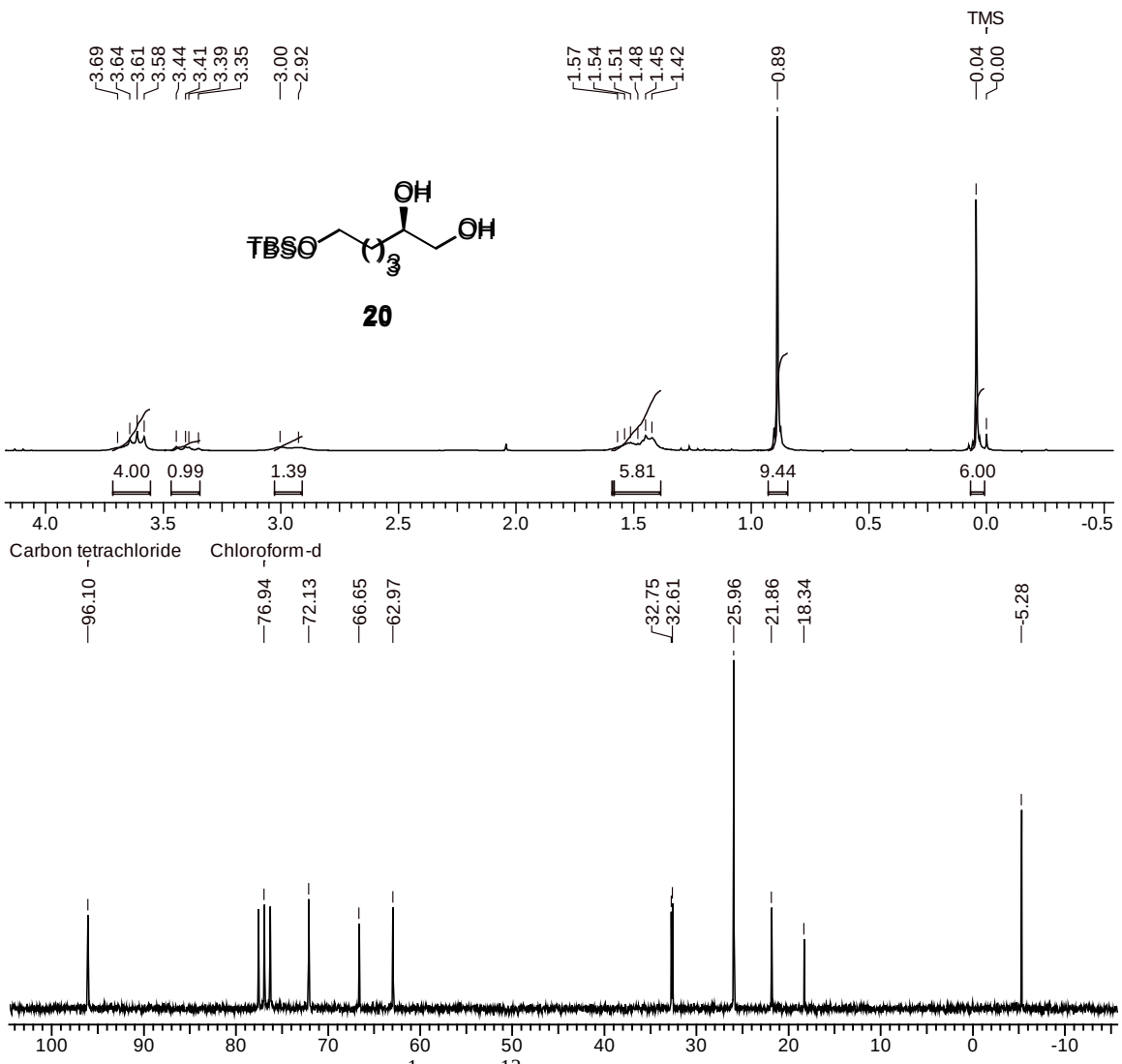


Figure 6: ^{1}H and ^{13}C NMR spectra of diol **20**

Selective tosylation of primary hydroxyl group in diol **20** (TsCl, Et_3N, Bu_2SnO) followed by treatment with K_2CO_3 in MeOH gave the optically pure terminal epoxide **14** in 92% yield over two steps. The formation of epoxide **14** was confirmed by the presence of multiplets at δ 2.42-2.46, 2.71-2.75 and 2.87-2.90 which were attributed to the protons of the epoxide group. Its ^{13}C NMR displayed signals at δ 46.8, 52.1 and 62.8 which were due to carbons attached to oxygen (**Figure 7**).

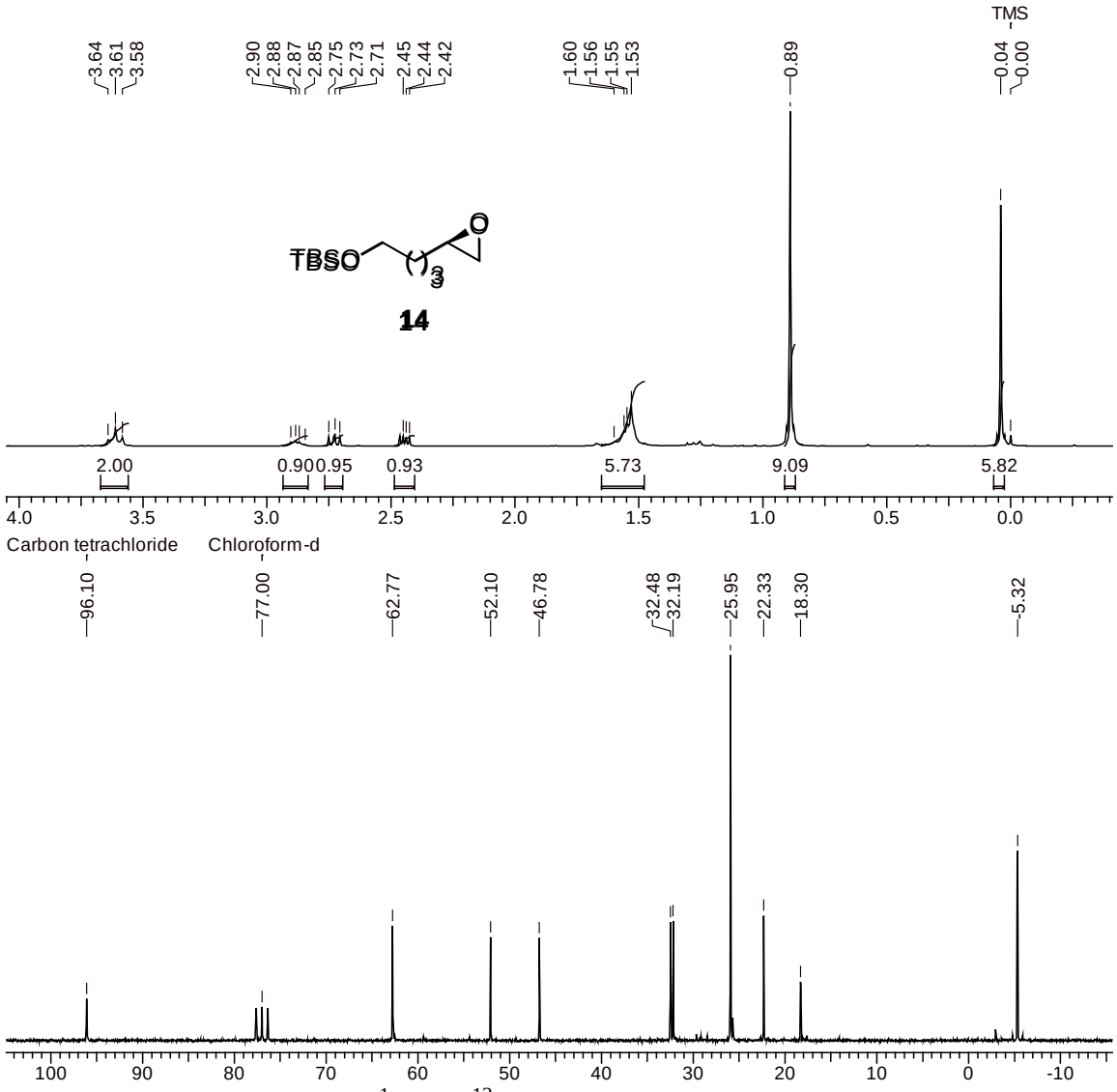


Figure 7: ^{1}H and ^{13}C NMR spectra of epoxide **14**

Regioselective opening of epoxide **14** into the corresponding allylic alcohol **17** was readily achieved by using Corey-Chaykovsky reagent ($S^{+}Me_3I^{-}$, NaH, DMSO) in 70% yield. Conversion of alcohol **17** to carboxylic acid **6** was achieved in three steps with an overall yield of 27.3% and 98% ee as described before (**see Scheme 5**). The formation of carboxylic acid **6** was confirmed by the presence of a broad singlet (br s) at δ 10.67 in its ^{1}H NMR spectrum. This was further substantiated by the appearance of a typical signal at δ 179.9 in its ^{13}C NMR spectrum. The disappearance of signals corresponding to

methylene (-**CH$_2$**OH) in its ^{1}H NMR spectrum further confirmed the completion of this oxidation reaction (**Figure 8**).

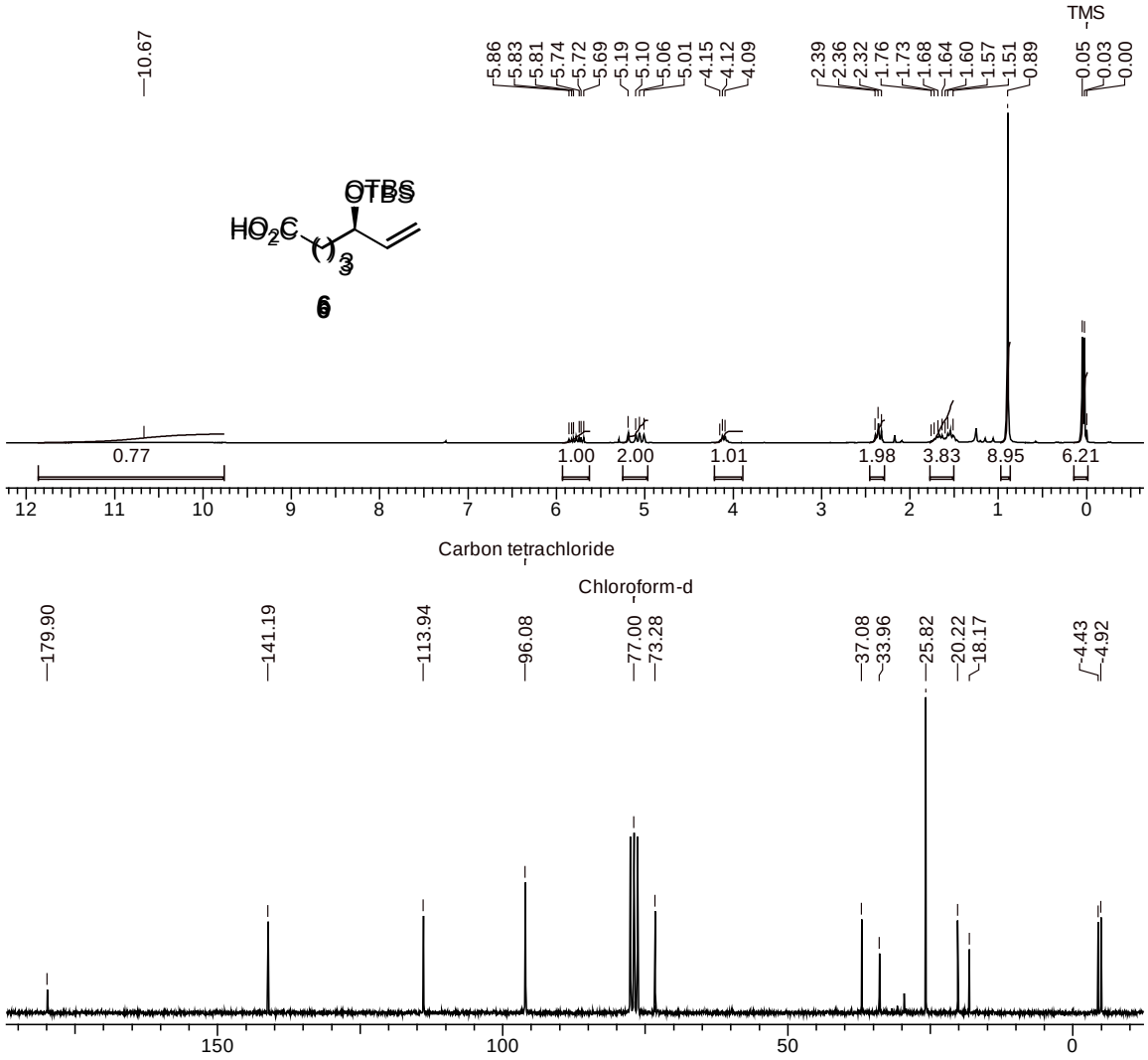


Figure 8: ^{1}H and ^{13}C NMR spectra of carboxylic acid **6**

With both the fragments **4** and **6** now in hand, we then carried out the coupling of these two fragments using Steglich esterification (EDCI, Et_3N, 88%). The coupled product **21** was confirmed by the presence of a typical multiplet at δ 4.03-4.13 corresponding to methine proton (-**CH**-OCO) attached to ester linkage. This was further substantiated by

the presence of carbon signals at δ 113.8, 117.7, 133.6 and 141.4 in its ^{13}C NMR spectrum which were attributed to four olefinic carbons (**Figure 9**).

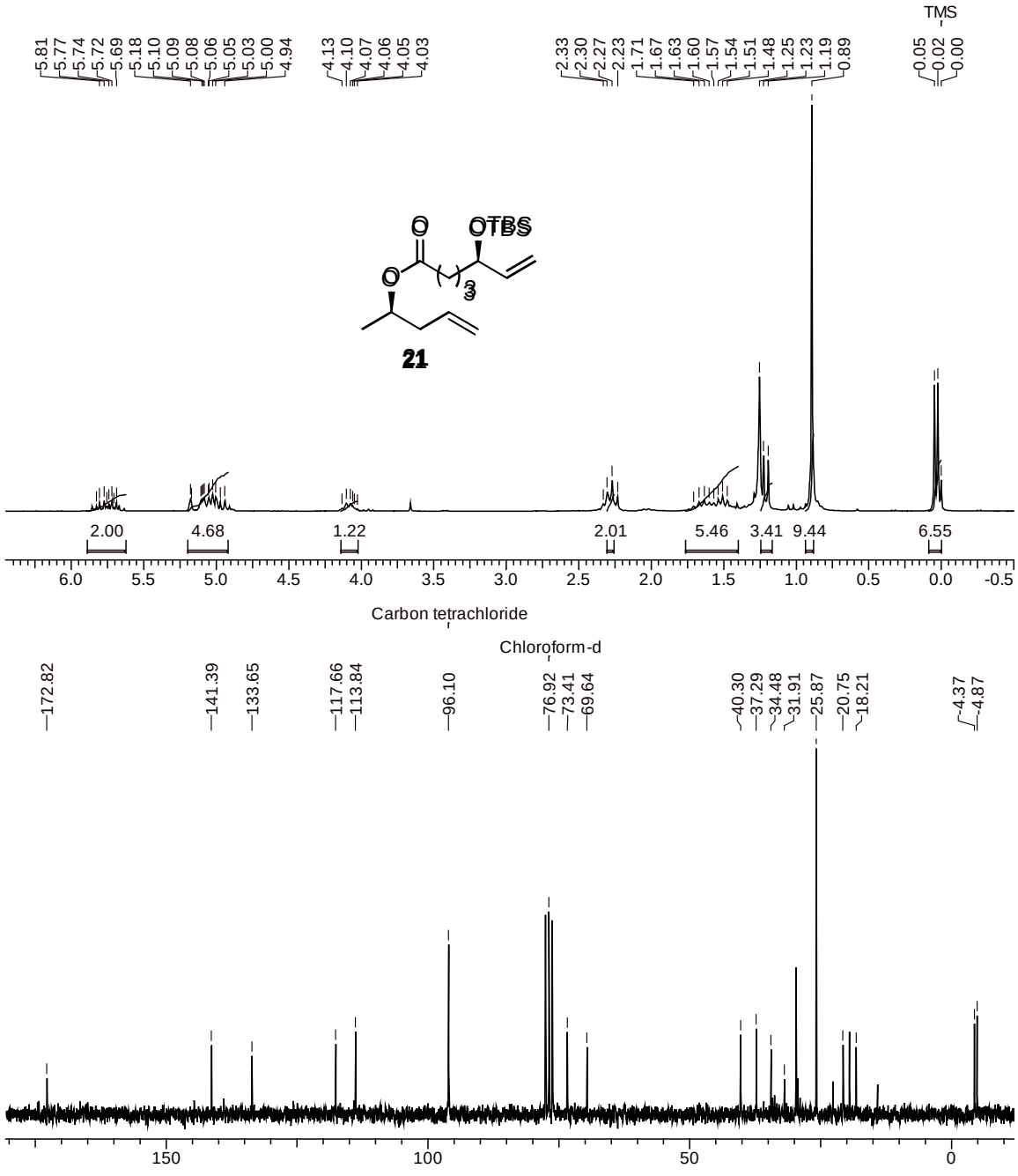
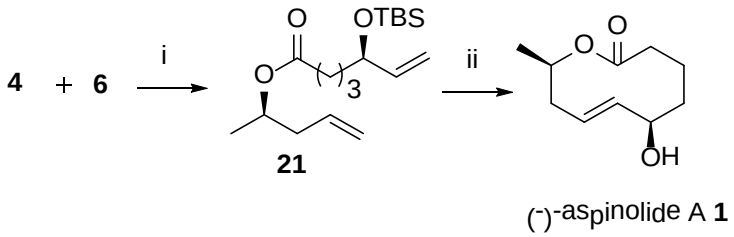


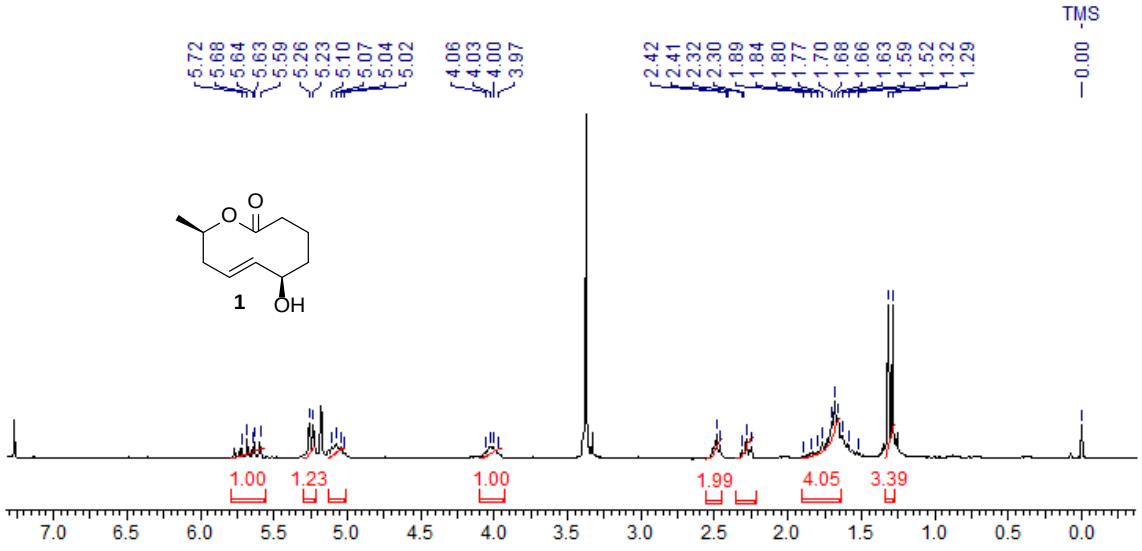
Figure 9: ^{1}H and ^{13}C NMR spectra of coupled product **21**

Finally, the TBS group was removed (TBAF, THF) and cyclic core was then constructed smoothly in 69% yield *via* a RCM strategy using Grubbs second generation catalyst, thus affording the final compound (-)-aspinolide A **1** in 11.2% overall yield and 98% ee. Its optical purity was based on comparison of its optical rotation with the reported values $[\alpha]_D^{25}$ -40.7 (*c* 0.3, MeOH) {lit.[3] $[\alpha]_D^{25}$ -41.6 (*c* 0.25, MeOH)} (**Scheme 7**).



Scheme 7: (i) EDCI·HCl, Et_3N, CH_2Cl_2, 25 °C, 6 h, 86%; (ii) (a) TBAF, THF, 0 °C, 2 h; (b) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 24 h, 62% (over two steps).

The ^{1}H NMR spectrum of **1** showed typical signals at δ 5.23 (m, 1H) and 5.59-5.72 (m, 1H) corresponding to the two olefinic protons, which was further ascertained by the appearance of carbon signals at δ 131.7 and 137.4 in its ^{13}C NMR spectrum. The characteristic multiplets at δ 3.97-4.06 (1H) and 5.02-5.10 (1H) accounted for the methine protons (-**CH**-O-) attached to oxygen atom (**Figure 10**).



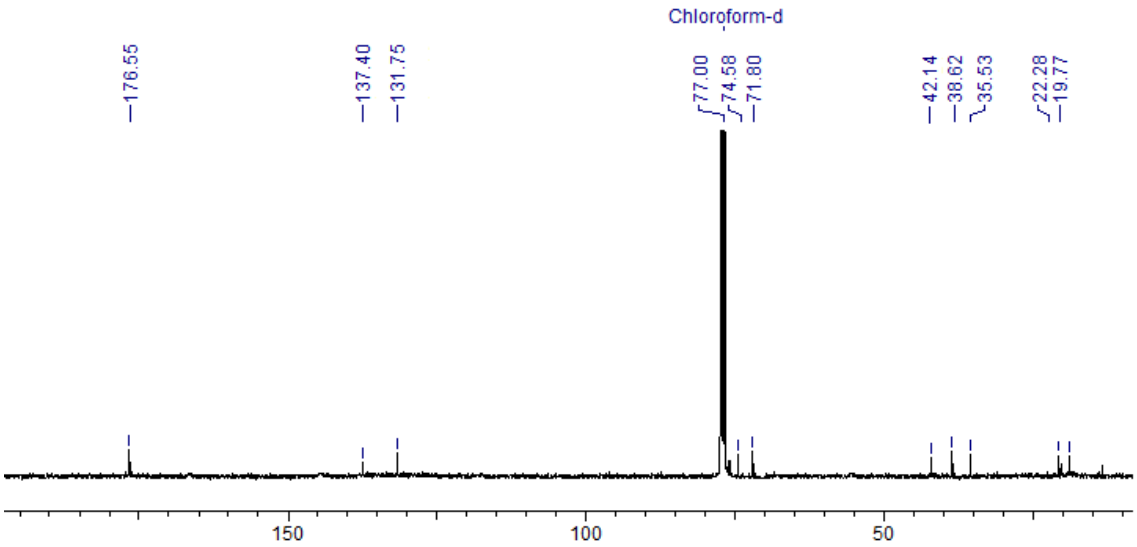


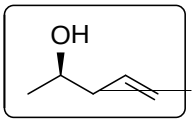
Figure 10: ^{1}H and ^{13}C NMR spectra of (-)-aspinolide A **1**

2.1.4 Conclusion

In conclusion, we have demonstrated the use of organocatalytic α-aminooxylation and asymmetric epoxidation strategy for the concise synthesis of (-)-aspinolide A **1** with an enantiomeric excess of 98%. Simple procedures, easy to use reagents, cheap, readily available starting materials and flexible synthetic scheme are some of the salient features of this approach. The synthetic strategy described herein has significant potential for further extension to other decanolides-based bioactive molecules.

2.1.5 Experimental section

(*R*)-Pent-4-en-2-ol (4)

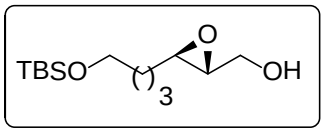


To a stirred solution of (-)-Ipc_2B(allyl)borane (150 mmol) in dry Et_2O (200 mL) at -78 ^{o}C was added a solution of acetaldehyde **11** (6 g , 136.37 mmol) in dry Et_2O (20 ml). The reaction mixture was stirred at -78 °C for 1 h, after which 3N NaOH (111 mL, 330 mmol) and 35% H_2O_2 (45 mL) was added to this reaction mixture and the contents stirred at 25 ^{o}C for additional 2 h. After the completion of

reaction (monitored by TLC), the organic layer was separated and the aqueous layer extracted with Et_2O, washed with brine, and dried over anhydrous Na_2SO_4. After the removal of solvent the residue was distilled (bp 115 °C) giving (*R*)-(-)-4-penten-2-ol **4** (9.04 g) as a colorless liquid.

Yield: 77%; $[\alpha]_D^{25}$ -9.67 (*c* 3.0, Et_2O) {lit.[3,6] $[\alpha]_D^{25}$ -9.84 (*c* 3.1, Et_2O)}; **IR** ($CHCl_3$): υ_{max} 914, 1071, 1243, 1432, 1457, 1562, 2975, 2931, 3078, 3409 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.0 Hz, 3H), 1.97 (br s, 1H), 2.14-2.26 (m, 2H), 3.83-3.84 (m, 1H), 5.10-5.14 (m, 2H), 5.76-5.87 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.7, 43.7, 66.8, 117.9, 134.8; **Anal.** Calcd for $C_5H_{10}O$ requires C, 69.72; H, 11.70; found C, 69.63; H, 11.78%.

((2*R*,3*R*)-3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)oxiran-2-yl)methanol (12)

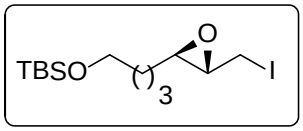


The catalyst (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol tri-methylsilyl ether (1.2 g, 10 mol%) was added at ambient temperature to a solution of the α,β-unsaturated aldehyde **13** (5 g, 20.6 mmol) in CH_2Cl_2 (50 mL) followed by the addition of 35% H_2O_2 (aq.) (2.6 mL, 26.8 mmol). After the completion of reaction (monitored by TLC), it was diluted with MeOH (50 mL) and cooled to 0 °C followed by the addition of $NaBH_4$ (1.72 g, 30.9 mmol). The mixture was then stirred for 10 min, quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography with petroleum ether/EtOAc (8:2 v/v) to give epoxy alcohol **12** (2.3 g) as yellow colored liquid.

Yield: 43%; $[\alpha]_D^{25}$ -16.5 (*c* 1.7, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 746, 878, 1099, 1454, 1717,

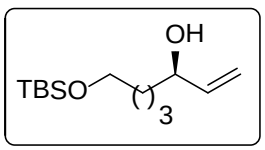
2862, 2936, 3063, 3414 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.53-1.63 (m, 6H), 2.04 (br s, 1H), 2.89-2.97 (m, 2H), 3.58-3.63 (m, 3H), 3.86-3.93 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 22.3, 25.9, 31.3, 32.4, 55.8, 58.5, 61.6, 62.7; **Anal.** Calcd for $C_{13}H_{28}O_3Si$ requires C, 59.95; H, 10.84; found C, 60.03; H, 10.91%.

***tert*-Butyl(2-((2*R*,3*S*)-3-(iodomethyl)oxiran-2-yl)ethoxy)dimethylsilane (16)**



To a stirred solution of epoxy alcohol **12** (1.3 g, 5 mmol) in dry ether-acetonitrile mixture (3:1, 40 mL) at 0 °C under nitrogen atmosphere were added imidazole (570 mg, 7.5 mmol), triphenylphosphine (1.96 g, 7.5 mmol), and iodine (1.91 g, 7.5 mmol) successively. The mixture was stirred for 1 h at the same temperature followed by stirring at 25 °C for additional 1h. After the completion of reaction (monitored by TLC) diluted with cold ether (20 mL), and filtered through a sintered funnel. The residue was washed with ether (3 × 50 mL) and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (9:1 v/v) to afford epoxy iodide **16** (1.72 g) as yellow colored liquid.

Yield: 90%; $[\alpha]_D^{25}$ +8.0 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 669, 767, 1216, 2854, 2927, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.53-1.56 (m, 6H), 2.76-2.79 (m, 1H), 2.98-3.04 (m, 2H), 3.21-3.32 (m, 1H), 3.58-3.61 (m, 2H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 4.8, 18.3, 22.3, 25.9, 31.4, 32.4, 58.1, 62.2, 62.7; **Anal.** Calcd for $C_{13}H_{27}IO_2Si$ requires C, 42.16; H, 7.35; found C, 42.21; H, 7.40%.



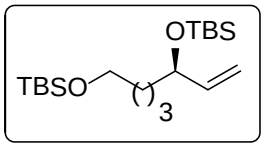
(*R*)-5-(*tert*-Butyldimethylsilyloxy)pent-1-en-3-ol (17)

A mixture of epoxy iodide **16** (1.3 g, 3.5 mmol), NaI (1.1 g, 7.0

mmol) and freshly activated zinc powder (50 mg, 20 mol%) in dry MeOH (50 mL) was refluxed for 3 h under nitrogen atmosphere. After the completion of reaction (monitored by TLC), the solution was filtered and the residue washed with MeOH (2 × 25 mL). The combined filtrates were concentrated and the residue was purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to afford the allylic alcohol **17** (770 mg) as a colorless liquid.

Yield: 90%; $[\alpha]_D^{25}$ +7.1 (*c* 2.4, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 993, 1018, 1217, 1458, 1465, 2864, 2926, 3018, 3307, 3427 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.38-1.65 (m, 7H), 3.58-3.64 (t, *J* = 5.9 Hz, 2H), 4.04-4.13 (m, 1H), 5.06-5.26 (m, 2H), 5.77-5.94 (m, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 21.6, 25.9, 32.6, 36.6, 62.9, 73.0, 114.0, 141.2; **Anal.** Calcd for $C_{13}H_{28}O_2Si$ requires C, 63.87; H, 11.55; found C, 63.94; H, 11.59%.

(*R*)-2,2,3,3,9,9,10,10-octamethyl-5-vinyl-4,8-dioxa-3,9-disilaundecane (18)

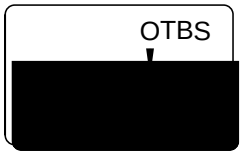


To a solution of allylic alcohol **17** (1 g, 4.1 mmol) and imidazole (556 mg, 8.2 mmol) in dry CH_2Cl_2 (40 mL) was added TBSCl (738 mg, 4.9 mmol) under nitrogen over 5 min at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 6 h. After the completion of reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether gave TBS ether **18** (1.3 g) as a

colorless liquid.

Yield: 86%; $[\alpha]_D^{25}$ +6.0 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 929, 1033, 1216, 2854, 2927, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02 (s, 12H), 0.89 (s, 18H), 1.25-1.57 (m, 6H), 3.56 (t, *J* = 5.9 Hz, 2H), 4.02-4.10 (m, 1H), 4.97-5.16 (m, 2H), 5.69-5.86 (m, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, - 4.7, - 4.2, 18.2, 21.5, 26.0, 32.8, 37.9, 63.1, 73.8, 113.5, 141.8 ; **Anal.** Calcd for $C_{19}H_{42}O_2Si_2$ requires C, 63.62; H, 11.80; found C, 63.69; H, 11.74%.

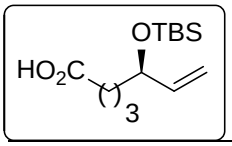
(*R*)-3-(*tert*-Butyldimethylsilyloxy)pent-4-en-1-ol (19)



To a stirred solution of **18** (900 mg, 2.72 mmol) in MeOH (20 mL) was added (+)-camphor-10-sulfonic acid (6 mg, 1 mol%) and the reaction mixture stirred for 5 min. After the completion of reaction (monitored by TLC), H_2O (1 mL) was added and extraction was done with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatographic purification of the crude product using petroleum ether/EtOAc (8:2 v/v) gave alcohol **19** (371 mg) as a colorless liquid.

Yield: 63%; $[\alpha]_D^{25}$ -9.2 (*c* 1.3, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 775, 836, 1078, 1215, 1255, 2957, 3441 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.36-1.57 (m, 7H), 3.60 (t, *J* = 5.9 Hz, 2H), 4.05 (q, *J* = 6.1 Hz,, 1H), 4.99-5.12 (m, 2H), 5.72-5.79 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.2, 18.3, 21.3, 25.9, 32.7, 37.8, 62.8, 73.8, 113.7, 141.7; **Anal.** Calcd for $C_{13}H_{28}O_2Si$ requires C, 63.87; H, 11.55; found C, 63.81; H, 11.47%.

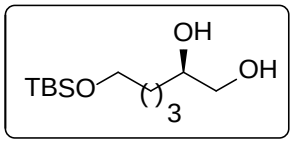
(*R*)-3-(*tert*-Butyldimethylsilyloxy)pent-4-enoic acid (6)



To a solution of alcohol **19** (450 mg, 1.85 mmol) in CH_3CN/H_2O (4:1) were added in one portion (diacetoxyiodo)benzene (1.2 g, 3.7 mmol) and TEMPO (86.3 mg, 0.55 mmol). The reaction mixture was then allowed to stir at 25 ^oC for 4 h. After completion of reaction (monitored by TLC), it was quenched by the addition of saturated solution of aq. sodium thiosulfate. The organic layer was separated, washed with brine and subjected to column chromatographic purification with petroleum ether/EtOAc (7:3 v/v) to afford the carboxylic acid **6** (384 mg) as a colorless liquid.

Yield: 80%; $[\alpha]_D^{25}$ -6.4 (*c* 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ -6.56 (*c* 1.15, $CHCl_3$)}; **IR** ($CHCl_3$): υ_{max} 1109, 1257, 1425, 1462, 1707, 2858, 2931, 3070, 3444, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.51-1.76 (m, 4H), 2.32-2.39 (t, *J* = 6.1 Hz, 2H), 4.09-4.15 (m, 1H), 5.02-5.19 (m, 2H), 5.69-5.86 (m, 1H), 10.67 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.4, 18.2, 20.2, 25.8, 33.9, 37.1, 73.3, 113.9, 141.2, 179.9 ; **Anal.** Calcd for $C_{13}H_{26}O_3Si$ requires C, 60.42; H, 10.14; found C, 60.47; H, 10.23%.

(*R*)-4-(*tert*-Butyldimethylsilyloxy)butane-1,2-diol (20)

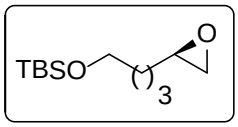


To a stirred pre-cooled (-20 °C) acetonitrile (100 mL) solution of aldehyde **15** (6.1 g, 26.5 mmol) and nitrosobenzene (2.8 g, 26.5 mmol) was added L-proline (608 mg, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 24 h followed by the addition of MeOH (60 mL) and $NaBH_4$ (1.94 g, 51 mmol) to the reaction mixture, which was stirred for 10 min. After the completion of reaction (monitored by TLC), the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude aminooxy alcohol which was directly taken up for the

next step without purification. To a well stirred solution of crude aminooxy alcohol in methanol was added 10% Pd/C and the reaction mixture stirred overnight at 25 ^{o}C under H_2 atmosphere. After completion of reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and solvent evaporated under reduced pressure to afford the crude diol. Purification by column chromatography with petroleum ether/ethyl acetate (5:5 v/v) gave the diol **20** (5.1 g) as a colorless liquid.

Yield: 77%; $[\alpha]_D^{25}$ -7.0 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1376, 1466, 2872, 2969, 3381 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.42-1.57 (m, 6H), 2.92 (br s , 2H), 3.35-3.44 (m, 1H), 3.58-3.69 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 21.9, 25.9, 32.6, 32.7, 62.97, 66.65, 72.13; **Anal.** Calcd for $C_{12}H_{28}O_3Si$ requires C, 58.01; H, 11.36; found C, 58.09; H, 11.43%.

(*R*)-*tert*-Butyldimethyl(2-(oxiran-2-yl)ethoxy)silane (14)

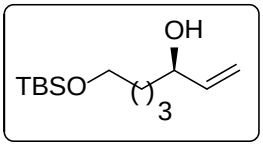


A solution of diol **20** (2.94 g, 11.8 mmol) in CH_2Cl_2 (50 mL) was treated with TsCl (2.25 g, 11.8 mmol), Bu_2SnO (883.8 mg, 30 mol%), Et_3N (4.21 mL, 30 mmol) and DMAP (cat.) at 0 °C. After being stirred for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude tosylate. To a solution of crude tosylate 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 was then purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to give epoxide **14** (2.5 g) as a

colorless oil.

Yield: 92%; $[\alpha]_D^{25}$ -5.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 877, 985, 1216, 1387, 1452, 1607, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.53-1.60 (m, 6H), 2.42-2.45 (m, 1H), 2.71-2.75 (m, 1H), 2.85-2.90 (m, 1H), 3.61 (t, *J* = 6.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 22.3, 25.9, 32.2, 32.5, 46.8, 52.1, 62.8; **Anal.** Calcd for $C_{12}H_{26}O_2Si$ requires C, 62.55; H, 11.37; found C, 62.41; H, 11.02%.

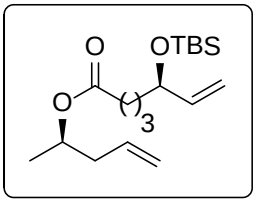
(*R*)-5-(*tert*-Butyldimethylsilyloxy)pent-1-en-3-ol (17)



To a stirred suspension of trimethylsulfonium iodide (2 equiv, 11 mmol, 2.24 g) in dry THF (50 mL) was added *n*-BuLi (2 equiv, 11 mmol, 6.8 mL of 2 M hexane solution) at -10 ^oC. After 30 min, epoxide **14** (1.2 g, 5.2 mmol) in dry THF (30 mL) was introduced dropwise and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to give allyl alcohol **17** (1.12 g)**.**

Yield: 89%; $[\alpha]_D^{25}$ +7.5 (*c* 2.4, $CHCl_3$)

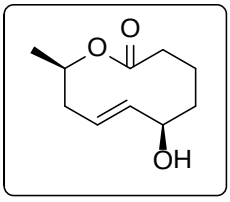
(*R*)-((*R*)-Pent-4-en-2-yl) 3-(*tert*-butyldimethylsilyloxy)pent-4-enoate (21)



To a stirred solution of acid **6** (200 mg, 0.8 mmol), EDCI·HCl (176.4 mg, 0.9 mmol) and Et_3N (242.2 mg, 2.4 mmol) in anhydrous CH_2Cl_2 (25 mL) was added alcohol **4** (67 mg, 0.8 mmol) and the reaction mixture stirred for 6 h at 25 ^oC. After completion of the reaction (monitored by TLC), it was quenched with H_2O and extracted with CH_2Cl_2 (3 × 50). The combined

organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography with petroleum ether/EtOAc (8:2 v/v) to give dienic ester **21** (225 mg) as colorless liquid. **Yield:** 88%; $[\alpha]_D^{25}$ -18.3 (*c* 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ -14.9 (*c* 0.5, $CHCl_3$)}; **IR** ($CHCl_3$): υ_{max} 1425, 1462, 1642, 1735, 2855, 2926 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.48 (d, *J* = 6.1 Hz, 3H), 1.51-1.71 (m, 6H), 2.23-2.33 (m, 2H), 4.03-4.13 (m, 1H), 4.94-5.18 (m, 5H), 5.69-5.83 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.4, 18.2, 20.7, 25.9, 31.9, 34.4, 37.2, 40.3, 69.6, 73.4, 113.8, 117.7, 133.6, 141.4, 172.8; **Anal.** Calcd for $C_{18}H_{34}O_3Si$ requires C, 66.21; H, 10.49; found C, 66.34; H, 10.55%.

(-)-Aspinolide A (1)



To a well stirred solution of silyl ether **21** (200 mg, 0.48 mmol) in dry THF (5 mL) was added 1 M solution of tetrabutylammonium fluoride (1 mL, 1 mmol) at 0 ^oC. The reaction mixture was stirred at this temperature for additional 2 h. After the completion of reaction (monitored by TLC), it was quenched with H_2O (1 mL) and the reaction mixture extracted with Et_2O (3 x 20 mL). then washed with brine, dried over anhydrous Na_2SO_4. After the removal of solvent, the crude product was dissolved in freshly distilled degassed anhydrous CH_2Cl_2 (50 mL). The reaction mixture was treated with Grubb's II catalyst (82 mg, 20 mol%) and heated at reflux for 24 h under inert atmosphere. After the completion of reaction (monitored by TLC), the solvent was then distilled off and the residue was purified by column chromatography with petroleum ether/EtOAc (9:1 v/v) to afford **1** (54 mg) as viscous yellow liquid.

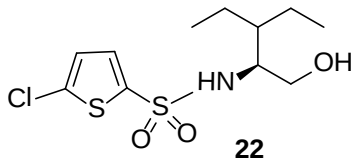
Yield: 69%; $[\alpha]_D^{25}$ -40.7 (*c* 0.3, MeOH) {lit.[3] $[\alpha]_D^{25}$ -41.6 (*c* 0.25, MeOH)}; **IR** ($CHCl_3$,): υ_{max} 1275, 1460, 970, 1730, 2852, 2920, 3436 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.1 Hz, 3H), 1.52-1.89 (m, 4H), 2.30 (t, *J* = 7.1 Hz, 2H), 2.40-2.42 (m, 2H), 3.97-4.06 (m, 1H), 5.02-5.07 (m, 1H), 5.23 (d, *J* = 7.6 Hz, 1H), 5.59-5.72 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.8, 22.3, 35.5, 38.6, 42.1, 71.8, 74.6, 131.7, 137.4, 176.5; **Anal.** Calcd for $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75; found C, 65.11; H, 8.86%.

Section II

A facile enantioselective synthesis of (*S*)-*N*-(5-Chlorothiophene-2-sulfonyl)-β,β-diethylalaniol (7.b.2) *via* proline-catalyzed asymmetric α-aminooxylation and α-amination of aldehyde

2.2.1 Introduction and Pharmacology

Alzheimer's disease (AD) is a chronic, neurodegenerative disorder, which is characterized by a loss of cognitive ability, severe behavioral abnormalities and ultimately death.[9] A key event in the pathogenesis of AD is now believed to be the deposition of β-amyloid (Aβ) plaques on the outside of the nerve cells in areas of the brain that are produced by the proteolytic cleavage of amyloid precursor protein (APP) by β and γ-secretase.[10] A "β-amyloid cascade" hypothesis has emerged to account for various experimental facts including genetic variations related to the production and elimination of Aβ.[9a,11a] Recent studies have further shown that neuritic plaques and neurofibriliary tangles are accepted pathological hallmarks of AD as confirmed at autopsy.[11] γ-Secretase inhibitors like BMS-299897, LY-450139 and MK-0752 have entered clinical trials. Recently (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **22** (**7.b.2**), a Notch-1-sparing γ-secretase inhibitor (with EC_{50}= 28 nM), has been found to be effective in reduction of Aβ production *in vivo* (**Figure 11**).[12]



22

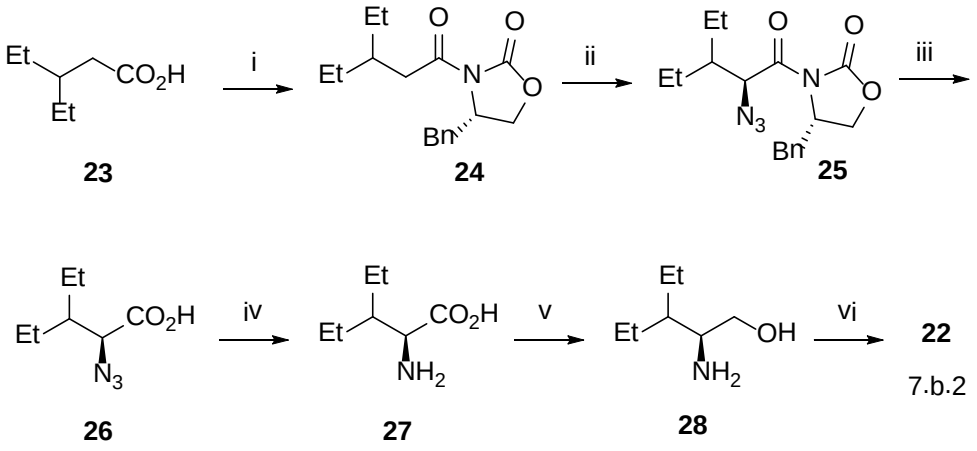
Figure 11: Structure of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol (**22**)

2.2.2 Review of Literature

Literature search revealed that there are only two reports available on the synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **22**, which are described below.

Mayer's approach (2008)[13]

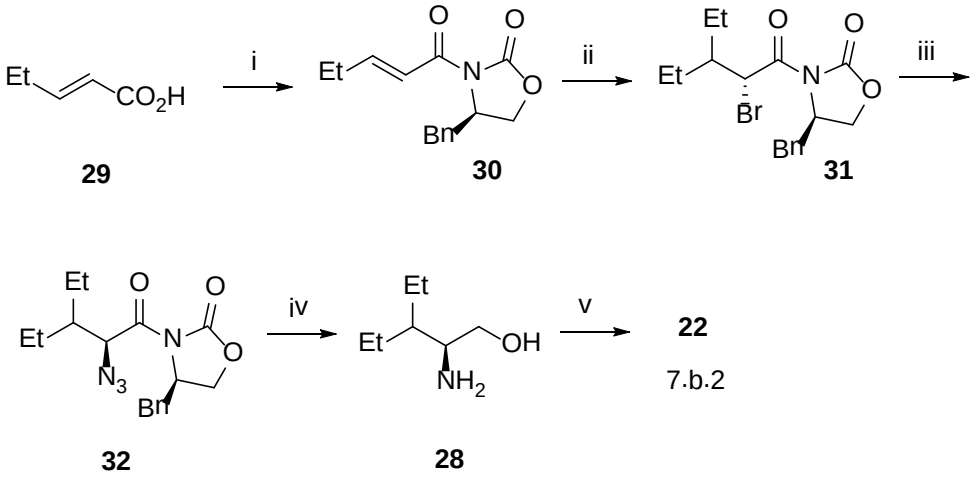
Mayer *et al.* have reported the synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **22** starting from 3-ethylpentanoic acid **23** which was coupled with (*S*)-4-benzyl-2-oxazolidinone to give the alkenoyloxazolidin-2-one **24**. Chiral α-azidination of **24** with KHMDS as base and 2,4,6-triisopropylbenzenesulfonyl azide as azide source gave **25**. Azide **25** was converted to amino alcohol **28** by employing a three step reaction sequence: (i) hydrolysis of **25** with LiOH; (ii) catalytic reduction of **26** with 10% Pd/C and (iii) reduction of acid functionality in **27** by its treatment with lithium aluminum hydride. Amino alcohols **28** were reacted with 5-chlorothiophene-2-sulfonyl chloride to give the desired 5-chlorothiophene-2-sulfonyl amino alcohols **22** with an overall yield of 16.1% **(Scheme 8)**.



Scheme 8: (i) (*S*)-4-benzyl-2-oxazolidinone, $(CH_3)_3CCOCl$, Et_3N, THF, (ii) (a) KHMDS, THF, -78 ^oC, 30 min; (b) 2,4,6-triisopropylbenzenesulfonyl azide, THF -78 ^oC; (iii) LiOH, THF/H_2O (3:1), 25 ^oC; (iv) 10% Pd/C, H_2 (40 psig), AcOH, H_2O; (v) $LiAlH_4$, THF, 60 ^oC, 55.3% (over three step); (vi) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, THF, 85%.

Cole's approach (2009)[14]

Cole *et al.* have reported the synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **22** starting from 2-pentenoic acid **29** which was coupled with (*R*)-4-benzyl-2-oxazolidinone to give the alkenoyloxazolidin-2-one products **30**. Cuprate reagents prepared *in situ* by the addition of Grignard reagent to CuBr·DMS under carefully controlled temperature conditions, underwent Michael addition and the anion was trapped with N-bromosuccinimide (NBS) to give the α-bromo derivatives **31**. Displacement of the bromide in **31** with N,N,N',N'-tetramethylguanidinium azide yielded the corresponding azide **32**. Simultaneous reduction of amide and azide moieties on treatment with lithium aluminum hydride yielded the corresponding amino alcohols **28**, which were reacted with 5-chlorothiophene-2-sulfonyl chloride to give the desired 5-chlorothiophene-2-sulfonyl amino alcohols **22** (**Scheme 9**).

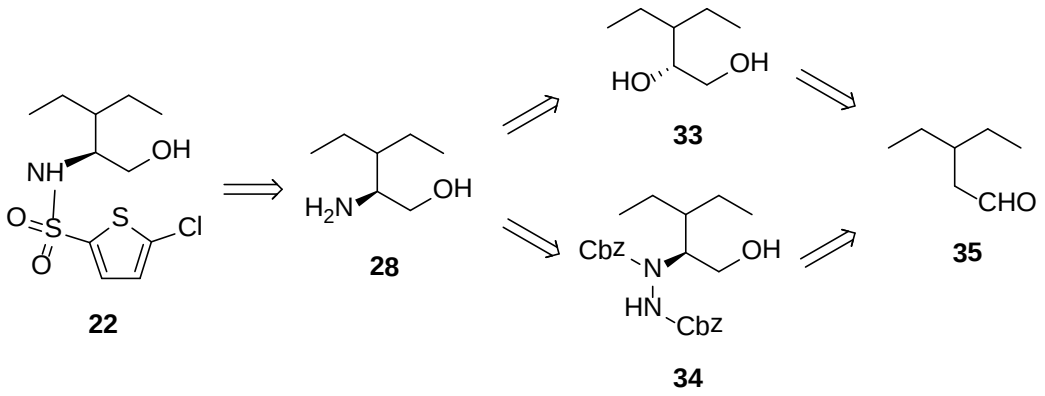


Scheme 9: (i) (*R*)-4-benzyl-2-oxazolidinone, $(CH_3)_3CCOCl$, Et_3N, THF, (ii) *n*-BuLi, THF; (iii) (a) EtMgBr, CuBr·DMS, THF -40 to -15 °C; (b) NBS, -78 °C; (c) *N*,*N*,*N*',*N*'-tetramethylguanidinium azide, CH_3CN, 25 °C; (iv) $LiAlH_4$, THF, 60 °C; (iv) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, THF.

2.2.3 Present Work

2.2.3.1 Objective

Reported methods for the synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **22**, employ the use of stoichiometric amount of chiral auxillary for the generation of chirality and are not atom-economical. Organocatalytic asymmetric synthesis has provided several new methods for obtaining chiral compounds.[15] In particular, proline, an abundant, inexpensive amino acid available in both enantiomeric forms has emerged arguably as the most practical and versatile organocatalyst.[16] In continuation of our work on proline-catalyzed synthesis of bioactive molecules, in this section, a facile synthesis of **22**, whose activity makes it an attractive synthetic target is described. The retrosynthetic analysis of **22**, wherein proline-catalyzed α-aminooxylation[8] and α-amination[17] reactions constitute the key steps for the introduction of chirality, is presented in **Schemes 10**. Evidently, amino alcohol **28** has emerged as the key intermediate in the synthesis of **22**.



Scheme 10: The retrosynthesis of 7.b.2 (**22**)

2.2.3.2. Results and Discussion

Our synthesis of anti-Alzheimer's agent 7.b.2 (**22**) commenced from 3-pentanone **36**, which on Horner-Wardsworth-Emmons olefination (triethyl phosphonoacetate, NaH, THF), gave the corresponding α,β-unsaturated ester **37** in 93% yield. The formation of **37**

was confirmed by its ^{1}H NMR spectrum which showed the presence of a typical singlet at δ 5.59 corresponding to olefinic proton; this was further ascertained by its ^{13}C NMR spectrum which showed typical carbon signals at δ 113.0 and 166.5 due to olefinic carbons (**Figure 12**).

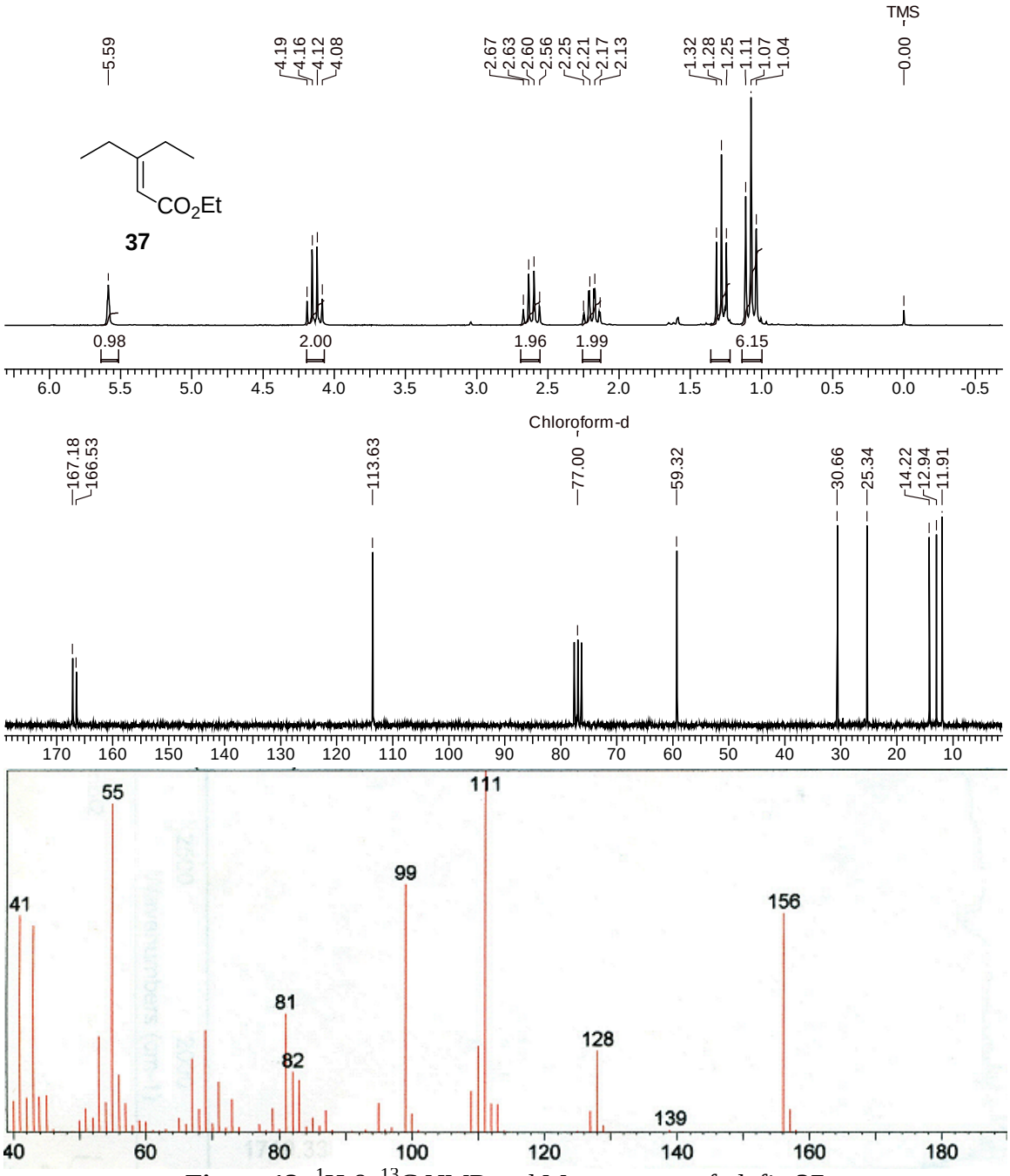


Figure 12: ^{1}H & ^{13}C NMR and Mass spectra of olefin **37**

Hydrogenation [10% Pd/C, H_2 (1 atm), MeOH] of the unsaturated ester **37** produced the crude saturated ester, which was directly subjected to reduction with $LiAlH_4$ in THF affording the saturated primary alcohol **38** in 83% yield over two steps. The disappearance of resonance signals corresponding to olefinic and ester functionality in its ^1H & ^{13}C NMR spectra and the appearance of a broad singlet at δ 2.35 in its ^1H NMR spectrum confirmed the formation of alcohol **38**. This was further substantiated by its IR spectrum analysis, which showed a broad absorption band at υ_{max} 3355 cm^{-1} due to -OH stretching frequency (**Figure 13**).

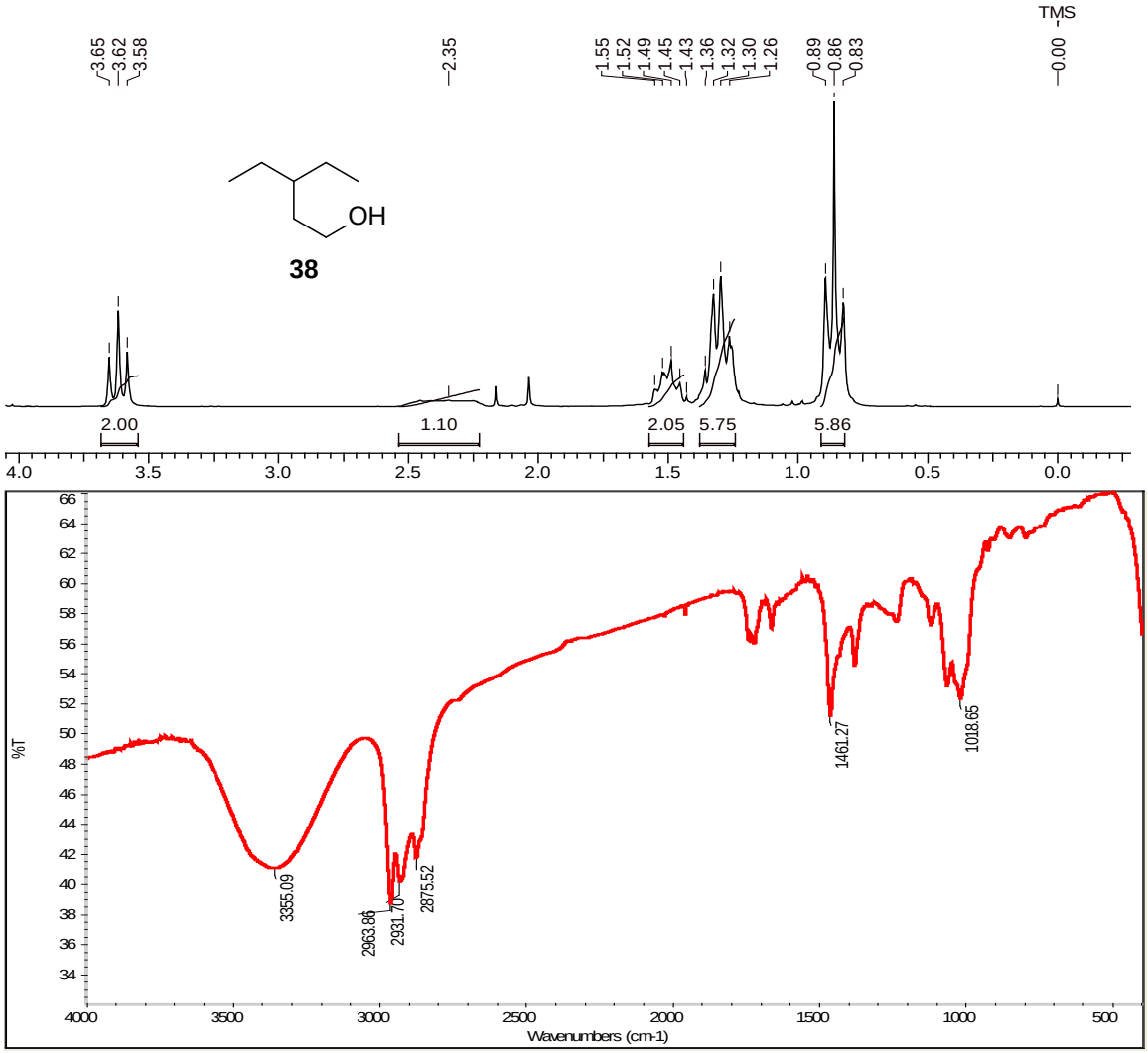
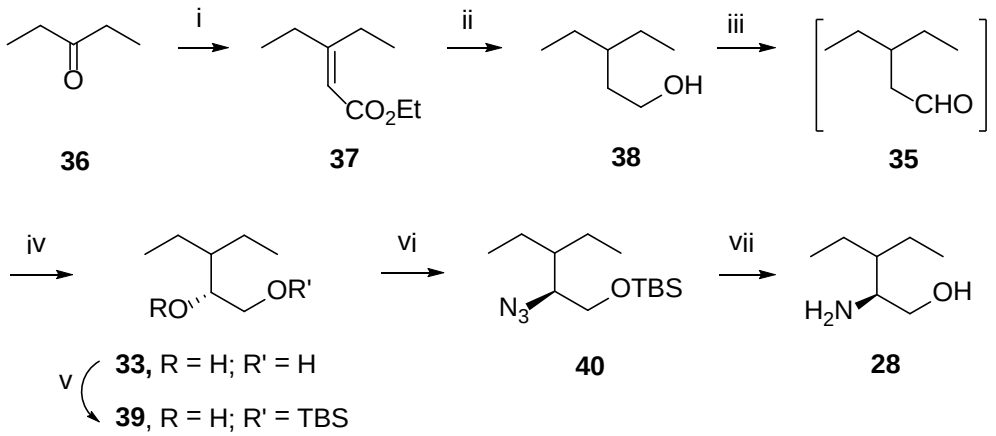


Figure 13: ^1H NMR and IR spectra of alcohol **38**

Oxidation of primary alcohol **38** with IBX/DMSO mixture gave the key precursor aldehyde **35**, which was found to be highly labile and volatile. Hence, upon solvent extraction, it was immediately (without purification) subjected to proline-catalyzed α-aminooxylation and α-amination reactions respectively (**Schemes 11 and 12**).



Scheme 11: (i) triethyl phosphonoacetate, NaH, dry THF, 0-25 ºC, 8 h, 93%; (ii) (a) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 25 ºC; (b) $LiAlH_4$, dry THF, 0-25 ºC, 12 h, 83% (over two steps); (iii) IBX, dry DMSO, 25 ºC, 1 h; (iv) (a) PhNO, L-proline (20 mol %), CH_3CN, -20 ºC, 24 h then MeOH, $NaBH_4$, 10 min; (b) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 25 ºC, 77% (over two steps); (v) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 2 h, 81%. (vi) (a) MsCl, Et_3N, 45 min; (b) NaN_3, dry DMF, 60 ºC, 30 h, 78%; (vii) $LiAlH_4$, dry THF, 50 ºC, 12 h, 75%.

Firstly, the L-proline-catalyzed α-aminooxylation of aldehyde **35** was carried out in a two-step reaction sequence: (i) reaction of aldehyde **35** with nitrosobenzene as the oxygen source in the presence of 20 mol% L-proline in CH_3CN at -20 ºC followed by its reduction with $NaBH_4$ in MeOH gave the crude α-aminooxy alcohol *in situ* and (ii) subsequent reduction of the crude α-aminooxy alcohol with 10% Pd/C over H_2 (1 atm) furnished chiral diol **33** in 77% yield over two steps. The formation of diol **33** was confirmed by its ^{1}H NMR spectrum, which showed a multiplet at δ 3.49-3.66 (3H) corresponding to methylene (-**C**$\mathbf{H_2}$-OH) and methine (-**CH**-OH) protons respectively. This was further ascertained by its ^{13}C NMR spectrum, which displayed characteristic

carbon signals at δ 64.9 and 73.6 corresponding to methylene (-**CH_2**-OH) and methine (-**CH**-OH) carbons attached to the oxygen atom (**Figure 14**).

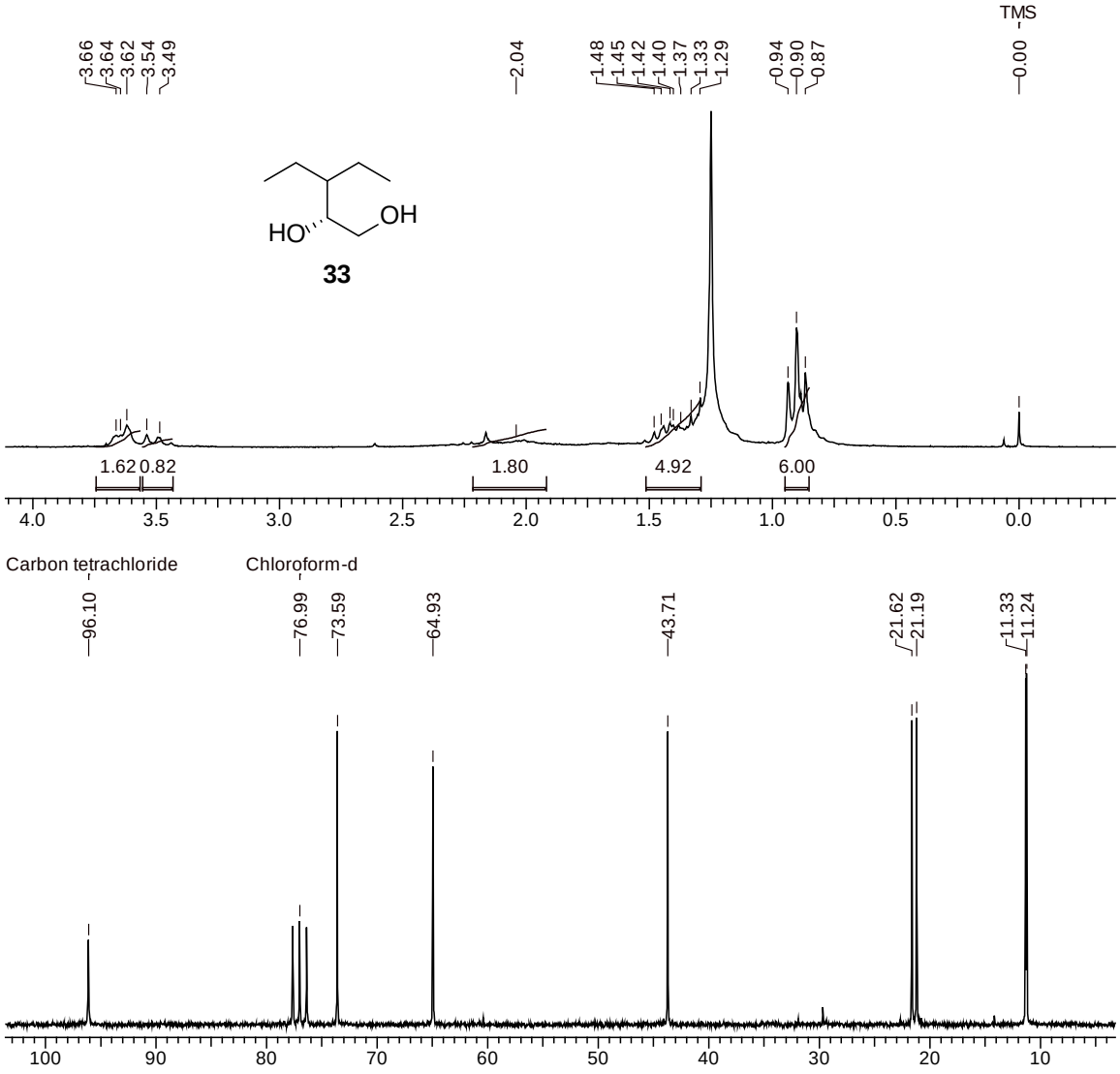
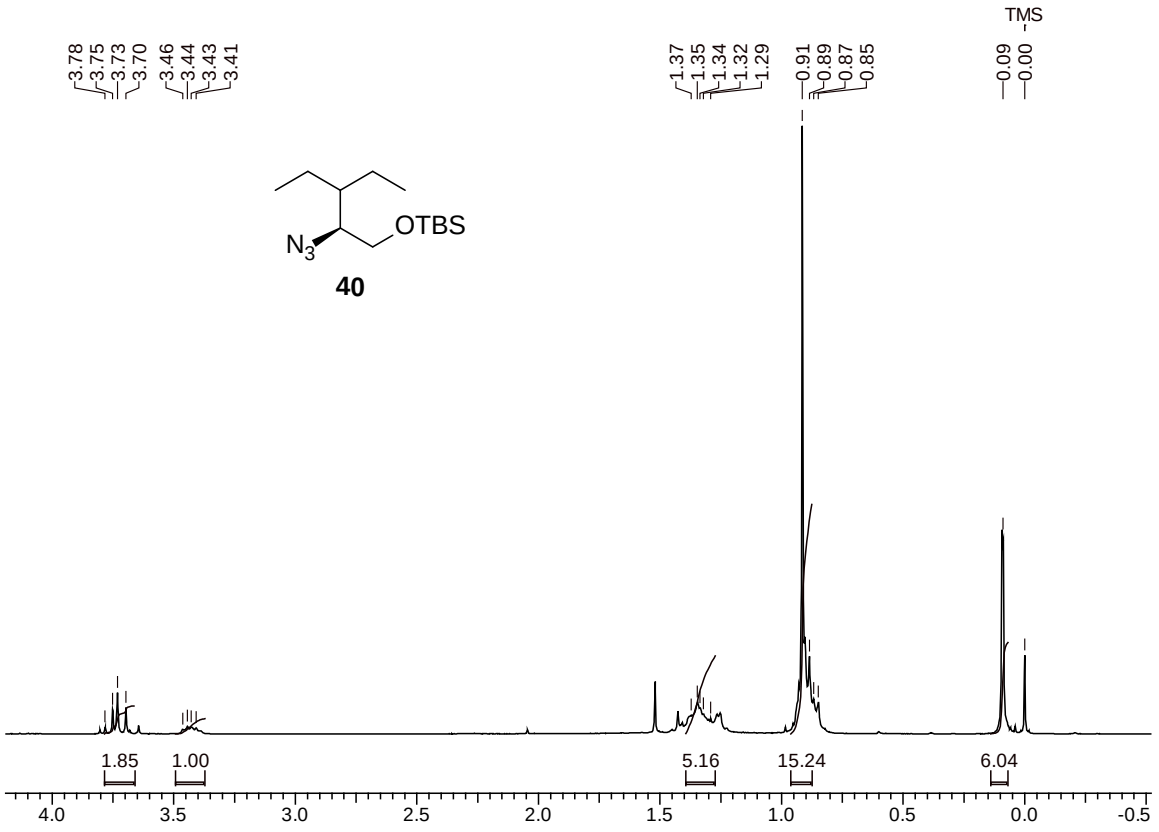


Figure 14: ^{1}H and ^{13}C NMR spectra of diol **33**

Selective protection of primary hydroxyl group in diol **33** (TBSCl, imid, CH_2Cl_2) was achieved to produce the TBS ether **39** in 81% yield. The formation of silyl ether **39** was confirmed by the appearance of characteristic singlets in its ^{1}H NMR spectrum at δ 0.08 and 0.91 due to protons corresponding to TBS ether group. This was substantiated by analyzing its ^{13}C NMR spectrum, which showed typical carbon signals at δ -5.3 (**CH_3**-

Si), -5.2 **(CH_3-Si)**, 18.3 [-Si-**C**$(CH_3)_3$] and 25.9 [-Si-C(**CH_3**$)_3$] for carbons of the TBS group. Mesylation (MsCl, Et_3N, CH_2Cl_2) of the secondary alcohol functionality present in **39** gave the corresponding mesylate. However, attempts to purify the mesylate *via* column chromatography proved problematic due to its instability. This crude mesylate was therefore treated immediately with sodium azide (DMF, 60 ºC) to afford the azido derivative **40** in 78% yield {$[\alpha]_D^{25}$ -21.3 (*c* 1.6, $CHCl_3$)}. The formation of azido derivative **40** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 2097 cm^{-1} typical for azide functionality. The ^{1}H NMR spectrum of **40** showed the appearance of a multiplet at δ 3.41-3.46 (1H) corresponding to methine proton (-**CH**-N_3). This was further confirmed by its ^{13}C NMR spectrum, which showed the methine carbon (-**CH**-N_3) appearing at δ 65.0 (**Figure 15**).



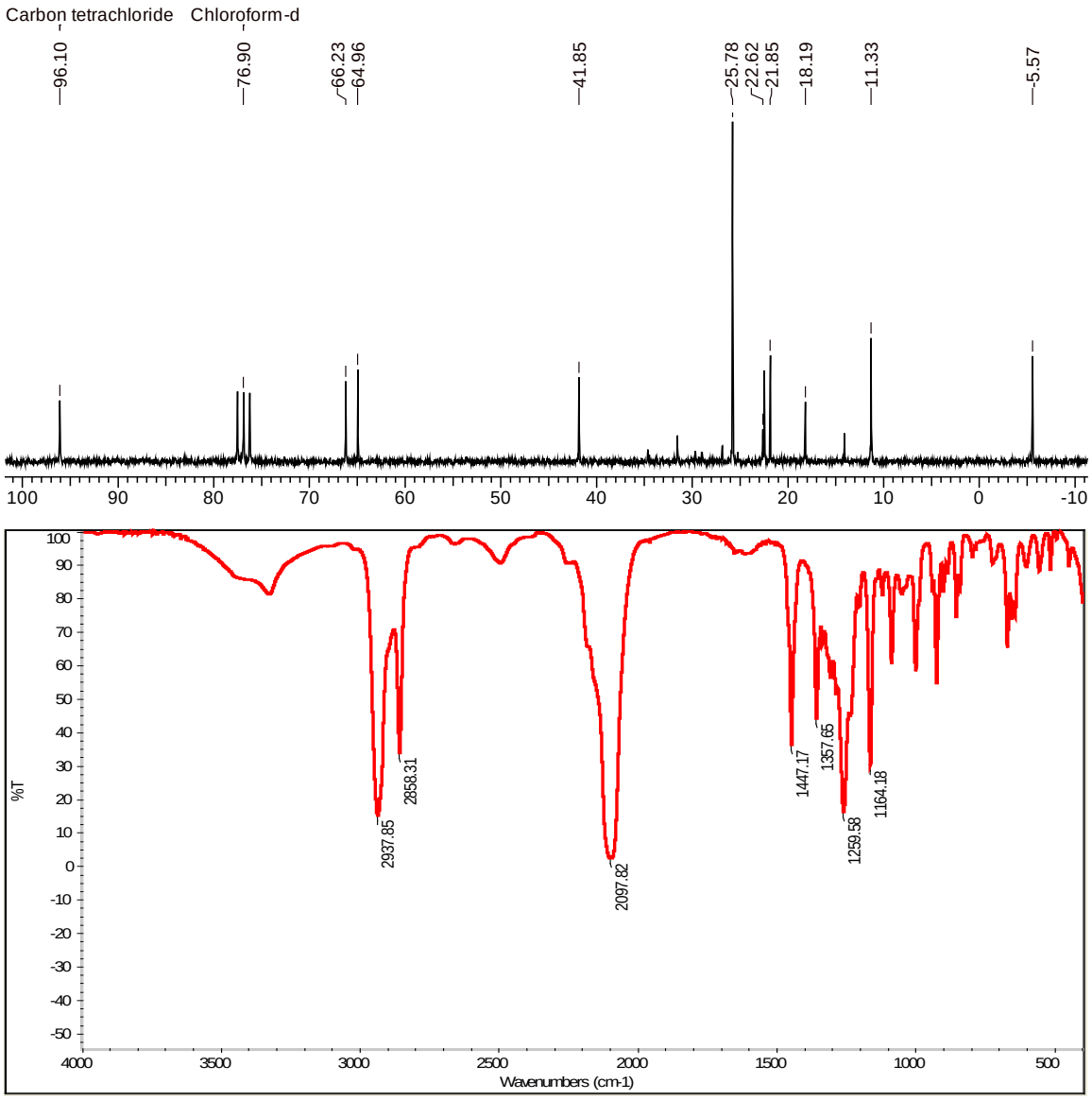


Figure 15: ^{1}H & ^{13}C NMR and IR spectra of azide **40**

The $LiAlH_4$ reduction of TBS azide **40** in THF at 50 °C afforded the key intermediate (*S*)-2-amino-3-ethylpentan-1-ol **28** in 75% yield with 99% ee accompanied with the simultaneous removal of TBS group (**Scheme 11**). The ^{1}H NMR spectrum of **28** showed a characteristic broad singlet at δ 2.36 corresponding to amine and hydroxyl protons (-**NH_2** and –**OH**). Its ^{13}C NMR spectrum showed carbon signals at δ 64.3 and 54.9 corresponding to methylene (-**CH_2**-OH) and methine (-**CH**-NH_2) carbons. The

disappearance of signals corresponding to TBS ether group in its ^{1}H NMR and ^{13}C NMR spectra gave further evidence of this transformation. Its IR spectrum showed a broad absorption band at υ_{max} 3441 cm^{-1} due to -NH and -OH groups (**Figure 16**).

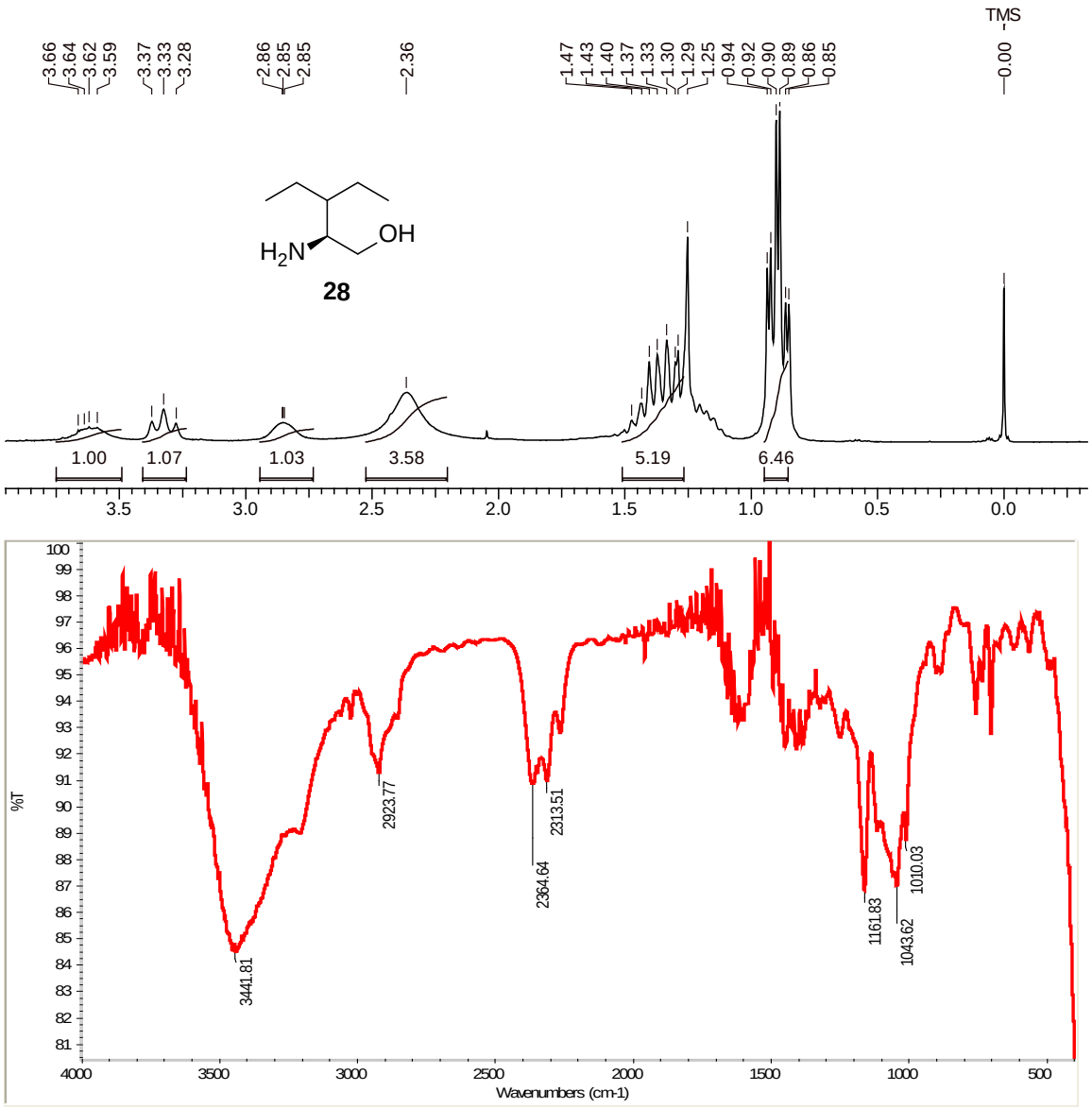
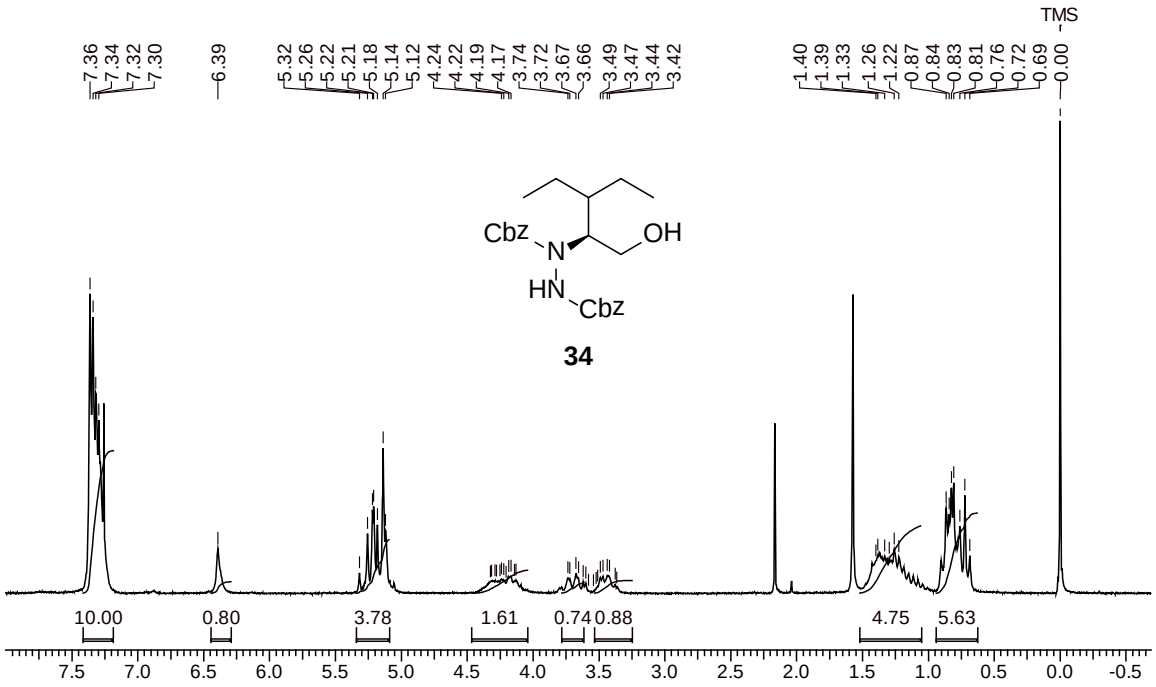
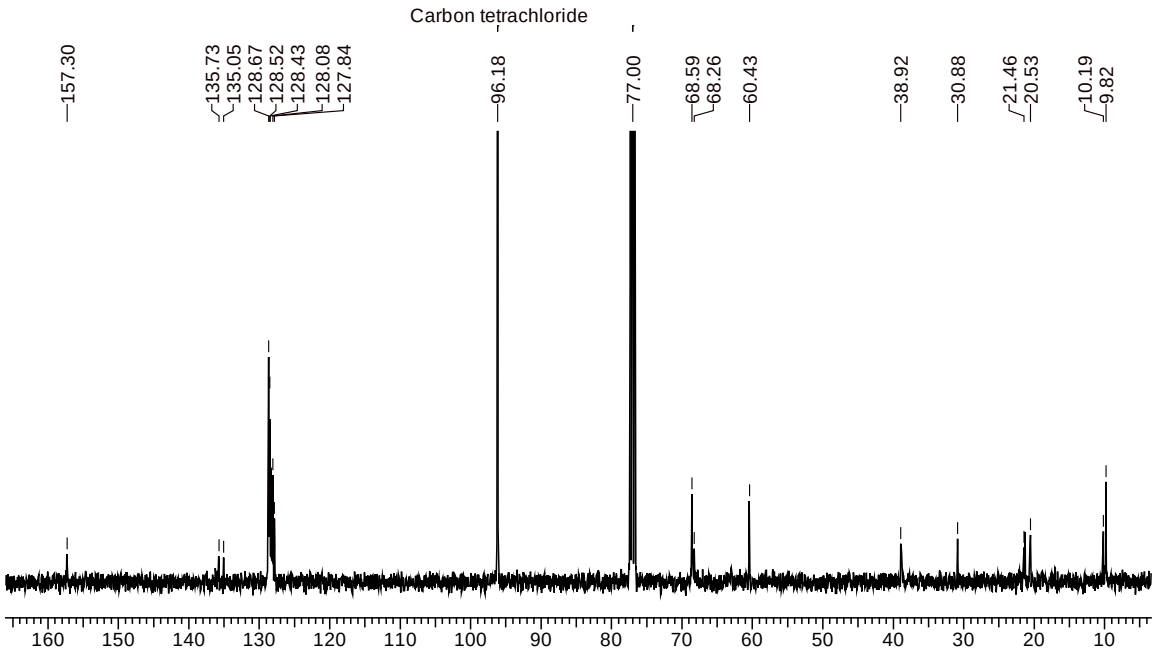


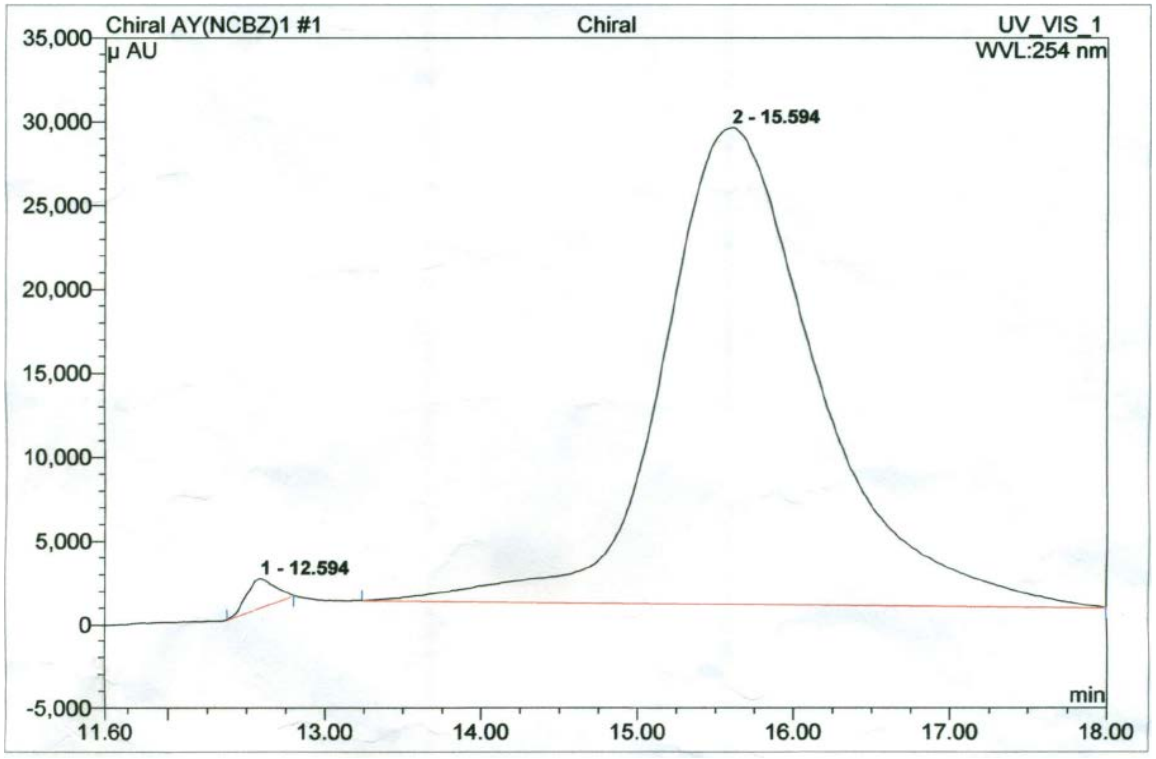
Figure 16: ^{1}H NMR and IR spectra of amino alcohol **28**

Since the number of steps involved in the α-aminooxylation process is relatively too many thereby limiting the overall yield (25.5%), we have explored alternative chemistry that involved a direct α-amination approach.

Asymmetric α-amination of aldehydes using proline as the catalyst represents a burgeoning field of synthetic efforts toward synthesizing chiral building blocks, such as α-amino acids and alcohols.[17] Thus, α-amination of aldehyde **35** was carried out using List's protocol.[17a] Accordingly, aldehyde **35** was subjected to α-amination with dibenzyl azodicarboxylate in the presence of D-proline (10 mol%) to produce the α-amino aldehyde, which upon *in situ* reduction with $NaBH_4$ afforded the protected amino alcohol **34** in 92% yield and 98% ee (determined by chiral HPLC); $[\alpha]_D^{25}$ +20.0 (*c* 1.0, $CHCl_3$). The formation of aminated alcohol was established by the analysis of its ^1H NMR spectrum, which showed a typical multiplet at δ 7.26-7.36 corresponding to ten aromatic protons of Cbz groups. Further evidence was provided by its ^{13}C NMR spectrum which exhibited characteristic carbon signals at δ 127.8, 128.1, 128.3, 128.4, 128.5, 128.7, 135.0 and 135.7 indicative of the aromatic carbons. The enantiomeric purity of **34** was determined as 98% ee from its chiral HPLC analysis (**Figure 17**).

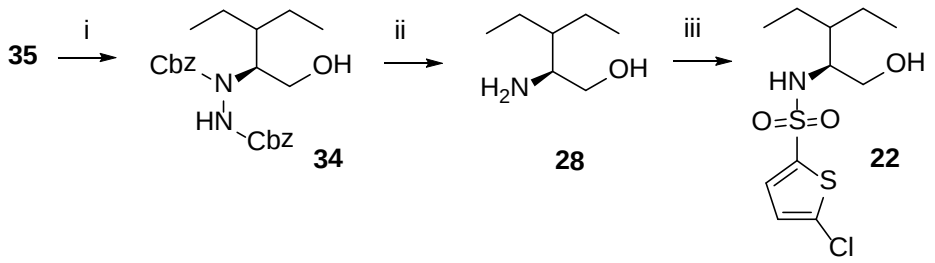






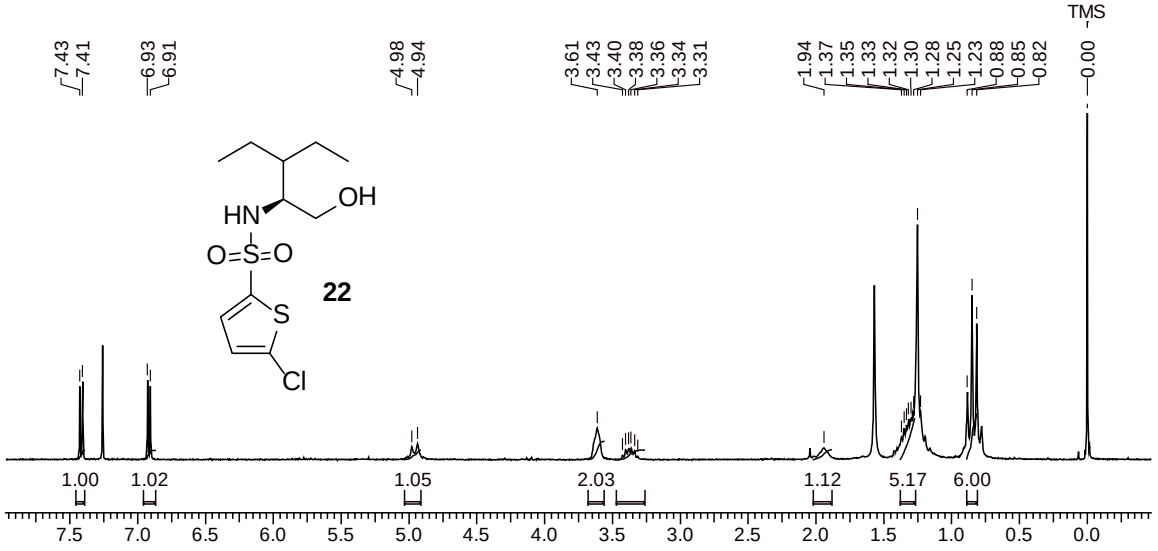
Retention Time	Area	Area %
12.59	363.360	1.10
15.59	32669.367	98.90
Totals	1823559748	100.00

Figure 17: ^{1}H & ^{13}C NMR spectra and HPLC chromatogram of aminated alcohol **34**



Scheme 12: (i) dibenzyl azodicarboxylate, D-proline (10 mol%), CH_3CN, 0-25 °C, 3 h then MeOH, $NaBH_4$, 92%; (ii) H_2 (11.8 atm), Raney Ni, MeOH, AcOH, 70%; (iii) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, dry CH_2Cl_2, 0-25 °C, 30 min., 91%.

The aminated alcohol **34** was then hydrogenated [Raney Ni, H_2 (11.8 atm), MeOH, AcOH (5 drops)] to give (*S*)-2-amino-3-ethylpentan-1-ol **28** in 70% yield.[18] Finally, the amino alcohol **28** was condensed with 5-chlorothiophene-2-sulfonyl chloride in the presence of Et_3N to afford the target molecule **22** in 91% yield and 98% ee (determined by chiral HPLC) (**Scheme 12**). The formation of title compound **22** was confirmed by its ^{1}H NMR spectrum which showed typical signals at δ 6.91 (d, *J* = 4.0 Hz, 1H) and 7.41 (d, *J* = 4.0 Hz, 1H) due to aromatic protons. This was further demonstrated by analysis of its ^{13}C NMR spectrum, which displayed characteristic carbon signals at δ 126.5, 131.5, 137.2 and 140.1 corresponding to aromatic carbons (**Figure 18**).



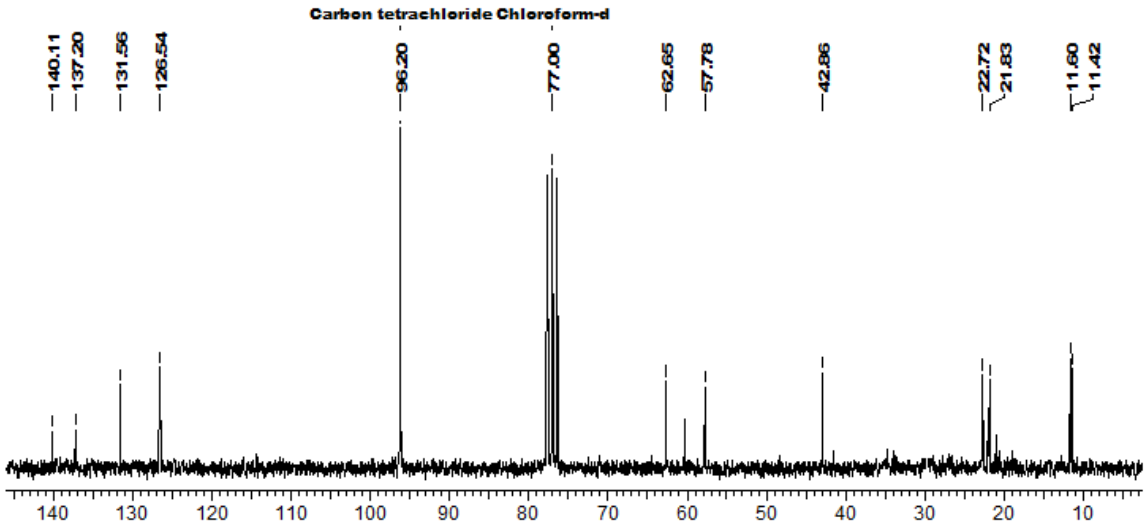


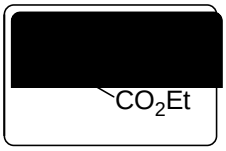
Figure 18: ^{1}H and ^{13}C NMR spectra of 7.b.2 (**22**)

2.2.4 Conclusion

In conclusion, we have described a short synthetic route to anti-Alzheimer's agent **22** incorporating a successful application of D-proline-catalyzed asymmetric α-amination of aldehyde **35** to give the corresponding amino alcohol **34** in 98% ee with an overall yield of 45.2%. The operationally simple reactions with less number of steps, high overall yields requiring a relatively low amount of inexpensive and non-toxic proline as catalyst make this approach an attractive and useful process.

2.2.5 Experimental Section

Ethyl 3-ethylpent-2-enoate (37)

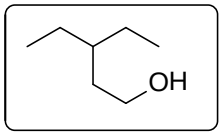


To a stirred suspension of activated NaH (3.34 g, 139.32 mmol) in dry THF (150 mL) a solution of triethyl phosphonoacetate (39.04 g, 174.16 mmol) in dry THF (150 mL) was added dropwise at 0 ^{o}C followed by the addition of a solution of 3-pentanone **36** (10.0 g, 116.10 mmol) in dry THF (100 mL). The reaction mixture was then stirred at 25 ^{o}C for 8 h. After completion of reaction

(monitored by TLC), it was quenched with saturated solution of ammonium chloride and the product extracted with diethyl ether. The combined organic layer was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) gave the α,β-unsaturated ester **37** (16.86 g) as a colorless liquid.

Yield: 93%; **IR** ($CHCl_3$): υ_{max} 867, 1147, 1273, 1444, 1634, 1719, 2877, 2972 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.07 (t, *J* = 7.8 Hz, 6 H), 1.28 (t, *J* = 7.7 Hz, 3 H), 2.17 (q, *J* = 6.5 Hz, 2 H), 2.60 (q, *J* = 8.1 Hz, 2 H), 4.12 (q, *J* = 8.1 Hz, 2 H), 5.59 (s, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.9, 12.9, 14.2, 25.3, 30.7, 59.3, 113.6, 166.5, 167.2; **Anal.** Calcd for $C_9H_{16}O_2$ required C, 69.19; H, 10.32; found C, 69.29; H, 10.37%.

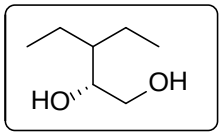
3-Ethyl pentan-1-ol (38)



A mixture of α,β-unsaturated ester **37** (15 g, 96.02 mmol) and 10% Pd/C was stirred under H_2 (1 atm.) at 25 ^oC. After completion of reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and solvent evaporated under reduced pressure to afford the saturated ester. The saturated ester obtained was pure enough to be used in next reaction. To a suspension of $LiAlH_4$ (5.47 g, 144.03 mmol) in dry THF (100 mL), a solution of saturated ester in THF (100 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 25 ^oC for 12 h. After completion of reaction (monitored by TLC), it was quenched with aq. 20% solution of sodium hydroxide (2 mL) at 0 °C. The reaction mixture was filtered through sintered funnel, dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography with petroleum ether/ethyl acetate (7:3 v/v) gave the alcohol **38** (9.26 g) as a colorless liquid.

Yield: 83%; **IR** ($CHCl_3$): υ_{max} 1018, 2875, 2931, 2964, 3355 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.8 Hz, 6 H), 1.26-1.36 (m, 5 H), 1.43-1.55 (m, 2 H), 2.35 (br s, 1 H), 3.62 (t, *J* = 8.1 Hz, 2 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.9, 25.7, 38.3, 41.3, 64.7; **Anal.** Calcd for $C_7H_{16}O$ required C, 72.35; H, 13.88; found C, 72.42; H, 13.85%.

3-Ethylpentane-1,2-diol (33)



To a well stirred solution of alcohol **38** (8.0 g, 68.84 mmol) in DMSO (100 mL), 2-iodoxybenzoic acid (23.13 g, 82.61 mmol) was added in one portion. The reaction mixture was then stirred for 1 h at 25 ^oC. After the completion of reaction (monitored by TLC), it was diluted with water and diethyl ether. Subsequent filtration (diethyl ether eluent) and washing the filtrate with water, brine followed by drying over anhydrous Na_2SO_4 and removal of solvent under reduced pressure gave crude aldehyde **35** which was pure enough to be directly used for next reaction. To a stirred solution of nitrosobenzene (7.37 g, 68.84 mmol) and D-proline (1.58 g, 20 mol %) in CH_3CN (200 mL) was added precursor aldehyde at -20 °C. The reaction mixture was stirred at the same temperature for 24 h followed by the addition of MeOH (100 mL) and $NaBH_4$ (10.42, 275.36 mmol) and stirring for another 10 min. After completion of reaction (checked by TLC) the reaction mixture was quenched with saturated aq. solution of NH_4Cl. The removal of solvent under vaccum followed by extraction with EtOAc gave the crude product. Purification of the crude product by column chromatography with petroleum ether/ EtOAc (7:3 v/v) gave the corresponding aminooxy alcohol as a yellow colored liquid.

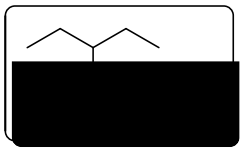
$[\alpha]_D^{25}$ +12.2 (*c* 2.0, $CHCl_3$); **IR** (neat): υ_{max} 1039, 1072, 1127, 1461, 1502, 1600, 2960, 3405 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 6.2 Hz, 6 H), 1.25-1.60 (m, 5 H),

3.78–3.88 (m, 2 H), 3.91-3.97 (m, 1 H), 6.93-6.98 (m, 3 H), 7.20-7.28 (m, 2 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.8, 11.9, 21.8, 21.9, 44.3, 65.0, 73.9, 123, 126, 130, 153. **Anal.** Calcd for $C_{13}H_{21}NO_2$ required C, 69.92; H, 9.48; N, 6.27; found C, 69.99; H, 9.56; N, 6.21%.

To a well stirred solution of aminooxy alcohol in methanol was added 10% Pd/C and the reaction mixture stirred overnight at 25 ^oC under H_2 atmosphere. After completion of reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and solvent evaporated under reduced pressure to afford the crude diol. Purification by column chromatography with petroleum ether/EtOAc (5:5 v/v) gave the diol **33** (7.0 g) as a colorless liquid.

Yield: 77%; $[\alpha]_D^{25}$ -4.9 (*c* 1.0, $CHCl_3$); IR (neat): υ_{max} 1073, 1124, 1379, 1461, 2875, 2961, 3387 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.4 Hz, 6 H), 1.29-1.48 (m, 5 H), 2.04 (br s, 2 H), 3.49-3.66 (m, 3 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.2, 11.3, 21.2, 21.6, 43.7, 64.9, 73.6. **Anal.** Calcd for $C_7H_{16}O_2$ required C, 63.60; H, 12.20; found C C, 63.66; H, 12.25%.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-3-ethylpentan-2-ol (39)



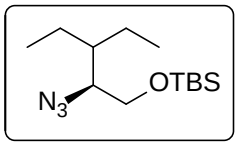
To a solution of diol **33** (2 g, 15.14 mmol) in dry CH_2Cl_2 (50 mL) at 0 ^oC was added imidazole (1.54 g, 22.7 mmol) and *tert*-butyldimethylsilyl chloride (2.51 g, 16.65 mmol). The reaction mixture was then stirred at 25 ^oC for 2 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2, washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product, which was then purified by

column chromatography with petroleum ether/ EtOAc (8:2 v/v) to give **39** (3.02 g) as a colorless

liquid.

Yield: 81%; $[\alpha]_D^{25}$ -5.0 (*c* 1.6, $CHCl_3$); **IR** (neat): υ_{max} 1164, 1259, 1447, 2097, 2858, 2937 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.86-0.98 (m, 15H), 1.33–1.53 (m, 6 H), 2.37 (br.s, 1H), 3.46-3.69 (m, 3 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, -5.2, 11.2, 11.4, 18.3, 21.1, 21.6, 25.9, 43.2, 65.5, 72.9; **Anal.** Calcd for $C_{13}H_{30}O_2Si$ required C, 63.35; H, 12.27 found C, 63.43; H, 12.21%.

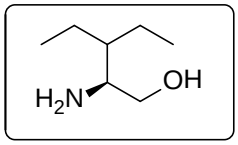
((*S*)-2-Azido-3-ethylpentyloxy)(tert-butyl)dimethylsilane (40)



To a stirred solution of alcohol **39** (312 mg, 1 mmol) and triethylamine (303 mg, 3 mmol) in dry CH_2Cl_2 (15 mL), at 0 ^oC, methanesulfonyl chloride (229.2 mg, 2 mmol) was added, and then the resulting solution was stirred at 0 ^oC for 45 min. After TLC showed that the reaction was complete, excess CH_2Cl_2 (20 mL) was added. The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After the solvent was removed under vaccum, the crude product was dissolved in DMF and NaN_3 (390 mg, 6 mmol) was added. The reaction mixture was then stirred at 60 ^oC for 30 h. After the completion of reaction (monitored by TLC), it was then partitioned between EtOAc and brine. The organic layer was further washed with brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic purification with petroleum ether/EtOAc (4:6 v/v) gave the corresponding azide **40** (212 mg) as yellow oil.

Yield: 78%; $[\alpha]_D^{25}$ -21.3 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1164, 1259, 1447, 2097, 2858, 2937 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.85-0.91 (m, 15H), 1.29-1.37 (m, 5H), 3.41-3.46 (m, 1H), 3.70-3.78 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.6, 11.3, 18.2, 21.8, 22.6, 25.8, 41.8, 65.0, 66.2; **Anal.** Calcd for $C_{13}H_{29}N_3OSi$ requires C, 57.52; H, 10.77; N, 15.48; found C, 57.67; H, 10.83; N, 15.41%.

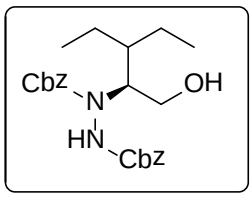
(*S*)-2-Amino-3-ethylpentan-1-ol (28)



To a suspension of $LiAlH_4$ (250 mg, 6.4 mmol) in dry THF (15 mL), a solution of azide **40** (1.25 g, 6.06 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was then stirred at 50 ^oC for 12 h. After completion of reaction (monitored by TLC), it was quenched with aq. 20% solution of sodium hydroxide (2 mL) at 0 °C. The reaction mixture was filtered through sintered funnel, dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography with petroleum ether/EtOAc/Et_3N (60: 38:2) gave the amino alcohol **28** (600 mg) as a yellow oily liquid.

Yield: 75%; $[\alpha]_D^{25}$ -12.3 (*c* 1.0, $CHCl_3$) {lit.[13] $[\alpha]_D^{25}$ -3.7 (1% solution, DMSO)};; **IR** (neat): υ_{max} 1010, 1043, 1161, 2313, 2364, 2923, 3441 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.85-0.94 (m, 6H), 1.25-1.47 (m, 5H), 2.36 (br s, 3H), 2.85 (m, 1H), 3.28-3.37 (m, 1H), 3.59-3.68 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.4, 11.5, 21.4, 21.8, 44.8, 54.9, 64.3; **Anal.** Calcd for $C_7H_{17}NO$ required C, 64.07; H, 13.06; N, 10.67; found C, 64.12; H, 13.10; N, 10.75%.

(*S*)-Dibenzyl 1-(3-ethyl-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (**34)**

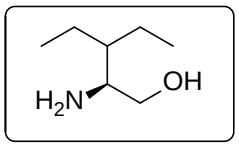


To a mixture of of dibenzyl azodicarboxylate (1.57 g, 5.26 mmol) and D-proline (60 mg, 10 mol%) in CH_3CN (40 mL) at 0 ^oC was

added aldehyde **35** (600 mg, 5.26 mmol) and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 25 ºC within 1 h. After the reaction mixture became colorless, it was cooled to 0 ºC again and then treated with EtOH (50 mL) and $NaBH_4$ (1.0 g) for 10 min at 0 ºC. After completion of reaction, it was quenched by adding half-concentrated aq. ammonium chloride solution and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with petroleum ether/EtOAc (8:2 v/v) to give **34** (2.0 g) as colorless crystalline solid.

Yield: 92%; m.p. 121 ^oC (crystallized from ethanol); $[\alpha]_D^{25}$ +20.0 (*c* 1.0, $CHCl_3$); Optical purity 98% ee from **HPLC analysis**: Column: ODH, mobile phase: hexane/isopropyl alcohol (9/1), flow rate: 0.5 mL/min, retention time: 12.59 min (-)-isomer, 15.59 min (+)-isomer. **IR** ($CHCl_3$): υ_{max} 1267, 1380, 1455, 1537, 1681, 1721, 2878, 2959, 3258, 3510 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.69-0.87 (m, 6H), 1.22-1.40 (m, 5H), 3.42-3.74 (m, 2H), 4.17-4.24 (m, 1H), 4.32 (br s, 1H), 5.12-5.32 (m, 4H), 6.39 (br s, 1H), 7.30-7.36 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.8, 10.1, 20.5, 21.3, 38.9, 60.4, 62.9, 68.2, 68.5, 127.8, 128.1, 128.3, 128.4, 128.5, 128.6, 135.1, 135.7, 157.3; **Anal.** Calcd for $C_{23}H_{30}N_2O_5$ requires C, 66.65; H, 7.30; N, 6.76; found C, 66.53; H, 7.10; N, 6.89%.

(*S*)-2-Amino-3-ethylpentan-1-ol (28)

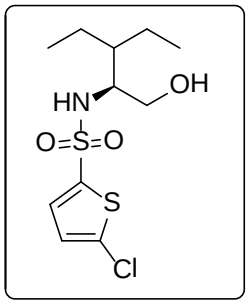


Aminated alcohol **34** (1.8 g, 4.34 mmol) was dissolved in MeOH (20 mL), AcOH (10 drops) and treated with Raney nickel (2.0 g, excess) for 24 h under 11.8 atm pressure of hydrogen atmosphere. The

reaction mixture was filtered over celite and concentrated to give the corresponding amino alcohol **28** (398 mg) as a colorless liquid.

Yield: 70%; $[\alpha]_D^{25}$ -12.3 (*c* 1.0, $CHCl_3$).

(*S*)-*N*-(5-Chlorothiophene-2-sulfonyl)-β,β-diethylalaninol (22)



To a solution of amino alcohol **28** (50 mg, 0.4 mmol) in dry CH_2Cl_2 (5 mL) at 0 ºC was added Et_3N (121 mg, 1.2 mmol). After stirring for 10 min., 5-chlorothiophene-2-sulfonyl chloride (87 mg, 0.4 mmol) was added and the reaction mixture was stirred at 25 ºC for 30 min. After completion of reaction (monitored by TLC), solvent was removed under reduced pressure and the crude product purified by column chromatography using petroleum ether/EtOAc (7:3) to give **22** (113 mg) as a colorless crystalline solid.

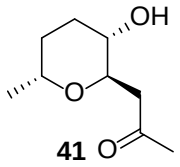
Yield: 91%; m.p. 115-117 ^oC (crystallized from heptane:ethylacetate 4:1) {lit.[13] m.p. 115-117.6 ^oC}; $[\alpha]_D^{25}$ +10.3 (*c* 0.3, MeOH) {lit.[13] $[\alpha]_D^{25}$ +10.81 (1% solution, MeOH)}; Optical purity 98% ee from **HPLC analysis**: Column: ODH, mobile phase: hexane/isopropyl alcohol (9/1), flow rate: 0.5 mL/min,: retention time: 13.01 min (+)-isomer, 13.56 min (-)-isomer). **IR** ($CHCl_3$): υ_{max} 1090, 1130, 1337, 1456, 1615, 2881, 2957, 3034, 3068, 3301, 3519, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.82-0.88 (m, 6H), 1.23-1.37 (m, 5H), 1.94 (br s, 1H), 3.31-3.43 (m, 1H), 3.61 (m, 2H), 4.94 (br s, 1H), 6.91 (d, *J* = 4.0 Hz, 1H), 7.41 (d, *J* = 4.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.4, 11.6, 21.9, 22.7, 42.8, 57.7, 62.6, 126.5, 131.5, 137.2, 140.1; **Anal.** Calcd for $C_{11}H_{18}ClNO_3S_2$ requires C, 42.37; H, 5.82; N, 4.49; found C, 42.26; H, 5.76; N, 4.50%.

Section III

A concise enantioselective synthesis of (+)-Decarestrictine L *via* proline-catalyzed sequential α-aminooxylation and Horner-Wadsworth-Emmons olefination

2.3.1 Introduction and Pharmacology

The decarestrictines consist of a family of thirteen secondary metabolites that were isolated from various *Penicillium* strains. These metabolites exhibit an inhibitory effect on cholesterol biosynthesis.[19] This beneficial effect is corroborated by in vivo studies with normolipidemic rats where it is found that cholesterol biosynthesis in HEP-G2 liver cells was significantly inhibited.[20] Additionally, it appears that the decarestrictines are highly selective in that they exhibit no significant antibacterial, antifungal, anti-protozoal, or antiviral activity.[21] While the majority of the decarestrictines contain a 10-membered lactone ring in their structure, decarestrictine L **41** is unique in possessing a tetrahydropyranyl nucleus (**Figure 19**).[22] The interesting biological property of this molecule, coupled with the extreme scarcity of the natural material make it an appealing synthetic target.



41

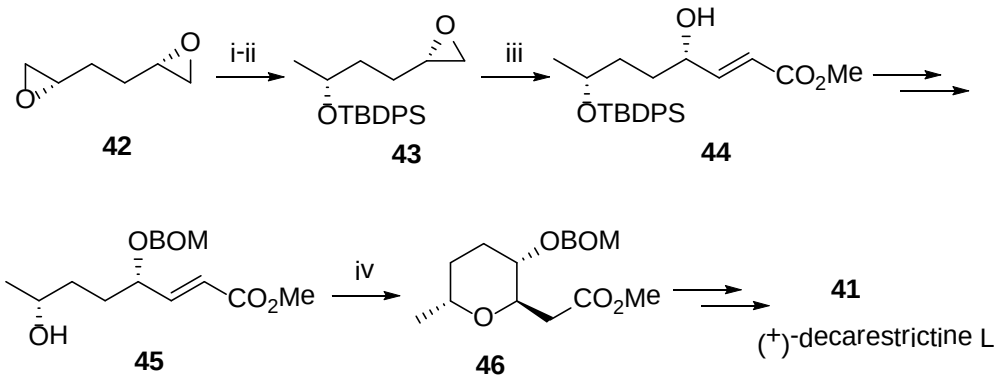
Figure 19: Structure of (+)-decarestrictine L (**41**)

2.3.2 Review of literature

Various syntheses of (+)-decarestrictine L **41** have been documented in the literature. Some of the interesting and important synthetic routes to (+)-decarestrictine L **41** are described below.

Kibayashi's approach (1993)[23]

Kibayashi *et al.* have achieved the synthesis of (+)-decarestrictine L **41** starting from C_2 symmetrical diepoxide chiral synthon **42**. Reductive epoxide opening in **42** with vitride followed by silyl protection gave **43**. Regioselective ring opening of epoxide **43** with 2-(phenylthio)acetic acid and subsequent elimination with *m*CPBA afforded **44**. Subsequent oxa-Michael addition of **45** under thermodynamically equilibrated conditions (K_2CO_3, THF, reflux, 12 h) gave pyran **46** in exclusive *trans* (with respect to C-2 and C-3) se1ectivity. Compound **46** was then converted into (+)-decarestrictine L **41** in an overall yield of 10.6% (**Scheme 13**).

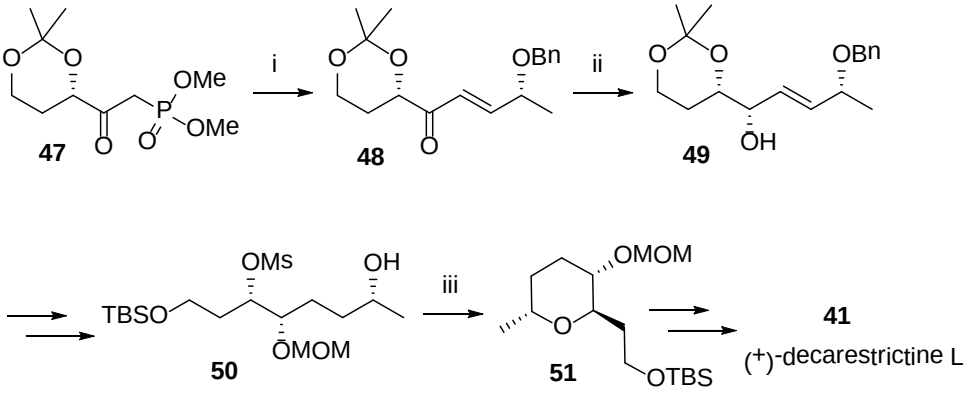


Scheme 13: (i) Vitride, THF, 73%; (ii) TBDPSCl, DMAP, 84%; (iii) $PhSCH_2CO_2H$, LDA, THF then CH_2N_2, 64%; (iv) K_2CO_3, THF, reflux, 12 h, 60%.

Carreno's approach (1998)[24]

Carreno *et al. have* described a convergent enantioselective synthesis of **(+)-41**, which commences with the coupling of phosphonate **47** with (*R*)-2-(benzyloxy)propanal (**A**) under basic condition. The coupling partners **47** and **A** were obtained from commercially available (*S*)-malic acid and (*R*)-isobutyl lactate respectively. The third chiral centre was created by stereoselective reduction of (*R*)-hydroxy ketone **48** with L-selectride, and an intramolecular S_N2-type reaction, which allowed the stereocontrolled

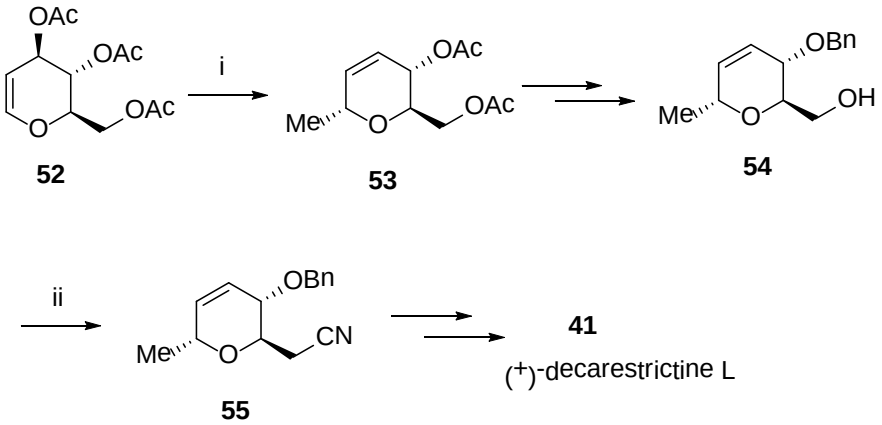
formation of the tetrahydropyranyl ring **51**. Title compound **41** was then obtained in an overall yield of 28% (**Scheme 14**).



Scheme 14: (i) (*R*)-2-(benzyloxy)propanal (**A**), NaH, THF, -40 °C, 90%; (ii) L-selectride, THF, -78 °C, 95%; (iii) NaH, DMSO, toluene, reflux, 90%.

Lukesh's approach (2003)[25]

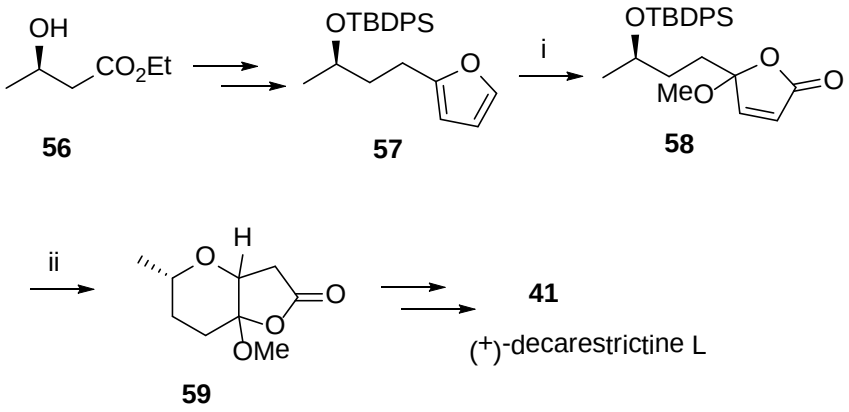
Lukesh *et al.* have described the synthesis of (+)-decarestrictine L **41** beginning from commercially available tri-*O*-acetyl-D-glucal **52**. Alkylation with trimethylaluminum introduced the axial methyl group at C-2 in a stereoselective fashion giving **53** in 94% yield. Chain extension in **54** at the C-6 carbon was accomplished by generation of the primary tosylate, followed by displacement with cyanide anion. The synthesis of **41** was completed in 13 steps with 6.3% overall yield (**Scheme 15**).



Scheme 15: (i) Me_3Al, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 94%; (ii) (a) TsCl, Et_3N, CH_2Cl_2; (b) NaI, NaCN, DMF, 80 °C, 84%.

Garcia approach (2006)[26]

Garcia *et al.* have described a 12-step enantioselective synthesis of (+)-decarestrictine L **41** from commercially available chiral hydroxyester **56** using a methodology based on the oxidation of a furan ring with singlet oxygen, which gave lactone **58**. This was followed by an intramolecular hetero Michael addition furnishing bicyclic lactone **59**. The synthesis of (+)-decarestrictine L **41** was completed in 17 steps with an overall yield of 14.3% (**Scheme 16**).

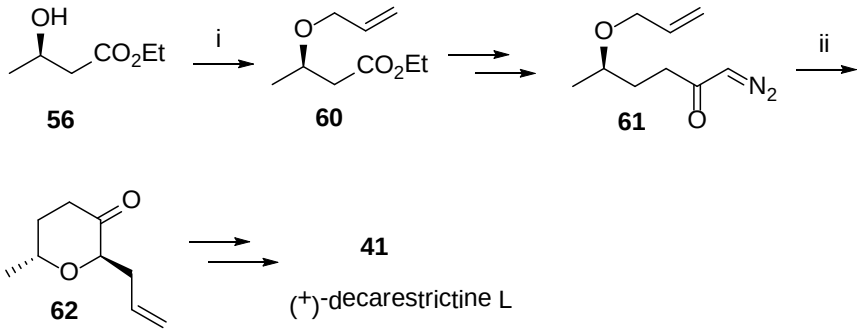


Scheme 16: (i) (a) $^1O_2$, MeOH, rose bengal; (b) Ac_2O, py, DMAP, 96% (over two steps); (ii) TBAF, THF, 25 ^oC, 72%.

Clark's approach (2006)[27]

Clark *et al.* have described a stereoselective synthesis of the fungal metabolite decarestrictine L **41**, which commenced from commercially available ethyl (*R*)-3-hydroxybutyrate **56**. The treatment of **56** with allyl 2,2,2-trichloroacetimidate and a substoichiometric amount of triflic acid afforded the allyl ether **60** in 82% yield. The key reaction in the synthesis is a Cu (II) trifluoroacetylacetonate catalyzed tandem oxonium ylide formation and the rearrangement of diazo ketone **61** for the diastereoselctive construction of the tetrahydropyranyl core **62** of the natural product. The total synthesis of (+)-decarestrictine L **41** was accomplished in a 10 step synthetic sequence with an

overall yield of 9% (**Scheme 17**).

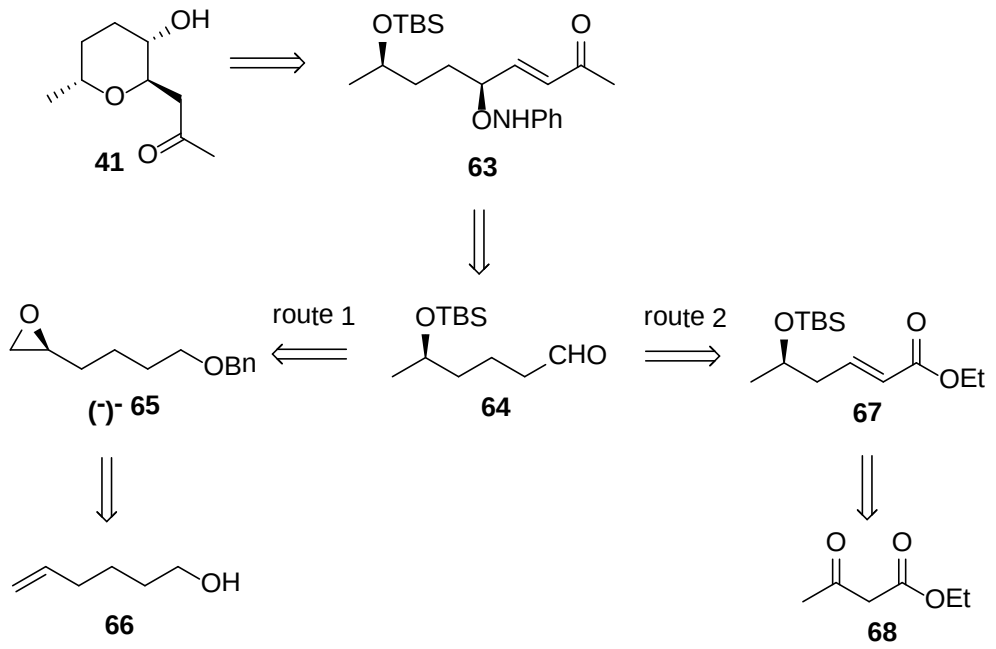


Scheme 17: (i) $CH_2CHCH_2OC(NH)CCl_3$, CF_3SO_3H, CH_2Cl_2-C_6H_{14}, 25 ^oC 82%; (ii) $Cu(tfacac)_2$, CH_2Cl_2, reflux, 60% (dr = 91:9).

2.3.3 Present work

2.3.3.1 Objective

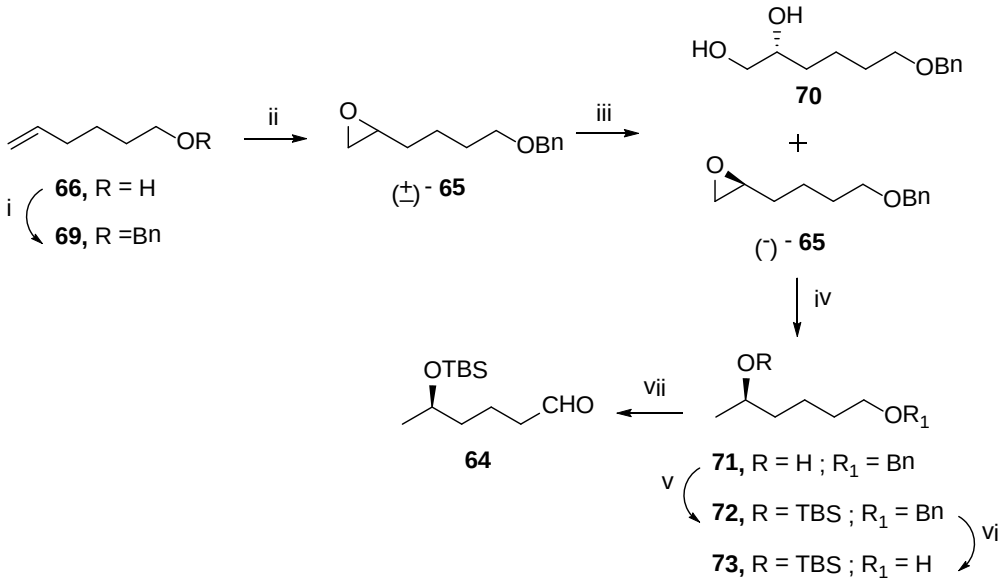
As can be seen from the above discussion, several syntheses of decarestrictine L **41** have been reported but many suffer from one or more disadvantages, which include use of chiral building blocks, long reaction sequences and low yields. In continuation of our work on the application of proline-catalyzed sequential reactions in the synthesis of bioactive molecules,[28] we describe in this section an efficient synthesis of (+)-decarestrictine L **41** from readily available raw materials *via* a D-proline catalyzed sequential aminooxylation–olefination[29] reaction followed by intramolecular conjugate 1,4-addition as the key reactions. The retrosynthetic approach of (+)-decarestrictine L **41** is outlined in **Scheme 18** in which decarestrictine L **41** is envisioned to be obtained *via* intramolecular cyclization involving 1,4-conjugate addition of enone **63**. We, thus, envisaged a D-proline catalyzed sequential aminooxylation–olefination of aldehyde **64** for the efficient construction of enone moiety **63**. Aldehyde **64**, a suitable intermediate, could be obtained by two routes: i) Jacobsen's hydrolytic kinetic resolution (HKR)[30] of terminal epoxide **(±)-65** and ii) Noyori's asymmetric reduction[31] of β-ketoester **68.**



Scheme 18: Retrosynthetic analysis of (+)-decarestrictine L (**41**)

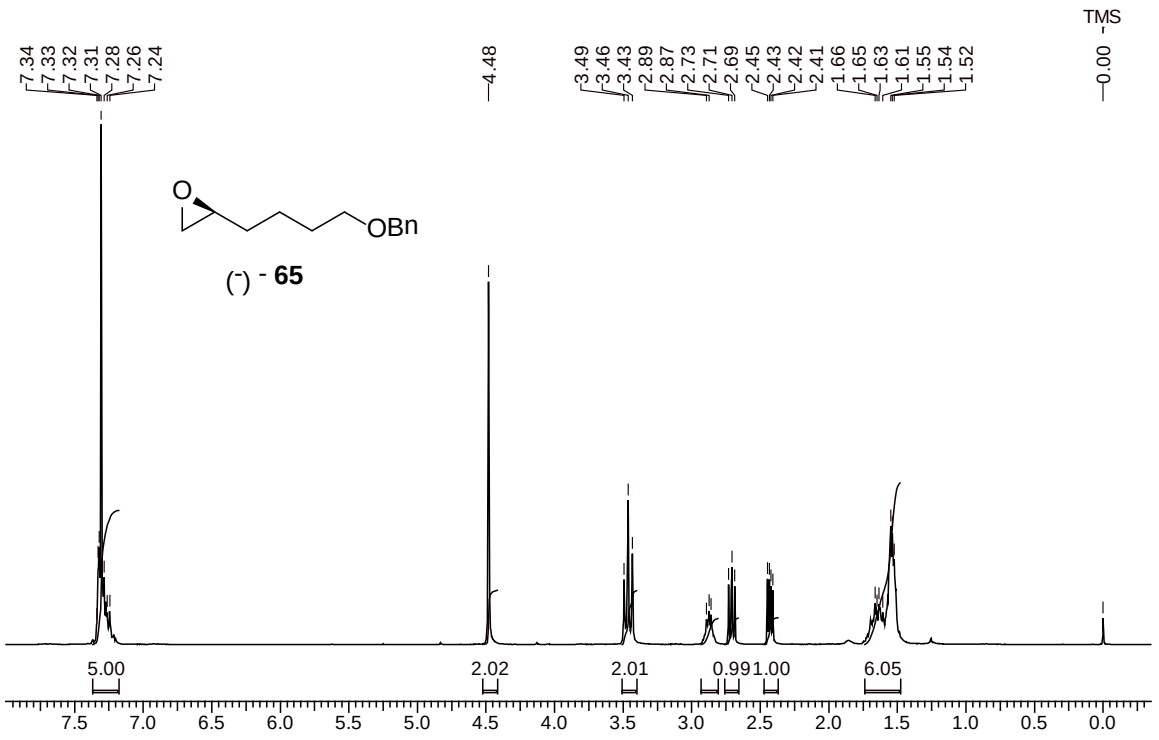
2.3.3.2 Results and Discussion

Scheme 19 presents the synthetic scheme for obtaining intermediate aldehyde **64**.



Scheme 19: (i) BnBr, NaH, THF, 0-25 ºC, 6 h, 97%; (ii) *m*CPBA, $CHCl_3$, 25 ºC, 6 h, 85%; (iii) (*S*,*S*)-(–)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (0.5 mol %), H_2O (0.55 equiv), 24 h, 43%, 99% ee; (iv) $LiAlH_4$, THF, 0 ºC, 30 min, 92%, 99% ee; (v) TBSCl, imid., CH_2Cl_2, 0-25 ºC, 2 h, 98%; (vi) H_2 (1 atm), 10% Pd/C, Et_3N, MeOH, 12 h, 25 ºC, 97%; (vii) IBX, DMSO, 25 ºC 2 h, 98%.

The synthesis of **64** commences with commercially available 5-hexene-1-ol **66**, protected as its benzyl ether **69**. The olefinic function in **69** was epoxidized smoothly {*m*CPBA, $CHCl_3$} to give racemic epoxide **(±)-65**, which was subjected to Jacobsen's HKR {(*S*,*S*)-cobalt salen, H_2O} to give the corresponding enantiomerically pure epoxide **(-)-65** in 43% yield and 99% ee (HPLC analysis), {$[\alpha]_D^{25}$ -5.1 (*c* 2.0, $CHCl_3$)} along with the separable diol **70** in 47% yield (**Scheme 19**). The formation of epoxide (-)-**65** was confirmed by its ^{1}H NMR spectrum, which showed resonance signals at δ 2.43 (dd, *J* = 2.8, 5.2 Hz, 1 H), 2.69 (dd, *J* = 4.0, 5.1 Hz, 1 H) and 2.87–2.89 (m, 1 H) corresponding to epoxide protons. This was substantiated by its ^{13}C NMR spectrum, which showed carbon signals at δ 46.8 and 52.0 due to carbons attached to epoxide oxygen. The other carbon signals at δ 127.3, 127.4, 128.2 and 138.5 were due to aromatic carbons (**Figure 20**). The signals at δ 3.46 (t, *J* = 6.0 Hz) and 4.48 (s) integrating for two protons each accounted for methylene group of -**CH₂**-OBn and -O-**CH₂**-Ph respectively.



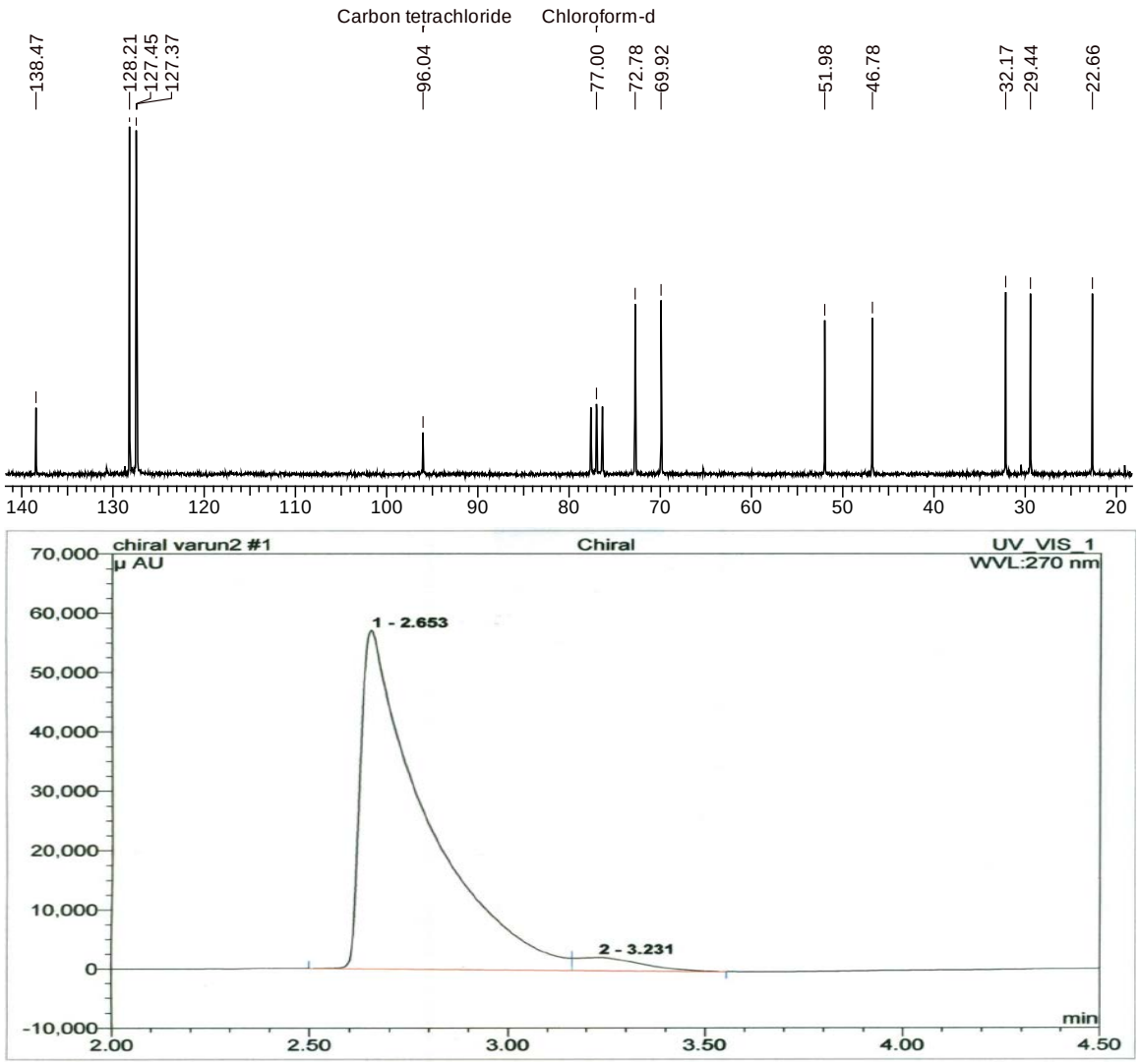


Figure 20: ^{1}H & ^{13}C NMR spectra and chiral HPLC chromatogram of epoxide **(-)-65**

The chiral epoxide **(-)-65,** readily purified by column chromatography, was subjected to regioselective reductive ring opening with $LiAlH_4$ in THF at 0 °C to afford the secondary alcohol **71** as the exclusive product in 92% yield and 99% ee (HPLC analysis). The formation of **71** was confirmed by the appearance of a typical broad absorption band at υ_{max} 3354 cm^{-1} for hydroxyl group. Its ^{1}H NMR spectrum showed a multiplet at δ 3.69-3.80 (1H) corresponding to methine protons (-**CH**-OH). Further, its ^{13}C NMR spectrum showed a characteristic signal at δ 67.4 for methine carbon (-**CH**-OH) (**Figure 21**).

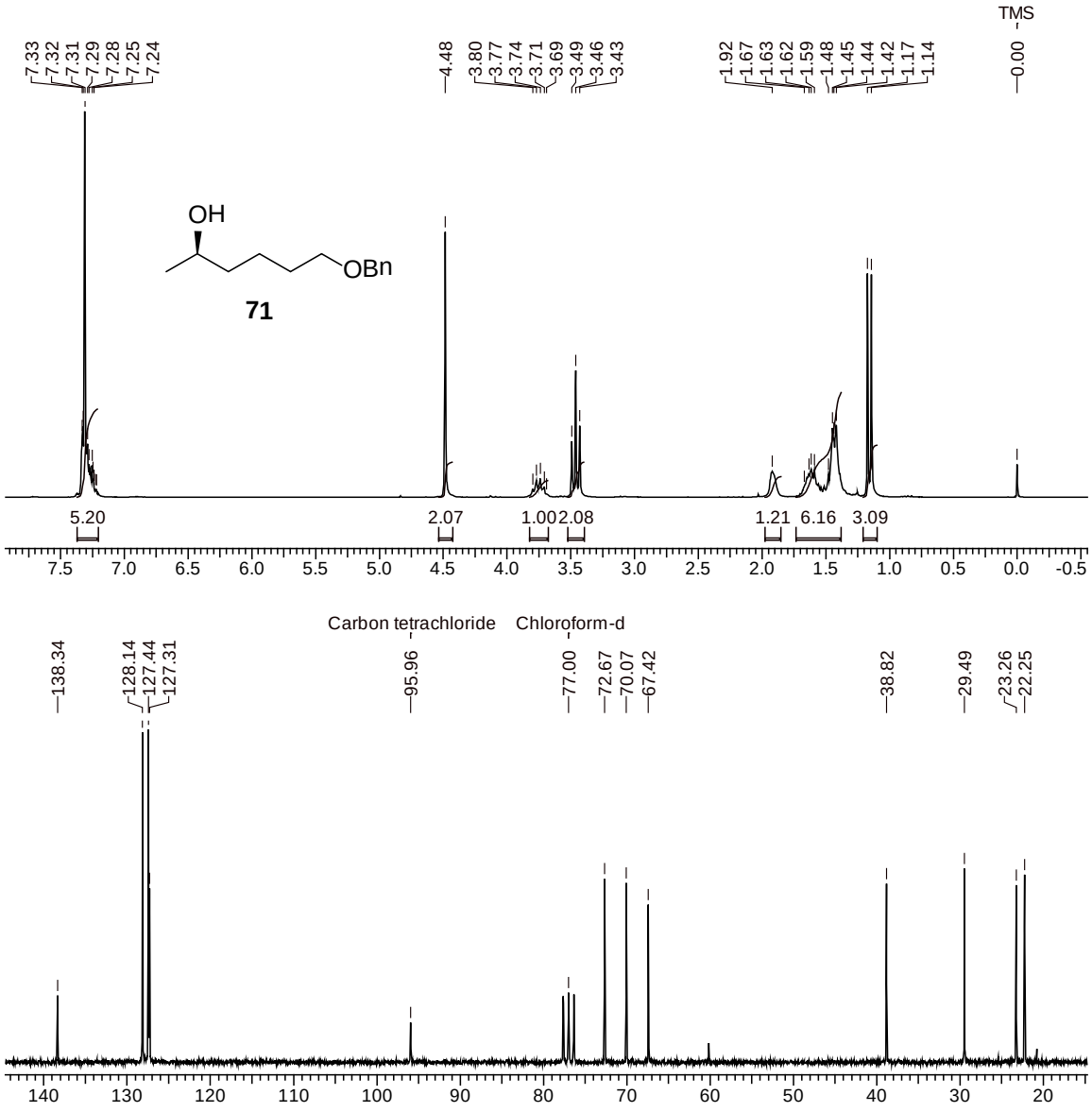


Figure 21: ^{1}H & ^{13}C NMR and IR spectra of alcohol **71**

Alcohol **71** was protected as its TBS ether (TBSCl, imid.) and the benzyl ether **72** was subsequently deprotected under hydrogenolysis condition {10% Pd/C, H_2 (1 atm.), Et_3N} to give the primary alcohol **73** in 97% yield. The ^{1}H NMR spectrum of **73** displayed a signal at δ 3.62 (t, J = 6.3 Hz, 2H) corresponding to protons of the methylene group (-**CH_2**-OH). Its ^{13}C NMR spectrum showed signals at δ 62.6 and 68.5 corresponding to methylene (-**CH_2**-OH) and methine (-**CH**-OTBS) carbons respectively (**Figure 22**).

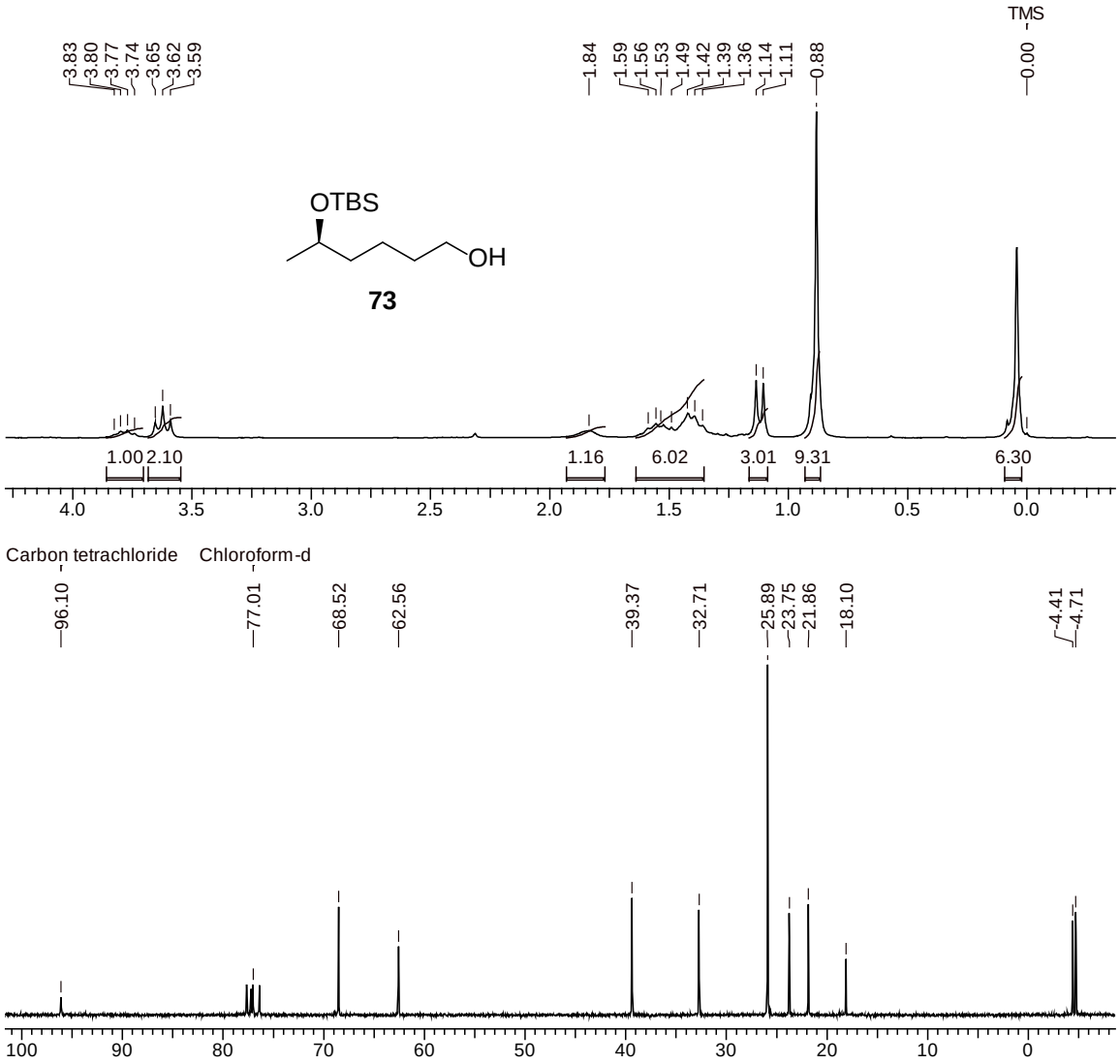


Figure 22: ^{1}H and ^{13}C NMR spectra of alcohol **73**

The oxidation of alcohol **73** (IBX, DMSO) produced the key intermediate aldehyde **64** in 98% yield $\{[\alpha]_D^{25}$ -12.0 (*c* 3.0, $CHCl_3$). The formation of aldehyde **64** was confirmed by its ^{1}H NMR spectrum, which showed a typical signal for aldehydic proton at δ 9.76 (s, 1H). This was further ascertained by the appearance of a typical carbon signal at δ 201.4 in its ^{13}C NMR spectrum (**Figure 23**). The multiplet at δ 3.73-3.88 in its ^{1}H NMR spectrum accounted for the methine protons (-**CH**-OTBS), while its ^{13}C NMR spectrum showed a carbon signal at δ 67.3 for methine carbon (-**CH**-OTBS).

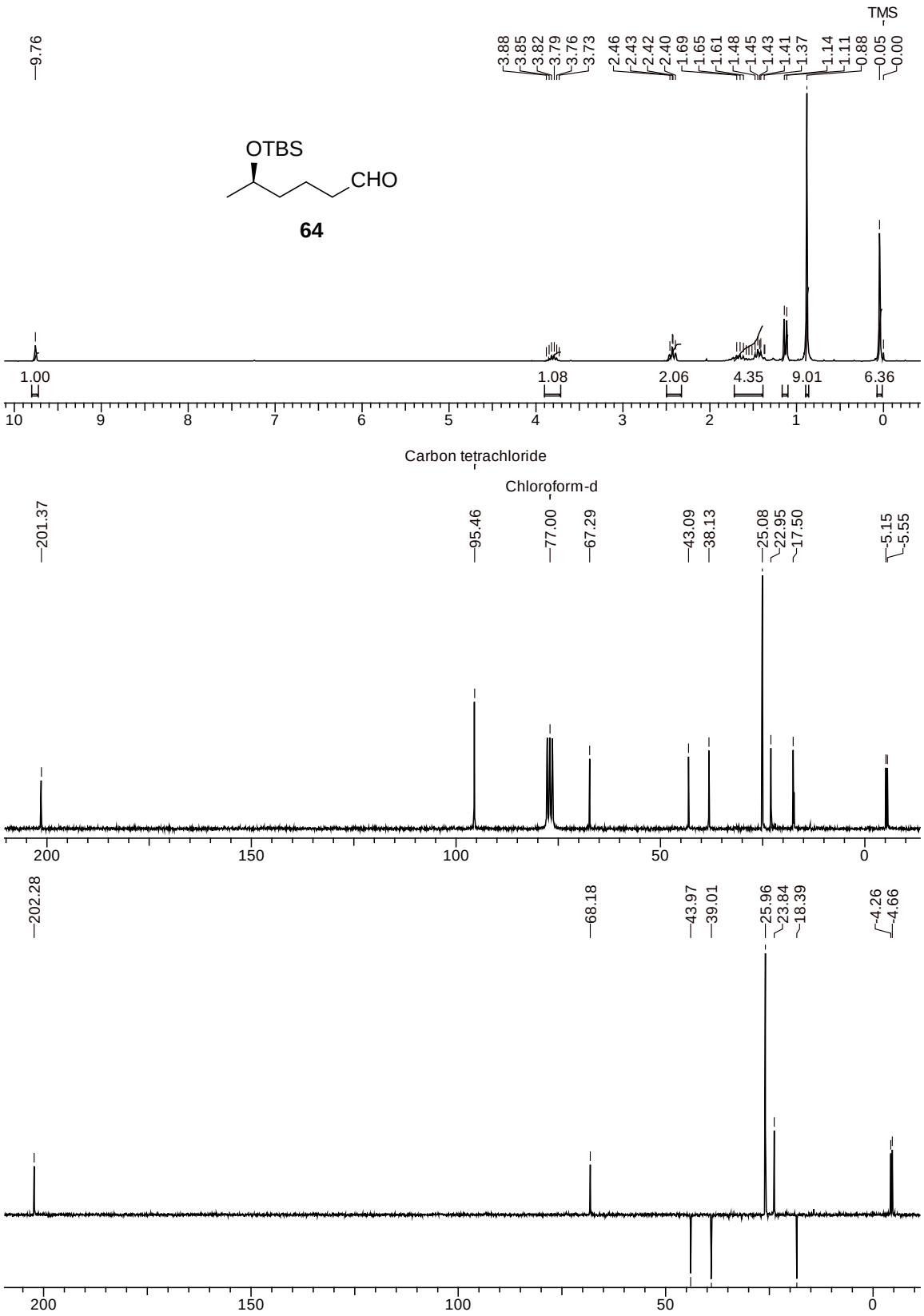
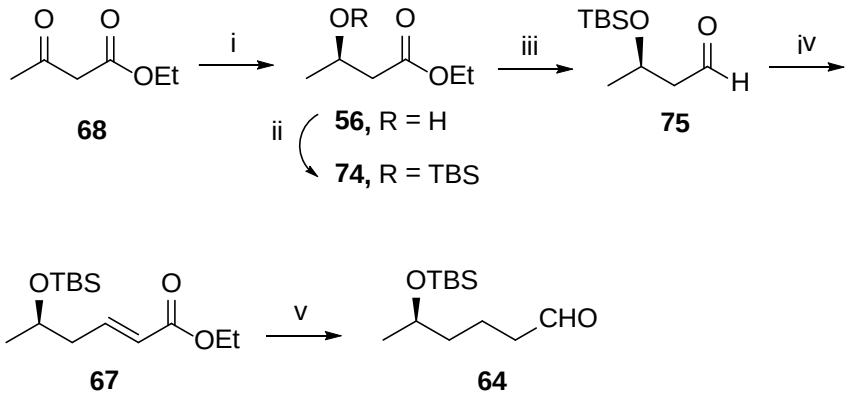


Figure 23: ^{1}H & ^{13}C and DEPT NMR spectra of aldehyde **64**

Since the overall yield that could be realized for intermediate aldehyde **64** in HKR route (**Scheme 19**) was considerably lower (30%), we envisioned an alternate route for its synthesis.

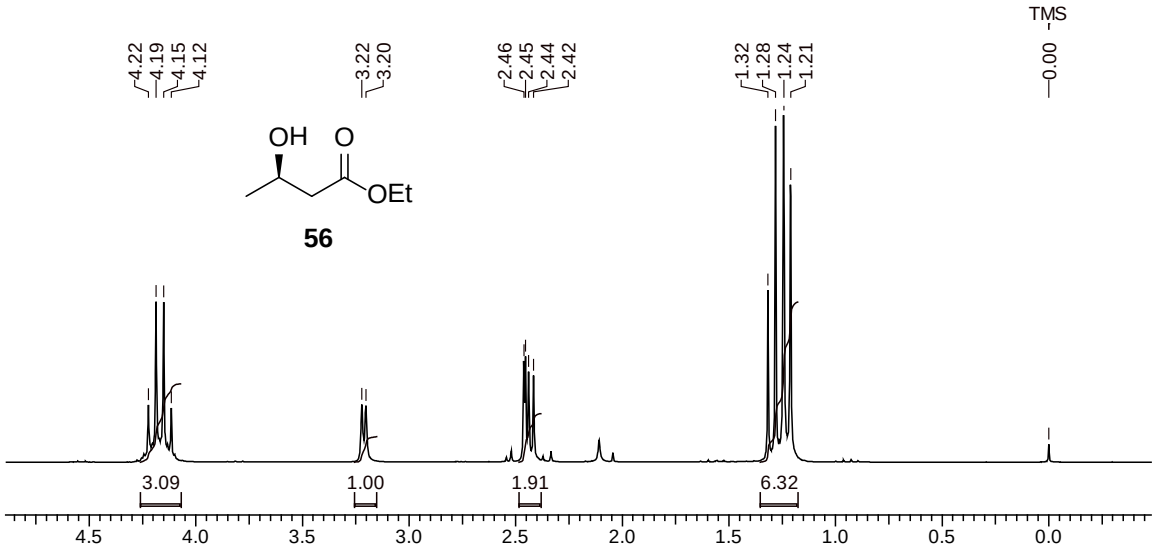
Noyori's discovery of rhodium (I) and ruthenium (II) complexes of BINAP enantiomers have revolutionized stereoselective organic synthesis.[31a] In particular, stereo- and chemoselective reduction of β-ketoesters to the corresponding β-hydroxyesters can be achieved in high yields and excellent enantioselectivity.[31b] Our second approach towards the synthesis of intermediate aldehyde **64** involved Ru-catalyzed asymmetric reduction[31c] {[(*R*)-Ru(BINAP)Cl_2]$_2$·NEt_3, 2N HCl, H_2 (100 psi)} of ethyl acetoacetate **68** that produced (*R*)-ethyl 3-hydroxybutyrate **56** in 95% yield with high enantiopurity (98% ee, Mosher ester); $[\alpha]_D^{25}$ -46.0 (*c* 1.0, $CHCl_3$) (**Scheme 20**).

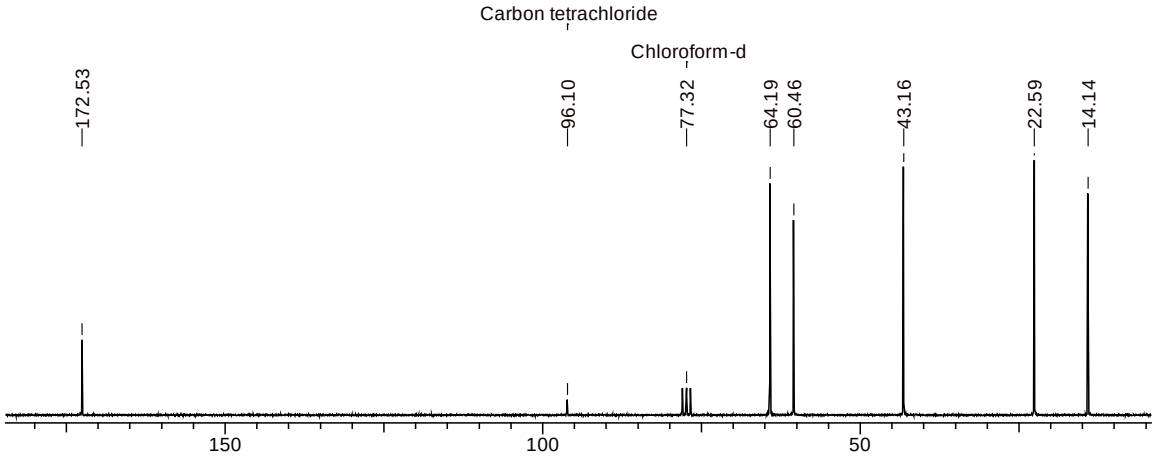


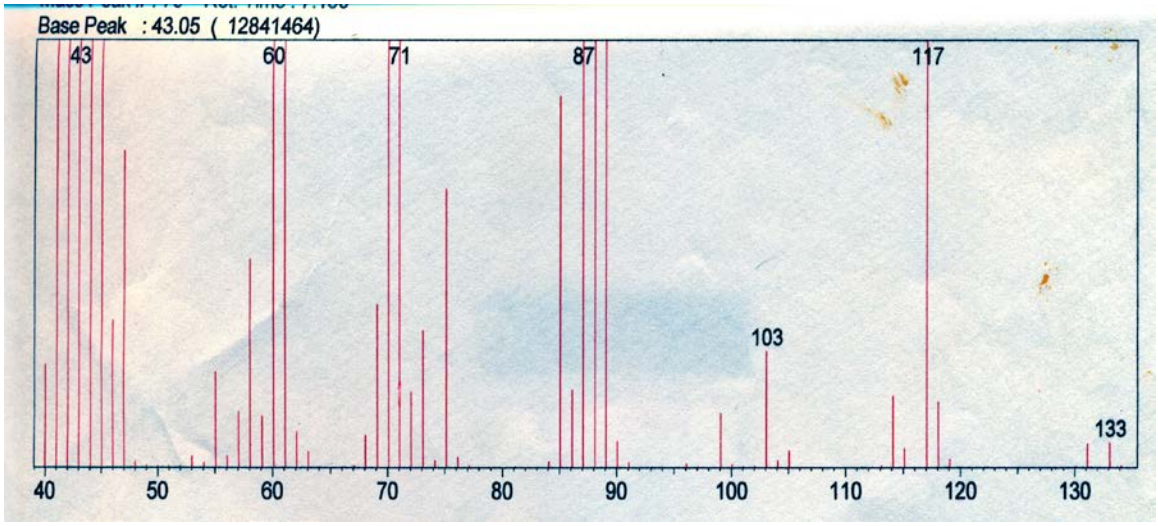
Scheme 20: (i) [(R)-Ru(BINAP)Cl_2]$_2$· NEt_3 (0.1 mol%), 2N HCl (0.1 mol%), MeOH, H_2(100 psig), 50 ºC, 16 h, 95%, 98% ee; (ii) TBSCl, imid., CH_2Cl_2, 0-25 ºC, 2 h, 97%; (iii) DIBAL-H, toluene, -78 ºC, 1 h, 85%; (iv) Ph_3P=$CHCO_2Et$, THF, 25 ºC, 12 h, 93%; (v) a) H_2 (1 atm), 10% Pd/C,Et_3N, MeOH, 12 h; b) DIBAL-H, toluene, -78 ºC, 1 h, 82% (over two steps).

The formation of alcohol **56** was confirmed by its IR spectrum which showed a strong and broad absorption band at υ_{max} 3441 cm^{-1} due to the hydroxyl functionality. It was further ascertained by its ^1H and ^{13}C NMR spectral analysis which showed resonance signals at δ 3.20 (1H) for hydoxy proton and at δ 60.5 for methine carbon (-**CH**-OH)

respectively (**Figure 24**).







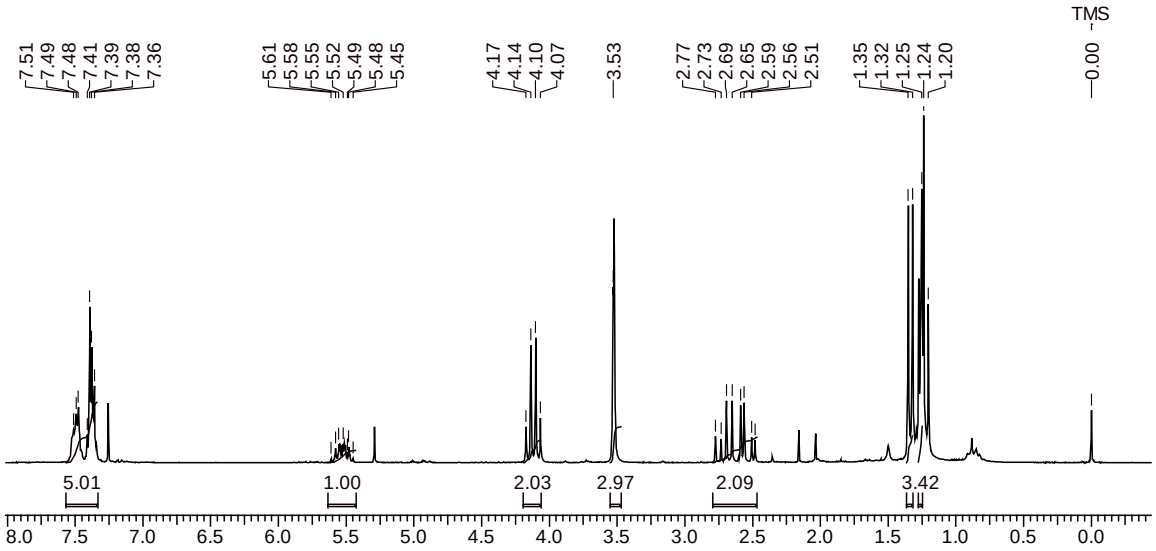
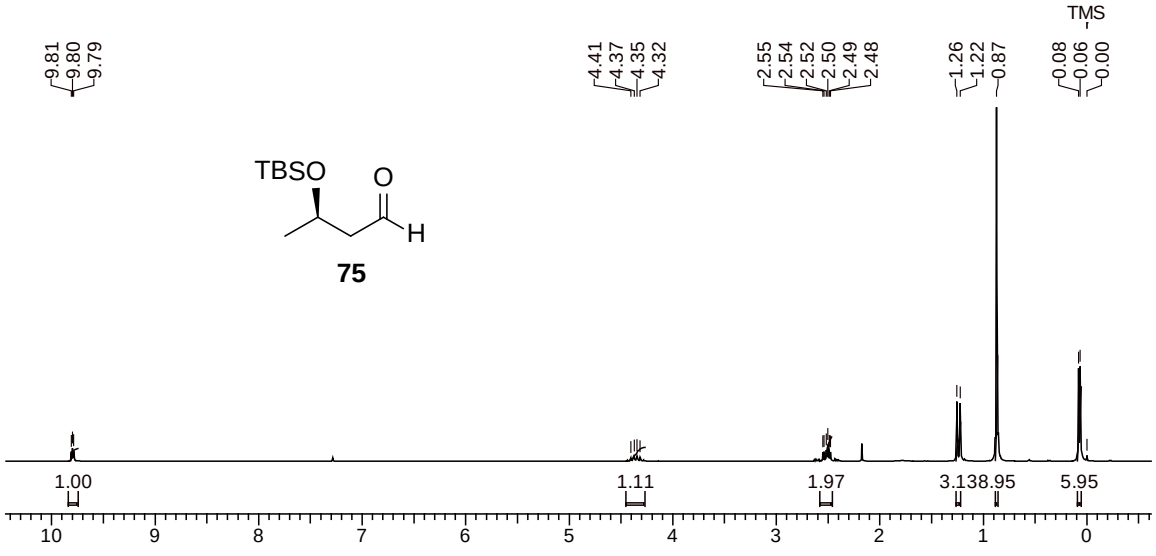


Figure 24: ^{1}H, ^{13}C & Mosher ester NMR and Mass spectra of alcohol **56**

After protecting as its TBS ether, the resulting ester **74** was subjected to selective reduction with DIBAL-H at -78 °C that afforded the corresponding aldehyde **75** in 85% yield. The formation of aldehyde **75** was confirmed by the appearance of an aldehydic proton signal at δ 9.79 (t, J = 2.1, 1H) in its ^{1}H NMR spectrum. Further evidence was provided by its ^{13}C NMR spectrum which showed a characteristic carbon signal at δ 201.9 due to the aldehydic carbon (**Figure 25**).



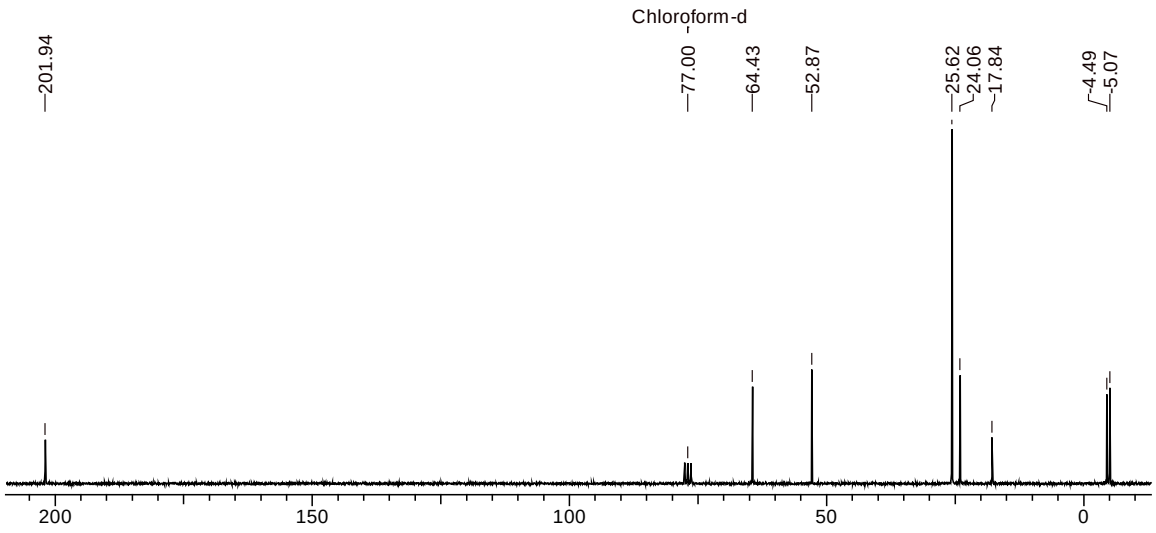
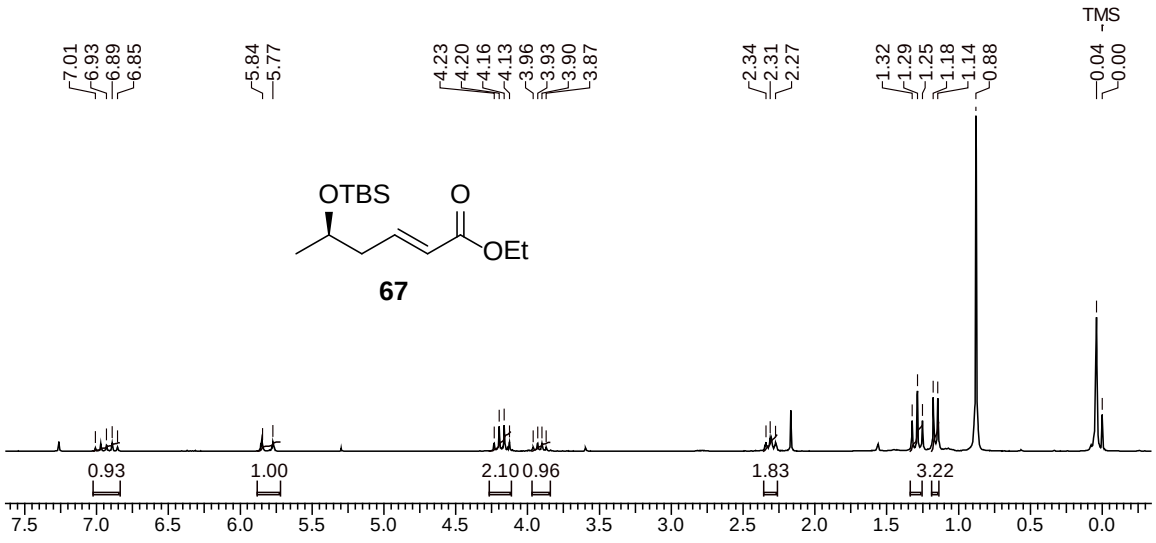


Figure 25: ^{1}H and ^{13}C NMR spectra of aldehyde **75**

Aldehyde **75** was immediately reacted with stabilized Wittig salt to give α,β-unsaturated ester **67** in 93% yield, $\{[\alpha]_D^{25}$ -15.8 (*c* 2.4, $CHCl_3$)}. The formation of olefinic ester **67** was confirmed by its ^{1}H and ^{13}C NMR spectra which showed the appearance of proton signals at δ 5.84 (d, *J* = 15.5 Hz, 1H) & 6.85-7.01 (m, 1H) and carbon signals at δ 145.8 & 123.2 corresponding to the presence of olefinic function respectively. A quartet at δ 4.20 (*J* = 7.1 Hz, 2H) in its ^{1}H NMR spectrum and a carbon signal at δ 166.2 in its ^{13}C NMR spectrum further indicated the presence of ester functionality in **67** (**Figure 26**).



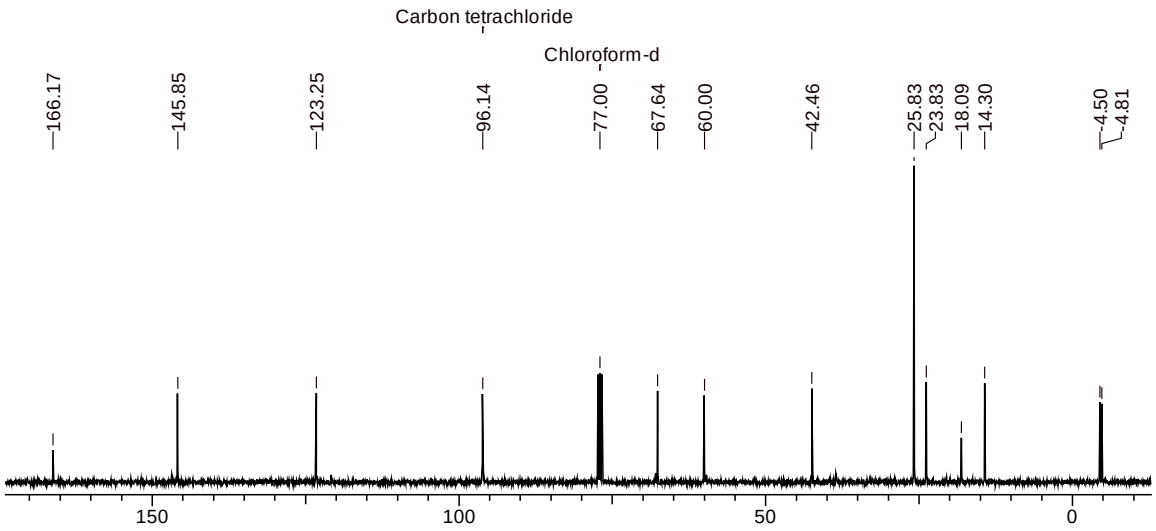
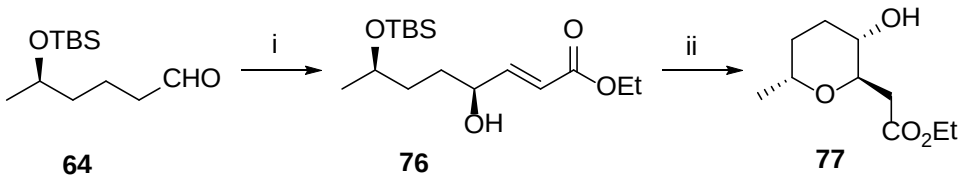


Figure 26: ^{1}H and ^{13}C NMR spectra of ester **67**

Exposure of the ester **67** to 10% Pd/C under H_2 (1 atm) followed by its selective reduction with DIBAL-H at -78 ^{o}C furnished the key aldehyde **64** in 60% overall yield. With the intermediate aldehyde **64** now available in plenty, we carried out the sequential aminoxylation-olefination on aldehyde **64** catalyzed by D-proline at -20 ^{o}C, followed by anilinoxy deprotection {$Cu(OAc)_2$, EtOH} that resulted in the formation of the γ-hydroxy olefinic ester **76** in 57% yield (**Scheme 21**).



Scheme 21: (i) (a) PhNO, D-proline (20 mol %), -20 ºC, 24 h then triethylphosphonoacetate, DBU, LiCl, -20 - 0 ºC, 2 h,; (b) $Cu(OAc)_2$, EtOH, 25 ºC, 12 h, 57% (over two steps); (ii) TBAF, THF, 25 ºC, 4 h, 65%.

The formation of **76** was confirmed by the appearance of a quartet at δ 4.19 (*J* = 7.2 Hz, 2H) in its ^{1}H NMR spectrum, corresponding to methylene protons (-CO_2-**CH_2**-) of ester groups. The presence of double doublets at δ 6.02 (*J* = 1. 8, 15.7 Hz, 1H) and 6.89 (*J* = 4.5, 15.7 Hz, 1H) accounted for the olefin functionality in **76**. Further evidence to this

was provided by its ^{13}C NMR spectrum which showed typical carbon signals at δ 120.1, 150.4 and 166.6 for the olefin and ester groups respectively (**Figure 27**).

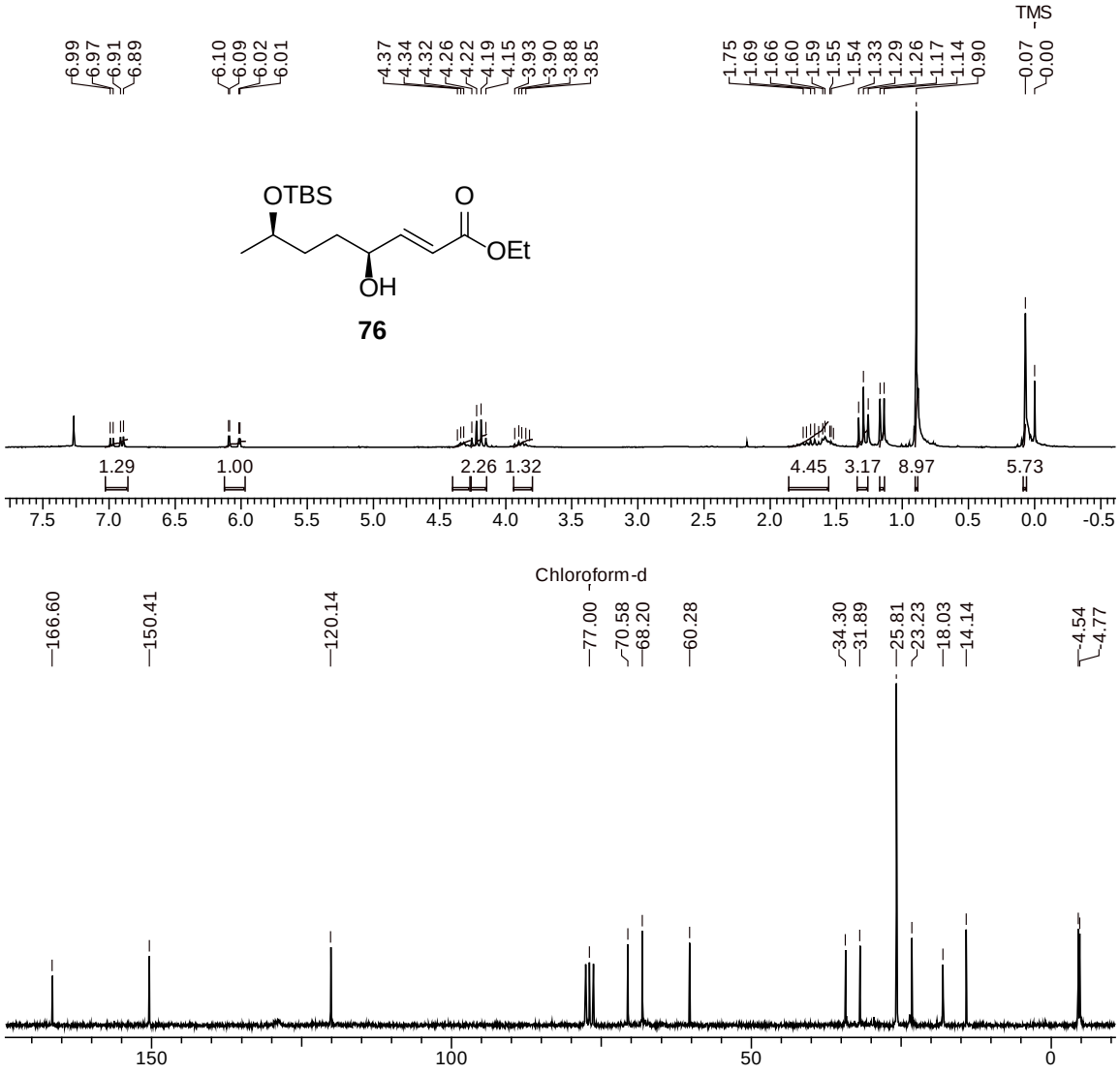


Figure 27: ^{1}H and ^{13}C NMR spectra of ester **76**

The next step was the TBAF mediated deprotection of TBS ether in **76**, which resulted in simultaneous cyclization to produce tetrahydropyranyl skeleton **77**. The pyran **77** can be converted into the natural product **41** by following a known sequence of reaction.[23] The ^{1}H NMR spectrum of pyran **77** showed multiplets at δ 3.48 and 3.97-4.03 for methine (-**CH**-O) protons. The disappearance of proton signals corresponding to olefin function

confirmed the formation of **77**. Its ^{13}C NMR spectrum showed signals at δ 60.7, 67.3, 69.0 and 72.8 corresponding to carbons attached to oxygen atom (**Figure 28**).

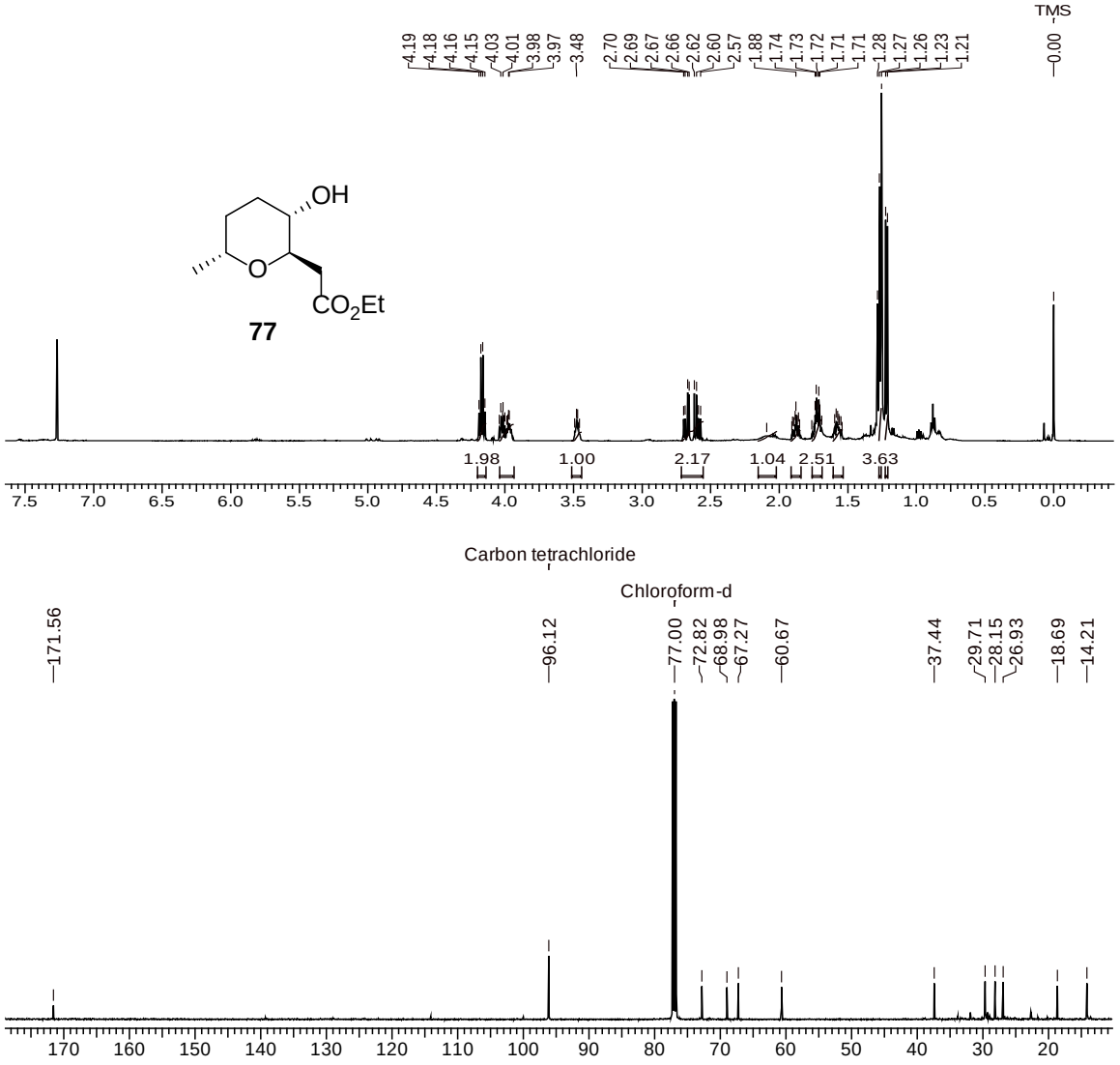
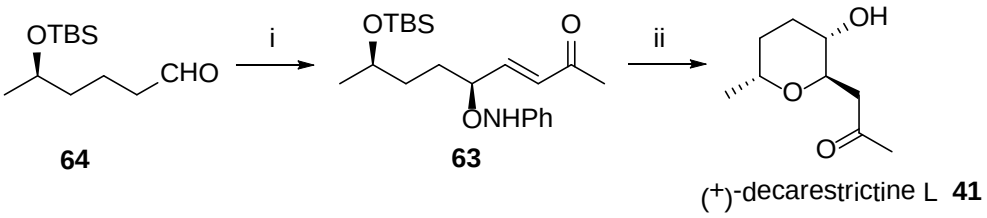


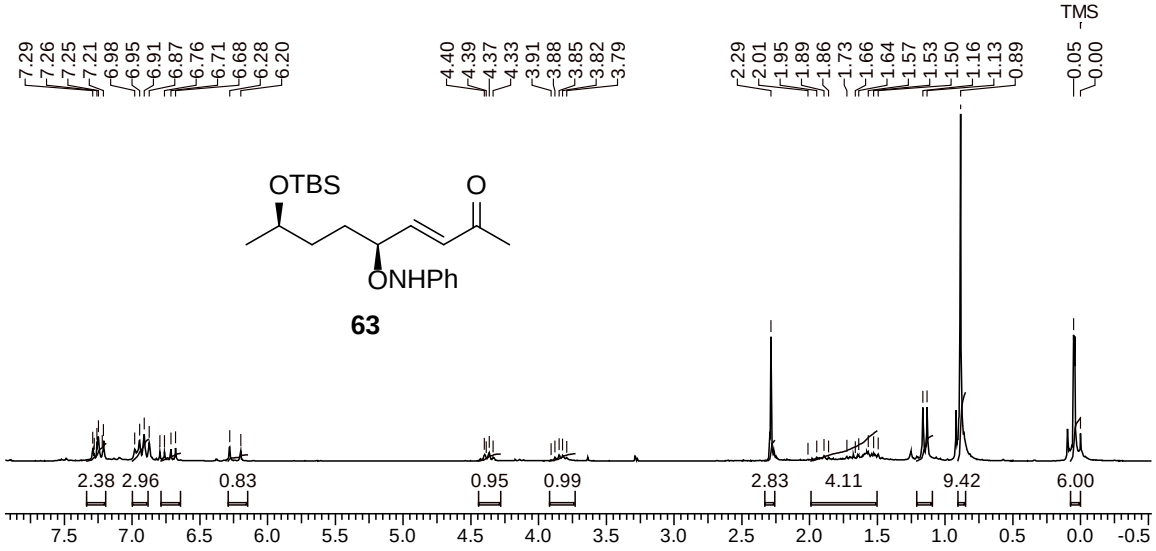
Figure 28: ^{1}H and ^{13}C NMR spectra of pyran **77**

With the tandem desilylation-oxa Michael reaction condition optimized, we thought of a shorter and higher yielding route to **41** by directly incorporating the enone moiety **63**. Thus, the intermediate aldehyde **64** underwent sequential aminoxylation-olefination catalyzed by D-proline at -20 ^{o}C with diethyl(2-oxopropyl)phosphonate, that resulted in the formation of the precursor aminooxy enone **63** in 60% yield (**Scheme 22**).



Scheme 22: (i) PhNO, D-proline (20 mol %), -20 ºC, 24 h then diethyl(2-oxopropyl)phosphonate, Cs_2CO_3, -20-0 ºC, 2 h, 60%; (ii) (a) $Cu(OAc)_2$, EtOH, 25 ºC, 6 h; (b) TBAF, THF, 25 ºC, 6 h, 60% (over two steps).

The formation of **63** was confirmed by the analysis of its ^{1}H and ^{13}C NMR spectra. Its ^{1}H NMR spectrum showed a doublet at δ 6.20 (J = 16.2 Hz, 1H) and a double doublet at δ 6.68 (J = 6.6, 16.2 Hz, 1H) for the olefinic protons. Further, the multiplets at δ 6.87-6.98 (3H) and 7.21-7.29 (2H) in its ^{1}H NMR spectrum were due to aromatic protons. A proton singlet at δ 2.29 (3H) was attributed to methyl group attached to carbonyl carbon. This was further substantiated by its ^{13}C NMR spectrum which showed typical carbon signals at δ 114.2, 122.0, 128.8, 131.5, 145.8 and 148.3 for olefinic and aromatic carbons. The signals at δ 68.0 and 83.0 in its ^{13}C NMR spectrum were indicative of the methine carbons; -**CH**-OTBS and -**CH**-ONHPh respectively. The carbonyl signal for enone functionality resonated at δ 197.8 (**Figure 29**).



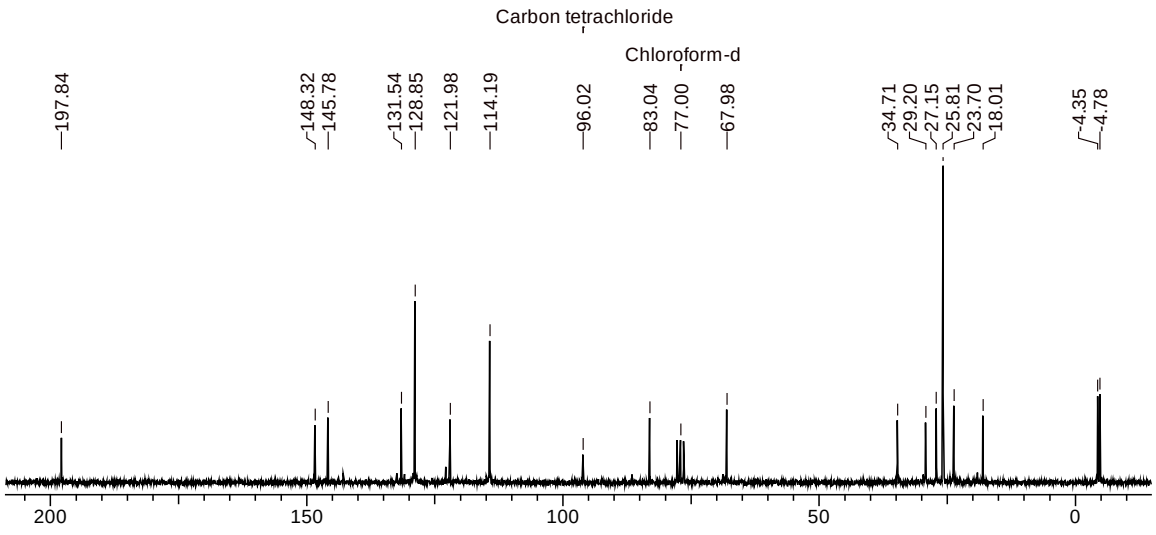


Figure 29: ^{1}H and ^{13}C NMR spectra of enone **63**

With **63** made available sucessfully in hand, we thought to postpone the anilinoxy deprotection to a last stage, since the anilioxy deprotection under catalytic reduction condition (10% Pd/C, H_2) should provide higher yield of the corresponding free alcohol. Consequently, the next step was the TBAF mediated deprotection of TBS ether in **63**, which should result in simultaneous cyclization to produce tetrahydropyranyl skeleton **41**. Unfortunately, the desired 1,4- conjugate addition did not proceed to give the desired product even after the use of several Lewis acids (eg. $BF_3{\cdot}OEt_2$, $Cu(OTf)_2$, CuI of $AuCl_3$). In turn, the reaction produced complex mixtures, which were difficult to separate. However, the removal of anilinoxy group in **63,** {$Cu(OAc)_2$, EtOH} followed by desilylation (TBAF, THF) of the crude product induced an instantaneous intramolecular 1,4-conjugate addition to afford (+)-decarestrictine L **41** in 60% yield over two steps. The synthetic (+)-decarestrictine L **41** was identical in all respects to the natural product.[23]

The formation of (+)-decarestrictine L **41** was confirmed by the disappearance of olefinic signals from its ^{1}H and ^{13}C NMR spectra. The multiplets at δ 3.39-3.43 (1H), 3.94-3.97 (1H) and 4.00-4.04 (1H) were due to methine (-**CH**-O) protons. This was further ascertained by the appearance of signals at δ 67.4, 69.4 and 72.0 for methine (-**CH**-O) carbons (**Figure 30**).

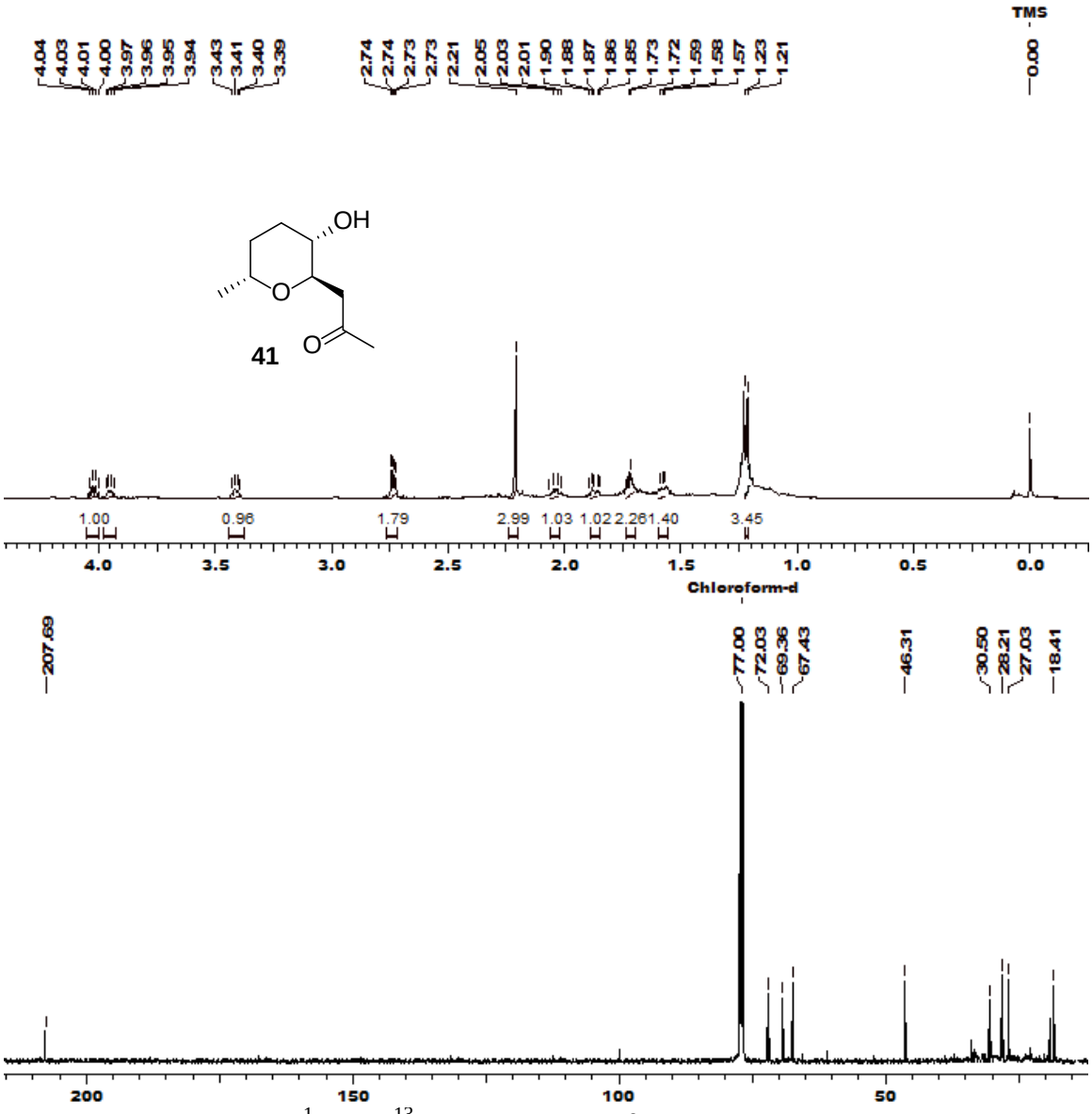


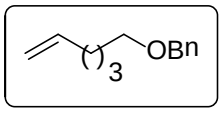
Figure 30: ^{1}H and ^{13}C NMR spectra of (+)-decarestrictine L **41**

2.3.4 Conclusion

In conclusion, we have demonstrated the use of D-proline catalyzed sequential α-aminooxylation-olefination strategy for the concise synthesis of (+)-decarestrictine L **41** with an overall yield of 22% (route 2). Simple procedures, easy to use reagents, cheap and readily available starting materials are some of the salient features of this approach.

2.3.5 Experimental section

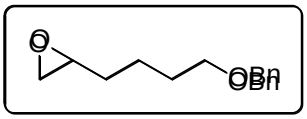
1-Benzyloxy-hex-5-ene (69)



To a stirred suspension of activated NaH (2.88 g, 119.81 mmol) in dry THF (100 mL) a solution of 5-hexen-1-ol **66** (10.0 g, 99.84 mmol) in dry THF (100 mL) was added dropwise at 0 ^{o}C followed by the addition of benzyl bromide (20.49 g, 119.81 mmol). The reaction mixture was then stirred at 25 ^{o}C for 6 h. After completion of reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride and the product extracted with diethyl ether. The combined organic layer was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and column chromatographic purification with petroleum ether/ethyl acetate (49:1 v/v) gave the benzyl ether **69** (18.43 g) as a colorless liquid.

Yield: 97% yield; **IR** ($CHCl_3$): υ_{max} 1454, 1496, 1640, 2857, 2976, 3030, 3065 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.38–1.70 (m, 4 H), 2.00 (q, *J* = 7.1 Hz, 2 H), 3.51 (t, *J* = 6.2 Hz, 2 H), 4.54 (s, 2 H), 4.97-5.10 (m, 2 H), 5.78–5.86 (m, 1 H), 7.29 -7.32 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.6, 29.4, 33.7, 70.3, 72.9, 114.7, 127.5, 127.6, 128.4, 138.6, 138.8; **Anal.** Calcd for $C_{13}H_{18}O$ required C, 82.06; H, 9.53; found C, 82.08; H, 9.55%.

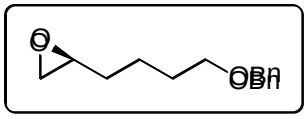
2-[4-(Benzyloxy)butyl]oxirane [(±)-65]



To a stirred solution of olefin **69 (**18.0 g, 94.60 mmol) in dry $CHCl_3$ (350 mL) was added *m*-chloroperbenzoic acid (48.97 g, 283.80 mmol) and the mixture stirred at 25 ^oC for 6 h. After completion of reaction (monitored by TLC), solvent was removed under reduced pressure and the residue extracted with ethylacetate. The organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product which was subjected to column chromatographic purification with petroleum ether/ethyl acetate (19:1 v/v) to give the racemic epoxide **(±)-65 (**16.59 g) as a colorless liquid.

Yield: 85%; **IR** ($CHCl_3$): υ_{max} 1362, 1410, 1454, 1496, 1637, 2859, 3032 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.52–1.66 (m, 6 H), 2.43 (dd, *J* = 2.8, 5.2 Hz, 1 H), 2.69 (dd, *J* = 4.0, 5.1 Hz, 1 H), 2.87–2.89 (m, 1 H), 3.46 (t, *J* = 6.0 Hz, 2 H), 4.48 (s, 2 H), 7.24-7.34 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.7, 29.4, 32.2, 46.8, 52.0, 69.9, 72.8, 127.3, 127.4, 128.2, 138.5; **Anal.** Calcd for $C_{13}H_{18}O_2$ required C, 75.69; H, 8.80; found C, 75.67; H, 8.80%.

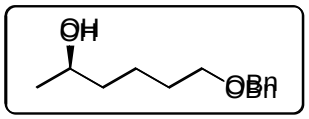
(*S*)-2-[4-(Benzyloxy)butyl]oxirane [(-)-65]



To a suspension of (*S*,*S*)-(-)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane- diaminocobalt (190 mg, 0.5 mol%) in toluene (2 mL) was added acetic acid (0.026 mL, 0.1 mol %) and the mixture stirred while open to air for 1 h at 25 ^oC. The solvent was then removed under reduced pressure and the brown residue dried under vacuum. The racemic epoxide **(±)-65** (13.0 g, 63.10 mmol) was added in one portion and the reaction mixture was then cooled in an ice bath. Water (0.55 equiv. 0.64 mL) was added slowly, followed by stirring at

25 ^{o}C for 24 h. After completion of reaction (monitored by TLC), the reaction mixture was subjected to column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) to afford the (*S*)-epoxide **(-)-65** in 43% yield (5.60 g); $[\alpha]_D^{25}$ -5.1 (*c* 2.0, $CHCl_3$); Optical purity 99% ee from **HPLC analysis**: Column: Lichrocart^{R} (250 x 4.6 mm), Merck 5 μm, mobile phase: isopropylalcohol/n-hexane (2/98), wavelength: 254 nm, flow rate: 1.0 mL/ min, retention time: 2.65 min (-)-isomer, 3.23 min (+)-isomer.

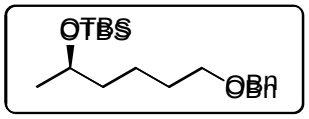
(*R*)-6-(Benzyloxy)hexan-2-ol (71)



To a suspension of $LiAlH_4$ (1.01 g, 26.66 mmol) in dry THF (30 mL), a solution of epoxide **(-)-65** (5.0 g, 24.24 mmol) in THF (50 mL) was added dropwise at 0 °C. The reaction mixture was stirred at this temperature for 30 min. After completion of reaction (monitored by TLC), it was quenched with aq. 20% solution of sodium hydroxide (2 mL) at 0 °C. The reaction mixture was filtered through sintered funnel, dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography with petroleum ether/EtOAc (9:1 v/v) gave the secondary alcohol **71** (4.65 g) as a colorless liquid.

Yield: 92%; $[\alpha]_D^{25}$ -7.9 (*c* 2.0, $CHCl_3$); Optical purity 99% ee from **HPLC analysis**: Column: Lichrocart^{R} (250 x 4.6 mm), Merck 5 μm, mobile phase: isopropylalcohol/ n-hexane (1/99), wavelength: 254 nm, flow rate: 1.0 mL/ min, retention time: 2.94 min (+)-isomer, 5.63 min (-)-isomer; **IR** (neat,): υ_{max} 1300, 1375, 1416, 1460, 1657, 2935, 3354 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.2 Hz, 3 H), 1.42–1.67 (m, 6 H), 1.92 (br s, 1H), 3.46 (t, *J* = 6.2 Hz, 2 H), 3.69-3.80 (m, 1 H), 4.48 (s, 2 H), 7.24–7.33 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.2, 23.4, 29.5, 39.8, 67.4, 70.1, 72.7, 127.3, 127.4,

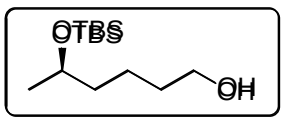
128.1, 138.3; **Anal.** Calcd for $C_{13}H_{20}O_2$ required C, 74.96; H, 9.68; found C, 75.75; H, 9.66%.



(*R*)-[6-(Benzyloxy)hexan-2-yloxy] - *tert*-butyldimethylsilane (72): To a solution of alcohol **71** (4.50 g, 21.60 mmol) in dry CH_2Cl_2 (80 mL) at 0 ^oC was added imidazole (2.94 g, 43.20 mmol) and *tert*-butyldimethylsilyl chloride (4.88 g, 32.40 mmol). The reaction mixture was then stirred at 25 ^oC for 2 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2, washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product which was then purified by column chromatography with pure petroleum ether to give **72** (6.83 g) as a colorless liquid.

Yield: 98%; $[\alpha]_D^{25}$ -10.0 (*c* 1.0, $CHCl_3$); **IR** (neat): υ_{max} 1361, 1373, 1455, 1462, 1471, 2856, 2929 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.12 (d, *J* = 6.1 Hz, 3 H), 1.33–1.63 (m, 6 H), 3.45 (t, *J* = 6.4 Hz, 2 H), 3.72–3.81 (m, 1 H), 4.48 (s, 2 H), 7.31–7.33 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.4, 18.1, 22.4, 23.8, 25.9, 29.8, 39.5, 68.4, 70.3, 72.8, 127.3, 127.5, 128.2, 138.7; **Anal.** Calcd for $C_{19}H_{34}O_2Si$ required C, 70.75; H, 10.62 found C, 70.78; H, 10.77%.

(*R*)-5-(*tert*-Butyldimethylsilyloxy)hexan-1-ol (73)

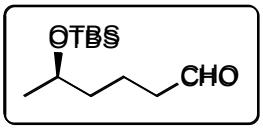


A mixture of benzyl ether **72** (6 g, 18.60 mmol), 10% Pd/C and catalytic amount of triethylamine (2 drops) was stirred under H_2 (1 atm.) at 25 ^oC. After completion of reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and solvent evaporated under reduced pressure to afford the title compound **73** (4.19 g) as a slightly yellow colored oil.

Yield: 97%; $[\alpha]_D^{25}$ -13.8 (*c* 1.6, $CHCl_3$); **IR** (neat): υ_{max} 1050.13, 1099.5, 1225.6, 2857.9, 2930.4, 3438.4 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.84 (s, 9H), 1.11 (d, *J* = 6.1 Hz, 3H), 1.36–1.59 (m, 6 H), 1.84 (br s, 1 H), 3.59 (t, *J* = 6.3, 2 H), 3.74–3.83 (m, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.4, 18.1, 21.9, 23.7, 25.9, 32.7, 39.4, 62.6, 68.5; **Anal.** Calcd for $C_{12}H_{28}O_2Si$ required C, 62.01; H, 12.14; found C, 62.07; H,

12.14%.

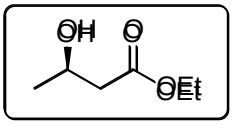
(*R*)-5-(*tert*-Butyldimethylsilyloxy)hexanal (64)



To a well stirred solution of alcohol **73** (4.00 g, 17.21 mmol) in DMSO (30 mL), 2-iodoxybenzoic acid (9.64 g, 34.42 mmol) was added in one portion. The reaction mixture was then stirred for 1 h at 25 ^oC. After the completion of reaction (monitored by TLC), it was diluted with water and diethyl ether. Subsequent filtration (diethyl ether eluent) and washing the filtrate with water, brine followed by drying over anhydrous Na_2SO_4 and removal of solvent under reduced pressure gave crude product which on chromatographic separation with petroleum ether/EtOAc (9:1 v/v) gave the intermediate aldehyde **64** (3.89 g) as a light yellow colored liquid.

Yield: 98%; $[\alpha]_D^{25}$ -12.0 (*c* 3.0, $CHCl_3$); **IR** (neat,): υ_{max} 1215, 1472, 1572, 1722, 2857, 2930, 3020cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.88 (s, 9H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.37-1.43(m, 2H), 1.54–1.69 (m, 2H), 2.40-2.46 (dt, *J* = 7.1, 8.8 Hz, 2H), 3.73-3.88 (m, 1H), 9.76 (t, *J* = 1.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, -5.1, 17.5, 25.1, 38.1, 43.1, 67.3, 201.4; **Anal.** Calcd for $C_{12}H_{26}O_2Si$ required C, 62.55; H, 11.37; found C, 62.65; H, 11.77%.

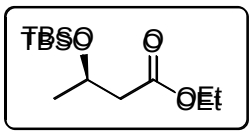
(*R*)-Ethyl (-)-3-hydroxybutyrate (56)



Ethyl acetoacetate **68** (7.50 g, 57.69 mmol) and dry methanol (25 mL) were mixed and deoxygenated with flowing nitrogen for five minutes. The catalyst $[(R)\text{-Ru(BINAP)Cl}_2]_2 \cdot NEt_3$ (50 mg, 0.1 mol %) was added along with 2N HCl (0.05 mL, 0.1 mol %). The mixture was transferred to a standard Parr reactor apparatus and flushed by evacuating and refilling with hydrogen several times. The apparatus was heated at 50 ^oC with stirring under 100 psi of hydrogen for 16 h. After completion of reaction (monitored by TLC), the reaction was cooled and concentrated under reduced pressure. The residue was subjected to column chromatographic purification with petroleum ether/EtOAc (8:2 v/v) to get pure (*R*)-alcohol **56** (7.23 g) as a colorless liquid.

Yield: 95%; $[\alpha]_D^{25}$ -46.0 (*c* 1.0, $CHCl_3$) {lit.[32] $[\alpha]_D^{25}$ -46.0 (*c* 1.0, $CHCl_3$)}; Optical purity 98% ee from Mosher ester analysis; **IR** ($CHCl_3$,): υ_{max} 1458.1, 1636.1, 1734.0, 2935.7, 2978.6, 3441.7 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.21-1.31 (m, 6H), 2.42-2.46 (m, 2H), 3.20 (d, *J* = 3.8 Hz, 1H), 4.12 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 43.2, 60.5, 64.2, 172.5; **Anal.** Calcd for $C_6H_{12}O_3$ requires C, 54.53; H, 9.15; found C, 54.56; H, 9.35%.

(*R*)-(-)-Ethyl (*tert*-butyldimethyl silyloxy)butyrate (74)

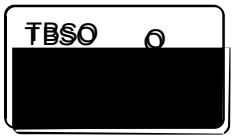


To a solution of ethyl (*R*)-(-)-3-hydroxybutyrate **56** (7.0 g, 52.97 mmol) in dry CH_2Cl_2 (300 mL) at 0 ^oC was added imidazole (7.21 g, 105.94 mmol) and *tert*-butyldimethylsilyl chloride (11.98 g, 79.46 mmol). The reaction mixture was then stirred at 25 ^oC for 2 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2, washed with water, brine and dried over anhydrous

Na_2SO_4, Concentration and purification by column chromatography with petroleum ether/EtOAc (49:1 v/v) gave aldehyde **74** (12.66 g) as a colorless liquid.

Yield: 97%; $[\alpha]_D^{25}$ -26.0 (*c* 1.0, CH_2Cl_2); **IR** ($CHCl_3$): υ_{max} 2958, 2931, 2897, 2857, 1739, 1473, 1447 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.82 (s, 9H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 2.32 (dd, *J* = 5.4, 14.5 Hz, 1H), 2.44 (dd, *J* = 7.4, 14.5 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.19-4.28 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.0, -4.5, 14.2, 17.9, 23.9, 25.7, 44.8, 59.9, 65.8, 171.2; **Anal.** Calcd for $C_{12}H_{26}O_3Si$ requires C, 58.49; H, 10.63 found C, 58.54; H, 10.56%.

(*R*)-(-)-Ethyl (*tert*-butyldimethylsilyloxy)butanal (75)

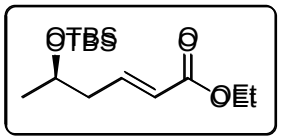


To a stirred solution of ester **74 (**11.50 g, 46.69 mmol) in dry toluene (250 mL), a solution of diisobutylaluminium hydride (46.8 mL, 1M in cyclohexane) was added dropwise at -78 ^oC and stirred at this temperature for 1 h. After completion of reaction (monitored by TLC), it was diluted with a saturated 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 phase was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) gave aldehyde **75** (8.03 g) as a colorless liquid.

Yield: 85%; $[\alpha]_D^{25}$ -13.6 (*c* 1.6, CH_2Cl_2); lit.[32] $[\alpha]_D^{25}$ -11.3 (*c* 1.0, CH_2Cl_2); **IR** ($CHCl_3$): υ_{max} 1362, 1377, 1463, 1473, 1729, 2858, 2896, 2930, 2957 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.22 (d, *J* = 6.2 Hz, 3H), 2.48-2.55 (m, 2H), 4.32-4.41 (m, 1H), 9.79 (t, *J* = 2.7 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.1, -4.5,

17.8, 24.1, 25.6, 52.9, 64.4, 201.9; **Anal.** Calcd for $C_{10}H_{22}O_2Si$ requires C, 59.35; H, 10.96; found C, 59.38; H, 10.97%.

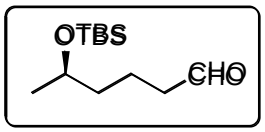
(*R*)-(-)-Ethyl 5-*tert*-butyldimethylsiloxyhex-2-enoate (67)



To a solution of aldehyde **75** (7.00 g, 34.59 mmol) in dry THF (200 mL) at 25 ^oC was added Ph_3P=CHCOOEt (18.08 g, 51.89 mmol) and the reaction mixture was stirred for 12 h. After completion of reaction (monitored by TLC), solvent was distilled off under reduced pressure and the crude mass on column chromatographic purification with petroleum ether/ EtOAc (9:1 v/v) gave the α,β- unsaturated ester **67** (8.76 g) as a slightly yellow colored liquid.

Yield: 93%; $[\alpha]_D^{25}$ -15.8 (*c* 2.4, $CHCl_3$, cm^{-1}); **IR** ($CHCl_3$): υ_{max} 1376, 1463, 1655, 1724, 2857, 2930 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 2.27-2.34 (m, 2H), 3.87-3.96 (m, 1H), 4.2 (q, *J* = 7.1 Hz, 2H), 5.84 (d, *J* = 15.5 Hz, 1H), 6.85-7.01 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.8, -4.5, 14.3, 18.1, 23.8, 25.8, 42.5, 60.0, 67.6, 123.2, 145.8, 166.2; **Anal.** Calcd for $C_{14}H_{28}O_3Si$ requires C, 61.72; H, 10.36; found C, 61.90; H, 11.86%.

(*R*)-(-)-Ethyl (*tert*-butyldimethylsilyloxy)hexanal (64)

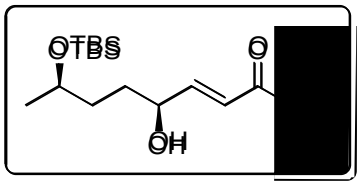


A mixture of α,β-unsaturated ester **67** (8 g, 29.36 mmol), 10% Pd/C and catalytic amount of triethylamine (2 drops) in MeOH (40 mL) was stirred under H_2 (1 atm.) at 25 ^oC for 12 h. After completion of reaction (monitored by TLC), it was filtered over celite plug (MeOH eluent) and solvent evaporated under reduced pressure to give the corresponding saturated ester. To a stirred solution of the saturated ester in dry toluene (150 mL), a solution of diisobutylaluminium hydride (29.4 mL, 1 M in cyclohexane) was added dropwise at -78 ^oC and stirred at this

temperature for 1 h. After completion of reaction (monitored by TLC) the reaction mixture 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 phase was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and column chromatographic purification with petroleum ether/ EtOAc (9:1 v/v) gave aldehyde **64** (5.55 g) as a colorless liquid.

Yield: 82% (over two steps); $[\alpha]_D^{25}$ -12.0 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$,): υ_{max} 1439, 1472, 1572, 1722, 2857, 2956, 2930, 3019 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.76 (t, *J* = 1.8 Hz, 1H), 3.68-3.83 (m, 1H), 2.34-2.41 (dt, *J* = 7.1, 8.8 Hz, 2H), 1.58-1.70 (m, 2H), 1.35-1.43 (m, 2H), 1.10 (d, *J* = 6.1 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 202.0, 67.6, 43.4, 38.5, 25.4, 23.3, 17.8, 17.6, -4.84. -5.23; **Anal.** Calcd for $C_{12}H_{26}O_2Si$ required C, 62.55; H, 11.37; found C, 62.65; H, 11.38%.

(4*S*,7*R*,E)-Ethyl 7-(*tert*-butyldimethylsilyloxy)-4-hydroxyoct-2-enoate (76)

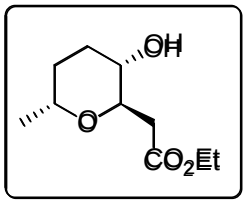


To a stirred solution of nitrosobenzene (419 mg, 3.91 mmol) and D-proline (90 mg, 20 mol %) in CH_3CN (20 mL) was added precursor aldehyde **64** (1 g, 4.35 mmol) at -20 °C. The reaction mixture was stirred at the same temperature for 24 h followed by the addition of triethylphosphonoacetate (1.32 g, 5.86 mmol), LiCl (246 g, 5.86 mmol) and DBU (594 mg, 3.91 mmol) sequentially. After stirring for 2 h at 0 °C, reaction mixture was quenched with saturated NH_4Cl and extracted with ethylacetate (3 × 20 mL). The Combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in EtOH and $Cu(OAc)_2$ (30 mol %)

was added. The reaction mixture was then stirred at 25 ^{o}C for 24 h. Removal of solvent and purification by column chromatography with petroleum ether/ EtOAc (8:2 v/v) afforded hydroxy olefinic ester **76** (730 mg) as a yellow oily liquid.

Yield: 57%; $[\alpha]^{25}_{D}$ -12.5 (*c* 4.0, $CHCl_3$); **IR** (neat): υ_{max} 1377, 1472, 1677, 2857, 2930, 2956, 3155 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.90 (s, 9H), 1.14 (d, *J* = 6.1 Hz, 3H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.54-1.75 (m, 4H), 3.85-3.93 (m, 1H), 4.15 (q, *J* = 7.3 Hz, 2H), 4.32-4.37 (m, 1H), 6.10 (d, *J* = 16.2 Hz, 1H), 6.89-6.99 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)): δ -4.8, -4.5, 14.1, 18.0, 23.2, 25.8, 31.9, 34.3, 60.3, 68.2, 70.6, 120.1, 150.4, 166.6; **Anal.** Calcd for $C_{16}H_{32}O_4Si$ requires C, 60.72; H, 10.19; Found C, 60.75; H, 10.23%.

Ethyl 2-((2*R*,3*S*,6*R*)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)acetate (77)

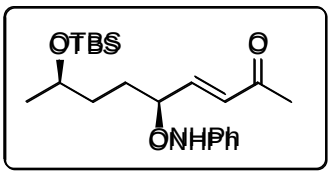


To a well stirred solution of hydroxy olefinic ester **76** (100 mg, 0.3 mmol) in dry THF was added a solution of 1M tetrabutylammonium fluoride (0.6 mL, 2 equiv) was added at 25 ^{o}C. The reaction mixture was stirred at this temperature for 4 h after which solvent was removed under reduced pressure and the residue subjected to column chromatography with petroleum ether/ethyl acetate (7:3 v/v) to afford pyran **77** (42 mg) as an oily liquid.

Yield: 65%; $[\alpha]^{25}_{D}$ +20.0 (*c* 0.1, $CHCl_3$); **IR** (neat): υ_{max} 1275, 1462, 2859, 2959, 3430 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.3 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.54-1.60 (m, 1H), 1.69-1.76 (m, 2H), 1.85-1.91 (m, 1H), 2.05 (br s, 1H), 2.60 (dd, *J* = 8.0, 14.9 Hz, 1H), 2.67 (dd, *J* = 5.2, 14.8 Hz, 1H), 3.48 (m, 1H), 3.97-4.03 (m, 2H), 4.18 (q, *J* = 6.9, 14.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.2, 18.7, 26.9, 28.1, 37.4,

60.7, 67.3, 69.0, 72.8, 171.6,; **Anal.** Calcd for $C_{10}H_{18}O_4$ requires C, 59.39; H, 8.97; Found C, 59.43; H, 8.94%.

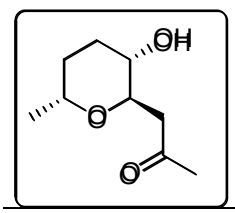
(5*S*,8*R*,E)-8-(*tert*-Butyldimethylsilyloxy)-5-(phenylaminooxy)non-3-en-2-one (63)



To a stirred solution of nitrosobenzene (800 mg, 8.20 mmol) and D-proline (210 mg, 20 mol%) in CH_3CN (80 mL) was added precursor aldehyde **64** (2.11 g, 9.11 mmol) at -20 °C. The reaction mixture was stirred at the same temperature for 24 h followed by the addition of diethyl(2-oxopropyl)phosphonate (2.65 g, 13.67 mmol) and Cs_2CO_3 (4.45 g, 13.67 mmol). After stirring for 2 h at 0 °C, reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc (3 × 60 mL). The Combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography with petroleum ether/ethyl acetate (9:1 v/v) afforded aminooxy olefinic ketone **63** (2.06 g) as a yellow oily liquid.

Yield: 60%; $[\alpha]^{25}_D$ -5.5 (*c* 4.0, $CHCl_3$) ; **IR** (neat): υ_{max} 1370, 1499, 1657, 1721, 2856, 2928, 3437 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.13 (d, *J* = 6.1 Hz, 3H), 1.50-2.01 (m, 4H), 2.29 (s, 3H), 3.79-3.91 (m, 1H), 4.33-4.40 (m, 1H), 6.20 (d, *J* = 14.8 Hz, 1H), 6.68 (dd, *J* = 1.8, 15.7 Hz, 1H), 6.87-6.98 (m, 3H), 7.21-7.29 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.8, -4.3, 18.0, 23.7, 25.8, 27.1, 29.2, 34.7, 68.0, 83.0, 114.2, 122.0, 128.8, 131.5, 145.8, 148.3, 197.8; **Anal.** Calcd for $C_{21}H_{35}NO_3Si$ requires C, 66.80; H, 9.34; N, 3.71; Found C, 66.85; H, 9.38; N, 3.91%.

Decarestrictine L (41)



To a well stirred solution of aminooxy olefinic ketone **63** (500 mg, 1.23 mmol) in ethanol was added copper acetate (750 mg, 30 mol %).

The reaction mixture was then stirred overnight at 25 ^{o}C. After completion of reaction (monitored by TLC), the solvent was removed under reduced pressure and the residue dissolved in dry THF. To this, a solution of 1M tetrabutylammonium fluoride (2.55 mL, 2 equiv.) was added at 25 ^{o}C. The reaction mixture was stirred at this temperature for 6 h after which solvent was removed under reduced pressure and the residue subjected to column chromatography with petroleum ether/ethyl acetate (17:3 v/v) to afford decarestrictine L **41** (127 mg) as an oily liquid.

Yield: 60%; $[\alpha]^{25}_{D}$ +28.6 (*c* 0.5, $CHCl_3$) lit.[23] $[\alpha]_{D}^{25}$ +28.8 (*c* 0.49, $CHCl_3$); **IR** (neat): υ_{max} 1440, 1598, 1712, 2853, 2965, 3415 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.22 (d, *J* = 6.5 Hz, 3H), 1.57-1.90 (m, 4H), 2.04 (br s, 1H), 2.21 (s, 2H), 2.73 (d, *J* = 6.5 Hz, 2H), 3.39-3.43 (m, 1H), 3.94-3.97 (m, 1H), 4.03 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 18.4, 27.0, 28.2, 30.5, 46.3, 67.4, 69.4, 72.0, 207.7; **Anal.** Calcd for $C_9H_{16}O_3$ requires C, 62.77; H, 9.36; Found C, 62.68; H, 9.38%.

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Chapter III

A New Concise Method for the Synthesis of Chiral Tetrahydroquinolin-3-ols, (-)-Sumanirole (PNU 95666-E) and 1-[(S)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2H)-yl]propan-1-one, (S)-903

Section I

Organocatalytic sequential α-aminooxylation/reductive cyclization of *o*-nitrohydrocinnamaldehydes: A high yield synthesis of chiral tetrahydroquinolin-3-ols

3.1.1 Introduction

The 1,2,3,4-tetrahydroquinoline (THQ) is a very common structural motiff found in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[1,2] For example, (-)-sumanirole **1** (PNU-95666E) is a selective and high affinity agonist at the dopamine D_2 receptor subtype and has proven as a potential agent for the treatment of Parkinson's disease and restless leg syndrome.[3] Also, 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propanone [(*S*)-903] **2** has recently been identified as a potentially interesting positive inotropic agent,[4] while (+)-duocarmycin D1 **3** has exhibited potent antitumor activity (**Figure 1**).

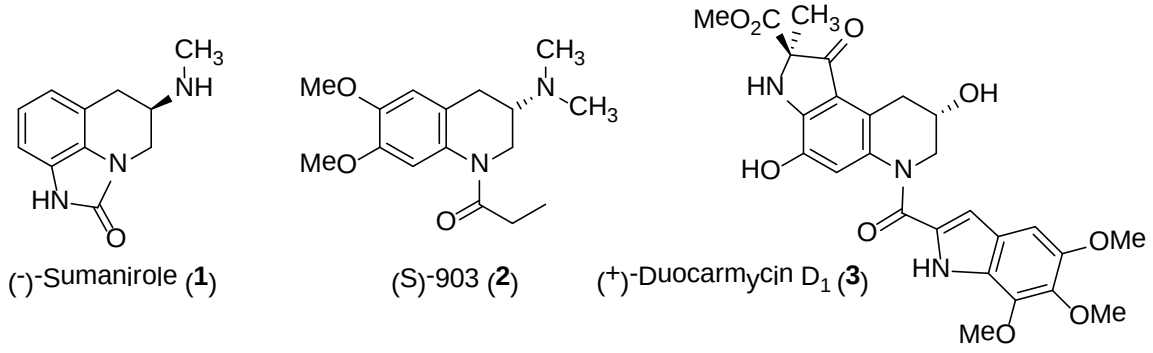


Figure 1: Structures of some THQ containing bioactive molecules

Moreover, besides pharmaceutical applications, tetrahydroquinoline derivatives are useful as pesticides,[5] antioxidants,[6] and corrosion inhibitors,[7] Also tetrahydroquinolines are widely used as active components of dyes[8] and photosensitizers in photography.[9] Due to the significance of these scaffolds in drug discovery and medicinal chemistry,[10]

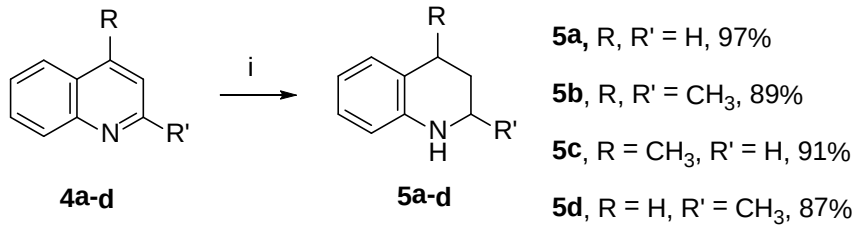
the development of new methodologies for the synthesis of 3-substituted THQs derivatives continue to be very active field of research in recent years.[11]

3.1.2 Review of literature

Literature search revealed that there are various reports available for the synthesis of tetrahydroquinoline derivatives; some of which are described below.

Murahashi's approach (1987)[12]

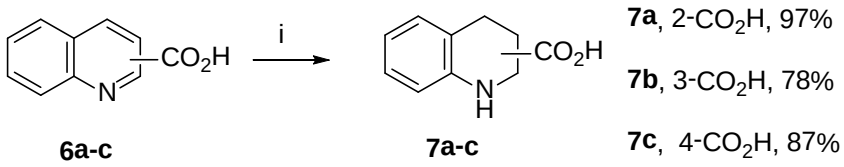
Murahashi *et al*. have used hexarhodiumhexadecacarbonyl complex for the synthesis of tetrahydroquinolines **4a-d** from quinolines **5a-d** using carbon monoxide and water as efficient reducing agent (**Scheme 1**).



Scheme 1: (i) Catalytic $Rh_6(CO)_{16}$, CO, H_2O.

Gracheva's approach (1988)[13]

Gracheva *et al.* reported the use of Ni-Al alloy for the reduction of quinolinecarboxylic acid **6a-c** to obtain tetrahydroquinolinecarboxylic acid **7a-c** (**Scheme 2**).

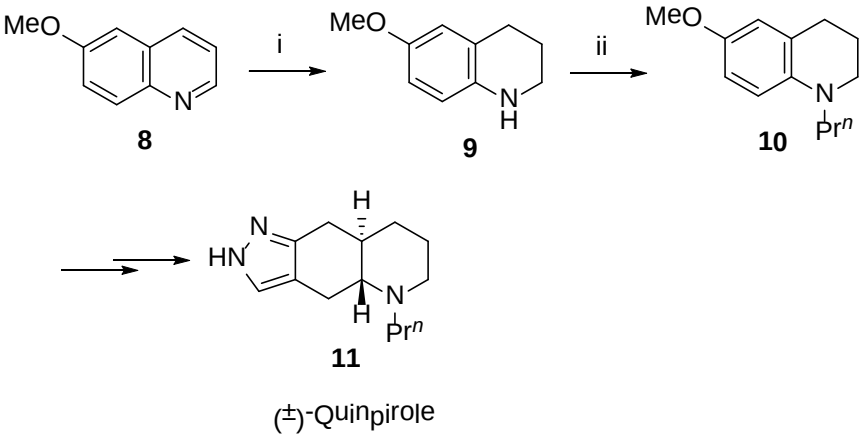


Scheme 2: (i) Ni-Al, aq. NaOH, 50 °C, 12 h.

Schaus's approach (1990)[14]

Schaus *et al.* have reported the synthesis of (±)-quinpirole **11** using hydrogenation [catalytic PtO_2, H_2 (60 psig)] of 6-methoxyquinoline **8** which afforded 6-methoxy-l,2,3,4-tetrahydroquinoline **9**. Reductive alkylation of **9** [propanaldehyde, 10% Pd/C, H_2 (60

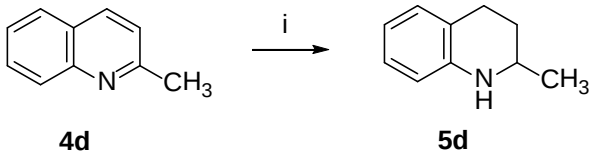
psig)] furnished tetrahydroquinoline **10** in 36 % yield over two steps. Further **10** was converted into (±)-quinpirole **11** by employing a sequence of reactions (**Scheme 3**).



Scheme 3: (i) PtO_2 (10 wt%), H_2 (60 psig), 50 °C, 12 h, MeOH, 66%; (ii) 10% Pd/C, H_2 (60 psig), EtCHO, EtOH, 50 °C, 12 h, 54%.

Bouyssou's approach (1992)[15]

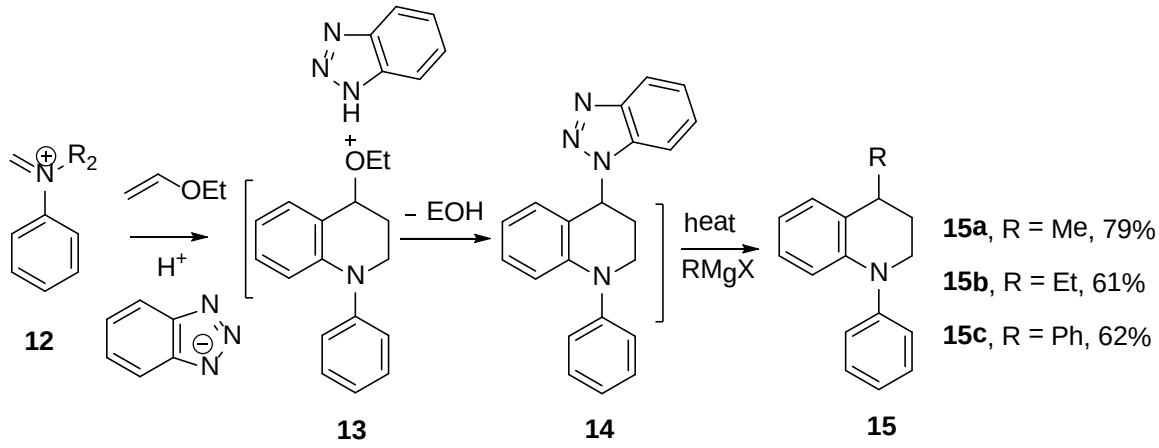
Bouyssou *et al.* have employed transfer hydrogenation (10% Pd/C, HCO_2H/Et_3N) as a method for reducing quinoline **4d** to afford the corresponding tetrahydroquinoline **5d** in 85 % yield (**Scheme 4**).



Scheme 4: (i) 10% Pd/C, HCOOH, Et_3N, 50 °C, 12 h, 85%.

Katritzky's approach (1995)[16]

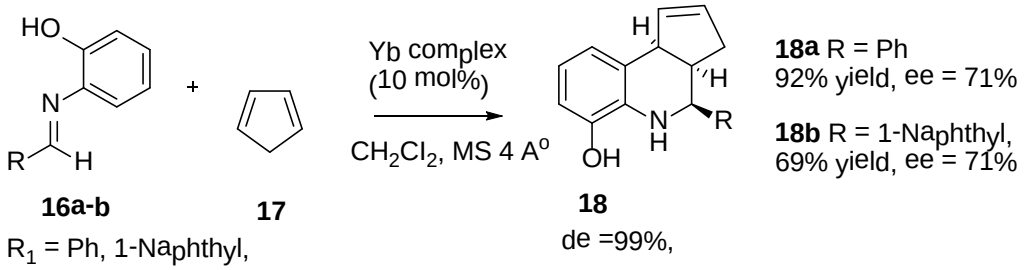
Katritzky *et al.* have reported acid catalyzed Diels-Alder reaction of *N*-methylaniline derivative **12** with ethyl vinyl ether to give reactive intermediate 4-ethoxy-1,2,3,4-tetrahydroquinoline **13** which underwent *in situ* substitution by benzotriazol to provide 4-(benzotriazolyl)-1,2,3,4-tetrahydroquinoline **14** in 48% yield. At elevated temperatures, ionization of **14** gives immonium cation which can be trapped *in situ* by Grignard reagent to provide 4-substituted tetrahydroquinolines **15** in good yields (**Scheme 5**).



Scheme 5: (i) **12**, ethyl vinyl ether, PTSA, 22 ºC, 30 min. then 120 ºC, 10 min; (ii) RMgX, Et_2O, reflux, 1 h.

Kobayashi's approach (1996)[17]

Kobayashi *et al*. have used asymmetric Aza Diels-Alder reactions of imine **16a-b** and cyclopentadiene **17** catalysed by a Yb(OTf)$_3$·(*R*)-BINOL catalyst to provide tetrahydroquinoline derivatives **18a-b** in 69-92% yields and 71% ee (**Scheme 6**).

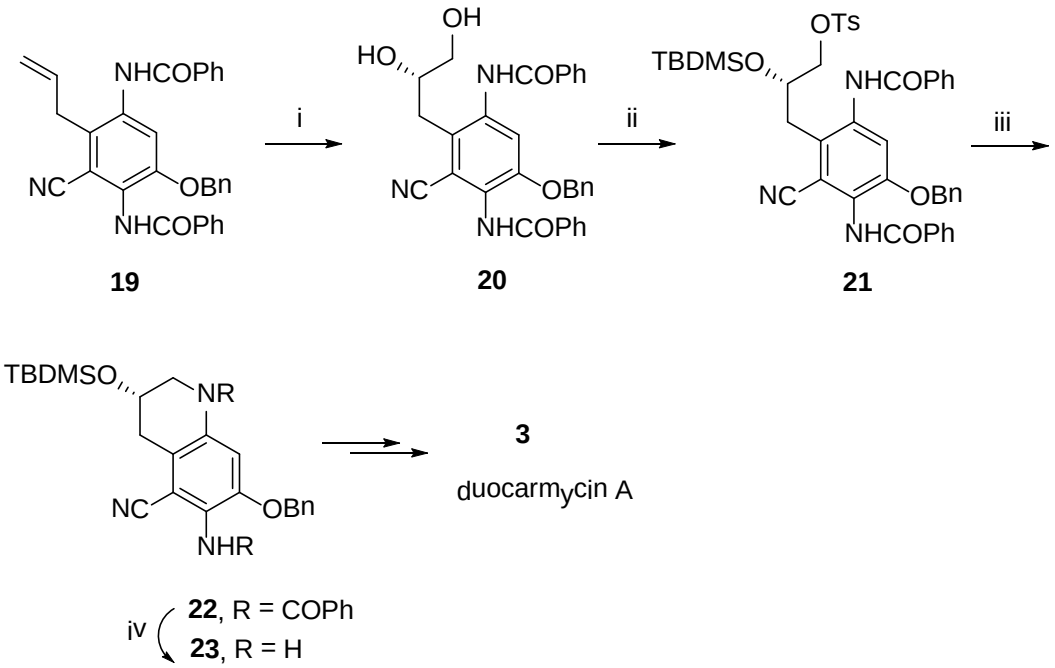


Scheme 6: (i) Yb(OTf)$_3$:(*R*)-BINOL:DBU (20 mol%), 2,6-Di-^{t}butylpyridine, CH_2Cl_2, 4 A^o MS, -15-0 ºC, 20 h.

Boger's approach (1997)[18]

Boger *et al.* have used asymmetric dihydroxylation as a key step for the synthesis of duocarmycin-A **3**. Asymmetric dihydroxylation of olefin **19** gave diol **20** in 95 % yield. Tosylation of primary alcohol and protection of secondary alcohol as silyl ether in **20** gave **21**. Intramolecular nucleophilic displacement of tosylate **21** with amide anion provided key intermediate **22**, which on hydrolysis (N_2H_4, sealed tube, 140 ºC) gave

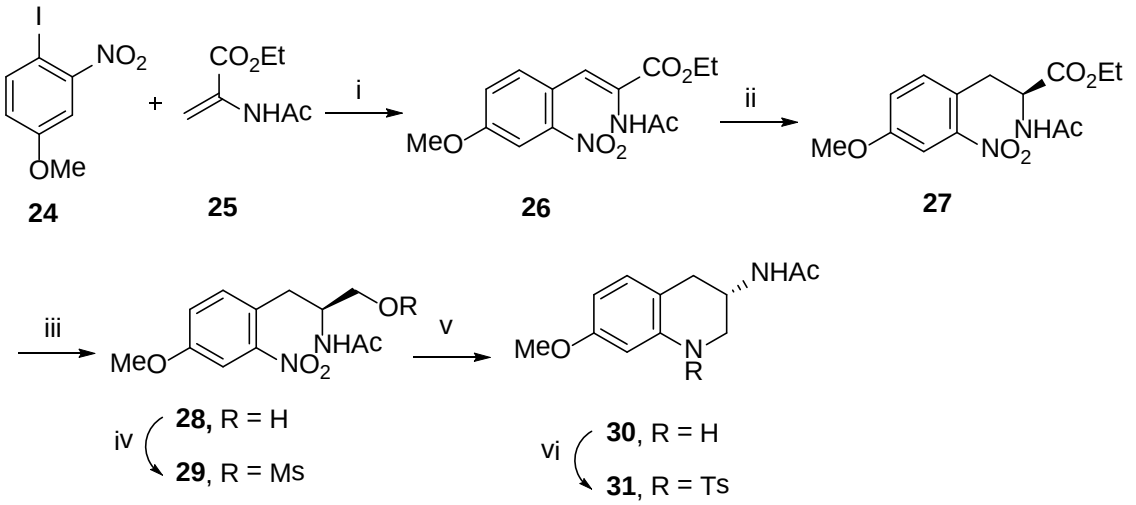
diamine **23**. By sequential transformations, **23** was further converted to duocarmycin A **3** (**Scheme 7**).



Scheme 7 : (i) OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, THF:H_2O (4:1), 0-25 °C, 24 h, 92%; (ii) (a) Bu_2SnO, toluene-THF (10:1), reflux, 6 h; (b) TsCl, Et_3N, CH_2Cl_2, 25 °C, 12 h, 89%; (c) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 67%; (iii) NaH, THF, 0 °C, 2 h, 92%; (iv) NH_2NH_2, EtOH, 140 °C, 12 h, sealed tube, 85%.

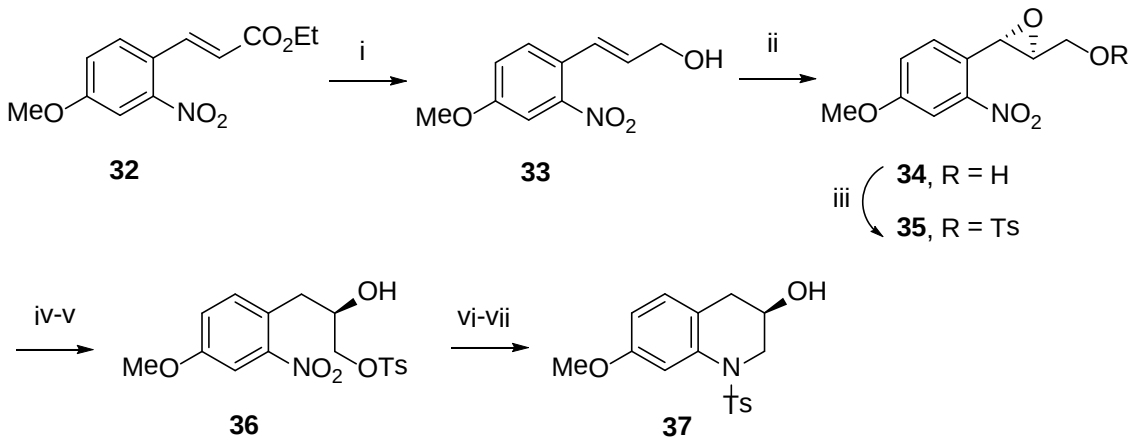
Rajan Babu's approach (2001)[19]

Rajan Babu *et al.* have used Rh-catalyzed asymmetric hydrogenation as a key reaction for the synthesis of aminotetrahydroquinoline **31**. Rh-catalyzed asymmetric hydrogenation of α-acetamido-2 nitrocinnamate ester **26** gave α-acetamido ester **27** in 96% yield and 98% ee. Further reduction of ester functionality with super hydride afforded the corresponding alcohol **28** which was subsequently transformed into its mesylate **29**. Reduction (H_2, 10% Pd/C) of nitro in **29** to amine followed by cyclization provided 3-aminotetrahydroquinoline **30** which was transformed (TsCl/ Et_3N) as its tosylamide **31** (**Scheme 8**).



Scheme 8: (i) $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, sealed tube, 80 ºC, 24 h, 80%; (ii) Rh catalyst, H_2 (40 psig.), THF, 96%, 98% ee; (iii) super hydride, 0 ºC; (iv) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 30 min; (v) H_2, Pd/C, 1 h, 25 ºC; (vi) TsCl, Et_3N, CH_2Cl_2, 0 ºC.

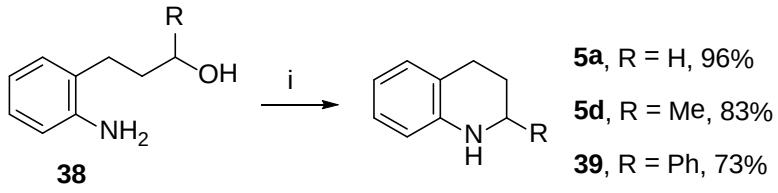
In another approach, 2-nitrocinnamate **32** was reduced to the corresponding allyl alcohol **33** using DIBAL-H. Sharplesss asymmetric epoxidation of allyl alcohol **33** gave the chiral epoxy alcohol **34,** which was transformed into its tosylate **35** (TsCl, Et_3N)**.** Reductive opening of epoxide **35** over PtO_2 furnished alcohol **36** in 70 % yield. Finally reduction (Fe/HCl, H_2O and DMF) of nitro functionality to amine gave 3-hydroxy tetrahydoquinoline, which on tosylation gave tosylamide **37** in 66% yield (**Scheme 9**).



Scheme 9: (a) DIBAL-H, toluene, 0 ºC, 75%; (b) $Ti(O^iPr)_4$, (+)-diethyl tartrate, ^{t}BuOOH, CH_2Cl_2, -30 ºC, 6 days, 60%, >90% ee; (c) TsCl, Et_3N, CH_2Cl_2, DMAP, 0 ºC, 80%; (d) MgI_2, Toluene, -55 ºC; (e) PtO_2, H_2(40 psig), Et_3N, THF, 70% over two steps; (f) Fe, HCl, H_2O, DMF, 70 ºC; (g) TsCl, Et_3N, CH_2Cl_2, 66% (over two steps).

Fujita's approach (2002)[20]

Fujita *et al.* have employed $[CpIrCl_2]_2/K_2CO_3$ catalyzed cyclization of 3-(2-aminophenyl)propanol (**38**) to give tetrahydroquinoline (**5a, 5d** and **39**) in high yields (**Scheme 10**).

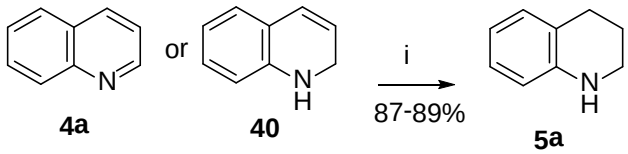


38

Scheme 10: (i) $[CpIrCl_2]_2$ (5.0 mol % Ir), K_2CO_3 (10 mol%), toluene, 111 °C, 20 h.

Fujita's approach (2004)[21]

Fujita *et al.* have used Ir-catalyzed transfer hydrogenation of quinoline **4a** and dihydroquinoline **40** to provide tetrahydroquinoline **5a** in high yields. Addition of acid (CF_3CO_2H or $HClO_4$) considerably accelerates the rate of the reaction whereas addition of water minimizes the formation of byproducts (**Scheme 11**).



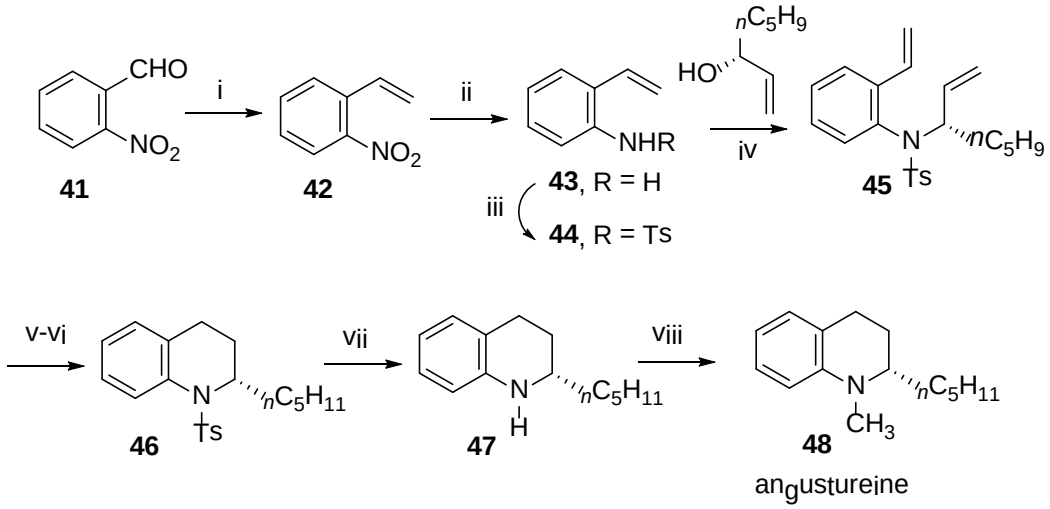
4a **40** **5a**

Scheme 11: (i) $[CpIrCl_2]_2$ (1mol %), aq. HClO4, 2-propanol, H_2O, reflux, 17 h.

Nishida's approach (2005)[22]

This approach utilized Ru-catalyzed ring closing metathesis (RCM) to construct dihydroquinoline core. Wittig olefination of *o*-nitrobenzaldehyde **41** gave nitrostyrene **42**, which was subjected to reduction of nitro group (Zn/AcOH) to give the corresponding *o*-aminostyrene **43**. Protection of amine in **43** as tosymide **44** (TsCl, Py, CH_2Cl_2), followed by Mitsunobu reaction with (*R*)-oct-1-en-3-ol (99% ee) [DEAD and PPh_3] provided the

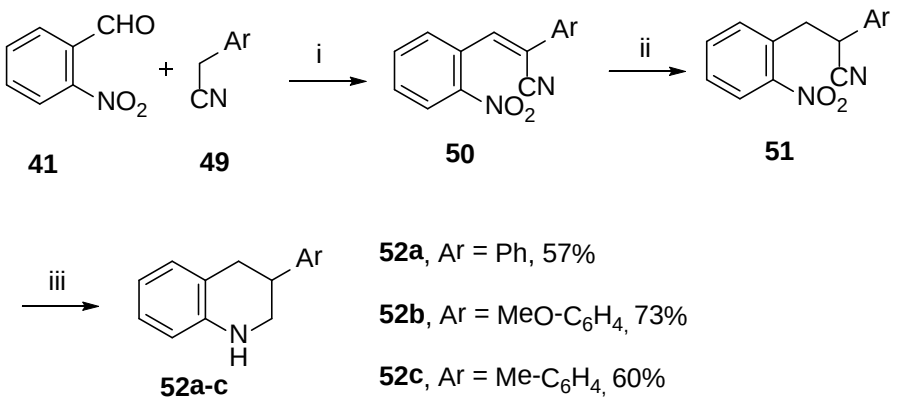
desired diene **45** in 78% yield. The diene **45** was subjected to ring closing metathesis (RCM) with Grubbs' II catalyst to give the corresponding 1,2-dihydroquinoline in 92% yield which was subsequently hydrogenated over Adam's catalyst in MeOH to provide tetrahydroquinoline **46** in 94% yield and 99.7% ee. Finally detosylation of **46** to free amine **47** and subsequent methylation of the free nitrogen gave (+)-(*S*)-angustureine **48** in 80% yield (**Scheme 12**).



Scheme 12: (i) Ph_3PMeBr, $KN(TMS)_2$, THF, 25 ºC, 1 h, 90%; (ii) Zn powder, AcOH, 25 ºC, overnight, 72%; (iii) TsCl, pyridine, CH_2Cl_2, 25 ºC, 1 h, 86%; (iv) DEAD, PPh_3, THF, 25 ºC, 2 h, 78%; (v) Grubbs II, CH_2Cl_2 (0.01 M), 50 ºC, 1 h, 92%; (vi) PtO_2, H_2, MeOH, 25 ºC, 12 h, 94%; (vii) anthracene sodium, DME, -65 ºC, 10 min, 99%; (viii) MeI, K_2CO_3, THF, reflux, 10 h, 80%.

Yang's approach (2006)[23]

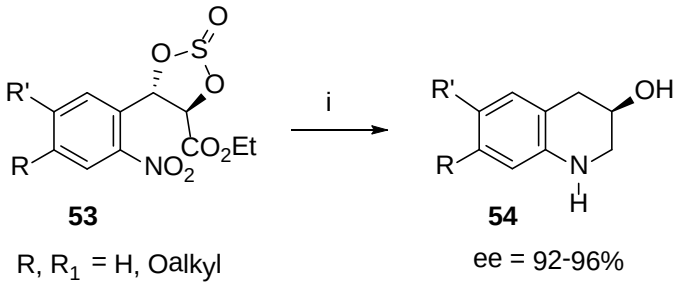
Yang *et al*. have reported reductive cyclization of **51** using H_2 over Pd/C to give 3-aryl tetrahydroquinoline **52a-c**. Condensation of 2-nitrobenzaldehyde **41** with aryl propionitrile **49** and subsequent reduction of double bond with $NaBH_4$ provided **50,** which was subjected to reduction with H_2 over 30% Pd/C followed by reductive cyclization with cyano group afforded 3-aryltetrahydroquinoline **52a-c** in 57-73% yields (**Scheme 13**).



Scheme 13: (i) Na, C_2H_5OH, 5 h; (ii) $NaBH_4$, THF, CH_3OH; (iii) H_2, 30% Pd/C, THF, CH_3OH.

Sudalai's approach (2009)[24]

Sudalai's approach describes a new method for the construction of chiral 3-substituted tetrahydroquinoline derivatives **54** based on asymmetric dihydroxylation and $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulfites **53** with $NaBH_4$ (**Scheme 14**).



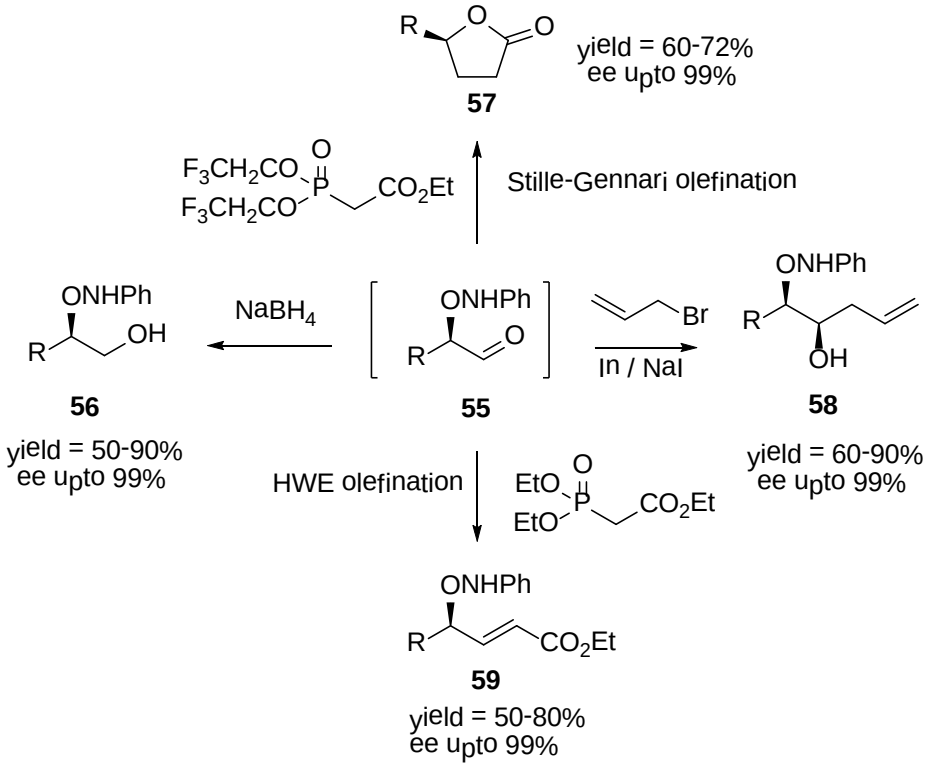
Scheme 14: (a) 1 mol% $CoCl_2$, $6H_2O$, $NaBH_4$, EtOH, 0-25 °C, 12 h.

3.1.3 Present Work

3.1.3.1 Objective

As can be seen only a few methods exist in the literature for the asymmetric synthesis of tetrahydroquinilin-3-ols, most of which are based on chiral pool resources. The use of expensive chiral reagents, lengthy reaction sequence, use of protection and deprotection of various functional groups along with low overall yield are some of the drawbacks of the existing routes. In this regard, an organocatalytic protocol that provides for the

efficient synthesis of chiral 3-substituted THQs is highly desirable. Proline catalyzed α-functionalization and its sequential reactions are arguably one of the most extensively studied and developed asymmetric catalytic reaction.[25,26] Yet the full synthetic potential of the use α-functionalized aldehydes that are readily available by this route in excellent enantioselectivity, remains to be further exploited. In proline-catalyzed direct α-aminooxylation of aldehydes, the reactive intermediate **55**, generated *in situ* can be transformed into several functionalized organic derivatives: for instance it can be reduced to 1,2-aminooxy alcohol **56**,[26f] cyclized to γ-butyrolactone **57** with Stille-Gennari olefination,[26i] it can also undergo diastereoselective In-mediated allylation to give diol **58**,[26m] or can be converted to γ-aminooxy α,β-unsaturated esters and ketones **59** (**Scheme 15**).[26n] In this connection, it is of interest to design experiments in trapping the intermediate **55** with other reagents.

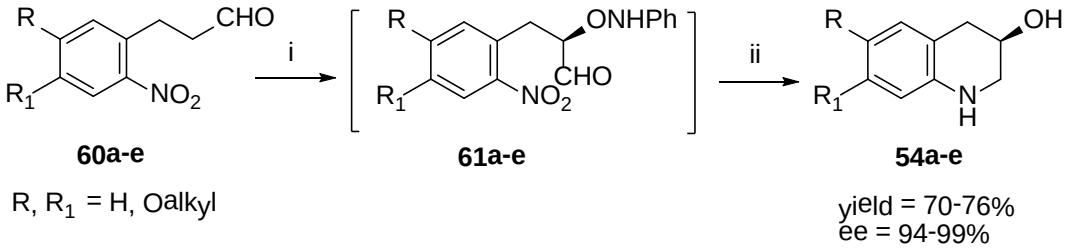


Scheme 15: Sequential trapping of α-aminooxy aldehyde **55**

In this section, we wish to disclose, for the first time, a sequential protocol involving α-aminooxylation of *o*-nitrohydrocinnamaldehydes and Pd-catalyzed intramolecular reductive cyclization that provides easy access to chiral 3-hydroxy THQs in high yields.

3.1.3.2 Results and Discussion

In continuation of our work on the utilization and application of enantiomerically-enriched α-functionalized aldehydes,[26i,27] we envisaged that sequential trapping of α-aminooxylated *o*-nitrohydrocinnamaldehydes **60a-e** with Pd-catalyzed reductive cyclization should provide enantiomerically pure 3-hydroxy THQs **54a-e** *via* the intermediate **61a-e** (**Scheme 16**).

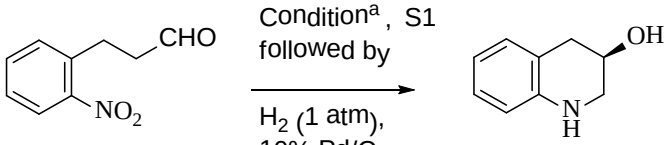


Scheme 16: (i) L-proline (20 mol%), PhNO (1 equiv), DMSO, 15 min; (ii) Pd/C, H_2 (1 atm), 25 ^oC, 6 h.

In a preliminary study, the α-aminooxylation reaction between *o*-nitrohydrocinnamaldehyde **60a** with nitrosobenzene as oxygen source was carried out in the presence of L-proline (20 mol%) in CH_3CN at -20 ^oC for 24 h to obtain α-aminooxy aldehydes **61a** *in situ*. Since these α-aminooxy aldehydes like **61a** are prone to racemization, it was immediately subjected to catalytic hydrogenation [10% Pd/C, (1 atm) H_2] by distilling out CH_3CN under reduced pressure and adding MeOH to it, which gave 3-hydroxy THQ **54a** in 62% yield with moderate enantioselectivity (82% ee). The low enantioselectivity could possibly be due to the racemization occurring during the removal of CH_3CN at slightly elevated temperature (45 ^oC). Optimizing the reaction

parameters, therefore, was essential in order to obtain high enantioselectivity. Thus, when a mixed solvent system of CH_3CN/MeOH (1:3) was used, **54a** was obtained in higher enantioselectivity (96% ee) with low yield (52%). In order to improve the yield, we performed several experiments to identify the most effective and suitable reaction conditions by conducting experiments in several solvent systems ($CHCl_3$, CH_2Cl_2 and THF). However, there was no significant improvement in yields observed in each case. Finally, the best result (71% yield, 96% ee, entry 7, **Table 1**) for **54a** was obtained when aminooxylation was carried out in DMSO and the intramolecular reductive cyclization done in MeOH in a sequential manner at ambient temperature. The results of the optimization study are summarized in **Table 1**.

Table 1: Optimization studies for L-proline-catalyzed α-aminooxylation/reductive cyclization of *o*-nitrohydrocinnamaldehyde (**60a**)



60a **54a**

Entry	S1	S2	Yield (%)[b]	ee (%)[c]
1	CH_3CN	MeOH	62	82
2[d]	CH_3CN	CH_3CN/MeOH	52	96
3[d]	CH_2Cl_2	CH_2Cl_2/MeOH	35	nd
4	CH_2Cl_2	MeOH	39	75
5	THF	MeOH	15	nd
6	$CHCl_3$	MeOH	30	nd
7[e]	DMSO	MeOH	71	96

[a] Condition: L-proline (20 mol%), *o*-nitrohydrocinnamaldehyde (5 mmol), PhNO (5 mmol), -20 °C, 24 h; [b] isolated yield after column chromatography; [c] ee determined by chiral HPLC analysis; [d] solvent ratio (1:3); [e] reaction was carried out at 25 °C for 15 min followed by ether extraction. S1 = solvent for α-aminooxylation, S2 = solvent for reductive cyclization.

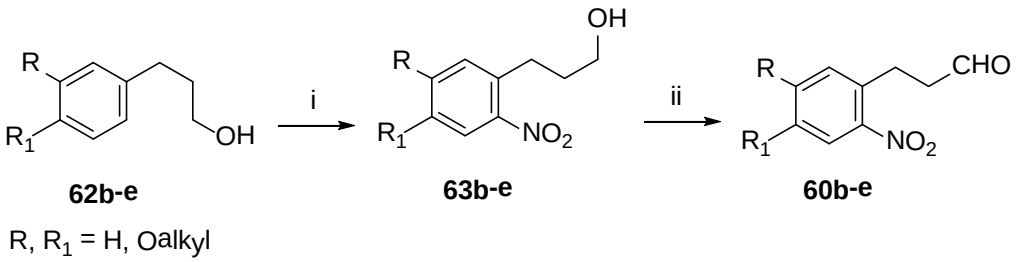
With the optimized condition, we then turned our attention to briefly investigate the scope of reaction by subjecting several *o*-nitrohydrocinnamaldehydes **60a-e** to sequential α-aminooxylation/reductive cyclization protocol. When subjected to L-proline catalyzed α-aminooxylation with 1 equiv of PhNO, several *o*-nitrohydrocinnamaldehydes **60a-e** gave the corresponding (*R*)-3-hydroxy THQ **54a-e** (70-76%) derivatives with excellent enantiomeric excess (94-99% ee). The results of such studies are presented in **Table 2**.

Table 2. L-proline-catalyzed sequential α-aminooxylation/reductive cyclization of *o*-nitrohydrocinnamaldehydes (**60a-e**)[a]

		products **(54a-e)**	
Entry	Substrates **(60a-e)**	Yield (%)[b]	ee (%)[c]
a	R = R_1 = H	71	96
b	R = R_1 = OMe	76	98
c	R, R_1 = -O-CH_2-O-	75	94
d	R = O-pentyl ; R_1 = OMe	72	96
e	R = OTBDPS ; R_1 = OMe	70	99

[a] L-Proline (20 mol%), *o*-nitro hydrocinnamaldehyde (5 mmol), nitroso benzene (5 mmol), DMSO (20 mL); ether extraction followed by H_2 (1 atm), 10% Pd/C (5 wt%), MeOH (20 mL); [b] isolated yieds of THQ-3-ol; [c] ee determined by chiral HPLC analysis.

o-Nitrohydrocinnamaldehydes **60b-e**, the starting materials were efficiently prepared from the corresponding hydrocinnamyl alcohols **62b-e** in two steps. Regiospecific aromatic nitration of **62b-e** with conc. HNO_3 gave nitro compounds **63b-e** in 80-95% yield (**Scheme 17**).



62b-e **63b-e** **60b-e**

R, R_1 = H, Oalkyl

Scheme 17: (i) HNO_3, CH_2Cl_2, 0 °C, 80-95%; (ii) PCC, CH_2Cl_2, 25 °C, 80-85%.

The formation of *o*-nitrohydrocinnamyl alcohols **63c** was confirmed from its ^{1}H NMR spectrum, which showed a triplet at δ 3.70 (J = 6.2 Hz, 2H) corresponding to methylene (-**CH$_2$**-OH) protons. Two singlets at δ 6.8 (1H) and 7.5 (1H) indicated the presence of aromatic protons. Its ^{13}C NMR spectrum showed signal at δ 102.7 indicative of the methylene carbon having dioxo linkage (-O-**CH$_2$**-O) (**Figure 2**).

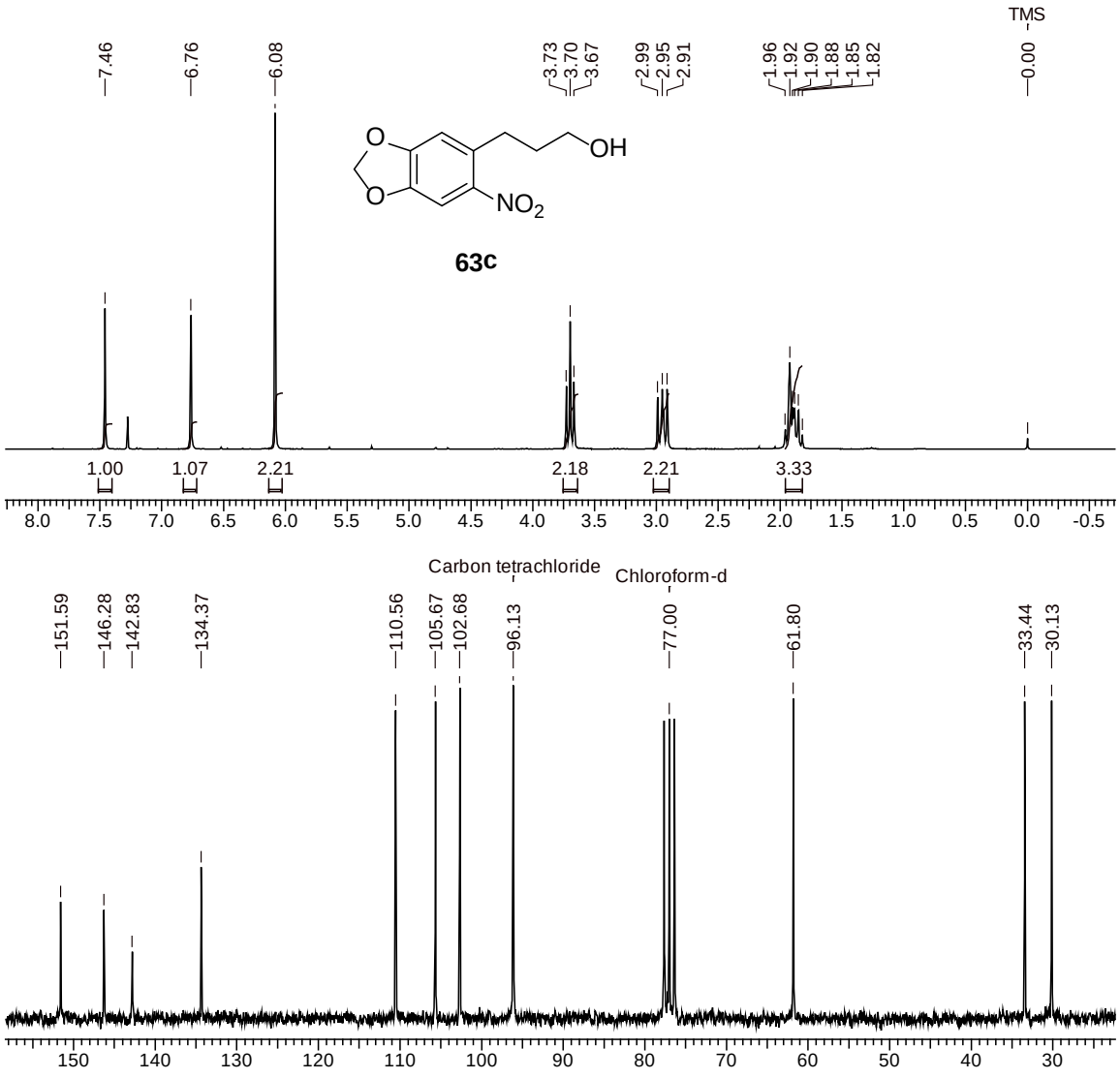


Figure 2: ^{1}H and ^{13}C NMR spectra of *o*-nitrohydrocinnamyl alcohols **63c**

Subsequent oxidation of nitro alcohols **63b-e** with PCC gave **60b-e** in 80-85% yield. The ^{1}H NMR spectrum of *o*-nitrohydrocinnamaldehyde **60c** showed a characteristic proton

signal at δ 9.82 for aldehydic proton. This was further evidenced by its ^{13}C NMR spectrum, which showed the appearance of carbon signal at δ 200.1 corresponding to aldehydic carbon (**Figure 3**).

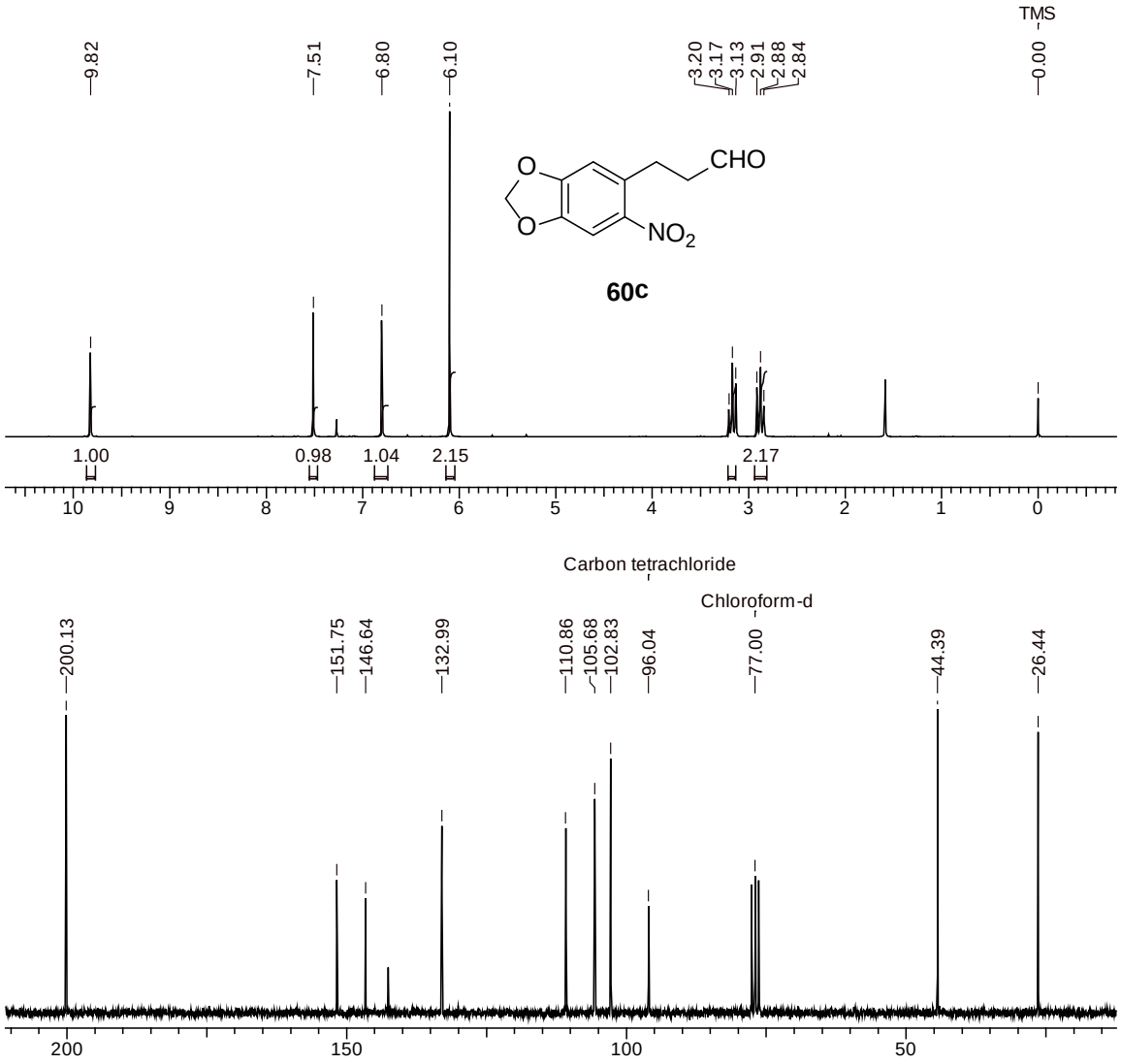
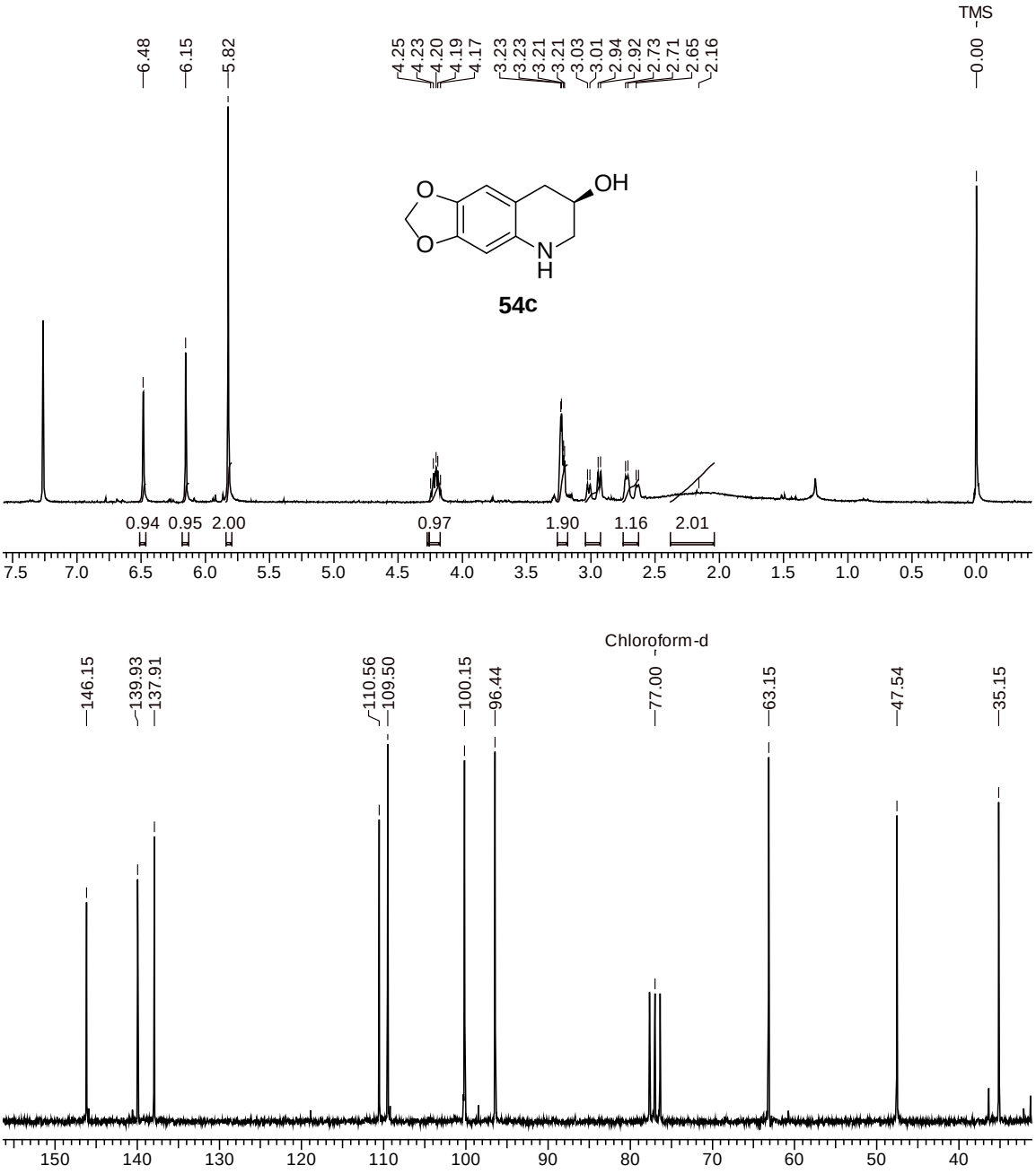
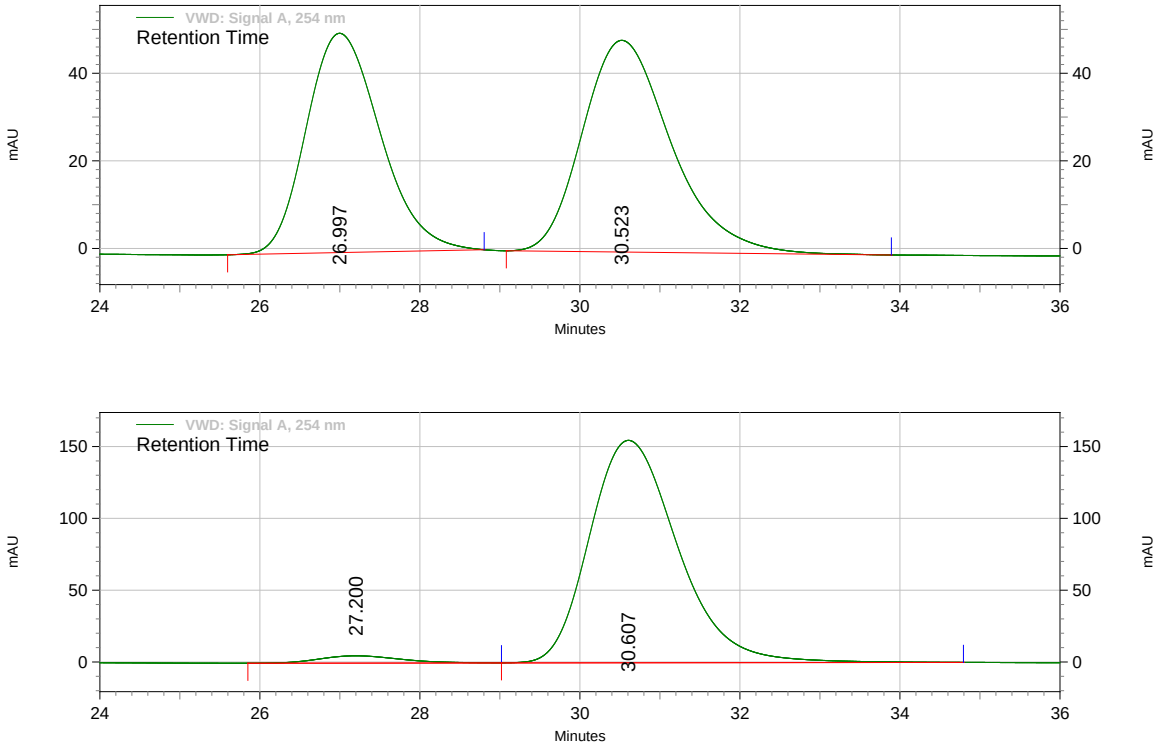


Figure 3: ^{1}H and ^{13}C NMR spectra of *o*-nitrohydrocinnamaldehyde **60c**

The formation of all intermediates along with the final products (THQs **54a-e**) was established unambiguously from their corresponding ^{1}H & ^{13}C NMR, IR and HRMS spectral data. Their optical purity was established from their chiral HPLC analyses. **Example 1:** The ^{1}H NMR spectrum of THQ **54c** showed a multiplet at δ 4.17-4.25

corresponding to methine (-**CH**-OH) proton, while the multiplet at δ 3.21-3.23 indicated the presence of methylene (-**CH_2**-NH-) protons. The ^{13}C NMR spectrum of **54c** showed typical signals at δ 100.1, 109.5, 110.6, 137.9, 139.9 and 146.1 corresponding to aromatic carbons, while the carbon signals at δ 63.1 and 96.4 were indicative of methine (-**CH**-OH) and methylene (-O-**CH_2**-O) carbons respectively (**Figure 4**).

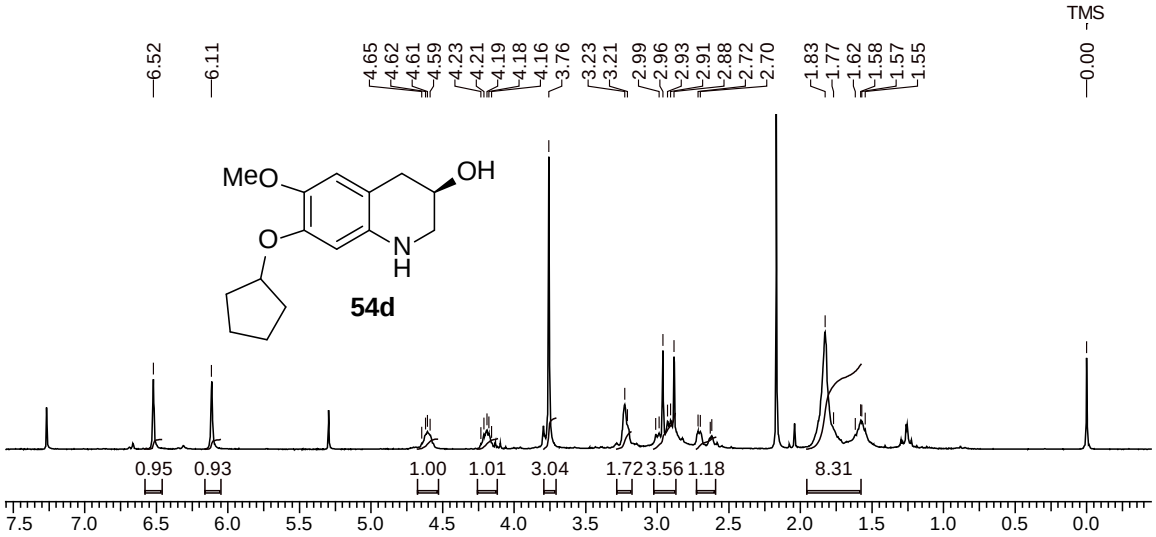


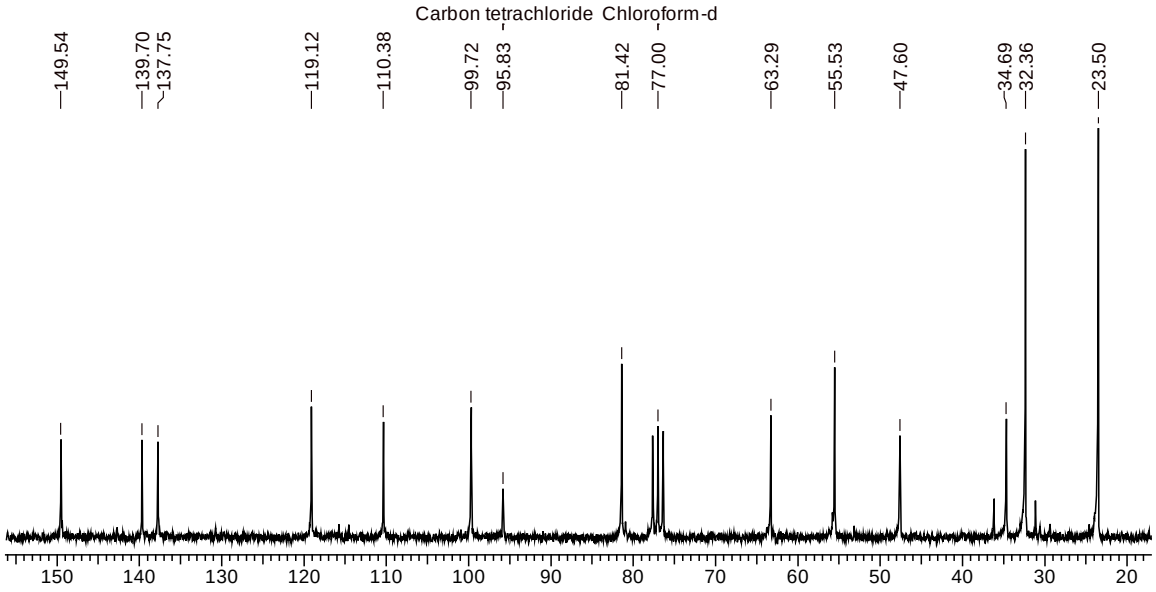


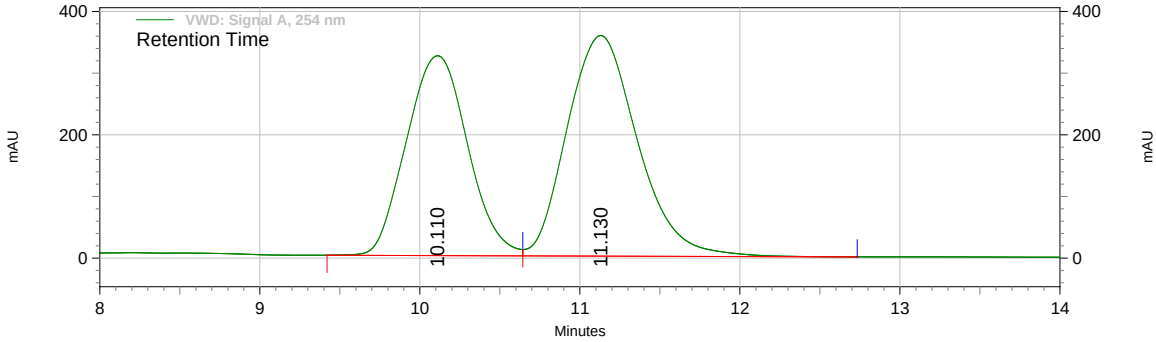
Retention Time	Area	Area %	Height	Height %
27.200	6026001	2.94	85701	3.19
30.607	198857225	97.06	2598245	96.81
Totals	204883226	100.00	2683946	100.00

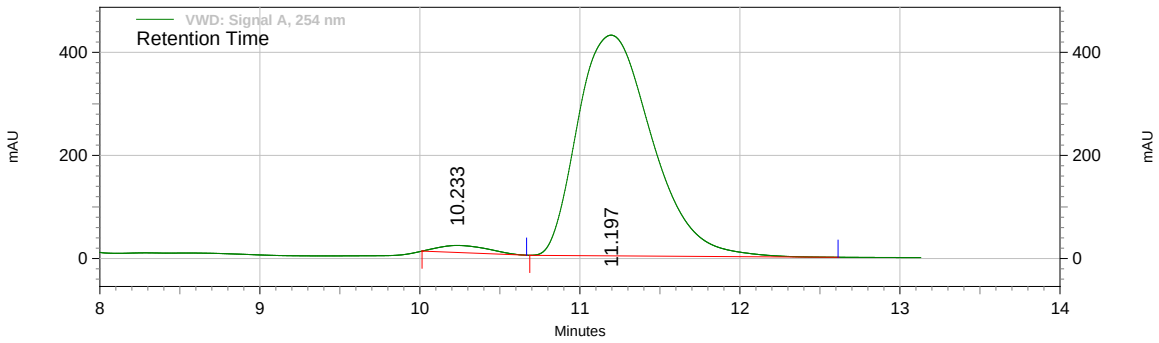
Figure 4: ^{1}H & ^{13}C NMR spectra and HPLC chromatogram of THQ **54c**

Example 2: The formation of THQ **54c** was confirmed by its ^{1}H NMR spectrum which showed a multiplet at δ 4.16-4.23 and 4.59-4.65 corresponding to methine (-**CH**-O-) proton, while a multiplet at δ 3.21-3.23 indicated the presence of methylene (-**CH$_2$**-NH-) protons. The multiplets at δ 1.55-1.83 were due to methylene protons of cyclopentyl group. The ^{13}C NMR spectrum of **54c** showed resonance signals at δ 99.7, 110.4, 119.1, 137.7, 139.7 and 149.5 corresponding to aromatic carbons, while the carbon signals at δ 63.3 and 81.4 were indicative of methine carbons (-**CH**-OH) and (-**CH**-O) respectively (**Figure 5**).


TMS
6.52
6.11
4.65
4.62
4.61
4.59
4.23
4.21
4.19
4.18
4.16
3.76
3.23
3.21
2.99
2.96
2.93
2.91
2.88
2.72
2.70
1.83
1.77
1.62
1.58
1.57
1.55
0.00
MeO
O
OH
N
H
54d
0.95
0.93
1.00
1.01
3.04
1.72
3.56
1.18
8.31


Carbon tetrachloride
Chloroform-d
149.54
139.70
137.75
119.12
110.38
99.72
95.83
81.42
77.00
63.29
55.53
47.60
34.69
32.36
23.50


VWD: Signal A, 254 nm
Retention Time
mAU
10.110
11.130
Minutes



Retention Time	Area	Area %	Height	Height %
10.233	4980694	2.10	229461	3.10
11.197	231657212	97.90	7181886	96.90
Totals	236637906	100.00	7411347	100.00

Figure 5: ^{1}H & ^{13}C NMR spectra and HPLC chromatogram of THQ **54c**

3.1.4 Conclusion

In conclusion, we have developed a new sequential strategy for the construction of chiral 3-substituted THQs in high yields. Although two different catalysts were used for the reaction, the operation is convenient to carry out under milder conditions with a sequential operation and the enantioselectivity is excellent. We believe that this strategy will find applications in the synthesis of optically pure terahydroquinoline-3-ols owing to the flexible nature of synthesis of substituted *o*-nitrohydrocinnamaldehydes and the ready availability of both enantiomers of proline.

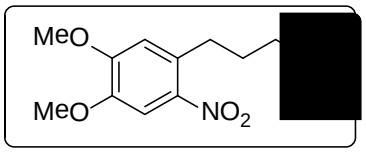
3.1.5 Experimental Section:

A general experimental procedure for the preparation of *o*-nitrohydrocinnamyl alcohol (63b-e)

To a stirred solution of alcohol **62b-e** (10 mmol) in CH_2Cl_2 (40 mL), conc. HNO_3 (2 mL, *d* =1.4) was added dropwise at 0 °C. Reaction mixture was stirred for 30 min and the progress of reaction was monitored by TLC. After completion of reaction, 50 mL of

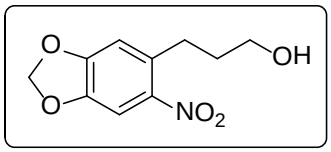
water was added. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and then passed through a thick pad of silica gel (230-400 mesh) with CH_2Cl_2 as eluent. The organic layer was concentrated under reduced pressure to give **63b-e** in pure form.

3-(4,5-Dimethoxy-2-nitrophenyl)propan-1-ol (63b)



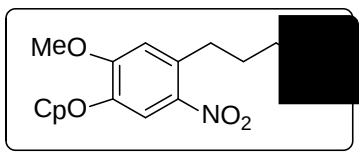
Yield: 95% (2.3 g); gum, **IR** ($CHCl_3$): υ_{max} 745, 945, 1120, 1378, 3412 cm^{-1}; ^1H **NMR** (200 MHz, $CDCl_3$): 1.87-1.95 (m, 2H), 2.97-3.05 (m, 2H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 6.74 (s, 1H), 7.57 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.1, 33.5, 56.2, 61.9, 108.2, 113.4, 132.4, 141.2, 147.2, 153.0; **Anal.** Calcd for $C_{11}H_{15}NO_5$ requires C, 54.77; H, 6.27; N, 5.81; found C, 54.86; H, 6.33; N, 5.87%.

3-(6-Nitrobenzo[1,3]dioxol-5-yl)propan-1-ol (63c)



Yield: 93% (2.1 g); gum, **IR** ($CHCl_3$): υ_{max} 857, 968, 1060, 1460, 3498 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.82-1.96 (m, 3H), 2.91-2.99 (m, 2H), 3.73 (t, *J* = 6.2 Hz, 2H), 6.08 (s, 2H), 6.76 (s, 1H), 7.46 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.1, 33.4, 61.8, 102.7, 105.7, 110.6, 134.4, 142.8, 146.3, 151.6; **Anal.** Calcd for $C_{10}H_{11}NO_5$ requires C, 53.33; H, 4.92; N, 6.22; found C, 53.43; H, 4.98; N, 6.27%.

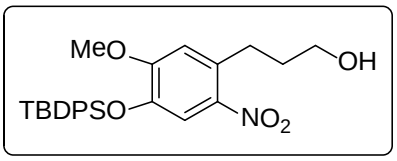
3-(4-(Cyclopentyloxy)-5-methoxy-2-nitrophenyl)propan-1-ol (63d)



Yield: 87% (2.6 g); gum, **IR** ($CHCl_3$): υ_{max} 754, 1129, 1324, 1460, 3467 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.58 (br s, 1H), 1.82-2.03 (m, 10H), 3.01 (t, *J* = 7.5 Hz, 2H), 3.72 (t, *J* =

6.0 Hz, 2H), 3.92 (s, 3H), 4.78-4.82 (m, 1H), 6.71 (s, 1H), 7.56 (s, 1H); **^{13}C NMR** (50 MHz $CDCl_3$): 23.9, 30.0, 32.5, 33.3, 56.0, 61.7, 80.6, 110.7, 113.5, 131.9, 140.8, 145.6, 153.8; **Anal.** Calcd for $C_{15}H_{21}NO_5$ requires C, 61.00; H, 7.17; N, 4.74; found C, 61.08; H, 7.23; N, 4.75%.

3-(4-(*tert*-Butyldiphenylsilyloxy) - 5 -methoxy-2-nitrophenyl) propan-1-ol (63e)

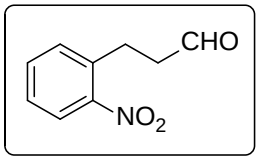


Yield: 80% (3.7g); gum, **IR** ($CHCl_3$): υ_{max} 907, 1172, 1068, 1531, 3367 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.13 (s, 9H), 1.31(br s, 1H), 1.61-1.71 (m, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 3.54 (s, 3H), 3.65 (t, *J* = 6.1 Hz, 2H), 6.55 (s, 1H), 7.34-7.44 (m, 8H), 7.64-7.69 (m, 4H); **^{13}C NMR** (50 MHz $CDCl_3$): δ 19.9, 26.7, 30.1, 33.5, 55.3, 62.0, 113.7, 117.2, 127.7, 130.0, 132.5, 132.8, 135.3, 141.1, 143.2, 154.6 ; **Anal.** Calcd for $C_{26}H_{31}NO_5Si$ requires C, 67.07; H, 6.71; N, 3.01; found C, 67.12; H, 6.73; N, 3.09%.

A general experimental procedure for the oxidation of alcohols (60b-e)

To a stirred solution of alcohol **63a-e** (5 mmol) in dry CH_2Cl_2 (10 mL), PCC (10 mmol) was added slowly at 25 °C. It was then stirred for further 6 h. After completion of the reaction (monitored by TLC), it was passed through a short pad of silica gel (230-400 mesh) using CH_2Cl_2 as eluent. The combined organic layers were concentrated under reduced pressure to give the aldehyde **60a-e** which was pure enough to be used in the next step.

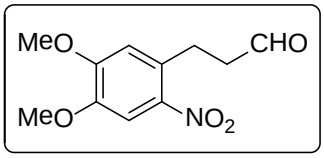
3-(2-Nitrophenyl)propanal (60a)



Yield: 85% (761 mg); gum; **IR** ($CHCl_3$): υ_{max} 765, 1166, 1225, 1235, 1454, 1712, 2989, 3123; **NMR** (200 MHz, $CDCl_3$): δ 2.89 (t, *J* = 7.3 Hz, 2H), 3.20 (t, *J* = 7.3 Hz, 2H), 7.28-7.59 (m, 3H), 7.92

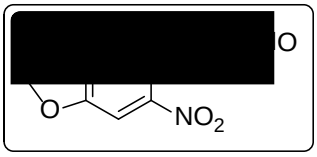
(d, *J* = 7.9, 1H), 9.82 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 25.6, 44.4, 124.9, 127.5, 132.3, 133.1, 135.7, 199.9; **Anal.** Calcd for $C_9H_9NO_3$ requires: C, 60.33; H, 5.06; N, 7.82; found: C, 60.45; H, 5.13; N, 7.91%.

3-(4,5-Dimethoxy-2-nitrophenyl)propanal (60b)



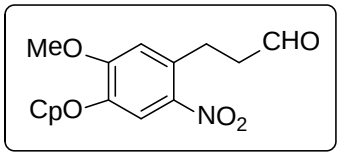
Yield: 85% (1.07 g); gum; **IR** ($CHCl_3$): υ_{max} 1155, 1215, 1278, 1371, 1720, 2935, 2983 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.91 (t, *J* = 7.1 Hz, 2H), 3.23 (t, *J* = 7.3 Hz, 2H), 3.94 (s, 3H), 3.97 (s, 3H), 6.82 (s, 2H), 7.61 (s, 1H), 9.83 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.4, 44.4, 56.2, 108.1, 113.8, 131.0, 140.8, 147.4, 153.1, 200.4; **Anal.** Calcd for $C_{11}H_{13}NO_5$ requires: C, 55.23; H, 5.48; N, 5.86; found: C, 55.29; H, 5.57; N, 5.90%.

3-(6-Nitrobenzo[d][1,3]dioxol-5-yl)propanal (60c)



Yield: 85% (948 mg); gum; **IR** ($CHCl_3$): υ_{max} 1253, 1348, 1496, 1608, 1718, 2987 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.84 (t, *J* = 7.2 Hz, 1H), 3.17 (t, *J* = 7.0 Hz, 1H), 6.10 (s, 2H), 6.80 (s, 1H), 7.51 (s, 1H), 9.82 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.4, 44.4, 102.8, 105.7, 110.7, 133.0, 146.6, 151.7, 200.1; **Anal.** Calcd for $C_{10}H_9NO_5$ requires: C, 53.82; H, 4.06; N, 6.28; found: C, 53.72; H, 3.93; N, 6.21%.

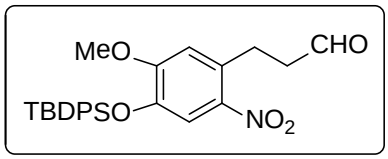
3-(4-(Cyclopentyloxy)-5-methoxy-2-nitrophenyl)propanal (60d)



Yield: 82% (1.20 g); gum; **IR** ($CHCl_3$): υ_{max} 1233, 1312, 1608, 1718, 2913, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, CDCl3): 1.64-2.02 (m, 8H), 2.90 (t, *J* = 6.9 Hz, 2H), 3.21 (t, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 4.76-4.84 (m, 1H), 6.78 (s, 1H), 7.59 (s, 1H), 9.83 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.9, 26.3, 32.5, 44.4, 56.0, 80.6, 110.6, 113.9, 127.2, 130.0, 130.4,

137.2, 140.6, 145.9, 153.9, 200.2; **Anal.** Calcd for $C_{15}H_{19}NO_5$ requires: C, 61.42; H, 6.53; N, 4.78; found: C, 61.46; H, 6.48; N, 4.87%.

3-(4-(*tert*-Butyl diphenyl silyloxy)-5-methoxy- 2 - nitrophenyl) propanal (60e)



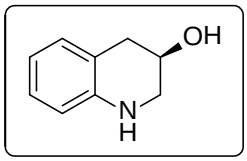
Yield: 80% (1.85 g); gum; **IR** ($CHCl_3$): **IR** ($CHCl_3$): υ_{max} 1155, 1215, 1357, 1718, 2984 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (s, 9H), 2.82 (t, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 3.56 (s, 3H), 6.61 (s, 1H), 7.34-7.39 (m, 8H), 7.64-7.68 (m, 4H), 9.78 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.8, 26.5, 26.7, 44.6, 55.4, 114.2, 117.2, 127.7, 130.0, 131.4, 132.6, 135.3, 143.5, 154.8, 200.6; **Anal.** Calcd for $C_{26}H_{29}NO_5Si$ requires: C, 67.36; H, 6.31; N, 3.02; found: C, 67.43; H, 6.41; N, 3.09%.

A general experimental procedure for the preparation of (*R*)-1,2,3,4-tetrahydro-6,7-dialkyloxyquinolin-3-ol (54a-e)

To the stirred solution of *o*-nitrohydrocinnamaldehyde **60a-e** (6 mmol) and PhNO (6 mmol) in DMSO (20 mL), L-proline (20 mol%) was added at 25 ºC and allowed to stir for 20 min. After completion of reaction, as indicated by the change in color from green to yellow, large excess (200 mL) of diethyl ether was poured into the reaction mixture and stirred for additional 10 min. The combined organic mixture was washed with H_2O (5 x 20 mL). The organic layer was separated and aqueous layer was extracted with diethyl ether (2 x 50 mL). Combined organic layers were washed with brine (5 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude α-aminooxylated aldehyde **61a-e** was dissolved in MeOH (20 mL) and to this mixture 10% Pd/C (5 wt%) was added. The reaction mixture was then stirred at 25 ^oC for additional 6 h. After the completion of reaction (monitored by TLC), it was

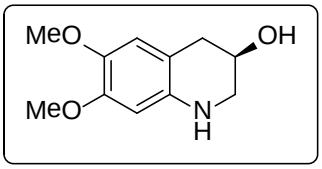
filtered through celite (MeOH eluent) and the solvent evaporated under reduced pressure. Chromatographic purification of the crude product [flash silica gel (230-400 mesh) and petroleum ether:EtOAc:Et_3N (60:38:2)] gave the pure (*R*)-tetrahydroquinolin-3-ol derivatives **54a-e**.

(*R*)-1,2,3,4-Tetrahydroquinolin-3-ol (54a)



Yield: 71% (635 mg); Gum; $[\alpha]^{D}_{25}$ +12.3 (*c* 1, $CHCl_3$); Optical purity 96% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropylalcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5mg/mL, injection vol.: 10uL, retention time: 30.073 min (-)-isomer, 33.890 min (+)-isomer; **IR** ($CHCl_3$): υ_{max} 753, 1312, 1500, 1604, 3370, 3413 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.35 (br s, 1H), 2.76 (dd, *J* = 3.7, 16.5 Hz, 1H), 3.01 (dd, *J* = 4.3, 16.9 Hz, 1H), 3.26-3.38 (m, 2H), 4.21-4.29 (m, 1H), 6.53 (d, *J* = 9.0 Hz, 1H), 6.65 (dt, *J* = 1.1, 7.5 Hz, 1H), 6.97-7.05 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.3, 47.5, 63.2, 114.1, 117.9, 118.7, 126.9, 130.4, 143.5; **ESIMS** (*m*/*z*) 150 $[M+H]^+$; **HRMS** (ESI) calcd for $C_9H_{11}NO$ $[M+H]^+$ 150.0919; found 150.0910.

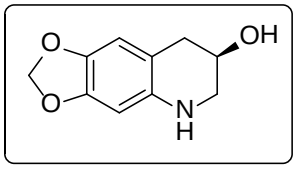
(*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxyquinolin-3-ol (54b)



Yield: 76% (954 mg); Gum; $[\alpha]^{D}_{25}$ +27.1 (*c* 1.26, $CHCl_3$); Optical purity 98% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropylalcohol/n-hexane (20/80), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5mg/mL, injection vol.: 10uL, retention time: 34.543 min (-)-isomer, 40.990 min (+)-isomer; **IR** ($CHCl_3$): υ_{max} 756, 1217, 1464, 1519, 3456 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.71 (dd, *J* = 3.9,

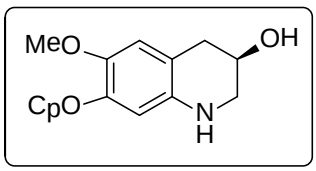
16.5 Hz, 1H), 2.85-3.00 (m, 1H), 3.19-3.22 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 4.15-4.23 (m, 1H), 6.12 (s, 1H), 6.50 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.7, 47.6, 55.6, 56.4, 63.3, 99.8, 110.5, 114.2, 136.7, 142.2, 148.0; **ESIMS** (*m*/*z*) 210 $[M+H]^+$; **HRMS** (ESI) calcd for $C_{11}H_{15}NO_3$ $[M+H]^+$ 210.1130; found 210.1108.

(*R*)-5,6,7,8-Tetrahydro-[1,3]dioxolo[4,5-*g*]quinolin-7-ol (54c)



Yield: 75% (869 mg); Gum; $[\alpha]^{D}_{25}$ +28.2 (*c* 1, $CHCl_3$); Optical purity 94% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropylalcohol/ n-hexane (20/80), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5mg/mL, injection vol.: 10uL, retention time: 27.200 min (-)-isomer, 30.607 min (+)-isomer; **IR** ($CHCl_3$): υ_{max} 1037, 1215, 1484, 2853, 2924, 3355 cm^{-1}; **^{1}H NMR (**200 MHz, $CDCl_3$): δ 2.16 (br s, 2H), 2.65(dd, *J* = 3.5, 16.7 Hz, 1H), 2.92 (dd, *J* = 4.2, 16.7 Hz, 1H), 3.21-3.23 (m, 2H), 4.17-4.25 (m, 1H), 5.82 (s, 2H), 6.15 (s, 1H), 6.48 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.1, 47.5, 63.1, 96.4, 100.1, 109.5, 110.6, 137.9, 139.9, 146.1; **ESIMS** (*m*/*z*) 194 $[M+H]^+$; **Anal.** Calcd for $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25; found C, 62.11; H, 5.81; N, 7.30%.

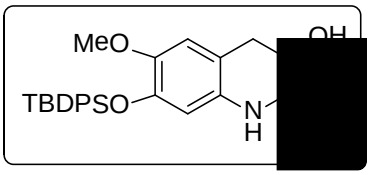
(*R*)-7-(Cyclopentyloxy)- 6-methoxy-1,2,3,4-tetrahydroquinolin-3-ol (54d)



Yield: 72% (1.14g); Gum; $[\alpha]^{D}_{25}$ +25.7 (*c* 1, $CHCl_3$); Optical purity 96% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropylalcohol/ n-hexane (50/50), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5mg/mL, injection vol.: 10uL, retention time: 10.233 min (-)-isomer, 11.197 min (+)-isomer; **IR** ($CHCl_3$): υ_{max}

769, 1217, 1456, 1504, 2927, 3402 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.55-1.83 (m, 8H), 2.72 (dd, *J* = 3.5, 16.5 Hz, 1H), 2.91-2.99 (m, 3H), 3.21-3.23 (m, 2H), 3.76 (s, 3H), 4.16-4.23 (m, 1H), 4.59-4.65 (m, 1H), 6.11 (s, 1H), 6.52 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.5, 32.4, 34.7, 47.6, 55.5, 63.3, 81.4, 99.7, 110.4, 119.1, 137.7, 139.7, 149.5; **ESIMS** (*m*/*z*) 264 $[M+H]^+$; **Anal.** Calcd for $C_{15}H_{21}NO_3$ requires: C, 68.42; H, 8.04; N, 5.32; found: C, 68.38; H, 8.10; N, 5.39%.

(*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-methoxy-1,2,3,4-tetrahydroquinolin-3-ol (54e)



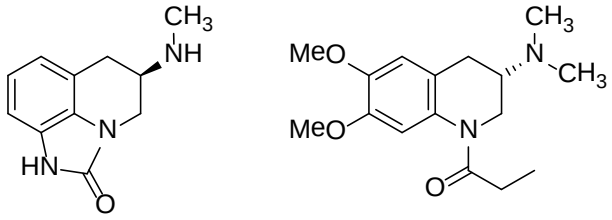
Yield: 70% (1.82 g); Gum; $[\alpha]^D_{25}$ +21.3 (*c* 1, $CHCl_3$); Optical purity 99% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropylalcohol/ n-hexane (2.5/97.5), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5mg/mL, injection vol.: 10uL, retention time: 17.103 min (-)-isomer, 19.443 min (+)-isomer; **IR** ($CHCl_3$): υ_{max} 758, 1226, 1517, 2856, 2929, 3392 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 2.59 (dd, *J* = 3.9, 14.5 Hz, 1H), 2.86 (dd, *J* = 3.7, 14.3 Hz, 1H), 3.03-3.51 (m, 2H), 3.51 (s, 3H), 4.08-4.16 (m, 1H), 5.90 (s, 1H), 6.42 (s, 1H), 7.31-7.39 (m, 6H), 7.69-7.73 (m, 4 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.8, 26.7, 29.7, 35.1, 47.6, 56.7, 63.5, 107.0, 116.0, 127.5, 129.6, 133.7, 135.4, 137.3, 143.7, 144.5; **ESIMS** (*m*/*z*) 434 $[M+H]^+$; **Anal.** Calcd for $C_{26}H_{31}NO_3Si$ requires C, 72.02; H, 7.21; N, 3.23; found C, 72.09; H, 7.18; N, 3.27%.

Section II

Asymmetric synthesis of (-)-Sumanirole (PNU-95666E) and 1-[(*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl] propanone [(*S*)-903]

3.2.1 Introduction and Pharmacology

Parkinson's disease, a neurodegenetive disease characterized by deteriorating motor function, is brought about by the loss of cells in the brain responsible for synthesizing the neurotransmitter dopamine.[28] Sumanirole **1** (PNU-95666E) (**Figure 6**) is a potent dopamine receptor agonist with high *in vitro* and *in vivo* selectivity for the D2 receptor subtype and possesses potential as a treatment for Parkinson's disease with greatly diminished side-effect liability. It has greater than 200-fold selectivity for the D2 receptor subtype versus the other dopamine receptor subtypes in radioligand binding assays and thus shows better efficiency for the treatment of Parkinson's disease in the early stages.[3]



1 **2**

Figure 6: Structures of (-)-sumanirole (**1**) and (*S*)-903 (**2**)

Although excellent diuretics and ACE inhibitors are available for the treatment of congestive heart failures, the only current approach that relies on the stimulation of cardiac contractility is the use of cardiac glycosides with a variety of therapeutic limitations. 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propa –none **2 [**(*S*)-903] have recently been identified as potentially interesting positive

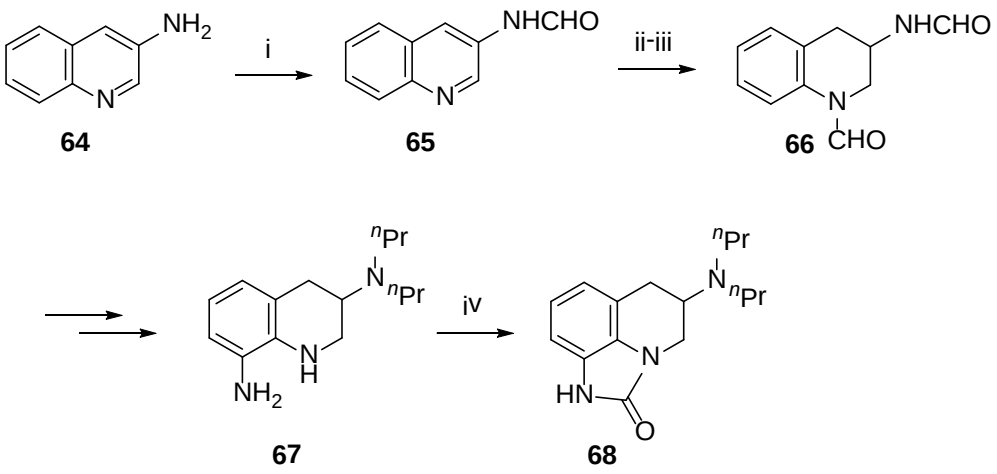
inotropic agents.[4]

3.2.2 Review of literature

Literature search has revealed that there are only few reports available for the synthesis of Sumanirole **1** and 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propanone **2 [**(*S*)-903] which are described below.

Moon's approach (1992)[29]

The synthesis by Moon *et al.* commenced from 3-amino quinoline **64**; its *N*-formylation gave amide **65**. Catalytic hydrogenation (PtO_2) of 3-amidoquinoline **65** followed by its amine protection provided diamidotetrahydroquinoline **66**. Amine **67** from **66** was converted to sumanirole derivative **68** by its treatment with 1,1'-carbonyldiimidazole, which provided racemic **68** in 83% yield (**Scheme 18**).

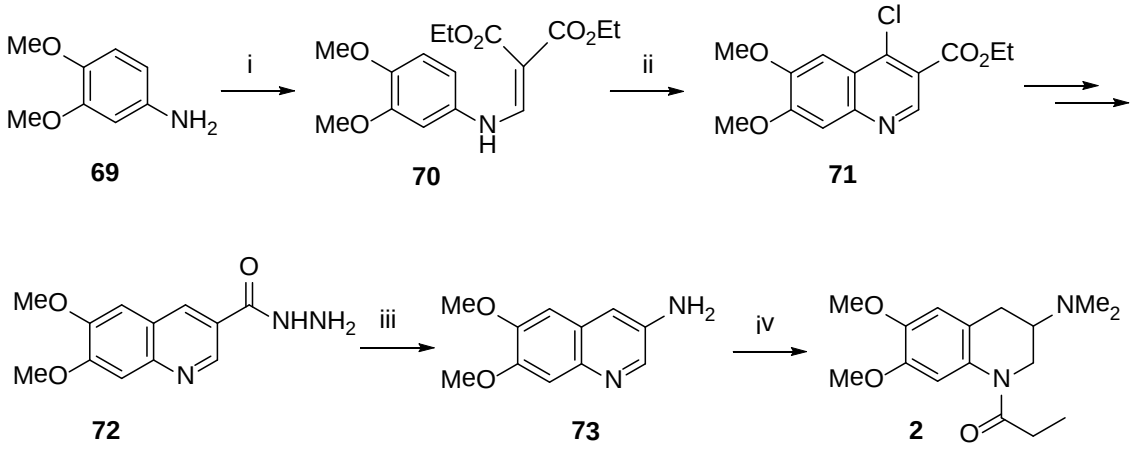


Scheme 18: (i) HCO_2H, Ac_2O, THF, 0 °C, 15 min, 84%; (ii) PtO_2 (10 mol%), H_2 (50 lb), AcOH, 25 °C, 3 h, 69%; (iii) HCO_2H, Ac_2O, THF, 0 °C, 15min, 84%; (iv) 1,1'- carbonyldiimidazole, DMF, 100 °C, 1 h, 83%.

Vecchietti's approach (1994)[30]

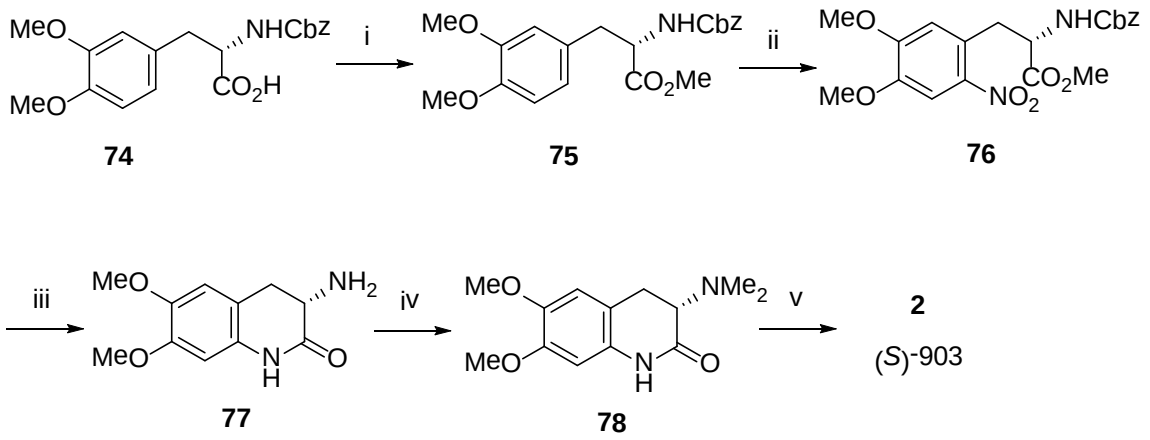
Vecchietti *et al.* have reported racemic synthesis of **2** (*S*)-903 starting from aniline **69**. Diethyl 2-[(3,4-dimethoxyphenylamino)methylene]malonate **70,** obtained by the condensation of ethoxymethylene malonate with 3,4-dimethoxyaniline **69**, was cyclized

($POCl_3$ and DMF) to give chloro tetrahydroquinoline derivative **71**. Hydrazine amide **72** obtained from **71** was converted to **73** *via* Curtius rearrangement. Subsequently, reductive amination of **73** (HCHO and HCO_2H) followed by catalytic hydrogenation (10%Pd/C, H_2 and AcOH) and acylation (propionyl chloride, CH_2Cl_2) furnished amide **2** (**Scheme 19**).



Scheme 19: (i) $C_2H_5OCH{=}C(COOC_2H_5)_2$, heat; (ii) $POCl_3/PCl_5$; (iii) $NaNO_2$; (iv) (a) $HCHO/HCO_2H$; (b) H_2, 10% Pd/C, acetic acid, 80%; (c) propionyl chloride, Et_3N, CH_2Cl_2

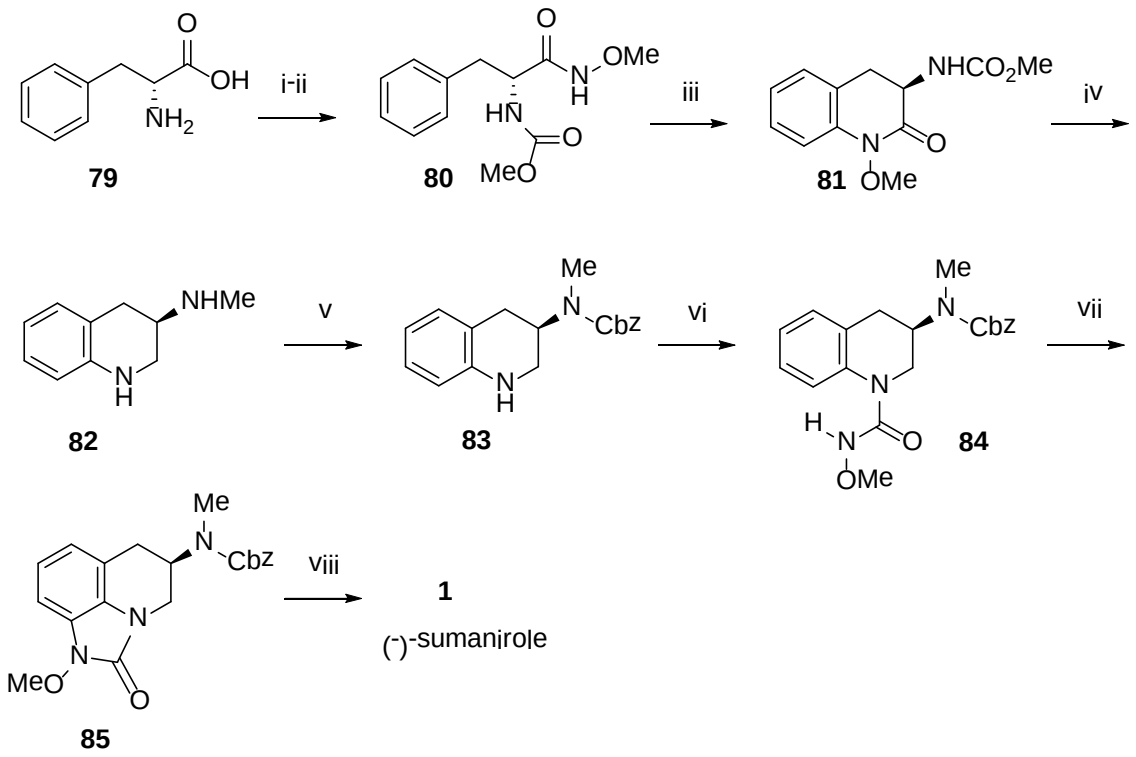
In another approach, the same authors have described the asymmetric synthesis of **2** (*S*)-903 starting from chiral pool resources. *N*-Cbz protected L–DOPA derivative **74** was esterified to give methyl ester **75,** which was regioselectively nitrated (conc. HNO_3, AcOH) to give nitro derivative **76**. Nitro ester **76** was reduced [10% Pd/C, H_2 (4 atm) and AcOH] to give (*S*)-3-amino-3,4-dihydro-6,7-dimethoxyquinolin-2(1*H*)-one **77,** which on reductive amination (10% Pd/C, HCHO and MeOH) gave *N, N*-dimethylamino quinolin-2-one **78.** Finally, Compound **78** was then converted to **2** *via* a known sequence of reactions which include: (i) $LiAlH_4$ mediated reduction and; (ii) protection of amine functionality with propionyl chloride and Et_3N (**Scheme 20**).



Scheme 20: (i) CH_3I, K_2,CO_3, acetone, 60 °C, 6 h, 73%; (ii) HNO_3, CH_3CO_2H, 15 °C, 3 h 76%; (iii) 10% Pd/C, H_2 (4 atm), CH_3CO_2H, 91%; (iv) 10% Pd/C, HCHO, 2N HCl, Et_2O, 40-50 °C, 90%; (v) (a) $LiAlH_4$, DME, reflux, 24 h, 28%; (b) propionyl chloride, Et_3N, CH_2Cl_2.

Romero's approach (1997)[31]

Romero *et al.* have reported the synthesis of (-)-sumanirole **1** by making use of D-phenylalanine **79** as chiral starting material. Protection of amine as its carbamate in **79** followed by amidation of acid moiety provided **80** in 61% yield. Bis(trifluoroacetoxy)iodobenzene/TFA mediated oxidative cyclization of **80** afforded lactam **81** in 85% yield. $BH_3{\cdot}SMe_2$ reduction of lactam **81** gave 3-methylamino-tetrahydroquinoline **82,** which was then subjected to selective protection of methyl amine to its benzyl carbamate **83** in 65% yield. Free amine group in **83** was converted to methoxyamine urea derivative **84** ($COCl_2$, Et_3N, $MeONH_2$ in THF). The subsequent oxidative cyclization of **84** provided benzo-fused urea **85** in 78% yields. Finally, deprotection of benzyl carbamate and simultaneous hydrogenolysis of N-OMe [H_2 (50 psig), 20% $Pd(OH)_2$] gave (-)-sumanirole **1** in 84% (**Scheme 21**).

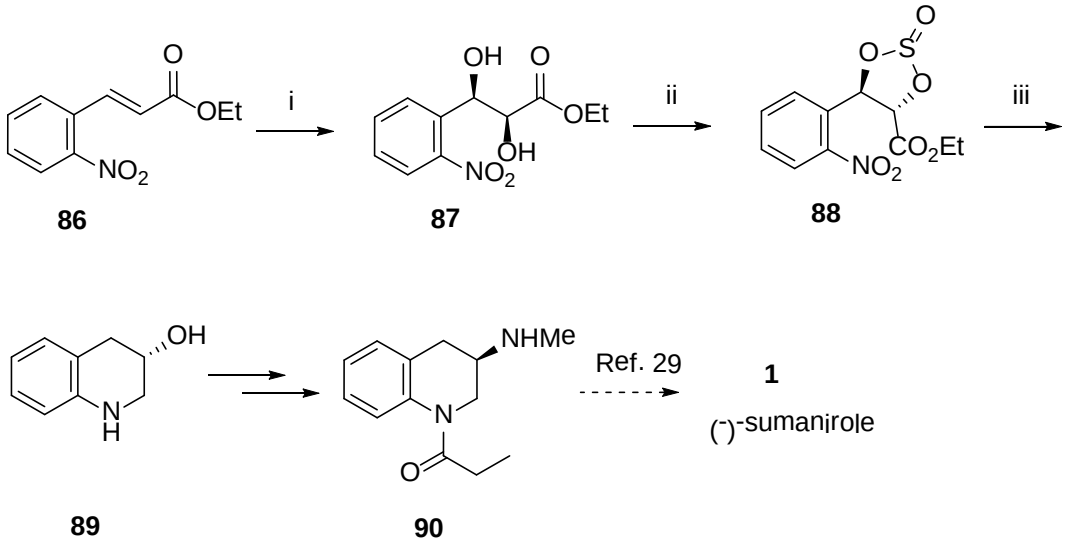


Scheme 21: (i) $ClCO_2OMe$, aq. NaOH, THF, -15-25 °C, 2 h; (ii) NH_2OMe, EDC, 25 °C, 22 h, 61% (over two steps); (iii) $PhI(O_2CCF_3)_2$, CF_3CO_2H, CH_2Cl_2 , 0 °C, 1 h, 85%; (iv) $BH_3{\cdot}SMe_2$, THF, 80 °C, 22 h; (v) *N*-(benzyloxycarbonyloxy)succinimide, Toluene, -40 °C, 30 min. 65% over two steps; (vi) $COCl_2$, Et_3N, THF, 0 ºC, 1 h, then $MeONH_2$, Et_3N, 25 ºC, 48 h; (vii) $PhI(O_2CCF_3)_2$, $CHCl_3$, 0-25 °C, 2 h, 78% over two steps; (viii) H_2 (50 psig), 20% $Pd(OH)_2$, EtOH, 19 h, 84%.

Sudalai's approach (2009)[24,32]

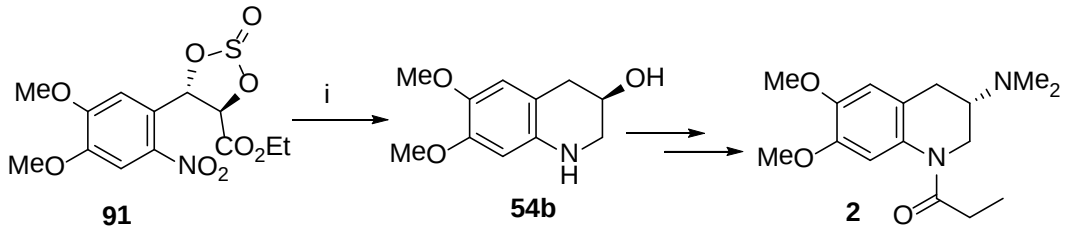
Sudalai *et al.* have used a novel $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulfites with $NaBH_4$ for the formal synthesis of PNU-95666E. Unsaturated nitroesters **86** prepared from Wittig-Horner olefination of the corresponding nitrobenzaldehyde was converted to the corresponding diol **87** in 82% yield *via* Os-catalyzed asymmetric dihydroxylation using $(DHQD)_2$-PHAL as chiral ligand. The diol **87** was readily converted into the corresponding nitro cyclic sulphite **85** ($SOCl_2$ and Et_3N in CH_2Cl_2) in 95% yield. Catalytic one-pot reduction of cyclic sulphite **88** using $CoCl_2$ (1 mol%) and $NaBH_4$ gave the 3-hydroxy tetrahydroquinoline **89** in 81% yield. Synthesis of

(-)-sumanirole **1** from amide **90** has been reported in the literature (**Scheme 22**).[29]



Scheme 22: (i) K_2OsO_4 (0.2 mol%), $(DHQD)_2$-PHAL (1 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (1 equiv.), *tert*-BuOH:H_2O (1:1), 25 °C, 24 h, 82%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 95%; (iii) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$, EtOH, 0-25 °C, 6 h, 81%;

The same author's extended their chemistry for the construction of chiral 3-substituted tetrahydroquinoline derivatives **54b** based on asymmetric dihydroxylation (ADH) and $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulfites **94** with $NaBH_4$ (**Scheme 23**). **54b** was then converted into the title compound **2** in five additional steps.

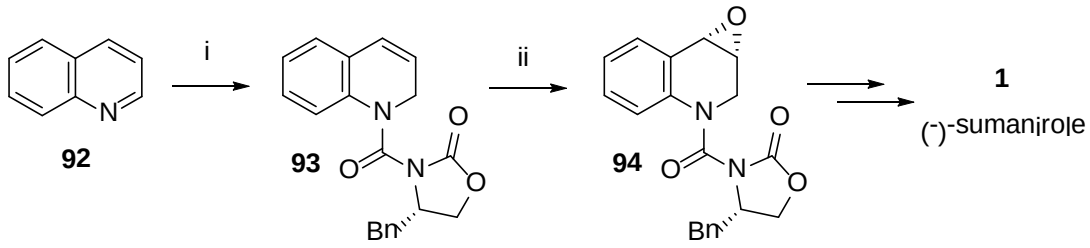


Scheme 23: (i) 1 mol% $CoCl_2$, $6H_2O$, $NaBH_4$, EtOH, 0-25 °C, 12 h.

Gerards's approach (2009, 2012)[33]

In gerards's approach quinoline **92** was first treated with DIBAL-H followed by addition of (*S*)-4-benzyl-2-oxooxazolidine-3-carbonyl chloride in CH_2Cl_2, which gave oxazolidine **93**. The key reaction in the synthesis was the treatment of **93** with *m*CPBA

which gave a diatereomeric mixture of epoxides **94** in dr = 9:1. Epoxide **94** was then converted to (-)-sumanirole **1** in further 10 steps with an overall yield of 3.7% (**Scheme 24**).



Scheme 24: (i) (a) DIBAL-H, CH_2Cl_2, 20 °C, 1 h; (b) (S)-4-benzyl-2-oxooxazolidine-3-carbonyl chloride, CH_2Cl_2, 0-20 °C, 5 h, 60%; (ii) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 20 °C, 18 h.

3.2.3 Present work

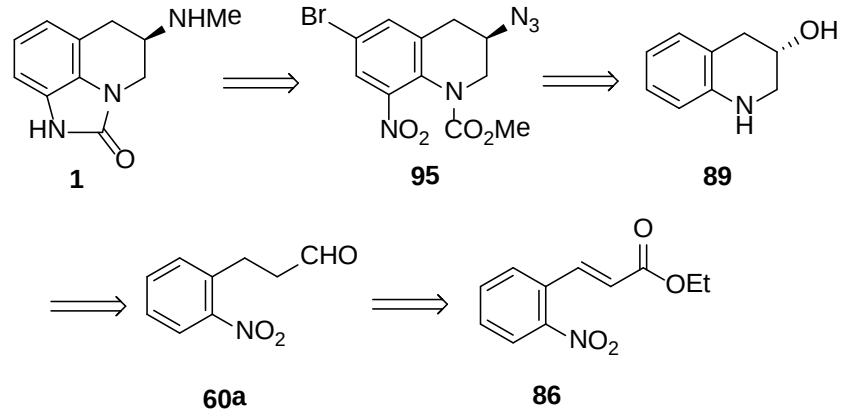
3.2.3.1 Objective

Literature search reveals that only few strategies are available for the synthesis of *anti*-Parkinson's agent (-)-sumanirole **1** and positive inotropic agent **2** (*S*)-903. However, use of chiral pool resources, the dependence on metal catalyst for introduction of chirality, as well as the need to have several protecting groups in the synthesis make the existing routes uneconomical. In **Section I** of this chapter, a new sequential organocatalytic method for the synthesis of chiral 3-hydroxytetrahydroquinoline derivatives (THQs, **54a-e**) [yield upto 76%, ee upto 99%] based on α-aminooxylation followed by reductive cyclization of *o*-nitrohydrocinnamaldehydes **60a-e** has been described. Among the various applications of this sequential protocol, an enantioselective synthesis of (-)-sumanirole **1** and (*S*)-903 **2** seemed attractive to us due to their pharmacological importance.[3,4]

3.2.3.2 Results and Discussion

A) Synthesis of (-)-sumanirole 1:

Retrosynthetic analysis reveals that, for the synthesis of (-)-sumanirole **1**, 6-bromo-8-nitro-THQ **95** was envisaged to be the key intermediate, which could be easily prepared from (*S*)-tetrahydroquinolin-3-ol **89**. We further visualized that amino alcohol **89** could be prepared from D-proline-catalyzed sequential α-aminooxylation/ reductive cyclization of *o*-nitrohydrocinnamaldehyde **60a**. The precursor aldehyde **60a** could be obtained from nitro cinnamate ester **86** (**Scheme 25**).



Scheme 25: Retrosynthetic analysis of (-)-sumanirole **1**

The present synthetic route employed for the synthesis of (-)-sumanirole **1** is shown in **Scheme 26**. Our synthesis of **1** started from unsaturated ester **86**, which was readily prepared from the corresponding aldehyde followed by its Wittig olefination with $Ph_3P{=}CHCO_2Et$. The $CoCl_2{\cdot}6H_2O/iPr_2NH$-catalyzed chemoselective reduction of ester **86** with $NaBH_4$ afforded the saturated alcohol **63a**. The formation of *o*-nitrohydrocinnamyl alcohol **63a** was confirmed from its ^1H NMR and other spectral analysis. Its ^1H NMR spectrum showed the appearance of a broad singlet at δ 2.14, characteristic proton signal for hydroxyl functionality. The triplet at δ 3.70 (J = 6.2 Hz, 2H) and 2.98 (J = 7.6 Hz, 2H) were attributed to methylene (-$\mathbf{CH_2}$-OH) and benzylic

protons respectively. The formation of alcohol **63a** was further ascertained by the appearence of a broad absorption band at υ_{max} 3430 cm^{-1} in its IR spectrum (**Figure 7**).

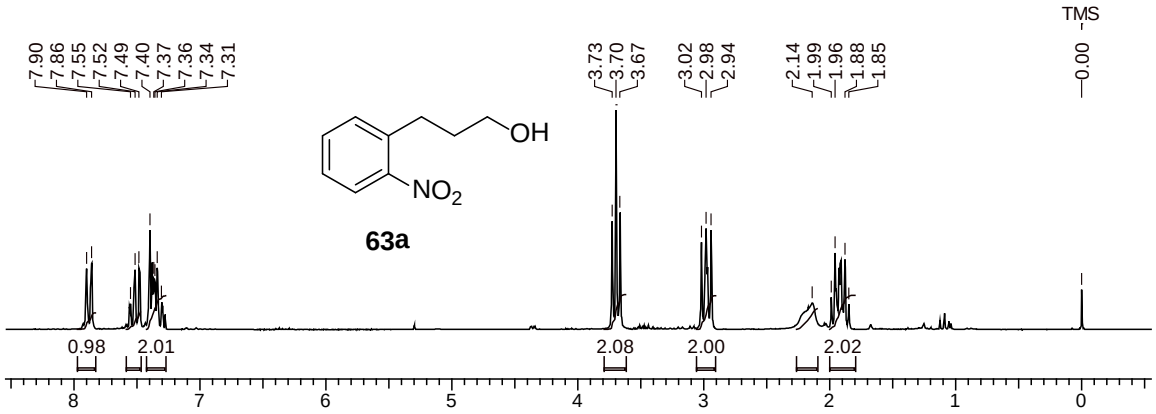
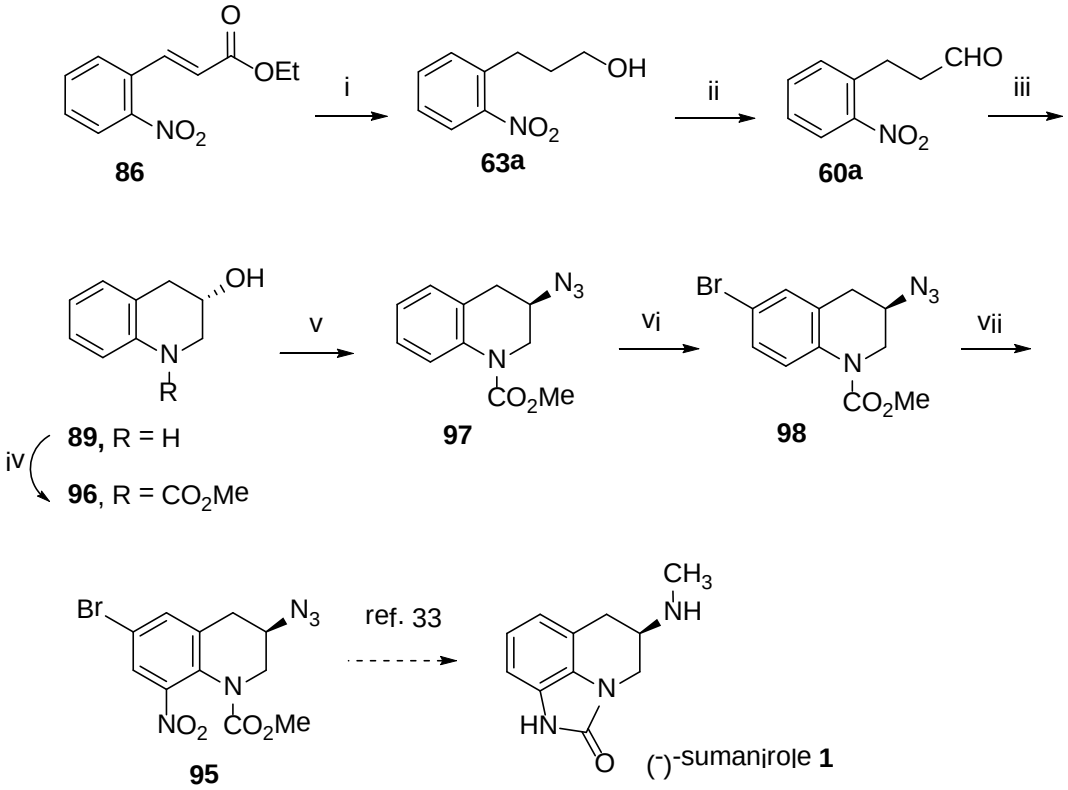


Figure 7: ^{1}H NMR spectrum of *o*-nitrohydrocinnamyl alcohol **63a**

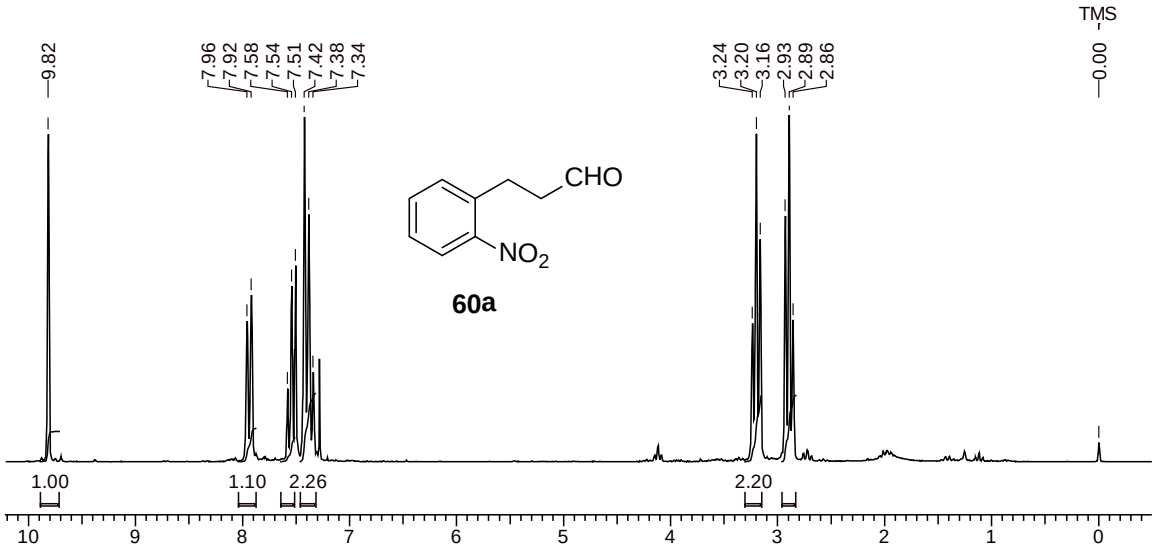
Oxidation of alcohol **63a** with PCC gave *o*-nitrohydrocinnamaldehyde **60a**, the starting material for the proline-catalyzed sequential α-aminooxylation/ reductive cyclization reaction.



Scheme 26: (i) $CoCl_2.6H_2O$, $^iPr_2NH$, $NaBH_4$, EtOH, 25-60 ^oC, 85%; (ii) PCC,

CH_2Cl_2, 25 °C, 85%; (iii) (a) PhNO, D-proline, DMSO, 25 °C, 15 min; (b) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 12 h, 71%; (iv) $ClCO_2Et$, K_2CO_3, CH_2Cl_2 / H_2O (4:1), 0-25 °C, 6 h, 98% ; (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min; (b) NaN_3, DMF, 80 °C, 4 h, 93% (over two steps); (vi) Br_2, AcOH, NaOAc, 25 °C, 1h, 95%; (vii) $NaNO_3$, TFA, 25 °C, 30 min, 95%.

The formation of aldehyde **60a** was established by its ^{1}H NMR spectrum which showed a singlet at δ 9.82 characteristic of aldehydic proton, while the triplets at δ 2.89 (*J* = 7.3 Hz, 2H) and 3.20 (*J* = 7.3 Hz, 2H) were due to methylene protons. This was further substantiated by the appearance of typical signal at δ 199.9 for aldehydic carbon in its ^{13}C NMR spectrum, while the signals at δ 25.6 and 44.4 were due to methylene carbons. Its IR spectrum showed a sharp absorption band at υ_{max} 1712 cm^{-1} due to C=O stretching vibrations (**Figure 8**).



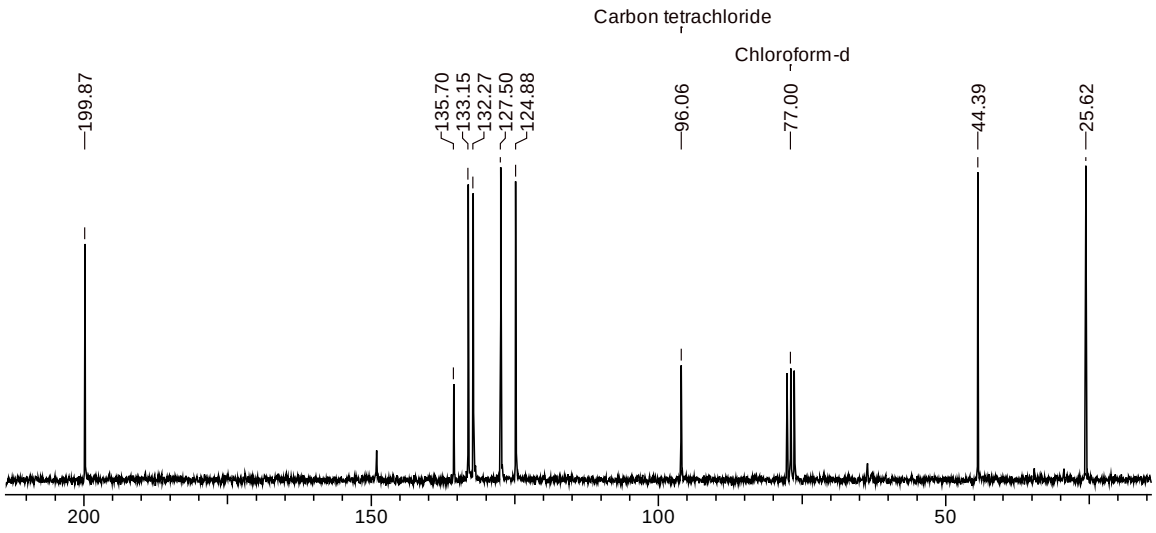
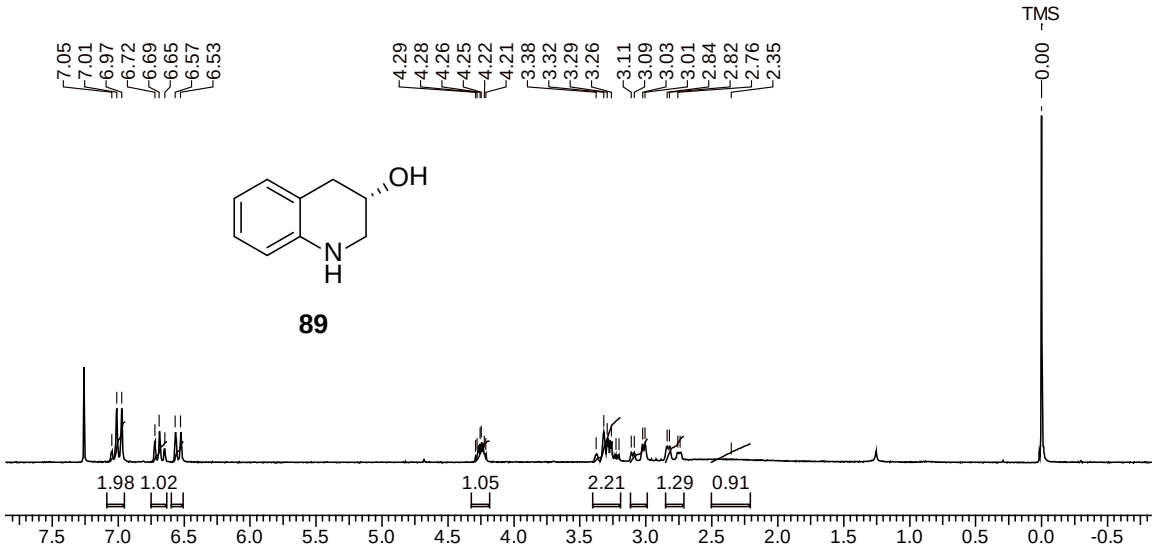
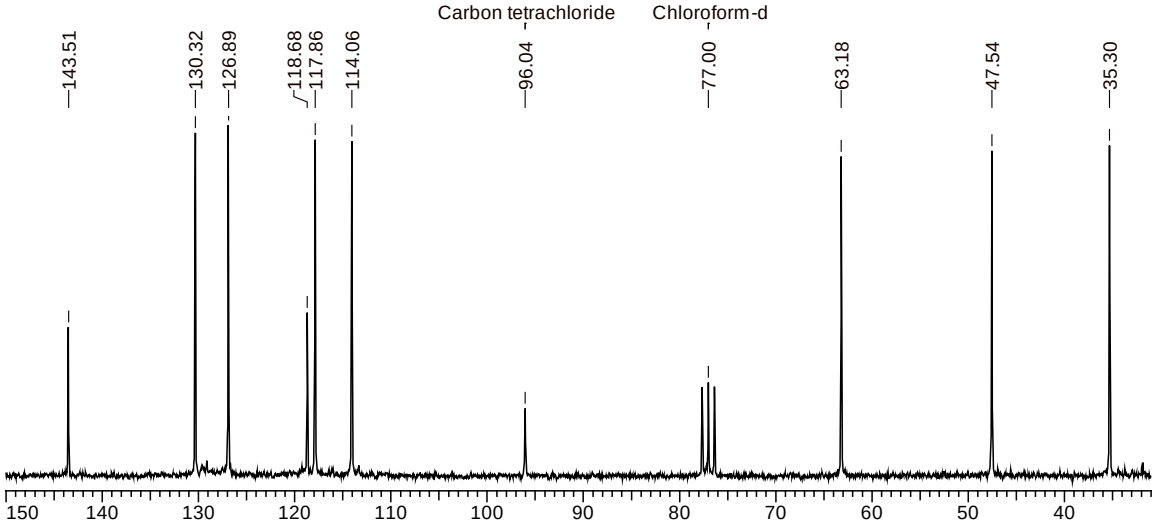


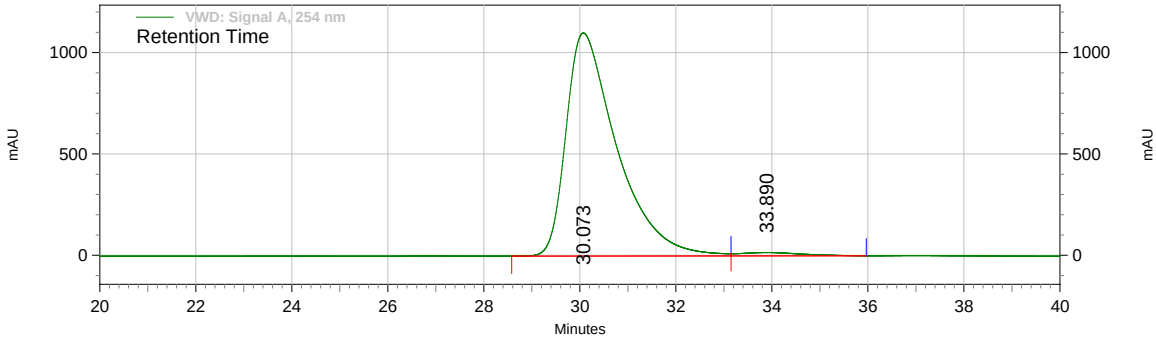
Figure 8: ^{1}H and ^{13}C NMR spectra of *o*-nitrohydrocinnamaldehyde **60a**

o-Nitrohydrocinnamaldehyde **60a** was readily converted into the corresponding THQ **89** in 71% yield *via* sequential reaction involving D-proline catalyzed α-aminooxylation followed by Pd/C catalyzed reductive cyclization under H_2 pressure (1 atm). The ^{1}H NMR spectrum of **89** showed characteristic signals at δ 2.76 (dd, J = 3.7, 16.5 Hz, 1H) and 3.03 (dd, J = 4.3, 16.9 Hz, 1H) due to benzylic methylene protons. Also multiplets at δ 3.26-3.38 and 4.21-4.29 accounted for methylene (*N*-C**H**$_2$) and methine (-C**H**-OH) protons respectively. Its ^{13}C NMR showed two methylene and one methine (-**C**H-OH) carbon signals typically at δ 35.3, 47.5 and 63.2 respectively (**Figure 9**).



89





Retention Time	Area	Area %	Height	Height %
30.073	1355549414	98.23	18466607	98.52
33.890	24389470	1.77	278235	1.48
Totals	1379938884	100.00	18744842	100.00

Figure 9: ^{1}H & ^{13}C NMR spectrum and chiral HPLC chromatogram of THQ **89**

The amine functionality in 3-hydroxy quinoline **89** was then converted into its carbamate **96** by reacting with methyl chloroformate. The formation of carbamate **96** {$[\alpha]^{D}_{25}$ +21.9 (*c* 1, $CHCl_3$)} was confirmed by its spectral data. Its ^{1}H NMR spectrum showed a typical singlet at δ 3.77 due to the methyl carbamate protons ($-CO_2\mathbf{CH_3}$), while a multiplet at δ 4.21 was due to methine protons (-**CH**-OH). Its ^{13}C NMR spectrum showed characteristic carbonyl carbon signals at δ 155.7 (**Figure 10**).

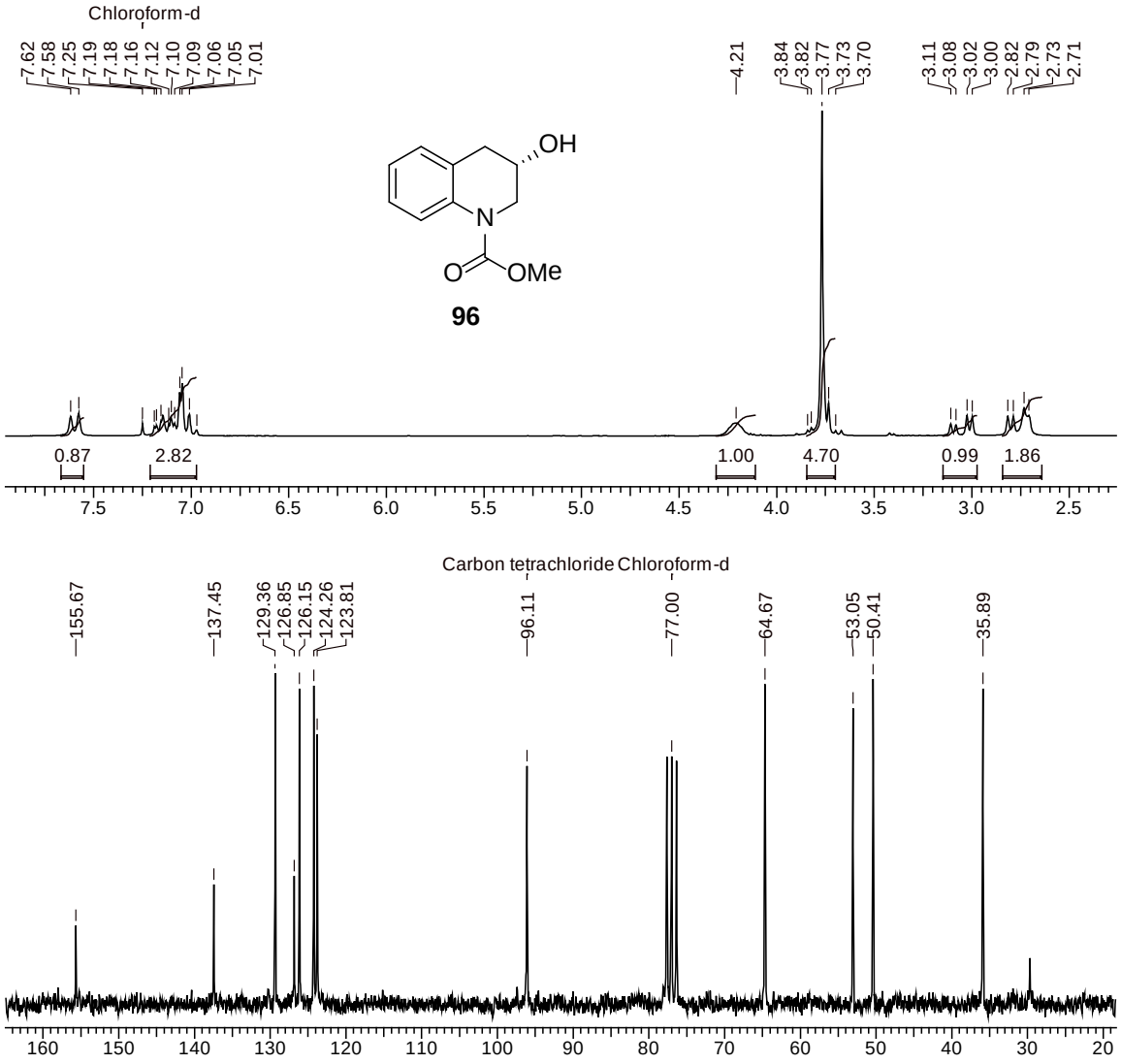
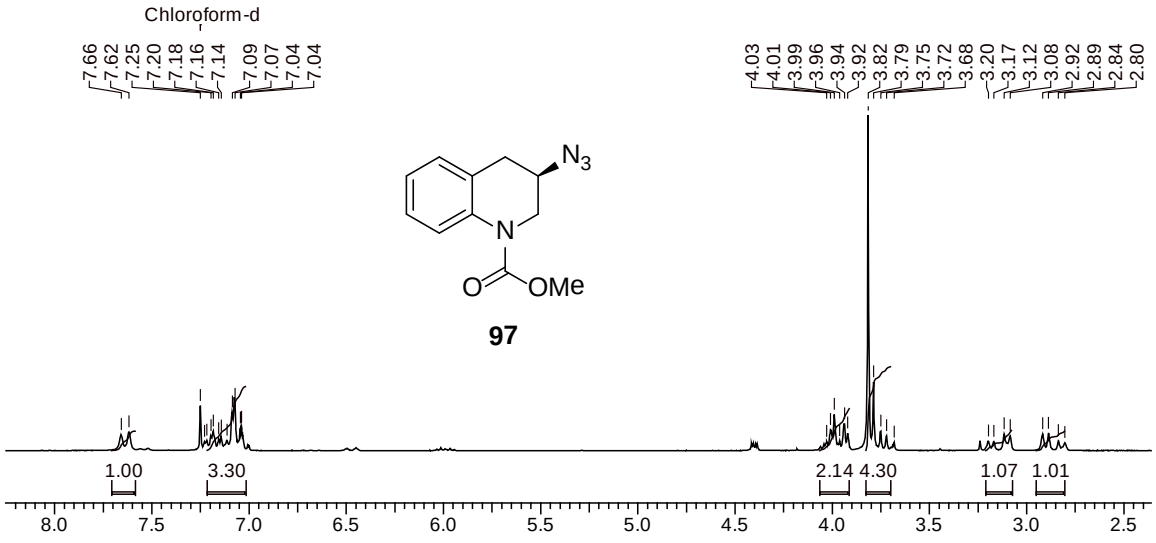


Figure 10: ^{1}H and ^{13}C NMR spectra of carbamate **96**

Alcohol functionality in **96** was then mesylated and the crude mesylate subjected to nucleophilic displacement with N_3 anion to give azide **97** in 93 % yield with complete inversion. The presence of azide functionality was confirmed from its IR spectroscopy, which showed a strong absorption band at 2104 cm^{-1}. Its ^{1}H NMR spectrum showed a typical signals at δ 3.69 (m) due to the methine proton (-**CH**-N_3). Its ^{13}C NMR spectrum showed methine (-**CH**-N_3) and carbonyl carbon signals at δ 47.6 and 155.0 respectively (**Figure 11**).



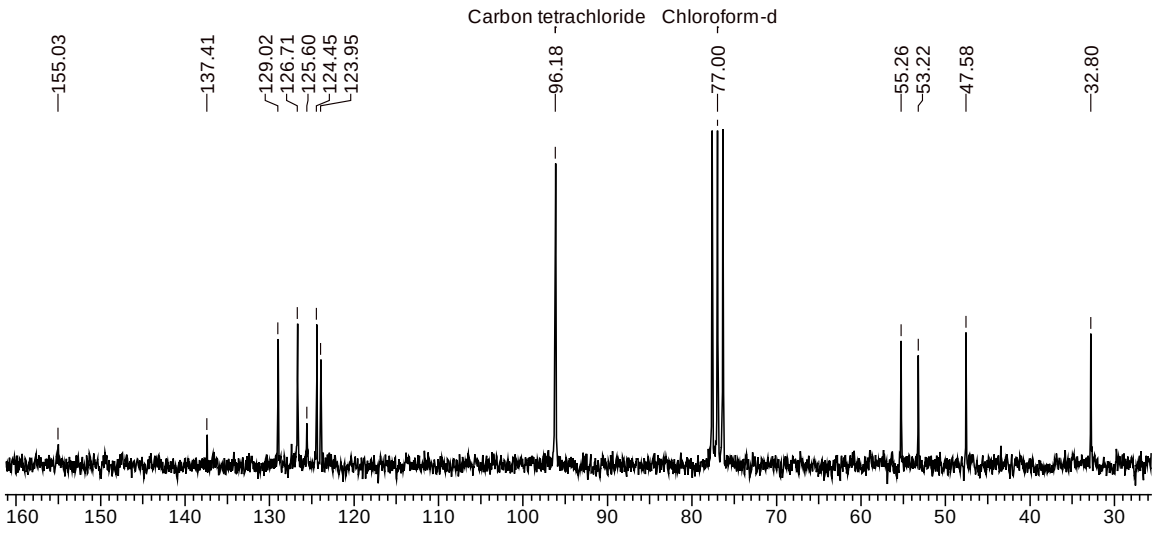


Figure 11: ^{1}H and ^{13}C NMR spectra of azide **97**

Next, installation of a NH_2 group at C8 was envisaged *via* reduction of $-N_3$. Hence **97** was treated with *sec*-butyllithium to generate the anion at the C-8 position followed by quenching with tosyl azide**.** Unfortunately, a complex mixture was obtained, which did not contain the desired product. Alternately, nitration was attempted to place a nitro group at C-8 position. Since C-6 position was expected to be more electrophilic, the latter had to be protected with a removable group. We thus examined a bromination-nitration sequence as a means of introducing a NH_2 group at C-8. Gratifyingly bromination of azido carbamate **97** proceeded smoothly to give its expected 6-bromo derivative **98**. Its ^{1}H NMR spectrum showed signals at δ 7.24–7.30 (m, 2 H) and 7.56 (d, J = 8.7 Hz, 1 H) which indicated the presence of three aromatic protons. A multiplet at δ 4.01-4.04 (m, 1 H) was due to the methine proton (-**CH**-N_3), while the signal at δ 3.88 (s, 3 H) was indicative of methyl of carbamate group. Its IR spectrum showed two strong absoption bands at υ_{max} 1716 and 2103 cm^{-1} corresponding to carbonyl and azide functionalities respectively (**Figure 12**).

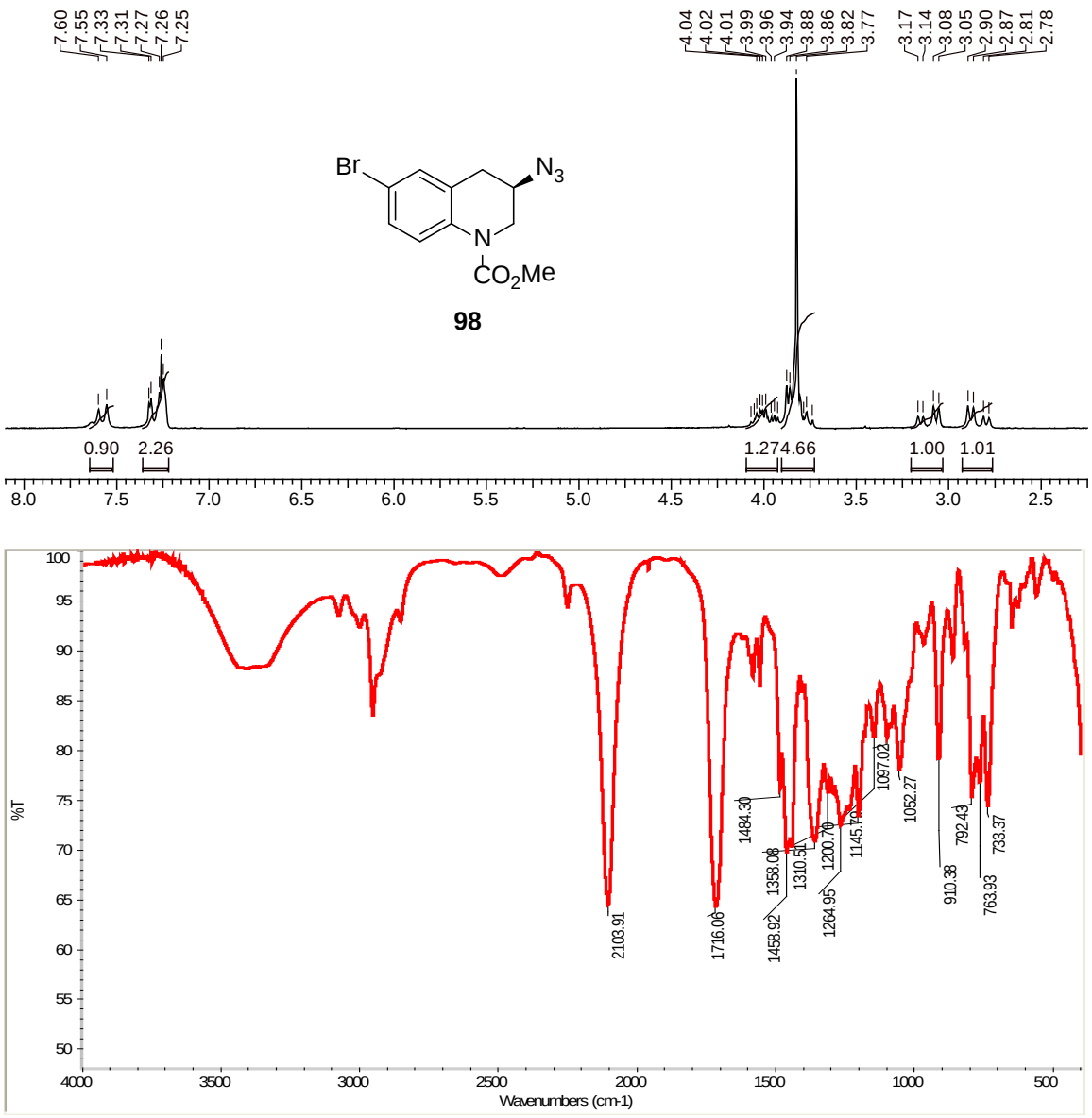


Figure 12: ^{1}H NMR and IR spectra of 6-bromo carbamate **98**

Subsequently, regioselective nitration of **98** was effected by the action of $NaNO_3$ in TFA to give compound **95** with an overall yield of 42.2% and 96% ee. Its ^{13}C NMR spectrum showed typical carbon signals at δ 47.5, 53.3 and 55.5 corresponding to the methine (-**CH**-N_3), methylene (-**CH_2**-N) and methyl (**CH_3**-O-) carbons respectively. The signals at δ 7.51 (1H) and 7.92 (1H) in its ^{1}H NMR spectrum were due to the aromatic protons

(**Figure 13**). As the conversion of **95** to **1** has been reported previously in four steps, this work thus constitutes a formal synthesis of **1**.[33]

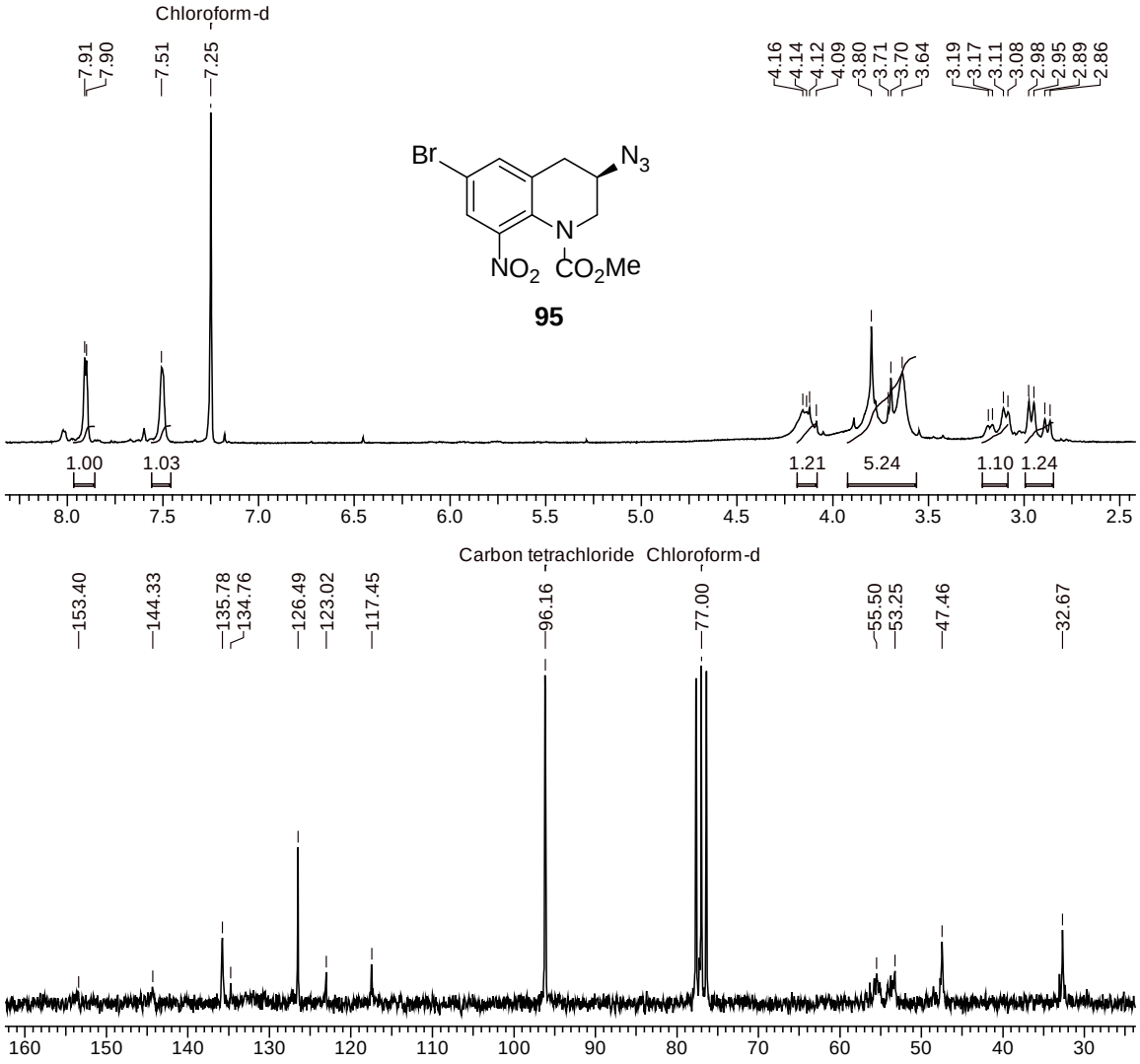
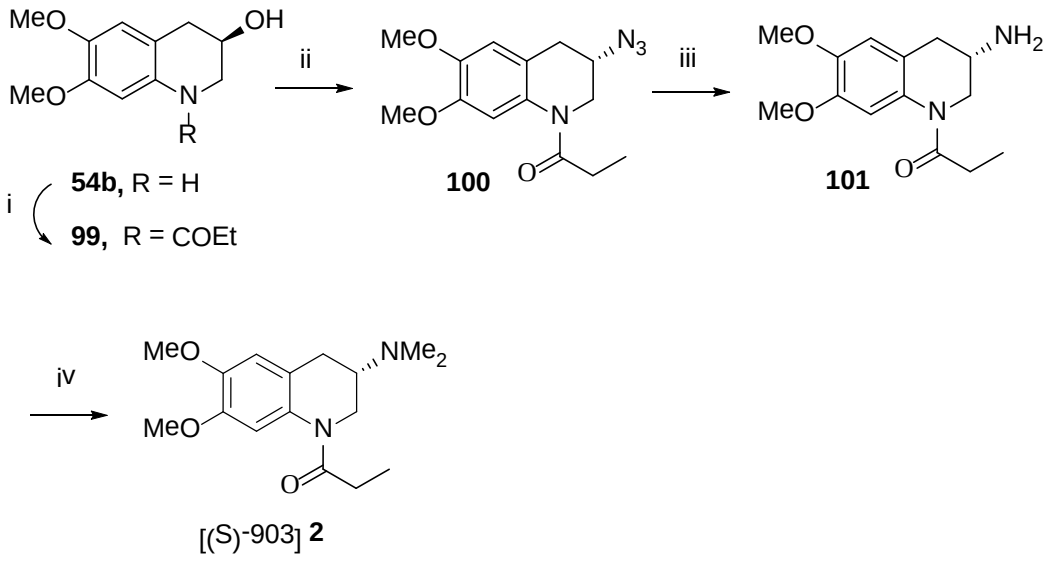


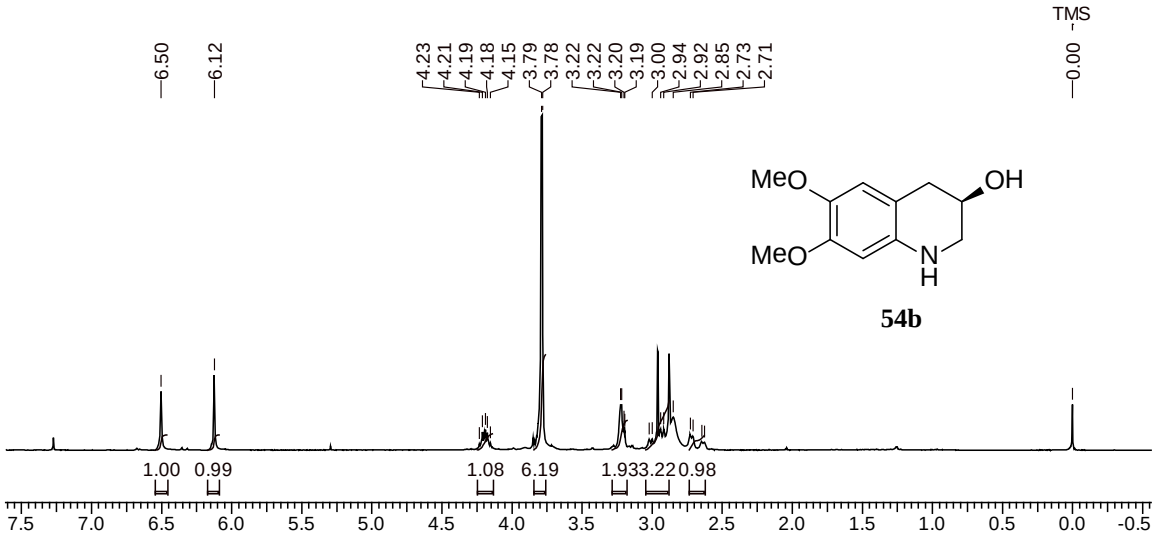
Figure 13: ^{1}H and ^{13}C NMR spectra of 6-bromo-8-nitro carbamate **95**

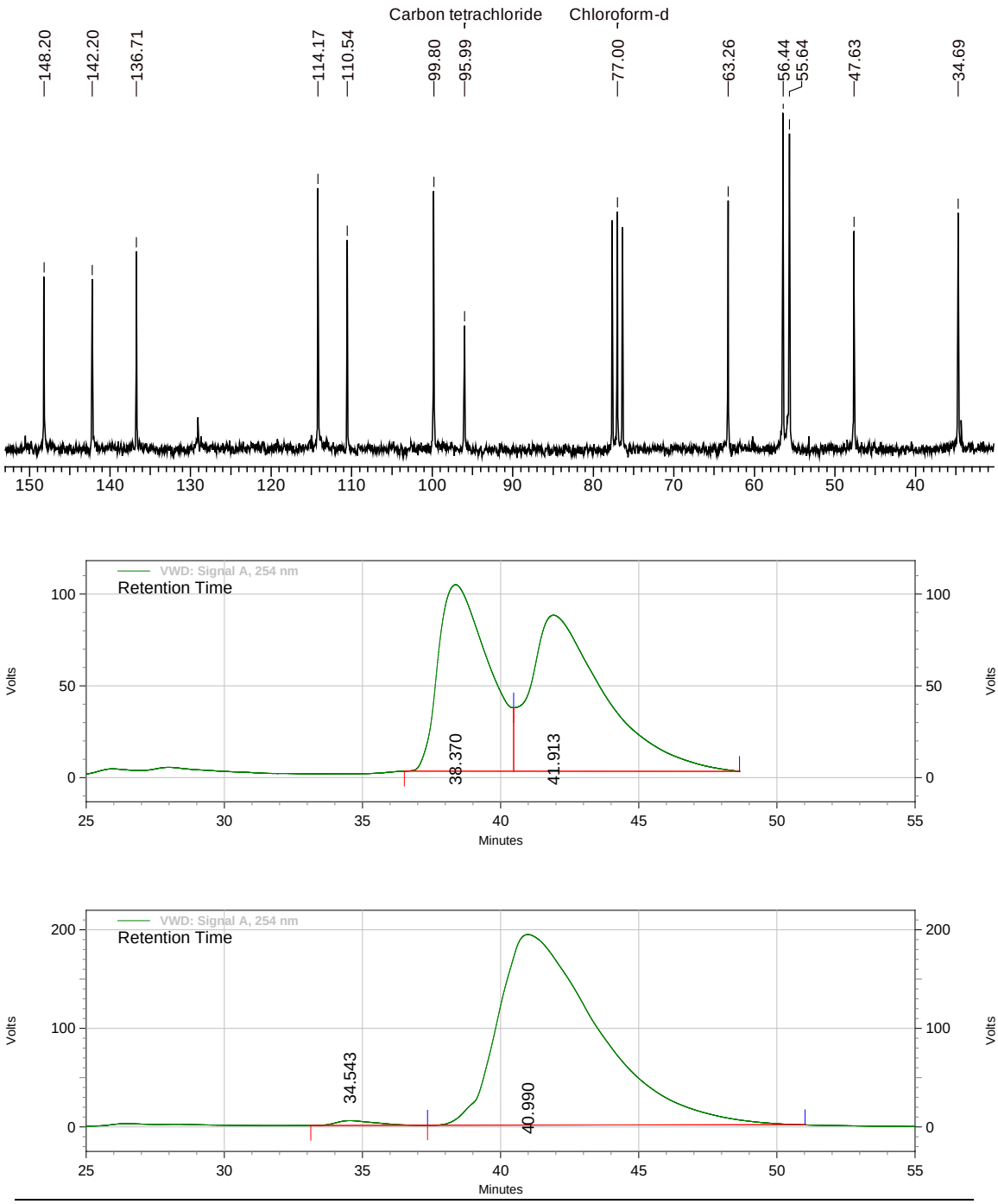
B) Synthesis of (S)-903: Additionally, a concise enantioselective synthesis of **2** (*S*)-903 was undertaken to demonstrate another application of α-aminooxylation-reductive cyclization protocol in synthesis of biologically active molecules. Thus, the synthesis of **2** commenced with THQ **54b** (**Scheme 27**), which was prepared using L-proline as catalyst and PhNO as oxygen source by following the optimized condition described in **Section I**.



Scheme 27: (i) $(EtCO)_2O$, K_2CO_3, CH_2Cl_2/H_2O (4:1), 25 °C, 3 h, 98%; (ii) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min; (b) NaN_3, DMF, 80 °C, 12 h, 94% (over two steps); (iii) H_2 (1atm), 10% Pd/C, MeOH, 25 °C, 12 h, 96%; (iv) HCHO, HCO_2H, 80 °C, 3 h, 91%.

The formation of THQ **54b** was confirmed by its ^{1}H NMR spectrum which showed typical multiplets at δ 3.19-3.22 (m) and 4.15-4.23 (m) corresponding to methylene (*N*-C**H**$_2$) and methine (-C**H**-OH) protons respectively, while singlets at δ 3.78 and 3.79 were due to methyl protons (**CH$_3$**-OH). Its ^{13}C NMR spectrum displayed two methylene and one methine (-**CH**-OH) carbons typically at δ 34.7, 47.6 and 63.3 respectively, while the signals at δ 55.6 and 56.4 were due to methyl carbons attached to oxygen (**Figure 14**).





Retention Time	Area	Area %	Height	Height %
34.543	8287172	1.00	82649	2.48
40.990	816959267	99.00	3246502	97.52
Totals	825246439	100.00	3329151	100.00

Figure 14: ^{1}H & ^{13}C NMR spectra and HPLC chromatogram of THQ **54b**

Amine function in **54b** was protected as its amide **99** [$(EtCO)_2O$, K_2CO_3, CH_2Cl_2/H_2O (4:1)] in 98% yields; $[\alpha]^{D}_{25}$ +8.9 (*c* 1.0, $CHCl_3$). Its ^1H NMR spectrum showed typical proton signals at δ 1.18 (t, *J* = 7.3 Hz, 3H) and 2.34 (q, *J* = 7.4 Hz, 2H) corresponding to the methyl (-$COCH_2\mathbf{CH_3}$) and methylene (-$CO\mathbf{CH}_2CH_3$) protons respectively. A multiplet at δ 4.30-4.37 (m, 1H) was due to methine (-C**H**OH) protons. Its ^{13}C NMR spectrum showed a carbonyl signal at δ 174.4 thus confirming the formation of amide carbonyl group (**Figure 15**).

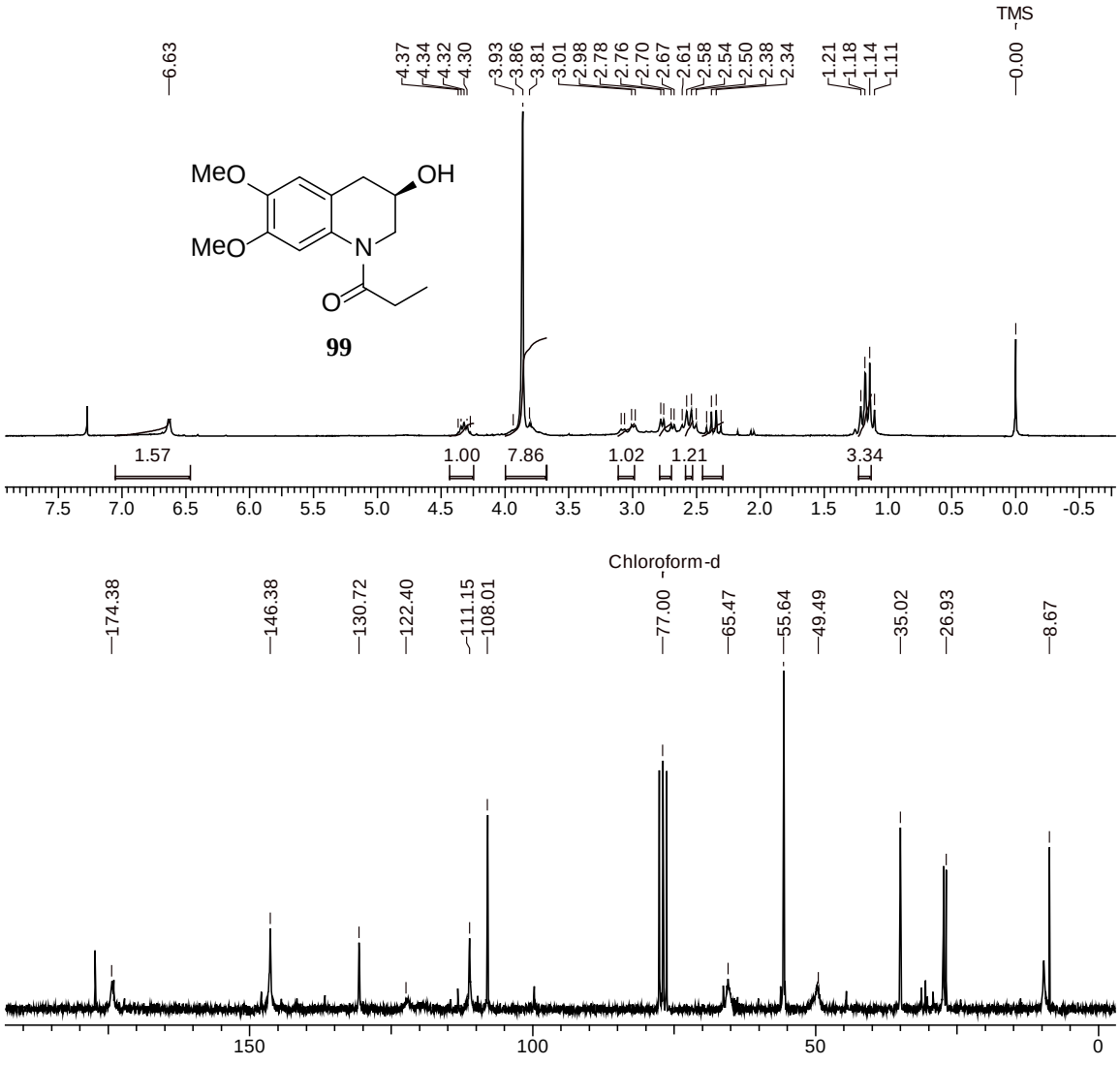


Figure 15: ^1H and ^{13}C NMR spectra of amido alcohol **99**

Free hydroxyl functionality in **99** was then protected as its mesylate (MsCl, Et_3N, CH_2Cl_2) followed by its displacement with azide anion (NaN_3, DMF) to give azido quinolines **100** {$[\alpha]^{D}_{25}$ +40.7 (*c* 2, $CHCl_3$)} in 94% yield. The ^{1}H NMR spectrum of azide **100** showed a multiplet at δ 3.77 due to methine (-**CH**-N_3) proton. Its ^{13}C NMR spectrum also showed a downfield shift at δ 55.7 for methine (-**CH**-N_3) carbon. Its IR spectrum showed a characteristic strong absorption band at 2110 cm^{-1} for azide group confirming the formation of azide product (**Figure 16**).

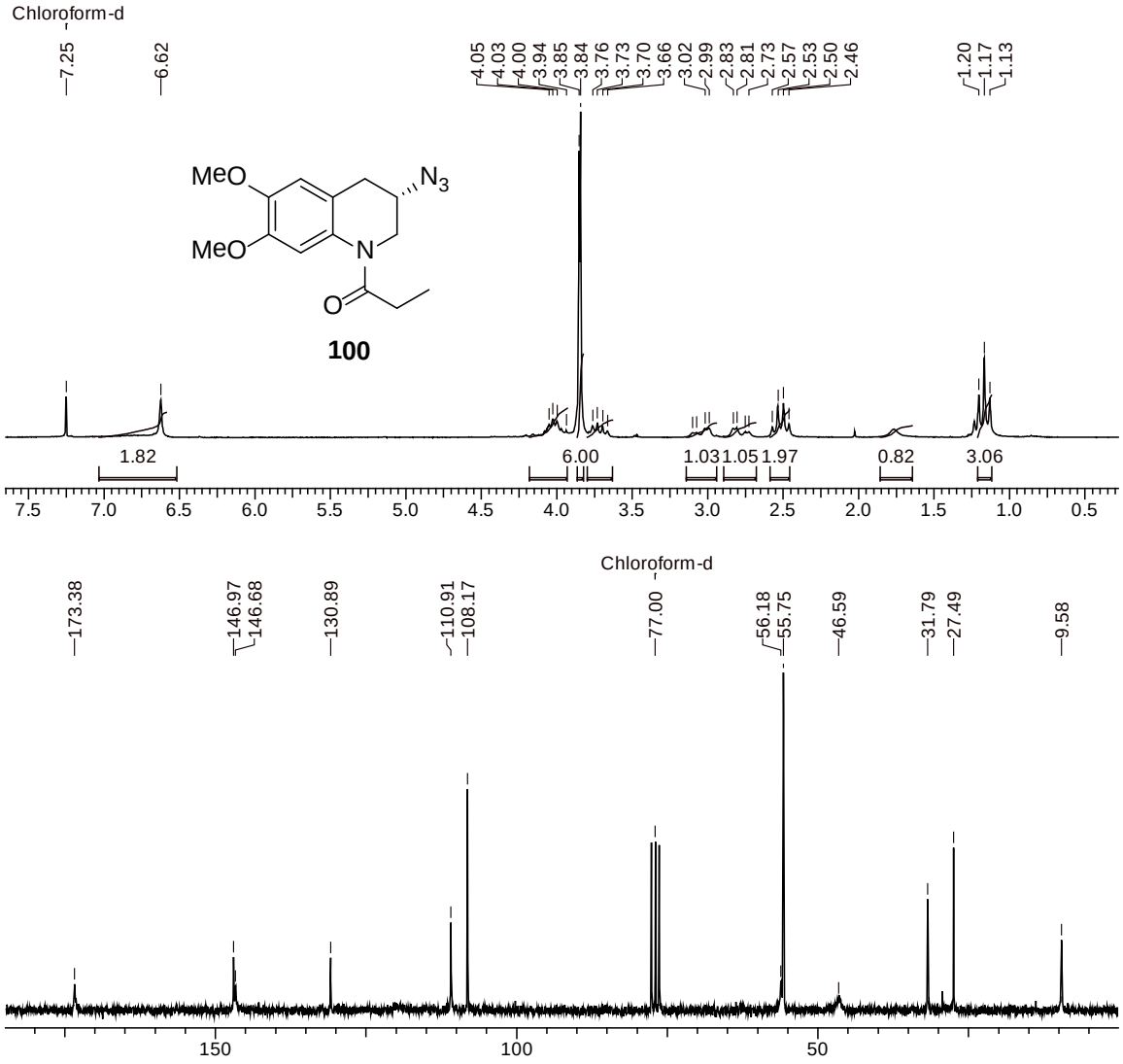


Figure 16: ^{1}H and ^{13}C NMR spectra of azide **100**

Catalytic hydrogenation of azide function in **100** was carried out to give the corresponding amine **101**. The ^{1}H and ^{13}C NMR spectra of amine **101** are presented in **Figure 17**. A multiplet at δ 4.04-4.18 (2H) was due to the overlapping of methine (-**CH**-NH_2) and amine protons. Its ^{13}C NMR spectrum displayed a carbon signal at δ 49.7 indicating the presence of methine carbon (-**CH**-NH_2) (**Figure 17**).

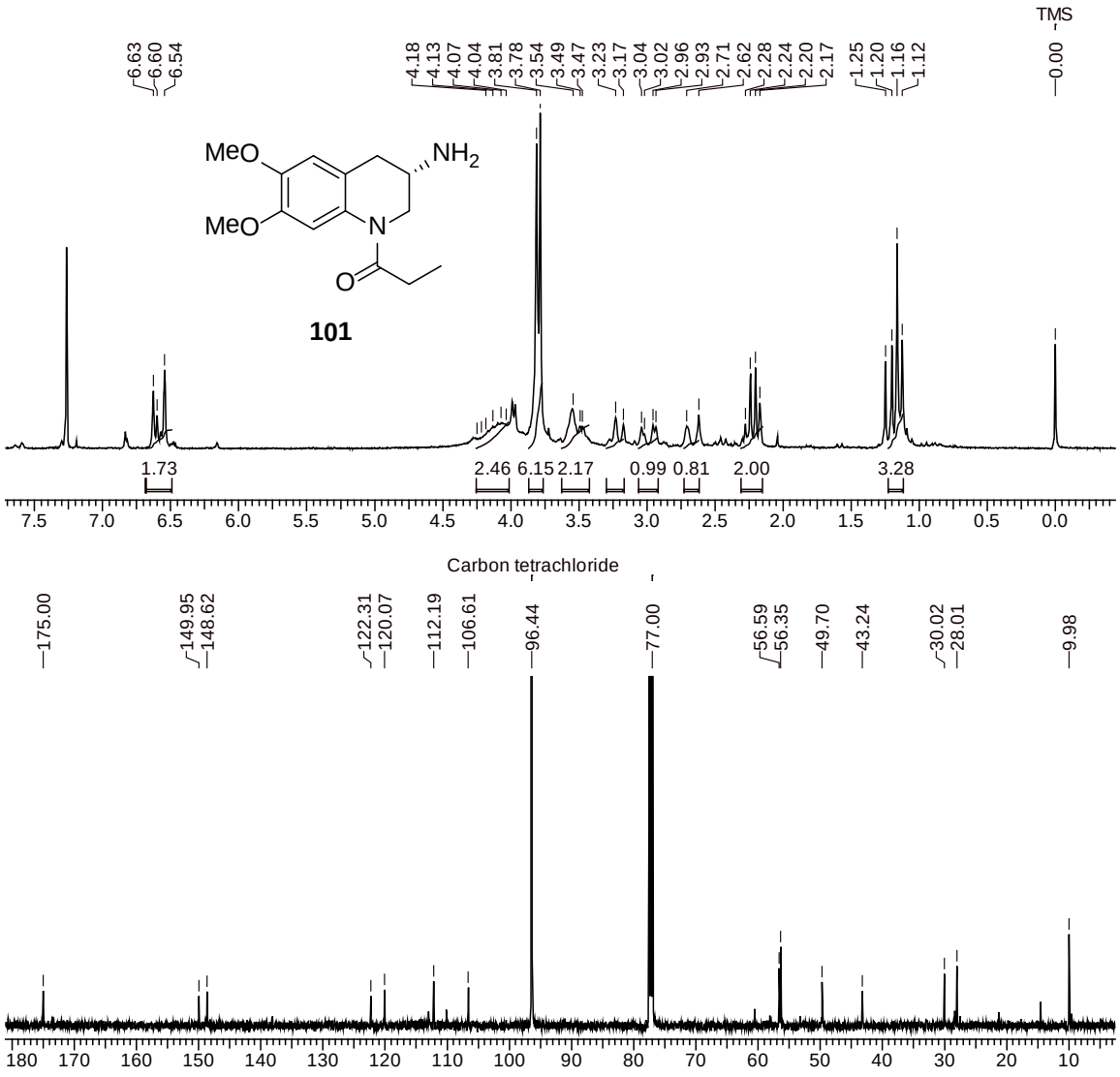


Figure 17: ^{1}H and ^{13}C NMR spectra of amine **101**

With the free amine **101** in hand, the next step towards its completion was the reductive cylization reaction under the Eschweiler–Clarke reaction conditions (HCHO, HCO_2H),

which produced 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]propanone **2** with an overall yield of 71.6% and 98% ee. The ^{1}H NMR spectrum of **2** showed a typical singlet at δ 2.35 due to methyl amine protons [-N(**CH$_3$**)$_2$]. The other signals at δ 41.33 and 41.46 in its ^{13}C NMR spectrum were due to methyl amine carbons (**Figure 18**).

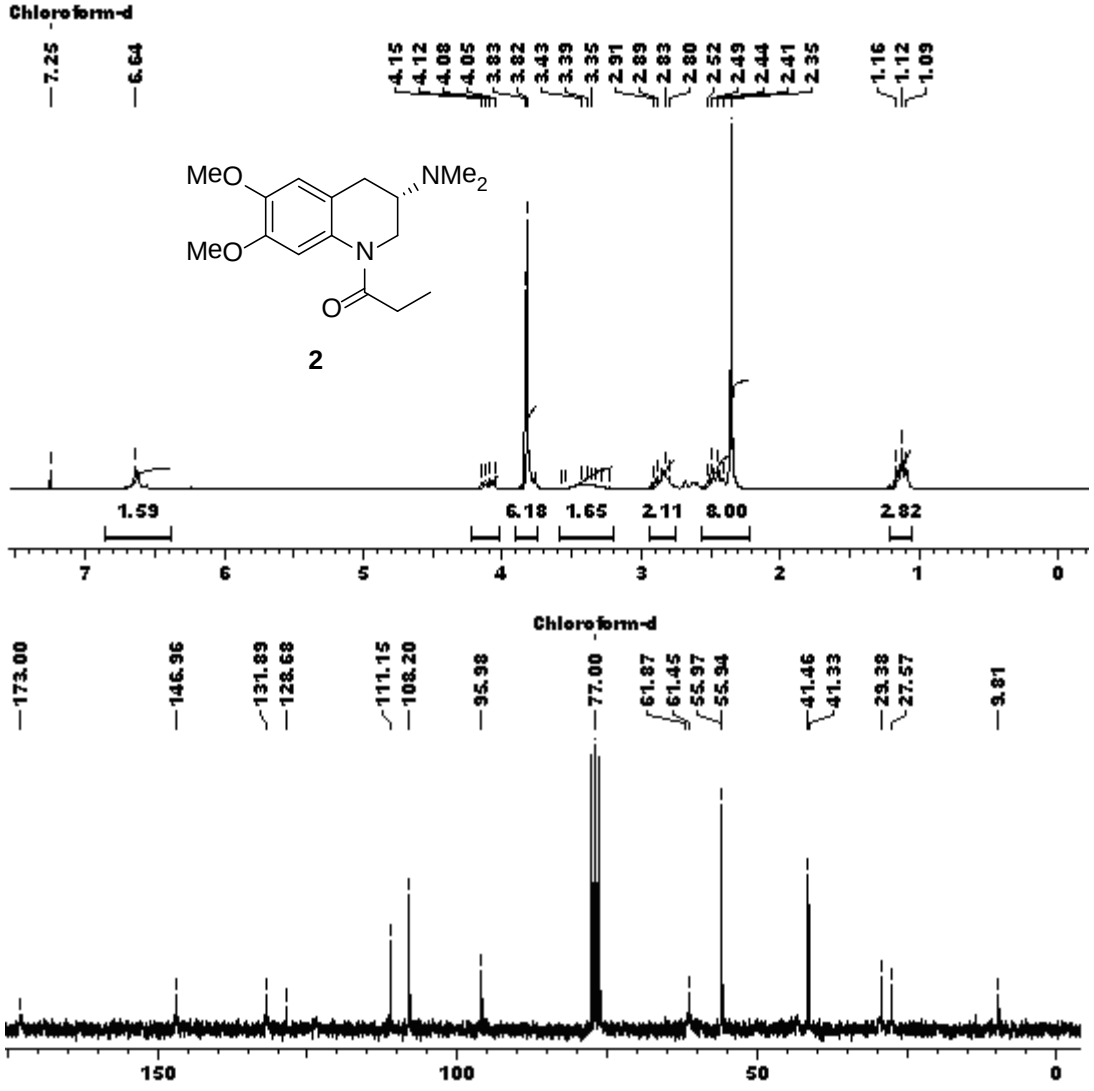


Figure 18: ^{1}H and ^{13}C NMR spectra of **2** (*S*)-903

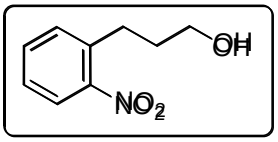
3.2.4 Conclusion

In conclusion, we have achieved the formal synthesis of (-)-sumanirole **1** (42.2% overall

yield till known intermediate **95** with 96% ee) and 1-[(*S*)-3-(dimethylamino)-6,7-dimethoxytetrahydroquinoline propanone **2** (71.6% overall yield from THQ **54b** with 98% ee). We have successfully applied a novel sequential protocol based on α-aminooxylation followed by reductive cyclization of *o*-nitrohydrocinnamaldehydes as key steps for the synthesis of (-)-sumanirole **1** and **2** [(S)-903]**.**

3.2.5 Experimental section

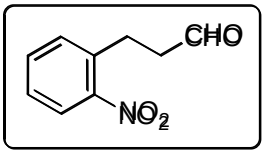
2-(2-Nitrophenyl)ethanol (63a)



To a stirred solution of ester **86** (7.0 g, 31.7 mmol), $CoCl_2 \cdot 6H_2O$ (377 mg, 5 mol %) and diisopropyl amine (320 mg, 10 mol %) in 95% ethanol (100 mL) was added $NaBH_4$ (4.8 g, 126.8 mmol) slowly at 25 °C. It was then stirred for 24 h at 50-60 °C. After completion of the reaction (monitored by TLC), it was quenched with addition of water (20 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of crude product with petroleum ether/ethyl acetate (7:3 v/v) afforded alcohol **63a** (5.74 g) as gum.

Yield: 85%; **IR** ($CHCl_3$): υ_{max} 857, 968, 1029, 1060, 1245, 1440, 1507, 3430 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.85-1.99 (m, 2H), 2.14 (br s, 1H), 2.98 (t, *J* = 7.6 Hz, 2H), 3.70 (t, *J* = 6.2 Hz, 2H), 7.31-7.55 (m, 3H), 7.86 (d, *J* = 7.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.1, 33.2, 61.6, 124.4, 126.8, 131.8, 132.8, 136.7, 149.1; **Anal.** Calcd for $C_9H_{11}NO_3$ requires C, 59.66; H, 6.12; N, 7.73; found C, 59.71; H, 6.15; N, 7.79%.

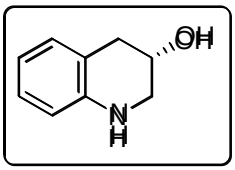
3-(2-Nitrophenyl)propanal (60a)



To a stirred solution of alcohol **63a** (5 g, 27.60 mmol) in dry CH_2Cl_2 (100 mL), PCC (11.9 g, 55.20 mmol) was added slowly at 25 °C. It was then stirred for further 6 h. After completion of the reaction (monitored by TLC), it was passed through a short pad of silica gel (230-400 mesh) using CH_2Cl_2 as eluent. The combined organic layers were concentrated under reduced pressure to give aldehyde **60a** (4.2 g) which was pure enough to be used for the next step.

Yield: 85%; gum; **IR** ($CHCl_3$): υ_{max} 667, 756, 850, 1155, 1215, 1253, 1278, 1345, 1476, 1712, 2989, 3123 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.89 (t, *J* = 7.3 Hz, 2H), 3.20 (t, *J* = 7.3 Hz, 2H), 7.34-7.58 (m, 3H), 7.92 (d, *J* = 7.9, 2H), 9.82 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 25.6, 44.4, 124.9, 127.5, 132.3, 133.1, 135.7, 199.9; **Anal.** Calcd for $C_9H_9NO_3$ requires: C, 60.33; H, 5.06; N, 7.82; found: C, 60.38; H, 5.11; N, 7.76%.

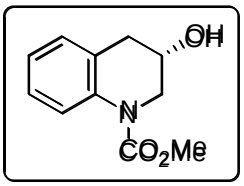
(*S*)-1,2,3,4-Tetrahydroquinolin-3-ol (89)



Yield: 71%; gum, $[\alpha]^D_{25}$ –20.9 (*c* 1, $CHCl_3$); 96% ee (HPLC).

(For experimental procedure and spectral data see **Section 1**)

(*S*)-Methyl 3-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate (96)

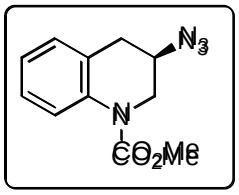


To a stirred solution of tetrahydroquinolin-3-ol **89** (200 mg, 1.34 mmol) and methyl chloroformate (1 mL, 13 mmol) in CH_2Cl_2/H_2O (4:1), was added K_2CO_3 (1.8 g, 13 mmol) at 0 ºC and the reaction mixture was further allowed to stir for 6 h at 25 ºC. Progress of reaction was monitored by TLC and after completion of reaction, a saturated solution of NH_4Cl (20 mL) was added. The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (2

x 50 mL). Combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude products. Chromatographic purification of crude product with petroleum ether/ethyl acetate (6: 4 v/v) as eluent gave **96** (291 mg) as oily liquid.

Yield: 98%; $[\alpha]^{D}_{25}$ +21.9 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1469, 1589, 1608, 1704, 3419 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.71-2.82 (m, 2H), 3.00 (dd, *J* = 5.3, 16.7 Hz, 1 H), 3.70-3.84 (m, 5H), 4.21 (m, 1H), 7.01-7.19 (m, 3H), 7.58 (d, *J* = 8.1 Hz, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.9, 50.4, 53.0, 64.7, 123.8, 124.3, 126.1, 126.8, 129.4, 137.4, 155.7; **ESIMS** (m/z) 208 $[M+H]^+$; **HRMS** (ESI): calcd. for $C_{11}H_{13}NO_3$ 208.0974; found 208.0969.

(*R*)-Methyl 3-azido-3,4-dihydroquinoline-1(2H)-carboxylate (97)

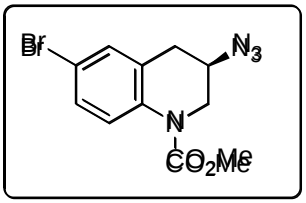


To a stirred solution of alcohol **96** (170 mg, 0.84 mmol) in anhydrous CH_2Cl_2 (16 mL) kept at 0 °C under nitrogen were successively added freshly distilled Et_3N (0.4 mL, 2.5 mmol) and mesyl chloride (0.1 mL, 1.26 mmol). After stirring was continued for 45 min, CH_2Cl_2 (90 mL) was added to the reaction mixture, which was then washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. To a solution of this crude mesylate in anhydrous DMF (10 mL) kept at 80 °C under nitrogen was added sodium azide (0.199 g, 3.1 mmol). The resulting solution was stirred at 80 °C for 4 h. Progress of the reaction was monitored by TLC and after completion of reaction, it was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated in vacuo. The crude product was purified by column chromatography with petroleum ether/EtOAc (9:1 v/v) to give azide

97 (181 mg) as yellow liquid.

Yield: 93%; $[\alpha]^{D}_{25}$ -28.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1493, 1708, 2104, 2953 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.80 (dd, *J* = 6.2, 16.4 Hz, 1 H), 3.08 (dd, *J* = 6.3, 17.0 Hz, 1 H), 3.68-3.82 (m, 4H), 3.92-4.03 (m, 2H), 7.04-7.20 (m, 3H), 7.62 (d, *J* = 8.1 Hz, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.8, 47.6, 53.2, 55.3, 123.9, 124.4, 125.6, 126.7, 129.0, 137.4, 155.0; **ESIMS** (m/z) 255 $[M+Na]^+$; **HRMS** (ESI): calcd. for $C_{11}H_{12}N_4O_2$ 255.0858; found 255.0889.

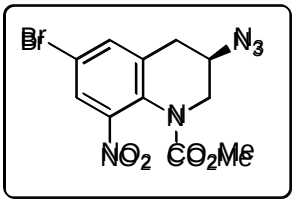
(*R*)-Methyl 3-azido-6-bromo-3,4-dihydroquinoline-1(2H)-carboxylate (98)



To a solution of alcohol **97** (120 mg, 0.52 mmol) in acetic acid were successively added anhydrous AcONa (212 mg, 1.9 mmol) and Br_2 (0.3 mL, 0.52 mmol). The mixture was stirred at 25 °C for 1 h and then quenched with water (30 mL). The resulting solution was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified over column chromatography with petroleum ether/EtOAc (9:1 v/v) to give bromo azide **98** (153 mg) as thick liquid.

Yield: 95%; $[\alpha]^{D}_{25}$ -14.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 910, 1264, 1458, 1716, 2103 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.78 (dd, *J* = 5.9, 16.8 Hz, 1H), 3.08 (dd, *J* = 5.7, 16.8 Hz, 1H), 3.77-3.96 (m, 5H), 4.01-4.04 (m, 1H), 7.25-7.33 (m, 2H), 7.55 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.7, 50.32, 53.3, 64.4, 117.0, 130.0, 124.5, 125.7, 128.9, 129.6, 132.3, 136.4, 155.1; **ESIMS** (m/z) 332 $[M+Na]^+$; **HRMS** (ESI): calcd. for $C_{11}H_{11}BrN_4O_2$ 332.9963; found 332.9998.

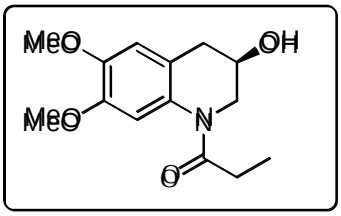
(*R*)-Methyl 3-azido-6-bromo-8-nitro-3,4-dihydroquinoline-1(2H)-carboxylate (95)



To a solution of sodium nitrate (30 mg, 0.40 mmol) in trifluoroacetic acid (5 mL) was added bromo azide **98** (100 mg, 0.32 mmol). The resulting solution was stirred at 25 °C for 30 min and then concentrated under reduced pressure. The crude product was then dissolved in EtOAc (50 mL) and the organic portion washed sequentially with saturated aqueous sodium hydrogen carbonate (10 mL), NaOH (1 M solution, 10 mL), and water (10 mL), dried with anhydrous Na_2SO_4, and then concentrated under reduced pressure. It was purified by column chromatography with petroleum ether/EtOAc (6:4 v/v) to give nitro compound **95** (108 mg) as a thick liquid.

Yield: 95%; $[\alpha]^{D}_{25}$ +59.3 (*c* 1, $CHCl_3$) {lit.[33] $[\alpha]^{D}_{25}$ +58.4 (*c* 0.51, $CHCl_3$)}; **IR** ($CHCl_3$): υ_{max} 1265, 1456, 1717, 2105 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.86 (dd, *J* = 5.4, 16.8 Hz, 1H), 3.08 (dd, *J* = 5.1, 16.7 Hz, 1H), 3.64-3.80 (m, 5H), 4.09-4.16 (m, 1H), 7.51 (s, 1H); 7.91 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.7, 47.5, 53.2, 55.5, 117.4, 123.0, 126.5, 134.8, 135.8, 144.3, 153.4; **ESIMS** (m/z) 393 $[M+K]^+$; **HRMS** (ESI): calcd. for $C_{11}H_{10}BrN_5O_4$ 393.9553; found 393.9513.

(*R*)-1-(3-Hydroxy-6,7-dimethoxy-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (99)

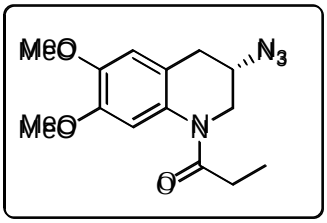


To a stirred solution of tetrahydroquinolin-3-ol **54b** (740 mg, 5 mmol) and K_2CO_3 (2.07 g, 15 mmol) in 20 mL of CH_2Cl_2/H_2O (4:1), propionic anhydride (1.95 g, 15 mmol) was added at 25 ºC. Reaction mixture was stirred for 3 h. Progress of the reaction was monitored by TLC and after the completion of reaction, a saturated $NaHCO_3$ (30 mL) was added. The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL),

dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product with petroleum ether/EtOAc (6:4 v/v) gave 1.3 g of pure amide **99**.

Yield: 98%; $[\alpha]^{D}_{25}$ +8.9 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 761, 1051, 1245, 1755, 2358, 3463 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.54 (q, *J* = 7.4 Hz, 2H), 2.58-2.70 (m, 1H), 2.76 (dd, *J* = 4.9, 16.5 Hz, 1H), 3.01 (dd, *J* = 5.7, 16.5 Hz, 1H), 3.81-3.93 (m, 8H), 4.30-4.37 (m, 1H), 6.63 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 8.7, 26.9, 35.0, 49.5, 55.6, 65.5, 108.0, 111.1, 122.4, 130.7, 146.4, 174.4; **Anal.** Calcd for $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28; found C, 63.45; H, 7.27; N, 5.34%.

(S)-1-(3-Azido-6,7-dimethoxy-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (100)

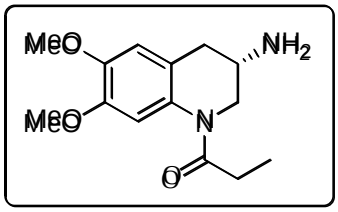


To a stirred solution of amide **99** (531 mg, 2 mmol) and triethyl amine (0.7 mL, 5 mmol) in 20 mL of CH_2Cl_2, mesyl chloride (2.5 mmol, 0.25 mL) was added at 0 ºC. It was then stirred for 45 min. After completion of the reaction (monitored by TLC), a saturated solution of $NaHCO_3$ (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude mesylate product. To the stirred solution of this crude mesylate in dry DMF (10 mL), was added NaN_3 (650 mg, 10 mmol). It was then stirred for 12 h at 80 ºC. After completion of the reaction (monitored by TLC), it was poured into 50 mL of ice cold water and extracted with ethyl acetate (3 x 50mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. Chromatographic purification of crude

product with petroleum ether/EtOAc (7:30 v/v) gave azide **100** (546 mg) in pure form.

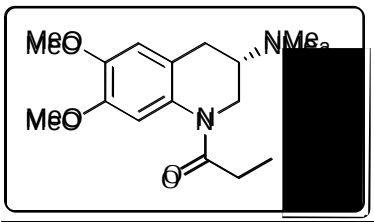
Yield: 94%; Gum; $[\alpha]^{D}_{25}$ +39.7 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$): 757, 1043, 1217, 1514, 1650, 1735, 2110, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.3 Hz, 3H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.73 (dd, *J* = 5.5, 16.0 Hz, 1H), 3.02 (dd, *J* = 5.4, 16.6 Hz, 1H), 3.66-3.76 (m, 1H) 3.84 (s, 3H), 3.85 (s, 3H), 3.94-4.05 (m, 1H), 6.68 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.6, 27.5, 31.8, 46.6, 55.7, 56.2, 108.2, 110.9, 130.9, 146.7,150.0, 173.4; **Anal.** Calcd for $C_{14}H_{18}N_4O_3$ requires C, 57.92; H, 6.25; N, 19.30; found C, 57.88; H, 6.20; N, 19.33%.

(*S*)-1-(3-Amino-6,7-dimethoxy-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (101)



To a stirred solution of azide (290 mg, 1 mmol) in methanol (10 mL), was added 10% Pd/C. It was stirred under H_2 atmosphere (balloon pressure) for 12 h. After the completion of reaction (monitored by TLC), it was passed through the celite and concentrated under reduced pressure that afforded amine **101** (253 mg) pure enough for the next reaction.

Yield: 96%; Gum; $[\alpha]^{D}_{25}$ -15.7 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$): 1277, 1534, 1615, 1731, 2987. 3418 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12-1.25 (m, 3H), 2.17-2.28 (m, 2H), 2.62 (dd, *J* = 5.1, 16.1 Hz, 1H), 3.02 (dd, *J* = 5.4, 16.8 Hz, 1H), 3.47-3.54 (m, 2H) 3.78 (s, 3H), 3.84 (s, 3H), 4.04-4.18 (m, 2H), 6.54-6.66 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.0, 28.0, 30.0, 43.2, 49.7, 56.3, 56.6, 106.6, 112.2, 120.1, 122.3, 148.6, 149.9, 175.0; **Anal.** Calcd for $C_{14}H_{20}N_2O_3$ requires C, 63.62; H, 7.63; N, 10.60; found C, 63.73; H, 7.69; N, 10.66%.



1-[(*R*)-3-(Dimethylamino)-3,4-dihydro - 6,7 - dimethoxy quinolin-1(2H)-yl]propan-1-one (2): To a stirred solution

of crude amine 40% aq. solution HCHO (1 mL) and HCO_2H (2 mL) was added, resulting reaction mixture was refluxed for 3 h. After completion of reaction saturated $NaHCO_3$ solution (10 mL) was added and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhyd. Na_2SO_4, concentrated under reduced pressure. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: triethyl amine (60:38:2) as eluent] gave pure **2** (237 mg) as colorless solid.

Yield: 91%; m.p. 137 °C [lit.[30]135-137 °C]; $[\alpha]^{D}_{25}$ –3.7 (*c* 1, EtOH) {lit.[30] $[\alpha]^{D}_{25}$ –3.3 (*c* 1, EtOH)}[5]; **IR** ($CHCl_3$): 760, 1049, 1211, 1511, 1647, 1743, 3018, 3450 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.3 Hz, 3H), 2.35 (s, 6H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.80-2.91 (m, 2H), 3.23-3.54 (m, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 6.64 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.8, 27.5, 29.5, 41.3, 41.4, 55.9, 55.9, 61.4, 61.8, 108.2, 111.1, 128.6, 131.8, 146.9, 173.0; **Analysis** for $C_{15}H_{21}N_2O_3$ requires C, 64.96; H, 7.63; N, 10.10; found C, 64.82; H, 7.60; N, 10.27%.

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Chapter IV

Pd-catalyzed Hydrosilylation of Aryl Aldehydes and Chemoselective Reduction of aryl α,β-Unsaturated Carbonyls

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"Palladium-Catalyzed Hydrosilylation of Aryl ketones and Aldehyde" Pandurang V. Chouthaiwale, Varun Rawat, Gurunath Suryavanshi, Arumugam Sudalai *Tetrahedron Letters* **2012**, *53*, 148.

Section I

Pd-catalyzed hydrosilylation of aryl aldehydes with triethylsilane

4.1.1 Introduction

Reduction of carbonyl and pseudo-carbonyl functions represents a ubiquitous protocol in organic synthesis. Transition-metal catalysis has been successfully applied to the reduction of olefins, alkynes and many carbonyl compounds *via* hydrogenation or hydrosilylation.[1] Hydrogenation reactions often proceed in good yields but only under high pressure or elevated temperature. In contrast, since the first report of metal-catalyzed hydrosilylation of ketones in the presence of Wilkinson's catalyst,[2] smooth reaction conditions have been devised and in consequence over-reduced products are rarely detected. Recently, hydrosilylation reactions using various metals such as Zn, Fe, Rh, Cu, Re, etc have been reported. Furthermore, asymmetric hydrosilylations with high enantioselectivities have also been well-documented.[3] In industry, hydrosilylation has become an appropriate method to produce organosilicon compounds, in particular with respect to the functionalization of polymers.[4] A general sequence involving hydrosilylation of carbonyl compounds followed by hydrolysis leads to the formation of alcohols, but the silyl group may also be retained as a protecting group, a process that can be of great interest in organic synthesis.[5] Moreover, a great majority of hydrosilanes employed in this reaction are easy to handle and are economical.

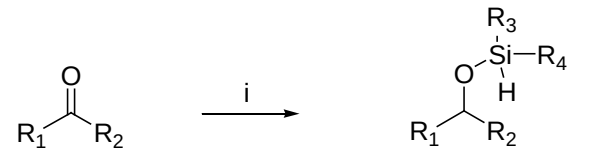
4.1.2 Review of Literature

In literature a wide variety of catalytic systems in combination with different hydrosilanes have been employed to selective reduction of carbonyl functional groups attached to aliphatic and aromatic structures. The discovery of more active catalysts and

its asymmetric version has made this process more popular. Some of the recent developments on this reaction are discussed below.

Ojima's approach (1972)[6]

Ojima et al. have reported hydrosilylation of aldehydes and ketones **1** with various hydrosilane and rhodium(I) complex to give silyl ethers **2** in very high yields (**Scheme 1**). In case of α,β−unsaturated ketones and aldehydes the corresponding saturated silyl ether derivatives were obtained in fairly high yields.



1 **2**

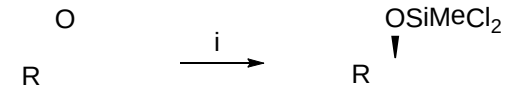
R_1 = alkyl, Ph
R_2 = H, Me, Ph

R_3 = Me, Et, Ph
R_4 = Me, Et, Ph

Scheme 1: (i) hydrosilane, $(Ph_3P)_3RhCl$ (1 mol %), n-hexane, 25 ^oC, 93-98%.

Pregosin's approach (1988)[7]

In this approach, the catalyst $PtCl_2(PhCH{=}CH_2)_2$ was shown to catalyze the hydrosilylation of various methyl ketones **3** with dichloromethylsilane in the presence of pyridine or aniline as co-catalyst to give silyl ethers **4** in 51-98% yield (**Scheme 2**). The authors have observed that the completion of this reaction required more than 24 h.



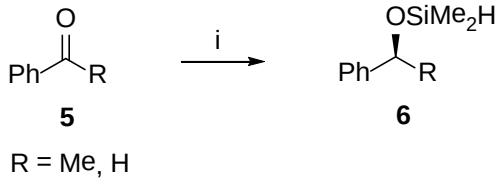
3 **4**

R = alkyl, aryl

Scheme 2: (i) $PtCl_2(PhCH{=}CH_2)$ $(PhNH_2)$, $MeCl_2SiH$, 25 ^oC, 24-41 h, 51-98%.

Samuel's approach (1999)[8]

Samuel et al. have reported bis (benzene) chromium as a pre-catalyst for the hydrosilylation of α-aryl carbonyl compounds to give the corresponding silyl ethers in 39-50% yield (**Scheme 3**).



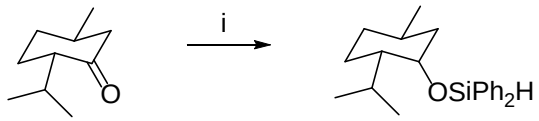
5 **6**

R = Me, H

Scheme 3: (i) Bis(benzene)chromium (0.06 mmol), $Me_2OEtSiH$, PhH, 45 °C, 3 h, 39-50%.

Lee's approach (2002)[9]

Lee et al. have described a catalytic method for the synthesis of silyl ether **8** using Grubbs' I[st] generation catalyst ($Cl_2(PCy_3)_2Ru=CHPh$). Silyl ether **8** is thus obtained from the reaction of a variety of silanes by the hydrosilylation of carbonyl compound **7** under neat conditions (**Scheme 4**).



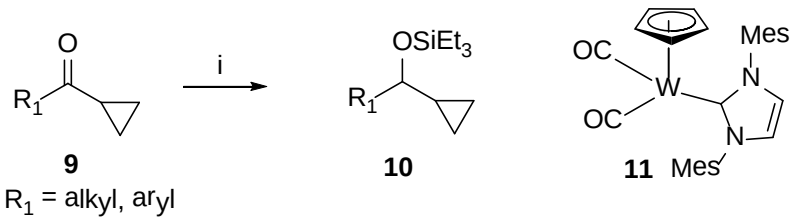
7 **8**

Scheme 4: (i) $Cl_2(PCy_3)_2Ru=CHPh$ (0.5 mol%), Ph_2SiH_2, neat, 50-80 °C, 80%.

Dioumaev's approach (2003)[10]

Dioumaev et al. have reported tungsten and molybdenum N-heterocyclic carbene complexes **11** for the hydrosilylation of carbonyl compounds **9** under mild condition accompanied by precipitation of catalysts at the end of reaction. The reaction exhibits

good rates, high conversion and excellent selectivity for hydrosilylation (**Scheme 5**).



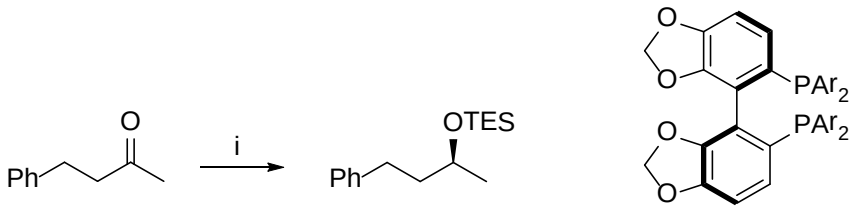
9 **10** **11**

R_1 = alkyl, aryl

Scheme 5: (i) ketone, cat,**11** (0.2 mol%), Et_3SiH, neat, 23 ^oC, 77-98%.

Lipshutz's approach (2003)[11]

Lipshutz *et al*. have developed a simple protocol for the single-flask conversion of dialkyl ketones **12** to the corresponding TES or TBS ethers **13** based on *in situ* generated catalyst i.e. hydrido copper complex (**Scheme 6**).



12 **13** **14**

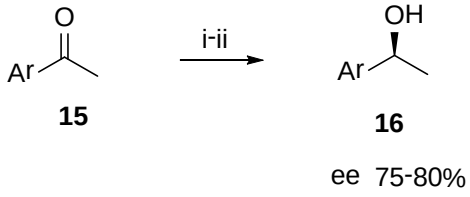
ee upto 99

(DM-SEGPHOS)

Scheme 6: (i) CuCl (0.5 mol%), NaOMe, DM-SEGPHOS, (1 mol %), Et_3SiH, Et_2O, 25 ^oC, 95%.

Yun's approach (2004)[12]

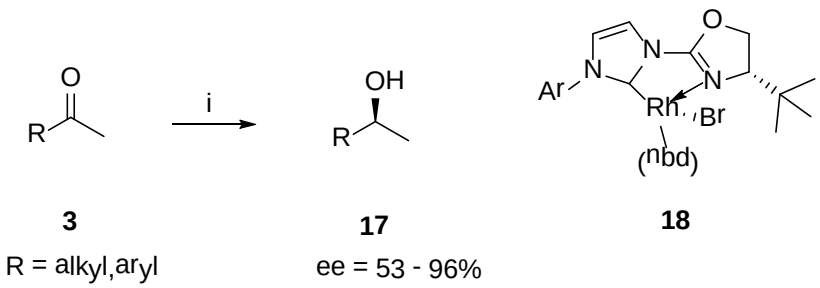
Yun *et al.* have used air and moisture stable copper(II) salts to catalyze the hydrosilylation of aromatic ketones **15**. The combination of catalytic amounts of copper(II) acetate or copper(II) acetate monohydrate and BINAP in the presence of organosilanes as the stoichiometric reducing agent generates an active catalyst for the asymmetric hydrosilylation of ketones (**Scheme 7**).



Scheme 7: (i) (i) $Cu(OAc)_2.H_2O$ (1.3 mol%), (S)-BINAP (1.3 mol %), PMHS, toluene, 0 ^oC; (ii) TBAF work up, 81-96%.

Gade's approach (2004)[13]

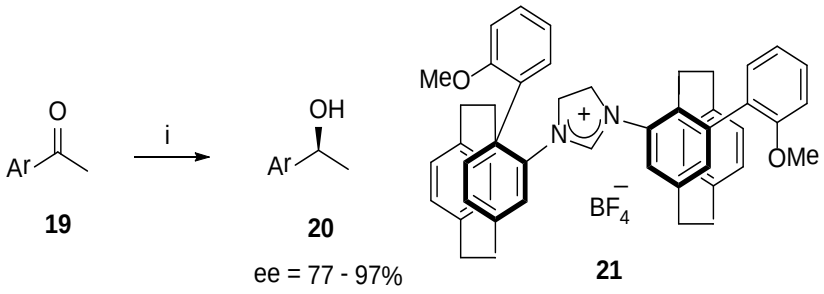
Gade *et al.* have described Rh-catalyzed asymmetric hydrosilylation of methyl ketones **3** by using chiral *N*-heterocyclic carbene as a ligand to give the corresponding alcohol **17** up to 96% ee (**Scheme 8**).



Scheme 8: (i) Rh-cat.**18** (1 mol%), $AgBF_4$ (1.2 mol%), Ph_2SiH_2, CH_2Cl_2, -60 ^oC then K_2CO_3, MeOH, 77 - 91%.

Andrus's approach (2005)[14]

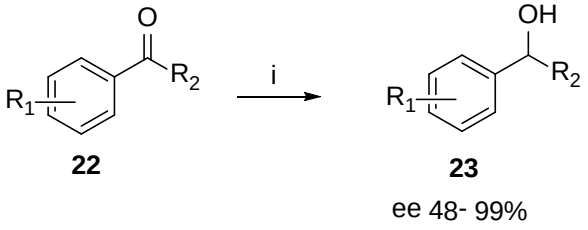
Andrus *et al.* have reported new chiral *bis*-paracyclophane *N*-heterocyclic carbene (NHC) ligands for ruthenium catalyzed asymmetric hydrosilylation of ketones **19** using diphenyl silane to give enantioenriched alcohols **20**. These ligands provide for efficient asymmetric reduction in the presence of silver(I) triflate (1 mol %) at room temperature with high reactivity and selectivity. Acetophenone was reduced with 1 mol % catalyst in 96% isolated yield, 97% ee (**Scheme 9**).



Scheme 9: (i) $RuCl_2(PPh_3)_3$ (0.5 mol%), ligand-**21** (1.2 mol %), $AgBF_4$, Ph_2SiH_2, THF, 25 °C then HCl, H_2O, 81-98%

Beller's approach (2008)[15]

Beller *et al.* have reported Fe-catalyzed enantioselective hydrosilylation of ketones **22** with various phosphine ligands. Good to excellent enantioselectivities were obtained for electronically rich and sterically hindered aryl ketones. For example, diaryl and dialkyl ketones were converted into the corresponding alcohols **23** in good to excellent enantioselectivities (up to 99% ee) (**Scheme 10**).

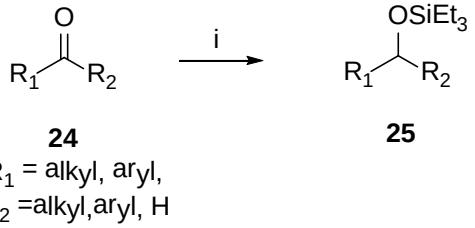


Scheme 10: (i) $Fe(OAc)_2$ (5 mol%), chiral phosphenes (10 mol %), PMHS, THF, 25-100 °C. then NaOH, MeOH, 45-99%.

Berke's approach (2009)[16]

Berke *et al.* have reported the easily available $[Re(CH_3CN)_3Br_2(NO)]$rhenium(I) complex that catalyzes the homogeneous hydrosilylation of a great variety of organic carbonyl compounds (ketones and aldehydes). Various aliphatic and aromatic silanes were tested as hydride source. Excellent yields were achieved at 85 °C in chlorobenzene

using triethylsilane. The reaction proceeded with TOF values of up to 495 h^{-1} (**Scheme 11**).



24

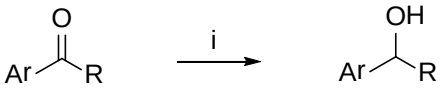
R_1 = alkyl, aryl,
R_2 =alkyl,aryl, H

25

Scheme 11: (i) $[Re(CH_3CN)_3Br_2(NO)]$ (1 mol%), Et_3SiH, CH_2Cl_2, 85 ^oC, 71-99%.

Nishiyama's approach (2009)[17]

Nishiyama *et al.* have reported zinc acetate as an efficient catalyst for hydrosilylation of ketones and aldehydes in combination with $(EtO)_2MeSiH$ to give the corresponding alcohols in 91-99% yield (**Scheme 12**).



26

R = Me, H

27

Scheme 12: (i) $Zn(OAc)_2$ (5 mol%), $(EtO)_2MeSiH$, THF, 65 ^oC then H_3O^+, 91-99%.

4.1.3 Present Work

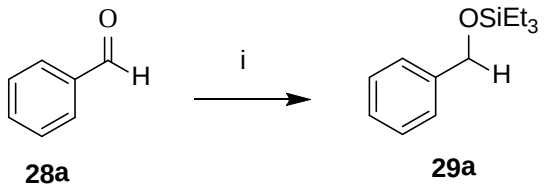
4.1.3.1 Objective

In recent years, considerable progress has been made in hydrosilylation of various organic carbonyl compounds. It has become a major tool of synthetic organic chemistry and organosilicon chemistry, thus providing an efficient and versatile access to new organo silicon compounds. There are many methods available in the literature for hydrosilylation of carbonyl compounds using a variety of metal catalysts and hydrosilanes. Moreover, metals such as palladium have not been studied extensively for

the hydrosilylation of aldehydes.[18] In this section, we describe an efficient and selective method for the hydrosilylation of various aryl aldehydes catalyzed by palladium using triethylsilane as the hydride source.

4.1.3.2 Results and Discussion

It has been reported in the literature that the reaction of aryl carbonyl compounds with $PdCl_2$ as catalyst and triethylsilane in ethanol led to the formation of reduction product namely alkyl arenes.[19] We found however, that when the same reaction was carried out on benzaldehyde **28a** in the presence of $PdCl_2$ as catalyst using DMF as solvent, it took a different course to give the triethylsilyl protected alcohol **29a** in good yield (**Scheme 13**).



28a **29a**

Scheme 13: (i) benzaldehyde (1 equiv), $PdCl_2$ (0.5 mol%), Et_3SiH (1.2 equiv.), DMF, 25 °C, 2 h, 78%

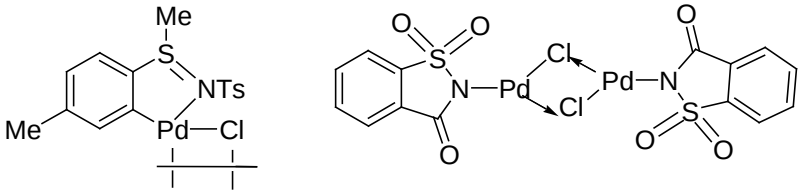
In order to study this catalytic reaction in a systematic manner, several Pd-catalysts have been screened with benzaldehyde **28a** as a model substrate and the results of such a study are shown in **Table 1**.

Table 1: Pd-catalyzed hydrosilylation of benzaldehyde **28a**: effect of catalysts[a]

Entry	Catalyst	Yield of 29a (%)
1	$Pd(OAc)_2$	93
2	$PdCl_2$	78
3	$Pd(PhCN)_2Cl_2$	80
4	$Pd(dba)_2$	60
5	$Pd(Ph_3P)_4$	76
6	Sulfimine palladacycle (**30**)	78
7	Saccharine complex (**31**)	67
8	10% Pd/C	82

Reaction conditions: [a]benzaldeyhde (1 mmol), Pd-catalyst (0.5 mol%), Et_3SiH (1.2 mmol), DMF (2 ml), 25 ^oC, 1 h.

All the palladium catalysts screened gave excellent yields of hydrosilylated product **29a**. The maximum yield of silyl ether was obtained with $Pd(OAc)_2$ (93%), whereas $Pd(dba)_2$ (60%) gave the lowest yield. Sulfilimine palladacycle[20] **30** and water soluble palladium saccharine compex[21] **31** (**Fig. 1**) also gave good yields of silyl ether **29a**.



30 **31**

Figure 1: Structures of palladium catalysts **30** and **31**

The results from **Table 2** have shown that out of a variety of solvents screened, DMF was found to be more suitable for Pd-catalyzed hydrosilylation of benzaldehyde. However, when DMF-water (4: 1) or water was employed as solvent,[22] the corresponding benzyl alcohol was obtained as the only product in good yields.

Table 2: $Pd(OAc)_2$-catalyzed hydrosilylation of benzaldehyde **28a**: effect of solvents[a]

Entry	Solvent	Time (h)	Yield of 29a (%)[b]
1	CH_2Cl_2	20	0
2	CH_3CN	6	60
3	toluene	20	0
4	water	6	40[c]
5	DMF- water (4:1)	1	75[c]
6	DMF	1	93
7	DMF	20[d]	0
8	DMF	20[e]	0

Reaction condition: [a]benzaldehyde (1 mmol), $Pd(OAc)_2$ (0.5 mol%), Et_3SiH (1.2 mmol), solvent (2 ml), 25 ^oC, 1 h; [b]isolated yield; [c] benzyl alcohol was obtained; [d] PMHS is used as as hydride source; [e] diphenyl silane is used .

When other hydrosilanes such as Ph_2SiH_2, PMHS etc were used as a hydride source with DMF as solvent, we observed that the reaction failed to give any product.

In order to understand the scope and generality of the reaction, a wide range of functionalized aromatic aldehydes including indole-3-carboxaldehyde **28l** were subjected to the optimized conditions. Indeed, this protocol gave excellent yields of the respective hydrosilylated products (**Table 3**). The method has shown high tolerance for other sensitive functional groups such as ester, fluoro, hydroxyl, amine, imine, olefin and alkyne present either on aromatic nucleus or aliphatic system. In case of chloro substituted aryl aldehydes, the corresponding dehaloganated silyl ether was obtained in 51-54% yield along with 10% of dechlorinated benzaldehyde (entry f). For bromobenzaldehydes, the exclusive product obtained was the debrominated benzaldehyde (entry g). On the other hand, p-fluorobenzaldehyde underwent the reaction smoothly to give the corresponding hydrosilylated product without the fluoro group being affected (entry h).

Table 3: $Pd(OAc)_2$-catalyzed hydrosilylation of aryl aldehydes[a]

Entry	Substrates (28)	Product (29)	Yield (%)[b]
a	benzaldehyde	benzyloxytriethylsilane	93
b	4-methylbenzaldehyde	4-methylbenzyloxy-triethylsilane	93
c	4-methoxy-benzaldehyde	4-methoxybenzyloxy-triethylsilane	96

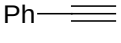
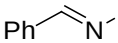
d	4-(methylthio)-benzaldehyde	4-(methylthio)benzyloxy-triethylsilane	75
e	3,4-(methylenedioxy)-benzaldehyde	3,4-(methylenedioxy)benzyloxy-triethylsilane	96
f	2-, 3- or 4-chloro-benzaldehyde	benzyloxytriethylsilane	51-54[c]
g	2- , 3- or 4-bromo-benzaldehyde	benzaldehyde	87-88
h	4-fluorobenzaldehyde	4-fluorobenzyloxytriethylsilane	81
i	4-(trifluoromethyl)-benzaldehyde	4-(trifluoromethyl)benzyloxy-triethylsilane	90
j	methyl 2-formyl 3,5-dimethoxybenzoate	methyl 3,5-dimethoxy-2-((triethylsilyloxy)methyl) benzoate	92
k	4-hydroxy-3-methoxy-benzaldehyde	4-hydroxy-3-methoxybenzyl-oxytriethylsilane	81
l	indole-3-carboxaldehyde	3-(((triethylsilyl)oxy)-methyl)-indole	87
m	methyl 3-(4-formyl-phenyl)acrylate	methyl 3-(4-(((triethylsilyl)-oxy)methyl)phenyl)acrylate	86

n	methyl 3-(4-formyl-phenyl)propanoate	methyl 3-(4-(((triethylsilyl)oxy) methyl)phenyl)propanoate	85

Reaction condition**:** [a]aryl aldehyde (1 mmol), $Pd(OAc)_2$ (0.5 mol%), Et_3SiH (1.2 mmol), dry DMF (2 ml), 25 ^oC, 1 h; [b] isolated yield [c] ~ 10% of the corresponding unsubstituted benzaldehyde was obtained.

However, the reaction failed in the case of aliphatic aldehydes, which is a limitation of this protocol. This catalytic system can be unique in selectively hydrosilylating aromatic aldehydes in presence of aliphatic aldehydes. This has been demonstrated by carrying out the competitive experiments involving 1:1 molar equivalents of aliphatic ketones / aldehydes and aromatic ketones / aldehydes, results of which are presented in **Table 4**. As can be seen from **Table 4**, acetylene and imine groups were not affected in the presence of aromatic aldehyde.

Table 4: $Pd(OAc)_2$-catalyzed hydrosilylation of carbonyl compounds: competitive experiments[a]

Entry	Substrates	Product	Yield (%)[b]
a	$PhCH_2CH_2COCH_3$ + $PhCOCH_3$	$PhCH(OSiEt_3)CH_3$	96
b	$PhCH_2CH_2COCH_3$ + PhCHO	$PhCH_2OSiEt_3$	91
c	$PhCH_2CH_2COCH_3$ + $PhCOCH_3$	$PhCH(OSiEt_3)CH_3$	94
d	$PhCH_2CH_2CHO$ + PhCHO	$PhCH_2OSiEt_3$	88
e	PhCHO + $PhCOCH_3$	$PhCH_2OSiEt_3$	84
f	4-CF_3 PhCHO + 4-CH_3 PhCHO	4-CF_3 $PhCH_2OSiEt_3$ + 4-CH_3 $PhCH_2OSiEt_3$	90 (2.5:1)
g	 + PhCHO	$PhCH_2OSiEt_3$	91
h	 + Ph-CHO	$PhCH_2OSiEt_3$	83

Reaction condition**:** [a] 1:1 molar equivalents of substrates (5 mmol each), $Pd(OAc)_2$ (0.5 mol%), Et_3SiH (6 mmol), dry DMF (10 ml), 25 ^oC, 1 h; [b] isolated yield

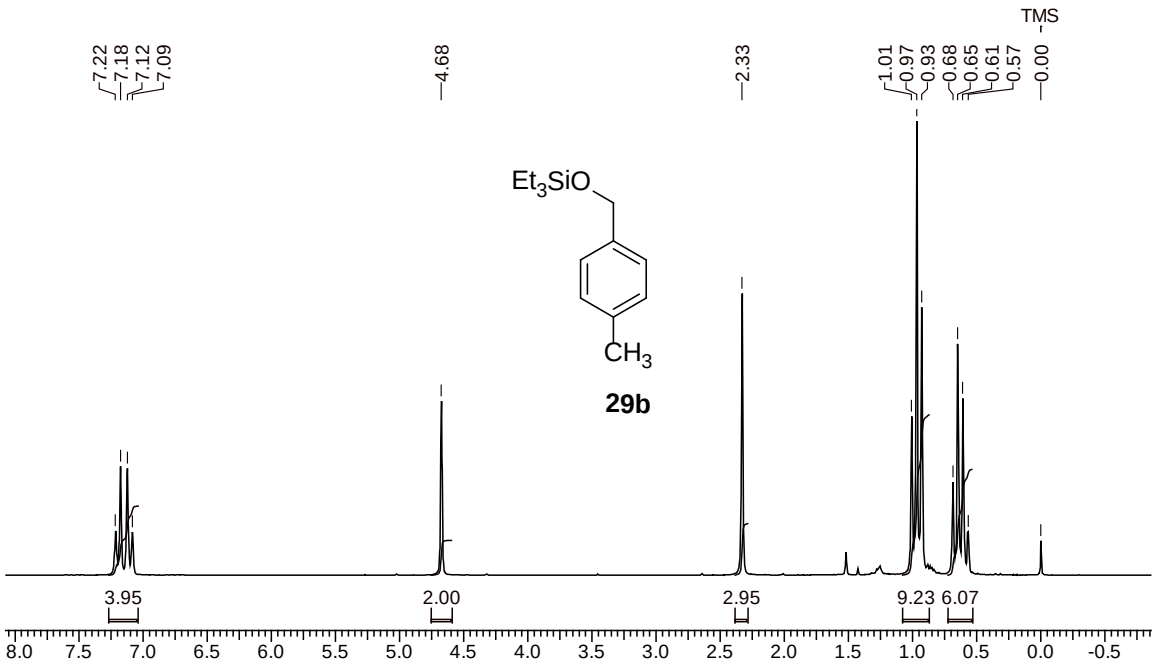
A noteworthy feature of this protocol is that when reaction was carried out in DMF-water (4:1) solvent system, the corresponding benzylic alcohols **32a-c** were produced in high yields (**Table 5**). Thus, both hydrosilylation and deprotection of the silyl ether were achieved in a single step by using a simple modification of the solvent system.

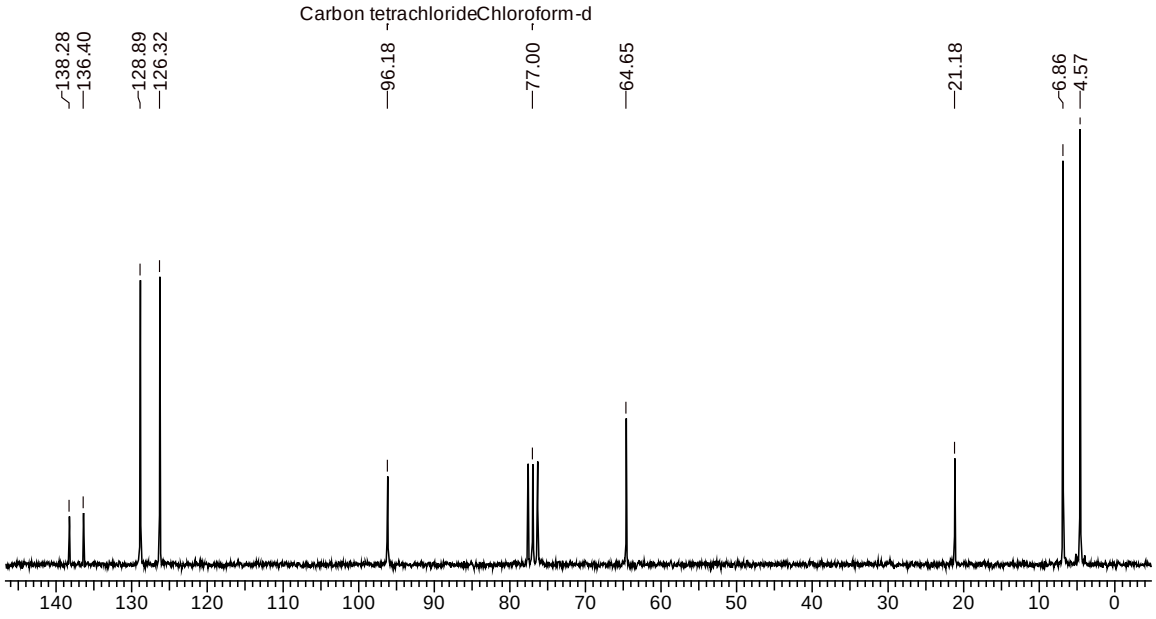
Table 5: $Pd(OAc)_2$-catalyzed hydrosilylation using DMF:H_2O as solvent system.[a]

Entry	Substrate	Product (32)	Yield (%)[b]	
			$Pd(OAc)_2$	Saccharine-Pd complex
a	benzaldehyde	benzyl alcohol	87	76
b	4-methoxy-benzaldehyde	4-methoxy-benzyl alcohol	90	75
c	3,4-(methylenedioxy)-benzaldehyde	3,4-(methylenedioxy)-benzyl alcohol	90	77

Reaction condition: [a] aromatic aldehydes (1 mmol), $Pd(OAc)_2$-catalyzed (0.5 mol%), Et_3SiH (1.2 mmol), DMF: water (1.5:0.5 ml), 25 ^oC, 2 h ; [b]isolated yield.

The formation of silyl ethers **29a-n** was confirmed by ^1H and ^{13}C-NMR spectroscopy. **Example 1:** The ^1H NMR spectrum of **29b** showed signal at δ 4.68 (s) for methylene (Ph-**CH_2**-OSi) protons. Its ^{13}C-NMR spectrum showed a typical signal at δ 64.65 due to carbon attached to silyloxy group (**Figure 2)**.


TMS
7.22
7.18
7.12
7.09
4.68
2.33
1.01
0.97
0.93
0.68
0.65
0.61
0.57
0.00
Et3SiO
CH3
29b
3.95
2.00
2.95
9.23
6.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Carbon tetrachloride
Chloroform-d
138.28
136.40
128.89
126.32
96.18
77.00
64.65
21.18
6.86
4.57
140
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120
110
100
90
80
70
60
50
40
30
20
10
0

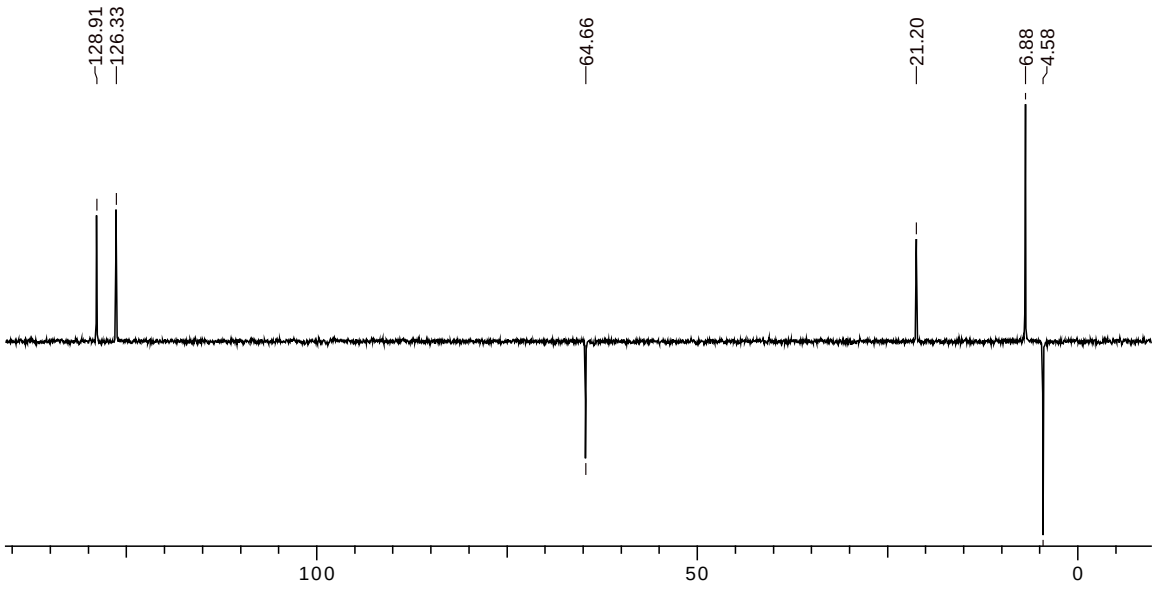


Figure 2: ^{1}H & ^{13}C and DEPT NMR spectra of **29b**

Example 2: The ^{1}H NMR spectrum of hydrosilylation reaction of a mixture containing *p*-methyl benzaldehyde and *p*-trifluromethyl benzaldehyde (1:1) displayed signals at δ 4.68 (s) and 4.77 (s) for methylene (Ar-**CH_2**-OSi) protons. Its ^{13}C-NMR spectrum showed typical carbon signals at δ 64.6 and 64.0 due to carbon attached to silyloxy group (**Figure 3).**

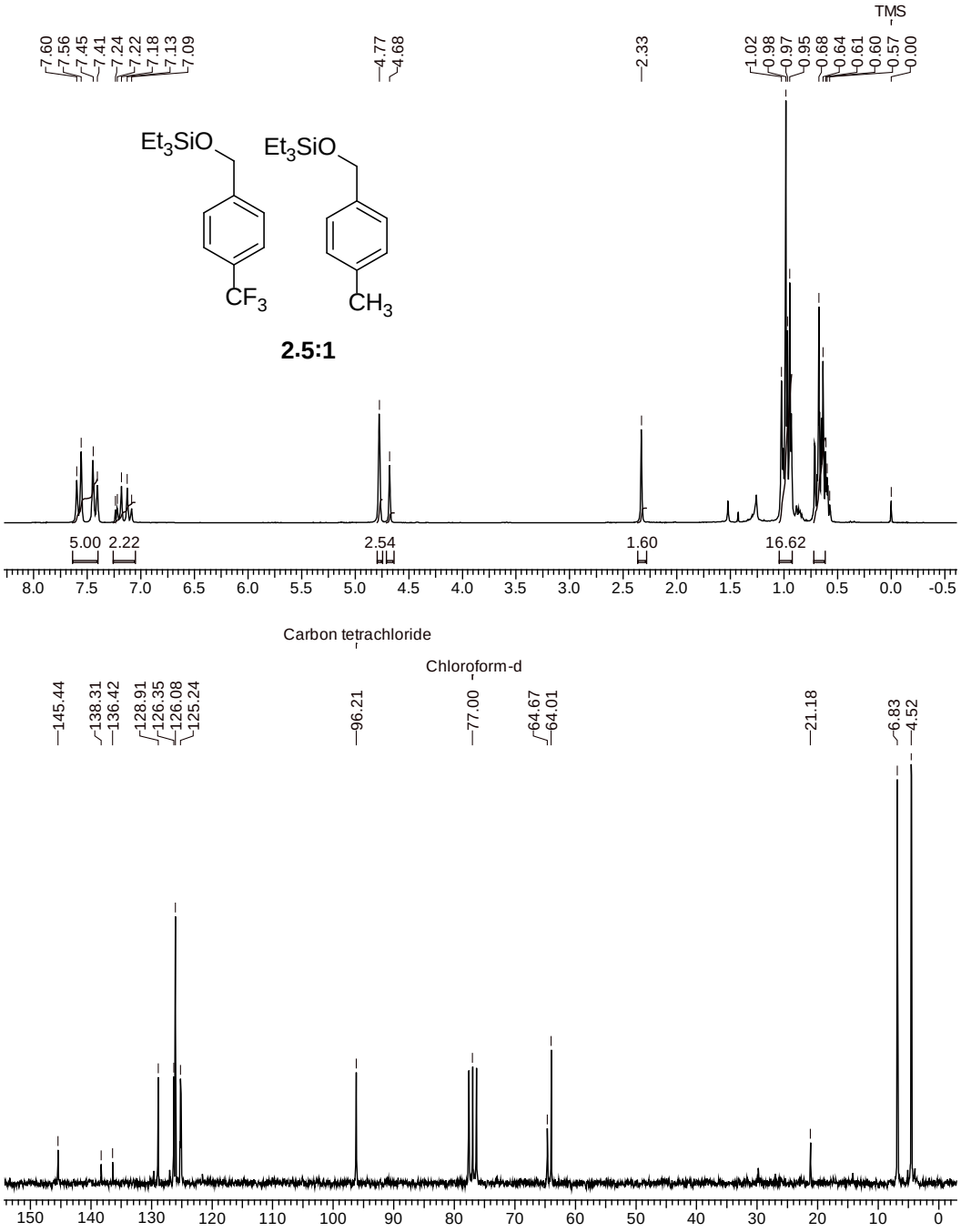


Figure 3: ^{1}H and ^{13}C NMR spectra of entry f, **Table 4**

Example 3: The ^{1}H NMR spectrum of **32c** showed a typical singlet at δ 4.55 for benzylic (Ph-**CH_2**-OH) protons. Its ^{13}C-NMR spectrum showed a typical signal at δ 64.74 due to carbon attached to hydroxy group (**Figure 4)**.

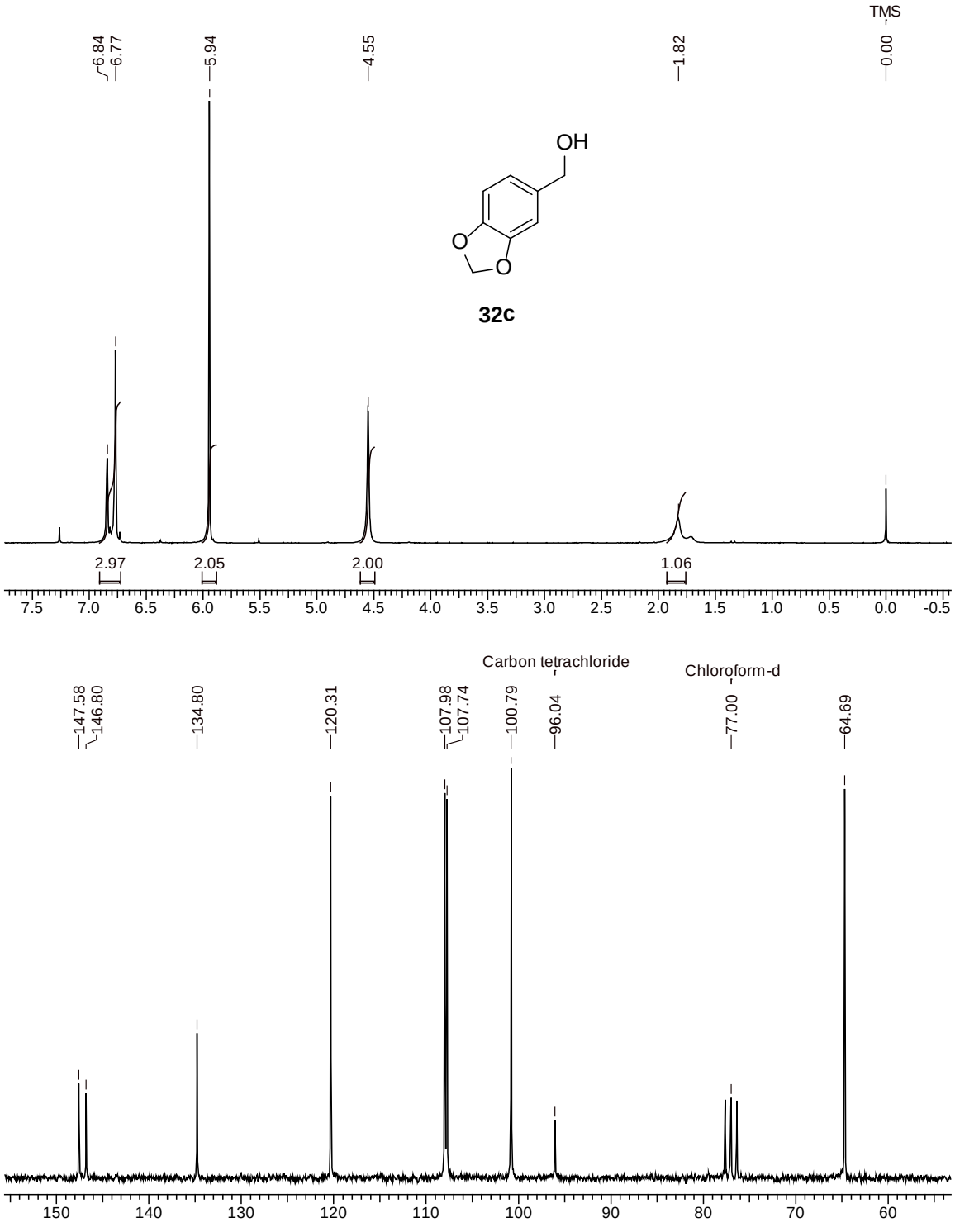
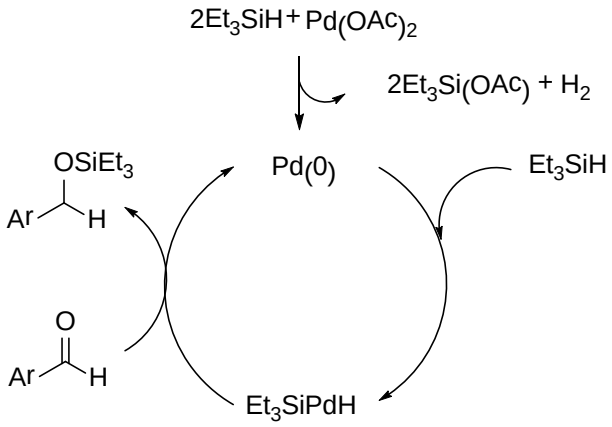


Figure 4: ^{1}H and ^{13}C NMR spectra **32c**

4.1.3.3 Mechanism

The catalytic cycle for the oxidative process is shown in **Scheme 14.** The first step corresponds to the reaction of palladium acetate with Et_3SiH leading to the formation of active metallic Pd(0) entity in the catalyzed reaction.[23] Oxidative addition of Et_3SiH to Pd(0) leads to the formation of Et_3SiPdH complex, which is co-ordinating with aryl aldehyde. Then hydride transfer to aryl aldehyde followed by reductive elimination generates the desired silylated product with liberation of Pd(0).



Scheme 14: Proposed mechanism for Pd-catalyzed hydrosilylation of aryl aldehyde

4.1.4 Conclusion

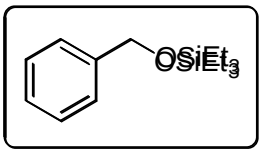
In conclusion, we have demonstrated, for the first time, that Pd is a highly effective catalyst for selective hydrosilylation of aryl aldehydes in DMF at room temperature using triethylsilane as a hydride source. Also we found that benzyl alcohol was obtained in excellent yields, when reaction was performed in DMF: H_2O (4:1) as solvent system in a single step.

4.1.5 Experimental Section

General experimental procedure for the hydrosilylation of aromatic aldehydes

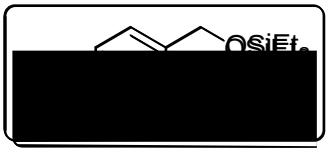
To a 10 mL two-neck round-bottomed flask with a magnetic stir bar was added palladium catalyst (0.5 mol%) in DMF (2.0 mL). To this was added aromatic aldehyde **28a-n** (1.0 mmol) followed by triethylsilane (1.2 mmol). The resulting solution was stirred for 1 h. After completion of the reaction, it was subsequently loaded directly onto the column (silica gel 60-120 mesh) for purification using petroleum ether as eluent to afford pure **29a-n**.

Benzyloxytriethylsilane (29a)



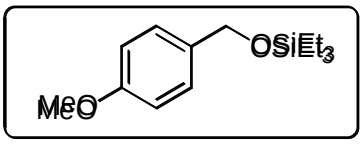
Yield: 93% (207 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1256, 1335, 1445, 1517, 2898 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.58 (q, *J* = 7.7 Hz, 6H), 0.94 (t, *J* = 7.7 Hz , 9H), 4.73 (s, 2H), 7.20-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.5, 6.8, 64.7, 126.1, 126.9, 128.2, 141.2 ; **Anal.** Calcd for $C_{13}H_{22}OSi$ requires C, 70.21; H, 9.97; found C, 70.19; H, 10.1%.

4-Methylbenzyloxytriethylsilane (29b)



Yield: 93% (220 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1315, 1415, 1432, 2997, 3109 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.57 (q, *J* = 7.9 Hz, 6H), 0.97 (t, *J* = 8.2 Hz , 9H), 2.33 (s, 3H), 4.68 (s, 2H), 7.09-7.22 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.6, 6.9, 21.2, 64.6, 126.3, 128.9, 136.4, 138.3; **Anal.** Calcd for $C_{14}H_{24}OSi$ requires C, 71.12; H, 10.23; found C, 71.18; H, 10.35%.

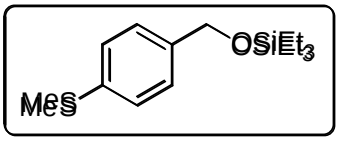
4-Methoxybenzyloxytriethylsilane (29c)



Yield: 96% (242 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1245, 1365, 1414, 1624 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.57 (q, *J* = 8.0 Hz, 6H), 0.93 (t, *J* = 8.2 Hz , 9H), 3.78 (s, 3H), 4.65 (s, 2H),

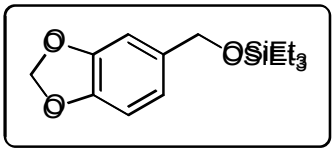
6.86 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.4, 6.7, 54.9, 64.3, 113.5, 127.5, 133.3, 158.6; **Anal.** Calcd for $C_{14}H_{24}O_2Si$ requires C, 66.61; H, 9.58; found C, 66.53; H, 9.60%.

4-(Methylthio)benzyloxytriethylsilane (29d)



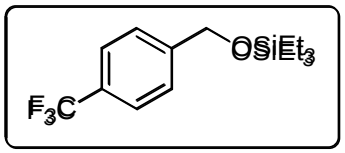
Yield: 75% (201 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1113, 1238, 1424, 2876 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.61 (q, *J* = 8.0 Hz, 6H), 0.91 (t, *J* = 8.1 Hz , 9H), 2.46 (s, 3H), 4.67 (s, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.5, 6.8, 16.2, 64.3, 126.8, 128.0, 136.7, 136.8; **Anal.** Calcd for $C_{14}H_{24}OSSi$ requires C, 62.63; H, 9.01; found C, 62.61; H, 9.09%.

3,4-(Methylenedioxy)benzyloxytriethylsilane (29e)



Yield: 96% (255 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1213, 1465, 1514, 1123 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.61 (q, *J* = 8.0 Hz, 6H), 0.93 (t, *J* = 8.3 Hz , 9H), 4.61 (s, 2H), 5.93 (s, 2H), 6.74 (d, *J* = 1.0 Hz, 2H), 6.82 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.4, 6.7, 64.5, 100.6, 107.1, 107.8, 119.3, 135.2, 146.4, 147.5; **Anal.** Calcd for $C_{14}H_{22}O_3Si$ requires C, 63.12; H, 8.32; O; found C, 63.38; H, 8.40%.

4-(Trifluoromethyl)benzyloxytriethylsilane (29i)

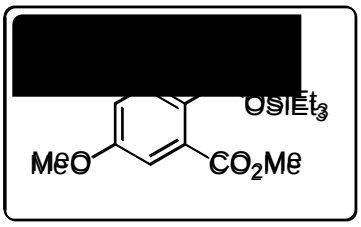


Yield: 90% (261 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1375, 1609, 2908, 3091 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.68 (q, *J* = 7.8 Hz, 6H), 0.98 (t, *J* = 8.3 Hz , 9H), 4.78 (s,

2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.5, 6.7, 64.0, 125.1, 125.22, 125.24, 126.0, 145.5; **Anal.** Calcd for $C_{14}H_{21}F_3OSi$ requires

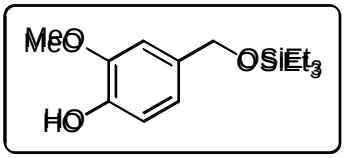
C, 57.90; H, 7.29; found C, 58.10; H, 7.35%.

Methyl 3,5-dimethoxy-2-((triethylsilyloxy)methyl)benzoate (29j)



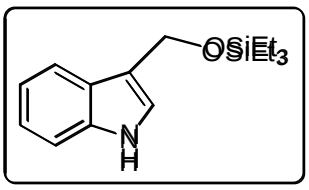
Yield: 92% (313 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1234, 1514, 1564, 1724, 2997 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.59 (q, *J* = 8.1 Hz, 6H), 0.93 (t, *J* = 8.2 Hz , 9H), 3.81 (s, 6H), 3.87 (s, 3H), 4.89 (s, 2H), 6.53 (d, *J* = 2.4 Hz , 1H), 6.78 (d, *J* = 2.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.4, 6.7, 52.0, 55.3, 55.4, 55.7, 101.4, 105.1, 122.2, 133.6, 158.6, 159.5, 168.8; **Anal.** Calcd for $C_{17}H_{28}O_5Si$ requires C, 59.97; H, 8.29; found C, 59.87; H, 8.26%.

4-Hydroxy-3-methoxy benzyloxytriethylsilane (29k)



Yield: 81% (217 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1345, 1514, 2897, 3340 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.53 (q, *J* = 8.7 Hz, 6H), 0.93 (t, *J* = 8.2 Hz , 9H), 3.89 (s, 3H), 4.64 (s, 2H), 5.56 (br s, 1H), 6.74-6.88 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.7, 6.6, 55.6, 64.7, 109.3, 114.2, 119.3, 133.1, 144.7, 146.5; **Anal.** Calcd for $C_{14}H_{24}O_3Si$ requires C, 62.64; H, 9.01; found C, 62.58; H, 8.97%.

3-(((Triethylsilyl)oxy)methyl)-indole (29l)

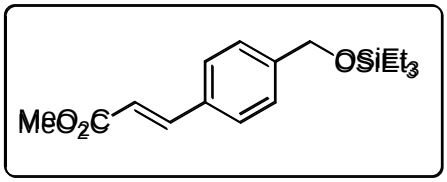


Yield: 87% (227 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1345, 1387, 1514, 3332 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.58 (q, *J* = 7.8 Hz, 6H), 0.93 (t, *J* = 8.2 Hz , 9H), 4.92 (s, 2H), 7.0-

7.44 (m, 4H), 7.08-7.31 (m, 4H), 7.64 (d, J = 7.4, 1H), 8.19 (brs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.4, 6.8, 57.6, 111.0, 116.1, 119.1, 119.3, 121.9, 122.2, 126.5, 136.4; **Anal.** Calcd for $C_{15}H_{23}NOSi$ requires C, 68.91; H, 8.87; N, 5.36; found C, 68.87; H, 8.94; N,

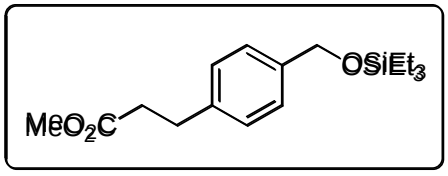
5.42%.

Methyl 3-(4-(((triethylsilyl)oxy)methyl)phenyl)acrylate (29m)



Yield: 86% (263 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 987, 1345, 1469, 1517, 1714 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.56 (q, *J* = 7.9 Hz, 6H), 0.93 (t, *J* = 8.2 Hz , 9H), 3.79(s, 3H), 4.74 (s, 2H), 6.37 (d, *J* = 15.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.5, 6.7, 64.2, 64.5, 117.1, 126.4, 128.0, 133.1, 143.9, 144.8, 167.4; **Anal.** Calcd for $C_{17}H_{26}O_3Si$ requires C, 66.62; H, 8.55; found C, 66.56; H, 8.45%.

Methyl 3-(4-(((triethylsilyl)oxy)methyl)phenyl)propanoate (29n)

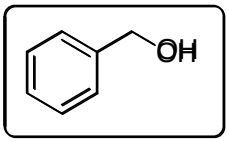


Yield: 85% (262 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 987, 1129, 1394, 1481, 1722 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.53 (q, *J* = 8.1 Hz, 6H), 0.93 (t, *J* = 8.2 Hz , 9H), 2.57 (t, *J* = 8.1 Hz, 2H), 2.89 (t, *J* = 7.3 Hz, 2H), 3.65 (s, 3H), 4.68 (s, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 9.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.4, 6.7, 30.5, 35.7, 51.4, 64.4, 126.4, 128.0, 139.0, 139.1, 173.1; **Anal.** Calcd for $C_{17}H_{28}O_3Si$ requires C, 66.19; H, 9.15; found C, 66.21; H, 9.20%.

General experimental procedure for the hydrosilylation of aryl aldehyde in DMF-water:

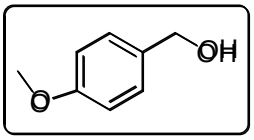
To a 10 mL two-neck round-bottomed flask with a magnetic stir bar was added palladium catalyst (0.5 mol%) in DMF: water (1.5: 0.5 mL). To this was added aryl aldehyde (1.0 mmol) followed by triethylsilane (1.2 mmol). The resulting solution was stirred for 2 h. It was subsequently quenched with water, extracted with EtOAc (3x10 mL) and dried over anhyd. Na_2SO_4. The solvent was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (petroleum ether/EtOAc as eluent) to afford the pure alcohols **32a-c**.

Benzyl alcohol 32a



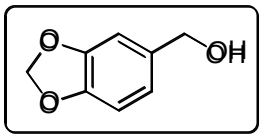
Yield: 87% (94 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1229, 1354, 1456, 2908, 3398 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.78 (br s, 1H), 4.65 (s, 2H), 7.31-7.42 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 65.0, 126.9, 127.4, 128.4, 140.8; **Anal.** Calcd for C_7H_8O requires C, 77.75; H, 7.46; found C, 77.77; H, 7.49%.

***p*-Methoxybenzyl alcohol 32b**



Yield: 90% (124 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1116, 1254, 1459, 2967, 3378 cm^{-1} **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.82 (br s, 1H), 3.79 (s, 3H), 4.57 (s, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 64.5, 113.7, 128.5, 133.1, 158.9; **Anal.** Calcd for $C_8H_{10}O_2$ requires C, 69.54; H, 7.30; found C, 69.34; H, 7.38%.

3,4-(methylenedioxy)benzyl alcohol 32c



Yield: 90% (137 mg); yellow solid; m.p. 52-54 ^oC; **IR** ($CHCl_3$): υ_{max} 1226, 1323, 1489, 2887, 3405 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.82 (br s, 1H), 4.55 (s, 2H), 5.94 (s, 2H), 6.77 (s, 2H), 6.82 (s, 1H); **^{13}C NMR**

(50 MHz, $CDCl_3$): δ 64.7, 100.8, 107.7, 108.0, 120.3, 134.8, 146.8, 147.6; **Anal.** Calcd for $C_8H_8O_3$ requires C, 63.15; H, 5.30; found C, 63.14; H, 5.34%.

Section II

Pd-catalyzed chemoselective reduction of aryl α,β-unsaturated carbonyls with triethylsilane

4.2.1 Introduction

Transition-metal catalyzed hydrogenation methods have been successfully applied to a number of chemical transformation of functional groups.[24] Chemoselective hydrogenation amomg some reducible functionalities has been one of the most desirable transformation in the field of synthetic chemistry. Although Pd/C is known as the most universal catalyst for hydrogenation and its reaction often proceed in good yields but the use of high pressure or elevated temperature along with the poor selectivity due to its efficient catalytic activity makes this approach highly undesirable.[25] In contrast, several other metal-catalyzed reductions with smooth reaction conditions have been devised for the chemoselective reduction of aromatic α,β-unsaturated carbonyls. Most of the procedures reported for the selective reduction of activated (conjugated) olefins involve a pyrophoric hydride source or an expensive catalyst. The metals and metallic hydrides include metals such as iron, tin, zinc, nickel, copper, sodium, boron and aluminium. The expensive catalytic systems include rhodium, molybdenum, cobalt and platinum. However, the highly hydridic nature of most of these metals (primarily sodium, boron and aluminium and their metal hydrides, but also the platinum or rhodium catalysts (used for hydrogenation) limits their usefulness when high chemoselectivity is required. Despite the fact that a plethora of reducing reagents is available for this operation, new reagents, especially the catalytic chemoselective versions, are still highly desirable.

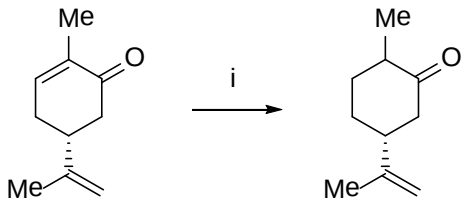
4.2.2 Review of Literature

In literature a wide variety of catalytic systems are known for selective reduction of α,β-

unsaturated carbonyl functional groups attached to aliphatic and aromatic structures. The discovery of more active catalysts and its asymmetric version has made this process more popular. Since a number of monograms and reviews are available in literature[26] only the latest developments will be presented below.

Magnus's approach (2000)[27]

Magnus *et al.* have reported the synthesis of various saturated ketones from a variety of α,β-unsaturated ketones, by treatment with 2 equiv. of $PhSiH_3$ in the presence of $Mn(dpm)_3$ (3 mol%) as catalyst in isopropyl alcohol as solvent. The saturated ketones were obtained in moderate to good yields (**Scheme 15**).

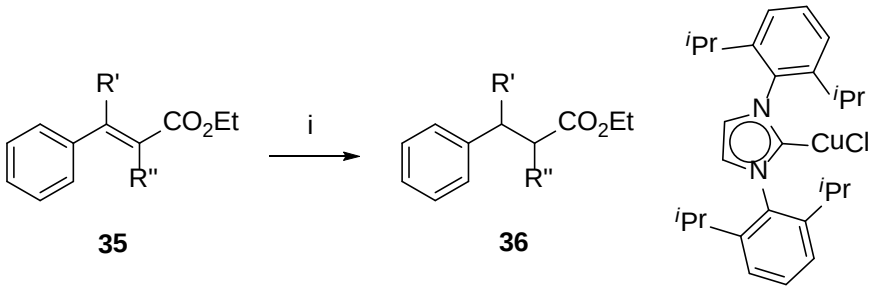


33 **34**

Scheme 15: (i) $Mn(dpm)_3$ (3 mol %), $PhSiH_3$ (2 equiv), 25 ^{o}C, 50%.

Buchwald's approach (2003)[28]

In this approach, N-heterocyclic carbene copper chloride (NHC-CuCl) complex **5** has been prepared and used to catalyze the conjugate C=C reduction of α,β-unsaturated carbonyl compounds. The combination of catalytic amounts of **37** and NaO*t*-Bu with poly(methylhydrosiloxane) (PMHS) as the stoichiometric reductant generates an active catalyst for the 1,4-reduction of tri- and tetrasubstituted α,β-unsaturated esters and cyclic enones (**Scheme 16**).



35 **36** **37**

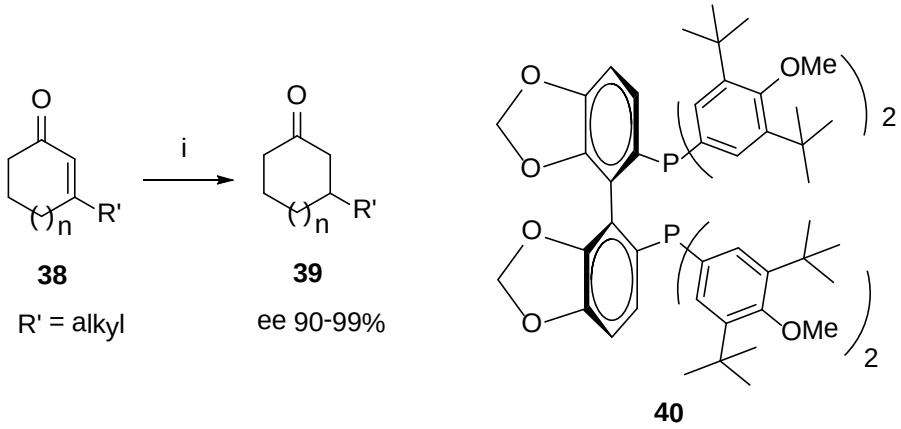
R' = Me, Et

R'' = H, CN

Scheme 16: (i) **37**, NaO*t*-Bu, PMHS (4 equiv), t-BuOH (4 equiv), toluene, 25 °C, 1 h, 91-97%.

Lover's approach (2004)[29]

Lover *et al.* have reported that the reagent combination of copper hydride (1 mol%) ligated by a nonracemic SEGPHOS ligand leads *in situ* to an extremely reactive species capable of effecting asymmetric hydrosilylations of conjugated cyclic enones in very high enantioselectivity. An unprecedented substrate to-ligand ratio as high as 275 000:1 for this transformation has been reported (**Scheme 17**).



38 **39** **40**

R' = alkyl

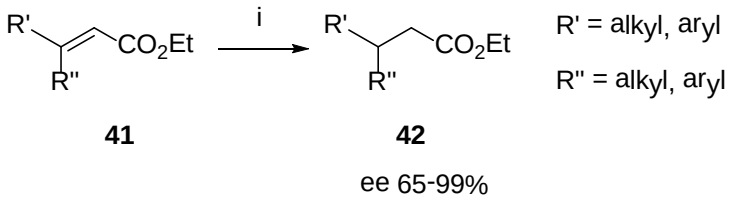
ee 90-99%

Scheme 17: (i) **40** (0.1 mol%), Ph_3PCuH (1 mol%), PMHS (2 equiv), benzene, -78 °C, 16 h, 80-90%.

Taft's approach (2004)[30]

Taft *et al.* have described a new catalytic method for the C=C reduction of α,β-

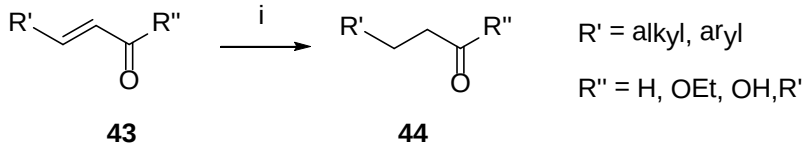
unsaturated esters. The authors have used catalytic amounts of CuH with a nonracemic SEGPHOS ligand, together with stoichiometric PMHS which leads to exceedingly efficient and highly enantioselective 1,4-reductions of β,β-disubstituted enoates and lactones (**Scheme 18**).



Scheme 18: (i) **37** (1 mol%), Ph_3PCuH (5 mol%), PMHS (2 equiv), *t*-BuOH, benzene, 0 ^{o}C, 10-20 h, 70-85%.

Alonso's approach (2006)[31]

Alonso et al. have developed a catalytic system comprising of nickel(II) chloride, lithium metal and ethanol, which has been efficiently applied to the conjugate reduction of a variety of α,β-unsaturated carbonyl compounds (ketones and carboxylic acid derivatives) under very mild reaction conditions (**Scheme 19**).

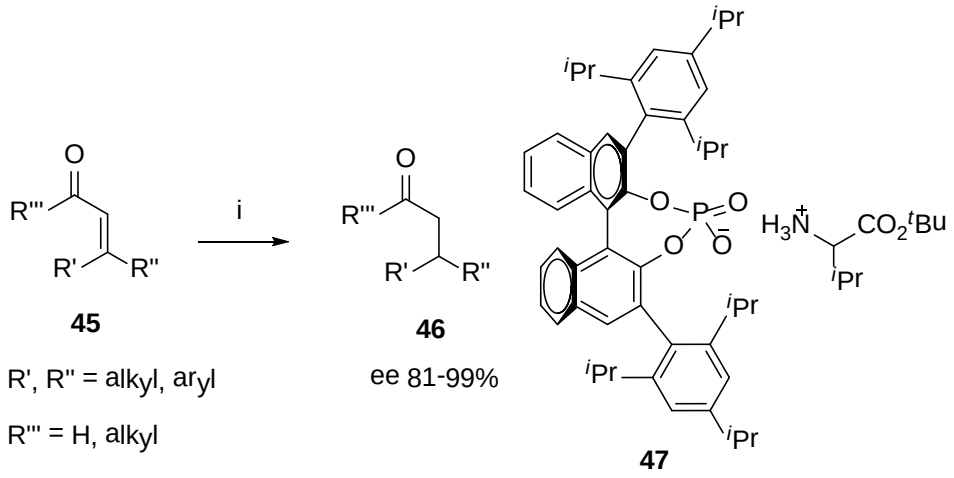


Scheme 19: (i) $NiCl_2$ (1 equiv), Li (4 equiv), EtOH (2.2 equiv), THF, 25 ^{o}C, 24 h, 72-98%.

List's approach (2006)[32]

List *et al*. have describe an efficient and highly enantioselective conjugate transfer hydrogenation of α,β-unsaturated ketones and aldehydes that is catalyzed by a salt made from *tert*-butyl valinate and chiral phosphoric acid catalyst (TRIP). This salt **47** can function as highly enantioselective iminium catalysts in the conjugate reduction of α,β-

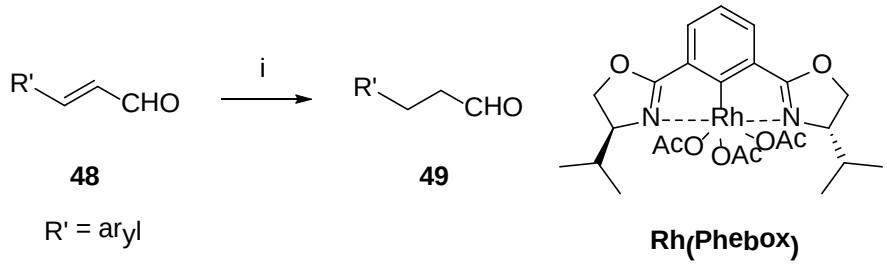
unsaturated ketones and aldehydes with Hantzsch ester (**Scheme 20**).



Scheme 20: (i) **47** (20 mol%), Hantzsch ester, 1,4-dioaxane, 60 °C, 48 h, 68-99%.

Nishiyama's approach (2006)[33]

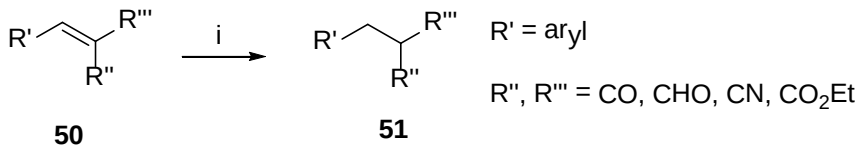
In this approach, α,β-unsaturated aldehydes were selectively reduced using rhodium(bisoxazolinylphenyl) complexes to give exclusive 1,4-selectivity in the combination of alkoxyhydrosilanes (**Scheme 21**).



Scheme 21: (i) Rh(Phebox) (1 mol%), $(EtO)_2MeSiH$ (1.5 equiv), toluene, 60 °C then TBAF, KF.

Chandrasekhar's approach (2006)[34]

Chandrasekhar *et al.* have described a highly chemoselective conjugate reduction of electron deficient Michael acceptors, including α,β-unsaturated ketones, carboxylic esters, nitriles and nitro compounds with PMHS as hydride source in the presence of catalytic $B(C_6F_5)_3$ (**Scheme 22**).

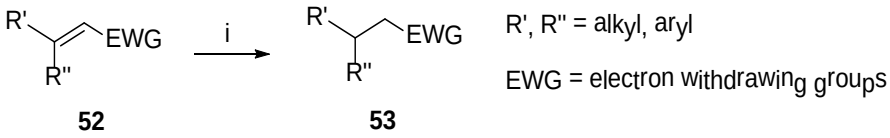


50 **51**

Scheme 22: (i) $B(C_6F_5)_3$ (0.5 mol%), PMHS (2 equiv), CH_2Cl_2, 25 °C, 12 h, 71-89%.

Baker's approach (2008)[35]

In this approach a new, economically attractive, storable, and yet highly kinetically reactive source of catalytic copper hydride has been developed based on a readily available bisphosphine ligand (BDP). This species, (BDP)CuH, is especially useful in 1,4-reductions of a variety of activated alkenes and alkynes, including hindered substrates (**Scheme 23**).

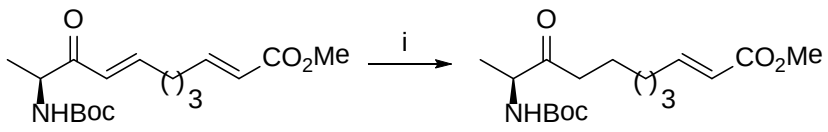


52 **53**

Scheme 23: (i) $Cu(OAc)_2 \cdot H_2O$ (1 mol%), BDP (0.1 mol%), PMHS (3 equiv), ^{t}BuOH (3 equiv), toluene, 25 °C, 19 h, 82-96%.

Koskinen's approach (2009)[36]

Koskinen *et al.* have developed a highly chemoselective non racemizing conjugate reduction of easily epimerizable unsaturated α-aminoketones using triisopropyl phosphite ligated copper hydride as the catalyst. The method shows very good substrate compatibility (**Scheme 24**).

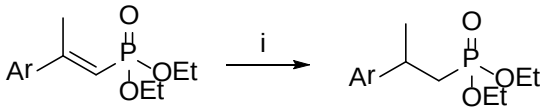


54 **55**

Scheme 24: (i) $Cu(OAc)_2 \cdot H_2O$ (1 mol%), P(*i*-OPr)$_3$ (2 mol%), $Me(EtO)_2SiH$, toluene, 25 °C, 81%.

Zheng's approach (2009)[37]

In this report a series of chiral alkylphosphonates bearing β-stereogenic center were synthesized in good enantioselectivities (up to 95% ee) via the CuH-catalyzed asymmetric conjugate reduction of β-substituted α,β-unsaturated phosphonates under optimal conditions using $Cu(OAc)_2 \cdot H_2O$ as the catalyst, (*R*)-SEGPHOS as the ligand, PMHS as the hydride source and *t*-BuOH as the additive (**Scheme 25**).

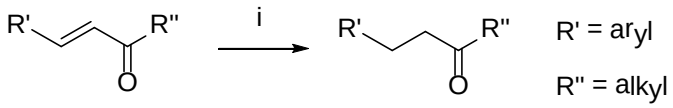


56 **57**

Scheme 25: (i) $Cu(OAc)_2 \cdot H_2O$ (5 mol%), (*R*)-SEGPHOS (6 mol%), PMHS, *t*-BuOH, Et_2O/THF (4/1), 25 °C, 24 h, 90-95%.

Dengs's approach (2008)[38]

Deng *et al.* have demonstrated that chemoselectivity can be switched from C=O to C=C bonds in the transfer hydrogenation of α,β-unsaturated ketones, even in the absence of other electron-withdrawing functional groups, which is catalyzed by the *in situ* prepared amido-rhodium complex with sodium formate as hydride source in aqueous media. This methodology has been applied to a variety of α,β-unsaturated ketones, where in 93-100% chemoselectivity has been achieved (**Scheme 26**).



58 **59**

Scheme 26: (i) $[RhCl_2Cp]_2$, TsEN, HCO_2Na (1.5 equiv), H_2O, 60 °C.

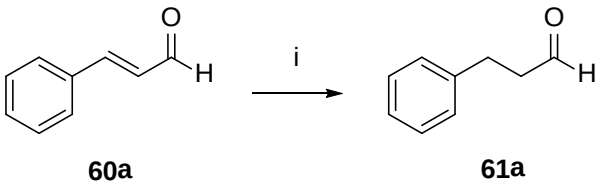
4.2.3 Present Work

4.2.3.1 Objective

The hydrogenation of α,β-unsaturated carbonyl compounds is a useful but challenging transformation. As both 1,2- and 1,4-conjugate reductions readily occur, low selectivity for either of the two pathways is common. Further, catalytic hydrogenations of α,β-unsaturated carbonyls are possible, yet the chemoselectivity is often found to be low. Further, additional functional groups that are sensitive to hydrogenation conditions such as the benzyloxy, nitro, and nitrile groups are usually not tolerated. Undoubtedly, an ecofriendly, safe and economically viable protocol would be a welcome addition to the repertoire of existing methodologies.

4.2.3.2 Results and Discussion

In the previous section of this chapter we had described a new reagent system [$Pd(OAc)_2$-Et_3SiH-DMF] for the chemoselective hydrosilylation of aromatic aldehydes. During the experimentation involving hydrosilylation of aromatic aldehydes, we found that the addition of excess (2 equiv) of Et_3SiH during the reduction of methyl 3-(4-formylphenyl)acrylate **28m**, resulted in the formation of methyl 3-(4-(((triethylsilyl)oxy)methyl)phenyl) propanoate **29m** in 20% yield. In this section, we have described a variant of the above mentioned reducing system and its application to the selective conjugate reduction of a variety of aromatic α,β-unsaturated carbonyl compounds. We observed, that when the same reaction was carried out on cinnamaldehyde **60a** using DMF as solvent, in the presence of $Pd(OAc)_2$ (0.5 mol%) as catalyst with Et_3SiH (1.2 equiv) as hydride source, the desired product, hydrocinnamaldehyde **61a** was obtained in good yield (69%) (**Scheme 27**).



60a **61a**

Scheme 27: (i) cinnamaldehyde (1 equiv), $Pd(OAc)_2$ (0.5 mol%), Et_3SiH (1.2 equiv), DMF, 25 °C, 1 h, 69%

In order to improve the yield, we performed several experiments to identify the most effective and suitable conditions, such as variation of catalyst, solvents etc. In this regard, several Pd-catalysts have been screened with cinnamaldehyde **60a** as a model substrate and the results of such a study are shown in **Table 6**.

Table 6: Pd-catalyzed reduction of cinnamaldehyde **60a**: effect of catalysts[a]

Entry	Catalyst	Yield of 61a (%)
1	$Pd(OAc)_2$	69
2	$Pd(OAc)_2$	73[b]
3	$PdCl_2$	56
4	$Pd(PhCN)_2Cl_2$	64
5	$Pd(dba)_2$	34
6	$Pd(Ph_3P)_4$	20
7	10% Pd/C	67
8	Pd [(*R*, *R*)-BINAP]Cl_2	15[c]
9	Pd[(-)-sparteine]$(OAc)_2$	16[c]

Reaction conditions: [a] cinammaldehyde (1 mmol), Pd-catalyst (0.5 mol%), Et_3SiH (1.2 mmol), DMF (2 ml), 25 ^oC, 1 h; [b] Pd-catalyst (1 mol%); [c] no chiral induction with **60b and 60l** as starting material.

The maximum yield of **61a** was obtained with 1 mol% $Pd(OAc)_2$ (73%) whereas $Pd(Ph_3P)_4$ (20%) gave the lowest yield (entry 2 and 6). We also attempted to induce chirality in substrate **60b** and **60l** with chiral Pd-catalyst (entry 8 and 9) but no asymmetric induction was observed.

Next, the optimization for solvent system and time was done, the results of which are presented in **Table 7**. During the screening of variety of solvents, it was found that DMF when used with 1 mol% $Pd(OAc)_2$ and 2 equiv. of Et_3SiH gave the best yield of the saturated product **61a** (85%) in 4 h. When other hydrosilanes such as Ph_2SiH_2 was used as a hydride source with DMF as solvent, we observed that the yield of the product was miserably low (27%).

Table 7: $Pd(OAc)_2$-catalyzed reduction of cinnamaldehyde **60a**: effect of solvents[a]

Entry	Solvent	Time (h)	Yield of 61a (%) [b]
1	CH_2Cl_2	10	0
2	CH_3CN	5	24
3	Toluene	10	0
6	DMF	1	73
7	DMF	4	74
7	DMF	4	85[c]
8	DMF	10	85[c]

Reaction condition: [a]cinnamaldehyde (1 mmol), $Pd(OAc)_2$ (1 mol%), Et_3SiH (1.2 mmol), solvent (2 ml), 25 ^oC, 4 h; [b]isolated yield; [c] Et_3SiH (2 mmol).

At this point, we reasoned that reduction of aromatic α,β-unsaturated ketone and esters could provide a direct access to saturated carbonyls compounds under the optimized conditions. For example, when reduction of 4-phenylbut-3-en-2-one **60d** was carried out in the presence of $Pd(OAc)_2$ (1 mol%) as catalyst with Et_3SiH (2 equiv) as hydride source and DMF as solvent, the desired saturated ketone **61d** was obtained in 87% yield. Similarly, when the optimized condition was tested for the reduction of aromatic α,β-unsaturated ester **60h**, to our delight this protocol gave the saturated ester **61h** in

excellent yield (83%).

In order to understand the generality of the reaction, we turned our attention to briefly investigate the scope of the reaction by subjecting a wide range of functionalized aromatic α,β-unsaturated aldehydes, ketones and esters (**Table 8**). Indeed, the protocol gave excellent yields of the respective reduced products in moderate to excellent yields. The method has shown high tolerance for other sensitive functional groups such as ester, hydroxyl and ether present either on aromatic nucleus or aliphatic side chain. In case of chloro substituted α,β-unsaturated carbonyl compounds, the corresponding dehaloganated α,β-unsaturated carbonyl compound obtained exclusively in 74% yield (entry f).

Table 8: Pd-catalyzed reduction of aryl α,β-unsaturated carbonyls[a]

Entry	Substrates (60)	Product (61)	Yield (%)[b]
a	cinnamaldehyde	hydrocinnamaldehyde	85
b	(*E*)-3-phenylbut-2-enal	3-phenylbutanal	78
c	(*E*)-4,5-dimethoxy-2-(3-oxoprop-1-enyl)benzonitrile	4,5-dimethoxy-2-(3-oxopropyl)benzonitrile	76
d	(*E*)-4-phenylbut-3-en-2-one	4-phenylbutan-2-one	87
e	(*E*)-chalcone	1,3-diphenylpropan-1-one	83
f	(*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one	(E)-chalcone	74
g	(2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one	1,5-diphenylpentan-1-one	54
h	ethyl cinnamate	ethyl 3-phenylpropanoate	83
i	(*E*)-ethyl 3-(2-hydroxyphenyl) acrylate	ethyl 3-(2-hydroxyphenyl) propanoate	81

j	(*E*)-ethyl 3-p-tolylacrylate	ethyl 3-p-tolylpropanoate	77
k	(*E*)-ethyl 3-(4-hydroxy-3-methoxyphenyl)acrylate	ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate	79
l	(*E*)-ethyl 3-phenylbut-2-enoate	ethyl 3-phenylbutanoate	83
m	(*E*)-ethyl 3-(4-((triethylsilyloxy) methyl)phenyl)acrylate	ethyl 3-(4-((triethylsilyloxy) methyl)phenyl)propanoate	89
n	(*E*)-3-(benzo[d][1,3]dioxol-5-yl)acrylaldehyde	3-(benzo[d][1,3]dioxol-5-yl)propanal	89
o	(*E*)-ethyl hex-2-enoate	(E)-ethyl hex-2-enoate	no reaction

Reaction condition**:** [a] α,β-unsaturated carbonyls (1 mmol), $Pd(OAc)_2$ (1 mol%), Et_3SiH (2 mmol), dry DMF (2 ml), 25 ^oC, 4 h; [b] isolated yield

However, the reaction failed in the case of aliphatic α,β-unsaturated carbonyl compounds (entry o), thus this catalytic system can be unique in selectively reducing aromatic α,β-unsaturated carbonyl compounds in preference to aliphatic ones.

The formation of aryl saturated carbonyl compounds **61a-o** was confirmed by their IR, ^1H and ^{13}C-NMR spectral analysis.

Example 1: The formation of reduced product **61c** was confirmed by the disappearance of signals corresponding to olefinic functionality from its ^1H and ^{13}C NMR spectra. Further proof was provided by the appearance of triplets at δ 2.81 (*J* = 7.1 Hz, 2H) and 3.04 (*J* = 7.5 Hz, 2H) for methylene protons in its ^1H NMR spectrum. Its ^1H NMR spectrum also showed a signal at δ 9.76 (s, 1H) corresponding to aldehydic proton, while singlets at δ 6.77 and 6.95 were due to aromatic protons. Its ^{13}C-NMR spectrum showed a typical signal at δ 199.7 due to carbonyl carbon. The other carbon signals at δ 55.9 and 56.1 were due to methoxyl carbons (-O-$\mathbf{CH_3}$) (**Figure 5)**.

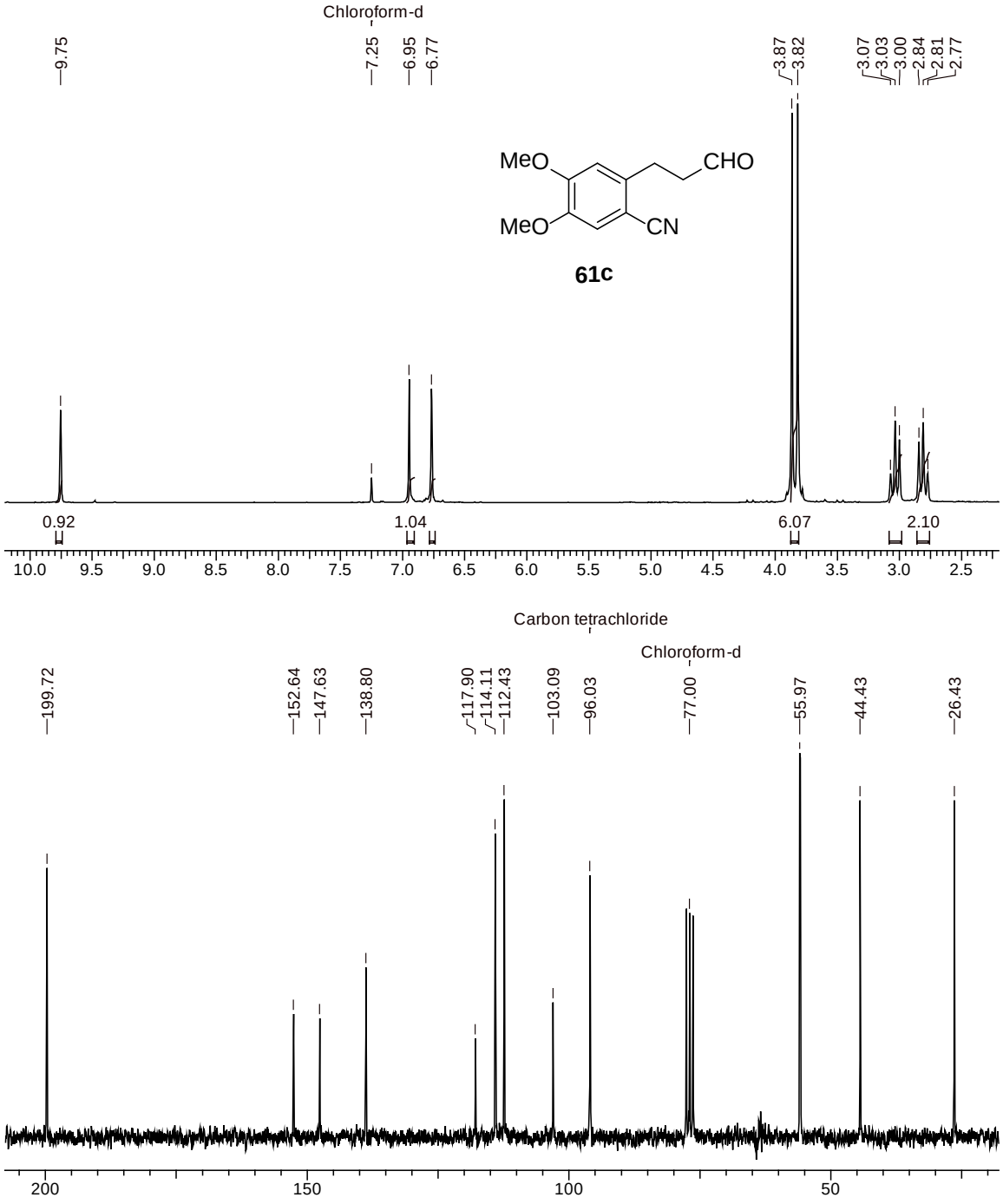


Figure 5: ^{1}H and ^{13}C NMR spectra of aldehyde **61c**

Example 2: The formation of **61d** was confirmed by its ^{1}H NMR spectrum which showed the disappearance of olefinic protons. A singlet at δ 2.12 (3H) in its ^{1}H NMR spectrum was due to methyl protons. The appearance of a multiplet at δ 2.69-2.92 in its

^{1}H NMR spectrum due to the four methylene protons further confirmed the reduction. Its ^{13}C-NMR spectrum showed a typical signal at δ 207.2 due to carbonyl carbon (**Figure 6)**.

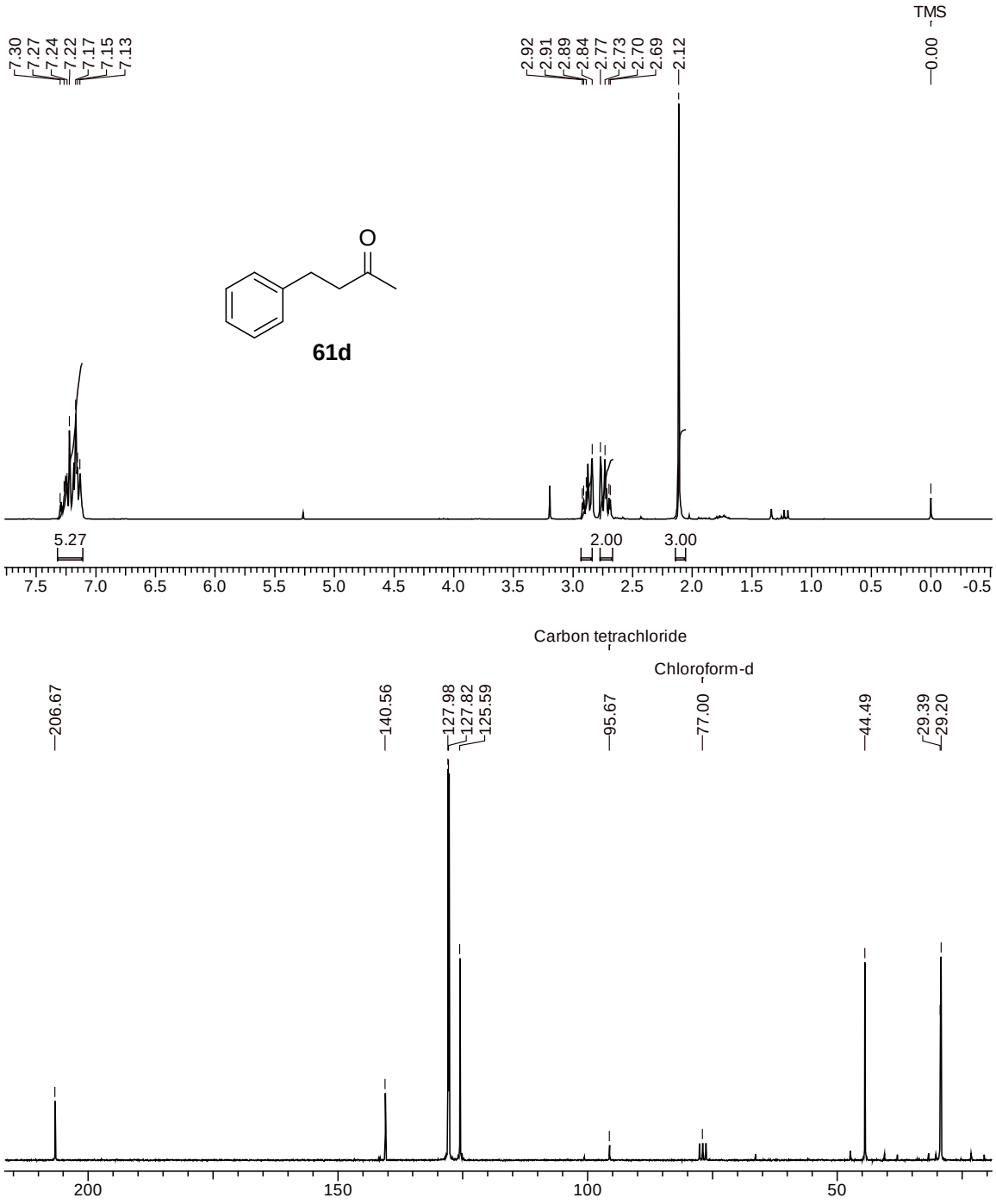


Figure 6: ^{1}H and ^{13}C NMR spectra of ketone **61d**

Example 3: The ^{1}H NMR spectrum of **61k** showed a characteristic singlet at δ 3.83 for methoxyl (-O-**CH_3**) protons. A broad singlet at δ 5.76 in its ^{1}H NMR spectrum assigned to phenolic proton. The appearance of two triplets at δ 2.56 (*J* = 7.8 Hz, 2H) and 2.84 (*J* = 7.5 Hz, 2H) further substantiated the formation of reduced product. Its ^{13}C-NMR spectrum showed typical carbon resonances at δ 30.6, 36.2 and 60.3 due to methylene carbons (**Figure 7)**.

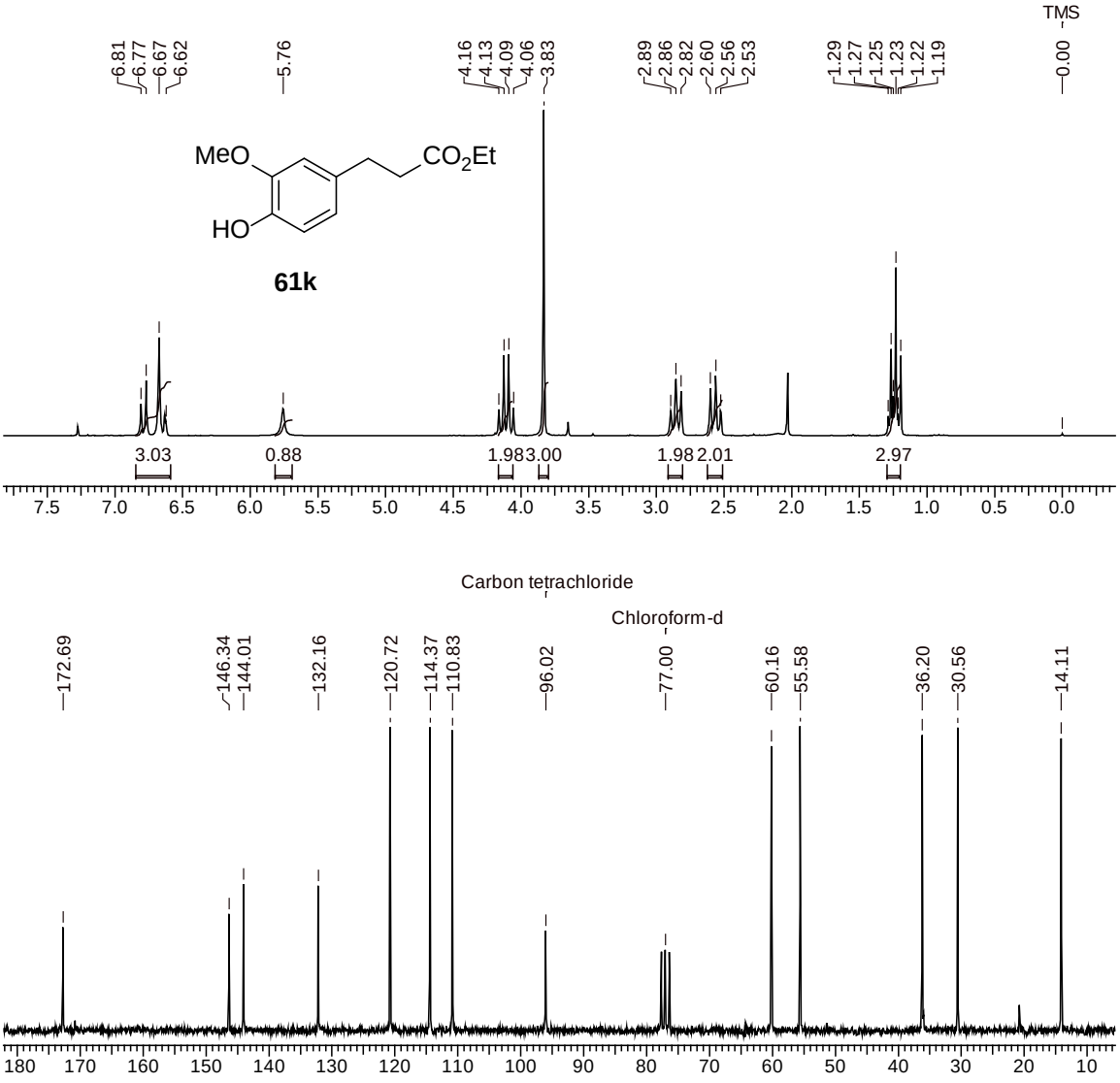


Figure 7: ^{1}H and ^{13}C NMR spectra ester of **61k**

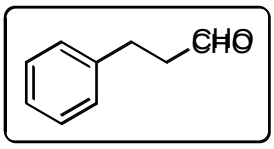
4.2.4 Conclusion

In conclusion, we have demonstrated that Pd-Et_3SiH-DMF is a highly effective catalytic system for the chemoselective C=C reduction of aryl α,β-unsaturated carbonyl compounds. While displaying great reactivity, a high level of functional group tolerance was also observed.

4.2.5 Experimental Section

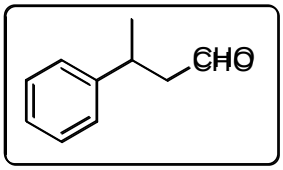
General experimental procedure for the 1,4-reduction of aryl α,β-unsaturated carbonyl To a 10 mL two-neck round-bottomed flask with a magnetic stir bar was added palladium catalyst (1 mol%) in DMF (2.0 mL). To this was added aromatic α,β-unsaturated carbonyl compound (1.0 mmol) followed by triethylsilane (2 mmol). The resulting solution was stirred for 4 h. After completion of the reaction, it was quenched by the addition of water and the mixture extracted with EtOAc. The organic layer was further washed with brine (5 x 10 mL), dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (petroleum ether/EtOAc as eluent) to afford the pure carbonyl compounds **61a-o**.

Hydrocinnamaldehyde (61a)



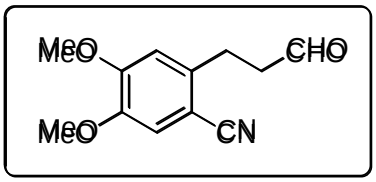
Yield: 85% (114 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1345, 1465, 1514, 1724 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.67-2.81 (m, 2H), 2.91-2.99 (m, 2H), 7.16-7.32 (m, 5H), 9.81 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.1, 30.6, 35.5, 45.3, 126.3, 128.2, 128.4, 140.2, 178.3, 201.1; **Anal.** Calcd for $C_9H_{10}O$ requires C, 80.56; H, 7.51; found C, 80.63; H, 7.56%.

3-Phenylbutanal (61b)



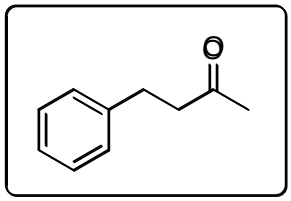
Yield: 78% (116 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1198, 1245, 1434, 1721 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (d, *J* = 7.2 Hz, 3H), 2.66-2.71 (m, 1H), 2.76-2.83 (m, 1H), 3.37-3.40 (m, 1 H), 7.18–7.23 (m, 3H), 7.28–7.34 (m, 2H), 9.72 (t, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.31, 34.39, 51.76, 126.3, 126.5, 128.4, 145.1, 201.3; **Anal.** Calcd for $C_{10}H_{12}O$ requires C, 81.04; H, 8.16; found C, 81.09; H, 8.24%.

4,5-Dimethoxy-2-(3-oxopropyl)benzonitrile (61c)



Yield: 76% (167 mg); gum; **IR** ($CHCl_3$): υ_{max} 998, 1019, 1564, 1723, 2218 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.81 (t, *J* = 7.1 Hz, 2H), 3.03 (t, *J* = 7.5 Hz , 2H), 3.82 (s, 3H), 3.87 (s, 3H), 6.77 (s, 1H), 6.96 (s, 1H), 9.75 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.4, 44.4, 56.0, 103.1, 112.4, 114.1, 117.9, 138.8, 147.6, 152.6, 199.7; **Anal.** Calcd for $C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98; N, 6.39; found C, 65.80; H, 6.06; N, 6.47%.

4-Phenylbutan-2-one (61d)



Yield: 87% (129 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 876, 985, 1113, 1264, 1727 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.12 (s, 3H), 2.69-2.92 (m, 4H), 7.13-7.25 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.2, 29.4, 44.5, 125.6, 127.8, 128.0, 140.6, 206.7; **Anal.** Calcd for $C_{10}H_{12}O$ requires C, 81.04; H, 8.16; found C, 81.09; H, 8.23%.

1,3-Diphenylpropan-1-one (61e)

Yield: 83% (174 mg); colorless solid; mp 72-75 ^oC; **IR** ($CHCl_3$):

υ_{max} 1245, 1279, 1329, 1435, 1718 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.08 (t, J = 7.5 Hz, 2H), 3.32 (t, *J* = 7.5 Hz, 2H), 7.20-7.35 (m, 5H), 7.45 (m, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.1, 40.4, 126.1, 128.0, 128.4, 128.5, 128.6, 133.0, 136.9, 141.3, 199.2; **Anal.** Calcd for $C_{15}H_{14}O$ requires C, 85.68; H, 6.71; found: C, 85.74; H, 6.66; %.

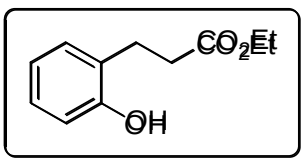
1,5-Diphenylpentan-1-one (61g)

Yield: 54% (129 mg); yellow liquid; **IR** ($CHCl_3$): υ_{max} 1443, 1523, 1718, 2918 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.68-1.84 (m, 4H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 7.17-7.60 (m, 8H), 7.92 (d, *J* = 7.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.1, 31.1, 35.8, 38.4, 125.7, 125.8, 128.0, 128.3, 128.4, 128.5, 132.9, 137.0, 142.2, 199.7; **Anal.** Calcd for $C_{17}H_{18}O$ requires C, 85.67; H, 7.61; found C, 85.75; H, 7.67%.

Ethyl 3-phenylpropanoate (61h)

Yield: 83% (148 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1298, 1465, 1567, 1623, 1716, 3013 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.1 Hz , 3H), 2.58 (t, *J* = 7.2 Hz , 2H), 2.93 (t, *J* = 7.4 Hz , 3H), 4.05 (q, *J* = 7.2 Hz, 2H), 7.15-7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 30.9, 35.8, 60.1, 126.1, 128.2, 128.3, 140.4, 172.5; **Anal.** Calcd for $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92; found C, 74.19; H, 7.99%.

Ethyl 3-(2-hydroxyphenyl)propanoate (61i)



Yield: 81% (156 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1345, 1474, 1717, 2989, 3356 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ

1.22 (t, *J* = 7.1 Hz, 3H), 2.68 (t, *J* = 6.8 Hz , 2H), 2.90 (t, *J* = 6.9 Hz , 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 6.77-6.84 (m, 2H), 7.02-7.09 (m, 2H), 7.45 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 25.2, 34.9, 61.1, 116.6, 120.5, 127.1, 127.8, 130.0, 154.4, 175.2; **Anal.** Calcd for $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.27; found C, 68.06; H, 7.34%.

Ethyl 3-p-tolylpropanoate (61j)

Yield: 77% (148 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 876, 982, 1087, 1123, 1458, 1714 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.3 Hz, 3H), 2.31 (s, 3H), 2.54 (t, *J* = 7.1 Hz , 2H), 2.92 (t, *J* = 7.1 Hz , 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 7.09 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 19.2, 28.3, 34.7, 60.3, 126.1, 126.4, 128.5, 130.3, 135.8, 138.6, 172.8; **Anal.** Calcd for $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39; found C, 75.04; H, 8.49%.

Ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (61k)

Yield: 79% (177 mg); gum; **IR** ($CHCl_3$): υ_{max} 1237, 1385, 1456, 1712, 3412 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3H), 2.56 (t, *J* = 7.8 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 3.82 (s, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.76 (br s, 1H), 6.62-6.81 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 30.6, 36.2, 55.6, 60.2, 110.8, 114.4, 120.7, 132.2, 144.0, 146.3, 172.7; **Anal.** Calcd for $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19; found C, 64.31; H, 7.23%.

Ethyl 3-phenylbutanoate (61l)

Yield: 83% (160 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 1381, 1654, 1717, 3012 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.16 (t,

J = 7.2 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 2.56 (m, 2H), 3.24 (m, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 7.15-7.30 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 21.9, 36.5, 43.0, 60.1, 126.4, 126.7, 128.5, 145.7, 172.1; **Anal.** Calcd for $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39; found C, 74.89; H, 8.41%.

Methyl 3-(4-(((triethylsilyl)oxy)methyl)phenyl)propanoate (61m)

Yield: 89% (274 mg); colorless liquid; **IR** ($CHCl_3$): υ_{max} 987, 1129, 1394, 1481, 1722 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.53 (q, *J* = 8.1 Hz, 6H), 0.93 (t, *J* = 8.2 Hz , 9H), 2.57 (t, *J* = 8.1 Hz, 2H), 2.89 (t, *J* = 7.3 Hz, 2H), 3.65 (s, 3H), 4.68 (s, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 9.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 4.4, 6.7, 30.5, 35.7, 51.4, 64.4, 126.4, 128.0, 139.0, 139.1, 173.1; **Anal.** Calcd for $C_{17}H_{28}O_3Si$ requires C, 66.19; H, 9.15; found C, 66.21; H, 9.20%.

Ethyl 3-(benzo[d][1,3]dioxol-5-yl)propanoate (61n)

Yield: 89% (198 mg); gum; **IR** ($CHCl_3$): υ_{max} 1205, 1381, 1420, 1716 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 3H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 5.91 (s, 2H), 6.61-6.72 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 30.7, 36.2, 60.3, 100.7, 108.4, 108.8, 121.1, 134.3, 145.9, 147.6, 172.7; **Anal.** Calcd for $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35; found C, 64.93; H, 6.38 %.

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LIST OF PUBLICATIONS

1. "A concise enantioselective synthesis of (+)-decarestrictine L via proline-catalyzed sequential alpha-aminooxylation and Horner-Wadsworth-Emmons olefination" Varun Rawat, Pandurang V. Chouthaiwale, Gurunath Suryavanshi, Arumugam Sudalai *Tetrahedron Asymmetry* **2009**, *20*, 2173.
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6. "Organocatalytic sequential α-aminooxylation or –amination/reductive cyclization of o-nitrohydrocinnamaldehyde: A high yield synthesis of chiral 3-substituted tetrahydroquinolines" Varun Rawat, B. Senthil Kumar, Arumugam Sudalai (Manuscript communicated).
7. "A diastereoselective tandem desilylation-oxy Michael addition reaction for the asymmetric synthesis of 3-*epi*-jaspine B and (+)-oxybiotin" Varun Rawat, Anil M. Shelke, Arumugam Sudalai (Manuscript communicated).
8. **"**Asymmetric synthesis of (+)-stagonolide C and (-)-aspinolide A *via* organocatalysis**"** Anil M. Shelke, Varun Rawat, Gurunath Suryavanshi, Arumugam Sudalai (Manuscript communicated).