Enantioselective synthesis of bioactive molecules *via* organocatalysis and synthetic methodologies on C-C, C-N bond formations

Thesis Submitted to 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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June 2017

DEDICATED TO
MY BELOVED FAMILY

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AND

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules via Organocatalysis and Synthetic Methodologies on C-C, C-N Bond Formations"*** submitted by *Mr.* ***Anil Maruti Shelke*** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the degree of ***Doctor of Philosophy* in *Chemical Sciences***, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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DECLARATION

I hereby declare that the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules via Organocatalysis and Synthetic Methodologies on C-C, C-N Bond Formations"*** 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.

June, 2017
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CONTENTS

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I would like to express my sincere gratitude to my PhD supervisor ***Dr. Gurunath Suryavanshi*** *for his advice during my doctoral research endeavor for the past six and half years. As my supervisor, he has constantly forced me to remain focused on achieving my goal. His observations and comments helped me to establish the overall direction of the research. I thank him for providing me the personal freedom and opportunity to work with a talented team of researchers. I am especially grateful for his devotion to his student's research and success. I have not heard of another mentor who goes so far out of his/her ways to make sure students are prepared for whatever the next step in their journeys may be. His discipline, principles, simplicity, caring attitude, criticism and provision of fearless work environment will be helpful to grow as a chemist. His constant effort to instill us with several most essential habits, like weekly seminars, group meetings and daily planning, made me confident to start an independent scientific career and hence I preserve an everlasting gratitude for him. I am certain that the ethics and moral values which I learnt from him will go a long way in making me a better human being.*

I thank Dr. S. S. Tambe, Head, CE-PD division, for their help and support. I want to highly acknowledge Dr. A. Sudalai for his constant enthusiasm. I also thank the DAC members Dr. Thirumalaiswamy Raja, Dr. C. V. Ramanna, and Dr. Asish Kumar Bhattacharya *for evaluation of my research work. It's my privilege to thank the Director, CSIR-NCL for giving me this opportunity and providing all necessary infrastructure and facilities. I specially thank UGC, New Delhi for the JRF and SRF fellowship.*

I thank NMR group Dr. P. R. Rajmohan, Mr. Dinesh Shinde, elemental analysis group Dr. B. Santhakumari, X-ray Crystallography group Dr. Rajesh Gonnade and Mr. Shridhar Thorat for their help in obtaining the analytical data. I thank the library staff, chemical stores & purchase staff and glass blowing section staff of NCL for their cooperation. I also thank Dr. Dr. M. S. Shashidhar, Dr. Chetan Gadgil, Ms. Kolhe, Miss. Komal and Miss. Vaishali Student Academic Office at NCL for their help in verifying all my documents. I thank PD office staff Mr. Bhosale, Mr. Kakade and Suresh Kaka for their cooperation.

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I am thankful to my teachers from School and College for their inspirational teaching, ethics and discipline. I sincerely thank Prof. ***G.C.Kulkarni,*** *for his constant encouragement and support during M.Sc to succeed in NET examination.*

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No word would suffice to express my gratitude and love to my mother ***Janabai*** *for her struggle, patience, sacrifices a main inspiration of my life, also, my brother* ***Sandip,*** *vahini (****Manjushree****),* ***Ram****,* ***Piyush****,* ***Yash*** *and sisters* ***Shobha*** *and* ***Manisha*** *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 best friend-cum-soulmate ***Swati*** *for her love, dedication, patience and encouragement throughout my career.*

I wish to thank the great scientific community whose constant encouragement source of inspiration for me.

I would like to say thank you to all the peoples who came in to my life and made it outstanding, and also to all the people who walked out of my life and made it fantastic!

Above all, I thank God Almighty for His enormous blessings.

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

Anil M. Shelke

June 2017

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
Bz	Benzoyl
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
Cbz	Benzyloxy carbonyl
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutyl aluminium hydride
DMP	Dess–Martin periodinane
DMF	Dimethyl formamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulphoxide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
g	Grams
h	Hours
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
imid.	Imidazole
IR	Infra red
IBX	2-Iodoxybenzoic acid
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
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, app = apparent.
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 *via* Organocatalysis and Synthetic Methodologies on C-C, C-N Bond Formations

Research Student: **Anil Maruti Shelke**

AcSIR Roll: **10CC11J26092**

Research Guide: **Dr. Gurunath Suryavanshi**

The thesis entitled **"Enantioselective Synthesis of Bioactive Molecules *via* Organocatalysis and Synthetic Methodologies on C-C, C-N Bond Formations''** is divided into four chapters. The title of the thesis clearly reflects the objective, which is to utilize organocatalyzed reactions for the enantioselective synthesis of bioactive molecules and develop useful synthetic methodologies which involve new C-C, C-N bond formation reactions. **Chapter I** deals with the enantioselective total synthesis of (+)-Oxybiotin, 3-*epi*-Jaspine B *via* intramolecular tandem desilylation oxa-michael addition reaction and Stagonolide C using organocatalytic *α*-aminooxylation and Jorgenson's epoxidation strategy. **Chapter II** describes the total synthesis of Stagonolide F by employing an organocatalytic *α*-aminooxylation and asymmetric epoxidation strategy and formal synthesis of Pinolide *via* L-proline-catalyzed sequential *α*-aminooxylation and Horner-Wadsworth-Emmons olefination-Sharpless asymmetric dihydroxylation strategy. **Chapter III** deals with the synthesis of 3,3'-spiro-phosphonylpyrazole-oxindole skeleton *via* [1,3]-dipolar cycloaddition reaction of Bestmann-Ohira reagent with

Methyleneindolinones. **Chapter IV** describes the fluoride-assisted synthesis of 1,4,5,6-tetrahydropyridazines *via* [4+2] cyclodimerization of in situ-generated azoalkenes followed by a C-N bond cleavage and synthesis of 1,4-dihydrocinnolines *via* [4+2] cycloaddition of in situ-generated 1,2-diaza-1,3-dienes with arynes.

Introduction

In recent years, particularly, in the field of pharmaceuticals, enantiomeric synthesis is one of the key processes. Over the past decades, enantioselective syntheses of various bioactive natural and derivatized molecules have been reported using novel chemical reactions such as organocatalyzed reaction,[1a] transition metal catalysis,[1b] chiral epoxidation[1c] and classical and kinetic resolution.[1d] The present research work deals with the asymmetric synthesis of various bioactive molecules such as (+)-Oxybiotin,[2] 3-*epi*-Jaspine B,[3] (+)-Stagonolide C,[4] (+)-Stagonolide F[5] and Pinolide[6] using organocatalyzed α-aminooxylation, Jorgensens epoxidation of aldehydes, Sharpless asymmetric dihydroxylation and L-proline catalyzed sequential α-aminooxylation-HWE olefination reactions as the key reactions. The 3,3′-spiro-oxindoles are valuable structural cores present in many natural alkaloids and pharmacological agents and exhibit interesting structural as well as biological properties.[7] We have developed a new, one pot methodology for the synthesis of 3,3′-spiro-phosphonylpyrazole-oxindole (**3a-n**).[8] 1,4,5,6-Tetrahydropyridazines and pyridazines are important six-membered aza-heterocycles widely present as core structures in a large number of natural products.[9a] We have demonstrated a simple and facile transformation of α-halo N-acylhydrazones (**1a-o**, **4a-o**) into highly functionalized 1,4,5,6-tetrahydropyridazines (**2a-o**, **5a-o**) in excellent yields.[9b] Also,

we have developed a very mild method for the synthesis of 1,4-Dihydrocinnoline derivatives (**3a-j**) from α-halo N-tosyl hydrazones (**1a-j**) and arynes.

Statement of Problem

The interesting biological activities of these molecules have attracted many research groups. However, the reported synthesis of these bioactive molecules suffer from disadvantages such as lengthy reaction sequences including the protection and deprotection of various functional groups, use of chiral auxiliaries, enzymatic resolution, expensive organometallic reagents and poor atom economy, etc. Hence, the need for a short and catalytic method for their synthesis from commercially available materials with high diastereo- and enantioselectivity is of current interest.

Methodology used

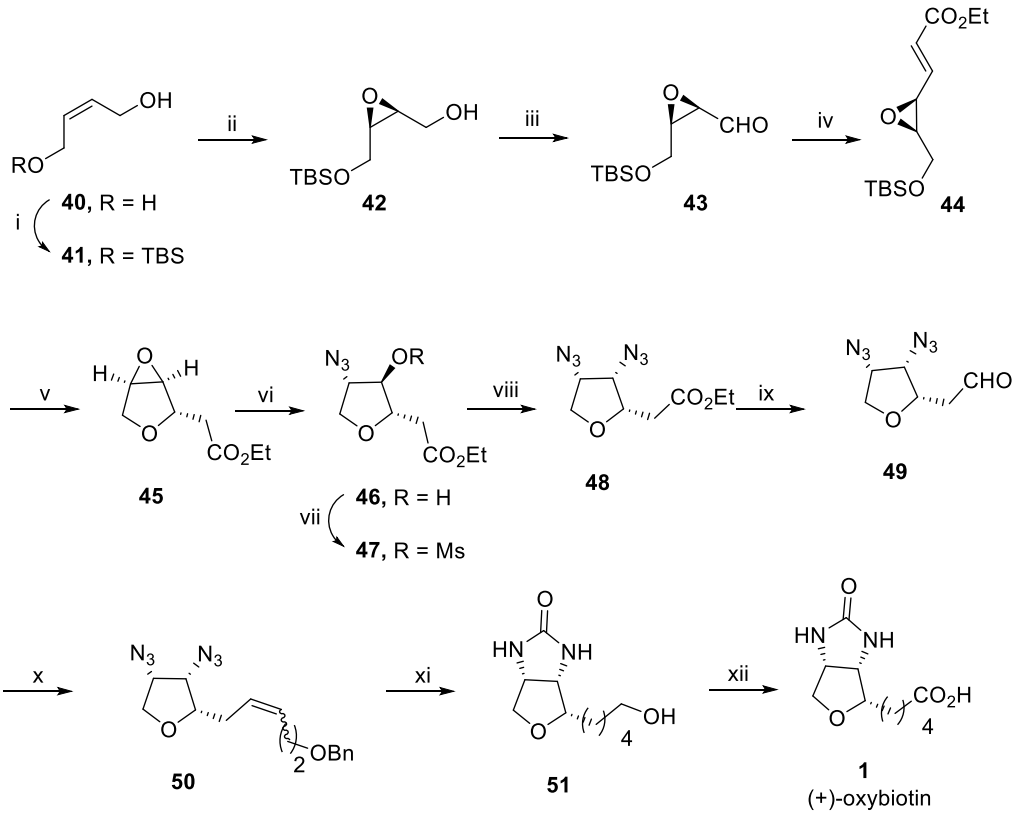
1. Several biologically important molecules have been synthesized and characterized by advanced analytical and spectroscopic techniques such as NMR (^{1}H & ^{13}C), FT-IR, LC-MS and HRMS.
2. The structure and regioslectivity of final products were confirmed by Single Crystal X-ray analysis and NOESY NMR studies. The optical purity of chiral intermediates and final molecules was determined from chiral HPLC analysis and by comparing their specific rotation with those reported in the literature.

CHAPTER I

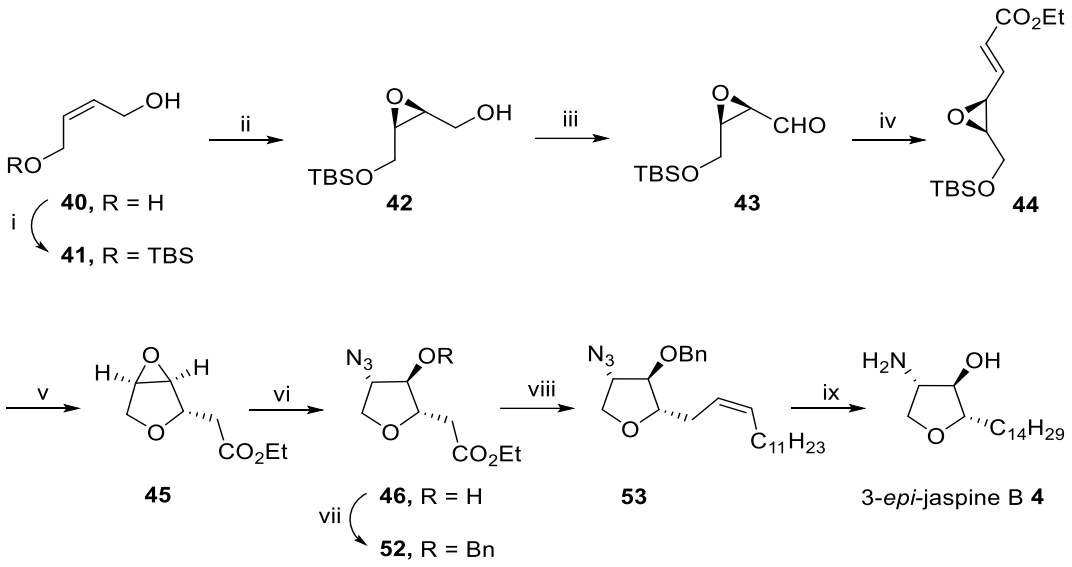
Enantioselective Total Synthesis of (+)-Oxybiotin, 3-*epi*-Jaspine B and Stagonolide C

In this chapter, total synthesis of (+)-Oxybiotin **1** and 3-*epi*-Jaspine B **4** is described *via* Sharpless asymmetric epoxidation and a novel tendem desilylation oxa-michael addition

reaction starting from readily available cis-2-butene-1,4-diol with excellent diastereo- and enantioselectivity. The method comprises operationally simple reactions with fewer steps, high overall yields with the use of inexpensive & non toxic reagents.

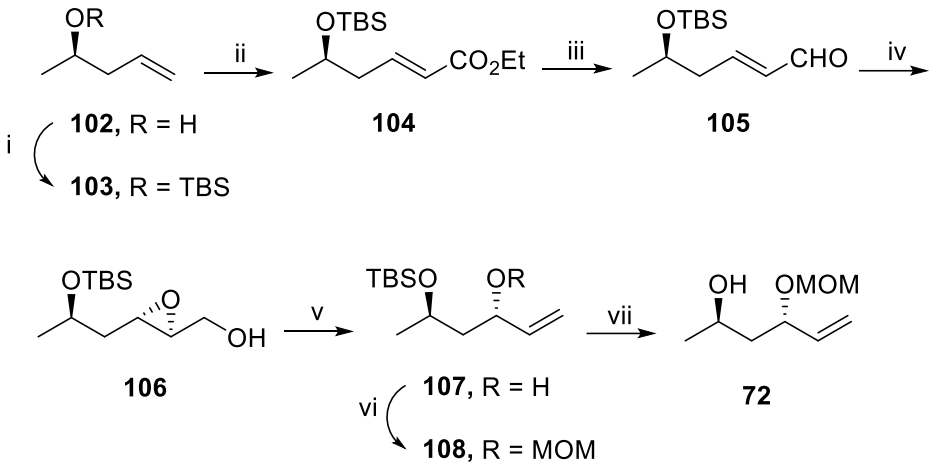


Scheme 1: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (+)-DET, $Ti(O^iPr)_4$, anhydrous TBHP (5-6 M in decane), 4 Å molecular sieves, dry CH_2Cl_2, -10 ºC, 12 h, 93%; (iii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (iv) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, 25 ºC, 2 h, 92%; (v) TBAF, THF, 25 ºC, 2 h, 93%, de > 99%; (vi) NaN_3, NH_4Cl, $EtOH/H_2O$ (4:1), 80 ºC, 12 h, 91%; (vii) MsCl, NEt_3, CH_2Cl_2, 0 ºC, 1 h; (viii) NaN_3, DMF, 120 ºC, 24 h, 75%; (ix) DIBAL-H, toluene, -78 ºC, 1 h; (x) KO^tBu, $BnO(CH_2)_3P^+Ph_3I^-$, THF, 0 ºC, 75%; (xi) H_2 (1 atm.), 10% Pd/C, MeOH, 25 ºC, 24 h, then $(Cl_3CO)_2CO$, Et_3N, CH_2Cl_2, 0 ºC, 2 h, then rt, 20 h, 76%; (xii) TEMPO/BAIB in $CH_3CN{:}H_2O$ (4:1), 25 ºC, 4 h, 99%.

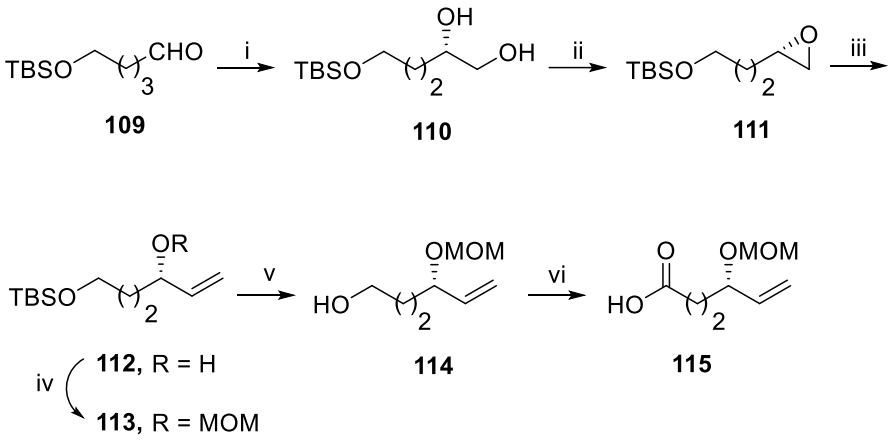


Scheme 2: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (+)-DET, $Ti(O^iPr)_4$, anhydrous TBHP (5-6 M in decane), 4 Å molecular sieves, dry CH_2Cl_2, -10 ºC, 12 h, 93%; (iii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (iv) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, 25 ºC, 2 h, 92%; (v) TBAF, THF,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

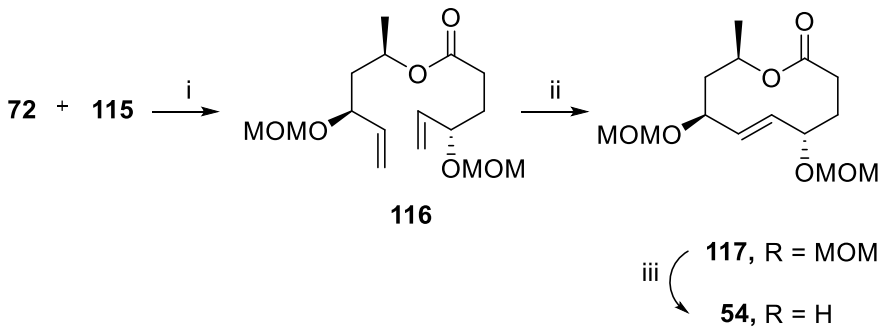
The second section includes the use of organocatalytic α-aminooxylation and Jorgensen's epoxidation strategy for the concise synthesis of important fungal metabolite namely (+)-Stagonolide C **54** (17% overall yield; 96% ee) The operationally simple reactions with less number of steps, high overall yields requiring a relatively low amount of inexpensive and non-toxic proline as catalyst make this approach an attractive and useful route (**Scheme 3, 4 & 5**).



Scheme 3: (i) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 6 h, 76% (ii) ethyl acrylate, Grubbs-II (2 mol%), dry CH_2Cl_2, reflux, 12 h, 65%; (iii) DIBAL-H, toluene, -78ºC, 1h, 73%; (iv) H_2O_2, CH_2Cl_2, (10 mol%) 2[bis(3,5bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine, 25 ºC, 4 h then $NaBH_4$, MeOH, 0 ºC,1 h, 53%; (v) (a) I_2, PPh_3, imid., Et_2O/CH_3CN (3:1), 0-25 ºC, 2 h; (b) Zn, NaI, MeOH, reflux, 3 h, 90% (for two steps); (vi) MOMCl, DIPEA, dry CH_2Cl_2, 16 h, 90%; (vii) TBAF, THF, 2 h, 82%.



Scheme 4: (i) (a) PhNO (1 equiv.), D-proline (20 mol %), CH_3CN, -20 ºC, 24 h then $NaBH_4$, MeOH, 0 ºC,1 h; (b) 10% Pd/C, H_2, MeOH, 24 h, 77% (over two steps); (ii) (a) TsCl, Et_3N, Bu_2SnO, DMAP; (b) K_2CO_3, MeOH, 30 min., 92%; (iii) $S^+(CH_3)_3I^-$, NaH, DMSO, 25 ºC. 2 h, 87%; (iv) MOMCl, DIPEA, dry CH_2Cl_2, 16 h, 90%; (v) TBAF, THF, 2 h, 88%; (vi) TEMPO, $PhI(OAc)_2$, CH_3CN: H_2O (4:1), 25 ºC, 4 h, 86%.

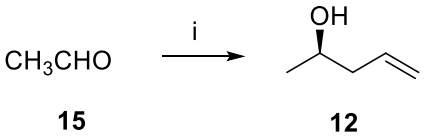


Scheme 5: (i) EDCI·HCl, Et_3N, DMAP, CH_2Cl_2, 0-25 ºC, 6 h, 86%; (ii) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 24 h, 62%; (iii) Me_3SiBr, CH_2Cl_2 , -40 ºC, 6 h, 76%.

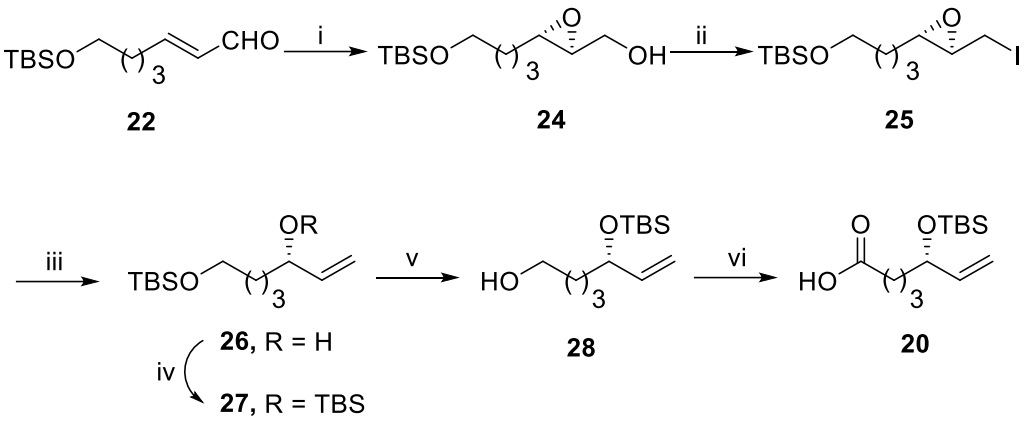
CHAPTER II

Total Synthesis of Stagonolide F and Formal Synthesis of Pinolide

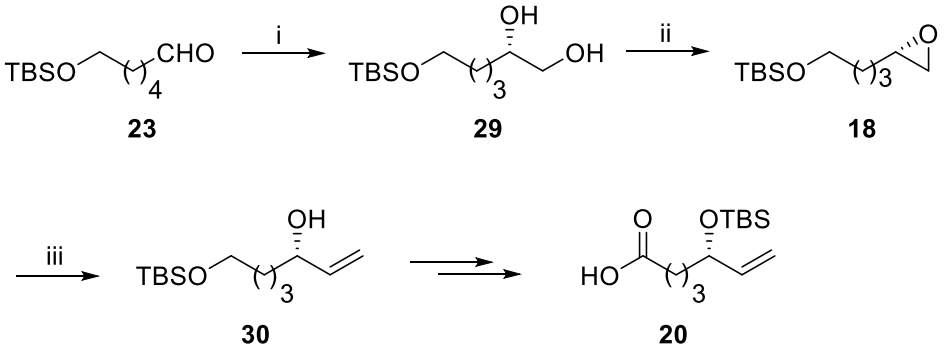
This chapter describes a concise and convergant approach for the total synthesis of (+)-Stagonolide F **1** in a highly stereoselective manner by employing an organocatalytic *α*-aminooxylation and asymmetric epoxidation strategy with an enantiomeric excess of 98% in 10.1% overall yield. The synthetic strategy described herein has significant potential for further extention to other decanolides-based bioactive molecules (**Scheme 6, 7, 8 & 9**).



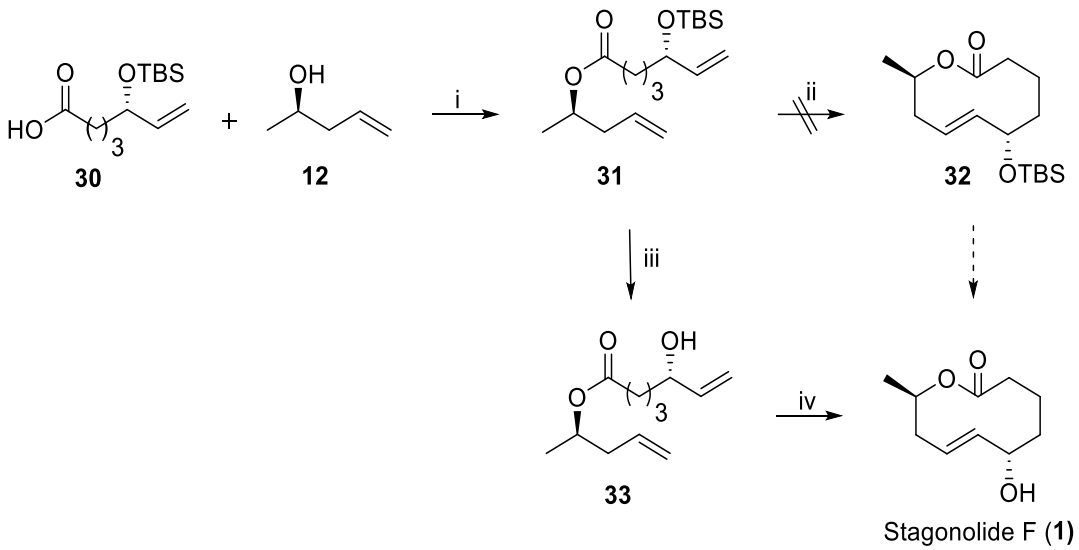
Scheme 6: (i) (-)-*B*-allyldiisopinocamphenylborane, Et_2O-pentane, -78 °C, 1 h, NaOH, aq. 35% H_2O_2, 77%, 95% ee.



Scheme7: (i)H_2O_2,CH_2Cl_2, (*R*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol tri-methylsilyl ether (**A**), 25 ºC, 4 h then $NaBH_4$, MeOH, 0 ºC, 10 min, 43%, 99% ee; (ii) I_2, PPh_3, imid., Et_2O/CH_3CN (3:1), 0-25 ºC, 2 h, 90%; (iii) Zn, NaI, MeOH, reflux, 3 h, 90%; (iv) TBSCl, imidazole, CH_2Cl_2, 0-25 ºC, 6 h, 86%; (v) (+)-camphor-10-sulfonic acid, MeOH, 25 ºC, 5 min, 63%; (vi) TEMPO, $PhI(OAc)_2$, CH_3CN:H_2O (4:1), 25 ºC, 4 h, 80%.

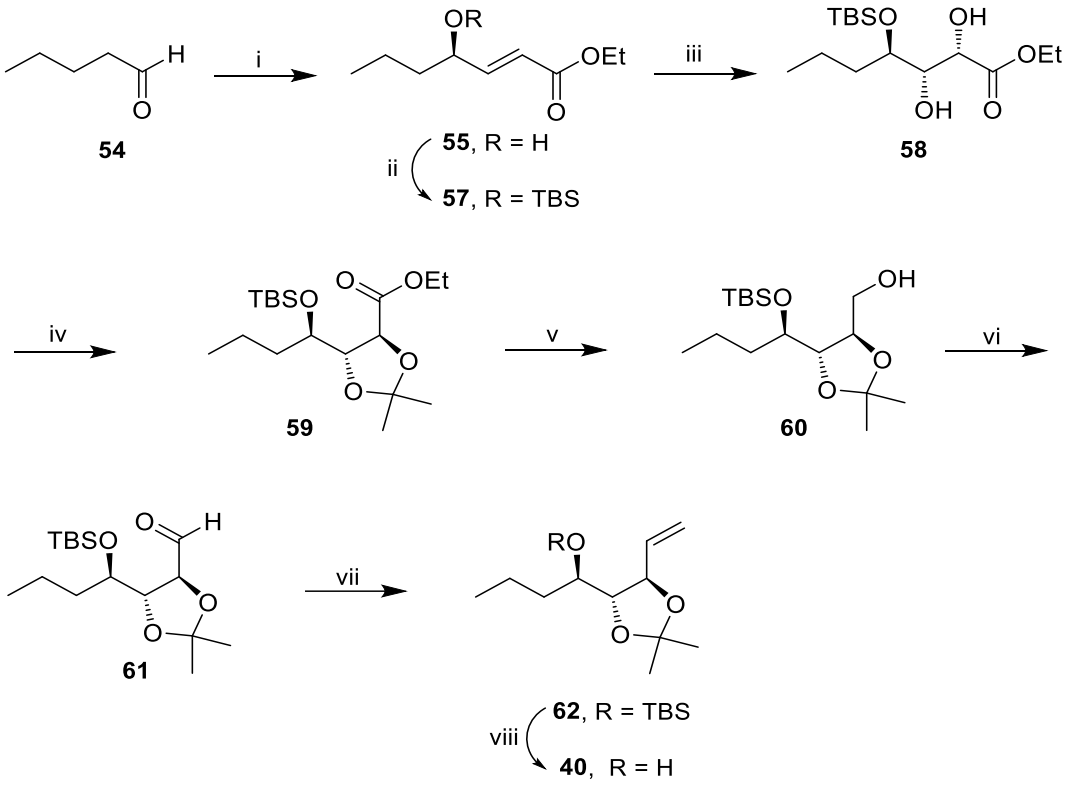


Scheme 8: (i) (a) PhNO (1 equiv.), D-proline (20 mol%), CH_3CN, -20 ºC, 24 h then $NaBH_4$, MeOH, 0 ºC, 10 min; (b) 10% Pd/C, H_2, MeOH, 24 h, 77% (over two steps); (ii) (a) TsCl, Et_3N, Bu_2SnO, DMAP; (b) K_2CO_3, MeOH, 30 min., 92% (over two steps); (iii) $S^+Me_3I^-$, NaH, DMSO, 0 ºC, 2 h, 89%.

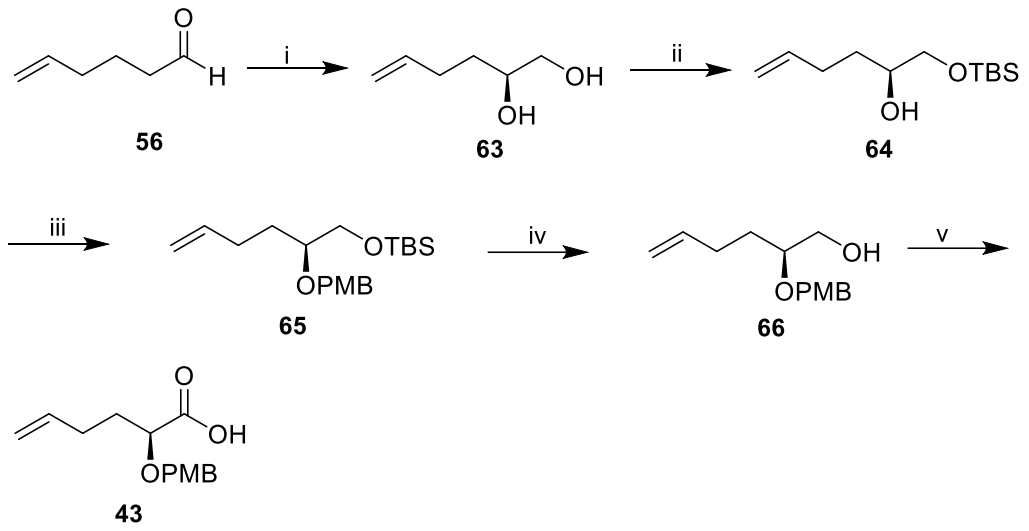


Scheme 9: (i) EDCI·HCl, Et_3N, CH_2Cl_2, 25 ºC, 6 h, 88%; (ii) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 48 h (iii) TBAF, THF, 0 ºC, 2 h, 80% (iv) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 24 h, 69%.

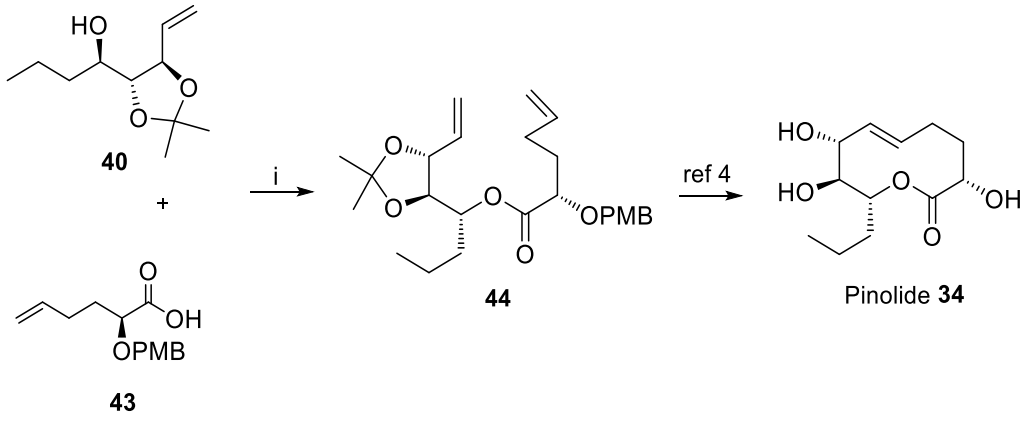
In the second section, we have achieved an efficient formal enantioselective synthesis of Pinolide **34** by employing L-proline catalyzed sequential *α*-aminooxylation-HWE olefination reaction of the respective *n*-valeraldehyde and Sharpless asymmetric dihydroxylation strategy as the key reactions for the induction of chirality. The operationally simple reactions with less no. of steps, high overall yields, requiring a relatively low amount of inexpensive and non-toxic proline as the catalyst make this approach an attractive and useful route (Scheme **10**, **11** and **12**).



Scheme 10: Reagents and conditions: (i) (a) PhNO, L-proline (20 mol%),CH_3CN, -20 °C, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h; (b) $CuSO_4.5H_2O$ (30 mol%), MeOH, 25 °C, 12 h, 77%, 99% *ee*; (ii) TBSCl, imid., CH_2Cl_2, 0–25 °C, 3 h, 98%; (iii) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), $K_2OsO_4.2H_2O$ (0.2 mol%), 0 °C, 5 h, 86%, (*dr*=3:1); (iv) 2,2 dimethoxypropane, cat. CSA, CH_2Cl_2, rt, 12 h, 96%; (v) $LiAlH_4$, THF, 0-5 °C, 1 h, 93%; (vi) IBX, EtOAc, 80 °C, 2 h, 86%; (vii) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, 0 °C, 1 h, 75%; (viii) TBAF, THF, 0-25 °C, 2 h, 82%.



Scheme 11: Reagents and conditions: (i) (a) PhNO, D-proline (20 mol%), CH_3CN, -20 °C, 24 h then MeOH, $NaBH_4$, 20 min.; (b) $CuSO_4.5H_2O$ (30 mol%), MeOH, 0 °C, 12 h, 87% (over two steps), 99% *ee*; (ii) TBSCl, imid., CH_2Cl_2, 0–25 °C, 2 h, 96%; (iii) PMB imidate, PTSA (cat), dry CH_2Cl_2, 0 °C to rt, 8h, 90%; (iv) CSA, MeOH, 25 °C, 30 min, 63%; (v) TEMPO, $PhI(OAc)_2$, CH_3CN: H_2O (4:1), 25 °C, 4 h, 86%.

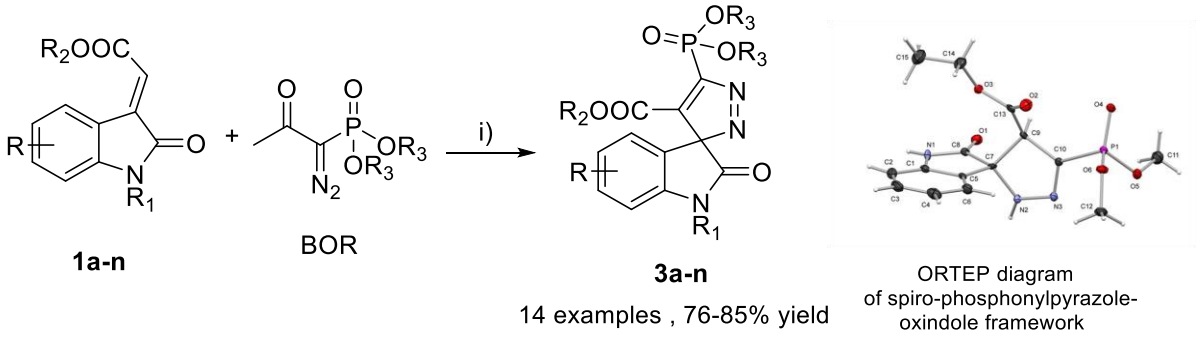


Scheme 12: Reagents and conditions: (i) EDCI·HCl, Et_3N, DMAP, CH_2Cl_2, 0-25 °C, 6 h, 88%.

CHAPTER III

Synthesis of 3,3'-Spiro-phosphonylpyrazole-oxindole Skeleton *via* [1,3]-Dipolar Cycloaddition Reaction of Bestmann-Ohira Reagent

In this chapter, a simple one pot, highly efficient and completely regioselective synthesis of 3,3′-spiro-phosphonylpyrazole-oxindoles **3a-n** has been reported *via* base mediated 1,3-dipolar cycloaddition reaction between methyleneindolinones (**1a-n**) and Bestmann-Ohira reagent (BOR) (**Scheme 13**).



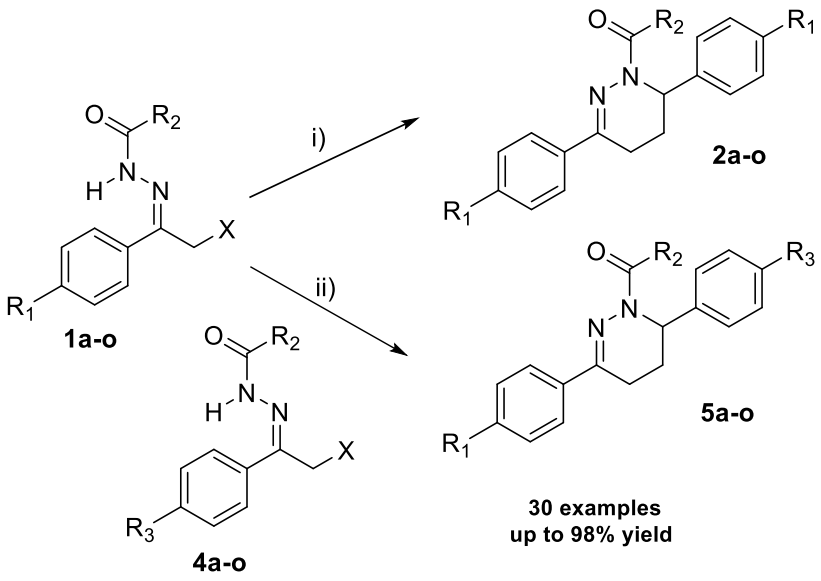
Scheme 13: (i) **1a-1n** (0.1 mmol), BOR (0.2 mmol), KOH (0.2 mmol), MeOH, rt, 10 min., 76-85%.

CHAPTER IV

Synthesis of 1,4,5,6 Tetrahydropyridazines and 1,4-Dihydrocinnolines *via* [4+2] Cyclodimerization of in Situ Generated Azoalkenes

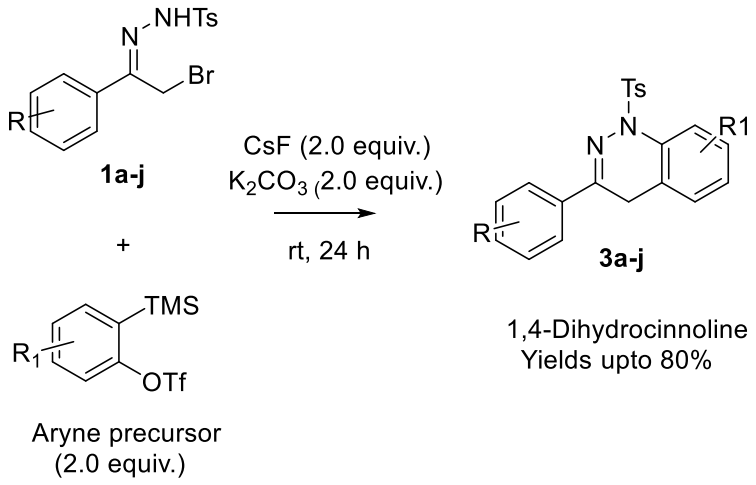
This chapter describes an unexpected CsF-assisted C-N bond cleavage to synthesize highly functionalized and biologically important 1,4,5,6-tetrahydropyridazine derivatives **2a-o** and **5a-o** from α-halo N-acyl hydrazones **1a-o** in excellent yields. The extrusion of nitrogen and the [4+2] cycloaddition between in *situ* generated azoalkenes is a key reaction in the process. The identified methodology is suitable for synthesizing a wide variety of

analogues of tetrahydropyridazines, which are prevalent in many medicinally important small molecules. The reaction conditions are mild, high yielding and amenable for the gram scale (**Scheme 14**).



Scheme 14: (i) **1a-o** (0.5 mmol), K_2CO_3 (1.0 mmol), CsF (1.0 mmol), CH_3CN (dry, 3 mL), rt 24 h; (ii) **1a-o** (0.5 mmol), **4a-o** (0.25 mmol), (K_2CO_3 (1.0 mmol), CsF (1.0 mmol), CH_3CN (dry, 3 mL) rt, 24 h.

Further, we have developed a simple and mild method for the synthesis of 1,4-dihydrocinnoline derivatives (**3a-j**) from α-halo N-tosyl hydrazones (**1a-j**) and arynes via [4+2] cycloaddition of in Situ generated 1,2 diaza-1,3-dienes (**Scheme 15**).



Scheme 15: Synthesis of 1,4-Dihydrocinnoline derivatives from α-halo N-acyl hydrazones.

References:

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CHAPTER I

Enantioselective Total Synthesis of (+)-Oxybiotin, 3-*epi*-Jaspine B and Stagonolide C

1. "A short enantioselective synthesis of 3-*epi*-jaspine B and (+)-oxybiotin *via* an intramolecular tandem desilylation oxa-Michael addition strategy" **Shelke, A. M.;** Rawat, V.; Sudalai, A.; Suryavanshi, G., *RSC Advances* **2014**, *4*, 49770.

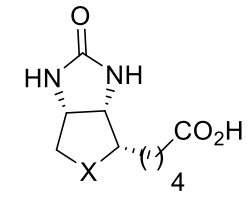
2. "Asymmetric synthesis of (+)-stagonolide C and (-)-aspinolide A *via* organocatalysis" **Shelke, A. M.;** Rawat, V.; Sudalai, A.; Suryavanshi, G., *Tetrahedron: Asymmetry* **2012**, *23*, 1534.

Section I

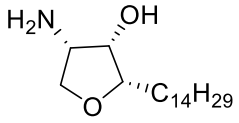
A Short Enantioselective Synthesis of (+)-Oxybiotin and 3-*epi*-Jaspine B *via* an Intramolecular Tandem Desilylation Oxa-Michael Addition

1.1.1 Introduction and Pharmacology

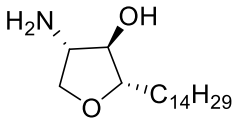
Oxybiotin (**1**), the oxygenated analogue of biotin in which an oxygen atom replaces sulfur, was synthesized by Hofmann[1] and shown to exhibit a high biotin-like growth stimulatory activity towards some microorganisms.[2] Like biotin (**2**) itself, oxybiotin supports the growth of some microorganisms whereupon it has been confirmed that the analogue is not converted to biotin in vivo. Poly-substituted tetrahydrofurans (THFs) represents an important class of five-membered heterocycles that can be found as structural elements of many natural products and pharmaceutically important substances.[3] Tri-substituted THFs like 3-*epi*-jaspine B **4** (**Figure 1**) and its stereoisomers have shown remarkable cytotoxic activity against A549 human lung carcinoma cell lines (LD_{50} = 1.50 ±0.03 μM) and MCF7 primary breast cancer cells (IC_{50} = 1.50 ±0.03 μM).[4]



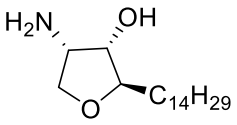
X = O; (+)-Oxybiotin (**1**)
X = S; (+)-Biotin (**2**)



Jaspine B (**3**)



3-*epi*-Jaspine B (**4**)



2-*epi*-Jaspine B (**5**)

Figure 1: Structure's of some of the bioactive molecules

It was initially believed that 3-*epi*-jaspine B **4** and its stereoisomers inhibit sphingomyelin synthase and thus increases the intracellular ceramide level, inducing apoptotic cell death by a caspase dependent pathway.[4] Toxic effects of **4** were investigated by flow cytometry analysis after double labelling with annexin V (AV) and propidium iodide (PI). The results on A549 cells cultured in the presence of **4** at different concentrations as well as control experiments indicated that the percentage of AV-stained cells (2%) was not significantly increased. Finally, a concentration-dependent increase in the percentage of PI positive cells were observed in all cases.[4,5] These results demonstrate that apoptosis only accounts for a minor percentage of cell death and therefore, a different cell death mechanism must be implicated.[5]

1.1.2 Review of literature

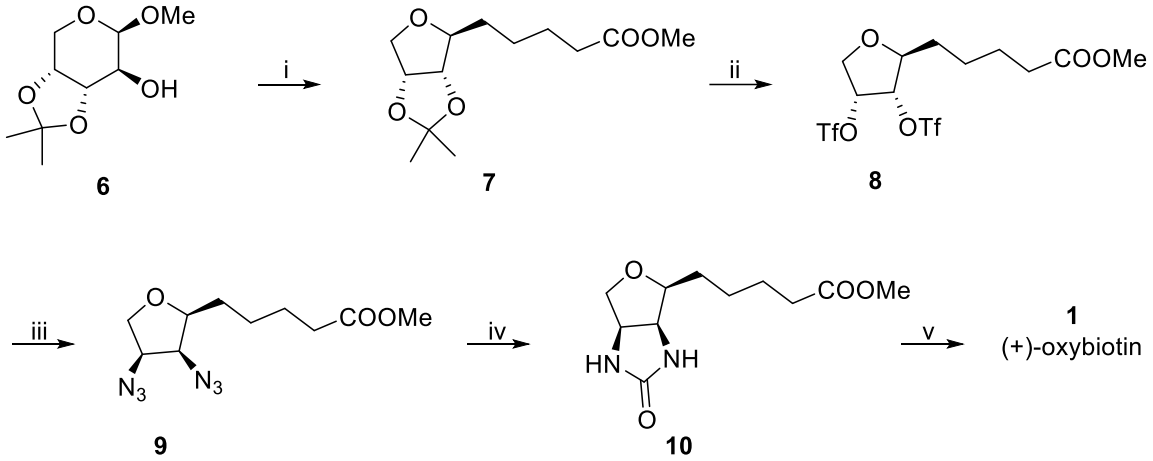
(a) Review of literature of (+)-oxybiotin

Few approaches have been reported in the literature for the synthesis of (+)-oxybiotin, most of which are based on the chiral pool strategies. A few interesting and recent synthesis of (+)-oxybiotin (**1**) are described below.

Popsavin's approach (2002)[6]

Popsavin *et al* have reported the synthesis of (+)-oxybiotin (**1**) from known methyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside **6** which on treatment with triflic anhydride followed by a Wittig reaction with 3-(methoxycarbonyl)-2-propenylidene triphenylphosphorane and catalytic hydrogenation gave the saturated ester **7** as an inseparable mixture of *E*- and *Z*-isomers. Hydrolytic removal of the isopropylidene protective group in **7** gave an excellent yield of the expected diol which on treatment with triflic anhydride in pyridine gave the corresponding 3,4-ditriflate **8**. Subsequent treatment

of **8** with sodium azide in HMPA afforded the corresponding 3,4-diazido derivative **9**. Reduction of diazide derivative **9** over PtO_2 in dichloromethane followed by in-Situ carbonyl insertion with triphosgene gave the imidazolidinone **10** in 66% yields. Treatment of **10** with an aqueous solution of sodium hydroxide followedby neutralization with Amberlyst 15, gave an almost quantitative yield of (+)-oxybiotin (**1**).

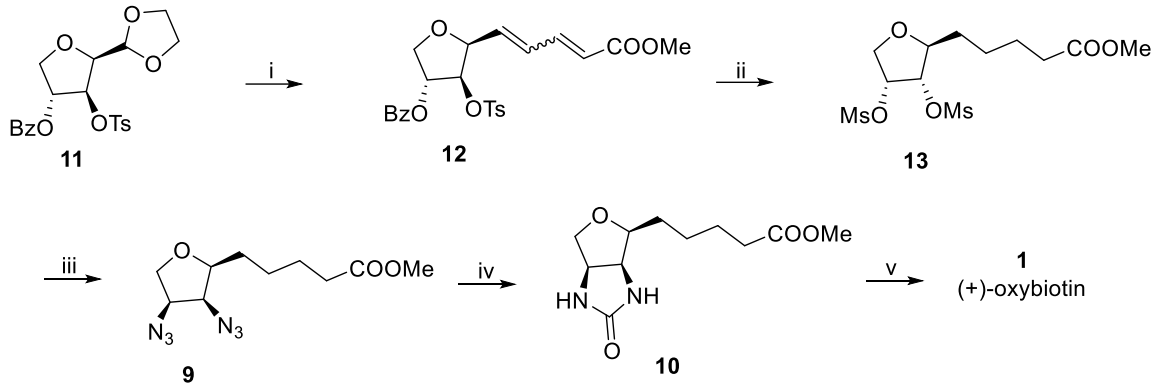


Scheme 1: (i) (a) Tf_2O, Py, CH_2Cl_2, -10 °C, 0.5 h; (b) KOBz, DMF, rt, 24 h, 99% from **6**; (c) MeONa, MeOH, rt, 1.5 h; (d) Ph_3P:CHCH:$CHCO_2Me$, MeOH, rt, 1.5 h; (e) H_2, PtO_2, MeOH, rt, 24 h, 88%. (ii) (a) 9:1 TFA-H_2O, rt, 0.5 h, 95%; (b) Tf_2O, Py, CH_2Cl_2, 0 °C, 1.5 h; (iii) NaN_3, HMPA, rt, 1.5 h; (iv) H_2, PtO_2, CH_2Cl_2, rt, 24 h, then $(Cl_3CO)_2CO$, Et_3N, 0 °C, 2 h, rt 22 h, 66%; (v) NaOH, H_2O, 100 °C, 1 h, then Amberlyst 15, rt, 0.5h, 99%.

Popsavin's second approach (2002)[7]

Popsavin *et al* have achieved the synthesis of (+)-oxybiotin (**1**) starting from D-xylose by use of 2,5-anhydro-D-xylose ethylene acetal derivative **11** as key intermediate. Hydrolytic removal of the dioxolane protective group in **1** gave a hydrated form of the corresponding aldehyde which on treatment with 3-methoxycarbonyl-2-propenylidene triphenylphosphorane afforded the α,β-unsaturated ester **12** as a mixture of *E* and *Z* isomers. Subsequent catalytic hydrogenation of **12** and solvolysis in wet *N*,*N*-dimethylformamide, in the presence of calcium carbonate followed by *O*-Debenzoylation

with with sodium methoxide in methanol afforded the expected diol. Mesylation of diol with mesyl chloride in dichloromethane, in the presence of triethylamine, gave the corresponding di-*O*-mesyl derivative **13**. Reaction of **13** with NaN_3 in *N*,*N*-dimethylformamide at 150 °C for 20 h, in the presence of ammonium chloride, gave the key intermediate **9**. One-pot catalytic reduction of **9** followed by a subsequent triphosgene treatment provided the desired intermediate **10** in 68% yield. Compound **10** was finally converted to (+)-oxybiotin (**1**) by hydrolysis with barium hydroxide in an almost quantitative yield.

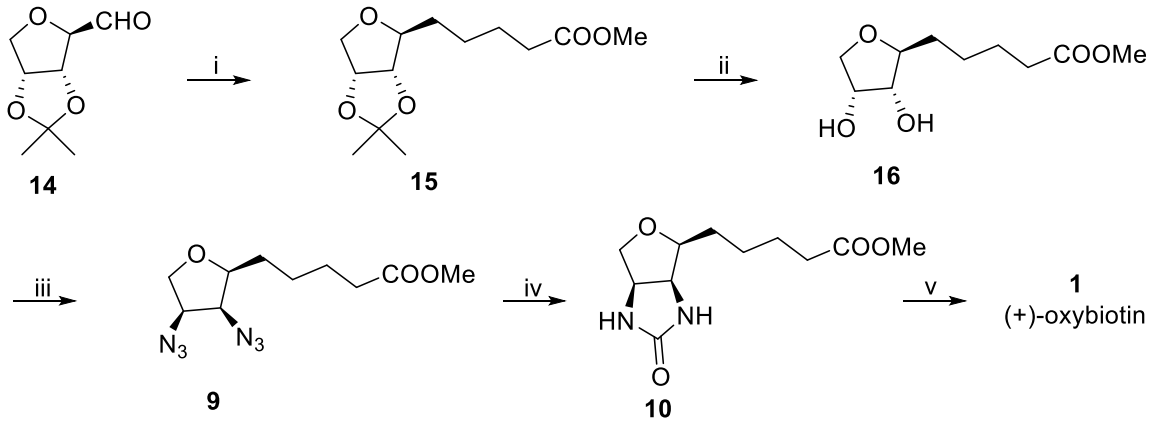


Scheme 2: (i) (a) TFA, 6 M HCl, rt, 12 h, 60%; (b) $[Ph_3P{=}CHCH{=}CHCO_2Me]^+ Br^-$, CH_2Cl_2, NaOH, H_2O, rt 1 h, 59%; (ii) (a) H_2/PtO_2, AcOH, rt, 20 h, 90%; (b) $CaCO_3$, 95% aq. DMF, 150 °C, 10 h, 65%; (c) NaOMe, MeOH, rt, 1 h, 81%;(d) MsCl, Et_3N, CH_2Cl_2, -10 °C, 0.5 h, 91%. (iii) NaN_3, NH_4Cl, DMF, 150 °C, 20 h, 47%; (iv) H_2/PtO_2, CH_2Cl_2, rt, 6 h, then Et_3N, triphosgene, 0 °C, 1 h, rt, 18 h, 68%; (v) $Ba(OH)_2$, H_2O, 100 °C, 1.5 h, 98%.

Popsavin's third approach (2004)[8]

In another approach, Popsavin *et al* have reported the synthesis of (+)-oxybiotin (**1**) by chirality transfer from D-arabinose. Treatment of aldehyde **14** (prepared from D-arabinose) with 3-(carbomethoxy-2-propenylidene) triphenylphosphorane followed by catalytic hydrogenation over PtO_2 in methanol furnished the saturated ester **15**. Hydrolytic removal of the isopropylidene protective group in **15** gave expected diol **16** in

95% yield. Reaction of **16** with triflic anhydride in pyridine and dichloromethane gave the corresponding 3,4-ditriflate which on reaction with NaN_3 in HMPA afforded the corresponding 3,4-diazido derivative **9**. The diazide **9** was then reduced over PtO_2 in dichloromethane and reacted with triphosgene which gaves imidazolidinone **10** in 66% yield. And finally treatment of compound **10** with an aqaqueous solution of sodium hydroxide, followed by neutralization with Amberlyst 15, gave an almost quantitative yield of (+)-oxybiotin (**1**).



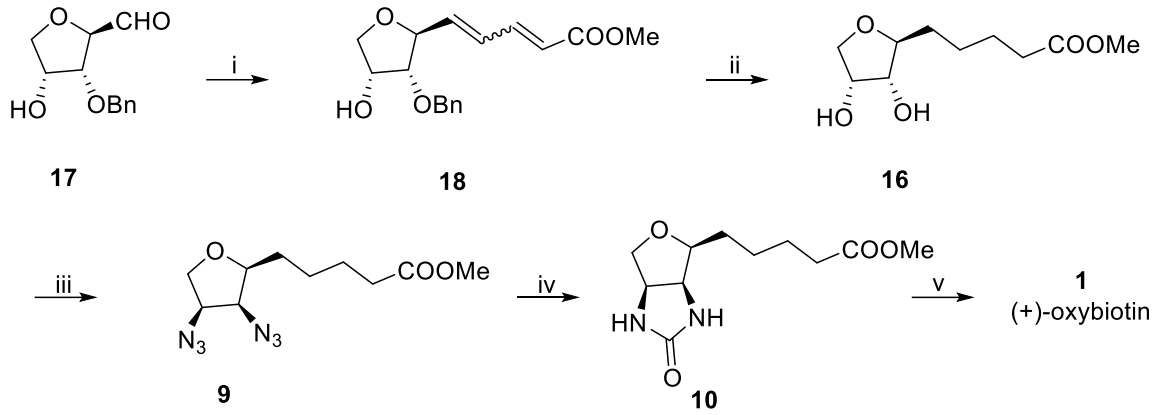
Scheme 3: (i) (a) Ph_3P=CHCH=$CHCO_2Me$, MeOH, rt, 2 h, 41% (b) H_2, PtO_2, MeOH, rt, 24 h; (ii) 9:1 TFA-H_2O, rt, 0.5 h, 95%; (iii) (a) Tf_2O, Py, CH_2Cl_2, 0 °C, 1.5 h; (b) NaN_3, HMPA, rt, 1.5 h, 68%; (iv) (a) H_2, PtO_2, CH_2Cl_2, rt, 22 h, (b) $(Cl_3CO)_2CO$, Et_3N, 0 °C, 2 h, then rt, 21 h, 66%; (v) NaOH, H_2O, rt, 24 h, then Amberlyst 15, rt, 1 h, 99%.

Shaw's approach (2008)[9]

Shaw *et al* have reported a versatile approach for the synthesis of (+)-oxybiotin **1** starting from aldehyde **17** (which was prepared from 3,4,6-tri- O-benzyl-D-glucal in 4 steps).

The Wittig olefination of the aldehyde 8 with the freshly prepared 3-(carbomethoxy-2-propenylidene) triphenylphosphorane gave the ester **18**. The catalytic hydrogenation of the C2 benzyl and two double bonds in the side chain of **18** over $Pd(OH)_2$ in methanol furnished the diol **16** in 98% yield. Reaction of diol **16** with Tf_2O in presence of pyridine

afforded corresponding ditriflate derivative which on treatment with NaN_3 in HMPA gaves diazido derivative **9**. diazide **9** was hydrogenated in the presence of catalytic amount of PtO_2 to diamine which was subsequently protected with triphosgene to obtain the methyl ester **10** of the oxybiotin (**1**). Treatment of **10** with 1 M NaOH followed by neutralization with properly cleaned Amberlyst 15 resin furnished the target compound **1** in quantitative yield.



Scheme 4: (i) $Ph_3P{=}CHCH{=}CHCO_2Me$, CH_2Cl_2, rt, 2 h, 65% (ii) H_2, $Pd(OH)_2$, MeOH, rt, 24 h,98%; (iii) (a) Tf_2O, Py, CH_2Cl_2, 0 °C, 1.5 h; (b) NaN_3, HMPA, rt, 1.5 h, 68%; (iv) (a) H_2, PtO_2, CH_2Cl_2, rt, 22 h, (b) $(Cl_3CO)_2CO$, Et_3N, 0 °C, 2 h, then rt, 21 h, 66%; (v) NaOH, H_2O, rt, 24 h, then Amberlyst 15, rt, 1 h, 98%.

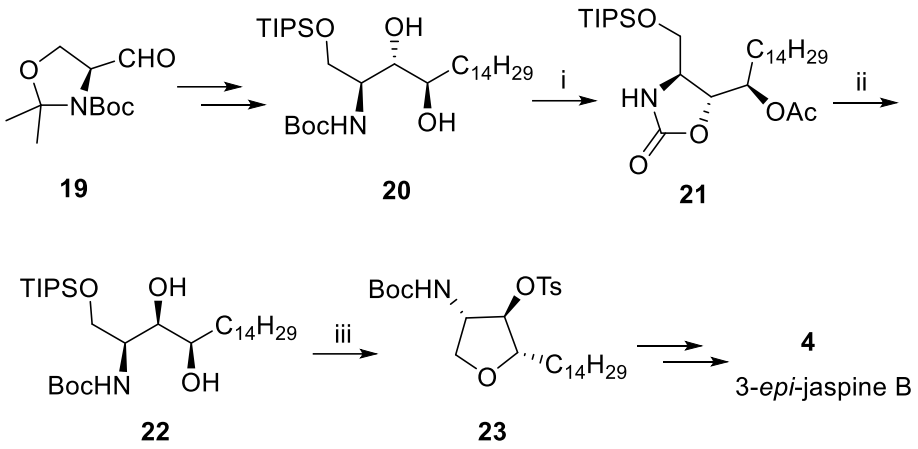
(b) Review of literature of 3-*epi*-jaspine B

Various syntheses of 3-*epi*-jaspine B **4** have been documented in the literature, most of which are based on chiral pool strategies. Some of the interesting and important synthetic routes are described below.

Yoshimitsu's approach (2009)[10]

Yoshimitsu *et al*. have employed a stereoselective synthesis of 3-*epi*-jaspine B **4** by use of regio- and stereospecific ring-opening reaction of the oxazolidin-2-one **21** assisted by a Boc group. This key step gave *syn*-diol **22**. Reaction of **20** with $MeC(OMe)_3$ in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ directly afforded the desired oxazolidinone **21**

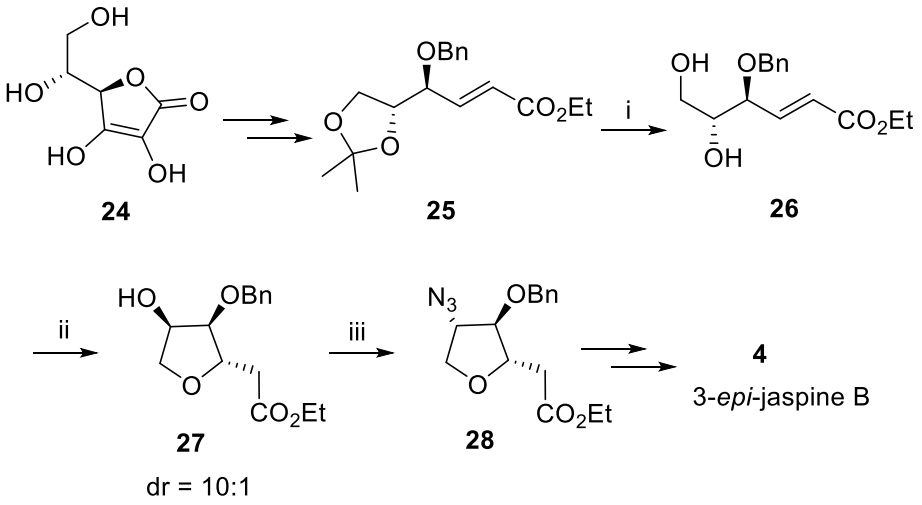
in excellent yield, *via* orthoester formation, followed by regioselective nucleophilic attack of the Boc oxygen toward C-3. The three stereogenic centers were constructed starting from Garner's aldehyde **19** as the sole chiral source; the title compound **4** was obtained in 11 steps with an overall yield of 23.4% (**Scheme 5**).



Scheme 5: (i) $MeC(OMe)_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25 °C, 96%; (ii) (a) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C; (b) NaOMe, MeOH, 25 °C, 75% (over two steps); (iii) (a) TsCl, Et_3N, CH_2Cl_2, 25 °C; (b) TBAF, THF, 25 °C, 70% (over two steps).

Basha's approach (2010)[11]

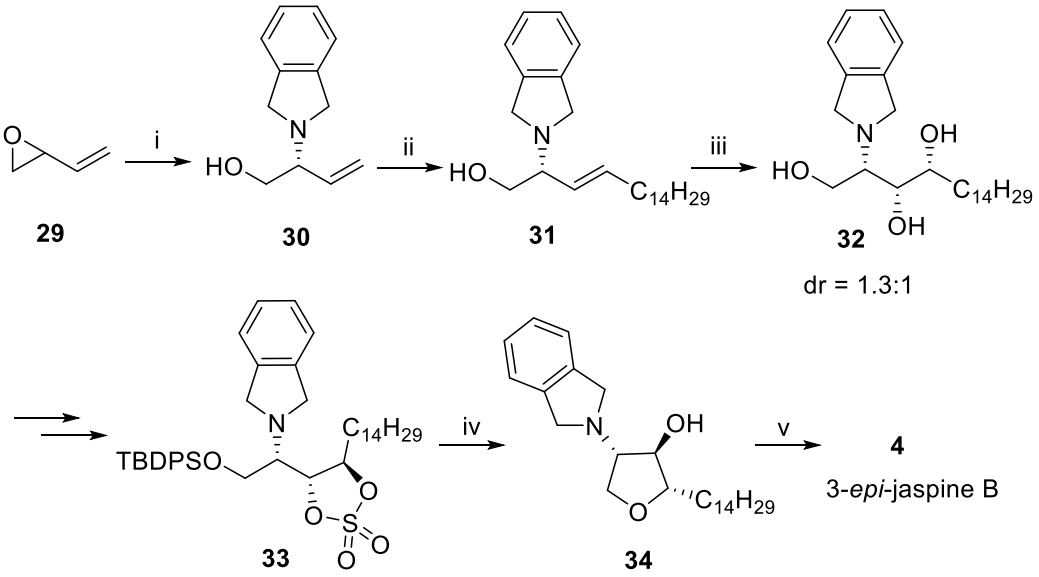
Basha *et al*. have described a stereoselective synthesis of 3-*epi*- jaspine B **4** from D-(-)-isoascorbic acid **24** as the starting material. The key reaction of the synthesis is the base catalyzed intramolecular oxa-Michael addition of diol **26**, which afforded the tetrahydrofuran derivative **27** in dr = 10:1. Conversion of alcohol **27** to **28** was done in two steps: (i) Mesylation and (ii) Azidation. The seven-step conversion from isoascorbic acid **24** to intermediate **28** was achieved with an overall yield of 55.5% (**Scheme 6**).



Scheme 6: (i) 80% aq. AcOH, 0 °C, 8 h, 98%; (ii) NaH, THF, 0.5 h, -40 °C, 96%; (iii) (a) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h; (b) NaN_3, DMF, 120°C, 8 h, 90% (over two steps).

Castillon's approach (2011)[12]

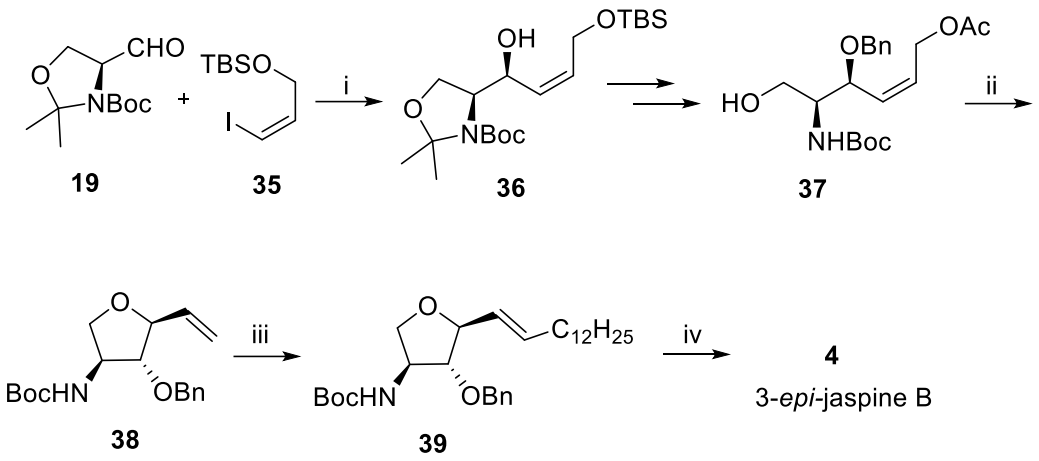
In Castillon's approach, butadiene monoepoxide **29** was treated with phthalimide in the presence of Pd/(*S*,*S*)-DACH-naphthyl to afford 2-*N*-phthalimido-3-buten-1-ol **30** *via* a Pd-catalyzed DYKAT process. Compound **30** was treated with an excess amount of 1-hexadecene in the presence of the second generation Grubbs catalyst to afford compound **31**.Substrate-controlled dihydroxylation of olefin **31** by using osmium catalysis provided diol **32**. Diol **32** was converted to cyclic sulfite **33** by a series of known reactions. Compound **33** was treated with TBAF in THF at room temperature to afford protected tetrahydrofuran **34** *via* desilylative cyclization and sulfate hydrolysis in 93% yield over two steps. Finally, removal of the phthalimido group with methylamine afforded **4** with an overall yield of 24% (**Scheme 7**).



Scheme 7: (i) Pd/(*S*,*S*)-DACH-naphthyl, Na_2CO_3, CH_2Cl_2, 25 °C, 8 h, 94%, 98%ee; (ii) Grubbs' II,1-hexadecene, CH_2Cl_2, 12 h, reflux, 99%; (iii) K_2OsO_4, $(DHQD)_2$-PYR, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *tert*-BuOH:H_2O (1:1), 25 °C, 24 h, 98%;(iv) (a) TBAF, THF, 25 °C, 2 h; (b) H_2SO_4, THF, H_2O, 25°C, 2 h, 93% (over two steps); (v) $MeNH_2$, 1h, 50 °C, 85%.

Koskinen's approach (2011)[13]

This route consists of nine steps from the commercially available Garner's aldehyde **19**. Iodide **35**, prepared from propargyl alcohol, was coupled with Garner's aldehyde **19** using *n*-BuLi as base and $ZnCl_2$ as additive giving alcohol **36** (*syn*/*anti* = 5.7:1). The furan framework **38** was obtained from alcohol **37** *via* an η^3-allylpalladium intermediate using $Pd(PPh_3)_4$ as catalyst. Cross metathesis between **38** and 1-tetradecene using Grubbs' second generation catalyst was used for the introduction of aliphatic side chain. The final hydrogenation and global deprotection was performed on olefin **39**. Firstly, the double bond and benzyl ether were hydrogenated over Pd/C at an atmospheric pressure of H_2 gas. Next the *t*-butyl carbamate was cleaved off with HCl in MeOH at 0 °C and after basic work up **4** was obtained in an overall yield of 2% only (**Scheme 8**).



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

1.1.3 Present Work

1.1.3.1 Objective

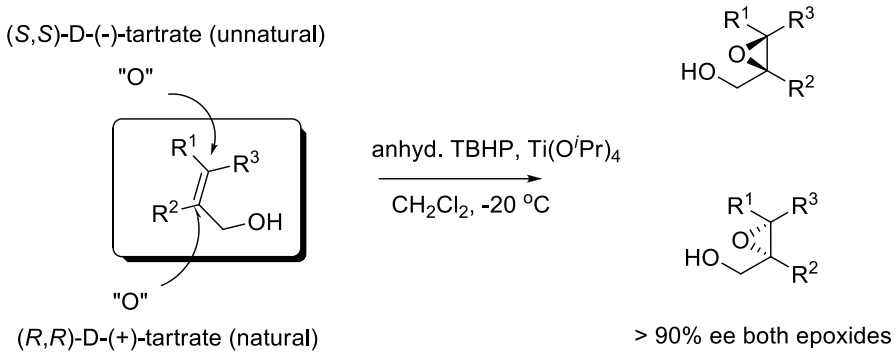
As can be seen from the review section, different synthetic methods involving a chiral pool approaches like Garner aldehyde,[14] isoascorbic acid,[15] D-glucose,[16] D-xylose,[17] D-arabinose,[8] and 3,4,6-tri-O-benzyl-D-glucal,[9] as the starting materials and in other cases asymmetric catalysis[18] have been developed for the total synthesis of jaspine B (**3**), its isomers (**4** & **5**) & (+)-oxybiotin (**1**) (**Figure 1**). However, many of the reported methods suffer from one or more disadvantages, which include use of chiral pool strategy, [8, 9, 14-18] longer reaction sequence with exotic reagents and low yields.

In view of elucidating the effect of stereochemistry and substitution on the biological activity as well as study of mode of action of jaspine and its stereoisomers, a useful synthetic route with high flexibility, yield and stereoselectivity is required. In continuation of our interest in the asymmetric synthesis of bioactive molecules,[19] we report, herein an efficient synthesis of (+)-oxybiotin **1** and 3-*epi*-jaspine B **4** by employing Sharpless asymmetric epoxidation (AE) and diastereoselective tandem

desilylation oxa-Michael addition reaction as the key reactions for the induction of chirality.

1.1.3.2 Sharpless asymmetric epoxidation (AE) [20]

Asymmetric epoxidation of allylic alcohols is one of the leading areas of investigation in synthetic organic chemistry, mainly due to the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents. The Sharpless epoxidation is a popular laboratory and industrial process due to its both enantioselective and catalytic nature. The reaction mixture includes a titanium tetraalkoxide, a chiral tartrate diester, an allylic alcohol substrate, and an alkyl hydroperoxide as the oxidant. The consistency of the reaction is remarkable, excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. In addition to being able to asymmetrically oxidize prochiral substrates to products of predictable absolute configuration, the reaction is extremely sensitive to pre-existing chirality in selected positions of the allylic alcohols. For example, kinetic resolution of racemic secondary allylic alcohols is very efficient since it can be used for generating chiral allylic alcohols as well as *anti*-epoxyalcohols in high enantiomeric excess. Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product (**Scheme 9**).



Scheme 9: 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.[21] Sharpless suggested that epoxidation was catalyzed by a single Ti center in a dimeric complex with a C_2 symmetric axis (**Figure 2**).[22]

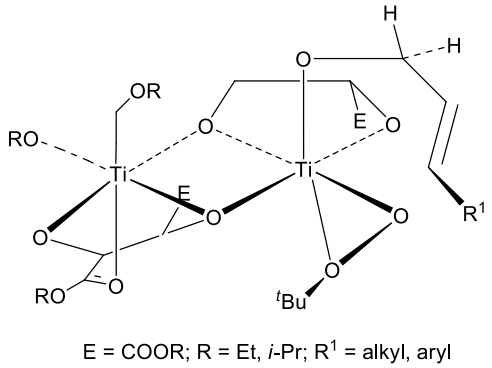


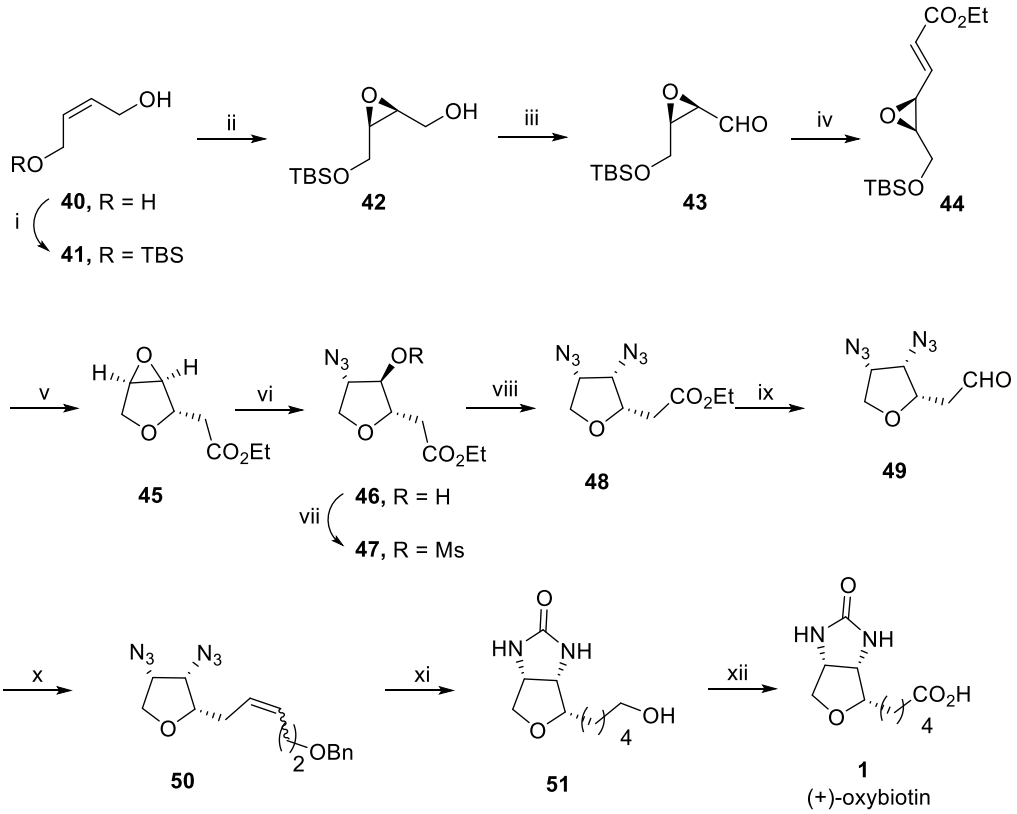
Figure 2: Structure of dinuclear Ti-tartrate complex

1.1.3.3 Results and Discussion

(a) Concise enantioselective synthesis of (+)-oxybiotin *via* an intramolecular tandem desilylation oxa-Michael addition

During our initial attempt in the synthesis of (-)-oseltamivir, we came across unexpectedly a one-pot tandem desilylation oxa-Michael addition reaction for the facile construction of optically & diastereochemically pure tetrahydrofurans. Because of the presence of tri-substituted THF ring in (+)-oxybiotin **1** and, 3-*epi*-jaspine B **4** a common structural motif present in a large number of bioactive molecules, we envisioned cyclic epoxide **45** as the key precursor in the synthesis of 3-*epi*-jaspine B **4** and (+)-oxybiotin **1**.

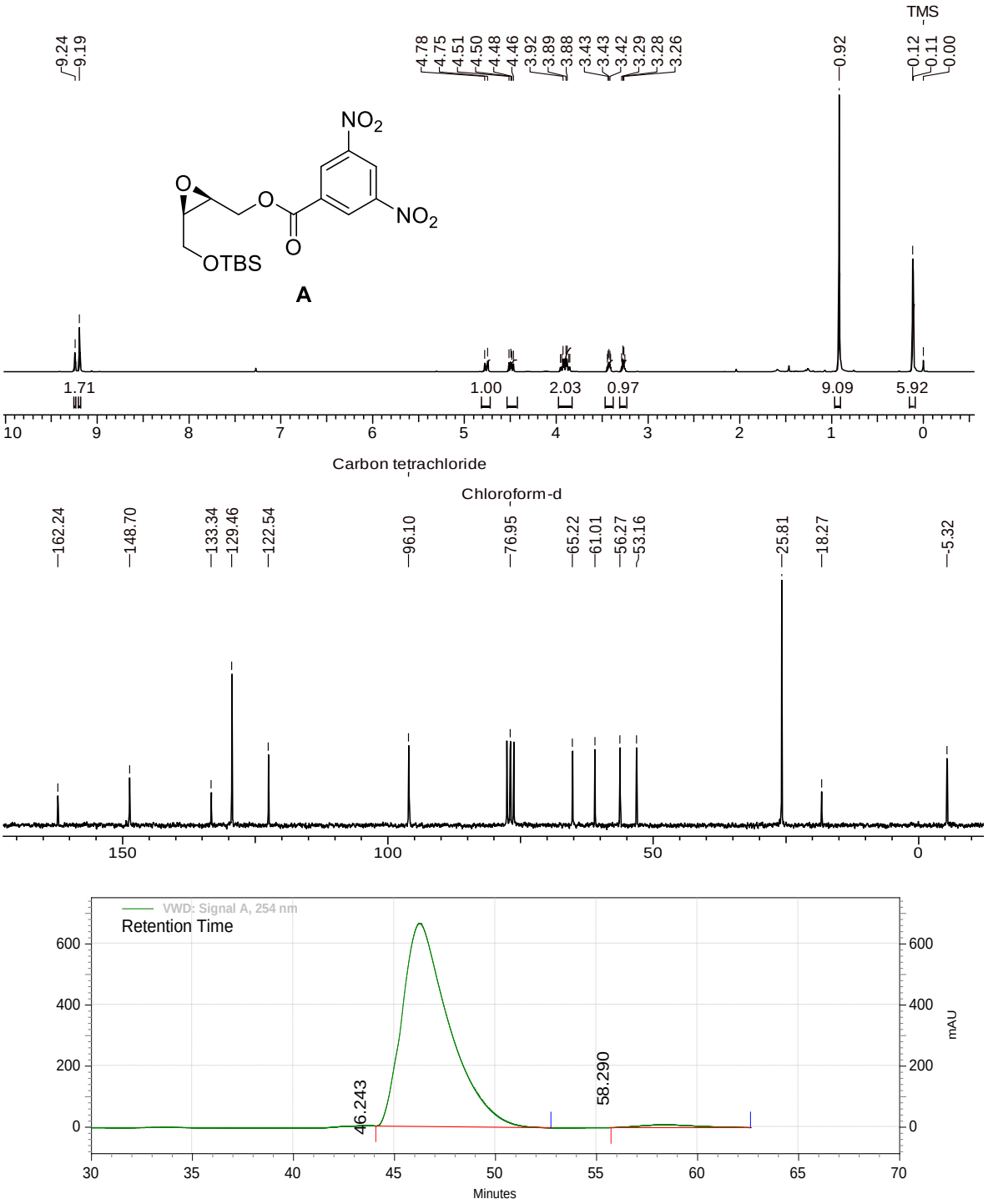
The present synthetic route to (+)-oxybiotin **1** is shown in **Scheme 10**. Accordingly, epoxy alcohol **42** was readily prepared from commercially available *cis*-2-butene-1,4-diol **40** (97% ee confirmed by HPLC analysis of the corresponding 3,5-dinitro benzoate **A**) in two steps : (i) monosilylation of diol **40** (TBSCl, imid., 73%) and (ii) AE of allylic alcohol **41** [$Ti(OiPr)_4$, (+)-DET, anhydrous TBHP, 93%]. The ^1H NMR spectrum of the 3, 5-dinitro benzoate derivative of alcohol (**A**) showed signals at δ 9.19 (s, 2H) and 9.24 (s, 1H) which accounted for the three aromatic protons.



Scheme 10: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (+)-DET, $Ti(O^iPr)_4$, anhydrous TBHP (5-6 M in decane), 4 Å molecular sieves, dry CH_2Cl_2, -10 ºC, 12 h, 93%; (iii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (iv) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, 25 ºC, 2 h, 92%; (v) TBAF, THF, 25 ºC, 2 h, 93%, de > 99%; (vi) NaN_3, NH_4Cl, EtOH/H_2O (4:1), 80 ºC, 12 h, 91%; (vii) MsCl, NEt_3, CH_2Cl_2, 0 ºC, 1 h; (viii) NaN_3, DMF, 120 ºC, 24 h, 75%; (ix) DIBAL-H, toluene, -78 ºC, 1 h; (x) KO^tBu, $BnO(CH_2)_3P^+Ph_3I^-$, THF, 0 ºC, 75%; (xi) H_2 (1 atm.), 10% Pd/C, MeOH, 25 ºC, 24 h, then $(Cl_3CO)_2CO$, Et_3N, CH_2Cl_2, 0 ºC, 2 h, then rt, 20 h, 76%; (xii) TEMPO/BAIB in CH_3CN:H_2O (4:1), 25 ºC, 4 h, 99%.

Its ^{13}C NMR spectrum showed carbon signal at δ 162.2 which was attributed to ester carbonyl, while other peaks at δ 122.5, 129.5, 133.3 and 148.7 were indicative of the aromatic carbons. Its IR spectrum showed a typical carbonyl stretching frequency band at υ_{max} 1737 cm^{-1} (**Figure 3**). The multiplets at δ 3.26-3.29 (1H) and 3.24-3.44 (1H) in its ^1H NMR spectrum indicated the presence of epoxide protons. Methine and methylene carbons attached to the oxygen atom gave signals at δ 53.2, 56.3, 61.0 and 66.2 in its ^{13}C

NMR spectrum. Its chiral HPLC gave an enantiomeric excess of 97% (Column: Chiracel OD-H retention time: 46.24 min (-)-isomer, 58.29 min (+)-isomer).



Retention Time	Area	Area %	Height	Height %
46.243	1792753436	98.31	11156727	98.56

58.290	30806312	1.69	162754	1.44
Totals	1823559748	100.00	11319481	100.00

Figure 3: ^{1}H & ^{13}C NMR spectra and chiral HPLC chromatogram of benzoate **A**

Oxidation of epoxy alcohol **42** (TEMPO, BAIB, 95%) gave the aldehyde **43** in 64.5% yield. The ^{1}H NMR spectrum of **43** showed a characteristic signal for aldehydic proton at δ 9.47. Other signals at δ 3.34-3.44 (m, 2H) and 3.96-4.00 (m, 2H) were due to methine (-**CH**-O-**CH**-) and methylene (-**CH$_2$**-OTBS) protons. Its ^{13}C NMR spectrum showed a typical signal at δ 197.2 due to aldehyde carbon while other carbon signals at δ 57.3, 59.6 and 59.7 were indicative of carbons attached to oxygen atom (**Figure 4**).

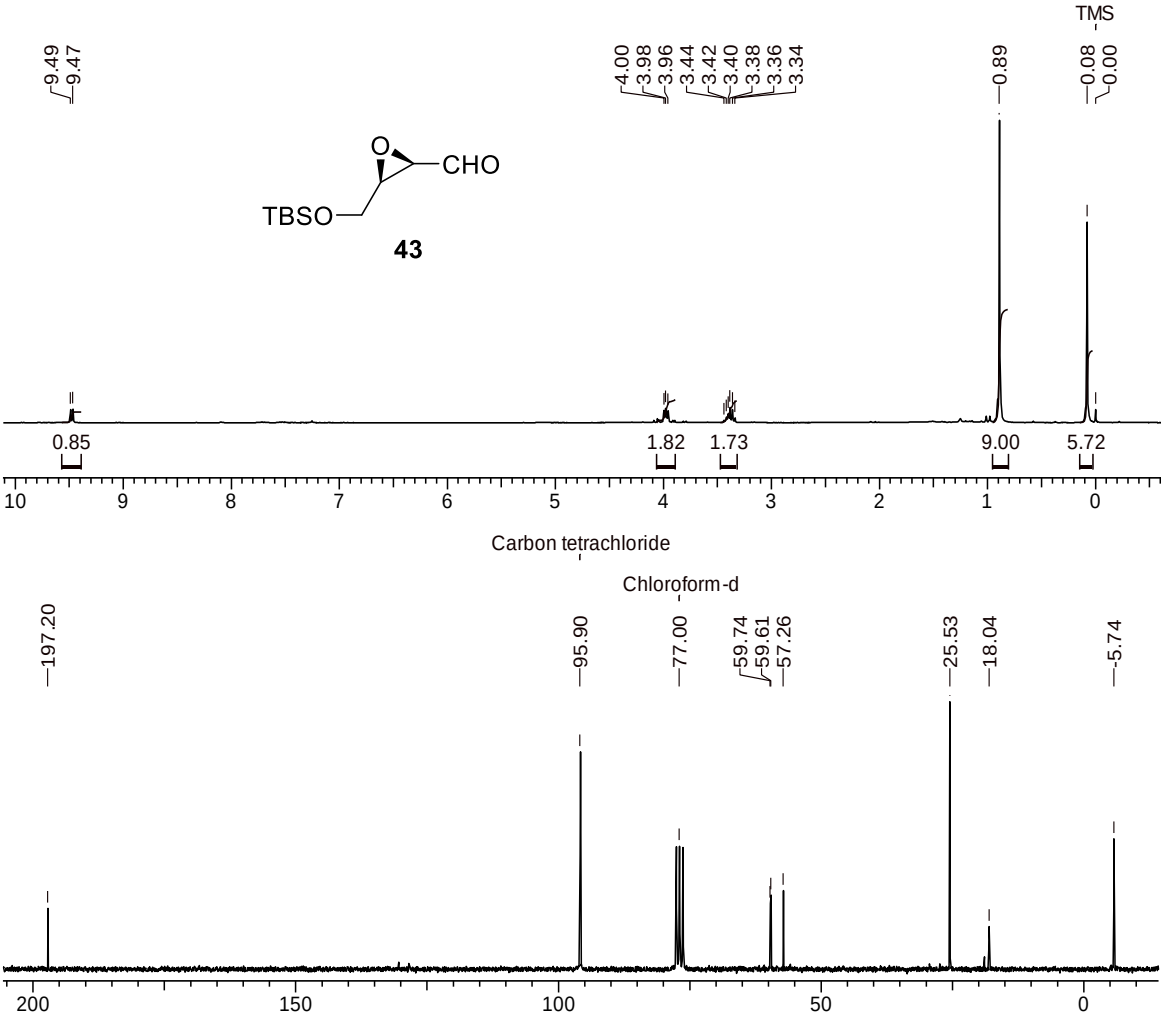
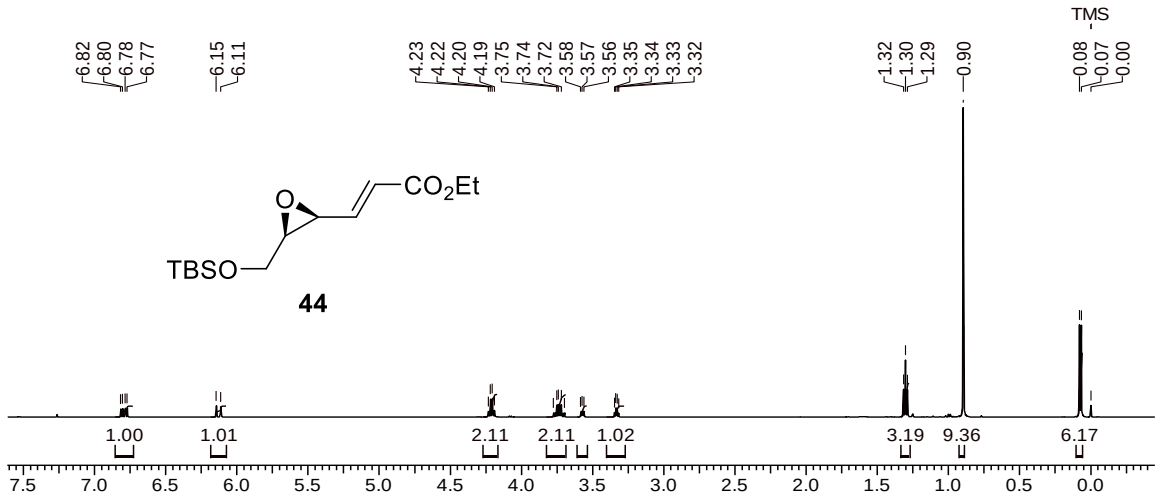


Figure 4: ^{1}H and ^{13}C NMR spectra of epoxy aldehyde **43**

Wittig olefination of epoxy aldehyde **43** with $Ph_3P{=}CHCO_2Et$ gave α,β-unsaturated ester **44** in 92% yield. The formation of α,β-unsaturated ester **44** was confirmed by its ^1H, ^{13}C NMR and IR spectral analysis. Its ^1H NMR spectrum showed signals at δ 3.32-3.35 (m) and 3.56-3.58 (m) due to methine protons attached to epoxide group. The signals at δ 3.72-3.75 (m) and 4.19 (q, J = 7.1 Hz, 2H) were attributed to methylene protons attached to silyl ether (-**CH_2**-OTBS) and ester (-OCO**CH_2**CH_3) groups respectively. Its ^{13}C NMR spectrum showed typical signals at δ 54.6 and 59.1 due to epoxide carbons, while the signals appearing at δ 60.5 and 60.8 were due to methylene carbons attached to oxygen (**Figure 5)**. The characteristic carbon signal at δ 165.1 accounted for ester carbonyl function. The IR spectrum of epoxy ester **44** showed a strong absorption band at υ_{max} 1722 cm^{-1} for ester carbonyl frequency.



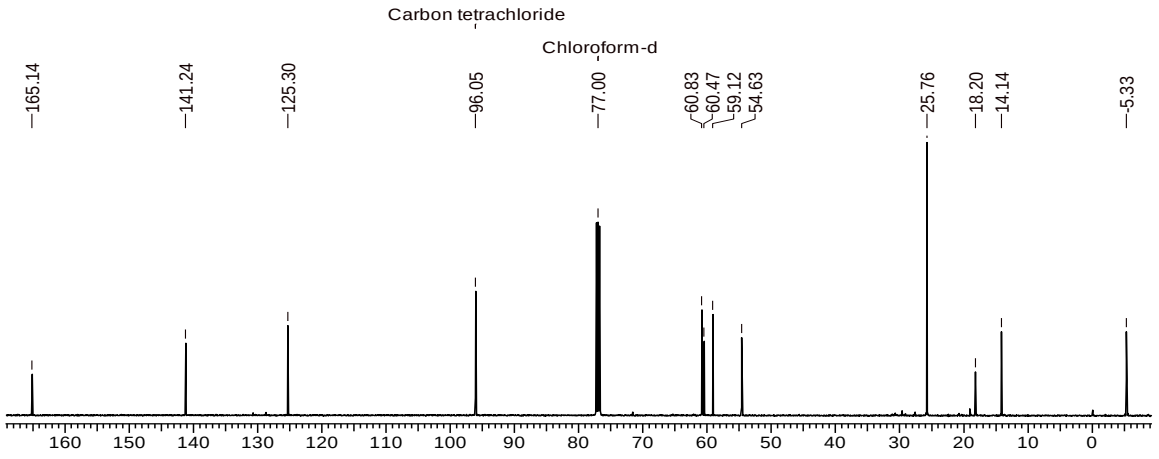
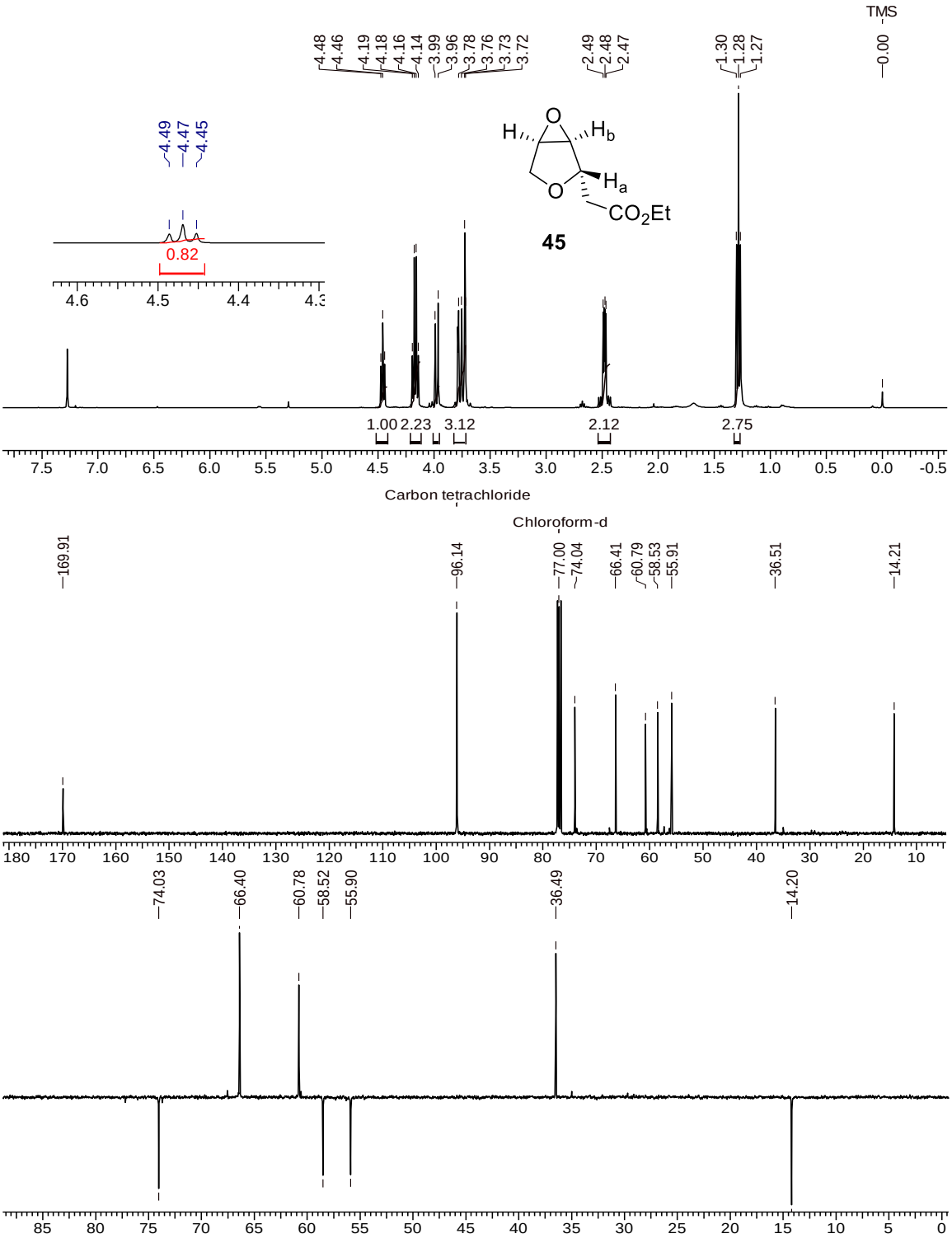


Figure 5: ^{1}H and ^{13}C NMR of epoxy ester **44**

The THF core **45** was then constructed as a single diastereomer in 93% yield *via* a diastereoselective tandem desilylation-oxa Michael addition reaction of silyl ether **44** mediated by tetrabutylammonium fluoride (TBAF). The stereoselectivity and diastereoslectivity (dr > 99) of cyclic epoxide **45** was confirmed by ^{1}H NMR and 2D NMR spectra analysis. The disappearance of signals corresponding to olefinic functionality from its ^{1}H NMR and ^{13}C NMR spectra provided evidence for a successful Michael addition reaction. The ^{1}H NMR spectrum of **45** showed a triplet at δ 4.46 for methine proton attached to furanyl oxygen. This indicated *anti*-relationship between the two adjacent methine protons attached to oxygen of furan (**H_a**) and epoxide (**H_b**). This was further confirmed by its 2D NMR studies, which did not show any correlation between the two adjacent protons (**H_a** and **H_b**). The proton signals at δ 3.72-3.78 (m, 3H), 3.96 (d, J = 10.5 Hz, 1H) and 4.18 (q, J = 7.0 Hz, 2H) were indicative of methine and methylene groups attached to oxygen atom. Its ^{13}C NMR spectrum showed a typical signal at δ 74.0 corresponding to methine carbon attached to furanyl oxygen, while a peak at δ 169 was due to ester carbonyl function (**Figure 6**).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4.46
4.19
4.18
4.16
4.14
3.99
3.96
3.78
3.76
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2.49
2.48
2.47
1.30
1.28
1.27
0.00
4.49
4.47
4.45
0.82
4.6
4.5
4.4
4.3
H
O
Hb
Ha
O
CO2Et
45
1.00
2.23
3.12
2.12
2.75
7.5
7.0
6.5
6.0
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1.0
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0.0
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Chloroform-d
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77.00
74.04
66.41
60.79
58.53
55.91
36.51
14.21
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170
160
150
140
130
120
110
100
90
80
70
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30
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10
74.03
66.40
60.78
58.52
55.90
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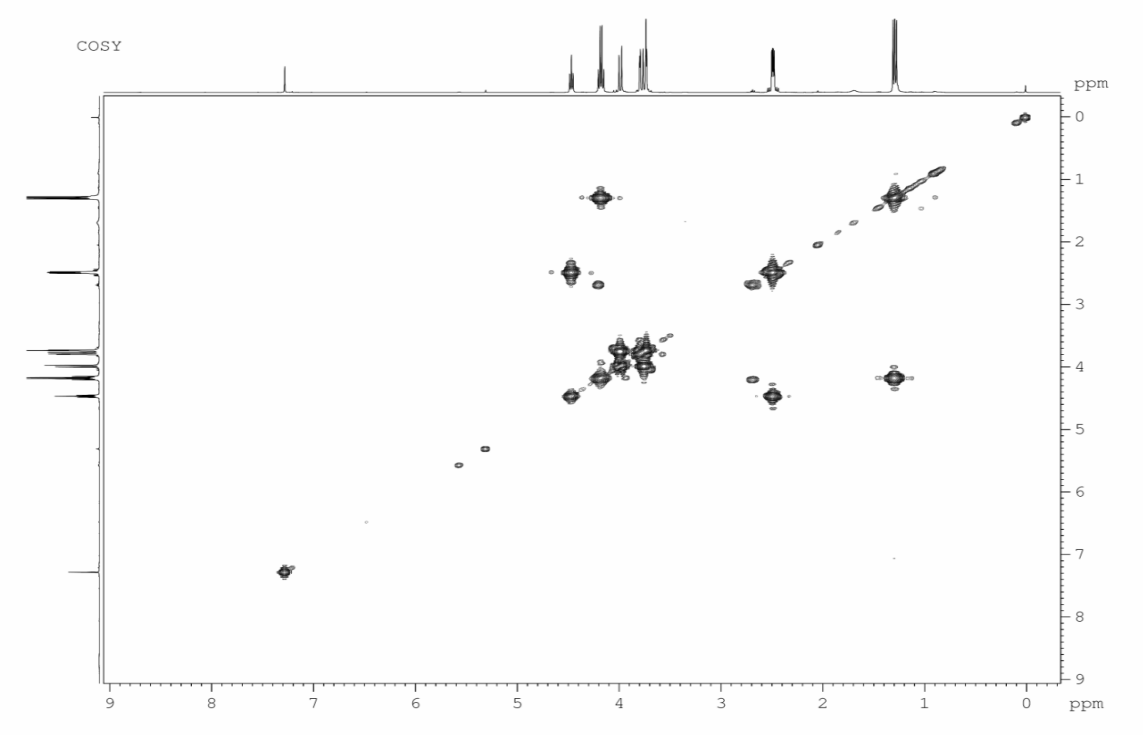
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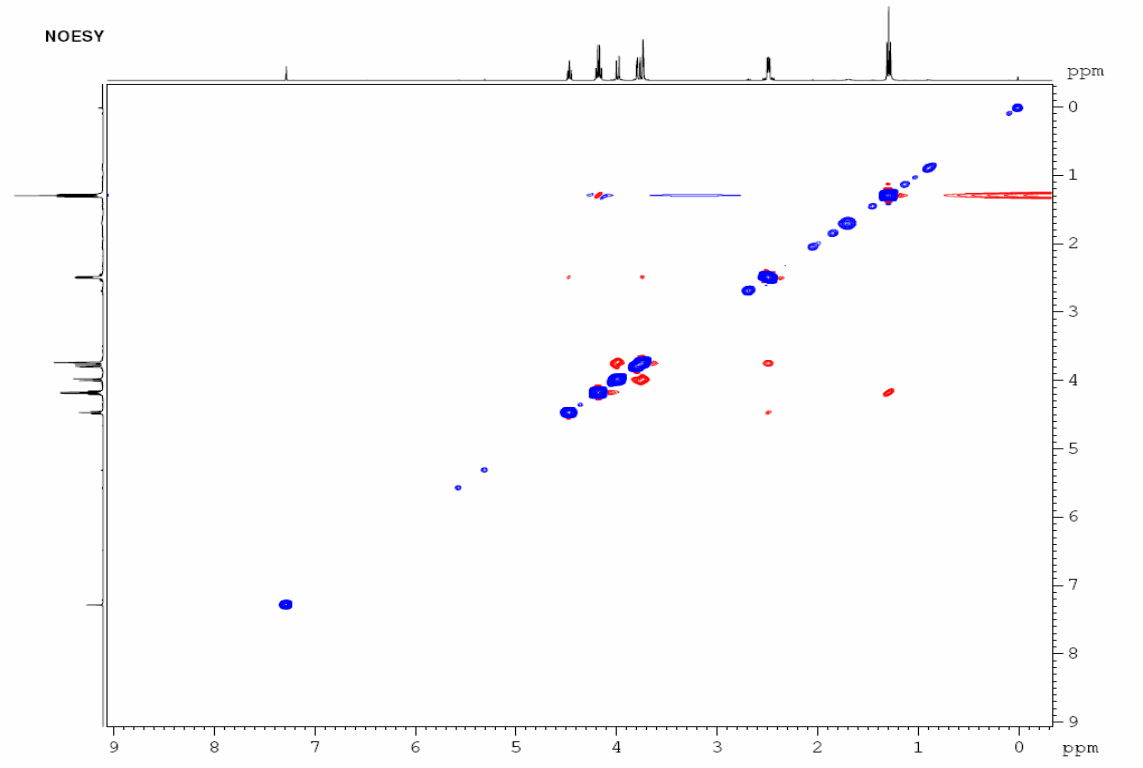
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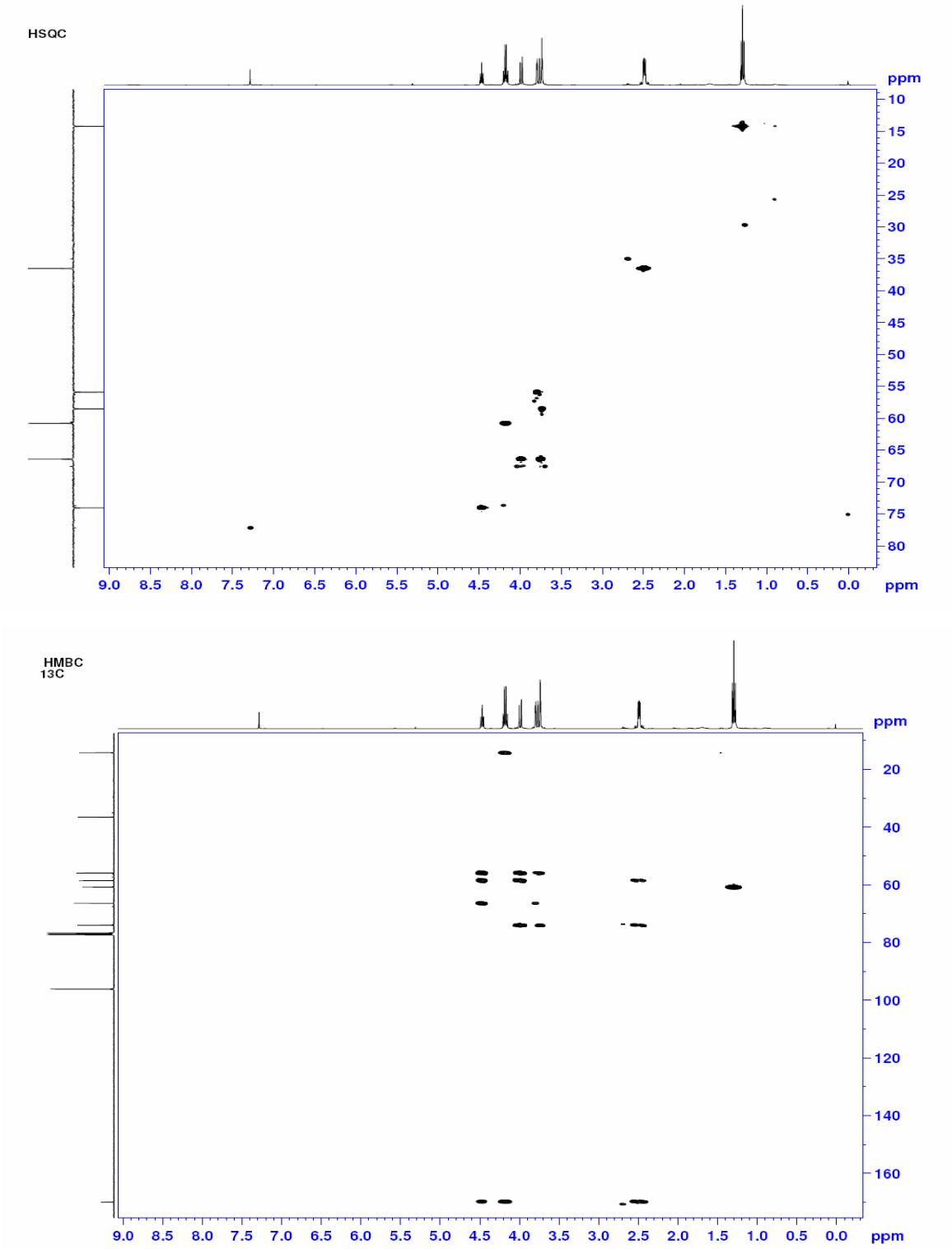


Figure 6: ^{1}H, ^{13}C NMR, DEPT, COSY, NOESY, HSQC and HMBC NMR spectra of epoxy THF **45**

Regioselective opening of epoxide **45** with NaN_3 in presence of NH_4Cl was accomplished

smoothly in a solvent mixture of EtOH/H_2O (4:1) giving the azido alcohol **46** in 91% yield; $[\alpha]_D^{25}$ +10.2 (*c* 0.4, $CHCl_3$). The formation of azido alcohol **46** was proved by its IR spectrum analysis, which showed the appearance of absorption peaks at υ_{max} 2105 and 3439 cm^{-1} corresponding to azide and alcohol functionalities. The multiplet at δ 3.88-4.03 (m, 5H) was indicative of methine and methylene protons attached to furanyl oxygen while a broad singlet at δ 3.38 (1H) was due to alcohol functionality, thus confirming the presence of hydroxyl group. Its ^{13}C NMR spectrum showed typical signals at δ 61.2, 67.5, 70.5, 81.2 and 81.5 which was attributed to the presence of carbons attached to oxygen atom (**Figure 7**).

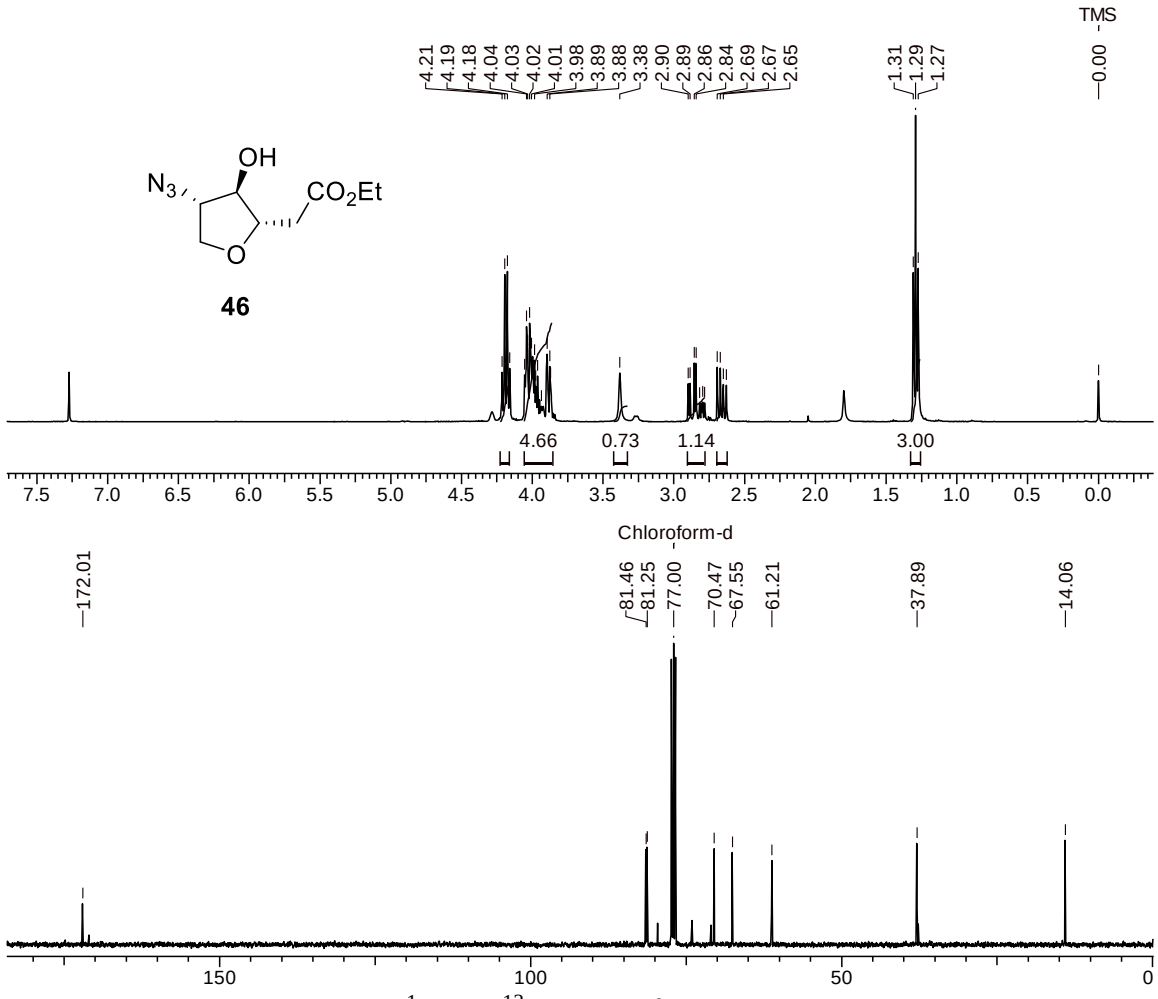


Figure 7: ^1H and ^{13}C NMR of azido alcohol **46**

The hydroxyl group in **46** was then protected as its mesylate **47** using mesyl chloride and NEt_3 as a base which was then subjected to SN^2 displacement with azide ion (NaN_3, DMF, 120 0 ^oC) to produce the diazide **48** in 75% yield with complete stereochemical inversion. The formation of diazide derivative **48** was confirmed by its IR spectrum, which showed a strong vibrational band υ_{max} 2105 cm^{-1} due to azide functionality. Its ^1H NMR spectrum showed a multiplet at δ 3.96-3.98 (m, 1H) corresponding to methine proton (-**CH**-O).

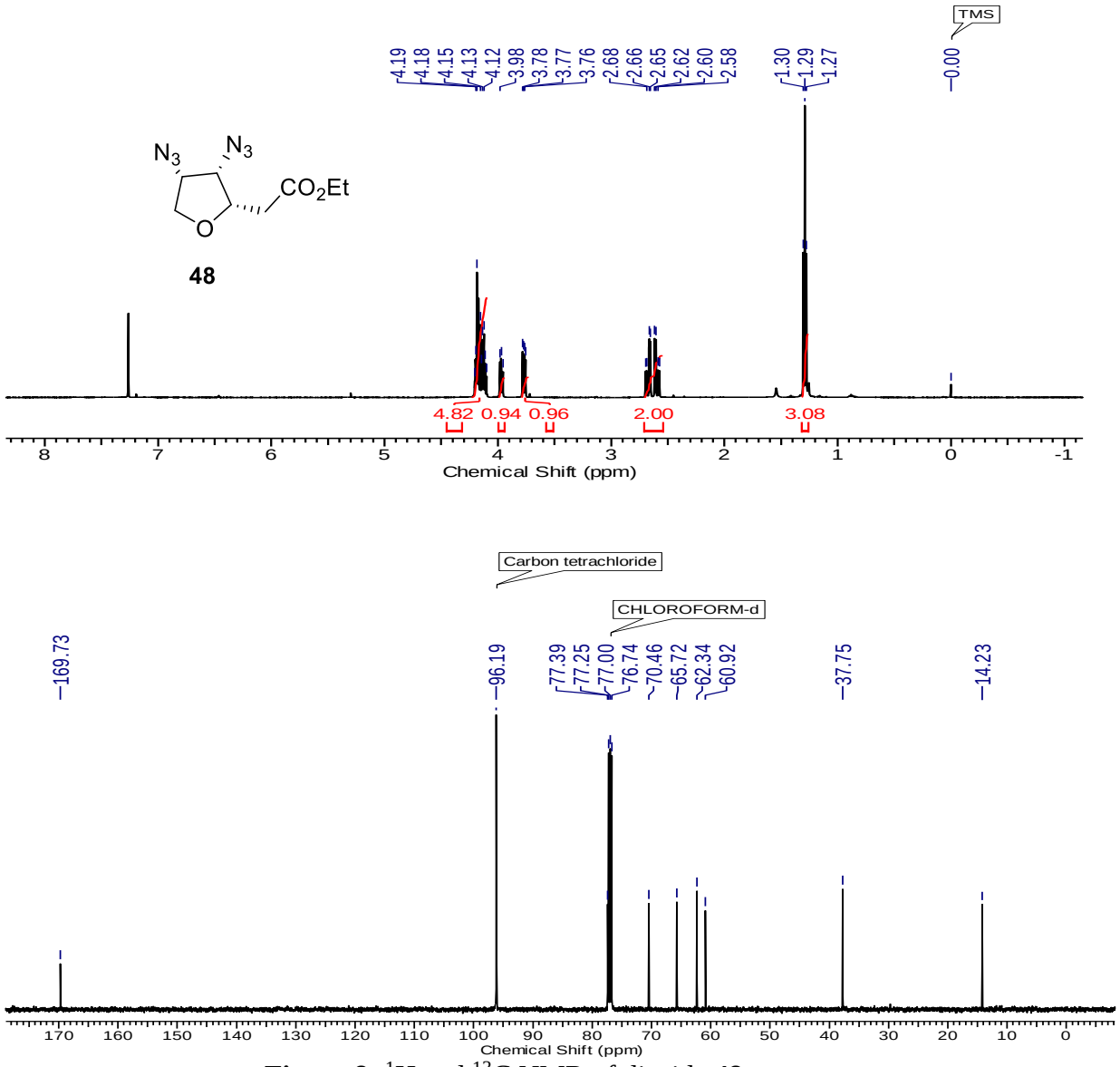


Figure 8: ^1H and ^{13}C NMR of diazide **48**

Its structure was further confirmed from ^{13}C NMR spectrum, which showed a typical methine carbon (-**CH**-O) appearing at δ 70.3 (**Figure 8**). Ester functionality in diazide derivative **48** was then selectively reduced with DIBAL-H to give diazide aldehyde **49** *in situ* which was transformed to a inseparable mixture of E and Z olefins **50** under Wittig reaction conditions (KO^tBu, $BnO(CH_2)_3P^+Ph_3I^-$, THF, 0 °C) in 75% yield.

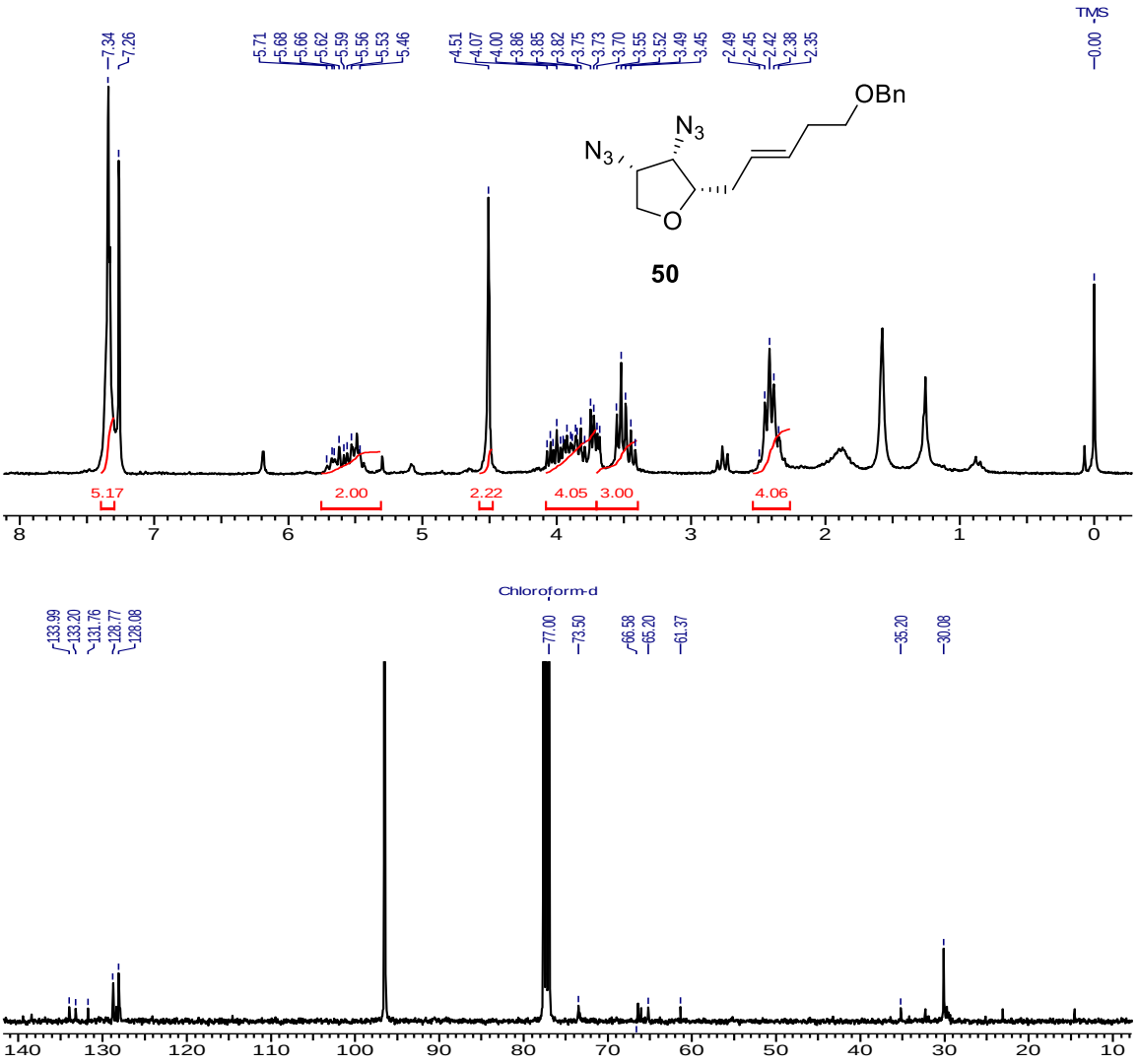


Figure 9: ^1H and ^{13}C NMR of olefin **50**

The formation of **50** was confirmed by its ^1H NMR, which showed two typical proton signals at δ 4.51 (s, 2H) and 7.34 (s, 5H) for benzylic (-**CH**$_2$-O) and aromatic protons and

olefinic proton signals at δ 5.46-5.71 (m, 2H). Its ^{13}C NMR spectrum showed a tyical cabon signal at δ 133.9 for aromatic carbon, which confirmed the formation of olefin **50** (**Figure 9**).

The Pd catalyzed hydrogenation of olefin **50** was carried out in MeOH for 24 h which generates diamine followed by its in situ protection with triphosgene gave the alcohol **51** in 76% yield.

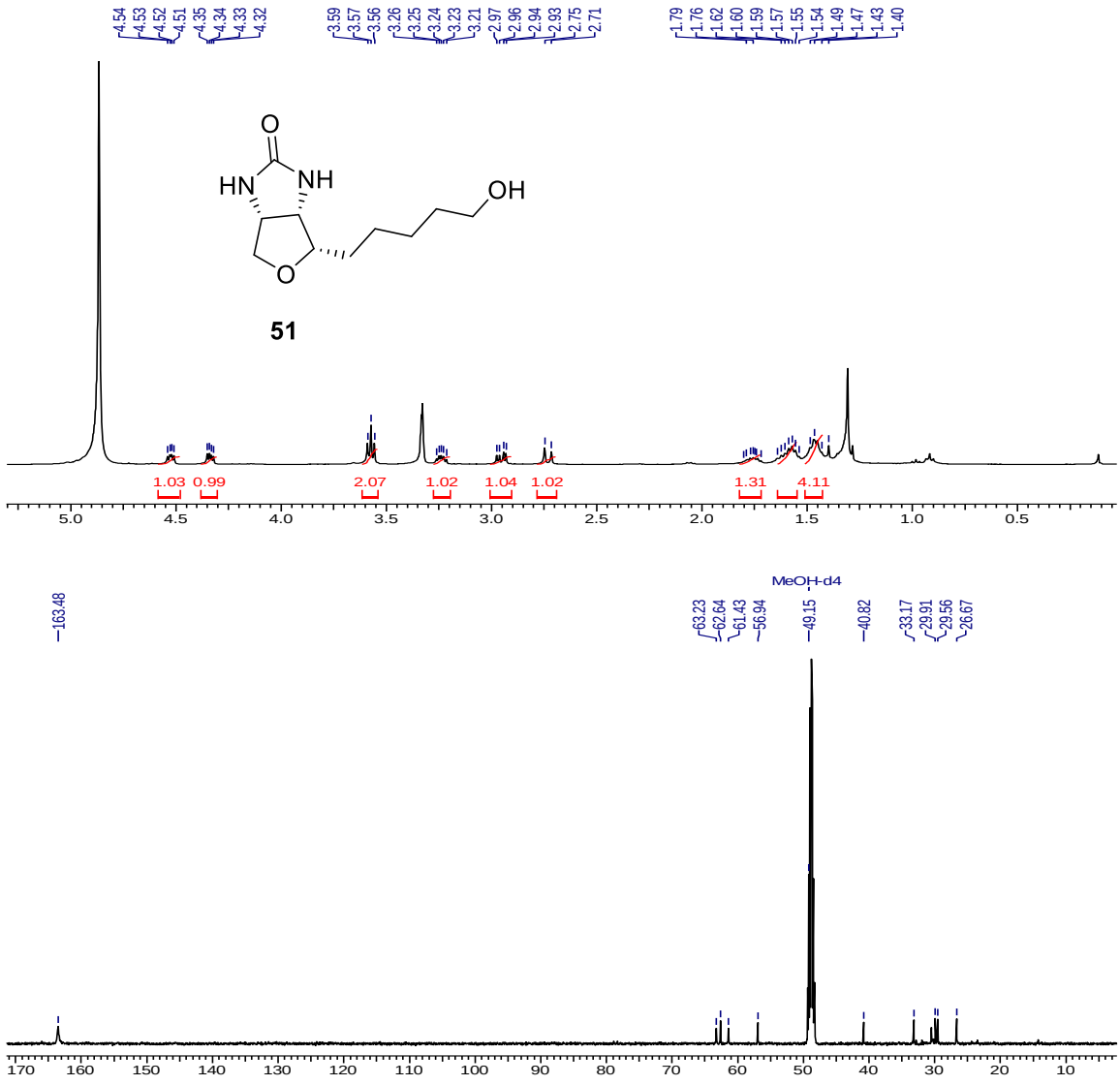
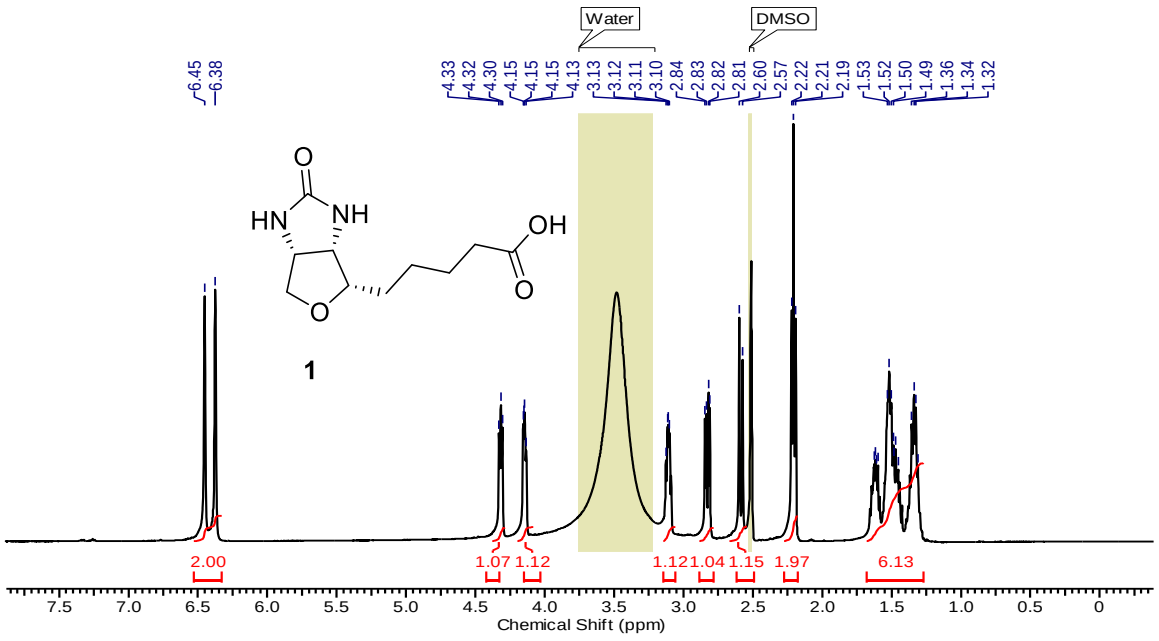


Figure 10: ^{1}H and ^{13}C NMR of alcohol **51**

The ^{1}H NMR spectrum of alcohol **51** showed disappearance of the olefinic proton signals at δ 5.46-5.71 and showed new peak at δ 1.40-1.46 (m, 4H) corresponding to methylene protons (C-**CH$_2$**-C).The formation of alcohol **51** was confirmed by its IR spectrum, which showed a strong vibrational band υ_{max} 1700 cm^{-1} due to presence of carbonyl group (-NH-**CO**-NH-). Its structure was further confirmed by ^{13}C NMR spectrum, which showed a typical carbon signal at δ 163.4 for (-NH-**CO**-NH-) carbonyl functional group (**Figure 10**).

The complete oxidation of alcohol **51** under TEMPO/BAIB in CH_3CN:H_2O (4:1) conditions was carried out to give final compound (+)-oxybiotin (**1**) in quantitative yield. The formation of **1** was confirmed by its ^{1}H NMR spectrum, which shows typical proton signals at δ 2.21 (t, 2H) corresponds to methylene protons (-**CH$_2$**-) attached to (-COOH) This finally further confirmed from its ^{13}C NMR spectrum, which showed a typical carbon signal at δ 174.3 for acid (-**CO**OH) carbonyl carbon (**Figure 11**).



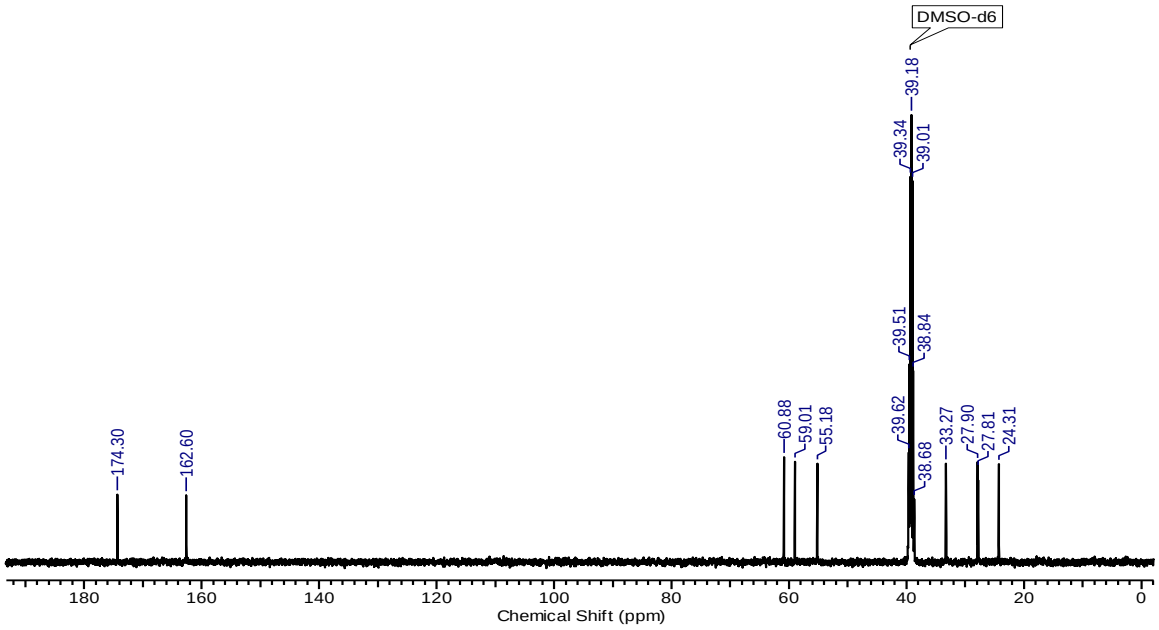
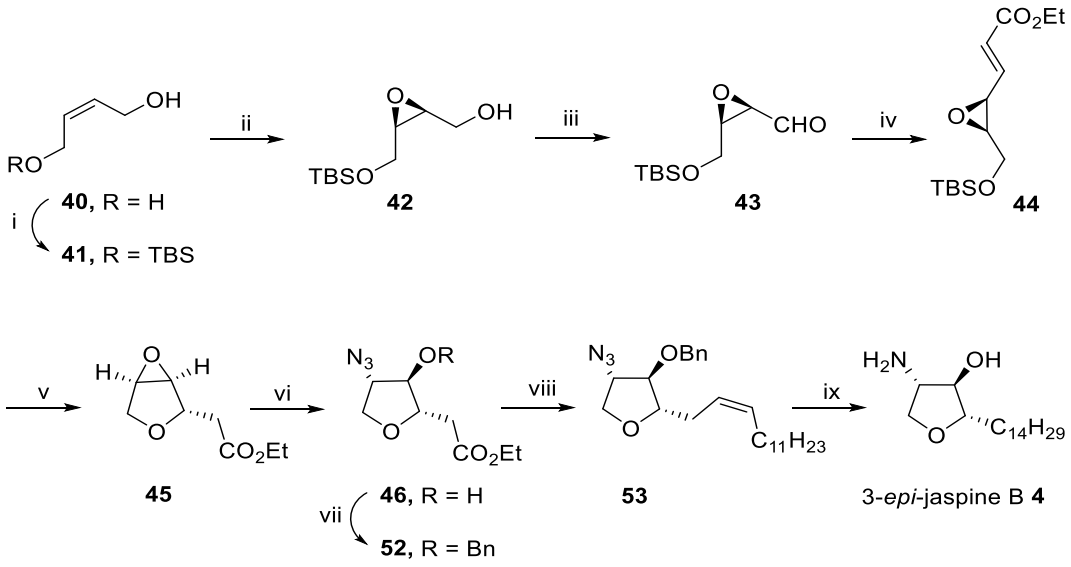


Figure 11: ^{1}H and ^{13}C NMR of (+)-oxybiotin **1**

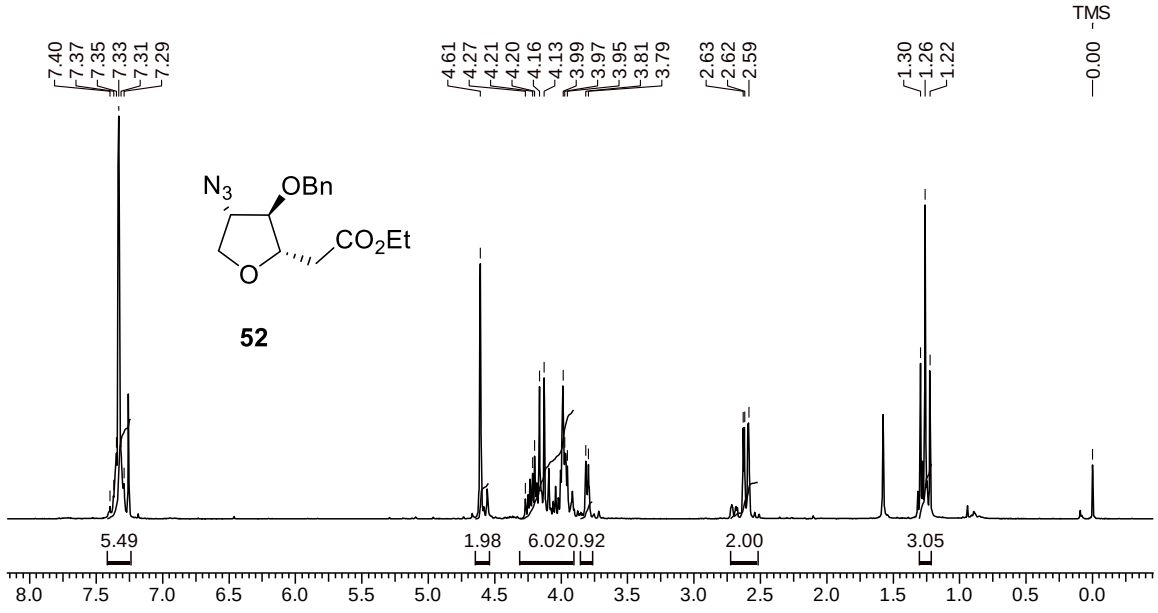
(a) Concise enantioselective synthesis of 3-*epi*-jaspine B *via* an intramolecular tandem desilylation oxa-Michael addition

The complete synthetic sequence for 3-*epi*-jaspine B **4** wherein Sharpless asymmetric epoxidation and a novel tandem desilylation oxa-Michael addition reaction strategy to construct a tetrahydrofuran core (dr >99%) as the key steps is presented in Scheme **11**.



Scheme 11: (i) TBSCl, imid., dry CH_2Cl_2, 0 ºC, 6 h, 73%; (ii) (+)-DET, $Ti(O^iPr)_4$, anhydrous TBHP (5-6 M in decane), 4 Å molecular sieves, dry CH_2Cl_2, -10 ºC, 12 h, 93%; (iii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 95%; (iv) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, 25 ºC, 2 h, 92%; (v) TBAF, THF, 25 ºC, 2 h, 93%, de > 99%; (vi) NaN_3, NH_4Cl, EtOH/H_2O (4:1), 80 ºC, 12 h, 91%; (vii) BnBr, Ag_2O, dry CH_2Cl_2, 0-25 ºC, 6 h, 95%; (viii) (a) DIBAL-H, toluene, -78 ºC, 1 h; (b) *n*-BuLi, $PPh_3{}^+C_{12}H_{25}Br^-$, THF, -78-0 ºC, 3 h, 75%; (ix) H_2 (1 atm), 10% Pd/C, MeOH, 25 ºC, 12 h, 97%.

For the synthesis of 3-*epi*-jaspine B **(4)**, a similar reaction sequence was followed as in the case of (+)-oxybiotin (**1**) upto the key azido alcohol intermediate **46**. The hydroxyl group in **46** was then protected (BnBr, Ag_2O) to give the benzyl ether **52** in 95% yield. Benzyl protection was confirmed by the presence of a multiplet at δ 7.29-7.40 corresponding to five aromatic protons. The benzylic protons appeared at δ 4.61 (s, 2H) in its ^{1}H NMR spectrum. Its ^{13}C NMR showed the characteristic ester carbonyl signal at δ 170.3 while the other resonance absorptions at δ 14.2 and 38.2 were due to methyl (-CO_2**CH_2**CH_3) and methylene (-**CH_2**CO_2Et) carbons respectively (**Figure 12**).



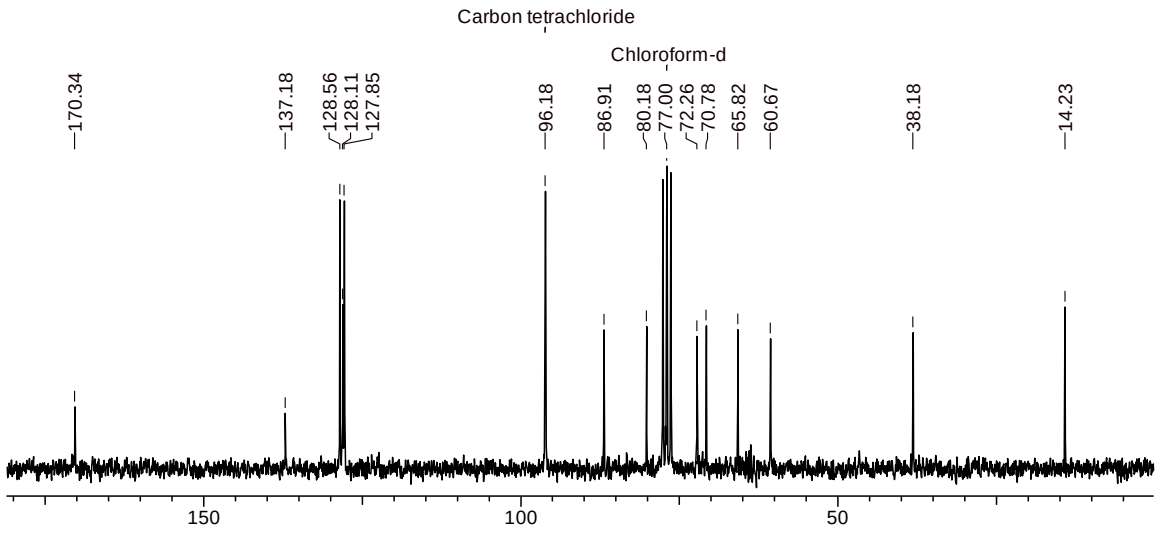


Figure 12: ^{1}H and ^{13}C NMR of benzyl ether **52**

The ester functionality in **52** was selectively reduced with DIBAL-H in dry toluene at -78 ^{o}C to produce the corresponding aldehyde, which was used as such without purification due to its instability on silica gel column. Thus, the crude aldehyde upon Wittig olefination (*n*-BuLi, $PPh_3^+C_{12}H_{25}Br^-$, THF) gave olefin **53** in 75% yield $[\alpha]_D^{25}$ +7.4 (*c* 1.0, $CHCl_3$). The formation of olefin **53** was confirmed by the presence of multiplets at δ 5.33-5.35 (1H) and 5.42-5.45 (1H) corresponding to olefinic protons. This was further substantiated by the appearance of carbon signals at δ 127.9 and 133.0 in its ^{13}C NMR spectrum (**Figure 13**).

The final step in the synthesis was the global reduction which included the reduction of azide and olefin functions along with benzyl deprotection. Accordingly, compound **53** was subjected to reduction under catalytic hydrogenation condition [10% Pd/C, H_2 (1 atm.), 97%] which gave the title compound 3-*epi*-jaspine B **4** with an overall yield of 34.7%. The formation of **4** was confirmed by the appearance of broad absorption band at υ_{max} 3359 cm^{-1} and the disappearance of sharp absorption band for azide functionality in its IR spectrum.

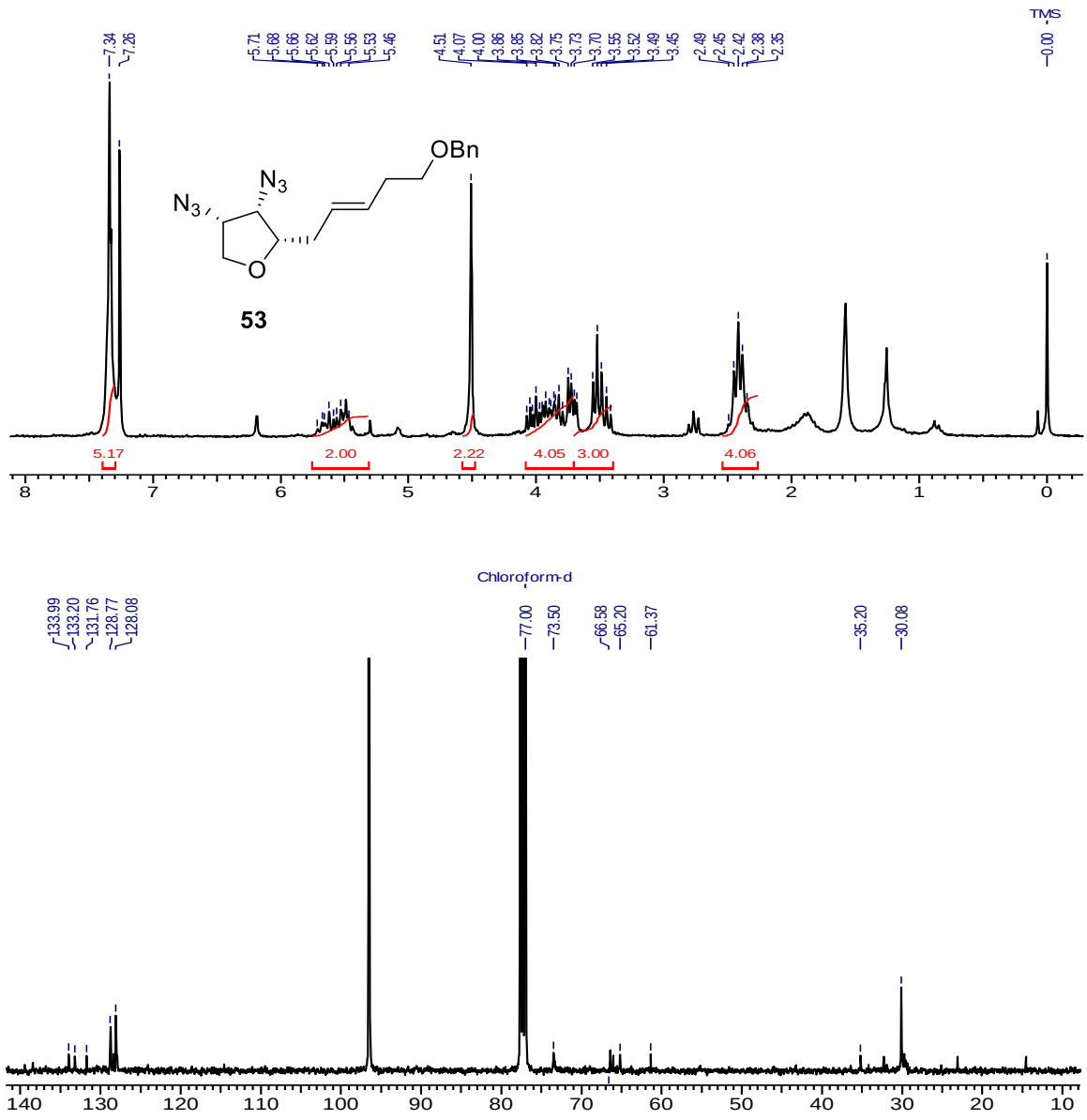


Figure 13: ^{1}H and ^{13}C NMR of olefin **53**

This was further evidenced by the disappearance of signals corresponding to benzyl and olefin functionality from its ^{1}H and ^{13}C NMR spectra (**Figure 14**). The spectroscopic data along with physical properties like specific rotation and melting point of the final product thus obtained were in agreement with the literature values.[12, 13]

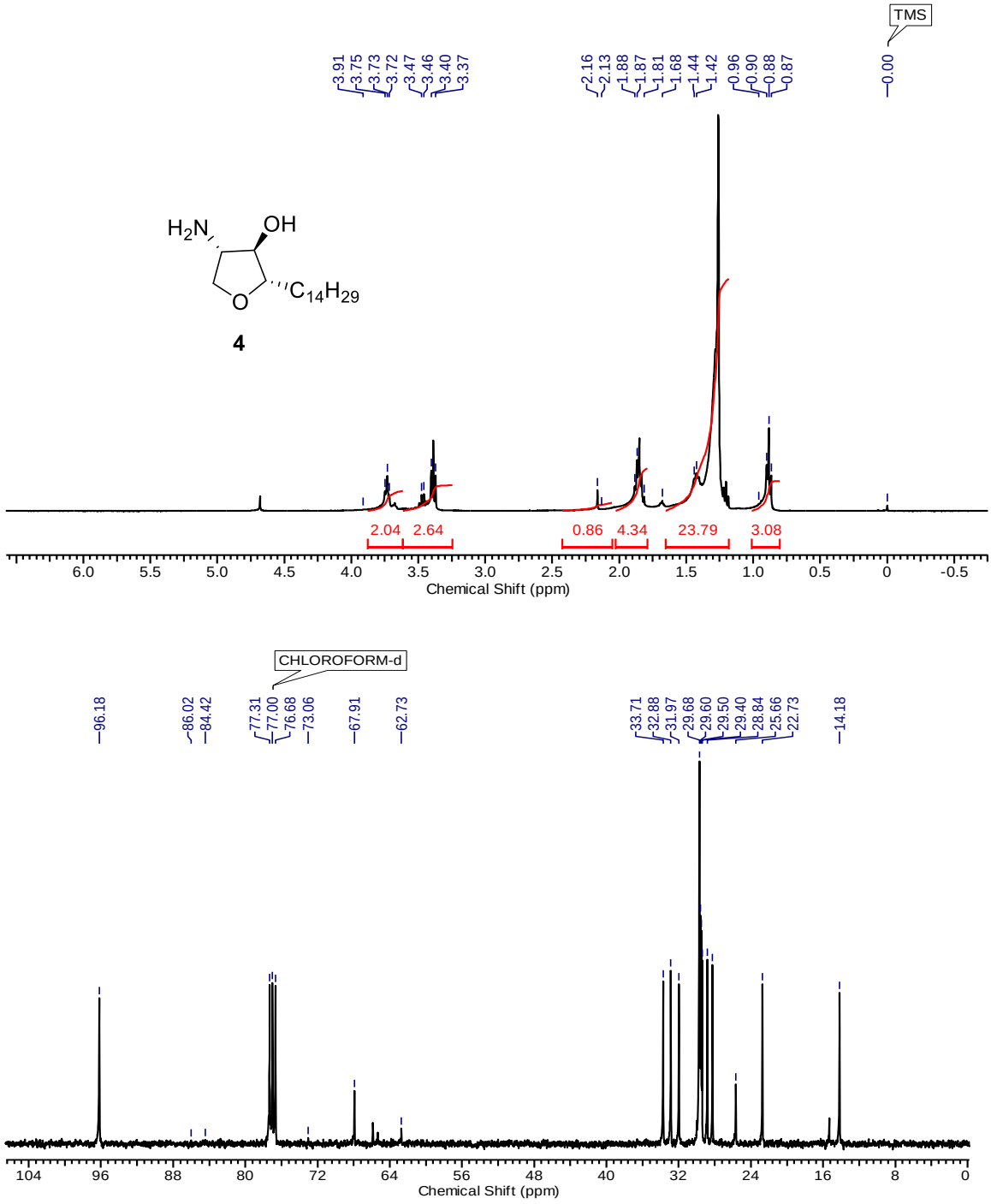


Figure 14: ^{1}H and ^{13}C NMR of 3-*epi*-jaspine B **4**

1.1.4 Conclusion

In conclusion, we have accomplished a new enantioselective synthesis of (+)-oxybiotin (**1**) (21.2% overall yield) and 3-*epi*-jaspine B (**4**) (34.7% overall yield) starting from

readily available cis-2-butene-1,4-diol. This method comprises operationally simple reactions with fewer steps, high overall yields with the use of inexpensive & non toxic reagents. The strategy of the diastereoselective tandem desilylation oxa-Michael addition reaction employed here can be applied to the synthesis of other THF based bioactive molecules and studies pertaining to that are currently underway.

1.1.5 Experimental section

(*Z*)-4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol (41)

To a solution of alcohol **40** (20 g, 227.27 mmol) in dry CH_2Cl_2 (700 mL) at 0 ^oC was added imidazole (23.21 g, 340.91 mmol) and *tert*-butyldimethylsilyl chloride (37.68 g, 250 mmol). The reaction mixture was then stirred at 0 ^oC for 6 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2, washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product which was then purified by column chromatography with petroleum ether/EtOAc (9:1 v/v) to give **41** (33.57 g) as a colorless liquid.

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

(2*S*,3*S*)-3-((*tert*-Butyldimethylsilyloxy)methyl)oxirane-2-carbaldehyde (43)

To a solution of alcohol **41** (15.02 g, 69.44 mmol) in dry CH_2Cl_2 was added in one portion (diacetoxyiodo)benzene (24.34, 75.62 mmol) and TEMPO (1.07 g, 6.91 mmol). The reaction mixture was then allowed to stir at 25 ^oC for 1 h. After completion of

reaction (monitored by TLC), the reaction mixture was quenched by the addition of saturated solution of aq. sodium thiosulphate. The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified using coulumn chromatography with petroleum ether/EtOAc (9:1 v/v) as eluent to afford the epoxy aldehyde **43** (14.27 g) as yellow colored liquid.

Yield: Yield: 95%; $[\alpha]_D^{25}$ +41.9 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 778, 838, 1099, 1256, 1472, 1720, 2858, 2930 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.89 (s, 9H), 3.34-3.44 (m, 2H), 3.96-4.00 (m, 2H), 9.47 (d, *J* = 4.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.7, 18.0, 25.5, 57.3, 59.6, 59.7, 197.2; **Anal.** Calcd for $C_{10}H_{20}O_3Si$ requires C, 55.52; H, 9.32; Found: C, 55.60; H, 9.43%.

(E)-Ethyl ((2*R*,3*S*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)acrylate (44)

To a stirred solution of aldehyde **43** (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 **44** (12.18 g) as a slightly yellow colored liquid.

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

Ethyl 2-((1*S*, 2*S*, 5*R*)-3,6-dioxabicyclo[3.1.0]hexan-2-yl)acetate (45)

To a well stirred solution of silyl ether **44** (6 g, 20.97 mmol) in THF (40 mL) was added 1 M solution of tetrabutylammonium fluoride (30 mL, 41.95 mmol) at 25 ^{o}C. The reaction mixture was stirred at this temperature for 2 h after which the solvent was removed under reduced pressure and the residue was subjected to column chromatography purification with petroleum ether/EtOAc (5:5 v/v) to afford furan derivative **45** (3.34 g) as a single diastereomer.

Yield: 93%; colorless liquid; $[\alpha]_D^{25}$ -6.2 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$): ν_{max} 838, 1256, 1719, 2876 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 2.47 (m, 2H), 3.72-3.78 (m, 3H), 3.96 (d, *J* = 10.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.46 (t, *J* = 6.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 36.2, 55.6, 58.2, 60.4, 66.1, 73.7, 169.5; **Anal.** Calcd for $C_8H_{12}O_4$ requires C, 55.81; H, 7.02; Found: C, 55.85; H, 6.94%; **HRMS** (*m/z*): calculated $[M+Na]^+$ for $C_8H_{12}O_4$: 195.0633, found: 195.0636.

Ethyl 2-((2*S*,3*R*,4*S*)-4-azido-3-hydroxytetrahydrofuran-2-yl)acetate (46)

To a solution of epoxide **45** (3 g, 17.43 mmol) in EtOH/H_2O (80:20 mL) was added NaN_3 (6.83 g, 104.59 mmol) and NH_4Cl (5.6 g, 104.59 mmol) at 25 ^{o}C. The mixture was then stirred at 80 ^{o}C for 12 h. After completion of reaction (monitored by TLC), EtOH was removed by rotary evaporation. The reaction mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with H_2O (20 mL x 3), brine (20 mL x 3) and dried (anhydrous Na_2SO_4). After evaporation of the solvent, the residue was purified using coulumn chromatography with petroleum ether/EtOAc (6:4 v/v) to give the azido alcohol **46** (3.41 g) as yellow colored liquid.

Yield: 91%; yellow liquid; $[\alpha]_D^{25}$ +10.2 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$): ν_{max} 1073, 1725, 2105, 3439 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.0 Hz, 3H), 2.65 (dd, *J* = 8.9, 16.8 Hz, 1H), 2.84 (dd, *J* = 5.3, 16.8 Hz, 1H), 3.38 (br s, 1H), 3.88-4.03 (m, 5H), 4.18 (q, *J* = 7.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 37.8, 61.2, 67.5, 70.4, 81.2, 81.4, 172.0; **Anal.** Calcd for $C_8H_{13}N_3O_4$ requires C, 44.65; H, 6.09; N, 19.53; Found: C, 44.71; H, 6.13; N, 19.60%; **HRMS** (*m/z*): calculated $[M+Na]^+$ for $C_8H_{13}N_3O_4$: 238.0803 found: 238.0806.

Ethyl 2-((2*S*,3*S*,4*R*)-3,4-diazidotetrahydrofuran-2-yl)acetate (48)

To a well stirred and cooled solution (0 °C) of azido alcohol **46** (2.0 g, 9.29 mmol) in dry CH_2Cl_2 (50 mL) was added Et_3N (3.8 mL, 27.5 mmol) and MsCl (0.84 mL, 11.15 mmol). Stirring was continued for 0.5 h and the mixture was diluted with CH_2Cl_2 (30 mL), washed successively with aq 5% HCl (2×15 mL), satd aq $NaHCO_3$ (15 mL) and water (15 mL). The organic solution was dried and evaporated to give a crude mesylate **47** as a yellow syrup which was used as such for the next reaction.

To a stirred solution of crude mesylate **47** (2.2 g, 7.50 mmol) in dry DMF (20 mL) were added NaN_3 (2.92 g, 45.05 mmol) & the resulting suspension was stirred at 120 ^oC for 24 h. After completion of reaction (monitored by TLC), the solution was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (20 mL x 3) and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified using column chromatography with petroleum ether/ethyl acetate (7:3 v/v) to give the diazide **48** (1.35 g) as yellow liquid.

Yield: 75%; yellow liquid; $[\alpha]_D^{25}$ +27.70 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$): ν_{max} 1740, 2105, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27-1.30 (t, *J* = 7.0 Hz, 3H), 2.57-2.62 (dd, *J* =

6, 16 Hz, 1H), 2.65-2.70 (dd, *J* = 6, 16 Hz, 1H), 3.75-3.78 (dd, *J* = 6, 16 Hz, 1H), 3.96-3.98 (m, 1H), 4.10-4.20 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 37.6, 60.8, 62.2, 65.6, 70.3, 169.6; **Anal.** Calcd for $C_8H_{12}N_6O_3$ requires C, 40.00; H, 5.04; N, 34.98; Found: C, 40.10; H, 5.12; N, 35.02%; **HRMS** (*m/z*): calculated $[M+Na]^+$ for $C_8H_{12}N_6O_3$: 263.0868 found: 263.0886.

(2*S*,3*S*,4*R*)-3,4-diazido-2-(5-(benzyloxy)pent-2-en-1-yl)tetrahydrofuran (50)

To a stirred solution of ester **48 (**1.0 g, 4.16 mmol) in dry toluene (50 mL), a solution of diisobutylaluminium hydride (4.5 mL, 4.57 mmol, 1M in cyclohexane) was added dropwise at -78 ^oC and stirred at this temperature for 1 h. After completion of the reaction (monitored by TLC), it was diluted with a saturated solution of potassium sodium tartrate (Rochelle salt) and stirred for further 3 h. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phase was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude aldehyde **49** which was used as such for the next reaction.

At 0 °C, a solution of the crude aldehyde **49** (0.500 g, 2.55 mmol) in ether (4 mL) was treated with a solution of the ylide [generated from $BnO(CH_2)_3P^+Ph_3I^-$ (4.2 g, 7.65 mmol) using KO^tBu (0.714 g, 6.37 mmol) in THF (5 mL) at 0 °C] and stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by column chromatography (90:10 petroleum ether/EtOAc) gave olefin **50** (0.627 g, 75%) as colorless liquid.

Yield: 75%; Colorless liquid; $[\alpha]_D^{25}$ +31.33 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): ν_{max} 698, 737, 1095, 1262, 2106, 2855 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.35-2.49 (m, 4H), 3.42-3.55 (m, 3H), 3.68-4.07 (m, 4H), 4.51 (s, 2H), 5.46-5.71 (m, 2H), 7.34 (s, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 30.0, 35.2, 61.3, 65.2, 66.5, 73.5, 128.0, 128.7, 131.7, 133.2, 133.9; **Anal.** Calcd for $C_{16}H_{20}N_6O_2$ requires C, 58.52; H, 6.14; N, 25.29; Found C, 58.64; H, 6.20; N, 25.35%; **HRMS** (*m/z*): calculated $[M+Na]^+$ for $C_{16}H_{20}N_6O_2$: 351.1648 found: 351.1650.

(3a*S*,4*S*,6a*R*)-4-(5-hydroxypentyl)tetrahydro-1H-furo[3,4-d]imidazol-2(3H)-one (51)

To a stirred Methanolic solution of olefin **50** (150 mg, 0.45 mmol, 15 mL) was added Pd/C (10% on carbon, 15 mg) and the reaction mixture stirred under an H_2 atmosphere at room temperature for about 24 h. After the completion of reaction it was filtered over celite plug (MeOH eluent) and solvent evaporated under reduced pressure to give crude di-amino alcohol as a gummy liquid which was then diluted with dry CH_2Cl_2. the reaction mixture was cooled to 0 ^oC and to it were added Et_3N (0.2 mL, 1.47 mmol) and a solution of triphosgene (47 mg, 0.16 mmol) in dry CH_2Cl_2. After stirring for 2 h under the same temperature, the reaction mixture was left for stirring at room temperature. After 20 h, the catalyst was filtered off and washed thrice with CH_2Cl_2. Concentration of the filtrate under vacuum provided the crude residue which on column chromatography with ethyl acetate/methanol (8:2 v/v) afforded pure **51**(73 mg) as a white solid.

Yield: 76%; white solid; m.p. 162-164 ^oC; $[\alpha]_D^{25}$ +40.35 (*c* 1.5, MeOH); **IR** : ν_{max} 1700, 2935, 3445 cm^{-1}; **^{1}H NMR** (400 MHz, CD_3OD): δ 1.40-1.46 (m, 4H), 1.51-1.63 (m, 3H), 1.69-1.77 (m, 1H), 2.69 (d, *J* = 13 Hz, 1H), 2.95 (dd, *J* = 4.8, 13 Hz, 1H), 3.24 (ddd, *J* = 4.6, 6.1 & 9.0 Hz, 1H), 3.56 (t, *J* = 6.2 Hz ,2H), 4.33 (dd, *J* = 5.0, 7.7 Hz, 1H), 4.50, (dd,

J = 4.9, 8.1 Hz, 1H). **^{13}C NMR** (100 MHz, CD_3OD): δ 26.6, 29.5, 29.9, 33.1, 40.8, 56.9, 61.4, 62.64, 63.2, 163.4; **Anal.** Calcd for $C_{10}H_{18}N_2O_3$ requires C, 56.06; H, 8.47; N, 13.07; Found C, 56.15; H, 8.52; N, 13.15%; **HRMS** (*m/z*): calculated $[M+Na]^+$ for $C_{10}H_{18}N_2O_3$: 237.1317 found: 237.1315.

(+)-Oxybiotin (1)

To a stirred solution of alcohol **51** (60 mg, 0.28 mmol) in CH_3CN/H_2O (4:1) were added in one portion (diacetoxyiodo)benzene (196 g, 0.61 mmol) and TEMPO (14 mg, 0.084 mmol). The reaction mixture was then allowed to stir at 25 ºC for 4 h. After completion of the reaction (monitored by TLC), it was quenched by the addition of a saturated solution of aq. sodium thiosulfate. The combined aqueous solution was evaoprated by co-distillation with a mixture of 1:1 toluene:EtOH to give crude residue which was then subjected to column chromatographic purification with MeOH/EtOAc (5:5 v/v) to give **1** as a white powder which on recrystallization from water gave pure (+)-oxybiotin **1** (63 mg) as a silky crystals.

Yield: 99%; White Solid; m.p. 184-187 ºC; {lit.[6b] m.p. 185-187 ºC}; $[\alpha]_D^{25}$ +57.5 (*c* 0.65, in 1 M NaOH) {lit.[6b] $[\alpha]_D^{25}$ +57.7 (*c* 0.8, in 1 M NaOH)}; **IR**: ν_{max} 1670, 1705, 3405 cm^{-1}; **^{1}H NMR** (400 MHz, Me_2SO-d_6): δ 1.16-1.56 (m, 6H), 2.21 (t, *J* = 6.0 Hz , 2H), 3.32 (m, 1H), 3.40 (dd, *J* = 9.8, 4.6 Hz 1H), 3.66 (d,1H), 4.09 (dd, *J* = 8.5 Hz, 1H), 4.22 (dd, 1H), 6.35 (br s , 1H) , 6.41 (br s , 1 H); ^{13}C NMR (100 MHz, Me_2SO-d_6): δ 25.3, 26.0, 28.3, 34.4, 57.5, 59.2, 74.4, 82.9, 164.0, 174; Anal. Calcd for $C_{10}H_{16}N_2O_4$ requires C, 52.62; H, 7.07; N, 12.27; Found: C, 52.67; H, 7.12; N, 12.30%; HRMS (m/z): calculated [M+Na]+ for $C_{10}H_{16}N_2O_4$: 251.1008 found: 251.1006.

Ethyl 2-((2*S*,3*R*,4*S*)-4-azido-3-(benzyloxy)tetrahydrofuran-2-yl)acetate (52)

To a solution of azido alcohol **46** (2.1 g, 9.76 mmol) in dry CH_2Cl_2 (60 mL) was added Ag_2O (3.39 g, 14.64 mmol) followed by BnBr (2.0 g, 11.71 mmol) at 0 ^oC. The reaction mixture was stirred for 6 h at 25 ^oC and then filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was purified by column chromatography with petroleum ether/EtOAc (8:2 v/v) to give **52** (2.82 g) as a yellow colored syrup.

Yield: 95%; yellow syrup; $[\alpha]_D^{25}$ +15.8 (*c* 1.0, $CHCl_3$) {lit.[5] $[\alpha]_D^{25}$ +15.4 (*c* 1.1, $CHCl_3$)}; **IR** ($CHCl_3$): ν_{max} 747, 1020, 1171, 1436, 1497, 1737, 2105, 3031 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.59 (dd, *J* = 1.9, 7.1 Hz, 2H), 3.79 (d, *J* = 2.1 Hz, 1H), 3.95-4.27 (m, 6H), 4.61 (s, 2H), 7.29-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.2, 60.7, 65.8, 70.8, 72.3, 80.2, 86.9, 127.8, 128.1, 128.6, 137.2, 170.3; **Anal.** Calcd for $C_{15}H_{19}N_3O_4$ requires C, 59.01; H, 6.27; N, 13.76; Found: C, 59.08; H, 6.31; N, 13.80%. **HRMS** (*m/z*): calculated $[M+Na]^+$ for $C_{15}H_{19}N_3O_4$: 328.1259 found: 328.1261.

(2*S*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((*Z*)-tetradec-2-enyl)tetrahydrofuran (53)

To a stirred solution of ester **52 (**1.0 g, 3.27 mmol) in dry toluene (50 mL), a solution of diisobutylaluminium hydride (3.6 mL, 3.6 mmol, 1M in cyclohexane) was added dropwise at -78 ^oC and stirred at this temperature for 1 h. After completion of reaction (monitored by TLC), it was diluted with a saturated solution of potassium sodium tartrate (Rochelle salt) and stirred for further 3 h. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phase was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude aldehyde which was used as such for the next reaction.

To a stirred solution of dodecyl triphenylphosphonium bromide (2.05 g, 4.0 mmol) in 20 mL of dry THF at -78 ^{o}C was added *n*-BuLi (1.6 M solution in hexane 2.5 mL, 3.8 mmol) dropwise and the resulting solution was stirred for 30 min. The crude aldehyde obtained above was dissolved in dry THF (5 mL) and added dropwise with stirring to the ylide solution at -78 ^{o}C. The reaction mixture was then brought to 0 ^{o}C and stirred for 3 h. The reaction was quenched with 6 mL of saturated NH_4Cl solution at 0 ^{o}C, the solvent was evaporated under reduced pressure; the residue was extracted with EtOAc (2 x15 mL), and dried with anhydrous Na_2SO_4. After evaporation of ethyl acetate the residue was chromatographed (silica gel, 230-400 mesh, petroleum ether/EtOAc (9.5:0.5 v/v) to obtain **53** (1.02 g) as viscous liquid.

Yield: 75%; Colorless liquid; $[\alpha]_D^{25}$ +6.8 (*c* 2.5, $CHCl_3$) {lit.[5] $[\alpha]_D^{25}$ +6.7 (*c* 2.8, $CHCl_3$)}; **IR** ($CHCl_3$): ν_{max} 747, 1081, 1460, 1729, 2853, 2937 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.1 Hz, 3H), 1.31-1.34 (m, 18H), 2.01-2.02 (m, 2H), 2.45-2.47 (m, 2H), 3.63 (dd, *J* = 3.2, 9.8 Hz, 1H), 3.83-3.85 (m, 2H), 3.97-4.01 (m, 1H), 4.14 (dd, *J* = 5.7, 9.5 Hz, 1H), 4.52 (d, *J* = 12.3 Hz, 1H), 4.62 (d, *J* = 11.1 Hz, 1H), 5.33-5.35 (m, 1H), 5.42-5.45 (m, 1H), 7.29-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.8, 22.7, 27.3, 29.3, 29.5, 29.6, 30.9, 31.9, 65.9, 70.6, 72.2, 84.0, 87.1, 123.9, 127.7, 127.9, 128.4, 133.0, 137.2; **Anal.** Calcd for $C_{25}H_{39}N_3O_2$ requires C, 72.60; H, 9.50; N, 10.16; Found C, 72.56; H, 9.55; N, 10.21%; **HRMS** (*m/z*): calculated $[M+Na]^+$ for $C_{25}H_{39}N_3O_2$: 436.1543 found: 436.1540.

3-*epi* Jaspine B (4)

To a stirred ethanolic solution of olefin **53** (50 mg, 0.12 mmol, 5 mL) was added Pd/C (10% on carbon, 5 mg) and the reaction mixture stirred under an H_2 atmosphere at room

temperature for about 12 h. After the completion of reaction it was filtered over celite plug (EtOH eluent) and solvent evaporated under reduced pressure to give 3-*epi*-jaspine B **4** (35 mg) as colorless solid.

Yield: 97%; Colorless solid; m.p.75-77 ^{o}C; {lit.[13] m.p. 75-76 ^{o}C}; $[\alpha]_D^{25}$ -3.4 (*c* 0.6, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ -3.2 (c 0.8, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3359, 2924, 2857, 1637, 1435 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25 (m, 24H), 1.55-1.67 (m, 2H), 2.12 (br s, 3H), 3.32 (dd, *J* = 4.9, 6.6Hz, 1H,), 3.60 (dd, *J* = 4.8, 9.4 Hz, 1H), 3.62-3.64 (m, 2H), 4.01 (dd, *J* = 5.9, 9.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.7, 26.0, 29.3, 29.57, 29.60, 29.65, 29.67, 31.9, 34.0, 60.5, 73.6, 84.1, 85.2; **Anal.** Calcd for $C_{18}H_{37}NO_2$ requires C, 72.19; H, 12.45; N, 4.68; Found: C, 72.24; H, 12.52; N, 4.71%; **HRMS** (*m/z*): calculated $[M+Na]^+$ for $C_{18}H_{37}NO_2$: 322.2722 found: 322.2725.

Section II

Asymmetric Synthesis of (+)-Stagonolide C *via* Organocatalysis

1.2.1 Introduction and Pharmacology

Naturally occurring 10-membered ring lactones generally called decanolides are abundant substances that represent the core of many natural products.[23] This family of natural products displays a wide range of pharmacologically interesting properties such as antibacterial, antitumoral, antifungal, antifeedant, plant growth inhibition, and the inhibition of cholesterol biosynthesis.[24] **Figure 15** shows the structures of some of the most important decanolides. For instance, (+)-stagonolide C **54**, a new phytotoxic nonenolide, was recently isolated [24b] from Stagonospora cirsii, a fungal pathogen from Cirsium arvense and was proposed as a potential mycoherbicide by causing necrotic lesions on leaves, while (-)-aspinolide A **55** was isolated from cultures of Aspergillus ochraceus.[24a] Due to their interesting structural features as well as various biological activities, these macrolides have attracted considerable attention from synthetic organic chemists.[25] The reported synthetic routes to these fungal metabolites mainly involve asymmetric dihydroxylations, hydrolytic kinetic resolutions, enzymatic hydrolysis, and chiral pool strategies as the key stereochemistry inducing steps.[26]

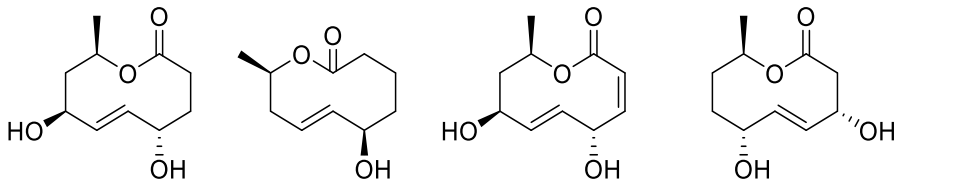


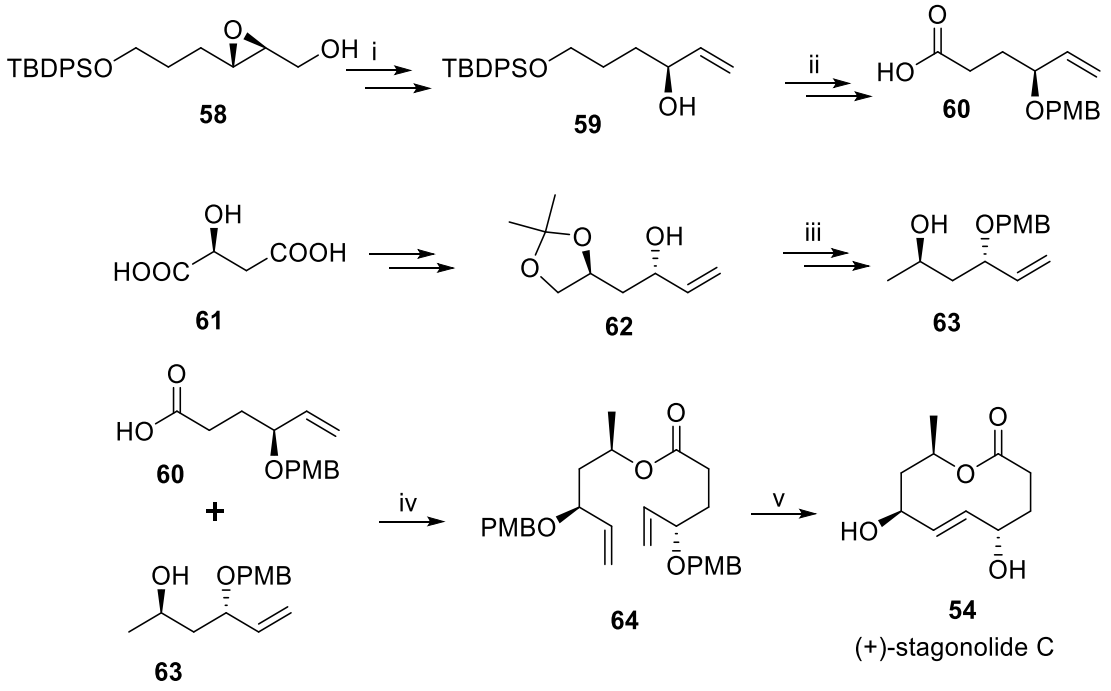
Figure 15: Some naturally occurring small ring macrolides

1.2.2 Review of Literature

Till date six synthetic routes [26-27] have been documented in the literature for the synthesis (+)-stagonolide C **54** which is described below.

Yadav's approach (2009)[26a]

Yadav *et al.* have achieved the synthesis of (+)-stagonolide C **54** starting from commercially available L-malic acid and 1,4-butane diol. The key reactions involved were Sharpless asymmetric epoxidation, activated zinc dust mediated reductive elimination and ring-closing metathesis.



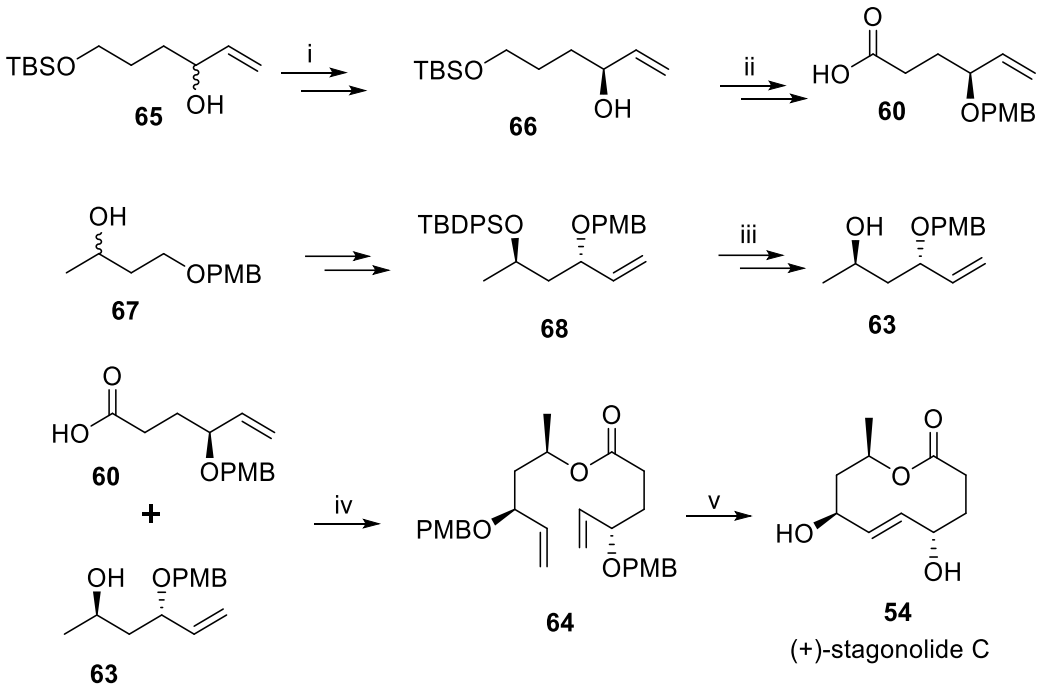
Scheme 12: (i) (a) I_2, PPh_3, imid., THF, 0 °C, 15 min.; (b) Zn dust, NaI, MeOH, reflux, 4 h, 76% over 2 steps; (ii) (a) NaH, PMBBr, THF, 0 °C to rt, 4 h, 84%; (b) IBX, THF, DMSO, rt, 3 h; (c) $NaClO_2$, $NaH_2PO_4.2H_2O$, 2-methyl-2-butene, *t*-BuOH-H_2O, 0 °C to rt, 2h, 84% over 2 steps; (iii) (a) NaH, PMBBr, THF, 0 °C to rt, 4 h, 84%; (b) TsOH, MeOH, 0 °C to rt, 3 h, 90%; (c) TsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 6 h, then LAH, THF, 0 °C to rt, 76% over 2 steps; (iv) EDC, DMAP, CH_2Cl_2, 0 °C, 14 h, 85%; (v) (a) DDQ, CH_2Cl_2-H_2O, 0 °C, 40 min.,85%; (b) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 30 h, 68%.

The epoxy alcohol **58** was converted to the corresponding allylic alcohol **59** using appel reaction condition (I_2, PPh_3, imid., THF, 0 °C) followed by reductive ring opening with

activated Zn. The completion of acid fragment **60** was achieved in four steps: (i) PMB protection; (ii) silyl deprotection; (iii) IBX oxidation and (iv) pinnick oxidation of primary alcohol. The synthesis of alcohol fragment **63** involves a Sharpless asymmetric epoxidation of allylic alcohol obtained from L-malic acid **61**. Alcohol fragment **63** and carboxylic acid fragment **60** were coupled using 3-(ethyliminomethyleneamino)-*N*,*N*-dimethyl-propan-1-amine (EDCI) followed by PMB deprotection and Ring Closing Metathesis (RCM) to give (+) stagonolide C **54** in 68% yield (**Scheme 12**).

Nanda's approach (2009)[26b]

Nanda *et al* have reported the synthesis of (+)-stagonolide C by a chemo-enzymatic approach. The alcohol **65** was subjected to DKR (dynamic kinetic resolution) reaction by coupling enzyme-catalyzed transesterification reaction with a metal-catalyzed racemization method to give the corresponding acetate which on hydrolysis furnished desired enantiomerically pure alcohol **66** in 94% yield. The alcohol **66** was then converted into acid fragment **60** in 72 % yields in 3 steps: (i) PMB protection of **66** (PMB acetimidate, CSA, 85%; (ii) TBS deprotection (PPTS) and (iii) oxidation of primary alcohol. The synthesis of alcohol fragment **63** was achieved from racemic alcohol **67**. Metal-enzyme combined DKR reaction of **67** afforded enantiomerically pure alcohol which on series of protection-deprotection reaction sequences led to the formation of compound **68**. Silyl deprotection of compound **68** gaves alcohol fragment **63** in 90% yields Alcohol fragment **63** and carboxylic acid fragment **60** were coupled using 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) followed by PMB deprotection and Ring Closing Metathesis (RCM) to give (+) stagonolide C **54** in 66% yield (**Scheme 13**).

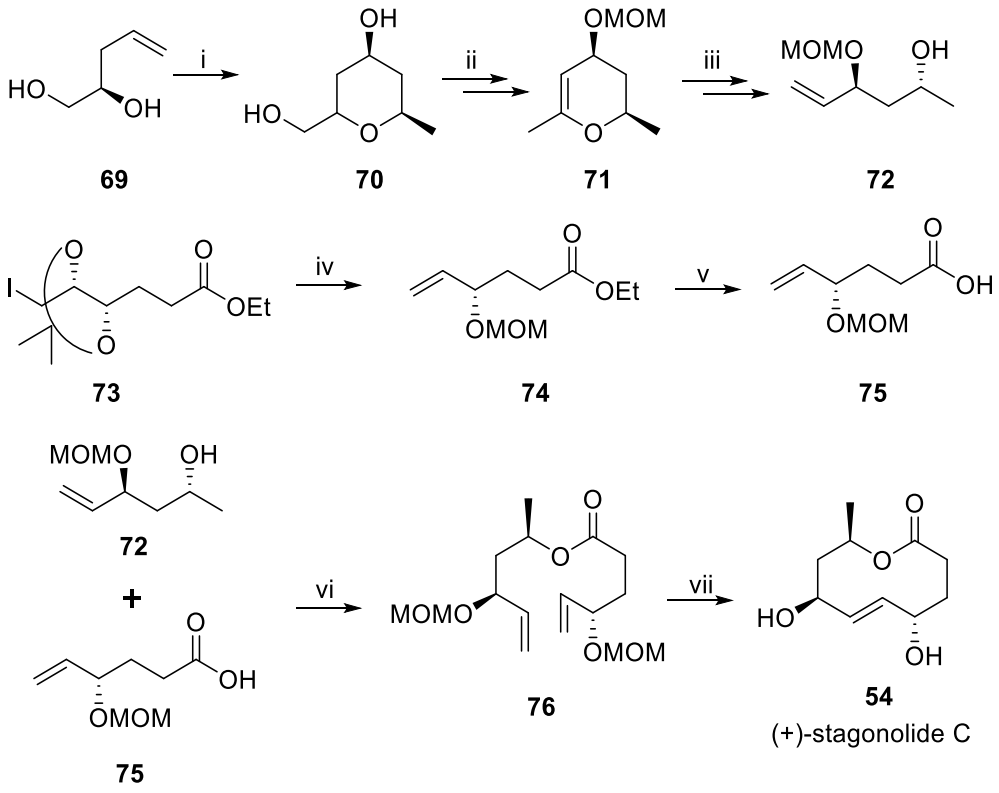


Scheme13: (i) CAL-B, isopropenyl acetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II), K_2CO_3, KO^tBu, 90%; (ii) (a) PMBO-(C=NH)-CCl_3, CSA, 85%; (b) PPTS, MeOH, 88%; (c) PDC, DMF, 72%; (iii) TBAF, THF, 90%; (iv) EEDQ, THF, 92%; (v) (a) DDQ, DCM/H_2O (19:1), 85%; (b) Grubbs-II, DCM, 66%.

Yadav's approach (2012)[26d]

In yet another approach Nanda *et al* have achieved the synthesis of (+)-stagonolide C **54** involving Prins cyclization and RCM as the key steps. Prins cyclization between the known homoallylic alcohol **69** and acetaldehyde in the presence of trifluoroacetic acid resulted in the formation of compound **70.** Compound **70** was then converted into rearranged product **71** in 5 steps: (i) tosylation of **70** (TsCl, Et_3N) ; (ii) MOM protection ($MeOCH_2Cl$, $^iPr_2EtN$) (iii) iodination (NaI) (iv) elimination and (v) rearrangement. Ozonolysis of **71** followed by treatment with methylenetriphenylphosphorane furnished the open-chain olefinic acetate which on hydrolysis provided the corresponding alcohol fragment **72** in 96% yield. Reductive elimination of iodo derivative **73** promoted by Zn/EtOH afforded secondary alcohol derivative which was protected as its MOM-ether

gave compound **74**. Subsequent saponification of the ester group with 2N NaOH and MeOH afforded acid fragment **75** in 85% yield. Coupling of acid fragment **75** with alcohol fragment **72** using DCC followed by Ring Closing Metathesis (RCM) of coupled product **76** gave (+) stagonolide C **54 in** 76% yield (**Scheme 14**).

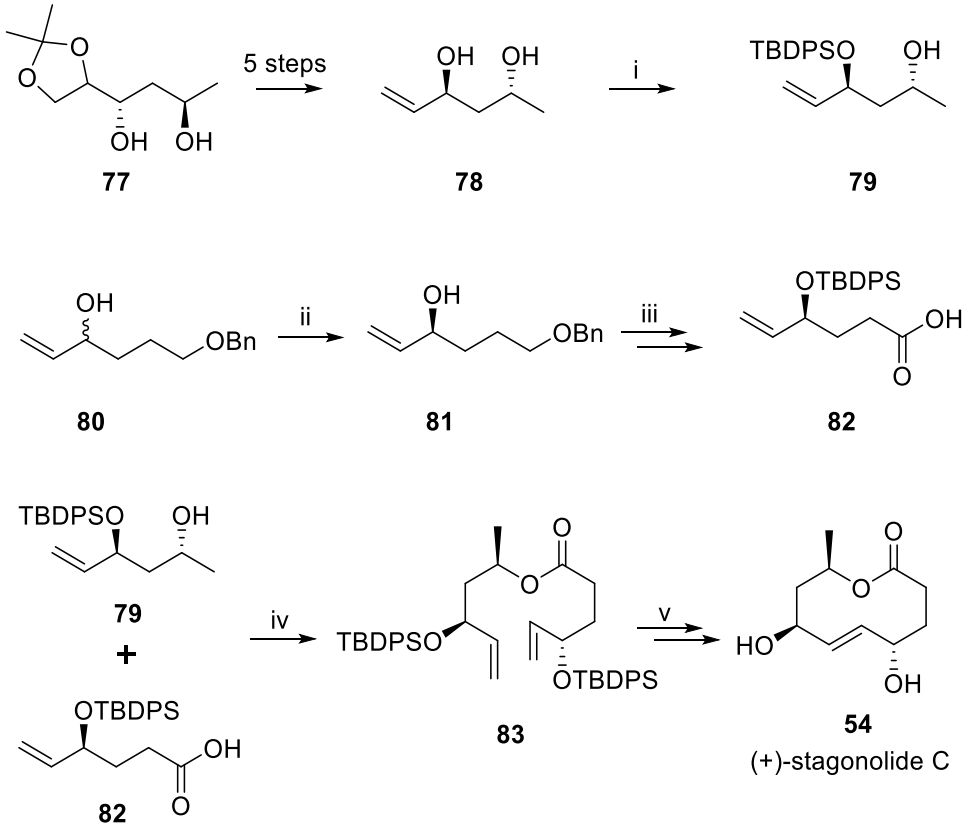


Scheme 14: (i) MeCHO, CF_3COOH, CH_2Cl_2 , then K_2CO_3 , MeOH, r.t, 5 h; 55%; (ii) (a) TsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 3 h; 90%; (b) $MeOCH_2Cl$, $^iPr_2EtN$, CH_2Cl_2, 0 °C to r.t., 3 h; 90%. (c) NaI, acetone, reflux, 24 h; 95%; (d) NaH, DMF, r.t., 6 h; (e) SiO_2, 72%; (iii) (a) O_3, Ph_3P, CH_2Cl_2 , then $Ph_3P{=}CH_2$, THF, -78 °C to 0 °C, 74%; (b) K_2CO_3, MeOH, r.t., 2 h, 96%; (iv) (a) Zn, EtOH, reflux, 2 h, 86%; (b) $MeOCH_2Cl$, $^iPr_2EtN$, N,N-dimethylpyridin-4-amine DMAP (cat.), CH_2Cl_2, 0 °C to r.t., 3 h, 82%; (v) 2N NaOH, MeOH, r.t., 6 h, 85%; (vi) DCC, DMAP, CH_2Cl_2, 0 °C to r.t.,2 h, 80%; (vi) (a) Grubbs 2nd-gen. catalyst, CH_2Cl_2, reflux, 24 h, 60%; (b) Me_3SiBr, CH_2Cl_2 , -40 °C, 15 min; 76%.

Nagaiah's approach (2012)[27]

Nagaiah *et al* have described the synthesis of (+)-stagonolide C **54** using Barbier allylation, chiral-auxiliary mediated acetate aldol addition, a 1,3-anti-reduction, a

Sharpless kinetic resolution and Yamaguchi macrolactonization and ring-closing metathesis as the key reactions. The alcohol fragment **79** was prepared from a key intermediate **77**. The compound **77** was then converted into diol **78** in 5 steps. Hydroxyl group in diol **78** was then protected as its silyl ether to give alcohol **79**. The rac-vinyl carbinol **80** upon Sharpless kinetic resolution afforded enantiomerically pure allylic alcohol **81**. The acid fragment **82** was obtained from alcohol **81** in 4 steps: (i) TBDPS protection; (ii) benzyl deprotection; (iii) PCC oxidation and (iv) pinnick oxidation. Coupling of acid fragment **82** with alcohol fragment **79** using Yamaguchi macrolactonization followed by Ring Closing Metathesis (RCM) to give (+) stagonolide C **54** in 68% yield (**Scheme 15**).

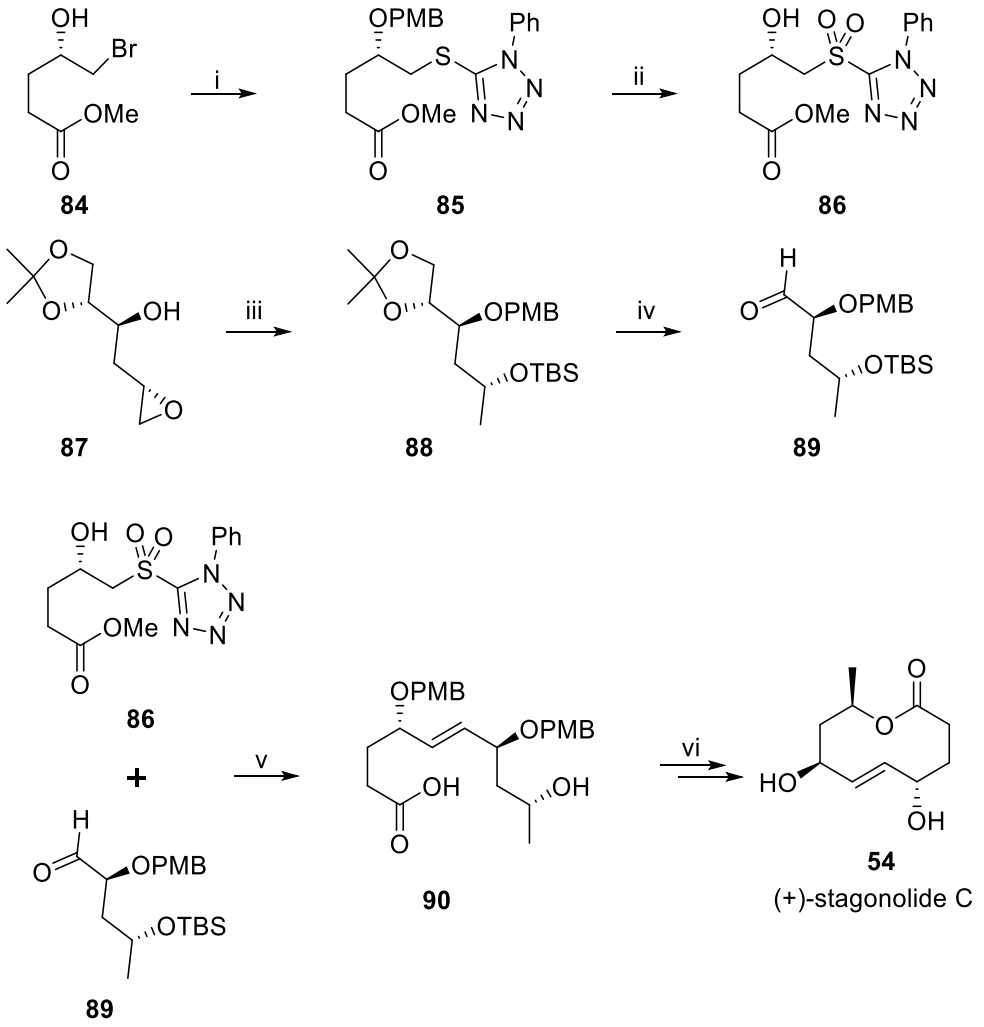


Scheme 15: (i) TBDPSCl, imid., CH_2Cl_2, 0 °C, 5 h, 90%; (ii) (-)-DET, Ti (Oi-pr)$_4$, TBHP, CH_2Cl_2, -20 °C, 6 h, 46%; (iii) (a) TBDPSCl, imid., CH_2Cl_2, rt, 8 h, 95%; (b) DDQ, CH_2Cl_2-H_2O, reflux, 4 h.,90%; (c)

PCC, NaOAC, CH_2Cl_2, rt, 5 h, 90%; (d) $NaClO_2$, NaH_2PO_4,2-methyl-2-butene, t-BuOH, H_2O, 0 ^oC to r.t., 10 h, 92% (iv) 2,4, 6 tribenzoyl chloride, NEt_3,THF, DMAP 0 ^oC, 14 h, 86%; (v) (a) HF/pyridine, THF, 0 ^oC, 8 h, 84%; (b) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 24 h, 68%.

Qiao's approach (2012)[26c]

Qiao *et al* have reported the synthesis of (+)-stagonolide C **54** using chiral pool approach as discussed below. The synthesis of sulfone **86** commences from a key intermediate **84** which was prepared from L-glutamic acid in 5 steps.



Scheme 16: (i) (a) PMBO-(C=NH)-CCl_3, PPTS, CH_2Cl_2, 70%; (b) 1-phenyl-5-mercapto-tetrazole, K_2CO_3, acetone, 84%; (ii) m-CPBA, CH_2Cl_2, 82%; (iii) (a) PMBCl, NaH., 86%; (b) LAH, 96%; (c) TBSOTf, 2,6 lutidine, CH_2Cl_2, 100%; (iv) (a) 50% TFA, CH_2Cl_2, 50%; (b) $NaIO_4$, THF/H_2O; (v) (a) NaHMDS, HMPA,

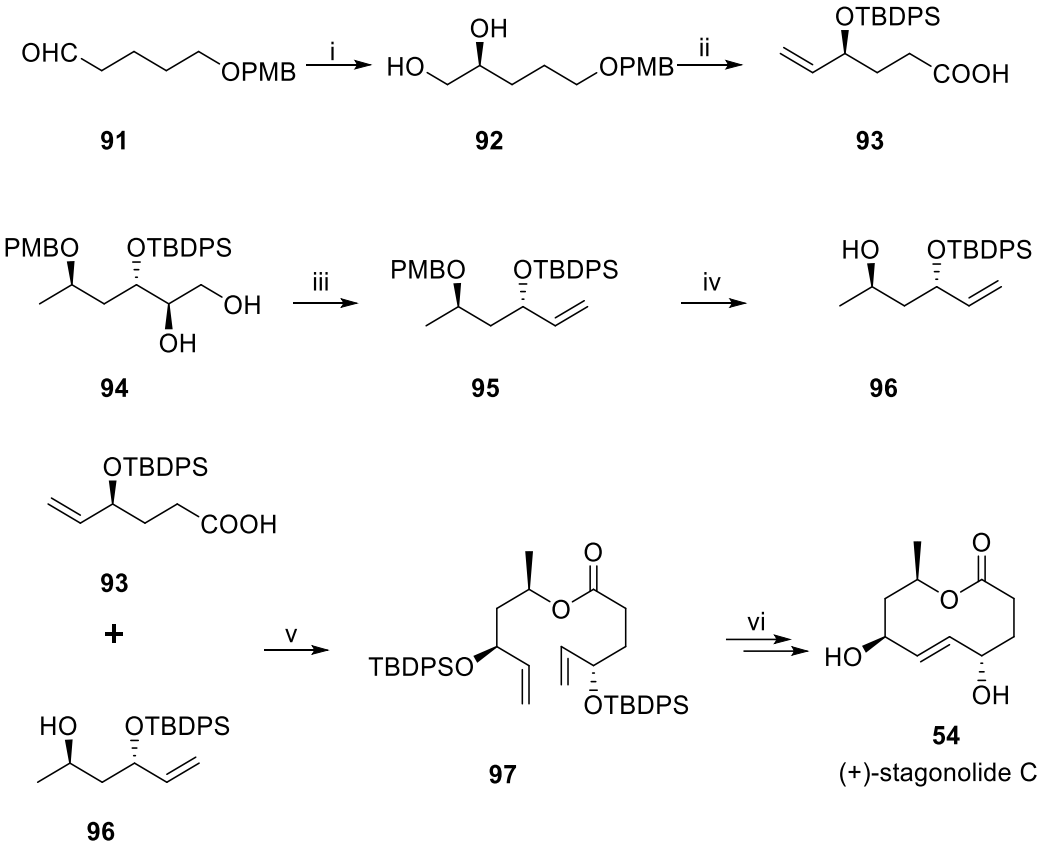
-78 ^{o}C, 60%; (b) CSA, MeOH, 68%; (c) LiOH, 98%; (vi) (a) 2,4,6 trichlorobenzoyl chloride, NEt_3,THF then DMAP, benzene, 63%; (b) CAN, CH_3CN:H_2O,100%.

PMB protection of hydroxyl group in compound **84** and subsequent thianation with N-Phenyl-5-mercaptotetrazole/K_2CO_3 gave **85** in 83% yield. Compound **85** then subjected to m-CPBA oxidation to give sulfone fragment **86**. The synthesis of aldehyde fragment **89** began with Mulzer' epoxide **87**, which was prepared from D-glucono-1,5-lactone. The Mulzer' epoxide **87** was then converted into acetonide **88** in 3 steps *i.e* PMB protection, epoxide ring opening with LAH and TBS protection. Hydrolysis of acetonide **88** followed by subsequent treatment with $NaIO_4$/H_2O-THF led to the required aldehyde **89**. The sulfone fragment **86** and aldehyde fragment **89** were then coupled using Julia-Lythgoe olefination which on TBS deprotection and ester hydrolysis gave the seco acid **90**. Yamaguchi esterification of seco acid **90** and cleavage of PMB protecting groups using CAN afforded (+) stagonolide C **54** in quantitative yield (**Scheme 16**).

Kumar's approach (2016)[26e]

Kumar *et al* have described an organocatalytic approach for the synthesis of (+)-stagonolide C **54**. The synthesis of acid fragment **93** starts with aldehyde **91** which was subjected to D-proline catalyzed sequential α-aminooxylation followed by reduction with $NaBH_4$ and cleavage of the O-N bond afforded diol **92**. Diol **92** was then converted into acid fragment **93** in six steps: (i) monotosylation of diol; (ii) epoxide formation with K_2CO_3 in MeOH; (iii) epoxide opening with sulphur ylide; (iv) TBS protection; (v) PMB deprotection and (vi) oxidation to acid. Alcohol fragment **96** was prepared from chiral intermediate diol **94**. Diol **94** was subjected to direct reductive elimination with iodine, Ph_3P and imidazole at reflux for 4 h to give olefin **95** in 83 % yield. Cleavage of the PMB

protecting group with DDQ furnished the target alcohol **96** in 80 % yield. The alcohol **96** was then coupled with acid **93** under the Shiina protocol to give diene **97** in 93 % yield. Finally, TBDPS deprotection followed by RCM afforded (+) stagonolide C **54 in** 78% yield (**Scheme 17**).



Scheme 17: (i) (a) (1) D-proline, PhNO, DMSO; (2) $NaBH_4$, MeOH, rt, 0.5 h; (b) $CuSO_4 \cdot 5\,H_2O$, MeOH, 10 h, 78 % (over three steps); (ii) (c) (1) Bu_2SnO, TsCl, NEt_3, CH_2Cl_2; (2) K_2CO_3, MeOH, 0.5 h, rt, 80 % (over two steps); (d) (1) $(CH_3)_3S^+I^-$, *n*BuLi, THF, –20 °C; (2) TBSCl, imidazole, CH_2Cl_2, 82 % (over two steps); (e) (1) DDQ, CH_2Cl_2/H_2O (18:1), room temp.,1 h; (2) TEMPO (catalytic), BAIB, CH_3CN/H_2O (3:1), rt, 7 h. 75 % (over two steps); (iii) Ph_3P, I_2, imidazole, THF, reflux, 4 h, 83 %; (iv) DDQ, CH_2Cl_2/H_2O (18:1), room temp.,1 h, 80 %; (v) 2-methyl-6-nitrobenzoic anhydride, NEt_3, DMAP, CH_2Cl_2, 6 h, 93 %; (vi) (a) (i) NH_4F, MeOH, 40 °C, 24 h; (b) second-generation Grubbs catalyst (10 mol%), CH_2Cl_2, reflux, 48 h, 78 % (over two steps).

1.2.3. Present Work

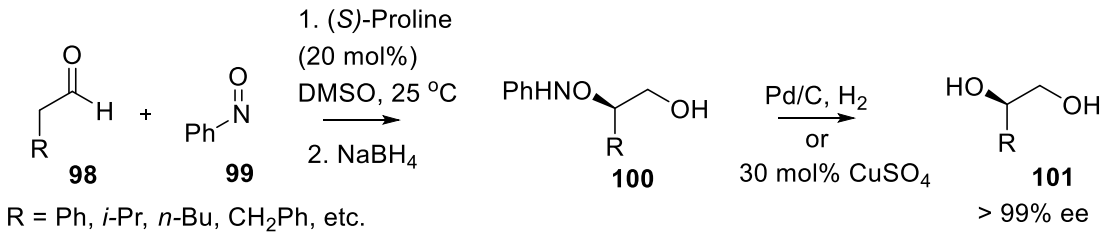
1.2.3.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of (+)-stagonoide C **54**, either employ chiral starting materials or use of kinetic resolution protocol for the induction of chirality, apart from employing expensive reagents and longer reaction sequences. Recently, asymmetric synthesis *via* organocatalysis has emerged as one of the most useful method for obtaining chiral materials. In particular, proline and its derivatives have proven to be practical and versatile organocatalysts in natural product synthesis.[28] In a continuation of our work on the proline-catalyzed synthesis of bioactive molecules, we herein report a concise synthesis of (+)-stagonolide C **54** starting from readily available raw materials. Proline catalyzed asymmetric *α*-aminooxylation and Jorgensen's epoxidation of aldehyde are the key reactions employed in the introduction of chirality.

1.2.3.2 Proline-catalyzed *α*-Aminooxylation

Optically active *α*-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1, 2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective *α*-oxygenations include the use of Davis oxaziridine,[29a] Sharpless dihydroxylation of enol ethers,[29b] manganese-salen epoxidation of enol ethers,[29c] and Shi epoxidation of enol ethers.[29d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[30] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde.

Recently, proline has been found to be an excellent asymmetric catalyst for *α*-aminooxylation of carbonyl compounds. When an aldehyde **98** without substitution at α-position was reacted with nitrosobenzene **99** in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde takes place at the *α*-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminooxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **101** in very high enantioselectivities (**Scheme 18**).



Scheme 18: α-Aminooxylation of aldehydes

The catalytic cycle of the α-aminooxylation reaction is shown in **Figure 16**. The observed enantioselectivitiy of the catalytic α-aminooxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair like transition state where the *Si* face of an *E*-enamine formed from the aldehyde and L-proline approaches the less-hindered oxygen atom of nitrosobenzene to provide a chiral *α*-aminoxyaldehyde with *R* configuration.

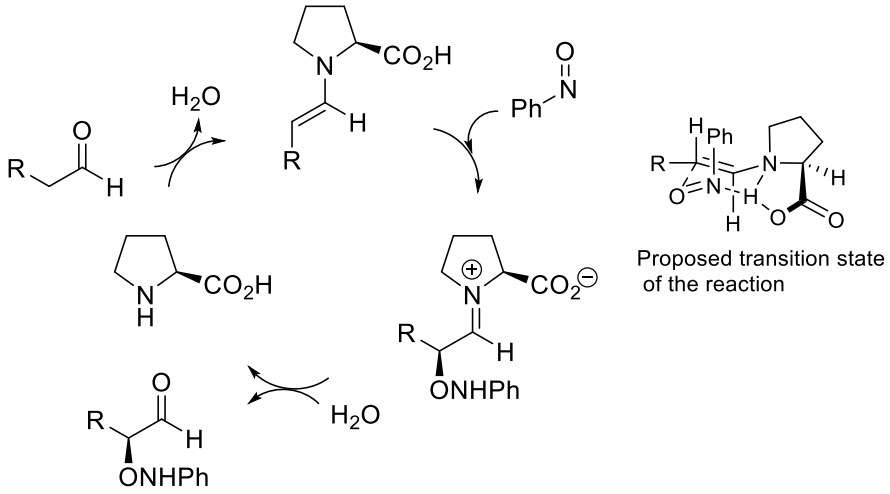
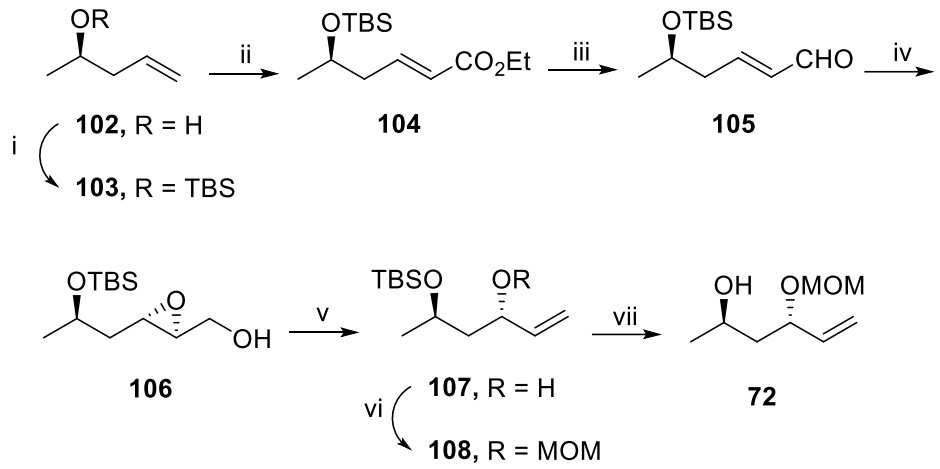


Figure 16: Proposed mechanism of the *α*-aminooxylation reaction

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

1.2.4. Results and Discussion

Based on retrosynthetic analysis, we visualized that alcohol **72** and carboxylic acid **115** could form the key fragments for (+)-stagonolide C **54**. The synthesis of (+)-stagonolide C **54** commenced with the homoallylic alcohol **102**, prepared readily from acetaldehyde in 71% yield and 99% ee using Brown's allylation protocol.[31] (**Scheme 19**).



Scheme 19: (i) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 6 h, 76% (ii) ethyl acrylate, Grubbs-II (2 mol%), dry CH_2Cl_2, reflux, 12 h, 65%; (iii) DIBAL-H, toluene, -78ºC, 1h, 73%; (iv) H_2O_2, CH_2Cl_2, (10 mol%) 2-[bis(3,5-bistrifluoromethylphenyl) trimethylsilanyloxymethyl]pyrrolidine, 25 ºC, 4 h then $NaBH_4$, MeOH, 0 ºC,1 h, 53%; (v) (a) I_2, PPh_3, imid., Et_2O/CH_3CN (3:1), 0-25 ºC, 2 h; (b) Zn, NaI, MeOH, reflux, 3 h, 90% (for two steps); (vi) MOMCl, DIPEA, dry CH_2Cl_2, 16 h, 90%; (vii) TBAF, THF, 2 h, 82%.

Compound **102** on silylation (TBSCl, imid) gave silyl ether **103** in 76% yield. Its formation was confirmed by ^1H and ^{13}C NMR spectral analysis, which showed a typical proton singlet at δ 0.03 (s, 6H) and singlet at δ 0.87 (s, 9H) corresponding to methyl protons of silyl group in its ^1H NMR spectrum. Its ^{13}C NMR spectrum displayed typical carbon signals at δ 68.4 and -4.4, -4.6 due to methine and methyl carbons attached to silyl group (**Figure 17)**.

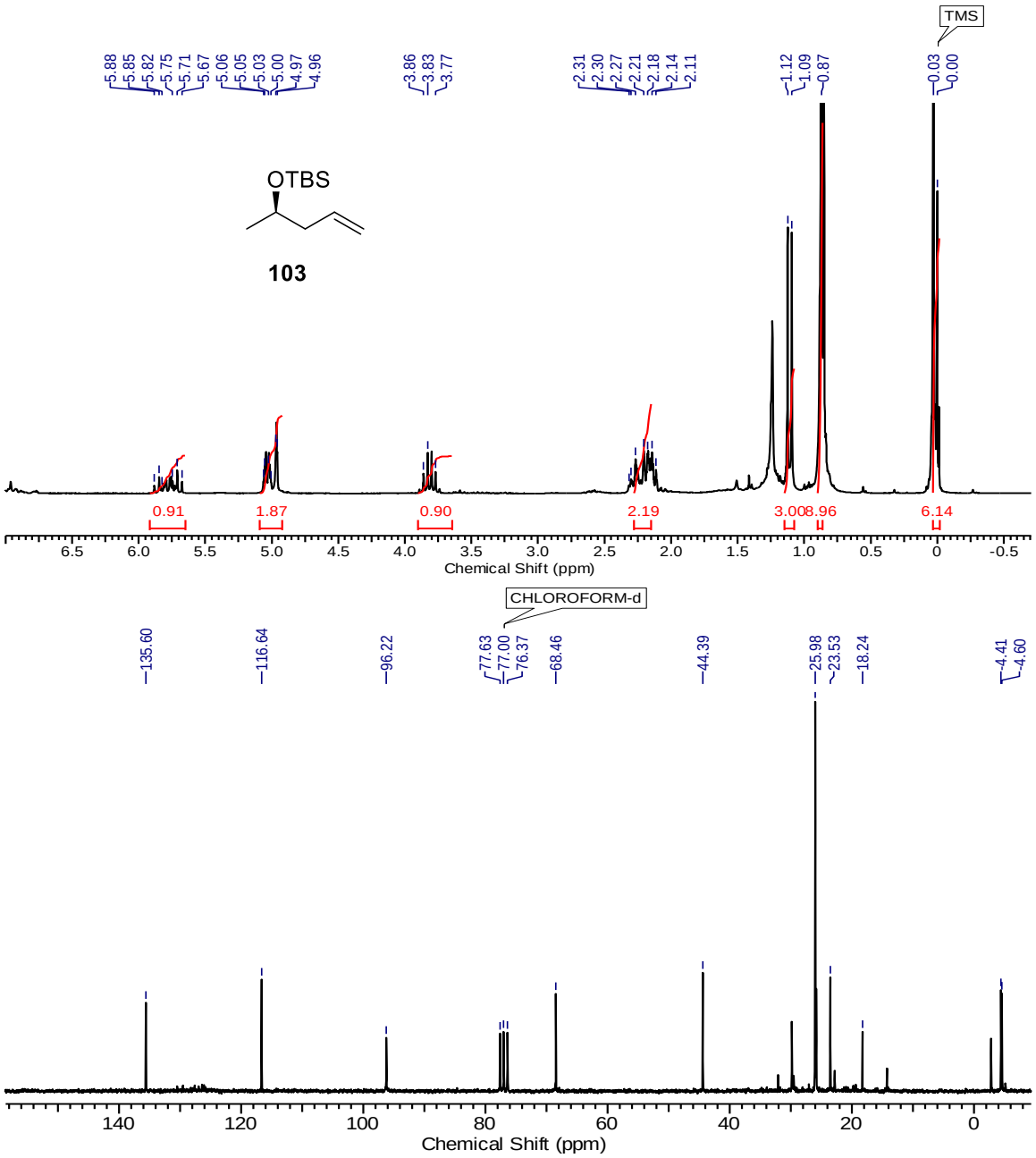


Figure 17: ^{1}H and ^{13}C NMR spectra of silyl ether **103**

Silyl ether **103** on cross metathesis with cross-metathesis with ethyl acrylate using Grubb's II catalyst afforded α,β-unsaturated ester **104** in 65% yield. The ^{1}H NMR spectrum of **104** showed a doublet at δ 5.73-5.80 (d, J = 15.81 Hz, 1H) and multiplet at δ 6.81-6.97 (m, 1H) attributed to olefinic protons present in α,β-unsaturated ester **104**. It was

further supported by a typical carbon signal at δ 123.2 and 145.8 due to olefinic carbons. (**Figure 18)**.

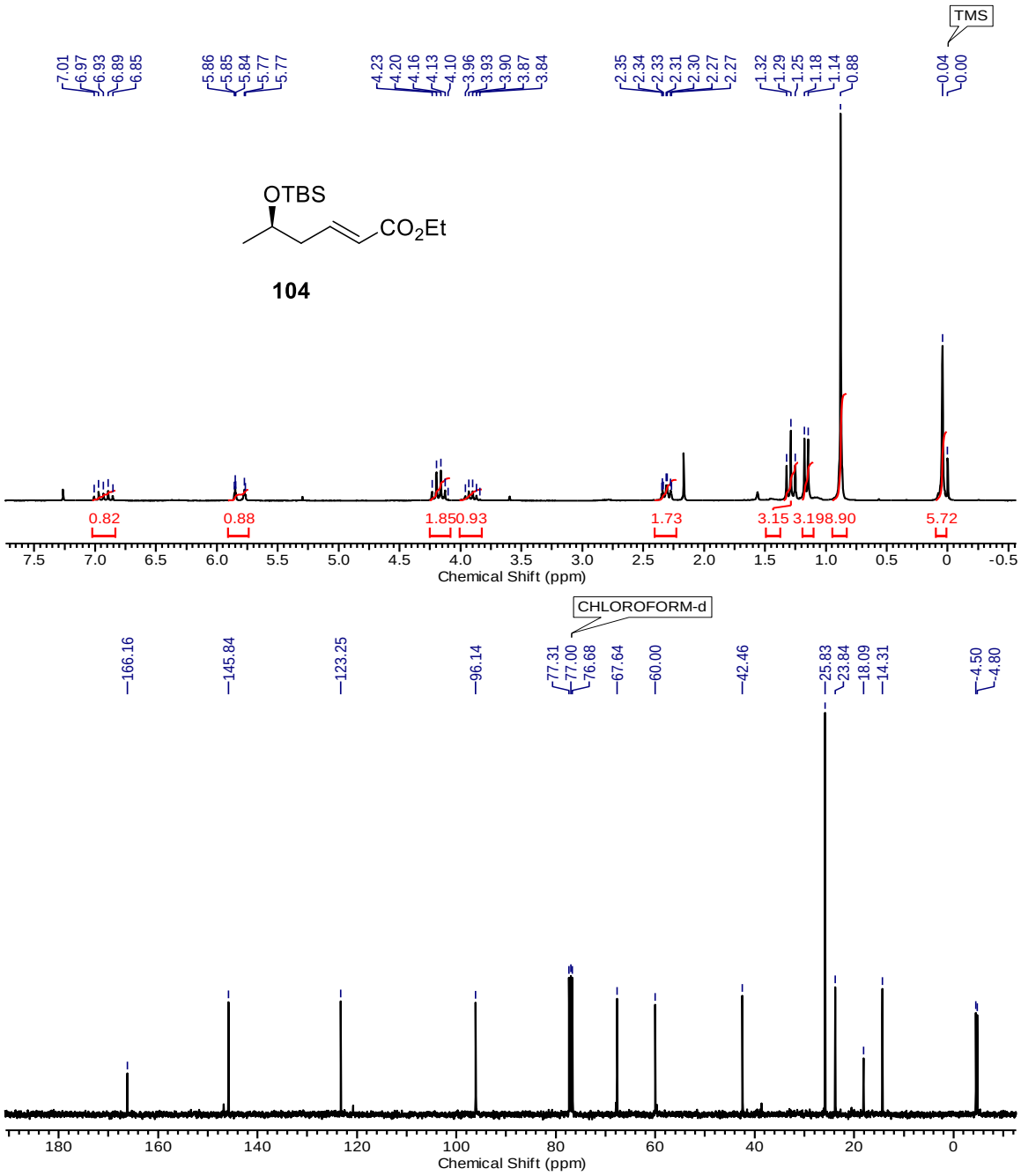


Figure 18: ^{1}H and ^{13}C NMR spectra of α,β-unsaturated ester **104**

Mild reduction of **104** with DIBAL-H at -78 ºC furnished α,β-unsaturated aldehyde **105** in 70% yield. Its formation was confirmed by the appearance of characteristic signal

doublet at δ 9.5 due to aldehyde functionality in compound **105**. Its ^{13}C NMR NMR spectrum showed a typical carbon signal at δ 193.4 indicative of aldehydic carbon (-**C**HO) atom (**Figure 19)**.

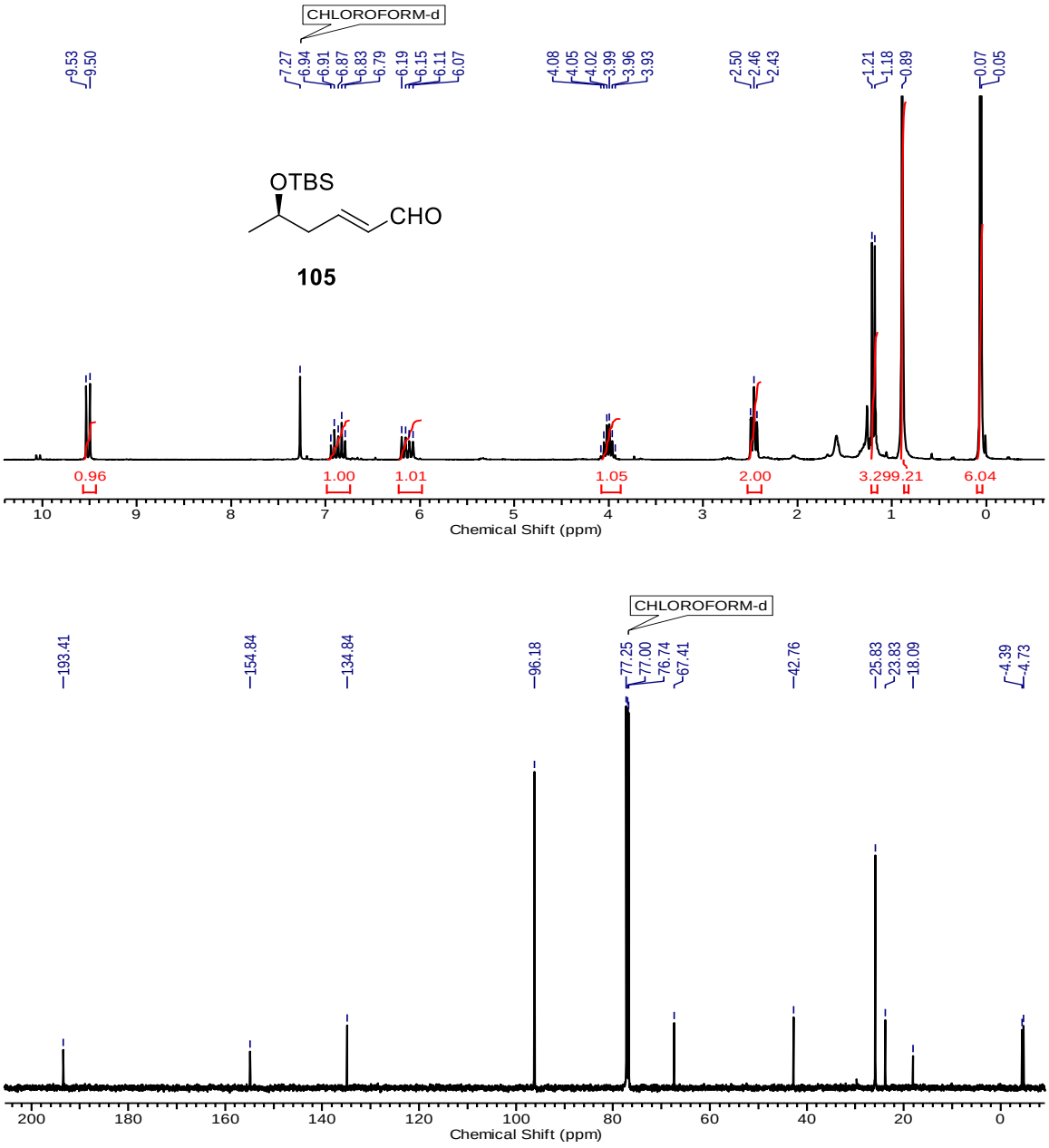


Figure 19: ^{1}H and ^{13}C NMR spectra of α,β-unsaturated aldehyde **105**

The α, β-unsaturated aldehyde **105** was then subjected to Jorgensen's asymmetric epoxidation (H_2O_2, CH_2Cl_2, 10 mol% of 2-[bis(3,5-

bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine) followed by *in situ* reduction with $NaBH_4$ gave the epoxy alcohol **106** in 53% yield (**Figure 20)**.

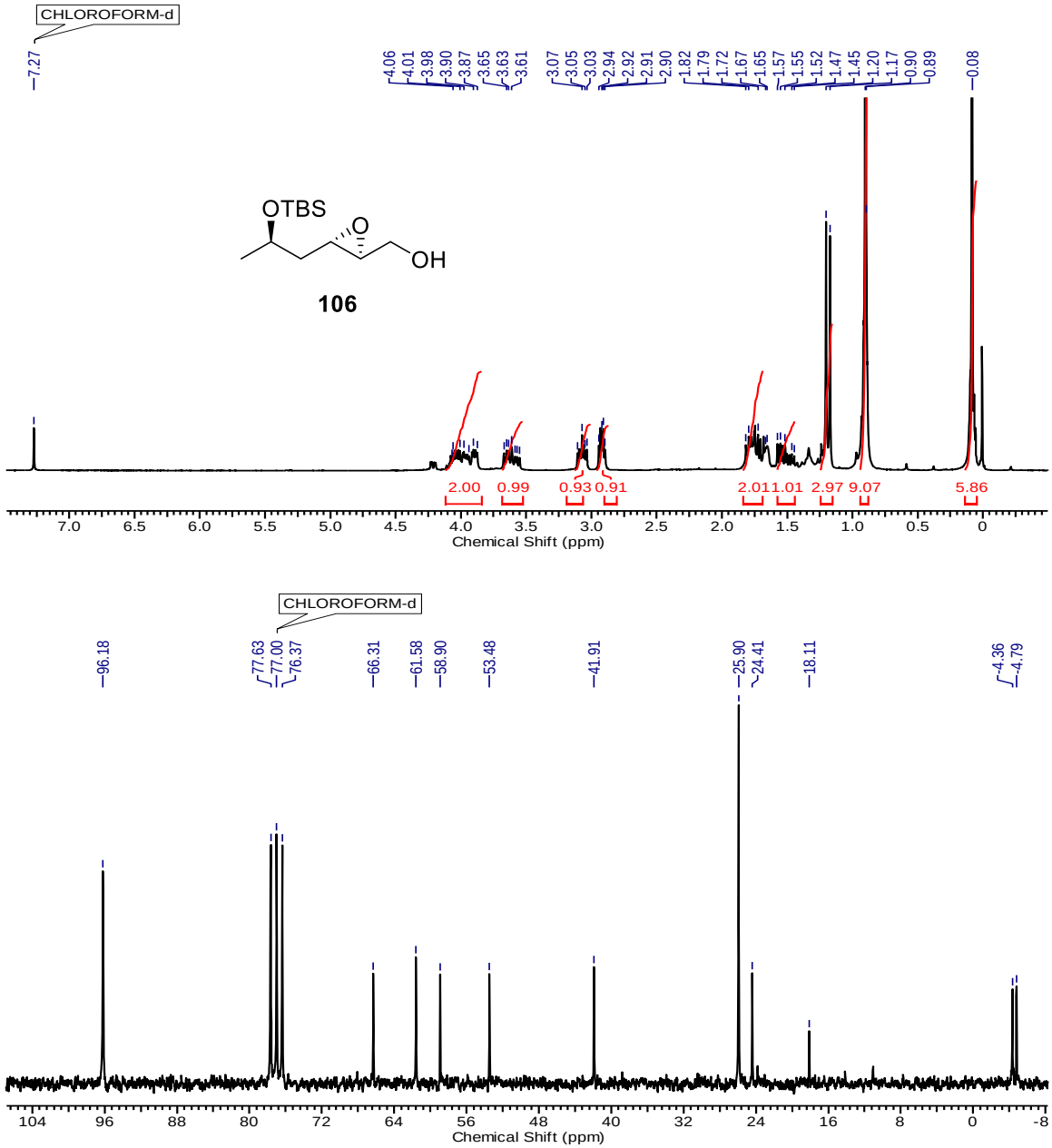


Figure 20: ^{1}H and ^{13}C NMR spectra of epoxy alcohol **106**

The formation of **106** was confirmed from its ^{1}H NMR spectrum, which showed the disappearance of olefinic protons and the appearance of a two typical proton signals at δ 2.89-2.93 (m, 1H) and 3.02-3.09 (m, 1H) due to epoxy protons present in compound **106**. Further, its structure was supported by ^{13}C NMR spectrum, which displayed a typical carbon signal at δ 53.4 and 58.9.

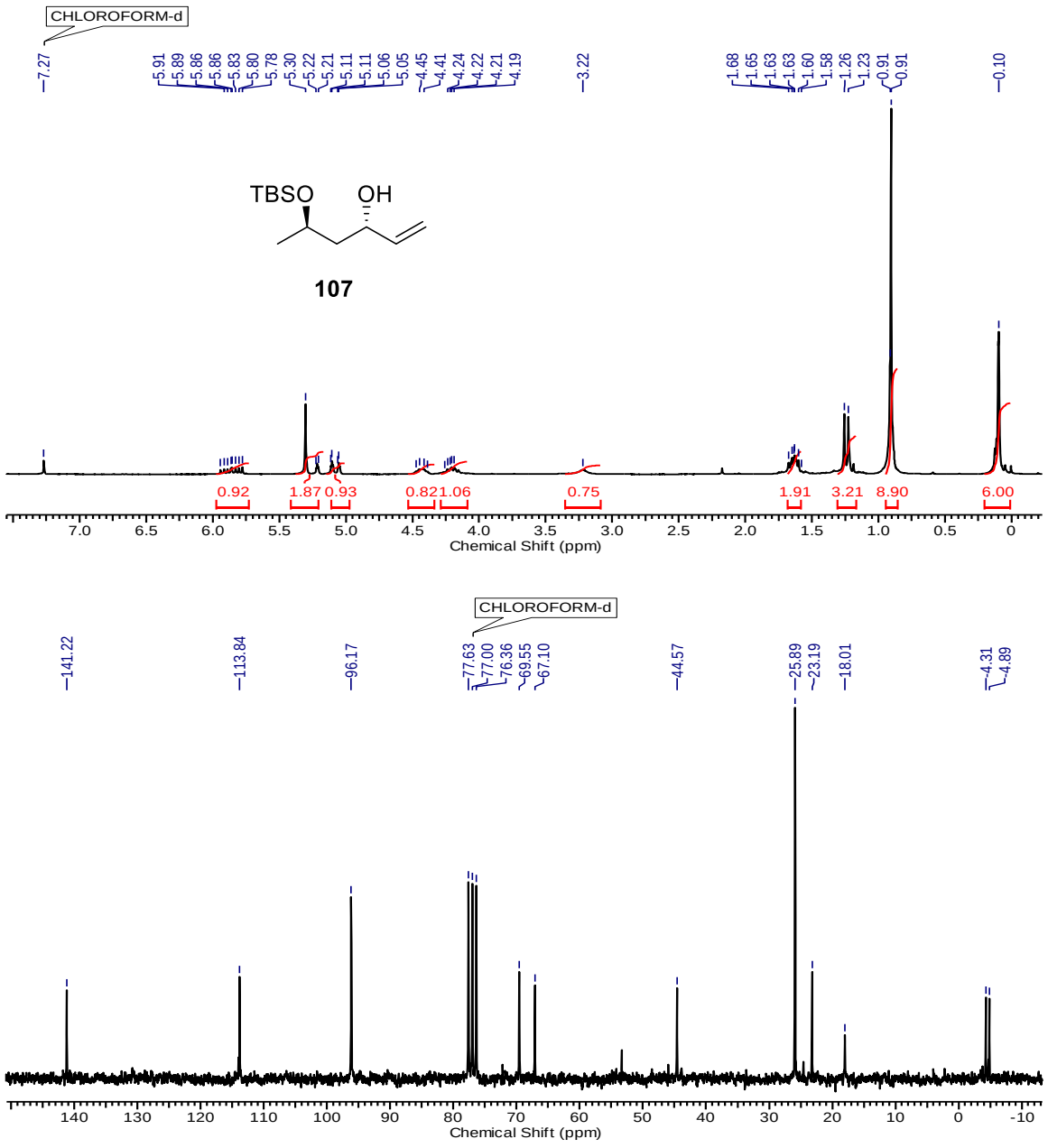
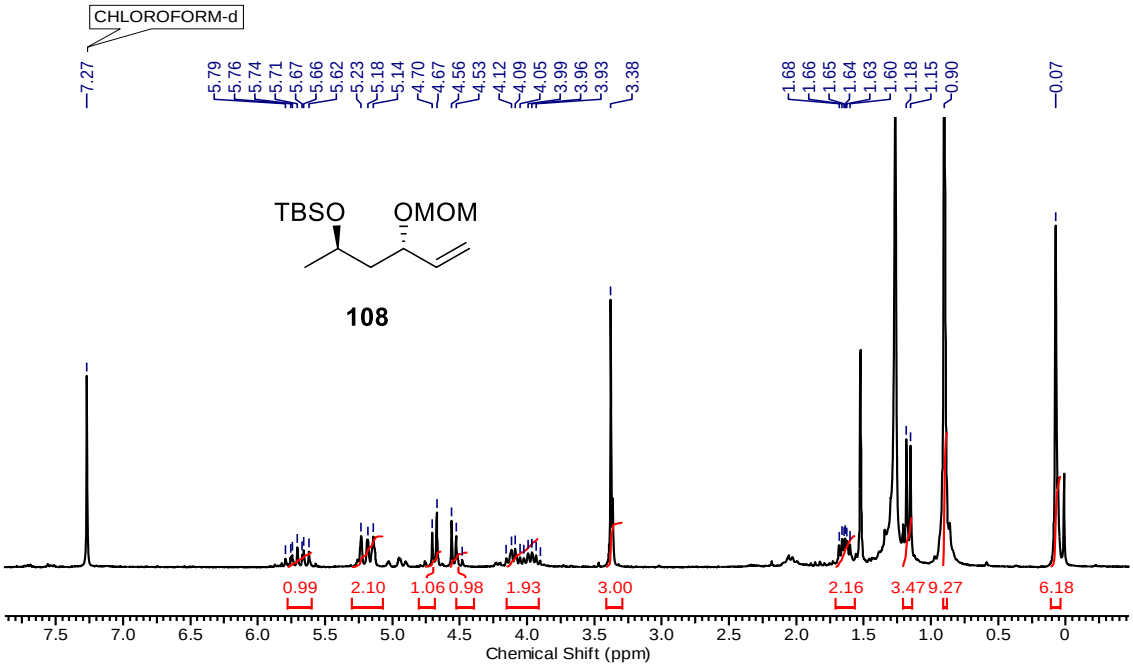


Figure 21: ^{1}H and ^{13}C NMR spectra of alcohol **107**

Compound **106** was then subjected to reductive ring opening to give alcohol **107** in two steps: (i) iodination of **106** under Appel reaction condition (I_2, PPh_3, imid); (ii) followed by reductive ring opening with Zn and NaI. The formation of alcohol **107** was confirmed by the ^1H and ^{13}C NMR spectra, which displayed multiplets at δ 5.78-5.91 (m, 1H) and 5.05-5.30 (m, 2H) due to the presence of olefinic protons. Also olefinic carbon signals appered at δ 141.2 and 113.8 (**Figure 21)**.

The secondary alcohol functionality in **107** was then protected as its MOM ether (MOMCl, Et_3N) to give compound **108**. Its ^1H NMR spectrum showed a typical proton signal singlet at δ 3.38 (s, 3H) corresponding to methyl group (-C**H**$_3$) of MOM. It was further supported by its ^{13}C NMR spectrum which shows carbon signal at δ 44.5 due to methyl carbon (-**C**H_3) of MOM group (**Figure 22)**.



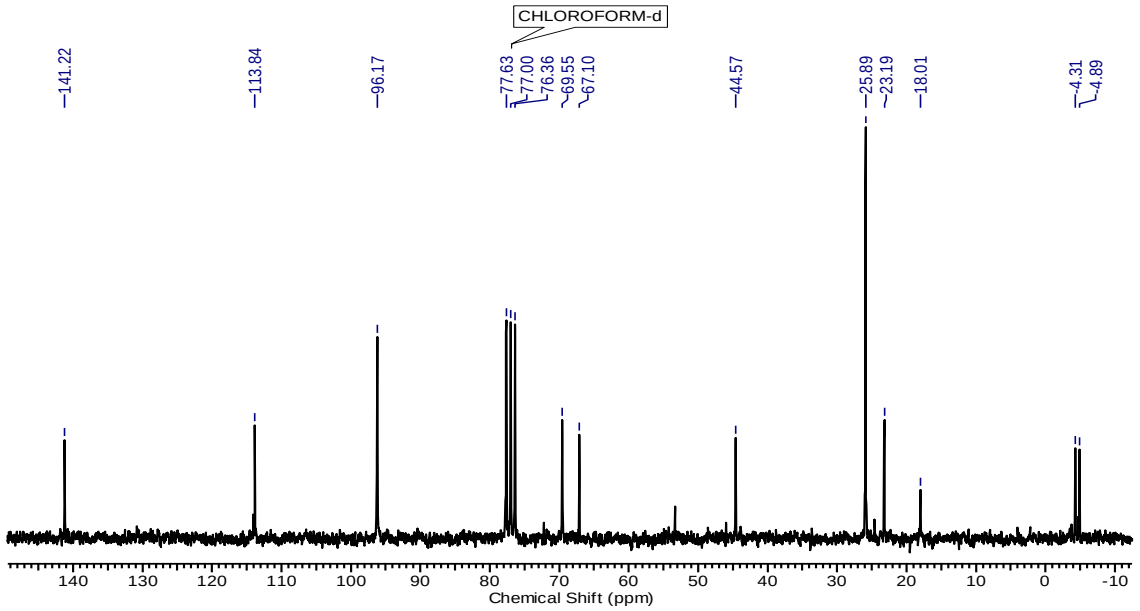
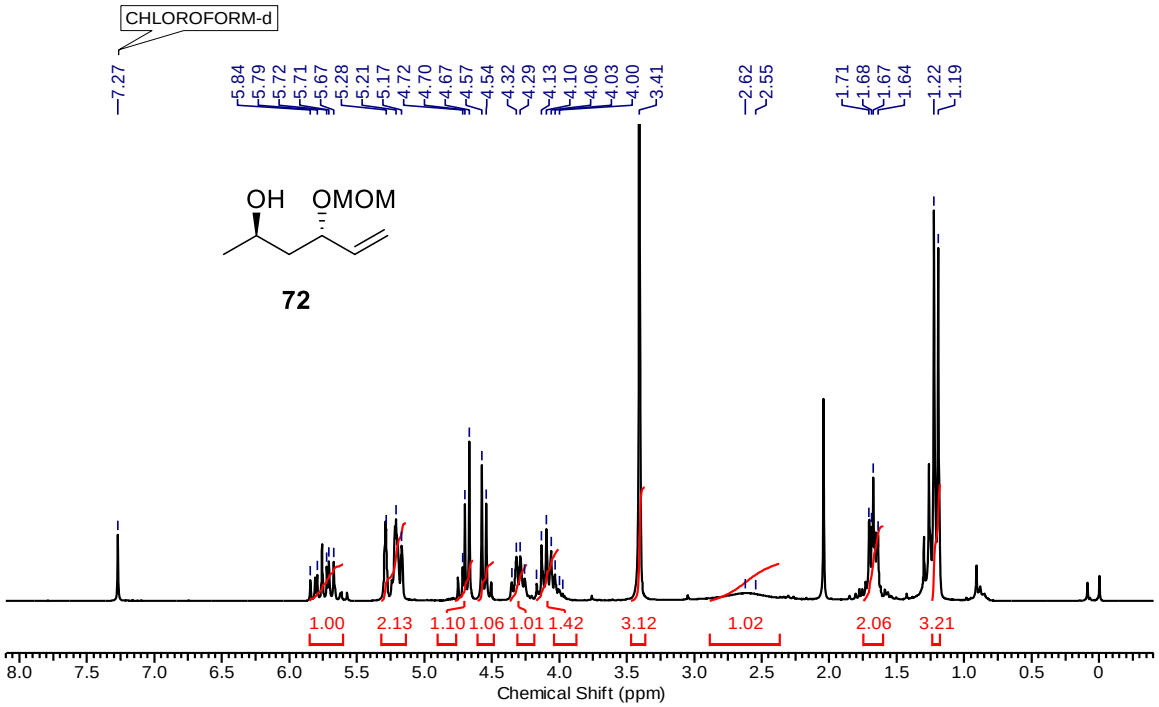


Figure 22: ^{1}H and ^{13}C NMR spectra of compund **108**

Further de-silylation of compound **108** with TBAF in THF furnished the secondary alcohol fragment **72** in 12.2% overall yield and 96% ee. The formation of alcohol fragment **72** was confirmed by its ^{1}H and ^{13}C NMR spectrum which shows disappearance of the proton signals due to the MOM protective group (**Figure 23)**.



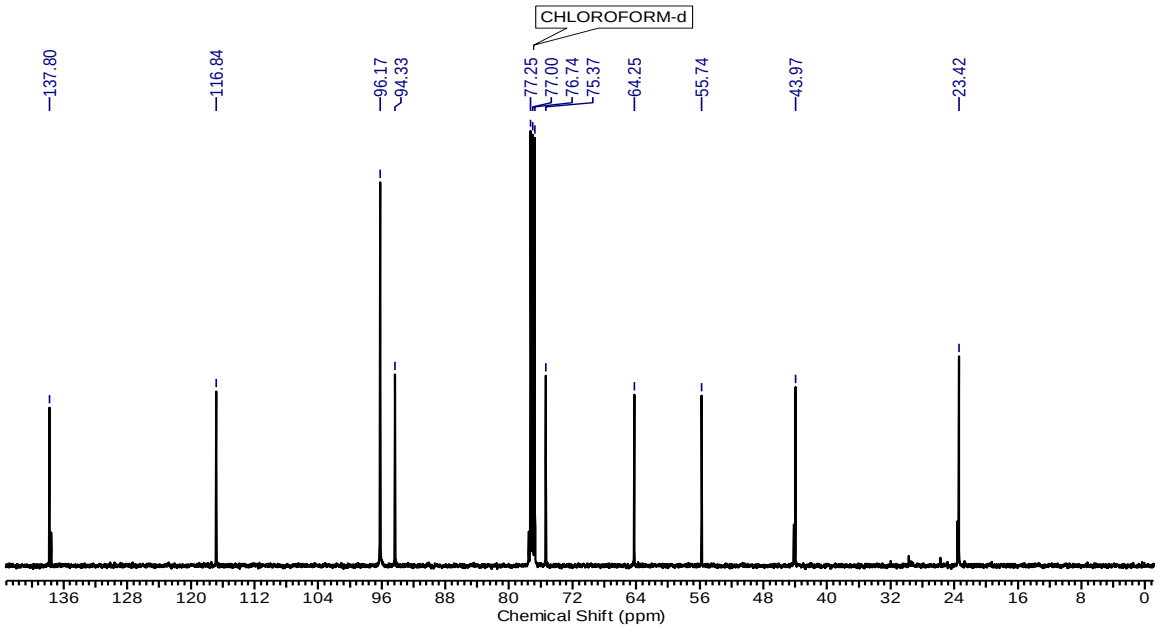
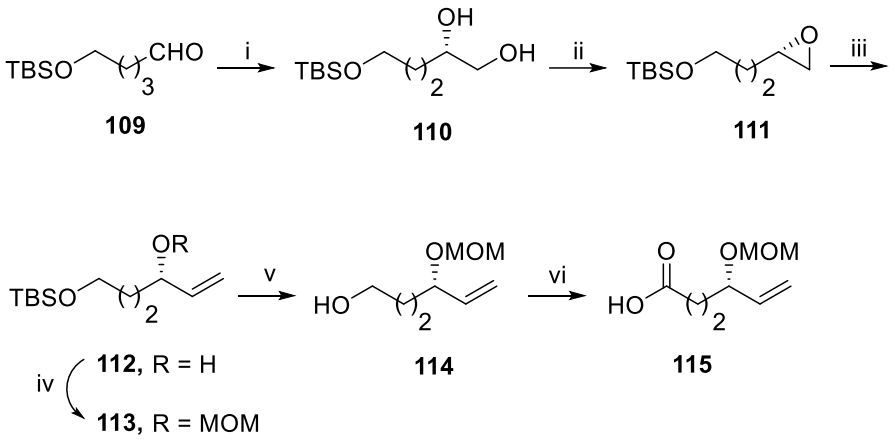


Figure 23: ^{1}H and ^{13}C NMR spectra of alcohol fragment **72**

Scheme 20 presents the synthesis of acid fragment **115**, which starts from aldehyde **109**. D-proline catalyzed *α*-aminooxylation of aldehyde **109** followed by *in-situ* reduction with $NaBH_4$ and subsequent catalytic hydrogenation of the crude *α*-aminoxy alcohol with 10 % Pd/C over H_2 (1 atm) furnished chiral diol **110** in 77% yield (**Scheme 20**).



Scheme 20: (i) (a) PhNO (1 equiv.), D-proline (20 mol %), CH_3CN, -20 ºC, 24 h then $NaBH_4$, MeOH, 0 ºC,1 h; (b) 10% Pd/C, H_2, MeOH, 24 h, 77% (over two steps); (ii) (a) TsCl, Et_3N, Bu_2SnO, DMAP; (b) K_2CO_3, MeOH, 30 min., 92%; (iii) $S^+(CH_3)_3I^-$, NaH, DMSO, 25 ºC. 2 h, 87%; (iv) MOMCl, DIPEA, dry CH_2Cl_2, 16 h, 90%; (v) TBAF, THF, 2 h, 88%; (vi) TEMPO, $PhI(OAc)_2$, CH_3CN: H_2O (4:1), 25 ºC, 4 h, 86%.

The formation of diol **110** was confirmed by the presence of a broad singlet (br s) at δ 2.49 in its ^{1}H NMR spectrum, corresponding to hydroxyl protons. The multilplets at δ 3.39-3.89 (6H) in its ^{1}H NMR spectrum was assigned to methine (-**CH**-OH) and methylene (-**CH$_2$**-OH, -**CH$_2$**-OTBS) protons attached to oxygen atoms.

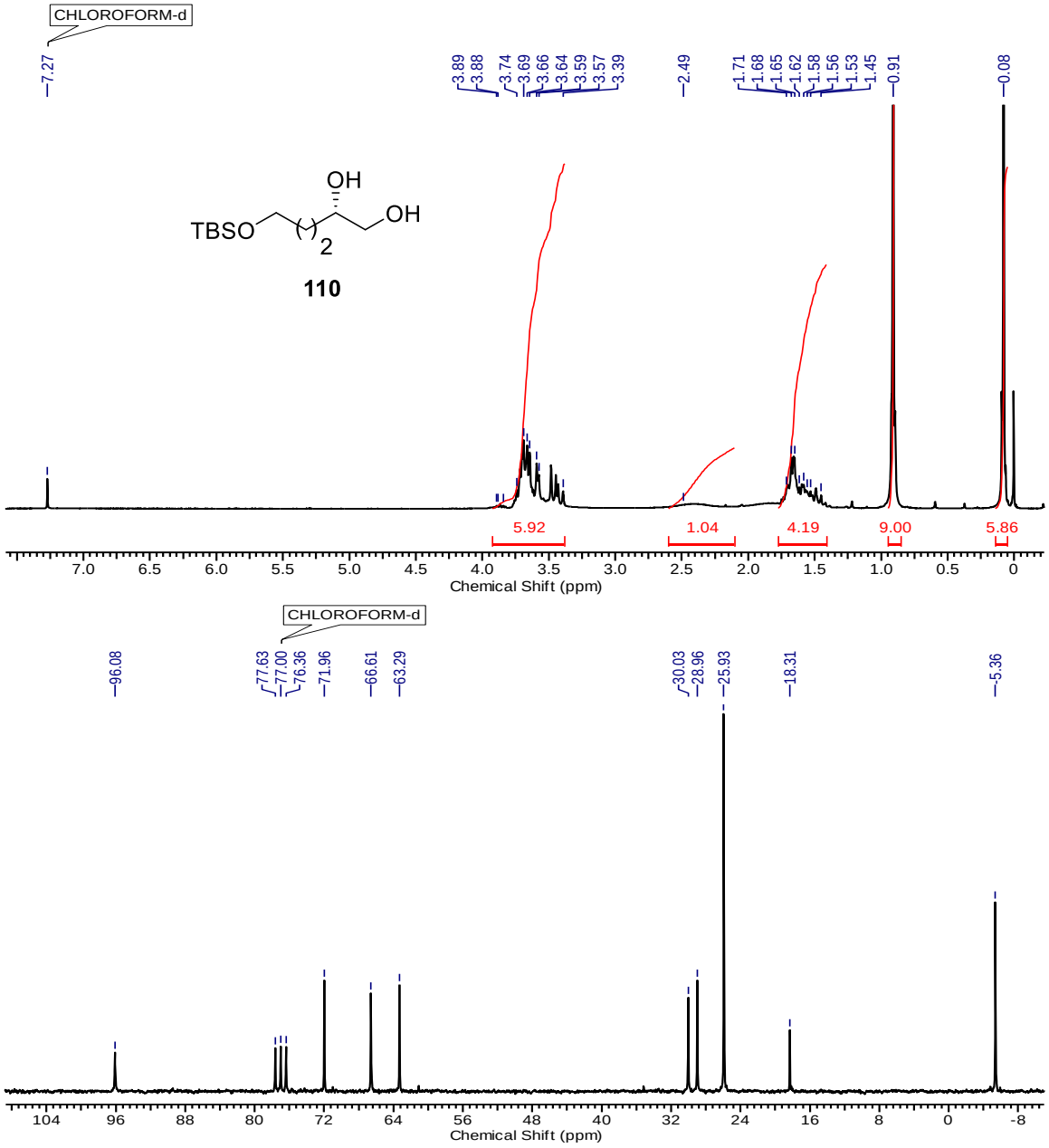
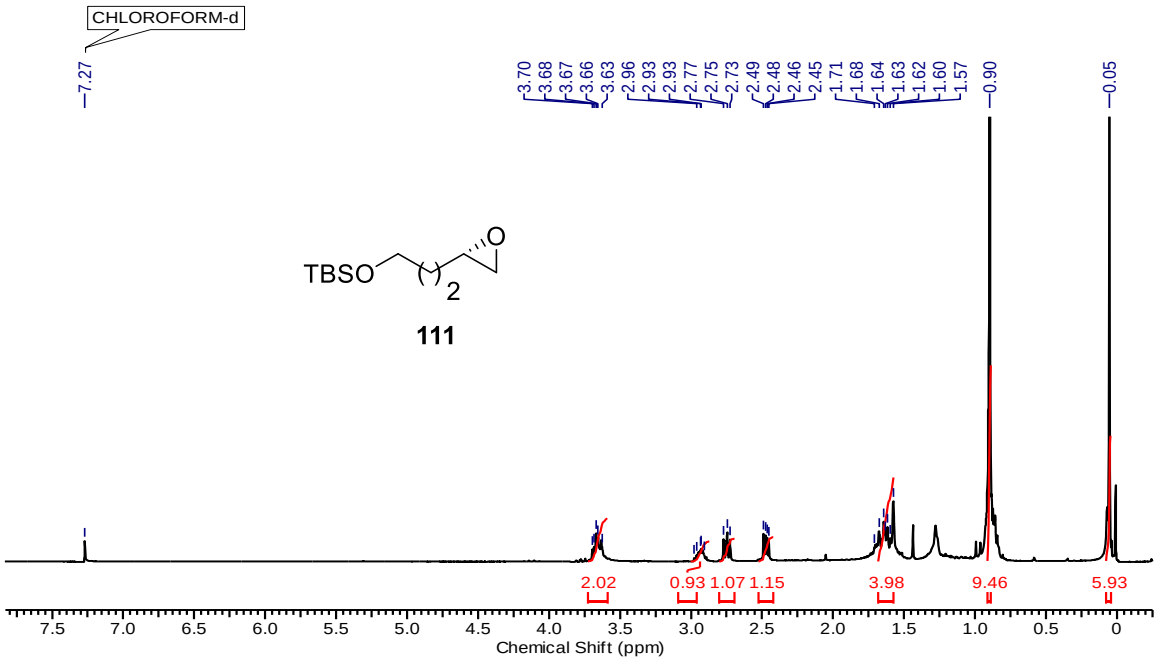


Figure 24: ^{1}H and ^{13}C NMR spectra of diol **110**

Another multiplet at δ 1.45-1.71 was due to the four internal methylene protons (**-CH_2-CH_2-**). Its ^{13}C NMR spectrum showed signals at δ 63.2, 66.6 and 71.9 corresponding to methylene and methine carbons attached to oxygen atoms respectively (**Figure 24**).

Selective tosylation of diol **110** (TsCl, Et_3N, Bu_2SnO) followed by its treatment with anhydrous K_2CO_3 in MeOH gave the optically pure terminal epoxide **111** in 92% yield over two steps. The formation of epoxide **111** was confirmed by the presence of multiplets at δ 2.45-2.49, 2.73-2.77 and 2.93-2.96 which were attributed to the protons of the epoxide group. Its ^{13}C NMR displayed signals at δ 46.9, 52.0 and 62.5 which were due to carbons attached to oxygen (**Figure 25**).



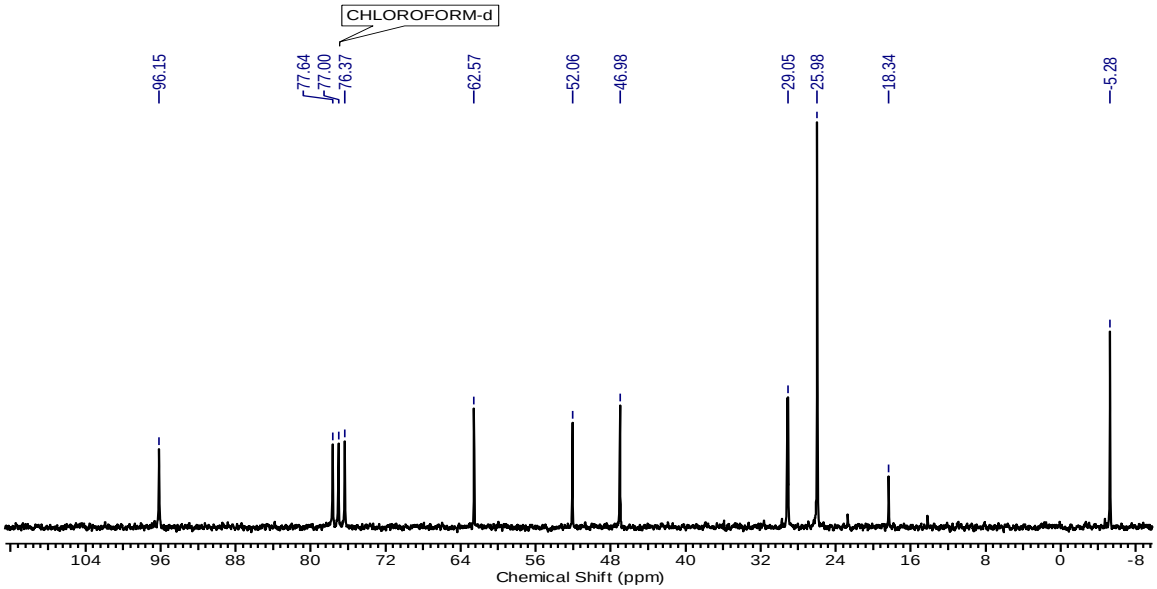


Figure 25: ^{1}H and ^{13}C NMR spectra of epoxide **111**

Regioselective opening of epoxide **111** into the corresponding allylic alcohol **112** was readily achieved by using Corey-Chaykovsky reagent ($S^{+}Me_3I^{-}$, NaH, DMSO) in 87% yield. The formation of allylic alcohol **112** was confirmed by the presence of multiplet at δ 5.07-5.30 (m, 2H) and 5.78-5.92 (m, 1H) in its ^{1}H NMR spectrum due to olefin functionality in compound **112**. This was further substantiated by the appearance of typical signals at δ 114.3 and 141.2 in its ^{13}C NMR spectrum (**Figure 26**).

Protection of allylic alcohol **112** (MOMCl, DIPEA, 90%) furnished MOM ether **113**. Its ^{1}H NMR spectrum shows a typical proton signal singlet at δ 3.37 corresponding methyl group ($-CH_3$) of MOM in allylic alcohol **112**. Its formation was further supported by ^{13}C NMR spectrum (**Figure 27**).

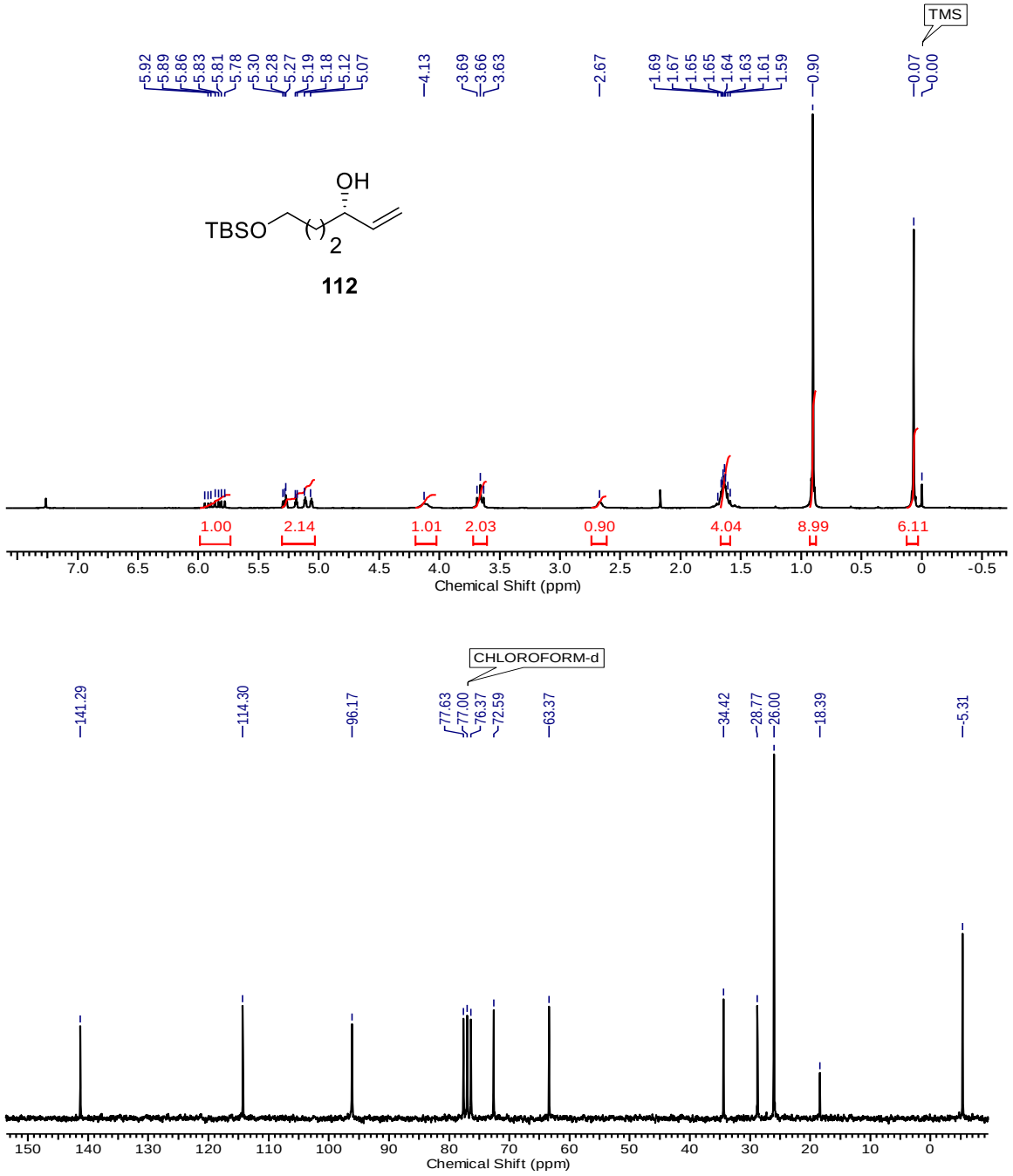


Figure 26: ^{1}H and ^{13}C NMR spectra of allylic alcohol **112**

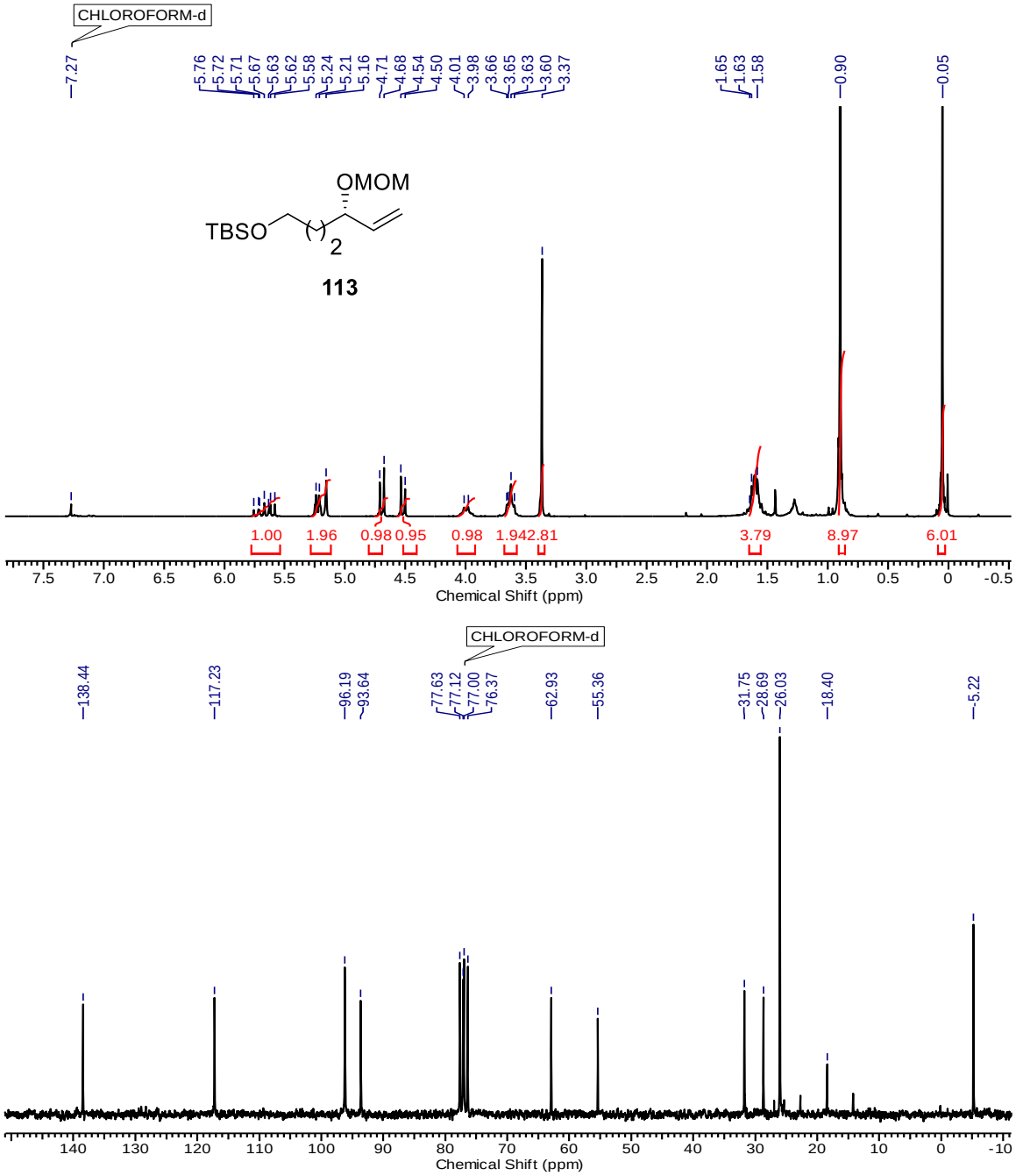


Figure 27: ^{1}H and ^{13}C NMR spectra of MOM ether **113**

Desilylation of MOM ether **113** afforded the alcohol **114** in 88% yield. The formation of alcohol **114** was confirmed by its ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of alcohol **114** showed disappearance of proton signals due to silyl group. It was also confirmed from its ^{13}C NMR spectrum (**Figure 28**).

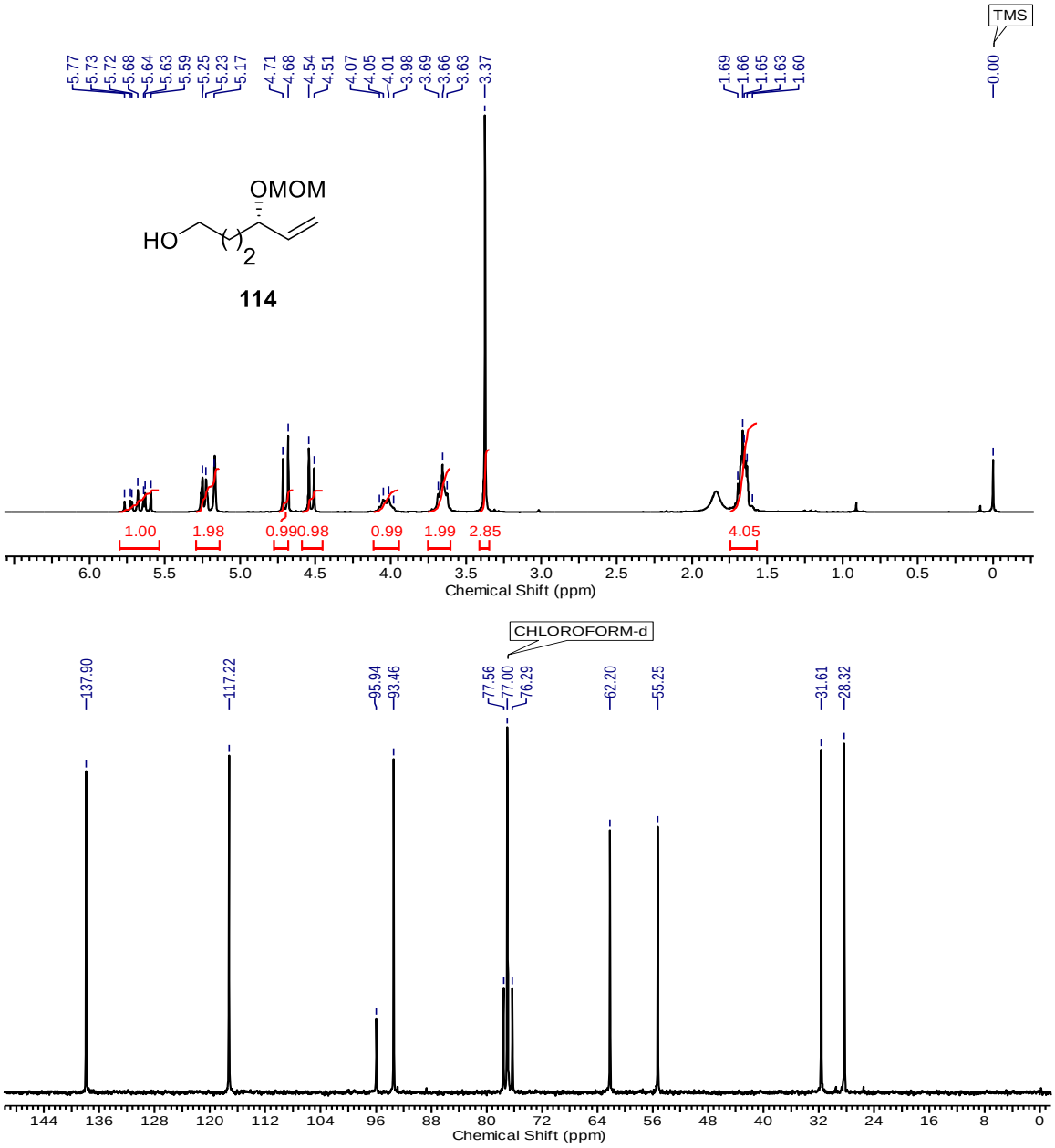


Figure 28: ^{1}H and ^{13}C NMR spectra of alcohol **114**

Oxidation of alcohol **114** [TEMPO, $PhI(OAc)_2$] afforded the acid fragment **115** in 86% yield. The formation of carboxylic acid **115** was confirmed by the presence of quartet at δ 1.84 (q, J = 6.79, 13.59 Hz, 2H) in its ^{1}H NMR spectrum due to methylene attached to acid group. This was further substantiated by the appearance of a typical signal at δ 179.3

in its ^{13}C NMR spectrum. The disappearance of signals corresponding to methylene (-**CH_2**OH) in its ^{1}H NMR spectrum further confirmed the completion of this oxidation reaction (**Figure 29**).

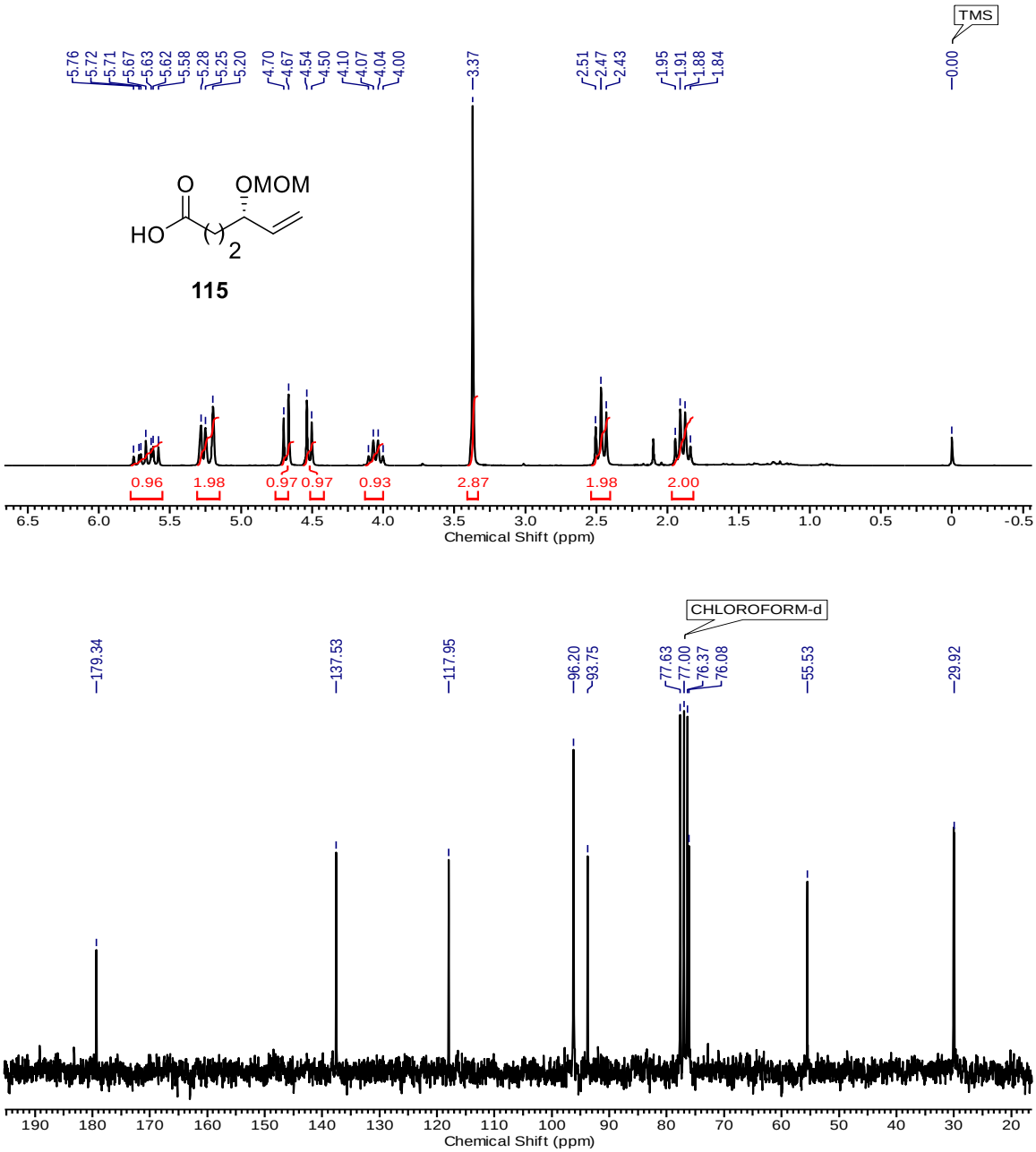
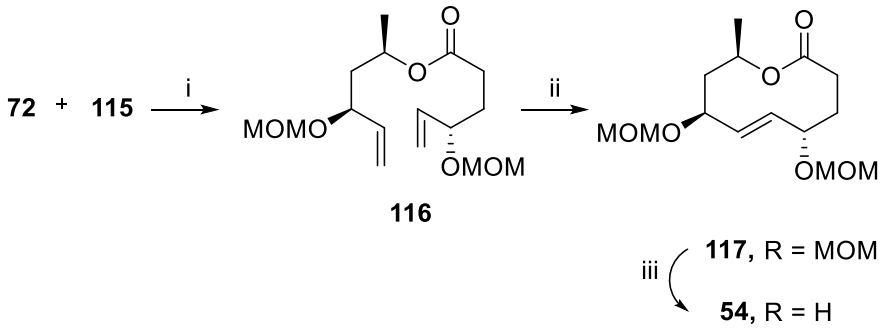
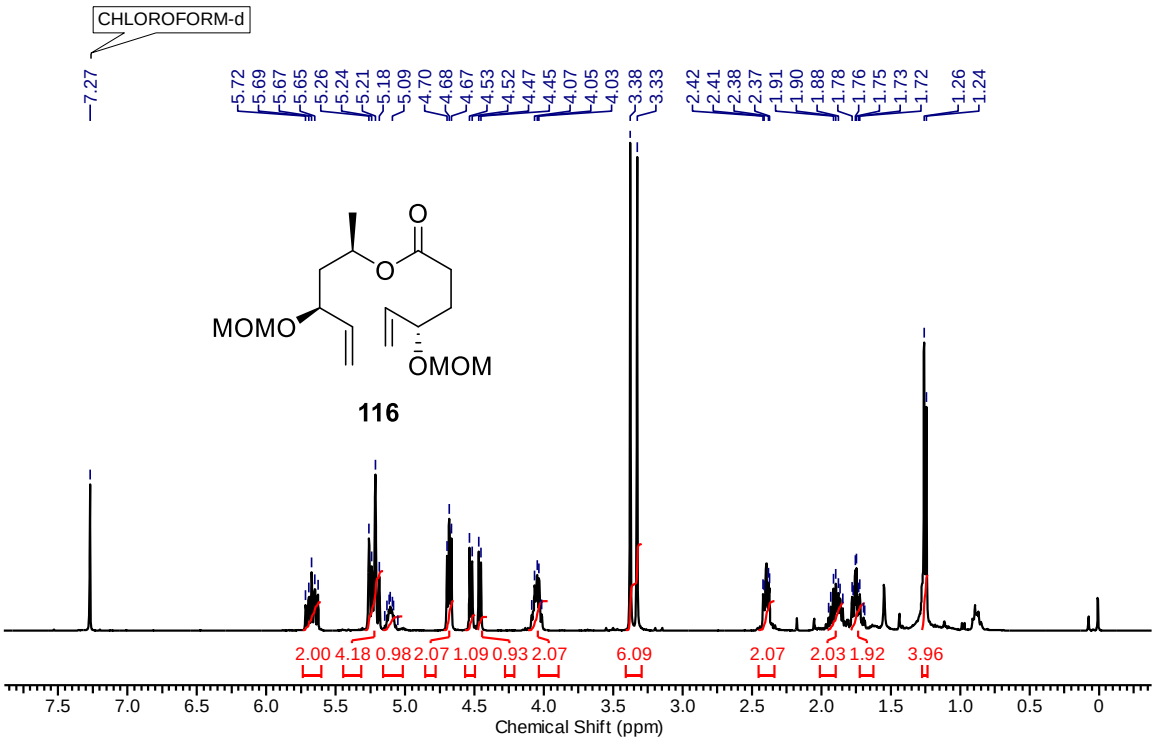


Figure 29: ^{1}H and ^{13}C NMR spectra of carboxylic acid **115**

Scheme 21 shows the final step in the synthesis of (+)-stagonolide C **54** that employs: (i) Steglich esterification between alcohol **72** and carboxylic acid **115**, furnishing the coupled product **116** in 86% yield; (ii) RCM of **116** with Grubbs II catalyst gave the core product **117**; (iii) Me_3SiBr-mediated MOM deprotection of 21 gave (+)-stagonolide C **54** in 17% overall yield (**Figure 30**).



Scheme 21: (i) EDCI·HCl, Et_3N, DMAP, CH_2Cl_2, 0-25 ºC, 6 h, 86%; (ii) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 24 h, 62%; (iii) Me_3SiBr, CH_2Cl_2, -40 ºC, 6 h, 76%.



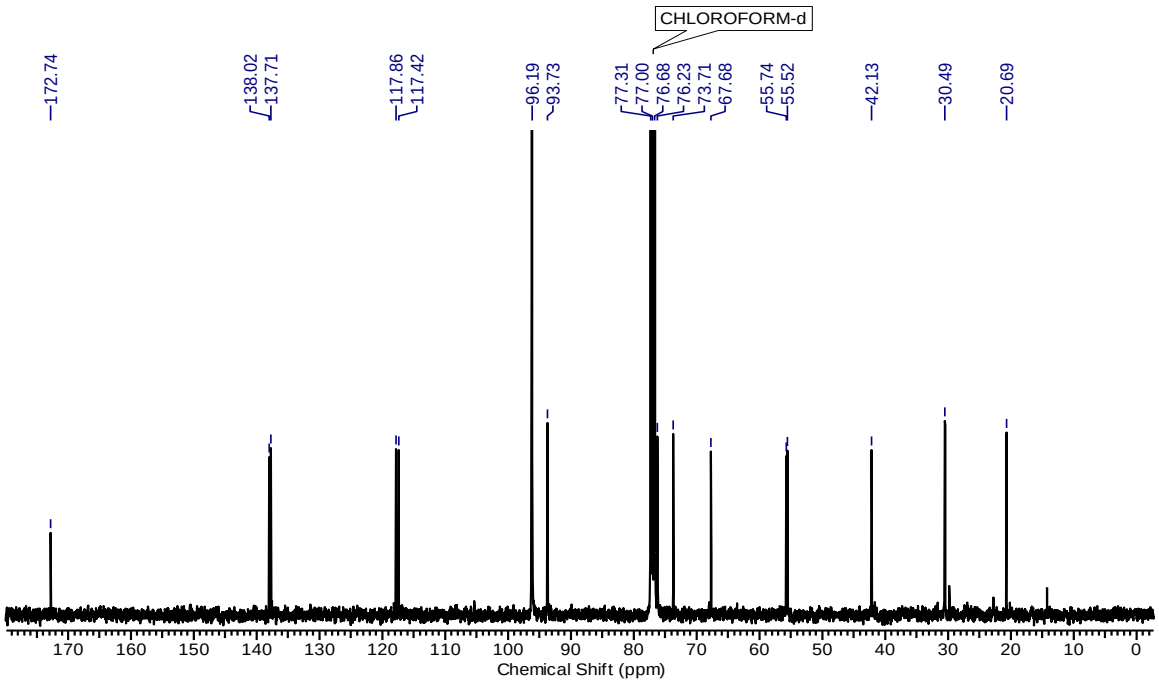


Figure 30: ^{1}H and ^{13}C NMR spectra of coupled product **116**

1.2.5 Conclusion

In conclusion, we have demonstrated the use of organocatalytic α-aminooxylation and Jorgenson's epoxidation strategy for the concise synthesis of important fungal metabolite namely (+)-stagonolide C **54** (17% overall yield; 96% ee). The operationally simple reactions with less number of steps, high overall yields requiring a relatively low amount of inexpensive and non-toxic proline as catalyst make this approach an attractive and useful route.

1.2.6 Experimental section

(*R*) Pent-4-en-2-ol (102)

To a stirred solution of (-)-Ipc_2B (allyl)borane (150 mmol) in dry Et_2O (200 mL) at -78 ^{o}C was added a solution of acetaldehyde (6 g , 136.4 mmol) in dry Et_2O (20 ml). The reaction mixture was stirred at -78 °C for 1 h, after which 3M NaOH (111 mL, 330

mmol) and 35% H_2O_2 (45 mL) was added to this reaction mixture and the contents stirred at 25 °C for additional 2 h. After the completion of reaction (monitored by TLC), the organic layer was separated and the aqueous layer extracted with Et_2O, washed with brine, and dried over anhydrous Na_2SO_4. After the removal of solvent the residue was distilled (bp 115 °C) giving (*R*)-(-)-4-penten-2-ol **102** (9.0 g) as a colorless liquid.

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

(*R*)-*tert*-Butyldimethyl(pent-4-en-2-yloxy)silane (103)

To a solution of alcohol **102** (8 g, 92.88 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C were added imidazole (12.63 g, 185.76 mmol) and *tert*-butyldimethylsilyl chloride (20.95 g, 139 mmol). The reaction mixture was then stirred at 25 °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 solvent under reduced pressure gave the crude product which was then purified by column chromatography with petroleum ether /EtOAc (9.5:0.5 v/v) to give silyl ether **103** as a colorless liquid.

Yield: 76%; $[\alpha]_D^{25}$ -9.8 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 2960, 2932, 2859, 1477, 1261, 1095, 1036, 840, 780 ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.87 (s, 9H), 1.09-1.12 (d, *J*= 7.1 Hz, 3H), 2.11-2.31 (m, 2H), 3.77-3.86 (m, 1H), 4.96-5.05 (m, 2H), 5.67-5.88 (m 1H), **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.6, -4.4, 18.2, 23.5, 25.9, 44.3, 68.4,

116.6, 135.6 ; **Analysis**: $C_{11}H_{24}OSi$ requires C, 65.93; H, 12.07; found C, 66.01; H, 12.13%.

(*R,E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)hex-2-enoate (104)

To a solution of compound **103** (12 g, 60 mmol) in dry CH_2Cl_2 was added ethyl acrylate (12 g, 120 mmol) at room temperature. To the reaction mixture was added Grubbs' second generation catalyst (420 mg, 10 mol %). The resultant mixture was refluxed under an argon atmosphere for 5 h. It was then cooled to room temperature and the solvent was removed under reduced pressure. The resulting crude residue was purified by silica gel column chromatography with petroleum ether /EtOAc (9:1 v/v) to give unsaturated ester **104** (10.6 g) as a colorless oil.

Yield: 65%; $[\alpha]_D^{25}$ -15.8 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 2957, 2930, 2857, 1723, 1317, 1258, 1222, 1175, 1093, 1045, 1003, 836, 775 ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.14 (d, *J* = 6.6 Hz 3H), 1.25 (t, *J* = 6.6 Hz, 3H), 2.23-2.31 (m, 2H), 3.80-3.95 (m, 1H), 4.09-4.19 (q, *J* =7.0 Hz, 2H), 5.73-5.80 (d, *J* = 15.8 Hz, 1H), 6.81-6.97 (m, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.5, -4.2, 14.3, 18.1, 24.2, 26.1, 42.8, 60.0, 67.6, 123.2, 145.9, 166.2; **Analysis:** $C_{14}H_{28}O_3Si$ requires C, 61.72; H, 10.36 found C, 61.64; H, 10.40%.

(*R,E*)-5-(*tert*-butyldimethylsilyloxy)hex-2-en-1-ol (105)

To a stirred solution of ester **104 (**8 g, 29.4 mmol) in dry toluene (100 mL), a solution of di isobutylaluminium hydride (29.4 mL, 1M in cyclohexane) was added dropwise at -78 ^oC and stirred at this temperature for 1 h. After completion of reaction (monitored by TLC), it was diluted with a saturated solution of Rochelle salt and stirred for further 3 h. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2.

The combined organic phase was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and chromatographic purification with petroleum ether /EtOAc (9:1 v/v) gave *α-β* unsaturated aldehyde **105** (4.89 g) as a colorless liquid.

Yield: 73%; $[\alpha]_D^{25}$ -1.2 (*c* 0.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 2956, 2929, 2856, 1696, 1637, 1463, 1377, 1361, 1255, 1125, 1077, 1046, 1004, 835, 775; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.90 (s, 9H), 1.17 (d, *J* = 6.8 Hz 3H), 2.42-2.48 (m, 2H), 3.95-4.07 (m, 1H), 6.06-6.18 (m, 1H), 6.78-6.93 (m, 1H), 9.49-9.52 (d, *J* = 7.7 Hz, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.4, 18.0, 23.8, 25.8, 42.7, 67.3, 134.8, 154.8, 193.3; **Analysis**: $C_{12}H_{24}O_2Si$ requires C, 62.55; H, 11.37; found C, 62.61; H, 11.44%.

((2*S*,3*S*)-3-((*R*)-2-(*tert*-butyldimethylsilyloxy)propyl)oxiran-2-yl)methanol (106)

Catalyst (*R*)-α,α-[bis(3,5-trifluoromethylphenyl) tri-methylsilanyloxymethyl]-2-pyrrolidine (1.2 g, 10 mol%) was added at ambient temperature to a solution of aldehyde **105** (4.5 g, 19.73 mmol) in CH_2Cl_2 (60 mL) followed by the addition of 35% H_2O_2 (aq.) (1.3 equiv.). After completion of the reaction (monitored by TLC), it was diluted with MeOH (60 ml) and cooled to 0 °C followed by the addition of $NaBH_4$ (1.49 g, 39.47 mmol). The mixture was then stirred for 10 min, quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography with petroleum ether /EtOAc (8:2 v/v) to give epoxy alcohol 106 (2.57 g) as a colourless liquid.

Yield: 53%; $[\alpha]_D^{25}$ -17.0 (*c* 0.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 3437, 2956, 2929, 2857, 1256, 1130, 1072, 1050, 1006, 836, 775 ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.89 (s,

9H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.44-1.56 (m, 1H), 1.67-1.81 (m, 2H), 2.89-2.93 (m, 1H), 3.02-3.09 (m, 1H), 3.54-3.66 (m, 1H), 3.88-4.07 (m, 2H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.4, 18.0, 24.3, 25.8, 41.8, 53.3, 58.8, 61.5, 66.2 ; **Analysis**: $C_{12}H_{26}O_3Si$ requires C, 58.49; H, 10.63; found C, 58.56; H, 10.71%.

(3*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)hex-1-en-3-ol (107)

To a stirred solution of epoxy alcohol **106** (2.5 g, 10.14 mmol) in a dry ether-acetonitrile mixture (3:1, 40 ml) at 0 ^oC under a nitrogen atmosphere were added imidazole (1.03 g, 15.21 mmol), triphenylphosphine (3.98 g, 15.21 mmol) and iodine (4.61 g, 18.25 mmol) successively. The resulting reaction mixture was stirred for 1 h at the same temperature and then diluted with cold ether (20 mL), and filtered through a sintered funnel. The residue was washed with ether (3×50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the crude residue by column chromatography (9:1 v/v) gave the pure product epoxy iodide (3.5 g) as a pale yellow liquid.

A mixture of the above epoxy iodide (3.47 g, 9.74 mmol), NaI (3.62 g, 24.36 mmol) and freshly activated zinc (0.126 g, 1.94 mmol) in dry MeOH (45 ml) was refluxed for 6 h under a nitrogen atmosphere. The solution was filtered and the residue was washed with MeOH (2×25 mL). The combined filtrates were concentrated and the residue was taken in ethyl acetate (50 mL), washed with water (2×25 mL) and brine (3×50 mL), and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to afford the allyl alcohol **107** (2.0 g) as a colorless oil.

Yield: 90%; $[\alpha]_D^{25}$ -30.1 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 3453, 3020, 2950, 2932, 2865, 1625, 1466, 1429, 1354, 1260, 1058, 940; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H),

0.90 (s, 9H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.59-1.67 (m, 2H), 3.21 (br s, 1H), 4.15-4.27 (m, 1H), 4.38-4.46 (m, 1H), 5.04-5.29 (m, 2H), 5.77-5.93 (m, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.3, 18.0, 23.2, 25.8, 44.5, 67.1, 69.9, 113.8, 141.2; **Analysis:** $C_{12}H_{26}O_2Si$ requires C, 62.55; H, 11.37; found C, 62.49; H, 11.31%.

(5*S*,7*R*)-7,9,9,10,10-pentamethyl-5-vinyl-2,4,8-trioxa-9-silaundecane (108)

To a stirred solution of allyl alcohol **107** (1.8 g, 7.82 mmol) and DIPEA (4.08 mL, 23.47 mmol) in dry DCM (20 mL) was added MOM-Cl (1.78 mL, 23.47 mmol) at 0 ^oC and the mixture stirred for 2 h at room temperature. After completion of the reaction as monitored by TLC, water was added, and the reaction mixture was extracted with CH_2Cl_2 (20 mL), and the organic layer dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give a crude residue, which was purified by column chromatography with petroleum ether/EtOAc (9:1 v/v) to afford MOM ether **108** (1.92 g) in 90% yield as a colorless liquid.

Yield: 90%; $[\alpha]_D^{25}$ -13.7 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 2954, 2928, 2860, 1476, 1260, 1100, 1040, 836, 776 ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.89 (s, 9H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.59-1.67 (m, 2H), 3.37 (s, 3H), 3.89-4.14 (m, 2H), 4.52-4.69 (m 2H), 5.13-5.22 (m, 2H), 5.61-5.81 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.8, -4.3, 18.0, 23.1, 25.8, 44.5, 67.1, 69.9, 113.8, 141.2; **Analysis:** $C_{14}H_{30}O_3Si$ requires C, 61.26; H, 11.02; found C, 61.31; H, 11.07%.

(2*R*, 4S)-4-(methoxymethoxy) hex-5-en-2-ol (72)

To a solution of **108** (1.8 g, 6.56 mmol) in dry THF was added dropwise a 1 M solution of tetrabutylammonium fluoride (13.1 mL, 2 equiv.) at 25 ^oC and the mixture stirred at this temperature for 6 h. After completion of the reaction (monitored by TLC), the

solvent was removed under reduced pressure and the residue extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The crude product was then subjected to column chromatography with petroleum ether/EtOAc (8:2 v/v) to afford alcohol **72** (860 mg) as a light yellow-colored liquid.

Yield: 82%; $[\alpha]_D^{25}$ -108.6 (*c* 1.6, CH_2Cl_2); lit.[12] $[\alpha]_D^{25}$ -109.2 (*c* 1.50, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 3433, 2925, 1597, 1153, 1099, 1037; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.63-1.72 (m, 2H), 2.56 (br s, 1H), 3.40 (s, 1H), 3.97-4.16 (m, 1H), 4.25-4.34 (m, 1H), 4.53-4.66 (m, 2H), 5.16-5.27 (m, 2H), 5.56-5.83 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.6, 44.2, 56.0, 64.5, 75.6, 94.5, 117.1, 138.1; **Analysis**: $C_8H_{16}O_3$ requires C, 59.97; H, 10.07; found C, 60.06; H, 10.12%.

(*S*)-5-(*tert*-butyldimethylsilyloxy)pentane-1,2-diol (110)

To a stirred, precooled (-20 °C) acetonitrile (120 mL) solution of aldehyde **109** (10 g, 46.21 mmol) and nitrosobenzene (5.22 g, 46.21 mmol) was added D-proline (1.1 g, 20 mol %). The reaction mixture was allowed to stir at the same temperature for 24 h followed by the addition of MeOH (80 mL) and $NaBH_4$ (5.24 g, 138.63 mmol) to the reaction mixture. After completion of the reaction (monitored by TLC), the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly taken up for the next step without purification. To a well stirred solution of this aminooxy alcohol in methanol was added 10% Pd/C and the reaction mixture was stirred overnight at 25 ^oC under H_2 (1 atm). After completion of reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and the solvent was evaporated under

reduced pressure to afford the crude diol. Purification by column chromatography with petroleum ether/ethyl acetate (5:5 v/v) gave the diol **110** (8.32 g) as a colorless liquid.

Yield: 77%; $[\alpha]_D^{25}$ -2.3 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 3361, 2954, 2929, 2857, 1471, 1463, 1256, 1097, 1006, 835, 775, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.83 (s, 9H), 1.37-1.67 (m, 4H), 2.42 (br s, 1H), 3.35-3.86 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 25.9, 28.9, 30.0, 63.3, 66.6, 71.9; **Anal.** Calcd for $C_{11}H_{26}O_3Si$ requires C, 56.36; H, 11.18; Found: C, 56.41; H, 11.23%.

(*S*)-*tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane (111)

A solution of diol **110** (8 g, 34.12 mmol) in CH_2Cl_2 (70 mL) was treated with TsCl (7.80 g, 40.95 mmol), Bu_2SnO (100 mg), Et_3N (9.52 mL, 68.24 mmol), and DMAP (400 mg) at 0 °C. After being stirred for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude tosylate. To this crude tosylate in MeOH (50 mL) was added K_2CO_3 (4.52 g, 32.79 mmol) and the mixture was stirred at 25 °C for 1 h. After the reaction was completed (monitored by TLC), the solvent was evaporated and the residue was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give epoxide **111** (6.8 g) as a colorless oil.

Yield: 92%; $[\alpha]_D^{25}$ -2.9 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 2954, 2857, 1472, 1256; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.57-1.71 (m, 4H), 2.44-2.48 (m, 1H), 2.72-2.78 (m, 1H), 2.91-2.97 (m, 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 -5.2, 18.3, 25.9,

29.0, 29.1, 46.9, 52.0, 62.5; **Anal.** Calcd for $C_{11}H_{24}O_2Si$ requires C, 61.05; H, 11.18; Found: C, 61.10; H, 11.23%.

(*S*)-6-(*tert*-butyldimethylsilyloxy) hex-1-en-3-ol (112)

To a stirred solution of trimethylsulfonium iodide (7.98 g, 39.12 mmol) in dry THF (90 mL) was added NaH (1.38 g, 60.18 mmol) at 25 °C. After 30 min, epoxide **111** (6.5 g, 30.09 mmol) in dry THF (15 mL) was added dropwise and the reaction mixture stirred for 2 h. After completion of the reaction (monitored by TLC), it was quenched with water and extracted with diethyl ether (3×100 mL). The combined extracts were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give allylic alcohol **112** (6.0 g) as a colorless liquid.

Yield: 87%; $[\alpha]_D^{25}$ -0.7 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 3354, 2956, 1471, 1443, 1388, 1361, 1255, 1104, 1005, 969, 939, 837, 736, 692; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.84 (s, 9H), 1.54-1.60 (m, 4H), 2.61 (br s, 3H), 3.56-3.62 (t, J=6 Hz, 2H), 4.06 (m, 1H), 4.99-5.23 (m, 2H), 5.71-5.88 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 26.0, 28.7, 34.4, 63.3, 72.5, 114.3, 141.2; **Anal.** Calcd for $C_{12}H_{26}O_2Si$ requires C, 62.55; H, 11.37; Found: C, 62.50; H, 11.46,%.

(*S*)-10,10,11,11-tetramethyl-5-vinyl-2,4,9-trioxa-10-siladodecane (113)

To a stirred solution of allyl alcohol **112** (5.8 g, 25.21 mmol) and DIPEA (13.17 mL, 75.63 mmol) in dry CH_2Cl_2 (60 mL) was added MOMCl (5.74 mL, 75.63 mmol) at 0 ^oC and the mixture was stirred for 10 h at room temperature. After completion of the reaction (monitored by TLC), water was added, and the reaction mixture was extracted into CH_2Cl_2 (3x 100 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in

vacuo to give a crude residue, which was purified by column chromatography using petroleum ether /ethyl acetate (9:1) to afford MOM ether **113** (6.2 g) in 90% yield as a colorless liquid.

Yield: 90%; $[\alpha]_D^{25}$ -34.1 (*c* 0.64, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 2953, 2929, 2857, 1474, 1257, 1097, 1037, 835, 775; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.90 (s, 9H), 1.57-1.66 (m, 4H), 3.36 (s, 3H), 3.59-3.65 (t, *J* = 6.0 Hz, 2H), 3.97-4.0 (m, 1H), 4.50-4.70 (m, 2H), 5.15-5.24 (m, 2H), 5.57-5.75 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.5, 19.0, 26.6, 29.3, 32.3, 55.9, 63.5, 94.2, 117.8, 139.1; **Anal.** Calcd for $C_{14}H_{30}O_3Si$ requires C, 61.26; H, 11.02; Found: C, 61.34; H, 11.07%.

(*S*)-4-(methoxymethoxy) hex-5-en-1-ol (114)

To a solution of **113** (6.0 g, 21.89 mmol) in dry THF was added dropwise 1 M solution of tetrabutylammonium fluoride (42 mL, 43.79 mmol) at 25 ^oC and stirred at this temperature for 6 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the residue extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The crude product was then subjected to flash column chromatography to afford alcohol **114** (3.08 g) as a colorless liquid.

Yield: 88%; $[\alpha]_D^{25}$ -114.0 (*c* 0.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 3415, 2933, 1643, 1447, 1097; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.58-1.74 (m, 4H), 1.85 (br s , 1H), 3.37 (s, 3H), 3.66 (t, *J* = 6.0 Hz, 2H), 4.01 (q, *J* = 5.2 Hz, 1H), 4.51-4.68 (m, 2H), 5.17 (br s, 1H), 5.23 (d, *J* = 7.5 Hz, 1H), 5.68 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 31.6, 55.2, 62.1, 77.0, 93.4, 177.2, 137.9; **Anal.** Calcd for $C_8H_{16}O_3$ requires C, 59.97; H, 10.07; Found: C, 60.06; H, 10.12%.

(*S*)-4-(methoxymethoxy)hex-5-enoic acid (115)

To a solution of alcohol **114** (2.8 g, 17.5 mmol) in CH_3CN/H_2O (4:1) was added, in one portion bis-acetoxy iodobenzene (12.39 g, 38.5 mmol) and TEMPO (0.546 g, 3.5 mmol). The reaction mixture was then allowed to stir at 25 ^oC for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by the addition of a saturated solution of aq. ammonium thiosulphate. The organic layer was separated, washed with brine and subjected to column chromatographic purification with petroleum ether/EtOAc (7:3 v/v) to afford carboxylic acid **115** (2.58 g) as a colorless liquid.

Yield: 86%; $[\alpha]_D^{25}$ -101.4 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 3447, 2937, 2888, 1711, 1424, 1255, 1149, 1096, 1029, 920 ; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.86 (q, *J* = 6.7, 2H), 2.46 (t, *J* = 6.7 Hz, 2H), 3.36 (s, 3H), 4.02 (q, *J* = 6.7 Hz, 2H), 4.49 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 5.19 (d, *J* = 7.5 Hz, 1H), 5.24 (d, *J* = 7.5 Hz, 1H), 5.66 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.4, 30.1, 54.8, 75.7, 93.1, 117.3, 136.9, 178.7; **Anal.** Calcd for $C_8H_{14}O_4$ requires C, 55.16; H, 8.10; Found: C, 55.20; H, 8.16, %.

(4*S*)-(2*R*,4*S*)-4-(methoxymethoxy)hex-5-en-2-yl 4-(methoxymethoxy)hex-5-enoate (116)

To a stirred solution of carboxylic acid **115** (499.4 mg, 2.87 mmol), EDCI.HCl (613 mg, 3.2 mmol), Et_3N (870 mg, 8.6 mmol) and DMAP (cat.) in anhydrous CH_2Cl_2 (25 mL) was added alcohol **72** (459 mg, 2.87 mmol) and the reaction mixture stirred for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude

product was then purified by column chromatography using pet ether: EtOAc (9:1 v/v) as eluent) to give bis olefin ester **116** (780 mg) as **a** colorless liquid.

Yield: 86%; $[\alpha]_D^{25}$ -125.6 (*c* 1.6, $CHCl_3$); lit.[12] $[\alpha]_D^{25}$ -127.6 (*c* 0.60, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 2930, 1732, 1150, 1096, 1030, 993, 920; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.3 Hz, 3H), 1.69-1.77 (m, 2H), 1.84-1.94 (m, 2H), 2.37-2.41 (m, 2H), 3.32 (s, 3H), 3.37 (s, 3H), 4.02 (m, 2H), 4.46 (d, *J* = 6.7 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.66-4.69 (m, 2H), 5.06-5.14 (m, 1H), 5.18-5.25 (m, 4H), 5.62-5.71 (m, 2H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.6, 30.4, 30.4, 42.0, 55.4, 55.6, 67.6, 73.6, 77.2, 93.6, 117.3, 117.8, 137.6, 137.9, 172.7; **Analysis:** $C_{16}H_{28}O_6$ requires C, 60.74; H, 8.92; found C, 60.83; H, 8.88%.

(6*E*,5*S*,8*S*,10*R*)-4,5,9,10-tetrahydro-5,8-bis(methoxymethoxy)-10-methyl-3H-oxecin-2(8H)-one (117)

To a stirred solution of Grubb's 2nd generation catalyst (67 mg, 20 mol %) in CH_2Cl_2 (10 ml) was added a solution of diene **116** (120 mg, 0.4 mmol) in CH_2Cl_2 (50 ml). The mixture was stirred under reflux at 45 °C for 12 h. The solvent was evaporated and the crude product was purified by using column chromatography using pet ether: EtOAc (8:2 v/v) to give **117** (72 mg) as a colorless oil.

Yield: 62%; $[\alpha]_D^{25}$ -42.6 (*c* 1.6, $CHCl_3$); lit.[12] $[\alpha]_D^{25}$ -42.8 (*c* 1.21, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 2932, 2860, 2854, 1955, 1857, 1729, 1450, 1262, 1098, 1030; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.7 Hz, 3H), 1.75-1.87 (m, 2H), 1.96-2.13 (m, 3H), 2.27-2.32 (m, 1H), 3.31 (s, 3H), 3.32 (s, 3H), 4.48 (m, 2H), 4.51 (d, *J* = 6.8 Hz, 1H), 4.65-4.69 (m, 2H), 5.38-5.42 (dd, *J* = 9.0, 16.1 Hz, 2H), 5.49-5.56 (dd, *J* = 9.6, 15.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 31.2, 31.7, 41.6, 55.2, 55.3, 67.6, 75.1, 77.8, 92.7, 93.8, 133.2, 135.3, 175.2; **Analysis:** $C_{14}H_{24}O_6$ requires C, 58.32; H, 8.39; found C, 58.40; H, 8.43%.

(+)-Stagonolide C (54)

At first, Me_3SiBr (0.8 ml, 0.45 mmol) was added dropwise to a cold (-40 ^oC) stirred solution of **117** (43 mg, 0.15 mmol) in CH_2Cl_2 (50 ml). The mixture was stirred at -40 ^oC for 2 h. After the completion of the reaction (monitored by TLC), the reaction mixture was poured into a saturated aq. $NaHCO_3$ solution, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The residue was then purified with column chromatography using pet ether: EtOAc (6:4 v/v) to give stagonolide C **54** (20 mg) as a colorless liquid.

Yield: 76%; $[\alpha]_D^{25}$ +44.7 (*c* 0.9, $CHCl_3$); lit.[12] $[\alpha]_D^{25}$ +45.6 (*c* 1.00, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 3385, 2926, 2850, 1720, 1445, 1370, 1098, 1235, 1110, 1040; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.8 Hz, 3H), 1.72-1.96 (m, 2H), 1.99-2.10 (m, 3H), 2.20-2.34 (m, 1H), 4.02-4.14 (m, 2H), 5.06-5.20 (m, 1H), 5.41 (dd, *J* = 8.9, 15.8 Hz, 1H), 5.56 (dd, *J* = 9.0, 16.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.0, 31.5, 34.4, 43.3, 67.4, 72.1, 74.5, 132.9, 174.0; . **Analysis:** $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05; found C, 60.03; H, 8.12%.

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CHAPTER II

Total Synthesis of Stagonolide F and Formal Synthesis of Pinolide

1. "An efficient organocatalytic route for asymmetric total synthesis of Stagonolide F" **Shelke, A. M.;** Suryavanshi, G., *Tetrahedron Letters* **2015**, *56*, 6207.

2. "A formal total synthesis of Pinolide *via* L-proline-catalyzed sequential α-aminooxylation and Horner-Wadsworth-emmons olefination-Sharpless asymmetric dihydroxylation strategy**" Shelke, A. M.;** Suryavanshi, G., *Tetrahedron: Asymmetry* **2012**, *23*, 1534.

Section I

An Efficient Organocatalytic Route for Asymmetric Total Synthesis of Stagonolide F

2.1.1 Introduction and Pharmacology

Macrolides, comprises a small class of naturally occurring 10-membered lactone origin isolated from various fungal metabolites. These macrolides have attracted considerable attention due to their interesting pharmacological features such as antibacterial, antitumoral, or hypolipidemic properties.[1] Stagonolide F (**1)**, a macrolide which was isolated from *Stagonospora circii*, a fungal pathogen of *Cirsium arvense* and exhibits potent antibacterial, antifungal, mycoherbicidal and cytotoxic activities.[2] Some representatives of 10-membered lactones (**Figure 1)** are Stagonolide F (**1)**, Stagonolide C (**2)**, Aspinolide A (**3**), Modiolide A (**4**), Putaminoxin (**5**), 5-O-Acrtylputaminoxin (**6**), Stagonolide B (**7**), Stagonolide E (**8**) and Stagonolide D (**9**) which possesses some

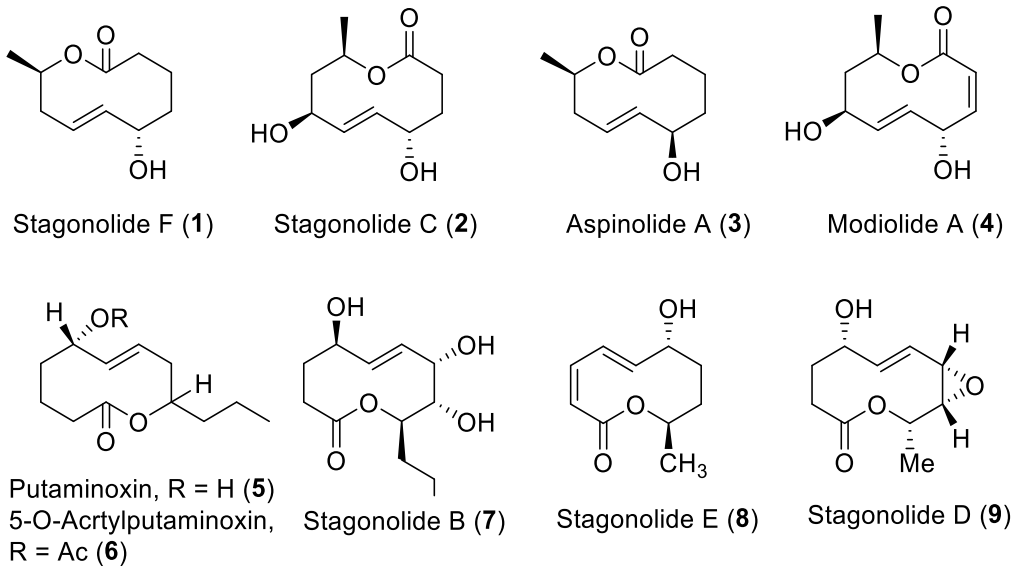


Figure 1: Some naturally occurring small ring macrolides

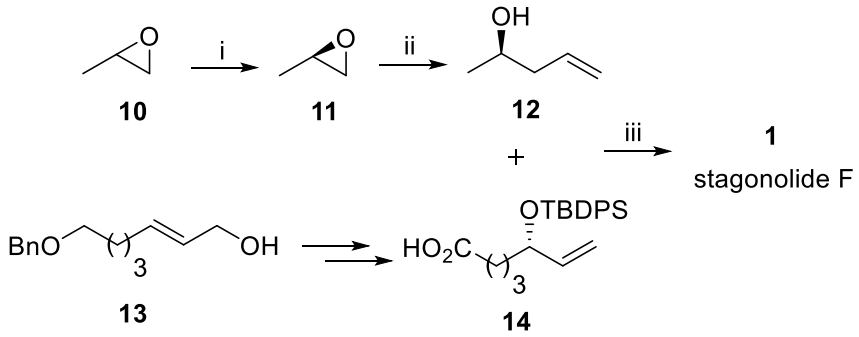
common interesting structural features such as olefinic function with well-defined geometry and stereochemically pure hydroxyl groups which make them challenging targets.

2.1.2 Review of Literature

Till date three synthetic routes have been documented in the literature for the synthesis Stagonolide F **1** which is described below.

Rao's approach (2009)[3]

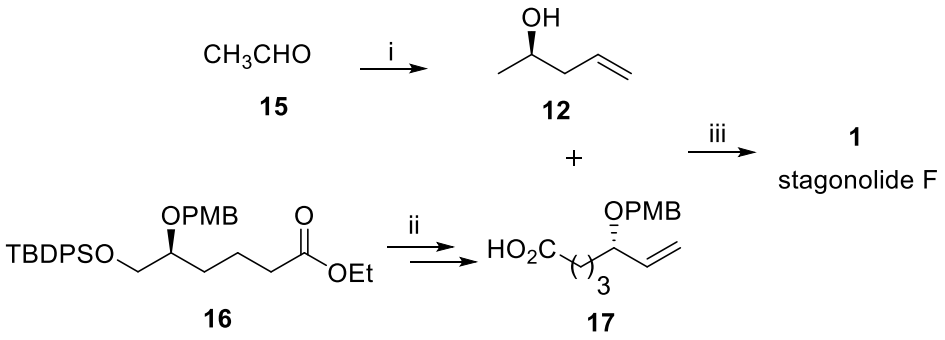
The total synthesis of stagonolide F **1** described by Rao *et al.* is based on hydrolytic kinetic resolution of terminal epoxide **10** and Sharpless asymmetric epoxidation of allylic alcohol **13** for the introduction of chirality. (*R*)-Propylene oxide **11** was treated with vinylmagnesium bromide in the presence of cuprous iodide to give the required homoallylic alcohol **12** in 85% yield. The synthesis of acid fragment **14** involves a Sharpless epoxidation of allylic alcohol **13** using (+)-DET as chiral source. Alcohol fragment **12** and carboxylic acid fragment **14** were coupled using steglich esterification condition (DCC) followed by desilylation and Ring Closing Metathesis (RCM) (**Scheme 1**).



Scheme 1: (i) (*R*,*R*)-salen-Co-(OAc) (0.5 mol %), H_2O (0.55 equiv), rt, 40%; (ii) vinylmagnesium bromide, THF, CuI, -78 ^oC, 85%, 12 h; (iii) (a) DCC, DMAP, CH_2Cl_2, 0 ^oC-rt, 65%; (b) HF-pyridine, CH_2Cl_2, rt, 12 h, 75%; (c) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (12 mol %), CH_2Cl_2, reflux, 48 h, 55%.

Kamal's approach (2011)[4]

Kamal *et al* have described the synthesis of stagonolide F **1** by utilizing (*S*) and (*R*)-malic acid *via* Horner-Wittig olefination, double bond reduction and steglich esterification as the key reactions. Olefinic chiral homoallyl alcohol (2*R*)-4-penten-2-ol **12** were synthesized in one step by utilizing Brown's asymmetric allylboration of acetaldehyde with (-)-B-allyldiisopinocampheylborane in Et_2O-pentane (1:1) at -100 °C. The acid fragment **17** was synthesized from key chiral intermediate **16** in 3 steps in 86% yield. Homoallyl alcohol fragment **12** and carboxylic acid fragment **17** were coupled by employing Steglich esterification conditions (DCC) followed by PMB deprotection and Ring Closing Metathesis (RCM) to give stagonolide F **1** in 55% yield (**Scheme 2**).

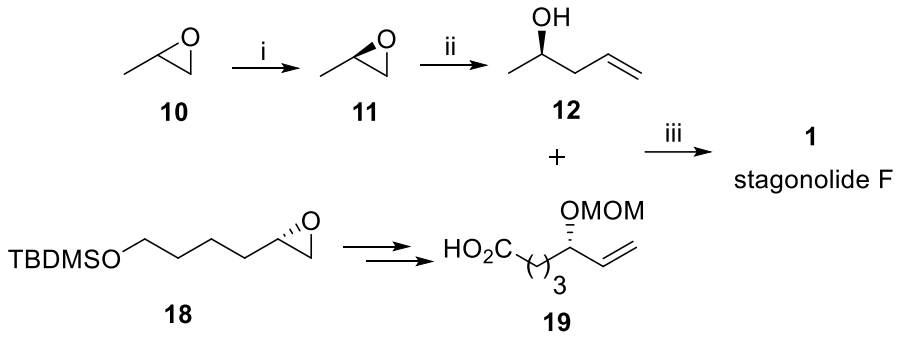


Scheme 2: (i) (-)-Ipc_2BCl, allyl MgBr, E_2O-pentane (1:1), -100 °C, NaOH and H_2O_2, 70%; (ii) (f) TBAF (1M), THF, 0.5 h, 88%; (g) (i) $(COCl)_2$, DMSO, Et_3N, -78 °C, 1 h; (ii) $MePh_3Br$, t-BuOK, THF, 0 °C, 1 h, 55 % over two steps; (h) LiOH, MeOH:THF:H_2O (1:2:1), 0 °C to rt, 4 h, 86%. (iii) (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 3 h, 81%; (b) DDQ, H_2O:CH_2Cl_2 (1:9), 0 °C to rt, 1 h, 78%; (c) 20 mol% Ru-1, CH_2Cl_2, reflux, 48 h, 55%.

Venkateswarlu's approach (2012)[5]

Venkateswarlu *et al* have achieved the synthesis of stagonolide F **1** starting from commercially available 5-hexen 1-ol using asymmetric dihydroxylation, Jacobsen's hydrolytic kinetic resolution (HKR), regioselective epoxide ring opening with

vinyl Grignard reaction, esterification, and ring-closing metathesis (RCM) as key steps. (*R*)-Propylene oxide **11** was treated with vinylmagnesium bromide in the presence of cuprous iodide to give the homoallylic alcohol **12** in 85% yield. The acid fragment **19** was prepared from chiral epoxide **18** in 3 steps. Steglich esterification of alcohol fragment **12** and carboxylic acid fragment **19** leads to the formation bis olefin ester which on desilylation and Ring Closing Metathesis (RCM) gave stagonolide F in 10 steps with overall yield of 11.29% (**Scheme 3**).



Scheme 3: (i) (*R*,*R*)-salen-Co-(OAc) (0.5 mol %), distilled H_2O (0.55 equiv), 0 °C, 46%; (ii) vinylmagnesium bromide, THF, CuI, -20 °C 1 h, 85%; (iii) (a) DCC, DMAP, CH_2Cl_2, 0 °C-rt, 65%; (b) HF-pyridine, CH_2Cl_2, rt, 12 h, 75%; (c) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (12 mol %), CH_2Cl_2, reflux, 48 h, 55%.

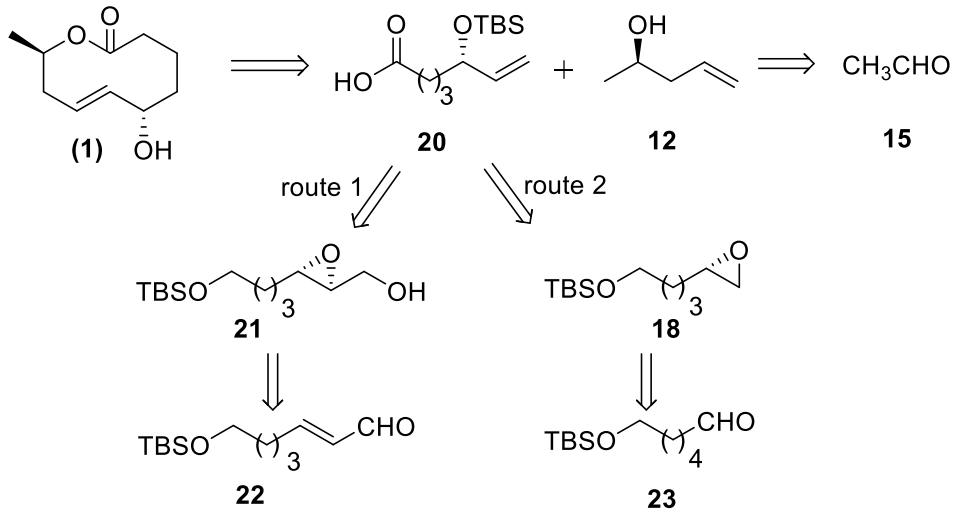
2.1.3. Present Work

2.1.3.1 Objective

The reported methods for the synthesis of stagonolide F **1**, either employs chiral starting materials or use of HKR protocol for the induction of chirality, apart from employing expensive reagents and longer reaction sequences. Therefore in view of biological activity and importance of the macrolactone **1**, new synthetic strategy that would allow an easy access to this compound is needed. As part of our continuing interest aimed at developing enantioselective synthesis of biologically active natural products based on asymmetric organocatalysis,[6] herein we report a simple, concise and flexible route for the

total synthesis of stagonolide F **1**, using organocatalytic asymmetric α-epoxidation, α-aminooxylation and Brown asymmetric allylation as the key steps for the introduction of chirality in the molecule starting from readily available raw material.

Our retrosynthetic analysis of stagonolide F **1** reveals that it could be synthesized by means of esterification of alkenoic acid fragment **20** with homoallylic alcohol fragment **12**. The homoallylic alcohol fragment **12** could easily be accessed by known Brown allylation protocol from commercially available acetaldehyde **15**.[7] The acid fragment **20** was in turn envisioned *via* two routes: (i) Jorgensen's asymmetric epoxidation[8] of unsaturated aldehyde **22** and (ii) asymmetric α-aminooxylation[9] of aldehyde **23** (**Scheme 4**).

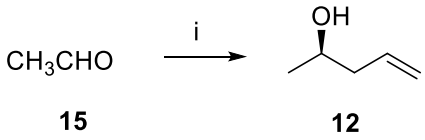


Scheme 4: Retrosynthetic analysis of stagonolide F (**1**)

2.1.4. Results and Discussion

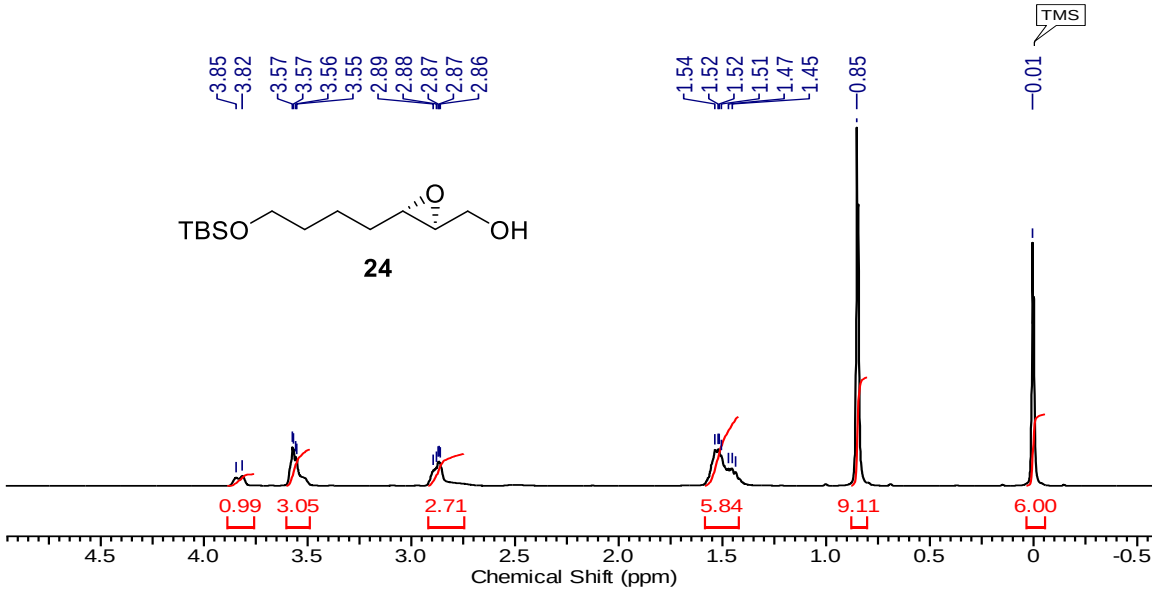
The synthesis of homoallylic alcohol **12** began with a known protocol involving Brown allylation of acetaldehyde **15**, which gave the homoallylic alcohol **12** in 77% yield. The optical purity of **12** was determined as 95% enantiomeric excess (ee) by comparing its

optical rotation with the reported values $[\alpha]_D^{25}$ -9.67 (*c* 3.0, Et_2O) {lit.[3,6] $[\alpha]_D^{25}$ -9.84 (*c* 3.1, Et_2O)} (**Scheme 5**).



Scheme 5: (i) (-)-*B*-allyldiisopinocamphenylborane, Et_2O-pentane, -78 °C, 1 h, NaOH, aq. 35% H_2O_2, 77%, 95% ee.

The synthesis of intermediate carboxylic acid fragment **20** commences with (*R*)-*α,α*-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**A**) catalyzed epoxidation[10] of *α,β*-unsaturated aldehyde **22** in a "one-pot" reaction sequence: thus, treatment of aldehyde **22** with 35% H_2O_2 as the oxygen source in the presence of 10 mol% pyrrolidine catalyst **A** with CH_2Cl_2 as solvent at 25 ºC followed by its reduction with $NaBH_4$ in MeOH gave the crude *α*-epoxy alcohol **24** *in situ* (**Scheme 6**). The ^1H NMR spectrum of **24** showed characteristic epoxy proton signals at δ 2.86-2.89 (m, 3H). The signals at δ 55.9, 58.6, 61.7 and 62.8 in its ^{13}C NMR spectrum were due to carbons attached to oxygen atom (**Figure 2**).



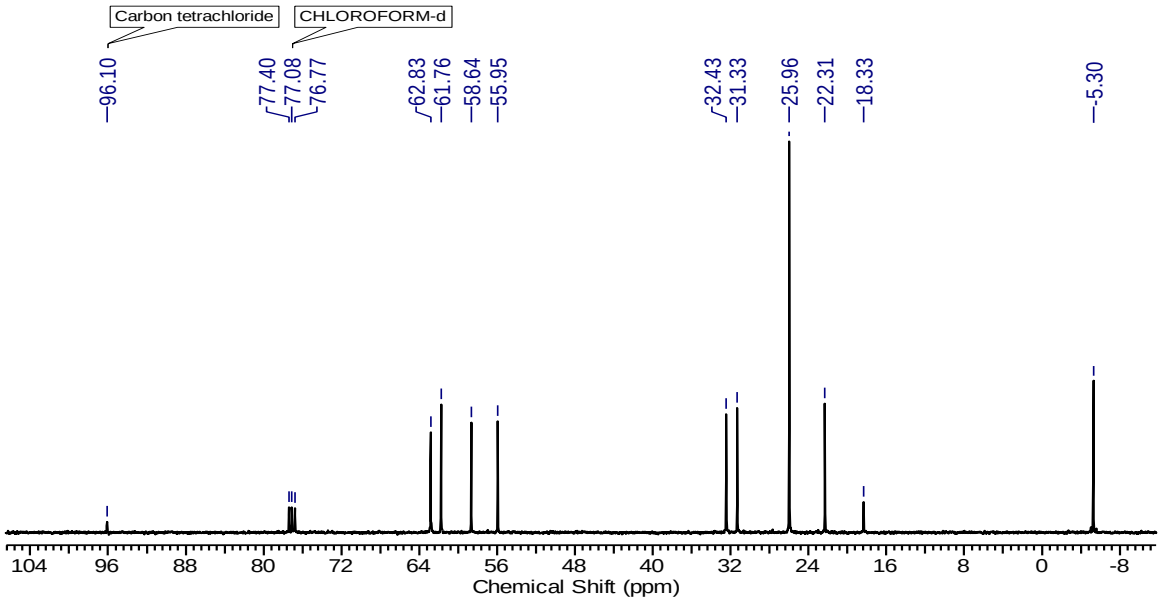
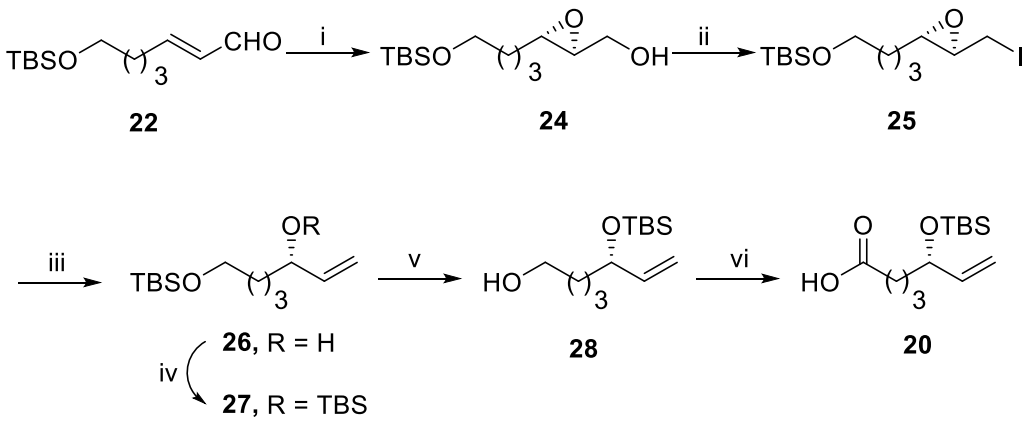


Figure 2: ^{1}H and ^{13}C NMR spectra of epoxy alcohol **24**



Scheme 6: (i) H_2O_2, CH_2Cl_2, (*R*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**A**), 25 ºC, 4 h then $NaBH_4$, MeOH, 0 ºC, 10 min, 43%, 99% ee; (ii) I_2, PPh_3, imid., Et_2O/CH_3CN (3:1), 0-25 ºC, 2 h, 90%; (iii) Zn, NaI, MeOH, reflux, 3 h, 90%; (iv) TBSCl, imidazole, CH_2Cl_2, 0-25 ºC, 6 h, 86%; (v) (+)-camphor-10-sulfonic acid, MeOH, 25 ºC, 5 min, 63%; (vi) TEMPO, $PhI(OAc)_2$, CH_3CN:H_2O (4:1), 25 ºC, 4 h, 80%.

Conversion of epoxy alcohol **24** to epoxy iodide **25** was achieved using Appel reaction condition: I_2, PPh_3 and imid.; $[\alpha]_D^{25}$ -8.1 (*c* 1.5, $CHCl_3$). Its ^{1}H NMR spectrum showed multiplets at δ 2.78-2.81 (m, 1H), 2.98-3.04 (m, 2H), and 3.23-3.29 (m, 1H) corresponding to -**CH**$_2$I and -**CH**-O-**CH**- protons. The typical carbon signals at δ 58.2,

62.4 and 62.7 in its ^{13}C-NMR spectrum were attributed to carbons attached to oxygen atom (**Figure 3**).

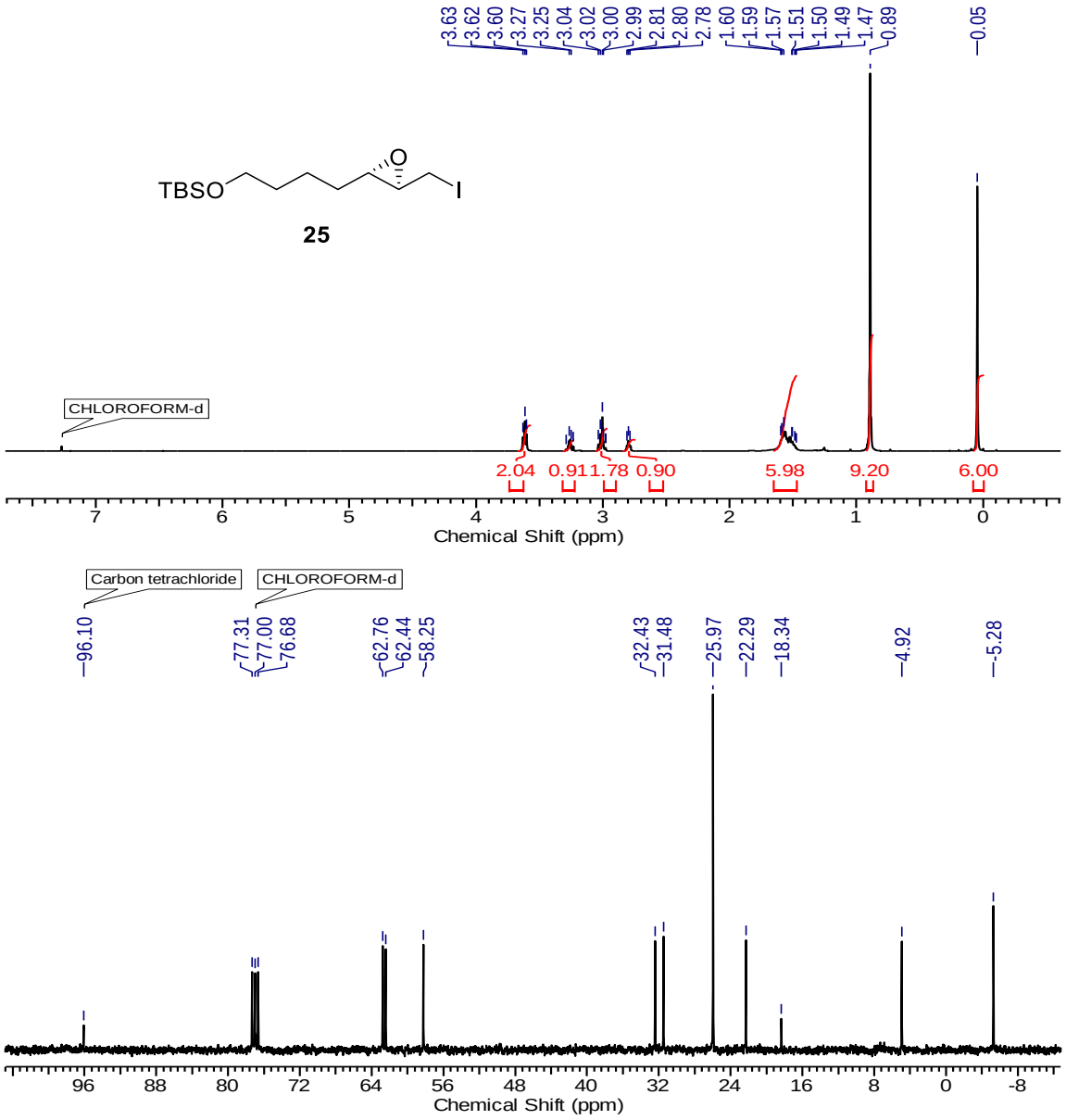


Figure 3: ^{1}H and ^{13}C NMR spectra of epoxy iodide **25**

Next step in the synthesis of carboxylic acid **20** was the reductive ring opening of epoxide **25** in the presence of Zn powder, which was accomplished smoothly to give allylic alcohol **26** in 90% yield. The formation of **26** was confirmed by the analysis of its

^{1}H and ^{13}C NMR spectra. The multiplets at δ 5.07-5.27 (m, 2H) and 5.78-5.95 (m, 1H) in its ^{1}H NMR spectrum indicated the formation of olefinic protons. The presence of olefin functionality in **26** was further substantiated by the presence of carbon signals at δ 114.5 and 141.2 in its ^{13}C NMR spectrum (**Figure 4**).

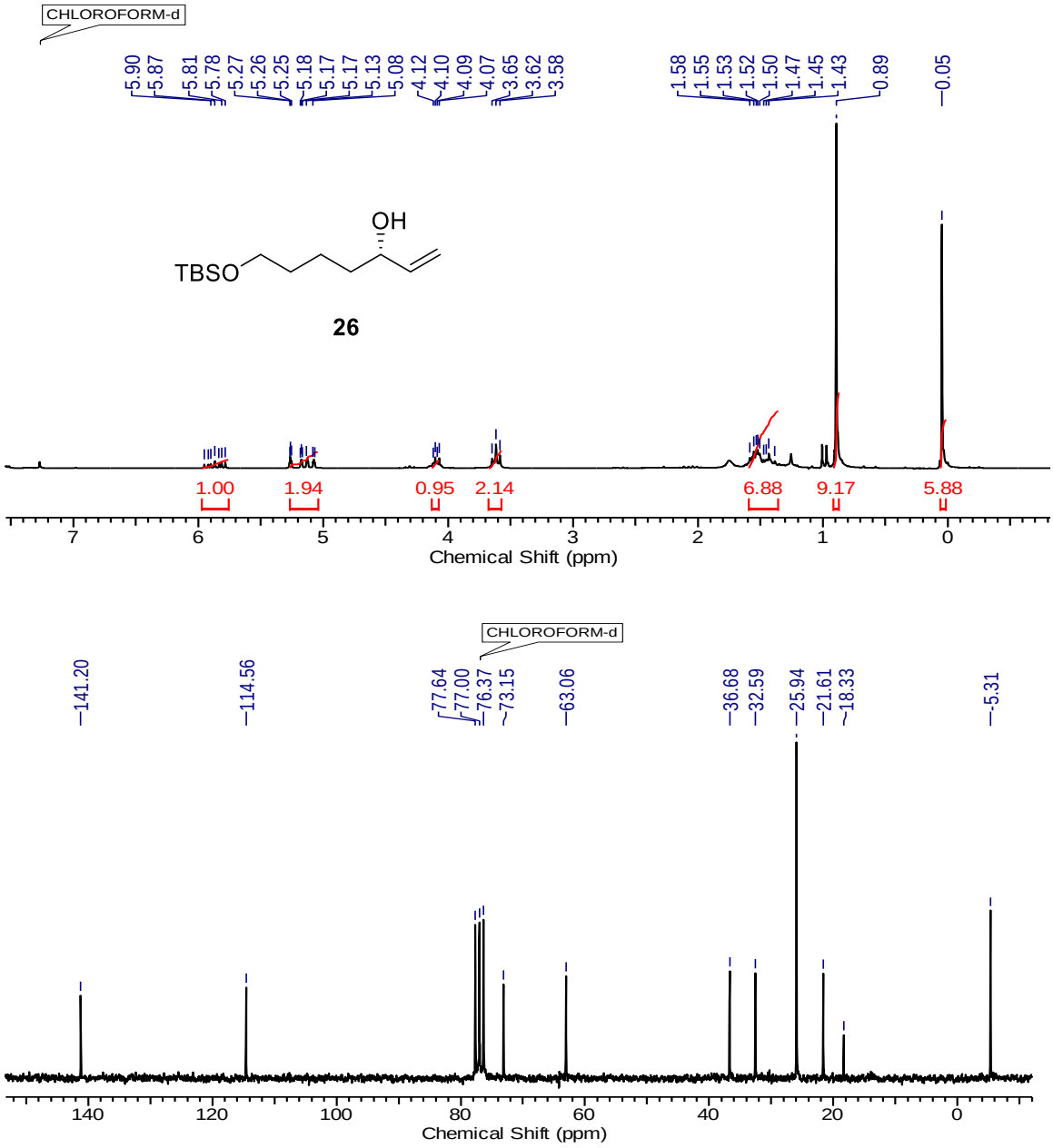
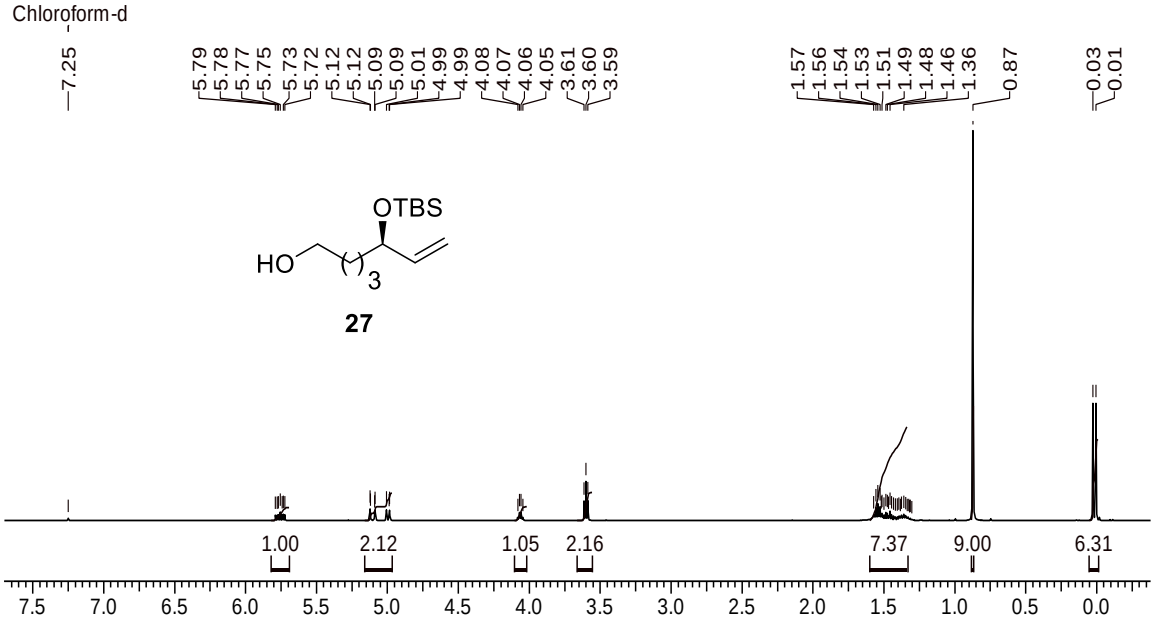


Figure 4: ^{1}H and ^{13}C NMR spectra of allylic alcohol **26**

Conversion of allylic alcohol **26** to carboxylic acid **20** was achieved in three steps as described here: (i) silylation of secondary alcohol functionality in **26**, (ii) chemoselective desilylation in **27** with (+)-camphor-10-sulfonic acid (CSA, MeOH, 63%), (iii) oxidation of **28** to carboxylic acid **20** using TEMPO/BAIB mixture in CH_3CN/H_2O (3:1) solvent combination. Carboxylic acid fragment **20** was obtained with an overall yield of 15.1% in 98% ee, determined by comparing its optical rotation with the reported values $[\alpha]_D^{25}$ +6.5 (*c* 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ +6.6 (*c* 1.15, $CHCl_3$)} (**Scheme 6**). The formation of primary alcohol **28** was confirmed by its IR spectrum which showed a strong absorbtion band at υ_{max} 3441 cm^{-1} corresponding to alcohol functionality. Its ^1H NMR spectrum showed signals at δ 3.59 (t, *J* = 5.9 Hz, 2H) and 4.05 (q, *J* = 6.1 Hz, 1H) indicative of methylene (-**CH**$_2$-OH) and methine (-**CH**-OTBS) protons respectively. The signals at δ -4.7, -4.2, 18.3 and 25.9 in its ^{13}C NMR spectrum were attributed to carbons of TBS ether functionality, while the resonance peaks at δ 62.8 and 73.8 accounted for methylene (-**CH**$_2$-OH) and methine (-**CH**-OTBS) carbons respectively (**Figure 5**).



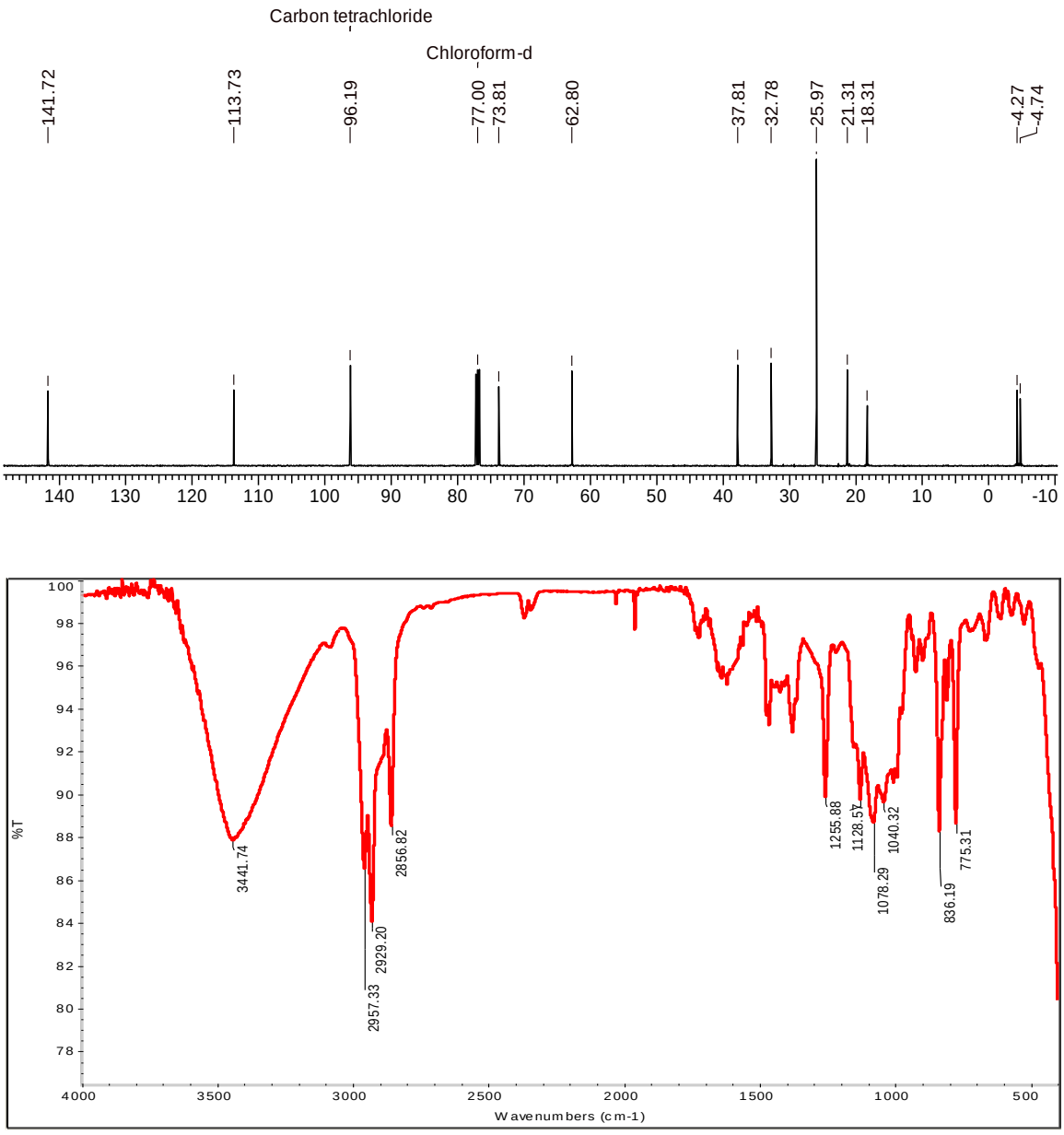
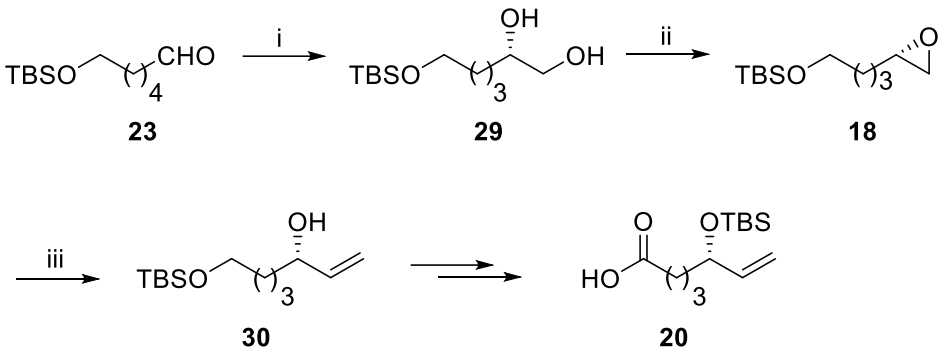


Figure 5: ^{1}H & ^{13}C NMR and IR spectra of alcohol **27**

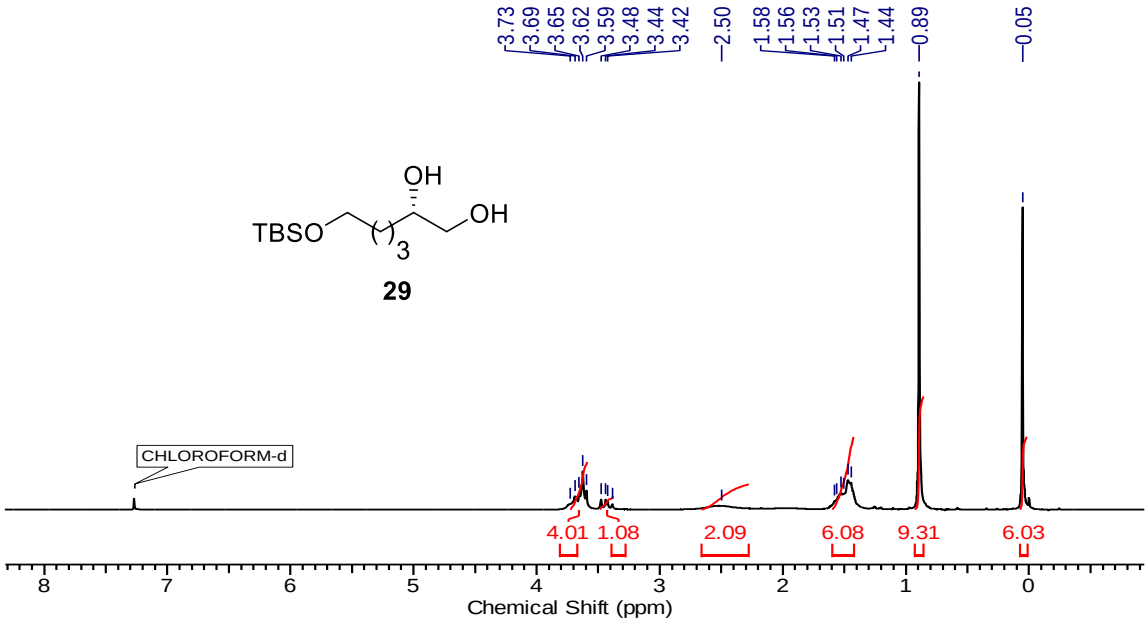
Since the overall yield that could be realized for intermediate acid fragment **20** in epoxidation route was considerably lower (15.1%), we envisioned an alternate route for its synthesis. Our second approach for the synthesis of acid fragment **20** commenced from aldehyde **23**, which was subjected to D-proline catalyzed *α*-aminooxylation in a two-step reaction sequence: (i) reaction of aldehyde **23** with nitrosobenzene as the

oxygen source in the presence of 20 mol% D-proline in CH_3CN at -20 ºC followed by its reduction with $NaBH_4$ in MeOH gave the crude *α*-aminoxy alcohol *in-situ*; (ii) subsequent reduction of the crude *α*-aminoxy alcohol using 10 % Pd/C over H_2 (1 atm) furnished chiral diol **29** in **77**% yield over two steps (**Scheme 7**).



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

The formation of diol **29** was confirmed by the presence of a broad singlet (br s) at δ 2.50 in its ^1H NMR spectrum, corresponding to hydroxyl protons.



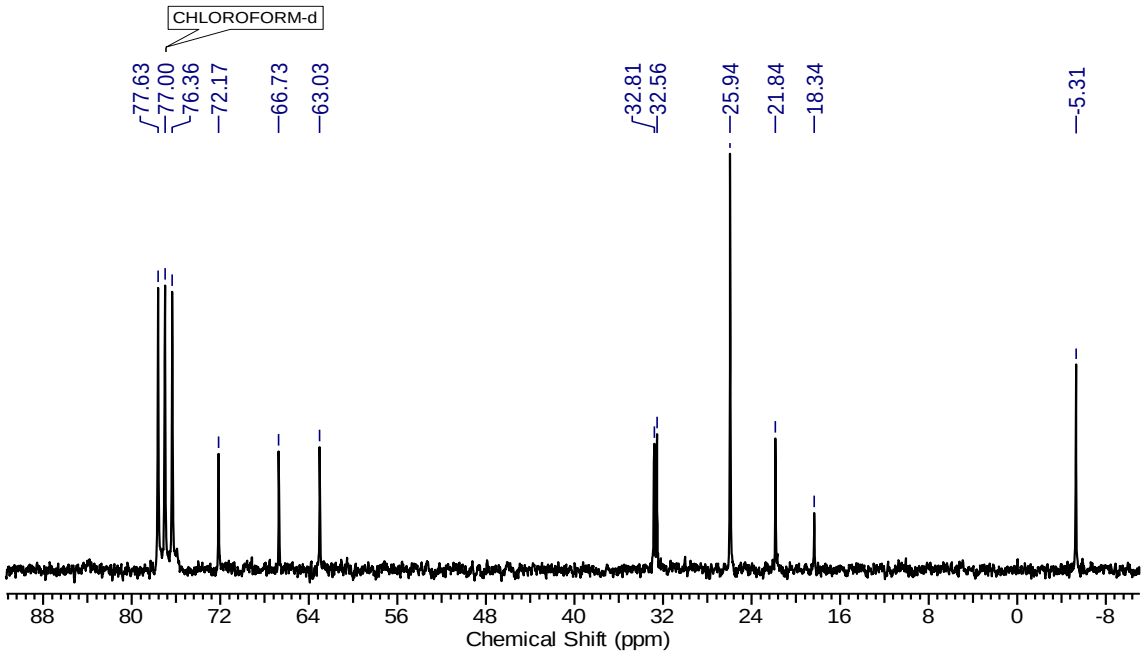


Figure 6: ^{1}H and ^{13}C NMR spectra of diol **29**

The multilplets at δ 3.38-3.48 (1H) and 3.59-3.73 (4H) in its ^{1}H NMR spectrum was assigned to methine (-**CH**-OH) and methylene (-**CH_2**-OH, -**CH_2**-OTBS) protons attached to oxygen atoms. Another multiplet at δ 1.44-1.58 was due to the six internal methylene protons (-**CH_2**-**CH_2**-**CH_2**-). Its ^{13}C NMR spectrum showed signals at δ 63.0, 66.7 and 72.1 corresponding to methylene and methine carbons attached to oxygen atoms respectively (**Figure 6**). Selective tosylation of primary hydroxyl group in diol **29** (TsCl, Et_3N, Bu_2SnO) followed by treatment with K_2CO_3 in MeOH gave the optically pure terminal epoxide **18** in 92% yield over two steps. The formation of epoxide **18** was confirmed by the presence of multiplets at δ 2.46-2.50, 2.74-2.78 and 2.88-2.94 which were attributed to the protons of the epoxide group. Its ^{13}C NMR displayed signals at δ 47.0, 52.3 and 62.9 which were due to carbons attached to oxygen (**Figure 7**).

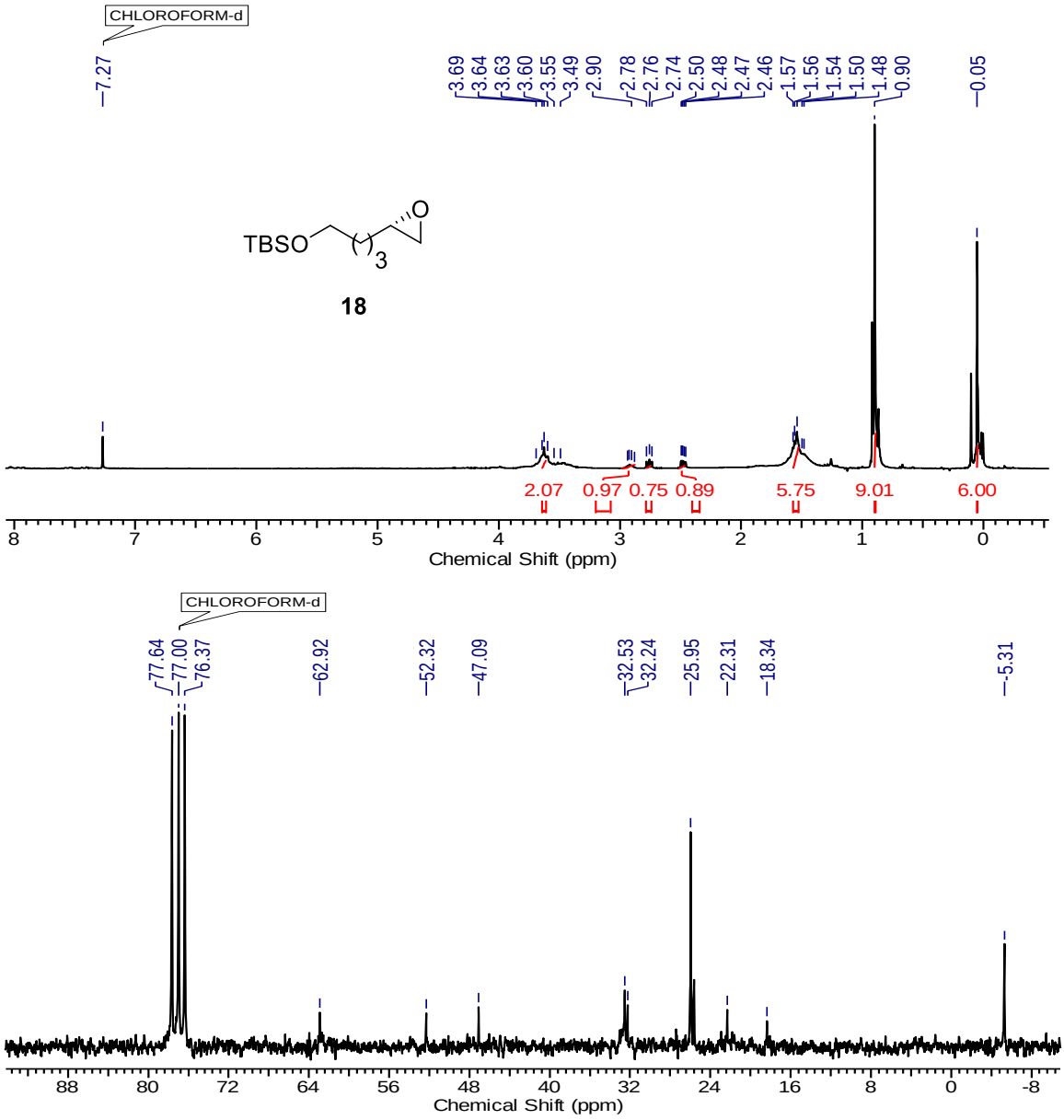


Figure 7: ^{1}H and ^{13}C NMR spectra of epoxide **18**

Regioselective opening of epoxide **18** into the corresponding allylic alcohol **30** was readily achieved by using Corey-Chaykovsky reagent ($S^{+}Me_3I^{-}$, NaH, DMSO) in 89% yield. Conversion of alcohol **30** to carboxylic acid **20** was achieved in three steps with an overall yield of 27.3% and 98% ee as described before (**see Scheme 5**). The formation of carboxylic acid **20** was confirmed by the presence of a broad singlet (br s) at δ 10.67 in its ^{1}H NMR spectrum. This was further substantiated by the appearance of a typical

signal at δ 179.9 in its ^{13}C NMR spectrum. The disappearance of signals corresponding to methylene (-**CH_2**OH) in its ^{1}H NMR spectrum further confirmed the completion of this oxidation reaction (**Figure 8**).

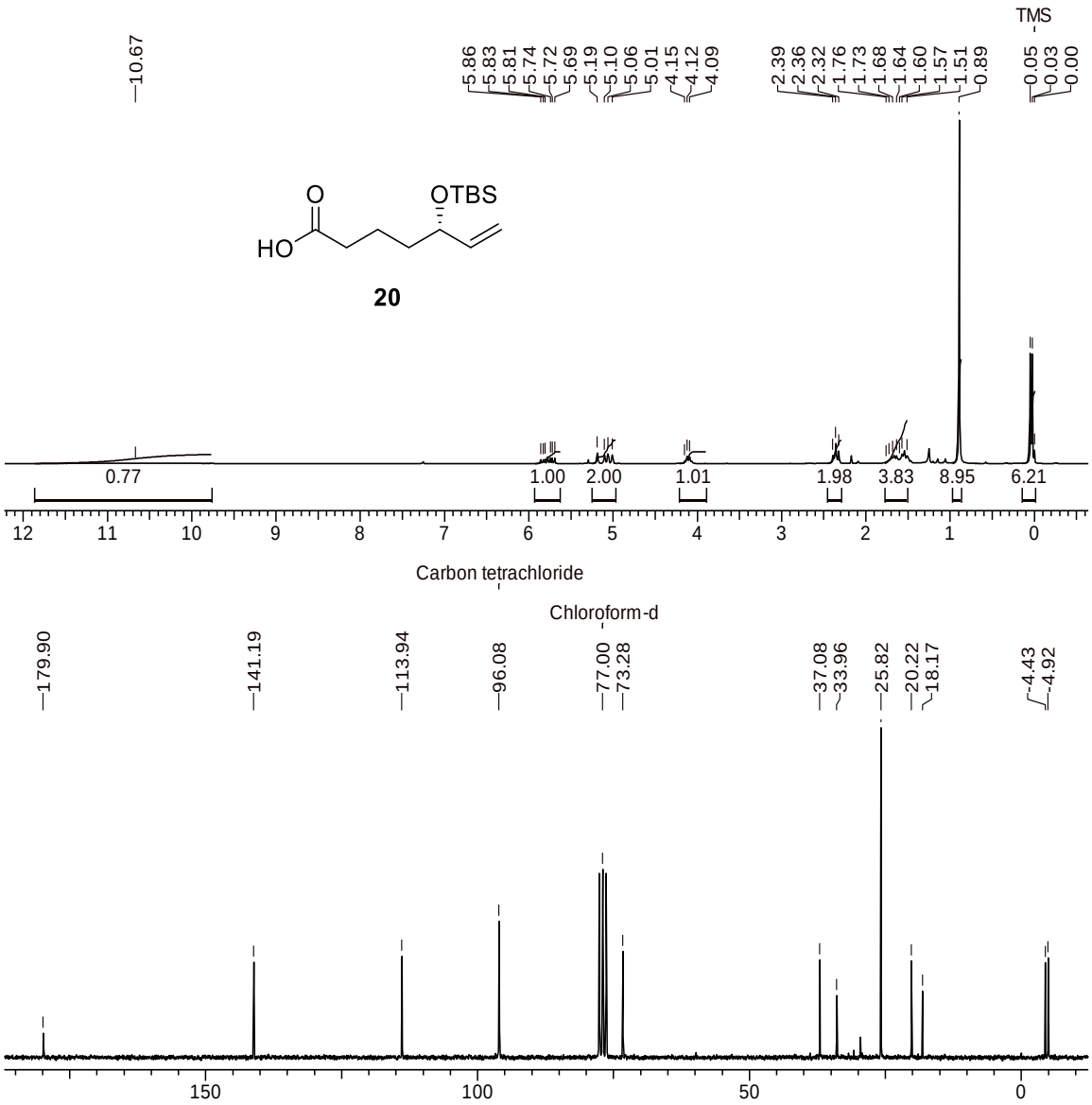


Figure 8: ^{1}H and ^{13}C NMR spectra of carboxylic acid **20**

With both the fragments **12** and **20** now in hand, we then carried out the coupling of these two fragments using Steglich esterification (EDCI, Et_3N, 88%) which gave coupled product **31 (Scheme 8)**. The coupled product **31** was confirmed by the presence of a

typical multiplet at δ 4.06-4.15 corresponding to methine proton (-**CH**-OCO) attached to ester linkage. This was further substantiated by the presence of carbon signals at δ 113.8, 117.6, 133.7 and 141.4 in its ^{13}C NMR spectrum which were attributed to four olefinic carbons (**Figure 9**).

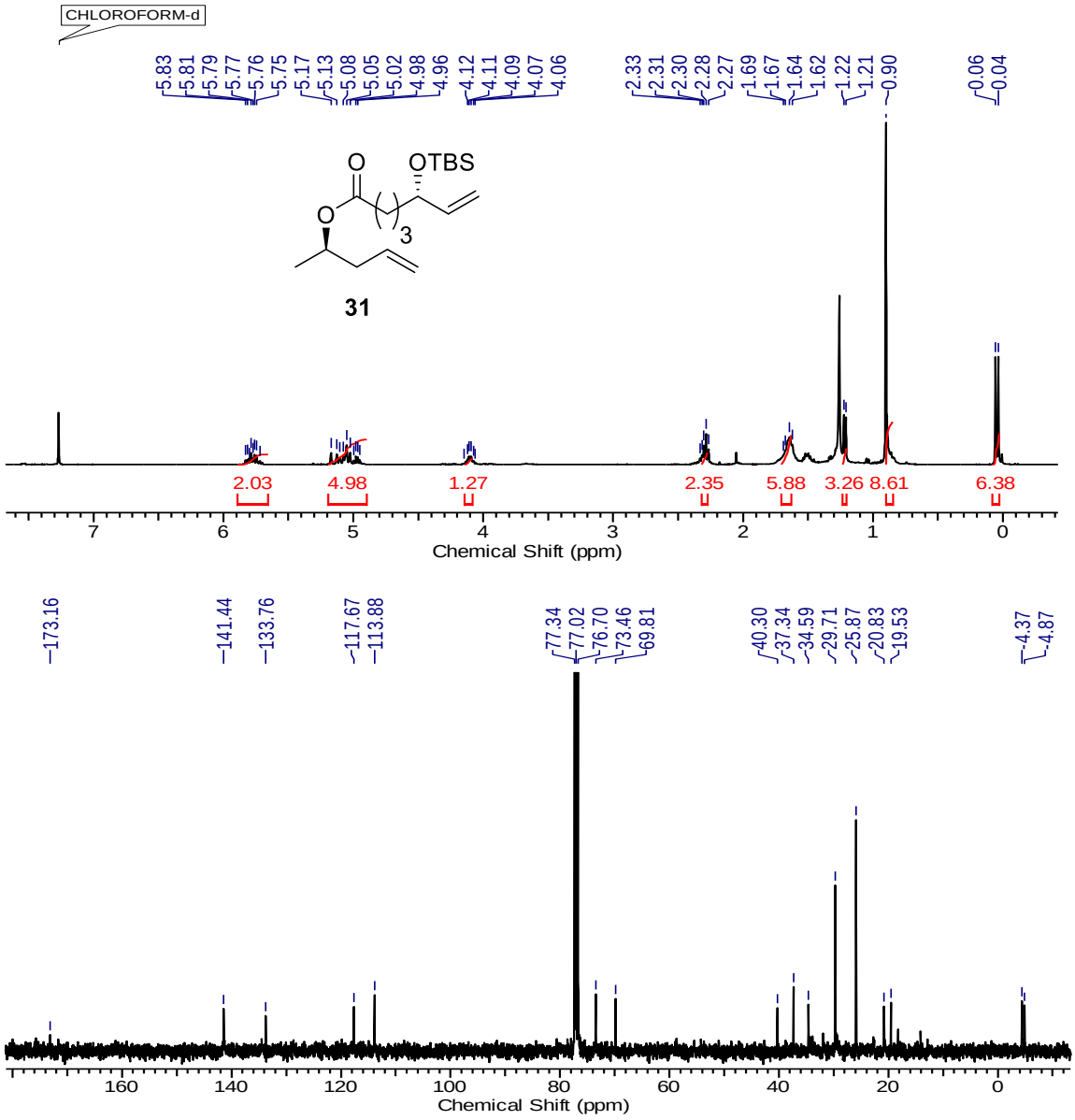
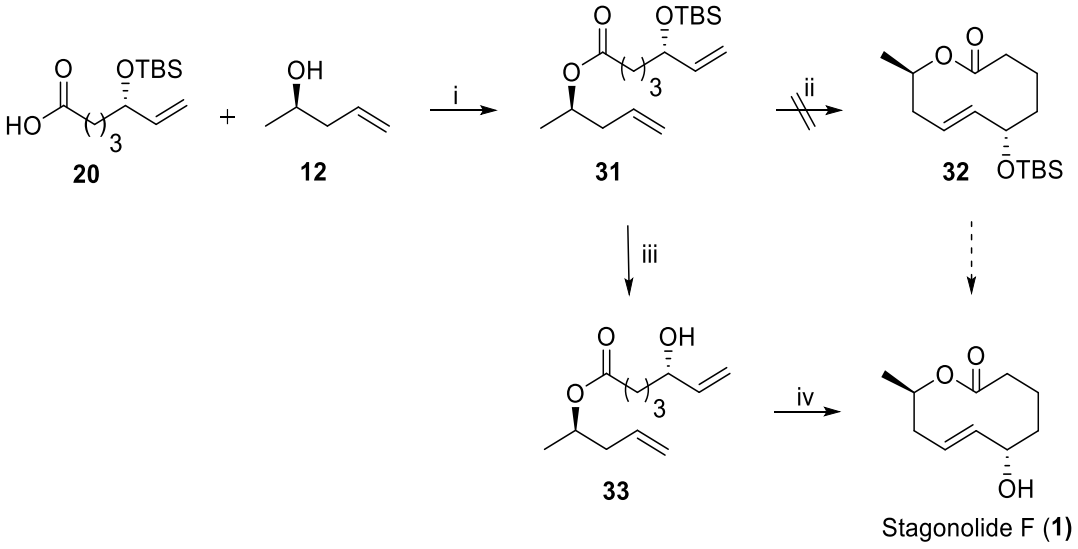


Figure 9: ^{1}H and ^{13}C NMR spectra of coupled product **31**

Our next task was to do the critical ring-closing metathesis reaction. But unfortunately ring-closing metathesis reaction of coupled compound **31** with 10 mol% Grubbs' second-generation catalyst failed to provide required ten-membered lactone core **32** when heated under reflux condition even up to 48 h in anhydrous dichloromethane. Finally, the TBS group in compound **31** was removed (TBAF, THF) to give bis-olefin **33**.



Scheme 8: (i) EDCI·HCl, Et_3N, CH_2Cl_2, 25 °C, 6 h, 88%; (ii) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 48 h (iii) TBAF, THF, 0 °C, 2 h, 80% ; (iv) Grubbs-II (10 mol%), dry CH_2Cl_2, reflux, 24 h, 69%.

The formation of bis-olefin **33** was confirmed by its ^1H and ^{13}C NMR spectrum. Its ^1H NMR spectrum shows disapperance of proton signals at δ -4.8 and -4.3 due to the silyl group and it was further supported by its ^{13}C NMR spectrum. The cyclic core was then constructed smoothly in 69% yield *via* a RCM strategy using Grubb's second-generation catalyst, thus affording the final compound stagonolide F (**1)** in 10.1% overall yield and 98% ee. Its optical purity was based on comparison of its specific rotation with the reported value $[\alpha]_D^{25}$ -26.5 (*c* 0.2, $CHCl_3$) {lit.[2] $[\alpha]_D^{25}$ -27 (*c* 0.35, $CHCl_3$)} (**Scheme 8**).

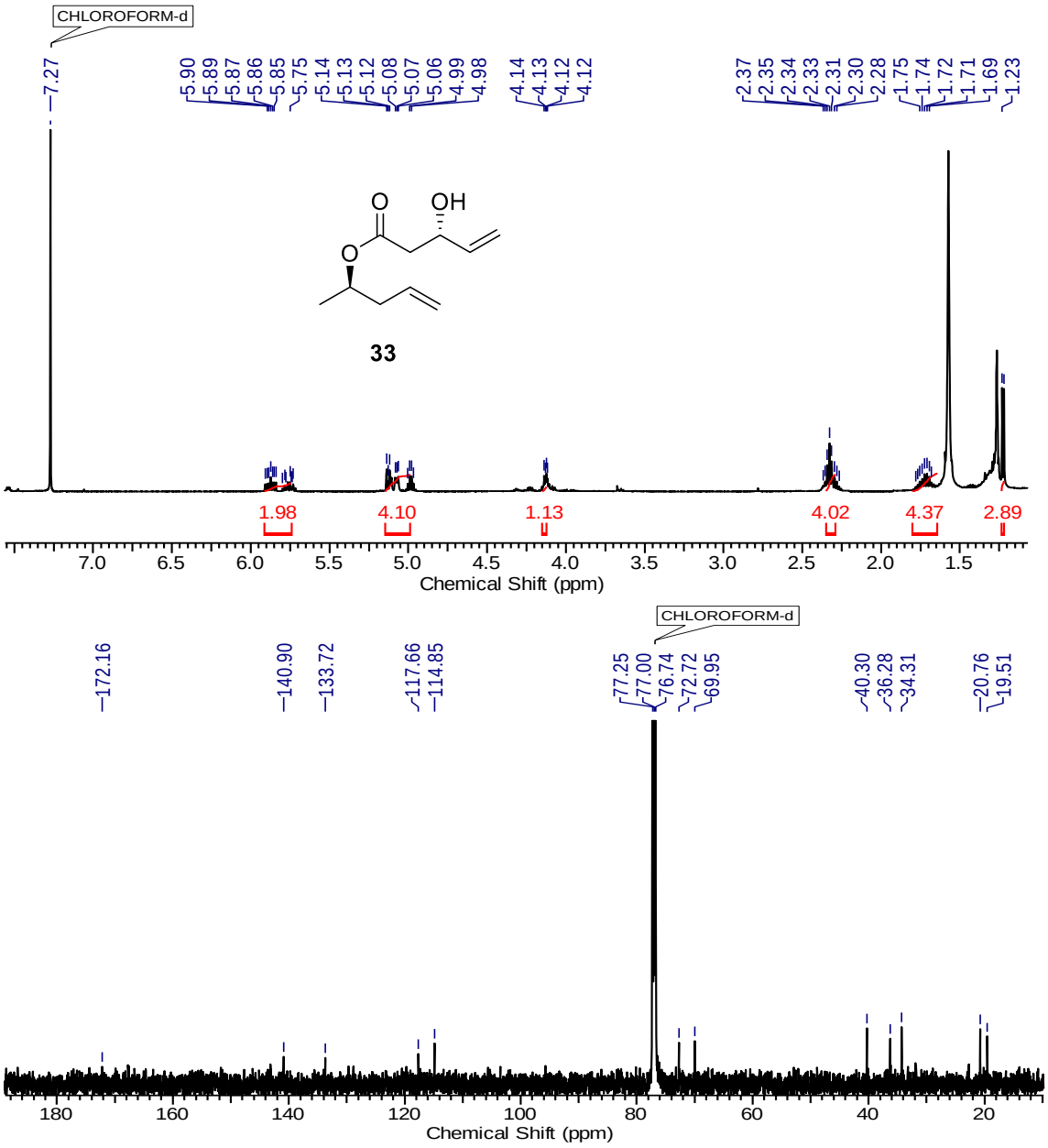


Figure 10: ^{1}H and ^{13}C NMR spectra of bis-olefin **33**

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

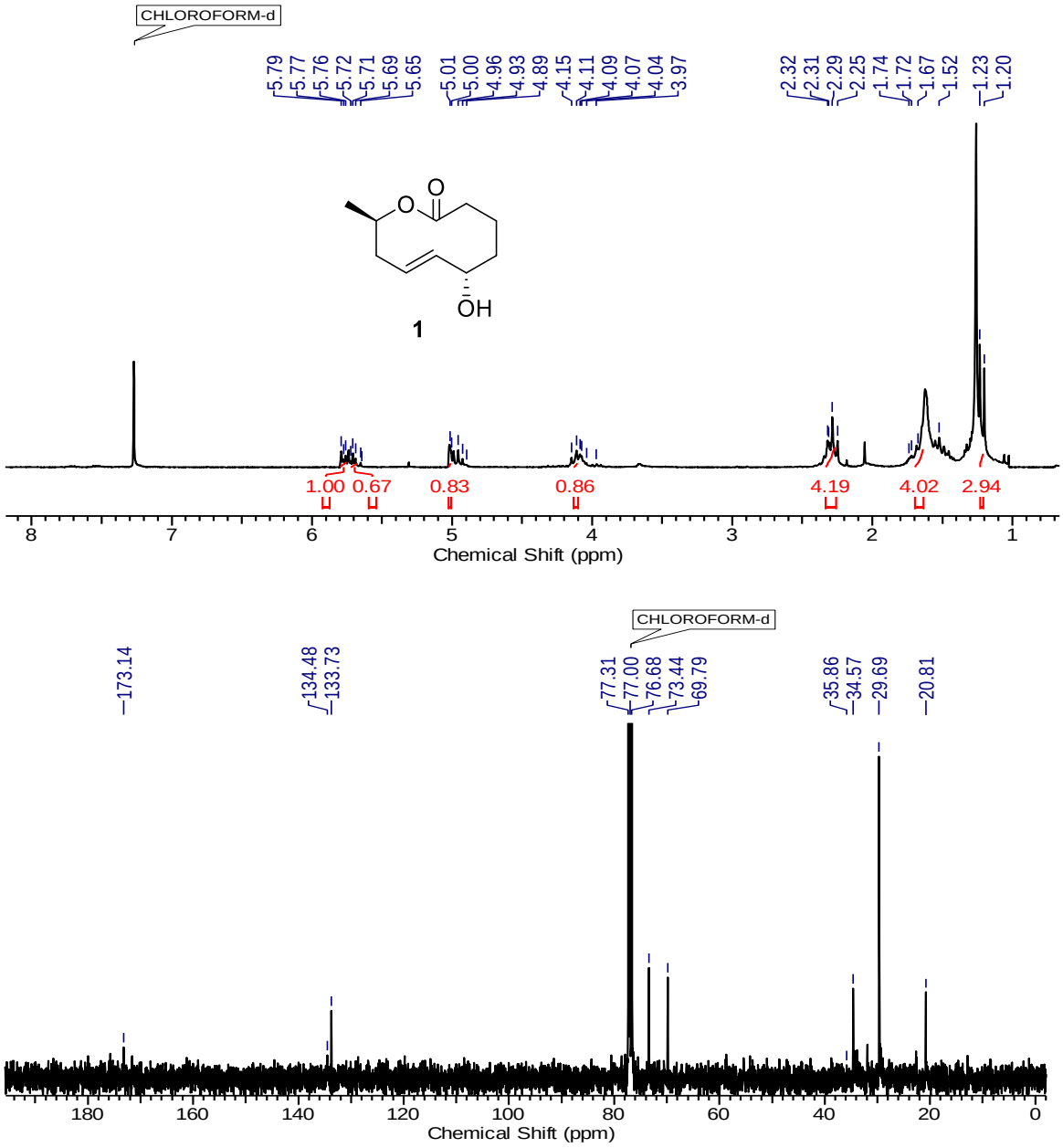


Figure 10: ^{1}H and ^{13}C NMR spectra of stagonolide F **1**

2.1.5 Conclusion

In conclusion, we have developed a concise and convergant approach for the total synthesis stagonolide F in a highly stereoselective manner by employing an organocatalytic α-aminooxylation and asymmetric epoxidation strategy with an

enantiomeric excess of 98% in 10.1% overall yield. Simple procedures, easy to use reagents, high overall yield, cheap, readily available starting materials and flexible synthetic scheme are some of the salient features of this approach. The synthetic strategy described herein has significant potential for further extension to other decanolides-based bioactive molecules.

2.1.6 Experimental section

((2*S*, 3*S*)-3-(4-(*tert*-butyldimethylsilyloxy)ethyl)oxiran-2-yl)methanol (24)

Catalyst (*R*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol tri-methylsilyl ether (1.2 g, 10 mol%) was added at ambient temperature to a solution of the α,β-unsaturated aldehyde **22** (5 g, 20.6 mmol) in CH_2Cl_2 (50 mL) followed by the addition of 35% H_2O_2 (aq.) (2.6 mL, 26.8 mmol). After completion of the reaction (monitored by TLC), it was diluted with MeOH (50 mL) and cooled to 0 °C followed by the addition of $NaBH_4$ (1.7 g, 30.9 mmol). The mixture was then stirred for 10 min, after which it was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography with petroleum ether/EtOAc (8:2 v/v) to give epoxy alcohol **24** (2.3 g) as a yellow colored liquid.

Yield: 43%; $[\alpha]_D^{25}$ = +16.9 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3414, 3063, 2936, 2862, 1717, 1454, 1099, 878, 746 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.85 (s, 9H), 1.45-1.54 (m, 6H), 2.86-2.89 (m, 3H), 3.55-3.57 (m, 3H), 3.82-3.85 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -5.3, 18.3, 22.3, 25.9, 31.3, 32.4, 55.9, 58.6, 61.7, 62.8; **HRMS** (m/z): calculated [M+H]+ for $C_{13}H_{29}O_3Si$: 261.1886 found: 261.1883.

Tert-butyl (4-((2*S*, 3*R*)-3-(iodomethyl)oxiran-2-yl)butoxy)dimethylsilane (25)

To a stirred solution of epoxy alcohol **24** (1.3 g, 5 mmol) in dry ether-acetonitrile mixture (3:1, 40 mL) at 0 °C under a nitrogen atmosphere were successively added imidazole (570 mg, 7.5 mmol), triphenylphosphine (1.96 g, 7.5 mmol), and iodine (1.90 g, 7.5 mmol). The mixture was stirred for 1 h at the same temperature followed by stirring at 25 °C for an additional 1h. After completion of the reaction (monitored by TLC) it was diluted with cold ether (20 mL), and filtered through a sintered funnel. The residue was washed with ether (3 × 50 mL) and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (9:1 v/v) to afford epoxy iodide **25** (1.7 g) as a colorless liquid.

Yield: 90%; $[\alpha]_D^{25}$ = -8.1 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3018, 2927, 2854, 1216, 767, 669 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.47-1.60 (m, 6H), 2.78-2.81 (m, 1H), 2.98-3.04 (m, 2H), 3.23-3.29 (m, 1H), 3.60-3.63 (m, 2H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ -5.2, 4.9, 18.3, 22.2, 25.9, 31.4, 32.4, 58.2, 62.4, 62.7; **HRMS** (m/z): calculated [M+H]+ for $C_{13}H_{28}O_2ISi$: 371.0903 found: 371.0901.

(*S*)-7-(*tert*-butyldimethylsilyloxy)hept-1-en-3-ol (26)

A mixture of the above epoxy iodide **25** (1.3 g, 3.5 mmol), NaI (1.1 g, 7.0 mmol) and freshly activated zinc powder (50 mg, 20 mol%) in dry MeOH (50 mL) was refluxed for 6 h under a nitrogen atmosphere. After completion of the reaction (monitored by TLC), the solution was filtered and the residue washed with MeOH (2 × 25 mL). The combined filtrates were concentrated and the residue was purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to afford the allylic alcohol **26** (770 mg) as a colorless liquid.

Yield: 90%; $[\alpha]_D^{25}$ = -7.3 (*c* 2.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3427, 3307, 3018, 2926, 2864, 1465, 1458, 1217, 1018, 993, 927, 769, 669 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.38-1.58 (m, 7H), 3.58 (t, *J* = 6.0 Hz, 2H), 4.07-4.12 (m, 1H), 5.07-5.27 (m, 2H), 5.78-5.95 (m, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 21.6, 25.9, 32.5, 36.6, 63.0, 73.1, 114.5, 141.2; **HRMS** (m/z): calculated [M+Na]+ for $C_{13}H_{28}NaO_2Si$: 267.1756 found: 267.1758.

(*S*)-2,2',3,3',11,11',12,12'-octamethyl-5-vinyl-4,10-dioxa-3,11-disilatridecane (27)

To a solution of allylic alcohol **26** (1 g, 4.1 mmol) and imidazole (556 mg, 8.2 mmol) in dry CH_2Cl_2 (40 mL) was added TBSCl (738 mg, 4.9 mmol) under nitrogen over 5 min at 0 °C, and the mixture was then allowed to warm to room temperature and stirred for 6 h. After completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether gave TBS ether **27** (1.3 g) as a colorless liquid.

Yield: 86%; $[\alpha]_D^{25}$ = -6.2 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3018, 2927, 2854, 1216, 1033, 929 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 12H), 0.90 (s, 18H), 1.41-1.61 (m, 6H), 3.57 (t, *J* = 6.1 Hz, 2H), 4.04-4.11 (m, 1H), 4.98-5.18 (m, 2H), 5.72-5.88 (m, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, -4.7, -4.2, 18.4, 21.6, 26.0, 32.9, 37.9, 63.1, 73.9, 113.5, 141.8; **HRMS** (m/z): calculated [M+Na]+ for $C_{19}H_{42}NaO_2Si_2$: 381.2661 found: 381.2660.

(*S*)-5-(*tert*-butyldimethylsilyloxy)hept-6-en-1-ol (28)

To a stirred solution of **27** (900 mg, 2.72 mmol) in MeOH (20 mL) was added (+)-camphor-10-sulfonic acid (6 mg, 1 mol%) and the reaction mixture was stirred for 5 min. After completion of the reaction (monitored by TLC), H_2O (1 mL) was added and extraction was done with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatographic purification of the crude product using petroleum ether/EtOAc (8:2 v/v) gave alcohol **28** (371 mg) as a colorless liquid.

Yield: 63%; $[\alpha]_D^{25}$ = +9.2 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3441, 2957, 1215, 836, 775 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.36-1.57 (m, 7H), 3.59 (t, *J* = 5.9 Hz, 2H), 4.05-4.08 (m, 1H), 4.99-5.12 (m, 2H), 5.72-5.79 (m, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.2, 18.3, 21.3, 25.9, 32.7, 37.8, 62.8, 73.8, 113.7, 141.7; **HRMS** (m/z): calculated [M+H]+ for $C_{13}H_{29}O_2Si$: 245.1937 found: 245.1940.

(*S*)-5-(*tert*-butyldimethylsilyloxy)hept-6-enoic acid (20)

To a solution of alcohol **28** (450 mg, 1.85 mmol) in CH_3CN/H_2O (4:1) were added in one portion (diacetoxyiodo)benzene (1.2 g, 3.7 mmol) and TEMPO (86.3 mg, 0.55 mmol). The reaction mixture was then allowed to stir at 25 ^oC for 4 h. After completion of reaction (monitored by TLC), it was quenched by the addition of saturated solution of aq. sodium thiosulfate. The organic layer was separated, washed with brine and subjected to column chromatographic purification with petroleum ether/EtOAc (7:3 v/v) to afford the carboxylic acid **20** (383.9 mg) as a colorless liquid.

Yield: 80%; $[\alpha]_D^{25}$ +6.5 (*c* 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ +6.6 (*c* 1.15, $CHCl_3$)}; **IR** ($CHCl_3$): υ_{max} 3444, 3070, 2931, 2858, 1707, 1462, 1425, 1257, 1109 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.47-1.73 (m, 4H), 2.32 (t, *J* = 7.0 Hz, 2H), 4.08-4.16 (m, 1H), 5.01-5.28 (m, 2H), 5.71-5.85 (m, 1H), 6.46 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, - 4.4, 18.2, 20.4, 25.8, 29.6, 34.1, 37.2, 73.3, 113.9, 141.3, 179.3; **HRMS** (m/z): calculated [M+Na]+ for $C_{13}H_{26}NaO_3Si$: 281.1549 found: 281.1544.

(*S*)-6-((*tert*-butyldimethylsilyl)oxy)hexane-1,2-diol (29)

To a stirred pre-cooled (-20 °C) acetonitrile (100 mL) solution of aldehyde **23** (6.1 g, 26.5 mmol) and nitrosobenzene (2.8 g, 26.5 mmol) was added D-proline (608 mg, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 24 h followed by the addition of MeOH (60 mL) and $NaBH_4$ (1.94 g, 51 mmol) to the reaction mixture, which was stirred for 10 min. After the completion of reaction (monitored by TLC), the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude aminooxy alcohol which was directly taken up for the next step without purification. To a well stirred solution of crude aminooxy alcohol in methanol was added 10% Pd/C and the reaction mixture stirred overnight at 25 ^oC under H_2 atmosphere. After completion of the reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and solvent evaporated under reduced pressure to afford the crude diol. Purification by column chromatography with petroleum ether/ethyl acetate (5:5 v/v) gave the diol **29** (5.1 g) as a colorless liquid.

Yield: 77%; $[\alpha]_D^{25}$ = +7.2 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1376, 1466, 2872, 2969,3381 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.44-1.58 (m, 6H), 2.50 (br s , 2H), 3.38-3.48 (m, 1H), 3.59-3.73 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 21.8, 25.9, 32.5, 32.8, 63.0, 66.7, 72.1; **HRMS** (m/z): calculated [M+Na]+ for $C_{12}H_{28}NaO_3Si$: 271.1705 found: 271.1700.

(*S*)-*tert*-butyldimethyl(4-(oxiran-2-yl)butoxy)silane (18)

A solution of diol **29** (2.94 g, 11.8 mmol) in CH_2Cl_2 (50 mL) was treated with TsCl (2.25 g, 11.8 mmol), Bu_2SnO (883.8 mg, 30 mol %), Et_3N (4.21 mL, 30 mmol) and DMAP (cat.) at 0 °C. After being stirred for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude tosylate. To a solution of crude tosylate in MeOH (50 mL) was added K_2CO_3 (1.79 g, 13 mmol) and the mixture was stirred at 0 °C for 30 min. After the reaction was complete (monitored by TLC), solvent was evaporated and the residue was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was then purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to give epoxide **18** (2.5 g) as a colorless oil.

Yield: 92%; $[\alpha]_D^{25}$ = +5.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1102, 1222, 1255, 2930, 2955 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.90 (s, 9H), 1.48-1.57 (m, 6H), 2.46-2.50 (m, 1H), 2.74-2.78 (m, 1H), 2.88-2.94 (m, 1H), 3.49-3.69 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 22.3, 25.9, 32.2, 32.5, 47.0, 52.3, 62.9; **HRMS** (m/z): calculated [M+Na]+ for $C_{12}H_{26}NaO_2Si$: 253.1600 found: 253.1603.

(*S*)-7-(*tert*-butyldimethylsilyloxy)hept-1-en-3-ol (30)

To a stirred suspension of trimethylsulfonium iodide (2 equiv, 11 mmol, 2.24 g) in dry THF (50 mL) was added *n*-BuLi (2 equiv, 11 mmol, 6.8 mL of 2 M hexane solution) at -10 ^{o}C. After 30 min, epoxide **18** (1.2 g, 5.2 mmol) in dry THF (30 mL) was introduced dropwise and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to give allyl alcohol **30** (1.12 g)**.**

(*R*)-pent-4-en-2-yl (*S*)-5-((tert-butyldimethylsilyl)oxy)hept-6-enoate (31)

To a stirred solution of acid **20** (200 mg, 0.8 mmol), EDCI.HCl (176.4 mg, 0.9 mmol) and Et_3N (242.2 mg, 2.4 mmol), and DMAP (cat.) in anhydrous CH_2Cl_2 (25 mL) was added alcohol **12** (67 mg, 0.8 mmol) and the reaction mixture stirred for 6 h at 25 °C. After completion of the reaction (monitored by TLC), it was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to give bis olefin ester **31** (224.6 mg) as a colorless liquid.

Yield: 88%; $[\alpha]_D^{25}$ = +5.2 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2926, 2855, 1735, 1642, 1462, 1425, 1216, 1110, 761; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.21 (d, *J* = 6.1 Hz, 3H), 1.62-1.69 (m , 6H), 2.27-2.33 (m, 2H), 4.06-4.15 (m, 1H), 4.95-5.17 (m, 5H), 5.72-5.83 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.8, -

4.3, 14.1, 18., 19.5, 20.8, 22.6, 25.8, 29.6, 31.9, 34.5, 37.3, 40.2, 69.7, 73.4, 113.8, 117.6, 133.7, 141.4, 173.1;. **HRMS** (m/z): calculated [M+Na]+ for $C_{18}H_{34}NaO_3Si$: 349.2175 found: 349.2174 .

(R)-pent-4-en-2-yl (S)-5-hydroxyhept-6-enoate (33)

To a well stirred solution of bis olefin ester **31** (200 mg, 0.48 mmol) in dry THF (5 ml) was added a 1 M solution of tetrabutylammonium fluoride (1 mL, 1 mmol) at 0 ^oC. The reaction mixture was stirred at this temperature for an additional 2 h. After completion of the reaction (monitored by TLC), it was quenched with H_2O (1 mL) and the reaction mixture extracted with Et_2O (3 × 20 mL). Next, it was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to give bis olefin **33** as colorless syrup.

Yield: 80%; $[\alpha]_D^{25}$ = +6.7 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2925, 2854, 1730, 1642, 1461, 1374, 1218; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.1 Hz, 3H), 1.68-1.78 (m, 4H), 2.27-2.37 (m, 4H), 4.12-4.14 (m, 1H), 4.97-5.14 (m, 4H), 5.73-5.91 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.5, 20.7, 34.3, 36.2, 40.3, 69.9, 72.7, 114.8, 117.6, 133.7, 140.9, 172.1;. **HRMS** (m/z): calculated [M+Na]+ for $C_{12}H_{20}NaO_3$: 235.1310 found: 235.1309.

stagonolide F (1)

Bis olefin 33 (50 mg, 0.23 mmol) was dissolved in freshly distilled degassed anhydrous CH_2Cl_2 (50 mL).The reaction mixture was treated with Grubb's catalyst II (82 mg, 20 mol %) and reflux for 24 h under an inert atmosphere. After completion of the reaction (monitored by TLC), the solvent was then distilled off and the residue was purified by

column chromatography with petroleum ether/EtOAc (9:1 v/v) to afford **1 (**54 mg) as colorless liquid.

Yield: 69%; $[\alpha]_D^{25}$ -26.5 (*c* 0.20, $CHCl_3$) {lit.[2] $[\alpha]_D^{25}$ = -27 (*c* 0.35, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}) 3436, 2920, 2852, 1730, 1460, 1275, 970; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.20 (d, *J* = 6.10 Hz 3H), 1.52-1.74 (m, 4H), 2.30 (t, *J* = 7.10 Hz 2H), 2.42 (m, 2H), 3.97-4.08 (m, 1H), 5.01-5.04 (m, 1H), 5.28 (dd, *J* = 15.0, 9.6 Hz, 1H), 5.58-5.79 (ddd, *J* = 15.5, 10.0, 4.6 Hz 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.8., 29.6., 34.5, 35.8, 42.1, 73.6, 74.8, 133.6, 134.2, 173; **HRMS** (m/z): calculated [M+H]+ for $C_{10}H_{17}O_3$: 185.1178 found: 185.1176.

Section II

A Formal Synthesis of Pinolide *via* L-Proline-Catalyzed Sequential *α*-Aminooxylation and Horner-Wadsworth-Emmons Olefination-Sharpless Asymmetric Dihydroxylation Strategy

2.2.1 Introduction and Pharmacology

Pinolide **34**, a naturally occurring nonenolide was recently isolated from the liquid culture of CO-99 of *Didymella Pinodes* together with herbarumin I **36**, herbarumin II **37** and 2-epi-herbarumin II **35** (**Figure 11)**.[11] The 10-membered, naturally-occurring decanolides are the most abundant substances that represents the core of many natural products.[12] Many of these lactones have been found to display a wide range of pharmacologically interesting features such as antifungal, antifeedant, antibacterial, herbicidal, antitumoral, plant growth inhibition and the inhibition of cholesterol biosynthesis.[13] All nonenolides shown in Figure **11** possess some common interesting structural features, such as the olefinic function with well-defined geometry as well as stereochemically pure hydroxyl appendages which make them challenging synthetic targets.

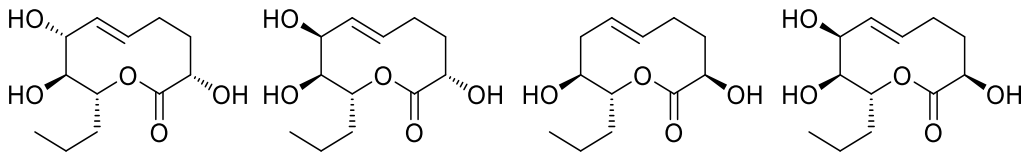


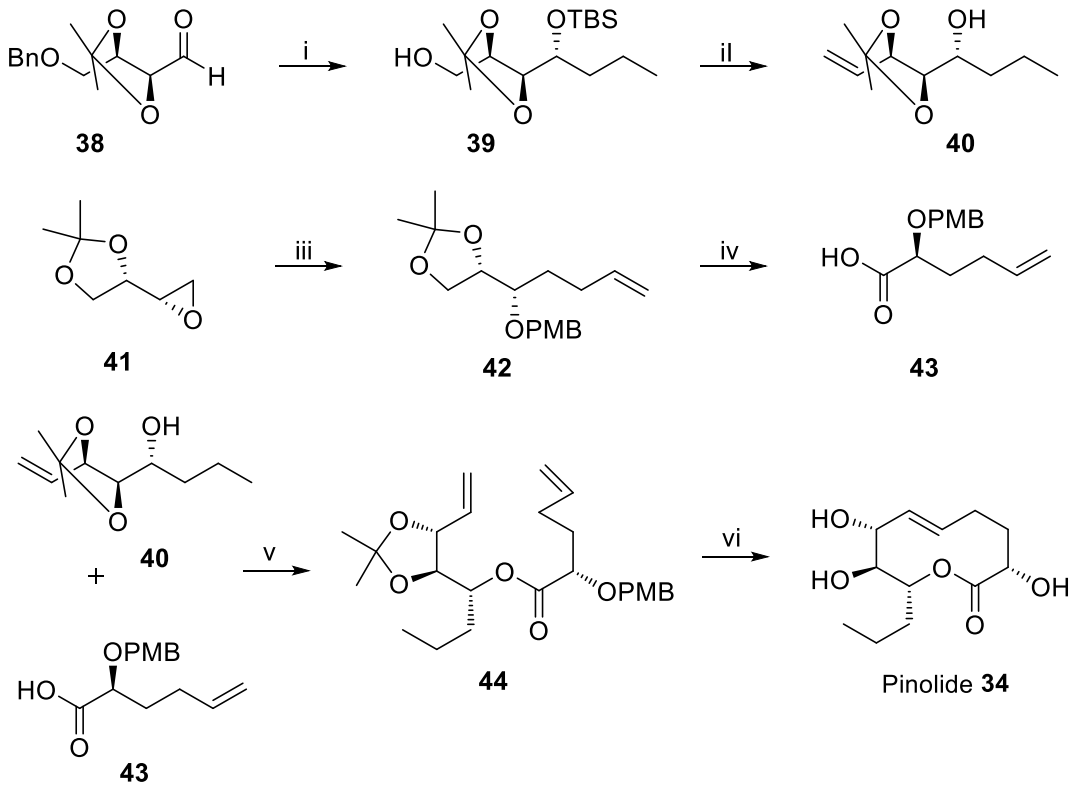
Figure 11: Some naturally occurring small ring macrolides (**34-37**)

2.2.2 Review of Literature

Literature search revealed that there are two reports available for the synthesis of pinolide due to its high pharmaceutical importance which are described below.

Yadav's approach (2013)[14]

Yadav *et al.* reported the first total synthesis of pinolide **34** starting from readily available (-)-Tartaric and L-ascorbic acid. The key synthetic steps include Barbier allylation, Yamaguchi esterification and ring-closing metathesis (RCM) reactions.



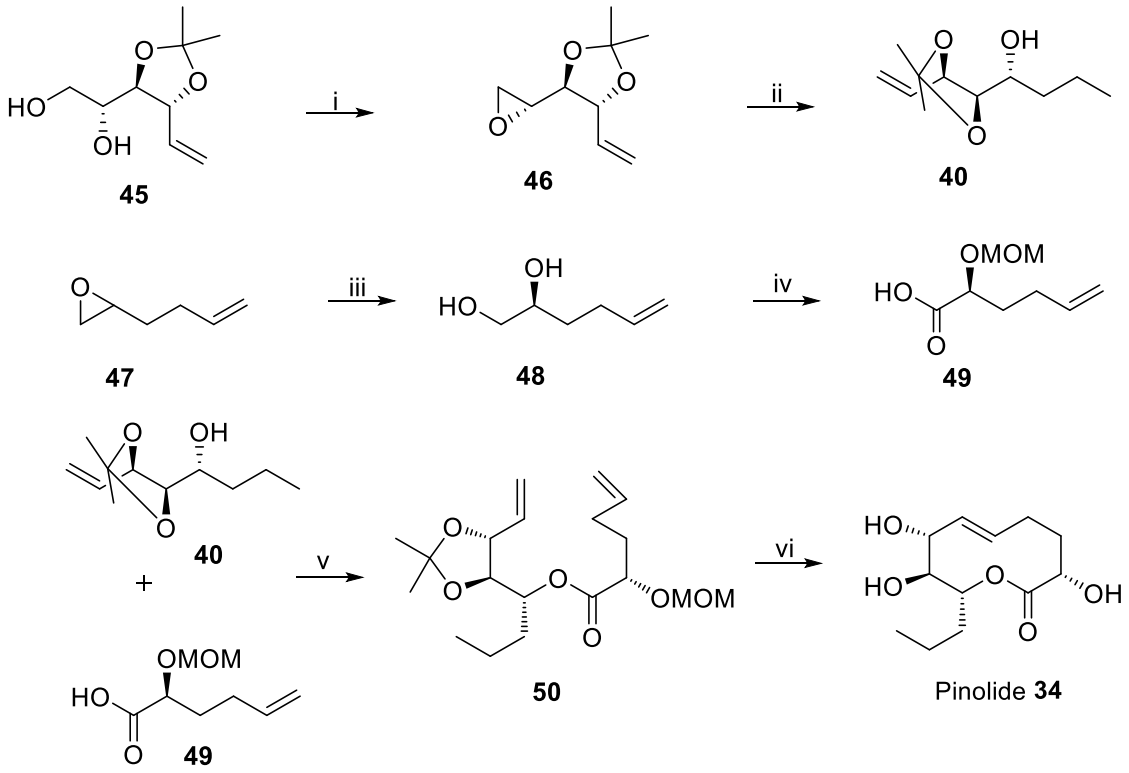
Scheme 9: (i) (a) allyl bromide, zinc, I_2, THF, 0 °C to rt., 1 h, 92%; (b) TBSCl, CH_2Cl_2, imidazole, 0 °C to rt, 2 h, 97%; (c) H_2, Pd/C, MeOH, 5 h, 90%; (ii) (a) $(COCl)_2$/DMSO, Et_3N, CH_2Cl_2, -78 °C, 1.5 h; (b) $Ph_3P{=}CH_2I$, *n*BuLi, THF, 0 °C, 1 h, 76% (for two steps); (c) TBAF, THF, 0 °C, 2 h, 86%; (iii (a) allyl chloride, Mg, anhydrous THF, 0 °C, 30 min, 93 %; (b) PMB-Cl, NaH, THF, 0 °C, 3 h, 92%; (iv) (a) PTSA/MeOH, 2 h, rt, 86%; (b) i. $NaIO_4$/ CH_2Cl_2, $NaHCO_3$(cat), 2 h; ii. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, 0 °C to rt, 7 h, 70%; (v) 2,4,6-trichlorobenzoyl chloride, Et_3N, catalytic DMAP, THF, then alcohol **3** in toluene, 4 h, 85%; (vi) (a) Grubbs' I catalyst (10 mol%), CH_2Cl_2, reflux, 16 h, 73%; (b) DDQ, CH_2Cl_2, 1 h, 85%; (d) 2N HCl, THF, reflux, 1 h, 82%.

The synthesis of alcohol fragment **40** starts with chiral aldehyde **38** which was prepared from (-)-DET. Aldehyde **38** was converted into alcohol **39** in 3 steps: (i) allylation with allyl magnesium bromide; (ii) TBS protection of hydroxyl group and (iii) Reduction of the double bond. Swern oxidation of alcohol **39** followed by one carbon Wittig reaction and desilylation furnished alcohol fragment **40** in 86% yield. Ring opening of chiral epoxide (prepared from L-Ascorbic acid) **41** with allyl Mg chloride followed by PMB protection gave acetonide **42**. Treatment of acetonide **42** with PTSA in MeOH leads to the formation of corresponding diol which on reaction with sodium metaperiodate gave aldehyde followed by pinnick oxidation affords acid fragment **43**. Both acid fragment **43** and alcohol fragment **40** were coupled using Yamaguchi's protocol [2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 4-(*N*,*N*-dimethylamino)pyridine (DMAP)] to give bis-olefin **44**. And finally Ring Closing Metathesis (RCM) and deprotection of acetonide and PMB group furnished pinolide **34** in 82% yield (**Scheme 9**).

Das's approach (2014)[15]

Das *et al.* described the synthesis of pinolide **34** using D-mannitol and 1,2-epoxyhex-5-ene as the starting materials. The synthesis involves the Jacobsen's hydrolytic kinetic resolution, Yamaguchi esterification, and intramolecular ring closing metathesis as the key steps. D-mannitol was converted into known diol **45** by a reported method. The diol **45** was then treated with dibutyltin oxide and 4-toluenesulfonyl chloride in triethylamine and subsequently with methanolic potassium carbonate to afford the epoxyalkene **46**. The epoxide ring of **46** was then opened with ethyl magnesium bromide using copper (I) iodide to produce the required alcohol fragment **40**. The enantiomeric acid **49** was prepared from racemic epoxide **47**. Hydrolytic kinetic resolution (HKR) of epoxide **47**

with Jacobsen's (*R, R*)-(Salen) Co(III) complex and acetic acid furnished the diol **48** in 96% ee. The diol **48** was then converted into acid fragment **49** in 84% yield *i.e* (i) protection of the primary hydroxy group of **48**; (ii) protection of the secondary hydroxy group as MOM ether; (iii) deprotection of TBS ether group and (iv) oxidation of primary hydroxy group to the acid fragment **49**. The alcohol fragment **40** was then coupled with the acid fragment **49** using 2,4,6- trichlorobenzoyl chloride, triethylamine, and 4-(dimethylamino) pyridine under the Yamaguchi esterification protocol to produce the bis-olefin ester **50**. Finally, Ring closing metathesis (RCM) and deprotection of MOM and acetonide gave desired pinolide **34** in 90% yield (**Scheme 10**).



Scheme 10: (i) (a) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2, rt, 30 min; (b) K_2CO_3, MeOH, rt, 1 h, 75%; (ii) EtMgBr, CuI, -20 °C to rt, 84%; (iii (*R,R*)-(salen)Co(III)OAc (0.5 mol%), distilled H_2O (0.45 equiv), AcOH, THF, 0 °C, 24 h, 46% (96% ee); (iv) (a) TBSCl, imidazole, THF, rt, 96%; (b) MOMBr, *i*-Pr_2NEt, CH_2Cl_2, 45 °C, 100%; (c) TBAF, THF, 0 °C-rt, 100%; (d) $PhI(OAc)_2$, TEMPO, MeCN-H_2O (2:1), rt, 3 h; 84%; (v) 2,4,6-

trichlorobenzoyl chloride, Et_3N, DMAP, THF, rt, 93%; (vi) (a) Grubbs II catalyst, CH_2Cl_2, 50 °C, 83%; (b) 4 M HCl, MeCN, 0 °C to rt, 8 h, 90%.

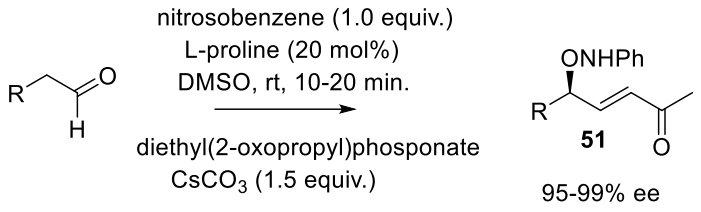
2.2.3. Present Work

2.2.3.1 Objective

As can be seen from the above discussion, the reported methods suffer from several disadvantages, such as the use of chiral building blocks as starting materials, longer reaction sequences, and low overall yields.[14,15] Organocatalysis is a rapidly growing research field in organic synthesis and has the advantages of being highly selective and reduces synthetic manipulations.[16] Proline-catalyzed sequential transformation is an emerging area of research in the organic synthesis of complex organic molecules, which can be synthesized using a one-pot procedure. In continuation of our work on the sequential proline-catalyzed synthesis of bioactive molecules,[6] we herein report a simple and efficient asymmetric synthesis of pinolide **34** from readily available starting materials *via* L-proline catalyzed sequential aminooxylation-olefination[17] of *n*-valeraldehyde and Sharpless asymmetric dihydroxylation reaction as the key chiral inducing steps. Since this section utilizes the proline catalyzed sequential α-aminooxylation-olefination and asymmetric dihydroxylation as the key reactions to introduce chiral centres, a brief account of both the key reactions is described below.

2.2.3.2 Sequential aminooxylation-olefination of aldehydes [18]

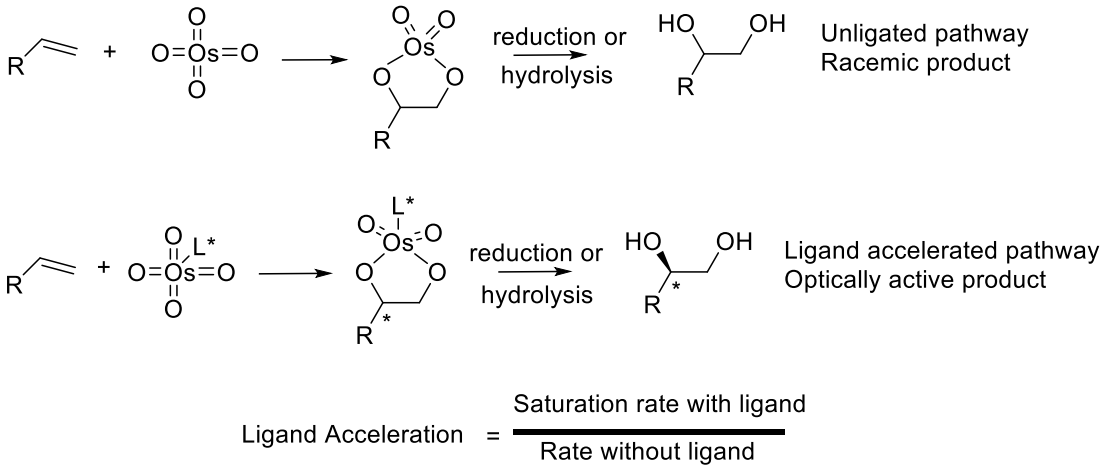
Zhong *et al*. have reported a sequential α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted α, β-unsaturated ketones **51** in excellent enantioselectivities using Cs_2CO_3 (**Scheme 11**).



Scheme 11: Sequential aminooxylation-olefination

2.2.3.3 Sharpless asymmetric dihydroxylation

In recent years, much attention has been focused on the catalytic asymmetric synthesis. It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[19] among all these reactions, Sharpless catalytic Asymmetric Dihydroxylation (AD) is one of the most important practical and widely used reactions in organic synthesis. It has become the most general method for the preparation of optically active *vicinal*-*syn*-diols from activated as well as inactivated olefins.[20]



Scheme 12: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless *et al.*[21] demonstrated that asymmetric induction could be achieved when chiral amines

were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ) (**Scheme 12**).[22] To improve the enantiomeric excess of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions (**Figure 12**).

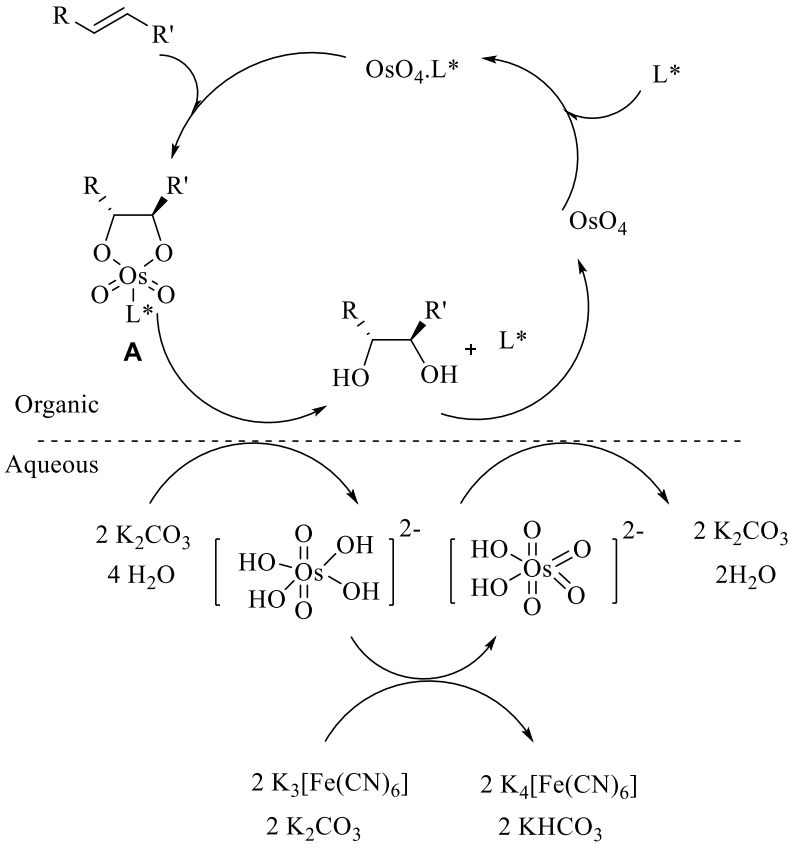
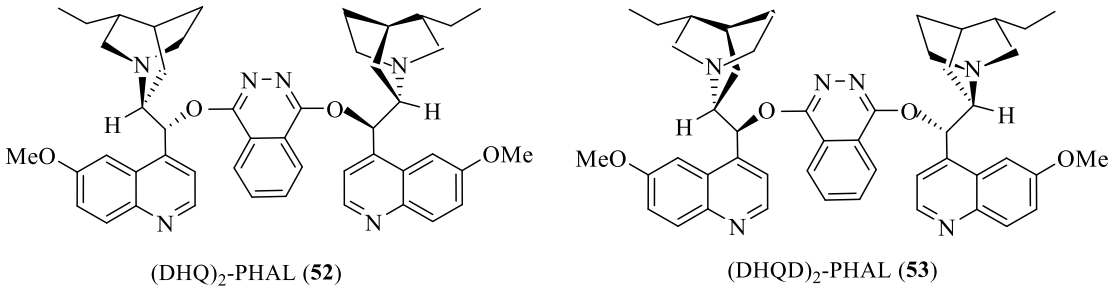


Figure 12: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant

These conditions helped in protecting the organic osmate-(VI) monoglycolate ester from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) obtains reoxidized and recycled into the catalytic cycle. Further improvement in the AD

was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species A, thus facilitating the dihydroxylation smoothly. Addition of methyl sulfonamide also allowed carrying out the reactions of 1,2-di- tri- and tetrasubstituted olefins at 0 ºC, which improved the selectivity as well as enantiomeric excess.

In order to develop the asymmetric version of the Os-catalyzed AD reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the *bis*-DHQ **52** or DHQD **53** ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselective diols (**Figure 13**).[23]



$(DHQ)_2$-PHAL (**52**) $(DHQD)_2$-PHAL (**53**)

Figure 13: Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[24] Sharpless *et al.*[21] have shown that the facial selectivity for both ligands **52** and **53** is different, based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model (**Figure 14**) in which olefin with the constraints will be attacked either from the top (i.e. α) face in the presence of dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

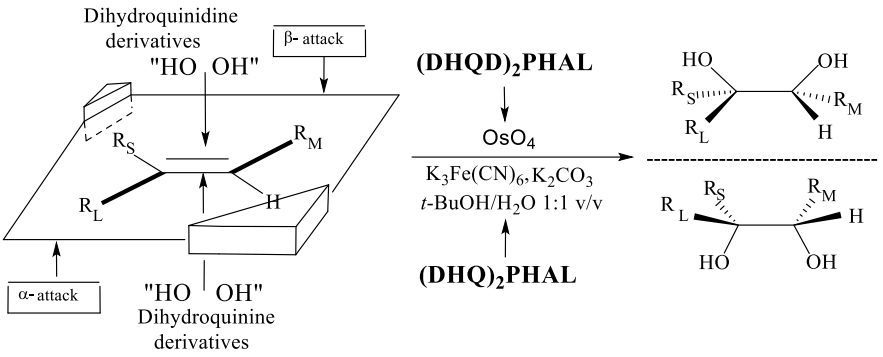
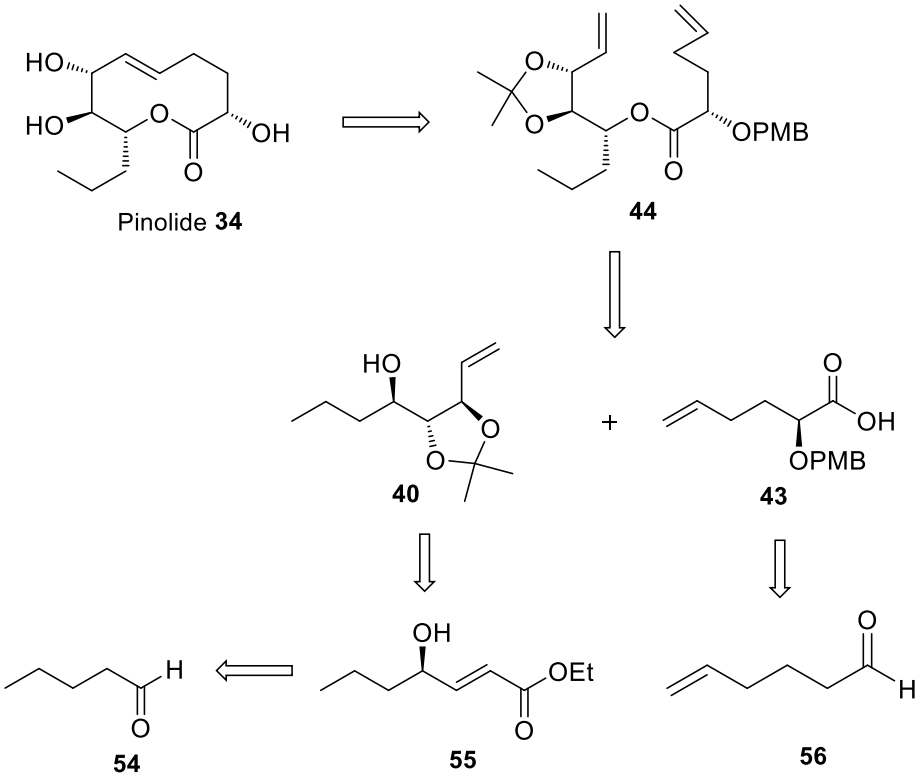


Figure 14: Enantioselectivity mnemonic scheme

Our approach to the asymmetric synthesis of pinolide **34** is shown in Scheme **13**.



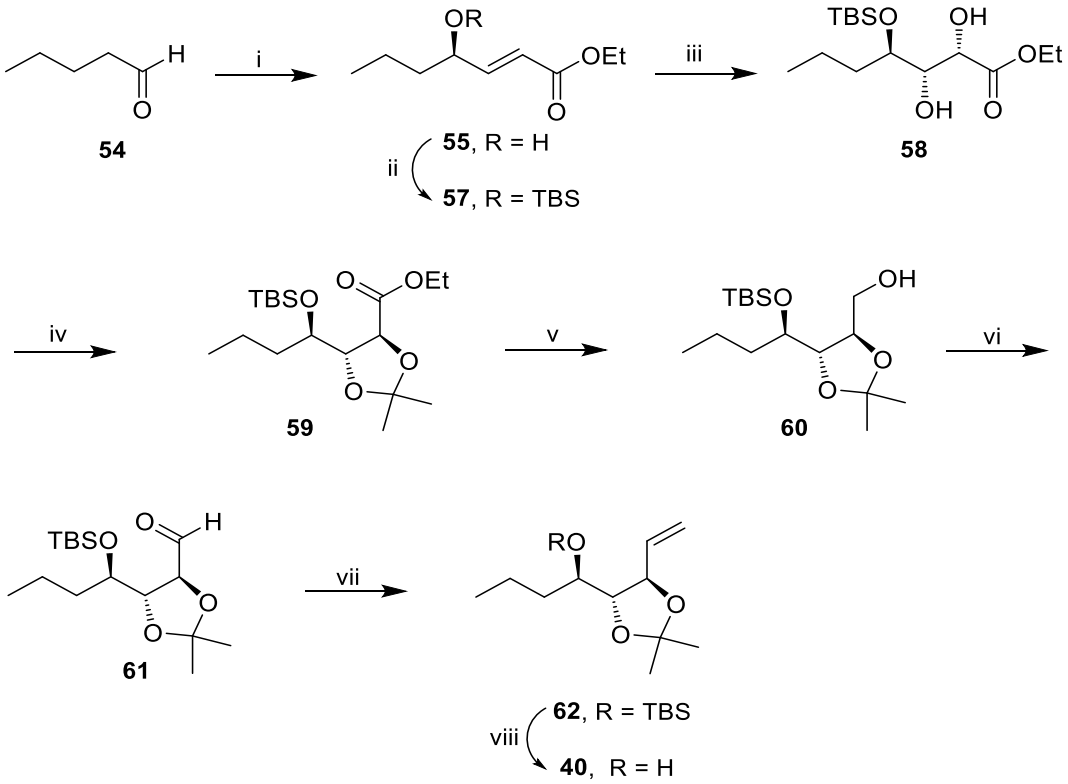
Scheme 13: Retrosynthetic plan for pinolide (**34**)

We envisioned that the required ring closing metathesis precursor **44** (**Scheme 13**) should, in turn, be accessible from secondary alcohol fragment **40** and carboxylic acid fragment **43** *via* Steglich esterification. The secondary alcohol fragment **40** can be

derived from *n*-valeraldehyde **54** *via* proline-catalyzed sequential α-aminooxylation and Horner-Wadsworth-Emmons olefination while the acid fragment **43** from hex-5-enal **56** as the starting material *via* α-aminooxylation (**Scheme 13**).

2.2.4. Results and Discussion

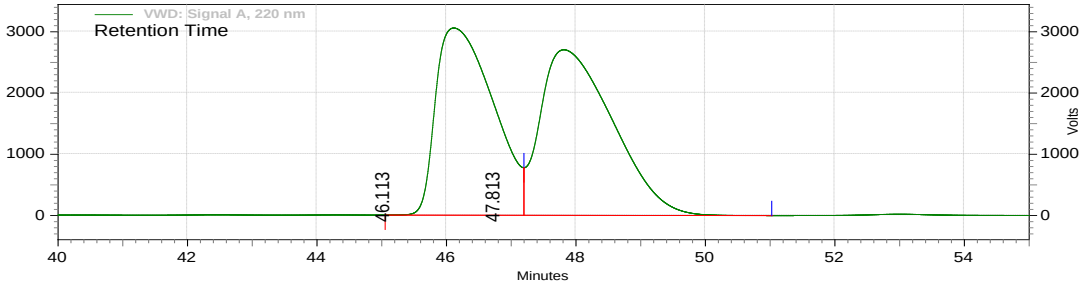
The Synthetic sequence began with the synthesis of alcohol fragment **40** from commercially available *n*-valeraldehyde **54** (Scheme **14**).



Scheme 14: Reagents and conditions: (i) (a) PhNO, L-proline (20 mol%),CH_3CN, -20 °C, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h; (b) $CuSO_4.5H_2O$ (30 mol%), MeOH, 25 °C, 12 h, 77%, 99% *ee*; (ii) TBSCl, imid., CH_2Cl_2, 0–25 °C, 3 h, 98%; (iii) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), $K_2OsO_4.2H_2O$ (0.2 mol%), 0 °C, 5 h, 86%, (*dr*=3:1); (iv) 2,2 dimethoxypropane, cat. CSA, CH_2Cl_2, rt, 12 h, 96%; (v) $LiAlH_4$, THF, 0-5 °C, 1 h, 93%; (vi) IBX, EtOAc, 80 °C, 2 h, 86%; (vii) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, 0 °C, 1 h, 75%; (viii) TBAF, THF, 0-25 °C, 2 h, 82%.

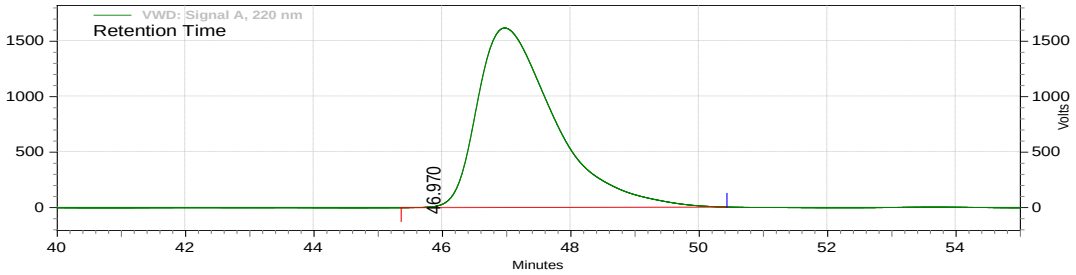
Thus, *n*-valeraldehyde **54** was subjected to α-aminooxylation with nitrosobenzene as the oxygen source and L-proline at -20 °C, followed by *in situ* Horner–Wadsworth–Emmons

(HWE) olefination with LiCl and DBU (Masamune-Roush protocol)[25] to furnish crude α-aminooxy olefinic ester. Subsequent reduction of the crude α-aminooxy product with 30 mol% $CuSO_4.5H_2O$[26] in MeOH yielded the γ-hydroxy ester **55** in 77% yield. The enantiomeric purity of γ-hydroxy ester **55** was determined as 99% by chiral HPLC analysis [Chiralpak AD-H, IPA:n-Hexane, 2:98, 0.5ml/min] (**Figure 15**).



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
46.113	3163589139	47.28	51277883	53.06
47.813	3527339737	52.72	45361616	46.94
Totals	6690928876	100.00	96639499	100.00



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
46.970	2270689518	100.00	27158337	100.00
Totals	2270689518	100.00	27158337	100.00

Figure 15: HPLC chromatogram of γ-hydroxy ester **55**

The formation of γ-hydroxy ester **55** was confirmed from its ^{1}H NMR spectrum, which showed a characteristic doublet of doublet at δ 6.01 (dd, *J* = 15.5, 1.6 Hz, 1H) and 6.92 (dd, *J* = 15.7, 5.0 Hz, 1H) corresponding to two olefinic protons of γ-hydroxy ester. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 166.6 corresponding to -C=O of ester whereas signal at δ 150.2 and 120.0 due to olefinic carbon atoms (**Figure 16**).

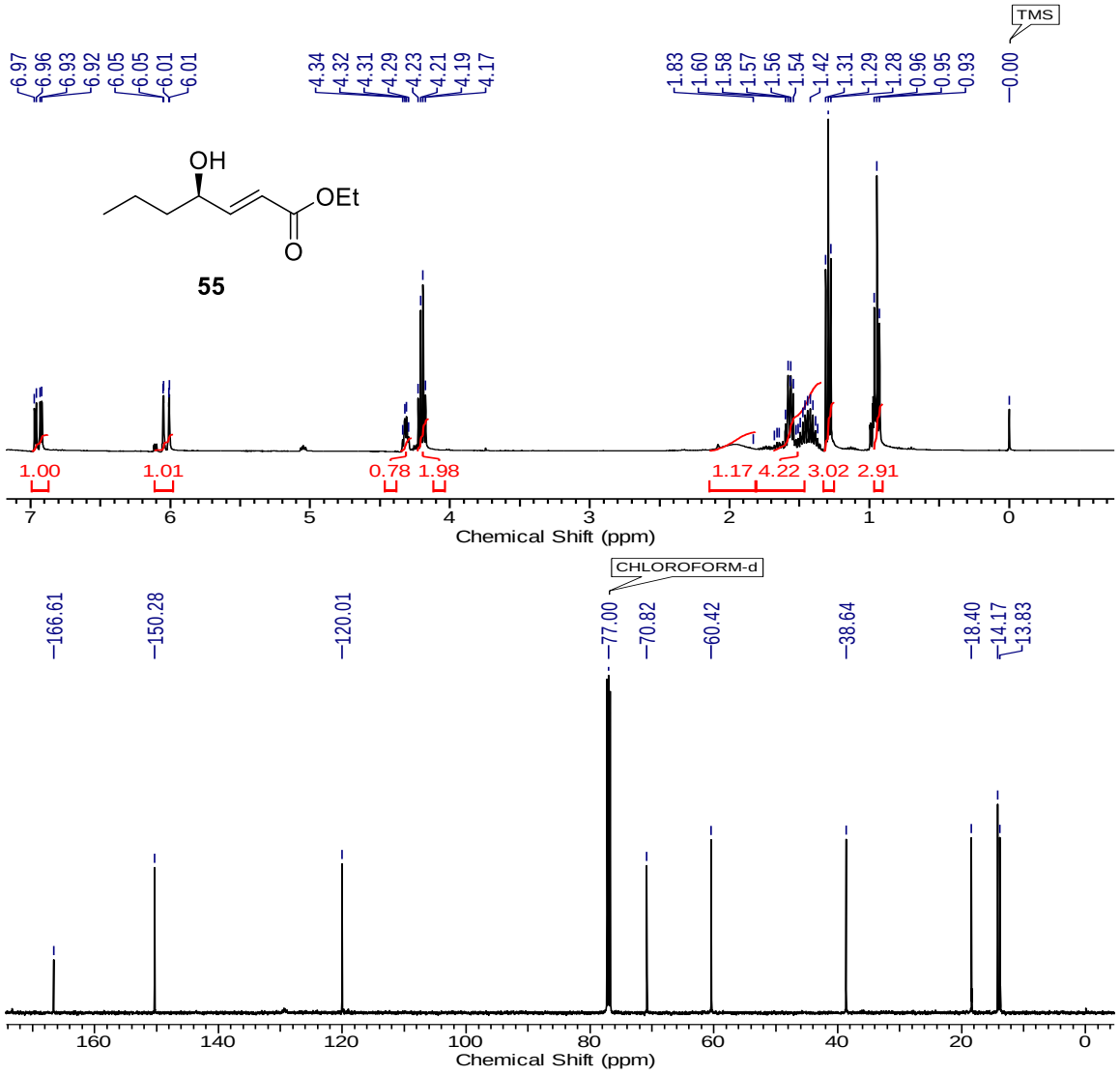


Figure 16: ^{1}H and ^{13}C NMR spectra of γ-hydroxy ester **55**

Hydroxyl group in compound **55** was protected as its TBS ether to give *α, β* unsaturated ester **57** in 98% yield. Its formation was confirmed by its ^{1}H and ^{13}C spectral analysis,

which showed a typical proton multiplet at δ 0.06 (m, 6H) and 0.92 (s, 9H) corresponding to methyl protons of silyl group in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum displayed typical carbon signals at δ -4.9, -4.6 due to methyl carbons attached to silyl group (**Figure 17**). Its IR spectrum displayed a strong vibrational frequency at 1720 cm^{-1} due to –C=O of ester group.

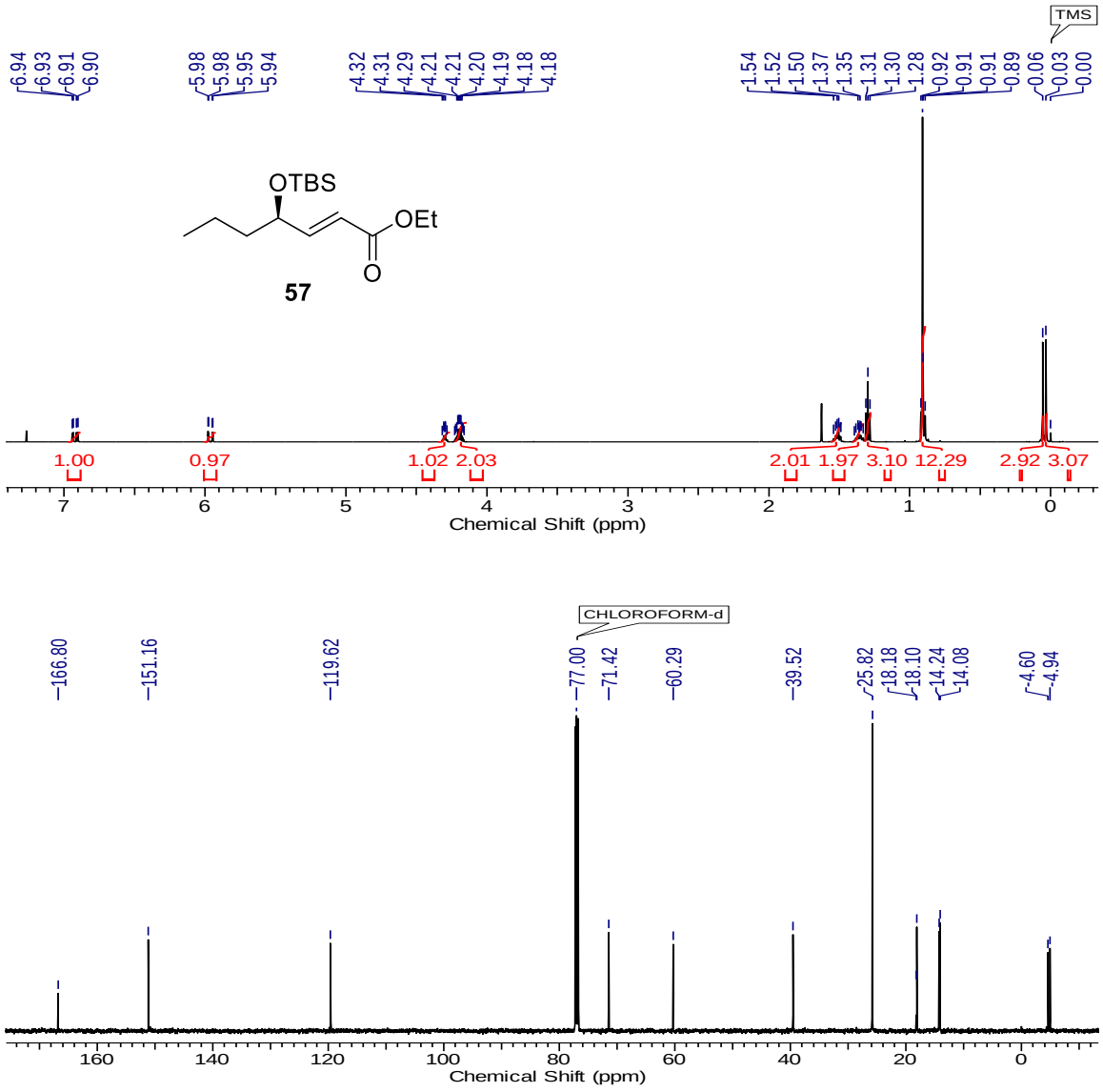


Figure 17: ^{1}H and ^{13}C NMR spectra of *α,β*-unsaturated ester **57**

The dihydroxylation of the *α,β*-unsaturated ester **57** was carried out under the Sharpless asymmetric dihydroxylation conditions [$(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-$BuOH/H_2O$ (1:1), $K_2OsO_4.2H_2O$ (0.2 mol%)] to give dihydroxylated ester **58** in 86% yield with a diastereomeric ratio of 3:1 (*anti/syn*) determined by its ^1H NMR analysis. The specific rotation of the diol was found to be $[\alpha]_D^{25}$ -5.5 (*c* 1.6, $CHCl_3$). The ^1H NMR spectrum of **58** confirmed the formation of diol **58** as it exhibited typical peak patterns at δ 3.15-3.33 (br s, 1H), 3.77-3.89 (m, 2H), 4.21-4.46 (m, 3H) (**Figure 18**).

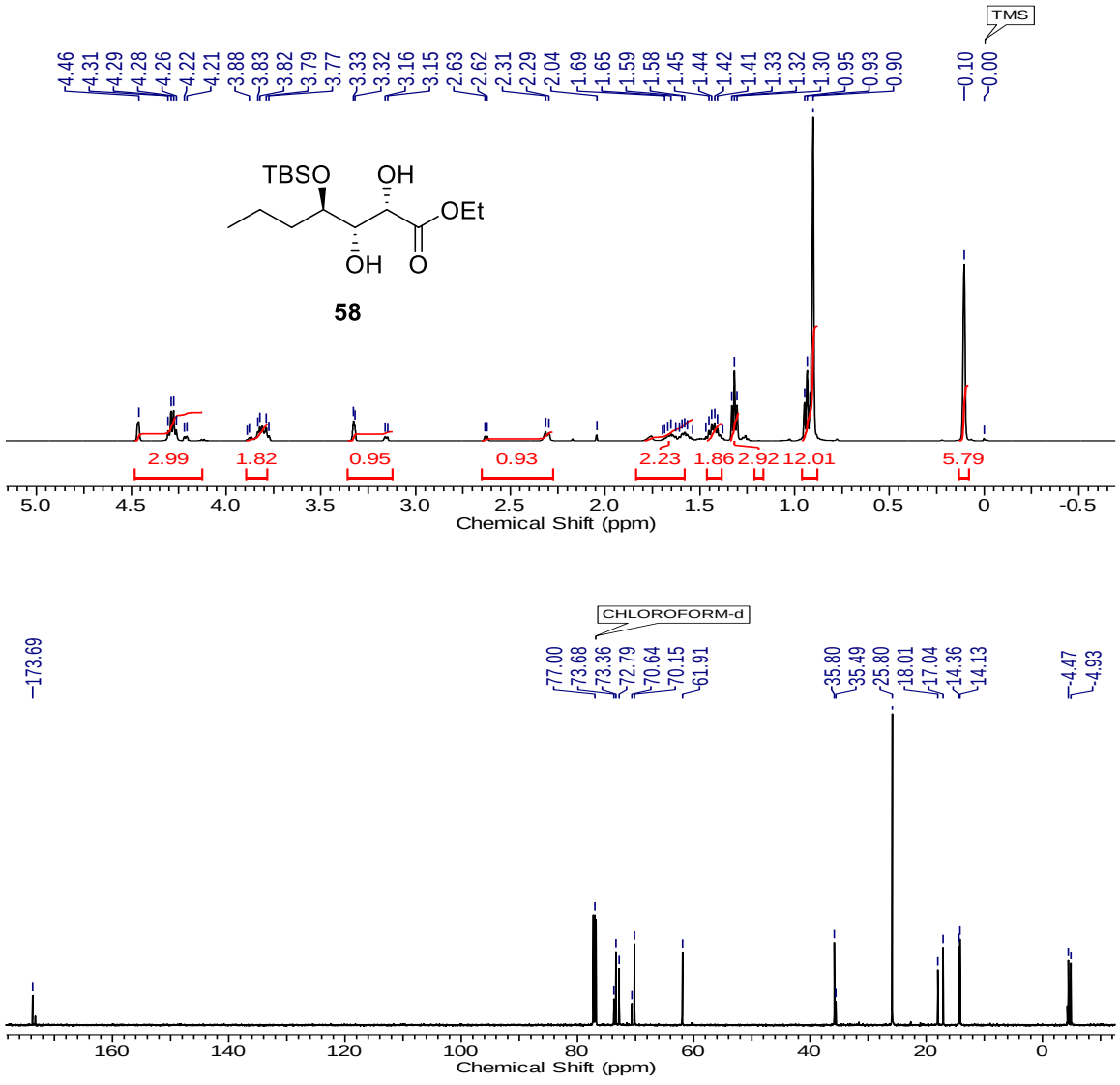


Figure 18: ^1H and ^{13}C NMR spectra of diol **58**

Its ^{13}C NMR spectrum showed a characteristic carbon signal at δ 173.6 corresponding to the carbonyl carbon. Diol **58** was then protected as its acetonide (2,2-dimethoxy propane, catalytic camphorsulfonic acid)[27] to afford acetonide **59** in 96% yield. The formation of acetonide **59** was confirmed by Its ^{1}H NMR spectrum which shows signal at δ 1.29-1.53 (m, 13H). Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 25.9, 26.7 due to two methyl carbons of acetonide **59** (**Figure 19**).

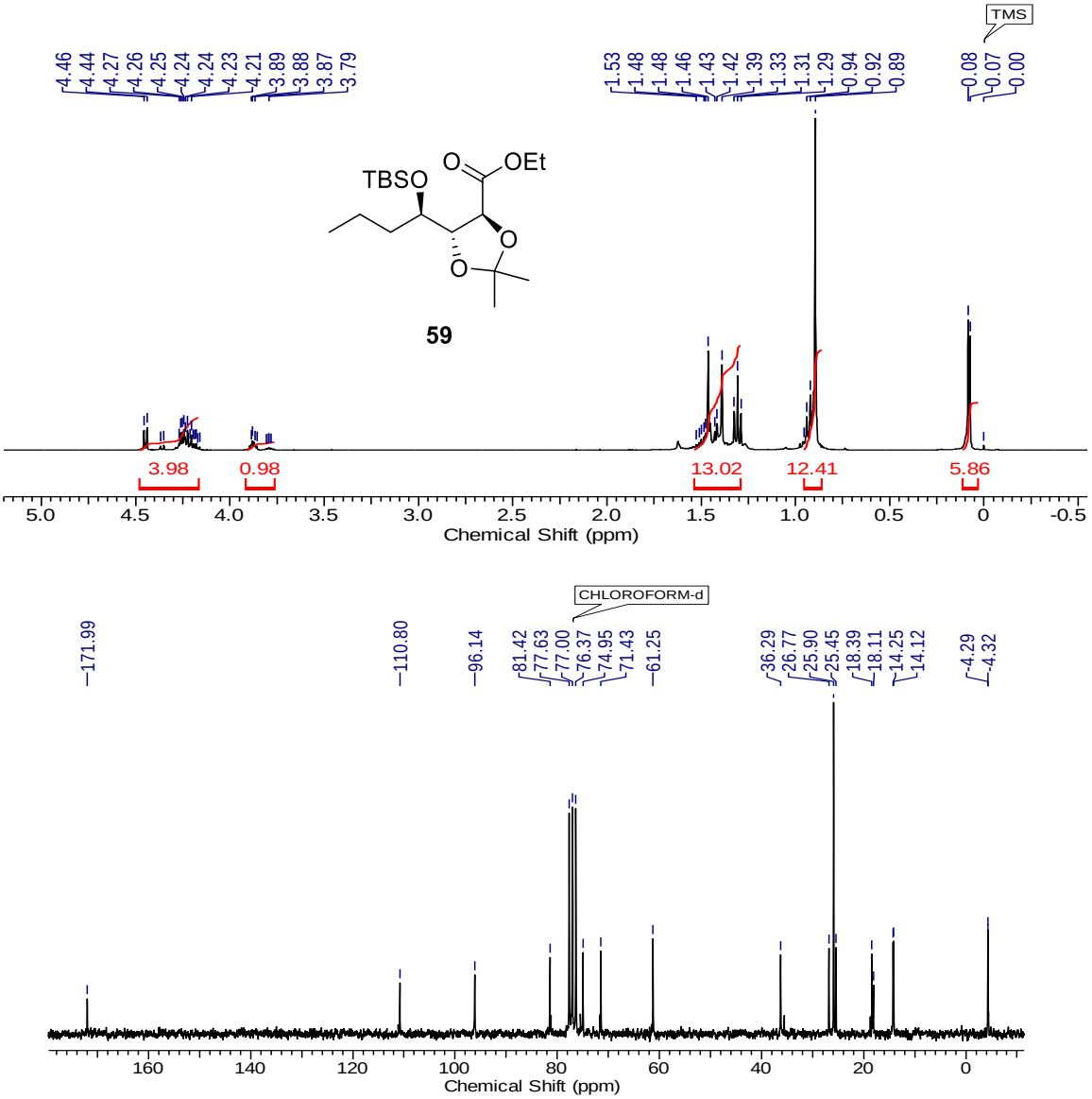


Figure 19: ^{1}H and ^{13}C NMR spectra of acetonide **59**

Further, ester functionality in acetonide **59** was reduced with $LiAlH_4$ to afford the corresponding alcohol **60** in 93% yield. The ^{1}H NMR spectrum of alcohol **60** showed the proton signals at δ 3.49-3.63 (m, 1H), 3.65-3.78 (m, 3H), 3.90-3.99 (m, 1H) corresponding to five protons attached to oxygen. Its ^{13}C NMR signal displayed four characteristics carbon signals at δ 63.5, 73.1, 78.4 and 79.6 corresponding to the carbons attached to heteroatoms (**Figure 20**).

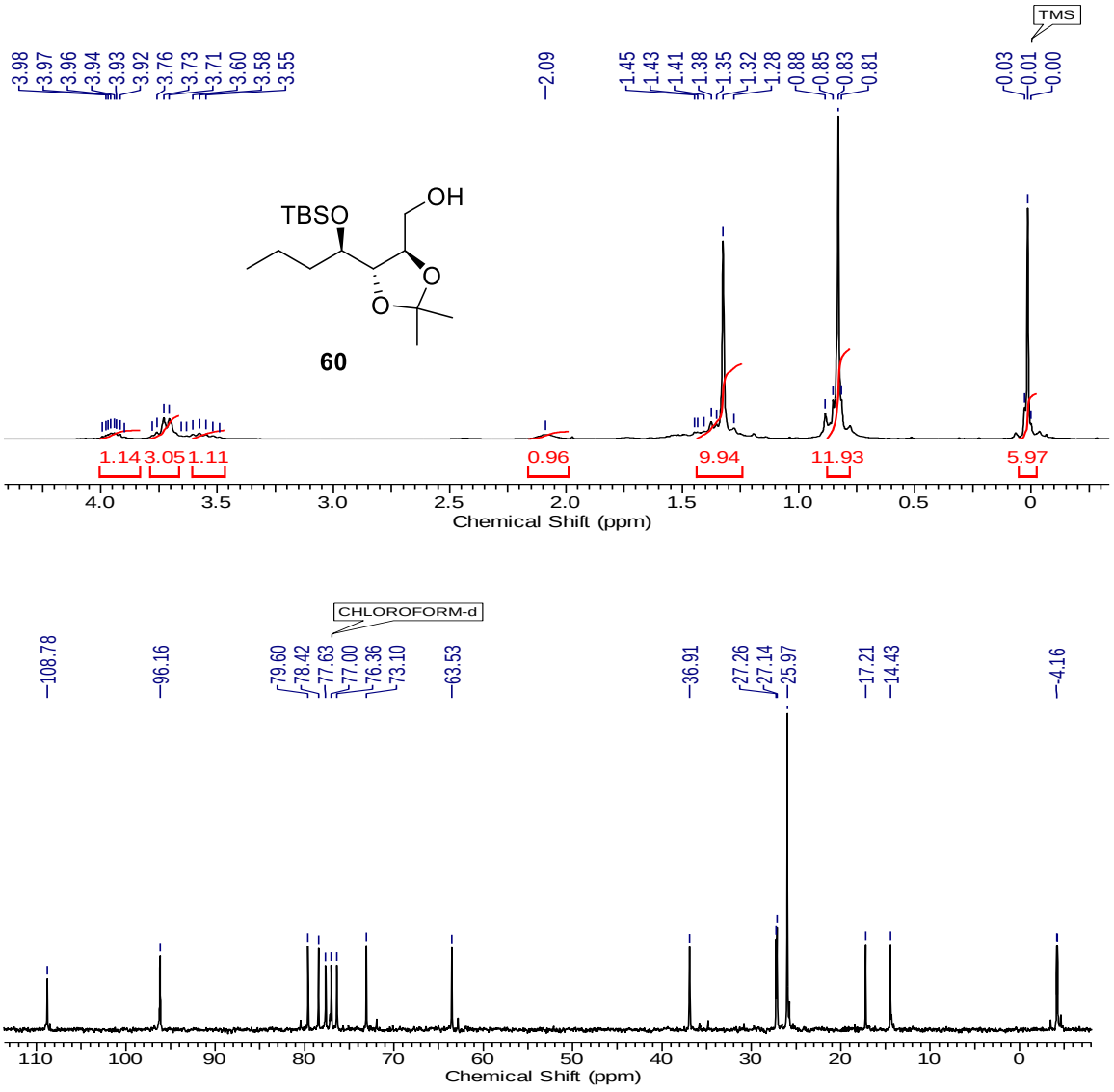


Figure 20: ^{1}H and ^{13}C NMR spectra of alcohol **60**

Oxidation of alcohol **60** with IBX provided aldehyde **61** in 86% yield. The formation of aldehyde **61** was confirmed by its ^{1}H and ^{13}C NMR analysis. The ^{1}H NMR spectrum of **61** shows characteristics peak of aldehyde (-C**H**O) doublet at δ 9.77. Its ^{13}C NMR spectrum shows typical carbon signal at δ 201.4 corresponding to carbonyl carbon of aldehyde (-**C**HO) (**Figure 21**).

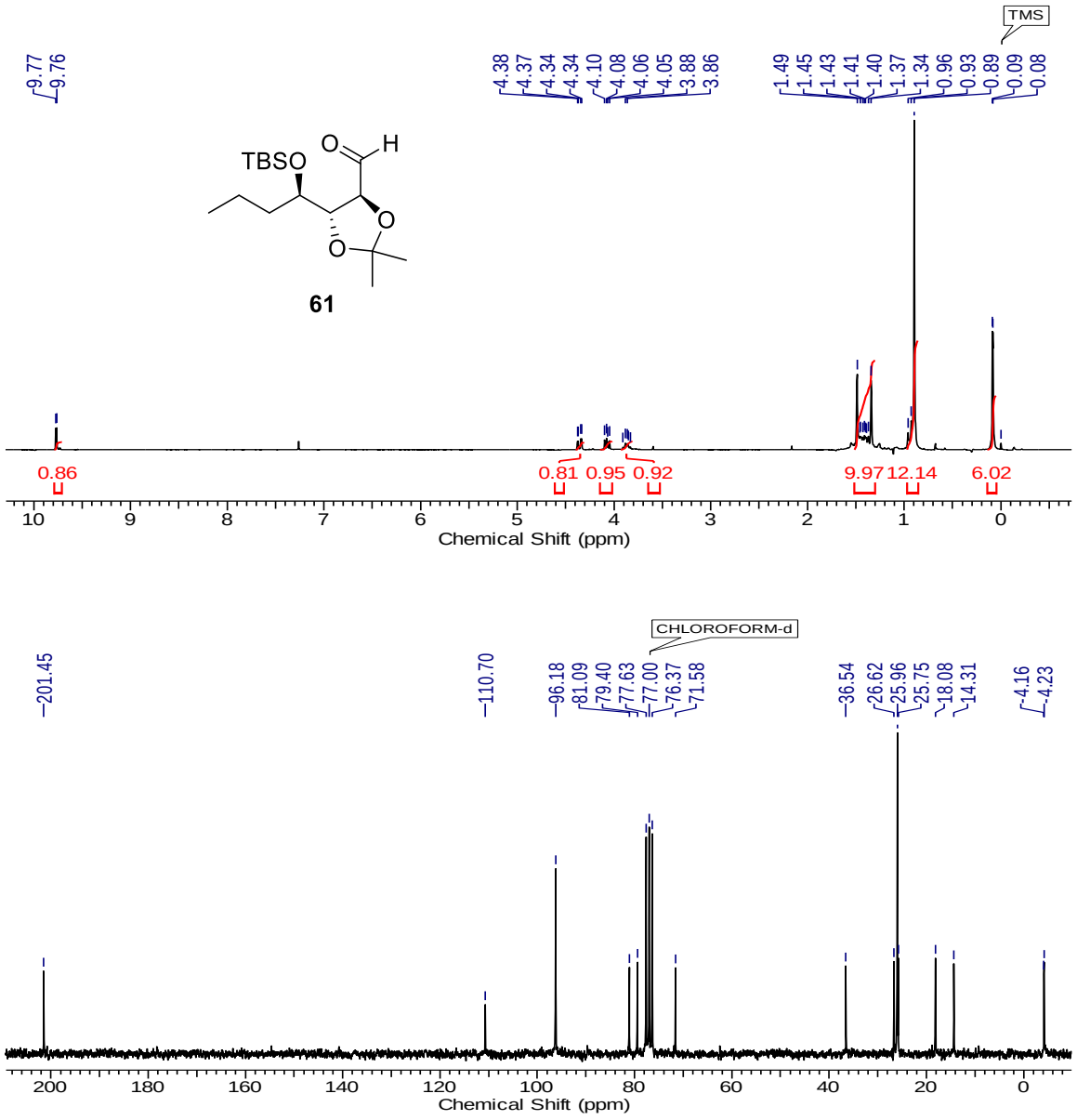


Figure 21: ^{1}H and ^{13}C NMR spectra of aldehyde **61**

Aldehyde **61** was subsequently treated with iodomethyltriphenylphosphine in the presence of *n*-BuLi as a base to give terminal olefin **62** in 75% yield. The formation of olefin **62** was confirmed from its ^{1}H NMR spectrum, which showd a characteristic peak signals at δ 5.16-5.22 (m, 1H), 5.32-5.42 (m, 1H), 5.78-5.95 (m, 1H) corresponding to olefinic protons (-C**H**=). It was further supported by a typical carbon signal at δ 108.4, 117.2, 137.0 corresponding to olefinic carbon atoms (**Figure 22**).

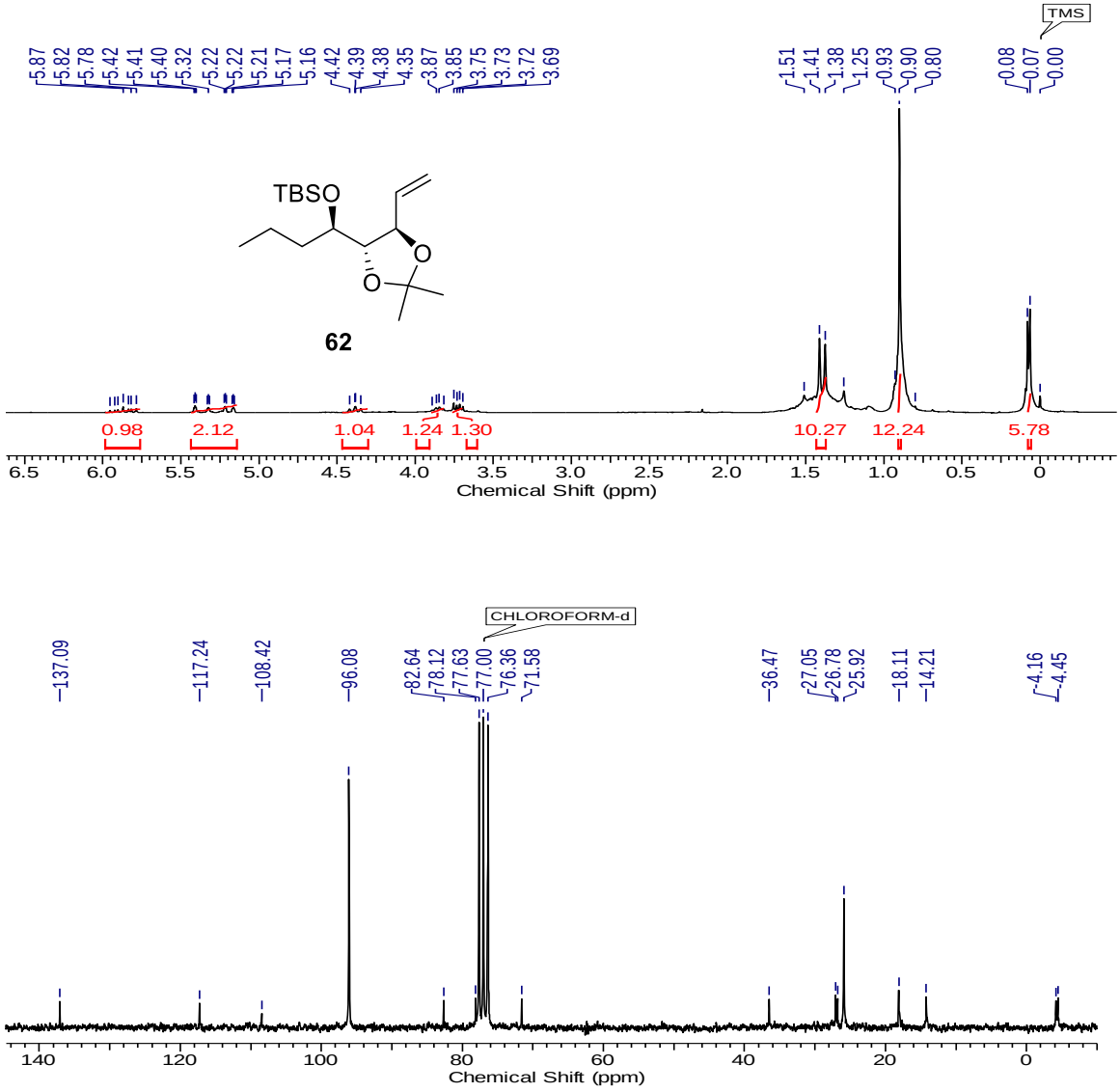


Figure 22: ^{1}H and ^{13}C NMR spectra of olefin **62**

Finally, silyl deprotection in olefin **62** with TBAF yielded the key alcohol fragment **40** in 82% yield. Its ^{1}H NMR spectrum showed disapperance of the peak signals corresponding to methyl protons attached to silyl group and shows broad singlet at δ 2.08 (br s, 1H) corresponds to –O**H** group (**Figure 22**). It was further supported by ^{13}C NMR spectrum which shows disapperance of the peak signals at δ -4.4, -4.1, 14.2, 18.1, and 18.2 (**Figure 23**).

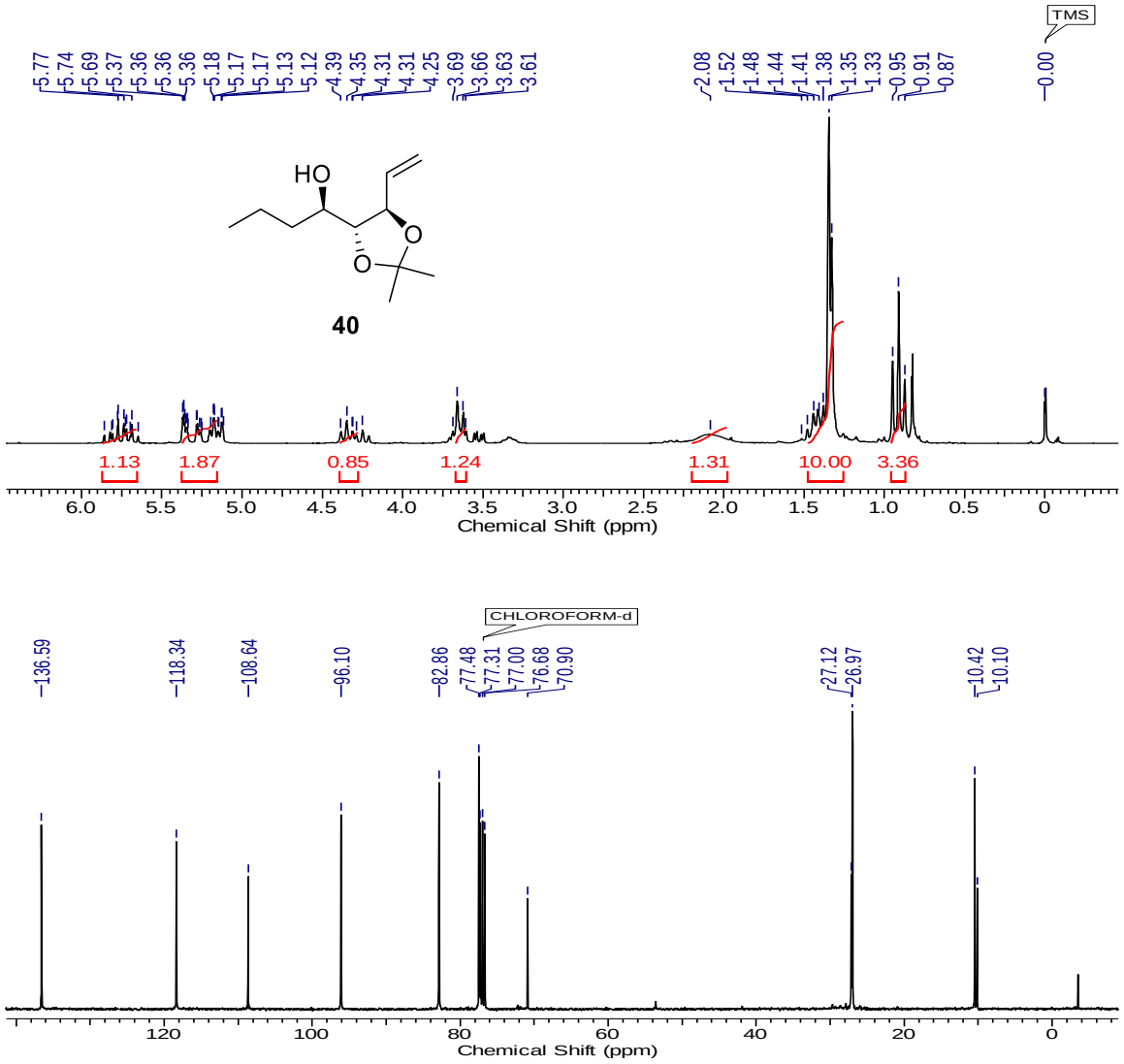
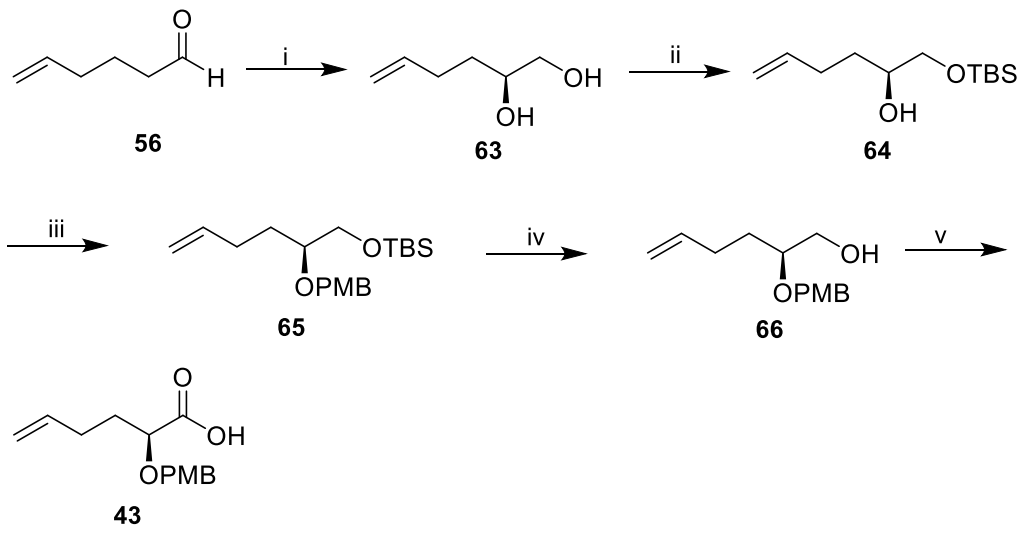


Figure 23: ^{1}H and ^{13}C NMR spectra of alcohol **40**

The synthesis of acid fragment **43** was achieved from commercially available hex-5-enal **56** as shown in **Scheme 15**.



Scheme 15: Reagents and conditions: (i) (a) PhNO, D-proline (20 mol%), CH_3CN, -20 °C, 24 h then MeOH, $NaBH_4$, 20 min.; (b) $CuSO_4.5H_2O$ (30 mol%), MeOH, 0 °C, 12 h, 87% (over two steps), 99% *ee*; (ii) TBSCl, imid., CH_2Cl_2, 0–25 °C, 2 h, 96%; (iii) PMB imidate, PTSA (cat), dry CH_2Cl_2, 0 °C to rt, 8h, 90%; (iv) CSA, MeOH, 25 °C, 30 min, 63%; (v) TEMPO, $PhI(OAc)_2$, CH_3CN: H_2O (4:1), 25 °C, 4 h, 86%.

The hex-5-enal **56** was subjected to D-proline catalyzed α-aminooxylation followed by *in situ* reduction with $NaBH_4$ and subsequent reduction of the crude aminoxy product with 30 mol% $CuSO_4.5H_2O$ yielded the chiral diol **63** in 87% yield over two steps. The enantiomeric purity of chiral diol **63** was determined as 99% by its Mosher ester analysis. The formation of diol **63** was confirmd from its ^{1}H NMR spectrum, which showed a typical peak at δ 3.43 (m, 1H) and 3.60-3.79 (m, 4H) corresponding to two -O**H** group and methine protons (-C**H**-O) attached to oxygen atom. Its ^{13}C NMR spectrum showed two characteristics typical carbon signals at δ 66.4 and 72.7 due to carbons attached to oxygen atom (**Figure 24**).

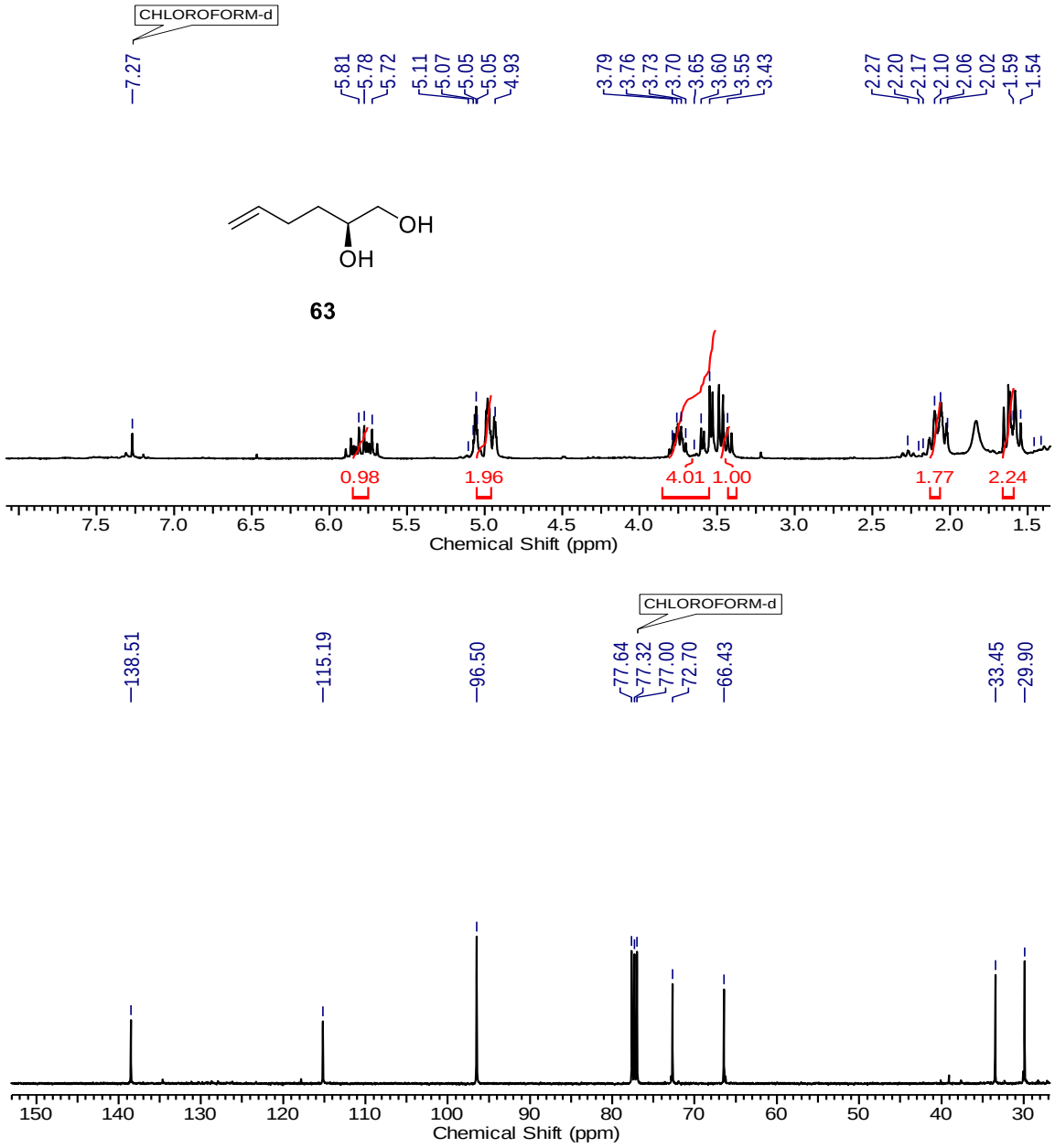


Figure 24: ^{1}H and ^{13}C NMR spectra of diol **63**

Selective silyl protection of primary alcohol in diol **63** (TBSCl, imid.) gave mono-TBS protected alcohol **64** in 96% yield. The formation of alcohol **64** was confirmed by its ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of alcohol **64** showed two characteristic peaks at δ 0.10 (s, 6H) and 0.82 (s, 9H) for methyl protons of silyl group.

Its ^{13}C NMR spectrum displayed typical carbon signals at δ -4.3 and 25.9 due to methyl carbons attached to silyl group (**Figure 25**).

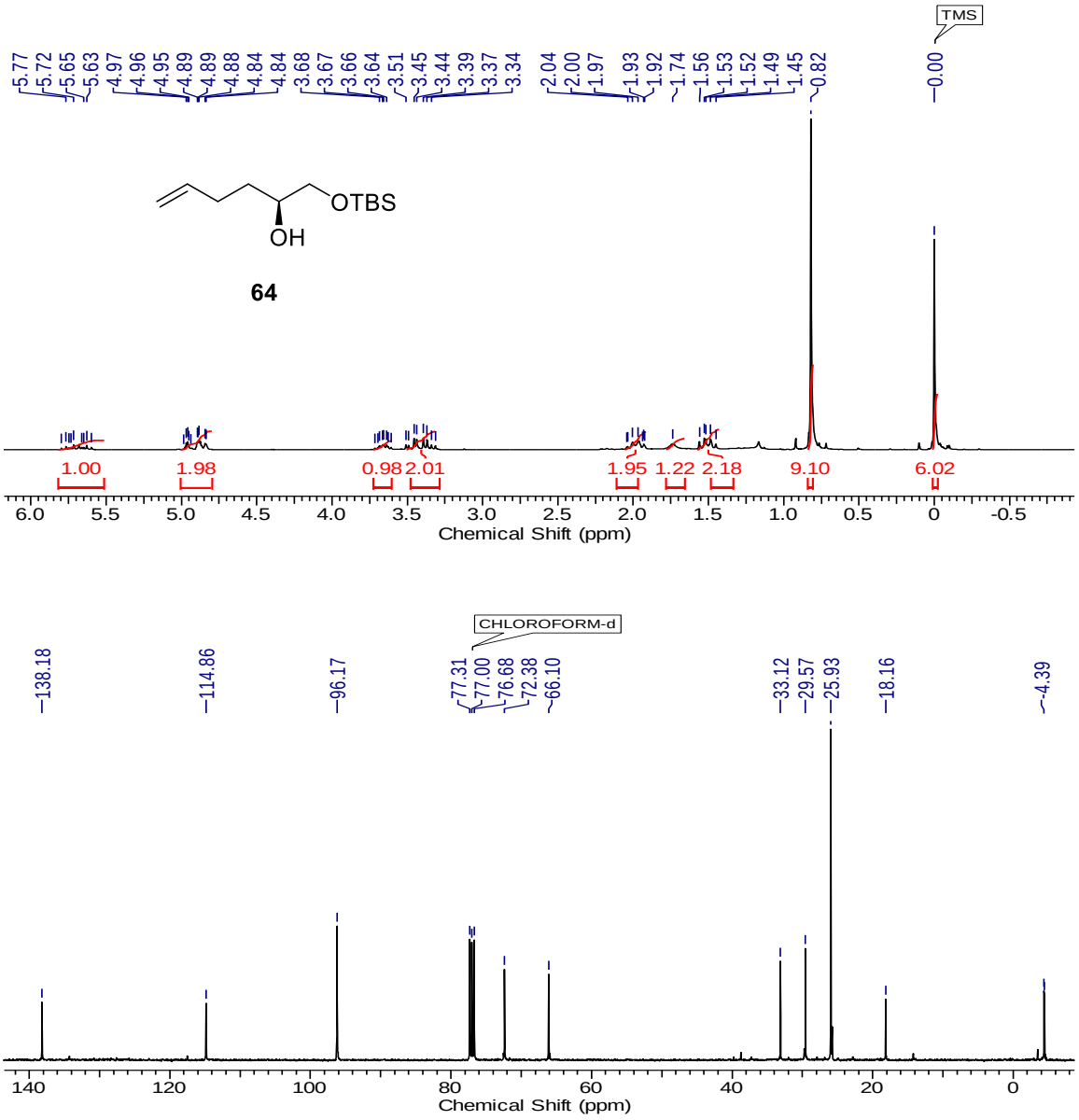


Figure 25: ^{1}H and ^{13}C NMR spectra of alcohol **64**

Alcohol **64** upon subsequent PMB ether formation using PMB-trichloroacetimidate (derived from PMB-OH) and catalytic PTSA at 0 °C provided olefin **65** in 90% yield. The formation of olefin **65** was confirmed from its ^{1}H NMR spectrum, which displayed

singlet at δ 3.80 (s, 3H) for methyl protons and multiplet at δ 6.80-6.90 (m, 2H), 7.24-7.33 (m, 2H) for the aromatic protons of PMB group. The typical carbon signals at δ 55.2 corresponding to methyl carbon (O-**C**H_3) of PMB group (**Figure 26**).

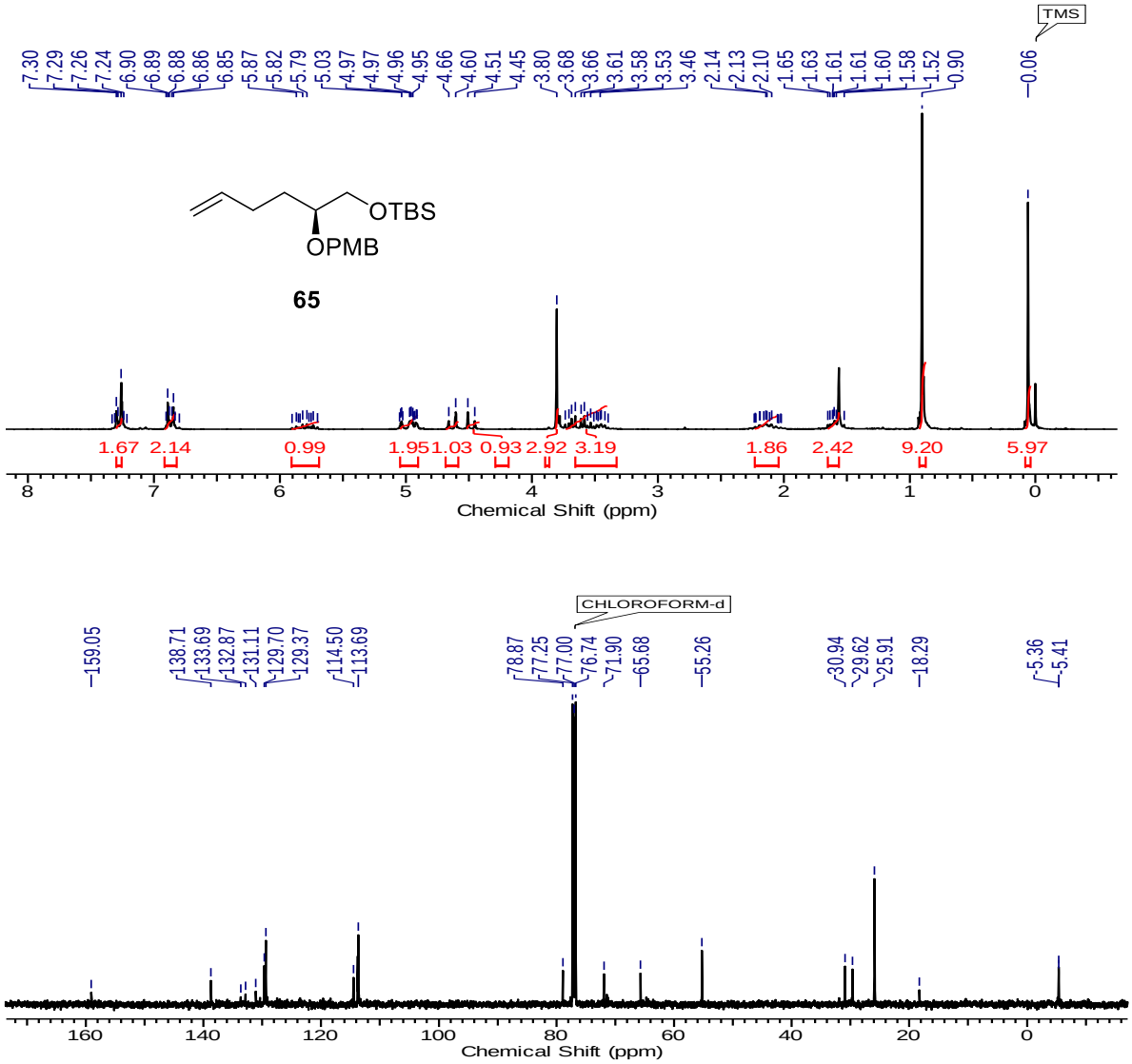
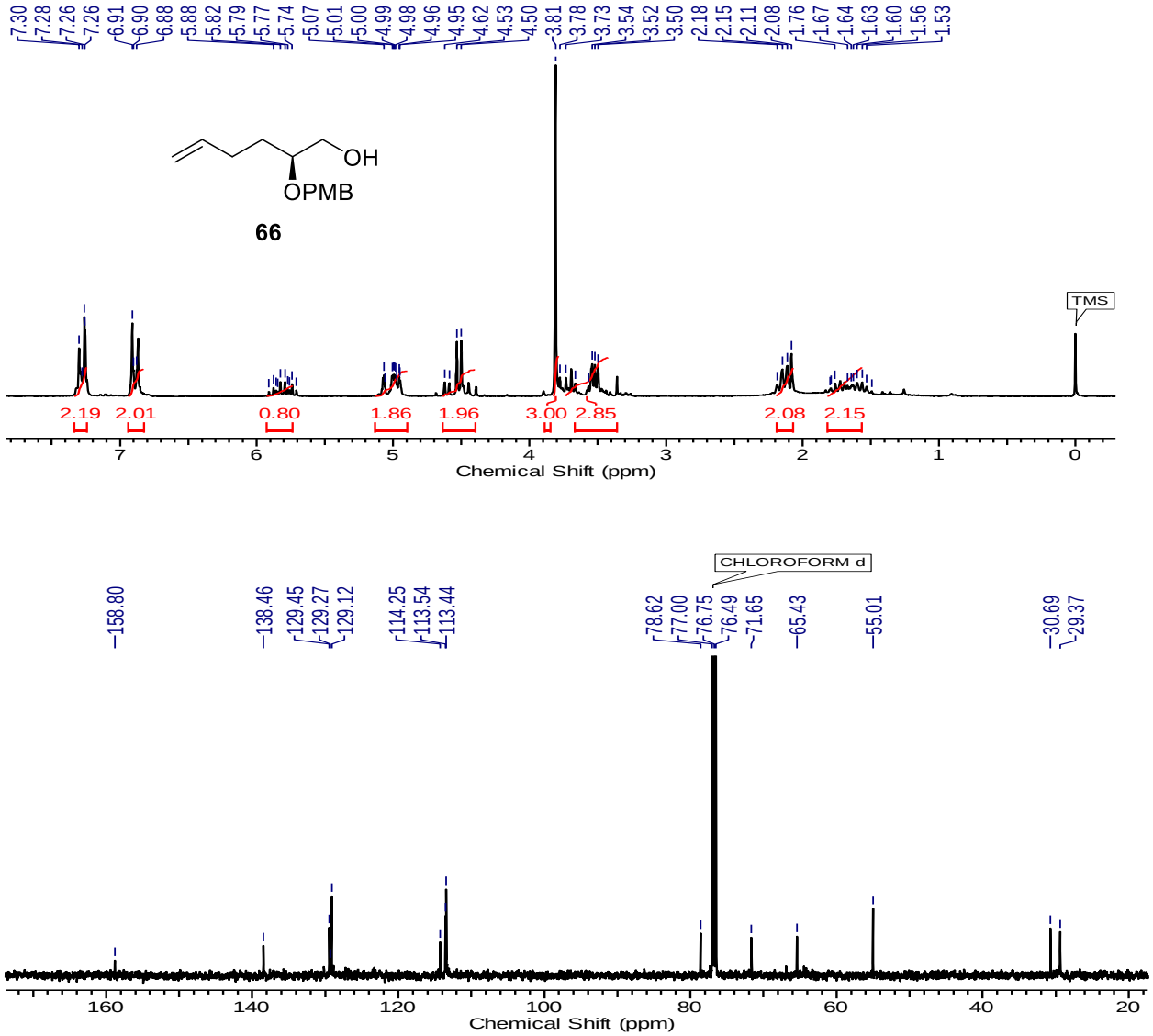


Figure 26: ^{1}H and ^{13}C NMR spectra of olefin **65**

TBS deprotection of olefin **65** was then carried out with catalytic amount of camphorsulfonic acid (CSA) to give alcohol 66 **in** 63% yield. The ^{1}H NMR spectrum of **66** showed disappearance of the peak signals at δ 0.06 (s, 6H) and 0.90 (s, 9H) for methyl

protons of silyl group. The formation of alcohol **66** was further supported by its ^{13}C NMR spectrum which shows missing of carbon signals at δ -5.4, -5.3 due to the carbons of silyl group. The IR spectrum of alcohol **66** shows a strong absorbtion band at υ_{max} 3441 cm^{-1} corresponding to alcohol functionality (**Figure 27**). Finally, Oxidation of 66 with TEMPO, PhI $(OAc)_2$ afforded the acid fragment **43** in 86% yield.



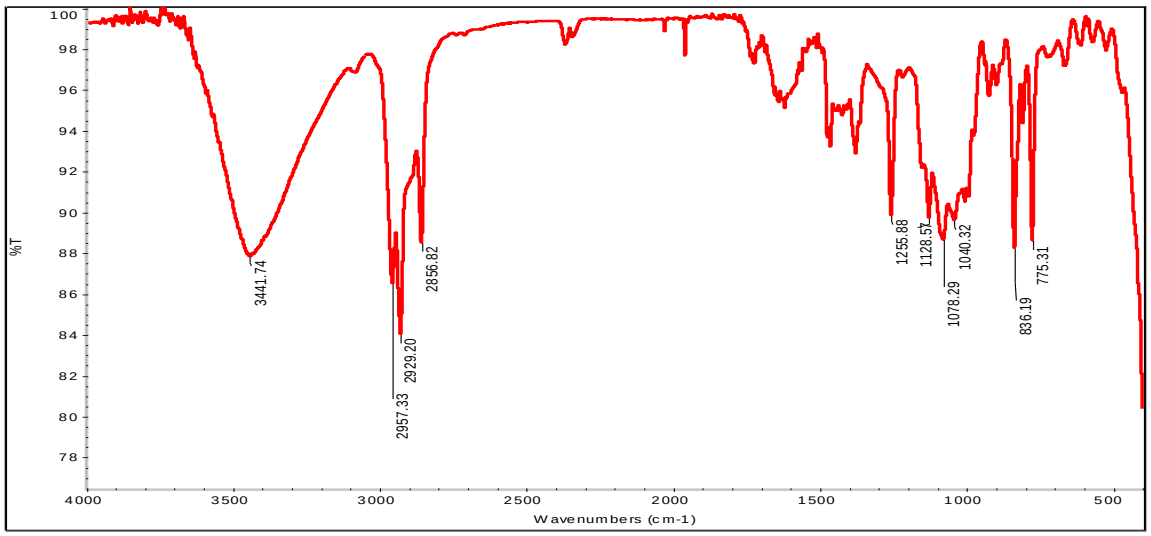
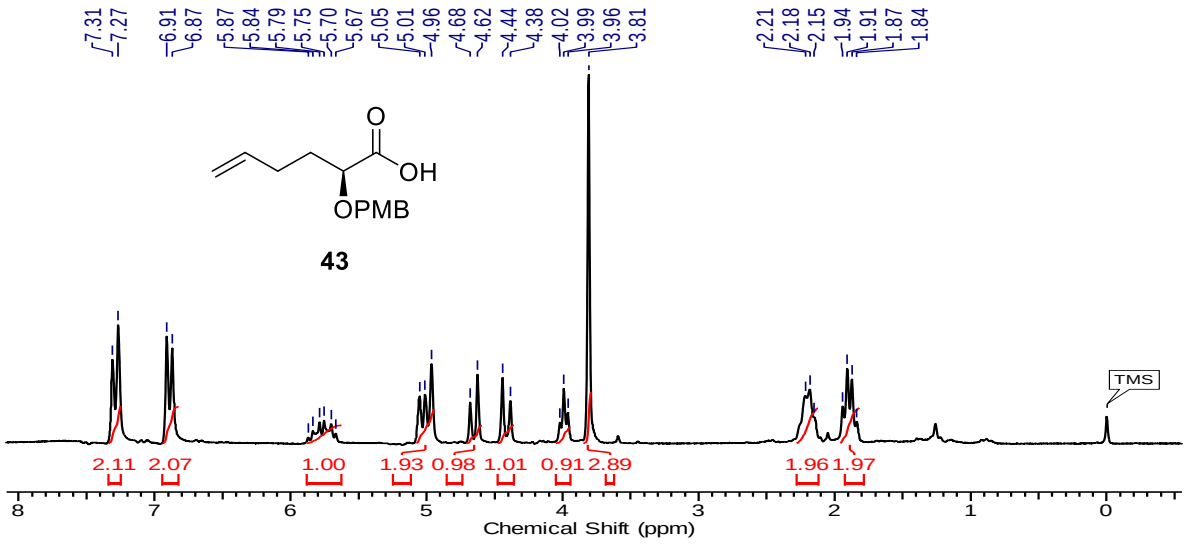


Figure 27: ^{1}H & ^{13}C NMR and IR spectra of alcohol **66**

The formation of carboxylic acid **43** was confirmed by the presence of a typical signal at δ 4.62 (d, *J* = 11.0 Hz, 1H) in its ^{1}H NMR spectrum corresponds to methine proton (-C**H**-CO-) attached to carbonyl group of acid. After the successful construction of both fragments, we carried out the final coupling of key alcohol fragment **40** and acid fragment **43** using a Steglich esterification condition (EDCI.HCl, Et_3N) to afford RCM



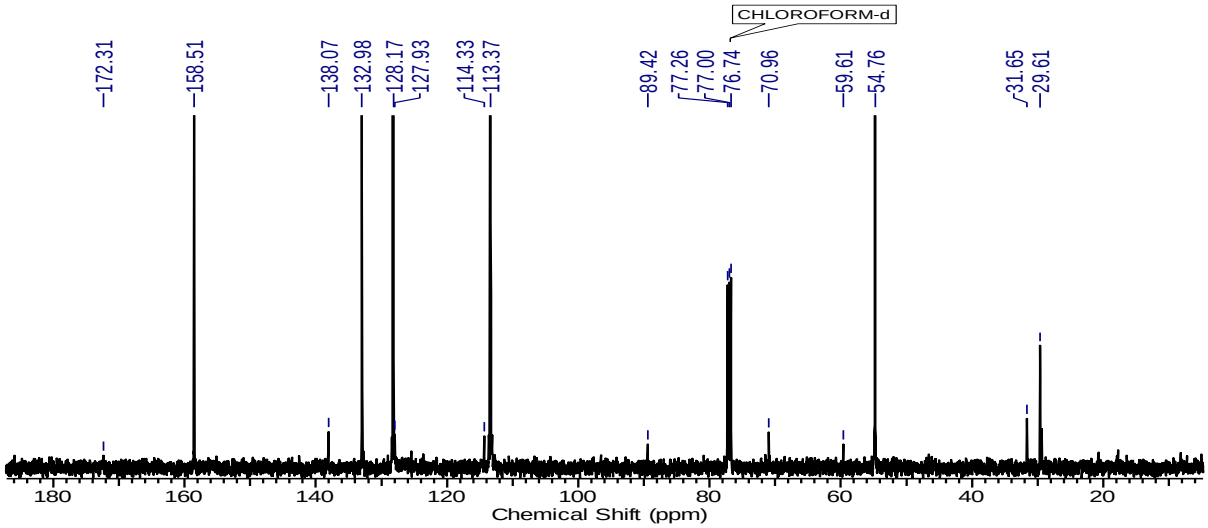
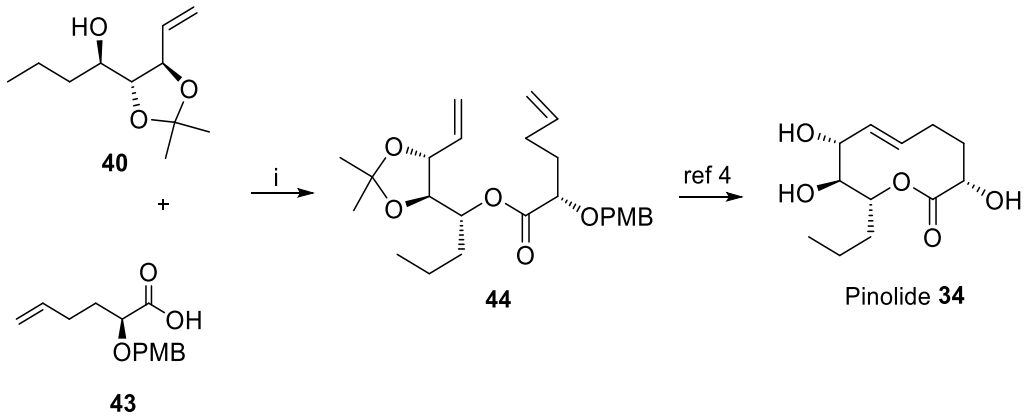


Figure 28: ^{1}H and ^{13}C NMR spectra of acid **43**

precursor **44** in 88% yield. Finally ring-closing metathesis (RCM) of **44** and deprotection of protecting groups (PMB and acetonide) that delivers the final product, **34** have been well-established in the literature,[14] thereby constituting a formal synthesis of **34** (**Scheme 16**).



Scheme 16: Reagents and conditions: (i) EDCI·HCl, Et_3N, DMAP, CH_2Cl_2, 0-25 °C, 6 h, 88%.

2.2.5 Conclusion

In conclusion, a convergent, formal enantioselective synthesis of pinolide **34** has been achieved. The strategy mainly comprises of the L-proline-catalyzed sequential *α*-aminooxylation-HWE olefination reaction of *n*-valeraldehyde and Sharpless asymmetric dihydroxylation as the key reactions for the induction of chirality. The overall yields for both the fragments, that are alcohol fragment **40** and acid fragment **43**, were calculated to be 30.6% and 40.7% respectively, with an excellent enantioselectivity of 99% *ee.* The operationally simple reactions with less number of steps, high overall yields, requiring a relatively low amount of inexpensive and non-toxic proline as the catalyst make this approach an attractive and useful route. This methodology can be applied to the synthesis of other members of decanolides as well.

2.2.6 Experimental section

Ethyl (*R*,*E*)-4-hydroxyhept-2-enoate (55)

To a solution of nitrosobenzene (5.5 g, 58.13 mmol) and L-proline (1.33 g, 20 mol %) in CH_3CN (120 mL) was added *n*-valeraldehyde **54** (5.0 g, 58.13 mmol) at -20 ^oC. The reaction mixture was stirred at the same temperature for 24 h followed by the addition of anhydrous LiCl (3.4 g, 87.19 mmol), triethyl phosphonoacetate (19.53 g, 87.19 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (8.8 g, 58.13 mmol). After stirring for 1 h, the reaction mixture was quenched with half saturated NH_4Cl and extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude *α*-aminooxy olefinic ester, which was directly used for the next step without further purification. To a well-stirred solution of crude *α*-aminooxy olefinic ester in MeOH (50 ml) was added

$CuSO_4.5H_2O$ (4.3 gm, 30 mol%) at 25 °C. The reaction mixture was then allowed to stir for 12 h at this temperature. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure to afford the crude *γ*-hydroxy ester. The crude product was then purified by column chromatography over silica gel using petroleum ether and ethyl acetate (7:3) as eluents to afford *γ*-hydroxy ester **55** (7.7 g).

Yield: 77%; colorless liquid; $[\alpha]_D^{25}$ -21.2 (*c* 1.0, $CHCl_3$); **IR ($CHCl_3$):** 1280, 1660, 1715, 2930, 3442 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.3 Hz, 3H), 1.37-1.68 (m, 4H), 1.83 (br s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.29 (m, 1H), 6.01 (dd, *J* = 15.5, 1.6 Hz, 1H), 6.92 (dd, *J* = 15.7, 5.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 14.2, 18.4, 38.6, 60.4, 70.8, 120.0, 150.3, 166.6; **HRMS** (m/z): calculated [M+Na]+ for $C_9H_{16}NaO_3$: 195.0997 found: 195.0995.

Ethyl (*R*, *E*)-4-((tert-butyldimethylsilyl) oxy) hept-2-enoate (57)

To a solution of γ-hydroxy ester **55** (6.4 g, 37.20 mmol) in anhydrous CH_2Cl_2 (80 mL) were added imidazole (5.0 g, 74.4 mmol) and TBSCl (6.6 g, 44.65 mmol) at 0 °C. The resultant mixture was warmed to room temperature and stirred for 3 h. The reaction was immersed in an ice bath, and saturated aqueous NH_4Cl (20 mL) was added. The layers were separated, the aqueous layer was washed with CH_2Cl_2 (220 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by column chromatography using petroleum ether and ethyl acetate (9:1) as eluents to give TBS ether **57** (10.42 g).

Yield: 98%; pale yellow liquid; $[\alpha]_D^{25}$ -15.2 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 1185, 1412, 1462, 1720, 2863, 2935, 2965; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.06 (s, 3H), 0.89-0.92 (m, 12H), 1.30 (t, *J* = 6.6 Hz, 3H), 1.33-1.39 (m, 2H), 1.49-1.54 (m,

2H), 4.16-4.23 (m, 2H), 4.28-4.32 (m, 1H), 5.94-5.98 (dd, *J* = 15.7, 1.6 Hz, 1H), 6.90-6.94 (dd, *J* = 15.4, 4.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.6, 14.0, 14.2, 18.10, 18.18, 25.8, 39.5, 60.2, 71.4, 119.6, 151.1, 166.8; **HRMS** (m/z): calculated [M+Na]+ for $C_{15}H_{30}NaO_3Si$: 309.1856 found: 309.1853.

Ethyl (2*S*,3*S*,4*R*)-4-((tert-butyldimethylsilyl)oxy)-2,3-dihydroxyheptanoate (58)

To a mixture of $K_3Fe(CN)_6$ (17.25 g, 52.44 mmol), K_2CO_3 (7.23 g, 52.44 mmol), and $(DHQ)_2$-PHAL (135 mg, 1 mol%), in *t*-BuOH/H_2O (1:1, 200 mL) cooled at 0 °C was added $K_2OsO_4.2H_2O$ (12 mg, 0.2 mol%) followed by methanesulfonamide (1.66 g, 17.48 mmol). After being stirred for 5 min at 0 °C, TBS protected ether **57** (5 g, 17.48 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 5 h and then the reaction was quenched with solid sodiumsulfite. The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 X 100 mL). The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The crude residue was then purified by column chromatography using petroleum ether and ethyl acetate (85:15) as eluents gave the diol **58** (4.73 g).

Yield: 86%; yellow gum; $[\alpha]_D^{25}$ -5.5 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 775, 972, 1010, 1103, 1253, 1640, 1734, 2950, 3448; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.90-0.95 (m, 12H), 1.30-1.33 (t, *J* = 6.9 Hz, 3H), 1.38-1.47 (m, 2H), 2.29-2.63 (br s , 1H), 3.15-3.33 (br s, 1H), 3.77-3.89 (m, 2H), 4.21-4.46 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.4, 14.1, 14.3, 17.0, 18.0, 25.8, 35.4, 35.8, 61.9, 70.1, 70.6, 72.7, 173.6; **HRMS** (m/z): calculated [M+Na]+ for $C_{15}H_{32}NaO_5Si$: 343.1911 found: 343.1907.

Ethyl (4*S*,5*S*)-5-((*R*)-1-((tert-butyldimethylsilyl)oxy)butyl)-2,2-dimethyl1,3dioxolane-4-carboxylate (59)

A solution of diol **58** (4.0 g, 12.5 mmol) in CH_2Cl_2 (40 mL) was treated with 2,2-dimethoxypropane (7.6 mL, 62.5 mmol) and CSA (290 mg, 10 mol%). The resulting solution was stirred at room temprature for 12 h. After completion of the reaction (monitored by TLC) reaction was quenched by the addition of Et_3N (1 mL) and the mixture was concentrated under reduced pressure. The crude residue was then purified by column chromatography using petroleum ether and ethyl acetate (95:5) as eluents to give acetonide **59** (4.3 g).

Yield: 96%; colorless liquid; $[\alpha]_D^{25}$ +24.0 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 780, 1105, 1255, 1735, 2857, 2935, 2962; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89-0.95 (m, 12H), 1.29-1.53 (m, 13H), 3.78-3.89 (m, 1H), 4.16-4.46 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.3, -4.2, 14.1, 14.2, 18.1, 18.3, 25.4, 25.9, 26.7, 36.2, 61.2, 71.4, 74.9, 81.4, 110.0, 171.9; **HRMS** (m/z): calculated [M+Na]+ for $C_{18}H_{36}NaO_5Si$: 383.2224 found: 383.2222.

((4*R*,5*S*)-5-((*R*)-1-((tert-butyldimethylsilyl)oxy)butyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (60)

To a stirred suspension of $LiAlH_4$ (0.411 g, 11.11 mmol) in THF (40 mL) at 0 °C was added acetonide **59** (4 g, 11.11 mmol) in THF (40 mL). After 1 h stirring at 0 °C the reaction mixture was quenched with H_2O (1.8 mL), 15% aqueous NaOH (1.8 mL) and H_2O (5.0 mL). The precipitate was filtered through a Celite pad and washed with hot ethyl acetate (80 mL) and the filtrate was concentrated under reduced pressure and purified by purified by column chromatography using petroleum ether and ethyl acetate (8:2) as eluents to give alcohol **60** (3.2 g).

Yield: 93%; colorless liquid; $[\alpha]_D^{25}$ -2.3 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 1085, 1255,

1460, 2935, 2960, 3450; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.81-0.88 (m, 12H), 1.28-1.45 (m, 10H), 2.09 (br s, 1H), 3.49-3.63 (m, 1H), 3.65-3.78 (m, 3H), 3.90-3.99 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.2, -4.1, 14.4, 17.2, 25.9, 27.1, 27.2, 36.9, 63.5, 73.1, 78.4, 79.6, 108.7; **HRMS** (m/z): calculated [M+Na]+ for $C_{16}H_{34}NaO_4Si$: 341.2119 found: 341.2116.

(4*S*,5*S*)-5-((*R*)-1-((tert-butyldimethylsilyl)oxy)butyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (61)

To a stirred solution of alcohol **60** (3.0 g, 9.43 mmol) in (40 mL) ethyl acetate was added IBX (5.28 g, 18.86 mmol) and refluxed for 2 h. After the reaction was complete (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with ethyl acetate (30 mL). The organic layer was washed with water (50 mL), brine (50 mL), and dried over Na_2SO_4. The residue obtained after evaporation of the solvent afforded the crude aldehyde, which was purified by column chromatography using petroleum ether/ethyl acetate (9:1) as eluent to furnish aldehyde **61** (2.56 g).

Yield: 86%; colorless liquid; $[\alpha]_D^{25}$ -13.7 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 776, 1255, 1470, 1715, 2860, 2935, 2962 ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.89-0.96 (m, 12H), 1.34-1.49 (m, 10H), 3.83-3.91 (m, 1H), 4.05-4.10 (dd, *J* = 4.0, 6.3 Hz, 1H), 4.34-4.38 (dd, *J* = 1.6, 6.6 Hz 1H), 9.77 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.4, -4.1, 14.2, 18.0, 25.7, 25.9, 26.7, 27.0, 36.4, 71.5, 78.1, 82.6, 108.4, 117.2, 137.0; **HRMS** (m/z): calculated [M+Na]+ for $C_{16}H_{32}NaO_4Si$: 339.1968 found: 339.1967.

Tert-butyl((*R*)-1-((4*S*,5*R*)-2,2-dimethyl-5-vinyl1,3dioxolan4yl)butoxy)dimethylsilane (62)

To a stirred solution of iodomethyltriphenylphosphine (5.13 g, 12.65 mmol) in THF (50 mL) was added *n*-BuLi (7.9 mL, 1.6 M, 12.65 mmol) dropwise at 0 °C. After 30 min, aldehyde **61** (2.0 g, 6.32 mmol) was added and the reaction mixture was allowed to warm to room temperature over 15 min. The resultant mixture was quenched with saturated aqueous NH_4Cl, diluted with ethyl acetate (25 mL). The combined organic layer was washed with water and then brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using petroleum ether as eluent to give olefin **62** (1.49 g)

Yield: 75%; colorless liquid; $[\alpha]_D^{25}$ +11.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 1100, 1260, 1470, 2935, 2960; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.80-0.93 (m, 12H), 1.25-1.51 (m, 10H), 3.09-3.75 (m, 1H), 3.82-3.89 (m, 1H), 4.35-4.42 (m, 1H), 5.16-5.22 (m, 1H), 5.32-5.42 (m, 1H), 5.78-5.95 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.4, -4.1, 14.2, 18.1, 18.2, 25.9, 26.7, 27.0, 36.4, 71.5, 78.1, 82.6, 108.4, 117.2, 137.0; **HRMS** (m/z): calculated [M+Na]+ for $C_{17}H_{34}NaO_3Si$: 337.2169 found: 337.2166.

(*R*)-1-((4*R*, 5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)butan-1-ol (40)

To a stirred solution of olefin **62** (1.3 g, 4.14 mmol) in THF (20 mL) at 0 °C, TBAF (8.27 mL, 8.28 mmol, 1 M solution in THF) was added dropwise. The mixture was allowed to stir at room temperature over 2 h. The resultant mixture was quenched with water and diluted with diethyl ether (5 mL).The organic layer was washed with water and then with brine, respectively. The combined organic layers was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (9:1) as eluent to give alcohol **40** (678 mg).

Yield: 82%; colorless liquid; $[\alpha]_D^{25}$ +7.7 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 1105, 1254, 1380, 1466, 1640, 2865, 2960, 3455; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87-0.95 (t, *J* = 7.1 Hz, 3H), 1.33-1.52 (m, 10H), 2.08 (br s, 1H), 3.63 (dd, *J* = 3.8, 8.0 Hz, 1H),3.76-3.80 (m, 1H), 4.25-4.39 (m, 1H), 5.12-5.37, (m, 2H), 5.65-5.86 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.8, 19.1, 26.9, 34.3, 70.1, 77.3, 83.0, 108.7, 118.7, 136.4; **HRMS** (m/z): calculated [M+Na]+ for $C_{11}H_{20}NaO_3$: 223.1310 found: 223.1307.

(*S*)-hex-5-ene-1,2-diol (63)

To a stirred, precooled (-20 ℃) acetonitrile (100 mL) solution of aldehyde **56** (5 g, 51.02 mmol) and nitrosobenzene (4.91 g, 45.91 mmol) was added D-proline (1.17 g, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 24 h followed by the addition of MeOH (20 mL) and $NaBH_4$ (2.83 g, 76.53 mmol) to the reaction mixture, which was stirred for 20 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude aminooxy alcohol which was directly taken up for the next step without purification.

To a well-stirred solution of crude α-aminooxy alcohol in MeOH (50 ml) was added $CuSO_4.5H_2O$ (3.81 gm, 30 mol%) at 0 °C. The reaction mixture was then allowed to stir for 12 h at this temperature. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure to afford the crude diol. The crude product was then purified by column chromatography over silica gel using petroleum ether and ethyl acetate (7:3) as eluents to afford pure diol **63** (5.1 g).

Yield: 87%; colorless liquid; $[\alpha]_D^{25}$ -14.02 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 1097, 1420, 1645, 2954, 3430; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41-1.59 (m, 2H), 2.02-2.27 (m, 2H),

3.43 (m, 1H), 3.60-3.79 (m, 4H), 4.93-5.11 (m, 2H), 5.72-5.81 (m, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.9, 33.4, 66.4, 72.7, 115.1, 138.5; **HRMS** (m/z): calculated [M+Na]+ for $C_6H_{12}NaO_2$: 139.0735 found: 139.0733.

(*S*)-1-((tert-butyldimethylsilyl)oxy)hex-5-en-2-ol (64)

To a solution of diol **63** (4.5 g, 38.79 mmol) in anhydrous CH_2Cl_2 (100 mL) were added imidazole (5.27 g, 77.58 mmol) and TBSCl (6.9 g, 46.54 mmol) at 0 °C. The resultant mixture was warmed to room temperature and stirred for 3 h. The reaction was immersed in an ice bath, and saturated aqueous NH_4Cl (20 mL) was added. The layers were separated, the aqueous layer was washed with CH_2Cl_2 (150 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (9:1) as eluent to give alcohol **64** (8.5 g).

Yield: 96%; colorless liquid; $[\alpha]_D^{25}$ +7.3 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 782, 835, 1117, 1258, 2858, 2928, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.82 (s, 9H), 1.49-1.56 (m, 2H), 1.74 (br s, 1H), 1.97-2.04 (m, 2H), 3.44-3.68 (m, 3H), 4.88- 4.97 (m, 2H), 5.63-5.77 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.3, 18.1, 25.9, 29.5, 33.1, 66.1, 72.3, 114.8, 138.1; **HRMS** (m/z): calculated [M+Na]+ for $C_{12}H_{26}NaO_2Si$: 253.1600 found: 253.1601.

(*S*)-tert-butyl((2-((4-methoxybenzyl)oxy)hex-5-en-1-yl)oxy)dimethylsilane (65)

To a cooled (0 °C) solution of alcohol **64** (6.0 g, 26.08 mmol) in dry CH_2Cl_2 (80 mL) was added PMB imidate (14.70 g, 52.16 mmol) followed by PTSA (catalytic amount) and the reaction was stirred at room temperature for 8 h. After completion of the reaction, it was quenched with triethylamine, diluted with water (50 mL), and extracted into CH_2Cl_2 (3 ×

50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was then purified by column chromatography on silica gel using petroleum ether/ethyl acetate (9:1) as eluent to give compound **65** (8.19 g).

Yield: 90%; colorless liquid; $[\alpha]_D^{25}$ -21.8 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 1242, 1512, 1588, 1615; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.90 (s, 9H), 1.52-1.65 (m, 2H), 2.10-2.14 (m, 2H), 3.40-3.74 (m, 3H), 3.80 (s, 3H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.91-5.05 (m, 2H), 5.70-5.91 (m, 1H), 6.80-6.90 (m, 2H), 7.24-7.33 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -5.3, 18.2, 25.9, 30.9, 55.2, 65.6, 71.9, 78.8, 113.6, 114.5, 129.7, 131.1, 132.8, 133.6, 138.7, 159.0; **HRMS** (m/z): calculated [M+Na]+ for $C_{20}H_{34}NaO_3Si$: 373.2175 found: 373.2173.

(*S*)-2-((4-methoxybenzyl)oxy)hex-5-en-1-ol (66)

To a stirred solution of compound **65** (5.0 g, 14.28 mmol) in MeOH (40 mL) was added (+)-camphor-10-sulfonic acid (6 mg, 14.28 mmol) at room temperature and the reaction mixture was stirred for 30 min. After completion of the reaction (monitored by TLC), H_2O (6 mL) was added and extraction was done with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Column chromatographic purification of the crude product using petroleum ether/EtOAc (8:2) as eluent gave alcohol **66** (8.19 g).

Yield: 63%; colorless liquid; $[\alpha]_D^{25}$ -34.0 (*c* 0.64, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 820, 915, 1035, 1250, 1516, 1615, 1642, 2936, 3000, 3428; **^{1}H NMR** (200 MHz, $CDCl_3$):δ 1.49-1.80 (m, 2H), 2.08-2.18 (m, 2H), 3.50-3.78 (m, 3H), 3.81 (s, 3H), 4.50-4.62 (m, 2H),

4.95-5.07 (m, 2H), 5.71-5.91 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.5, 19.0, 26.6, 29.3, 32.3, 55.9, 63.5, 94.2, 117.8, 139.0; **HRMS** (m/z): calculated [M+Na]+ for $C_{14}H_{20}NaO_3$: 259.1310 found: 259.1308.

(*S*)-2-((4-methoxybenzyl)oxy)hex-5-enoic acid (43)

To a solution of alcohol **66** (1.5 g, 6.35 mmol) in CH_3CN/H_2O (4:1) was added in one portion bis-acetoxy iodobenzene (6.13, 19.05 mmol) and TEMPO (0.296 g, 1.90 mmol). The reaction mixture was then allowed to stir at 25 ^oC for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched by addition of saturated solution of aq. ammonium thiosulphate. The organic layer was separated, washed with brine and subjected to column chromatographic purification with petroleum ether/EtOAc (8:2 v/v) to afford the acid **43**.

Yield: 86%; Yellow liquid; $[\alpha]_D^{25}$ -45.0 (*c* 0.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 772, 815, 916, 1100, 1235, 1460, 1610, 1720, 2850, 2923, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.84-1.94 (m, 2H), 2.15-2.21 (m, 2H), 3.81 (s, 3H), 3.96 (t, *J* = 6.0 Hz, 1H), 4.38 (d, *J* = 11.0 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.96-5.05 (m, 2H), 5.67-5.87 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.2, 31.8, 55.2, 72.2, 113.8, 115.5, 129.1, 129.8, 137.2, 159.4, 177.3; **HRMS** (m/z): calculated [M+Na]+ for $C_{14}H_{18}NaO_4$: 273.1103 found: 273.1102.

(*R*)-1-((4*R*,5*R*)2,2dimethyl5vinyl1,3dioxolan4yl)butyl(*S*)2((4methoxybenzyl)oxy)hex-5-enoate (44)

To a stirred solution of carboxylic acid **43** (500 mg, 2.0 mmol), EDCI.HCl (613 mg 3.2 mmol), Et_3N (0.86 ml, 6.0 mmol), and DMAP (cat.) in anhydrous CH_2Cl_2 (25 mL) was added alcohol **40** (400 mg, 2.0 mmol) and the reaction mixture was stirred for 12 h. After

completion of the reaction (monitored by TLC), it was quenched with H_2O, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography with petroleum ether/EtOAc (9:1 v/v) to give bis-olefin ester **44** as a colorless liquid.

Yield: 88%; Colorless liquid; $[\alpha]_D^{25}$ -16.5 (*c* 0.5, $CHCl_3$) lit.$[\alpha]_D^{25}$ -16.5 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 1100, 1240, 1456, 1730, 2865, 2925, 3458; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.92 (t, *J* = 8.0 Hz, 3H), 1.23-1.38 (m, 2H), 1.40 (s, 6H), 1.57-1.70 (m, 2H), 1.80-1.86 (m, 2H), 2.10-2.26 (m, 2H), 3.81 (s, 3H), 3.82 (dd, *J* = 2.0, 6.0 Hz, 1H), 3.91 (dd, *J* = 2.0, 6.0 Hz, 1H), 4.27-4.36 (m, 2H), 4.64 (dd, *J* = 1.0, 11.0 Hz, 1H), 4.95-5.02 (m, 2H), 5.21-5.29 (m, 2H), 5.40 (d, *J* = 17.0 Hz, 1H), 5.72-5.88 (m, 2H), 6.88 (d, *J* = 9.0 Hz, 2 H), 7.29 (d, *J* = 9.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.8, 18.4, 26.7, 26.8, 29.4, 32.3, 33.1, 55.2, 71.8, 73.1, 73.2, 76.8, 76.2, 81.1, 109.3, 113.6, 115.4, 118.8, 129.6, 129.8, 135.7, 137.3, 159.5, 172.2; **HRMS** (m/z): calculated [M+Na]+ for $C_{25}H_{36}NaO_6$: 455.2397 found: 455.2399.

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CHAPTER III

Synthesis of 3,3'-Spiro-phosphonylpyrazole-oxindole Skeleton *via* [1,3]-Dipolar Cycloaddition Reaction of Bestmann-Ohira Reagent

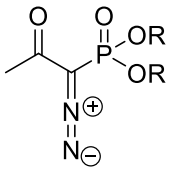
1. "An efficient one pot regioselective synthesis of a 3,3'-spirophosphonylpyrazole-oxindole framework *via* base mediated [1,3]-dipolar cycloaddition reaction of the Bestmann–Ohira reagent with methyleneindolinones" **Shelke, A. M.;** Suryavanshi, G. *Org. Biomol. Chem.*, **2015,** *13*, 8669.

Section I

Bestmann-Ohira Reagent: A Versatile Reagent in Organic Synthesis (Minireview)

3.1.1 Introduction

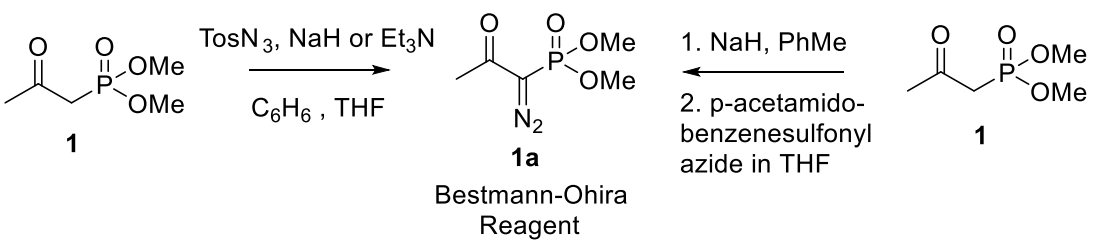
The Bestmann-Ohira reagent (BOR) [1-diazo-2-oxopropyl) phosphonate] (**Figure 1**) a modified version of Seyferth-Gilbert reagent is well known and found new applications in organic chemistry as a cycloaddition partner for the synthesis of phosphonylpyrazoles, triazoles and oxazoles *via* 1,3-dipolar cycloaddition, Cu-catalyzed alkyne azide cycloaddition (CuAAC) (click chemistry) and multicomponent reactions.



1a, R=Me
1b, R=Et

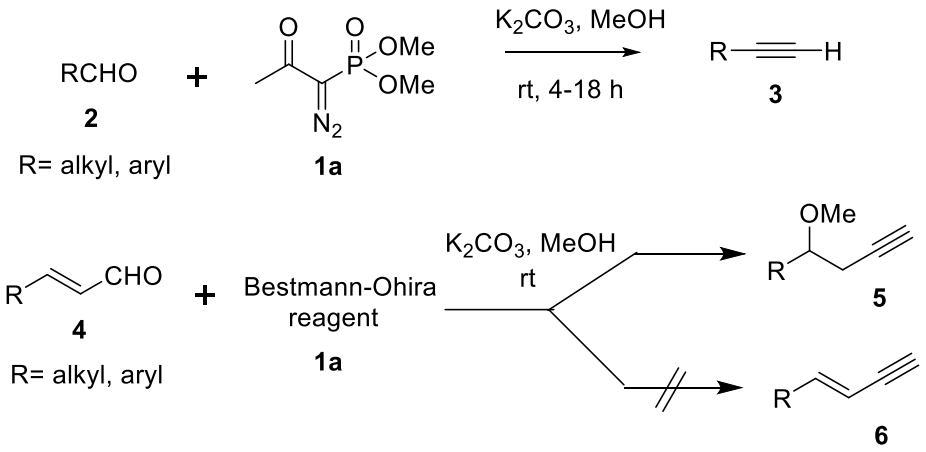
Figure 1: Bestmann-Ohira Reagent (BOR)

Bestmann-Ohira reagent (BOR) can be easily synthesized by the reaction of dimethyl-2-oxopropylphosphonate **1**, tosyl azide[1a] or p-acetamidobenzenesulfonyl azide[1b] with NaH, *t*-BuOK or Et_3N in benzene and THF (**Scheme 1**). An alternative way for the preparation of BOR is the use of polymer-supported sulfonyl azide and *t*-BuOK in



Scheme 1: Preparation of Bestmann-Ohira Reagent (BOR)

methylenchloride.[1c] The applications of Bestmann-Ohira reagent involves in the conversion of primary alcohols, aldehydes, ketones and amides into alkynes. Recently, it was utilized in the synthesis of pyrazoles as well as in the synthesis of 1,3-oxazoles. The use of the Bestmann-Ohira reagent (BOR) is an alternative route to the Fritsch-Buttenberg-Wiechell-type rearrangement and the Corey-Fuchs procedure that allows the addition of the Bestmann-Ohira reagent to an aldehyde under mild reaction conditions, which avoids the use of a strong base under low-temperature conditions. The reaction works very well with alkyl and aryl as well as with hindered aldehydes **2**. In case of *α, β*-unsaturated aldehydes **4** the main products were isolated as homopropargylic methyl ethers **5** and not compound **6**. The reaction can be easily performed under one-pot conditions (**Scheme 2**).[2]



Scheme 2: Reaction of Bestmann-Ohira reagent **1a** with aldehyde **2** and **4**

In this context, this review is intended to provide information regarding the application of BOR **1a** in the synthesis of functionalized pyrazoles, triazoles, and oxazoles in one-pot processes.

3.1.2 Review of literature

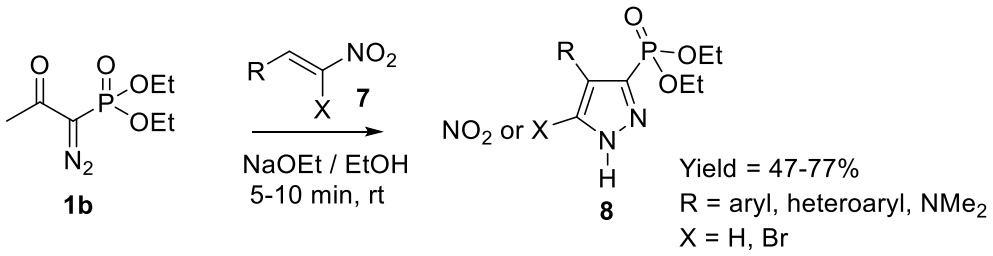
Literature search revealed that there are various reports available for the synthesis of

functionalized pyrazoles, triazoles and oxazoles using Bestmann-Ohira reagent (BOR) as the cycloaddition partner; some of which are described below.

3.1.2.1 Bestmann-Ohira reagent in the synthesis of phosphonyl pyrazoles

Namboothiri first approach (2007)[3]

Namboothiri *et al.* have reported a new method which uses BOR **1b** as a cycloaddition partner with various nitroalkenes **7** for the regioselective synthesis of phosphonyl-pyrazoles **8** under mild reaction conditions. The methodology involves a base-mediated 1,3-dipolar cycloaddition of BOR **1b** with conjugated nitro alkenes **7** in a one-pot reaction that provides regioselectively pure phosphonylpyrazoles **8** at room temperature. Several nucleophilic base and solvents were screened for this reaction but NaOEt in EtOH gave the best yield (77%). A variety of aromatic, heteroaromatic, and aliphatic nitroalkenes were compatible to this reaction condition, giving single regioisomer. Aromatic nitroalkenes with both electron-donating and electronwithdrawing substituents as well as parent nitrostyrene provided the cycloadducts in very good yields (**Scheme 3**).

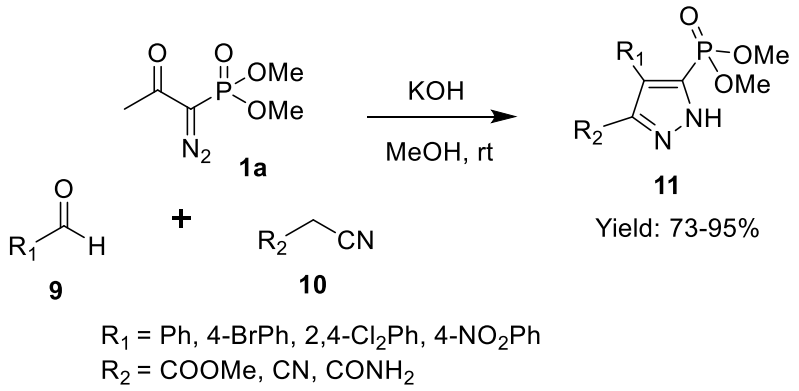


Scheme 3: 1, 3-Dipolar cycloaddition reaction of nitroalkenes **7** with Bestmann-Ohira reagent **1b** in the presence of NaOEt in EtOH.

Mohanan approach (2010)[4]

Mohanan and coworkers developed a novel mulicomponent reaction strategy using BOR **1a,** aldehyde **9** and cyanoacetic derivatives **10**. Based on a domino Knoevenagel

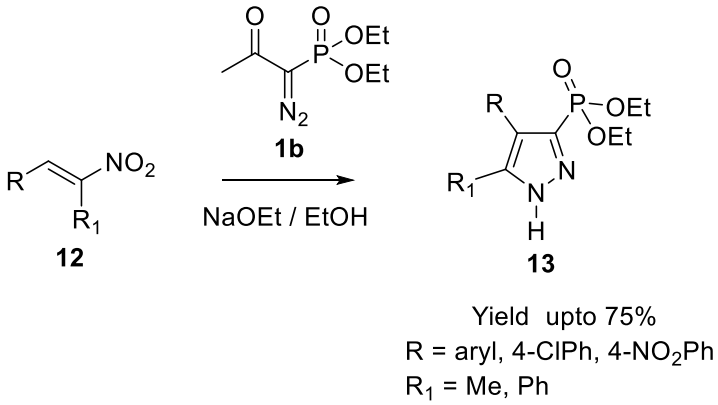
condensation/formal 1,3-dipolar cycloaddition reaction, the three-component reaction of aldehydes **9**, BOR **1a**, and cyanoacetic derivatives **10** generates 5-phosphonyl pyrazole scaffolds **11** through the formation of two C-C bonds and one C-N bond. Attractive features of this domino process are its versatility, readily available starting material and efficiency in creating a complex core in a single operation (**Scheme 4**).



Scheme 4: One-pot, three-component synthesis of phosphonyl pyrazoles **11** using aldehydes **9**, BOR **1a** and cyanoacetic derivatives **10**.

Namboothiri second approach (2010)[5]

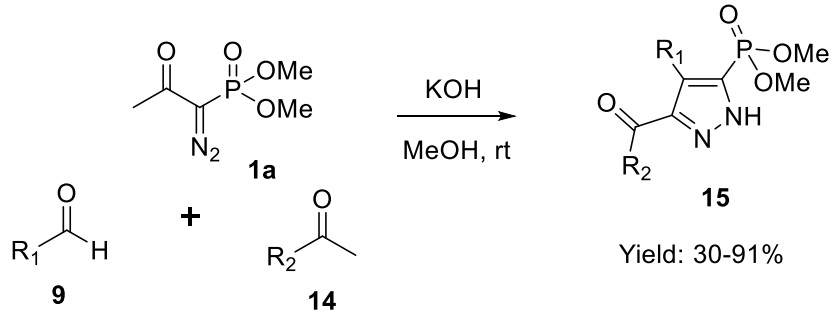
Namboothiri and coworkers investigated application of diethyl 1-diazo-2-oxopropylphosphonate (Bestmann-Ohira reagent) **1b** as a cycloaddition partner with nitroalkenes **12**. Base-mediated reaction of the Bestmann-Ohira reagent **1b** with various nitroalkenes **12** such as *β*-substituted, *α,β*-disubstituted, and nitroethylene that are part of a carbocyclic or heterocyclic ring provided functionalized phosphonylpyrazoles **13** through a one-pot regioselective reaction at room temperature in high yield. The substituted nitroalkenes employed in these reactions also included Morita-Baylis-Hillman adducts of conjugated nitroalkenes with various electrophiles (**Scheme 5**).



Scheme 5: 1,3-Dipolar reaction of *α, β*-disubstituted nitroethylenes **12** with BOR **1b** in the presence of NaOEt in EtOH at room temperature

Martin's approach (2011)[6]

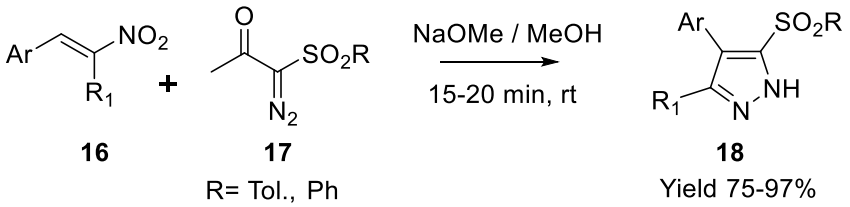
Martin and coworkers further shown the emerging role of the BOR **1a** as 1, 3-dipolar precursor by developing a more general and straightforward procedure for the regioselective preparation of 3-carbo-5-phosphonylpyrazoles **15**. Based on an unprecedented Claisen-Schmidt/1,3-dipolar cycloaddition/oxidation sequence, an aldehyde **10**, a methyl ketone **12**, and the BOR **1a** in one-pot reactions afforded the phosphonyl pyrazoles **15** in excellent yields (**Scheme 6**).



Scheme 6: One-pot, three-component sequential synthesis of 3-oxo-5 phosphonylpyrazole **15** using aldehyde **9**, a methyl ketone **14**, and the BOR **1a**.

Namboothiri third approach (2011)[7]

Kumar and Namboothiri in 2011 further developed a one-pot regioselective method for the synthesis of sulfonylpyrazoles **18** *via* a base-mediated reaction of sulfur analogue of BOR (*i.e.*, *α*-diazo-*β*-ketosulfone **17**) with nitroalkenes **16** in a one-pot reaction at room temprature with excellent yield. Aryl, heteroaryl, styrenyl, alkyl, hydroxymethyl and hydrazinyl groups were introduced on the pyrazole ring by this method with the appropriate choice of nitroalkenes **16**. No significant changes were observed on the yield or rate of the reaction when various *β*-aryl nitroalkenes **16** were used. Nitroethylenes with diverse β-substituents as cycloaddition partner afforded the sulfonylpyrazoles **18** under mild basic conditions (NaOMe/MeOH) in good to excellent yields. Highly substituted sulfonylpyrazoles **18** were synthesized by employing *α, β*-disubstituted nitroethylenes. They also reported the synthesis of sulfonylpyrazole fused to other heterocycles using nitroethylene as a part of the heterocyclic ring and applied the methodology to an expedient synthesis of a pyrazole alkaloid, withasomnine (**Scheme 7**).

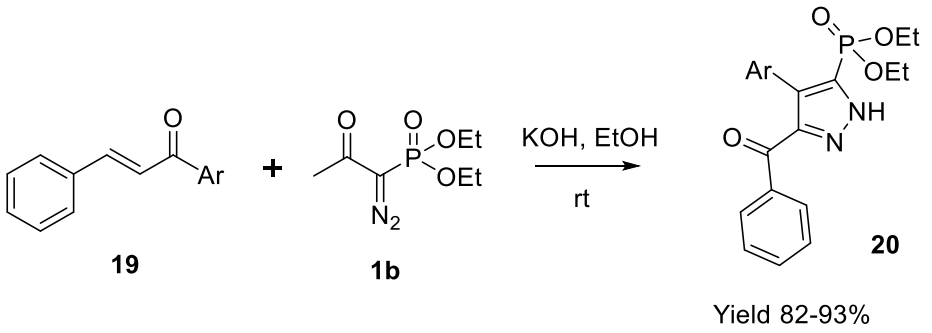


Scheme 7: Synthesis of aryl sulfonylpyrazoles **18** from *β*-aryl nitroethylenes **16** and diazo-sulfone **17**.

Namboothiri fourth approach (2011)[8]

Namboothiri *et al* reported the synthesis of novel carbonylated pyrazole phosphonates **20** by 1,3-dipolar cycloaddition reaction of BOR **1b** with conjugated enones **19** under mild basic (KOH/EtOH) conditions at room temperature. With *α, β*-unsaturated ketones **19** (chalcones), BOR afforded pyrazole phosphonates **20** as single

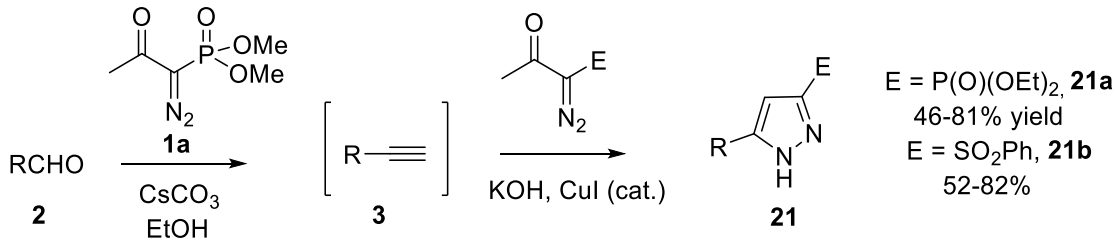
regioisomer in good to excellent yields in the presence of KOH/EtOH. Strongly electron-donating and electron-withdrawing substituents in conjugation with the reacting π-system reduced the reactivity of chalcone and provided the product in slightly lower yield (**Scheme 8**).



Scheme 8: Synthesis of phosphonylpyrazoles **20** from chalcones **19** and Bestmann-Ohira reagent **1b**.

Namboothiri approach (2012)[9]

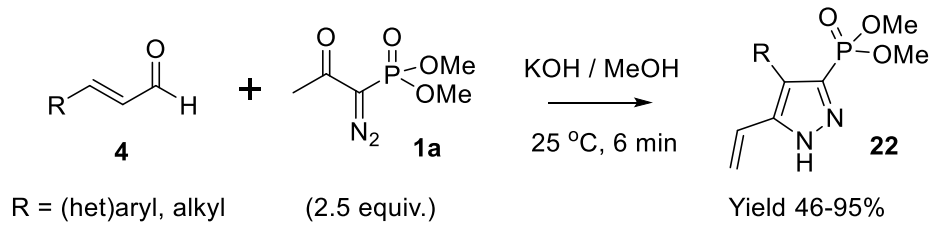
Namboothiri *et al* developed a strategy that enables us to synthesize a variety of 5-substituted 3-phosphonylpyrazoles **21** that are regioisomeric to the pyrazoles (4-substituted 3-phosphonyl) synthesized previously from nitroalkenes and Bestmann-Ohira reagent. The method involves reaction of BOR **1a** with aldehydes **2** to generate terminal acetylenes **3** and subsequent reaction of BOR with the *in situ* generated acetylenes under simple Cu (I) catalyzed conditions to generate phosphonylpyrazoles **21** (**Scheme 9**).



Scheme 9: Synthesis of phosphonylpyrazoles **21a** and sulfonylpyrazoles **21b**.

Mohanan's approach (2015)[10]

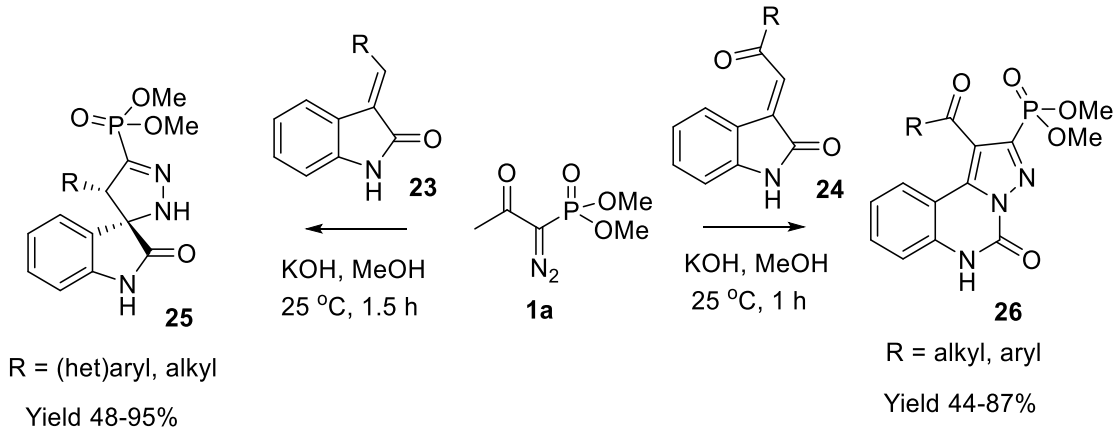
Mohanan *et al* developed a domino reaction for the mild, rapid and efficient synthesis of vinylpyrazoles. The reaction involves a formal 1,3-dipolar cycloaddition/HWE homologation of the resulting pyrazoline carboxaldehyde/1,3-H shift sequence to afford 5-vinylpyrazole derivatives. This reaction represents the first report on the dual reactivity of the Bestmann-Ohira reagent as a homologation reagent and cycloaddition reactant in a domino reaction (**Scheme 10**).



Scheme 10: Synthesis of densely functionalized vinylpyrazoles **22** from *α,β*-unsaturated aldehyde **4** and Bestmann-Ohira reagent **1a.**

Mohanan's approach (2015)[11]

Mohanan *et al* developed a very mild and efficient reaction of the Bestmann-Ohira reagent **1a** with N-unprotected isatin-derived olefins **23** & **24** for the selective synthesis of spiro-pyrazoline-oxindoles **25** and tricyclic pyrazoles **26**.



Scheme 11: Reaction of BOR **1a** with activated olefins **23** and **24**

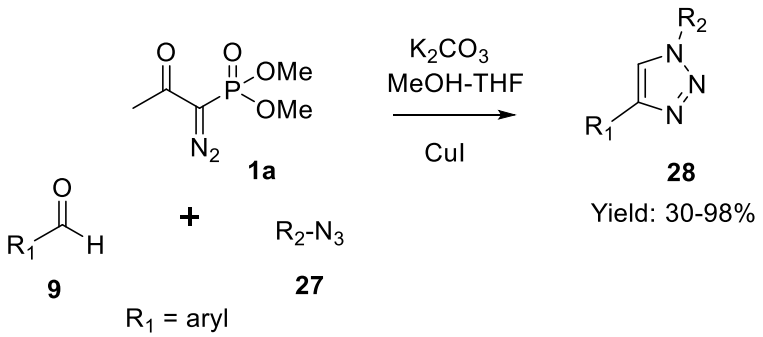
The reaction features an attractive product-selectivity depending on the substituent on isatin-derived olefin. Treatment of 3-aryl/alkylideneoxindoles **23**/**24** with BOR **1a** afforded spiro-pyrazoline-oxindoles **25**, whereas 3-phenacylideneoxindoles furnished pyrazoloquinazolinones **26** *via* a unique ring expansion reaction (**Scheme 11**).

3.1.2.2 Bestmann-Ohira reagent in the synthesis of 1, 2, 3-Triazoles

The efficiency of BOR in the regioselective synthesis of triazoles has been reflected in the copper-catalyzed alkyne-azide cycloaddition (CuAAC) reactions.

Luvino's approach (2007)[12]

Luvino *et al.* in 2007 presented a reliable and operationally simple one-pot reaction for the construction of triazole scaffold **28** using BOR **1a**, aldehydes **9**, and organic azides **27** *via* Cu-catalyzed azide-alkyne click reaction under mild reaction conditions. The protocol involved the sequential addition of the *in situ*-generated alkynes from aldehydes **9** and BOR **1a** under mild conditions followed by 1, 3-dipolar cycloaddition with azides **27** in the presence of CuI to afford 1,4-disubstituted 1,2,3-triazoles **28** in good yields without the need for isolation of the alkyne intermediates.



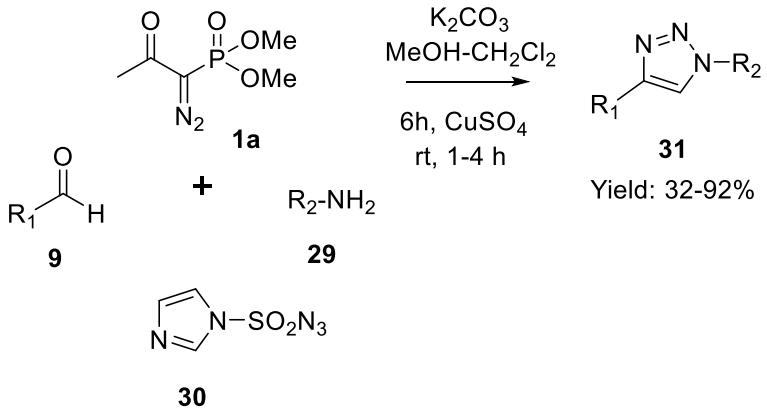
Scheme 12: One-pot synthesis of triazoles **28** from aldehydes **9** *via in situ*-generated alkynes.

This homologation click protocol has tolerated a variety of polyfunctional synthons. Electron-rich and electron-poor aldehydes were shown to react smoothly, along with sterically demanding aldehydes. The method is also very useful for the synthesis of

glyco-, peptido-, and nucleosido-bioconjugates with a wide range of functional groups. Moreover, the protocol demands the first synthesis of new boronic acid-based fluorescent sensors (trizolylaryl boronates) from commercially available ormyl boronic acids (**Scheme 12**).

Maisonneuve's approach (2009)[13]

Maisonneuve and Xie in 2009 developed a one-pot, three-step sequential synthesis of 1,4-disubstituted 1,2,3-triazoles **31** from aldehyde **9** and amine **29**. The sequential method involved *in situ* transformation of aldehyde to alkyne by BOR **1a**, followed by diazotransfer of amine **29** to azide using imidazole-1-sulfonyl azide **30** hydrochloride as an efficient and shelf-stable diazo-transfer reagent and subsequent cycloaddition reaction to generate triazoles **31.**

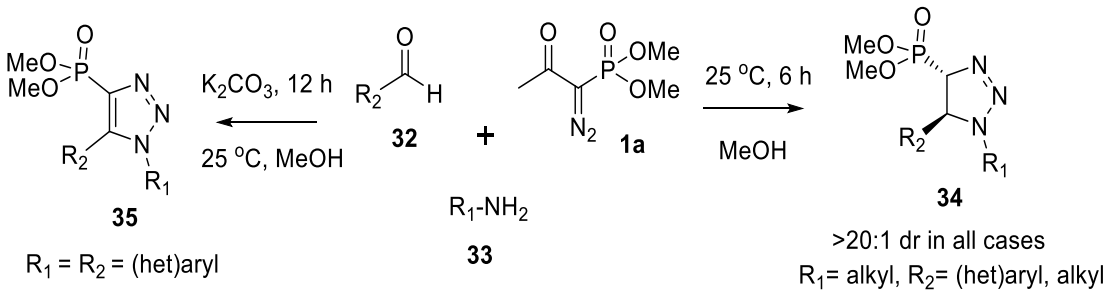


Scheme 13: One-pot, three-step synthesis of 1,2,3-triazoles **31**.

Improved yields (up to 92%) were obtained by adding ascorbic acid in place of sodium ascorbate, as it neutralizes the reaction mixture and reduces Cu (II) to Cu (I), which facilitates the reaction. As azide precursors, amino esters, dipeptides, and C-glycosyl amines have been proven successful. Not only aryl aldehydes but also glycosyl aldehydes can be used as alkyne precursors (**Scheme 13**).

Mohanan's approach (2016)[14]

Recently, Mohanan and coworkers reported an efficient, three-component domino reaction between aldehydes **32**, amines **33**, and the Bestmann-Ohira reagent **1a** that enables a general, mild, and straightforward access to 1,4,5-trisubstituted 1,2,3-triazolines **34** and triazoles **35**. The reaction proceeds through a domino-condensation/1,3-dipolar cycloaddition sequence to afford the triazoline derivatives **34** with excellent diastereoselectivity. Moreover, when both amine **33** and aldehyde **32** employed for this reaction are aromatic, a spontaneous oxidation afforded 1,4,5-trisubstituted triazoles **35** in moderate yields (**Scheme 14**).

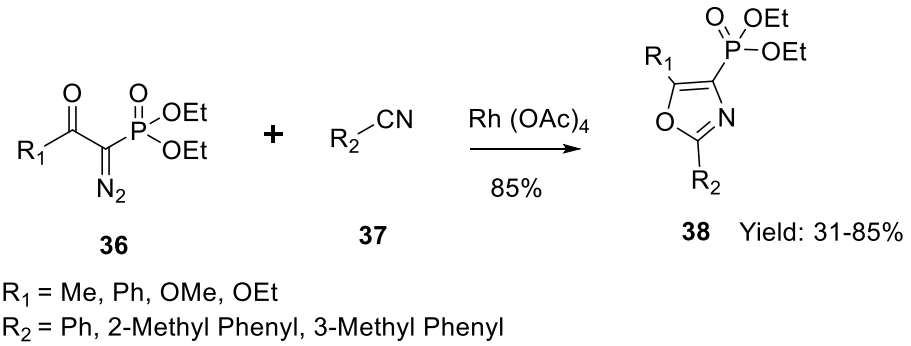


Scheme 14: Metal-free three-component domino approach to phosphonylated Triazolines and Triazoles

3.1.2.3 Bestmann-Ohira reagent in the synthesis of 1, 3-Oxazoles

Rhodium (II)-catalyzed reactions of diazocarbonyl compounds with nitriles for the construction of oxazoles were reported by Connell and coworkers. A similar strategy based on the concept of palladium-catalyzed reaction for the construction of 1,3 oxazoles using BOR was adopted by Gong *et al.*[15] They reported the synthesis of a series of 4-phosphoryl-substituted 1,3-oxazoles **38** conveniently by reaction of BOR **36** and aromatic nitriles **37** in the presence of a catalytic amount of rhodium (II) acetate *via* an intermolecular cycloaddition reaction. Aromatic nitriles afforded moderate yields whereas aliphatic nitriles, including acetonitrile and chloroacetonitrile, were unsuccessful in this reaction. Similarly, the use of aryl

phosphonates gave a lower yield than those obtained from other alkylphosphonate derivatives, probably because of the electronic and steric effects of the phenyl group (**Scheme 15**).



36 **37** **38** Yield: 31-85%

R_1 = Me, Ph, OMe, OEt
R_2 = Ph, 2-Methyl Phenyl, 3-Methyl Phenyl

Scheme 15: Synthesis of oxazoles **38** from BOR **36**.

3.1.3 Conclusion

As a classical synthetic reagent, the BOR has found versatile applications in organic synthesis but its application to the construction of heterocyclic scaffolds is in the infancy stage. Until now it has been limited to the synthesis of functionalized phosphonyl 1,2-diazoles, 1,2,3-triazoles, and 1,3-oxazole scaffold only. Even if the classical methods are still the most commonly used procedures for the construction of these heterocyclic scaffolds, new one-pot approaches using BOR have been developed with the aim of increasing yields, regioselectivities, and operational simplicity in their synthesis. There is plenty of room for the development of new methodologies where BOR will find application for the construction of other unexplored heterocyclic scaffolds found in a myriad of useful natural products and synthetic compounds.

Section II

An Efficient One Pot Regioselective Synthesis of 3,3'-Spiro-phosphonylpyrazole-oxindole Framework *via* Base Mediated [1,3]-Dipolar Cycloaddition Reaction of Bestmann-Ohira reagent with Methyleneindolinones

3.2.1 Introduction

The 3,3'-spiro-oxindoles are valuable structural core present in many natural alkaloids and pharmacological agents. They exhibits interesting structural as well as biological properties[16] (**Figure 2**). Hence, considerable efforts have been devoted to develop new and efficient synthetic strategies to access these important structural motifs.[17] Similarly, organophosphonates also an important structural units posses remarkable biological activities[18,19] and attracts much attention due to their role as metabolic probes,[20] peptide mimetics,[21] pharmacological agents,[22] antibiotic and biomolecules. Very recently, the synthesis of natural and non-natural phosphonate analogues incorporating nucleotides, azaheterocycles and their biological activities have been reviewed.[23,24]

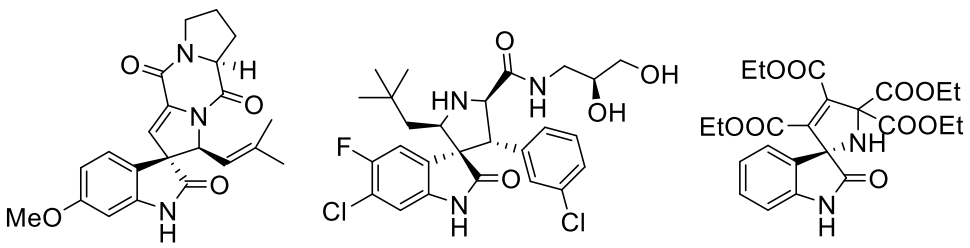


Figure 2: Biologically active compounds containing spiro-oxindole core

Therefore in view of the importance of heterocycles fused with phosphonate groups, it is imperative to have a straightforward access of these versatile building blocks[18,25,26]

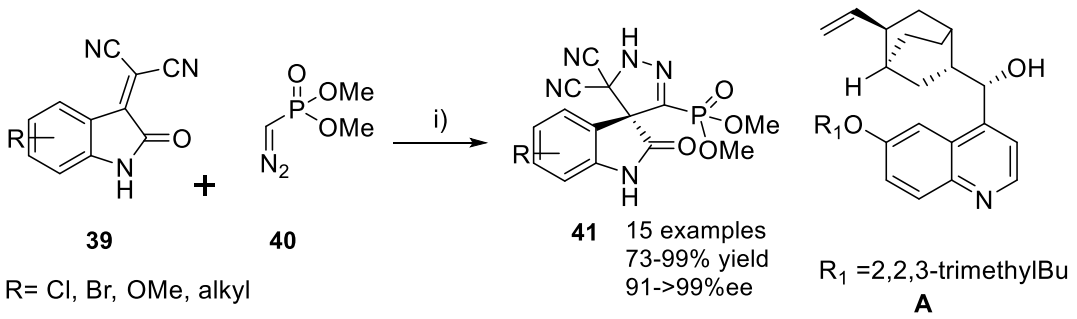
by developing new synthetic methodologies. Among the various biologically active heterocycles, pyrazoles occupies a central stage due to its wide applications in the pharmaceutical industry, agrochemicals,[27,28], biological agents,[29] and also plays a central role in coordination chemistry.[30] Few pyrazoles such as Withasomnine,[31,32] celecoxib and Viagra exhibits important therapeutic potential (Withasomnine: analgesic and CNS depressant; Celecoxib: nonsteroidal antiarthritic drug and Viagra: phosphodiesterase inhibitor). Bestmann-Ohira reagent (BOR) a modified version of Seyferth-Gilbert reagent[33] is well-known for the conversion of aldehydes into terminal alkynes under mild basic conditions.

3.2.2 Review of Literature

Literature search reveals that there is only one report available in the literature for the synthesis of chiral spiro-phosphonylpyrazoline-oxindoles which is described below.

Peng's Approach (2016)[34]

Peng *et al*. have developed a new method for the catalytic enantioselective 1,3-dipolar cycloaddition of the Seyferth-Gilbert reagent (SGR) **40** to isatylidene malononitriles **39** using a cinchona alkaloid derivative as a catalyst. This method allowed for the synthesis of a series of chiral spiro-phosphonylpyrazoline-oxindoles **41** in good yields with excellent enantioselectivities. The synthetic utility of this method was further



Scheme 16: (i) **A** (10 mol%), CPME/DCM=1/3, -60 °C, 4-9 d.

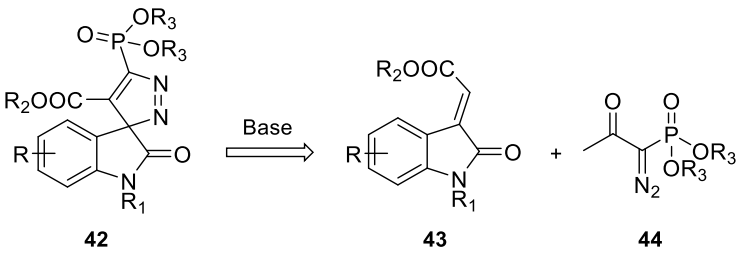
demonstrated by its use in a three-component domino reaction involving isatin, malononitrile, and SGR based on sequential Knoevenagel condensation and 1,3-dipolar cycloaddition reactions (**Scheme 16**).

3.2.3 Present Work

3.2.3.1 Objective

In recent years, due to their structural complexity and high biological activity several methods for the synthesis of phosphonyl pyrazoles have been reported in the literature using Bestmann-Ohira reagent (BOR) as the cycloaddition partner.

However, base mediated 1,3-dipolar cycloaddition reactions of methyleneindolinones with Bestmann-Ohira reagent has not been documented in the literature. During the course of our study, Peng and co-workers reported the synthesis of chiral spiro-phosphonylpyrazoline-oxindoles using organocatalytic enantioselective 1,3-dipolar cycloadditions between Seyferth-Gilbert reagent and isatylidene malononitriles.[34] Considering the importance of 3,3'-spiro-oxindoles and as part of our ongoing research in the development of new and efficient methodologies involving construction of C-C and C-N bond formation reactions,[35] we herein disclose for the first time, one pot construction of 3,3'-spiro-phosphonylpyrazole-oxindole skeleton *via* base mediated 1,3-dipolar cycloaddition reaction between Bestmann-Ohira reagent with substituted methyleneindolinones (**Scheme 17**).



42 43 44

Scheme 17: One pot access to 3, 3'-spiro-phosphonylpyrazole-oxindole **42**

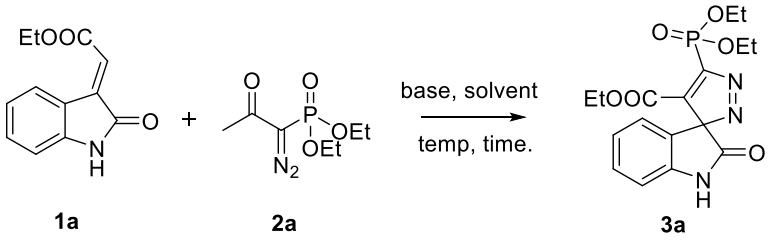
To achieve this goal, we envisioned that 3,3'-spiro-phosphonylpyrazole-oxindole core could be constructed by 1,3-dipolar reaction between various substituted methyleneindolinones **43** and Bestmann-Ohira reagent (BOR) **44** in the presence of base.

3.2.4. Results and Discussions:

To explore the feasibility of this proposed strategy shown in Scheme **17**, we commenced our study by choosing methyleneindolinone **1a** and Bestmann-Ohira reagent (BOR) **2a** as model substrate to optimize the reaction conditions in the presence of various bases and solvents at room temperature (Table 1).

To our delight, when methyleneindolinone **1a** was treated with Bestmann-Ohira reagent **2a** in the presence of 2.0 equiv. K_2CO_3 in anhydrous MeOH at room temperature in an open air, the desired 3,3'spiro-phosphonylpyrazole-oxindole **3a** was obtained in 40% yield at 25 °C after 12 h (Table 1, **entry 1**). The reaction was highly regioselective, with the carbon end of the dipole adding to the *β*-position of the methyleneindolinone **1a** which was further confirmed by detailed spectroscopic analysis and X-ray crystallography. Encouraged by these results, we set out to find a compatible base for our 1,3-dipolar cycloaddition reaction. Several organic and inorganic bases (2.0 equiv.) were screened in protic as well as aprotic solvents to promote cycloaddition reaction between methyleneindolinone **1a** and Bestmann Ohira reagent (BOR) **2a** at room temperature. Among the bases examined, potassium hydroxide (KOH) provided **3a** in the highest yield (80%) as a single regioisomer within a short reaction time (Table 1, **entry 7**). However, the attempts to use other weak organic bases like triethyl amine, afforded a complex reaction mixture (Table 1, **entry 4**). The use of the base DBU gives less yield of **3a** (Table 1, **entry 5**). In the presence of sodium methoxide (NaOMe), **3a** was obtained in moderate yield (Table 1,

Table 1 Optimization of the reaction conditions for the 1,3-dipolar cycloaddition reactions of methyleneindolinone (**1a**) with Bestmann-Ohira reagent (**2a**) [a]



1a **2a** **3a**

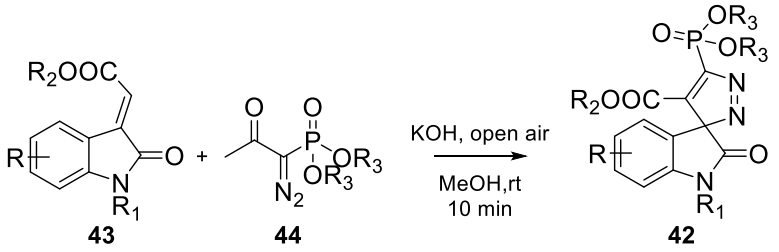
Entry	Base	Solvent	Temp (^oC)	Time	Yield[b] (%)
1	K_2CO_3	MeOH	25	12 h	40
2	-	MeOH	25	24 h	n.r.
3	-	MeOH	reflux	4 days	n.r.
4	NEt_3	MeOH	25	24 h	complex
5	DBU	MeOH	25	24 h	traces
6	NaOMe	MeOH	25	18 h	55
7	**KOH**	**MeOH**	**25**	**10 min**	**80**
8	KOH	EtOH	25	10 min	75
9	KOH	CH_3CN	25	24 h	n.r.
10	KOH	DMSO	25	24 h	n.r.
11	KOH	THF	25	24 h	30
12	NaOEt	EtOH	25	24 h	65

[a]Unless specified All reactions were performed on 0.1 mmol scale using **1a** (0.1 mmol), **2a** (0.2 mmol) and base (0.2 mmol) in anhydrous solvents at room temperature in open air. [b]Isolated yield after silica gel column chromatography.

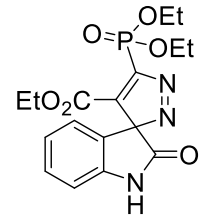
entry 6). Further attempts to improve the yield of the reaction we focused on the solvent screening. Moreover, solvents other than methanol/ethanol did not affect the 1,3-dipolar reaction even after 24 h (Table 1, **entry 9**, **10** and **11**).

After detailed optimization of reaction condition, we confirmed the requirement of a nucleophilic base and protic solvent for 1, 3-dipolar reaction (Table 1, **entry 7**). Based on the results obtained, we used MeOH as the ideal solvent and KOH as the suitable base for further studies. With the optimized conditions in hand, the generality and scope of this base mediated 1,3-dipolar cycloaddition reaction was next investigated to see its functional group tolerance. Much to our satisfaction, the reaction demonstrated good compatibility and proved to be a general method to build structurally diverse 3,3'-spiro-phosphonylpyrazole-oxindoles in generally high yields (76-85%) with excellent regioselectivity. First, the influence of N-substituents of the indolinone motif was investigated by using substrates with N-H groups, N-benzyl, N-methyl, N-Boc (Table 2, **entries 3a-3d**), which revealed that both N-protected and N-unprotected methyleneindolinones **1** could successfully take part in the dipolar cycloaddition reaction to afford the spiro-products **3**. As observed, the protecting groups did not affect the yield significantly and all of the corresponding 3,3'-spiro-phosphonylpyrazole-oxindoles were obtained in good yields (Table 2, **entry 3a-3d**, 78-84%). The scope of the substrates was further successfully extended to various halogenated substrates (Table 2, **entry 3f-3h**, **3m** and **3n** 76-84%) which provides the possibility for further functionalization. The results disclosed that the electronic nature and the position of the halogen substituents at C-4, C-5 as well as C-6 of methyleneindolinones **43** were seen to have little influence on the efficiency of this reaction, because all of these substrates uniformly afforded the 3,3'-spiro-phosphonylpyrazole -oxindoles with structural diversity in excellent regioselectivity with good yields. As shown in Table 2, attachment of both electron-donating substituents such as OMe, OCF_3 and electron withdrawing substituents such as NO_2 at the C-5 position on the aromatic ring of methyleneindolinones **43** was well tolerated,

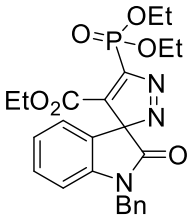
Table 2 Substrate scope for the 1,3-dipolar cycloaddition reactions between methyleneindolinones (**43**) and Bestmann-Ohira Reagent (**44**)[a]



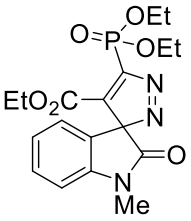
43 **44** **42**



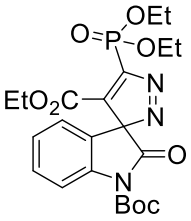
3a, 84%



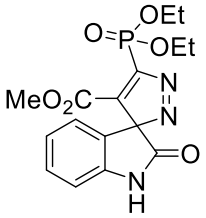
3b, 82%



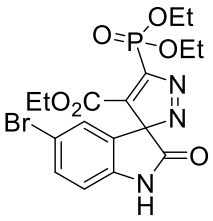
3c, 78%



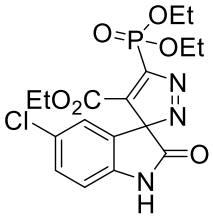
3d, 80%



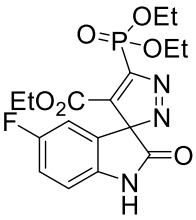
3e, 77%



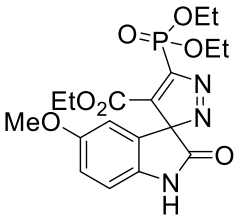
3f, 81%



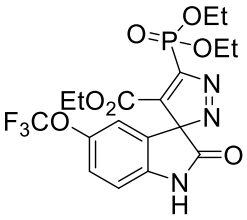
3g, 80%



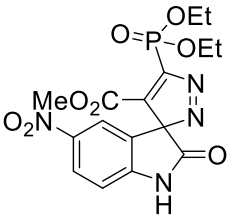
3h, 76%



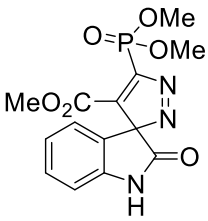
3i, 85%



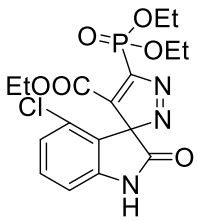
3j, 82%



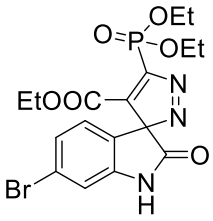
3k, 79%



3l, 83%



3m, 79%



3n, 84%

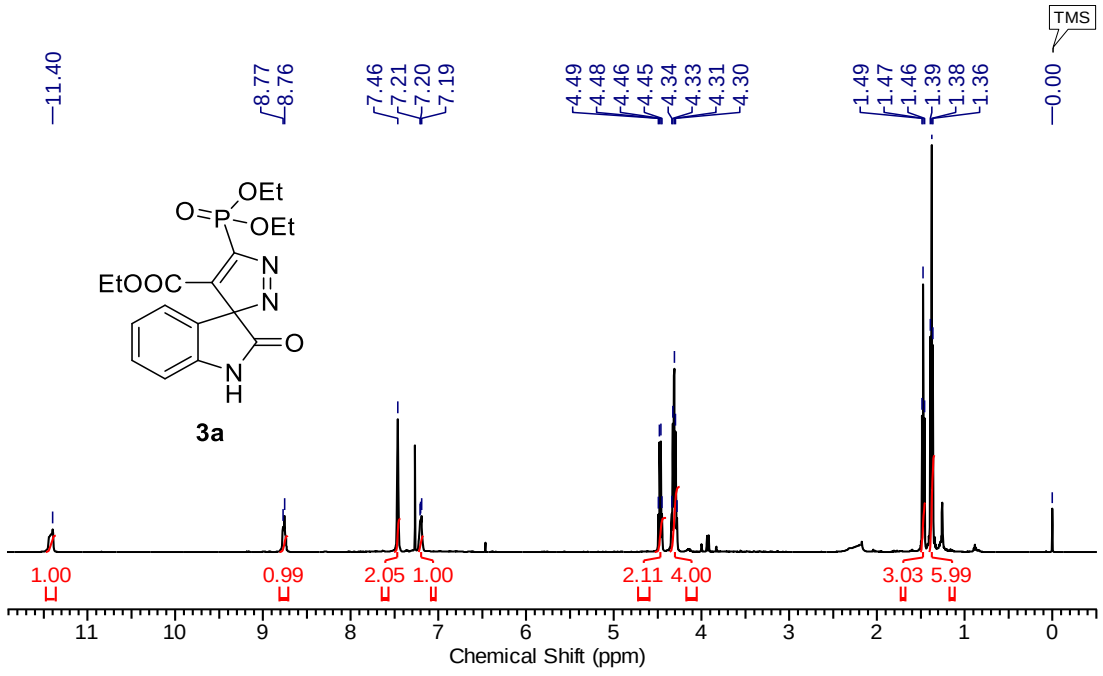
[a]All reactions were performed on 0.1 mmol scale using **43** (0.1 mmol), **44** (0.2 mmol) and KOH (0.2 mmol) in anhydrous MeOH for 10 min at room temperature. Isolated yield after silica gel column chromatography.

with the corresponding products being obtained in good yields with high regioselectivity (Table 2, **entry 3i-3k**, 79-85%). In most of the cases, 3,3'-spiro-phosphonylpyrazole-oxindole could be isolated in good yields after column chromatography.

The formation of **3a-3n** was established unambiguously from their corresponding ^{1}H, ^{13}C & ^{31}P NMR, IR and HRMS spectral data.

Example 1:

The structure of 3,3'spiro-phosphonylpyrazole-oxindole **3a** was confirmed from its ^{1}H NMR spectrum, which showed multiplet at δ 1.36-1.39 (m, 6H) and 1.46 (t, J = 7.6 Hz, 3H) due to the presence of protons in methyl group (-C**H**$_3$) in **3a.** It was further confirmed from its ^{13}C NMR spectrum which shows characteristic carbon signal at δ 150.4 and 163.3 due to the presence of carbonyl group of amide and ester in compound **3a**. Its ^{31}P NMR spectrum shows singlet at δ 6.59 due to presence of phosprous.



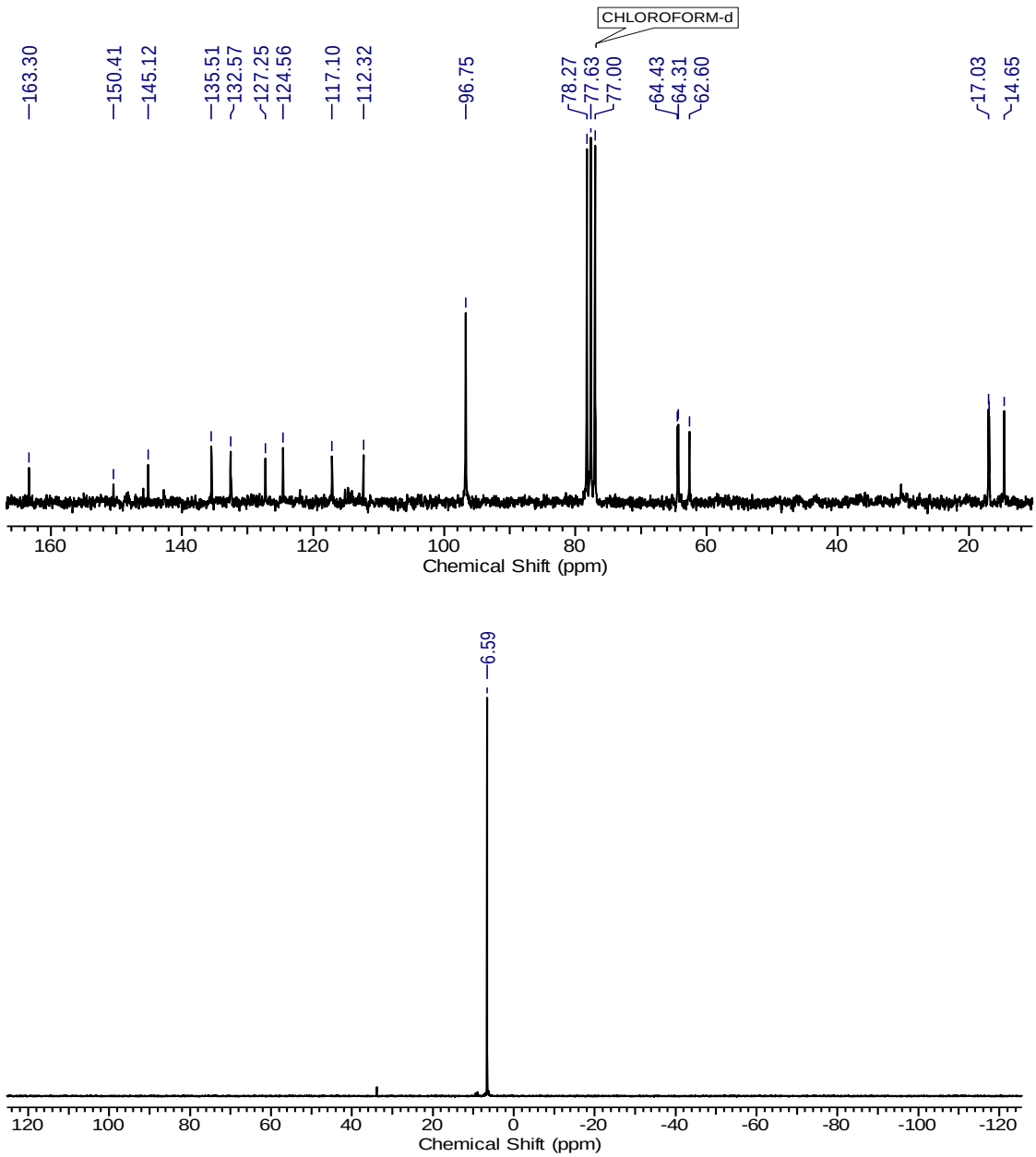
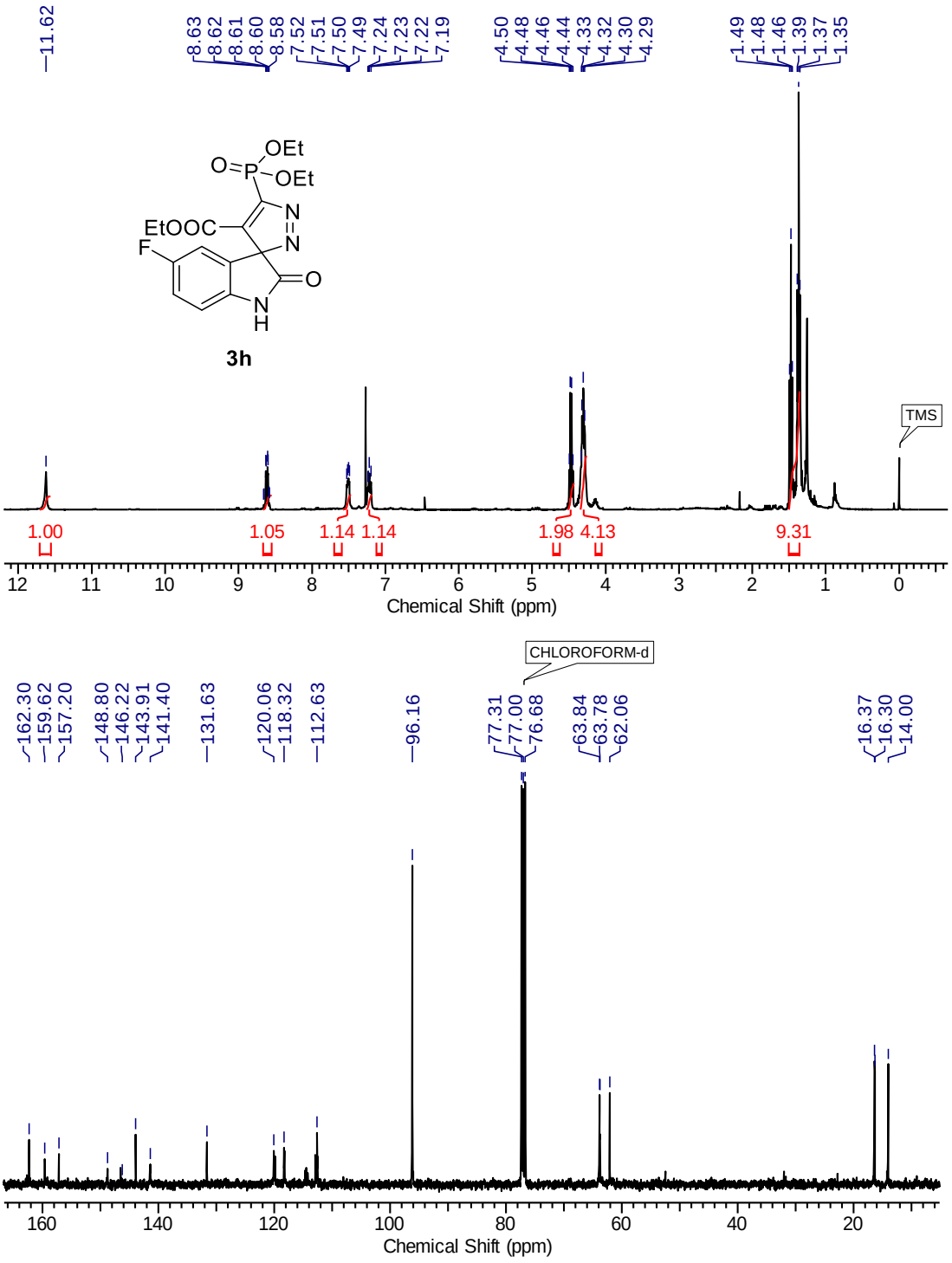


Figure 2: ^{1}H, ^{13}C NMR and ^{31}P NMR spectra of 3,3'spiro-phosphonylpyrazole oxindole **3a**

Example 2:

The formation of 3,3'spiro-phosphonylpyrazole-oxindole **3h** was determined from its ^{1}H NMR spectrum, which indicated the appearance of a proton signal at δ 1.35-1.49 (m, 9H) due to the presence of three methyl groups in compound **3h**. Also its formation was confirmed from its ^{13}C and ^{31}P NMR spectrum. Its ^{13}C NMR spectrum shows characteristic signal peak at δ 62.0, 63.7 (d, J_{C-P} = 6.5 Hz) and 63.8 (d, J_{C-P} =

6.5 Hz) due to carbons attached to oxygen atom. The ^{31}P NMR spectrum of compound **3h** shows singlet at δ 5.50.



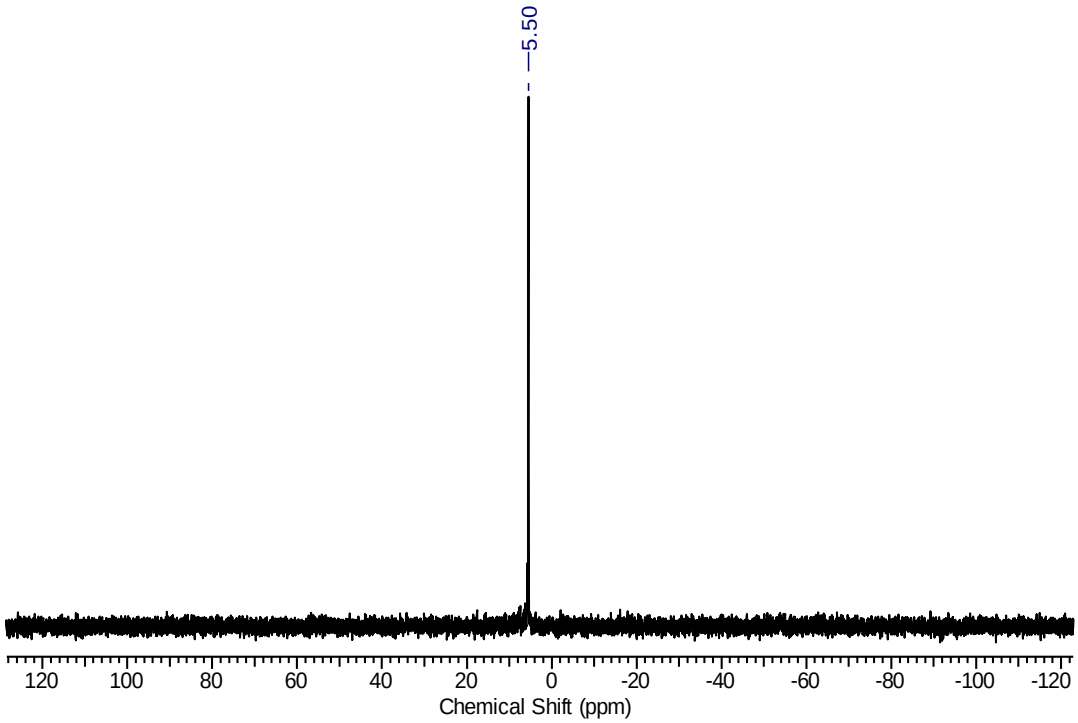
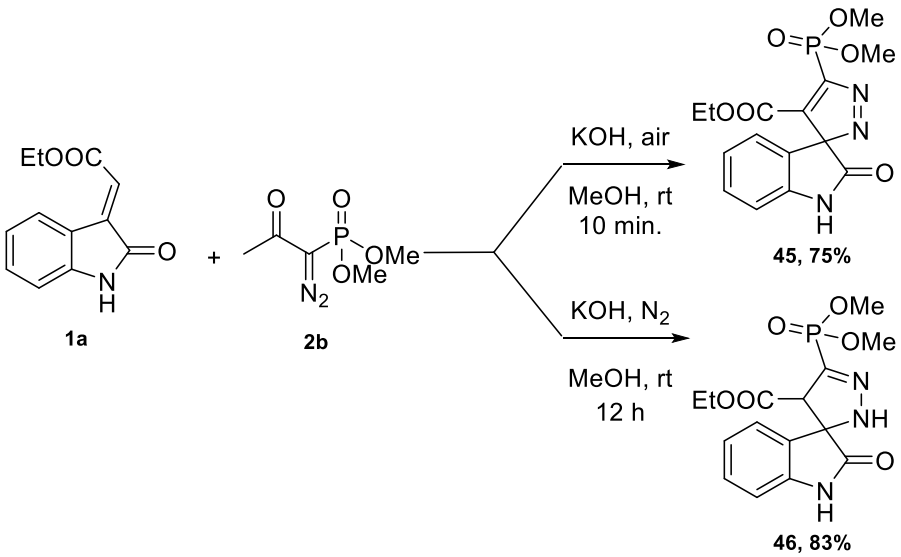


Figure 3: ^{1}H, ^{13}C NMR and ^{31}P NMR spectra of 3,3'spiro-phosphonylpyrazole oxindole **3h**

In order to gain some insight into the mechanistic details of the 1,3-dipolar reaction, the following two experiments were conducted under the optimal conditions: (Scheme **18**)



Scheme 18: Control experiments to investigate the role of air oxygen.

(a) When methyleneindolinone **1a** was treated with Bestmann-Ohira reagent **2b** in the presence of potassium hydroxide in open air, within a short reaction time (10 min.) we observed the formation of desired 3,3'-spiro-phosphonylpyrazole- oxindole **45** in good yields (75%). (b) While the same reaction when we carried out in nitrogen atmosphere, even after 12 h we did not observe formation of desired product **45** instead we got unoxidized product **46** in 83% yield. Both these experiments clearly indicate that the transformation of **45** into **46** may need the assistance of air oxygen for further oxidation to get desired product **45**.

The structure and regioselectivity of 3,3-'spiro-phosphonylpyrazole-oxindoles were unambiguously determined by X-ray crystallography of **47** (Figure 4).

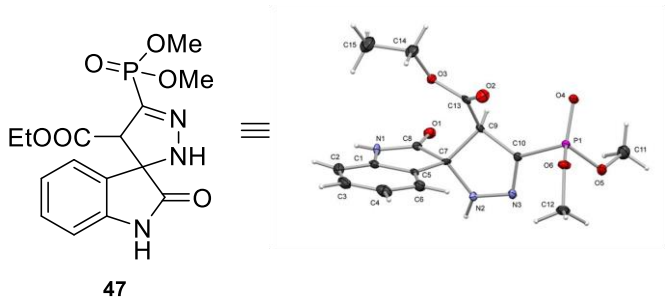
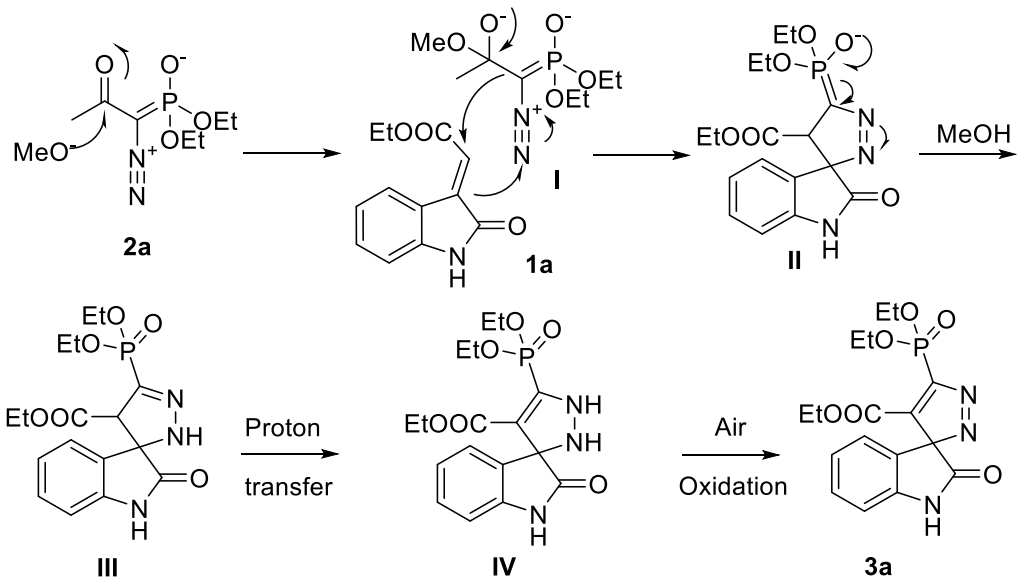


Figure 4: ORTEP diagram of **47**.

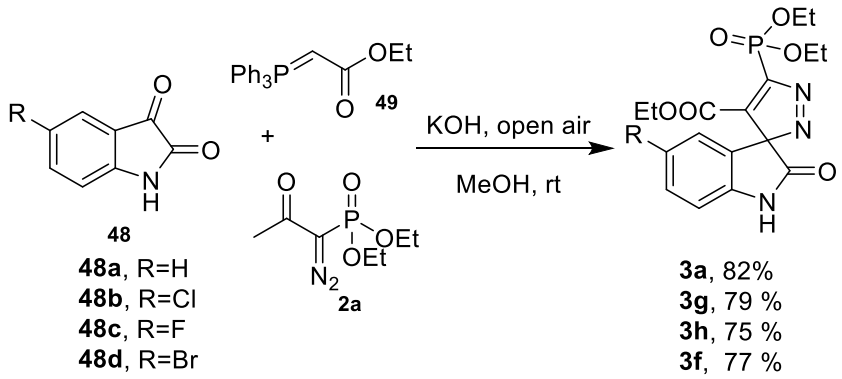
On the basis of the above experimental results, together with the related reports of 1,3-dipolar cycloaddition reaction of Bestmann-Ohira reagent, a plausible mechanism for the formation of 3,3'-spiro-phosphonylpyrazole-oxindoles is illustrated in Scheme 19. The mechanism involves deacylation of Bestmann-Ohira reagent **2a** by the nucleophilic methoxide followed by reaction of the diazo- phosphonate anion arising from I which is well known in the literature with methyleneindolinone **1a** in a 1,3-dipolar fashion to afford the initial cycloadduct II. Subsequent protonation of intermediate **II** in methanol to form Pyrazoline **III**, followed by proton transfer

(tautomerism) gives rise to intermediate **IV**. And finally air oxidation completes the reaction giving final compound **3a** (**Scheme 19**).



Scheme 19: Proposed mechanistic pathway for the formation of 3,3'-spiro phosphonylpyrazole-oxindoles **3a** from BOR **2a** and methyleneindolinone **1a**.

To demonstrate the application of our present methodology for the efficient synthesis of 3,3'-spiro-phosphonylpyrazole-oxindole, we devised a sequential multicomponent reaction (MCR) strategy as shown in Scheme 20.



Scheme 20: Sequential multicomponent reaction of isatin **48**, phosphonium ylide **49** and Bestmann-Ohira reagent (BOR) **2a**.

Based on domino Wittig reaction/1,3-dipolar cycloaddition reaction sequence, we conducted a three-component reaction between readily available isatin **48**,

phosphonium ylide **49**, and BOR reagent **2a** which smoothly proceeded to give good yields of products.

3.2.5 Conclusion

In summary, we have developed a simple one pot highly efficient and completely regioselective synthesis of 3,3'-spiro-phosphonylpyrazole-oxindoles in good yields *via* base mediated 1,3-dipolar cycloaddition reaction between methyleneindolinones and Bestmann-Ohira reagent. Attractive features of this process are 1) its versatility, mild reaction condition, short reaction time, high yield and the efficiency in creating a complex core in a single operation. 2) Provides an efficient access to series of biologically important 3,3'-spiro-phosphonylpyrazole-oxindole in good yield with excellent regioselectivity. The scope of the reaction was expanded with the development of multicomponent reaction sequence in single step. This methodology is fascinating because it provides a quick and easy access to libraries of molecules of pharmaceutical interests under mild reaction condition.

3.2.6 Experimental Section

A general experimental procedure for 1,3-dipolar cycloaddition reaction of Bestmann-Ohira reagent 44 with methyleneindolinones 43

To an oven-dried round bottom flask was added methyleneindolinones **43** (0.1 mmol, 1.0 equiv.) dissolved in 3 mL of MeOH. Subsequently, a solution of Bestmann-Ohira reagent **44** (0.2 mmol, 2.0 equiv.) in 2 mL of MeOH was added to the reaction mixture with constant stirring. After the addition of potassium hydroxide (0.2 mmol, 2.0 equiv.), the reaction mixture was stirred at 25 °C for 10 min. The solvent was evaporated and the crude reaction mixture was extracted using ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The

residue was then purified using column chromatography (100–200 mesh silica gel) using pet ether-ethyl acetate as the eluent.

A general experimental procedure for sequential multicomponent reaction of isatin 48, phosphonium ylide 49, and BOR reagent 2a

To a solution of the corresponding substituted isatin **48** (5 mmol, 1 equiv.) in methanol (30 mL) was added phosphonium ylide **49** (5 mmol, 1.1 equiv) and the mixture was stirred at room temperature for 12 h. Then a solution of Bestmann-Ohira reagent **2a** in 2 ml of MeOH was added to the reaction mixture. After the completion of reaction, as indicated by TLC, the solvent was evaporated and the crude reaction mixture was extracted using ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified using column chromatography (100–200 mesh silica gel) using pet ether-ethyl acetate as the eluent.

Ethyl 5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3a)

Yield: 84%; White solid; **mp:** 120-122 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.36-1.39 (m, 6H), 1.46 (t, *J* = 7.6 Hz, 3H), 4.28- 4.34 (m, 4H), 4.45 (q, *J* = 7.6 Hz, 1H), 7.19-7.21 (m, 1H), 7.46 (m, 2H), 8.76-8.77 (m, 1H), 11.4 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 14.6, 16.9 (d, $J_{C–P}$ = 6.4 Hz), 17.0 (d, $J_{C–P}$ = 6.4 Hz), 62.6, 64.3 (d, $J_{C–P}$ = 5.9 Hz), 64.4 (d, $J_{C–P}$ = 5.9 Hz), 112.3, 117.1, 124.5, 127.2, 132.5, 135.5, 145.1, 150.4, 163.3; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.59; **HRMS** (ESI) calcd for $C_{17}H_{20}N_3O_6NaP$ $[M+Na]^+$ 416.0982; found 416.0979.

Ethyl 1-benzyl-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3b)

Yield: 82%; White solid; **mp:** 168-170 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.41-1.51 (m, 9H), 4.29-4.37 (m, 4H), 4.48 (q, *J* = 7.5 Hz, 2H), 5.59 (s, 2H), 7.28-7.36 (m, 2H),

7.48-7.53 (m, 1H), 9.01- 9.03 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 13.3, 15.6 (d, J_{C-P} = 6.6 Hz), 15.8 (d, J_{C-P} = 6.6 Hz),, 47.5, 61.5, 63.0 (d, J_{C-P} = 6.0 Hz), 63.1(d, J_{C-P} = 6.0 Hz), 112.1, 114.9, 123.5, 125.9, 127.1 (d, J_{C-P} = 12.5 Hz), 127.3 (d, J_{C-P} = 12.5 Hz), 128.4, 131.5, 134.1, 135.0, 144.5, 162.2; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.12; **HRMS** (ESI) calcd for $C_{24}H_{26}N_3O_6NaP$ $[M+Na]^+$ 506.1451; found 506.1451.

Ethyl 5'-(diethoxyphosphoryl)-1-methyl-2-oxospiro [indoline-3,3'-pyrazole]-4'-carboxylate (3c)

Yield: 78%; White solid; **mp:** 210-212 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40-1.53 (m, 9H), 3.84 (s, 3H), 3.92- 4.40 (m, 6H), 7.59-7.67 (m, 1H), 8.94- 8.98 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 13.8, 16.1(d, J_{C-P} = 6.4 Hz), 16.3 (d, J_{C-P} = 6.4 Hz), 31.4, 61.8, 63.3 (d, J_{C-P} = 6.1 Hz), 63.4 (d, J_{C-P} = 6.1 Hz), 112.3, 113.7, 114.4, 123.8, 127.3, 132.0, 136.1, 140.3, 144.4, 150.1, 162.6; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.17; **HRMS** (ESI) calcd for $C_{18}H_{22}N_3O_6NaP$ $[M+Na]^+$ 430.1138; found 430.1137.

1-(tert-butyl)4'-ethyl 5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-1,4'-dicarboxylate (3d)

Yield: 80%; White solid; **mp:** 155-157 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.17 (t, *J* = 7.6 Hz, 3H), 1.32-1.41 (m, 6H), 1.46 (s, 9H), 4.18- 4.35 (m, 6H), 7.05-7.09 (m, 1H), 7.30-7.40 (m, 1H), 7.55-7.67 (m, 1H), 7.99-8.01 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 13.8, 16.32 (d, J_{C-P} = 6.6 Hz), 16.39 (d, J_{C-P} = 6.6 Hz), 28.3, 61.0, 63.7 (d, J_{C-P} = 6.0 Hz), 63.8 (d, J_{C-P} = 6.0 Hz), 80.4, 122.8, 128.3, 130.0, 130.9, 136.7, 153.2, 162.3; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 5.03; **HRMS** (ESI) calcd for $C_{22}H_{28}N_3O_8NaP$ $[M+Na]^+$ 516.1512; found 516.1515.

Methyl 5'-(diethoxyphosphoryl)-2-oxospiro [indoline-3,3'-pyrazole]-4'-carboxylate (3e)

Yield: 77%; Yellow orange powder; **mp:** 178-180 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.34-1.42 (m, 6H), 4.0 (s, 3H), 4.28-4.35 (m, 4H), 7.36-7.43 (m, 2H), 7.50-7.56 (m, 1H), 8.78-8.85 (m, 1H), 11.0 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 16.3 (d, J_{C-P} = 6.9 Hz), 16.4 (d, J_{C-P} = 6.9 Hz), 52.5, 63.82 (d, J_{C-P} = 6.4 Hz), 63.87 (d, J_{C-P} = 6.4 Hz), 117.7, 116.3, 124.2, 126.8, 132.1, 134.6, 144.5, 163.0; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.26; **HRMS** (ESI) calcd for $C_{16}H_{18}N_3O_6NaP$ $[M+Na]^+$ 402.0825; found 402.0846.

Ethyl 5-bromo-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3f)

Yield: 81%; White solid; **mp:** 175-177 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.35-1.50 (m, 9H), 4.29-4.33 (m, 4H), 4.46-4.50 (q, J = 7.2 Hz, 2H), 7.39-7.55 (m, 2H), 9.00-9.03 (m, 1H), 11.6 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.0, 16.34 (d, J_{C-P} = 5.4 Hz), 16.39 (d, J_{C-P} = 5.4 Hz), 62.1, 63.80 (d, J_{C-P} = 6.1 Hz), 63.85 (d, J_{C-P} = 6.1 Hz), 113.1, 116.6, 118.2, 129.2, 131.9, 134.1 (d, J_{C-P} = 16.4 Hz), 134.8 (d, J_{C-P} = 16.4 Hz), 140.8, 143.9, 148.7, 162.2; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.52; **HRMS** (ESI) calcd for $C_{17}H_{20}N_3O_6BrP$ $[M+H]^+$ 472.0268; found 472.0265.

Ethyl 5-chloro-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3g)

Yield: 80%; White solid; **mp:** 190-192 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.35-1.50 (m, 9H), 4.27-4.33 (m, 4H), 4.45-4.50 (q, J = 7.2 Hz, 2H), 7.37-7.47 (m, 2H), 8.86 (d, J = 2.0 Hz ,1H), 11.6 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.0, 16.32 (d, J_{C-P} = 6.4 Hz), 16.38 (d, J_{C-P} = 6.4 Hz), 62.0, 63.83 (d, J_{C-P} = 5.7 Hz), 63.89 (d, J_{C-P} = 5.7 Hz), 112.7, 118.0, 126.2, 129.2, 132.0 (d, J_{C-P} = 22.6 Hz), 133.7 (d, J_{C-P} = 22.6 Hz), 140.9, 143.7, 146.5, 148.8, 162.2; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.45; **HRMS** (ESI) calcd for $C_{17}H_{20}N_3O_6ClP$ $[M+H]^+$ 428.0775; found 428.0773.

Ethyl 5'-(diethoxyphosphoryl)-5-fluoro-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3h)

Yield: 76%; White solid; **mp:** 194-196 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.35-1.49 (m, 9H), 4.29-4.33 (m, 4H), 4.44- 4.50 (q, *J* = 7.0 Hz, 2H), 7.19-7.23 (m, 1H), 7.49-7.52 (m, 1H), 8.60-8.63 (m, 1H), 11.6 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.0, 16.30 (d, J_{C-P} = 6.1 Hz), 16.37 (d, J_{C-P} = 6.1 Hz), 62.0, 63.7 (d, J_{C-P} = 6.5 Hz), 63.8 (d, J_{C-P} = 6.5 Hz), 112.6, 118.3, 120.0, 131.6, 141.4, 143.9, 146.2, 148.8, 157.2, 159.6, 162.3; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 5.50; **HRMS** (ESI) calcd for $C_{17}H_{20}N_3O_6FP$ $[M+H]^+$ 412.1068; found 412.1065.

Ethyl 5'-(diethoxyphosphoryl)-5-methoxy-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3i)

Yield: 85%; White solid; **mp:** 212-214 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.37-1.49 (m, 9H), 3.84 (s, 3H), 4.29- 4.48 (m, 6H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 8.48 (s, 1H),11.1 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 14.0, 14.3, 16.4, 55.6, 61.9, 63.7 (d, J_{C-P} = 6.4 Hz), 63.8 (d, J_{C-P} = 6.4 Hz), 108.7, 112.4, 114.0, 114.2, 117.6, 121.1, 128.7, 142.3, 144.3, 156.0, 162.6; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.52; **HRMS** (ESI) calcd for $C_{18}H_{22}N_3O_7PNa$ $[M+Na]^+$ 446.1088; found 446.1106.

Ethyl5'(diethoxyphosphoryl)2oxo5(trifluoromethoxy)spiro[indoline-3,3'-pyrazole]-4'-carboxylate (3j)

Yield: 82%; White solid; **mp:** 164-166 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.37-1.49 (m, 9H), 3.84 (s, 3H), 4.29-4.48 (m, 6H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 8.48 (s, 1H),11.1 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.0, 16.4 (d, J_{C-P} = 6.6 Hz), 16.5 (d, J_{C-P} = 6.6 Hz), 62.1 (d, J_{C-P} = 5.8 Hz), 62.2 (d, J_{C-P} = 5.8 Hz), 64.3, 112.6, 117.8, 118.4, 118.9, 119.3 (d, J_{C-P} = 25.4 Hz), 119.5 (d, J_{C-P} = 25.4 Hz),

121.8, 125.3, 144.9, 153.3, 162.0; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.54; **HRMS** (ESI) calcd for $C_{18}H_{19}N_3O_7F_3PNa$ $[M+Na]^+$ 500.0805; found 500.0824.

Ethyl 5'-(diethoxyphosphoryl)-5-nitro-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3k)

Yield: 79%; Brown solid; **mp:** 185-187 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.32-1.44 (m, 9H), 3.87 (q, *J* = 7.2 Hz, 2H), 4.13 (m, 4H), 7.68 (s, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 8.16 (dd, *J* = 2.0, 7.2 Hz, 1H), 9.91 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 13.7, 16.3 (d, J_{C-P} = 6.5 Hz), 16.4 (d, J_{C-P} = 6.5 Hz), 61.9, 63.4 (d, J_{C-P} = 5.7 Hz), 63.6 (d, J_{C-P} = 5.7 Hz), 111.0, 121.1, 137.1, 139.5, 143.2, 148.1, 165.9, 177.6; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.27; **HRMS** (ESI) calcd for $C_{17}H_{19}N_4O_8PNa$ $[M+Na]^+$ 461.0838; found 461.0842.

Methyl 5'-(dimethoxyphosphoryl)-2-oxospiro[indoline-3,3' pyrazole]-4'-carboxylate (3l)

Yield: 83%; White solid; **mp:** 202-204 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 3.99 (s, 3H), 4.04 (s, 3H), 7.30-7.37 (m, 1H), 7.41-7.60 (m, 2H), 8.85 (d, *J* = 7.2 Hz, 1H), 11.1 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 52.5, 54.13 (d, J_{C-P} = 5.0 Hz), 54.17 (d, J_{C-P} = 5.0 Hz), 111.8, 114.2, 116.3, 124.2, 127.0, 132.1, 134.8, 142.4, 144.5, 146.5, 162.8; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.01; **HRMS** (ESI) calcd for $C_{14}H_{14}N_3O_6PNa$ $[M+Na]^+$ 374.0512; found 374.0893.

Ethyl 4-chloro-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3m)

Yield: 79%; White solid; **mp:** 180-182 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.34-1.52 (m, 9H), 4.24- 4.55 (m, 6H), 7.39-7.63 (m, 3H), 11.4 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 13.9, 16.2 (d, J_{C-P} = 6.2 Hz), 16.3 (d, J_{C-P} = 6.2 Hz), 62.0, 63.7 (d, J_{C-P} = 5.2 Hz), 63.8 (d, J_{C-P} = 5.2 Hz), 112.5, 112.6, 112.8, 114.4 (d, J_{C-P} = 28.2 Hz) , 114.6

(d, J_{C-P} = 28.2 Hz), 118.2, 119.7, 120.0, 131.6, 141.3, 143.8, 146.5, 148.7, 157.1, 159.5, 162.2; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 5.50; **HRMS** (ESI) calcd for $C_{17}H_{20}N_3O_6ClP$ $[M+H]^+$ 428.0775; found 428.0774.

Ethyl 6-bromo-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3n)

Yield: 84%; White solid; **mp:** 168-170 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.36-1.54 (m, 9H), 4.25-4.57 (m, 6H), 7.41-7.74 (m, 2H), 8.99 (d, *J* = 8.0 Hz, 1H), 10.5 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 13.6, 15.9 (d, J_{C-P} = 6.3 Hz), 16.0 (d, J_{C-P} = 6.3 Hz), 61.7, 63.4 (d, J_{C-P} = 5.3 Hz), 63.5 (d, J_{C-P} = 5.3 Hz), 112.2, 112.3, 112.5, 114.1 (d, J_{C-P} = 22.5 Hz), 114.3 (d, J_{C-P} = 22.5 Hz), 117.9, 119.5, 119.7, 131.3, 141.0, 143.6, 146.2, 148.4, 156.8, 159.3, 161.9; **^{31}P NMR** (202.4 MHz, $CDCl_3$) δ: 6.26; **HRMS** (ESI) calcd for $C_{17}H_{20}N_3O_6BrP$ $[M+H]^+$ 472.0268; found 472.0266.

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CHAPTER IV

Synthesis of 1,4,5,6 Tetrahydropyridazines and 1,4-Dihydrocinnolines *via* [4+2] Cyclodimerization of in Situ Generated Azoalkenes

1. "Fluoride assisted synthesis of 1, 4, 5, 6 tetrahydropyridazines *via* [4+2] cyclodimerization of *in situ* generated azoalkenes followed by a C-N bond cleavage" **Shelke, A. M.;** Suryavanshi, G., *Org. lett.* , **2016**, *18*, 3968.

2. "[4+2] Cycloaddition of in situ generated 1,2-diaza-1,3-dienes with arynes: facile approaches to 1,4 dihydrocinnolines" **Shelke, A. M.;** Suryavanshi, G. (*manuscript under preparation*)

Section I

Fluoride-Assisted Synthesis of 1,4,5,6-Tetrahydropyridazines *via* [4+2] Cyclodimerization of in Situ-Generated Azoalkenes Followed by a C-N Bond Cleavage

4.1.1 Introduction

1,4,5,6-Tetrahydropyridazines[1] and pyridazines[2] are important six-membered aza-heterocycles widely present as core structures in a large number of natural products (e.g. pyridazomycin[3] and azamerone[4]) as well as a structural subunit found in a variety of bioactive molecules and pharmaceuticals[5,6] such as the antihypertensives hydralzine, dihydralzine, and endralazine and the antidepressants pipofezine and minaprine[7] (**Figure 1**). Moreover, pyridazine derivatives are currently considered to be one of the most developable heterocyclic skeletons for small molecule-based drug design.[2,8]

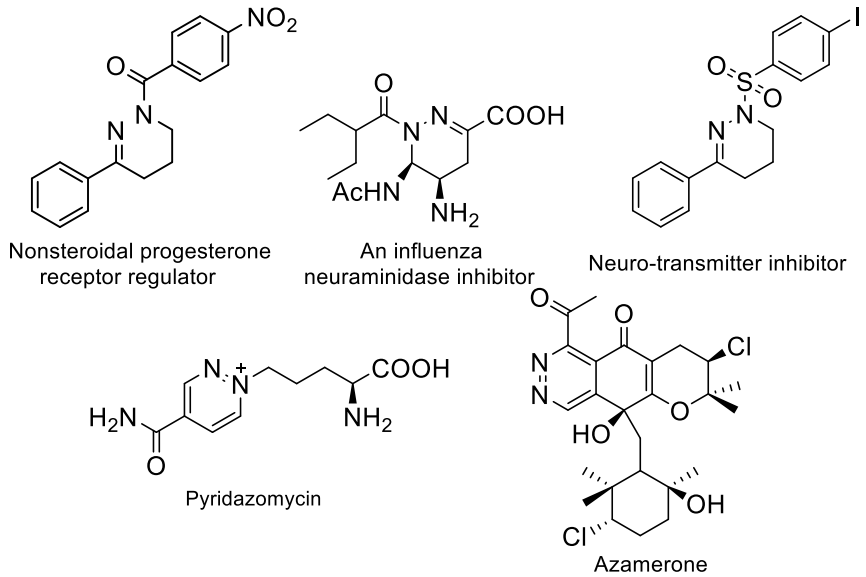


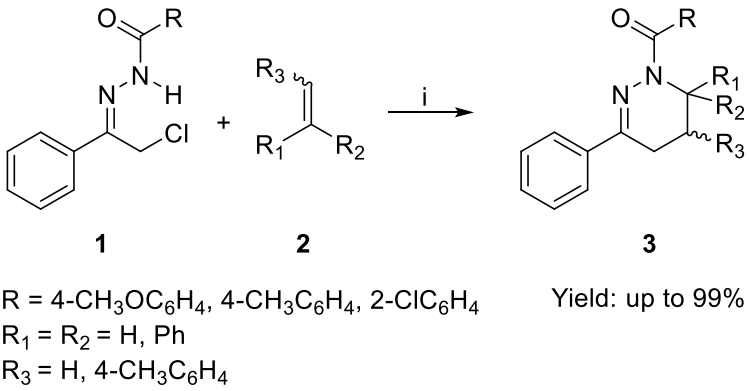
Figure 1: Biologically active tetrahydropyridazine derivatives and natural products containing a pyridazine core.

4.1.2 Review of Literature

Literature search revealed that there are few methods available for the synthesis of 1,4,5,6-tetrahydropyridazines [9-13], some of which are described below.

Luo's approach (2015)[9]

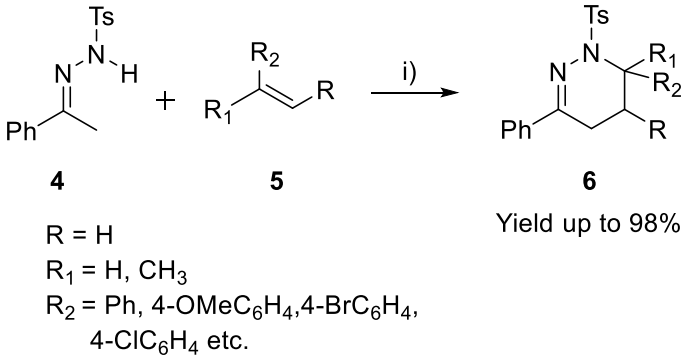
Luo *et al*. have described a catalyst-free [4+2] annulation process between *in-situ* generated 1,2-diaza-1,3-butadienes from various substituted *α*-chloro N-benzoyl hydrazone **1** and substituted olefins **2** for the synthesis of 1,4,5,6-tetrahydropyridazines **3**. Under mild reaction conditions, the reactions afforded 1,4,5,6-tetrahydropyridazines **3**, which feature a wide range of bioactive compounds, with high yields (up to 99% yield) (**Scheme 1**).



Scheme 1: (i) **1** (0.40 mmol), **2** (3.0 equiv.) K_2CO_3 (2.0 equiv.), CH_2Cl_2, rt, 24 h.

Luo's second approach (2016)[10]

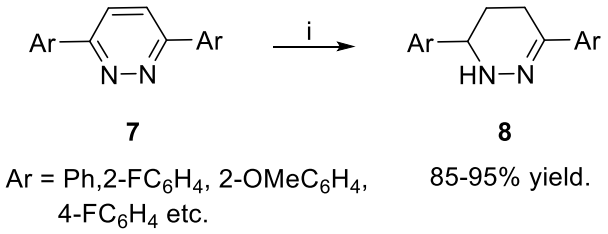
In another approach, Luo *et al.* have developed an unprecedented binary acid accelerated oxidative radical annulation of sulfonyl hydrazones **4** with simple and substituted olefins **5** which leads to the formation of 1,4,5,6-tetrahydropyridazines **6**. Notably, this method provides a novel oxidative radical cycloaddition for the construction of six-membered heterocycles. The yields of the products were obtained upto 98% yield (**Scheme 2**).



Scheme 2: (i) I_2 (5 mol%), TBHP (4.0 equiv.), Cu (I), $(PhO)_2P(O)OH$, CH_3CN, rt, 24 h .

Du's approach (2016)[11]

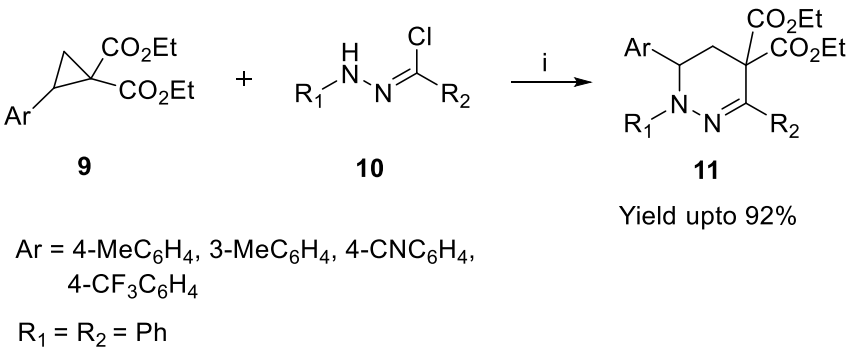
Du *et al.* have achieved the synthesis of 1,4,5,6-tetrahydropyridazine derivatives **8** *via* metal free hydrogenation of 3,6-diarylpyridazines **7** using $B(C_6F_5)_3$ as a catalyst. A variety of 1,4,5,6-tetrahydropyridazine derivatives **8** were furnished in 85-95% yields (**Scheme 3**).



Scheme 3: (i) $B(C_6H_5)_3$ (10 mol%), H_2 (20 bar), toluene, 120 °C, 6 h.

Werz's approach (2016)[12]

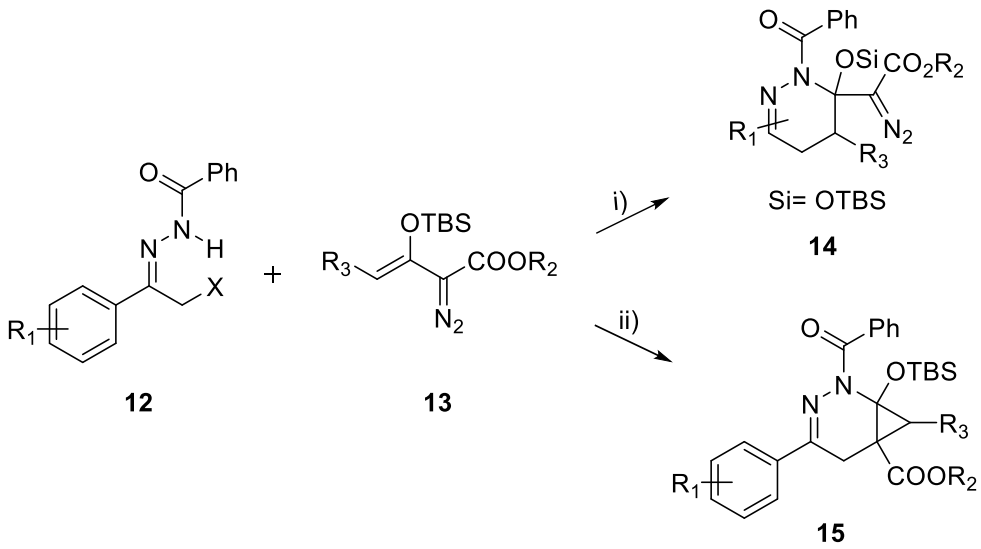
Werz *et al*. have reported a useful method for the synthesis of tetrahydropyridazines **11** from Donor-acceptor cyclopropanes **9** and hydrazonyl chlorides **10** under the influence of a Lewis acid. This transformation occurs through [3+3]-cycloaddition of three-membered rings and nitrile imines generated *in-situ*. This efficient method provides fast access to a variety of structurally diverse pyridazine derivatives **11** (**Scheme 4**).



Scheme 4: (i) **9** (0.15 mmol, **10** (0.10 mmol), imidazole (0.15 mmol), $TiCl_4$ (20 mol%) CH_2Cl_2 (2 ml), 45 °C, 16 h.

Doyle's approach (2016)[13]

Doyle *et al.* reported the synthesis of tetrahydropyridazine **14** & **15** and tetrahydro-1,2-diazepine scaffolds through cycloaddition reactions of azoalkenes with enol diazoacetates **13**. A [4+2]-cycloaddition of enol diazoacetates **13** with *in situ* formed azoalkenes produces tetrahydropyridazinyl-substituted diazoacetates promoted by only Cs_2CO_3. The Donor-acceptor cyclopropenes, which are formed *in situ* from enol diazoacetates by $Rh_2(OAc)_4$-catalyzed dinitrogen extrusion, undergo [4+2]-cycloaddition with azoalkenes to yield bicyclo[4.1.0]tetrahydropyridazines **15**).



Scheme 5: (i) **12** (0.3 mmol, 1.5 equiv.), **13** (0.20 mmol, 1.0 equiv.), $CsCO_3$ (0.40 mmol, 2 equiv.), 4 Å MS, dichloromethane, 30 min., rt; (ii) **12** (0.3 mmol, 1.5 equiv.), **13** (0.20 mmol, 1.0 equiv.), $CsCO_3$ (0.40 mmol, 2 equiv.), $Rh_2(OAc)_4$ (0.002 mmol), 4 Å MS, 3h, rt.

(**Scheme 5)**.

4.1.3 Present Work

4.1.3.1 Objective

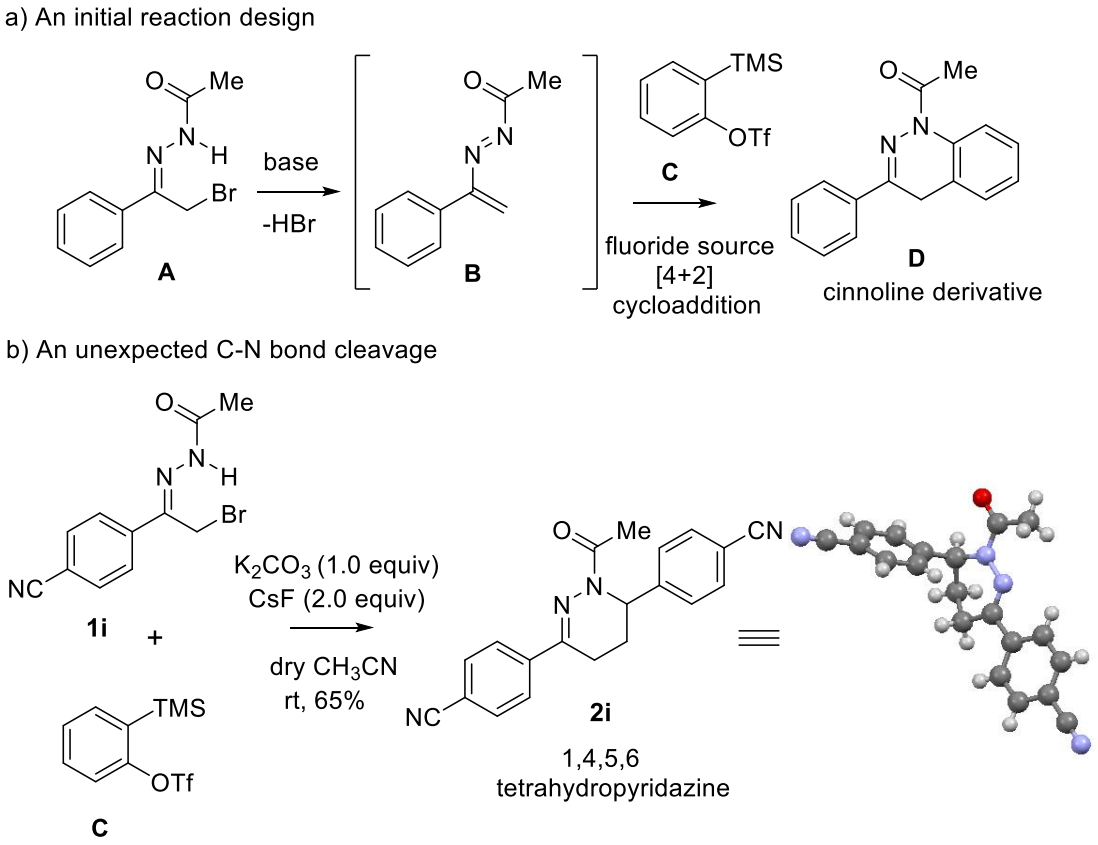
As can be seen from the above discussion, several research groups have been engaged in the development of protocols to synthesize these privileged structures using various methods such as aza-Diels-Alder reactions of 1,2-diaza-1,3-dienes with olefins,[14] nucleophilic addition reactions,[15] and rearrangement reactions.[16] Conventional methods for tetrahydropyridazine synthesis are based on the reaction of hydrazine or its derivatives with 1,4- dicarbonyl compounds.[6a,17,18] Recently, the research groups of Luo[9-10] and Du[11] have developed an efficient method for the synthesis of 1,4,5,6-tetrahydropyridazines. Later, Werz and coworkers described an alternative method for the preparation of functionalized tetrahydropyridazines using a Lewis acid *via* a [3+3] cycloaddition reaction.[12]

The few interesting methods known in the literature for the synthesis of 1,4,5,6-tetrahydropyridazines[9-13] suffer from many disadvantages, such as limited substrate scope,[14d,g–i,k,19,20] the requirement of a large excess of alkene as the dienophile partner,[9] and harsh reaction conditions.[11,14m] Therefore, the development of more general strategies that allow rapid access to these structurally diversified 1,4,5,6-tetrahydropyridazines from readily accessible starting materials is still highly desirable and challenging in synthetic organic chemistry. Herein we report a simple, versatile, and novel route to highly functionalized 1,4,5,6-tetrahydropyridazine derivatives from α-halo N-acylhydrazones as the only starting material, which acts as both the diene and the dienophile. Azoalkenes (1,2-diaza-1,3-dienes),[19] which can be easily generated in situ from α-halo hydrazones, have been commonly introduced as a valuable synthetic intermediate for the construction of various N-heterocycles.

Recently, a broad range of transformations has been established using azoalkenes as a suitable chemical handle.

4.1.4 Results and Discussion

In this context, considering the high reactivity of azoalkenes and as a part of our ongoing efforts to transform readily accessible substrates into synthetically important N-heterocycles,[20] we envisioned that treatment of *α*-halo N-acylhydrazone **A** with base would afford azadiene **B** in situ, which upon treatment with aryne precursor **C** would facilitate an intermolecular [4+2] cycloaddition reaction to offer cinnoline derivative **D** (**Scheme 6**). In order to test our hypothesis, *α*-halo N-acylhydrazone **1i** was treated with K_2CO_3 (1.0 equiv) in the presence of freshly generated benzyne in CH_3CN at room temperature.



Scheme 6: Initial Reaction Design and an Unexpected C-N Bond Cleavage

After 24 h, a single product **2i** (65% yield) was observed, which was confirmed unambiguously as 4,4′-(1-acetyl-1,4,5,6-tetrahydropyridazine-3,6-diyl)dibenzonitrile by single-crystal XRD analysis.[21] The formation of **2i** was further confirmed by its ^{1}H and ^{13}C NMR analysis.

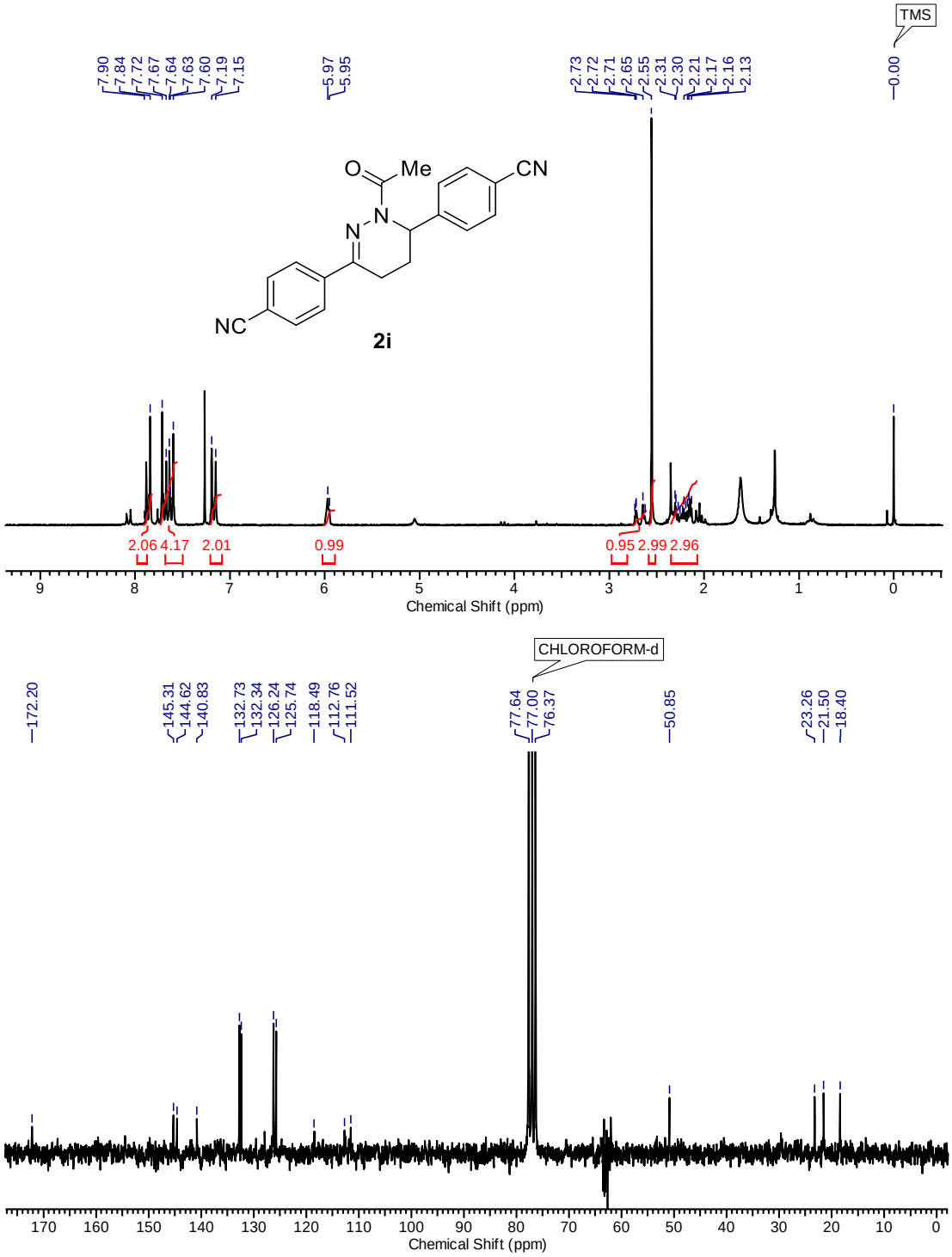


Figure 2: ^{1}H and ^{13}C NMR spectra of **2i**

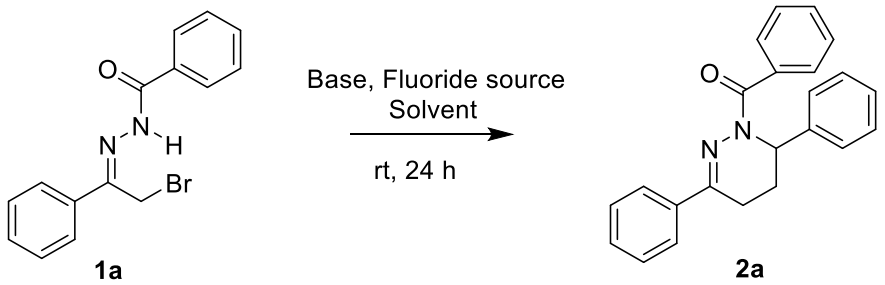
The ^{1}H NMR spectrum of compound **2i** showed doublet at δ 5.95 (d, 1H) due to the presence of benzylic proton (-C**H**-N) attached to nitrogen in compound **2i** and multiplet at δ 2.13-2.31 (m, 3H) and 2.73 (m, 1H) due to the four methylene protons (-C**H**$_2$-) in compound **2i**. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 18.4 and 23.2 due to the presence of two methylene carbons (-**C**H$_2$-) in compound **2i**. The presence of carbonyl group (-**C**O-) was confirmed by the presence of a characteristics signal at δ 172.2 due to the amide functionality **(Figure 2)**. 1,2-Diaza-1,3-dienes bearing no substituents at C4 show a tendency to self-condense, giving cyclic dimers in the presence of base when unsuitable or inefficient partners for the cycloaddition reaction are present.[22] Although the desired cinnoline derivative was not obtained, we were surprised to observe an unexpected C-N bond cleavage in the presence of fluoride leading to 1,4,5,6- tetrahydropyridazine derivatives in quite good yields under very mild reaction conditions. This result inspired us to examine the scope and generality of the present methodology.

Optimization of the Reaction Conditions:

We started our investigation by taking **1a** as a model substrate for determining optimal reaction conditions for the cyclodimerization reaction to form **2a (**Table **1)**. Several experiments were performed to investigate the effect of solvent, base and fluoride source on the reaction. As highlighted in Table **1**, the choice of base as well as fluoride source had a great influence on the reaction. Initially, treatment of **1a** with 2.0 equiv of Na_2CO_3 in the presence of CsF (2.0 equiv) as the fluoride source in CH_2Cl_2, delivered 35% of the desired 1,4,5,6 tetrahydropyridazine product **2a** (Table **1**, entry **1**). Gratifyingly, solvent switching from CH_2Cl_2 to CH_3CN improved the yield of **2a** (Table **1**, entry **2**) whereas yields dropped when Et_2O, THF, toluene are used (Table **1**, entry **3**, **4** and **8**) and no product formed in H_2O (Table **1**, entry **7**).

After screening of solvents, we moved our attention to find out compatible base and fluoride source for the cyclodimerization reaction. Notably, the inorganic bases 2.0 equiv (Na_2CO_3, K_2CO_3, Cs_2CO_3 and KOH) gave comparatively good results (Table **1**, entry **2**, **5**, **12** and **13**) while use of organic bases such as triethyl amine and pyridine

Table 1. Optimization of reaction condition for the fluoride assisted unexpected C-N bond cleavage for the synthesis of 1,4,5,6 tetrahydropyridazines [a, b]



1a **2a**

Entry	Fluoride-source (2.0 equiv)	Base (2.0 equiv)	Solvent	Yield (%)[b]
1	CsF	Na_2CO_3	CH_2Cl_2	35
2	CsF	Na_2CO_3	CH_3CN	62
3	CsF	K_2CO_3	Et_2O	20
4	CsF	K_2CO_3	Toluene	traces
5	**CsF**	**K_2CO_3**	**CH_3CN**	**91**
6	-	K_2CO_3	CH_3CN	0
7	CsF	K_2CO_3	H_2O	No reaction
8	CsF	K_2CO_3	THF	traces
9	CsF	K_2CO_3	MeOH	42
10	CsF	NEt_3	CH_3CN	30
11	TBAF	DIPEA	CH_3CN	No reaction
12	TBAF	Cs_2CO_3	CH_3CN	60

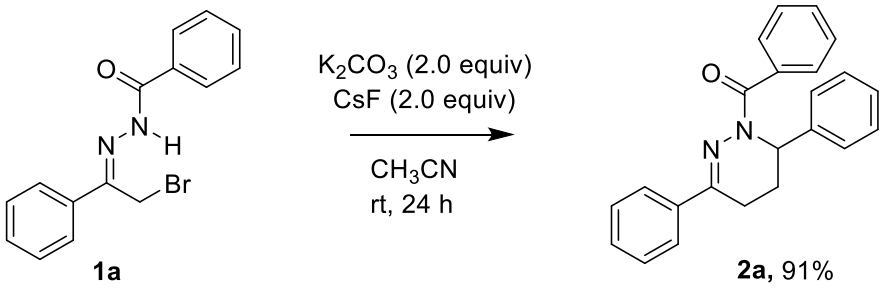
13	KF/18 crown 6	KOH	CH_3CN	65
14	CsF	Pyridine	CH_3CN	traces

[a] Substrate **1a** (0.5 mmol), fluoride source (1 mmol), base (1 mmol) solvent (3 mL), 24 h; [b] Isolated yield after column chromatographic purification.

results in decreased reaction yields (Table **1**, entry **10** and **14**). A control experiment without fluoride source showed no formation of **2a**, thus confirming the crucial role of cesium fluoride in the reaction (Table **1**, entry **6**). After examining a series of organic and inorganic bases along with fluoride sources such as CsF, TBAF and KF/18 crown 6, K_2CO_3 (2.0 equiv) as a base, CsF (2.0 equiv) as a fluoride source and CH_3CN as a solvent was selected as the best reaction condition for cyclodimerization reaction, resulting in the 91% yield of **2a** (Table **1,** entry **5**). Attempts to decrease the amount of both fluoride source and base resulted in much lower yields of desired product **2a**.

After performing various experiments, we were pleased to find that the cyclodimerization reaction proceeded very well in the presence of K_2CO_3 (2.0 equiv) and CsF (2.0 equiv) in CH_3CN as the solvent, resulting in a 91% yield of **2a** (**Scheme 7**).

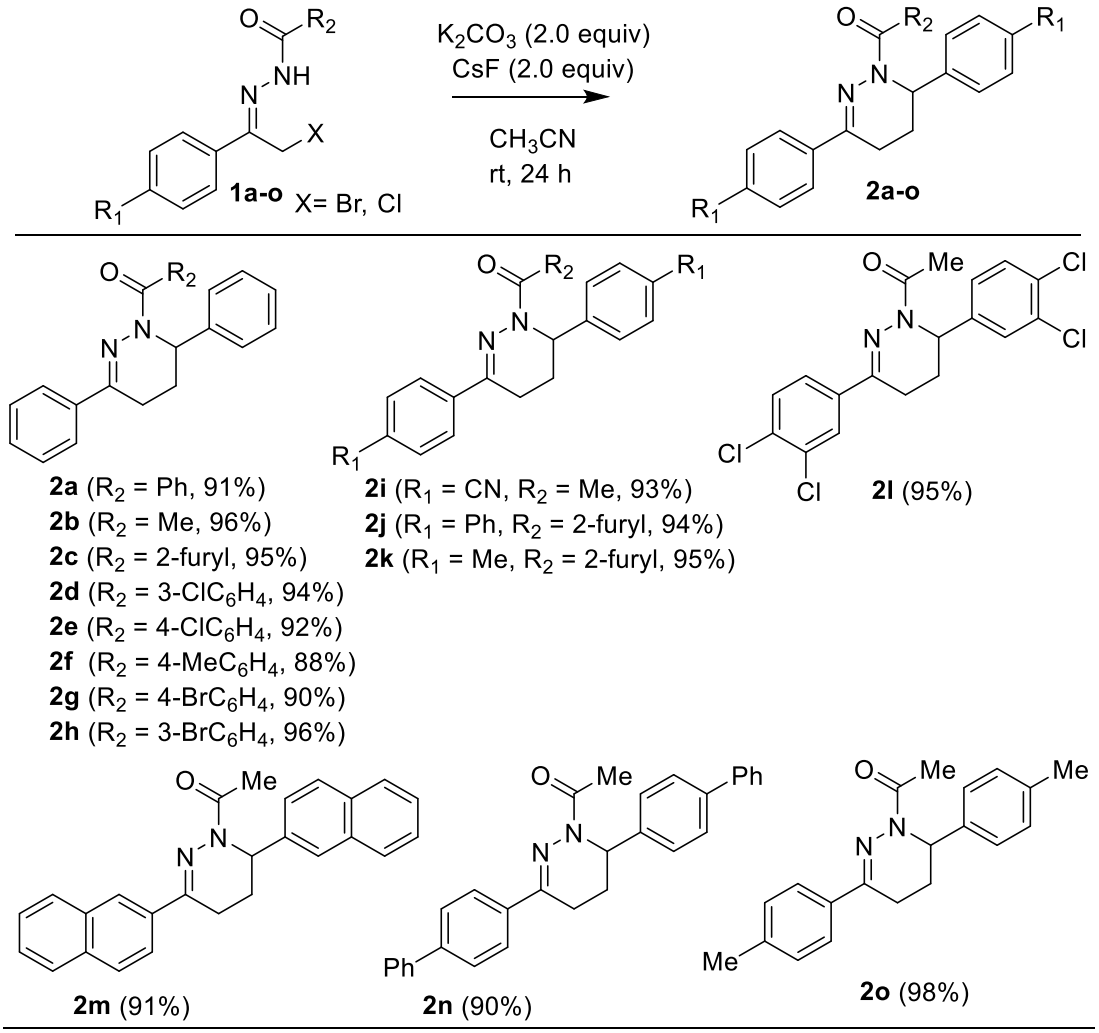
Scheme 7: 1,4,5,6-Tetrahydropyridazine Synthesis



With these optimized reaction conditions in hand, the substrate scope of this unique transformation and limitations of the homocyclodimerization reaction were studied by evaluating a variety of α-halo N-acylhydrazones in order to investigate the generality

of this reaction. As illustrated in **Scheme 8**, the reaction proceeded effectively with several substrates and was not found to be much dependent on the electronic nature of the substituents, affording a wide range of 1,4,5,6-tetrahydropyridazines (**2a-o**) in good to excellent yields. In most of the cases, 1,4,5,6-tetrahydropyridazines could be

Scheme 8: Scope of the Homocyclodimerization Reaction[a,b]



[a]The reaction were carried out with **1a-o** (0.5 mmol), K_2CO_3 (1.0 mmol), CsF (1.0 mmol), CH_3CN (dry, 3 mL) at rt for 24 h; [b]Isolated yields after column chromatographic purification.

isolated in greater than 90% yield after column chromatography on silica gel. The flexibility of the process allows the strategic placement of functional groups. For instance, **2d**, **2e**, **2g**, **2h**, and **2l**, which contain chlorine and bromine atoms, were easily prepared and could be additionally derivatized, thereby providing a convenient

alternative for the generation of a broad range of analogues. To our delight, not much electronic effect of R_2 on the aromatic ring was observed. Electron-donating, -withdrawing, and -neutral groups gave almost similar yields of 1,4,5,6-tetrahydropyridazines (**Scheme 8**). Meta-substituted derivatives also worked well, providing comparatively better yields than their para-substituted counterparts (**2d** vs **2e** and **2h** vs **2g**). Notably, 2-furoic hydrazones could undergo homocyclodimerization, giving good yields of the desired products (**2c**, **2j**, and **2k**). Variations of the R_1 group were also tested. As can be seen from **Scheme 8**, electron-donating and -withdrawing groups could be equally applied in this reaction, giving good yields of products. The formation of **2a-2o** was established unambiguously from the corresponding ^1H, ^{13}C, IR & and HRMS spectral data as presented in the following examples.

For Homocyclodimerization:

Example 1:

The structure of 1,4,5,6 tetrahydropyridazine derivative **2a** was confirmed from its ^1H NMR spectrum, which showed singlet at δ 6.07 (s, 1H) due to the presence of benzylic proton (-C**H**-N) attached to nitrogen in **2a** and multiplet at δ 2.12-2.39 (m, 3H) and 2.62-2.67 (m, 1H) due to the four methylene protons (-C**H**$_2$-) in compound **2a**. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 18.5 and 23.8 due to presence of two methylene carbons (-**C**H$_2$-) in compound **2a**. The presence of carbonyl group (-CO-) was ascertained by the presence of a characteristics signal at δ 170.1 due to amide group in **2a (Figure 3)**.

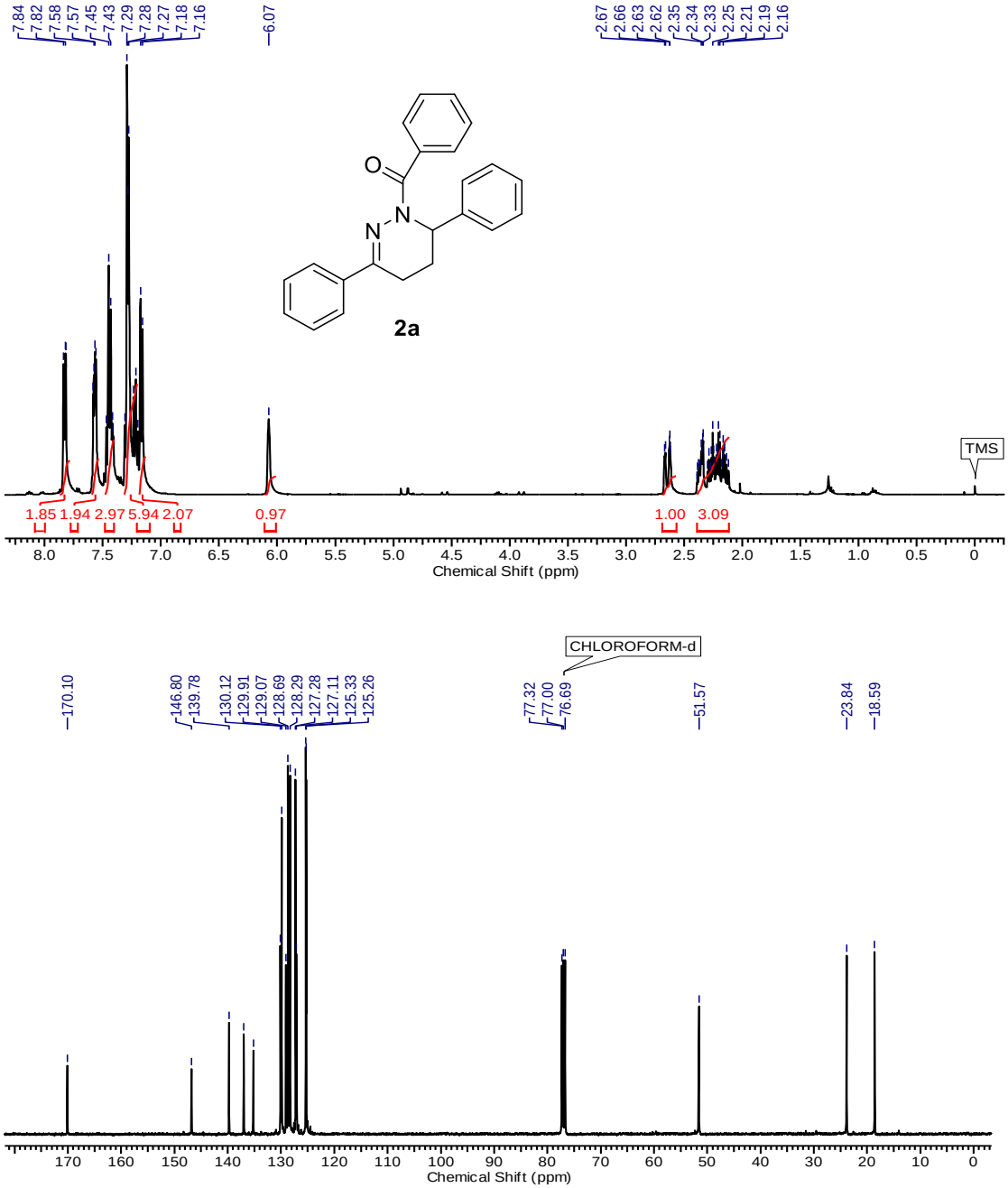


Figure 3: ^{1}H and ^{13}C NMR spectra of **2a**

Example 2:

The ^{1}H NMR spectrum of **2m** showed a typical singlet at δ 6.13 (s, 1H) corresponding to the benzylic proton (-C**H**-N) attached to nitrogen in **2m**. Also, its ^{13}C NMR spectrum displayed two carbon signals at δ 18.6 and 21.7 due to the presence of two methylene carbons (-**C**H_2-) in compound **2m (Figure 4)**.

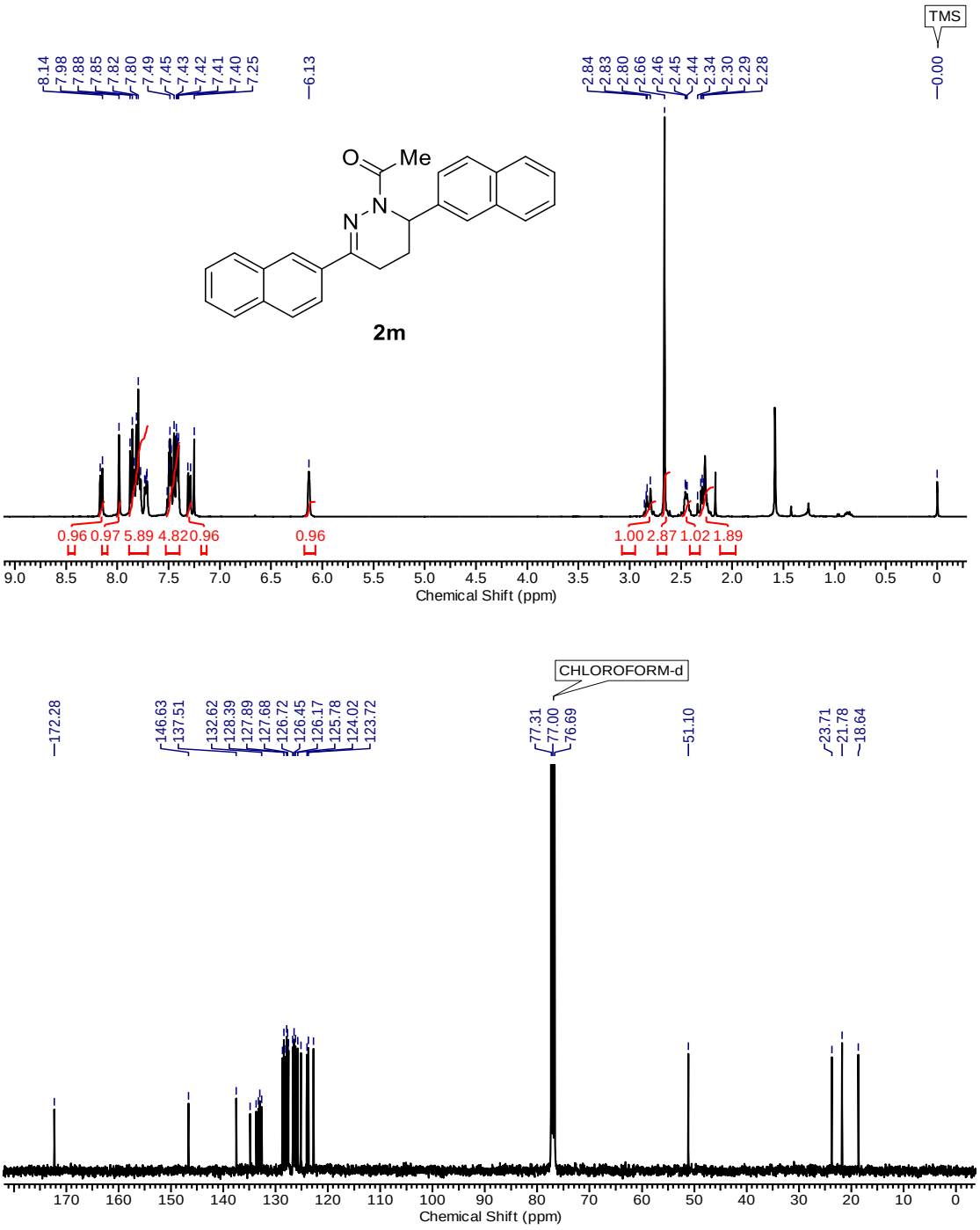
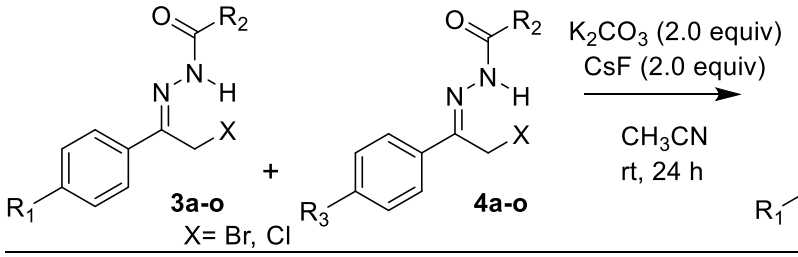


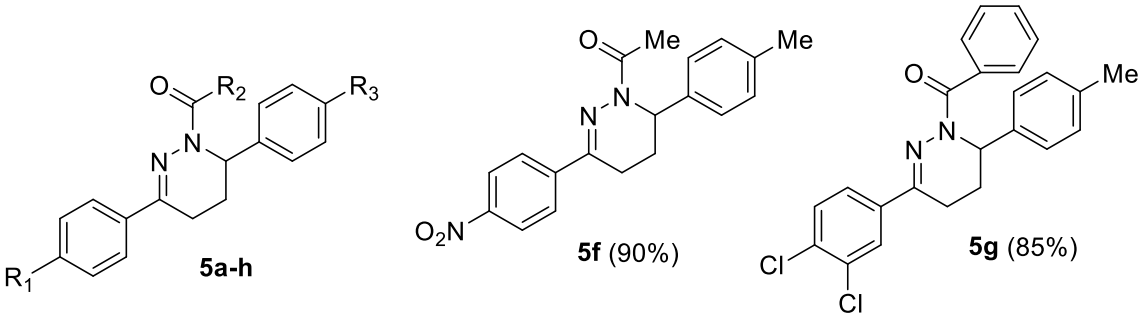
Figure 4: ^{1}H and ^{13}C NMR spectra of **2m**

The success in the homocyclodimerization prompted us to investigate the cross-cyclodimerization reaction. Competition experiments between an *α*-halo N-acylhydrazone with another *α*-halo N-acylhydrazone in excess resulted in the formation of the heterocyclodimerization products in good yields (e.g., **5a-o** in **Scheme 9**). As presented in **Scheme 9**, both electron-donating and -withdrawing

groups on the aromatic ring of the α-halo Nacylhydrazone were compatible with this cross-cyclodimerization reaction, yielding the desired products in 85-98% yield. This indicates the broad substrate scope and importance of the present reaction. Alkyl-substituted hydrazones, α-substituted aryl hydrazones, other electron-deficient olefins, and alkynes failed to give the desired products.

Scheme 9: Scope of the Cross-Cyclodimerization Reaction[a,b]





5a (R_1 = Ph, R_2 = Me, R_3 = H, 94%)
5b (R_1 = 2-naphthyl, R_2 = Me, R_3 = H, 90%)
5c (R_1 = 2-naphthyl, R_2 = Me, R_3 = Me, 92%)
5d (R_1 = CN, R_2 = Ph, R_3 = H, 98%)
5e (R_1 = NO_2, R_2 = Me, R_3 = H, 94%)
5h (R_1 = 3,4$Cl_2C_6H_4$, R_2 = Ph, R_3 = H, 88%)
5i (R_1 = NO_2, R_2 = Ph, R_3 = H, 96%)
5j (R_1 = NO_2, R_2 = Ph, R_3 = Me, 90%)
5k (R_1 = 2-naphthyl, R_2 = Me, R_3 = OMe, 94%)
5l (R_1 = 3,4$Cl_2C_6H_4$, R_2 = Ph, R_3 = OMe, 86%)
5m (R_1 = NO_2, R_2 = Me, R_3 = OMe, 93%)
5n (R_1 = NO_2, R_2 = Ph, R_3 = OMe, 92%)
5o (R_1 = 2-naphthyl, R_2 = Me, R_3 = Cl, 92%)

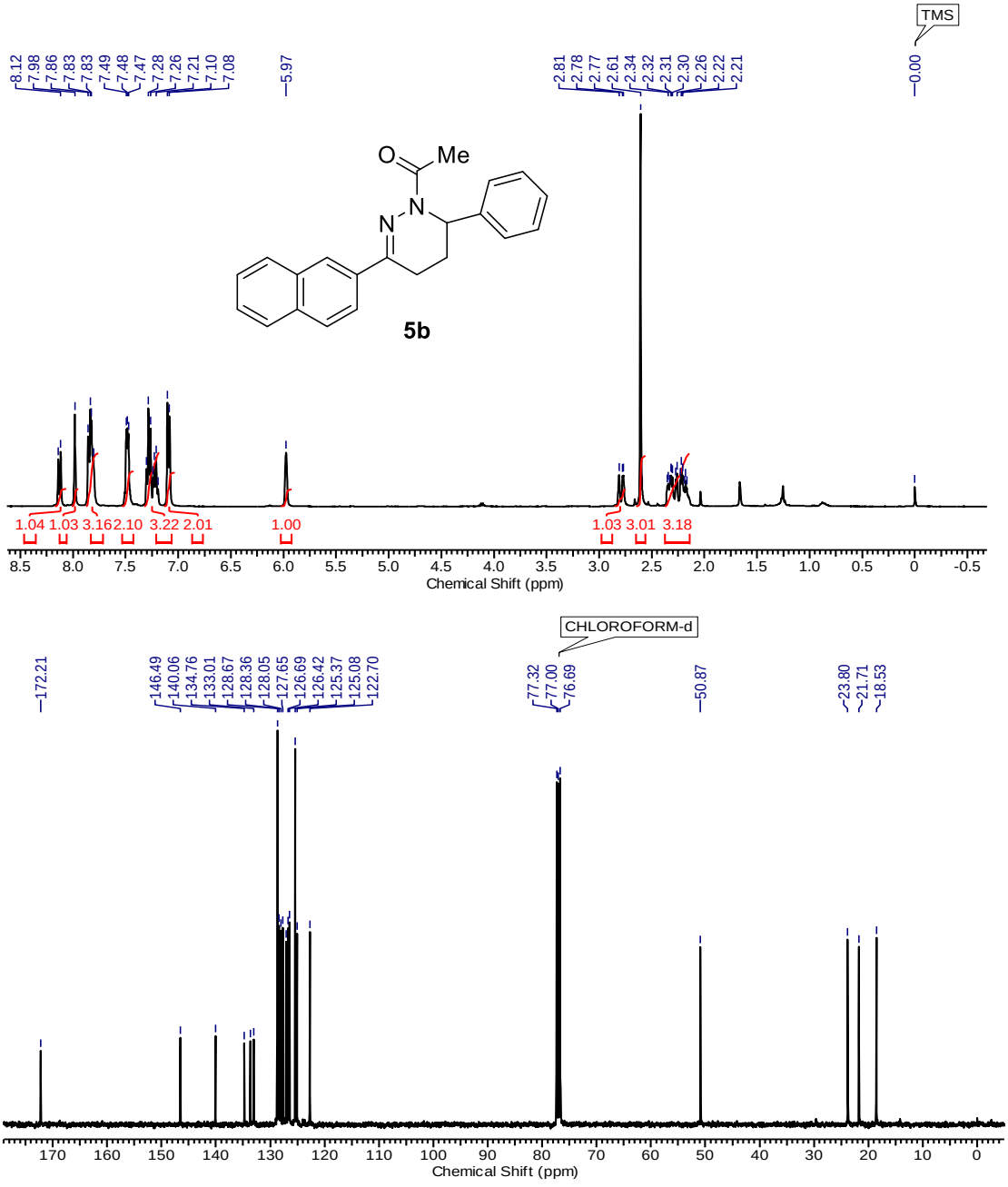
[a]The reaction were carried out with **3a-o** (0.5 mmol), **4a-o** (0.25 mmol), (K_2CO_3 (1.0 mmol), CsF (1.0 mmol), CH_3CN (dry, 3 mL) at rt for 24 h; [b]Isolated yields after column chromatographic purification.

The formation of heterocyclodimerization products **5a-o** was established unambiguously from the corresponding ^1H, ^{13}C, IR and HRMS spectral data as presented in the following examples.

For Heterocyclodimerization:

Example 1:

The ^{1}H NMR spectrum of 1,4,5,6- tetrahydropyridazine derivative **5b** showed typical proton singlet at δ 5.97 (s, 1H) corresponding to the benzylic proton (-C**H**-N) attached to nitrogen in **5b**. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 18.5 and 21.7 due to the presence of two methylene carbons (-CH_2-) in compound **5b** **(Figure 5)**.



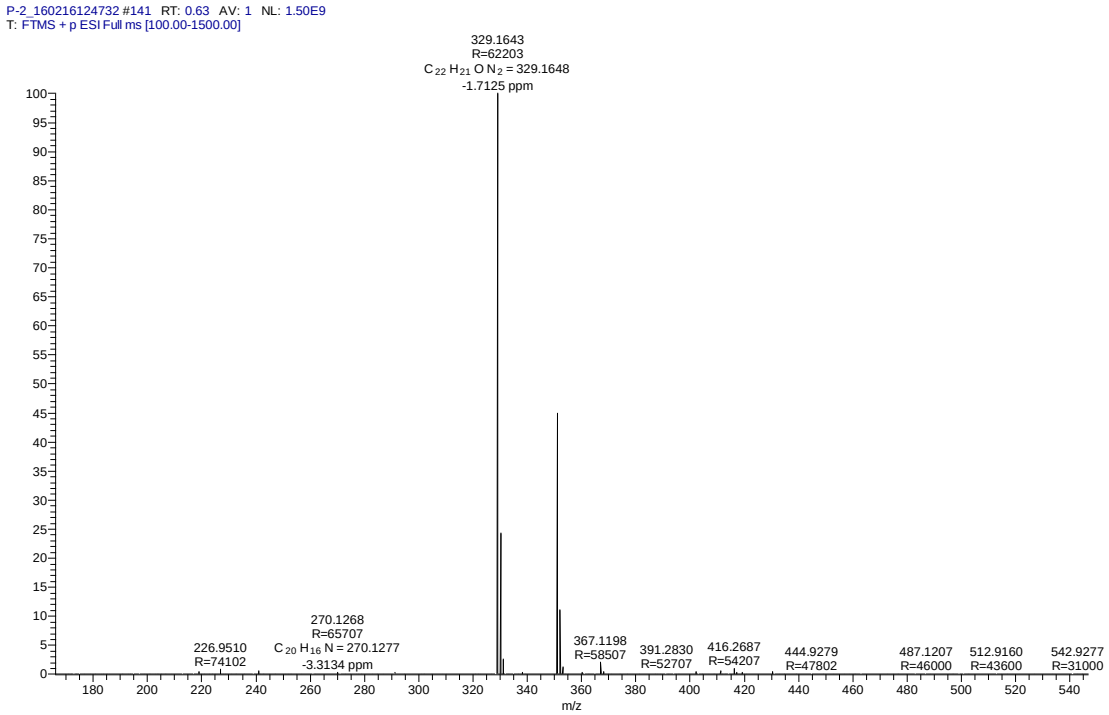
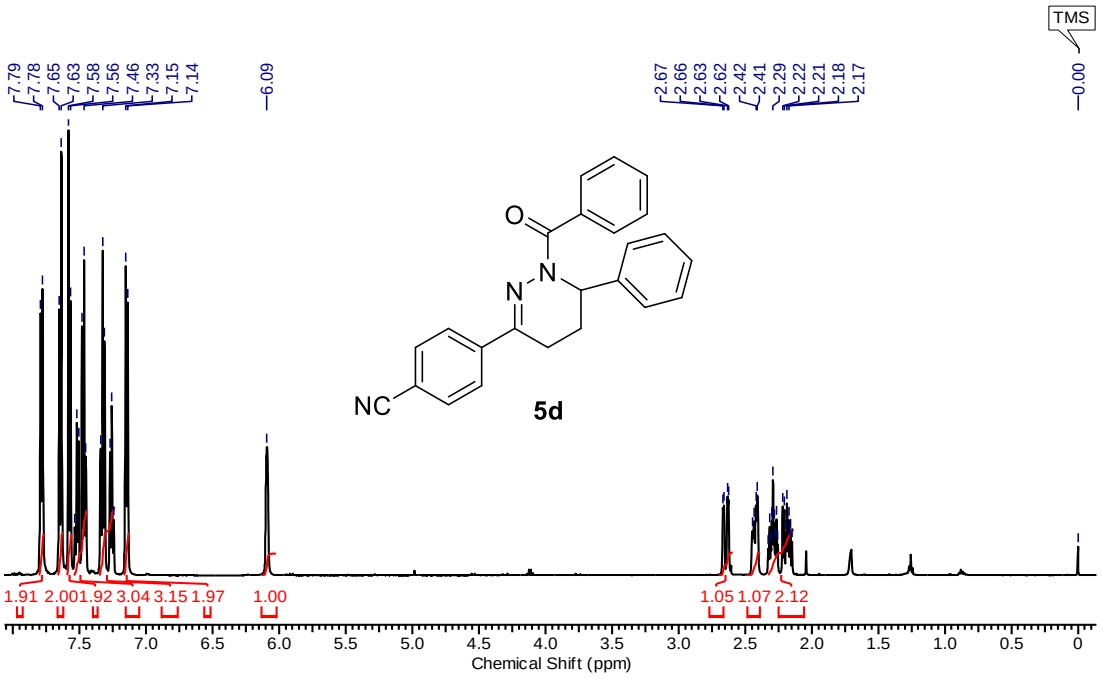


Figure 5: ^{1}H, ^{13}C NMR and HRMS spectra of **5b**

Example 2:

The ^{1}H NMR spectrum of **5d** showed a typical singlet at δ 6.09 (s, 1H) corresponding to the benzylic proton (-C**H**-N) attached to nitrogen in **5d**. Its ^{13}C NMR spectrum displayed two carbon signals at δ 18.6 and 21.7 due to the presence of two methylene carbons (-CH_2-) in compound **5d (Figure 6)**.



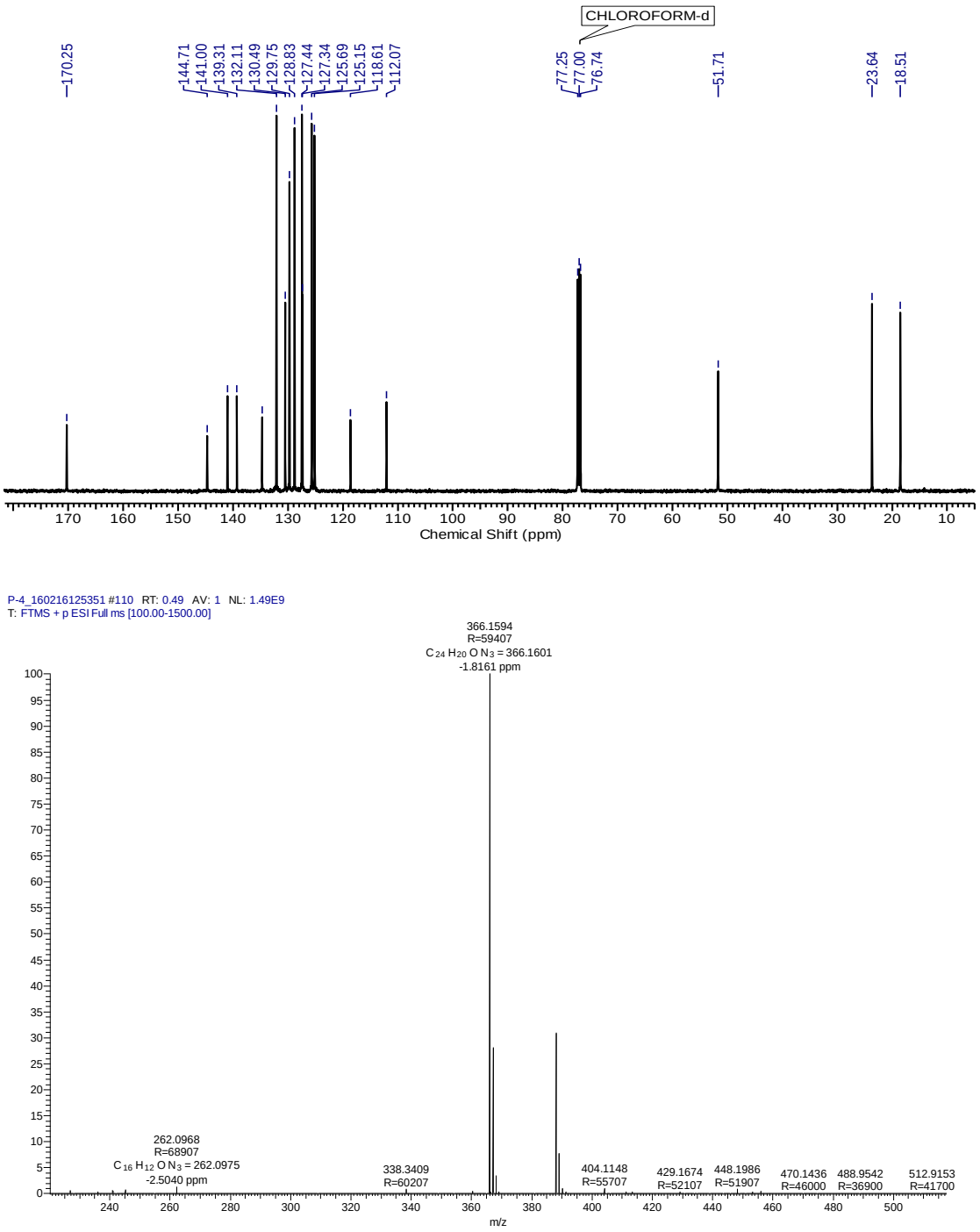
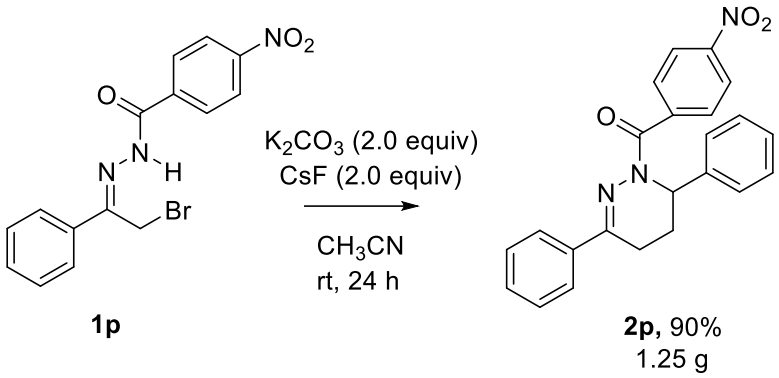


Figure 6: ^{1}H, ^{13}C NMR and HRMS spectra of **5d**

To show the synthetic potential of our present methodology, we carried out the reaction of (*Z*)-N′-(2-bromo-1-phenylethylidene)-N-4-nitrobenzoyl hydrazide (**1p**) under our optimized reaction conditions, which afforded **2p**, an analogue of a

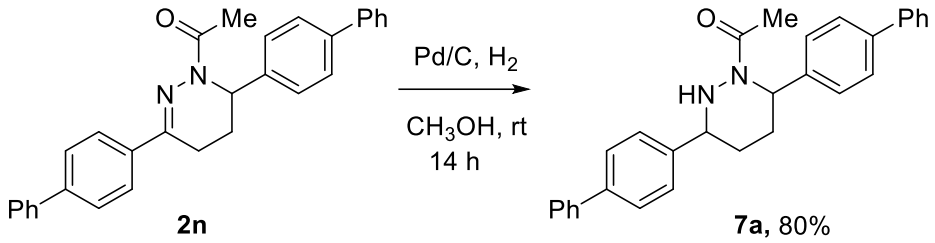
nonsteroidal progesterone receptor regulator, on a gram scale (1.25 g, 90% yield; **Scheme 10**).

Scheme 10: Gram-Scale Synthesis of **2p**, an Analogue of a Nonsteroidal Progesterone Receptor Regulator



Furthermore, to demonstrate the utility of the reaction, product **2n** was subjected to hydrogenation reaction conditions using Pd/C as the catalyst to give hexahydropyridazine **7a** in 80% yield, which could be further converted to a pharmaceutically important 1,4-diamine adduct (**Scheme 11**).[23]

Scheme 11: Transformation of Product **2n** into **7a**



The formation of hexahydropyridazine **7a** was established unambiguously from the corresponding ^{1}H & ^{13}C NMR, IR and HRMS spectral data. The ^{1}H NMR spectrum of **7a** showed a doublet at δ 6.07 (d, J = 4.0 Hz, 1H) corresponding to the benzylic proton (-C**H**-N) attached to nitrogen in compound **7a**. And ^{13}C NMR spectrum shows characteristic carbon signals at δ 21.1 and 25.9 due to the methylene carbons (-CH_2-) present in compound **7a** (**Figure 7**).

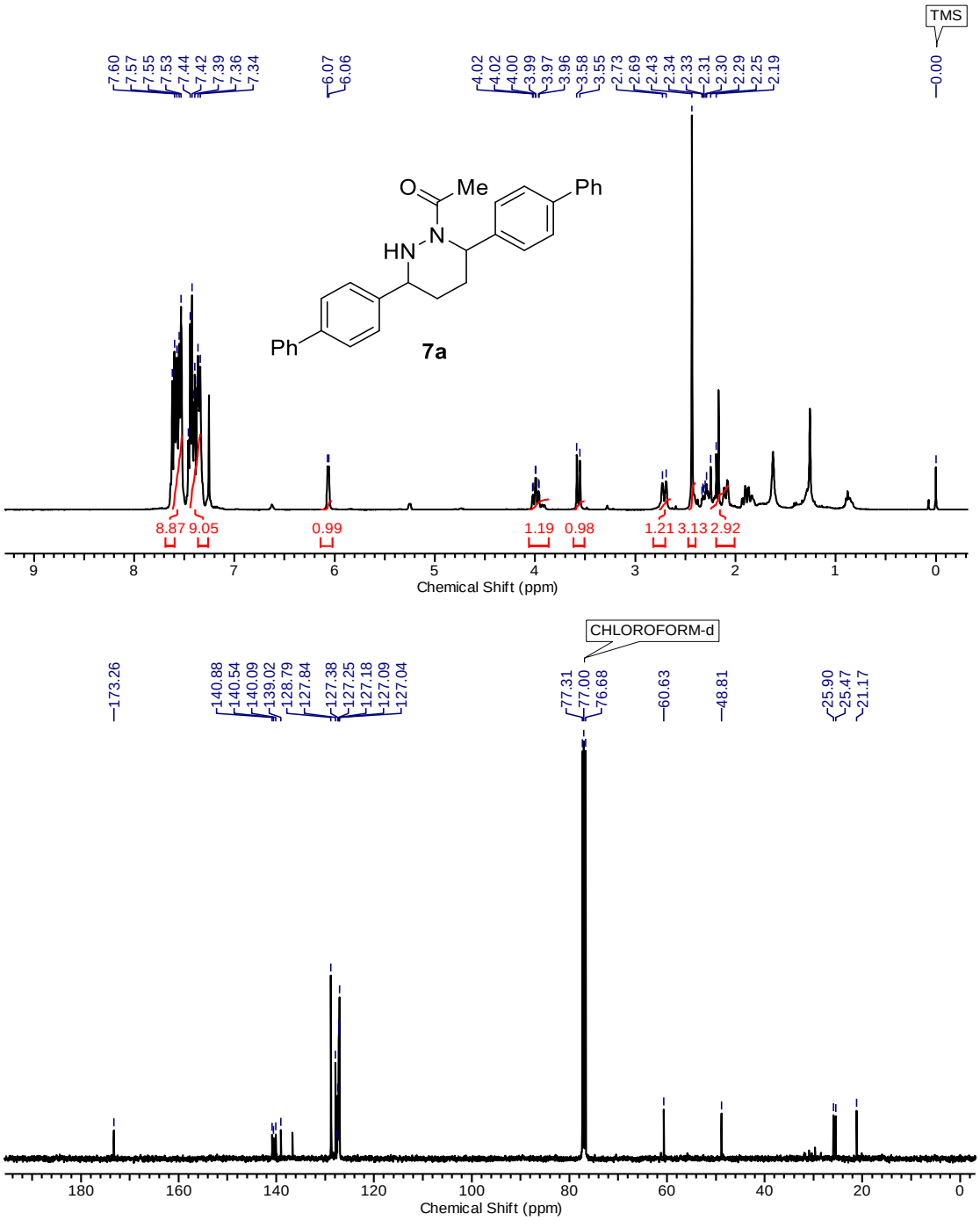
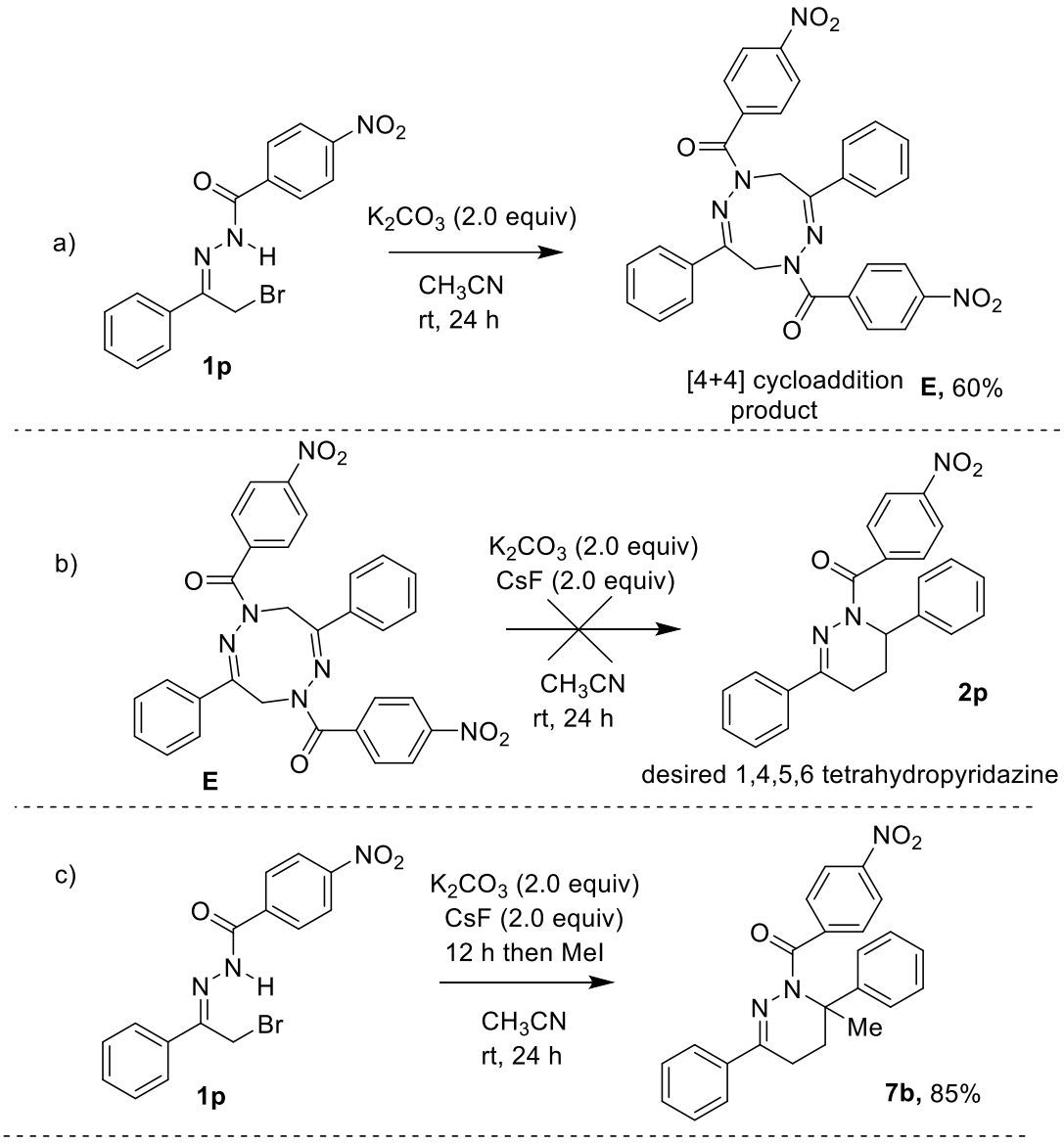


Figure 7: ^{1}H and ^{13}C NMR spectra of **7a**

In order to gain insight into the mechanistic details of the reaction, we conducted the following experiments (**Scheme 12**): (a) When α-bromo N-acylhydrazone **1p** was treated with K_2CO_3 in the absence of CsF, we did not observe the formation of the desired product **2p**; instead we got [4+4] cycloaddition product **E** (structure

confirmed by ^{1}H, ^{13}C, and 2D NMR and HRMS analyses) in 60% yield, which proves the significant role of cesium fluoride to get **2p** (**Figure 8-11**).

Scheme 12: Control Experiment



(b) Next, we subjected compound **E** to our optimized reaction conditions, but unfortunately, the starting material remained intact and was not converted into the expected product **2p**. This control experiment suggests that the reaction does not go through compound **E** as an intermediate.

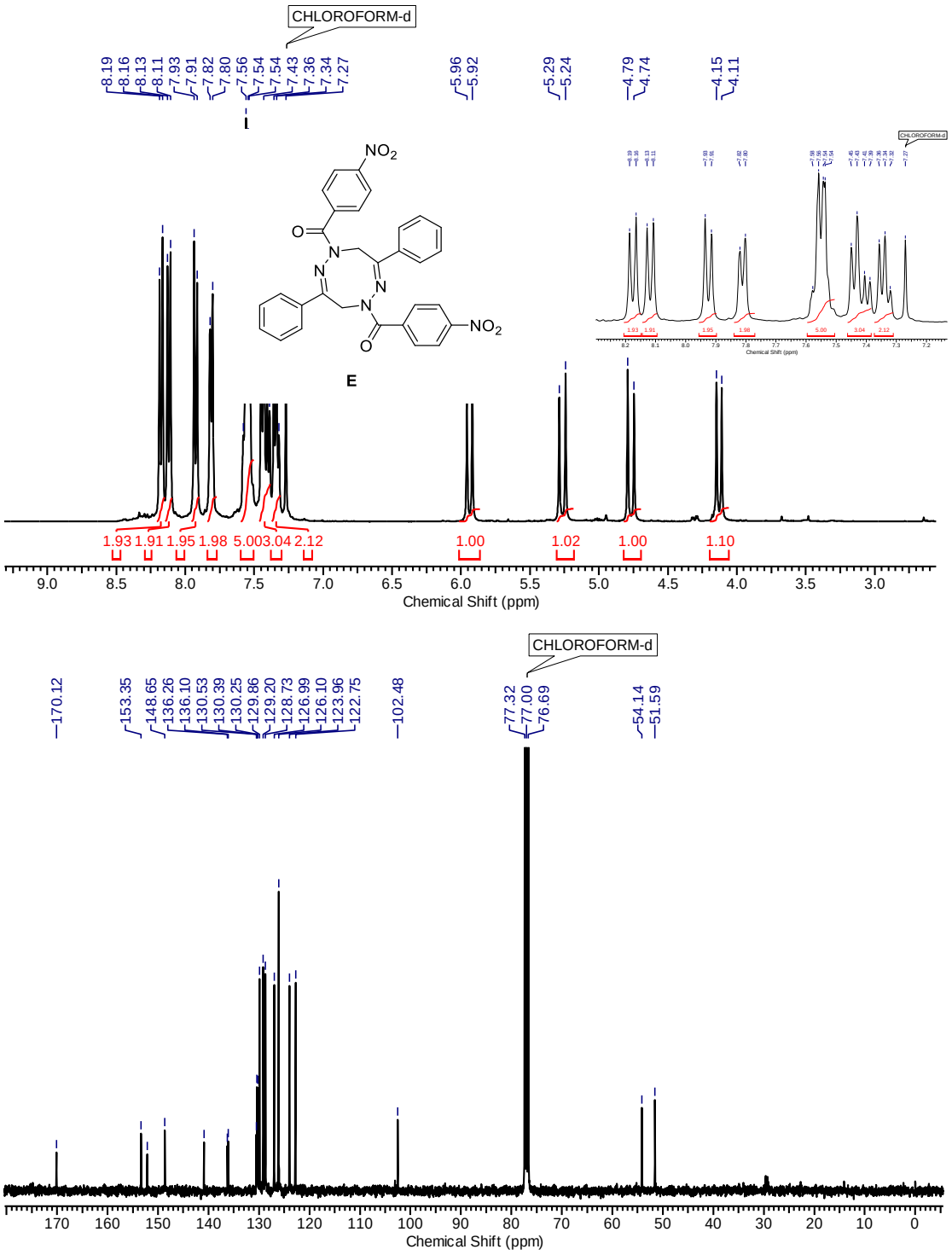


Figure 8: ^{1}H and ^{13}C NMR spectra of **E**

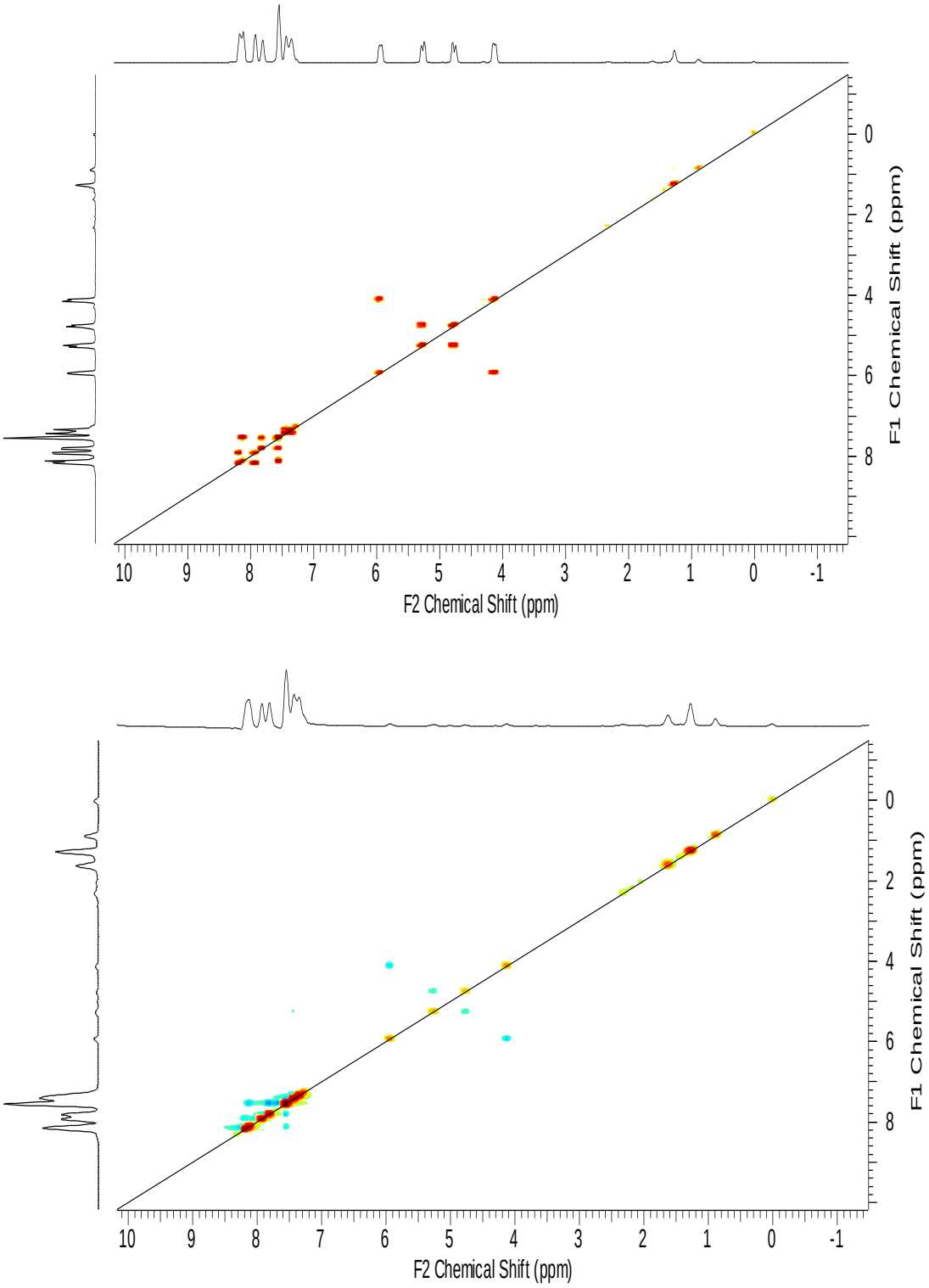


Figure 9: COSY and NOESY of compound **E**

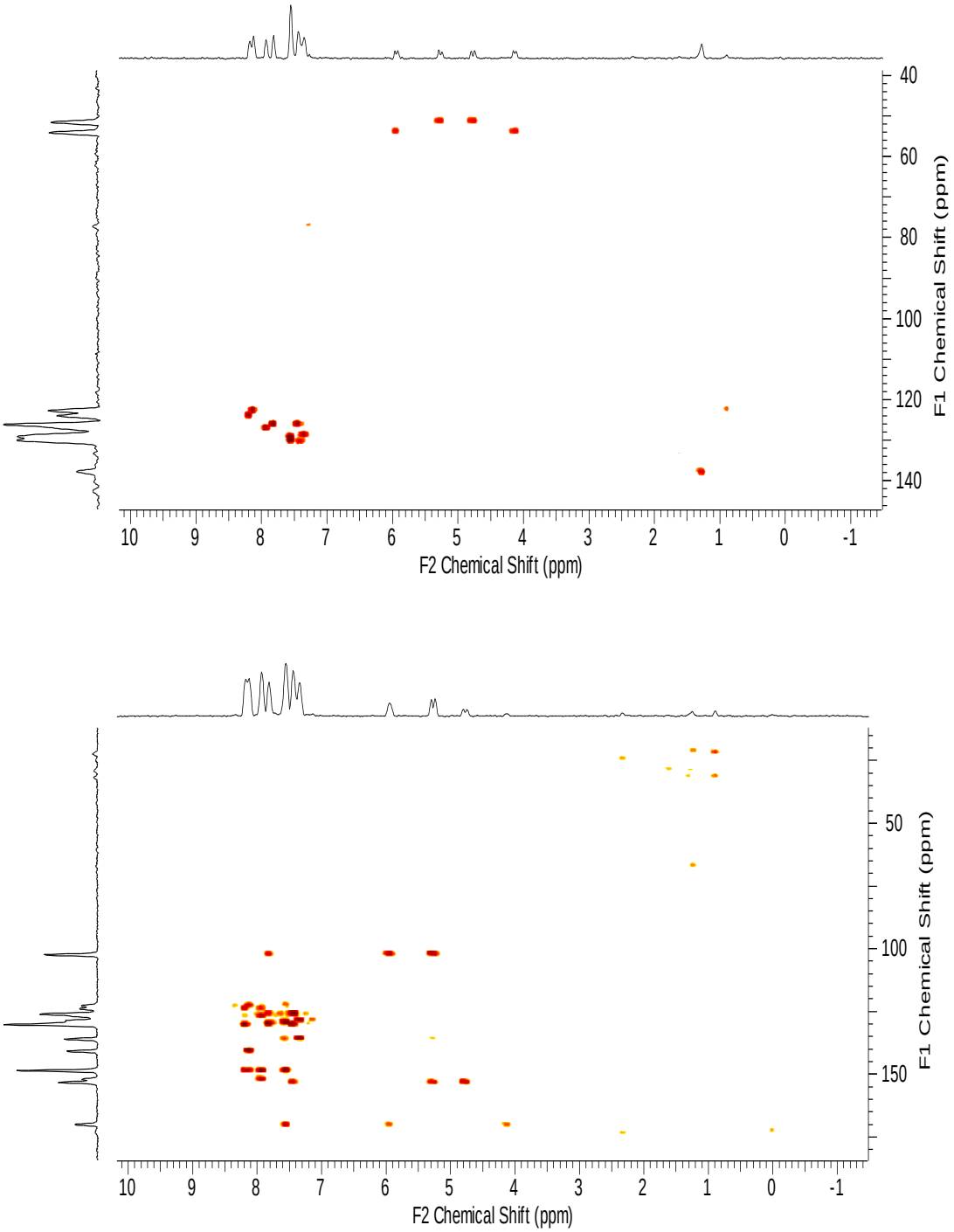


Figure 10: HSQC and HMBC of compound **E**

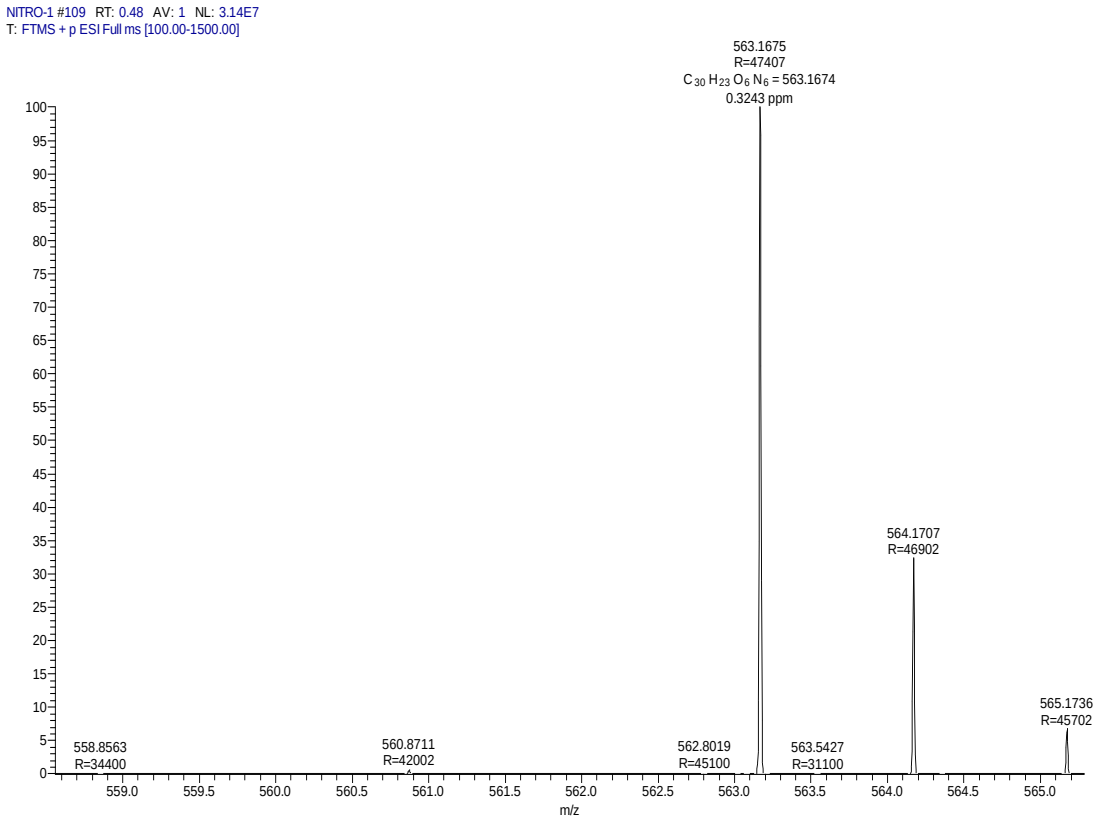


Figure 11: HRMS of compound **E**

(c) Additionally, when **1p** was subjected to our optimized reaction conditions in the presence of excess methyl iodide (>5.0 equiv), interestingly, the methylated product **7b** (85% yield) was obtained, confirming the generation of the carbanion at the benzylic position during the course of the cyclodimerization reaction. The formation of the methylated product **7b** was ascertained by its ^{1}H, ^{13}C NMR and HRMS spectral analysis (**Figure 12 & 13**). This experiment also suggests that compound **G** is undoubtedly the key intermediate in the reaction (**Scheme 13**).

The ^{1}H NMR spectrum of **7b** showed a singlet at δ 2.14 (s, 3H) corresponding to the methyl proton (-C**H**$_3$-C) attached to benzylic carbon atom present in compound **7b**. Its ^{13}C NMR spectrum shows characteristic carbon signals at δ 20.1 due to the methyl carbons (-**C**H$_3$-) present in compound **7b** (**Figure 7**).

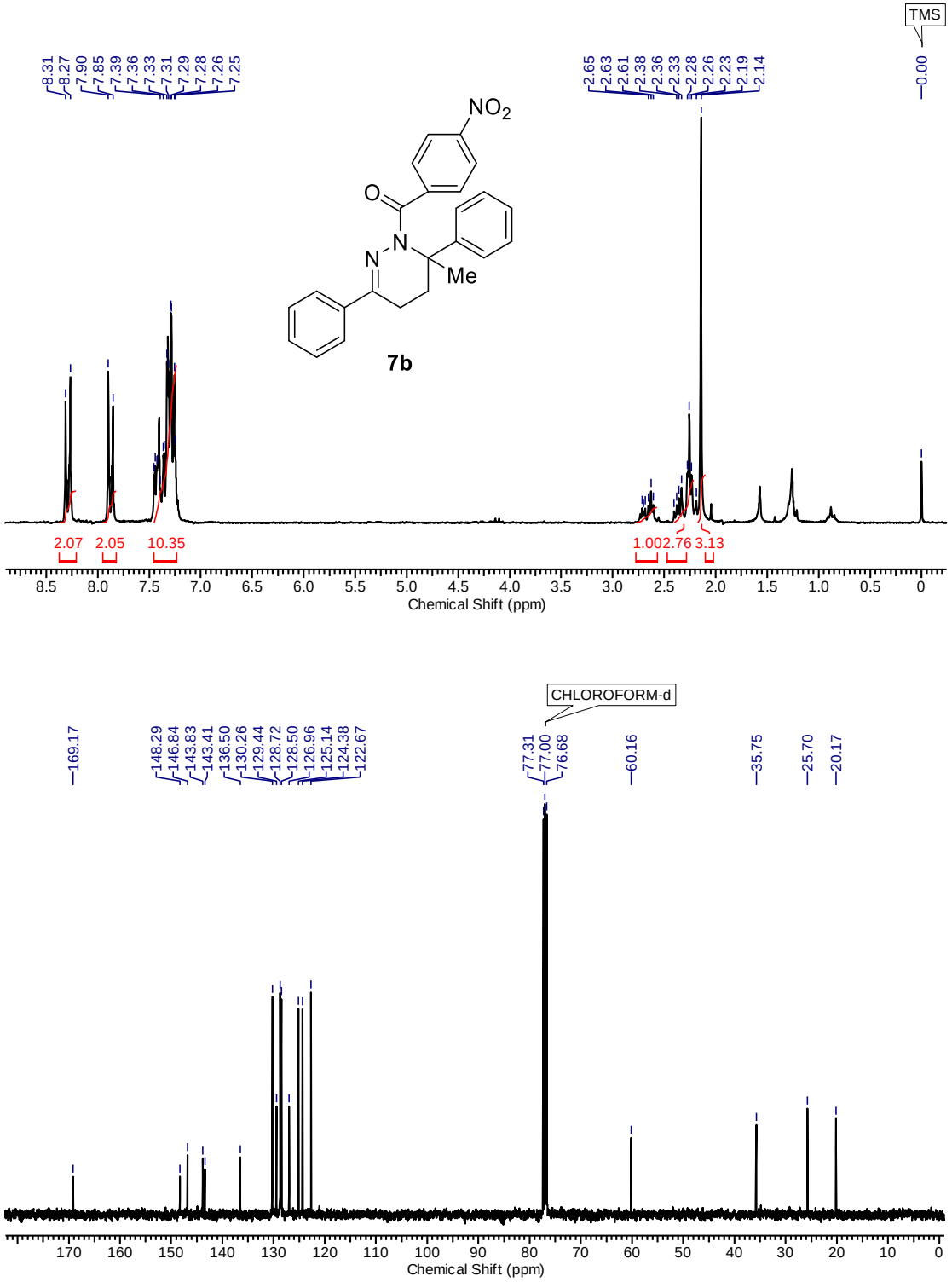


Figure 12: ^{1}H and ^{13}C NMR spectra of **7b**

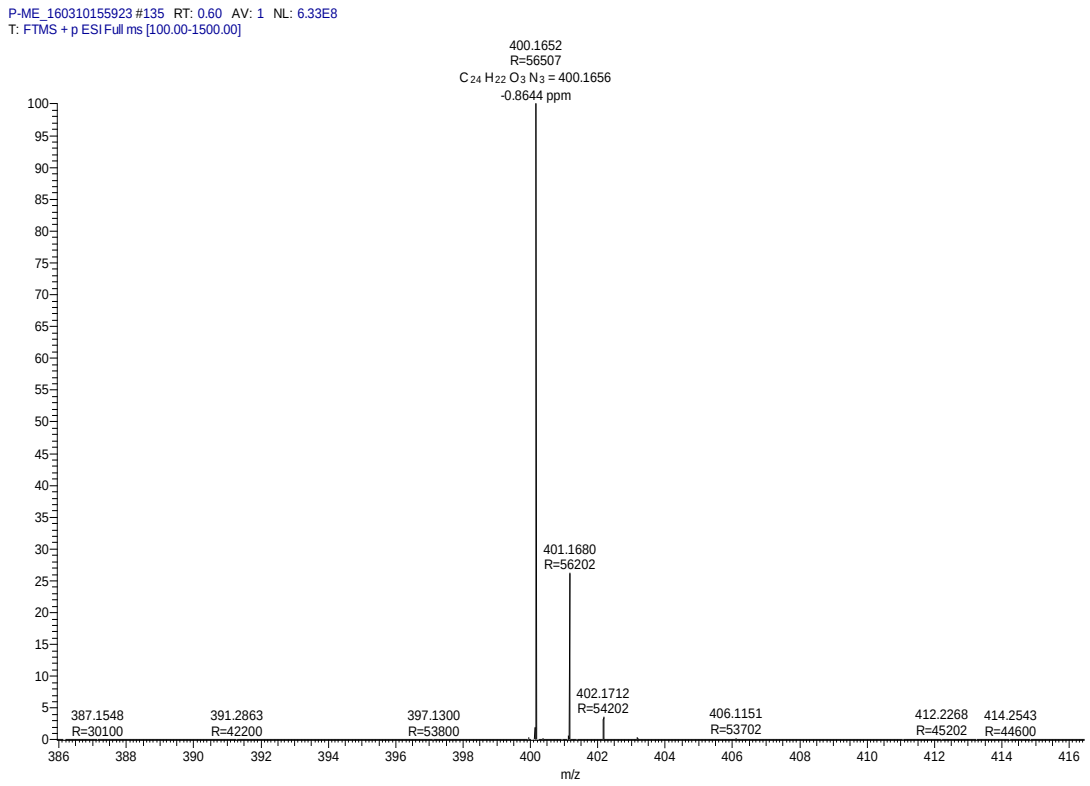
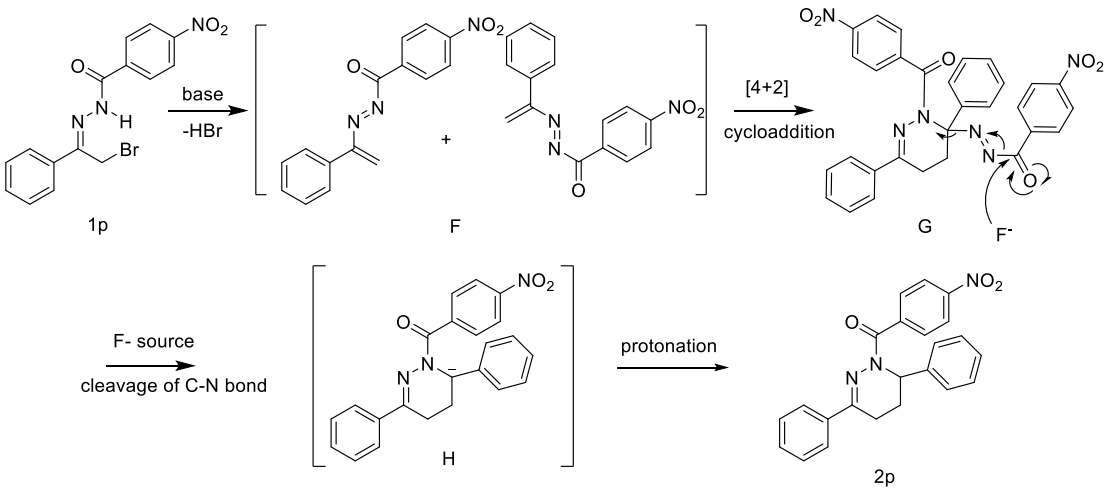


Figure 13: HRMS spectra of **7b**

On the basis of the above control experiments and literature precedents,[24] a probable mechanism is proposed in Scheme **8**. Treatment of the α-halo hydrazone with base generates azoalkene **F** (1,2-diaza-1,3-diene), which then undergoes cyclodimerization (regioselective intermolecular [4+2] cycloaddition of the transient azoene) to give pyridazine **G**. Since fluoride is the only active nucleophilic species under rigorously anhydrous conditions, the most likely mechanism for the C-N bond cleavage is regioselective nucleophilic attack of fluoride anion at one of the acyl carbonyl groups of **G** followed by nitrogen elimination and breaking of the C-N bond, resulting in unstable carbanion intermediate **H**, which undergoes protonation to afford the desired 1,4,5,6-tetrahydropyridazine. Notably, the fluoride anion attack is highly regioselective. Nitrogen elimination may be the driving force for this high regioselectivity.

Scheme 13: Proposed Mechanism

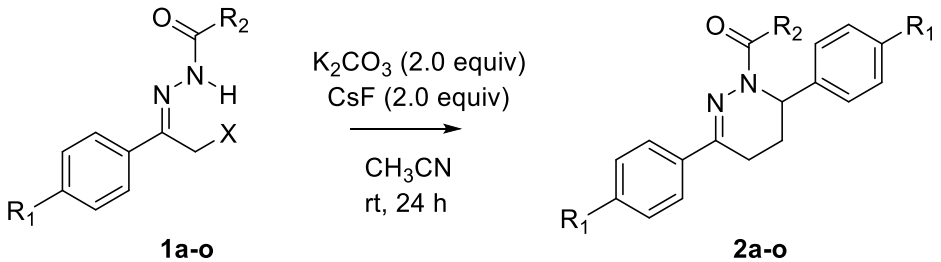


4.1.5 Conclusion

In summary, we have demonstrated a simple and facile transformation of α-halo N-acylhydrazones into highly functionalized 1,4,5,6-tetrahydropyridazines in excellent yields using CsF and K_2CO_3 under very mild reaction conditions *via* fluoride assisted unexpected C-N bond cleavage. Mild reaction conditions, readily accessible starting materials, high yields, and broad functional group tolerance are some of the notable features of the present methodology. Mechanistically, this reaction involves cyclodimerization (regioselective intermolecular [4+2] cycloaddition of the transient azoene followed by regioselective deacylation) and the extrusion of nitrogen using cesium fluoride as the nucleophile.

4.1.6 Experimental Section

General procedure for the homocyclodimerization reaction of *α*-halo N-Acyl hydrazones 1a-o for the synthesis of substituted 1,4,5,6 tetrahydropyridazines 2a-o:

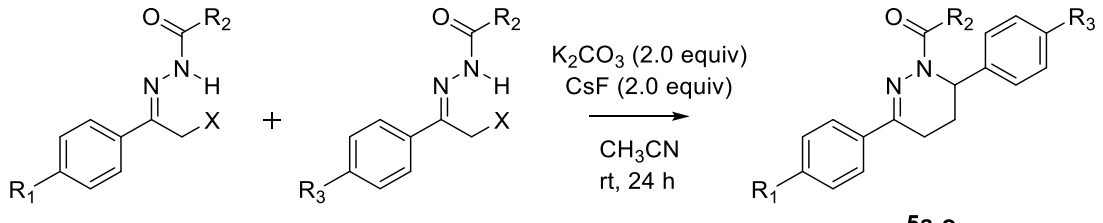


1a-o
X= Br, Cl

2a-o

To a solution of hydrazones **1a-o** (0.5 mmol) in dry CH_3CN (3.0 ml) K_2CO_3 (1.0 mmol) and CsF (1.0 mmol) was added under N_2 atmosphere at room temperature. Then the reaction mixture was stirred for 24 h. After completion of the reaction (as monitored by TLC), solvent was evaporated and the crude reaction mixture was directly loaded on a silica column and purified using column chromatography (100-200 mesh silica gel) using pet.ether-ethyl acetate as the eluent to give 1,4,5,6 tetrahydropyridazine derivatives **2a-o** (for example **2a** in 91% yield) with high purity.

General procedure for the cross-cyclodimerization of *α*-halo N-Acyl hydrazones 3a-o and 4a-o for the synthesis of substituted 1,4,5,6 tetrahydropyridazines 5a-o:



3a-o
X= Br, Cl

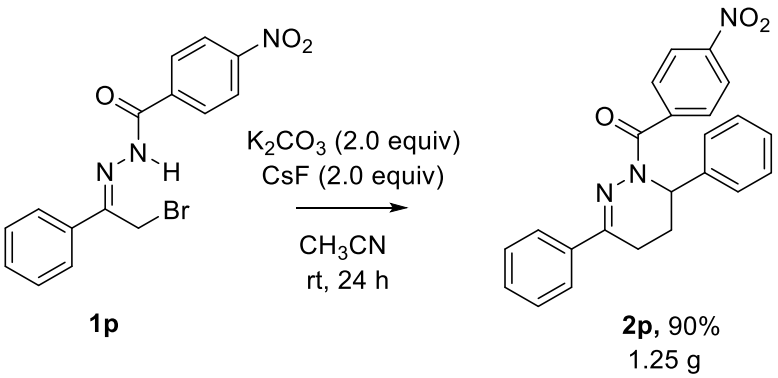
4a-o

5a-o

To a mixture of hydrazones **3a-o** (0.5 mmol) and hydrazone **4a-o** (0.25 mmol) in dry CH_3CN (3.0 ml) K_2CO_3 (1.0 mmol) and CsF (1.0 mmol) was added under N_2 atmosphere at room temperature. Then the reaction mixture was stirred for 24 h. After

completion of the reaction (as monitored by TLC), solvent was evaporated and the crude reaction mixture was directly loaded on a silica column and purified using column chromatography (100-200 mesh silica gel) using pet.ether-ethyl acetate as the eluent to give 1,4,5,6 tetrahydropyridazine derivatives **5a-o** (for example **5a** in 94% yield) with high purity.

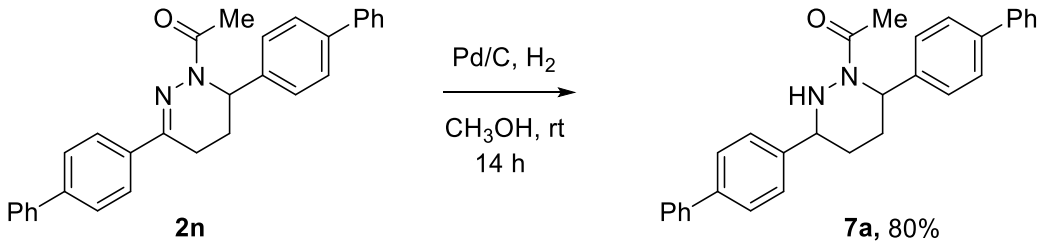
Gram scale synthesis of an analogue of nonsteroidal progesterone receptor regulator 2p from 1p:



1p **2p,** 90%
1.25 g

The synthesis of **2p** (3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)(4-nitrophenyl)methanone from **1p** ((*Z*)-N'-(2-bromo-1-phenylethylidene)-4-nitrobenzohydrazide) was followed according to a similar procedure for the preparation of 1,4,5,6 tetrahydropyridazine derivatives **2a-o** described in **4.1.6.**

Transformation of product 2n into 7a:



2n **7a,** 80%

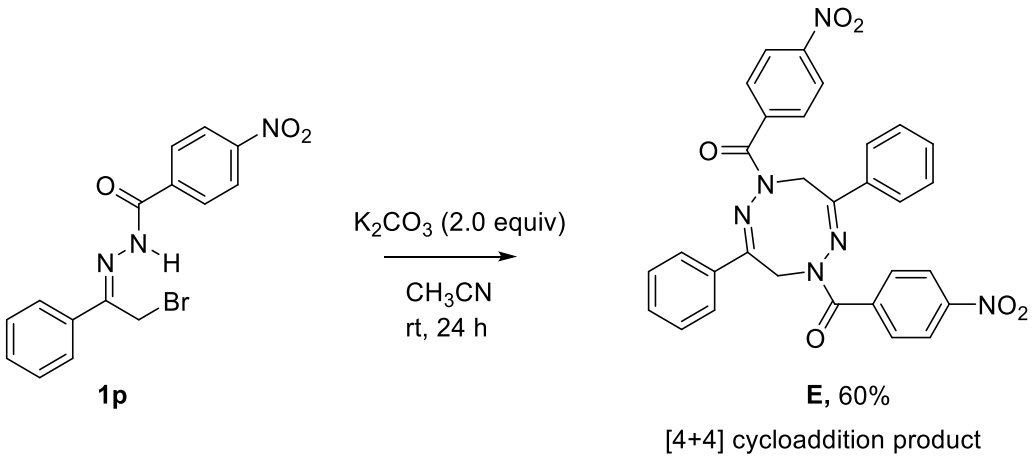
Procedure: Degassed methanol (4.0 ml) was added to the mixture of Pd/C (10 wt %) and **2n** (0.5 mmol, 215 mg). After stirring under 1 atm pressure of hydrogen for 14 h at room temperature, the reaction mixture was filtered, and then evaporated under reduced pressure. The crude product was then purified by flash column

chromatography to give hydrogenated product **7a** (172 mg, 80%) as a white solid.

Control experiments:

In order to study the mechanism of present homo and cross-cyclodimerization reaction of α-halo N-Acyl hydrazones for the synthesis of substituted 1,4,5,6 tetrahydropyridazines, we performed certain experiments which are described below:

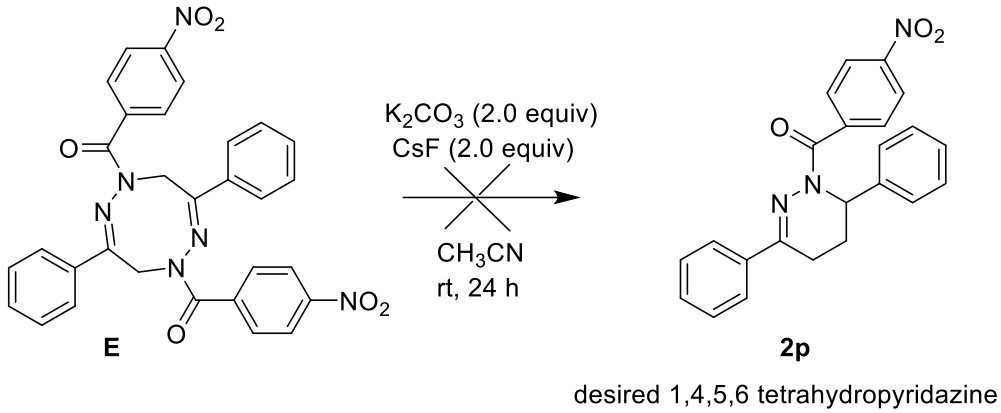
(a) Experimental procedure for the cyclodimerization when reaction carried out in the absence of cesium fluoride (formation of [4+4] cycloaddition product E):



When α-bromo N-acyl hydrazone **1p**, was treated with K_2CO_3 in the absence of CsF we did not observe formation of desired 1,4,5,6 tetrahydropyridazine product **2p** instead we got [4+4] cycloaddition product **E** (structure confirmed by ^1H, ^{13}C, HRMS and 2D NMR analysis) in 60% yield which proves crucial role of cesium fluoride to get **2p.**

Procedure: To a solution of hydrazone **1p** (0.5 mmol) in dry CH_3CN (3.0 ml) K_2CO_3 (1.0 mmol) was added under N_2 atmosphere at room temperature. Then the reaction mixture was stirred for 24 h. After completion of the reaction (as monitored by TLC), solvent was evaporated and the crude reaction mixture was directly loaded on a silica column and purified using column chromatography (100-200 mesh silica gel) using pet.ether-ethyl acetate as the eluent to give [4+4] cycloaddition product **E** in 60% yield (84 mg).

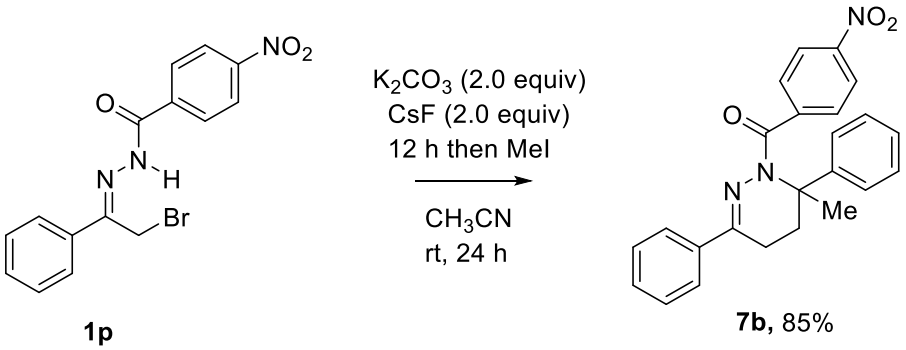
(b) Reaction of intermediate E with optimized reaction conditions:



When we subjected compound **E** to our optimized reaction condition unfortunately, reaction didn't proceed and we ended up with starting material. This control experiment suggests that reaction is not going through compound **E** as an intermediate.

Procedure: A similar procedure was followed according to procedure for the preparation of 1,4,5,6 tetrahydropyridazine derivatives **2a-o** described in **4.1.6**

(c) Experimental procedure for the synthesis of methylated product 7b when reaction carried out with 1p in the presence of excess of MeI (methyl iodide):



Additionally, when α-bromo N-acyl hydrazone **1p**, was subjected to our optimized reaction condition in the presence of excess MeI (more than 5.0 equiv.) interestingly methylated product **7b** (85% yield) was obtained, confirming the generation of carbanion at the benzylic position during the course of cyclodimerization reaction.

Procedure: To a solution of hydrazone **1p** (0.5 mmol) in dry CH_3CN (3.0 ml) K_2CO_3 (1.0 mmol) and CsF (1.0 mmol) was added under N_2 atmosphere at room temperature. The resulting mixture was then stirred for approximately 12 h. After which excess of MeI (more than 5.0 equiv.) was added in the reaction mixture and further stirred for additional 12 h. After the reaction was complete (as monitored by TLC), solvent was evaporated and the crude reaction mixture was directly loaded on a silica column and purified using column chromatography (100-200 mesh silica gel) using pet.ether-ethyl acetate as the eluent to give methylated product **7b** 84 mg, in 85% yield.

(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)(phenyl)methanone (2a)

Yield: 77 mg, 91%; White solid; **mp:** 148-150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.12-2.39 (m, 3H), 2.62-2.67 (m, 1H), 6.07 (s, 1H), 7.18 (d, *J* = 7.4 Hz, 2H), 7.22-7.31 (m, 6H), 7.41-7.47 (m, 3H), 7.56-7.58 (m, 2H), 7.84 (dd, *J* = 1.5, 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 18.5, 23.8, 51.5, 125.2, 125.3, 127.1, 127.2, 128.2, 128.6, 129.0, 129.9, 130.1, 135.1, 137.0, 139.7, 146.8, 170.1; **HRMS** (ESI) calcd for $C_{23}H_{21}N_2O$ $[M+H]^+$ 341.1648; found 341.1645.

1-(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (2b)

Yield: 66 mg, 96%; White solid; **mp:** 120-122 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.10-2.30 (m, 3H), 2.55 (s, 3H), 2.61-2.69 (m, 1H), 5.95 (d, *J* = 4.0 Hz, 1H), 7.05-7.10 (m, 2H), 7.21-7.33 (m, 3H), 7.35-7.43 (m, 3H), 7.75-7.80 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.6, 21.6, 23.7, 50.7, 125.2, 125.3, 127.0, 128.4, 128.6, 129.2, 137.3, 140.0, 146.6, 172.1; **HRMS** (ESI) calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1492; found 279.1493.

(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)(furan-2-yl)methanone (2c)

Yield: 77 mg, 95%; White solid; **mp:** 126-128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.18-2.41 (m, 3H), 2.68-2.76 (m, 1H), 6.08 (s, 1H), 6.59 (dd, *J* = 1.8, 3.5 Hz, 1H),

7.13 (m, 2H), 7.19-7.30 (m, 3H), 7.40-7.45 (m, 3H), 7.58 (d, *J* = 3.5 Hz, 1H), 7.65 (s, 1H), 7.74-7.77 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 19.4, 23.8, 51.5, 111.5, 120.3, 125.4, 125.8, 127.1, 128.60, 128.69, 129.3, 137.5, 139.6, 145.3, 146.4, 148.7, 158.7; **HRMS** (ESI) calcd for $C_{21}H_{19}N_2O_2$ $[M+H]^+$ 331.1441; found 331.1440.

(3-chlorophenyl)(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)methanone (2d)

Yield: 87 mg, 94%; Gummy liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.19-2.43 (m, 3H), 2.67-2.73 (m, 1H), 6.06 (s, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.31-7.41 (m, 6H), 7.45-7.60 (m, 3H), 7.69-7.85 (m, 2H), 8.18 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 18.6, 23.9, 51.7, 125.3, 126.9, 127.3, 128.1, 128.4, 128.7, 128.8, 129.0, 129.3, 130.2, 133.3, 136.9, 139.6, 147.5, 168.6; **HRMS** (ESI) calcd for $C_{23}H_{20}N_2OCl$ $[M+H]^+$ 375.1259; found 375.1259.

(4-chlorophenyl)(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)methanone (2e)

Yield: 85 mg, 92%; Gummy liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.17-2.41 (m, 3H), 2.67-2.72 (m, 1H), 6.06 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.26-7.35 (m, 4H), 7.41-7.44 (m, 2H), 7.53-7.59 (m, 3H), 7.78-7.94 (m, 2H), 8.15-8.18 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 18.7, 23.9, 51.7, 124.1, 125.3, 126.9, 127.2, 127.6, 128.4, 128.8, 129.0, 129.3, 130.0, 131.6, 133.5, 136.1, 136.9, 139.7, 147.4, 169.0; **HRMS** (ESI) calcd for $C_{23}H_{20}N_2OCl$ $[M+H]^+$ 375.1259; found 375.1259.

(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)(p-tolyl)methanone (2f)

Yield: 77 mg, 88%; Gummy liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.16-2.43 (m, 3H), 2.44 (s, 3H), 2.66-2.70 (m, 1H) 6.08 (s, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.23-7.33 (m, 8H), 7.61-7.63 (m, 2H), 7.77-7.78 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 18.7, 21.5, 23.9, 51.6, 125.3, 125.4, 127.1, 127.5, 127.7, 128.0, 128.1, 128.3, 128.4, 128.7, 129.0, 132.0, 137.2, 139.9, 140.5, 146.6, 170.0; **HRMS** (ESI) calcd for $C_{24}H_{23}N_2O$ $[M+H]^+$ 355.1810; found 355.1808.

(4-bromophenyl)(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)methanone (2g)

Yield: 93 mg, 90%; Gummy liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.18-2.42 (m, 3H), 2.69-2.72 (m, 1H), 6.06 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 7.23 (m, 1H), 7.30-7.36 (m, 5H), 7.57-7.60 (m, 4H), 7.72 (d, *J* = 7.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 18.7, 23.9, 51.7, 124.8, 125.3, 127.3, 128.5, 128.8, 129.3, 130.6, 131.8, 134.0, 136.9, 139.6, 147.7, 169.0; **HRMS** (ESI) calcd for $C_{23}H_{20}N_2OBr$ $[M+H]^+$ 419.0754; found 419.0752.

(3-bromophenyl)(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)methanone (2h)

Yield: 99 mg, 96%; Gummy liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.17-2.42 (m, 3H), 2.67-2.88 (m, 1H), 6.05 (s, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.25-7.35 (m, 4H), 7.51-7.63 (m, 4H), 7.75-7.79 (m, 1H), 7.86- 8.09 (m, 2H), 8.18 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 18.6, 23.9, 51.7, 121.3, 124.1, 125.3, 126.9, 127.3, 128.4, 128.5, 128.6, 128.8, 129.3, 133.1, 136.8, 137.0, 139.5, 147.5, 168.4; **HRMS** (ESI) calcd for $C_{23}H_{20}N_2OBr$ $[M+H]^+$ 419.0754; found 419.0752.

4,4'-(1-acetyl-1,4,5,6-tetrahydropyridazine-3,6-diyl)dibenzonitrile (2i)

Yield: 66 mg, 93%; White solid; **mp:** 160-162 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.13-2.31 (m, 3H), 2.55 (s, 3H), 2.62-2.73 (m, 1H), 5.97 (d, *J* = 3.7 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.60-7.72 (m, 4H), 7.90 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.4, 21.5, 23.2, 50.8, 111.5, 112.7, 118.4, 125.7, 126.2, 132.3, 132.7, 140.8, 144.6, 145.3, 172.2; **HRMS** (ESI) calcd for $C_{20}H_{17}N_4O$ $[M+H]^+$ 329.1397; found 329.1394.

(3,6-di([1,1'-biphenyl]-4-yl)-5,6-dihydropyridazin-1(4H)-yl)(furan-2 yl) methanone (2j)

Yield: 112 mg, 94%; White solid; **mp:** 178-180 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.34-2.42 (m, 3H), 2.79-2.87 (m, 1H), 6.14 (d, *J* = 4.0 Hz, 1H), 6.62 (dd, *J* = 1.8, 3.5

Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.31-7.54 (m, 10H), 7.62-7.69 (m, 6H), 7.89 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 19.5, 23.8, 51.4, 111.6, 120.4, 125.9, 126.3, 127.0, 127.2, 127.3, 127.5, 128.7, 128.8, 138.7, 140.2, 142.1, 145.5, 148.4, 158.8; **HRMS** (ESI) calcd for $C_{33}H_{27}N_2O_2$ $[M+H]^+$ 483.2073; found 483.2072.

(3,6-di-p-tolyl-5,6-dihydropyridazin-1(4H)-yl)(furan-2-yl)methanone (2k)

Yield: 84 mg, 95%; White solid; **mp:** 178-180 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.21-2.39 (m, 9H), 2.67-2.74 (m, 1H), 6.04 (d, *J* = 4.0 Hz, 1H), 6.58 (dd, *J* = 1.8, 4.0 Hz, 1H), 7.04-7.11 (m, 4H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.56-7.67 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 19.5, 23.8, 51.4, 111.6, 120.4, 125.9, 126.3, 127.0, 127.2, 127.3, 127.5, 128.7, 128.8, 138.7, 140.2, 142.1, 145.5, 148.4, 158.8; **HRMS** (ESI) calcd for $C_{23}H_{23}N_2O_2$ $[M+H]^+$ 359.1754; found 359.1751.

1-(3,6-bis(3,4-dichlorophenyl)-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (2l)

Yield: 97 mg, 95%; Gummy liquid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.21-2.41 (m, 9H), 2.68-2.75 (m, 1H), 6.05 (d, *J* = 4.0 Hz, 1H), 6.59 (dd, *J* = 1.8, 4.0 Hz, 1H), 7.05-7.23 (m, 4H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.58-7.68 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 19.4, 20.9, 21.2, 23.9, 51.3, 111.5, 120.2, 125.4, 125.7, 129.3, 134.9, 136.7, 139.5, 145.2, 146.6, 148.8, 158.6; **HRMS** (ESI) calcd for $C_{18}H_{15}Cl_4N_2O$ $[M+H]^+$ 414.9938; found 414.9936.

1-(3,6-di(naphthalen-2-yl)-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (2m)

Yield: 85 mg, 91%; White solid; **mp:** 97-99 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.28-2.34 (m, 2H), 2.44-2.46 (m, 1H), 2.66 (s, 3H), 2.80-2.86 (m, 1H), 6.13 (s, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 7.40-7.51 (m, 5H), 7.71-7.88 (m, 6H), 7.98 (s, 1H), 8.17 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 18.6, 21.7, 23.7, 51.1, 122.7, 123.7, 124.0, 125.1, 125.7, 126.1, 126.4, 126.7, 127.5, 127.6, 127.8, 128.0, 128.3, 128.6,

132.6, 133.0, 133.2, 133.7, 134.8, 137.5, 146.6, 172.2; **HRMS** (ESI) calcd for $C_{26}H_{23}N_2O$ $[M+H]^+$ 379.1805; found 379.1805.

1-(3,6-di([1,1'-biphenyl]-4-yl)-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (2n)

Yield: 96 mg, 90%; White solid; **mp:** 177-179 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.20-2.41 (m, 3H), 2.59 (s, 3H), 2.68-2.80 (m, 1H), 6.00 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.33-7.56 (m, 10H), 7.60-7.66 (m, 4H), 7.90 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.7, 21.6, 23.7, 50.6, 125.7, 125.8, 127.0, 127.2, 127.4, 127.6, 128.7, 128.8, 136.2, 139.1, 140.1, 140.7, 142.0, 146.3, 172.2; **HRMS** (ESI) calcd for $C_{30}H_{27}N_2O$ $[M+H]^+$ 431.2118; found 431.2116.

1-(3,6-di-p-tolyl-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (2o)

Yield: 74 mg, 98%; Gummy liquid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.09-2.24 (m, 3H), 2.28 (s, 3H), 2.37 (s, 3H), 2.53 (s, 3H), 2.56-2.69 (m, 1H), 5.88 (d, *J* = 3.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.24 (m, 2H), 7.68 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.5, 20.9, 21.2, 21.5, 23.7, 50.5, 125.1, 125.2, 129.0, 129.2, 134.6, 136.5, 137.1, 139.2, 146.6, 172.0; **HRMS** (ESI) calcd for $C_{20}H_{23}N_2O$ $[M+H]^+$ 307.1810; found 307.1808.

1-(3-([1,1'-biphenyl]-4-yl)-6-(p-tolyl)-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (5a)

Yield: 94 mg, 94%; White solid; **mp:** 192-194 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.13-2.18 (m, 2H), 2.28-2.33 (m, 1H), 2.57 (s, 3H), 2.63-2.70 (m, 1H) 5.96 (s, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.1 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 8.0 Hz, 4H), 7.84 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 18.6, 21.6, 23.7, 50.7, 125.3, 125.6, 126.9, 127.0, 127.6, 128.6, 128.8, 136.2, 140.0, 145.3, 141.9, 146.2, 172.1; **HRMS** (ESI) calcd for $C_{24}H_{23}N_2O$ $[M+H]^+$ 355.1805; found 355.1799.

1-(3-(naphthalen-2-yl)-6-phenyl-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (5b)

Yield: 80 mg, 90%; White solid; **mp:** 145-147 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.17-2.35 (m, 3H), 2.61 (s, 3H), 2.77-2.81 (m, 1H) 5.97 (s, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 7.19-7.30 (m, 3H), 7.47-7.49 (m, 2H), 7.80-7.86 (m, 3H), 7.98 (s, 1H), 8.12 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 18.5, 21.7, 23.8, 50.8, 122.7, 125.0, 125.3, 126.4, 126.6, 127.1, 127.6, 128.0, 128.3, 128.6, 133.0, 133.6, 134.7, 140.0, 146.4, 172.2; **HRMS** (ESI) calcd for $C_{22}H_{21}N_2O$ $[M+H]^+$ 329.1648; found 329.1643.

1-(3-(naphthalen-2-yl)-6-(p-tolyl)-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (5c)

Yield: 82 mg, 92%; White solid; **mp:** 169-171 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.13-2.20 (m, 1H), 2.25-2.33 (m, 5H), 2.60 (s, 3H), 2.77-2.82 (m, 1H) 5.94 (s, 1H), 6.97 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 7.47-7.51 (m, 2H), 7.81-7.86 (m, 3H), 7.99 (s, 1H), 8.14 (d, *J* = 9.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 18.5, 20.9, 21.7, 23.8, 50.6, 122.7, 125.0, 125.2, 126.4, 126.6, 127.6, 128.0, 128.3, 129.3, 133.0, 133.6, 134.8, 136.6, 137.0, 146.4,172.1; **HRMS** (ESI) calcd for $C_{23}H_{23}N_2O$ $[M+H]^+$ 343.1805; found 343.1799.

4-(1-benzoyl-6-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)benzonitrile (5d)

Yield: 92 mg, 98%; White solid; **mp:** 206-208 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.15-2.33 (m, 2H), 2.41-2.45 (m, 1H), 2.62-2.67 (m, 1H), 6.09 (s, 1H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.24-7.34 (m, 3H), 7.45-7.53 (m, 3H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 18.5, 23.6, 51.7, 112.0, 118.6, 125.1, 125.6, 127.3, 127.4, 128.8, 129.7, 130.4, 132.1, 134.7, 139.3, 141.0, 144.7, 170.2; **HRMS** (ESI) calcd for $C_{24}H_{20}N_3O$ $[M+H]^+$ 366.1601; found 366.1594.

1-(3-(4-nitrophenyl)-6-phenyl-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (5e)

Yield: 81 mg, 94%; Yellow solid; **mp:** 204-206 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.14-2.22 (m, 2H), 2.32-2.39 (m, 1H), 2.57 (s, 3H), 2.64-2.68 (m, 1H), 5.96 (s, 1H), 7.04 (d, *J* = 7.5 Hz, 2H), 7.21-7.31 (m, 3H), 7.91 (d, *J* = 8.2 Hz, 2H), 8.22 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 18.6, 21.5, 23.4, 50.8, 123.6, 125.0, 125.8, 127.2, 128.7, 139.5, 142.9, 144.1, 147.7, 172.1; **HRMS** (ESI) calcd for $C_{18}H_{18}N_3O_3$ $[M+H]^+$ 324.1343; found 324.1336.

(3-(4-nitrophenyl)-6-(p-tolyl)-5,6-dihydropyridazin-1(4H)-yl)(phenyl)methanone (5f)

Yield: 79 mg, 90%; gummy liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.12-2.25 (m, 2H), 2.30-2.35 (m, 4H), 2.56 (s, 3H), 2.62-2.66 (m, 1H) 5.93 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 8.23 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 18.6, 20.9, 21.6, 23.4, 50.7, 123.6, 125.0, 125.8, 129.4, 136.5, 136.9, 143.0, 144.1, 147.7, 172.1; **HRMS** (ESI) calcd for $C_{19}H_{20}N_3O_3$ $[M+H]^+$ 338.1499; found 338.1494.

(3-(3,4-dichlorophenyl)-6-(p-tolyl)-5,6-dihydropyridazin-1(4H)-yl)(phenyl)methanone (5g)

Yield: 96 mg, 85%; White solid; **mp:** 188-190 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.14-2.39 (m, 6H), 2.52-2.61 (m, 1H), 6.03 (s, 1H), 7.00-7.14 (m, 4H), 7.35-7.48 (m, 5H), 7.63 (s, 1H), 7.76-7.81 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.4, 20.9, 23.6, 51.5, 124.3, 125.1, 127.3, 129.4, 130.3, 132.5, 132.8, 134.9, 136.4, 136.8, 137.0, 144.4, 170.0; **HRMS** (ESI) calcd for $C_{24}H_{21}N_2OCl_2$ $[M+H]^+$ 423.1025; found 423.1019.

(3-(3,4-dichlorophenyl)-6-phenyl-5,6-dihydropyridazin-1(4H) yl)(phenyl) methanone (5h)

Yield: 97 mg, 88%; White solid; **mp:** 177-179 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.05-2.39 (m, 3H), 2.52-2.61 (m, 1H), 6.07 (s, 1H), 7.11-7.15 (m, 2H), 7.23-7.34 (m, 5H), 7.42-7.48 (m, 3H), 7.63(s, 1H), 7.77-7.81 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.7, 20.9, 23.6, 51.5, 123.5, 125.0, 125.8, 127.4, 129.5, 129.7, 130.4, 134.8, 136.3, 137.0, 142.8, 144.4, 147.6, 170.2; **HRMS** (ESI) calcd for $C_{23}H_{19}N_2OCl_2$ $[M+H]^+$ 409.0869; found 409.0866.

(3-(4-nitrophenyl)-6-phenyl-5,6-dihydropyridazin-1(4H)-yl)(phenyl)methanone (5i)

Yield: 85 mg, 96%; Yellow solid; **mp:** 242-244 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.16-2.48 (m, 3H), 2.61-2.73 (m, 1H), 6.10 (s, 1H), 7.14-7.18 (m, 2H), 7.28-7.38 (m, 3H), 7.42-7.53 (m, 3H), 7.67-7.82 (m, 4H), 8.12-8.17 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.7, 23.6, 51.7, 123.6, 125.1, 125.9, 127.40, 127.49, 128.8, 129.7, 130.5, 134.7, 139.3, 142.8, 144.4, 147.7, 170.3; **HRMS** (ESI) calcd for $C_{23}H_{20}N_3O_3$ $[M+H]^+$ 386.1499; found 386.1493.

(3-(4-nitrophenyl)-6-(p-tolyl)-5,6-dihydropyridazin-1(4H)-yl)(phenyl)methanone (5j)

Yield: 91 mg, 90%; White solid; **mp:** 218-220 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.20-2.47 (m, 6H), 2.60-2.71 (m, 1H), 6.06 (s, 1H), 7.01 (d, *J* = 7.4 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 2H), 7.46-7.53 (m, 3H), 7.67-7.81 (m, 4H), 8.11 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.7, 20.9, 23.6, 51.5, 123.5, 125.0, 125.8, 127.4, 129.5, 129.7, 130.4, 134.8, 136.3, 137.0, 142.8, 144.4, 147.6, 170.2; **HRMS** (ESI) calcd for $C_{24}H_{22}N_3O_3$ $[M+H]^+$ 400.1656; found 400.1651.

1-(6-(4-methoxyphenyl)-3-(naphthalen-2-yl)-5,6-dihydropyridazin-1(4H)-yl)eth an-1-one (5k)

Yield: 86 mg, 94%; White solid; **mp:** 170-172 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.11-2.41 (m, 3H), 2.60 (s, 3H), 2.74-2.83 (m, 1H), 3.74 (s, 3H), 5.92 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.46-7.51 (m, 2H), 7.80-7.86 (m, 3H), 7.99 (s, 1H), 8.10 (dd, *J* = 1.6, 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.5, 21.6, 23.8, 50.3, 55.1, 114.0, 122.6, 125.0, 126.3, 126.4, 126.6, 127.6, 128.0, 128.3, 132.1, 133.0, 133.6, 134.7, 146.4, 158.6, 172.1; **HRMS** (ESI) calcd for $C_{23}H_{23}N_2O_2$ $[M+H]^+$ 359.1754; found 359.1746.

(3-(3,4-dichlorophenyl)-6-(4-methoxyphenyl)-5,6-dihydropyridazin-1(4H)-yl) (ph enyl)methanone (5l)

Yield: 98 mg, 86%; White solid; **mp:** 185-187 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.08-2.39 (m, 3H), 2.53-2.63 (m, 1H), 3.77 (s, 3H), 6.03 (s, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 7.37-7.52 (m, 5H), 7.64 (s, 1H), 7.76 (dd, *J* = 1.8, 7.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.5, 23.8, 51.1, 55.2, 114.2, 124.3, 126.4, 127.3, 127.4, 129.8, 130.2, 130.4, 131.4, 132.7, 133.0, 134.9, 137.1, 144.4, 158.8, 170.1; **HRMS** (ESI) calcd for $C_{24}H_{21}N_2O_2Cl_2$ $[M+H]^+$ 439.0975; found 439.0969.

1-(6-(4-methoxyphenyl)-3-(4-nitrophenyl)-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (5m)

Yield: 83 mg, 93%; Gummy liquid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.17-2.34 (m, 3H), 2.56 (s, 3H), 2.61-2.68 (m, 1H), 3.76 (s, 3H), 5.92 (s, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.89 (d, *J* = 9.1 Hz, 2H), 8.22 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.7, 21.5, 23.6, 50.4, 55.2, 114.2, 123.7, 125.8, 126.3, 131.6, 143.1, 144.1, 147.8, 158.8, 170.1; **HRMS** (ESI) calcd for $C_{19}H_{20}N_3O_4$ $[M+H]^+$ 354.1448; found 354.1440.

(6-(4-methoxyphenyl)-3-(4-nitrophenyl)-5,6-dihydropyridazin-1(4H)-yl) (phenyl) methanone (5n)

Yield: 96 mg, 92%; Gummy liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.17-2.43 (m, 3H), 2.61-2.72 (m, 1H), 3.76 (s, 3H), 6.06 (s, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.42-7.53 (m, 3H), 7.67-7.81 (m, 4H), 8.12 (d, *J* = 9.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.7, 23.7, 51.2, 55.2, 114.3, 123.6, 125.9, 126.3, 127.5, 129.7, 130.5, 131.3, 134.8, 142.8, 144.4, 147.7, 158.8, 170.3; **HRMS** (ESI) calcd for $C_{24}H_{22}N_3O_4$ $[M+H]^+$ 416.1605; found 416.1598.

1-(6-(4-chlorophenyl)-3-(naphthalen-2-yl)-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (5o)

Yield: 86 mg, 92%; Gummy liquid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.15-2.29 (m, 3H), 2.60 (s, 3H), 2.77-2.83 (m, 1H), 5.93 (s, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.46-7.51 (m, 2H), 7.82-7.87 (m, 3H), 7.98 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.3, 21.6, 23.6, 50.3, 122.5, 125.1, 126.4, 126.7, 126.8, 127.6, 128.0, 128.3, 128.8, 132.90, 132.95, 133.6, 134.5, 138.6, 146.5, 172.1; **HRMS** (ESI) calcd for $C_{22}H_{20}N_2OCl$ $[M+H]^+$ 363.1259; found 363.1254.

(3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)(4-nitrophenyl)methanone (2p)

Yield: 1.25 g, 90%; Yellow solid; **mp:** 160-162 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.18-2.45 (m, 3H), 2.67-2.82 (m, 1H), 6.07 (s, 1H), 7.16-7.20 (m, 2H), 7.27-7.40 (m, 6H), 7.50-7.55 (m, 2H), 7.92 (d, *J* = 8.5 Hz, 2H), 8.29 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.4, 20.9, 23.6, 51.3, 124.3, 125.1, 127.2, 127.3, 129.4, 129.7, 130.1, 130.3, 132.5, 132.8, 134.9, 136.4, 136.8, 137.0, 144.4, 170.0; **HRMS** (ESI) calcd for $C_{23}H_{20}N_3O_3$ $[M+H]^+$ 386.1499; found 386.1495.

1-(3,6-di([1,1'-biphenyl]-4-yl)tetrahydropyridazin-1(2H)-yl)ethan-1-one

(7a)Yield: 172 mg, 80%; White solid; **mp:** 142-144 °C; **^{1}H NMR** (400 MHz, $CDCl_3$)

δ: 2.19-2.34 (m, 3H), 2.43 (s, 3H), 2.73 (d, *J* = 13.0 Hz, 1H), 3.58 (d, *J* = 12.0 Hz, 1H), 3.96-4.02 (td, *J* = 2.0 and 10.0 Hz, 1H), 6.07 (d, *J* = 4.0 Hz, 1H), 7.34 -7.46 (m, 9H), 7.53-7.55 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.1, 25.4, 25.9, 48.8, 60.6, 127.04, 127.09, 127.1, 127.2, 127.3, 127.4, 127.5, 127.8, 128.7, 139.0, 140.0, 140.4, 140.5, 140.8, 173.2; **HRMS** (ESI) calcd for $C_{30}H_{29}N_2O$ $[M+H]^+$ 433.2280; found 433.2278.

(6-methyl-3,6-diphenyl-5,6-dihydropyridazin-1(4H)-yl)(4-nitrophenyl)methanone (7b)

Yield: 84 mg, 85%; White solid; **mp:** 178-180 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 2.19-2.40 (m, 3H), 2.61-2.71 (m, 1H), 7.25-7.45 (m, 10H), 7.85 (d, *J* =8.3 Hz, 2H), 8.27 (d, *J* =8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.1, 25.7, 35.7, 60.1, 122.6, 124.3, 125.1, 126.9, 128.5, 128.7, 129.4, 130.2, 136.5, 143.4, 143.8, 146.8, 148.2, 169.1; **HRMS** (ESI) calcd for $C_{24}H_{22}N_3O_3$ $[M+H]^+$ 400.1656; found 400.1652.

((2*Z*,6*Z*)-3,7-diphenyl-1,2,5,6-tetrazocine-1,5(4H,8H)-diyl)bis((4-nitrophenyl) met hanone) (E)

Yield: 84 mg, 60%; Yellow solid; **mp:** 152-154 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.11 (d, *J* =16.0 Hz, 1H), 4.74 (d, *J* =19.0 Hz, 1H), 5.24 (d, *J* =19.0 Hz, 1H), 5.92 (d, *J* =16.0 Hz, 1H), 7.32 (m, 2H), 7.39 (dd, *J* =8.0 and 8.0 Hz, 3H), 7.54-7.58 (m, 5H), 7.80 (d, *J* =7.3 Hz, 2H), 7.91 (d, *J* =8.6 Hz, 2H), 8.11 (d, *J* =8.0 Hz, 2H), 8.16 (d, *J* =9.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 51.5, 54.1, 102.4, 122.7, 123.9, 126.1, 126.9, 128.7, 129.2, 129.8, 130.2, 130.3, 130.5, 136.1, 136.2, 140.9, 148.6, 152.1, 153.3, 170.1; **HRMS** (ESI) calcd for $C_{30}H_{23}N_6O_6$ $[M+H]^+$ 563.1674; found 563.1675.

Section II

[4+2] Cycloaddition of in Situ-Generated 1,2-Diaza-1,3-dienes with Arynes: Facile Approach to 1,4-Dihydrocinnolines

4.2.1 Introduction

The cinnoline skeleton is common in fluorescent chemicals and biologically active and other functional molecules.[25-29] For example, some of its derivatives (**Figure 14**) exhibit fluorescent properties for cell-based imaging,[26] antitrypanosomiasis activity,[27] inhibitory activity toward Bruton's tyrosine kinase,[28] and antiallergic activities.[29] Cinnoline and its derivatives also play a role in organic synthesis[30] and electrochemistry,[31] and they have useful optical[32a] and luminescent properties.[32b] Despite this, the synthesis of cinnolines has been less frequently investigated. Cinnoline is also an important nitrogen-containing heterocyclic compound, and its derivatives exhibit widespread potent biological and pharmaceutical activities, such as inhibitory activity toward CSF-1R, inhibited ulceration, anti-inflammatory, antitumor, and anticancer activity.[33]

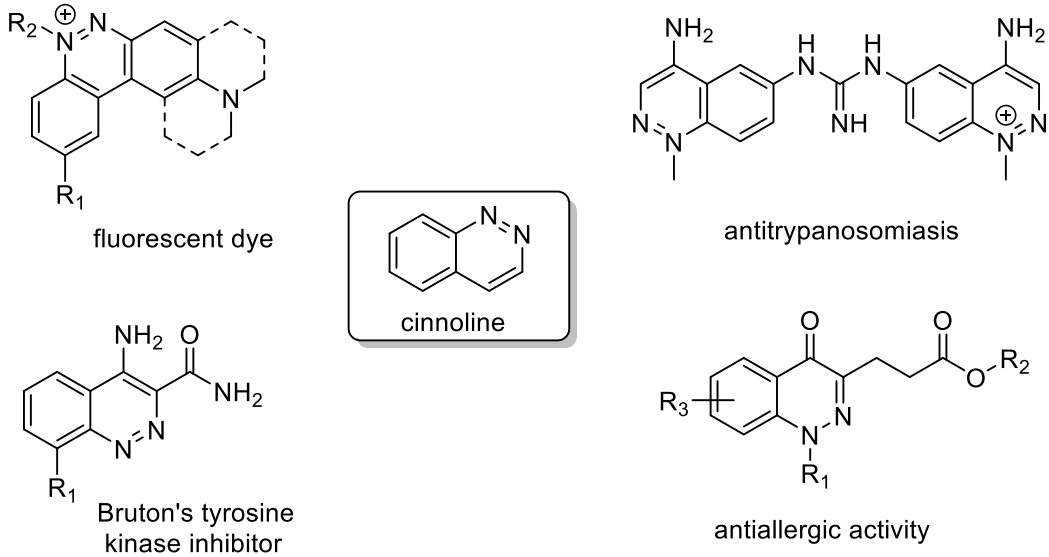
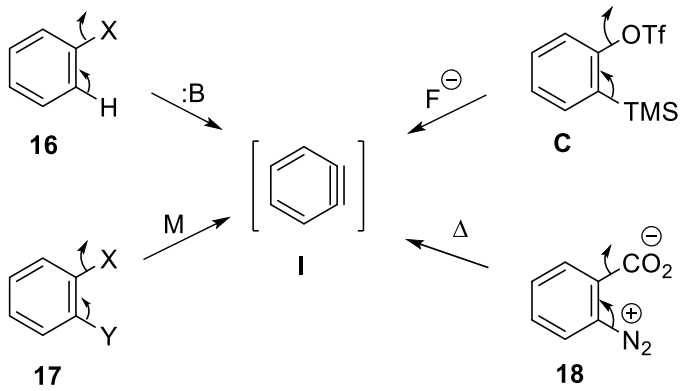


Figure 14: Functional molecules containing the cinnoline skeleton.

4.2.2. The Chemistry of Arynes

The term 'arynes' is used to refer both 1,2-dehydrobenzene derivatives (benzyne) and their heterocyclic analogues (heteroarynes). Arynes are highly reactive intermediates obtained formally by the removal of two adjacent atoms from, respectively, an aromatic ring or a heterocyclic aromatic ring as depicted in **Scheme 14**.



Scheme 14: Methods for the generation of arynes.

O-Benzyne is an important reactive intermediate and many methods are available in literature for their generation[34] (**Scheme 14**). Because of their high reactivity, arynes must be generated *in situ*. An aromatic halide **16** can be treated with a strong base such as an amide,[34a] to remove the *o*-aromatic proton and generate benzyne **I** *via* an anion. The use of strong bases which may act as nucleophiles can be avoided by the treatment of *o*-dihalosubstituted benzenes **17** with a metal (lithium or magnesium) to give the desired aryne **I** by elimination.[35] Arynes may also be obtained from anthranilic acid, by the decomposition of the internal benzenediazonium-2-carboxylate **18**.[36] Use of *o*-silyl aryl triflates **C** to generate arynes is the most promising and mild method compared to other routes.[37] For example, fluoride ion displacement of the trimethylsilyl group provides a convenient route to benzyne under

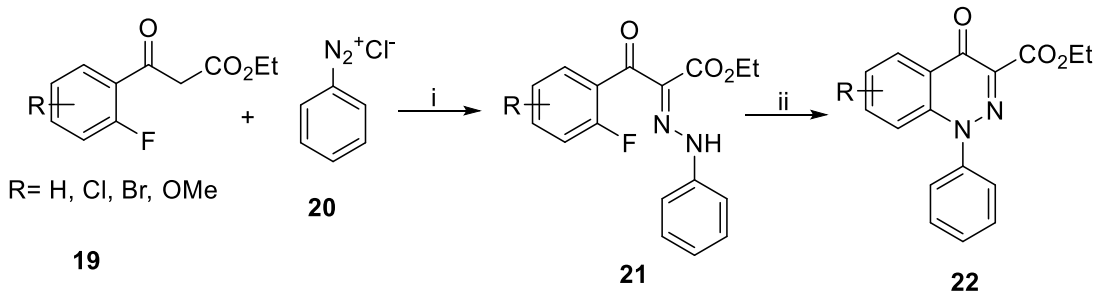
mild reaction conditions. Even at low temperatures, arynes are extraordinary reactive. Their reactions can be divided into three major groups: (i) the pericyclic reactions of arynes; (ii) the nucleophilic additions to arynes and (iii) the transition metal-catalysed reactions of arynes. The pericyclic reactions can be divided into several categories such as: (i) Diels-Alder reactions occurring in an inter- or intramolecular mode; (ii) the [2+2] cycloadditions; (iii) the 1,3-dipolar cycloadditions; (iv) the 1,4-dipolar cycloadditions; and (v) the ene reactions. Arynes react with practically all kinds of nucleophiles; from a synthetic point of view, the most interesting are the nitrogen-bearing nucleophiles and carbanions.

4.2.3 Review of Literature

Literature survey revealed that there are number of methods known for the synthesis of cinnoline scaffold[38-49] and its derivatives involving arenediazonium salts, arylhydrazones, arylhydrazines, nitriles, and transition metal catalyzed coupling; some of which are described briefly below.

Ames's approach (1983)[38]

Ames *et al*. developed an efficient method, which involved the reaction of diazonium salt **20** with ethyl 2-fluorobenzoyl acetate derivatives **19** under basic conditions to afford cinnoline-3-carboxylic esters **22** *via* the isolable intermediate **21**. The strongly electron-attracting fluoride act as a good leaving group while steric hindrance to the

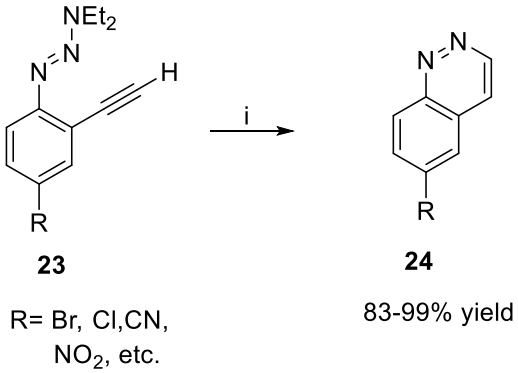


Scheme 15: (i) Na_2CO_3, EtOH, 0 °C, 2 h; (ii) K_2CO_3, 2-butanone, 110 °C, 6 h.

reaction is minimized (**Scheme 15**).

Haley's approach (2000)[39]

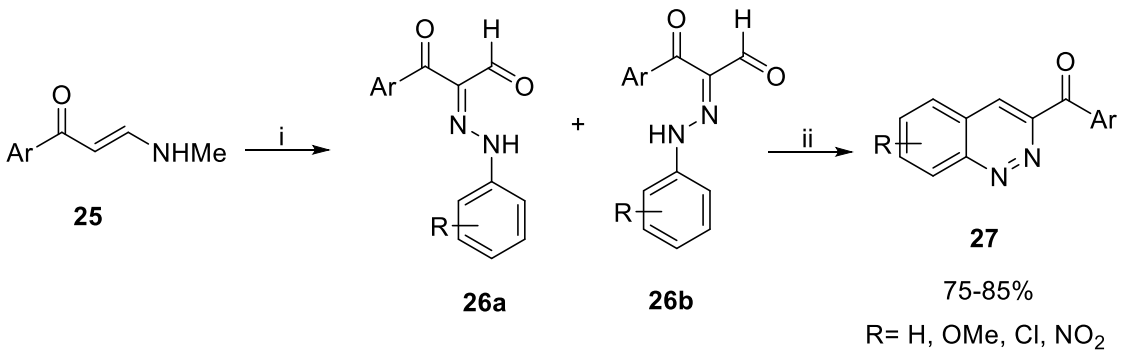
Haley's *et al* have reported an efficient synthesis of 6-substituted cinnolines **24** directly from (4-substituted-2-ethynylphenyl)triazenes **23** via intramolecular cyclization of **23** when carried out under neutral conditions at 200 °C (**Scheme 16**).



Scheme 16: (i) o-Cl_2Ph, 200 °C.

Al-Awadi's approach (2001)[40]

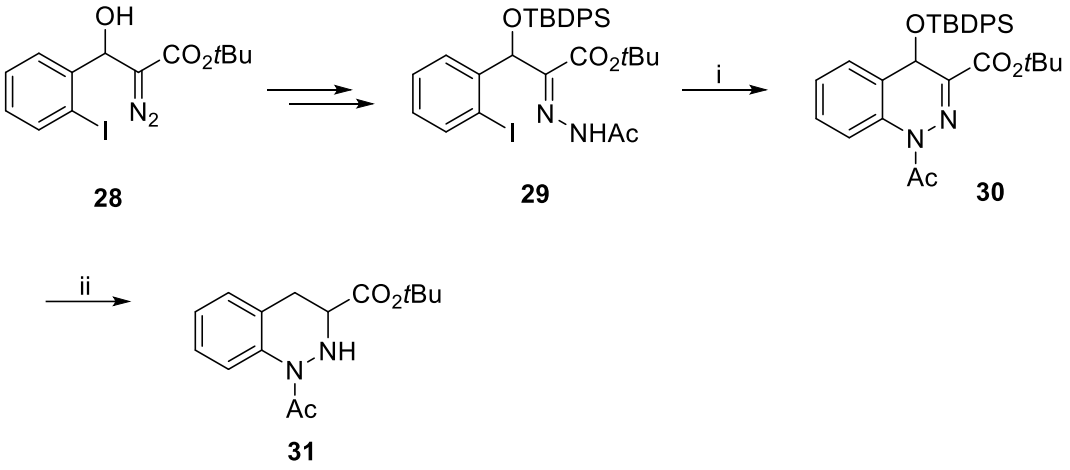
Al-Awadi *et al* have reported an efficient synthesis of 3-aroylcinnolines **27** starting from the appropriate enamine **25**. The enamine **25** on reaction with aryl diazonium chloride gave the corresponding 3-oxo-3-aryl-2-arylhydrazonopropanals **26a & 26b**, which upon acid-catalyzed cyclization in conc. H_2SO_4 led to the isolation of 3-aroylcinnolines **27** in high yields (**Scheme 17**).



Scheme 17: (i) $RC_6H_4N_2Cl$, NaOH, EtOH; (ii) conc. H_2SO_4, 100 °C, 3-5 min..

Nishida's approach (2008)[41]

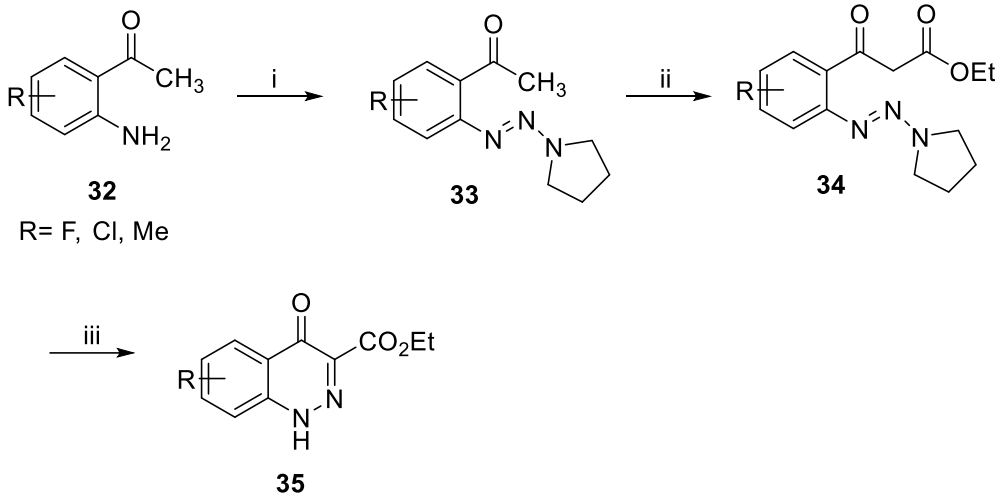
Nishida *et al*. have demonstrated that iodo hydrazones **28** are useful precursors for the facile synthesis of cinnoline **30**, dihydrocinnoline derivatives **31** by Cu-catalyzed intramolecular N-Arylation. The hydrazones as cyclization precursors are obtained from 3-haloaryl-3-hydroxy-2-diazopropanoates **28** in 4 steps (**Scheme 18**).



Scheme 18: (i) CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (2.0 equiv.), DMSO, 25 °C, 10 min., 89%; (ii) H_2 (1 atm), 5 % Pd/C, MeOH, 6 h, 55 %.

Scott's approach (2011)[42]

Scott *et al*. have reported a diazotization strategy in which o-aminoacetophenone **32** is reacted with pyrrolidine for the synthesis of dihydrocinnoline ester **35** in high yields. In this reaction *in situ* generated diazonium salt of **32** was trapped with pyrrolidine to give **33**, which on reaction with diethyl carbonate gave **34**, isolated as its sodium salt. The cyclization of **34** in TFA gave the corresponding dihydrocinnoline ester **35** (**Scheme 19**).



32

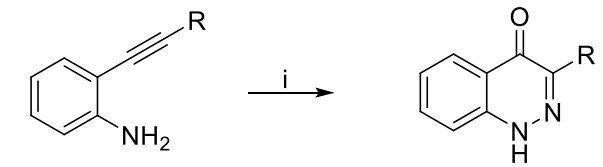
R= F, Cl, Me

33 **34** **35**

Scheme 19: (i) conc. HCl, $NaNO_2$, H_2O, 0 °C then pyrrolidine, 0.4 N aq. NaOH; (ii) CO $(OEt)_2$, NaH, THF, reflux; (iii) TFA, 0 °C.

Ranu's approach (2011)[43]

Ranu *et al* have developed a general and green protocol for the synthesis of cinnolines **37** starting from commercially available 2-alkylethynyl aniline **36** through diazotization strategy. The yields were found to be excellent so that the protocol can be applied for the large scale synthesis (**Scheme 20**).



36 **37**

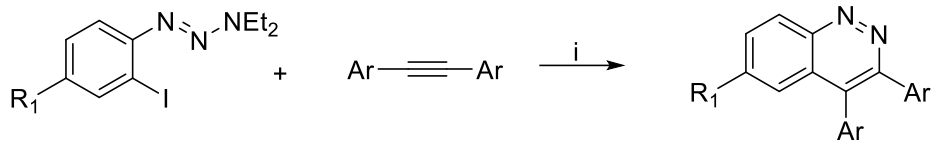
R= aryl, alkyl 80-92% yield

Scheme 20: (i) $NaNO_2$/HCl, H_2O, 0-5 °C, 5 min.

Yamane's approach (2011)[44]

Yamane *et al.* have developed a useful method for the synthesis of 3,4-disubstituted cinnolines **40** *via* Pd-catalyzed annulation of 2-iodophenyltriazenes **38** with an internal alkyne **39** in moderate to good yields. Several internal alkynes are applicable

to this reaction and the method is compatible with a number of functional groups as well (**Scheme 21**).



38 **39** **40**

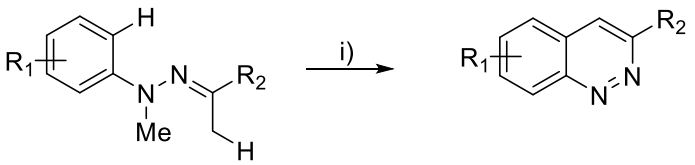
R1= NO_2, Cl, CN, OMe etc.

35-84% yield

Scheme 21: (i) $PdCl_2$ (8 mol%), P(o-tolyl)$_3$ (16 mol%), n-Bu_3N (50 mol%), DMF, 90 °C.

Ge's approach (2012)[45]

Ge *et al*. have developed an efficient Cu-catalyzed aerobic intramolecular dehydrogenative cyclization reaction of N-methyl-N-phenylhydrazones **41** through sequential Csp^3-H oxidation, cyclization, and aromatization processes. This transformation is the first example of Cu-catalyzed coupling reactions of hydrazones through a Csp^3-H bond functionalization pathway. This novel method provides an efficient route to produce cinnoline derivatives **42** (**Scheme 22**).



41 **42**

R_1= Cl, Br, CN, OMe, etc

R_2= Aryl, Br, CN, OMe, etc

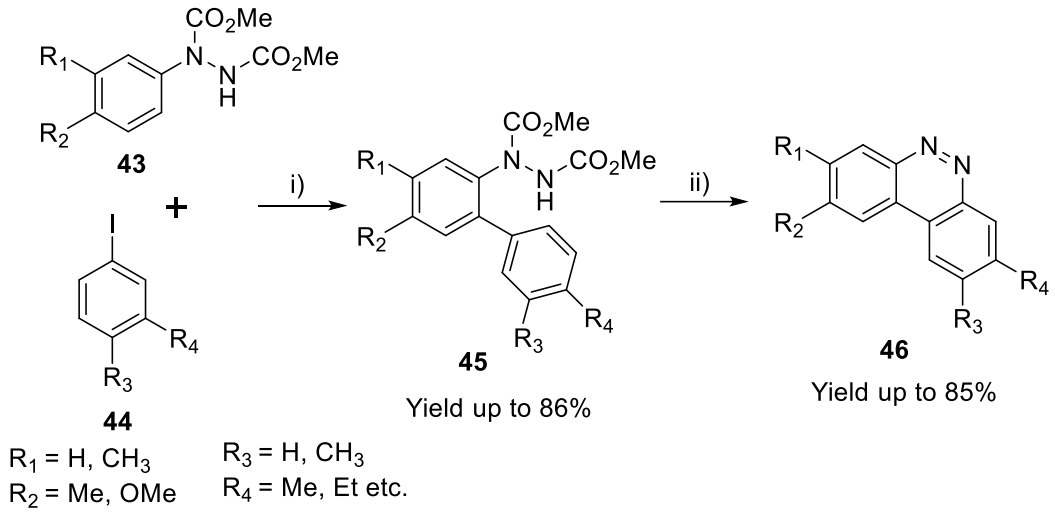
47-96% yield

Scheme 22: (i) $CuSO_4$ (1.5 mol%), CuI (7.5 mol%), pyridine (3.5 equiv.), CF_3SO_3H (1 equiv.), O_2 (1 atm), DMF, 110 °C.

Reddy's approach (2016)[46]

Reddy's *et al*. has developed a novel strategy for the synthesis of benzo[*c*]cinnoline derivatives **46** through a sequential C-C and C-N bond formation by means of C-H activation. The reaction proceeds *via* the C-arylation of 1-arylhydrazine-1,2-

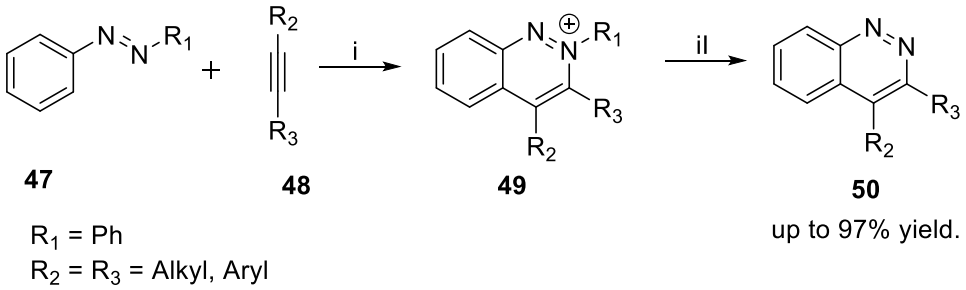
dicarboxylate **43** with aryl iodide **44** using $Pd(OAc)_2$/AgOAc followed by an oxidative N-arylation in the presence of PhI/oxone in trifluoroacetic acid. This method provides a direct access to biologically relevant benzo[c]cinnoline scaffolds from aryl hydrazine dicarboxylates *via* the substrate-directed oxidative functionalization. However, this method fails to generate biaryls with electron-deficient nitro- and cyano-substituted aryl iodides (**Scheme 23**).



Scheme 23: (i) $Pd(OAc)_2$ (10 mol%), AgOAc (1.5 equiv.), AcOH, 135 °C, 8 h .

Zhao's approach (2016)[47]

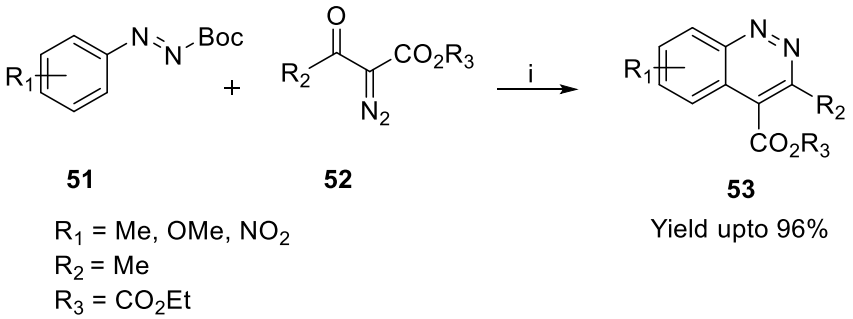
Zhao *et al.* have developed a highly efficient and general method to create both cinnoline **50** and cinnolinium frameworks **49** through the rhodium(III)-catalyzed oxidative C-H activation/cyclization of azo compounds **47** with alkynes **48**, which exhibits an unprecedented capacity to install versatile functional groups at various positions of the cinnoline ring (**Scheme 24**).



Scheme 24: (i) $[RhCl_2(cp^*)]_2$ (2.0 mol%), $Cu(OAc)_2$ (2.0 equiv.), Ag_2CO_3 (10 mol%), $NaBF_4$ (2.0 equiv.), *t*-AmylOH, 110 °C, 16 h; (ii) Pyridine, 140 °C, 8h.

Lin's approach (2016)[48]

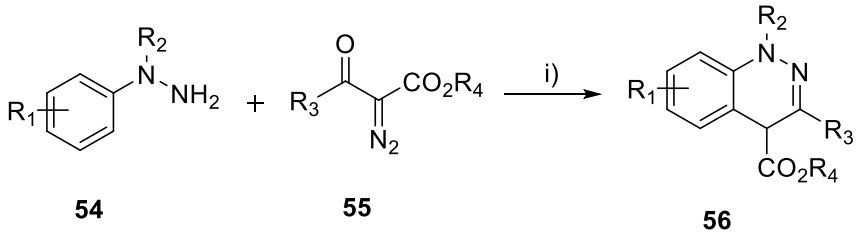
Lin *et al*. have reported a Rh-catalyzed redox-neutral annulation reaction between azo and diazo compounds **51** & **52**, representing an efficient and economical protocol to cinnolines **53** in one step under mild conditions. The procedure involved C-H activation and C-N bond formation (**Scheme 25**).



Scheme 25: (i) **51** (0.75 mmol, 1.5 equiv.), **52** (0.5 mmol, 1.0 equiv.), $[Cp^*RhCl_2]_2$ (0.0125 mmol, 2.5 mol%), $AgSbF_6$ (0.1 mmol, 20 mol%), 2 mL PivOH/DCE (v:v = 1:20), 50 °C, 24 h.

Zhu's approach (2016)[49]

Zhu *et al.* reported the synthesis of the cinnoline scaffold **56** through the use of C-H activation of 1-alkyl-1phenylhydrazines **54** and *α*-diazo-*β*-ketoesters **55** as the redox-neutral coupling partners using Rh (III)-catalyst. A successive C-H activation/C-C coupling/ intramolecular dehydration are some of the key steps involved during the course of reaction (**Scheme 26)**.



54 **55** **56**

Scheme 26: (i) **54** (0.25 mmol, 1.0 equiv.), **55** (1.1 equiv.), MeOH (1.0 ml), 50 °C, 16h.

4.2.4 Present Work

4.2.4.1 Objective

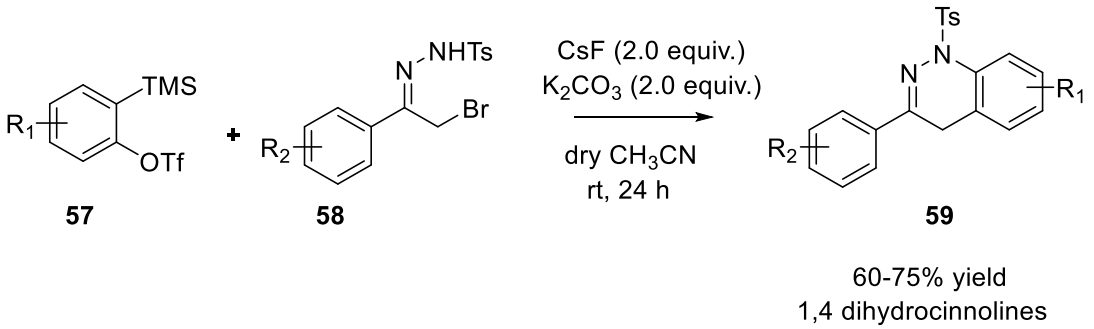
From the above discussion, it is clear that there are number of strategies available for the synthesis of substituted aromatic cinnoline and its derivatives due to the biological importance of cinnoline scaffolds. However, the reported methods available in the literature have some drawbacks such as require expensive metal salts, harsh reaction conditions and high temperature. Therefore, a general method, which overcomes the above limitations for the synthesis of cinnoline derivatives, is of interest to synthetic organic chemists.

4.2.5. Results and Discussion

Kobayashi's discovery of generating highly reactive aryne intermediates using a very mild fluoride-induced 1,2-elimination reaction of *o*-(trimethylsilyl) aryl triflates **C**, has seen plenty of new synthetic applications in the past few years. Because of the high reactivity of arynes, it becomes an important synthetic tool for the construction of novel cyclic and heterocyclic compounds. In recent years, our group has been engaged in the development of novel methodologies for the construction of pharmaceutically important nitrogen-containing heterocyclic compounds. Herein, we report a transition-metal-free [4+2] cycloaddition of in situ-generated 1,2-Diaza-1,3-dienes from *α*-halo N-tosyl hydrazones **58** with substituted *o*-(trimethylsilyl) aryl triflates **57** which gives direct access to 1,4-dihydrocinnoline derivatives **59**.

Advantages of this method are the use of commercially available starting materials and mild reaction conditions (**Scheme 27**).

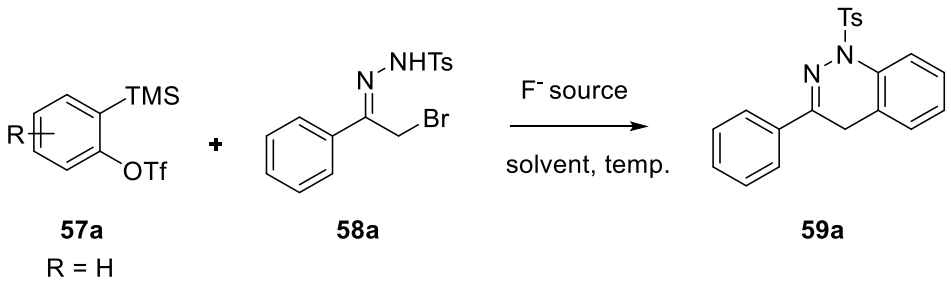
Scheme 27: Transition-metal free synthesis of 1,4-dihydrocinnolines



Optimization of the Reaction Conditions:

Our initial investigations of this new route to 1,4 dihydrocinnolines focused on the [4+2] cycloaddition of in situ-generated 1,2-Diaza-1,3-dienes from 2-(trimethylsilyl)-phenyl triflate (**57a**) and α-halo N-tosylhydrazone (**58a**).

Table 1 Optimization of the reaction condition for the synthesis of 1,4, dihydrocinnolines [a, b]



Entry	Fluoride-source (equiv)	Solvent	Temp. (°C)	Yield (%)[b]
1	TBAF (1.0)	THF	25	30
2	TBAF (2.0)	THF	25	40
3	CsF (2.0)	dioxane	25	45
4	CsF (1.5)	CH_3CN	25	50

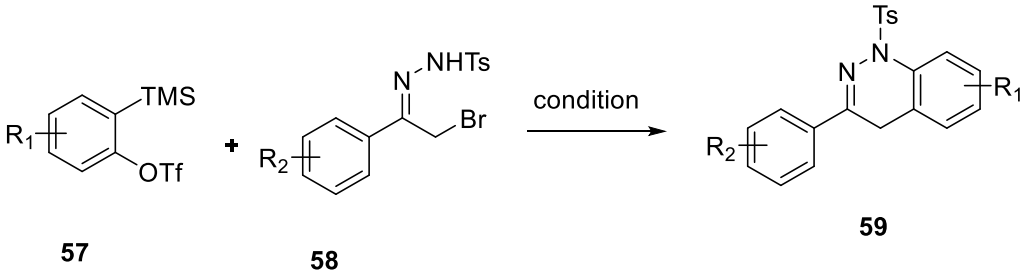
5	**CsF (2.0)**	**CH_3CN**	**25**	**66**
6	CsF (2.5)	CH_3CN	50	67

[a] Substrate **57a** (4.0 equiv.), **58a** (1.0 equiv.), K_2CO_3 (2.0 equiv.), fluoride source, solvent, temperature 24 h; [b]Isolated yield after column chromatographic purification.

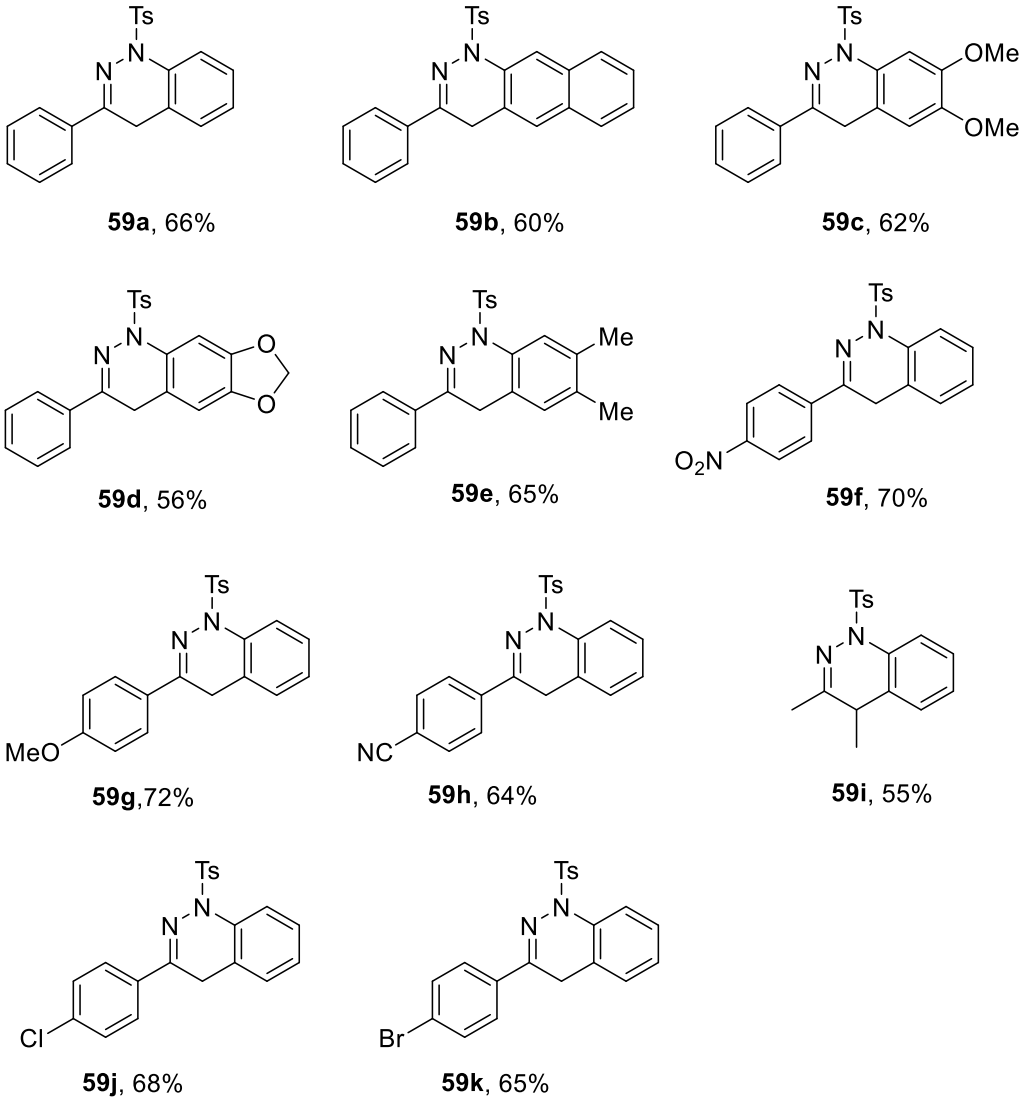
As a model substrate, when *α*-halo N-tosylhydrazone (**58a**) was treated with benzyne precursor **57a**, using TBAF as the fluoride source and THF as solvent at 25 °C in the presence of 2.0 equiv. of K_2CO_3, 1,4 dihydrocinnoline **59a** was obtained in 30% yield (**Table 1**, **entry 1**). Increase in the amount of fluoride source from 1.0 to 2.0 equivalent results in the slight increase in the amount of yields of **59a** (**Table 1**, **entry 2**). When we used CsF as the fluoride source instead of TBAF in dioxane, we observed further increase in the yield of **59a** (**Table 1**, **entry 3**). Switching to MeCN as solvent provided a significant increase in yield of desired product **59a** (**Table 1**, **entry 5**). However, screening of various other reaction parameters such as stoichiometry between the two coupling partners, fluoride source, solvents or temperature all failed to offer any further improvement in yield of the product (**Table 1**, **entry 4 & 6**).

With this optimized reaction conditions in hand, the substrate scope of the reaction was subsequently examined, and the results are summarized in **Table 2**. A range of differently substituted *α*-halo N-tosylhydrazones **58** underwent the [4+2] cycloaddition reaction between *in situ* generated azoalkenes with various aryne precursors **57** smoothly to afford the corresponding 1,4 dihydrocinnolines (**59a-k**). The electronic properties and varied positions of the substituted groups on the aromatic ring had no apparent effect on the reaction yields (**Table 2**, **59a-k**).

Table 2: Substrate scope for [4+2]-cycloaddition reaction[a]



57 **58** **59**



59a, 66% **59b**, 60% **59c**, 62%

59d, 56% **59e**, 65% **59f**, 70%

59g,72% **59h**, 64% **59i**, 55%

59j, 68% **59k**, 65%

[a] Reaction condition: Aryne precursor **57** (4 equiv), α-halo N-tosylhydrazones **58** (1 equiv), CsF (2.0 equiv), K_2CO_3 (2.0 equiv.) CH_3CN, 25 °C, 6 h.

The structure of 1,4 dihydrocinnolines (**59a-k**) was established unambiguously from the respective ^1H & ^{13}C NMR, IR and HRMS spectral data.

Example 1: The formation of 1,4 dihydrocinnoline **59i** was confirmed from its ^{1}H NMR spectrum, wherein presence of doublet at δ 1.55 (d, *J* = 7.0 Hz, 3H) and quartet at δ 4.03 (q, *J* = 7.0 Hz, 1H) due to the presence of methyl (-C**H**$_3$) and methine protons (-C**H**-) clearly indicates the formation of 1,4 dihydrocinnoline **59i**.

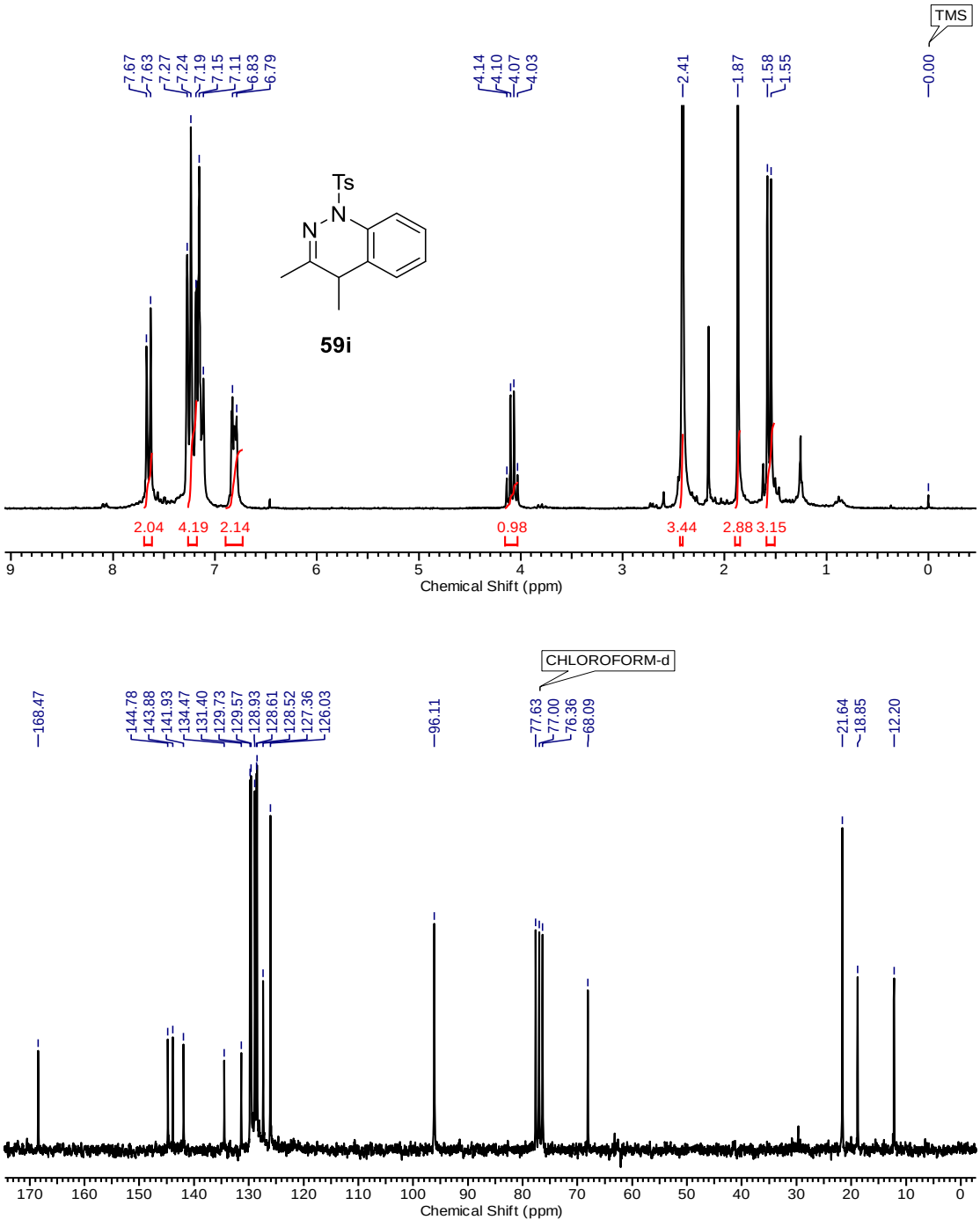


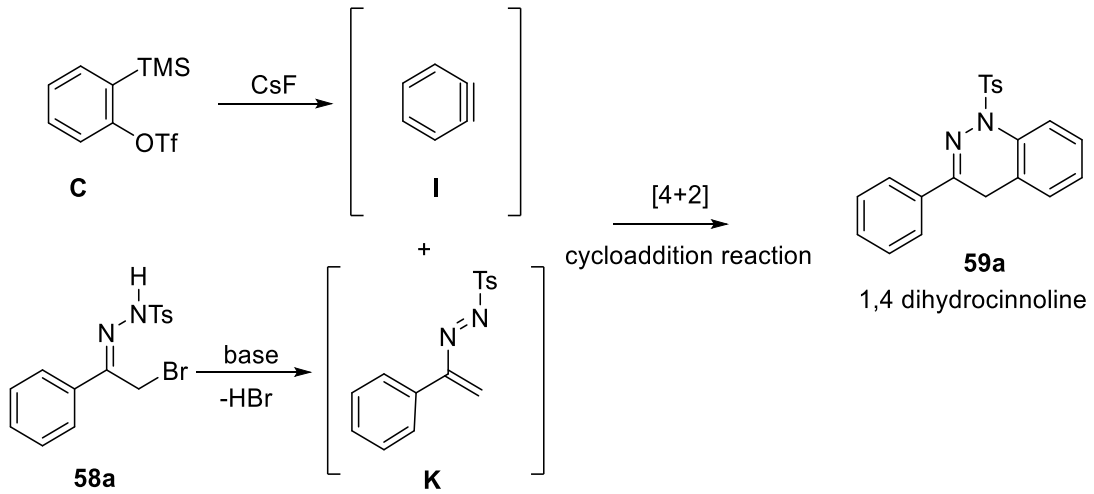
Figure 15: ^{1}H and ^{13}C NMR spectra of **59i**

This was further ascertained by the presence of characteristic carbon signals at δ 12.2, 18.8, 21.6 and 68.0 in its ^{13}C NMR spectrum corresponding to carbons of three methyl groups (-**C**H_3) and methine benzylic carbon (-**C**H-Ph) respectively. Further, the formation of **59i** was substantiated by its molecular mass $[(C_{17}H_{18}N_2O_2S)Na]^+$ (M+Na) obtained from HRMS (ESI) which was found to be 337.0980, in agreement with the calculated value of 337.0987 (**Figure 15**).

4.2.6 Mechanism

On the basis of the literature precedence, we have shown a probable reaction mechanism for the synthesis of 1,4 dihydrocinnolines **59a** (**Scheme 28**). Treatment of the *α*-halo hydrazone **58a** with base generates azoalkene **K** (1,2-diaza-1,3-diene) and treatment of aryne precursor **C** with cesium fluoride generates benzyne **I** *in situ* which then undergoes intramolecular [4+2] cycloaddition reaction to form 1,4 dihydrocinnoline **59a**.

Scheme 28: Proposed Mechanism



4.2.7 Conclusion `

In summary, we have developed a novel transition-metal-free method for the synthesis of 1,4 dihydrocinnoline derivatives by simple treatment with K_2CO_3 and

CsF in the absence of catalyst. This method allows the formation of new C-C and C-N bond in a single step. Mild reaction condition, broad substrate scope, high yields and good functional group tolerance are some of the attractive features of this methodology.

4.2.8 Experimental Section

General procedure for the [4+2] cycloaddition reaction of *α*-halo N-tosyl hydrazones 58 with arynes 57 for the synthesis of substituted 1,4,dihydrocinnolines 59:

To a solution of hydrazones **58** (0.5 mmol) and aryne **57** (2.0 mmol) in dry CH_3CN (3.0 ml) K_2CO_3 (1.0 mmol) and CsF (1.0 mmol) was added under N_2 atmosphere at room temperature. Then the reaction mixture was stirred for 24 h. After completion of the reaction (as monitored by TLC), solvent was evaporated and the crude reaction mixture was directly loaded on a silica column and purified using column chromatography (100-200 mesh silica gel) using pet.ether-ethyl acetate as the eluent to give 1,4 dihydrocinnoline derivatives **59** in high yields (for example **59g** in 72% yield) with high purity.

3-phenyl-1-tosyl-1,4-dihydrocinnoline (59a)

Yield: 66%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 4.0 (d, *J* = 16 Hz, 1H), 4.31 (d, *J* = 16 Hz, 1H), 7.15-7.53 (m, 11H), 7.91-8.07 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.6, 61.3, 122.3, 25.7, 127.3, 127.3, 127.9, 128.5, 128.5, 128.7, 129.6, 129.7, 129.9, 133.6, 137.1, 139.1, 144.5, 157.8; **HRMS** (ESI) calcd for $C_{21}H_{19}N_2O_2S$ $[M+H]^+$ 363.1167; found 36.1165.

3-phenyl-1-tosyl-1,4-dihydrobenzo[g]cinnoline (59b)

Yield: 60%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 4.2 (d, *J* = 16 Hz, 1H), 4.32 (d, *J* = 16 Hz, 1H), 7.20-7.56 (m, 10H), 7.63-7.94 (m, 5H); **^{13}C NMR** (100 MHz,

$CDCl_3$) δ: 21.4, 61.5, 121.2, 127.5, 127.7, 127.8, 128.2, 128.3, 129.0, 129.8, 134.0, 137.3, 138.2, 138.9, 140.1, 144.5; **HRMS** (ESI) calcd for $C_{25}H_{21}N_2O_2S$ $[M+H]^+$ 412.1210; found 412.1213.

6,7-dimethoxy-3-phenyl-1-tosyl-1,4-dihydrocinnoline (59c)

Yield: 62%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.75 (s, H), 3.80 (s, 3H), 4.1 (d, *J* = 15 Hz, 1H), 4.4 (d, *J* = 15 Hz, 1H), 7.55-7.84 (m, 6H), 7.85-7.92 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.6, 56.2, 57.3, 63.1, 104.3, 115.9, 118.3, 128.7, 128.9, 131.0, 134.1, 136.7, 140.8, 147.6, 155.6; **HRMS** (ESI) calcd for $C_{23}H_{23}N_2O_4S$ $[M+H]^+$ 422.1312; found 422.1314.

3-phenyl-1-tosyl-1,4-dihydro-[1,3]dioxolo[4,5-g]cinnoline (59d)

Yield: 56%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 4.40 (d, *J* = 15 Hz, 1H), 4.30 (d, *J* = 15 Hz, 1H), 6.05 (s, 2H), 7.14 (s, 1H), 7.38-7.53 (m, 8H), 7.94 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.3, 60.8, 100.3, 101.4, 114.8, 118.5, 128.7, 128.8, 131.0, 134.4, 136.5, 137.6, 140.7, 145.1, 145.3, 155.6; **HRMS** (ESI) calcd for $C_{22}H_{19}N_2O_4S$ $[M+H]^+$ 406.1015; found 406.1012.

6,7-dimethyl-3-phenyl-1-tosyl-1,4-dihydrocinnoline (59e)

Yield: 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.20 (s, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 4.10 (d, *J* = 16 Hz, 1H), 4.31 (d, *J* = 16 Hz, 1H), 7.38-7.50 (m, 6H), 7.62-7.54 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 19.0, 19.2, 21.4, 63.0, 115.7, 122.0, 126.6, 128.8, 128.9, 131.0, 131.2, 136.7, 136.8, 144.5, 155.2; **HRMS** (ESI) calcd for $C_{23}H_{23}N_2O_2S$ $[M+H]^+$ 390.1412; found 390.1411.

3-(4-nitrophenyl)-1-tosyl-1,4-dihydrocinnoline (59f)

Yield: 70%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 4.30 (d, *J* = 16 Hz, 1H), 4.35 (d, *J* = 16 Hz, 1H), 7.08-7.20 (m, 1H), 7.36-7.40 (m, 2H), 7.50-7.68 (m, 5H), 8.08 (t, *J* = 10 Hz, 2H), 8.32 (t, *J* = 10 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.5,

58.6, 116.2, 118.8, 125.1, 126.2, 126.4, 128.4, 128.7, 137.6, 129.3, 140.2, 147.5, 150.2, 155.6; **HRMS** (ESI) calcd for $C_{21}H_{18}N_3O_4S$ $[M+H]^+$ 407.0910; found 407.0914.

3-(4-methoxyphenyl)-1-tosyl-1,4-dihydrocinnoline (59g)

Yield: 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 3.8 (s, 3H), 4.34 (d, *J* = 16 Hz, 1H), 4.34 (d, *J* = 16 Hz, 1H), 4.45 (d, *J* = 16 Hz, 1H), 7.05-7.07 (m, 3H), 7.38-7.68 (m, 7H), 7.91 (t, *J* = 9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.3, 60.1, 56.9, 114.4, 114.5, 116.1, 118.6, 128.3, 128.5, 129.4, 129.7, 137.8, 147.4, 155.2, 162.8; **HRMS** (ESI) calcd for $C_{22}H_{21}N_2O_3S$ $[M+H]^+$ 392.1214; found 392.1216.

4-(1-tosyl-1,4-dihydrocinnolin-3-yl)benzonitrile (59h)

Yield: 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 4.36 (d, *J* = 16 Hz, 1H), 4.48 (d, *J* = 16 Hz, 1H), 7.07 (m, 1H), 7.38-7.68 (m, 9H), 7.99 (t, *J* = 10 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.2, 61.8, 114.8, 118.6, 118.7, 125.2, 125.3, 129.2, 129.3, 132.1, 132.3, 133.7, 134.8, 148.2, 155.8; **HRMS** (ESI) calcd for $C_{22}H_{18}N_3O_2S$ $[M+H]^+$ 387.1008; found 387.1009.

3,4-dimethyl-1-tosyl-1,4-dihydrocinnoline (59i)

Yield: 72%; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.55 (d, *J* = 7.2 Hz, 2H), 1.87 (s, 3H), 2.41 (s, 3H), 4.03-4.14 (q, *J*=7.0 Hz, 1H), 8.79 (m, 2H), 7.15 (m, 4H), 7.63 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 12.2, 18.8, 21.6, 68.0, 76.3, 77.0, 126.0, 127.3, 128.5, 128.6, 128.9, 129.5, 129.7, 131.4, 134.4, 141.9, 143.8, 144.7, 168.4; **HRMS** (ESI) calcd for $C_{17}H_{19}N_2O_2S$ $[M+H]^+$ 315.1167; found 314.1161.

3-(4-chlorophenyl)-1-tosyl-1,4-dihydrocinnoline (59j)

Yield: 68%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 4.41 (d, *J* = 16 Hz, 1H), 4.58 (d, *J* = 16 Hz, 1H), 7.07 (m, 1H), 7.40-7.70 (m, 9H), 8.01 (t, *J* = 10 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.7, 59.5, 116.4, 118.8, 125.1, 125.3, 128.7, 129.9,

132.0, 137.4, 137.6, 147.6, 154.4; **HRMS** (ESI) calcd for $C_{21}H_{18}ClN_2O_2S$ $[M+H]^+$ 396.0712; found 396.0711.

3-(4-bromophenyl)-1-tosyl-1,4-dihydrocinnoline (59k)

Yield: 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 4.42 (d, *J* = 16 Hz, 1H), 4.50 (d, *J* = 16 Hz, 1H), 7.08 (m, 1H), 7.38 (t, *J* = 10 Hz, 2H), 7.52 (m, 2H), 7.63-7.70 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.4, 60.3, 116.4, 118.6, 125.3, 125.5, 128.4, 128.6, 129.3, 129.4, 131.8, 136.5, 137.2, 142.4, 156.2; **HRMS** (ESI) calcd for $C_{21}H_{18}BrN_2O_2S$ $[M+H]^+$ 440.0216; found 440.0218.

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List of Publications

1. "Asymmetric synthesis of (+)-stagonolide C and (-)-aspinolide A *via* organocatalysis" **Shelke, A. M.;** Rawat, V.; Sudalai, A.; Suryavanshi, G., ***Tetrahedron : Asymmetry*** **2012**, *23*, 1534.
2. "A short enantioselective synthesis of 3-*epi*-jaspine B and (+)-oxybiotin *via* an intramolecular tandem desilylation oxa-Michael addition strategy" **Shelke, A. M.;** Rawat, V.; Sudalai, A.; Suryavanshi, G., ***RSC Advances*** **2014**, *4*, 49770.
3. "An efficient organocatalytic route for asymmetric total synthesis of Stagonolide F" **Shelke, A. M.;** Suryavanshi, G., ***Tetrahedron Letters*** **2015**, *56*, 6207.
4. "An efficient one pot regioselective synthesis of a 3,3'-spirophosphonylpyrazole-oxindole framework via base mediated [1,3]-dipolar cycloaddition reaction of the Bestmann–Ohira reagent with methyleneindolinones" **Shelke, A. M.;** Suryavanshi, G. ***Org. Biomol. Chem***. **2015,** *13*, 8669.
5. "Fluoride assisted synthesis of 1, 4, 5, 6 tetrahydropyridazines *via* [4+2] cyclodimerization of *in situ* generated azoalkenes followed by a C-N bond cleavage" **Shelke, A. M.;** Suryavanshi, G. ***Org. lett.*** **2016**, *18*, 3968.
6. "A formal total synthesis of Pinolide *via* L-proline-catalyzed sequential α-aminooxylation and Horner-Wadsworth-emmons olefination-Sharpless asymmetric dihydroxylation strategy**"** **Shelke, A. M.;** Suryavanshi, G. ***Tetrahedron: Asymmetry*** **2016**, *23*, 1534.
7. "An efficient Sn(II)-catalyzed one-pot synthesis of 3-substituted azetidine-2,4-dione framework" Chavan S. S.; Supekar, M. V.; Burate P. A.; Rupanwar, B. D.; **Shelke A. M**.; Suryavanshi, G. ***Org. Biomol. Chem***. **2017,** *15*, 2385.
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List of Patents

1 "Organocatalytic process for asymmetric synthesis of decanolides " **Shelke, A. M.;** Rawat, V.; Dey, S.; Sudalai, A.; Suryavanshi, G., **US9353077, US20160272608 A1, US20160272609 A1, WO2014037964 A2, WO2014037964 A3.**

2 "A new method for formation of ortho alkynyl anilines a key intermediate of dihydroquinolinones system *via* copper catalyzed multicomponent reactions (MCR) of terminal alkynes, aryness and azodicarboxylates " **Shelke, A. M.**; Suryavanshi, G.; 2014**, WO 2014057500 A1.**

3 "Regioselective synthesis of 3,3'spirophosphonyl pyrazole-2-oxindoles framework *via* base mediated base mediated 1,3 dipolar cycloaddtion reaction of bestmann ohira reagent with oxindolylidene acetates" **Shelke, A. M.;** Suryavanshi, G.; **2015-NF-0043**

4 "Novel substituted tetrahydrofuran compounds and process for preparation thereof" **Shelke, A. M.;** Suryavanshi, G.; 2015**, WO, 2015102024 A2.**