Enantioselective Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving Formation of Quinoline and Coumarin Derivatives *via* Rh-Catalyzed *ortho* C-H Bond Activation of Aromatics

Thesis Submitted to the AcSIR for the Award of

The Degree of

DOCTOR OF PHILOSOPHY

In Chemical Sciences

SUBMITTED BY

Sunita K. Gadakh

AcSIR Roll: 10CC11J26017

UNDER THE GUIDANCE OF

Dr. A. Sudalai

Chemical Engineering and Process Development Division
CSIR-National Chemical Laboratory
Pune-411008, INDIA

August 2015

Dedicated TO

MY BELOVED FATHER

FAMILY MEMBERS, TEACHERS AND FRIENDS

सीएसआयआर-राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग, पुणे - 411 008. भारत
CSIR-NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

Dr. A. Sudalai +91 20 2590 2547
Senior Principal Scientist
a.sudalai@ncl.res.in
Chemical Engineering &
Process Development Division

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving Formation of Quinoline and Coumarin Derivatives via Rh-catalyzed ortho C-H Bond Activation of Aromatics"*** which is being submitted to the ***AcSIR*** for the award of ***Doctor of Philosophy*** in ***Chemical Sciences*** by ***Ms. Sunita K. Gadakh*** was carried out by her under my supervision at the CSIR-National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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

CSIR-NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Enantioselective Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving Formation of Quinoline and Coumarin Derivatives via Rh-catalyzed ortho C-H Bond Activation of Aromatics"*** 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.

August, 2015
NCL, Pune

Sunita K. Gadakh
CE & PD Division
CSIR-National Chemical Laboratory
Pune-411 008, INDIA.

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Real scientific thinking is to be on the lookout for new ideas, new methods, new inventions all the time, in every direction, even using the old if it is useful. This is what my research guide ***Dr. A. Sudalai*** *believes. He has always been my inspiration for developing innovative ideas. He always gave me the freedom to put forward my opinion and views on the research. He has been very friendly throughout my tenure as student. Not many people have got this kind of nature. I feel very lucky to have him as my guide. Unending discussions with him and his day to day guidance enabled me to complete this research work fruitfully. It is a matter of great privilege and pleasure for me to offer my profound gratitude to him for his constant support and all he has done for me. I am indeed fortunate to have worked under his able, superlative leadership.*

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Indeed I am blessed to have elder sister like ***Meenakshi.*** *I am lost for words to describe her as individuals and it should suffice to say that I am simply blessed to have her ever by my side. She has been great in putting up with a lot of my gibberish and form an indispensable part of my life.*

No word would suffice to express my gratitude and love to my father ***Khanderao*** *for supporting me in whatever I choose or did, my mother* ***Chandrakala,*** *my brothers* ***Jalindar*** *and* ***Sanju****, my grandmother and Archana vahini, my niece Vicky for being a strong pillars of support for me and continuous showering of boundless affection on me. This Ph. D. thesis is a result of the extraordinary will, efforts and sacrifices of my family. I would like to dedicate this moment of joy to my family. My successes are dedicated to them now and always.*

I would like to thanks and respect my family specially my husband ***Dr. Kiran Phatangare*** *and others my father-in-law, mother-in-law, Suverna tai, Ashwini, Kaveri, Abhi, Shreya, Macchindra, Balasaheb, Baba, Ganesh, Anil, Sunil, Nilesh, Swati, Kiran and late Shital, also to my uncles & aunties , my bhabhi's Beby, Jyoti, Archana, Maneesha and Pramila for their constant encouragement. I would like to extend my gratitude towards my jiju Mr. Kisan Ambre and Krishna mama for their support and guidance.*

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*I wish to express my gratitude towards "****God-lord Shiva****", who gave me the strength and courage to fulfil my dreams. Last but not least* ***National Chemical Laboratory*** *for replenishing the state of art-knowledge in me, and exploring to the fascinating world of research.*

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

....Sunita

CONTENTS

ABBREVATIONS

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

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

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (230-400 mesh).
5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 MHz, Brucker Avance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.
8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.
9. Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a chiral column.
10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.
11. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
12. Elemental analysis was done on Carlo ERBA EA 110B instrument.
13. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

ABSTRACT

Enantioselective Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving Formation of Quinoline and Coumarin Derivatives *via* Rh-Catalyzed *ortho* C-H Bond Activation of Aromatics

Research Student: Sunita K. Gadakh

AcSIR Roll: 10CC11J26017

Research Guide: Dr. A. Sudalai

The thesis entitled **"Enantioselective Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving Formation of Quinoline and Coumarin Derivatives *via* Rh-Catalyzed *ortho* C-H Bond Activation of Aromatics''** is divided into four chapters. The title of the thesis clearly reflects the objective, which is to synthesize the bioactive molecules and utilizes the Rh catalysis for the development of synthetic methodologies applied to the synthesis of bioactive molecules and their intermediates. **Chapter I** deals with the synthesis of HIV protease inhibitor **amprenavir, saquinavir, nelfinavir** and **its analogue** *via* Co-catalyzed hydrolytic kinetic resolution (HKR) of racemic *anti*-azido epoxides with two consecutive stereocentres to generate the corresponding diols and epoxides in high enantiomeric purity (97–99% ee) in a single step. **Chapter II** describes the synthesis of other important molecules like **yashabushidiols A and B and lactone unit of compactin and mevinolin** by employing same chiral inducing step (i.e. Co-catalyzed two stereocentred HKR of β–hydroxy epoxide). Also, in this chapter we have presented

the enantioselective synthesis of *anti-Helicobacter* agent (+)-spirolaxine methyl ether using brown allylation and noyori's asymmetric reduction strategy. **Chapter III** deals with a simple and efficient synthesis of isocoumarins and alkylidenephthalides from 3-(1-hydroxycarbethoxy/alkyl)phthalides with DEAD/PPh_3 and catalytic amount of TBHP system. Its application is demonstrated in the total synthesis of bioactive molecules such as **cytogenin** and **(*Z*)-3-butylidene-7-hydroxy-5-methoxyphthalide**. **Chapter IV** describes Rh-catalyzed regioselective oxidative cyclization of aromatic anilines with alkyl propiolates for the synthesis of **quinoline carboxylates** and its application in the synthesis of quinolone antibiotic oxolinic acid. Also, in this chapter, we have utilized same catalytic system for the synthesis of bioactive **coumarin derivatives** in high yields.

Introduction

Jacobsen's Hydrolytic Kinetic Resolution (HKR) has emerged as an effective method for obtaining chiral epoxides and 1,2-diols in a highly enantioenriched forms.[1] In view of the importance of these chiral building blocks we have recently reported a flexible method that employs the Co-catalyzed hydrolytic kinetic resolution (HKR) of racemic *anti*-azido epoxides with two consecutive stereocentres to generate the corresponding diols and epoxides in high enantiomeric purity (97–99% ee) in a single step.[2] Looking towards the biological importance we have applied this methodology for the synthesis of HIV protease inhibitor amprenavir **(10),** saquinavir **(12),**[2] nelfinavir mesylate and its analogue **(22)**. Also the same chiral inducing step (Co-catalyzed two stereocentred HKR) was used for the synthesis of other important molecules like yashabushidiols **A (29)** and **B (30)** and

lactone unit of compactin and mevinolin **(31)**.[3] In the continuation of synthesis of enantioselective bioactive molecules we have completed the formal synthesis of spirolaxine methyl ether **(40a)** using brown allylation and asymmetric epoxidation strategy. The Mitsunobu reaction is a powerful and widely used for the dehydrative coupling of an alcohol with an acidic component to form esters, ethers, imides, and so on.[5] In this context, a simple and efficient synthesis of isocoumarins (**42**) and alkylidenephthalides (**43**) from 3-(1-hydroxycarbethoxy/alkyl)phthalides (**41**) with DEAD/PPh_3 and TBHP system is presented here. Its application is demonstrated in the total synthesis of bioactive molecules such as cytogenin **(44)** and (*Z*)-3-butylidene-7-hydroxy-5-methoxyphthalide **(45)**.[6] Recently, metal-catalyzed chelation-assisted oxidative cyclization of the *ortho*-aromatic or alkenyl C–H bond with C–C π-components has gained considerable attention to synthesize cyclic compounds.[7] In this oxidative cyclization reaction, mostly rhodium and palladium complexes have been widely used as catalysts. Herein, we wish to present the Rh-catalyzed regioselective oxidative cyclization of aromatic anilines **46** with alkyl propiolates catalytic Rh for the synthesis of quinolines a series of carboxylates **47-50** and same catalytic cycle utilized for the synthesis of coumarin derivatives **53** from phenyl acetate **52** and methyl acrylates. Also, the present methodology was demonstrated in the total synthesis of quinolone antibiotic oxolinic acid (**51**).

Statement of Problem

Since these molecules possess interesting biological activities, the need for a short and catalytic method for their synthesis from commercially available materials is of current interest. The reported synthesis of these highly bioactive molecules suffer from

disadvantages such as lengthy reaction sequences, enzymatic resolution, use of chiral auxiliaries, chiral pool approaches, and poor atom economy, etc.

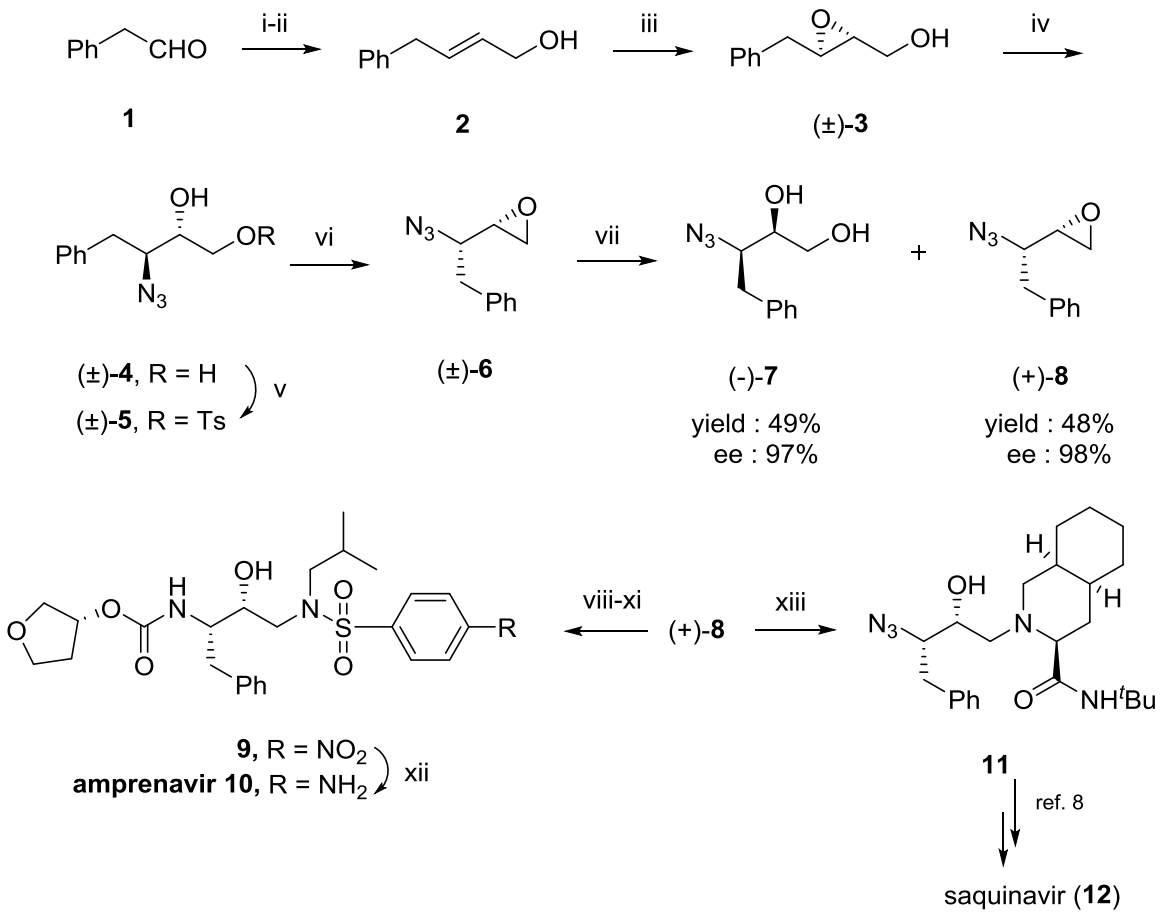
Methodology used

1. Biologically important molecules have been synthesized and their structures characterized by the advanced analytical and spectroscopic techniques such as high field NMR (^{1}H &^{13}C), FT-IR, LC-MS and HRMS.
2. The assignment of stereochemistry was carried out by NOESY NMR studies unambiguously.
3. The optical purity of chiral intermediates and final drug molecules has been determined from chiral HPLC analysis and comparing their specific rotation with those reported in the literature.
4. Percentage incorporation of isotope in isotopic labeling experiments have been determined by HRMS and/or high field NMR studies.

Chapter-I

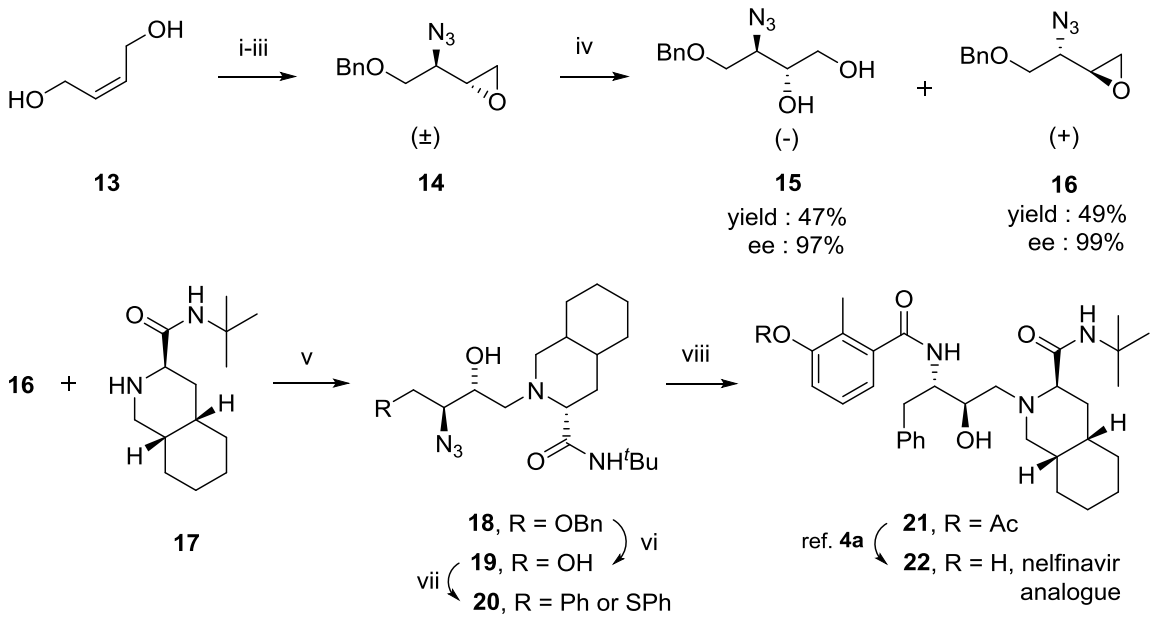
Enantioselective Synthesis of HIV Protease Inhibitors Amprenavir, Saquinavir and Nelfinavir *via* Co-Catalyzed HKR of Azido Epoxides

The present chapter deals with the total synthesis of amprenavir (**10**) and formal synthesis of saquinavir (**12**) has been achieved *via* Co-catalyzed HKR of 2-(1-azido-2-phenylethyl)oxirane **6** as the key steps starting from phenyl acetaldehyde **1** with overall yield of 21.7% and 27% respectively (**Scheme 1**).



Scheme 1: (i) $Ph_3P{=}CHCO_2Et$, PhH, 90 °C, 6 h, 96%; (ii) $LiAlH_4$, $AlCl_3$, Et_2O, 0 °C, 1 h, 87%; (iii) *m*CPBA, CH_2Cl_2, 0 °C, 8 h, 88%; (iv) $Ti(O^iPr)_4$, $TMSN_3$, C_6H_6, 70 °C, 5 h, 96%; (v) *p*-TsCl, Bu_2SnO, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; (vi) K_2CO_3, MeOH, 0 °C, 30 min (90% over two steps); (vii) (*S,S*) - Co(salen)OAc (0.5 mol %), THF, H_2O (0.5 equiv), 25 °C, 14 h; (viii) $^iBuNH_2$, ^{i}PrOH, 50 °C, 5 h; (ix) *p*-$NO_2C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 12 h, 89% (over two steps); (x) PPh_3, H_2O, THF, 25 °C, 29 h; (xi) *N*-hydroxysuccinimidyl carbonate of (*S*)-3-hydroxytetrahydrofuran, Et_3N, CH_2Cl_2, 25 °C, 2 h, (89% over two steps); (xii) $SnCl_2{\cdot}2H_2O$, EtOAc, 70 °C, 1 h, 90%; (xiii) [3*S*-(3*α*,4aβ,8aβ)]-*N*-(*tert*-butyl)decahydro-3-isoquinolinecarboxamide, silica gel (230-400, 6Å mesh), $CHCl_3$, 25 °C, 16 h, 85%.

The second section includes the asymmetric synthesis of nelfinavir and its analogue (**22**), which was achieved using the same protocol i.e. HKR of racemic azido epoxide **14**. Synthesis of these molecules was started with readily available *cis*-2-butene-1,4-diol (**13**) with overall yield of 23.7% and 21.1% respectively (**Scheme 2**).



Scheme 2: (i) NBS, NaN_3, CH_3CN:H_2O (3:1), 0 °C, 2 h, 89%; (ii) NaOH, THF, 0 °C, 3 h, 84%; (iii) BnBr, NaH, DMF, -0 °C, 2 h, 94%; (iv) (*S*,*S*)-Co(III)(salen) (0.5 mol %), H_2O (0.5 equiv), 0 to 25 °C, 12 h; (v) Silica gel (230-400, 6Å mesh), $CHCl_3$, 25 °C, 16 h, 85%; (vi) DDQ, CH_2Cl_2, 0 °C to rt, 4 h, 90%; (vii) (a) MsCl, DMAP, CH_2Cl_2, 0 °C, 1 h; (b) PhMgBr, THF, 0 °C-rt, 0.5 h, 90% over 2 steps; (viii) (a) Ph_3P, H_2O, THF, rt, 16 h; (b) 3-hydroxy-2-methyl benzoic acid, DCC, HOBt, -10 °C, THF, 48 h, 89% over 2 steps.

Chapter II

Enantioselective Synthesis of Yashabushidiols A and B and Lactone Unit of Compactin and Mevinolin and Formal Synthesis of Spirolaxine Methyl Ether

Chapter **II** describes the enantioselective synthesis of *β*-hydroxy-*δ*-lactone **31** (14.7% overall yield; 98% ee) *via* HKR of racemic *β*-silyl protected epoxide **26** starting from commercially available hydrocinnamaldehyde (**23)**. We have also described a short asymmetric synthesis of yashabushidiols **A 29** and **B 30** from the common key intermediates chiral epoxide **28** and diol **27** respectively (**Scheme 3**).

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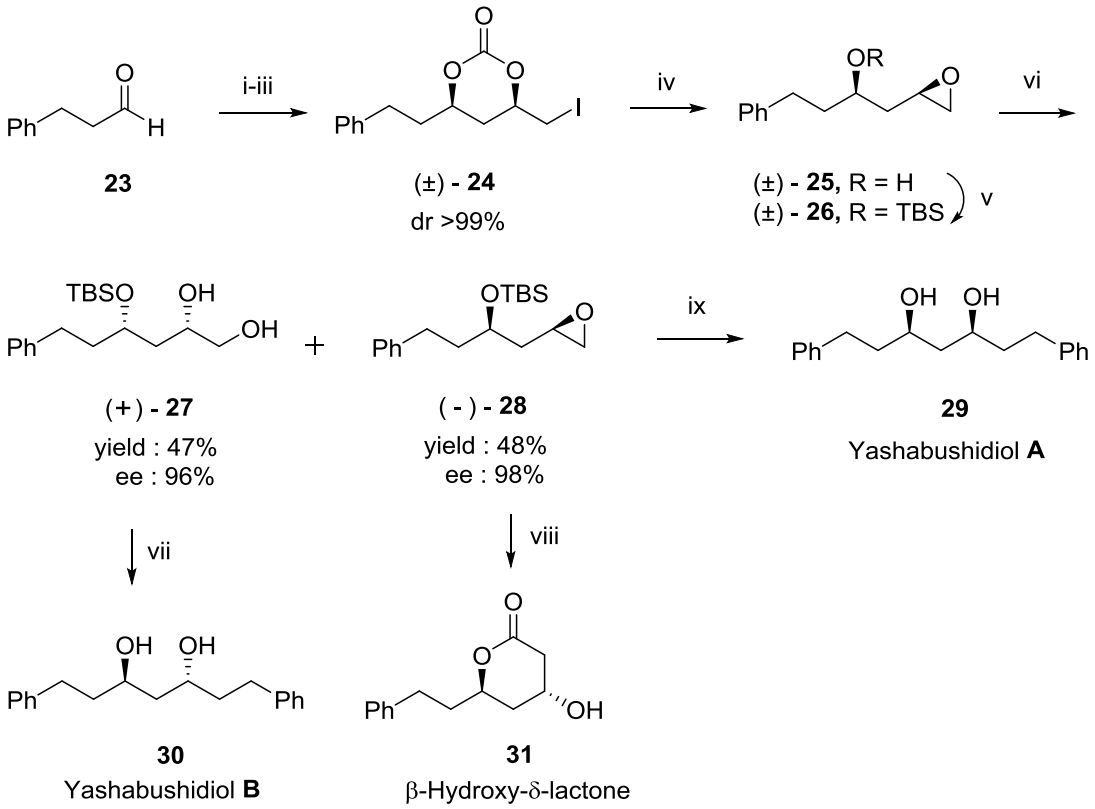
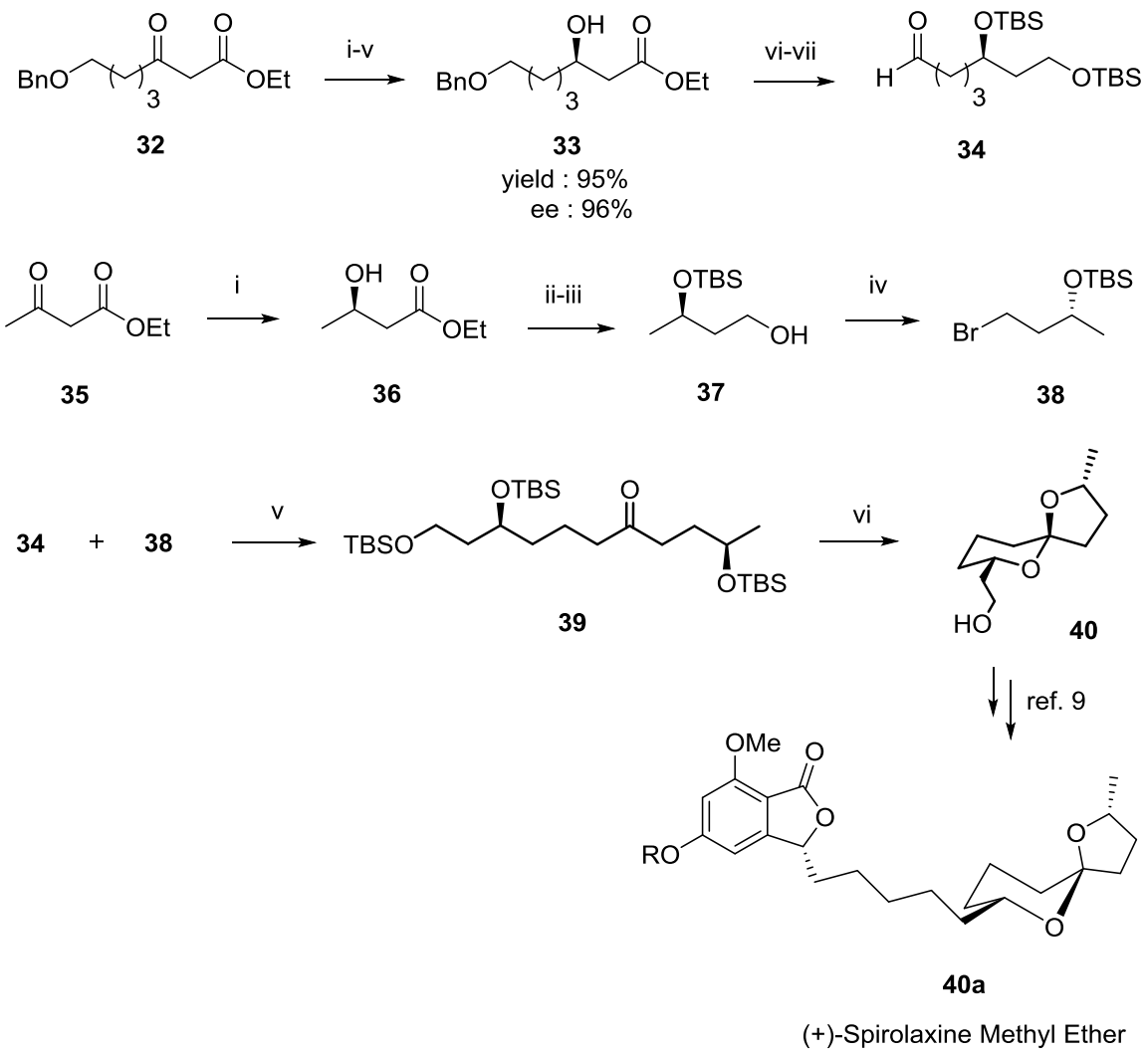


Scheme 3: (i) allyl bromide, Zn, NH_4Cl, CH_3CN, 0 °C, 3 h, 87%; (ii) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 0 ^oC, 1 h, 91%; (iii) N-iodosuccinimide, CH_3CN, -40 ^oC to 0 ^oC, 12 h, 85%; (iv) K_2CO_3, MeOH, 0 ^oC, 0.5 h, 84%; (v) TBSCl, imid., CH_2Cl_2, 0 ^oC, 1 h, 90%; (vi) (*R,R*)-(salen)Co(III)OAc (0.5 mol %), THF, H_2O (0.49 equiv), 25 °C, 14 h; (vii) NaCN, TFA (10 mol %), CH_2Cl_2, 60 ^oC, 4 h, 84%; (vii) (a) PivCl, Et_3N, cat. DMAP, 25 °C, 2 h, 90%; (b) MsCl, Et_3N, cat. DMAP, 25 °C, 2 h, 90%; (c) K_2CO_3, MeOH, 0 °C, 0.5 h, 89%; (d) BnBr, Mg, CuI, THF, 0-25 °C, 1 h, 88%; (viii) aq. HCl, MeOH, 50 ^oC, overnight, 79%; (ix) BnBr, Mg, CuI, THF, 0-25 °C, 1 h, 88%.

This chapter also deals with the formal synthesis of spirolaxine methyl ether **40a**, which was achieved by noyori's asymmetric reduction strategy. The chiral aldehyde fragment **34** and alkyl fragment **38** was obtained by Ru-catalyzed asymmetric reduction (96% ee) from the corresponding β-keto esters, which was used for the synthesis of final spiroketal **40**, further conversion has already been reported in the literature,[9] thereby constituting the formal synthesis of spirolaxine methl ether **40a**.

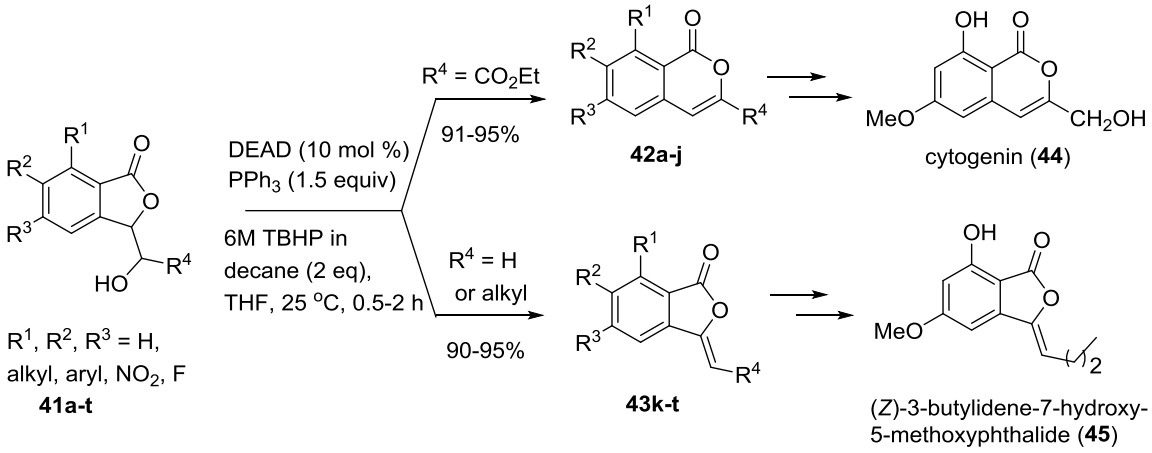


Scheme 4: (i) BnBr, NaH, DMF, 0 °C to rt, 4 h, 89%; (ii) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, rt, 1 h, 95%; (iii) ethyl bromoacetate, Zn, THF, reflux, 4 h, 90%; (iv) IBX, EtOAc, rt, 1 h, 87%; (v) $[(R)\text{-}Ru(BINAP)Cl_2]_2{\cdot}NEt_3$ (0.1 mol %), 2 M HCl (0.1 mol %), MeOH, H_2 (100 psi), 50 °C, 16 h, 95% yield, 96% ee; (vi) (a) $LiAlH_4$, THF, 0 °C, 3 h, 90%; (b) TBSCl, imid., CH_2Cl_2, 0 °C, 1 h, 85%; (vii) (a) 5% $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 2 h, 80%; (b) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, rt, 1 h, 88% (over two steps). (i) $[(R)\text{-}Ru(BINAP)Cl_2]_2{\cdot}NEt_3$ (0.1 mol %), 2 M HCl (0.1 mol %), MeOH, H_2 (100 psi), 50 °C, 16 h, 94%; (ii) TBSCl, imid., CH_2Cl_2, 0 °C, 2 h, 90%; (iii) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 85%; (iv) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h, 89%;(v) (a) Mg, 1,2-dibromoethane, THF, 0 °C to rt, 5 h; (b) IBX, EtOAc, 60 °C, 2 h, 75 % over 2 steps; (vi) CSA (cat.), CH_2Cl_2, 0 °C, 2 h, 76%.

Chapter III

A Simple and Efficient Synthesis of Isocoumarins and Alkylidenephthalides and Bioactive Molecule Cytogenin and (*Z*)-3-Butylidene-5-hydroxy-7-methoxyphthalide

The isocoumarins (**42a-h**) and alkylidenephthalides (**43k-t**) have been achieved *via* Mitsunobu reaction (DEAD/PPh_3/TBHP) strategy starting from phthalates (**41a-t**). This strategy has been employed in the synthesis of two bioactive molecules namely cytogenin (**44**) and (*Z*)-3-butylidene-7-hydroxy-5-methoxyphthalide (**45**) as shown in the **Scheme 5**.



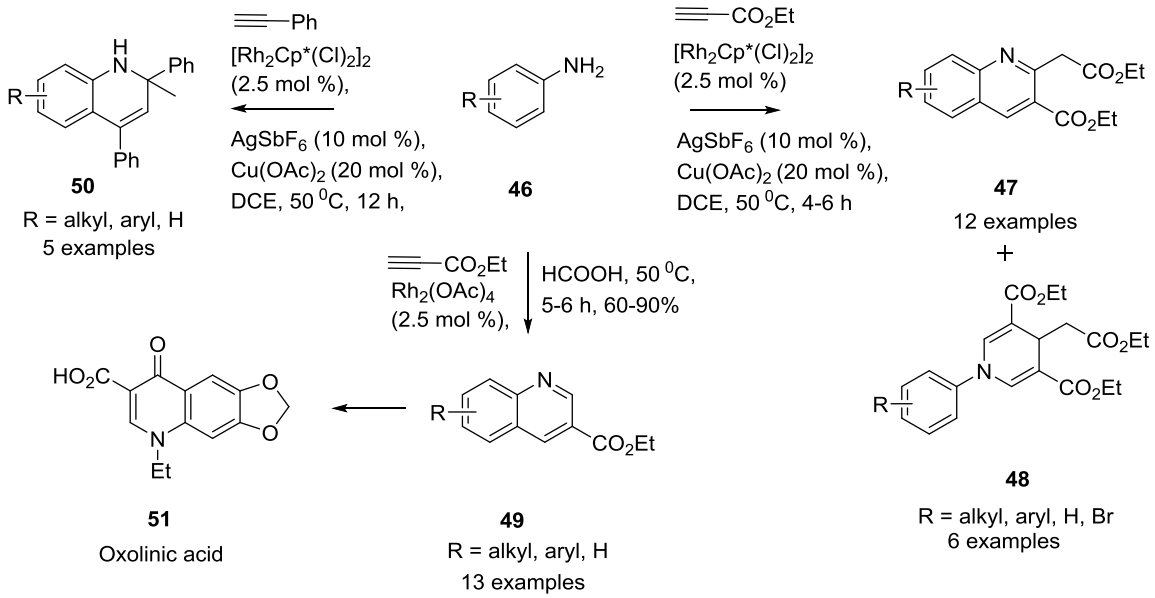
Scheme 5: Synthesis of isocoumarin and alkylidenephthalide derivatives and cytogenin.

Chapter IV

Development of Synthetic Methodologies Involving Formation of Quinoline and Coumarin Derivatives *via* Rh-Catalyzed *ortho* C-H Bond Activation of Aromatics

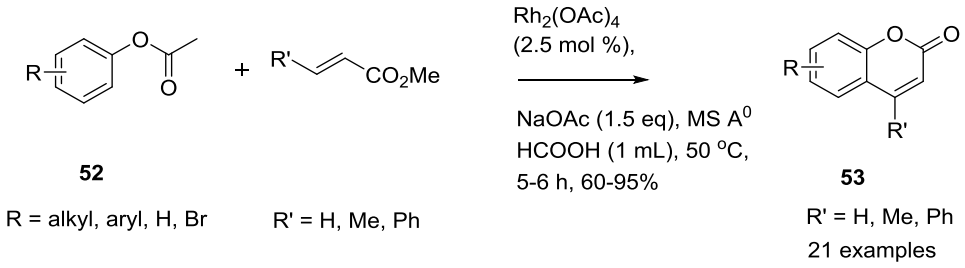
A simple rhodium catalyzed annulation strategy for the synthesis of substituted quinoline derivatives **47-50** from the corresponding substituted anilines **46** has been developed. Deuterium labelling studies establishes that this cyclization undergoes *via ortho* C-H bond

activation of anilines. Finally, this methodology has been successfully demonstrated in the synthesis of quinolone antibiotic namely oxolinic acid **51** (**Scheme 6**).



Scheme 6: Synthesis of substituted quinoline derivatives and oxolinic acid.

Also, describes the synthesis of biologically active coumarin derivatives **53** *via* rhodium catalyzed C-H activation of phenyl acetates **52** and coupling with methyl acrylates in high yields 60-95% (**Scheme 7**).



Scheme 7: Synthesis of substituted coumarin derivatives.

References:

1. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science*, **1997**, *277*, 936.
2. Reddy, R. S.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun.* **2010**, *46*, 5012.
3. Gadakh, S. K.; Reddy, S. R.; Sudalai, A. *Tetrahedron*: *Asymmetry*, **2012,** *23*, 898.
4. Gadakh, S. K.; Sudalai, A. *Tetrahedron*: *Asymmetry*, **2015**, *26*, 118.
5. (a) Mitsunobu, O. Synthesis, **1981**, 1; (b) Hughes, D. L. *Org. React*., **1992,** *42*, 335; (c) Hughes, D. L. *Org. Prep. Proced. Int*., **1996**, *28*, 127.
6. Gadakh, S. K.; Sudalai, A. *RSC Adv.*, **2014**, *4*, 57658.
7. Selected reviews for C–H bond activation: H. M. L. Davies, J. D. Bois and J.-Q. Yu, *Chem. Soc. Rev.*, **2011**, *40*, 1855, references cited therein.
8. Parkes, Kevin E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem*. **1994**, *59*, 3656.
9. Singh, M.; Argade, N. P. *Synthesis*, **2011**, 7, 1137.

CHAPTER I

Enantioselective Synthesis of HIV Protease Inhibitors Amprenavir, Saquinavir and Nelfinavir *via* Co-Catalyzed HKR of Azido Epoxides

Enantioselective synthesis of HIV protease inhibitor amprenavir *via* Co-catalyzed HKR of 2-(1-azido-2-phenylethyl)oxirane; **Gadakh**, **S. K.**; Reddy, R. S.; Sudalai, A. *Tetrahedron: Asymmetry*, **2012**, *13*, 898.

Section I

Concise Enantioselective Synthesis of HIV Protease Inhibitor Amprenavir *via* Co-catalyzed HKR of 2-(1-Azido-2-phenylethyl)oxirane

1.1.1 Introduction

The human immunodeficiency virus type 1 (HIV-1), the etiologic agent that causes acquired immunodeficiency syndrome (AIDS), encodes for a specific aspartyl proteinase (HIV-protease).[1] The inhibition of HIV-proteases by peptidomimetic structures incorporating a hydroxyethylamine (HEA) isostere offers a promising approach for the treatment of AIDS.[2] Many potent members of this class of inhibitors, such as amprenavir **1**,[3] fosamprenavir **2**,[4] and saquinavir **3**,[5] which belong to the HEA class, have complex structures equipped with multiple stereogenic centers (**Fig. 1**).

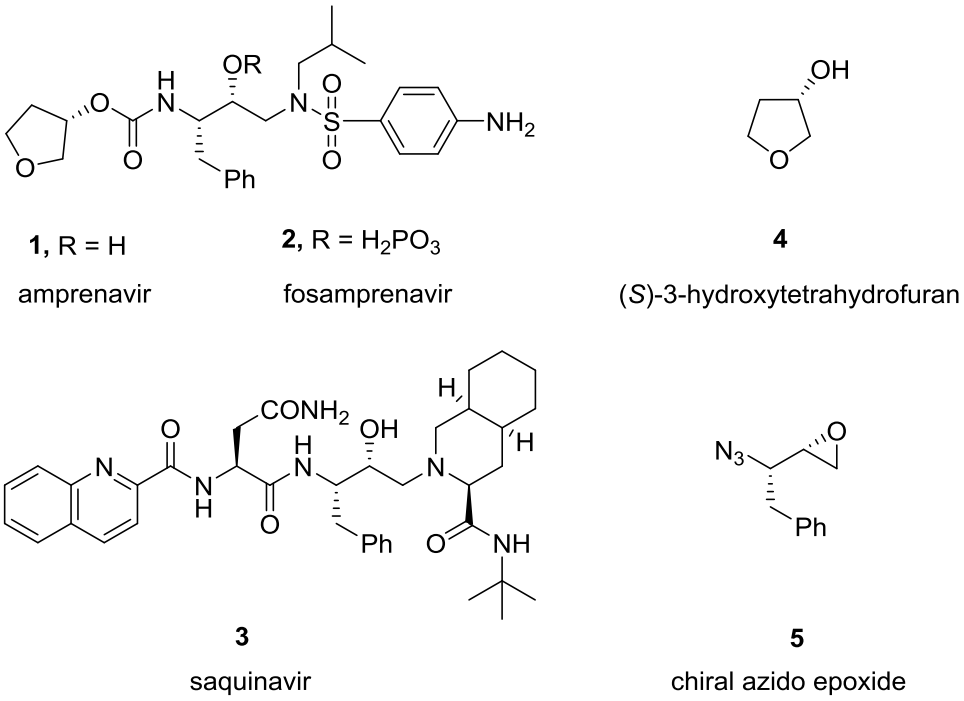


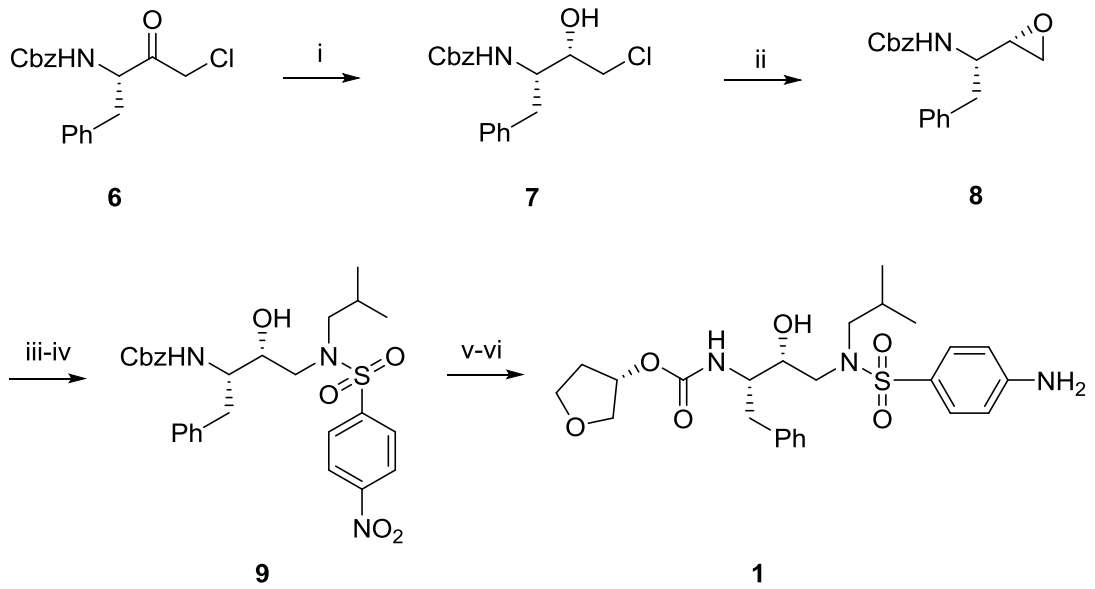
Fig. 1: HIV protease inhibitors and their key intermediates

1.1.2 Review of Literature

Due to the wide applicability and potential biological importance of these HIV inhibitors, considerable effort has been directed at methods for their synthesis.[6] Out of which some of the important and interesting synthetic routes to synthesize amprenavir **1** are described below.

Izawa's approach (2004)[6b]

Izawa *et al.* have reported the synthesis of amprenavir **1** using chiral pool approach as discussed below. Chloromethyl ketone **6** was obtained as a key intermediate in two steps from cross-Claisen condensation between methyl ester and *tert*-butyl acetate (68% yield). Distereoselective reduction of ketone **6** using $NaBH_4$ gave amino alcohol derivative **7** (*S,S*)/(*R,S*) = 84:16, which was further converted to amino epoxide **8** by base treatment. Opening of epoxide ring with isobutyl amine was achieved followed by its protection as its nosylate that afforded **9** in 85% yield.



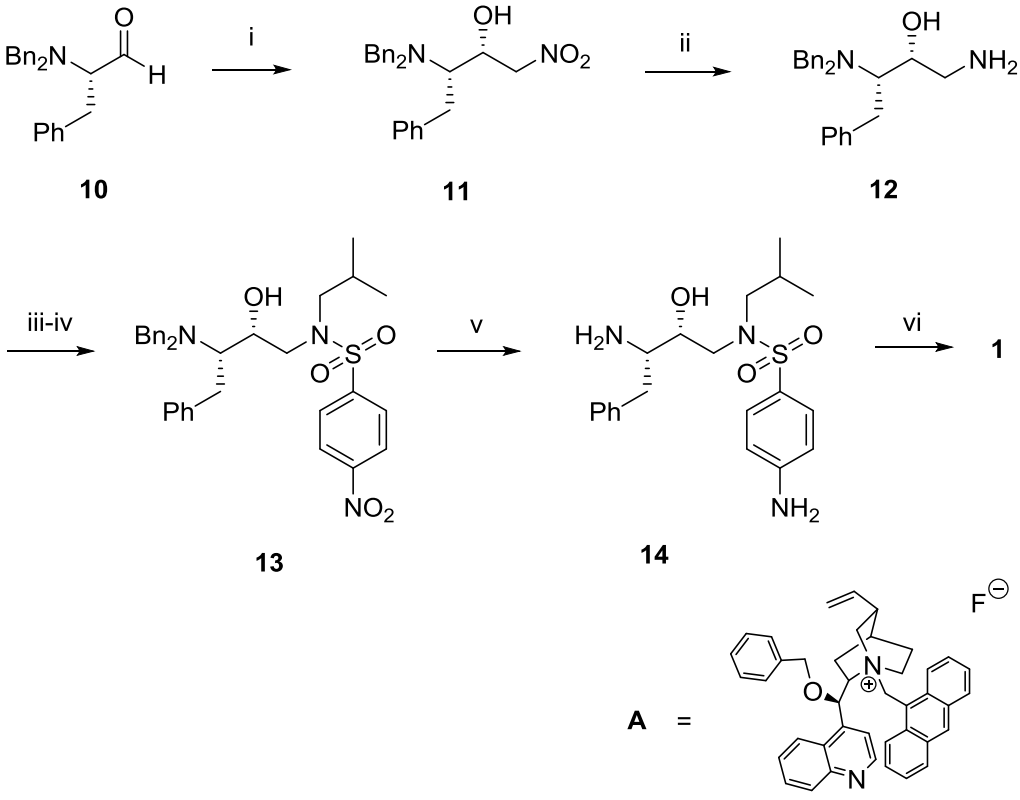
6 **7** **8** **9** **1**

Scheme 1: (i) (a) $NaBH_4$, CH_2Cl_2, MeOH, 0 °C; (b) AcOH; (ii) K_2CO_3, MeOH, ambient temp., 82%; (iii) *i*-$BuNH_2$, EtOH, 70 °C; (iv) nosyl chloride, aq. Na_2CO_3, ambient temp., 85%; (v) 30% HBr in AcOH, CH_2Cl_2, 17 °C; (vi) (*S*)-3-hydroxytetrahydrofuran, 15% K_2CO_3, CH_2Cl_2, 15 °C, 63%.

Deprotection of Cbz group with HBr/acetic acid, followed by a Schotten Baumann reaction with chloroformate, prepared by the treatment of (3*S*)-3-hydroxytetrahydrofuran with triphosgene, furnished the condensed product which on reduction gave **1** in 63% yield (**Scheme 1**).

Corey's approach (1999)[6a]

In Corey's approach, the synthesis of amprenavir **1** commences from the nitro aldol reaction of N,N-dibenzyl-(*S*)-phenylalaninal **10** with a mixture of quaternary ammonium salt **A**, nitromethane and KF in THF that afforded nitro alcohol **11** (dr = 17.1) in 86% yield; purified by flash chromatography. Treatment of nitro alcohol **11**

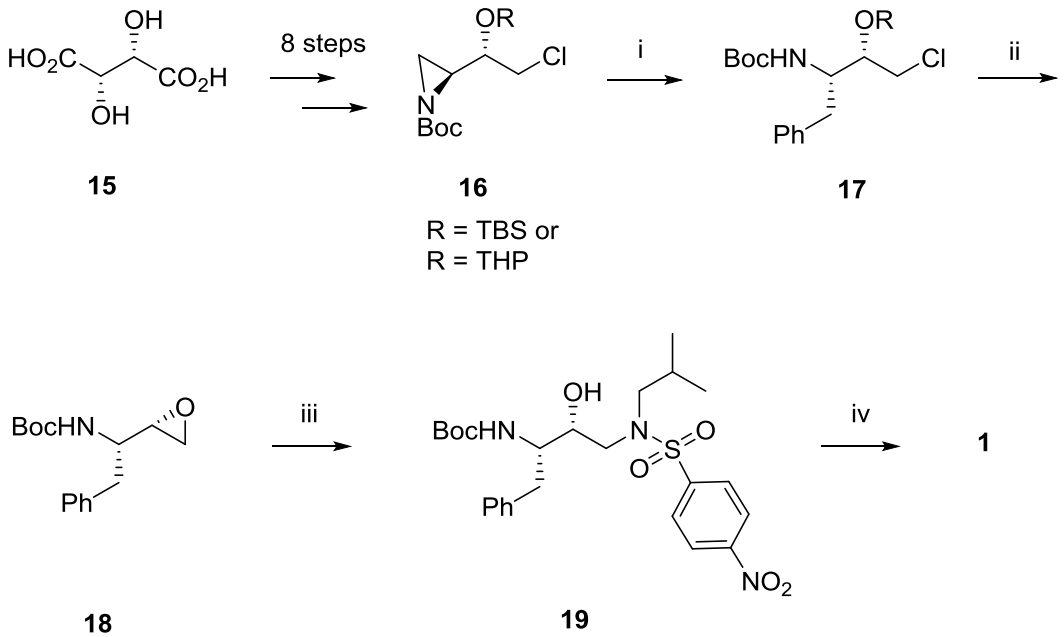


Scheme 2: (i) **A**, CH_3NO_2, KF, THF, -10 °C, 86%; (ii) $NiCl_2$, $NaBH_4$, MeOH, 0 °C, 85%, (iii) *iso*-butyraldehyde/$MgSO_4$, $NaBH_4$, EtOH, 0-23 °C, 82%; (iv) *p*-nitrobenzenesulfonyl chloride/Et_3N, CH_2Cl_2, 23 °C, 94%; (v) 5% $Pd(OH)_2/C$, H_2 (1 atm), MeOH, 23 °C; (vi) (*S*)-3-tetrahydrofuranyl N-oxysuccinimidyl carbamate, Et_3N, CH_2Cl_2, 23°C (95% over two steps).

with $NiCl_2$ and $NaBH_4$ in MeOH provided the corresponding amino alcohol **12** in 85% yield, which was then alkylated with *iso*-butyraldehyde/$MgSO_4$ followed by its protection with *p*-nitrobenzenesulfonyl chloride/Et_3N in CH_2Cl_2 produced sulfonamide **13** (94%). Further, amprenavir **1** was obtained in two steps as follows: (i) catalytic hydrogenation; (ii) condensation with (*S*)-3-tetrahydrofuranyl N-oxysuccinimidyl carbamate in 95% yield (**Scheme 2**).

Kim's approach (2001)[21]

Kim *et al. have* reported the synthesis of amprenavir **1** starting from chiral azidirine **16** which was obtained from *d*-tartaric acid **15** in 8 steps. Further, the chiral aziridine functionality was opened with lithium diphenylcuprates to afford ring opened product **17** in 75% yield. It was subsequently treated with TBAF and base to produce epoxide **18** in good yield.

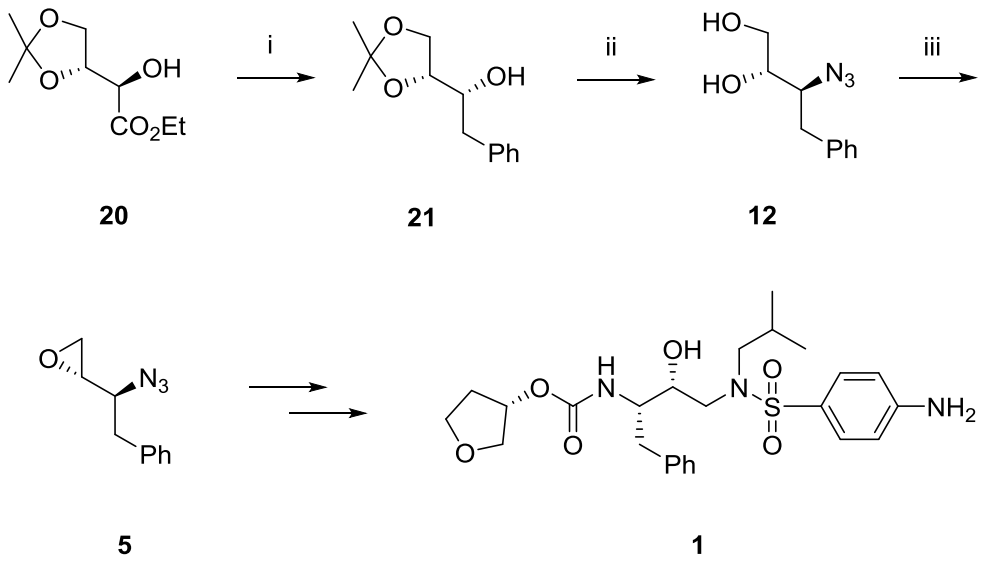


Scheme 3: (i) PhLi, $CuBr \cdot SMe_2$, THF, 75%; (ii) TBAF, THF; (iii) (a) $^{i}BuNH_2$, $^{i}PrOH$; (b) *p*-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, 88%; (iv) (a) HCl (g), CH_2Cl_2; (b) (*S*)-3-tetrahydrofuranyl N-oxysuccinimidyl carbamate, Et_3N, CH_2Cl_2; (c) $SnCl_2 \cdot 2H_2O$, EtOAc, 87% (over two steps).

Opening of epoxide with *iso*-butylamine (90% yield) followed by reaction with *p*-nitrobenznesulfonyl chloride afforded **19** in 88% yield. Deprotection of the Boc group followed by treatment with 3(*S*)-hydroxytetrahydrofuran N-oxysuccinimidyl carbonate and nitro group reduction using $SnCl_2 \cdot 2H_2O$ (87% yield) completed the synthesis of amprenavir **1** (**Scheme 3**).

Kang's approach (2008)[7b]

Kang *et al.* have described a novel chiral pool approach for the synthesis of 2(*S*)-[1(*S*)-azido-2-phenylethyl]oxirane **5** as an intermediate of amprenavir starting from acetonide **20**, which was readily prepared from *d-iso*-ascorbic acid. Hydroxyl group of **20** was then converted to its mesylate followed by ester reduction with $NaBH_4$ afforded intermediate alcohol which on immediate treatment with PhMgBr resulted in alcohol **21** (underwent *in situ* demesylation) with 80% overall yield.



Scheme 4: (i) (a) MsCl, Py; (b) $NaBH_4$, MeOH; (c) NaH, THF, -20 °C to rt; (d) PhMgBr, CuI, THF, -40 °C to 0 °C, 80% (overall 4 steps); (ii) (a) MsCl, Py; (b) 1N HCl, THF; (c) CsN_3, 18-crown-6, PhH, reflux; (iii) (a) 2-acetoxyisobutyryl chloride, $CHCl_3$; (b) NaOMe, THF, 60% (overall 3 steps).

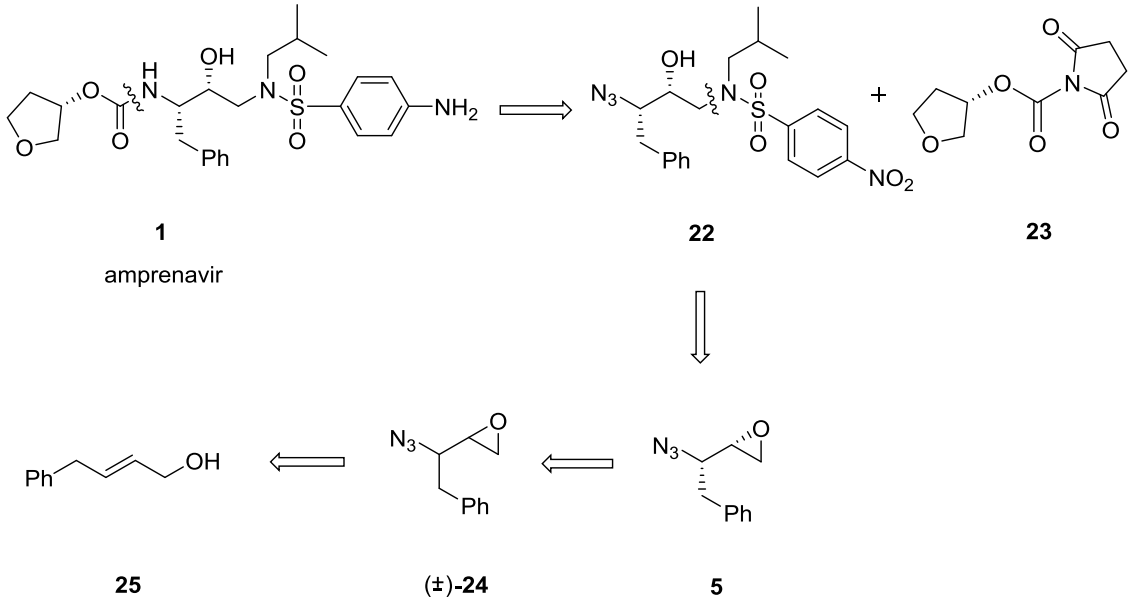
Further, alcohol **21** was protected as its mesylate followed by acetonide hydrolysis and azide displacement with CsN_3 afforded azido diol **12**. The resulting azido diol **12** was reacted with 2-acetoxyisobutyryl chloride and subsequently with NaOMe that resulted in the formation of chiral azido epoxide **5**, the key intermediate of **1** in 60% overall yield (**Scheme 4**).

1.1.3 Present Work

1.1.3.1 Objective

As can be seen from the above discussion, several synthetic approaches to 2-(1-azido-2-phenylethyl)oxirane (**5)**, the key chiral building block in the synthesis of HEA-based HIV protease inhibitors, have been reported in the literature.[7] Some of these methods, however, suffer from certain limitations[8] such as the use of chiral building blocks, introduction of chirality in the early stages, long reaction sequences, the use of expensive catalysts, low % ee, and so on, and hence are not amenable for scale-up studies.

Retrosynthetic analysis of amprenavir (**1**) showed that chiral azido alcohol **22** could be visualized as an intermediate. Chiral azido alcohol **22** could be obtained by means of Lewis acid-mediated epoxide ring opening of *syn*-chiral azido epoxide **5** with isobutylamine followed by protection of secondary amine as its nosylate. The *syn*-azido epoxide **5** could in turn be obtained by performing Co-catalyzed two-stereocentered hydrolytic kinetic resolution (HKR) of the corresponding racemic *syn*-azido epoxide **24**. The requisite racemic *syn*-azido epoxide **24** could be easily prepared from homoallylic alcohol **25** (**Scheme 5**).

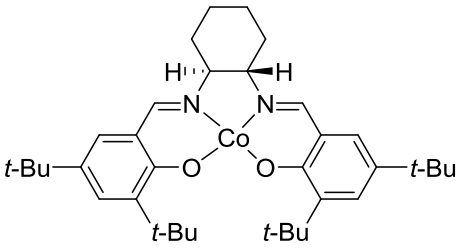


Scheme 5: Retrosynthetic analysis of amprenavir (**1**)

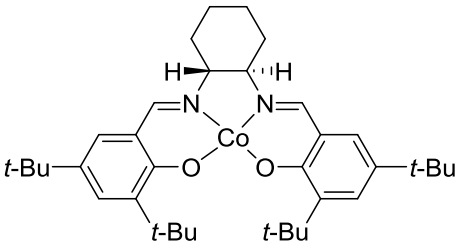
1.1.3.2 Hydrolytic Kinetic Resolution (HKR)

Epoxides are an important structural unit containing strained three-membered ring widely used in organic synthesis and found in many biological important natural products.[9] Simple epoxide ring opening allows straightforward elaboration to the new functionality and also sometime incorporation of new carbon-carbon bonds. Indeed, in the synthetic utility of epoxides, it can be opened with nucleophiles, Lewis acids, free radicals, reducing agents, oxidizing agents, acids and bases which has been well-incorporated in literature and utilized in synthesis.[10] Thus, epoxides are important and versatile building blocks for the synthesis of many biological important molecules. However, enantiomerically pure terminal epoxides are also the most important subclass of these epoxide compounds, but it is available in racemic mixtures and there is no economic and practical method available for their production. So, the kinetic resolution is an attractive, economic and simple method for the synthesis of optically active epoxide from the cheaply available terminal epoxides. Readily available chiral cobalt-

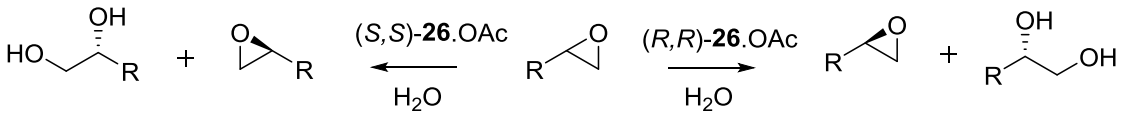
salen complexes[11] **26** have been used for the asymmetric resolution and hydrolysis of terminal epoxides. This resolution technique involves water as the only reagent, no solvent, and low recyclable catalyst loading (0.5 mol %), and it furnished valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric excess. However, except the significant disadvantage of a 50% maximum yield of chiral substrate recovery there are many advantages of this resolution process as it satisfies the following criteria of resolution:[12] (i) the racemic epoxides must be inexpensive or readily available from commercial source; (ii) catalyst must be readily available in both enantiomeric forms, used in small quantity and recyclable; (iii) nucleophile should be inexpensive and easily handled; (iv) chiral epoxides must be obtained in good yields and very high enantiomeric excess and easily separable from diols; (v) ring-opened byproducts should also be important chiral building blocks.



(*S*,*S*)-**26**



(*R*,*R*)-**26**



(*R*)-**29** (*S*)-**28** (±)-**27** (*R*)-**28** (*S*)-**29**

Scheme 6: Jacobsen's Hydrolytic Kinetic Resolution (HKR) of racemic epoxide, (±)-**27**

Catalyst (salen)Co-**26** has been well-established for the catalytic hydrolytic kinetic resolution (HKR) of a variety of terminal racemic epoxides **27** (**Scheme 6**).[13] Racemic 1,2-epoxides are generally obtained commercially from the corresponding olefins or

aldehydes in a single step at low cost. Also the other starting material of racemic epoxides such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are as cheaper as common organic solvents. Secondly, the ligands of the catalyst had been prepared commercially on a ton scale in the context of (salen)Mn epoxidation catalysts.[14] The cobalt analogues (*R,R)*-**26** and (*S,S)*-**26** are available in bulk and water is an ideal hydrolyzing agent for resolution: as it is inexpensive, safe, and the rate of the ring-opening reaction can be controlled by the simple rate of addition of water to the epoxide catalyst reaction mixture. Finally, the present HKR protocol provide highly enantiopure epoxide and useful enantioenriched 1,2-diols, which is otherwise difficult.[15] Two different methods for the generation of complex **26**.OAc have been developed.

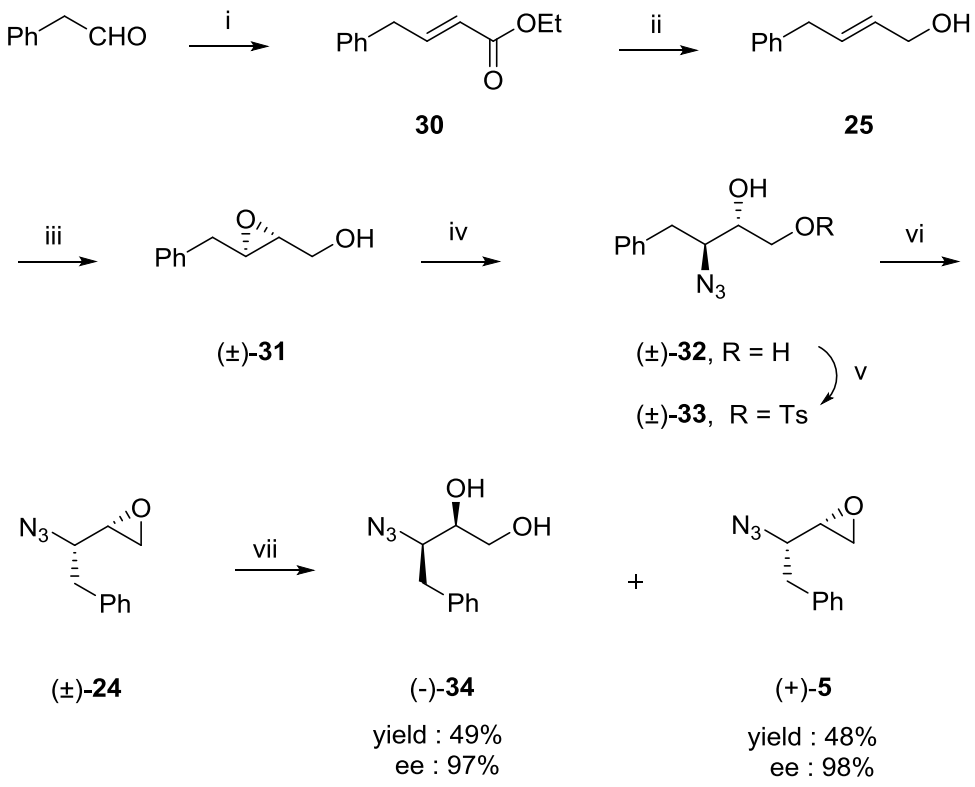
Method A involves isolation of **26**.OAc as a crude solid prior to the HKR. The Co(II) complex **26** is dissolved in toluene to generate ~1 M solution, and acetic acid (2 equiv) is added. The reaction mass stirred in an open air at room temperature for 30 min, during that color of the catalyst mixture changes from orange to dark brown. All volatile liquid are removed in *vacuo,* furnishing **26**.OAc as a brown solid residue which can be used further without purification.

Method B involves *in situ* generation of **26**.OAc under HKR conditions by suspension of the Co(II) complex **26** in epoxide or epoxide/solvent and addition of AcOH under an aerobic atmosphere. Despite these achievements, HKR has been only applied to the resolution of simple terminal epoxides with one stereocentre and not applicable for two stereocenters.[16] To overcome this drawback, a flexible method has recently been reported from our laboratory that employs Co-catalyzed Hydrolytic Kinetic Resolution (HKR) of racemic *anti*-azidoepoxides with two consecutive stereocentres to generate the corresponding diols and epoxides in high enantiomeric purity (97-99% ee) in a

single step.[17] This section describes a short enantioselective synthesis of amprenavir (**1**) and a formal synthesis of saquinavir (**3**) based on two-stereocentred HKR of racemic azido epoxide **24** giving chiral azidoepoxide **5**, the common key intermediate (**Schemes 7 & 8**).

1.1.3.3 Results and Discussions

Firstly, the synthesis of the key intermediate azido epoxide **5** was achieved from commercially available phenylacetaldehyde as shown in **Scheme 7**. Thus, allylic alcohol **25** was prepared in quantitative yield from phenylacetaldehyde in two steps as follows:



Scheme 7: (i) $Ph_3P{=}CHCO_2Et$, PhH, 90 °C, 6 h, 96%; (ii) $LiAlH_4$, $AlCl_3$, Et_2O, 0 °C, 1 h, 87%; (iii) *m*CPBA, CH_2Cl_2, 0 °C, 8 h, 88%; (iv) $Ti(O^iPr)_4$, $TMSN_3$, C_6H_6, 70 °C, 5 h, 96%; (v) *p*-TsCl, Bu_2SnO, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; (vi) K_2CO_3, MeOH, 0 °C, 30 min (90% over two steps); (vii) (*S*,*S*) -Co(salen)OAc **26** (0.5 mol %), THF, H_2O (0.5 equiv), 25 °C, 14 h.

(i) Wittig-Horner reaction ($PhCH_2CHO$, $Ph_3P{=}CHCO_2Et$, PhH, 90 °C), which afforded α,β-unsaturated ester **30** in 96% yield. The formation of ester **30** was supported by ^1H NMR spectrum, which showed two olefinic proton signals at δ 6.43 (d, J = 15.6 Hz, 1H) and 6.29-6.35 (m, 1H); also its ^{13}C NMR spectrum displayed a carbon signal at δ 166.2 for -C=O of ester group (**Fig. 2**).

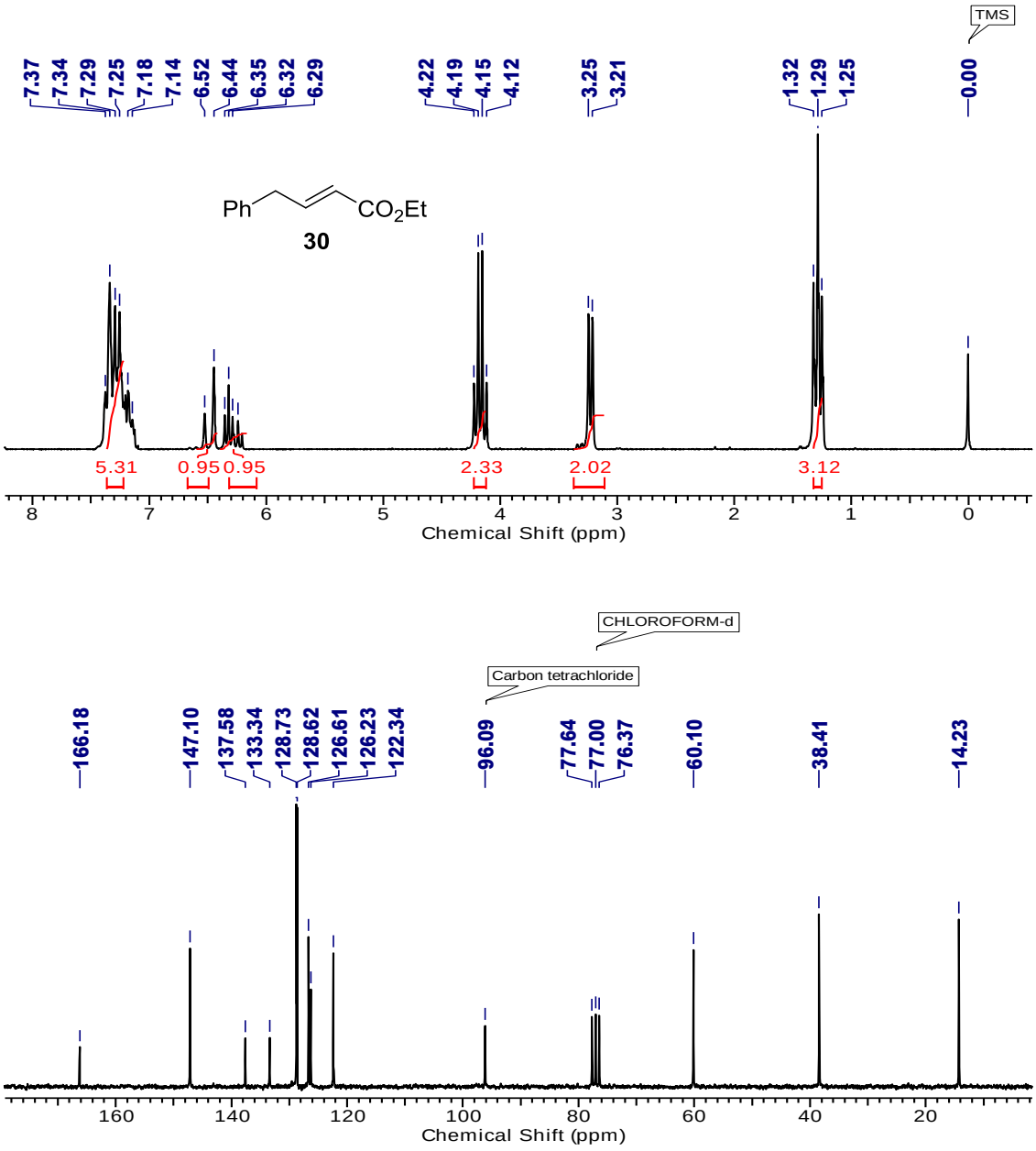


Fig. 2: ^1H and ^{13}C NMR spectra of α,β-unsaturated ester **30**

(ii) selective ester reduction of compound **30** ($LiAlH_4$, catalytic $AlCl_3$, dry ether, 0 °C) gave alcohol **25** in 87% yield. The formation of allylic alcohol **25** was confirmed by the appearance of two typical olefinic protons as multiplets at δ 6.19 (m, 1H) and 6.49 (m, 1H) in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed two characteristic olefinic carbon signals at δ 128.5 and 132.7, which confirmed the formation of allylic alcohol **25**. Also, its IR spectrum showed a strong & broad peak at υ_{max} 3385 cm^{-1} due to –OH functionality (**Fig. 3**).

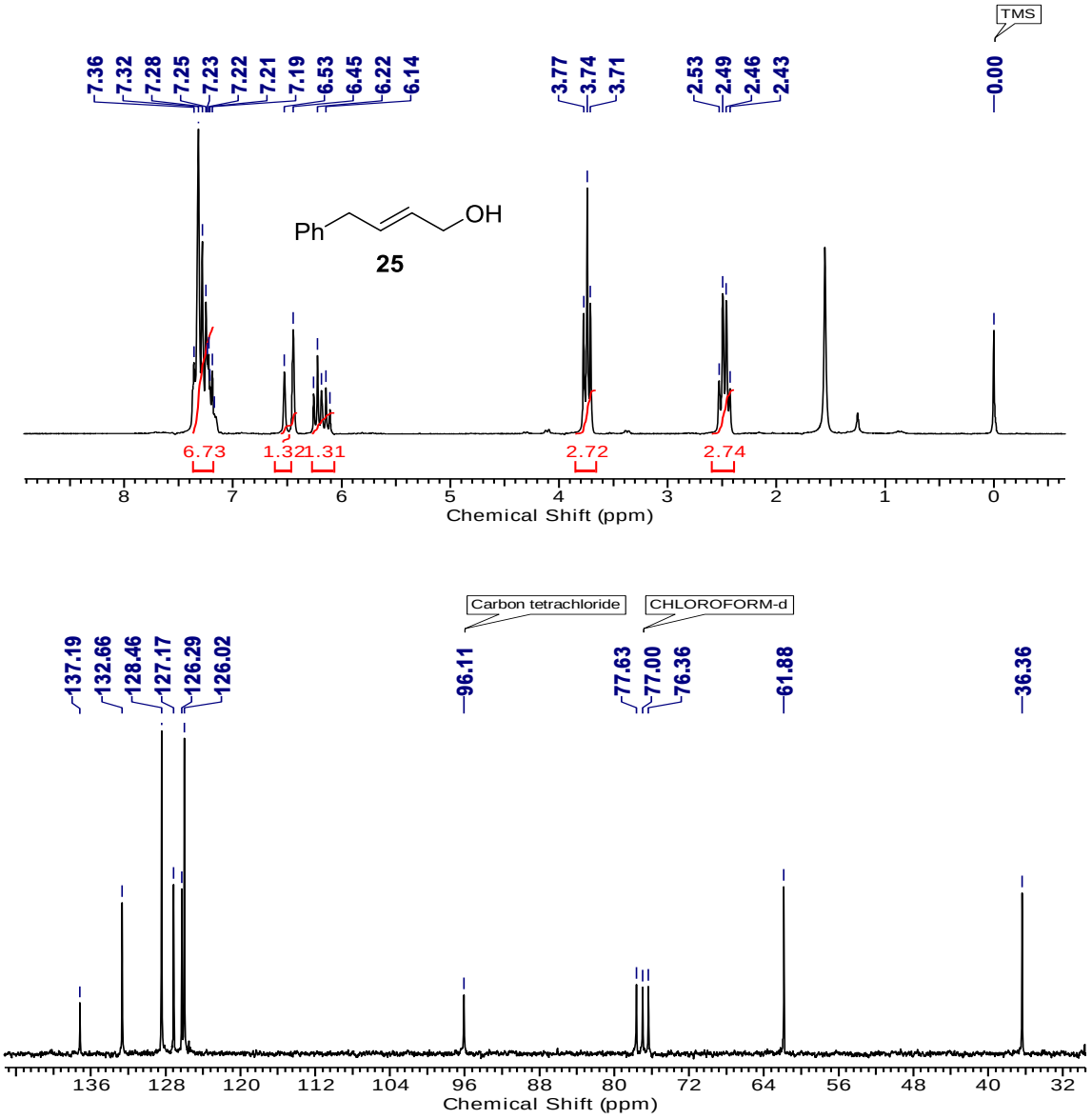


Fig. 3: ^{1}H and ^{13}C NMR spectra of allylic alcohol **25**

Alcohol **25** was then subjected to epoxidation with *m*-chloroperbenzoic acid (*m*CPBA) to obtain racemic epoxy alcohol **31** in 88% yield. The formation of epoxy alcohol **31** was confirmed from its ^{1}H NMR spectrum, which showed two doublet of doublets at δ 3.65 (dd, *J* = 12.6 and 4.2 Hz, 1H) and δ 3.87 (dd, *J* = 12.6 and 2.5 Hz, 1H) corresponding to two diastereotopic methylene protons of epoxide moiety. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 78.7 and 67.1 indicative of the methine carbons of epoxide, thus confirming the formation of epoxy alcohol **31** (**Fig. 4**).

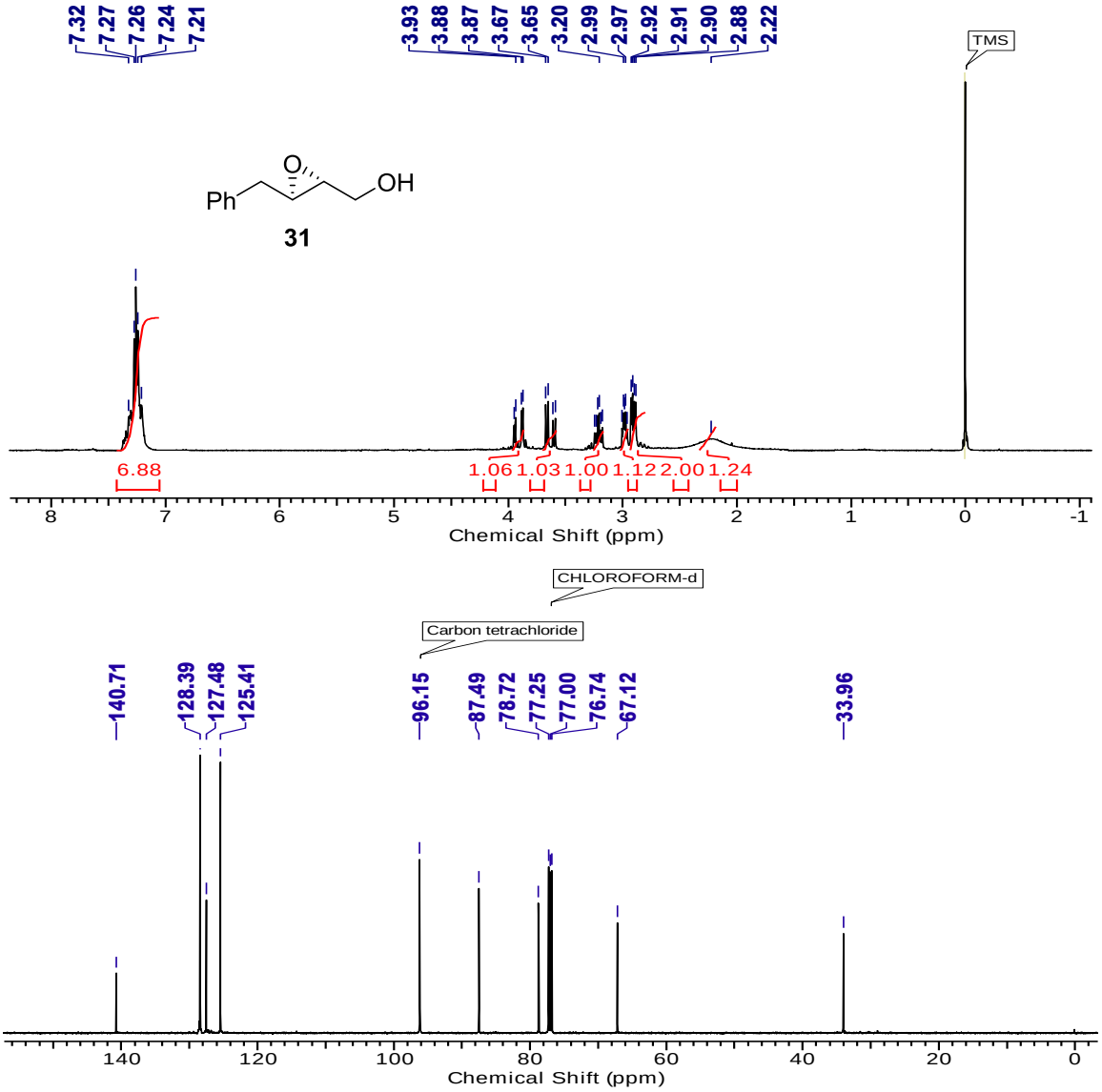
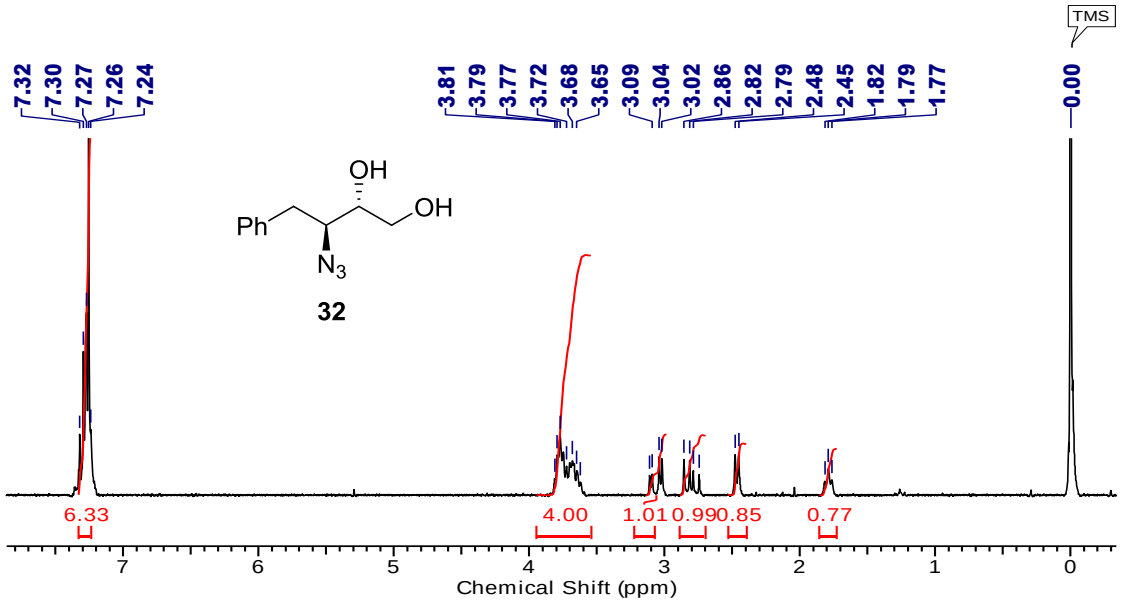


Fig. 4: ^{1}H and ^{13}C NMR spectra of epoxy alcohol **31**

Lewis acid-catalyzed ring opening of epoxide **31** with azide anion produced the *anti*-azido alcohol **32** (96% yield) in a highly regioselective manner (regioisomer distribution: 27:1) as determined from its ^{1}H NMR spectral studies.[18]

The desired regioisomer **32** was readily separated from column chromatographic purification. The ^{1}H NMR spectrum of azido alcohol **32** showed two typical proton signals at δ 1.19 (t, J = 5.3 Hz, 1H) and 2.45 (d, J = 5.3 Hz, 1H) corresponding to primary and secondary hydroxyl groups respectively, while its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 62.2 and 75.7 due to methylene and methine carbons attached to two hydroxyl groups respectively. Also its IR spectrum showed two characteristic strong & broad absorption bands at υ_{max} 3280 and 2105 cm^{-1} due to presence of the –OH and -N_3 functionalities respectively (**Fig. 5**).



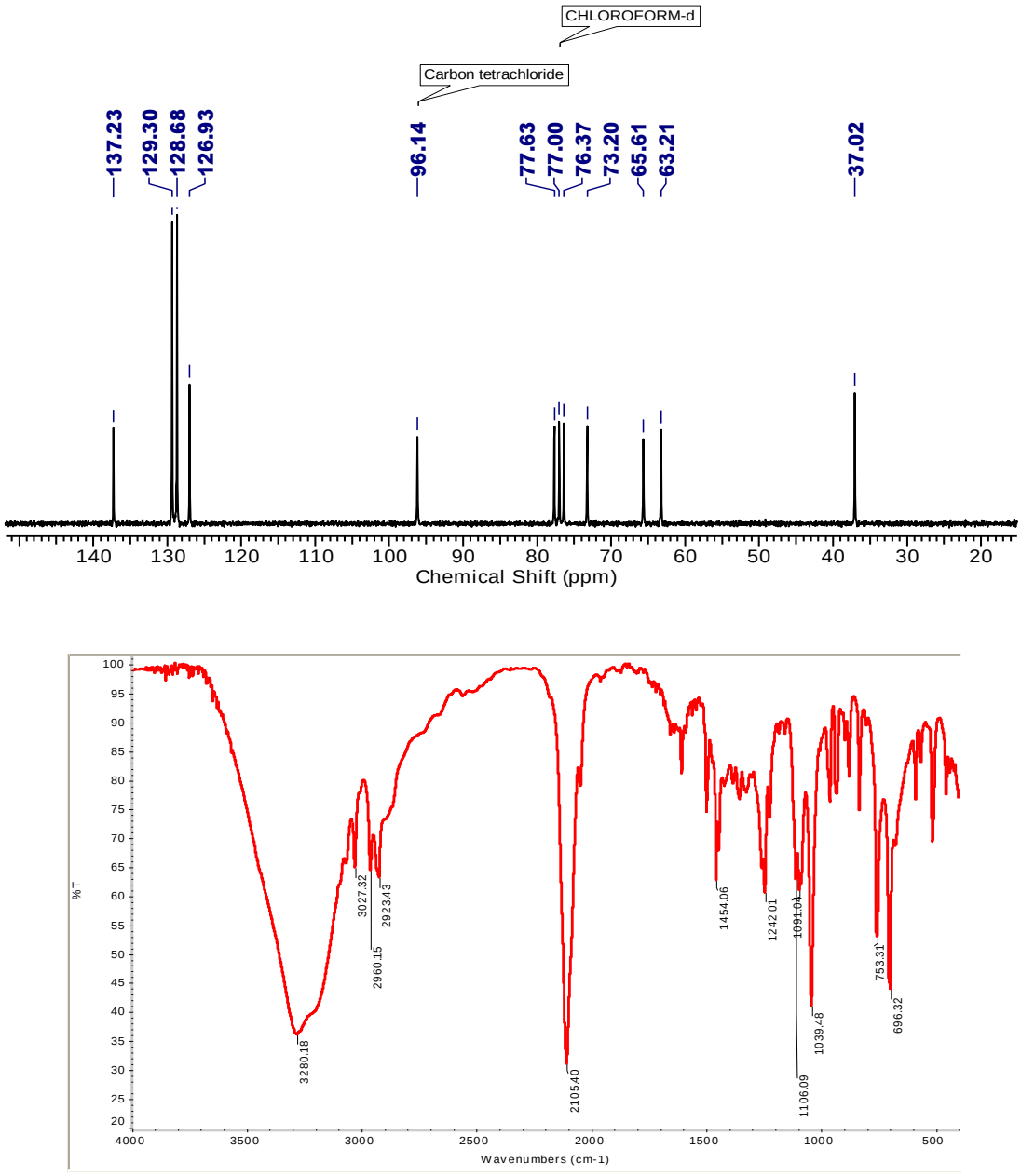


Fig. 5: ^{1}H, ^{13}C NMR and IR spectra of azido alcohol **32**

Then *anti*-azido diol **32** was transformed to racemic azido epoxide **24** with an overall yield of 90% in two steps as follows: (i) selective tosylation of primary alcohol (TsCl, Bu_2SnO (2 mol %), Et_3N, DMAP (10 mol %), CH_2Cl_2, 0 °C) to afford tosylate **33** and (ii) its base treatment (K_2CO_3, MeOH, 0 °C) to obtain epoxide **24**. The formation of racemic *anti*-azido epoxide **24** was confirmed from its ^{1}H NMR spectrum, which

showed a multiplet at δ 3.56 (m, 1H) corresponding to methine protons of epoxide ring. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 43.8 and 55.0 corresponding to methylene and methine carbons of the epoxide moiety respectively (**Fig. 6**).

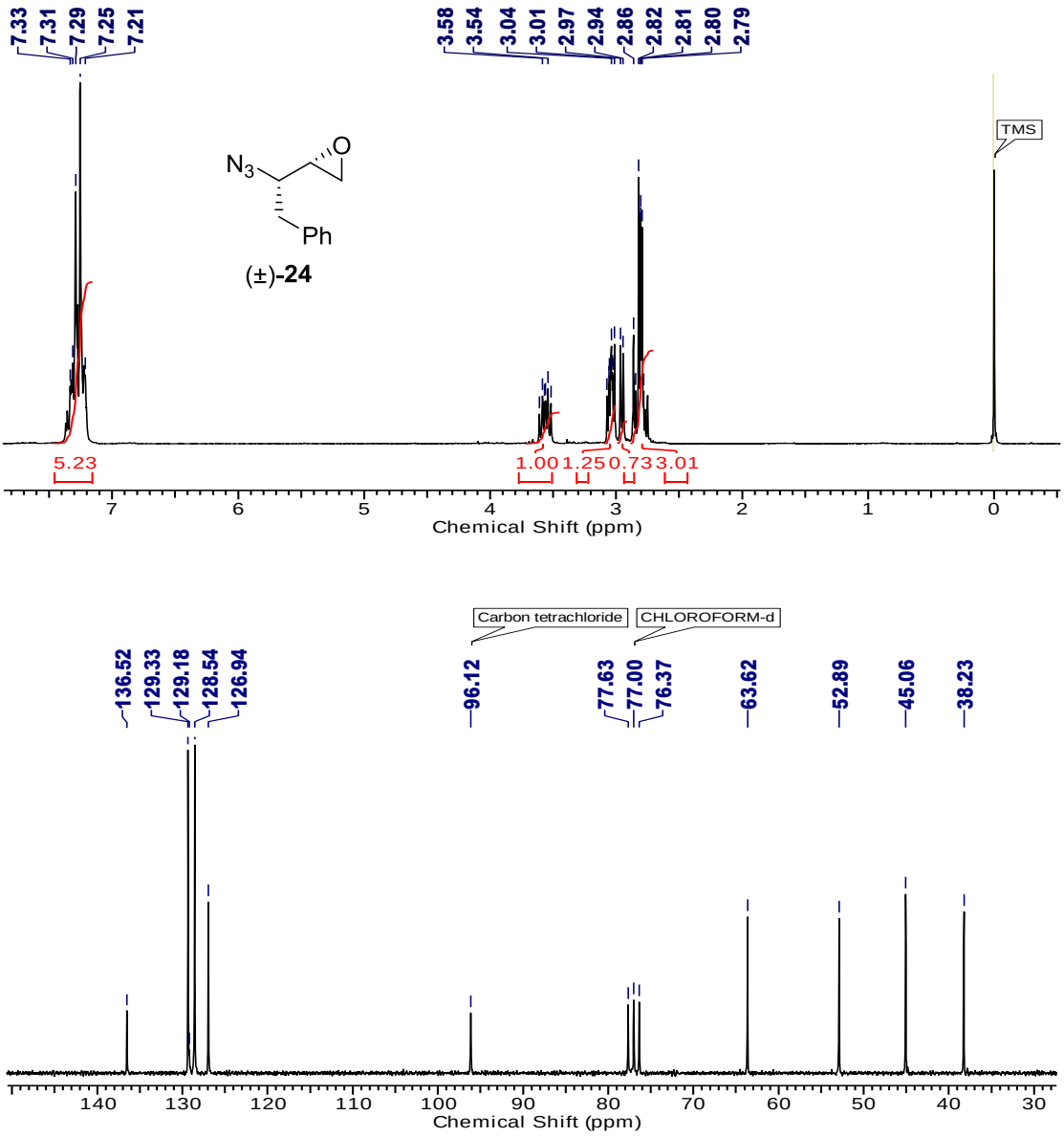
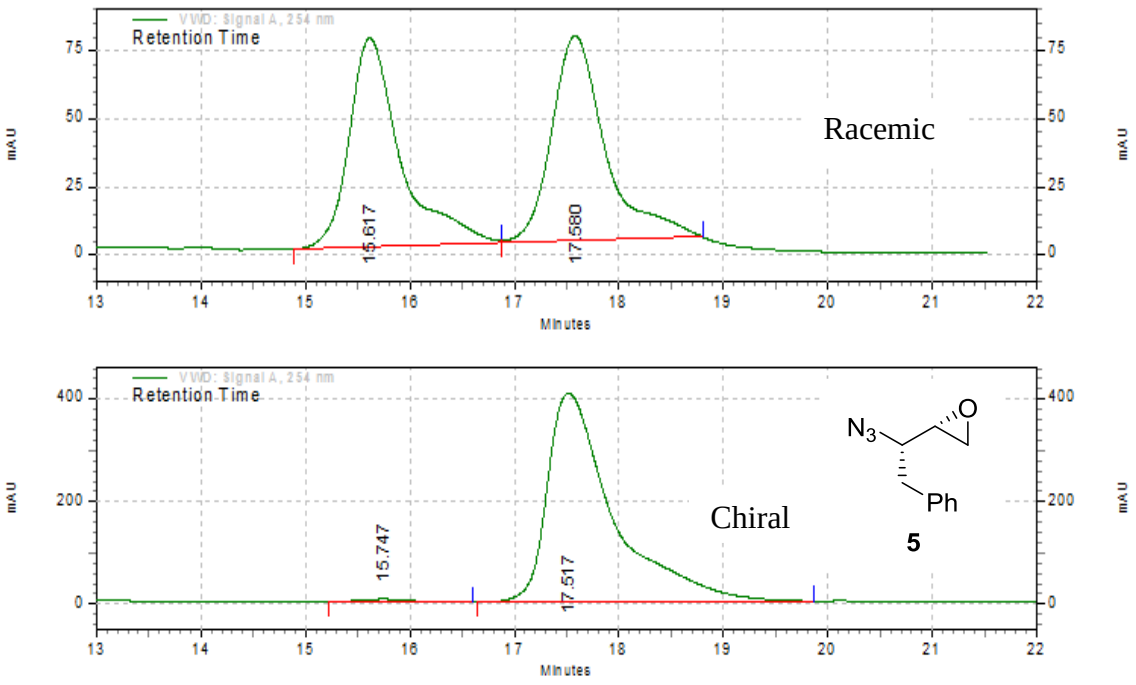


Fig. 6: ^{1}H and ^{13}C NMR spectra of (±)-azido epoxide **24**

Racemic azido epoxide **24** was then subjected to HKR with (*S*,*S*)-salen Co(OAc) complex-**26** (0.5 mol %) and H_2O (0.49 equiv), which produced the corresponding diol (2*R*,3*R*)-3-azido-4-phenylbutane-1,2-diol **34** (49% yield and 97% ee) and epoxide 2(*S*)-

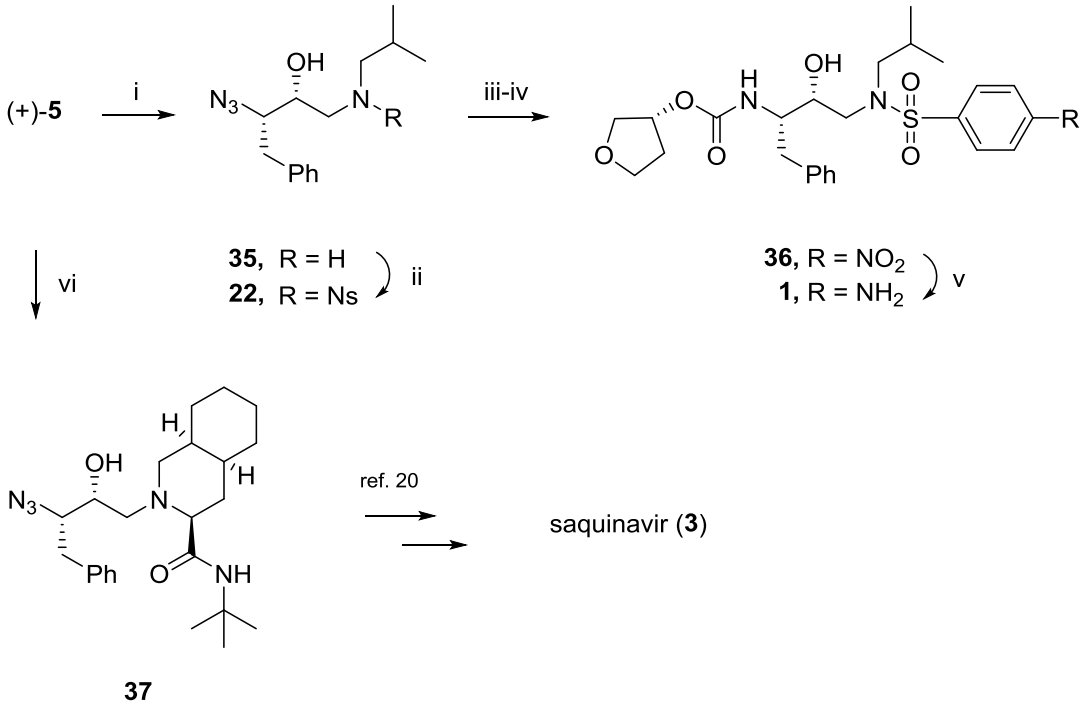
[1'(*S*)-azido-2-phenylethyl]oxirane **5** (48% yield and 98% ee) in high enantiomeric purity. The azido epoxide (+)-**5** was, however, readily separated from diol **34** by a simple flash column chromatographic purification over silica gel (**Scheme 7**).



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

Fig. 7: HPLC chromatogram of chiral azido epoxide **5**

The optical purity of chiral azido epoxide **5** was determined to be 98% ee by chiral HPLC analysis (Chiralcel OD-H column, *n*-hexane/*i*PrOH, 97:03, 0.5 mL/min) retention time 17.517 (99.14%) and 15.747 (0.86%) for azido epoxide **5** (**Fig. 7**).



Scheme 8: (i) $^{i}BuNH_2$, $^{i}PrOH$, 50 °C, 5 h; (ii) *p*-$NO_2C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 12 h, 89% (over two steps); (iii) PPh_3, H_2O, THF, 25 °C, 29 h; (iv) *N*-hydroxysuccinimidyl carbonate of (*S*)-3-hydroxytetrahydrofuran, Et_3N, CH_2Cl_2, 25 °C, 2 h, (89% over two steps); (v) $SnCl_2 \cdot 2H_2O$, EtOAc, 70 °C, 1 h, 90%; (vi) [3*S*-(3*α*,4aβ,8aβ)]-*N*-(*tert*-butyl)decahydro-3-isoquinolinecarboxamide, silica gel (230-400, 6Å mesh), $CHCl_3$, 25 °C, 16 h, 85%.

The chiral azido epoxide **5** was then subjected to the regiospecific ring opening with *iso*-butylamine in *iso*-butanol to give azido alcohol **35**, which was subsequently protected as its nosylate azide **22** (*p*-NO_2PhSO_2Cl, Et_3N, CH_2Cl_2, 0 °C) in 89% yield for two steps. The formation of nosyl azide **22** was confirmed from its ^{1}H NMR spectrum, which showed a multiplet at δ 0.08 (m, 6H) corresponding to two methyl protons of *iso*butyl group. Also, two doublets at δ 7.97 (d, J = 8.8 Hz, 6H) and 8.39 (d, J = 8.8 Hz, 6H) in the aromatic region showed the presence of aromatic protons with *ortho* coupling of J = 8.8 Hz. Also, it was supported by its ^{13}C NMR spectrum, which showed two methyl carbon signals at δ 19.8 and 20.1 corresponding to isobutyl functionality (**Fig. 8**).

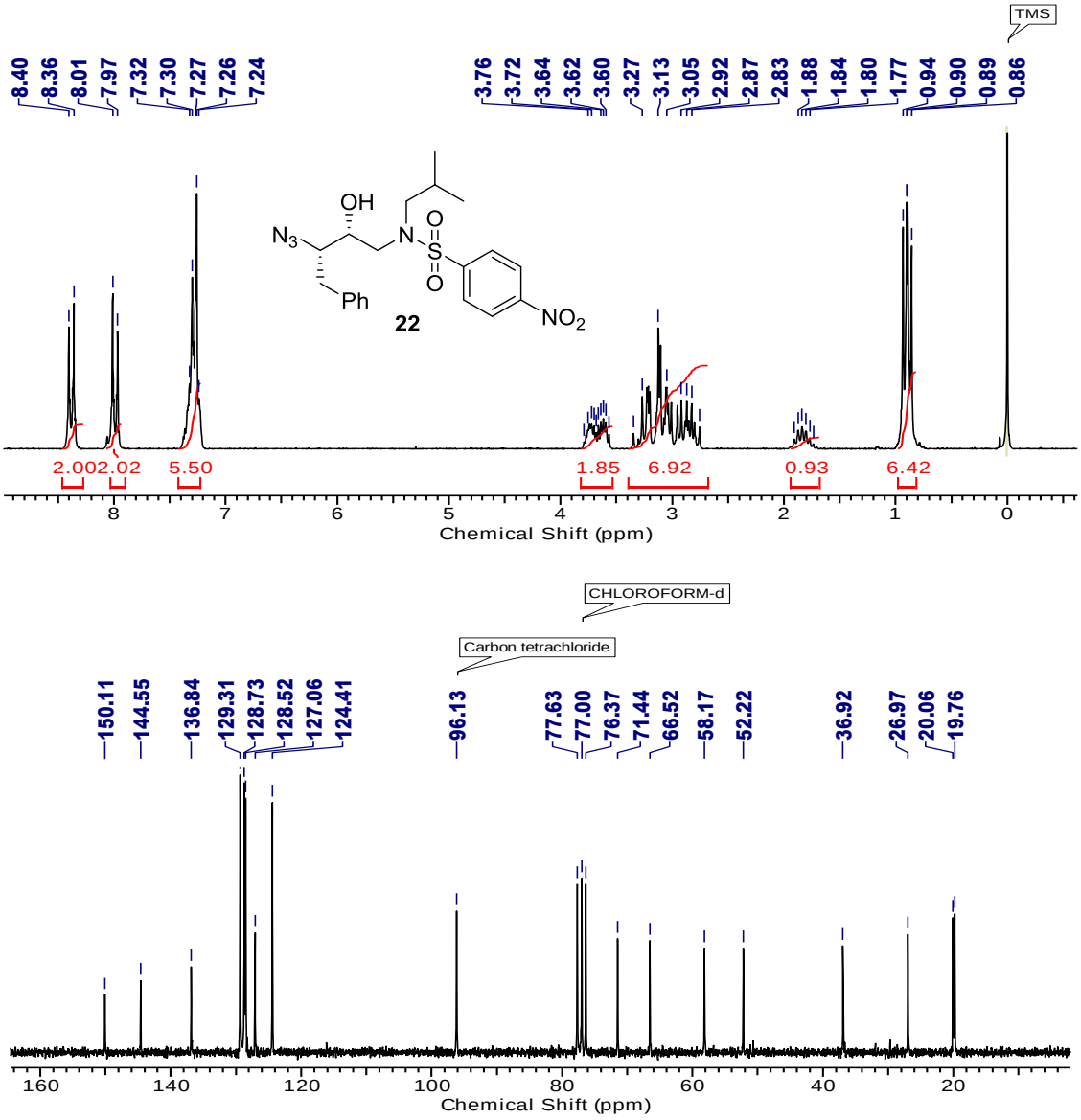


Fig. 8: ^{1}H and ^{13}C NMR spectra of nosyl azido alcohol **22**

Azido nosylate **22** was finally transformed to amprenavir (**1**) in three steps with an overall yield of 80% by following a standard sequence of reactions: (i) azide reduction; (ii) condensation with (*S*)-3-hydroxytetrahydrofuran (**23**) furnishing compound **36**, which showed two typical mutliplets at 4.86 (m, 1H) and 5.13 (m, 1H) in its ^{1}H NMR spectrum corresponding to methine protons of secondary alcohol and tetrahydrofuran moiety respectively. Its ^{13}C NMR spectrum displayed a carbon signal at δ 156.2 due to carbonyl group of amide linkage (**Fig 9**).

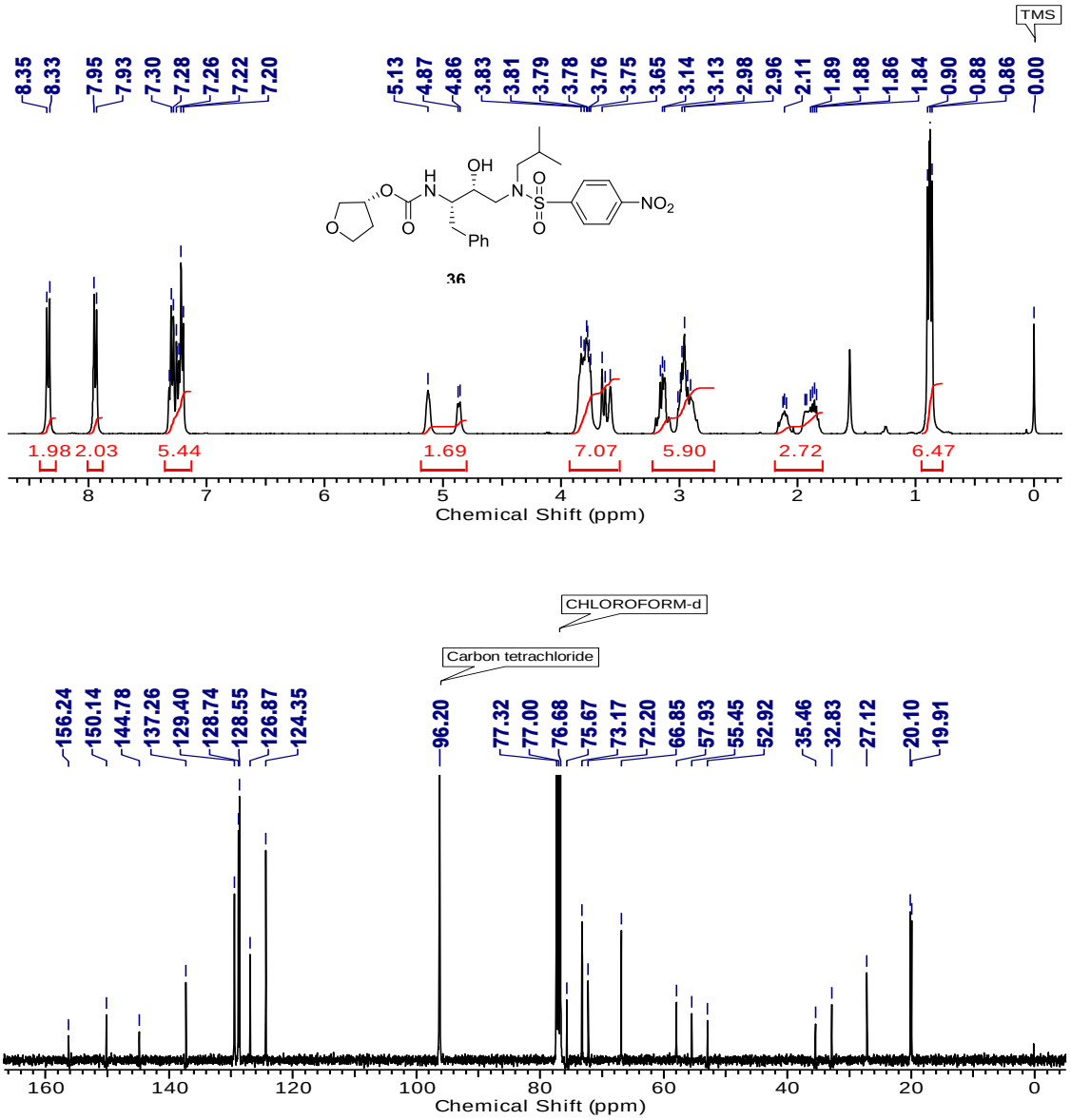


Fig. 9: ^{1}H and ^{13}C NMR spectra of compound **36**

(iii) The final step involved the reduction of nitro group to amine functionality by using stannous chloride (90% yield). The formation of **1** was confirmed from its ^{1}H NMR spectrum, which showed the appearance of a typical proton singlet at δ 3.81 (br.s, 1H) for –NH group. It was subsequently ascertained by its ^{13}C NMR spectrum, wherein a quaternary carbon signal was displaced from δ 144.8 to 137.7 due to reduction of NO_2 to NH_2 group respectively (**Fig 10**).

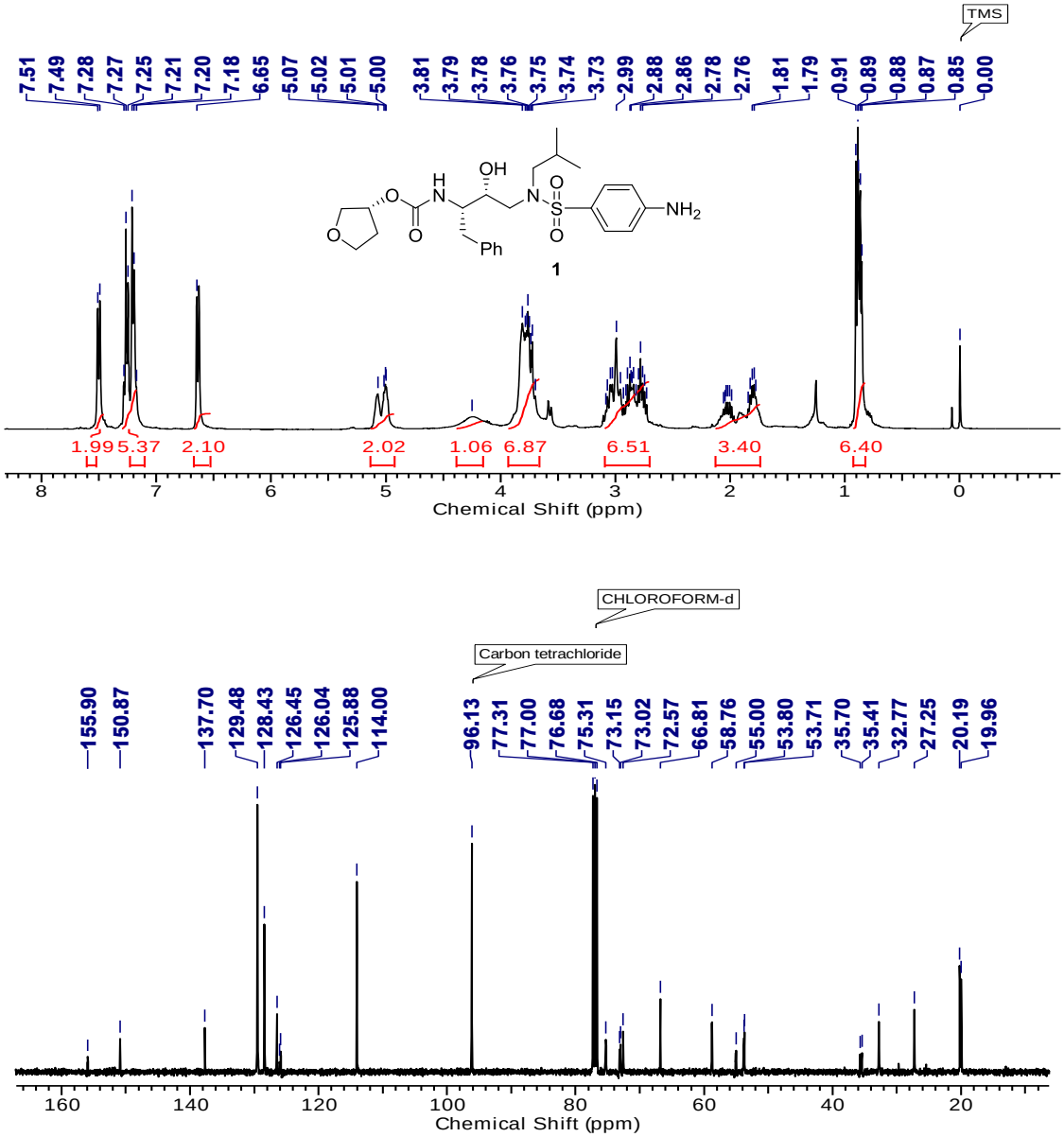


Fig. 10: ^{1}H and ^{13}C NMR spectra of amprenavir (**1**)

For the synthesis of saquinavir (**3**), treatment of azido epoxide **5** with commercially available [3*S*-(3*α*,4*αβ*,8*αβ*)]-*N*-(*tert*-butyl)decahydro-3-isoquinolinecarboxamide[19] was attempted that produced the key azido alcohol **37** in 85% yield in a highly regioselective fashion. The transformation of **37** to saquinavir (**3**) has already been reported in the literature (**Scheme 8**).[20] The formation of **37** was supported by the ^{1}H NMR spectrum, which showed a broad singlet at δ 5.84 due to secondary -NH group

and a singlet at δ 1.33 (s, 9H) for *tert*-butyl group. Also its ^{13}C NMR spectrum showed a typical carbon signal at δ 173.3 corresponding to carbonyl signal of amide functionality (**Fig 11**). Also its IR spectrum showed two characteristic absorption bands at 3439 and 2101 cm^{-1} due to –OH and N_3 functionalities respectively.

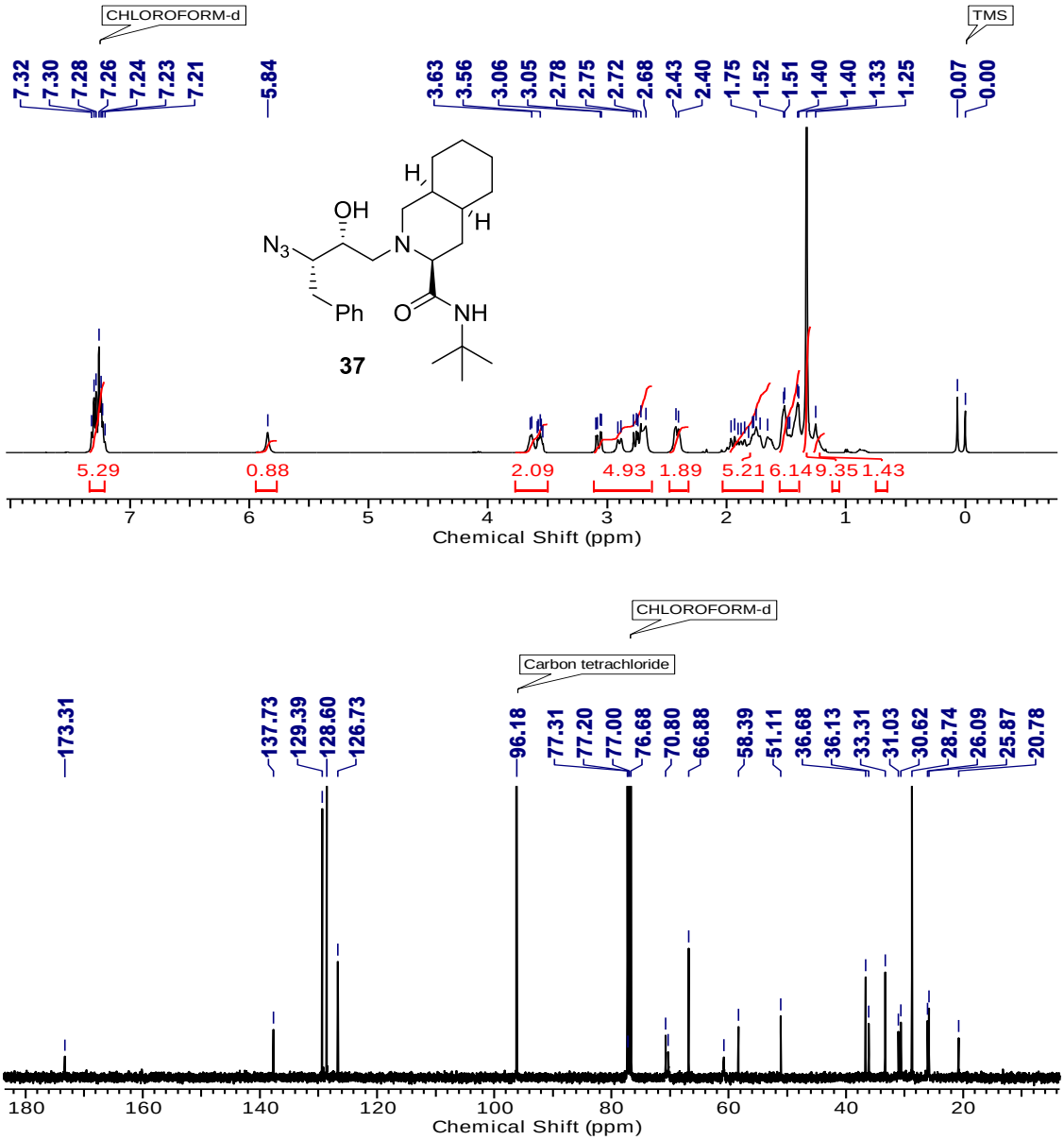
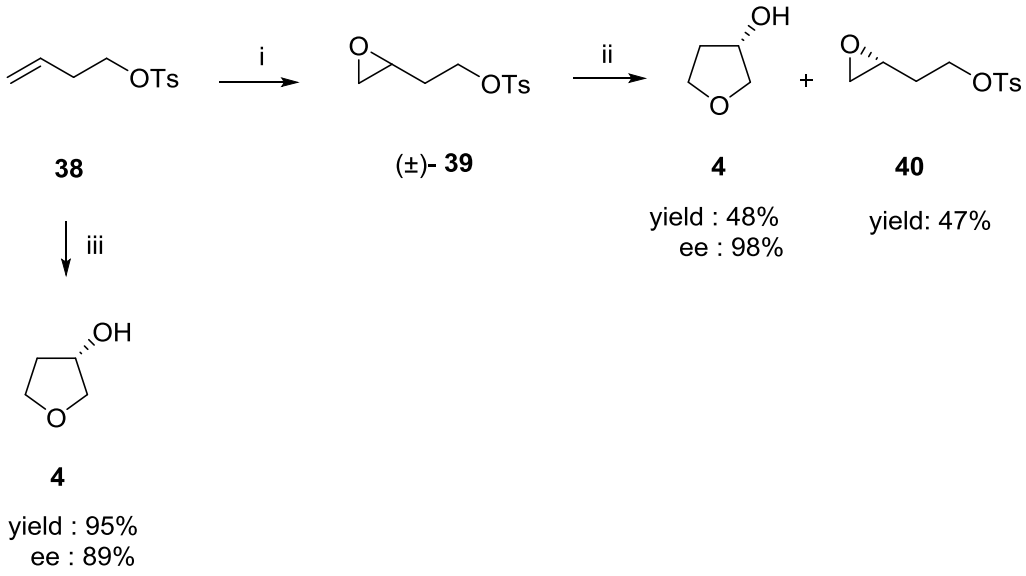


Fig. 11: ^{1}H and ^{13}C NMR spectra of key intermediate **37**

The spectral data of amprenavir (**1**) and its key intermediate **37** are in complete agreement with the reported values.[20, 21]

Finally, the efficient preparation of optically active alcohol **4** is crucial to economic synthesis of amprenavir (**1**) and fosamprenavir (**2**). Thus, olefinic tosylate **38** was prepared readily from the corresponding commercially available homoallylic alcohol in single step.



Scheme 9: (i) *m*CPBA, CH_2Cl_2, 0 °C, 5 h, 88%; (ii) (*R*,*R*)-Co(salen)OAc-**26** (0.5 mol %), THF, H_2O (0.49 equiv), 25 °C 14 h; (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 °C, 5 h, 95%.

The formation of **38** was confirmed by the ^1H and ^{13}C NMR spectra, which displayed two doublets at δ 7.32 (d, *J* = 8.8 Hz, 2H) and 7.76 (d, *J* = 8.8 Hz, 2H) due to the presence of aromatic protons of tosyl group. Also methyl carbon of tosyl group signal appeared at δ 21.5 in its ^{13}C NMR spectrum (**Fig. 12**).

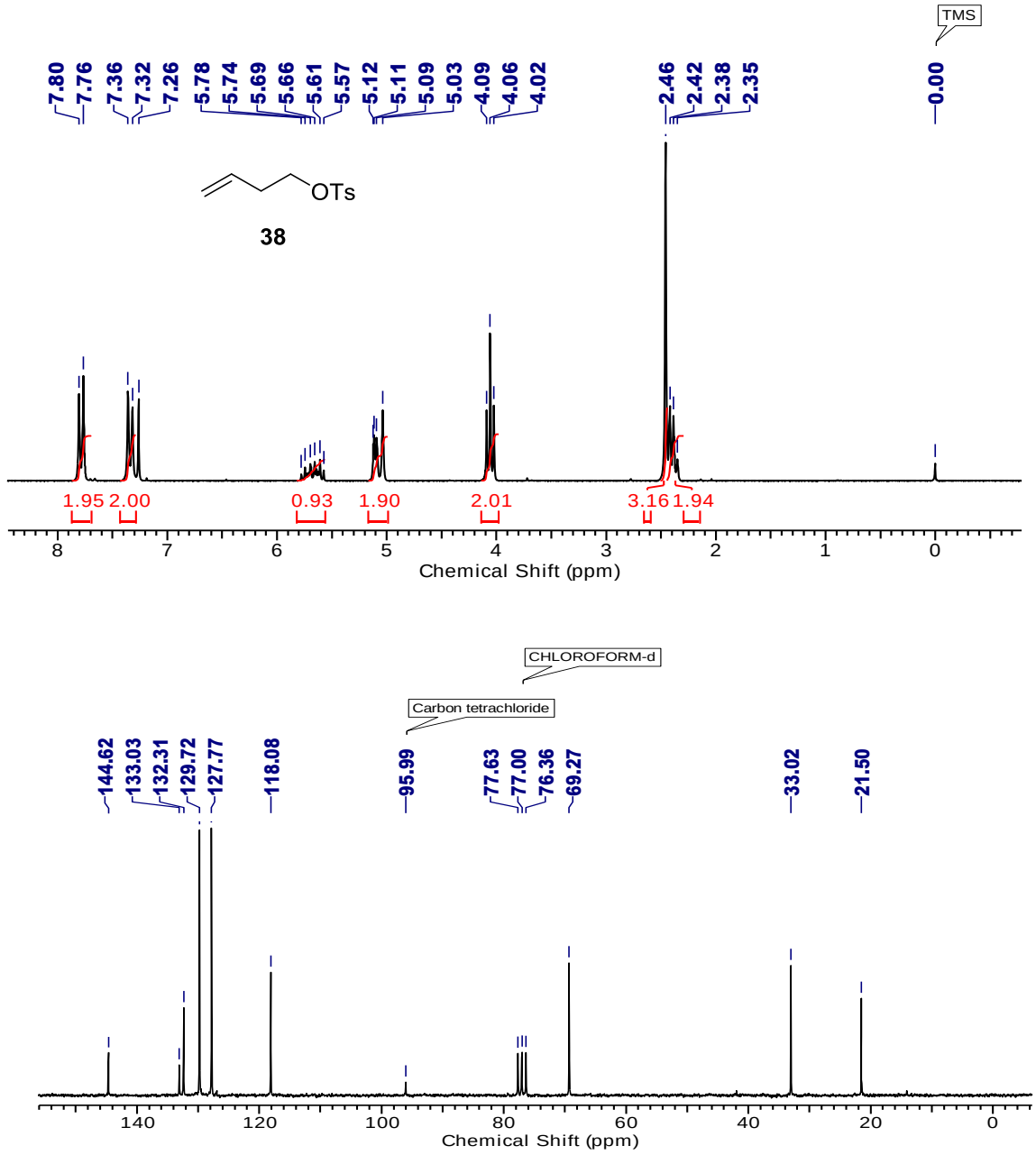


Fig. 12: ^{1}H and ^{13}C NMR spectra of olefinic tosylate **38**

Further, the olefinic tosylate **38** was dihydroxylated under the Sharpless Asymmetric Dihydroxylation conditions that furnished the cyclized alcohol **4** in 95% yield with moderate enantiomeric purity (89% ee). The formation of **38** was confirmed by the ^{1}H NMR spectrum which showed a multiplet at δ 4.49 (m, 1H) corresponding to methine

proton attached to -OH group. A characteristic signal appeared at δ 75.4 for methine carbon in its ^{13}C NMR spectrum (**Fig. 13**).

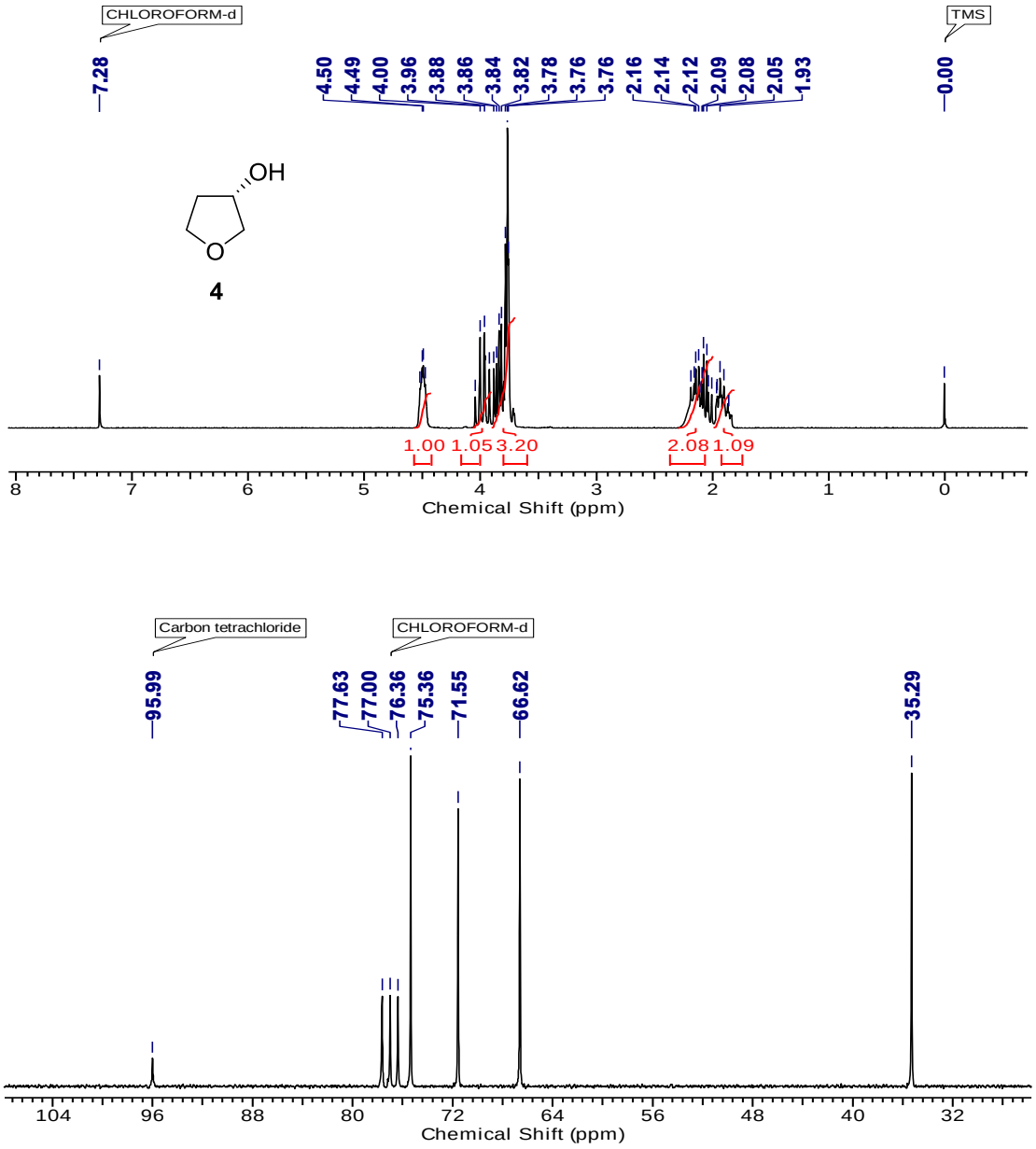


Fig. 13: ^{1}H and ^{13}C NMR spectra of (*S*)-3-hydroxytetrahydrofuran (**4**)

Alternatively, subjecting tosylate **38** to epoxidation with *m*CPBA yielded the racemic epoxide **39** in 88% yield. The formation of epoxide **39** was ascertained by ^{1}H and ^{13}C NMR spectra, which showed the disappearance of olefinic proton signal and appearance of a multiplet at δ 4.15 (m, 2H) for methylene proton of epoxide ring and

two carbon signals at 127.9 and 129.8 are due to aromatic carbons of tosyl group (**Fig. 14**).

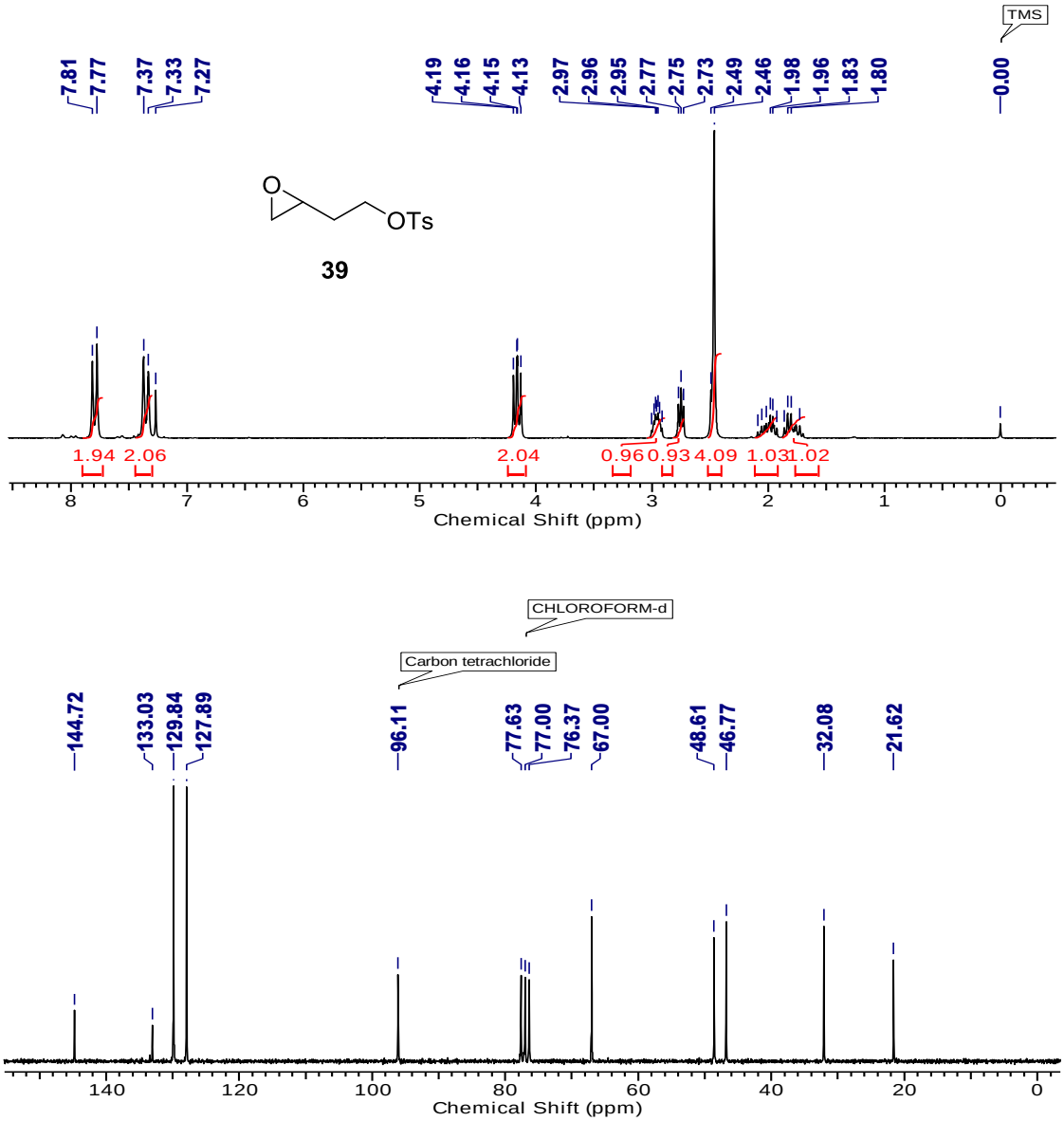


Fig. 14: ^{1}H and ^{13}C NMR spectra of tosyl epoxide **39**

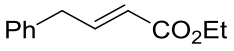
The Co-catalysed HKR of (±)-**39** produced the desired alcohol **4** (48% yield; 98% ee) in a single step along with chiral epoxide **40** (47% yield). In both the cases, the diol formed *in situ* underwent facile intramolecular cyclization under the reaction conditions to produce (*S*)-3-hydroxytetrahydrofuran (**4**) in high yields (**Scheme 9**).

1.1.4 Conclusion

In conclusion, we have described a short and economic synthesis of HIV protease inhibitor amprenavir (**1**) (21.7% overall yield; 99% ee) and its key intermediate (*S*)-3-hydroxytetrahydrofuran (**4**; 98% ee) starting from commercially available phenyl acetaldehyde and 1-butene-4-ol respectively. Also described is the formal asymmetric synthesis of saquinavir (**3**) from the common intermediate **5**. The strategy employed herein mainly comprises of Co-catalyzed two-stereocentred HKR of racemic azido epoxide **24** as the key chiral inducing step. This methodology is expected to find wide scope for the synthesis of other similar HEA multifunctional HIV protease inhibitors.[22]

1.1.5 Experimental Section

(*E*)-Ethyl 4-phenylbut-2-enoate (30)

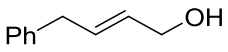


To a stirred solution of phenyl acetaldehyde (7.0 g, 58.3 mmol) in benzene (150 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (22.3 g, 64.1 mmol) and the resulting mixture heated under reflux for 6 h. After the reaction was complete, solvent was removed under reduced pressure to provide the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (19:1) to give α,β unsaturated ester **30**.

Yield: 96% (10.6 g), as a colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 1041, 1098, 1158, 1270, 1301, 1669, 1721, 1782, 2858, 2984; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.23 (d, *J* = 6.8 Hz, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 6.21-6.35 (m, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 7.14-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.4,

60.1, 122.4, 126.7, 128.6, 128.7, 137.6, 147.1, 166.2; **Anal. Calcd for** $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.65; H, 7.41%.

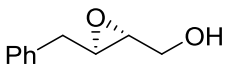
(*E*)-4-Phenylbut-2-en-1-ol (25)



To a stirred suspension of $LiAlH_4$ (2.4 g, 63.1 mmol) in dry Et_2O (60 mL) at 0 °C under nitrogen atmosphere was added dropwise a solution of anhydrous $AlCl_3$ (1.7 g, 12.6 mmol) in dry Et_2O (30 mL). The reaction mixture was stirred at the same temperature for 30 min. To this stirred suspension, ester **30** (8.0 g, 42.1 mmol) in dry Et_2O (30 mL) was added dropwise over a period of 15 min and the resulting mixture stirred at 0 °C for 1 h. Then it was quenched with ice- water and filtered through celite and the residue was washed with ethyl acetate (3 x 30 mL). The combined organic layer was dried over anhyd. Na_2SO_4, concentrated and the crude product was purified by column chromatography using petroleum ether/EtOAc (4:1) to afford the pure allylic alcohol **25**.

Yield: 87% (5.4 g), as a colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 744, 966, 1049, 1107, 1364, 1454, 2857, 2932, 3385; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.22 (br s, 1H), 3.38 (d, *J* = 6.4 Hz, 2H), 4.12 (t, *J* = 4.8 Hz, 2H), 5.62-5.93 (m, 2H), 7.15-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.4, 61.9, 126.0, 126.3, 127.2, 128.5, 132.7, 137.2; **Anal. Calcd for** $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.02; H, 8.15%.

(3-Benzyloxiran-2-yl)methanol (31)

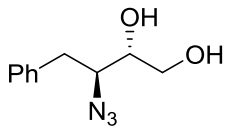


To a solution of allylic alcohol **25** (5.0 g, 33.7 mmol) in dry CH_2Cl_2 (60 mL) at 0 °C was added *m*-chloroperbenzoic acid (8.7 g, 50.6 mmol) in small portions. The resulting

solution was stirred for 8 h until complete consumption of starting materials (the progress of the reaction was monitored by TLC). The reaction mixture was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with aq. 10% solution of $NaHCO_3$ (15 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc (4:1) to give the corresponding epoxide **31**.

Yield: 88% (4.8 g), as a viscous gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 991, 1028, 1055, 1106, 1452, 2921, 3404; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.88-2.99 (m, 3H), 3.17-3.23 (m, 1H), 3.57-3.72 (m, 1H), 3.85-3.95 (m, 1H), 7.18-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.2, 67.1, 78.9, 87.5, 125.5, 127.5, 128.4, 140.8; **Anal. Calcd for** $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.25; H, 7.47%.

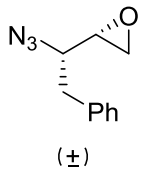
3-Azido-4-phenylbutane-1,2-diol (32)



A mixture of freshly distilled $Ti(O^iPr)_4$ (9.5 mL, 32.1 mmol) and $TMSN_3$ (8.4 mL, 64.1 mmol) was refluxed in dry benzene (20 mL) under nitrogen for 5 h until the solution became clear. To this was added a solution of the epoxy alcohol **31** (3.5 g, 21.3 mmol) in 40 mL dry benzene. The resulting mixture was heated under reflux for 15 min, cooled to room temperature and the solvent was removed in *vaccuo*. The concentrate was diluted with 20 mL of diethyl ether and treated with 15 mL of aq. 5% H_2SO_4. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated to afford the crude product which was purified by column chromatography using petroleum ether/EtOAc (3:2) to give azido diol **32**.

Yield: 96% (4.2 g), as a colorless solid; **mp**: 80-81 ^{o}C (lit.[10] mp 80.5-82 ^{o}C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 753, 1039, 1106, 1242, 1554, 2105, 2923, 2960, 3280; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.79 (t, *J* = 5.3 Hz, 1H), 2.47 (d, *J* = 5.2 Hz, 1H), 2.80 (dd, *J* = 14.2, 8.6 Hz, 1H), 3.02 (dd, *J* = 14.1, 4.2 Hz, 1H), 3.59-3.81 (m, 4H), 7.24-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.0, 63.2, 65.6, 73.2, 126.9, 128.7, 129.3, 137.2; **Anal. Calcd for** $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.85; H, 6.28; N, 20.22%.

2-(1-Azido-2-phenylethyl)oxirane (24)



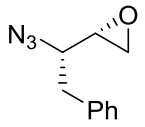
(±)

A mixture containing dry Et_3N (4.0 mL, 28.9 mmol), Bu_2SnO (72 mg, 2 mol %), and *N*,*N*-Dimethyl-4-aminopyridine (177 mg, 10 mol %) was added to a solution of azido diol **32** (3 g, 14.5 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C. Solid *p*-toluene sulfonyl chloride (2.9 g, 15.9 mmol) was then added to the reaction mixture. The resulting mixture was allowed to stir at room temperature for 3 h. It was then diluted with water (10 mL) and extracted with dichloromethane (3 x 20 mL). The organic phase was washed with brine solution, dried over anhyd. Na_2SO_4 and concentrated in *vacuo* to give the crude product **10** (5.0 g), which was used in the next step without purification. To a solution of tosylate **10** (3.0 g, 8.3 mmol) in methanol (25 mL) was added K_2CO_3 (2.3 g, 16.6 mmol) at 0 °C and the resulting mixture was stirred at 25 °C for 1 h. After the completion reaction (monitored by TLC), solvent was evaporated and the residue was extracted with diethyl ether (3 x 20 mL). The combined ether layer was 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 (19:1) to give the azido epoxide **24**.

Yield: 90% over two steps (1.5 g), as a colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 701, 760, 930, 1082, 1216, 1455, 1496, 2109, 2401, 2927, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.79-2.86 (m, 3H), 2.94 (dd, *J* = 13.9, 4.6 Hz, 1H), 3.01-3.07 (m, 1H), 3.51-3.61 (m, 1H), 7.22-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.2, 45.0, 52.9, 63.6, 126.9, 128.5, 129.3, 136.5; **Anal. Calcd for** $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. found: C, 63.58; H, 5.55; N, 22.19%.

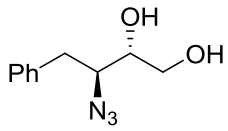
2(*S*)-[1'(*S*)-Azido-2-phenylethyl]oxirane (5)



To a solution of (*S,S)*-Co-complex (43 mg, 0.1 mmol) in toluene (4.0 mL) was added acetic acid (40 mg, 7.3 mmol). It was allowed to stir at 0 °C in open air for 30 min over which time the color of the solution changed from orange-red to a dark brown. It was then concentrated in *vaccuo* to obtain the Co-salen complex as brown-colored solid. To a solution of Co-salen complex-**26** (16 mg, 0.5 mol %) and azido epoxide **24** (1.0 g, 5.3 mmol) in THF (0.5 mL) at 0 °C was added H_2O (46 mg, 2.6 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to 25 °C and stirred for 14 h. After completion of reaction (monitored by TLC), solvent was removed *in vaccuo*. The crude product was purified by column chromatography over silica gel. Solvent system: petroleum ether: EtOAc (19:1) for chiral azido epoxides **5** and petroleum ether: EtOAc (3:2) for chiral azido diol **34**.

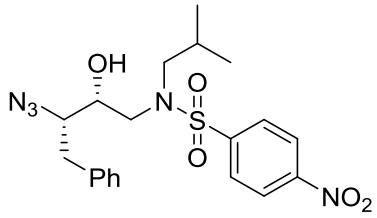
Yield: 48% (0.480 g), colorless oil; $[\alpha]_D^{20}$: +13.1 (*c* 1, $CHCl_3$) {lit.[7] $[\alpha]_D^{20}$: +12.9 (*c* 1.15, $CHCl_3$)}; **HPLC**: 98% ee; (Chiralcel OD-H column, *n*-hexane/*i*PrOH, 97:03, 0.5 mL/min) retention time 17.517 (99.60%) and 15.747 (0.40%).

(2*R*,3*R*)-3-Azido-4-phenylbutane-1,2-diol (34)



Yield: 49% (0.537 g), colorless liquid; $[\alpha]_D^{20}$: -30.8 (*c* 1, $CHCl_3$); **HPLC**: 97% ee (Chiralcel OD-H column, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 13.512 (98.02%) and 13.020 (0.98%).

Preparation of nosylate (22)

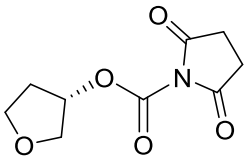


To a solution of azido epoxide **5** (0.2 g, 1.1 mmol) in dry isopropanol (2.0 mL), isobutylamine (0.5 mL, 5.3 mmol) was added and the reaction mixture was stirred for 5 h at 50 °C. It was concentrated under reduced pressure and dried *in vaccuo* to give 263 mg of amino alcohol **35**, which was used for the next step without purification. To a stirred solution of **35** (0.1 g, 0.4 mmol) in of dry CH_2Cl_2 (2.0 mL) was added triethylamine (64 µL, 0.5 mmol) and 4-nitrobenzenesulfonyl chloride (0.11 g, 0.5 mmol) at 0 °C. The resulting mixture was stirred for 30 min at this temperature and warmed to room temperature. It was stirred for 12 h and poured into saturated aq. $NaHCO_3$ solution (3 mL) and extracted with Et_2O (3 x 5 mL). The organic layer was

dried over anhyd. Na_2SO_4 and concentrated to give the crude product. Column chromatographic purification using petroleum ether:EtOAc (4:1) provided nosylate **22**.

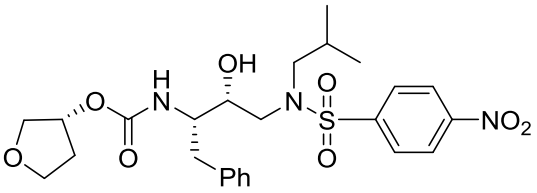
Yield: 89% over two steps (160 mg), colorless solid; **mp**: 115-117 °C; $[\alpha]_D^{20}$: -5.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 607, 745, 1089, 1160, 1312, 1350, 1531, 2110, 2957, 3499; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86-0.93 (m, 6H), 1.74-1.91 (m, 1H), 2.76-2.96 (m, 2H), 3.01-3.14 (m, 3H), 3.20-3.23 (m, 1H), 3.57-3.79 (m , 2H), 7.24-7.36 (m, 5H,), 7.98 (d, *J* = 8.9 Hz, 2H), 8.38 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.7, 20, 26.9, 36.9, 52.2, 58.1, 66.49, 71.4, 124.4, 127.0, 128.5, 128.7, 129.3, 136.8, 144.5, 150.1; **Anal. Calcd for** $C_{20}H_{25}N_5O_5S$: C, 53.68; H, 5.63; N, 15.65; S, 7.17. Found: C, 53.58; H, 5.54; N, 15.45; S, 7.12%.

***N*-Hydroxyl succinimidyl carbamate of (*S*)-3-hydroxytetrahydrofuran (23)**



To a magnetically stirred solution of (*S*)-3-hydroxytetrahydrofuran **4** (0.2 g, 2.3 mmol) in 7 mL of dry acetonitrile was added dry triethylamine (0.9 mL, 6.8 mmol) followed by *N*,*N*- disuccinimidyl carbonate (0.9 g, 3.4 mmol) at room temperature. The mixture was stirred for 4 h and poured into EtOAc (15 mL). The ethyl acetate layer was washed with saturated aq. $NaHCO_3$ solution (5 mL) and dried over anhyd. Na_2SO_4. The organic extract was concentrated under reduced pressure to give the crude product **23**. Silica gel column chromatographic purification provided the carbamate compound (0.4 g, 82%).

4-Nitro-*N*-((2*R*(*syn*),3*S*)-2-hydroxy-4-phenyl-3-((*S*)-tetrahydrofuran-3-yloxycarbonylamino)-butyl)-*N*-isobutylbenzenesulfonamide (36)

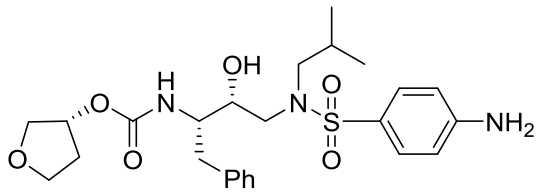


To a stirred solution of nosylate **22** (0.1 g, 0.2 mmol) in 2 mL of dry THF, triphenyl phosphine (0.06 g, 0.2 mmol) was added as a lump at 25 °C and the reaction mixture was stirred for 30 min. To this H_2O (0.004 g, 0.2 mmol) was added and the stirring continued for 29 h. After completion of reaction, solvent was removed in *vaccuo*, water was added and extracted with ethyl acetate (3 x 5 mL). The organic layer was washed with brine, dried over anhyd. Na_2SO_4, concentrated to give the crude amine (0.09 g) as a yellow solid which was used in the following step without purification. To a solution of the above crude amine (0.08 g, 0.2 mmol) in 1 mL of dry CH_2Cl_2 was added *N*-hydroxyl succinimidyl carbamate of (*S*)-3-hydroxytetrahydrofuran (0.04 g, 0.2 mmol) (see previous experiment for its preparation) and dry triethylamine (32 µL, 0.2 mmol) at room temperature. The reaction mixture was stirred for 2 h and concentrated to remove solvent. The residue was dissolved in ethyl acetate and washed with 5% saturated aq. $NaHCO_3$ followed by 5% aq. solution of citric acid. The combined organic layers were washed with brine and dried over anhyd. Na_2SO_4. The mixture was concentrated to give the crude product, which was purified by column chromatography using petroleum ether:EtOAc (7:3) to give carbamate derivative **36**.

Yield: 89% over two steps (0.09 g), colorless solid; **mp**: 161-163 °C; $[\alpha]_D^{20}$: +15.5 (*c* 0.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 606, 745, 1029, 1088, 1109, 1159, 1312, 1350, 1530, 1605, 1709, 2960, 3388; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.9 Hz, 3H),

0.89 (d, *J* = 6.9 Hz, 3H), 1.83-1.94 (m, 2H), 2.09-2.13 (m, 1H), 2.93-2.96 (m, 4H), 3.13-3.16 (m, 2H), 3.59-3.65 (m, 2H), 3.75-3.83 (m, 5H), 4.88 (br s, 1H), 5.13 (br s, 1H), 7.22-7.32 (m, 5H), 7.95 (d, *J* = 8.8 Hz, 2H), 8.4 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.6, 19.8, 26.8, 32.5, 35.1, 52.6, 55.1, 57.5, 66.5, 71.9, 72.7, 75.4, 124.0, 126.6, 128.2, 128.4, 129.1, 136.94, 144.5, 149.8, 155.9; **Anal. Calcd for** $C_{25}H_{33}N_3O_8S$: C, 56.06; H, 6.21; N, 7.85; S, 5.99. Found: C, 56.16; H, 6.18; N, 7.65; S, 5.93%.

Preparation of amprenavir (1)

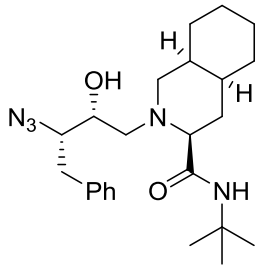


To a solution of carbamate nitro derivative **36** (0.05 g, 0.09 mmol) in 2 mL of EtOAc was added $SnCl_2 \cdot 2H_2O$ (0.1 g, 0.5 mmol) at 70 °C. The reaction mixture was heated for 1 h until starting material disappeared and the solution cooled to room temperature. It was then poured into saturated aq. $NaHCO_3$ solution and extracted with EtOAc. The organic extract was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. It was purified over chromatography using petroleum ether:EtOAc (3:2) to give pure amprenavir **1**.

Yield: 90% (0.04 g), off-white solid; **mp**: 72-74 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1090, 1149, 1316, 1504, 1597, 1633, 1705, 2960, 3371; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86 (d, *J* = 5.7 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 1.78-2.21 (m, 3H), 2.75-3.11 (m, 6H), 3.58-4.11 (m, 7H), 4.25 (s, 2H), 5.01 (br s, 1H), 5.07 (br s, 1H), 6.65 (d, *J* = 8.4 Hz, 2H), 7.20-7.28 (m, 5H), 7.51 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.9, 20.2, 27.3, 32.8, 35.4, 35.7, 53.8, 55.0, 58.6, 66.8, 72.6, 73.2, 75.3, 114.0, 125.9, 126.5,

128.4, 129.5, 137.7, 150.9, 155.9; **Anal. Calcd for** $C_{25}H_{35}N_3O_6S$: C, 59.39; H, 6.98; N, 8.31; S, 6.34. Found: C, 59.36; H, 6.81; N, 8.25; S, 6.29%.

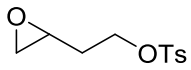
2-(3(*S*)-Amino-2(*R*)-hydroxy-4-phenylbutyl)-*N*-*tert*-butyldecahydro-(4aS,8aS) isoquinoline-3(*S*)-carbaxomide (37)



Silica gel (Merck grade 60, 230-400 mesh, 6Å; 0.2 g), was added to a solution of [3*S*-(3*α*,4aβ,8aβ)]-*N*-(*tert*-butyl)decahydro-3-isoquinolinecarboxamide (0.06 g, 0.3 mmol) and epoxide **5** (0.05 g, 0.3 mmol) in $CHCl_3$ (1 mL) and the resulting suspension was concentrated under reduced pressure. After standing at room temperature for 16 h, the light brown solid obtained was loaded to a column packed with silica gel and eluted with petroleum ether:EtOAc (7:3) to give the azido alcohol **37**, essentially a single diastereomer.

Yield: 85% (0.09 g), colorless solid; **mp**: 154.2 °C (lit.[20] mp 153-5 °C); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -75.5 (*c* 1 $CHCl_3$) {lit.[7] $[\alpha]_D^{20}$: -75.7 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1045, 1153, 1226, 1385, 1454, 1519, 1652, 2101, 2861, 2924, 3439; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33 (s, 9H), 1.25-2.05 (m, 12H), 2.43 (m, 2H), 2.68-3.09 (m, 5H), 3.56-3.64 (m, 3H), 5.84 (s, 1H), 7.23-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.8, 25.9, 26.1, 28.7, 30.6, 31, 33.3, 36.1, 36.7, 51.1, 58.4, 60.8, 66.9, 70.3, 126.7, 128.6, 129.4, 137.7, 173.3; **ESI-MS**: *m/z* 450.5 $[M+Na]^+$ **Anal. Calcd for** $C_{24}H_{37}N_5O_2$: C, 67.42; H, 8.72; N, 16.38. Found: C, 67.40; H, 8.83; N, 16.35%.

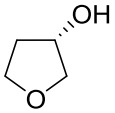
2-(Oxiran-2-yl)ethyl 4-methylbenzenesulfonate (39)



To a solution of olefinic tosylate **38** (5 g, 22.1 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added *m*-chloroperbenzoic acid (5.7 g, 33.1 mmol) in small portions. The resulting solution was stirred for 5 h until complete consumption of starting materials (the progress of the reaction was monitored by TLC). The reaction mixture was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with an aq. 10% solution of $NaHCO_3$ (15 mL). The combined organic layer was dried (anhydrous Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by silica gel column chromatography petroleum ether/EtOAc (8:2) to give the corresponding epoxide **39**.

Yield: 88% (4.7 g), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 554, 664, 817, 942, 1178, 1189, 1359; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.70-1.86 (m, 1H), 1.92-2.09 (m, 1H), 2.46 (s, 3H), 2.49 (m, 1H), 2.75 (t, *J* = 4.6 Hz, 1H), 2.91-3.0 (m, 1H), 4.16 (t, *J* = 5.5 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 32.1, 46.8, 48.6, 67.0, 127.9, 129.8, 133, 144.7; **Anal. Calcd for** $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.40; H, 5.83; S, 13.15%.

(*S*)-3-Hydroxytetrahydrofuran (4): HKR route



HKR of epoxide **39** was conducted by following the exact procedure as given under the preparation of compound **5**.

(*S*)-3-Hydroxytetrahydrofuran (**4**)-**Yield**: 48%; $[\alpha]_D^{20}$: +17.2 (*c* 1, MeOH) {lit.[6b] $[\alpha]_D^{20}$: +17.6 (*c* 1, MeOH)} 98% ee.

2-(*R*)-Oxiran-2-yl)ethyl 4-methylbenzenesulfonate (**40**)-**Yield**: 47%; $[\alpha]_D^{20}$: -13.5 (*c* 1, $CHCl_3$).

(*S*)-3-Hydroxytetrahydrofuran (4): ADH route

To a mixture of $K_3Fe(CN)_6$ (8.7 g, 26.6 mmol), K_2CO_3 (3.7 g, 26.6 mmol), and $(DHQ)_2$-PHAL (0.07 g, 1 mol %), in *t*-BuOH/H_2O (1:1, 60 mL) cooled at 0 °C was added $K_2OsO_4.2H_2O$ (0.02 g, 0.2 mol %) followed by addition of methanesulfonamide (0.84 g, 8.8 mmol). After being stirred for 5 min at 0 °C, olefinic tosylate **38** (2 g, 8.8 mmol) was added in one portion. The reaction was stirred at 0 °C for 6 h and then quenched with solid sodium bisulfite (1 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/ EtOAc (3:2) as an eluent gave the alcohol **4**.

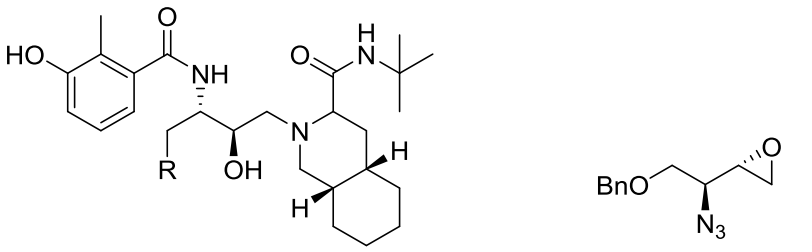
Yield: 95% (0.7 g), colorless liquid; $[\alpha]_D^{20}$: +15.4 (*c* 1, MeOH) {lit.[21] $[\alpha]_D^{20}$: +17.6 (*c* 1, MeOH)}, 89% ee; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1067, 1121, 2878, 2953, 3404; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.83-1.96 (m, 1H), 2.0-2.18 (m, 2H), 3.76-3.86 (m, 2H), 3.88-4.04 (m, 1H), 4.47-4.52 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.3, 66.6, 71.6, 75.4; **Anal. Calcd for** $C_4H_8O_2$: C, 54.53; H, 9.15. Found: C, 54.40; H, 9.13%.

Section II

A Concise Formal Synthesis of the Potent HIV Protease Inhibitor Nelfinavir and its Analogue

1.2.1 Introduction

Inhibitors of human immunodeficiency virus protease (HIV-PR) are proven as an effective chemotherapeutic agents against AIDS.[23,24] Nelfinavir **41** has been well-known for its potent nonpeptidic HIV-protease inhibitor activity and used in the treatment of HIV infection, recently approved by the US FDA.[25] According to a previous investigation, nelfinavir **41** has proven for the best inhibitory effects against the chymotrypsin-like activity of 20S proteasome. Several clinical trials proved that nelfinavir has been involved in the inhibition of Akt pathway–actually an enzymatic pathway, which helps in the arrest of apoptosis and prolongation of cell survival in many types of cancers. Therefore, this potent nature has made nelfinavir **41** a very promising HIV-PR for the anticancer therapy development.



41 R = SPh nelfinavir

42 R = Ph nelfinavir analogue

43 benzyloxy azido epoxide

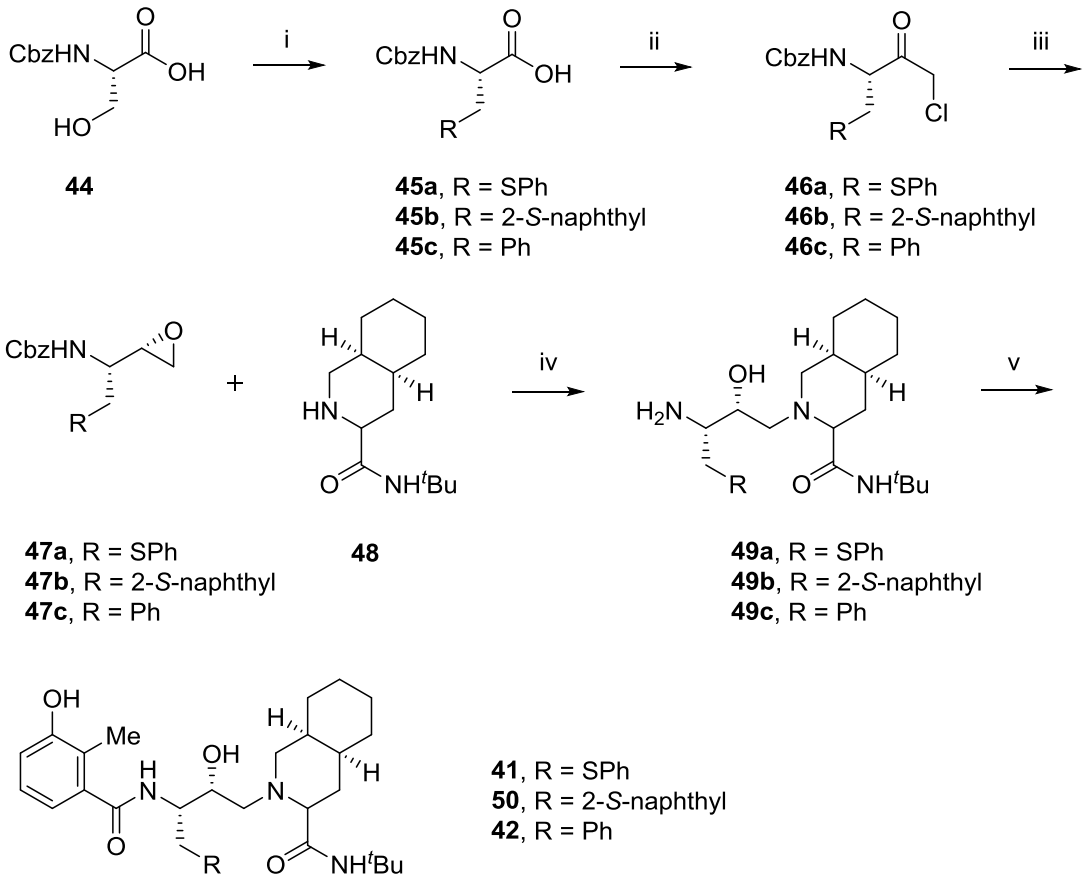
Fig. 15: HIV protease inhibitors (**41 & 42**) and its key intermediates (**43**)

1.2.2 Review of Literature

Due to the wide applicability and potential biological importance of these HIV inhibitors, considerable efforts has been directed at methods for their synthesis.[26] Out of which, some of the important and recent synthetic routes to synthesize nelfinavir **41** are described below.

Reich' approach (1997)[26a]

Reich *et al.* have developed a very useful and short synthetic route for the synthesis of nelfinavir **41** and its analogue **42** *via* chiral pool approach as summarized in **Scheme**

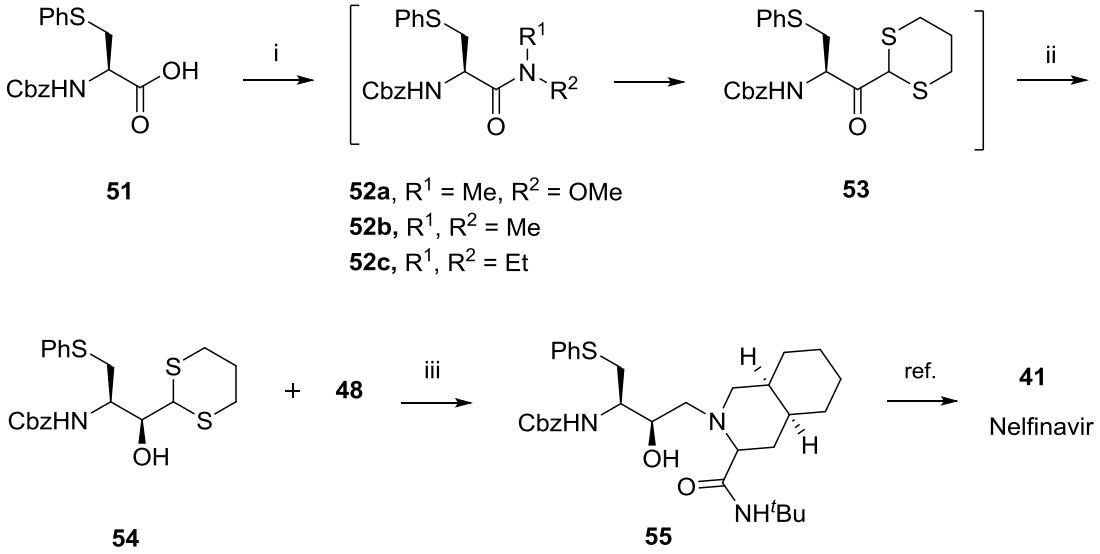


Scheme 10: (i) PPh_3, DMAD, THF, -55 °C, 12 h followed by Na-aryl thiolate, THF, rt, 2.5 h, 3 h, 39%; (ii) (a) *i*-BuOCOCl, Et_3N, EtOAc, CH_2N_2, rt, 2 h; (b) HCl, Et_2O, -20 °C, 4 h, 73% over two steps; (iii) (a) $NaBH_4$, THF, 0 °C, 30 min, 39%; (b) KOH, EtOH, 0 °C -rt, 2 h, 85%; (iv) (a) EtOH, 80 °C, 8 h, 40%; (b) 30% HBr, AcOH, rt, 1 h, 71% ; (v) (a) 3-hydroxy-2-methylbenzoic acid, DCC, HOBt, DMF, -10 °C, 59%; (b) $MeSO_3H$, CH_2Cl_2, 0 °C, 5 min, 99%.

10. The amino acids **45a-c** were prepared from N-Cbz-L-serine **44** by formation of the corresponding β-lactone followed by *in situ* opening with sodium aryl thiolate.[27] Then the reaction of amino acids **45a-c** with respective diazoketones in hydrochloric acid afforded chloromethyl ketones **46a-c**. Keto derivatives were then reduced with sodium borohydride to give the corresponding chloromethyl alcohols as a mixture of diastereomers followed by base induced cyclization furnished amino epoxides **47a-c**. Regioselective opening of epoxides **47a-c** with the known secondary amine **48** resulted in N-Cbz-protected amino alcohols, which were subsequently treated with HBr-acetic acid that liberated deprotected amines **49a-c**. Final targets **41a, 50** and **42b** were achieved by coupling of amines **49a-c** with 2-methyl-3-hydroxybenzoic acid followed by its mesylate formation.

Rieger's approach (1997)[26b]

Rieger *et al.* have reported chiral pool approach for the synthesis of nelfinavir **41** starting from N-Cbz-*S*-phenyl-L-cysteine (**51**). Acid **51** was converted to Weinreb

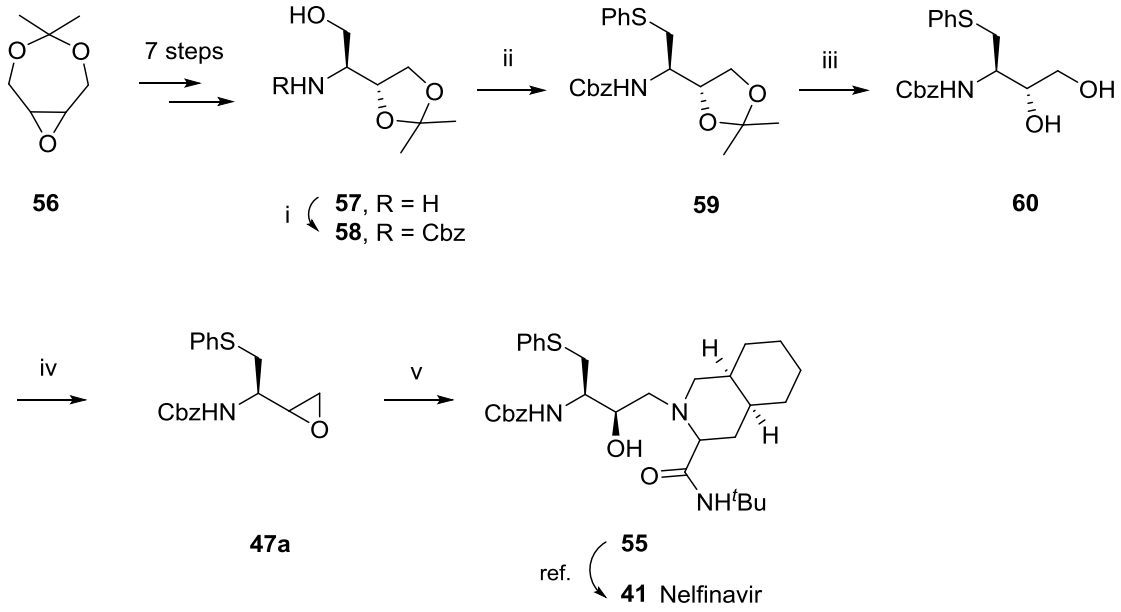


Scheme 11: (i) PivCl, N-methylmorpholine (NMM), R_2NH, CH_3CN, -15 °C, 1 h; followed by 1,3-dithiane, *n*-BuLi, 10 °C, 1 h; (ii) $NaBH_4$, MeOH/THF, 4 °C, 15 min, 70% over two steps; (iii) (a) $Hg(ClO_4)_2.3H_2O$, *iso*-propyl alcohol, H_2O, $CHCl_3$, rt, 1 h; (b) **48**, benzotriazole, THF, 4Å MS, then $NaBH_4$, 25 h, 68% over two steps.

amides **52a-c** *via* its protection as pivalate followed by addition of 2-lithio-1,3-dithiane (generated from 1,3-dithiane and *n*-BuLi at 0 °C) afforded ketone **53**. Keto derivative **53** was then reduced with $NaBH_4$ to furnish the dithianyl alcohol **54** in 64% yield (dr: 82:18). Further, dithianyl group was deprotected to furnish the corresponding (*R*)-hydroxy aldehyde. Reductive amination of this aldehyde with perhydroisoquinoline **48** resulted in derivatives **55.** Further conversion of **55** to nelfinavir **41** has been already reported in the literature (**Scheme 11**).

Inaba's approach (2000)[26c]

Inaba *et al*. have described the synthesis of nelfinavir **41** starting from epoxide **56**, which was converted to amine **57** in 7 steps with an overall yield of 73%. The free amine functionality was protected as its Cbz group **58**, which was then successively treated with MsCl and PhSH giving thioether **59**. Acid mediated deprotection of

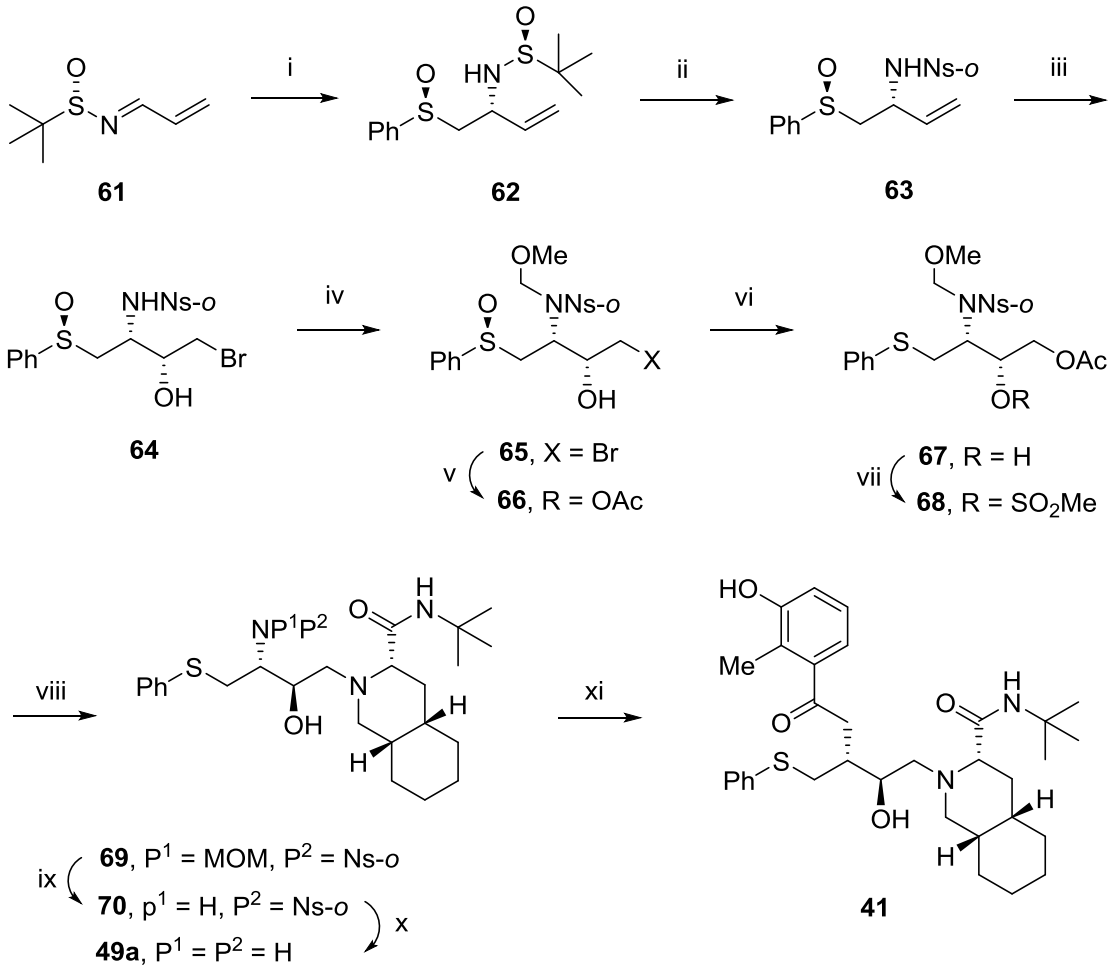


Scheme 12: (i) Cbz-Cl, K_2CO_3, toluene, H_2O; (ii) (a) MsCl, NEt_3, toluene; (b) PhSH, NaOH, Bu_4NBr, toluene, H_2O; (iii) HCl, MeOH, H_2O, 95%; (iv) (a) PNB-Cl, 2-picoline, EtOAc; (b) MsCl, NEt_3, EtOAc; (c) KOH, 1,4-dioxane, H_2O; (v) **48**, K_2CO_3, H_2O, MeOH, 86%.

acetonide afforded diol **60** in 95% yield. Further, stereochemical inversion of the secondary hydroxyl group in diol **60** was achieved *via* (i) mesylation; (ii) PMB protection; followed by (iii) base treatment resulted in epoxide **47a**. Finally, opening of epoxide ring with perhydroisoquinoline **48** in the presence of K_2CO_3 gave derivative **55** in 86% yield. Conversion of **55** to nelfinavir **41** has already been documented in the literature (**Scheme 12**).

Raghavan's approach (2009)[26d]

Raghavan *et al*. have envisaged the synthesis of nelfinavir **41** from the key chiral intermediate sulfinamide **62**, which was achieved from distereoselective addition of (*S*)-sulfoxide onto the sulfinylimines **61** (dr 98:2) in 94% yield. The sulfonamide **62** was then deprotected and treated with arenesulfonyl chlorides to afford the sulfonamides **63** in a single step. Further, reaction of **63** with NBS proceeded smoothly to furnish bromohydrin **64** in 77% yield. Bromohydrin **64** was then treated with MOM-Cl to give the N-Mom derivative **65** followed by bromine displacement with acetate afforded acetate **66**. Sulfonamide **66** was reduced to sulfide **67** in the presence of TFAA and NaI. Epoxide formation was achieved by mesylation of hydroxyl group and hydrolysis of acetate in **67**; followed by opening of the epoxide *in situ* by addition of commercially available amine **48** at the same reaction mixture furnished derivative **69**. The N,O-acetal group was deprotected with aq. 4 N HCl to give sulfonamide **70** followed by its deprotection afforded amine **49a**. Finally, condensation of amine **49a** with acid chloride followed by removal of the acetyl group yielded nelfinavir **41** (**Scheme 13**).

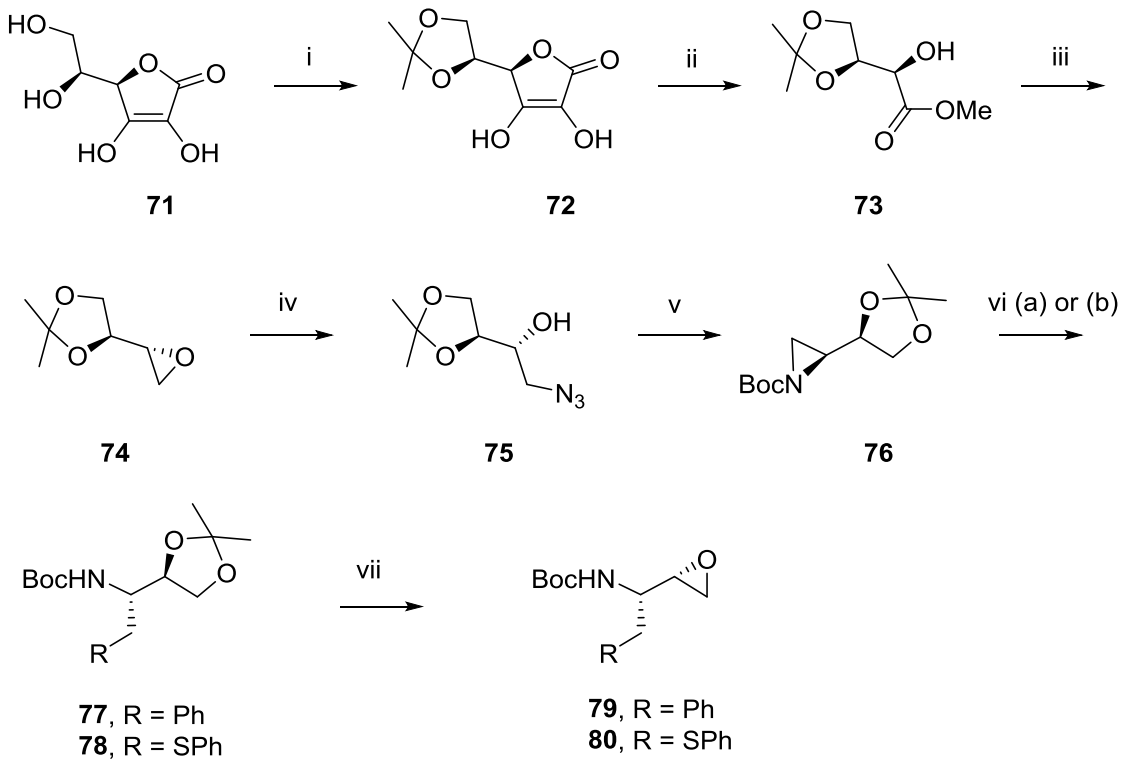


Scheme 13: (i) (*S*)-PhSOMe, LDA, THF, -78 °C, 5 min, 94%; (ii) 4N HCl, dioxane, MeOH, rt, 1 h, followed by *o*-NsCl, Et_3N, CH_2Cl_2, rt, 1 h, 71%; (iii) NBS, H_2O, 2,6-lutidine, $PhCH_3$, rt, 77%; (iv) MOM-Cl, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 1 h, 89%; (v) NaOAc, DMF, 90 °C, 8 h, 84%; (vi) TFAA, NaI, acetone, 82%; (vii) Ms-Cl, Et_3N, CH_2Cl_2, 93%; (viii) K_2CO_3, MeOH, rt; then **48**, rt, 8 h, 89%; (ix) 4N, HCl, rt, 30 min, 90%; (x) mercapto ethanol, DBU, DMF, rt, 1 h, 86%; (xi) 3-hydroxy-2-methylbenzoic acid, EtOAc, aq. $NaHCO_3$, followed by 28% NH_3, MeOH, rt, 1 h, 89% for 2 steps.

Kim's approach (2012)[26e]

Kim *et al*. have reported the synthesis of key chiral intermediate chiral epoxides **79** & **80** of nelfinavir **41** and its analogue **42** from the naturally available source ascorbic acid **71**. Protection of acid **71** in the presence of 2,2-dimethoxypropane and concentrated sulfuric acid afforded compound **72** followed by its oxidation (H_2O_2/aq. $NaHCO_3$) and subsequent methyl ester formation with dimethyl sulfate gave α-hydroxy ester **73**. The

hydroxyl group in **73** was tosylated and ester group was reduced with *in situ* generated $Ca(BH_4)_2$ ($NaBH_4$ and $CaCl_2$) followed by base treatment afforded epoxide **74** in overall 81% yield from L-ascorbic acid **71**. Opening of epoxide **74** with NaN_3 in presence of methyl formate provided azido alcohol **75** in 95% yield. Further, reduction of azide moiety furnished the cyclized aziridine ring followed by its Boc protection afforded Boc derivative **76**. Aziridine **76** was opened with phenylmagnesiumcuprate or thiophenoxide to provide **77** or **78** respectively. Finally, epoxide **79** or **80** was obtained in 78% overall yield in 3 steps: (i) deprotection; (ii) selective protection of primary hydroxyl group; and (iii) base treatment (**Scheme 14**). Further, its conversion to nelfinavir **41** has already been reported in the literature.



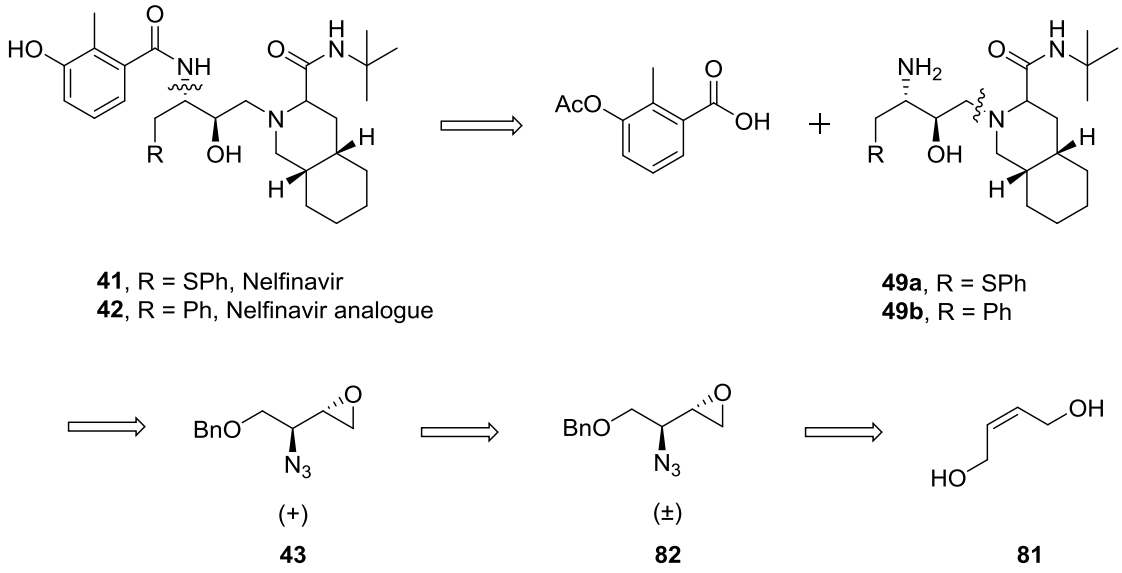
Scheme 14: 2,2-dimethoxypropane, H_2SO_4, acetone, 0 °C, 5 h; (ii) H_2O_2, Me_2SO_4, $NaHCO_3$, 5 h, 50 °C; (iii) *p*-TsCl, CH_2Cl_2, pyridine, 5 °C, 3 h, 81% overall yield; (b) $NaBH_4$, $CaCl_2$, EtOH, -5 °C, 3 h; (c) KOH, MeOH, 10 °C, 3 h; (iv) NaN_3, $MeCO_2H$, H_2O, 60 °C, 6 h, 95% for 4 steps; (v) Ph_3P, CH_3CN, reflux; 12 h; (b) $(Boc)_2O$, $NaHCO_3$, dioxane, 0 °C, 1 h, 95% over two steps; (vi) (a) PhMgBr, $CuBr.SMe_2$, $PhCH_3$, -10 °C, 1 h; (b) PhSH, NaH, THF, 0 °C, 1 h; (vii) (a) *p*-TsOH, MeOH, H_2O, 50 °C, 6 h; (b) *p*-TsCl, pyridine, -10-5 °C, 1 h; (c) KOH, MeOH, 0 °C, 2 h; 78% over 3 steps.

1.2.3 Present Work

1.2.3.1 Objective

As can be seen from the above discussion, several synthetic approaches for the synthesis of nelfinavir **41** and its key chiral building blocks of HEA-based HIV protease inhibitors, have been reported in the literature.[26] Some of these methods, however, suffer from certain limitations such as the use of chiral building blocks, introduction of chirality in the early stages, long reaction sequences, low % ee, and hence are not amenable for scale-up studies.[28] Recently we have reported an elegant method of synthesis of HIV protease inhibitor amprenavir[29] *via* Co-catalyzed HKR of 2-(1-azido-2-phenylethyl)oxirane, (see previous section). In this section, we have extended its scope to the synthesis of other HIV-PI. In this section, a simple and concise synthetic route to the formal synthesis of nelfinavir **41** and its analogue **42** *via* Co-catalyzed HKR of benzyloxy azido epoxide **82** is presented.

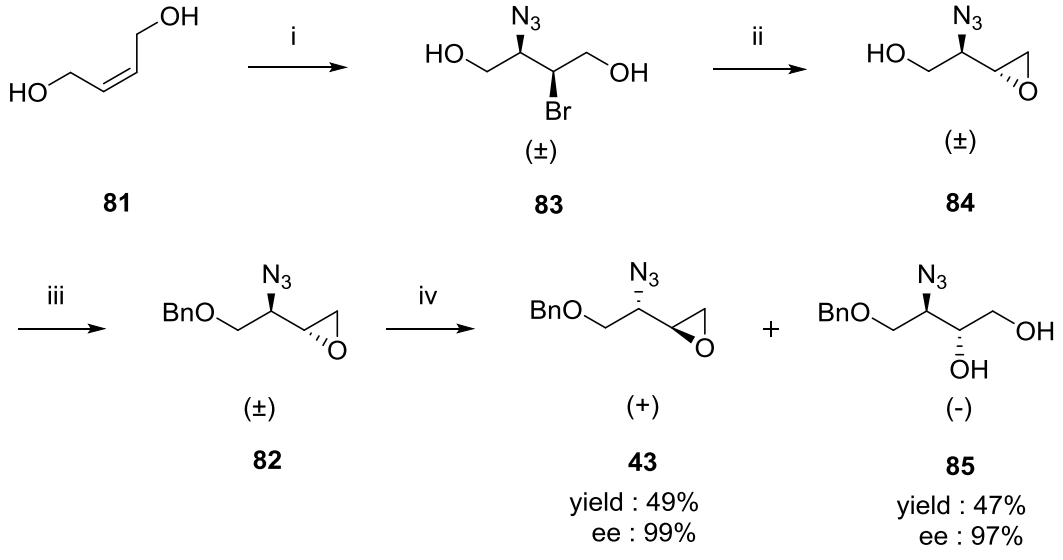
Retrosynthetic analysis of nelfinavir **41** showed that chiral amino alcohols **49a** and **49b** could be visualized as intermediates. These chiral amino alcohols could be obtained by means of the regioselective ring opening of chiral *syn*-benzyloxy azido epoxide **43** with commercially available perhydroisoquinoline moiety **48,** from which nelfinavir can be obtained by means of reactions such as debenzylation; displacement with thiophenol; and azide reduction, respectively. The chiral *syn*-benzyloxy azido epoxide **43** could in turn be obtained by performing Co-catalyzed two-stereocentered hydrolytic kinetic resolution (HKR) of the corresponding racemic *syn*-benzyloxy azido epoxide **82**, which can be easily prepared from *cis*-2-butene-1,4-diol **(81)** (**Scheme 15**).



Scheme 15: Retrosynthetic analysis of nelfinavir **41**

1.2.3.2 Results and Discussion

Accordingly, the formal synthesis of nelfinavir **41** has commenced with commercially available *cis*-2-butene-1,4-diol (**81**), which on treatment with NBS in the presence of NaN_3 gave bromo azide **83** in 89% yield (**Scheme 16**).



Scheme 16: (i) NBS, NaN_3, CH_3CN:H_2O (3:1), 0 °C, 2 h, 89%; (ii) NaOH, THF, 0 °C, 3 h, 84%; (iii) BnBr, NaH, DMF, -0 °C, 2 h, 94%; (iv) (*S*,*S*)-Co(III)(salen) (0.5 mol %), H_2O (0.5 equiv), 0 to 25 °C, 12 h.

The formation of azido bromide, (±)-**83** was confirmed by ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **83** showed a typical multiplet at δ 4.12-4.20 (m, 1H) corresponding to methine (-CH-N_3) proton attached to –N_3 group. Further it was supported by its ^{13}C NMR spectrum, which showed two typical carbon signals at δ 54.3 and 62.4 due to carbons attached to bromo and azide groups respectively (**Fig. 16**). Its IR spectrum displayed strong and broad vibrational stretching frequencies at 2104 and 3361 cm^{-1} indicating the presence of -N_3 and –OH functionalities respectively.

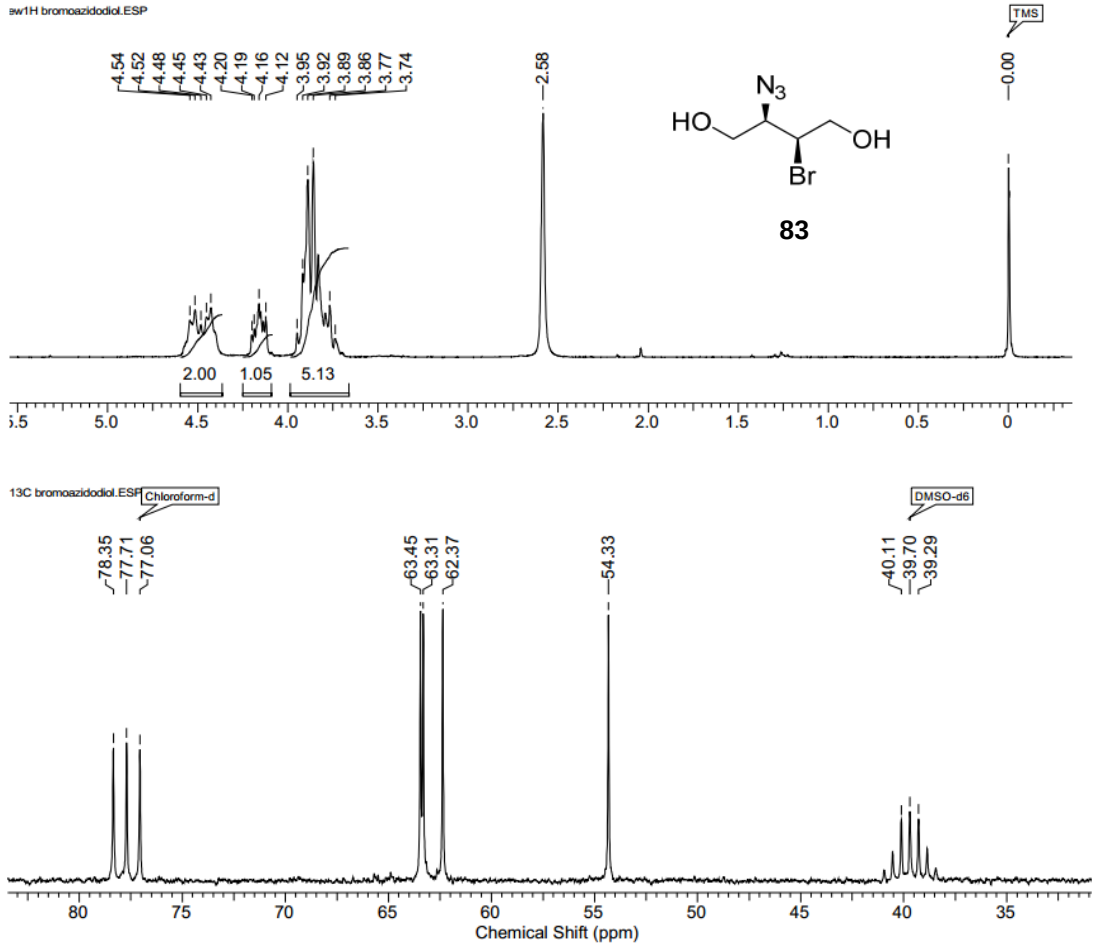


Fig. 16: ^{1}H and ^{13}C NMR spectra of azido bromide **83**

The bromo azide **83** was readily transformed into racemic *anti* azido epoxide **84** under base treatment (NaOH, dry THF, 0 °C) in 84% yield. The ^{1}H NMR spectrum of **84**

showed two multiplets at δ 2.82-2.90 (m, 2H) and 3.47-3.49 (m, 1H) corresponding to methylene and methine protons of epoxide ring respectively. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 44.8 and 50.61 corresponding to the methylene and methine carbons of epoxide ring (**Fig. 17**). Also, its IR spectrum displayed strong and broad vibrational stretching frequencies at 2104 and 3350 cm^{-1} due to the presence of $–N_3$ and –OH functionalities respectively.

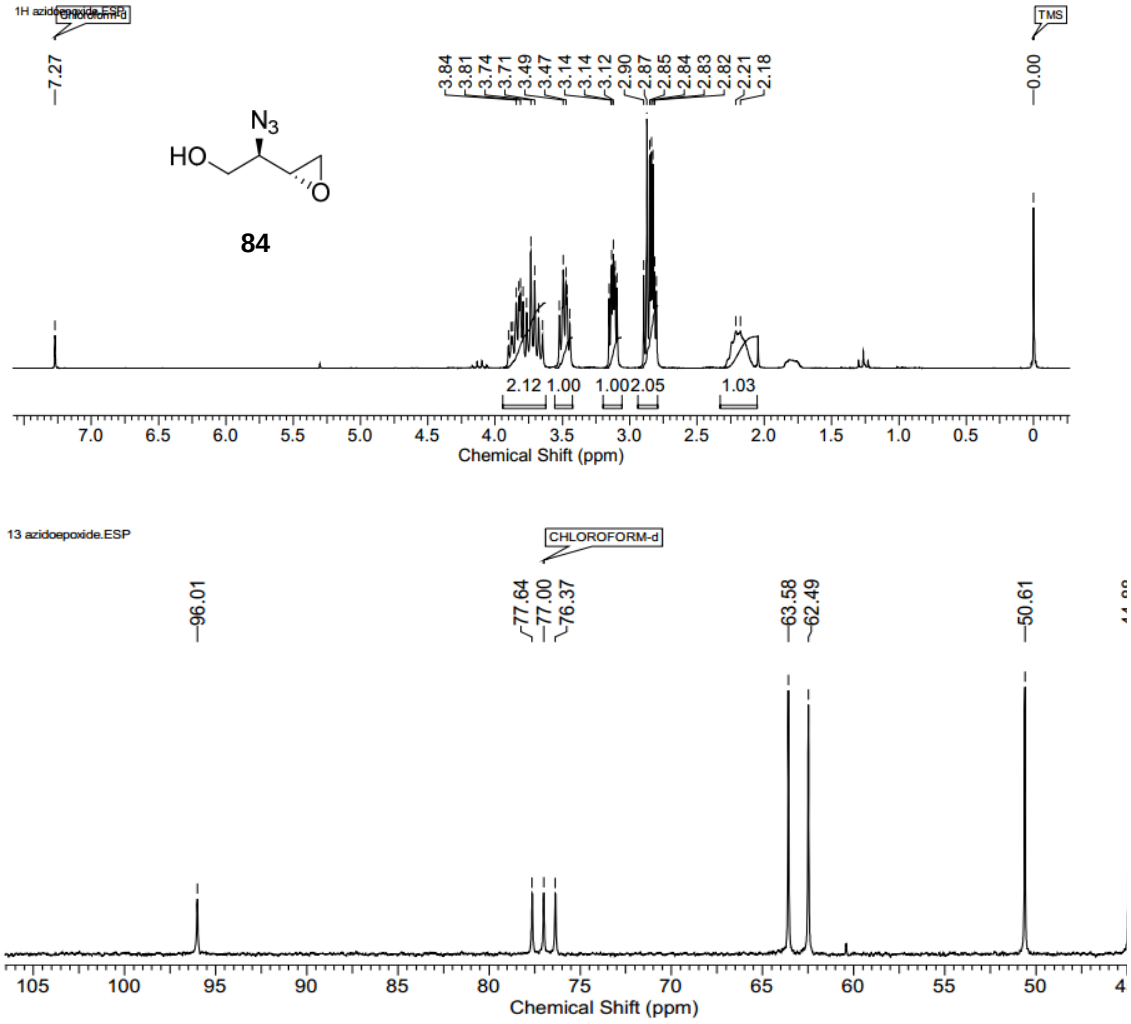


Fig. 17: ^{1}H and ^{13}C NMR spectra of epoxide **84**

The protection of primary hydroxyl group in azido epoxide **84** as its benzyl ether (BnBr, NaH, DMF, -40 °C) was achieved to give protected racemic benzyloxy azido

epoxide (±)-**82** in 94% yield. The formation of compound **82** was confirmed by the appearance of a multiplet at δ 7.33 (m, 5H) and a sharp singlet at δ 4.59 (s, 2H) in its ^{1}H NMR spectrum due to aromatic and methylene protons of benzyl group respectively. Further, its structure was substantiated by ^{13}C NMR spectrum, which displayed a typical carbon signal at δ 73.4 for benzylic methylene carbon thus, confirming the formation of benzyl ether **82** (**Fig. 18**).

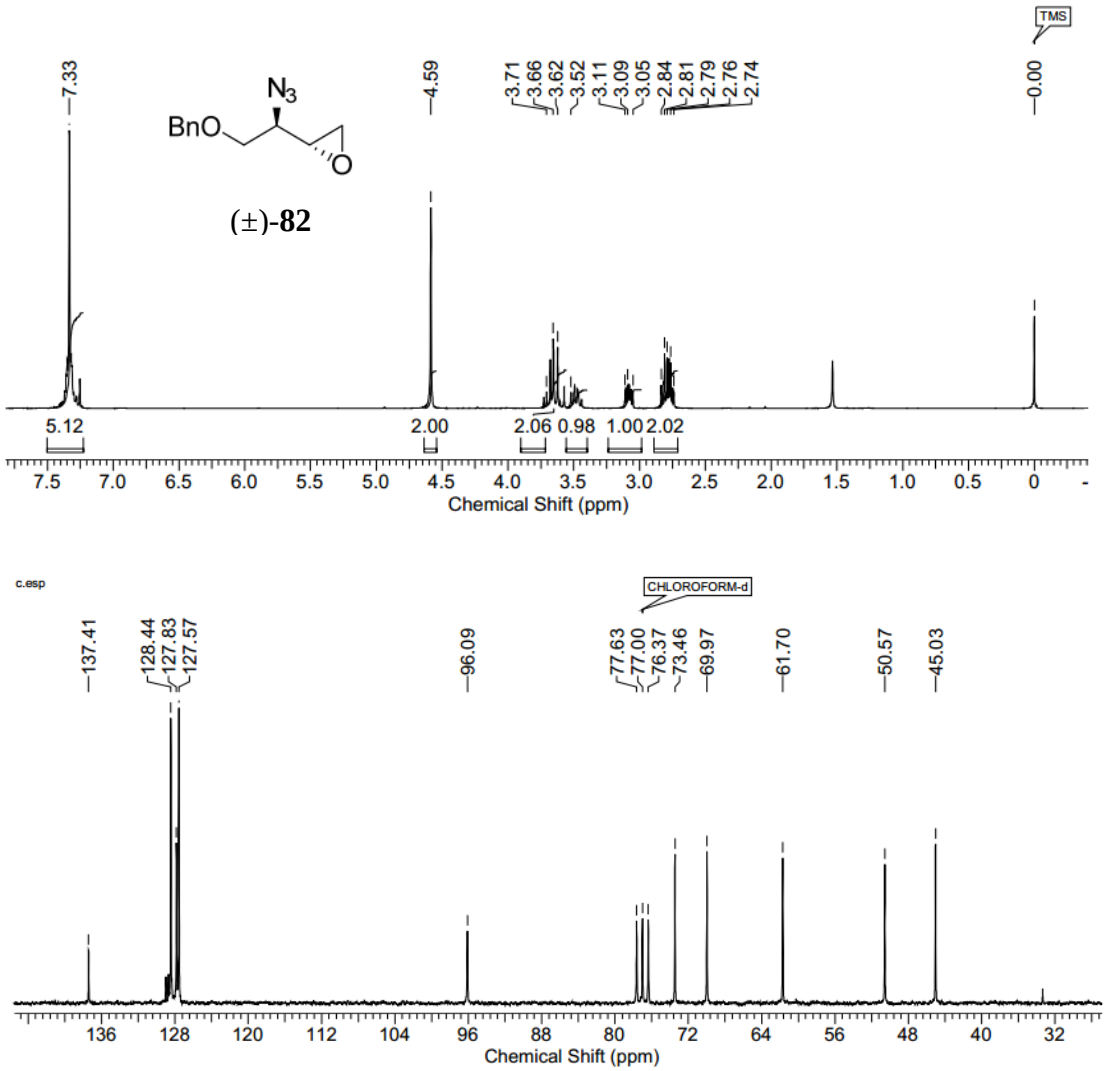
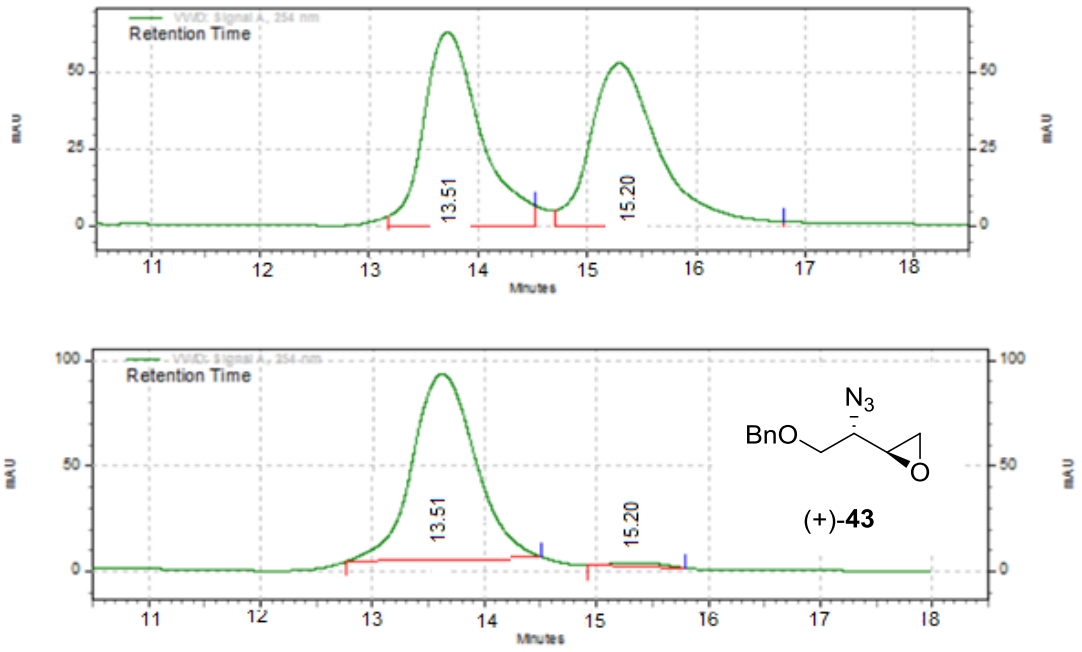


Fig. 18: ^{1}H and ^{13}C NMR spectra of benzyloxy azido epoxide **82**

Compound **82** was then subjected to HKR with (*S*,*S*)-salen Co(III)OAc complex (0.5 mol %) and H_2O (0.49 equiv), which gave the corresponding diol **85** (47%, 97% ee)

and chiral epoxide **43** (49%, 99% ee) in high optical purity (**Scheme 16**). The diol (-)-**85** was, however, readily separated from epoxide (+)-**43** by a simple flash column chromatographic purification over silica gel. The enantiomeric excess of chiral benzyloxy epoxide (+)-**43** was determined from chiral HPLC analysis using Chiralpak OD-H column.



Retention Time	Area	Area%	Height	Height %
13.51	2578055	99.55	86067	1.24
15.20	297132318	0.45	6829082	98.76
Totals	299710373	100.0	6915149	100

Fig. 19: HPLC chromatogram of epoxide (+)-**43**

The optical purity of chiral azido epoxide **43** was determined to be 99% ee by chiral HPLC analysis (Chiralcel OD-H column, *n*-hexane/*i*PrOH, 97:03, 0.5 mL/min, 254 nm) Retention times: t_{major} = 13.51 (99.55%) and t_{minor} = 15.20 min. (0.45%) for azido epoxide **43** (**Fig. 19**).

The formation of azido diol (-)-**85** was confirmed by the appearance of two broad singlets at δ 2.54 (s, 1H) and 3.12 (s, 1H) due to the presence of two hydroxyl protons and another singlet at δ 4.56 (s, 1H) due to benzylic protons respectively in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 63.3 and 71.3 for the methine and methylene carbons attached to hydroxyl groups respectively (**Fig. 20**). Its IR spectrum exhibited strong and broad vibrational stretching frequencies at 2106 and 3350 cm^{-1} accounting for the presence of $-N_3$ and –OH functionalities respectively.

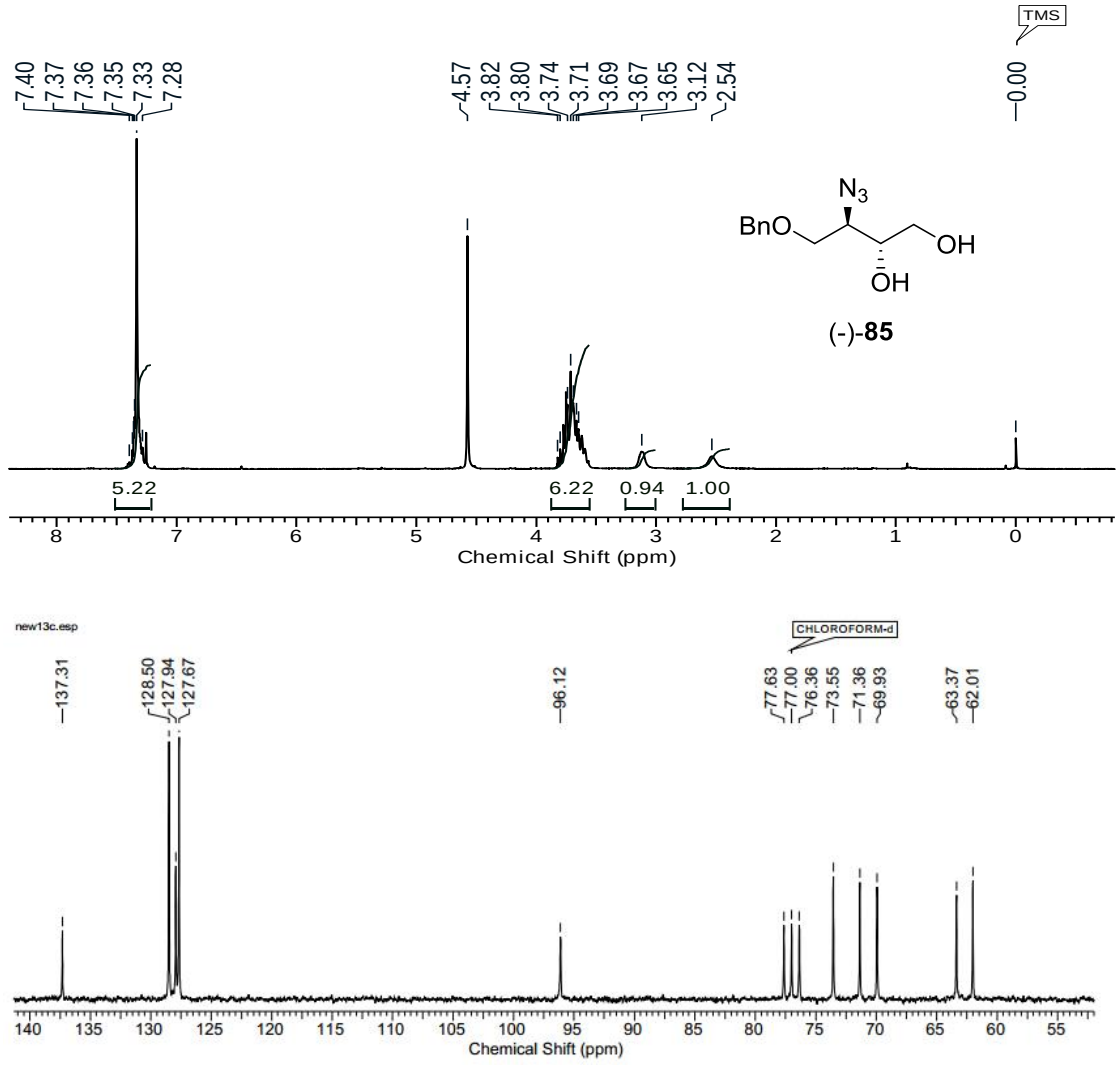
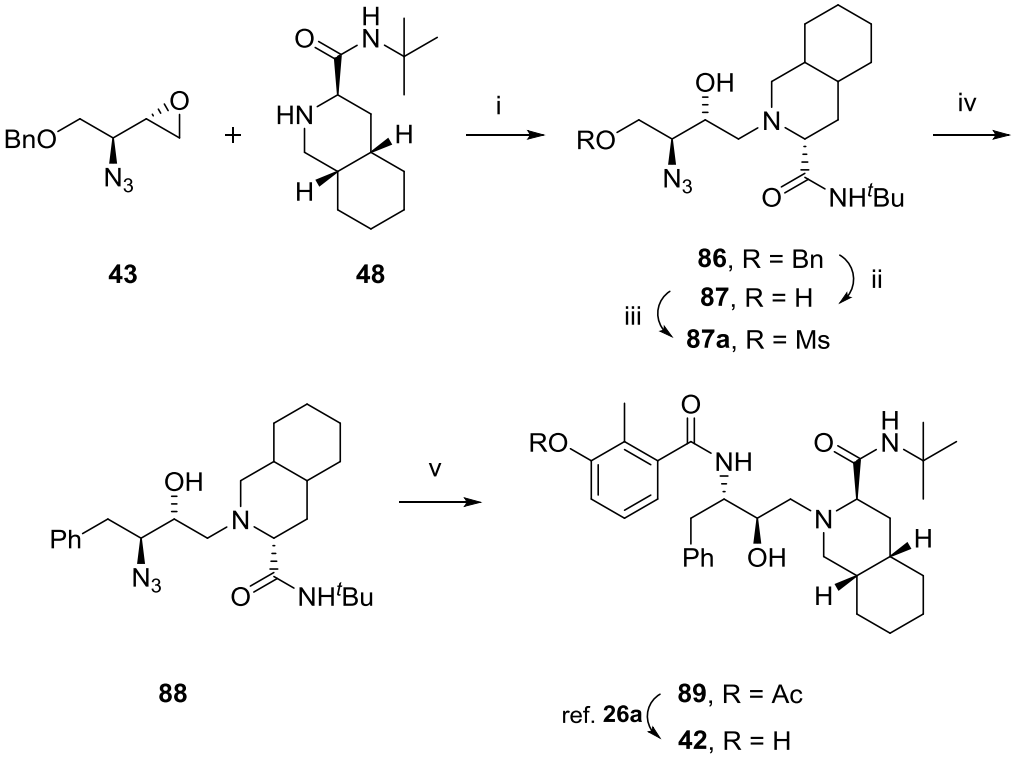


Fig. 20: ^{1}H and ^{13}C NMR spectra of benzyloxy diol **85**

The key chiral intermediate azido epoxide **43** was then used for the synthesis of nelfinavir **41** and its analogue **42**. Treatment of chiral azido epoxide **43** with commercially available [3*S*-(3*α*,4*aβ*,8*aβ*)]-*N*-(*tert*-butyl)decahydro-3-isoquinolinecarboxamide **48** was attempted that produced azido alcohol **86** in 85% yield in a highly regioselective fashion (**Scheme 17**).



Scheme 17: (i) Silica gel (230-400, 6Å mesh), $CHCl_3$, 25 °C, 16 h, 85%; (ii) DDQ, CH_2Cl_2, 0 °C to rt, 4 h, 90%; (iii) MsCl, DMAP, CH_2Cl_2, 0 °C, 1 h; (iv) PhMgBr, THF, 0 °C-rt, 0.5 h, 90% over 2 steps; (v) (a) Ph_3P, H_2O, THF, rt, 16 h; (b) 3-acetoxy-2-methyl benzoic acid, DCC, HOBt, -10 °C, THF, 48 h, 89% over 2 steps.

The formation of azido alcohol **86** was confirmed from its ^{1}H NMR spectrum, which showed a typical multiplet at δ 3.45-3.54 (m, 1H) and a singlet at δ 5.86 (s, 1H) corresponding to the methine proton of perhydroisoquinoline ring and –NH proton respectively. Also, its ^{13}C NMR spectrum showed two typical carbon signals at δ 29.2 and 170.6 due to *tert*-butyl and –C=O carbons respectively (**Fig. 21**). Its IR spectrum

displayed three strong and broad vibrational stretching frequencies at 3439, 2101 and 1662 cm^{-1} due to presence of –OH, $–N_3$ and –C=O functionalities respectively.

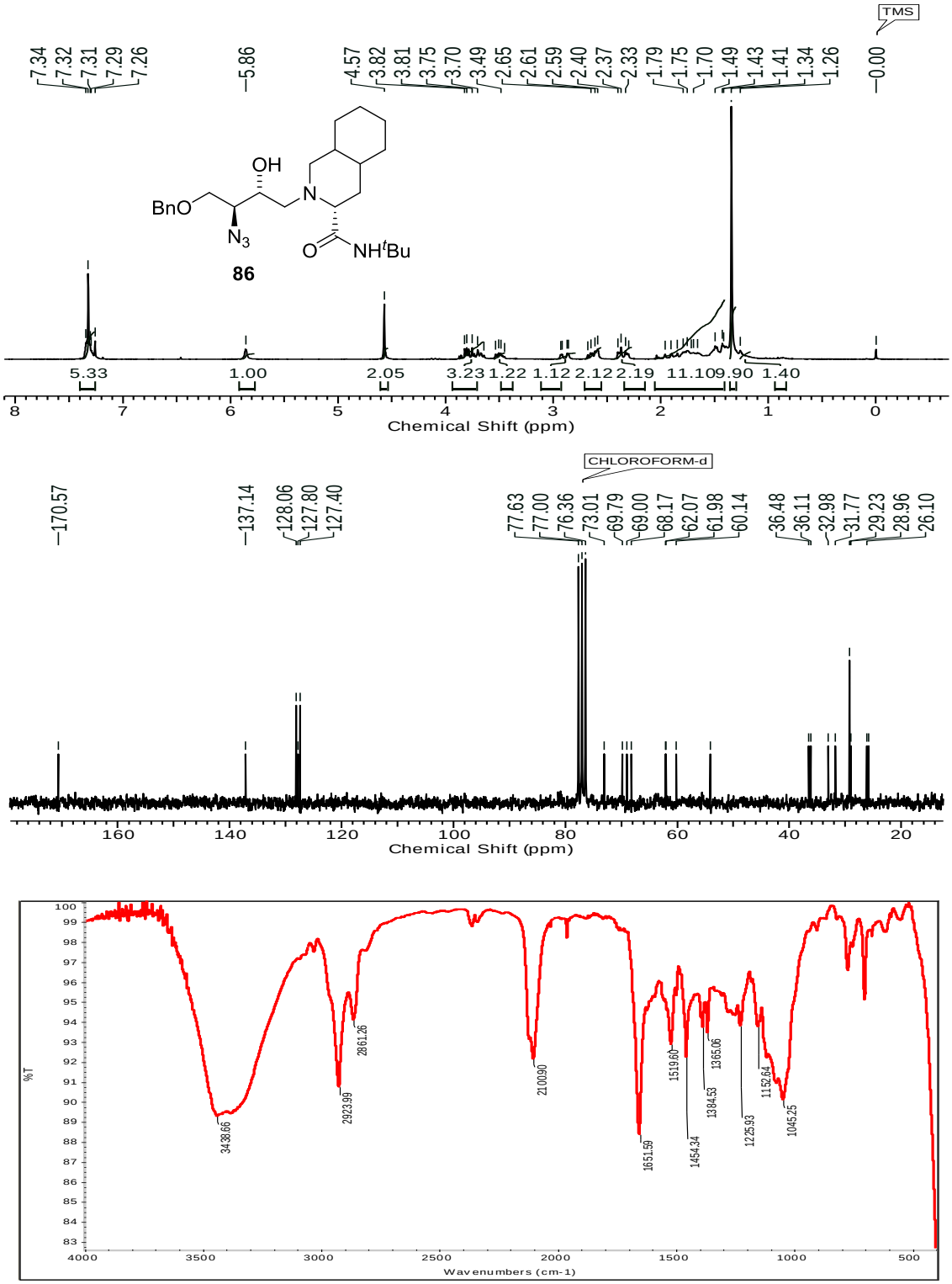


Fig. 21: ^{1}H and ^{13}C NMR spectra of azido alcohol **86**

The common intermediate alcohol **86** was further used for the synthesis of nelfinavir analogue **42**. The benzyl ether **86** was subjected to debenzylation under the reaction conditions (DDQ, CH_2Cl_2, 0 °C) to provide alcohol **87,** which was subsequently treated with MsCl, DMAP to give mesylate followed by coupling of PhMgBr in THF at 0 °C under Grignard reaction conditions afforded the corresponding phenyl azido alcohol **88** in 86% yield over two steps. The formation of **88** was unambiguously confirmed by the ^1H and ^{13}C NMR spectra, which have already been discussed in **Section I** (**Fig. 11**).

Phenyl azide **88** was reduced under Staudinger reaction conditions (Ph_3P, H_2O, rt) to afford the corresponding amino alcohol **49c** followed by its coupling with 2-methyl-3-hydroxybenzoic acid (HOBt, DCC, THF, -10 °C) to furnish amide derivative **89** in excellent 89% yield over two steps. Its specific rotation and spectral values were in complete agreement with the literature values {$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -75.5 (*c* 2 $CHCl_3$), lit.[4e] $[\alpha]_D^{20}$: -75.0 (*c* 2, MeOH)}.

The formation of amide derivative **89** was ascertained by ^1H NMR spectrum, which showed two doublets at δ 6.93 (d, *J* = 7.1 Hz, 1H) and 6.98 (d, *J* = 6.9 Hz, 1H) corresponding to the aromatic protons and another two sharp singlets at δ 2.28 (s, 3H) and 2.95 (s, 3H) due to the presence of methyl protons of –OAc and Ar-CH_3 respectively. Its ^{13}C NMR spectrum exhibited appearance of two carbon signals at δ 12.7 and 20.7 due to the presence of methyl carbons and another two carbon signals at δ 168.9 and 170.0 indicating the presence of –C=O of OAc group and amide linkage respectively (**Fig. 22**). Its IR spectrum displayed strong and broad stretching frequencies at 3350 and 1713 cm^{-1} indicating the presence of –NH, -OH and -C=O functionalities respectively. Further, the transformation of amide derivative **89** to

nelfinavir analogue **42** can be achieved by removal of acetate group, which has already been reported in the literature.[26a]

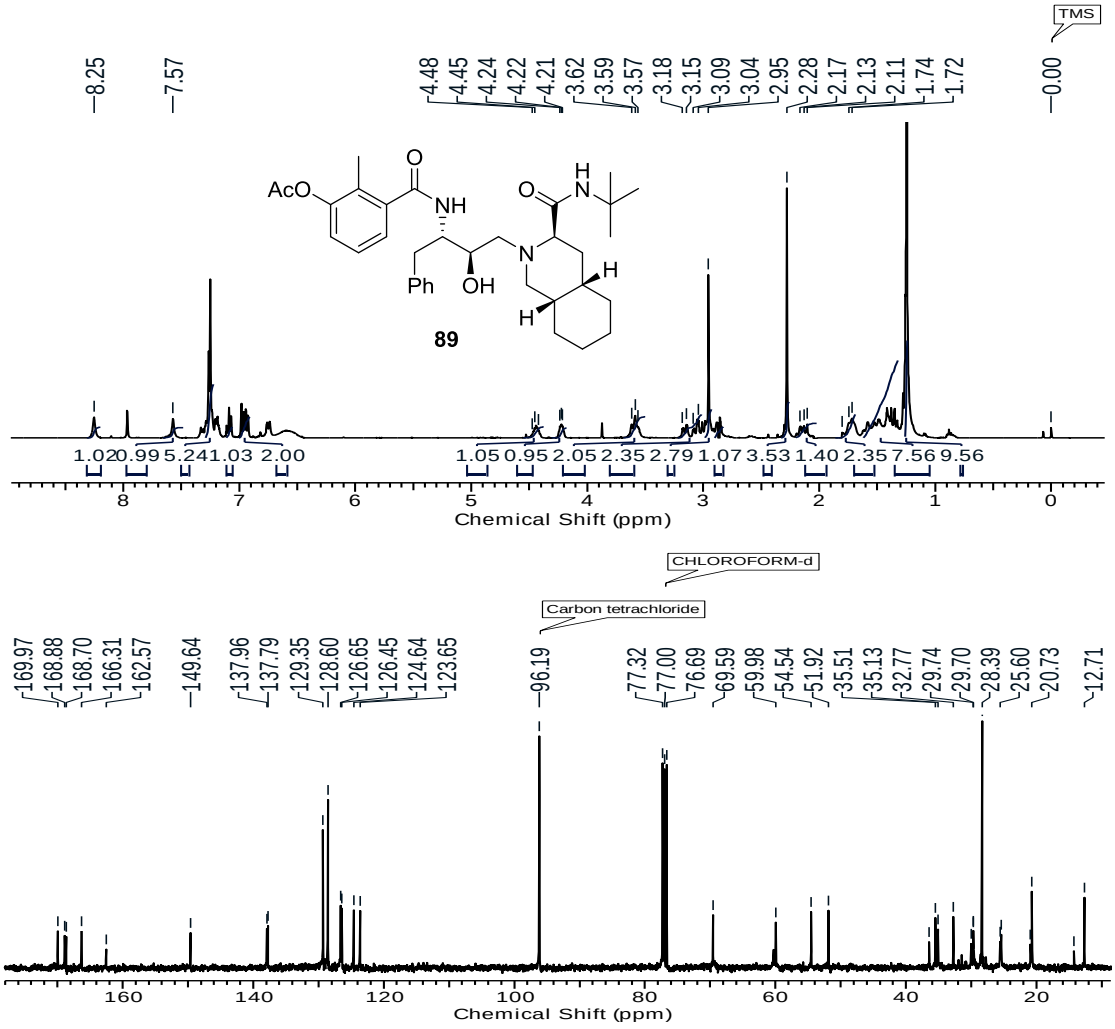
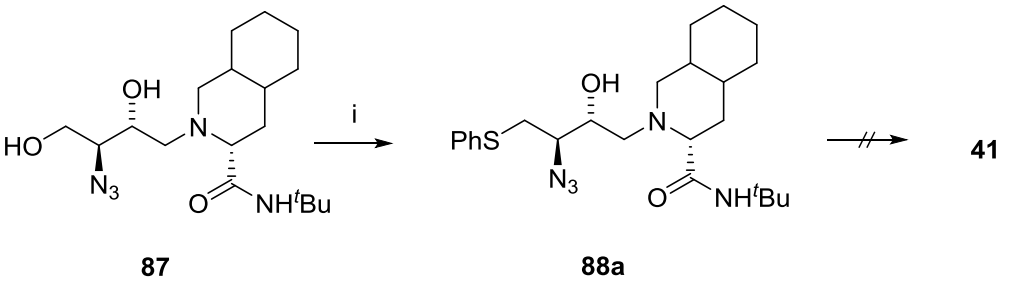


Fig. 22: ^{1}H and ^{13}C NMR spectra of amide derivative **89**

Finally, the conversion of chiral intermediate azido alcohol **87** to nelfinavir **41** was attempted as shown in the **Scheme 18**. Thus, alcohol **87** was converted to thioether derivative **88a** under Mitsunobu reaction protocol (Ph_3P, DEAD, THF followed by PhSH, NaH) in 90% yield. Then, azide reduction of **88a** to amine underwent smoothly. However, coupling reaction of **88a** with carboxylic acid failed, thereby constituting the formal synthesis of nelfinavir **41**.



87 **88a**

Scheme 18: (i) PPh_3, DEAD, THF, -55 °C, followed by PhSH, NaH, 4 h, 90%.

The formation of thioether derivative **88a** was confirmed by the appearance of a typical multiplet at δ 2.58-2.69 (m, 2H) corresponding to the methylene protons attached to –

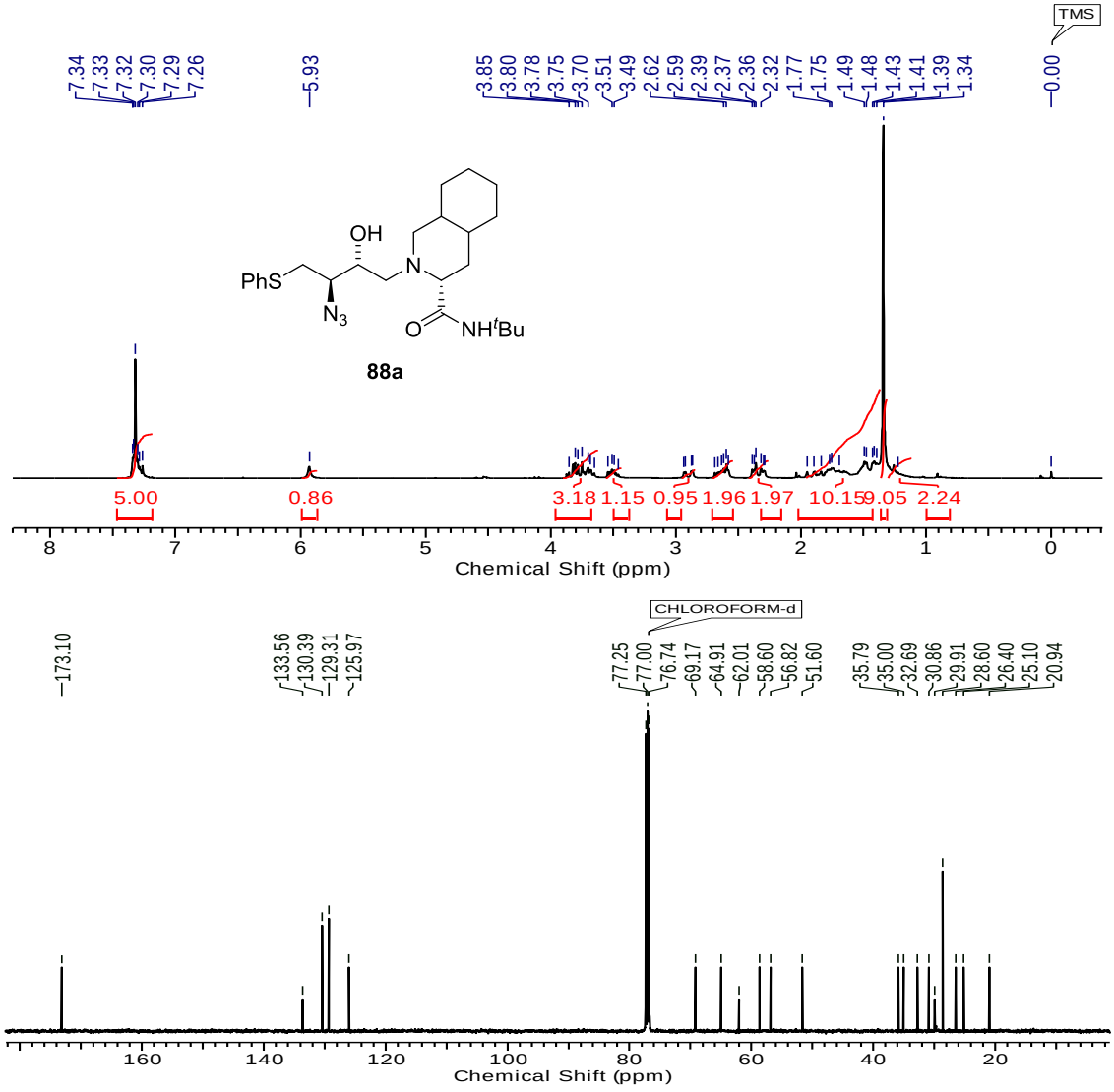


Fig. 23: ^{1}H and ^{13}C NMR spectra of thioether derivative **88a**

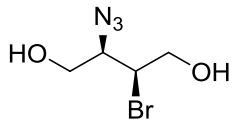
SPh group in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed a characteristic carbon signal at δ 32.7 due to the presence of shielded methylene carbon attached to –SPh group **(Fig. 23**).

1.2.4 Conclusion

In conclusion, we have described a short and economic formal synthesis of HIV protease inhibitor nelfinavir (**41,** 23.7% overall yield, 99% ee) and its analogue (**42**, 21.1% overall yield; 99% ee) starting from commercially available *cis*-2-butene-1,4-diol (**81**). The strategy employed herein mainly comprises of Co-catalyzed two-stereocentred HKR of racemic benzyloxy azido epoxide **82** as the key chiral inducing step. This methodology is expected to find wide scope for the synthesis of other similar HEA multifunctional HIV protease inhibitors.

1.2.5 Experimental Section

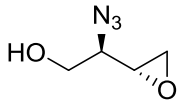
2-Azido-3-bromobutane-1,4-diol (83)



To a mixture of *cis*-2-butene-1,4-diol **81** (10 g, 113.63 mmol), and NaN_3 (14.77 g, 227.27 mmol) in CH_3CN/H_2O (180:60 mL), NBS (24.13 g, 136.36 mmol) was added slowly *via* solid addition funnel, with stirring at 0 °C. After completion of reaction as monitored by TLC, the reaction mixture was diluted with EtOAc (80 mL), and the aq. layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography using petroleum ether: ethyl acetate (50:50) to afford pure product **83** as colorless solid.

Yield: 89% (21.2 g), colorless solid; **mp**: 52 °C; **IR** ($CHCl_3$, cm-1): υ_{max} 1035, 1267, 2104, 3361; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 3.74-3.95 (m, 5H), 4.12-4.20 (m, 1H), 4.43-4.54 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6): δ 54.3, 62.4, 63.3, 63.5; **Anal. Calcd for** $C_4H_8BrN_3O_2$ requires C, 22.87; H, 3.84; N, 20.01; Found: C, 22.80; H, 3.82; N, 20.06%.

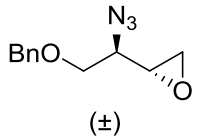
2-Azido-2-(oxiran-2-yl)ethanol (83)



Azido bromide **83** (8 g, 38.27 mmol) was taken in THF (50 mL) and NaOH powder (1.83 g, 45.93 mmol) was added slowly with stirring at 0 °C for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with EtOAc (60 mL) and water (50 mL). The organic layer was further separated and the aq. layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column chromatography using petroleum ether: ethyl acetate (8:2) as eluents to afford **84** as colourless oil.

Yield: 84% (4.13 g), colorless oil; **IR** ($CHCl_3$, cm-1): υ_{max} 1264, 2104, 2931, 3383; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.18 (br s, 1H), 2.80-2.90 (m, 2H), 3.09-3.15 (m, 1H), 3.44-3.52 (m, 1H), 3.65-3.90 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.2, 50.0, 61.9, 62.9; **Anal. Calcd for** $C_4H_7N_3O_2$ requires C, 37.21; H, 5.46; N, 32.54; Found C, 37.28; H, 5.56; N, 32.46%.

2-(1-Azido-2-(benzyloxy)ethyl)oxirane (82)



(±)

To a suspension of sodium hydride (1.7 g, 42.63 mmol) in DMF (80 mL), a solution of epoxy alcohol **84** (5 g, 38.75 mmol) in DMF (10 mL) was added. To this reaction mixture, BnBr (5 mL, 42.63 mmol) was added slowly and stirred for an additional 2 h at -40 °C. After completion of reaction (monitored by TLC), it was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 50 mL). The combined organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude product was purified by column chromatography over silica gel using petroleum ether: ethyl acetate (95:5) to give product **82**.

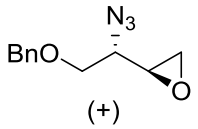
Yield: 94% (2.71 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 1453, 2102, 2864; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.74-2.83 (m, 2H), 3.05-3.11 (m, 1H), 3.44-3.52 (m, 1H), 3.57-3.73 (m, 2H), 4.59 (s, 2H), 7.28-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 45.0, 50.5, 61.7, 70.0, 73.5, 127.6, 127.8, 128.4, 137.4; **Anal. Calcd for** $C_{11}H_{13}N_3O_2$ requires C, 60.26; H, 5.98; N, 19.17; Found: C, 60.24; H, 5.90; N, 19.20%.

HKR of 2-(1-Azido-2-(benzyloxy)ethyl)oxirane (±)-82

To a solution of (*S,S*)-Co-salen (0.027g, 0.5 mol %) in toluene (2 mL), AcOH (0.02 g, 0.36 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min. During this time the color changed from orange-red to a dark brown, it was then dried under vacuum. To this racemic azido epoxide **82** (2 g, 9.13 mmol) and H_2O (0.08 mL, 4.47 mmol) was added at 0 °C. Then the reaction was allowed to stir for 12 h at 25 °C. After completion of reaction (monitored by TLC), the crude product was purified by column

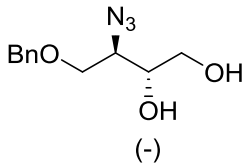
chromatography over silica gel to give chiral azido epoxide (+)-**43**, [solvent system; petroleum ether: ethyl acetate (95:5)] and chiral azido diol (-)-**85** [solvent system; petroleum ether: ethyl acetate (6:4)] in pure form.

(*S*)-2-((*S*)-1-Azido-2-(benzyloxy)ethyl)oxirane [(+)-43]



Yield: 48% (0.955 g), colorless oil; $[\alpha]_D^{20}$: +29.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 1453, 2102, 2864; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.74-2.83 (m, 2H), 3.05-3.11 (m, 1H), 3.44-3.52 (m, 1H), 3.57-3.73 (m, 2H), 4.59 (s, 2H), 7.28-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 45.0, 50.5, 61.7, 70.0, 73.5, 127.6, 127.8, 128.4, 137.4; **Anal. Calcd for** $C_{11}H_{13}N_3O_2$ requires C, 60.26; H, 5.98; N, 19.17; Found: C, 60.24; H, 5.90; N, 19.20%; **Optical purity**: 99% ee determined from HPLC analysis (Chiral OD-H column, n-hexane/ 2-propanol (95:5), 0.5 mL/min, 254 nm), Retention time: t_{major} = 13.51 and t_{minor} = 15.20 min.

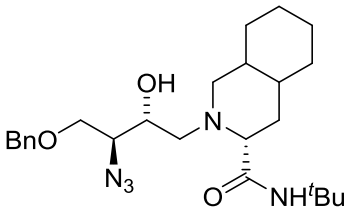
(2*R*, 3*R*)-3-Azido-4-(benzyloxy) butane-1,2-diol (85)



Yield: 47% (0.96 g), colorless oil; $[\alpha]_D^{20}$: -37.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1271, 1453, 2099, 2870, 2929, 3384; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.60 (br s, 1H), 2.81 (br s, 1H), 3.59-3.83 (m, 6H), 4.59 (s, 2H), 7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 62.0, 63.4, 69.9, 71.4, 73.6, 127.7, 127.9, 128.5, 137.3; **Anal. Calcd for** $C_{11}H_{15}N_3O_3$ requires C, 55.69; H, 6.37; N, 17.71; Found: C, 55.70; H, 6.48; N, 17.65%;

Optical purity: 97% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{major} = 21.25 and t_{minor} = 24.82 min.

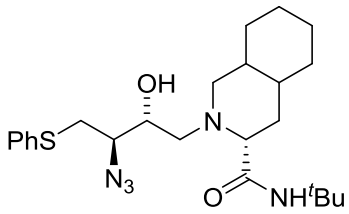
(3*R*)-2-((2*R*,3*S*)-3-Azido-4-(benzyloxy)-2-hydroxybutyl)-N-(*tert*-butyl)decahydroisoquinoline-3-carboxamide (86)



Silica gel (Merck grade 60, 230-400 mesh, 6Å; 2 g), was added to a solution of [3*S*-(3*α*,4aβ,8aβ)]-*N*-(*tert*-butyl)decahydro-3-isoquinolinecarboxamide (1.04 g, 4.38 mmol) and epoxide **43** (0.8 g, 3.65 mmol) in $CHCl_3$ (5 mL) and the resulting suspension was concentrated under reduced pressure. After standing at room temperature for 16 h, the light brown solid obtained was loaded to a column packed with silica gel and eluted with petroleum ether:EtOAc (6:4) to give the azido alcohol **86**, essentially a single diastereomer.

Yield: 85% (1.36 g), colorless solid; **mp**: 160.2 °C; $[\alpha]_D^{20}$: -70.5 (*c* 1 $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1045, 1153, 1226, 1385, 1454, 1519, 1652, 2101, 2861, 2924, 3439; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26-1.96 (m, 12H), 1.34 (s, 9H), 2.27-2.46 (m, 2H), 2.55-2.71 (m, 2H), 2.89 (dd, *J* = 11.9, 2.4 Hz, 1H), 3.44-3.55 (m, 1H), 3.65-3.88 (m, 3H), 4.57 (s, 2H), 5.86 (s, 1H), 7.26-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.8, 26.1, 29.0, 29.2, 31.8, 33.0, 36.1, 36.5, 54.1, 60.1, 62.0, 62.1, 68.2, 69.0, 69.8, 73.0, 127.4, 127.8, 128.1, 137.1, 170.6; **Anal. Calcd for** $C_{25}H_{39}N_5O_3$ requires C, 65.62; H, 8.59; N, 15.30; Found: C, 65.60; H, 8.55; N, 15.32%.

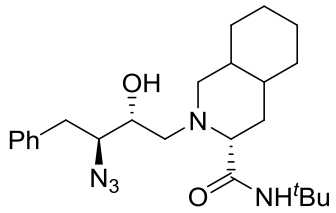
(3*R*)-2-((2*R*,3*R*)-3-Azido-2-hydroxy-4-(phenylthio)butyl)-N-(*tert*-butyl) decahydroisoquinoline-3-carboxamide (88a)



To the stirred solution of benzyl ether **86** (2 g, 4.27 mmol), DDQ (1.16 g, 5.13 mmol) in CH_2Cl_2 (20 mL) was added slowly at 0 °C. After 30 min the reaction mixture was warmed to room temperature and further stirred for 4 h. It was quenched with saturated aq. Na_2CO_3 and then diluted with CH_2Cl_2. The organic phase was separated, washed (sat. aq. Na_2CO_3), dried (anhyd. Na_2SO_4), and concentrated. The crude reaction mixture was filtered through a pad of silica gel (with ethyl acetate as an eluent) to give alcohol **87**, which was used in the next step without purification. To a cooled (-55 °C) solution of triphenylphosphine (0.356 g, 1.36 mmol) in CH_2Cl_2 was added diethyl azodicarboxylate (0.336 g, 1.36 mmol) in 10 mL of CH_2Cl_2 dropwise. To the same reaction mixture, alcohol **87** (0.5 g, 1.36 mmol) was added dropwise in 10 mL THF. The reaction mixture was stirred at room temperature for 12 h. In an another flask, thiophenol (0.149 g, 1.36 mmol) in THF (10 mL) under N_2 atmosphere was treated with 60% NaH (0.054 g, 1.36 mmol) at room temperature for 30 min. Then the crude mass solution in THF (10 mL) was added to this reaction mixture slowly and stirred for next 2 h and the solvent was removed under *vaccum*. The reaction mass was extracted twice with CH_2Cl_2/H_2O and the organic layer was washed with 1 M $NaHSO_4$ twice. The aqueous phase was then extracted with ethyl acetate once, and the combined ethyl acetate layers were washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography with petroleum ether:EtOAc (7:3) to give thioether **88a**.

Yield: 85% (1.67 g), thick gum; $[\alpha]_D^{20}$: -57.8 (*c* 1 $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1055, 1135, 1352, 1520, 1660, 2102, 2861, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.22-1.96 (m, 12H), 1.34 (s, 9H), 2.26-2.42 (m, 2H), 2.54-2.71 (m, 2H), 2.90 (dd, *J* = 11.7, 2.3 Hz, 1H), 3.4 -3.56 (m, 1H), 3.62-3.90 (m, H), 5.93 (s, 1H), 7.18-7.47 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.9, 25.1, 26.4, 28.6, 29.9, 30.9, 32.7, 35.0, 35.8, 51.6, 56.8, 58.6, 62.0, 64.9, 69.2, 126.0, 129.3, 130.4, 133.6, 173.1; **Anal. Calcd for** $C_{24}H_{37}N_5O_2S$ requires C, 62.71; H, 8.11; N, 15.24; Found: C, 62.72; H, 8.15; N, 15.22%.

(3*R*)-2-((2*R*,3*S*)-3-Azido-2-hydroxy-4-phenylbutyl)-N-(*tert*-butyl) decahydroisoquinoline-3-carboxamide (88b)

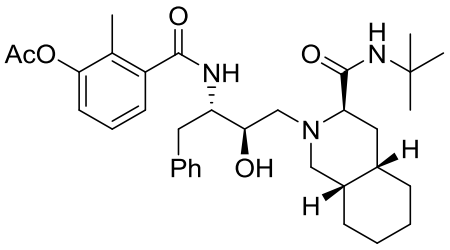


Alcohol **87** (0.50 g, 1.42 mmol) and triethylamine (0.2 mL, 1.56 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and the solution was cooled to 0 ^oC. Methanesulfonyl chloride (0.32 mL, 2.84 mmol) and DMAP (0.021 g, 0.142 mmol) were added and the resulting solution was stirred at 0 ^oC for 1 h. After TLC showed that the reaction was complete, additional CH_2Cl_2 (10 mL) was added. The organic phase was washed with brine and then dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give crude mesylate (**87a**), which was used in the next step without purification. To a stirred solution of mesyl ether (0.304 g, 1.67 mmol) in dry THF (5 mL) at 25 °C taken in a RB flask equipped with condenser (cool water circulation) was added phenyl magnesium bromide (0.29 mL, 2.45 mmol) in a drop wise manner and the mixture was allowed to stir for 0.5 h. On completion, the reaction was quenched with saturated NH_4Cl solution

(10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to yield crude product, which was purified by column chromatography (petroleum ether: ethyl acetate, 6:4) to afford pure **88b**.

Yield: 85% (0.50 g); spectral data of this compound has already been discussed in Section I (**experimental section 1.1.6**).

Nelfinavir analogue (89)



To a stirred solution of azide **88b** (0.1 g, 0.23 mmol) in 2 mL of dry THF, triphenyl phosphine (0.06 g, 0.23 mmol) was added as a lump at 25 °C and stirred for 30 min. To this H_2O (0.004 g, 0.2 mmol) was added and the stirring continued for 29 h. After completion of reaction, solvent was removed in *vaccuo*, water was added and extracted with ethyl acetate (3 x 5 mL). The organic layer was washed with brine, dried over anhyd. Na_2SO_4, concentrated to give the crude amine **49c** as a yellow sticky mass, which was used further without purification. To a chilled (-10 °C) solution of amine **49c** (0.1 g, 0.249 mmol), 2-methyl-3-hydroxybenzoic acid (0.048 g, 0.249 mmol) and 1-hydroxybenzotriazole hydrate (0.32 g, 0.249 mmol) in 8 mL of THF was added 1,3-dicyclohexylcarbodiimide (0.043 g, 0.249 mmol). The reaction mixture was then warmed to rt and stirred for 48 h, and then the mixture was concentrated under *vaccuo* and then dissolved in ethyl acetate. The mixture was filtered through Celite, and the resulting solution was washed sequentially with saturated sodium bicarbonate and

brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography with petroleum ether:EtOAc (5:5) to give nelfinavir analogue **89**.

Yield: 85% (0.09 g), colorless solid; **mp**: 177.2 °C, (lit.[4e] mp 177-178 °C); $[\alpha]_D^{20}$: -75.5 (*c* 2 $CHCl_3$), {lit.[4b] $[\alpha]_D^{20}$: -75.0 (*c* 2, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 689, 735, 801, 1026, 1119, 1156, 1221, 1287, 1366, 1466, 1482, 1530, 1586, 1627, 2862, 2925, 3297; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25 (s, 9H), 1.35-1.58 (m, 7H), 1.68-1.77 (m, 2H), 2.02-2.20 (m, 1H), 2.28 (s, 3H), 2.86-2.88 (m, 1H), 2.95 (s, 3H), 3.01-3.12 (m, 2H), 3.16 (d, *J* = 13.2 Hz, 1H), 3.57-3.62 (m, 2H), 4.18-4.31 (m, 1H), 4.37-4.55 (m, 1H), 6.93-6.98 (m, 2H), 7.08 (d, *J* = 7.1 Hz, 1H), 7.24-7.29 (m, 5H), 7.57 (br. s., 1H), 8.25 (br. s., 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 12.7, 14.3, 20.7, 21.0, 25.4, 25.6, 28.4, 29.7, 29.7, 30.1, 32.8, 35.1, 35.5, 36.5, 51.9, 54.5, 60.0, 69.6, 123.7, 124.6, 126.4, 126.6, 128.6, 129.3, 137.8, 138.0, 149.6, 162.6, 166.3, 168.7, 168.9, 170.0; **Anal. Calcd for** $C_{34}H_{47}N_3O_5$ requires C, 70.68; H, 8.20; N, 7.27; Found: C, 70.69; H, 8.23; N, 7.28%.

1.2.6 References

1 (a) Barre-Sinoussi, F.; Chermann, J.-C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Brun-Vezinet, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868; (b) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, G. M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, P. D. *Science* **1984**, *224*, 500.

2 (a) Darke, P. L.; Huff, J. R. *Advances in Pharmacology*, 25; August, J. T.; Anders, M. W.; Murad, F. Eds.; Academic Press: San Diego, **1994**, 399; (b) Debouck, C. *Human Retroviruses* **1992**, *8*, 153; (c) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305.

3 Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 1181.

4 (a) Tung, R. D.; Hale, M. R.; Baker, C. T.; Furfine, E. S.; Kaldor, I.; Kazmierski, W. W.; Spaltenstein, A.R. Vertex Pharmaceuticals, PCT Int. Appl., WO 9933815, **1999**. (b) Tung, R.

D.; Hale, M. R.; Baker, C. T.; Furfine, E. S.; Kaldor, I.; Kazmierski, W. W.; Spaltenstein, A. R. Vertex Pharmaceuticals, U.S. Patent 6 559 137, **2003**.

5 Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galphin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, Kelvin E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358.

6 (a) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed*. **1999**, *38*, 1931; (b) Honda, Y.; Katayama, S.; Kojima, M.; Suzuki, T.; Kishibata, N.; Izawa, K. *Org. Biomol. Chem*. **2004**, *2*, 2061; (c) Ghosh, A. K.; Hussain, K. A.; Fidanze, S. *J. Org. Chem.* **1997**, *62*, 6080.

7 (a) Gurjar, M. K.; Devi, N. R. *Tetrahedron: Asymmetry* **1994**, *5*, 755; (b) Park, S, Lee, S., Kang, H.-J. *Bull. Korean Chem. Soc.*, **2008**, *29*, 1073; (c) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem*. **1993**, *36*, 2300; (d) Girijavallabhan, V. M.; Bennett, F.; Patel, N. M.; Ganguly, A. K.; Dasmahapatra, B.; Butkiewicz, N.; Hart, A. *Bioorg*. *Med*. *Chem*. **1994**, *2*, 1075.

8 (a) Ghosh, A. K.; McKee, S. P.; Lee, H. Y.; Thompson, W. J. *J. Chem. Soc., Chem. Commun*., **1992**, 273; (b) Bennett, F.; Girijavallabhan, V. M.; Patel, N. *J. Chem. Soc., Chem. Commun*., **1993**, 737; (c) Park, S.; Lee, S.; Kang, H.-J. *Bull. Korean Chem*. Soc. **2008**, *29*, 1073.

9 (a) Wilkinson, R. G.; Shepherd, R. G.; Thomas, J. P.; Baughn, C. *J. Am. Chem. Soc*. **1961**, *83*, 2212; (b) Shepherd, R. G.; Wilkinson, R. G. *J. Med. Chem*. **1962**, *5*, 823; (c) Wilkinson, R. G.; Cantrall, M. B.; Shepherd, R. G. *J. Med. Chem*. **1962**, *5*, 835.

10 Some among many notable examples: (a) Fumagillin: Tarbell, D. S.; Carman, R. M.; Chapman, D. D.; Cremer, S. E.; Cross, A. D.; Huffman, K. R.; Kuntsmann, M.; McCorkindale, N. J.; McNally, J. G.; Rosowsky, A.; Varino, F. H. L.; West, R. L. *J. Am. Chem. Soc*. **1961**, *83*, 3096; (b) Ovalicin: Sigg, H. P.; Weber, H. P. *Helv. Chim. Acta* **1968**, *51*, 1395; (c) Coriolin: Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215; (d) Disparlure: Bierl, B. A.; Beroza, M.; Collier, C. W. *Science* **1970**, *170*, 87.

11 For reviews and lead references, see: (a) Winstein, S.; Henderson, R. B. *Heterocyclic Compounds*, Vol. 1; Elderfield, R. C., Ed.; Wiley: New York, 1950; Chapter 1; (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev*. **1959**, *59*, 737; (c) Bartok, M.; Lang, K. L. Small Ring Heterocycles In The Chemistry of Heterocyclic Compounds, Vol. 42, Part 3; Hassner, A., Ed.; Wiley: New York, **1985**; Chapter 1.

12 Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 6776.

13 For an in depth discussion of practical considerations in kinetic resolution reactions, see: Keith, J.
M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth., Catal*. **2001**, *343*, 5.

14 a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem*. **1994**, *59*, 1939; (b) Larrow, J. F.; Jacobsen, E. N. *Org. Synth*. **1997**, *75*, 1.

15 For the most effective catalyst developed thus far for the asymmetric dihydroxylation of

terminal olefins, see: (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 448. For a general review of the AD reaction, see: (b) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.

16 (a) Kumar, P.; Naidu, S. V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745; (b) Kumar, P.; Gupta, P. *Synlett*, **2009**, 1367; (c) Yu, Q.; Wu, Y.; Xia, L. J.; Tang, M. H.; Wu, Y. L. *Chem. Commun.* **1999**, 129.

17 (a) Reddy, R. S.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun*. **2010**, *46*, 5012; (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (c) Chaithanya Kiran, I. N.; Reddy, R. S.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.* **2011**, *52*, 438.

18 Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem*. **1988**, *53*, 5185.

19 [3*S*-(3*α*,4aβ,8aβ)]-*N*-(*tert*-butyl)decahydro-3-isoquinolinecarboxamide-Purchased from Aldrich, USA.

20 Parkes, Kevin E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem*. **1994**, *59*, 3656.

21 Kim, B. M.; Bae, S. J.; So, S. M.; Yoo, H. T.; Chang, S. K.; Lee, J. H.; Kang, J. S. *Org. Lett.* **2001**, *3*, 2349.

22 (a) Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635; (b) Gaucher, B.; Rouquayrol, M.; Roche, D.; Greiner, J.; Aubertin, A.-M.; Vierling, P. *Org. Biomol. Chem*. **2004**, *2*, 345; (c) Beaulieu, P. L.; Lavalle´e, P.; Abraham, A.; Anderson, P. C.; Boucher, C.; Bousquet, Y.; Duceppe, J.-S.; Gillard, J.; Gorys, V.; Grand-Maıtre, C.; Grenier, L.; Guindon, Y.; Guse, I.; Plamondon, L.; Soucy, F.; Valois, S.; Wernic, D.; Yoakim, C. *J. Org. Chem.* **1997**, *62*, 3440.

23 Flexner, C. *New Eng. J. Med*. **1998**, *338*, 1281.

24 For reviews on the development of HIV PR inhibitors, see: (a) Huff, J. R. *J. Med. Chem*. **1991**, *34*, 2305; (b) Meek, T. D. *J. Enz. Inhib*. **1992**, *5*, 65; (c) Wlodwer, A.; Erickson, J. W. *Annu. Rev. Biochem*. **1993**, 543; (d) Martin, J. A. *Antiviral Research* **1992**, *17*, 265; (e) Tomasselli, A. G.; Heinrikson, R. L. *Biochim. Biophys. Acta* **2000**, 189.

25 Appelt, K.; Bacquet, R. J.; Bartlett, C.; Booth, C. L. J.; Freer, S. T.; Fuhry, M. M.; Gehring, M. R.; Herrmann, S. M.; Howland, E. F.; Janson, C. A.; Jones, T. R.; Kan, C. C.; Kathardekar, V.; Lewis, K. K.; Marzoni, G. P.; Mathews, D. A.; Mohr, C.; Moomaw, E. W.; Oatley, S. J.; Ogden, R. C.; Reddy, M. R.; Reich, S. H.; Schoettlin, W. S.; Smith, W. W.; Varney, M. D.; Villafranca, J. E.; Ward, R. W.; Webber, S.; Webber, S. E.; Welsh, K. M.; White, J. *J. Med. Chem*. **1991**, *34*, 1925; (b) Patick, A.; Hongmei, M.; Markowitz, M.; Ho, D.; Webber, S. Proc. 2nd Nat. Conf. Human Retroviruses and Related Infections, **1995**, abstr. *184*, 88; (c) Shetty, B. V.; Kosa, M. B.; Khalil, D. A.; Webber, S. *Antimicrob. Agents Chemother*. **1996**, *40*, 11.

26 (a) Stephen W. K.; Vincent J. K.; Davies, J. F. II; Shetty, B. V.; Fritz, J. E.; Appelt K., Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A K.; Reich, S. H.; Kenneth, S. S.; Tatlock, J. H. *J. Med. Chem*. **1997**, *40*, 3979; (b) Rieger, D. L. *J. Org. Chem*.

1997, *62*, 8546; (c) Inaba, T.; Birchler, A. G.; Yamada, Y.; Sagawa, S.; Yokota, K.; Ando, K.; Uchida, I. *J. Org. Chem.* **1998**, *63*, 7582; (d) Raghavan, S.; Krishnaiah, V. S. B. *J. Org. Chem.* **2010**, *75*, 498; (e) Chang, S. K.; So, S. M.; Lee, S. M.; Kim, M. K.; Seol, K. M.; Kim, S. M.; Kang, J. S.; Choo, D. J.; Lee, J. Y.; Kim, B. M. *Bull. Korean Chem. Soc*. **2012**, *33*, 2213.

27 (a) Kaldor, S. W.; Appelt, K.; Fritz, J. E.; Hammond, M.; Crowell, T. A.; Baxter, A. J.; Hatch, S. D.; Wiskerchen, M.; Muesing, M. A. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 715; (b) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc*. **1985**, *107*, 7105.

28 (a) Albizati, K. F.; Babu, S.; Birchler, A.; Busse, J. K.; Fugett, M.; Grubbs, A.; Haddach, A.; Pagan, M.; Potts, B.; Remarchuk, T.; Rieger, D.; Rodriguez, R.; Shanley, J.; Szendroi, R.; Tibbetts, T.; Whitten K.; Borer, B. C. *Tetrahedron Letters*, **2001**, *42*, 6481; (b) Zook, S. E.; Busse J. K.; Borer, B. C. *Tetrahedron Letters*, **2000,** *41*, 7017; (c) Ikunaka, M.; Matsumoto, J.; Fujima, Y.; Hirayama, Y. *Organic Process Research & Development*, **2002**, *6*, 49; (d) Ma, D.; Zou, B.; Zhu, W.; Xu, H. *Tetrahedron Letters*, **2002,** *43*, 8511.

29 (a) Gadakh, S. K.; Reddy, R. S.; Sudalai, A. *Tetrahedron: Asymmetry*, **2012**, *23*, 898.

CHAPTER 2

Enantioselective Synthesis of Yashabushidiols A and B and Lactone Unit of Compactin and Mevinolin and Formal Synthesis of Spirolaxine Methyl Ether

Co-catalyzed two-stereocentered hydrolytic kinetic resolution: application to the synthesis of yashabushidiols A and B and the lactone unit of compactin and mevinolin; **Gadakh, S. K.**; Sudalai, A. *Tetrahedron: Asymmetry*, **2015**, *26*, 118.

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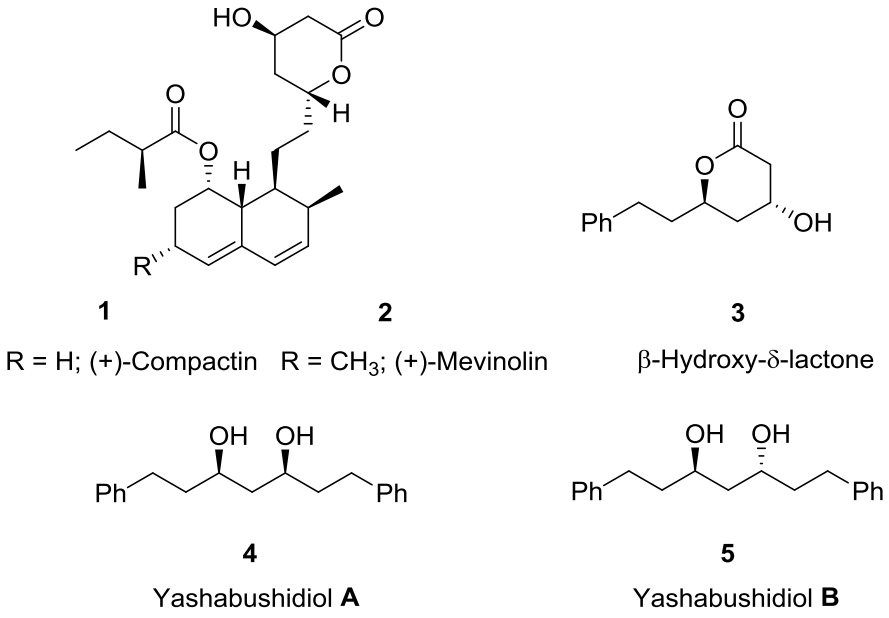
Section I

Co-Catalyzed Two-Stereocentered Hydrolytic Kinetic Resolution: Application to the Synthesis of Yashabushidiols A and B and the Lactone unit of Compactin and Mevinolin

2.1.1 Introduction

The fungal metabolites compactin **1** and mevinolin **2**, isolated from the fungus *Aspergillus terreus* sp., are potent inhibitors of cholesterol biosynthesis at the level of the rate-limiting enzyme 3-hydroxy-3 methylglutaryl-CoA (HMG-CoA) reductase,[1] which plays a central role in the production of cholesterol in the liver. The common structural feature in these molecules essential for biological activity is the β-hydroxy-δ-lactone unit **3** with a (4*R*,6*R*)-configuration closely resembling the HMG portion of the enzyme that reduces cholesterol levels in blood. Diarylheptanoids **4 & 5**, first isolated from the male flowers of *Alnus sieboldiana*, are a family of natural plant metabolites with a 1,3-diol system that exhibit interesting biological and pharmaceutical activities.[4]



1 **2** **3**

R = H; (+)-Compactin R = CH_3; (+)-Mevinolin β-Hydroxy-δ-lactone

4 **5**

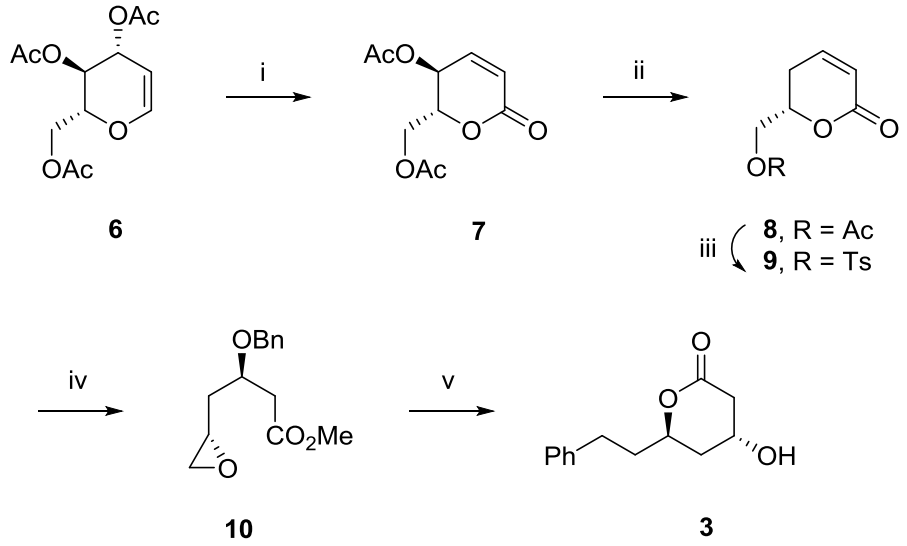
Yashabushidiol **A** Yashabushidiol **B**

Fig. 1: Structures of (+)-compactin (**1**), (+)-mevinolin (**2**), β-hydroxy-δ-lactone unit (**3**) and yashabushidiols A and B (**4 & 5**).

2.1.2 Review of Literature

Several analogues of the lactone moiety have been reported in the literature.[2,3] The introduction of the required stereocenters at the C-3 and C-5 position of lactone **3** is vital for biological activity and has proven to be an important synthetic feature. Consequently, several methods for the enantioselective synthesis of the lactone moiety, have appeared mostly involving the elaboration of chiral pool materials and quite recently catalytic asymmetric synthesis.[5] Also, in case of diarylheptanoids **4 & 5**, only a few reports on their synthesis are available in the literature, again starting from chiral pool resources.[6] Some of the interesting and important synthetic routes to β-hydroxy-δ-lactone unit **3** are described below.

Roark's approach (1988)[5h]



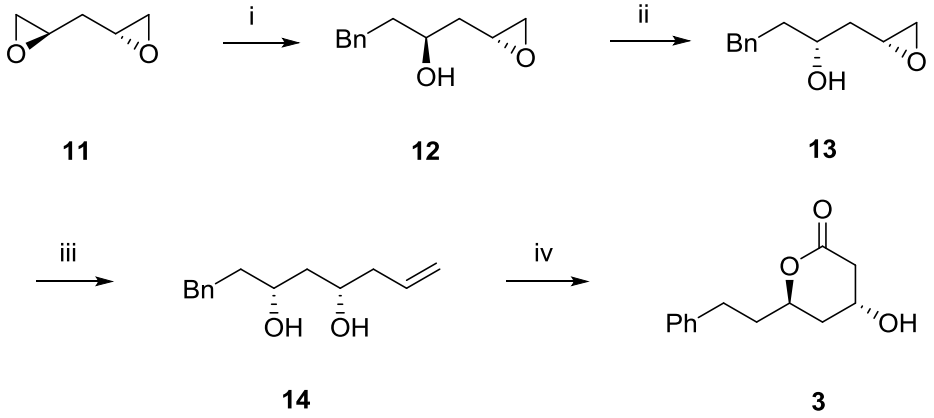
Scheme 1: (i) PCC, CH_2Cl_2, 40 °C, 85%; (ii) Zn/AcOH, 80 °C; Et_3N, EtOAc, rt, 92%; (iii) 2N HCl, rt; TsCl, Et_3N, 0 °C, 92%; (iv) BnONa, MeOH, -43 °C to 0 °C, 55%; (v) $PhCH_2MgCl$, THF, $CuBr{\cdot}SMe_2$, -78 °C; H_2 (1 atm), 10% Pd/C, dioxane:H_2O, 50 °C, 50%.

Roark *et al.* has reported the chiral pool approach for the synthesis of lactone **3** starting with tri-*O*-acetyl-D-glucal **6**, which on refluxing with PCC in CH_2Cl_2 afforded the

unsaturated lactone **7** in 85% yield. Reductive deconjugation using Zn/HOAc followed by reconjugation produced the 5-deoxygenated lactone **8**. Further, the acetate hydrolysis followed by tosylation afforded the compound **9** which was subsequently treated with sodium benzyl alcoholate to produce epoxide **10** in 87% yield (de = 32:1). Epoxide ring opening of **10** with dibenzyl cuprate followed by benzyl deprotection afforded target lactone **3** in 50% yield (**Scheme 1**).

Rychnovsky's approach (1991)[5m]

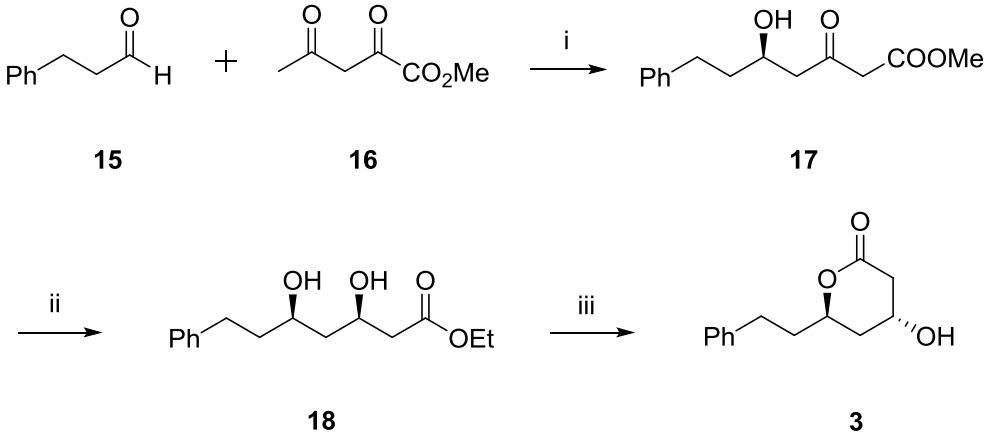
Rychnovsky *et al.* has envisaged the synthesis of lactone **3** starting from diepoxide **11**, which was prepared from reduction of the corresponding diketone in three steps. Bezyllithium reagent was added to diepoxide **11** catalyzed by $BF_3{\cdot}Et_2O$ to form monoadduct epoxy alcohol **12** in 62% yield as the key step. Further, the stereogenic center of alcohol was inverted by using the Mitsunobu protocol, which afforded *syn* epoxy alcohol **13**. It was then treated with vinyl lithium to give the desired *syn* 1,3-diol **14**. Ozonolysis of terminal alkene **14** followed by bromine treatment resulted in target lactone **3** in 43% yield (**Scheme 2**).



Scheme 2: (i) BnLi, $BF_3{\cdot}OEt_2$, Et_2O, -78 C, 62%; (ii) benzoic acid, DEAD, PPh_3, rt, 86%; (iii) CH_2=CHLi, $BF_3{\cdot}OEt_2$, THF, 70%; (iv) (a) O_3, -78 °C, Me_2S; H_3O^+; (b) Br_2, MeOH, $NaHCO_3$, 45% (over two steps).

Bonini's approach (1991)[5g]

Bonini *et al.* targeted the synthesis of lactone **3** by a biocatalytic pathway. Synthesis of **3** was thus started with direct aldol condensation of phenyl acetaldehyde **15** with the dianion of acetoacetate **16**, which furnished the β-hydroxy ester **17** in 61% yield. Keto group of **17** was reduced selectively using $NaBH_4$ affording the *syn*-3,5-dihydroxy esters **18** in 41% overall yield. Further, diol ester **18** under biocatalytic lactonization condition (aqueous solution with PLE) led to the corresponding cyclized lactone **3** in < 50% yield (**Scheme 3**).

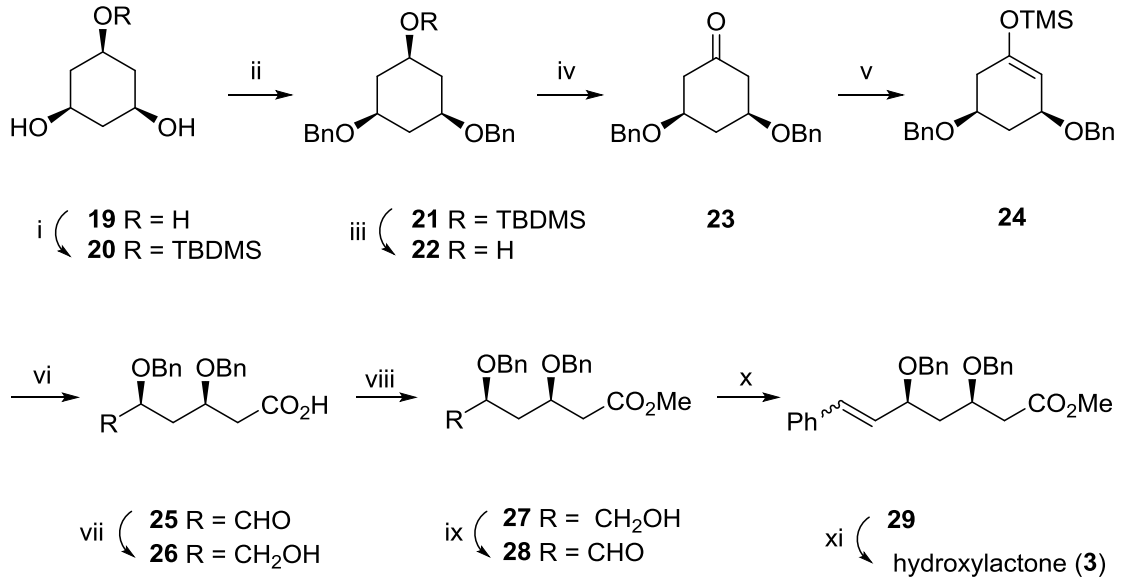


Scheme 3: (i) LDA, ^{n}BuLi, THF, -78 °C, 61%; (ii) $Ti(O^{i}Pr)_4$, $NaBH_4$, THF, -80 °C, 41%; (iii) 0.1 M phosphate buffer solution, $(NH_4)_2S0_4$, 1 M NaOH, rt, 50%.

Honda's approach (1997)[5d]

Honda *et al.* have reported the synthesis of **3** starting from *cis,cis*-1,3,5-trihydroxycyclohexane **19**, which was silylated to give the mono-silyl ether **20**. Further, benzylation of both hydroxyl groups was achieved with benzyl bromide furnishing the dibenzyl ether **21** in quantitative yield. Desilylation of silyl ether **21** followed by the corresponding oxidation afforded ketone **23**. Ketone **23** was then kept for an enantioselective deprotonation reaction with lithium (*S,S*)-α,α'-dimethyldibenzylamide

as chiral base and TMSCl provided the silyl ether **24**. Ozonolysis of **24** followed by PPh_3 treatment resulted in aldehyde **25**, which was subsequently reduced to alcohol **26** with $NaBH_4$. Further, esterification of **26** with iodomethane in N,N-dimethylformamide provided the ester **27** in 90% yield and low enantiomeric excess (70.2%), which constitutes the drawback of this method. Aldehyde **28** was achieved by Swern oxidation of alcohol **27** followed by treatment with benzyltriphenylphosphonium chloride and *n*BuLi furnished olefin **29** (*E/Z* 1:4). Finally, deprotection of benzyl group followed by acid mediated lactonization with PTSA provided the desire lactone **3** in 67% yield (**Scheme 4**).

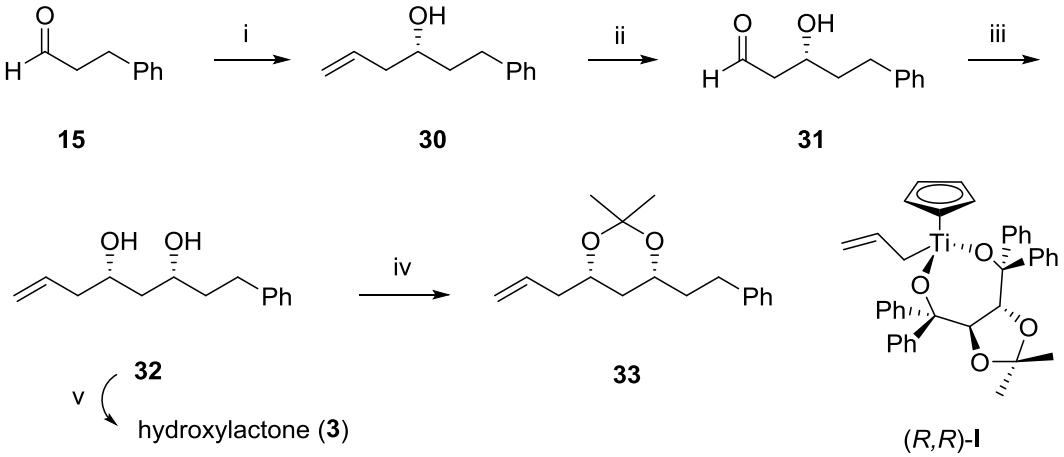


Scheme 4: (i) NaH, pyridine, rt, then TBDMSCl, THF, 0 °C, 84%; (ii) NaH, BnBr, nBu$_4$Nl, THF, rt, 100%; (iii) TBAF, THF, rt; (iv) PCC, AcONa, Celite, CH_2Cl_2, rt, 76% (over two steps); (v) Li-(*S*,*S*')-α,α'-dimethyldibenzylamide, TMSCl, THF, -100 °C, 62%; (vi) O_3, CH_2Cl_2, -78 °C, then PPh_3, 71%; (vii) $NaBH_4$, MeOH, rt, 68%; (viii) MeI, K_2CO_3, DMF, rt, 90%; (ix) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C to -45 °C, 95%; (x) $PhCH_2PPh_3CI$, ^{n}BuLi, THF, 0 °C, 95%; (xi) 10% $Pd(OH)_2/C$, H_2 (1 atm), EtOH, rt, then *p*-TsOH, PhH, rt, 67%.

Cossy's approach (2000)[5b]

Cossy *et al.* have reported Ru-catalyzed asymmetric allylation of aldehyde as the key reaction for the synthesis of lactone **3**. Synthesis of **3** was thus started with addition of

cyclopentadienyldialkoxyallyltitanium complex (*R,R*)-**I** onto 2-phenylpropionaldehyde **15** that led to the formation of homoallylic alcohol **30** with 90% yield and good enantiopurity (93% ee). Further, homoallylic alcohol **30** was converted to aldehyde **31** by hydroboration followed by the corresponding oxidation of alcohol. Aldehyde **31** was then treated for second allylation with the same complex-**I** at -78 °C to furnish *syn*-1,3-diol **32** with de = 95%. The relative configuration of 1,3-diol (+)-**32** was determined by its acetonide protection to form **33**. Finally, olefinic diol **32** underwent oxidative cleavage using $RuCl_3/NaIO_4$ followed by acid catalyzed cyclization afforded lactone **3** with very low yield 29% (**Scheme 5**).

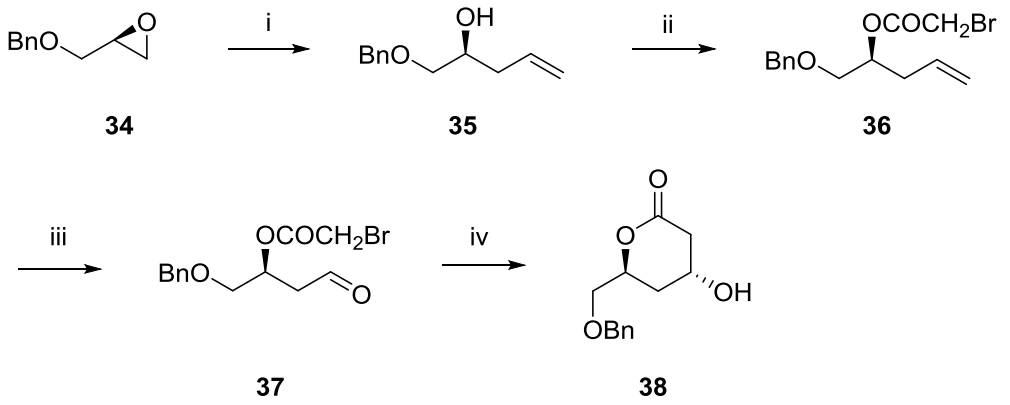


Scheme 5: (i) (*R,R*)-**I**, -78 °C, H_2O, 12 h, 90%; (ii) OsO_4, $NaIO_4$, Et_2O, H_2O, 90%; (iii) (*R,R*)-**I**, -78 °C, H_2O, 12 h, 80%; (iv) DMP, acetone, CSA, 0 °C, 94%; (v) $RuCl_3.3H_2O$, AcOH/THF, 29%.

Uang's approach (2002)[5n]

Uang *et al.* have reported the synthesis of lactone **38**, precursor of lactone **3** from glycidyl ether **34** which was treated with vinylmagnesium bromide and catalytic amount of copper(I) cyanide to form homoallylic alcohol **35** in 95% yield. Bromoacetylation of **35** followed by ozonolysis led to isolation of (3*S*)-4-benzyloxy-3-

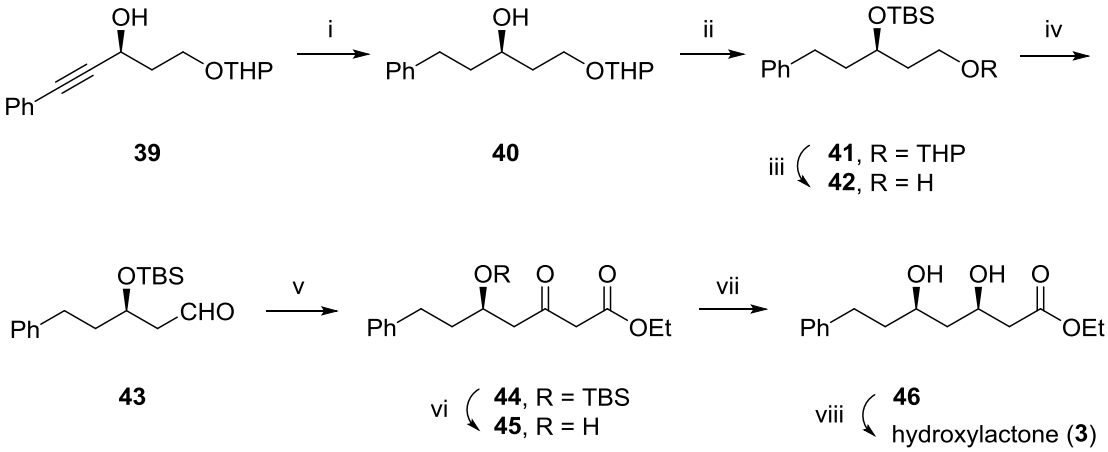
bromoacetoxybutanal **37**. Finally, **37** underwent chelation-controlled SmI_2 mediated cyclization to afford lactone **38** with excellent yield 91% (**Scheme 6**).



Scheme 6: (i) CH_2=CH-MgBr, CuCN, -10 °C, 95%; (ii) $BrCOCH_2Br$, 2,6-lutidine, 0 °C, 89%; (iii) O_3, CH_2Cl_2:MeOH; DMS; (iv) SmI_2, THF, 0 °C, 91%.

Sabitha's approach (2007)[5a]

Sabitha *et al.* have achieved the synthesis of β-hydroxy-δ-lactone unit **3** starting from alkyne **39**, which can be obtained from cross-coupling reaction of alkynes with iodobenzene using a Pd/C-CuI-PPh_3 as the catalytic system. The alkyne unit of compound **39** was reduced to saturated chain **40** followed by its protection gave silyl

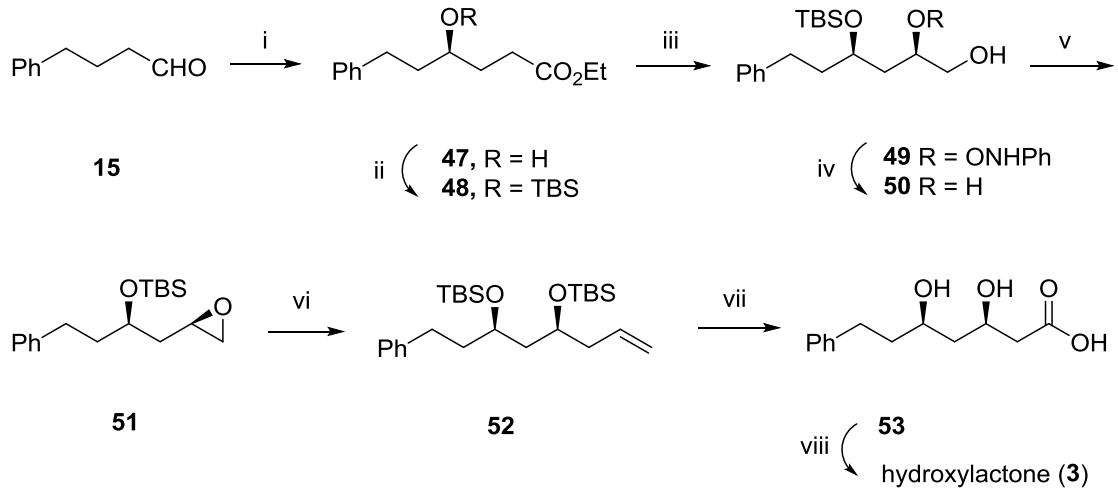


Scheme 7: (i) 5% Pd/C, H_2 (1 atm), EtOH, 2 h, 90%; (ii) TBSCl, imid., CH_2Cl_2, DMAP, 2 h, 95%; (iii) PPTS, MeOH, 12 h, 90%; (iv) 2-iodoxybenzoic acid, DMSO, CH_2Cl_2, 0 °C to rt, 2 h, 90%; (v) $SnCl_2$, N_2CHCO_2Et, CH_2Cl_2, 0 °C to rt, 40 min, 80%; (vi) TBAF, THF, 2 h, 85%; (vii) catecholborane, THF, -10 °C, 4 h, 95%; (viii) *p*TSA, CH_2Cl_2, 3 h, 84%.

ether **41**. Further, acid catalyzed deprotection of the tetrahydropyran (THP) group led to the formation of alcohol **42**. The alcohol **42** was then oxidized to aldehyde **43**, which was converted into β-keto ester **44** by Sn-catalyzed reaction with ethyl diazoacetate in 80% yield. Desilylation followed by diastereoselective reduction of **45** afforded *syn*-1,3-diol **46**, which on acid catalyzed lactonization furnished the lactone **3** in 84% yield (**Scheme 7**).

Pradeep Kumar's approach (2010)[50]

Pradeep Kumar *et al.* have used L-proline catalyzed α-aminoxylation followed by Horner–Wadsworth–Emmons (HWE)-olefination reaction as the chiral inducing step for the synthesis of lactone **3**. Commercially available aldehyde **15** was subjected to sequential α-aminoxylation using L-proline followed by HWE-olefination that furnished *O*-amino-substituted allylic alcohol which was subsequently hydrogenated to

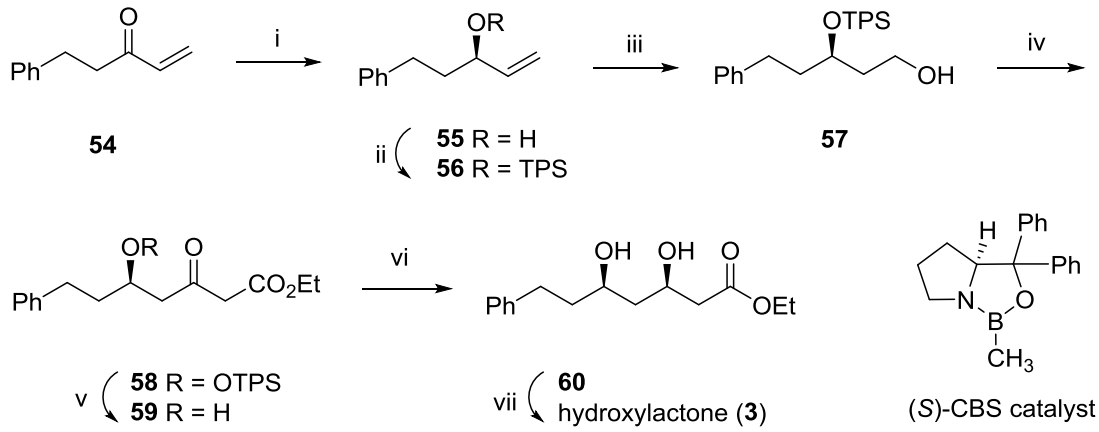


Scheme 8: (i) nitrosobenzene, L-proline, DMSO; $(EtO)_2P(O)CH_2COOEt$, DBU, LiCl, CH_3CN; (ii) (a) 5% Pd/C, H_2 (1 atm), EtOAc, 8 h, 65%; (b) TBSCl, imidazole, DMF, overnight, 91%; (c) DIBAL-H, CH_2Cl_2, -78 °C; (iii) (a) L-proline, nitrosobenzene, DMSO; (b) $NaBH_4$, MeOH, 0.5 h, 70% (over three steps); (iv) 5% Pd/C, H_2 (1 atm), EtOAc, 8 h, 92%; (v) (a) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 2 h; (b) K_2CO_3, MeOH, rt, 1 h, 82% (over two steps); (vi) (a) vinylmagnesium bromide, 1 h, 81%; (b) TBSCl, imidazole, DMF, overnight, 88%; (vii) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4:H_2O:CH_3CN = 4:1:1, 5 h, 44%, (viii) cat. HCl, MeOH, overnight, 79%.

γ-hydroxy ester **47** in 65% yield and 97% ee. The hydroxyl group was then protected as TBS ether **48** followed by ester group reduction of ester using DIBAL-H led to aldehyde which underwent *in situ* α-aminoxylation and reduction resulting in *O*-amino-substituted diol **49** with an overall 70% yield and 92% de. *O*-amino-substituted diol **49** was subjected to catalytic hydrogenation to afford diol **50**, which on monotosylation followed by base treatment gave epoxide **51** in 82% yield. Opening of epoxide ring with vinylmagnesium bromide followed by protection of free –OH group as its TBS ether resulted in compound **52**. Finally, Ru-catalyzed olefinic oxidation of **52** resulted in acid **53** followed by concomitant cyclization under acidic condition afforded lactone **3** (**Scheme 8**).

Chandra Rao's approach (2013)[5p]

Chandra Rao *et al.* have achieved the synthesis of lactone **3** from α-unsaturated ketone **54**, which was reduced with (*S*)-CBS-oxazaborolidine to produce chiral allylic alcohol **55** in 90% yield. It was then protected as its TPS ether **56**. Selective hydroboration of olefin **56** using BH_3·DMS resulted in alcohol **57** (89% yield). Alcohol **57** was then



Scheme 9: (i) (*S*)-CBS catalyst, THF, -40 °C, BH_3.DMS, 2 h, 90%; (ii) TBDPSCl, imid., CH_2Cl_2, 0 °C to rt, 4 h, 95%; (iii) BH_3·DMS, THF, 0 °C to rt, 4 h, NaOH, H_2O_2, 89%; (iv) (a) IBX, THF, DMSO, rt, 3 h, 80%; (b) $FeCl_3$, N_2CHCO_2Et, CH_2Cl_2, rt, 2 h, 68%; (v) TBAF, THF, 2 h, 85%; (vi) catecholborane, THF, -10 °C, 5 h, 95%; (vii) PTSA, CH_2Cl_2, 3 h, 85%.

oxidized and reacted with ethyl diazoacetate using catalytic amount of $FeCl_3$ resulted in β-keto ester **58**. Further, TBS ether **58** was deprotected using TBAF and subsequent stereoselective reduction of keto group afforded *syn*-1,3-diol ester **60** in 95% yield. Finally, acid catalyzed lactonization of diol **60** led to isolation of lactone **3** in 85% yield (**Scheme 9**).

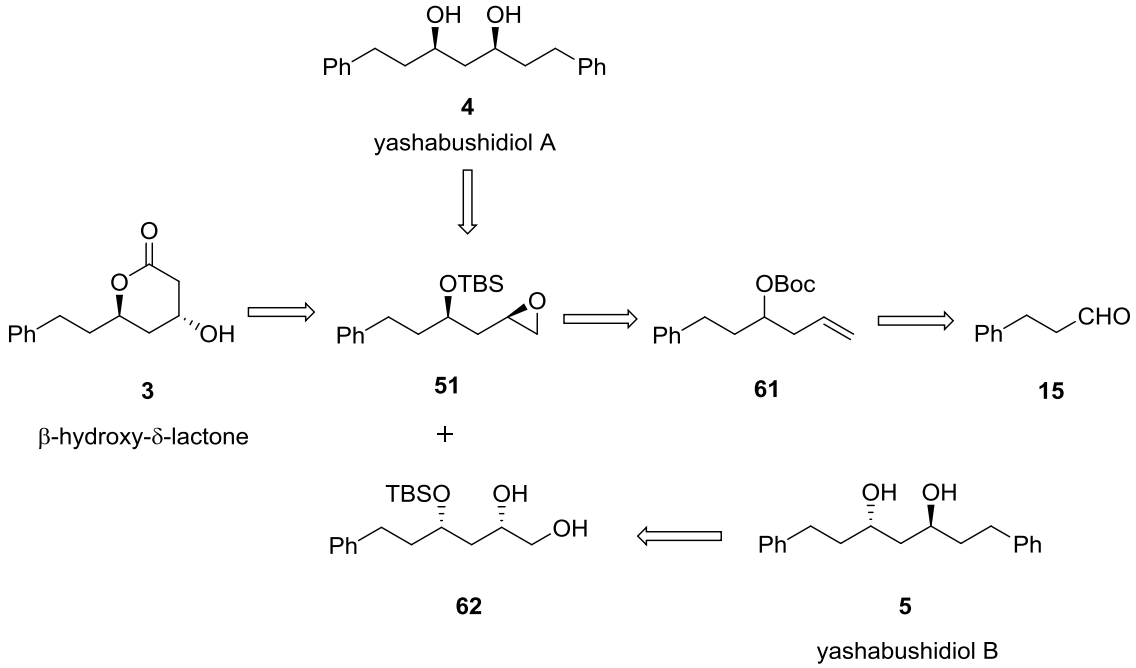
2.1.3 Present Work

2.1.3.1 Objective

The reported methods for the synthesis of yashabushidiol A & B suffer from certain limitations such as the use of chiral building blocks, the introduction of chirality in the early stages, long reaction sequences, and low enantiomeric excess and thus are not amenable for scale-up studies.[7, 6a] Recently, we have reported a protocol involving a two-stereocentered Co-catalyzed hydrolytic kinetic resolution of racemic terminal epoxides bearing adjacent C–O, C–N and C–C binding substituents that furnished enantiopure *syn*- or *anti*-alkoxy and azido epoxides and the corresponding diols with high enantiomeric purity (up to 99% ee).[8] In this section, we have extended its scope for the synthesis of natural products. Thus, this section presents a simple and concise synthetic route to lactone moiety **3** and yashabushidiols A and B **4 & 5** (**Fig. 1**) *via* an iodine-induced intramolecular electrophilic addition followed by Co(salen) catalyzed HKR of racemic epoxides (**Schemes 12 & 13**).

The retrosynthesis of β-hydroxy-δ-lactone unit (**3**) along with yashabushidiol A & B (**4 & 5**) is shown in **Scheme 10**. We envisioned that the synthesis of **3** could be achieved from the key chiral β-hydroxy epoxide **51**, which can be prepared the HKR of the corresponding racemic epoxide, obtained from Boc protected homoallylic alcohol **61** in two steps. The synthesis of **61** could be realized by simple allylation followed Boc protection of commercially available hydrocinnamaldehyde **15**. Additionally,

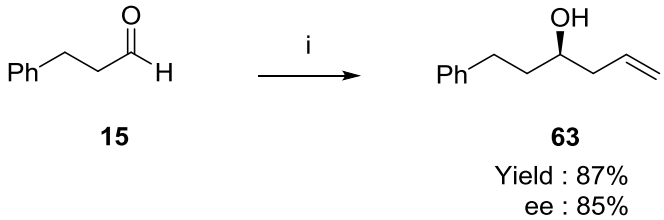
yashabushidiol A **4** can be obtained by the Grignard addition of phenylmagnesium bromide onto common intermediate epoxide **51** while yashabushidiol B **5** could be got from diol **62** (byproduct of HKR) by the inversion of stereocenter at C2 position followed by Grignard addition.



Scheme 10: Retrosynthetic analysis of β-hydroxy-δ-lactone unit (**3**) and yashabushidiols A and B (**4 & 5**).

2.1.3.2 Results and Discussion

The synthesis of lactone **3** was commenced by the asymmetric Brown allylation[9] of commercially available hydrocinnamaldehyde **15** [(-)-Ipc_2(allyl)borane, Et_2O at -78 °C]



Scheme 11: (i) (-)-Ipc_2(allyl)borane, Et_2O, -78 ^oC, 1 h then, 1N NaOH, 30% aq. H_2O_2, 87%.

to give homoallylic alcohol **63** (87% yield) with moderate ee (85%), which could be further elaborated upon (**Scheme 11**). The formation of homo allylic alcohol **63** was confirmed from its ^{1}H NMR spectrum, which showed a characteristic doublet at δ 5.15 (dd, *J* = 11.8 and 1.6 Hz, 1H) and a multiplet at δ 5.70-5.91 (m, 1H) corresponding to two olefinic protons of allylic alcohol. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 69.8 indicative of methine carbon attached to secondary alcohol group, thus confirming the formation of homo allylic alcohol **63** (**Fig. 2**). Also, its IR spectrum displayed a broad band at υ_{max} 3379 cm^{-1} due to the presence of –OH functionality.

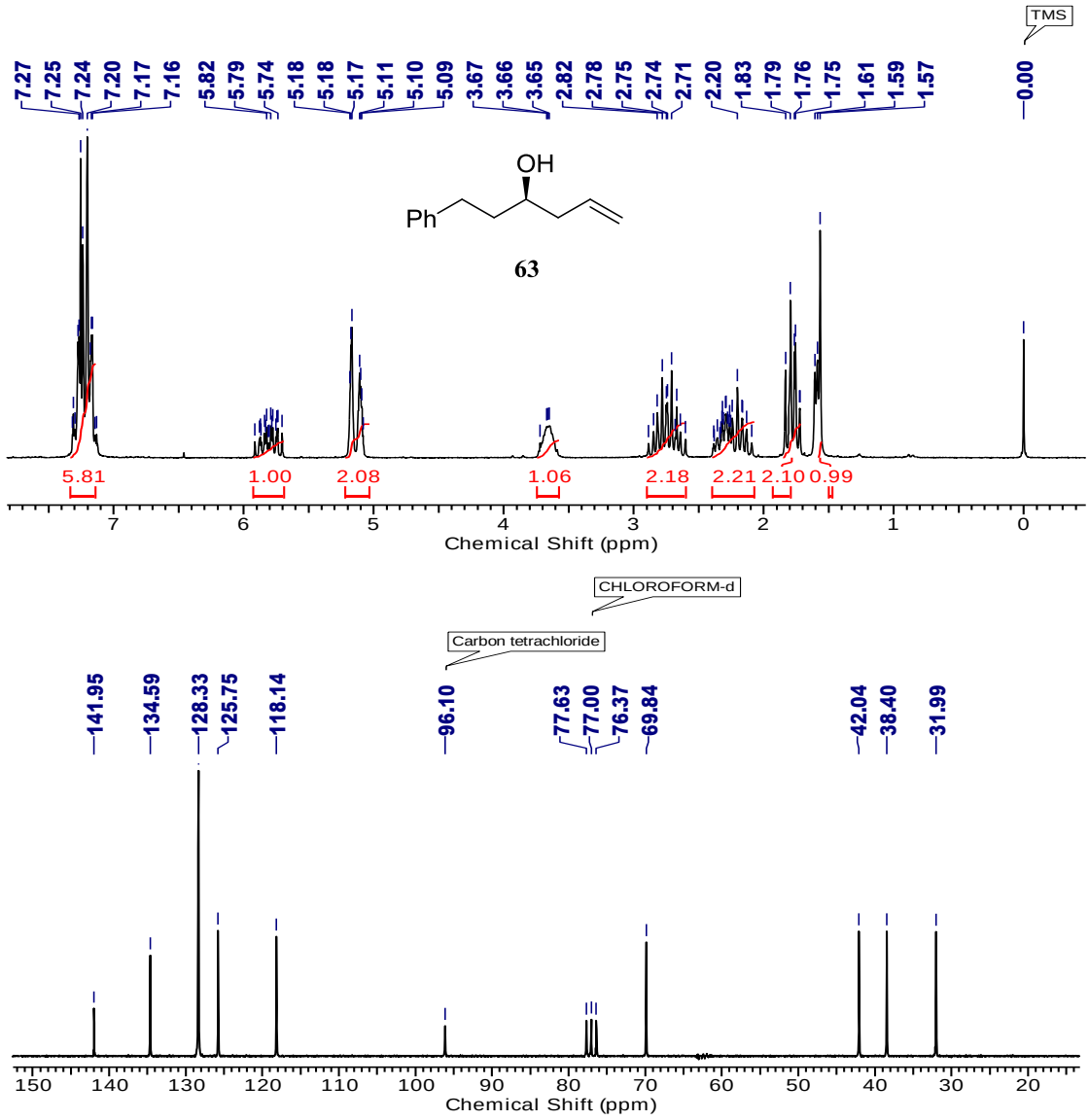


Fig. 2: ^{1}H and ^{13}C NMR spectra of allylic alcohol **63**

In order to improve the enantiomeric excess of the allylation process, an alternate route was envisaged in which a hydrolytic kinetic resolution of a functionalized epoxide was undertaken (**Scheme 12**). Accordingly, simple allylation of aldehyde **15** was carried out to give the corresponding racemic secondary alcohol **64** (87% yield), which was protected as its Boc derivative **61** in 91% yield. The formation of carbonate **61** was confirmed by the appearance of a typical *tert*. butyl proton signal at δ 1.82 (s, 9H) in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 27.8 and 153.2 due to *tert*. butyl and -C=O of carbonate group respectively (**Fig. 3**).

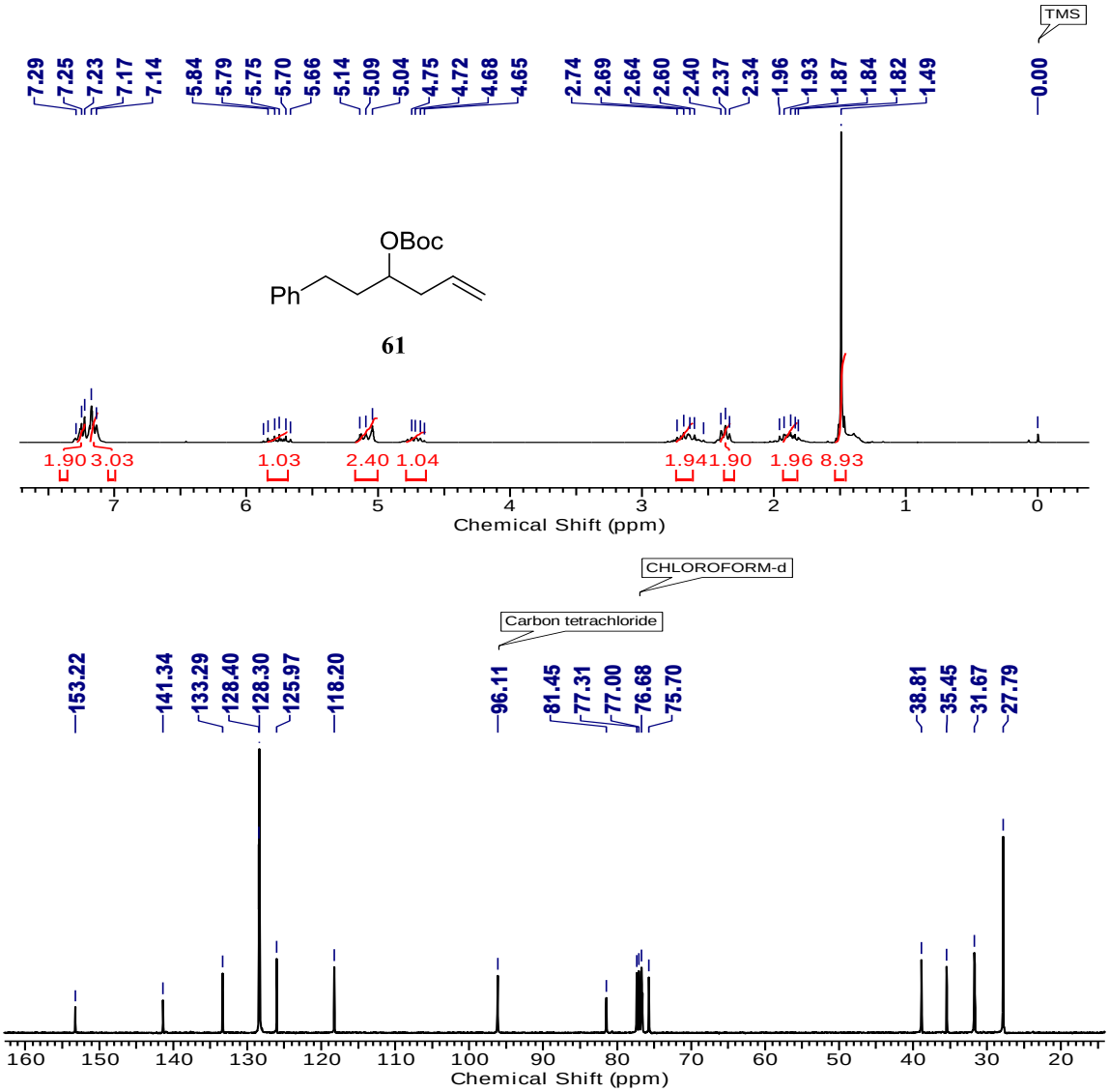


Fig. 3: ^{1}H and ^{13}C NMR spectra of Boc derivative **61**

N-Iodosuccinimide-induced intramolecular electrophilic addition[10] of carbonate **61** resulted in the formation of iodocyclic carbonate **65** in 85% yield as a single diastereoisomer (dr >99%). The ^{1}H NMR spectrum of iodocyclic carbonate **65** showed two multiplets at δ 4.34-4.40 (m, 2H) and 3.19-3.36 (m, 2H) corresponding to two methine and methylene protons of cyclic carbonate respectively, while its ^{13}C NMR spectrum showed a characteristic carbon signal at δ 77.4 due to methylene carbon of cyclic carbonate moiety (**Fig. 4**). Also, its IR spectrum displayed a strong band at υ_{max} 1722 cm^{-1} due to –C=O stretching vibration of carbonate unit.

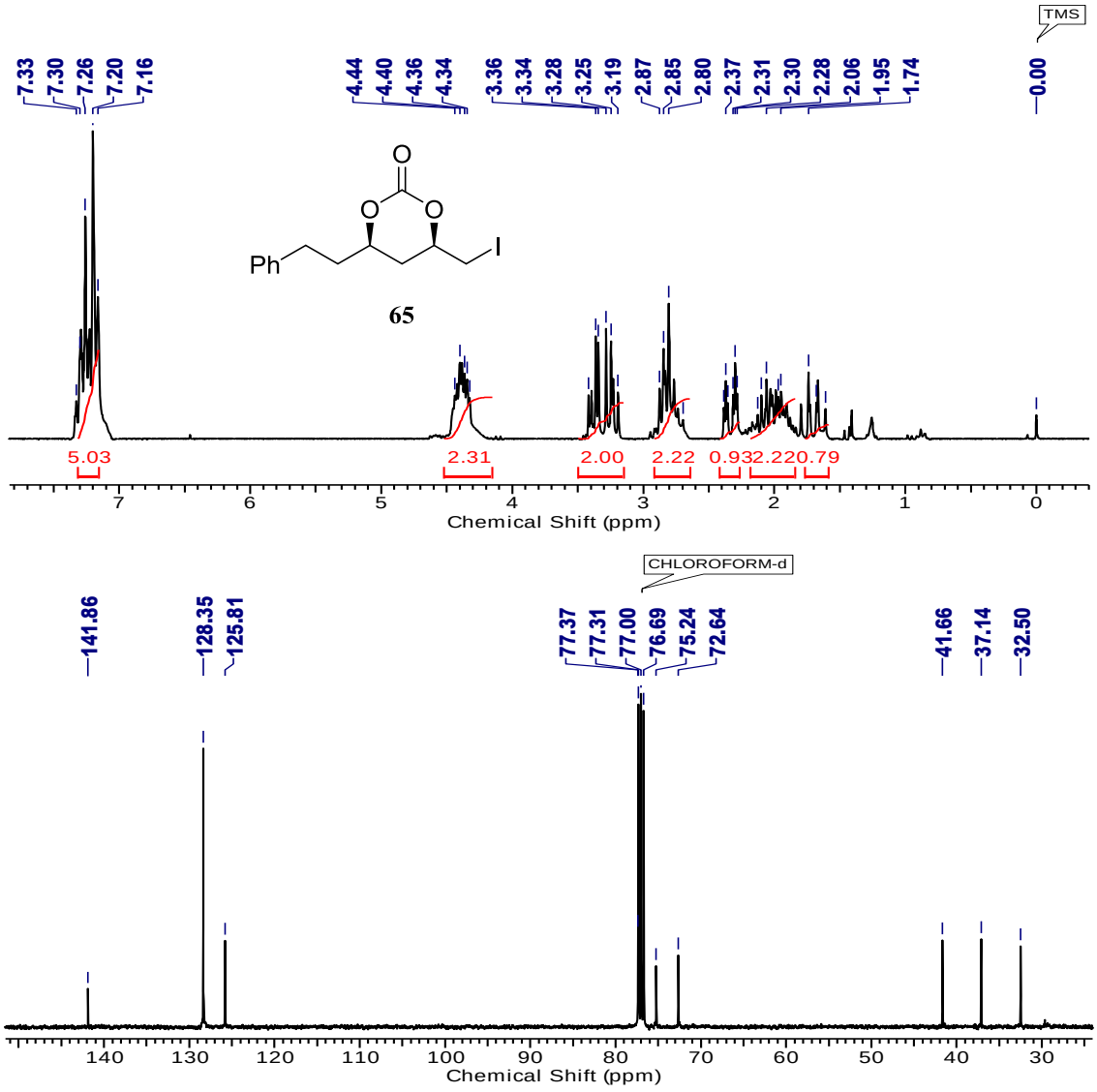
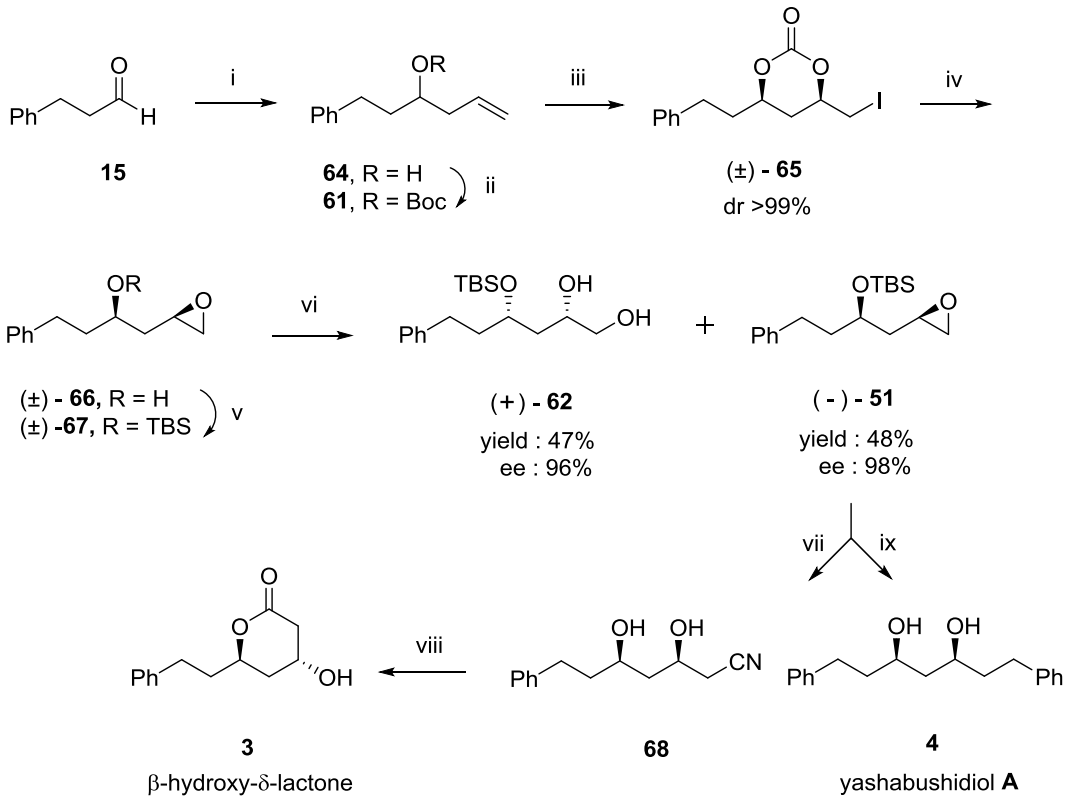


Fig. 4: ^{1}H and ^{13}C NMR spectra of iodocyclic carbonate **65**



Scheme 12: (i) allyl bromide, Zn, NH_4Cl, CH_3CN, 0 °C, 3 h, 87%; (ii) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C, 1 h, 91%; (iii) N-iodosuccinimide, CH_3CN, -40 °C to 0 °C, 12 h, 85%; (iv) K_2CO_3, MeOH, 0 °C, 0.5 h, 84%; (v) TBSCl, imid., CH_2Cl_2, 0 °C, 1 h, 90%; (vi) (*R,R*)-(salen)Co(III)OAc (0.5 mol %), THF, H_2O (0.49 equiv), 25 °C, 14 h; (vii) NaCN, TFA (10 mol %), CH_2Cl_2, 60 °C, 4 h, 84%; (viii) aq. HCl, MeOH, 50 °C, overnight, 79%; (ix) BnBr, Mg, CuI, THF, 0-25 °C, 1 h, 88%.

Further, the iodocyclic carbonate **65** on treatment with K_2CO_3 afforded β-hydroxy epoxide **66** in 84% yield. The formation of racemic *syn*-β-hydroxy-epoxide **66** was confirmed from its ^{1}H NMR spectrum, which showed two multiples at δ 3.89-3.92 (m, 1H), 2.79-2.81 (m, 1H) and broad singlet at δ 2.15 (br. s, 1H) corresponding to methine proton attached to secondary hydroxyl group, epoxide moiety and -OH group respectively. Further, it was confirmed by ^{13}C NMR spectrum, which displayed two typical carbon signals at δ 69.8 and 50.5 corresponding to methine carbons attached to –OH and epoxide moiety respectively. Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} 3448 cm^{-1} due to the presence of secondary –OH group (**Fig. 5**).

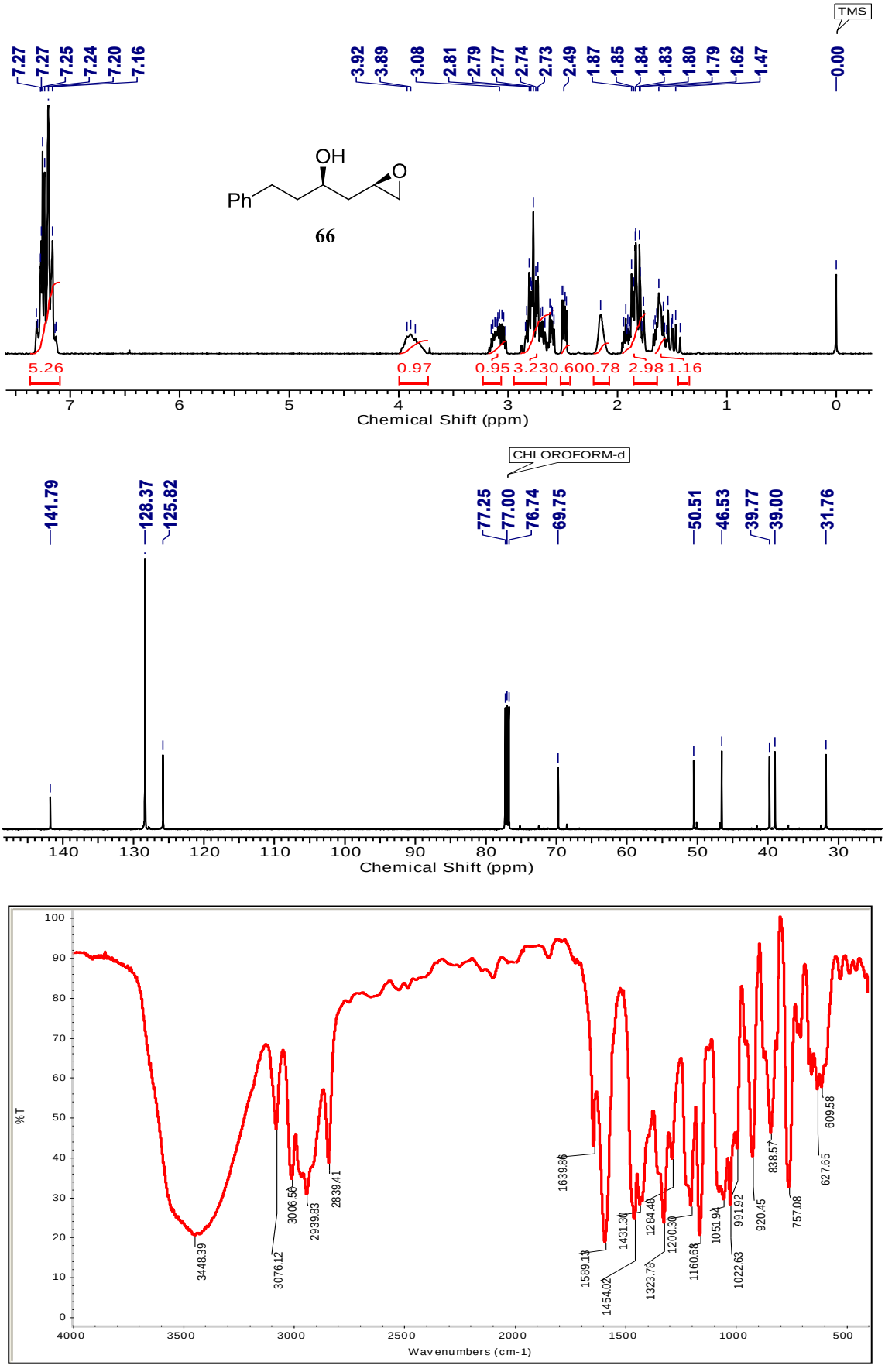


Fig. 5: ^{1}H, ^{13}C NMR and IR spectra of β-hydroxy epoxide **66**

Further, the formed hydroxy epoxide **66** was protected as its TBS ether **67** in 90% yield. Its ^{1}H NMR spectrum showed typical two signlets at δ -0.01 (s, 6H) and 0.84 (s, 9H) corresponding to methyl protons attached to -Si atom. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ -4.57 and 25.9 due to methyl carbon attached to silyl ether respectively. Thus, confirming the formation of TBS ether **67** (**Fig. 6**).

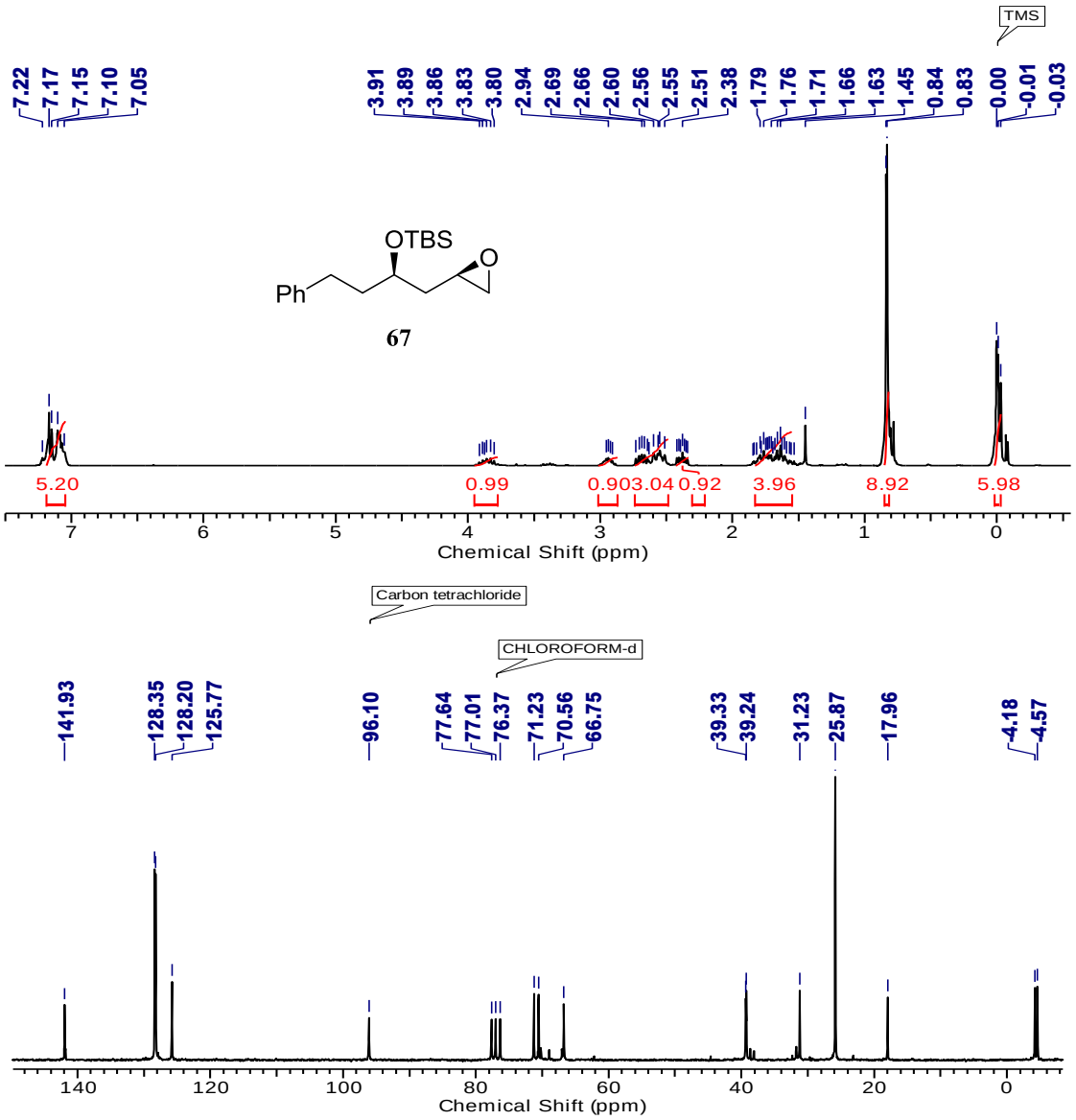


Fig. 6: ^{1}H and ^{13}C NMR spectra of TBS-epoxide **67**

Racemic TBS protected epoxide **67** was then subjected to a Co-catalyzed two-stereocentered hydrolytic kinetic resolution using (*R*,*R*)-(salen)Co(III)OAc (0.5 mol %)

as catalyst and H_2O (0.49 equiv) as the nucleophile, which produced the corresponding chiral diol **62** (47%, 96% ee) and epoxide **51** (48%, 98% ee) with high enantiomeric purity. The enantiomeric purity of compounds **51** and **62** was determined from chiral HPLC analysis as given below.

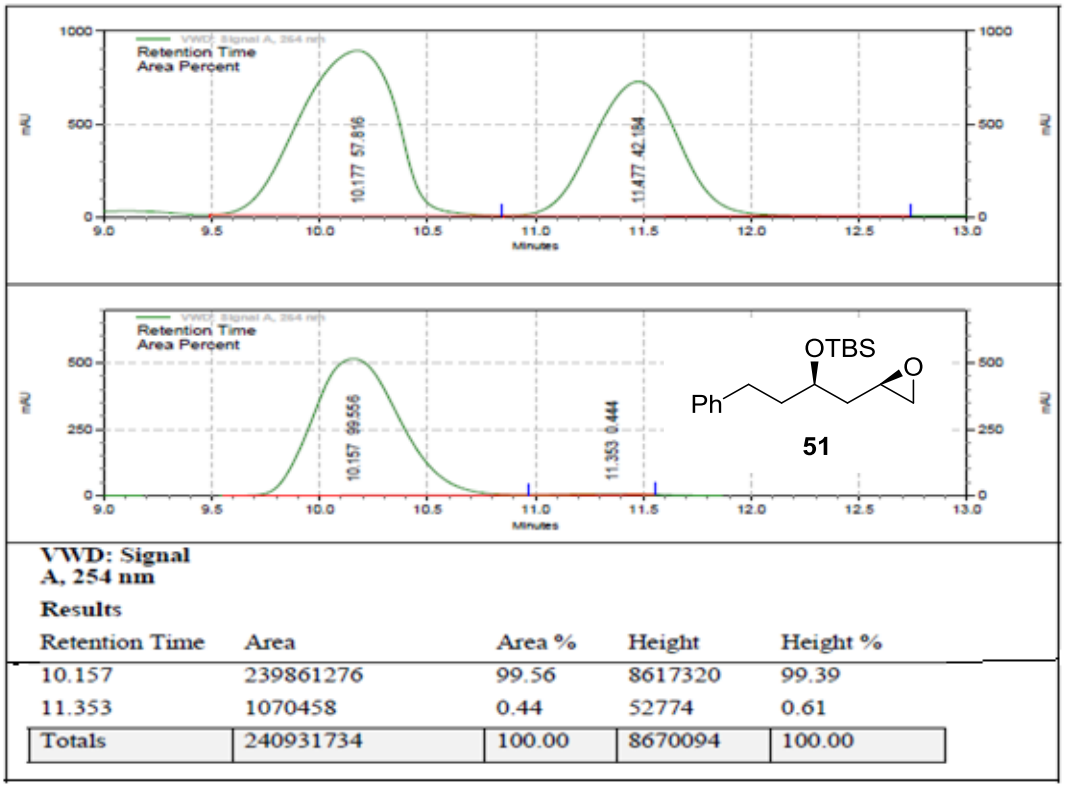


Fig. 7: HPLC chromatogram of chiral epoxide **51**

The enantiomeric excess was found to be 98% ee determined by chiral HPLC analysis (Chiralcel OD-H column, *n*-hexane: *i*PrOH, 97:03, 0.5 mL/min) retention time 10.157 (99.56%) and 11.353 (0.44%) for chiral epoxide **51** (**Fig. 7**). The silylated chiral epoxide **51** was then readily separated from chiral diol **62** by the flash column chromatographic purification over silica gel (**Scheme 12**). Also, the chiral diol **62** was characterized by the ^{1}H and ^{13}C NMR spectra. Its ^{1}H NMR spectrum showed a multiplet at δ 3.54-3.93 (m, 2H) corresponding to two methine protons attached to secondary hydroxyl and TBS groups respectively. Also its ^{13}C NMR spectrum

displayed a carbon signal at δ 49.2 due to methine carbon attached to secondary –OH group (**Fig. 8**). Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} 3320 cm^{-1} due to the presence of –OH functionality.

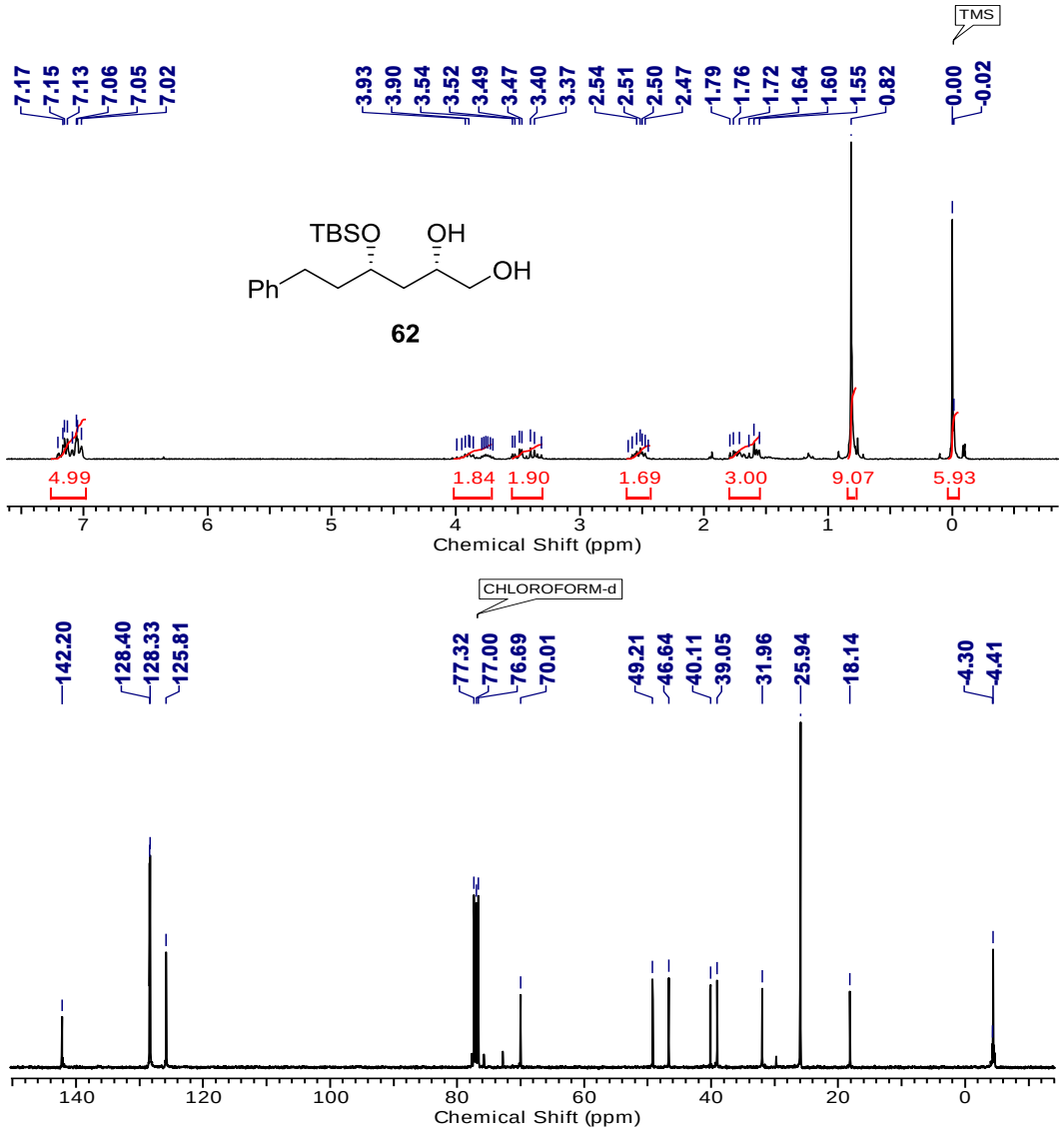


Fig. 8: ^{1}H and ^{13}C NMR spectra of TBS-diol **62**

Both compounds **51** and **62** thus emerged as key intermediates in the synthesis of these natural products. The synthesis of β-hydroxy-δ-lactone **3** was then achieved by the TFA-catalyzed regioselective ring opening of epoxide **51** with NaCN to produce desilylated cyano derivative **68** in 84% yield, which showed a multiplet at δ 3.65-3.85 (m, 4H) in its ^{1}H NMR spectrum corresponding to two methine protons of two

secondary hydroxyl group and one methylene proton attached to -CN functionality respectively. Its ^{13}C NMR spectrum displayed characteristic nitrile carbon signals at δ 120.9 which confirmed the formation of cyano derivative **68** (**Fig. 9**). Also, its IR spectrum showed two strong and broad vibrational stretching frequencies at υ_{max} 3379 and 2127 cm^{-1} due to –OH and –CN functionalities respectively.

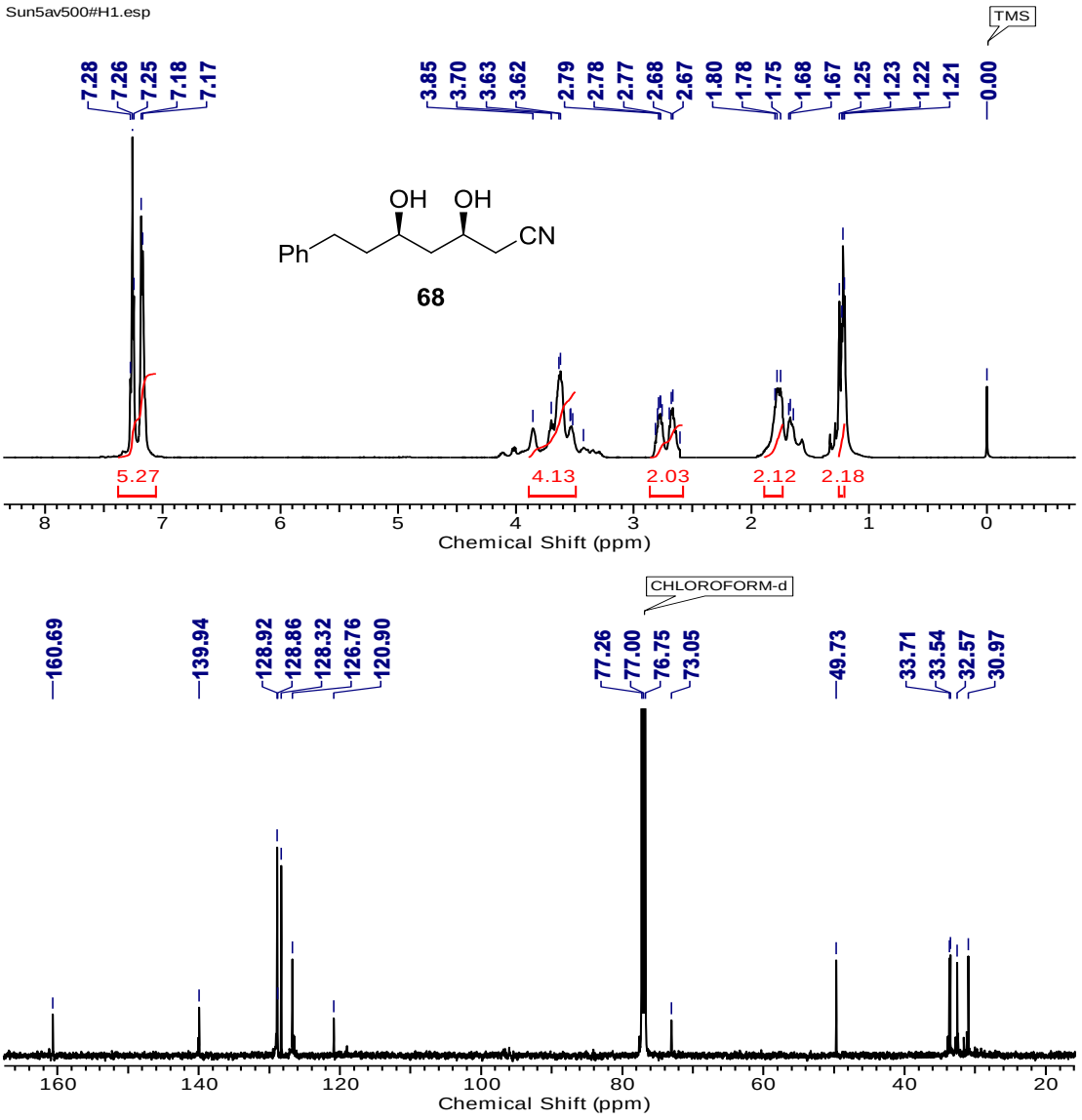


Fig. 9: ^{1}H and ^{13}C NMR spectra of cyano diol **68**

The cyano derivative **68** underwent acid hydrolysis readily to furnish **3** as a colorless solid (79% yield). It should be noted that acid hydrolysis of **68** resulted in concomitant cyclization to afford lactone **3** in a single step. Its specific rotation and melting point

were in complete agreement with the reported value [mp: 106-107; lit.[4e] mp: 108 °C ($[\alpha]_D^{20}$ +67.5 (*c* 2, $CHCl_3$); lit.[4h] $[\alpha]_D^{20}$ +68.88 (*c* 2.29, $CHCl_3$)].

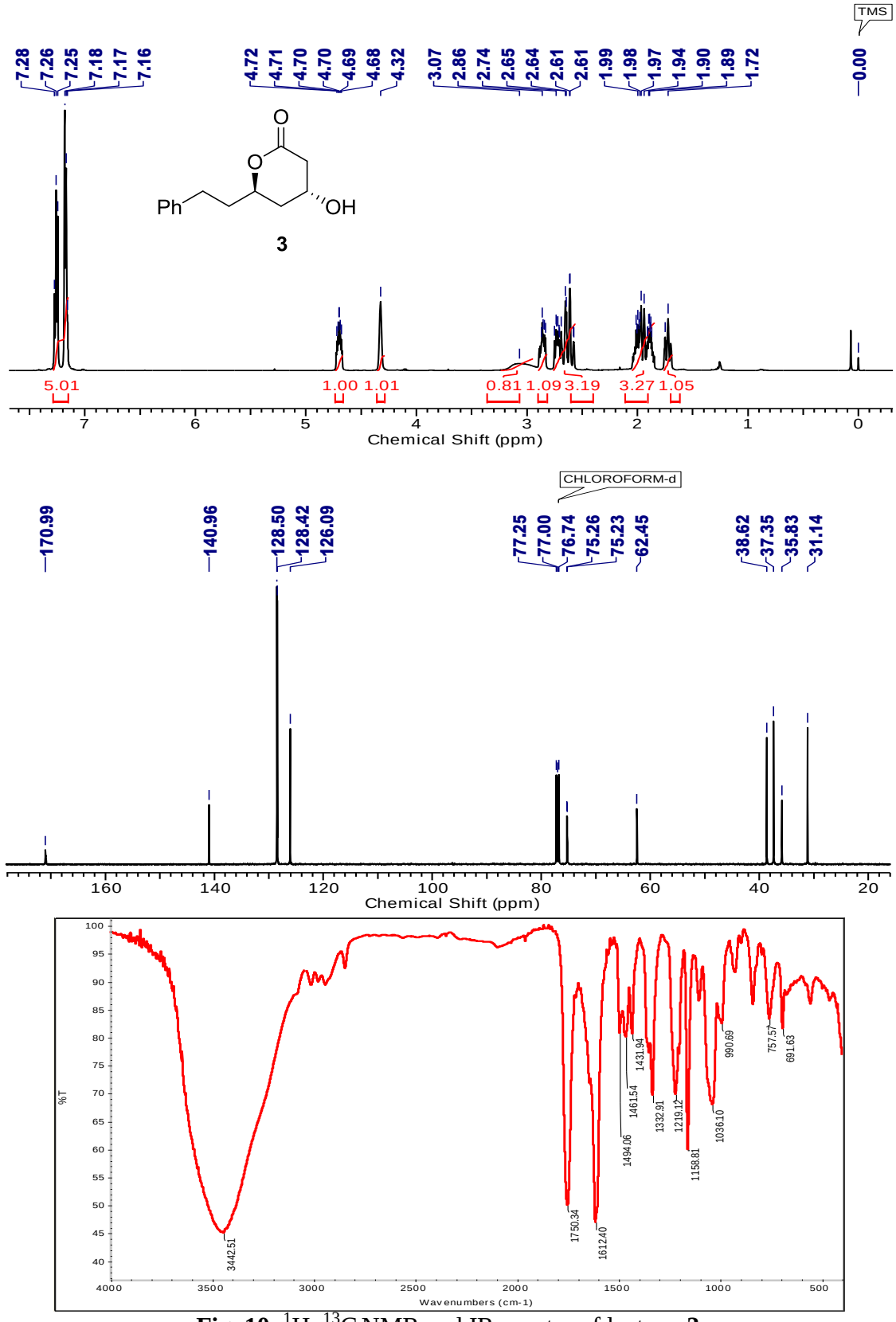


Fig. 10: ^1H, ^{13}C NMR and IR spectra of lactone **3**

The formation of hydroxylactone compound **3** was confirmed from ^{1}H NMR spectrum, which showed the appearance of two deshielded proton signals at δ 4.32 (s, 1H) and 4.68-4.72 (m, 1H) corresponding to methine protons of lactone unit. Also, a broad singlet at δ 3.07 (s, 1H) showed the presence of secondary hydroxyl group. Its ^{13}C NMR spectrum accounted for carbon signal at δ 170.9 corresponding to carbonyl carbon of lactone unit **3**. Also, IR spectrum showed strong vibrational frequencies at υ_{max} 3442 and 1750 cm^{-1} due to –OH and –C=O groups respectively (**Fig. 10**).

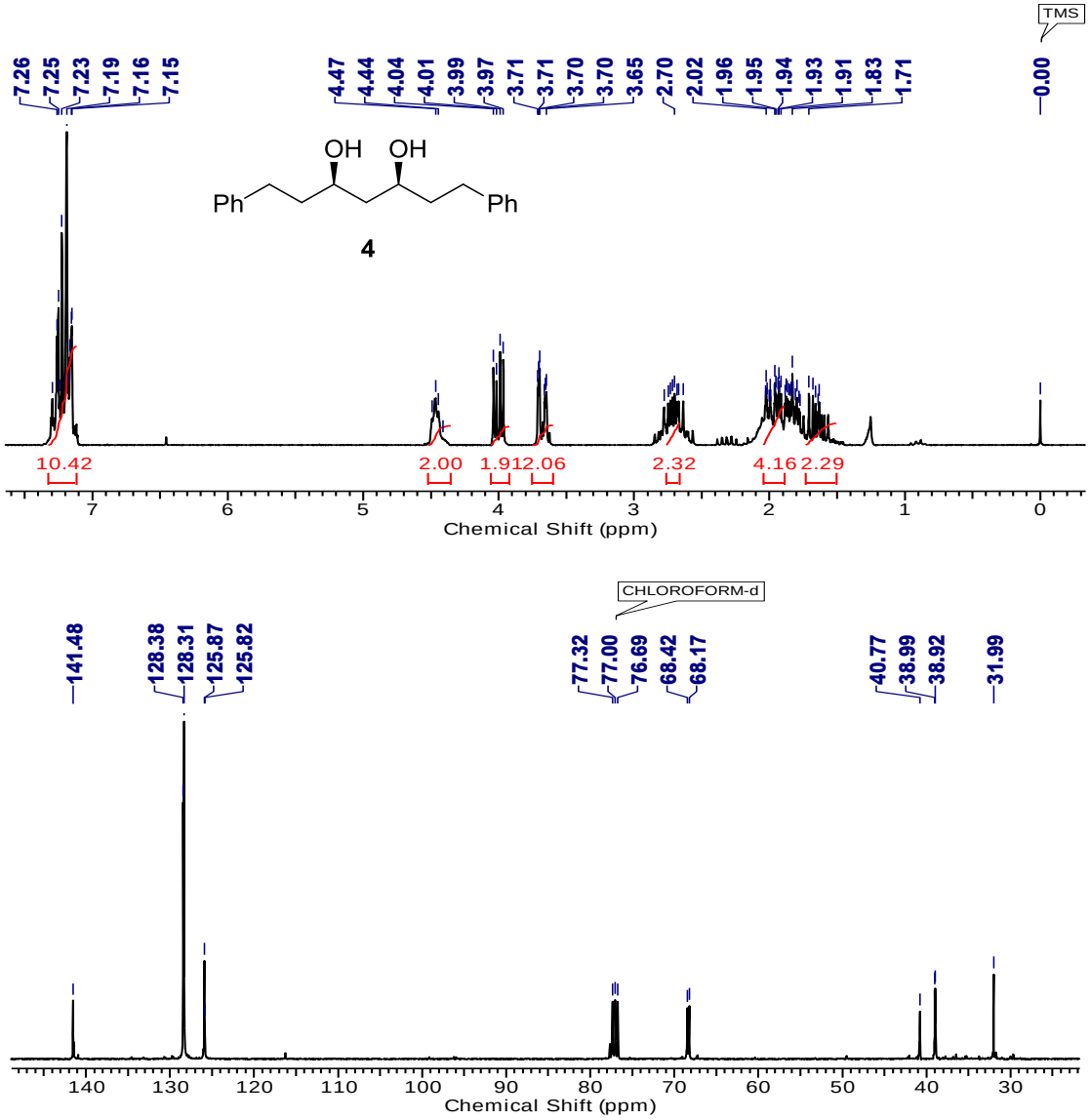
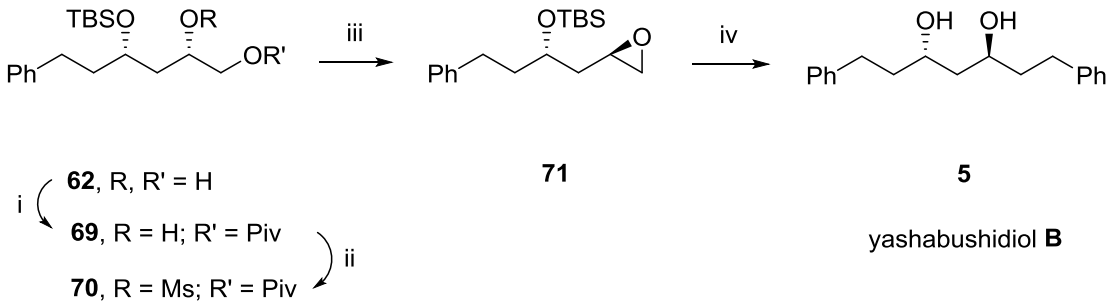


Fig. 11: ^{1}H and ^{13}C NMR spectra of yashabushidiol **A 4**

Chiral epoxide **51** was subjected to a Cu-catalyzed regioselective ring opening with Grignard reagent (BnMgBr, CuI at 0 °C) to afford yashabushidiol A **4** in 88% yield. Its spectroscopic data are in complete agreement with the reported values.[6] The formation of **4** was supported by the ^{1}H NMR spectrum, which showed two multiplets at δ 4.47-4.49 (m, 2H) and 7.15-7.26 (m, 10H) due to two secondary –OH group and aromatic protons respectively. Also its ^{13}C NMR spectrum showed two typical carbon peaks at δ 68.2 and 68.4 for methine carbons attached to two hydroxyl groups respectively. Its IR spectrum displayed a characteristic strong vibrational frequency at υ_{max} 3404 cm^{-1} due to –OH functionality (**Fig. 11**).

Finally, chiral diol **62** was selectively protected as its pivalate ester **69** followed by its mesylate **70** derivatives in high yields, which was then treated with K_2CO_3 in MeOH to give epoxide **71** (90% over three steps) with complete inversion of configuration at the C-2 position (**Scheme 13**).



Scheme 13: (i) PivCl, Et_3N, cat. DMAP, 25 °C, 2 h, 90%; (ii) MsCl, Et_3N, cat. DMAP, 25 °C, 2 h, 90%; (iii) K_2CO_3, MeOH, 0 °C, 0.5 h, 89%; (iv) BnBr, Mg, CuI, THF, 0-25 °C, 1 h, 88%.

The formation of **71** was confirmed from ^{1}H NMR spectrum which showed a typical multiplet at δ 3.91-3.92 (m, 1H) corresponding to the methine proton attached to silyl group. Further it was ascertained by carbon signals at δ 70.6 and 71.2 due to methine

carbons attached to silyl group and epoxide ring respectively in its ^{13}C NMR spectrum (**Fig. 12**).

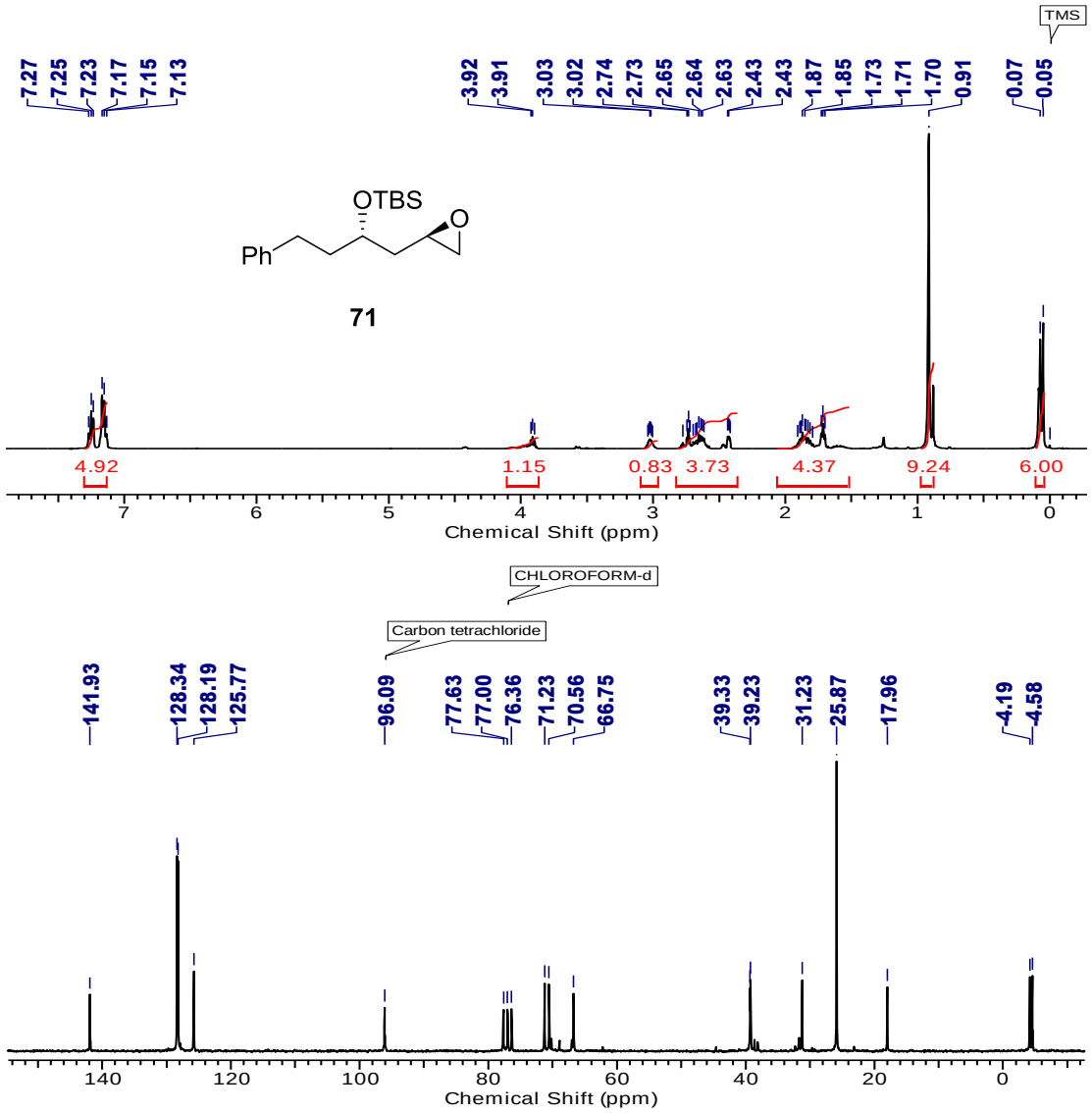


Fig. 12: ^{1}H and ^{13}C NMR spectra of TBS ether **71**

Regioselective ring opening of epoxide **71** with Grignard reagent gave yashabushidiol B **5** in 88% yield. The specific rotation value of **5** matched well with the literature value $[\alpha]_D^{20}$ -7.0 (*c* 1, $CHCl_3$); lit.[6a] $[\alpha]_D^{20}$ -7.3 (*c* 1, $CHCl_3$). Its ^{1}H NMR spectrum showed a typical multiplet at δ 4.45-4.50 (m, 2H) due to the presence of two methine protons attached to –OH group. Further its ^{13}C NMR spectrum displayed two characteristic

carbon signals at δ 68.6 and 68.2 corresponding to two methine carbons attached to –OH group, which confirmed the formation of **5** (**Fig. 13**).

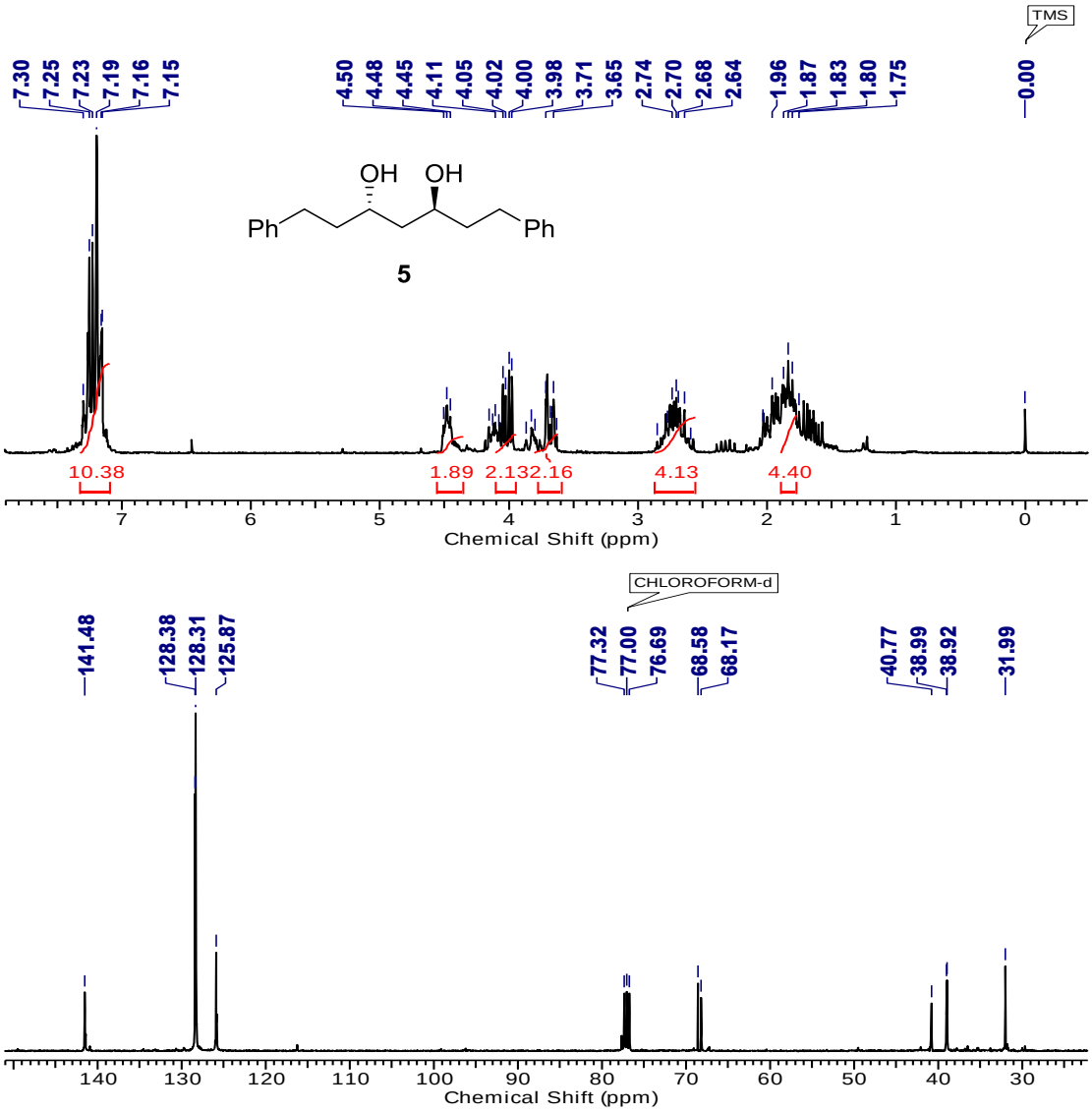


Fig. 13: ^{1}H and ^{13}C NMR spectra of yashabushidiol (**5**)

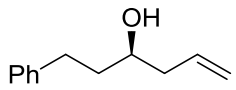
2.1.4 Conclusion

In conclusion, we have described a short and economical synthesis of β-hydroxy-δ-lactone moiety **3** (14.7% overall yield; 98% ee) starting from commercially available hydrocinnamaldehyde. We have also described a short asymmetric synthesis of yashabushidiols **A 4** and **B 5** from the common intermediates **51** and **62** respectively. The strategy employed herein mainly comprises of iodine induced intramolecular

electrophilic addition of carbonate and Co-catalyzed two-stereocentered HKR of racemic epoxide **67** as the key chirality inducing steps.

2.1.5 Experimental procedure

(*R*)-1-Phenylhex-5-en-3-ol (63)

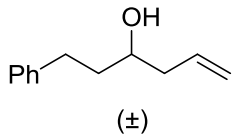


To a mixture of (-)-Ipc_2(allyl)borane (4.1 mL, 8.20 mmol) in dry diethyl ether (15 mL) previously cooled to -75 °C under vigorous stirring, a solution of hydrocinnamaldehyde **15** (1 g, 7.45 mmol) in diethyl ether (25 mL) was added dropwise over 20 min *via* syringe, maintaining the temperature below -70 °C. The resulting mixture was vigorously stirred at -75 °C for 1.5 h, then it was allowed to warm to room temperature over 1 h. A solution of 3M NaOH (5 mL) and aq. 30% H_2O_2 (6 mL) were carefully added *via* the dropping funnel over 10 min (exothermic), keeping the temperature below 15 °C, followed by the addition of saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was vigorously stirred for 10 h at room temperature to completely hydrolyze boronate ester products. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 x 20 mL). After the combined organic layers were washed with brine (2 x 10 mL), the ether solution dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated by rotary evaporator to afford light yellow oil which was purified by column chromatography with petroleum ether: ethyl acetate (9:1) to provide pure homoallylic alcohol **63**.

Yield: 85% (1.12 g, 87% ee), colorless oil; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +17.8 (*c* 1, $CHCl_3$) {lit.[4b] $[\alpha]_D^{20}$: +19.0 (*c* 2.8, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 916, 1453, 1640, 2857, 2927, 3026, 3070, 3379; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.61 (d, *J* = 3.9 Hz, 1H), 1.75-1.83 (m,

2H), 2.16-2.32 (m, 2H), 2.67-2.89 (m, 2H), 3.65-3.67 (m, 1H), 5.14 (d, *J* = 11.8, 1.6 Hz, 2H), 5.70-5.91 (m, 1H), 7.16-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.0, 38.4, 42.1, 69.8, 118.1, 125.8, 128.3, 134.6, 142.0; **Anal. Calcd for** $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.75; H, 9.11%.

Phenylhex-5-en-3-ol) (64)

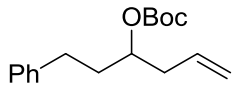


(±)

To a pre-cooled (0 ^{o}C) well-stirred mixture of hydrocinnamaldehyde **15** (5 g, 37.26 mmol), Zn dust (2.4 g, 37.26 mmol) and allyl bromide (6.44 mL, 74.52 mmol) in 120 mL of CH_3CN was added a saturated solution of NH_4Cl (10 mL). The mixture was stirred for 6 h at ambient temperature until aldehyde **15** was totally consumed (monitored by TLC). The mixture was filtered and the precipitate was thoroughly washed with CH_3CN (3 x 20 mL). The solvent was then removed under vacuum and the residue solution extracted with EtOAc. Organic layer was then washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic separation with petroleum ether: ethyl acetate (9:1) racemic gave homoallylic alcohol **64**.

Yield: 87% (5.7 g), yellow colored liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 916, 1453, 1640, 2857, 2927, 3026, 3070, 3379; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.61 (d, *J* = 3.9 Hz, 1H), 1.75-1.83 (m, 2H), 2.16-2.32 (m, 2H), 2.67-2.89 (m, 2H), 3.65-3.67 (m, 1H), 5.14 (d, *J* = 11.8, 1.6 Hz, 2H), 5.70-5.91 (m, 1H), 7.16-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.0, 38.4, 42.1, 69.8, 118.1, 125.8, 128.3, 134.6, 142.0; **Anal. Calcd for** $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.74; H, 9.13%.

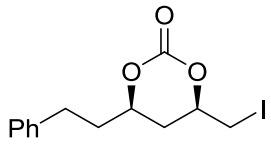
***tert*-Butyl (1-phenylhex-5-en-3-yl) carbonate (61)**



To a solution of alcohol **64** (5 g, 28.4 mmol) in CH_2Cl_2 (90 mL) were added di-*tert*-butyl dicarbonate (Boc_2O) (6.2 g, 28.4 mmol), DMAP (0.076 g, 0.28 mmol) and Et_3N (4.3 mL, 31.22 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 1 h until starting material was consumed. Organic phase was washed with 5% HCl solution (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under *vaccuo*. Purification by flash chromatography (petroleum ether: ethyl acetate 9:1) afforded **61**.

Yield: 91% (7.1 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1010, 1250, 1560, 1643, 1741, 2981, 3079; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.82-1.96 (m, 2H), 2.37 (t, *J* = 6.8 Hz, 2H), 2.60-2.74 (m, 2H), 4.65-4.75 (m, 1H), 5.09 (d, *J* = 11.2, 1.8 Hz, 2H), 5.66-5.84 (m, 1H), 7.14-7.30 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.8, 31.7, 35.5, 38.8, 75.7, 81.6, 118.2, 126.0, 128.3, 128.4, 133.3, 141.3, 153.2; **Anal. Calcd for** $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.85; H, 8.70%.

4-(Iodomethyl)-6-phenethyl-1,3-dioxan-2-one (65)

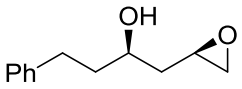


To a solution of carbonate **61** (4 g, 15.4 mmol) in dry CH_3CN (50 mL) at -40 °C was slowly added a solution of N-iodosuccinimide (6.9 g, 30.8 mmol) by addition funnel. After being stirred at -40 °C for 5 h, the resulting mixture was quenched with a mixture containing 20% $Na_2S_2O_3$ (10 mL)/5% $NaHCO_3$ (10 mL) solution, which was diluted

with ether (20 mL). The aqueous phase was extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether: ethyl acetate 7:3) to give **65**, which was quickly used in the next step to avoid its extensive decomposition on storage.

Yield: 85% (4.25 g), gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1057, 1178, 1550, 1722, 3024, 3030; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.63-2.05 (m, 4H), 2.62-2.81 (m, 2H), 3.69-3.73 (m, 1H), 4.01-4.04 (m, 1H), 4.12-4.17 (m, 1H), 4.49-4.51 (m, 1H), 7.16-7.30 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.5, 37.1, 41.7, 72.6, 75.2, 77.3, 125.8, 128.4, 141.9, 151.5; **Anal. Calcd for** $C_{13}H_{15}IO_3$: C, 45.11; H, 4.37. Found: C, 45.10; H, 4.35%.

1-(Oxiran-2-yl)-4-phenylbutan-2-ol (66)

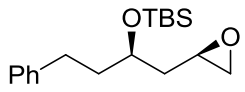


To a solution of iodolactone **65** (4 g, 11.56 mmol) in anhydrous MeOH (50 mL) at 0 °C was added anhydrous K_2CO_3 (4.8 g, 34.68 mmol) and the reaction mixture was stirred for 1 h. MeOH was removed under vacuum and the mixture diluted with ethyl acetate. Organic layer was washed with brine and aqueous phase was extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent was removed under vacuum and the crude product purified by flash chromatography (petroleum ether: ethyl acetate 6:4) affording **66**.

Yield: 84% (1.87 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1022, 1061, 1220, 1200, 1323, 1454, 1599, 2809, 3005, 3076, 3448; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.47-1.87 (m, 4H), 2.15 (s, 1H), 2.47-2.84 (m, 4H), 3.02-3.15 (m, 1H), 3.85-3.92 (m, 1H), 7.16-

7.21 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.8, 39.0, 39.8, 46.5, 50.5, 69.8, 125.8, 128.4, 141.8; **Anal. Calcd for** $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.01; H, 8.40%.

***tert*-Butyldimethyl((1-(oxiran-2-yl)-4-phenylbutan-2-yl)oxy)silane (67)**



To a solution of secondary alcohol **66** (1.5 g, 7.81 mmol) in dry CH_2Cl_2 (30 mL) at 0 ^oC were added imidazole (1.1 g, 15.63 mmol) and *tert*-butyldimethylsilyl chloride (1.77 g, 11.72 mmol). The reaction mixture was then stirred at 0 ^oC for 1 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 over silica gel with petroleum ether: ethyl acetate (9:1) to give **67**.

Yield: 90% (2.15 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1062, 1108, 2856, 2928, 3048; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.03 (s, 6H), 0.83 (s, 9H), 1.53-1.84 (m, 4H), 2.34-2.42 (m, 1H), 2.51-2.73 (m, 3H), 2.91-2.95 (m, 1H), 3.80-3.91 (m, 1H), 7.05-7.22 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.6, 18.0, 25.9, 31.2, 39.2, 66.8, 70.6, 71.2, 125.8, 128.2, 128.4, 141.9; **Anal. Calcd for** $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.55; H, 9.83%.

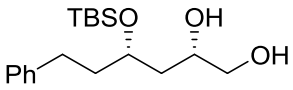
***tert*-Butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)-4-phenylbutan-2-yl)oxy)silane (51)**

To a solution of (*R,R*)-(salen)Co(II) complex (0.043 g, 0.1 mmol) in toluene (4.0 mL) was added acetic acid (0.04 g, 7.3 mmol). It was then allowed to stir at 0 °C in open air for 30 min over which time color of the solution changed from orange-red to dark brown. It was then concentrated in *vaccuo* to obtain the (*R,R*)-(salen)Co(III) complex as

a brown solid. To a solution of Co-salen complex (0.02 g, 0.5 mol %) and racemic epoxide **67** (2 g, 6.55 mmol) in THF (1 mL) at 0 °C was added H_2O (0.059 g, 3.27 mmol) slowly over 5 min. The reaction mixture was allowed to warm to 0 °C and stirred for 14 h. After completion of the reaction (monitored by TLC), solvent was removed in *vaccuo.* The crude product was purified by column chromatography over silica gel. Solvent system is petroleum ether: ethyl acetate (19:1) for chiral epoxide **51** and petroleum ether: ethyl acetate (7:3) for chiral diol **62**.

Yield: 48% (0.96 g); $[\alpha]_D^{20}$**:** -5.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max}702, 1063, 1108, 1427, 2858, 2932, 3048; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.03 (s, 6H), 0.83 (s, 9H), 1.53-1.84 (m, 4H), 2.34-2.42 (m, 1H), 2.51-2.73 (m, 3H), 2.91-2.95 (m, 1H), 3.80-3.91 (m, 1H), 7.05-7.22 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.6, 18.0, 25.9, 31.2, 39.2, 66.8, 70.6, 71.2, 125.8, 128.2, 128.4, 141.9; **Anal. Calcd for** $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.55; H, 9.83%; **HPLC**: 98% ee by chiral HPLC analysis (Chiralcel OD-H column, *n*-hexane: *i*PrOH, 97:03, 0.5 mL/min) retention time 10.157 (99.56%) and 11.353 (0.44%).

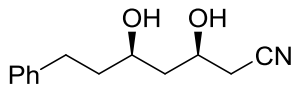
(2*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-phenylhexane-1,2-diol (62)



Yield: 47% (0.98 g), viscous liquid; $[\alpha]_D^{20}$: +30.7 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 702, 1061, 1108, 1427, 1456, 2858, 2932, 3024, 3068, 3359; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.02 (s, 6H), 0.82 (s, 9H), 1.55-1.79 (m, 4H), 2.41-2.61 (m, 2H), 3.31-3.54 (m, 2H), 3.72-3.79 (m, 1H), 3.90-4.05 (m, 1H), 7.02-7.21 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.4, 18.1, 25.9, 32.0, 39.1, 40.1, 46.6, 49.2, 70.0, 125.8, 128.3, 128.4, 142.4; **Anal. Calcd for** $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.61; H, 9.90%; **HPLC:**

96% ee by chiral HPLC analysis (Chiralcel OD-H column, *n*-hexane: *i*PrOH, 90:10, 0.5 mL/min) retention time 13.512 (98.02%) and 13.020 (1.98%).

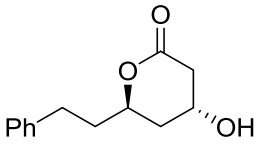
(3*S*,5*R*)-3,5-Dihydroxy-7-phenylheptanenitrile (68)



To a mixture of sodium cyanide (0.16 g, 3.27 mmol) and the silylated epoxide **51** (0.5 g, 1.63 mmol) in ethanol (6 mL) was added Trifluoroacetic acid (0.019 g, 0.16 mmol) and the resulting bright yellow solution was refluxed under nitrogen at 60 °C for 4 h. After completion of reaction (monitored by TLC), it was cooled to room temperature and excess cyanide was quenched with aqueous $NaClO_2$, diluted with water (3 mL) and EtOAc (10 mL). Organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The aqueous layer after extraction was poured into aqueous $KMnO_4$ solution and then disposed off. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography with petroleum ether: ethyl acetate (7:3) to give **68**.

Yield: 84% (0.3 g), colorless liquid; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -5.1 (*c* 0.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 906, 1453, 1640, 2127, 2857, 2927, 3026, 3070, 3379; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.21-1.80 (m, 6H), 2.66-2.80 (m, 2H), 3.53-3.85 (m, 4H), 7.17-7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.0, 32.6, 33.5, 33.7, 49.7, 73.1, 120.9, 126.8, 128.3, 128.9, 139.9; **Anal. Calcd for** $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81. Found: C, 71.15; H, 7.90%.

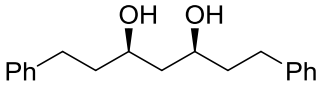
(+)-(4*R*,6*R*)-4-Hydroxy-6-(2-phenylethyl)-tetrahydro-2*H*-pyran-2-one (3)



To the solution of cyano diol **68** (0.2 g, 0.91 mmol) in MeOH (5 mL) was added aq. HCl (2 mL). The reaction mixture was stirred at 50 °C for 12 h. Solvent was removed under reduced pressure, the residue extracted with ethyl acetate and organic layer washed with brine, aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography using petroleum ether: ethyl acetate (6:4) as eluent to afford lactone **3**.

Yield: 79% (0.158 g), colorless solid; **mp**: 106-107 °C (lit.[4e] mp 108 °C); $[\alpha]_D^{20}$: +67.5 (*c* 2, $CHCl_3$) {lit.[4h] $[\alpha]_D^{20}$: +68.8 (*c* 2.29, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1036, 1135, 1370, 1435, 1650, 1750, 2980, 3442; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.73-2.01 (m, 4H), 2.61-2.86 (m, 4H), 3.05 (s, 1H), 4.32-4.39 (m, 1H), 4.68-4.72 (m, 1H), 7.16-7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.1, 35.8, 37.6, 38.6, 62.5, 75.3, 126.1, 128.4, 128.5, 141.0, 171.0; **Anal. Calcd for** $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.85; H, 7.30%.

Yashabushidiol A (4)

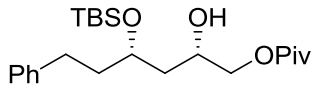


To a suspension of Mg (0.06 g, 2.45 mmol) in anhyd. THF (5 mL) at 25 °C taken in a RB flask equipped with condenser (cool water circulation) was added benzyl bromide (0.29 mL, 2.45 mmol) in a drop wise manner followed by CuI (0.031 mg, 0.16 mmol)

and the mixture was allowed to stir for 0.5 h. The mixture was then cooled to 0 °C and chiral epoxide **51** (0.5 g, 1.63 mmol) in THF (3 mL) was added. The reaction mixture was warmed to 25 °C and stirred for 1 h. On completion, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to yield crude product, which was purified by column chromatography (petroleum ether: ethyl acetate, 6:4) to afford pure **4**.

Yield: 88% (0.408 g), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1067, 1120, 1236, 1450, 1514, 2817, 2962, 3024, 3404; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.63-2.03 (m, 6H), 2.64-2.78 (m, 2H), 3.65-3.71 (m, 2H), 3.97 (d, *J* = 4.0, 1H, -OH), 4.01 (d, *J* = 4.0, 1H, -OH), 4.44-4.49 (m, 2H), 7.15-7.30 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.0, 38.9, 39.0, 40.8, 68.2, 68.4, 125.9, 128.3, 128.4, 141.5; **Anal. Calcd for** $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.23; H, 8.50%.

(2*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-6-phenylhexyl pivalate (69)

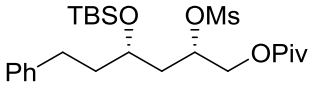


Compound **62** (0.5 g, 1.54 mmol) and triethylamine (0.136 mL, 1.84 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and the solution was cooled to 0 ^oC. Pivaloyl chloride (0.284 mL, 2.31 mmol) and DMAP (0.019 g, 0.154 mmol) were added simultaneously and then the resulting solution was stirred at 0 ^oC for 1 h. Progress of the reaction was monitored by TLC. After completion, additional CH_2Cl_2 (10 mL) was added. Organic phase was washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic purification over

silica gel with petroleum ether: ethyl acetate (9:1) gave the corresponding protected alcohol **69**.

Yield: 90% (0.565 g), colorless oil; $[\alpha]_D^{20}$: +6.5 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 703, 1051, 1118, 1427, 1486, 1510, 1667, 2858, 2932, 3024, 3068, 3359; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.91 (s, 9H), 1.23 (s, 9H), 1.70 (t, *J* = 6.0 Hz, 2H), 1.77-1.93 (m, 2H), 2.63 (dd, *J* = 7.2, 2.0 Hz, 2H), 2.85 (br. s, 1H -OH), 3.91-4.12 (m, 4H), 7.13-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.5, 18.1, 25.9, 27.3, 31.3, 38.9, 39.4, 39.7, 68.3, 68.4, 71.2, 125.2, 128.3, 128.5, 141.9, 178.4; **Anal. Calcd for** $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87. Found: C, 67.55; H, 9.85%.

(2*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-((methylsulfonyl)oxy)-6-phenylhexyl pivalate (70)

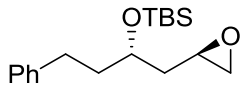


Compound **69** (0.5 g, 1.22 mmol) and triethylamine (0.2 mL, 1.27 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and the solution was cooled to 0 ^oC. Methanesulfonyl chloride (0.19 mL, 2.44 mmol) and DMAP (0.015 g, 0.122 mmol) were added and the resulting solution was stirred at 0 ^oC for 1 h. After TLC showed that the reaction was complete, additional CH_2Cl_2 (10 mL) was added. The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic purification over silica gel with petroleum ether/ethyl acetate (1:19) gave the corresponding compound **70**.

Yield: 90% (0.535 g), colorless oil; $[\alpha]_D^{20}$: +7.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 750, 1071, 1108, 1427, 1466, 2858, 2932, 3044, 3060; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.82 (s, 9H), 1.12 (s, 9H), 1.67-1.87 (m, 4H), 2.56-2.70 (m, 2H), 2.92 (s,

3H), 3.66-3.73 (m, 1H), 3.93-4.30 (m, 2H), 7.13-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.5, 18.2, 25.9, 27.2, 31.3, 38.8, 39.0, 39.4, 39.7, 68.3, 68.4, 71.2, 125.2, 128.3, 128.5, 141.9, 178.4; **Anal. Calcd for** $C_{24}H_{42}O_6SSi$: C, 59.22; H, 8.70. Found: C, 59.21; H, 8.68%.

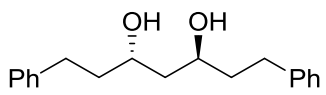
***tert*-Butyldimethyl(((*S*)-1-((*R*)-oxiran-2-yl)-4-phenylbutan-2-yl)oxy)silane (71)**



To a solution of **70** (0.5 g, 1.03 mmol) in anhydrous MeOH (5 mL) at room temperature was added anhydrous K_2CO_3 (0.425 g, 3.08 mmol) and the reaction mixture was stirred for 1 h. After completion of reaction, it was diluted with water and extracted with ethyl acetate (3 x 10 mL). Organic extracts were washed with brine (5 mL), dried over anhydrous $MgSO_4$ and filtered. Solvent was removed under vacuum and purified by the flash chromatography (petroleum ether: ethyl acetate 19:1), affording epoxide **71**.

Yield: 89% (0.28 g), colorless oil; $[\alpha]_D^{20}$: +4.77 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 702, 1063, 1108, 1427, 2858, 2932, 3048; **^{1}H NMR** (200 MHz, $CDCl_3$): -0.02 (s, 6H), 0.82 (s, 9H), 1.63-1.84 (m, 4H), 2.38-2.51 (m, 1H), 2.55-2.73 (m, 3H), 2.91-2.94 (m, 1H), 3.80-3.91 (m, 1H), 7.05-7.21 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.6, 18.0, 25.9, 31.2, 39.2, 66.8, 70.6, 71.2, 125.8, 128.2, 128.4, 141.9; **Anal. Calcd for** $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.51; H, 9.85%.

Yashabushidiol B (5)



To a suspension of Mg (0.06 g, 2.45 mmol) in anhyd THF (5 mL) at 25 °C in a RB flask equipped with a condenser (cool water circulation), was added benzyl bromide (0.29 mL, 2.45 mmol) in a drop wise manner followed by CuI (0.031 g, 0.16 mmol) and the entire mixture was allowed to stir for 0.5 h. Then the mixture was cooled to 0 °C followed by the addition of epoxide **71** (0.5 g, 1.63 mmol) in THF (3 mL). The reaction was warmed to 25 °C and stirred for 1 h. On completion, the reaction was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to yield crude product, which was purified by column chromatography (petroleum ether: EtOAc 6:4) to afford pure yashabushidiol B (**5**) .

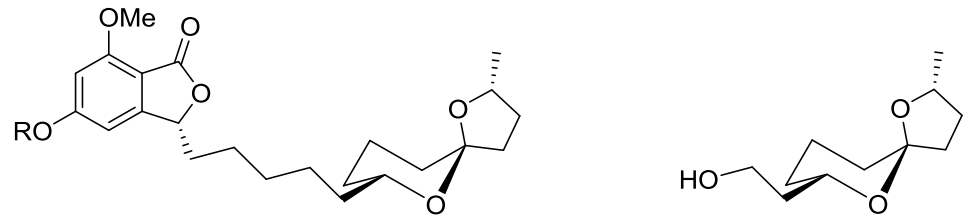
Yield: 88%, (0.41 g), colorless viscous liquid; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ -7.0 (*c* 1, $CHCl_3$); lit.[6a] $[\alpha]_D^{20}$ -7.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 830, 1060, 1236, 1450, 1514, 2858, 2939, 3024, 3353; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.64-2.02 (m, 6H), 2.63-2.78 (m, 2H), 3.65-3.71 (m, 2H), 3.97-4.01 (m, 2H), 4.44-4.49 (m, 2H), 7.15-7.30 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.0, 38.9, 39.0, 40.8, 68.2, 68.4, 125.9, 128.3, 128.4, 141.5; **Anal. Calcd for** $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.25; H, 8.50%.

Section II

Enantioselective Synthesis of (+)-Spirolaxine Methyl Ether

2.2.1 Introduction

About 80% of human beings are infected by gastric mucosa caused by *Helicobacter pylori* (*H. Pylori*) organisms (gram-negative bacteria) wordwide.[12] Infection of such disease can persist for longer time depending upon the age and origin[13a,b] of the victim. Over the decades, infected human with *H. pylori* can be tolerated in some cases with few or no symptoms.[14] However, peptic ulceration[15] and adenocarcinoma of the distal stomach[16] are caused due to the infection of this bacteria increases risk factor for life. Therapy for removal of these *H. pylori* from gastroduodenal tract involves combination of one or more antibiotics with H_2 blockers. However, currently no powerful treatment is available for complete eradication.[17]



72 **73** **74**

R = H, spirolaxine; R = CH_3, spirolaxine methyl ether spiroketal

Fig. 14: Bioactive molecules spirolaxine (**72**), spirolaxine methyl ether (**73**), and spiroketal (**74**)

Spirolaxine **72** and spirolaxine methyl ether **73** (**Fig. 14**) are produced by various strains of white rot fungi belonging to the genera *Sporotrichum* and *Phanerochaete*.[18] Such helicobactericidal compounds possesses the potent bioactivity and are very useful against the treatment of a gastroduodenal disorders and the prevention of gastric

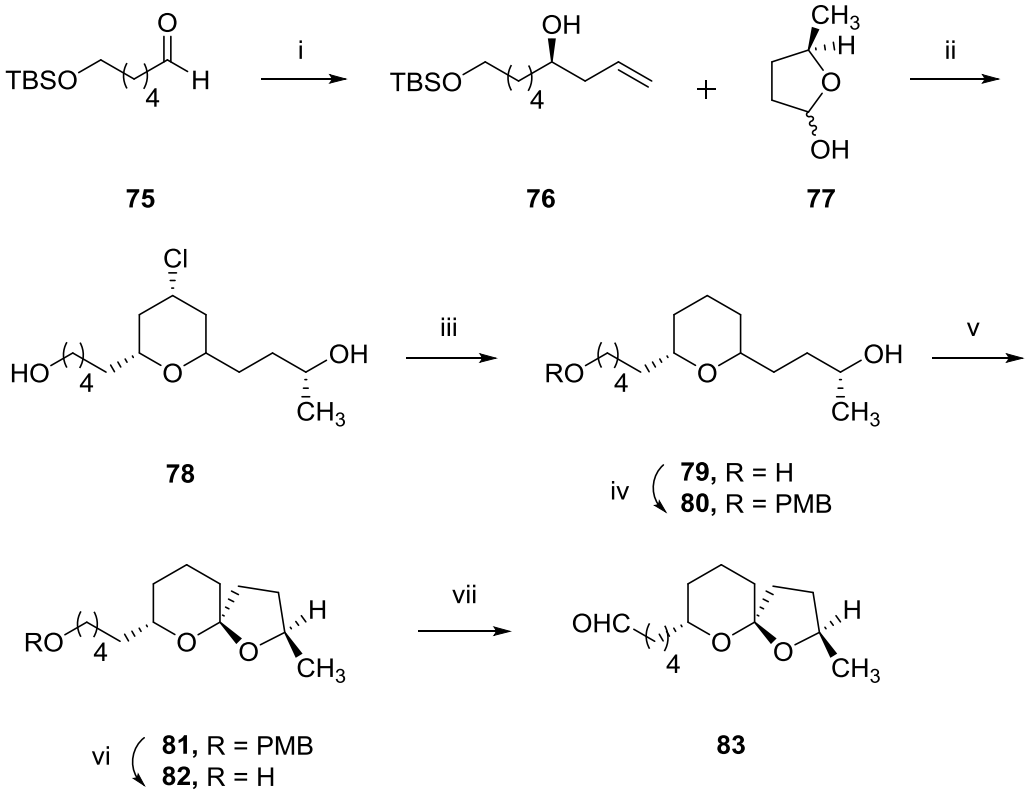
cancer.[19] Dekker *et al.*,[20] have reported such phthalide-containing helicobactericidal compounds with 5,5-spiroketal moiety showing promising activity against *H. pylori*-related diseases.

2.2.2 Review of Literature

Due to the biological importance, there are several reports available in the literature for the synthesis of spirolaxine methyl ether **73** and its intermediate **74.** [21] Some of the recent synthetic reports are described below.

Dallavalle's approach (2006)[21a]

Dallavalle *et al.* have described the synthesis of precursor **83** using diastereoselective Prins cyclization starting from aldehyde **75**, which was achieved by selective mono

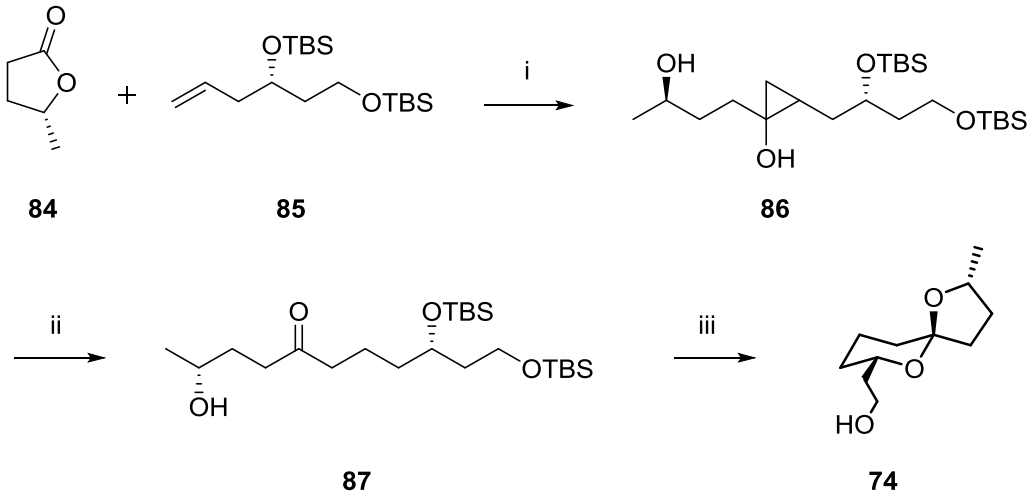


Scheme 14: (i) (-)-Ipc_2allylborane, -78 °C, 1 h, rt; followed by NaOH (3 N), H_2O_2, 1 h, reflux, 82%; (ii) $TiCl_4$, CH_2Cl_2, -70 °C, 4 h, then -20°C, 1 h, 63%; (iii) $NaBH_4$, DMSO, 130 °C, 8 h, 96%; (iv) (PMB)Cl, NaH, DMF, rt, 3 days, 50%; (v) HgO, I_2, hv, cyclohexane, 9 h, 68%; (vi) CAN, CH_3CN/H_2O, rt, 2 h, 68%; (vii) TEMPO, KBr, NaOCl, 3 h, 100%.

silylation of 1,6-hexanediol followed by its oxidation. Brown allylation of aldehyde **75** with (-)-Ipc_2allylborane furnished the chiral homoallylic alcohol **76** (82% yield; >96% ee). Further, Prins cyclization was performed between 4-(*R*)-hydroxypentanal **76** and alcohol **77** using $TiCl_4$ (as Lewis catalyst) at low temperature to form chlorotetrahydropyran **78** in 63% yield. This was followed by reductive dechlorination to afford compound **79**. Alcohol **79** was then protected as its *p*-methoxybenzyl ether **80** and subsequently underwent HgO/I_2-mediated oxidative cyclization to afford spiroketal **81** in 68% yield. Finally, PMB deprotection followed by oxidation of alcohol **82** with TEMPO resulted in aldehyde **83** in a quantitative yield. Aldehyde **83** was used as an equivalent to **74** for further synthesis of **73** (**Scheme 14**).

Phillips's approach (2006)[21b]

Phillips *et al.* have developed the shortest and useful route to the synthesis of spiroketal alcohol **74** employing Kulinkovich reaction. The synthesis began with readily made



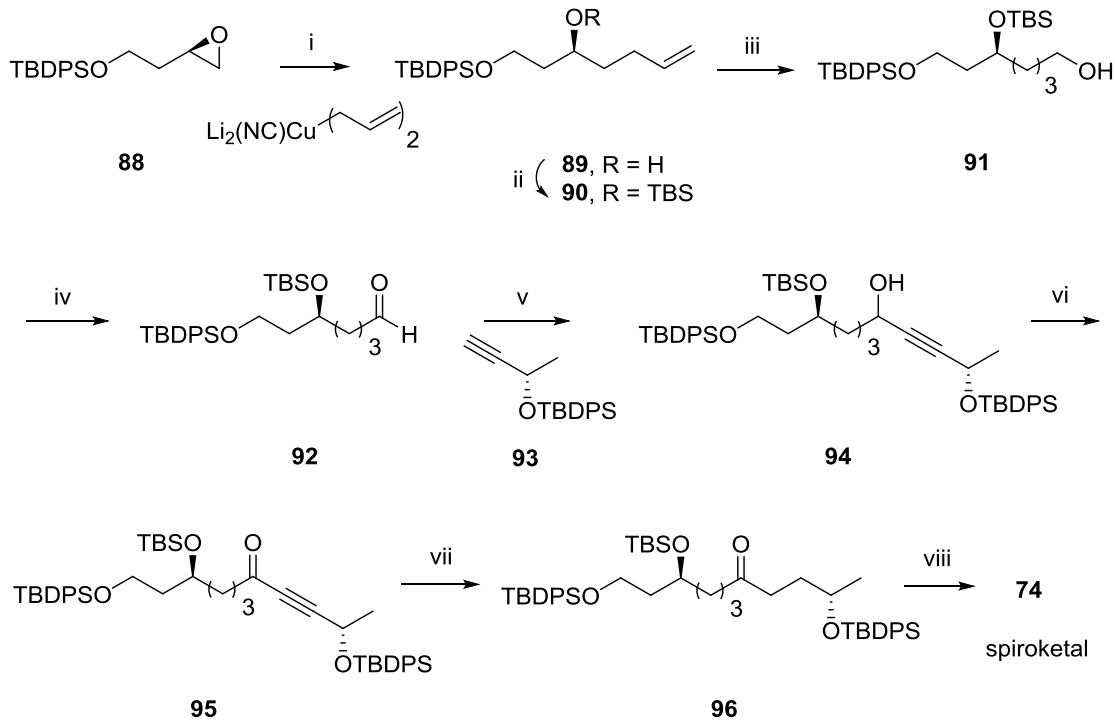
Scheme 15: (i) *c*-$C_6H_{11}MgBr$, $Ti(O^iPr)_4$, PhMe, 25 °C, 92%; (ii) $Fe(NO_3)_3$, Bu_2SnH, DMF, 75%; (iii) HF, CH_3CN, 89%.

olefin **85**,[22] which was coupled with commercially available (*R*)-γ-valerolactone **84** (*cyclo*-$C_6H_{11}MgBr$, $Ti(O^iPr)_4$, toluene, 25 °C) to furnish cyclopropanol **86** in 92% yield.

Cyclopropanol **86** was then reacted with $Fe(NO_3)_3$ and Bu_3SnH to afford ketone **87** in 75% yield. Acid catalyzed deprotection of silyl ether and subsequent cyclization furnished the spiroketal moiety **74** in 89% yield (**Scheme 15**).

Brimble's approach (2007)[21c]

Brimble *et al.* have achieved the synthesis of **74** from epoxide **88**, which was prepared from (*S*)-aspartic acid in 3 steps: (by bromine displacement, carboxylic acid reduction, and further silyl ether protection; 90% over 3 steps). The Cu(I) catalyzed ring opening of epoxide **88** with diallylcyanocuprates resulted in homo allylic alcohol **89** in 90% yield and 94% ee. Alcohol **89** was then protected as its silyl ether **90** followed by hydroboration provided alcohol **91**.

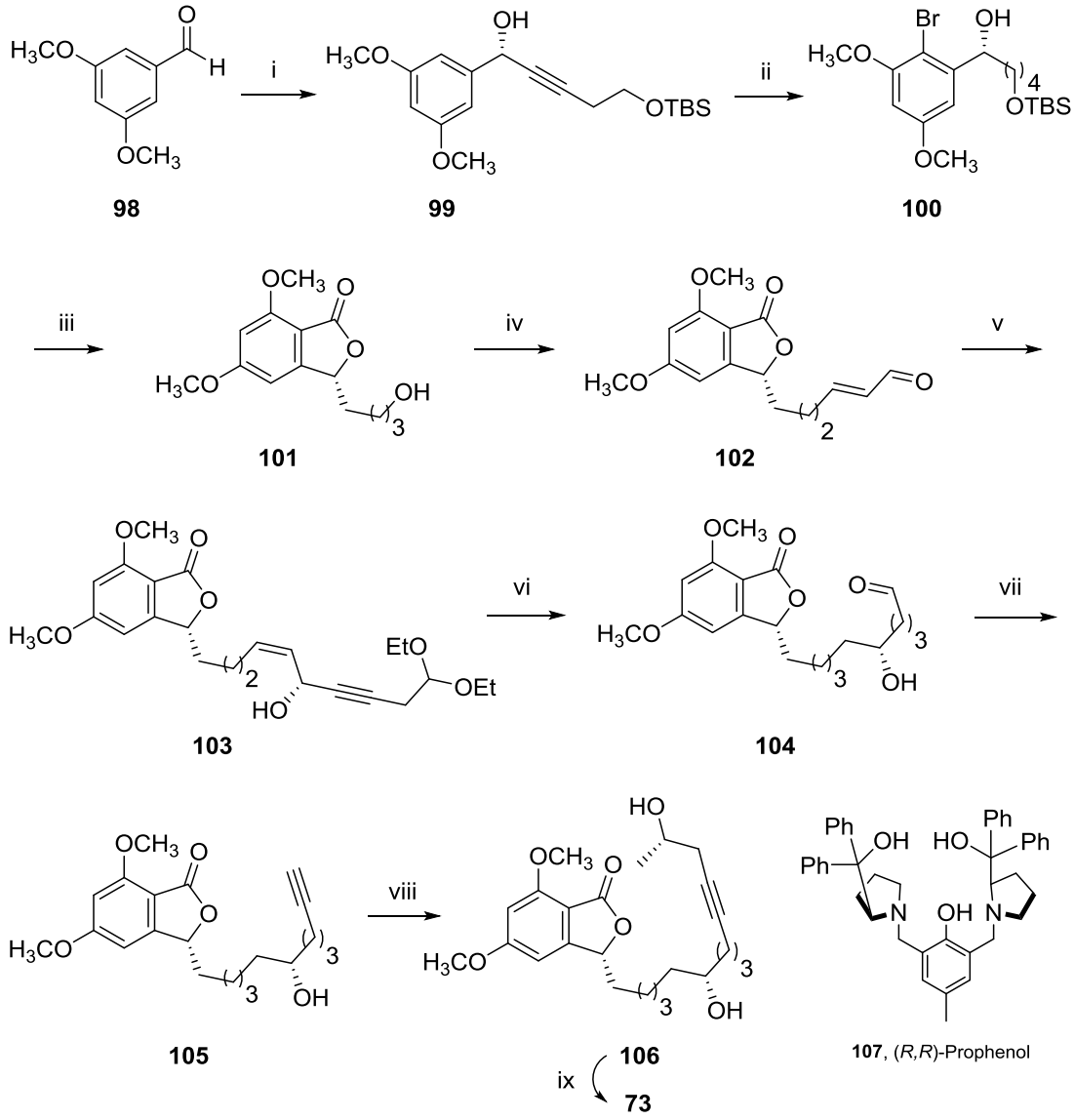


Scheme 16: (i) allytributyltin, MeLi, LiCl, CuCN, THF, -78 °C, 4 h, 90%; (ii) TBSCl, DMAP, imid., CH_2Cl_2, 0 °C, 12 h, 98%; (iii) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt, 12 h, 83%; (iv) Dess-Martin periodinane, pyridine, CH_2Cl_2, 0 °C to rt, 2 h, 86%; (v) *n*-BuLi, LiBr, THF, -78 °C, 6 h, 86%; (vi) $RuO_4N(^tBu)_4$, NMO, CH_2Cl_2, 0 °C, 2 h, 97%; (vii) 10% Pd/C, H_2 (1 atm), dil. H_2SO_4, MeOH, 48 h, 86%; (viii) (a) CSA, CH_2Cl_2, 0 °C, 2 h, 86%; (b) TBAF, THF, rt, 2 h, 68%.

Alcohol **91** was oxidized with Dess–Martin periodinane reagent to furnish aldehyde **92**, which on subsequent condensation with acetylide **93** derived from (*S*)-acetylene, acetylene alcohol **94** was resulted in 86% yield. Compound **94** was then oxidized to keto derivatives **95** followed by alkyne hydrogenation over 10% Pd/C provided saturated compound **96**. Finally, acid catalyzed selective deprotection of silyl ethers provided the final spiroketal **74** in 68% yield (**Scheme 16**).

Trost's approach (2007)[21d]

Trost *et al.* envisaged a long reaction sequence for the synthesis of spirolaxine methyl ether **73** starting from 3,5-dimethoxybenzaldehyde **98**. Prophenol-catalyzed anion addition of 4-(*tert*-butyldimethylsilyloxy)-1-butyne onto aldehyde **98** produced propargylic alcohol **99** in 82% yield and 90% ee. Alkyne **99** was then hydrogenated with Adams catalyst (PtO_2) followed by bromination afforded compound **100**. *Ortho*-lithiation of **100** with *n*-BuLi and subsequent CO_2 trapping provided after acidic workup the phthalide unit **101** (90%). Alcohol **101** was then oxidized and homologated with Wittig salt to provide enal **102**. (*S*,*S*)-**107**-catalyzed diastereoselective alkynylation of enal **102** with 4,4-diethoxybut-1-yne[23] furnished the propargylic alcohol **103** in 52% yield (d.r. = 5:1). Then, alcohol **103** was protected as its silyl ether followed by alkyne reduction with Adam's catalyst resulted in saturated compound, which on further acid hydrolysis provided alkoxy aldehyde **104**. Aldehyde **104** underwent homologation to give terminal alkyne **105** under Ohira–Bestmann[24] alkynylation condition. Target compound **73** was obtained in 3 steps: alkyne addition onto (*R*)-propylene oxide; desilylation of TBS group; and $[PdCl_2(PhCN)_2]$ promoted spiroketalization in 79% yield (**Scheme 17**).

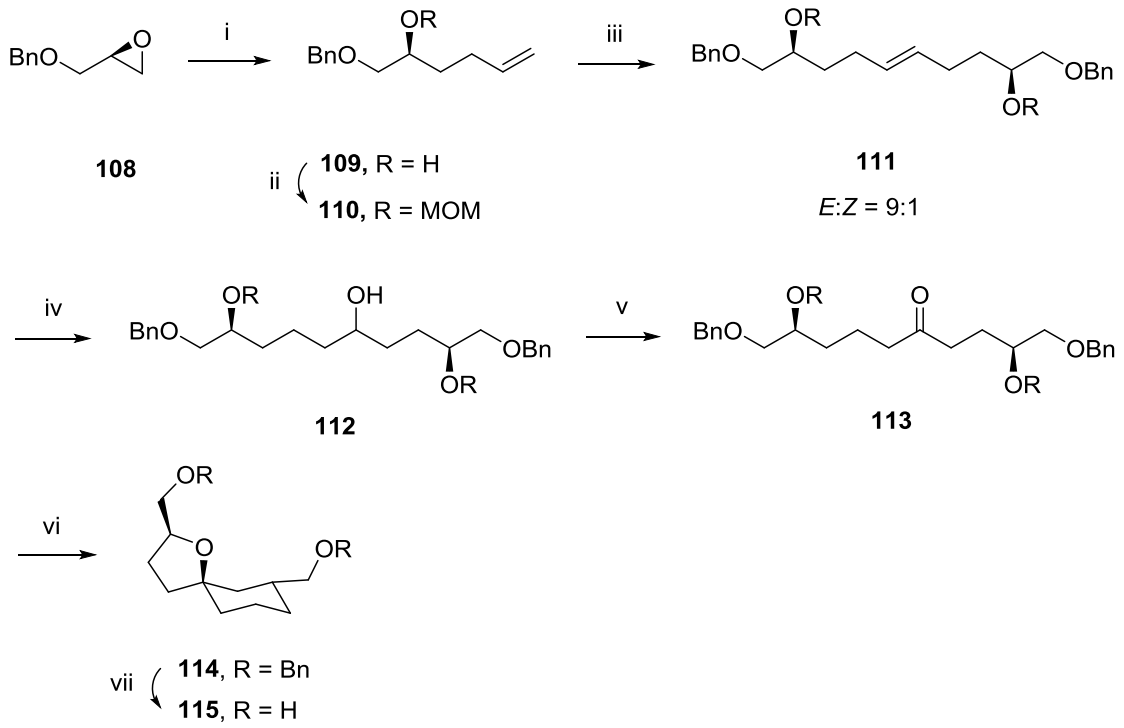


Scheme 17: (i) (*R*,*R*)-**107** (10 mol %), Me_2Zn, 4-(*tert*-butyldimethylsilyloxy)-1-butyne, toluene, 82%; (ii) (a) H_2 (1 atm), PtO_2, EtOAc, quant.; (b) NBS, $CHCl_3$, 99%; (iii) *n*-BuLi, THF, 78 °C then CO_2, HCl/H_2O, 90%; (iv) (a) TEMPO (5 mol %), bisacetoxyiodobenzene, 84%; (b) (triphenylphosphoranylidene) acetaldehyde, PhH, 80 °C, 56%; (v) 4,4-diethoxybut-1-yne, Me_2Zn, (*S*,*S*)-**107** (10 mol %), $PhCH_3$, 52%, d.r. = 5:1; (vi) (a) TBSCl, imid., CH_2Cl_2, 71%; (b) H_2 (1 atm), PtO_2, EtOAc, 91%; (c) PPTS, acetone, 98%; (vii) Ohira–Bestmann, K_2CO_3, MeOH, 75%; (viii) *n*-BuLi, $BF_3{\cdot}Et_2O$, (*R*)-(+)-propyleneoxide; HCl/H_2O, 51% (2 steps); (ix) $[PdCl_2(PhCN)_2]$, THF:CH_3CN (3:1), 79%.

Rao's approach (2008)[21e]

Rao *et al.* have initiated the synthesis of **115** with regioselective ring opening of epoxide **108** by allylmagnesium bromide to provide olefinic alcohol **109** in 87% yield.

Alcohol **109** was protected as its MOM ether **110**. Self cross-metathesis of alkene **110** by Grubbs' first generation catalyst furnished the olefin (C2-symmetric dimer) **111** in 94% yield (*E*:*Z* = 9:1). Hydroboration-oxidation of olefin **111** gave alcohol **112** followed by its oxidation with Dess–Martin periodinane reagent afforded keto compound **113**. Keto derivative **113** was then subjected to acid catalyzed spiroketalization to form cyclized spiro compound **114**. Finally, deprotection of benzyl group was achieved with Na/liq.NH_3 to furnish spiroketal **115** in 85% yield, a precursor for **74** (**Scheme 18**).

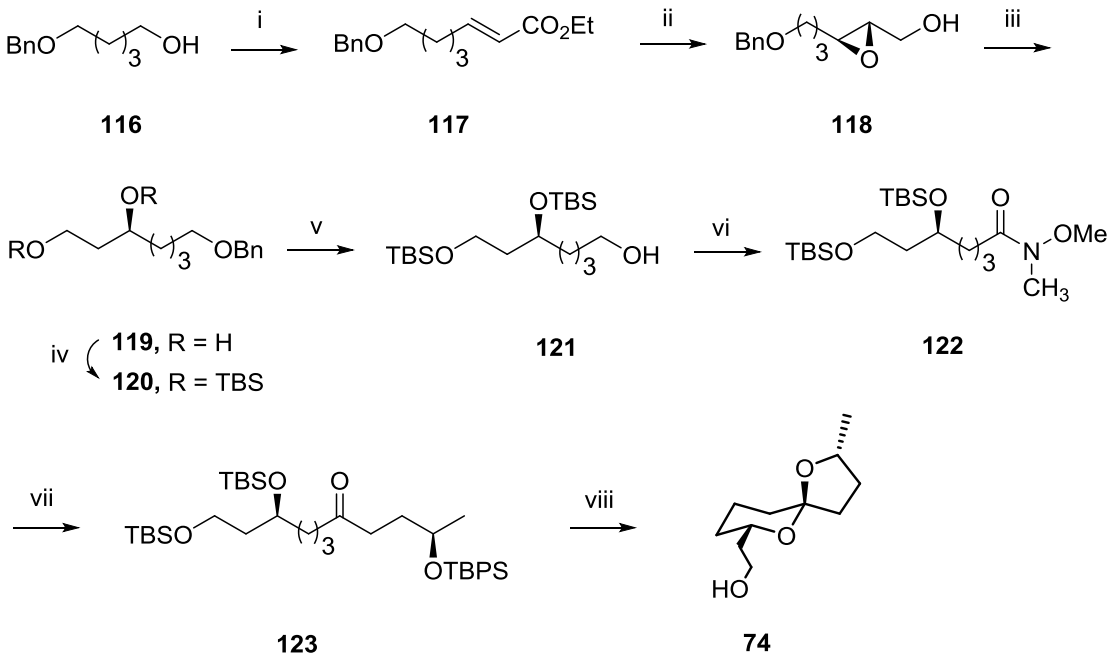


Scheme 18: (i) CH_2=CH-CH_2MgBr, CuI, Et_2O, -20 °C, 12 h, 87%; (ii) MOM-Cl, DIPEA, DMAP, CH_2Cl_2, 0 °C to rt, 4 h, 90%; (iii) 10 mol % Grubbs 1stgeneration catalyst, CH_2Cl_2, 40 °C, 12 h, 94%; (iv) BH_3·DMS, H_2O_2, NaOH, THF, 0 °C to rt, 8 h, 85%; (v) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 3 h, 88%; (vi) conc. HCl, MeOH, 40 °C, 10 min., 92%; (vii) Na in liq. NH_3, THF, -78 °C, 5 h, 85%.

Yadav's approach (2010)[21f]

Yadav *et al*. have reported the synthesis of spiroketal **74** starting from monobenzyl ether **116**. Oxidation of primary hydroxyl group and subsequent quenching with Wittig

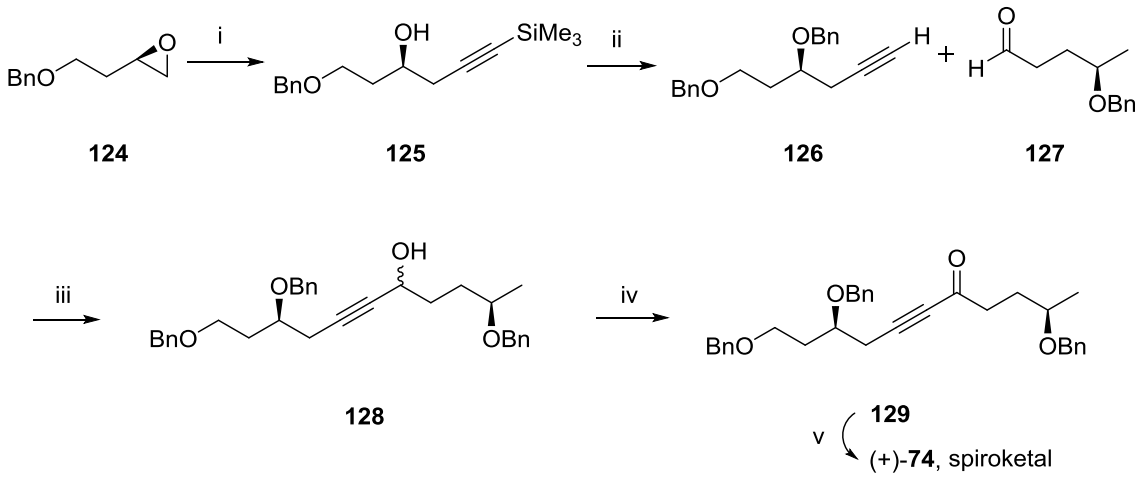
salt resulted in α,β-unsaturated ester **117** (*E*-isomer). Selective ester reduction of **117** was achieved with $LiAlH_4/AlCl_3$ followed by Sharpless asymmetric epoxidation of allyl alcohol afforded epoxy alcohol **118** (89% yield, 94% ee). Epoxide **118** was then regioselectively opened with Red-Al to form diol **119**, which on protection as its silyl ether **120** followed by debenzylation provided alcohol **121** in 82% yield (**Scheme 19**). Oxidation of alcohol **121** furnished aldehyde which was converted into its Weinreb amide **122** in 64% yield. Alkyne **93** was added onto Weinreb amide **122** in presence of LDA to give the corresponding ketone followed by alkyne hydrogenation resulted in saturated keto derivative **123** without affecting silyl ether group. Deprotection of silyl ether and subsequent cyclization led finally to thermodynamically stable 6,5-spiroketal **74** in 89% yield.



Scheme 19: (i) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 86%; (b) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 83%; (ii) (a) $LiAlH_4/AlCl_3$, Et_2O, 0 °C, 81%; (b) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 °C, 91%; (iii) Red-Al, THF, 88%; (iv) ^{t}BuMe$_2$Si-Cl, imid., CH_2Cl_2, 0 °C to rt, 90%; (v) Li/naphthalene, THF, -30 °C, 82%; (vi) (a) BAIB, TEMPO, CH_3CN:H_2O (2:1), 89%; (b) DCC/CH_3CN/Pyr, MeO(H)-NMe_3.HCl, 64%; (vii) **93**, LDA, THF, 0 °C to -30 °C then Weinreb amide **122** in THF, 88%; (viii) (a) Lindlar catalyst, H_2 (1 atm), EtOAc, rt, 92%; (b) aq. HF, CH_3CN, 89%.

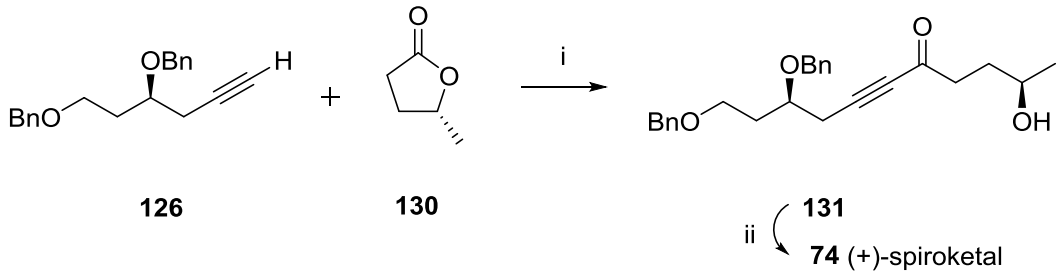
Argade's approach (2011) [21g]

Argade *et al.* have commenced the synthesis of spiroketal **74** by opening of enantiopure (*R*)-oxirane **124** with TMS-protected acetylene that provided alkynol **125** in 89% yield. *O*-Benzyl protection followed by *in situ* desilylation of **125** provided acetylene derivative **126** in 77% yield. Then, aldehyde **127**[10] was condensed with acetylenic carbanion of **126** to yield inseparable diastereomeric mixture of alcohol **128** (~1:1), which was subsequently oxidized to alkynone **129** (85% yield). Catalytic hydrogenation of alkyne **9** and global deprotection of benzyl ether groups resulted in diastereomerically pure (+)-spiroketal **74** in 82% yield (**Scheme 20**).



Scheme 20: (i) *n*-BuLi, $BF_3.OEt_2$, THF, -78 °C, 1 h, 89%; (ii) NaH, BnBr, DMF, 4 h, 77%; (iii) *n*-BuLi, THF, -78 °C, 1 h, 75%; (iv) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 45 min. 85%; (v) 5% Pd/C, H_2 (1 atm), MeOH, 60 psi, 8 h, 82%.

In yet another approach by Argade *et al.* have reported the addition of an acetylenic carbanion of **126** onto pure (*R*)-γ-valerolactone **130** to afford alkynonol **131** in 89% yield, followed by debenzylation and dehydrogenation furnished the pure compound (+)-**74** with an improved overall yield of 87% (**Scheme 21**).

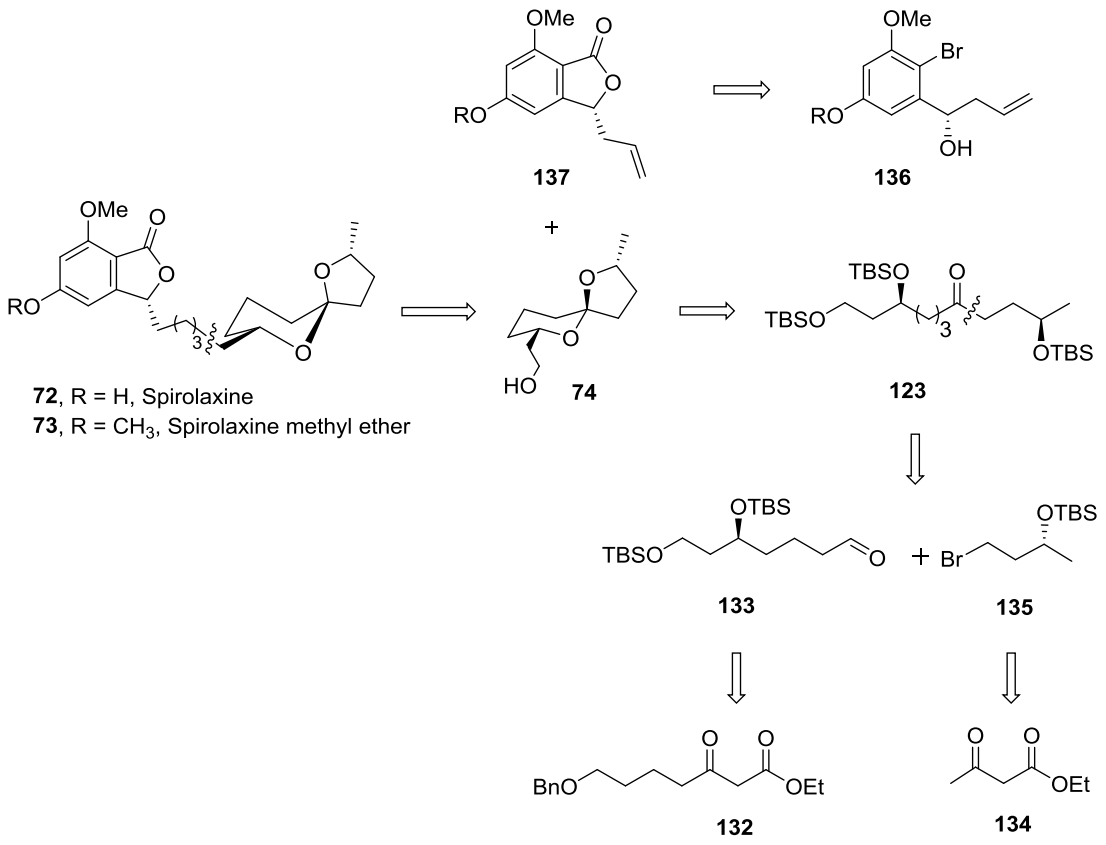


Scheme 21: (i) *n*-BuLi, $BF_3.OEt_2$, THF, -78 °C, 1 h, 89%; (ii) 5% Pd/C, H_2 (1 atm), MeOH, 60 psi, 8 h, 80%.

2.2.3 Present Work

2.2.3.1 Objective

The reported methods for the synthesis of spirolaxine methyl ether **73** suffered from certain limitations such as the use of chiral building blocks, the introduction of chirality in the early stages, long reaction sequences, and low enantiomeric excess and thus are not amenable for scale-up studies.[21] In this context, a more practical method for the synthesis of (+)-spirolaxine methyl ether **73** is highly desirable. In this section, we described a practical, synthesis of crucial spiroketal part **74** and phthalide fragment **137** with an improved enantiomeric excess (96% ee). The synthesis entails Noyori's asymmetric reduction and Brown allylation as the key chirality inducing steps that established complete stereochemistry of spirolaxine methyl ether **73** (**Schemes 23-26**).

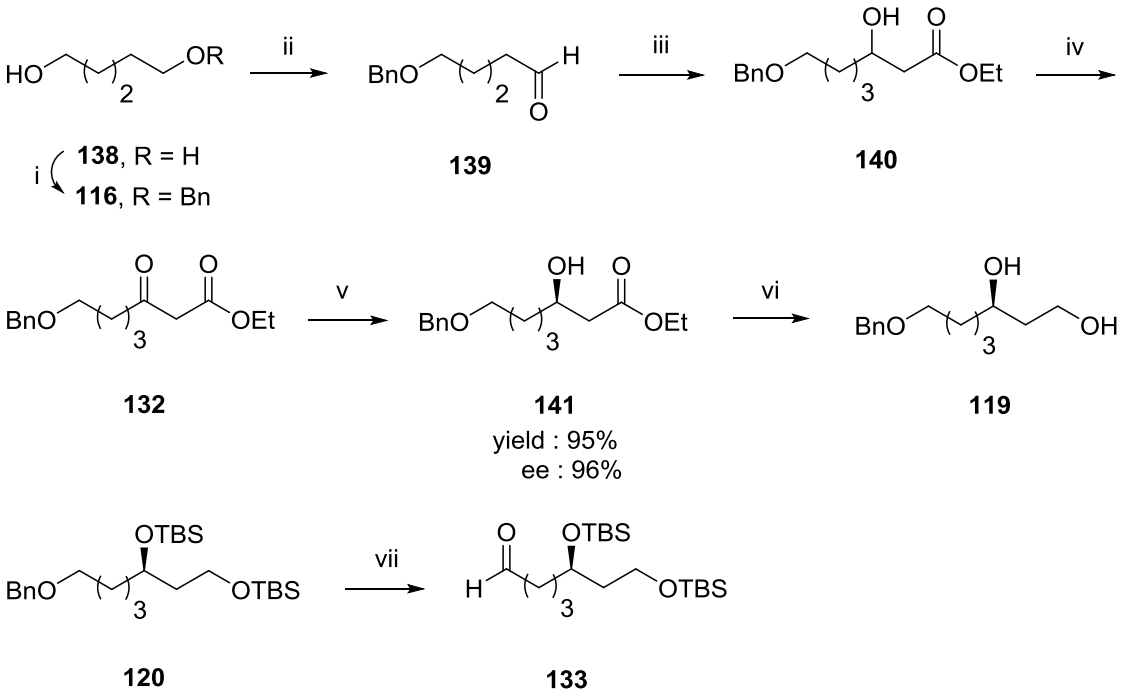


Scheme 22: Retrosynthetic analysis of spirolaxine methyl ether **73**.

The retrosynthesis of spirolaxine methyl ether **73** is shown in **Scheme 22**. We envisioned that the synthesis of **73** could be achieved from the key chiral intermediate spiroketal **74**, which could be prepared from acid catalyzed cyclization of ketone **123**. The synthesis of keto ether **123** could be achieved by the Grignard addition of alkyl bromide **135** onto aldehyde **133**. Also, aldehyde **133** could be obtained from β-keto ester **132**, which in turns can be achieved by Reformatsky reaction of the corresponding aldehyde with ethyl bromoacetate. Similarly, fragment **135** could be obtained by the same chiral reduction strategy from easily available ethyl acetoacetate **134**. Phthalide fragment **137** could be obtained by Cu-catalyzed CN-assisted lactonization of alcohol **136**.

2.2.3.2 Results and Discussion

The synthesis of spirolaxine methyl ether **73** commenced with construction of the key chiral intermediate spiroketal **74**, which was synthesized from commercially available starting material 1,5-pentanediol (**138**). Selective benzylation of **138** resulted in monobenzyl ether **116** in 89% yield followed by its oxidation using TEMPO and BIAB conditions furnished aldehyde **139** in 95% yield (**Scheme 23**).



Scheme 23: (i) BnBr, NaH, DMF, 0 °C to rt, 4 h, 89%; (ii) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, rt, 1 h, 95%; (iii) ethyl bromoacetate, Zn, THF, reflux, 4 h, 90%; (iv) IBX, EtOAc, rt, 1 h, 87%; (v) $[(R)\text{-}Ru(BINAP)Cl_2]_2 \cdot NEt_3$ (0.1 mol %), 2 M HCl (0.1 mol %), MeOH, H_2 (100 psi), 50 °C, 16 h, 95% yield, 96% ee; (vi) (a) $LiAlH_4$, THF, 0 °C, 3 h, 90%; (b) TBSCl, imid., CH_2Cl_2, 0 °C, 1 h, 85%; (vii) (a) 5% $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 2 h, 80%; (b) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, rt, 1 h, 88% (over two steps).

The formation of aldehyde **139** was confirmed by the appearance of a typical aldehydic proton signal at δ 9.75 (t, J = 1.6 Hz, 1H) in its ^{1}H NMR spectrum. Further, it was ascertained by the ^{13}C NMR spectrum, which displayed a characteristic carbon signal at δ 201.8 due to aldehydic functionality (**Fig. 15**).

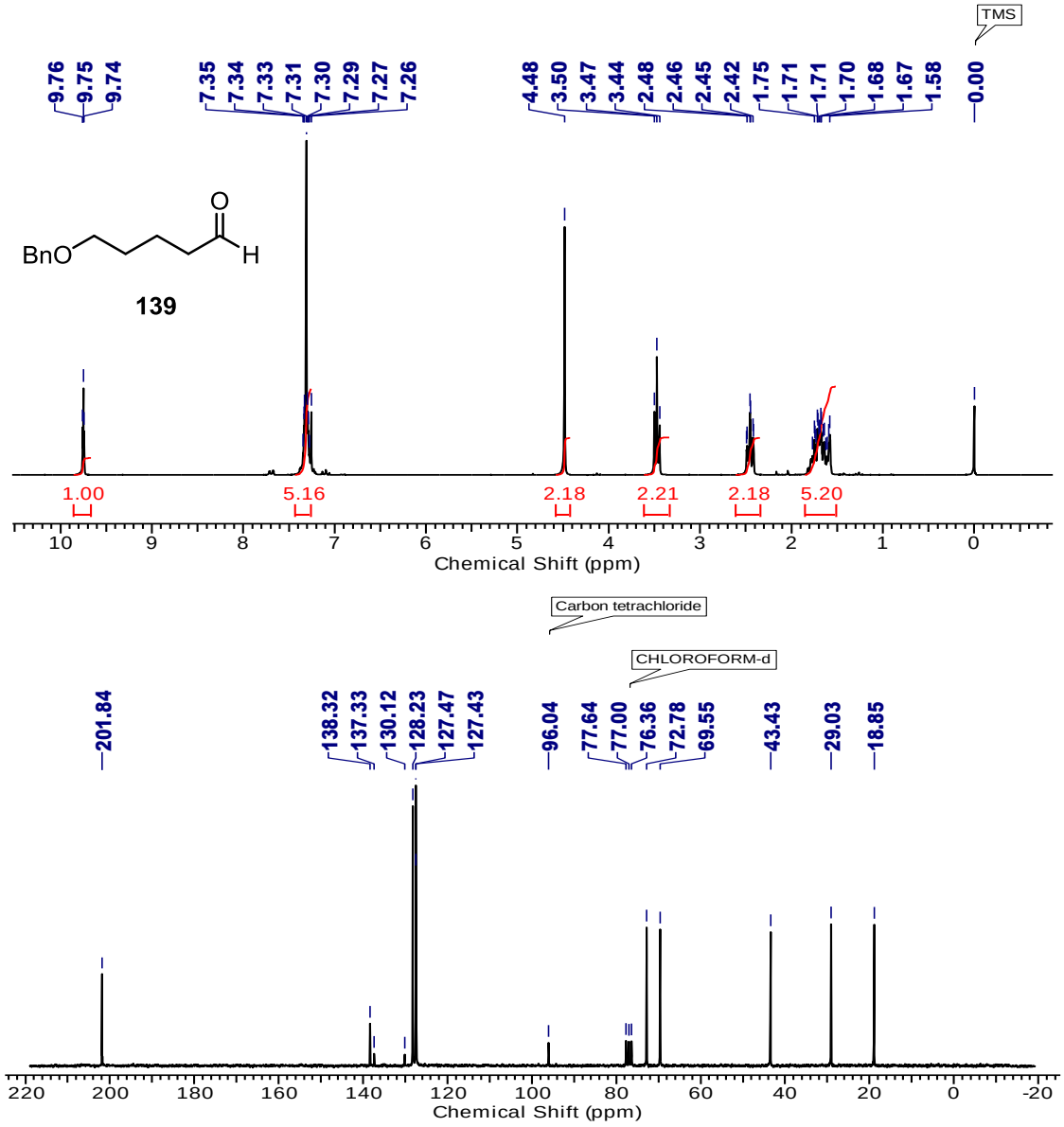


Fig. 15: ^{1}H and ^{13}C NMR spectra of aldehyde **139**

Noyori's discovery of rhodium (I) and ruthenium (II) complexes of BINAP enantiomers have revolutionized stereoselective organic synthesis.[25a] In particular, Noyori's asymmetric reduction is a very useful tool for the chiral reduction of β-keto ester with high enantioselectivity.[25b,c] In view of this, we have planned our synthesis to achieve the chiral β-hydroxy ester **141**. Thus, we have treated benzyl protected aldehyde **139** with ethyl bromoacetate under Reformatsky reaction conditions (Zn, NH_4Cl, THF, 0 °C) that furnished racemic β-hydroxy ester **140** in 90% yield.

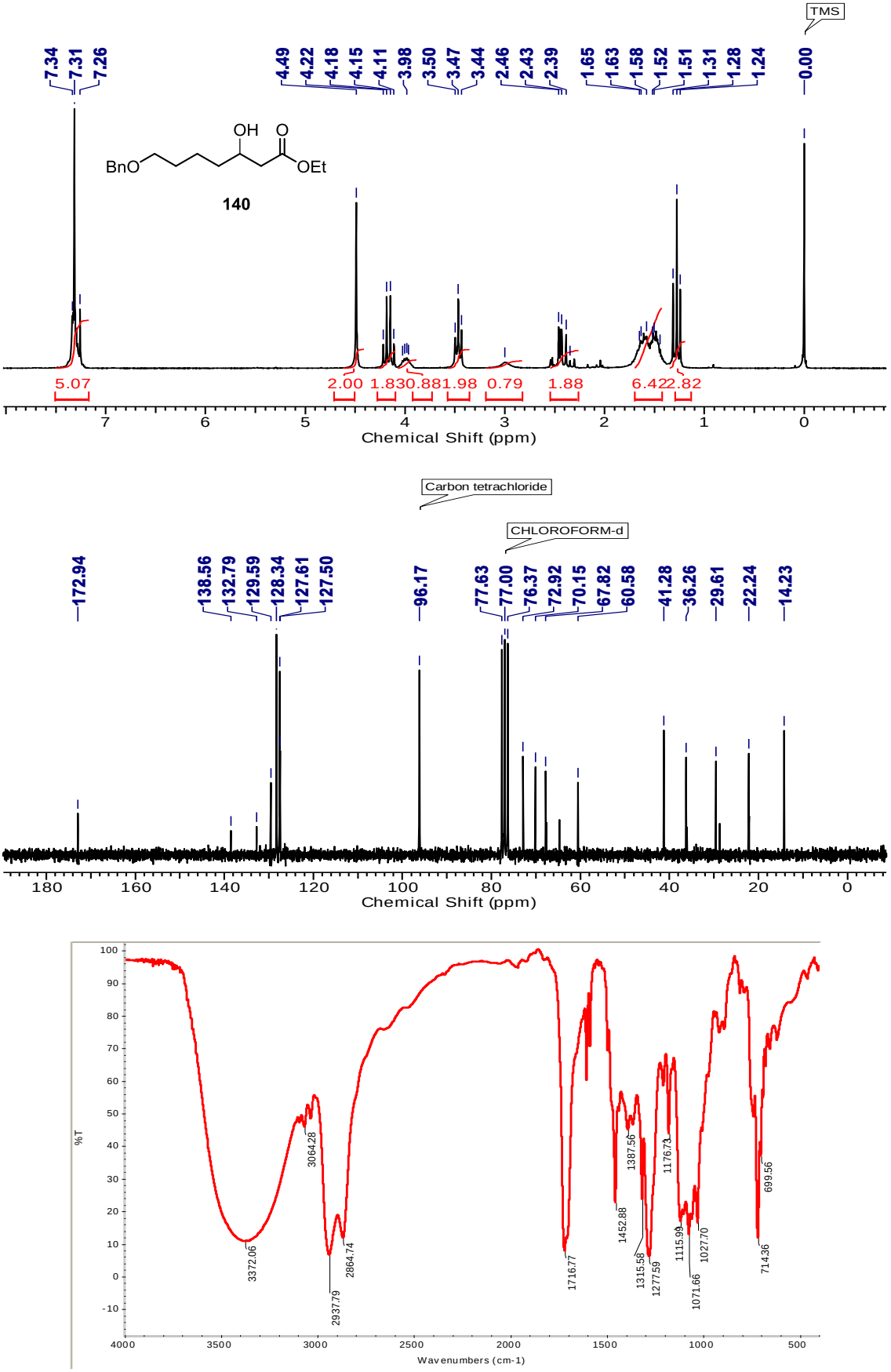


Fig. 16: ^{1}H, ^{13}C NMR and IR spectra of β-hydroxy ester **140**

The ^{1}H NMR spectrum of racemic β-hydroxy ester **140** showed a multiplet at δ 3.96-4.02 (m, 1H) and a singlet at δ 3.00 (br. s, 1H) corresponding to methine and –OH protons respectively. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 172.9 and 67.8 due to -C=O carbon and methine carbon attached to –OH group, thereby confirming the formation of β-hydroxy ester **140**. Also, its IR spectrum displayed two strong vibrational stretching frequencies at 3372 and 1716 cm^{-1} due to the presence of –OH and –C=O functionality respectively (**Fig. 16**).

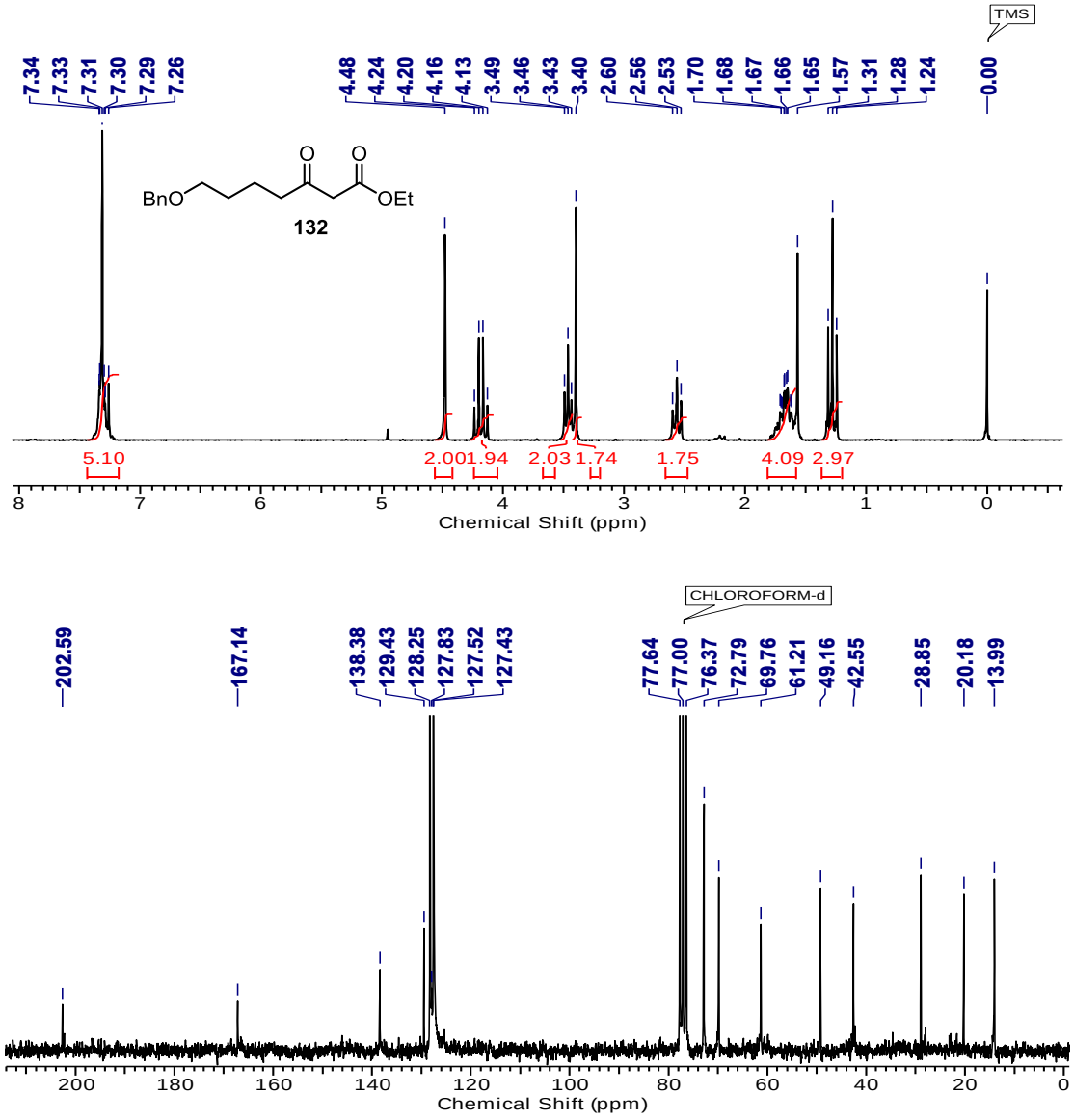
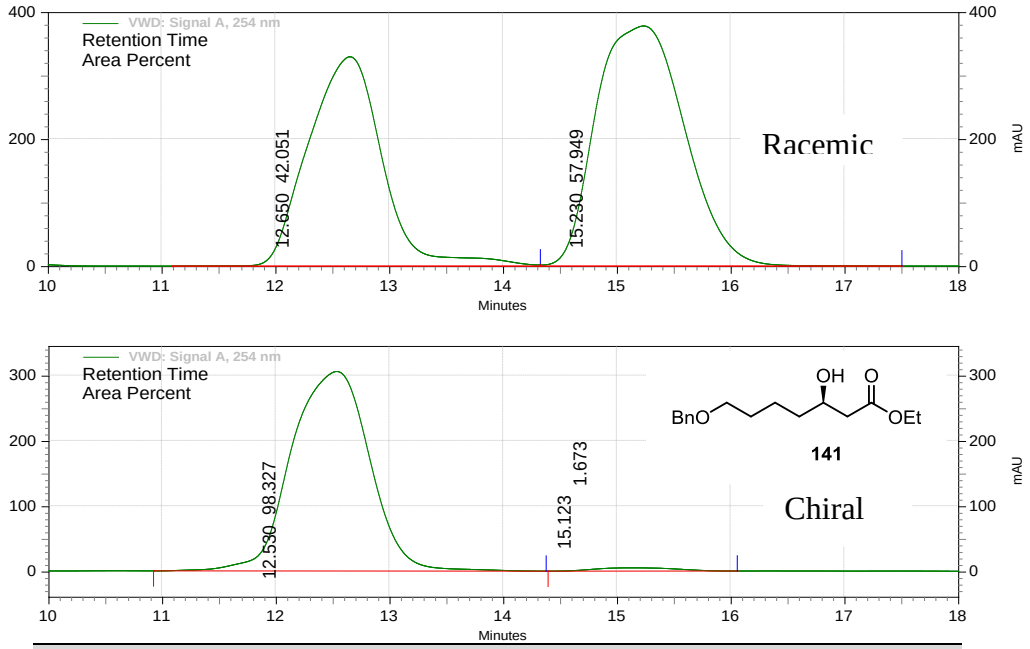


Fig. 17: ^{1}H and ^{13}C NMR spectra of β-ketoester **132**

Further, alcohol **140** was oxidized using IBX to provide β-keto ester **132** in excellent yield (87%). The formation of β-ketoester **132** was confirmed from its ^{1}H NMR spectrum, which showed a typical singlet at δ 3.40 (s, 2H) corresponding to methylene proton attached to two –C=O groups. Also, its ^{13}C NMR spectrum displayed carbon two signals at δ 202.6 and 167.1 indicative of –C=O carbons of keto and ester groups respectively (**Fig. 17**). Its IR spectrum accounted for two strong vibrational stretching frequencies at 1717 and 1736 cm^{-1} due to –C=O of keto and ester groups respectively.



VWD: Signal A, 254 nm Results				
Retention Time	Area	Area %	Height	Height %
12.530	244951558	98.35	5128098	98.40
15.123	4168475	1.65	83636	1.60
Totals	249120033	1 0.00	5211734	100.00

Fig. 18: HPLC chromatogram of chiral β-hydroxyester **141**

Now, racemic β-keto-ester **132** was reduced using Noyori's asymmetric catalytic conditions: {[(*R*)-Ru(BINAP)Cl_2]$_2$·NEt_3, 2M HCl (0.1 mol %), MeOH, H_2 (100 psi), 50 °C} to afford the corresponding chiral β-hydroxyester **141** with excellent yield (95%) and enantiopurity (96% ee). The enantiomeric excess was determined to be 96% ee by

chiral HPLC analysis (Chiralcel OD-H column, *n*-hexane: *i*PrOH, 97:03, 0.5 mL/min) retention time 12.530 (98.35%) and 15.123 (1.65%) for chiral β-hydroxyester **141** (**Fig. 18**).

Reduction of ester **141** with $LiAlH_4$ resulted in the formation of chiral 1,3-diol **119** in 90% yield. The formation of **119** was confirmed from its ^{1}H NMR spectrum, which showed the disappearance of ethyl protons of ester group and the appearance of a typical broad singlet at 2.04 (s, 2H) due to two hydroxyl protons. Further, its structure was supported by ^{13}C NMR spectrum, which displayed a typical carbon signal at δ 60.6

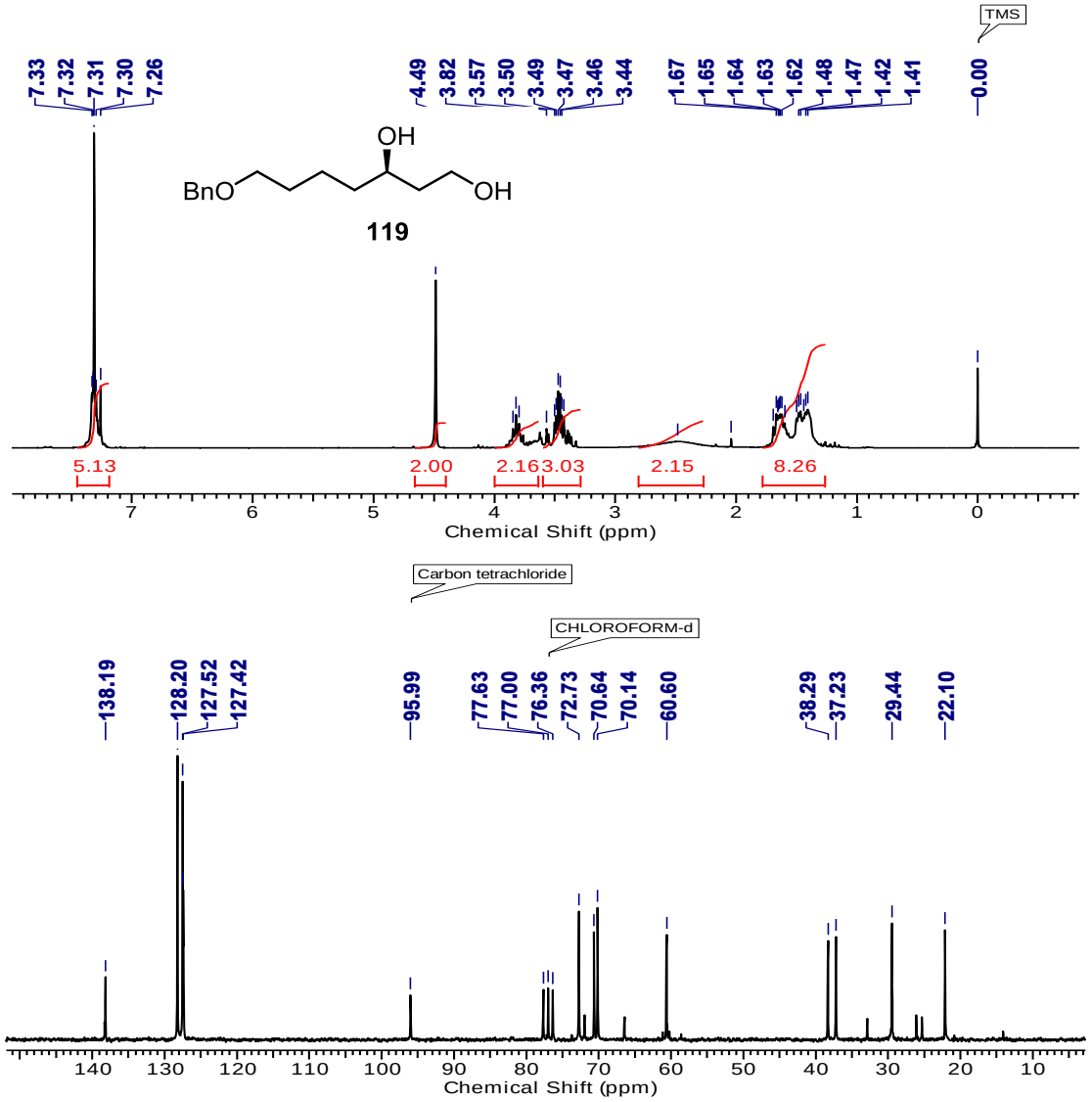


Fig. 19: ^{1}H and ^{13}C NMR spectra of chiral 1,3-diol **119**

corresponding to newly generated methylene carbon. Also, its IR spectrum displayed two strong and broad vibrational stretching frequencies at 3300 and 3290 cm^{-1} indicative of two –OH groups (**Fig. 19**).

Then, global protection of diol **119** as silyl ether was carried out using TBSCl and imidazole to provide protected ether **120** in 85% yield. The chiral silyl ether **120** was characterized by the ^{1}H and ^{13}C NMR spectral analysis. The ^{1}H NMR spectrum of **120** showed two characteristic peaks at δ 0.89 (s, 18H) and -0.02-0.08 (m, 12H) due to

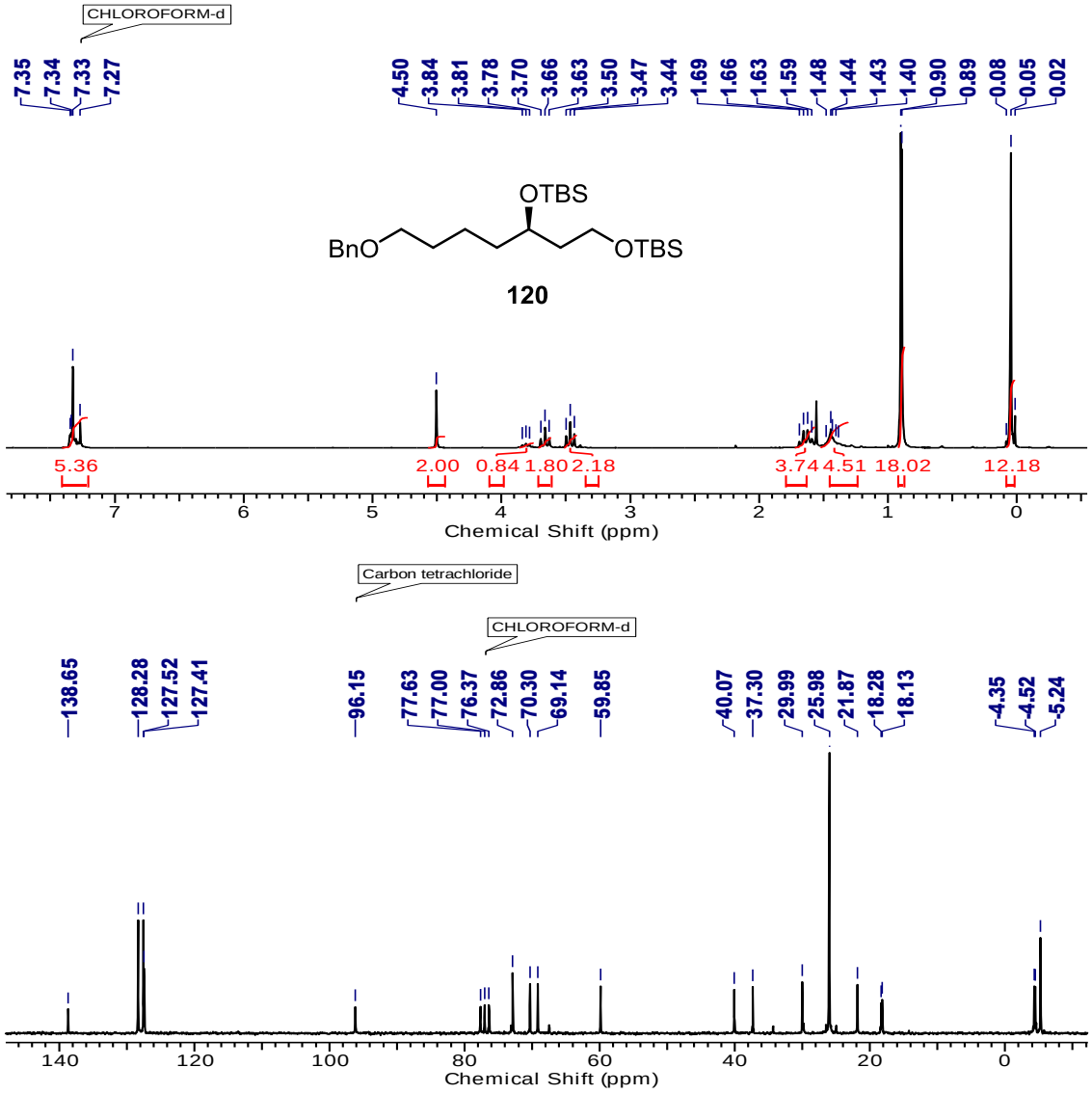


Fig. 20: ^{1}H and ^{13}C NMR spectra of silyl ether **120**

presence of methyl protons of silyl groups. Its ^{13}C NMR spectrum showed two typical carbon signals at δ -4.6 and 26.0 corresponding to methyl and quaternary carbons attached to silicon atoms respectively (**Fig. 20**).

Selective deprotection of benzyl ether of **120** was achieved under mild reaction condition using 10% $Pd(OH)_2/C$ as catalyst to furnish the corresponding debenzylated alcohol **121** in 80% yield. Alcohol **121** was subjected to oxidation with TEMPO, BIAB to give aldehyde **133** in 88% yield. Its formation was supported by ^1H NMR spectrum,

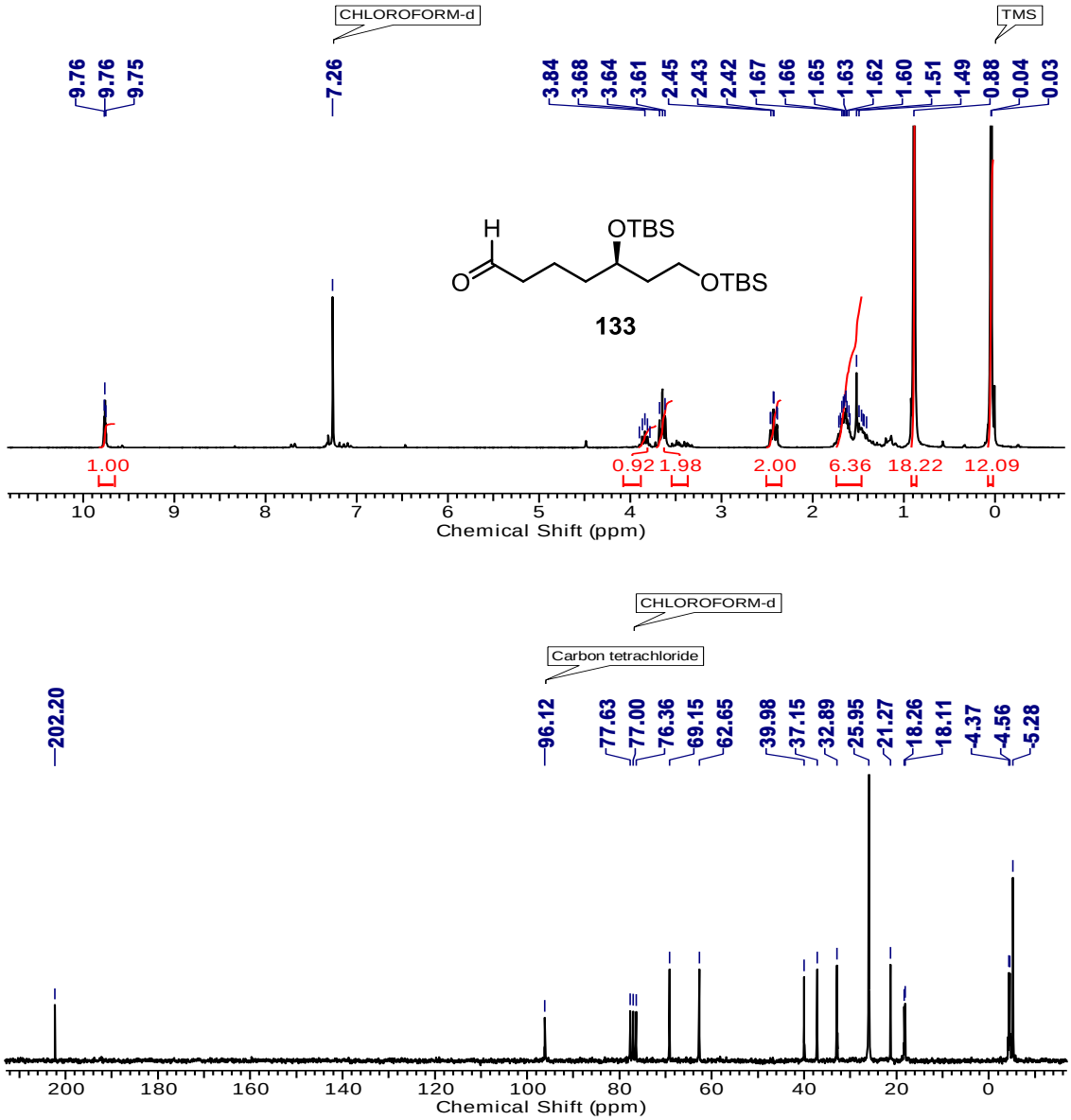
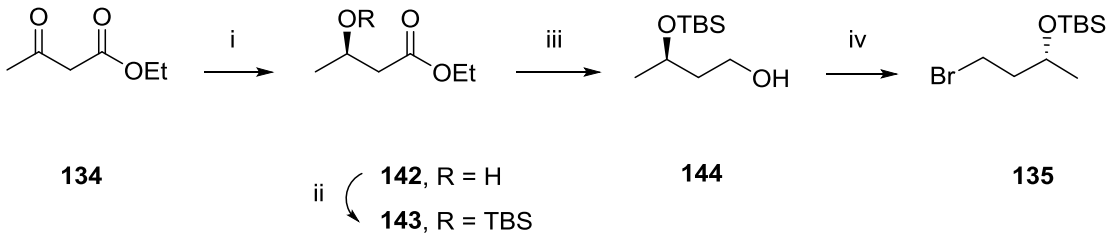


Fig. 21: ^1H and ^{13}C NMR spectra of aldehyde **133**

which displayed a characteristic aldehydic proton triplet at δ 9.76 (t, *J* = 1.6 Hz, 1H). Also, its ^{13}C NMR spectrum showed a typical carbon peak at δ 202.2 indicative of the aldehydic carbon confirming the structure of **133** (**Fig**. **21**).

With aldehyde fragment **133** in hand, we have turned our attention towards the synthesis of alkyl fragment **135**, which was synthesized by the asymmetric reduction of readily available starting material ethyl acetoacetate **134** using Noyori's catalyst {([(*R*)-Ru(BINAP)Cl_2]$_2$·NEt_3, 2M HCl (0.1 mol %), MeOH, H_2 (100 psi), 50 °C)} to produce chiral (*R*)-ethyl 3-hydroxybutyrate **142** in 94% yield and 98% enantiomeric excess. Its specific rotation was in close agreement with the reported value [$[\alpha]_D^{20}$ -45.0 (*c* 1.0, $CHCl_3$); lit.[26] $[\alpha]_D^{20}$ -46.0 (*c* 1.0, $CHCl_3$)] (**Scheme 24**).



Scheme 24: (i) [(*R*)-Ru(BINAP)Cl_2]$_2$·NEt_3 (0.1 mol %), 2 M HCl (0.1 mol %), MeOH, H_2 (100 psi), 50 °C, 16 h, 94%; (ii) TBSCl, imid., CH_2Cl_2, 0 °C, 2 h, 90%; (iii) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 85%; (iv) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h, 89%.

The formation of alcohol **142** was confirmed from its IR spectrum, which showed a strong and broad absorption band at 3441 cm^{-1} corresponding to hydroxyl functionality. Also, its structure was further ascertained by the ^{1}H and ^{13}C NMR spectral analysis, which displayed a typical proton resonance signal at δ 3.21 (d, *J* = 1.6 Hz, 1H) due to the presence of hydroxyl proton and a typical carbon resonance at δ 60.4 due to the methine carbon attached to –OH group respectively (**Fig. 22**).

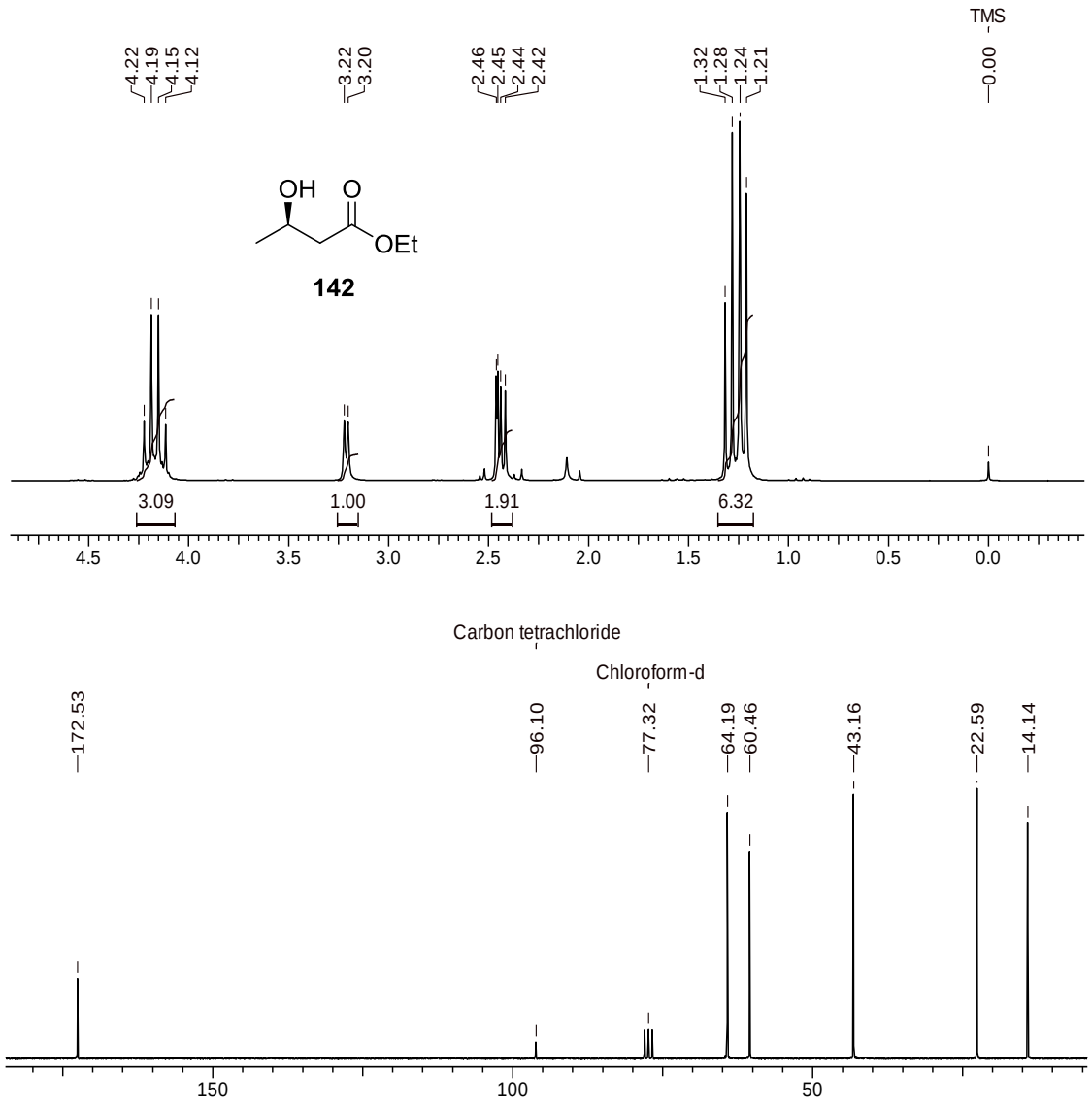


Fig. 22: ^{1}H and ^{13}C NMR spectra of (*R*)-ethyl 3-hydroxybutyrate (**142**)

Secondary hydroxyl functionality in **142** was protected as its silyl ether **143** in 90% yield. Its formation was confirmed by ^{1}H and ^{13}C NMR spectral analysis, which showed a typical proton multiplet at δ -0.0-0.07 (m, 6H) and a singlet at δ 0.87 (s, 9H) corresponding to methyl protons of silyl group in its ^{1}H NMR spectrum. Its ^{13}CNMR spectrum displayed typical carbon signals at δ 65.6 and -4.7, -5.2 due to methine and methyl carbons attached to silyl group (**Fig. 23**). Its IR spectrum displayed a strong vibrational stretching frequency at 1720 cm^{-1} due to –C=O of ester group.

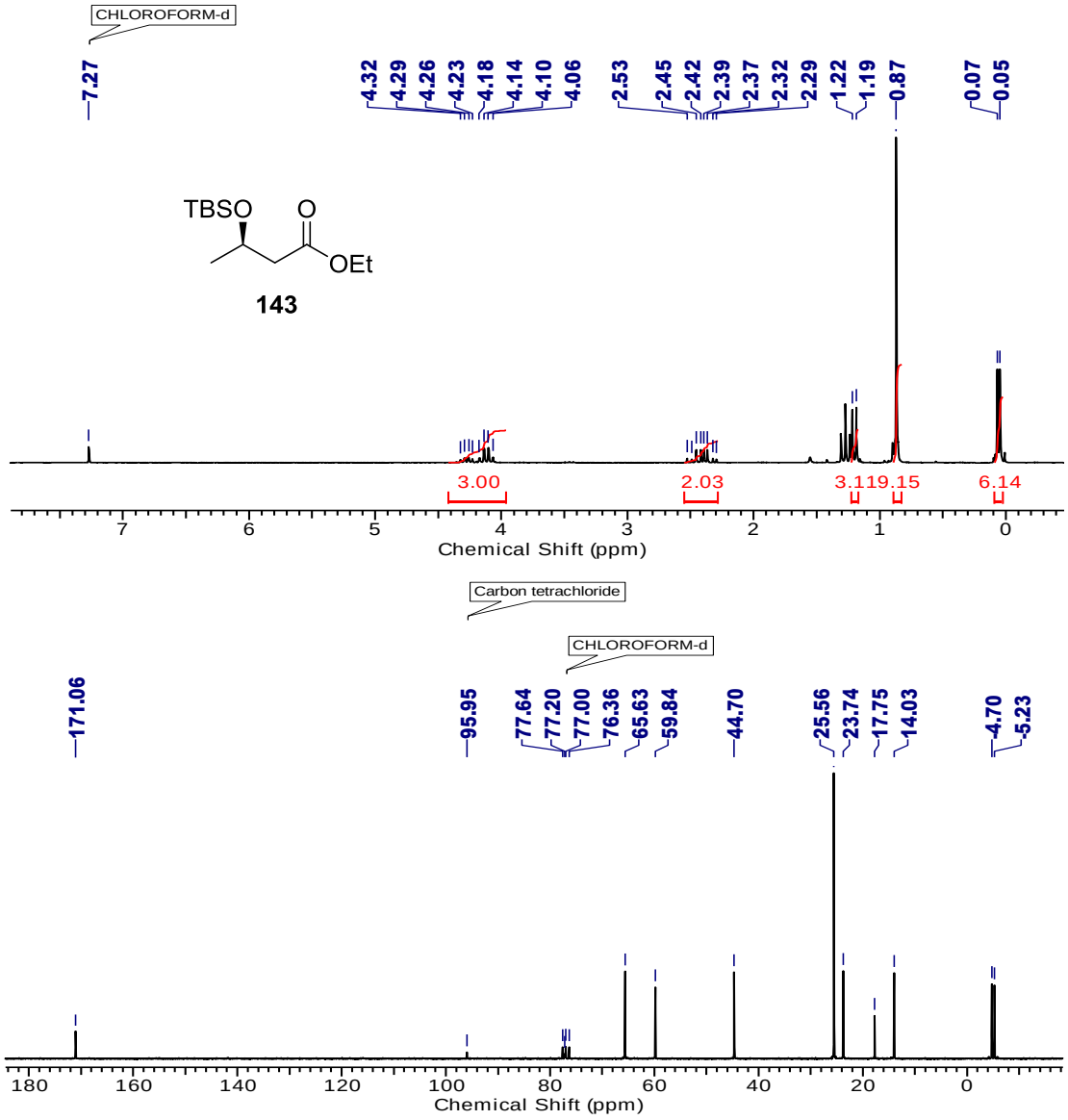


Fig. 23: ^{1}H and ^{13}C NMR spectra of ester **143**

The resulting ester **143** was subjected to reduction with DIBAL-H at 0 °C to provide the corresponding alcohol **144** in 85% yield. The ^{1}H NMR spectrum of **144** showed a multiplet at δ 3.60-3.79 (m, 2H) and a broad singlet at δ 2.51 (br.s, 1H) attributed to methylene protons attached to primary –OH group and –OH functionality respectively. It was further supported by a typical carbon signal at δ 60.3 due to methylene carbon attached to –OH group and also disappearance of –C=O carbon signal in its ^{13}C NMR

spectrum, confirming the formation of **144** (**Fig. 24**). Its IR spectrum displayed a strong vibrational stretching frequency at 3338 cm^{-1} due to –OH functionality.

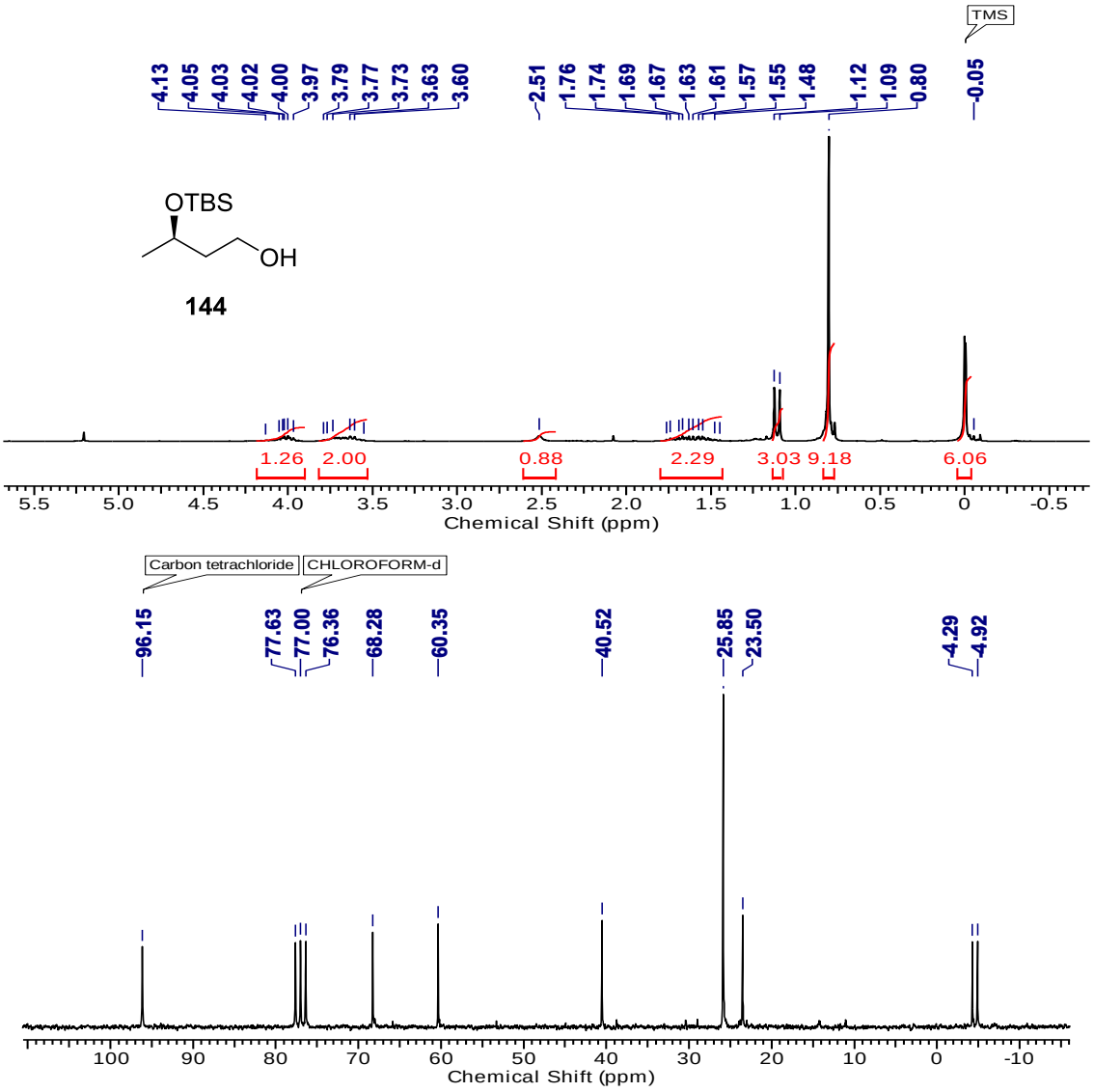


Fig. 24: ^{1}H and ^{13}C NMR spectra of alcohol **144**

Now, free primary hydroxyl group **144** was converted into its bromide under Appel reaction protocol (CBr_4, Ph_3P, CH_2Cl_2, 0 °C) providing alkyl bromide derivative **135** in 89% yield. Its formation was confirmed by the appearance of a multiplet at the shielded region δ 3.43-3.50 (m, 2H) for methylene proton attached to -Br group in its ^{1}H NMR spectrum. Further evidence was provided by its ^{13}C NMR spectrum, which showed a

shielding of methylene carbon signal from δ 60.3 to 30.4 due to the displacement of –OH by –Br group (**Fig. 25**).

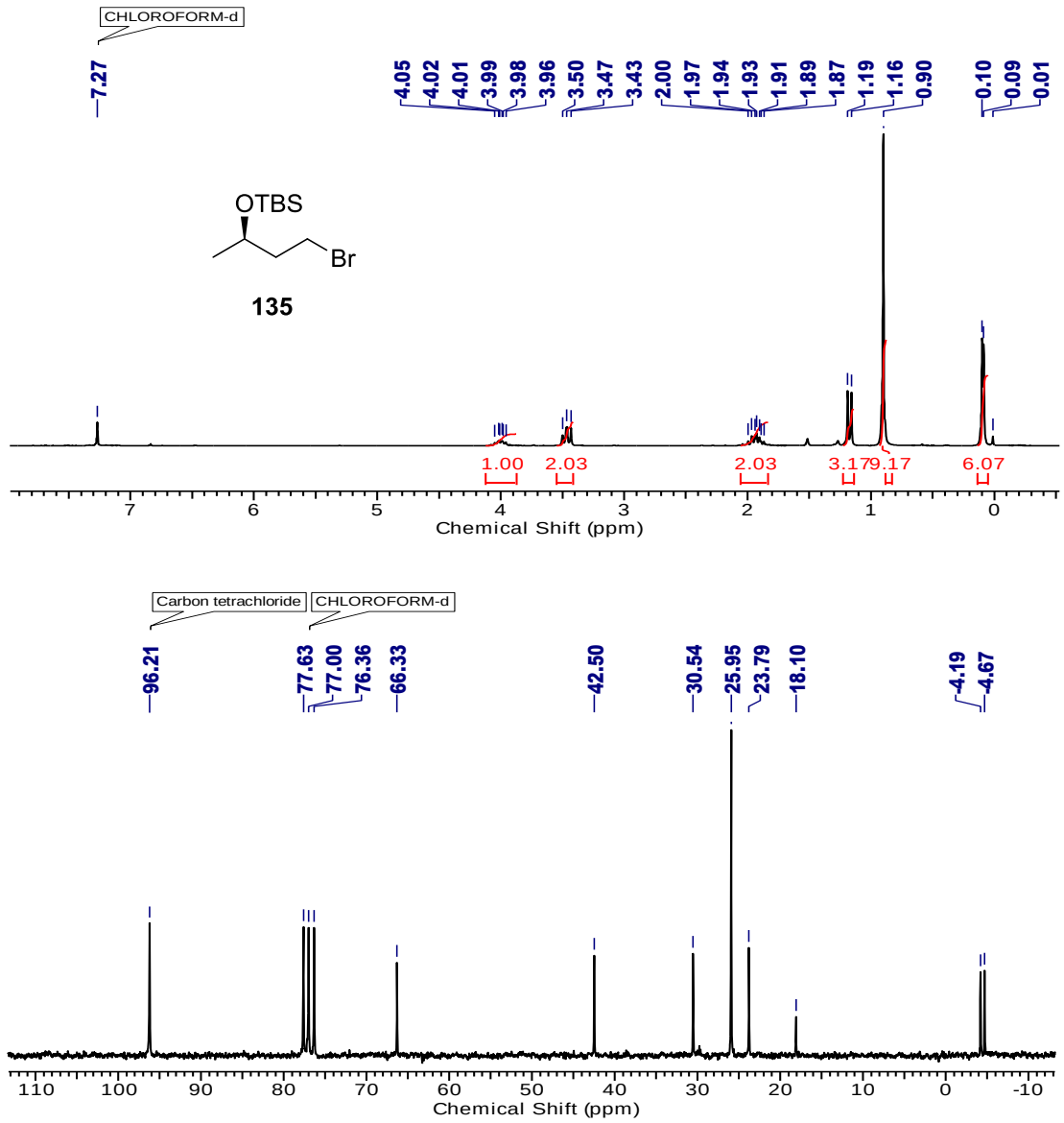
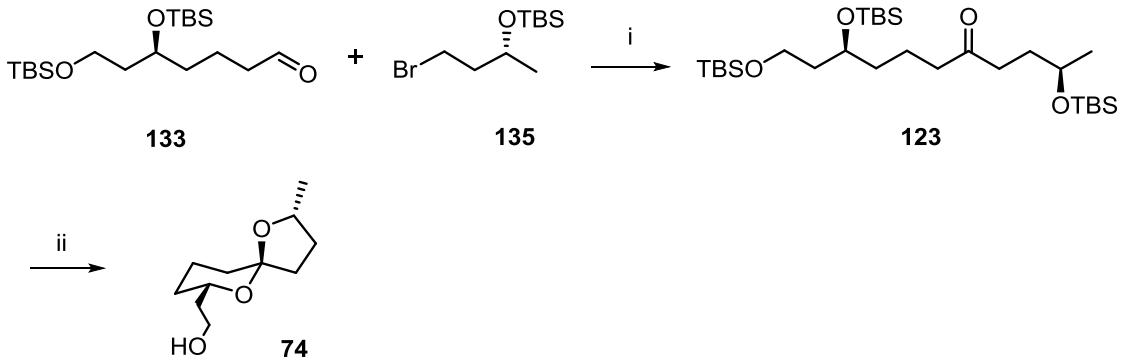


Fig. 25: ^{1}H and ^{13}C NMR spectra of alkyl fragment **135**

Both the fragments **133** and **135** were coupled under Grignard conditions that resulted in the formation of alcohol *in situ*, which was subsequently oxidized using IBX to furnish keto derivative **123** in 75% yield for two steps, without affecting the silyl ether functionality (**Scheme 25**).



Scheme 25: (i) (a) Mg, 1,2-dibromoethane, THF, 0 °C to rt, 5 h; (b) IBX, EtOAc, 60 °C, 2 h, 75 % over 2 steps; (ii) CSA (cat.), CH_2Cl_2, 0 °C, 2 h, 76%.

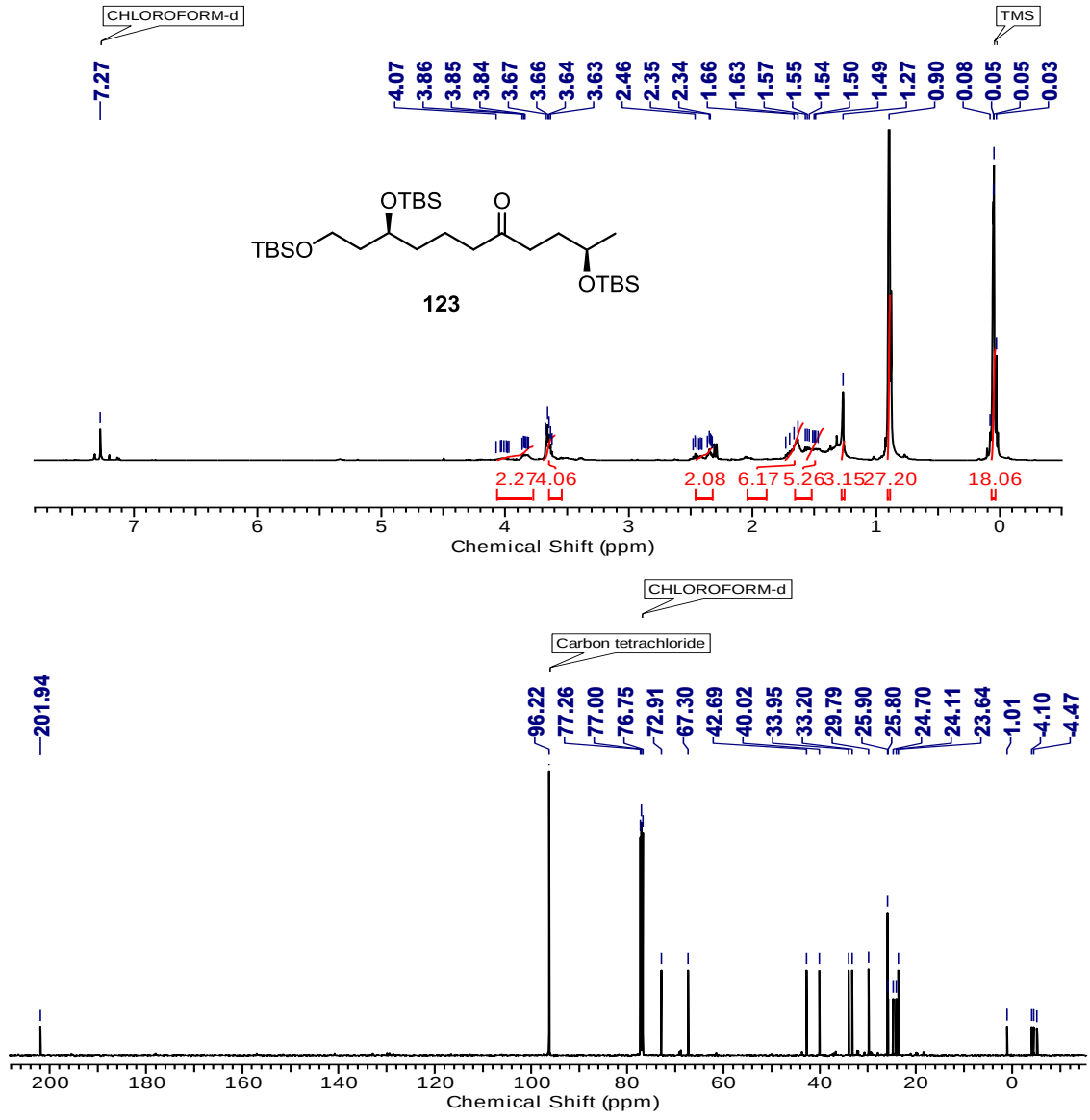


Fig. 26: ^{1}H and ^{13}C NMR spectra of **123**

The ^{1}H NMR spectrum of **123** showed a typical doublet at δ 1.47 (d, *J* = 6.6 Hz, 3H) due to methyl group and other signals at δ 0.90 (s, 27H) and 0.03-0.08 (m, 18H) are attributed to the three silyl groups. Further, its structure was supported by a characteristic carbon signal at δ 201.9 corresponding to carbonyl carbon in its ^{13}C NMR spectrum, which confirmed the formation of ketone **123** (**Fig. 26**). Also, its IR spectrum displayed a strong –C=O vibrational stretching frequency at 1713 cm^{-1} due to presence of keto group.

Finally, acid catalyzed cumulative deprotection of the three *tert*-butyldimethylsilyl ethers in keto derivative **123** followed by concomitant cyclization resulted in the formation of spiroketal moiety **74** in 76% yield (camphor sulfonic acid, dichloromethane, 0 °C). Its specific rotation value was in complete agreement with the literature value {$[\alpha]_D^{20}$ +65.2 (*c* 1.0, $CHCl_3$); lit.[21g] $[\alpha]_D^{20}$ +65.4 (*c* 1.0, $CHCl_3$)} (**Scheme 25**).

The ^{1}H NMR spectrum of spiroketal **74** showed two multiplets at δ 4.18-4.24 (m, 1H) and 4.01-4.05 (m, 1H) corresponding to methine protons of tetrahydrofuran ring, while its ^{13}C NMR spectrum displayed characteristic carbon signals at δ 106.2 and 62.2 accounting for spiro carbon and methylene carbon attached to –OH group respectively, confirming the formation of **74**. Its IR spectrum showed a strong vibrational stretching frequency at 3355 cm^{-1}due to the presence of –OH functionality (**Fig. 27**).

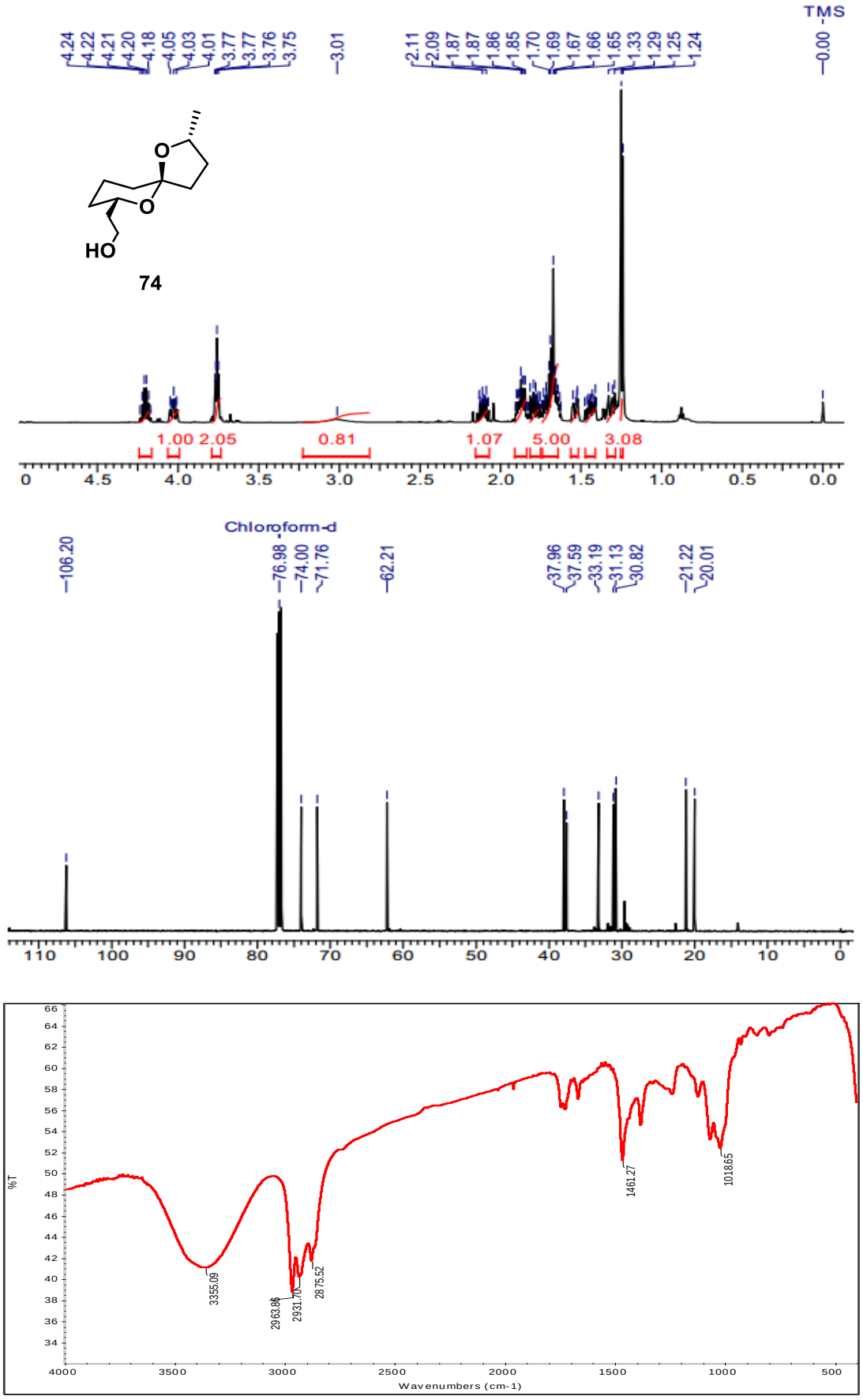
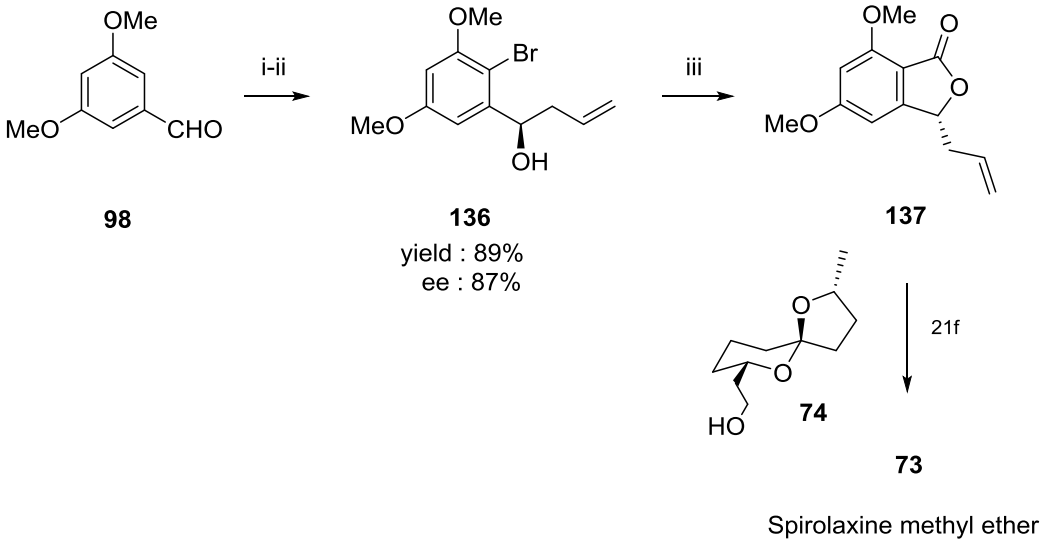


Fig. 27: ^{1}H, ^{13}C NMR and IR spectra of spiroketal **74**



Scheme 26: (i) NBS, CH_3CN:H_2O (4:1), rt, 4 h, 92%; (ii) (-)-Ipc_2(allyl)borane, Et_2O, -78 ^oC, 1 h then, 1N NaOH, 30% aq. H_2O_2, 89%, 87% ee; (iii) NaCN, CuBr, 1,10-phenothroline, DMF, 120 ^oC, 12 h, 88%.

Having synthesized spiroketal **74**, our next task was to undertake the preparation of the phthalide precursor **137**, which was crucial for the synthesis of spirolaxine methyl ether **73**. Recently we have developed a general protocol for the synthesis of phthalide unit by simple annulation using copper(I) bromide as catalyst and sodium cyanide as C1 source in a stoichiometric amount.[26] Application of this simple synthetic methodology was demonstrated in the synthesis of phthalide precursor **137**. Thus, regioselective *ortho* bromination of 3,5-dimethoxybenzaldehyde **98** gave 2-bromo-3,5-dimethoxybenzaldehyde followed by Brown allylation using (-)-Ipc_2B(allyl)borane at -78 ºC afforded bromoallylic alcohol **136** in excellent yield and good enantiomeric excess (89% yield; 87% ee).

The formation of homoallylic alcohol **136** was confirmed from ^{1}H NMR spectrum, which displayed olefinic proton signals at δ 5.90 (td, J = 17.1, 7.1 Hz, 1H) and 5.15-5.24 (m, 2H) and 5.09-5.15 (m, 1H) corresponding to methine and methylene protons of olefin respectively. Also, a broad signal at δ 2.14 (d, J = 4.5 Hz, 1H) showed the

presence of secondary -OH group. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 134.5 and 118.4 due to olefinic carbons and another at δ 72.0 due to methine carbon attached to –OH group respectively (**Fig. 28**).

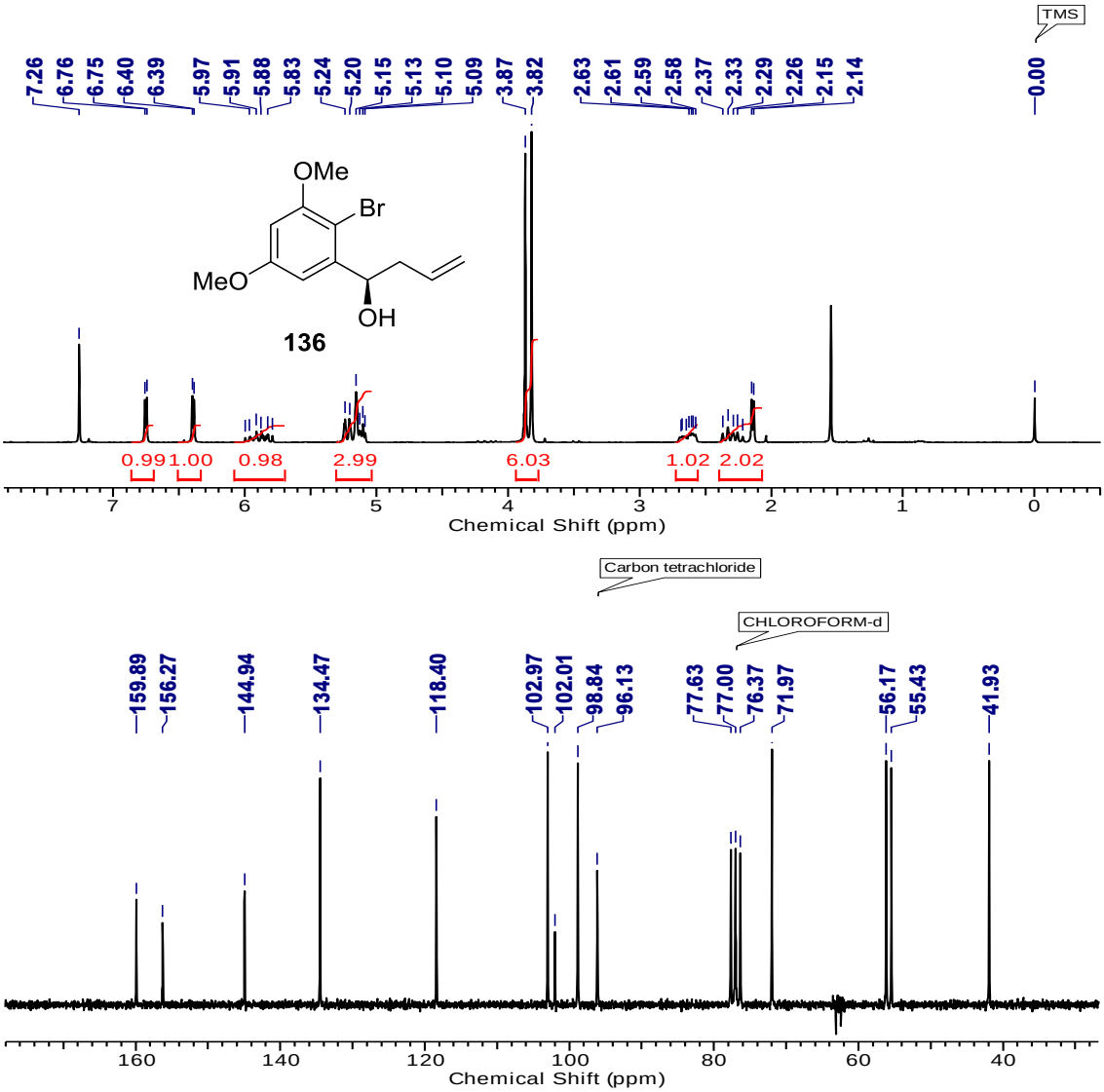


Fig. 28: ^{1}H and ^{13}C NMR spectra of allylic alcohol **136**

Cu(I) mediated displacement of bromide with cyanide was achieved using NaCN as C1 source followed by nitrile assisted *in situ* lactonization furnished the cyclized phthalide moiety **137** with excellent yield (88%). Its specific rotation was in complete agreement with literature value [$[\alpha]_D^{20}$ +31.5 (*c* 1.0, $CHCl_3$); lit.[21h] $[\alpha]_D^{20}$ +31.5 (*c* 1.37, $CHCl_3$)]. The formation of phthalide **137** was ascertained by its ^{1}H NMR spectrum, which

showed a typical triplet at δ 5.31 (t, J = 5.8 Hz, 1H) due to methine proton of phthalide unit. Further, it was supported by ^{13}C NMR spectrum, which showed characteristic carbon signals at δ 167.8 and 78.7 corresponding to –C=O and methine carbons of lactone respectively (**Fig. 29**). Its IR spectrum displayed a strong vibrational stretching frequency at 1750 cm^{-1} due to –C=O group of lactone unit.

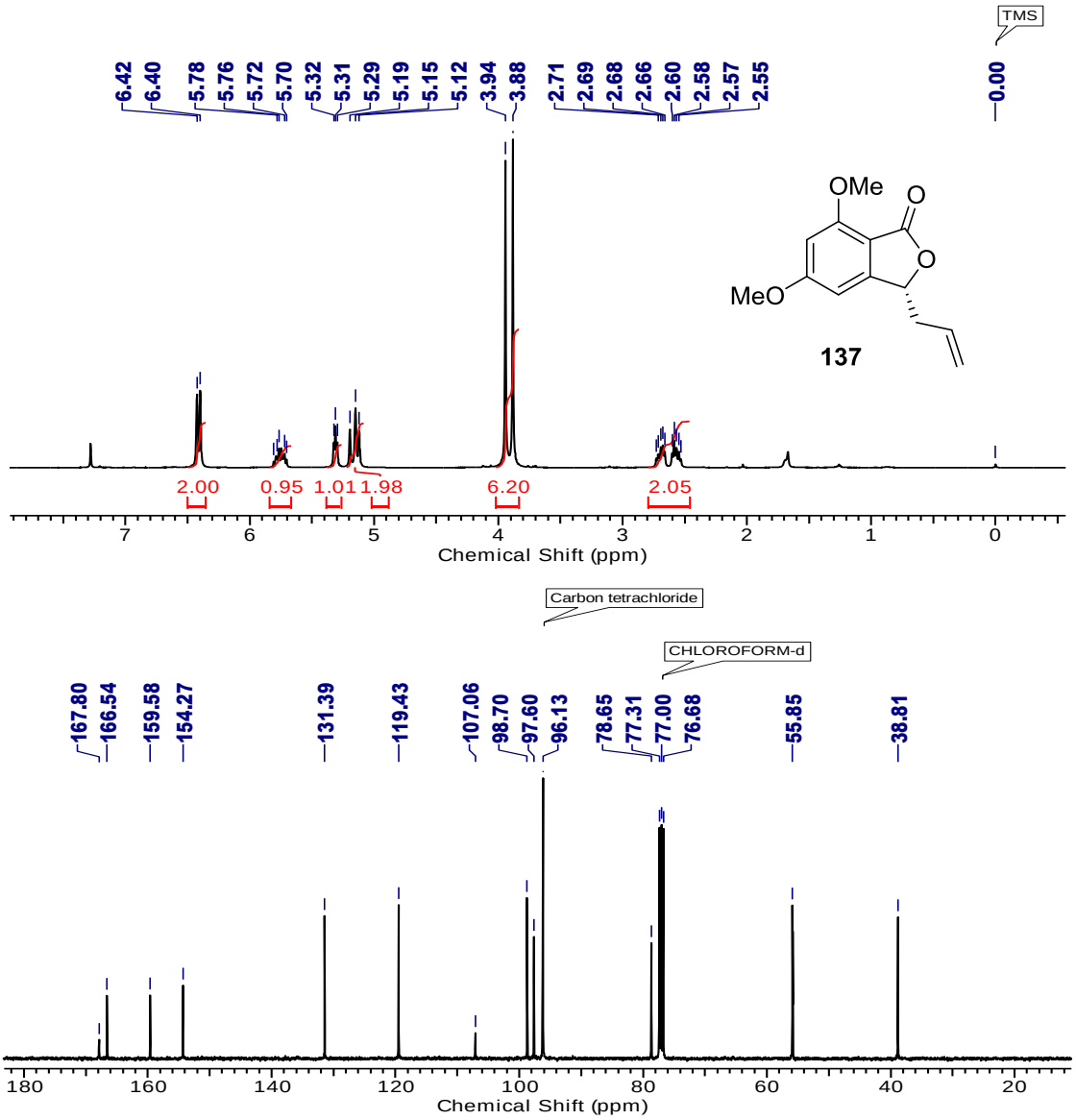


Fig. 29: ^{1}H and ^{13}C NMR spectra of phthalide **137**

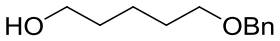
Finally, conversion of spirokatal **74** to spirolaxine methyl ether **73** *via* alkyl–alkyl Suzuki coupling has already been reported in the literature (**Scheme 26**).[21g]

2.2.4 Conclusion

A convergent enantioselective formal synthesis of *anti-Helicobacter pylori* agent (+)-spirolaxine methyl ether **73** has been achieved. The key chiral step for the introduction of stereochemistry in phthalide **137** and spiroketal portions **74** has been established by Brown allylation and Noyori's asymmetric reduction (96% ee) protocol. The carbon framework of spiroketal was constructed from commercially available 1,5-pentanediol (**116**).

2.2.5 Experimental Section

5-(Benzyloxy)pentan-1-ol (116)

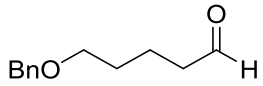


To a stirred suspension of 60% dispersion of NaH in mineral oil (2.30 g, 57.69 mmol) was added a solution of 1,5-pentanediol **138** (5.0 g, 48.07 mmol) in dry DMF (150 mL) slowly over a period of 15 min at 0 °C. Then the reaction mixture was stirred at room temperature for 1 h followed by addition of benzyl bromide (5.75 mL, 48.07 mmol) over 15 min and stirred for additional 2 h at the same temperature. The reaction mixture was quenched with ice cold water. The crude mixture was extracted with ethyl acetate (2 x 30 mL) and the organic layer was washed with brine (3 times) and dried over anhydrous Na_2SO_4 and concentrated under *vacuum*. The residue was purified by silica gel column chromatography using pet ether-ethyl acetate (7:3) as eluent give benzyl ether **116**.

Yield: 89% (7.87 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 714, 1028, 1072, 1116, 1177, 1278, 1316, 1388, 1453, 2865, 2938, 3064, 3372; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.47-1.70 (m, 6H), 3.47 (t, *J* = 6.3 Hz, 2H), 3.62 (t, *J* = 6.1 Hz, 2H), 4.49 (s, 2H), 7.31

(s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.3, 29.3, 32.3, 62.2, 70.2, 72.8, 127.5, 128.2, 138.3; Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.34%.

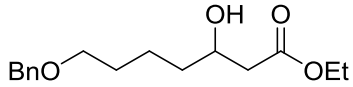
5-(Benzyloxy)pentanal (139)



To a stirred solution of benzylated alcohol **116** (5.0 g, 25.77 mmol) in CH_2Cl_2 (80 mL) at rt was added TEMPO (40 mg, 2.57 mmol) and reaction the mixture was stirred for 10 min, followed by the addition of iodobis(acetoxy)benzene (9.13 g, 28.35 mmol). The mixture was stirred for additional 1 h and then diluted with CH_2Cl_2 (20 mL). The mixture was then washed with sat. aq $Na_2S_2O_3$ (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo* followed by purification with silica gel column chromatography using pet ether: ethyl acetate (20:1) as eluent afforded pure aldehyde **139**.

Yield: 95% (4.70 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 753, 1039, 1098, 1106, 1242, 12.75, 1454, 1710, 2941; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.51-1.85 (m, 5H), 2.34-2.61 (m, 2H), 3.47 (t, *J* = 5.9 Hz, 2H), 4.48 (s, 2H), 7.26-7.43 (m, 5H), 9.75 (t, *J* = 1.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.9, 29.0, 43.4, 69.6, 72.8, 127.5, 128.2, 130.1, 138.3, 201.8; Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.98; H, 8.38%.

Ethyl 7-(benzyloxy)-3-hydroxyheptanoate (140)

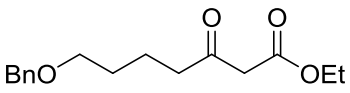


To a pre-cooled (0 °C), well stirred mixture of aldehyde **139** (4 g, 20.83 mmol), Zn dust (2.73 g, 41.66 mmol) and ethyl bromoacetate (4.61 mL, 41.66 mmol) in 70 mL of dry benzene was added a saturated solution of NH_4Cl (8 mL). The mixture was stirred for 4

h at ambient temperature until the aldehyde was totally consumed (monitored by TLC). The mixture was then filtered and the precipitate was thoroughly washed with THF (3 x 10 mL). THF was then removed under *vacuo* and the remaining solution extracted with EtOAc. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. Further it was purified by column chromatographic separation with petroleum ether/ethyl acetate (8:2) to afford hydroxyester **140**.

Yield: 90% (6.56 g), yellow colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1026, 1097, 1161, 1276, 1720, 2930, 3441; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.43-1.70 (m, 6H), 2.26-2.55 (m, 2H), 3.00 (br. s, 1H), 3.47 (t, *J* = 6.2 Hz, 2H), 3.96-4.02 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.49 (s, 2H), 7.17-7.51 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 22.2, 29.6, 36.3, 41.3, 60.6, 67.8, 70.2, 72.9, 127.5, 127.6, 128.3, 129.6, 132.8, 138.6, 172.9; **Anal. Calcd for** $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. found: C, 68.52; H, 8.62%.

Ethyl 7-(benzyloxy)-3-oxoheptanoate (132)

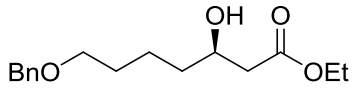


To a well-stirred solution of alcohol ester **140** (4.0 g, 17.85 mmol) in ethyl acetate (60 mL), 2-iodoxybenzoic acid (7.5 g, 26.78 mmol) was added in one portion. The reaction mixture was then stirred for 1 h at room temprature. After completion of the reaction (monitored by TLC), it was diluted with water and diethyl ether. Subsequent filtration (diethyl ether eluent) and washing the filtrate with water, brine, followed by drying over anhydrous Na_2SO_4, and removal of the solvent under reduced pressure gave a crude

product, which upon chromatographic separation with pet ether/ethyl acetate (9:1 v/v) result in pure β-keto ester **132**.

Yield: 87% (4.31 g), light yellow colored liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 757, 1216, 1717, 1736, 3019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.58-1.81 (m, 4H), 2.66 (t, *J* = 6.7 Hz, 2H), 3.40 (s, 2H), 3.46 (t, *J* = 5.9 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.48 (s, 2H), 7.18-7.44 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 20.2, 28.1, 42.6, 49.2, 61.2, 69.8, 72.8, 127.4, 127.5, 127.8, 128.3, 129.4, 138.4, 167.1, 202.6; **Anal. Calcd for** $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.04; H, 7.99%.

(*R*)-ethyl 7-(benzyloxy)-3-hydroxyheptanoate (141)

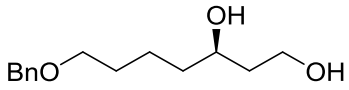


β-Keto ester **132** (4 g, 17.98 mmol) and dry methanol (25 mL) were mixed and deoxygenated with flowing nitrogen for five minutes. The catalyst [(*R*)-$Ru(BINAP)Cl_2]_2 \cdot NEt_3$ (50 mg, 0.1 mol %) was added along with 2N HCl (0.05 mL, 0.1 mol %). The mixture was then transferred to a Parr reactor apparatus and flushed by evacuating and refilling with hydrogen several times. The apparatus was heated at 50 ^oC with stirring under 100 psi of hydrogen for 16 h. After completion of reaction (monitored by TLC), the reaction mixture was cooled and concentrated under reduced pressure. Further, the residue was purified by column chromatographic purification using pet ether/ethyl acetate (8:2 v/v) to afford pure (*R*)-β-hydroxy ester **141**.

Yield: 95% (3.82 g), colorless oil; $[\alpha]_D^{20}$ +34.5 (c, 1 $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1026, 1097, 1161, 1276, 1720, 2930, 3441; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.41-1.70 (m, 6H), 2.39-2.46 (m, 2H), 2.99 (s, 1H), 3.47 (t, *J* = 6.2 Hz, 2H), 3.91-3.02 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.49 (s, 1H), 7.26-7.34 (m, 5H); **^{13}C**

NMR (50 MHz, $CDCl_3$): δ 14.2, 22.2, 29.6, 36.3, 41.3, 60.6, 64.8, 67.8, 70.2, 72.9, 127.6, 128.3, 129.6, 138.6; **Anal. Calcd for** $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. found: C, 68.53; H, 8.62%; **HPLC:** 96% ee (Chiralcel OJ-H column, *n*-hexane: *i*PrOH, 97:03, 0.5 mL/min) retention time 12.530 (98.35%) and 15.123 (1.65%).

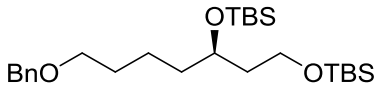
(*R*)-7-(Benzyloxy)heptane-1,3-diol (119)



To a stirred solution of ester **141** (3 g, 10.71 mmol) in dry THF (30 mL) was added 6.3 mL of $LiAlH_4$ (0.58 g, 16.07 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 3 h. After the reaction was completed (monitored by TLC), it was warmed to rt, diluted with ice cold water slowly, and filtered over celite. The organic phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organic phase was then washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure and column chromatographic purification with petroleum ether:ethyl acetate (6:4 v/v) afforded diol **119.**

Yield: 90% (2.3 g), colorless liquid; $[\alpha]_D^{20}$ -1.7 (*c* 1, $CHCl_3$); (**IR** ($CHCl_3$, cm^{-1}): υ_{max} 611, 698, 739, 908, 1098, 1205, 1453, 1646, 2861, 2936, 3383; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26-1.78 (m, 8H), 2.48 (br. s, 2H), 3.29-3.60 (m, 3H), 3.82 (t, *J* = 5.2 Hz, 2H), 4.49 (s, 2H), 7.19-7.45 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 22.2, 28.7, 29.6, 36.3, 41.3, 60.6, 64.8, 67.7, 67.8, 70.2, 72.9, 127.5, 127.6, 128.3, 129.6, 132.8, 138.6, 172.9; **Anal. Calcd for** $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. found: C, 70.52; H, 9.31%.

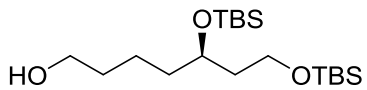
(*R*)-DiTBS derivative (120)



To a solution of diol **119** (2 g, 8.40 mmol) in dry CH_2Cl_2 (10 ml) was added imidazole (2.28 g, 33.31 mmol) under nitrogen atmosphere followed by *tert*-butyldimethysilyl chloride (3.8 g, 25.2 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. After completion of reaction (monitored by TLC), it was quenched with saturated NH_4Cl solution and the resulting mixture was extracted with ether (2 x 10 mL). The combined extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Further purification was done by silica gel column chromatography using pet ether-ethyl acetate (20:1) as eluent to afford pure disilyl ether **120**.

Yield: 85% (3.33 g), colorless liquid; $[\alpha]_D^{20}$ +5.4 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 836, 1099, 1216, 1256, 2857, 2930, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.03 (s, 12H), 0.90 (d, *J* = 1.4 Hz, 18H), 1.31-1.52 (m, 5H), 1.64 (q, *J* = 6.6 Hz, 4H), 3.47 (t, *J* = 6.4 Hz, 2H), 3.66 (t, *J* = 6.6 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 1H), 4.50 (s, 2H), 7.21-7.41 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, -4.5, -4.3, 18.1, 18.3, 21.9, 26.0, 30.0, 37.3, 40.1, 59.8, 69.1, 70.3, 72.9, 127.4, 127.5, 128.3, 138.7; **Anal. Calcd for** $C_{26}H_{50}O_3Si_2$: C, 66.89; H, 10.80. found: C, 66.88; H, 10.81%.

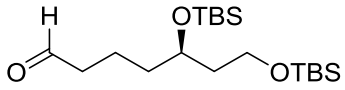
(*R*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)heptan-1-ol (121)



To a mixture of benzyl ether **120** (3 g, 6.42 mmol) in EtOAc (20 mL) was added 10% $Pd(OH)_2$ on carbon (50 mg) and it was stirred under H_2 (1 atm, ballon) at 25 °C. After completion of the reaction (monitored by TLC), it was filtered through Celite (EtOAc eluent) and the solvent was evaporated under reduced pressure to afford crude residue, which was further purified by column chromatography (pet ether: ethyl acetate 7:3 v/v) to give alcohol **121** as a slightly yellow colored oil.

Yield: 80% (1.93 g), yellow colorled oil; $[\alpha]_D^{20}$ +7.1 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 701, 738, 774, 835, 1112, 1256, 1427, 1471, 2858, 2930, 3346 br (OH); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02-0.12 (m, 12H), 0.90 (s, 18H), 1.38-1.65 (m, 8H), 3.65 (td, *J* = 6.4, 3.0 Hz, 4H), 3.82 (t, *J* = 5.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, -4.6, -4.4, 18.1, 18.3, 21.3, 26.0, 32.9, 37.1, 40.0, 59.9, 62.6, 69.1; **Anal. Calcd for** $C_{10}H_{11}N_3O$: C, 43.48; H, 5.86. found: C, 43.50; H, 5.85%.

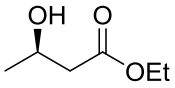
(*R*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)heptanal (133)



To a stirred solution of alcohol **121** (1.5 g, 3.98 mmol) in CH_2Cl_2 (15 mL) at room temperature was added TEMPO (62 mg, 0.98 mmol) and the reaction mixture was further stirred followed by the addition of iodobis(acetoxy)benzene (1.41 g, 4.37 mmol). The mixture was stirred for additional 1 h and then diluted with CH_2Cl_2 (5 mL). It was washed with saturated aq. $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 mL) and dried over anhyd. Na_2SO_4. Removal of the solvent in *vacuo* followed by silica gel column chromatography of the resulting residue using pet ether: ethyl acetate (20:1) as eluent afforded aldehyde **133**.

Yield: 88% (1.31 g), colorless oil; $[\alpha]_D^{20}$ +2.1 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1455, 1715, 2948; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (d, *J* = 1.3 Hz, 12H), 0.88 (s, 18H), 1.46-1.74 (m, 6H), 2.34-2.51 (m, 2H), 3.64 (t, *J* = 6.4 Hz, 2H), 3.84 (quintet, *J* = 5.7 Hz, 1H), 9.76 (t, *J* = 1.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, -4.6, -4.4, 18.1, 18.3, 21.3, 26.0, 32.9, 37.1, 40.0, 62.6, 69.1, 202.2; **Anal. Calcd for** $C_{19}H_{42}O_3Si_2$: C, 60.90; H, 11.30. found: C, 60.92; H, 11.30%.

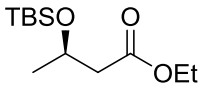
(*R*)-Ethyl (-)-3-hydroxybutyrate (142)



Ethyl acetoacetate **134** (3 g, 23.05 mmol) and dry methanol (25 mL) were mixed and deoxygenated with flowing nitrogen for some time. The catalyst [(*R*)-$Ru(BINAP)Cl_2]_2{\cdot}NEt_3$ (24 mg, 0.1 mol %) was added along with 2N HCl (0.04 mL, 0.1 mol %) carefully. The mixture was then transferred to a standard Parr reactor apparatus and flushed with hydrogen several times. The apparatus was charged with H_2 (100 psi) and heated at 50 ^oC with stirring for 14 h. After completion of reaction, it was cooled and concentrated under reduced *vacuo*. The crude was purified by column chromatographic purification with pet ether/ethyl acetate (9:1 v/v) as eluent to obtain pure (*R*)-alcohol **142**.

Yield: 94% (2.86 g), colorless liquid; $[\alpha]_D^{20}$ -46.0 (*c* 1.0, $CHCl_3$) {lit.[27] $[\alpha]_D^{20}$ -46.0 (*c* 1.0, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1458, 1636, 1734, 2935, 2978, 3441; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.21-1.31 (m, 6H), 2.42-2.46 (m, 2H), 3.20 (d, *J* = 3.8 Hz, 1H), 4.12 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 43.2, 60.5, 64.2, 172.5; **Anal.** Calcd for $C_6H_{12}O_3$ requires C, 54.53; H, 9.15; found C, 54.56; H, 9.16%.

Ethyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butanoate (143)

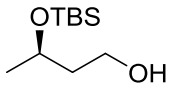


To a solution of alcohol **142** (2 g, 15.13 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added imidazole (1.23 g, 18.16 mmol) and *tert*-butyldimethylsilyl chloride (3.42 g, 22.69 mmol). The reaction mixture was then stirred at 0 ^oC for 1 h. After completion of reaction (monitored by TLC), it was diluted 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) to give silyl ether **143**.

Yield: 90% (3.35 g), colorless liquid; $[\alpha]_D^{20}$ -26.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1097, 1160, 1276, 1720, 2938; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.06 (d, *J* = 4.6 Hz, 6H), 0.87 (s, 9H), 1.20 (d, *J* = 6. 1 Hz, 3H), 2.28-2.55 (m, 2H), 4.05-4.19 (m, 2H), 4.21-4.34 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, -4.7, 14.0, 17.7, 23.7, 25.6, 44.7, 59.8, 65.6, 95.9, 171.1; **Anal. Calcd for** $C_{12}H_{26}O_3Si$: C, 58.49; H, 10.64. found: C, 58.50; H, 10.67%.

(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)butan-1-ol (144)

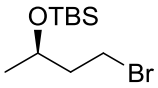


To a stirred solution of silyl ether **143** (2 g, 8.11 mmol) in dry THF (20 mL) was added 1 M DIBAL-H in THF (6.1 mL, 8.11 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h. After the reaction was complete (monitored by TLC), it was warmed to rt and diluted with a saturated solution of Rochelle salt, and stirred for further 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4 and concentrated. Crude residue was purified by column chromatography with pet ether/ethyl acetate (9:1 v/v) as eluent to afford in pure alcohol **144**.

Yield: 85% (1.41 g), colorless liquid; $[\alpha]_D^{20}$ -22.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1050, 1099, 1225, 2857, 2930, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (d, *J* = 2.4 Hz, 6H), 0.90 (s, 9H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.83-2.06 (m, 2H), 3.41-3.55 (m, 2H), 3.87-4.12 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.2, 18.1, 23.8, 25.9, 30.5,

42.5, 66.3; **Anal. Calcd for** $C_{10}H_{24}O_2Si$: C, 58.77; H, 11.84. found: C, 58.75; H, 11.87%.

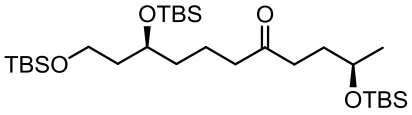
(*R*)-((4-Bromobutan-2-yl)oxy)(*tert*-butyl)dimethylsilane (135)



To a solution of triphenylphosphine (1.92 g, 7.33 mmol) in CH_2Cl_2 (20 mL) was added bromotrichloromethane (0.953 g, 7.33 mmol), and the resulting solution was stirred for 20 min. at rt. Thereafter, alcohol **144** (1 mg, 4.89 mmol) was added to this mixture and the resulting solution stirred for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and extracted with water (3 x 10 mL). The combined organic layer was washed with aq. NaOH (5 mL) and subsequently with conc. HCl (3 mL conc. HCl in 7 mL of H_2O). The organic layer was then dried over anhyd. Na_2SO_4 and concentrated and purified over silica gel packed column (pet ether: ethyl acetate 20:1) to give alkyl bromide **135**.

Yield: 89% (1.16 g), colorless liquid; $[\alpha]_D^{20}$ -30.1 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1050, 1099, 1225, 2857, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.87-4.12 (m, 1H), 3.41-3.55 (m, 2H), 1.83-2.06 (m, 2H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.09 (d, *J* = 2.4 Hz, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.2, 18.1, 23.8, 25.9, 30.5, 42.5, 66.3; **Anal. Calcd for** $C_{10}H_{23}BrOSi$: C, 44.94; H, 8.67. found: C, 44.96; H, 8.68%.

Keto derivative (123)

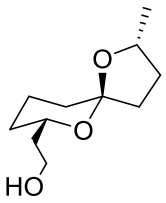


To a suspension of Mg (0.130 g, 1.99 mmol) in anhyd THF (5 mL) at 25 °C in a RB flask equipped with a condenser (cool water circulation), was added alkyl bromide **135**

(0.355 g, 1.99 mmol) in a drop wise manner and the entire mixture was allowed to stir for 0.5 h. Then the mixture was cooled to 0 °C followed by the addition of aldehyde **133** (0.5 g, 1.33 mmol) in THF (3 mL). The reaction mixture was warmed to 25 °C and stirred for 1 h. On completion, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to yield crude product, which was treated with iodoxy benzoic acid (0.55 g, 1.99 mmol) in ethyl acetate (10 mL) at room temperature without further purification. The reaction mixture was stirred for 3 h and then diluted with EtOAc (5 mL). The mixture was filtered and extracted with ethyl acetate and water (3 x 5 mL). Combined organic layer was washed with brine, dried (anhyd. Na_2SO_4), concentrated and purified by column chromatography (pet ether: EtOAc 9:1 as an eluent) to afford pure keto derivative **123**.

Yield: 75%, (0.561 g), colorless viscous; $[\alpha]_D^{20}$ -1.1 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 938, 1005, 1094, 1254, 1376, 1463, 1713, 2857, 2930, 2954, 3416; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (m, 18H), 0.90 (s, 27H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.42-1.56 (m, 5H), 1.58-1.74 (m, 6H), 2.32-2.38 (m, 1H), 2.43 (dd, *J* = 13.3, 7.8 Hz, 1H), 3.59-3.69 (m, 4H), 3.77-3.92 (m, 2H), 3.92-4.07 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, -4.5, -4.1, 1.0, 23.6, 24.1, 24.7, 25.8, 25.9, 29.8, 33.2, 33.9, 40.0, 42.7, 67.3, 72.9, 76.7, 77.3, 96.2, 201.9; **Anal. Calcd for** $C_{29}H_{64}O_4Si_3$: C, 62.08; H, 11.50. found: C, 62.10; H, 11.55%.

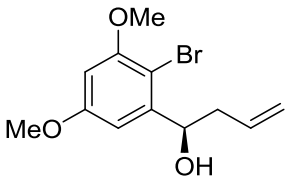
2-((2*R*,5*R*,7*S*)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl)ethan-1-ol (74)



To a stirred solution of keto derivative **123** (0.500 g, 0.89 mmol) in dichloromethane (10 mL) at 0 °C under an atmosphere of nitrogen was added camphorsulfonic acid (0.433 g, 1.87 mmol). After stirring for 2 h, the mixture was filtered through a pad of celite, and the solvent removed under reduced pressure. Column chromatographic purification using pet ether/ethyl acetate (6:3) as eluent afforded the spiroketal **74**.

Yield: 76% (0.135 g), colorless oil; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ +65.2 (*c* 1, $CHCl_3$), {lit.[21g] $[\alpha]_D^{20}$ +65.4 (*c* 0.76, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1016, 1461, 2875, 2931, 2963, 3355; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25 (d, *J* = 5 Hz, 3H), 1.27-1.37 (m, 1H), 1.40-1.48 (m, 1H), 1.51-1.56 (m, 1H), 1.62-1.93 (m, 8H), 2.04-2.18 (m, 1H), 3.03 (br. s, 1H), 3.72-3.80 (m, 2H), 4.03 (tq, *J* = 10.1, 5.2 Hz, 1H), 4.03 (sextet, *J* = 10 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.1, 21.2, 30.8, 31.1, 33.2, 37.6, 38.0, 62.2, 71.8, 74.0, 106.2; **Anal. Calcd for** $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. found: C, 65.99; H, 10.09%.

(*R*)-1-(2-Bromo-3,5-dimethoxyphenyl)but-3-en-1-ol (136)

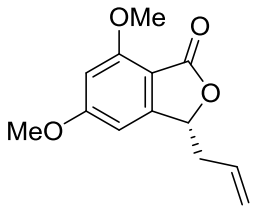


To a cooled mixture of (-)-Ipc_2(allyl)borane (2.92 g, 8.97 mmol) in dry diethyl ether (15 mL) at -75 °C, a solution of 2-bromo-3,5-dimethoxybenzaldehyde **98** (2 g, 8.16 mmol) in diethyl ether (20 mL) was added dropwise over 20 min *via* syringe (maintaining the temperature below -70 °C). The resulting mixture was stirred vigorously at -75 °C for 1.5 h and warmed to room temperature over 1 h. A solution of 3M NaOH (4.7 mL) and 30% aq. H_2O_2 (6 mL) was carefully added *via* the dropping funnel, keeping the temperature below 15 °C, followed by addition of saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was stirred for 10 h at the same temperature to completely hydrolyze boronate ester product. Organic phase was then diluted with diethyl ether,

extracted with the same solvent (3 x 20 mL) and combined organic layers were washed with brine (2 x 10 mL). The resulting layers then dried over anhyd. Na_2SO_4 and concentrated by rotary evaporation to afford light yellow oil which was purified by column chromatography with pet ether/ethyl acetate (9:1) to provide pure homoallylic alcohol **136**.

Yield: 89%, (2.08 g), colorless oil; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ -57.4 (*c* 1, $CHCl_3$) {lit.[21h] $[\alpha]_D^{20}$ -57.5 (*c* 3.40, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 838, 919, 1022, 1071, 1200, 1431, 1589, 2839, 2939, 3435 br (OH),; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.07-2.40 (m, 2H), 2.56-2.72 (m, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 5.04-5.31 (m, 3H), 5.90 (td, *J* = 17.1, 7.1 Hz, 1H), 6.39 (d, *J* = 2.8 Hz, 1H), 6.75 (d, *J* = 2.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 41.9, 55.4, 56.2, 72.0, 98.8, 102.0, 103.0, 118.4, 134.5, 144.9, 156.3, 159.9; **Anal. Calcd for** $C_{12}H_{15}BrO_3$: C, 50.19; H, 5.27. found: C, 50.20; H, 5.28%.

(*R*)-3-Allyl-5,7-dimethoxyisobenzofuran-1(3*H*)-one (137)



To a stirred solution of bromoallylic alcohol **136** (1 g, 3.48 mmol) in dry DMF (15 mL) were added NaCN (0.187 g, 3.82 mmol), CuBr (5 mg, 0.34 mmol) and 1,10-phenanthroline (7 mg, 0.34 mmol). The reaction mixture was then heated to 120 °C under N_2 for 10 h (monitored by TLC). The reaction mixture was then cooled to room temperature and excess cyanide was quenched with aqueous $NaClO_2$, diluted with water (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The aqueous layer after extraction was poured into aqueous $KMnO_4$ solution and then disposed off. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure to afford crude residue which was purified by column chromatography [silica gel (230–400 mesh) and pet ether:EtOAc (7:3) as an eluent] to obtain the cyclized phthalide moiety **137**.

Yield: 88% (72 mg), colorless solid; **mp**: 95-98 °C, lit. [21h] mp: 94-96 °C; [$[\alpha]_D^{20}$ +31.5 (*c* 1.0, $CHCl_3$); lit.[21h] $[\alpha]_D^{20}$ +31.5 (*c* 1.37, $CHCl_3$)].; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 839, 1030, 1159, 1221, 1332, 1460, 1615, 1750, 2948; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.46-2.63 (m, 1H), 2.63-2.79 (m, 1H), 3.88 (s, 3H), 3.94 (s, 3H), 5.08-5.22 (m, 2H), 5.31 (t, *J* = 5.8 Hz, 1H), 5.67-5.84 (m, 1H), 6.40 (s, 1H), 6.42 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.8, 55.8, 55.9, 97.6, 98.7, 107.1, 119.4, 131.4, 154.3, 159.6, 166.5, 167.8; **Anal. Calcd for** $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. found: C, 66.68; H, 6.05%.

2.2.6 References

1 (a) Endo, A. *J. Med. Chem.*, **1985**, *28*, 401; (b) Vega, L.; Crundy, S. *J. Am. Med. Assoc*., **1987**, *257*, 33 and references cited therein.

2 Goldstein, J. L.; Brown, M. S. *Annu. Rev. Biochem*., **1977**, *46*, 897.

3 (a) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J. Jr.; Deana, A. A.; Gilfilan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.*, **1985**, *28*, 347; (b) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J. Jr.; Deana, A. A.; Evans, B. E.; Gilfilan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. *J. Med. Chem*., **1986**, *29*, 170; (c) Yadav, V. K.; Kapoor, K. K. *Ind. J. Chem.*, **1996**, *35B*, 1125.

4 (a) Akiyama, K.; Aoki, H.; Kikuzaki, T.; Okuda, A.; Lajis, N. H.; Nakatani, N. *J. Nat. Prod*., **2006**, *69*, 1637; (b) Matsuda, H.; Ando, S.; Kato, T.; Morikawa, T.; Yoshikawa, M. *Bioorg. Med. Chem*., **2006**, *14*, 138; (c) Kim, H.-J.; Yeom, S.-H.; Kim, M.-K.; Shim, J.-G.; Paek, I.-N.; Lee, M.-W. *Arch. Pharmacol. Res*., **2005**, *28*, 177; (d) Mohamad, H.; Lajis, N. H.; Abas, F.; Ali, A. M.; Sukari, M. A.; Kikuzaki, H.; Nakatani, N. *J. Nat. Prod*., **2005**, *68*, 285; (e) Yadav, P. N.; Liu, Z.; Rafi, M. M. J. *J. Pharmacol. Exp. Ther*., **2003**, *305*, 925; (f) Ishida, J.; Kozuka, M.; Tokuda, H.; Nishino, H.; Nagumo, S.; Lee, K.-H.; Nagai, M. *Bioorg. Med. Chem*., **2002**, *10*, 3361; (g) Chun, K.-S.; Park, K.-K.; Lee, J.; Kang, M.; Surh, Y.-J. *Oncol. Res*., **2002**, *13*, 37; (h) Matsuda, H.; Morikawa, T.; Tao, J.; Ueda, K.; Yoshikawa, M. *Chem. Pharm. Bull*., **2002**, *50*, 208; (i) Ali, M. S.; Tezuka, Y.; Awale, S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod*., **2001**, *64*, 289; (j) Lee, M.-W.; Kim, J.-H.; Jeong, D.-W.; Ahn, K.-H.; Toh, S.-H.; Surh, Y.-J. *Biol. Pharm. Bull*., **2000**, *23*, 517; (k) Hashimoto, T.; Tori, M.; Asakawa, Y.

Chem. Pharm. Bull., **1986**, *34*, 1846.

5 For the synthesis of arylethyl or (*E*)-arylethenyl substituted β-hydroxy-δ-lactone, see: (a) Sabitha, G.; Sudhakar, K.; Srinivas, C.; Yadav, J. S. *Synthesis,* **2007**, 705; (b) Bouzbouz, S.; Cossy, J. *Tetrahedron Lett*., **2000**, *41*, 3363; (c) Kiyooka, S.-I.; Yamaguchi, T.; Maeda, H.; Kira, H.; Hena, M. A.; Horiike, M. *Tetrahedron Lett*., **1997**, *38*, 3553; (d) Honda, T.; Ono, S.; Mizutani, H.; Hallinan, K. O. *Tetrahedron: Asymmetry*, **1997**, *8*, 181; (e) Solladie, G.; Bauder, C.; Rossi, L. *J. Org. Chem*., **1995**, *60*, 7774; (f) Minami, T.; Takahashi, K.; Hiyama, T. *Tetrahedron Lett*., **1993**, *34*, 513; (g) Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem*., **1991**, *56*, 4050; (h) Roth, B. D.; Roark, W. H. *Tetrahedron Lett*., **1988**, *29*, 1255; (i) Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett*., **1987**, *28*, 1385; (j) Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett*., **1985**, *26*, 1185; (k) Prasad, K.; Repic, O. *Tetrahedron Lett*., **1984**, *25*, 2435; (l) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett*., **1984**, *25*, 2101; (m) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S. and Skalitzky, D. J. *J. Org. Chem.*, **1991**, *56*, 5161; (n) Reddy, P. P.; Yen, K.-F. and Uang, B.-J.; *J. Org. Chem.* **2002**, *67*, 1034; (o) Kumar, P.; Pandey, M.; Gupta, P.; Dhavale, D. D. *Tetrahedron Lett.*, **2010**, *51*, 5838; (p) Chandra Rao, D.; Reddy, D. K.; Chinnababu, B.; Shekhar, V. and Venkateswarlu, Y. *Synthetic Communications*, **2013,** *43*, 2980.

6 (a) Pawar, V. U.; Shinde, V. S. *Tetrahedron: Asymmetry*, **2011**, *22*, 8; (b) Narasimhulu, M.; Srikanth Reddy T.; Mahesh, K. C.; Sai Krishna, A.; Venkateswara Rao, J.; Venkateswarlu, Y. *Bioorg. Med. Chem. Lett*., **2009**, *19*, 3125.

7 (a) Mitsuru, O.; Michiyasu, T.; Kunio, O. *Synlett*, **1997**, 1111; (b) Fernandes, R. A.; Kumar, P. *Eur. J. Org., Chem*., **2002**, 2921.

8 (a) Reddy, R. S.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun*., **2010**, *46*, 5012; (b) Devalankar, D. A.; Karabal, P. U.; Sudalai, A. *Org. Biomol. Chem*., **2013**, *11*, 1280; (c) Gadakh, S. K.; Reddy, R. S.; Sudalai, A. *Tetrahedron: Asymmetry*, **2012**, *23*, 898.

9 (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc*., **1983**, *105*, 2092; (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc*., **1986**, *108*, 5919; (c) Racherla, U. S.; Brown, H. C. *J. Org. Chem.*, **1991**, *56*, 401.

10. (a) Bartlett, P. A.; Meadows, J. D.; Brown, E.G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.*, **1982**, *47*, 4013; (b) Duan, J. J-W.; Smith, A. B. *J. Org. Chem.*, **1993**, *58*, 3703.

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

12 (1) (a) Blaser, M. *J. Clin. Infect. Dis.* **1992**, *15*, 386; (b) Taylor, D. N.; Blaser, M. *J. Epidemiol. Rev*. **1991**, *13*, 42.

13 (2) (a) Mackay, J.; Jemal, A.; Lee, N. C.; Parkin, D. M. The Cancer Atlas, 2nd ed.; American Cancer Society: New York, **2006**; (b) Stoicov, C.; Saffari, R.; Cai, X.; Hasyagar, C.; Houghton, *J. Gene.* **2004**, *341*, 1.

14 (3) Dooley, C. P.; Cohen, H.; Fitzgibbons, P. L.; Bauer, M.; Appleman, M. D.; Perez-Perez, G. I.; Blaser, M. J. N. *Engl. J. Med*. **1989**, *321*, 1562.

15 (4) (a) Nomura, A.; Stemmermann, G. N.; Chyou, P. H.; Perez-Perez, G. I.; Blaser, M. *J. Ann. Intern. Med*. **1994**, *120*, 977; (b) Peterson, W. L. N. *Engl. J. Med*. **1991**, *324*, 1043.

16 (a) Nomura, A.; Stemmermann, G. N.; Chyou, P. H.; Kato, I.; Perez-Perez, G. I.; Blaser, M. J. N. *Engl. J. Med.* **1991**, *325*, 1132; (b) Parsonnet, J.; Friedman, G. D.; Vandersteen, D. P.; Chang, Y.;

Vogelman, J. H.; Orentreich, N.; Sibley, R. K.N. *Engl. J. Med*. **1991**, *325*, 1127; (c) Sipponen, P.; Varis, K.; Fraki, O.; Korri, U. M.; Seppala, K.; Siurala, M. Scand. *J. Gastroenterol*. **1990**, *25*, 966; (d) Graham, D. Y.; Lew, G. M.; Klein, P. D.; Evans, D. G.; Evans, D. J.; Saeed, Z. A.; Malaty, H. M. Ann. *Intern. Med*. **1992**, *116*, 705; (e) Hentschel, E.; Brandstatter, G.; Dragosics, B.; Hirschl, A. M.; Nemec, H.; Schutze, K.; Taufer, M.; Wurzer, H. N. *Engl. J. Med*. **1993**, *328*, 308; (f) Marshall, B. J.; Goodwin, C. S.; Warren, J. R.; Murray, R.; Blincow, E. D.; Blackbourn, S. J.; Phillips, M.; Waters, T. E.; Sanderson, C. R. *Lancet*, **1988**, *11*, 1437; (g) Rauws, E. A. J.; Tytgat, G. N. *J. Lancet*, **1990**, *335*, 1233.

17 A. Arnone, G. Assante, G. Nasini and O. Vajna de Pava, *Phytochemistry*, **1990**, *29*, 613; M. A. Gaudliana, L. H. Huang, T. Kaneko, P. C. Watts, PCT Int. Appl., **1996**, W0 9605204; CAN 125:58200.

18 (a) Walsh, J. H.; Peterson, W. L. N. *Engl. J. Med*. **1995**, *333*, 984; (b) Rathbone, B. *Scrip Magazine*, **1993**, 25.

19 (a) Arnone, A.; Assante, G.; Nasini, G.; Vajna de Pava, O. *Phytochemistry* **1990**, *29*, 613; (b) Gaudliana, M. A.; Huang, L. H.; Kaneko,T.; Watts, P. C.PCT Int. Appl., **1996**, W0 9605204; CAN 125:58200.

20 Dekker, K. A.; Inagake, T.; Gootz, T. D.; Kaneda, K.; Nomura, E.; Sakakibara, T.; Sakemi, S.; Sugie, Y.; Yamauchi, Y.; Yoshikawa, N.; Kojima, N. J. *J. Antibiot*. **1997**, *50*, 833.

21 (a) Nannei, R.; Dallavalle, S.; Merlini,; Bava, A.; Nasini, G. *J. Org. Chem*. **2006,** *71*, 6277; (b) Keaton, K. A.; Phillips, A. J. *Org. Lett*. **2007**, *9*, 2717; (c) Robinson, J. E.; Brimble, M. A. *Chem. Commun*., **2005**, 1560; (d) Trost, B. M.; Weiss, A. H. *Angew. Chem. Int. Ed*. **2007**, *46*, 7664; (e) Ramu, E. Rao, B. V. *Tetrahedron:Asymmetry*, **2008,** 19, 1820; (f) Yadav, J. S.; Sreenivas, M.; Reddy, A. S.; Reddy, B. V. S. *J. Org. Chem*. **2010**, *75*, 8307; (g) Singh, M.; Argade, N. P. *Synthesis*, **2011**, 7, 1137; (h) James E. Robinson and Margaret A. Brimble, *Org. Biomol. Chem*., **2007**, *5*, 2572; (i) Brimble, M. A.; Bryant, C. J. *Chem. Commun*., **2006**, 4506;

22 Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J.; White, J. D. *J. Org. Chem.* **2005**, *70*, 5449.

23 Stoller, A.; Mioskowski, C.; Sepulchre, C.; Bellamy, F. *Tetrahedron Lett*. **1990**, *31*, 361.

24 (a) Ohira, S. *Synth. Commun*. **1989**, *19*, 561; (b) Roth, G. J.; Bernd, L.; MMller, S. G.; Bestmann, H. J. *Synthesis*, **2004**, 59.

25 (a) Noyori, R.; Takaya, H. *Acc. Chem. Res*. **1990**, *23*, 345; (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Organic syntheses* **1993**, *Coll. Vol. 9*, 589; (c) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.

26 Prasad, P. K.; Sudalai, A. *Adv. Synth. Catal.*, **2014**, *356*, 2231.

27 Turcu, M.C.; Kiljunen, E.; Kanerva, L.T. *Tetrahedron: Asymmetry* **2007**, *18*, 1682.

CHAPTER 3

A Simple and Efficient Synthesis of Isocoumarins and Alkylidenephthalides and Bioactive Molecule Cytogenin and (Z)-3-Butylidene-5-hydroxy-7-methoxyphthalide

A simple and efficient synthesis of isocoumarins and alkylidenephthalides from 3-(1-hydroxycarbethoxy/alkyl)phthalides with a DEAD/PPh_3/TBHP system; **Gadakh, S. K.**; Sudalai, A. *RSC Adv.*, **2014**, *4*, 57658.

Section I

A Simple and Efficient Synthesis of Isocoumarins and Alkylidenephthalides from 3-(1-Hydroxycarbethoxy/alkyl)phthalides with DEAD/PPh_3/TBHP System

3.1.1 Introduction

Isocoumarins and 3-alkylidenephthalides are naturally-occurring lactones, which are structural subunits present in numerous natural products (**1-3**) that exhibit a wide range of biological and pharmacological activities such as antiinflammatory, antifungal, antiplasmodic, etc.[1] They are also important in medicinal chemistry as building blocks for the synthesis of other biologically active heterocyclic[2] and carbocyclic[3] compounds. Due to their wide range of biological activities, a series of efficient methods have been developed recently for the construction of isocoumarins and 3-alkylidenephthalides frameworks (**Fig. 1**).

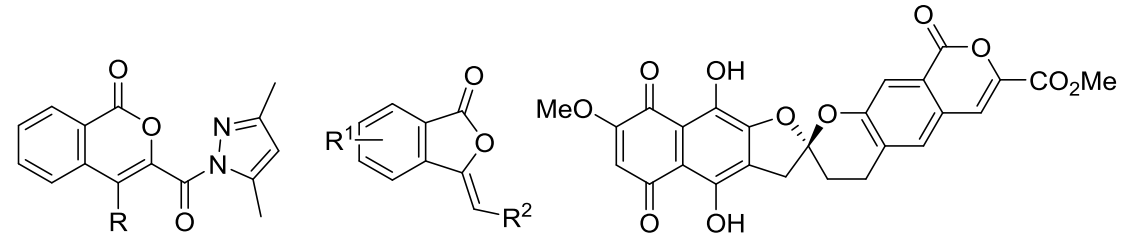


Fig. 1: Bioactive molecules with isocoumarin and alkylidenephthalide skeletons

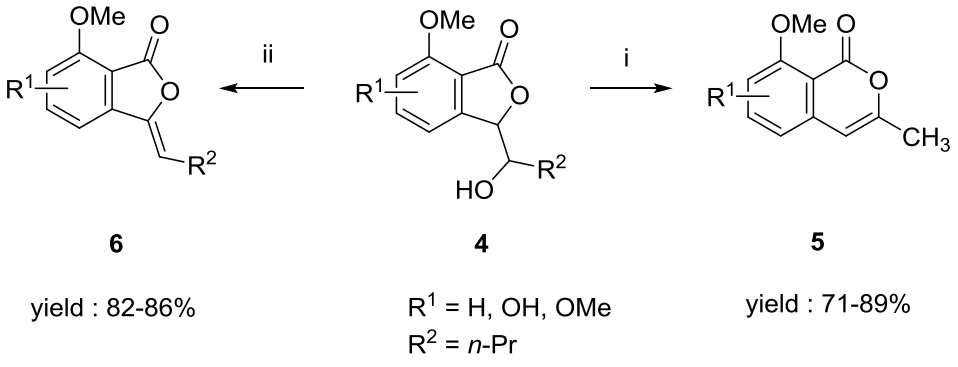
3.1.2 Review of Literature

For isocoumarins, the most useful method is based on the catalytic cyclization of *o*-alkynylbenzoic acid derivatives,[4] while in the case of phthalides, the attractive route is

the reaction between *o*-halobenzoic acid derivatives and terminal alkynes.[5] Quite recently, use of copper[6] or palladium[7] salts as catalysts for the construction of isocoumarins and 3-alkylidenephthalides frameworks has attracted considerable attention due to their economic attractiveness and good functional group tolerance. Some of the literature reports are discussed below.

Mali's approach (1998)[8]

Mali *et al.* have reported acid-catalyzed dehydration method for the synthesis of both (*Z*)-3-butylidenephthalides **6** and 3-alkyl-8-hydroxy/methoxy isocoumarins **5** from the phthalides **4**. Reaction of hydroxyphthalides **4** with a mixture of orthophosphoric acid and formic acid afforded eliminated product (*Z*)-3-butylidenephthalides **6**, while the hydroxyphthalides **4** with *p*-toluenesulfonic acid resulted in the ring expansion to 3-alkylisocoumarins **5** (**Scheme 1**).

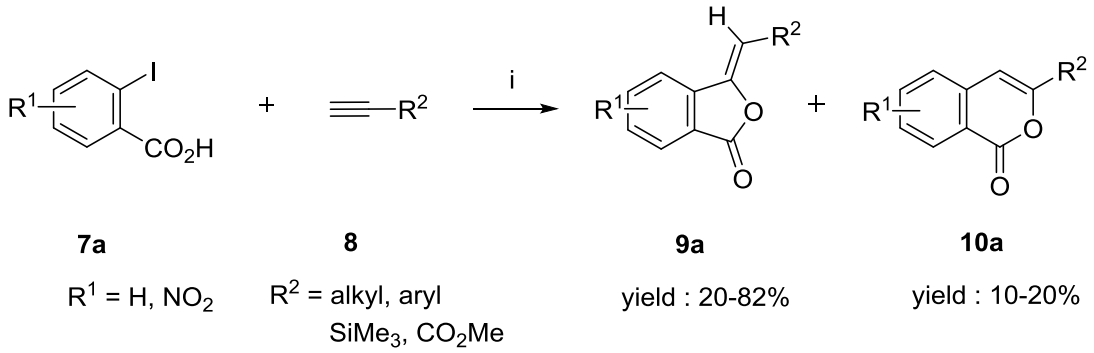


Scheme 1: (i) *p*-TsOH, dry toluene, reflux; (ii) HCO_2H, H_3PO_4, 80 °C, 8 h.

Jiang's approach (2007)[5c]

Jiang *et al.* have developed a protocol for the synthesis of phthalides **9a** as a major product and isocoumarin **10a** as a minor *via* Pd/CNTs-catalyzed tandem coupling-cyclization reaction of *o*-iodobenzoic acid with a variety of terminal alkynes **8**. Thus,

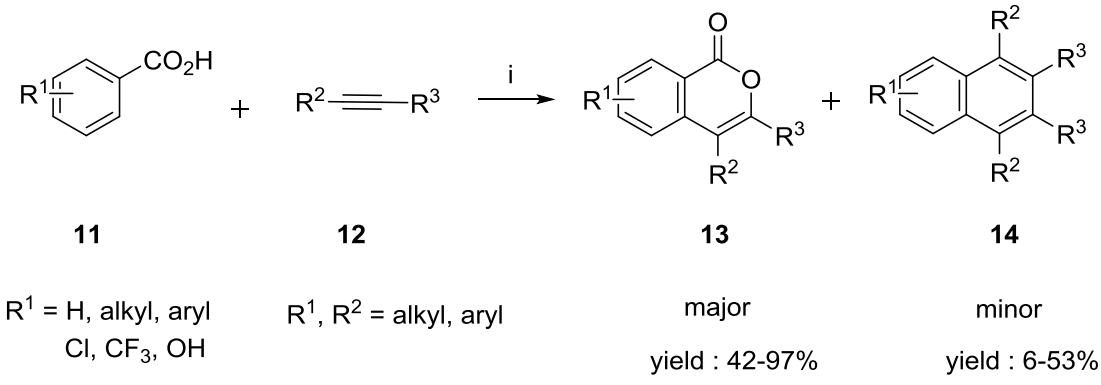
Pd (0.1 mol %) immobilized on –CNTs showed high catalytic activity towards the synthesis of phthalides **9a** in moderate to good yields (32-96%) depending upon substituents present on the aromatic ring (**Scheme 2**).



Scheme 2: Pd/CNTs (0.1 mol %), NaOAc (2 equiv), DABCO (0.4 equiv), DMF/H_2O (20:1), 100 °C, 8-24 h.

Miura's approach (2007)[11a]

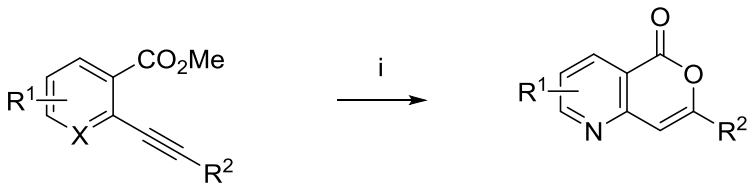
Miura *et al.* have reported the oxidative coupling of benzoic acids **11** with internal alkynes **12** with catalyst $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2 \cdot H_2O$ as an oxidant to afford the corresponding isocoumarin derivatives **13** in 42-97% yield as a major product along with minor decarboxylative product naphthalene derivative **14** in 6-53% yield (**Scheme 3**).



Scheme 3: (i) $[Cp^*RhCl_2]_2$ (1 mol %), $Cu(OAc)_2.H_2O$ (4 equiv), *o*-xylene, 120 °C, N_2, 2-10 h.

Bihel's approach (2008)[12b]

Bihel *et al.* have envisaged the regiocontrolled method for the synthesis of heterocyclic isocoumarins **16** employing 6-*endo*-dig cyclization of 2-(2-arylethynyl)heteroaryl esters **15** under Brønsted acidic condition and Lewis acid $Cu(OTf)_2$ as catalyst. This protocol was found applicable to the synthesis of variety of substituted heterocyclic lactones with good yields upto 98% (**Scheme 4**).



15

X = N, C
R^1 = alkyl, aryl
heteroaryl

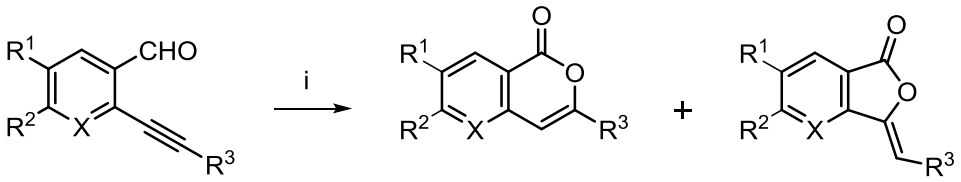
16

R^2 = aryl
yield : 82-98%

Scheme 4: (i) $Cu(OTf)_2$ (5 mol %) under microwave irradiation. 100 °C, 20 min, TFA (1 mL).

Youn's approach (2011)[12e]

Youn *et al.* have described NHC-catalyzed oxidative cyclization of *o*-alkynylbenzaldehydes **17** having an unactivated alkyne moiety as an internal electrophile to provide the *o*-heterocycles **18** as a major product in 32-96% along with minor product **19** in 22-84% yield depending on substituents present on aromatic ring. DBU showed its basic ability to generate the active NHC catalytic species, followed by activation of internal alkyne *via* conjugate acid coordination, which resulted in the formation of isocoumarin **18** using molecular oxygen as an oxidant (**Scheme 5**).



17 **18** **19**

R^1, R^2 = H, OMe, F, Cl
R^3 = alkyl, aryl, H, TMS
X = C, N

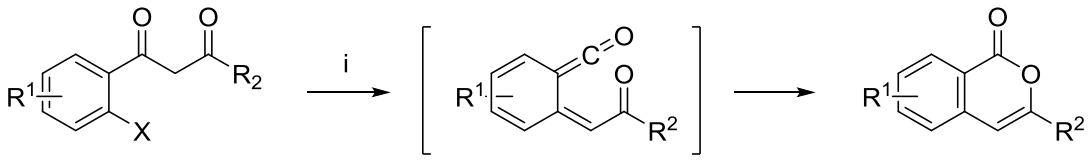
yield : 32-96%

yield : 22-84%

Scheme 5: (i) NHC (20 mol %), DBU (40 mol %), MeCN, air, 80 °C, 2-24 h.

Shen's approach (2012)[6c]

Shen *et al.* have presented a protocol using readily available 1-(2-halophenyl)-1,3-diones **20** (obtained from reaction of 2-haloarylcarboxylic acid chloride and ketones) as a starting materials under CuI/2-picolinic acid/K_2CO_3 catalytic system for the synthesis of isocoumarin units **22** in 47-98% yield. This reaction involves an intramolecular-sequential copper-catalyzed C−C coupling reaction and a rearrangement process of intermediate ketene **21** for the synthesis of isocoumarins **22** (**Scheme 6**).



20 **21** **22**

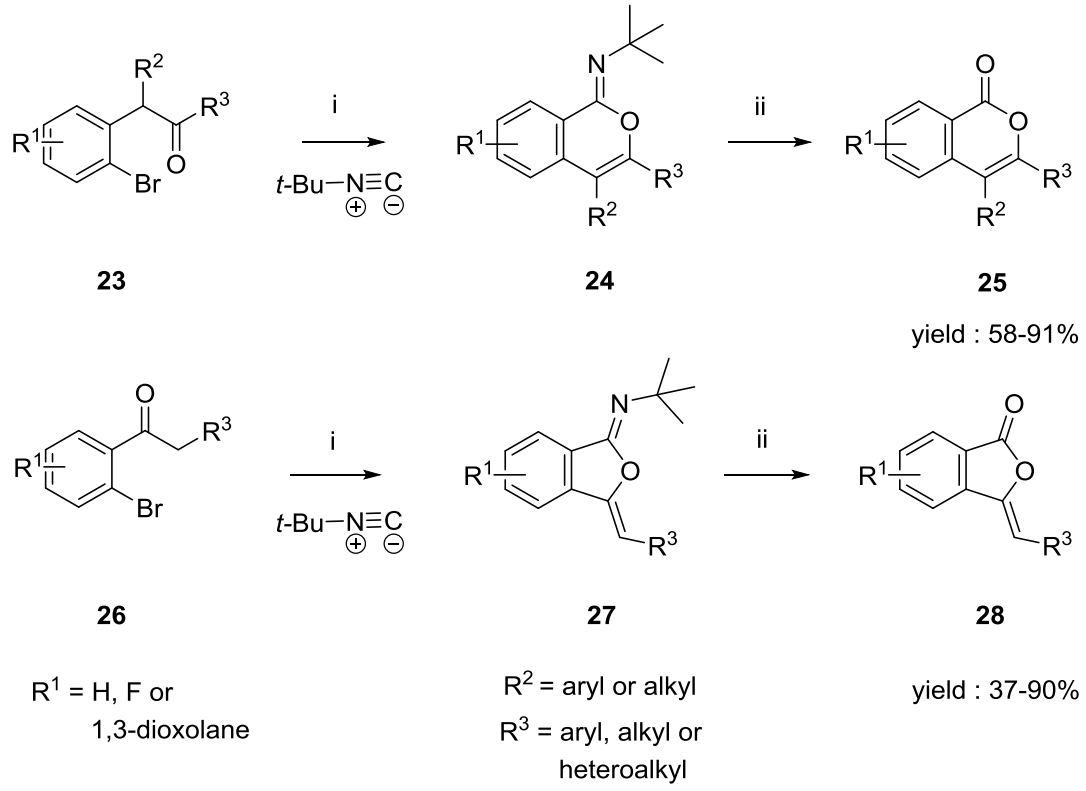
X = Cl, I
R^1 = H, alkyl, aryl
R^2 = aryl

yield : 47-98%

Scheme 6: (i) CuI (0.05 mmol), 2-picolinic acid (0.1 mmol), K_2CO_3 (1.0 mmol), toluene (2 mL), 110 °C, 5-12 h.

Shun-Jun Ji's approach (2012)[7b]

Shun-Jun Ji *et al.* have reported an efficient method for the synthesis of isocoumarins **25** and alkylidenephthalides **28** using $Pd(OAc)_2$/DPEPhos as a catalyst system, *tert*-butyl isocyanide as a carbon source and HCl, hydrolyzing agent in two steps with moderate to good yield. The 3-substituted phthalides **28** possess *Z*-configuration with excellent yields (**Scheme 7**).

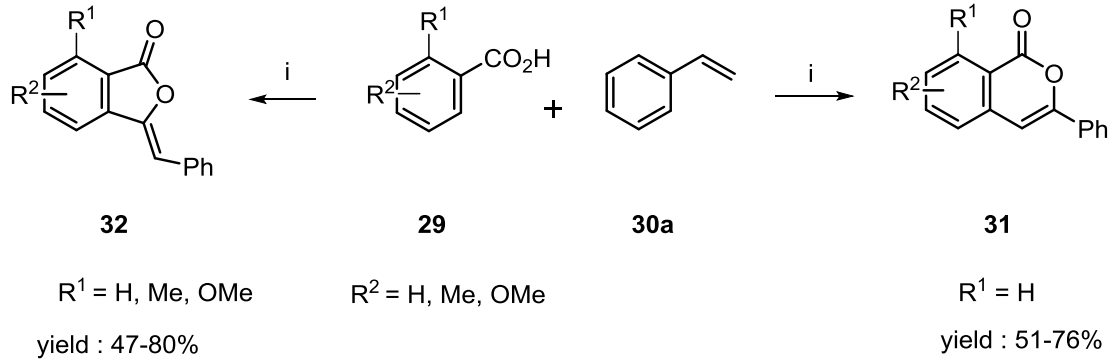


Scheme 7: (i) $Pd(OAc)_2$ (2.5 mol %), DPEPhos (5 mol %), K_2CO_3 (1.0 mmol), DMF (3 mL), 120°C, 2 h, followed by refluxing in THF; (ii) HCl, THF, reflux, 2 h.

Lee's approach (2013)[7d]

Lee *et al.* have developed a useful synthetic route for the preparation of isocoumarins **31** and 3-benzylidenephthalides **32** *via* Pd-catalyzed oxidative coupling reaction of

benzoic acids **29** and vinylarenes **30** *via* C−H olefination. The product formation was dependent upon the substituents present on benzoic acids **29** (**Scheme 8**).



Scheme 8: (i) $Pd(OAc)_2$ (5 mol %), Ag_2O (1 equiv), DMF, 110 °C, MS 4 Å, 20 h.

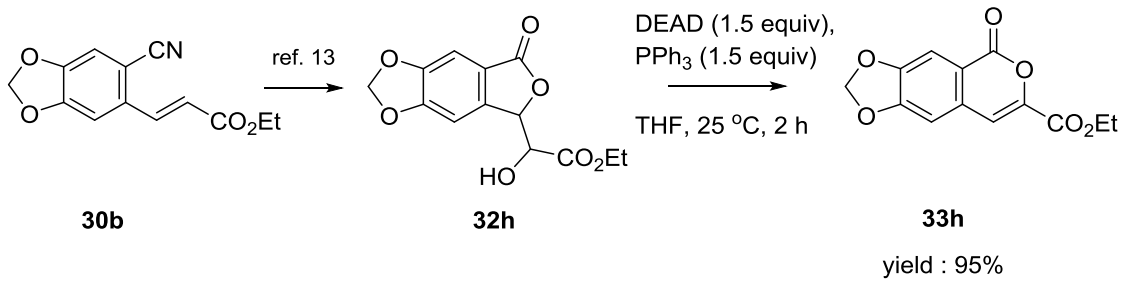
3.1.3 Present Work

3.1.3.1 Objective

Although several efficient synthetic methods are known, they are significantly limited by substrate availability.[8] In addition, these methods involve multistep sequences,[9] harsh conditions,[10] expensive catalysts and ligands[11] or use of either excess acid/strong bases,[12] often leading to products with low selectivity.

Recently, we have reported a new protocol of CN-assisted cyclization *via* asymmetric dihydroxylation process of cyanocinnamates **30b** and styrene derivatives leading to the synthesis of a wide variety of 3-substituted phthalides (**32a-t**) and their structural analogues.[13] In continuation of this methodology, we anticipated that a simple functional group manipulation ($OH \rightarrow N_3$)[14] in phthalide **32h** under typical Mitsunobu condition (PPh_3, DEAD, DPPA),[15] followed by reduction, would enable us to construct biologically important tetrahydroquinoline skeletons. Surprisingly, phthalide **32h**, when subjected to the above reaction condition in *stoichiometric* amounts, with or without

DPPA, underwent intramolecular ring expansion to afford isocoumarin derivative **33h** exclusively in 95% yield at ambient conditions (**Scheme 9**).



30b **32h** **33h**

yield : 95%

Scheme 9: Intramolecular ring expansion of 3-(1-hydroxycarbethoxy)phthalide **32h**

3.1.3.2 Results and Discussion

Encouraged by this result, we became interested in the catalytic use of DEAD, as the stoichiometric use of DEAD leads to the formation of 1,2-dicarbethoxyhydrazine as side product, which was difficult to separate from the desired product. In the literature, it was reported that 1,2-dicarbethoxyhydrazine could be reoxidized to DEAD using iodobenzene diacetate (BIAB) as an oxidizing agent.[16] However, in our case, use of oxidants like BIAB, NMO, or TEMPO resulted in negligible formation of **33h**. However, other oxidants such as H_2O_2 and cumene hydroperoxide (CHP) indeed gave the desired product **33h** in 40% and 30% yields respectively (**Table 1**).

The aprotic solvents like 1,4-dioxane, CH_2Cl_2, CH_3CN and Et_2O were found to be less suitable for the reaction as compared to THF. The optimal temperature was found to be 25 °C, as at higher temperatures, there was a slight decrease in the yield (entry 6 and 7) so also in the case of the excess use of TBHP. Thus, after several experimental optimizations, the optimized conditions were determined as phthalide **32h** (1 mmol),

Ph_3P (1.5 mmol) with TBHP (2 mmol) in the presence of DEAD (0.1 mmol) in THF at 25 °C to afford the desired product **33h** in 95% yield (**Table 1**, entry 12).

Table 1: Intramolecular ring expansion of phthalide **32h**

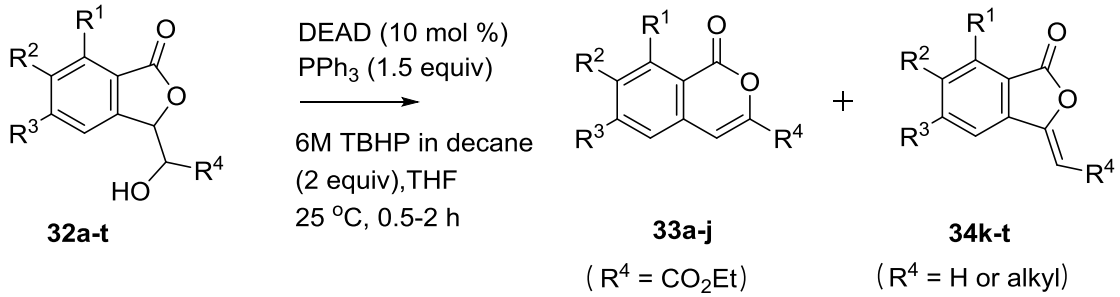
Role of oxidants and solvents[a]

entry	oxidants (equiv)	solvents	temp (°C)	time (h)	yield of **33h** (%)[b]
1	aq. H_2O_2 (1.5)	THF	25	2	40
2	CHP (1.5)	THF	25	3.5	30
3	H_2O_2 (3)	THF	25	2	50
4	TBHP (3)	THF	25	2	70
5	TBHP (2)	1,4-dioxane	25	2	40
6	TBHP (2)	THF	50	3	40
7	TBHP (2)	THF	70	3	30
8	TBHP (2)	CH_2Cl_2	25	2.5	50
9	TBHP (3)	THF	25	2.5	50
10	TBHP (2)	Et_2O	25	1.5	30
11	TBHP (2)	CH_3CN	25	3	10
12	TBHP (2)	THF	25	2	95

[a] Reagents and conditions; phthalide **32h** (1 mmol), PPh_3 (1.5 mmol), DEAD (10 mol %). [b] Isolated yield after column chromatographic purification.

Substrates scope was then evaluated and the results are summarized in **Table 2**. Substrates having both electron-poor and electron-rich substituents on the aromatic ring underwent the reaction smoothly to give products in excellent yields.

Table 2: Reaction of 3-substituted phthalides with DEAD/PPh_3/TBHP: substrate scope



32a-t **33a-j** (R4 = CO_2Et) **34k-t** (R4 = H or alkyl)

entry	R^1	R^2	R^3	R^4	yield (%)[a]	
					33a-j	**34k-t**
a	H	H	H	CO_2Et	94	-
b	H	OMe	H	CO_2Et	96	-
c	OMe	OMe	H	CO_2Et	92	-
d	OMe	H	OMe	CO_2Et	92	-
e	OMe	OMe	OMe	CO_2Et	90	-
f	H	OBn	OMe	CO_2Et	92	-
g	H	F	H	CO_2Et	95	-
h	H	-O-CH_2-O-		CO_2Et	95	-
i	H	NO_2	H	CO_2Et	90	-
j	(*E*)-ethyl 3-(1-cyanonaphthalene-2-yl)acrylate			CO_2Et	93	-
k	H	H	H	H	-	95
l	H	OMe	H	H	-	95
m	OMe	OMe	H	H	-	93
n	H	OMe	OMe	H	-	94
o	OMe	H	OMe	H	-	92
p	OMe	OMe	OMe	H	-	94
q	H	OBn	OMe	H	-	93
r	H	-OCH_2O-		H	-	94
s	OMe	H	OMe	Me	-	94
t	OM e	OMe	OMe	pentyl	-	91

[a]Isolated yield after column chromatographic purification.

As can be seen from **Table 2**, it was observed that if the substituent R^4 = CO_2Et, intramolecular ring expansion took place to give isocoumarin derivatives (**33a-j**) and that if the substituents R^4 = H or alkyl, it led to simple eliminated products (**34k-t**) with complete *Z*-stereoselectivity. In every case, the reaction proceeded rapidly within 0.5-2 h giving the desired products (**33a-j** or **34k-t**) in excellent yields up to 95%. All the starting materials (**32a-t**) were prepared by the corresponding substituted benzaldehydes *via* two carbon-homologation followed by bromide displacement with cyanide as reported in our previous work.[13] The formation of eliminated products alkylidenephthalides (**34k-t**) was confirmed from their ^1H, ^{13}C and IR spectra and also their *Z*-stereoselectivity confirmed from NOESY NMR studies.

The formation of isocoumarin derivatives (**33a-j**) was established unambiguously from the corresponding ^1H, ^{13}C NMR and IR spectral analysis as shown in the examples.

For Isocoumarins:

<u>Example 1</u>:

The formation of isocoumarin derivative **33h** was ascertained by the presence of a characteristic olefinic singlet at δ 7.36 (s, 1H) and also it showed two signals at 1.42 (t, *J* = 7.8 Hz, 3H) and 4.41 (q, *J* = 7.2 Hz, 2H) corresponding to ethyl protons of $–CO_2Et$ group respectively in its ^1H NMR spectrum. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 160.4 and 111.9 due to presence of –C=O and olefinic carbons respectively. Also, its IR spectrum displayed two strong vibrational stretching frequencies at υ_{max} 1711 and 1728 cm^{-1} indicative of –C=O group of an ester and lactone moiety respectively (**Fig. 2**).

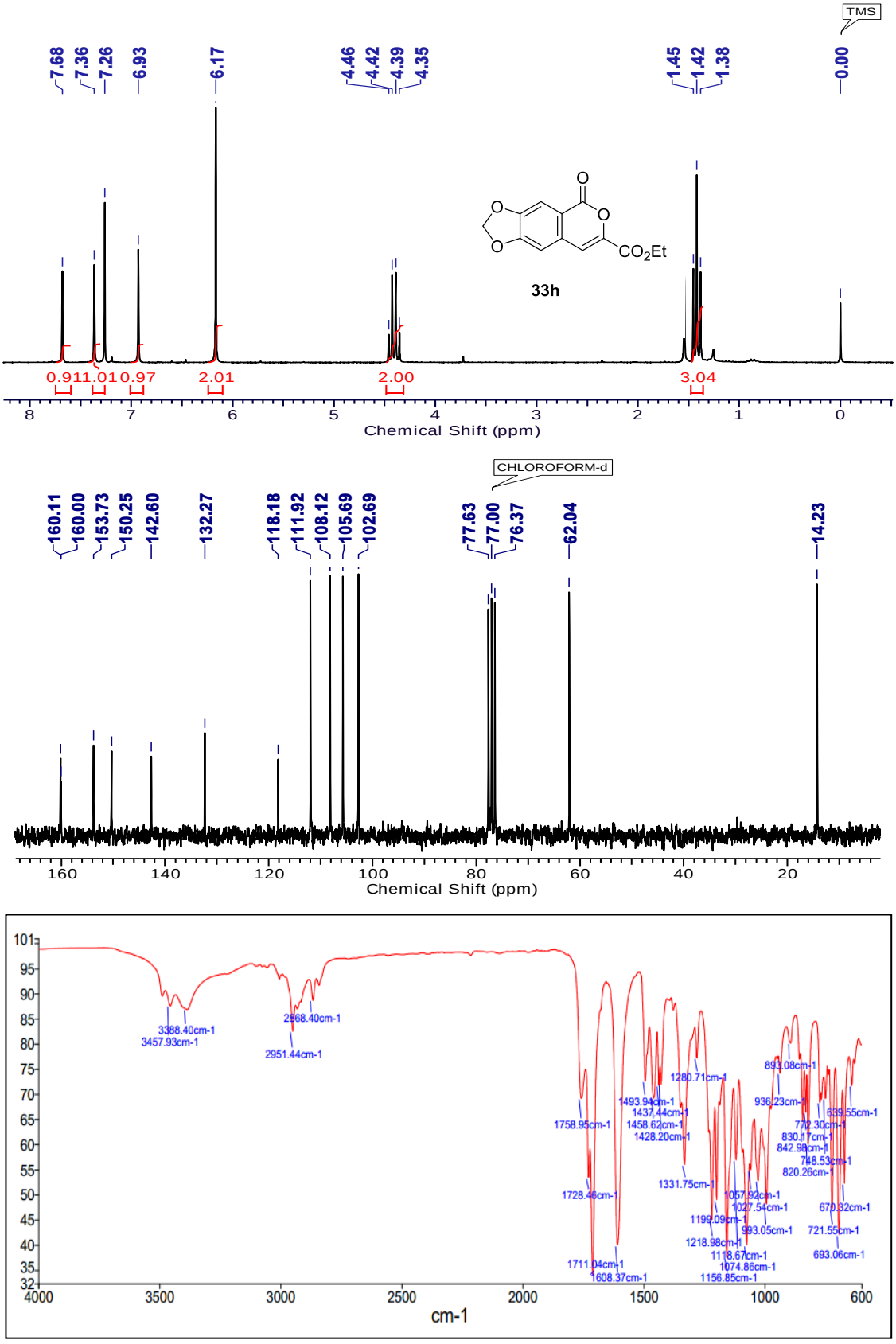


Fig. 2: ^{1}H, ^{13}C NMR and IR spectra of isocoumarin derivative **33h**

Example 2:

The ^{1}H NMR spectrum of ethyl 1-oxo-1*H*-benzo[*h*]isochromene-3-carboxylate **33j** showed a typical singlet at δ 7.54 (s, 1H) corresponding to the olefinic proton. Also, its ^{13}C NMR spectrum displayed two carbon signals at δ 160.0 and 159.8 due to the presence of carbonyl carbon and ester group of isocoumarin unit and another typical carbon signal at δ 112.4 for olefinic carbon respectively (**Fig. 3**).

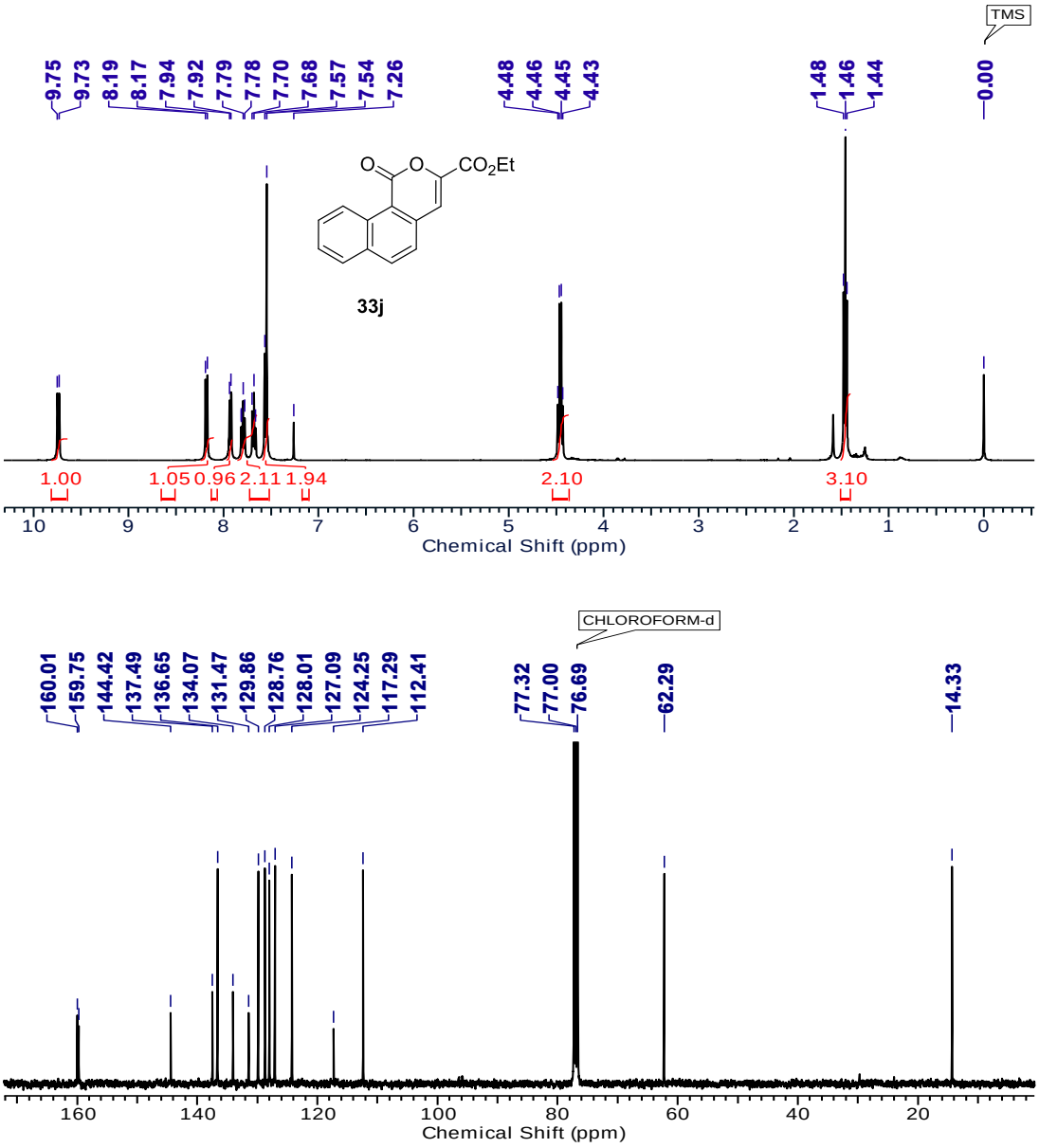


Fig. 3: ^{1}H and ^{13}C NMR spectra of isocoumarin derivative **33j**

For alkylidenephthalides:

Example 1:

The ^{1}H NMR of **34l** showed two doublets at δ 5.16 (d, *J* = 3.0 Hz, 1H) and 5.19 (d, *J* = 3.0 Hz, 1H) accounting for olefinic protons. Further, its structure was ascertained by ^{13}C NMR spectrum, which showed the appearance of carbonyl carbon at δ 166.3 and two olefinic carbon signals at δ 117.8 and 90.8 respectively, confirming the formation of **34l** (**Fig. 4**). Its IR spectrum showed a strong vibrational stretching frequency at υ_{max} 1763 cm^{-1} due to presence of carbonyl group of lactone.

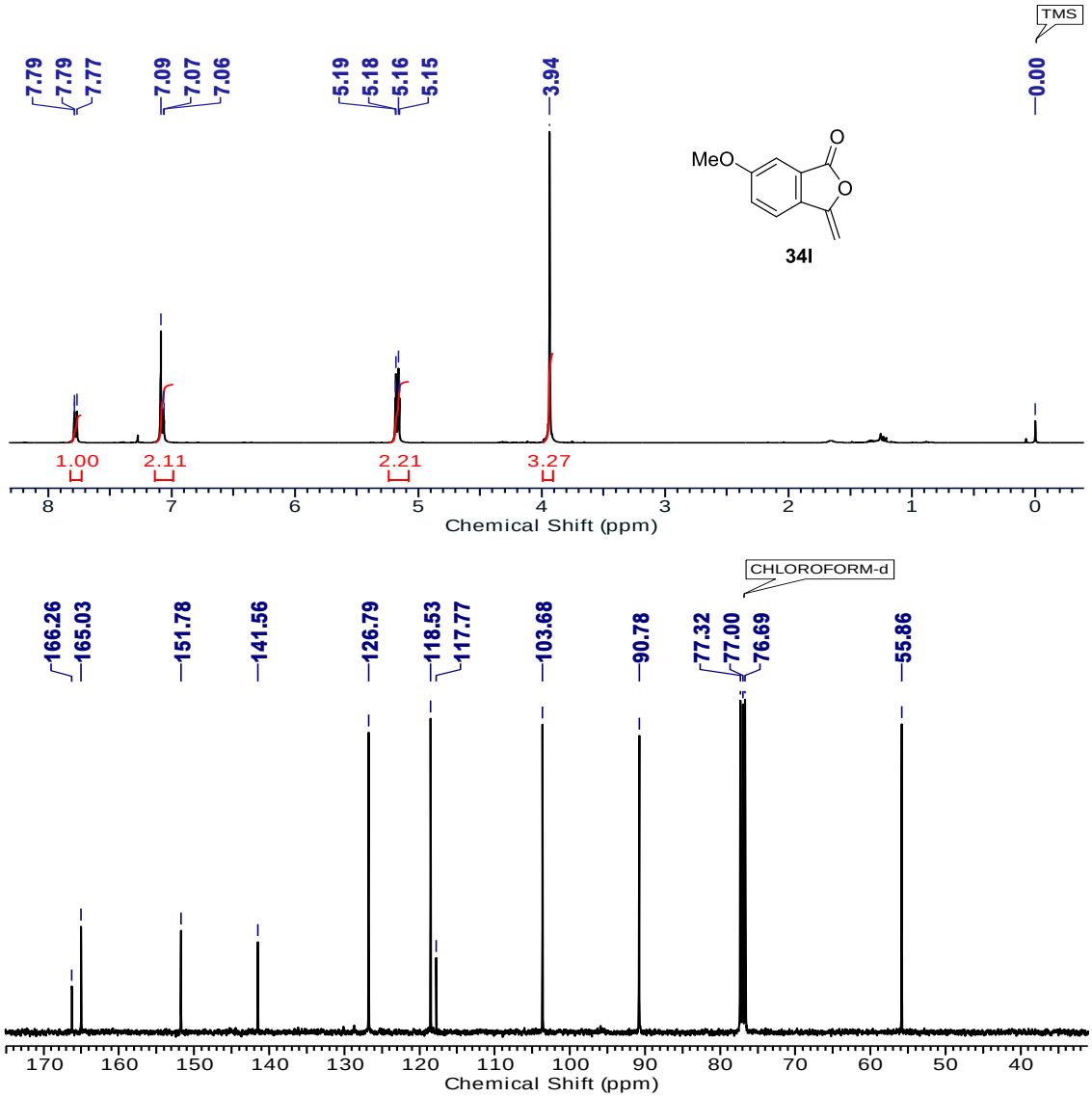
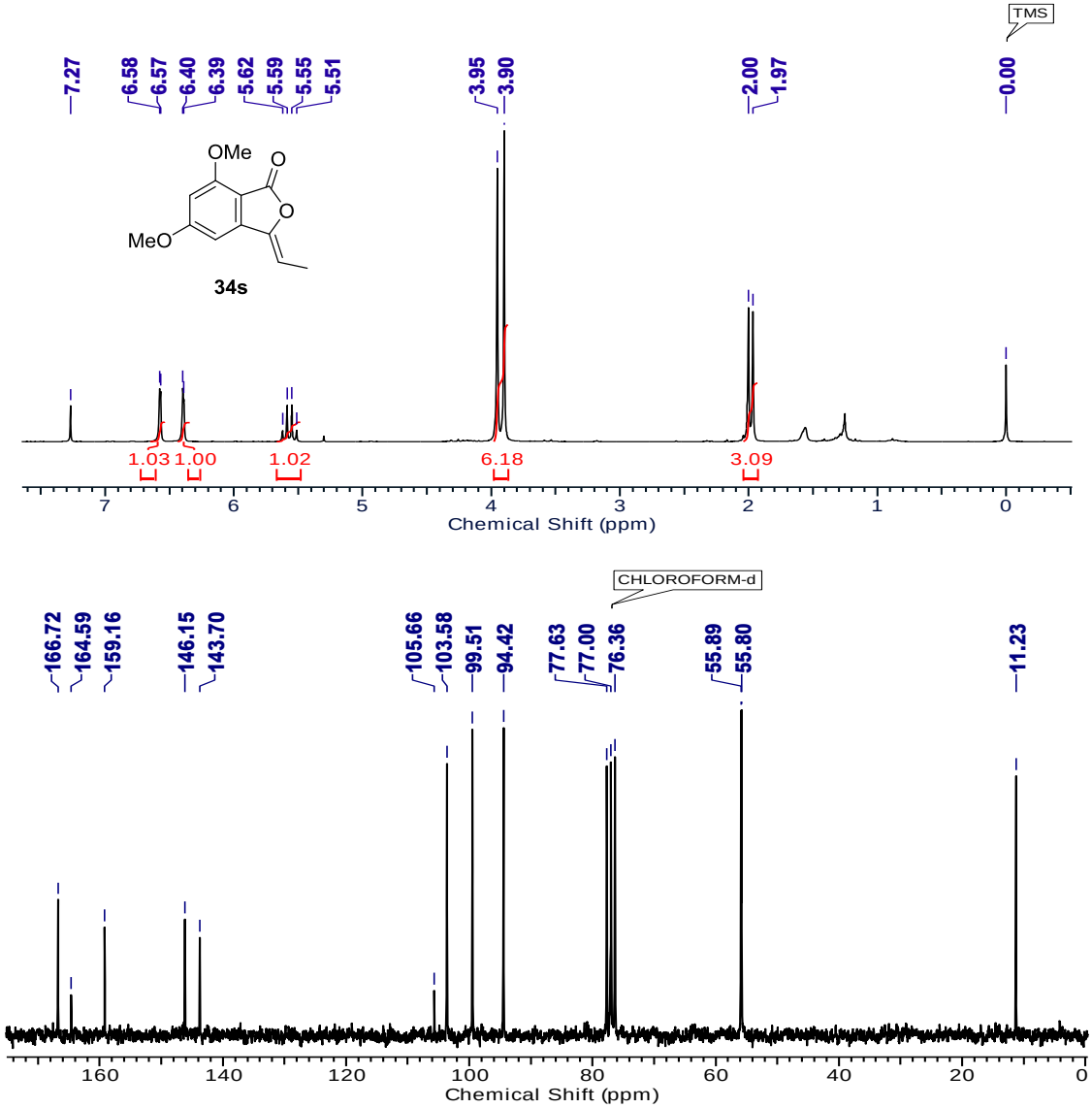


Fig. 4: ^{1}H and ^{13}C NMR spectra of alkylidenephthalide derivative **34l**

Example 2:

The exclusive *Z*-selectivity of alkylidenephthalide (**34k-t**) was assigned from their ^{1}H, ^{13}C and NOESY NMR spectra. The formation of **34s** was confirmed by the appearance of deshielded characteristic proton resonance signals at δ 5.56 (q, *J* = 7.1 Hz, 1H) and 1.97 (d, *J* = 7.1 Hz, 3H) corresponding to *oxo* olefinic proton (=CH-) and methyl proton (=CH-CH_3) of phthalide moiety in its ^{1}H NMR spectrum respectively. Further, its



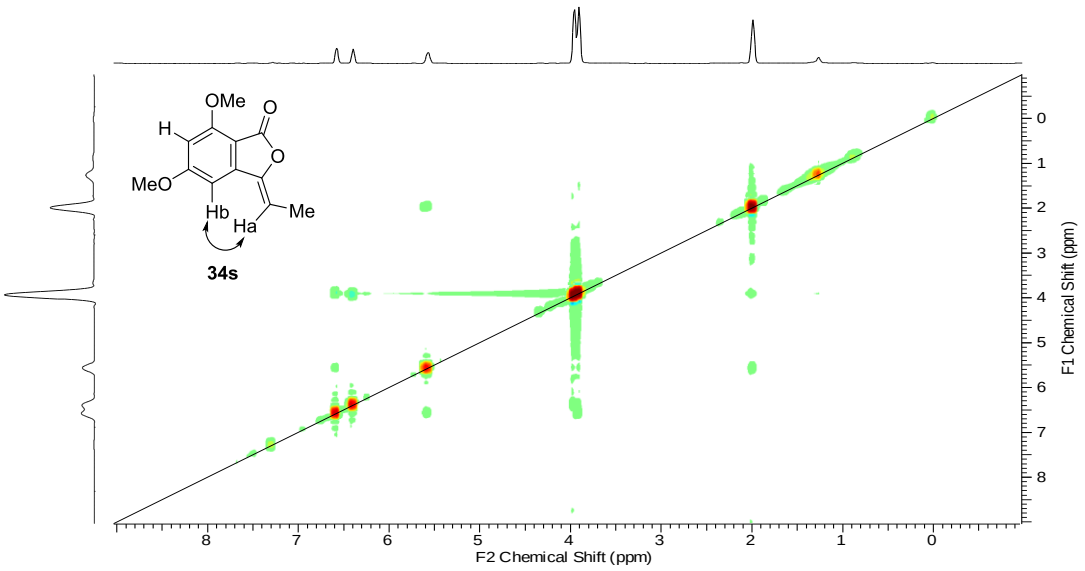
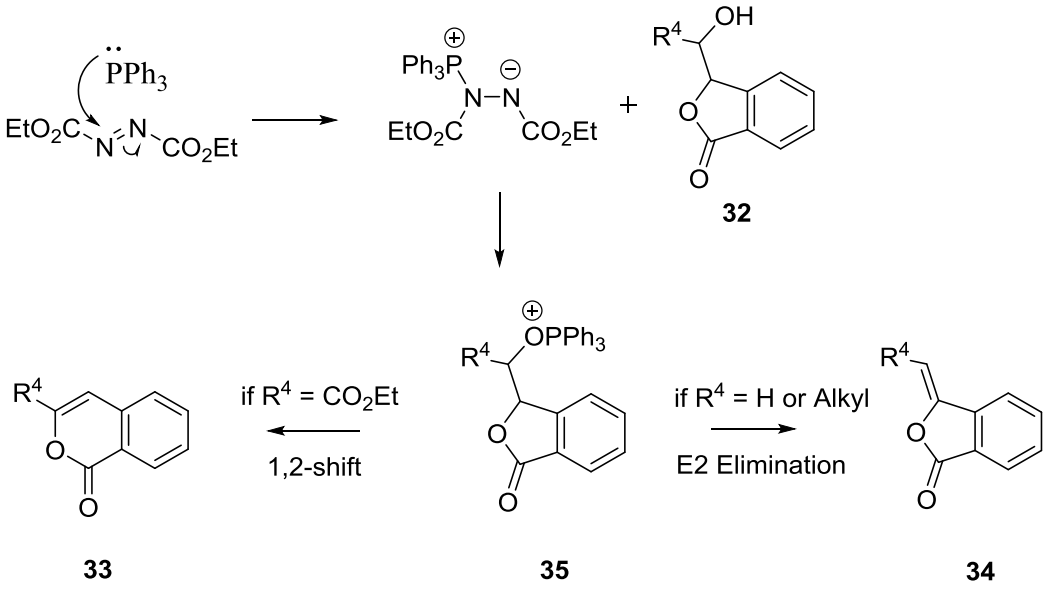


Fig. 5: ^{1}H, ^{13}C and NOESY NMR spectra of alkylidenephthalide derivative **34s**

structure was supported by ^{13}C NMR spectrum, which displayed three carbon signals at δ 164.6, 94.4 and 11.2 corresponding to –C=O, olefinic methine (=CH-) and methyl carbons (=CH-CH_3) respectively. *Z*-selectivity of compound **34s** was assigned with NOESY spectrum, which displayed the correlative rectangular between olefinic proton of phthalide ring and aromatic protons. Thus, there was a NOE correlation between H_a (δ 5.56, q, *J* = 7.1 Hz, 1H) and H_b (δ 6.57, d, *J* = 2.2 Hz, 1H). These results clearly revealed that the *Z*-stereochemistry of compound **34s** was assigned correctly (**Fig. 5**).

3.1.3.3 Mechanistic study

A probable mechanistic pathway similar to the Mitsunobu reaction mechanism[17] is shown in **Scheme 10**. Firstly, PPh_3 adds onto DEAD to generate a phosphonium ion intermediate, which readily deprotonates alcoholic proton in α-hydroxyphthalides **32** to provide phosphoxonium intermediate **35**. Intermediate **35** undergoes either ring expansion or elimination depending upon substituent R^4 and the stability of the products formed. For example, if R^4 = CO_2Et, it undergoes 1,2-type rearrangement of α-



Scheme 10: Pathway for the formation of isocoumarin and alkylidenephthalide frameworks.

oxycarbocation to oxonium ion resulting in intramolecular ring expansion producing thermodynamically stable isocoumarin derivatives **33**. If R^4 = H or alkyl, it undergoes facile E2 elimination resulting in the formation of kinetic products **34**. The *Z*-selectivity can be explained by the *anti*-E2 elimination process of β-hydrogen and Ph_3PO, which was proven by NOESY NMR studies. The role of TBHP was to reoxidize 1,2-dicarbethoxyhydrazine back to DEAD.

3.1.4 Conclusion

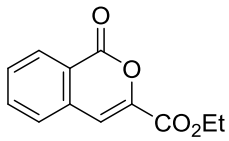
In conclusion, we have developed a simple synthetic procedure for the preparation of 3-carbethoxy isocoumarins and 3-alkylidenephthalides directly from 3-(1-hydroxycarbethoxy/alkyl) phthalides using DEAD/PPh_3/TBHP as the reagent system. With this reagent system, intramolecular ring expansion or elimination takes place depending upon the substituents present on the phthalides (**32a-t**). This procedure is practical as the products were obtained in excellent yields showing broad substrate scope and good functional group tolerance.

3.1.5 Experimental section

3.1.5.1 General experimental procedure for the preperation of 3-substituted isocoumarins (33a-j) and alkylidenephthalides (34k-t):

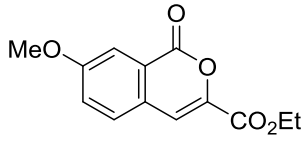
To a stirred solution of 3-(1-hydroxycarbethoxy/alkyl)phthalides derivatives (**32a-t**) (1 mmol) in THF (10 mL) was added diethyl azodicarboxylate (DEAD, 10 mol %), PPh_3 (1.5 mmol) and *tert*-butyl hydroperoxide (2 mmol) and the mixture allowed to stirr at 25 °C for 0.5 to 2 h. After the completion of reaction (as monitored by TLC), THF was distilled out to give the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (7:3) as eluent] afforded 3-substituted isocoumarin derivatives (**33a-j**) or 3-substituted alkylidene phthalides (**34k-t**) as the case may be.

Ethyl 1-oxo-1*H*-isochromene-3-carboxylate (33a)



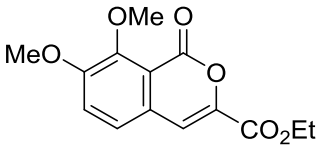
Yield: 94% (0.433 g); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 684, 751, 815, 1070, 1237, 1482, 1509, 1626, 1718, 1737, 3068, 2919; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.1 Hz, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.41 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 62.2, 112.0, 122.9, 127.5, 130.1, 130.6, 135.0, 135.1, 143.6, 160.2, 160.5; **Anal. Calcd for** $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.07; H, 4.65%.

Ethyl 7-methoxy-1-oxo-1*H*-isochromene-3-carboxylate (33b)



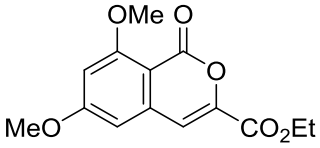
Yield: 96% (0.447 g); colorless solid; **mp**:128-129 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 749, 785, 827, 1072, 1257, 1510, 1601, 1720, 1736, 2934, 3067; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 3.94 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 7.16 (dd, *J* = 8.9 and 2.6 Hz, 1H), 7.4 (s, 1H), 8.26 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 55.7, 62.2, 109.7, 112.0, 115.8, 118.6, 132.3, 137.4, 144.2, 160.2, 164.9; **Anal. Calcd for** $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.87; H, 4.85%.

Ethyl 7,8-dimethoxy-1-oxo-1*H*-isochromene-3-carboxylate (33c)



Yield: 92% (0.432 g); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 721, 997, 1018, 1119, 1194, 1261, 1360, 1437, 1473, 1592, 1655, 1719, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.3 Hz, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 4.44 (q, *J* = 7.0 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 1H), 7.18 (s, 1H), 7.59 (d, *J* = 8.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 61.6, 61.7, 65.2, 113.4, 121.8, 122.6, 131.0, 137.1, 152.2, 153.7, 162.2, 164.4; **Anal. Calcd for** $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.49; H, 5.05%.

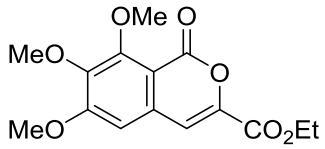
Ethyl 6,8-dimethoxy-1-oxo-1*H*-isochromene-3-carboxylate (33d)



Yield: 92% (0.432 g); colorless solid; **mp**: 87-89 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 711, 997, 1018, 1159, 1194, 1261, 1360, 1467, 1473, 1592, 1655, 1720, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.0 Hz, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.33 (q, *J* = 7.0 Hz, 2H), 6.53 (d, *J* = 1.8 Hz, 1H), 6.58 (d, *J* = 1.8 Hz, 1H), 7.28 (s, 1H); **^{13}C NMR**

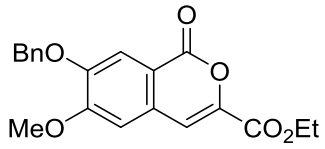
(50 MHz, $CDCl_3$): δ 14.2, 55.8, 56.5, 62.2, 100.9, 102.3, 112.0, 120.4, 127.3, 135.7, 156.2, 163.5, 165.6; **Anal. Calcd for** $C_{14}H_{14}O_6$: C, 60.63; H, 5.07. Found: C, 60.65; H, 5.10%.

Ethyl 6,7,8-trimethoxy-1-oxo-1*H*-isochromene-3-carboxylate (33e)



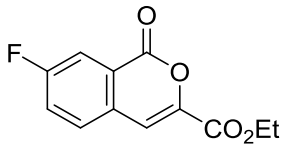
Yield: 90% (0.425 g); colorless solid; **mp**: 122-123 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 721, 997, 1018, 1119, 1194, 1261, 1360, 1437, 1473, 1592, 1655, 1719, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.8 Hz, 3H), 3.96 (s, 1H), 3.97 (s, 1H), 3.99 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 6.83 (s,1H), 7.17 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 55.9, 61.2, 62.0, 62.1, 105.0, 110.2, 131.5, 133.6, 134.5, 144.2, 154.8, 157.3, 159.3, 161.2; **Anal. Calcd for** $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.47; H, 5.25%.

Ethyl 7-(benzyloxy)-6-methoxy-1-oxo-1*H*-isochromene-3-carboxylate (33f)



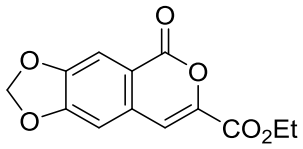
Yield: 92% (0.437 g); yellow solid; **mp**: 146-148 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 689, 765, 844, 1062, 1234, 1341, 1485, 1643, 1718, 1731, 2959, 3068; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.2 Hz, 3H), 4.01 (s, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 5.24 (s, 2H), 6.95 (s, 1H), 7.32-7.49 (m, 6H), 7.78 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 56.3, 62.0, 71.1, 108.0, 111.7, 112.0, 116.5, 127.7, 128.4, 128.8, 130.5, 135.6, 142.7, 150.8, 155.6, 160.5; **Anal. Calcd for** $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.74; H, 5.15%**.**

Ethyl 7-fluoro-1-oxo-1*H*-isochromene-3-carboxylate (33g)



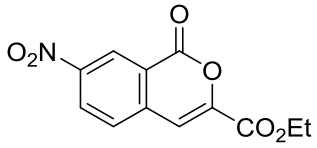
Yield: 95% (0.441 g); colorless solid; **mp**: 122-123 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 892, 1026, 1256, 1439, 1573, 1640, 1715, 1726, 2930, 3048; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.1 Hz, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 7.22-7.38 (m, 2H), 7.42 (s, 1H), 8.38 (dd, *J* = 5.5 and 8.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 62.5, 111.1 (d, *J* = 2.6 Hz), 113.2 (d, *J* = 22.5 Hz), 118.7 (d, *J* = 22.6 Hz), 119.3 (d, *J* = 2.6 Hz), 133.6 (d, *J* = 10.2 Hz), 137.8 (d, *J* = 10.2 Hz), 144.8, 159.6, 159.9, 166.9 (d, *J* = 256.3 Hz); **Anal. Calcd for** $C_{12}H_9FO_4$: C, 61.02; H, 3.84. Found: C, 61.05; H, 3.88%.

Ethyl 5-oxo-5*H*-[1,3]dioxolo[4,5-*g*]isochromene-7-carboxylate (33h)



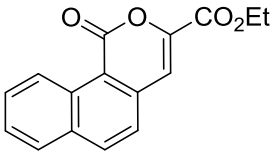
Yield: 95% (0.444 g); colorless solid; **mp**: 162-163 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 832, 895, 955, 1065, 1160, 1341, 1482, 1643, 1711, 1728, 2928, 3054; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.8 Hz, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 6.16 (s, 2H), 6.93 (s, 1H), 7.36 (s, 1H), 7.68 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 62.0, 102.7, 105.7, 108.1, 111.9, 118.2, 132.3, 142.6, 150.3, 153.7, 160.1; **Anal. Calcd for** $C_{13}H_{10}O_6$: C, 59.55; H, 3.84. Found: C, 59.57; H, 3.85%.

Ethyl 7-nitro-1-oxo-1*H*-isochromene-3-carboxylate (33i)



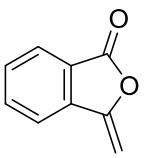
Yield: 90% (0.421 g); yellow solid; **mp**: 162-166 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 755, 804, 1062, 1224, 1349, 1485, 1653, 1719, 1721, 2950, 3078; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (t, *J* = 7.2 Hz, 3H), 4.45 (q, *J* = 7.0, 2H), 7.56 (s, 1H), 8.42 (dd, *J* = 2.2 and 8.6 Hz, 1H), 8.45 (d, *J* = 2.1 Hz, 1H), 8.52 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 62.8, 110.6, 122.5, 124.5, 126.7, 132.2, 136.4, 145.6, 151.8, 158.8, 159.4; **Anal. Calcd for** $C_{12}H_9NO_6$: C, 54.76; H, 3.45, N, 5.32. Found: C, 54.77; H, 3.41, N, 5.31%.

Ethyl 1-oxo-1*H*-benzo[*h*]isochromene-3-carboxylate (33j)



Yield: 93% (0.435 g); colorless solid; **mp**: 164-165 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 680, 748, 819, 852, 1065, 1185, 1368, 1488, 1632, 1718, 1732, 2935, 3054; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.46 (t, *J* = 7.3 Hz, 3H), 4.45 (q, *J* = 7.5 Hz, 2H), 7.54-7.57 (m, 2H), 7.68 (dt, *J* = 7.8 and 1.3 Hz, 1H), 7.79 (dt, *J* = 7.7 and 1.5 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H); 8.18 (d, *J* = 8.9 Hz, 1H), 9.74 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 62.3, 112.4, 117.3, 124.3, 127.1, 128.0, 128.8, 129.9, 131.5, 134.1, 136.7, 137.5, 144.8, 159.8, 160.0; **Anal. Calcd for** $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.67; H, 4.55%.

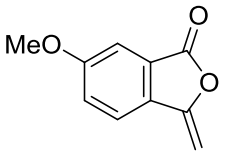
3-Methyleneisobenzofuran-1(3*H*)-one (34k)



Yield: 95% (0.422 g); colorless solid; **mp**: 57-58 °C; IR ($CHCl_3$, cm^{-1}): υ_{max} 956, 1018, 1278, 1478, 1784, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.24 (dd, *J* = 3.0 and 6.2 Hz,

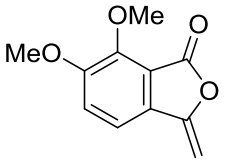
2H), 7.57-7.62 (m, 1H), 7.72 (d, *J* = 4.0 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 91.1, 120.6, 125.2, 130.4, 134.4, 139.0, 151.8, 166.8; **Anal. Calcd for** $C_9H_6O_2$: C, 73.97; H, 4.14. Found: C, 73.92; H, 4.12%.

6-Methoxy-3-methyleneisobenzofuran-1(3*H*)-one (34l)



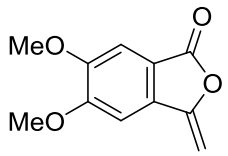
Yield: 95% (0.430 g); colorless solid; **mp**: 87-88 °C; IR ($CHCl_3$, cm^{-1}): υ_{max} 756, 1026, 1100, 1180, 1240, 1303, 1346, 1456, 1491, 1606, 1660, 1774, 2943, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.94 (s, 3H), 5.15 (d, *J* = 3.0 Hz, 1H), 5.18 (d, *J* = 2.9 Hz, 1H), 7.06-7.09 (m, 2H), 7.79 (dd, *J* = 7.9 and 1.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.9, 90.8, 103.7, 117.8, 118.5, 126.8, 141.6, 151.8, 165.0, 166.3; **Anal. Calcd for** $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.16; H, 4.59%.

6,7-Dimethoxy-3-methyleneisobenzofuran-1(3*H*)-one (34m)



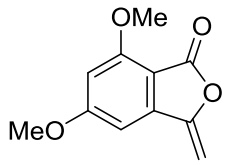
Yield: 94% (0.432 g); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1024, 1275, 1458, 1499, 1719, 1773, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.94 (s, 3H), 4.14 (s, 3H), 5.02 (d, *J* = 2.8 Hz, 1H), 5.06 (d, *J* = 2.9 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.9, 62.5, 88.8, 115.3, 119.4, 121.4, 132.5, 148.1, 151.3, 153.7, 164.2; **Anal**. **Calcd for** $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.10; H, 4.91%.

5,6-Dimethoxy-3-methyleneisobenzofuran-1(3*H*)-one (34n)



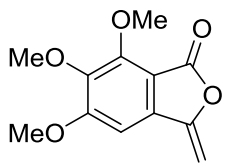
Yield: 93% (0.427 g); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1022, 1104, 1229, 1278, 1321, 1369, 1466, 1504, 1764, 2919; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.01 (s, 3H), 5.05 (d, *J* = 2.8 Hz, 1H), 5.13 (d, *J* = 2.9 Hz, 1H), 7.05 (s, 1H), 7.25 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.2, 56.7, 89.5, 101.5, 105.3, 117.8, 133.4, 151.8, 151.9, 155.1, 166.7; **Anal**. **Calcd for** $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.10; H, 4.87%.

5,7-Dimethoxy-3-methyleneisobenzofuran-1(3*H*)-one (34o)



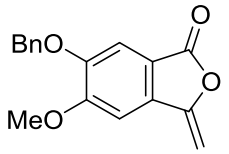
Yield: 92% (0.423 g), colorless solid; **mp**: 228-229 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 779, 856, 1024, 1275, 1458, 1499, 1719, 1773, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.96 (s, 3H), 4.01 (s, 3H), 5.06 (d, *J* = 2.8 Hz, 1H), 5.12 (d, *J* = 2.9 Hz, 1H), 7.05 (s, 1H), 7.24 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.4, 56.4, 89.5, 101.5, 105.4, 118.0, 133.5, 151.9, 152.0, 155.2, 166.7; **Anal. Calcd for** $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.10; H, 4.88%.

5,6,7-Trimethoxy-3-methyleneisobenzofuran-1(3*H*)-one (34p)



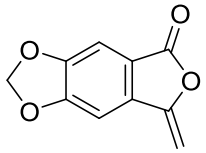
Yield: 94% (0.436 g); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1019, 1112, 1199, 1262, 1345, 1418, 1480, 1597, 1771, 2853, 2942; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.99 (s, 3H), 4.16 (s, 3H), 5.06 (d, *J* = 2.9 Hz, 1H), 5.11 (d, *J* = 3.2 Hz, 1H), 6.85 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.4, 61.4, 62.2, 89.6, 97.7, 109.9, 136.3, 151.5, 151.9, 159.9; **Anal. Calcd for** $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.05; H, 5.09%.

6-(Benzyloxy)-5-methoxy-3-methyleneisobenzofuran-1(3*H*)-one (34q)



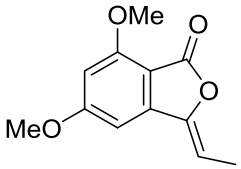
Yield: 93% (0.437 g); colorless solid; **mp**: 235-236 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 980, 1035, 1136, 1182, 1273, 1352, 1415, 1482, 1588, 1775, 2953, 3040; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.01 (s, 3H), 5.0 (d, *J* = 2.9 Hz, 1H), 5.1 (d, *J* = 2.9 Hz, 1H), 5.20 (s, 2H) 7.1 (s, 1H), 7.28-7.5 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.3, 71.0, 89.5, 101.8, 107.2, 117.8, 127.4, 128.3, 128.7, 133.7, 135.6, 151.0, 151.8, 155.6, 166.6; **Anal. Calcd for** $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.31; H, 5.04%.

7-Methylene-[1,3]dioxolo[4,5-*f*]isobenzofuran-5-(7*H*)-one (34r)



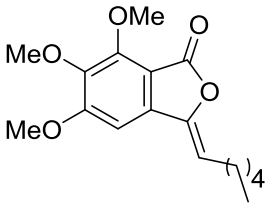
Yield: 94% (0.429 g); colorless solid; **mp**: 263-265 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 770, 866, 1024, 1275, 1458, 1499, 1719, 1773, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.01 (d, *J* = 3.0 Hz, 1H), 5.11 (d, *J* = 2.9 Hz, 1H), 6.15 (s, 2H), 7.01 (s, 1H), 7.18 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 90.1, 99.9, 102.8, 103.4, 119.7, 135.6, 150.5, 151.6, 153.9, 166.1; **Anal**. **Calcd for** $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 63.14; H, 3.18%.

(*Z*)-3-Ethylidene-5,7-dimethoxyisobenzofuran-1(3*H*)-one (34s)



Yield; 94% (0.434 g); colorless solid; **mp**: 147-148 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 668, 756, 1032, 1052, 1160, 1215, 1342, 1496, 1691, 1763, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.97 (d, *J* = 7.1 Hz, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 5.56 (q, *J* = 7.1 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.2, 55.8, 55.8, 94.4, 99.5, 103.6, 105.7, 143.7, 146.2, 159.2, 164.6, 166.7; **Anal**. **Calcd for** $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.41; H, 5.48%.

(*Z*)-5,6,7-Trimethoxy-3-pentylideneisobenzofuran-1(3*H*)-one (34t)



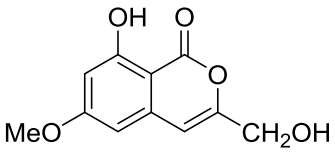
Yield: 91% (0.429 g); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 660, 760, 1052, 1152, 1160, 1215, 1342, 1496, 1691, 1764, 3030; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.34-1.52 (m, 6H), 1.55-1.66 (m, 4H), 3.87 (s, 3H), 3.95 (s, 3H), 4.14 (3H), 5.21 (d, *J* = 5.2 Hz, 1H), 6.68 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.5, 22.7, 25.8, 29.2, 31.8, 61.3, 62.2, 62.3, 81.7, 99.8, 111.4, 142.0, 145.2, 152.5, 156.7, 167.9; **Anal. Calcd for** $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.68; H, 7.28%.

Section II

Synthesis of Bioactive Molecules Cytogenin and (*Z*)-3-Butylidene-5-Hydroxy-7-Methoxyphthalide

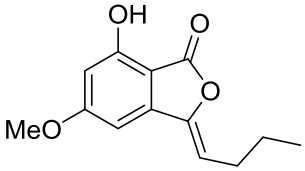
3.2.1 Introduction

Cytogenin (**36**), a natural isocoumarin was first found in the cultured broth of *Streptoverticillium eurocidicum* MI43-37F11 and possesses the potent antitumor bioactivity against Ehrlich carcinoma.[18] In addition, it has shown anti-inflammatory activity against collagen-induced arthritic model in mice.[19,20] Studies on the activity of cytogenin have futher claimed that it exerts antitumor effects by activation or modulation of macrophages and T-cells.[21] Also, alkylidenephthalide moieties (**37 & 38**) possesses an important structural motif due to their potent biological activities and have shown promising activities as antidiabetic,[22] antispasmodic,[23] anticoagulant,[24] and antiproliferative.[25] Also they are widely used as an attractive intermediates for the synthesis of a variety of heterocyclic and carbocyclic compounds (**Fig 6**).



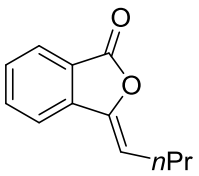
36

Cytogenin



37

(*Z*)-3-Butylidene-7-hydroxy-5-methoxyphthalide



38

3-Butylidenephthalide

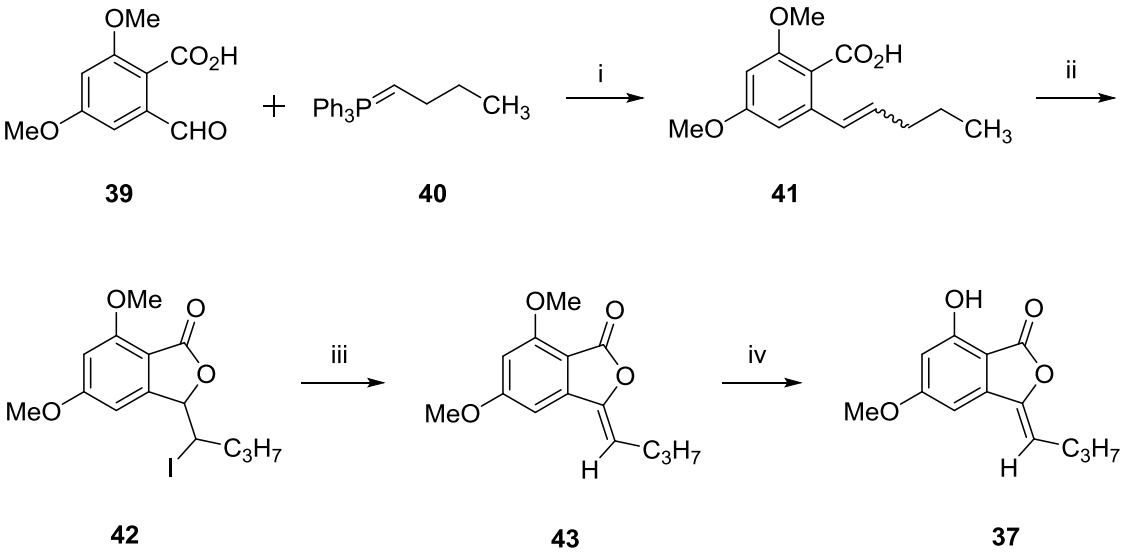
Fig. 6: Bioactive molecules with isocoumarin (**36**) and alkylidenephthalides (**37 & 38**) skeleton

3.2.2 Review of Literature

Literature search revealed that there are very less reports available for the total synthesis of cytogenin (**36**) and (*Z*)-3-butylidene-7-hydroxy-5-methoxypthalide (**37**) which are described below:

Mali's approach (1990)[26]

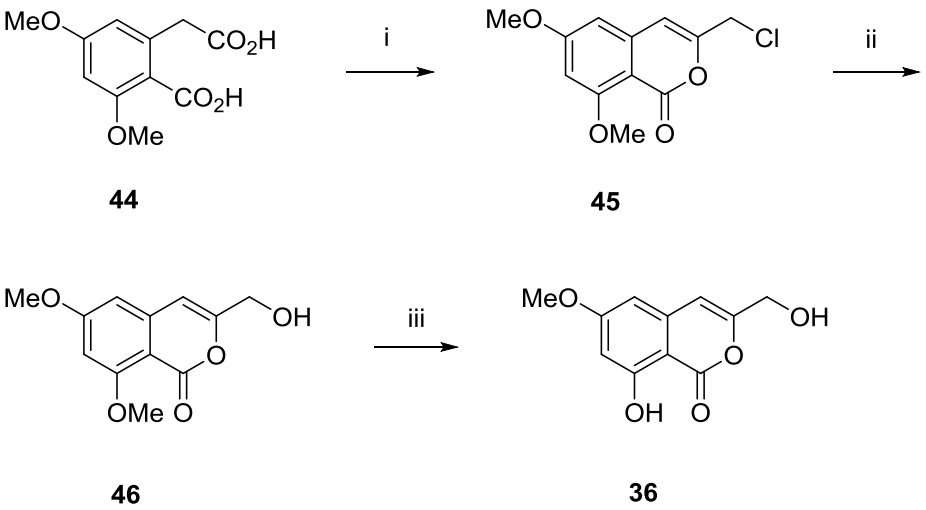
Mali *et al.* have described the iodine catalyzed lactonization for the synthesis of (*Z*)-3-butylidene-5,7-dihydroxyphthalide (**37**). Thus, 2-formyl-4,6-dimethoxybenzoic acid (**39**) was treated with *n*-butylidenetriphenylphosphorane **40** (generated *in situ* from *n*-butyltriphenylphosphonium bromide and potassium *tert*-butoxide) to afford 2-olefinic-benzoic acid **41** in 86% yield. Olefin **41** was then dissolved in sodium bicarbonate and reacted with a solution of iodine in aq. potassium iodide to obtain iodophthalide **42** in 79% yield. Refluxing of iodophthalide **42** in sodium acetate furnished the (*Z*)-3-butylidene-5,7-methoxy-phthalide **43**, which was subsequently demethylated to obtain (*Z*)-3-butylidene-7-hydroxy-5-methoxypthalide (**37**) in 77% yield (**Scheme 11**).



Scheme 11: (i) *tert*-BuOK, THF, 0 °C, 1 h, 86%; (ii) I_2, aq. KI, $NaHCO_3$, rt, 2 h, 79%; (iii) NaOAc, EtOH, reflux, 2 h, 63%; (iv) $AlCl_3$, CH_2Cl_2, rt, 1 h, 77%.

Saeed's approach (2004)[27]

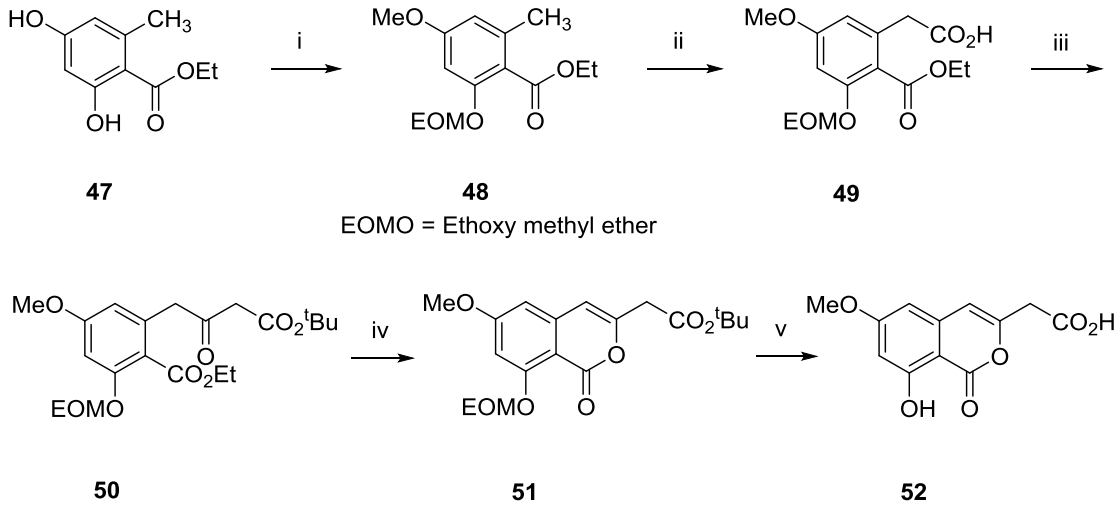
Saeed *et al.* have developed a novel route to the synthesis of cytogenin (**36**) *via* the condensation of dimethoxyhomophthalic acid **44** with chloroacetyl chloride at higher temperature (200 °C) to provide 3,5-dimethoxyisocoumarin (**45**) in 65% yield. Then, isocoumarin **45** underwent hydrolysis with aq. NaOH to furnish alcohol **46** followed by selective demethylation resulted in cytogenin **36** in 78% yield (**Scheme 12**).



Scheme 12: (i) $ClCH_2COCl$, 200 °C, 4 h, 65%; (ii) 0.05% aq. NaOH (0.1 to 0.05%), THF, reflux, 4h; (iii) $AlCl_3$, $C_6H_5NO_2$, 80 °C, 78%.

Taylor's approach (2004)[28]

Taylor *et al.* have commenced the synthesis of phthalide **52** from readily available ethyl orsellinate **47**, which on regioselective methylation under MacKenzie's conditions afforded 4-methoxy derivative followed by protection of phenolic hydroxyl group as its ethoxymethyl ether **48** in 96% yield. Further, methoxy ether (EOMO) **48** was treated with LDA to generate benzylic anion, which was subsequently quenched with carbon dioxide to result in homophthalic acid **49**.



Scheme 13: (i) (a) MeI, K_2CO_3, acetone, 6 h, 90%; (b) $^{i}Pr_2NEt$, CH_2Cl_2, 25 °C overnight, 96%; (ii) LDA, CO_2, THF, -78 °C, 1.5 h, 75%; (iii) Meldrum's acid, DCC, DMAP, CH_2Cl_2, 25 °C, 24 h, followed by *tert*-BuOH, PhH, reflux, 14 h, 96%; (iv) LDA, -78 °C, 40 min., THF, 65%; (v) (a) HCl, *i*-PrOH, 25 °C, 0.5 h; (b) TFA, Et_3SiH, CH_2Cl_2, 94% for two steps.

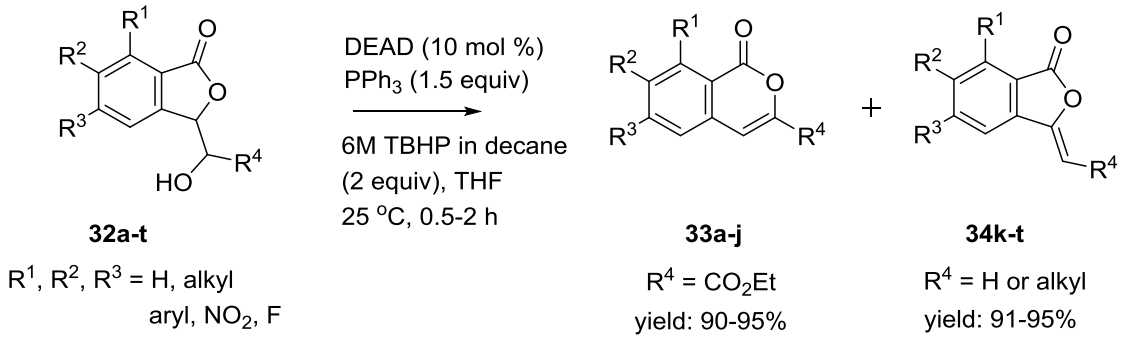
Coupling reaction of acid **49** with meldrum's acid under heating condition furnished the β-ketoester **50**, which was followed by lactonization in the presence of LDA to afford isocoumarin **51**. Acid hydrolysis of ester **51** to gave the corresponding acid, which on further deprotection of its methyl ether resulted in compound **52**, a precursor of **36** in 94% yield (**Scheme 13**).

3.2.3 Present Work

3.2.3.1 Objective

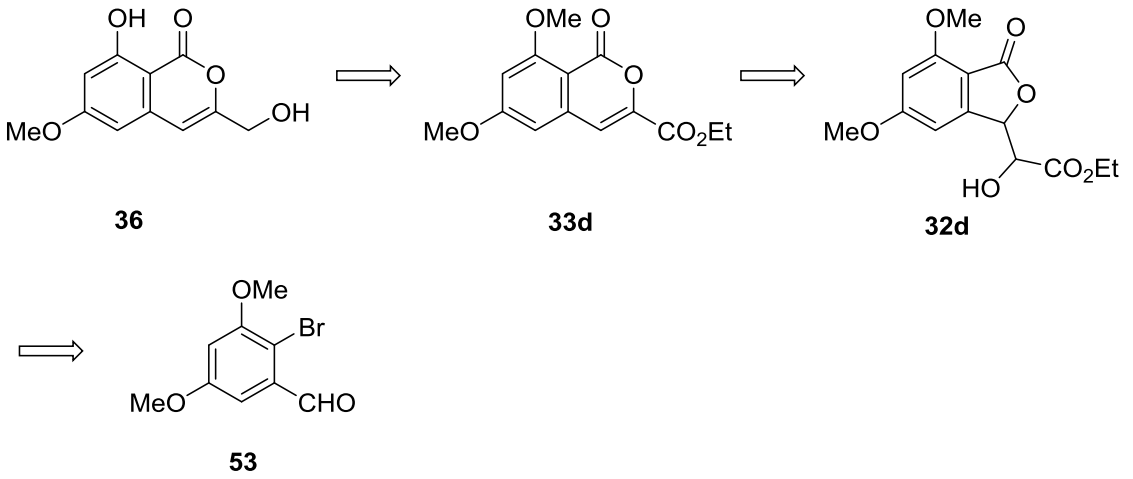
As can be seen from the literature, many of the reported methods suffer from certain drawbacks like multistep reaction sequences, use of excess acid and low yields. In this regard, an efficient protocol for the synthesis of these bioactive molecules (**36 and 37**) is highly desirable.

Recently, we have developed a new synthetic route involving the ring expansion of 3-substituted phthalide **32a-t** under typical Mitsunobu conditions (PPh_3, DEAD, THF) leading to the formation of isocoumarins **33a-j** and the eliminated products alkylidenephthalides **34k-t** (**Scheme 14**).[29] In this section, an application of this methodology to a short synthesis of two biologically active molecules namely cytotoxic agent cytogenin (**36**), and formal synthesis of antiarteriosclerotic agent (Z)-3-butylidene-7-hydroxy-5-methoxyphthalide (**37**) is presented.



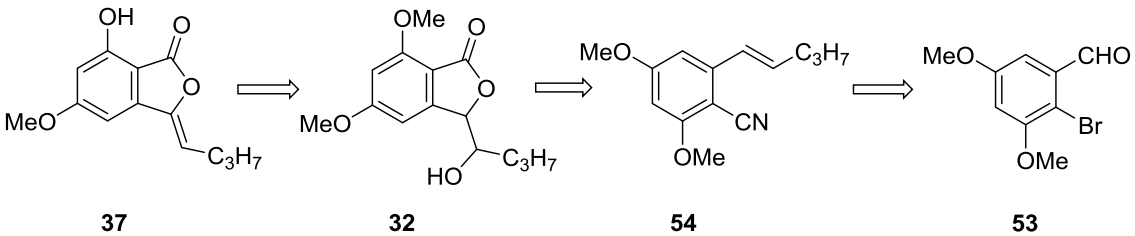
Scheme 14: Intramolecular ring expansion or elimination of 3-(1-hydroxycarbethoxy)phthalide (**32**)

The retrosynthetic scheme of cytogenin (**36**) is shown in **Scheme 15**. We envisaged that the synthesis of **36** could be achieved from isocoumarin **33d**, which could in turn be obtained by the ring expansion of phthalide **32d** under Mitsunobu reaction protocol. The synthesis of **32d** could be realized by CN-assisted lactonization of a cyano cinnamate, which could be obtained from two carbon-homologation and -Br displacement with -CN of 2-bromo-3,5-dimethoxybenzaldehyde (**53**).



Scheme 15: Retrosynthetic analysis of cytogenin (**36**)

Retrosynthetic analysis of (*Z*)-3-butylidene-7-hydroxy-5-methoxypthalide (**37**) revealed that phthalide **32** could be visualized as an intermediate. The phthalide **32** could be obtained from



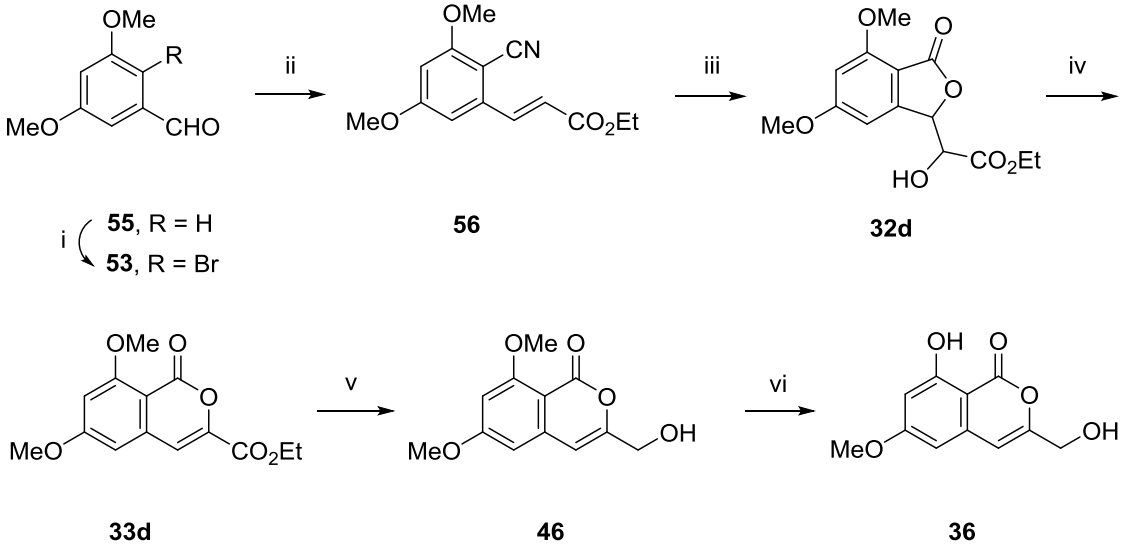
Scheme 16: Retrosynthetic analysis of (*Z*)-3-butylidene-7-hydroxy-5-methoxypthalide (**37**)

cyano cinnamate **54** by CN-assisted lactonization, which could in turn be achieved by –Br displacement with –CN and Julia-olefination of 2-bromo-3,5-dimethoxybenzaldehyde **53** (**Scheme 16**).

3.2.4 Results and Discussion

3.2.4.1 Synthesis of Cytogenin (36)

The complete synthetic sequences for the synthesis of cytogenin (**36**) are shown in **Scheme 17**. Its synthesis commenced with the commercially available starting material 3,5-dimethoxybenzaldehyde (**55**), which was subjected to bromination with N-bromosuccinamide to afford the 2-bromo-3,5-dimethoxybenzaldehyde (**53**) in 90% yield.



Scheme 17: (i) NBS, CH_3CN:H_2O (4:1), 3 h, rt, 90%; (ii) (a) Ph_3P=$CHCO_2Et$, benzene, reflux, 6 h; (b) CuCN, DMF, reflux for overnight, 85% for two steps; (iii) OsO_4, NMO, acetone:H_2O (4:1), rt, 12 h, 87%; (iv) DEAD, Ph_3P, TBHP, THF, rt, 3 h, 92%; (v) $NaBH_4$, THF followed MeOH, 0 °C, 4 h, 87%; (vi) BBr_3, CH_2Cl_2, -5 °C, 1 h, 76%.

The formation of compound **53** was confirmed from ^{1}H NMR spectrum, which showed two doublets at δ 7.03 (d, *J* = 2.8 Hz, 1H) and 6.70 (d, *J* = 2.8 Hz, 1H) corresponding to

a two aromatic protons with *meta* coupling. Also its ^{13}C NMR spectrum displayed two carbon signals at δ 107.7 and 108.9 due to presence of two aromatic carbons (**Fig. 7**).

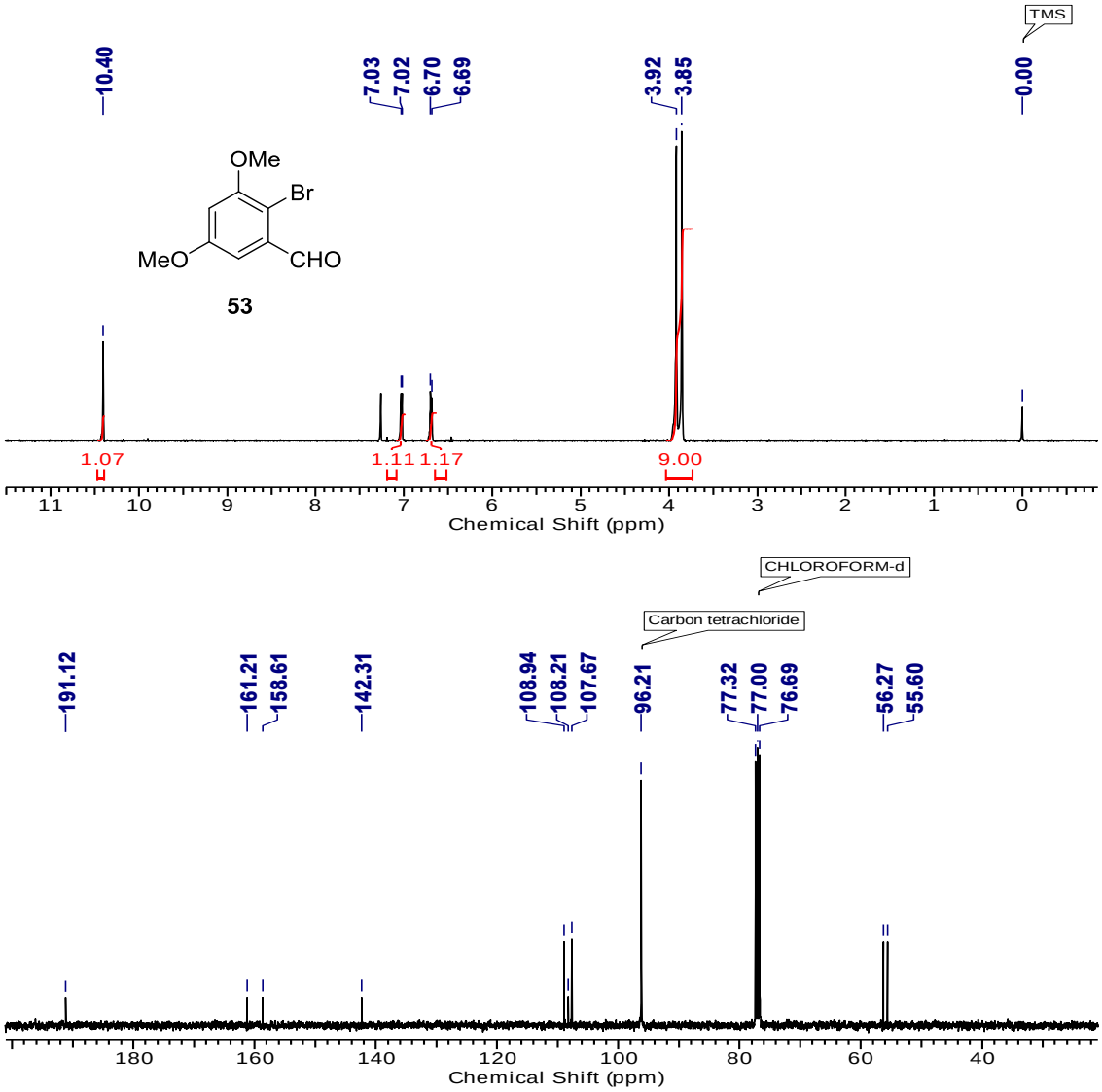


Fig. 7: ^{1}H and ^{13}C NMR spectra of aldehyde **53**

Then, aldehyde **53** was subjected to Wittig-Horner olefination reaction ($Ph_3P{=}CHCO_2Et$, PhH, 90 °C) to afford α,β-unsaturated ester, which was subsequently treated under Rosenmund-von Braun reaction conditions (NaCN, DMF, 150 °C) that gave cyanocinnamate derivative **56** in 85% for two steps. The ^{1}H NMR spectrum of **56** showed two typical doublets at δ 6.48 (d, J = 15.6 Hz, 1H) and 7.88 (d, J = 15.6 Hz, 1H) corresponding to *trans* olefinic protons of cyanocinnamate. Further, its structure

was supported by ^{13}C NMR spectrum, which displayed two carbon peaks at δ 165.6 and 114.8 indicating a carbonyl carbon of an ester and –CN group respectively (**Fig. 8**). Its IR spectrum showed appearance of strong vibrational stretching frequencies at 2212 and 1656 cm^{-1} due to presence of –CN and ester carbonyl functionalities respectively.

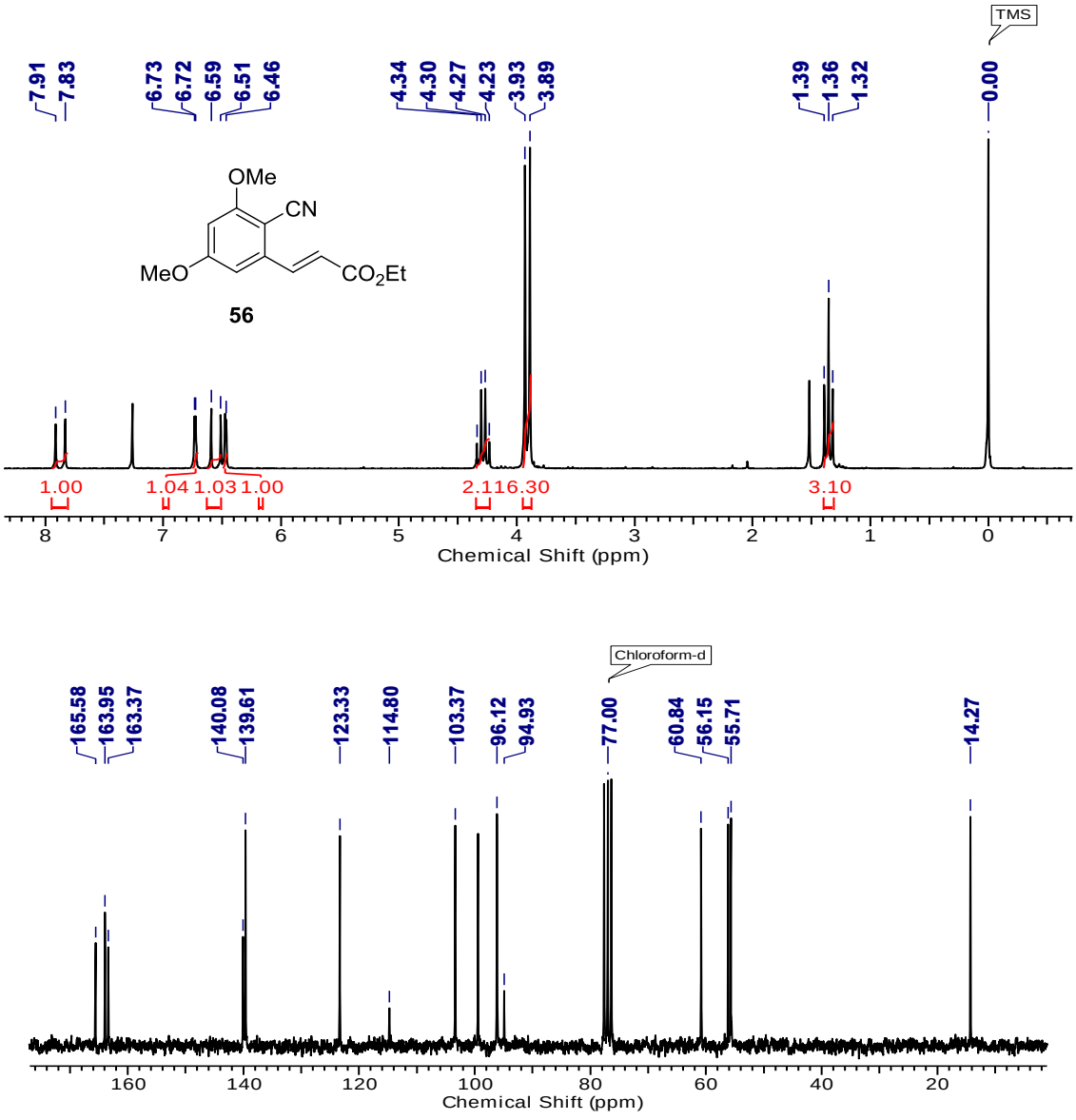


Fig. 8: ^{1}H and ^{13}C NMR spectra of cyanocinnamate **56**

Further, cyanocinnamate **56** was dihydroxylatd under Sharpless dihydroxylation condition (OsO_4/NMO, acetone:H_2O 4:1, rt) followed by *in situ* CN-assisted lactonization that afforded 3-substituted phthalide **32d** in excellent yield (87%) and diastereomeric ratio (>98%). The structure of 3-substituted phthalide **32d** was

confirmed from ^{1}H NMR spectrum, which showed two typical singlets appearing at δ 5.67 (s, 1H) and 4.61 (s, 1H) indicative of the presence of methine protons of phthalide ring and secondary hydroxyl group respectively. It was further substantiated by the appearance of two typical carbon signals at δ 170.6 and 172.5 corresponding to –C=O carbons of ester and lactone group respectively in its ^{13}C NMR spectrum (**Fig. 9**). Its IR spectrum displayed three strong and broad vibrational stretching frequencies at 1723, 1762 and 3414 cm^{-1} confirming the presence of ester, γ-lactone-carbonyl and –OH groups respectively.

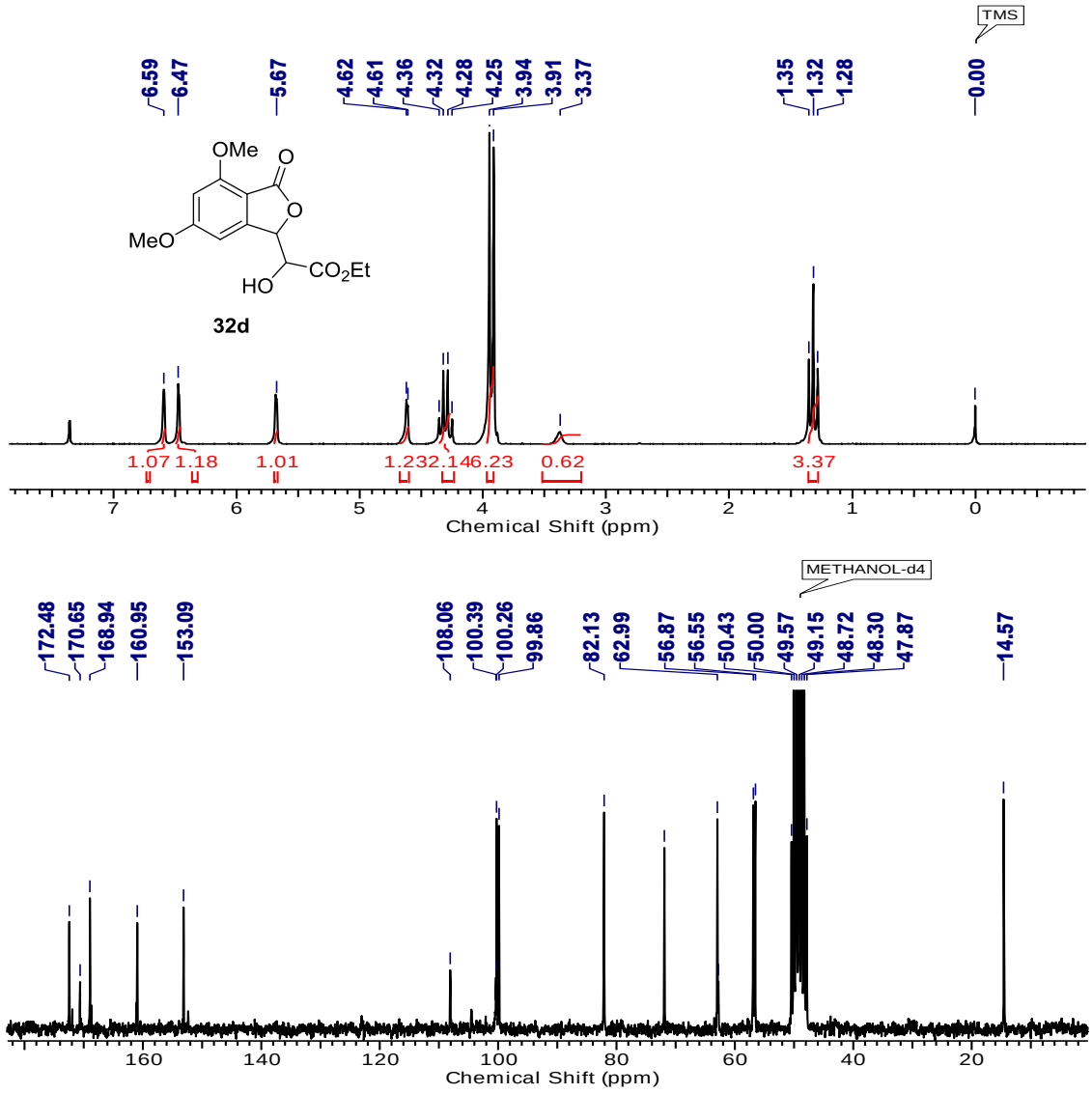


Fig. 9: ^{1}H and ^{13}C NMR spectra of phthalide **32d**

The 3-substituted phthalide **32d** then underwent intramolecular ring expansion under Mitsunobu reaction conditions (TBHP, DEAD, THF, rt) to provide the corresponding isocoumarin **33d** in 92% yield. Its ^{1}H NMR spectrum showed a singlet at δ 7.22 (s, 1H) attributed to olefinic proton of isocoumarin unit while two carbon signals at δ 165.5 and 120.4 are due to presence of carbonyl and olefinic carbons respectively in its ^{13}C NMR spectrum (**Fig. 10**), thus, confirming the formation of isocoumarin **33d**.

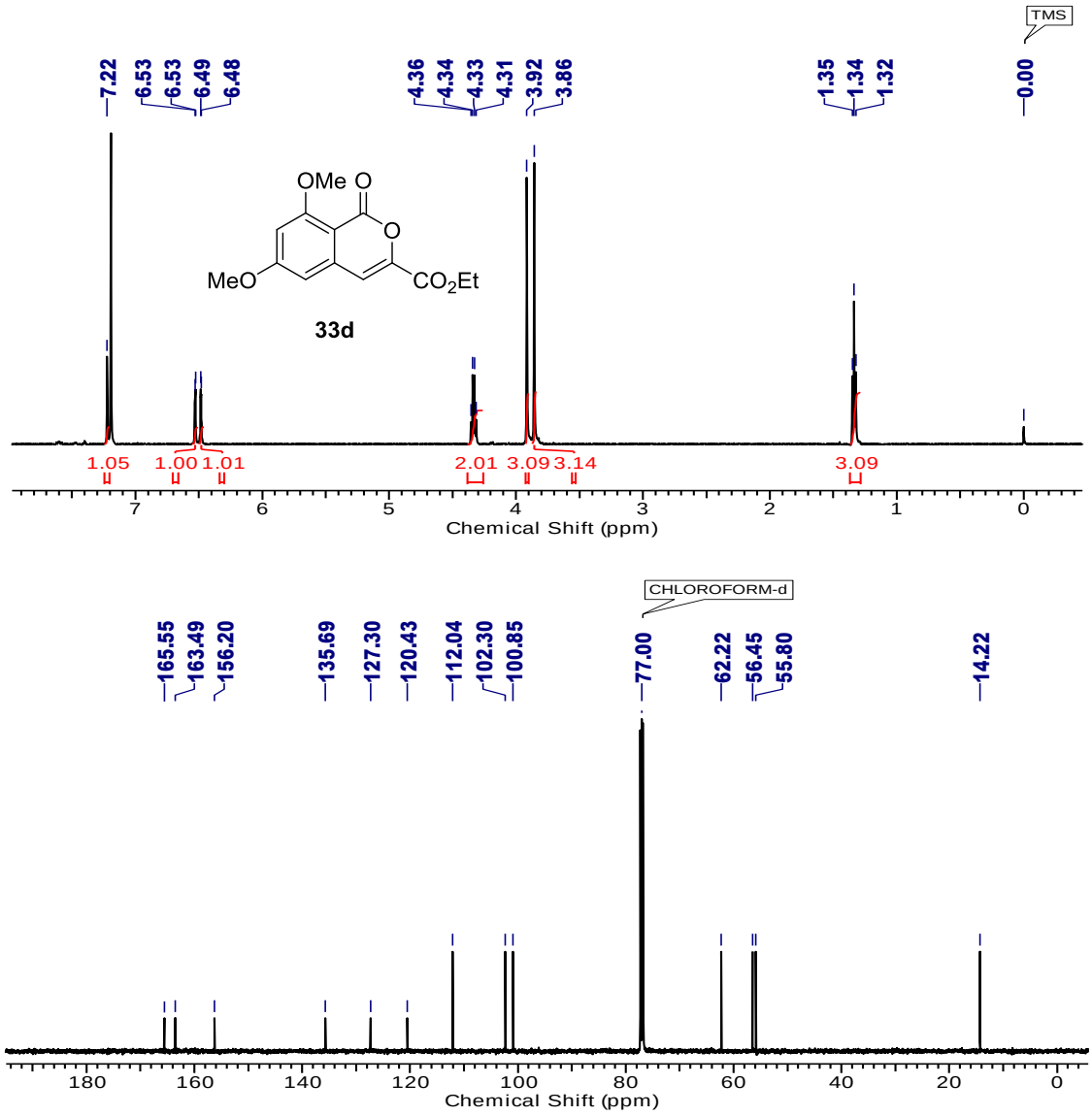


Fig. 10: ^{1}H and ^{13}C NMR spectra of isocoumarin **33d**

The ester functionality of isocoumarin **33d** was selectively reduced with $NaBH_4$ to afford alcohol **46** in 87% yield. Its structure was ascertained by a typical singlet appearing at δ 4.42 (s, 2H) corresponding to methylene protons attached to –OH group in its ^{1}H NMR spectrum. Further, it was supported by ^{13}C NMR spectrum, which showed a carbon signal at δ 61.3 due to presence of methylene carbon attached to –OH group (**Fig. 11**). Also, its IR spectrum displayed a strong and broad vibrational stretching frequency at 3460 cm^{-1} due to –OH functionality.

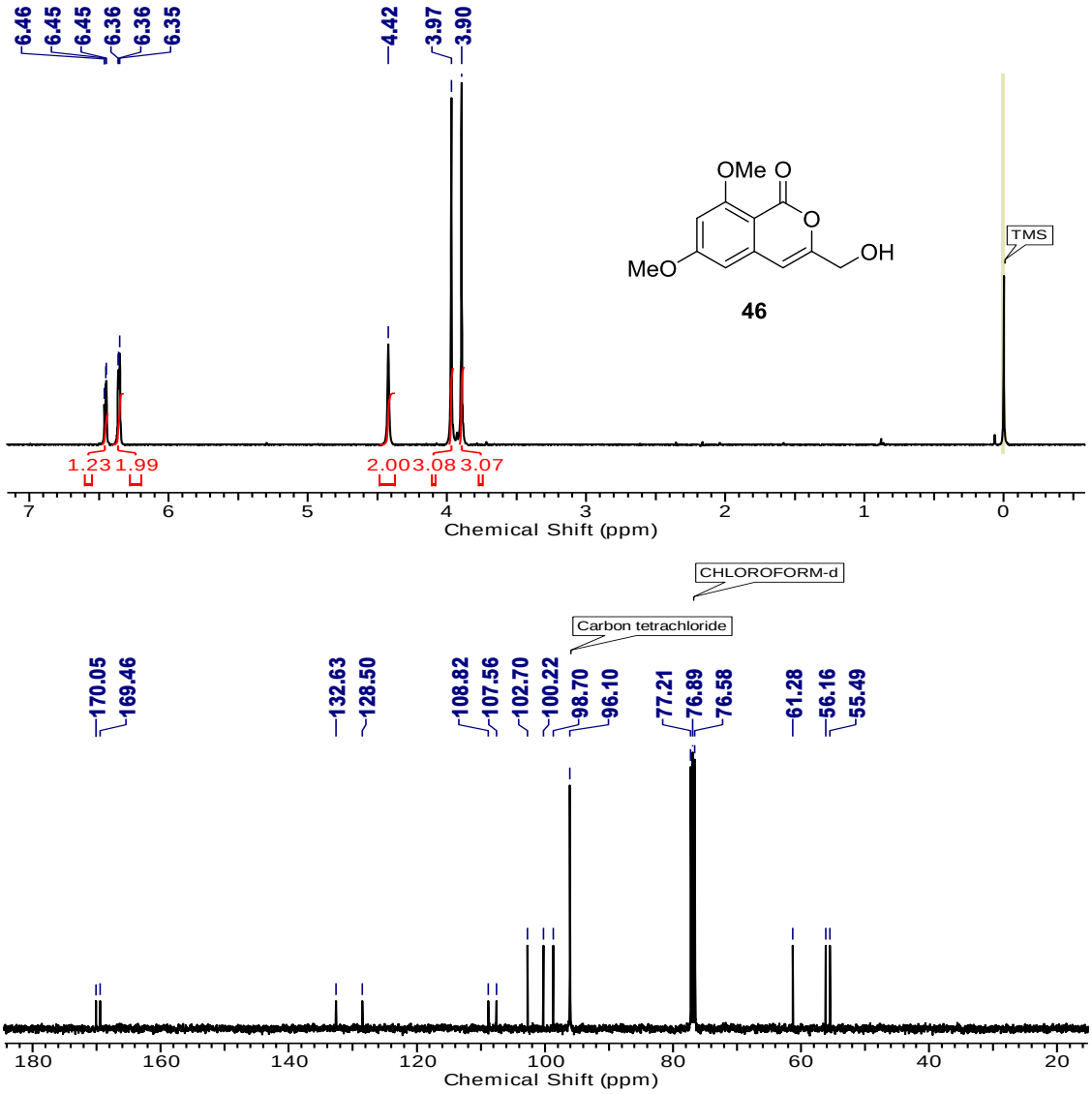


Fig. 11: ^{1}H and ^{13}C NMR spectra of alcohol **46**

Finally, selective demethylation of compound **46** under BBr_3, MeOH reaction conditions resulted in final molecule cytogenin (**36**) in 76% yield. The formation of cytogenin (**36**) was confirmed from ^1H NMR spectrum, which showed appearance of a typical singlet at δ 11.11 (s, 1H) corresponding to phenolic –OH group. Also, its ^{13}C NMR spectrum showed the presence of carbon signal at δ 56.4 due to methoxy group (**Fig 12**). Its IR spectrum displayed a strong and broad absorption band at 3460 cm^{-1} attributable to –OH functionality.

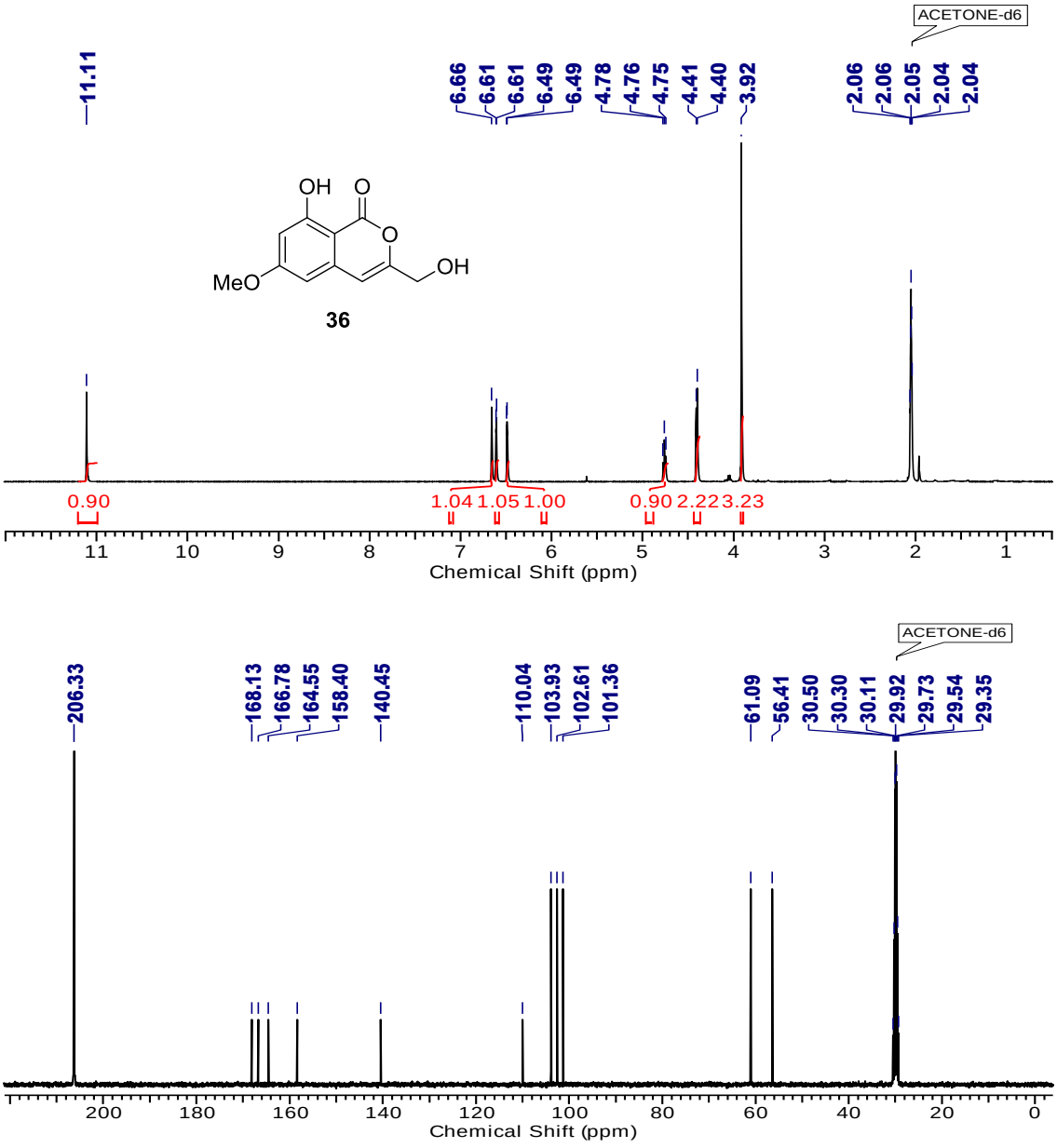
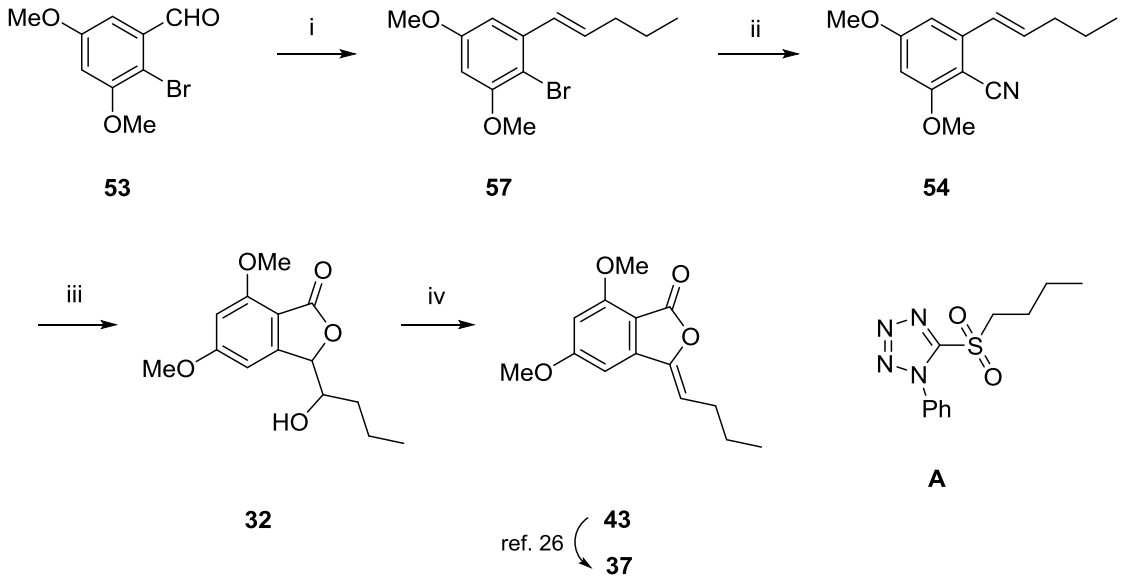


Fig. 12: ^1H and ^{13}C NMR spectra of cytogenin **36**

3.2.4.2 Synthesis of (*Z*)-3-butylidene-7-hydroxy-5-methoxy phthalide (37)

The formal synthesis of (*Z*)-3-butylidene-7-hydroxy-5-methoxy phthalide (**37**) was achieved in 5 steps starting from 2-bromo-3,5-dimethoxybenzaldehyde (**53**). Julia olefination of aldehyde **53** with sulfone **A** using NaHMDS as base furnished olefin **57** (*E*:*Z* = 98:2) in 85% yield (**Scheme 18**).



Scheme 18: (i) sulfone **A**, NaHMDS, THF, -78 °C, 8 h, 85%; (ii) NaCN, DMF, 150 °C, 12 h, 84%; (iii) OsO_4, NMO, acetone:H_2O (4:1), 25 °C, 12 h, 90%; (iv) DEAD, TBHP, Ph_3P, THF, 25°C, 3 h, 92%.

The formation of olefin **57** was confirmed from ^{1}H NMR spectrum, which showed a characteristic multiplet at δ 6.0-6.15 (m, 1H) and a doublet at δ 6.73 (d, *J* = 15.6 Hz, 1H) corresponding to olefinic protons with *trans* stereochemistry. Also, its ^{13}C NMR spectrum displayed typical carbon signals at δ 35.2, 22.4 and 18.9 accounting for the carbons of alkyl group (**Fig. 13**).

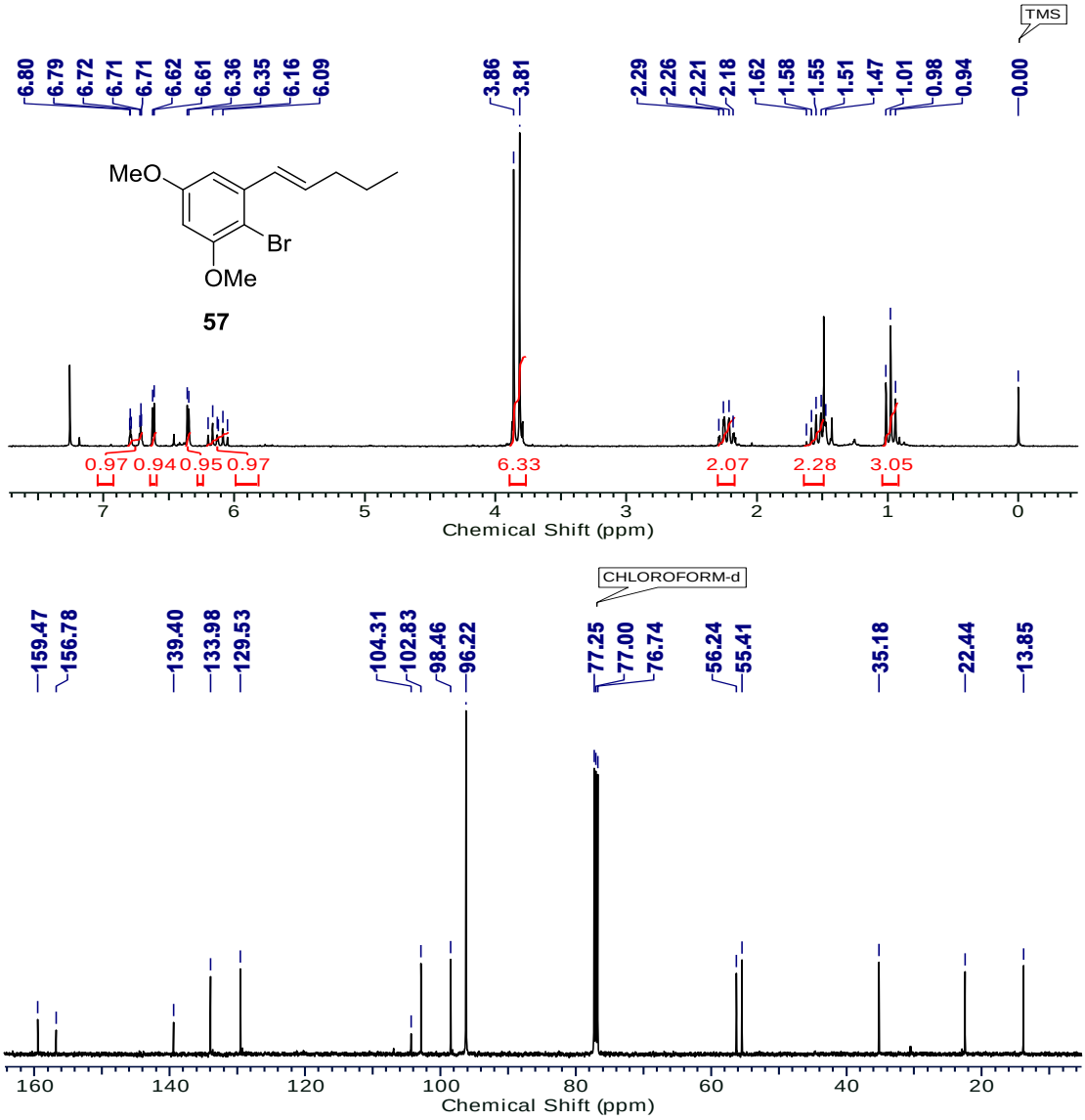


Fig. 13: ^{1}H and ^{13}C NMR spectra of olefin **57**

Olefin **57** then underwent bromide displacement with cyanide (NaCN, DMF, reflux overnight) to afford cyano derivative **54** with good yield (84%). The IR spectrum of **54** showed a strong vibrational stretching frequency at 2210 cm^{-1} due to presence of –CN group. Its ^{1}H NMR spectrum displayed a shielded multiplet at δ 6.27-6.39 (m, 1H) and a doublet at δ 6.64 (d, *J* = 15.8 Hz, 1H) corresponding to two *trans* olefinic protons respectively. Further, its structure was supported by ^{13}C NMR spectrum, which showed two typical carbon signals at δ 93.4 and 115.8 due to the aromatic quaternary carbon

attached to -CN group and carbon of –CN functionality respectively, thus, confirming the formation of **54** (**Fig. 14**).

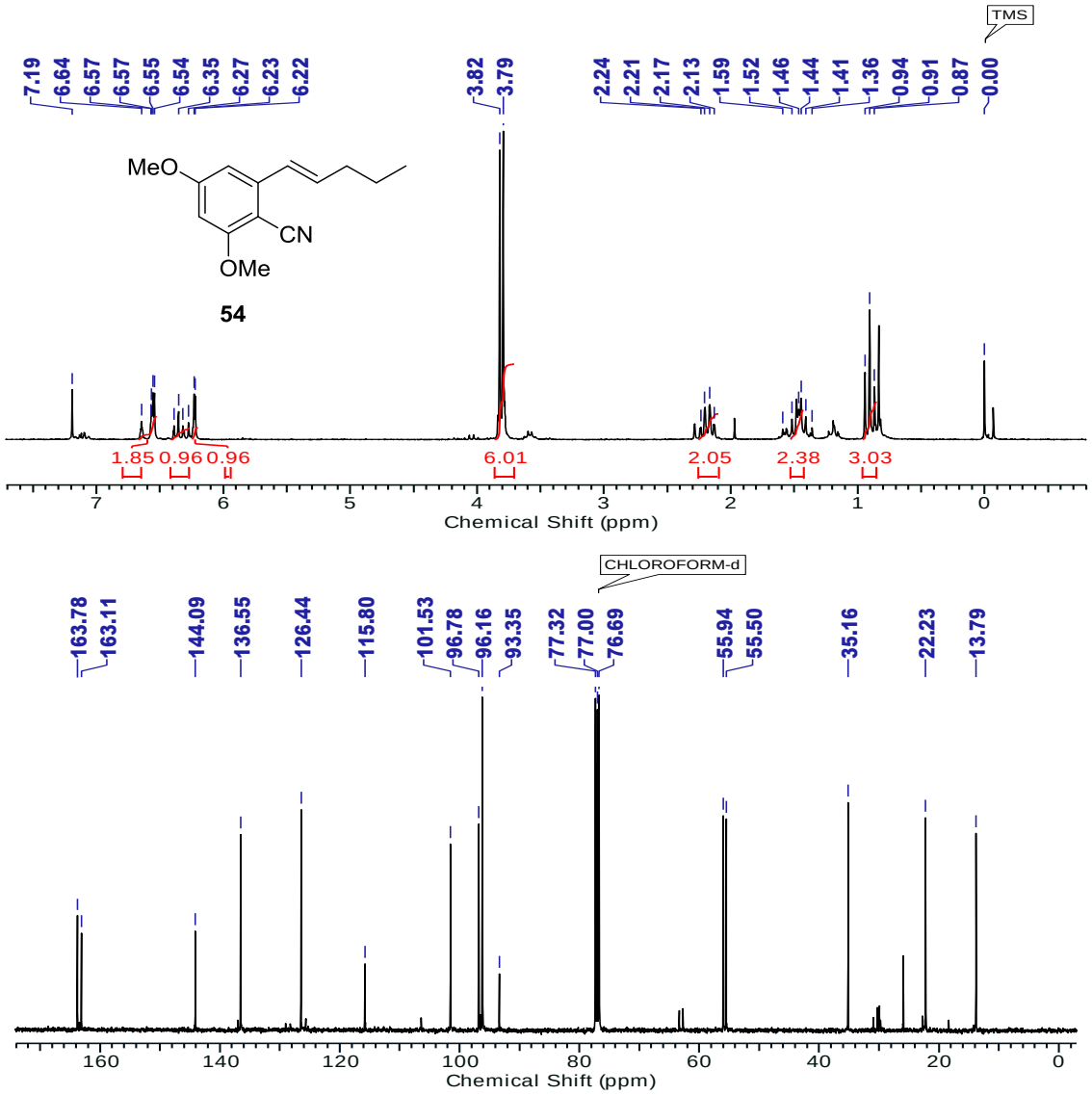
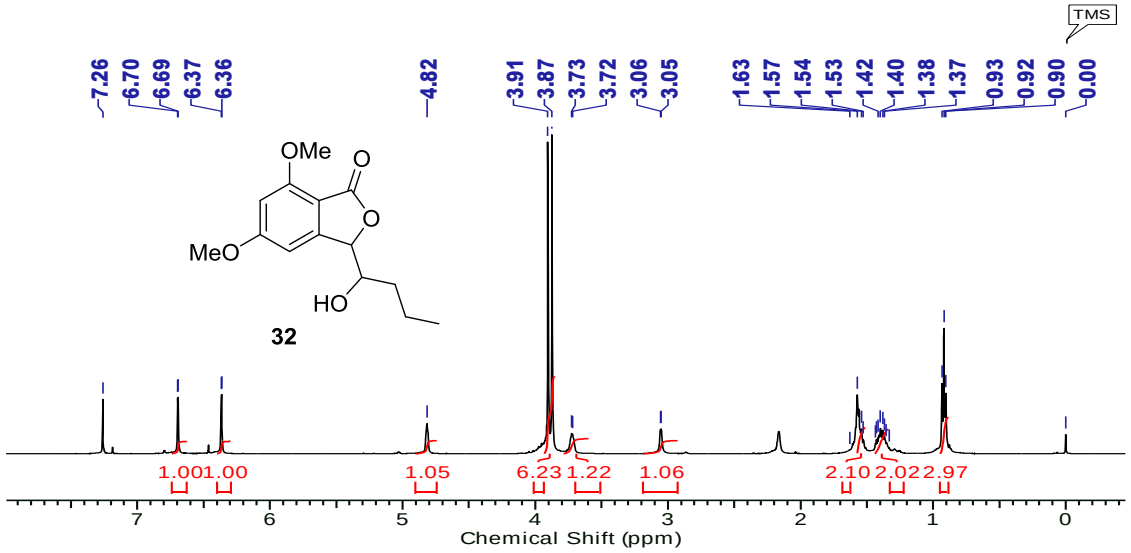


Fig. 14: ^{1}H and ^{13}C NMR spectra of cyano derivative **54**

Cyano derivative **54** was dihydroxylated under ADH reaction conditions (OsO_4/NMO, acetone:H_2O 4:1, rt) to afford the 3-substituted phthalide moiety **32** in excellent yield (90%) and diastereomeric ratio (>98%). The formation of 3-substituted phthalide **32** was ascertained by ^{1}H NMR spectrum, which displayed a typical singlet at δ 4.82 (s, 1H) and a doublet at δ 3.71 (d, J = 3.4 Hz, 1H) corresponding to the methine proton of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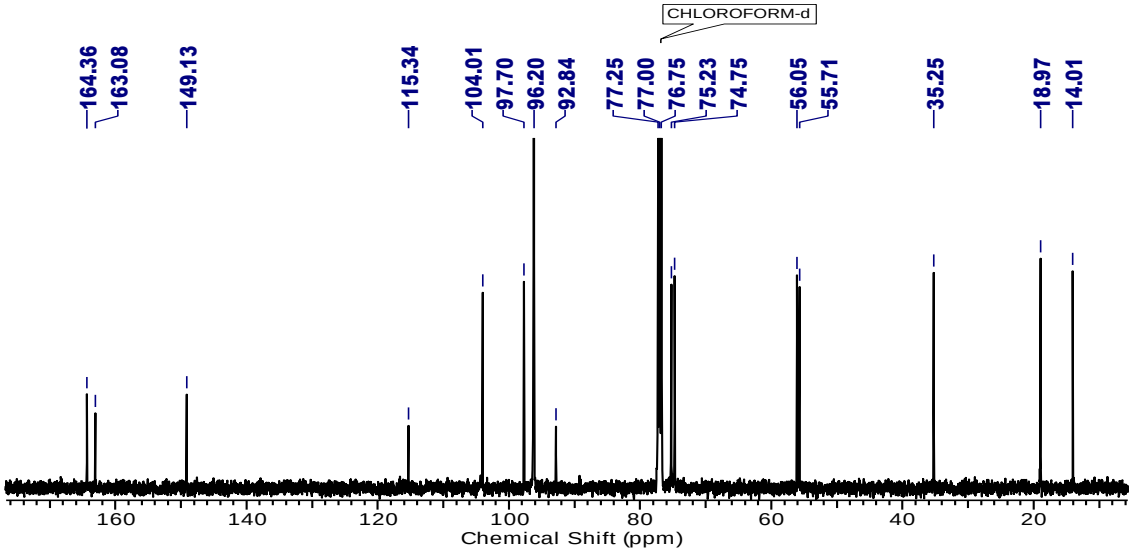
7.26
6.70
6.69
6.37
6.36
4.82
3.91
3.87
3.73
3.72
3.06
3.05
1.63
1.57
1.54
1.53
1.42
1.40
1.38
1.37
0.93
0.92
0.90
0.00
OMe
O
O
MeO
HO
32
1.00
1.00
1.05
6.23
1.22
1.06
2.10
2.02
2.97
Chemical Shift (ppm)


CHLOROFORM-d
164.36
163.08
149.13
115.34
104.01
97.70
96.20
92.84
77.25
77.00
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74.75
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55.71
35.25
18.97
14.01
Chemical Shift (ppm)

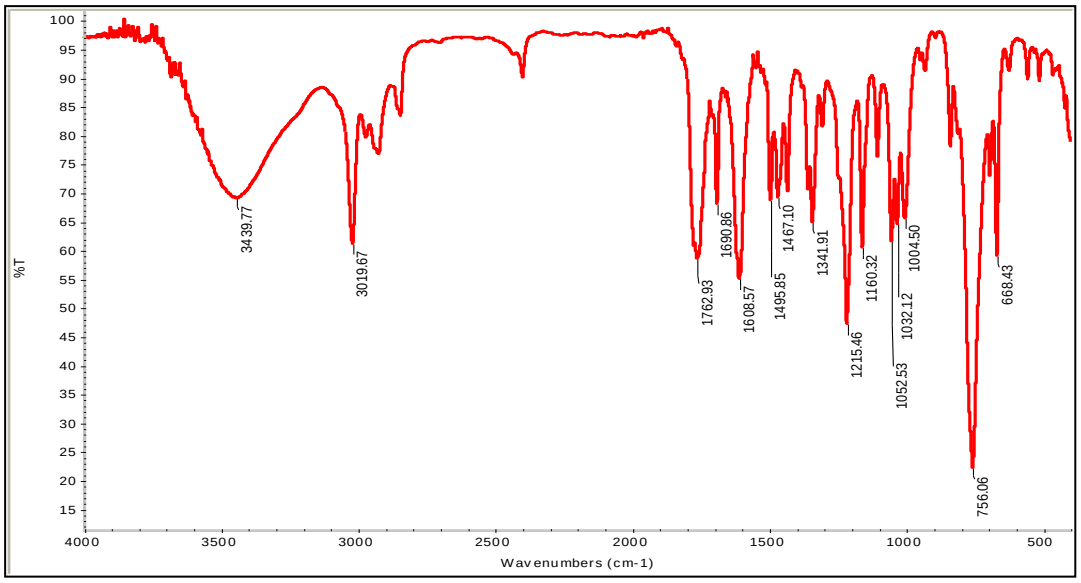

%T
3439.77
3019.67
1762.93
1690.86
1608.57
1495.85
1467.10
1341.91
1215.46
1160.32
1052.53
1032.12
1004.50
756.06
668.43
Wavenumbers (cm-1)

Fig. 15: ^{1}H, ^{13}C NMR and IR spectra of phthalide **32**

phthalide ring and secondary hydroxyl group respectively. It was further supported by the appearance of characteristic carbon signals at δ 75.2 and 74.8 indicating the methine carbons attached to –OH group and phthalide moiety and also another carbon signal at δ 164.4 due to -C=O carbon of lactone ring in its ^{13}C NMR spectrum respectively. Its IR spectrum displayed two strong vibrational stretching frequencies at 3440 and 1763 cm^{-1} due to the presence of –OH and lactone –C=O functionalities respectively (**Fig. 15**).

Finally, 3-substituted phthalide **32** underwent *anti* elimination of β-hydrogen and $Ph_3P=O$ under TBHP-mediated Mitsunobu reaction conditions (TBHP, DEAD, THF, rt) to give the eliminated product alkylidenephthalide **43** in 80% yield with required (*Z*)-selectivity. Its ^{1}H NMR spectrum showed a typical singlet at δ 5.54 (d, J = 5.6 Hz, 1H) indicating the olefinic proton. Also, carbon signals at δ 143.4 and 102.5 are due to quaternary carbon of *exo* double bond and olefinic carbon in its ^{13}C NMR spectrum respectively thus, confirming the formation of **43** (**Fig. 16**). Its IR spectrum displayed a strong vibrational stretching frequency at 1762 cm^{-1} due to the presence of lactone –C=O functionality. Finally, selective demethylation of **43** to the (*Z*)-3-butylidene-5-hydroxy-7-methoxyphthalide (**37**) has already been reported in the liturature.[26]

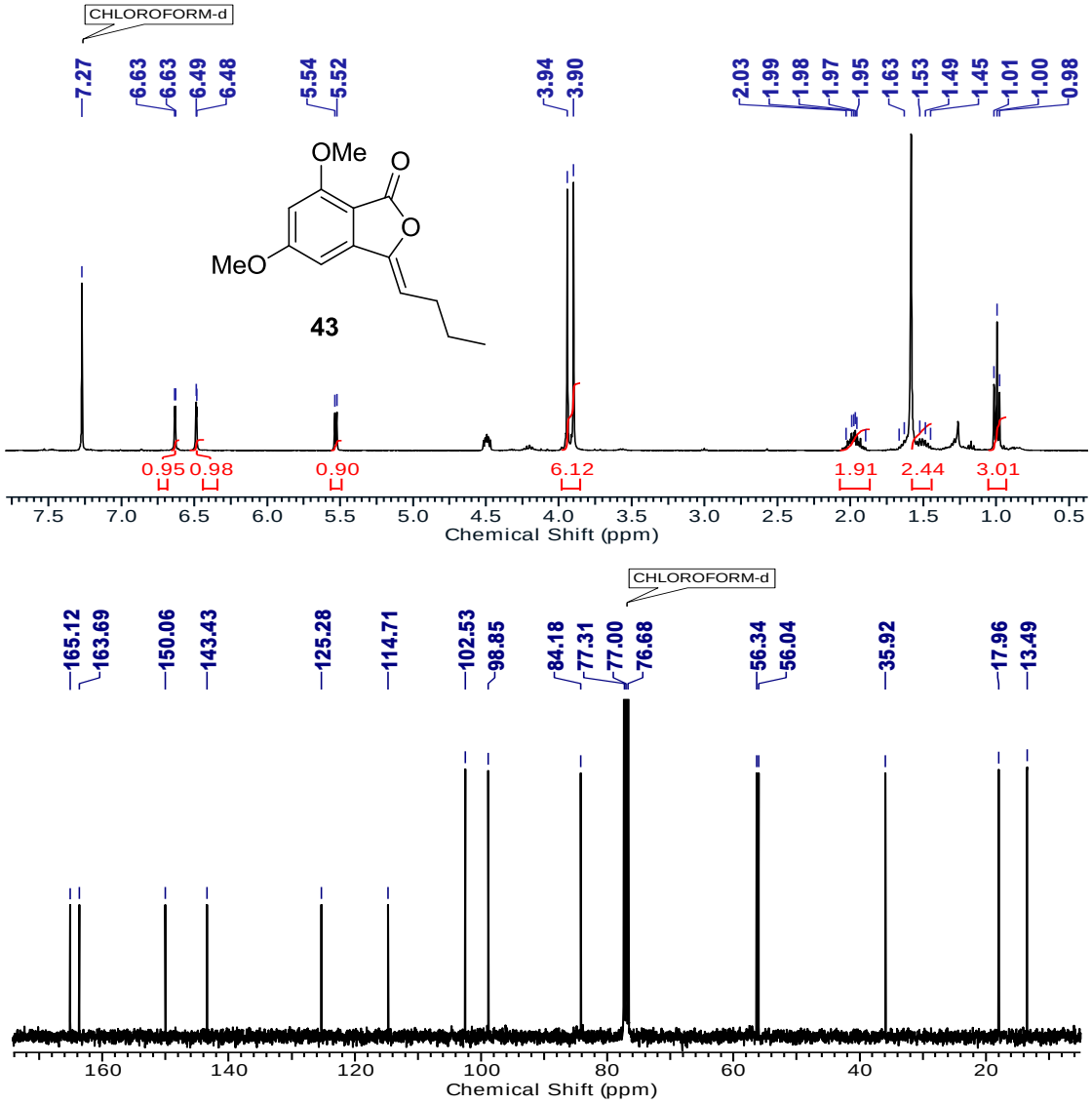


Fig. 16: ^{1}H and ^{13}C NMR spectra of **43**

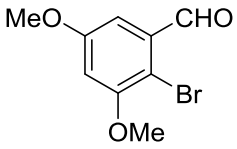
3.2.5 Conclusion

In conclusion, we have described a short and economic total synthesis of cytogenin (**36**) (53.2% overall yield) and a formal synthesis of (*Z*)-3-butylidene-7-hydroxy-5-methoxy phthalide (**37**) (40.5% overall yield) starting from commercially available 3,5-dimethoxybenzaldehyde **53**. The strategy employed herein mainly comprises of TBHP mediated ring expansion or elimination of 3-substituted phthalides (**32d & 32**) to the

corresponding isocoumarin and alkylidenephthalide as the key step. This methodology is expected to find wide scope for the synthesis of other similar bioactive molecules.

3.2.6 Experimental Section

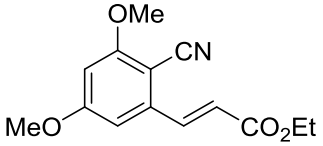
2-Bromo-3,5-dimethoxybenzaldehyde (53)



To a solution of 3,5-dimethoxybenzaldehyde **55** (4 g, 7.1 mmol) in CH_3CN (30 mL) was added NBS (1.4 g, 7.8 mmol) and the reaction mixture was stirred at 25 °C for 6 h. After completion of the reaction (monitored by TLC), it was quenched with sat. $Na_2S_2O_3$ (10 mL) and solvent was removed over high *vaccum.* The reaction mass was then extracted with ethyl acetate (3 x 25 mL) and water, washed with brine solution and combined organic layers were dried over anhyd. Na_2SO_4. Solvent was concentrated to afford the crude, followe by its purification by column chromatography over silica gel using petroleum ether:EtOAc (9:1) furnished the brominated aldehyde **53**.

Yield: 92% (3.8 g); colorless solid; **mp**: 110-112 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 724, 867, 968, 1030, 1086, 1119, 1259, 1308, 1386, 1389, 1456, 1578, 1612, 1636, 1699, 2212, 2985, 3029; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 10.40 (s, 1H), 7.03 (d, *J* = 2.8 Hz, 1H), 6.69 (d, *J* = 2.9 Hz, 1H), 3.85 (s, 5H), 3.92 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 191.1, 161.2, 158.6, 142.3, 108.9, 108.2, 107.7, 56.3, 55.6; **Anal. Calcd for** $C_9H_9BrO_3$: C, 44.11; H, 3.70; Br, 32.60. Found: C, 44.12; H, 3.70; Br, 32.60%.

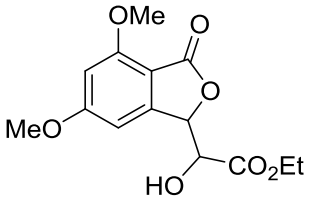
Ethyl (*E*)-3-(2-cyano-3,5-dimethoxyphenyl)acrylate (56)



To astirred solution of 2-bromo-3,5-dimethoxybenzaldehyde **53** (2 g, 7.9 mmol) in benzene (40 mL), $Ph_3P{=}CHCO_2Et$ (3.1 g, 8.6 mmol) was added. The reaction mixture was refluxed for 12 h under nitrogen atmosphere. Completion of reaction was monitored by TLC. After that benzene was removed on high *vaccum* to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (90:10) as eluent] furnished the bromo cinnamate ester derivative (1.4 g yield). 2-bromo cinnamate ester (1 mmol) was dissolved in dry DMF (10 mL) and CuCN (3 mmol) was added slowly and refluxed under N_2 for 12 h. After completion of reaction (monitored by TLC), it was cooled to room temperature, and then diluted with water (30 mL) and EtOAc (25 mL). Aqueous layer was extracted with EtOAc (3 x 20 mL) after separation of organic layer. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was further purified by column chromatographic technique [petroleum ether: EtOAc (7:3) as an eluent] to give cyanocinnamate derivative **56**.

Yield: 83% (1.80 g), colorless solid; **mp**: 76-79 ºC; **IR** ($CHCl_3$ cm^{-1}): υ_{max} 724, 867, 968, 1030, 1086, 1119, 1259, 1308, 1386, 1389, 1456, 1578, 1612, 1636, 1656, 2212, 2985, 3029; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.00 (s, 3H), 5.40 (d, *J* = 10.8 Hz, 1H), 5.79 (d, *J* = 17.6 Hz, 1H), 6.94 (dd, *J* = 10.8, 17.6 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.5, 55.9, 93.6, 97.5, 101.7, 115.5, 118.9, 133.1, 143.4, 163.0, 163.8; **Anal. Calcd for** $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.79, H, 5.78, N, 7.39%.

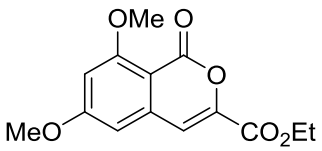
3-(Hydroxymethyl)-5,7-dimethoxyisobenzofuran-1(3*H*)-one (32d)



To a stirred solution of aryl cyanide **56** (0.6 g, 2.59 mmol) in acetone (12 mL) and water (4 mL) catalytic amount of OsO_4 (0.010 g, 1 mol%) was added at 25 °C followed by the addition of NMO (0.426 g, 3.63 mmol). The reaction mixture was stirred for 12 h at 25 °C and quenched with saturated sodium thiosulphate (5 mL). After completion of reaction, the organic layer was separated and the aquous layer extracted with ethyl acetate (3 x 10 mL). Both the layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, crude product was then purified using column chromatography [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (3:2) as eluent] to give pure colorless solid **32d**.

Yield: 94% (0.620 g), colorless solid; **mp**: 152-153 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 746, 985, 1130, 1287, 1514, 1723, 1762, 2954, 3085, 3414; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.32 (t, *J* = 7.2 Hz, 3H), 3.37 (br. s, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.61 (s, 1H), 5.67 (s, 1H), 6.47 (s, 1H), 6.59 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.5, 56.5, 56.8, 62.9, 71.9, 82.1, 99.8, 100.2, 108.0, 153.0, 160.9, 168.9, 170.6, 172.4; **Anal. Calcd for** $C_{14}H_{16}O_7$: C, 64.36; H, 5.79. Found C, 64.34; H, 5.76%.

Ethyl 6,8-dimethoxy-1-oxo-1*H*-isochromene-3-carboxylate (33d)

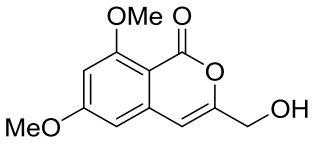


To a stirred solution of 3-substituted phthalide derivative **32d** (0.2 g, 0.751 mmol) in THF (10 mL) was added diethyl azodicarboxylate (0.013 mL, 10 mol%) followed by

the addition of PPh_3 (0.295 g, 1.5 mmol), and *tert*-butyl hydroperoxide (0.135 mL, 2 mmol) and the mixture allowed to stirr for 2 h at 25 °C. After the completion of reaction (as monitored by TLC), THF was distilled out to give crude product, which was purified by chromatography [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (7:3) as eluent] to obtain isocoumarin **33d**.

Yield: 92% (0.171 g), colorless solid; **mp**: 87-89 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 711, 997, 1018, 1159, 1194, 1261, 1360, 1467, 1473, 1592, 1655, 1720, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.0 Hz, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.33 (q, *J* = 7.0 Hz, 2H), 6.53 (d, *J* = 1.8 Hz, 1H), 6.58 (d, *J* = 1.8 Hz, 1H), 7.28 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 55.8, 56.5, 62.2, 100.9, 102.3, 112.0, 120.4, 127.3, 135.7, 156.2, 163.5, 165.6; **Anal. Calcd for** $C_{14}H_{14}O_6$: C, 60.63; H, 5.07. Found: C, 60.75; H, 5.10%.

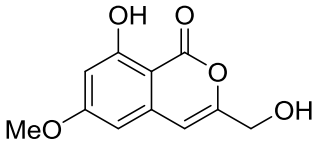
6,8-Dimethoxy-3-hydroxymethylisocoumarin (46)



Sodium borohydride powder (0.054 g, 1.43 mmol) was added to a stirred solution of isocoumarin ester **33d** (0.2 g, 0.718 mmol) in THF (3 ml) at 0 °C. The resulting suspension was stirred at 25 °C for 15 min. Methanol (3 ml) was then added drop wise. After 4 h, the reaction mixture was quenched with 2N HCl (10 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4) and concentrated to obtain a solid residue. Further purification was done with column chromatography [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (1:1) as eluent] to afford pure alcohol **46**.

Yield: 87% (0.147 g), colorless solid; **mp**: 101-104 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1074, 1272, 1559, 1575, 1602, 1685, 1704, 1730, 2820, 2924, 3460; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.97 (s, 3H), 4.42 (s, 2H), 6.35 (s, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.6, 56.3, 61.4, 98.8, 100.3, 102.8, 107.7, 108.9, 128.6, 132.7, 169.6, 170.2; **Anal.** Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.1; H, 5.14%.

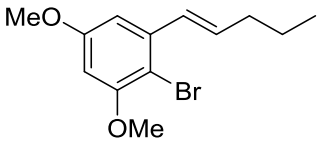
Cytogenin (36)



A solution of boron tribromide [(0.22 mL (1M in dichloromethane), 1.27 mmol)] was slowly added with a syringe to a stirred solution of alcohol **46** (0.1 g, 0.423 mmol) in dichloromethane (4 mL) under nitrogen at -5 °C. After complete addition, the mixture was stirred for 1 h and then aq. $NaHCO_3$ was added. The organic layer was separated and aqueous layer extracted with ethyl acetate twice, combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified using column chromatography [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (4:1) as eluent] to afford pure product **36**.

Yield: 76% (0.071 g), colorless solid; **mp**: 150-152 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 741, 1162, 1271, 1480, 1580, 1665, 1685, 2650, 3460; **^{1}H NMR** (200 MHz, acetone-d_6): δ 3.92 (s, 3H), 4.40 (d, *J* = 5.6 Hz, 2H), 4.76 (t, *J* = 6.1 Hz, 1H), 6.49 (d, *J* = 2.2 Hz, 1H), 6.61 (d, *J* = 2.2 Hz, 1H), 6.66 (s, 1H), 11.11 (s, 1H); **^{13}C NMR** (50 MHz, acetone-d_6): δ 56.4, 61.1, 101.4, 102.6, 103.9, 110.0, 140.4, 158.4, 164.6, 166.8, 168.1; **Anal. Calcd for** $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.45; H, 4.54%.

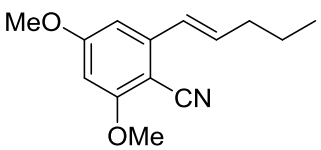
(*E*)-2-Bromo-1,5-dimethoxy-3-(pent-1-en-1-yl)benzene (57)



To a stirred solution of 5-(butane-1-sulfonyl)-1-phenyl-1H-tetrazole **A** (1.4 g, 5.28 mmol) in dry THF (25 mL) at -78 °C under N_2 was added drop wise the NaHMDS (5.8 mL, 1.0 M in THF, 5.80 mmol). After stirring at -78 °C for 30 min, neat aldehyde **53** (2.05 g, 7.92 mmol) was added. After stirring for 3 h, the reaction mixture was allowed to warm slowly at 25 °C and stirred overnight, whereupon H_2O and Et_2O were added and the mixture shaken well. The organic layer was separated and dried over anhyd. Na_2SO_4 to get crude product, which was purified by column chromatography [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (9:1) as eluent] to afford product **57**.

Yield: 85% (1.32 g), colorless oil; **IR** ($CHCl_3$ cm^{-1}): υ_{max} 770, 912, 1012, 1108, 1276, 1339, 1486, 1505, 1604, 1615, 2990, 3040; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.49-1.57 (m, 2H), 2.23 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 6.0-6.15 (m, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.73 (d, *J* = 15.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 113.9, 22.4, 35.2, 55.4, 56.2, 98.5, 102.8, 129.5, 134.0, 139.4, 156.8, 159.5; **Anal. Calcd for** $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01. Found: C, 54.74; H, 6.10%.

(*E*)-2,4-Dimethoxy-6-(pent-1-en-1-yl)benzonitrile (54)

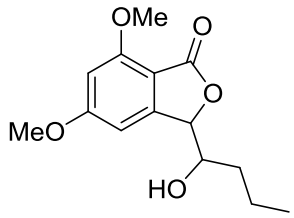


Olefin **57** (1 g, 3.52 mmol) was dissolved in dry DMF (15 mL) and CuCN (1.10 g, 12.32 mmol) was added to it. The entire solution was refluxed under N_2 for 12 h (monitored by TLC); the reaction mixture was then cooled to room temperature and

diluted with water (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product which was purified by column chromatography [silica gel (230-400 mesh) and petroleum ether: Ethyl acetate (4:1) as eluent] to obtain product **54**.

Yield: 84% (0.68 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 748, 876, 932, 1032, 1098, 1276, 1339, 1486, 1505, 1604, 1615, 2220, 2989, 3054; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.41-1.52 (m, 2H), 2.17 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 6.22 (d, *J* = 2.2 Hz, 1H), 6.27-6.39 (m, 1H), 6.54 (d, *J* = 2.2 Hz, 1H), 6.64 (d, *J* = 15.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 17.8, 22.2, 35.2, 55.5, 56.0, 93.4, 96.8, 101.5, 115.8, 126.4, 136.6, 144.1, 163.1, 163.8; **Anal. Calcd for** $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.75; H, 7.40%.

3-(1-Hydroxybutyl)-5,7-dimethoxyisobenzofuran-1(3*H*)-one (32)

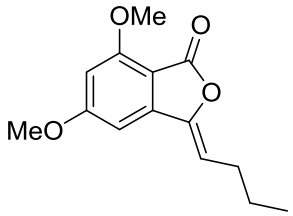


To a stirred solution of aryl cinnamate **54** (0.6 g, 2.59 mmol) in acetone (12 mL) and water (4 mL), catalytic amount of OsO_4 (0.010 g, 1 mol%) was added at 25 °C followed by the addition of NMO (0.426 g, 3.63 mmol). The reaction mixture was stirred for 12 h at 25 °C and quenched with saturated sodium thiosulphate (5 mL). The organic layer was separated and the aquous layer extracted with ethyl acetate (3 x 10 mL). Both the layers were combined and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to give crude product was purified using column chromatography

[silica gel (230-400 mesh) and petroleum ether: ethyl acetate (3:2) as eluent] to afford pure **32**.

Yield: 90% (0.620 g), colorless solid; **mp**: 110-112 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 668, 756, 1004, 1032, 1052, 1160, 1215, 1341, 1467, 1495, 1608, 1691, 1763, 3020, 3340; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 6.8 Hz, 3H), 1.37-1.43 (m, 2H), 1.53-1.63 (m, 2H), 3.05 (d, *J* = 3.4 Hz, 1H), 3.72 (d, *J* = 3.4 Hz, 1H), 3.87 (s, 1H), 3.91 (s, 1H), 4.82 (t, *J* = 4.6 Hz, 1H), 6.36 (d, *J* = 2.3 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 19.0, 35.3, 55.7, 56.1, 74.8, 75.2, 92.8, 97.7, 104.0, 115.3, 149.1, 163.1, 164.4; **Anal. Calcd for** $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.17; H, 6.84%.

(*Z*)-3-Butylidene-5-7-dimethoxyphthalide (43)



To a stirred solution of 3-substituted phthalide derivative **32** (0.2 g, 0.751 mmol) in THF (10 mL) was added diethyl azodicarboxylate (0.013 mL, 10 mol%) followed by the addition of PPh_3 (0.295 g, 1.5 mmol) and *tert*-butyl hydroperoxide (0.135 mL, 2 mmol). The reaction mixture was allowed to stirr for 2 h at 25 °C. After the completion of reaction (as monitored by TLC), THF was distilled out to give crude product, which was purified by chromatography [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (7:3) as eluent] to afford viscous gum **43**.

Yield: 92% (0.171 g), viscous gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 866, 1104, 1221, 1253, 1322, 1499, 1653, 1762, 2919; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98-1.01 (t, *J* = 7.3 Hz, 3H), 1.45-1.66 (m, 2H), 1.90-2.03 (m, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 5.52 (d, *J*

= 5.6 Hz, 1H), 6.48 (d, *J* = 2.0 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.5, 18.0, 35.9, 55.0, 56.3, 84.2, 98.9, 102.5, 114.7, 125.3, 143.4, 150.1, 163.7, 165.1; 164.4; **Anal. Calcd for** $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.77; H, 6.50%.

3.2.7 References

1 (a) Urita, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry*, **1986**, *25*, 517; (b) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.; Nakajima, S. *Chem. Pharm. Bull*., **1981**, *29*, 2689; (c) Whyte, A. C.; Gloer, J. B.; Scoot, J. A.; Mallock, D. *J. Nat. Prod*., **1996**, *59*, 765; (d) Matsuda, H.; Shimoda, H.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 215.

2 (a) Jose, V.; Pablo, G.-H.; Roberto, F.-P.; Chicotem, M.-T. *Organometallics*, **2011**, *30*, 1079; (b) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett*., **1986**, *28*, 171; (c) Aidhen, I. S.; Narasimhan, N. S. *Tetrahedron Lett*., **1989**, *30*, 5323; (d) Gore, V. G.; Chordia, M. D.; Narasimhan, N. S. *Tetrahedron*, **1990**, *46*, 2483; (e) Chordia, M. D.; Narasimhan, N. S. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 371; (f) Ciattini, P. G.; Mastropietro, G.; Morera, E; Ortar, G. *Tetrahedron Lett.*, **1993**, *34*, 3763; (g) Lacova, M.; Paulov, S.; Paulovava, J. *J. Czech*, *Cs*. **1981**, *190*, 783; *Chem. Abstr*., **1982**, *97*, 67833v; (h) Lacova, M.; Brondos, M. *Chem. Zvesti*, **1982**, *36*, 245; *Chem. Abstr*. **1982**, *97*, 9205z.

3 (a) Beugelmans,R.; Ginsburg, H.; Bois-Choussy, M. J. *Chem. Soc. Perkin Trans. 1*, **1982**, 1149; (b) Lewis, C. N.; Staunton, J.; Sunter, D. C. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 747; (c) Minami, T.; Nishimoto, A.; Nakamura, Y.; Hanaoka, H. *Chem. Pharm. Bull*., **1994**, *42*, 1700.

4 (a) Yoshikawa, M.; Harada, E.; Naitoh, Y.; Inoue, K.; Matsuda, H.; Shimoda, H.; amahara, J. S.; Murakami, N. *Chem. Pharm. Bull*., **1994**, *42*, 2225; (b) Kanevskaya, S. I.; Malinina, S. I. *J. Gen. Chem*. (USSR), **1956**, *25*, 727; (c) Jones, J. B.; Pinde, A. R. *J. Chem. Soc*., **1958**, 2612.

5 (a) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.*, **1995**, *60*, 3711; (b) Guo, X.-X. *J. Org. Chem*. **2013**, *78*, 1660; (c) Lei, Z.; Jiang, H.-F. *Tetrahedron Lett.*, **2007**, *48*, 8449.

6 (a) Kavala, V.; Wang, C.-C.; Barange, D. K.; Kuo, C.-W.; Lei P.-M.; Ching-Fa, Y. *J. Org. Chem*., **2012**, *77*, 5022; (b) Ge, Z.-Y.; Fei, X.-D.; Tang, T.; Zhu, Y.-M.; Shen, J.-K. *J. Org. Chem*., **2012**, *77*, 5736; (c) Cai, S.; Wang, F.; Xi, C. *J. Org. Chem*., **2012**, *77*, 2331.

7 (a) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem*., **1995**, *60*, 3711; (b) Fei, X.-D.; Ge, Z.-Y.; Tang, T.; Zhu, Y.-M.; Ji, S.-J. *J. Org. Chem*., **2012**, *77*, 10321; (c) Shahzad, S. A.; Venin, C.; Wirth, T. *Eur. J. Org. Chem.*, **2010**, *18*, 3465; (d) Nandi, D.; Ghosh, D.; Chen, S.-J.; Kuo, B.-C.; Wang, N. M.; Lee, H. M. *J. Org. Chem*., **2013**, *78*, 3445.

8 Mali, R. S.; Babu, K. N. *J. Org. Chem*., **1998**, *63*, 2488.

9 Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979.

10 Wang. L.; Shen, W. *Tetrahedron Lett*., **1998**, *39*, 7625.

11 (a) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.*, **2007**, *72*, 5362; (b) Cai, S.; Wang, F.; Xi, C.

Synthesis, **2012**, *44*, 1892; (c) Waters, S. P.; Kozlowski, M. C. *Tetrahedron Lett*., **2001**, *42*, 3567; (d) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron*, **2000**, *56*, 2533; (e) Subramanian, V.; Batchu, V. R; Barange, D.; Pal, M. *J. Org. Chem*., **2005**, *70*, 4778.

12 (a) Brasholz, M.; Luan, X.; Reissig, H.-U. *Synthesis*, **2005**, *20*, 3571; (b) Hellal, M.; Bourguignon, J.-J.; Bihel, F. J.-J. *Tetrahedron Lett*., **2008**, *49*, 62; (c) Thrash, T. P.; Welton, T. D.; Behar, V. *Tetrahedron Lett.*, **2000**, *41*, 29; (d) Qin, D.; Ren, R. X.; Siu, T.; Zheng, C.; Danishefsky, S. J. *Angew. Chem. Int. Ed*., **2001**, *40*, 4709; (e) Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett*., **2011**, *13*, 9.

13 Reddy, R. S.; Chaithanya Kiran, I. N.; Sudalai, A. *Org. Biomol. Chem.*, **2012**, *10*, 3655.

14 Scott, J. P.; Alam, M.; Bremeyer, N.; Goodyear, A.; Lam, T.; Wilson, R. D.; Zhou, G. *Org. Process Res. Dev*., **2011**, *15*, 1116.

15 DEAD: diethyl azodicarboxylate, DPPA: Diphenyl phosphoryl azide.

16 Yuen, T.; But, S.; Toy, P. H. *J. Am. Chem. Soc*., **2006**, *128*, 9636.

17 Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.*, **1967**, *40*, 935.

18 Kumagai, H. T.; Masuda, M.; Ohsono, S.; Hattori, H.; Naganawa, T.; Sawa, M.; Hamada, M.; Ishizuka; Takeuchi, T. *J. Antibiotics* **1990,** *43*, 1505.

19 Hirano, S.; Wakazono, K.; Agata, N.; Mase, T.; Yamamoto, R.; Matsufuji, M.; Sakata, N.; Iguchi, H.; Tone, H.; Ishizuka, M.; Takeuchi, T. *Int. J. Tiss. Reac*., **1994**, *16*, 155.

20 Abe, C; Hirano, S.; Wakazono, K.; Mase, T.; Yamamoto, R.; Matsufuji, M.; Sakata, N.; Agata, N.; Iguchi, H.; Ishizuka M.; Takeuchi, T.: Effects ofcytogenin on spontaneous arthritis in MRL/1mice andon pristane-induced arthritis (PIA) in DBA/1J mice. *Int. J. Tiss. Reac*., **1995**, *17*, 175.

21 (a) Kumagai, H.; Masuda, T.; Ishizuka, M.; Takeuchi, T. J. *Antibiotics*, **1995**, *48*, 175; (b) Ishizuka, M.; awatsu, M.; Yamashita, T.; Ueno, M.; Takeuchi, T. *Int. J. Immunopharmac.*, **1995**, *17*, 133.

22 Brindis, F.; Rodriguez, R.; Bye, R.; Gonzlez-Andrade, M.; Mata, R. *J. Nat. Prod*., **2011**, *74*, 314.

23 Ko, W.-C. *Japan. J. Pharmacol.*, **1980**, *30*, 85.

24 (a) Teng, C.-M.; Chen, W.-Y.; Ko, W.-C.; Ouyang, C.; *Biochim. Biophys. Acta*, **1987**, *924*, 375; (b) Shimizu, M.; Matsuzawa, T.; Suzuki, S.; Yoshizaki, M.; Morita, N. *Chem. Pharm. Bull*., **1991**, *39*, 2046.

25 Tsai, N.-M.; Chen, Y.-L.; Lee, C.-C.; Lin, P.-C.; Cheng, Y.-L.; Chang, W.-L.; Lin, S.-Z.; Harn, H.-J. *J. Neuro chem.*, **2006**, *99*, 1251.

26 Mali, R. S.; Patil, S. R. *syn. Comm.*, **1990**, 20, 167.

27 Yuan, H.; Junker, B.; Helquist, P.; Taylor, R. E. *Current Organic Synthesis*, **2004**, *1*, 1.

28 Saeed, A. *J. Heterocyclic chem.*, **2004**, *41*, 975.

29 Gadakh, S. K.; Sudalai, A. *RSC Adv.*, **2014**, *4*, 57658.

CHAPTER 4

Development of Synthetic Methodologies Involving Formation of Quinoline and Coumarin Derivatives *via* Rh-Catalyzed *ortho* C-H Bond Activation of Aromatics

Section I

Rh-Catalyzed Quinoline Carboxylate Synthesis *via* C-H Bond Activation and Cyclization Reactions of Arylamines with Terminal Alkynic Esters

4.1.1 Introduction

a. C-H Activation:

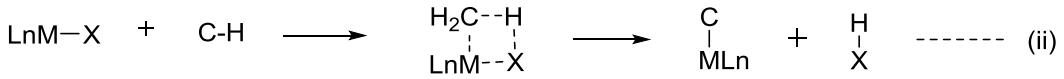
Due to high demand for green and sustainable chemistry, chemists have inspired to seek efficient and economic ways to build the chemical bonds during the course of synthesis of bioactive molecules.[1] In this regard, formation of C–C, C–O, and C–N bonds are important in most organics and the construction of these bonds constitutes streamline of a synthetic chemistry. Beside this, C–H bonds are ubiquitous in organic molecules. Thus, direct activation and functionalization of C–H to the corresponding C-X (X = C, N, O) bonds becomes the most important and potential techniques for the synthesis of complex structures. The C-H bonds posses a high dissociation energy (105 kcal mol^{-1} for methane and 110 kcal mol^{-1} for benzene), and hence metal-coordination is often necessary to make it a weak bond.[2-6] As organic molecules bearing many C-H bonds, regioselective C-H bond activation and further functionalization often represent a big task. Another big challenge in C-H activation methods is to achieve high selectivity, which often utilize a directing group. Coordination of directing group to the transition metal results in chelation assisted C-H bond activation *via* metallacycle.

The first example of directing group C-H activation was developed in 1963 by Kleiman and Dubeck,[7] in which homogenous transition metal complex dicyclopentadienylnickel (Cp_2Ni), successfully cleaved an unactivated C-H bond of azobenzene. The different pathway of the C-H bond cleavage was extensively studied by different research groups during the past decades. Computational studies together with experimental results

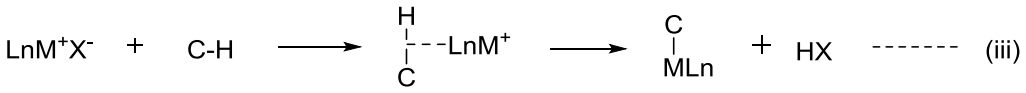
suggested four types of cleavage of C-H bond depending on the catalyst and the reaction conditions.[8]

(a) C-H activation happens when the oxidative addition transition metal into the C-H bond take place producing a higher oxidation state of metal with 2 new ligands in its coordination sphere. It is possible with electron rich complexes of late transition metals (Rh, Re, Ir, Ru, Pt) whereby a change of geometry is allowed (equation i).

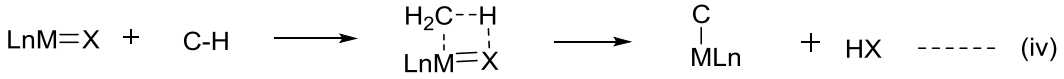
(b) σ-Bond metathesis involves a transfer of hydrogen *via* a concerted four-center, four electron transition state without change of the oxidation state of the metal. This mechanism occurs generally with early transition metals (groups 3 and 4 metals) (equation ii).



(c) If the metal species coordinates the C-H bond, it weakens the bond and therefore electrophilic activation results. This facilitates the loss of a proton in forming a carbometal intermediate. This proton is trapped by a base or solvent present in the reaction mixture (equation iii).

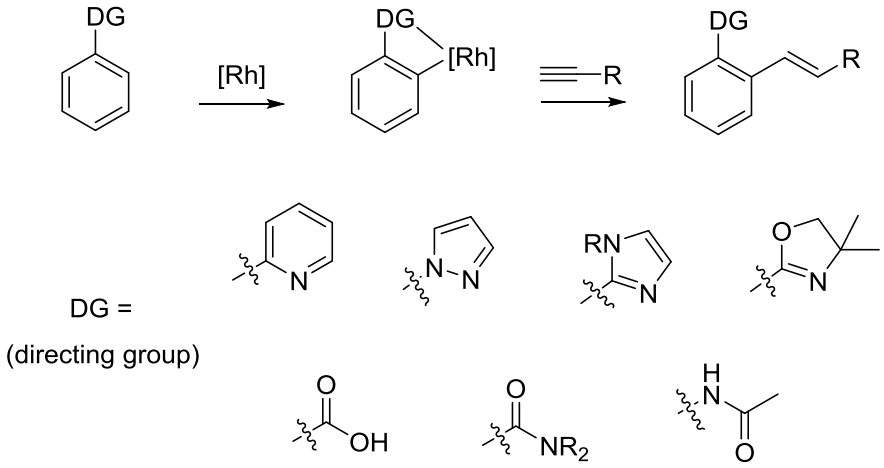


(d) 1,2-Addition resembles σ-bond metathesis but M-X bond is still present in the final complex. The C-H bond is added across the unsaturated M=X bond (equation iv).



In general, in comparison with ruthenium catalysts, rhodium catalysts were found to have broader functional tolerance specifically, when nitrogen-containing directing

groups are the coordinating species. Rhodium catalysts are found to be more stable towards air and moisture, which make it easier for reaction to carry out. In the study of examples of heteroatom-directed Rh catalysis, two mechanistically distinct reaction pathways are proposed. In one case, the heteroatom acts as a chelator to bind the Rh catalyst, facilitating reactivity at a proximal site. The formation of a five-membered metallacycle provides a favorable driving force to induce reactivity at the desired location, which can be further functionalized. In the other case, the heteroatom initially coordinates the Rh metal and then acts to stabilize the formation of a metal-carbon bond at a proximal site.

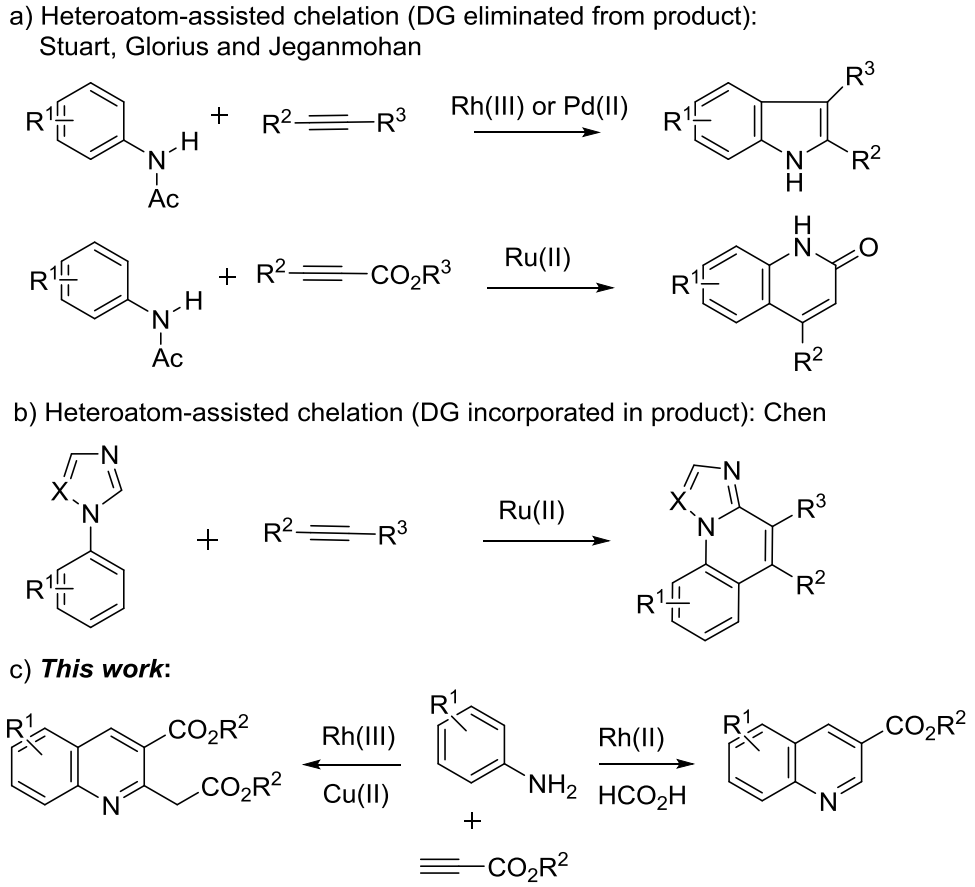


Scheme 1: Examples of directing groups (DG) for the rhodium catalyzed directed C-H activation

These directing groups (DG) usually possess a lone pair that can coordinate to the metal catalyst to direct *ortho* functionalization *via* a five or six-membered metallocycle. For example, nitrogen-containing heterocycles such as 2-pyridinyl, 1-pyrazolyl and 2-imidazolyl, have the same ability as directing group to facilitate the regioselective C-H bond activation and further functionalization (**Scheme 1**).[5] In some specific cases, carboxylic acids, acetanilide and amides also plays the same role.

b. Quinoline carboxylates:

Quinoline carboxylates are ubiquitous heterocyclic units found extensively in many natural products and pharmaceuticals and possess anti-malarial, anti-HIV, anti-microbial and anti-TB activities.[9,10] The prevalence of quinoline units in bioactive molecules has prompted the development of many useful methods for their synthesis and functionalization.[11] More recently, transition metal-catalyzed functionalization of a variety of less active C-H bonds has received substantial importance because of its sustainable, atom economical and environmentally benign features.[12] In particular, Rh(III), Ru(II), Pd(II) and Cu(II) metal complexes have provided exciting opportunities for the efficient synthesis of condensed heterocycles *via* chelation-assisted directing group C-H bond functionalization (*e.g*. indoles, pyrroles, pyridines, isoquinolones,



Scheme 2: Transition metal-catalysed synthesis of heterocycles *via* heteroatom-assisted chelation

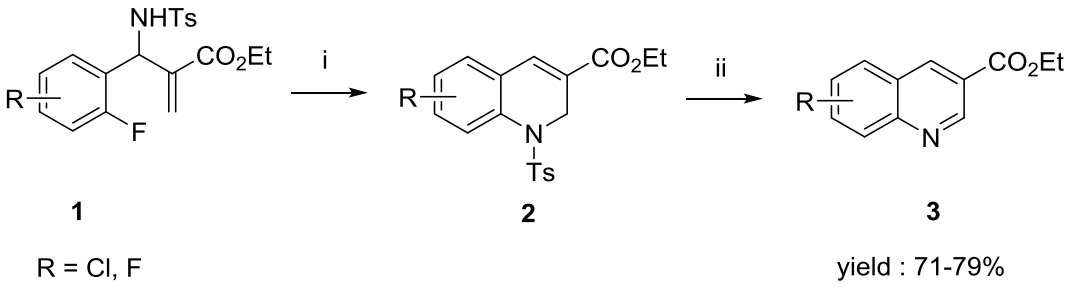
isocoumarins, and indolines).[13-18] However, for directing group-assisted intermolecular cyclization with alkynes, the elimination of heteroatom-assisted chelation is often required in the early reaction stage[19,20] (**Scheme 2**).

4.1.2 Review of Literature

The prevalence of quinoline units in bioactive molecules has prompted the development of many useful methods for their synthesis and functionalization. Some of the recent literature recent methods are given below:

Kim's approach (2001)[11a]

Kim *et al*. have reported a useful methods for the synthesis of quinoline 3-carboxylic esters **3** from Baylis–Hillman adducts **1**, which was prepared from a one-pot reaction of *o*-halobenzaldehydes with N-tosylamines under basic condition (K_2CO_3) giving 1,2-dihydroquinoline derivatives **2** in high yield. Further elimination of *p*-toluenesulfinic acid **2** was carried out in the presence of DBU in THF that gave quinoline 3-carboxylates **3** in 71-79% yields (**Scheme 3**).

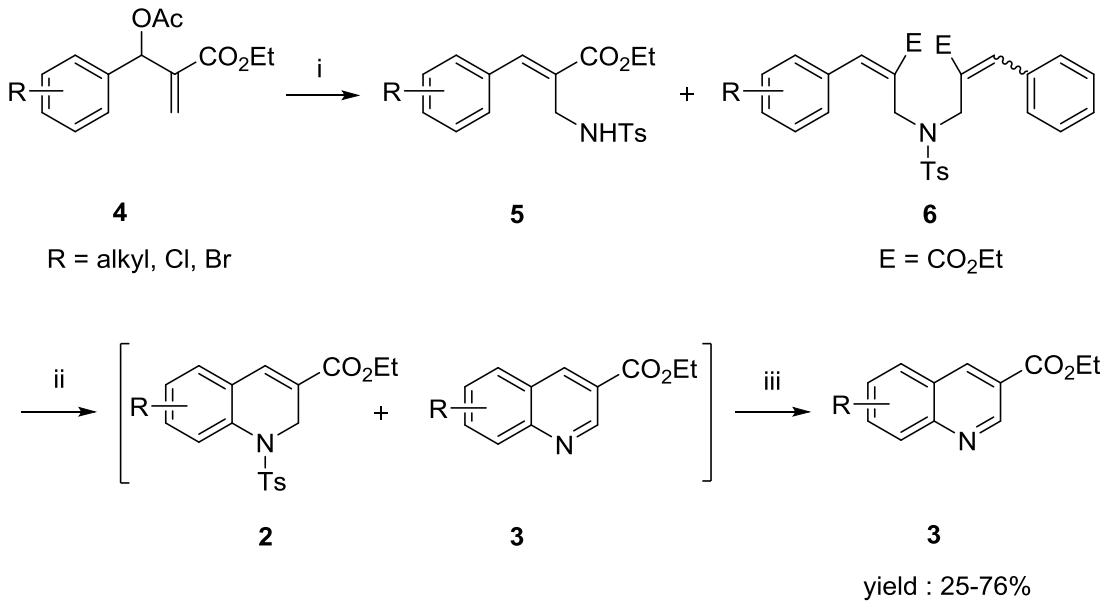


Scheme 3: (i) $TsNH_2$ (1.0 equiv), K_2CO_3 (3.0 equiv), DMF, 80-90 °C, 2-10 h; (ii) DBU, THF, rt, 24 h.

Kim's approach (2002)[11b]

In yet another approach, Kim *et al*. have developed a modified protocol for the synthesis of quinoline 3-carboxylate derivatives **3** from the Baylis–Hillman acetates **4**.

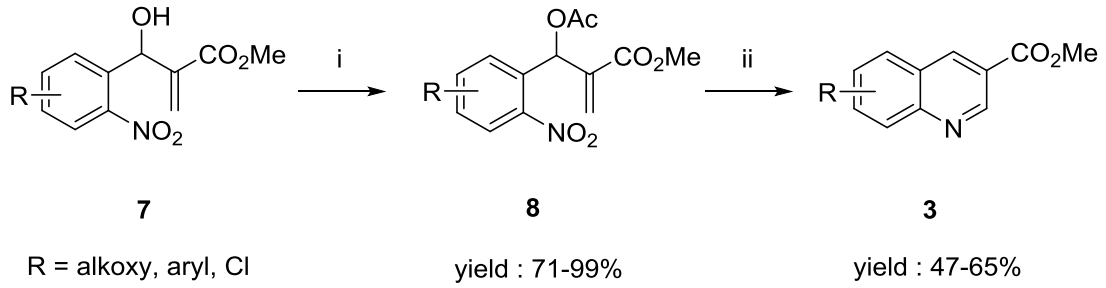
The reaction of adduct **4** in the presence of K_2CO_3 in DMF afforded rearranged tosyamide derivatives **5** along with side product **6**. Further, the reaction of **5** with iodobenzene diacetate and iodine resulted in quinoline 3-carboxylates **3 (**25-76% yields) *via* the oxidative cyclization reaction of the N-tosylamidyl radical (**Scheme 4**).



Scheme 4: (i) $TsNH_2$, K_2CO_3, DMF, 40-50 °C, 3 h; (ii) $PhI(OAc)_2$ (1.6 equiv), I_2 (1 equiv), 60-70 °C, 2 h; (iii) (a) work up; (b) K_2CO_3 (4 equiv), DMF, 40-50 °C, 4 h.

Nicholas's approach (2003)[21a]

Nicholas *et al.* have described a reductive cyclization protocol for the synthesis of quinoline 3-carboxylates **3**. The reductive cyclization of *o*-nitro-substituted Baylis-

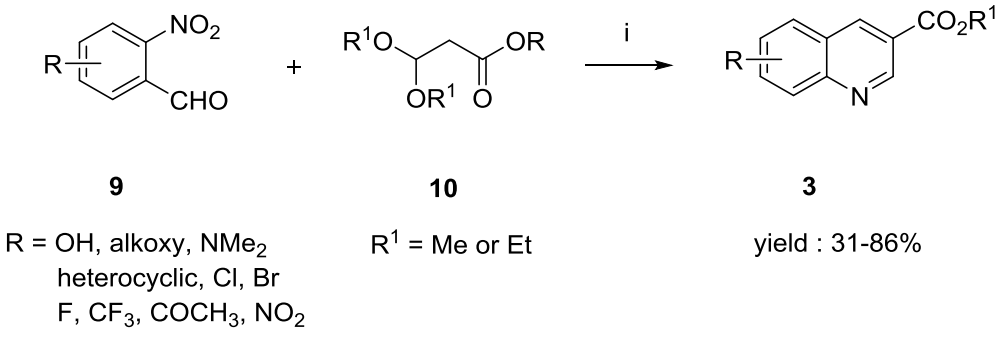


Scheme 5: (i) Ac_2O, H_2SO_4, rt, 1 h; (ii) $[Cp^*Fe(CO)_2]_2$, CO (10 mol %, 6 atm), dioxane, 150 °C.

Hillman acetates **8** (prepared from the acylation of nitro adduct **7**) by carbon monoxide, catalyzed by $[Cp^*Fe(CO)_2]_2$ furnished quinoline 3-carboxylates **3** in moderate to good yields (47-65%) (**Scheme 5**).

Venkatesan's approach (2010)[21c]

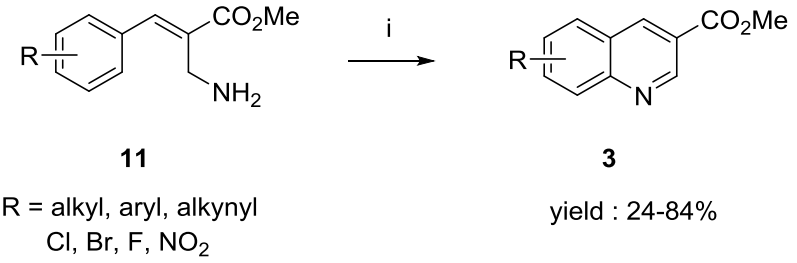
Venkatesan *et al.* have envisaged a simple and short reductive cyclization strategy for the synthesis of quinoline 3-carboxylates **3**. The Sn-catalyzed reductive cyclization of substituted *o*-nitrobenzaldehydes **9** with commercially available 3,3-diethoxypropionic acid ethyl ester **10** afforded quinoline 3-carboxylates **3** in 31-86% yields (**Scheme 6**).



Scheme 6: (i) $SnCl_2 \cdot 2H_2O$, EtOH, 90 °C, 3 h.

Batra's approach (2012)[21e]

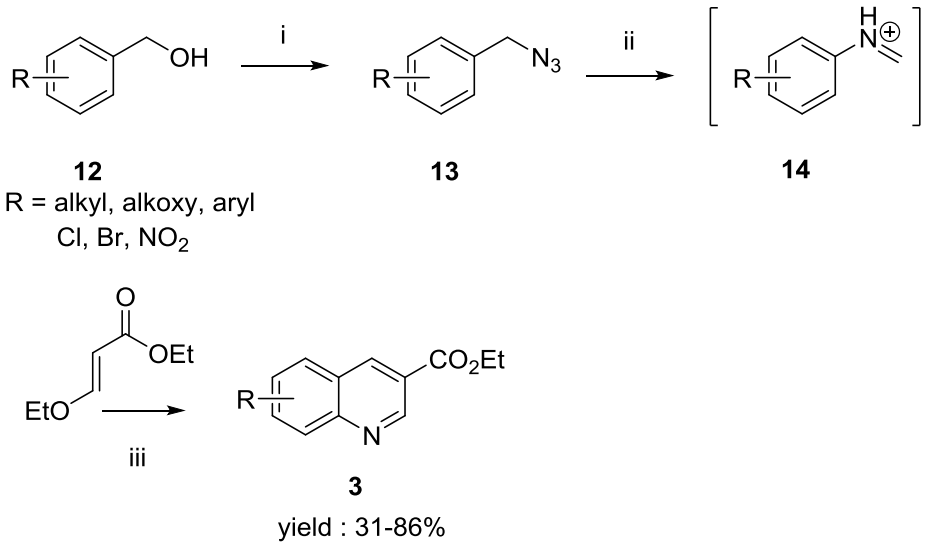
Another useful single step method was developed by Batra *et al*. starting from similar Baylis–Hillman adduct i.e substituted primary allylamines **11**, which underwent unprecedented iodine mediated intramolecular electrophilic aromatic cyclization leading to the synthesis of quinoline 3-carboxylate **3** under mild reaction conditions in 24-84% yields (**Scheme 7**).



Scheme 7: (i) I_2 (3 equiv), K_2CO_3 (3 equiv), $CHCl_3$, 30 min, rt.

Tummatorn's (2013)[21d]

Tummatorn *et al.* have reported an elegant method of synthesis of quinoline-3-carboxylic acid ethyl esters **3** *via* a domino process employing arylmethyl azides **13** as the precursor, which was obtained directly from the corresponding benzyl alcohols **12**. Acid-promoted rearrangement of azide **13** furnished N-aryl iminium ion **14** followed by the addition of ethyl 3-ethoxyacrylate, *in situ* underwent intramolecular electrophilic substitution, followed by elimination and subsequent oxidation, to give quinoline 3-carboxylates **3** in moderate to excellent yields 31-86% (**Scheme 8**).



Scheme 8: (i) (a) PBr_3, CH_2Cl_2, rt, 0.5 h; (b) NaN_3, DMSO, overnight, 52-99% for two steps; (ii) TfOH (1.0 equiv), toluene, rt, 3 h; (iii) DDQ (1.0 equiv), EtOAc, rt, 5 min.

4.1.3. Present Work

4.1.3.1 Objective

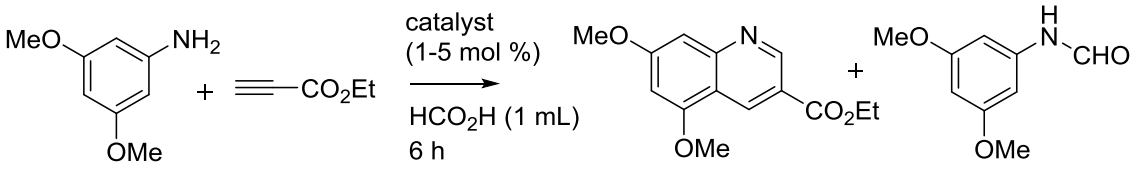
As can be seen from the literature, most of the methods suffer from limited availability of substrates, complicated multi-step procedures, and low regioselectivity, leading to low yields of products in most cases.[21]

Quite recently, Chen *et al*[22] have reported utilization of a directing group that is incorporated in the product. In this context, we reasoned that N-formyl derivative **17a** generated *in situ* could serve as a directing group for C-H functionalization to construct the quinoline carboxylate units. In this section, the first efficient and direct approach to quinoline carboxylates **3** & **18** from simple and readily available anilines and alkynic esters by using C-H activation *via* Rh catalysis with either formic acid as C1 source or $Cu(OAc)_2$ as oxidant is presented.

4.1.3.2 Results and Discussion

We commenced our optimization study by examining reaction of 3,5-dimethoxyaniline **15a** (1 mmol) with ethyl propiolate **16a** (1.2 equiv) in excess of formic acid (1 mL) at various temperatures under N_2 atmosphere (**Table 1**). When $[Rh_2(OAc)_4]$ (5 mol %) was employed at 100 °C, a mixture of cyclized quinoline-3-carboxylate (**3a**, 48%) along with N-formyl derivative (**17a**, 45%) was obtained (entry 1).

Table 1: Rhodium catalyzed reaction of 3,5-dimethoxyaniline with ethyl propiolate and HCO_2H: optimization studies[a]



15a **16a** **3a** **17a**

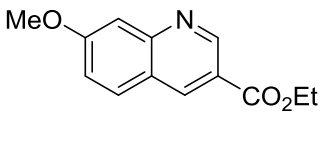
entry	catalyst	catalyst (mol %)	*t* (°C)	products (%)[b]	
				3a	**17a**
1	$Rh_2(OAc)_4$	5	100	48	45
2		5	70	61	34
3		5	50	84	11
4		5	35	50	40
5		2.5	50	85	10
6		2.5	35	40	45
7		1	50	41	42
8	$[RhCOCl_2]_2$	2.5	50	30	48
9	$Pd(OAc)_2$	2.5	50	31	44
10	Rh/Al_2O_3	2.5	50	15	85
11	no catalyst	-	50	-	91

[a] Arylamines (1 mmol), ethyl propiolate (1.2 mmol), HCO_2H (1 mL), 6 h. [b] Isolated yield after chromatographic purification.

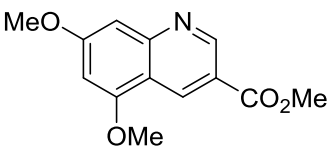
In order to improve the yield of **3a**, both Rh catalyst concentration and temperature were reduced. At 70 °C, the cyclization efficiency was significantly improved to give **3a** in 61% yield. Interestingly, on further lowering the temperature to 50 °C, a dramatic improvement in the yield of **3a** (84%) was realized (entry 3), probably due to the higher stability of rhodacycle **II** at lower temperature. Finally, the best result could be obtained when the reaction was conducted at 50 °C with the lowered catalyst concentration (2.5

mol %; entry 5). However, further lowering of either the temperature (35 °C) of the reaction or the catalyst loadings (1 mol %) had a deleterious effect on the product distribution (entry 4 & 7). Surprisingly, other catalysts were found to be less effective in improving the product distribution (entry 8 & 9); so also with the use of other solvents such as toluene or chlorinated solvents for the reaction. The catalyst control experiment, however, gave exclusively the N-formyl derivative **17a** (91%).

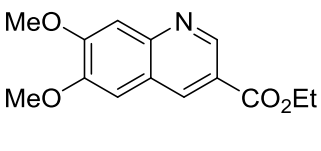
Scheme 9: Rh(II)-catalyzed synthesis of quinoline-3-carboxylate: substrate scope[a-c]



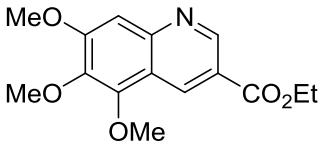
3b; 81%



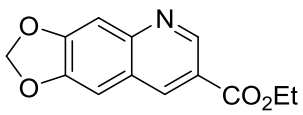
3c[d]; 78%



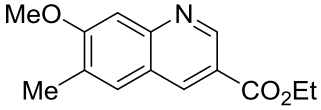
3d; 75%



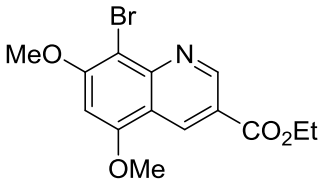
3e; 75%



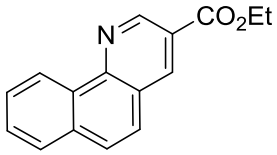
3f; 80%



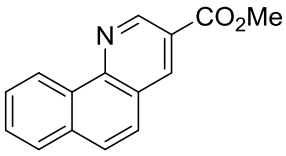
3g; 80%



3h; 65%



3i; 83%



3j[d]; 66%

[a] Arylamines (1 mmol), ethyl propiolate (1.2 mmol), $Rh_2(OAc)_4$ (2.5 mol %), HCO_2H (1 mL), 50 °C, 6 h. [b] Isolated yield after column purification. [c] 5-10% yield of N-formyl derivative **17b-j** was isolated in all the cases studied; [d] Methyl propiolate was used.

With the optimized reaction conditions established, we next examined the reaction scope of a variety of anilines with alkynic esters. The results are summarized in **Scheme 9**. Activated aniline bearing bromo, methoxy, methylenedioxy and methyl

groups on the aromatic nucleus including naphthyl group were well-tolerated under the reaction conditions. For all the cases studied, the annulated products **3a-j** were indeed obtained in high yields (65-83%) with excellent regioselectivity. In all substrate evaluation study, we observed that the *ortho* C-H bond activation was strongly promoted by the electron-donating groups present at the *meta* to NH_2 group of the substrates. However, in the case of substrates with weakly electron-donating groups (aniline, 3,4-dimethyl or dichloroaniline), only 5-10% of the required quinoline-3-carboxylate **3** was formed (GCMS analysis) with the major product being N-formyl derivative **17** (~90%). Also, in the case of internal alkynes, there was no annulation product formed. The formation of quinoline 3-carboxylate derivatives (**3a-j**) was established unambiguously from the corresponding ^{1}H, ^{13}C NMR, HRMS and IR spectral data, as presented in the following representative examples.

Example 1:

The formation of quinoline 3-carboxylate derivative **3b** was ascertained by ^{1}H NMR spectrum, which showed two characteristic singlets at δ 8.72 (s, 1H) and 9.35 (s, 1H) corresponding to aromatic protons of quinoline ring respectively. Further, its structure was confirmed from ^{13}C NMR spectrum, which displayed typical two carbon signals at δ 130.1 and 150.5 corresponding to olefinic carbons of quinoline ring respectively. Also, appearance of a strong vibrational stretching frequency at 1722 cm^{-1} attributed to the presence of ester –C=O group in its IR spectrum (**Fig. 1**).

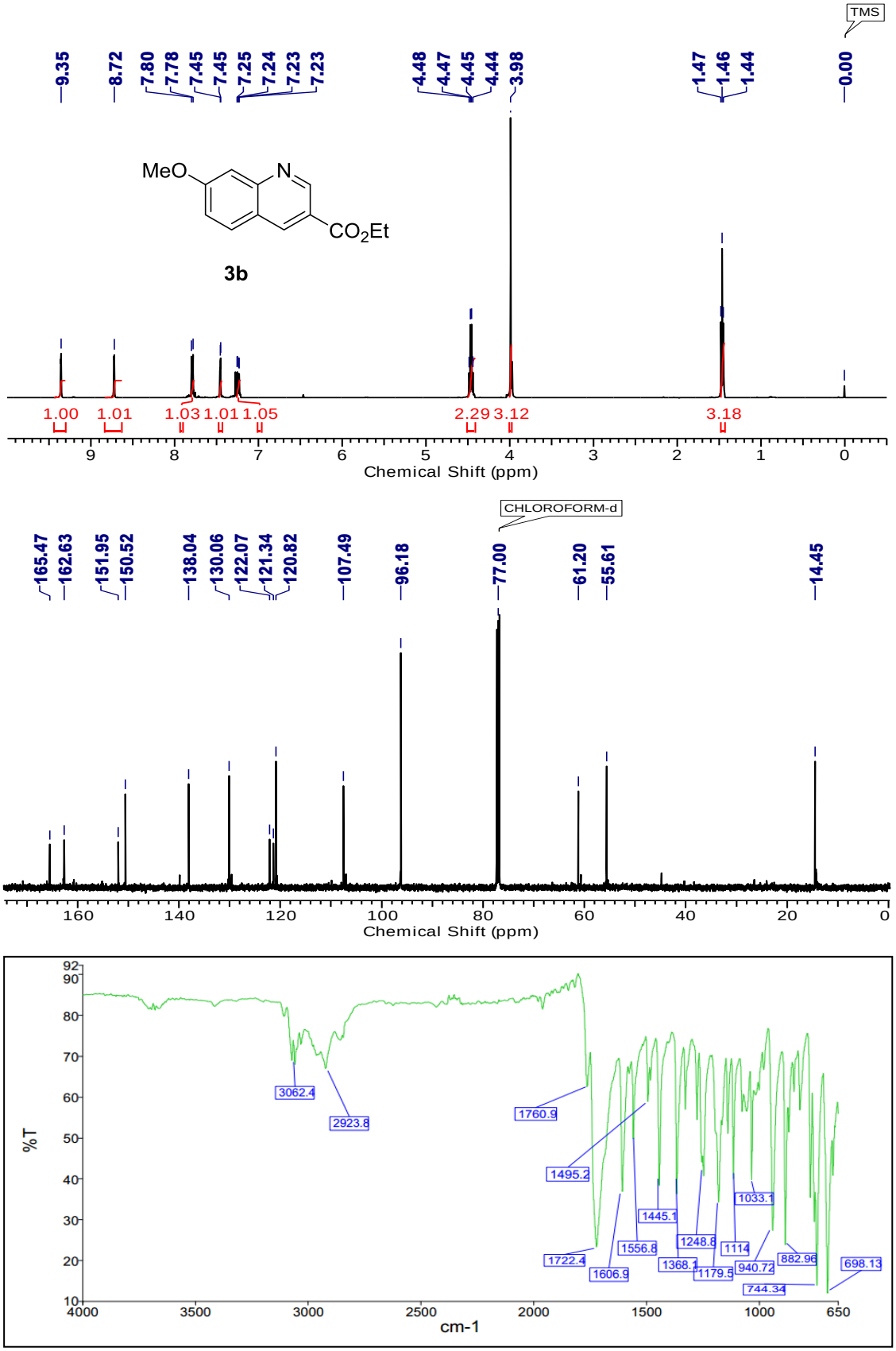


Fig. 1: ^{1}H, ^{13}C NMR and IR spectra of quinoline 3-carboxylate derivative **3b**

Example 2:

The ^{1}H NMR spectrum of quinoline 3-carboxylate derivative **3i** showed two typical doublets at δ 8.79 (d, *J* = 1.8 Hz, 1H) and 9.52 (d, *J* = 1.8 Hz, 1H) corresponding to two aromatic protons of quinoline moiety with *meta* coupling respectively. Also, its ^{13}C NMR spectrum displayed two typical carbon signals at δ 137.6 and 149.0 due to olefinic carbons of quinoline part and another characteristic carbon signal appeared at δ 165.5 attributed to –C=O carbon of ester group respectively (**Fig. 2**). Its IR spectrum showed a strong absorption band at 1716 cm^{-1} due to the presence of ester carbonyl

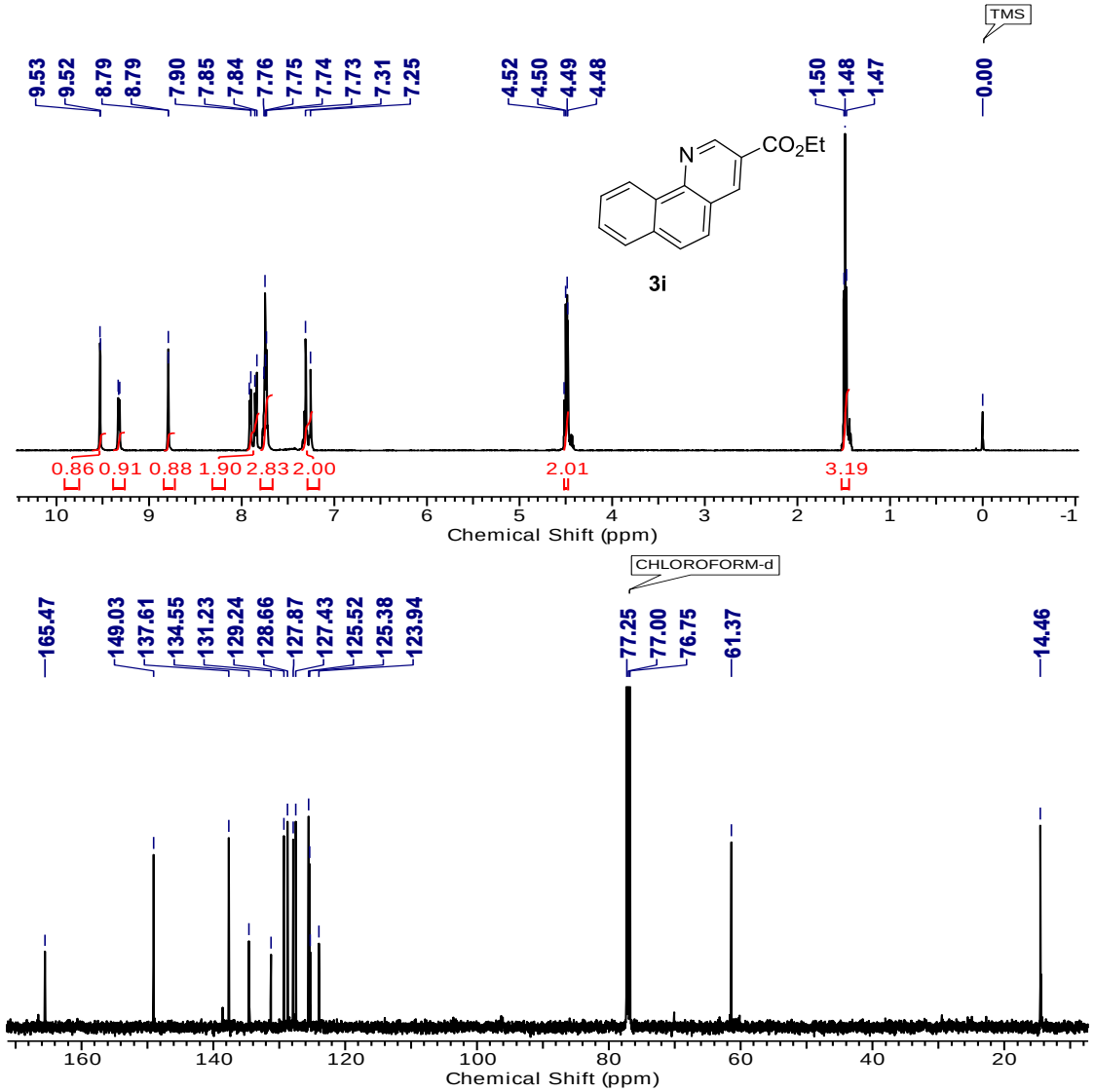
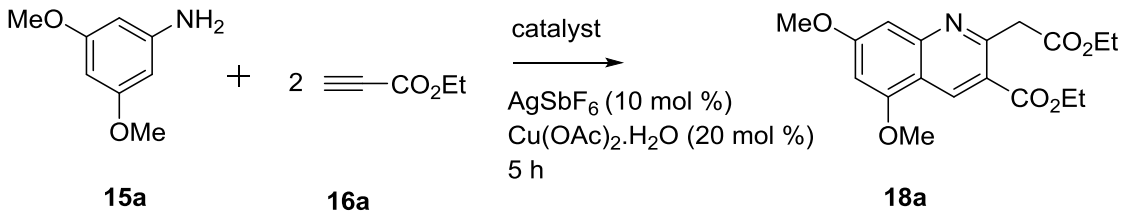


Fig. 2: ^{1}H and ^{13}C NMR spectra of quinoline 3-carboxylate derivative **3i**

functionality, thus confirming the formation of **3i**. In order to improve the C-H activation protocol applicable to a variety of aniline substrates, we examined a new catalytic system [Rh(III)/Cu(II)]. Surprisingly, under the new condition {[$RhCp^*Cl_2]_2$, (5 mol %), $Cu(OAc)_2.H_2O$ (10 mol %), $AgSbF_6$ (20 mol %), 1,2-dichloroethane (DCE), 80 °C, 5 h)}, 3,5-dimethoxyaniline **15a** underwent oxidative coupling with ethyl propiolate (**16a**) to afford the corresponding 2,3-disubstituted quinoline dicarboxylate (**18a**) in 71% yield (**Table 2,** entry 1).

Table 2: Rh(III)-catalyzed reaction of 3,5-dimethoxyaniline and ethyl propiolate: optimization study[a]



15a **16a** **18a**

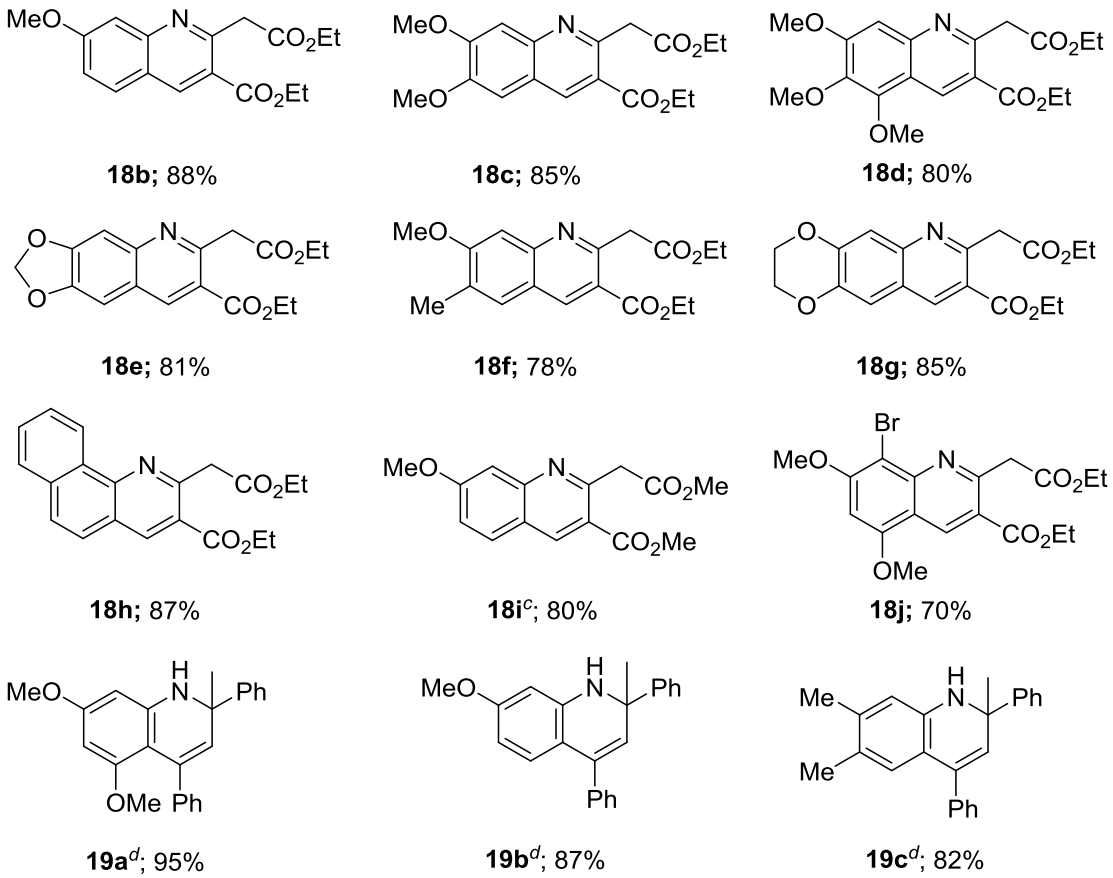
entry	catalyst	catalyst (mol %)	solvent	*t* (°C)	yield of **18a** (%)[b]
1	$[RhCp^*Cl_2]_2$	5	DCE	80	71
2		2.5	DCE	80	74
3		1	DCE	50	40
4		2.5	DCE	50	88
5		2.5	CH_2Cl_2	40	35
6		2.5	dioxane	80	50
7	$[RhCOCl_2]_2$	2.5	DCE	50	33
8	$RhCl_3$	2.5	DCE	50	10

[a] Substrate **15a** (1 mmol), ethyl propiolate (2.1 mmol), $AgSbF_6$ (20 mol %), $Cu(OAc)_2.H_2O$ (10 mol %) in 2 mL solvent, 5 h. [b] Isolated yields after chromatographic purification.

After several experimentations, it was thus found that a combination of aniline **15a** (1 mmol), ethyl propiolate (2.1 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %) and

$Cu(OAc)_2$ (20 mol %) in DCE at 50 °C for 5 h was the best optimized condition in achieving excellent product yields **18a-j** (70-88%). Among the solvents screened, DCE was found to be the best choice possibly due to its high dielectric constant coupled with optimum reaction temperature (50 °C).

Scheme 10: Rh(III)-catalyzed reaction of electron-rich anilines and ethyl propiolates or phenyl acetylene: substrate scope[a,b]



[a] Substrate **15a** (1 mmol), ethyl propiolate (2.1 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2.H_2O$ (10 mol %), 1,2-dichloroethane (2 mL), 50 °C, 5 h. [b] Isolated yields. [c] methyl propiolate was used. [d] phenyl acetylene was used.

Scheme 10 summarizes the results of its substrate scope study. In case of internal alkynyl esters, only the Michael addition products were produced. The formation of 2,3-disubstituted quinoline dicarboxylate derivatives (**18a-j**) was established

unambiguously from the corresponding ^{1}H, ^{13}C NMR and HRMS spectral data, as illustrated in following examples which are only representative.

Example 1:

The formation of 2,3-disubstituted quinoline dicarboxylate derivative **18a** was ascertained by ^{1}H NMR spectrum, which showed a characteristic singlet at δ 9.05 (s, 1H) corresponding to olefinic proton of quinoline moiety. Also, its ^{13}C NMR spectrum displayed carbon signals at δ 166.1 and 170.6 accounting for the presence of carbonyl

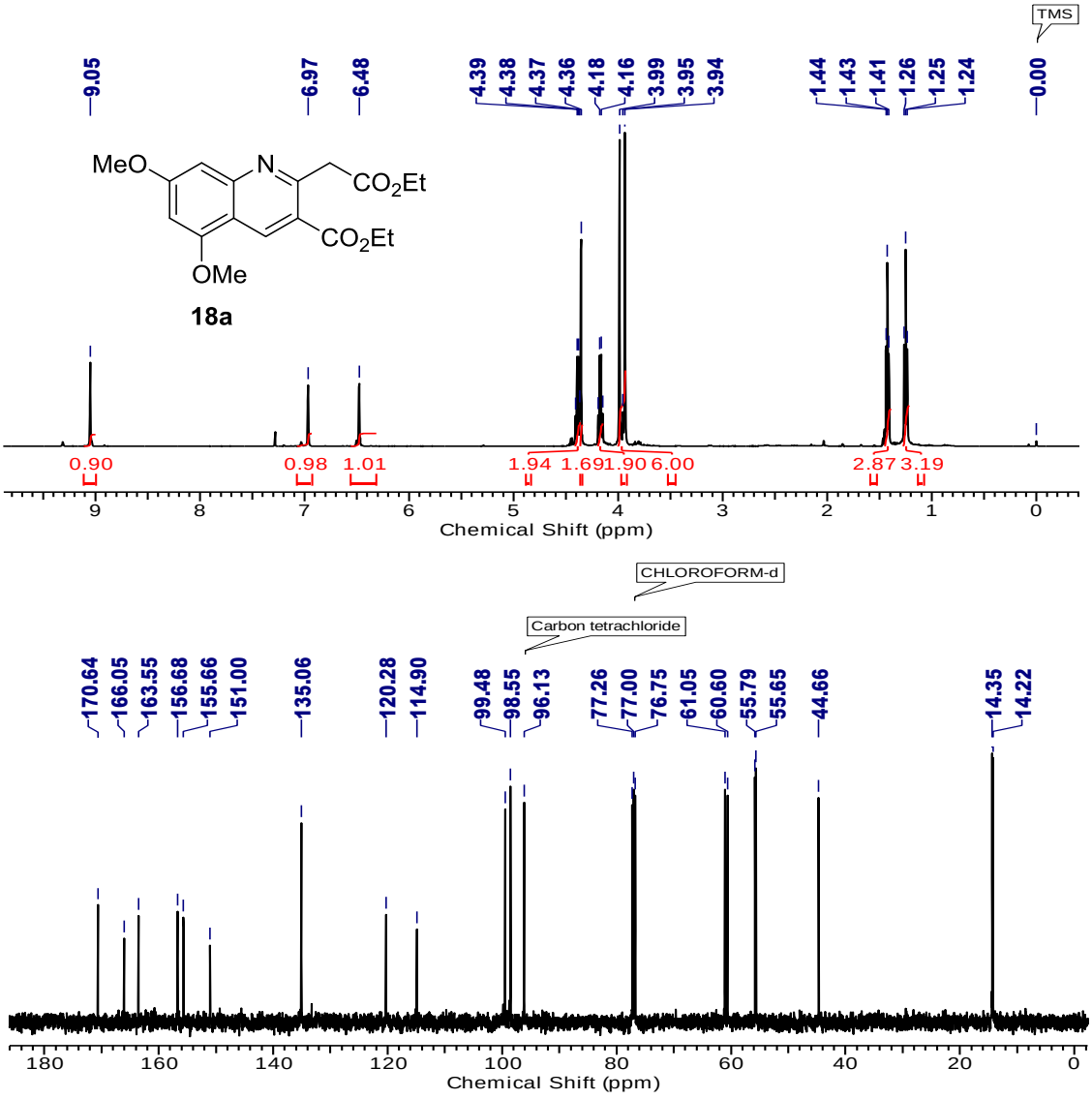


Fig. 3: ^{1}H and ^{13}C NMR spectra of **18a**

carbon of two ester groups respectively (**Fig. 3**). Its IR spectrum showed strong vibrational stretching frequencies at 1711 and 1728 cm^{-1} indicating the presence of two ester functionalities respectively.

Example 2:

2,3-Disubstituted quinoline dicarboxylate derivative **18e** was confirmed from ^{1}H NMR spectrum, which displayed a characteristic proton singlet at δ 4.33 (s, 2H) corresponding to methylene proton attached to ester group. Further, its structure was

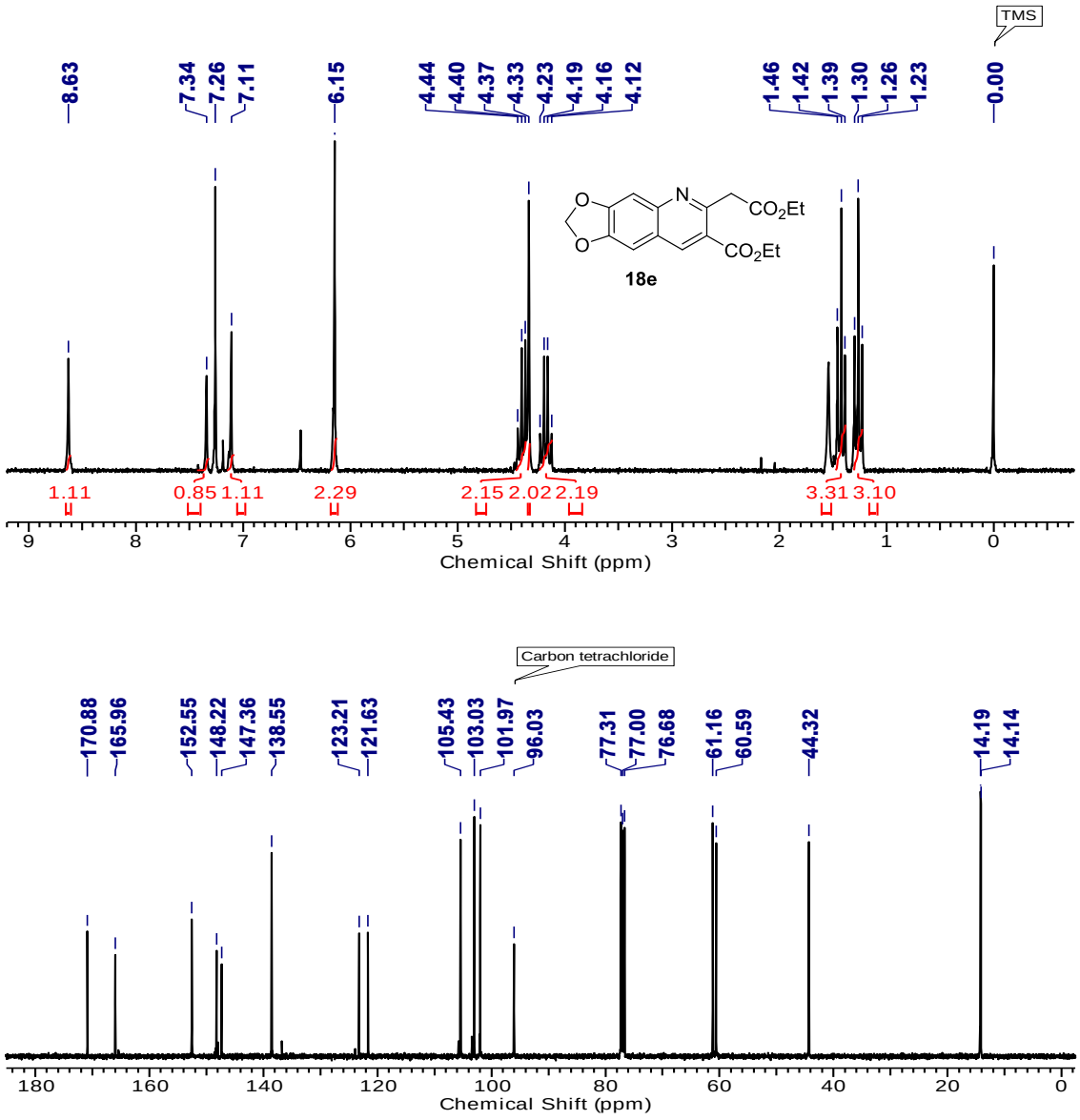


Fig. 4: ^{1}H and ^{13}C NMR spectra of **18e**

supported by ^{13}C NMR spectrum, which showed two typical carbon signals at δ 14.1 and 14.2 due to presence of methyl carbons of two ester groups and another at δ 44.3 for methylene carbon attached to ester group respectively (**Fig. 4**). Also, its IR spectrum exhibited two strong vibrational stretching frequencies at 1692 and 1718 cm^{-1} indicating two ester functionalities.

Additionally, when the coupling partner was changed to simple phenyl acetylene (2.1 equiv), under same reaction conditions, 1,2-dihydroquinoline derivatives **19a-c** with double addition of reaction partners were obtained in high yields (82-95%).

The formation of 1,2-dihydroquinoline derivatives **19a-c** was established from the corresponding ^{1}H, ^{13}C and DEPT NMR spectral data, as given below:

Example 1:

The formation of 1,2-dihydroquinoline derivative **19b** was ascertained by ^{1}H NMR spectrum, which showed a sharp singlet at δ 1.73 (s, 3H) and a broad singlet at δ 4.16 (br. s. 1H) corresponding to methyl and secondary –NH protons of dihydroquinoline moiety and another resonance singlet at δ 5.57 (s, 1H) due to the presence of olefinic proton respectively. Its ^{13}C NMR spectrum displayed a characteristic carbon signal at 55.1 corresponding to quaternary carbon attached to –NH and –Ph group, which disappeared in its DEPT NMR spectrum (**Fig. 5**).

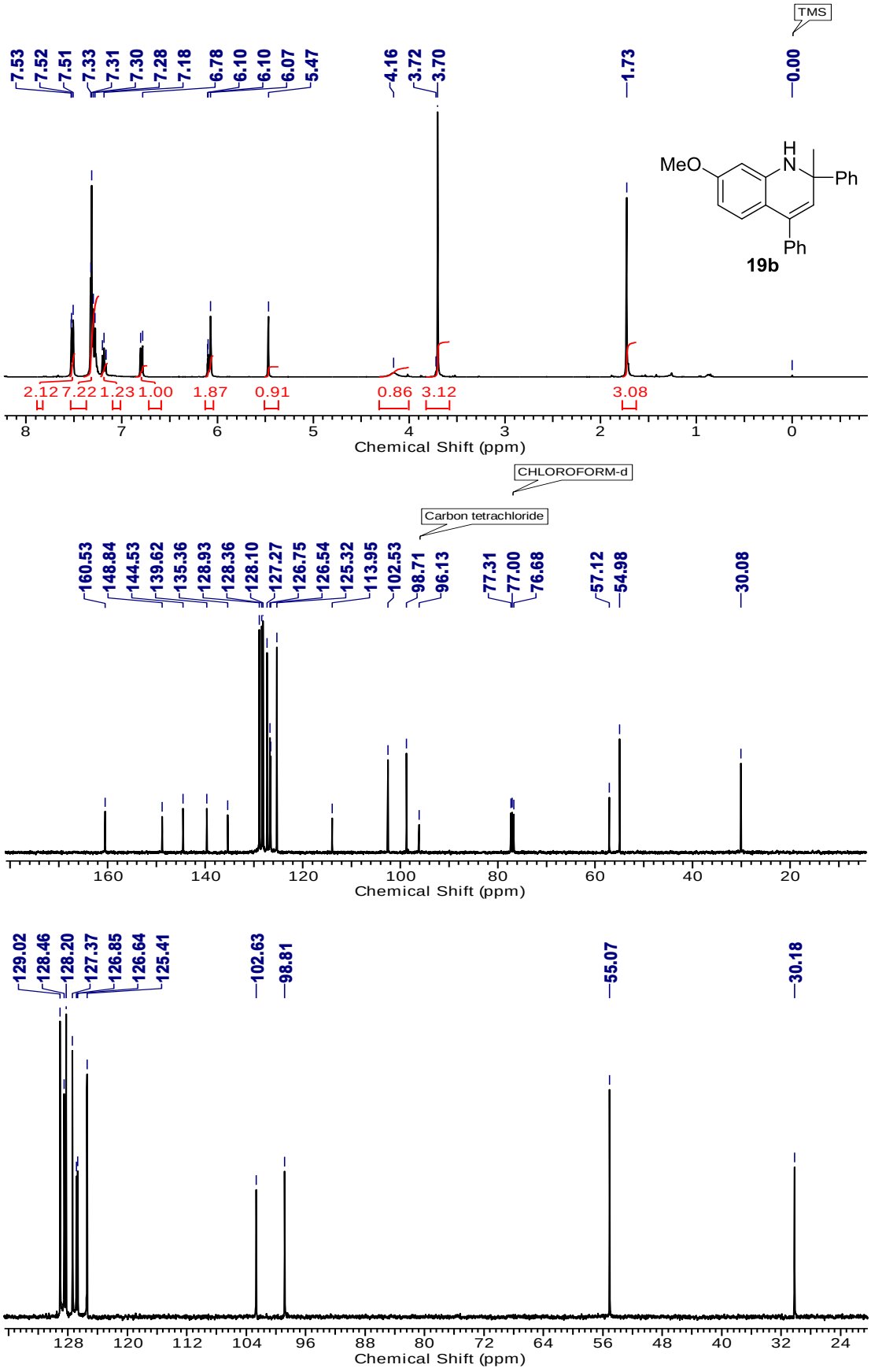
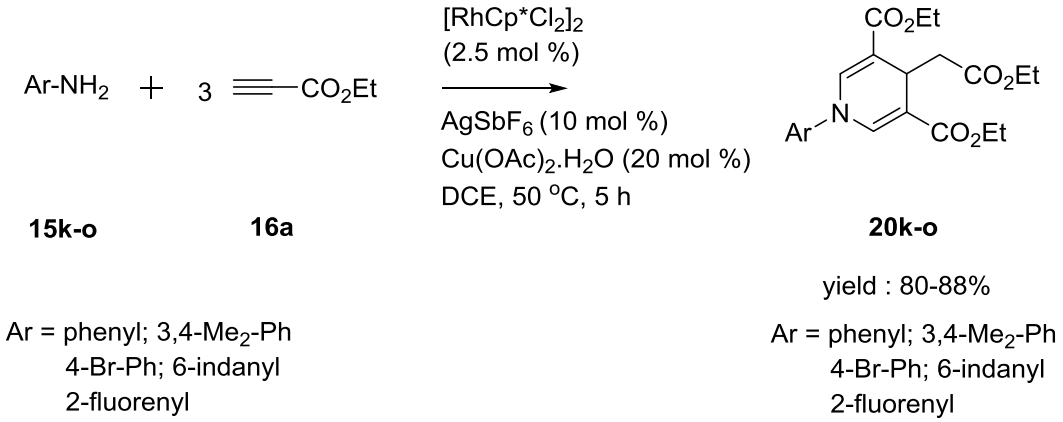


Fig. 5: ^{1}H, ^{13}C and DEPT NMR spectra of 1,2-dihydroquinoline derivative **19b**

Further, in the case of moderately electron-donating anilines, the oxidative coupling with ethyl propiolate (3 equiv) under Rh(III)/Cu(II)/Ag^+ catalysis conditions proceeded to give interesting 1,4-dihydropyridine derivatives **20k-o**, which are potent Ca^{2+} channel blockers used in the treatment of cardiovascular diseases, in excellent yields (80-88%) following presumably Hantzsch type mechanism[23] (**Scheme 11**).



Scheme 11: Rh(III)-catalyzed reaction of moderately electron-rich anilines with ethyl propiolate

The formation of 1,4-dihydropyridine derivatives **20k-o** was established from the corresponding ^1H, ^{13}C and DEPT NMR spectral data, as given below:

Example 1:

The formation of 1,4-dihydropyridine derivatives **20k** was confirmed from the ^1H NMR spectrum, which showed a typical doublet at δ 2.57 (d, J = 4.9 Hz, 2H) and a singlet at δ 7.55 (s, 2H) attributable to methylene protons attached to ester group and olefinic protons of pyridine moiety respectively. Also, its ^{13}C NMR spectrum displayed characteristic carbon signals at δ 29.7 and 40.5 due to the presence of methylene and methine carbons of dihyropyridine ring respectively. Further, the formation of **20k** was substantiated by its mass spectrum (**Fig. 6**).

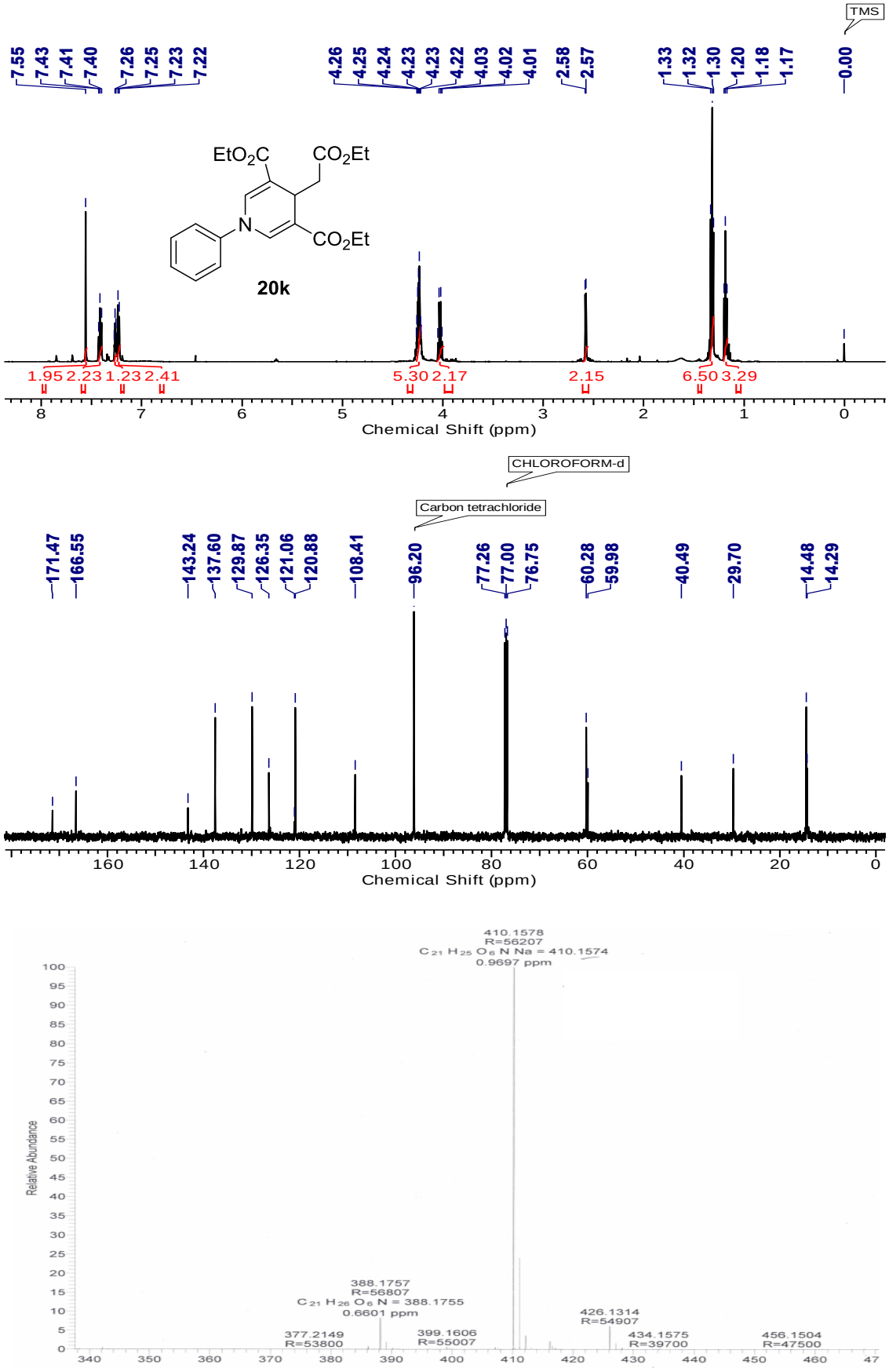
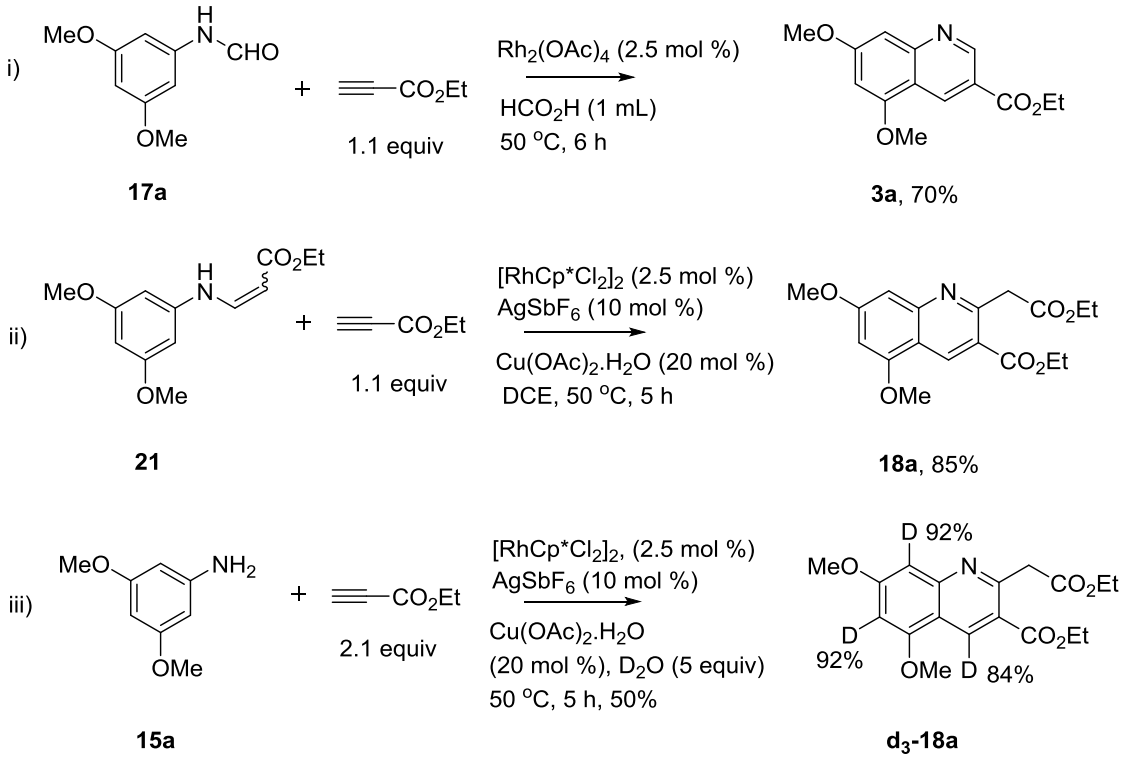


Fig. 6: ^{1}H, ^{13}C NMR and Mass spectra of 1,4-dihydropyridine derivatives **20k**

4.1.3.3 Mechanistic Discussion

To gain some insight into the mechanistic details of the reaction, the following experiments were conducted (**Scheme 12**): (a) when N-formyl derivative **17a** was reacted with ethyl propiolate in the presence of Rh(II)/HCO_2H combination, **3a** was obtained in 70% yield; also in the absence of Rh catalyst, neither coupling reaction proceeded nor deuterium exchange occurred; (b) additionally, when enamine ester **21** was treated with ethyl propiolate under Rh(III)/Cu(II)/Ag^+ conditions, **18a** was formed in 85% yield; (c) when aniline **15a** was subjected to oxidative coupling with ethyl propiolate under Rh(III)/Cu(II)/Ag^+ conditions in the presence of D_2O as solvent, deuterated quinoline derivative **d_3-18a** was isolated in 50% yield, in which deuterium incorporation of 84% at C-4 carbon and 92% each at C-6 and C-8 carbons was observed (^{1}H NMR and HRMS proven).



Scheme 12: Experiments to probe mechanism

This study clearly establishes that the *ortho* C-H bond cleavage in aryl amines has occurred *via* C-H bond activation (**Fig. 7**).

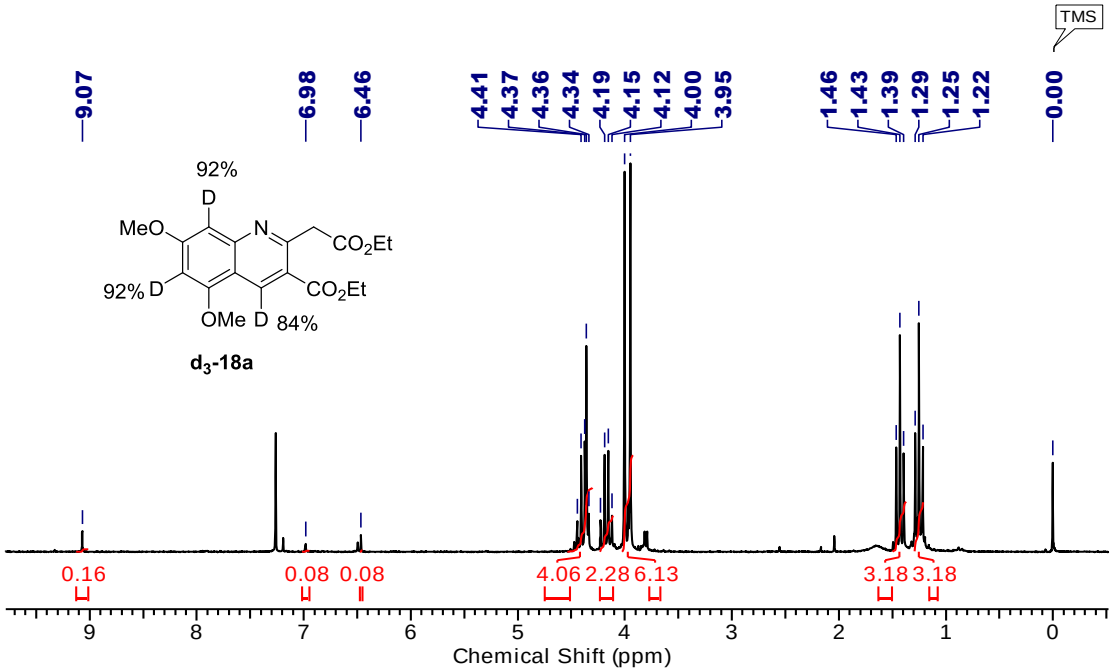
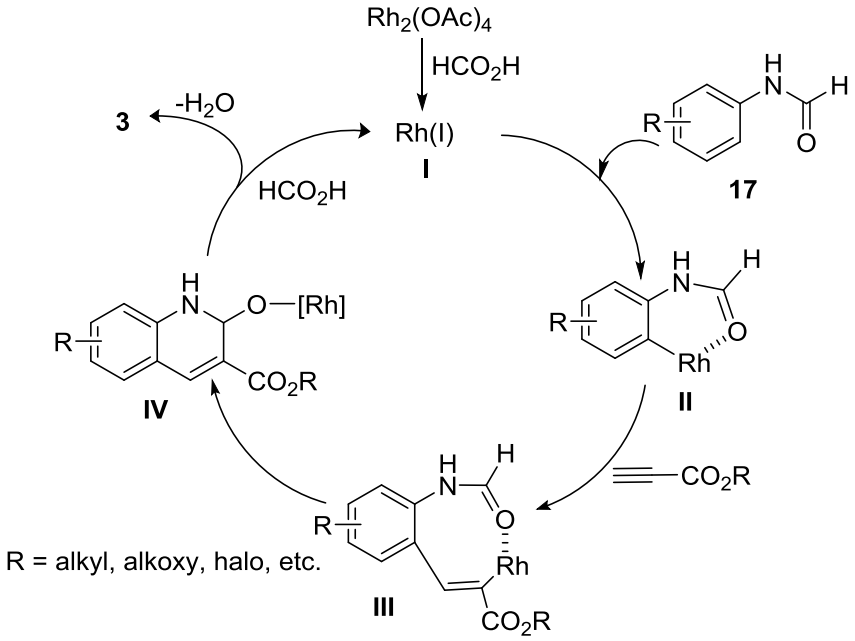


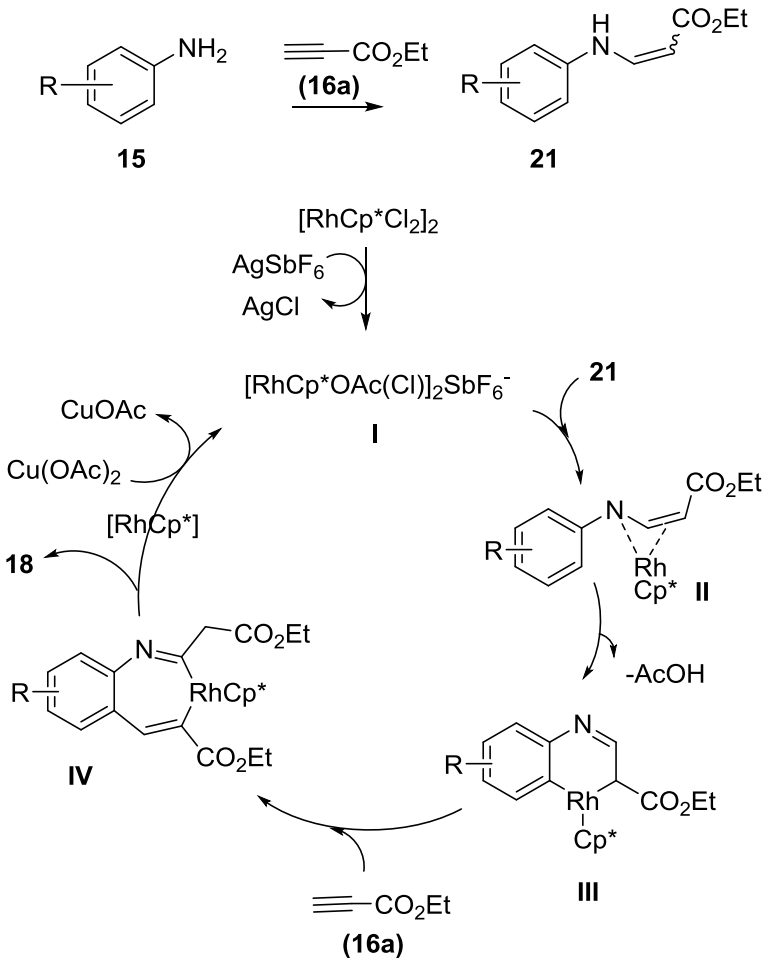
Fig. 7: ^{1}H NMR Spectrum of **d_3-18a**

Scheme 13 shows the plausible catalytic cycle for the reaction based on the above experimental studies. Rh(I) species **I** obtained from $[Rh_2(OAc)_4]$ on reduction with formic acid, undergoes *ortho* metalation regioselectively with N-formyl derivative **17**, formed *in situ* from aniline and formic acid, to form a six membered rhodacycle **II**. Coordinative insertion of alkyne into the Rh-C bond of species **II** provides the cyclic intermediate **III** followed by intramolecular cyclization led to the formation of cyclized species **IV**. Protonation at Rh-O bond in **IV** finally results in the generation of Rh(I) species. This process is accompanied by the elimination of H_2O molecule thereby affording the desired quinoline derivatives **3**.



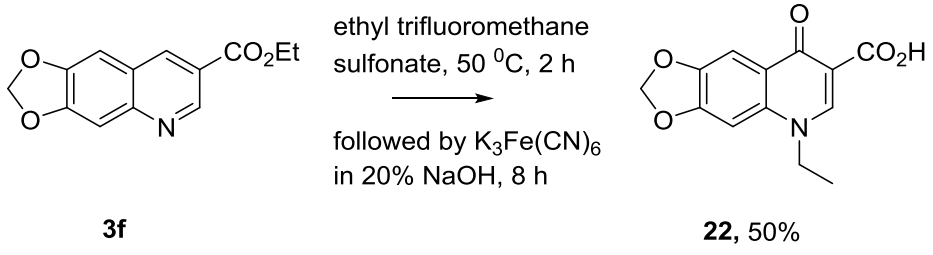
Scheme 13: Plausible mechanism for quinoline-3-carboxylate

In order to explain the formation of **18** a probable catalytic cycle involving *ortho*-C-H bond activation is provided in **Scheme 14**. This proceeds *via* addition reaction followed by *ortho*-C-H bond activation. To begin with, aniline **15** undergoes Michael addition with ethyl propiolate **16a** to form enamine ester **21**. The additive $AgSbF_6$ probably removes the Cl^- ligand from the catalyst $[RhCp^*Cl_2]_2$ complex, giving a cationic rhodium species **I**. Coordination of lone pair of nitrogen and double bond of imine species **21** to a cationic Rh species **I** leads to intermediate **II** followed by acetate accelerated *ortho*-metalation affords a six-membered rhodacycle **III**. The coordinative insertion of second molecule of ethyl propiolate **16a** into the Rh-C bond of rhodacycle **III** gives intermediate **IV**. Reductive elimination of Rh in intermediate **IV** in the presence of $Cu(OAc)_2$ gives the desired product **18** with the regeneration of active rhodium species **II** for the next catalytic cycle.



Scheme 14: Plausible mechanism for 2,3-disubstituted quinoline carboxylates **18**

This catalytic procedure was successfully demonstrated in the synthesis of oxolinic acid **22**, a quinolone antibiotic and antibacterial agent used in the treatment of urinary tract infections and psoriasis. Thus, quinoline carboxylate **3f**, obtained from 3,4-methylenedioxyaniline by the present protocol, was subjected to N-alkylation with ethyl trifluoromethane sulfonate followed by oxidation with $K_3Fe(CN)_6$[24] in a single



3f **22,** 50%

Scheme 15: Concise short synthesis of oxolinic acid (**22**)

step to give oxolinic acid[25] **22** (50% yield) (**Scheme 15**). Its formation was confirmed by ^{1}H NMR spectrum, which showed a typical singlet at δ 9.12 (s, 1H) due to olefinic proton of quinoline ring; and a triplet at δ 1.69 (t, *J* = 7.2 Hz, 3H) and a quartet at δ 4.71 (q, *J* = 7.2 Hz, 2H) corresponding to ethyl group attached to nitrogen atom. In its ^{13}C NMR spectrum, carbon signals at δ 169.8 and 158.6 were attributed to –C=O carbon of quinoline and acid moieties respectively (**Fig. 8**). Its IR spectrum displayed strong vibrational stretching frequencies at 1620 and 3420 cm^{-1} due to the presence of –C=O and –OH of carboxylic acid functionalities respectively.

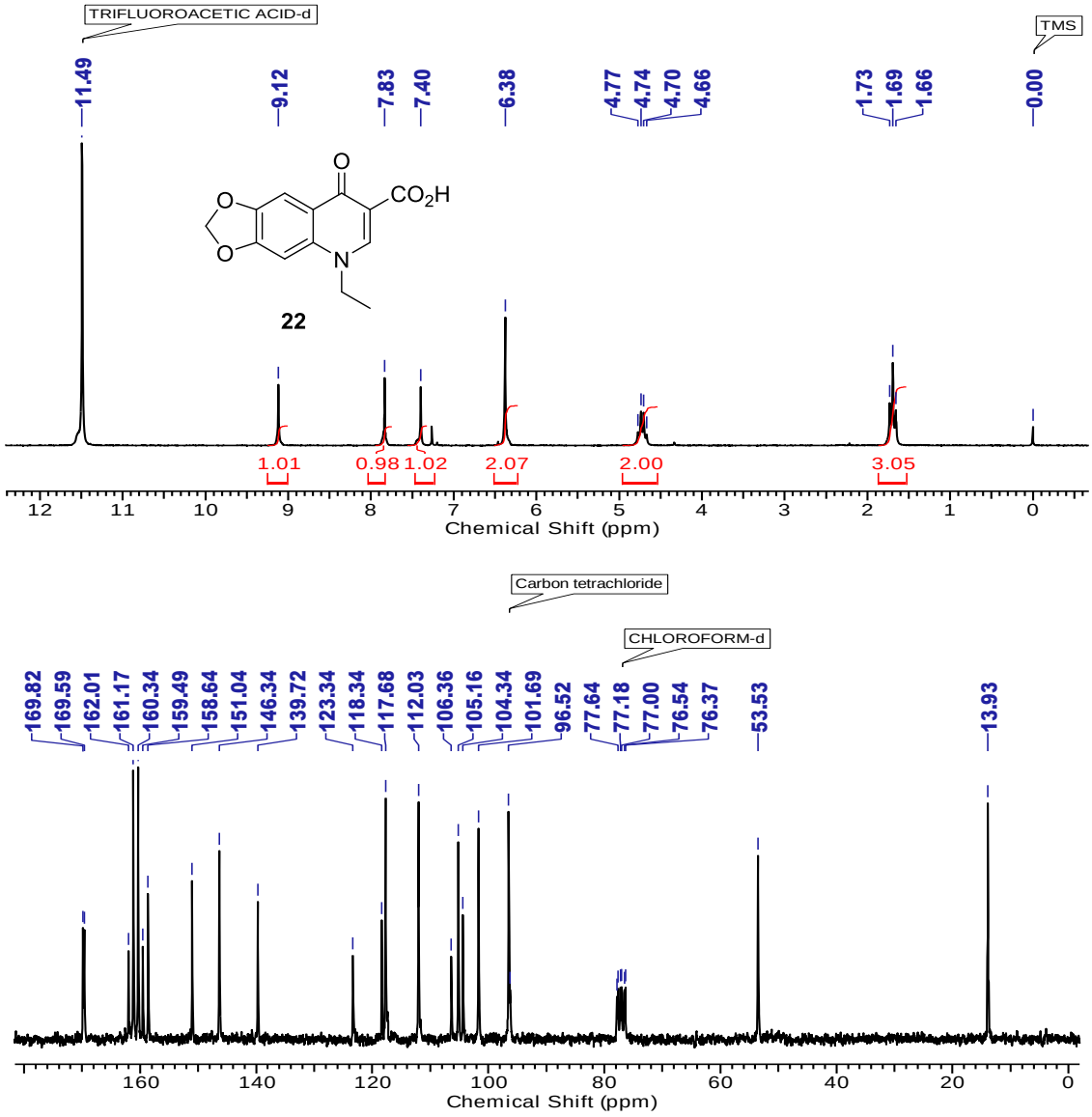


Fig. 8: ^{1}H and ^{13}C NMR spectra of oxolinic acid **22**

4.1.4 Conclusion

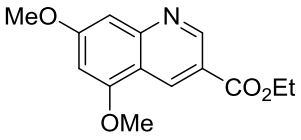
In summary, we have presented, for the first time, a simple annulation strategy that affords a variety of 2,3-disubstituted quinolines carboxylates **3a-j** and **18a-j** in high yields from the corresponding substituted anilines **15a-j** *via* rhodium catalyzed cyclization in a single step. This cyclization strategy involves rhodacycles as the intermediates formed by the *ortho* C-H activation of anilines supported by deuterium incorporation studies. We believe that this single-step cyclization strategy will find tremendous applications in the synthesis of bioactive heterocyclic scaffolds as demonstrated amply herein the high yield synthesis of oxolinic acid **22**. Further exploration of the reaction scope and other types of cyclization is currently under investigation in our laboratory.

4.1.5 Experimental procedure

4.1.5.1 General experimental procedure for the preparation of quinoline 3-carboxylate derivatives (3a-j):

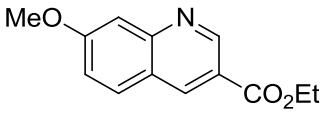
To a mixture of substituted anilines (**15a-j**) (1 mmol), $Rh_2(OAc)_4$ (2.5 mol %) and formic acid (1 mL) under nitrogen atmosphere was added ethyl propiolate **16a** (1.2 mmol). The resulting brown solution was stirred at 50 °C for 6 h. After completion of reaction (monitored by TLC), it was diluted with ethyl acetate (10 mL), and washed with water (10 mL), 5% aqueous sodium bicarbonate (15 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in *vacuo* to give a brown solid. On purification with flash chromatography using pet ether and ethyl acetate (7:3), quinoline 3-carboxylic acid esters (**3a-j**) were isolated as solids.

Ethyl 5,7-dimethoxyquinoline-3-carboxylate (3a)



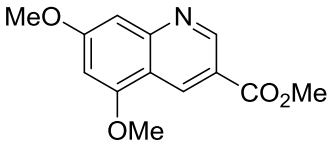
Yield: 85%; (0.144 g), colorless solid; **mp**: 122-123 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1722, 1618, 1599, 1505, 1432; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.31 (s, 1H), 9.05 (s, 1H), 7.05 (s, 1H), 6.51 (s, 1H), 4.46 (q, *J* = 7.3 Hz, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 1.46 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 165.5, 163.5, 156.9, 152.1, 150.9, 133.4, 120.3, 115.6, 99.8, 98.8, 61.1, 55.8, 55.7, 14.5; **HRMS** (ESI): calc. for [($C_{14}H_{15}NO_4$)H] (M+Na) 284.0899; Found: 284.0893.

Ethyl 7-methoxyquinoline-3-carboxylate (3b)



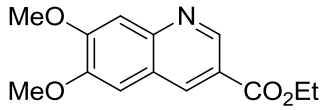
Yield: 81% (0.151 g), Yellow solid; **mp**: 110-112 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2981, 1717, 1601, 1279, 1243, 1027; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.36 (d, *J* = 1.7 Hz, 1H), 8.73 (d, *J* = 1.7, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 7.23 (d, *J* = 9.0, 2.5 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 165.5, 162.6, 152.0, 150.5, 138.0, 130.1, 122.1, 121.3, 120.9, 107.5, 61.2, 55.6, 14.5; **HRMS** (ESI): calc. for [($C_{13}H_{13}NO_3$)H] (M+H) 232.0974; Found: 232.0968.

Methyl 5,7-dimethoxyquinoline-3-carboxylate (3c)



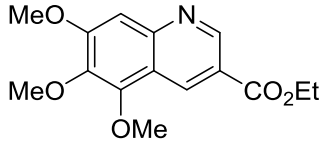
Yield: 78% (0.126 g), colorless solid; **mp**: 134-135 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1722, 1618, 1599, 1505, 1432; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.31 (d, *J* = 1.4 Hz, 1H), 9.06 (d, *J* = 1.4 Hz, 1H), 7.05 (s, 1H), 6.51 (d, *J* = 2.3 Hz, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 166.0, 163.6, 156.9, 152.2, 151.0, 133.5, 120.0, 115.6, 99.8, 98.8, 55.9, 55.7, 52.2; **HRMS** (ESI): calc. for $[(C_{13}H_{13}NO_4)H]$ (M+H) 248.0845; Found: 248.0858.

Ethyl 6,7-dimethoxyquinoline-3-carboxylate (3d)



Yield: 75% (0.128 g), colorless solid; **mp**: 161-163 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1722, 1618, 1599, 1505, 1432; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.65 (d, *J* = 1.9 Hz, 1H), 7.46 (s, 1H), 7.11 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 3H), 4.03 (s, 3H), 1.46 (s, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 170.9, 165.5, 154.4, 150.5, 148.1, 138.3, 136.5, 122.6, 121.7, 108.0, 105.9, 61.2, 56.2, 56.0, 14.5; HRMS (ESI): calc. for $[(C_{14}H_{15}NO_4)H]$ (M+H) 262.1079; Found: 262.1082.

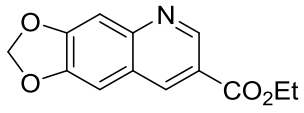
Ethyl 5,6,7-trimethoxyquinoline-3-carboxylate (3e)



Yield: 75% (0.119 g), colorless solid; **mp**: 170-172 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3000, 1718, 1607, 1479, 1278, 1020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.28 (s, 1H), 8.98 (s, 1H), 7.28 (s, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 4.12 (s, 3H), 4.04 (s, 3H), 3.97 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 165.8, 158.4, 149.9, 148.2, 148.0,

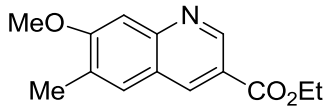
147.9, 141.4, 133.4, 121.5, 104.3, 61.0, 61.5, 56.5, 30.0, 14.8; **HRMS** (ESI): calc. for $[(C_{15}H_{17}NO_5)H]$ (M+H) 292.1185; Found: 292.1179.

Ethyl [1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (3f)



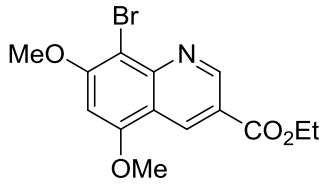
Yield: 80% (0.143 g), colorless solid; **mp**: 210-213 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1709, 1611, 1277, 1203, 1077; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.21 (d, *J* = 1.9 Hz, 1H), 8.58 (d, *J* = 2.1 Hz, 1H), 7.40 (s, 1H), 7.11 (s, 1H), 6.15 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.8 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 165.4, 161.9, 152.5, 148.7, 148.1, 136.8, 124.0, 122.3, 106.0, 103.5, 102.1, 61.2, 14.4; **HRMS** (ESI): calc. for $[(C_{13}H_{11}NO_4)H]$ (M+H) 246.0766; Found: 246.0761.

Ethyl 7-methoxy-6-methylquinoline-3-carboxylate (3g)



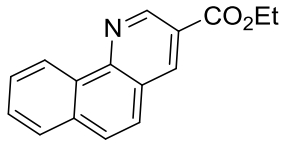
Yield: 80% (0.142 g), colorless solid; **mp**: 110-112 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3081, 1716, 1611, 1299, 1250, 1033; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.65 (s, 1H), 7.61 (s, 1H), 7.40 (s, 1H), 4.45 (q, *J* = 6.9 Hz, 2H), 4.01 (s, 3H), 2.39 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 165.6, 161.6, 150.9, 149.4, 137.2, 130.5, 129.0, 121.9, 121.1, 106.2, 61.0, 55.7, 16.8, 14.4; **HRMS** (ESI): calc. for $[(C_{14}H_{15}NO_3)H]$ (M+H) 246.1130; Found: 246.1125.

Ethyl 8-bromo-5,7-dimethoxyquinoline-3-carboxylate (3h)



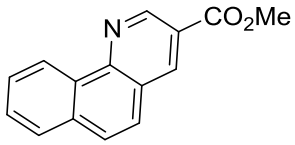
Yield: 65% (0.095 mg), colorless solid; **mp**: 156-158 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2987, 1717, 1605, 1478, 1264, 1002; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.48 (d, *J* = 1.8 Hz, 1H), 9.09 (d, *J* = 1.8 Hz, 1H), 6.70 (s, 1H), 4.46 (q, *J* = 7.0 Hz, 2H), 4.10 (s, 3H), 4.08 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 165.4, 159.3, 157.1, 152.2, 148.0, 134.8, 134.0, 120.9, 115.9, 94.2, 61.4, 57.0, 56.1, 14.4; **HRMS** (ESI): calc. for [($C_{14}H_{14}BrNO_4$)H] (M+H) 340.0184; Found: 340.0182.

Ethyl benzo[*h*]quinoline-3-carboxylate (3i)



Yield: 83% (0.145 g), colorless solid; **mp**: 105-107 °C; lit[21d] mp 106-107 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2983, 1716, 1598, 1314, 1260, 1212, 750; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.52 (d, *J* = 1.8 Hz, 1H), 9.32 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.79 (d, *J* = 1.8 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.76-7.73 (m, 3H), 7.32-7.25 (m, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 165.5, 149.0, 137.6, 134.6, 131.2, 129.2, 128.7, 127.8, 127.4, 125.5, 125.4, 125.2, 123.9, 61.4, 14.5; **HRMS** (ESI): calc. for [($C_{16}H_{13}NO_2$)H] (M+H) 252.1025; Found: 252.1019.

Methyl benzo[*h*]quinoline-3-carboxylate (3j)



Yield: 66% (0.108 g), colorless solid; **mp**: 124-125 °C; lit[21a] mp 125-127 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2980, 1717, 1600, 1374, 1250, 1222, 750; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.49 (d, *J* = 1.8 Hz, 1H), 9.29 (dd, *J* = 9.1, 2.3 Hz, 1H), 8.76 (d, *J* = 2.3 Hz, 1H), 7.88 (dd, *J* = 6.9, 1.8 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.75-7.69 (m, 3H), 4.02 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 165.9, 148.9, 148.9, 137.7, 134.5, 131.1, 129.3, 128.7, 127.8, 127.4, 125.5, 125.4, 125.2, 125.6, 123.6, 52.4; **HRMS** (ESI): calc. for [($C_{15}H_{11}NO_2$)H] (M+H) 238.0868; Found: 238.0860.

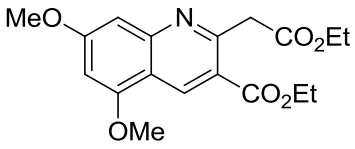
4.1.5.2 General experimental procedure for the preparation of quinoline carboxylate derivatives (18a-j) and (19a-c):

A two-neck round-bottomed flask with septum was charged with $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2.H_2O$ (20 mol %) and $AgSbF_6$ (20 mol %) and evacuated, purged with nitrogen gas three times ($AgSbF_6$ was added inside the glove box). To this reaction mixture, was added anilines **15a-j** (1 mmol), ethyl propiolate **16a** (2.1 equiv), and 1,2-dichloroethane (2.0 mL) *via* syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. The reaction mixture was then allowed to stir at 50 °C for 5 h. It was cooled to room temperature and diluted with CH_2Cl_2, filtered through Celite. The filtrate was washed with water and the organic layer was extracted with CH_2Cl_2 and dried over anhyd. Na_2SO_4. Later, the solution was concentrated under reduced pressure. The crude residue was purified through silica gel column using pet

ether and ethyl acetate (7:3) as eluent to give pure 2,3-disubstituted quinoline carboxylates (**18a-j)**.

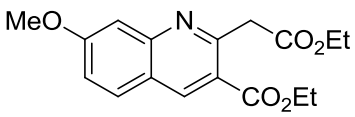
Also, the same procedure was followed for the formation of 1,2-dihydroquinolines (**19a-c**) using phenylacetylene (2.1 equiv). In case of formation of 1,4-dihydropyridine derivatives (**20k-o**), an excess amount ethyl propiolate **16a** (3 equiv) was used under the same procedure.

Ethyl 2-(2-ethoxy-2-oxoethyl)-5,7-dimethoxyquinoline-3-carboxylate (18a)



Yield: 88% (0.198 g), colorless solid; **mp**: 128-129 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2949, 1718, 1692, 1628, 1577, 1514, 1439, 1319, 1245, 1221, 1171, 1145, 993; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.05 (s, 1H), 6.97 (s, 1H), 6.48 (s, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 4.36 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 170.6, 166.1, 163.6, 156.7, 155.7, 151.0, 135.1, 120.3, 114.9, 99.5, 98.6, 61.1, 60.6, 55.8, 55.7, 44.7, 14.4, 14.2; **HRMS** (ESI): calc. for [($C_{18}H_{21}NO_6$)H] (M+H) 348.1447; Found: 348.1442.

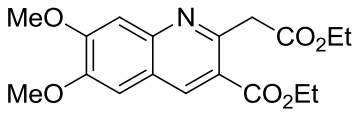
Ethyl 2-(2-ethoxy-2-oxoethyl)-7-methoxyquinoline-3-carboxylate (18b)



Yield: 88% (0.226 g), colorless solid; **mp**: 132-134 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2954, 1722, 1706, 1638, 1577, 1559, 1507, 1439, 1369, 1336, 1284, 1224, 1179, 1147, 808; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.38 (s, 1H), 7.20

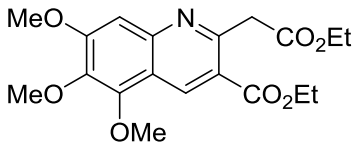
(d, *J* = 8.5 Hz, 1H), 4.42-4.37 (m, 4H), 4.18 (q, *J* = 6.9 Hz, 2H), 3.96 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 170.7, 165.9, 162.7, 155.1, 150.6, 139.9, 129.6, 121.5, 121.3, 120.6, 106.9, 61.2, 60.7, 55.6, 44.7, 14.3, 14.2; **HRMS** (ESI): calc. for $[(C_{17}H_{19}NO_5)H]$ (M+H) 318.1341; Found: 318.1331.

Ethyl 2-(2-ethoxy-2-oxoethyl)-6,7-dimethoxyquinoline-3-carboxylate (18c)



Yield: 85% (0.192 g), colorless solid; **mp**: 150-152°C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2890, 1718, 1692, 1628, 1577, 1514, 1439, 1319, 1245, 1221, 1171, 1145, 993; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.69 (s, 1H), 7.39 (s, 1H), 7.11 (s, 1H), 4.48-4.33 (m, 4H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 1.47-1.39 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.0, 166.1, 154.5, 152.6, 150.3, 146.2, 138.3, 121.9, 121.7, 107.6, 105.5, 61.2, 60.7, 56.2, 56.0, 44.5, 14.3, 14.2; **HRMS** (ESI): calc. for $[(C_{18}H_{21}NO_6)H]$ (M+H) 348.1446; Found: 348.1448.

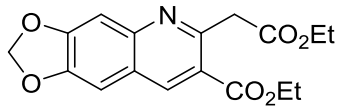
Ethyl 2-(2-ethoxy-2-oxoethyl)-5,6,7-trimethoxyquinoline-3-carboxylate (18d)



Yield: 75% (0.192 g), gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2880, 1716, 1680, 1577, 1514, 1446, 1255, 1220, 1160; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.22 (s, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 4.38 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.12 (s, 3H), 4.02 (s, 3H), 3.98 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 170.8, 166.2, 158.1, 154.2, 147.5, 146.5, 140.8, 134.7, 121.2, 117.4,

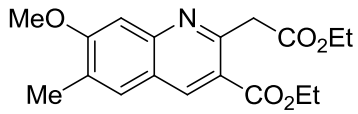
103.6, 61.7, 61.2, 61.2, 60.7, 56.2, 44.6, 14.2, 14.1; **HRMS** (ESI): calc. for $[(C_{19}H_{23}NO_7)H]$ (M+H) 378.1553; Found: 378.1557.

Ethyl 6-(2-ethoxy-2-oxoethyl)-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (18e)



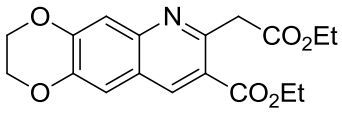
Yield: 81% (0.195 g), colorless solid; **mp**: 168-170 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2990, 1718, 1692, 1628, 1577, 1514, 1439, 1319, 1245, 1221, 1171, 1145, 993; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.63 (s, 1H), 7.34 (s, 1H), 7.11 (s, 1H), 6.15 (s, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.33 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 170.9, 166.0, 152.6, 148.2, 147.4, 138.6, 123.2, 121.6, 105.4, 103.0, 102.0, 61.2, 60.6, 44.3, 14.2, 14.1; **HRMS** (ESI): calc. for $[(C_{17}H_{17}NO_6)H]$ (M+H) 332.1134; Found: 332.1129.

Ethyl 2-(2-ethoxy-2-oxoethyl)-7-methoxy-6-methylquinoline-3-carboxylate (18f)



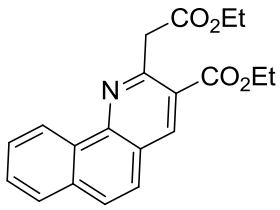
Yield: 78% (0.187 g), colorless solid; **mp**: 120-122 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2900, 1738, 1727, 1567, 1560, 1500; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.73 (s, 1H), 7.62 (s, 1H), 7.26 (s, 1H), 4.45-4.35 (m, 4H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 3H), 2.40 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.4, 153.8, 152.7, 145.2, 132.4, 128.7, 121.6, 121.2, 106.3, 105.5, 61.3, 60.8, 55.9, 16.9, 14.4, 14.3; **HRMS** (ESI): calc. for $[(C_{18}H_{21}NO_5)H]$ (M+H) 332.1498; Found: 332.1496.

Ethyl 7-(2-ethoxy-2-oxoethyl)-2,3-dihydro-[1,4]dioxino[2,3-*g*]quinoline-8-carboxylate (18g)



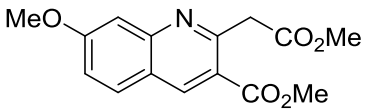
Yield: 85% (0.193 g), colorless solid; **mp**: 110-112 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2954, 1740, 1730, 1577, 1559, 1507; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.64 (s, 1H); 7.48 (s, 1H), 7.27 (s, 1H), 4.41-4.31 (m, 4H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.0, 166.1, 153.0, 148.9, 144.8, 138.9, 122.3, 121.9, 113.9, 112.7, 64.5, 64.2, 61.3, 60.7, 44.5, 29.7, 14.3, 14.2; **HRMS** (ESI): calc. for [($C_{18}H_{19}NO_6$)H] (M+H) 346.1291; Found: 346.1290.

Ethyl 2-(2-ethoxy-2-oxoethyl)benzo[*h*]quinoline-3-carboxylate (18h)



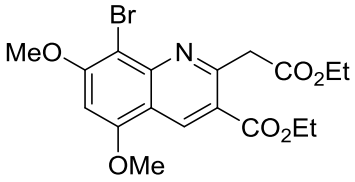
Yield: 87% (0.204 g), colorless solid; **mp**: 174-176 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2980, 1740, 1729, 1570, 1589, 1507; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.39-9.22 (m, 1H), 8.81 (s, 1H), 7.89 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.72 (dd, *J* = 8.9, 2.3 Hz, 3H), 4.54 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.0, 166.1, 153.8, 147.5, 139.4, 134.6, 130.9, 129.1, 128.4, 127.8, 127.3, 125.4, 125.1, 124.5, 123.9, 61.4, 60.7, 44.9, 14.4, 14.3; **HRMS** (ESI): calc. for [($C_{20}H_{19}NO_4$)H] (M+H) 338.1392; Found: 338.1387.

Methyl 7-methoxy-2-(2-methoxy-2-oxoethyl)quinoline-3-carboxylate (18i)



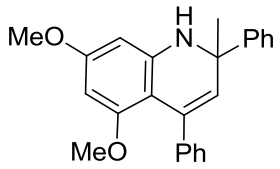
Yield: 80% (0.187 g), colorless solid; **mp**: 107-109 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2954, 1722, 1706, 1638, 1577, 1559, 1507, 1439, 1369, 1336, 1284, 1224, 1179, 1147, 808; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.22 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.39 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 3.72 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.2, 166.4, 162.9, 155.0, 150.8, 140.1, 129.7, 121.5, 120.8, 107.0, 55.7, 52.3, 52.0, 44.5; **HRMS** (ESI): calc. for $[(C_{17}H_{19}NO_5)H]$ (M+H) 290.1028; Found: 290.1025.

Ethyl-8-bromo-2-(2-ethoxy-2-oxoethyl)-5,7-dimethoxyquinoline-3-carboxylate (18j)



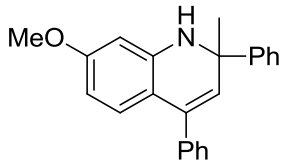
Yield: 70% (0.128 g), colorless solid; **mp**: 144-146 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3031, 1725, 1710, 1605, 1498, 1266, 1022; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.12 (s, 1H), 6.69 (s, 1H), 4.46 (s, 2H), 4.40 (q, *J* = 7.3 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 3H), 4.09 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 170.9, 166.0, 159.3, 156.9, 156.7, 146.7, 135.7, 121.0, 115.1, 93.9, 61.4, 60.8, 57.0, 56.1, 45.1, 14.3, 14.2; **HRMS** (ESI): calc. for $[(C_{18}H_{20}BrNO_6)H]$ (M+H) 426.0552; Found: 426.0557.

5,7-Dimethoxy-2-methyl-2,3-diphenyl-1,2-dihydroquinoline (19a)



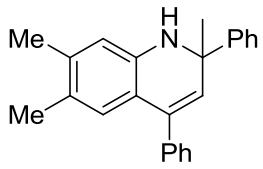
Yield: 95% (0.221 g), colorless solid; **mp**: 128-130 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3399, 2934, 2832, 1606, 1494, 1247, 699; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.30-7.25 (m, 2H), 7.22 (s, 4H), 7.20-7.14 (m, 2H), 5.86 (d, *J* = 2.2 Hz, 1H), 5.76 (d, *J* = 2.0 Hz, 1H), 5.50 (s, 1H), 4.31 (br. s., 1H), 3.74 (s, 3H), 3.28 (s, 3H), 1.67 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.2, 158.0, 148.4, 146.4, 142.9, 134.9, 128.2, 127.9, 127.4, 127.1, 126.7, 126.0, 125.4, 103.9, 92.0, 89.9, 56.3, 55.0, 54.9, 29.4; **HRMS** (ESI): calc. for [($C_{24}H_{23}NO_2$)H] (M+H) 358.1807; Found: 358.1805.

7-Methoxy-2-methyl-2,3-diphenyl-1,2-dihydroquinoline (19b)



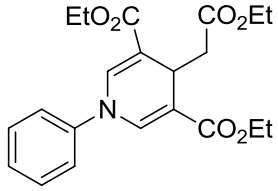
Yield: 87% (0.230 g), colorless solid; **mp**: 108-110 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3381, 2955, 2928, 1613, 1465, 1166, 823; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.40-7.24 (m, 7H), 7.23-7.14 (m, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.13-6.04 (m, 2H), 5.47 (s, 1H), 4.16 (br. s., 1H), 3.70 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 160.5, 148.8, 144.5, 139.6, 135.4, 128.9, 128.4, 128.1, 127.3, 126.8, 126.5, 125.3, 114.0, 102.5, 57.1, 98.7, 55.0, 30.1; **HRMS** (ESI): calc. for [($C_{23}H_{21}NO$)H] (M+H) 328.1701; Found: 328.1708.

2,6,7-Trimethyl-2,3-diphenyl-1,2-dihydroquinoline (19c)



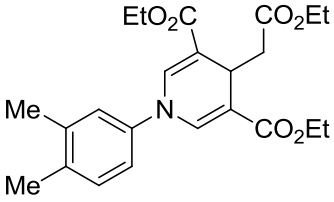
Yield: 82% (0.220 g), colorless solid; **mp**: 119-120 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3381, 3022, 1631, 1493, 1443, 699; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.6 (d, *J* = 2.0 Hz, 2H), 7.52 (d, *J* = 1.9 Hz, 2H), 7.51 (s, 1H), 7.39-7.36 (m, 3H), 7.34-7.33 (m, 3H), 7.31-7.29 (m, 1H), 7.26 (s, 1H), 2.17 (s, 6H), 1.57 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 149.0, 141.3, 132.5, 131.5, 129.2, 128.9, 128.8, 128.8, 128.6, 128.4, 128.3, 128.2, 126.3, 121.9, 108.2, 81.5, 74.1, 30.1, 29.8, 29.7; **HRMS** (ESI): calc. for [($C_{23}H_{21}NO$)H] (M+H) 326.1909; Found: 326.1905.

Diethyl 4-(2-ethoxy-2-oxoethyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (20k)



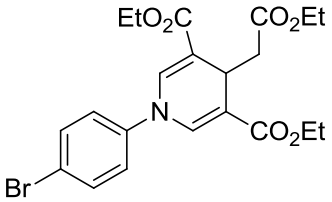
Yield: 88% (0.366 g), gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2951, 1713, 1596, 1495, 1436, 1211, 1084, 755, 715, 696; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.55 (s, 2H), 7.41 (s, 2H), 7.27-7.25 (m, 1H), 7.24-7.22 (m, 2H), 4.25-4.23 (m, 5H), 4.03 (q, *J* = 7.3 Hz, 2H), 2.57 (d, *J* = 4.9 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.5, 166.6, 143.2, 137.6, 129.9, 126.4, 121.1, 120.9, 108.4, 60.3, 60.0, 40.5, 29.7, 14.5, 14.3; **HRMS** (ESI): calc. for [($C_{21}H_{25}NO_6$)Na] (M+Na) 410.1580; Found: 410.1574.

Diethyl-1-(3,4-dimethylphenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (20l)



Yield: 82% (0.280 g), gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2900, 1719, 1586, 1429, 1221, 1004, 758; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.51 (s, 2H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.99-6.95 (m, 2H), 4.26-4.22 (m, 5H), 4.03 (q, *J* = 7.0 Hz, 2H), 2.56 (d, *J* = 4.9 Hz, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.18 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.5, 166.7, 141.1, 138.3, 138.0, 134.9, 130.7, 122.2, 118.3, 107.8, 60.2, 60.0, 40.7, 29.7, 19.9, 19.2, 14.4, 14.2; **HRMS** (ESI): calc. for $[(C_{23}H_{29}NO_6)H]$ (M+H) 416.2073; Found: 416.2070.

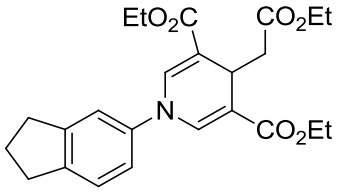
Diethyl-1-(4-bromophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (20m)



Yield: 85% (0.230 g), gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2947, 1728, 1696, 1638, 1438, 1362, 1337, 1259, 1238, 1196, 1177, 881; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.6 Hz, 2H), 7.50 (s, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 4.26-4.21 (m, 5H), 4.02 (q, *J* = 7.1 Hz, 2H), 2.58 (d, *J* = 4.9 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 6H), 1.18 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.4, 166.4, 142.2, 137.1, 132.9, 122.3, 119.6,

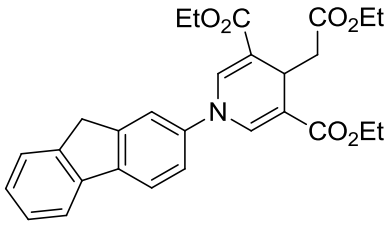
108.9, 60.4, 60.0, 40.2, 29.6, 14.4, 14.3; **HRMS** (ESI): calc. for [($C_{21}H_{24}BrNO_6$)H] (M+H) 466.0865; Found: 466.0860.

Diethyl-1-(2,3-dihydro-1*H*-inden-5-yl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (20n)



Yield: 86% (0.276 g), gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2960, 1715, 1600, 1490, 1209, 1004, 750, 710; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.51 (s, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 6.99 (dd, *J* = 8.0, 2.0 Hz, 2H), 4.28-4.18 (m, 5H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.90 (q, *J* = 7.1 Hz, 4H), 2.55 (d, *J* = 4.8 Hz, 2H), 2.19-2.04 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.5, 166.6, 146.1, 142.6, 141.8, 138.1, 125.2, 119.2, 117.4, 107.6, 60.1, 59.9, 40.5, 32.9, 32.3, 29.6, 25.7, 14.4, 14.2; **HRMS** (ESI): calc. for [($C_{24}H_{29}NO_6$)H] (M+H) 428.2073; Found: 428.2070.

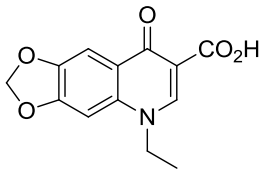
Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(9*H*-fluoren-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (20o)



Yield: 80% (0.209 g), gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2945, 1710, 1590, 1510, 1430, 1211, 1084; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.76 (t, *J* = 8.3 Hz, 2H), 7.60 (s,

2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 4.28-4.24 (m, 5H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 2H), 2.60 (d, *J* = 4.7 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 6H), 1.19 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 171.5, 166.6, 145.0, 14.3, 143.1, 142.0, 140.6, 140.3, 138.0, 127.1, 125.1, 120.8, 119.9, 117.9, 112.0, 108.2, 60.3, 60.0, 40.6, 37.0, 29.7, 14.5; **HRMS** (ESI): calc. for $[(C_{28}H_{29}NO_6)H]$ (M+H) 476.2073; Found: 476.2072.

4.1.6.3 Procedure for the synthesis of oxolinic acid (22)



A mixture of quinoline **3f** (0.1 g) and ethyl trifluoromethane sulfonate (0.15 g) was warmed at 50 °C for 1 h. After removal of ethyl trifluoromethane sulfonate in *vaccuo*, the residue was added to a suspension of $K_3Fe(CN)_6$ (0.25 g) in 20% NaOH (10 mL) and stirred at room temperature for 2 h. The mixture was extracted with ethyl acetate, and the extract was washed with brine and dried over anhyd. $MgSO_4$. After removal of ethyl acetate, the residue was purified by silica gel (CH_2Cl_2:MeOH = 50:1) to give quinolone **22**.

Yield: 50% (0.053 g), colorless solid; **mp**: 314-316 °C; lit.[23] mp 314-316 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3420, 1620, 1600, 1580, 1550, 1298, 1250, 1033; **^{1}H NMR** (200 MHz, CF_3CO_2D): δ 9.12 (s, 1H), 7.83 (s, 1H), 7.40 (s, 1H), 6.38 (s, 2H), 4.71 (q, *J* = 7.2 Hz, 2H), 1.69 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (50 MHz, CF_3CO_2D): δ 169.8, 158.6, 151.0, 146.3, 139.7, 123.3, 117.7, 112.0, 105.1, 101.7, 96.2, 53.5, 13.9; **HRMS** (ESI): calc. for $[(C_{13}H_{11}NO_5)H]$ (M+H) 262.0715; Found: 261.0711.

Section II

Rh-Catalyzed Novel Synthesis of Coumarin Derivatives from Phenolic Acetates and Acrylates *via* C-H Bond Activation

4.2.1 Introduction

The functionalization of C-H bonds of aromatic hydrocarbons is one of the most challenging processes since these C-H bonds are relatively strong for chemical transformations. It is also an environment-friendly process as it does not require toxic halogens for activation. Thus, directed metallation of aromatic substrates has emerged as one of the most versatile methods to functionalize the C-H bonds of aromatic hydrocarbons.[26] Coumarin derivatives[27] are important natural products widely found in plants and exhibit excellent biological and pharmacological activity including anti-tumor,[28a] anti-HIV,[28b-c] anti-coagulation, anti-bacterial,[28d] anti-inflammatory[28e-f] and anti-oxidant.[28g] In addition, they are also widely used as food additives, in cosmetics, as optical brightening agents, light-emitting diodes, as fluorescent probes and laser dyes[29] (**Fig. 9**).

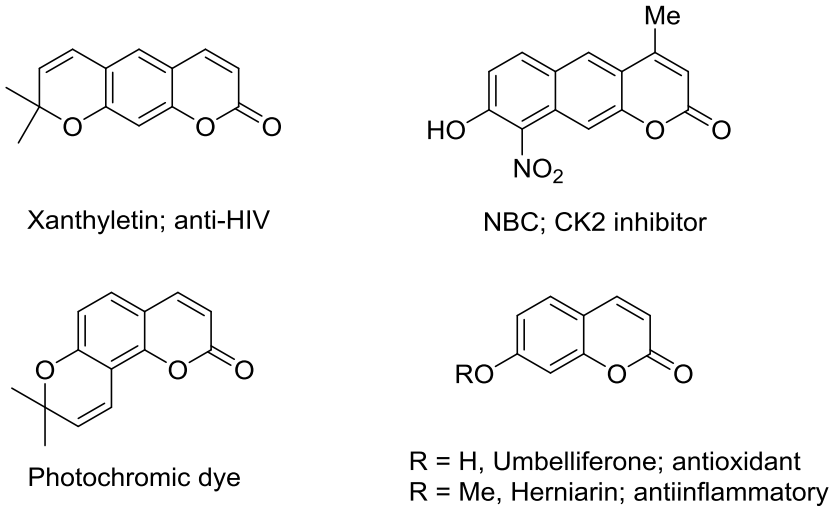


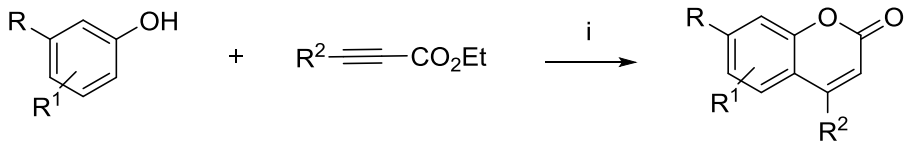
Fig. 9: Some of bioactive coumarin derivatives

4.2.2 Review of Literature

The prevalence of coumarin units in bioactive molecules has prompted the development of many useful methods for their synthesis and functionalization. Some of the recent literature methods of coumarin synthesis are given below:

Trost's approach (2003)[33b]

Trost *et al*. have described a useful strategy to achieve *ortho* substitution of phenols initiated by *ortho*-palladation to construct coumarin units. Indeed, treatment of alkynoates **24** with electron-rich phenols **23** in the presence of a palladium catalyst [$Pd(OAc)_2$] and an acid (HCO_2H) does generate coumarin derivatives **25** in 41-88% yields (**Scheme 16**).



23

R = Electron donating groups

R^1 = H, alkyl, alkoxy Br

24

R^2 = Me, Ph
$(CH_3)_2CO_2Et$
$(CH_3)_2CN$
$Si(Ph)(CH_3)_2$
CH_2OH

25

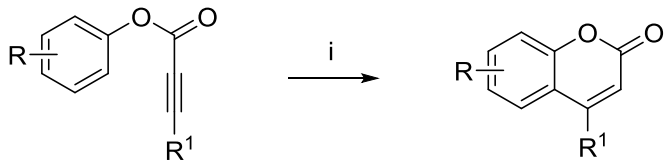
yield : 41-88%

Scheme 16: (i) $Pd_2(dba)_3$ (5 mol %), NaOAc (20 mol %), HCO_2H, 50 °C, 16 h.

He's approach (2004)[32k]

He *et al*. have developed gold(III)-catalyzed synthesis of bioactive coumarins, in which reaction of phenyl alkynoates **26** with a combination of 5 mol % of $AuCl_3$/3AgOTf resulted in coumarin derivative **25** in 44-99% yields. This strategy worked successfully

for aryl alkynoates **26** that bear different substituted groups including electron-withdrawing groups (**Scheme 17**).



26 **25**

R = H, alkoxy, aryl, Br

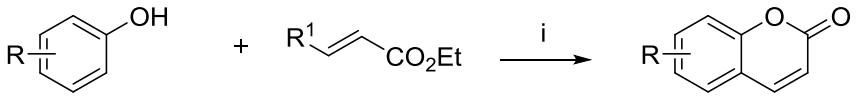
R^1 = H, Me, Ph

yield : 44-99%

Scheme 17: (i) of $AuCl_3$/3AgOTf (5 mol %), $ClCH_2CH_2Cl$, 70 °C.

Kitamura's approach (2005)[32j]

Kitamura *et al*. have developed a simple methodology for the synthesis of coumarin **25**, in which reaction of phenols **23** with ethyl acrylates **27** in the presence of $Pd(OAc)_2$ catalyst in trifluoroacetic acid was carried out to give coumarins derivative **25** in 11-75% yields. The role of $K_2S_2O_8$ was to act as an oxidant that has increased the yield of coumarins (**Scheme 18**).



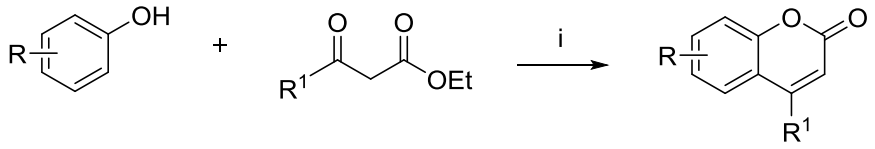
23 **27** **25**

R = OH, alkyl, alkoxy R^1 = Me, Ph yield : 11-75%

Scheme 18: (i) $Pd(OAc)_2$ (5 mol %), $K_2S_2O_8$ (1 mmol), TFA (1 mL), 70 h, rt.

Valizadeh's approach (2005)[32i]

Valizadeh *et al.* have disclosed the titanium (IV) catalyzed Pechmann condensation reaction of phenols **23** with β-keto esters **28** to afford coumarin derivative **25**. The reaction was carried out in the absence of solvent and represents an improvement on the classical Pechmann conditions giving products with moderate to good yields (60-97%) and less time duration (**Scheme 19**).



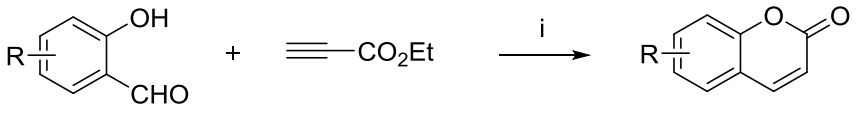
23 **28** **25**

R = H, OH, alkyl aryl, Cl, NO_2 | R^1 = Me, CF_3 CH_2Cl | yield : 60-97%

Scheme 19: (i) $TiCl_4$, solvent free, rt, 1 h.

Reddy's approach (2013)[31c]

Reddy *et al.* have developed a novel route to the synthesis of coumarins **25** from readily available starting materials i.e. salicylaldehydes **29** and ethyl propiolate **24**, through a concomitant cycloisomerization followed by hydrolysis of the resultant vinyl ether that



29 **24** **25**

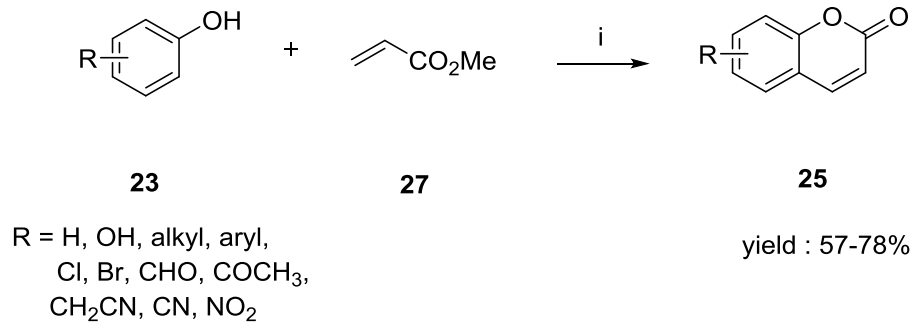
R = H, alkyl, alkoxy, aryl Cl, Br, $COCH_3$ | yield : 9-84%

Scheme 20: CuI, pyrrolidine, CH_3CN, 100 °C, 1 h.

afforded coumarins **25**. The reaction was catalyzed by pyrrolidine and copper iodide, *via* cooperative catalytic system that gave products in good to moderate yields (9-84%) (**Scheme 20**).

Maiti's approach (2013)[34b]

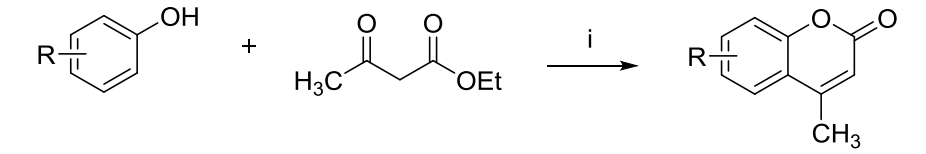
Maiti *et al*. have reported Pd-catalyzed C-H activation of phenols for the synthesis of coumarin derivatives **25**. Phenols **23** were reacted with methyl acrylate **27** in the presence of catalyst $Pd(OAc)_2$, ligand 1,10-phenothroline and a base NaOAc to afford coumarin derivatives **25** in 57-78% yields. This methodology was successfully employed to an electron withdrawing substrates very well (**Scheme 21**).



Scheme 21: (i) $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline (10 mol %), $Cu(OAc)_2$ (0.5 mmol), NaOAc (1.5 mmol), 4 Å molecular sieves, $ClCH_2CH_2Cl$, 110 °C, 24 h.

Farhang's approach (2014)[32h]

Farhang *et al*. have described the synthesis of coumarin derivatives **25** using $CuFe_2O_4$ nanoparticles as catalyst in water at room temperature. The reaction of phenol **23** with ethyl acetoacetate **28** in the presence of 5 mol % of $CuFe_2O_4$ afforded coumarin derivative **25** in excellent yields (82-98%) (**Scheme 22**).



23 **28** **25**

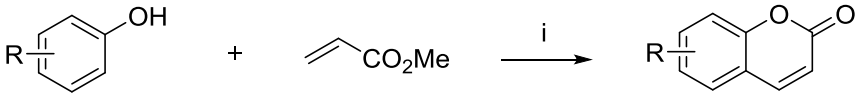
R = OH, alkyl, aryl
Cl, NO_2, NH_2

yield : 82-98%

Scheme 22: (i) $CuFeO_4$ (5 mol %)-nanoparticals, H_2O, rt, 15 min.

Shi's approach (2014)[34a]

Shi *et al*. have envisaged a palladium-catalyzed base-accelerated *ortho*-selective C–H alkenylation of phenols **23** to synthesize bioactive coumarin derivatives **25**. The reaction of phenol **23** with methyl acrylate **27** under the reaction conditions [$Pd(CH_3CN)_4](BF_4)_2$ (10 mol %), $Cu(OAc)_2$ (2.0 equiv), NaOPiv (0.80 equiv), 120 °C] afforded coumarin derivatives **25** in moderate to excellent yields (39-73%). The reaction conditions were mild and tolerate both electron-neutral and electron-deficient phenols, which is complementary to the other reported methods to synthesize electron-rich coumarins (**Scheme 23**).



23 **27** **25**

R = H, alkyl, aryl, CF_3, OTS
Cl, Br, CHO, $COCH_3$,
CH_2CN, CN, NO_2

yield : 39-73%

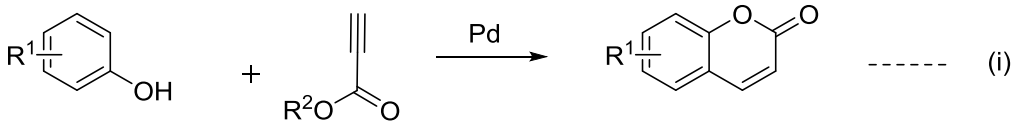
Scheme 23: (i) $[Pd(CH_3CN)_4](BF_4)_2$ (10 mol %), $Cu(OAc)_2$ (2.0 equiv), NaOPiv (0.80 equiv), mesitylene, 120 °C, 20 h.

4.2.3 Present Work

4.2.3.1 Objective

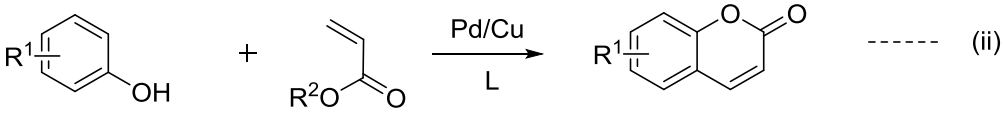
Traditionally, the most common approach to coumarins synthesis is undoubtedly the Pechmann condensation[30] and its variants[31] such as Perkin, Knoevenagel, Wittig, Ponndorf, Horner–Wittig and Houben–Hoesch. Although these methods are widely used and efficient, harsh conditions and stoichiometric quantities of strong Lewis or Brønsted acids are usually required, often leading to mixtures of regioisomers. Transition metal-catalyzed coupling reactions (Heck reaction, carbonylation, etc.) partially solved this problem.[32] However, prefunctionalization of the starting materials

a) Phenols with alkynic esters:



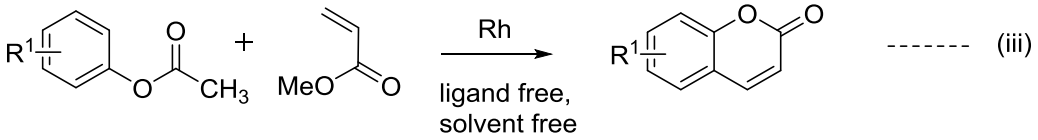
R^1 = EDG

b) Phenols with alkenic esters:



R^1 = EDG and EWG

c) Phenolic acetates with alkenic esters: ***this work***



R^1 = EDG and EWG

EDG = electron donating group
EWG = electron withdrawing group
L = 1,10-Phenanthroline

Scheme 24: Synthesis of coumarins *via* C-H activation strategy

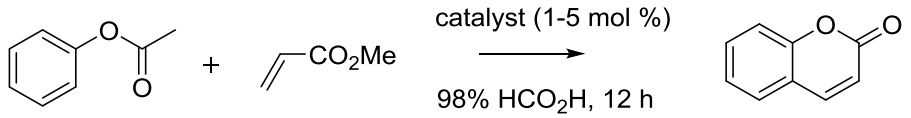
(halides and organometallic reagents) made these reactions unfavorable environmentally. Transition metal-catalyzed direct C–H bond addition to alkynes developed by Trost and Fujiwara is atom economical and has found wide applications in recent years.[33] However, this reaction is generally limited to electron-rich phenols and involves a Friedel–Crafts rather than a C–H activation pathway. Direct C–H bond alkenylation of phenols with acrylates using Pd/Cu as catalyst and expensive ligand, provides another strategy for the synthesis of coumarins[34] (equation i-ii, **Scheme 24**).

4.2.3.2 Results and Discussion

In continuation of our interest on new catalytic synthesis of heterocyclic scaffolds, we have recently developed an elegant Rh(II)/HCO_2H catalytic system for the synthesis of quinoline carboxylates proceeding through rhodacycle as an intermediate. In this section, a Rh-catalyzed *ortho* C−H bond activation of phenolic acetates with acrylates in presence of NaOAc as base and HCO_2H as reducing agent that produces synthetically useful coumarin derivatives **25a-ω** is presented (equation iii, **Scheme 24**).

Our initial efforts toward the synthesis of coumarin structural units *via* annulation of phenyl acetate (1 mmol) with methyl acrylate (1.2 mmol) focused on catalytic system comprising Rh(+2) acetate (5 mol %) in excess formic acid (1 mL) and heating at 70 °C (**Table 1**).

Table 1: Rhodium catalyzed reaction of phenyl acetate with methyl acrylate: optimization studies[a]



29a **27a** **25a**

entry	catalyst	catalyst (mol %)	solvent (2 mL)	additive	*t* (°C)	**25a**[b] (%)
1	$Rh_2(OAc)_4$	5	-	-	70	18
2		5	-	NaOAc	70	50
3		5	-	NaOAc	80	68
4		5	-	NaOAc	100	71
5		2.5	-	NaOAc	100	71
6		1	-	NaOAc	100	41
7		2.5	-	Na_2CO_3	100	19
8		2.5	-	K_2CO_3	100	20
9		2.5	-	Cs_2CO_3	100	19
10		2.5	$PhCH_3$	NaOAc	100	30
11		2.5	PhH	NaOAc	100	21
12		2.5	DMF	NaOAc	100	20
13		2.5	EDC[c]	NaOAc	100	25
14		2.5	-	NaOAc	80	62
15	Rh/Al_2O_3	2.5	-	NaOAc	100	11
16	$[RhCOCl_2]_2$	2.5	-	NaOAc	100	30
17	$Pd(OAc)_2$	2.5	-	NaOAc	100	31
18	No catalyst	-	-	NaOAc	100	-

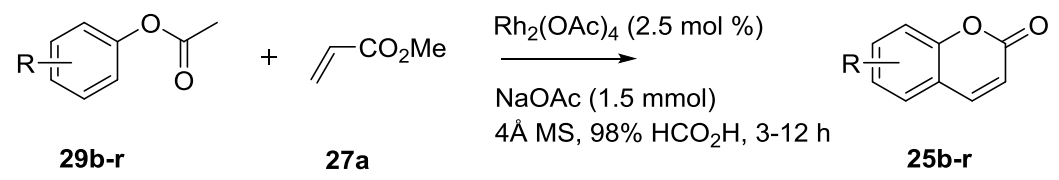
[a] Phenyl acetate (1 mmol), methyl acrylate (1.2 mmol), 98% HCO_2H (1 mL, 26 mmol), additive (1.5 mmol), 4 Å molecular sieves, 12 h. [b] Isolated yield of **25a** after chromatographic purification. [c] 1,2-dichloroethane.

However, under these conditions, only 18% of the desired coumarin **25a** was obtained. However, conducting the reaction in presence of NaOAc (1.5 equiv) as a base

moderately increased the yield of **25a** (50%), which could be gradually improved to 71% by increasing the temperature from 80 to 100 °C. Screening of other bases was attempted and found to be less effective to promote *ortho* C-H bond activation (entry 7-9); so also with other catalysts (entry 15-17). Interestingly, by lowering catalyst loading to 2.5 mol %, the product yield (71%) was not affected, although further lowering to 1 mol % led to a significant reduction in the yield of the product (41%). Thus, proper choice of catalyst and base is critical in order to realize high yields of **25a**. Also, by lowering the concentration of HCO_2H (5 mmol) a decrease in yield of **25a** was observed. Use of other solvents such as toluene, benzene, 1,2-dichloroethane, or DMF was found to be less suitable for the reaction (only 20-30% yield). Control experiment has however proven that, in the absence of catalyst, no reaction took place. Also, with use of AcOH or TFA as reaction medium instead of HCO_2H, only deprotection of phenyl acetate took place forming phenol exclusively; thus proving that HCO_2H acts as a better reducing agent in addition to being used as solvent.

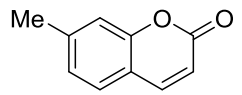
We have then applied the optimized procedure of Rh-catalyzed annulation process to a variety of phenolic acetates (**29b-r)** to determine the scope of the process and the results are presented in **Scheme 25**. Thus, several phenolic acetates with electron-donating and –withdrawing groups underwent this annulation process successfully and produced the corresponding coumarin derivatives (**25b-r**) in excellent yields. Remarkably, substrates having –CHO, -Br, -CN, $-NO_2$ and $-COCH_3$ groups (**25l-q**) were well-tolerated under the reaction conditions. In the case of unsymmetrical phenolic acetates, complete regiocontrolled products were obtained as C-H activation has occurred at the less sterically hindered position exclusively (**25b**, **25e-f**, **25h**, **25j-k**). 2-Naphthyl acetate was also annulated regiospecifically with methyl acrylate to afford the corresponding coumarin **25r** in 90% yield.

Scheme 25: Substrate scope for Rh catalyzed annulation[a,b]

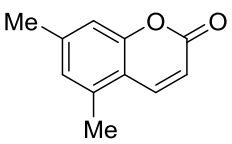


29b-r **27a** **25b-r**

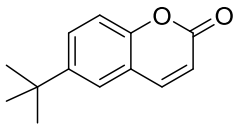
R = alkyl, alkoxy, aryl, CHO, Br, CN, NO_2, $COCH_3$



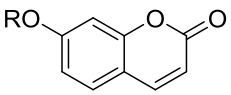
25b; 8 h, 81%



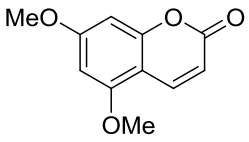
25c; 7 h, 83%



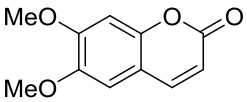
25d; 8 h, 82%



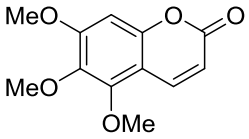
R = H, **25e;** 3 h, 92%
R = Me, **25f;** 3 h, 88%



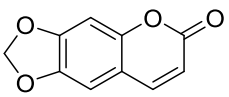
25g; 4 h, 95%



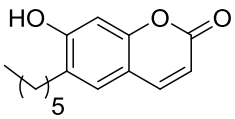
25h; 4 h, 85%



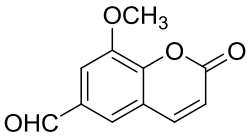
25i; 5 h, 88%



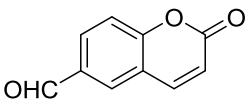
25j; 4 h, 89%



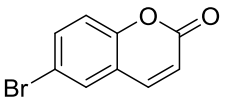
25k; 6 h, 87%



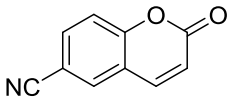
25l; 7 h, 91%



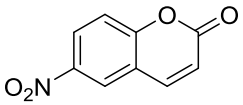
25m; 8 h, 90%



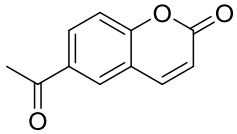
25n; 9 h, 81%



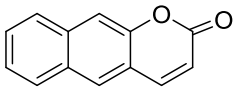
25o; 11 h, 74%



25p; 12 h, 64%



25q; 12 h, 92%



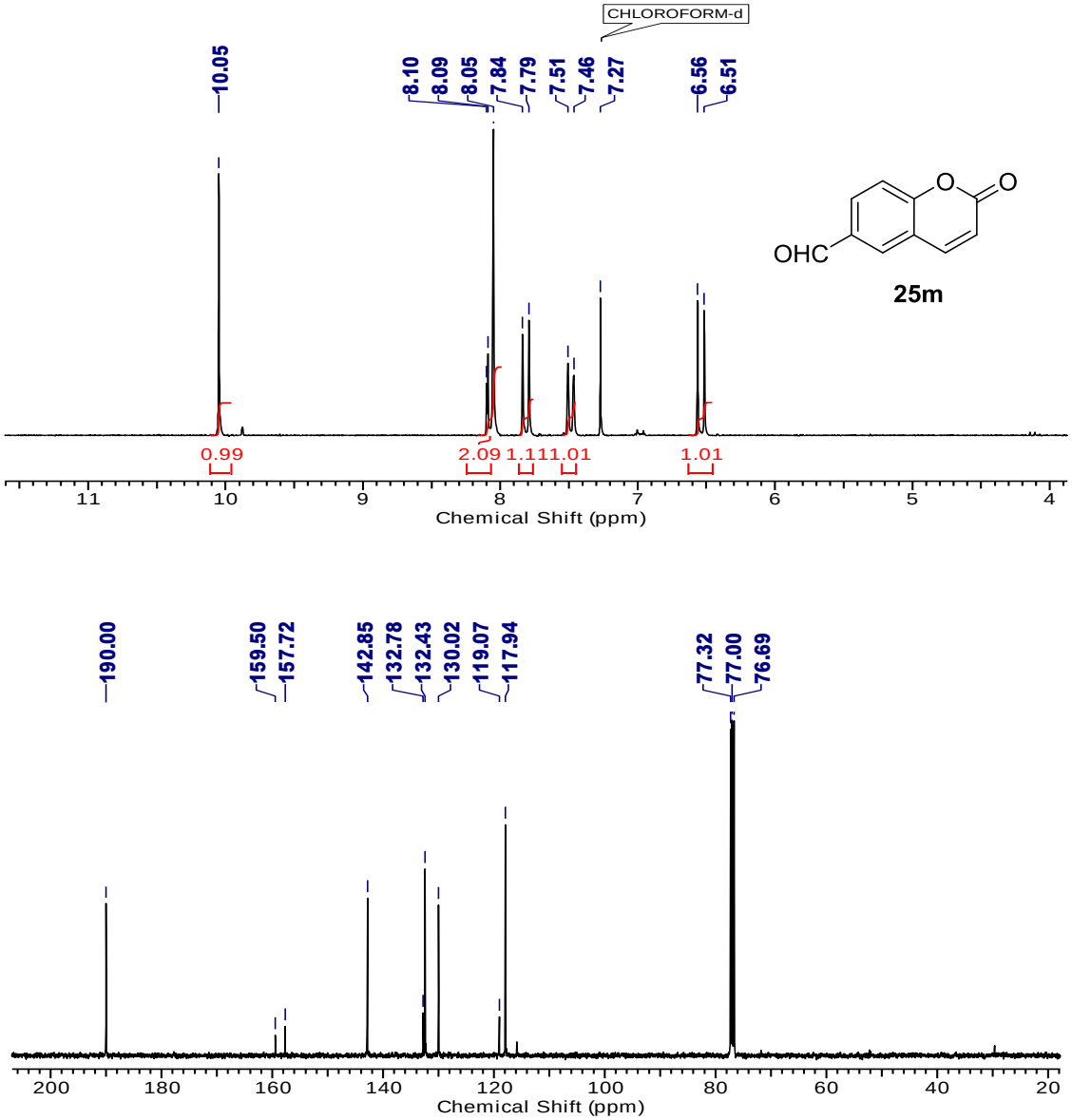
25r; 6 h, 90%

[a] Phenolic acetates (1 mmol), methyl acrylate (1.5 mmol), $Rh_2(OAc)_4$ (2.5 mol %), NaOAc (1.5 mmol), 4 Å molecular sieves, 98% HCO_2H (1 mL), 100 °C, 3-12 h. [b] Isolated yield after column purification.

The formation of coumarin derivatives (**25a-r**) was established unambiguously from the corresponding ^1H, ^{13}C NMR, IR and HRMS spectral data, as presented in the following examples.

Example 1:

The formation of coumarin derivative **25m** was confirmed by ^{1}H NMR spectrum, which showed two typical doublets at δ 7.81 (d, *J* = 9.6 Hz, 1H) and 6.54 (d, *J* = 9.6 Hz, 1H) corresponding to olefinic protons of coumarin ring. Its ^{13}C NMR spectrum displayed two characteristic carbon signals at δ 159.5 and 190.0 attributed to carbonyl carbon of lactone and aldehyde group respectively. Its IR signal showed strong vibrational stretching frequencies at δ 1719 and 1689 cm^{-1} due to presence of –C=O and -CHO groups respectively (**Fig. 10**).



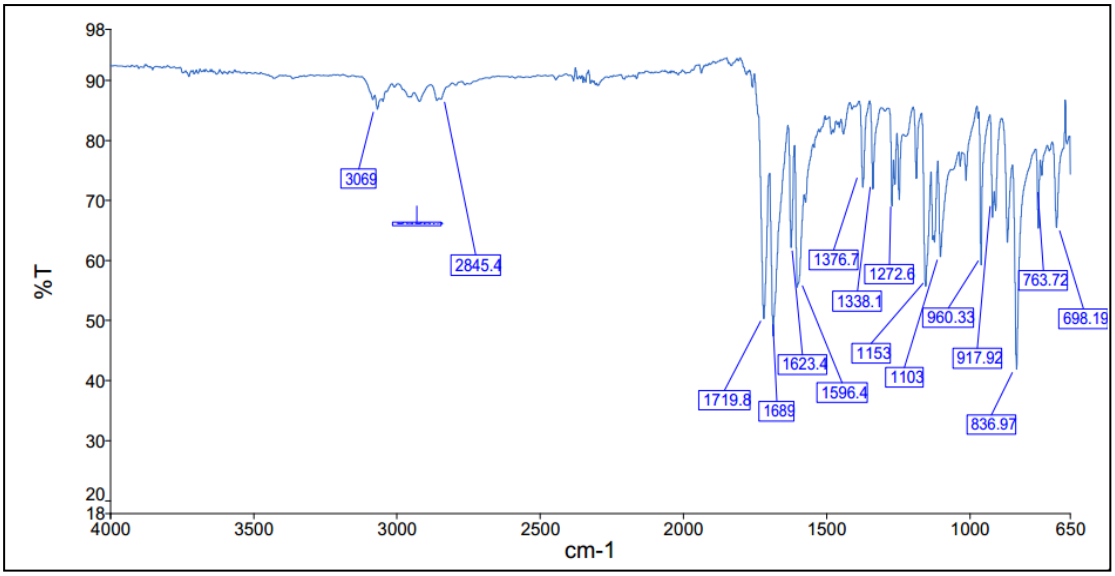


Fig. 10: ^{1}H, ^{13}C NMR and IR spectra of coumarin derivative **25m**

Example 2:

The formation of coumarin derivative **25k** was confirmed from the ^{1}H NMR spectrum, which showed two characteristic doublets at δ 6.22 (d, *J* = 9.5 Hz, 1H) and 7.66 (d, *J* = 9.4 Hz, 1H) due to the presence of olefinic protons of coumarin ring. Further its structure was supported by ^{13}C NMR spectrum, which displayed a characteristic carbon signal at δ 163.2 due to –C=O group and other two signals at δ 111.8 and 144.8 corresponding to olefinic carbons of coumarin moiety respectively. Its IR spectrum exhibited a strong vibrational stretching frequency at 1710 cm^{-1} indicating the presence of –C=O functionality. Further, the formation of **25k** was substantiated by its mass spectrum (**Fig. 11**).

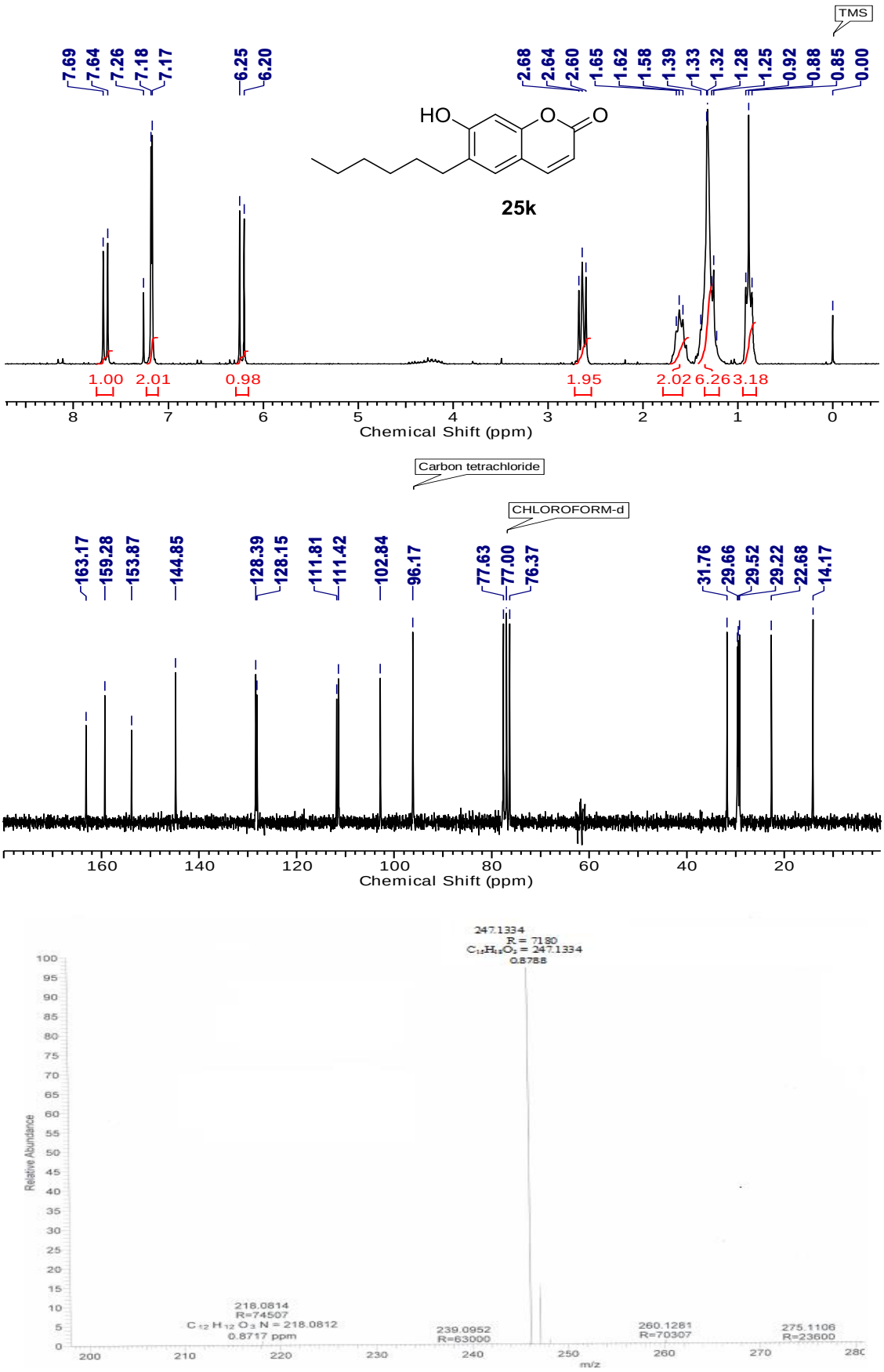
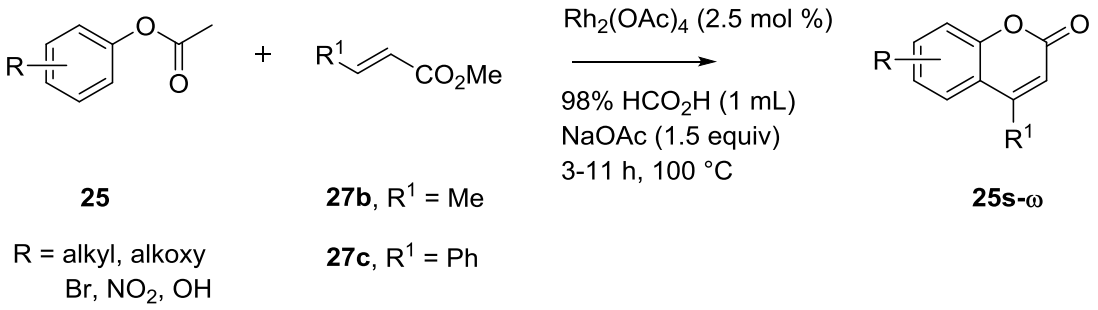


Fig. 11: ^{1}H, ^{13}C NMR and mass spectra of coumarin derivative **25k**

Next, we turned our attention to examine the substituents' effect on acrylates and the results are given in **Scheme 26**. As can be seen, sterically hindered phenyl acrylate **27c** (R^2 = Ph) showed comparable activity for the annulation process as that of acrylate **27b** (R^2 = Me). Here again, substrates with electron-donating and –withdrawing groups have reacted smoothly with β-substituted acrylates to afford coumarin derivatives **25s-ω** in excellent yields.

Scheme 26: Olefin variation in the annulation process[a,b]



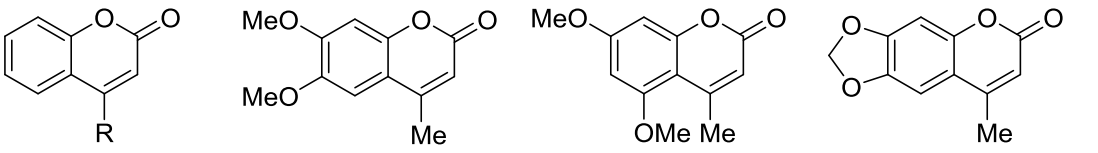
25

R = alkyl, alkoxy
Br, NO_2, OH

27b, R^1 = Me

27c, R^1 = Ph

25s-ω

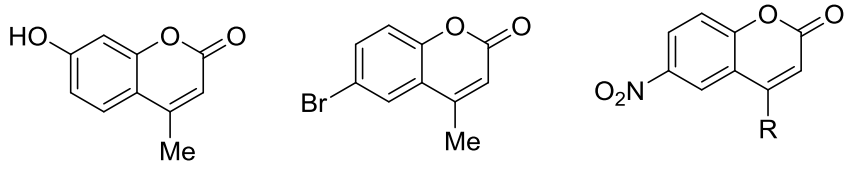


R = Me, **25s;** 11 h, 78%
R = Ph, **25t;** 10 h, 80%

25u; 4 h, 85%

25v; 5 h, 80%

25w; 5 h, 80%



25x; 4 h, 88%

25y; 9 h, 81%

R = Me, **25z;** 10 h, 70%
R = Ph, **25ω**; 11 h, 72%

[a] For reaction conditions, refer to the foot-note under Table 1 and methyl crotonate or cinnamate (1.2 mmol) was used. [b] Isolated yield after column chromatographic purification.

The formation of coumarin derivatives (**25a-r**) was established unambiguously from the corresponding ^{1}H, ^{13}C NMR and IR spectral data, as presented in the following examples.

Example 1:

Substituted coumarin derivative **25t** was ascertained by ^{1}H NMR spectrum, which displayed a characteristic singlet at δ 6.38 (s, 1H) and a multiplet at δ 7.38-7.59 (m, 5H) corresponding to olefinic and phenyl protons respectively. Its ^{13}C NMR spectrum displayed a typical carbon at δ 160.6 due to the presence of carbonyl carbon of coumarin moiety (**Fig. 12**). Its IR spectrum displayed a strong vibrational stretching frequency at 1710 cm^{-1} indicating the presence of –C=O functionality of coumarin unit.

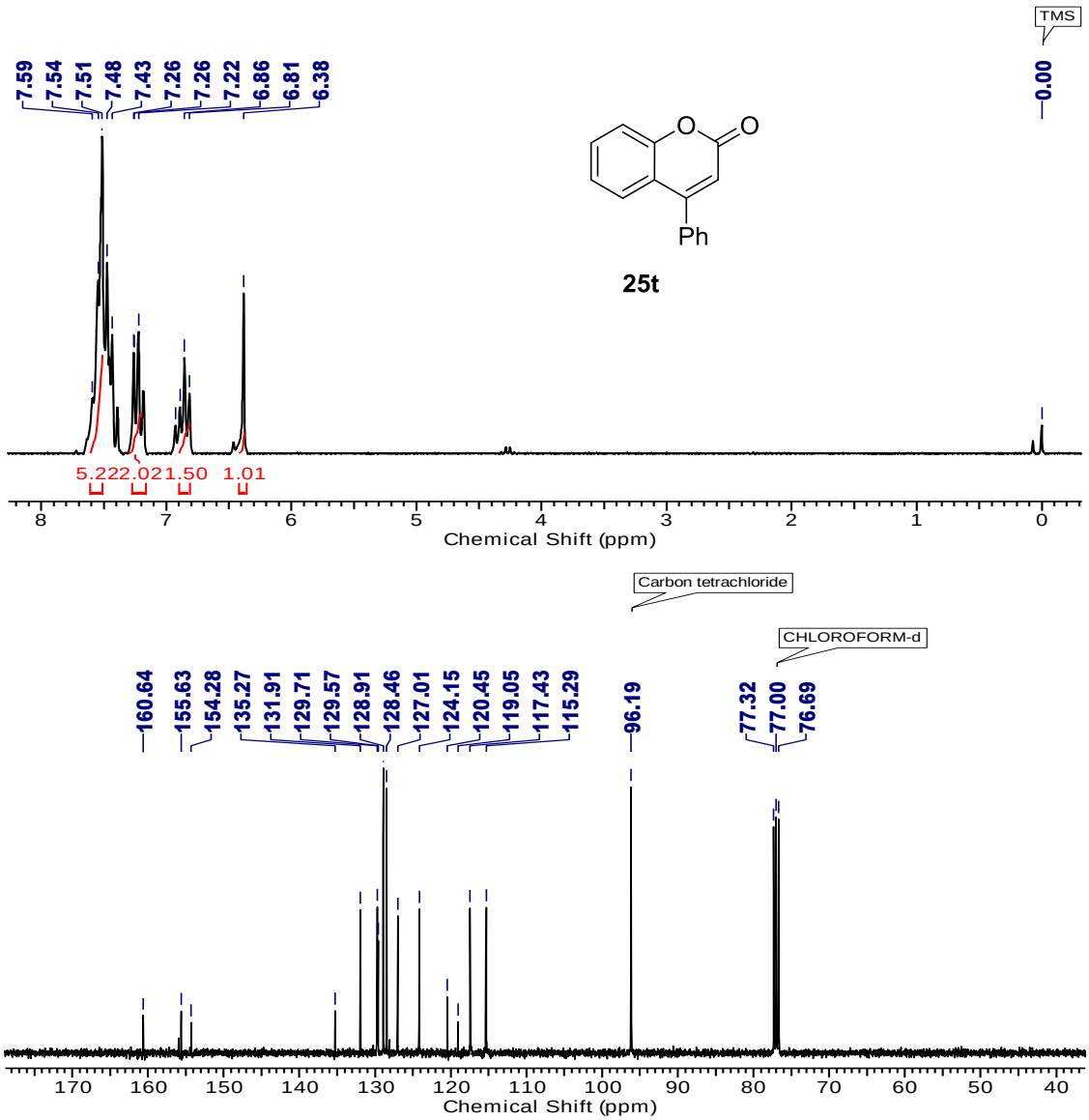


Fig. 12: ^{1}H and ^{13}C NMR spectra of coumarin derivative **25t**

Example 2:

The formation of coumarin derivative **25y** was ascertained by ^{1}H NMR spectrum, which showed a typical two singlets at δ 2.43 (s, 3H) and 6.33 (s, 1H) corresponding to methyl and olefinic protons respectively. Its ^{13}C NMR spectrum displayed characteristic three carbon signals at δ 18.6, 116.9 and 160.0 due to the presence of methyl, quaternary carbon attached to $–CH_3$ group and –C=O carbon of lactone respectively (**Fig. 13**). Its IR spectrum showed a strong vibrational stretching frequency at δ 1748 cm^{-1} due to presence of –C=O group.

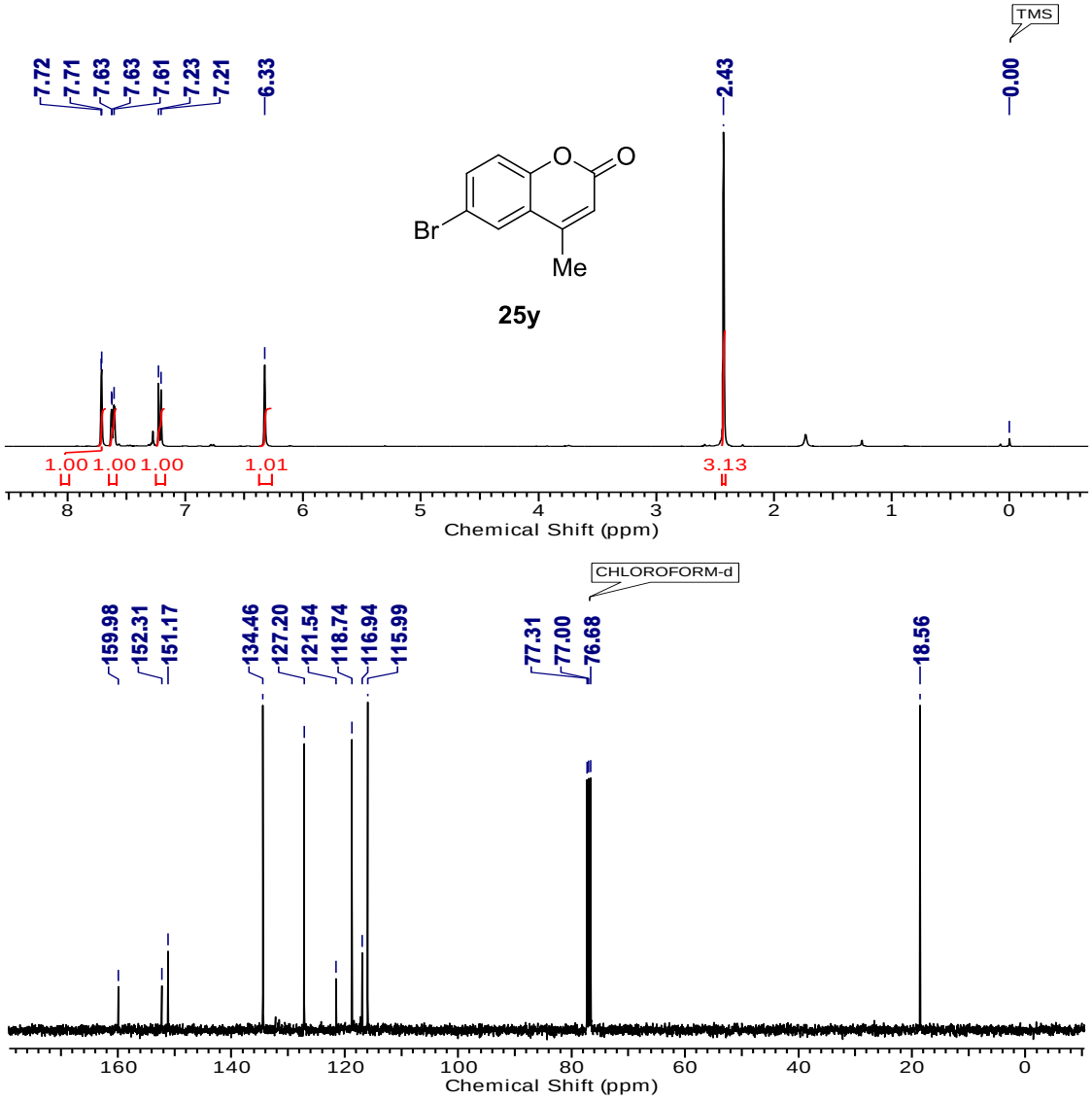
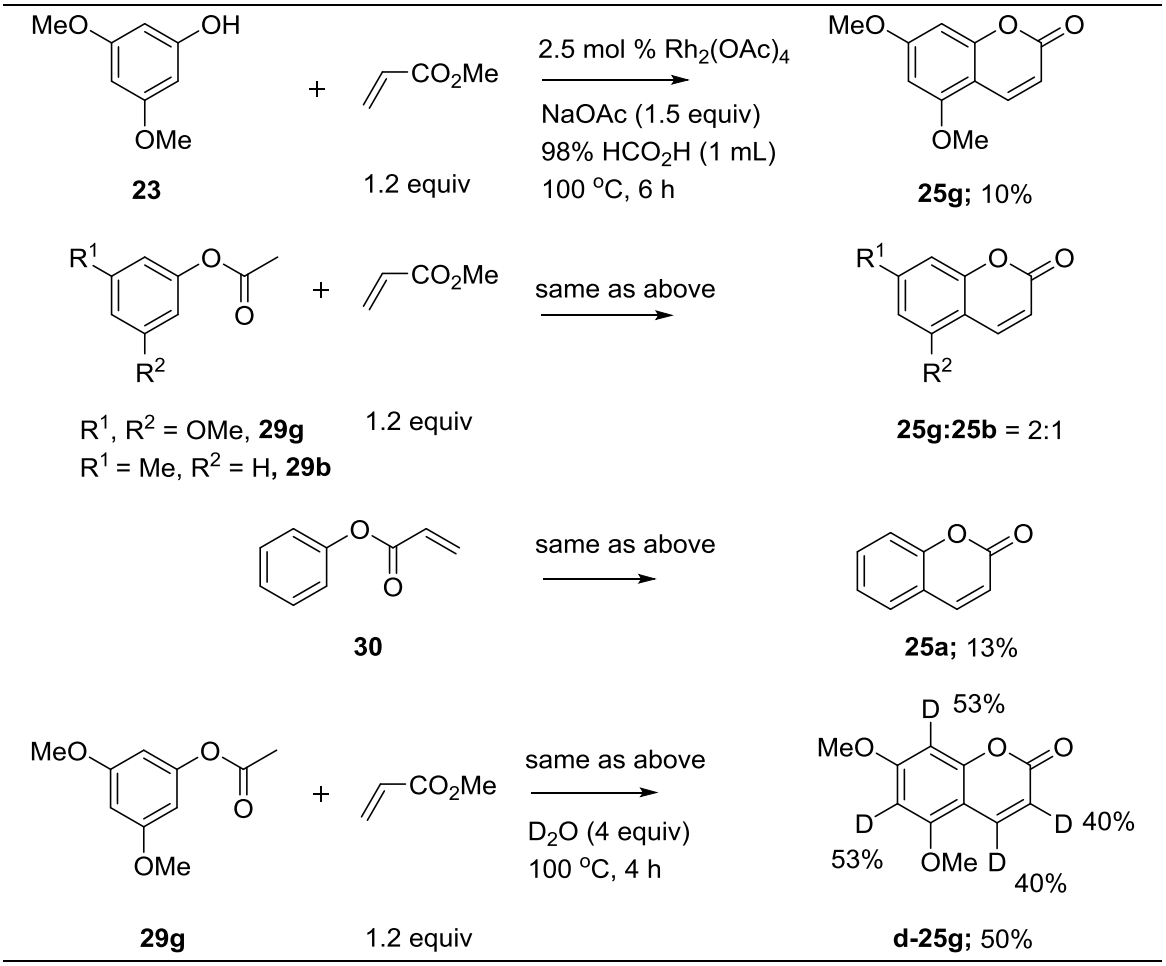


Fig. 13: ^{1}H and ^{13}C NMR spectra of coumarin derivative **25y**

4.2.3.3 Mechanistic Discussion

Scheme 27 shows results of several control experiments that were carried out in order to obtain some insights into mechanistic course of the reaction: (i) when 3,5-dimethoxyphenol **23** was subjected to oxidative coupling with methyl acrylate under the reaction conditions, only 10% of the desired product **25g** was obtained, indicating that directing acetate group is required for forming rhodacycle **II**; (ii) competitive experiments (**29g** and **29b**) have been shown that electron-rich phenolic acetates have generally reacted faster for the annulation process *via* C-H annulation (**25g:25b** = 2:1); (iii) to know whether the reaction proceeds *via* C-H alkenylation or Friedal-Crafts' type acid catalyzed reaction, we have conducted an experiment involving phenyl acrylate **29**



Scheme 27: Control experiments to probe mechanism

as substrate under the same reaction conditions, that gave coumarin **25a** in low yield (13%), the rest being phenol; thus proving that C-H alkenylation occurs first; (iv) when **29g** was reacted with methyl acrylate in the presence D_2O under the reaction conditions, product **d-25g** was isolated in 50% yield, in which 40% of deuterium was incorporated at the C-3 and C-4 position of the coumarin derivative, along with 53% deuterium incorporation each at C-6 and C-8 of **d-25g**. This result clearly supports that the *ortho* C-H bond cleavage in phenolic acetate occurs in a reversible manner. This result clearly established that the *ortho* C-H bond cleavage in phenolic acetate occurs in a reversible manner (**Fig. 14**).

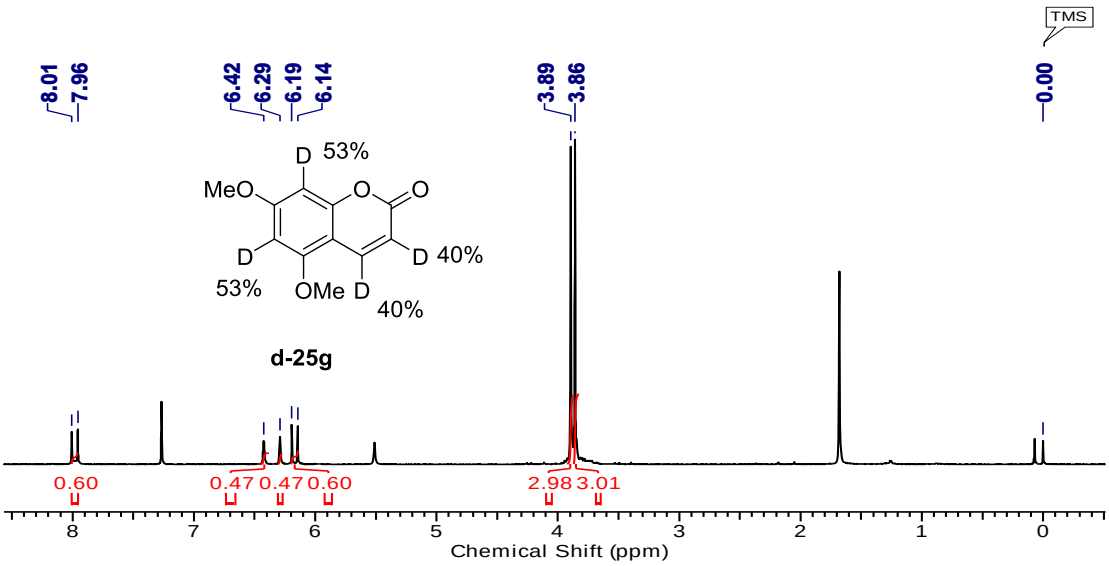
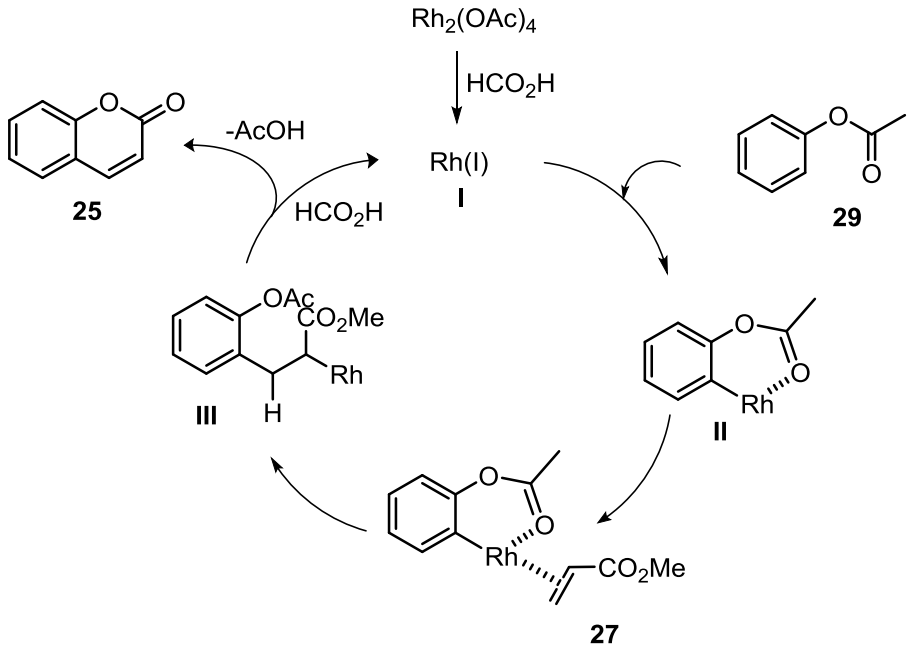


Fig. 14: ^{1}H NMR spectrum of coumarin derivative **d-25g**

A probable catalytic cycle based on the control experiments for the formation of coumarin derivatives **25a-ω** is shown in **Scheme 28**. Coordination of the carbonyl group of phenyl acetate to Rh species **I,** obtained from $[Rh_2(OAc)_4]$ on reduction with formic acid, followed by *ortho*-metallation provides a 6-membered rhodacycle intermediate **II**. Coordinative regioselective insertion of alkenic ester **2** into the Rh−C bond of intermediate **II** gives the intermediate **III** followed by the β-hydride elimination released the alkenated product *in situ*. Acetate deprotection under acidic

condition followed by intramolecular cyclization produced coumarins **25** with the regeneration of active rhodium species **I** for the next catalytic cycle.



Scheme 28: Proposed catalytic cycle for coumarin derivatives **25**

4.2.4 Conclusion

In conclusion, we have disclosed a simple annulation strategy that affords a variety of substituted coumarin derivatives **25a-ω** in excellent yields from the corresponding phenolic acetates and acrylates *via* rhodium catalyzed C-H bond activation in a single step. This protocol is quite remarkable in the case of phenolic substrates with electron-deficient groups and is complementary to the reported methods generally applicable for electron-donating substrates only; thus providing for the diversity-oriented synthesis of bioactive coumarin derivatives in high yields. This cyclization strategy proceeds through rhodacycle as the intermediate formed by the *ortho* C-H bond activation of phenolic acetates and is well supported by deuterium incorporation studies. We believe that this method will find tremendous applications in the synthesis of various bioactive

coumarin derivatives as it is convenient to carry out under mild conditions displaying a wide range of substrate scope.

4.2.5 Experimental procedure

4.2.5.1 General experimental procedure for the synthesis of phenolic acetates:

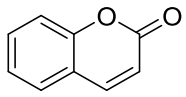
Phenolic acetates (**29a-r**) were readily prepared from the corresponding phenols as follows:

Phenols (1 mmol) were dissolved in 5 mL dry pyridine and the resulting solution was cooled to 0 °C. Acetic anhydride (1.5 mmol) was added dropwise to it. The reaction mixture was allowed to rise to room temperature and stirred for 0.5-1 h. Then pyridine was removed under high *vacuo* and the remaining reaction mass dissolved in ethyl acetate. The organic layer was washed with water/aq HCl/water, dried over anhydrous Na_2SO_4, concentrated to give the pure phenolic acetates (**29a-r**), which were used further for studies without purification.

4.2.5.2 General experimental procedure for the preparation of coumarin derivatives (25a-ω):

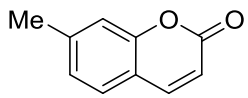
To a mixture of substituted phenolic acetates (**29a-r**) (1 mmol), $Rh_2(OAc)_4$ (2.5 mol %) and commercially available 98% formic acid (1 mL) under nitrogen atmosphere was added methyl acrylate **27a** or methyl crotonate **27b** or cinnamate **27c** (1.2 mmol) as the case may be. The resulting brown solution was stirred at 100 °C for 3-12 h. After completion of reaction (monitored by TLC), it was diluted with ethyl acetate (10 mL), and washed with water (10 mL), 5% aqueous sodium bicarbonate (15 mL), and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to give brown solids. On purification with flash chromatography using pet ether and ethyl acetate (7:3), coumarin derivatives (**25a- ω**) were obtained as solids.

2*H*-Chromen-2-one (25a)



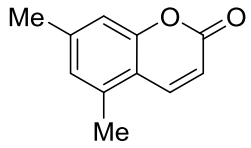
Yield: 71% (0.110 g), colorless solid, **mp**: 71 °C (lit.[7g] mp 70-72 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3060, 2958, 1715, 1605, 1453, 1106; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.70 (d, *J* = 9.6 Hz, 1H), 7.45-7.60 (m, 2H), 7.24-7.39 (m, 2H), 6.42 (d, *J* = 9.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 160.4, 154.2, 143.2, 131.8, 127.8, 124.4, 118.9, 117.0, 116.9; **HRMS** (ESI): calc. for $[(C_9H_6O_2)H]$ (M+H) 147.0446; Found: 147.0440.

7-Methyl-2*H*-chromen-2-one (25b)



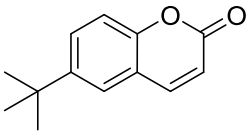
Yield: 81% (0.120 g), colorless solid, **mp**: 165-167 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3079, 2930, 1716, 1620, 1573, 1530; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.67 (d, *J* = 9.5 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.06-7.14 (m, 2H), 6.35 (d, *J* = 9.5 Hz, 1H), 2.45 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.1, 154.1, 143.4, 143.1, 127.5, 125.6, 117.0, 116.4, 115.4, 21.8; **HRMS** (ESI): calc. for $[(C_{10}H_8O_2)H]$ (M+H) 161.0603; Found: 161.0605.

5,7-Dimethyl-2*H*-chromen-2-one (25c)



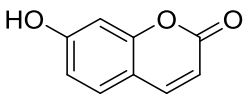
Yield: 83% (0.118 g), colorless solid, **mp:** 104-105 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1710, 1623, 1437; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.87 (d, *J* = 9.8 Hz, 1H), 6.97 (s, 1H), 6.93 (s, 1H), 6.35 (d, *J* = 9.8 Hz, 1H), 2.48 (s, 3H), 2.40 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.1, 154.7, 142.7, 140.4, 135.6, 126.9, 115.3, 115.0, 114.6, 21.6, 18.1; **HRMS** (ESI): calc. for $[(C_{11}H_{10}O_2)H]$ (M+H) 175.0759; Found: 175.0765.

6-(*tert*-Butyl)-4-phenyl-2*H*-chromen-2-one (25d)



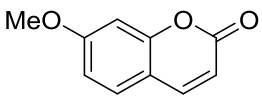
Yield: 82% (0.110 g), liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2936, 1728, 1610, 1556, 1507, 1282; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.71 (d, *J* = 9.5 Hz, 1H), 7.58 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 6.41 (d, *J* = 9.5 Hz, 1H), 1.36 (s, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.1, 152.0, 147.5, 143.9, 129.5, 124.1, 118.2, 116.4, 116.4, 31.3; **HRMS** (ESI): calc. for $[(C_{13}H_{14}O_2)H]$ (M+H) 203.1072; Found: 203.1077.

7-Hydroxy-2*H*-chromen-2-one (25e)



Yield: 92% (0.120 g), colorless solid, **mp:** 235 °C (lit.[8g] mp 234-237 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3220, 1705, 1670, 1380, 1237, 1077, 986, 570; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.86 (d, *J* = 9.8 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 6.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.75 (s, 1H), 6.16 (d, *J* = 9.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 162.3, 161.2, 157.1, 144.8, 130.5, 113.9, 112.9, 112.8, 103.4; **HRMS** (ESI): calc. for $[(C_9H_6O_3)H]$ (M+H) 163.0395; Found: 163.0398.

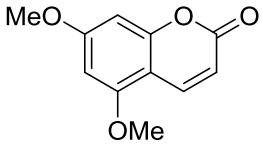
7-Methoxy-2*H*-chromen-2-one (25f)



Yield: 88% (0.124 g), colorless solid; **mp**: 122-123 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2936, 1728, 1610, 1556, 1507, 1282; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.62 (d, *J* = 9.3 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.78-6.87 (m, 2H), 6.24 (d, *J* = 9.5 Hz, 1H), 3.88 (s, 3H); **^{13}C**

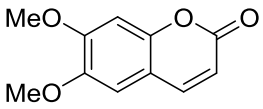
NMR (50 MHz, $CDCl_3$): δ 162.8, 160.8, 156.0, 143.1, 128.6, 113.2, 112.6, 112.5, 100.8, 55.6; **HRMS** (ESI): calc. for [($C_{10}H_8O_3$)H] (M+H) 177.0552; Found: 177.0558.

5,7-Dimethoxy-2*H*-chromen-2-one (25g)



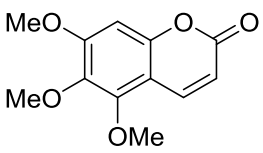
Yield: 95% (0.127 g), colorless solid; **mp**: 148-150 °C (lit.[8g] mp 147-148 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2936, 1725, 1615, 1552, 1509, 1382, 1130; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.6 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 6.15 (d, *J* = 9.7 Hz, 1H), 3.86 (s, 3 H), 3.90 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 163.7, 161.2, 156.9, 138.5, 111.1, 104.0, 94.8, 92.8, 55.9, 55.7; **HRMS** (ESI): calc. for [($C_{11}H_{10}O_4$)H] (M+H) 207.0657; Found: 207.0654.

6,7-Dimethoxy-2*H*-chromen-2-one (25h)



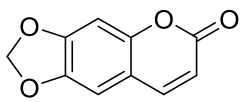
Yield: 85% (0.113 g), colorless solid; **mp**: 140-142 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2970, 1725, 1615, 1552, 1509; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.60 (d, *J* = 9.5 Hz, 1H), 6.84 (s, 2H), 6.28 (d, *J* = 9.5 Hz, 1H), 3.92 (s, 3H), 3.95 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.0, 152.8, 150.1, 146.3, 143.0, 108.0, 100.0, 56.2; **HRMS** (ESI): calc. for [($C_{11}H_{10}O_4$)H] (M+H) 207.0657; Found: 207.0659.

5,6,7-Trimethoxy-2*H*-chromen-2-one (25i)



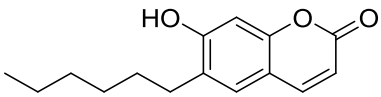
Yield: 88% (0.113 g), colorless solid; **mp**: 147-149 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2933, 1722, 1617, 1558, 1509, 1382, 1130; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.91 (d, *J* = 9.5 Hz, 1H), 6.60 (s, 1H), 6.22 (d, *J* = 9.5 Hz, 1H), 4.03 (s, 3H), 3.93 (s, 3H), 3.85 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 160.9, 157.1, 151.5, 149.2, 138.6, 138.0, 112.5, 107.1, 95.4, 61.7, 61.1, 56.2; **HRMS** (ESI): calc. for [($C_{12}H_{12}O_5$)H] (M+H) 237.0763; Found: 237.0763.

6*H*-[1,3]Dioxolo[4,5-*g*]chromen-6-one (25j)



Yield: 89% (0.122 g), colorless solid; **mp**: 218-220 °C (lit.[8g] mp 223 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3087, 1721, 1640, 1500, 1455, 1146, 1130; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.57 (d, *J* = 9.1 Hz, 1H), 6.82 (s, 2H), 6.27 (d, *J* = 9.3 Hz, 1H), 6.07 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.0, 151.3, 144.9, 143.3, 113.5, 112.7, 105.0, 102.3, 98.5; **HRMS** (ESI): calc. for [($C_{10}H_6O_4$)H] (M+H) 191.0344; Found: 191.0349.

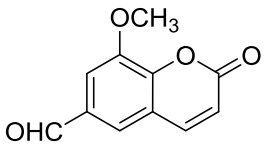
6-Hexanoyl-7-hydroxy-2*H*-chromen-2-one (25k)



Yield: 87% (0.110 g), colorless solid; **mp**: 202-203 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3220, 1710, 1670, 1380, 1224, 1056, 967, 580; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.66 (d, *J* = 9.4 Hz, 1H), 7.17 (s, 1H), 7.18 (s, 1H), 6.22 (d, *J* = 9.5 Hz, 1H), 2.64 (d, *J* = 7.3 Hz, 2H), 1.51-1.72 (m, 2H), 1.27-1.42 (m, 6H), 0.81-0.95 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 163.2, 159.3, 153.9, 144.8, 128.4, 128.1, 111.8, 111.4, 102.8, 31.8, 29.7,

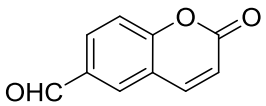
29.5, 29.2, 22.7, 14.2; **HRMS** (ESI): calc. for [($C_{15}H_{18}O_3$)H] (M+H) 247.1334; Found: 247.1334.

8-Methoxy-2-oxo-2*H*-chromene-6-carbaldehyde (25l)



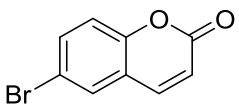
Yield: 91% (0.122 g), colorless solid; **mp**: 182-183 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3085, 1729, 1717, 1615, 1506, 1440, 1136, 1125; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.79 (d, *J* = 9.5 Hz, 1H), 7.60 (d, *J* = 3.1 Hz, 2H), 6.54 (d, *J* = 9.5 Hz, 1H), 4.04 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 190.1, 159.0, 148.3, 147.9, 142.9, 132.8, 123.5, 119.3, 118.0, 111.1, 56.4; **HRMS** (ESI): calc. for [($C_{11}H_8O_4$)H] (M+H) 205.0501; Found: 205.0505.

2-Oxo-2*H*-chromene-6-carbaldehyde (25m)



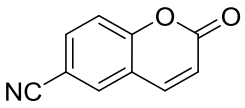
Yield: 90% (0.128 g), colorless solid; **mp**: 192-194 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3085, 1727, 1714, 1630; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.99-8.16 (m, 2H), 7.81 (d, *J* = 9.6 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 6.54 (d, *J* = 9.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 190.0, 159.5, 157.7, 142.8, 132.8, 132.4, 130.0, 119.1, 117.9, 117.9; **HRMS** (ESI): calc. for [($C_{10}H_6O_3$)H] (M+H) 175.0395; Found: 175.0390.

6-Bromo-2*H*-chromen-2-one (25n)



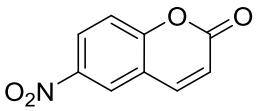
Yield: 81% (0.105 g), colorless solid; **mp**: 156-158 °C (lit.[7g] mp 156-159 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3085, 1727, 1615, 1556, 1470, 1126, 1130; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.51-7.77 (m, 4H), 7.22 (d, *J* = 9.4 Hz, 1H), 6.45 (d, *J* = 9.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 159.5, 153.0, 141.9, 134.6, 130.1, 120.3, 118.7, 118.0, 117.0; **HRMS** (ESI): calc. for [($C_9H_5BrO_2$)H] (M+H) 224.1551; Found: 224.1555.

2-Oxo-2*H*-chromene-6-carbonitrile (25o)



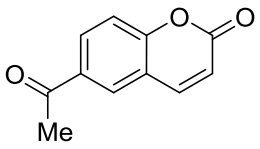
Yield: 74% (0.106 g), colorless solid; **mp**: 150-152 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3096, 2990, 2219, 1727; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.76-7.88 (m, 2H), 7.72 (d, *J* = 9.6 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.56 (d, *J* = 9.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 158.9, 156.3, 141.8, 134.7, 132.3, 119.4, 118.7, 118.3, 117.4, 108.6; **HRMS** (ESI): calc. for [($C_{10}H_5NO_2$)H] (M+H) 172.0399; Found: 172.0398.

6-Nitro-2*H*-chromen-2-one (25p)



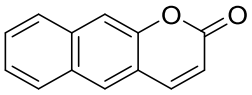
Yield: 64% (0.088 g), colorless solid; **mp**: 181-183 °C (lit.[7g] 180-182 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3070, 1735, 1610, 1518, 1340; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.45 (d, *J* = 2.4 Hz, 1H), 8.41 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.82 (d, *J* = 9.8 Hz, 1H), 7.48 (d, *J* = 9.2 Hz, 1H), 6.60 (d, *J* = 9.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 158.8, 157.5, 144.0, 142.2, 126.6, 123.7, 118.8, 118.1; **HRMS** (ESI): calc. for [($C_9H_5NO_4$)H] (M+H) 192.0297; Found: 192.0295.

6-Acetyl-4-phenyl-2*H*-chromen-2-one (25q)



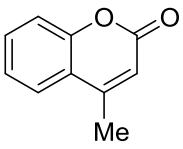
Yield: 92% (0.127 g), colorless solid; **mp**: 122-123 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3070, 1730, 17122, 1610, 1515, 1344; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.11-8.24 (m, 2H), 7.79 (d, *J* = 9.5 Hz, 1H), 7.41 (d, *J* = 9.3 Hz, 1H), 6.51 (d, *J* = 9.5 Hz, 1H), 2.66 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 196.0, 159.8, 156.9, 143.2, 133.5, 131.7, 128.6, 118.6, 117.6, 117.3, 26.6; **HRMS** (ESI): calc. for [($C_{11}H_8O_3$)H] (M+H) 189.0552; Found: 189.0558.

2*H*-Benzo[*g*]chromen-2-one (25r)



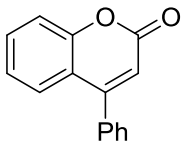
Yield: 90% (0.122 g), colorless solid; **mp**: 119-121 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3077, 2929, 1717, 1630, 1563, 1514, 1175; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.48 (d, *J* = 9.6 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.68 (td, *J* = 7.7, 1.1 Hz, 1H), 7.53-7.61 (m, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 6.57 (d, *J* = 10.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 160.7, 154.0, 139.0, 133.1, 130.4, 129.1, 128.3, 126.1, 121.4, 117.2, 115.8, 113.0; **HRMS** (ESI): calc. for [($C_{13}H_8O_2$)H] (M+H) 197.0603; Found: 197.0609.

4-Methyl-2*H*-chromen-2-one (25s)



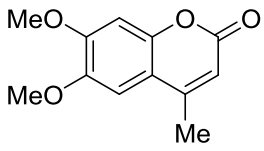
Yield: 78% (0.132 g), colorless solid; **mp**: 83 °C (lit.[5b] mp 83-84 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3075, 2988, 1725, 1605, 1453; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45-7.65 (m, 2H), 7.26-7.39 (m, 2H), 6.29 (d, *J* = 1.1 Hz, 1H), 2.46 (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 160.4, 153.7, 151.9, 131.7, 124.5, 124.1, 120.0, 117.2, 115.4, 18.7; **HRMS** (ESI): calc. for $[(C_{10}H_8O_2)H]$ (M+H) 161.0603; Found: 161.0610.

4-Phenyl-2*H*-chromen-2-one (25t)



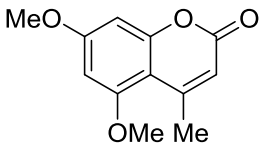
Yield: 80% (0.188 g), viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3050, 2930, 1715, 1675, 1353; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.49-7.60 (m, 5H), 7.15-7.32 (m, 2H), 6.78-6.97 (m, 2H), 6.38 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 160.6, 155.6, 154.3, 135.3, 131.9, 129.7, 129.6, 128.9, 128.5, 127.0, 124.2, 120.5, 119.1, 117.4, 115.3; **HRMS** (ESI): calc. for $[(C_{15}H_{10}O_2)H]$ (M+H) 223.0759; Found: 223.0760.

6,7-Dimethoxy-4-methyl-2*H*-chromen-2-one (25u)



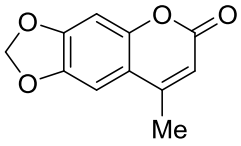
Yield: 85% (0.121 g), colorless solid; **mp**: 128-129 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3060, 2958, 1715, 1605, 1453, 1106, 1018, 956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.82 (s, 1H), 6.15 (s, 1H), 3.93 (s, 3H), 3.94 (s, 3H), 2.41 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.2, 152.7, 152.1, 149.4, 146.1, 112.4, 112.3, 105.1, 100.0, 56.3, 56.2, 18.8; **HRMS** (ESI): calc. for $[(C_{12}H_{12}O_4)H]$ (M+H) 221.0814; Found: 221.0810.

5,7-Dimethoxy-4-methyl-*2H*-chromen-2-one (25v)



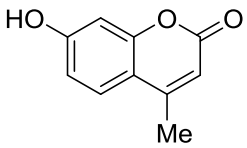
Yield: 80%, (0.114 g), colorless solid; **mp**: 171-173 °C (lit.[8h] mp 174 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3110, 2999, 1722, 1625, 1453, 1230, 1051, 986; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.41 (d, *J* = 2.3 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 5.88-5.99 (m, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 2.52 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 162.8, 160.8, 159.1, 157.1, 154.2, 111.5, 104.9, 95.5, 93.4, 55.7, 55.6, 24.2; **HRMS** (ESI): calc. for $[(C_{12}H_{12}O_4)H]$ (M+H) 221.0814; Found: 221.0810.

8-Methyl-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-one (25w)



Yield: 80% (0.118 g), colorless solid; **mp**: 120-121 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3033, 2984, 1711, 1605, 1453; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.81 (s, 1H), 6.15 (s, 1H), 6.07 (s, 2H), 2.37 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 161.0, 152.2, 151.0, 150.7, 144.9, 113.8, 112.4, 102.3, 102.1, 98.5, 19.2; **HRMS** (ESI): calc. for $[(C_{11}H_8O_4)H]$ (M+H) 205.0501; Found: 205.0505.

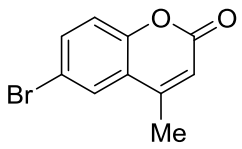
7-Hydroxy-4-methyl-2*H*-chromen-2-one (25x)



Yield: 88% (0.140 g), colorless solid; **mp**: 183-186 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3165, 1675, 1383, 1237, 1067, 985, 856, 758, 572, 525, 426; **^{1}H NMR** (200 MHz, $CDCl_3$): δ

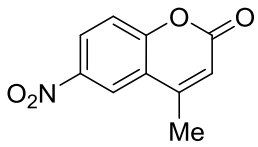
9.63 (s, 1H), 7.59 (d, *J* = 8.9 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.07 (s, 1H), 2.38- 2.42 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 162.0, 161.2, 156.3, 154.0, 127.3, 113.6, 111.8, 103.3, 18.6; **HRMS** (ESI): calc. for [($C_{10}H_8O_3$)H] (M+H) 177.0552; Found: 177.0555.

6-Bromo-4-methyl-2*H*-chromen-2-one (25y)



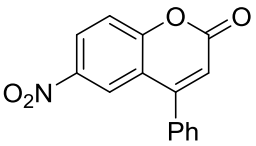
Yield: 81% (0.112 g), colorless solid; **mp:** 186-187 °C (lit.[7g] 187-189 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3092, 2929, 1748, 1590, 1550, 1479, 1413, 1385, 1257; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.72 (d, *J* = 1.7 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.33 (s, 1H), 2.43 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 160.0, 152.3, 151.2, 134.5, 127.2, 121.5, 118.7, 116.9, 116.0, 18.6; **HRMS** (ESI): calc. For [($C_{10}H_7BrO_2$)H] (M+H) 238.9708; Found: 238.9710.

4-Methyl-6-nitro-2*H*-chromen-2-one (25z)



Yield: 70% (0.103 g), colorless solid; **mp**: 183-185 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3077, 1736, 1610, 1518, 1344; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.54 (d, *J* = 2.7 Hz, 1H), 8.42 (dd, *J* = 9.1, 2.7, Hz, 1H), 7.48 (d, *J* = 9.1 Hz, 1H), 6.46 (s, 1H), 2.55 (s, 3H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 158.9, 157.1, 151.3, 150.0, 126.6, 120.8, 120.3, 118.2, 116.9, 29.7, 18.7; **HRMS** (ESI): calc. For [($C_{10}H_7NO_4$)H] (M+H) 206.0453; Found: 206.0458.

6-Nitro-4-phenyl-2*H*-chromen-2-one (25ω)



Yield: 72% (0.138 g), colorless solid; **mp**: 209-210 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3077, 1730, 1616, 1555, 1240; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.41-8.46 (m, 2H), 7.59-7.64 (m, 3H), 7.55 (d, *J* = 9.8 Hz, 1H), 7.48 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.53 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 159.0, 157.7, 154.7, 144.0, 133.8, 130.5, 129.4, 128.2, 126.7, 123.1, 119.3, 118.5, 116.7; **HRMS** (ESI): calc. for [($C_{15}H_9NO_4$)H] (M+H) 268.0610; Found: 268.0615.

4.2.6 References

1 Green Chemistry Theory and Practice, ed. P. T. Anastas and J. C. Warner, Oxford University Press, New York, **1998**

2 Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*., **2007**, *107*, 174.

3 Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev*., **2007**, *107*, 5318.

4 Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.*, **2009**, *48*, 5094.

5 Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*., **2010**, *110*, 624.

6 McGlacken , G. P.; Bateman, L. M. *Chem. Soc. Rev*., **2009**, *38*, 2447.

7 Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc*. **1963**, *85*, 1544.

8 Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev*. **2010**, *110*, 749 and the references therein

9 (a) Michael, J. P. *Nat. Prod. Rep*. **2008**, *25*, 166; (b) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds.; Pergamon: Oxford, UK, **1996**, *5*, 167; (c) Wagman, A. S.; Wentland, M. P. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B.; Triggle, D. J. Eds.; Elsevier Ltd: Oxford, UK, **2006**, *7*, 567.

10 (a) Charris, J. E.; Dominguez, J. N.; Gamboa, N.; Rodrigues, J. R.; Angel, J. E. *Eur. J. Med. Chem*. **2005**, *40*, 875; (b) Dayam, R.; Al-Mawsawi, L. Q.; Zawahir, Z.; Witvrouw, M.; Debyser, Z.; Neamati, N. *J. Med. Chem*. **2008**, *51*, 1136; (c) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem*. **2000**, *35*, 1021; (d) Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. *J. Med. Chem*. **1994**, *37*, 2129.

11 For synthesis of quinoline carboxylate derivative: (a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; H. S. Kim. *Tetrahedron Lett*. **2001**, *42*, 3737; (b) Kim, J. N.; Chung; Y. M.; Im, Y. J. *Tetrahedron Lett*., **2002**, *43*, 6209; (c) Kim, H. J.; Jeong, E. M.; Lee, K.-J. *J. Heterocycl. Chem*., **2011**, *48*, 965.

12 For recent reviews on the C−H functionalization, see: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev*. **2011**, *40*, 5068; (b) Delord, J.-W; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc.*

Rev. **2011**, *40*, 4740; (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315; (d) Mc Murray, L.; O'Hara, F.; Gaunt, M. *Chem. Soc. Rev*. **2011**, *40*, 1885; (e) Yeung, C. S.; Dong, V. M. *Chem. Rev*. **2011**, *111*, 1215; (f) White, M. C. *Science* **2012**, *335*, 807; (g) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res*. **2012**, *45*, 788; (h) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed*. **2012**, *51*, 8960; (i) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936; (j) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, 110, 624.

13 (a) Masters, K. S.; Rauws, T. R. M.; Yadav, A. K.; Herrebout, W. A.; Veken, B. V. D.; Maes, B. U. W. *Chem. Eur. J*. **2011**, *17*, 6315; (b) Wang, H.-G.; Wang, Y.; Peng, C.-L.; Zhang, J.-C.; Zhu, Q. *J. Am. Chem. Soc*. **2010**, *132*, 13217; (c) Nakao, Y.; Kanyiva, K.-S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc*. **2006**, *128*, 8146; (d) Yeung, C. S.; Dong, V. M., *Chem. Rev*. **2011**, *111*, 1215; (e) Daugulis, O. *Top. Curr. Chem*. **2009**, *292*, 57; (f) Ackermann, L. *Chem. Commun*. **2010**, *46*, 4866.

14 (a) Wurtz, S.; Rakshit, S.; Neumann, J. J.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230; (b) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474; (c) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572; (d) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078; (e) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676; (f) Chen, J.; Song, G.; Pan, C.-L.; Li, X. *Org. Lett.* **2010**, *12*, 5426.

15 Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585.

16 (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908; (b) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744; (c) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565; (d) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487; (e) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462.

17 (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407; (b) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362.

18 Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagne´, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066.

19 (a) Song, G.-Y.; Gong, X.; Li, X.-W. *J. Org. Chem*. **2011**, *76*, 7583; (b) Shimizu, M. Tsurugi, H.; Satoh, T.; Miura, M. *Chem. Asian J*. **2008**, *3*, 881; (c) Imai, M.; Tanaka, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem*. **2007**, *72*, 2543; (d) Stemmler, R. T.; Bolm, C. *Adv. Synth. Catal*. **2007**, *349*, 1185. (e) Mochida, S.; Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Asian J*. **2010**, *5*, 847; (f) Uto, T.; Shimizu, M.; Ueura, K.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Org. Chem*. **2008**, *73*, 298; (g) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M., *Chem. Commun*. **2009**, 5141; (h) Colby, D. A.; Bergman, R. G.;Ellman, J. A. *J. Am. Chem. Soc*. **2008**, *130*, 3645; (i) Li, L.; Brennessel, W. W.; Jones, W. D., *J. Am. Chem. Soc*. **2008**, *130*, 12414; (j) 1Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050; (k) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474; (l) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem*. **2008**, *120*, 4083; *Angew. Chem., Int. Ed*. **2008**, *47*, 4019; (m) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem.* **2011**, *123*, 4255; *Angew. Chem., Int. Ed*. **2011**, *50*, 4169; (n) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett*. **2010**, *12*, 5688;

(o) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc*. **2010**, *132*, 18326; (p) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814; (q) Li, B. J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3948; (r) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13; (s) Satoh, T.; Miura, M.; *Chem. Eur. J.* **2010**, *16*, 11212; (t) Song, G.-Y.; Wang, F.; Li, X.-W. *Chem. Soc. Rev*. **2012**, *41*, 3651.

20 (a) Ackermann, L. Vicente, R. *Top. Curr. Chem.* **2009**, *292*, 211; (b) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed*. **2011**, *123*, 6503; *Angew. Chem., Int. Ed.* **2011**, *50*, 6379; (c) Li, B.; Feng, H.-L.; Xu, S.-S.; Wang, B.-Q. *Chem. Eur. J.* **2011**, *17*, 12573; (d) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (e) Manikandan, R; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 3568.

21 (a) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem*. **2003,** *68*, 6427; (b) Lutz, R. E.; Ohnmacht, Jr. C. J.; Davis, F. *J. Med. Chem*. **1971**, *14*, 17; (c) Venkatesan, H. F.; Hocutt, M. T.; Jones K.; Rabinowitz, M. H. *J. Org. Chem*. **2010**, *75*, 3488; (d) Tummatorn, J.; Thongsornkleeb, C.; Ruchirawata, S.; Gettongsonga, T. *Org. Biomol. Chem*. **2013**, *11*, 1463; (e) Harikrishna, B.; Bhattacharyya, S.; Batra, S. *Org. Lett*. **2012**, *14*, 63.

22 Huang, J.-R.; Dong, L. Han, B.; Peng, C.; Chen, Y.-C. *Chem. Eur. J*. **2012**, *18*, 8896.

23 For 1,4-dihydro-pyridine: (a) Kikuchi,S.; Iwai, M.; Murayama, H.; Fukuzawa, S. *Tetrahedron Letters,* **2008,** *49*, 114; (b) Sirijindalert, T.; Hansuthirakul, K.; Rashatasakhon, P.; Sukwattanasinitt, M.; Ajavakom, A. *Tetrahedron,* **2010,** *66*, 5161.

24 Koyama, J.; Toyokuni, I.; Tagahara, K. *Chem. Pharm. Bull*. **1999**, *47*, 1038.

25 The Merck Index, 12th ed., Entry; 7079.

26 (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.*, **1997**, *97*, 2879; (b) Dyker, G. *Angew. Chem., Int. Ed.*, **1999**, *38*, 1698; (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.*, **2001**, *34*, 633; (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.*, **2002**, *102*, 1731; (e) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.*, **2002**, *35*, 826; (f) Miura, M.; Nomura, M. *Top. Curr. Chem*., **2002**, *219*, 211; (g) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal*., **2003**, *345*, 1077; (h) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem*., **2003**, *680*, 3.

27 (a) Venugopala, K. N.; Rashmi, V.; Odhav, B. *Bio Med Res. Int.*, **2013**, 963248; (b) Fedorov, A. Y.; Nyuchev, A. V.; Beletskaya, I. P. *Chem. Heterocycl. Compd*., **2012**, *48*, 166; (c) Jerezano, A.; Jimenez, F.; Cruz, M. d. C.; Montiel, L. E.; Delgado, F.; Tamariz, J. *Helv. Chim. Acta*, **2011**, *94*, 185; (d) Riveiro, M. E.; De, K. N.; Moglioni, A.; Vazquez, R.; Monczor, F.; Shayo, C.; Davio, C. *Curr. Med. Chem.*, **2010**, *17*, 1325; (e) Kostova, I. *Curr. Med. Chem*.: *Anti-Cancer Agents*, **2005**, *5*, 29; (f) Garazd, M. M.; Garazd, Y. L.; Khilya, V. P. *Chem. Nat. Compd*., **2005**, *41*, 245; (g) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem*., **2005**, *12*, 887; (h) Lacy, A.; O'Kennedy, R. *Curr. Pharm. Des*., **2004**, *10*, 3797; (i) Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Des*., **2004**, *10*, 3813; (j) Sardari, S.; Nishibe, S.; Daneshtalab, M. Stud. *Nat. Prod. Chem*., **2000**, *23*, 335; (k) Malikov, V. M.; Saidkhodzhaev, A. I. *Chem. Nat. Compd*., **1998**, *34*, 202; (l) Estevez-Braun, A.; Gonzalez, A. G. *Nat. Prod. Rep*., **1997**, *14*, 465; (m) Hoult, J. R. S.; Paya, M. *Gen. Pharmacol*., **1996**, *27*, 713; (n) Murray, R. D. H.

Nat. Prod. Rep., **1995**, *12*, 477; (o) Murray, R. D. H. *Prog. Chem. Org. Nat. Prod*., **1991**, *58*, 83; (p) Sethna, S. M.; Shah, N. M. *Chem. Rev*., **1945**, *36*, 1.

28 (a) Zhao, H.; Donnelly, A. C.; Kusuma, B. R.; Brandt, G. E. L.; Brown, D.; Rajewski, R. A.; Vielhauer, G.; Holzbeierlein, J.; Cohen, M. S.; Blagg, B. S. J. *J. Med. Chem*., **2011**, *54*, 3839; (b) Dayam, R.; Gundla, R.; Al-Mawsawi, L. Q.; Neamati, N. *Med. Res. Rev*., **2008**, *28*, 118; (c) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem*., **1999**, *42*, 2662; (d) Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A.-L.; Chinou, E.; Chinou, I. *J. Nat. Prod*., **2005**, *68*, 78; (e) Gosselin, F.; Britton, R. A.; Davies, I. W.; Dolman, S. J.; Gauvreau, D.; Hoerrner, R. S.; Hughes, G.; Janey, J.; Lau, S.; Molinaro, C.; Nadeau, C.; O'Shea, P. D.; Palucki, M.; Sidler, R. *J. Org. Chem*., **2010**, *75*, 4154; (f) Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J. *J. Med. Chem*., **2005**, *48*, 6400; (g) Symeonidis, T.; Chamilos, M.; Hadjipavlou-Litina, D. J.; Kallitsakis, M.; Litinas, K. E. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 1139.

29 (a) Sheng, R.; Wang, P.; Gao, Y.; Wu, Y.; Liu, W.; Ma, J.; Li, H.; Wu, S. *Org. Lett*., **2008**, *10*, 5015; (b) Koefod, R. S.; Mann, K. R. *Inorg. Chem.*, **1989**, *28*, 2285; (c) Xu, X.; Hu, X.; Wang, J. *Beilstein J. Org. Chem*., **2013**, *9*, 254; (d) Zhou, Y.; Liu, K.; Li, J.-Y.; Fang, Y.; Zhao, T.-C.; Yao, C. *Org. Lett*., **2011**, *13*, 1290.

30 (a) Joule, J. A.; Mills, K. Heterocyclic Chemistry, 4th ed., Blackwell, UK, 2000; (b) Hassan, V.; Shockravi, A. *Tetrahedron Letters*, **2005**, *46*, 3501.

31 (a) Audisio, D.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem*., **2010,** 1046; (b) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Sitler, T. C. *J. Org. Chem*., **2006**, *71*, 409; (c) Reddy, M. S.; Thirupathi, N.; Haribabu, M. *Beilstein J. Org. Chem*., **2013**, *9*, 180.

32 (a) Valente, S.; Kirsch, G. *Tetrahedron Lett*., **2011**, *52*, 3429; (b) Giguere, D.; Cloutier, P.; Roy, R. *J. Org. Chem*., **2009**, *74*, 8480; (c) Yamamoto, Y.; Kirai, N. *Org. Lett*., 2008, *10*, 5513; (d) Catellani, M.; Chiusoli, G. P.; Marzolini, G.; Rossi, E. *J. Organomet. Chem*., **1996**, *525*, 65; (e) Sasano, K.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc*., **2013**, *135*, 10954; (f) Ferguson, J.; Zeng, F.; Alper, H. *Org. Lett.*, **2012**, *14*, 5602; (g) Schmidt, B.; Krehl, S. *Chem. Commun*., **2011**, *47*, 5879; (h) Baghbanian, S. M.; Farhang, M. *Synthetic Communications*, **2014**, *44*, 697; (i) Valizadeh, H.; Shockravi, A. *Tetrahedron Letters*, **200**5, *46*, 3501; (j) Aoki, S.; Oyamada, J.; T. Kitamura, *Bull. Chem. Soc. Jpn*., **2005,** *78*, 468; (k) Shi, Z.; He, C. *J. Org. Chem.*, **2004**, *69*, 3669.

33 (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science*, **2000**, *287*, 1992; (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.*, **1996**, *118*, 6305; (c) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc*., **2000**, *122*, 7252; (d) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc*., **2003**, *125*, 4518; (e) Shi, Z.; He, C. *J. Org. Chem*., **2004**, *69*, 3669; (f) Wegner, H. A.; Ahles, S.; Neuburger, M. *Chem.–Eur. J.*, **2008**, *14*, 11310; (g) Cao, J.-L.; Shen, S.-L.; Yang P.; Qu, *J. Org. Lett.*, **2013**, *15*, 3856; (h) Aoki, S.; Oyamada, J.; Kitamura, T. *Bull. Chem. Soc. Jpn.*, **2005**, *78*, 468.

34 (a) Zhang, X.-S.; Li, Z.-W.; Shi, Z.-J. *Org. Chem. Front*., **2014**, *1*, 44; (b) Sharma, U.; Naveen, T.; Maji, A.; Manna, S.; Maiti, D. *Angew. Chem., Int. Ed*., **2013**, *52*, 12669.

LIST OF PUBLICATIONS AND PATENTS

1. Enantioselective synthesis of HIV protease inhibitor amprenavir *via* Co-catalyzed HKR of 2-(1-azido-2-phenylethyl)oxirane; **Gadakh**, **S. K.**; Reddy, R. S.; Sudalai, A. *Tetrahedron: Asymmetry*, **2012**, *13*, 898.
2. A simple and efficient synthesis of isocoumarins and alkylidenephthalides from 3-(1-hydroxycarbethoxy/alkyl)phthalides with a DEAD/PPh_3/TBHP system; **Gadakh, S. K**.; Sudalai, A. *RSC Adv*., **2014**, *4*, 57658.
3. Co-catalyzed two-stereocentered hydrolytic kinetic resolution: application to the synthesis of yashabushidiols A and B and the lactone unit of compactin and mevinolin; **Gadakh, S. K**.; Sudalai, A. *Tetrahedron: Asymmetry*, **2015**, *26*, 118.
4. Rh-Catalyzed Quinoline Carboxylate Synthesis *via* C-H Bond Activation and Cyclization Reactions of Arylamines with Terminal Alkynic Esters; **Gadakh, S. K.**; Dey, S; Sudalai, A. (*Manuscript under revision*).
5. Rh-Catalyzed Novel Synthesis of Coumarin Derivatives from Phenolic Acetates and Acrylates *via* C-H Bond Activation; **Gadakh, S. K.**; Dey, S; Sudalai, A. (*Manuscript communicated*).
6. Titanium superoxide- A Stable Heterogeneous Catalyst for Oxidative Esterification of Aldehydes with Alkylarenes or Alcohols using TBHP as Oxidant; Dey, S; **Gadakh, S. K.**; Sudalai, A. (*Manuscript communicated*).
7. Enantioselective Synthesis of (+)-Spirolaxine Methyl Ether; **Gadakh, S. K.**; Sudalai, A. (*Manuscript under preparation*).
8. A Concise Formal Synthesis of the Potent HIV Protease Inhibitor Nelfinavir Mesylate and its Analogue; **Gadakh, S. K.**; Sudalai, A. (*Manuscript under preparation*).
9. A New Process for the Synthesis of Amprenavir and Sequinavir, HIV Protease Inhibitor; **Gadakh, S. K.**; Sudalai, A. **WOPCT/IN2013/000021, US 14/371466 and IN14/371466.**
10. Rhodium Catalyzed *ortho* C-H Activation of Anilines with Ethyl Propiolate and Formic Acid: A Facile Entry to the Synthesis of Quinolines: **Gadakh, S. K.**; Sudalai, A. **IN/1700/DEL/2004.**
11. Rhodium Catalyzed *ortho* C-H Activation of Phenolic Esters: A Facile Entry to the Synthesis of Coumarin Derivatives; **Gadakh, S. K.**; Sudalai, A. **(Indian filing, INV-2015-73).**