Enantioselective Synthesis of Bioactive Molecules and Development of Methodologies Involving Catalytic Oxidative Esterification of Aldehydes and Cleavage of N-N Bonds

Thesis Submitted to the AcSIR For the Award of
The Degree of
DOCTOR OF PHILOSOPHY
In Chemical Sciences

By
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UNDER THE GUIDANCE OF
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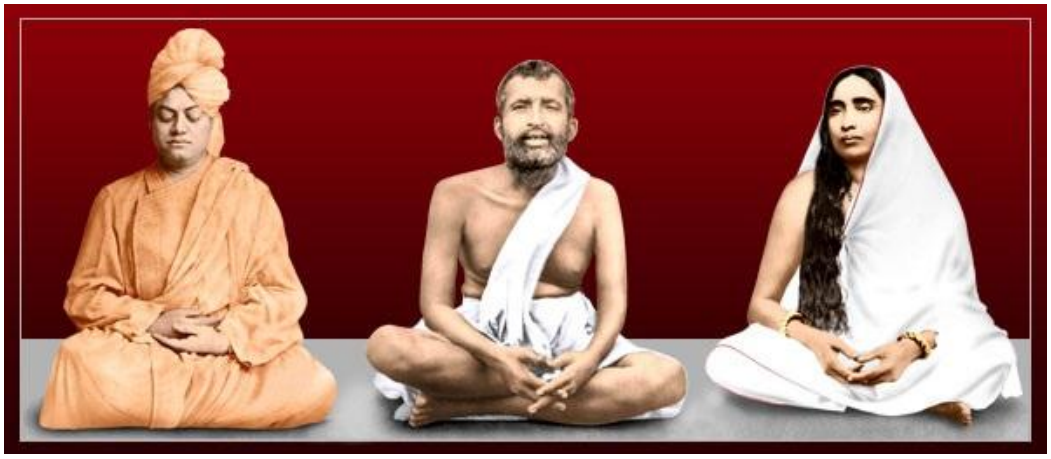

DEDICATED TO

MY BELOVED FAMILY & MAHARAJAS of RKM

MISSION

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules and Development of Methodologies Involving Catalytic Oxidative Esterification of Aldehydes and Cleavage of N-N Bonds"*** which is being submitted to the ***AcSIR*** for the award of ***Doctor of Philosophy*** in ***Chemical Sciences*** by ***Mr. Soumen Dey*** was carried out by him under my supervision at the CSIR-National Chemical Laboratory, Pune. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

September 2015 **Dr. A. Sudalai**
Pune (Research Guide)

CSIR-NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules and Development of Methodologies Involving Catalytic Oxidative Esterification of Aldehydes and Cleavage of N-N Bonds"*** submitted to **AcSIR** for the award of degree of Doctor of Philosophy in Chemical Sciences, has not been submitted by me to any other university or institution. This work was carried out at the CSIR-National Chemical Laboratory, Pune, India.

September 2015
Pune

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CONTENTS

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No word would suffice to express my gratitude and love to my ***Maa****,* ***Baba*** *and* ***Papai*** *(brother) for their continuous showering of boundless affection on me and supporting me in whatever I choose or did. The warmth and moral value of my parents have stood me in good stead throughout my life and I would always look up to them for strength no matter what I have to go through. This Ph. D. thesis is a result of the extraordinary will, efforts and sacrifices of my family.*

I owe much towards my wife ***Supriya*** *for her love, dedication, patience and encouragement throughout my career. Also my sincere thanks go to father-in-law, mother-in-law and Chiro for their support and trust in me.*

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Though, many have not been mentioned, none is forgotten.

Soumen Dey
September 2015

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
$(Boc)_2O$	Di*tert*-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
Cbz	Benzyloxy carbonyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutyl aluminium hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
g	Grams
h	Hours
HPLC	High pressure liquid chromatography
imid.	Imidazole
IR	Infra red
IBX	2-Iodoxybenzoic acid
LAH	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
M+	Molecular ion
Me	Methyl
MOM	Methoxymethyl
min	Minutes
mg	Miligram
mL	Milliliter
mp	Melting point

MS	Mass spectrum
Ms	Mesyl
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromate
Ph	Phenyl
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethyl-1-piperidinyl)oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid

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, Brucker Avance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.
8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.
9. Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a chiral column.
10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.
11. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
12. Elemental analysis was done on Carlo ERBA EA 110B instrument.
13. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

ABSTRACT

Enantioselective Synthesis of Bioactive Molecules and Development of Methodologies Involving Catalytic Oxidative Esterification of Aldehydes and Cleavage of N-N Bonds

Research Student: **Soumen Dey**

AcSIR Roll: **10CC11J26005**

Research Guide: **Dr. A. Sudalai**

The thesis entitled **"Enantioselective Synthesis of Bioactive Molecules and Development of Methodologies Involving Catalytic Oxidative Esterification of Aldehydes and Cleavage of N-N Bonds''** is divided into four chapters. The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules, drugs and to utilize synthetic organic chemistry for the development of new methodologies involving heterogeneous Ti superoxide and Pd catalysis **Chapter I** deals with the synthesis of *anti*-influenza agent **(-)-Oseltamivir free base, (-)-Methyl 3-*epi*-shikimate, (-)-Codonopsinine** and **Radicamine B** *via* Sharpless asymmetric epoxidation of allylic alcohols and Corey-Chaykovsky reaction of aminated aldehyde with sulfone. **Chapter II** describes the synthesis of other important molecules like **Stagonolide E, (-)-(6*R*,11*R*,14*R*)-Colletallol and (*S*)-3-Hydroxypiperidine** by employing proline catalyzed aminooxylation and its sequential reactions as key reactions. **Chapter III** deals with enantioselective synthesis of drug molecules: **(*R*)-Selegiline, (*S*)-Benzphetamine** and **(*S*)-3-Amino-4-(2,4,5-**

trifluorophenyl)butanoic Acid, key intermediate for the synthesis of **(*R*)-Sitagliptin** *via* Evans' electrophilic azidation of chiral imide enolates and organocatalysis. **Chapter IV** describes heterogeneous Ti superoxide catalysed oxidative esterification of adehydes and its application to synthesize 3-nbutylphthalide. Also, in this chapter, we have utilized Pd catalysis to cleave N-N bond in dibenzyl alkylhydrazine-1,2-dicarboxylate by PMHS as hydride source to generate various useful reactive intermediates.

Introduction

A key challenge for synthetic chemists is the design and synthesis of compound libraries spanning large tract of biologically relevant chemical space. Over the past decades, apart from the classical functional group transformation, the field of organic synthesis has been extended for discovering novel chemical reactions such as organocatalyzed reactions[1], transistion metal catalysis[2], chiral epoxidation[3], kinetic resolution[4] and asymmetric hydrogenation.[5] These methods have found tremendous applications in the synthesis of various bioactive molecules and drugs with high enantio- and diastereoselectivity. The present work provides for the asymmetric synthesis of various bioactive molecules such as *anti*-influenza agent oseltamivir phosphate or tamiflu **1** and methyl-3-*epi* shikimate **2**,[6] *anti*-cancer agent (-)-codonopsinine **3**,[7] (-)-radiacamine B **4**,[8] and cytotoxic stagonolide E **5**,[9] (-)-(6*R*,11*R*,14*R*)-Colletallol **6**,[10] naturally active (*S*)-3-hydroxypiperidine **7**,[11] by organocatalyzed α-functionalization of aldehydes, drug molecules *anti*-Parkinson's agent (*R*)-selegiline **8**, *anti*-obesity agent (*S*)-benzphetamine **9**, *anti*-diabetic agent sitagliptin **10**[12] *via* Evans' chiral azidation.[13] Also included in the present work are a mild and convenient heterogeneous Ti-superoxide[14] catalyzed oxidative

esterification process of aldehydes and environmentally benign Pd-catalyzed selective N-N bond cleavage[15] of dibenzyl alkylhydrazine-1,2-dicarboxylate to provide amino alcohols, lactams, and oxazolidinones.

Statement of Problem

The reported synthesis of these highly bioactive molecules suffer from disadvantages such as lengthy reaction sequences, several use of chiral auxiliaries, and expensive organometallic reagents, chiral pool approaches, classical/kinetic resolution, low yields etc. Hence, the need for alternative routes for their synthesis enhancing overall yields and ee from commercially available achiral starting materials is of current interest. Also, eco-friendly heterogeneously catalyzed oxidative esterification of aldehydes and cleavage of N-N bonds is rarely explored till date.

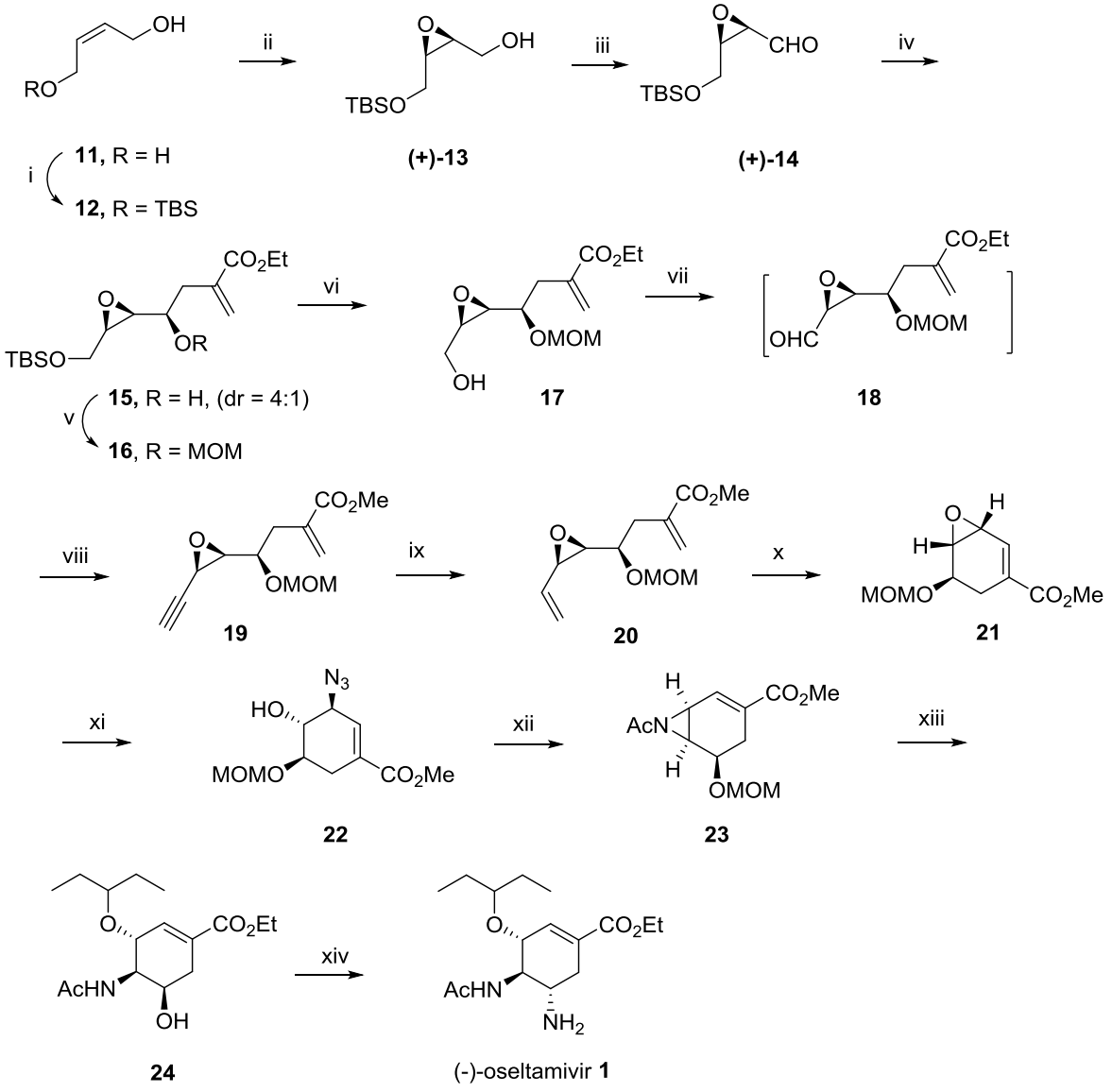
Methodology used

1. Several biologically important molecules have been synthesized *via* enamine catalysis involving α-aminooxylation, α-amination reaction of aldehydes, Sharpless asymmetric epoxidation, Evans' chiral azidation. Heterogeneous Ti superoxide and $PdCl_2$ as catalysts have been used for oxidative esterification and reductive N-N bond cleavage of organic compounds respectively. The structures are characterized by the advanced analytical and spectroscopic techniques such as high field NMR (^{1}H & ^{13}C), FT-IR, LC-MS, HRMS and elemental analysis.
2. The assignment of stereochemistry was carried out by COSY and NOESY NMR studies unambiguously.
3. The optical purity of chiral intermediates and final drug molecules has been determined from chiral HPLC analysis and comparing their specific rotations with

those reported in the literature.

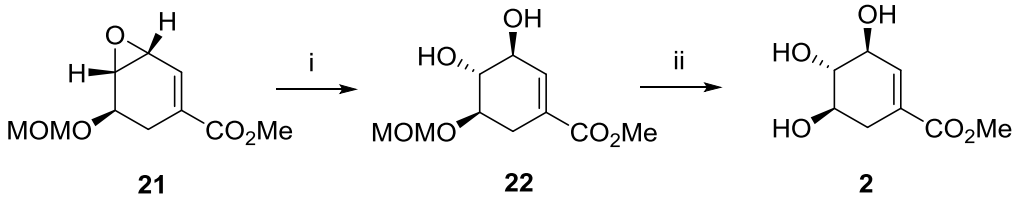
CHAPTER I

Oseltamivir phosphate is an orally effective drug, marketed as Tamiflu (**1**·H_3PO_4), widely used for the treatment and prevention of human influenza (H1N1) and avian influenza (H5N1) infections and represents the prototype of neuraminidase inhibitors. The key steps involve Sharpless asymmetric epoxidation (SAE), diastereoselective Barbier allylation and ring closing metathesis (RCM) (**Scheme 1**).



Scheme 1: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (+)-DET, $Ti(PrO^i)_4$, anhyd. TBHP (5.5 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) ethyl 2-(bromomethyl)acrylate, Zn dust, NH_4Cl, THF/H_2O (4:1), 0-25 ºC, 10 h, 64% (for syn-selectivity); (v) MOMCl, DIPEA, dry CH_2Cl_2, 0-25 ºC, 12 h, 90%; (vi) TBAF, THF, 0 ºC, 2 h, 88%; (vii) IBX, dry DMSO, 25 ºC, 1 h; (viii) diethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 25 ºC, 2 h, 82% (over two steps); (ix) H_2, Lindlar's catalyst, pyridine/1-octene/EtOAc (1:1:10), 6 h, 95%; (x) Grubbs-II (10 mol %), dry CH_2Cl_2, reflux, 14 h, 90%; (xi) NaN_3, NH_4Cl, DMF/EtOH/H_2O (4:4:1), 0-25 ºC, 10 h, 83%; (xii) (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); (xiii) (a) 3-pentanol, $BF_3.OEt_2$, -10 ºC, 30 min, (b) 2 N HCl, EtOH, 25 ºC, 12 h, 64% (over two steps); (xiv) (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).

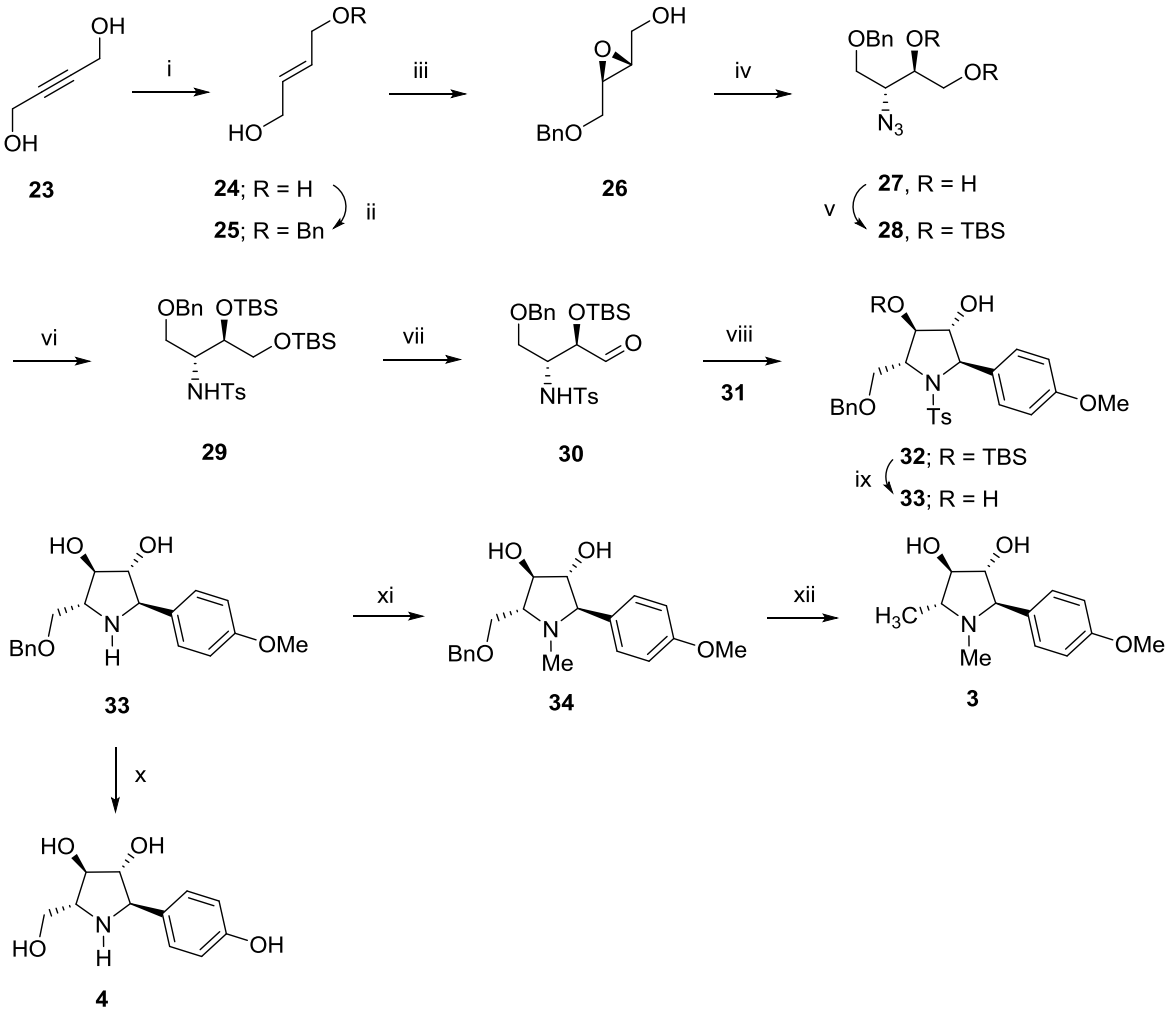
Additionally, a concise enantioselective synthesis of 3-*epi*-shikimate **2** was undertaken to demonstrate the direct application of cyclic epoxide **21**, an important precursor for the synthesis of 3-*epi*-shikimate **2** (**Scheme 2**).



21 **22** **2**

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

Further, polyhydroxylated pyrrolidines, such as, (-)-codonopsinine **3** and radicamine B **4** have shown significant biological activities, like, potent inhibition of glycosidases, anti-viral agents and acaricides. Sharpless asymmetric epoxidation (SAE) and Corey-Chaykovsky reaction of aminated aldehyde with sulfone are the key reactions employed to construct these iminosugars (**Scheme 3**).

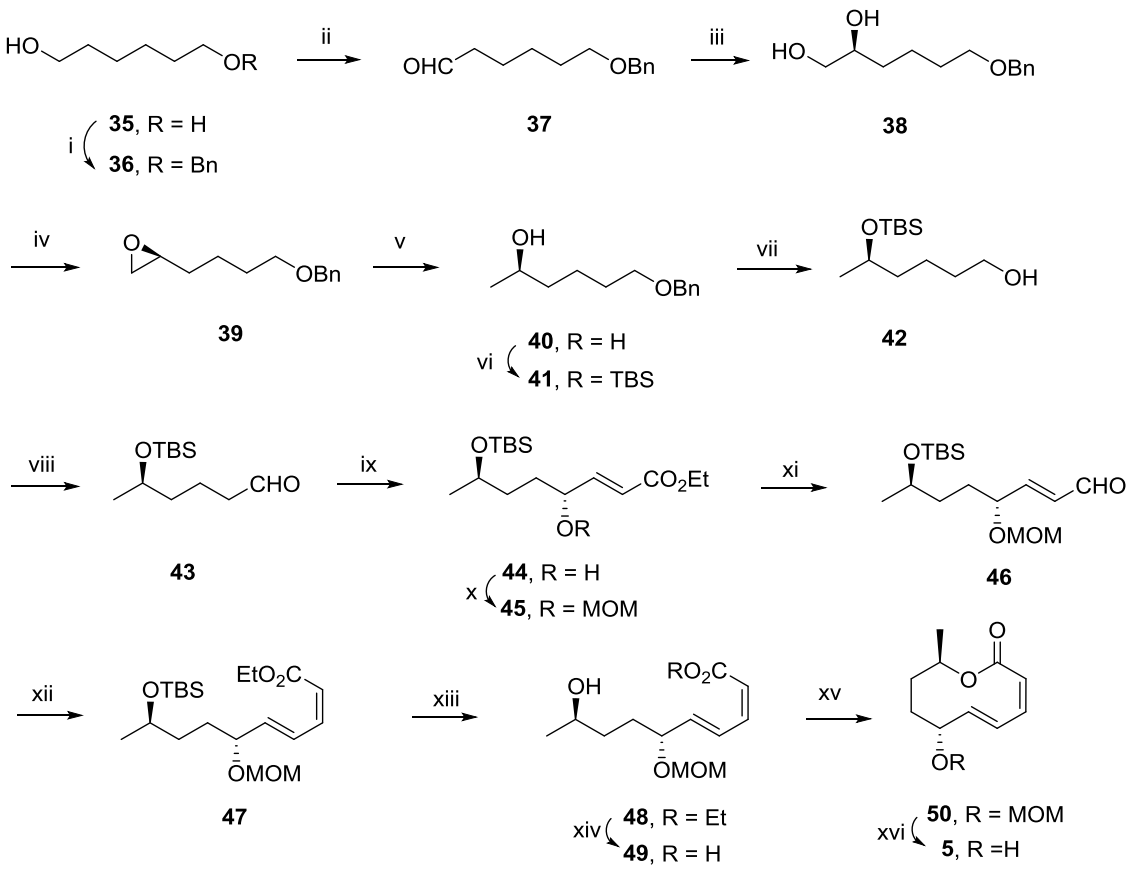


Scheme 3: (i) $LiAlH_4$, THF, 70 ºC, 4 h, 70%, *Z/E* = 1:2; (ii) BnBr, NaH, DMF, 0-25 ºC, 4 h, 90%; (iii) (+)-DET, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2, -20 ºC, 8 h, 88%; (iv) $Ti(O^iPr)_4$, $TMSN_3$, benzene, 80 ºC, 4 h, 96%; (v) TBSCl, imid, CH_2Cl_2, 98%; (vi) (a) Ph_3P, THF, 70 ºC, 2 h; (b) TsCl, Et_3N, CH_2Cl_2, 25 ºC, 2 h, 80%; (vii) (a) CSA, MeOH, 0 ºC, 1 h; (b) IBX, DMSO, 25 ºC, 2 h, 95%; (viii) **85**, ^{n}BuLi, THF, 0 ºC, 3 h, 80%; (ix) $Ti(O^iPr)_4$, TMSCl, Mg, THF, 50 ºC, 10 h; (x) 1M BBr_3, CH_2Cl_2, 0-25 ºC, 8 h, 80%; (xi) NaH, DMF/THF (4:1), 0-25 ºC, 2 h, 70%; (xii) (a) H_2 (1 atm), 10% Pd/C, MeOH, 1 h; (b) TsCl, Et_3N, CH_2Cl_2, 0 ºC, 1 h; (c) $LiAlH_4$, THF, reflux, 6 h, 60% (over three steps).

CHAPTER II

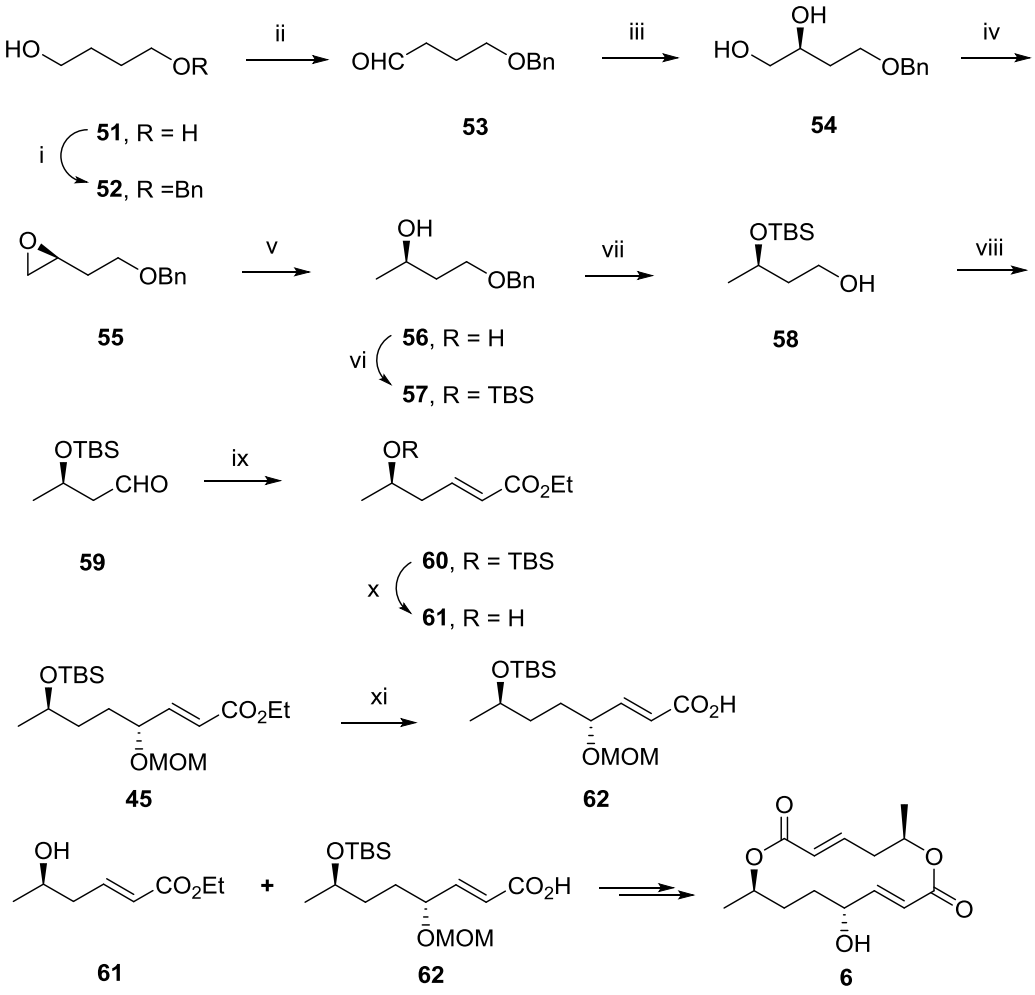
It describes the enantioselective syntheses of stagonolide E, (-)-(6*R*,11*R*,14*R*)-colletallol and (*S*)-3-hydroxypiperidine *via* Organocatalysis.

A stereoselective total synthesis of stagonolide E (**5**) was accomplished (8.5% overall yield; 98% ee) *via* an organocatalytic approach employing easily accessible starting materials (**Scheme 4**).



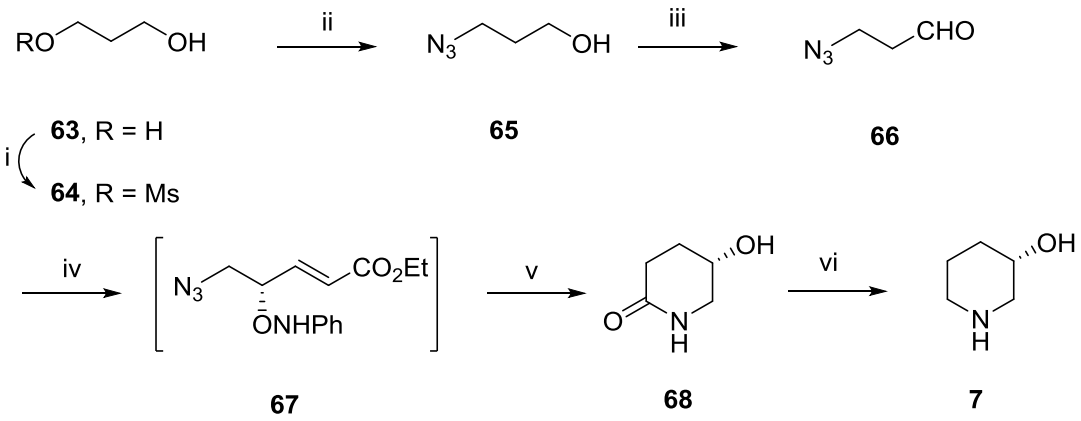
Scheme 4: (i) BnBr, NaH, THF, 0-25 ºC, 96%; (ii) IBX, DMSO, 25 ºC, 2 h, 98%; (iii) PhNO, D-proline (20 mol %), CH_3CN, -20 ºC, 16 h then MeOH, $NaBH_4$, 0 ^oC, 45 min; then $CuSO_4$, EtOH, 25 ^oC, 10 h, 60%; (iv) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2, 1 h then K_2CO_3, MeOH, 0 ^oC, 30 min, 70% ; (v) $LiAlH_4$, THF, 0 ºC, 98%; (vi) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 3 h, 98%; (vii) H_2 (1 atm), 10% Pd/C, EtOAc, 4 h, 96%; (viii) IBX, DMSO, 25 ºC, 2 h, 98%;(ix) PhNO, L-proline (20 mol %), CH_3CN, -20 ^oC, 16 h then triethyl phosphonoacetate, DBU, LiCl, 0 ^oC, 1 h; then $CuSO_4$, EtOH, 25 ^oC, 8 h, 65%; (x) MOMCl, DIPEA, CH_2Cl_2, 0-25 ºC, 3 h, 90%; (xi) DIBAL-H, dry toluene, -78^oC, 1 h, 96%; (xii) ethyl (diphenoxylphosphinoxy) acetate , dry THF, 0 ^oC, 1 h, 92%, (*Z,E/E,E* = 97:3); (xiii) TBAF, THF, 0 ^oC, 1 h, 88%; (xiv) LiOH, MeOH/ THF/ H_2O (3:1:1), 2 h, 90%; (xv) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, toluene, 25 ºC, 65%; (xvi) 2N HCl, THF, 88%.

Further, an efficient route to the formal synthesis of (-)-(6*R*,11*R*,14*R*)-colletallol (**6**) was described here employing proline-catalyzed asymmetric α-aminooxylation and its sequential reactions in 97% ee with an overall yield of 3.6% (**Scheme 5**).



Scheme 5: (i) BnBr, NaH, THF, 0-25 ºC, 6 h, 97%; (ii) IBX, DMSO, 25 ºC. 2 h, 98%; (iii) PhNO, D-proline (20 mol %), -20 ºC, 24 h then MeOH, $NaBH_4$; then $CuSO_4$, EtOH, 24 h, 75%; (iv) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2 then K_2CO_3, MeOH, 65%; (v) $LiAlH_4$, THF, 0 ºC, 30 min., 95%; (vi) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 2 h, 98%; (vii) H_2 (1 atm), 10% Pd/C, Et_3N, MeOH, 12 h, 25 ºC, 96%; (viii) IBX, DMSO, 25 ºC. 2 h, 98%; (ix) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 3 h, 95%; (x) TBAF, THF, rt, 6 h, 80%; (xi) LiOH, THF/H_2O (1:1), 25 ºC, 1 h, 70%.

Also the concise synthesis of (*S*)-piperidine-3-ol (**7**) (38% overall yield; 97% ee) *via* the use of organocatalytic sequential α-aminooxylation followed by HWE reaction was demonstrated (**Scheme 6**).

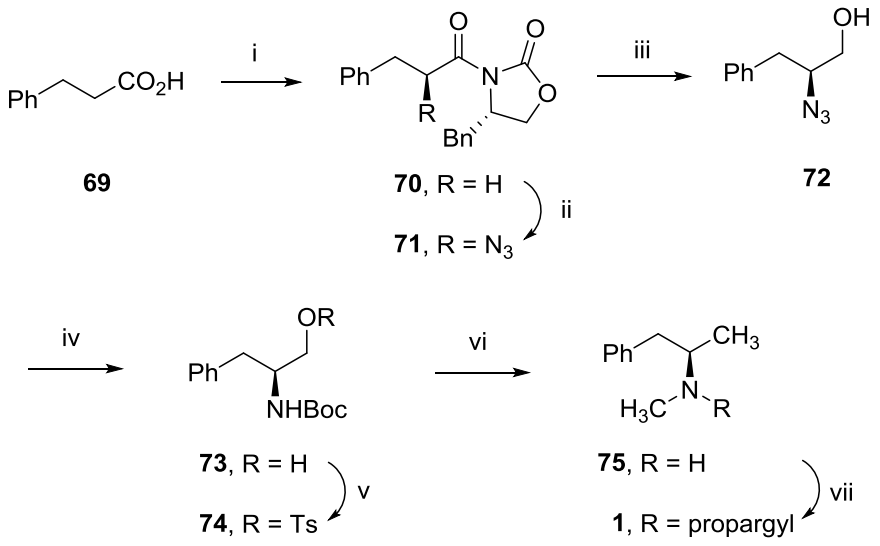


Scheme 6: (i) MsCl, Et_3N, DMAP, CH_2Cl_2; (ii) NaN_3, DMF, 80 °C, 70% (over two steps); (iii) PCC, CH_2Cl_2, 25 °C, 2 h, 98%; (iv) L-proline (10 mol %, PhNO, CH_3CN, 24 h, -20 ºC, then triethyl phosphono acetate, DBU, LiCl, 0 °C, 2 h; (v) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 2 h, 65%. (over three steps); (vi) $BH_3.SMe_2$, THF, reflux, 12 h, 87%.

CHAPTER III

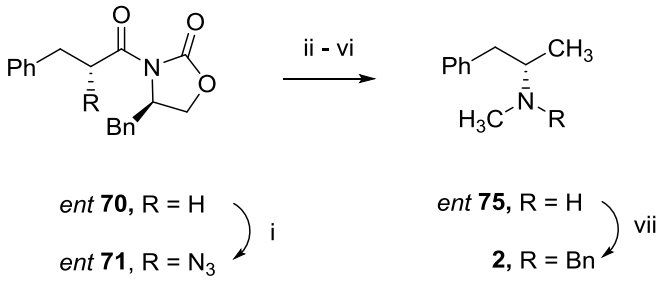
It deals with the enantioselective synthesis of *anti*-Parkinson's agent (*R*)-selegiline **8**, *anti*-obesity agent (*S*)-benzphetamine **9**, *anti*-diabetic agent sitagliptin **10** *via* Evans' chiral azidation.

An efficient procedure for the enantioselective synthesis of two important drugs namely, (*R*)-selegiline (**8**) (30% overall yield; 97% ee) employing Evans' chiral azidation reaction from commercially available hydrocinnamic acid (**Scheme 7**).



Scheme 7: (i) pivolyl chloride, Et_3N, dry THF, -20 ^oC, 3 h then (*S*)-4-benzyloxazolidin-2-one, LiCl, -20-25 ^oC, 8 h, 90%; (ii) KHMDS, -78 ^oC, dry THF, 45 min, then 2,4,6-triisopropylbenzenesulfonyl azide, 5 min, then HOAc, -78-25 ^oC, 12 h, 85%; (iii) $NaBH_4$, THF/ H_2O (3:1), 0-25 ^oC, 2 h, 95%; (iv) H_2 (1 atm), 10% Pd/C, Boc_2O, MeOH, 5 h, 90%; (v) TsCl, Et_3N, CH_2Cl_2, 0-25 ^oC, 3 h; (vi) $LiAlH_4$, THF, reflux, 4 h, 65% (over two steps); (vii) propargyl bromide, K_2CO_3, CH_3CN, 3 h, 25 ^oC, 71%.

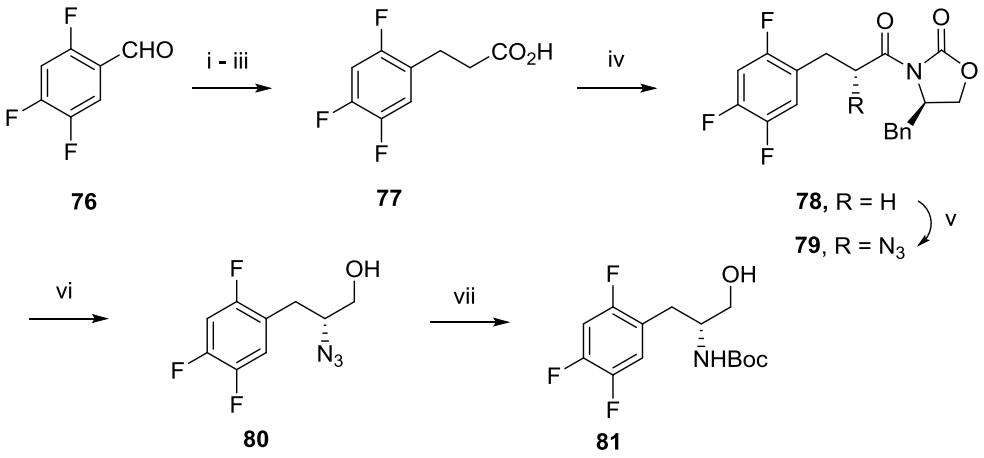
(*S*)-benzphetamine (**9**) (31% overall yield; 97% ee) employing Evans' chiral azidation reaction was also achieved following similar reaction sequence except that the chiral auxiliary chosen was (*R*)-4-benzyloxazolidin-2-one (**Scheme 8**).



Scheme 8: For (i – vi), see reaction conditions under **Scheme 7**; (vii) benzyl bromide, K_2CO_3, CH_3CN, 2 h, 25 ^oC, 73%.

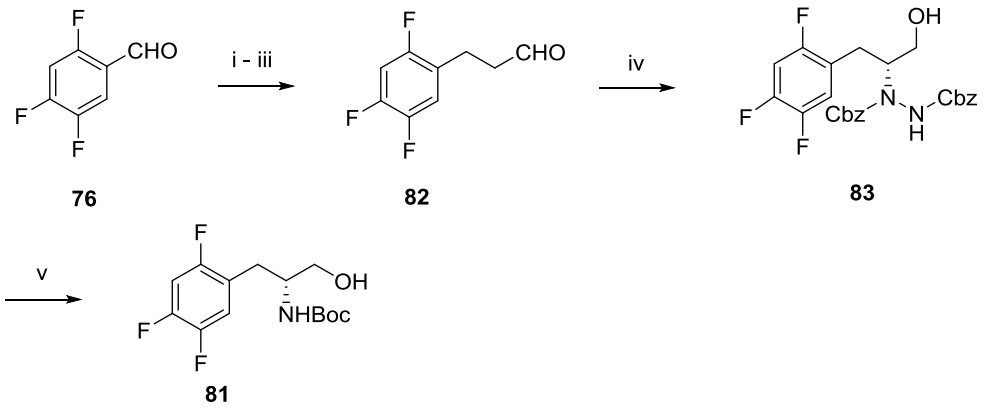
A formal synthesis of (*R*)-Sitagliptin (**10**), a potent DPP-IV inhibitor enzyme, was accomplished *via* two routes (i) Evans'chiral azidation (36% overall yield till known intermediate with 98% ee) and (ii) proline catalyzed α-amination reaction (35% overall yield up to with 95% ee) (**Scheme 9-11**).

(i) Evans' chiral azidation approach:



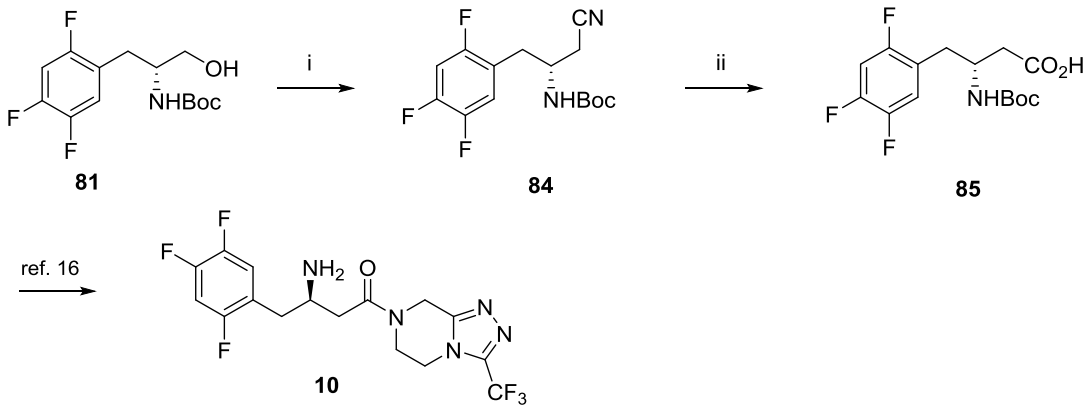
Scheme 9: (i) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 98%; (ii) H_2 (1 atm), 10% Pd/C, MeOH, 1 h, 98%; (iii) LiOH, THF/MeOH/H_2O (3:1:1), 2 h, 96%; (iv) pivolyl chloride, Et_3N, dry THF, -20 ºC, 3 h then (*R*)-4-benzyloxazolidin-2-one, LiCl, -20-25 ^oC, 8 h, 94%; (v) KHMDS, -78 ^oC, dry THF, 45 min, then 2,4,6-triisopropylbenzenesulfonyl azide, 5 min, then HOAc, -78-25 ^oC, 12 h, 88%; (vi) $NaBH_4$, THF/ H_2O (3:1), 0-25 ^oC, 2 h, 98%; (vii) H_2 (1 atm), 10% Pd/C, Boc_2O, MeOH, 3 h, 98%.

(ii) Organocatalytic approach:



Scheme 10: (i) $Ph_3P=CHCO_2Et$, benzene, reflux, 4 h; (ii) H_2 (1 atm), 10% Pd/C, MeOH, 1 h; (iii) DIBAL-H, toluene, -78 ºC, 1 h, 92% (over 3 steps); (iv) L-proline (10 mol%), DBAD (0.9 equiv), CH_3CN, 0 ºC, 3 h, then $NaBH_4$, MeOH, 1 h, 90%; (v) $PdCl_2$ (5 mol %), Boc_2O (5 mmol), PHMS, MeOH/Deionized water (1:1), 25 ^oC, 10 h, 88%.

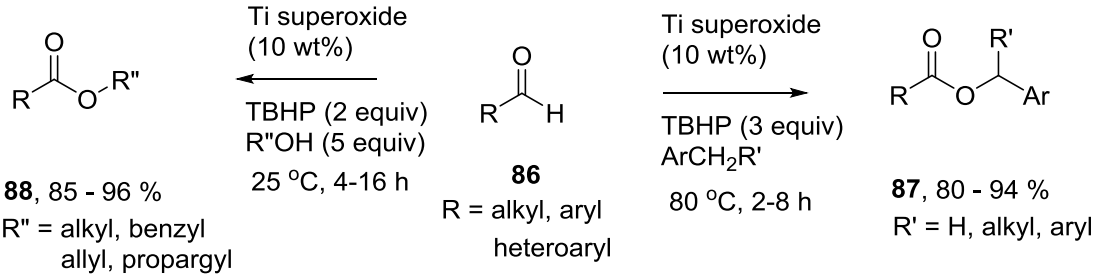
(iii) Completion of synthesis:



Scheme 11: (i) TsCl, Et_3N, CH_2Cl_2, 1 h then NaCN, DMF, 80 ^oC, 4 h, 65% (over two steps); (ii) 3N NaOH, H_2O_2, 100 ^oC, 3 h, 75%.

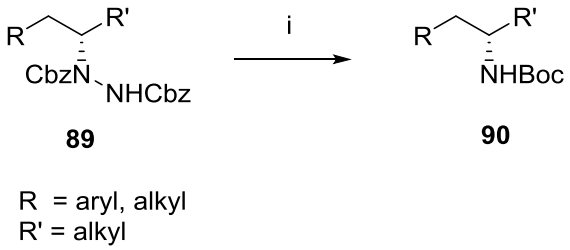
Chapter IV

Titanium superoxide efficiently catalyses the oxidative esterification of aldehydes (**86**) with alkylarenes or alcohols, under truly heterogeneous manner, to afford the corresponding benzyl (**87**) and alkyl (**88**) esters in excellent yields. Mechanistic studies have established that this "one pot" direct oxidative esterification process proceeds through radical pathway, proven by FTIR spectral study of titanium superoxide-aldehyde complex as well as spin trapping experiments with TEMPO. The intramolecular version of this protocol has been successfully demonstrated in the concise synthesis of 3-butylphthalide, an anti-convulsant drug (**Scheme 12**).



Scheme 12: Ti superoxide catalysed esterification of aldehydes with alkyl arenes or alcohols

Also, an environmental benign approach involving Pd-catalyzed reductive N-N bond cleavage in dibenzyl-1-alkylhydrazine-1,2-dicarboxylates (**89**) leading to the synthesis of *N*-(*tert*-butoxy)carbamates (**90**) under very mild conditions has been described. PMHS serves as inexpensive source of hydride in MeOH/deionized H_2O medium (**Scheme 13**).



Scheme 13: (i) $PdCl_2$ (5 mol %), PMHS (4 equiv), Boc_2O, DI water/MeOH (1:1), 25 °C, 10 h, 70-88%.

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CHAPTER I

Enantioselective Synthesis of *anti*-influenza agent (-)-Oseltamivir free base, (-)-Methyl 3-*epi*-shikimate, (-)-Codonopsinine and Radicamine B *via* Sharpless Asymmetric Epoxidation and Corey-Chaykovsky Reaction

Synthesis of the anti-influenza agent (-)-Oseltamivir free base and (-)-methyl-3-epi-shikimate, Rawat, V.; **Dey, S.**; Sudalai, A. *Org. Biomol. Chem*. **2012**, *10*, 3988.

Section I

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

1.1.1 Introduction and Pharmacology

Oseltamivir phosphate is an orally effective drug,[1] marketed as Tamiflu (**1**·H_3PO_4, **Fig. 1**), widely used for the treatment and prevention of human influenza (H1N1) and avian influenza (H5N1) infections[2] and represents the prototype of neuraminidase inhibitors. Release of the virus particles from the host cells requires the action of the virus-associated neuraminidase breaking off the terminal sialic acid, which is 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 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 first discovered by Gilead Sciences and subsequently licensed to Roche for production. Roche's manufacturing process of tamiflu utilizes (-)-shikimic acid as starting material. Shikimic acid and several of its epimers (e.g. methyl 3-*epi*-shikimate **2**) form the core of various natural products of biological importance and, hence, their syntheses have gained much attention.[5]

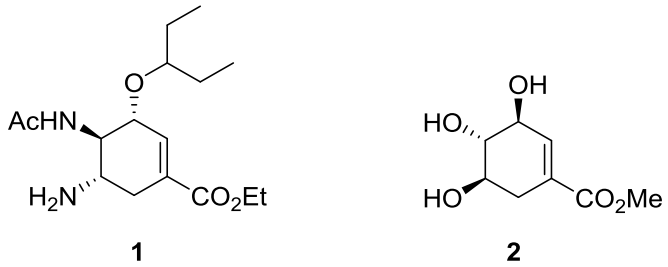


Fig. 1: Structures of oseltamivir (**1**) and methyl 3-*epi*-shikimate (**2**)

1.1.2 Review of Literature

Various syntheses of (-)-oseltamivir **1** are known in literature, which include mainly chiral pool and asymmetric induction. Since the syntheses have been excessively reviewed before[6] some ineresting 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**

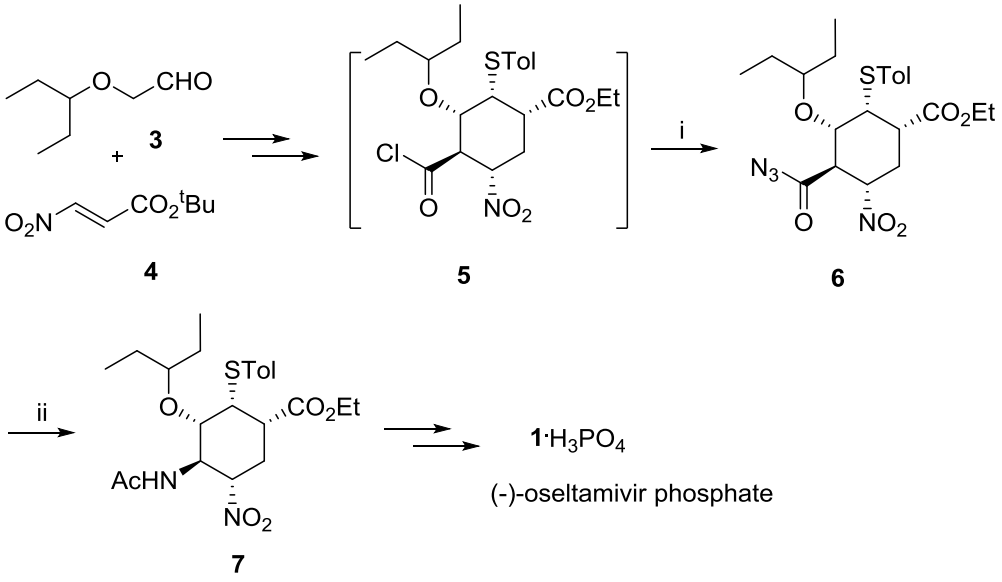
Sources	Starting material	Steps	Overall yield (%)
Gilead Sciences (1997)	(-)-shikimic acid	14	15
Gilead Sciences (1997)	(-)-quinic acid	6	40
F. Hoffmann-La Roche Ltd. (1999)	(-)-quinic acid	8	35
F. Hoffmann-La Roche Ltd. (1999)	(-)-shikimic acid	4	66
F. Hoffmann-La Roche Ltd. (2001)	(-)-quinic acid	6	35
F. Hoffmann-La Roche Ltd. (2004)	(-)-quinic acid	8	61
F. Hoffmann-La Roche Ltd. (2004)	furan and ethyl acrylate	9	3.2
F. Hoffmann-La Roche Ltd. (2004)	1,6-dimethoxyphenol	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 1*H*-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
Saicic (2013)	(*S*)-pyroglutamic acid	22	2.3
Shi (2013)	Roche's epoxide	4	35
Chavan (2014)	D-mannitol	9	5.5

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

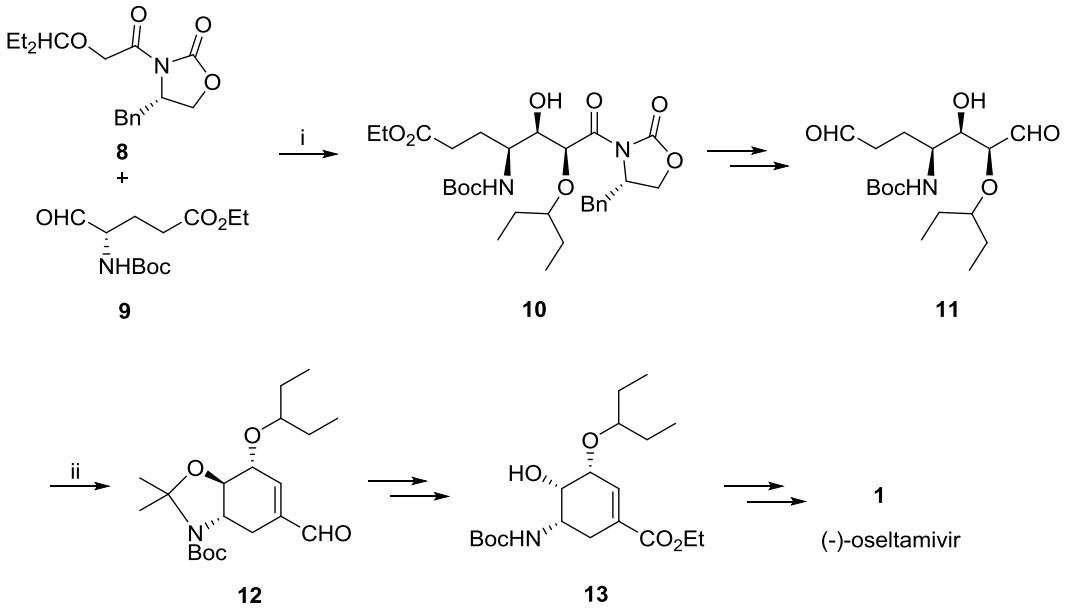
isocyanate with a nucleophile to give acetamide **7**. Purification of **7** by recystallization followed by another one-pot reaction sequence furnished tamiflu. This synthesis requires nine reactions, a total of three separate one-pot operations, and one recrystalization. The total yield of (-)-oseltamivir 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]

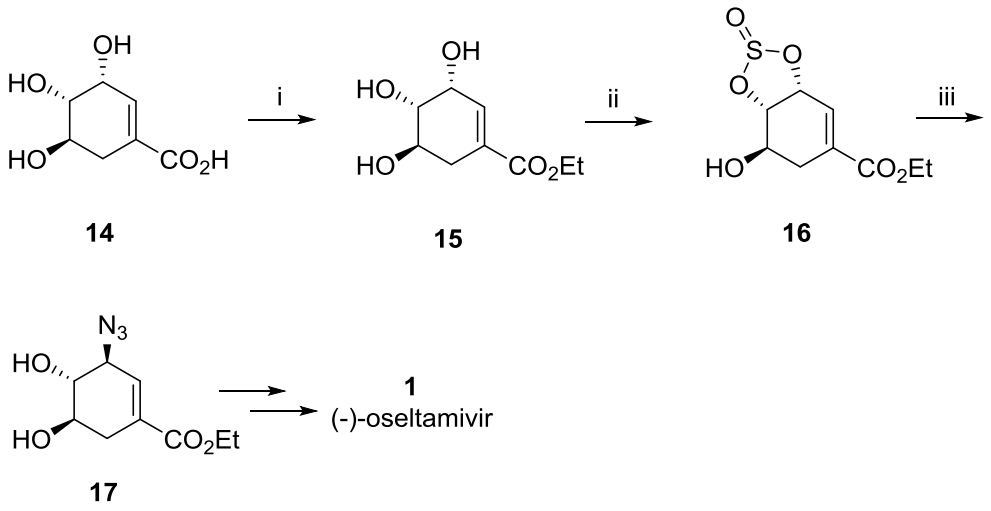
In Saicic's approach, formation of all carbon–carbon bonds and stereocenters, was achieved using two aldol reactions: three stereocenters in the acyclic intermediate **10** were installed in the reaction of the Evans oxazolidinone derived boron enolate of **8** with glutaraldehyde **9**, while the cyclization was achieved *via* enamine catalyzed intramolecular condensation of aldehyde **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]

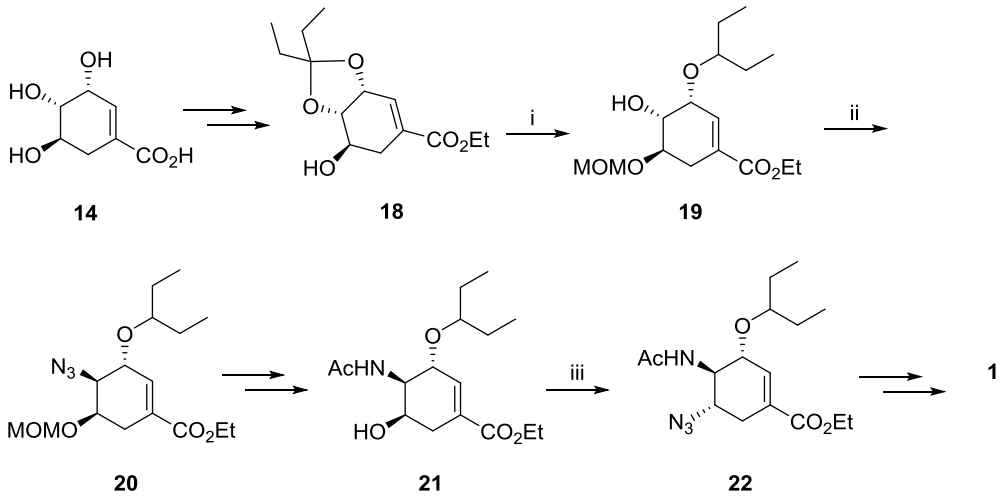
Lu *et al.* have described asymmetric synthesis of oseltamivir **1** from (-)-shikimic acid **14**. Esterification of **14** gave ethyl shikimate **15**, which was then converted into cyclic sulfite **16**. The characteristic step of the synthesis is the regio- and stereospecific nucleophilic substitution 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, 2 h then 25 ^oC for 12 h, 98%; (iii) NaN_3, EtOH, reflux, 12 h, 93%.

Park's approach (2012)[10a]

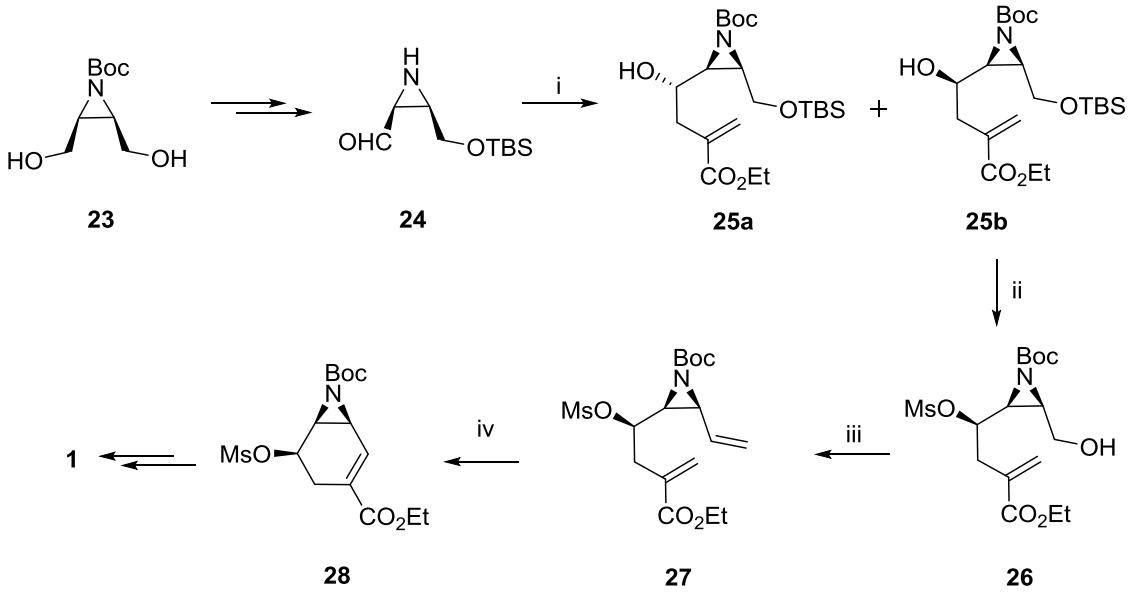
Park *et al.* have reported the synthesis of oseltamivir **1** in 9 steps with a 27% overall yield from commercially available (-)-shikimic acid **14**. Selective ring opening reaction of ketal **18** and Mitsunobu reaction for facile replacement of a hydroxyl group by the N_3 group at the C-3 position 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%.

Han-Young Kang's approach (2012)[10b]

Han-Young Kang *et al* have used enzyme catalyzed desymmetrization of Boc protected *cis*-2,3-bis(hydroxymethyl)aziridine **23**, which was then converted to its aldehyde substrate **24**. Addition of allylzinc reagent to **24** successfully produced homoallyl alcohols **25a** and **25b** in a ratio of 1:3 (25 and 71% yields respectively). Mesylation of –OH functionality in **25a** followed by removal of TBS group provided **26**. The primary alcohol in **26** was oxidized to its aldehyde and subjected to Wittig reaction furnished diene **27**. Cyclohexene core **28** was produced from diene *via* RCM strategy using Hoveyda-Grubbs catalyst. Finally, target compound **1** was obtained from a known six-step reaction sequences.



Scheme 5: (i) ethyl 2-(bromomethyl)acrylate, Zn, THF: aq. NH_4Cl (1:1), 25 ºC; (ii) (a) MsCl, Et_3N, CH_2Cl_2, (b) TBAF, THF, 72%; (iii) KHMDS, PPh_3MeBr, THF, 63%; (iv) Grubbs-II, CH_2Cl_2, reflux, 68%.

1.1.3 Present Work

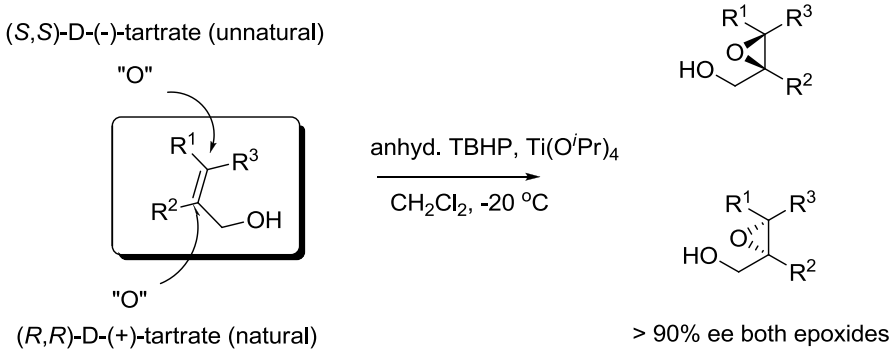
1.1.3.1 Objective

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. Due to its high bioactivity, several syntheses are known as can be seen from literature. However, most of them include chiral pool approach and low yields. 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 a concise synthesis of (-)-oseltamivir free base **1** and (-)-methyl 3-*epi*-shikimate **2**, an unnatural methyl ester of shikimic acid **14**, starting from *cis*-2-butene-1,4-diol 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 (SAE)[12]

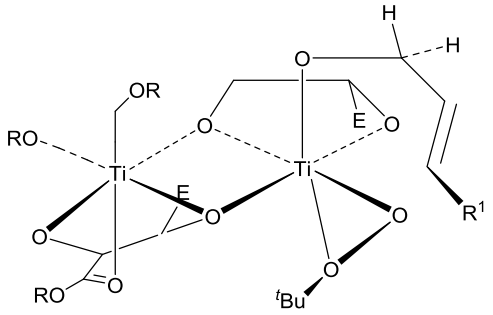
Sharpless asymmetric epoxidation (SAE) of allylic alcohols is one of the leading areas of investigation in synthetic organic chemistry, mainly because of the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents. Both of its enantioselective and catalytic nature make it popular tool for laboratory and industrial processes. Simple reagents like, a titanium tetraalkoxide, a chiral tartrate diester, an allylic alcohol substrate, and an alkyl hydroperoxide as the oxidant, constitute the reaction mixture. The efficiency of the reaction is remarkable; excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. Additionally, for 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 *trans*-epoxyalcohols in high enantiomeric purity. The fact that 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 6**).



Scheme 6: The Sharpless epoxidation reaction

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

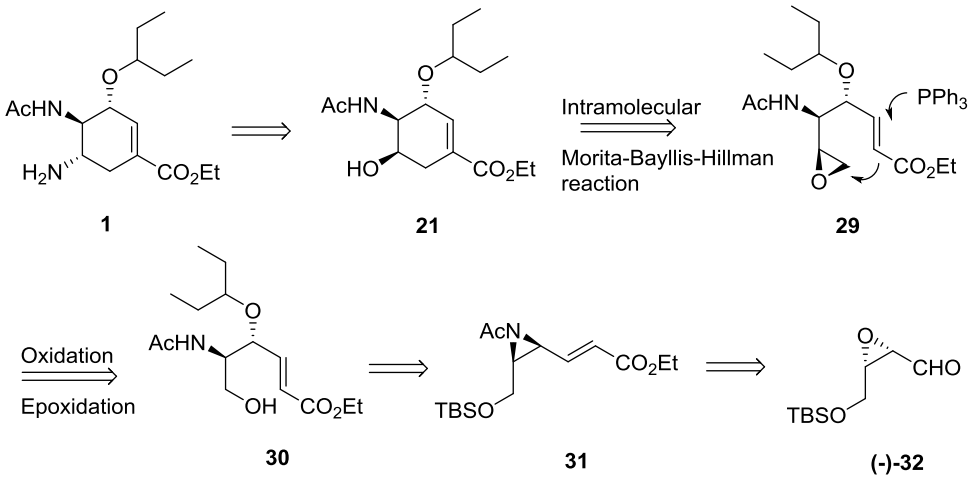


E = CO_2R; R = Et, *i*-Pr; R^1 = alkyl, aryl

Fig. 2: Structure of dinuclear Ti-tartrate complex

1.1.3.3 Results and Discussion

The retrosynthetic scheme for functionalized cyclohexene core **21**, the key intermediate in the synthesis of oseltamivir **1**, is depicted in **Scheme 7**. It was envisioned that cyclic alcohol **21** could be obtained *via* an intramolecular Morita-Bayllis-Hillman cyclization of epoxide **29**.[15] The epoxide **29** could in turn be obtained by a sequence of reactions such as oxidation, olefination and diastereoselective epoxidation of alcohol **30**. Ester **30** was envisaged from aziridine **31** by the regioselective aziridine opening with 3-pentanol. Protected aziridine **31** could in turn be obtained from epoxy aldehyde **(-)-32**.



Scheme 7: Initial attempt towards the synthesis of oseltamivir **1**

To start with, epoxy aldehyde **(-)-32** was prepared in 64.5% yield from commercially available *cis*-2-butene-1,4-diol (**33**) in three steps: (i) monosilylation of diol **33** (TBSCl, imid., 73%); (ii) AE of allylic alcohol **34** [$Ti(OiPr)_4$, (-)-DET, anhydrous TBHP, 93%]; (iii) oxidation of epoxy alcohol **(+)-35** (TEMPO, BAIB, 95%) (**Scheme 8**). The ^{1}H NMR spectrum of **(-)-32** 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) are due to methine (-**CH**-O-**CH-**) and methylene (-**CH_2**-OTBS) protons respectively. 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 are indicative of carbons attached to oxygen atom (**Fig. 3**).

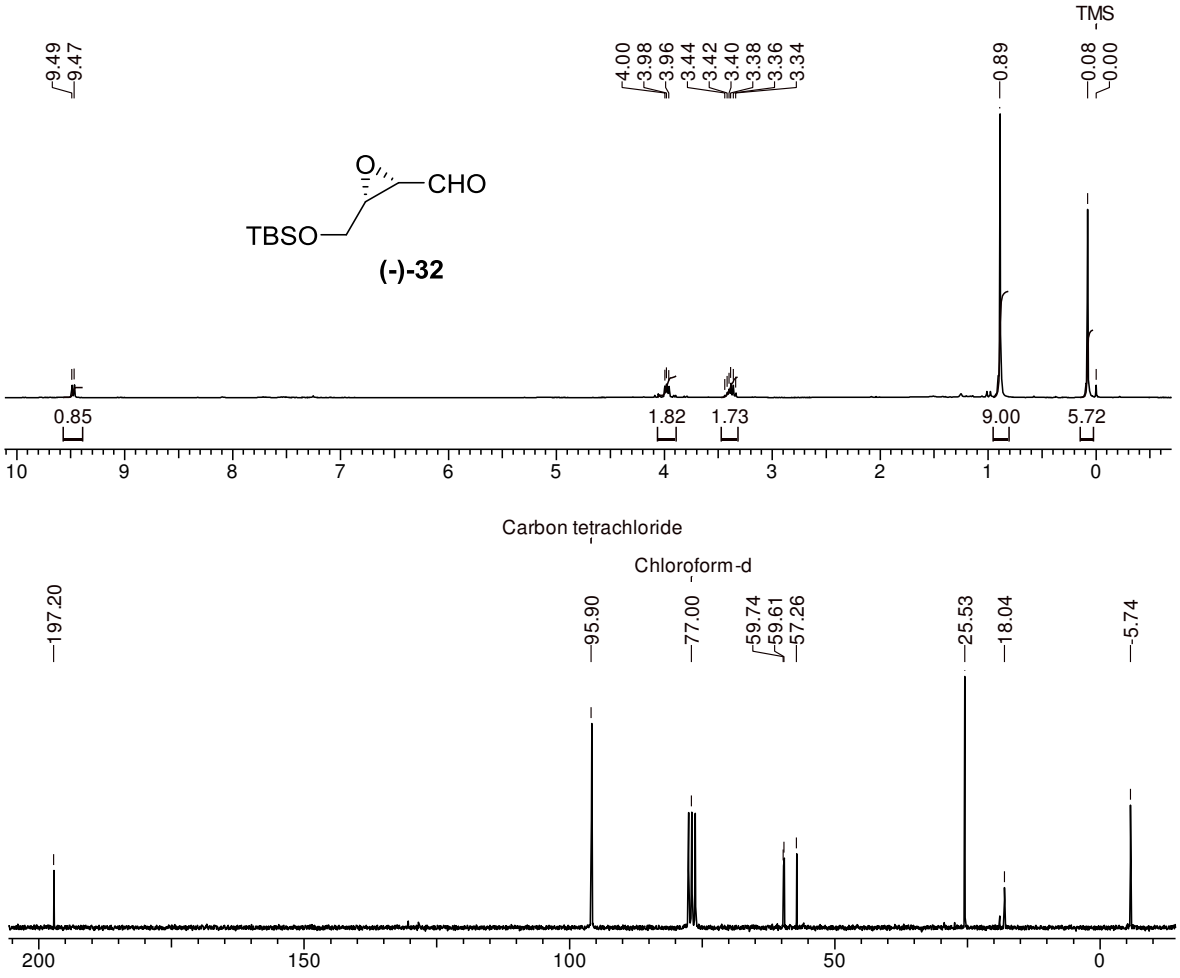
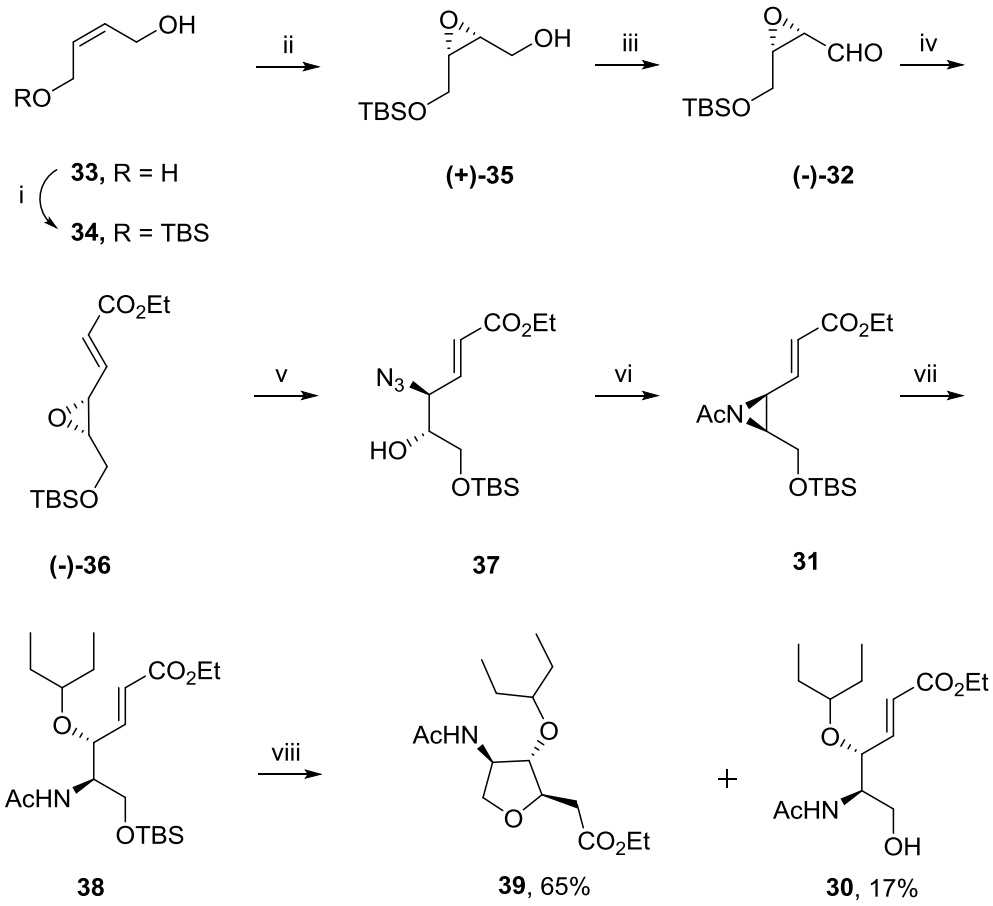


Fig. 3: ^{1}H and ^{13}C NMR spectra of epoxy aldehyde **(-)-32**



Scheme 8: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (-)-DET, $Ti(PrO^i)_4$, anhyd. TBHP (5.5 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, 12 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, $BF_3.OEt_2$, -10 ºC, 30 min, 75%; (viii) TBAF, THF, 0 ºC, 2 h.

Wittig olefination of **(-)-32** with $Ph_3P{=}CHCO_2Et$ gave the α,β-unsaturated epoxy ester **(-)-36** in 92% yield. Regioselective ring opening of **(-)-36** at the allylic position with azide ion in presence of NH_4Cl was accomplished to give azido alcohol **37** in 85% yield. Staudinger reaction (Ph_3P, toluene) followed by *N*-acetylation (Ac_2O, DMAP, Et_3N) afforded protected aziridine **31**; $[\alpha]_D^{25}$ +60 (*c* 2.0, $CHCl_3$). The ^1H NMR spectrum of **31** showed multiplets at δ 2.82-2.91 (m, 1H) and 3.15-3.22 (m, 1H) 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 (**Fig. 4**).

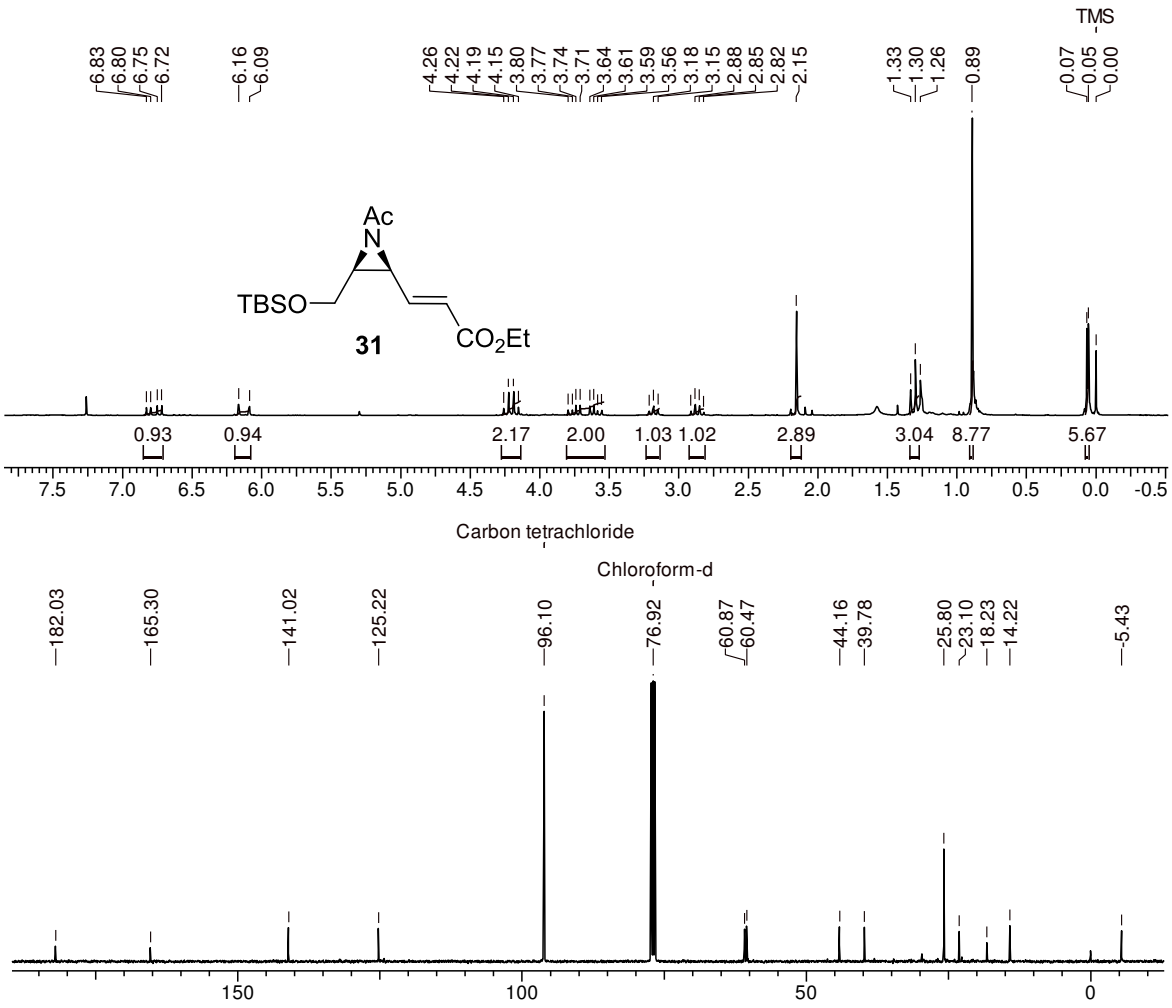


Fig. 4: ^{1}H and ^{13}C NMR spectra of aziridine **31**

Regioselective ring opening of **31** with 3-pentanol in presence of $BF_3{\cdot}OEt_2$ proceeded smoothly to furnish α,β-unsaturated ester **38** as the exclusive product in 75% yield. The formation of **38** was confirmed from its ^{1}H and ^{13}C NMR spectra, which displayed multiplets at δ 3.67-3.74 (m, 1H) and 4.35-4.37 (m, 1H) for methine protons and other signals at δ 80.6 and 73.2 due to methine and methylene carbons attached to oxygen atom (**Fig. 5**). The proton signals at δ 0.06 (s, 6H) and 0.85 (s, 9H) in its ^{1}H NMR spectrum and

carbon signals at δ -5.5, -5.3, 18.1 and 25.8 in its ^{13}C NMR spectrum are attributed to the TBS ether functionality.

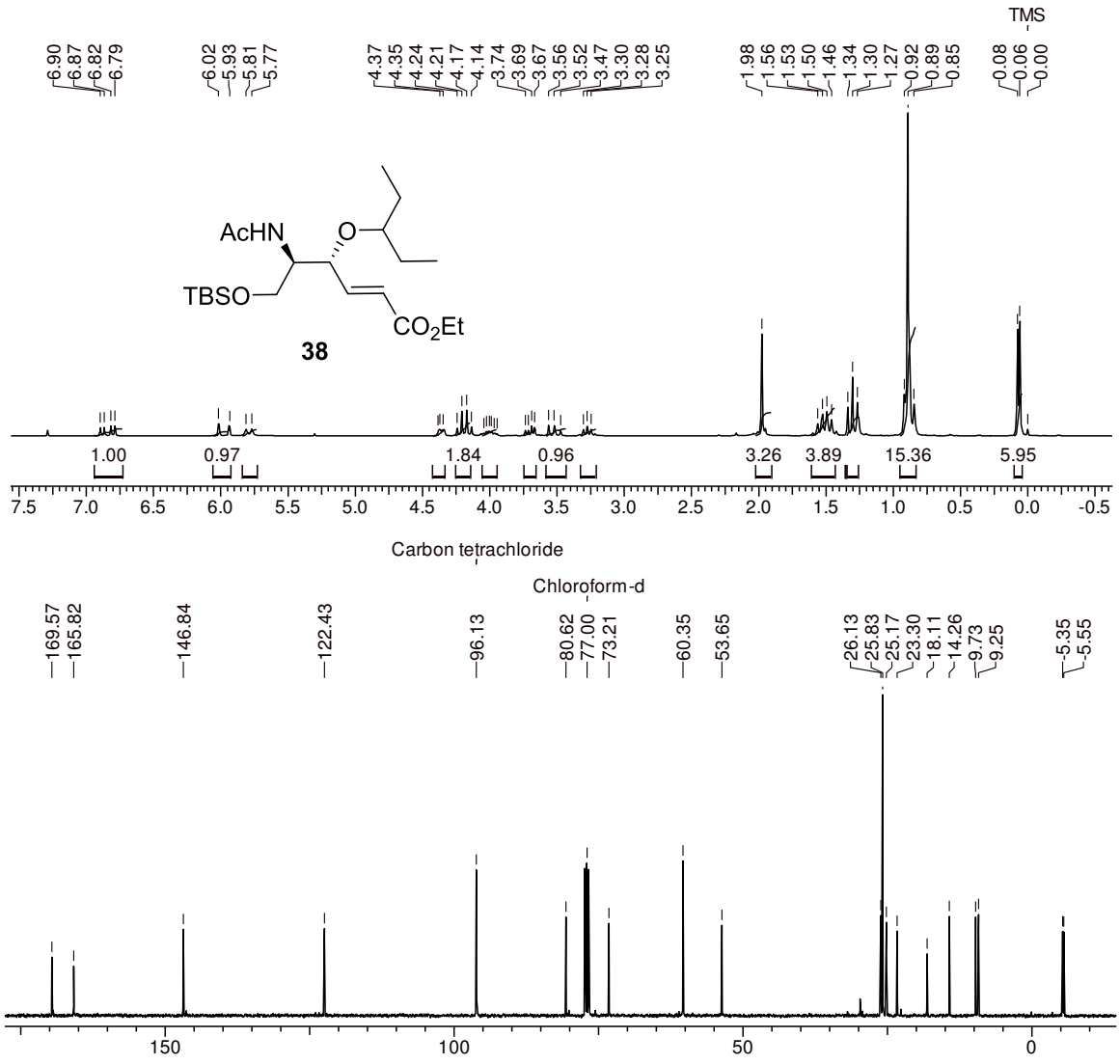


Fig. 5: ^{1}H and ^{13}C NMR spectra of ester **38**

On desilylation with TBAF, **38** unexpectedly gave the furan derivative **39**, a Michael adduct, as the major product (65% yield) along with the desired alcohol **30** in minor amounts (17% yield). The formation of the desired alcohol **30** 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 (m, 1H) and 6.77-6.88 (m, 1H) are attributed to the olefinic

protons. The carbon signals at δ 170.5 and 165.7 are due to amide and ester carbonyl functionalities, while other carbon signals at δ 145.8 and 123.1 account for olefinic function (**Fig. 6**).

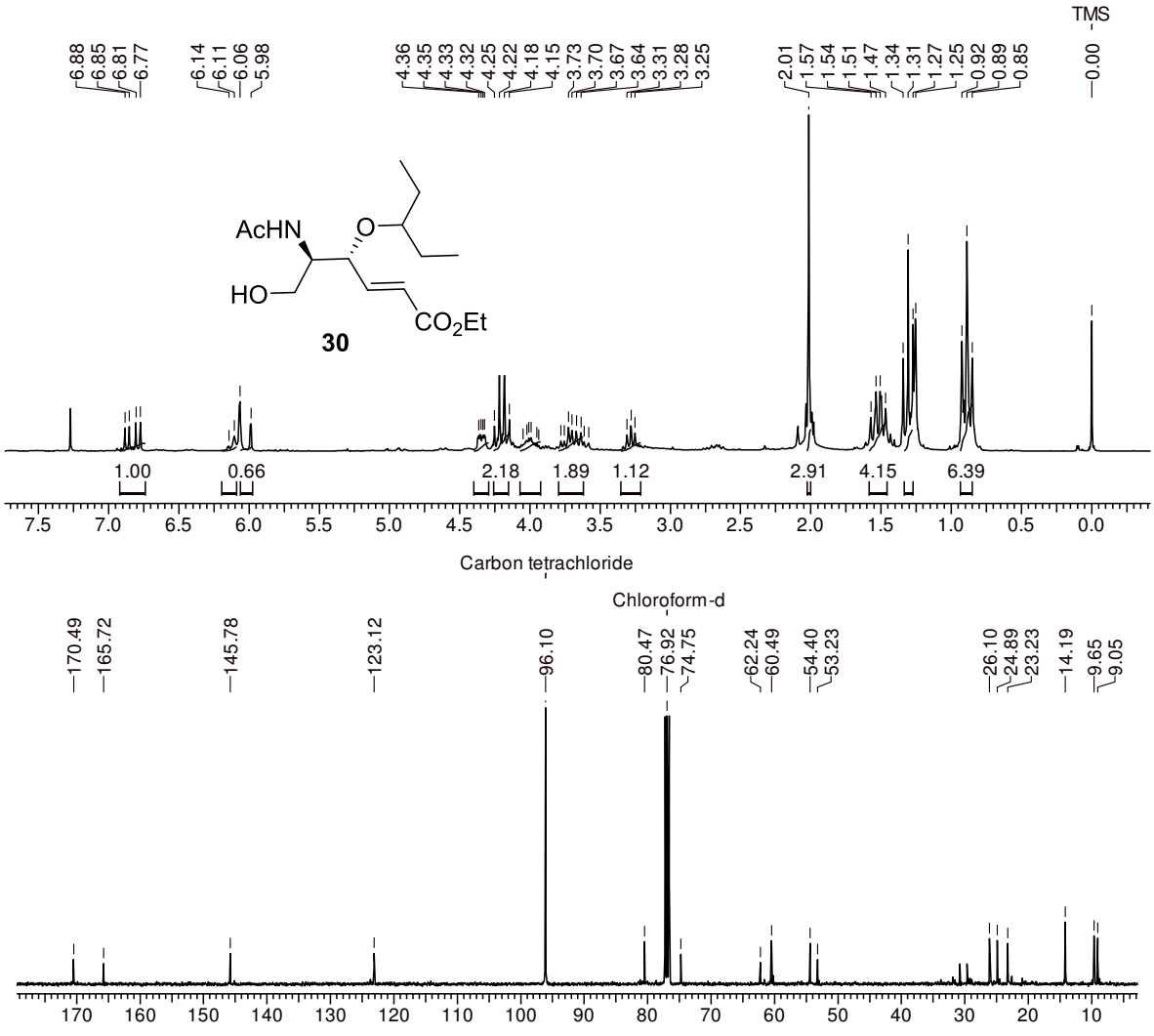


Fig. 6: ^{1}H and ^{13}C NMR spectra of alcohol **30**

The formation of intramolecular Michael addition product **39** 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 (m, 1H), 3.81-3.92 (m, 3H) and 4.12-4.29 (m, 3H) due to protons of methine and methylene groups attached to

oxygen atom. A singlet at δ 2.0 (s, 3H) is attributed to methyl protons of acetyl group (**Fig. 7**).

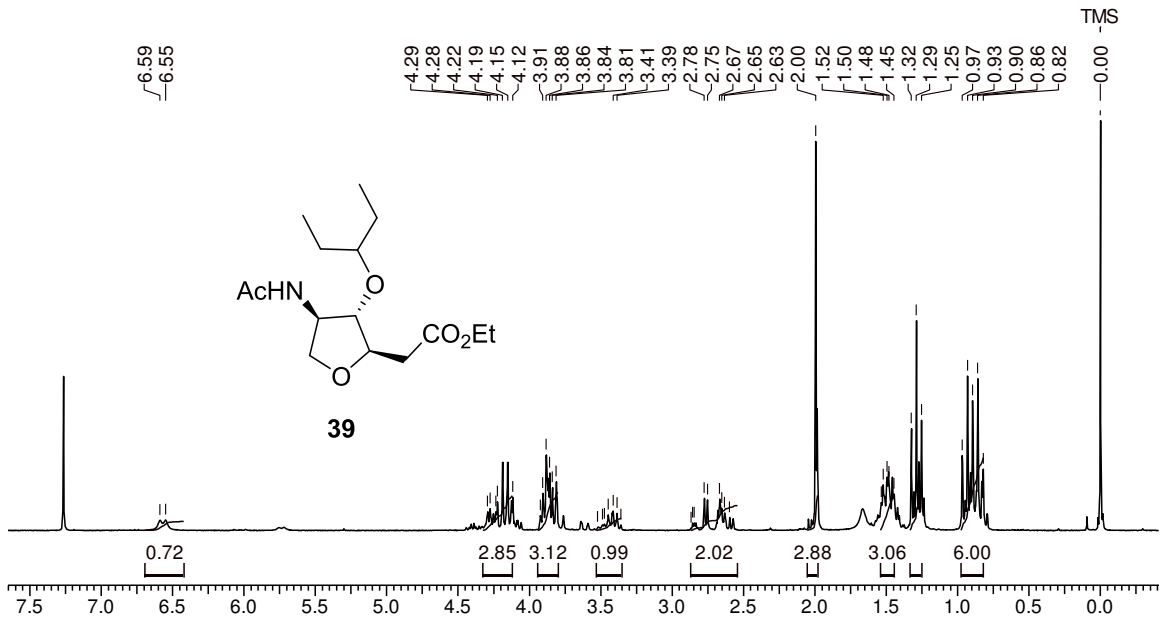
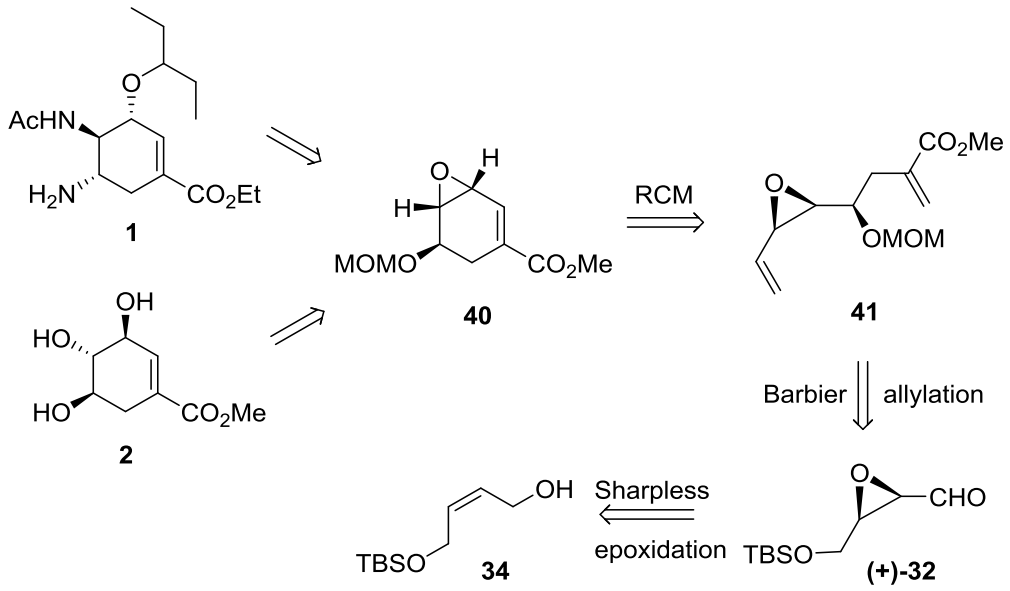


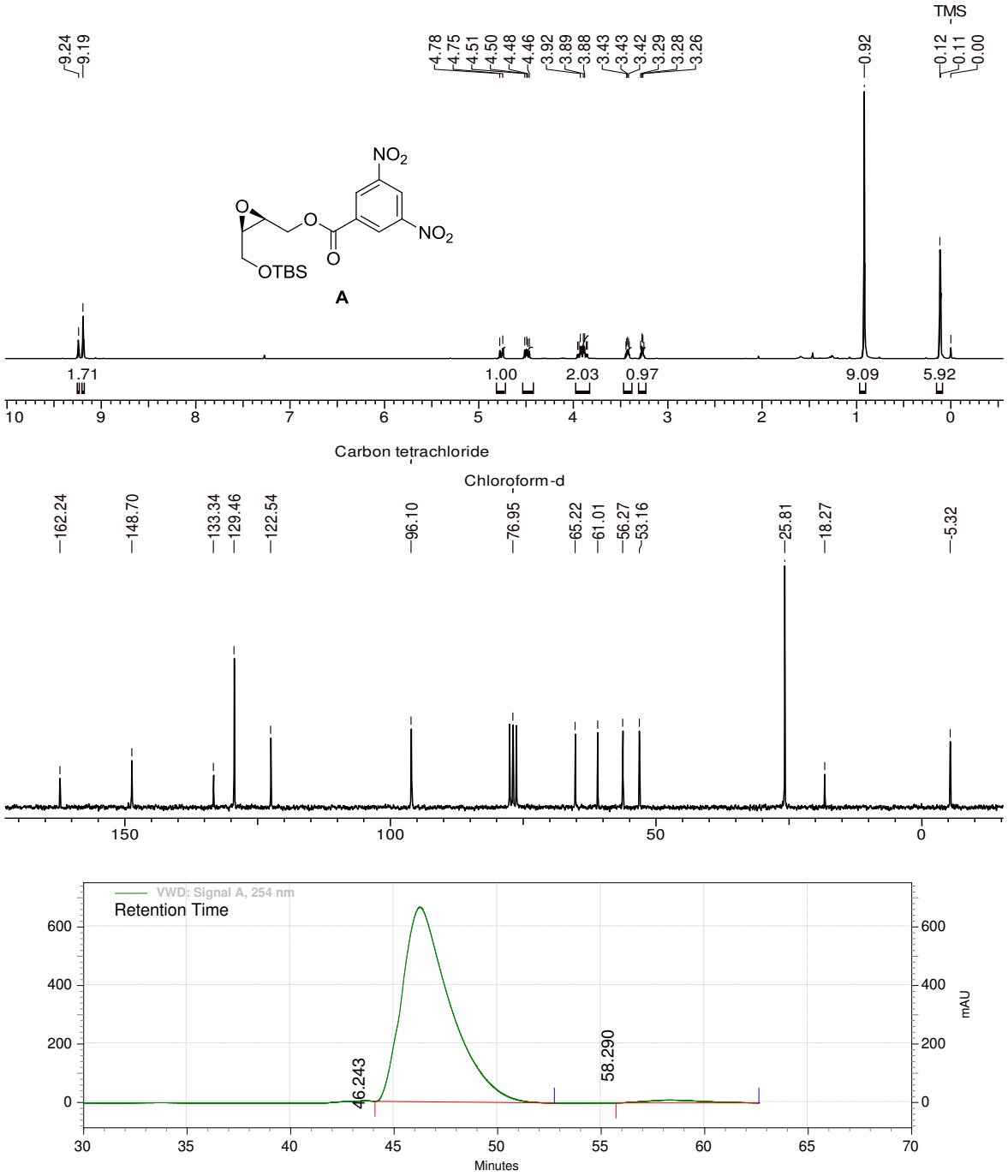
Fig. 7: ^{1}H NMR spectrum of furan **39**

Since the yield of **30** was miserably low, an alternate route to oseltamivir **1** was undertaken. Based on retrosynthetic analysis, we visualized that epoxide **40** can be considered as the key precursor in the synthesis of Tamiflu **1**·H_3PO_4 and (-)-methyl 3-*epi*-shikimate **2** (**Scheme 9**). Cyclic epoxide **40** was envisaged to arise from ring closing metathesis (RCM) of diene **41**. Epoxy alcohol **42** can in turn be obtained from diastereoselective Barbier allylation of chiral epoxy aldehyde **(+)-32**. Sharpless asymmetric epoxidation of allylic alcohol **34** can be employed for the introduction of chirality.



Scheme 9: Retrosynthetic analysis of oseltamivir free base (**1**) and methyl 3-*epi*-shikimate (**2**)

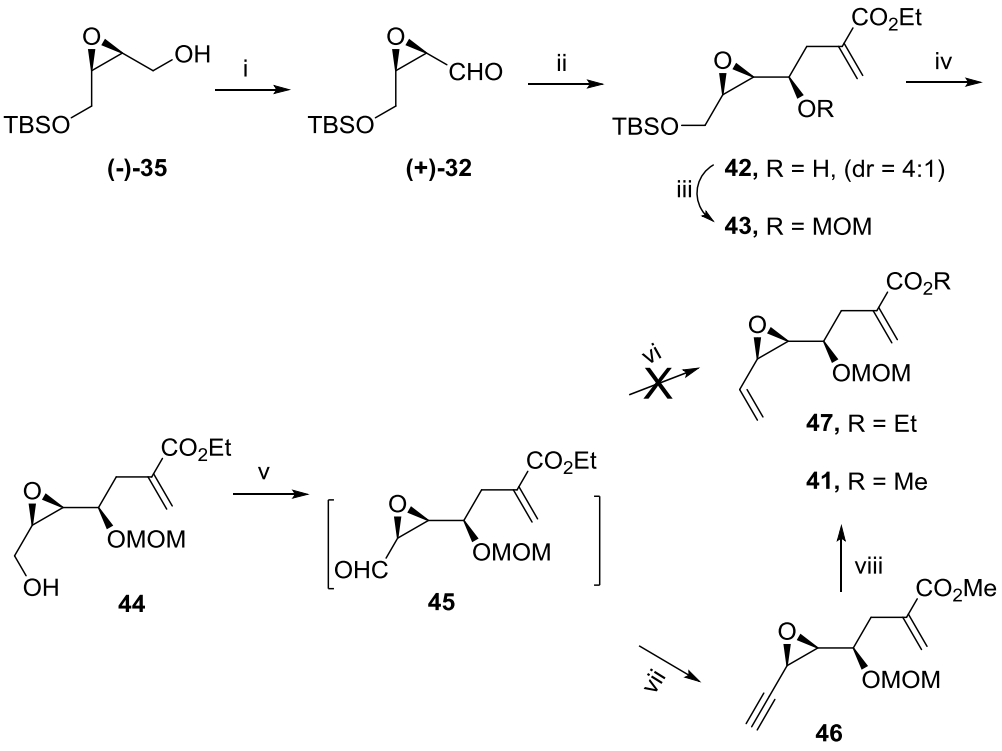
Accordingly, in the second approach, antipode epoxy alcohol **(-)-35** was readily prepared [97% ee confirmed by HPLC analysis of the corresponding 3,5-dinitrobenzoate **A**] in two steps as described earlier in **Scheme 8**: (i) monosilylation and (ii) SAE with (+)-DET as chiral source. The ^{1}H NMR spectrum of the 3,5-dinitrobenzoate derivative of alcohol **(-)-35** showed two singlets at δ 9.19 (s, 2H) and 9.24 (s, 1H), which accounted for the three aromatic protons. The multiplets at δ 3.26-3.29 (m, 1H) and 3.24-3.44 (m, 1H) indicated the presence of epoxide protons. Its typical carbon signal at δ 162.2 is attributed to ester carbonyl, while other peaks at δ 122.5, 129.5, 133.3 and 148.7 are indicative of the aromatic carbons. Methine and methylene carbons attached to the oxygen atom showed signals at δ 53.2, 56.3, 61.0 and 66.2 in its ^{13}C NMR spectrum. Its IR spectrum showed a characteristic carbonyl stretching frequency band at υ_{max} 1737 cm^{-1}. Its chiral HPLC gave



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

Fig. 8: ^{1}H & ^{13}C NMR spectra and Chiral HPLC chromatogram of benzoate **A**

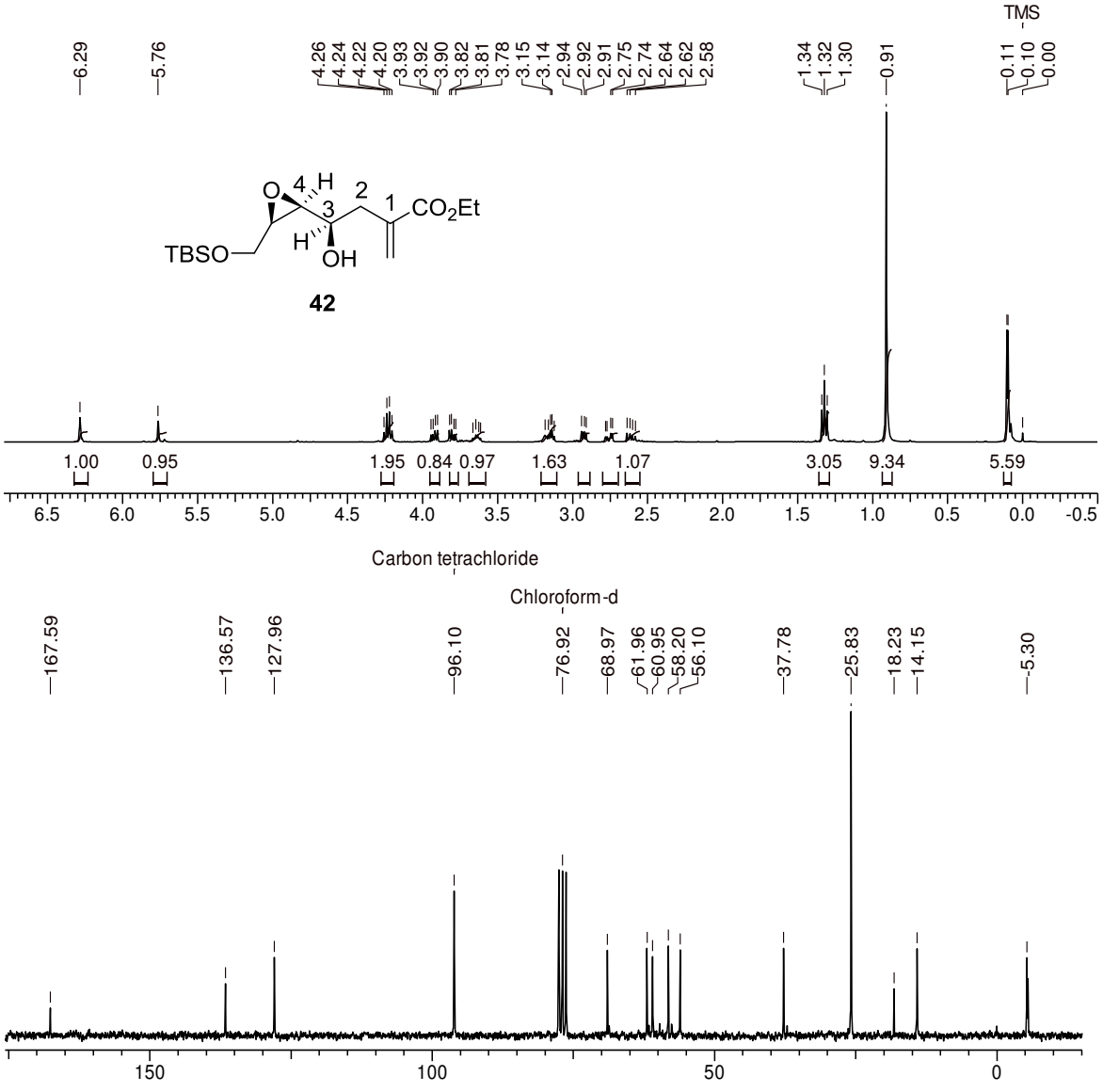
an ee of 97% (Column: Chiracel OD-H retention time: 46.24 min (-)-isomer, 58.29 min (+)-isomer) (**Fig. 8**). Oxidation of **(-)-35** (TEMPO, BAIB) gave the aldehyde **(+)-32**, which upon purification was subjected to Barbier allylation with ethyl 2-(bromomethyl)acrylate to afford the homoallylic alcohol **42** in 64% yield (dr = 4:1) (**Scheme 10**).

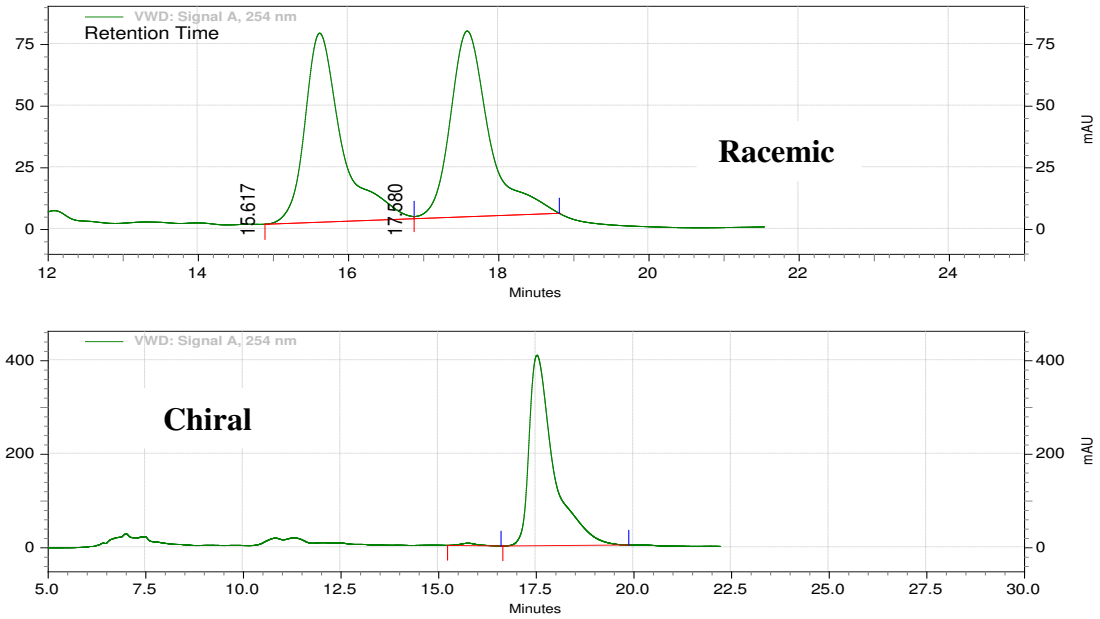


Scheme 10: (i) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (ii) ethyl 2-(bromomethyl)acrylate, Zn dust, NH_4Cl, THF/H_2O (4:1), 0-25 ºC, 10 h, 64% (for syn-selectivity); (iii) MOMCl, DIPEA, dry CH_2Cl_2, 0-25 ºC, 12 h, 90%; (iv) TBAF, THF, 0 ºC, 2 h, 88%; (v) IBX, dry DMSO, 25 ºC, 1 h; (vi) n-BuLi, $Ph_3P^+CH_3I^-$, 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 **41**.

The ^1H NMR spectrum of *syn*-epoxy alcohol **42** showed two singlets at δ 5.76 (s, 1H) and 6.29 (s, 1H) due to the two olefinic protons. The other doublet of doublets at δ 3.78 (dd, J = 5.8, 11.8 Hz, 1H) and 3.90 (dd, J = 5.8, 11.5 Hz, 1H) are attributed to methylene group attached to silyl ether group. A multiplet at δ 3.61 is due to the methine proton 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 are indicative of the carbons attached to oxygen atom. A significant COSY and NOESY correlation was observed between H_4 and H_3 in **42** (**Fig. 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

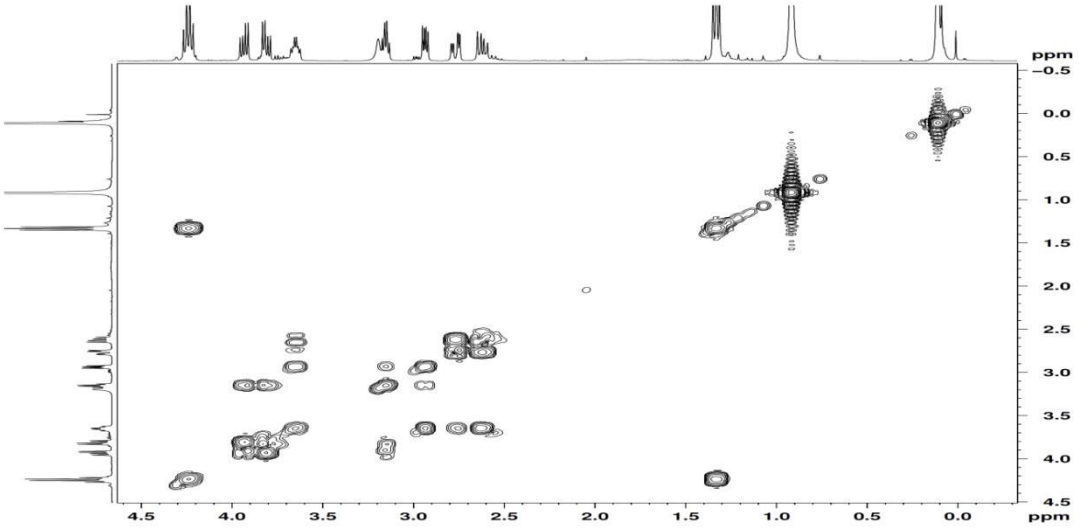


Fig. 9: ^{1}H, ^{13}C & COSY NMR spectra and HPLC chromatogram of epoxy alcohol **42**

The hydroxyl group in **42** was then protected as its MOM ether (MOMCl, DIPEA, 90%) and TBS group in **43** deprotected with 1M TBAF solution in THF to produce alcohol **44**; $[\alpha]_D^{25}$ +4.1 (*c* 0.6, $CHCl_3$). This transformation was confirmed by analyzing the ^{1}H and ^{13}C

NMR spectra of compound **44**. The disappearance of signals corresponding to TBS ether confirmed the deprotection. Its ^{1}H NMR spectrum showed two typical signals at δ 5.59 (s, 1H) and 6.16 (s, 1H) corresponding to olefinic protons, while a typical carbon signal at δ 72.7 in its ^{13}C NMR spectrum accounted for methylene carbon of MOM ether group (**Fig. 10**).

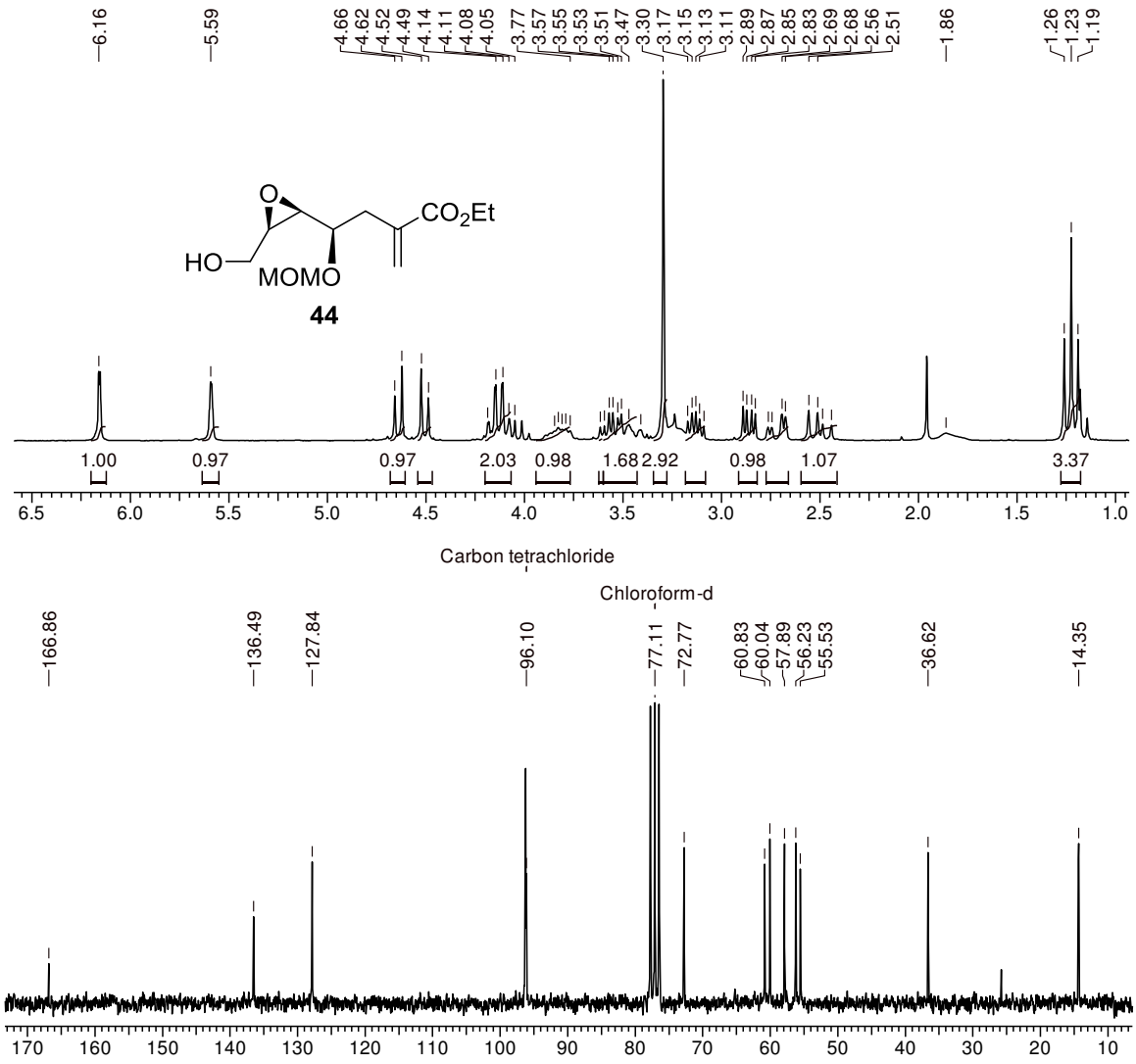


Fig. 10: ^{1}H and ^{13}C NMR spectra of alcohol **44**

Primary alcohol **44** was then subjected to oxidation (IBX/DMSO) to give the labile aldehyde **45**. Several attempts to perform Wittig olefination (*n*-BuLi, $PPh_3^+CH_3I^-$, THF) of **45** to produce diene **47** were quite unsuccessful, due to its rapid decomposition under the

strongly basic condition. Alternately, the crude aldehyde **45** was subjected to Seyferth-Gilbert homologation using Bestman-Ohira reagent[16] in presence of K_2CO_3 and MeOH, which gave the terminal alkyne **46** 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 **46** was confirmed from its IR spectrum, which showed a characteristic

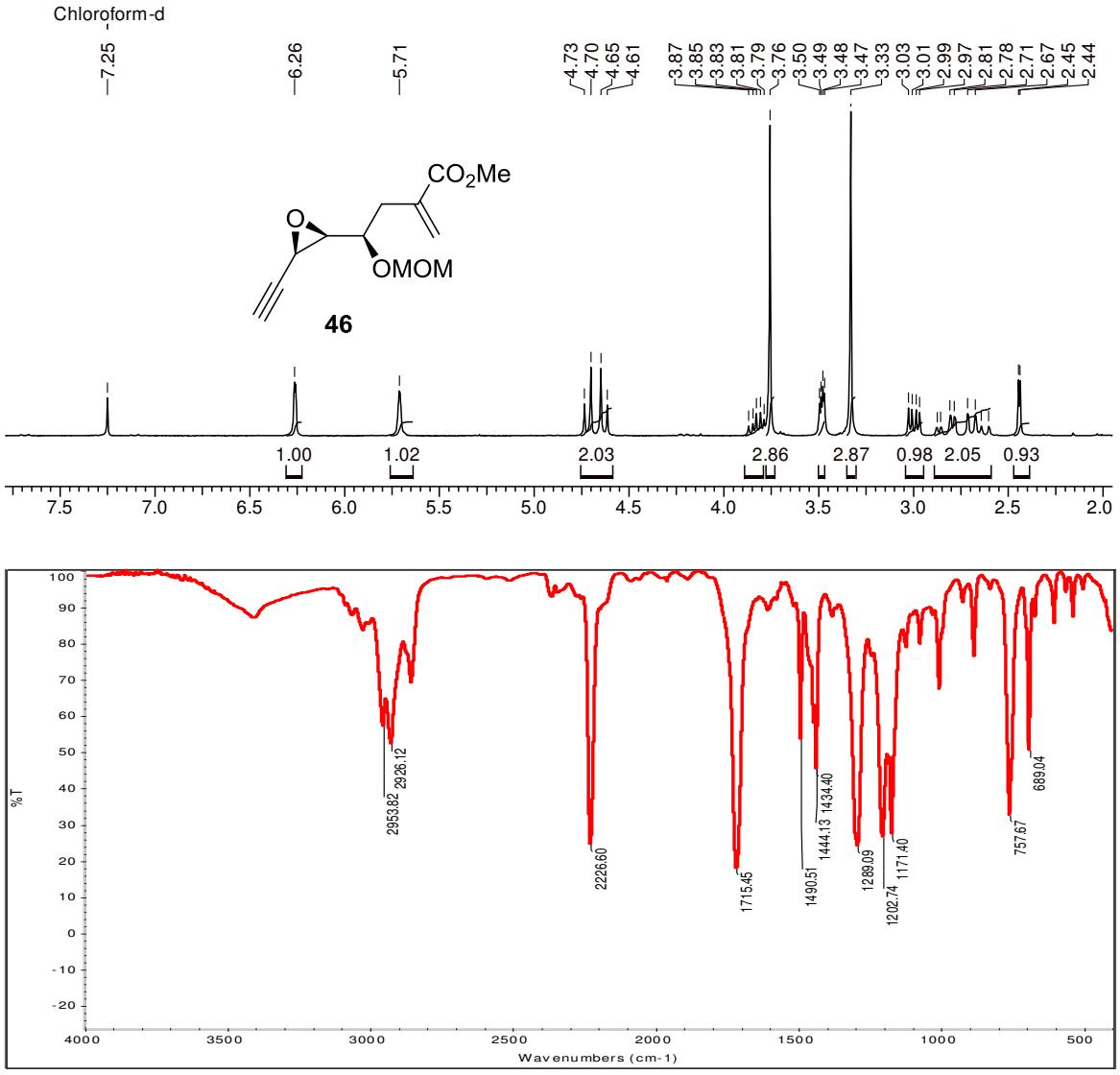


Fig. 11: ^{1}H NMR and IR spectra of alkyne **46**

strong absorption band at υ_{max} 2226 cm^{-1}. Its ^1H NMR spectrum showed a doublet at δ 2.45 (d, *J* = 1.6 Hz, 1H) indicative of acetylenic proton and a singlet at δ 3.76 (s, 3H) confirming the presence of methyl ester (**Fig. 11**).

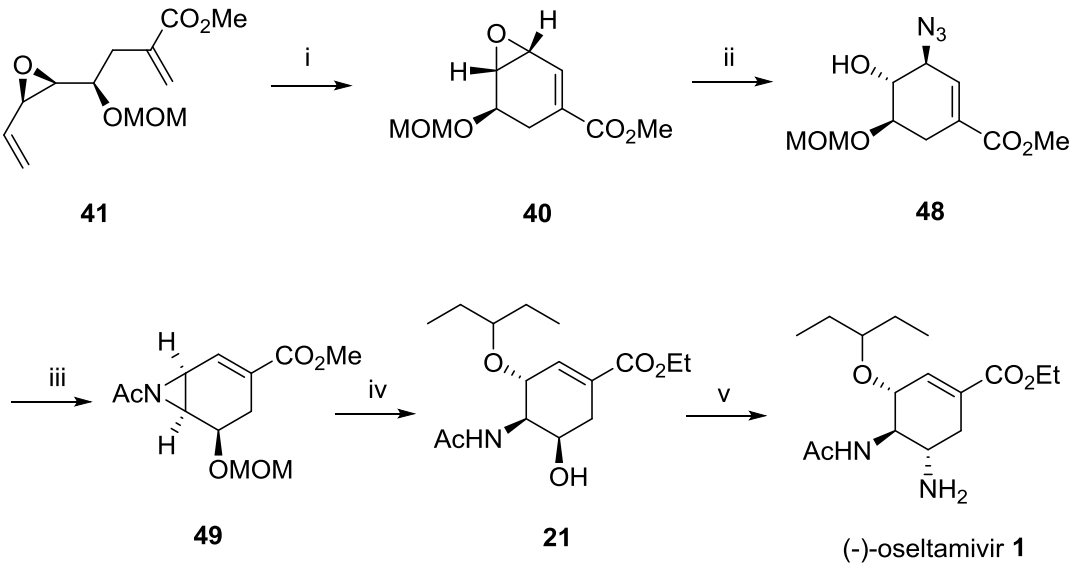
Next, a systematic study of selective catalytic hydrogenation [H_2 (1 atm), Lindlar's catalyst, additives, solvents] of alkyne **46** to alkene **41** was undertaken and the results are summarized in **Table 2**. As can be seen, ethyl acetate and pyridine combination gave good yields (64%) of diene **41**; $[\alpha]_D^{25}$ -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 **41** 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 ºC, 6 h; [b] 1.2 equiv; [c] 10 mol % was used; [d] isolated yield; [e] py/1-octene/EtOAc (1:1:10).

The cyclohexene core **40** was then constructed smoothly in 90% yield *via* a RCM strategy using Grubbs II catalyst under high dilution (**Scheme 11**).



Scheme 11: (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 **40** was confirmed by its ^{1}H NMR spectrum which showed a characteristic triplet of olefinic proton at δ 6.99 (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. A significant NOESY correlation was observed between H_4 and H_3 in cyclic epoxide **40** (**Fig. 12**).

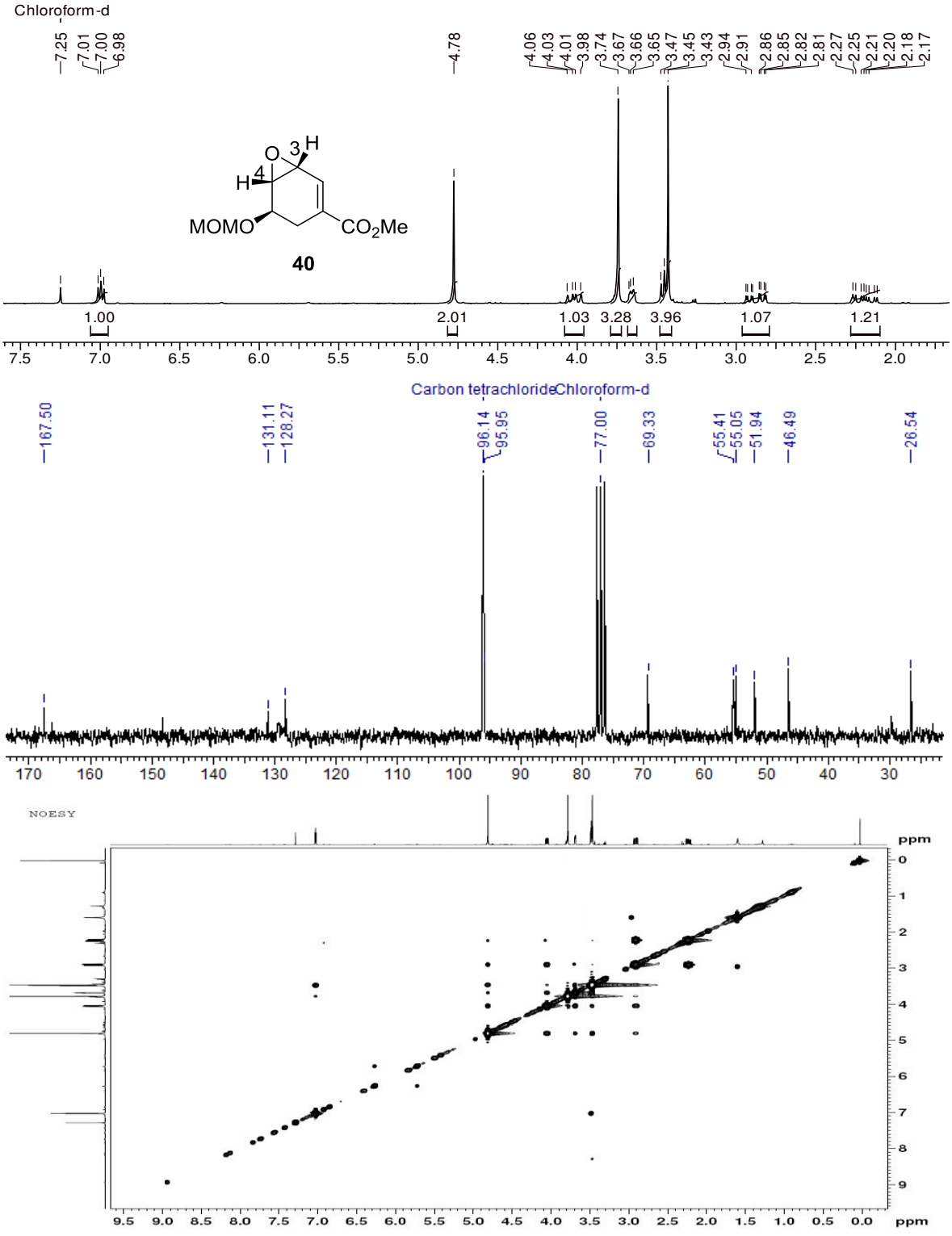


Fig. 12: ^{1}H, ^{13}C and NOESY NMR spectra of cyclic epoxide **40**

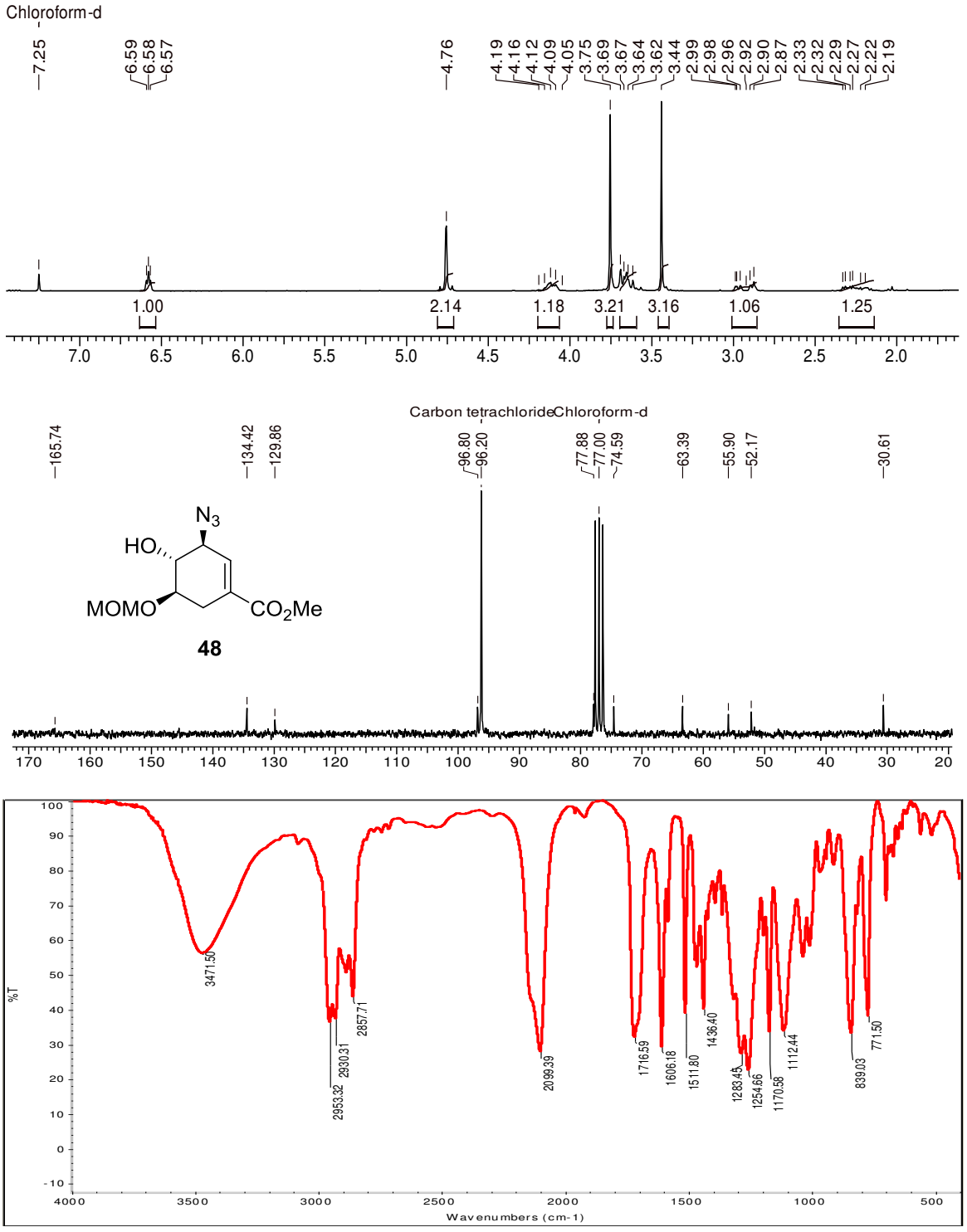


Fig. 13: ^{1}H & ^{13}C NMR and IR spectra of azido alcohol **48**

The conversion of **40** to aziridine **49** was achieved using a sequence of reactions similar to the one described in **Scheme 8**. Consequently, the regioselective epoxide opening of **40**

was achieved in 83% yield with azide anion [NaN_3, NH_4Cl, DMF/EtOH/H_2O (4:4:1)]. The structure of azido alcohol **48** was confirmed by its IR, ^1H and ^{13}C NMR spectral analysis as shown in **Fig. 13**. Its ^1H NMR spectrum showed a triplet at δ 6.59 (t, *J* = 2.5 Hz, 1H), which indicated the presence of olefinic proton, while a singlet at δ 3.77 (s, 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. Compound **48** 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 **49** in 81% yield; $[\alpha]_D^{25}$ -57.8 (*c* 0.5, $CHCl_3$).

Regioselective ring opening of aziridine **49** 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 ^1H NMR spectrum of **21** showed a singlet at δ 6.84 (s, 1H) indicating the presence of olefinic proton. A multiplet at δ 4.41 (m, 1H), is 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 other signals at δ 0.90 (t, *J* = 6.7 Hz, 6H) and 1.42 (m, 4H) in its ^1H NMR spectrum accounted for methylene and methyl protons of 3-pentyl ether

respectively (**Fig. 14**). Its IR spectrum showed a strong absorption band at υ_{max} 3396 cm^{-1} attributed to the hydroxyl stretching vibrations.

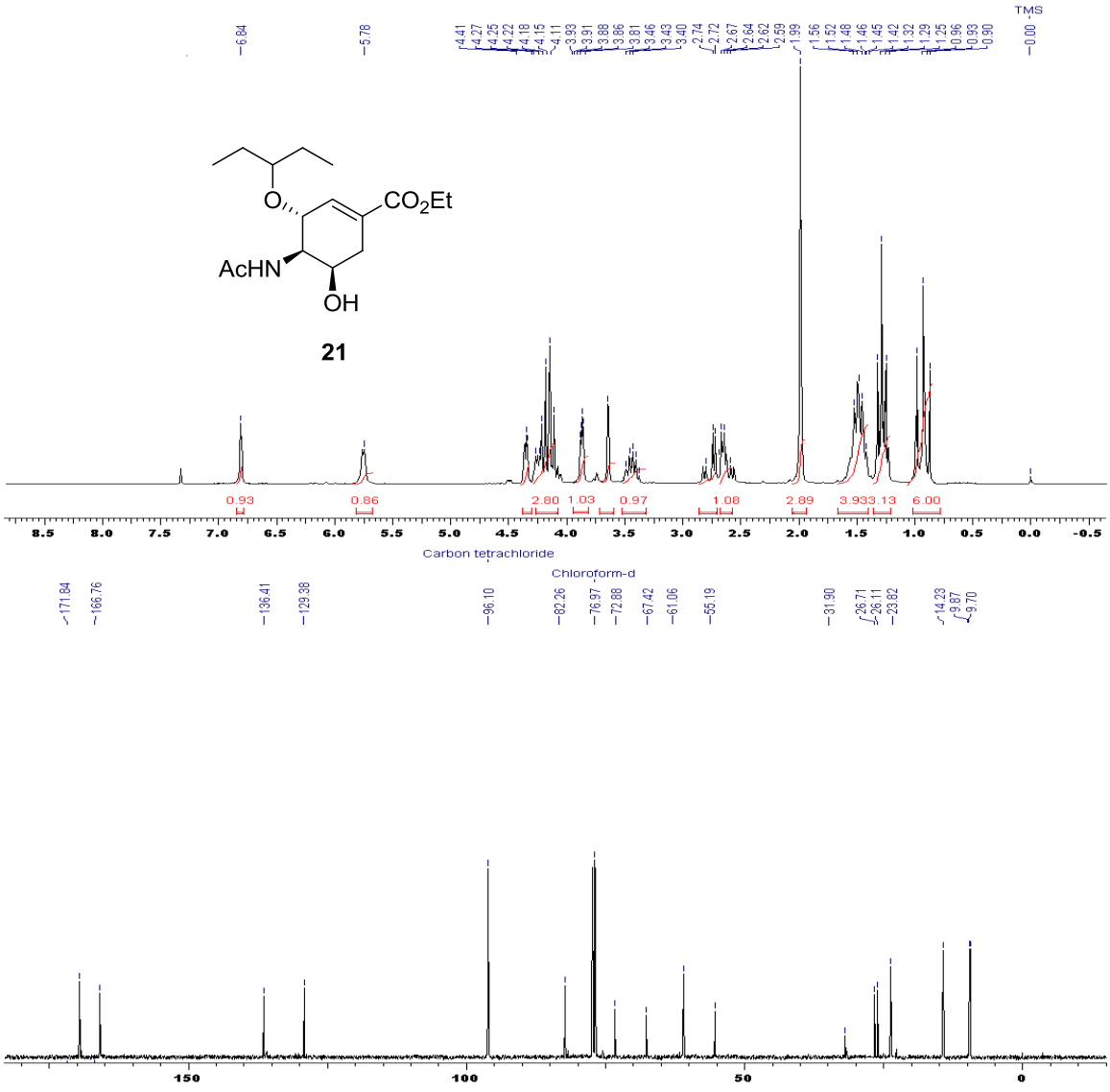
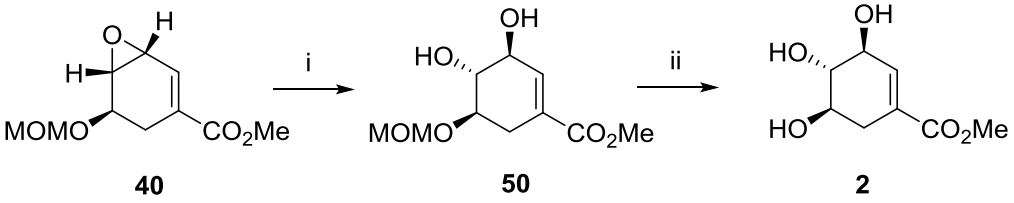


Fig. 14: ^{1}H and ^{13}C NMR spectra of alcohol **21**

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 **40**, an important precursor for the synthesis of 3-*epi*-shikimate **2**. Thus, cyclic epoxide **40** 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 **50** with 2N HCl in MeOH (**Scheme 12**). The comparison of spectral data of **2** with the reported values[5b,c] further establishes the absolute configuration of cyclic epoxide **40**.

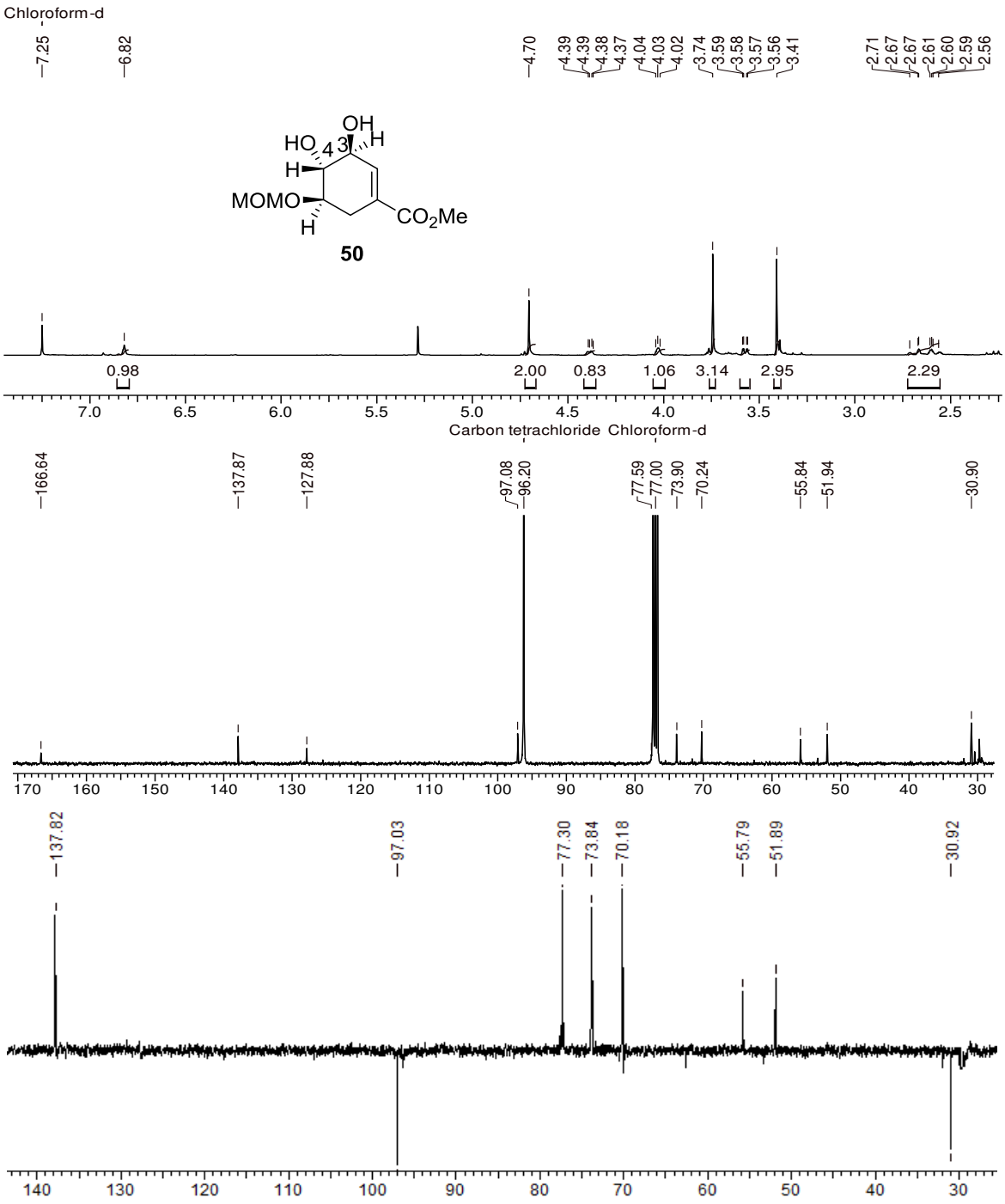


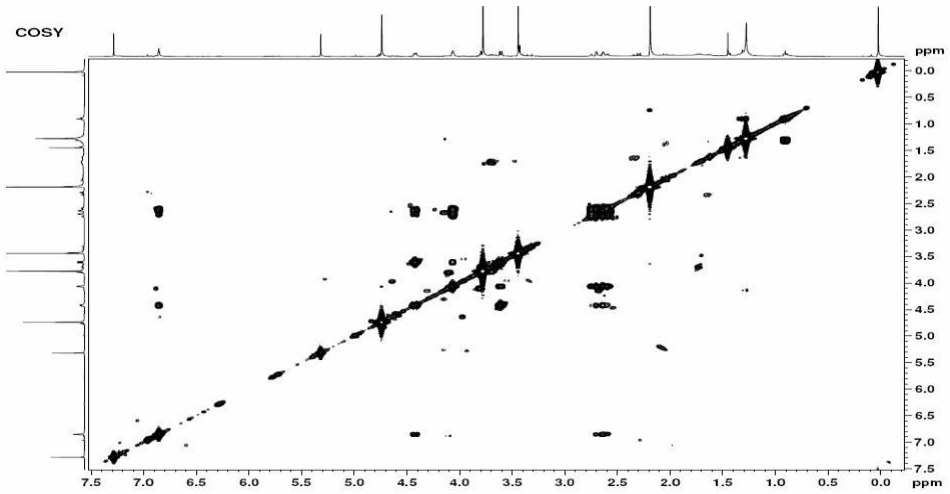
40 **50** **2**

Scheme 12: (i) H_2SO_4, THF/H_2O (3:1), 0-25 ºC, 2 h, 96%; (ii) 2 N HCl, MeOH, 25 ºC, 6 h, 74%.

The ^{1}H NMR spectrum of **50** 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 are due to methyl protons of ester and MOM ether respectively. The multiplets at δ 3.56-3.59 (m, 1H), 4.03-4.04 (m, 1H) and 4.37-4.39 (m, 1H) are assigned to the methine protons attached to oxygen atom. Its ^{13}C NMR spectrum showed typical 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 are due to carbons attached to oxygen atom. The 2D NMR studies of compound **50**

showed *anti*-relationship between proton H_3 and H_4 (**Fig. 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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1.5
2.0
2.5
3.0
3.5
4.0
4.5
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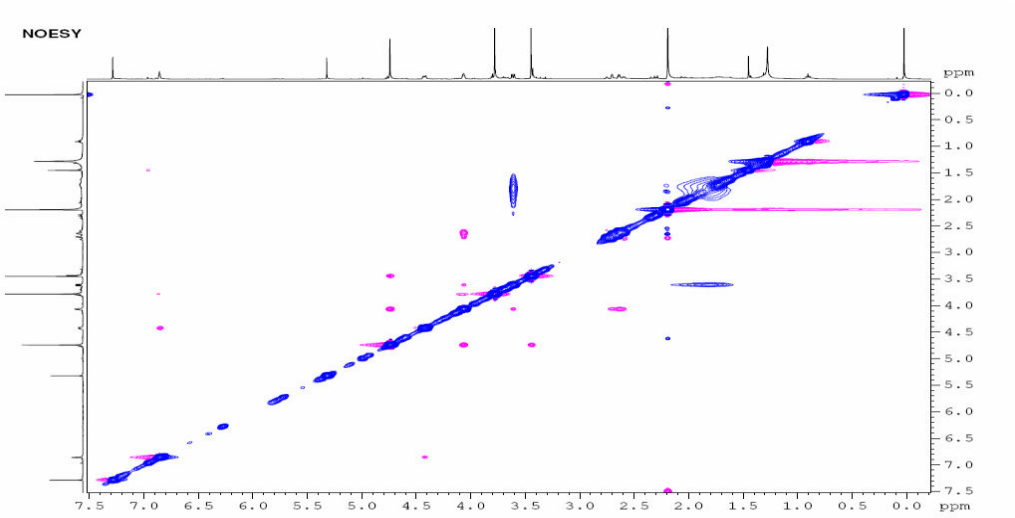
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm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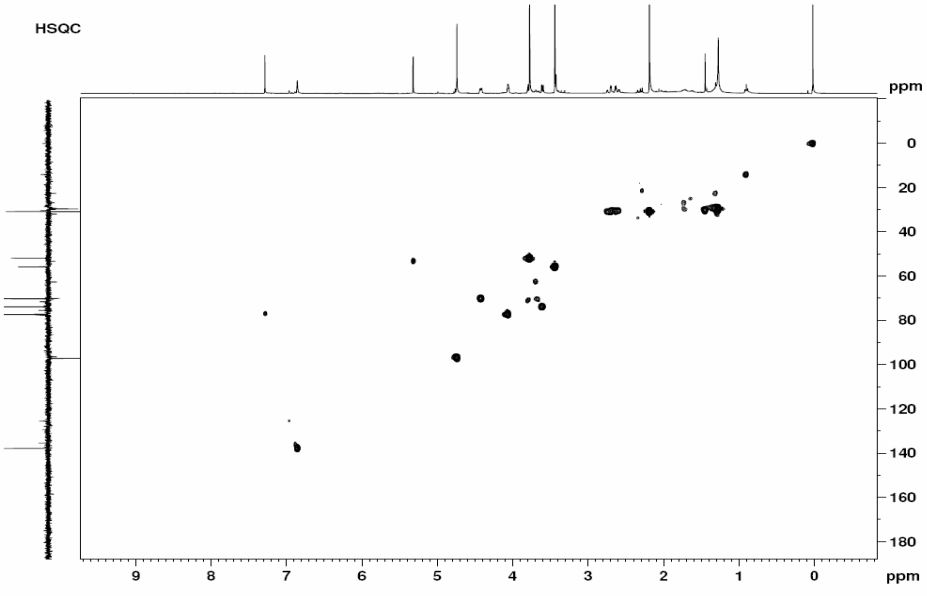
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9 8 7 6 5 4 3 2 1 0 ppm

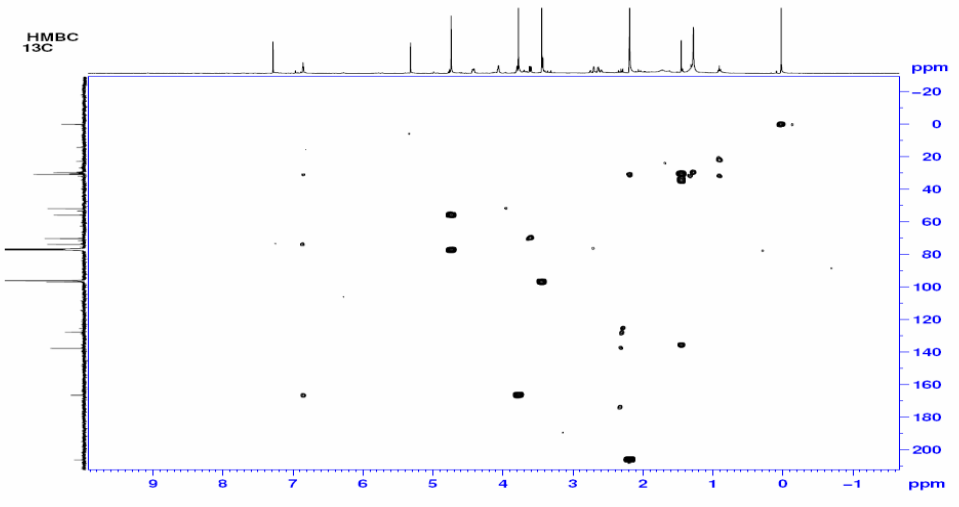


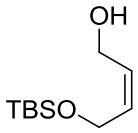
Fig. 15: ^{1}H,^{13}C, DEPT, COSY, NOESY, HSQC and HMBC NMR spectra of *anti*-diol **50**

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-butenediol **33**. 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 (34)

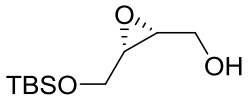


To a solution of alcohol **33** (20 g, 227.27 mmol) in dry CH_2Cl_2 (700 mL) at 0 ^{o}C was added imidazole (23.21 g, 340.91 mmol) and *tert*-butyldimethylsilyl chloride (37.68 g, 250.0 mmol). The reaction mixture was then stirred at 0 ^{o}C for 6 h. After completion of reaction

(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 **34** (33.57 g) as a colorless liquid.

Yield: 33.57 g, 73%; colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 777, 837, 1033, 1088, 1255, 1471, 2857, 2929, 3354; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.86 (s, 9H), 2.2 (br s, 1H), 4.17-4.26 (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 [(+)-35]

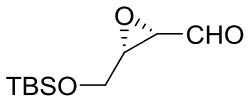


To a stirred suspension of powdered 4 Å molecular sieves (10.0 g, 45.87 mmol) in dry CH_2Cl_2 (700 mL), titanium tetraisopropoxide (5.68 g, 20 mol %) was added under nitrogen atmosphere. The reaction mixture was cooled to -10 ºC and (-)-diethyl tartrate (6.11 g, 30 mol %) added and stirred for 10 min. 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 **34** (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 **(+)-35** (20.07 g) as a colorless liquid.

Yield: 20.07 g, 93%; colorless liquid; $[\alpha]_D^{25}$ +11.7 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 777, 837, 1047, 1257, 1472, 2858, 2955, 3441; **^{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, 18.6, 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%.

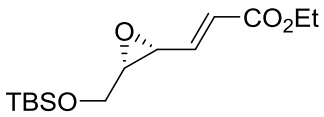
(2*S*,3*S*)-3-((*tert*-Butyldimethylsilyloxy)methyl)oxirane-2-carbaldehyde [(-)-32]



To a solution of alcohol **(+)-35** (15.02 g, 69.44 mmol) in dry CH_2Cl_2 was added in one portion (diacetoxyiodo)benzene (24.34 g, 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 thiosulfate. 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 **(-)-32** (14.27 g).

Yield: 14.27 g, 95%; yellow colored liquid; **$[\alpha]_D^{25}$** -41.7 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 838, 1099, 1256, 1472, 1720, 2858, 2930; **^{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%.

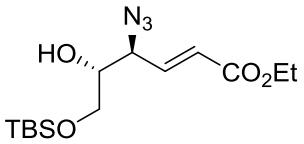
(E)-Ethyl-(2*R*,3*S*)-3-((*tert*-butyl dimethyl silyloxy)methyl(oxiran-2-yl)acrylate [(-)-36]



To a stirred solution of aldehyde **(-)-32** (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 **(-)-36** (12.18 g) as a slightly yellow colored liquid.

Yield: 12.18 g, 92%; slightly yellow colored liquid; $[\alpha]_D^{25}$ -13.7 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 838, 1035, 1260, 1722, 2858, 2930; **^{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, 156.1; **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 (37)

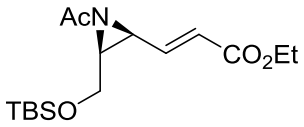


To a solution of epoxy ester **(-)-36** (9 g, 31.44 mmol) in DMF/EtOH/ H_2O (80:80:20 mL) were added NH_4Cl (10.2 g, 189 mmol) and NaN_3 (12.6 g, 189 mmol) at 0 ^oC. The mixture was then stirred at 25 ^oC for 10 h. After completion of reaction (monitored by TLC), EtOH

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 **37** (8.79 g) as yellow colored liquid.

Yield: 8.79 g, 85%; yellow colored liquid; $[\alpha]_D^{25}$ +15.1 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 668, 765, 835, 1110, 1250, 1515, 1585, 1610, 1740, 2106, 2955, 3320; **^{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 (31)

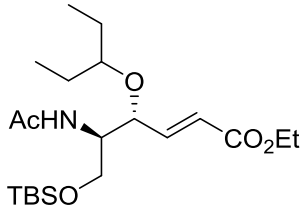


To a solution of azido alcohol **37** (5 g, 15.18 mmol) in toluene (30 mL) was added triphenyl phosphine (4.38 g, 16.70 mmol) and the reaction mixture was refluxed for 3 h. After removal of the solvent under reduced pressure, diethylether (10 mL) was added, and the mixture cooled with ice-bath. The precipitated 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 ^{o}C for further 45 minutes. After completion of reaction (monitored by TLC), it 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 **31** (4.02 g) as a yellow liquid.

Yield: 4.02 g, 81%; yellow viscous liquid; **$[\alpha]_D^{25}$** +60.0 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 973, 1187, 1256, 1356, 1472, 1643, 1715, 2858, 2930; ^{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 (38)



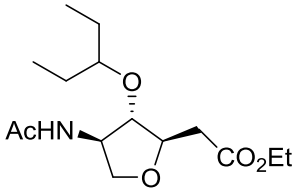
To a well stirred solution of acetamide **31** (4 g, 12.21 mmol) in 3-pentanol (30 mL), a solution of $BF_3{\cdot}Et_2O$ in 3-pentanol was added at -10 ^{o}C, followed by stirring at this temperature for additional 30 minutes. After the completion of reaction (monitored by TLC), it was quenched with a saturated aq. solution of K_2CO_3. The organic layer was 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 **38** (3.81 g) as a light yellow colored liquid. **Yield**: 3.81 g, 75%; light yellow colored liquid; $[\alpha]_D^{25}$ +23.6 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 768, 838, 1199, 1345, 1472, 1645, 1720, 2959, 2930, 3320; **^{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 (39) and (4*R*,5*R*,*E*)-Ethyl 5-acetamido-6-hydroxy-4-(pentan-3-yloxy)hex-2-enoate (30)

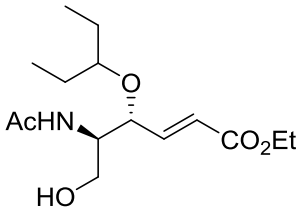
To a well stirred solution of silyl ether **38** (200 mg, 0.48 mmol) was added 1 M solution of tetrabutylammonium fluoride (1 mL, 1 mmol) at 0 ^oC. The reaction mixture was stirred at this temperature for 2 h after which the solvent was removed under reduced pressure and the residue was subjected to column chromatography with petroleum ether/EtOAc (5:5 v/v) to afford furan derivative **39** (94 mg) as major product (65%) and free alcohol **30** (25 mg) as minor product (17%).

Compound 39:



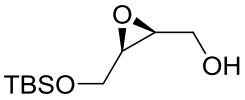
Yield: 0.094 g, 65%; viscous liquid; **$[\alpha]_D^{25}$** +41.7 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1085, 1218, 1231, 1346, 1373, 1545, 1643, 1710, 2978, 3320, 3416; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.82-0.97 (m, 6H), 1.29 (t, *J* = 8.0 Hz, 3H), 1.45-1.54 (m, 4H), 2.00 (s, 3H), 2.60-2.87 (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 30:



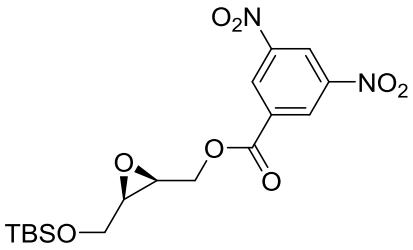
Yield: 0.025 g, 17%; viscous liquid; $[\alpha]_D^{25}$ +34.8 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1165, 1274, 1266, 1306, 1455, 1485, 1659, 1710, 2968, 3311, 3377; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.89 (t, *J* = 7.5 Hz, 6H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.47-1.57 (m, 4H), 2.01 (s, 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 [(-)-35]



To a stirred suspension of powdered 4 Å molecular sieves (10.0 g, 45.87 mmol) 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 **34** (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 **(-)-35** as a colorless liquid. $[\alpha]_D^{25}$ -11.1 (*c* 2.0, $CHCl_3$).

3,5-Dinitrobenzoate of alcohol (-)-35 (A)

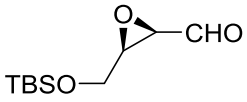


To a stirred solution of 3,5-dinitrobenzoyl chloride (230 mg, 1 mmol) in dry CH_2Cl_2 was added Et_3N (303 mg, 3 mmol) at 0 ^oC. To the cooled solution was added epoxy alcohol **(-)-35** (218.4 mg, 1 mmol) in CH_2Cl_2 and DMAP (2 mg). The reaction was then stirred at 25 ^oC for further 2 h. After completion of the reaction (monitored by TLC), it was diluted with CH_2Cl_2 and quenched with H_2O. The organic layer was further washed with brine, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure. The crude product was 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.

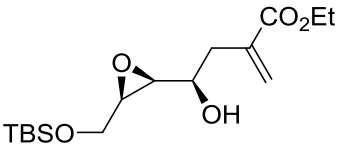
Yield: 0.395 g, 96%; pale yellow liquid; $[\alpha]_D^{25}$ -8.8 (*c* 3.0, $CHCl_3$); **Optical purity**: 97% ee from HPLC analysis [Column: Chiracel OD-H (4.6 X 250 nm), mobile phase: hexane/isopropyl alcohol (80/20), flow rate: 0.5 mL/min, retention time: 46.24 min (-)-isomer, 58.29 min (+)-isomer]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 721, 888, 1099, 1276, 1462, 1737, 2857, 2929, 3103; **^{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 [(+)-32]



To a solution of alcohol **(-)-35** (15.02 g, 69.44) in dry CH_2Cl_2 was added in one portion (diacetoxyiodo)benzene (24.34 g, 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 **(+)-32**; $[\alpha]_D^{25}$ +43.0 (*c* 3.0, $CHCl_3$).

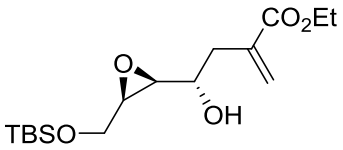
(*R*)-Ethyl-4-((2*S*,3*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)-4-hydroxyl-2-methylenebutanoate (42)



To a pre-cooled (0 ^{o}C), well stirred mixture of **(+)-32** (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 was 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 **42** (3.91 g) along with minor amount of its corresponding diastereomer (977 mg) as a yellow colored liquid in 4:1 ratio.

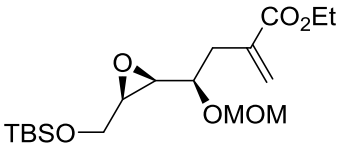
Yield: 0.977 g, 64%; yellow colored liquid; $\mathbf{[\alpha]_D^{25}}$ -19.2 (*c* 2.0, $CHCl_3$); **Optical purity**: 98% ee from HPLC analysis [Column: Chiracel OJ-H (4.6 X 250 nm), mobile phase: hexane/isopropyl alcohol (90/10), flow rate: 0.5 mL/min, retention time: 15.747 min (+)-isomer, 17.517 min (-)-isomer]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 838, 1097, 1256, 1472, 1715, 2857, 2956, 3471; ^{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), 3.78-3.81 (m, 1H), 3.82 (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.

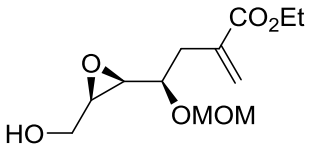
(*R*)-Ethyl 4-((2*S*,3*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)-4-methoxymethoxy) -2-methylenebutanoate (43)



To a solution of compound **42** (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 **43** (3.39 g) as a colorless oil.

Yield: 3.39 g, 90%; colorless oil; $[\alpha]_D^{25}$ +2.9 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 838, 1150, 1257, 1716, 2857, 2955; **^{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-(methoxymethoxy)-2-methylene butanoate (44)

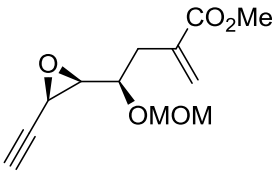


To a well stirred solution of silyl ether **43** (1.1 g, 2.94 mmol) was added 1 M solution of tetrabutylammonium fluoride (6.2 mL, 5.87 mmol) at 0 ^oC. The reaction mixture was stirred at this temperature for 2 h after which the solvent was removed under reduced pressure and the residue was subjected to column chromatography with petroleum ether/EtOAc (6:4 v/v) to afford free alcohol **44** (673 mg) oily liquid.

Yield: 0.673 g, 88%; oily liquid; $[\alpha]_D^{25}$ +4.1 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 919, 1048, 1305, 1410, 1632, 1716, 2983.3, 3453; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.23 (t, *J* = 7.1 Hz, 3H), 2.44 (dd, *J* = 9.0, 14.0 Hz, 1H), 2.68 (dd, *J* = 3.4, 13.6 Hz, 1H), 2.83-2.89 (m, 1H), 3.13-3.15 (m, 1H), 3.24 (br s, 1H), 3.30 (s, 3H), 3.51-3.57 (m, 2H), 3.79-4.08 (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 14.2, 36.5, 55.4, 56.1, 57.8, 59.9, 60.7,

72.6, 96.0, 127.7, 136.4, 166.7; **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 (46)

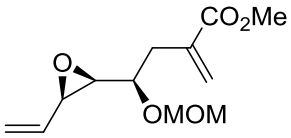


To a solution of epoxy alcohol **44** (1.4 g, 5.34 mmol) in DMSO (5 mL) in a round-bottomed flask was added IBX (1.68 g, 6 mmol) in one portion and the reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was quenched with diethylether (5 mL), H_2O (0.5 mL) and filtered through 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 **45**, which was pure enough and used in the next step without further purification. To a solution of crude aldehyde **45** 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 was continued until the reaction is complete as indicated by TLC (2 h). The reaction mixture was 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 **46** (1.05 g) as a colorless liquid.

Yield: 1.05 g, 82%; colorless liquid; $[\alpha]_D^{25}$ -9.4 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1171, 1289, 1441, 1409, 1715, 2226, 2953; **^{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; O, 33.30; Found: C, 60.02; H, 6.78%.

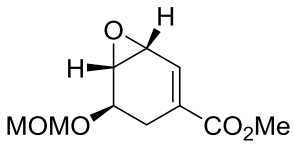
(*R*)-Methyl-4-(methoxymethoxy)-2-methylene-4-((2*S*,3*R*)-3-vinyloxiran-2-yl)butanoate (41)



To a solution of **46** (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 pressure of H_2 (1 atm) 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 **41** (230 mg) as colorless liquid.

Yield: 0.23 g, 95%; colorless viscous liquid; **$[\alpha]_D^{25}$** -5.4 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 878, 1169, 1204, 1341, 1514, 1711, 2924, 3034; **^{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%.

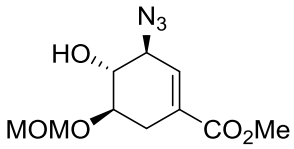
(1*R*,5*R*,6*S*)-Methyl-5-(methoxymethoxy)-7-oxabicyclo[4.1.0]hept-2-ene-3-carboxylate (40)



A mixture of diene **41** (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 **40** (318 mg) as gum.

Yield: 0.318 g, 90%; clorless gum; $[\alpha]_D^{25}$ -32.7 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1091, 1139, 1235, 1387, 1497, 1579, 1719, 2986; **^{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), 3.64-3.66 (m, 1H), 3.67 (s, 3H), 3.74-4.03 (m, 1H), 4.79 (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)cyclohex-1-enecarboxylate (48)

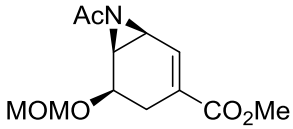


To a solution of cyclic epoxy ester **40** (107 mg, 0.5 mmol) in DMF/EtOH/ H_2O (4:4:1 mL) were added NH_4Cl (160.5 g, 3 mmol) and NaN_3 (197.4 g, 3 mmol) at 0 ^oC. The mixture was then stirred at 25 ^oC for 10 h. After completion of reaction (monitored by TLC), EtOH was removed by rotary evaporation. 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: 0.106 g, 83%; yellow liquid; **$[\alpha]_D^{25}$** +17.3 (*c* 0.7, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1073, 1176, 1235, 1365, 1448, 1489, 1561, 1714, 2106, 2994, 3345; **^{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 (49)

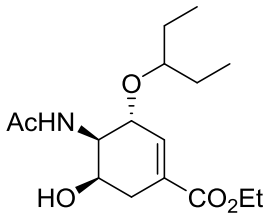


To a solution of azido alcohol **48** (150 mg, 0.58 mmol) in toluene (5 mL) was added triphenylphosphine (152 mg, 0.58 mmol) and the reaction mixture was refluxed for 3 h. After removal of the solvent under reduced pressure, diethylether (1 mL) was added, and the mixture cooled with ice-bath. The precipitated 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 **49** (120 mg) as colorless viscous liquid.

Yield: 0.12 g, 81%; colorless viscous liquid; **$[\alpha]_D^{25}$** -57.8 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1073, 1195, 1255, 1324, 1369, 1448, 1708, 1732, 2987, 3115; **^{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)

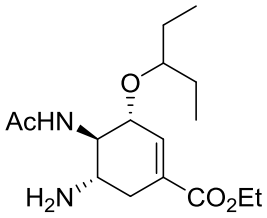


To a well stirred solution of cyclic acetamide **49** (160 mg, 0.64 mmol) in 3-pentanol (10 mL), a solution of 1.5 equiv. of $BF_3{\cdot}Et_2O$ (0.96 mmol) in 3-pentanol (2 mL) was added at -10 ^oC, followed by stirring at this temperature for additional 30 min. After completion of reaction (monitored 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: 0.128 g, 64%; colorless solid; **m.p.** 129-131 ^oC {lit.[9] m.p. 131.9-132.2 ^oC}; **$[\alpha]_D^{25}$** -84.8 (*c* 1.0, EtOAc) {lit.[9] $[\alpha]_D^{25}$ -104 (*c* 3, EtOAc)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1085, 1274, 1266, 1306, 1373, 1455, 1585, 1649, 1707, 2963, 3311, 3396; **^{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)



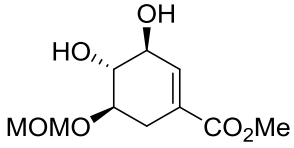
Compound **21** (312 mg, 1 mmol) and triethylamine (303 mg, 3 mmol) were dissolved in dry CH_2Cl_2 (15 mL), and the solution cooled to 0 ^oC. Methanesulfonyl chloride (229.2 mg, 2 mmol) was added, and then the resulting solution was stirred at 0 ^oC for 1 h. After TLC showed that the reaction was complete, 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: 0.224 g, 72%; gum**; $[\alpha]_D^{25}$** -48.2 (*c* 1, EtOH) {lit.[4a] $[\alpha]_D^{25}$ -49.2 (*c* 9.33, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1068, 1127, 1255, 1374, 1456, 1568, 1644, 1714, 2977, 3289; **^{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%.

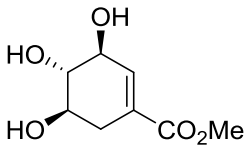
(3*R*,4*S*,5*R*)-Methyl-3,4-dihydroxy-5-(methoxymethoxy)cyclohex-1-enecarboxylate (50)



To a well stirred solution of epoxide **40** (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 was 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 **50** (111 mg) as viscous liquid.

Yield: 0.11 g, 96%; viscous liquid; $[\alpha]_D^{25}$ -45.1 (*c* 0.5, EtOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1088, 1300, 1373, 1717, 2878, 2967, 3387, 3468; **^{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, 70.9, 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 **50** (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 was 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.

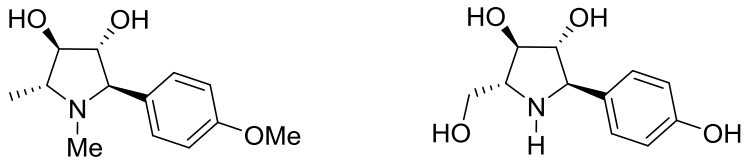
Yield: 0.057 g, 74%; colorless solid; **m.p.** 131-133 ^{o}C {lit.[13] m.p. 132 ^{o}C}; **$[\alpha]_D^{25}$** -13.1 (*c* 0.5, MeOH) {lit.[13] $[\alpha]_D^{25}$ -13.4 (*c* 0.5, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1089, 1176, 1245, 1378, 1489, 1661, 1714, 2106, 2994, 3456; **^{1}H NMR** (200 MHz, 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

Asymmetric Synthesis of (-)-Codonopsinine and Radicamine B *via* Sharpless Asymmetric Epoxidation and Corey-Chaykovsky Reaction

1.2.1 Introduction and Pharmacology

Poly-substituted pyrrolidines represent an important class of five-membered heterocycles that can be found as structural elements in many natural products and pharmaceutically important substances.[17] Polyhydroxylated pyrrolidines, such as, (-)-codonopsinine **51** and radicamine B **52** (**Fig. 16**) have shown significant biological activities, like, potent inhibition of glycosidases, anti-viral agents and acaricides.[18] More importantly, (-)-codonopsinine **51**, isolated in 1969 from *Codonopsis clematidea*,[19] has displayed antibiotic as well as hypotensive activities without affecting central nervous system in animal test,[20] while radicamine B **52** was isolated from *Lobelia chinensis* (Campanulaceae), which are commonly used as a Chinese folk medicine for the treatment of a wide range of human diseases including α-glucosidase inhibitory activity, antidiuretic, and anticarcinostatic properties for stomach cancer.[21] From a structural point of view, both (-)-codonopsinine **51** and radicamine B **52** possess aromatic substituent on



51 (-)-codonopsinine

52 radicamine B

Fig. 16: Structure of pyrrolidine iminosugars (-)-codonopsinine **51** and radicamine B **52**

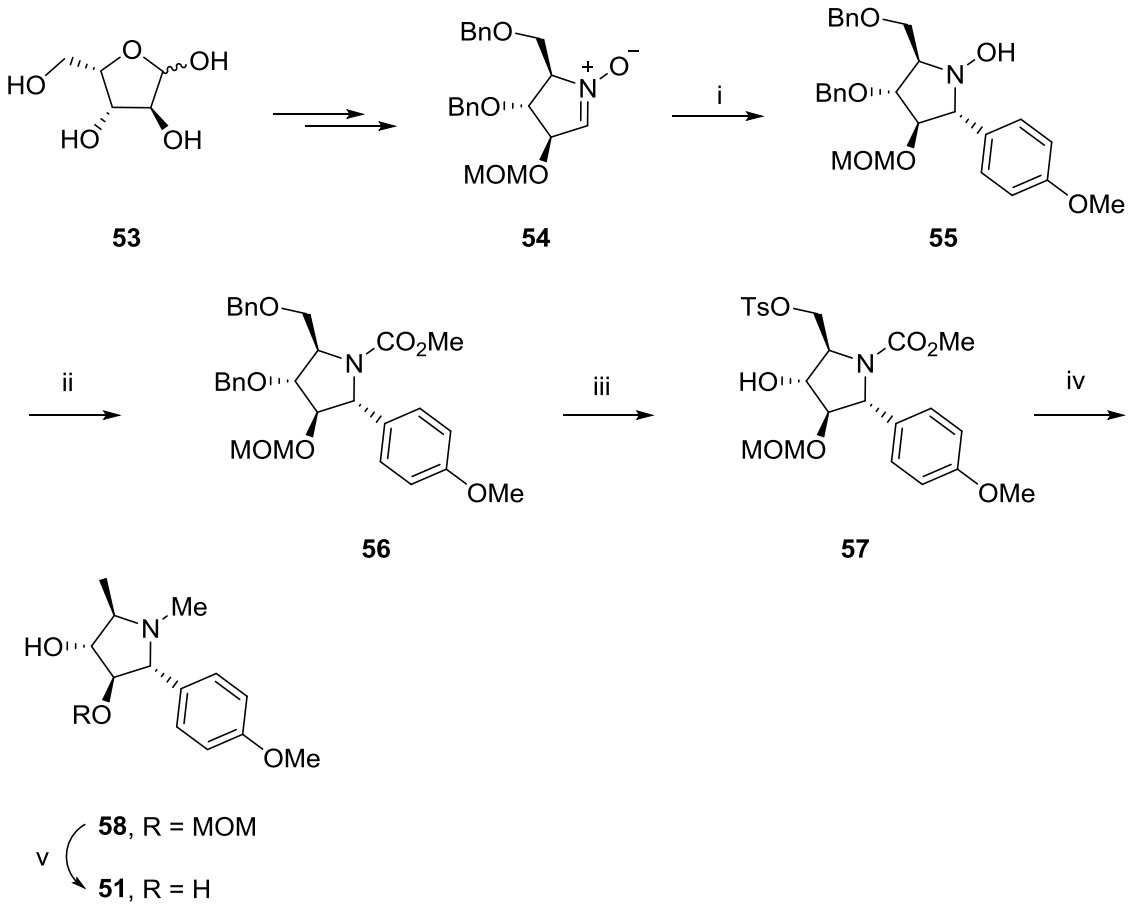
the iminosugar ring. They exhibit 1,2,3,4,5-penta-substituted pyrrolidine structures bearing four contiguous stereogenic centers, which are situated in all *trans* positions. Despite being isolated three decades ago, these molecules continue to attract synthetic chemists due to their challenging structural moieties and biological importance.

1.2.2 Review of literature

Various syntheses of (-)-codonopsinine **51** and radicamine B **52** have been documented in the literature, most of which are based on chiral pool strategies. Some of the interesting synthetic routes are described below.

Ishibashi's approach (2003)[22]

Ishibashi *et al*. have accomplished the synthesis of (-)-codonopsinine **51** involving an addition of five-membered cyclic nitrone **54** (readily obtained from L-xylose **53**) with the Grignard reagent. Thereby, treatment of **54** with 4-methoxyphenylmagnesium bromide in dry THF at -45 °C rapidly caused a nucleophilic addition to give hydroxylamine **55** as a single diastereomer in 95% yield. Reduction of **55** with zinc dust and ammonium chloride followed by protection of the secondary amine with methyl chloroformate afforded carbamate **56** in excellent yield (99%). Carbamate **56** was subjected to hydrogenolysis and the resultant alcohol was then transformed into tosylate **57** in 86% yield. Refluxing **57** with $LiAlH_4$ in THF simultaneously caused removal of the tosyl group and reduction of the methoxy carbonyl group to provide amine **58**. Finally, deprotection of the MOM group with hydrochloride acid gave (–)-**51** (**Scheme 13**).

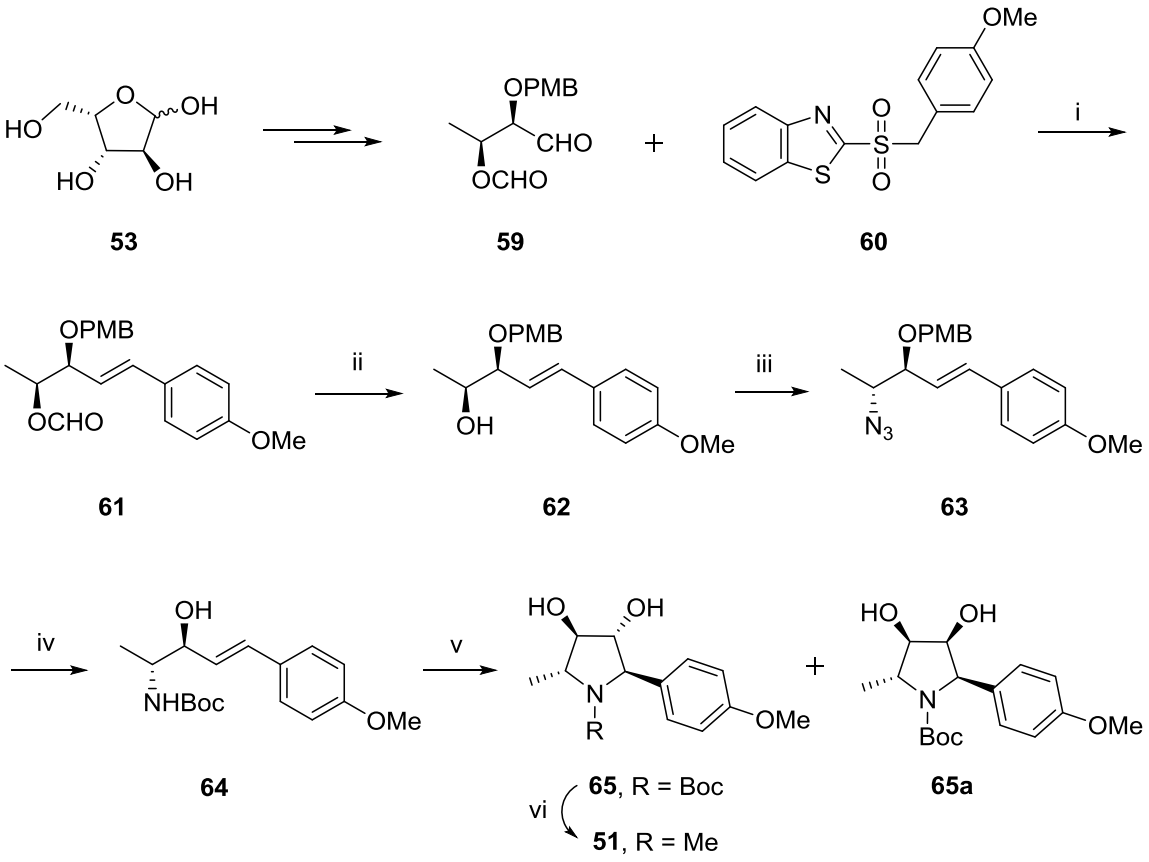


Scheme 13: (i) 4-Methoxyphenylmagnesium bromide, THF, –45 °C, 5 min, 95%; (ii) (a) Zn, aq NH_4Cl, EtOH, reflux; (b) methyl chloroformate, aq. $NaHCO_3$, CH_2Cl_2, 99%; (iii) (a) 10% Pd/C, H_2 (1 atm), MeOH; (b) TsCl, pyridine–CH_2Cl_2, 86%; (iv) $LiAlH_4$, THF, reflux, 92%; (v) 3N HCl, MeOH, 50 °C, 97%.

Chandrasekhar's approach (2005 and 2011)[23]

Chandrasekhar *et al*. have described a stereoselective synthesis of (-)-codonopsinine **51** from L-xylose **53** as the starting material employing Julia *trans* olefination and cascade epoxidation–cyclisation as key strategies. Thus, the aldehyde **59** formed from L-xylose **53**, had undergone Julia olefination with sulfone **60**, which was prepared from *p*-methoxybenzyl bromide and mercaptobenzothiazole, to give **61** in 72% yield. The formate group in compound **61** was deprotected with $NaBH_4$ in MeOH followed by mesyl

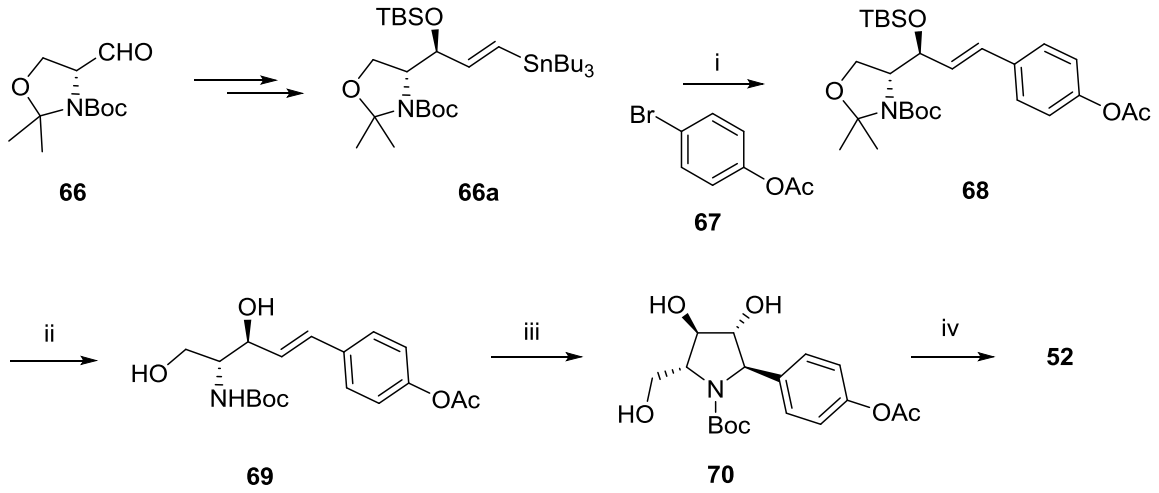
protection of the hydroxyl group in compound **62** and subsequent azidation with NaN_3 in DMF (70 ºC) gave **63** in 89% overall yield. Removal of PMB goup, reduction of azide and subsequent protection with Boc_2O gave allyl alcohol **64**. Then, the allyl alcohol **64** was subjected to *m*-CPBA epoxidation to afford pyrrolidine diols **65** and **65a** (dr = 1:1). Finally, the Boc group in **65** was converted onto methyl group using Red-Al in toluene under reflux for 2 h yielding (-)-codonopsinine **51** in 83% yield (**Scheme 14**).



Scheme 14: (i) NaHMDS, THF, -78 C, 72%; (ii) $NaBH_4$, MeOH, 97%; (iii) (a) MsCl, Et_3N, 0 ºC; (b) NaN_3, DMF, 70 ºC, 89%; (iv) (a) $ZrCl_4$, acetonitrile; (b) TPP, benzene, H_2O, 45 ºC; (c) Boc_2O, Et_3N, 88%; (v) *m*CPBA, CH_2Cl_2, 0 ºC, 89%, dr = 1:1; (vi) Red-Al, toluene, reflux, 2 h, 83%.

In another approach, Chandrasekhar *et al.* have achieved the synthesis of radicamine B **52** by employing Stille coupling of intermediate **66a**, formed from (*R*)-Garner aldehyde **66**,

with 4-acetoxybromobenzene **67** using $Pd(PPh_3)_4$ in toluene to furnish the styrene derivative **68**. The silyl and ketal deprotection with TFA furnished compound **69** in 80% yield. Compound **69** was subjected to domino epoxidation-pyrrolidine construction reaction by treating with *m*-CPBA to afford pyrrolidine core **70** followed by global deprotection with TFA furnished radicamine B **52** in 80% yield (**Scheme 15**).

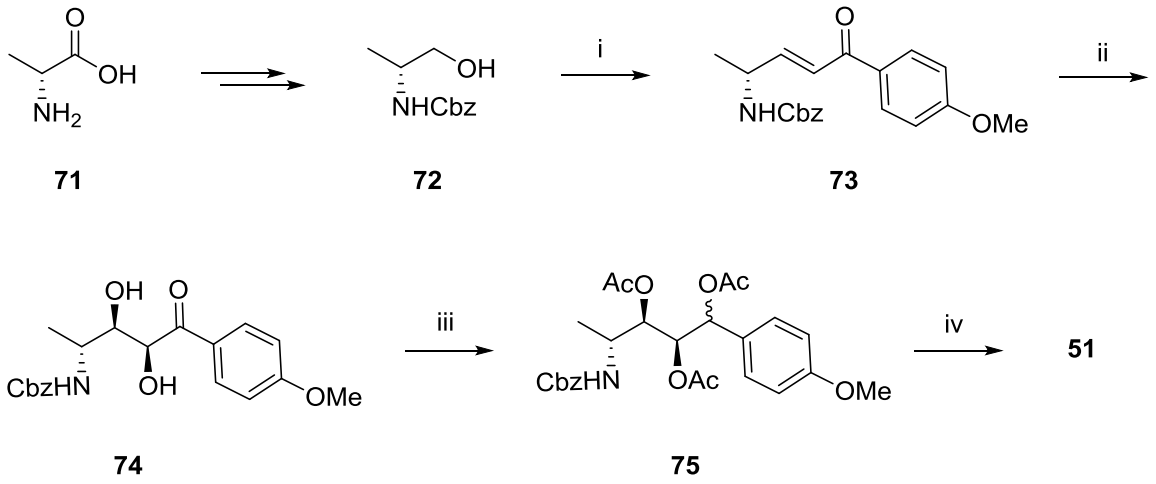


Scheme 15: (i) $Pd(PPh_3)_4$, toluene, reflux, 6 h, 60%; (ii) TFA:CH_2Cl_2 (9:1), 4 h, 80%; (iii) (a) *m*CPBA, CH_2Cl_2; (b) $NaHCO_3$, MeOH, 4 h, 60%; (iv) TFA, 12 h, 80%.

Rao's approach (2007 and 2011)[24]

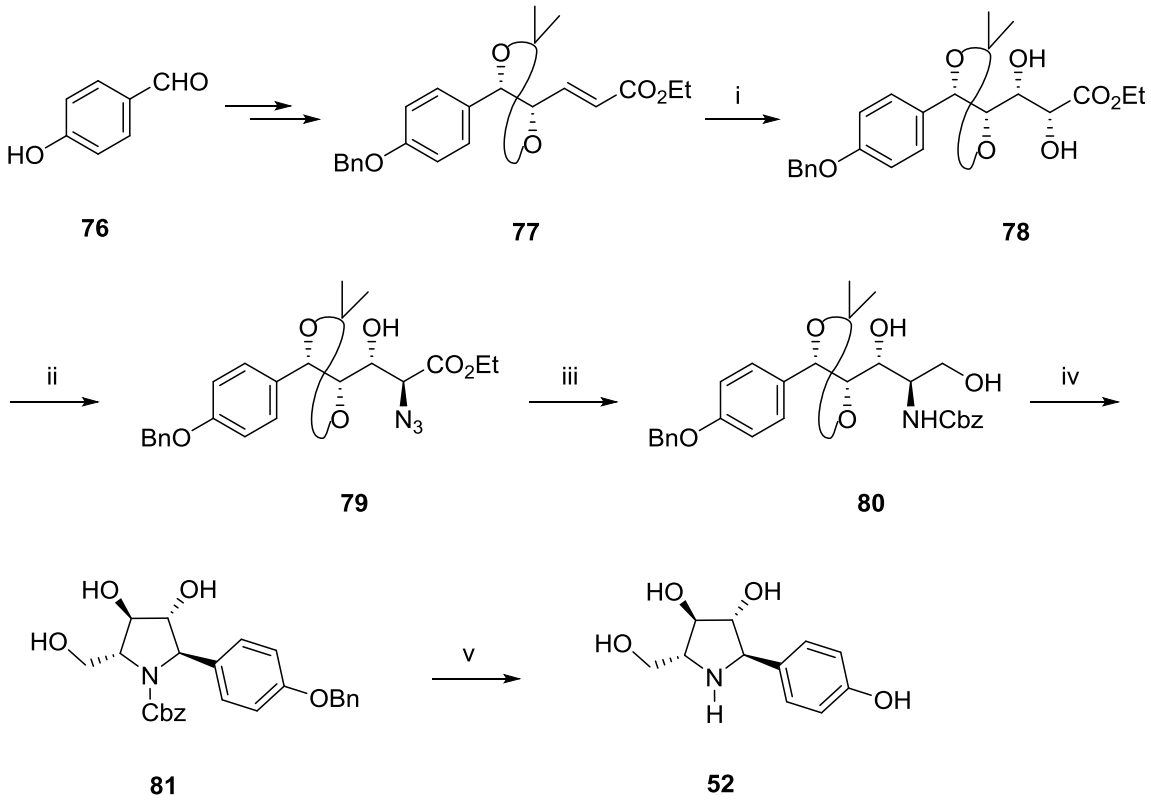
In Rao's approach, N-Cbz-protected alaninol derivative **72**, obtained from L-alanine **71** by literature procedure was used as starting material. The primary alcohol **72** was oxidized to aldehyde under Swern condition to furnish aldehyde, followed by Wittig reaction with (4-methoxyphenacyl)triphenylphosphorane yielded the *trans*-α,β-unsaturated ketone **73** (86%). The compound **73** was dihydroxylated under Sharpless asymmetric dihydroxylation condition to provide diol **74**. The keto functionality in **74** was reduced with $NaBH_4$ followed by acetyl protection with acetic anhydride to provide triacetate **75**.

Trifluoroacetic acid (TFA)-mediated amidocyclization of **75** followed by reduction of N-Cbz to N-Me with $LiAlH_4$ in THF reflux gave (-)-codonopsinine **51** in 74% yield (**Scheme 16**).



Scheme 16: (i) (a) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ºC; (b) *p*-$OMeC_6H_4COCHPPh_3$, CH_2Cl_2, rt, 86%; (ii) $(DHQD)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH:H_2O, 0 ºC, 99%; (iii) (a) $NaBH_4$, MeOH; (b) Ac_2O, Et_3N, CH_2Cl_2; (iv) (a) TFA, CH_2Cl_2, 0-25 ºC, 4 h; (b) $LiAlH_4$, THF, reflux, 74%.

In another approach, Rao *et al.* have envisaged the synthesis of radicamine B **52** from 4-hydroxybenzaldehyde **76**. α,β-Unsaturated ester **77**, prepared from **76**, was subjected to Sharpless asymmetric dihydroxylation to afford diol **78** in 95% (dr 5.5:1). S_N2 displacement of –OH group with azide *via* cyclic sulfite provided azido alcohol **79** in 84% yield. Compound **80** was prepared from azido alcohol **79** in 76% yield following (i) reduction of the azide with TPP/ethanol; (ii) protection of the amine with CbzCl; (iii) reduction of the ester functionality with $LiBH_4$. Treatment of compound **80** with TFA:CH_2Cl_2 (1:1) for 4 h at room temperature gave directly diastereomeric cyclic pyrrolidine compound **81** (dr 1.3:1) in 78% yield. Finally, compound **81** was converted into **52** on global deprotection by hydrogenolysis in 80% yield (**Scheme 17**).

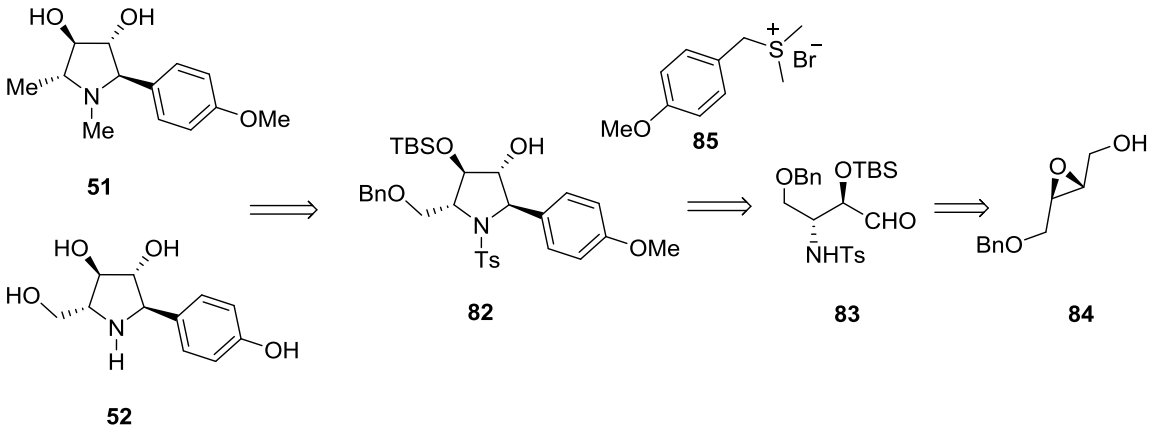


Scheme 17: (i) $(DHQ)_2PHAL$, OsO_4, K_2CO_3, $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, *t*BuOH:water, 92%; (ii) (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0-25 0 ºC, 30 min; (b) NaN_3, DMF, 80 ºC, 2 h, 84%; (iii) (a) TPP, ethanol, rt, 6 h; (b) CbzCl, Na_2CO_3, ethanol, rt, 8 h; (c) LiCl, $NaBH_4$, ethanol, THF, 0 ºC, 3 h, 78%; (iv) TFA:CH_2Cl_2 (1:1), rt, 4 h, 78%; (v) $PdCl_2$, H_2 (1 atm), MeOH, 12 h, 80%.

1.2.3 Present Work

1.2.3.1 Objective

As can be seen from the review section, several methods of synthesis for (-)-codonopsinine **51** and radicamine B **52** have been reported. However, many of them suffer from one or more disadvantages, which include use of chiral pool strategy, poor diastereoselectivity 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 pyrrolidines, a useful synthetic route with high flexibility in yields and stereoselectivity is required. This section describes the application of Sharpless asymmetric epoxidation and a novel Corey-Chaykovsky strategy[25] in the synthesis of (-)-codonopsinine **51** and radicamine B **52**.



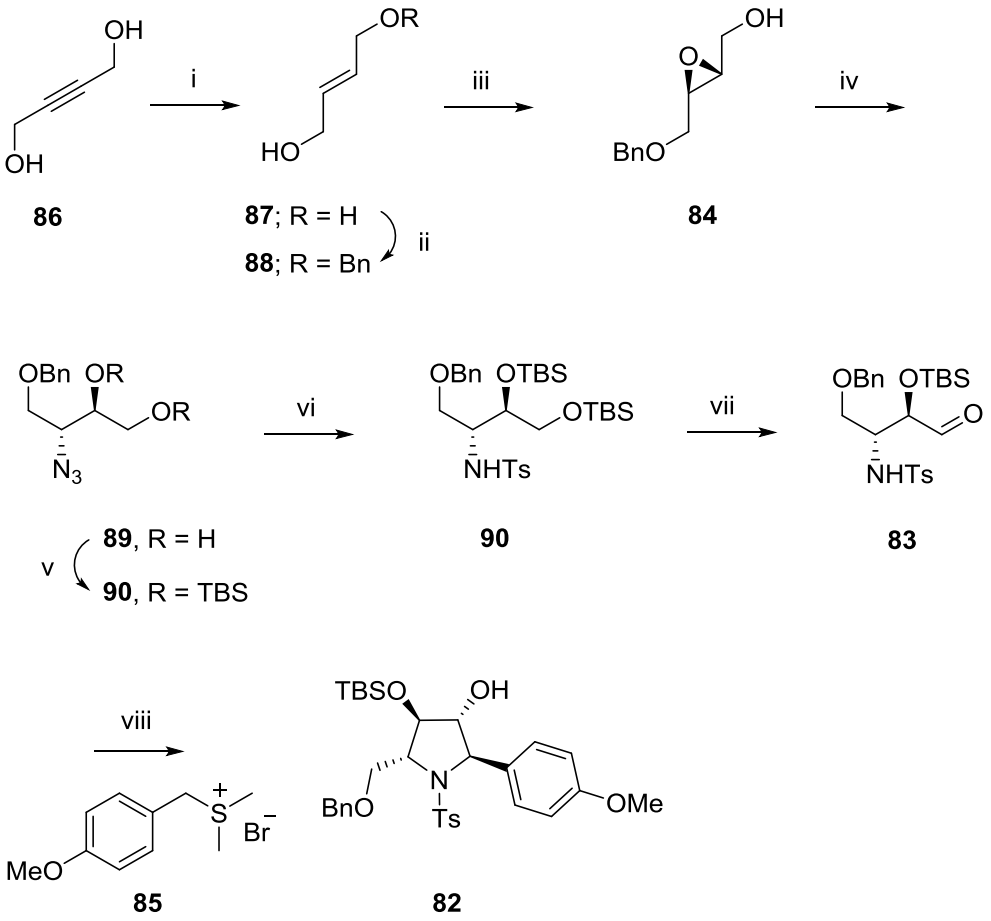
Scheme 18: Retrosynthetic analysis of (-)-codonopsinine **51** and radicamine B **52**

Based on retrosynthetic analysis, we visualized that (-)-codonopsinine **51** and radicamine B **52** could be obtained from common intermediate **82**, which in turn could be envisaged from aldehyde **83** employing a novel Corey-Chaykovsky reaction with sulfonium salt **85**

(**Scheme 18**). Aldehyde **83** can be obtained from chiral epoxide **(+)-84** *via* simple functional group transformation reactions.

1.2.3.2 Results and Discussion

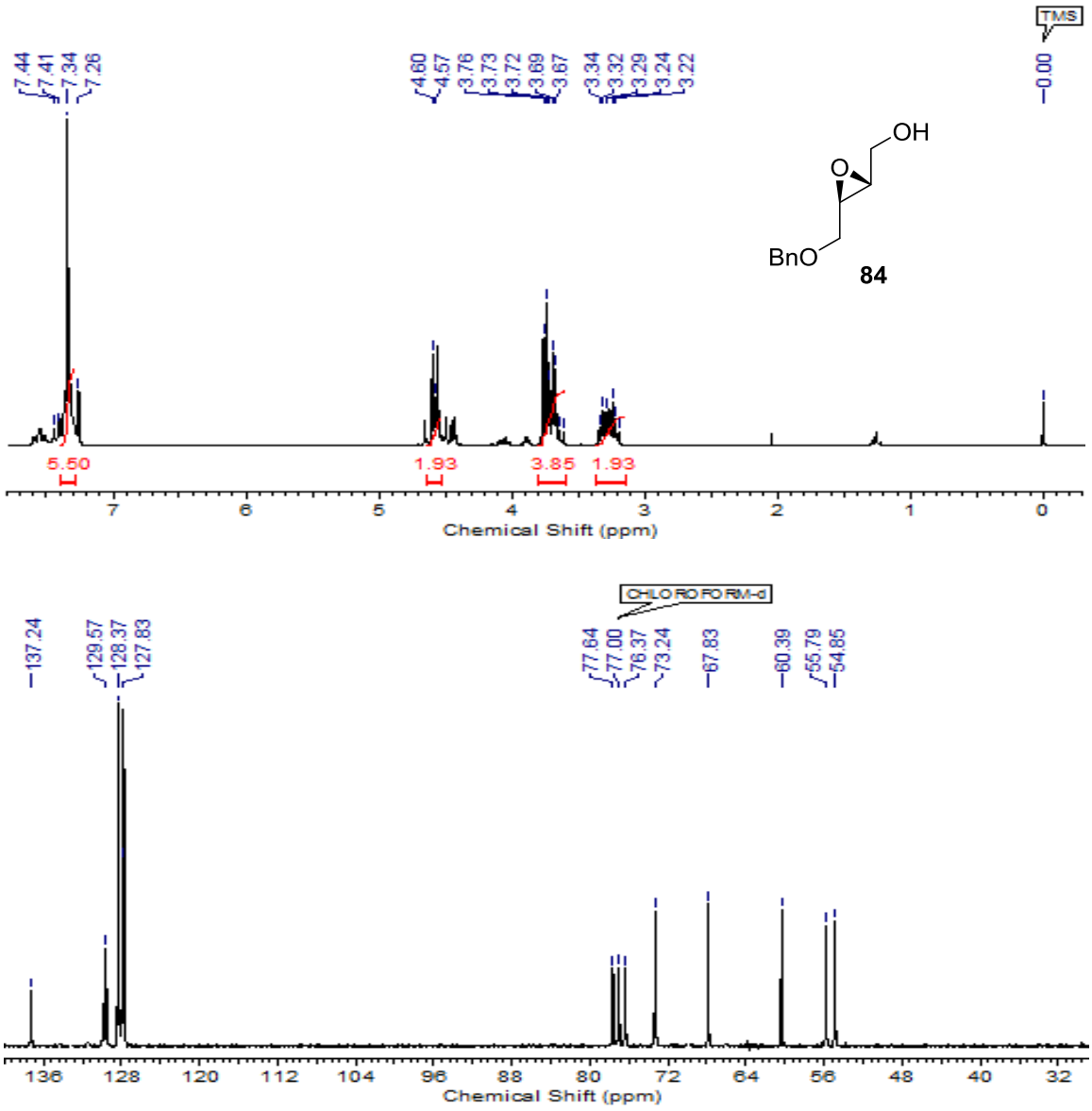
The present synthetic route to intermediate pyrrolidine core **82** is shown in **Scheme 17**.

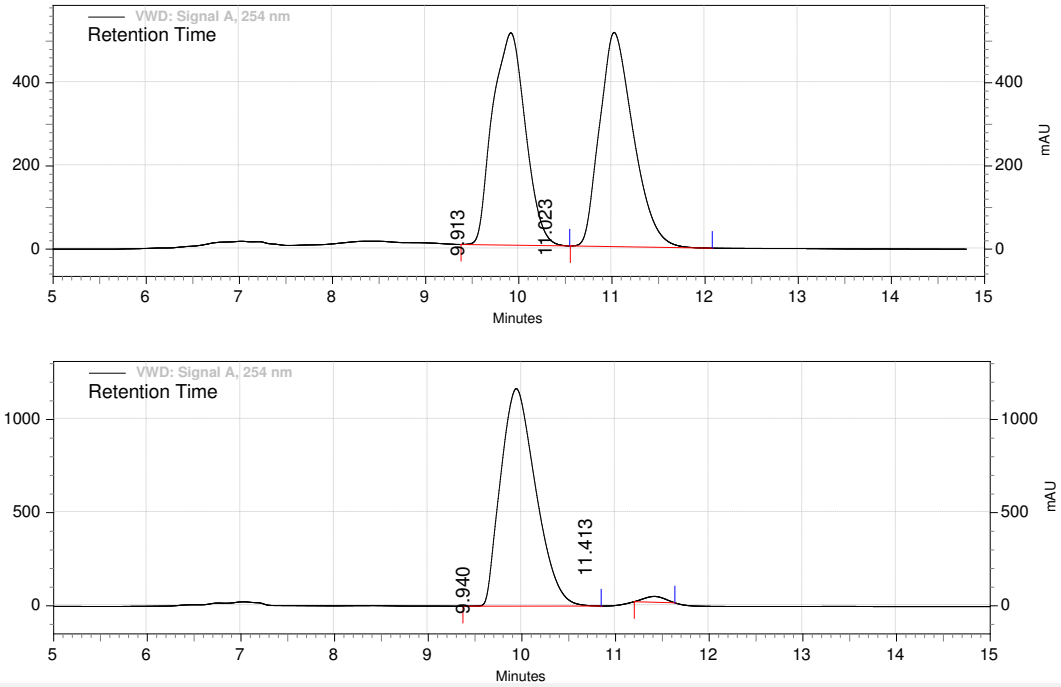


Scheme 19: (i) $LiAlH_4$, THF, 70 ºC, 4 h, 70%, *Z/E* = 1:2; (ii) BnBr, NaH, DMF, 0-25 ºC, 4 h, 90%; (iii) (+)-DET, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2, -20 ºC, 8 h, 88%; (iv) $Ti(O^iPr)_4$, $TMSN_3$, benzene, 80 ºC, 4 h, 96%; (v) TBSCl, imid, CH_2Cl_2, 98%; (vi) (a) Ph_3P, THF, 70 ºC, 2 h; (b) TsCl, Et_3N, CH_2Cl_2, 25 ºC, 2 h, 80%; (vii) (a) CSA, MeOH, 0 ºC, 1 h; (b) IBX, DMSO, 25 ºC, 2 h, 95%; (viii) **85**, ^{n}BuLi, THF, 0 ºC, 3 h, 80%.

To begin with, epoxy alcohol **(+)-84** was prepared with an overall yield of 55.44% from commercially available 2-butyne-1,4-diol **86** in three steps: (i) conversion of **86** into *trans*-

2-butene-1,4-diol **87** in 70% yield by reduction with $LiAlH_4$ in refluxing condition ($LiAlH_4$, THF, 70 ºC, 4 h, *Z/E* = 1:2); (ii) selective monobenzylation of diol **87** (BnCl, NaH, 90%); (iii) Sharpless asymmetric epoxidation of allylic alcohol **88** [$Ti(O^iPr)_4$, (+)-DET, anhydrous TBHP, 88%]. The formation of epoxy alcohol **84** was confirmed by its ^1H and ^{13}C NMR spectral analysis. The ^1H NMR spectrum of **84** showed two typical multiplets at δ 3.22-3.35 (m, 2H) due to methine protons attached to epoxide group and at δ 3.67-3.76 (m, 4H) due to methylene protons attached oxygen atoms respectively.





Retention Time	Area	Area %	Height	Height %
9.940	509230213	98.35	19588723	98.55
11.413	7897113	1.65	522812	1.45
Totals	517127326	100.00	20111535	100.00

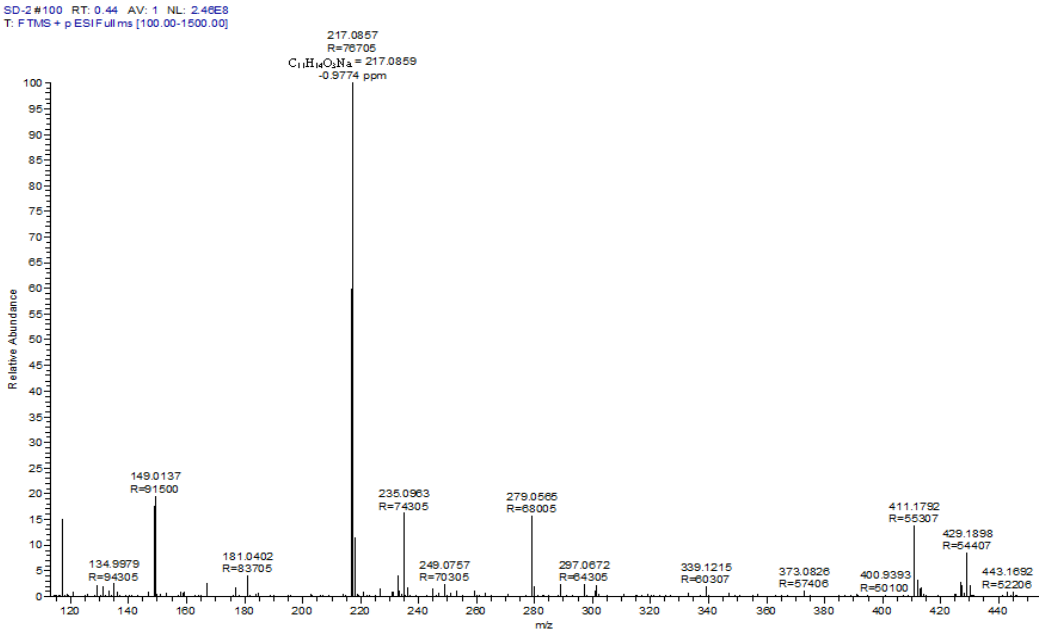
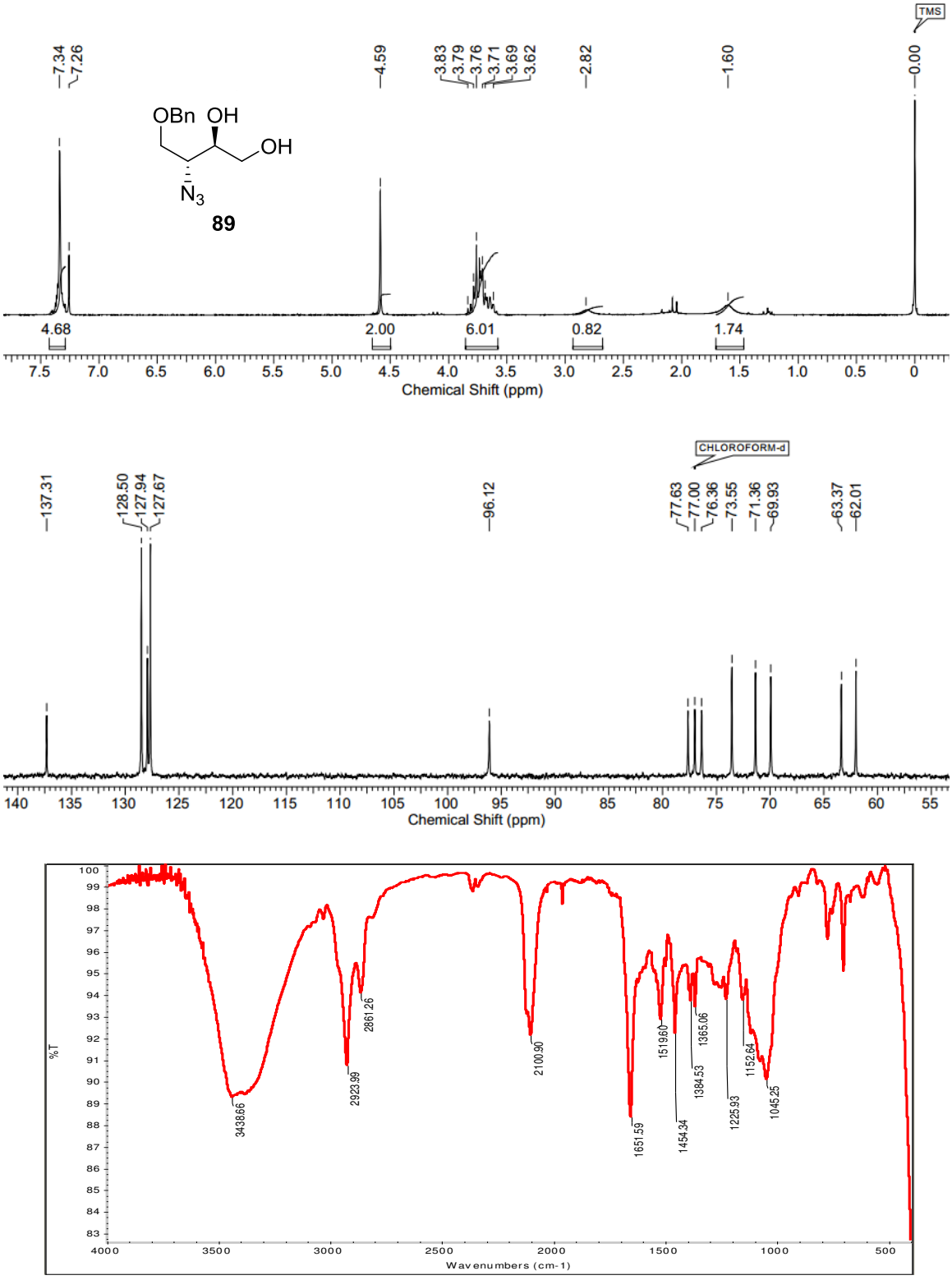


Fig. 17: ^{1}H, ^{13}C NMR, HPLC & HRMS chromatogram of epoxide **84**

Its ^{13}C NMR spectrum showed two typical carbon signals at δ 54.8 and 55.7 corresponding to epoxide carbons, while the carbon signals appearing at δ 67.8 and 60.3 were due to methylene carbons attached to oxygen. The optical purity of epoxide **84** was found to be 97% determined by HPLC [Chirapak OD-H, 2-Propanol/*n*-Hexane = 05/95, flow rate 0.5 mL/min, λ = 254 nm, retention times: t_{major} = 9.94 min and t_{minor} = 11.41 min]. Its molecular mass from HRMS (ESI) spectrum for [$(C_{11}H_{14}O_3)$Na] (M+Na) was found to be 217.0857, which was in well agreement with the calculated value 217.0859 (**Figure 17**). Its IR spectrum showed a vibrational stretching frequency at υ_{max} 3441 cm^{-1} indicating the presence of hydroxyl group.

The Lewis acid catalyzed ring opening of epoxide **84** with azide anion produced *anti*-azido diol **89** in 96% yield as a single regioisomer; $[\alpha]_D^{25}$ -37.04 (*c* 2, $CHCl_3$) {lit.[26c] $[\alpha]_D^{25}$ -37.8 (*c* 1, $CHCl_3$). The appearance of two broad singlets in its ^1H NMR spectrum at δ 2.82 (br s, 1H) and 1.60 (br s, 1H) due to the presence of hydroxyl protons and a singlet at δ 4.56 (s, 2H) due to benzylic protons confirmed the formation of azido diol **89**. Its ^{13}C NMR spectrum showed two characteristic signals at δ 63.3 and δ 71.3 for the methine and methylene carbons attached to hydroxyl groups respectively. Its IR spectrum showed two vibrational stretching frequencies at υ_{max} 3438 and 2100 cm^{-1} due to the presence of hydroxyl and azide groups respectively (**Fig. 18**).



<u>Fig. 18</u>: ^{1}H & ^{13}C NMR and IR spectra of azido diol **89**

Global TBS protection (TBSCl, imid) of both hydroxyl groups in **89** provided **90** in 98% yield. The formation of compound *bis*-TBS ether **90** was confirmed by its ^{1}H NMR spectrum, which showed the appearance of two singlets at δ 0.80 (s, 9H) and δ 0.82 (s, 9H) due to *tert*-butyl protons. The other proton signals at δ -0.06 (s, 6H) and δ -0.02 (s, 6H) are assigned to methyl protons attached to silicon atom. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 25.8 and 25.9 due to methyl carbons of *tert*-butyl group attached to silicon atom in TBS group (**Fig. 19**). Its IR spectrum showed a vibrational stretching frequency at υ_{max} 2165 cm^{-1} due to the presence of azide group.

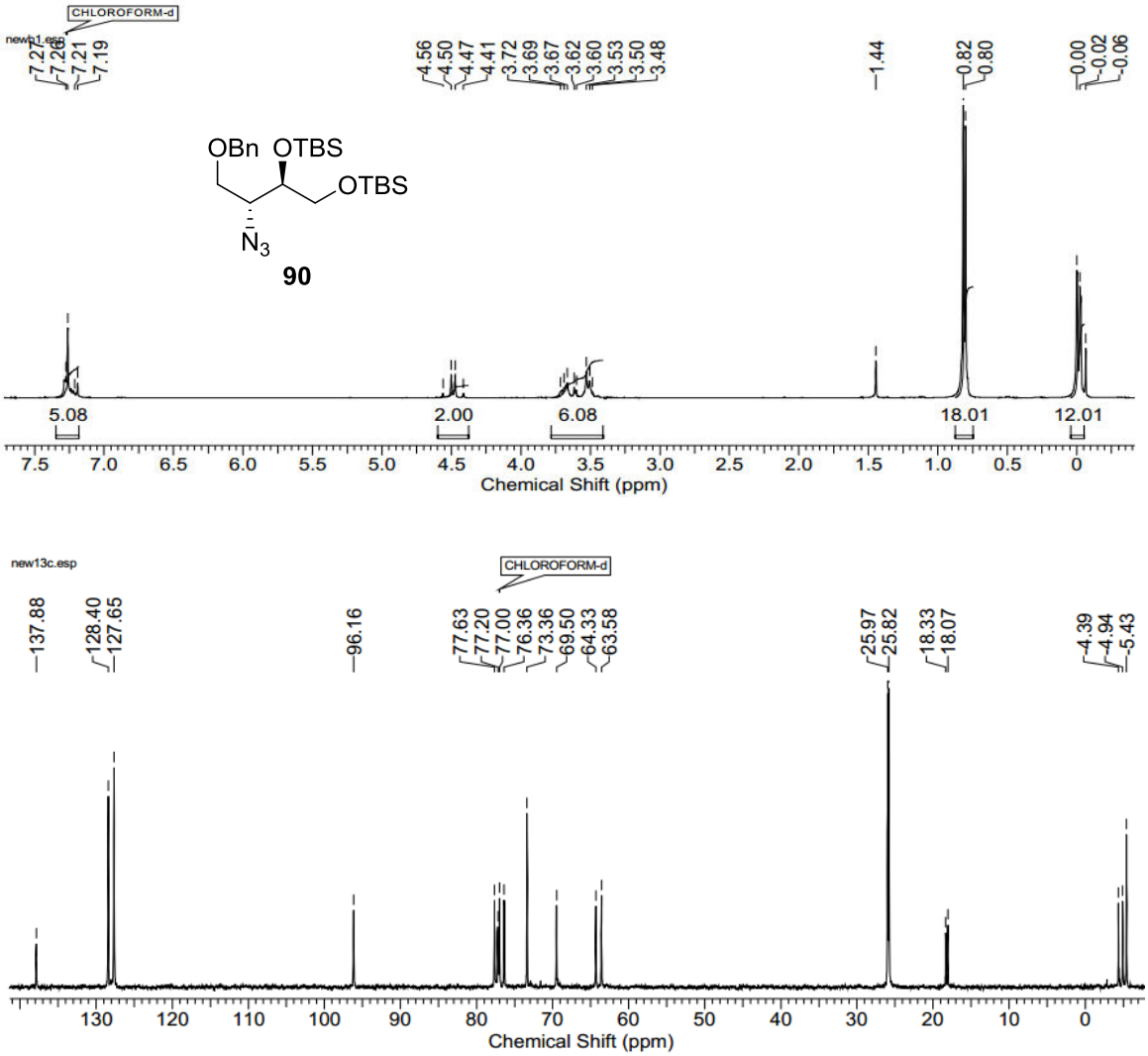


Fig. 19: ^{1}H and ^{13}C NMR spectra of TBS ether **90**

The selective azide reduction in **90** under Staudinger reaction (PPh_3, THF/H_2O, reflux) and its subsequent tosyl protection (TsCl, Et_3N, CH_2Cl_2) afforded compound **91** in 88% yield. The formation of compound **91** was confirmed by the appearance of a characteristic multiplet at δ 5.07-5.11 (m, 1H) for N-H proton and a typical singlet δ 2.40 (s, 3H) integrating for methyl proton of tosyl group in its ^{1}H NMR spectrum. It was further confirmed by ^{13}C NMR spectrum, which showed a typical carbon signal at δ 56.2 for methine carbon attached to –NHTs group and other signal at δ 23.8 due to methyl carbon of tosyl group (**Fig. 20**).

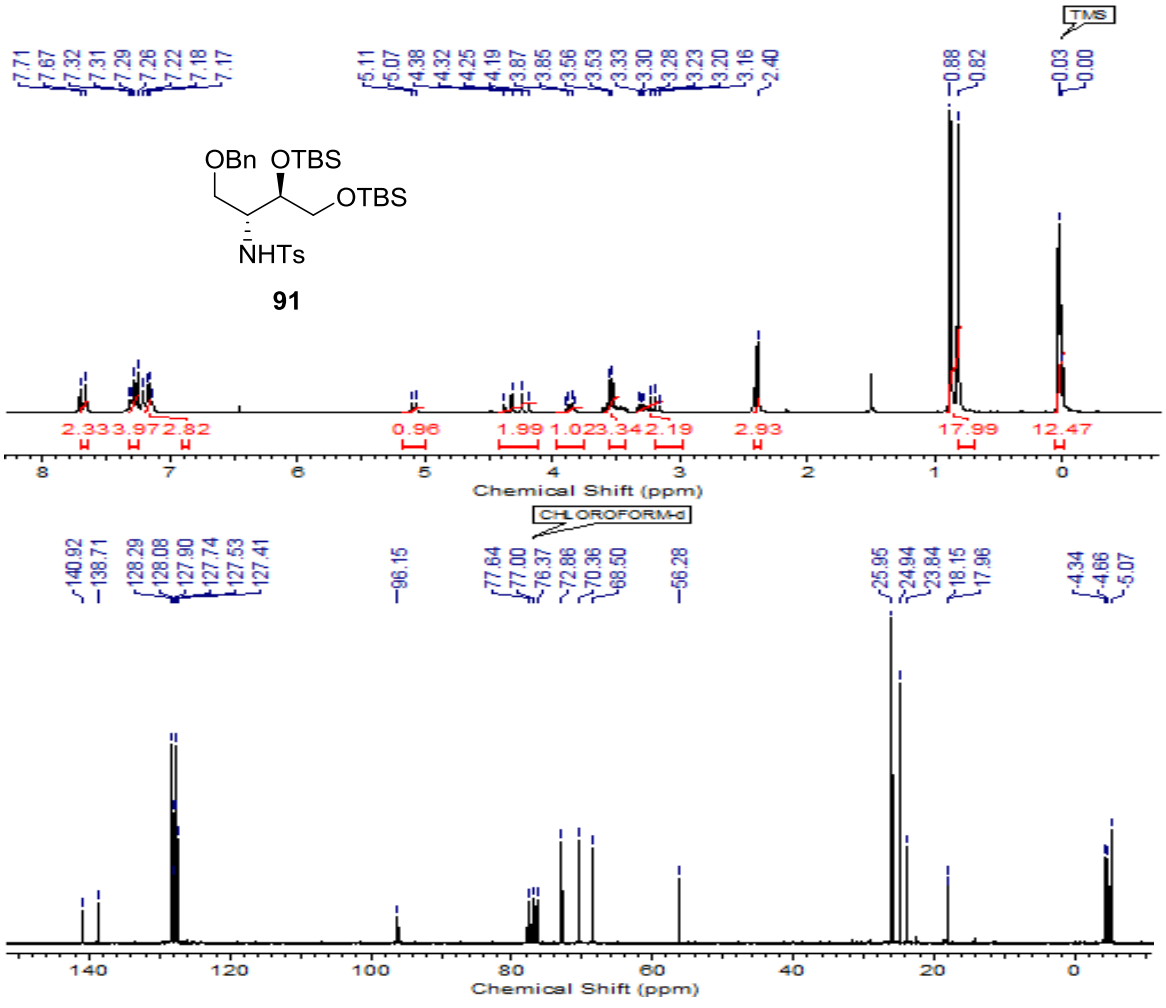
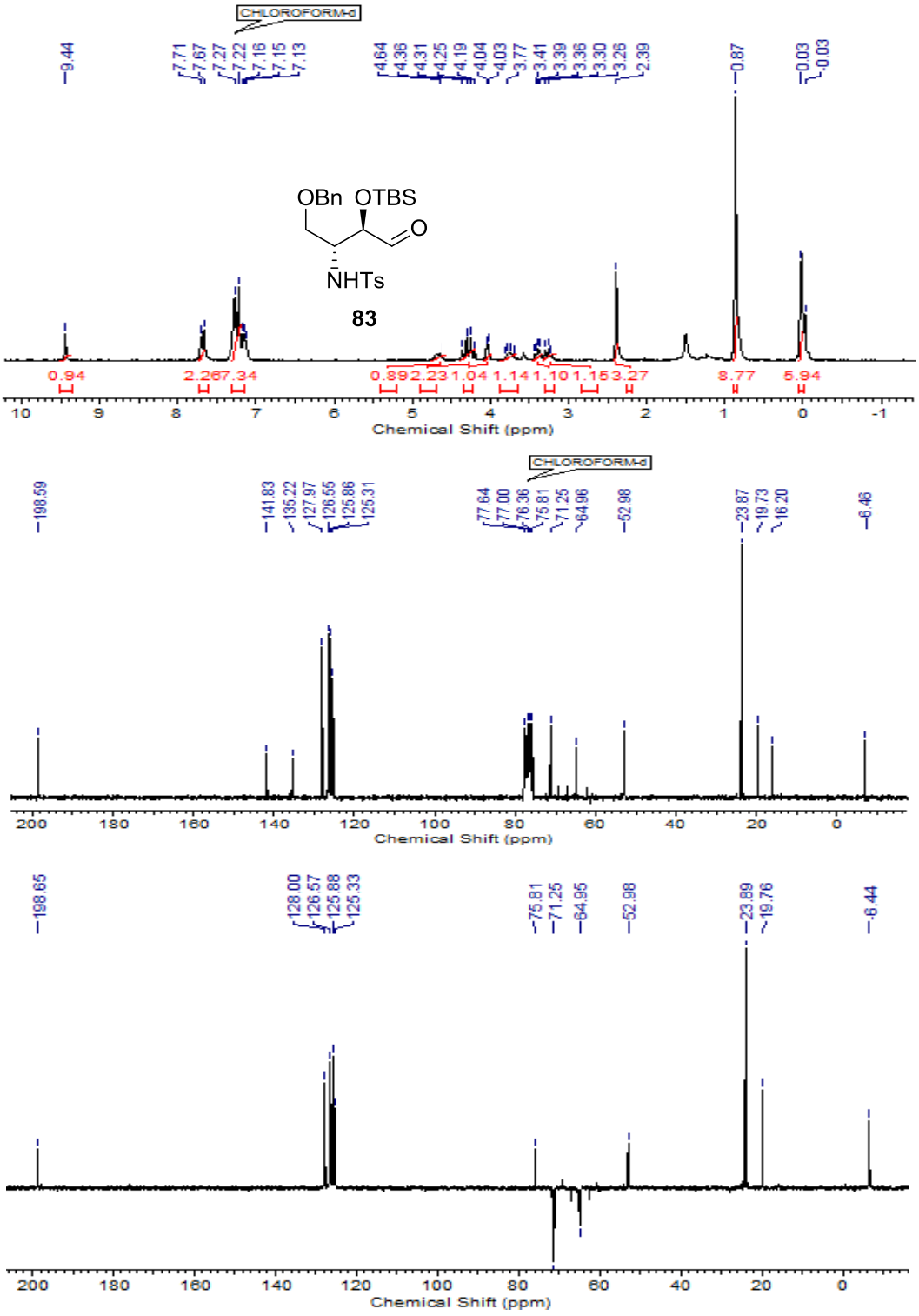


Fig. 20: ^{1}H and ^{13}C NMR spectra of compound **91**

Further, the selective deprotection of primary silyl ether in **91** followed by its oxidation using IBX to produce the corresponding crude aldehyde **83** in 91% yield. The aldehyde **83** was confirmed by the appearance of a characteristic signal at δ 9.44 for aldehydic



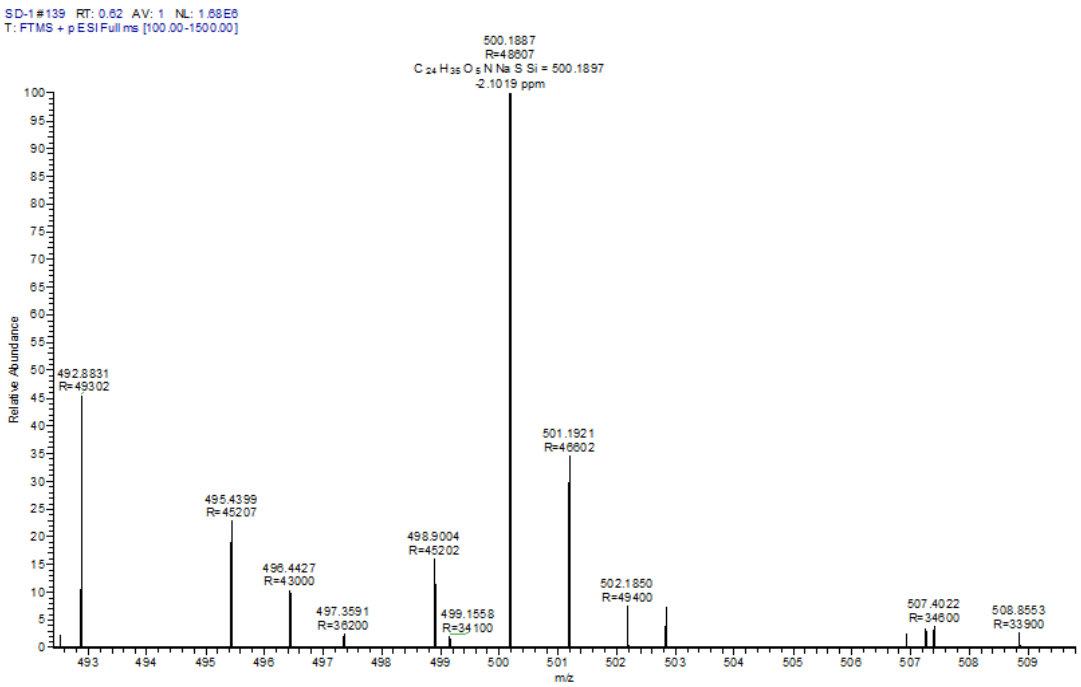


Fig. 21: ^{1}H, ^{13}C & DEPT NMR and HRMS spectra of aldehyde **83**

proton in its ^{1}H NMR spectrum. Again, a characteristic signal at δ 198.5 in its ^{13}C NMR spectrum, confirmed the presence of aldehydic carbonyl group in **83**. Its molecular mass from HRMS (ESI) spectrum for $[(C_{24}H_{35}NO_5SSi)Na]$ (M+Na) was found to be 500.1887, which was in well agreement with the calculated value 500.1897 (**Fig. 21**). Its IR spectrum showed a characteristic vibrational stretching frequency at υ_{max} 1720 cm^{-1} due to the presence of aldehydic carbonyl group.

The pyrrolidine core **82** was then constructed as a single diastereomer in 93% yield *via* a diastereoselective Corey-Chaykovsky reaction of aldehyde **83** with (4-methoxybenzyl)dimethylsulfonium bromide **85** (compound **85** was prepared by the reaction between 4-methoxybenzyl bromide and dimethyl sulfide) using ^{n}BuLi as base in dry THF at 0 °C; $[\alpha]_D^{25}$ +111.3 (*c* 0.5, $CHCl_3$).

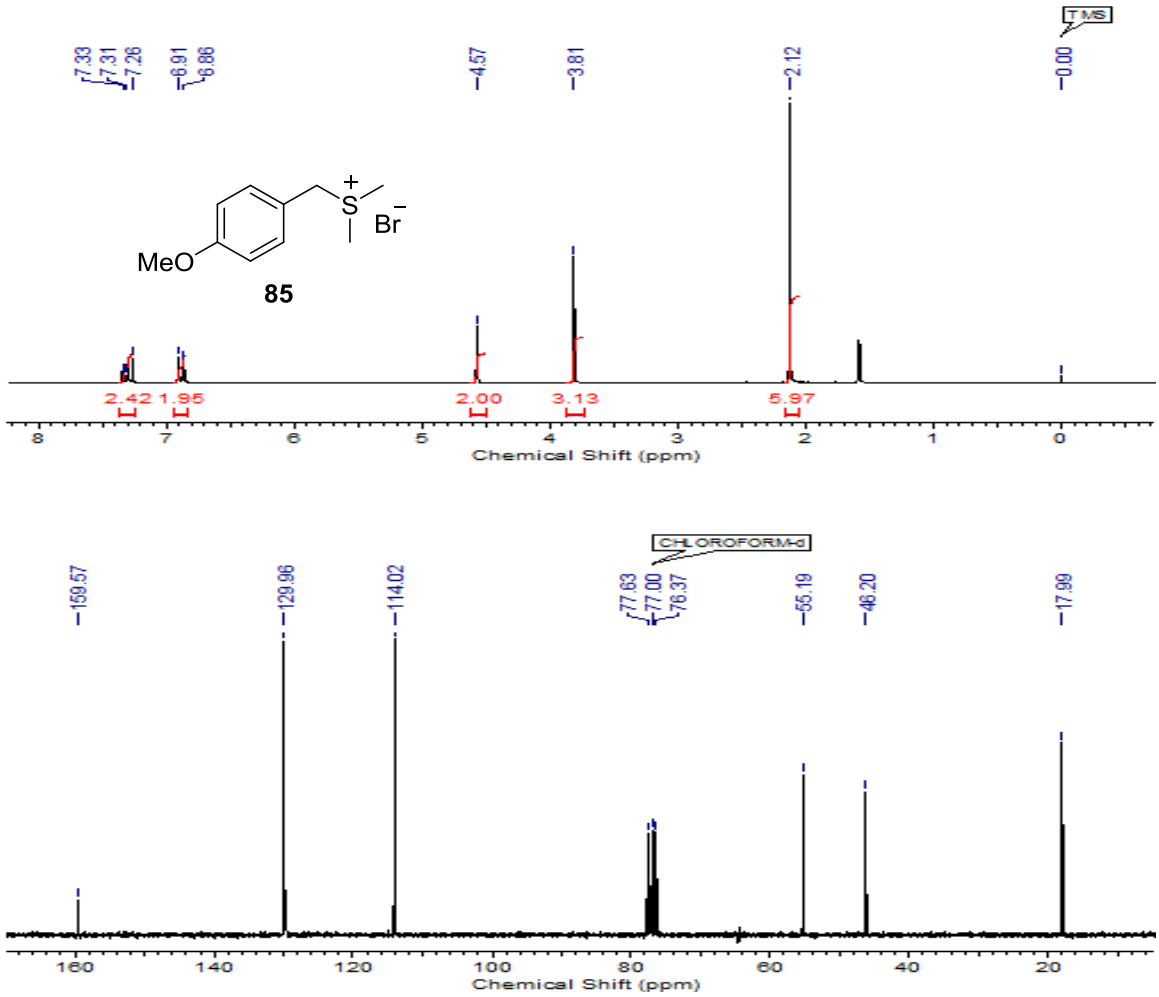
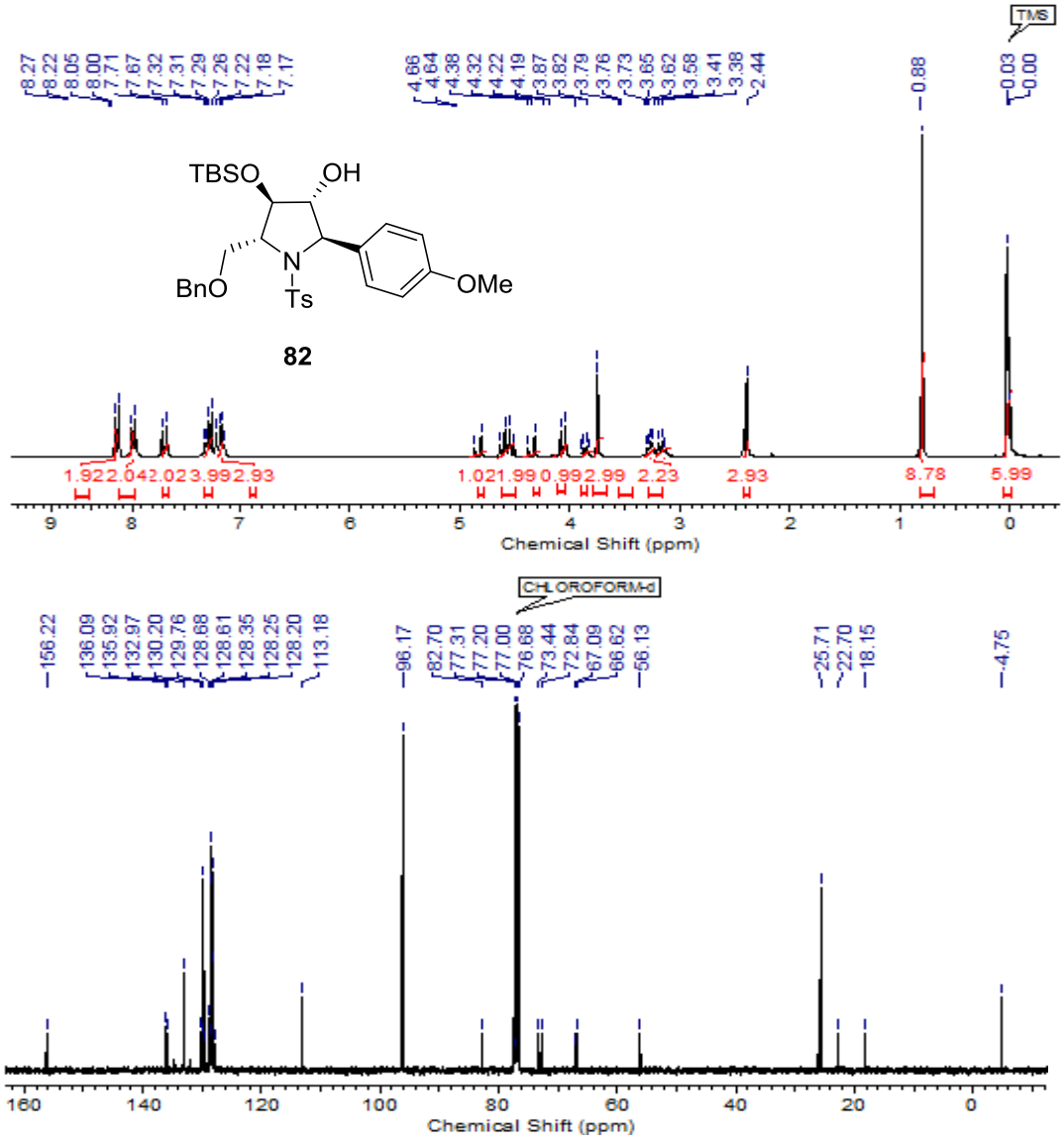


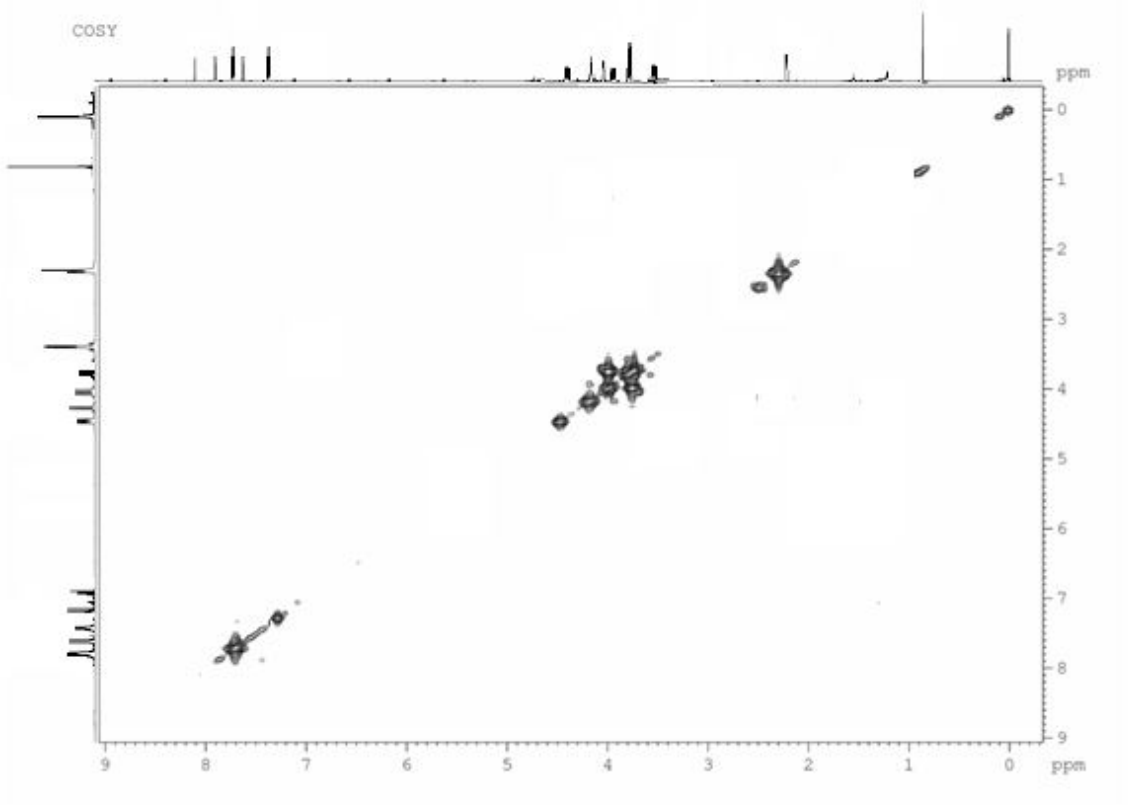
Fig. 22: ^{1}H and ^{13}C NMR spectra of (4-methoxybenzyl)dimethylsulfonium bromide **85**

Now, the formation of sulfonium salt **85** was established by the appearance of two typical singlets at 2.12 (s, 6H) due to the methyl protons of S-(C**H**$_3$)$_2$ group and at δ 4.57 (s, 2H) due to benzylic protons in its ^{1}H NMR spectrum. It was further ascertained by its ^{13}C NMR spectrum which showed characteristic carbon signals at δ 17.9 for methyl carbons of S-(**C**H$_3$)$_2$ group and at δ 55.1 due to benzylic carbon respectively (**Fig. 22**).

The formation of pyrrolidine **82** was confirmed by ^{1}H and ^{13}C NMR spectral analysis. The appearance of two typical doublet of doublets in its ^{1}H NMR spectrum at δ 4.64 (dd, *J* = 3.9, 6.4 Hz, 1H) and at δ 4.32 (dd, *J* = 3.8, 4.2 Hz, 1H) due to methine protons (-C**H**OH)

and (-C**H**OTBS) confirmed the *anti* stereochemistry of **82**. It was also confirmed from 2D NMR studies (COSY & NOESY spectra). A doublet at δ 4.19 (d, *J* = 6.4 Hz, 1H) and a multiplet at δ 3.82-3.87 due to methine protons attached to N-Ts group. It was further ascertained by the characteristic carbon signals at δ 82.7 and 73.4 due to the methine carbons (-**C**HOH) and (-**C**HOTBS) respectively. Its molecular mass from HRMS (ESI) spectrum for [($C_{32}H_{43}NO_6SSi$)Na] (M+Na) was found to be 620.5263, which was in well agreement with the calculated value 620.5260 (**Fig. 23**).




COSY
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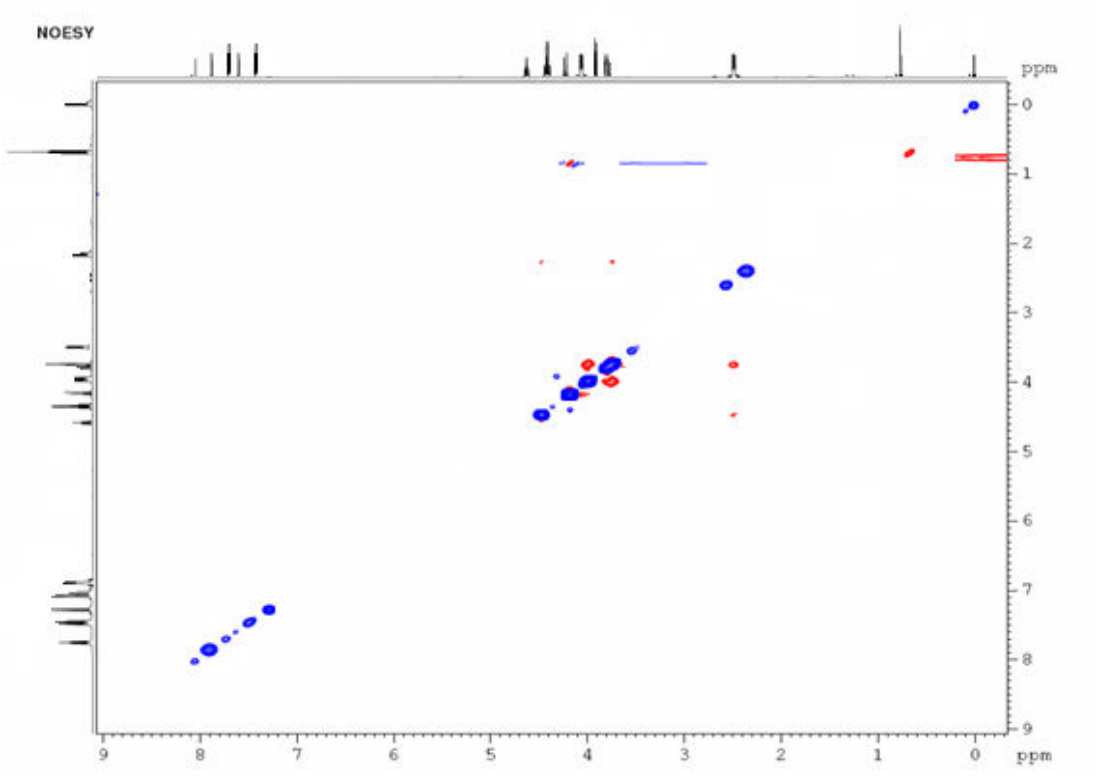
NOESY
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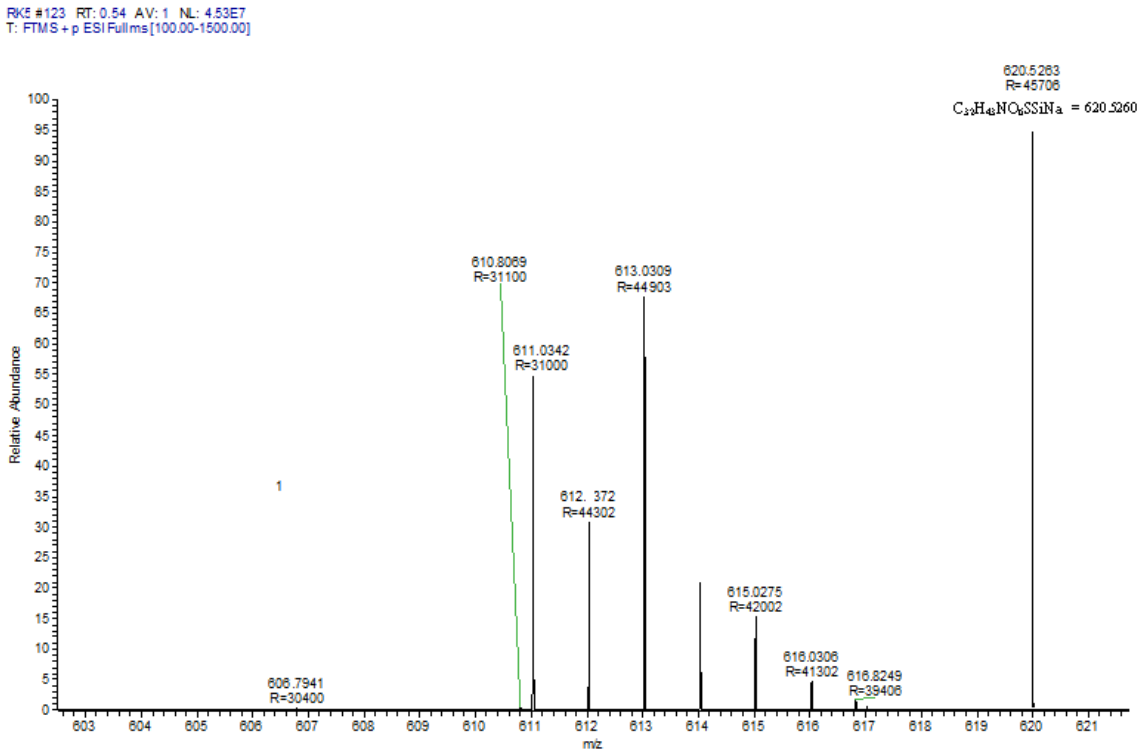
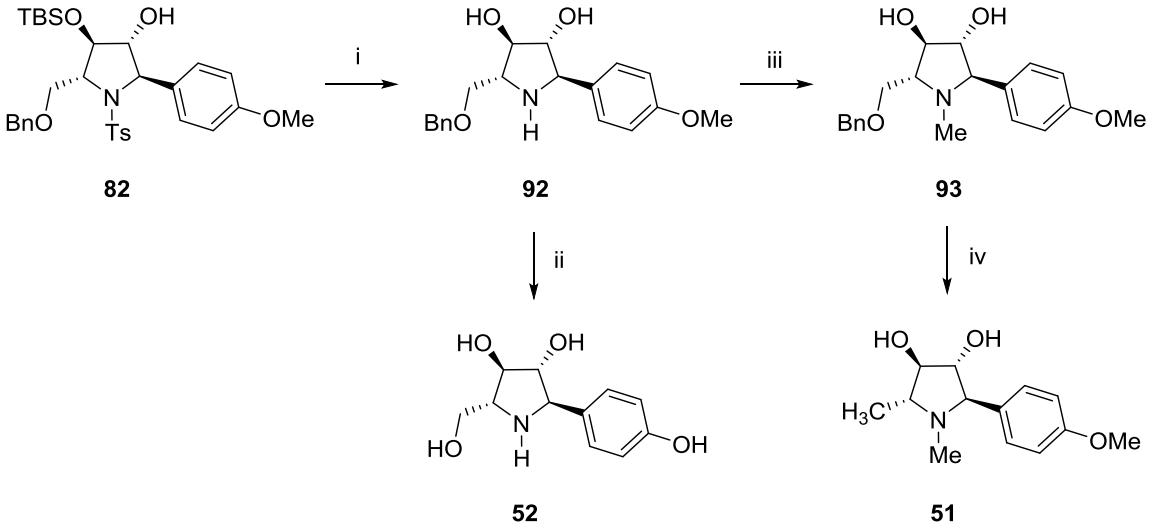


Fig. 23: ^{1}H, ^{13}C, COSY, NOESY NMR and HRMS spectra of pyrrolidine core **82**

Its IR spectrum showed a vibrational stretching frequency at υ_{max} 3389 cm^{-1} due to the presence of hydroxyl group.

Next, tosyl group in **82** was deprotected under Okamoto protocol[26b] [$Ti(OiPr)_4$, TMSCl, Mg, THF, 50 ºC] to furnish free amine functionality **92**, which was without further characterization, converted to the corresponding target molecules **51** or **52** according to reaction sequences shown in **Scheme 20**.



Scheme 20: (i) $Ti(O^iPr)_4$, TMSCl, Mg, THF, 50 ºC, 10 h; (ii) 1M BBr_3, CH_2Cl_2, 0-25 ºC, 8 h, 80%; (iii) NaH, DMF/THF (4:1), 0-25 ºC, 2 h, 70%; (iv) (a) H_2 (1 atm), 10% Pd/C, MeOH, 1 h; (b) TsCl, Et_3N, CH_2Cl_2, 0 ºC, 1 h; (c) $LiAlH_4$, THF, reflux, 6 h, 60% (over three steps).

Thus, on global deprotection of **92** using BBr_3 (1M in CH_2Cl_2) in CH_2Cl_2 furnished the target molecule radicamine B **52** in 80% yield. The formation of radicamine B **52** was established by its ^1H and ^{13}C NMR spectral analysis. The disappearance of the typical proton signals due to the TBS, Bn and –OMe groups in its ^1H NMR spectrum and the appearance of characteristic carbon signals in its ^{13}C NMR spectrum at δ 85.1 and 83.9 due to the methine carbons attached to hydroxyl groups confirmed the formation of **52** (**Fig. 24**). Its IR spectrum showed a vibrational stretching frequency at υ_{max} 3420 cm^{-1} due to the presence of hydroxyl group. The enantiomeric purity of the synthetic molecule **52** was determined to be 94% ee based on comparison of its specific rotation with the reported value $[\alpha]_D^{25}$ +68.14 (*c* 0.15, H_2O) {lit.[18b] $[\alpha]_D^{25}$ +72.0 (*c* 0.1, H_2O)}.

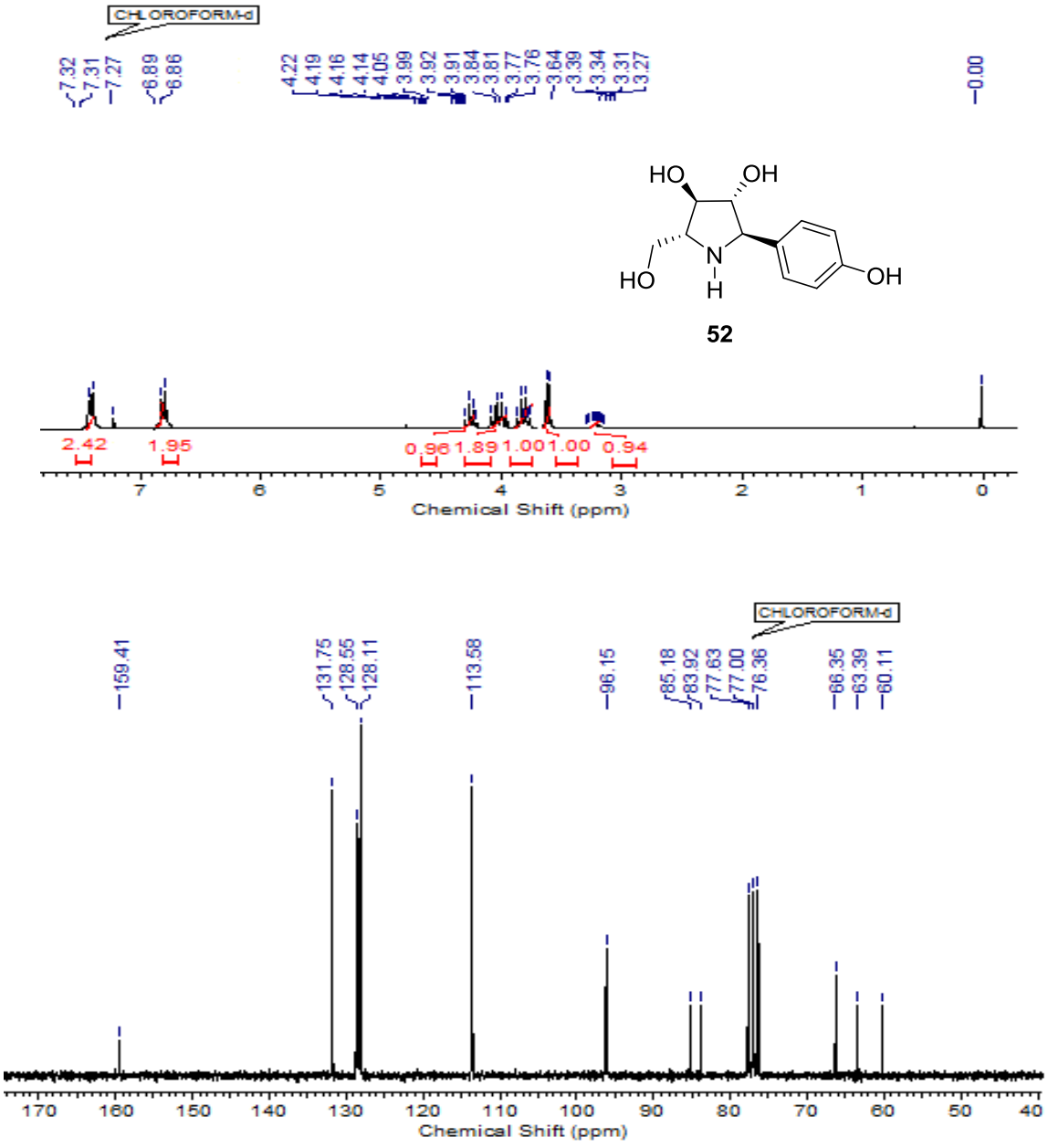


Fig. 24: ^{1}H and ^{13}C NMR spectra of radicamine B **52**

Again, compound **92** was subjected to *N*-methylation [MeI, NaH, DMF/THF (4:1)] that afforded compound *N*-methyl compound **93** in 70% yield. Next, compound **93** was smoothly converted to synthetic target molecule (-)-codonopsinine **51** as colorless solid in 60% yield in three steps; mp: 166-169 ºC; {lit[20] mp 169-170 ºC}: (i) debenzylation using

hydrogenolysis [H_2 (1 atm), 10% Pd/C, MeOH, 25 ºC]; (ii) tosyl protection of primary alcohol (TsCl, Et_3N, CH_2Cl_2) and (iii) reduction of tosylate using $LiAlH_4$ in THF solvent. The formation of (-)-codonopsinine **51** was confirmed from its ^1H NMR spectrum by the occurrence of a characteristic doublet at δ 1.36 (d, J = 6.8 Hz, 3H) corresponding to the methyl protons and a typical singlet at δ 2.16 (s, 3H) due to N-methyl protons.

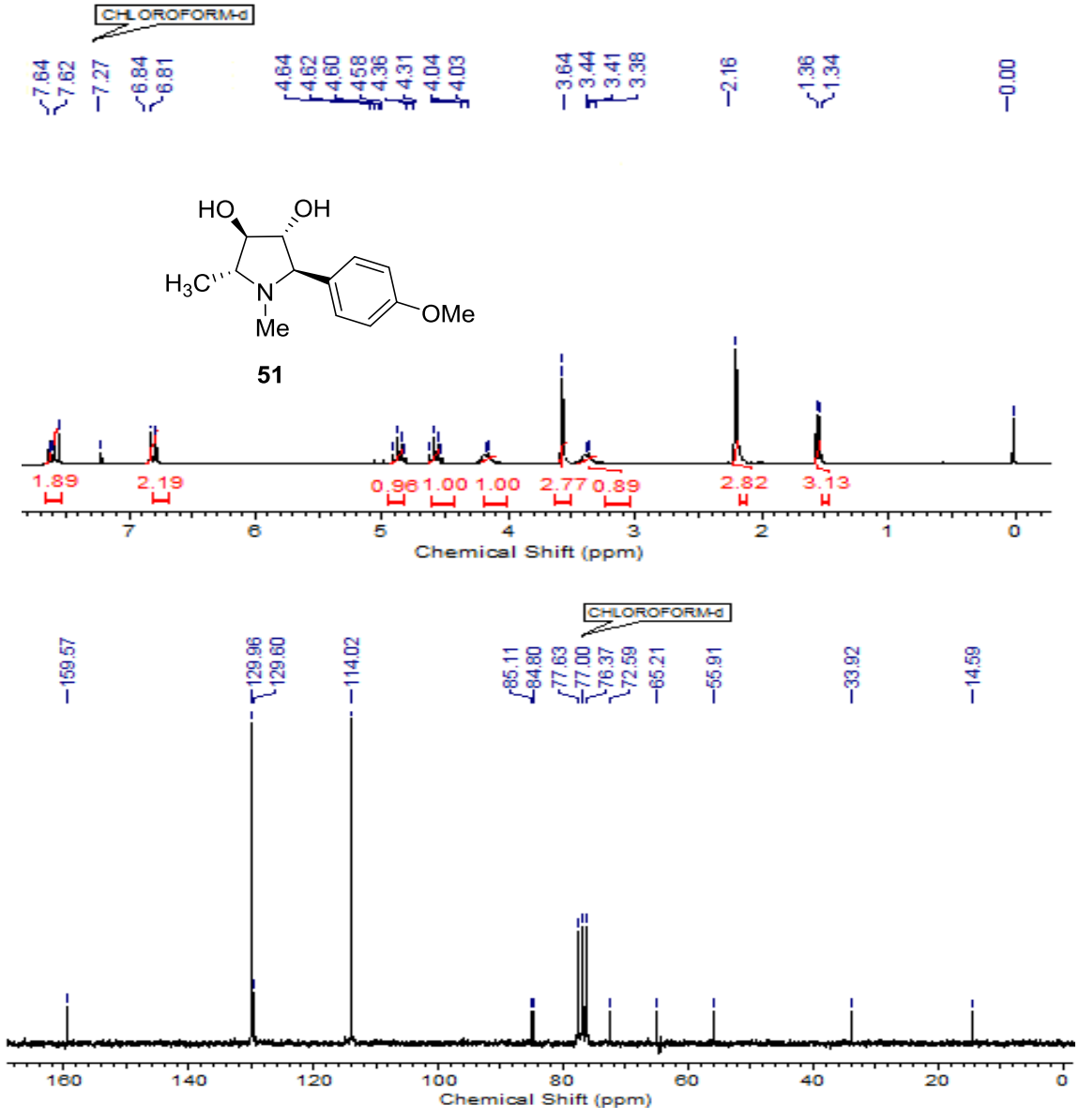


Fig. 26: ^1H and ^{13}C NMR spectra of (-)-codonopsinine **51**

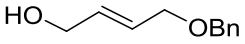
Its ^{13}C NMR spectrum showed two typical signals at δ 14.5 (-CH-**C**H_3) and 33.9 (-N**C**H_3) attributed to the presence of methyl carbons (**Fig. 26**). The enantiomeric purity of the synthetic molecule **51** was determined to be 95% ee based on the comparison of its specific rotation with the reported value $[\alpha]_D^{25}$ -11.21 (*c* 0.20, MeOH) {lit.[20] $[\alpha]_D^{25}$ -11.8 (*c* 0.69, MeOH)}. The spectroscopic data of the final synthetic products **51** and **52** thus obtained are in agreement with the literature values.[18, 20]

1.2.4 Conclusion

In conclusion, we have described an elegant and concise synthetic route to (-)-codonopsinine **51** (13.3% overall yield with 95% ee) and radicamine B **52** (25.3% overall yield with 94% ee). Our strategy is based on two key reactions i.e. Sharpless asymmetric epoxidation and diastereoselective Corey-Chaykovsky reaction. The protocol is facile, flexible and hence can be applied to the synthesis of other pyrrolidine-based bioactive molecules as well.

1.2.5 Experimental section

(*E*)-4-(Benzyloxy)but-2-en-1-ol (88)

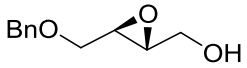


To a solution of diol **87** (15.02 g, 170.04 mmol) in dry DMF (200 mL) was added in one portion NaH (6.8 g, 170.04 mmol) and BnBr (20.1 mL, 170.04 mmol). The reaction mixture was then allowed to stir at 0 ^oC for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched by the addition of saturated solution of aq. NH_4Cl solution. The organic layer was extracted with EtOAc, 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 mono benzyl ether **88**.

Yield: 27.3 g, 90%; yellow colored liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 838, 1099, 1256, 1472, 2858, 2930, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.8 (br s, 1H), 4.04 (m, 2H), 4.8 (s, 2H), 5.88 (m, 1H), 6.12 (m, 1H), 7.27-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 63.5, 67.9, 72.9, 120.4, 127.4, 127.8, 128.6, 137.5, 140.5; **Anal. Calcd.** for $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92; Found: C, 74.10; H, 7.88%.

((2*R*, 3*R*)-3-((Benzyloxy)methyl)oxiran-2-yl)methanol (84)

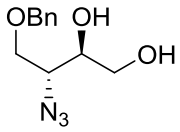


To a stirred suspension of powdered 4 Å molecular sieves (10.0 g) in dry CH_2Cl_2 (500 mL), titanium tetraisopropoxide (6.3 g, 20 mol %) was added under nitrogen atmosphere. The reaction mixture was cooled to -10 ºC and (+)-diethyl tartrate (6.94 g, 30 mol%) added and stirred for 10 min. To the above solution, *tert*-butyl hydroperoxide 5-6 M solution in decane (40.5 mL, 224.58) was added and stirred at -10 ºC for further 30 min, after which allylic alcohol **88** (20 g, 112.29 mmol) dissolved in dry CH_2Cl_2 (150 mL) was added and stirred at ⁻10 ºC for 8 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 epoxy alcohol **(+)-84** as a liquid.

Yield: 19.0 g, 88%; slightly yellow colored liquid; **$[\alpha]_D^{25}$** +13.5 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 838, 1035, 1260, 1564, 2858, 2930, 3441; **^{1}H NMR** (200 MHz, $CDCl_3$): δ

3.22-3.34 (m, 2H), 3.67-3.76 (m, 4H), 4.57 (d, *J* = 6.5 Hz, 2H), 7.34-7.44 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.8, 55.7, 60.3, 67.8, 73.2, 128.3, 129.5, 137.2; **Optical purity**: 97% determined by HPLC chromatogram [Chirapak OD-H, 2-Propanol/*n*-Hexane = 05/95, flow rate 0.5 mL/min, λ = 254 nm, retention times: t_{major} = 9.94 min and t_{minor} = 11.41 min]; **HRMS** (ESI): [($C_{11}H_{14}O_3$)] (M+Na) 217.0859: Found 217.0857.

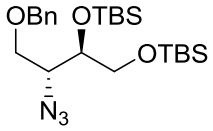
(2*R*, 3*R*)-3-Azido-4-(benzyloxy)butane-1,2-diol (89)



A mixture of freshly distilled Ti(O^iPr)$_4$ (11.4 mL, 38.64 mmol) and $TMSN_3$ (10.3 mL, 77.28 mmol) was refluxed in dry benzene (150 mL) under nitrogen for 4 h until the solution became clear. To this was added a solution of epoxy alcohol **84** (5.0 g, 25.76 mmol) in 50 mL of dry benzene. The resulting mixture was heated at reflux for 15 min, cooled to room temperature and the solvent was removed *in vacuo*. The concentrate was diluted with 200 mL of diethyl ether and treated with 15 mL of aq. 5% H_2SO_4. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford the crude product, which was purified by column chromatography using petroleum ether:EtOAc (3:2) to give azido diol **89** as a single diastereomer.

Yield: 5.8 g, 96%; colorless liquid; **$[\alpha]_D^{25}$** -37.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): ν_{max} 838, 1256, 1592, 2100, 2876, 3438 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.60 (br s, 2H), 2.81 (br s, 1H), 3.59-3.83 (m, 6H), 4.59 (s, 2H), 7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.0, 63.3, 69.9, 71.3, 73.5, 127.6, 127.9, 128.5, 137.3; **Anal. Calcd.** for $C_{11}H_{15}N_3O_3$ requires C, 55.69; H, 6.37; N, 17.71; Found: C, 55.64, H, 6.35, N, 17.70%.

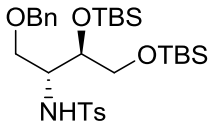
(*R*)-5-((*R*)-1-Azido-2-(benzyloxy)ethyl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane (90)



To a solution of azido diol **89** (4 g, 16.87 mmol) in CH_2Cl_2 (25 mL) at 25 ºC, TBSCl (5.59 g, 37.13 mmol) and imidazole (3.44 g, 50.63 mmol) was added. The resulting solution was stirred at 25 ºC for 24 h. It was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated reduced pressure to give the crude product. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (95:5) as eluent gave pure *bis*-TBS ether **90** as colorless oil.

Yield: 7.67 g, 98%, colorless oil; $[\alpha]_D^{25}$ -5.1 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1255, 1470, 2165, 2857, 2929 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.06 (s, 6H), -0.02 (s, 6H), 0.82 (s, 9H), 0.86 (s, 9H), 3.48-3.72 (m, 6H), 4.50 (d, *J* = 12.0 Hz, 1H), 7.19-7.27 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.43, -4.94,-4.39, 18.0 , 18.3, 25.8, 25.9, 63.5, 64.3, 69.5, 73.3, 77.2, 127.6, 128.4, 137.8; **Anal. Calcd.** for $C_{23}H_{43}N_3O_3Si_2$ requires C, 59.31; H, 9.31; N, 9.02; Found: C, 59.27; H, 9.28; N, 9.00%.

***N*-((2*R*,3*R*)-1-(Benzyloxy)-3,4-bis((*tert*-butyldimethylsilyl)oxy)butan-2-yl)-4-methylbenzenesulfonamide (91)**

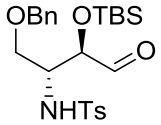


To a solution of *bis*-TBS ether **90** (7.0 g, 15.04 mmol) in THF (60 mL) was PPh_3 (11.83 g, 45.12 mmol) at 25°C. The reaction mixture was refluxed for 2 h at 70 °C. After the

completion of reaction (checked by TLC), solvent was evaporated. To the crude reaction mixture dissolved in dry CH_2Cl_2 (50 mL) were added TsCl (2.86 g, 15.04 mmol) and Et_3N (6.2 mL, 45.12 mmol) and the mixture stirred for 2 h. It was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated reduced pressure to give the crude product. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (9:1) as eluent gave pure **91**.

Yield: 7.14 g, 80%; yellow colored gum; $[\alpha]_D^{25}$ -35.8 (*c*1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 747, 1020, 1171, 1436, 1497, 1737, 2856, 3031, 3290, 3340; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.03 (s, 6H), 0.82 (s, 9H), 0.88 (s, 9H), 2.40 (s, 3H), 3.13-3.33 (m, 2H), 3.53-3.56 (m, 3H), 3.85-3.87 (m, 1H), 4.19-4.38 (m, 2H), 5.07-5.11 (m, 1H), 7.17-7.32 (m, 7H), 7.67-7.71 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.0, -4.6, -4.3, 17.9, 18.1, 23.8, 24.9, 25.9, 56.2, 68.5, 70.3, 72.8, 127.4, 127.5, 127.7, 127.9, 128.0, 128.2, 138.7, 140.9; **Anal. Calcd**. for $C_{30}H_{51}NO_5SSi_2$ requires C, 60.66; H, 8.65; N, 2.36; Found: C, 60.62; H, 8.62; N, 2.32%.

***N*-((2*R*,3*R*)-1-(Benzyloxy)-3-((tert-butyldimethylsilyl)oxy)-4-oxobutan-2-yl)-4-methylbenzenesulfonamide (83)**



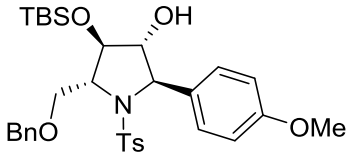
To a stirred solution of compound **91** (5.0 g, 0.84 mmol) in dry MeOH (30 mL), camphor sulfonic acid (18 mg, 0.08 mmol) was added and stirred at this temperature for 1 h. After completion of reaction (monitored by TLC), it was diluted with a saturated solution of sodium bicarbonate. The solvent was evaporated and the organic phase was 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 primary alcohol which was used as such for the next reaction.

To a stirred solution of the above crude product in DMSO (30 mL) at 25 ^oC was added IBX (0.235 g, 0.84 mmol) and the resulting solution was stirred for 2 h. The crude aldehyde obtained was filtered through Cilite pad (diethyl ether as eluent). After evaporation of solvent, the residue was purified through column chromatography (silica gel, 230-400 mesh, petroleum ether/EtOAc (9:1 v/v) to obtain aldehyde **83**.

Yield: 0.38 g, 95%; viscous liquid; $\mathbf{[\alpha]_D^{25}}$ -87.4 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 747, 1081, 1460, 1720, 2853, 2937; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.3 (s, 6H), 0.87 (s, 9H), 2.39 (s, 3H), 3.26-3.30 (m, 1H), 3.36-3.41 (m, 1H), 3.77 (m, 1H), 4.03-4.04 (m, 1H), 4.19-4.39 (m, 2H), 4.64 (br s, 1H), 7.13-7.27 (m, 7H), 7.67-7.71 (m, 2H), 9.44 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -6.93, -6.46, 16.2, 19.7, 23.8, 52.9, 64.9, 71.2, 75.8, 125.3, 125.8, 126.5, 127.9, 135.2, 141.8, 198.5; **HRMS** (ESI): [($C_{24}H_{35}NO_5SSi$)] (M+Na) 500.1897; Found: 500.1887.

(2*R*,3*R*,4*R*,5*R*)-5-((Benzyloxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)-1-tosylpyrrolidin-3-ol (82)



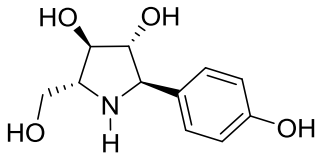
To a stirred solution of sulfonium salt **85** in dry THF (10 mL) was added ^{n}BuLi (0.5 mL, 0.5 mmol) at -10 °C and stirred for 30 min at same temperature. A pre-cooled (0 °C) solution of aldehyde **83** (1 g, 0.20 mmol) in dry THF (5 mL) was added to the reaction mixture at -10 °C slowly in dropwise manner *via* syringe. The reaction mixture was then

kept stirring at 0 °C for 3 h. After the reaction was complete (monitored by TLC), it was quenched with aq. NH_4Cl solution, and extracted with diethyl ether (3x50 mL). The organic extract was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Column chromatographic purification of crude with silica gel using petroleum ether: ethyl acetate (7:3) as eluent gave pure **82**.

Yield: 1 g, 80%; colorless gum; $[\alpha]_D^{25}$ +111.3 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 756, 1256, 1425, 1570, 1620, 2833, 2910, 3296, 3389; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.3 (s, 6H), 0.88 (s, 9H), 2.44 (s, 3H), 3.36-3.73 (m, 2H), 3.82 (s, 3H), 3.87 (m, 1H), 4.19 (d, *J* = 6.4 Hz, 1H), 4.32 (dd, *J* = 3.8, 4.2 Hz, 1H), 4.52 (dd, *J* = 3.9, 6.4 Hz, 1H), 7.1-7.26 (m, 3H), 7.29-7.32 (m, 4H), 7.67-7.71 (m, 2H), 8.0 (d, *J* = 6.4 Hz, 2H), 8.22 (d, *J* = 4.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ -4.7, 18.1, 22.7, 25.7, 56.1, 66.9, 67.0, 72.8, 73.4, 82.7, 113.2, 127.8, 128.0, 128.1, 128.5, 129.6, 136.1, 136.8, 144.1, 156.2; **HRMS** (ESI): [($C_{32}H_{43}NO_6SSi$)] (M+Na) 620.5260; Found: 620.5263.

(2*R*,3*R*,4*R*,5*R*)-2-(Hydroxymethyl)-5-(4-hydroxyphenyl)pyrrolidine-3,4-diol:

Radicamine B (52)



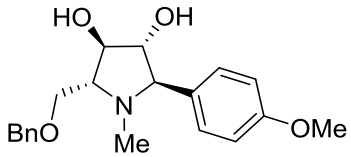
Under an argon atmosphere, to a mixture of sulfonamide **82** (0.5 g, 0.08 mmol) ang Mg powder (10 mg, 0.4 mmol) in dry THF (1 mL) were added $Ti(O^iPr)_4$ (0.03 mL, 0.08 mmol) and TMSCl (12 mg, 0.12 mmol). The resulting mixture was stirred at 50 °C. After checking consumption of the substrate by TLC analysis, aqueous 3M NaOH (0.4 mL), Et_2O (15 mL), anhydrous NaF (0.25 g) and Celite (0.5 g) were sequentially added at room temperature. After being stirred for additional 30 min, the mixture was filtered through a

pad of Celite. To the resulting filtrate was added aqueous 3M NaOH (15 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with aqueous 3M NaOH, dried over anhydrous Na_2SO_4, filtered and concentrated to get the crude amine **92**, which was without further purification was subjected to next reaction.

To a stirred solution of crude amine **92** (0.2 g) in CH_2Cl_2 (2 mL) was added 1 mL of BBr_3 (1M solution in CH_2Cl_2) at 0 °C and stirred it for 8 h at 25 °C. After the reaction was complete (monitored by TLC), it was quenched with aq. NH_4Cl solution and the organic phase was extracted twice with CH_2Cl_2. The organic extract was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography with neutral alumina using petroleum ether: chloroform (1:1) as eluent to give pure **52**.

Yield: 0.15 g, 80%; colorless gum; **$[\alpha]_D^{25}$** +68.14 (*c* 0.15, H_2O) {lit.[15] $[\alpha]_D^{25}$ +72.0 (*c* 0.1, H_2O); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 756, 1256, 1425, 1570, 1620, 2856, 2910, 3296, 3354, 3440; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.27-3.39 (m, 1H), 3.64 (dd, *J* = 6.3, 11.7 Hz, 1H), 3.76 (dd, *J* = 4.6, 11.7 Hz, 1H), 3.84-3.92 (m, 1H), 3.99-4.05 (m, 2H), 4.22 (dd, *J* = 7.5, 9.2 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 60.3, 63.1, 65.2, 83.5, 85.1, 114.0, 129.6, 129.9, 159.5; **Anal. Calcd.** for $C_{11}H_{15}NO_4$ requires C, 58.66; H, 6.71; N, 6.22; Found: C, 58.62; H, 6.68; N, 6.20%.

(2*R*,3*R*,4*R*,5*R*)-2-((Benzyloxy)methyl)-5-(4-methoxyphenyl)-1-methylpyrrolidine-3,4-diol (93)



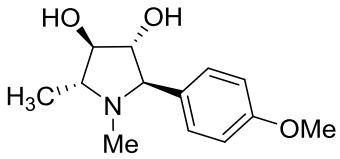
Similarly, the crude amine **92** was prepared following the procedure described above.

To a well-stirred solution of NaH (5 mg, 0.12 mmol) in DMF/THF (4:1) (2 mL) was added the crude amine **92** (0.2 g) in dry THF (2 mL) at 0 °C dropwise *via* a syringe. A solution of MeI (12 mg, 0.08 mmol) in dry THF (0.5 mL) was added to the reaction mixture at same temperature and kept stirring for 2 h at 25 °C. After the reaction was complete (monitored by TLC), it was quenched with aq. NH_4Cl solution and the organic phase was extracted twice with ether. The organic extract was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography with neutral alumina using petroleum ether: ethyl acetate (3:7) as eluent to give pure **93**.

Yield: 0.2 g, 70%; colorless gum; $[\alpha]_D^{25}$ +46.3 (*c* 0.21, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 852, 1358, 1542, 1585, 2885, 2996, 3100, 3196, 3240, 3420; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.24 (s, 3H), 3.26-3.41 (m, 2H), 3.77 (s, 3H), 3.92-4.01 (m, 1H), 4.15 (dd, *J* = 3.2, 5.7 Hz, 1H), 4.29-4.38 (m, 1H), 4.55 (dd, *J* = 3.6, 6.1 Hz, 1H), 7.11-7.22 (m, 7H), 7.41-7.45 (m, 2H), 7.71 (d, *J* = 6.6 Hz, 1H), 7.82 (d, *J* = 7.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 34.0, 55.2, 65.0, 67.4, 73.1, 74.5, 86.0, 87.2, 114.0, 125.3, 125.8, 126.5, 127.9, 135.2, 141.8, 159.8; **Anal. Calcd.** for $C_{20}H_{25}NO_4$ requires C, 69.95; H, 7.34; N, 4.08; Found: C, 69.91; H, 7.30; N, 4.05%.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-diol:

(-)-Codonopsinine (51)



A mixture of compound **93** (0.1 g, 0.29 mmol) in MeOH (5 mL) and 10% Pd/C (10 mg) was stirred under H_2 (1 atm) at 25 °C for 1 h. After completion of reaction (monitored by

TLC), it was filtered through Celite (EtOAc eluent) and the solvent was evaporated under reduced pressure to afford crude product, which was without further purification was used in the next reaction.

To a stirred solution of the above crude in dry CH_2Cl_2 (5 mL) were added TsCl (55 mg, 0.29 mmol) and Et_3N (1.1 mL, 0.87 mmol) at 0 °C and the resulting mixture was stirred for 1 h. After that it was extracted twice with CH_2Cl_2. The organic extract was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. To a solution of crude in dry THF (2 mL) was added $LiAlH_4$ (22 mg, 0.58 mmol) and refluxed for 6 h. After the reaction was complete (monitored by TLC), it was quenched with diethyl ether. The organic layer was extracted with diethyl ether, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography with silica using petroleum ether: chloroform (3:2) as eluent to give pure **51**.

Yield: 41 mg, 60%; colorless solid; **mp**: 168-170 °C {lit.[15] mp 169-170 °C}; **$[\alpha]_D^{25}$** -10.3 (*c* 0.20, MeOH) {lit.[15] $[\alpha]_D^{25}$ -11.8 (*c* 0.69, MeOH); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 790, 1164, 1385, 1586, 1610, 2985, 3119, 3235, 3456; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.36 (d, *J* = 6.8 Hz, 3H), 2.16 (s, 3H), 3.38-3.44 (m, 1H), 3.64 (s, 3H), 4.03 (d, *J* = 6.4 Hz, 1H), 4.31 (dd, *J* = 3.8, 4.2 Hz**,** 1H), 4.60 (dd, *J* = 4.3, 6.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 7.7 Hz, 1H);**^{13}C NMR** (125 MHz, $CDCl_3$): 14.5, 33.9, 55.9, 65.2, 72.5, 84.8, 85.1, 114.0, 129.6, 129.8, 159.6; **Anal. Calcd.** for $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90; Found: C, 65.75; H, 8.04; N, 5.86%.

1.2.6 References

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CHAPTER II

Asymmetric Synthesis of Stagonolide E, (-)-(6*R*,11*R*,14*R*)-Colletallol and (*S*)-3-Hydroxypiperidine *via* Organocatalysis

1. A concise enantioselective synthesis of marine macrolide-stagonolide E via organocatalysis **Dey, S.**; Sudalai, A. *Tetrahedron: Asymmetry* **2015**, *26*, 344.
2. Concise Enantioselective Synthesis of Naturally Active (*S*)-3-Hydroxypiperidine, **Dey, S.**; Sudalai, A. *Synth. Commun.* **2015**, *45*, 1559.

Section I

A Concise Enantioselective Synthesis of Marine Macrolide-Stagonolide E *via* Organocatalysis

2.1.1 Introduction and Pharmacology

Stagonolides (e.g. compounds **1**-**4**) generally represent a family of novel 10-membered ring lactone natural products (**Fig. 1**).[1] Among them stagonolide E (**1**) is a secondary metabolite of *Stagonospora cirsii*, a fungal pathogen of the weed *Cirsium arvense*. It was isolated from the fungus *Curvularia* sp. PSU-F22.[2] This family of natural products displays a wide range of pharmacologically interesting properties such as antibacterial, antitumoral, antifungal and the inhibition of cholesterol biosynthesis.[3] The scare availability of these macrolides coupled with their interesting biological profile continued to attract the attention of synthetic organic chemists worldwide.

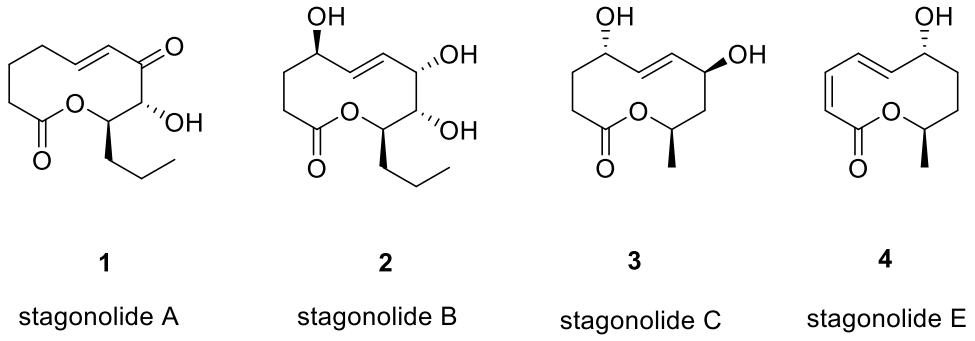


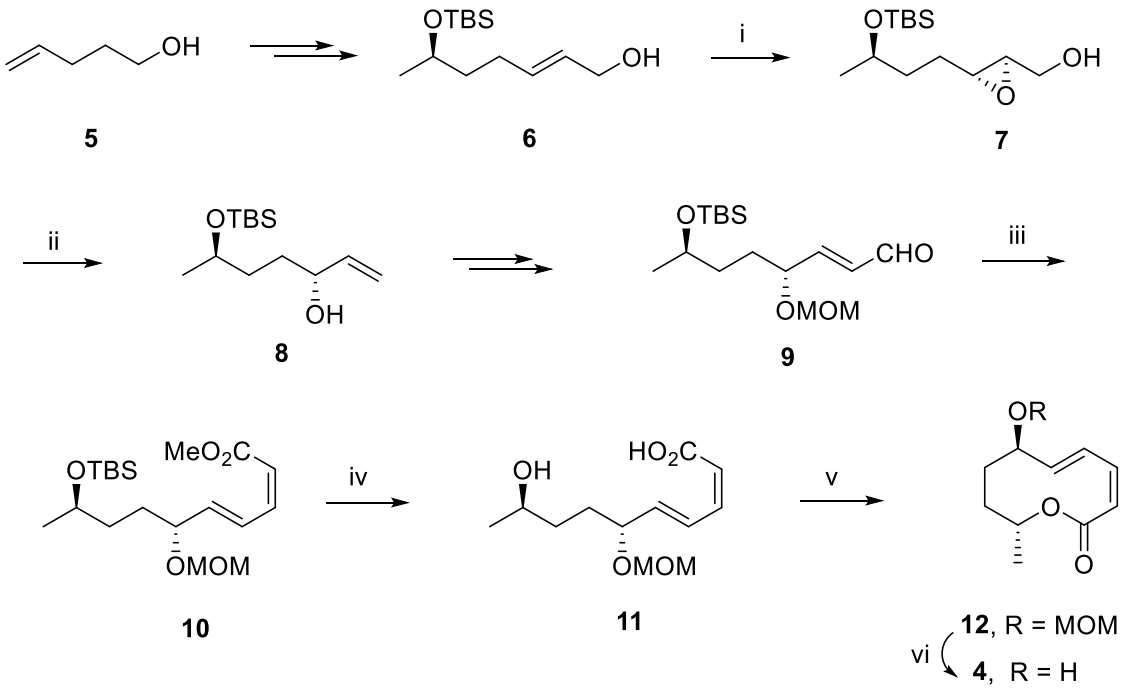
Fig. 1: Some naturally-occurring stagonolides **1**-**4**

2.1.2 Review of Literature

Till date only three approaches for its synthesis have been documented in the literature, which are described below.

Sabitha's approach (2010)[4]

The total synthesis of (-)-stagonolide E (**4**) described by Sabitha *et al.* is based on Sharpless asymmetric epoxidation (SAE) approach for the generation of chirality. Thus, allylic alcohol **6**, obtained from commercially available 4-penten-1-ol (**5**), was subjected to SAE to afford epoxy alcohol **7**. The epoxy alcohol **7** was converted to the corresponding secondary allylic alcohol **8** in 80% yield by treating with iodine, triphenylphosphine, and imidazole in a mixture of diethylether and acetonitrile in 3:1 ratio at 0-25 ºC followed by refluxing with activated zinc in ethanol.



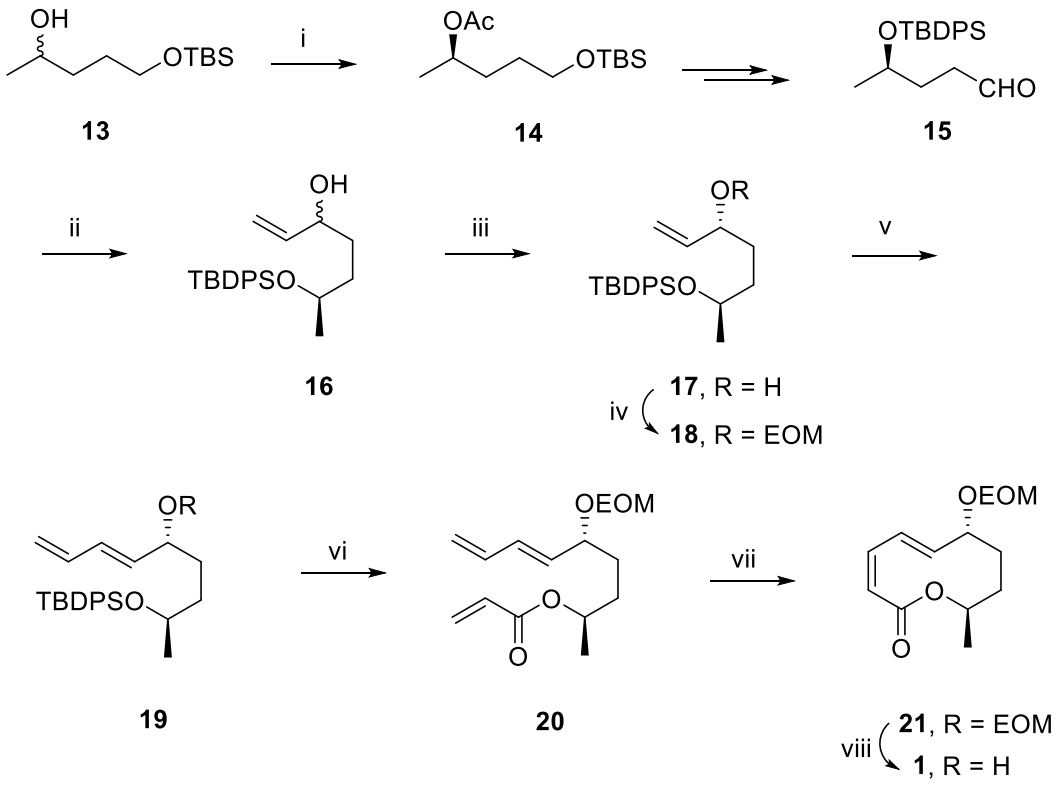
Scheme 1: (i) (-)-DET, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å MS, CH_2Cl_2, 20 ºC, 5 h, 75%; (ii) (a) I_2, Ph_3P, imid., ether:acetonitrile (3:1), 0 ºC to rt, 1 h; (b) activated Zn, EtOH, reflux, 2 h 80%; (iii) $(CF_3CH_2O)P(O)CH_2CO_2Me$, NaH, dry THF, -78 ºC, 2 h, 80%; (iv) (a) TBAF, THF, 0 ºC, 1 h; (b) LiOH H_2O, THF/MeOH/H_2O (3:1:1), 0 –25 ºC, overnight, 90%; (v) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux, 9 h, 70%; (vi) $CeCl_3 \cdot 7H_2O$, CH_3CN/MeOH (2:1), 48 h, reflux, 60%.

Next, α,β-unsaturated aldehyde **9**, obtained from secondary allylic alcohol **8** (in three steps), was treated with Stille-Gennari reagent (methyl *p,p'*-bis(2,2,2-trifluoroethyl)phosphono acetate) in the presence of NaH at -78 ºC to give dienic ester **10** in 80% yield with excellent stereoselectivity (*Z,E*/*E,E* = 95:5). Cleavage of the TBS ether in **7** using TBAF in THF and hydrolysis of ester using LiOH provided *seco* acid **11** in 90% yield. Then **11** was treated with Yamaguchi lactonization condition [2,4,6-trichlorobenzoyl chloride in refluxing toluene] to provide macrolactone **12** (ee >95%). Finally, removal of MOM group under neutral conditions completed the synthesis of the target molecule, stagonolide E **4** in 60% yield **(Scheme 1)**.

Nanda's approach (2012)[5]

Nanda *et al.* have achieved the synthesis of stagonolide E **4** by a series of reaction such as ME-DKR (metal enzyme combo dynamic kinetic resolution) reaction, asymmetric reduction using Noyori's BINAL-H reagent system, stereoselective cross metathesis, and RCM (ring closing metathesis). Thus, the secondary alcohol **13**, obtained from pentane-1,4-diol, was subjected to metal-enzyme combined DKR with CAL-B (*Candida antartica* lipase) and Ru-based racemization catalyst (DKR catalyst) in the presence of isopropenyl acetate to afford acetate **14** in an 88% yield and 97% ee. The aldehyde **15**, obtained from acetate **14** by functional group transformation reactions, was treated with vinylmagnesium bromide at -78 ºC to afford alcohol **16** as inseparable diastereomeric mixtures in 82% yield. Oxidation of the alcohol functionality in **16** under Swern condition afforded the ketone which was followed by asymmetric ketone reduction with Noyori's BINAL-H reagent (*M*-binapthol and $LiAlH_4$) afforded alcohol **17** in an 85% yield, which on protection with EOM-Cl (ethoxy methyl chloride) and DIPEA (diisopropylethyl amine)

afforded compound **18** in 87% yield. Compound **18** on cross metathesis (CM) with acrolein in the presence of Hoveyda–Grubbs metathesis catalyst (HG-II, 5 mol %)



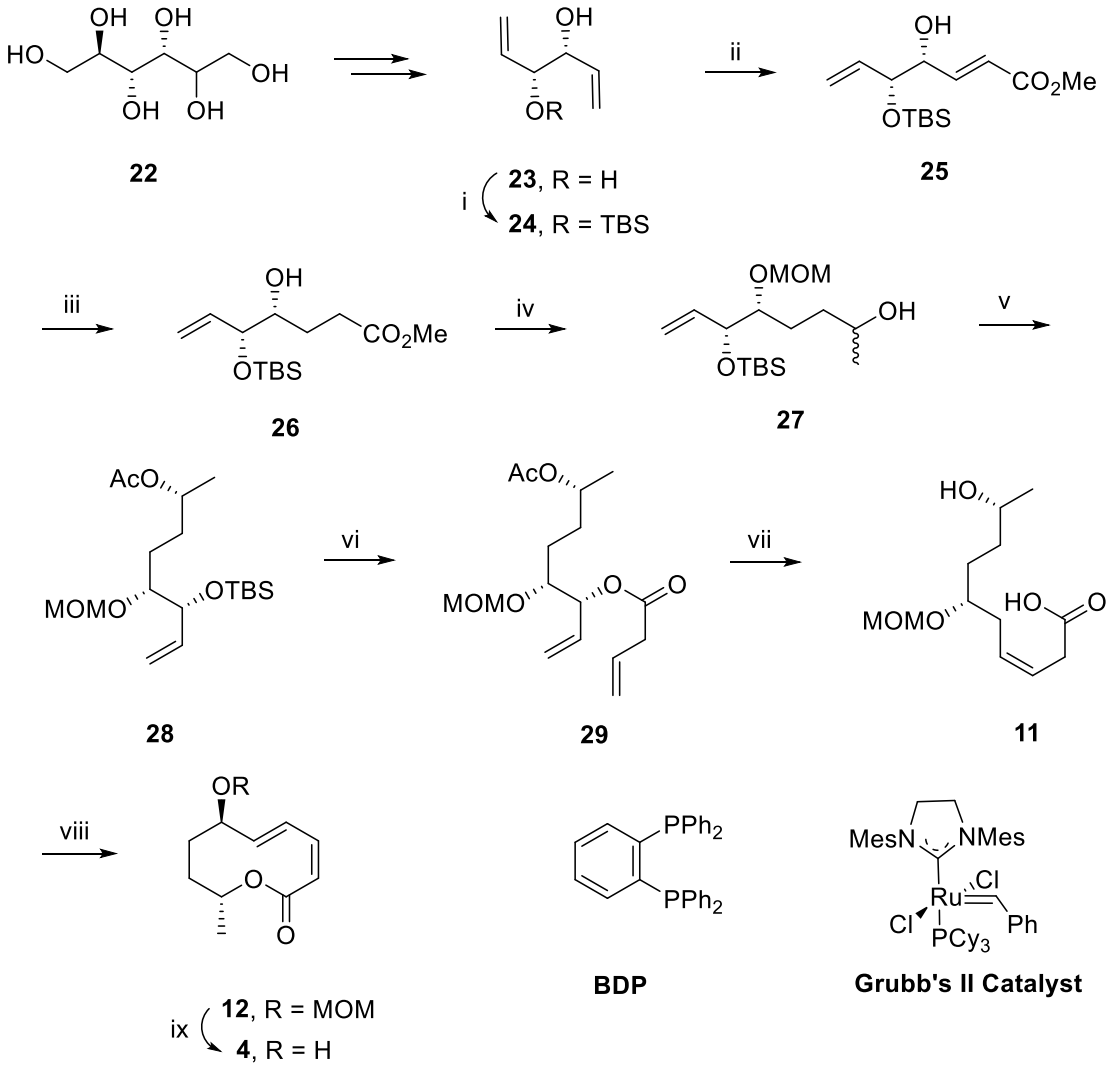
Scheme 2: (i) CAL-B, isopropenylacetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl)ruthenium(II), K_2CO_3, KO*t*Bu, 88%; (ii) CH_2=CHMgBr, THF, -78 ºC, 82%; (iii) (a) $(COCl)_2$, DMSO, Et_3N, -78 ºC, 90%; (b) *R*-(+)-binapthol, $LiAlH_4$, 100 ºC, 3 h then -78 ºC, 6 h, 85%; (iv) EOM-Cl, DIPEA, rt, 12 h, 87%; (v) (a) HG-II, acrolein, reflux, CH_2Cl_2, 6 h, 92%; (b) LHMDS, $Ph_3P^+MeI^-$, 0 ºC, 1 h, 80%; (vi) (a) TBAF, THF, rt, 3 h, 84%; (b) CH_2=CHCOCl, DIPEA, 6 h, rt, 80%; (vii) Grubbs-II, CH_2Cl_2, reflux, 6 h, 62%; (viii) 2 M HCl, THF, rt, 6 h, 88%.

afforded the unsaturated aldehyde, which on Wittig olefination with methyl triphenylphosphonium iodide in the presence of LHMDS afforded conjugated diene **19** in 80% yield. Deprotection of TBDPS group in compound **19** by TBAF followed by treatment with acryloyl chloride in the presence of DIPEA afforded the RCM precursor acrylic ester **20** in 80% yield. Ring closing metathesis reaction of compound **20** with

Grubbs-II catalyst in refluxing CH_2Cl_2 afforded compound **21** as a major product in 62% yield. Finally, deprotection of EOM group in **21** was achieved with 2 M HCl in THF to afford stagonolide-E (**4**) in 88% yield (**Scheme 2**).

Schmidt's approach (2013)[6]

Schmidt *et al*. have reported the synthesis of stagonolide E **4** from chiral pool building block, (*R, R*)-hexa-1,5-diene-3,4-diol **23**, obtained from D-mannitol **22**. TBS protection of **23** followed by treatment with Grubb's-II catalyst with methyl acrylate afforded **25** in 70% yield. Protection of free hydroxyl group in **25** with MOMBr followed by BDP–Cu hydride catalyzed selective reduction of olefin using PHMS as reducing agent gave compound **26** in 80% yield. Selective reduction of ester **26** to aldehyde using DIBAL-H followed by addition of MeMgBr at -78 ºC provided alcohol **27** in 95% yield. Then the compound **27** was treated with Ru–lipase-catalyzed dynamic kinetic resolution to form acetate **28** in 82% yield. Compound **28** was treated with TBAF to furnish vinyl alcohol, which was then coupled with vinylacetic acid under Steglich esterification condition to give diene **29** in 94% yield. Reaction of **29** with Grubbs-II catalyst, followed by treatment with NaH, resulted in the expected RCM/ring opening sequence, but also in a partial deacetylation. The crude reaction mixture was subsequently treated with aqueous NaOH to complete the ester cleavage, giving the macrolactonization precursor **30** in 81% yield. Finally, the completion of the synthesis was achieved in 90% yield by two steps: (i) Yamaguchi cyclization; (ii) MOM deprotection with TFA (**Scheme 3**).

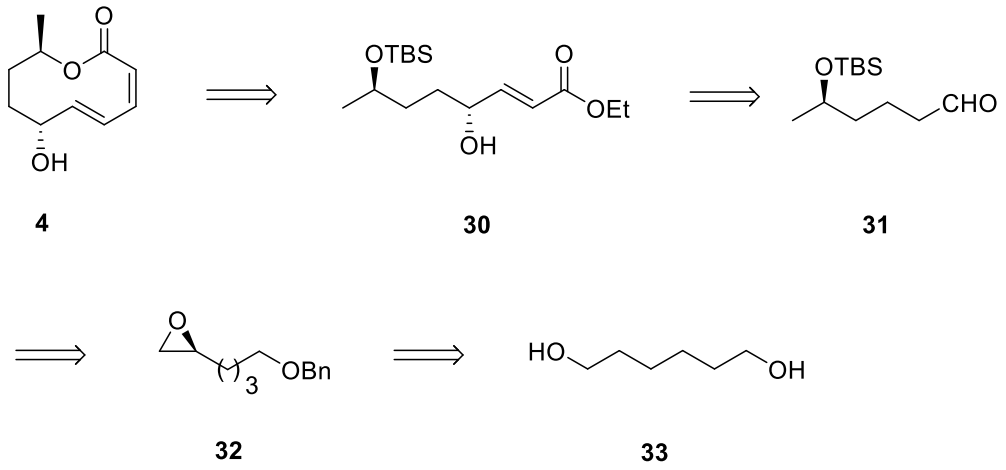


Scheme 3: (i) TBSCl, imid., CH_2Cl_2; (ii) methyl acrylate, Grubb's cat. (1 mol %), CH_2Cl_2, 40 ºC, 1 h; (iii) (a) MOMBr, DIPEA; (b) $Cu(OAc)_2.H_2O$, BDP, PHMS, tBuOH/toluene (2:1), 25 ºC, 12 h, 80%; (iv) DIBAL-H, THF, -78 ºC, 20 min, then MeMgCl, 25 ºC, 1 h, 95%; (v) Novozym-35, isopropenylacetate,chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl)ruthenium(II) ,K_2CO_3, KO*t*Bu, 82%; (vi) (a) TBAF, THF, 20 ºC, 12 h, 92%; (b) vinylacetic acid, DCC, DMAP, CH_2Cl_2, 20 ºC, 2 h, 94%; (vii) (a) Grubbs-II cat., toluene, 80 ºC, 30 min, then NaH, 1 h, then H_2O/H^+; (b) NaOH (4 M), 60 ºC, 30 min, 81% (over two steps); (viii) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene, 80 ºC, 8 h, 65%; (ix) TFA/CH_2Cl_2 (1:4), 25 ºC, 1.5 h, 90% .

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 Stagonolide E (**4**), either employ chiral starting materials or use kinetic resolution protocol for the introduction 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 products based on asymmetric organocatalysis,[7] we became interested in devising a simple concise and flexible route for the synthesis of stagonolide E (**4**). This section describes an enantioselective synthesis of **4**, employing organocatalytic asymmetric α-aminooxylation followed by HWE olefination, Ando's *cis* olefination and modified Yamaguchi protocol as the key steps.



4 **30** **31**

32 **33**

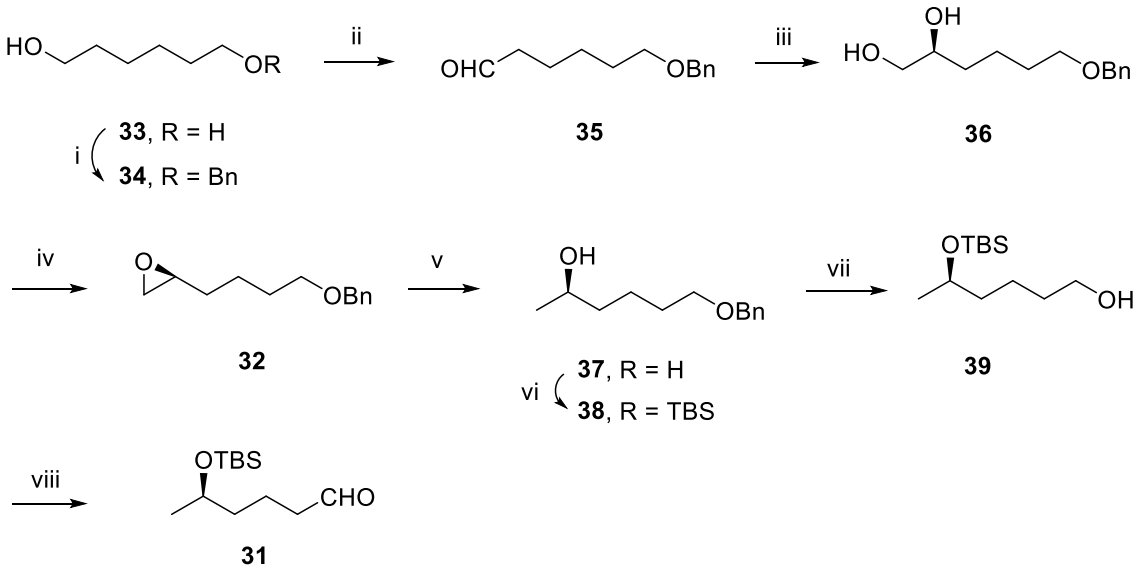
Scheme 4: Retrosynthetic analysis of stagonolide E (**4**)

Based on retrosynthetic analysis, we envisioned that stagonolide E (**4**) can be obtained from γ-hydroxy-α,β-unsaturated ester **30** by *cis*-Wittig olefination followed by intramolecular Yamaguchi cyclization. The key intermediate **30** could in turn be obtained

from aldehyde **31** *via* α-aminooxylation followed by Horner-Wadsworth-Emmons olefination in a sequential manner, while the epoxide **32** was readily obtained from 1,6-hexanediol **33** by standard sequences of reactions of aldehyde, followed by epoxide formation (**Scheme 4**).

2.1.3.2 Results and Discussion

The present synthetic route employed for the synthesis of intermediate aldehyde **31** is shown in **Scheme 5**.



Scheme 5: (i) BnBr, NaH, THF, 0-25 ºC, 96%; (ii) IBX, DMSO, 25 ºC, 2 h, 98%; (iii) PhNO, D-proline (20 mol %), CH_3CN, -20 ºC, 16 h then MeOH, $NaBH_4$, 0 ºC, 45 min; then $CuSO_4$, EtOH, 25 ºC, 10 h, 60%; (iv) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2, 1 h then K_2CO_3, MeOH, 0 ºC, 30 min, 70% ; (v) $LiAlH_4$, THF, 0 ºC, 98%; (vi) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 3 h, 98%; (vii) H_2 (1 atm), 10% Pd/C, EtOAc, 4 h, 96%; (viii) IBX, DMSO, 25 ºC, 2 h, 98%.

Accordingly, the synthesis began with the commercially available 1,6-haxanediol (**33**), which was mono protected as its benzyl ether **34** followed by its oxidation with IBX produced mono protected aldehyde **35** in 98% yield. The formation of aldehyde **35** was confirmed by the appearance of a characteristic aldehydic proton signal at δ 9.71 (s, 1H) in

its ^{1}H NMR spectrum. A typical carbon signal at δ 201.7 in its ^{13}C NMR spectrum due to carbonyl carbon further confirmed its formation (**Fig. 2**).

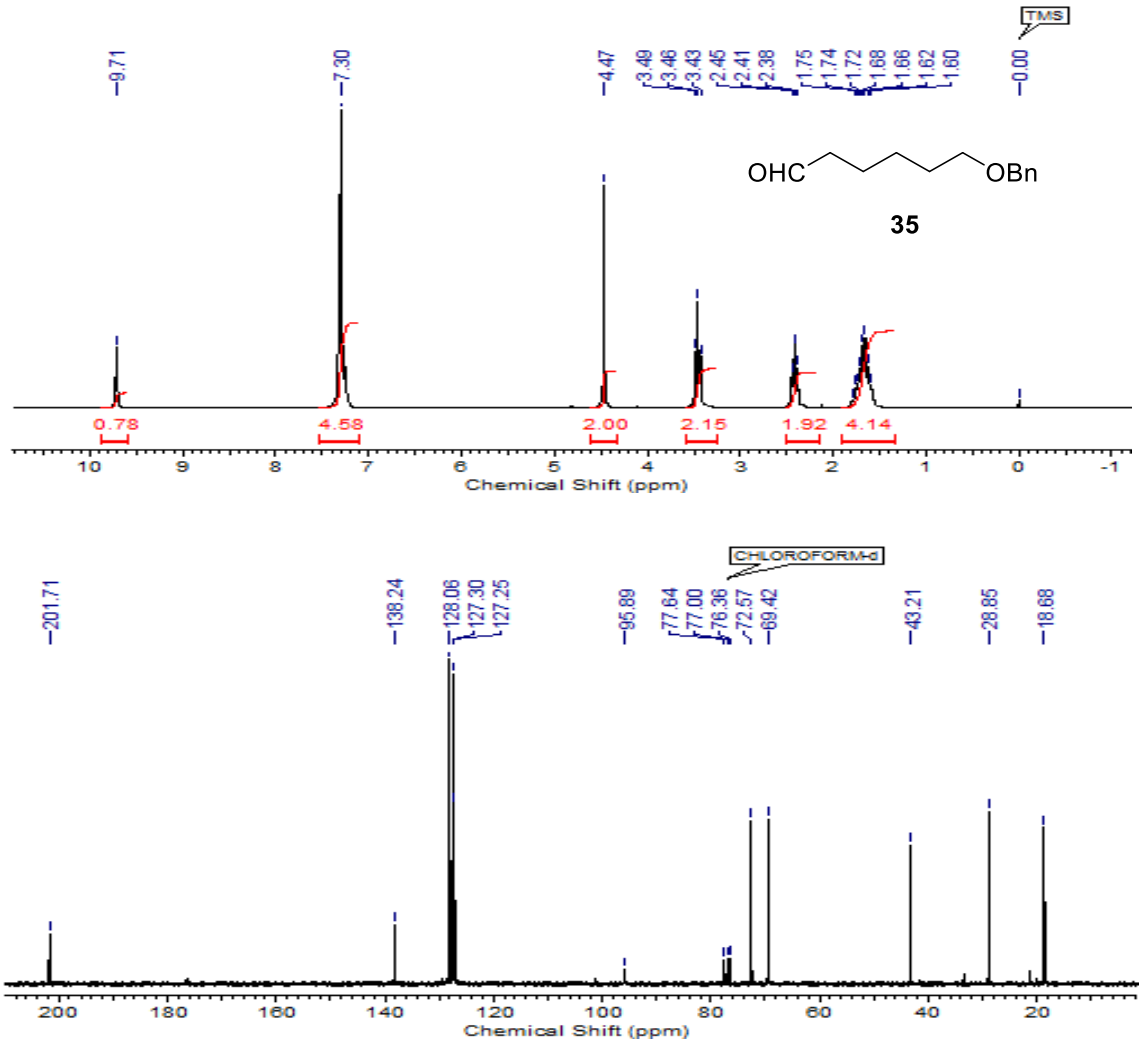


Fig. 2: ^{1}H and ^{13}C NMR spectra of aldehyde **35**

The D-proline catalyzed asymmetric α-aminooxylation[8] of aldehyde **35** gave the chiral diol **36**, which essentially involved two steps: (i) reaction of aldehyde **35** with nitrosobenzene in presence of D-proline as catalyst in CH_3CN at -20 ^{o}C followed by its treatment with

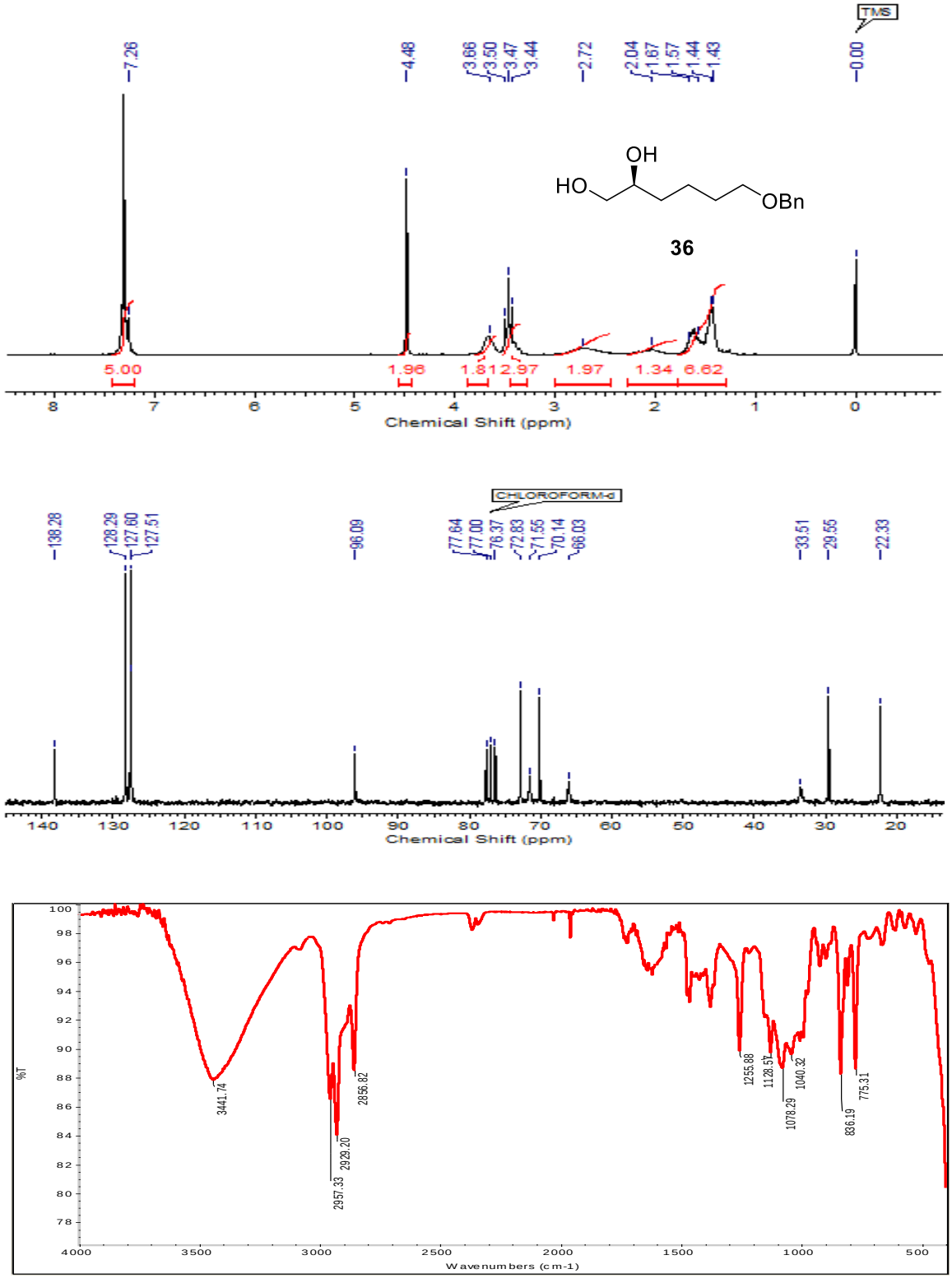


Fig. 3: ^{1}H, ^{13}C NMR and IR spectra of diol **36**

$NaBH_4$ in MeOH at 0 ^oC to give the crude aminooxy alcohol *in situ*; (ii) subsequent reduction of this crude aminooxy alcohol with 30% $CuSO_4$ in EtOH furnished the chiral diol **36** in 60% overall yield and 98% ee (by chiral HPLC analysis); $[\alpha]_D^{25}$ -3.2 (*c* 1.0, $CHCl_3$). Its ^1H NMR spectrum showed multiplets at δ 3.63-3.7 (m, 2H) and 3.40-3.51 (m, 3H) corresponding to protons attached to the oxygen atoms. The typical carbon signals at δ 66.3, 70.1 and 71.5 in its ^{13}C-NMR spectrum are attributed to carbons attached to oxygen atom. Its IR spectrum showed a characteristic strong vibrational stretching frequency at υ_{max} at 3441 cm^{-1} confirming the presence of hydroxyl group (**Fig. 3**).

The selective monotosylation of primary alcohol **36** was then achieved to afford the corresponding tosylate[9] *in situ*, which on treatment with K_2CO_3 in MeOH yielded the terminal chiral epoxide **32** in 70% yield and 98% ee (by chiral HPLC analysis); $[\alpha]_D^{25}$ -5.0 (*c* 2.5, $CHCl_3$). The formation of epoxide **32** was confirmed from its ^1H and ^{13}C NMR spectral analysis. Its ^1H NMR spectrum showed typical three doublet of doublets at δ 2.43 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.71 (dd, *J* = 5.0, 4.0 Hz, 1H) and 2.87 (dd, *J* = 3.9, 2.6 Hz, 1H) corresponding to the protons attached to epoxide ring. Its ^{13}C NMR spectrum displayed two characteristic carbon signals at δ 51.9 and 46.7 due to carbons attached to epoxide ring (**Fig. 4**).

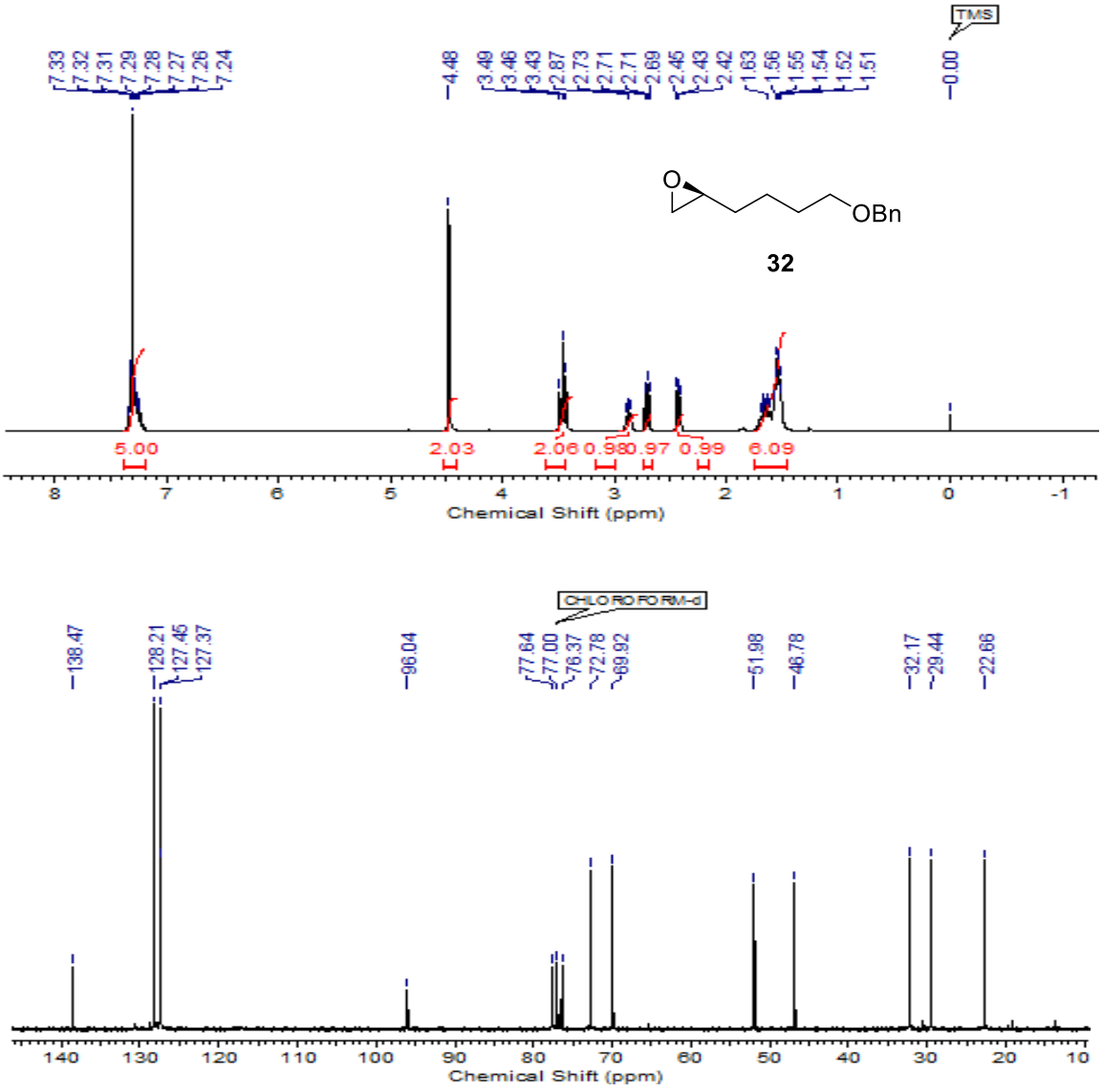


Fig. 4: ^{1}H and ^{13}C NMR spectra of epoxide **32**

The chiral epoxide (-)-**32** was subsequently subjected to regioselective reductive ring opening with $LiAlH_4$ in THF at 0 ^{o}C that afforded the secondary alcohol **37** as the exclusive product in 98% yield, which was then protected as its TBS ether **38** (TBSCl, imid). Its ^{1}H NMR spectrum showed signals at δ 3.66-3.77 (m, 1H) and 4.45 (s, 2H) indicative of methine (-CH-OTBS) and methylene ($-OCH_2$-Ph) protons respectively. The

signals at δ -4.6, -4.3, 18.1 and 25.9 in its ^{13}C NMR spectrum are attributed to carbons of TBS ether functionality, while the resonance peaks at δ 72.0 and 68.5 account for methine (-**C**H-OTBS) and methylene (-O**C**H_2-Ph) carbons respectively (**Fig. 5**).

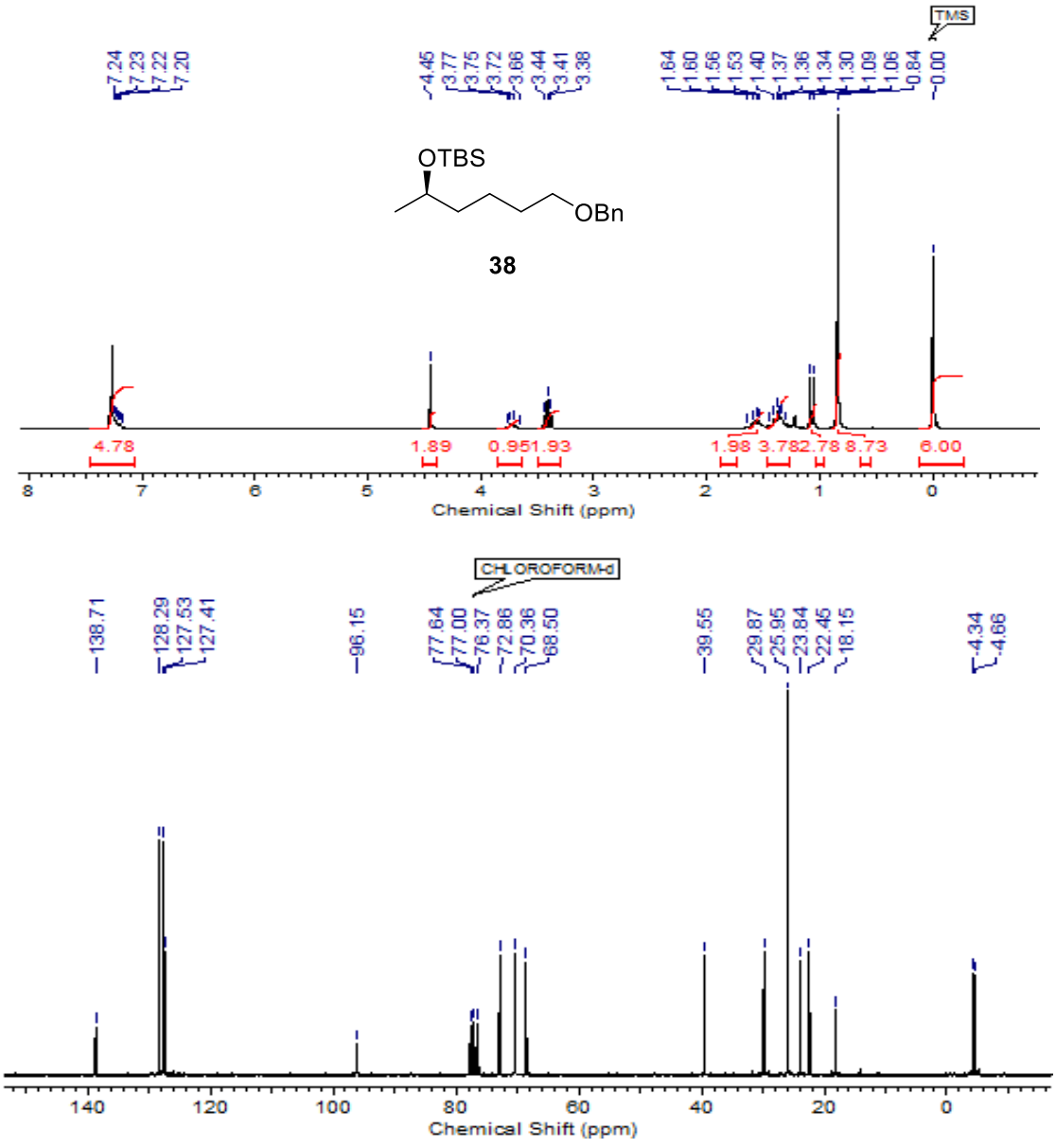


Fig. 5: ^{1}H and ^{13}C NMR spectra of compound **38**

The benzyl ether in **38** was selectively deprotected under hydrogenolysis conditions [10% Pd/C, H_2 (1 atm), EtOAc] to give the primary alcohol **39** in 96% yield. The formation of

the primary alcohol **39** was confirmed by the disappearance of proton signals due to [Ph-CH_2] group and the occurrence of a typical broad singlet at δ 1.83 (s, 2H) in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 62.5 corresponding to the methylene carbon attached to –OH group (**Fig. 6**). Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} at 3440 cm^{-1} indicating the presence of hydroxyl group.

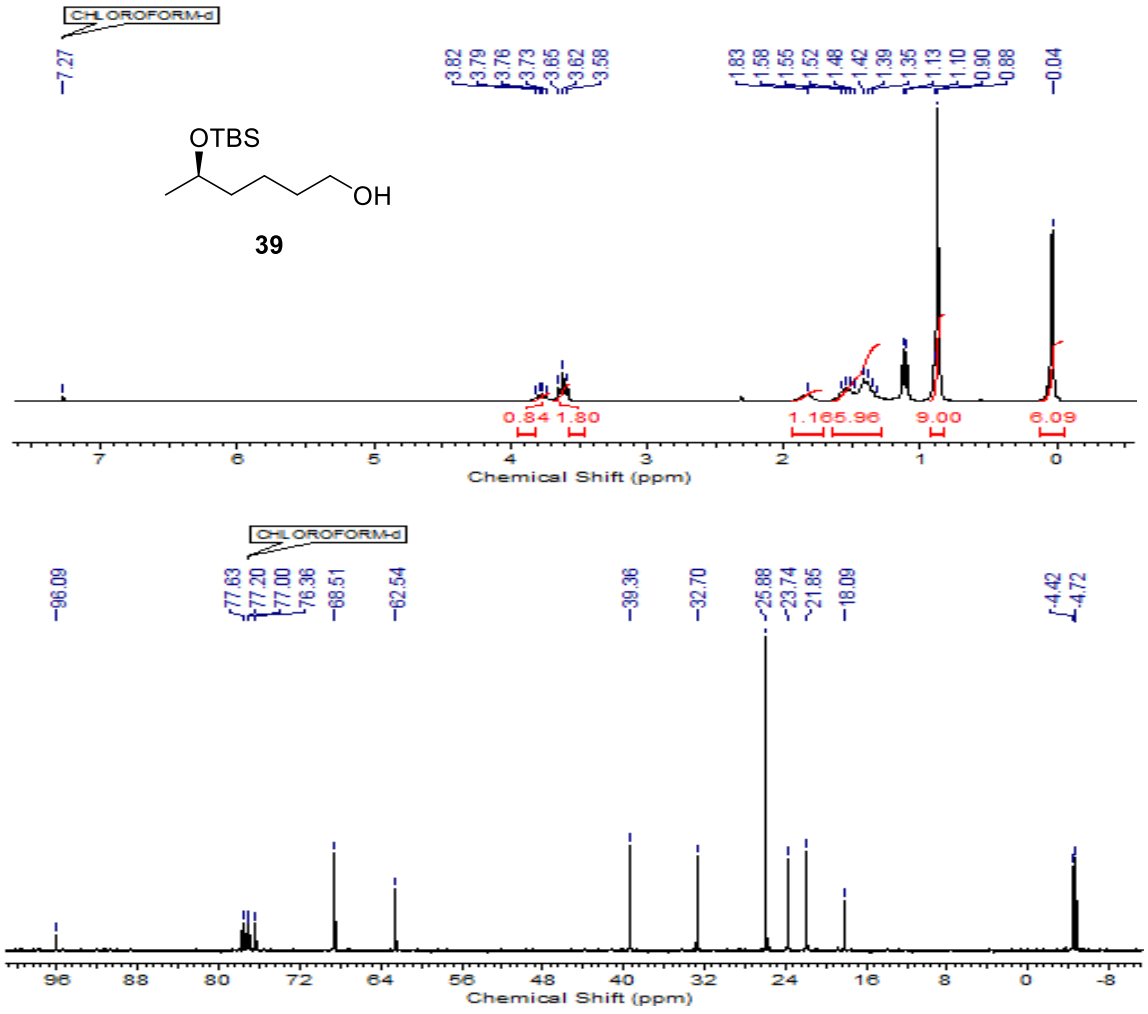


Fig. 6: ^{1}H and ^{13}C NMR spectra of primary alcohol **39**

The IBX oxidation of alcohol **39** in DMSO produced the key intermediate aldehyde **31** in 98% yield. The appearance of a characteristic triplet at δ 9.71 (t, *J* = 1.7 Hz, 1 H) due to the aldehydic proton in its ^{1}H NMR spectrum confirmed the formation of intermediate aldehyde **31**. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 202.0 due to the aldehydic carbon (**Fig. 7**). Its IR spectrum displayed a characteristic strong vibrational stretching frequency at υ_{max} at 1725 cm^{-1} due to the carbonyl group.

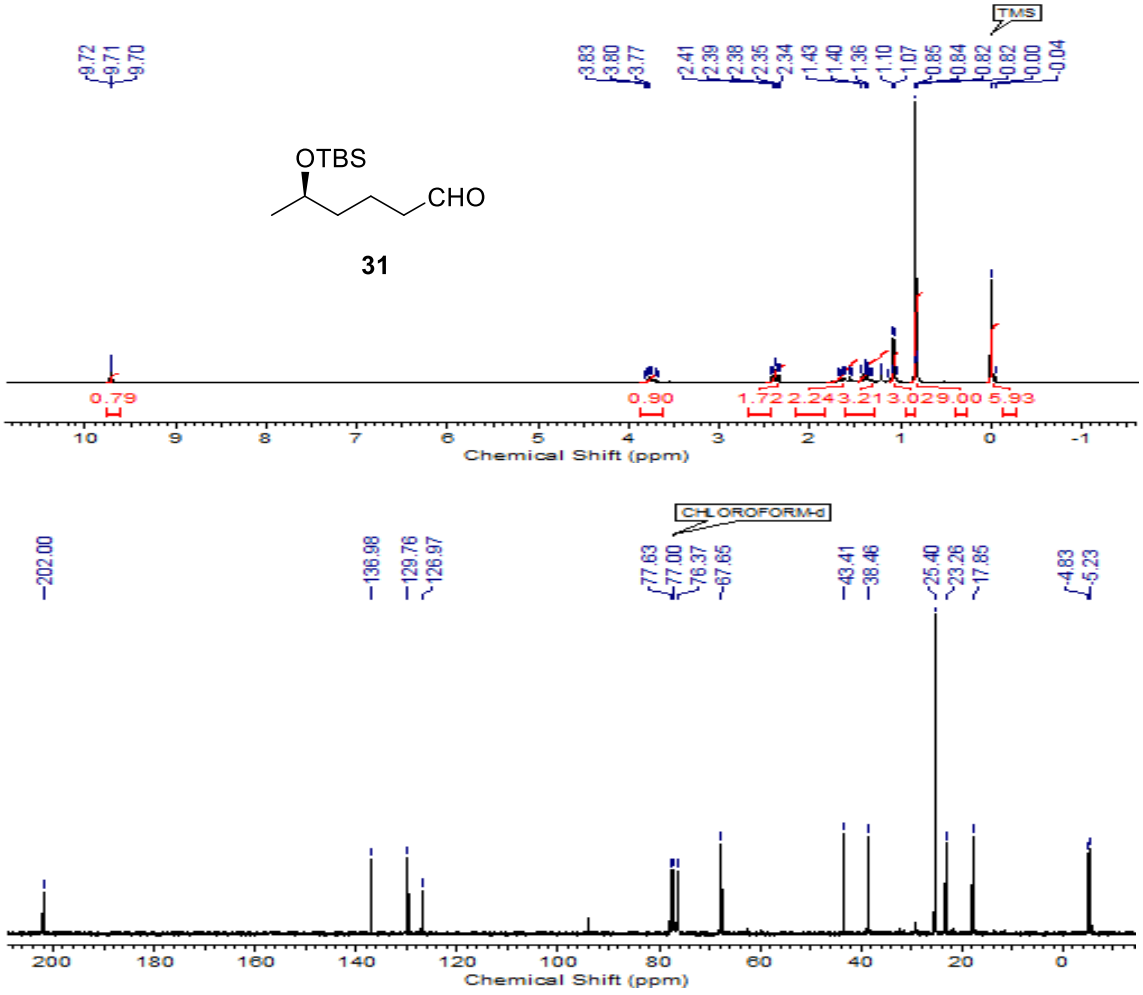
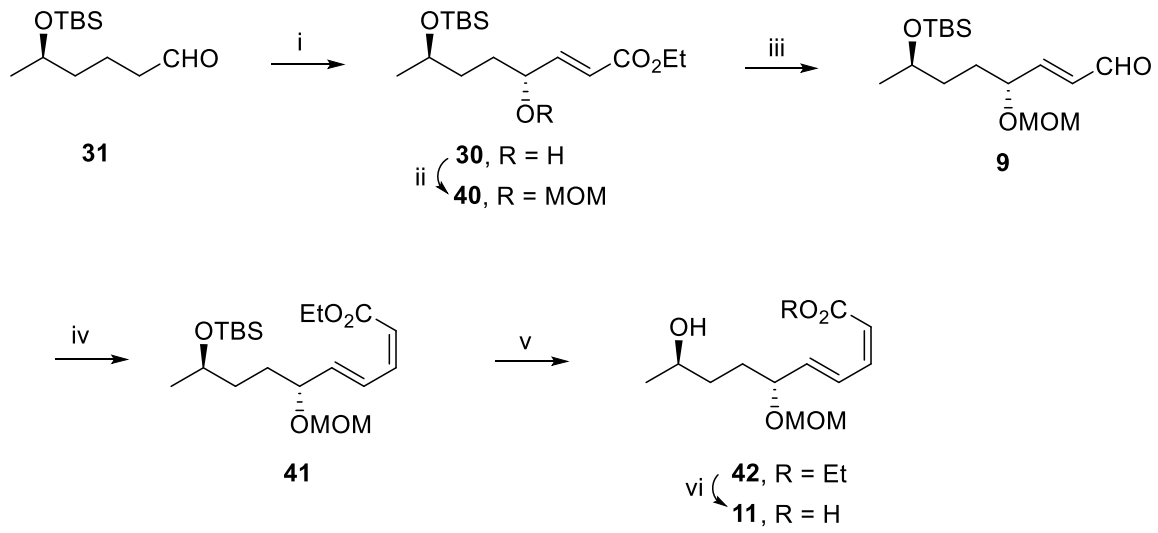


Fig. 7: ^{1}H and ^{13}C NMR spectra of aldehyde **31**

Scheme 6 shows the synthetic sequences for the formation of *seco* acid **11**.



Scheme 6: (i) PhNO, L-proline (20 mol %), CH_3CN, -20 °C, 16 h then triethyl phosphonoacetate, DBU, LiCl, 0 °C, 1 h; then $CuSO_4$, EtOH, 25 °C, 8 h, 65%; (ii) MOMCl, DIPEA, CH_2Cl_2, 0-25 °C, 3 h, 90%; (iii) DIBAL-H, dry toluene, -78°C, 1 h, 96%; (iv) ethyl (diphenoxylphosphinoxy) acetate , dry THF, 0 °C, 1 h, 92%, (*Z,E/E,E* = 97:3); (v) TBAF, THF, 0 °C, 1 h, 88%; (vi) LiOH, MeOH/ THF/ H_2O (3:1:1), 2 h, 90%.

The one-pot sequential asymmetric aminooxylation-HWE olefination[10] reaction of aldehyde **31** was readily carried out using L-proline as the organocatalyst in CH_3CN at -20 °C, which resulted in the formation of γ-hydroxy-α,β-unsaturated ester **30** in 65% yield and 98% de;[11] $[\alpha]_D^{25}$ -13.1 (*c* 1.8, $CHCl_3$). The formation of **30** was confirmed by the analysis of its ^1H and ^{13}C NMR spectra. The two doublet of doublets at 6.92 (dd, *J* = 15.7, 4.3 Hz, 1H) and 6.02 (dd, *J* = 15.6, 5.1 Hz, 1H) in its ^1H NMR spectrum are indicative of the olefinic protons. Also a quintet at δ 4.19 (quint, *J* = 14.5, 6.5 Hz, 2H) and a triplet at δ (t, *J* = 6.8 Hz, 3H) are due to the methylene protons (-OC**H**$_2$CH$_3$) and methyl protons (-OCH$_2$C**H**$_3$) respectively.

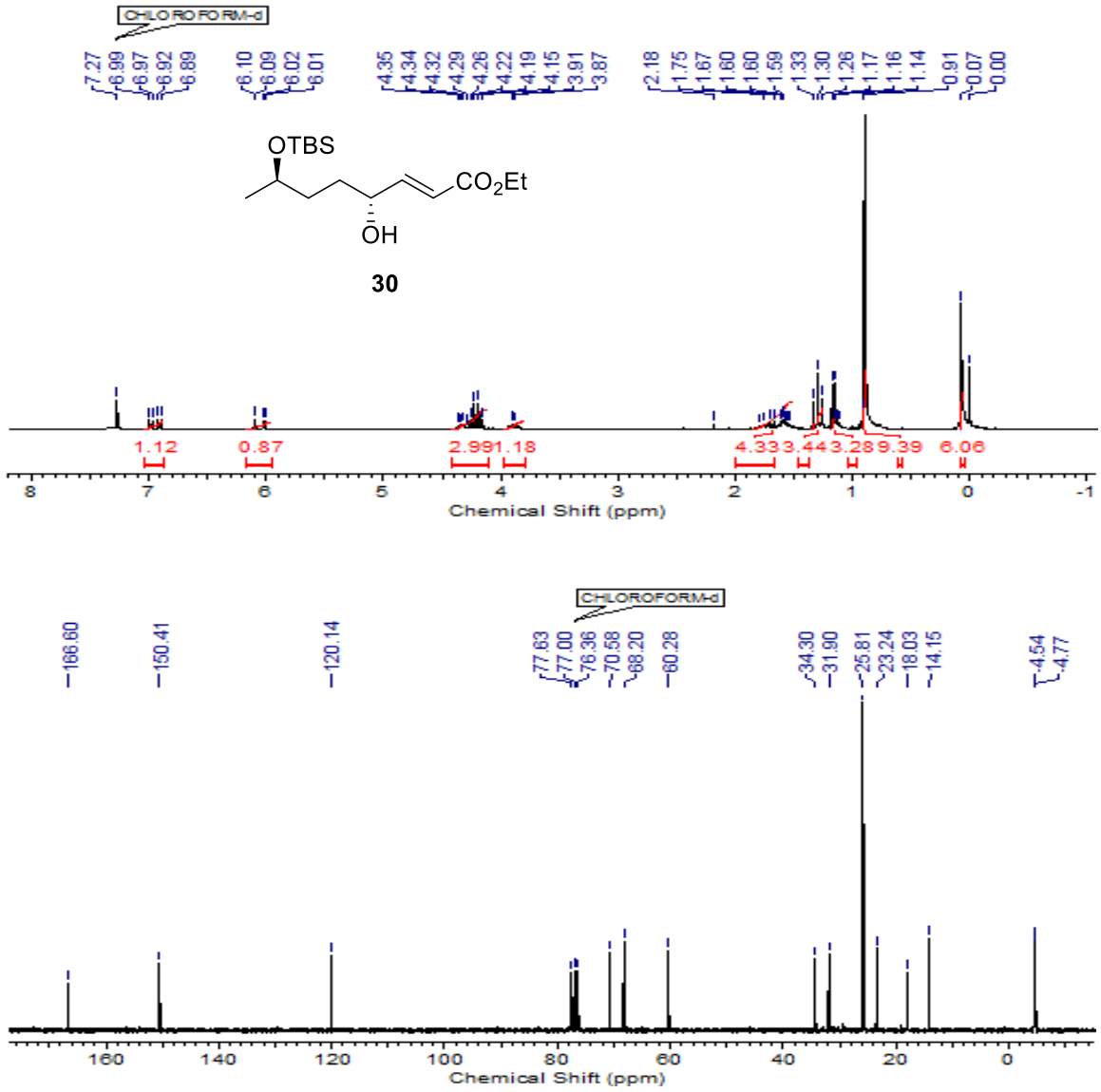
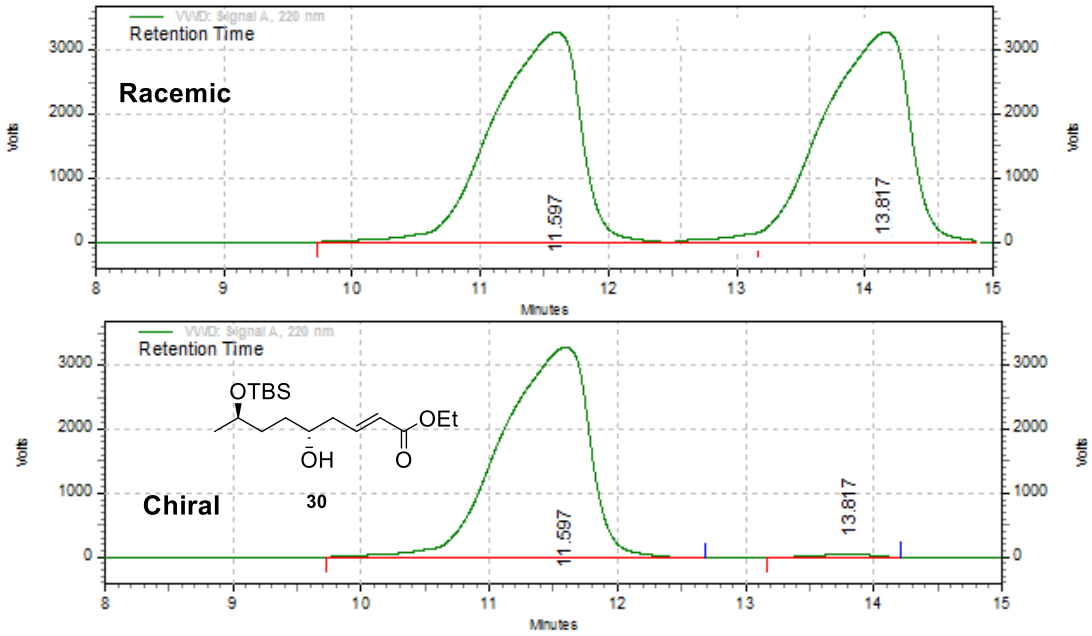


Fig. 8: ^{1}H and ^{13}C NMR spectra of γ-hydroxy-α,β-unsaturated ester **30**

The appearance of typical carbon signals 150.4 and 120.1 in its ^{13}C NMR spectrum due to olefinic carbons confirmed the formation of **30** (**Fig. 8**). Its IR spectrum showed characteristic strong vibrational stretching frequencies at υ_{max} 3425 and 1716 cm^{-1} indicative of the presence of hydroxyl and ester functional groups respectively. The optical purity of chiral γ-hydroxy-α,β-unsaturated ester **30** was determined to be 98% ee from

chiral HPLC analysis [Chirapak AD-H, 2-Propanol/n-Hexane = 2.5/97.5, flow rate 0.5 mL/min, λ = 220 nm, retention time: (minor) 11.59 min, (major) 13.81 min, ee 98%] (**Fig**.**9**).



Retention Time	Area	Area %	Height	Height %
11.597	2584819245	99.06	55143498	98.28
13.817	24412986	0.94	965125	1.72

Fig. 9: HPLC chromatogram of γ-hydroxy-α,β-unsaturated ester **30**

Then the chiral secondary alcohol functionality in **30** was protected as its MOM ether **40** (MOMCl, DIPEA) and the ester function in **40** was selectively reduced (DIBAL-H, toluene, -78 ^{o}C) to the corresponding aldehyde **9** in 96% yield. The ^{1}H NMR spectrum showed two doublet of doublet at δ 6.73 (dd, *J* = 6.0, 5.8 Hz, 1H) and 6.31 (dd, *J* = 7.1, 7.7 Hz, 1H) due to olefinic protons and a doublet at δ 9.57 (d, *J* = 7.8 Hz, 1H) due to aldehydic proton respectively. Its ^{13}C NMR spectrum showed typical carbon signals at δ 131.9 and 156.0 due to olefinic carbons and other signal at δ 192.5 due to the carbonyl carbon

respectively (**Fig. 10**). Its IR spectrum displayed a strong vibrational stretching frequency at υ_{max} 1720 cm^{-1} confirming the presence of aldehydic carbonyl group.

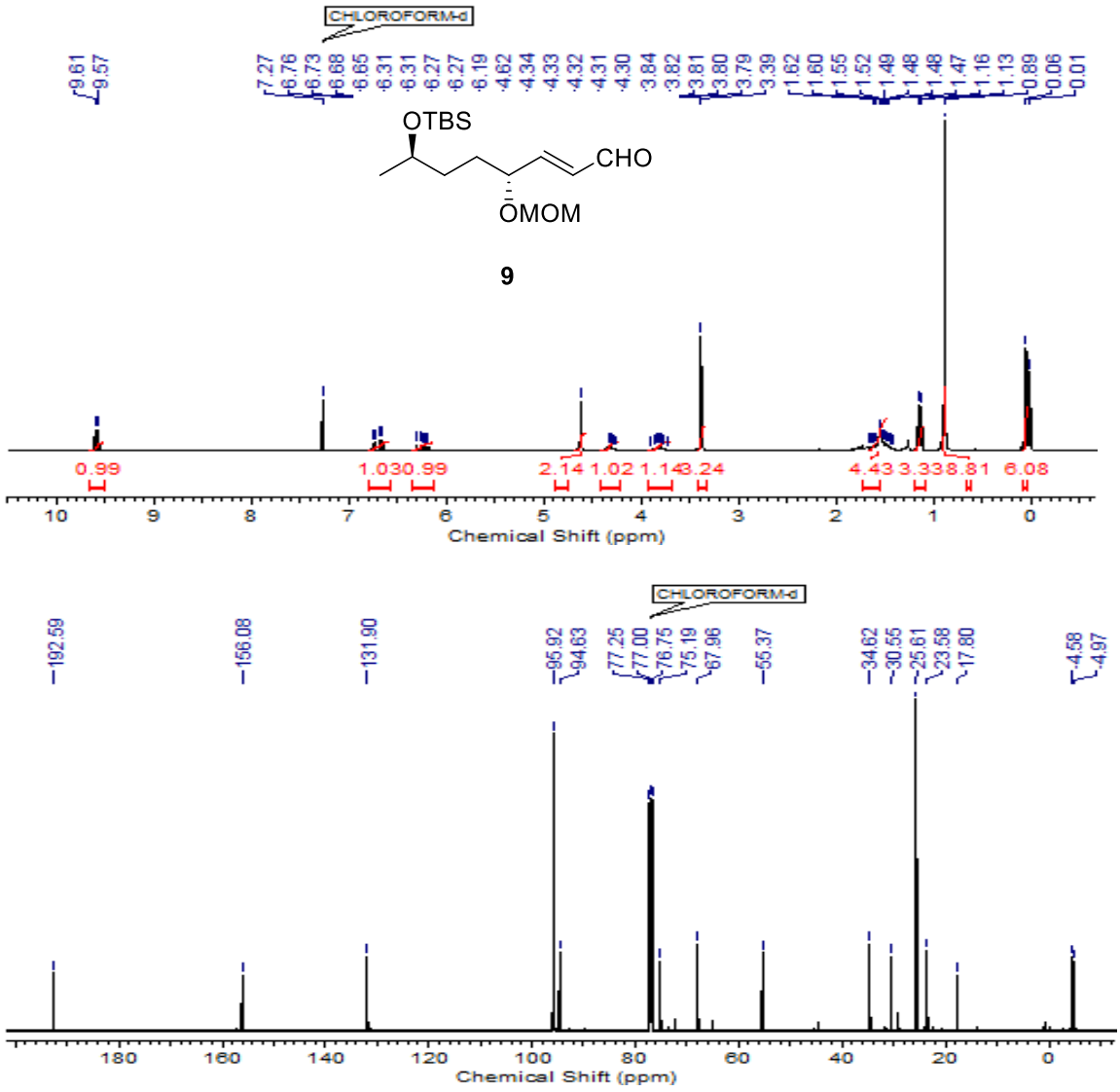


Fig. 10: ^{1}H and ^{13}C spectra of aldehyde **9**

Aldehyde **9** was then subjected to *cis* selective HWE-olefination by Ando's protocol[12] using ethyl (diphenoxylphosphinoxy) acetate, NaH at 0 ^{o}C to give ester **41** in 88% yield with excellent stereoselectivity (*Z,E*/*E,E* = 97:3). The formation of dienic ester **41** was confirmed by its ^{1}H NMR spectrum, which showed typical signals at δ 7.47 (dd, *J* = 11.5,

15.0 Hz, 1H), 6.55 (t, *J* = 11.5 Hz, 1H), 5.88 (dd, *J* = 15.0, 8.0 Hz, 1H) and 5.68 (d, *J* = 11.5 Hz, 1H) due to the olefinic protons. Its ^{13}C NMR spectrum showed typical signals at δ 165.9 due to the ester carbonyl carbon and other signals at δ 118.0, 127.9, 143.2 and 143.6 due to olefinic carbons respectively (**Fig. 11**). Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} 1726 cm^{-1} due to the presence of ester carbonyl group.

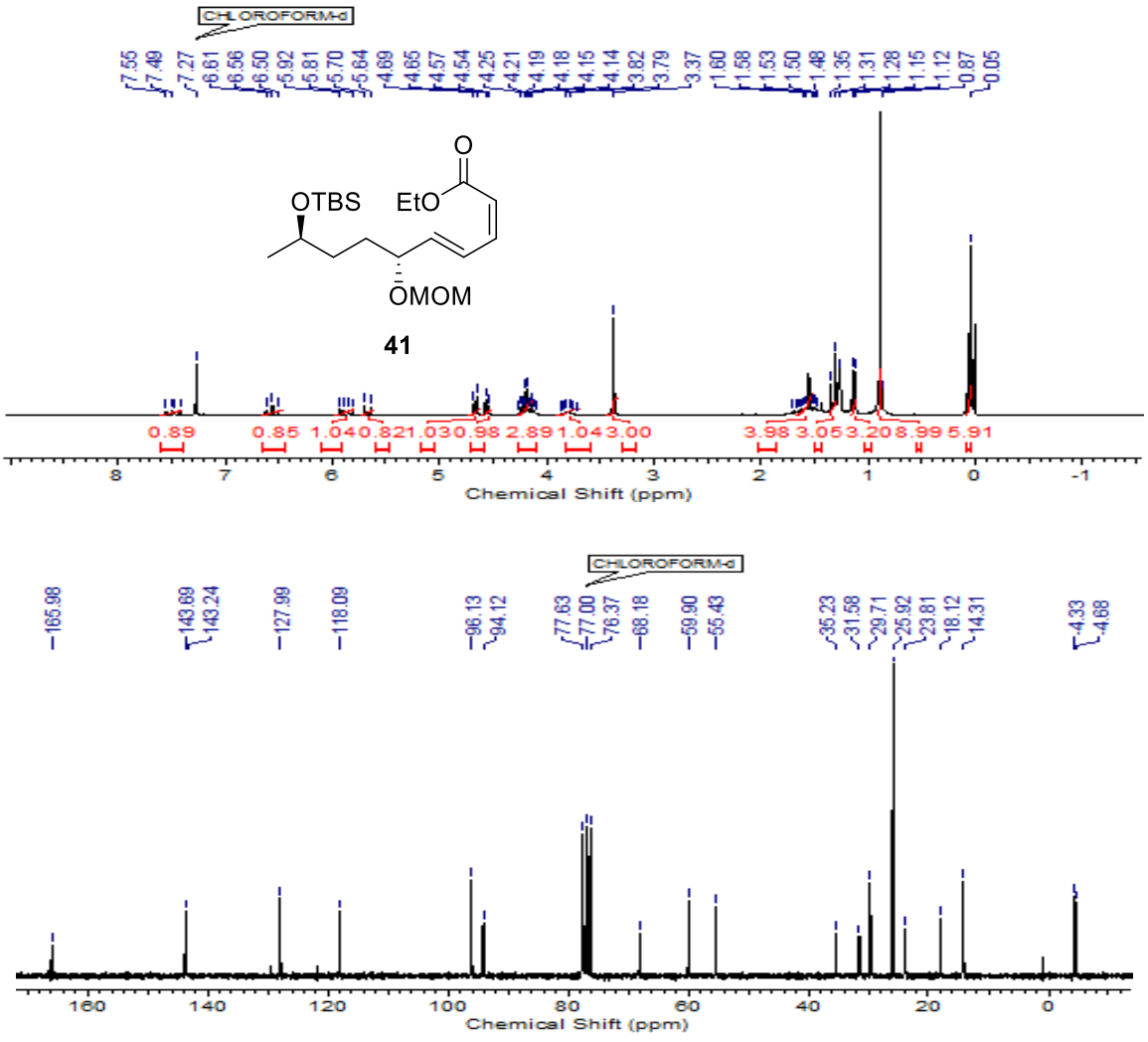
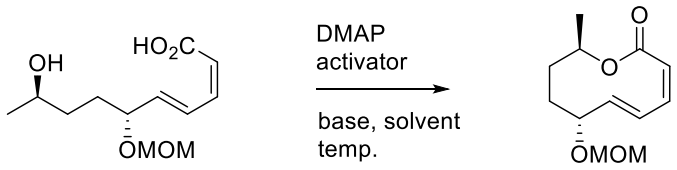


Fig. 11: ^{1}H and ^{13}C NMR spectra of ester **41**

The deprotection of TBS group in **41** followed by ester hydrolysis in **42** with LiOH gave *seco* acid **11** (**Scheme 6**). The *seco*-acid **11** was next subjected to standard Yamaguchi

cyclization[13] conditions that afforded the macrolactone MOM ether **12** but in low yield (21%). In order to improve the yield of the cyclization step, several experiments on optimization of macrolization were carried out and the results are presented in Table **1**.

Table 1: Optimization study for the macrocyclization of *seco* acid **11**



11 **12**

entry	activator (1 equiv)	base	solvent	T (°C)	yield of **12** (%)[b]
1	DCC		CH_2Cl_2	25	10
2	cyanuric chloride		CH_3CN	25	12
3	2,4,6-trichlorobenzoyl chloride	NEt_3	benzene	80	18
		NEt_3	toluene	110	21
		NEt_3	toluene	25	30
		NEt_3	THF	25	15
		iPr_2NEt	toluene	80	20
		NEt_3	toluene	25	65[c]
4	2-methyl-6-nitrobenzoic anhydride	NEt_3	toluene	25	62[c]

a: *seco*-acid **11** (5 mmol) used; b: isolated yield after column chromatographic purification; c: slow addition of *seco*-acid **11** dissolved in toluene was carried out.

Firstly, the cyclization was attempted using DCC and DMAP (10 mol %) in CH_2Cl_2 solvent, but resulted in poor yield (10%) of the macrolactone **12**. Subsequently, cyanuric chloride was used as an activator in CH_3CN, however found no improvement in the yield (12%) of the macrolactone. Under the Yamaguchi cyclization conditions with variation in bases and solvents, it gave a marginally improved yield (30%). Notably, the best yield of

the desired macrolactone **12** (65% isolated yield) was obtained using a modification of Yamaguchi's cyclization, wherein the *seco* acid **11** was added slowly to a stirred solution of DMAP, 2,4,6-trichlorobenzoyl chloride and triethylamine in dry toluene at room temperature. 2-Methyl-6-nitrobenzoic anhydride (MNBA)[14] was also found to be quite effective as an activating agent (62% yield). The formation of macrolactone **12** was confirmed from its ^{1}H NMR spectrum, where signals at δ 5.64 (dd, *J* = 9.6, 15.4 Hz, 1H), 5.85 (d, *J* = 10.5 Hz, 1H,), 6.16 (d, *J* = 15.1 Hz, 1H) and 6.62 (d, *J* = 10.3 Hz, 1H)

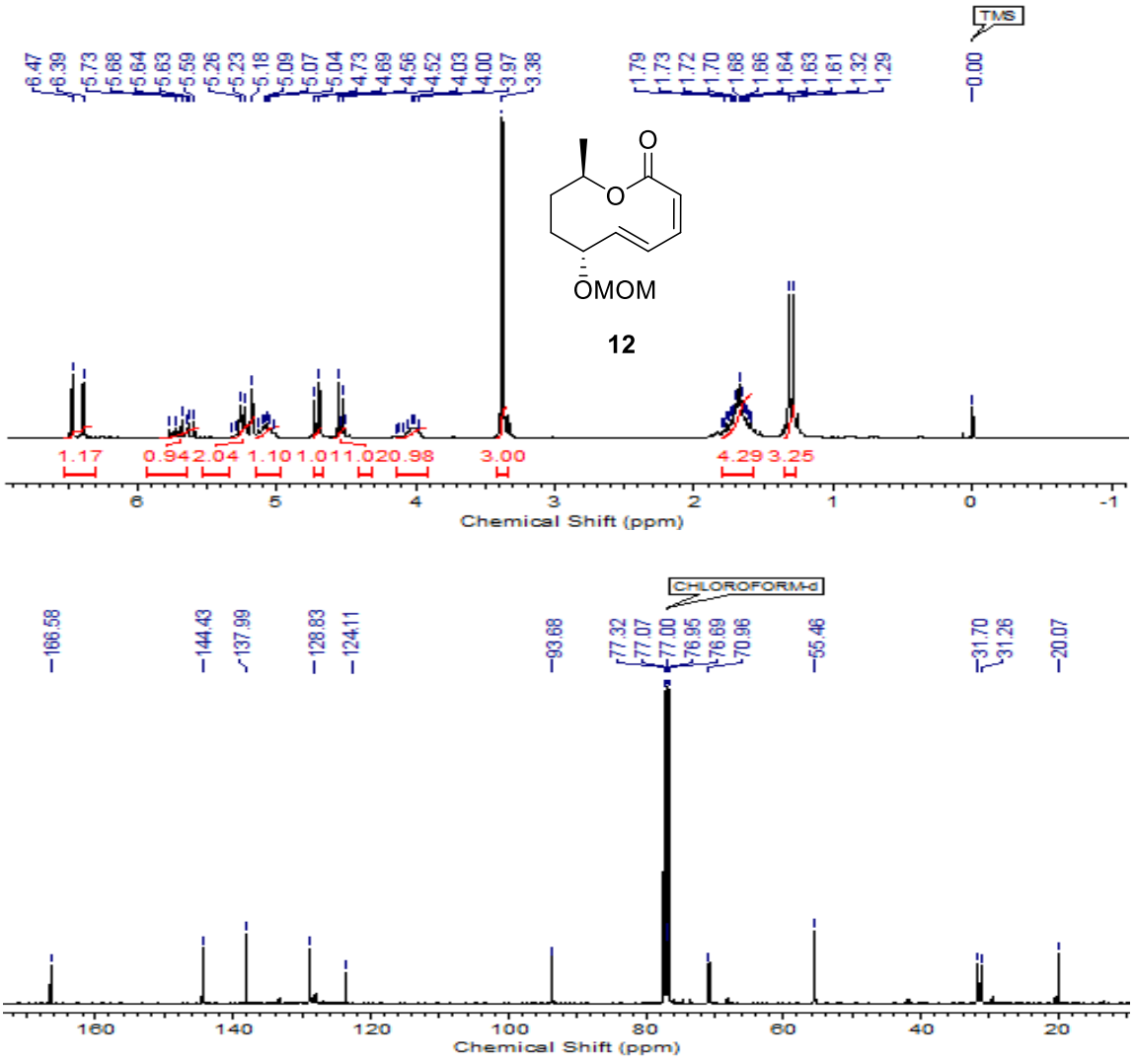


Fig. 12: ^{1}H and ^{13}C NMR spectra of macrolactone MOM ether **12**

correspond to the olefinic protons. A typical singlet at δ 3.35 (s, 3H) indicated the presence of methyl protons (C**H**$_3$-O) of the MOM group. Its ^{13}C NMR spectrum displayed a characteristic carbon signal at δ 168.5 due to the lactone carbonyl carbon (**Fig. 12**). Its IR spectrum showed a typical strong vibrational stretching frequency at υ_{max} 1710 cm^{-1} due to the presence of lactone carbonyl functional group. Its molecular mass [($C_{12}H_{18}O_4$)Na] (M+Na) was found to be 249.1089, which was well-matched with the calculated value 249.1103 (**Fig. 13**).

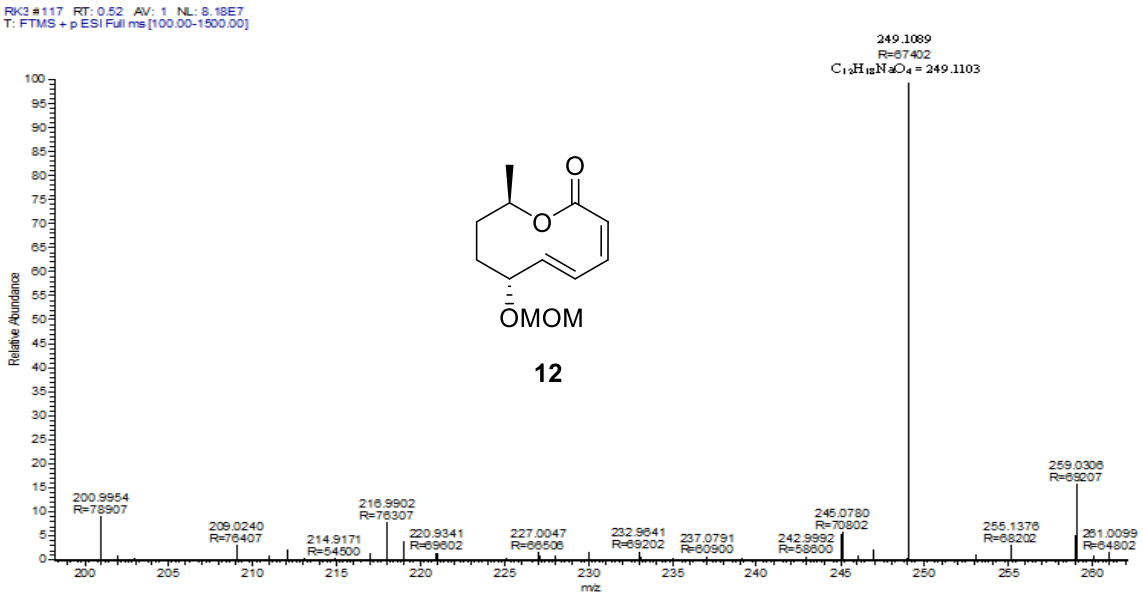


Fig. 13: HRMS spectrum of macrolactone **12**

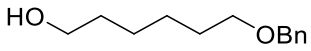
Finally, acid catalyzed removal of MOM group using 2N HCl in THF furnished the target molecule, stagonolide E (**4**) in 88% yield. The enantiomeric purity of **4** was determined to be 98% ee based on the comparison of its specific rotation with the reported value $[\alpha]_D^{25}$ -177.3 (*c* 0.48, $CHCl_3$) {lit.[4a] $[\alpha]_D^{25}$ -181 (*c* 0.28, $CHCl_3$)}. The spectral data of the synthetic molecule **4** thus obtained matched very well with the reported values.[15]

2.1.4 Conclusion

In summary, a stereoselective total synthesis of stagonolide E (**4**) was accomplished (8.5% overall yield; 98% ee) *via* an organocatalytic approach employing easily accessible starting materials. The strategy employed simple reaction sequences giving good yields, and requires relatively low amount of inexpensive and non-toxic commercially available proline as the catalyst. This new approach would permit maximum variability in product structure with regard to stereochemical diversity, which is important for making various synthetic analogues of stagonolides.

2.1.5. Experimental Procedure:

6-(Benzyloxy)hexan-1-ol (34)

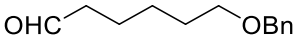


To a stirred solution of NaH (5.58 g, 139.7 mmol) in dry THF (100 mL), a solution of 1,6-hexanediol **33** (15 g, 127 mmol) in dry THF (100 mL) was added dropwise at 0 ^{o}C followed by the addition of benzyl bromide (19.5 g, 114.3 mmol). The reaction mixture was stirred for 6 h at 25 ^{o}C. After the completion of the reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride and the product was 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 (4:1 v/v) gave 6-(benzyloxy)hexan-1-ol **34** as colourless viscous liquid.

Yield: 25.4 g, 96%; viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3353, 3030, 2987,1590, 1389,1095, 980, 857; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.4 (m, 4H), 1.6 (m, 4H), 1.8 (br s, 1H), 3.4 (t, *J* = 5.3 Hz, 2H), 3.6 (t, *J* = 6.3 Hz, 2H), 4.5 (s, 2H), 7.3-7.4 (5H, m); **^{13}C NMR**

(50 MHz, $CDCl_3$): δ 25.6, 26.0, 29.7, 32.6, 62.6, 70.2, 72.8, 127.5, 127.6, 128.3, 138.5; **Anal. Calcd** for $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68; Found: C, 74.90; H, 9.69%.

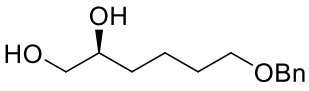
6-(Benzyloxy)hexanal (**35)**



To a well stirred solution of alcohol **34** (10 g, 48.0 mmol) in dry DMSO (100 mL), 2-iodoxybenzoic acid (26.8 g, 96.0 mmol) was added in one portion. The reaction mixture was then stirred for 2 h at 25 ºC. After completion of the reaction (monitored by TLC), itwas 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/ethyl acetate (19:1 v/v) gave the aldehyde **35** as colourless free flowing liquid.

Yield: 9.7 g, 98% yield; colourless free flowing liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3065, 3030, 2987, 1725, 1520, 1105, 1090, 956, 790; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.4 (m, 4H), 1.6 (m, 4H), 2.4 (t, *J* = 6.2 Hz, 2H), 3.5 (t, *J* = 5.8 Hz, 2H), 4.5 (s, 2H), 7.2-7.4 (m, 5H), 9.8 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.9, 25.8, 29.5, 43.8, 70.0, 72.9, 127.50, 127.6, 128.4, 138.5, 202.7; **Anal. Calcd** for $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80 ; Found: C, 75.64; H, 8.82 %.

(*S*)-6-(Benzyloxy)hexane-1,2-diol (36)



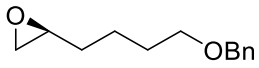
To a pre-cooled solution of aldehyde **35** (5 g, 24.23 mmlol) in CH_3CN (30 mL) at -20 ºC, nitrosobenzene (2.6 g, 24.23 mmol) and D-proline (0.55 g, 4.84 mmol) were added. The

reaction was then stirred at -20 ^{o}C for 24 h. Then it was diluted with MeOH (20 mL) at 0 ^{o}C, $NaBH_4$ (1.8 g, 48.46 mmol) was added to it and stirred for 30 min. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride. Then solvent was evaporated and the residue was extracted with EtOAc (3x50 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, concentrated to give the crude aminooxy alcohol, which was directly used for the next step without purification.

To a EtOH (50 mL) solution of the crude aminooxyalcohol was added $CuSO_4 \cdot 5H_2O$ (1.8 g, 7.26 mmol) at 0 ^{o}C. The reaction mixture was allowed to stir for 10 h at this temperature. After the addition of the phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3x50 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude diol, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4 v/v) to give **36** as a wine coloured viscous liquid.

Yield: 3.2 g, 60%; wine coloured viscous liquid; **$[\alpha]_D^{25}$** – 3.2 (*c* 1, $CHCl_3$) {lit.[1] $[\alpha]_D^{25}$ – 3.3 (*c* 1.0, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3439, 3102, 1516, 1470, 1325, 1170, 1050, 892; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.5 (m, 6H), 2.6 (br s, 2H), 3.4 (m, 3H), 3.6 (m), 2H), 4.5 (s, 2H), 7.2-7.4 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.4, 29.6, 33.6, 66.1, 70.2, 71.6, 72.9, 127.5, 127.6, 128.3, 138.3; **Anal. Calcd** for $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99; Found: C, 69.54; H, 9.05%; **Optical purity**: 98% ee determined by HPLC analysis (Chiracel AD-H column, Hex/*i*-PrOH 90:10, 0.5 mL/min, 220 nm). Retention time: t_{major}= 26.12 min and t_{minor}= 28.38 min.

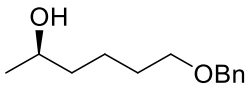
(*S*)-2-(4-(Benzyloxy)butyl)oxirane (32):



To a stirred solution of diol **36** (3 g, 13.38 mmol) in CH_2Cl_2 (30 mL) were added Bu_2SnO (0.66 g, 2.67 mmol), *p*-TsCl (2.5 g, 13.38 mmol) and Et_3N (1.8 mL, 13.38 mmol). The reaction mixture was stirred until TLC indicated complete consumption of the starting material. The mixture was filtered, and the filtrate was concentrated in *vacuo*. Then to the crude in MeOH (20 mL) at 0 ^oC, K_2CO_3 (3.6 g, 26.76 mmol) was added and stirred for 1 h. After completion of the reaction (monitored by TLC), solvent was evaporated and organic layer was extracted with EtOAc (3x50 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4 concentrated to give the crude product, which on column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) provided the oxirane **32**.

Yield: 1.93 g, 70% yield; colourless viscous liquid; **$[\alpha]_D^{25}$** - 5.0 (*c* 2.5, $CHCl_3$) {lit.[2] $[\alpha]_D^{25}$ – 5.1 (*c* 2, $CHCl_3$)}; **IR** ($CHCl_3$,cm^{-1}): υ_{max} 3032, 2859, 1637, 1496, 1454, 1410, 1362, 1142, 1010, 852, 780; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.51–1.66 (m, 6H), 2.43 (dd, *J* = 2.8, 5.2 Hz, 1H), 2.69 (dd, *J* = 4.0, 5.1 Hz, 1H), 2.86–2.88 (m, 1H), 3.46 (t, *J* = 6.0 Hz, 2H), 4.48 (s, 2H), 7.26-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.8, 29.6, 32.3, 46.9, 52.1, 70.1, 72.9, 127.5, 127.6, 128.3, 138.6; **Anal. Calcd** for $C_{13}H_{18}O_2$; C, 75.69; H, 8.80; Found: C 75.59; H 8.71%.

(*R*)-6-(Benzyloxy)hexan-2-ol (37)



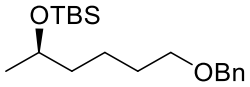
To a stirred solution of $LiAlH_4$ (1.01 g, 26.66 mmol) in dry THF (30 mL), a solution of epoxide (-)-**32** (5.0 g, 24.24 mmol) in dry THF (30 mL) was added dropwise at 0 ^oC. The

reaction was stirred at the same temperature for 30 min. After the completion of reaction (monitored by TLC), it was quenched with aq. 20% solution of sodium hydroxide (5 mL) at 0 ^{o}C. The reaction mixture was filtered through sintered funnel, dried over anhyd. Na_2SO_4 and concentrated. Purification by column chromatography with petroleum ether/ethyl

acetate (9:1 v/v) gave the secondary alcohol **37** as colourless free flowing liquid.

Yield: 4.9 g, 98% yield; colourless free flowing liquid; **$[\alpha]_D^{25}$** - 7.78 (*c* 2.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3454, 3214, 3010, 2935, 1657, 1460, 1416, 1375, 1300, 1050, 790; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15 (d, *J* = 6.2 Hz, 3H), 1.41–1.70 (m, 6H), 2.0 (br s, 1H), 3.46 (t, *J* = 6.2 Hz, 2H), 3.70–3.79 (m, 1H), 4.48 (s, 2H), 7.29–7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.4, 23.5, 29.7, 39.0, 67.6, 70.3, 72.9, 127.5, 127.6, 128.3, 138.5; **Anal. Calcd** for $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68; Found C, 74.81; H, 9.54%.

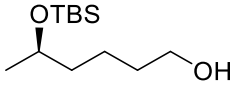
(*R*)-[6-(Benzyloxy)hexan-2-yloxy]-*tert*-butyldimethylsilane (38)



To a solution of alcohol **37** (4.50g, 21.60 mmol) in dry CH_2Cl_2 (80 mL) at 0 ^{o}C were 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 ^{o}C 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 the solvent under reduced pressure gave the crude product which was then purified by column chromatography with pure petroleum ether to give **38** as a colorless viscous liquid.

Yield: 6.83 g, 98%; colorless viscous liquid; **[α]D^{25}** -9.8 (*c* 2., $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3215, 3052, 2929, 2856, 1471, 1462, 1455, 1373, 1361, 1110, 1020, 852; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.33–1.63 (m, 6H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.72–3.81 (m, 1H), 4.48 (s, 2H), 7.31–7.33 (m, 5H); **^{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 $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.62; Found: C, 70.64; H, 10.51%.

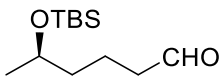
(*R*)-5-(*tert*-Butyldimethylsilyloxy)hexan-1-ol (39)



A mixture of benzyl ether **38** (6 g, 18.60 mmol) in EtOAc (20 mL) and 10% Pd/C (10 mg) was stirred under H_2 (1 atm) at 25 ^oC. After completion of reaction (monitored by TLC), it was filtered through Celite (EtOAc eluent) and the solvent was evaporated under reduced pressure to afford the title compound **39** as a pale yellow colored oil.

Yield: 4.19 g, 97%; pale yellow colored oil**; [α]D^{25}** -13.7 (*c* 2., $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3438, 3256, 3150, 2980, 2930, 2857, 1225, 1099, 1050, 960, 794; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.84 (s, 9H), 1.09 (d, *J* = 6.1 Hz, 3H), 1.32–1.55 (m, 6H), 1.62 (br s, 1H), 3.59 (t, *J* = 6.3 Hz, 2H), 3.70–3.78 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.4, 18.1, 21.7, 23.7, 25.9, 32.7, 39.4, 62.6, 68.5; **Anal. Calcd** for $C_{12}H_{28}O_2Si$: C, 62.01; H, 12.14; Found: C, 61.92; H, 12.02%.

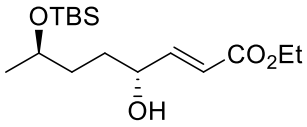
(*R*)-5-(*tert*-Butyldimethylsilyloxy)hexanal (31)



To a well-stirred solution of alcohol **39** (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 C. 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/ethyl acetate (19:1 v/v) gave the intermediate aldehyde **31** as a light yellow colored viscous liquid.

Yield: 3.89 g, 98%; light yellow colored viscous liquid; **$[\alpha]_D^{25}$** -3.0 (*c* 2.5, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3020, 2980, 2930, 2857, 1722, 1572, 1472,1215, 1110, 1050, 789; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.84 (s, 9H), 1.09 (d, *J* = 6.0 Hz, 3H), 1.35–1.43 (m, 2H), 1.54–1.70 (m, 2H), 2.33–2.39 (dt, *J* = 8.8, 7.1 Hz, 2H), 3.71–3.83 (m, 1H), 9.71 (t, *J* = 1.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, -4.8, 17.8, 23.2, 25.4, 38.4, 43.4, 67.6, 202.0; **Anal. Calcd** for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37; Found: C 62.65; H 11.77%.

Ethyl (4*R*, 7*R*, *E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxyoct-2-enoate (30)



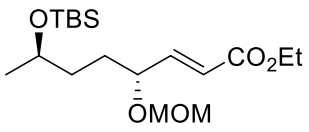
To a stirred solution of nitrosobenzene (1.4 g, 13.0 mmol) and L-proline (0.3 g, 2.6 mmol) in CH_3CN (40 mL) was added aldehyde **31** (3.0 g, 13.0 mmol) at -20 ^oC. The reaction was stirred at same temperature for 16 h, followed by the addition of triethylphosphono acetate (4.3 g, 19.5 mmol), DBU (3.0 g, 19.5 mmol) and LiCl (0.60 g, 14.3 mmol) at 0 ^oC for 2 h. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride. Then solvent was evaporated and organic layer was

extracted with EtOAc (3x50 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, concentrated to give the crude γ-aminooxy-α,β-unsaturated ester, which was directly used for the next step without purification.

To a EtOH (50 mL) solution of the crude γ-aminooxy-α,β-unsaturated ester was added $CuSO_4.5H_2O$ (0.9 g, 3.9 mmol) at 0 ^oC. The reaction mixture was allowed to stir for 10 h at this temperature. After the addition of the phosphate buffer, the resulting mixture was extracted with CH_2Cl_2 (3x50 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude γ-hydroxy-α,β-unsaturated ester, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (4:1 v/v) to give **30** as a yellow oil.

Yield: 2.67 g, 65%; yellow oil; **$[\alpha]_D^{25}$** -13.1 (*c* 1.8, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3420, 3250, 3105, 2980, 1725, 1590, 1350, 1115, 890; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.89 (s, 9H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.74-1.52 (m, 4H), 3.94-3.87 (m, 1H), 4.18 (q, *J* = 14.5 Hz, 2H), 4.28-4.20 (m, 1H), 6.02 (dd, *J* = 6.5, 15.6 Hz, 1H), 6.89 (dd, *J* = 5.8, 15.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.6, -4.3, 14.3, 18.1, 23.1, 25.9, 32.2, 35.3, 60.1, 68.4, 71.0, 120.0, 150.2, 166.3; **Anal. Calcd** for $C_{16}H_{20}O_4Si$: C, 60.72; H, 10.19; Found: C, 60.61; H, 10.10%; **Optical purity**: 98% from chiral HPLC analysis [Chirapak AD-H, 2-Propanol/n-Hexane = 2.5/97.5, flow rate 0.5 mL/min, λ = 220 nm, retention time: (minor) 11.59 min, (major) 13.81 min, ee 98%]

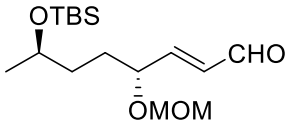
Ethyl (4*R*, 7*R*, *E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-(methoxymethoxy)oct-2-enoate (40)



To a stirred solution of γ-hydroxy-α,β-unsaturated ester **30** (2.5 g, 7.8 mmol) in CH_2Cl_2 (20 mL) were added MOMCl (0.753 g, 9.36 mmol) and DIPEA (1.5 g, 11.7 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h. After the reaction was complete (checked by TLC), the reaction was quenched with water, and the organic layer was extracted with CH_2Cl_2 (3x30 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 over silica gel using petroleum ether/EtOAc (9:1 v/v) to give **40** as a pale yellow free flowing liquid.

Yield: 2.5 g, 90%; pale yellow free flowing liquid; **$[\alpha]_D^{25}$** +23.5 (*c* 1.2, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3252, 3190, 3025, 2980, 2911, 1721, 1520, 1105, 856; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.4 (s, 6H), 0.84 (s, 9H), 1.23 (d, *J* = 4.0 Hz, 2H), 1.40 (t, *J* = 3.2 Hz, 3H), 3.81 (m, 1H), 4.14 (m, 3H), 4.57 (m, 2H), 5.96 (d, *J* = 4.2 Hz, 1H), 6.80 (dd, *J* = 6.3, 7.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ -4.6, -4.2, 14.2, 18.12, 23.8, 25.9, 30.7, 34.9, 55.5, 60.3, 68.0, 75.0, 94.4, 121.9, 147.7, 166.0; **Anal. Calcd** for $C_{18}H_{36}O_5Si$: C, 59.96; H, 10.06; Found: C, 59.72; H, 9.91%.

(4*R*, 7*R*, *E*)-7-(*tert*-butyldimethylsilyloxy)-4-(methoxymethoxy)-oct-2-enal (9)

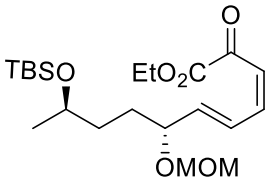


To a stirred solution of α,β-unsaturated ester **40** (2.3 g, 6.37 mmol) in dry toluene (20 mL) was added 6.3 mL of 1M in toluene of DIBAL-H (6.37 mmol) at -78 °C. The reaction mixture was stirred at same temperature for 1 h. After the reaction was complete (monitored by TLC), it was warmed to 25 °C, 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/ethyl acetate (19:1 v/v) gave aldehyde **9** as a colorless viscous liquid.

Yield: 1.9 g, 96%; colorless viscous liquid**; $[\alpha]_D^{25}$** +22.6 (*c* 1.0, $CHCl_3$) {lit.[4] $[\alpha]_D^{25}$ +22.5 (*c* 1.55, $CHCl_3$)}; **IR** (neat, cm^{-1}): υ_{max} 3112, 3054, 2931, 2909, 2857, 1720, 1650, 1042, 960, 752; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.4 (s, 6H), 0.84 (s, 9H), 1.14 (d, *J* = 6.0 Hz, 3H,), 1.35–1.83 (m, 4H), 3.36 (s, 3H), 3.74-3.84 (m, 1H), 4.24–4.35 (m, 1H), 4.6 (m, 2H), 6.16–6.28 (dd, *J* = 7.1, 7.7 Hz, 1H), 6.60–6.71 (dd, *J* = 5.8, 6.0 Hz, 1H), 9.8 (d, *J* = 7.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ -4.6, -4.2, 14.2, 18.1, 23.8, 25.9, 30.7, 34.9, 55.5, 60.3, 68.0, 75.0, 94.4, 121.9, 147.7, 193.3; **Anal. Calcd** for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19; Found: C, 60.61; H, 10.10%.

Ethyl-(2*Z*, 4*E*, 6*R*, 9*R*)-9-((*tert*-butyldimethylsilyl)oxy)-6-(methoxymethoxy)deca-2,4-dienoate (41)

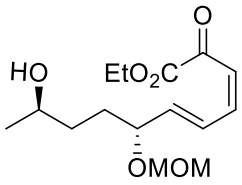


To a stirred solution of NaH (0.23 g, 5.9 mmol) in dry THF (10 mL) was added ethyl (diphenoxylphosphinoxy) acetate (2.0 g, 6.4 mmol) at 0 ^oC. After stirring for 30 min at 0 ^oC, α,β-unsaturated aldehyde **9** (1.7 g, 5.37 mmol) in dry THF (10 mL) was added to the reaction mixture dropwise over a time period of 30 min at same temperature. After the addition, the reaction mixture was stirred for an additional hour at 0 ^oC. It was then quenched with saturated solution of ammonium chloride. Solvent was evaporated and

organic layer was extracted with EtOAc (3x30 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, concentrated to give the crude diene product, which on column chromatographic purification with petroleum ether/ethyl acetate (9:1 v/v) gave dienic ester **41** (*Z,E/E,E* = 97:3) as a colorless viscous liquid.

Yield: 1.9 g, 92%; colorless viscous liquid; **$[\alpha]_D^{25}$** +81.2 (*c* 1.8, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3290, 3150, 2996, 2856, 1730, 1656, 1590, 1158, 1076, 880; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.12 (d, *J* = 6.2 Hz, 3H), 1.27 (t, *J* = 4.3 Hz, 3H), 1.42–1.68 (m, 4H), 3.33 (s, 3H), 3.78–3.80 (m, 1H), 4.13–4.17 (m, 3H), 4.56 (q, *J* = 6.5, 14.5 Hz, 2H,), 5.68 (d, *J* = 11.5 Hz, 1H), 5.88 (dd, *J* = 8.0, 15.0 Hz, 1H,), 6.55 (t, *J* = 11.5 Hz, 1H), 7.47 (dd, *J* = 11.5, 15.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ -5.5, -5.4, 13.2, 17.0, 22.7, 24.8, 30.2, 33.9, 54.3, 58.8, 67.1, 67.3, 93.0, 117.0, 126.9, 142.1, 142.6, 164.9; **Anal. Calcd** for $C_{20}H_{38}O_5Si$: C, 62.14; H, 9.91; Found: C, 62.20; H, 9.81%.

Ethyl (2*Z*, 4*E*, 6*R*, 9*R*)-9-hydroxy-6-(methoxymethoxy)deca-2,4-dienoate (42)



To a stirred solution of dienic ester **41** (1.5 g, 3.37 mmol) in THF (10mL) was added 4.5 mL of 1M THF solution of TBAF (4.6 mmol) at 0 ^oC. Then the reaction was stirred for 1 h. After completion of reaction (checked by TLC), the solvent was evaporated and organic layer was extracted with EtOAc (3x30 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, concentrated to give the crude product, which on column chromatographic purification with petroleum ether/ethyl acetate (4:1 v/v) gave alcohol compound **42** as colourless viscous liquid.

Yield: 0.92 g, 88%; colourless viscous liquid**; [α]$_D^{25}$** +68.0 (*c* 0.4, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3420, 3296, 3101, 2996, 2856, 1730, 1590, 1472, 1158, 1076, 946, 830; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.9 (br s, 1H), 1.39–1.78 (m, 4H), 3.33 (s, 3H), 3.78–3.80 (m, 1H), 4.13–4.24 (m, 3H), 4.56 (q, *J* = 14.5, 6.5 Hz, 2H), 5.68 (d, *J* = 11.5 Hz, 1H), 5.88 (dd, *J* = 8.0, 15.0 Hz, 1H), 6.55 (t, *J* = 11.5 Hz, 1H), 7.47 (dd, *J* = 11.5, 15.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 14.2, 23.7, 31.6, 34.7, 55.5, 59.9, 60.3, 67.8, 94.1, 118.2, 128.1, 142.1, 142.3, 166.6; **Anal. Calcd** for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88; Found: C, 61.54; H, 8.56%.

Optimization studies for the macrocyclization of *seco* acid 11:

1) **using DCC and DMAP**:

To a stirred solution of **11** (1.4 g, 5 mmol) in CH_2Cl_2 (20 mL) were added DCC (1.5 g, 7.5 mmol) and DMAP (0.06 g, 0.5 mmol) and the reaction mixture was stirred at 25 ^oC for 3 h. After monitoring the progress of reaction by TLC, the reaction was continued for another 3 h. Then it was quenched with water, and the organic layer extracted with CH_2Cl_2 (3x30 mL). Then 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 over silica gel using petroleum ether/EtOAc (9:1 v/v) to give **12** as a pale yellow liquid. **Yield**: 0.11 g, 10%.

2) **with cyanuric chloride**:

To a stirred solution of **11** (1.4 g, 5 mmol) in CH_3CN (20 mL) was added cyanuric chloride (1.3 g, 7.5 mmol) and the reaction mixture was stirred at 25 ^oC for 3 h. After checking the TLC, the reaction was continued for another 5 h and was quenched with water, and the organic layer was extracted with CH_2Cl_2 (3x30 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 over silica gel using petroleum ether/EtOAc (9:1 v/v) to give **12** as a pale yellow liquid. **Yield**: 0.13 g, 12%.

3) **with Yamaguchi condition**:

i) To a solution of *seco*-acid **11** (1.4 g, 5 mmol) in THF (20 mL) were added Et_3N (1.0 mL, 7.5 mmol) and 2,4,6-trichlorobenzoyl chloride (1.8 g, 7.5 mmol) and the reaction mixture was stirred for 2 h at room temperature under argon atmosphere and then diluted with benzene (100 mL). The resulting reaction mixture was added dropwise to a solution of DMAP (6.1 g, 50 mmol) in benzene (50 mL) at 80 °C over 1 h and the mixture was stirred for additional 1 h under reflux. It was washed with aq. citric acid solution and brine. Then the organic layer was dried (Na_2SO_4), concentrated to get the crude, which was purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1 v/v) to give **12** as a pale yellow liquid. **Yield**: 0.20 g, 18%.

ii) The above reaction was done in a similar way but the solvent chosen was toluene and refluxed at 110 ^oC for 2 h. **Yield**: 0.23 g, 21%.

iii) The above reaction was done using toluene at 25 ^oC for 2 h. **Yield**: 0.339 g, 30%.

iv) The above reaction was done at 25 ^oC using THF. **Yield**: 0.169 g, 15%.

v) The above Yamaguchi reaction was done using DIPEA (*N*,*N*-diisopropylethylamine) (0.96 g, 7.5 mmol) in toluene at 80 ^oC for 2 h. **Yield**: 0.22 g, 20%.

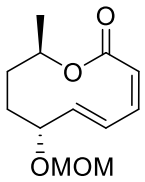
vi) The best yield of macrolactone **12** was obtained when the *seco* acid **11** (1.4 g, 5 mmol) dissolved in dry toluene (10 mL) were added to a solution of 2,4,6-trichlorobenzoyl chloride (1.8 g, 7.5 mmol), NEt_3 (1.0 mL, 7.5 mmol) and DMAP (0.91 g, 7.5 mmol) in dry

toluene (20 mL) over a time period of 1 h. Then the reaction mixture was stirred for an additional hour. **Yield**: 65%; 0.73 g.

4) **For Shiina's lactonization condition**:

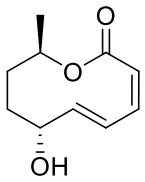
Similarly, the *seco* acid **11**(1.4 g, 5 mmol) dissolved in dry toluene (10 mL) were added to a solution of 2-methyl-6-nitrobenzoic anhydride (2.5 g, 7.5 mmol), NEt_3 (1.0 mL, 7.5 mmol) and DMAP (0.06 g, 0.5 mmol) in dry toluene (30 mL) over a time period of 1 h. Then the reaction mixture was stirred for an additional hour. **Yield**: 62%; 0.7 g.

(3*Z*, 5*E*, 7*R*, 10*R*)-7-(Methoxymethoxy)-10-methyl-7,8,9,10-tetrahydro-2H-oxecin-2-one (12)



$[\alpha]_D^{25}$ +47.1 (*c* 1.0, $CHCl_3$) {lit.[4] $[\alpha]_D^{25}$ +47.4 (*c* 0.8, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3296, 3106, 2856, 1710, 1625, 1582, 1158, 1120, 1076, 752; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (d, *J* = 6.2 Hz, 3H), 1.57–1.94 (m, 4H), 3.35 (s, 3H), 4.05 (td, *J* = 9.0, 4.0 Hz, 1H), 4.53 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 5.00 (m, 1H), 5.64 (dd, *J* = 9.6, 15.4 Hz, 1H), 5.85 (d, *J* = 10.5 Hz, 1H), 6.16 (d, *J* = 15.1 Hz, 1H), 6.62 (d, *J* = 10.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4, 29.7, 39.0, 55.5, 73.1, 73.2, 95.0, 124.1, 128.1, 138.5, 140.6, 168.0; **HRMS** (ESI): calcd. for $[(C_{12}H_{18}O_4)Na]$ (M+Na) 249.1103; Found: 249.1089.

(3*Z*, 5*E*, 7*R*, 10*R*)-7-Hydroxy-10-methyl-7,8,9,10-tetrahydrooxecin-2-one: stagonolide E (4)



To a stirred solution of the macrolactone MOM ether **12** (0.5 g, 2.2 mmol) in THF was added 2N HCl solution (10 mL) and stirred for 1 h. After completion of the reaction (monitored by TLC), the organic layer was extracted using ether and washed with brine and dried over anhydrous Na_2SO_4. Then solvent was removed *in vacuum* and concentrated. The crude was purified by column chromatography using petroleum ether/EtOAc (4:1 v/v) to give stagonolide E (**4**) as colorless viscous liquid.

Yield: 0.35 g, 88%; colorless viscous liquid; **$[\alpha]_D^{25}$** -177.3 (*c* 0.48, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ -181.0 (*c* 0.2, $CHCl_3$)};)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3445, 3260, 3106, 2856, 1715, 1585, 1090, 1056, 856; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.8 Hz, 3H), 1.73-1.66 (m, 4H), 4.16 (m, 1H), 4.86 (m, 1H), 5.72 (dd, *J* = 9.4, 15.3 Hz, 1H), 5.86 (d, *J* = 11.6 Hz, 1H), 6.18 (br d, *J* = 15.4 Hz, 1H), 6.68 (d, *J* = 11.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0, 31.1, 41.0, 72.8, 73.0, 124.5, 127.8, 138.9, 141.4, 168.5; **Anal. Calcd** for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74; Found: C, 65.82; H, 7.62%.

Section II

A Concise Formal Synthesis of (-)-(6*R*,11*R*,14*R*)-Colletallol *via* Organocatalysis

2.2.1 Introduction and Pharmacology

The 14-membered macrolactones (e.g. compounds **43**-**46**) usually represent a novel class of natural products displaying wide range of biological properties.[16] Among them (-)-colletallol (**46**) is a diolide, isolated from plant pathogen *Colletrichum capsici*.[17] This family of natural products displays a wide range of pharmacologically interesting properties such as antibacterial, antitumoral, antifungal and antibiotic activities. The scarce availability of these macrolides and their potent biological activities have attracted synthetic organic chemists worldwide (**Fig. 14**).[18]

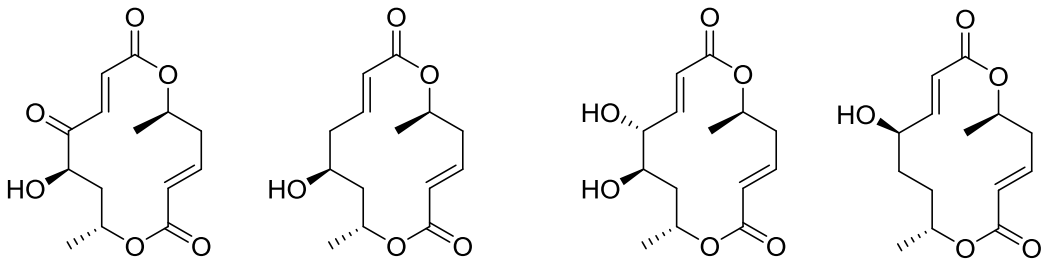


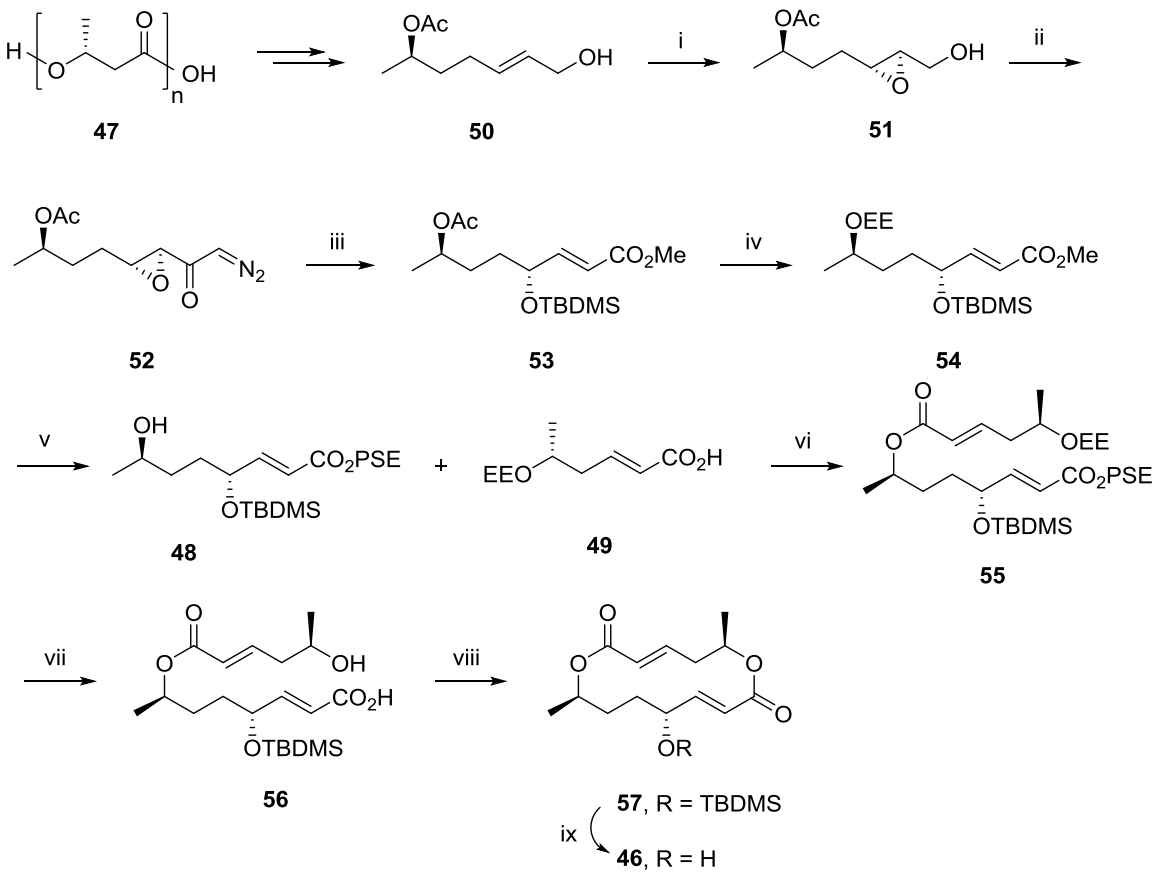
Fig. 14: Some naturally-occurring diolides (**43-46**)

2.2.2 Review of Literature

Literature search revealed that there are only two approaches available on the synthesis of (-)-(6*R*,11*R*,14*R*)-Colletallol **46**, which are described below.

Zwanenburg's approach (1991)[19]

Zwanenburg *et al.* have reported the synthesis of (-)-colletallol **46** using poly-(3-(*R*)-hydroxy butyric acid) **47** as common starting material to furnish both alcohol **48** and acid **49** fragments respectively. Thus, poly-(3-(*R*)-hydroxybutyric acid) **47** was converted



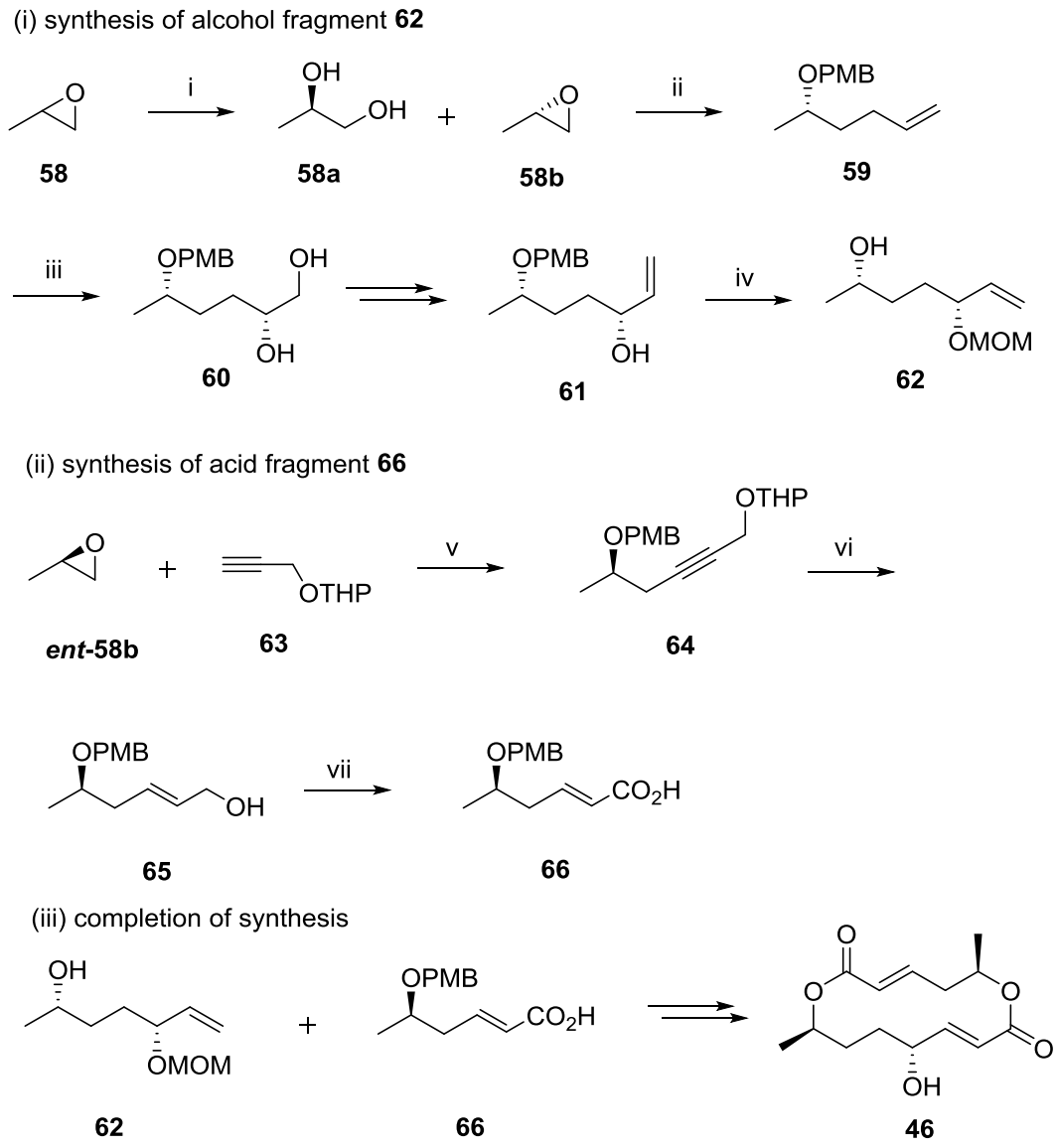
Scheme 7: (i) (-)-DET, tBuO$_2$H, Ti(O^{i}Pr)$_4$, 4 Å MS, CH_2Cl_2, 92%; (ii) RuO_4, $CH_3CN/CCl_4/H_2O$ (2:2:3), $ClCO_2tBu$, NEt_3, then CH_2N_2, 68% (over three steps); (iii) hγ, MeOH; then TBDMSCl, imid, DMF, 92%; (iv) (a) NaOMe, MeOH, 0 °C; (b) ethyl vinyl ether, PPTS, CH_2Cl_2, 88%; (v) (a) LiOH, THF/H_2O (1:1), 95%; (b) $PhSO_2CH_2CH_2OH$, DCC, DMAP, CH_2Cl_2, 85%; (c) $MgBr_2$, Et_2O, 70%; (vi) DCC, DMAP, CH_2Cl_2, 86%; (vii) (a) $MgBr_2$, Et_2O; (b) DBU, benzene, reflux, 80%; (viii) 2,6-$Cl_2C_6H_3COCl$, Et_3N then, DMAP, toluene, reflux, 45%; (ix) TBAF, THF, 75%.

to allylic alcohol **50**, which was subjected to Sharpless asymmetric epoxidation to give epoxy alcohol **51** in 92% yield. Epoxy alcohol **51** was converted into diazo ketone **52**,

without isolation of intermediate. Compound **52** on irradiation and followed by silylation [TBDMSCl, immid, DMF] furnished compound **53** in 92% yield. Next, OAc group in **53** was hydrolyzed [NaOMe, MeOH, 0 ^{o}C] and replaced with more stable ethoxy ether (EE) group in **54** in 88% yield. The unsaturated ester **54** was saponified with LiOH and the carboxylic acid was esterified with phenylsulfonyl ethanol (PSE) using DCC as coupling reagent. Subsequent removal of EE protecting group with $MgBr_2$ provided alcohol **48** fragment in 70% yield. Again poly-(3-(*R*)-hydroxybutyric acid) **38** was turned into the acid **49** fragment by standard functional group transformations. The coupling of alcohol **48** with acid **49** was accomplished using DCC as condensing agent to obtain compound **55**. The subsequent removal of EE group (by $MgBr_2$) and sulfur group (by DBU base) provided *seco* acid **56** in 80% yield, which was gratifyingly converted into **57** using Yamaguchi condition in 45% yield. Finally, removal of silyl ether **57** using TBAF accomplished the synthesis of (-)-colletallol **46** in 75% yield (**Scheme 7**).

Radha Krishna's approach (2009)[20]

Radha Krishna *et al.* have commenced the synthesis of (-)-colletallol **46** starting from propylene oxide **58** employing Jacobsen's hydrolytic kinetic resolution (HKR) to furnish alcohol **62** and acid **66** fragments. Thus, propylene oxide **58** was subjected to HKR using Co(III)-salen complex catalyst to furnish enantioenriched diol **58a** and epoxide **58b**. (*S*)-epoxide **58b** was regioselectively opened with allyl magnesium bromide [CuI, THF, -40 °C–rt] followed by protection of hydroxyl group with PMBCl to furnish olefin **59**. Asymmetric dihydroxylation of **59** with AD-mix-β gave diol **60**, which was converted into **61** by functional group transformations. MOM ether protection of alcohol in **61** followed by PMB ether deprotection afforded alcohol fragment **62** in 98% yield.



Scheme 8: (i) (*S*,*S*)-Co^{III}(salen)complex, H_2O, AcOH, rt, 12 h; (ii) (a) allyl magnesium bromide, CuI, THF, -40 °C–rt; (b) PMBCl, NaH, TBAI, THF, reflux, 8 h, 85%; (iii) AD-mix-β, *t*-BuOH/H_2O = 1:1, 0 °C, 48 h, 87%, 67% de; (iv) (a) MOMCl, DIPEA, NaI, DCM, reflux, 5 h, 98%; (b) DDQ, CH_2Cl_2, buffer, 0°C, 3 h, 98%; (v) (a) *n*-BuLi, $BF_3{\cdot}Et_2O$, dry THF, -78°C, 3 h; (b) PMB–Br, NaH,THF, rt, 6 h, 73%; (vi) (a) cat. PTSA, MeOH, rt, 1 h; (b) $LiAlH_4$, dry THF, 0 °C–rt, 2 h, 95%; (vii) (a) $(COCl)_2$, DMSO, -78 °C, 2 h; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/water (2:1), 0 °C–rt, 3 h, 80%.

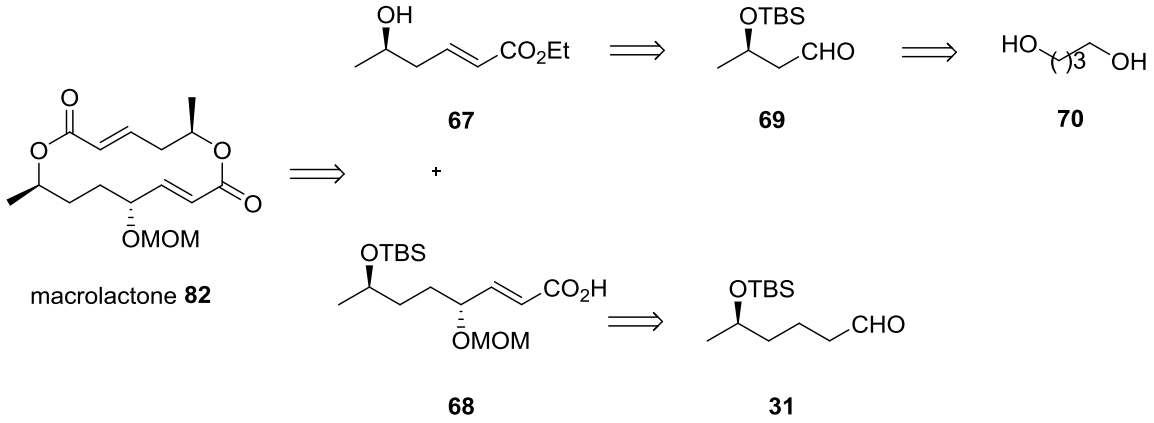
The acid fragment **66** was formed from (*R*)-propylene oxide (***ent*-58b**). Epoxide ***ent*-58b** was regioselectively opened with 2-(2-propynyl)tetrahydro-2*H*-pyran **63** in the presence of

n-BuLi and $BF_3 \cdot Et_2O$ in THF followed by treatment with PMB–Br and NaH in THF afforded **64** in 73% yield. THP group in **64** was deprotected with PTSA (5 mol %) in THF followed by reduction with $LiAlH_4$ afforded **65** in 95% yield. Swern oxidation of alcohol **65** gave the corresponding aldehyde, which on further oxidation with $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene in aq. ^{t}BuOH afforded acid fragment **66** in 80% yield. Finally, coupling of alcohol **63** with acid **66** fragments gave **46** with an overall yield of 2.1% (**Scheme 8**).

2.2.3 Present Work

2.2.3.1 Objective

As can be seen from the above discussion, reported methods for the synthesis of (-)-colletallol (**46**) are associated with certain drawbacks; such as the use of expensive transition metal as catalyst and chiral pool resources. Recently, organocatalysis emerged as an area of very rapid growth for chemical synthesis due to environmental friendliness. Particularly, proline has received much attention due to its dual role as a ligand and catalyst due to its abundant availability in both enantiomeric forms. In continuation of our work on proline-catalyzed synthesis of bioactive molecules, in this section, a facile formal synthesis of **46**, whose activity makes it an attractive synthetic target, is described. The retrosynthetic analysis of **46**, wherein proline-catalyzed α-aminooxylation[8] reaction constitutes the key step for the introduction of chirality, is presented in **Schemes 9**. Evidently, the macrolactone **82**, the key intermediate for (-)-colletallol **46**, could be obtained from Steglich esterification of alcohol **67** with acid **68** fragments. The alcohol fragment **67** could be formed from aldehyde **69**, which in turn could be obtained from 1,4-butanediol **70** by employing proline-catalyzed α-aminooxylation reaction.

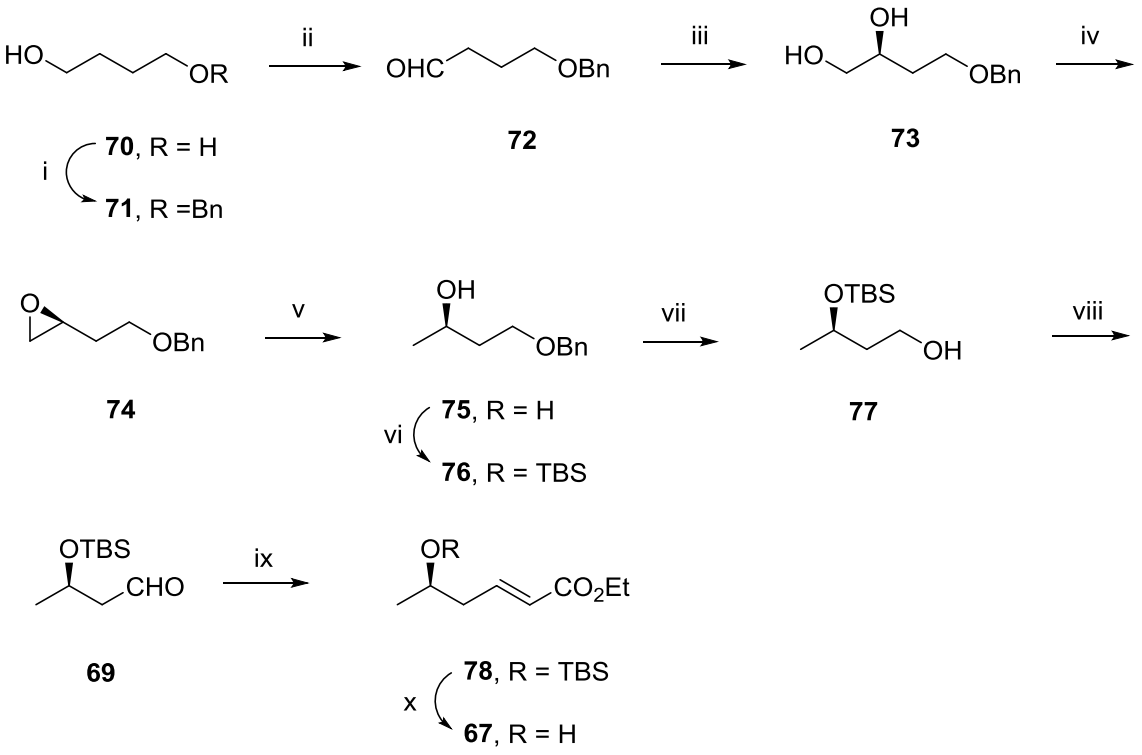


Scheme 9: Retrosynthetic scheme of macrolactone **82**

Moreover, the acid moiety **68** could be successively cccessed from aldehyde **31** *via* proline catalyzed sequential reactions.

2.2.3.2. Results and Discussion

Based on the retrosynthetic analysis, **Scheme 10** presents the total synthetic scheme of the alcohol fragment **67** starting from commercially available 1,4-butanediol (**70**). Firstly, diol **70** was monoprotected as its benzyl ether **71**, followed by its oxidation with IBX produced



Scheme 10: (i) BnBr, NaH, THF, 0-25 ºC, 6 h, 97%; (ii) IBX, DMSO, 25 ºC. 2 h, 98%; (iii) PhNO, D-proline (20 mol %), -20 ºC, 24 h then MeOH, $NaBH_4$; then $CuSO_4$, EtOH, 24 h, 75%; (iv) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2 then K_2CO_3, MeOH, 65%; (v) $LiAlH_4$, THF, 0 ºC, 30 min., 95%; (vi) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 2 h, 98%; (vii) H_2 (1 atm), 10% Pd/C, Et_3N, MeOH, 12 h, 25 ºC, 96%; (viii) IBX, DMSO, 25 ºC. 2 h, 98%; (ix) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 3 h, 95%; (x) TBAF, THF, rt, 6 h, 80%.

aldehyde **72**. The appearance of a typical triplet at δ 9.79 (t, J = 1.6 Hz, 1H) in its ^{1}H NMR spectrum confirmed the formation of aldehyde **72**. Also, a characteristic aldehydic carbon

signal at δ 201.7 in its ^{13}C NMR spectrum further ascertained its formation (**Fig. 15**). Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} 1720 cm^{-1} indicative of the presence of aldehydic carbonyl group.

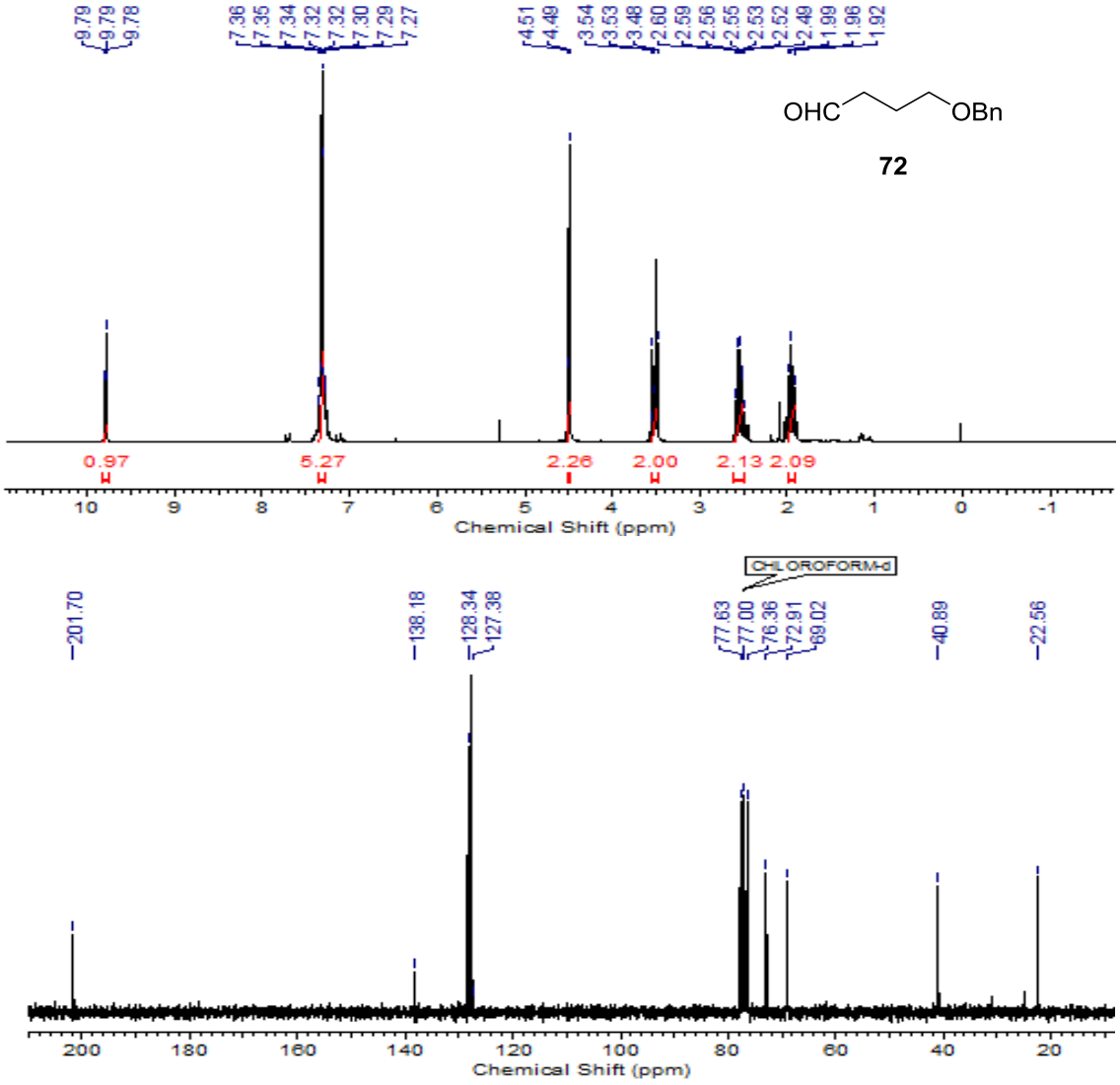


Fig. 15: ^{1}H and ^{13}C NMR spectra of aldehyde **72**

The D-proline catalyzed asymmetric α-aminooxylation of the aldehyde **72** gave the chiral diol **73**, which essentially involved two steps: (i) reaction of aldehyde **72** with nitrosobenzene in presence of D-proline as catalyst in CH_3CN at -20 ^{o}C followed by its

treatment with $NaBH_4$ in MeOH at 0 ^oC to give the crude aminooxy alcohol *in situ*; (ii) subsequent reduction of this crude aminooxy alcohol with 30% $CuSO_4$ in EtOH furnished the chiral diol **73** in 60% yield and 98% ee (determined by HPLC analysis).

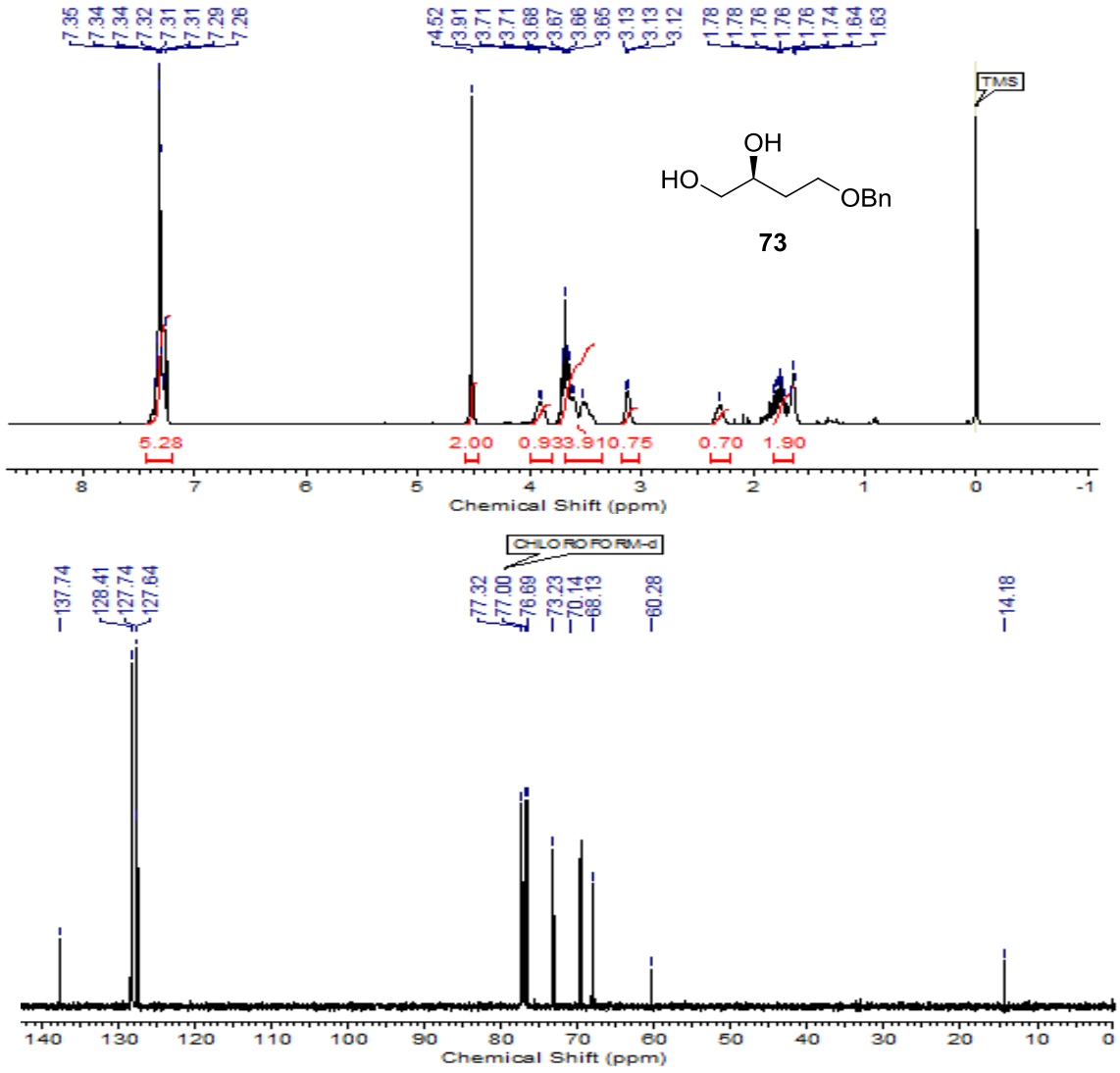
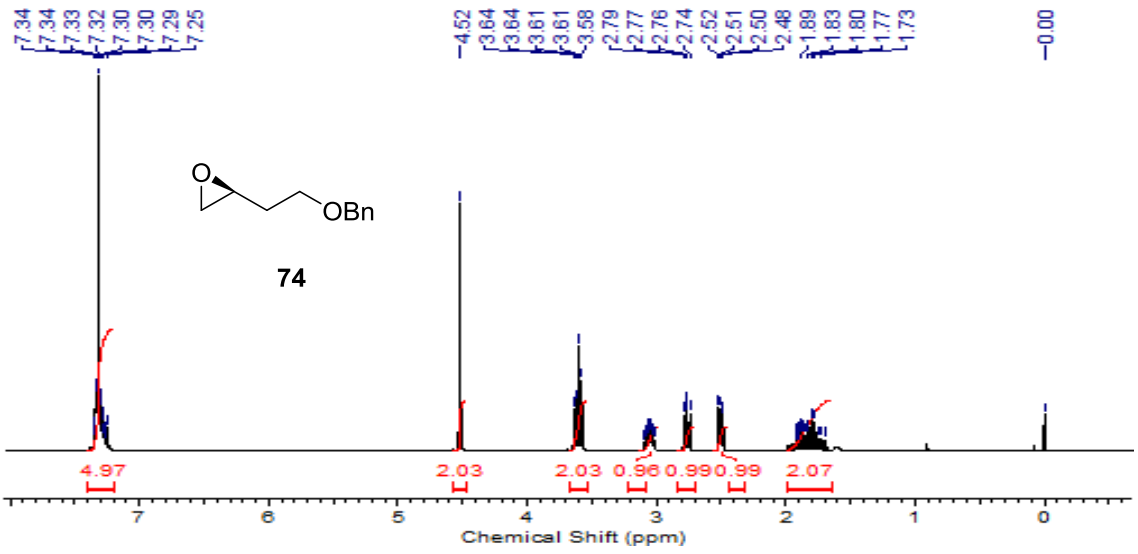


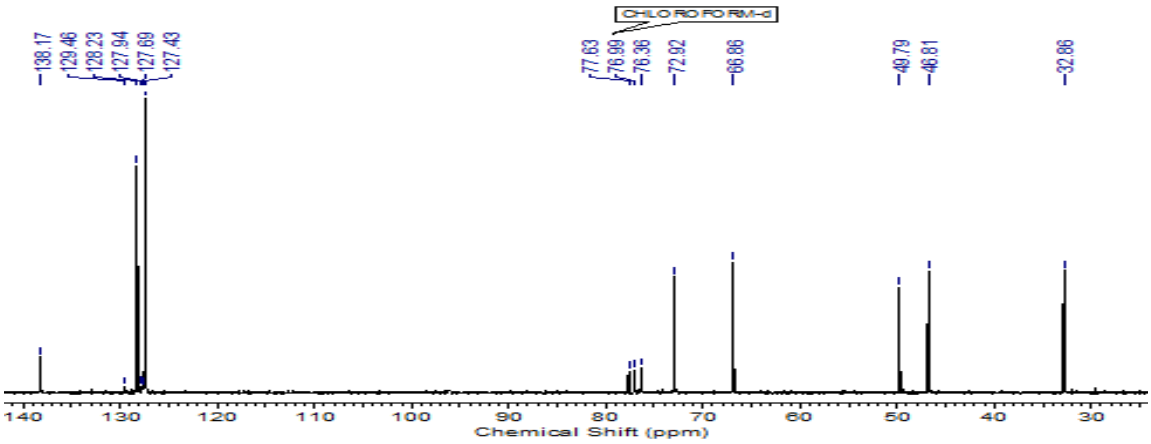
Fig. 16: ^1H and ^{13}C NMR spectra of diol **73**

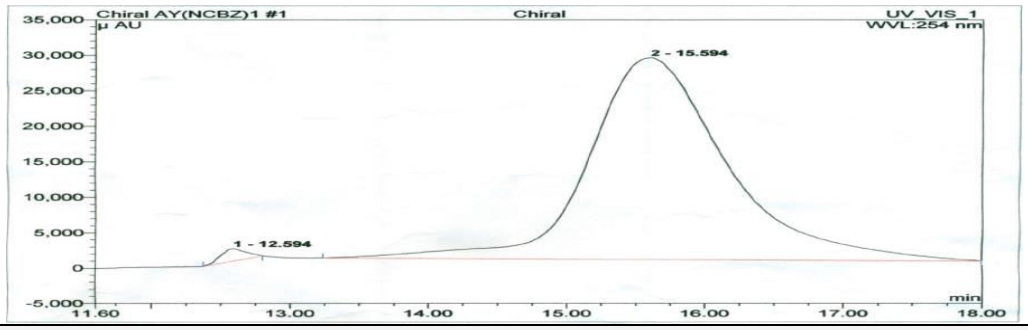
The formation of chiral diol was established by its ^1H and ^{13}C NMR spectral analysis. Its ^1H NMR spectrum displayed two typical multiplets at δ 3.91 (m, 1H) and 3.65-3.71 (m, 2H) due to the methine (-C**H**-OH) and methylene protons attached to oxygen atoms respectively. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 70.1 and 68.1

due to the methylene carbons attached to oxygen atoms respectively and the other signal at δ 60.2 corresponds to methine carbon attached to –OH group (**Fig. 16**). Its IR spectrum showed a characteristic strong vibrational stretching frequency at υ_{max} 3440 cm^{-1} due to the presence of hydroxyl group.

The selective monotosylation of primary alcohol **73** was then achieved to afford the corresponding tosylate *in situ*, which on treatment with K_2CO_3 in MeOH yielded the terminal chiral epoxide **74** in 70% yield and 98% ee determined by chiral HPLC analysis [Chirapak OD-H, 2-Propanol/*n*-Hexane = 2.5/97.5, flow rate 0.5 mL/min, λ = 254 nm, retention time: (minor) 12.59 min, (major) 15.59 min]; $[\alpha]_D^{25}$ - 5.0 (*c* 2.5, $CHCl_3$). Its ^1H NMR spectrum showed resonance signals at δ 2.50 (dd, *J* = 2.8, 5.1 Hz, 1H), 2.70 - 2.83 (m, 1H) and 3.05 (dddd, *J* = 2.8, 3.9, 4.8, 6.4 Hz, 1H) due to epoxide protons. The typical two carbon signals at δ 46.8 and 49.7 in its ^{13}C NMR spectrum corresponding to epoxide carbons further substantiated the formation of epoxide **74** (**Fig. 17**).







Retention Time	Area	Area %
12.59	363.360	1.10
15.59	32669.367	98.90
Totals	33032.727	100.00

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

The chiral epoxide (-)-**74** was readily purified by column chromatography and subjected to regioselective reductive ring opening with $LiAlH_4$ in THF at 0 °C to afford the secondary alcohol **75** as the exclusive product in 92% yield. The formation of **75** was confirmed by the appearance of a typical strong vibrational stretching frequency at υ_{max} 3454 cm^{-1} due to the presence of hydroxyl group. Its ^{1}H NMR spectrum showed a multiplet at δ 3.95-3.99 (m, 1H) corresponding to methine proton (-C**H**-OH) and a characteristic broad singlet at δ 2.89 (br s, 1H) due to the proton of –OH group. Further, its ^{13}C NMR spectrum showed a characteristic signal at δ 67.1 indicative of methine carbon attached to hydroxyl group (**Fig. 18**).

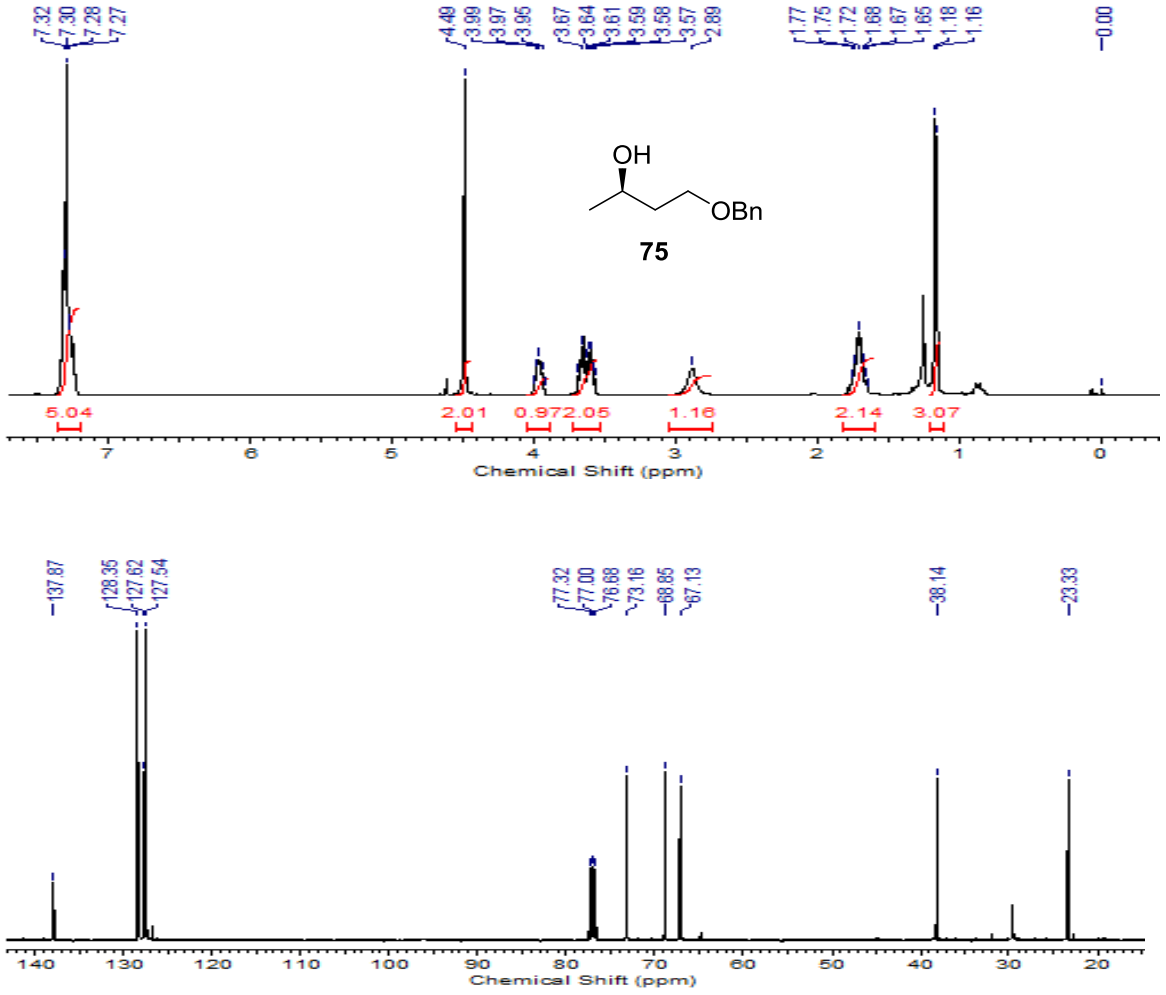


Fig. 18: ^{1}H and ^{13}C NMR spectra of secondary alcohol **75**

Alcohol **75** was protected as its TBS ether (TBSCl, imid.) and the benzyl ether **76** was subsequently deprotected under hydrogenolysis condition {10% Pd/C, H_2 (1 atm), Et_3N} to give the primary alcohol **77** in 97% yield. The ^{1}H NMR spectrum of **77** displayed a multiplet at δ 3.66-3.79 (m, 2H) due to protons of the methylene group (-C**H$_2$**-OH). Its ^{13}C NMR spectrum showed signals at δ 65.6 and 67.2 corresponding to methylene (-**C**H_2-OH) and methine (-**C**H-OTBS) carbons respectively. Its IR spectrum showed strong vibrational stretching frequency at υ_{max} 3404 cm^{-1} due to the presence of hydroxyl group (**Fig. 19**).

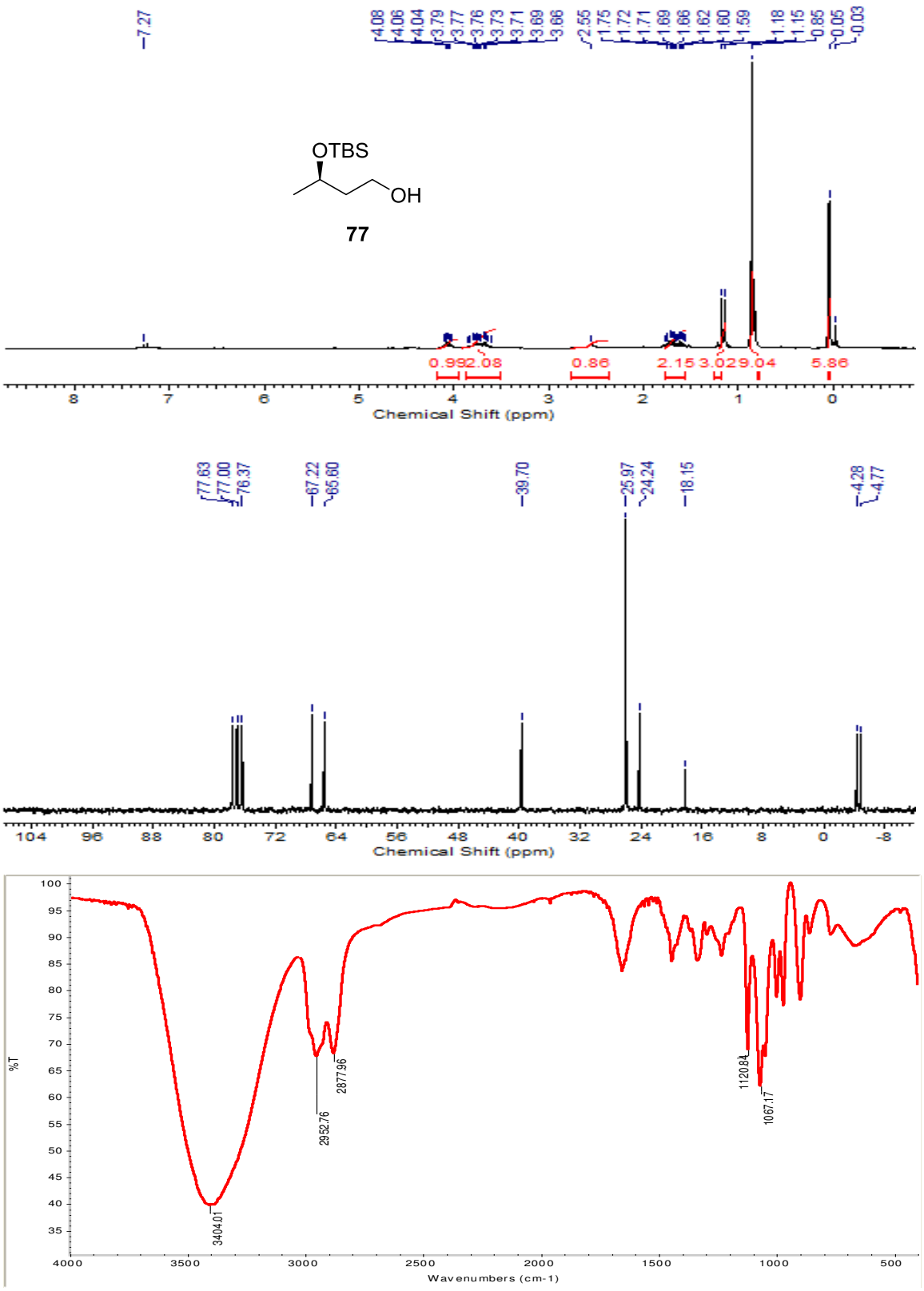


Fig. 19: ^{1}H & ^{13}C NMR and IR spectra of primary alcohol **77**

The oxidation of alcohol **77** (IBX, DMSO) produced aldehyde **69** in 98% yield {$[\alpha]_D^{25}$ -12.0 (*c* 3.0, $CHCl_3$). The formation of aldehyde **69** was confirmed by its ^1H NMR spectrum, which showed a typical proton signal for aldehydic proton at δ 9.76 (s, 1H). This was further ascertained by the appearance of a typical aldehydic carbon signal at δ 192.5 in its ^{13}C NMR spectrum (**Fig. 20**). A strong vibrational stretching frequency at υ_{max} 1720 cm^{-1} in its IR spectrum confirmed the presence of aldehydic group.

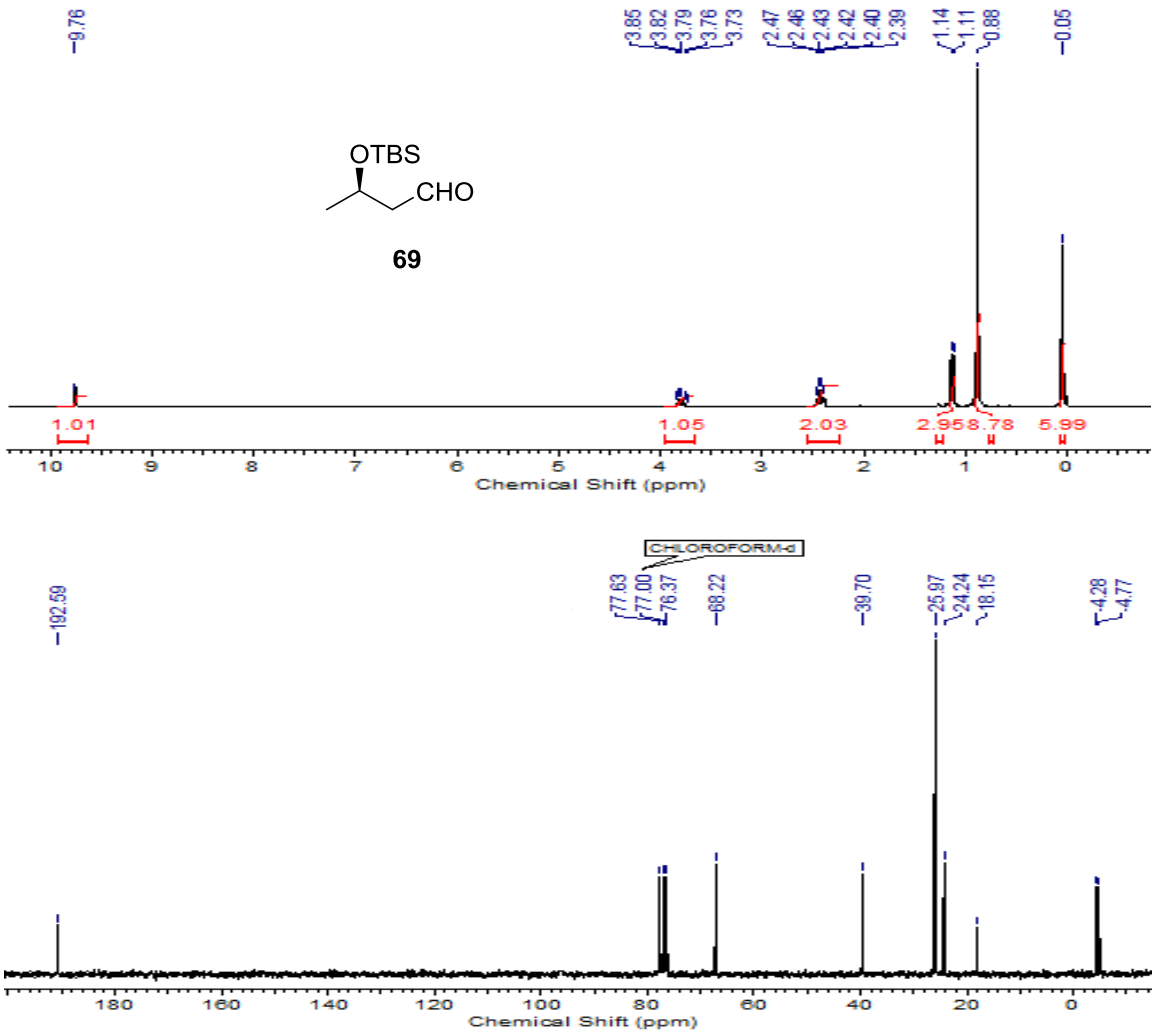


Fig. 20: ^1H and ^{13}C NMR spectra of aldehyde **69**

Aldehyde **69** was immediately reacted with stabilized Wittig salt to give α,β-unsaturated ester **78** in 93% yield, {$[\alpha]_D^{25}$ -15.8 (*c* 2.4, $CHCl_3$)}. The formation of olefinic ester **78** was confirmed by its ^1H and ^{13}C NMR spectra, which showed the appearance of proton signals at δ 5.84 (d, *J* = 15.5 Hz, 1H) and 6.85 (m, 1H) in its ^1H NMR spectrum and carbon signals at δ 123.2 and 145.8 in its ^{13}C NMR spectrum corresponding to the presence of olefinic functionality. A carbon signal at δ 166.2 in its ^{13}C NMR spectrum further confirmed the presence of ester carbonyl functionality in **78** (**Fig. 21**). Its IR spectrum showed a strong

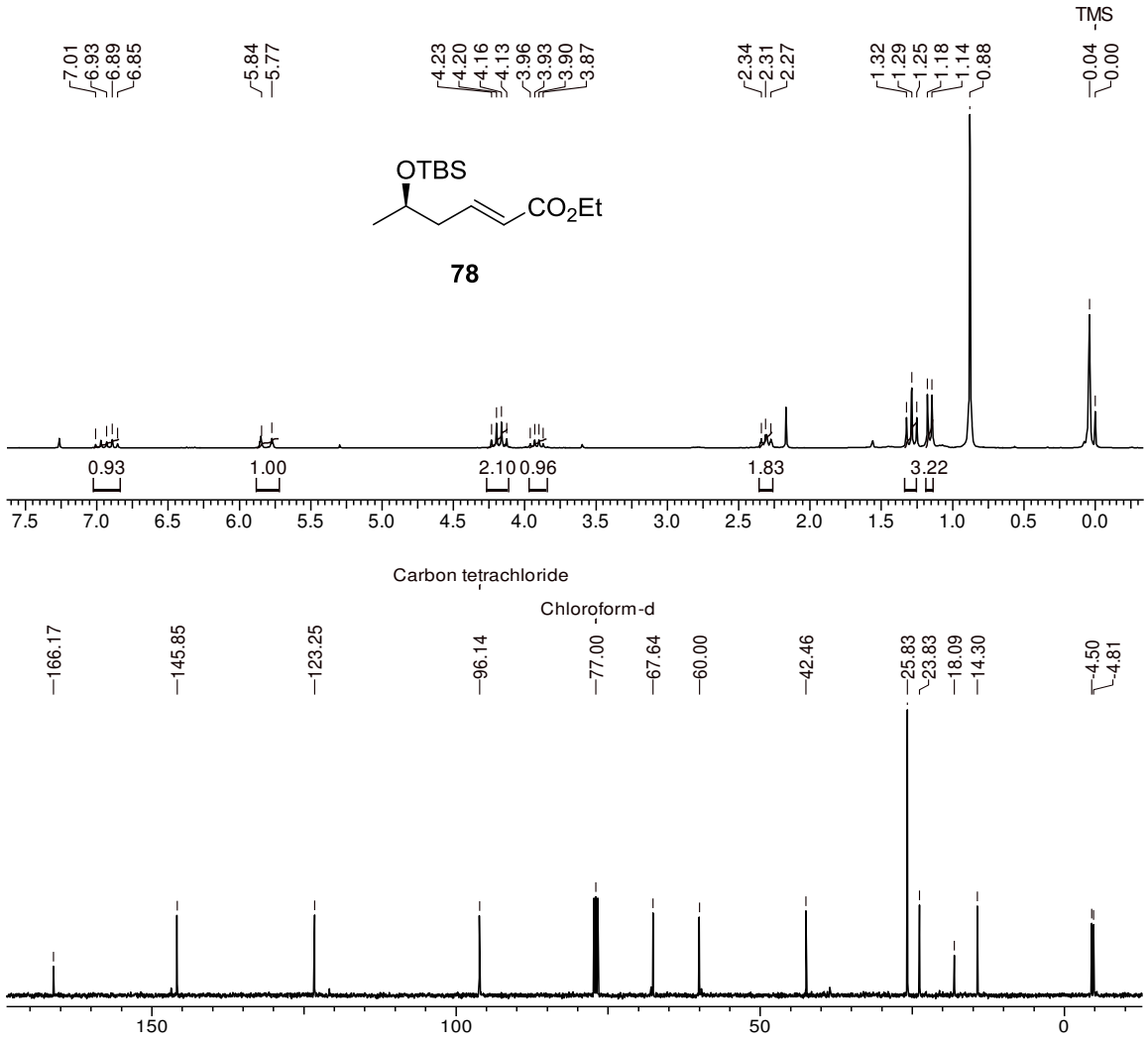
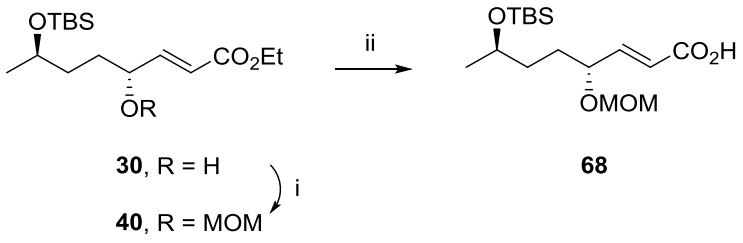


Fig. 21: ^1H and ^{13}C NMR spectra of α,β-unsaturated ester **78**

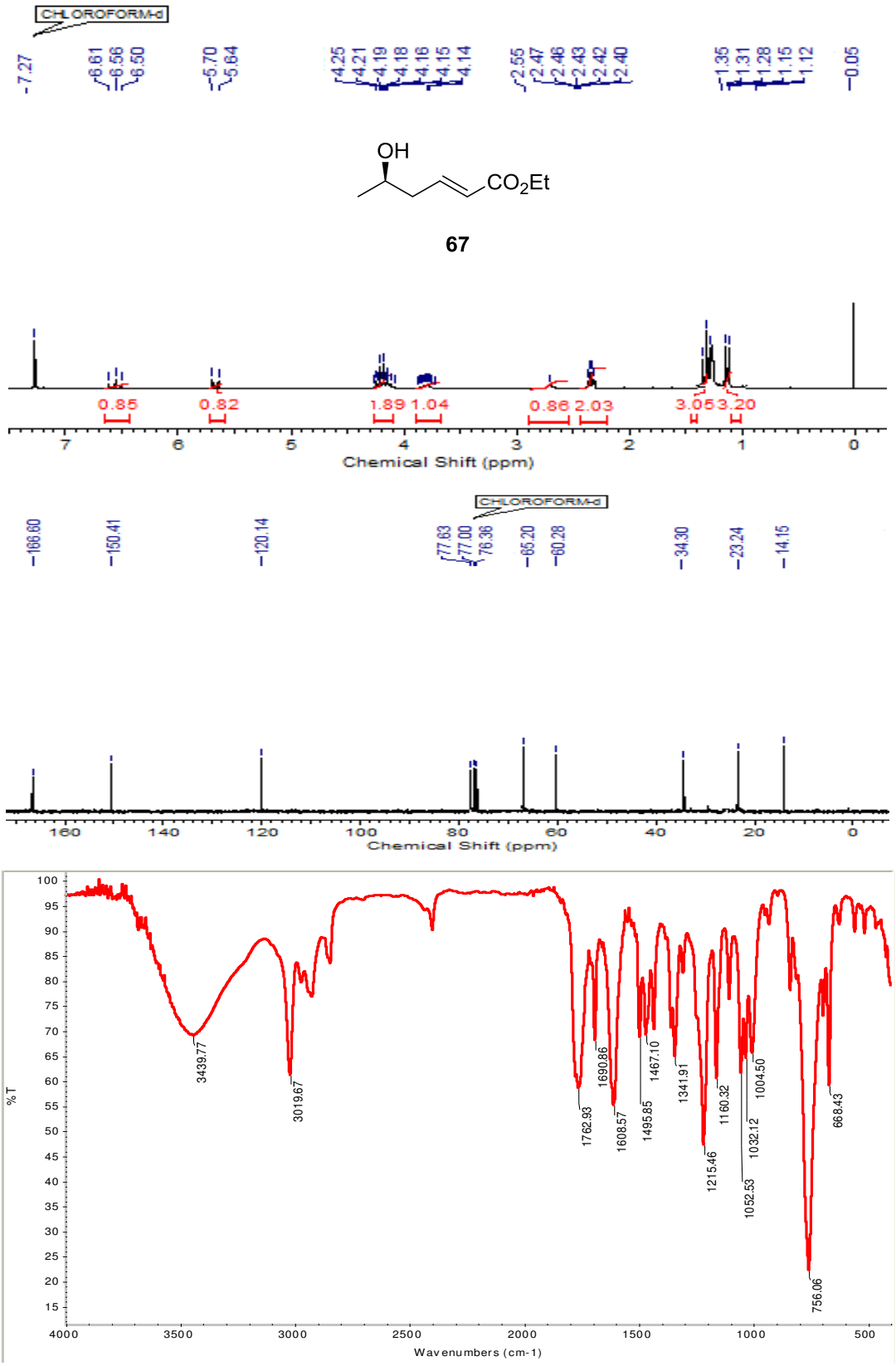
vibrational stretching frequency at υ_{max} 1715 cm^{-1} due to the ester carbonyl functional group.

The α,β-unsaturated ester **78** was then desilylated on treatment with TBAF to afford alcohol fragment **67** in 83% yield. The disappearance of resonance signals corresponding to TBS group in its ^{1}H and ^{13}C NMR spectra and the appearance of a broad singlet at δ 2.55 (br s, 1H) due to the proton of –OH group in its ^{1}H NMR spectrum confirmed the formation of alcohol **67**. This was further substantiated by its IR spectrum analysis, which showed two strong vibrational stretching frequencies at υ_{max} 3439 and 1762 cm^{-1} due to the presence of –OH and ester carbonyl groups respectively. Its molecular mass [$(C_8H_{14}O_3)Na$] (M+Na) from HRMS (ESI) was found to be 181.0402, which was in well-agreement with the calculated value 181.0406 (**Fig. 22**).

We have already discussed the synthesis of γ-hydroxy-α,β-unsaturated ester **30** (See **Section I** of this chapter). **Scheme 11** shows the synthesis of acid fragment **68**.



Scheme 11: (i) MOMCl, DIPEA, CH_2Cl_2, 25 ºC, 2 h, 86%; (ii) LiOH, THF/H_2O (1:1), 25 ºC, 1 h, 70%.


CHLOROFORM-d
7.27
6.61
6.56
6.50
5.70
5.64
4.25
4.21
4.19
4.18
4.16
4.15
4.14
2.55
2.47
2.46
2.43
2.42
2.40
1.35
1.31
1.28
1.15
1.12
0.05
OH
CO2Et
67
0.85
0.82
1.89
1.04
0.86
2.03
3.05
3.20
Chemical Shift (ppm)
CHLOROFORM-d
166.60
150.41
120.14
77.63
77.00
76.36
65.20
60.28
34.30
23.24
14.15
Chemical Shift (ppm)
%T
3439.77
3019.67
1762.93
1690.86
1608.57
1495.85
1467.10
1341.91
1215.46
1160.32
1052.53
1032.12
1004.50
756.06
668.43
Wavenumbers (cm-1)

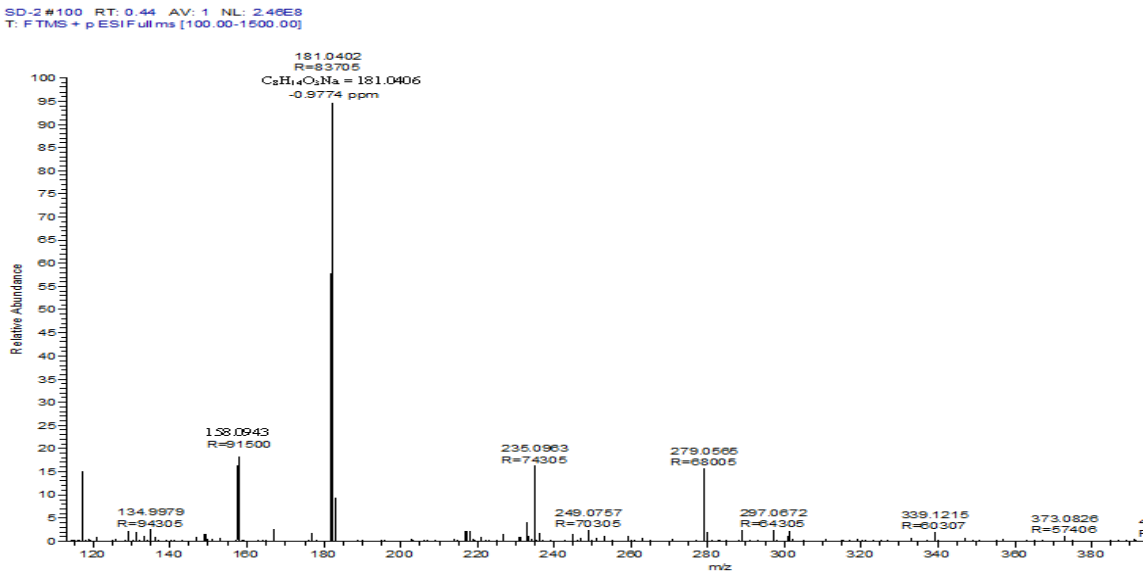


Fig. 22: ^{1}H, ^{13}C NMR, IR and HRMS spectra of alcohol fragment **67**

Thus, the chiral secondary alcohol functionality in **30** was protected as its MOM ether **40** (MOMCl, DIPEA). The formation of the MOM ether **40** was confirmed from its ^{1}H and ^{13}C NMR spectral analysis. Its ^{1}H NMR spectrum showed a multiplet at δ 4.55-4.64 (m, 2H) and a singlet at δ 3.37 (s, 3H) due to the presence of methylene and methyl protons respectively of attached MOM group. Its ^{13}C NMR spectrum displayed two typical signals at δ 94.5 and 55.5 corresponding to methylene and methyl carbon of the attached MOM group respectively (**Fig. 23**). Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} 1740 cm^{-1} due to the presence of ester carbonyl functional group.

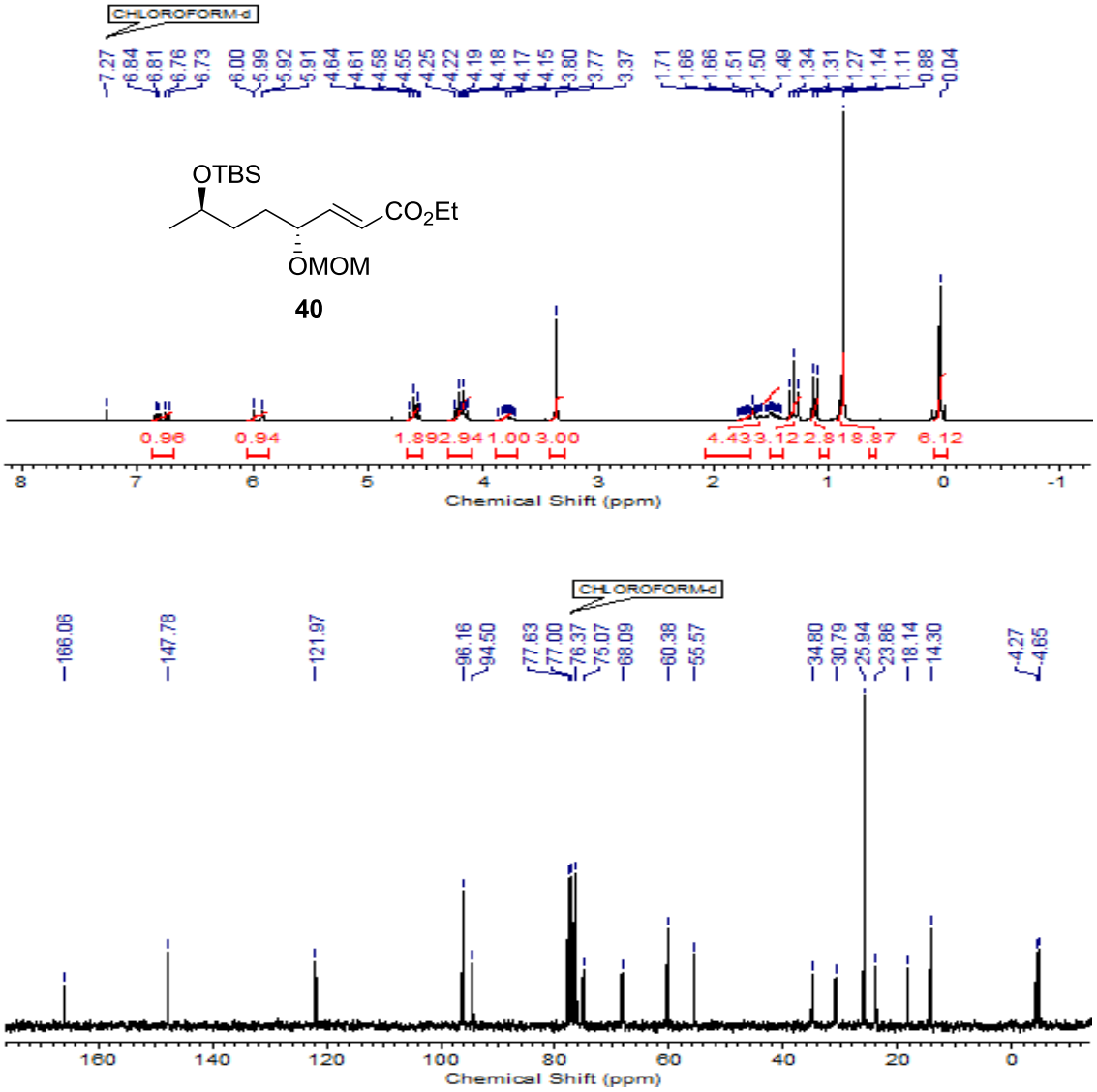
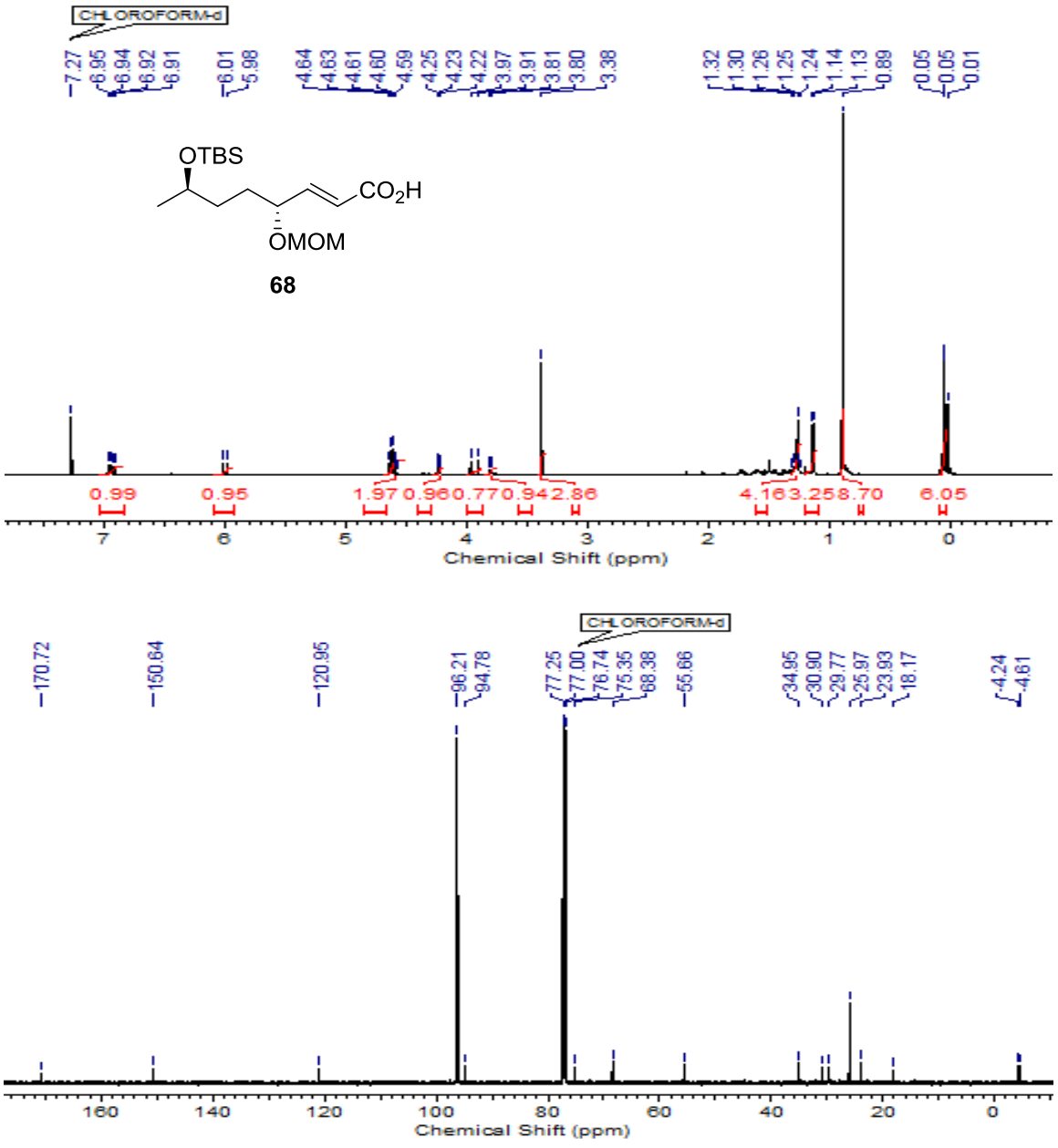


Fig. 23: ^{1}H and ^{13}C NMR spectra of MOM ether **40**

The ester **40** was then hydrolyzed under LiOH condition to furnish acid fragment **68** in 70% yield. Its formation was confirmed by the appearance of resonance at δ 6.91 (dd, *J* = 6.1, 15.5 Hz, 1H) signal due to olefinic proton attached to $–CO_2H$ group and disappearance of a triplet at δ 1.50 in its ^{1}H NMR spectrum as well as occurrence of a carbon signal at δ 170.72 due to the carbonyl carbon of $–CO_2H$ group in its ^{13}C NMR spectrum. Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} 1729 cm^{-1} indicating the

presence of acid functional group. Its molecular mass from HRMS (ESI) spectrum for [($C_{16}H_{32}O_5Si$)H] (M+H) was found to be 333.2150, which was in well agreement with the calculated value 333.2153 (**Fig. 24**).



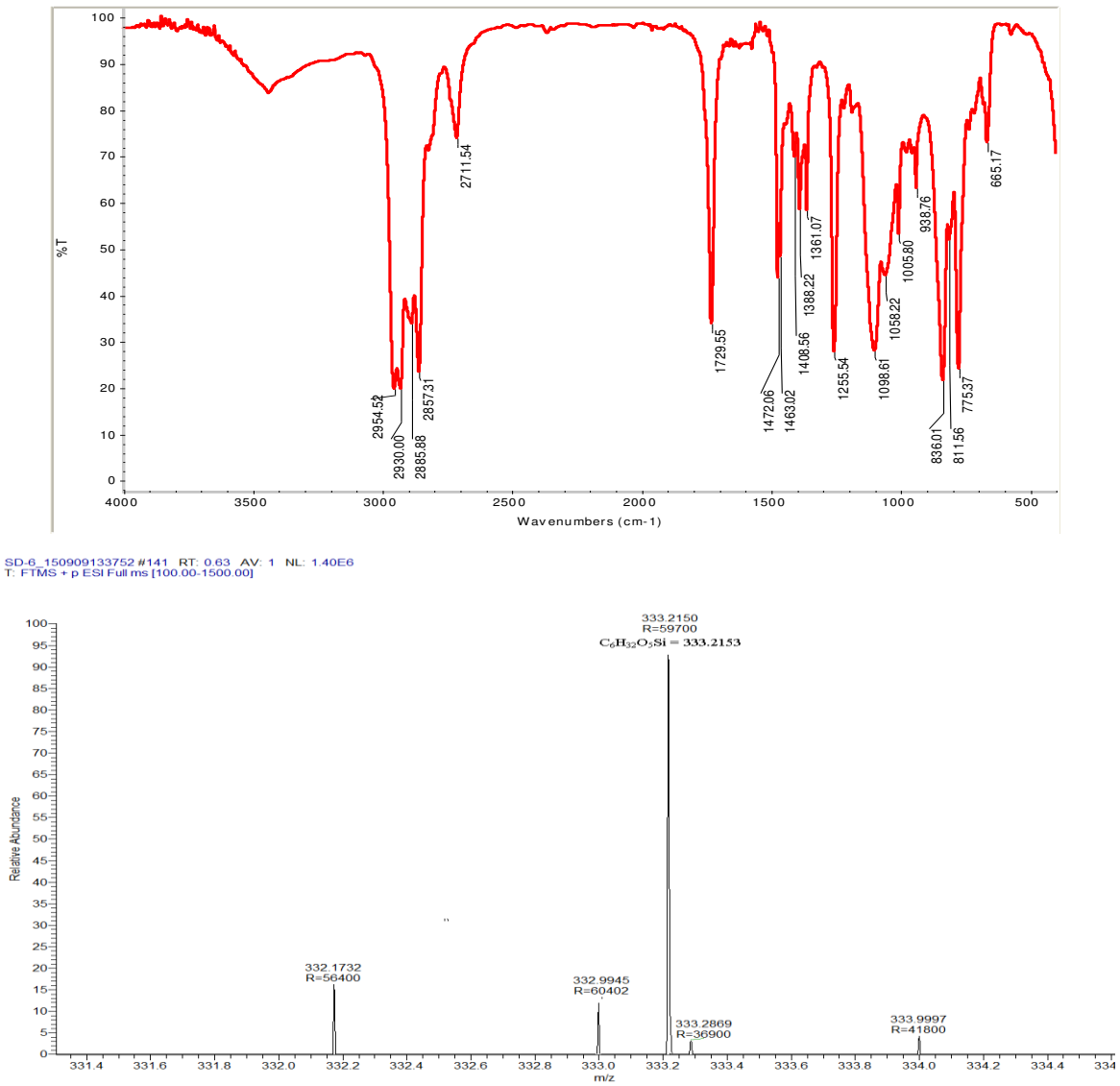
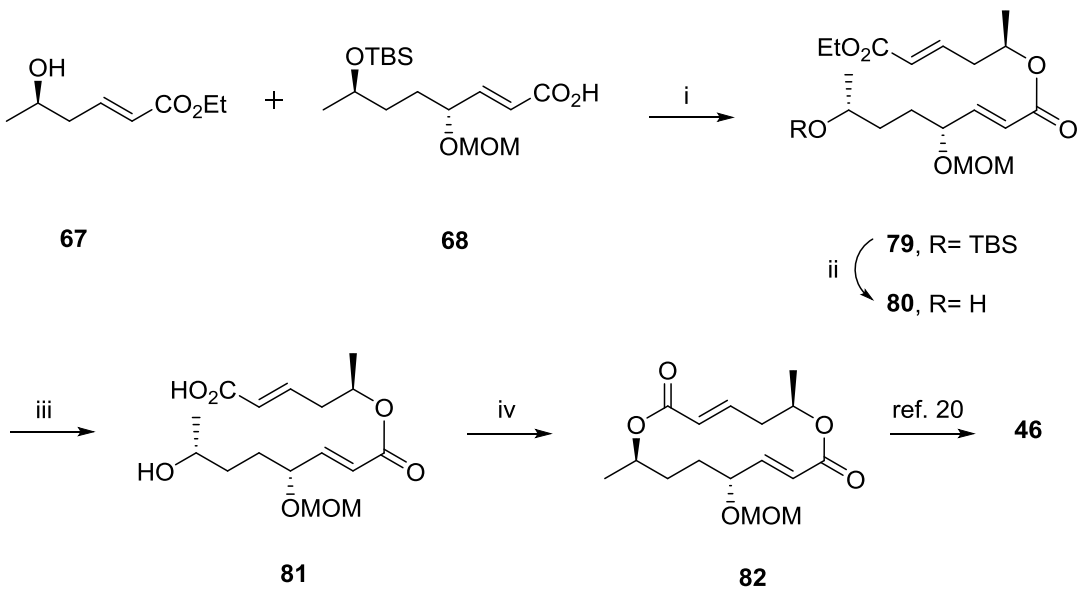


Fig. 24: ^{1}H, ^{13}C NMR, IR and HRMS spectra of acid fragment **68**

Scheme 12 presents the final synthetic scheme of intermediate **82**. Gratifyingly, alcohol **67** and acid **68** fragments were coupled under Steglich esterification condition (DCC, DMAP, CH_2Cl_2) to form ester **79** in 60% yield.



Scheme 12: (i) DCC, DMAP, CH_2Cl_2, 8 h, 60%; (ii) TBAF, THF, 2 h, 65%; (iii) LiOH, MeOH/H_2O (1:1), 1 h; (iv) 2,4,6-trichloro benzoyl chloride, Et_3N, DMAP, toluene, 25 ºC, 24 h, 45%; (v) 2N HCl, THF, 2 h, rt, 68%.

The formation of the compound **79** was established by its ^{1}H NMR spectrum, which showed proton resonance signals at δ 6.85-6.95 (m, 1H), 6.8 (dd, *J* = 6.3, 15.7 Hz, 1H), 5.95 (d, *J* = 15.8 Hz, 1H) and 5.88 (d, *J* = 15.6 Hz, 1H) due to olefinic protons respectively. It was further ascertained by the appearance of characteristic carbon signals in its ^{13}C NMR spectrum at δ 121.8, 124.3, 143.2 and 148.2 due to olefinic carbons respectively (**Fig. 25**). Its IR spectrum too displayed two typical strong vibrational stretching frequencies at υ_{max} 1710 and 1727 cm^{-1} indicative of the presence of carbonyl functional groups respectively.

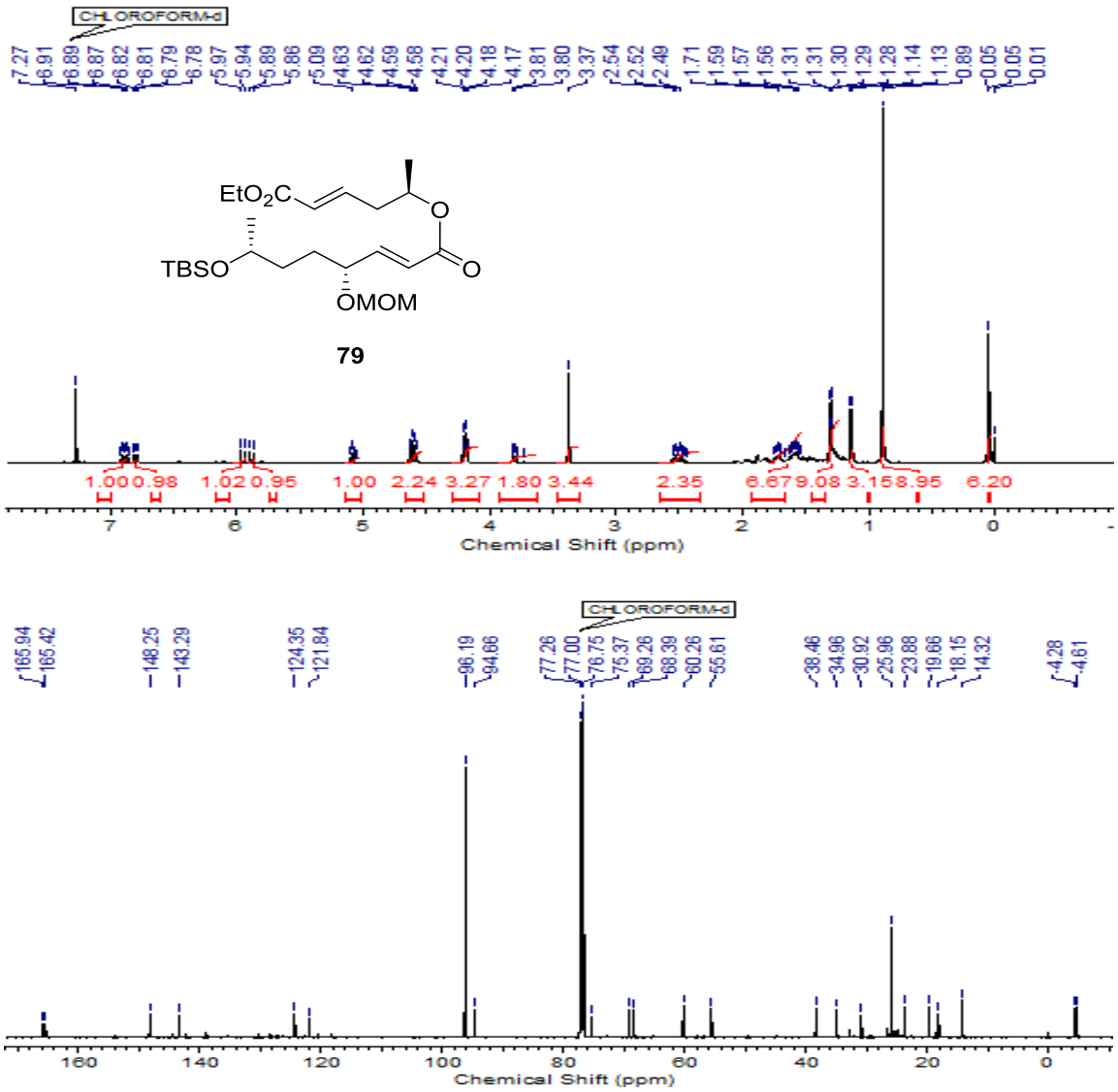


Fig. 25: ^{1}H and ^{13}C NMR spectra of coupled ester **79**

Next, the ester **79** was subjected to desilylation protocol (TBAF, THF, 0 ºC, 2 h) to produce hydroxy ester **80** in 65% yield. The disappearance of singlets at δ 0.89 (s, 9H) and 0.5 (s, 6H) corresponding to protons of TBS group in its ^{1}H NMR and the appearance of a carbon signal at δ 67.2 in its ^{13}C NMR spectrum due to the carbon attached to –OH group (-**C**H-OH) confirmed the formation of ester **80** (**Fig. 26**). Also, the appearance of

characteristic vibrational stretching frequencies at υ_{max} 3420, 1727 and 1717 cm^{-1} in its IR spectrum confirmed the presence of hydroxyl and ester carbonyl groups respectively.

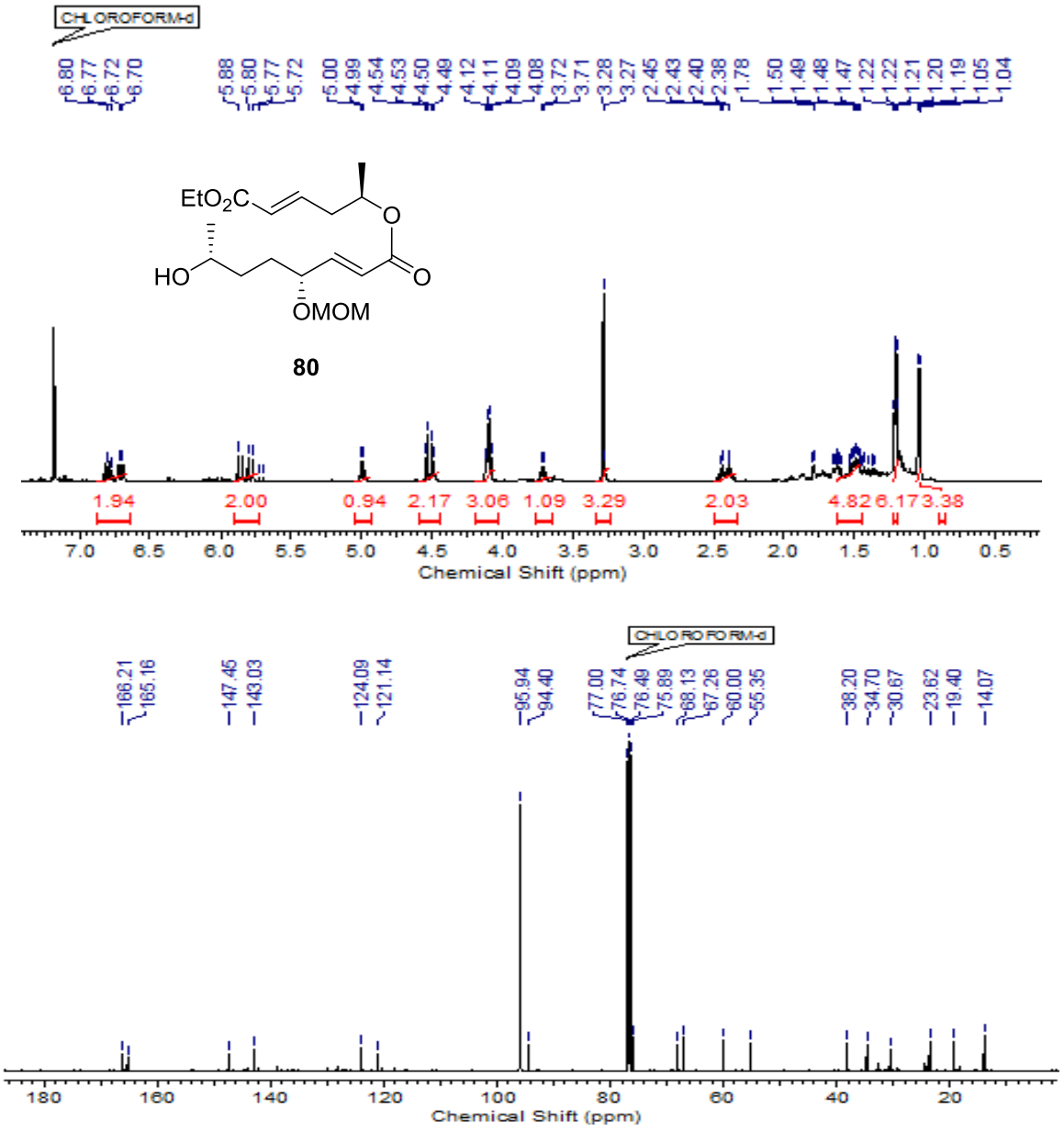
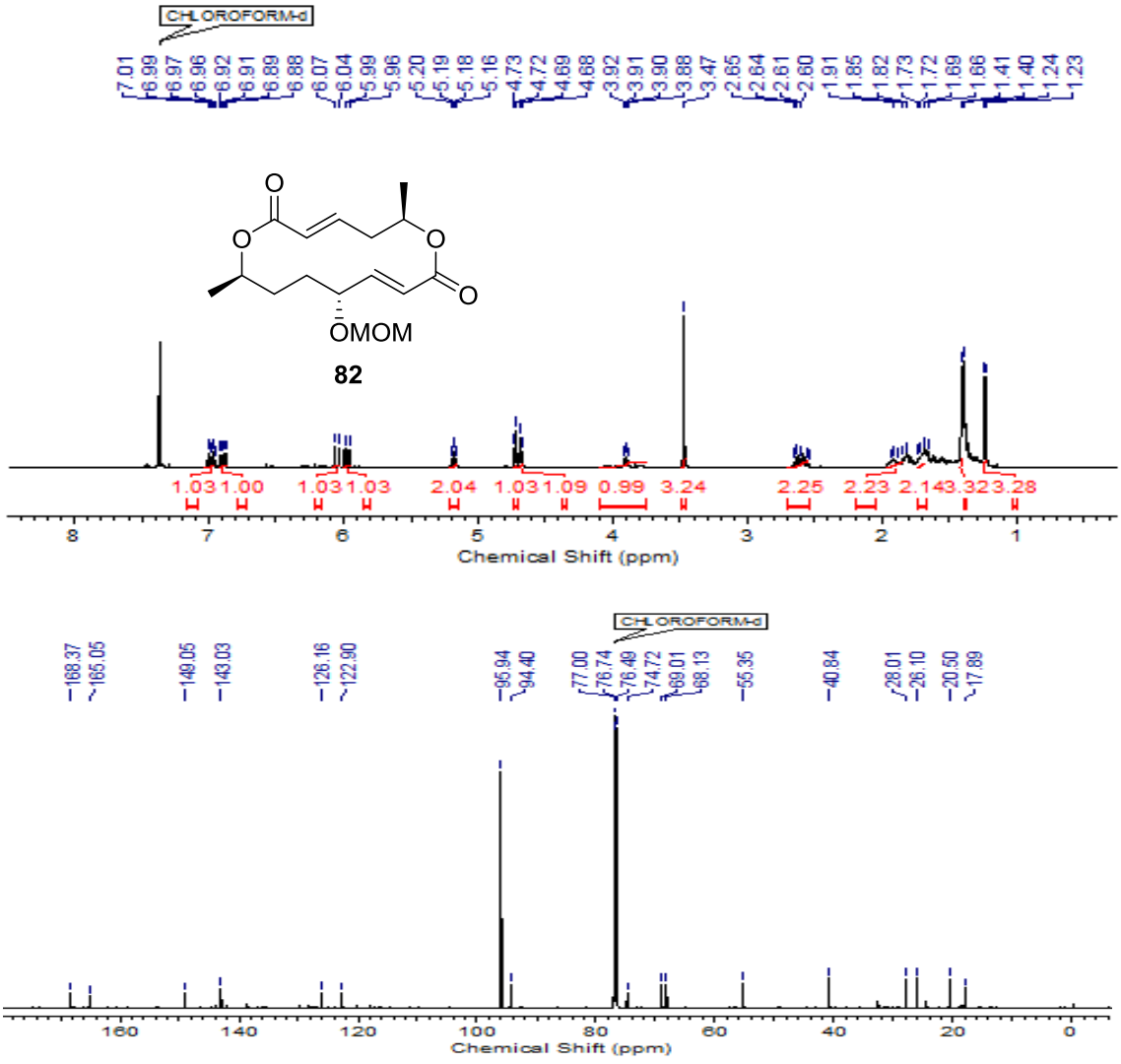


Fig. 26: ^{1}H and ^{13}C NMR spectra of hydroxy ester **80**

The ester functionality in **80** was hydrolyzed using LiOH in MeOH/H_2O (1:1) solvent to produce *seco* acid **81**, which was, without further characterization subjected to Yamaguchi

macrolactonization (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 25 ºC, 24 h) to furnish macrolactone **82** in 45% yield. The formation of macrolactone **82** was confirmed from its ^1H and ^{13}C NMR spectral analysis. The ^1H NMR spectrum of **82** showed a multiplet at δ 5.16-5.20 (m, 2H) due to the methine protons attached to oxygen atoms. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 68.1 and 69.0 corresponding to methine carbons attached to oxygen atoms (CH_3-**C**H-O) respectively. Its molecular mass from HRMS (ESI) spectrum for [($C_{16}H_{24}O_6$)H] (M+H) was found to be 313.1570, which was in well agreement with the calculated value 313.1573 (**Fig. 27**).



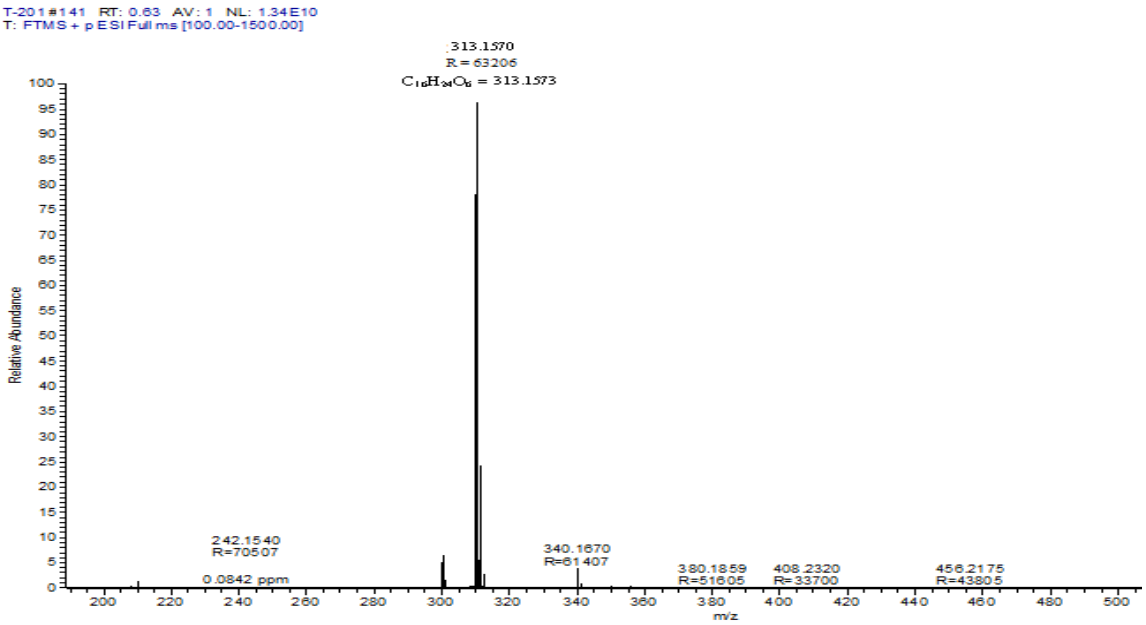


Fig. 27: ^{1}H, ^{13}C NMR & HRMS spectra of macrolactone **82**

Its IR spectrum showed two typical strong vibrational stretching frequencies at υ_{max} 1765 and 1774 cm^{-1} due to the presence of lactone carbonyl functionalities.

The enantiomeric purity of **82** was determined to be 97% ee based on the comparison of its specific rotation with the reported values $[\alpha]_D^{25}$ +120.1 (*c* 0.2, $CHCl_3$) {lit.[20] $[\alpha]_D^{25}$ +123.8 (*c* 0.06, $CHCl_3$)}. Intermediate **82** thus obtained was identical to the compound reported in the literature in all respects, thereby completing the formal synthesis of (-)-(6*R*,11*R*,14*R*)-colletallol **46**.[20]

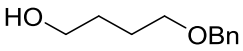
2.2.4 Conclusion

In conclusion, we have described an efficient synthetic route to macrolactone **82**, key intermediate for (-)-(6*R*,11*R*,14*R*)-colletallol, thereby constituting its formal synthesis. The strategy incorporates a successful application of proline-catalyzed asymmetric α-aminooxylation and its sequential reactions in 97% ee with an overall yield of 3.6%. The

operationally simple transformations, high overall yields requiring a relatively low amount of inexpensive and non-toxic proline as catalyst make this approach an attractive, flexible and useful process to make other analogue of diolide family.

2.2.5 Experimental Section

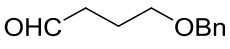
4-(Benzyloxy)butan-1-ol (71)



To a stirred solution of NaH (6.6 g, 166 mmol) in dry THF (100 mL), a solution of 1,4-butanediol **70** (15 g, 166 mmol) in dry THF (100 mL) was added dropwise at 0 ^{o}C followed by the addition of benzyl bromide (25.54 g, 149.4 mmol). The reaction mixture was stirred for 6 h at 25 ^{o}C. After the completion of the reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride and the product was 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 (4:1 v/v) gave 4-(benzyloxy)butan-1-ol **71**.

Yield: 29.2 g, 97%; colourless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3453, 3030, 2987,1389,1095, 1056, 895; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.6 (m, 4H), 1.8 (br s, 1H), 3.4 (t, *J* = 5.8 Hz, 2H), 3.6 (t, *J* = 4.3 Hz, 2H), 4.5 (s, 2H), 7.3-7.4 (5H, m); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.6, 26.0, 62.6, 70.2, 72.7, 127.5, 127.6, 128.3, 138.5; **Anal. Cald.** for $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95; Found: C, 73.16; H, 8.80%.

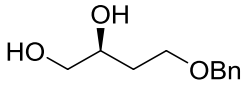
4-(Benzyloxy)butanal (72)



To a well stirred solution of alcohol **72** (10 g, 48.0 mmol) in dry DMSO (100 mL), 2-iodoxybenzoic acid (26.8 g, 96.0 mmol) was added in one portion. The reaction mixture was then stirred for 2 h at 25 ^{o}C. After completion of the 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/ethyl acetate (19:1 v/v) gave the aldehyde **72** as colourless viscous liquid.

Yield: 8.3 g, 98%; colourless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3065, 3030, 2987, 1725, 1520, 1105, 1090, 852; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.92-1.99 (m, 2H), 2.52-2.6 (m, 2H), 3.53 (t, *J* = 6.5 Hz, 2H), 4.5 (s, 2H), 7.29-7.36 (m, 5H), 9.79 (t, *J* = 1.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.5, 40.8, 69.0, 72.9, 127.3, 127.4, 128.3, 138.1, 202.5; **Anal. Cacld.** for $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92; Found: C, 74.08; H, 7.88%.

(*S*)-4-(Benzyloxy)butane-1,2-diol (73)

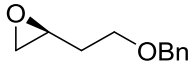


To a pre-cooled solution of aldehyde **72** (5 g, 28 mmlol) in CH_3CN (30 mL) at -20 ^{o}C, nitrosobenzene (0.91 g, 8.4 mmol) and D-proline (0.32 g, 2.8 mmol) were added. The reaction was then stirred at -20 ^{o}C for 24 h. Then it was diluted with MeOH (20 mL) at 0 ^{o}C, $NaBH_4$ (2.12 g, 56 mmol) was added to it and stirred for 30 min. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride. Then solvent was evaporated and organic layer was extracted with EtOAc (3x50

mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, concentrated to give the crude aminooxy alcohol, which was directly used for the next step without purification.

To a solution of the above crude aminooxyalcohol in EtOH (50 mL) was added $CuSO_4.5H_2O$ (2.1 g, 8.4 mmol) at 0 ^oC. The reaction mixture was allowed to stir for 10 h at this temperature. After the addition of the phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3x50 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude diol, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4 v/v) to give **73**. **Yield**: 4.12 g, 75%; colourless oil; **$[\alpha]_D^{25}$** –3.2 (*c* 1, $CHCl_3$) {lit.[1] $[\alpha]_D^{25}$ –3.3 (*c* 1.0, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3440, 3102, 1516, 1465, 1325, 1149, 1050, 890; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.55-1.93 (m, 2H), 2.18-2.42 (m, 1H), 3.01-3.19 (m, 1H), 3.42-3.74 (m, 4H), 3.81-4.03 (m, 1H), 4.45-4.60 (m, 2H), 7.19-7.44 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 60.2, 68.1, 70.1, 73.2, 127.5, 127.6, 128.3, 138.3; **Anal. Calcd.** for $C_{11}H_{16}O_2$ requires C, 67.32; H, 8.22; Found C, 67.15; H, 8.10%; **Optical purity**: 98% ee determined by HPLC analysis (Chiracel AD-H column, Hex/*i*-PrOH 90:10, 0.5 mL/min, 220 nm). Retention time: t_{major}= 26.12 min and t_{minor}= 28.38 min.

(*S*)-2-(2-(Benzyloxy)ethyl)oxirane (74)

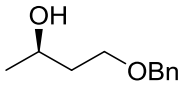


To a stirred solution of diol **73** (3 g, 15.29 mmol) in CH_2Cl_2 (30 mL) were added Bu_2SnO (0.87 g, 3.5 mmol), *p*-TsCl (2.9 g, 15.29 mmol) and Et_3N (2.1 mL, 15.29 mmol). The reaction mixture was stirred until TLC indicated complete consumption of the starting

material. The mixture was filtered, and the filtrate was concentrated in *vacuo*. Then to the crude in MeOH (20 mL) at 0 ^{o}C, K_2CO_3 (4.26 g, 30.58 mmol) was added and stirred for 1 h. After completion of the reaction (monitored by TLC), then solvent was evaporated and organic layer was extracted with EtOAc (3x50 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4 concentrated to give the crude product which on column chromatographic purification with petroleum ether/EtOAc (9:1 v/v) provided the oxirane **74**.

Yield: 1.77 g, 65%; colourless viscous liquid; $[\alpha]_D^{25}$ –4.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3215, 3103, 1540, 1456, 1225, 1150, 1094, 972, 789; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.64-2.00 (m, 2H), 2.50 (dd, *J* = 2.8, 5.1 Hz, 1H), 2.70-2.83 (m, 1H), 3.05 (dddd, *J* = 2.8, 3.9, 4.8, 6.4 Hz, 1H), 3.54-3.67 (m, 2H), 4.52 (s, 2H), 7.19-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.7, 33.0, 47.0, 49.9, 67.0, 73.1, 76.5, 127.6, 128.1, 127.8, 128.4, 129.6, 138.3; **Anal. Cacld.** for $C_{11}H_{14}O_2$ requires C, 74.15; H, 7.91; Found: C, 74.05, H, 7.81%; **Optical purity**: 98% ee determined by chiral HPLC analysis [Chirapak OD-H, 2-Propanol/n-Hexane = 2.5/97.5, flow rate 0.5 mL/min, λ = 254 nm, retention time: (minor) 12.59 min, (major) 15.59 min].

(*R*)-4-(Benzyloxy)butan-2-ol (75)

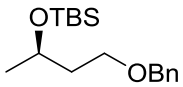


To a stirred solution of $LiAlH_4$ (1.06 g, 28.07 mmol) in dry THF (30 mL), a solution of epoxide (-)-**74** (5.0 g, 28.07 mmol) in dry THF (30 mL) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at the same temperature for 30 min. After the completion of reaction (monitored by TLC), it was quenched with aq. 20% solution of sodium hydroxide

(5 mL) at 0 ^{o}C. The reaction mixture was filtered through sintered funnel, dried over Na_2SO_4 and concentrated. Purification by column chromatography with petroleum ether/ethyl acetate (9:1 v/v) gave the secondary alcohol **75**.

Yield: 4.8 g, 95%; colourless free flowing liquid; **$[\alpha]_D^{25}$** - 6.18 (*c* 2.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3454, 3112, 2935, 1657, 1460, 1416, 1375, 1300, 1056, 754; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (d, *J* = 6.3 Hz, 3H), 1.65-1.79 (m, 2H), 2.89 (br s, 1H), 3.57-3.69 (m, 2H), 3.93-4.01 (m, 1H), 4.49 (s, 2H), 7.23-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.3, 38.1, 67.1, 68.8, 73.2, 127.5, 127.6, 128.3, 137.9; **Anal. Calcd.** for $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95; Found: C, 72.90; H, 8.85%.

(*R*)-((4-(Benzyloxy)butan-2-yl)oxy)(*tert*-butyl)dimethylsilane (76)

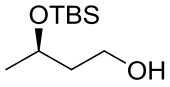


To a solution of alcohol **75** (4.50g, 24.98 mmol) in dry CH_2Cl_2 (80 mL) at 0 ^{o}C were added imidazole (1.69 g, 24.98 mmol) and *tert*-butyldimethylsilyl chloride (3.71 g, 24.98 mmol). The reaction mixture was then stirred at 25 ^{o}C for 2 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2, washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product which was then purified by column chromatography with pure petroleum ether to give **76** as a colorless free flowing liquid.

Yield: 7.2 g, 98%; colorless free flowing liquid; **$[\alpha]_D^{25}$** -9.8 (*c* 2., $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 2929, 2856, 1471, 1462, 1455, 1373, 1361, 1264, 1158, 1050; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.05 (s, 6H), 0.87 (s, 9H), 1.09 (dd, *J* = 6.2, 8.6 Hz, 3H), 1.54-1.75 (m, 2H), 3.36-3.56 (m, 2H), 3.85-4.03 (m, 1H), 4.42 (d, *J* = 3.9 Hz, 2H), 7.17-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.8, -4.3, 24.2, 26.0, 39.7, 65.6, 67.2, 73.0, 127.5, 127.7,

128.3, 138.6; **Anal. Calcd.** for $C_{17}H_{30}O_2Si$ requires C, 69.33; H, 10.27; Found: C, 69.21; H, 10.16%.

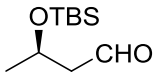
(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)butan-1-ol (77)



A mixture of benzyl ether **76** (6 g, 20.39 mmol) in EtOAc (20 mL) 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 pad (EtOAc eluent) and the solvent was evaporated under reduced pressure to afford the title compound **77**.

Yield: 3.9 g, 96%; slightly yellow colored oil; $\mathbf{[\alpha]_D^{25}}$ -11.7 (*c* 2., $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3404, 2930, 2857, 1225,1099, 1050; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.05 (m, 6H), 0.81 (s, 9H), 1.13 (dd, *J* = 6.5, 0.6 Hz,, 3H), 1.44-1.81 (m, 2H), 2.51 (br s, 1H), 3.46-3.79 (m, 2H), 3.88-4.16 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.2, 24.2, 25.9, 39.7, 65.6, 67.2; **Anal. Calcd.** for $C_{10}H_{24}O_2Si$ requires C, 58.77; H, 11.84; Found: C, 58.67; H, 11.75%.

(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)butanal (69)

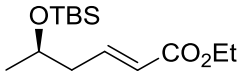


To a well-stirred solution of alcohol **77** (4.00 g, 19.59 mmol) in DMSO (30 mL), 2-iodoxybenzoic acid (10.9 g, 39.18 mmol) was added in one portion. The reaction mixture was then stirred for 1 h at 25 C. After the completion of reaction (monitored by TLC), it was diluted with water and diethyl ether. 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/ethyl acetate (19:1 v/v) gave the intermediate aldehyde **69**.

Yield: 3.89 g, 98%; light yellow colored viscous liquid; $[\alpha]_D^{25}$ -13.0 (*c* 2.5, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3020, 2930, 2857, 1722, 1572, 1472, 1215; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.88 (s, 9H), 1.08 (d, *J* = 6.1 Hz, 3H), 1.33-1.45 (m, 2H), 1.52 - 1.78 (m, 2H), 2.29-2.45 (m, 2H), 3.76 (d, *J* = 5.7 Hz, 1H), 9.71 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.2, 18.1, 24.2, 25.9, 39.7, 68.2, 192.5; **Anal. Cacld.** for $C_{10}H_{22}O_2Si$ requires C, 59.35; H, 10.96; Found: C, 59.27; H, 10.84%.

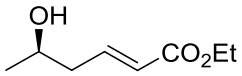
Ethyl (*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate (78)



To a solution of aldehyde **69** (3.00 g, 14.84 mmol) in dry THF (100 mL) at 25 ^oC was added $Ph_3P{=}CHCO_2Et$ (10.08 g, 29.68 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/ethyl acetate (19:1 v/v) gave the α,β-unsaturated ester **78**.

Yield: 3.83 g, 95%; pale yellow colored viscous liquid; $[\alpha]_D^{25}$ -15.8 (*c* 2.4, $CHCl_3$, cm^{-1}); **IR** (neat, cm^{-1}): υ_{max} 2930, 2857, 1724, 1655, 1463, 1376, 1158, 1050, 790; **^{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* = 6.3, 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, 61.64; H, 10.30%.

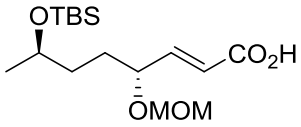
Ethyl-(*R*,*E*)-5-hydroxyhex-2-enoate (67)



To a stirred solution of TBS ether **78** (2 g, 7.3 mmol) in THF (10 mL) was added 7.2 mL of 1M THF solution of TBAF (7.3 mmol) at 0 ^{o}C. Then the reaction was stirred for 1 h. After completion of reaction (checked by TLC), the solvent was evaporated and organic layer was extracted with EtOAc (3x30 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, concentrated to give the crude product, which on column chromatographic purification with petroleum ether/ethyl acetate (4:1 v/v) gave hydroxyl compound **67**.

Yield: 0.92 g, 80%; colourless viscous liquid; $[\alpha]_D^{25}$ -7.8 (*c* 2.0, $CHCl_3$, cm^{-1}); **IR** (neat, cm^{-1}): υ_{max} 3439, 3010, 1762, 1645, 1463, 1376, 1285, 1160, 1020, 756; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 2.40-2.47 (m, 2H), 2.55 (br s, 1H), 4.19-4.25 (m, 1H), 5.64 (d, *J* = 15.5 Hz, 1H), 6.56 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 23.8, 34.3, 60.2, 65.2, 120.3, 150.4, 166.6; **HRMS** (ESI): calc. for $[(C_8H_{14}O_3)Na]$ (M+Na) 181.0406: Found: 181.0402.

(4*R*,7*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-4-(methoxymethoxy)oct-2-enoic acid (68)

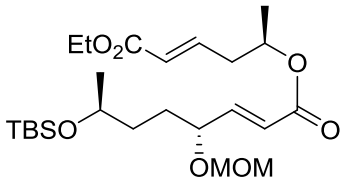


To a stirred solution of **40** (2.0 g, 5.5 mmol) dissolved in THF/MeOH /H_2O (3:1:1) (10 mL) was added LiOH.H_2O (0.346 g, 8.25 mmol) and stirred for 2 h at 25 ^{o}C. After completion of reaction (checked by TLC), the solvent was evaporated and organic layer was extracted with CH_2Cl_2. The aqueous layer was acidified and the extracted with CH_2Cl_2 (3x30 mL). The combined CH_2Cl_2 layers were dried over anhyd. Na_2SO_4, concentrated to

give the crude product, which on column chromatographic purification with petroleum ether/ethyl acetate (1:1 v/v) gave **68**.

Yield: 1.2 g, 70%; colorless viscous liquid; $[\alpha]_D^{25}$ +19.5 (*c* 1.0, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3250, 3114, 2980, 1729, 1520, 1260, 1050, 790; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.14 (d, *J* = 6.1 Hz, 3H), 1.24-1.32 (m, 4H), 3.38 (s, 3H), 3.78-3.82 (m, 1H), 3.91-3.97 (m, 1H), 4.18-4.28 (m, 1H), 4.50-4.68 (m, 2H), 6.00 (d, *J* = 15.6 Hz, 1H), 6.93 (dd, *J* = 6.1, 15.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ -4.6, -4.2, 18.2, 23.9, 26.0, 29.8, 30.9, 35.0, 55.7, 68.4, 75.4, 94.8, 121.0, 150.6, 170.7; **HRMS** (ESI): calc. for [($C_{16}H_{32}O_5Si$)H] (M+H) 333.2153, Found: 333.2150.

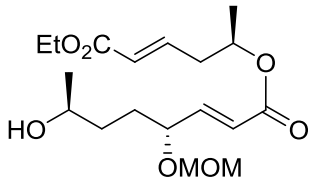
(*R*,*E*)-6-Ethoxy-6-oxohex-4-en-2-yl-(4*R*,7*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-(methoxymethoxy)oct-2-enoate (79)



To a stirred solution of acid **68** (1 g, 3.01 mmol) in CH_2Cl_2 (10 mL), DCC (0.68 g, 3.31 mmol) and DMAP (36 mg, 0.3 mmol) were added at 0 ºC and stirred it for 15 min. Then a solution of alcohol **67** (0.42 g, 2.7 mmol) in CH_2Cl_2 (5 mL) was added to the reaction mixture at same temperature in a dropwise manner and stirred it for overnight. After the reaction (checked by TLC), it was quenched with water, and the organic layer was extracted with CH_2Cl_2 (3x30 mL). Then 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 over silica gel using petroleum ether/EtOAc (9:1 v/v) to give **79**.

Yield: 0.85 g, 60%; pale yellow viscous liquid; $[\alpha]_D^{25}$ +155.5 (*c* 0.5, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 2980, 1710, 1727, 1620, 1455, 1210, 1150, 890; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.13 (d, *J* = 6.1 Hz, 3H), 1.23-1.33 (m, 9H), 1.52-1.66 (m, 4H), 1.72 (dt, *J* = 5.5, 18.8 Hz, 2H), 2.39-2.59 (m, 2H), 3.37 (s, 4H), 3.76-3.92 (m, 1H), 4.19 (q, *J* = 7.0, 10.8 Hz, 3H), 4.53-4.67 (m, 2H), 5.01-5.14 (m, 1H), 5.88 (d, *J* = 15.6 Hz, 1H), 5.95 (d, *J* = 15.9 Hz, 1H), 6.80 (dd, *J* = 6.3, 15.7 Hz, 1H), 6.85-6.95 (m, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ -4.6, -4.3, 14.3, 18.2, 19.7, 23.9, 26.0, 30.9, 35.0, 38.5, 55.6, 60.3, 68.4, 69.3, 75.4, 94.7, 121.8, 124.4, 143.3, 148.2, 165.4, 165.9; **Anal. Calcd.** for $C_{24}H_{44}O_7Si$ requires C, 60.98; H, 9.38; Found: C, 60.85; H, 9.28%.

(*R*,*E*)-6-Ethoxy-6-oxohex-4-en-2-yl-(4*R*,7*S*,*E*)-7-hydroxy-4-(methoxymethoxy)oct-2-enoate (80)

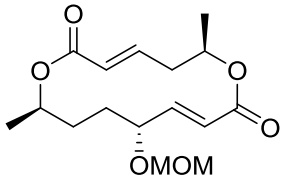


To a stirred solution of TBS ether **79** (0.5 g, 1.06 mmol) in THF (10 mL) was added 0.92 mL of 1M THF solution of TBAF (1.06mmol) at 0 ^oC. The reaction mixture was stirred for 1 h. After completion of reaction (checked by TLC), the solvent was evaporated and organic layer was extracted with EtOAc (3x30 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, concentrated to give the crude product, which on column chromatographic purification with petroleum ether/ethyl acetate (4:1 v/v) gave hydroxyl compound **80**.

Yield: 0.49 g, 65%; colourless viscous liquid; $[\alpha]_D^{25}$ +109.1 (*c* 0.32, $CHCl_3$); **IR** (neat, cm^{-1}): υ_{max} 3441, 3121, 2980, 1710, 1727, 1620, 1455, 1210, 890; **^{1}H NMR** (200 MHz,

$CDCl_3$): δ 1.04 (d, *J* = 6.1 Hz, 3H), 1.19-1.22 (m, 6H), 1.47-1.50 (m, 4H), 2.38-2.45 (m, 2H), 3.28 (s, 3H), 3.71-7.75 (m, 1H), 4.08-4.12 (m, 3H), 4.49-4.54 (m, 2H), 4.99-5.0 (m, 1H), 5.7 (d, *J* = 14.7 Hz, 1H), 5.8 (d, *J* = 15.2 Hz, 1H), 6.70 (d, *J* = 17 Hz, 1H), 6.8 (dd, J = 15.2, 4.5, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 14.0, 19.4, 23.6, 30.6, 38.2, 55.3, 60.0, 67.2, 68.1, 75.8, 94.4, 121.1, 124.0, 143.0, 147.0, 165.1, 166.2; **Anal. Calcd.** for $C_{18}H_{30}O_7$ requires C, 60.32; H, 8.44; Found: C, 60.25; H, 8.35%.

(3*E*,6*R*,9*E*,11*R*,14*R*)-11-(Methoxymethoxy)-6, 14-dimethyl-1, 7-dioxacyclotetradeca-3, 9-diene-2, 8-dione (82)



To a stirred solution of **80** (0.3 g, 0.83 mmol) dissolved in THF/MeOH /H_2O (3:1:1) (2 mL) was added LiOH.H_2O (34 mg, 0.83 mmol) and stirred for 2 h at 25 ^oC. After completion of reaction (checked by TLC), the solvent was evaporated and organic layer was extracted with CH_2Cl_2. The aqueous layer was acidified and the extracted with CH_2Cl_2 (3x30 mL). The combined CH_2Cl_2 layers were dried over anhyd. Na_2SO_4, concentrated to give the crude product, which on without further purification was subjected to Yamaguchi cyclization.

To a stirred solution of 2,4,6-trichlorobenzoyl chloride (0.2 g, 0.83 mmol) and DMAP (0.1 g, 0.83 mmol) in toluene (5 mL) at 25 ºC, the crude product dissolved in toluene (2 mL) was added slowly and stirred for 24 h. The reaction mixture was washed with aq. citric acid solution and brine. Then the organic layer was dried (Na_2SO_4) and concentrated, which

was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1 v/v) to give **82**.

Yield: 0.11 g, 45%; pale yellow gum; $[\alpha]_D^{25}$ +120.1 (*c* 0.25, $CHCl_3$) {lit.[20] $[\alpha]_D^{25}$ +123.8 (*c* 0.06, $CHCl_3$)}; **IR** (neat, cm^{-1}): υ_{max} 3241, 3121, 2980, 1774, 1765, 1620, 1455, 1210, 890; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.6 Hz, 3H), 1.4 (d, *J* = 5.8 Hz, 1H), 1.66-1.72 (m, 2H), 1.73-1.91 (m, 2H), 2.60-2.65 (m, 2H), 3.47 (s, 3H), 3.88-3.92 (m, 1H), 4.68-4.73 (m, 2H), 5.16-5.20 (m, 2H), 5.96 (d, *J* = 16.1 Hz, 1H), 6.07 (d, *J* = 15.8 Hz, 1H), 6.88 (dd, *J* = 5.5, 16.3 Hz, 1H), 6.96-7.01 (m, 1H) ; **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 17.8, 20.5, 26.1, 28.0, 40.8, 55.3, 68.1, 69.0, 74.7, 94.4, 122.9, 126.1, 143.0, 149.0, 165.0, 168.3; **HRMS** (ESI): calc. for [($C_{16}H_{24}O_6$)H] (M+H) 313.1573, Found: 313.1570.

Section III

Asymmetric Synthesis of (*S*)-3-Hydroxypiperidine Skeleton: A Key Element in Natural Product Synthesis

2.3.1 Introduction and Pharmacology

The functionalized piperidines are among the most ubiquitous heterocyclic building blocks of natural and synthetic compounds with potential biological activities.[21] In particular, piperidine-3-ols (**83-87**) are attractive target because of their widespread occurrence in bioactive natural products such as psuedoconhydrine (**85**)[22] and cassine (**86**)[23] (**Fig. 28**).

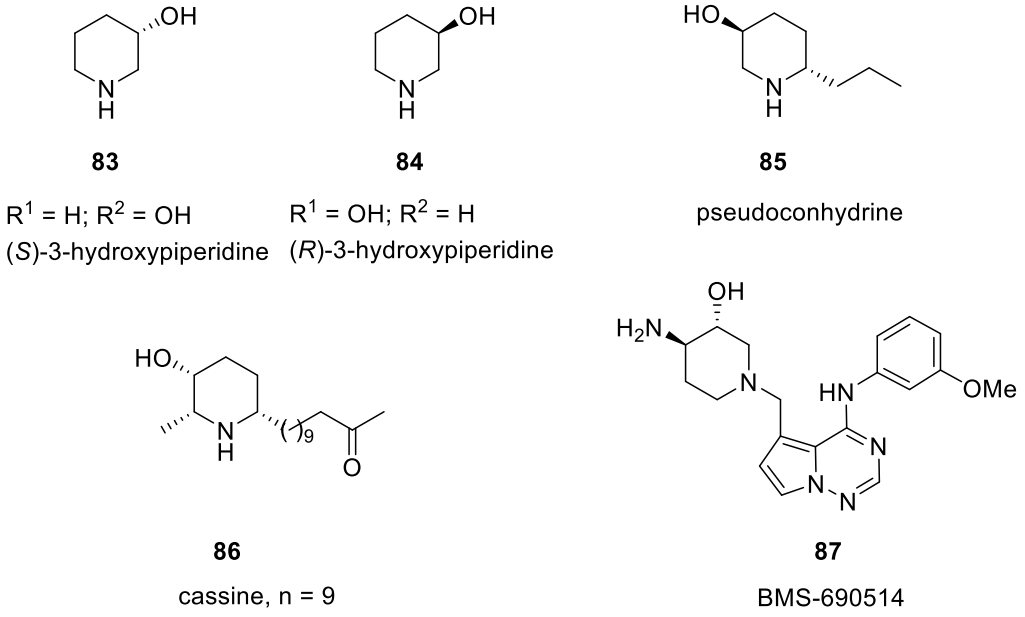


Fig. 28: Some of the structures of 3-hydroxypiperidine units present in bioactive molecules

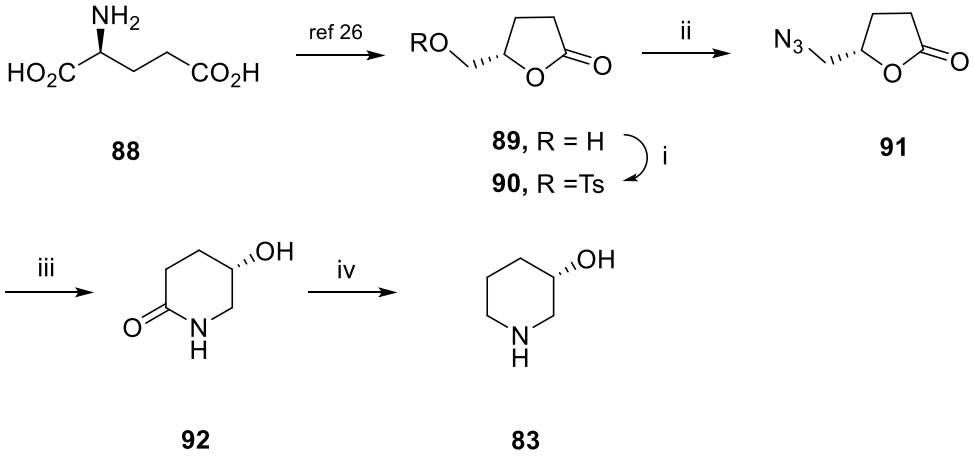
Medicinally, important examples containing 3-piperidinol fragments include cholinotoxic agents, anti-hypertensives and calcium antagonists, 2,3-oxydosqualine cyclase inhibitors, 5-HT4 agonists, nootropics, anti-arrhythmic or anti-cancer agents.[24] With these potential applications, our synthetic plan focused on the preparation of (*S*)-3-hydroxypiperidine (**83**), one of the potential building blocks.

2.3.2 Review of literature

Various syntheses of (*S*)-3-hydroxypiperidine (**83**) have been documented in the literature. Some of the interesting and important synthetic routes to **83** are described below.

Olsen approach (1985)[25]

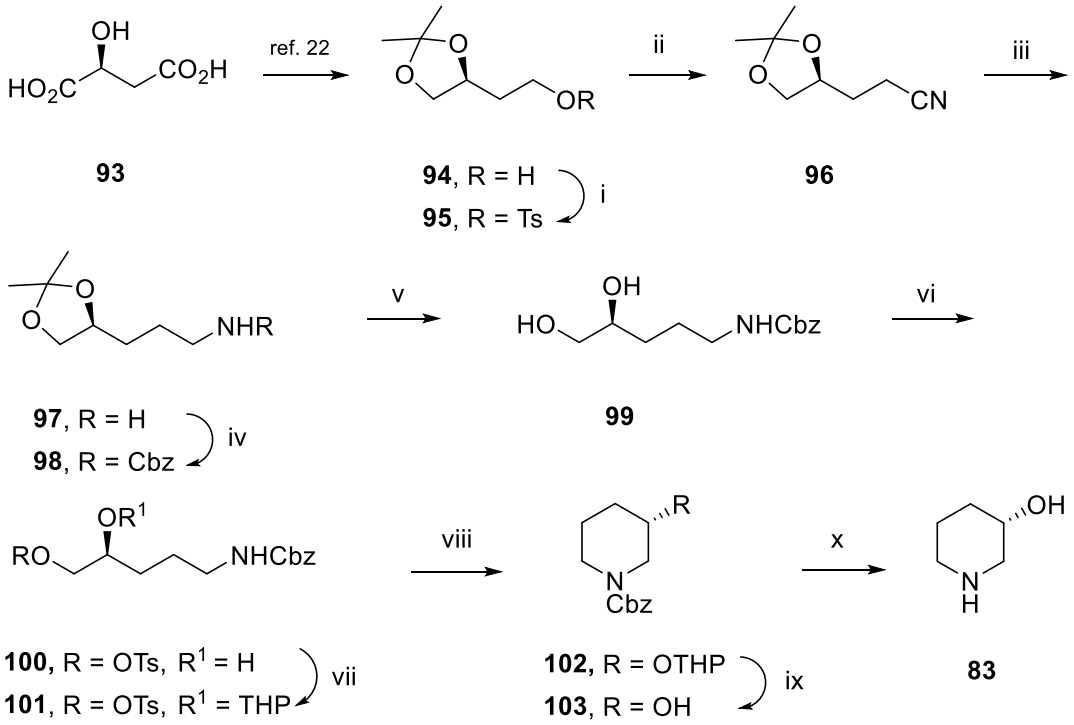
Olsen *et al*. have reported the synthesis of (*S*)-3-hydroxypiperidine **83** from L-(+)-glutamic acid **88**, which was converted into (*S*)-(+)-5-hydroxy-4-pentanolide **89**. The tosylation of primary hydroxyl in **89** gave tosylate **90** in 94% yield. Nucleophilic displacement of tosylate **90** with sodium azide resulted in 5-azido-4-pentanolide **91** in 87% yield. The catalytic reduction of the azide in **91** gave hydroxy lactam *(S)*-5-hydroxy-2-piperidinone **92** in 67% yield. Finally, reduction of the carbonyl functionality in **92** with $BH_3.SMe_2$ afforded (*S*)-3-piperidinol (**83**) in 68% yield (**Scheme 12**).



Scheme 12: (i) TsCl, pyridine, 94%; (ii) NaN_3, DMF, 87%; (iii) H_2 (1 atm), 10% Pd/C, 67%; (iv) BH_3.THF, 68%.

In yet another approach, Olsen *et al*. have envisioned the synthesis of (*S*)-3-hydroxypiperidine (**83**) from (*S*)-(-)-malic acid **93**. Reduction of acid **93** and protection of the formed diol with 2,2-dimethoxypropane afforded acetonide **94**. The formed acetonide **96** was transformed to the known intermediate acetonide **98** in 93% yield *via* (i) tosylation

of **94**, (ii) displacement of tosylate **95** with cyanide, (iii) reduction of CN **96** with $LiAlH_4$ and (iv) protection of amine **97** with CbzCl. Deprotection of acetonide **98** followed by **s**elective activation and protection of the primary and secondary alcohol functions afforded compound **101** in quantitative yield. Cyclization of **101** gave the protected 3-piperidinol **102** in 62% yield. Deprotection of THP moiety in **103** followed by hydrogenolysis furnished (*S*)-3-hydroxypiperidine **83** in 90% yield (**Scheme 13**).

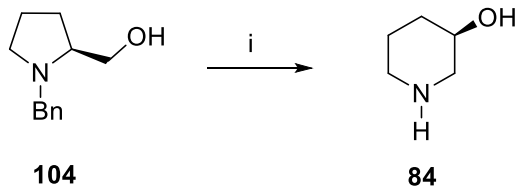


Scheme 13: (i) TsCl, pyridine, 92%; (ii) NaCN, DMF, 82%; (iii) $LiAlH_4$, Et_2O, 70%; (iv) CbzCl, MgO, H_2O, 93%; (v) 90% TFA, 60%; (vi) TsC1, pyridine, 80%; (vii) DHP, TsOH, Et_2O, 100%; (viii) NaH, THF, 62%; (ix) AcOH/H_2O/THF, 70%; (x) H_2 (1 atm), Pd/C, MeOH, 90%.

Cossy's approach (1995)[27]

Cossy *et al.* have reported the synthesis of (*R*)-3-hydroxypiperidine **84** starting from 2-hydroxymethyl-*N*-benzylpyrrolidine **104** *via* the treatment of trifluoroacetic anhydride in

THF followed by the treatment of triethylamine and then sodium hydroxide that led directly to the formation of (*R*)-3-hydroxypiperidine **84** in 66% yield (**Scheme 14**).

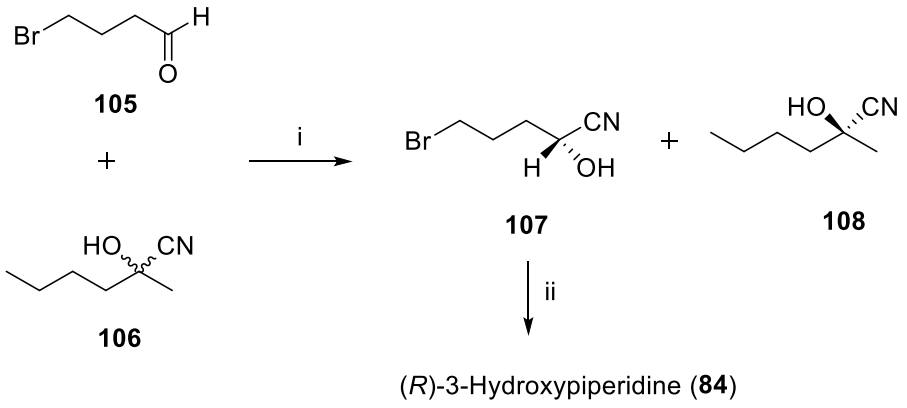


104 **84**

Scheme 14: (i) (a) $(CF_3CO)_2O$, THF, reflux; (b) Et_3N; (c) aq. 10% NaOH, 66%, 97% ee.

Gotor approach (1999)[28]

Gotor *et al*. have reported a novel enantioselective route to (*R*)-3-hydroxypiperidine **84**. The (*R*)-oxynitrilase-catalyzed transcyanation of bromoaldehyde **105** with (±)-2-methyl-2-hydroxyhexanenitrile **106** gave the longer chain (*R*)-bromocyanohydrin **107** in 65% yield. The reduction of bromocyanohydrin **107** with $BH_3.SMe_2$ afforded (*R*)-3-hydroxypiperidine (**84**) in 96% yield (**Scheme 15**).

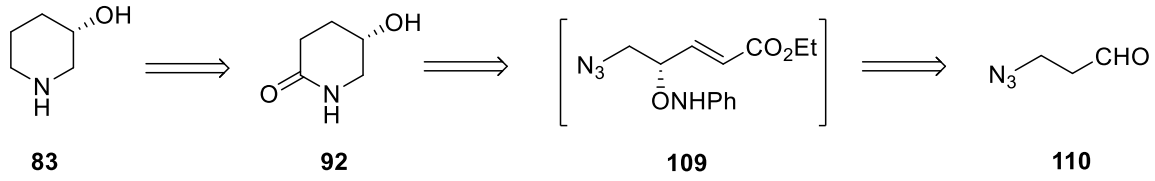


Scheme 15: (i) (*R*)-oxynitrilase, 65%; (ii) $BH_3 \cdot SMe_2$, THF, 0 °C, 96%.

2.3.3 Present work

2.3.3.1 Objective

As can be seen from the above discussions, access to these enantiomers of 3-hydroxypiperidines (**83**-**84**) have been realized through chemoenzymatic synthesis, chiral pool sources, such as (*S*)-malic acid or L-glutamic acid. Thus, long reaction sequences, low overall yields and dependence on chiral pool resources are the main drawbacks of the reported methods. In continuation of our work on the application of proline-catalyzed sequential reactions in the synthesis of bioactive molecules,[7] we describe in this section an efficient, short synthesis of (*S*)-3-hydroxypiperidine **83** from readily available raw materials *via* a L-proline catalyzed aminooxylation-olefination[10] reaction followed by intramolecular reductive cyclization as the key reactions.



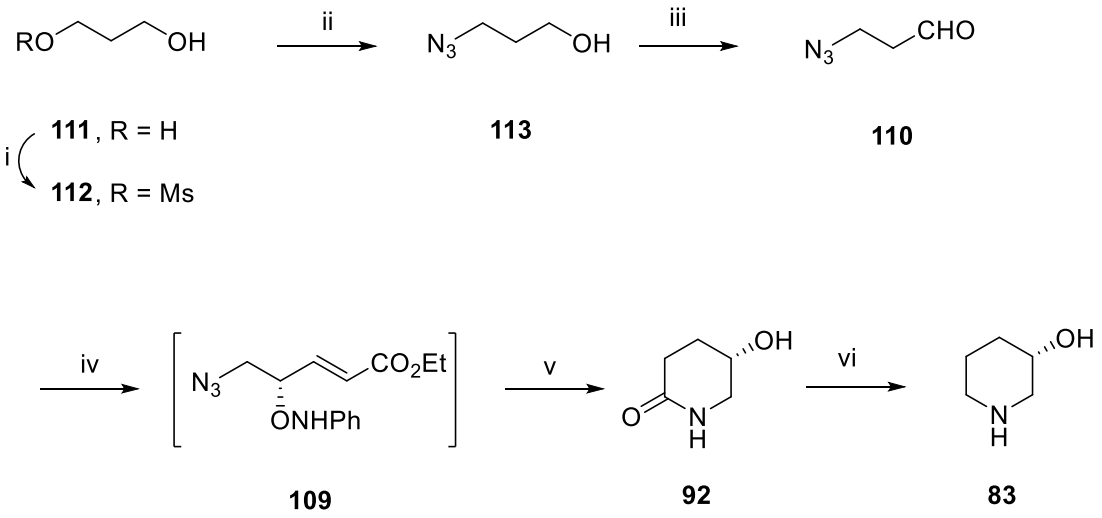
83 **92** **109** **110**

Scheme 16: Retrosynthetic analysis for (*S*)-3-hydroxy piperidine (**83**)

Based on the above retrosynthetic analysis, (*S*)-3-hydroxypiperidine **83** could be envisioned from piperidinone **92**, which could be obtained from γ-aminoxy-α,β-unsaturated ester **109** following reductive cyclization. The azido ester **109** can be readily obtained from azido aldehyde **110** by employing sequential L-proline catalyzed aminooxylation followed by HWE olefination (**Scheme 16**).

2.3.3.2 Results and Discussion

Scheme 17 presents the synthetic route for (*S*)-3-hydroxypiperidine **83**.



Scheme 17: (i) MsCl, Et_3N, DMAP, CH_2Cl_2; (ii) NaN_3, DMF, 80 ^oC, 70% (over two steps); (iii) PCC, CH_2Cl_2, 25 ^oC, 2 h, 98%; (iv) L-proline, PhNO, CH_3CN, 24 h, -20 ^oC, then triethyl phosphono acetate, DBU, LiCl, 0 ^oC, 2 h; (v) H_2 (1 atm), 10% Pd/C, MeOH, 25 ^oC, 2 h, 65%. (over three steps); (vi) $BH_3.SMe_2$, THF, reflux, 12 h, 87%.

The synthesis of **83** started from 1,3-propanediol (**111**), which was transformed to its 3-azidopropan-1-ol (**113**) in 70% yield *via* the standard sequences of monomesylation [MsCl, Et_3N, DMAP, CH_2Cl_2] and then azide displacement [NaN_3, DMF, 80 ^oC]. The primary alcohol **113** on PCC oxidation gave aldehyde **110** (98% yield). The appearance of a characteristic singlet at δ 9.71 (s, 1H) in its ^1H NMR spectrum due to the aldehydic proton confirmed the formation of compound **110**. It was further ascertained by the occurrence of a characteristic aldehydic carbon signal at δ 201.7 in its ^{13}C NMR spectrum (**Fig. 29**). The strong vibartional stretching frequencies at υ_{max} 2150 and 1720 cm^{-1} in its IR spectrum further established the presence of aldehyde and azide functional groups respectively.

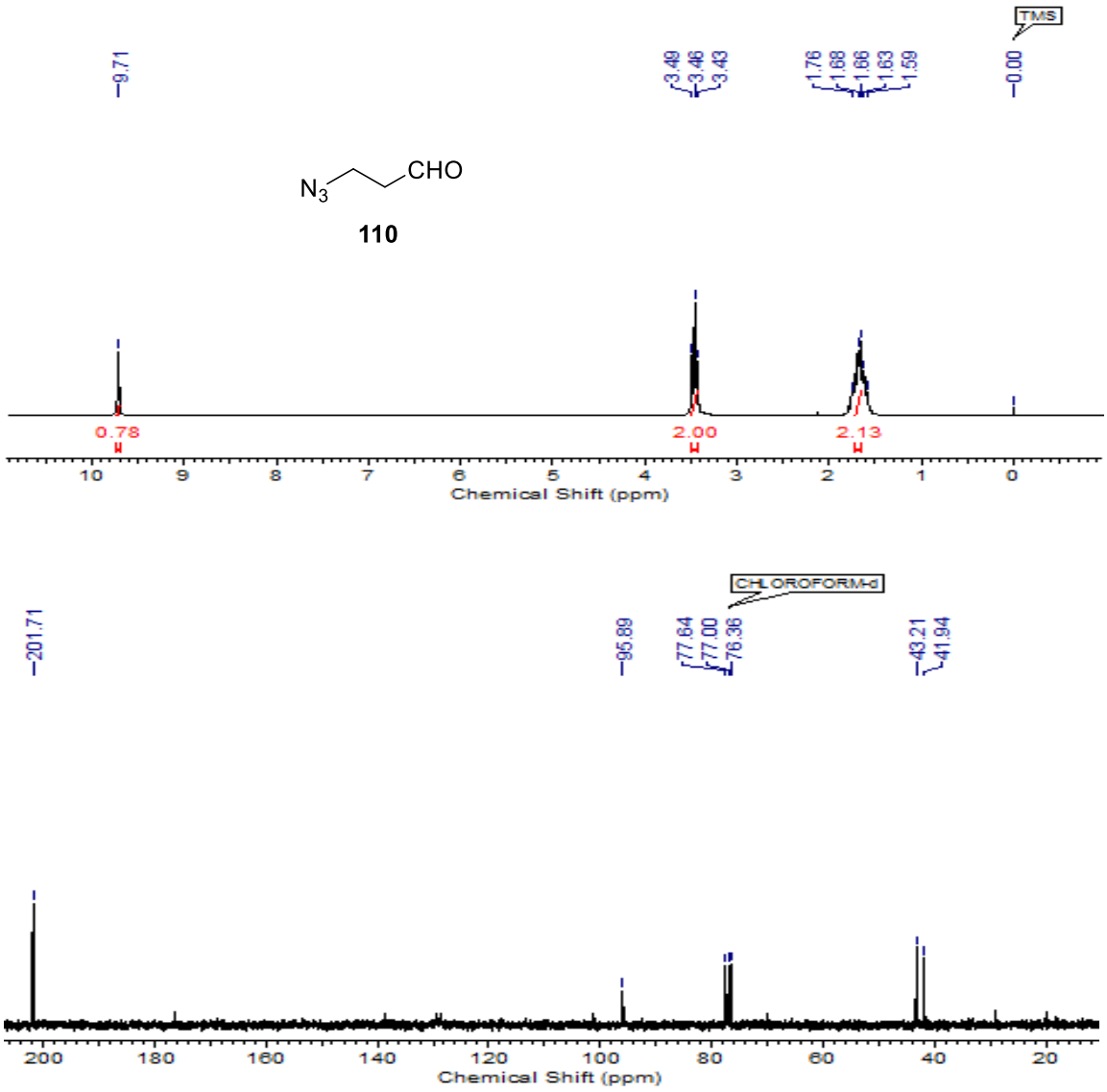


Fig. 29: ^{1}H and ^{13}C NMR spectra of azido aldehyde **110**

The aldehyde **110** was then subjected to sequential L-proline catalyzed aminooxylation[10] followed by HWE olefination {L-proline (30 mol %), PhNO, CH_3CN, 24 h, -20 ºC, then triethyl phosphono acetate, DBU, LiCl, 0 ºC, 2 h} gave the intermediate γ-aminoxy-α,β-unsaturated ester **109** *in situ*, which was then immediately subjected to reductive cyclization without further purification [H_2 (1 atm), 10% Pd/C, MeOH, 25 ºC, 2 h]

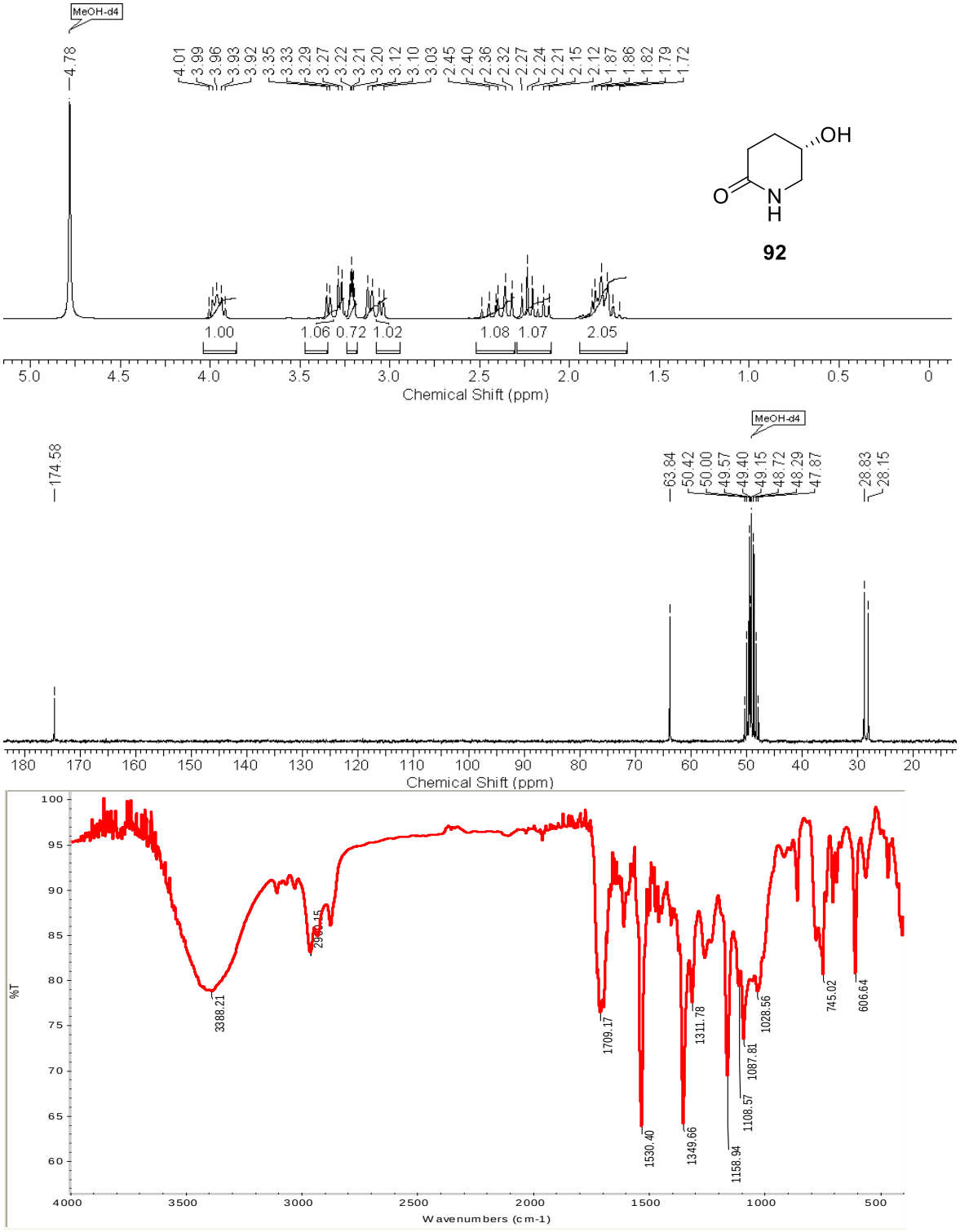


Fig. 30: ^{1}H, ^{13}C NMR and IR spectra of lactam **92**

furnishing piperidinone **92** in 65% yield; $[\alpha]_D^{25}$ -13.3 (*c* 1, MeOH) {lit.[24a] $[\alpha]_D^{25}$ -12.4 (*c* 0.5, MeOH)}. The formation of **92** was confirmed from its ^{1}H NMR spectrum, which showed a typical multiplet at δ 3.92-4.01 (m, 1H) corresponding to the methine proton attached to -C**H**-OH. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 174.5 for amide carbonyl carbon. Its IR spectrum showed strong vibrational stretching frequencies at υ_{max} 3388 and 1709 cm^{-1} due to the presence of hydroxyl and lactam carbonyl functionalities respectively (**Fig. 30**).

Finally, piperidinone **92** on reduction with $BH_3.SMe_2$ in THF provided the target molecule **83** in 87% yield (overall yield 38%). The formation of **83** was confirmed from its ^{1}H and ^{13}C NMR spectral analysis. Its ^{1}H NMR spectrum showed a typical multiplet at δ 2.97-3.01 (m, 2H) corresponding to methylene protons attached to C**H$_2$**NH and a singlet δ 3.54 (s, 1H) for methine proton (-C**H**-OH). It was further confirmed from its ^{13}C NMR spectrum, which showed a characteristic carbon signal at δ 66.2 for methine carbon attached to hydroxyl group (**Fig. 31**). The enantiomeric purity of **83** was determined to be 97% ee based on the comparison of its specific rotation with the reported values $[\alpha]_D^{25}$ -7.3 (*c* 2.5, MeOH) {lit.[29] $[\alpha]_D^{25}$ -7.5 (*c* 2, MeOH)}. The synthetic (*S*)-3-hydroxypiperidine (**83**) thus obtained was identical in all spectral respects to the natural product.[30]

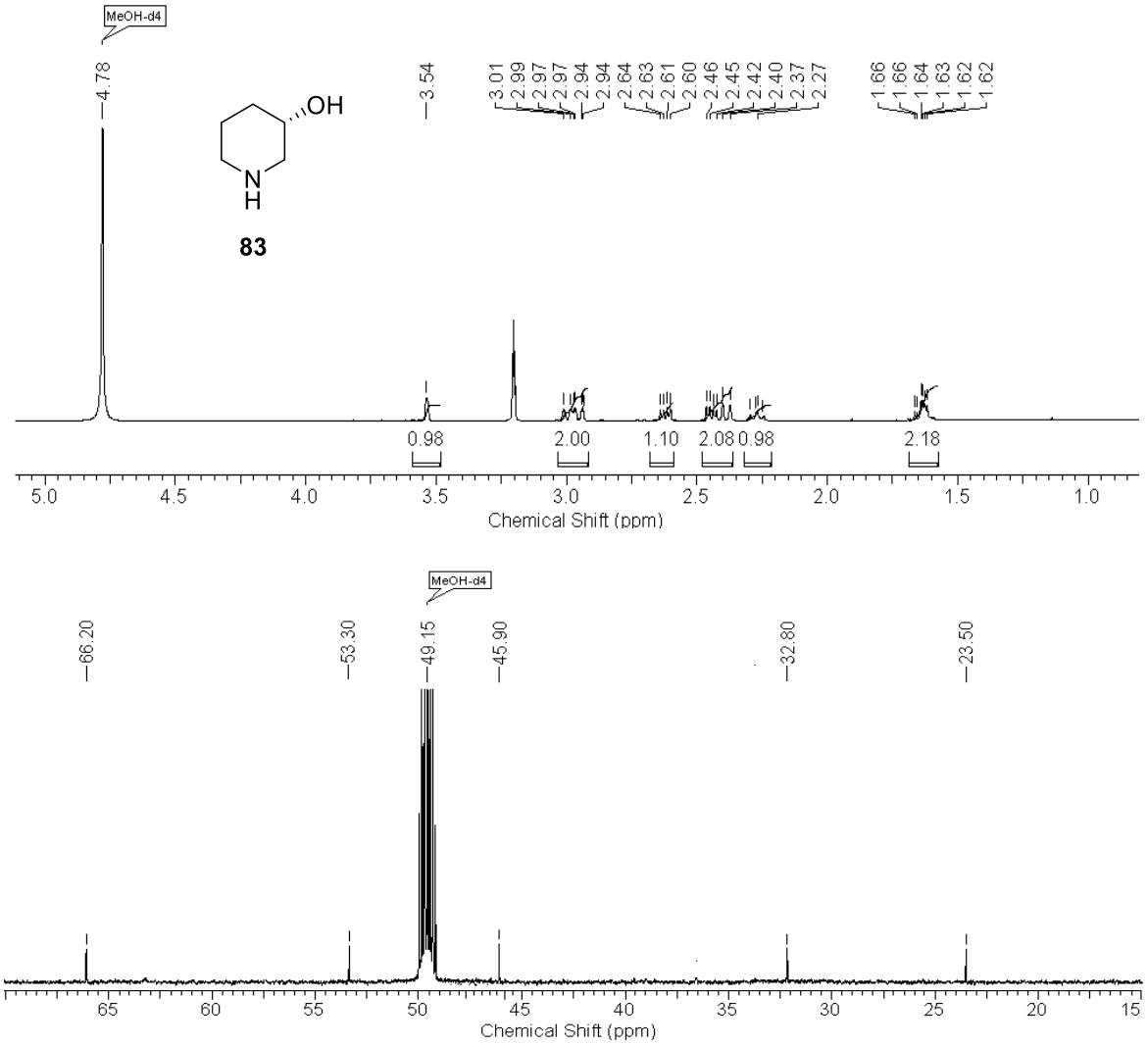


Fig. 31: ^{1}H and ^{13}C NMR spectra of (*S*)-3-hydroxypiperidine (**83**)

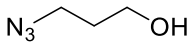
2.3.4 Conclusion

In conclusion, we have successfully demonstrated the use of organocatalytic sequential α-aminooxylation followed by HWE reaction for the concise synthesis of (*S*)-piperidine-3-ol (**83**) (38% overall yield; 97% ee). Simple reaction transformations, high overall yield, and the requirement of a relatively low amount of inexpensive and non-toxic proline as the

catalyst are the salient features of our strategy. This flexible approach will find a broad way in application to the synthesis of other naturally occurring 3-hydroxypiperidine analogues.

2.3.5 Experimental section

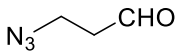
3-Azidopropan-1-ol (113)



To a stirred solution of 1,3-propanediol **111** (5 g, 65.71 mmol) and triethylamine (13.8 mL, 98.56 mmol) in CH_2Cl_2 (100 mL), mesyl chloride (6.1 mL, 31.03 mmol) was added at 0 ^oC under N_2 atmosphere. The resulting solution was stirred at the same temperature for 1 h. After completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude mesylate **112**, which was without further purification used for next reaction. To a stirred solution of crude mesylate **112** (8.3 g) in DMF (100 mL) was added sodium azide (25.6 g, 394.26 mmol). The reaction mixture was stirred for 8 h at 80 ^oC. After completion of the reaction (monitored by TLC), it was extracted with EtOAc (3 x 10 mL), washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude, which was purified by column chromatography with silica gel using petroleum ether/ethyl acetate (4:1 v/v) as eluent to give pure azido alcohol **113**.

Yield: 7.6 g; 70%; colourless oil; **IR** (neat, cm^{-1}): υ_{max} 3411, 2980, 2856, 2100, 1620, 1585, 1280, 790; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.48-1.57 (m, 4H), 3.51 (t, *J* = 6.6 Hz, 2H), 4.48 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.1, 45.3, 56.0; **Anal. Calcd**. for $C_3H_7N_3O$ requires C, 35.64; H, 6.98; N, 41.56; Found C, 35.52; H, 6.80; N, 41.40%.

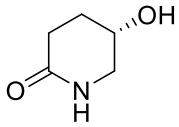
3-Azidopropanal (110)



To a stirred solution of 3-azidopropanol **113** (4 g, 39.56 mmol) in CH_2Cl_2 (100 mL) was added pyridium chloroformate (PCC) (17 g, 79.12 mmol). The reaction was stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered over Celite (CH_2Cl_2 elute) and the filtrate was concentrated under reduced pressure to give crude azido aldehyde, which was then purified by column chromatography using petroleum ether/ethyl acetate (9:1 v/v) as eluent to obtain pure azido aldehyde **110**.

Yield: 3.8 g; 98%; colourless viscous liquid; **IR** (neat, cm^{-1}): υ_{max} 3211, 3010, 2150, 1720, 1565, 1250, 1050, 850; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.54-1.68 (m, 2H), 3.42 (t, *J* = 4.8 Hz, 2H), 9.71 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 41.9, 43.2, 201.7; **Anal. Calcd**. for $C_3H_5N_3O$ requires C, 36.36; H, 5.09; N, 42.41; Found C, 36.29; H, 5.14; N, 42.46%.

(*S*)-5-Hydroxypiperidin-2-one (92)



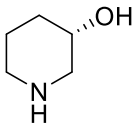
To a pre-cooled solution of aldehyde **110** (3 g, 30.27 mmlol) in CH_3CN (100 mL) at -20 ^oC, nitrosobenzene (3.4 g, 30.27 mmol) and L-proline (0.64 g, 6.0 mmol) were added. The reaction mixture was then stirred at -20 ^oC for 24 h, followed by the addition triethyl phosphono acetate (10.1 g, 45.4 mmol), DBU (6.9 g, 45.4 mmol) and LiCl (1.4 g, 33.29 mmol) at 0 ^oC for 2 h. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride. Then solvent was evaporated and organic layer was extracted with EtOAc (3x50 mL). The combined EtOAc layers were

dried over anhyd. Na_2SO_4, concentrated to give the crude γ-aminooxy-α,β-unsaturated ester **109**, which was directly used for the next step without purification.

To a stirred solution of crude γ-aminooxy-α,β-unsaturated ester **109** in MeOH (50 mL) was added 10% Pd/C (0.16 g, 1.51 mmol) under H_2 (1 atm) at 25 ^oC. The reaction mixture was stirred for 2 h at the same temperature. After completion of reaction (monitored by TLC), it was filtered through Celite (EtOAc eluent) and the solvent was evaporated under reduced pressure to afford the crude compound, which was purified by column chromatography using ethyl acetate/methanol (9:1 v/v) as eluent to obtain pure hydroxylactam **92**.

Yield: 2.2 g, 65%; pale yellow gum; **$[\alpha]_D^{25}$** -13.3 (*c* 1, MeOH) {lit.[24a] $[\alpha]_D^{25}$ -12.4 (*c* 0.5, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3388, 3200, 2974, 1709, 1536, 1252, 1039, 786; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 1.72-1.87 (m, 2H), 2.12-2.27 (m, 1H), 2.32-2.49 (m, 1H), 3.03-3.12 (dd, *J* = 4.8, 12.7 Hz, 1H), 3.20-3.22 (m, 1H), 3.35 (dd, *J* = 3.9, 12.7 Hz, 1H), 3.92-4.01 (m, 1H); **^{13}C NMR** (50 MHz, MeOH-d_4): δ 28.1, 28.8, 49.4, 63.8, 174.5; **Anal. Calcd** for $C_5H_9NO_2$ requires C, 52.16; H, 7.88; Found: C, 52.03; H, 7.75%.

(*S*)-Piperidin-3-ol (83)



To a solution of lactam **92** (1.2 g, 10.43 mmol) in dry THF (20 mL), $BH_3.SMe_2$ (0.95 mL, 8.68 mmol) was added dropwise at 0 ^oC under N_2 atmosphere and the reaction mixture was then refluxed for 6 h. After the completion of the reaction (monitored by TLC), THF was removed under reduced pressure to give the crude product, which was purified by column chromatography with neutral alumina using petroleum ether/chloroform (3:2) as eluent to give pure **83**.

Yield: 0.91g; 85%; light yellow viscous liquid; **$[\alpha]_D^{25}$** -7.3 (*c* 1.3, MeOH)}; {lit.[29] $[\alpha]_D^{25}$ -7.5 (*c* 2, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3410, 3356, 3256, 2940, 2811, 1620, 1582, 1420, 1110, 980; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 1.55-1.64 (m, 2H), 1.67-1.77 (m, 2H), 2.60-2.62 (m, 1H), 3.04-3.12 (m, 2H), 3.19-3.23 (m, 1H), 3.65-3.74 (m, 1H); **^{13}C NMR** (50 MHz, MeOH-d_4): δ 23.5, 32.8, 45.9, 53.3, 66.2; **Anal. Calcd** for $C_5H_{10}NO$ requires C, 59.37; H, 10.96; Found: C, 59.28; H, 10.85%.

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CHAPTER III

Enantioselective Synthesis of (*R*)-Selegiline, (*S*)-Benzphetamine and (*S*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoic Acid, Key Intermediate for the Synthesis of (*R*)-Sitagliptin *via* Electrophilic Azidation of Chiral Imide Enolates and Organocatalysis

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A concise enantioselective synthesis of (*R*)-selegiline, (*S*)-benzphetamine and formal synthesis of (*R*)-sitagliptin *via* electrophilic azidation of chiral imide enolates **Dey, S.**; Sudalai, A. *Tetrahedron: Asymmetry* **2015**, *26*, 67.

Section I

A Concise Enantioselective Synthesis of (*R*)-Selegiline and (*S*)-Benzphetamine *via* Electrophilic Azidation of Chiral Imide Enolates

3.1.1 Introduction

The chiral homobenzylic amines are subunits widely found in a range of biologically active compounds (*e.g.* **1**-**2**). Furthermore, they serve as extremely useful synthetic intermediates, since they can be transformed into an array of highly functionalized heterocycles. In particular, pharmaceutical substances belonging to this category such as (*R*)-selegiline (**1**) and (*S*)-benzphetamine (**2**) are currently used in the treatment of a variety of diseases. More importantly, (*R*)-selegiline (**1**) is a selective irreversible MAO-B inhibitor[1] that works by slowing breakdown of certain natural substances in brain (*e.g.* dopamine, norephinephrine and serotonin). It is usually used in combination with L-DOPA or carbidopa for the treatment of early-stage Parkinson's disease, depression and senile dementia, while (*S*)-benzphetamine (**2**), an anorectic drug, is an amphetamine

1 (*R*)-selegiline

2 (*S*)-benzphetamine

Fig. 1: Structure of (*R*)-selegiline (**1**) and (*S*)-benzphetamine (**2**)

derivative exhibiting appetite suppressant activity and is utilized for long-term management of obesity.[2] In addition, compound **2** is found to be a superior bronchodilator and a CNS stimulator, which increases heart rate and blood pressure (**Fig. 1**). Due to the

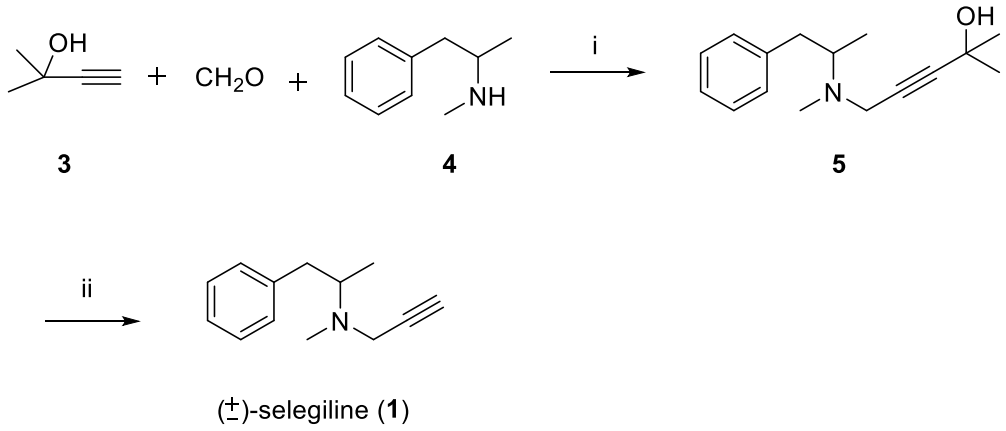
pharmaceutical applications of these scaffolds in medicinal industry,[3] the development of new synthesis of these molecules continue to be very active field of research in recent years.

3.1.2 Review of literature

Literature search revealed that there are various reports available for the synthesis of (*R*)-selegiline and (*S*)-benzphetamine which are described below.

Flower's approach (1977)[4]

Flower *et al.* have reported the synthesis of racemic selegiline (**1**) involving the Mannich reaction as a key step. Thus, reaction of 2-methyl-butyn-ol (**3**) and formaldehyde with deoxyephedrine (±**4**) gave compound **5**, which on subsequent base-catalyzed elimination of acetone gave racemic selegiline (**1**) in 33% yield (**Scheme 1**).

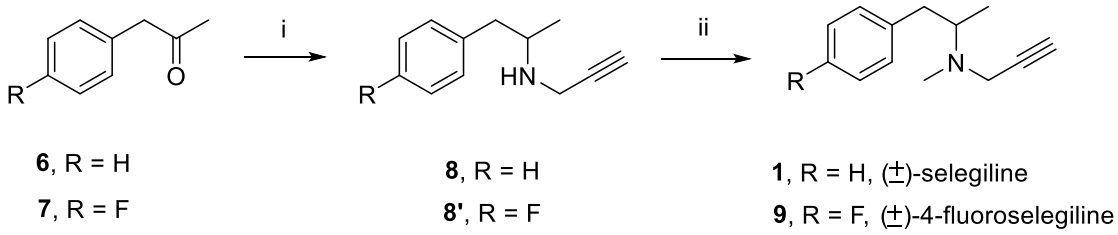


Scheme 1: (i) CuCl, 110 °C, 4 h, 60%; (ii) KOH, 150 °C, 33%.

Gyogy's approach (1988)[5]

Gyogy *et al.* have reported the preparation of racemic selegiline (**1**) and 4-fluoroselegiline (**9**). Phenylacetone **6** and propargylamine on treatment with $HgCl_2$ activated aluminum at

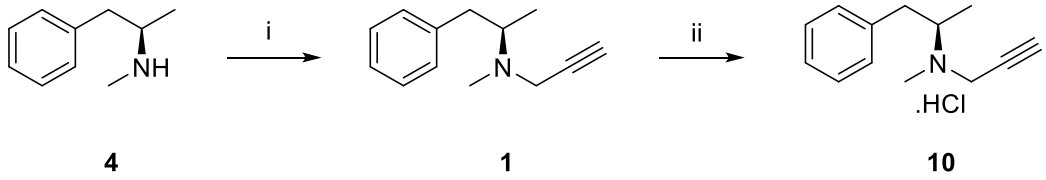
60 °C gave amine **8**, which on methylation yielded racemic selegiline (**1**). Similarly, (4-fluorophenyl)acetone (**7**) gave 4-fluoroselegiline (**9**) (**Scheme 2**).



Scheme 2: (i) propargylamine, $HgCl_2$-Al, EtOH, 60 °C; (ii) MeI, K_2CO_3, acetone.

Hajicek's approach (1988)[6]

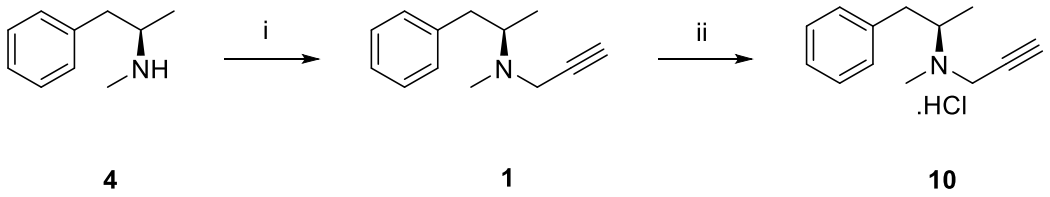
Hajicek *et al.* have prepared the title compound **1** by propargylation of chiral deoxyephedrine (**4**) with propargyl bromide, K_2CO_3 in an inert solvent. Subsequent treatment with HCl afforded (*R*)-selegiline hydrochloride (**10**) (**Scheme 3**).



Scheme 3: (i) propargyl bromide, K_2CO_3, 5 °C; (ii) HCl (gas)

Ott-Dombrowski's approach (1996)[7]

This process for the synthesis of (*R*)-selegiline (**1**) by Otto-Dombrowski *et al.* involves *N*-alkylation of deoxyephedrine (**4**) with propargyl bromide in two-phase system comprising of water and organic hydrocarbon without a catalyst followed by conversion to (*R*)-selegiline hydrochloride (**10**) using HCl (**Scheme 4**).

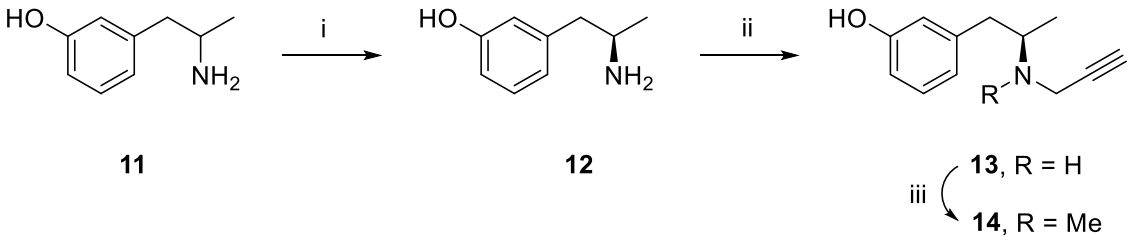


4 **1** **10**

Scheme 4: (i) propargyl bromide, H_2O, aromatic hydrocarbon; (ii) HCl (gas).

Sterling's approach (2002)[8]

Sterling *et al.* have reported the synthesis of (*R*)-3-hydroxyselegiline (**14**), involving classical resolution of amine **11** with D-tartaric acid to give optically pure amine **12**. Subsequent propargylation and reaction with ethyl formate gave formate derivative, which on reduction yielded (*R*)-3-hydroxyselegiline (**14**) (**Scheme 5**).



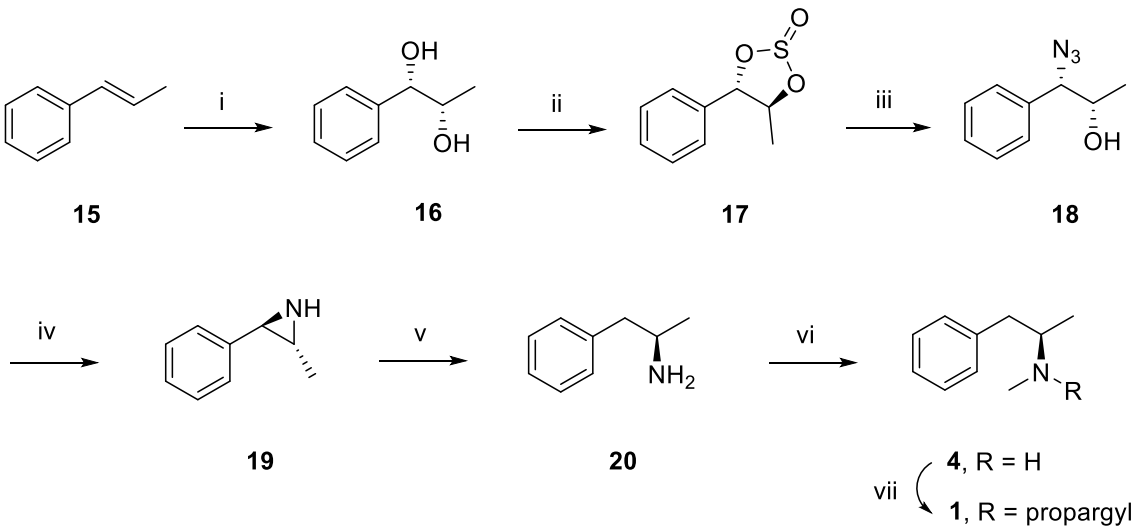
11 **12**

Scheme 5: (i) D-tartaric acid, MeOH, reflux; then 25% NH_4OH, 25 °C; (ii) propargyl bromide, K_2CO_3, 25 °C; (iii) HCO_2Et, reflux; then $LiAlH_4$, THF, 5-25 °C.

Sudalai's approach (2004 and 2009)[9]

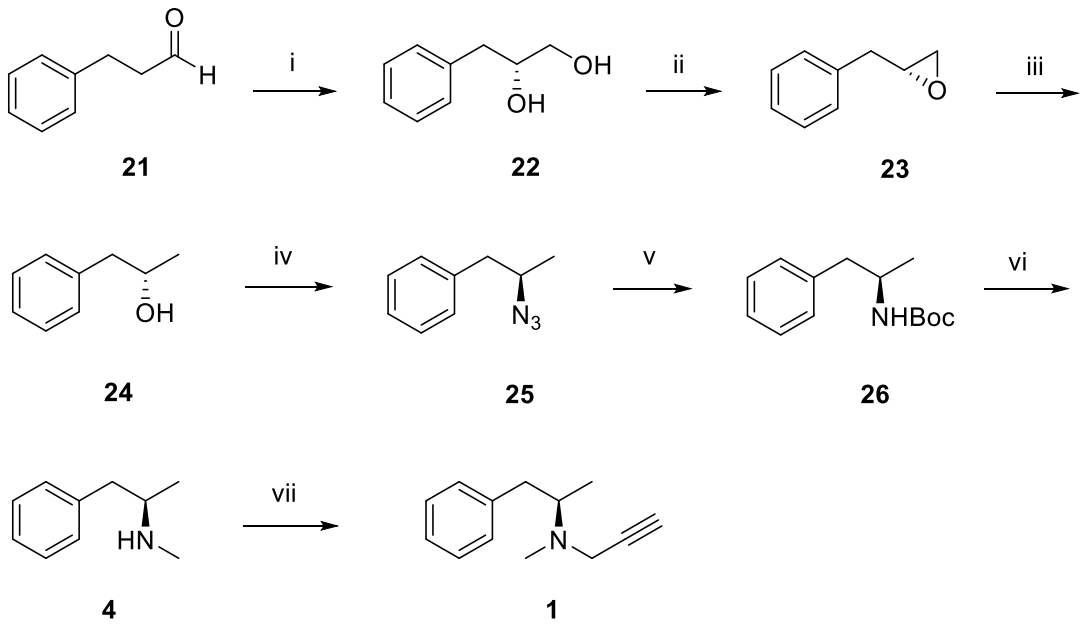
In this approach by Sudalai *et al.*, first β-methylstyrene **15** was subjected to Sharpless AD reaction to give chiral diol **16**, which on treatment with $SOCl_2$ gave the corresponding cyclic sulfite **17**. Treatment of cyclic sulfite **17** with sodium azide gave the corresponding azido alcohol **18**, which on treatment with triphenylphosphine produced chiral aziridine **19**. Aziridine **19** underwent stereospecific and regioselective ring opening at the benzylic

position using Pd-catalyzed reductive ring opening with ammonium formate under transfer hydrogenation conditions to produce amine **4**, which was converted to (*R*)-selegiline (**1**) (**Scheme 6**).



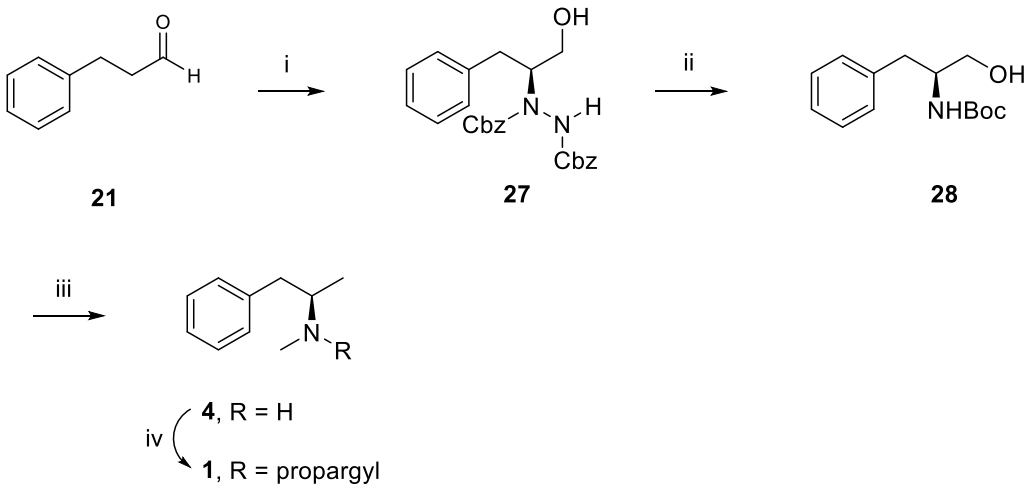
Scheme 6: (i) OsO_4, $(DHQ)_2$–PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O, 0 °C, 82%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 85%; (iii) NaN_3, acetone–H_2O, 80 °C, 82%; (iv) PPh_3, CH_3CN, 90%; (v) 10% Pd/C, HCO_2NH_4, MeOH, reflux, 88%; (vi) (a) $ClCO_2CH_3$, CH_2Cl_2, aq. K_2CO_3, 45 min, 90%; (b) $LiAlH_4$, dry THF, 65 °C, 65%; (vii) propargyl bromide, K_2CO_3, CH_3CN, 25 °C, 72%.

In yet another approach, Sudalai *et al.* have used organocatalyzed reaction to construct the target molecule **1** (**Scheme 7**). D-proline catalyzed α-aminoxylation of hydrocinnamaldehyde **21** provided chiral diol **22**. The diol **22**, on selective tosyl protection followed by base treatment, was converted into epoxide **23**. The epoxide was regioselectively opened with $LiAlH_4$ to give secondary alcohol **24**. On nucleophilic S_N2 displacement of **24** with NaN_3 followed by reduction furnished carbamate **25**. Finally, the carbamate **25** was reduced to secondary amine **4**, which was converted to title compound **1** by the treatment with propargyl bromide.



Scheme 7: (i) (a) PhNO, L-proline (10 mol %), DMSO, 25 °C, 20 min. then MeOH, $NaBH_4$, 86%; (ii) H_2 (1 atm.), 10% Pd/C, MeOH, 12 h, 88%; (iii) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, (b) NaH, DMF, 0 °C, 0.5 h, 81% for 2 steps; (iv) $LiAlH_4$, THF, reflux, 2 h, 92%; (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (b) NaN_3, DMF, 80 °C, 12 h, 76% for 2 steps; (vi) H_2 (1 atm), 10% Pd/C, MeOH, 2 h, 98%; (vii) Boc_2O, Et_3N, 0 °C, 1 h, 95%; (viii) $LiAlH_4$, THF, reflux, 4 h, 90%; (ix) propargyl bromide, anhyd. K_2CO_3, CH_3CN, 12 h, 72%, 99% ee.

Again, hydrocinnamaldehyde **21** was subjected to D-proline catalyzed α-amination reaction to provide α-amino alcohol **27**, which on Raney Ni catalyzed hydrogenolysis followed by *in situ* protection furnished carbamate **28**. Subsequent tosyl protection of hydroxyl group in **28** followed by global reduction with $LiAlH_4$ gave secondary amine **4**, which was converted to **1** by known procedure (**Scheme 8**).

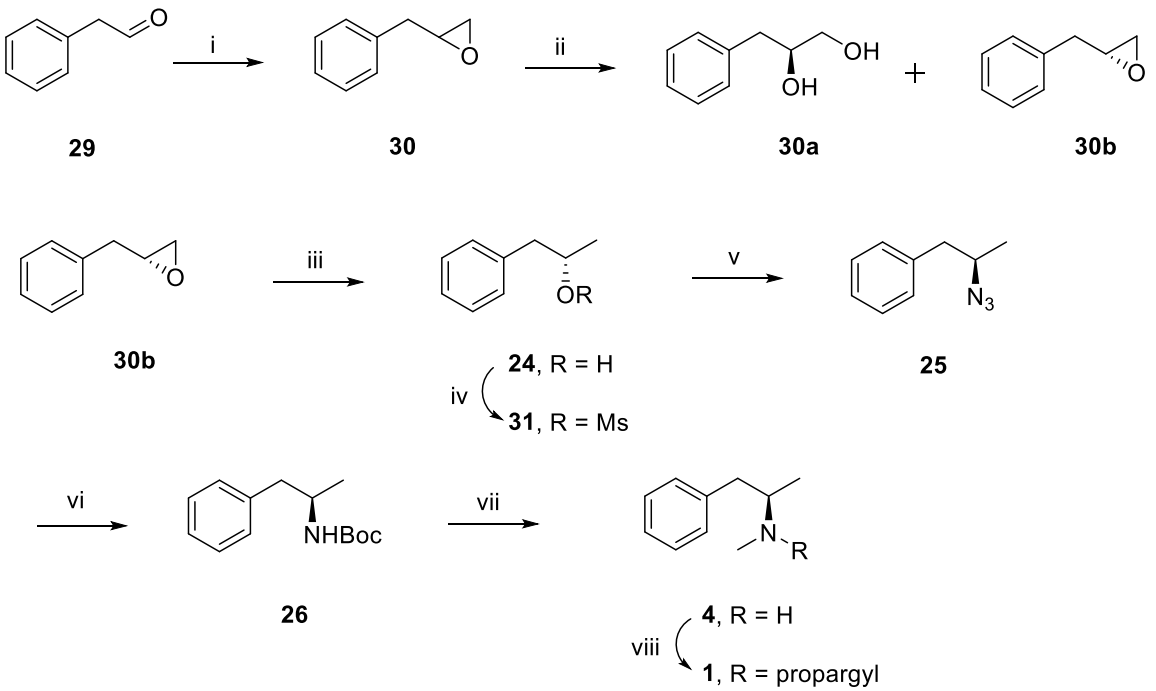


Scheme 8: (i) Dibenzyl azodicarboxylate, D-proline (10 mol%), 0-20 °C, 3 h then $NaBH_4$, EtOH, 95%; (ii) (a) H_2 (60 psi), Raney Ni, MeOH, AcOH, 16 h, (b) Boc_2O, Et_3N, 0 °C, 1 h, 66% for 2 steps; (iii) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, (b) $LiAlH_4$, THF, reflux, 4 h, 81% for 2 steps; (iv) propargyl bromide, K_2CO_3, CH_3CN, 12 h, 72%.

Kumar's approach (2011)[10]

Kumar *et al.* have reported the synthesis of (*R*)-selegiline **1** employing Jacobsen's hydrolytic kinetic resolution (HKR). Phenyl acetaldehyde **29**, on treatment with dimethylsulfoxonium methylide gave 2-benzyloxirane **30** in 82% yield. The racemic epoxide **30** was then subjected to Jacobsen's HKR using (*R,R*)-salen-Co-III(OAc) complex to afford diol **30a** in 45% yield and (*R*)-2-benzyloxirane **30b** as single enantiomer in 42% yield. Epoxide **30b** was then subjected to regioselective opening with sodium borohydride to furnish the alcohol **24** in 81% yield. The protection of the alcohol **24** with MsCl afforded compound **31** in excellent yield, which on treatment with sodium azide in dimethylformamide (DMF) furnished azide **25** with inversion of the configuration. The azide **25** was then subjected to hydrogenolysis and *in situ* protected with Boc_2O to furnish

carbamate **26**. Subsequently, the carbamate **26** was on reductive aminated to methyl amine **4**, which was then converted to **1** in 72% yield by known procedure.

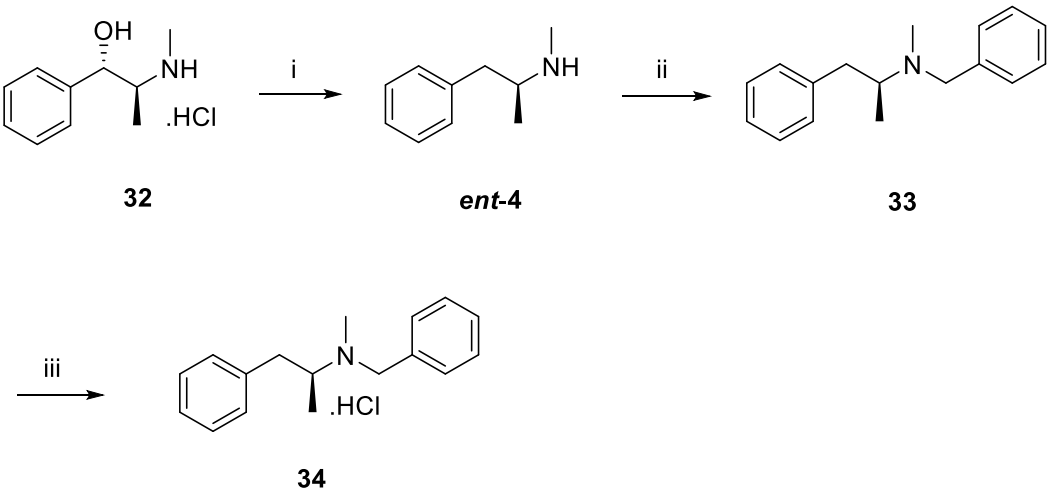


Scheme 9: (i) $(CH_3)_3SO$, NaH, DMSO, 82%; (ii) (*R*,*R*)-salen-Co^{III}-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 ºC, 8 h (45% for **30a**, 42% for **30b**); (iii) $NaBH_4$, EtOH, reflux, 2 h, 81%; (iv) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 ºC to rt, 85%; (v) NaN_3, DMF, 50 °C, 8 h, 61%; (vi) H_2 (1 atm), 10% Pd/C, Boc_2O, EtOAc, 90%; (vii) $LiAlH_4$, THF, reflux, 4 h, 90%; (viii) propargyl bromide, anhyd. K_2CO_3, CH_3CN, 12 h, 72%.

Pramanik's approach (2014)[11]

Pramanik *et al.* have reported the synthesis of (*S*)-benzphetamine **2** from commercially available pseudoephedrine hydrochloride **32** by employing hydrogenolysis/ deoxygenation using excess Raney Ni in isopropanol in an autoclave at 50-55 °C to afford exclusively methamphetamine **33**. Then the *N*-benzylation step was accomplished using benzyl chloride in the presence of K_2CO_3 in toluene which provided benzphetamine **2** freebase in almost quantitative yield and high purity. Finally, the free base **2** was dissolved in ethyl

acetate and treated with anhydrous HCl in ethyl acetate to furnish benzphetamine hydrochloride salt **34** in 70% yield (**Scheme 10**).

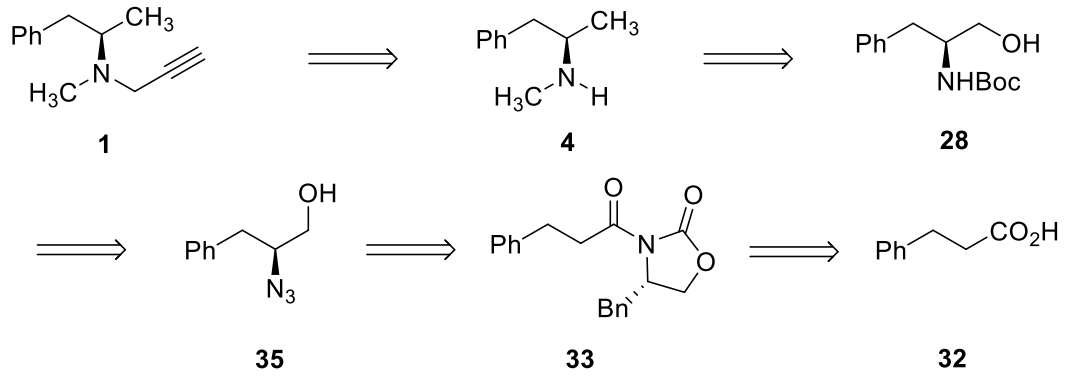


Scheme 10: (i) Raney Ni, 2-propanol, 50-55 ºC; (ii) BnCl, K_2CO_3, H_2O, 70-75 ºC; (iv) EtOAc, HCl, toluene, 70%.

3.1.3 Present Work

3.1.3.1 Objective

As can be seen from the literature for the asymmetric synthesis of (*R*)-selegiline (**1**) and (*S*)-benzphetamine (**2**), most of them are based on chiral pool resources. The use of expensive chiral reagents, lengthy reaction sequence along with low yields and diastereoselectivity are some of the drawbacks of the existing routes. In this regard, an efficient protocol that provides for the synthesis of these molecules is highly desirable. The use of Evans' chiral *N*-acyloxazolidinone auxiliaries to control absolute stereoinduction has found wide application in a variety of reactions over the last two decades.[12] The ready availability of the starting materials, ease of cleavage and application to a broad variety of stereoselective reactions allows oxazolidinone auxiliaries to endure as ideal intermediates for asymmetric synthesis. We envisioned that the chiral amine functionality could be introduced by Evans' electrophilic azidation of chiral imide enolates using chiral auxiliary followed by its reduction. In this section, we wish to describe a short, enantioselective synthesis of two drug molecules **1** and **2** on Evans' chiral azidation approach.

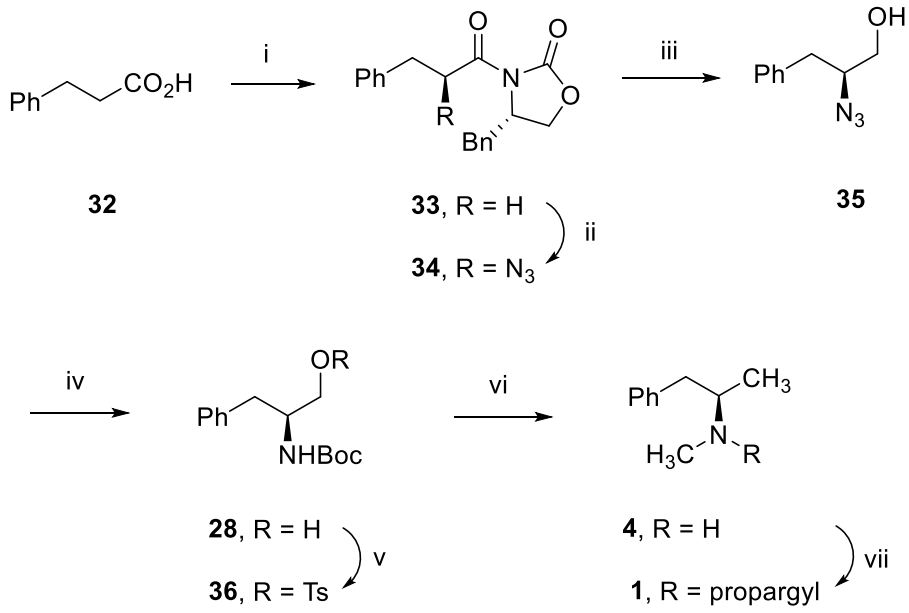


Scheme 11: Retrosynthetic analysis of (*R*)-selegiline (**1**)

Based on retrosynthetic scheme, we envisaged that (*R*)-selegiline (**1**) could be synthesized from (*R*)-*N*-methyl-1-phenylpropan-2-amine (**4**) on treatment with propargyl bromide. The methyl amine **4** could be obtained from carbamate **28**, which can be readily obtained from azido alcohol **35** followed by hydrogenolysis and *in situ* protection with Boc_2O. The azido alcohol **35** could be formed from oxazolidinone **33** employing Evans' chiral azidation followed by reduction, while oxazolidinone **33** can be easily furnished from commercially available hydrocinnamic acid **32** (**Scheme 11**). Again, (*S*)-benzphetamine (**2**) could be obtained from hydrocinnamic acid **32** following similar sequence of reactions as described in **Scheme 13**.

3.1.3.2 Results and Discussion

The complete synthetic sequences of the drug molecule (*R*)-selegiline **1** is shown in **Scheme 12**. Its synthesis was commenced from commercially available hydrocinnamic acid **32** employing Evans' chiral auxiliary protocol. Thus, the condensation of (*S*)-4-benzyloxazolidin-2-one, the chiral auxiliary, with hydrocinnamic acid **32** *via* the formation of pivolyl ester (pivolyl chloride, Et_3N, - 20 ^oC, THF, 3 h followed by (*S*)-4-benzyloxazolidin-2-one, LiCl, -20-25 ^oC, 8 h)[13] gave the oxazolidinone **33** in 90% yield. The formation of oxazolidinone **33** was established by its ^1H NMR spectrum, which showed a multiplet at δ 4.63 (m, 1H) characteristic of methine proton, while the multiplet at δ 4.14 (m, 2H) was due to methylene protons attached to oxygen atom. This was further substantiated by the appearance of two typical signals at δ 172.2 and 153.2 for carbonyl carbon in its ^{13}C NMR spectrum (**Fig. 2**). Its IR spectrum too displayed strong vibrational stretching frequencies at υ_{max} 1742 and 1720 cm^{-1} indicating the presence of carbonyl functional groups.



Scheme 12: (i) pivolyl chloride, Et_3N, dry THF, -20 °C, 3 h then (*S*)-4-benzyloxazolidin-2-one, LiCl, -20-25 °C, 8 h, 90%; (ii) KHMDS, -78 °C, dry THF, 45 min, then 2,4,6-triisopropylbenzenesulfonyl azide, 5 min, then HOAc, -78-25 °C, 12 h, 85%; (iii) $NaBH_4$, THF/ H_2O (3:1), 0-25 °C, 2 h, 95%; (iv) H_2 (1 atm), 10% Pd/C, Boc_2O, MeOH, 5 h, 90%; (v) TsCl, Et_3N, CH_2Cl_2, 0-25 °C, 3 h; (vi) $LiAlH_4$, THF, reflux, 4 h, 65% (over two steps); (vii) propargyl bromide, K_2CO_3, CH_3CN, 3 h, 25 °C, 71%.

The electrophilic azidation of chiral imide enolate **33** at the α-position of (KHMDS, 2,4,6,-triisopropylbenzenesulfonyl azide, THF, -78 °C; quenching with AcOH) was carried out to produce α-azido oxazolidinone **34** in 85% yield {$[\alpha]_D^{25}$ + 67.6 (*c* 1.0, CH_2Cl_2} (dr > 99%).[12a]

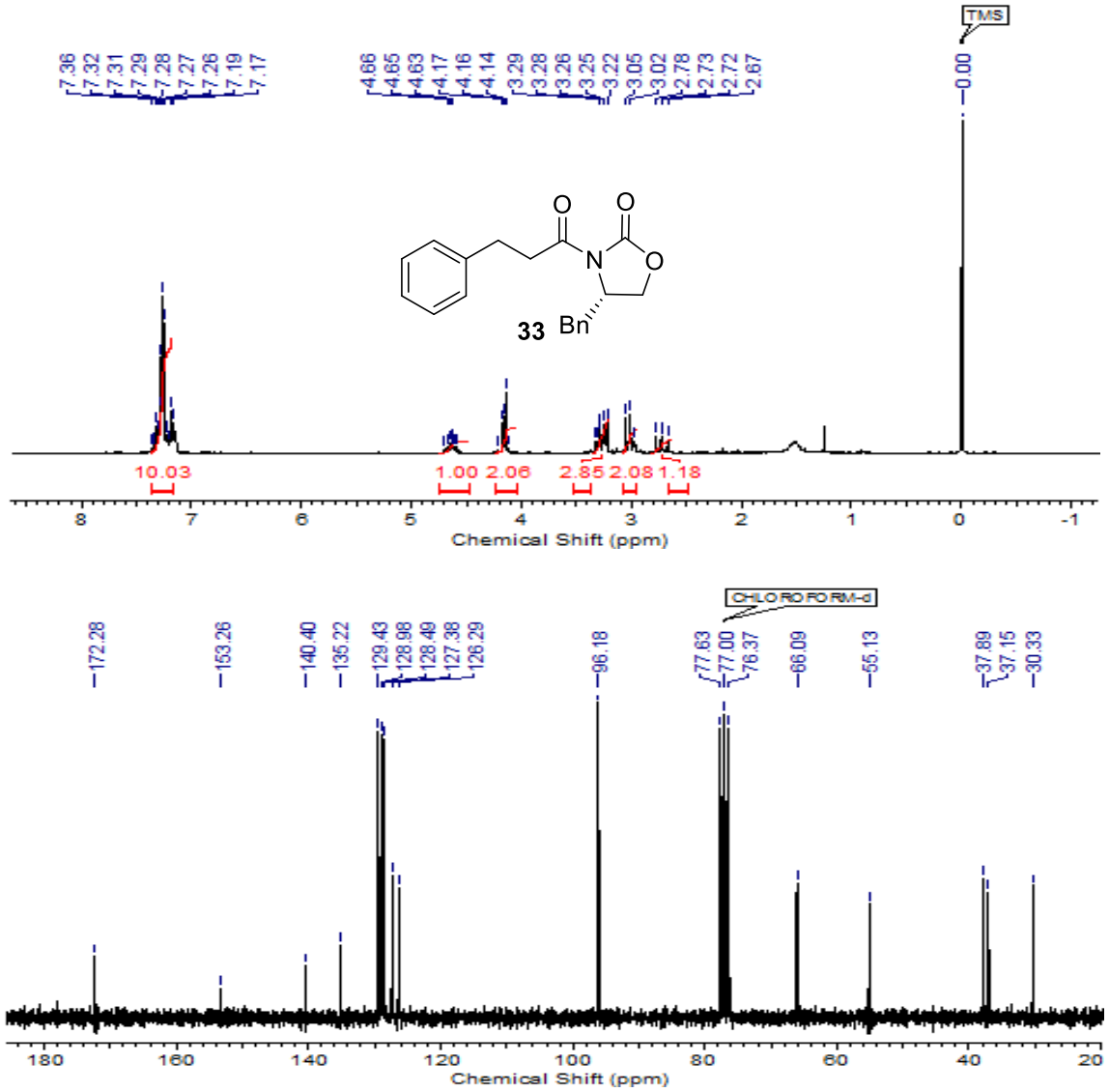


Fig. 2: ^{1}H and ^{13}C NMR spectra of oxazolidinone **33**

The formation of α-azido oxazolidinone **34** was confirmed from its ^{1}H and ^{13}C NMR spectral analysis. The ^{1}H NMR spectrum displayed a quintet at δ 5.20 (quint, *J* = 5.0, 6.8 Hz, 1H) for methine proton (C**H**-N_3) and four doublet of doublets at δ 3.34 (dd, *J* = 5.0, 13.5 Hz, 1H), 3.18 (dd, *J* = 3.1, 13.1 Hz, 1H), 3.03 (dd, *J* = 9.3, 13.6 Hz, 1H) and 2.67 (dd, *J* = 9.4, 13.3 Hz, 1H) for the four benzylic protons respectively. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 170.3 and 152.7 for carbonyl carbons and other signal at δ 61.3 corresponding to carbon attached to azide group (**Fig. 3**). Its IR spectrum

showed strong vibrational stretching frequencies at υ_{max} 2152, 1760 and 1716 cm^{-1} due to the presence of azide and carbonyl functionalities respectively.

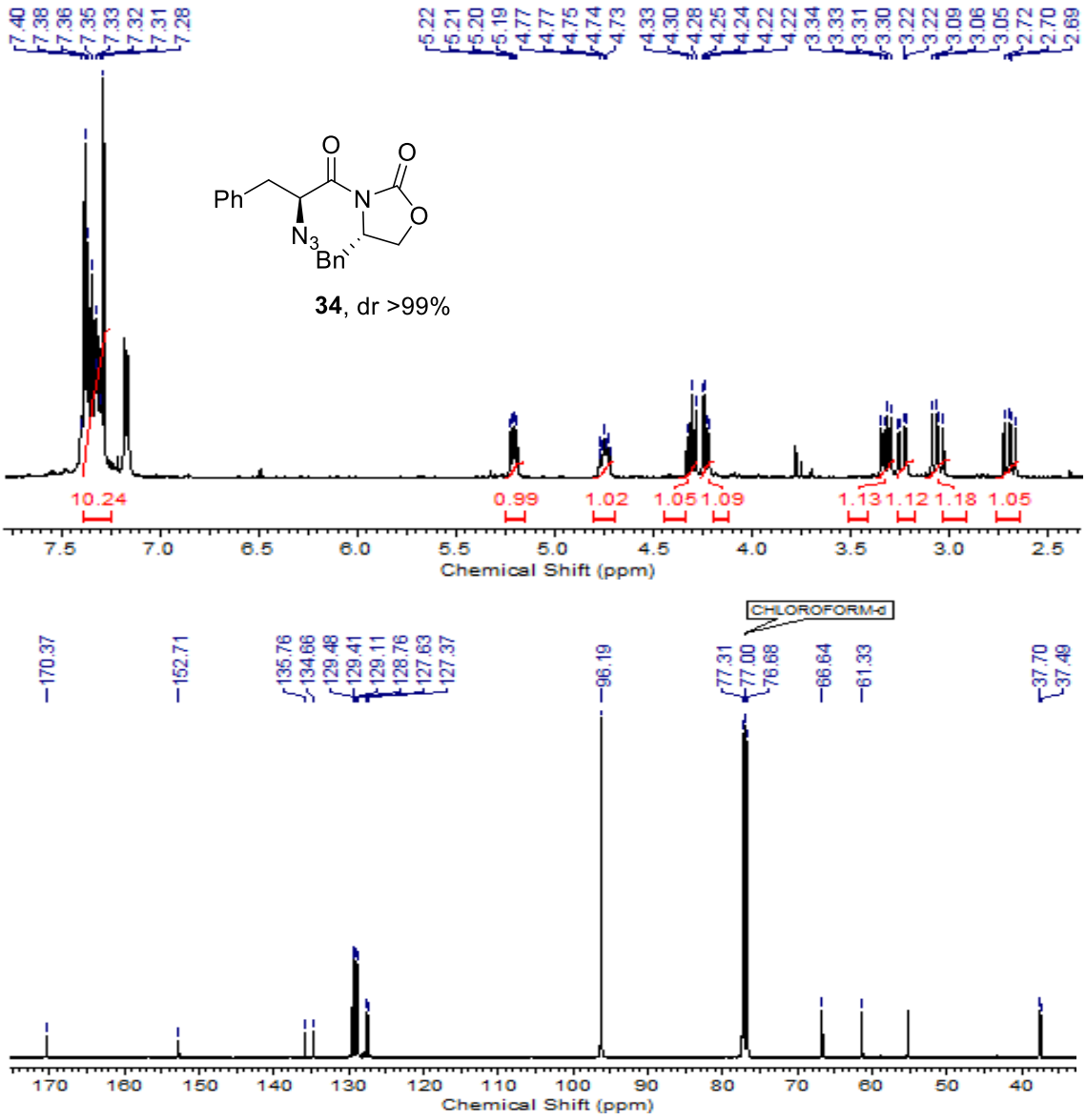


Fig. 3: ^{1}H and ^{13}C NMR spectra of α-azido oxazolidinone **34**

The reductive removal of chiral auxiliary was then achieved using $NaBH_4$ in THF/H_2O giving the free β-azido alcohol **35** in 95% yield; $[\alpha]_D^{25}$ -2.33 (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ -2.4 (*c* 1.0, $CHCl_3$)}. The formation of β-azido alcohol **35** was established by its ^{1}H and ^{13}C

NMR spectral analysis. Its ^{1}H NMR spectrum showed two multiplets at δ 3.72 (m, 2H) for methylene protons (-C**H**$_2$-OH) and 3.58 (m, 1H) for methine proton (-C**H**-N$_3$) and a singlet at δ 2.04 (br s, 1H) due to –O**H** proton. The appearance of carbon signals at δ 66.2 and 36.9 are due to methylene carbons and at δ 64.2 corresponding to methine carbon in its ^{13}C NMR spectrum (**Fig. 4**). Its IR spectrum exhibited strong vibrational stretching frequencies

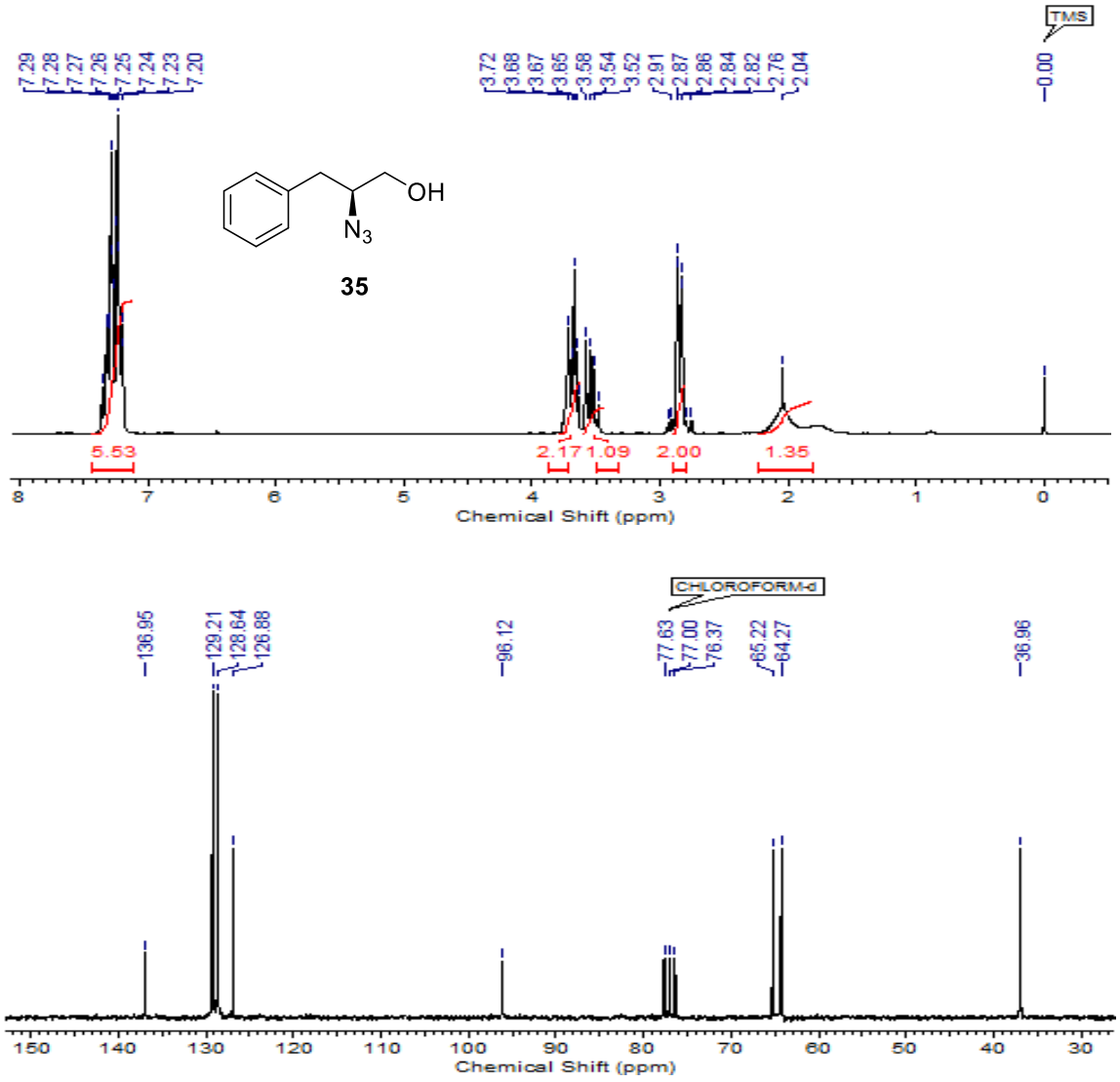
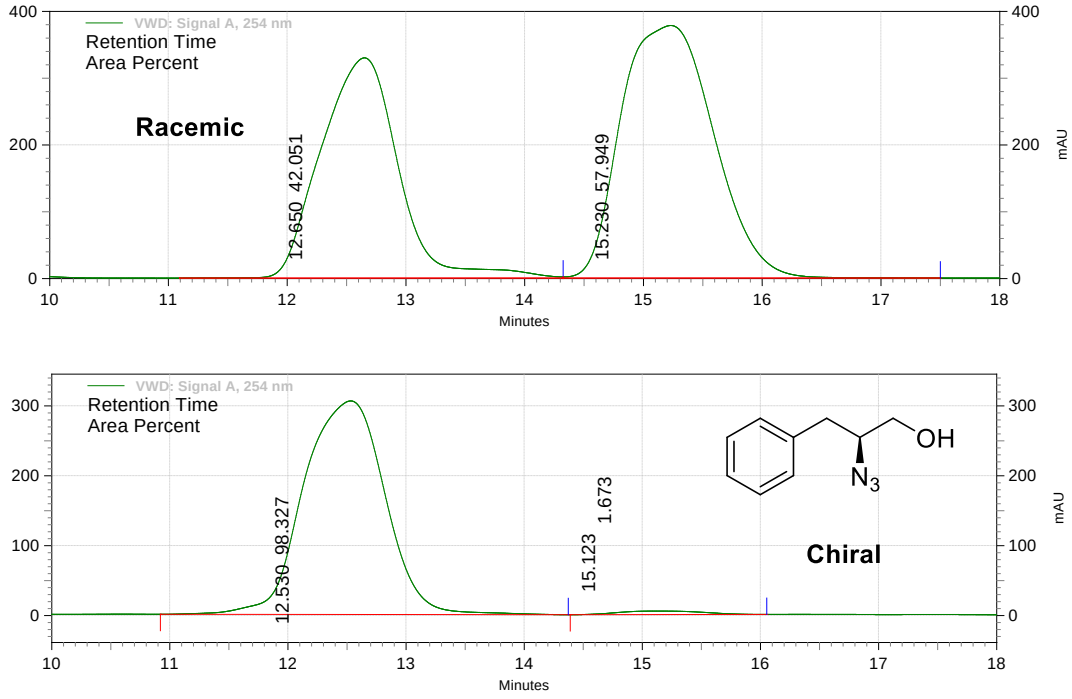


Fig. 4: ^{1}H & ^{13}C NMR spectra of β-azido alcohol **35**

at υ_{max} 2120 and 3410 cm^{-1} indicating the presence of azide and hydroxyl groups respectively. The optical purity of **35** was determined to be 97% ee by chiral HPLC analysis [Chirapak OD-H, 2-Propanol/n-Hexane = 2.5/97.5, flow rate 0.5 mL/min, λ = 254 nm, retention time: (minor) 12.53 min, (major) 15.12 min] (**Fig. 5**).



Retention Time	Area	Area %	Height	Height %
12.530	244951558	98.33	5128098	98.65
15.123	4168475	1.67	83636	1.35
Totals	249120033	100.00	5211734	100.00

Fig 5: HPLC Chromatogram of β-azido alcohol **35**

The catalytic hydrogenation [10% Pd/C, H_2 (1 atm), Boc_2O, MeOH] of azide **35** furnished the corresponding amino alcohol (90% yield) in which amine function was protected as carbamate **28**. The formation of carbamate **28** was determined from its ^1H and ^{13}C NMR spectral analysis. Its ^1H NMR spectrum showed a multiplet at δ 3.64-3.72 (m, 1H) due to

methine proton attached –NHBoc group and a singlet at δ 1.42 (s, 9H) corresponding to methyl protons of *tert*-butyl group. The ^{13}C NMR spectrum displayed a typical carbon signal at δ 196.0 for the carbonyl carbon and other signal at δ 79.5 due to tertiary carbon in *tert*-butyl group (**Fig. 6**). Its IR spectrum showed characteristic vibrational stretching frequencies at υ_{max} 3440 and 1710 cm^{-1} due to the presence of carbonyl and hydroxyl groups respectively.

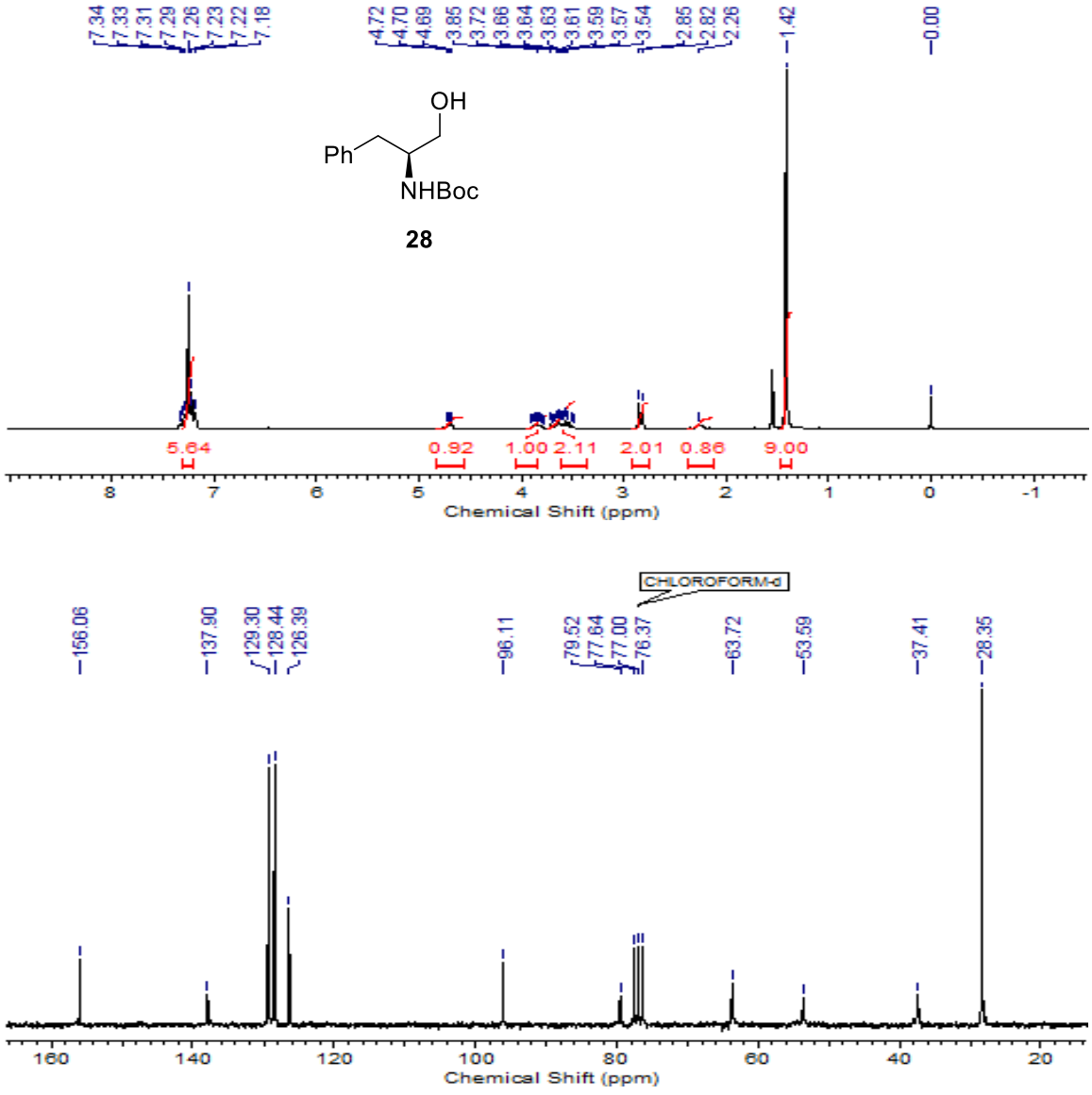


Fig. 6: ^{1}H and ^{13}C NMR spectra of carbamate **28**

The alcoholic function in carbamate **28** was subsequently protected as tosylate **36**. Reduction of **36** with $LiAlH_4$ gave secondary methyl amine **4**, which was readily *N*-alkylated with propargyl bromide affording (*R*)-selegiline (**1**) in 30% overall yield. The formation of (*R*)-selegiline (**1**) was confirmed from its ^{1}H NMR spectrum, which showed two doublets at δ 3.42 (d, *J* = 2.4 Hz, 2H) for methylene protons and 0.98 (d, *J* =

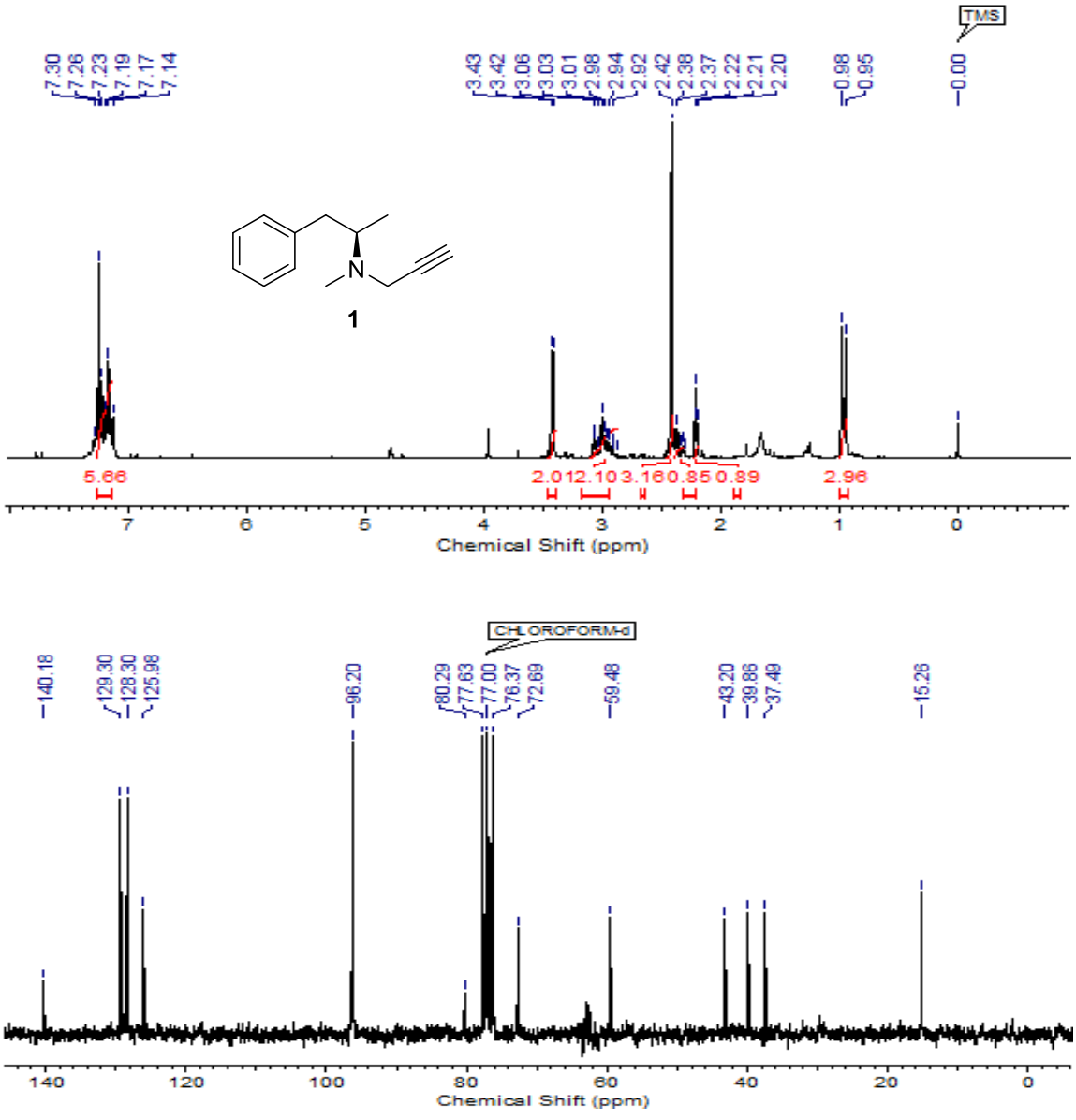
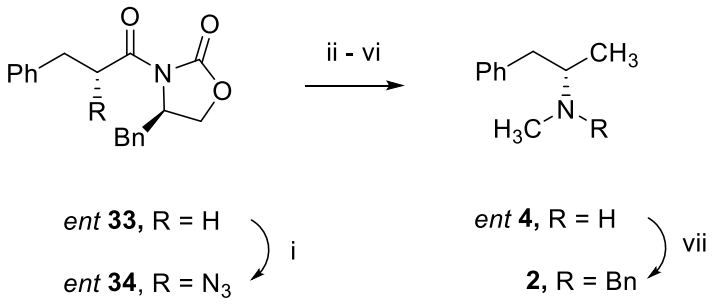


Fig. 7: ^{1}H and ^{13}C NMR spectra of (*R*)-selegiline **1**

6.6 Hz, 3H) for methyl proton and a triplet at δ 2.21 (t, *J* = 2.4 Hz, 1H) for alkynic protons respectively. Its ^{13}C NMR spectrum showed typical carbon signals at δ 80.2, 43.2 and 59.4 corresponding to the quaternary alkyne carbon, benzylic and homobenzylic carbons respectively. The N-CH_3 carbon showed characteristic signal at δ 37.4 (**Fig. 7**). The enantiomeric purity of **1** was determined to be 97% ee based on the comparison of its specific rotation with the reported values $[\alpha]_D^{25}$ -10.5 (*c* 6.3, EtOH) {lit.[15] $[\alpha]_D^{25}$ -10.8 (*c* 6.4, EtOH)}.

The synthesis of (*S*)-benzphetamine (**2**) was readily achieved by essentially following a similar sequence of reactions except that the chiral auxiliary chosen was (*R*)-4-benzyloxazolidin-2-one (**Scheme 13**). Excellent yields and ees were obtained in each step.



Scheme 13: For (i – vi), see reaction conditions under **Scheme 10**; (vii) benzyl bromide, K_2CO_3, CH_3CN, 2 h, 25 °C, 73%.

Benzylation of ***ent*-4** constitutes the final step to obtain (*S*)-benzphetamine (**2**) in 31% overall yield. The formation of **2** was established by its ^{1}H and ^{13}C NMR spectral analysis. Its ^{1}H NMR spectrum showed a singlet at δ 2.23 (s, 3H) and a doublet at δ 1.01 (d, *J* = 6.3 Hz, 3H) for the methyl protons. Its ^{13}C NMR spectrum displayed signals at δ 14.0 and 36.8 for the methyl carbons and other signal at δ 59.7 for methine carbon respectively (**Fig. 8**). The enantiomeric purity of **2** was determined to be 97% ee based on the comparison of its

specific rotation with the reported values $[\alpha]_D^{25}$ +52.33 (*c* 0.28,) {lit.[16] $[\alpha]_D^{25}$ +53.9 (*c* 1, $CHCl_3$}. The spectroscopic data of the synthetic compounds **1** and **2** are found to be in well-agreement with the reported values.[15,11]

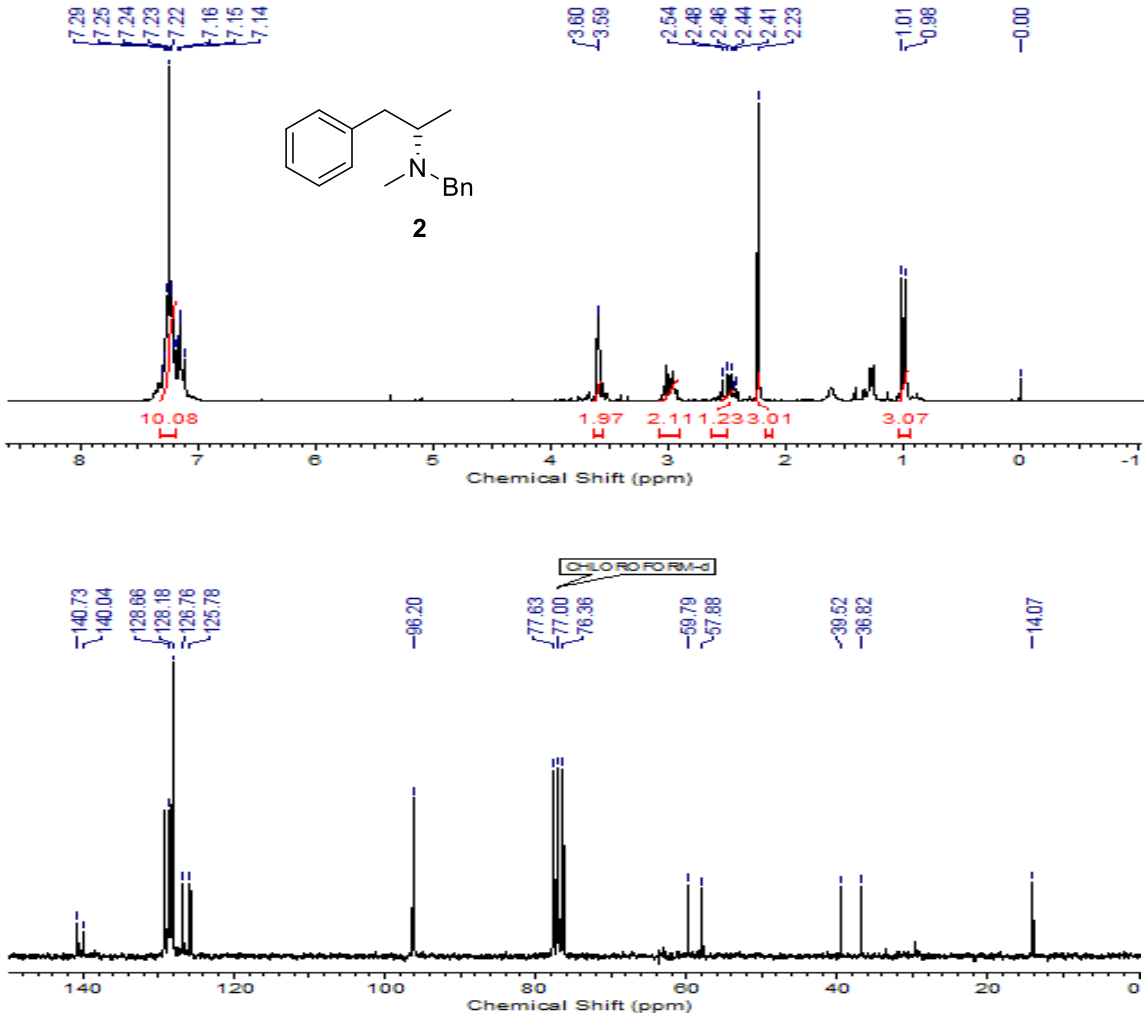


Fig. 8: ^1H and ^{13}C NMR spectra of (*S*)-benzphetamine **1**

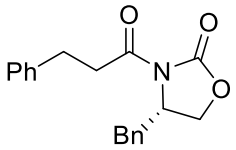
3.1.4 Conclusion

In conclusion, we have specifically provided an efficient procedure for the enantioselective synthesis of two important drugs namely, (*R*)-selegiline (**1**) (30% overall yield; 97% ee) and (*S*)-benzphetamine (**2**) (31% overall yield; 97% ee). In this approach, the key

intermediates were readily prepared in a high diastereoselective manner from the corresponding carboxylic acids by employing the Evans' asymmetric direct azidation reaction. This methodology will find wide applicability for the synthesis of many drug candidates having homobenzylic amine units with high enantioselectivity and diastereoselectivity.

3.1.5 Experimental Section

(*S*)-4-Benzyl-3-(3-phenylpropanoyl)oxazolidin-2-one (33):

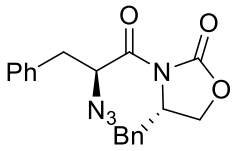


To a stirred solution of hydrocinnamic acid **32** (5 g, 33.2 mmol) in dry THF (100 mL) was added pivolyl chloride (4 g, 33.2 mmol) and Et_3N (10 g, 99.6 mmol) at -20 ^oC and the mixture was stirred at the same temperature for 4 h. To this stirred suspension, (*S*)-4-benzyloxazolidin-2-one (6.5 g, 36.52 mmol) in dry THF (20 mL) was added dropwise followed by the addition of LiCl (1.5 g, 33.2 mmol) and then it was stirred for additional 15 min at -20 ^oC and continued stirring at 25 ^oC for 8 h until complete consumption of starting materials (the progress of the reaction was monitored by TLC). The product was extracted with diethyl ether and the combined organic layer was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product which on column chromatographic purification with petroleum ether/ethyl acetate (4:1) gave **33** as colorless solid.

Yield: 9.07 g, 90%; colorless solid; **mp**: 101- 102 °C; **$[\alpha]_D^{25}$** + 66.56 (*c* 1.0, $CHCl_3$) {lit.[13] $[\alpha]_D^{25}$ +67.4 (*c* 0.98, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3065, 3030, 1742, 1720, 1620, 1387,

1212, 1050, 890; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.72 (dd, *J* = 9.7, 13.3 Hz, 1H), 3.02-3.05 (m, 2H), 3.23- 3.29 (m, 3H), 4.14- 4.17 (m, 2H), 4.63- 4.66 (m, 1H), 7.15- 7.32 (m, 10 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.3, 37.1, 37.8, 55.1, 66.0, 126.3, 127.3, 128.6, 128.9, 129.4, 135.2, 140.4, 153.2, 172.2; **Anal. Calcd** for $C_{19}H_{19}NO_3$ requires C, 73.77; H, 6.19; N, 4.53; Found: C, 73.65; H, 6.02; N 4.32%.

(2*R*,4*S*)-3-(2-Azido-3-phenyl-1-oxopropyl)-4-(phenylmethy1)-2-oxazolidinone (34):

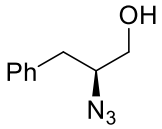


To a stirred solution of **33** (8.5 g, 28.02 mmol) in dry THF (90 ml), 61.55 ml of 0.5 M in toluene (30.82 mmol) of potassium hexamethyldisilazide (KHMDS) was added under N_2 at -78 ^oC and the mixture was stirred for 45 min. To this suspension of potassium enolate, being stirred at -78 ^oC, was added 2,4,6-triisopropyl azide (11.2 g, 36.42 mmol) in dry THF (30 mL). After 5 min, the reaction was quenched with 8 ml (140.1 mmol) of glacial acetic acid and stirred at 25 ^oC for 12 h. Then the solution was partitioned between CH_2Cl_2 and brine solution. The organic phase was washed with aqueous $NaHCO_3$, dried over anhy. Na_2SO_4 and evaporated *in vacuum*. On column chromatographic purification of the crude product with petroleum ether/ethyl acetate (4:1) gave **34** as a yellow solid.

Yield: 8.3 g, 85%; yellow solid; **mp**: 116-120 ^oC; **$[\alpha]_D^{25}$** + 67.6 (c 1.0, CH_2Cl_2); {lit.[12a] $[\alpha]_D^{25}$ + 68 (c 1.0, CH_2Cl_2)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3065, 3030, 2987, 2111, 1781, 1701, 1389, 1210, 1035, 780; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.67 (dd, *J* = 9.4, 13.3 Hz, 1H), 3.03 (dd, *J* = 9.3, 13.6 Hz, 1H), 3.18 (dd, *J* = 3.1, 13.1 Hz, 1H), 3.34 (dd, *J* = 5.0, 13.5 Hz, 1H), 4.19- 4.29 (m, 2H), 4.65- 4.77 (m, 1H), 5.18 (q, *J* = 5.0, 6.8 Hz, 1H), 7.13- 7.36 (m, 10 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.4, 37.7, 55.1, 61.3, 66.6, 127.3, 127.6, 128.7,

129.1, 129.4, 134.6, 135.7, 152.7, 170.3; **Anal. Calcd** for $C_{19}H_{18}N_4O_3$ requires C, 65.13; H, 5.18; N, 15.99; Found: C, 65.01; H, 4.89; N, 15.70%.

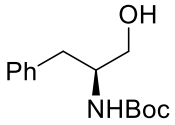
(*S*)-2-Azido-3-phenylpropan-1-ol (35):



To a stirred solution of **34** (5 g, 14.27 mmol) in THF (30 mL) was added a solution of sodium borohydride (1.0 g, 28.54 mmol) in water (10 mL) dropwise at 0 ^oC. After the addition, it was kept for stirring at 25 ^oC for 2 h. On completion of reaction (monitored by checking TLC) 2N HCl (20 mL) was added slowly so that the temperature is maintained at 25 ^oC. The reaction mixture was then extracted with ethyl acetate, washed with brine. The organic phase was concentrated and on column chromatographic purification with petroleum ether/ethyl acetate (3:7) gave **35** as a colorless viscous liquid.

Yield: 2.4 g, 95%; colorless viscous liquid; **$[\alpha]_D^{25}$** -2.33 (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ – 2.4 (*c* 1.0, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}) υ_{max} 3439, 3110, 2945, 2108, 1092, 1046, 975, 826; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30 (br s, 1H), 2.76- 2.87 (m, 2H), 3.54- 3.58 (m, 1H), 3.68 (d, *J* = 11.1 Hz, 2H), 7.21- 7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.9, 64.2, 65.2, 126.8, 128.6, 129.2, 136.9; **Anal. Calcd** for $C_9H_{11}N_3O$ requires C, 61.00; H, 6.26; N, 23.71; Found: C, 60.85; H, 6.05; N, 23.53%; **Optical purity**: 97% ee determined by HPLC analysis (Chiracel AD-H column, Hex/*i*-PrOH 90:10, 0.3 mL/min, 220 nm). Retention time: t_{major} = 12.53 min and t_{minor} = 15.12 min.

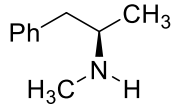
(*S*)-*tert*-Butyl-1-hydroxy-3-phenylpropan-2-yl-carbamate (28):



A mixture of azido alcohol **35** (2.5 g**,** 10.8 mmol), 10% Pd/C (10 mg) and di-*tert*-butyl dicarbonate Boc_2O (2.35 g, 10.8 mmol) in dry MeOH (20 mL) was stirred under H_2 (1 atm) at 25 ^oC for 5 h. After completion of reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and solvent evaporated under reduced pressure to afford crude, which was purified by column chromatography using petroleum ether: ethyl acetate (4:1) to give **28** as colorless solid.

Yield: 2.5 g, 90%; colorless solid; **mp**: 96-98 ^oC; **$[\alpha]_D^{25}$** -26.4 (*c* 1, MeOH) {lit.[16] $[\alpha]_D^{25}$ -27 (*c* 1, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3440, 2978, 2933, 1710, 1526, 1390, 1268, 1020, 760; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.32 (br s, 1H), 2.82 (d, *J* = 7.2 Hz, 2H), 3.51- 3.63 (m, 2H), 3.66- 3.83 (m, 1H), 4.69 (br s, 1H), 7.19- 7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 37.4, 53.5, 63.7, 79.5, 126.4, 128.4, 129.3, 137.9, 156.0; **Anal. Calcd** for $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42; N, 5.57; Found: C, 66.72; H, 8.20; N, 5.26%.

(*R*)-*N*-Methyl-1-phenylpropan-2-amine (11):

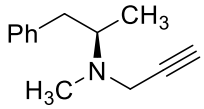


To a stirred solution of N-Boc protected amino alcohol **28** (0.5 mg, 1.98 mmol) in CH_2Cl_2 (5 mL) were added dry triethylamine (0.3 mL, 2.37 mmol) and *p*-toluenesulfonyl chloride (0.452 g, 2.37 mmol) in presence of catalytic amount of 4-dimethylaminopyridine (0.024 g,10 mol%) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 3 h and then quenched by addition of 10% $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, concentrated to give the crude tosylate, which was then dissolved in dry THF (5 mL), and added dropwise to a

suspension of $LiAlH_4$ (0.225 g, 3 mmol) in dry THF (10 mL). It was refluxed for 4 h and then cooled to 0 ^oC and the excess $LiAlH_4$ was quenched by the addition of EtOAc. It was then treated with aq. 20% NaOH (0.5 mL), the white precipitate formed was filtered off, and the residue was washed with EtOAc (3x10 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography over silica gel using $CHCl_3$ as eluent to afford the corresponding pure *N*-methyl amine **4**.

Yield: 0.192 g, 65%; colourless gum; **$[\alpha]_D^{25}$** – 10.8 (*c* 4.2, EtOH); {lit.[16] $[\alpha]_D^{25}$ -10.9 (*c* 4.2, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3274, 3119, 2917, 2839, 1614, 1572, 1438, 985, 742; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.08 (d, *J* = 5.9 Hz, 3H), 1.67 (m, 1H), 2.4 (s, 3H), 2.63- 2.82 (m, 3H), 7.15- 7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 33.8, 43.3, 56.3, 126.2, 128.4, 129.2, 139.2; **Anal. Calcd** for $C_{10}H_{15}N$ requires C, 80.48; H, 10.13; N, 9.39%; Found: C, 80.26; H, 10.03; N, 9.08%.

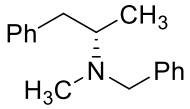
(*R*)-*N*-Methyl-*N*-(-1-phenylpropan-2-yl)prop-2-yn-1-amine: (*R*)-Selegiline (1):



To a stirred solution of (*R*)-2-(methylamino)-1-phenylpropane **4** (0.1 g, 0.67 mmol) in CH_3CN (3 mL) were added anhyd. K_2CO_3 (0.185 g, 1.34 mmol) and (0.1 mL, 0.73 mmol) propargyl bromide (80 wt. % solution in toluene). The reaction mixture was then stirred for 3 h at 25 ^oC, and then the solvent evaporated under reduced pressure to provide the crude product, which was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to give pure (*R*)-selegiline **1**.

Yield: 41 mg, 71%, gum; **[α]$_D^{25}$** -10.7 (*c* 6.5, EtOH);{lit.[15] [α]$_D^{25}$ -10.8 (*c* 6.4, EtOH)}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.6 Hz, 3H), 2.21 (t, *J* = 2.4 Hz, 1H), 2.37- 2.42 (m, 4H), 2.92- 3.08 (m, 2H), 3.42 (d, *J* = 2.4 Hz, 2H), 7.19- 7.14 (m, 3H), 7.26- 7.23 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.2, 37.4, 38.8, 43.2, 59.4, 72.6, 80.2, 125.9, 128.3, 129.3, 140.1; **Anal. Calcd** for $C_{13}H_{17}N$ requires C, 83.37; H, 9.15; N, 7.48; Found: C, 83.15; H, 8.96; N, 7.23%.

(*S*)-*N*-Benzyl-*N*-methyl-1-phenylpropan-2-amine: (*S*)-Benzphetamine (2):



To a stirred solution of (*S*)-2-(methylamino)-1-phenylpropane (*ent*-**4**) (0.080 g, 0.67 mmol) in CH_3CN (3 mL) were added anhyd. K_2CO_3 (0.146 g, 1.06 mmol) and (0.1 mL, 0.79 mmol) benzyl bromide. The reaction mixture was then stirred for 2 h at 25 ^oC, and then the solvent evaporated under reduced pressure to provide the crude product, which was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to give pure (*S*)-benzphetamine (**2**).

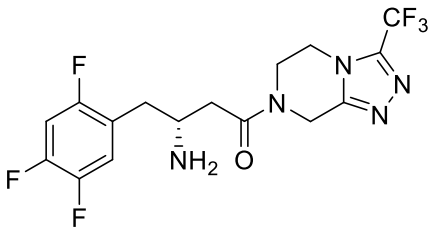
Yield: 98 mg, 79%; colourless gum; **[α]$_D^{25}$** +52.33 (*c* 0.28); {lit.[11a] [α]$_D^{25}$ +53.9 (*c* 1, $CHCl_3$}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.99 (d, *J* = 6.3 Hz, 3H), 2.24 (s, 3H), 2.42- 2.54 (m, 1H), 2.96- 3.04 (m, 2 H), 3.6 (d, *J* = 2.4 Hz, 2H), 7.12- 7.30 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 36.8, 39.5, 57.8, 59.7, 125.7, 126.7, 128.1, 128.6, 129.2, 140.0, 140.7; **Anal. Calcd** for $C_{17}H_{21}N$ requires C, 85.30; H, 8.84; N, 5.85; Found: C, 85.14; H, 8.62; N, 5.60%.

Section II

Asymmetric Synthesis of (*S*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoic Acid, Key Intermediate for the Synthesis of (*R*)-Sitagliptin

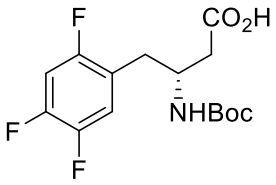
3.2.1 Introduction and Pharmacology

Type 2 *diabetes mellitus* is a vast growing progressive disease that almost affects one person among every twelve globally. It has been established that dipeptidyl peptidase IV (DPP-IV) inhibitors are known to stimulate insulin secretion indirectly by enhancing the action of the incretin hormones glucagen-like peptide I (GLP-I) and glucose-dependent insulintropic polypeptide (GIP) thereby decreasing the effect of diabetis.[17] In addition, it also functions as anti-hypertensive, lipids lowering, anti-inflammatory, anti-atherosclerosis and improving cardiac function agents. (*R*)-Sitagliptin (**37**), a β-amino acid derivative, is a potent DPP-IV inhibitor enzyme, which offers a new mechanism in achieving glycemic control for the treatment of type 2 diabetes. It is marketed under the trade name, Januvia (**Fig. 9**).



37

(*R*)-sitagliptin



38

β-amino acid

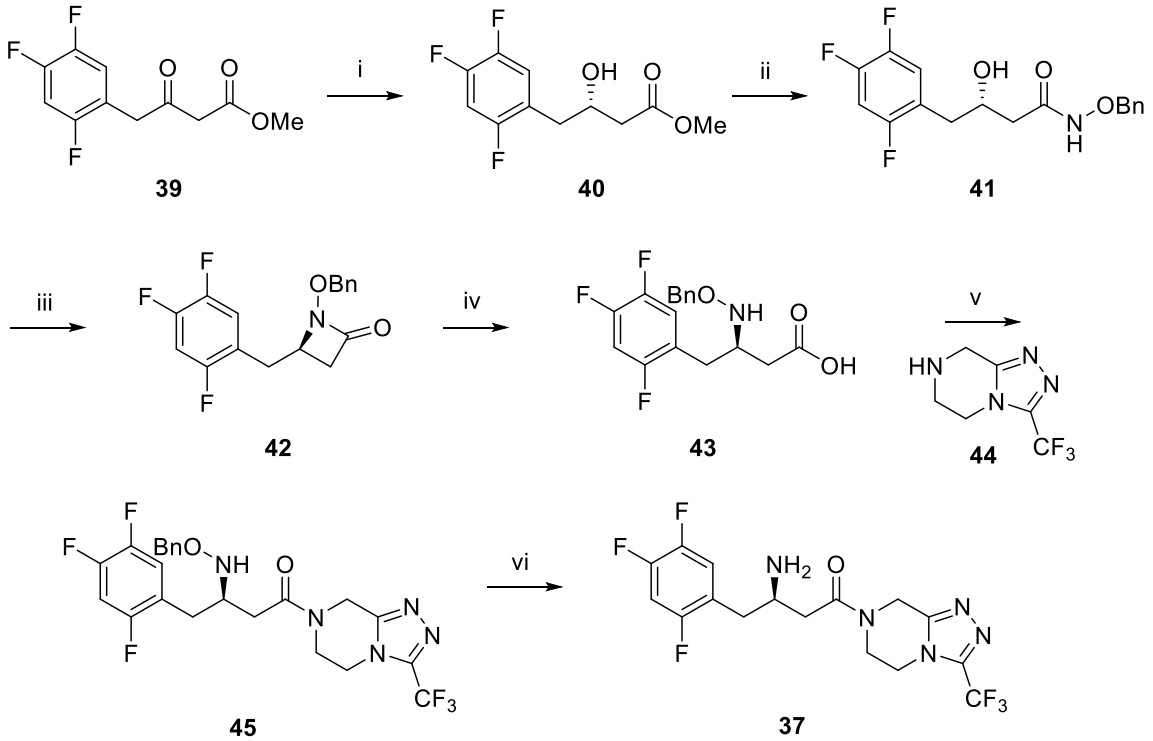
Fig. 9: Structure of (*R*)-sitagliptin (**37**) and β-amino acid intermediate (**38**)

3.2.2 Review of literature

Literature search has revealed that there are several reports available for the synthesis of (*R*)-sitagliptin (**37**) which are described below.

Hansen's approach (2005)[18]

Hansen *et al.* have commenced the synthesis of **37** from β-keto ester **39**; its reduction with (*S*)-BinapRuCl$_2$-triethylamine complex in methanol at 90 psi H_2 pressure gave β-hydroxy ester **40** in 83% yield. The ester **40** was hydrolyzed to carboxylic acid, which was coupled with BnONH$_2$·HCl to form hydroxymate **41**. The hydroxymate **41** was converted to β-lactam **42** in 81% yield on treatment with diisopropyl azodicarboxylate

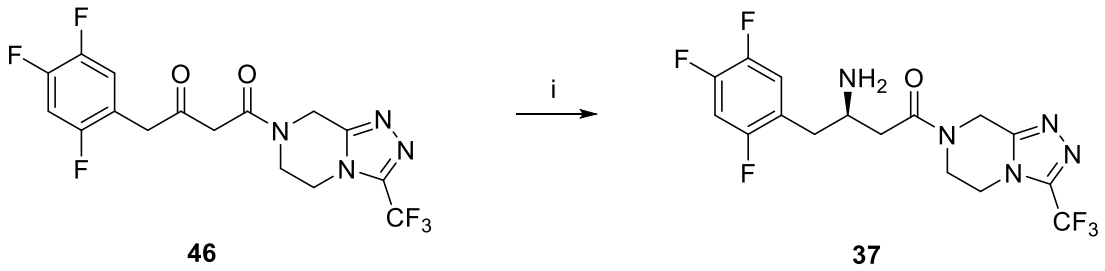


Scheme 14: (i) (a) (*S*)-BinapRuCl$_2$, HBr, 90 psi H_2, MeOH, 80 °C; (ii) (a) NaOH, MeOH/H_2O; (b) BnONH$_2$·HCl, EDC, LiOH, THF/H_2O, 83%; (iii) DIAD, PPh_3, THF, 81%; (iv) NaOH, THF/H_2O; (v) EDC, *N*-methyl morpholine, MeCN; (vi) H_2 (1 atm), 10% Pd/C, MeOH, 78%.

(DIAD) and triphenylphosphine. The lactam **42** was transformed into β-amino acid **43** by basic hydrolysis, which was coupled with triazole **44** to provide compound **45**. Finally, on hydrogenolysis of **45** furnished the target molecule **37** in 78% yield (**Scheme 14**).

Steinhuebel's approach (2009)[19]

Steinhuebel *et al.* have introduced asymmetric reductive amination of β-keto ester **46** as the key chiral inducing step. Thus, β-keto ester **46** was subjected to [$Ru(OAc)_2$((*R*)-dm-segphos)] catalyzed asymmetric reductive amination [H_2 (435 psi)] using ammonium salicylate in MeOH at 80 ºC to provide **37** in 96% yield and 99.5% ee (**Scheme 15**).



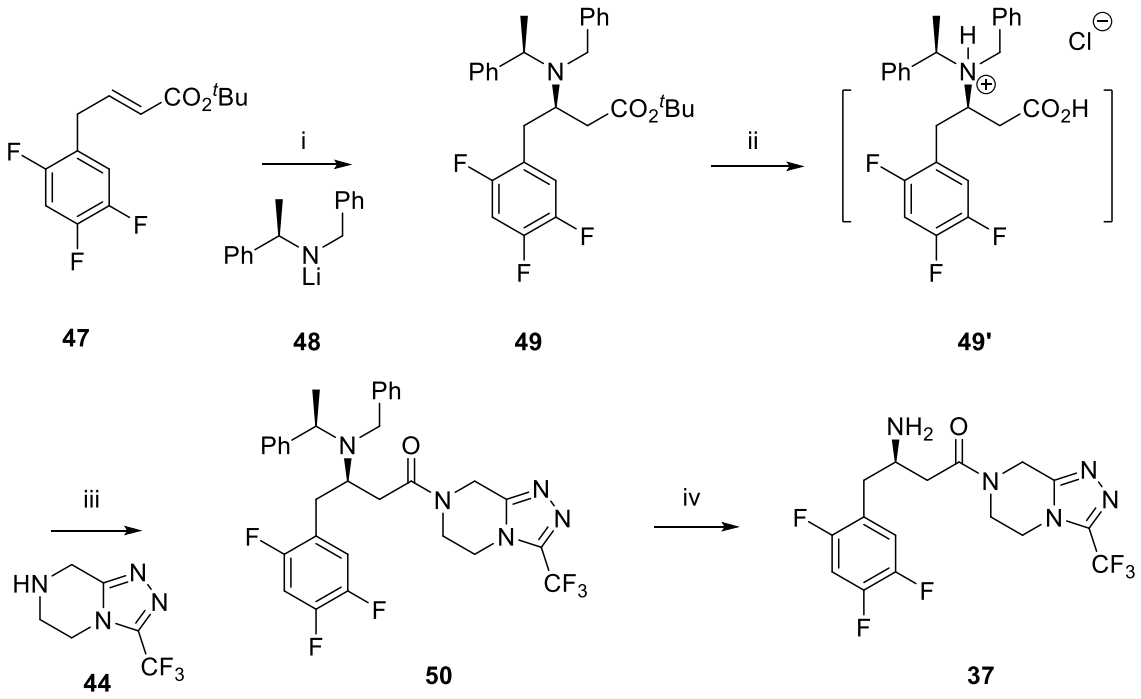
46 **37**

Scheme 15: (i) H_2 (435 psi), $Ru(OAc)_2$((*R*)-dm-segphos), ammonium salicylate (5 equiv), MeOH, 80 ºC.

Davies's approach (2012)[20]

Davies *et al.* have used a novel highly diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **48** to *tert*-butyl-4-(2´,4´,5´-trifluorophenyl)but-2-enoate **47** to provide β-amino ester **49** in 87% yield and >99:1 dr ratio as key step. *N*-Benzyl-*N*-α-methylbenzyl protected β-amino ester **49** was treated with 2.0 M aq. HCl at reflux to give the corresponding carboxylic acid hydrochloride salt **49'**. Subsequent HOBt/EDC mediated amide coupling of **50** with triazolopyrazine **44** gave amide **50** in 70% yield over two steps. Finally, removal of the N-protecting group by hydrogenolysis in the

presence of Pearlman's catalyst [$Pd(OH)_2/C$] gave (*R*)-sitagliptin (**37**) in 96% yield (**Scheme 16**).

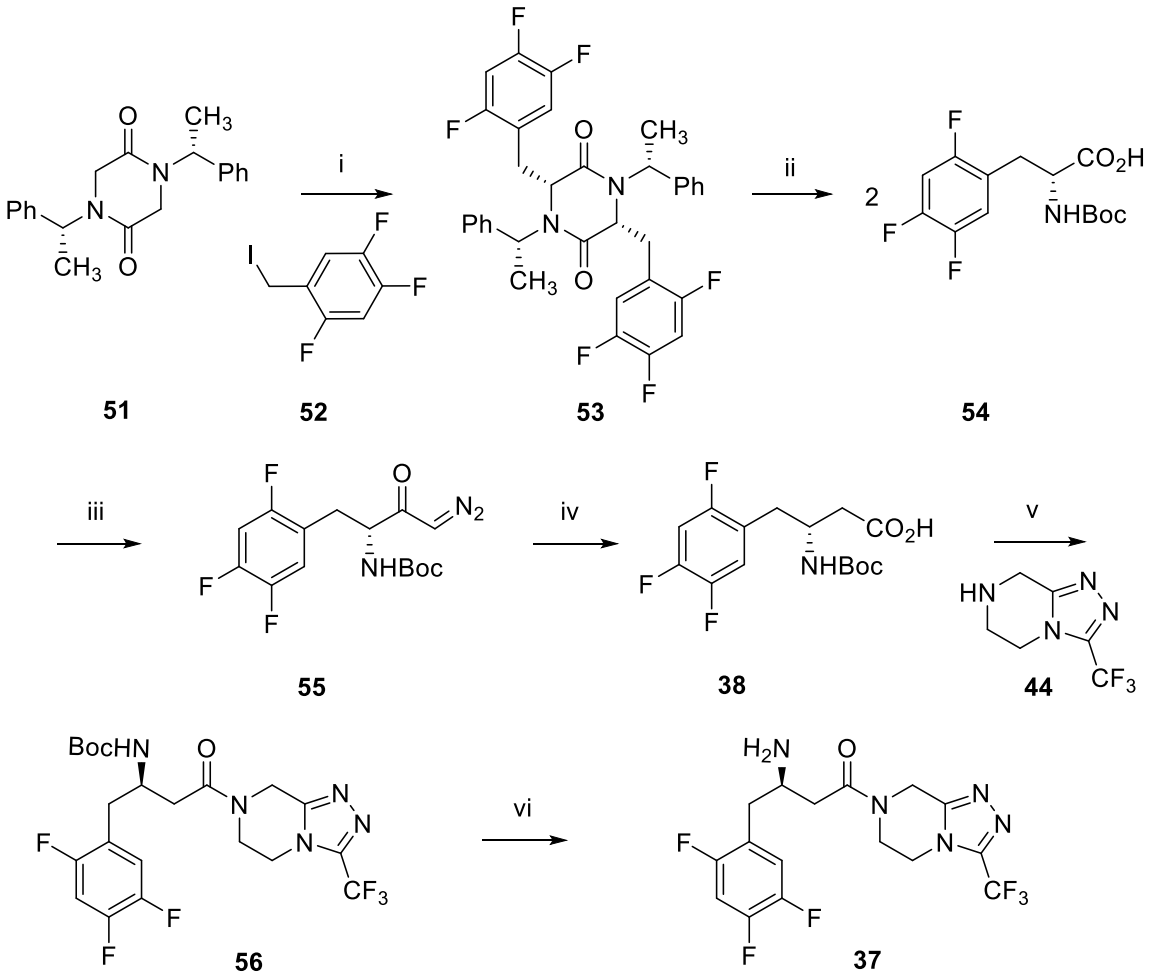


Scheme 16: (i) chiral base **48**, THF, -78 ºC, 2 h; (ii) HCl (2.0 M, aq), reflux, 6 h; (ii) HOBt, EDC·HCl, DIPEA, $CHCl_3$, 25 ºC, 16 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$ (30% w/w), MeOH, 25 ºC, 24 h, 96%.

Haq's approach (2014)[21]

Haq *et al.* have accomplished the synthesis of (*R*)-sitagliptin (**37**), starting from the chiral synthon (1,4-bis[(*R*)-1-phenylethyl]piperazine-2,5-dione) **51**, involving highly stereocontrolled (>98%) alkylation as a key step, with a good overall yield of 50%. Thus, one pot double alkylation of chiral synthon **51** using LHMDS with iodo derivative **52** at -78 ºC afforded *cis*-dialkyl derivative (3*R*,6*R*)-**53** in 73% yield. Cleavage of chiral synthon assembly **53** was achieved by refluxing in 57% HI for 3 h to give α-amino acid, which was then protected with Boc_2O to furnish **54**. Next, Arndt-Eistert homologation of α-amino

acid **54** upon treatment with *iso*-butylchloroformate followed by excess diazomethane gave diazo ketone **55**. Sonication of diazo ketone **55** using a silver benzoate in 1,4-dioxane/water (5:1) provided β-amino acid **38** in 94% yield. Coupling of **38** with triazolopiperazine **44** using EDC/HOBT afforded **56** in 92% yield. Finally, N-Boc protection was removed by treatment of compound **56** with concentrated HCl and MeOH at ambient temperature that afforded **37** in 90% yield (**Scheme 17**).

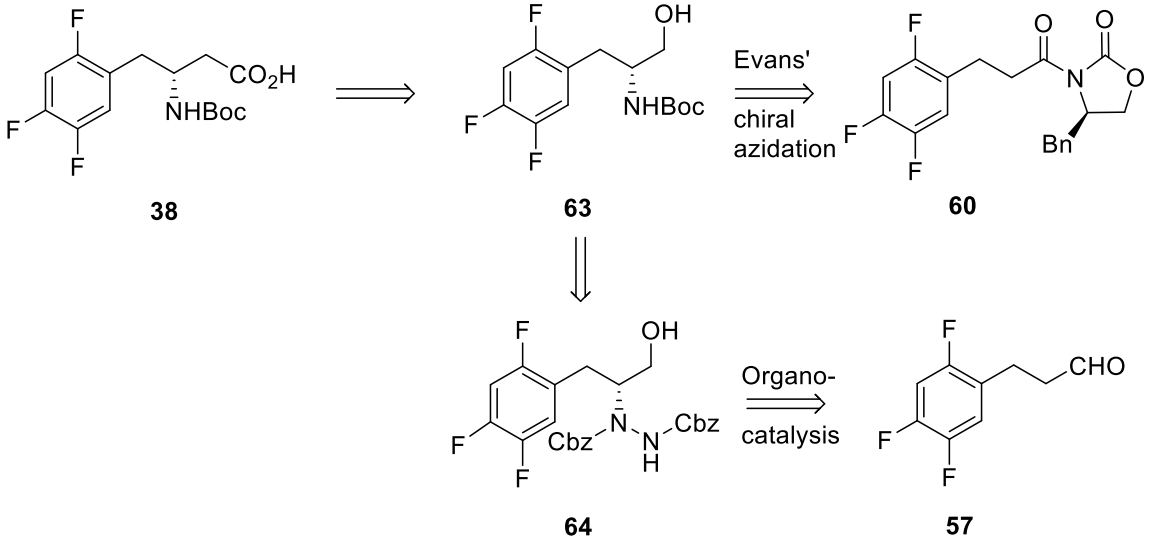


Scheme 17: (i) LHMDS, **52**, THF, -78 ºC, 73%; (ii) 57% HI, reflux, 3 h, Boc_2O, Na_2CO_3, 1,4-dioxane, water; (iii) Et_2O, Et_3N, *iso*-butyl chloroformate, -20 ºC, diazomethane; (iv) silver benzoate, 1,4-dioxane/H_2O (5:1), sonication, 25 ºC; (v) EDC/HOBT, DIPEA, DCM, 0-25 ºC, 24 h; (vi) conc. HCl, MeOH, 90%.

3.2.3 Present work

3.2.3.1 Objective

Because of its high bioactivity, (*R*)-sitagliptin (**37**) was synthesized by various groups as reported in the literature. In all reported syntheses, the key step to install the correct configuration for (*R*)-sitagliptin (**37**) heavily relied on use of chiral synthons as starting materials, asymmetric reductions, use of expensive transition metals as well as hazardous reaction conditions. Thus, a facile and efficient approach for the synthesis of (**37**) is highly desirable. Recently, organocatalytic asymmetric synthesis has provided several new methods for obtaining chiral compounds. In particular, proline,[22] an abundant, inexpensive amino acid and Evans' *N*-acyloxazolidinone auxiliaries, available in both enantiomeric forms, have emerged arguably as the most practical and versatile tools in asymmetric synthesis. Thus, in this section, we envisioned that both Evan's chiral azidation and organocatalytic approach can be employed to construct the β-amino acid (**38**), key intermediate for the synthesis of (*R*)-sitagliptin (**37**) (**Scheme 18**).

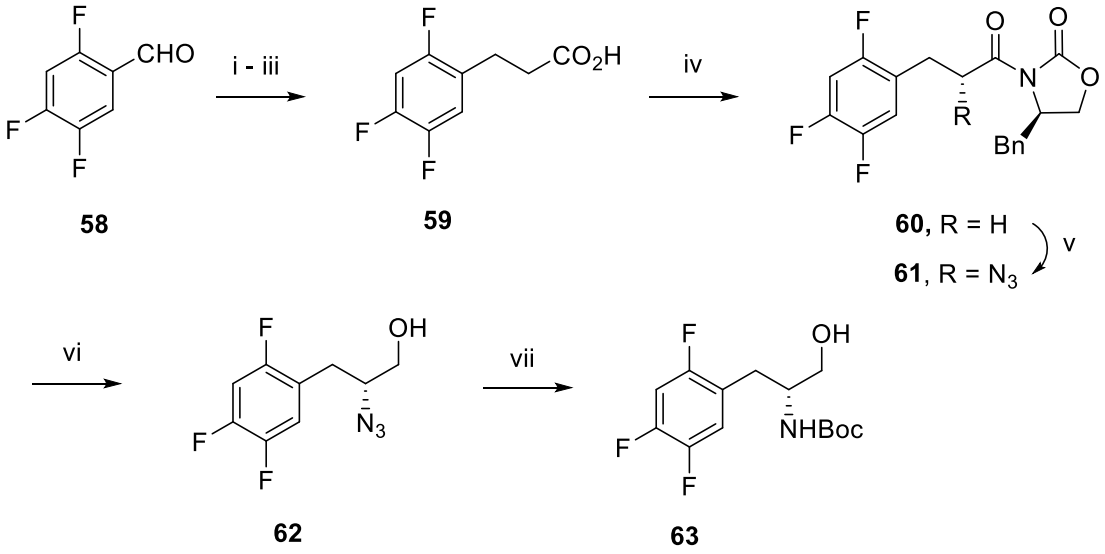


Scheme 18: Retrosynthetic analysis of intermediate, β-amino acid (**38**)

Based on retrosynthetic scheme, the intermediate β-amino acid **38** could be obtained from the carbamate **63**, which in turn could be formed either from oxazolidinone **60** employing Evans' chiral azidation reaction or from α-amino alcohol **64**. The amino alcohol **64** could be readily obtained from aldehyde **57** *via* proline catalyzed α-amination reaction (**Scheme 18**).

3.2.3.2 Results and Discussion

The synthetic sequence of carbamate **63** is shown in **Scheme 19** starting from 2,4,5-trifluorobenzaldehyde **58** employing Evans' chiral azidation reaction. Dihydrocinnamic acid **59** was obtained from aldehyde **58** by simple functional group manipulations: (i) two carbon homologation with stabilized Wittig ylide; (ii) hydrogenation of the benzylic C=C



Scheme 19: (i) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 98%; (ii) H_2 (1 atm), 10% Pd/C, MeOH, 1 h, 98%; (iii) LiOH, THF/MeOH/H_2O (3:1:1), 2 h, 96%; (iv) pivolyl chloride, Et_3N, dry THF, -20 °C, 3 h then (*R*)-4-benzyloxazolidin-2-one, LiCl, -20-25 °C, 8 h, 94%; (v) KHMDS, -78 °C, dry THF, 45 min, then 2,4,6-triisopropylbenzenesulfonyl azide, 5 min, then HOAc, -78-25 °C, 12 h, 88%; (vi) $NaBH_4$, THF/ H_2O (3:1), 0-25 °C, 2 h, 98%; (vii) H_2 (1 atm), 10% Pd/C, Boc_2O, MeOH, 3 h, 98%.

bond by 10% Pd/C over H_2 (1 atm); (iii) conversion of ester group into acid by LiOH-mediated hydrolysis. The formation of acid **59** was confirmed by its ^{1}H NMR spectrum, which showed two triplets at δ 2.67 (t, *J* = 7.3 Hz, 2H) and 2.92 (t, *J* = 7.3 Hz, 2H) for the two methylene protons. This was further ascertained by its ^{13}C NMR spectrum, which displayed a characteristic carbon signal at δ 178.4 corresponding to carbonyl carbon of acid

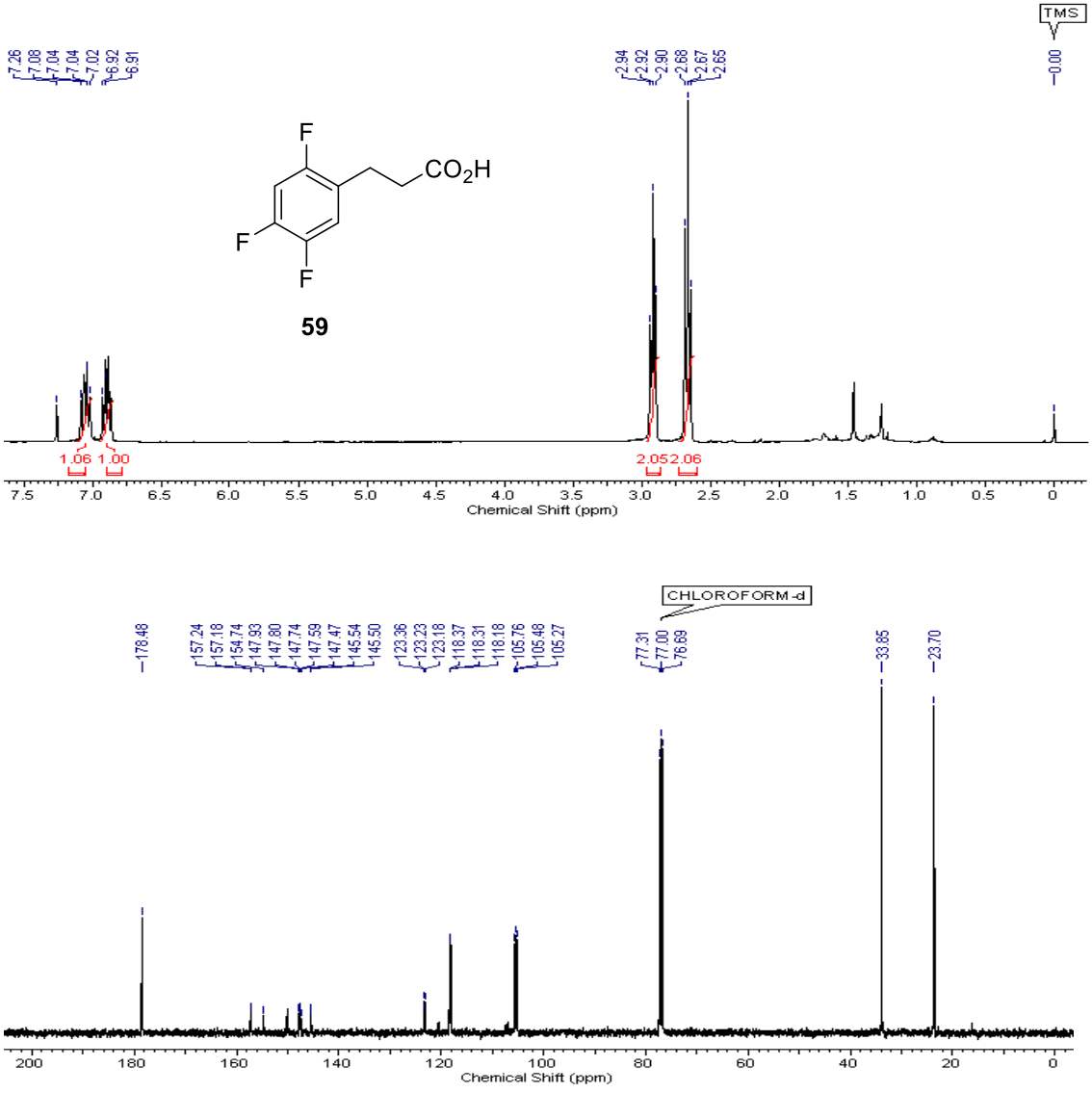
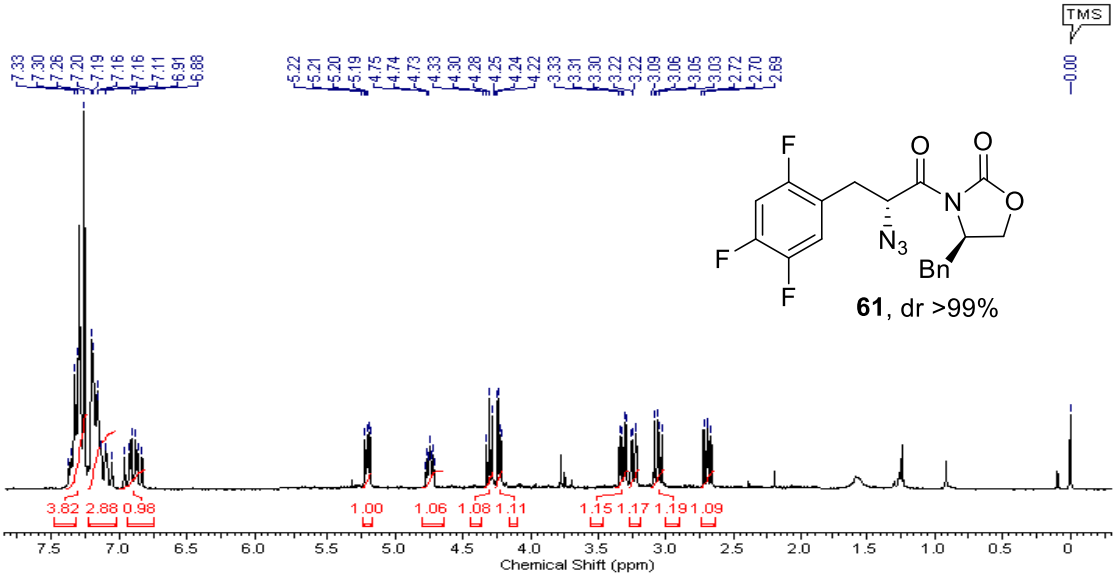


Fig. 10: ^{1}H and ^{13}C NMR spectra of hydrocinnamic acid **59**

group (**Fig. 10**). Its IR spectrum showed a vibrational stretching frequency at υ_{max} 1729 cm^{-1} indicating the presence of acid group. Next, oxazolidinone **60** was prepared from dihydrocinnamic acid **59** in 94% yield [pivolyl chloride, Et_3N, dry THF, -20 °C, 3 h then (*R*)-4-benzyloxazolidin-2-one, LiCl, -20-25 °C, 8 h]. Oxazolidinone **60** was then treated with Evans' chiral azidation reaction [KHMDS, -78 °C, dry THF, 45 min, then 2,4,6-triisopropylbenzenesulfonyl azide, 5 min, then HOAc, -78-25 °C, 12 h] to provide α-azidooxazolidinone **61** in 88% yield and dr>99%; $[\alpha]_D^{25}$ +57.2 (*c* 1.0, $CHCl_3$). The formation of **61** was confirmed from its ^1H and ^{13}C NMR spectral analysis. Its ^1H NMR spectrum showed a quintet at δ 5.20 (quint, *J* = 4.5, 6.8 Hz, 1H) due to methine proton (-C**H**N_3) attached to azide functionality; also the two characteristic carbon signals in its ^{13}C NMR spectrum at δ 171.5 and 151.1 are due to carbonyl carbons and other signal at δ 61.2 corresponding to carbon attached to azide group respectively (**Fig. 11**); its IR spectrum exhibited strong vibrational stretching frequencies at υ_{max} 1772, 1734 and 2115 cm^{-1} confirming the presence of carbonyl and azide functionalities respectively.



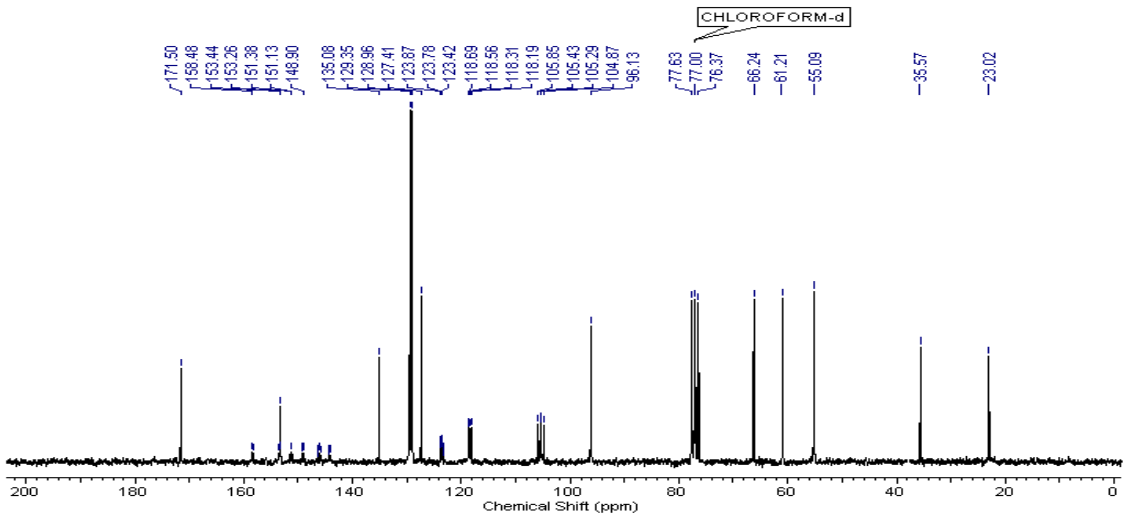


Fig. 11: ^{1}H and ^{13}C NMR spectra of α-azidooxazolidinone **61**

The reductive removal of chiral auxiliary in **61** was then achieved using $NaBH_4$ in THF/H_2O giving the free β-azido alcohol **62** in 98% yield; the formation of β-azido alcohol **62** was confirmed from its ^{1}H and ^{13}C NMR spectral analysis. The ^{1}H NMR spectrum of **62** showed nultiplets at δ 3.55-3.80 (m, 3H) due to methine (-C**H**N_3) and methylene protons (-C**H**$_2$-OH) attached to oxygen atom and a broad singlet at δ 1.82 (br s, 1H) due to the proton of hydroxyl group. Its structure was further established by its ^{13}C NMR spectrum, which showed two typical carbon signals at δ 64.3 and 29.8 for methylene (-**C**H_2-O) and benzyloxy (Ar-**C**H_2-) carbons respectively and other signal at δ 63.5 corresponding to methine carbon (-**C**HN_3) (**Fig. 12**). Its IR spectrum exhibited strong vibrational stretching frequencies at υ_{max} 3440 and 2115 cm^{-1} confirming the presence of hydroxyl and azide functionalities respectively.

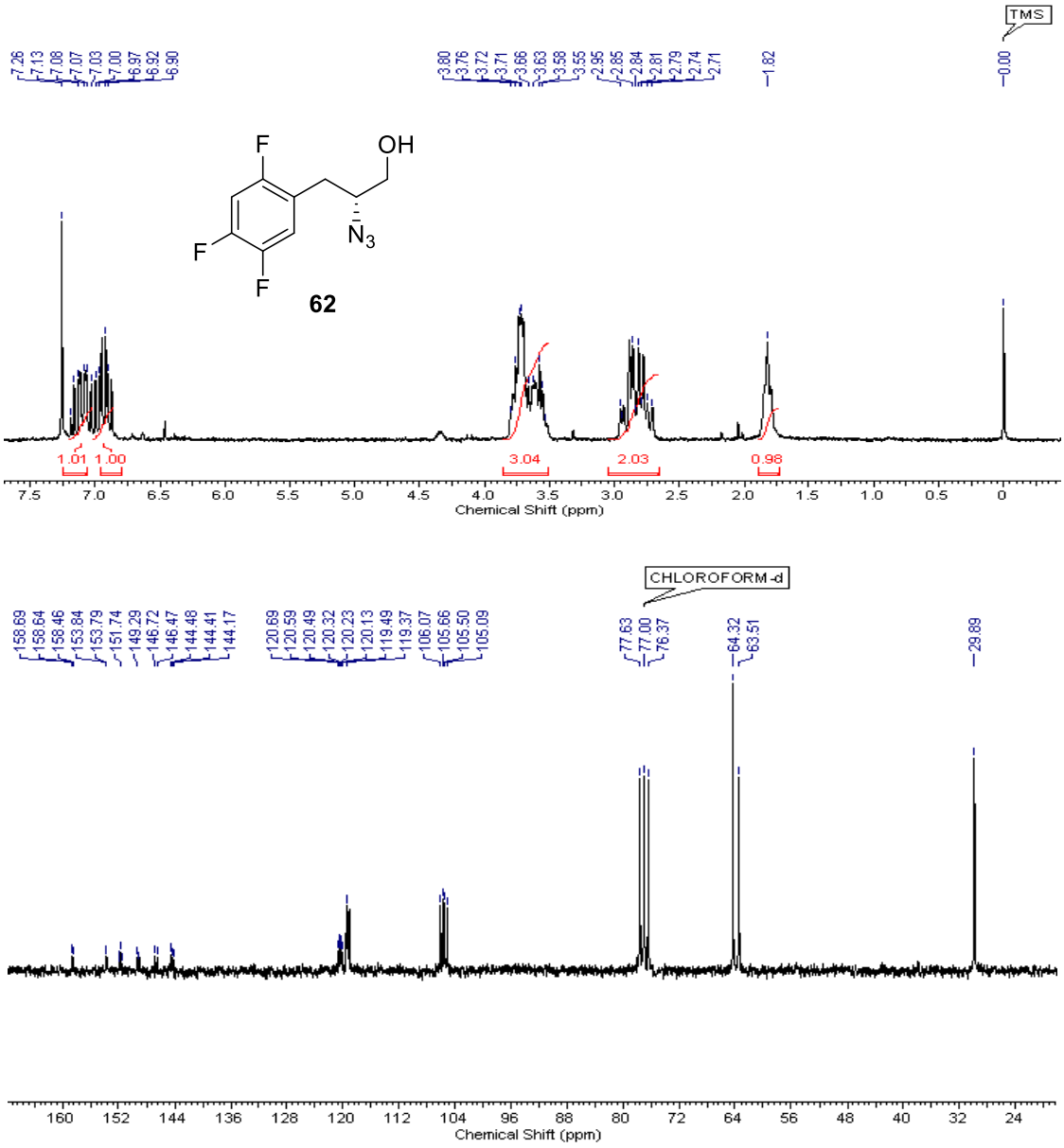
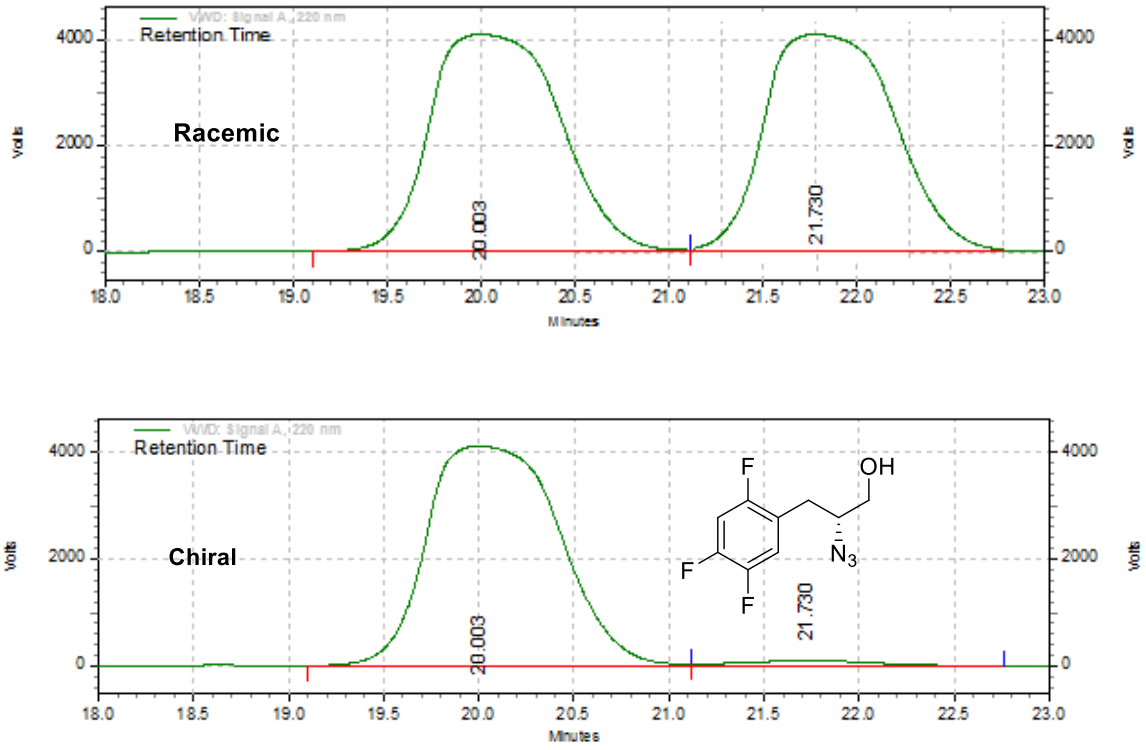


Fig. 12: ^{1}H and ^{13}C NMR spectra of azido alcohol **62**

The optical purity of azido alcohol **62** was determined to be 97% by HPLC [Chiracel AD-H column, *n*-Hexane/*i*-PrOH 95:05, 0.5 mL/min, 220 nm, retention time: t_{major} = 20.03 min and t_{minor} = 21.73 min] (**Fig. 13**).



Retention Time	Area	Area %	Height	Height %
20.003	3331917224	98.67	69013734	98.66
21.730	79609432	1.33	1651421	1.34
Totals	3411526656	100.00	70665155	100.00

Fig. 13: HPLC Chromatogram of azido alcohol **62**

Subsequently, the carbamate **63** was obtained in a single step using catalytic hydrogenation of azido alocohol **62** [10% Pd/C, H_2 (1 atm), Boc_2O, MeOH] in 98% yield. The formation of carbamate **63** was confirmed from its ^{1}H NMR spectrum, which showed a typical singlet at δ 1.42 (s, 9H) due to methyl protons of *tert*- butyl group and a multiplet at δ 3.83-3.84 (m, 1H) corresponding to methine proton (-C**H**NHBoc). It was further ascertained by its ^{13}C NMR spectrum, which showed carbon signals at δ 79.8 for tertiary carbon of Boc group and other signal at δ 155.0 due to carbonyl carbon (**Fig. 14**). Also, its IR spectrum

displayed strong vibrational stretching frequencies at υ_{max} 3420 and 1710 cm^{-1} confirming the presence of hydroxyl and carbonyl functionalities respectively.

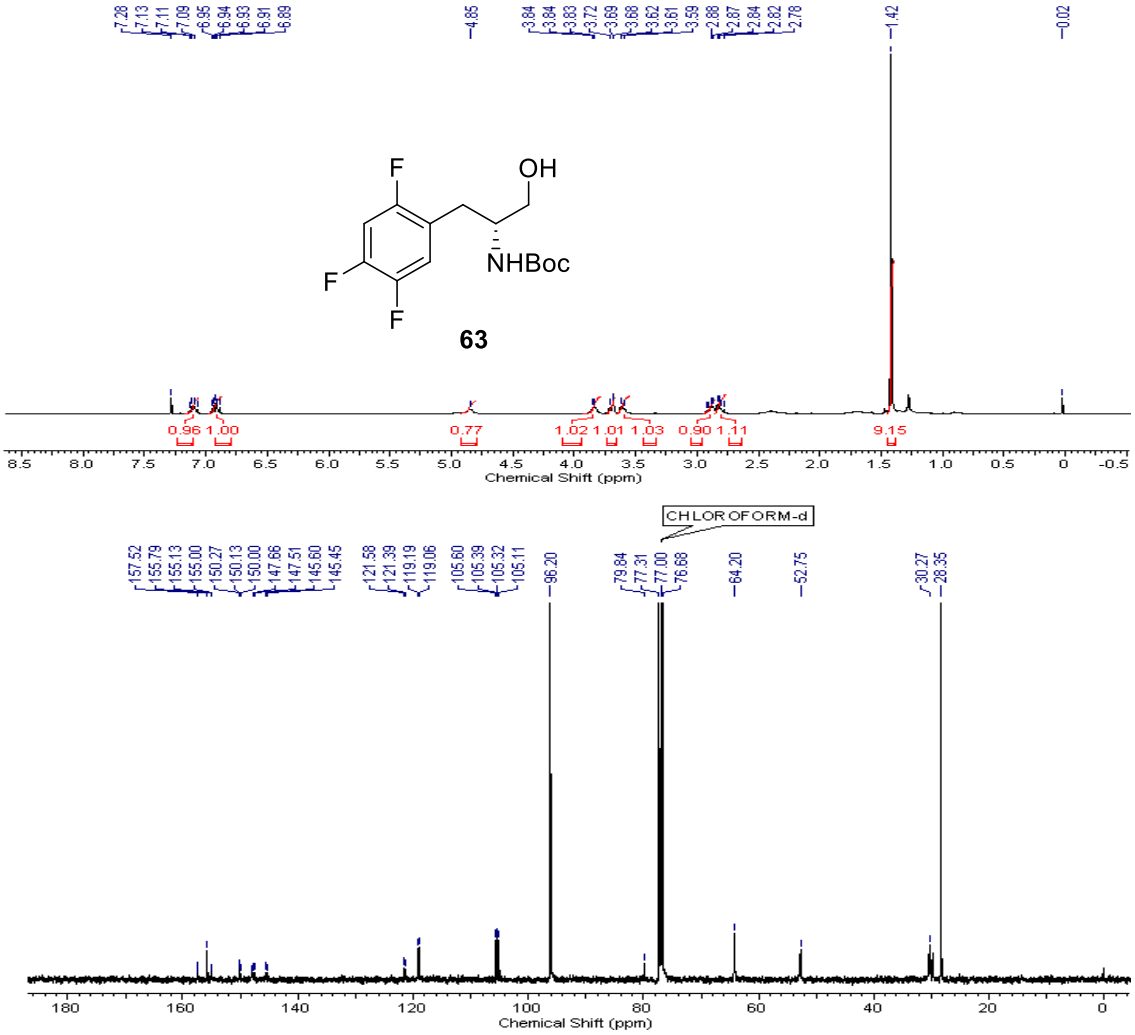
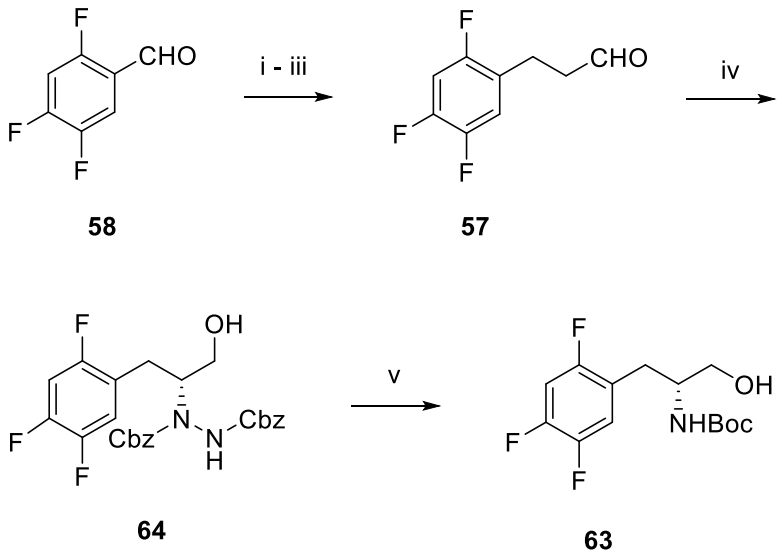


Fig. 14: ^{1}H and ^{13}C NMR spectra of carbamate **63**

Yet, in another approach, the synthesis of carbamte **63** was achieved as shown in **Scheme 20**, employing proline catalyzed amination reaction.



Scheme 20: (i) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h; (ii) H_2 (1 atm), 10% Pd/C, MeOH, 1 h; (iii) DIBAL-H, toluene, -78 ºC, 1 h, 92% (over 3 steps); (iv) L-proline (10 mol%), DBAD (0.9 equiv), CH_3CN, 0 ºC, 3 h, then $NaBH_4$, MeOH, 1 h, 90%; (v) $PdCl_2$ (5 mol %), Boc_2O (5 mmol), PHMS, MeOH/Deionized water (1:1), 25 ºC, 10 h, 88%.

Thus, 3-(2,4,5-trifluorophenyl)propanal **57** was prepared from **58** by a similar functional group transformation reactions: (i) two carbon homologation with stabilized Wittig ylide; (ii) hydrogenation of the benzylic C=C bond by 10% Pd/C over H_2 (1 atm); (iii) selective reduction of ester functionality to aldehyde by DIBAL-H. The aldehyde **57** was then subjetcted to proline catalyzed amination reaction [L-proline (10 mol%), DBAD (0.9 equiv), CH_3CN, 0 ºC, 3 h, then $NaBH_4$, MeOH, 1 h] to furnish α-amino alcohol **64** in 90% yield and 95% ee (determined by HPLC) [Chiracel AS-H column, *n*-Hexane/*i*-PrOH 95:05, 0.5 mL/min, 254 nm, retention time: t_{major} = 15.33 min and t_{minor} = 16.73 min]; $[\alpha]_D^{25}$ +41.8 (*c* 1, $CHCl_3$). The formation of α-amino alcohol **64** was confirmed from its ^1H and ^{13}C NMR spectral studies. Its ^1H NMR spectrum showed a characteristic singlet at δ 5.13 (s, 4H) due to the benzylic protons (Ph-C**H**$_2$) and broad singlet at δ 4.53 (br s, 1H) due to the proton of hydroxyl group. Its ^{13}C NMR spectrum showed a typical carbon signal at δ

54.7 due to methine carbon (**Fig. 15**). Its IR spectrum exhibited strong vibrational stretching frequencies at υ_{max} 3442, 1734 and 1730 cm^{-1} confirming the presence of hydroxyl and carbonyl functionalities respectively.

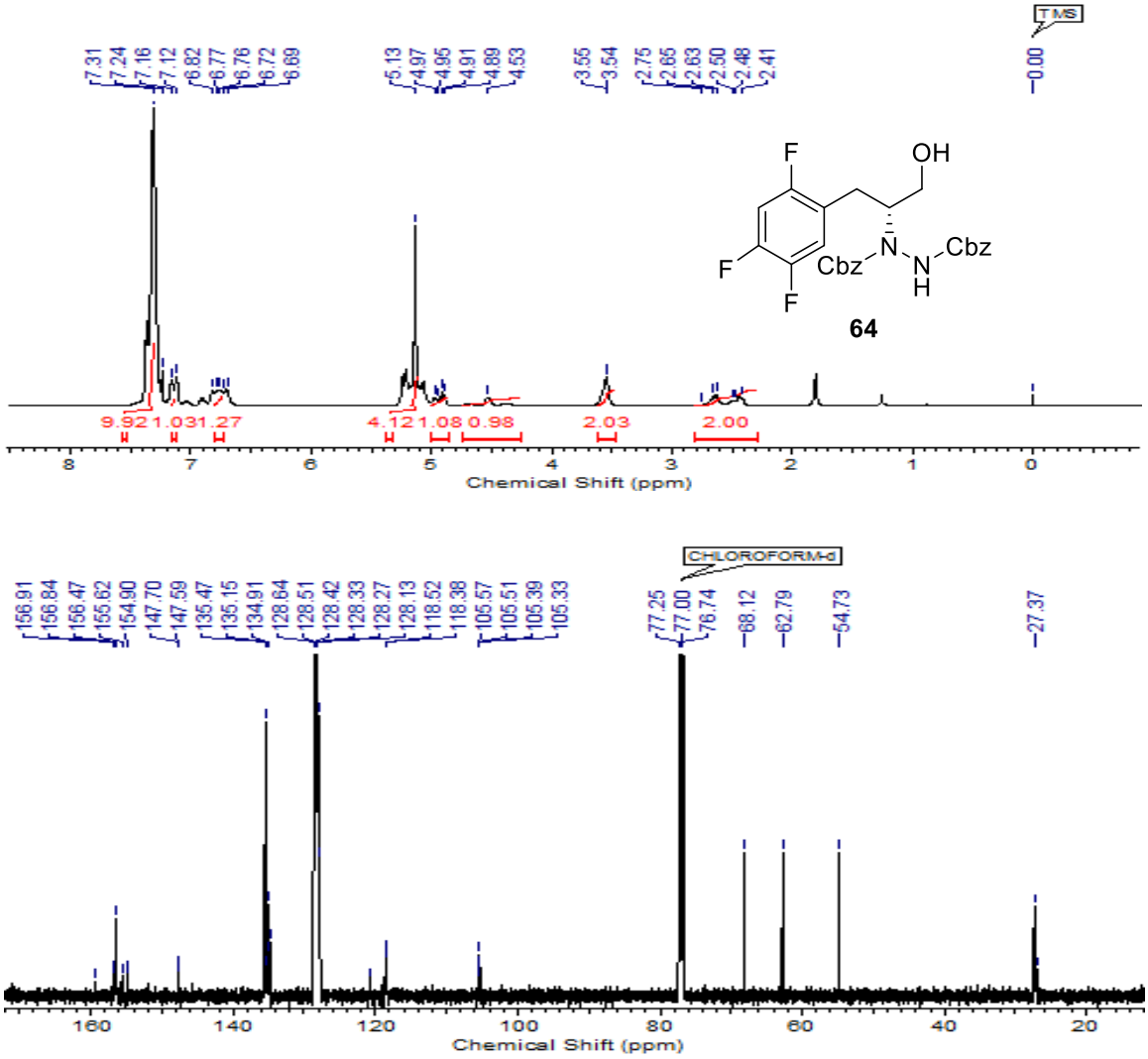
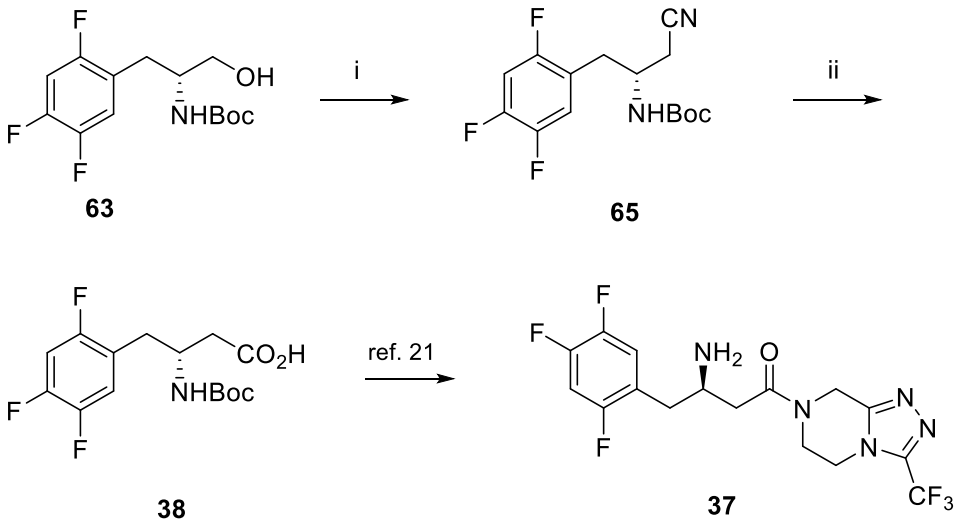


Fig. 15: ^{1}H and ^{13}C NMR spectra of amino alcohol **64**

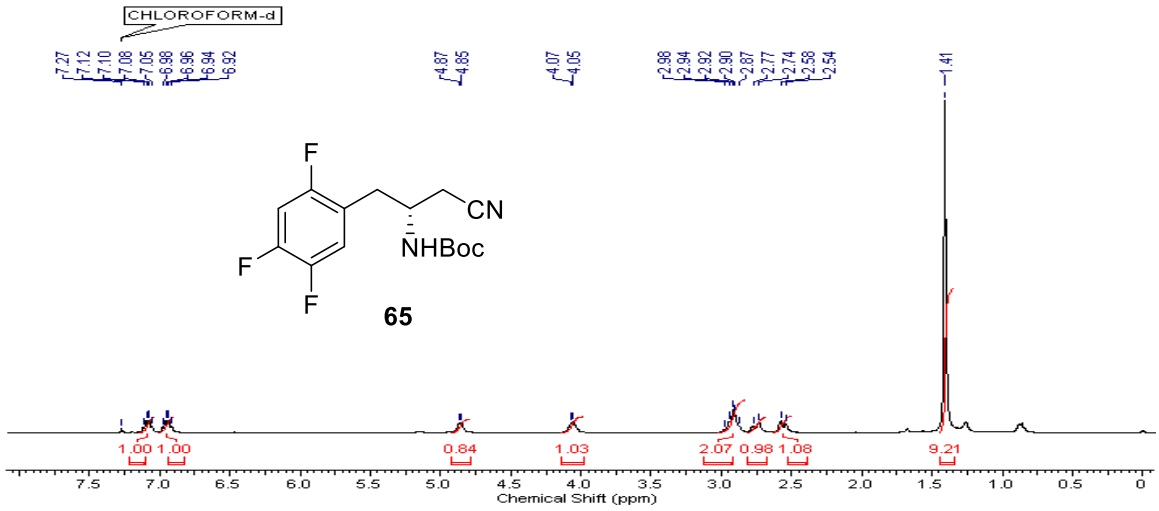
The α-amino alcohol **64** was treated with Pd catalyzed reductive N-N bond cleavage [$PdCl_2$ (5 mol %), Boc_2O (5 mmol), PHMS, MeOH/Deionized water (1:1), 25 ^{o}C, 10 h] to produce the carbamate **63** in 86% yield.

Scheme 21 presents the final synthetic reaction sequences to obtain intermediate β-amino acid **38**.



Scheme 21: (i) TsCl, Et_3N, CH_2Cl_2, 1 h then NaCN, DMF, 80 °C, 4 h, 65% (over two steps); (ii) 3N NaOH, H_2O_2, 100 °C, 3 h, 75%.

The alcohol functionality in **63** was readily transformed into cyanide **65** *via* S_N2 displacement of its tosylate. The presence of two multiplets at 2.74-2.77 (m, 1H) and 2.54-2.58 (m, 1H) due to methylene protons (-C**H**$_2$CN) attached to the cyanide group in its ^{1}H NMR spectrum confirmed the formation of **65**. Also, the appearance of a carbon signal at δ 118.8 due to cyanide functionality in its ^{13}C NMR spectrum further established the formation of **65**. Its IR spectrum showed strong vibrational stretching frequencies at υ_{max} 2103 and 1716 cm^{-1} confirming the presence of cyanide and carbonyl groups respectively. Its molecular mass from HRMS (ESI) spectrum for [($C_{15}H_{17}F_3N_2O_2$)H] (M+Na) was found to be 337.1129, which was in well agreement with the calculated value 337.1134 (**Fig. 16**).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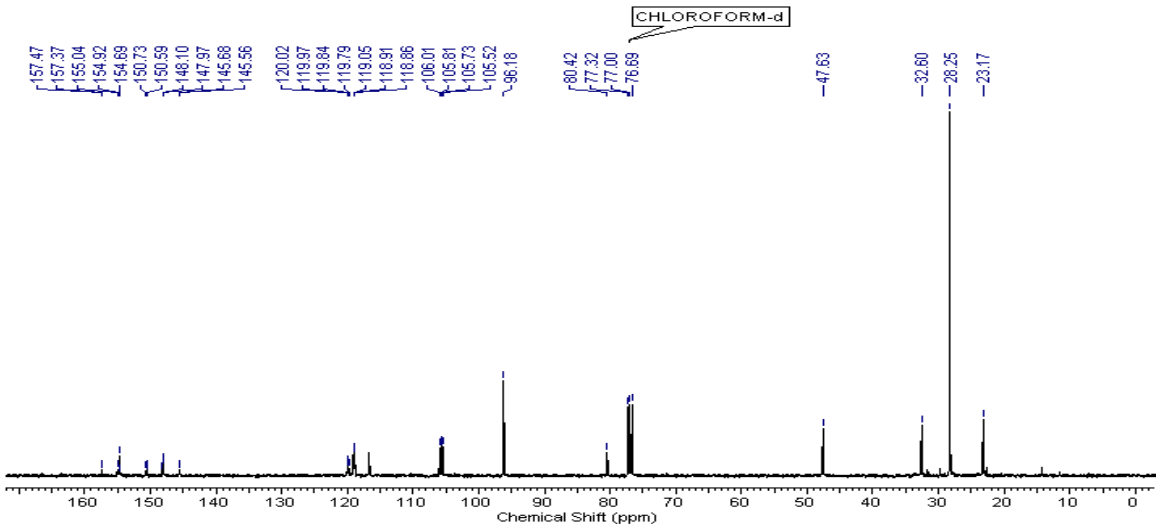
7.12
7.10
7.08
7.05
6.98
6.96
6.94
6.92
4.87
4.85
4.07
4.05
2.98
2.94
2.92
2.90
2.87
2.77
2.74
2.58
2.54
1.41
F
CN
NHBoc
F
F
65
1.00 1.00
0.84
1.03
2.07 0.98 1.08
9.21
Chemical Shift (ppm)


CHLOROFORM-d
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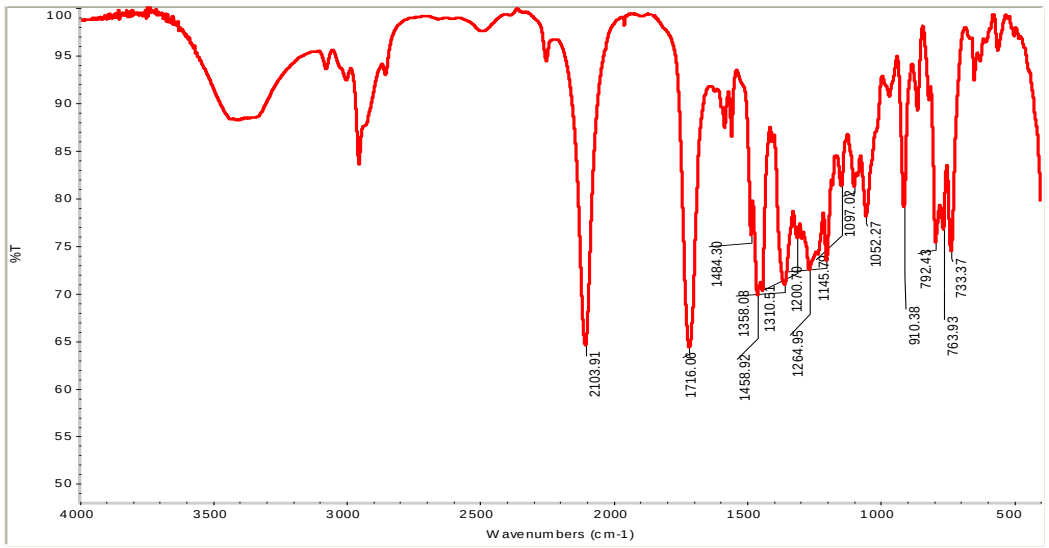
157.37
155.04
154.92
154.69
150.73
150.59
148.10
147.97
145.68
145.56
120.02
119.97
119.84
119.79
119.05
118.91
118.86
106.01
105.81
105.73
105.52
96.18
80.42
77.32
77.00
76.69
47.63
32.60
28.25
23.17
Chemical Shift (ppm)


%T
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1716.08
1484.30
1458.92
1358.08
1310.61
1264.95
1200.79
1145.72
1097.02
1052.27
910.38
792.43
763.93
733.37
Wavenumbers (cm-1)

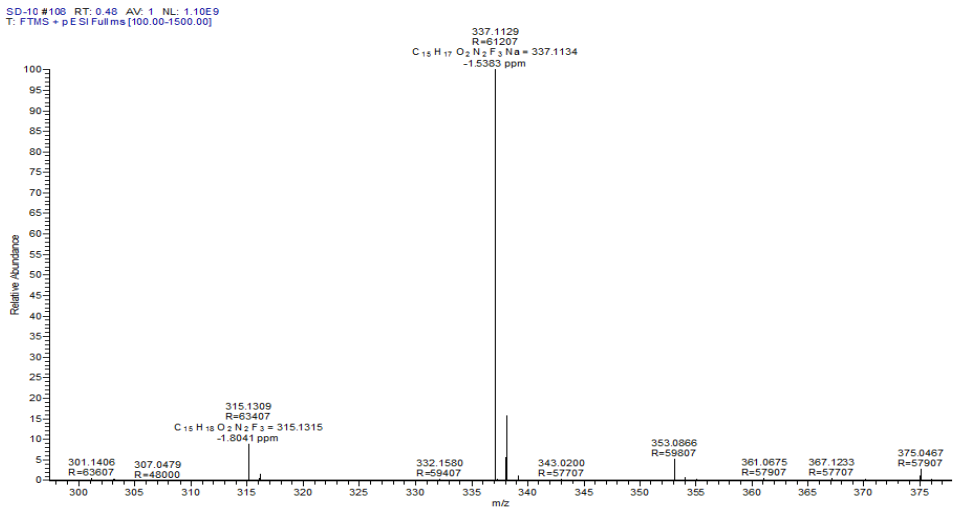


Fig. 16: ^{1}H, ^{13}C NMR, IR and HRMS spectra of cyanide **65**

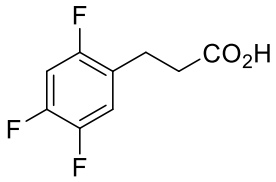
Subsequently, the cyanide functionality **65** was hydrolyzed to the corresponding carboxylic acid (3N NaOH, H_2O_2, reflux)[25] to give the known intermediate **38** in 75% yield, thereby constituting a formal synthesis of **37**. The enantiomeric purity of **38** was determined to be 98% ee based on the comparison of its specific rotation with the reported values $[\alpha]_D^{25}$ +31.8 (*c* 1, $CHCl_3$) {lit.[21] $[\alpha]_D^{25}$ +32.3 (*c* 1, $CHCl_3$)}. The spectroscopic values of synthetic material **38** were in complete agreement with the reported values.[18]

3.2.4 Conclusion

In conclusion, we have accomplished the formal synthesis of (*R*)-sitagliptin **37** *via* two routes (i) Evans'chiral azidation (36% overall yield till known intermediate **38** with 98% ee) and (ii) proline catalyzed α-amination reaction (35% overall yield up to **38** with 95% ee). These flexible methods will find wide applicability for the synthesis of other DPP-IV inhibitors due to the salient features: (1) easy availability of starting materials, (2) simple environmentally friendly procedure, and (3) cheap availability of proline and chiral auxiliary in both enantiomeric forms.

3.2.5 Experimental section

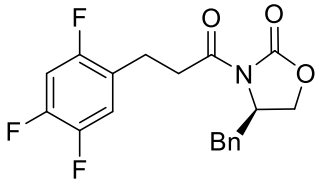
3-(2,4,5-Trifluorophenyl)propanoic acid (59)



To a stirred solution of 2,4,5-trifluorobenzaldehyde **58** (5 g, 31.23 mmol) in benzene (100 mL) stabilized Wittig salt $Ph_3P{=}CHCO_2Et$ (21.7 g, 62.46 mmol) was added and the mixture was refluxed overnight. After completion of the reaction (checked by TLC), the solvent was evaporated and pure adduct (4.9 g) was obtained after column chromatographic separation using petroleum ether/ethyl acetate (9:1). The product was then hydrogenated using 10% Pd/C, H_2 (1 atm) for 1 h in MeOH. After completion of the reaction (as monitored by TLC), it was filtered through Celite (MeOH eluent) and solvent was evaporated under reduced pressure to afford 3-(2,4,5-trifluorophenyl)ethyl propanoate (4.8 g), which was then hydrolyzed using LiOH (1.3 g, 56.1 mmol) in THF/MeOH/H_2O (3:1:1) to give **59** as a colorless gum.

Yield: 4.6 g, 96%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3105, 2903, 1722, 1052, 1016; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.67 (t, *J* = 7.3 Hz, 2H), 2.92 (t, *J* = 6.8 Hz, 2H), 6.91–7.02 (m, 1H), 7.04–7.26 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.7, 33.8, 105.4 (dd, *J* = 20.2, 27.1 Hz), 118.3 (dd, *J* = 6.4, 19.5 Hz), 123.2 (dd, *J* = 4.3, 9.2 Hz), 145.5 (ddd, *J* = 4.2, 5.7, 237.9 Hz), 147.5 (ddd, *J* = 3.5, 11.6, 250.5 Hz), 157.1 (ddd, *J* = 7.6, 10.2, 239.8 Hz); **Anal. Calcd** for $C_9H_7F_3O_2$ requires C, 52.95; H, 3.46; Found: C, 52.81; H, 3.26%.

(*R*)-4-Benzyl-3-(3-(2,4,5-trifluorophenyl)propanoyl)oxazolidin-2-one (60)

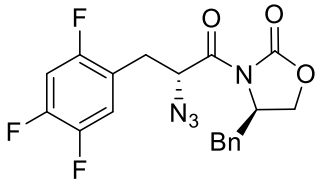


To a stirred solution of hydrocinnamic acid **59** (4 g, 19.5 mmol) in dry THF (100 mL) were added pivolyl chloride (2.36 g, 19.5 mmol) and Et_3N (10 mL, 78 mmol) at 20 ºC and the mixture was stirred at the same temperature for 4 h. To this stirred suspension, (*R*)-4-benzyloxazolidin-2-one (3.8 g, 21.5 mmol) in dry THF (20 mL) was added dropwise followed by the addition of LiCl (0.9 g, 19.5 mmol) and then stirred for an additional 15 min at 20 ºC and stirring continued at 25 ºC for 8 h until complete consumption of the starting materials (the progress of the reaction was monitored by TLC). The product was then extracted with diethyl ether and the combined organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product which upon column chromatographic purification with petroleum ether/ethyl acetate (4:1) gave oxazolidinone **60**.

Yield: 3.7 g, 94%; colorless solid; **mp**: 128-130 ºC; **$[\alpha]_D^{25}$** +62.89 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3065, 3030, 1781, 1700, 1387, 1212, 1156, 1020, 962; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.80 (dd, *J* = 9.7, 13.3 Hz, 1H), 3.03 (t, *J* = 7.3 Hz, 2H), 3.19- 3.27 (m, 3H), 4.17-4.21 (m, 2H), 4.61-4.67 (m, 1H), 6.91-6.93 (m, 1H), 7.12-7.19 (m, 3H),7.26-7.33 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.0, 35.5, 37.8, 55.0, 66.2, 105.4 (dd, *J* = 20.8, 28.1 Hz), 118.5 (dd, *J* = 6.4, 10.5 Hz), 123.7 (ddd, *J* = 4.3, 9.5, 17.5 Hz), 127.4, 128.3, 129.3, 135.0, 146.4 (ddd, *J* = 4.4, 5.1, 227.8 Hz), 148.9 (ddd, *J* = 2.9, 12.5, 255.5 Hz),

157.5 (ddd, *J* = 9.7, 11.2, 244.4 Hz); **Anal. Calcd** for $C_{19}H_{16}F_3NO_3$ requires C, 62.81; H, 4.40; N, 3.86; Found: C, 62.63; H, 4.32; N, 3.70%.

(*R*)-3-((*R*)-2-Azido-3-(2,4,5-trifluorophenyl)propanoyl)-4-benzyloxazolidin-2-one (61)

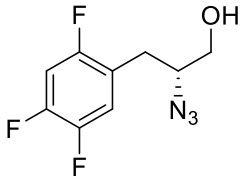


To a stirred solution of oxazolidinone **60** (3.8 g, 10.4 mmol) in dry THF (30 mL), 25 mL of 0.5 M in toluene (12.48 mmol) of potassium hexamethyldisilazide (KHMDS) was added under N_2 at -78 ^oC and the mixture was stirred for 45 min. To this suspension of potassium enolate, being stirred at -78 ^oC, was added 2,4,6-triisopropyl azide (4.27 g, 13.83 mmol) in dry THF (15 mL). After 5 min, the reaction was quenched with 3 mL (52 mmol) of glacial acetic acid and stirred at 25 ^oC for 12 h. Then the solution was partitioned between CH_2Cl_2 and brine solution. The organic phase was washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated *in vacuum*. On column chromatographic purification of the crude product with petroleum ether/ethyl acetate (4:1) gave **61** as a gum.

Yield: 3.3 g, 88%; colourless gum; $[\alpha]_D^{25}$ +57.2 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3219, 3050, 2852, 2115, 1772, 1734, 1389, 1112, 956; **^{1}H NMR** (200 MHz, $CDCl_3$):): δ 2.8 (dd, *J* = 9.3, 13.3 Hz, 2H), 3.01 (dd, *J* = 4.1, 13.5 Hz, 2H), 3.34 (dd, *J* = 5.0, 13.1 Hz, 2H), 4.61-4.74 (m, 1H), 5.2 (q, *J* = 4.5, 6.8 Hz, 1H), 6.84-6.97 (m, 1H), 7.02-7.22 (m, 3H), 7.33-7.20 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.4, 37.6, 55.0, 66.2, 71.5, 105.2 (dd, *J* = 19.6, 29.3 Hz), 118.5 (dd, *J* = 9.6, 15.8 Hz), 123.4 (dd, *J* = 4.6, 16.7 Hz), 126.3, 128.6, 129.2, 134.8, 148.9 (ddd, *J* = 3.8, 6.5, 242.8 Hz), 151.3 (ddd, *J* = 2.7, 12.5, 253.5 Hz),

158.4 (ddd, *J* = 6.3, 10.8, 250.8 Hz); **Anal. Calcd** for $C_{19}H_{16}F_3N_4O_3$ requires C, 56.44; H, 3.74; N, 13.8; Found: C, 56.31; H, 3.54; N, 13.61%.

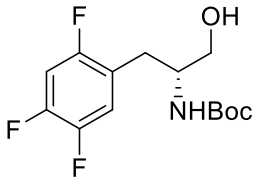
(*R*)-2-azido-3-(2,4,5-trifluorophenyl)propan-1-ol (62)



To a stirred solution of **61** (3 g, 7.42 mmol) in THF (20 mL) was added a solution of sodium borohydride (0.42 g, 11.13 mmol) in water (2 mL) dropwise at 0 ^oC. After the addition, it was kept for stirring at 25 ^oC for 2 h. On completion of reaction (monitored by checking TLC) 2N HCl (15 mL) was added slowly so that the temperature is maintained at 25 ^oC. The reaction mixture was then extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. The organic phase was concentrated and on column chromatographic purification with petroleum ether/ethyl acetate (4:1) gave **62**.

Yield: 2.94 g, 98%; colorless gum; $[\alpha]_D^{25}$ +4.2 (*c* 1, $CHCl_3$);)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3440, 2903, 2115, 1620. 1582, 1152, 1016; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.82 (br s, 1H), 2.71- 2.84 (m, 2H), 3.55- 3.78 (m, 3H), 6.87- 7.0 (m, 1H), 7.0- 7.16 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.8, 63.5, 64.3, 105.0 (dd, *J* = 20.2, 27.1 Hz), 119.3 (dd, *J* = 10.5, 6.4 Hz), 120.1 (dd, *J* = 4.3, 9.5 Hz), 146.4 (ddd, *J* = 4.4, 5.1, 241.8 Hz), 151.7 (ddd, *J* = 3.1, 11.6, 229.3 Hz), 158.6 (ddd, *J* = 8.7, 10.2, 239.4 Hz); **Anal. Calcd** for $C_9H_8F_3N_3O$ requires C, 46.76; H, 3.49; N, 18.18; Found: C, 46.58; H, 3.30; N, 18.09%; **Optical purity**: 97% ee was determined by HPLC analysis (Chiracel AD-H column, *n*-Hexane/*i*-PrOH 95:05, 0.5 mL/min, 220 nm). Retention time: t_{major} = 20.03 min and t_{minor} = 21.73 min.

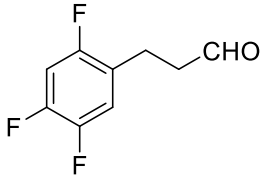
(*R*)-*tert*-Butyl-1-hydroxy-3-(2,4,5-trifluorophenyl)propan-2-yl)carbamate (63)



A mixture of azido alcohol **62** (2 g**,** 9.28 mmol), 10% Pd/C and di-*tert*-butyl dicarbonate (1.2 g, 9.28 mmol) in dry MeOH (20 mL) was stirred under H_2 (1 atm) at 25 ^oC for 3 h. After completion of reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and solvent evaporated under reduced pressure to afford crude, which on column chromatographic purification with petroleum ether/ethyl acetate (7:3) gave amino alcohol **63**.

Yield: 1.96 g, 98%; colorless solid; **mp**: 98-100 ^oC; **$[\alpha]_D^{25}$** +16.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3420, 3401, 2908, 2853, 1682, 1526, 1410, 1128; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.1 (br, s, 1H), 2.86 (t, *J* = 7.3 Hz, 2H), 3.59-3.67 (m, 2H), 3.78-3.84 (m, 1H), 4.77-4.84 (m, 1H), 6.88-6.94 (m, 1H), 7.09-7.11 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 30.2, 52.7, 64.2, 105.3 (dd, *J* = 20.2, 27.6 Hz), 119.0 (dd, *J* = 6.6, 10.2 Hz), 145.4 (ddd, *J* = 4.2, 5.7, 237.9 Hz), 147.5 (ddd, *J* = 3.5, 11.6, 250.5 Hz), 157.1 (ddd, *J* = 7.6, 11.4, 241.8 Hz); **Anal. Calcd** for $C_{14}H_{18}F_3NO_3$ requires C, 55.08; H, 5.94; N, 4.59; Found: C, 54.86; H, 5.72; N, 4.35%.

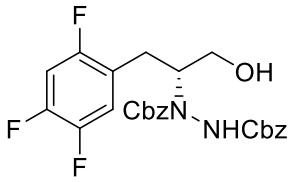
3-(2,4,5-Trifluorophenyl)propanal (57)



To a stirred solution of 2,4,5-trifluorobenzaldehyde **58** (5 g, 31.23 mmol) in benzene (100 mL), stabilized Wittig salt $Ph_3P{=}CHCO_2Et$ (21.7 g, 62.46 mmol) was added and refluxed overnight. After completion of the reaction (checked by TLC), the solvent was evaporated and pure adduct (4.9 g) was obtained by column chromatographic separation using petroleum ether/ethyl acetate (9:1). The product was then hydrogenated using 10% Pd/C, H_2 (1 atm) for 1 h in MeOH. After completion of the reaction (as monitored by TLC), it was filtered through Celite (MeOH eluent) and the solvent was evaporated off under reduced pressure to afford 3-(2,4,5-trifluorophenyl)ethyl propanoate (4.8 g). Then the crude product in dry toluene (100 mL) was added 20.3 mL, 20.67 mmol of DIBAL-H (1M solution in methylene chloride) at -78 ºC. The reaction mixture was stirred for 1 h. After the reaction was complete, it was quenched with aq. sodium potassium tartrate solution (Rochelle's salt) and then stirred it for additional 3 h. The organic layer was extracted with CH_2Cl_2 (3x30 mL). It was washed with brine, dried over anhy. Na_2SO_4. The organic phase was concentrated and on column chromatographic purification with petroleum ether/ethyl acetate (9:1) gave aldehyde **57**.

Yield: 5.5 g, 92%; colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3105, 2903, 1720, 1052, 1016; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.43 (t, *J* = 7.3 Hz, 2H), 2.89 (t, *J* = 7.3 Hz, 2H), 6.90–7.1 (m, 1H), 7.12–7.24 (m, 1H), 9.72 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.8, 33.8, 103.2 (dd, *J* = 18.7, 28.1 Hz), 119.4 (dd, *J* = 5.9, 20.7 Hz), 123.2 (ddd, *J* = 3.8, 9.8, 18.2 Hz), 143.5 (ddd, *J* = 4.8, 6.3, 241.7 Hz), 146.1 (ddd, *J* = 7.6, 10.1, 241.5 Hz) 159.7 (ddd, *J* = 6.2, 9.8, 245.3 Hz), 198.2; **Anal. Calcd** for $C_9H_7F_3O$ requires C, 57.45; H, 3.75; Found: C, 57.21; H, 3.58%.

Dibenzyl-(*R*)-1-(1-hydroxy-3-(2,4,5-trifluorophenyl)propan-2-yl)hydrazine-1,2-dicarboxylate (64)

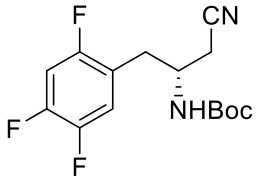


To a stirred solution of aldehyde **57** (2 g, 10.6 mmol) in CH_3CN (30 mL), dibenzylazodicarboxylate (DBAD) (3.15 g, 10.6 mmol) and L-proline (0.18 g, 1.59 mmol) were added at 0 ºC and stirred for 3 h. After the completion of reaction (monitored by TLC), the reaction mixture was diluted with MeOH (20 mL) and $NaBH_4$ (0.8 g, 21.2 mmol) was added to it and stirred it for additional 45 min. Then the reaction mixture was quenched with aqueous NH_4Cl solution. Solvent was evaporated and the organic layer was extracted with EtOAc. Then the combined EtOAc layers were dried over anhyd. Na_2SO_4, solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to afford the corresponding pure amino alcohol **64**.

Yield: 4.6 g, 90%; pale yellow gum; **$[\alpha]_D^{25}$** +41.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3426, 3362, 3105, 3010, 2903, 1734, 1720, 1052, 1016, 952, 790; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.24-2.75 (m, 2H), 3.54 (m, 2H), 4.53 (br s, 1H), 4.89-4.97 (m, 1H), 5.13 (s, 4H), 6.69–6.82 (m, 1H), 7.12 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.3, 54.7, 62.7, 68.1, 105.3 (dd, *J* = 19.9, 21.7 Hz), 118.5 (d, *J* = 6.8 Hz), 128.1 (dd, *J* = 4.3, 7.7 Hz), 128.5, 128.6, 134.9, 135.1, 135.4, 147.7 (ddd, *J* = 4.6, 11.8, 257.5 Hz), 154.9 (ddd, *J* = 7.6, 10.2, 239.8 Hz), 156.4, 156.8; **Anal. Calcd** for $C_{25}H_{23}F_3O_5N_2$ requires C, 61.47; H, 4.75, N, 5.74; Found: C, 61.18; H, 4.60, N, 5.55%; **Optical purity**: 95% ee (determined by

HPLC) [Chiracel AS-H column, *n*-Hexane/*i*-PrOH 95:05, 0.5 mL/min, 254 nm, retention time: t_{major} = 15.33 min and t_{minor} = 16.73 min].

(*R*)-3-(*tert*-Butyl-1-cyano-(2,4,5-trifluorophenyl)propan-2yl)carbamate (65)

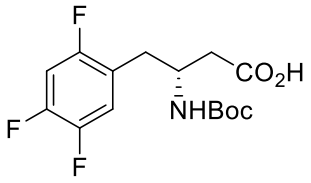


To a stirred solution of N-Boc protected amino alcohol **63** (1.5 g, 4.9 mmol) in CH_2Cl_2 (5 mL) were added dry triethylamine (1.3 mL, 9.8 mmol) and *p*-toluenesulfonyl chloride (1.12 g, 5.88 mmol) in presence of catalytic amount of 4-dimethylaminopyridine (0.059 g,10 mol%) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 3 h and then quenched by addition of 10% $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, concentrated to give the crude tosylate, which was then dissolved in DMF (5 mL), and added NaCN (1.4 g, 29.4 mmol) carefully. It was refluxed for 4 h and then cooled to RT and extracted with EtOAc (3x10 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to afford the corresponding pure cyano compound **65**.

Yield: 0.97 g, 65% (over two steps); colorless solid; **mp**: 110–112 ^oC; **$[\alpha]_D^{25}$** +22.2 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3101, 2956, 2105, 1685, 1456, 1128, 1115, 905; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.54-2.58 (m, 1H), 2.73-2.77 (m, 1H), 2.90- 2.98 (m, 2H), 4.05 (m, 1H), 4.87 (m, 1H), 6.62-6.98 (m, 1H), 7.05-7.12 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.1, 28.2, 32.6, 47.6, 80.4, 105.5 (dd, *J* = 20.7, 27.2 Hz), 118.8 (d, *J* =

6.4 Hz), 119.0 (ddd, *J* = 4.3, 9.5, 17.5 Hz), 145.5 (ddd, *J* = 4.8, 4.8, 230.8 Hz), 150.5 (ddd, *J* = 2.6, 12.5, 224.5 Hz), 154.6 (ddd, *J* = 9.3, 11.2, 255.4 Hz); **Anal. Calcd** for $C_{15}H_{17}F_3N_2O_2$ requires C, 57.32; H, 5.45; N, 8.91; Found: C, 57.33; H, 5.46; N, 8.94%. **HRMS** (ESI): [($C_{15}H_{17}F_3N_2O_2$)Na] (M+Na) 337.1134; Found: 337.1129.

(*R*)-3-((*tert*-Butoxycarbonyl)amino)-4-(2,4,5-trifluorophenyl)butanoic acid (38)



To a stirred solution of N-Boc protected cyano compound **65** (0.5 g, 1.5 mmol) was added 3M NaOH (10 mL), H_2O_2 (35%, 6 mL, 22 mmol) and refluxed at 100 ^oC for 3h. After the reaction was complete, the reaction mixture was cooled to 0 ^oC. To remove organic impurities, Et_2O (50 mL) was added and the ether phase was dispatched. Then the aqueous phase was acidified with 6 M HCl to neutralize pH and was extracted with Et_2O (50 mL), and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the crude product, which was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (4:1) to afford the corresponding pure compound **38**.

Yield: 0.375 g, 75%; colorless solid; **mp**: 122–125 ^oC; {lit.[21] mp: 124–125 ^oC}; **$[\alpha]_D^{25}$** +31.8 (*c* 1, $CHCl_3$) {lit.[21] $[\alpha]_D^{25}$ +32.3 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3269, 3101, 2956, 1770, 1685, 1366, 1095, 835; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (s, 9H), 2.44-2.47 (m, 1H), 2.63-2.67 (m, 1H), 2.82 (d, *J* = 4.9 Hz, 2H), 4.10 (br s, 1H), 5.07 (br s, 1H), 6.87-6.94 (m, 1H), 7.03-7.09 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.6, 29.8, 33.7, 48.0, 80.7, 105.8 (dd, *J* = 19.6, 28.5 Hz), 118.2 (dd, *J* = 5.8, 10.7 Hz), 121.5 (dd, *J* = 5.2, 9.5 Hz), 146.7 (ddd, *J* = 4.1, 5.5, 229.9 Hz), 147.9 (ddd, *J* = 2.9, 11.1, 255.5 Hz), 158.2 (ddd, *J*

= 9.7, 13.1, 244.4 Hz), 179.1; **HRMS** (ESI): [($C_{15}H_{18}F_3NO_4$)Na] (M+Na) 356.1086; Found: 356.1082.

3.2.6 References

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CHAPTER IV

Heterogeneous Ti superoxide Catalyzed Oxidative Esterification of Aldehydes and Pd Catalyzed Reductive N-N Bond Cleavage in dibenzyl alkylhydrazine-1,2-dicarboxylate by PHMS

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1. Titanium superoxide- a stable recyclable heterogeneous catalyst for oxidative esterification of aldehydes with alkylarenes or alcohols using TBHP as oxidant, **Dey, S.**; Gadakh, S.; Sudalai, A. *Org. Biomol. Chem*. **2015**, DOI: 10.1039/c5ob01586c.

2. Pd-catalyzed reductive cleavage of N-N bond in dibenzyl-1-alkylhydrazine-1,2-dicarboxylates with PMHS: application to a formal enantioselective synthesis of (*R*)-sitagliptin **Dey, S.**; Ahuja, B. B.; Gadakh, S. K.; Kamble, S. P.; Sudalai, A. *Tetrahedron Lett*. **2016**, (In press).

Section I

Titanium Superoxide-A Stable Recyclable Catalyst for Oxidaive Esterification of Aldehydes with Alkylarenes or Alcohols Using TBHP as Oxidant

4.1.1 Introduction

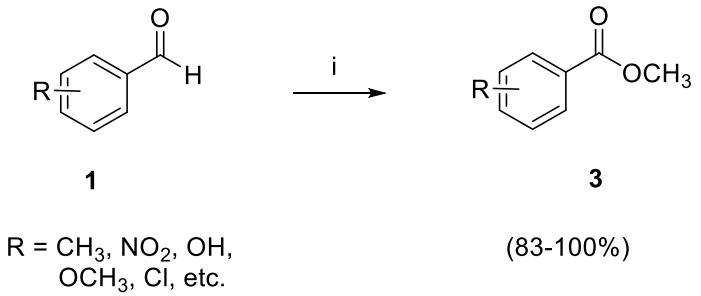
Carboxylic esters are not only among the most important and abundant functional groups in nature but also serve effectively as versatile 'building blocks' in the synthesis of fine chemicals, natural products, polymeric materials, etc. Further in industrial point of view, esterification process has widespread application with the synthesis of a variety of end-products such as fragrances, monomers, plasticizers, etc, many of which are classified as high production volume (HPV) chemicals. In particular, benzyl esters are useful functional groups found in medicinal and natural products and are widely used as protecting groups for a range of functionalities including carboxyl groups.[1] The traditional esterification processes involve a two-step procedure of stoichiometric activation of a carboxylic acid as an anhydride, acyl halide or activated ester followed by subsequent nucleophilic substitution with alcohols,[2] while benzyl esters are commonly prepared by way of nucleophilic displacement of a carboxylate ion on benzyl bromide.[3]

4.1.2 Review of Literature

In literature, there are several methods available for the direct transformation of aldehydes into the corresponding esters. Direct transformation of aldehydes into esters has been achieved using a variety of reagents, such as, use of stiotiometric inorganic reagents[4], electrochemical methods,[5] organocatalytic approach[6] as well as metal free approach.[7] Some of the recent advancements on this transformation are discussed below.

Gopinath's approach (2000)[8]

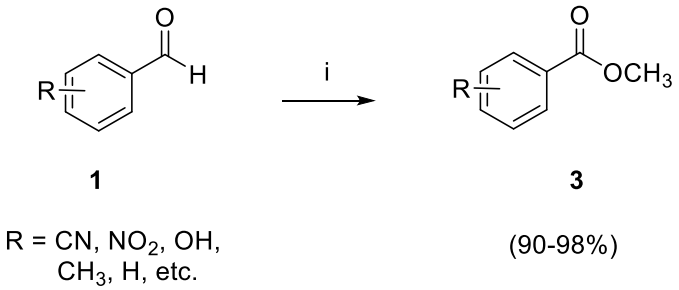
In Gopinath's approach, aldehydes **1**, in the presence of methanol, underwent oxidative transformation to the corresponding esters **3** upon treatment with catalytic amounts of V_2O_5 in combination with 30% aq. H_2O_2 as oxidant (**Scheme 1**).



Scheme 1: (i) V_2O_5 (cat.), 30% aq. H_2O_2, CH_3OH, 80 °C, 0.5-6 h.

Traivs' approach (2003)[9]

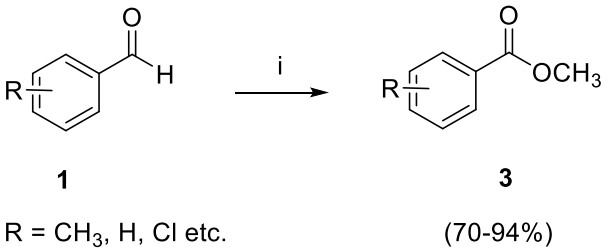
Travis et al. have developed a highly efficient, mild, and simple protocol for the oxidation of aldehydes **1** to the corresponding carboxylic acids utilizing oxone as the sole oxidant. Direct conversion of aldehydes **1** in alcoholic solvents to their corresponding ester products **3** has also been reported (**Scheme 2**).



Scheme 2: (i) Oxone, CH_3OH, 18 h, 25 °C.

Onami's approach (2004)[10]

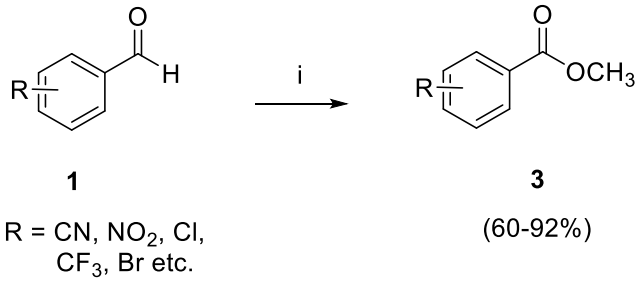
In this approach, the direct esterification of aldehydes with alcohols was carried out with pyridinium hydrobromide perbromide (PHPB) in water at 25 °C. A variety of aldehydes **1** were converted to their corresponding esters **3**. Further, a variety of aliphatic alcohols were also converted to the corresponding Tishchenko-like dimeric esters in good yields under the same reaction conditions (**Scheme 3**).



Scheme 3: (i) PHPB, CH_3OH, H_2O, 25 °C, 40-87 h.

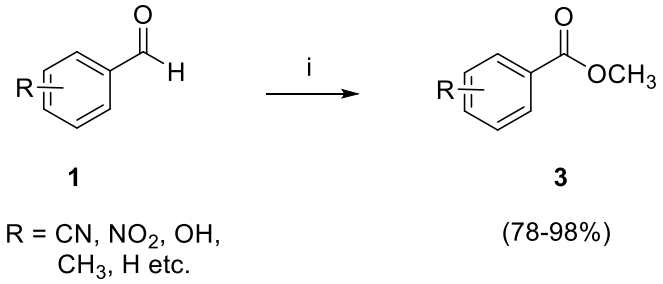
Sudalai's approach (2005 and 2007)[11,7a]

Sudalai *et al.* have described a simple procedure for the conversion of electron-deficient aldehydes **1** into the corresponding methyl esters **3** on reaction with methanol in excellent yields mediated by acetone cyanohydrin and base such as Et_3N (**Scheme 4**).



Scheme 4: (i) acetone cyanohydrin (5 mmol), Et_3N, CH_3OH, 25 °C, 2 h.

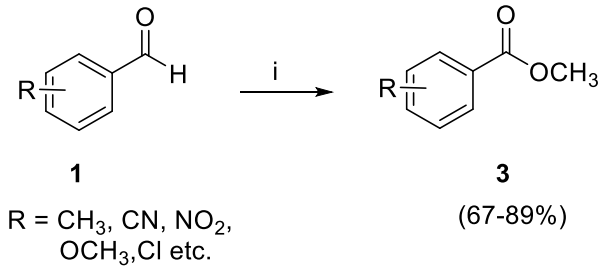
In yet another approach, these authors have converted aromatic aldehydes **1** directly to the corresponding aromatic methyl esters **3** in high yields on treatment with CH_3OH using sodium metaperiodate ($NaIO_4$)/LiBr as oxidant under acidic medium (**Scheme 5**).



Scheme 5: (i) LiBr, $NaIO_4$, conc. H_2SO_4, CH_3OH, 25 ^oC, 18 h.

Budhewar's approach (2006)[12]

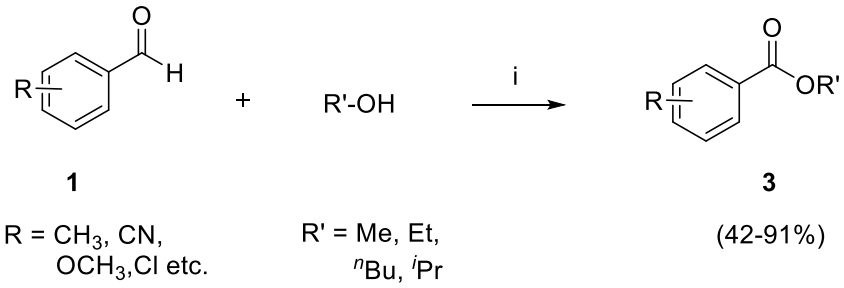
Budhewar *et al.* have developed a simple and mild procedure for the facile, direct oxidative methyl esterification of aldehydes **1** using molecular I_2 in combination with $PhI(OAc)_2$ in methanol (**Scheme 6**).



Scheme 6: (i) I_2, $PhI(OAc)_2$, CH_3OH, 25 ^oC, 10-14h.

Li's approach (2007)[13]

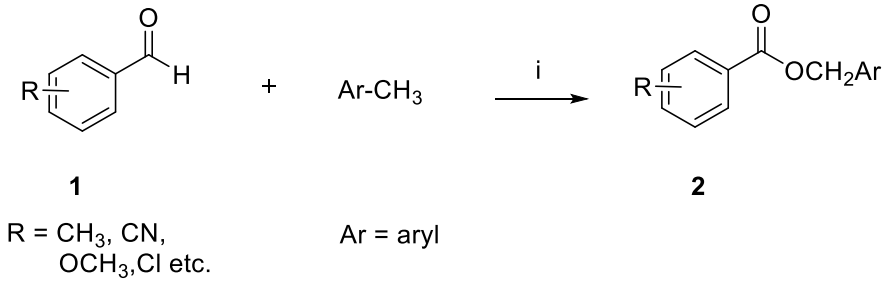
Li *et al*. have developed an oxidative esterification reaction between aldehydes **1** and alcohols catalyzed by a combination of $Cu(ClO_4)_2 \cdot 6H_2O$ and $InBr_3$ using TBHP as an oxidant (**Scheme 7**).



Scheme 7: (i) $Cu(ClO_4)_2 \cdot 6H_2O$, $InBr_3$, TBHP, 100 °C, 16 h.

Patel's approach (2012) [14]

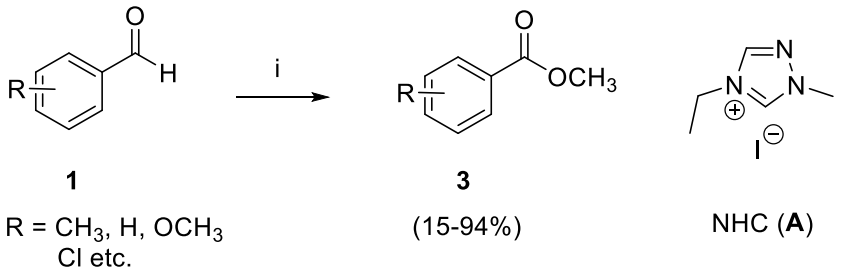
B. K. Patel *et al.* have demonstrated copper (II) catalyzed cross dehydrogenative coupling (CDC) reaction for the synthesis of benzyl esters **2** using aldehydes **1** and alkylbenzenes as coupling partners in presence of TBHP as oxidant at 100 °C (**Scheme 8**).



Scheme 8: (i) $Cu(OAc)_2 \cdot 2H_2O$, TBHP, 100 °C, 16 h, 60-91%.

Delany's approach (2013)[15]

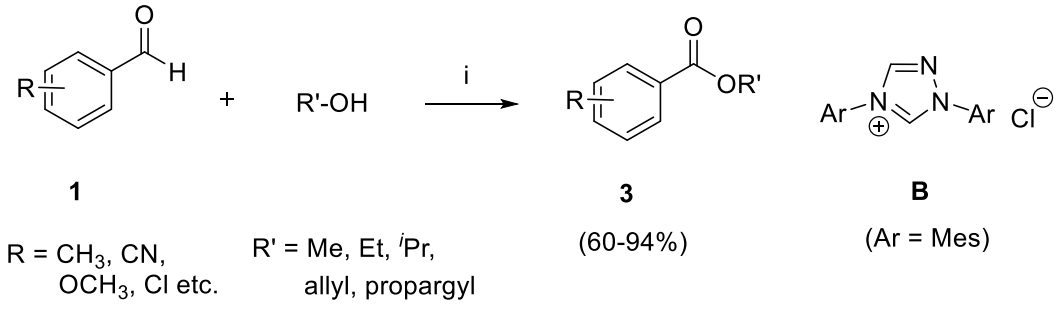
This methodology employs an additive-free mild protocol for triazolium NHC (**A**)-catalyzed direct esterification of aldehydes **1** with CH_3OH using O_2 as oxidant to give the corresponding methyl esters in high yields (**Scheme 9**).



Scheme 9: (i) NHC (**A**) (15 mol %), DBU, THF:CH_3OH (1:1), O_2, 25 °C, 12-92 h.

Sudalai's approach (2013)[16]

Sudalai *et al.* have reported a mild and simple NHC (**B**) catalyzed approach to convert aromatic aldehydes **1** into the corresponding esters **3** in high yields with alcohols employing O_2 as oxidant and DBU as base (**Scheme 10**).



Scheme 10: (i) NHC (**B**) (10 mol %), DBU (20 mol %), 25 °C, O_2 (1 atm).

4.1.3 Present Work

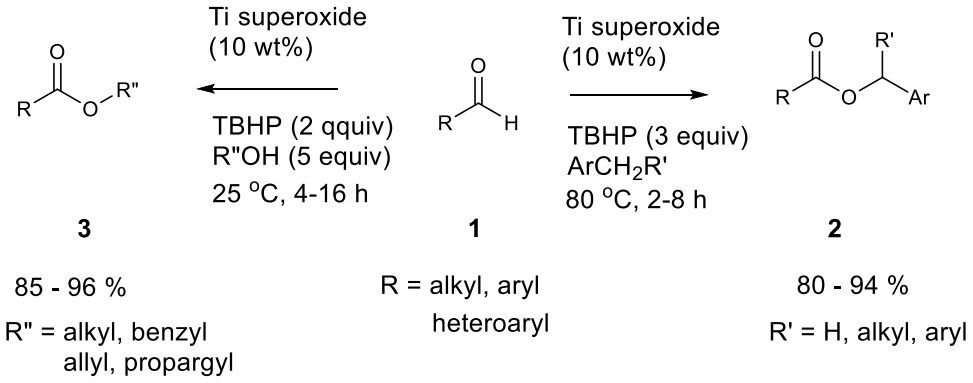
4.1.3.1 Objective

Quite recently, the oxidative esterification of aldehydes with alcohols or alkyl aromatics in the presence of oxidants and catalysts, has emerged as an alternative to traditional protocols since such raw materials are abundantly available in industry. Despite the fact that alkyl aromatics are less utilized in oxidative esterification due to low reactivity of sp^3 C-H bonds, a new method of esterification *via* C-H activation of alkyl aromatics with carboxylic acids has been developed and variety of transition metal (Pd, Cu, Rh and Pt) have shown excellent catalytic activity in this C-H bond activating esterification.[17] Further, a metal-free methodology for the synthesis of benzylic esters has been developed *via* oxidative C-O bond formation at the sp^3 benzylic carbon of various alkylbenzenes with carboxylic acids.[17] However, these approaches suffer from narrow substrate scope, use of stoichiometric amounts of toxic and hazardous heavy metal oxidants, dry reaction conditions, longer reaction time, poor yields as well as low reaction efficiency. The development of a single-step oxidative esterification of aldehydes under truly heterogeneous catalytic conditions that minimizes hazardous wastes, is highly desirable from both economic and environmental points of view. Sometime ago, we have reported a novel method for the preparation of a stable titanium superoxide catalyst from readily and cheaply available titanium tetraalkoxides and 50% H_2O_2.[18] Subsequently, its catalytic activities towards the oxidation of N-H bonds of aromatic and aliphatic 1° amines as well as O-H bonds of phenols[19] and *anti*-Markovnikov aminobromination of olefins[20] have been reported. To the best of our knowledge, metal catalyzed direct esterification of aldehydes with un-activated alkylbenzenes under heterogeneous condition has not explored. In this

section, we wish to describe Ti-superoxide catalyzed for the direct conversion of aldehydes into carboxylic esters *via* direct C-H activation of alkylarenes or using alcohols.

4.1.3.2 Results and Discussion

There have been several reports in the literature about oxidative esterification of aldehydes. In connection of our interest on Ti-superoxide, we thought of providing a cost-effective and environmental benign method of oxidative esterification of aldehydes *via* a recyclable heterogeneous catalysis (**Scheme 11**).



Scheme 11: Ti-superoxide catalysed esterification of aldehydes with alkylarenes or alcohols

In order to study this catalytic reaction in a systematic manner, 4-nitrobenzaldehyde **1a** as a model substrate with toluene or MeOH, have been screened and the results of such a study are shown in **Table 1**. 4-Nitrobenzaldehyde **1a** was oxidatively esterified with MeOH (1 equiv), in the presence of TBHP (3 equiv) and Ti superoxide (20 wt%) in excess toluene as solvent at 80 °C to obtain a mixture of the corresponding benzyl and methyl esters (**2a** & **3a**) in ratio 2:1 with 96% conversion.

Table 1: Oxidative esterification of 4-nitrobenzaldehyde with toluene or MeOH: optimization studies[a]

Entry	Reactants	Catalyst (wt%)	Oxidants (equiv)	T (°C)	2a or 3a (%)[b]
1	MeOH+ $PhCH_3$[c]	Ti superoxide (20)	TBHP[d] (3)	80	92[e]
2	$PhCH_3$	Ti superoxide (20	TBHP (1)	80	40
3	$PhCH_3$	Ti superoxide (20	TBHP (3)	80	75
4	$PhCH_3$	Ti superoxide (20	70% TBHP (3)	80	25
5	$PhCH_3$	Ti superoxide (20	30% H_2O_2 (3)	25	-[f]
6	$PhCH_3$	Ti superoxide (10)	TBHP (3)	80	89
7	MeOH	Ti superoxide (10)	TBHP (2)	25	90

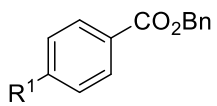
[a] 4-nitrobenzaldehyde (5 mmol), toluene or methanol (25 mmol), 5 h. [b] isolated yields of benzyl or methyl ester after chromatographic purification. [c] MeOH (5 mmol) and $PhCH_3$ used as solvent were used; [d] TBHP refers to *tert*-butyl hydroperoxide (5-6 M solution in decane); [e] a mixture of **2a** and **3a** was formed in 2:1 ratio; [f] yield of 4-nitrobenzoic acid.

When the reaction was conducted using 1 equiv of TBHP, in the absence of MeOH, and using toluene as solvent, benzyl ester **2a** indeed was obtained in 40% yield. However, when TBHP concentration was increased to 3 equiv, a reasonably high yield of **2a** (75%) was realized; while use of 70% TBHP under the same reaction conditions gave only low yield of **2a** (25%). Unexpectedly, with 30% H_2O_2 and stirring the mixture at 25 °C, the reaction proceeded to give 4-nitrobenzoic acid in 90% yield. Further, a considerable improvement in yield of **2a** (89%) was achieved when the Ti superoxide concentration was reduced to 10 wt% with TBHP (3 equiv) (entry 3), possibly due to less decomposition of TBHP on Ti superoxide matrix. A remarkable reactivity pattern was achieved when MeOH was used as the coupling partner with 2 equiv of TBHP, and carrying out the reaction at 25 °C to afford the corresponding methyl 4-nitrobenzoate **3a** in 90% yield. However, no

reaction took place with other catalysts such as titanium silicalite-I, $Ti(O^iPr)_4$ or TiO_2 [TBHP (3 equiv), toluene, 80 °C or 25 °C].

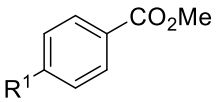
We have then applied the optimized procedure of Ti superoxide catalyzed esterification to a variety of aldehydes having both electron-donating and –withdrawing groups to determine the scope of the esterification process, and the results are presented in **Table 2**.

Table 2: Ti superoxide catalysed esterification of aldehydes with toluene or MeOH: Substrate scopes[a-b]



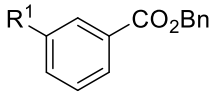
2a-f

2b, R^1 = OMe, 88%, 8 h
2c, R^1 = SMe, 79%, 8 h
2d, R^1 = H, 88%, 5 h
2e, R^1 = F, 92%, 3 h
2f, R^1 = CN, 96%, 4 h



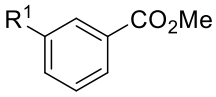
3a-f

3b, R^1 = OMe, 82%,10 h
3c, R^1 = SMe, 82%,10 h
3d, R^1 = Cl, 90%, 5 h
3e, R^1 = CF_3, 88%, 5 h
3f, R^1 = CN, 92%, 8 h



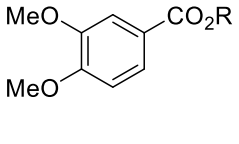
2g-i

2g, R^1 = NO_2,86%,4 h
2h, R^1 = Br, 94%, 6 h
2i, R^1 = Cl, 86%, 5 h

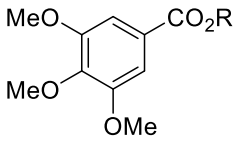


3g-i

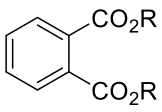
3g, R^1 = NO_2, 86%, 5 h
3h, R^1 = Br, 88%, 8 h
3i, R^1 = Cl, 90%, 6 h



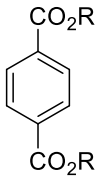
2j, R = Bn, 90%, 6 h
3j, R = Me, 86%, 12 h



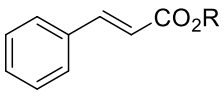
2k, R = Bn, 92%, 8 h
3k, R = Me, 84%, 12 h



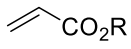
2l, R = Bn, 92%, 5 h



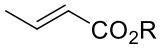
2m, R = Bn, 90%, 6 h
3l, R = Me, 86%, 8 h



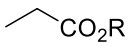
2n, R = Bn, 80%, 6 h
3m, R = Me, 76%, 12 h



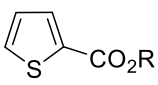
2o, R = Bn, 88%, 4 h
3n, R = Me, 70%, 8 h



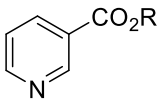
2p, R = Bn, 86%, 5 h
3o, R = Me, 72%, 8 h



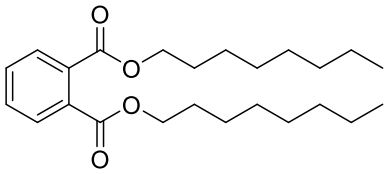
2q, R = Bn, 92%, 5 h



2r, R = Bn, 92%, 5 h
3p, R = Me, 88%, 10 h



2s, R = Bn, 90%, 6 h
3q, R = Me, 86%, 12 h

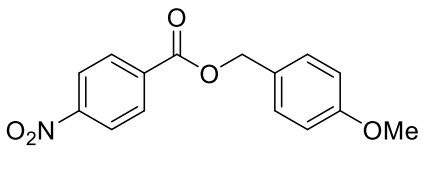


3r, 96%, 6 h; 100 g scale

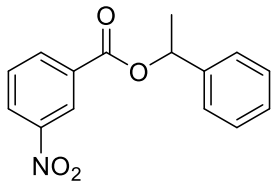
[a] Reaction conditions: for benzyl esters: aldehyde (1 mmol), Ti superoxide (10 wt%), TBHP (3 mmol), toluene (5 mmol), 80 °C; for methyl esters: aldehyde (1 mmol), Ti superoxide (10 wt%), TBHP (2 mmol), methanol (5 mmol), 25 °C. [b] isolated yield after column chromatographic purification.

As can be seen, several aldehydes (aromatic, aliphatic, heteroaromatic, α,β-unsaturated aldehydes, etc.) with electron-rich (OMe, SMe) and –deficient (CN, NO_2, halo) groups underwent esterification both with toluene and methanol and produced the corresponding benzyl and methyl esters respectively in excellent yields (70-94%). The present protocol is also found successful in diesterifying *o*- and *p*-phthalaldehyes in a single step to provide the respective diesters (**2l**, **2m**, **3l**) in 86-92% yields. Interestingly, this protocol is quite successful on a large scale production of dioctyl phthalate (**3r**), a plasticizer in polymer industry,[21] with excellent yields (96%) in 100 g scale.

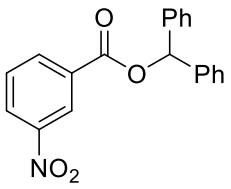
Table 3: Ti superoxide catalyzed esterification of nitroaldehydes with alkylarenes[a-b]



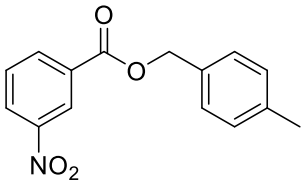
4a, 70%, 8 h



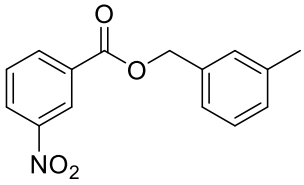
4b, 88%, 6 h



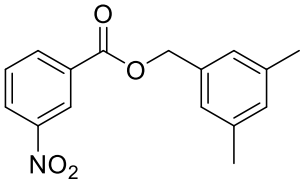
4c, 88%, 6 h



4d, 90%, 4 h



4e, 88%, 4 h



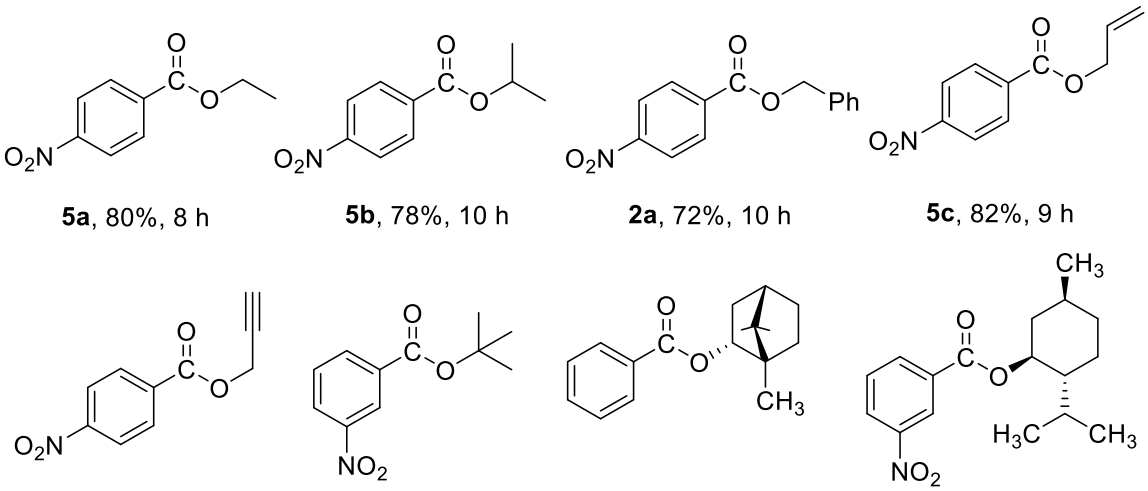
4f, 92%, 3 h

[a] Reaction conditions: nitrobenzaldehydes (1 mmol), Ti superoxide (10 wt%), TBHP (3 mmol), alkylarenes (1 mmol), CH_3CN, 80 ^oC [b] isolated yields of benzyl ester after chromatographic purification.

In order to further extend the scope of the esterification process, other aromatic hydrocarbons such as 4-OMe-toluene (**4a**), ethyl benzene (**4b**), xylenes (**4d-e**), and mesitylene (**4f**) were investigated under the reaction conditions with nitrobenzaldehydes as the substrate (**Table 3**). In all cases studied, excellent yields of benzylic esters (**4a-f**) were indeed obtained in 70-92% yields.

Additionally, a variety of simple alcohols (primary, secondary, even tertiary), unsaturated alcohols (allylic, propargylic) and optically active [(*S*)-borneol, (-)-menthol] alcohols can be successfully employed to afford the corresponding esters [(**5a-g**) and **2a**] in high yields (52- 82%) (**Table 4**).

Table 4: Ti superoxide catalyzed esterification of aldehydes with a variety of alcohols[a-b]



5a, 80%, 8 h | **5b**, 78%, 10 h | **2a**, 72%, 10 h | **5c**, 82%, 9 h

5d, 80%, 10 h | **5e**, 52%, 10 h | **5f**, 80%, 6 h, | **5g**, 81%, 6 h

[a] Reaction conditions: aldehydes (1 mmol), Ti superoxide (10 wt%), TBHP (2 mmol), alcohols (5 mmol), CH_3CN, 25 °C. [b] isolated yield after column chromatographic purification.

The enantiomeric purity of **5g** was determined to be 99.7% based on comparison of its specific rotation with the reported value $[\alpha]_D^{25}$ -83.5 (*c* 2, $CHCl_3$) {lit.[22] $[\alpha]_D^{25}$ -83.7 (*c* 1.5, $CHCl_3$), thereby confirming that optical integrity was retained in the product.

The formation of carboxylic esters was confirmed by ^1H and ^{13}C-NMR spectroscopic analysis.

Example 1: The ^1H NMR spectrum of **2f** showed a singlet at δ 5.39 (s, 2H) for benzylic protons. Its ^{13}C NMR spectrum showed two typical signals at δ 117.7 and 164.5 due to –

CN functionality and carbonyl carbon of the ester respectively (**Fig. 1)**. Its IR spectrum exhibited strong vibrational stretching frequencies at υ_{max} 2210 and 1715 cm^{-1} confirming the presence of –CN and ester functionalities respectively.

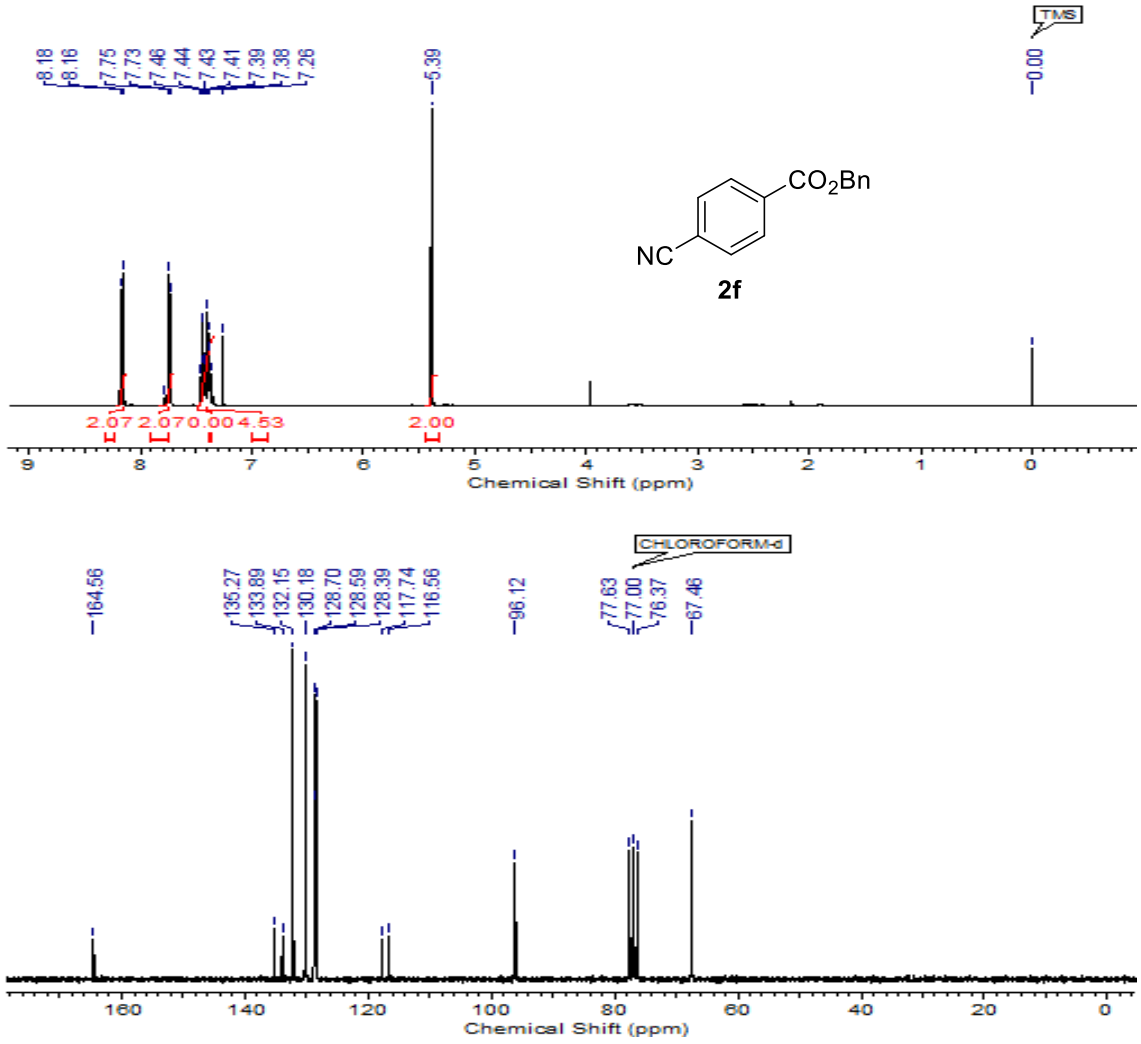


Fig. 1: ^{1}H and ^{13}C NMR spectra of **2f**

Example 2: The ^{1}H NMR spectrum of **3r** displayed a triplet at δ 4.28 (t, *J* = 6.7 Hz, 4H) for methylene (R-C**H**$_2$-O-C) protons. Its ^{13}C NMR spectrum showed typical carbon signals at δ 65.6 for methylene carbon attached to oxygen atom and at δ 167.4 due to carbonyl

carbon (**Fig. 2)**. Its IR spectrum displayed a strong vibrational stretching frequency at υ_{max} 1720 cm^{-1} due to the presence of ester carbonyl group.

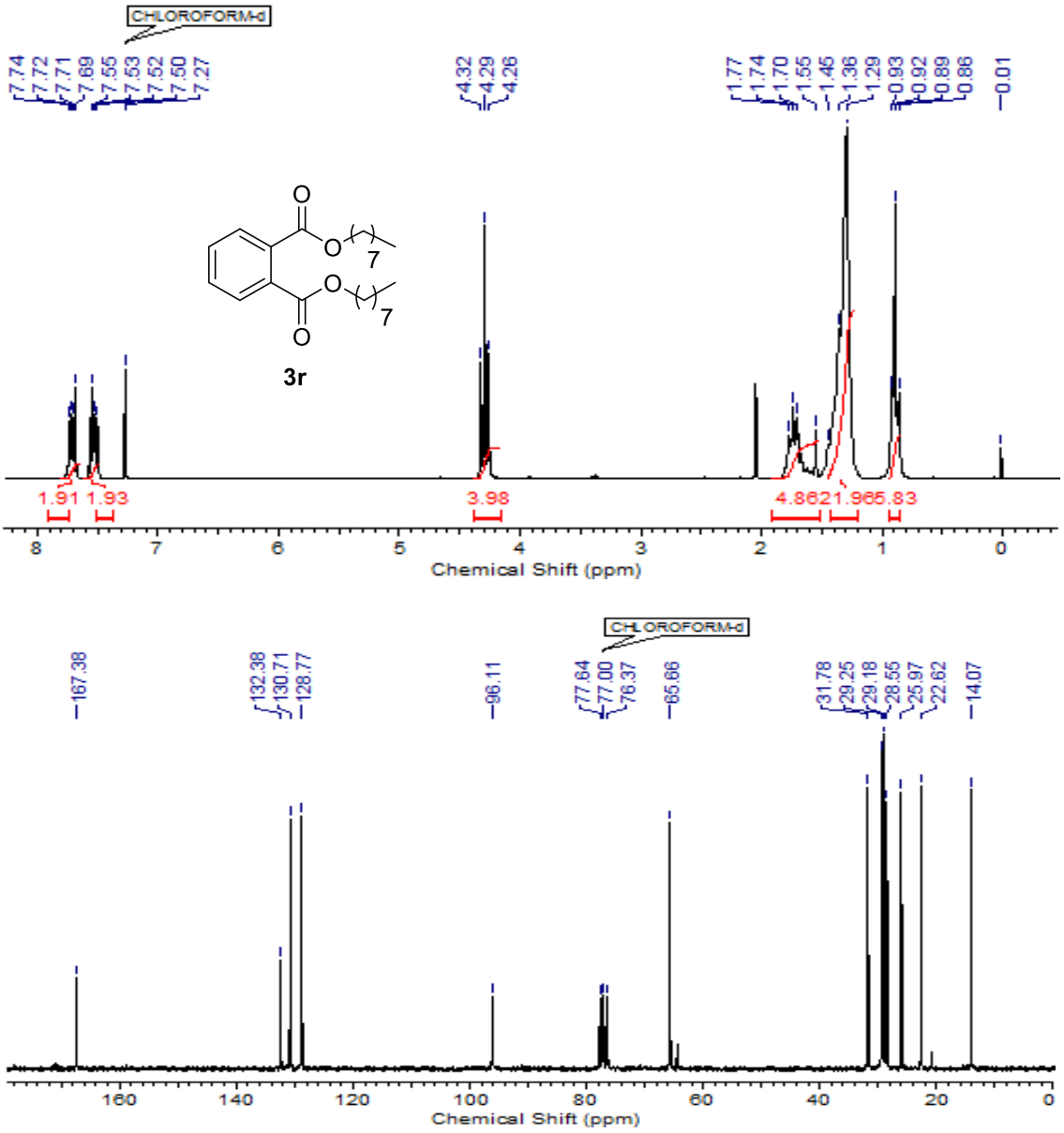
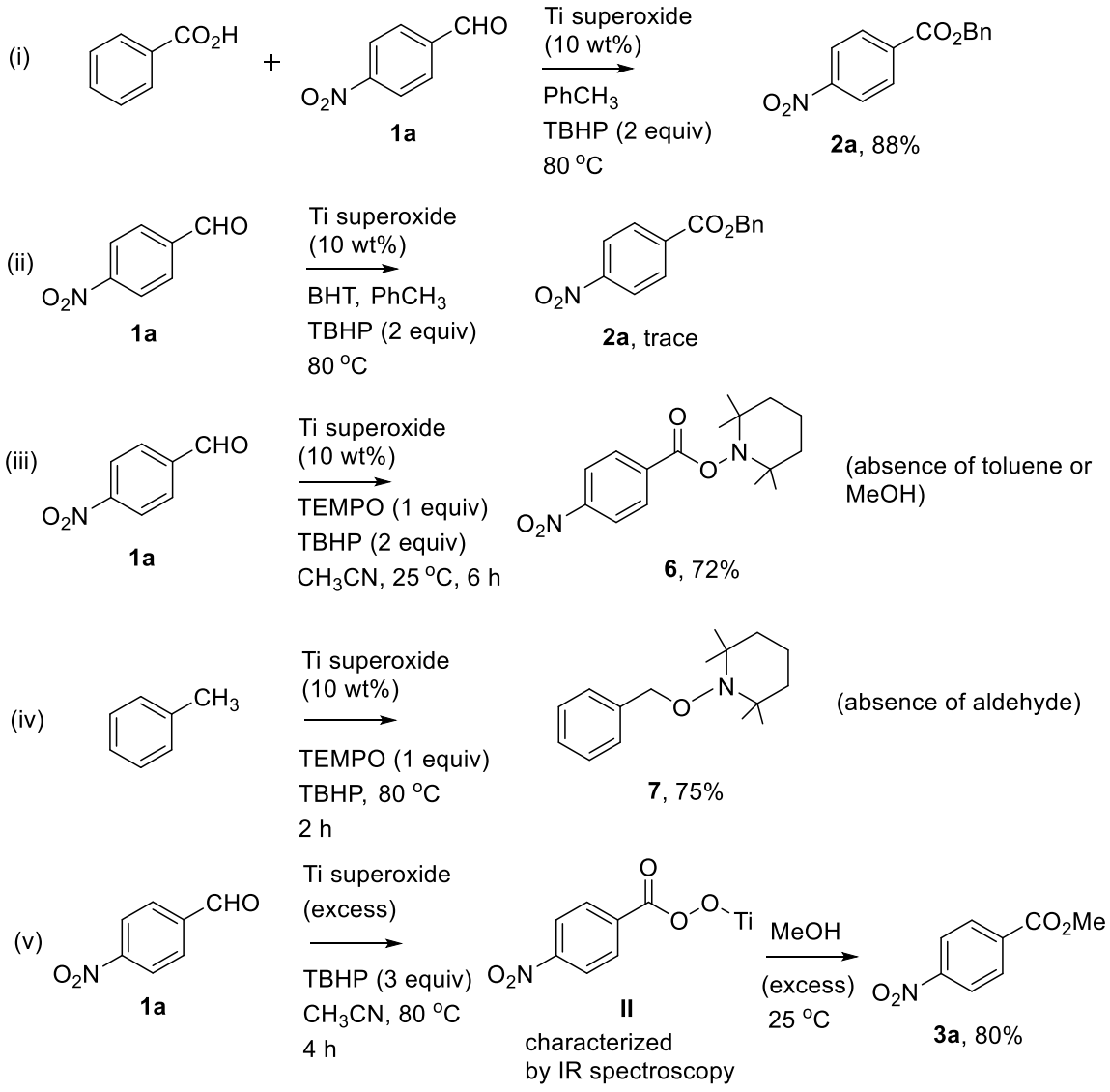


Fig. 2: ^{1}H and ^{13}C NMR Spectra of **3r**

4.1.3.3 Mechanistic Study

To gain some insight into the mechanism of the reaction, the following experiments were performed (**Scheme 12**): (i) a competetive esterification experiment involving benzoic acid and

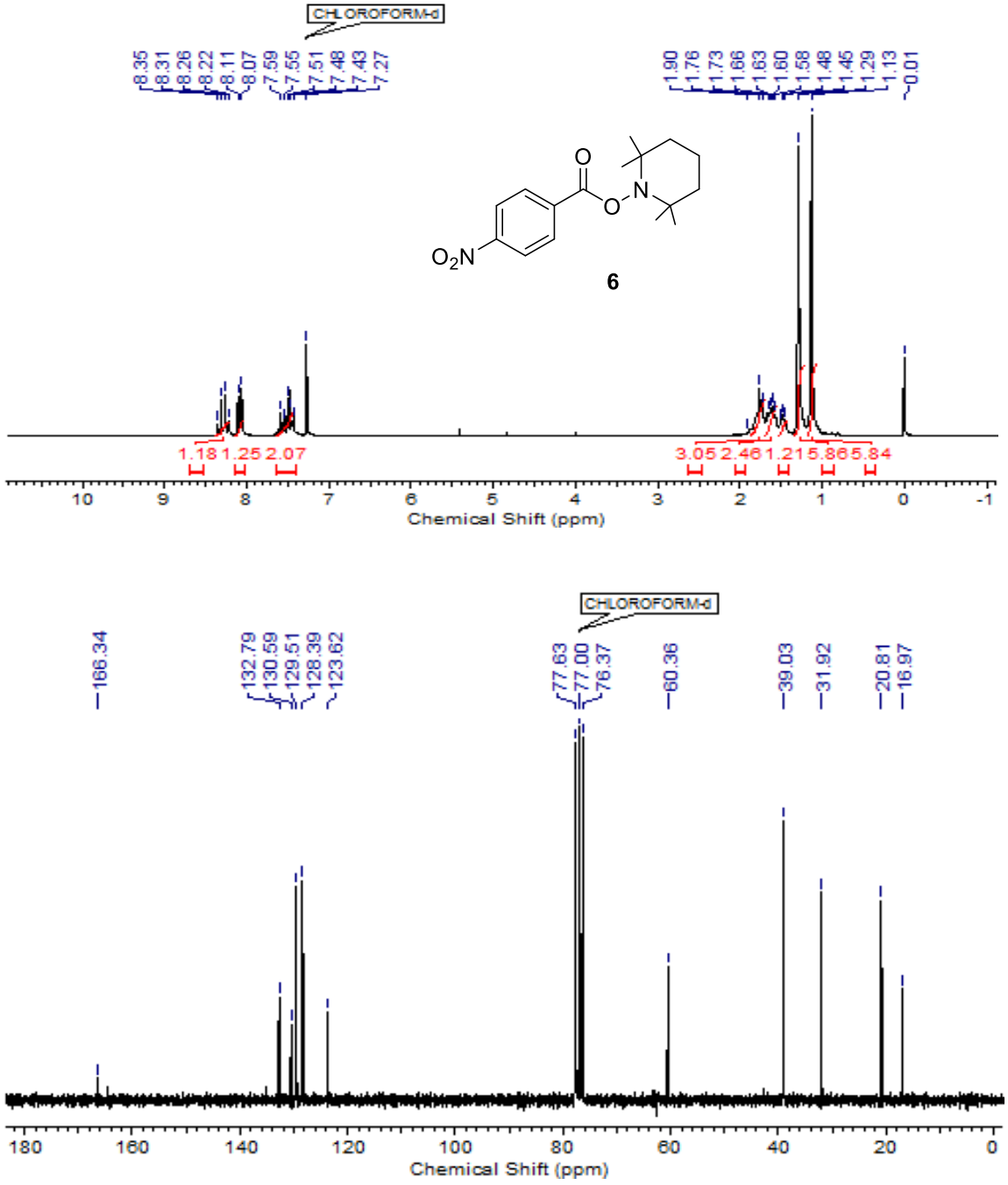
4-nitrobenzaldehyde (**1a**) with toluene under the reaction condition produced the corresponding 4-nitrobenzyl benzoate (**2a**) in 88% yield. This rules out the *in situ* formation of benzoic acid during the reaction course.



Scheme 12: Control experiments demonstrating radical pathway

(ii) Addition of BHT (2,6-di-*tert*-butyl-4-methylphenol) as a radical scavenger resulted in decrease of yield (trace amount) of ester products. (iii) Further, when TEMPO (1 equiv) was treated with **1a** in the absence of either toluene or MeOH, under the reaction conditions, the

corresponding TEMPO-ester adduct **6** was isolated in 72% yield. This result indicates the involvement of benzoyl radical in the catalytic cycle.



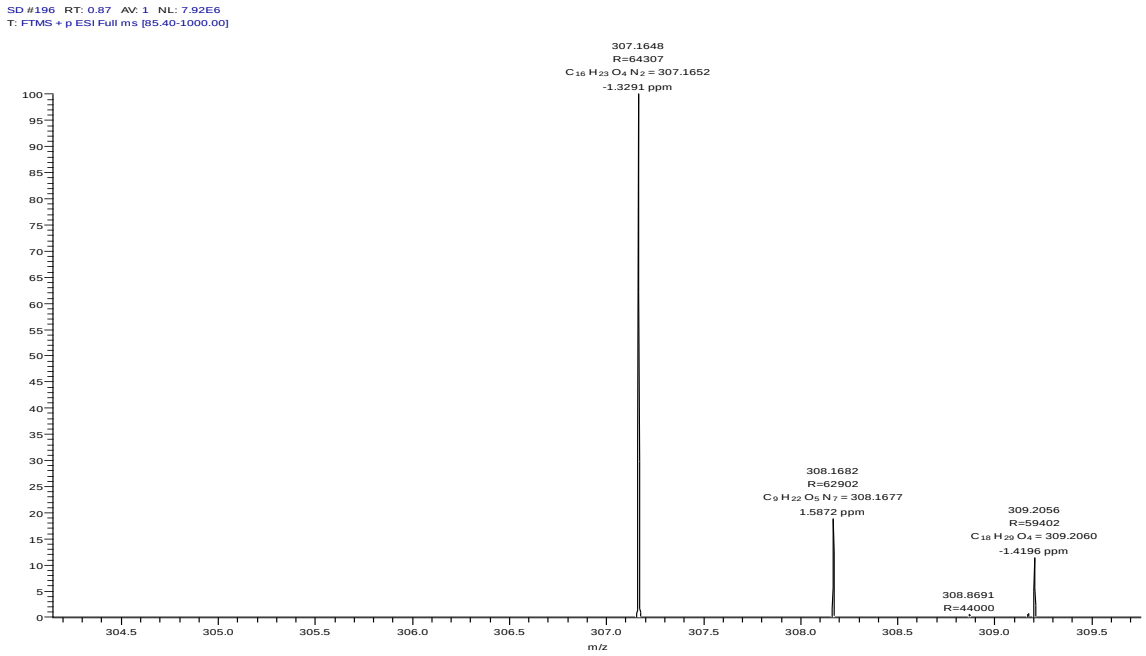


Fig.4: ^{1}H & ^{13}C NMR and HRMS spectra of **6**

The formation of **6** was confirmed from ^{1}H, ^{13}C and HRMS spectral analysis. Its ^{1}H NMR showed two typical singlets at δ 1.29 (s, 6H) and 1.13 (s, 6H) for methyl protons. The typical carbon signal in its ^{13}C NMR at δ 166.3 confirmed the presence of ester carbonyl carbon. Also its molecular mass from HRMS (ESI) spectrum for $[(C_{16}H_{22}N_2O_4)H]$ (M+H) was found to be 307.1648, which was in well agreement with the calculated value 307.1652 (**Fig. 4**).

(iv) It was further evidenced that reaction between toluene and TEMPO (1 equiv), under oxidative esterification, in the absence of aldehyde, producing benzyl oxyaminated product **7** in 75% yield; the formation of **7** was confirmed from HRMS spectral analysis. Its molecular mass from HRMS (ESI) spectrum for $[(C_{16}H_{25}O)H]$ (M+H) was found to be 248.2020, which was in well agreement with the calculated value 248.2009 (**Fig. 5**).

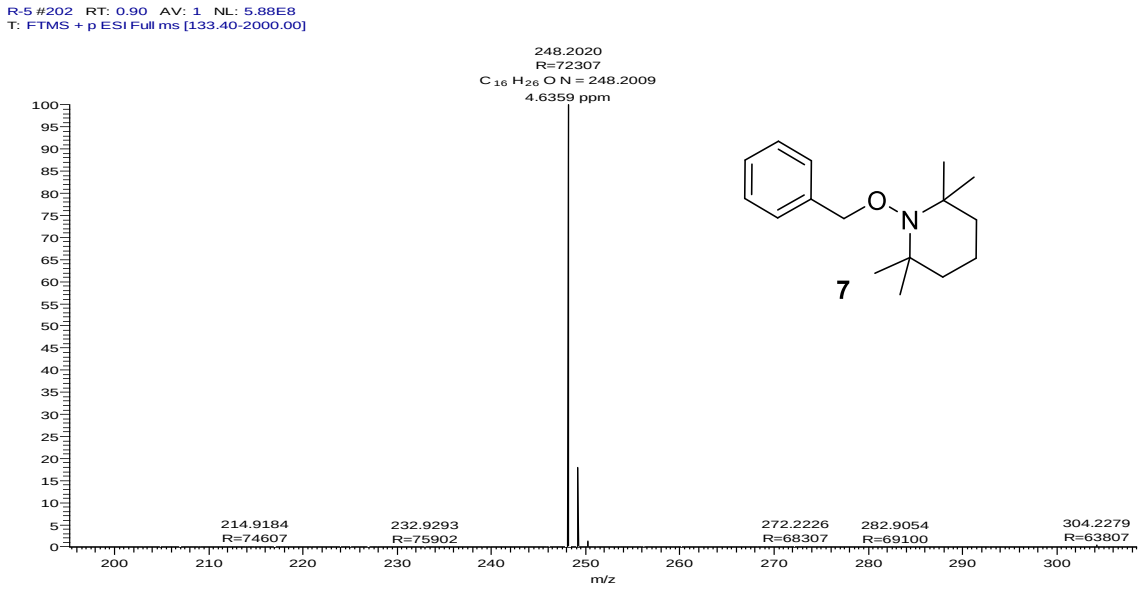


Fig. 5: HRMS spectrum of **7**

(v) In the absence of either toluene or methanol, **1a** under the same protocol with excess Ti superoxide gave the solid intermediate **II**, which was characterized by FTIR spectrum (a strong carbonyl absorption frequency at 1742 cm^{-1}) (**Fig. 6**). Compound **II** on further reaction with

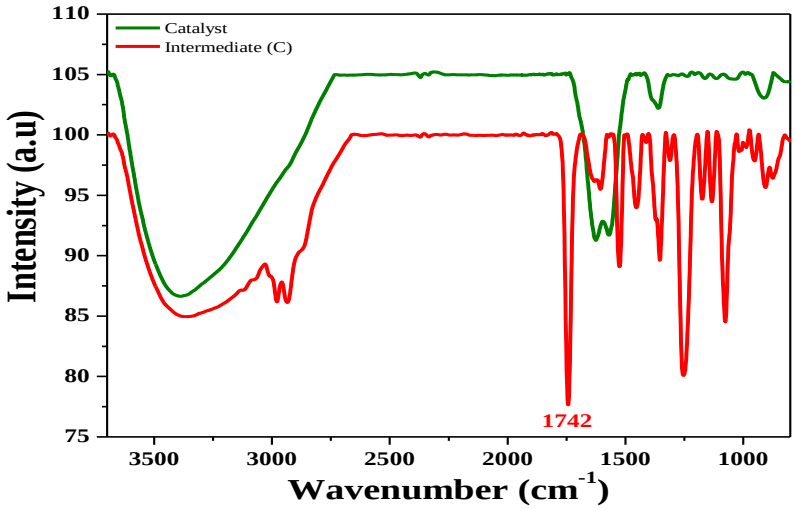


Fig. 6: FTIR spectra of Ti superoxide and peroxo intermediate (**C**)

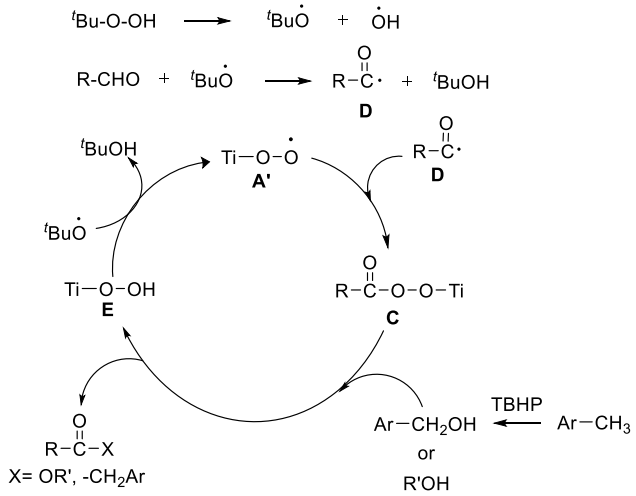
MeOH gave the methyl ester **3a** in 80% yield; this study confirms the formation of species **C** in the catalytic cycle.

(vi) When ethyl benzene was subjected to oxidation with TBHP (1 equiv) and Ti superoxide (10 wt%) in the absence of aldehyde gave 1-phenylethan-1-ol (60% yield).

(vii) When the aforementioned reaction was carried out in presence of light without catalyst, no reaction took place. This rules out the role of light in the reaction.

4.1.3.4 Mechanism

Based on above observation, a possible catalytic cycle is proposed in **Scheme 13**. Thermal decomposition of TBHP in presence of aldehyde generates acyl radical **D**, which subsequently couples with titanium superoxide radical ion to form a Ti peroxo species **C**. Nucleopholic attack of alcohol onto **C** produces ester with the liberation of hydroxyl species **E**. Finally, 1 mole of TBHP is utilized to oxidize **E** to regenerate catalyst **A′** ready for the next catalytic cyle.



Scheme 13: Catalytic cycle for oxidative esterification of aldehydes

4.1.3.5 Reusability Study

The catalyst can be recovered readily by simple filtration and was reused successfully for 5 cycles in the oxidative esterification of 4-nitrobenzaldehyde (**1a**) with methanol. The results are shown in **Fig. 7**, wherein, a slight decrease in catalytic efficiency could be observed after 4th cycle. However, by the addition of one more equivalent of TBHP after 4th cycle reaction mixture, its activity was restored to the original level (yield of ester: 80%). The catalyst was found to be quite active and not deteriorated as proven by reusability study, powder XRD of used catalyst and Atomic absorption spectroscopy (AAS) analysis of reaction sample for Ti leaching.

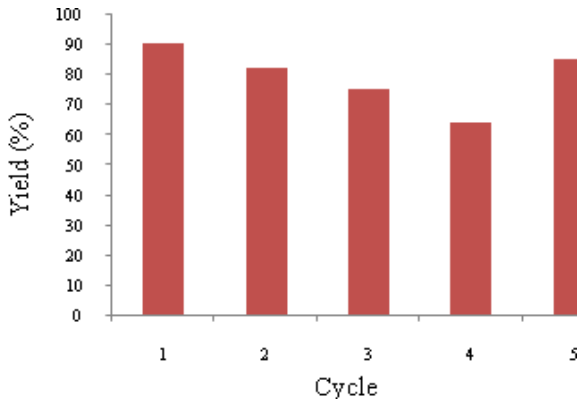
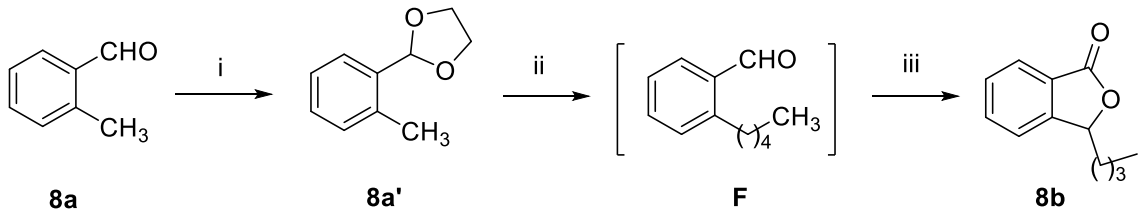


Fig. 7: Reusability study of the catalyst in the case of 4-nitrobenzaldehyde with methanol

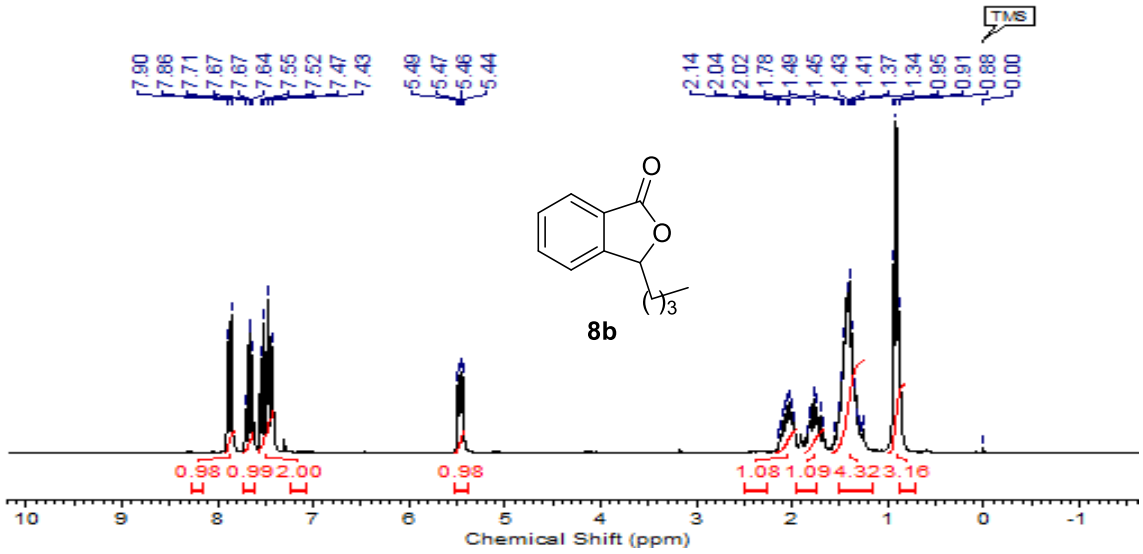
4.1.3.6 Application

Finally, its intramolecular version is demonstrated in the short synthesis of 3-*n*butylphthalide, an anti-convulsant agent used in the treatment of stroke. Thus, *o*-pentylbenzaldehyde (**F**), readily obtained from *o*-tolualdehyde (**8a**), was subjected to intramolecular oxidative esterification under the present protocol to afford **8b** in 70% yield (**Scheme 14**).



Scheme 14: (i) ethylene glycol, PTSA, CH_2Cl_2, 25 °C, 90%; (ii) ^{n}BuLi, THF, 0-25 °C then 1N HCl, 1 h; (iii) Ti superoxide (10 wt%), TBHP (3 equiv), 80 °C, 3 h, 70%.

The formation of 3-*n*butylphthalide (**8b**) was confirmed from ^{1}H and ^{13}C NMR spectral analysis. Its ^{1}H NMR spectrum showed a doublet of doublet at δ 5.47 (dd, *J* = 7.6, 4.1 Hz, 1H) corresponding to methine proton (-CH-O). A signal at δ 170.1 in its ^{13}C NMR spectrum corresponds to the ester carbonyl carbon (**Fig. 8**). Its IR spctrum exhibited a strong vibrational stretching frequency at υ_{max} 1760 cm^{-1} due to the lactone carbonyl functional group. The spectral data of synthetic 3-*n*butylphthalide **8b** were in well-agreement with the literature values.[23]



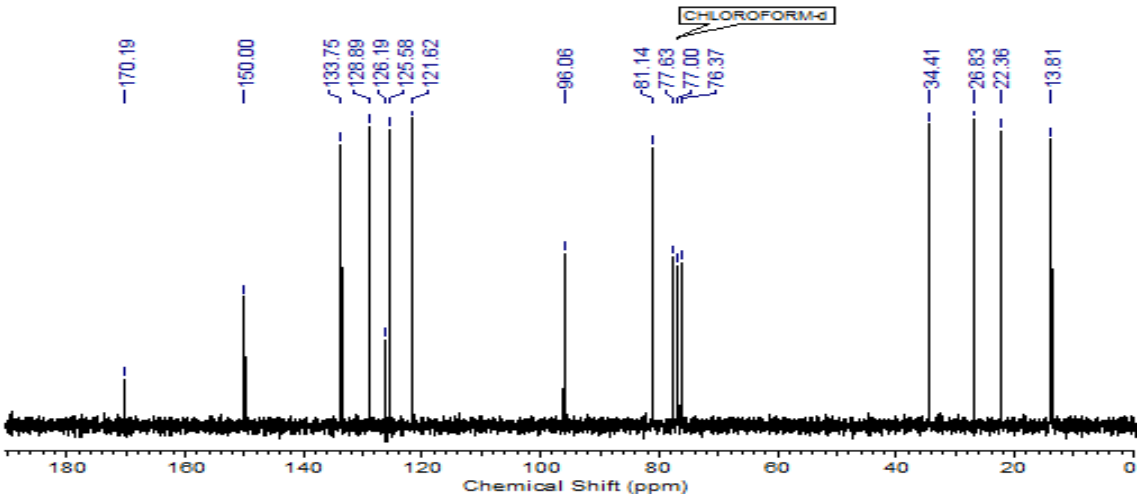


Fig. 8: ^{1}H and ^{13}C NMR spectra of **8b**

4.1.4 Conclusion

In summary, we have demonstrated, for the first time, a new, pratical, and truly heterogeneous catalytic procedure for the oxidative esterification of aldehydes with alkylarenes that leads to the production of a variety of esters in excellent yields. Also, we have successfully achieved its application to the sterically challenged and natural alcohols using the present protocol. The reaction is convenient to carry out under environmental benign and mild conditions, displaying wide range of substrate scope tolerating a variety of functional groups as demonstrated in the synthesis of 3-butyl phthalide.

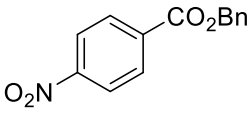
4.1.5 Experimental Section

4.1.5.1 General experimental procedure for the preparation of benzyl esters (2a-s):

In an oven dried round bottom flask, 4-nitrobenzaldehyde **1a** (1 g, 6.61 mmol) and titanium superoxide (0.1 g, 10 wt%) in dry toluene (3.0 g, 33.05 mmol) was added TBHP in decane (5-6 M) (3.6 mL, 19.83 mmol) in a dropwise manner under nitrogen atmosphere. The flask was fitted with a condenser and the mixture was heated at 80 ºC for 3 h. After complete

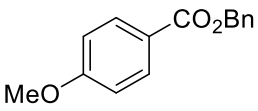
disappearance of aldehyde (judged by TLC; using DNP solution), the flask was cooled to 25 ºC, filtered through sintered funnel using CH_2Cl_2 as eluent. The organic layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography over silica (230-400 mesh) using petroleum ether/ ethyl acetate (19:1 v/v) as eluent to give benzyl 4-nitrobenzoate (**2a**).

Benzyl 4-nitrobenzoate (2a)



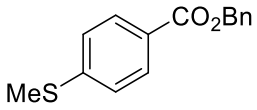
Yield: 90%; 1.53 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2910, 2828, 1717, 1605, 1523, 1330, 1262, 1128; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.40 (s, 2H), 7.28-7.52 (m, 5H), 8.09-8.40 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.6, 123.5, 128.5, 128.8, 130.8, 135.3, 135.5, 150.7, 164.4; **HRMS** (ESI): calc. for [($C_{14}H_{12}NO_4$)H] (M+H) 258.0766, Found: 258.0760.

Benzyl 4-methoxybenzoate (2b)



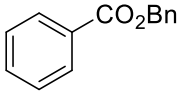
Yield: 88%; 1.56 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3021, 2937, 1711, 1520, 1125; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 5.33 (s, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 7.19-7.49 (m, 5H), 8.02 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.3, 66.4, 113.6, 122.6, 128.1, 128.6, 131.8, 136.3, 163.4, 166.0; **HRMS** (ESI): calc. for [($C_{14}H_{15}O_3$)H] (M+H) 243.1021, Found: 243.1025.

Benzyl 4-(methylthio)benzoate (2c)



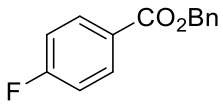
Yield: 79%; 1.3 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3027, 2953, 2923, 1712, 1307, 1269, 1254, 1162; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (s, 3H), 5.36 (s, 2H), 7.33-7.48 (m, 7H), 7.54 (d, *J* = 7.3 Hz, 1H), 8.08 (dd, *J* = 1.4, 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.7, 66.6, 127.8, 128.1, 128.2, 128.3, 128.5, 129.7, 130.1, 132.9, 136.0, 144.4, 166.2; **HRMS** (ESI): calc. for $[(C_{15}H_{14}O_2S)H]$ (M+H) 259.0793, Found: 259.0795.

Benzyl benzoate (2d)



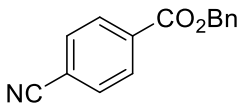
Yield: 72%; 1.44 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3021, 2957, 1721, 1600, 1525; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.38 (s, 2H), 7.31-7.51 (m, 7H), 7.52-7.63 (m, 1H), 8.09 (d, *J* = 7.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.7, 128.2, 128.4, 128.6, 129.8, 133.0, 136.1, 166.2; **HRMS** (ESI): calc. for $[(C_{14}H_{12}O_2)H]$ (M+H) 213.0916, Found: 213.0919.

Benzyl 4-fluorobenzoate (2e)



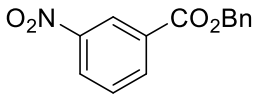
Yield: 92%; 1.7 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3030, 2812, 1725, 1610, 1525, 1101; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.34 (s, 2H), 7.02-7.17 (m, 1H), 7.33-7.46 (m, 5H), 7.98-8.16 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.8, 115.4, 115.6, 126.4, 126.4, 128.2, 128.3, 128.6, 129.7, 130.2, 132.2, 132.3, 132.9, 135.9, 136.1, 164.5, 165.3, 166.2, 167.1; **HRMS** (ESI): calc. for $[(C_{14}H_{11}FO_2)H]$ (M+H) 231.0821, Found: 231.0825.

Benzyl 4-cyanobenzoate (2f)



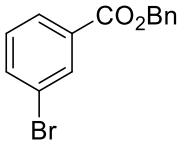
Yield: 96%; 1.7 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3011, 2982, 2115, 1717, 1610, 1501; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.39 (s, 2H), 7.33-7.49 (m, 5H), 7.73 (d, *J* = 8.7 Hz, 2H), 8.16 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.5, 116.6, 117.7, 128.4, 128.6, 128.7, 130.2, 132.1, 133.9, 135.3, 164.6; **HRMS** (ESI): calc. for [($C_{15}H_{11}NO_2$)H] (M+H) 238.0868, Found: 238.0860.

Benzyl 3-nitrobenzoate (2g)



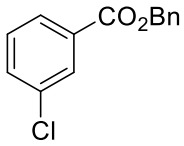
Yield: 86%; 1.4 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2975, 1718, 1512, 1421, 1115, 708; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.41 (s, 2H), 7.33-7.43 (m, 3H), 7.43-7.48 (m, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 8.30-8.48 (m, 2H), 8.88 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.3, 124.3, 127.2, 128.2, 128.4, 128.5, 129.4, 131.6, 135.0, 135.1, 148.0, 163.9; **HRMS** (ESI): calc. for [($C_{14}H_{11}NO_4$)H] (M+H) 258.0766, Found: 258.0770.

Benzyl 3-bromobenzoate (2h)



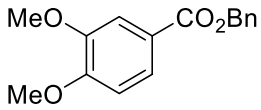
Yield: 94%; 1.4 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3100, 2980, 1720, 1421, 1125; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.36 (s, 2H), 7.38-7.48 (m, 6H), 7.55-775 (m, 1H), 7.98-8.21 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.1, 122.4, 128.1, 128.6, 129.9, 132.6, 133, 135.9, 165; **HRMS** (ESI): calc. for [($C_{14}H_{11}BrO_2$)H] (M+H) 291.0021, Found: 291.0021.

Benzyl 3-chlorobenzoate (2i)



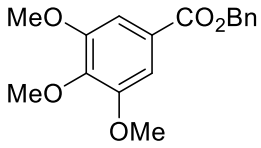
Yield: 86%; 1.5 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3105, 2920, 2810, 1715, 1580, 1417; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.36 (s, 2H), 7.34-7.45 (m, 5H), 7.49-7.62 (m, 1H), 7.96-8.15 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.7, 127.9, 128.2, 128.4, 128.6, 128.7, 129.8, 130.2, 133, 136.1, 166.3; **HRMS** (ESI): calc. for [($C_{14}H_{11}ClO_2$)H] (M+H) 247.0526, Found: 247.0522.

Benzyl 3,4-dimethoxybenzoate (2j)



Yield: 90%; 1.47 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2981, 2910, 1711, 1575, 1135, 763; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 3.93 (s, 3H), 5.34 (s, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 7.29-7.49 (m, 5H), 7.56 (d, *J* = 2.3 Hz, 1H), 7.70 (dd, *J* = 2.1, 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.1, 60.8, 66.7, 106.7, 106.9, 125, 128.1, 128.2, 128.5, 136, 142.2, 152.9, 165.9; **HRMS** (ESI): calc. for [($C_{16}H_{16}O_4$)H] (M+H) 273.1127, Found: 273.1132.

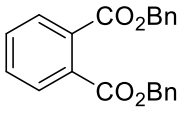
Benzyl 3,4,5-trimethoxybenzoate (2k)



Yield: 92%; 1.41 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3050, 2911, 1710, 1616, 1400; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.81-3.96 (m, 9H), 5.35 (s, 2H), 7.21-7.49 (m, 7H); **^{13}C**

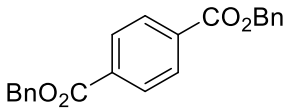
NMR (50 MHz, $CDCl_3$): δ 55.7, 66.3, 110.0, 111.9, 122.4, 123.5, 127.9, 128.2, 128.4, 130.0, 136.1, 148.4, 152.9,165.9; **HRMS** (ESI): calc. for [($C_{17}H_{18}O_5$)H] (M+H) 303.1232, Found: 303.1232.

1,2-Dibenzyl phthalate (2l)



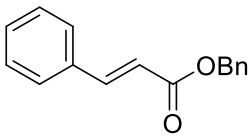
Yield: 92%; 2.37 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2971, 1811, 1720, 1541, 1410; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.20 (s, 4H), 7.27-7.37 (m, 10H), 7.47-7.58 (m, 2H), 7.67-7.79 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.3, 128.3, 128.4, 128.5, 129.0, 131.0, 132.0, 135.5, 167.1; **HRMS** (ESI): calc. for [($C_{22}H_{18}O_4$)H] (M+H) 347.1283, Found: 347.1285.

1,4-Dibenzyl phthalate (2m)



Yield: 90%; 2.32 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3071, 2911, 1720, 1611, 1580, 1051; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.37 (s, 4H), 7.33-7.46 (m, 10H), 8.07-8.14 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.1, 128.3, 128.5, 128.7, 129.7, 134.0, 135.7, 165.5; **HRMS** (ESI): calc. for [($C_{22}H_{18}O_4$)H] (M+H) 347.1283, Found: 347.1283.

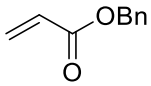
Benzyl cinnamate (2n)



Yield: 80%; 1.4 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3027, 2983, 2923, 1712, 1617, 1307, 1278, 1162, 805, 767; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.24 (s, 2H), 6.47 (d, *J* = 16.0

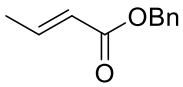
Hz, 1H), 7.28-7.54 (m, 11H), 7.72 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.3, 118.0, 128.2, 128.4, 128.6, 128.9, 130.4, 134.4, 136.1, 145.2, 166.6; **HRMS** (ESI): calc. for $[(C_{16}H_{14}O_2)H]$ (M+H) 239.1072, Found: 239.1075.

Benzyl acrylate (2o)



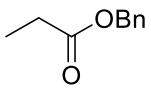
Yield: 88%; 2.54 g; colorless liduid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2931, 2848, 1720, 1621, 1580, 1515, 1421; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.21 (s, 3H), 5.87 (dd, *J* = 10.2, 1.6 Hz, 1H), 6.18 (dd, *J* = 17.3, 10.2 Hz, 1H), 6.48 (dd, *J* = 17.2, 1.7 Hz, 1H), 7.35-7.44 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.2, 128.2, 128.3, 128.5, 130.9, 135.8, 165.7; **HRMS** (ESI): calc. for $[(C_{10}H_{10}O_2)H]$ (M+H) 163.0759, Found: 163.0760.

Benzyl (*E*)-but-2-enoate (2p)



Yield: 88%; 2.21 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3010, 2971, 2882, 1725, 1652, 1568, 1312; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.89 (dd, *J* = 6.88, 1.7 Hz, 3H), 5.16 (s, 2H), 5.80-5.98 (m, 1H), 6.89-7.13 (m, 1H), 7.34 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.1, 66.0, 122.7, 128.2, 128.6, 136.3, 145.0, 166.1; **HRMS** (ESI): calc. for $[(C_{11}H_{12}O_2)H]$ (M+H) 177.0916, Found: 177.0910.

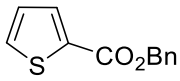
Benzyl propionate (2q)



Yield: 90%; 2.51 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2958, 2934, 2839, 1713, 1606, 1511, 1462, 1373, 1258, 1167, 1098, 1029, 847, 769, 741, 721; **^{1}H NMR** (200 MHz,

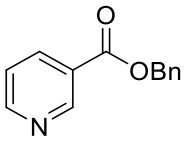
$CDCl_3$): δ 1.16 (t, *J* = 7. 6 Hz, 3H), 2.37 (q, *J* = 7.3, 10.1 Hz, 2H), 5.11 (s, 2H), 7.32-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.2, 27.6, 66.7, 128.2, 128.4, 128.5, 129.8, 133.0, 136.1, 166.2; **HRMS** (ESI): calc. for [($C_{10}H_{12}O_2$)H] (M+H) 165.0916, Found: 165.0917.

Benzyl thiophene-3-carboxylate (2r)



Yield: 92%; 1.79 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3027, 2923, 1712, 1524, 1417, 1374, 1356, 1273,1258, 1094; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.34 (s, 2H), 7.06-7.18 (m, 1H), 7.32-7.48 (m, 5H), 7.50-7.65 (m, 1H), 7.77-7.95 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.7, 127.7, 127.9, 128.2, 128.3, 128.6, 132.4, 133.6, 133.8, 134.0, 135.9, 161.9; **HRMS** (ESI): calc. for [($C_{12}H_{10}O_2S$)H] (M+H) 219.0480, Found: 219.0490.

Benzyl nicotinate (2s)



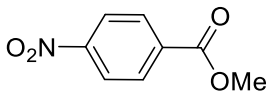
Yield: 90%; 1.79 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3102, 2987, 2897, 1720, 1624, 1528, 1325, 1014; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.39 (s, 2H), 7.25-7.50 (m, 6H), 8.31 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.77 (d, *J* = 3.5 Hz, 1H), 9.26 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.1, 123.2, 126.0, 128.3, 128.5, 128.7, 135.5, 137.1, 151.0, 153.4, 164.9; **HRMS** (ESI): calc. for [($C_{13}H_{11}NO_2$)H] (M+H) 214.0868, Found: 214.0873.

4.1.5.2 General experimental procedure for the preparation of methyl esters (3a-q):

In an oven dried round bottom flask, 4-nitrobenzaldehyde **1a** (1 g, 6.61 mmol) and titanium superoxide (0.1 g, 10 wt%) in dry MeOH (1.32 mL, 33.05 mmol) was added TBHP in decane (5-6 M) (2.4 mL, 13.22 mmol) in a dropwise manner under nitrogen atmosphere.

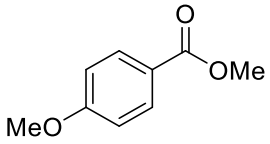
The flask was stirred at 25 ºC for 6 h. After complete disappearance of aldehyde (judged by TLC; using DNP solution), the reaction mixture was filtered through sintered funnel using CH_2Cl_2 as eluent. The organic layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography over silica (230-400 mesh) using petroleum ether/ ethyl acetate (19:1 v/v) as eluent to give methyl 4-nitrobenzoate (**3a**).

Methyl 4-nitrobenzoate (3a)



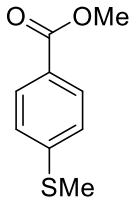
Yield: 88%; 1.0 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2810, 1718, 1620, 1524, 1105; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.97 (s, 3 H), 8.24 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.6, 123.3, 130.5, 135.3, 150.3, 164.9; **HRMS** (ESI): calc. for [($C_8H_7NO_4$)H] (M+H) 182.0453, Found: 182.0455.

Methyl-4-methoxybenzoate (3b)



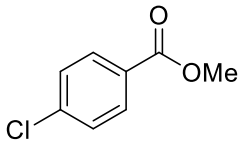
Yield: 82%; 1.0 g; colorless solid; **mp**: 49-51 ºC (lit.[16] **mp**: 49 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3050, 2980, 2910, 1716, 1615, 1548, 1258; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.87 (s, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.7, 55.2, 113.5, 122.6, 131.5, 163.2, 166.5; **HRMS** (ESI): calc. for [($C_9H_{10}O_3$)H] (M+H) 167.0708, Found: 167.0710.

Methyl 4-(methylthio)benzoate (3c)



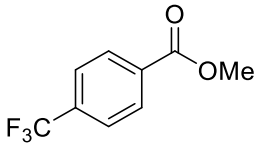
Yield: 82%; 0.98 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2920, 1718, 1658, 1541, 1325, 1258; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.90 (s, 3H), 7.16-7.33 (m, 2H), 7.86-8.02 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 51.7, 124.5, 125.9, 129.5, 145.2, 166.5; HRMS (ESI): calc. for [($C_9H_{10}SO_2$)H] (M+H) 183.0480, Found: 183.0485.

Methyl-4-chlorobenzoate (3d)



Yield: 90%; 1.09 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2952, 2937, 1725, 1613, 1548, 1256; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.1, 128.6, 130.9, 139.3, 165.9; **HRMS** (ESI): calc. for [($C_8H_7ClO_2$)H] (M+H) 171.0213, Found: 171.0215.

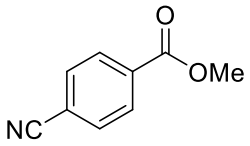
Methyl 4-(trifluoromethyl)benzoate (3e)



Yield: 88%; 1.03 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2972, 1725, 1657, 1585, 1158; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.70 (d, *J* = 8.2 Hz, 2H), 8.14 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.3, 120.8, 125.1, 125.2, 125.3, 125.4, 126.2, 128.0,

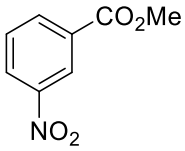
129.9, 132.5, 133.3, 134.1, 134.7, 135.4, 135.7, 165.5; **HRMS** (ESI): calc. for [($C_9H_7F_3O_2$)H] (M+H) 205.0476, Found: 205.0475.

Methyl-4-cyanobenzoate (3f)



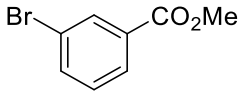
Yield: 90%; 1.13 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2974, 2225, 1725, 1658, 1425, 1121; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.75 (d, *J* = 8.6 Hz, 2H), 8.14 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.6, 116.5, 117.7, 130.1, 132.1, 133.9, 165.1; HRMS (ESI): calc. for [($C_9H_7NO_2$)H] (M+H) 162.0555, Found: 162.0559.

Methyl 3-nitrobenzoate (3g)



Yield: 86%; 1.03 g; colorless solid; **mp**: 78-80 ºC (lit.[16] **mp**: 78 ºC); IR (CHCl3, cm^{-1}): 2857, 1722, 1620, 1587, 1232; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.99 (s, 3H), 7.61-7.69 (m, 1H), 8.34-8.44 (m, 2H), 8.81-8.87 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.6, 124.4, 127.2, 129.5, 131.8, 135.1, 148.2, 164.6; **HRMS** (ESI): calc. For [($C_8H_7NO_4$)H] (M+H) 182.0453, Found: 182.0455.

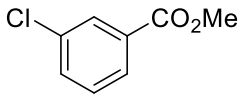
Methyl 3-bromobenzoate (3h)



Yield: 88%; 1.02 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2910, 1722, 1590, 1257, 1187; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.27-7.36 (m, 1H), 7.67 (d, *J* = 8.0 Hz, 1H),

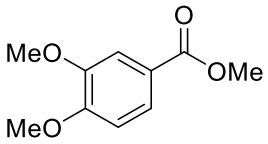
7.95 (d, *J* = 9.2 Hz, 1H), 8.16 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.2, 122.4, 128.1, 129.8, 132.0, 132.6, 135.7, 165.4; **HRMS** (ESI): calc. for [($C_8H_7BrO_2$)H] (M+H) 214.9708, Found: 214.9708.

Methyl 3-chlorobenzoate (3i)



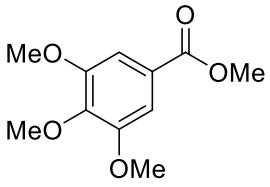
Yield: 90%; 1.09 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2910, 1728, 1535, 1283, 1125; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.47-7.56 (m, 1H), 7.90 (dt, *J* = 1.3, 7.7 Hz, 1H), 8.00 (t, *J* = 1.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.2, 127.6, 129.5, 131.8, 132.8, 134.5, 165.5; **HRMS** (ESI): calc. for [($C_8H_7ClO_2$)H] (M+H) 171.0213, Found: 171.0215.

Methyl-3,4-dimethoxybenzoate (3j)



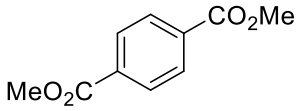
Yield: 86%; 1.0 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3110, 2911, 1715, 1625, 1368, 1152; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.93 (s, 6H), 6.87 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 1.9, 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.8, 55.8, 110.2, 111.9, 123.4, 148.6, 152.9, 166.6; **HRMS** (ESI): calc. for [($C_{10}H_{12}O_4$)H] (M+H) 197.0814, Found: 197.0815.

Methyl-3,4,5-trimethoxybenzoate (3k)



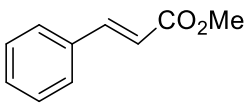
Yield: 84%; 0.96 g; colorless solid; **mp**: 82-85 ºC (lit.[16] **mp**: 82 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2991, 1720, 1547, 1180; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89-3.93 (m, 12H), 7.28 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.1, 56.1, 60.7, 106.8, 125.0, 142.1, 152.9, 166.4; **HRMS** (ESI): calc. for [($C_{11}H_{14}O_5$)H] (M+H) 227.0919, Found: 227.0920.

Dimethyl terephthalate (3l)



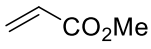
Yield: 88%; 1.27 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3012, 2987, 1725, 1645, 1058; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.74 (s, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.0, 128.0, 132.7, 144.7, 166.8; **HRMS** (ESI): calc. for [($C_{10}H_{10}O_4$)H] (M+H) 195.0657, Found: 195.0650.

Methyl cinnamate (3m)



Yield: 76%; 0.93 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.46 (d, *J* = 16.0 Hz, 1H), 7.35-7.44 (m, 3H), 7.48-7.59 (m, 2H), 7.71 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.6, 117.7, 128.0, 128.8, 130.2, 134.3, 144.8, 167.3; **HRMS** (ESI): calc. for [($C_{10}H_{10}O_2$)H] (M+H) 163.0759, Found: 163.0760.

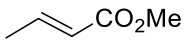
Methyl acrylate (3n)



Yield: 70%; 1.07 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1720, 1621, 1569, 1428, 1104; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.75 (s, 3H), 5.81 (dd, *J* = 10.3, 1.7 Hz, 1H), 6.11 (dd, *J* =

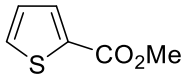
10.3, 17.2 Hz, 1H), 6.40 (dd, *J* = 1.7, 17.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.2, 127.9, 130.3, 166.2; **HRMS** (ESI): calc. for [($C_4H_6O_2$)H] (M+H) 87.0446, Found: 87.0445.

Methyl (*E*)-but-2-enoate (3o)



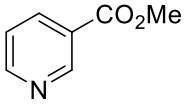
Yield: 72%; 1.02 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1725, 1652, 1590, 1442, 1236; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.88 (dd, *J* = 1.7, 6.9, Hz 3H), 3.72 (s, 3H), 5.85 (dd, *J* = 1.6, 15.5 Hz, 1H), 6.98 (dd, *J* = 6.9, 15.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 17.3, 50.7, 121.9, 144.1, 166.3; **HRMS** (ESI): calc. for [($C_5H_8O_2$)H] (M+H) 101.0603, Found: 101.0609.

Methyl thiophene-2-carboxylate (3p)



Yield: 88%; 1.11 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2912, 1725, 1645, 1560, 1512, 1464, 1237; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 7.11 (t, *J* = 4.3 Hz, 1H), 7.56 (d, *J* = 4.6 Hz, 1H), 7.81 (d, *J* = 3.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.0, 76.4, 77.6, 127.6, 132.2, 133.3, 133.4, 162.5; **HRMS** (ESI): calc. for [($C_6H_6SO_2$)H] (M+H) 143.0167, Found: 143.0169.

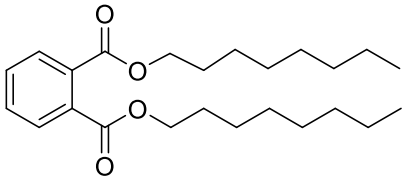
Methyl nicotinate (3q)



Yield: 86%; 1.10 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3011, 2987, 1718, 1625, 1485, 1201, 1101, 748; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.95 (s, 3H), 8.29 (m, 1H), 7.39 (m, 1H), 8.77 (m, 1H), 9.22 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.2, 123.1, 125.8, 136.9,

150.7, 153.3, 165.6; **HRMS** (ESI): calc. for [($C_7H_7NO_2$)H] (M+H) 138.0555, Found: 138.0559.

Dioctyl phthalate (3r)



To a well-stirred solution of phthaldialdehyde (**1r**) (100 g, 0.745 mol) in dry CH_3CN (1000 mL), 1-octanol (194.18 g, 1.491 mol) and titanium superoxide (10 g) were added. Then TBHP in decane (5-6 M) (542.56 mL, 2.98 mol) was added to the reaction mixture in a dropwise manner and kept stirring at 25 ºC for 6 h. After the reaction (checked by TLC), the reaction mixture was filtered through a sintered funnel. The organic layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the desired dioctyl phthalate (**3r**).

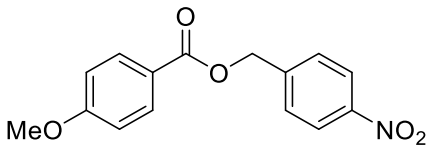
Yield: 96%; 279.53 g; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3112, 1720, 1621, 1580, 1460, 1150, 1012, 845; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.85-0.93 (m, 6H), 1.22-1.44 (m, 22H), 1.62-1.90 (m, 5H), 4.28 (t, *J* = 6.7 Hz, 4H), 7.46-7.60 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 26.0, 28.6, 29.2, 31.8, 65.7, 128.8, 130.7, 132.4, 167.4; **HRMS** (ESI): calc. for [($C_{24}H_{38}O_4$)H] (M+H) 391.2848, Found: 391.2840.

4.1.5.3 General experimental procedure for the preparation of esters (4a-f), (5a–h) and 2a:

To an oven dried round bottomed flask, benzaldehydes (1 equiv), alcohols or alkylbenzenes (1 equiv) and titanium superoxide (0.1 g, 10 wt%) in dry CH_3CN (10 mL) was added TBHP in decane (2 or 3 equiv) in a dropwise manner. The flask was stirred at

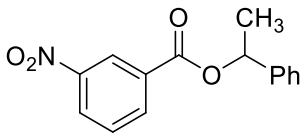
25 ºC or heated at 80 ºC. After complete disappearance of aldehyde (judged by TLC), the reaction mixture was filtered through a sintered funnel using CH_2Cl_2 as eluent. The organic layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography over silica (230-400 mesh) using petroleum ether/ ethyl acetate (19:1 v/v) as eluent to give corresponding esters.

4-Nitrophenyl 4-methoxybenzoate (4a)



Yield: 70%; 1.47 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3105, 2985, 1714, 1637, 1549, 1275, 812; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.88 (s, 3H), 5.42 (s, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 8.25 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.4, 64.9, 113.8, 123.9, 128.3, 131.9, 136.6, 143.6, 148.4, 156.0, 163.8; **HRMS** (ESI): calc. for [($C_{15}H_{13}NO_5$)H] (M+H) 288.0872, Found: 288.0875.

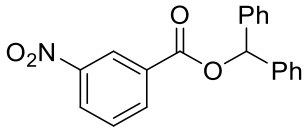
1-Phenylethyl 3-nitrobenzoate (4b)



Yield: 88%; 1.57 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3015, 2985, 2910, 1718, 1642, 1587, 1235, 1148; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.72 (d, *J* = 6.7 Hz, 3H), 6.16 (q, *J* = 6.6 Hz, 1H), 7.28-7.51 (m, 5H), 7.64 (t, *J* = 8.0 Hz, 1H), 8.33-8.47 (m, 2H), 8.88 (t, *J* = 1.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.2, 74.1, 124.5, 126.1, 127.3, 128.2, 128.7,

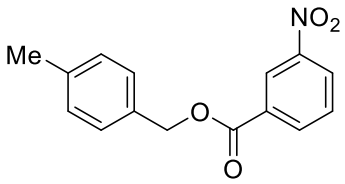
129.5, 132.3, 135.2, 140.9, 148.3, 163.5; **HRMS** (ESI): calc. for [($C_{15}H_{13}NO_4$)H] (M+H) 272.0923, Found: 272.0926.

Benzhydryl 3-nitrobenzoate (4c)



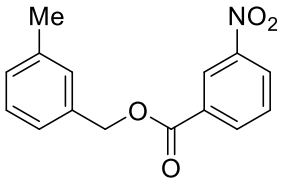
Yield: 88%; 1.94 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3120, 3050, 1717, 1630, 1545, 1289, 1110; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.14 (s, 1H), 7.26-7.32 (m, 2H), 7.32-7.38 (m, 4H), 7.39-7.44 (m, 4H), 8.31-8.48 (m, 2H), 8.82-9.02 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 78.4, 124.7, 127.2, 127.5, 128.3, 128.7, 129.6, 132.1, 135.3, 139.5, 148.4, 163.3; **HRMS** (ESI): calc. for [($C_{20}H_{15}NO_4$)H] (M+H) 334.1079, Found: 334.1082.

4-Methylbenzyl 3-nitrobenzoate (4d)



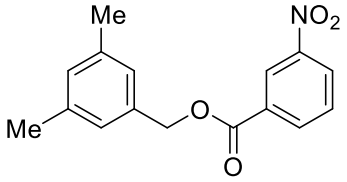
Yield: 90%; 1.61 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3012, 2950, 1718, 1655, 1584, 1431, 1165; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.36 (s, 2H), 7.14-7.26 (m, 2H), 7.29-7.45 (m, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 8.29-8.48 (m, 2H), 8.86 (t, *J* = 1.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 67.6, 124.7, 127.4, 128.7, 129.4, 132.1, 132.3, 135.3, 138.5, 148.3, 164.2; **HRMS** (ESI): calc. for [($C_{15}H_{13}NO_4$)H] (M+H) 272.0923, Found: 272.0920.

3-Methylbenzyl 3-nitrobenzoate (4e)



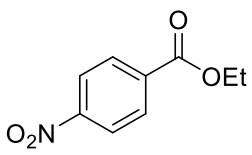
Yield: 88%; 1.57 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3050, 2965, 1718, 1650, 1580, 1480, 1257, 1106; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.35 (s, 2H), 7.08-7.18 (m, 1H), 7.19-7.33 (m, 3H),7.62 (t, *J* = 8.0 Hz, 1H), 8.37 (dt, *J* = 8.0, 2.0 Hz, 2H), 8.85 (t, *J* = 1.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 67.6, 124.6, 125.6, 127.3, 128.6, 129.2, 129.3, 129.5, 131.9, 135.1, 135.2, 138.3, 148.3, 164.1; **HRMS** (ESI): calc. for [($C_{15}H_{13}NO_4$)H] (M+H) 272.0923, Found: 272.0925.

3,5-Dimethylbenzyl 3-nitrobenzoate (4f)



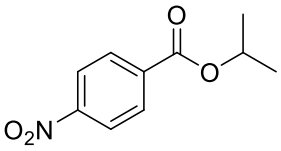
Yield: 92%; 1.73 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3140, 2980, 1720, 1620, 1580, 1465, 1290, 1108; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 6H), 5.34 (s, 2H), 6.92-7.15 (m, 3H), 7.65 (t, *J* = 8.0 Hz, 1H), 8.33-8.56 (m, 2H), 8.88 (t, *J* = 1.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.2, 67.6, 124.6, 126.4, 127.3, 129.4, 130.2, 132.0, 135.0, 135.2, 138.2, 148.3, 164.1; **HRMS** (ESI): calc. for [($C_{16}H_{15}NO_4$)H] (M+H) 286.1079, Found: 286.1075.

Ethyl 4-nitrobenzoate (5a)



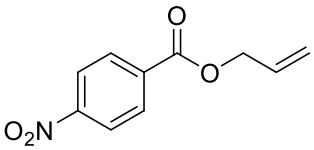
Yield: 80%; 1.03 g; colorless solid; **mp**: 97-99 ºC (lit.[16] **mp**: 97-98 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3102, 3010, 2950, 1724, 1620, 1580, 1456, 1140, 1011; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (t, *J* = 7.4 Hz, 3H), 4.43 (q, *J* = 7.3, 14.6 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 61.9, 123.5, 130.6, 135.8, 150.5, 164.4; **HRMS** (ESI): calc. for [($C_9H_9NO_4$)H] (M+H) 196.0610, Found: 196.0615.

Isopropyl-4-nitrobenzoate (5b)



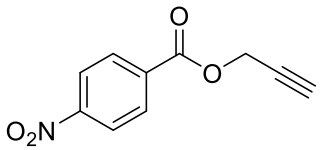
Yield: 78%; 1.07 g; colorless solid, **mp**: 105-108 ºC (lit.[16] **mp**: 105-106 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3112, 2980, 1713, 1620, 1509, 1480, 1253, 1120; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.40 (d, *J* = 6.1 Hz, 7H), 5.24-5.33 (m, 1H), 8.19 (d, *J* = 8.5 Hz, 2H), 8.27 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 69.6, 123.4, 130.5, 136.2, 150.3, 164.1; **HRMS** (ESI): calc. for [($C_{10}H_{11}NO_4$)H] (M+H) 210.0766, Found: 210.0761.

Allyl-4-nitrobenzoate (5c)



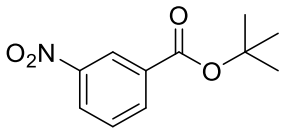
Yield: 82%; 1.12 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3115, 2980,1720, 1620, 1580, 1470, 1320, 1153; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.86 (d, *J* = 5.8 Hz, 2H), 5.28-5.50 (m, 2H), 5.93-6.14 (m, 1H), 8.17-8.34 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.3, 119.0, 123.5, 130.7, 131.6, 135.5, 150.6, 164.1; **HRMS** (ESI): calc. for [($C_{10}H_9NO_4$)H] (M+H) 208.0610, Found: 208.0615.

Prop-2-yn-1-yl 4-nitrobenzoate (5d)



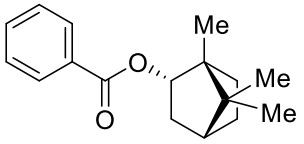
Yield: 80%; 1.08 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2990, 2975, 1716, 1620, 1580, 1410, 1260, 1150, 949, 748; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.54 (t, *J* = 2.5 Hz, 1H), 4.97 (d, *J* = 2.5 Hz, 2H), 8.19-8.36 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 53.2, 75.8, 123.6, 130.9, 134.7, 150.8, 163.8; **HRMS** (ESI): calc. for [($C_{10}H_7NO_4$)H] (M+H) 206.0453, Found: 206.0459.

***tert*-Butyl 3-nitrobenzoate (5e)**



Yield: 52%; 0.76 g; colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2996, 1725, 1610, 1520, 1490, 1260, 1152, 1050; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.65 (s, 9H), 7.51-7.74 (m, 1H), 8.25-8.53 (m, 2H), 8.79 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.1, 82.3, 124.3, 126.8, 129.2, 133.7, 135.0, 148.22, 163.2; **HRMS** (ESI): calc. for [($C_{11}H_{13}NO_4$)H] (M+H) 224.0923, Found: 224.0929.

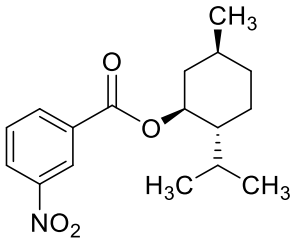
(1*R*, 2*S*, 4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl benzoate (5f)



Yield: 80%; 1.60 g; colorless liquid; **$[\alpha]_D^{25}$** -44.8 (*c* 2.5, $CHCl_3$) {lit.[23] $[\alpha]_D^{30}$ -45 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2980, 1720, 1630, 1528, 1470, 1125, 1080, 945; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.92 (s, 6H), 1.05-1.59 (m, 5H), 1.65-1.96 (m, 3H), 1.98-2.23 (m,

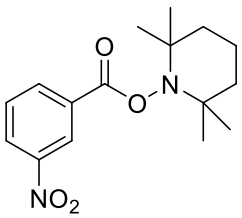
1H), 2.32-2.62 (m, 1H), 5.01-5.19 (m, 1H), 7.36-7.61 (m, 3H), 7.92-8.13 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 19.0, 19.8, 27.4, 28.2, 37.0, 45.0, 47.9, 49.1, 80.4, 128.3, 129.5, 130.9, 132.7, 166.6; **HRMS** (ESI): calc. for [($C_{17}H_{22}O_2$)H] (M+H) 259.1698, Found: 259.1690.

(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl 3-nitrobenzoate (5g)



Yield: 81%; 1.63 g; colorless liquid; **[α]$_D^{25}$** -83.5 (*c* 2, $CHCl_3$) {lit.[22] $[\alpha]_D^{25}$ -83.7 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3110, 2950, 1725, 1580, 1425, 1350, 1230, 1050, 948; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.80 (d, *J* = 7.0 Hz, 3H), 0.94 (dd, *J* = 3.4, 6.7 Hz, 6H), 1.01-1.20 (m, 3H), 1.22-1.34 (m, 1H), 1.53-1.67 (m, 2H), 1.69-1.86 (m, 2H), 1.86-2.21 (m, 1H), 4.99 (td, *J* = 4.5, 10.8, Hz 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 8.84 (s, 1H), 8.32-8.47 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 16.5, 20.8, 22.1, 23.6, 26.6, 31.5, 34.3, 40.9, 47.2, 76.1, 124.6, 127.2, 129.5, 132.6, 135.3, 148.4, 163.9; **HRMS** (ESI): calc. for [($C_{17}H_{23}NO_4$)H] (M+H) 306.1705, Found: 306.1710.

2,2,6,6-Tetramethylpiperidin-1-yl-3-nitrobenzoate (6)

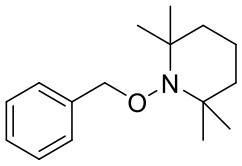


To a stirred solution of 3-nitrobenzaldehyde (0.5 g, 3.3 mmol), 2,2,6,6-Tetramethylpiperidinyloxy (TEMPO) (0.51 g, 3.3 mmol) and titanium superoxide (0.1 g,

10 wt%) in dry CH_3CN (10 mL), TBHP (5-6 M solution in decane) (1.2 mL, 6.6 mmol) was added dropwise *via* a syringe and kept stirring at 25 ºC for 6 h. After the reaction (checked by TLC), the reaction mixture was filtered through sintered funnel using CH_2Cl_2 as eluent. The organic layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography over silica (230-400 mesh) using petroleum ether/ ethyl acetate (4:1 v/v) as eluent to give **6**.

Yield: 72%; 1.45 g; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2985, 1725, 1620, 1590, 1435, 1156, 1085, 835; **^{1}H NMR** (200 MHz,$CDCl_3$): δ 1.13 (s, 6H), 1.29 (s, 6H), 1.41-1.53 (m, 1H), 1.62 (m, 2H), 1.70-1.87 (m, 3H), 7.40-7.65 (m, 2H), 8.09 (m, 1H), 8.29 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 17.0, 20.8, 31.9, 39.0, 60.4, 123.6, 128.4, 129.5, 130.6, 132.8, 166.3; **HRMS** (ESI): calc. for [($C_{16}H_{22}N_2O_4$)H] (M+H) 307.1652, Found: 307.1648.

(((2,2,6,6-Tetramethylcyclohexyl)oxy)methyl)benzene (7)



To a well-stirred solution of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) (1 g, 6.41 mmol) in dry toluene (10 mL), Ti superoxide (0.1 g, 10 wt%) and TBHP (5-6 M in decane) (2.3 mL, 12.82 mmol) were added in a dropwise manner and heated at 80 ºC for 2 h. After that, the reaction mixture was filtered through sintered funnel using CH_2Cl_2 as eluent. The organic layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated in *vacuu*. The crude product was purified by column chromatography over silica (230-400 mesh) using petroleum ether/ ethyl acetate (19:1 v/v) as eluent to give **7**.

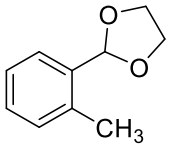
Yield: 75%; 2.03 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3011, 2980, 2851, 1621, 1590, 1365, 1150, 890, 748; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.16 (s, 6H), 1.27 (s, 6H), 1.43-1.65 (m, 6H), 4.84 (s, 2H), 7.29-7.43 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 17.1, 20.3, 33.1, 39.7, 60.0, 78.7, 127.3, 127.4, 128.2, 138.3; **HRMS** (ESI): calc. for [($C_{16}H_{25}O$)H] (M+H) 248.2009, Found: 248.2020.

Synthesis of 3-butylphthalide (8b)

To a stirred solution of *ortho*-tolualdehyde **8a** (1 g, 8.32 mmol) in CH_2Cl_2 (25 mL), ethylene glycol (0.516 g, 8.32 mmol) and PTSA (0.316 g, 1.66 mmol) were added and kept stirring at 25 ºC for 3 h. After the reaction was complete (judged by TLC), the organic layer was extracted with CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ solution, dried over dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography over silica (230-400 mesh) using petroleum ether/ ethyl acetate (9: 1 v/v) as eluent to furnish 2-(*o*-tolyl)-1,3-dioxolane **8a′** in 90% yield. To a stirred solution of **8a′** (1 g, 6.09 mmol) in dry THF (30 mL), ^{n}BuLi in hexane (1.6 M) (4.5 mL, 7.3 mmol) was added *via* syringe in a dropwise manner at 0 ºC and kept stirring for 30 min at same temperature. ^{n}BuI (1.12 g, 6.09 mmol) in dry THF (5 mL) was added to the reaction mixture at 0 ºC slowly and left for stirring at 25 ºC for 2 h. After the reaction was complete (checked by TLC), it was quenched with 2N HCl (10 mL) and kept stirring for another 1 h. The organic layer was then extracted with ether, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. After that, the crude product without further purification and characterization, was subjected to intra-molecular oxidative esterification using TBHP in decane (5-6 M) (3.3 mL, 18.27 mmol) and titanium superoxide (0.1 g, 10 wt%) and it was heated at 80 ºC for 3 h. After the reaction was

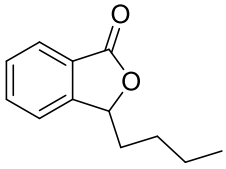
complete (checked by TLC), it was filtered through sintered funnel using CH_2Cl_2 as eluent. The organic layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography over silica (230-400 mesh) using petroleum ether/ ethyl acetate (9:1 v/v) as eluent to give 3-butylphthalide **8b** in 70% yield.

2-(*o*-Tolyl)-1,3-dioxolane (8a′)



Yield: 90%; 1.23 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3112, 2920, 1645, 1580, 1360, 1050, 845, 755; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.98-4.09 (m, 2H), 4.10-4.20 (m, 2H), 5.97 (s, 1H), 7.15-7.29 (m, 3H), 7.46-7.60 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.7, 65.1, 102.0, 125.6, 125.7, 128.8, 130.5, 133.5, 135.3, 136.5,; **Anal. Calcd.** for $[C_{10}H_{12}O_2]$ C, 73.15; H, 7.37: Found: C, 73.10: H, 7.21.

3-Butylphthalide (8b)



Yield: 70%; 0.81 g; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3112, 2920, 1735, 1612, 1520, 1186, 1070; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.81-0.99 (m, 3H), 1.23-1.58 (m, 4H), 1.65-1.87 (m, 1H), 1.94-2.16 (m, 1H), 5.47 (dd, *J* = 7.6, 4.1 Hz, 1H), 7.40-7.58 (m, 2H), 7.61-7.74 (m, 1H), 7.88 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.3, 26.8, 34.4, 81.1, 113.8, 121.6, 125.5, 126.2, 128.8, 133.7, 150.0, 170.1; **Anal. Calcd.** for $[C_{12}H_{14}O_2]$ C, 75.76; H, 7.42; Found: C, 75.55; H, 7.20.

Section II

A Facile Reductive Cleavage of N-N bonds in Dibenzyl Alkylhydrazine-1,2-Dicarboxylate by Pd Catalyst Under Hydrosilylation Conditions

4.2.1 Introduction

The development of mild and efficient methods for the synthesis of amine compounds is of great importance, since the products are frequently encountered as drugs in the pharmaceutical industries. Some of the representative examples of the top selling drugs containing amine as a functional group include (*R*)-selegiline, a drug for Parkinson's disease; (*S*)-benzphetamine, an anorectic drug; (*R*)-sitagliptine, an anti-diabetic drug and anisomysin, a psychiatric drug (**Fig. 9)**.

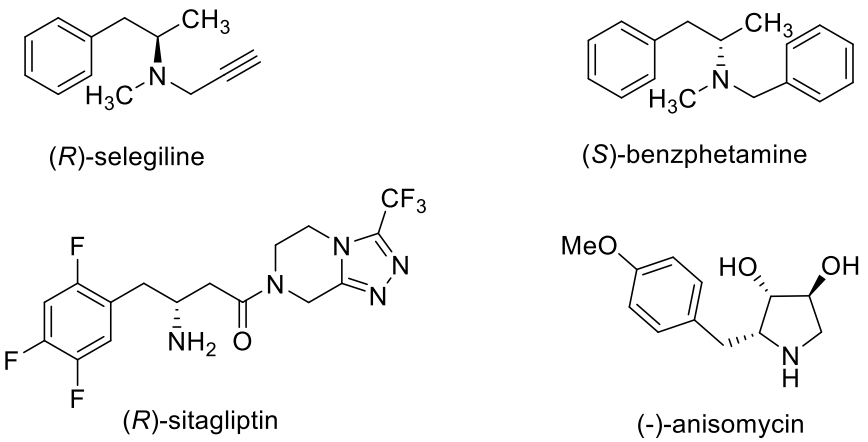


Fig. 9: Representative examples of top selling drugs containing amine functionality

Because of the importance of amine functionality various methods are known for its synthesis. Among them reduction of nitro compounds, imines, oximes and cleavage of N-N bonds are the most common approaches. However, for synthesis of chiral amine

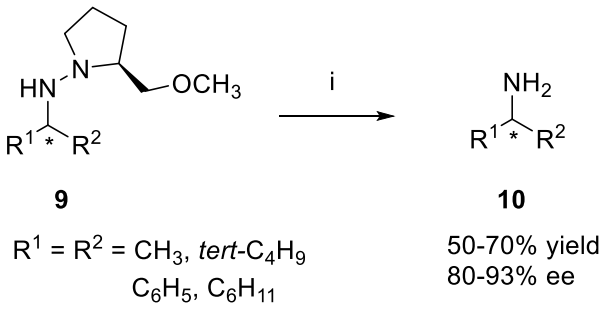
functionality, cleavage of N-N bond of hydrazine has gained much importance in recent times, since these hydrazine compounds can be easily synthesized with high enantiopurity *via* proline catalyzed α-amination reactions of aldehydes.[24] In recent years, transition-metal catalyzed reduction methods have been successfully applied to a number of chemical transformations of functional groups.[25] The N-N bond reductive cleavage among some reducible functionalities have been one of the most desirable transformations in the field of synthetic chemistry. Although Raney Ni is known to be the most universal catalyst for N-N bond cleavage and its reaction often proceeds in good yields, yet use of high pressure or elevated temperature is the major drawback of this process.[26] Despite the fact that a plethora of reducing reagents is available for this operation, new reagents, especially the environmental benign approaches, are still highly desirable.

4.2.2 Review of Literature

In literature a wide variety of catalytic systems are known for selective cleavage of N-N bonds in hydrazines. Some of the recent developments are described below.

Enders's approach (1986)[27]

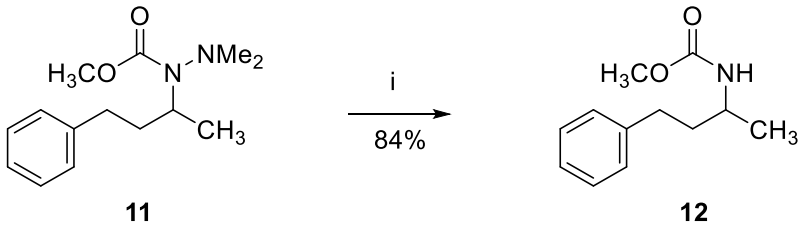
D. Enders *et al.* have reported the synthesis of α-substituted primary amines **10** from various chiral hydrazines **9** using Raney nickel with H_2 (3.5-3.8 bar) in moderate yields and 80-93% ee (**Scheme 15**).



Scheme 15: (i) Raney Ni, H_2 (3.5-3.8 bar), 20-40 °C, 24 h, 50-70%.

Denmark's approach (1990)[28]

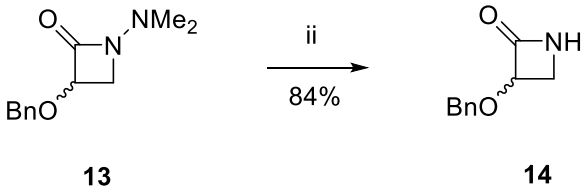
Denmark *et al.* have reported a novel method to cleave N-N bond in N-(methoxycarbonyl)hydrazines **11** using Li/liq. NH_3 reaction condition to produce of carbamate **12** in 84% yield (**Scheme 16**).



Scheme 16: (i) Li in liq. NH_3, THF, -33 °C.

Lassaletta's approach (2000)[29]

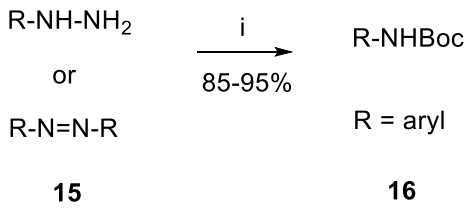
In this approach, N-N bond in 3-(benzyloxy)-1-(dimethylamino)azetidin-2-one **13** was oxidatively cleaved by magnesium monoperoxyphthalate (MMPP) to afford 3-(benzyloxy)azetidin-2-one **14** in good yields and ees (**Scheme 17**).



Scheme 17: (i) MMPP, MeOH, 25 °C, 24 h.

Chandrasekhar's approach (2001)[30]

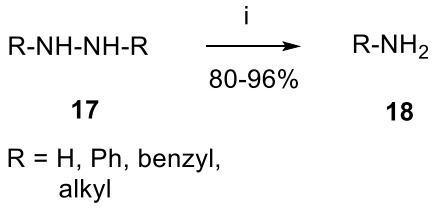
Chandrasekhar *et al.* have disclosed an one-step direct conversion of aromatic hydrazines and azo compounds **15** to *N*-(*tert*-butoxycarbonyl) amines **16** using Pd/C as catalyst and PHMS as reducing agent in good yields (**Scheme 17**).



Scheme 17: (i) 10% Pd/C, PHMS, Boc_2O, EtOH, 25 °C, 85-95%.

Luo's approach (2013)[31]

Luo *et al.* have described a new catalytic method for the N-N bond cleavage in hydrazines **17** to form amines **18** in good yields *via* a low valent titanium reagent prepared *in situ* by treatment of $TiCl_4$ and Mg powder in THF (**Scheme 18**).



Scheme 18: (i) Mg, $TiCl_4$, THF, 25 °C.

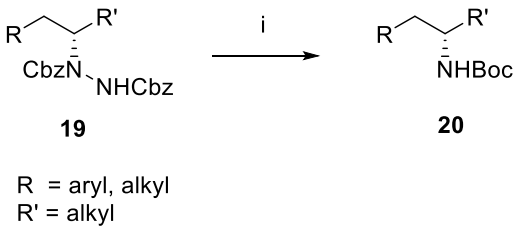
4.2.3 Present Work

4.2.3.1 Objective

The cleavage of N-N bonds is useful, yet a challenging transformation. As a consequence, a number of methods have been developed for N-N bond cleavage in hydrazine based substrates involving hydrogenation catalyzed on metals, by reduction with aluminium or boron hydrides, by electro-reductive process, e.g. Li/NH_3 or by making use of SmI_2 or by oxidative cleavage as can be seen in literature reports. However, these methods have been associated with certain drawbacks, such as lack of reactivity, use of acidic or basic condition, sluggish reaction conditions as well as use of handling of hazardous reagents, namely hydrogen. Undoubtedly, an eco-friendly, safe protocol would be a welcome addition to the repertoire of existing methodologies.

4.2.3.2 Results and Discussion

As a part of our program aimed at the synthesis of various drug molecules using organocatalytic amination approach, the cleavage of N-N bonds is often required to get useful intermediates. Herein, in this section, we present the results of $PdCl_2$ catalyzed cleavage of N-N bonds in dibenzyl alkylhydrazine-1,2-dicarboxylates in an environmentally attractive fashion; on aqueous MeOH medium at room temperature, effected by hydrogen generated from PMHS (polymethylhydrosiloxane) (**Scheme 19**).



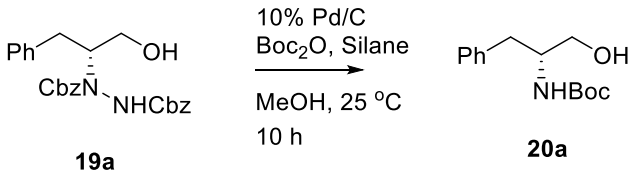
19 **20**

R = aryl, alkyl
R' = alkyl

Scheme 19: (i) $PdCl_2$ (5 mol %), PMHS (4 equiv), Boc_2O, DI water/MeOH (1:1), 25 °C, 10 h, 70-88%.

Initially, dibenzyl-1-(1-hydroxy-3-phenylpropan-2-yl)hydrazine-1,2-dicarboxylate (**19a**) as a model substrate was tested to provide carbamate (**20a**) *albiet* in low yield (22%) using 10% Pd/C and Et_3SiH (2 equiv) in MeOH at ambient temperature (**Table 2**; entry 1). Screening of silanes and siloxanes revealed certain variations in the rate of cleavage of N-N bond (entry 2-4). The rate of cleavage was thus found to be highest for PMHS (4 equiv), wherein carbamate (**20a**) could be obtained in 78% yield (entry 6). With increase in PMHS loading to 8 equiv, no significant increase in yield was observed. Also, no reaction took place with tetramethyldisiloxane (TMDS) as silane source. A byproduct of the silicone industry, PMHS is inexpensive and tends to be much more air and moisture stable than other silanes.[32a]

Table 2: Screening of the silane source[a]



19a **20a**

entry	silane source	equivalents	yields of **20a**[b]
1	Et_3SiH	2	22
2	Et_3SiH	4	25
3	$PhSiH_3$	2	20
4	Ph_2SiH_2	2	15
5	PMHS	2	40
6	PMHS	4	78
7	PMHS	8	70

[a] Substrate (5 mmol), 10% Pd/C (5 mol %), $(Boc)_2O$ (5 mmol), silane, MeOH (20 mL), 25 °C, 10 h; [b] isolated yields after column chromatography.

Other metals and their complexes were also tested on the aforementioned reaction (**Table 3**). Unfortunately, catalysts such as $Ni(COD)_2$, $NiCl_2.2H_2O$, $Cu(OAc)_2.2H_2O$ and

$Co(NO_3)_2.2H_2O$ did not lead to hydrogen generation from the silane, and therefore were ineffective in N-N bond cleavage. However, metal salt such as $PtCl_2$ produced hydrogen giving low yield of carbamate **20a** (28%). Other Pd salts, such as $Pd(dba)_2$ and $Pd(OAc)_2$ were also screened and less yield of carbamate **20a** was observed. Surprisingly, use of $PdCl_2$ (5 mol %) afforded the best yield (80%), compared to Pd/C. The increase in catalyst ($PdCl_2$) loading to 10 mol % did not increase the yield of **20a**.

Table 3: Screening of the metal salts[a]

entry	metal salts	mol %	yields of **20a**[b]
1	$PtCl_2$	5	28
2	$Pd(dba)_2$	5	20
3	$Pd(OAc)_2$	5	-
4	Pd/C	5	60
5	$PdCl_2$	5	80
6	$PdCl_2$	10	78

[a] For reaction condition, refer to the foot-note under **Table 2**, except only variation in using metal salts; [b] isolated yields after column chromatographic purification.

A number of organic solvents could be used to effect this reduction, as summarized in **Table 4**. Aprotic solvents such as CH_2Cl_2, toluene, Et_2O and CH_3CN were found to be ineffective, while protic solvents like EtOH or MeOH along with $PdCl_2$ produced moderate yield of carbamate **20a** (55-60%). The addition of deionized water in MeOH (1:1) provided the best yield of carbamate (86%). The need for water in these reactions could be indicative of a transfer hydrogenation process wherein hydrogen gas is formed from the silicon hydride and water *via* σ bond metathesis on the palladium.[32b] On heating the reaction mixture at 60 ^oC, we found no change in the yield. However, the yield of carbamate was reduced (30%), when deionized water was used alone as solvent. After standardizing the

reaction condition, we subjected other hydrazine compounds such as diethyl or diisopropyl-1-alkylhydrazine-1,2-dicarboxylates to the same reaction conditions and found that no reaction took place, which may be a limitation of this catalytic process.

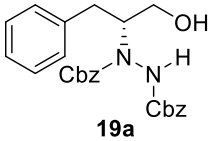
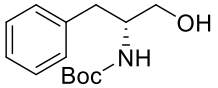
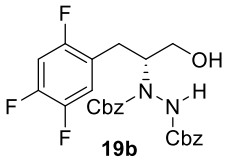
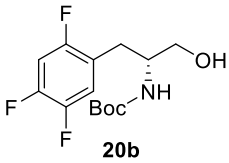
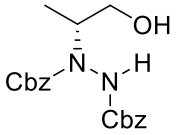
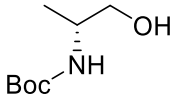
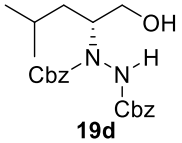
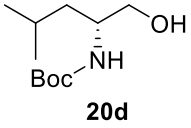
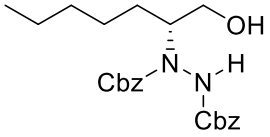
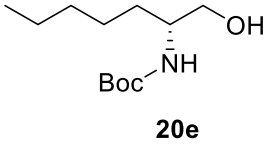
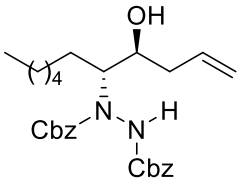
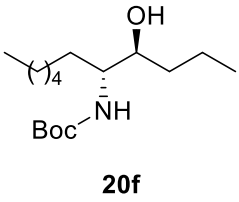
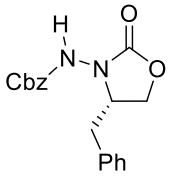
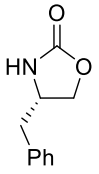
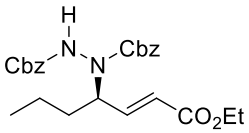
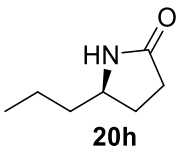
Table 4: Variation of reaction medium and temperature[a]

entry	medium	*t* (°C)	yields of **20a**[b] (%)
1	MeOH	25	60
2	EtOH	25	50
3	DMF	25	10
4	DI water	25	30
5	DI water/MeOH	25	86
6	DI water/MeOH	60	75

[a] For reaction condition, refer to the foot-note under **Table 2**, except only variation in reaction medium and temperature; [b] isolated yields after column chromatographic purification.

We have then applied the optimized procedure of Pd catalyzed reductive N-N bond cleavage to a variety of substrates, as shown in **Table 5**. As can be seen, several *N,N*-dibenzyl hydrazides underwent reductive cleavage to furnish carbamates in excellent yields (70-88%). Carbamates like, (**20a-b**) served as building blocks in various drug molecules. Hydrazines (**19c-e**) were then investigated under the protocol. In all cases studied, good yields of the respective carbamates (**20c-e**) were indeed obtained in 70-76%. Also, the more functionalized hydrazine derivative (**19f**) preceded reductive cleavage smoothly to produce functionalized carbamate (**20f**) in high yield (76%). Oxazolidinone **20g** was obtained in 80% yield using this protocol and can be found to be used as chiral auxiliary in organic synthesis.[33] Again, chiral α,β-unsaturated hydrazide **19h** under the standard reaction condition, led to the formation of lactum **20h** in 76% yield.

Table 5: Pd catalyaed Reductive cleavage of N-N bond with PMHS: Substrate scope[a]

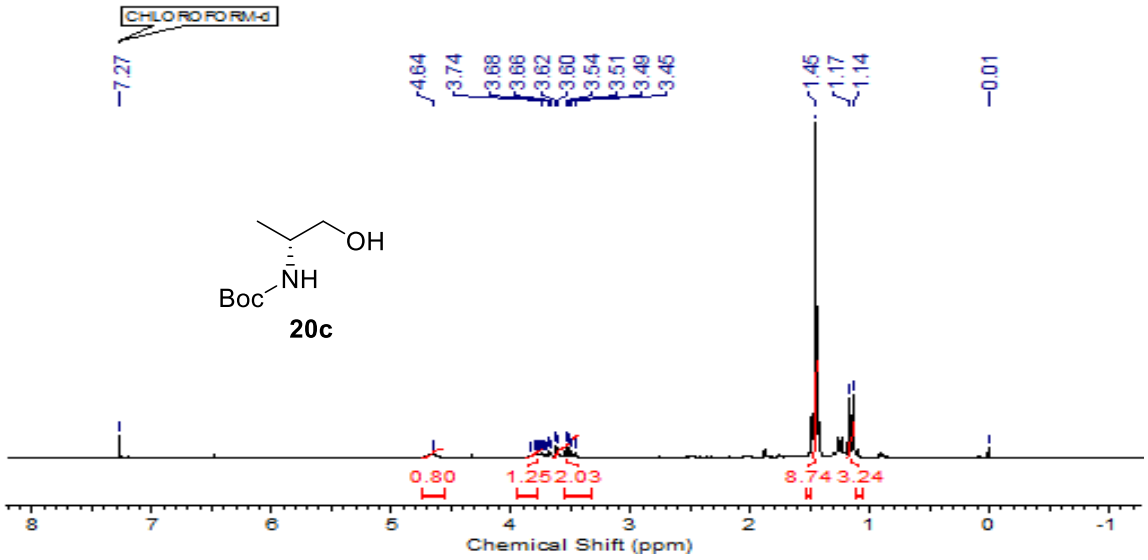
entry	substrates	products	yields (%)[b]
1	 **19a**	 **20a**	86
2	 **19b**	 **20b**	88
3	 **19c**	 **20c**	70
4	 **19d**	 **20d**	72
5	 **19e**	 **20e**	76
6	 **19f**	 **20f**	72
7[c]	 **19g**	 **20g**	80
8[c]	 **19h**	 **20h**	76

[a]Substrate (5 mmol), $PdCl_2$ (5 mol %), Boc_2O (5 mmol), PHMS (20 mmol), MeOH/Deionized water (1:1) (20 mL), 25 °C, 10 h; [b] isolated yields after column chromatography; [c] Boc_2O was not used here.

The enantiomeric purity of **20a** was determined to be 97.7% based on comparison of its specific rotation with the reported value $[\alpha]_D^{25}$ -26.4 (*c* 1, MeOH) {lit.[20] $[\alpha]_D^{25}$ -27 (*c* 1, MeOH)}, thereby confirming that optical integrity was retained in the product.

The formation of carbamates by our present protocol was confirmed from their ^{1}H and ^{13}C NMR spectral analysis.

Example 1: The ^{1}H NMR spectrum of **20c** showed a multiplet at δ 3.60-3.74 (m, 1H) corresponding to the methine carbon (-C**H**-NHBoc) and a typical singlet at δ 1.45 (s, 9H) due to methyl protons of *tert*-butyl group. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 166.7 and 79.6 due to carbonyl carbon of Boc group and methine carbon (-**C**H-NHBoc) respectively. Its IR spectrum showed strong absorption bands at υ_{max} 3388 and 1709 cm^{-1} confirming the presence of hydroxyl and carbonyl functionalities respectively. Its molecular mass [$(C_8H_{17}NO_3)H$] (M+H) from HRMS (ESI) was found to be 176.1205, which was in well-matched with calculated value 176.1208 (**Fig. 10**).



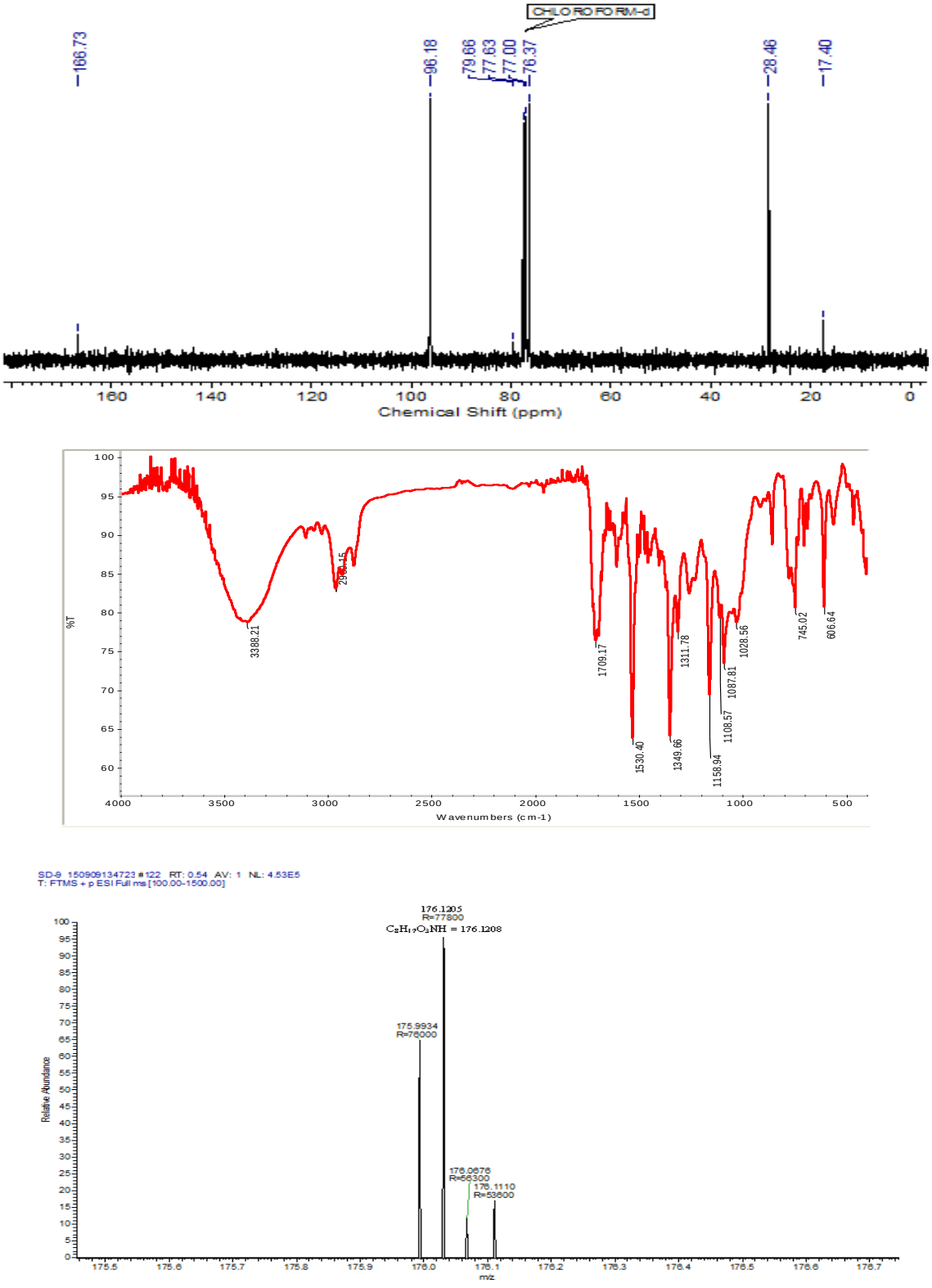
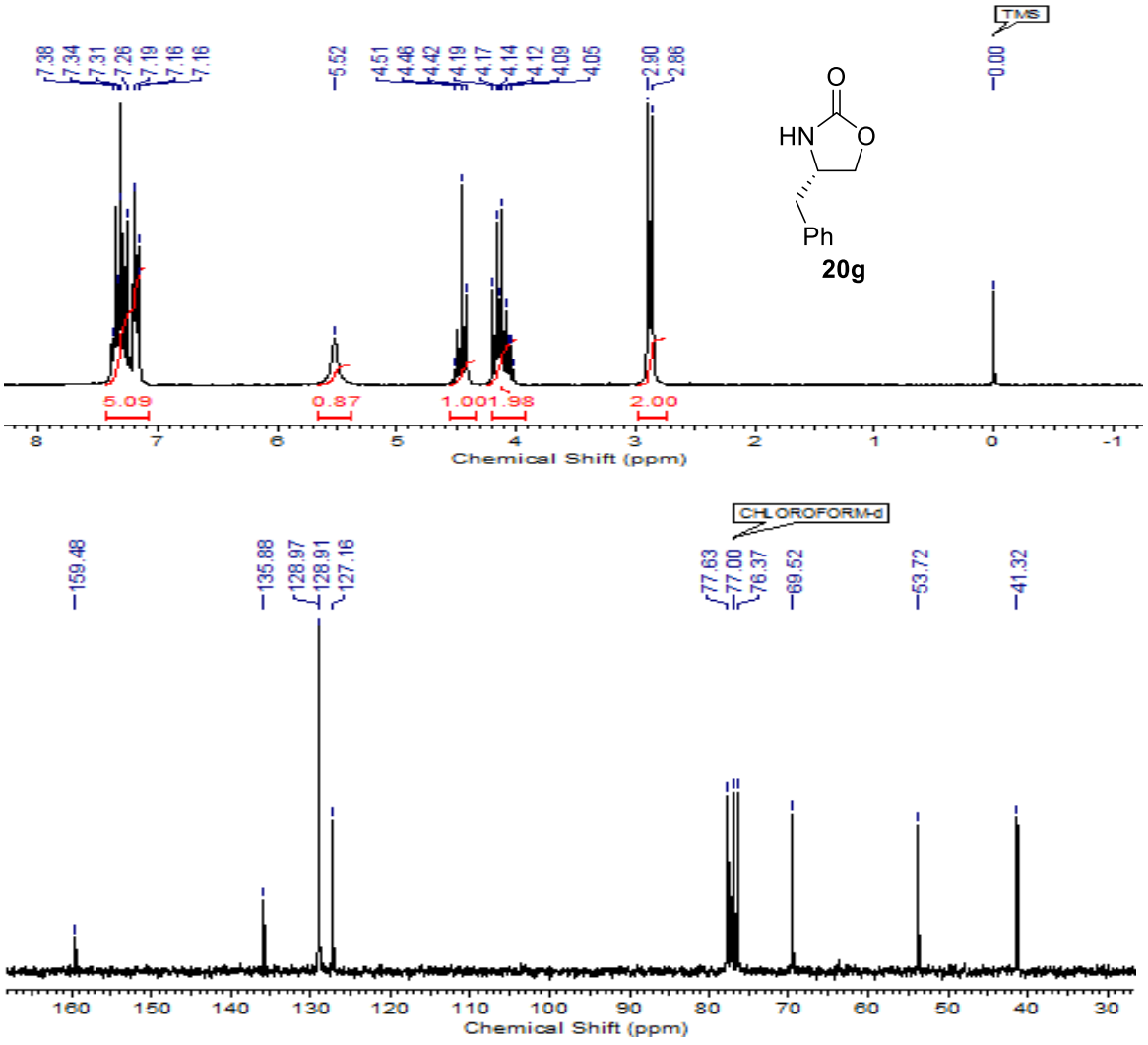


Fig. 10: ^{1}H, ^{13}C NMR, IR and HRMS spectra of carbamate **20c**

Example 2: The ^{1}H NMR spectrum of **20g** showed a characteristic broad singlet at δ 5.52 (br s, 1H) accounting for free N-**H** proton and a multiplet at δ 4.42-4.51 (m, 1H) due to methine proton (-C**H**N-). Its ^{13}C NMR spectrum displayed typical three carbon signals at δ 159.4, 69.5 and 53.7 corresponding to carbonyl carbon, methylene carbon attached to oxygen atom and methine carbon respectively. Its molecular mass [$(C_{10}H_{11}NO_2)Na$] (M+Na) from HRMS (ESI) was found to be 200.0681, which was in well-agreement with the calculated value 200.0682 (**Fig. 11**). Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} 1701 cm^{-1} due to the presence of amide carbonyl functionality.



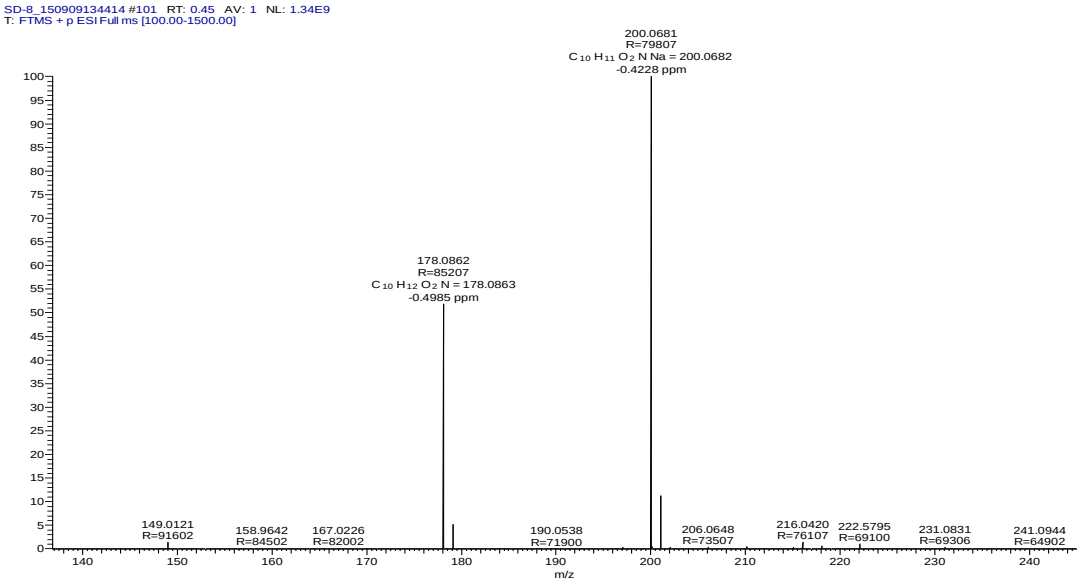
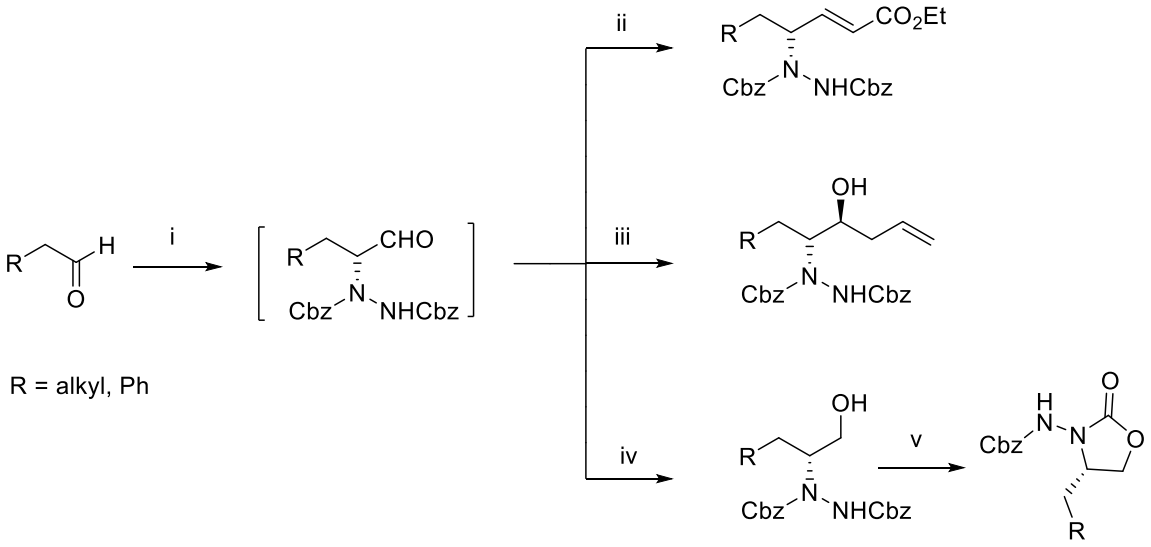


Fig. 11: ^{1}H, ^{13}C NMR and HRMS spectra of oxazolidinone **20g**



Scheme 20: (i) DBAD, L-proline (10 mol %), CH_3CN, 0 ºC, 2 h; (ii) triethyl phosphonoacetate, DBU, LiCl, 0 ºC, 45 min; (iii) allyl bromide, aq. NH_4Cl, 1 h, -20 ºC; (iv) $NaBH_4$, MeOH, 0 ºC, 15 min; (v) LiOH, THF, 25 ºC, 1h.

Substrates (**19a-h**) were effectively prepared from the corresponding aldehydes employing L-proline catalyzed amination and its sequential reactions following literature procedures[34] as shown in **Scheme 20**.

Example 1: The ^{1}H NMR spectrum of **19g** showed a typical singlet at δ 5.16 (s, 2H) due to benzylic protons (Ph-C**H**$_2$-O-) attached to oxygen atom and a multiplet at δ 3.96-4.37 (m, 3H) corresponding to methine and methylene protons attached to oxygen atom. Its ^{13}C NMR spectrum displayed two characteristic carbon signals at δ 157.3 and 155.3 due to the presence of carbonyl carbons and other signals at δ 67.8 and 67.0 corresponding to benzylic carbon (Ph-**C**H$_2$-O-) and methylene carbon (-**C**H$_2$-O-) attached to oxygen atoms respectively (**Fig. 12**). Its IR spectrum exhibited strong vibrational stretching frequencies at υ_{max} 1715 and 1705 cm^{-1} due to the presence of carbonyl functionalities.

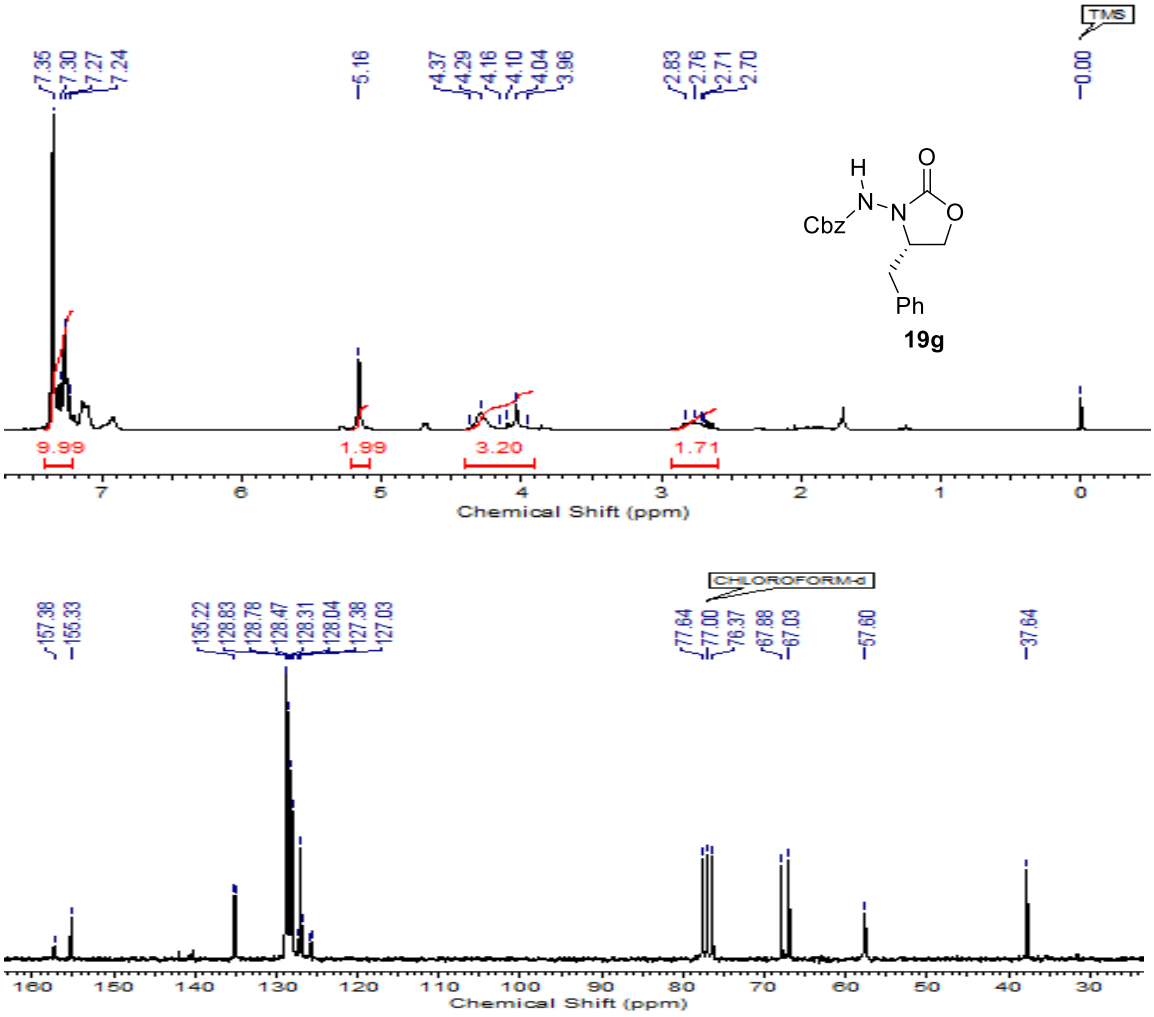


Fig. 12: ^{1}H and ^{13}C NMR spectra of **19g**

4.2.3.3 Mechanism

The catalytic cycle for Pd-catalyzed reductive N-N bond cleavage is shown in **Fig. 13** based on literature precedence.[36] The first step of catalytic cycle involves the reduction of $PdCl_2$ with PMHS to give active metallic Pd(0) species. This is followed by the oxidative addition of PMHS to Pd(0) leading to the formation of highly reactive species **I**. Pd(II) of species **I** co-ordinates with nitrogen atom of hydrazine to generate intermediate **II** followed by σ-bond migration that leads to formation of intermediate **III**. Subsequent reductive elimination of **III** regenerates active metal species Pd(0) for the next catalytic cycle along with free amine, which was *in situ* protected with Boc_2O present in medium to furnish the carbamate **20**.

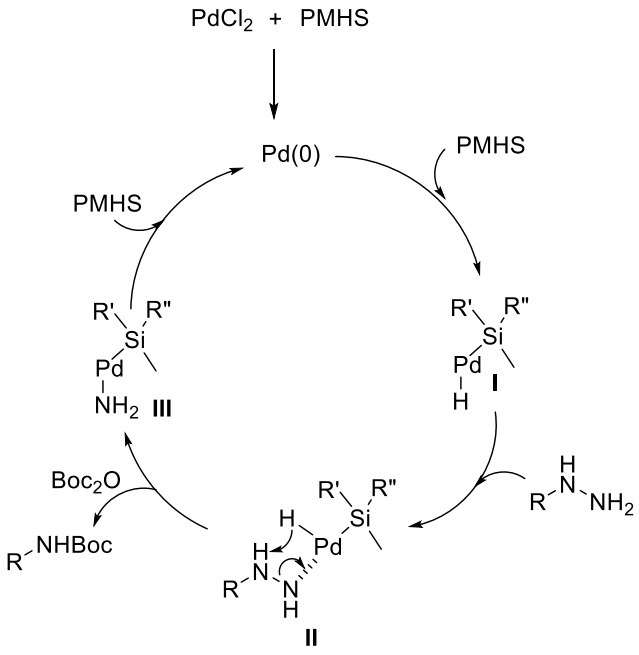


Fig 13: Proposed catalytic cycle for reductive N-N bond cleavage

4.2.4 Conclusion

In conclusion, we have demonstrated an efficient, environmental benign approach to cleave N-N bonds in dibenzyl hydrazides to furnish diverse free amine functionality, which can be

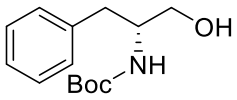
used as building blocks for drug synthesis. The use of polymethylhydrosiloxane (PMHS), an inexpensive, easy to handle, environmental benign reagent as reducing agent in our protocol makes it more viable than other reported methods.

4.2.5 Experimental Section

General experimental procedure for the reductive cleavage of N-N bond in *N,N*-dibenzyl alkylhydrazide-1,2-dicarboxylates

To a 10 mL one-neck round-bottomed flask with a magnetic stir bar was added *N,N*-dibenzyl hydrazides (**19a-h**) (0.5 g, 5 mmol) and Boc_2O (5 mmol) in deionized water/MeOH (1:1) (30 mL). To this was added PMHS (20 mmol) followed by catalyst $PdCl_2$ (5 mol %). The resulting mixture was stirred for 10 h at 25 ºC. After completion of the reaction, it was quenched by the addition of aqueous NaOH solution (10 mL) dropwise at 0 ºC and then stirred it for additional 3 h. The mixture was then extracted with EtOAc. The organic layer was further washed with brine (2 x 10 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) (4:1) as eluent to afford the pure carbamate compounds (**20a-h**).

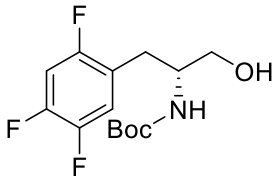
(*R*)-*tert*-Butyl -(1-hydroxy-3-phenylpropan-2-yl)carbamate (20a)



Yield: 0.24 g, 86%; **$[\alpha]_D^{25}$** -26.4 (*c* 1, MeOH) {lit.[20] $[\alpha]_D^{25}$ -27 (*c* 1, MeOH)}; **mp**: 96-98 ºC; **IR** ($CHCl_3$, cm^{-1}): 790, 1050, 1156, 1268, 1390, 1526, 1685, 2933, 2978, 3353, 3420; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.32 (br s, 1H), 2.82 (d, *J* = 7.2 Hz, 2H), 3.51-3.63 (m, 2H), 3.66-3.83 (m, 1H), 4.69 (br s, 1H), 7.19- 7.34 (m, 5H); **^{13}C NMR** (50

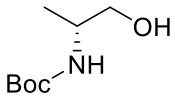
MHz, $CDCl_3$): δ 28.3, 37.4, 53.5, 63.7, 79.5, 126.4, 128.4, 129.3, 137.9, 156.0; **HRMS** (ESI): calc. for $[(C_{14}H_{21}NO_3)Na]$ $(M+Na)^+$ 274.1419; Found: 274.1416**.**

(*R*)-*tert*-Butyl (1-hydroxy-3-(2,4,5-trifluorophenyl)propan-2-yl)carbamate (20b)



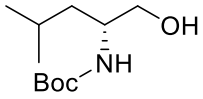
Yield: 0.27 g, 88%; **$[\alpha]_D^{25}$** +16.8 (*c* 1, $CHCl_3$); **mp**: 98-100 ^oC; **IR** ($CHCl_3$, cm^{-1}): 845, 956, 1128, 1410, 1526, 1712, 2853, 2908, 3441; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.1 (br s, 1H), 2.80-2.86 (t, *J* = 7.3 Hz, 2H), 3.59-3.67 (m, 2H), 3.78-3.84 (m, 1H), 4.77-4.84 (m, 1H), 6.88-6.94 (m, 1H), 7.09-7.11 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 30.2, 52.7, 64.2, 105.3 (dd, *J* = 20.2, 27.6 Hz), 119.0 (dd, *J* = 6.6, 10.2 Hz), 145.5 (ddd, *J* = 4.2, 5.7, 237.9 Hz), 147.5 (ddd, *J* = 3.5, 11.6, 250.5 Hz), 157.1 (ddd, *J* = 7.6, 10.2, 239.8 Hz); **HRMS** (ESI): calc. for $[(C_{14}H_{18}F_3NO_3)Na]$ $(M+Na)^+$ 328.1136; Found: 328.1132.

(*R*)-*tert*-Butyl-(1-hydroxypropan-2-yl)carbamate (20c)



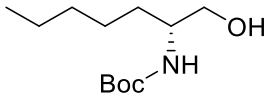
Yield: 0.17 g, 70%; gum; **$[\alpha]_D^{25}$** +7.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 606, 745, 1028, 1087, 1349, 1530, 1709, 2980, 3388; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.8 Hz, 3H), 1.45 (s, 9H), 3.43-3.88 (m, 4H), 4.64 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 17.4, 28.5, 51.4, 64.2, 79.7, 166.7; **HRMS** (ESI): calc. for $[(C_8H_{17}NO_3)H]$ $(M+Na)^+$ 176.1208; Found: 198.1205.

(*R*)-*tert*-Butyl-(1-hydroxy-4-methylpentan-2-yl)carbamate (20d)



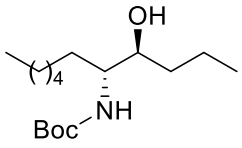
Yield: 0.19 g, 72%; gum; **[α]$_D^{25}$** +22.8 (*c* 1, $CHCl_3$) {lit.[35a] $[\alpha]_D^{25}$ +23 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 876, 985, 1113, 1264, 1727, 2990, 3112, 3256, 3326, 3430; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.93 (d, *J* = 6.6 Hz, 6H), 1.08-1.35 (m, 2H), 1.40-1.57 (m, 9H), 1.57-1.79 (m, 1H), 3.20-3.55 (m, 1H), 3.72-4.14 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.2, 23.3, 24.9, 28.5, 43.1, 49.7, 64.6, 80.0, 156.9; **HRMS** (ESI): calc. for $[(C_{11}H_{23}NO_3)Na]$ $(M+Na)^+$ 240.1576; Found: 240.1573.

(*R*)-*tert*-Butyl-(1-hydroxyheptan-2-yl)carbamate (20e)



Yield: 0.21 g, 76%; gum; **[α]$_D^{25}$** +17.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 796, 1085, 1150, 1284, 1456, 1727, 2956, 3110, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.83 (d, *J* = 5.8 Hz, 3 H), 1.25-1.38 (m, 7H), 1.42 (s, 9H), 1.46-1.55 (m, 1H), 3.43-3.56 (m, 1H), 3.56-3.67 (m, 2H), 4.78 (br s., 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.5, 25.7, 28.4, 31.7, 52.8, 65.7, 79.4, 156.5; **HRMS** (ESI): calc. for $[(C_{12}H_{25}NO_3)Na]$ $(M+Na)^+$ 254.1732; Found: 254.1729.

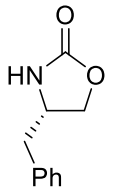
(4*R*,5*S*)-*tert*-Butyl-(5-hydroxyoctan-4-yl)carbamate (20f)



Yield: 0.2 g, 72%; colorless gum; **[α]$_D^{25}$** -27.3 (*c* 1, $CHCl_3$, cm^{-1}); **IR** ($CHCl_3$): υ_{max} 1245, 1279, 1329, 1435, 1718, 2910, 3125, 3315, 3445; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J*

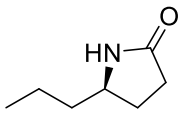
= 6.4 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H), 1.35-1.41 (m, 1H), 1.19-1.35 (m, 11H), 1.47 (br s, 9H), 1.50-1.66 (m, 3H), 2.61-2.75 (m, 1H), 2.80-3.04 (m, 1H), 3.72 (d, *J* = 9.2 Hz, 1H), 6.25 (br. s., 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 14.2, 19.8, 22.6, 26.3, 26.7, 28.3, 29.6, 31.7, 34.3, 65.1, 69.3, 81.1, 160.1; **HRMS** (ESI): calc. for $[(C_{13}H_{27}NO_3)Na]$ $(M+Na)^+$ 268.1889; Found: 268.1885.

(*S*)-4-Benzyloxazolidin-2-one (20g)



Yield: 0.21 g, 80%; yellow solid; **mp**: 86-88 ºC {lit. [35b] **mp**: 86-88 °C}; **$[\alpha]_D^{25}$** -62.8 (*c* 1, $CHCl_3$) {lit.[35b] $[\alpha]_D^{25}$ -63 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 876, 1105, 1275, 1443, 1523, 1701, 2918, 3102, 3112, 3325; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.80-2.95 (m, 2H), 4.04-4.20 (m, 2H), 4.39-4.53 (m, 1H), 5.37-5.63 (m, 1H), 7.15-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 41.3, 53.7, 69.5, 127.2, 128.9, 129.0, 135.9, 159.5; **HRMS** (ESI): calc. for $[(C_{10}H_{11}NO_2)Na]$ $(M+Na)^+$ 200.0687; Found: 200.0684.

(*R*)-5-Propylpyrrolidin-2-one (20h)



Yield: 0.106 g, 76%; colorless solid; **mp**: 46-48 °C {lit.[35c] **mp**: 48-50 °C}; **$[\alpha]_D^{25}$** -52.3 (*c* 1, $CHCl_3$); **IR (**$CHCl_3$, cm^{-1}): υ_{max} 859, 1020, 1298, 1465, 1567, 1623, 1716, 3013, 3250, 3356; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (m, *J* = 7.2 Hz, 3H), 1.28-1.73 (m, 3H), 1.45-1.54 (m, 1H), 1.60-1.69 (m, 1H), 2.14-2.25 (m, 1H), 2.26-2.32 (m, 2H), 3.61 (q, *J* = 6.4

Hz, 1H), 7.43-7.66 (m, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 19.2, 27.3, 30.4, 39.0, 54.6, 178.6; **HRMS** (ESI): calc. for $[(C_7H_{13}NO)Na]$ $(M+Na)^+$ 150.0895; Found: 150.0892.

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1. Synthesis of the anti-influenza agent (-)-Oseltamivir free base and (-)-methyl-3-epi-shikimate, Rawat, V.; **Dey, S.**; Sudalai, A. *Org. Biomol. Chem*. **2012**, *10*, 3988. {This work is highlighted in **Synfacts 2012**, 8, 0001; DOI: 10.1055/s-0032- 1316977}.
2. A concise enantioselective synthesis of (*R*)-selegiline, (*S*)-benzphetamine and formal synthesis of (*R*)-sitagliptin *via* electrophilic azidation of chiral imide enolates **Dey, S.**; Sudalai, A. *Tetrahedron: Asymmetry* **2015**, *26*, 67.
3. A concise enantioselective synthesis of marine macrolide-stagonolide E via organocatalysis **Dey, S.**; Sudalai, A. *Tetrahedron: Asymmetry* **2015**, *26*, 344.
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