Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving C-C, C-O and C-N Bond Formation *via* Cu(I) and Iodine Catalysis

Thesis Submitted to the AcSIR for the Award of

The Degree of

DOCTOR OF PHILOSOPHY

In Chemical Sciences

By

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UNDER THE GUIDANCE OF

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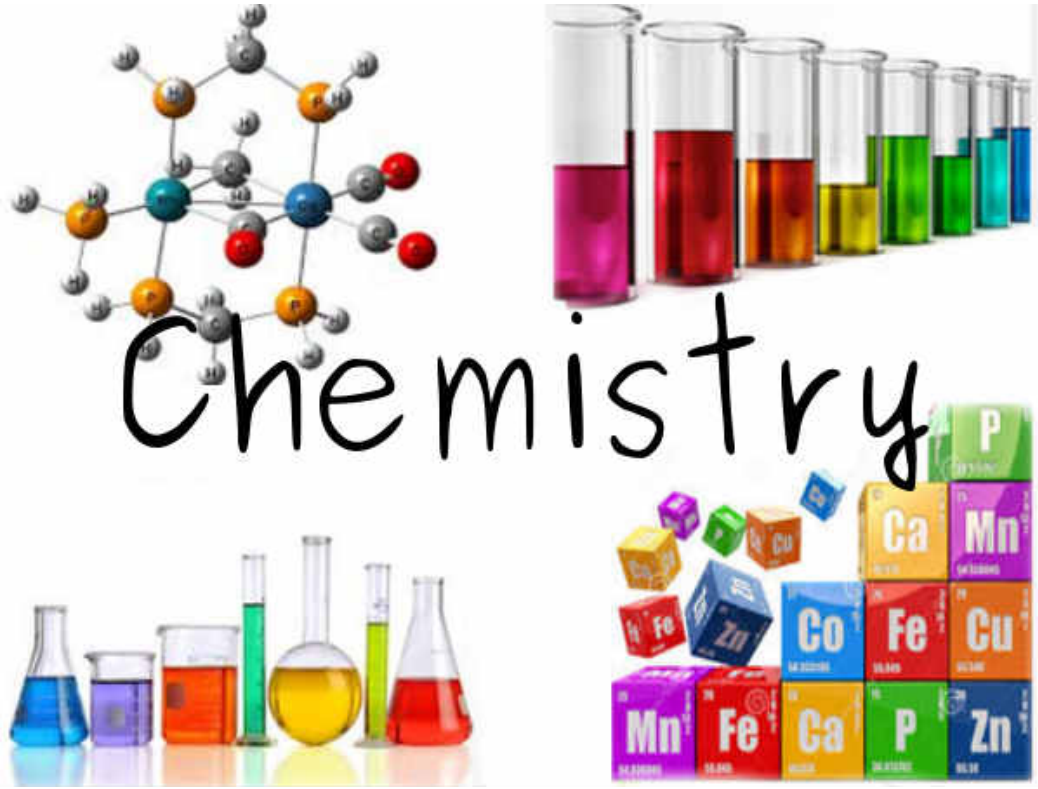

Dedicated TO

MY FAMILY, TEACHERS

&DEAR FRIENDS

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving C-C, C-O and C-N Bond Formation via Cu(I) and Iodine Catalysis"*** which is being submitted to the ***AcSIR*** for the award of ***Doctor of Philosophy*** in ***Chemical Sciences*** by ***Ms. Pragati Kishore Prasad*** 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.

July 2015
Pune

Dr. A. Sudalai
(Research Guide)

CSIR-NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving C-C, C-O and C-N Bond Formation via Cu(I) and Iodine Catalysis"*** 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.

Pragati Kishore Prasad.

July 2015
Pune

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I wish to express my heartfelt gratitude towards my research supervisor ***Dr. A. Sudalai****, for his care and providing me an opportunity to work in his laboratory where he established the platform for advancing the knowledge through sharing of his experience at every stage of my tenure which helped me to achieve this target. His suggestions, criticisms and constant encouragement helped me immensely to grow as a chemist. His constant effort to instill us with several most essential habits, like weekly seminars, group meetings and daily planning has made me confident to start an independent scientific career and hence I preserve an everlasting gratitude towards him. My sincere regards and reverence are for him, forever. I believe the better way of thanking him would be through my future contribution to the scientific community.*

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Though my name appears in bold in the thesis, the backbone of it is the patience of my beloved parents and my dear sisters Prachi and Pragya. Especially, I wish to thank immensely my parents who allowed me to live my dreams through chemistry and my sisters who have excelled in their respective professions and always set high standards for me. A name that deserves special mention here is my brother Mr. Vicky Singh Chouhan who has been my "conscience" and helped me handle all predicaments that came my way.

Dear parents, my family and my best friends, the core of my being, forever I am grateful to you. I would like you to know that I appreciate everything you've done for me. I would also like to extend my gratitude towards my brother-in-law, Mr. Debabrata and my dear niece, Aayushi (Sona) for becoming an inseparable part of my family and making our lives cheerful. The hard-work that I have been able to put in, is because of treatment provided by my doctor, Dr. Samuel George who has made me fit enough to pursue Ph. D in synthetic organic chemistry and I shall ever remain indebted to him.

I wish to thank the great scientific community whose achievements are constant source of inspiration for me. Above all, I thank my paternal & maternal grandparents who are no more physically with us still showering their blessings on us. Though, many have not been mentioned, none is forgotten.

Pragati Kishore Prasad

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
Boc	*N*-*tert*-Butoxycarbonyl
$(Boc)_2O$	Di*tert*-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
CDI	1,1'-Carbonyldiimidazole
Conc	Concentrated
DEAD	Diethyl azodicarboxylate
DIPT	Diisopropyl tartrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutyl aluminium hydride
DMEDA	*N,N*-Dimethylethylenediamine
DMF	*N,N*-Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
EDG	Electron donating group
EWG	Electron withdrawing group
g	Grams
h	Hours
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
H_2O_2	Hydrogen peroxide
IR	Infra red
IBX	2-Iodoxybenzoic acid
LAH	Lithium aluminum hydride
LD	Lethal dose
LDA	Lithium diisopropyl amide
LiHMDS	Lithium hexamethyldisilazide
LG	Leaving group
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
NOESY	Nuclear overhauser effect spectroscopy
ORTEP	Oak ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
Pet	Petroleum
Ph	Phenyl
PMB	*Para*-methoxybenzyl
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
Py	Pyridine
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethyl-1-piperidinyl)oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethyl silyl
TBHP	*tert*-Butylhydroperoxide
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

Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving C-C, C-O and C-N Bond Formation *via* Cu(I) and Iodine Catalysis

Research Student: Pragati Kishore Prasad

AcSIR Roll: 10CC11A26039

Research Guide: Dr. A. Sudalai

The thesis entitled **"Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving C-C, C-O and C-N Bond Formation *via* Cu(I) and Iodine Catalysis''** is divided into four chapters. The title of the thesis clearly reflects the objective, which is to utilize Cu(I) and I_2 catalysis for the development of synthetic methodologies applied to the enantioselective synthesis of bioactive molecules and their intermediates. **Chapter I** deals with CuBr-catalyzed carbonylative coupling of aryl halides **1a-y** with various nucleophiles **2** (phenols, alcohols, amines and acids) using NaCN as C_1 source providing for the synthesis of carboxylate derivatives **3a-y** and its application to the enantioselective total synthesis of antifungal antibiotic (-)-herbaric acid (**12**) and formal synthesis of (-)-isocladosporin (**20**). In addition, CuCN-mediated "one-pot" cyclization of 4-(2-bromophenyl)-2-butenoates **4a-k** leading to efficient synthesis of substituted naphthalene amino esters **5a-k** has been described. **Chapter II** describes I_2-catalyzed oxo-acyloxylation of alkenes and enol ethers, **21** with carboxylic acids for the high yield synthesis of α-acyloxyketones and esters **22**. Additionally, direct hydroxy-

acyloxylation of alkenes has been achieved with the sequential addition of $BH_3.SMe_2$ leading to monoprotected diol derivatives **23** in excellent yields. This protocol has been utilized in the asymmetric total synthesis of (+)-tanikolide (**27**) and formal synthesis of (-)-malyngolide (**31**). **Chapter III** deals with I_2 catalyzed vicinal azidohydroxylation of alkenes **21** leading to 1,2-azidoalcohols **32a-n** & **33a-n** using NaN_3 and *N,N*-dimethylformamide as *N* and *O*-sources respectively in high yields (up to 92%) and excellent dr (up to 98%). The regio- and stereodivergence in azidohydroxylation can be realized by merely changing the co-oxidants. The versatility of this methodology has been demonstrated in the short route syntheses of (±)-chloramphenicol (**34**) and (±)-cytoxazone (**35**). **Chapter IV** describes I_2-catalyzed double oxidation of enol ethers (**36a-i**) to yield α-ketoesters (**37a-i**) in good yields. Also, regioselective azidation of indoles (**38a-h**) with NaN_3 at C-3 has been realized by activation with I_2.

Introduction

Cu-mediated C-C and C-heteroatom bond formations are well documented in literature. However, Cu was not used in its full potential until in 2001 until the discovery of versatile copper/ligand systems emerged that could be employed in catalytic amounts under comparatively milder conditions (90–110 °C).[1] Since then spectacular resurgence of interest in developing more efficient Cu/ ligand systems has been observed. The present work deals with Cu(I)/1,10-phenanthroline catalyzed synthesis of carboxylate derivatives **3a-y** from carbonylative coupling[2] of aryl bromides with anilines, phenols and alcohol derivatives using NaCN as substitute to the existing "carbon monoxide"[3] as C_1 source. The methodology has successfully been applied to the short enantioselective synthesis of antifungal

natural products (-)-herbaric acid (**12**) and (-)-isocladosporin (**20**). Further, CuCN-mediated cascade cyclization of ethyl-4-(2-bromophenyl)but-2-enoates **4a-k** to naphthalene-1-amino-2-ester derivatives **5a-k** has also been described.[4] Recently, I_2 catalysis has been increasingly explored as environmentally benign reagent in place of rare or toxic heavy metal oxidants for C-C, C-O and C-N bond-forming reactions using either aq. H_2O_2 or *tert*-butyl hydroperoxide as water soluble co-oxidants.[5] In this context, I_2-catalyzed synthesis of α-acyloxyketones **22** and mono protected diols **23** by oxo- and hydroxy acyloxylation of alkenes is presented herein.[6] Its application is demonstrated in the total syntheses of brine shrimp toxin (+)-tanikolide (**27**) and (-)-malyngolide (**31**). In addition to this, I_2-catalysed regio- and stereodivergent hetero-difunctionalisation of alkenes leading to 1,2-azidoalcohols **32a-n** & **33a-n** has been disclosed.[7] These structural units are recurrent in drugs,[8a] natural products[8b] and synthetic materials[8c] and find tremendous utility in their syntheses as is evident from the concise total synthesis of a popular antibiotic, chloramphenicol (**34**) and microbial metabolite cytoxazone (**35**) which is identified as a selective modulator of T_H2 cytokine secretion. I_2-catalyzed oxidation of enol ethers to α-ketoesters **37a-i** and regioselective C-3 azidation of indole derivatives **38a-h** assisted by iodine under ambient reaction conditions have also been described.

Statement of Problem

The reported syntheses of these aforementioned highly bioactive molecules suffer from disadvantages such as lengthy reaction sequences including the protection and deprotection of various functional groups, use of chiral auxiliaries and expensive

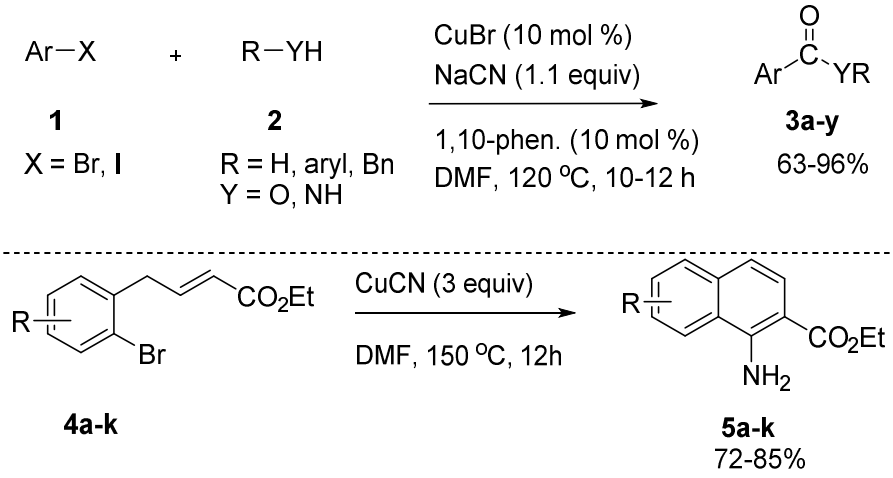
organometallic reagents, etc. Hence, need for a shorter synthetic sequence in high overall yields from commercially available achiral starting materials is of current interest.

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. Single Crystal X-ray Crystallographic study has been carried out to determine the regiochemistry unambiguously.
3. The optical purity of chiral intermediates and final drug molecules have 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.

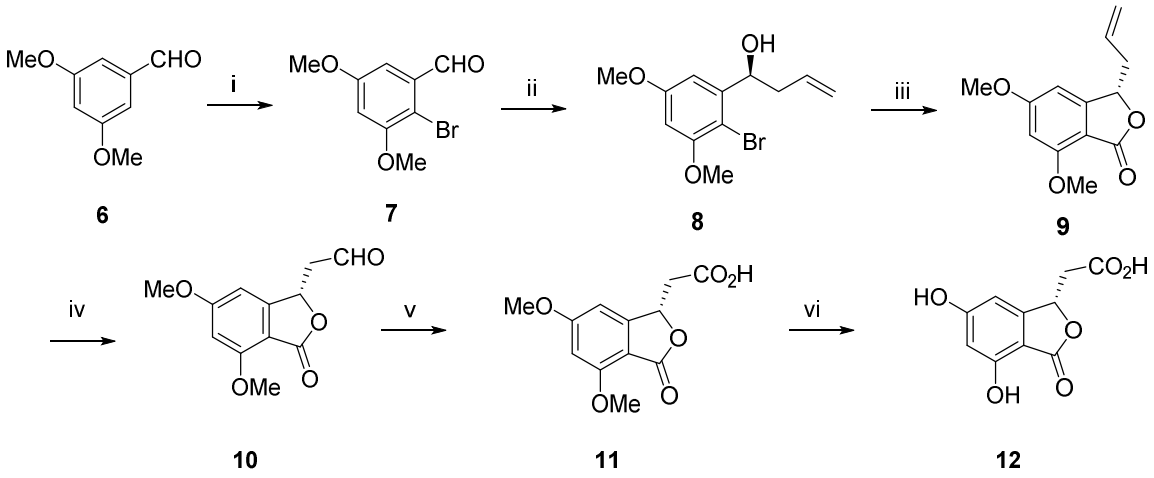
Chapter-I

CuBr-catalyzed carbonylative coupling of aryl halides **1** with various nucleophiles **2** (phenols, alcohols, amines and acids) using NaCN as C_1 source providing for the synthesis of carboxylate derivatives **3a-y** has been described. This reaction describes for the first time, "cyanide" as substitute to the existing "carbon monoxide" driven carbonylation processes. In continuation of this work, CuCN mediated cyanation-cyclization cascade of unsaturated ester **4a-k** that led to the synthesis of substituted naphthalene-1-amino-2-esters **5a-k** has also been reported (**Scheme 1**).

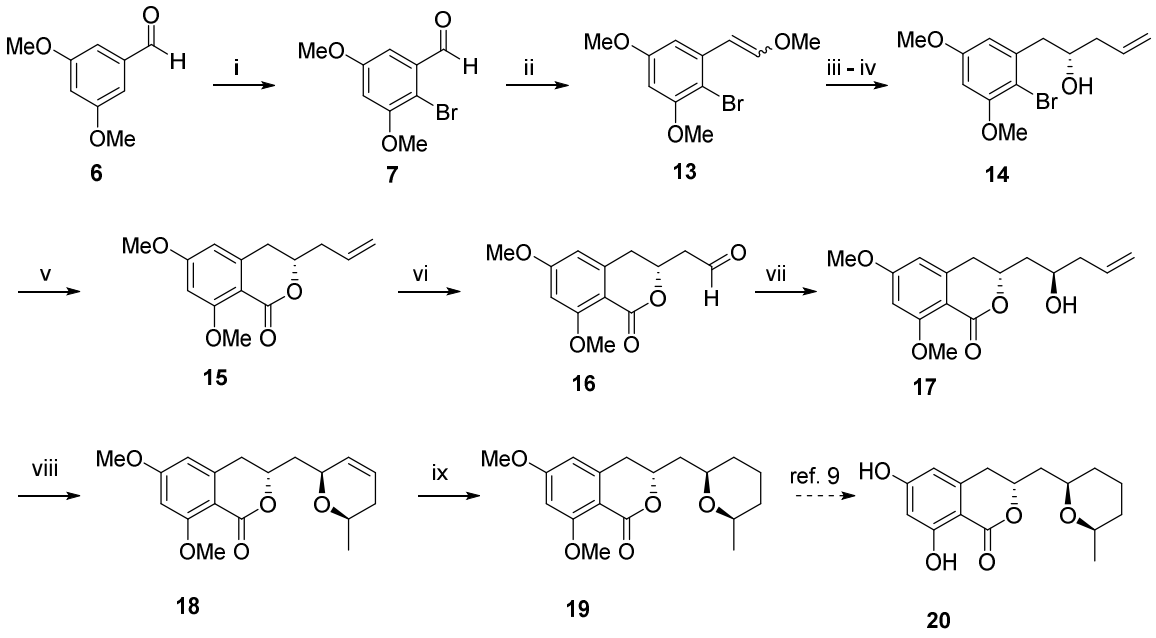


Scheme 1: Cu(I) assisted C-C, C-O & C-N bond formations using cyanide as C1 synthon.

Based on the Cu(I) catalyzed carbonylative coupling strategy, enantioselective synthesis of (-)-herbaric acid (**12**) (**Scheme 2**) and (-)-isocladosporin (**20**) (**Scheme 3**) have been achieved from **6** as common starting material involving CuBr catalyzed carbonylative coupling reaction and asymmetric Brown's allylation as the key steps in the synthesis.



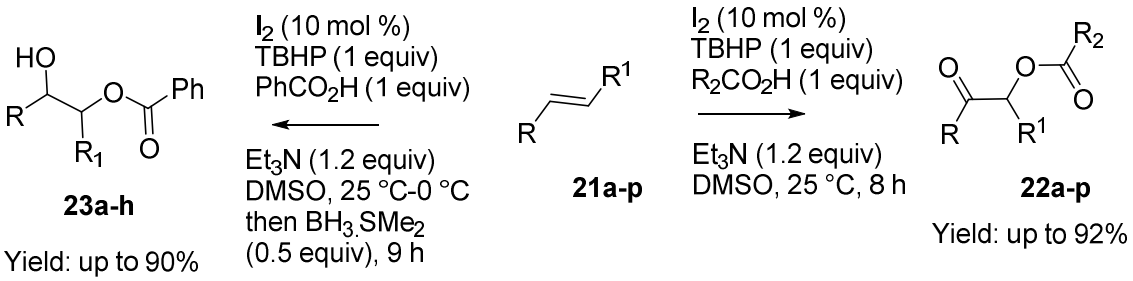
Scheme 2: (i) NBS (1.1 equiv), CH_3CN:H_2O (4:1), 25 °C, 4 h, 96%; (ii) (-)-Ipc_2B(allyl)borane, Et_2O, -78 °C, 1 h then 1N NaOH, 30% aq. H_2O_2, 80%, 90% ee; (iii) CuBr (10 mol %), 1,10- phenanthroline (10 mol %), NaCN (1.1 equiv), DMF, 110 °C, 12 h, 86%; (iv) K_2OsO_4 (1 mol %), NMO, acetone:H_2O (4:1), 25 °C, 12 h, then $NaIO_4$ on silica, 86%; (v) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, THF:H_2O:^{t}BuOH (1:1:1), 25 °C, 89%; (vi) BBr_3, CH_2Cl_2, -10 °C, 78%.



Scheme 3: (i) NBS (1.1 equiv), CH_3CN:H_2O (4:1), 25 °C, 4 h, 96%; (ii) methoxy methyltriphenylphosphonium chloride (1.2 equiv), K^{t}OBu (1.5 equiv), THF, 0 to 25 ºC, 4 h, 85%; (iii) 2N HCl, THF, 60 ºC, 3 h; (iv) (-)-Ipc_2B(allyl)borane, Et_2O, -78 ºC, 1 h then 1N NaOH, 30% H_2O_2, 80% (over 2 steps), 90% ee; (v) CuBr (10 mol %), 1,10- phenanthroline (10 mol %), NaCN (1.1 equiv), DMF, 110 ºC, 12 h, 88%; (vi) K_2OsO_4 (1 mol %), NMO, acetone:H_2O (4:1), 25 °C, 12 h, then $NaIO_4$ on silica, 86%; (vii) $MgBr_2$ (2 equiv) allylSn^nBu_3 (1 equiv), CH_2Cl_2, -20 °C, 8 h, 82%, dr: 98:2; (viii) TMSOTf (10 mol %), CH_3CHO, CH_2Cl_2, -5 ºC, 3 h, 78%, dr = 4:1; (ix) H_2 (1atm), Pd/C, MeOH, 25 °C, 4 h, 96%.

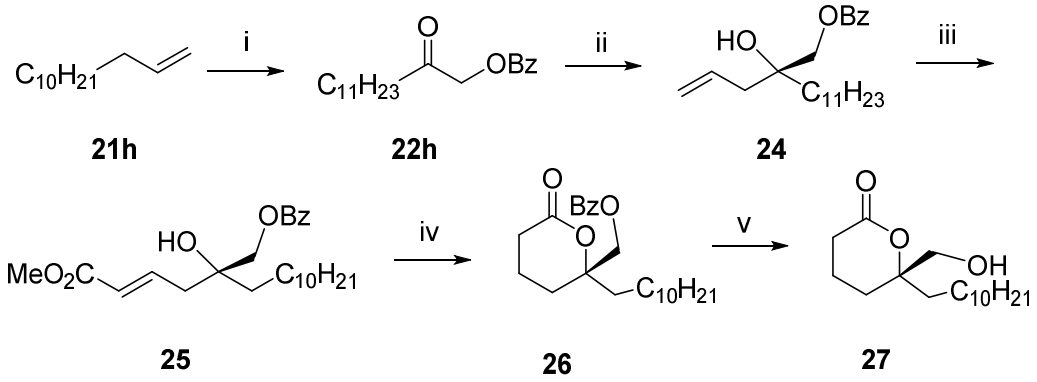
Chapter II

In this chapter, I_2-catalyzed oxo-acyloxylation of alkenes **21a-p** with carboxylic acids providing for the high yield synthesis of α-acyloxyketones **22a-p** has been developed. This unprecedented regioselective oxidative process employs TBHP and Et_3N in stoichiometric amounts under metal-free conditions in DMSO as solvent. Additionally, I_2-catalysis allows the direct hydroxy-acyloxylation of alkenes with the sequential addition of $BH_3.SMe_2$ leading to monoprotected diol derivatives **23a-h** in excellent yields (**Scheme 4**).

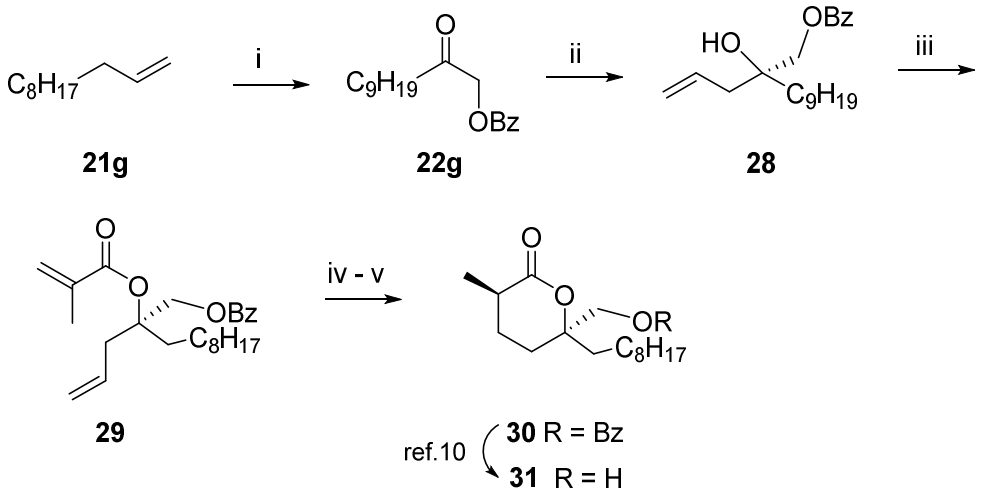


Scheme 4: I_2-catalyzed oxo- and hydroxyacyloxylation of alkenes and enol ethers

Based on the oxo-acyloxylation strategy, total synthesis of (+)-tanikolide (**27**) (**Scheme 5**) and formal synthesis of (-)-malyngolide (**31**) (**Scheme 6**) have been achieved in 5 steps each using asymmetric Brown's allylation and Grubbs' metathesis reaction as the other key steps in the synthetic sequence.



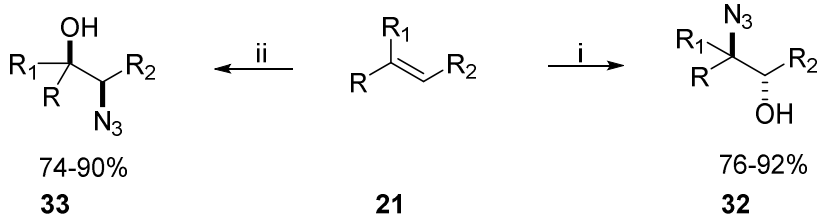
Scheme 5: (i) I_2 (10 mol %), TBHP (5.5 M in decane, 1 equiv), $PhCO_2H$ (1 equiv), Et_3N (1.2 equiv), DMSO, 0 - 25 °C, 12 h, 86%; (ii) $Ti(O^iPr)_4$ (10 mol %), (*R*)-BINOL (10 mol %), 4 Å° MS, allylSn^nBu_3 (1.1 equiv), CH_2Cl_2, -78° C to -20° C, 72 h, 81%, 81% ee; (iii) methyl acrylate (5 equiv), Grubbs' II (5 mol %), CH_2Cl_2, 25° C, 4 h, 88%; (iv) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h, 96%; (v) K_2CO_3 (1.5 equiv), MeOH, 25 °C, 6 h, 85%.



Scheme 6: (i) I_2 (10 mol %), TBHP (5.5 M in decane, 1 equiv), $PhCO_2H$ (1 equiv), Et_3N (1.2 equiv), DMSO, 0 to 25 °C, 12 h, 83%; (ii) $Ti(O^iPr)_4$ (10 mol %), (*S*)-BINOL (10 mol %), allylSn^nBu_3 (1.1 equiv), CH_2Cl_2, -78° C to -20° C, 72 h, 84%, 80% ee; (iii) Methacroyl chloride (1.2 equiv), Et_3N, CH_2Cl_2, 25° C, 3 h, 88%; (iv) Grubbs' II (1 mol %), CH_2Cl_2, 40 °C, 4h; (v) 10% Pd/C, H_2 (1 atm), MeOH, 25° C, 4 h, 71% (2 steps), dr = 3:1.

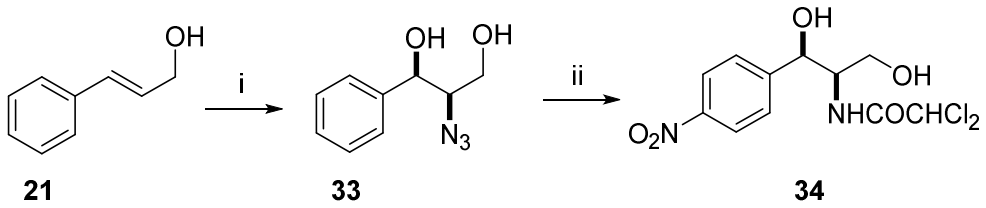
Chapter III

A novel, I_2 catalytic system for vicinal azidohydroxylation of alkenes leading to 1,2-azidoalcohols (**32a-n** & **33a-n**) in high yields (up to 92%) and excellent dr (up to 98%) has been disclosed. This unprecedented regio- and stereodivergent heterodifunctionalization of alkene employs NaN_3 and DMF as *N*- and *O*- nucleophiles respectively (**Scheme 7**).

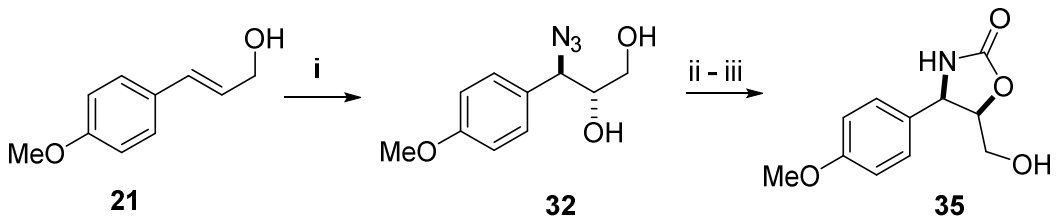


Scheme 7: (i) I_2 (10 mol %), 50% aq. H_2O_2 (2 equiv), Et_3N (1 equiv), NaN_3 (2 equiv) DMSO: DMF (v/v = 1:1), 0 °C to 25 °C, 8 h, 76-92%; (ii) I_2 (10 mol %), 5-6 M TBHP in decane (2 equiv), Et_3N (1 equiv), NaN_3 (2 equiv) DMSO:DMF (v/v = 1:1), 0 °C to 25 °C, 8 h, 74-90%.

The utility of this azidohydroxylation methodology has amply been illustrated in the concise diastereoselective total syntheses of antibiotic, chloramphenicol (**34**) (**Scheme 8**) and serotonin reuptake inhibitor, cytoxazone (**35**) (**Scheme 9**).



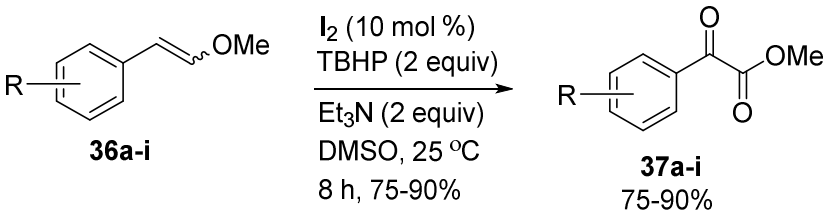
Scheme 8: (i) I_2 (10 mol %), Et_3N (1 equiv), 5-6 M TBHP in decane (2 equiv), NaN_3 (2 equiv), DMSO:DMF (1:1), 0 °C to 25 °C, 8 h, 80%, dr = 98:2 (*syn:anti*); (ii) (a) H_2 (1.1 atm), 10% Pd/C, MeOH, 25 °C, 4 h; (b) Cl_2CHCO_2Me (1 equiv), MeOH, 25 °C, 94% (2 steps); (c) conc. HNO_3: conc. H_2SO_4 (1:1), - 20 to 0 °C, 2 h, 75%.



Scheme 9: (i) **:** (i) I_2 (10 mol %), Et_3N (1 equiv), 50% aq. H_2O_2 (2 equiv), NaN_3 (2 equiv), DMSO:DMF (1:1), 0 °C to 25 °C, 8 h, 80%, dr = 92:8 (*syn:anti*); (ii) (a) H_2 (1.1 atm), 10% Pd/C, MeOH, 25 °C, 12 h; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 25 °C, 2 h, 76% (2 steps); (iii) NaH (2 equiv), THF, 0 to 25 °C, 3 h, 90%.

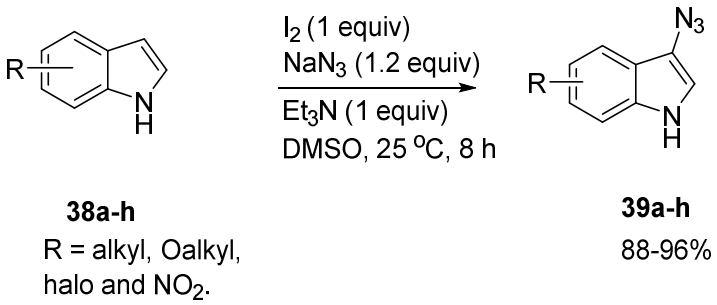
Chapter IV

This chapter describes, a high yield (75-90%) synthesis of α-keto esters **37a-i** from the corresponding methyl vinyl ethers **36a-i** *via* I_2 catalysis under DMSO/Et_3N conditions. The protocol is mild as the reaction has been carried out at room temperature (**Scheme 10**).



Scheme 10: I_2-catalyzed synthesis of α-keto esters

Additionally, in this chapter, regioselective azidation of indoles **38a-h** at C-3 has also been described. The umpolung in indole reactivity has been accomplished by usage of iodine in the reaction. The protocol is mild and high yielding (88-96%) and has been carried out under ambient reaction conditions (**Scheme 11**).



Scheme 11: I_2-mediated regioselective azidation of indoles

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CHAPTER I

Coupling of Aryl Halides with *C*/*N*/*O*-Nucleophiles *via* Cu(I) Catalysis using Cyanide as C1 synthon: Synthesis of (-)-Herbaric Acid & (-)-Isocladosporin

1. Copper(I) Bromide-Catalyzed Carbonylative Coupling of Aryl Halides with Phenols, Alcohols and Amines using Sodium Cyanide as C1 Source: A Synthesis of Carboxylic Acid Derivatives; **Pragati Kishore Prasad** and Arumugam Sudalai; *Adv. Synth. Catal.* **2014**, *10*, 2231-38.

2. CuCN-mediated Cascade Cyclization of 4-(2-bromophenyl)-2-butenoates: A High Yield Synthesis of Substituted Naphthalene Amino Esters; Rekula Santhosh Reddy, **Pragati Kishore Prasad**, Brij Bhushan Ahuja and Arumugam Sudalai; *J. Org. Chem.*, **2013**, *78*, 5045-50.

Section I

Copper(I) Bromide Catalyzed Carbonylative Coupling of Aryl Halides with Phenols, Alcohols and Amines using Sodium Cyanide as C_1 Source

1.1.1 Introduction

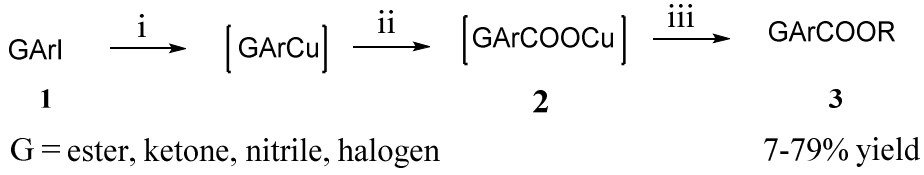
The catalysis of organic reactions by transition metals has clearly become an essential tool for both bulk and fine chemicals synthesis. While metals such as Pd, Pt or Rh have received considerable attention, copper catalysis, first reported a century ago in the pioneering and remarkable work of Fritz Ullmann[1] and Irma Goldberg[2] had remained quite undeveloped until the beginning of the 21st century. A significant drawback of copper catalysis was the requirement of high reaction temperatures which greatly limited the scope of this procedure. This shortcoming stimulated considerable effort to develop mild coupling conditions and the introduction of *N,O* or *N,N* bidentate ligands[3] to promote these reactions allowed for the development of highly efficient catalytic systems. In addition to the low cost of both metal sources and ligands, that clearly represents a great advantage over most other catalytic systems. The development of copper-mediated transformations for the C(aryl)-C, C(aryl)-N, C(aryl)-O, and C(aryl)-S bond formation is an important transformation and has been developed to include a wide range of substrates. Aromatic and heteroaromatic carboxylate derivatives that also involve C-Heteroatom bond formations are versatile raw materials in the manufacture of agrochemicals, dyes, pharmaceuticals, photosensitizers etc[4] and are known to be synthesized by and large *via* Pd catalysis. Owing to its synthetic importance, it has received considerable attention from many research groups thus improving the commercial viability of these large volume chemicals.

1.1.2 Review of Literature

In literature, conventional preparation of carboxylate derivatives involves condensation of activated carboxylic acids with alcohols/amines.[5] Direct transformation of aldehydes into esters has also been achieved using a variety of oxidation reagents.[6] Recently, *N*-heterocyclic carbenes (NHCs)-catalyzed oxidative esterification of aldehydes with alcohols,[7] alkyl halides[8] and boronic acids[9] has also been reported. Practical syntheses of carboxylate derivatives have been reported from coupling of halides **1**, C1 synthon and nucleophiles **2**.[10] Some of the significant developments in this transformation from haloarenes **1** are discussed below.

Ebert's approach (2005)[11]

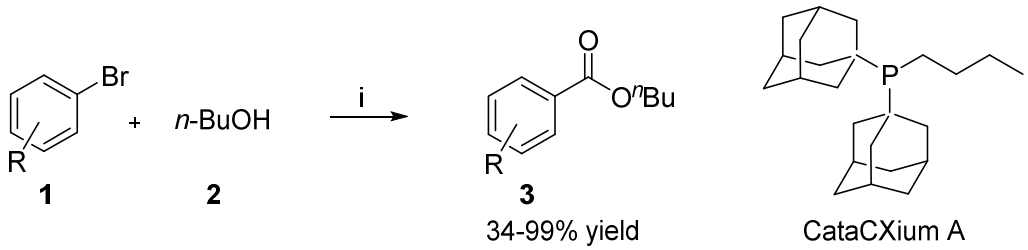
In Ebert's approach, organocopper compounds undergo carboxylation with CO_2 to form the corresponding copper benzoates **2**. In turn, these salts when treated with appropriate alkyl halides in the presence of a dipolar aprotic solvent generate the corresponding aryl esters **3**. This methodology permits the formation of functionalized esters that could not be generated by the carboxylation of organomagnesium compounds (**Scheme 1**).



Scheme 1: (i) Activated copper, THF, 25 °C, 0.5 h; (ii) CO_2 (1 atm), THF, 25 °C, 24 h; (iii) RI (3 equiv), THF:DMF (1:1), 70 °C, 5 h.

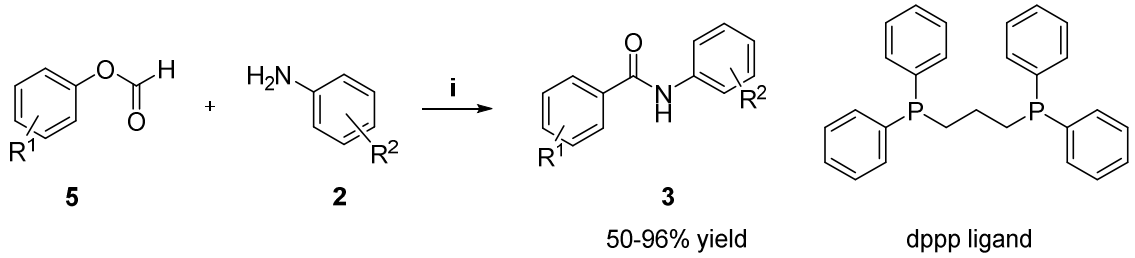
Beller's approach (2006)[12] **and (2014)**[17]

In Beller's approach, bromoarene **1** in the presence of bulky di-1-adamantyl-*n*- butyl-phosphine ligand (cataCXium A) undergo butoxycarbonylation at low Pd catalyst loadings (0.5 mol % or below) (**Scheme 2**).



Scheme 2: (i) Pd $(OAc)_2$ (0.5 mol %), cataCXium A (1.5 mol %), CO (20 bar), 115 °C, 12-18 h.

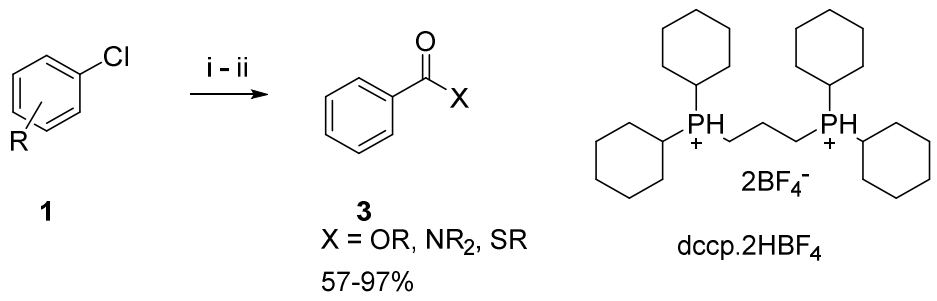
In yet another approach, Beller has disclosed a practical protocol for carbonylative reactions which rely on the cooperation of phenyl formate derivatives **5** and $C_4F_9SO_2F$ (nonaflate) for the *in situ* generation of CO. This protocol could be applied in carbonylations with *C, N,* and *O* nucleophiles (**Scheme 3**).



Scheme 3: (i) $Pd(OAc)_2$ (2 mol %), dppp (3 mol %), Et_3N (3 equiv), $C_4F_9SO_2F$ (2 equiv), CH_3CN, 80 °C, 6 h.

Buchwald's approach (2008)[13]

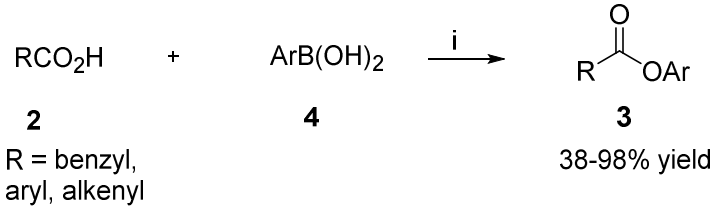
In Buchwald's approach, Pd catalyzed carbonylation of lesser reactive chloroarenes **1** is described using sodium phenoxide and carbon monoxide (at atmospheric pressure) affording phenyl esters. Phenyl esters served as acylating agents under mildly basic conditions to yield other acid derivatives *viz* esters, amides and thioesters **3** (**Scheme 4**).



Scheme 4: (i) $Pd(OAc)_2$ (2 mol %), dcpp.$2HBF_4$ (4 mol %), CO (1 atm), PhONa (1.2 equiv), DMF, 100 °C, 6- 24 h; (ii) XH (3 equiv), K_2CO_3 (0.5 equiv), DMF, 70 °C, 1 h.

Cheng's approach (2010)[14]

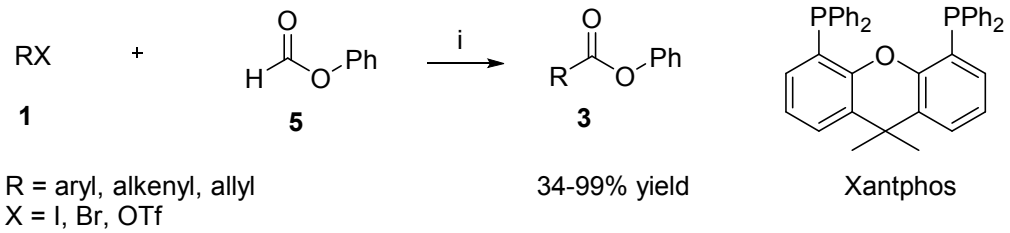
In Cheng's approach, copper triflate mediated Chan-Lam reaction of carboxylic acids with aryl boronic acid is described. It presents a facile method to access phenolic esters (**Scheme 5**).



Scheme 5: (i) $Cu(OTf)_2$ (40 mol %), $CO(NH_2)_2$ (1 equiv), EtOAc, 60 °C, 12 h.

Manabe's approach (2012)[15]

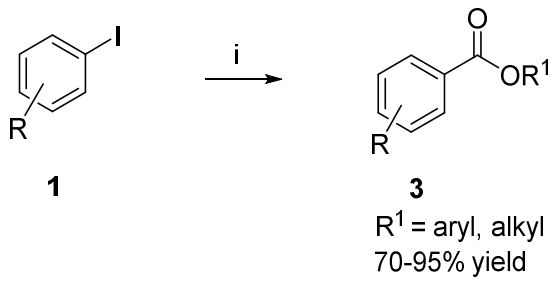
In Manabe's approach, palladium-catalyzed carbonylation of aryl, alkenyl, and allyl halides **1** with phenyl formate (**5**) has been reported. This procedure does not use carbon monoxide and affords homologated carboxylic acid phenyl esters in excellent yields (**Scheme 6**).



Scheme 6: (i) $Pd(OAc)_2$ (3 mol %), xantphos (12 mol %), Et_3N (2 equiv), CH_3CN, 80 °C, 12 h.

Bhanage's approach (2013)[16]

In this approach, immobilized palladium metal-containing ionic liquid (ImmPd-IL), has been explored as an immobilized, phosphine-free catalyst for carbonylation reactions of aryl iodides, including alkoxycarbonylation, phenoxycarbonylation, and aminocarbonylation reactions (**Scheme 7**).



Scheme 7: (i) ImmPd-IL (2 mol %), CO (10 MPa), Et_3N (3 equiv), R^1OH (2 equiv), toluene, 100 °C, 8 h.

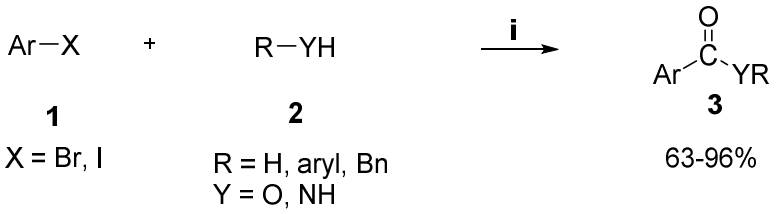
1.1.3 Present Work

1.1.3.1 Objective

As can be seen, there exists several reports for carbonylation of halo compounds leading to synthesis of carboxylic acid derivatives. However, there are certain drawbacks associated with them such as (i) heavy and expensive Pd metal (ii) costly phosphine ligands (iii) use of more than stoichiometric amounts of base (iv) necessity of highly specialized equipments capable of withstanding elevated pressure to enable safe handling of CO in academic laboratory. In this regard, an efficient protocol that eliminates the aforementioned difficulties is highly desirable. This section describes, for the first time, CuBr catalyzed carbonylative coupling of aryl bromides with phenols, alcohols and amines using "sodium cyanide" in place of "carbon monoxide" as the C_1 synthon.

1.1.3.2 Results and Discussion

Scheme 8 shows a new Cu-catalyzed "one-pot" methodology for the preparation of several carboxylate derivatives **3** directly from aryl halides **1** with phenols, alcohols, amines and H_2O as nucleophiles **2** using NaCN as C_1 source under neutral reaction conditions.



Scheme 8: (i) CuBr (10 mol %), 1,10-phen (10 mol %), NaCN (1.1 equiv), DMF, 120 °C, 12 h.

For determining optimal conditions (**Table 1**), bromobenzene and phenol were treated with CuCN (1 equiv) in DMF at 150 °C, which gave the corresponding phenylbenzoate

3a in 28% yield. The yield of **3a** was significantly improved to 45% when the CuCN quantity was increased (2 equiv) under the same reaction conditions. However, a remarkable increase in yield of **3a** (74%) was realized when CuCN concentration was further increased (3 equiv). On lowering the temperature (120 °C), product yield was reduced (46%). A brief evaluation of solvents showed that DMF was the most suitable one. In order to provide a catalytic process, we have carried out the carbonylative

Table 1: CuBr–catalyzed carbonylative coupling of bromobenzene with phenol using NaCN as C_1 source: optimization studies[a]

no.	catalyst (10 mol %)	ligand/additive (10 mol %)	CN source (equiv)	yield of **3a**(%)[b]
1[c]	--	--	CuCN (3)	74 (28[d], 45[e])
2	--	--	CuCN (3)	46
3	CuCN	--	NaCN (1.1)	19
4	CuBr	--	NaCN (1.1)	24
5	CuBr	*L*-proline	NaCN (1.1)	70
6	CuBr	1,10-phenanthroline	NaCN (1.1)	74 (37[f], trace[g])
7	CuI	1,10-phenanthroline	NaCN (1.1)	76
8	CuBr	ethylenediamine	NaCN (1.1)	38
9	CuBr	*N,N*-dimethyl-ethylenediamine	NaCN (1.1)	32
10	CuBr	*N,N*-diisopropyl-ethylenediamine	NaCN (1.1)	27
11	$Cu(OAc)_2$	KI	$K_4[Fe(CN)_6]$ (0.5)	Trace[h]

[a] PhBr (3 mmol), PhOH (3 mmol), DMF, 120 °C, 12 h; [b] isolated yield after column chromatographic purification; [c] reaction carried out at 150 °C; [d] 1 equiv CuCN used; [e] 2 equiv CuCN used; [f] 5 mol % CuBr used; [g] toluene used; [h] DMF + H_2O (1:1) used.

coupling with CuBr as the catalyst and NaCN, a relatively easy to handle solid as the CN source. Thus, by using CuBr (10 mol %) along with NaCN (1.1 equiv), **3a** was obtained in low yield (24%, entry 4). In order to improve the yield, a series of N-based ligands were screened along with CuBr (10 mol %) and giving **3a** in reasonably good yields (entries 5-10). After several experimentations, it was thus found that a combination of bromobenzene, phenol, NaCN (1.1 equiv), CuBr (10 mol %), 1,10- phenanthroline (10 mol %) in DMF at 120 °C for 12 h was the best optimised condition in achieving **3a** in high yields (74%, entry 6). The observed ligand based acceleration[3] can be rationalized by the fact that Cu(I) is electronically enriched when associated to bipyridine type ligands thus facilitating oxidative addition of ArX on Cu(I). Lowering CuBr concentration (5 mol %) afforded **3a** in low yields (37%). Use of $K_4[Fe(CN)_6]$ as the cyanide source was not useful either.

With the optimized reaction conditions in hand, next we sought to examine the scope and limitations of the reaction with various bromide and amine nucleophiles (**Table 2**). Table 2 illustrates a number of representative aryl halides that have been coupled with a variety of phenols and amines, indicative of considerable generality. Noteworthy among these are aryl halides bearing Me and OMe groups that are successful under these conditions. Electron-rich and electron-deficient nucleophiles such as phenols, alcohols, anilines, benzyl amine, etc gave good yields of the corresponding carboxylic esters and amides (63-76%). Other minor products isolated in these cases were the corresponding arylnitriles, unreacted nucleophiles (alcohol or amine) and traces of benzoic acid. Also, benzoic acid was obtained (70%) when water was used. However, in the case of 1-bromooctane,

only 1-cyanooctane (80%) was obtained under reaction conditions while long-chain aliphatic alcohols (C8 and C16) when reacted with bromobenzene, gave benzoic acid as the sole product, which may be a limitation of the catalytic process.

Table 2: CuBr–catalyzed carbonylative coupling of haloaromatics with nucleophiles[a]

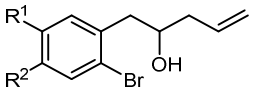
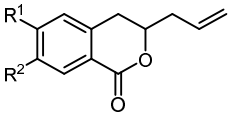
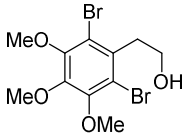
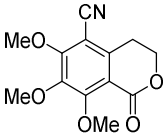
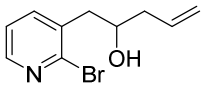
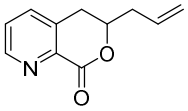
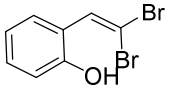
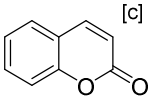
no.	substrates (**1**) (ArX)	nucleophiles (**2a-j**) (RYH)	products (**3a-j**)	yields (%)[b]
a	bromobenzene	phenol	phenylbenzoate	74
b	bromobenzene	4-NO_2-phenol	4-NO_2-phenylbenzoate	71
c	bromobenzene	4-OMe benzylalcohol	4-OMe-benzylbenzoate	76
d	bromobenzene	aniline	benzanilide	68
e	bromobenzene	2-Cl-aniline	2-Cl-benzanilide	70
f	bromobenzene	4-OMe-aniline	4-OMe-benzanilide	63
g	bromobenzene	2-Cl-benzylamine	2-Cl-benzylbenzamide	71
h	bromobenzene	water	benzoic acid	70
i	3-Br-toluene	phenol	3-Me-phenylbenzoate	68
j	4-MeO-bromobenzene	phenol	4-MeO-phenylbenzoate	71

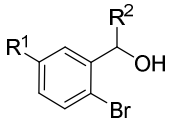
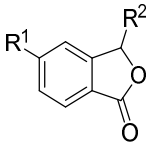
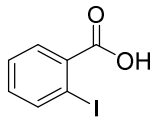
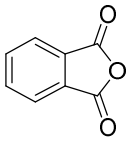
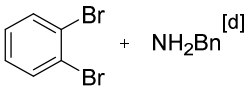
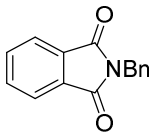
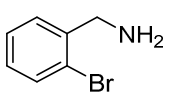
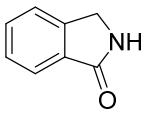
[a] reaction conditions: NaCN (3.3 mmol), CuBr (10 mol %), substrate (3 mmol), nucleophile (3 mmol), 1,10- phenanthroline (10 mol %), DMF, 120 °C, 12 h; [b] isolated yield after column chromatographic purification.

Next, its intramolecular versions were examined, which allowed for the synthesis of lactones, lactams,[20a] anhydrides and other heterocycles. As can be seen from **Table 3**, several substituted 2-bromophenethyl alcohol derivatives (**1k-p**), were

subjected to Cu-catalyzed intramolecular coupling with NaCN (1.1 equiv) that afforded the corresponding isochroman-1-ones (**3k-p**) in excellent yields (84-88%). Similarly, 2-bromobenzylic alcohol derivatives (**1r-v**) gave the corresponding isobenzfuranones (phthalides), (**3r-v**) in 78-92% yields. Interestingly, phthalic anhydride (**3w**) was also obtained in 96% yields from 2-iodobenzoic acid. Simple coumarin (entry **3q**) was also obtained in 81% yield from vinylic dibromophenol **1q.**[20b] The dicarbonylative coupling of *o*-dibromobenzene into phthalimide **3x**[20c] in a single step is remarkable.

Table 3: CuBr-catalyzed intramolecular carbonylative coupling: substrate scope[*a*]

substrates (**1k-y**)[*b*]	products (**3k-y**)
	
R^1 = H, R^2 = H; **1k**	R^1 = H, R^2 = H; **3k**, 84%
R^1 = H, R^2 = Me; **1l**	R^1 = H, R^2 = Me; **3l**, 86%
R^1 = OMe, R^2 = H; **1m**	R^1 = OMe, R^2 = H; **3m**, 87%
R^1 = F, R^2 = H; **1n**	R^1 = F, R^2 = H; **3n**, 88%
	
1o	**3o**, 84%
	
1p	**3p**, 84%
	
1q	**3q**, 81%

	
R^1 = F, R_2 = allyl; **1r**	R^1 = F, R^2 = allyl; **3r**, 92%
R^1 = OMe, R_2 = allyl; **1s**	R^1 = OMe, R^2 = allyl; **3s**, 85%
R^1 = Br, R_2 = H; **1t**	R^1 = Br, R^2 = H; **3t**, 78%
R^1 = H, R_2 = heptyl; **1u**	R^1 = H, R^2 = heptyl; **3u**, 91%
R^1 = H, R_2 = butyl; **1v**	R^1 = H, R^2 = butyl; **3v**, 88%
	
1w	**3w**, 96%
	
1x	**3x**, 73%
	
1y	**3y**, 81%

[a] for reaction condition, see footnote under table 2; [b] corresponding aldehydes were trapped with allyl bromide under Barbier allylation[18] conditions (see experimental section); [c] concomitant reduction of one of the Br to H takes place;[19] [d] 2 equiv NaCN used, 1 equiv of benzylamine used as nucleophile.

The formation of all carboxylic acid derivatives were confirmed unambiguously from their corresponding HRMS, ^{1}H, ^{13}C NMR and IR spectral data.

Example 1: ^{1}H NMR spectrum of 6,7,8-Trimethoxy-1-oxoisochromane-5-carbonitrile **(3o)**: showed three typical singlets at δ 3.85 (s, 3H), 3.95 (s, 3H) and 4.04 (s, 3H) corresponding to methoxyl protons (-OC**H$_3$**) and two triplets at δ 3.31 (t, *J* = 8.8 Hz, 2H) corresponding to benzylic (-C**H$_2$**) while another triplet at 4.65 (t, *J* = 8.8 Hz, 2H) corresponding to (-OC**H$_2$**). Its ^{13}C NMR spectrum showed a benzylic (-**C**H$_2$) carbon

signal at δ 27.2 while three characteristic carbon signals at δ 61.4, 61.8 and 62.2 are attributed to methoxyl carbon (-O**C**H_3). The other signals at δ 65.7 and 100.3 are due to –O**C**H_2 and –**C**N groups respectively. Aromatic carbon signals appear at δ, aromatic carbon signals appear δ 113.7, 115.2, 141.2, 145.1, 159.6 and 159.7 while ester carbonyl carbon (**C**=O) appears at δ 161.2 respectively (**Fig. 1**).

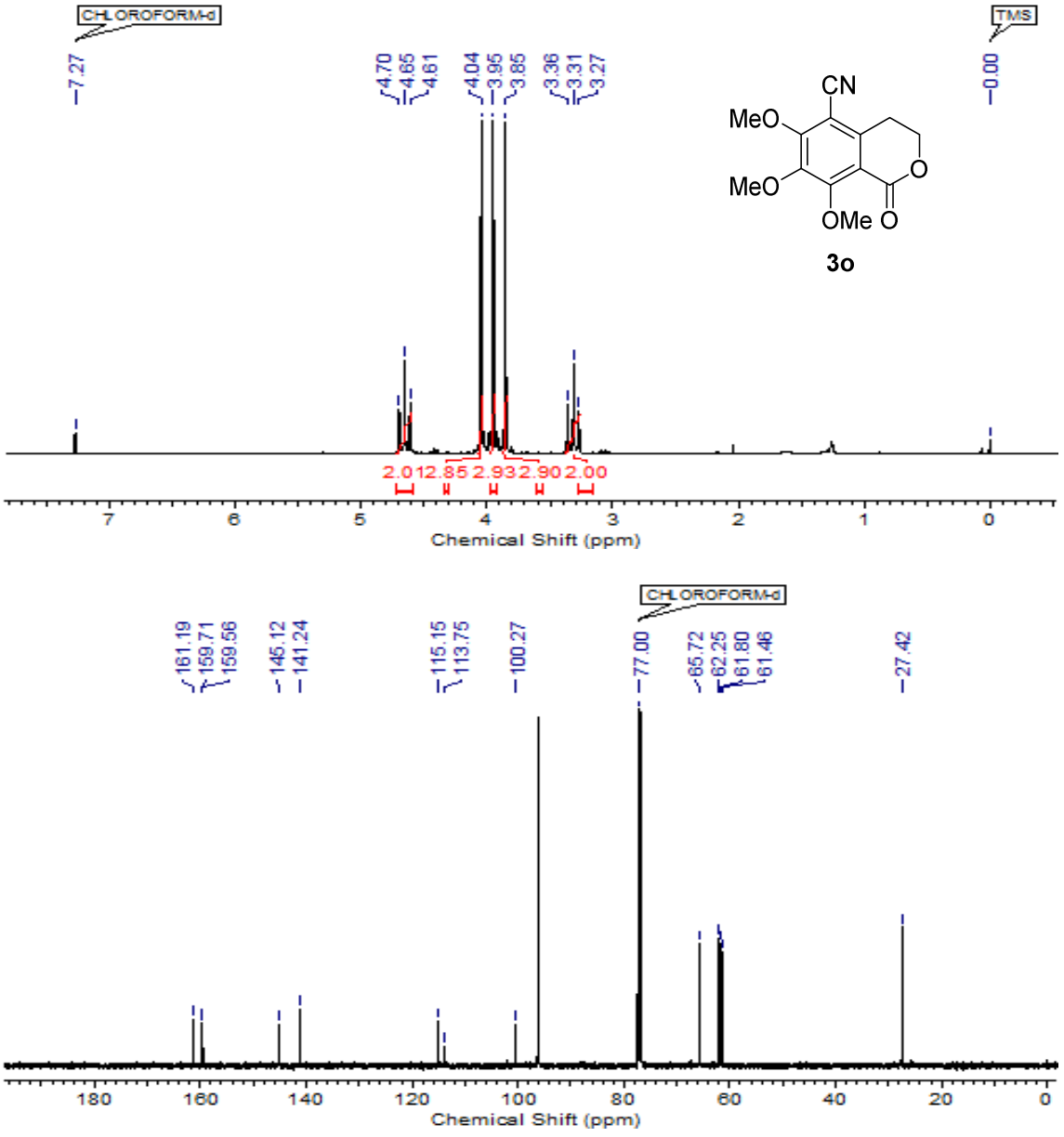


Fig. 1: ^{1}H and ^{13}C NMR spectra of **3o**

Example 2: The ^{1}H NMR spectrum of N-(2-chlorophenyl)benzamide (**3e**) shows a broad singlet at δ 8.46 (br. s, 1H) corresponding to –N**H** proton of amide while the ^{13}C NMR spectrum showed characteristic amide carbonyl carbon signal at δ 165.0 (**Fig. 2**).

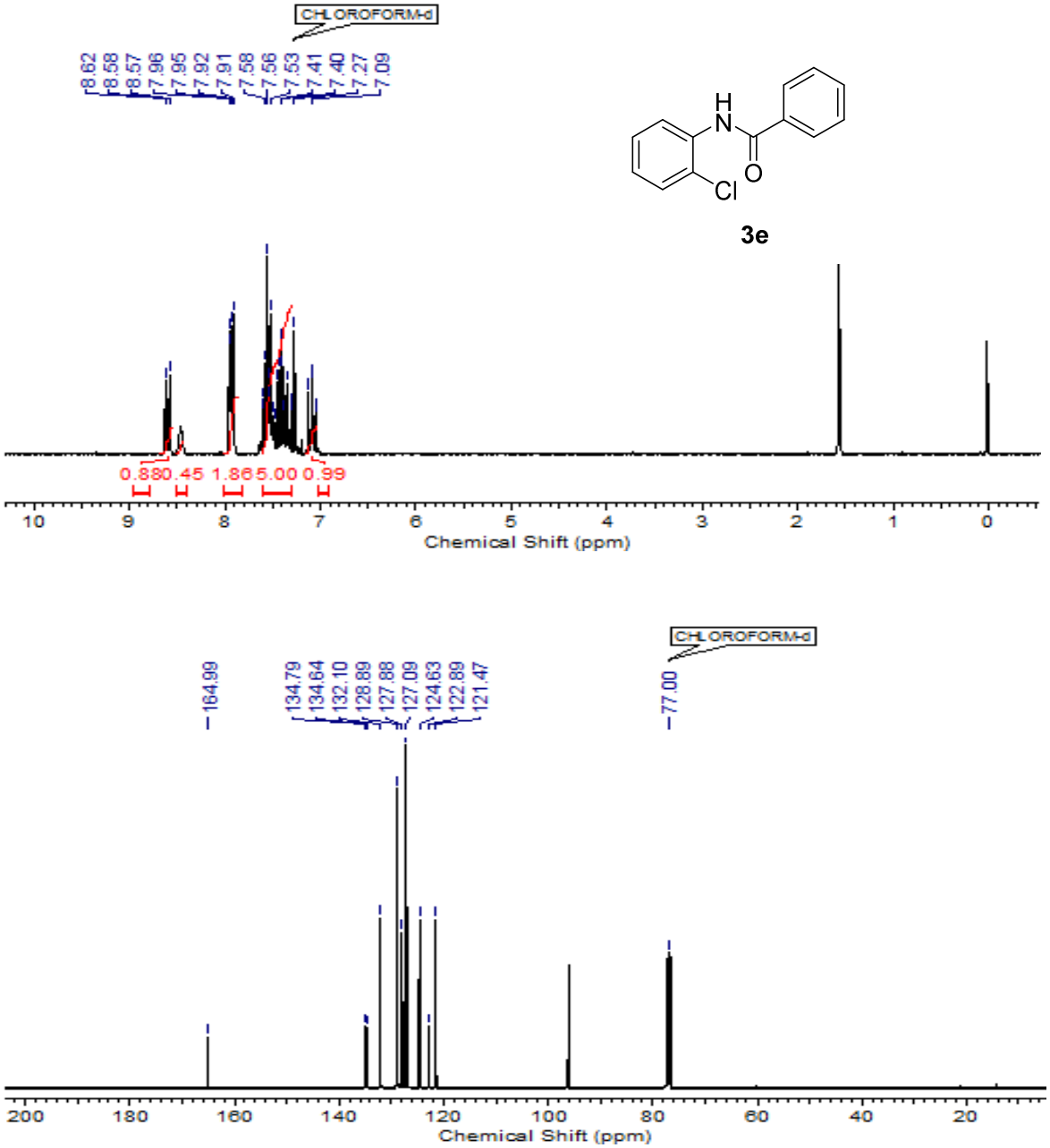


Fig. 2: ^{1}H and ^{13}C NMR spectra of **3e**

1.3.3.3 Mechanistic Discussion

In order to gain insight into the mechanistic details of the reaction, the following experiments were conducted: (a) when cyanobenzene (instead of bromobenzene) was subjected to the reaction conditions in the presence of phenol and CuBr catalyst, phenyl benzoate product **3a** was indeed obtained (78%) suggesting cyanobenzene as a possible intermediate formed in the course of the reaction; (b) carbonylative coupling reaction failed in the absence of CuBr catalyst suggesting the role of Cu(I) catalyst in activating the nitrile functionality for nucleophilic attack. Based on our control experiments and literature precedence,[21-22] a probable catalytic cycle has been proposed in **Fig**. **3**.

Mechanistically, Ar-X on oxidative addition with CuX forms arylCuX, which subsequently undergoes nucleophilic displacement with NaCN to generate ArCuCN (**I**).[21] Reductive elimination of ArCuCN produces ArCN (**II**) (isolated and characterized) which on σ - bond metathesis with nucleophiles (e.g. alcohols, phenols and amines) gives imine (**III**),[22] hydrolysis of which affords **3a-y** (**Fig. 3**).

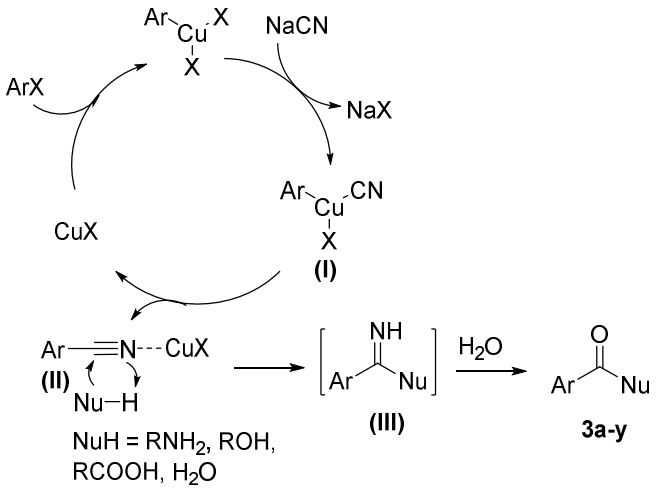


Fig. 3: Proposed catalytic cycle for carbonylative coupling reaction

1.1.4 Conclusion

In summary, we have developed a simple Cu-catalyzed protocol for the carbonylative coupling of aryl halides with a variety of nucleophiles and NaCN as C_1 source using 1,10-phenanthroline as ligand that provides for the synthesis of carboxylic acid derivatives in high yields (63-96%). Incorporation of the carbonyl moiety into organic molecules using a three component matrix with CN, an organic halide and a nucleophilic component constitutes a simple and diverse approach to the formation of benzoic acid derivatives. This transformation is very practical, as it could be conducted under air. We believe that this "CO-free" catalytic process will find tremendous applications in the commercial production of large volume chemicals such as aromatic carboxylic acids, esters, amides, lactones, anhydrides, coumarins, etc.

1.1.5 Experimental Section

General experimental procedure for the preparation of 1-(2-bromophenyl)alkenol (2k-n) and (2r-t):

To a stirred solution of substituted 2-bromobenzaldehyde or 2-(2-bromophenyl)acetaldehyde (5 mmol) in CH_3CN:H_2O (40 mL:10 mL) at 0 °C was added allyl bromide (6 mmol), activated Zn dust (6 mmol) and sat. NH_4Cl solution (10 mL). The reaction mixture was allowed to stir at room temperature for 2-3 h (monitored by TLC). The reaction mixture was then cooled to 0 °C and excess Zn was quenched with aq. NH_4Cl. CH_3CN was concentrated under reduced pressure and aqueous layer was diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (230-400 mesh) and petroleum ether: EtOAc (7:3) as an eluent to afford the corresponding 1-(2-bromophenyl)alkenols **1k-n** and **1r-t** in 80-92% yield.

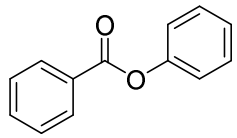
General experimental procedure for the preparation of carboxylic acid derivatives (3a-3j): To a stirred solution of haloarenes **1a-j** (3 mmol) and nucleophiles **2a-j** (3 mmol) in dry DMF (15 mL) was added NaCN (3.3 mmol), CuBr (0.3 mmol) and 1, 10-phenanthroline (0.3 mmol), the entire solution stirred at 120 °C under N_2 for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature and excess cyanide was quenched with aq. $NaClO_2$, diluted with water (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over

anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (230-400 mesh) and petroleum ether: EtOAc (7:3) as an eluent to afford corresponding esters and amides **3a-j** in 63-74% yield.

General experimental procedure for preparation of carboxylic acid derivatives (3k-3y):

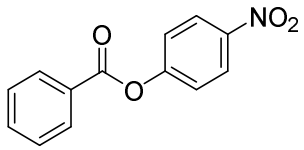
Procedure is the same as described for compounds **3a-j**

Phenyl benzoate (3a)



Yield: 74% (0.440 g, 2.222 mmol); Colorless solid; **mp:** 70 °C, (lit.[13] **mp**: 70-72 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 1080, 1260, 1500, 1718, 2980; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.18-7.30 (m, 3H), 7.39-7.53 (m, 4H), 7.58-7.67 (m, 1H), 8.20 (td, *J* = 1.7 and 6.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 121.7, 125.8, 128.5, 129.4, 129.7, 130.2, 133.5, 151.0, 164.9; **Analysis**: $C_{13}H_{10}O_2$ requires C, 78.77; H, 5.09; Found: C, 78.56; H, 5.34%.

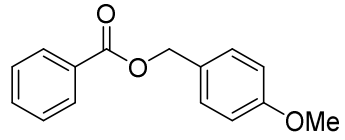
4-Nitrophenyl benzoate (3b)



Yield: 71% (0.517 g, 2.127 mmol); colorless solid; **mp:** 141 °C, (lit.[14] **mp**: 140-141ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 1060, 1206, 1340, 1530,1740, 3010; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.43 (td, *J* = 3.2 and 8.9 Hz, 2H), 7.50-7.61 (m, 2H), 7.70 (tt, *J*= 1.6 and 7.6 Hz, 1H), 8.19-8.24 (m, 2H), 8.34 (td, *J* = 3.2 and 8.9 Hz, 2H); **^{13}C NMR** (50 MHz,

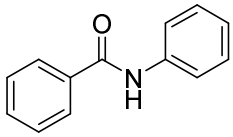
$CDCl_3$): δ 122.6, 125.2, 128.6, 128.8, 130.3, 134.2, 145.4, 155.7, 164.0; **Analysis**: $C_{13}H_9NO_4$ requires C, 64.20; H, 3.73; N, 5.76; Found: C, 64.46; H, 3.54; N, 5.67%.

4-Methoxybenzyl benzoate (3c)



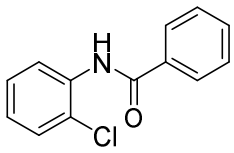
Yield: 76% (0.552 g, 2.280 mmol); Colorless solid; **mp**: 91 °C, (lit.[14] **mp**: 90-91 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 693, 1075, 1270, 1500, 1720, 2990; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.80 (s, 3H), 5.28 (s, 2H), 6.89 (td, *J* = 2.9 and 8.6 Hz, 2H), 7.35-7.45 (m, 4H), 7.53 (tt, *J* = 1.7 and 7.1 Hz, 1H), 8.04 (td, *J* = 1.7 and 7.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 66.4, 113.9, 128.2, 129.5, 129.6, 130.0, 130.3, 132.8, 159.6, 166.2; **Analysis**: $C_{15}H_{14}O_3$ requires C, 74.36; H, 5.82; Found: C, 74.35; H, 5.78%.

***N*-Phenylbenzamide (3d)**



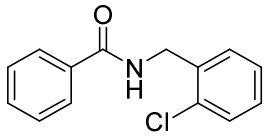
Yield: 68% (0.402 g, 2.040 mmol); colorless solid; **mp**: 163 °C, (lit.[13] **mp**: 162-163 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 780, 1305, 1430, 1530, 1600, 1670, 3330; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.63-6.77 (m, 2H), 7.13 (tt, *J* = 1.6 and 8.4 Hz, 2H), 7.32-7.65 (m, 5H), 7.86 (td, *J* = 1.6 and 6.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 120.2, 124.6, 127.1, 128.8, 129.1, 131.8, 135.1, 138.0, 165.5; **Analysis**: $C_{13}H_{11}NO$ requires C, 79.17; H, 5.62; N, 7.10; Found: C, 79.95; H, 5.54; N, 7.13%.

***N*-(2-Chlorophenyl)benzamide (3e)**



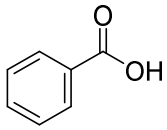
Yield: 70% (0.486 g, 2.099 mmol); colorless solid; **mp:** 101 °C, (lit.[15] **mp**: 100-102 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 788, 1310, 1415, 1510, 1600, 1680, 3310; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.07 (dt, *J* = 1.3 and 7.4 Hz, 1H), 7.29-7.59 (m, 5H), 7.93 (td, *J* = 1.3 and 6.1 Hz, 2H), 8.45 (br. s., 1H), 8.58 (dd, *J* = 1.6 and 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 121.5, 122.9, 124.6, 127.1, 127.9, 128.9, 128.9, 132.1, 134.6, 134.8, 165.0; **Analysis**: $C_{13}H_{10}ClNO$ requires C, 67.40; H, 4.35; Cl, 15.30; N, 6.05; Found: C, 67.87; H, 4.23; Cl, 15.18; N, 6.20%.

***N*-(2-Chlorobenzyl)benzamide (3f)**



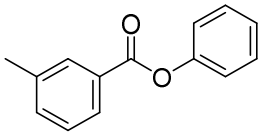
Yield: 71% (0.523 g, 2.130 mmol); colorless solid; **mp:** 99 °C, (lit.[14] **mp**: 98-99 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 688, 785, 1316, 1400, 1520, 1678, 3320; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.70 (d, *J* = 5.4 Hz, 2H), 6.73 (br. s., 1H) 7.20-7.26 (m, 2H), 7.35-7.52 (m, 5H), 7.77 (dd, *J* = 1.6 and 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 42.0, 127.0, 127.1, 128.6, 128.9, 129.6, 130.4, 131.5, 133.7, 134.3, 135.7, 167.2; **Analysis**: $C_{14}H_{12}ClNO$ requires C, 68.44; H, 4.92; Cl, 14.43; N 5.70; Found: C, 68.87; H, 4.23; Cl, 14.78; N 5.20%.

Benzoic acid (3g)



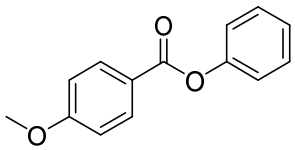
Yield: 70% (0.256 g, 2.098 mmol); colorless solid; **mp.** 123 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max}700, 1280, 1320, 1410, 1690, 3200; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 686, 1072, 1187, 1496, 1585, 1786, 3071, 3542; **^{1}H NMR** (400 MHz, acetone-d_6): δ ppm 7.43-7.48 (m, 2H), 7.50-7.55 (m, 1H), 7.93-7.96 (m, 2H); **^{13}C NMR** (50 MHz, acetone-d_6): δ 30.2, 128.3, 129.1, 132.1, 135.3, 169.1; **Analysis**: $C_7H_6O_2$ requires C, 68.85; H, 4.95; Found: C, 68.82; H, 4.97%.

Phenyl 3-methylbenzoate (3h)



Yield: 68% (0.433 g, 2.041 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 697, 1077, 1272, 1516, 1728, 2993; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.16-7.30 (m, 3H), 7.34-7.46 (m, 4H), 7.98-8.01 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.0, 121.5, 125.5, 127.0, 128.2, 129.1, 129.2, 130.4, 134.0, 137.9, 150.8, 164.7; **Analysis**: $C_{14}H_{12}O_2$ requires C, 79.23; H, 5.70; Found: C, 79.12; H, 5.97%.

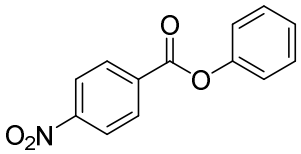
Phenyl 4-methoxybenzoate (3i)



Yield: 71% (0.485 g, 2.130 mmol); colorless solid; **mp:** 70 °C, (lit.[14] **mp**: 69-71ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 1067, 1212, 1343, 1534, 1738, 3011; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.97 (d, J = 9.1 Hz, 2H), 7.15-7.29 (m, 3H), 7.35-7.46 (m, 2H);

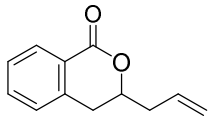
^{13}C NMR (125 MHz, $CDCl_3$): δ 55.4, 113.8, 121.8, 123.2, 125.7, 129.4, 132.3, 151.1, 163.9, 164.7; **Analysis**: $C_{14}H_{12}O_3$ requires C, 73.67; H, 5.30; Found: C, 73.75; H, 5.13%.

Phenyl 4-nitrobenzoate (3j)



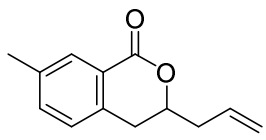
Yield: 71% (0.518 g, 2.130 mmol); colorless solid; **mp:** 128 ºC, (lit.[14] **mp**: 127-128 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 693, 1058, 1207, 1343, 1532,1738, 3007; **^{1}H NMR** (200 MHz, $CDCl_3$): δ ppm 7.16-7.50 (m, 5H), 8.36 (s, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 122.8, 123.8, 129.8, 131.3, 131.9, 134.6, 148.9, 151.0, 162.9; **Analysis**: $C_{13}H_9NO_4$ requires C, 64.20; H, 3.73; N, 5.76; Found: C, 64.38; H, 3.52; N, 5.81%.

3-Allylisochroman-1-one (3k)



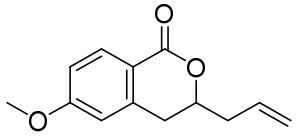
Yield: 86% (0.474 g, 2.521 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 745, 917, 1118, 1281, 1733, 2918, 3077; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45-2.72 (m, 2H) 2.87-3.07 (m, 2H), 4.51-4.62 (m, 1H), 5.13-5.24 (m, 2H), 5.79-5.97 (m, 1H), 7.21-7.56 (m, 3H), 8.07 (dd, J = 0.8 and 7.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 32.5, 39.2, 77.6, 118.8 , 125.2, 127.3, 127.6, 130.3, 132.3, 133.6, 138.9, 164.9; **HRMS** (ESI+, *m/z*): calcd for $(C_{12}H_{12}O_2)^+$ [$(M+Na)^+$] 211.0727; found: 211.0730.

3-Allyl-7-methylisochroman-1-one (3l)



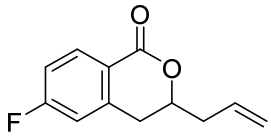
Yield: 86% (0.521g, 2.579 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 774, 921, 1082, 1194, 1733, 2923, 3078; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.51-2.68 (m, 2H), 2.82-2.94 (m, 2H), 4.48-4.61 (m, 1H), 5.12-5.23 (m, 2H), 5.77-6.00 (m, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.90 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.9, 32.1, 39.2, 77.7, 118.7, 124.8, 127.2, 130.4, 132.4, 134.4, 135.9, 137.3, 165.2; **HRMS** (ESI+, *m/z*): calcd for $(C_{13}H_{14}O_2)^+$ [$(M+Na)^+$] 225.0884; found: 225.0886.

3-Allyl-6-methoxyisochroman-1-one (3m)



Yield: 87% (0.569 g, 2.610 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 917, 1027, 1260, 1606, 1736, 2920, 3076; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.48-3.04 (m, 4H), 3.86 (s, 3 H), 4.49-4.60 (m, 1H), 5.16-5.24 (m, 2H), 5.83-6.00 (m, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 2.4 and 8.3 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.7, 39.1, 55.4, 77.4, 112.0 113.4, 117.5, 118.7, 132.3, 132.4, 141.2, 163.7, 165.3; **HRMS** (ESI+, *m/z*): calcd for $(C_{13}H_{14}O_3)^+$ [$(M+Na)^+$] 241.0831; found: 241.0835.

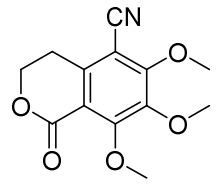
3-Allyl-6-fluoroisochroman-1-one (3n)



Yield: 88% (0.536 g, 2.640 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 755, 1107, 1267, 1615, 1735, 2919, 3079; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45-2.72 (m, 2H) 2.84-3.08 (m, 2H), 4.51-4.65 (m, 1H), 5.16-5.25 (m, 2H), 5.78-5.99 (m, 1H), 6.93 (dd, *J* = 2.3 and 8.1 Hz, 1H), 7.06 (dt, *J* = 2.3 and 8.1 Hz, 1H), 8.10 (dd, *J* = 5.6 and 8.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 32.6, 39.1, 77.5, 114.3, 115.3, 119.1, 121.5, 132.1, 133.3,

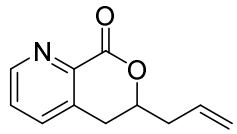
141.9, 164.0, 166.8; **HRMS** (ESI+, *m/z*): calcd for $(C_{12}H_{11}O_2F)^+$ $[(M+Na)^+]$ 229.0632; found: 229.0635.

6,7,8-Trimethoxy-1-oxoisochromane-5-carbonitrile (3o)



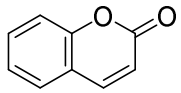
Yield: 84% (0.663g, 2.520 mmol); yellowish solid; **mp:** 107 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 802, 1036, 1130, 1579, 1677, 1733, 2922, 2949; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.31 (t, *J* = 8.5 Hz, 2H), 3.85 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 4.65 (t, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 27.4, 61.4, 61.8, 62.2, 65.7, 100.3, 113.8, 115.2, 141.2, 145.1 , 159.6, 159.7, 161.2; **HRMS** (ESI+, *m/z*): calcd for $(C_{13}H_{13}NO_5)^+$ $[(M+Na)^+]$ 286.0691; found: 286.0693.

6-Allyl-5,6-dihydro-8H-pyrano[3,4-b]pyridin-8-one (3p)



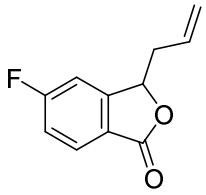
Yield: 84% (0.476 g, 2.518 mmol); yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 805, 1039, 1133, 1584, 1619, 1737, 2921, 2953; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.29-2.73 (m, 4H), 5.05-5.19 (m, 2H), 5.23 (s, 1H), 5.79-5.96 (m, 1H), 7.27 (dd, *J* = 4.9 and 7.6 Hz, 1H), 7.92 (dd, *J* = 1.5 Hz and 7.6 Hz, 1H), 8.28 (dd, *J* = 1.5 and 4.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 40.4, 42.0, 69.3, 118.9, 122.4, 133.3, 134.0, 140.4, 147.7, 151.5; **Analysis**: $C_{11}H_{11}O_2N$ requires C, 73.97; H, 4.14; Found: C, 73.94; H, 4.17%.

2*H*-Chromen-2-one (3q)



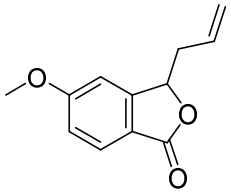
Yield: 81% (0.355 g, 2.430 mmol); colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 820, 1104, 1180, 1610, 1710, 3030; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.43 (d, *J* = 9.4 Hz, 1H), 7.28-7.57 (m, 4H), 7.77 (d, *J* = 9.4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 116.7, 116.9, 118.8, 124.4, 127.8, 131.8, 143.5, 154.0, 160.8; **Analysis**: $C_9H_6O_2$ requires C, 73.97; H, 4.14; Found: C, 73.94; H, 4.17%.

3-Allyl-5-fluoroisobenzofuran-1(3*H*)-one (3r)



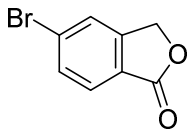
Yield: 92% (0.530 g, 2.760 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 988, 1100, 1247, 1483, 1604, 1624, 1766, 3100; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.62-2.78 (m, 2H), 5.12-5.25 (m, 2H), 5.48 (t, *J* = 6.1 Hz, 1H), 5.65-5.86 (m, 1H), 7.12-7.28 (m, 2H), 7.89 (dd, *J* = 4.8 and 8.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.2, 79.2, 109.3, 117.2, 119.8, 122.2, 127.8, 130.6, 151.9, 163.6, 168.7; **Analysis**: $C_{11}H_9FO_2$ requires C, 68.75; H, 4.72; F, 9.89; Found: C, 68.82; H, 4.97%.

3-Allyl-5-methoxyisobenzofuran-1(3*H*)-one (3s)



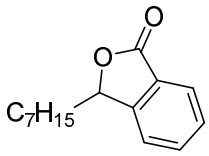
Yield: 85% (0.518 g, 2.551mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 692, 1073, 1103, 1259, 1605, 1744, 2997; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.56-2.81 (m, 2H), 3.91 (s, 3H), 5.15-5.25 (m, 2H), 5.42 (t, *J* = 6.1 Hz, 1H), 5.68-5.89 (m, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 7.02 (dd, *J* = 1.6 and 8.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.8, 55.7, 79.3, 106.1, 116.2, 118.7, 119.6, 127.2, 131.3, 152.0, 164.5, 169.8; **Analysis**: $C_{12}H_{12}O_3$ requires C, 70.58; H, 5.92; Found: C, 70.61; H, 5.67%.

5-Bromoisobenzofuran-1(3*H*)-one (3t)



Yield: 78% (0.498 g, 2.338 mmol); colorless solid; **mp**: 162 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 593, 1077, 1236, 1378, 1599, 1747, 3012; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.30 (s, 2H), 7.68 (t, *J* = 3.7 Hz, 2H), 7.77-7.81 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 68.8, 124.9, 125.6, 127.1, 129.2, 132.7, 148.2, 169.7; **Analysis**: $C_8H_5BrO_2$ requires C, 45.11; H, 2.37; Br 37.51; Found: C, 45.65; H, 2.24; Br, 38.13%.

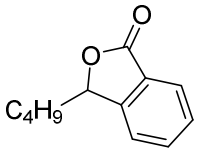
3-Heptylisobenzofuran-1(3*H*)-one (3u)



Yield: 91% (0.633 g, 2.728 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 767, 828, 1056, 932, 1130, 1275, 1534, 1625, 1768, 2938, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 3.5 Hz, 3H), 1.27-1.47 (m, 10H), 1.66-1.82 (m, 1H), 1.96-2.12 (m, 1H), 5.46

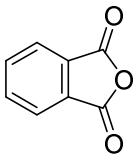
(dd, *J* = 4.0 and 7.4 Hz, 1H), 7.41-7.55 (m, 2H), 7.66 (dt, *J* = 1.6 and 7.6 Hz, 1H). 7.88 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.5, 24.8, 29.0, 29.3, 31.7, 34.7, 81.2, 121.6, 125.6, 126.2 128.9, 133.8, 150.0, 170.3; **Analysis**: $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68; Found: C, 77.58; H, 8.71%.

3-Butylisobenzofuran-1(3H)-one (3v)



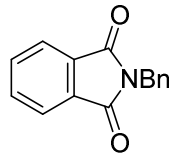
Yield: 87% (0.496 g, 2.610 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 679, 753, 888, 935, 1068, 1145, 1276, 1320, 1545, 1615, 1773, 2928, 3033; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.3 Hz, 3H), 1.26-1.52 (m, 4H), 1.71-1.82 (m, 1H), 1.98-2.12 (m, 1H), 5.46 (dd, *J* = 4.1 and 7.2 Hz, 1H), 7.50 (dd, *J* = 7.2 and 9.8 Hz, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 22.4, 26.8, 34.4, 81.1, 121.6, 125.6, 126.2, 128.9, 133.8,150.0, 170.2; **Analysis**: $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42; Found: C, 75.54; H, 7.57%.

Isobenzofuran-1,3-dione (3w)



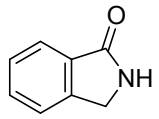
Yield: 96% (0.426 g, 2.878 mmol); colorless solid; **mp:** 131 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 758, 1052, 1307, 1604, 1748, 1772, 2924; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 2.0 and 6.0 Hz, 2H), 7.89 (dd, *J* = 2.0 and 6.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 123.6, 132.7, 134.28, 167.7; **HRMS** (ESI+, *m/z*): calcd for $(C_8H_5O_3)^+$ 149.0232; found: 149.0233.

2-Benzylisoindoline-1,3-dione (3x)



Yield: 73% (0.396 g, 2.187 mmol); colorless solid; **mp:** 115 °C; **IR** ($CHCl_3$, cm^{-1}): 717, 1062, 1331, 1391, 1453, 1715, 1764, 2853, 2924; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.84 (s, 2 H), 7.24-7.45 (m, 5H), 7.69 (dd, *J* = 2.9 and 5.6 Hz, 2H), 7.84 (dd, *J* = 2.9 and 5.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 41.6, 123.3, 127.8, 128.7, 132.2, 133.9, 136.4, 167.9; **HRMS** (ESI+, *m/z*): calcd for $(C_{15}H_{11}O_2NNa)^+$ $[(M+Na)^+]$ 260.0678; found: 260.0682.

Isoindolin-1-one (3y)



Yield: 81% (0.323 g, 2.430 mmol); colorless solid; **mp:** 150 °C, (lit. **mp**: 151 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 1013, 1205, 1378, 1598, 1689, 3298; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.41 (s, 2H), 7.41-7.53 (m, 4H), 7.81 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 45.7, 123.2, 123.7, 128.0, 131.7, 132.1, 143.6, 172.0; **HRMS** (ESI+, *m/z*): calcd for $C_8H_7NONa^+$ $[(M+Na)^+]$ 156.0425; found:156.0424.

Section II

Enantioselective Syntheses of (-)-Herbaric acid and (-)-Isocladosporin *via* CuBr Catalyzed Carbonylative Coupling Strategy

1.2.1 Introduction

Chiral phthalides [isobenzofuran-1(3*H*)-ones] **6** and isochroman-1-ones **7** are found in a large number of plant products displaying broad and potent biological activities.[23] Representative examples include herbaric acid (**6a**), hydrastine (**6b**)**,** fuscinarin (**6c**), virgatolide A (**6d**), 3-butylphthalide (**6e**), alcyopterosin (**6f**), matteucin A (**7a**), cladosporin (**7b**), and isocladosporin (**7c**) (**Fig. 4**). (-)-Herbaric acid was isolated[24] from fungus *Cladosporium herbarum* in 2002 while (-)-isocladosporin was isolated from *Cladosporium cladosporioides* in 1993.[25]

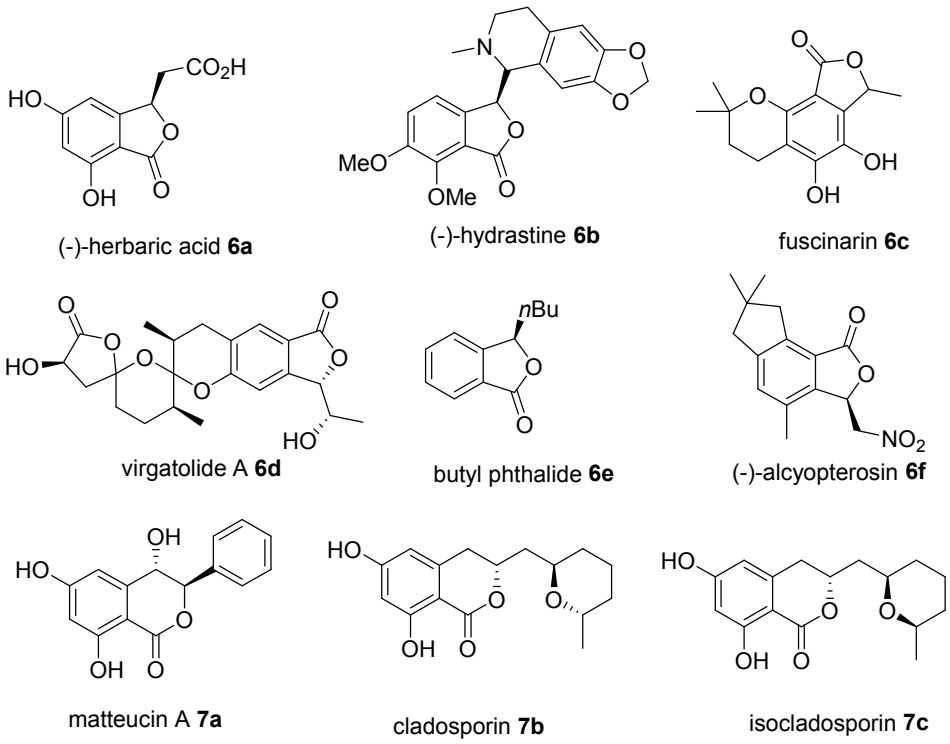


Fig. 4: Biologically active naturally occurring lactones

1.2.2 Pharmacology of (-)-Herbaric acid and (-)-Isocladosporin

(-)-Herbaric acid **(6a)** is the 5-hydroxyl derivative of the known toxin iso-ochracinic acid[26] previously isolated from *Alternaria kikuchiana*, a parasite responsible for the black spot disease on Japanese pears. It is also related to acetophthalidin,[27] a cytotoxic metabolite produced by *Aspergillus fumigatus*. It is interesting to note that the two strains of *C. herbarum* isolated from two different sponges differ completely with regard to the secondary compounds produced. (-)-Isocladosporin (**7c**) exhibits antifungal properties against plant pathogens.[28] It shows 50.4, 60.2, and 83.0% growth inhibition at 30 μM against *Colletotrichum fragariae*, *Colletotrichum gloeosporioides*, and *Phomopsis viticola* respectively.

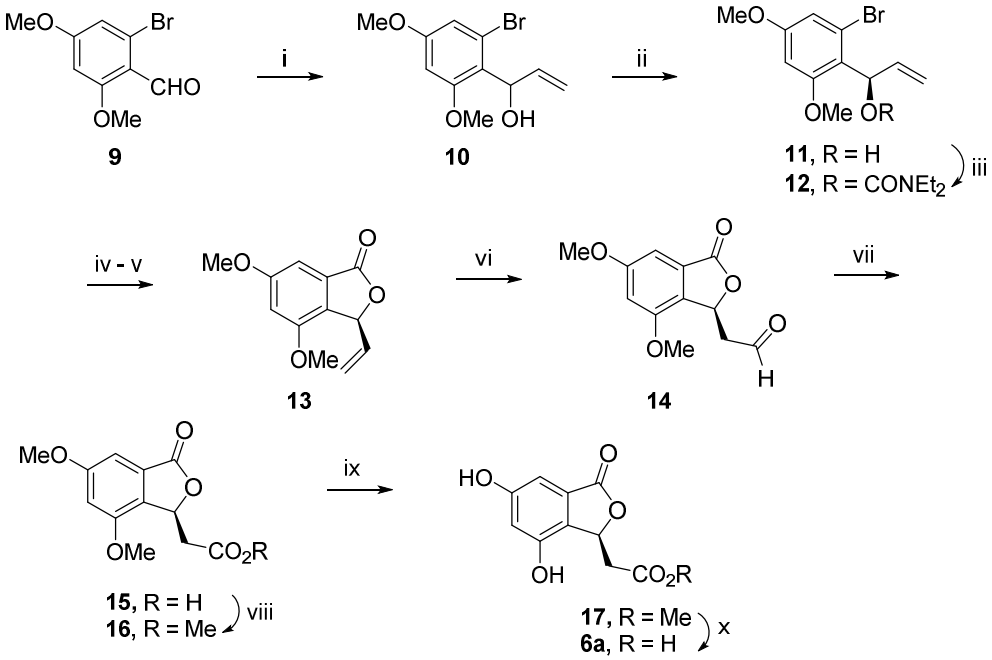
1.2.3 Review of Literature

1.2.3.1 Review of Literature for (-)-Herbaric acid

In literature, by far there are two methods available for the synthesis of (-)-herbaric acid (**6a**).

Brimble's approach (2010)[29]

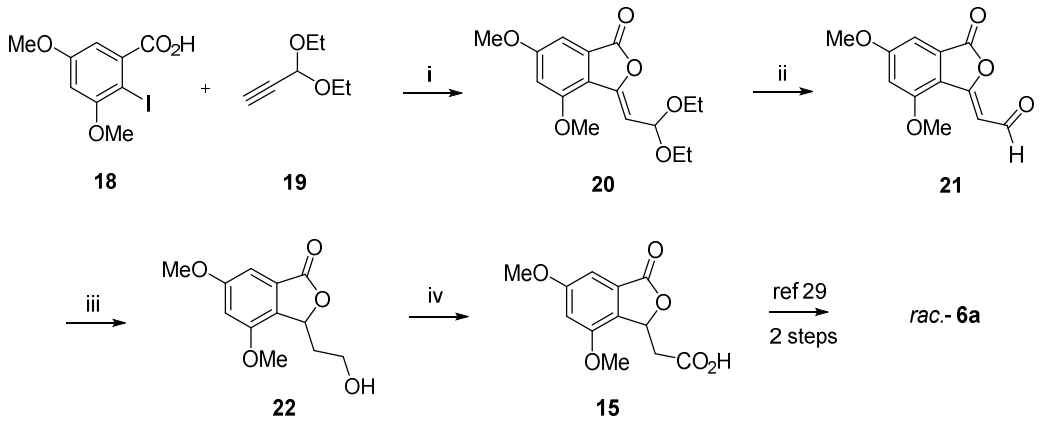
Brimble *et al*. have reported the first total synthesis of (-)-herbaric acid comprising of 10 linear steps. The synthesis commenced with vinylation of 2-bromo-3,5-dimethoxybenzaldehyde (**9**) followed by microwave-assisted chemoenzymatic resolution of allylic alcohol **10** to install the stereocenter in compound **11**. The free hydroxyl group was then protected as its carbamate followed by acid mediated cyclization to afford vinylphthalide core **13** which was further subjected to the heteroatom directed reverse Wacker oxidation, thus furnishing aldehyde **14**. Compound **14** was then oxidized with Oxone followed by final demethylation of methyl ethers with BBr_3 to yield target molecule **6a** (**Scheme 9**).



Scheme 9: (i) vinylmagnesium bromide (2 equiv), THF, -78 °C, 12 h, 85%; (ii) novozyme 435, *p*-chlorophenylacetate, toluene, MW, 55 °C, 48 h, 50%, 84% ee; (iii) CDI, Et_2NH, 90%; (iv) *n*-BuLi (1.1 equiv), THF; (v) HCl, dioxane, 74% for two steps; (vi) $PdCl_2$, CuCl, O_2, DMF-H_2O, 86%; (vii) oxone, DMF, 89%; (viii) H_2SO_4, MeOH, 82%; (ix) BBr_3, CH_2Cl_2, 77%; (x) NaOH, MeOH-H_2O, 85%.

Petrignet's approach (2014)[30]

Petrignet *et al.* have reported the formal synthesis of (±)-herbaric acid employing Cu-catalysed Sonogashira coupling/oxacyclization process as the key step in the synthesis affording the phthalide core. The synthesis commenced with Cu-catalyzed Sonogashira coupling of 2-iodo-3,5-dimethoxybenzoic acid (**18**) and 3,3-diethoxyprop-1-yne (**19**) to afford phthalide core **20** in one step followed by acid catalyzed acetal deprotection to afford α,β-unsaturated aldehyde **21**. Compound **21** was then subjected to a reduction-oxidation-deprotection sequence to afford (±)-herbaric acid (**6a**) (**Scheme 10**).



Scheme 10: (i) CuI (20 mol %), K_2CO_3 (3 equiv), DMF, 80 °C, 16 h; (ii) *p*TSA, THF:H_2O, 25 °C, 2 h, 74% (2 steps); (iii) H_2 (1 atm), Pd/C, EtOH, 25 °C, 4 h, 82%; (iv) CrO_3, H_2SO_4, acetone, 0 °C, 2 h, 72%.

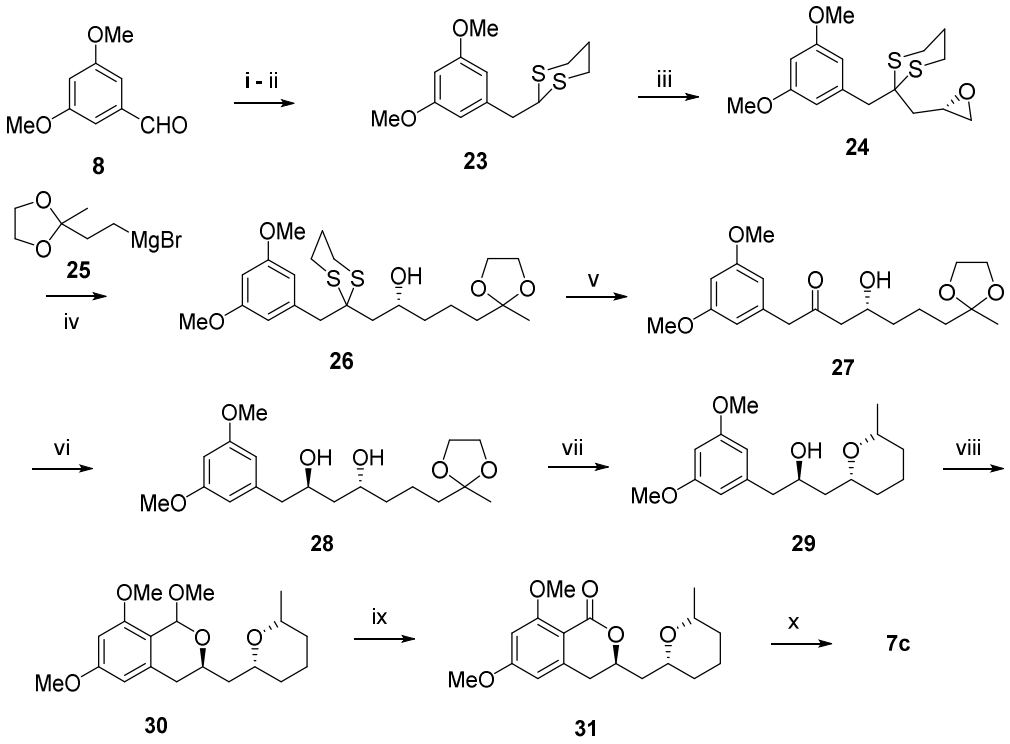
1.2.3.2 Review of Literature for (-)-Isocladosporin

In literature by far there is only one report known for the synthesis of (-)-isocladosporin, which is described below.

She's approach (2012)[31]

She *et al*. have reported the first total synthesis of (-)-isocladosporin from (*S*)-epichlorohydrin as chiral source in 10 linear steps. The synthesis commenced with protection of 3,5-dimethoxybenzaldehyde (**8**) using 1,3-propanedithiol to afford dithiane derivative **23**. Treatment of **23** with ^{t}BuLi in THF followed by the ring-opening of (*S*)-epichlorohydrin and concurrent epoxide formation afforded **24**. The ring-opening of epoxide **24** with Grignard reagent **25** afforded alcohol **26**. Deprotection of the 1,3-dithiane group in **26** with $I_2/CaCO_3$ and reduction of the formed β-hydroxy ketone **27** with $Me_4NBH(OAc)_3$ gave the desired 1,3-*anti*-diol **28**. Treatment of **28** with an excess of Et_3SiH (5 equiv) followed by TMSOTf (1.3 equiv) in CH_2Cl_2 at 0 °C led to the rapid formation of the 2,6-*cis*-THP derivative **29** as the sole diastereomer. The remaining steps involving oxa-Pictet-Spengler reaction, Jones oxidation, and deprotection of both the aromatic methyl ether functionalities were

carried out following standard procedures to afford the target molecule **7c** (**Scheme 11**).



Scheme 11: (i) Ph_3PCH_2OMeCl, LDA, THF, 0 °C, 3 h; (ii) 1,3-propanedithiol, BF_3. Et_2O, CH_2Cl_2, -10 °C, 79% for two steps; (iii) ^{t}BuLi, THF, -30 °C then (*S*)-epichlorohydrin, -30 °C to 25 °C, 77%; (iv) CuI, **25**, THF, -30 °C, 93%; (v) I_2, $CaCO_3$, THF/H_2O, 0 °C, 88%; (vi) $Me_4NBH(OAc)_3$, CH_3CN:AcOH, -30 °C, 91%; (vii) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C, 93%; (viii) $CH(OMe)_3$, *p*TSA, CH_2Cl_2, 25 °C, 95%; (ix) CrO_3, H_2SO_4, acetone, 25 °C, 74%; (x) AlI_3, TBAI, phloroglucinol, benzene, 0 °C, 89%.

1.2.4 Present Work

1.2.4.1 Objective

As can be seen, the reported methods for the synthesis of (-)-herbaric acid (**6a**) and (-)-isocladosporin (**7c**) rely on either resolution techniques (in which one of the enantiomers remains unutilised) or chiral starting materials. Again, the formation of lactone core warrants the use of strong acidic or basic reaction conditions. Thus, there is a need for an efficient and highly enantioselective synthesis of the key lactone core in phthalides and isochroman-1-ones in lesser number of steps, circumventing some of the disadvantages associated with the reported methods. Also no method is reported so far for their synthesis using asymmetric allylation strategy. In this section, we describe enantioselective synthesis of (-)-herbaric acid (**6a**) and (-)-isocladosporin (**7c**) using asymmetric Brown's allylation protocol for chirality induction and CuBr catalyzed carbonylative coupling strategy for the installation of lactone core.

Retrosynthetic analysis of (-)-herbaric acid (**6a**) is outlined in **Fig. 5**. It can be synthesized from oxidative cleavage of terminal olefinic compound **33** which in turn can be obtained by CuBr catalyzed carbonylative coupling of homoallylic alcohol **32**. The chiral homoallylic alcohol **32** can be obtained from the corresponding aldehyde **9** by asymmetric allylation protocol. Similar strategy can be applied for (-)-isocladosporin (**7c)** which can be formed from homoallylic alcohol **40** through an oxonium-ene cyclisation for the stereoselective construction of the 2,6-*cis*-disubstituted tetrahydropyran unit using acetaldehyde. The chiral homoallylic alcohol can be installed by chelation controlled diastereoselective allylation reaction of aldehyde **39** which in turn can be derived from homoallylic alcohol **37** *via* carbonylative coupling protocol. The chiral alcohol **37** can be obtained by the asymmetric allylation reaction of formed aldehyde from the acidic hydrolysis of enol

ether **36.** The methyl vinyl ether **36** can be derived from 3,5- dimethoxybenzaldehyde (**8**) using Wittig olefination reaction (**Fig. 5**).

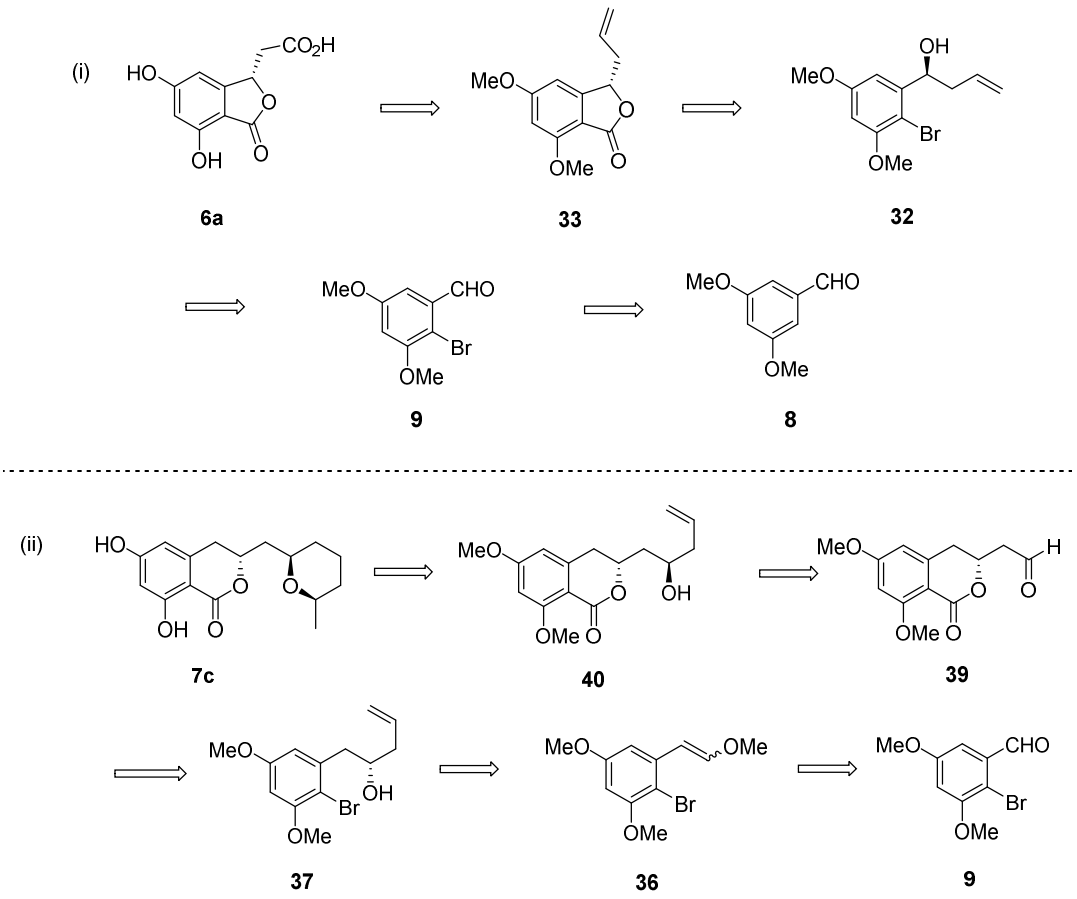
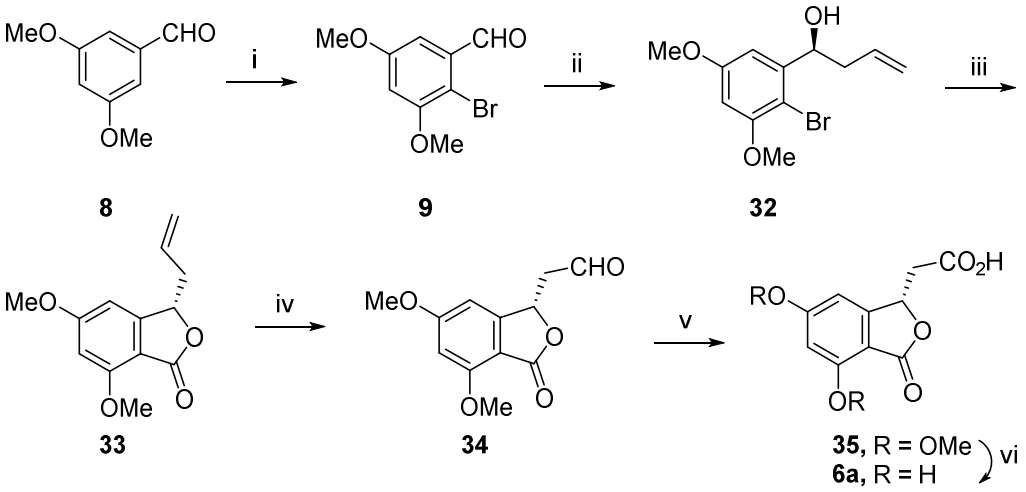


Fig. 5: Retrosynthetic analysis of (-)-herbaric acid (**6a**) and (-)-isocladosporin (**7c**)

1.2.5 Results and Discussion

1.2.5.1 Synthesis of (-)-Herbaric acid (6a)

The complete synthetic sequence for (-)-herbaric acid (**6a**) wherein CuBr catalyzed carbonylative coupling reaction[32] and asymmetric Brown allylation reaction[33] constitute the key steps is presented in **Scheme 12**.



Scheme 12: (i) NBS (1.1 equiv), CH_3CN:H_2O (4:1), 25 °C, 4 h, 96%; (ii) (-)-Ipc_2B(allyl)borane, Et_2O, -78 ºC, 1 h then 1N NaOH, 30% aq. H_2O_2, 80%, 90% ee; (iii) CuBr (10 mol %), 1,10- phenanthroline (10 mol %), NaCN (1.1 equiv), DMF, 110 ºC, 12 h, 86%; (iv) K_2OsO_4 (1 mol %), NMO, acetone:H_2O (4:1), 25 °C, 12 h, then $NaIO_4$ on silica, 86%; (v) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, THF:H_2O:^{t}BuOH (1:1:1), 25 °C, 89%; (vi) BBr_3, CH_2Cl_2, -10 °C, 78%.

Our synthesis of (-)-herbaric acid (**6a**) commenced with bromination of commercially available 3,5-dimethoxybenzaldehyde (**8**) using *N*-bromosuccinimide. The reaction was highly regioselective affording 2-bromo-3,5-dimethoxybenzaldehyde (**9**) as the only product in 96% isolated yield, owing to the activator methoxy groups at *ortho* and *para* positions to the incoming bromine electrophile. The bromo product showed two typical *meta* coupled protons at δ 6.70 (d, J = 2.8 Hz, 1H) and δ 7.03 (d, J = 2.8 Hz, 1H) in its proton NMR spectrum. The structure was further corroborated by its ^{13}C NMR spectrum that showed aldehydic carbonyl carbon signal at δ 191.7 (**Fig. 6**). Its IR spectrum showed an absorption band at 670 cm^{-1} characteristic of C-Br stretch. Accordingly, the obtained brominated aldehyde **9** was allylated using Brown's protocol of asymmetric allylation using (-)-Ipc_2B(allyl)borane reagent, which afforded chiral alcohol **32** in 80% yield and 90% ee (determined by chiral HPLC analysis). The ^{1}H NMR spectrum of the product **32** showed typical *meta* coupled aromatic protons as

two doublets at δ 6.37 (d, *J* = 2.8 Hz, 1H) and 6.73 (d, *J* = 2.8 Hz, 1H) integrating for one proton each. The benzylic proton signal appeared as doublet of doublet at δ 5.20

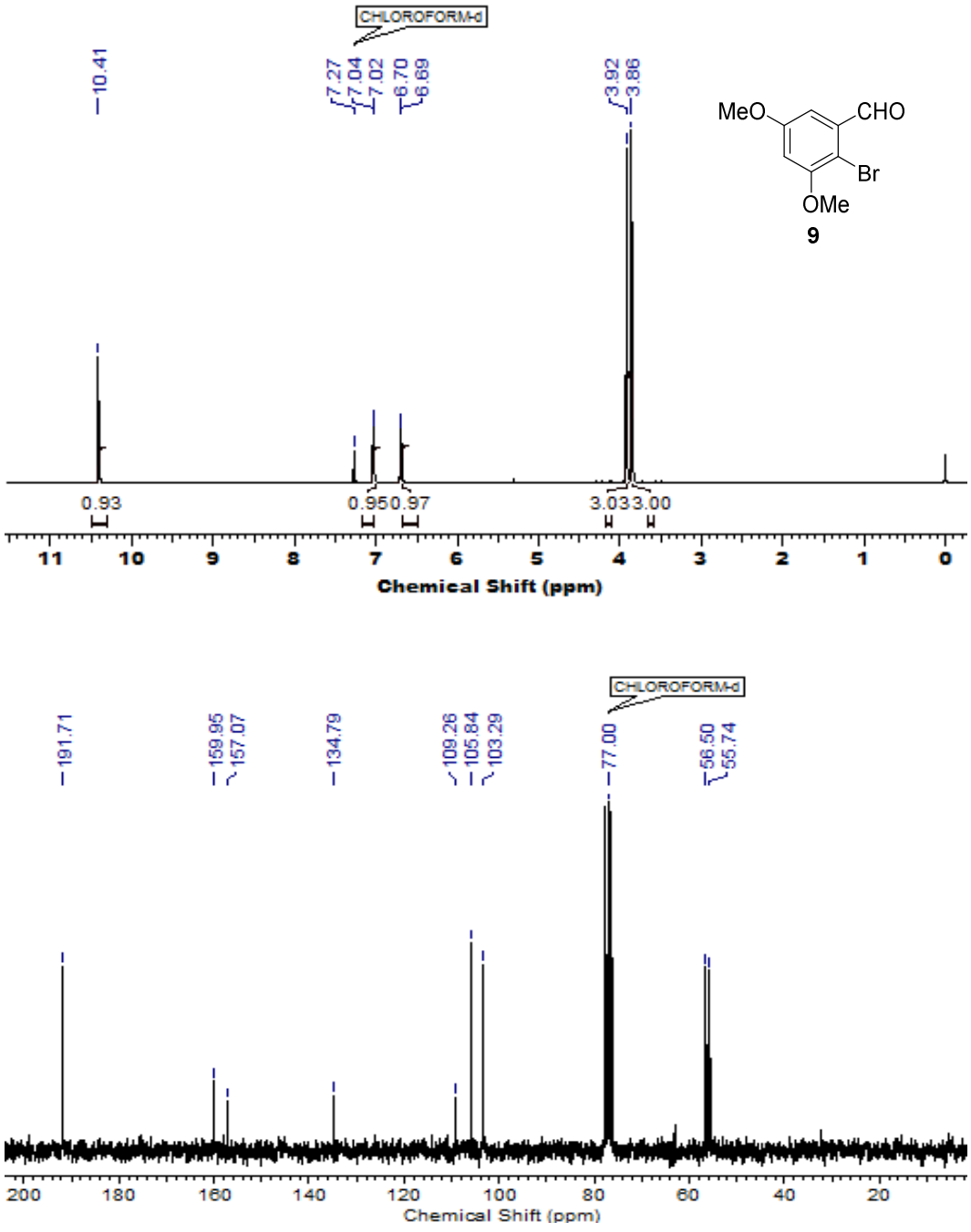
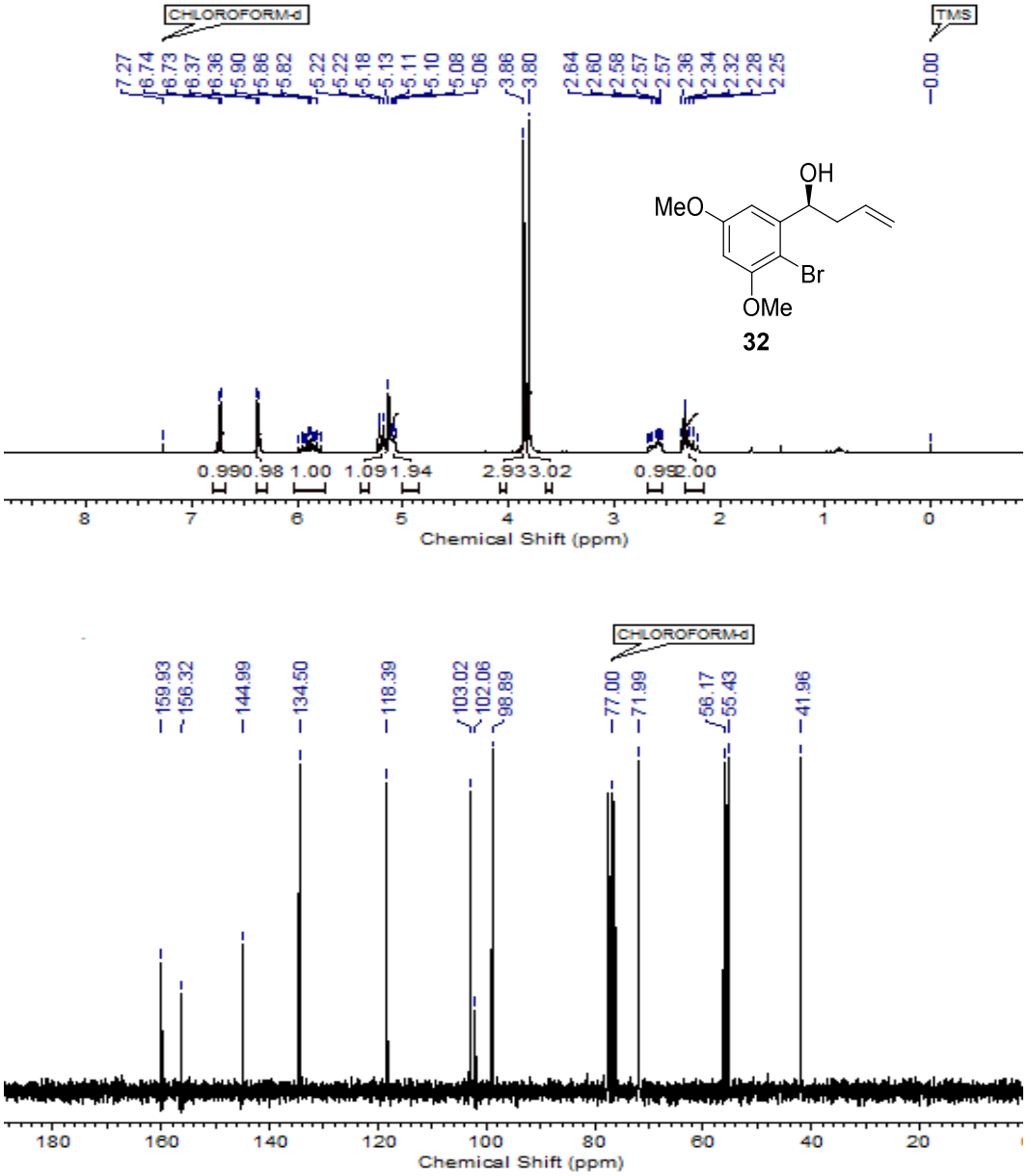
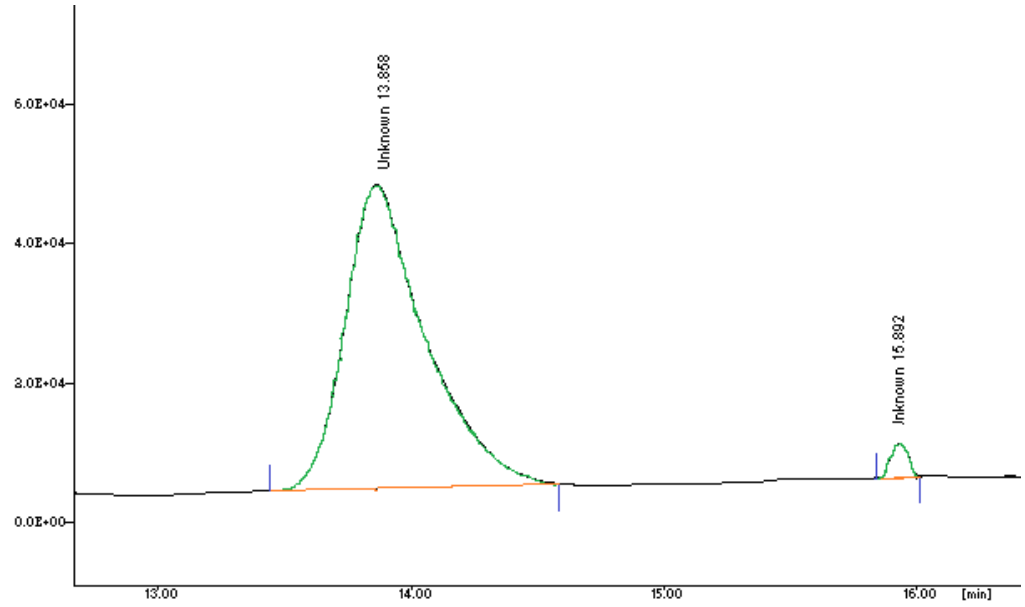


Fig. 6: ^{1}H and ^{13}C NMR spectra of **9**

(dd, J = 7.6, 1.1 Hz, 1H) while typical olefinic protons signals displayed as multiplets between δ 5.02-5.17 (m, 2H) and 5.74-6.02 (m, 1H) due to allylic couplings. The ^{13}C NMR spectrum showed olefinic carbon signals at δ 118.3 and 134.5 while benzylic carbon signal appeared at δ 72.0. The enantioselectivity of the chiral alcohol **32** was found to be 90% ee as determined from chiral HPLC analysis (**Fig. 7**).





Peak No.	Retention Time (min)	Area [µV.sec]	% Area
1	13.858	2830483.324	95.264
2	15.892	140716.000	4.736

Fig. 7: ^{1}H, ^{13}C NMR spectra and HPLC chromatogram of **32**

The homoallylic alcohol **32** was then subjected to our CuBr catalyzed lactonisation in presence of sodium cyanide to afford the enantiomerically enriched 3-substituted phthalide **33**. The formed product was thoroughly characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS. Its proton NMR spectrum showed a characteristic peak at δ 5.24 (t, J = 5.8 Hz, 1H) corresponding to the benzylic proton while its ^{13}C NMR spectrum showed the typical lactone carbonyl carbon signal at δ 166.4 (**Fig. 8**). Its IR spectrum displayed absorption frequency for lactone carbonyl carbon at 1752 cm^{-1}; thus, confirming the "one-pot" lactone formation from the homoallylic alcohol **32** leading to structural confirmation of phthalide **33**.

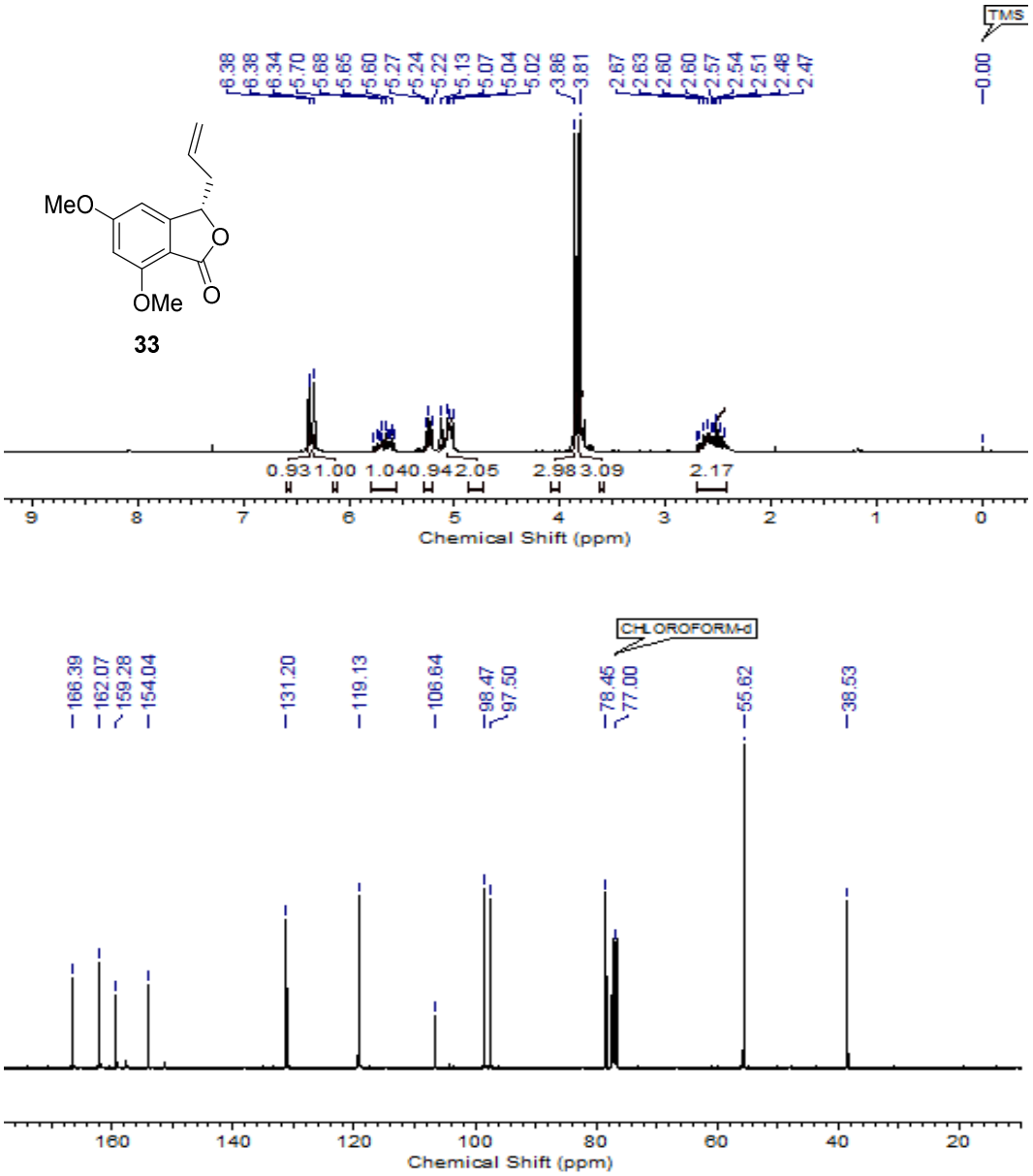


Fig. 8: ^{1}H and ^{13}C NMR spectra of **33**

The oxidative cleavage of terminal olefin in **33** was then carried out using a two-step reaction sequence of dihydroxylation followed by oxidative cleavage with $NaIO_4$ (adsorbed onto silica) affording aldehyde **34**, which was easily identifiable by aldehydic proton signal at δ 9.84 (s, IH) in its ^{1}H NMR spectrum and the corresponding ^{13}C NMR signal at δ 197.7 for aldehydic carbonyl carbon (**Fig. 9**).

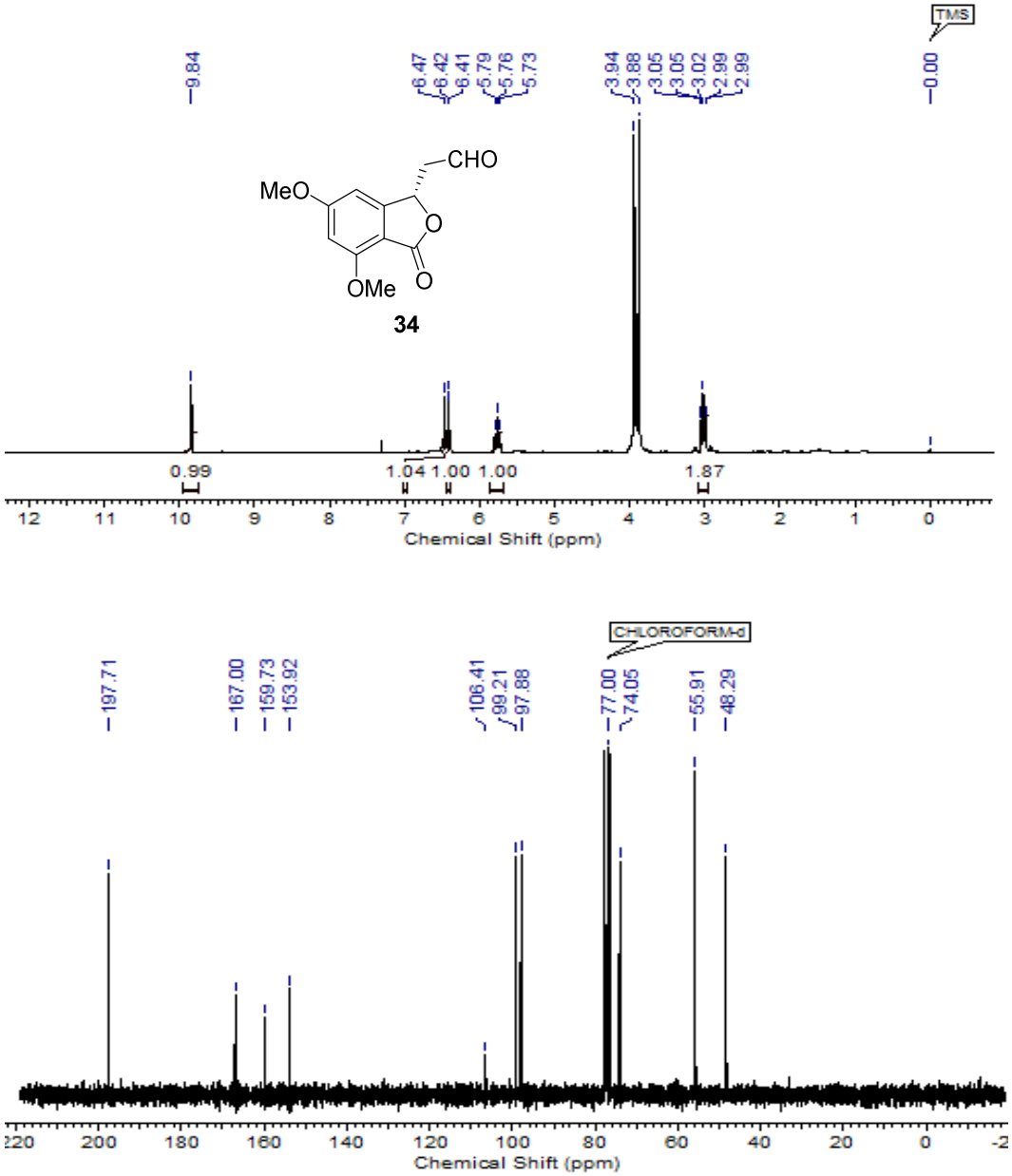


Fig. 9: ^{1}H NMR and ^{13}C NMR spectra of aldehyde **34**

Aldehyde **34** was subjected to Pinnick oxidation conditions to afford carboxylic acid **35** in 89% yield. The ^{13}C NMR spectrum displayed signals at δ 170.9 and 166.8 corresponding to the carbonyl carbons of carboxylic acid and lactone respectively (**Fig. 10**).

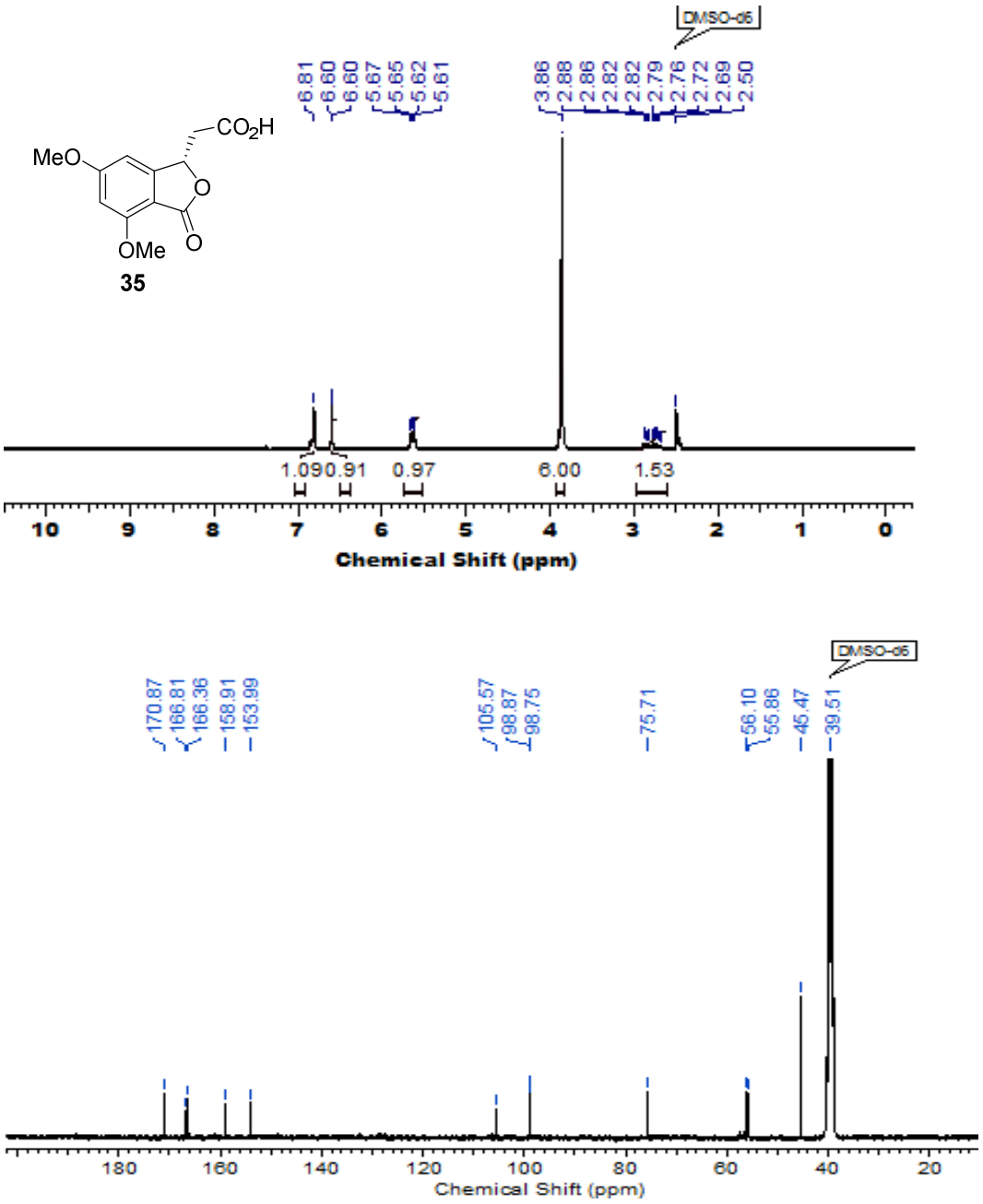


Fig. 10: ^{1}H & ^{13}C NMR spectra of **35**

The final demethylation of methyl ethers with BBr_3 following reported procedure[29] afforded (-)-herbaric acid (**6a**) in 78% yield. Its ^{1}H NMR spectrum showed phenolic proton signals in the deshielded region at δ 9.53 (s, 1H) and 10.03 (s, 1H) while absence of methoxyl carbon signals (-O**C**H_3) in the ^{13}C NMR confirmed the global

demethylation (**Fig. 11**). The observed optical rotation $[\alpha]^{25}_{D}$ = -24.3 (*c* 0.18, MeOH) of **6a** was in well agreement with the literature value {$[\alpha]^{25}_{D}$ = -27.0 (*c* 0.18, MeOH)}.[24]

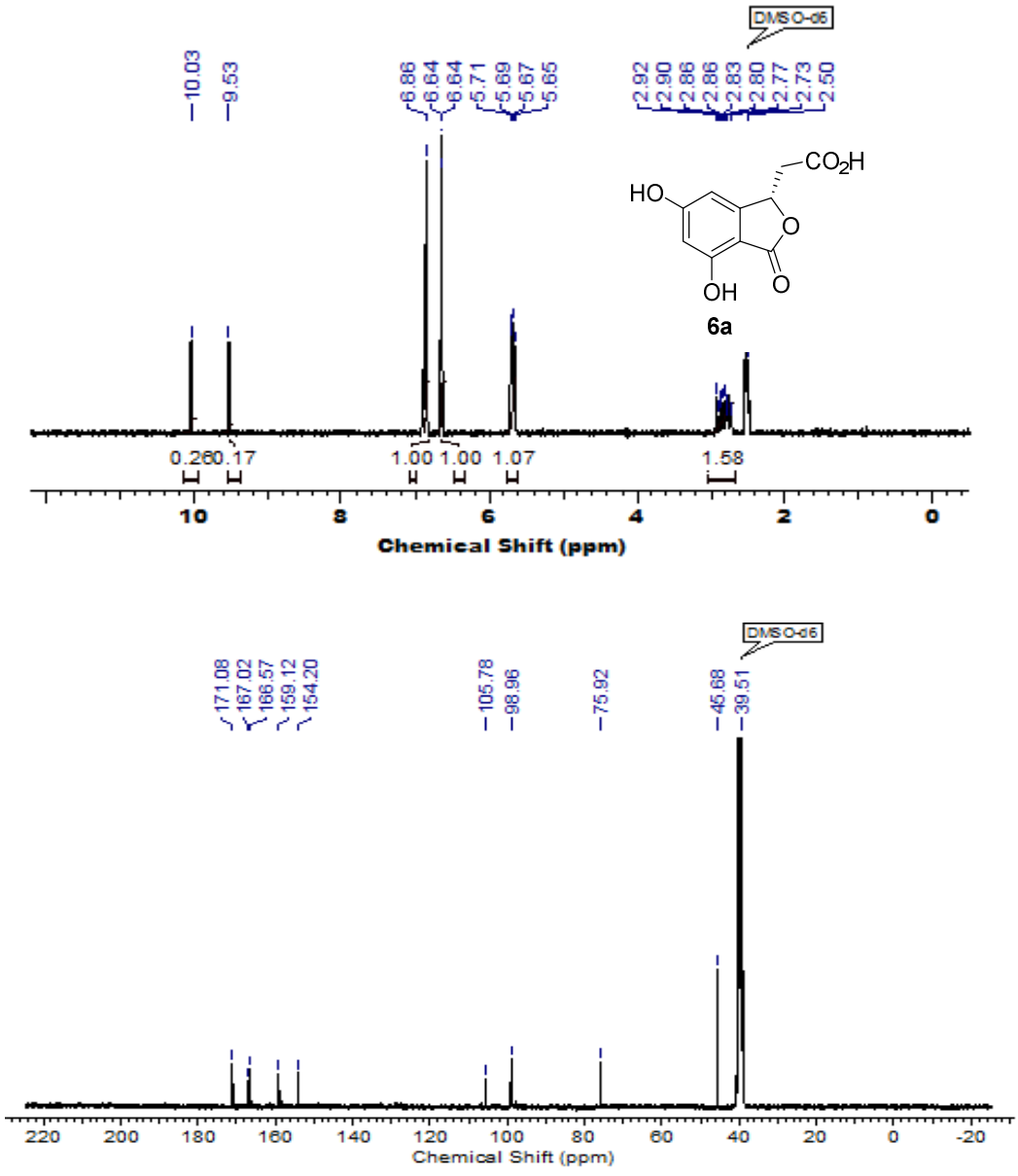
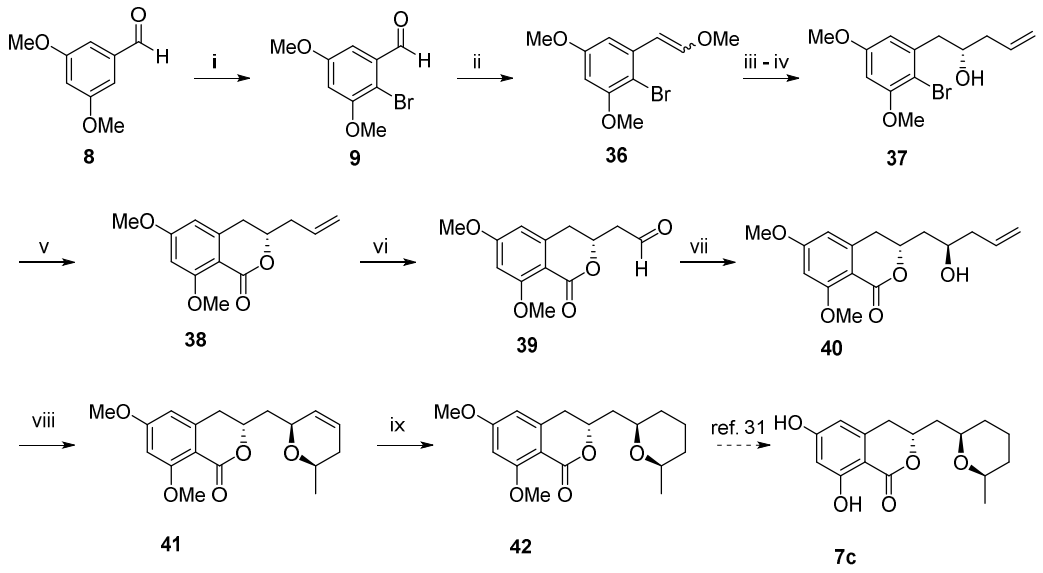


Fig. 11: ^{1}H and ^{13}C NMR spectra of **6a**

1.2.5.2 Formal Synthesis of (-)-Isocladosporin

The complete synthetic sequence for (-)-isocladosporin wherein asymmetric brown allylation reaction, CuBr catalyzed carbonylative coupling reaction and Lewis acid catalyzed oxonium-ene reaction constituting the key steps is presented in **Scheme 13**. For the synthesis of (-)-isocladosporin, a similar reaction sequence was followed as in the case of (-)-herbaric acid (**6a**) starting from regioselective bromination of 3,5-dimethoxy- benzaldehyde followed by MOM-Wittig olefination to yield enol ether **36** (E/Z = 3:2 as an inseparable mixture). The ^{1}H NMR spectrum of the product **36** showed characteristic olefinic proton signals at δ 6.12 (d, *J* = 12.9 Hz, 1H) and δ 6.97 (d, *J* = 12.9 Hz, 1H) corresponding to *E* isomer while olefinic proton signals at δ 5.66 (d, *J* = 7.3 Hz, 0.63H) and δ 6.23 (d, *J* = 7.3 Hz, 0.65H) correspond to *Z* isomer.



Scheme 13: (i) NBS (1.1 equiv), CH_3CN:H_2O (4:1), 25 °C, 4 h, 96%; (ii) methoxy methyltriphenylphosphonium chloride (1.2 equiv), K^{t}OBu (1.5 equiv), THF, 0 to 25 °C, 4 h, 85%; (iii) 2N HCl, THF, 60 °C, 3 h; (iv) (-)-Ipc_2B(allyl)borane, Et_2O, -78 °C, 1 h then 1N NaOH, 30% H_2O_2, 80% (over 2 steps), 90% ee; (v) CuBr (10 mol %), 1,10- phenanthroline (10 mol %), NaCN (1.1 equiv), DMF, 110 °C, 12 h, 88%; (vi) K_2OsO_4 (1 mol %), NMO, acetone:H_2O (4:1), 25 °C, 12 h, then $NaIO_4$ on silica, 86%; (vii) $MgBr_2$ (2 equiv) allylSn^nBu_3 (1 equiv), CH_2Cl_2, -20 °C, 8 h, 82%, dr: 98:2; (viii) TMSOTf (10 mol %), CH_3CHO, CH_2Cl_2, -5 °C, 3 h, 78%, dr = 4:1; (ix) H_2 (1atm), Pd/C, MeOH, 25 °C, 4 h, 96%.

Similarly, the ^{13}C NMR spectrum displayed olefinic carbon signals at δ 101.8 and 150.5 corresponding to *E* isomer while signals at δ 106.4 and 149.3 are due to *Z* isomer (**Fig. 12**).

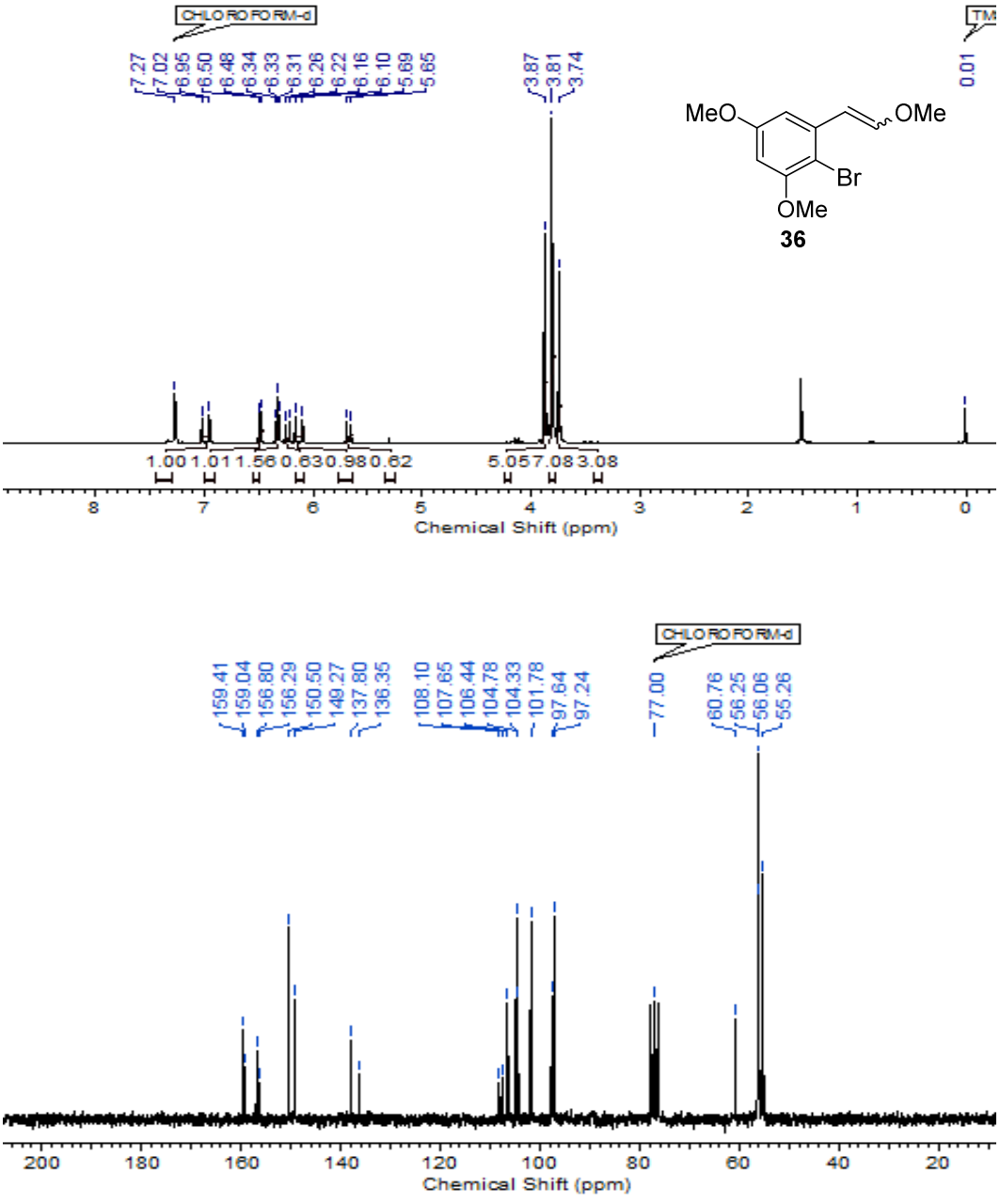
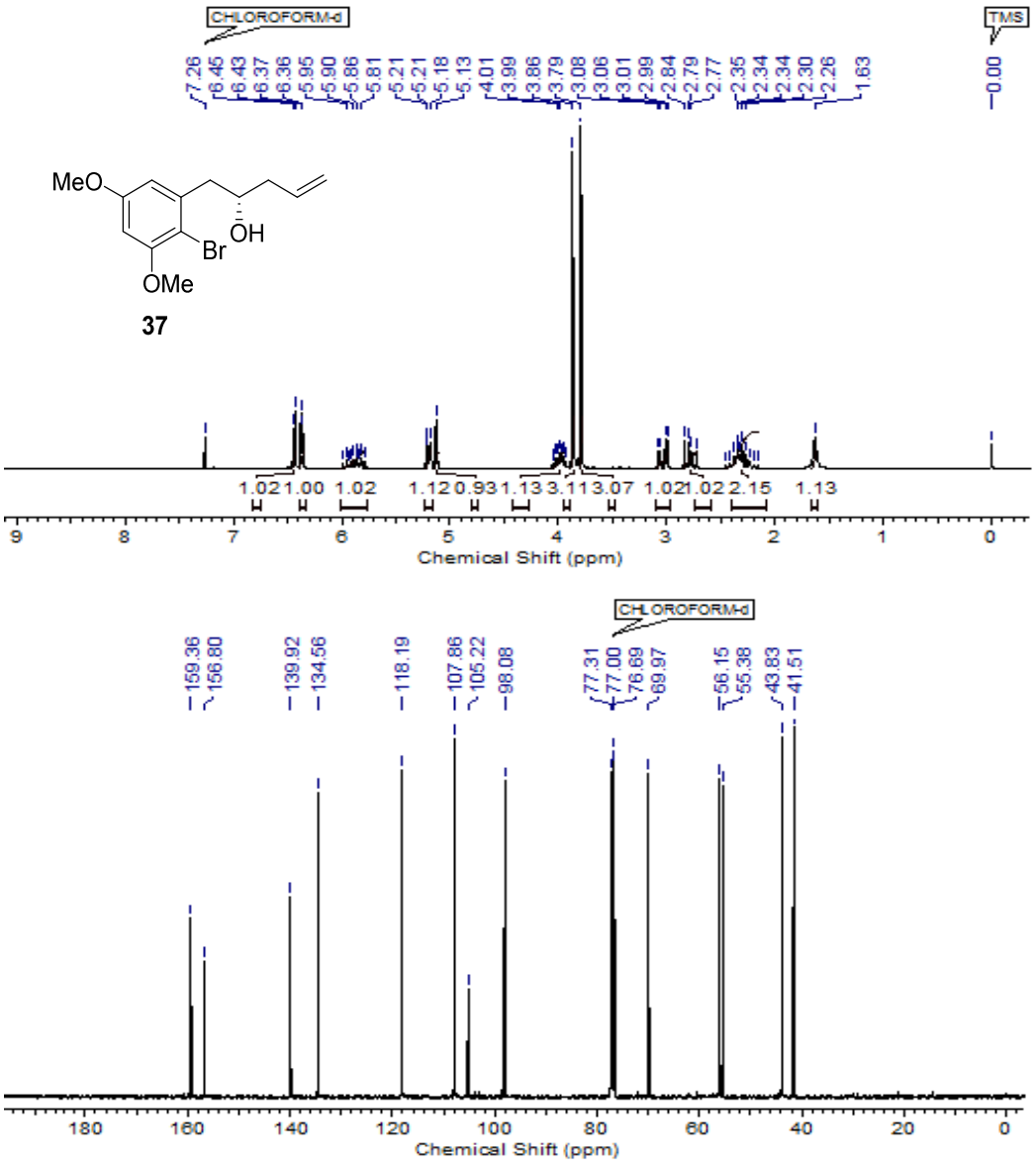
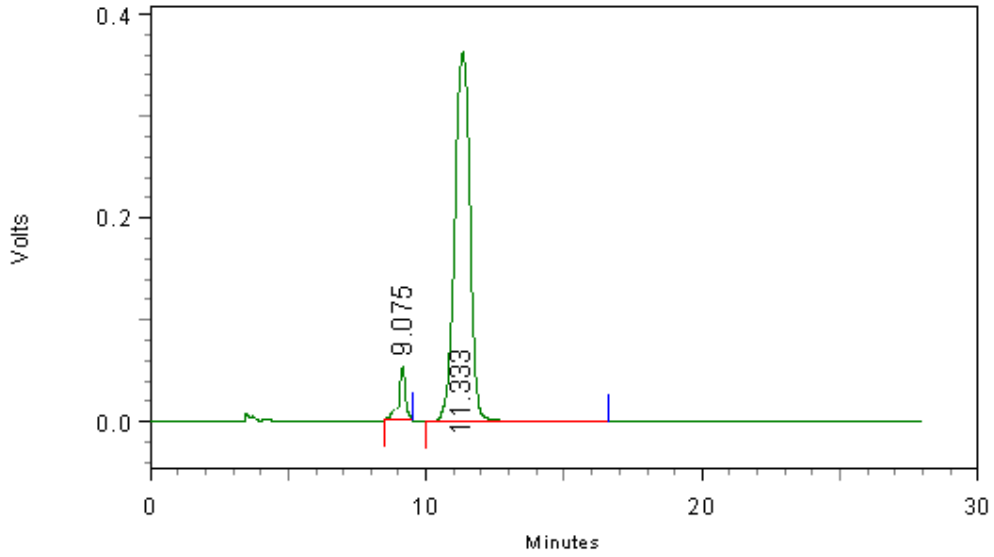


Fig. 12: ^{1}H and ^{13}C NMR spectra of **36**

The formed enol ether **36** was hydrolyzed under acidic conditions to form homologated aldehyde, which was subjected to asymmetric allylation reaction using reported procedure to afford chiral homoallylic alcohol **37** in 80% and 90% ee as determined by chiral HPLC analysis (**Fig. 13**). The ^{1}H NMR spectrum featured typical –O**H** proton signal as a broad singlet at δ 1.63 (br. s., 1H) while methine proton attached to hydroxyl group (-C**H**OH) appeared as multiplet at δ 3.91-4.07 (m,





Peak No.	Retention Time (min)	Area (µV-sec)	Area (%)
1	9.075	744357	5.03
2	11.339	14054002	94.97

Fig. 13: $^{1}H,^{13}C$ NMR spectra and HPLC chromatogram of **37**

1H). The ^{13}C NMR spectrum for the compound showed typical benzylic and allylic methylene carbon signals (-**C**H_2) at δ 41.5 and 43.8 while olefinic carbons signals appeared at δ 107.9 and 134.6. The homoallylic alcohol **37** was then subjected to Cu-catalysed carbonylative coupling to form isochroman-1-one **38** in 88% yield. The formed product showed lactone carbonyl carbon signal in its ^{13}C NMR spectrum at δ 164.2 (**Fig 14**). Its IR spectrum displayed absorption band for lactone carbonyl carbon at 1746 cm^{-1} which further confirmed the presence of lactone carbonyl functionality in **38**. The C=C bond in the product **38** was then oxidatively cleaved to afford aldehyde **39** by using a dihydroxylation-$NaIO_4$ cleavage sequence. The crude aldehyde was *in situ* trapped with allyltributyltin in presence of magnesium dibromide to afford homoallylic alcohol derivative **40** in dr = 98:2 (determined by HPLC) in favour of

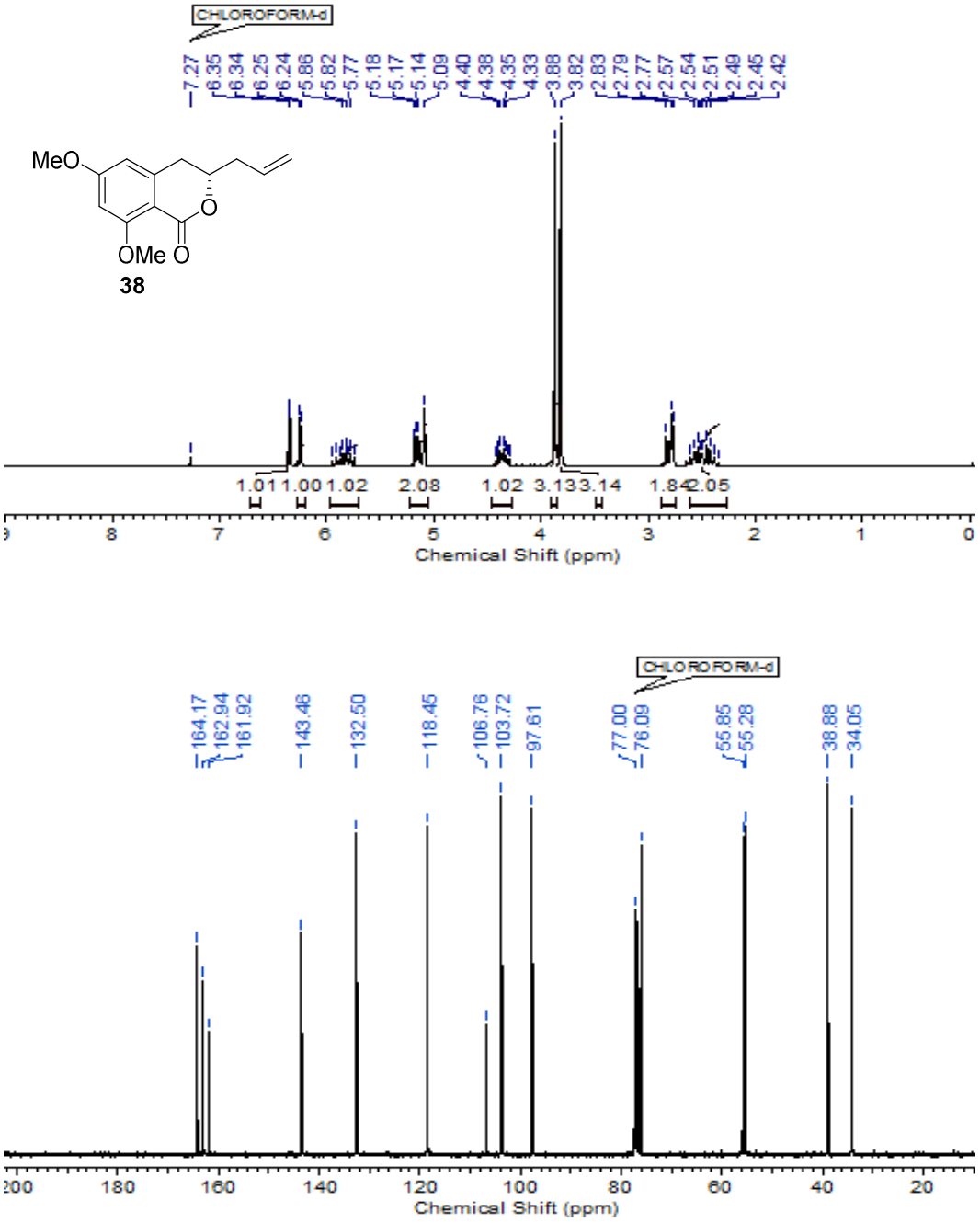


Fig 14: ^{1}H and ^{13}C NMR spectra of **38**

anti isomer which was characterized by typical proton signals at δ 5.72-5.83 (m, 1H) and δ 5.05-5.09 (m, 2H) corresponding to the olefinic protons in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum was characterized by olefinic (=**C**H_2) carbon signal

appearing at δ 97.6 and (=**C**H) signal at δ 134.4 (**Fig. 15**). The allylated product **40** when subjected to trimethylsilyltriflate catalyzed oxonium-ene cyclization using acetaldehyde, it afforded 2,6-*cis* disubstituted dihydropyran derivative **41** in 78%

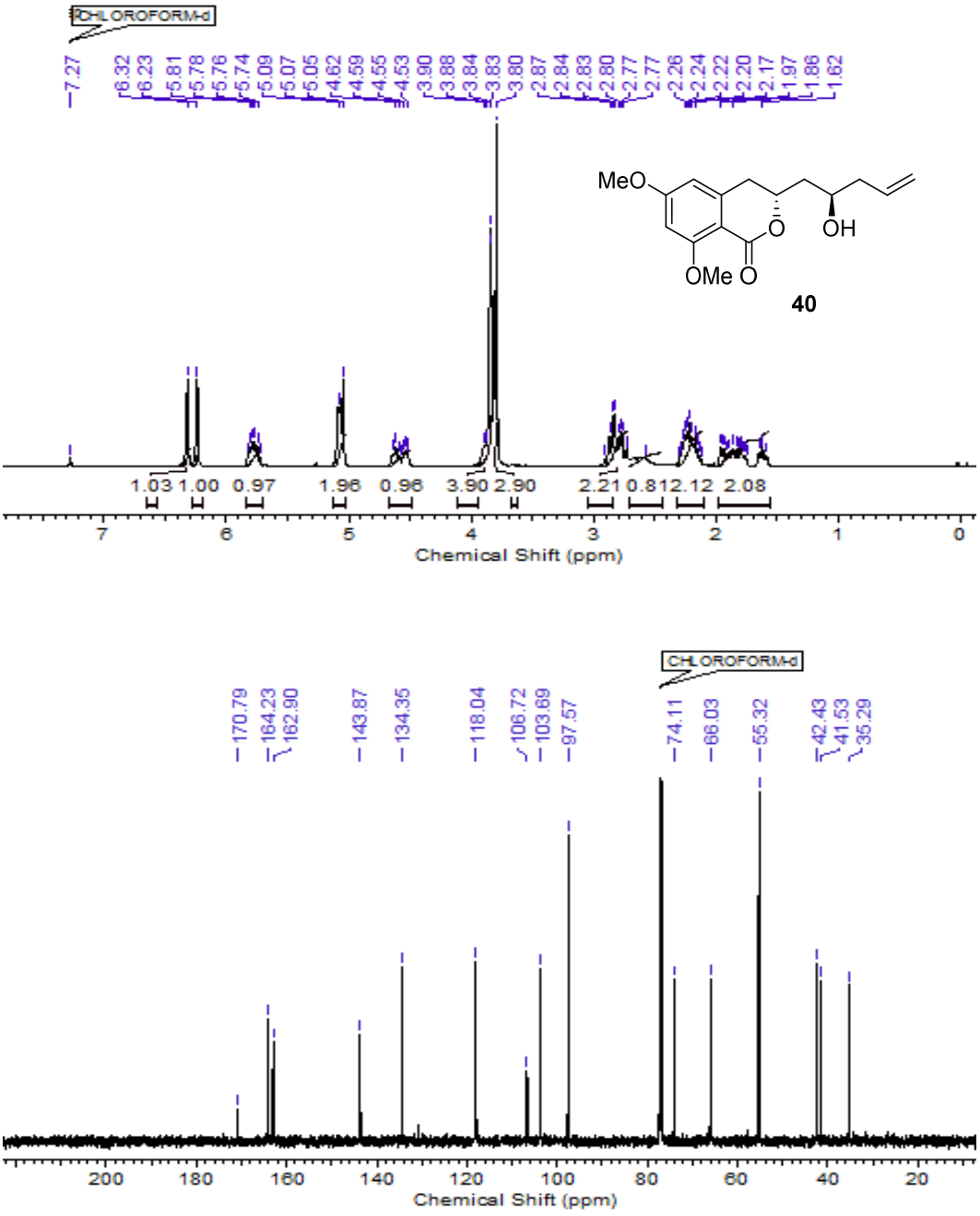


Fig 15: ^{1}H NMR and ^{13}C NMR spectra of **40**

Isolated yield in a moderate dr of 4:1 (*cis*:*trans* separated by column chromatography). The proton NMR spectrum for the newly incorporated methyl group (-C**H**$_3$) has shown a doublet at δ 1.19 (d, J = 6.4 Hz, 3H) while its carbon signal at δ 21.7 in its ^{13}C NMR spectrum. Further, its ^{13}C NMR spectrum showed two typical olefinic carbons (2 x **C**-H) at δ 125.3 and 130.2 (**Fig. 16**).

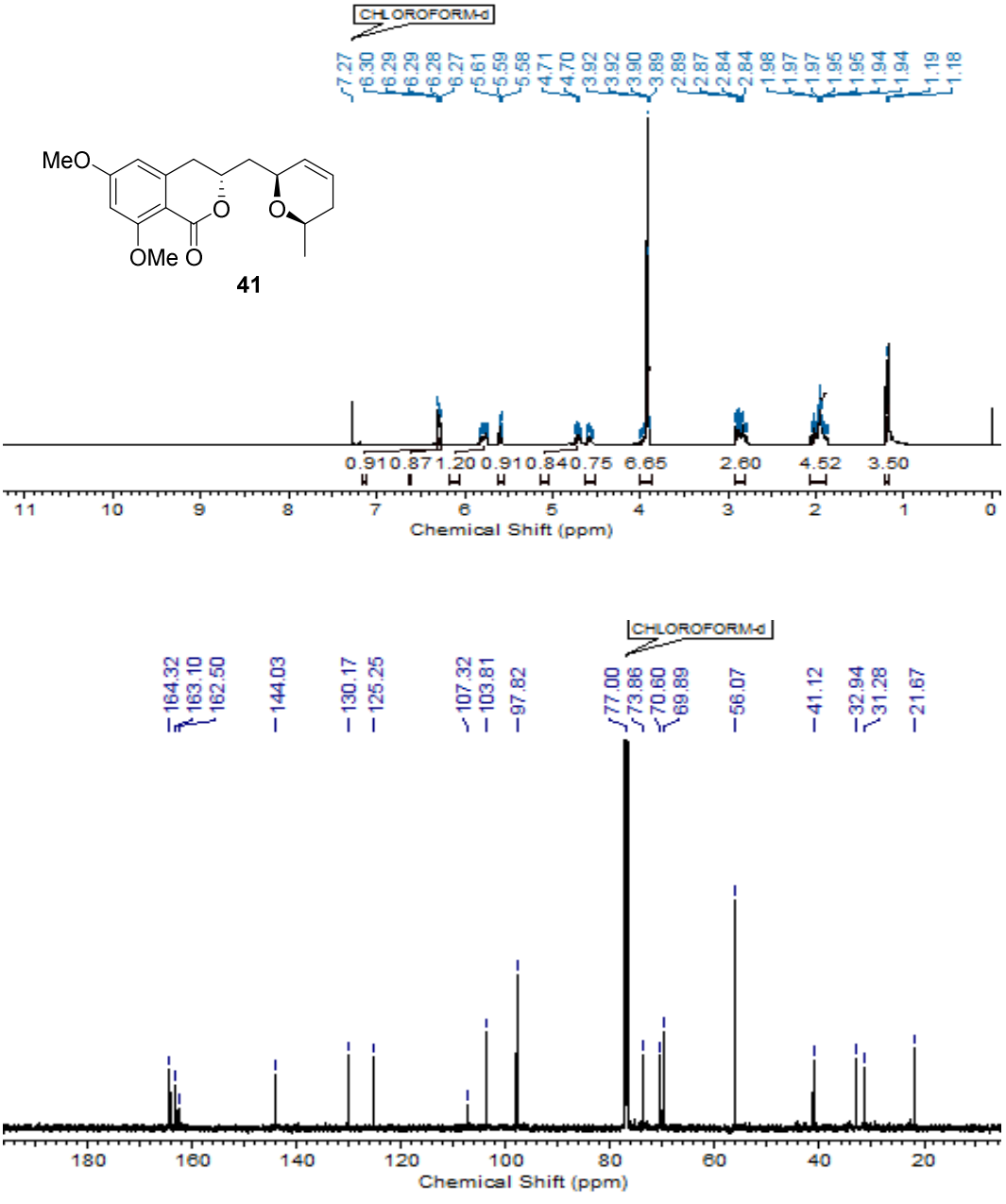


Fig. 16: ^{1}H and ^{13}C NMR spectra of **41**

The DHP derivative **41** was then reduced under H_2 (balloon pressure) to afford the 2,6-*cis* disubstituted tetrahydropyran derivative **42** marked by the disappearance of olefinic signals in ^{1}H NMR spectrum of (-)-isocladosporin precursor **42** (**Fig.17**).The optical rotation of the synthesized compound **42**, $[\alpha]^{25}_D$ = -62.9 (*c* = 1.0, $CHCl_3$) was in good agreement with that of the reported value {$[\alpha]^{25}_D$ = -70.0 (*c* = 1.0, $CHCl_3$)}.

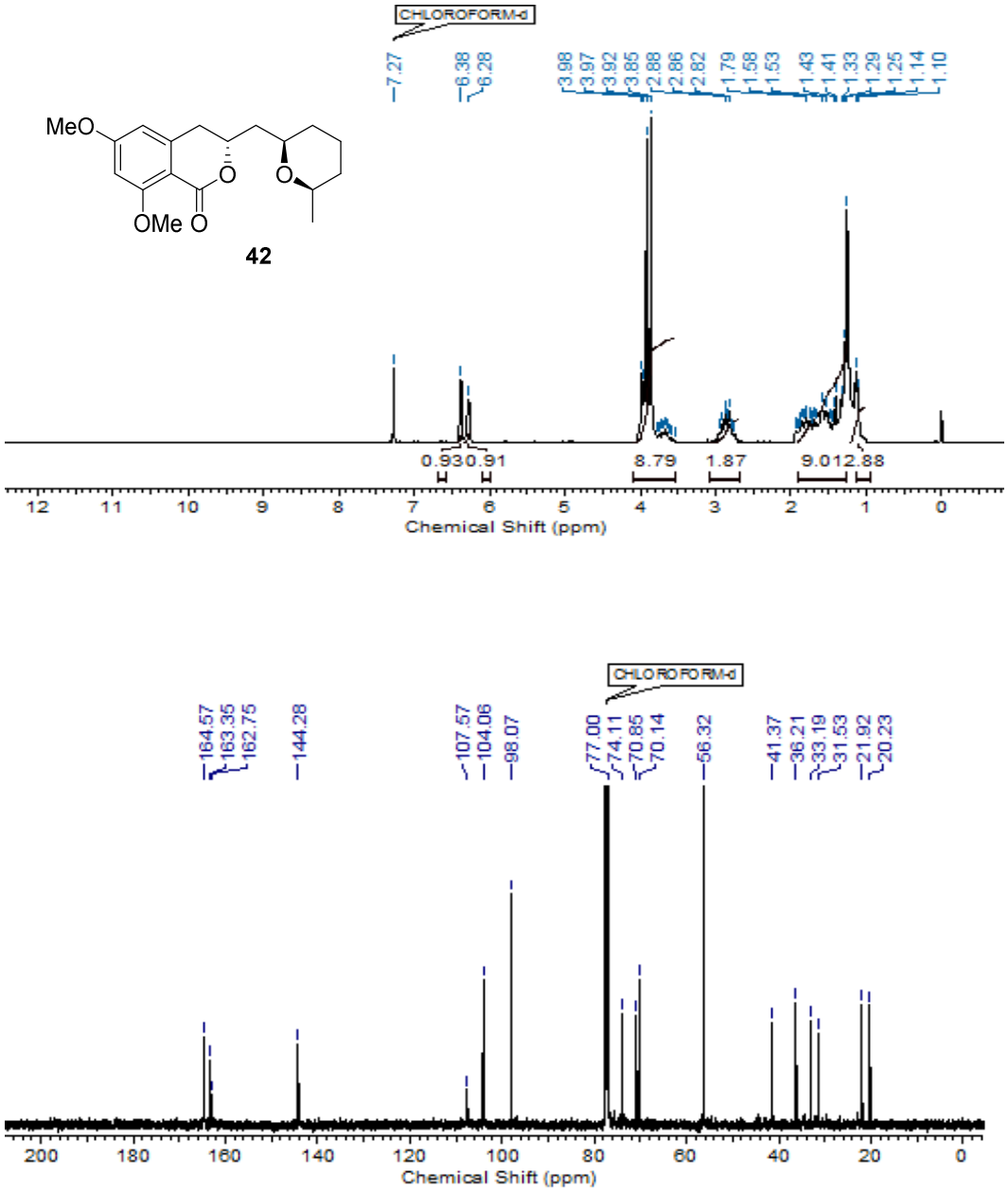


Fig. 17: ^{1}H and ^{13}C NMR spectra of **42**

The final step involves demethylation of its methyl ethers using reported procedure[31] that would afford (-)-isocladosporin (**7c**). This completes the formal synthesis of (-)-isocladosporin.

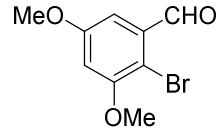
1.2.6 Conclusion

In conclusion, short and highly enantioselective methods for the syntheses of (-)-herbaric acid (**6a**) and (-)-isocladosporin (**7c**) have been described. The strategy employs asymmetric Brown allylation and Cu-catalysed carbonylative coupling reaction as the key steps. The overall yield of **6a** and **7c** were found to be 40% and 30.3% respectively with 90% enantiomeric excess each. The present protocol comprises of lesser number of steps, higher overall yield and avoids the use of harsh acidic conditions unlike the previous reports. We believe that this will be a flexible route in arriving at phthalides or isochroman-1-ones without any racemisation of the product at the cyclization stage.

1.2.7 Experimental Section

1.2.7.1 Synthesis of (-)-Herbaric Acid

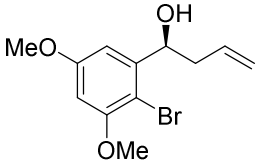
2-Bromo-3,5-dimethoxybenzaldehyde (9)



To a stirred solution of 3,5-dimethoxybenzaldehyde (5.0 g, 30.12 mmol) in CH_3CN:H_2O (80 mL:20 mL) at 0 ^oC was added *N*-bromosuccinimide (6.4 g, 36.15 mmol) and the mixture was stirred further at 25 ^oC for 3 h. After the completion of reaction (monitored by TLC), it was quenched with aq. solution $Na_2S_2O_3.5H_2O$ (hypo) followed by concentration of CH_3CN under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 x 50 mL, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give the crude bromo derivative **9**. The crude product was purified by flash column chromatographic purification [silica gel (230-400 mesh) with Pet. ether:EtOAc (90:10) as an eluent] to afford pure 2-bromo-3,5-dimethoxybenzaldehyde (**9**).

Yield: 96% (7.4 g); colorless solid; **mp:** 102-103 ºC, (lit. **mp**: 101-102 ºC); **IR** ($CHCl_3$, cm^{-1})**:** υ_{max} 670, 830, 841,1019,1074,1160,1198, 1288, 1448, 1582, 1677; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.91 (s, 3H), 6.69 (d, *J* = 2.8 Hz, 1H), 7.02 (d, *J* = 2.8 Hz, 1H), 10.40 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.7, 56.5, 103.3, 105.8, 109.3, 134.8, 157.1, 160.0, 191.7; **Analysis**: $C_9H_9BrO_3$ requires C, 44.11; H, 3.70; Br, 32.60; found: C, 44.33; H, 3.89; Br, 32.56%.

1-(2-Bromo-3,5-dimethoxyphenyl)but-3-en-1-ol (32)

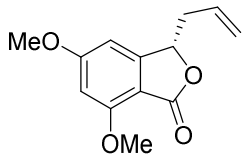


The optically pure solution of (-)-$(Ipc)_2B$(allyl) in THF (9.48 mmol) was cooled to −75 °C under vigorous stirring, then a solution of aldehyde (2.4 g, 9.48 mmol) in diethyl ether (35 mL) was added dropwise over 20 min *via* syringe, maintaining the temperature below −70 °C. The resulting mixture was vigorously stirred at −70 to −75 °C for 1.5 h, then the reaction mixture was allowed to warm to room temperature (25 °C) over 1 h. The reaction mixture was cooled to 0 °C with an ice bath and a premixed solution of 3N NaOH (20 mL) and 30% aq. H_2O_2 (10 mL) was carefully added *via* the dropping funnel over 10 min (exothermic), keeping the temperature below 15 °C, followed by addition of saturated aqueous $NaHCO_3$ (10 mL) over 3 min *via* syringe. The resulting biphasic mixture was stirred for 10 h at room temperature to completely hydrolyze borinate ester products, then the organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 × 40 mL). Further, the combined organic layers were washed with brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated under *vacuo* to yield the crude homoallylic alcohol. The crude product was then purified by flash column chromatography [silica gel (230-400 mesh) with Pet. ether:EtOAc (80:20) as an eluent] to afford pure homoallylic alcohol **32** in 80% yield.

Yield: 80% (2.24 g); colorless liquid; $\mathbf{[\alpha]^{D}_{25}}$ -18.1 (*c* 1.3, $CHCl_3$); **HPLC analysis**: 90% ee, [Chiracel OD-H column (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 13.86 (major) and 15.89 (minor)]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 832, 1025, 1065, 1168, 1204, 1333, 1455, 1589, 2933, 3440; **^{1}H NMR** (200 MHz,$CDCl_3$): δ 2.20-2.39 (m, 2H), 2.52-2.69 (br. s, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 5.04-5.27 (m, 3H), 5.76-6.01 (m, 1H), 6.37 (d, *J* = 2.8 Hz, 1H), 6.73 (d, *J* = 2.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 42.0, 55.4, 56.2, 72.0, 98.9, 102.1, 103.0, 118.4,

134.5, 145.0, 156.3, 159.9; **HRMS** (ESI) calcd for $C_{12}H_{16}O_3Br$ $[M + H]^+$ 287.0277, found 287.0275.

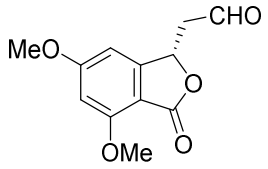
(*S*)-3-Allyl-5,7-dimethoxyisobenzofuran-1(3*H*)-one (33)



To a stirred solution of homoallylic alcohol **32** (1.4 g, 5 mmol) in dry DMF (20 mL) was added NaCN (0.245 g, 5 mmol), CuBr (0.072 g, 0.5 mmol) and 1,10-phenanthroline (0.09 g, 0.5 mmol), the entire solution stirred at 120 °C under N_2 atmosphere for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature and excess cyanide was quenched with aq. $NaClO_2$, diluted with water (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which was purified by column chromatography [silica gel (230-400 mesh) and Pet. ether:EtOAc (70:30)] as an eluent to afford corresponding lactone **33** in 86% yield.

Yield: 86% (1.0 g); colorless liquid; $[\alpha]^{D}_{25}$ -21.3 (*c* 1. 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 684, 740, 835, 890, 1027, 1255, 1266, 1335, 1474, 1508, 1752, 2922, 3015; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.33-2.72 (m, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 5.00-5.30 (m, 3H), 5.67 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 6.34 (s, 1H), 6.38 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 38.5 , 55.6 (2 x –O**C**H_3), 78.4, 97.5 , 98.5, 106.6, 119.1, 131.2, 154.0, 159.3, 166.4, 167.6; **HRMS** (ESI) calcd for $C_{13}H_{15}O_4$ [M + H]+ 235.0965, found 235.0963.

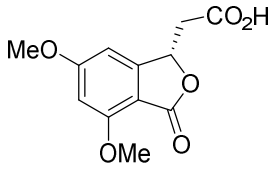
(*S*)-2-(6,8-Dimethoxy-1-oxoisochroman-3-yl)acetaldehyde (34)



The lactone **33** (1.0 g, 4.27 mmol) was dissolved in acetone:H_2O (4:1) and to this was added potassium osmate (14.8 mg, 0.04 mmol) and *N*-morpholine-*N*-oxide (0.5 g, 4.27 mmol) as stoichiometric co-oxidant. The reaction mixture was stirred at 25 ºC for 12 h. After completion of the reaction (as monitored by TLC), excess potassium osmate if any was quenched with sodium sulphite. Organic layer was evaporated under reduced pressure while the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), dried with Na_2SO_4, filtered, concentrated under *vacuo* to reduce the solvent volume to half (75 mL). To the solution was added $NaIO_4$ adsorbed on silica (*w/w* = 1/5). The reaction mixture was allowed to stir for 1 h at room temperature. After consumption of the starting material (monitored by TLC), the solution was filtered over celite 545 bed and the filtrate was concentrated to afford crude aldehyde **34.** Aldehyde **34** was further purified by column chromatography [silica gel (230-400 mesh) and Pet. ether:EtOAc (60:40)] as an eluent to afford pure product in 86% yield.

Yield: 86% (0.87 g) colorless liquid; $\mathbf{[\alpha]^{D}_{25}}$ -20.8 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 731, 839, 1026, 1158, 1200, 1212, 1334, 1601, 1749, 2848, 2929; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.95-3.09 (m, 2H), 3.88 (s, 3H), 3.94 (s, 3H), 5.76 (t, *J* = 6.3 Hz, 1H), 6.41 (d, *J* = 1.6 Hz, 1H), 6.47 (br. s, 1H), 9.84 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 48.3, 55.9, 55.9, 74.0, 97.9, 99.2, 106.4, 153.9, 159.7, 167.0, 197.7; **HRMS** (ESI) calcd for $C_{12}H_{13}O_5$ $[M + H]^+$ 237.0757, found 237.0757.

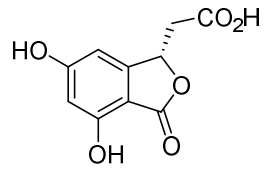
(*S*)-2-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid (35)



The aldehyde derivative **34** (0.8 g, 3.38 mmol) was dissolved in ^{t}BuOH:THF:H_2O (1:1:1 in 20 mL combined volume), to it, $NaClO_2$ (4.05 mmol) and NaH_2PO_4 (3.38 mmol) were added. The reaction mixture was stirred vigorously at room temperature for 2 h, diluted with saturated aqueous NaH_2PO_4 solution (5 mL), and organic layer was evaporated under reduced pressure, the resulting aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated to afford the desired compound which was further purified by flash column chromatography [silica gel (230-400 mesh)] and CH_2Cl_2: MeOH (5:1) as an eluent to afford corresponding acid **35** in 89% yield.

Yield: 89% (0.75 g); colorless viscous gum; $[\alpha]^{D}_{25}$ -18.4 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 836, 1009, 1060, 1164, 1204, 1225, 1330, 1601, 1711, 1738, 2983, 3171; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.61-2.97 (m, 2H), 3.86 (s, 6H), 5.64 (dd, *J* = 8.4, 3.6 Hz, 1H), 6.60 (d, *J* = 1.8 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 45.5, 55.9, 56.1, 75.7, 98.7, 98.9, 105.6, 154.0, 158.9, 166.4, 166.8, 170.9; **HRMS** (ESI) calcd for $C_{12}H_{13}O_6$ $[M+H]^+$ 253.0707 found 253.0708.

(-)-Herbaric acid (6a)



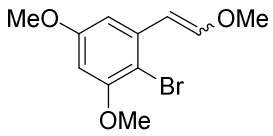
To a solution of target compound precursor **35** (0.5 g, 1.98 mmol) in dichloromethane (15 mL) was added BBr_3 (1.0 g, 4.0 mmol) at -10 °C. The solution was stirred at the

same temperature for 2 h, then at room temperature for 72 h. The reaction mixture was slowly quenched with 1 M HCl (3 x 5 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography [silica gel (230-400 mesh) using dichloromethane/methanol (5:1) as eluent] to give the title compounds **6a** as colorless solid.

Yield: 78% (0.35 g) colorless solid; **mp**: 191-193 ºC, (lit.[29] **mp**: 192-193 ºC); $[\alpha]^{25}_{D}$ = -24.3 (*c* 0.18, MeOH); {Lit[24] $[\alpha]^{25}_{D}$ = -27.0 (*c* 0.18, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3201, 2959, 1707, 1612, 1474, 1399, 1366, 1336, 1251, 1216, 1160, 1076, 1012, 823, 737, 693; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.68-3.04 (m, 2H), 5.68 (dd, *J* = 8.4, 3.6 Hz, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.86 (m, *J* = 1.6 Hz, 1H), 9.53 (s, 1H) and 10.03 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 45.7, 75.9, 99.0, 105.8, 154.2, 159.1, 166.6, 167.0, 171.1; **Analysis**: $C_{10}H_8O_6$ requires C, 53.58; H, 3.60; found: C, 53.33; H, 3.69%.

1.2.7.2 Synthesis of (-)-Isocladosporin

2-Bromo-1,5-dimethoxy-3-(2-methoxyvinyl)benzene (36)

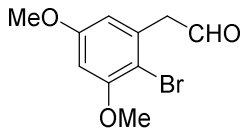


To a stirred solution of methoxymethyltriphenylphosphonium chloride (8.4 g, 24.39 mmol) in dry THF (150 mL) maintained at 0 ^oC was added K^{t}OBu (3.4 g, 30.48 mmol) and allowed to stir for 15 min at the same temperature to generate the ylide. A solution of 2-bromo-3,5-dimethoxybenzaldehyde (5 g, 20.32 mmol) in dry THF (50 mL) was added to the ylide and the reaction mixture was stirred for 3 h. After

completion of the reaction, it was quenched with ice and THF was concentrated under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 x 100 mL), dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give the crude enol derivative. The crude product was purified by flash column chromatographic purification [silica gel (230-400 mesh) with Pet. ether:EtOAc (90:10) as an eluent] to afford pure enol ether **36**.

Yield: 85% (4.7 g); colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 832, 951, 1024, 1121, 1163, 1333, 1434, 1455, 1588, 2838, 2938, 3003; **^{1}H NMR** (200 MHz, $CDCl_3$) ***E*-isomer**: δ 3.73 (s, 3H), 3.80 (s, 6H), 6.12 (d, *J* = 12.9 Hz, 1H), 6.32 (d, *J* = 2.7 Hz, 2H), 6.48 (d, *J* = 2.7 Hz, 1H), 6.98 (d, *J* = 12.9 Hz, 1H); ***Z*-isomer:** δ 3.73 (s, 3H), 3.86 (s, 6H), 5.66 (d, *J* = 7.3 Hz, 1H), 6.23 (d, *J* = 7.3 Hz, 1H), 6.32 (d, *J* = 2.7 Hz, 3H), 6.48 (d, *J* = 2.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.3, 56.1, 56.2, 60.8, 97.2, 97.6, 101.8, 104.3, 104.8, 106.4, 107.6, 108.1, 136.3, 137.8, 149.3, 150.5, 156.3, 156.8, 159.0, 159.4; **HRMS** (ESI): calcd for $C_{11}H_{13}O_3Br$ [M + H]+ 273.0121, found 273.0119.

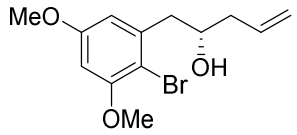
2-(2-Bromo-3,5-dimethoxyphenyl)acetaldehyde



To a stirred solution of methyl vinyl ether **36** (4.7 g, 17.3 mmol) in THF (70 mL) was added an aqueous solution of 1N aq. HCl (30 mL) at room temperature. The resulting reaction mixture was refluxed for 3 h (monitored by TLC). After evaporation of the organic solvent *in vacuo*, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$, dried over anhyd. Na_2SO_4, filtered and

concentrated under reduced pressure. The obtained crude aldehyde was subjected to asymmetric Brown allylation without further purification.

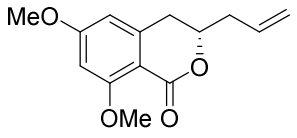
1-(2-bromo-3,5-dimethoxy- phenyl)-pent-4-en-2-ol (**37**)



The same procedure is followed as described for compound **32**.

Yield: 80% (2.12 g); colorless liquid; **[α]$^{D}_{25}$** -14.1 (*c* 1.3, $CHCl_3$); **HPLC analysis**: 90% ee, [Chiracel OD-H column (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 9.07 (minor) and 11.33 (major)]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 829, 1022, 1085, 1162, 1204, 1332, 1455, 1587, 2839, 2933, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.16-2.48 (m, 2H), 2.79 (dd, *J* = 13.5, 8.4 Hz, 1H), 3.05 (dd, *J* = 13.5, 4.4 Hz, 1H), 3.80 (s, 3H), 3.87 (s, 3H), 3.93-4.10 (m, 1H), 5.14 (s, 1H), 5.17-5.25 (m, 1H), 5.77-6.03 (m, 1H), 6.38 (d, *J* = 2.8 Hz, 1H), 6.45 (d, *J* = 2.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.5, 43.8, 55.4, 56.1, 70.0, 98.1, 105.2, 107.9, 118.2, 134.6, 139.9, 156.8, 159.4; **HRMS** (ESI) calcd for $C_{13}H_{18}O_3Br$ $[M + H]^+$ 301.0434, found 301.0435.

3-allyl-6,8-dimethoxyiso-chroman-1-one (38)

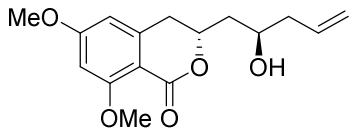


The same procedure is followed as described for compound **33**.

Yield: 88% (1.1 g); colorless liquid; **[α]$^{D}_{25}$** -19.4 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1040, 1084, 1200, 1342, 1462, 1581, 1604, 1746, 2842, 2941; **^{1}H NMR** (200

MHz, $CDCl_3$): δ 2.36-2.70 (m, 2H), 2.74-2.91 (m, 2H), 3.85 (s, 3H), 3.91 (s, 3H), 4.39 (dtd, *J* = 10.2, 6.1, 4.4 Hz, 1H), 5.09-5.24 (m, 2H), 5.72-6.00 (m, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 6.38 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 34.1, 38.9, 55.3, 55.9, 76.1, 97.6, 103.7, 106.8, 118.4, 132.5, 143.5, 161.9, 162.9, 164.2; **HRMS** (ESI) calcd for $C_{14}H_{17}O_4$ $[M + H]^+$ 249.1121, found 249.1126.

(*R*)-3-((*R*)-2-Hydroxypent-4-en-1-yl)-6,8-dimethoxyisochroman-1-one (40)

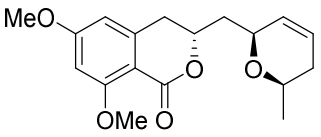


The alkene **38** (1.0 g, 4.03 mmol) was dissolved in acetone:H_2O (4:1) and to this was added potassium osmate (14.8 mg, 0.04 mmol) and *N*-morpholine-*N*-oxide (0.470 g, 4.03 mmol) as stoichiometric co-oxidant. The reaction mixture was stirred at 25 °C for 12 h. After completion of the reaction (as monitored by TLC), excess potassium osmate if any was quenched with sodium sulphite. Organic layer was evaporated under reduced pressure while the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), dried with Na_2SO_4, filtered, concentrated under *vacuo* to reduce the solvent volume to half (75 mL). To the solution was added $NaIO_4$ adsorbed on silica (*w/w* = 1/5). The reaction mixture was allowed to stir for 1 h at room temperature. After consumption of the starting material (monitored by TLC), the solution was filtered over celite 545 bed and the filtrate was concentrated to afford crude aldehyde **39.** To a stirred solution of aldehyde **39** in CH_2Cl_2 under complete N_2 atmosphere was added $MgBr_2.Et_2O$ (2.1 g, 8.0 mmol) at -20 °C, after 0.5 h addition of allyltributyltin (1.4 g, 4.0 mmol) was done slowly over 20 min by a dropping funnel. The reaction was allowed to stir for 8 h. After completion of the reaction (as monitored by TLC), it was brought to 0 °C, and quenched with sat. NH_4Cl solution. The reaction was filtered

over celite 545 pad to remove Sn halides. The residue was discarded while the filtrate was worked-up using CH_2Cl_2 (3 x 20 mL). Organic layer was concentrated under reduced pressure to afford crude product. The product was purified by flash column chromatography [silica gel (230-400 mesh)] and CH_2Cl_2: MeOH (5:1) as an eluent to afford homoallylic alcohol derivative **40** in 82% yield.

Yield: 82% (0.96 g); colorless liquid; $[\alpha]^{D}_{25}$ -32.8 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1020, 1050, 1174, 1244, 1320, 1570, 1611, 1740, 2983, 3171, 3350; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.62-2.16 (m, 2H), 2.19-2.27 (m, 2H), 2.59 (br. s., 1H), 2.73-2.91 (m, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 4.52-4.64 (m, 1H), 5.05-5.09 (m, 2H), 5.72-5.83 (m, 1H), 6.23 (br. s., 1H), 6.32 (br. s., 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 35.3, 41.5, 42.4, 55.3 (2 X –O**C**H_3), 66.0, 74.1, 97.6, 103.7, 106.7, 118.0, 134.4, 143.8, 162.9, 164.2, 170.8; **Analysis**: $C_{16}H_{20}O_5$ requires C, 65.51; H, 7.22; found: C, 65.51; H, 7.22%.

(*R*)-6,8-Dimethoxy-3-(((2*S*,6*R*)-6-methyl-5,6-dihydro-2H-pyran-2-yl)methyl)iso-chroman-1-one (41)

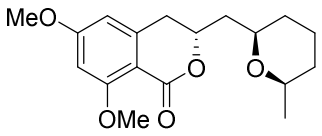


To a stirred solution of acetaldehyde (0.6 g, 11.95 mmol) in CH_2Cl_2 at -10 °C was added trimethylsilyl triflate (0.053 g, 0.239 mmol), the reaction mixture was stirred at the same temperature for 15 min followed by slow addition of homoallylic alcohol derivative **40** (0.7 g, 2.39 mmol) dissolved in CH_2Cl_2. The reaction was quenched with ice after completion (monitored by TLC). Aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product. The product was purified by

column chromatography [silica gel (230-400 mesh) and Pet. ether:EtOAc (40:60) as an eluent] to afford corresponding dihydropyran derivative **41** in 78% yield.

Yield: 78% (0.59 g); colorless liquid; $[\alpha]^{D}_{25}$ -57.5 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1490, 1603, 1743, 2921; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.17-1.21 (d, *J* = 6.4 Hz, 3H), 1.88-2.06 (m, 4H), 2.81-2.92 (m, 2H), 3.88-4.01 (m, 7H), 4.52-4.62 (m, 1H), 4.67-4.75 (m, 1H), 5.56-5.62 (m, 1H), 5.72-5.84 (m, 1H), 6.27 (t, *J* = 1.8 Hz, 1H), 6.29-6.32 (t, *J* = 1.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.7, 31.3, 32.9, 41.1, 56.1, 69.9, 70.6, 73.9, 97.8, 103.8, 107.3, 125.2, 130.2, 144.0, 162.5 163.1, 164.3; **Analysis**: $C_{18}H_{22}O_5$ requires C, 67.91; H, 6.97; found: C, 67.93; H, 6.93%.

(*R*)-6,8-Dimethoxy-3-(((2R,6R)-6-methyltetrahydro-2H-pyran-2-yl)methyl)iso-chroman-1-one (42)



To a stirred solution of 2,6- disubstituted dihydropyran derivative **41** (0.55 g, 1.71 mmol) in MeOH (20 mL) was added catalytic amount of 10% Pd/C and the resulting heterogeneous mixture was stirred under H_2 atmosphere (balloon pressure) for 12 h at 25 °C. The reaction mixture was then filtered through a pad of celite and the solvent was removed under reduced pressure to give the crude product, which was then purified by column chromatography [silica gel (230-400 mesh) and Pet. ether:EtOAc (60:40) as eluent] to afford corresponding tetrahydropyran derivative **42** in 96% yield.

Yield: 96% (0.53 g); colorless liquid; $[\alpha]^{25}_{D}$ = -62.9 (*c* = 1.0, $CHCl_3$); {Lit.[31] $[\alpha]^{25}_{D}$ = −70.0 (*c* = 1.0, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1205, 1490, 1535, 1740, 2921; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (d, *J* = 9.4 Hz, 3H), 1.26-1.93 (m, 8H), 2.67-2.96 (m, 2H), 3.65-3.98 (m, 9H), 6.28 (br. s., 1H), 6.38 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.2, 21.9, 31.5, 33.2, 36.2, 41.4, 56.3, 70.1, 70.8, 74.1, 98.1, 104.1, 107.6,

144.3, 162.8, 163.4, 164.6; **Analysis**: $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55; found: C, 67.43; H, 7.62%.

Section III

CuCN-Mediated "One-pot" Cascade Route to Ethyl 1-Amino-2-Naphthalenecarboxylate Derivatives

1.3.1 Introduction

Highly substituted bicyclic and polycyclic aromatic compounds are common structural motifs present in natural products and pharmaceuticals.[33] In recent years such aromatic systems have attracted considerable attention for the construction of organic light emitting diodes, organic semiconductors and luminescent materials.[34] Particularly, 2-aminobenzoic acids are important precursors for the generation of benzynes, which are efficient intermediates for the synthesis of a variety of polycyclic compounds.[35] 2-Aminobenzoic acid derivatives are also known as useful starting materials for the synthesis of heterocyclic compounds.[35] The synthetic utility of 1 (or 3)-amino-2-naphthalenecarboxylic acid derivatives, which are the benzo analogues of 2-aminobenzoic acid derivatives, is also well documented.[36] Therefore, the development of efficient methods for constructing polycyclic aromatic compounds have been a longstanding objective of synthetic organic chemist.

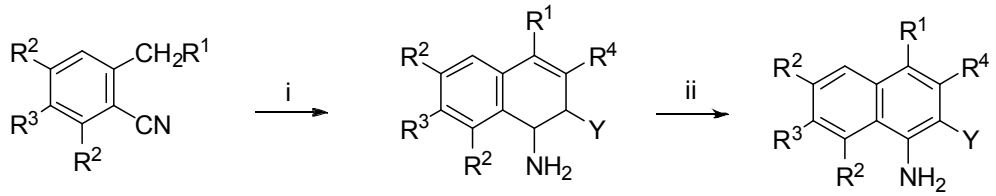
1.3.2 Review of Literature

Literature search revealed that there are a few reports available for the synthesis of 1-amino-2-naphthalene carboxylic acid derivatives, which are described below.

Kobayashi's Approach (1997)[37, 38]

Kobayashi *et al*. have described the synthesis of 1-amino-2-naphthalenecarboxylic acid derivatives **45** *via* sequential Michael addition/enolate-nitrile coupling route. Thus, the reaction of 2-(α-lithioalkyl)benzonitriles (generated *in situ* by treatment of 2-alkylbenzonitriles **43** with LDA in diglyme, with α,*β*-unsaturated carboxylates and nitriles) produced 1-amino-3,4-dihydro-2-naphthalenecarboxylates **44** in 54-98%

yields. This reaction proceeds through Michael addition of lithio nitriles to α,*β*-unsaturated carboxylic acid derivatives, followed by zinc iodide-promoted intramolecular enolate-nitrile coupling of the resulting enolate intermediates. The dihydronaphthalenecarboxylic acid derivatives **44** were converted to the corresponding 1-amino-2-naphthalenecarboxylic acid derivatives **45** in 43-99% yields on dehydrogenation with Pd/C in refluxing *p*-cymene (**Scheme 14**).



43 **44** **45**

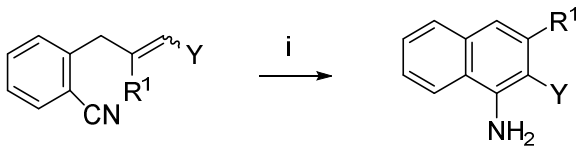
R^1= R^2= R^3= H, Ph, OMe, Me
R^4 = Me, Ph
Y = CO_2Me, CN, $CO_2{}^tBu$

54-98%

43-99%

Scheme 14: (i) (a) LDA, diglyme, -78 °C; (b) $R^4CH{=}CHY$, -78 °C; (ii) (a) ZnI_2, -78 to 25 °C, 54-98%; (b) 10% Pd/C, *p*-cymene, reflux, 43-49%.

The same group[38] has also synthesized 1-amino-2-naphthalenecarboxylic acid derivatives **45** by treating (2-cyanophenyl)butenoic acid derivatives **46** with NaH in DMF at 0 °C in 75-88% yield (**Scheme 15**).



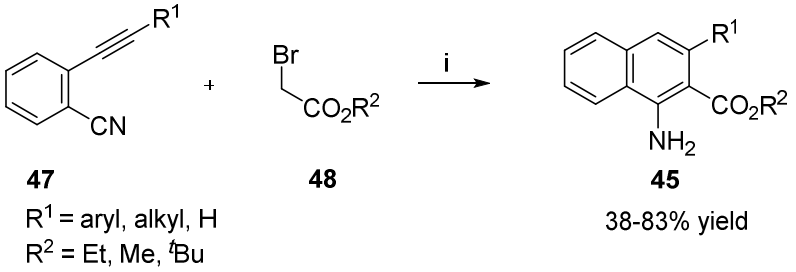
46
R^1 = Me, Ph
Y= CO_2Et, CN

45
75-88% yield

Scheme 15: (i) NaH, DMF, 0 °C, 1 h, 75-88%.

Srinivasan's approach (2014)[39]

Srinivasan *et al.* have described the action of a Reformatsky reagent on *o*-alkynylarenenitriles **47** providing a convenient access to naphthalene amino esters **45** *via* tandem 6-*endo*-dig carbannulation of *in situ* generated Blaise reaction intermediates. The products are formed in moderate to good yields with high chemo- and regioselectivity (**Scheme 16**).



47 **48** **45**

R^1 = aryl, alkyl, H

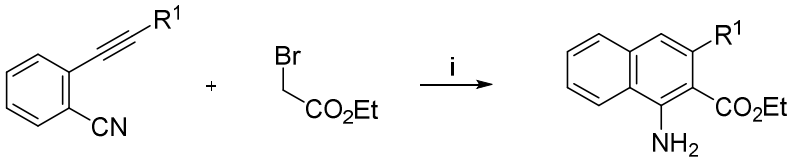
R^2 = Et, Me, ^{t}Bu

38-83% yield

Scheme 16: (i) Zn (7.5 equiv), dioxan, reflux, 2 h, 38-83%.

Fan's approach (2014)[40]

Fan *et al.* have recently described a tandem reaction of 2-alkynylbenzonitriles **47** with Reformatsky reagent (formed by action of Zn and ethyl 2-bromoacetate **48**) to afford 1-aminonaphthalene-2-carboxylates **45** in moderate to high yields (**Scheme 17**).



47 **48** **45**

R^1 = Ph, aryl, H

68-88% yield

Scheme 17: (i) Zn (3.0 equiv), THF, reflux, 0.5 h, 68-88%.

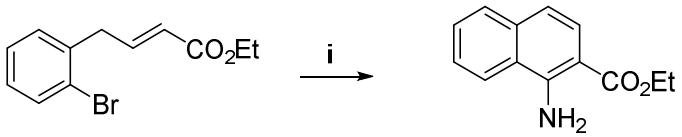
1.3.3 Present Work

1.3.3.1 Objective

As can be seen, there are only a few methods available in literature for the synthesis of 1-amino-2-naphthalenecarboxylic acid derivatives. These known methods require highly functionalized starting materials and necessitate the use of either excess amount of base or activated Zn metal. In this context, a more practical and efficient synthesis of functionalized 1-amino-2-naphthalenecarboxylate derivatives is highly desirable. In this section, we describe a novel CuCN-mediated "one-pot" cascade route to 1-amino-2-naphthalenecarboxylic acid derivatives **45a** directly from 4-(2-bromophenyl)-2-butenoates **49a** (**Scheme 18**).

1.3.3.2 Results and Discussion

It has been well documented in literature that the reaction of bromobenzene derivatives with CuCN (3 equiv) in DMF at reflux temperature (Rosenmund-Von Braun reaction) leads to the formation of the corresponding cyanobenzene derivatives namely benzonitriles.[41] We found however, that when the same reaction was carried out under identical conditions with ethyl 4-(2-bromophenyl)-2-butenoate **49a** as substrate in the presence of CuCN (3 equiv) under reflux conditions, it took a different course altogether to give an annulated product, namely ethyl 1-amino-2-naphthalenecarboxylate **45a** in excellent yield (**Scheme 18**).



49a **45a**

Scheme 18: (i) CuCN (3 equiv), DMF, 150 °C, 12 h, 85%.

For determining the optimal conditions (**Table 4**), substrate **49a** was treated with CuCN (1 equiv) in DMF at 150 °C, which gave the corresponding annulated product

45a in 28% yield. The yield of **45a** was significantly improved to 53% when the CuCN quantity was increased to 2 equivalents under the same reaction conditions.

Table 4: CuCN-mediated one-pot synthesis of ethyl 1-aminonaphthalene-2-carboxylate **45a**: optimization studies[a]

entry	CN-source (equiv)	T (ºC)	solvent	yield (%)[b]
1	CuCN (1)	150	DMF	28
2	CuCN (2)	150	DMF	53
3	CuCN (3)	150	DMF	85
4	CuCN (3.5)	150	DMF	85
5	CuCN (3)	120	DMF	48
6	CuCN (3)	150	DMSO	trace
7	CuCN (3)	150	DMAc	25
8	NaCN (1.2) + CuI (10 mol %)	110	toluene	30[c]
			DMF	--[d]
9	CuCN (1.3) + *L*-proline	120	DMF	49

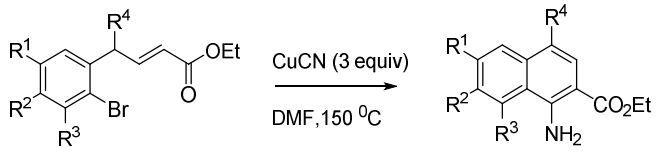
[a]substrate **49a** (1 mmol), CuCN (3 mmol), DMF (10 mL), 12 h; [b]isolated yield after column chromatographic purification; [c]substitution of Br with CN coupled with isomerized alkene was observed; [d] no reaction.

Interestingly, on further increasing the CuCN concentration to 3 equivalents, a dramatic improvement in the yield of **45a** (85%) was realized. However, lowering the temperature of the reaction had deleterious effect on the conversion (entry 5). A brief evaluation of solvents confirmed that DMF was the most suitable one. In order to provide a catalytic process, we carried out the Cu-catalyzed reaction[42] [CuI (10 mol %), KI, DMEDA, NaCN] in toluene, which however afforded cyanated product with isomerized alkene (30%). Further, use of *L*-proline as an additive[43] to minimize the CuCN quantity gave **45a** in moderate yield (49%). After several experimentations, it was thus found that a combination of *o*-bromo ester **49a** (1 equiv), CuCN (3 equiv) in

DMF at 150 ºC for 12 h was the best optimized conditions in achieving excellent product yields **45a-k** (**Table 5**).

When subjected to CuCN-mediated "one-pot" cascade reaction with 3 equiv of CuCN, several ethyl 4-(2-bromo-phenyl)-2-butenoate derivatives **49a-k** gave the corresponding annulated naphthalene derivatives **45a-k** in 73-91% yields. Results of such studies are presented in **Table 5**. As can be seen, this cascade cyclization took place smoothly to provide **45a-k** in a "one-pot" reaction, which comprised of several transformations taking place in a single step, with a variety of substituted ethyl 4-(2-bromo-phenyl)-2-butenoates **49a-k** and cheaply available CuCN reagent.

Table 5: CuCN-mediated one-pot synthesis of substituted naphthalene amino esters.



49a-k **45a-k**

entry	Substrates (**49a-k**)				Products (**45a-k**)
	R^1	R^2	R^3	R^4	Yield (%)[a]
a	H	H	H	H	85
b	OMe	H	H	H	78
c	OMe	OMe	H	H	74
d	H	OMe	OMe	H	73
e	OBn	OMe	H	H	76
f	H	Me	H	H	81
g	F	H	H	H	88
h	NO_2	H	H	H	91
i	-O-CH_2-O-		H	H	82
j	OMe	OMe	H	Me	86
k	H	Benzo fused		H	78

[a]Isolated yield after column chromatographic purification

For instance, substrates having halogen (entry g), methyl (entry f), highly electron rich (entry c & d) or electron deficient (entry h) substrates on the aromatic ring underwent this cascade cyclization smoothly affording the corresponding cyclized products **45a-k** with excellent yield in a single step. Interestingly, electron-deficient substrates gave relatively higher yields of products as compared to electron-rich substrates. This may be ascribed to the mesomeric effect, which probably increases electropositive character of carbon in cyano, thereby resulting in high yields of the cyclized product. It was found that the annulation is not merely restricted to the synthesis of naphthalene derivatives **45a-j**; it allows for the synthesis of phenanthrene derivative **45k** as well. The formation of products **45a-k** was confirmed from NMR, HRMS and X-ray crystallographic analysis (for **45h**).

Example 1: The formation of ethyl 1-amino-6-nitro-2-naphthoate (**45h**) was confirmed by the presence of broad singlet at δ 6.90 (br. s., 2H), indicative of presence of –N**H**$_2$ integrating for two protons in its ^{1}H NMR spectrum. It was further substantiated by the typical aromatic carbon signals at δ 107.3, 117.0, 118.3, 123.5, 124.5, 125.8, 129.1, 135.7, 147.1, and 148.3 in the ^{13}C NMR spectrum corresponding to ten carbons of the naphthalene nucleus (**Fig. 17**). The IR spectrum of **45h** displayed strong N-H stretching frequencies at 3335 and 3346 cm^{-1} indicating the presence of primary amine functional group. The regiochemistry of the formed product was unambiguously confirmed by its single crystal XRD (**Fig. 18**).

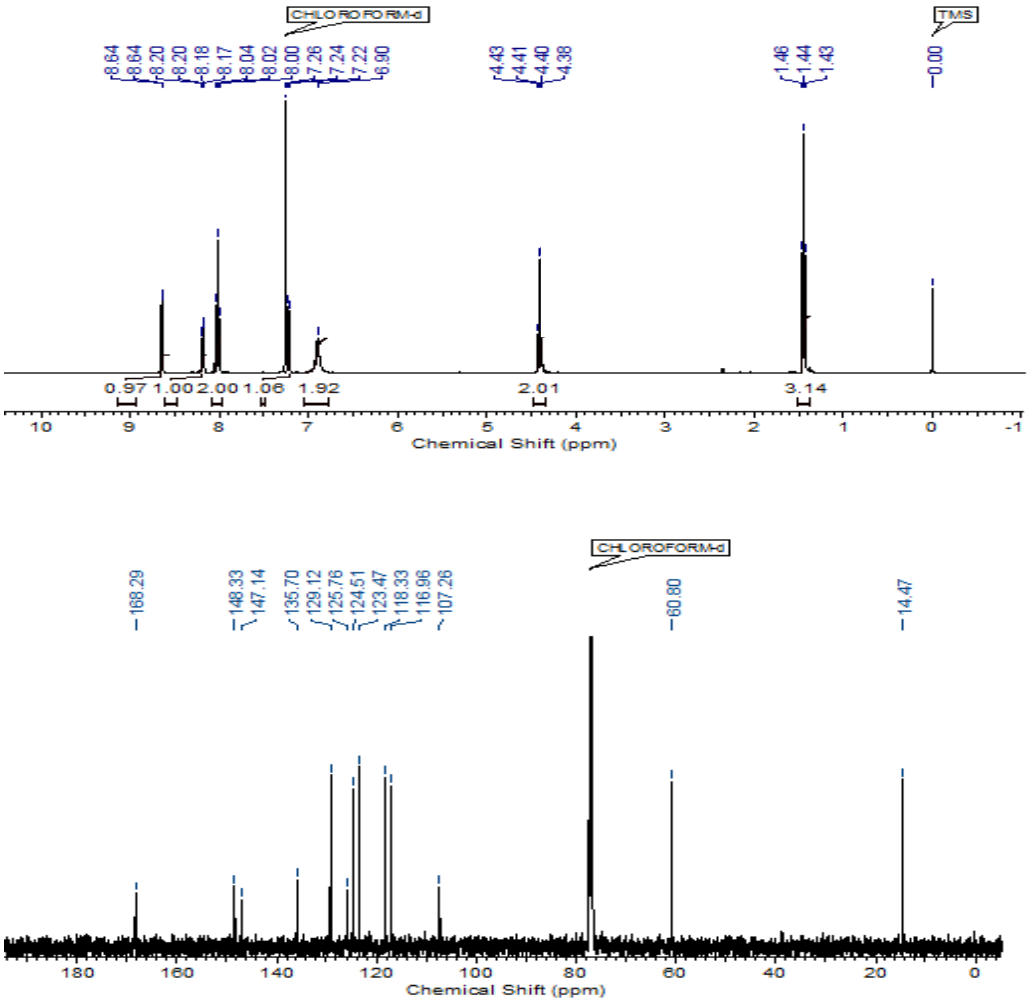
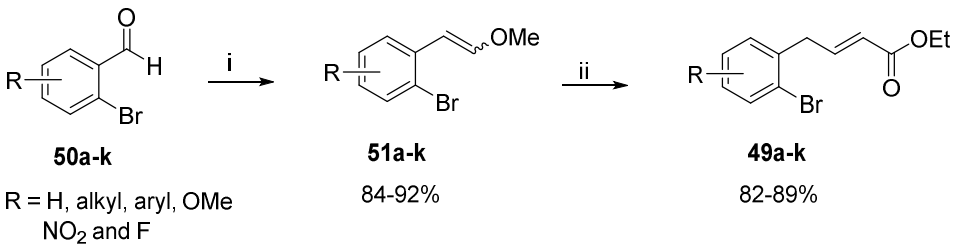


Fig. 18: ^{1}H, ^{13}C NMR spectra and ORTEP diagram of **45h**.

Ethyl 4-(2-bromophenyl)-2-butenoate derivatives **49a-k** were prepared in three steps starting from the corresponding *o*-bromobenzaldehydes **50a-k** using reported procedures. Accordingly, Wittig olefination of *o*-bromobenzaldehydes **50a-k** using $MeOCH_2PPh_3Cl$ and KO^{t}Bu in THF gave the corresponding methyl ethers **51a-k** in 84-92% yield with mixtures of E/Z isomers (~1.3:1). Acidic hydrolysis of methyl ethers **51a-k** afforded the corresponding phenyl acetaldehydes in good yields, which was then subjected to Horner-Wadsworth-Emmons reaction using triethylphosphonoacetate and NaH in THF that afforded ethyl 4-(2-bromophenyl)-2-butenoate derivatives **49a-k** in 84-93% yield (**Scheme 19**).



Scheme 19: (i) $MeOCH_2PPh_3Cl$, KO^{t}Bu, THF, 0 to 25 °C, 2 h; (ii) (a) 2N HCl, THF, reflux, 3 h; (b) $(OEt)_2POCH_2CO_2Et$, NaH, THF, 0 °C, 3 h.

The compounds **49a-k** were confirmed by ^1H, ^{13}C NMR and IR spectroscopy.

Example 1: The ^1H NMR spectrum of ethyl (*E*)-4-(2-bromo-4,5-dimethoxyphenyl)but-2-enoate (**49c**) showed a triplet at δ 1.28 (-C**H**$_3$) and a quartet at δ 4.17 (-OC**H**$_2$) characteristic of an ethyl signal and a triplet of doublet at δ 5.75 (td, *J* = 1.5, 15.7 Hz, 1H) corresponding to the olefinic proton with an *E*-geometry. Its structure was further supported by ester carbonyl carbon signal at δ 166.0 in its ^{13}C NMR spectrum (**Fig. 19**).

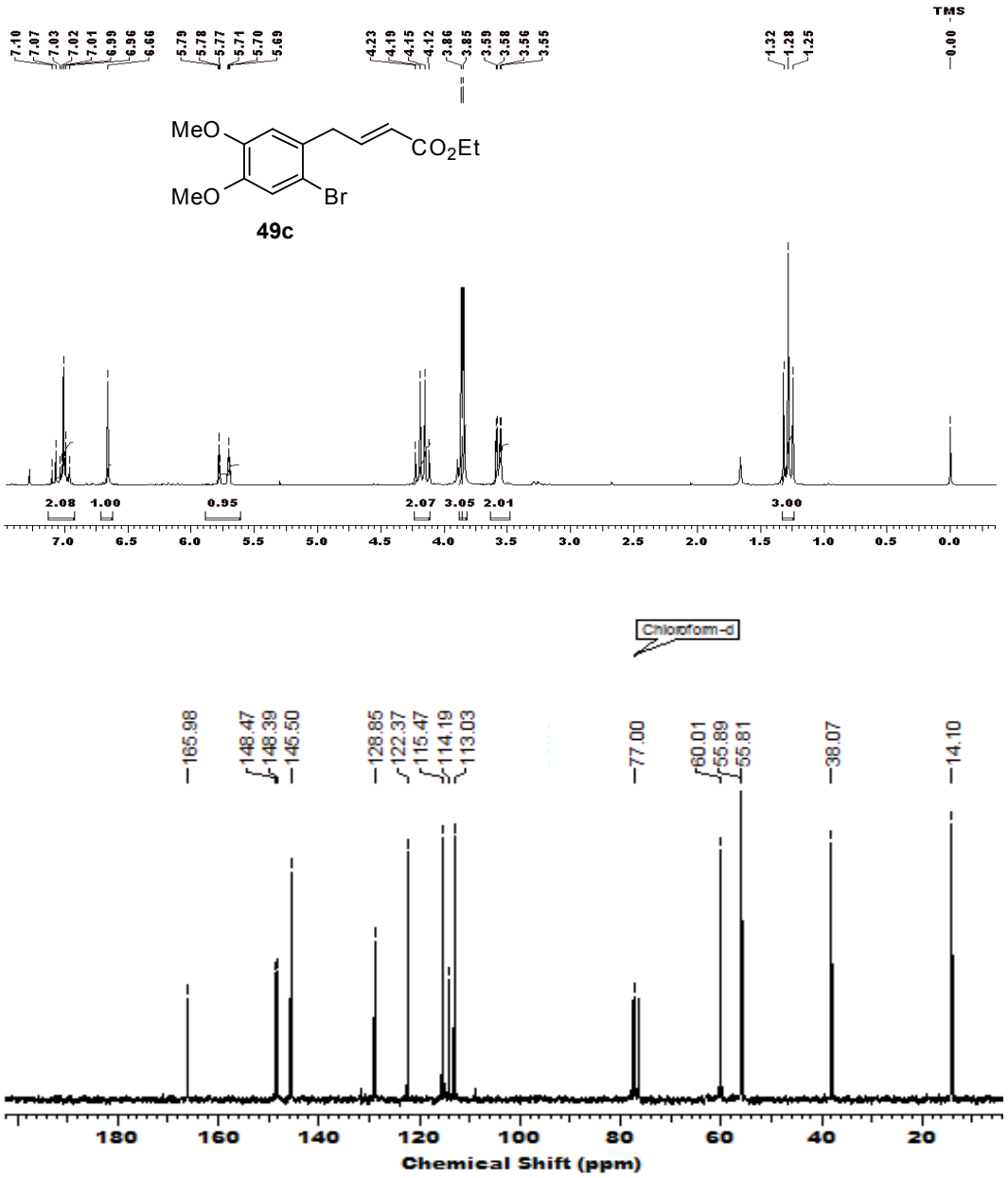
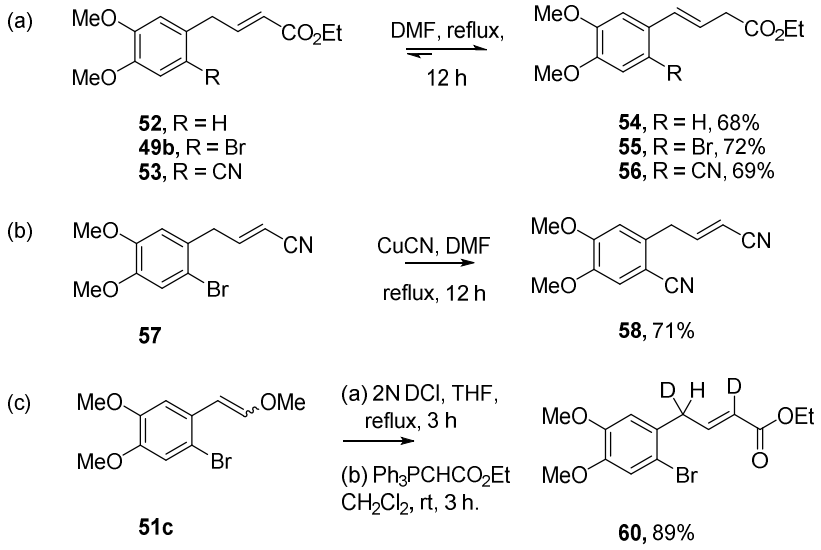


Fig. 19: ^{1}H and ^{13}C NMR spectra of **49c**

1.3.3.3 Mechanistic Discussion

In order to gain insight into the mechanistic details of the reaction, the following experiments were conducted: (a) when α,β-unsaturated ester **52**, **49c** or **53** was dissolved in DMF and refluxed at 150 °C in the absence of CuCN, the corresponding β,γ-unsaturated ester **54**, **55** or **56** respectively in equilibrium with starting materials

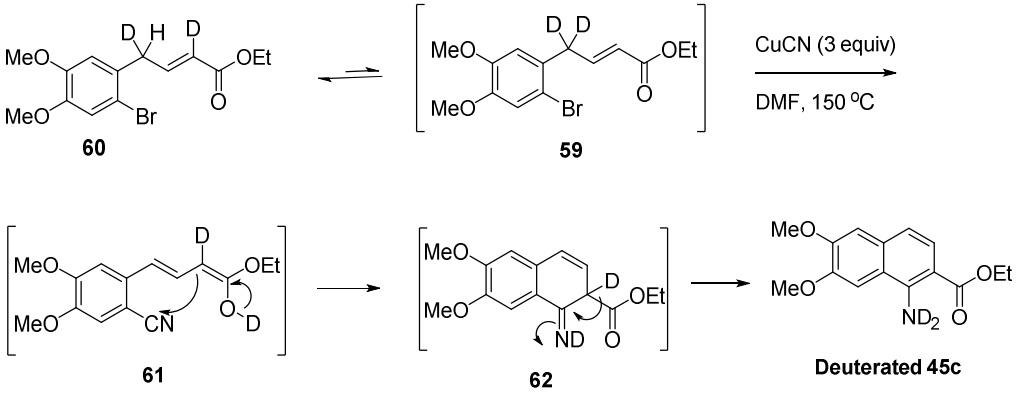
52, **49c** or **53** (ratio 3:2) were isolated; (b) additionally, when *o*-bromoaromatic derivative **57** was subjected to CuCN-mediated cyanation reaction, mere substitution of Br with CN took place giving **58** without the isomerisation of C=C bond. This observation suggests that, under thermal conditions, the isomerization of C=C bond might probably be involved;[44] (c) to support this hypothesis further, deuterium labeling experiments were carried out as follows: enol ether **51c** was hydrolysed with 2N DCl and the formed hydrolyzed product was *in situ* trapped with Wittig olefination reagent which led to the formation of **60** (showing 60% deuterium incorporation at α- position to ester functionality) (**Scheme 20**).



Scheme 20: Control experiments and deuterium labelling studies

Compound **60** on treatment with CuCN (3 equiv) in DMF resulted in deuterated amino ester *i.e.* deuterated compound of **45c** (73% yield), whose structure was established from deuterium NMR studies. Based on our control experiments and literature precedence, a probable mechanism has been proposed in **Scheme 21**. Firstly, olefin is believed to undergo thermal isomerisation of olefin by 1,5-Deuterium shift and concomitant conversion of bromo to cyano derivative (**60** to **61**) followed by

intramolecular C-C bond cyclization involving attack on the cyano carbon (**61** to **62**) and finally aromatization (**62** to deuterium compound of **45c**) to afford naphthalene core all occurring in a single step.



Scheme 21: Probable mechanistic pathway

1.3.4 Conclusion

To summarize, we have disclosed a simple annulation strategy that affords a variety of substituted naphthalene amino esters **45a-k** in high yields (78-91%) from the corresponding ethyl 4-(2-bromo-phenyl)-2-butenoate derivatives **49a-k** *via* CuCN-promoted cyclization in a single step. Mechanistically, this annulation involves isomerization of olefin, intramolecular C-C bond cyclization and aromatization as the key steps. We believe, that this one-pot cascade cyclization strategy will find tremendous applications in the synthesis of polyannulated aromatics and will serve as useful intermediates for the synthesis of complex bioactive molecules.

1.3.5 Experimental Section

General experimental procedure for the preparation of ethyl 4-(2-bromophenyl)-2-butenoate derivatives (49a-k)

To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (6.5 mmol) in THF (25 mL) under complete inert atmosphere at 0 °C was added KO^{t}Bu (5.75 mmol) which resulted in formation of a bright red-coloured solution. The resulting mixture was stirred at the same temperature for 0.5 h followed by slow dropwise addition of solution of 2-bromo aldehydes **50a-k** (5.0 mmol) in THF (10 mL) through a syringe over 10 min which led to slow decolorisation of the reaction mixture. The reaction mixture was then brought to 25 °C and allowed to stir further for 3 h until completion (as monitored by TLC). After completion of the reaction, excess base was quenched with ice and THF was concentrated *in vacuo*. The resulting solution was then diluted with ethyl acetate (25 mL), organic layer was separated and aqueous layer extracted further with ethyl acetate (3 x 25 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product.

To a stirred solution of crude methyl vinyl ether derivatives **51a-k** (5.0 mmol) in THF (10 mL) was added an aqueous solution of 1N aq. HCl (10 mL) at room temperature. The resulting solution was refluxed for 3 h. After evaporation of the THF *in vacuo*, water was added to the mixture, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$ solution, dried over anhyd. Na_2SO_4, filtered and concentrated *in vacuo*. The obtained crude aldehydes were immediately used for the next reaction without purification because of their instability to air and moisture.

To a stirred solution of triethylphosphonoacetate (5.5 mmol) in THF (20 mL) was added NaH (6.0 mmol) at 0 °C under complete inert atmosphere. After 15 min, dropwise addition of a solution of crude aldehyde (5.0 mmol) in THF was done over 10 min. The reaction mixture was then allowed to stir for 3 h at 25 °C. After completion of the reaction (as monitored by TLC after), excess NaH was quenched slowly with ice and THF was concentrated *in vacuo*. The resulting solution was then diluted with ethyl acetate (20 mL), organic layer was separated and aqueous layer extracted further with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and Pet. ether:EtOAc (90:10) as eluent] afforded the unsaturated esters **49a-k** in pure form.

Data analysis for the synthesis of new compounds.

(*E*)-Ethyl 4-(2-bromo-4, 5-dimethoxyphenyl)but-2-enoate (49c)

Yield: 84% (1.38 g, 4.192 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 780, 936, 1032, 1071, 1156, 1176, 1239, 1280, 1468, 1712, 2978; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.61 (dd, *J* = 1.6, 6.4 Hz, 2H), 3.86 (s, 3H), 3.87(s, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.76 (td, *J* = 1.5, 15.7 Hz, 1H), 6.81-7.13 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 38.1, 55.8, 60.0, 113.0, 114.2, 115.5, 122.4, 128.9, 146.7, 145.5, 148.4, 148.5, 166.0; **Analysis**: $C_{14}H_{17}BrO_4$ requires C, 51.08; H, 5.21; Br, 24.27; Found: C, 50.95; H, 5.13; Br, 24.34%.

(*E*)-Ethyl 4-(2-bromo-3,4-dimethoxyphenyl)but-2-enoate (49d)

Yield: 82% (1.35 g, 4.101 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 895, 978, 1024, 1050, 1142, 1188, 1245, 1276, 1477, 1714, 2965; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.61 (dd, *J* = 1.3, 7.1 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 6.81-7.27 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2,

38.1, 56.0, 60.1, 111.3, 120.3, 125.2, 130.2, 145.8, 146.7, 152.3, 166.2; **Analysis**: $C_{14}H_{17}BrO_4$ requires C, 51.08; H, 5.21; Br, 24.27; Found: C, 50.98; H, 5.14; Br, 24.32%.

(*E*)-Ethyl 4-(5-(benzyloxy)-2-bromo-4-methoxyphenyl)but-2-enoate (49e)

Yield: 84% (1.70 g, 4.195 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 780, 882, 1035, 1072, 1151, 1190, 1278, 1292, 1456, 1712, 2974; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 3.27 (dd, *J* = 1.4, 7.1 Hz, 2H), 3.89 (s, 3H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.10 (s, 2H), 6.14 (td, *J* = 7.2, 15.8 Hz, 1H), 7.02 (s, 2H), 7.32-7.44 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 38.1, 55.8, 60.0, 113.0, 114.2, 115.5, 122.4, 128.8, 145.5, 148.4, 166.0; **Analysis**: $C_{20}H_{21}BrO_4$ requires C, 59.27; H, 5.22; Br, 19.72; Found: C, 59.34; H, 5.28; Br, 19.65%.

(*E*)-Ethyl 4-(2-bromo-4-nitrophenyl)but-2-enoate (49h)

Yield: 84% (1.32 g, 4.202 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 768, 878, 1018, 1085, 1178, 1285, 1298, 1455, 1716, 2960; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3H), 3.63 (dd, *J* = 1.3, 7.1 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 5.74 (td, *J* = 3.8, 15.7 Hz, 1H), 6.36 (dd, *J* = 1.8, 2.9 Hz, 2H), 6.97-7.12 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.1, 60.2, 98.0, 105.1, 106.8, 122.7, 139.1, 145.3, 156.9, 159.6, 166.2; **Analysis**: $C_{12}H_{12}BrNO_4$ requires C, 45.88; H, 3.85; Br, 25.44; N, 4.46; Found: C, 45.76; H, 3.76; Br, 25.36; N, 4.39%.

(*E*)-Ethyl 4-(2-bromo-4,5-dimethoxyphenyl)pent-2-enoate (49j)

Yield: 89% (1.53 g, 4.458 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 856, 937, 1030, 1133, 1233, 1268, 1445, 1716, 2984; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.37 (d, *J* = 7.0 Hz, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.06 (qd, *J* = 5.5, 1.5 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.80 (dd, *J* = 15.8, 1.64 Hz, 1H), 6.63 (s, 1H), 7.01 (s, 1H), 7.09 (dd, *J* = 15.8, 5.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1,

19.1, 40.1, 55.8, 60.0, 110.6, 113.9, 115.5, 120.4, 134.0, 148.2, 148.7, 150.9, 166.2; **Analysis**: $C_{15}H_{19}BrO_4$ requires C, 52.49; H, 5.58; Br, 23.28; Found: C, 52.33; H, 5.12; Br, 23.18%.

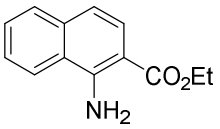
(*E*)-Ethyl 4-(1-bromonaphthalen-2-yl)but-2-enoate (49k)

Yield: 89% (1.49 g, 4.458 mmol); yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 872, 1058, 1175, 1184, 1245, 1468, 1713, 2962; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 3.89 (dd, *J* = 6.3, 1.6 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.77 (dt, *J* = 15.6, 1.6 Hz, 1H), 7.06-7.30 (m, 2H), 7.45-7.62 (m, 2H), 7.77 (t, *J* = 8.5 Hz, 2H), 8.30 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 39.8, 60.2, 122.9, 124.4, 126.3, 127.4, 127.5, 127.8, 128.0, 128.3, 132.6, 133.5, 135.2, 145.2, 166.1; **Analysis**: $C_{16}H_{15}BrO_2$ requires C, 60.21; H, 4.74; Br, 25.03; Found: C, 60.11; H, 4.32; Br, 24.90%.

General experimental procedure for substituted naphthalene derivatives (45a-k)

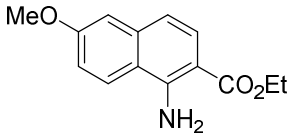
To a stirred solution of alkenes **49a-k** (1 mmol) in dry DMF (10 mL) was added CuCN (3 mmol) and the entire solution was refluxed under N_2 atmosphere for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature and diluted with water (20 mL). The reaction mixture was then filtered over celite 545 bed. The obtained filtrate was diluted with ethyl acetate, the organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic extracts were repeatedly washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give crude product which was purified by column chromatography [silica gel (230-400 mesh) and Pet. ether:EtOAc (7:3) as an eluent] to give ethyl-1-amino-2-naphthalene carboxylate derivatives (**45a-k**) in 73-91% yield.

Ethyl 1-aminonaphthalene-2-carboxylate (45a)



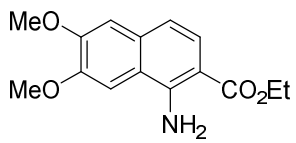
Yield: 85% (0.183 g, 0.850 mmol); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 798, 865, 964, 1015, 1135, 1157, 1232, 1264, 1471, 1665, 2965, 3335, 3346; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 1H), 7.44-7.53 (m, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.1, 104.2, 115.7, 121.4, 123.1, 125.0, 126.6, 128.2, 128.4, 136.4, 148.8, 168.8; **HRMS** (ESI): calcd for $(C_{13}H_{13}NO_2)^+$ $[(M+Na)^+]$ 238.0844; found: 238.0836.

Ethyl 1-amino-6-methoxynaphthalene-2-carboxylate (45b)



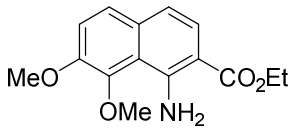
Yield: 78% (0.191 g, 0.778 mmol); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 870, 1076, 1245, 1340, 1599, 1672, 3346, 3457; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 3.92 (s, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 1H), 7.02-7.11 (m, 2H), 7.82 (t, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.5, 55.2, 60.0, 103.2, 107.0, 115.1, 117.0, 117.9, 123.3, 127.5, 138.3, 148.9, 159.6, 168.8; **HRMS** (ESI): calcd for $(C_{14}H_{15}NO_3)^+$ $[(M+Na)^+]$ 268.0950; found: 268.0944.

Ethyl 1-amino-6,7-dimethoxynaphthalene-2-carboxylate (45c)



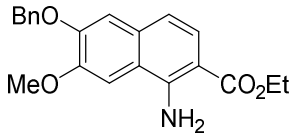
Yield: 74% (0.204 g, 0.741 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 798, 865, 964, 1015, 1135, 1157, 1232, 1264, 1471, 1665, 2965, 3335, 3346; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.00 (s, 3H), 4.01 (s, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 1H), 7.02 (s, 1H), 7.05 (s, 1H), 7.77 (d, *J* = 8.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 55.6 60.1, 101.1, 103.8, 107.1, 114.8, 117.6, 125.1, 132.4, 147.6, 148.6, 150.9, 168.8; **HRMS** (ESI): calcd for $(C_{15}H_{17}NO_4)^+$ $[(M+Na)^+]$ 298.1055; found: 298.1062.

Ethyl 1-amino-7,8-dimethoxynaphthalene-2-carboxylate (45d)



Yield: 73% (0.201 g, 0.730 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 779, 826, 956, 1018, 1267, 1579, 1672, 3334, 3464; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.2 Hz, 3H), 3.97 (s, 6H), 4.35 (q, *J* = 7.2 Hz, 2H), 6.82 (d, *J* = 10.4 Hz, 1H), 7.24-7.28 (m, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.5, 56.8, 61.5, 102.7, 114.1, 116.8, 118.0, 124.4, 125.3, 133.2, 147.0, 148.7, 151.1, 168.9; **HRMS** (ESI): calcd for $(C_{15}H_{17}NO_4)^+$ $[(M+Na)^+]$ 298.1055; found: 298.1049.

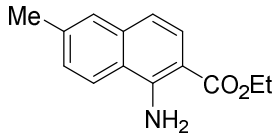
Ethyl 1-amino-6-(benzyloxy)-7-methoxynaphthalene-2-carboxylate (45e)



Yield: 76% (0.267 g, 0.759 mmol); colorless solid; **mp:** 144-145 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1247, 1483, 1619, 1676, 3434, 3452; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.1 Hz, 3H), 4.00 (s, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 5.26 (s, 2H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 7.18 (s, 1H), 7.30-7.51 (m, 5H), 7.76 (d, *J* = 8.8 Hz, 1H); **^{13}C**

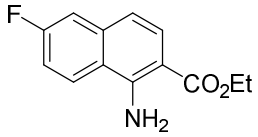
NMR (50 MHz, $CDCl_3$): δ 14.5, 55.8, 60.1, 71.3, 104.3, 107.6, 115.2, 117.9, 125.5, 127.4, 128.1, 128.7, 132.9, 136.7, 147.5, 147.9, 151.8, 168.9; **HRMS** (ESI): calcd for $(C_{21}H_{21}NO_4)^+$ $[(M+Na)^+]$ 374.1368; found: 374.1375.

Ethyl 1-amino-6-methylnaphthalene-2-carboxylate (45f)



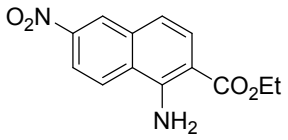
Yield: 81% (0.186 g, 0.811 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1078, 1222, 1239, 1257 1605, 1663, 3352, 3453; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.1 Hz, 3H), 2.54 (s, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.5, 22.0, 60.2, 104.9, 116.1, 120.9, 123.4, 125.7, 128.4, 130.4, 134.6, 134.9, 147.9, 168.9; **HRMS** (ESI): calcd for $(C_{14}H_{15}NO_2)^+$ $[(M+Na)^+]$ 252.1000; found: 252.0992.

Ethyl 1-amino-6-fluoronaphthalene-2-carboxylate (45g)



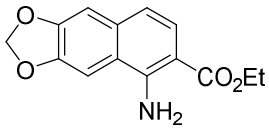
Yield: 88% (0.205 g, 0.870 mmol); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 767, 1249, 1604, 1673, 2987, 3347, 3447; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.2 Hz, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 1H), 7.15-7.24 (m, 1H), 7.34 (dd, *J* = 2.5, 7.1 Hz, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.9 (d, *J* = 8.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.2, 104.1, 111.8 (d, *J* = 20.8 Hz), 114.7 (d, *J* = 25.4 Hz), 115.1 (d, *J* = 3.9 Hz), 120.0, 124.2 (d, *J* = 10.0 Hz), 128.1, 138.0 (d, *J* = 9.2 Hz), 148.8, 162.2 (d, *J* = 249.7 Hz), 168.6; **HRMS** (ESI): calcd for $(C_{13}H_{12}FNO_2)^+$ $[(M+Na)^+]$ 256.0750; found: 256.0743.

Ethyl 1-amino-6-nitronaphthalene-2-carboxylate (45h)



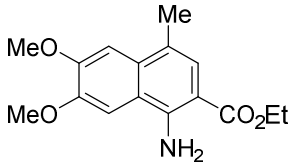
Yield: 91% (0.237 g, 0.911 mmol); red solid; **mp:** 176-177 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1243, 1345, 1602, 1674, 3352, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (t, *J* = 7.0 Hz, 3H), 4.41 (q, *J* = 7.0 Hz, 2H), 6.90 (br. s, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 8.02 (t, *J* = 8.8 Hz, 2H), 8.18 (dd, *J* = 9.3, 2.3 Hz, 1H), 8.65 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.8, 107.2, 116.9, 118.3, 123.4, 124.5, 125.7, 129.1, 135.7, 147.1, 148.3, 168.2; **HRMS** (ESI): calcd for $(C_{13}H_{12}N_2O_4)^+$ $[(M+Na)^+]$ 283.0695; found: 283.0687.

Ethyl 5-aminonaphtho[2,3-d][1,3]dioxole-6-carboxylate (45i)



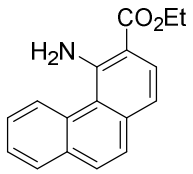
Yield: 82% (0.213 g, 0.822 mmol); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1243, 1345, 1602, 1674, 3352, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.0 Hz, 3H), 4.35 (q, *J* = 7.0 Hz, 2H), 6.05 (s, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 7.00 (s, 1H), 7.16 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.0, 98.7, 101.3, 104.5, 104.9, 115.6, 119.0, 125.5, 134.0, 147.4, 147.8, 149.2, 168.8; **HRMS** (ESI): calcd for $(C_{14}H_{13}NO_4)^+$ $[(M+Na)^+]$ 282.0742; found: 282.0747.

Ethyl 1-amino-6,7-dimethoxy-4-methylnaphthalene-2-carboxylate (45j)



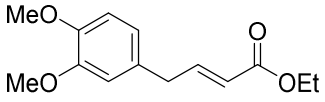
Yield: 81% (0.234 g, 0.809 mmol); yellow solid; **mp:** 135-137 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 798, 865, 964, 1063, 1205, 1232, 1250, 1462, 1482, 1513, 1602, 1674, 2980, 3352, 3471; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.1 Hz, 3H), 2.50 (s, 3H), 4.02 (s, 6H), 4.36 (q, *J* = 7.1 Hz, 2H), 7.11 (s, 1H), 7.13 (s, 1H), 7.61 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 18.9, 55.3, 55.4, 59.8, 101.7, 103.5, 103.6, 118.1, 120.1, 124.8, 131.5, 146.3, 148.0, 150.5, 168.7; **HRMS** (ESI): calcd for $(C_{16}H_{19}NO_4)^+$ $[(M+Na)^+]$ 312.1212; found: 312.1217.

Ethyl 1-aminophenanthrene-2-carboxylate (45k)



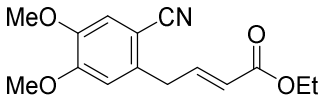
Yield: 71% (0.188 g, 0.709 mmol); yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 791, 845, 964, 1052, 1215, 1239, 1240, 1412, 1472, 1533, 1664, 2970, 3332, 3451; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (t, *J* = 7.1 Hz, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.11 (d, *J* = 8.6 , 1H), 7.49-7.64 (m, 3H), 7.73 (d, *J* = 8.7, 1H), 7.88 (dd, *J* = 9.0, 1.6, 1H), 8.05 (d, *J* = 8.5, 1H), 9.19 (d, *J* = 8.2, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.4, 108.2, 116.7, 119.1, 124.5, 125.6, 126.5, 127.0, 128.3, 129.1, 129.6, 130.8, 132.8, 137.1, 151.0, 169.1; **HRMS** (ESI): calcd for $(C_{17}H_{15}NO_2)^+$ $[(M+Na)^+]$ 288.1000; found: 288.1009; **Analysis**: $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28; found: requires C, 76.71; H, 5.51; N, 5.22%.

(*E*)-Ethyl 4-(3,4-dimethoxyphenyl)but-2-enoate (52)



IR ($CHCl_3$, cm^{-1}): υ_{max} 856, 965, 1054, 1144, 1163, 1241, 1263, 1312, 1456, 1714, 2864; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.45 (dd, *J* = 1.5, 6.6, Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.78 (td, *J* = 1.6, 15.5 Hz, 1H), 6.65-6.72 (m, 2H), 6.78-6.82 (m, 1H), 7.06 (td, *J* = 6.6, 15.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 37.8, 55.5, 55.6, 59.9, 111.2, 111.7, 120.6, 121.8, 129.8, 147.3, 147.6, 148.8, 166.1; **HRMS** (ESI): calcd for $(C_{14}H_{18}O_4)^+$ $[(M+Na)^+]$ 273.1103; found: 273.1108.

(*E*)-Ethyl 4-(2-cyano-4,5-dimethoxyphenyl)but-2-enoate (53)

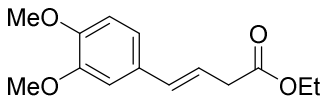


Potassium osmate dihydrate (36 mg, 0.1 mmol) and *N*-methylmorpholine *N*-oxide (2.3 g, 20 mmol) were added to a solution of 2-allyl-4,5-dimethoxybenzonitrile (2.03 g, 10 mmol) in acetone/H_2O (30 mL, 1:1 ratio) and stirred at room temperature until all the starting material had been consumed (monitored by TLC after 12 h). CH_2Cl_2 was added, and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). Organic extracts were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude diol, which was then directly taken for the next step without purification. To a vigorously stirred suspension of silica gel-supported $NaIO_4$ reagent (2.1 g, 10 mmol) in CH_2Cl_2 was added a solution of the crude vicinal diol in CH_2Cl_2. The reaction was monitored by TLC until disappearance of the starting material. The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with CH_2Cl_2. Organic extract was washed with brine, dried over anhydrous and concentrated to deliver crude aldehyde. To a stirred solution of this crude aldehyde in CH_2Cl_2 at 25 °C was added two carbon Wittig reagent *i.e*

$Ph_3P{=}CHCO_2Et$ (3.8 g, 11.1 mmol) and the resulting mixture was stirred further for 2 h at the same temperature. After completion of the reaction, CH_2Cl_2 was concentrated to afford the alkene product. Chromatographic purification of this crude product [silica gel (230-400 mesh) and Pet. ether:EtOAc (90:10) as eluent] afforded the unsaturated ester **53** in pure form in 62% yield.

Yield: 62% (1.7 g, 0.6 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 893, 964, 1051, 1142, 1163, 1241, 1263, 1456, 1712, 2213, 2965; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 3.57 (dd, *J* = 1.6, 6.3 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.17 (q, *J* = 7.0 Hz, 2H), 5.74 (td, *J* = 1.6, 15.5 Hz, 1H), 6.86 (s, 1H), 7.01 (s 1H), 7.02 (td, *J* = 6.4, 15.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.1, 56.0, 56.1, 60.9, 102.6, 107.3, 113.7, 118.0, 125.2, 129.1, 134.7, 148.7, 152.8, 171.1; **HRMS** (ESI): calcd for $(C_{15}H_{17}NO_4)^+$ $[(M+Na)^+]$ 298.1055; found: 298.1049.

(*E*)-Ethyl 4-(3,4-dimethoxyphenyl)but-3-enoate (54)

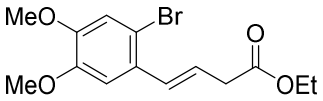


The (*E*)-ethyl 4-(3,4-dimethoxyphenyl)but-2-enoate **52** (0.25 g, 1 mmol) was taken in dry DMF (10 mL) and was heated at 150 ^{0}C under N_2 atmosphere for 12 h. The reaction mixture was then cooled to room temperature, and diluted with water (30 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography [silica gel (230-400 mesh) and Pet. ether:EtOAc (90:10) as an eluent] to give (*E*)-ethyl 4-(3,4-

dimethoxyphenyl)but-3-enoate **54** along with **52** (0.19 g, 0.77 mmol, combined yield of 89%).

Yield: 89% (0.19 g, 0.77 mmol); Colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 882, 978, 1045, 1148, 1175, 1248, 1275, 1390, 1412, 1718, 2890; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz, 3H), 3.21 (dd, *J* = 1.3, 7.1, Hz, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 6.07-6.25 (m, 1H), 6.33-6.46 (m, 1H), 6.76-6.80 (m, 1H), 6.85-6.92 (m, 2H); **HRMS** (ESI): calcd for $(C_{14}H_{18}O_4)^+$ $[(M+Na)^+]$ 273.1103; found: 273.1107.

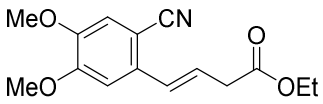
(*E*)-Ethyl 4-(2-bromo-4,5-dimethoxyphenyl)but-3-enoate (55)



Procedure is same as described for compound **54.**

Yield: 87% (0.285 g, 0.870 mmol); colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 893, 964, 1051, 1142, 1163, 1241, 1263, 1456, 1712, 2965; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.0 Hz, 3H), 3.31 (dd, *J* = 1.3, 5.6 Hz, 2H), 3.90 (s, 6H), 4.20 (q, *J* = 7.0 Hz, 2H), 5.74 (td, *J* = 7.0, 15.7 Hz, 1H), 6.78 (td, *J* = 1.2, 15.7 Hz, 1H), 6.98 (s, 1H), 7.05 (s, 1H); **HRMS** (ESI): calcd for $(C_{14}H_{17}BrO_4)^+$ $[(M+Na)^+]$ 351.0208; found: 351.0214.

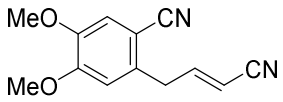
(*E*)-Ethyl 4-(2-cyano-4,5-dimethoxyphenyl)but-3-enoate (56)



Procedure ıs same as descrıbed for compound **54.**

Yield: 83% (0.198 g, 0.689 mmol); colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 848, 1092, 1219, 1268, 1485, 1514, 2212, 1714, 2961; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.0 Hz, 3H), 3.31 (dd, *J* = 7.0, 1.4 Hz, 2H), 3.90 (s, 3H), 3.96 (s, 3H), 4.20 (q, *J* = 7.0 Hz, 2H), 6.40 (td, *J* = 15.8, 7.0 Hz, 1H), 6.78 (d, *J* = 15.8 Hz, 1H), 6.98 (s, 1H), 7.05 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) of compound **56** + compound **53**: δ 14.2, 36.4, 38.1, 56.1, 60.3, 60.8, 102.6, 103.8, 107.3, 112.2, 113.6, 114.2, 117.9, 123.8, 125.2, 129.0, 134.6, 135.7, 144.6, 148.1, 148.7, 152.7, 165.8, 170.9; **HRMS** (ESI): calcd for $(C_{15}H_{17}NO_4)^+$ $[(M+Na)^+]$ 298.1055; found: 298.1051.

2-((*E*)-3-Cyanoallyl)-4,5-dimethoxybenzonitrile (58)



Procedure is same as described for compound **45.**

Yield: 71% (0.199 g, 0.71 mmol); Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1031, 1164, 1218, 1381, 1440, 1506, 2218, 2840, 2932, 3008; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.90 (d, *J* = 11.3 Hz, 2H), 3.93 (s, 3H), 5.48 (d, *J* = 10.8 Hz, 1H), 6.65 (td, *J* = 7.5, 10.8 Hz, 1H), 6.80 (s, 1H), 7.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.1, 56.1, 56.2, 101.4, 103.5, 112.3, 114.2, 115.5, 117.7, 135.0, 148.4, 150.3, 153.2; **HRMS** (ESI): calcd for $(C_{13}H_{12}N_2O_2)^+$ $[(M+Na)^+]$ 251.0796; found: 251.0791.

Experimental Procedure for the preparation of compound 60

To a stirred solution of 1-bromo-4,5-dimethoxy-2-((*E*)-2-methoxyvinyl)benzene **51c** (1.3 g, 5.0 mmol) in THF (10 mL) was added 1N DCl/D_2O (2 mL) at room temperature. The resulting solution was heated at 150 °C for 3 h. After evaporation of the organic solvent *in vacuo*, EtOAc was added to the mixture and acid was

neutralized by adding $NaHCO_3$. The organic layer was separated and dried over anhyd. Na_2SO_4, filtered and concentrated *in vacuo*. The obtained crude aldehyde was immediately used for the next reaction without purification because of their instability to air and moisture. To a stirred solution of the crude aldehyde in CH_2Cl_2 (5 mL) at 25 °C was added two carbon Wittig reagent *i.e* $Ph_3P{=}CHCO_2Et$ (1.9 g, 5.5 mmol) and the resulting mixture was stirred for 2 h at the same temperature. After the completion of reaction, CH_2Cl_2 was distilled out to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and Pet. ether:ethyl acetate (90:10) as eluent] afforded the deuterated unsaturated esters **60** in pure form in 82%.

Yield: 82%; (0.271 g, 0.81 mmol); Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 895, 978, 1024, 1050, 1142, 1188, 1245, 1276, 1477, 1714, 2965; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 3.48 (d, *J* = 1.3, 6.4 Hz, 0.42H), 3.85 (s, 3H), 3.86 (s, 3H), 4.18 (q, *J* = 7.0 Hz, 2H), 5.74 (d, *J* = 15.6 Hz, 0.38H), 6.66 (s, 1H), 6.98 (d, 15.6 Hz, 1H), 7.01 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 34.0, 34.2, 34.4, 34.6, 34.8, 55.9, 56.1, 59.9, 113.4, 114.0, 115.5, 119.7, 119.9, 120.2, 130.9, 146.5, 146.7, 148.3, 148.6, 166.2; **HRMS (ESI):** calcd for $(C_{14}H_{15}D_2BrNO_4)^+$ $[(M+Na)^+]$ 353.0333; found: 353.0337.

Experimental Procedure for the preparation of deuterated compound 45c

The deuterated (*E*)-ethyl 4-(2-bromo-4,5-dimethoxyphenyl)but-2-enoate **60** (1 mmol) was taken in dry DMF (10 mL) and CuCN (3 mmol) was added to it and the entire solution refluxed under N_2 atmosphere for 12 h. The reaction mixture was then cooled to room temperature and ^{2}H NMR spectra was recorded for crude product in DMF and the presence of dideuterium on Nitrogen (ND_2) in product **45c** was observed. Absence of benzylic deuterium in product **45c** was further confirmed by ^{1}H NMR spectrum.

1.3.6 References

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CHAPTER II

I_2 Catalyzed Oxo- & Hydroxyacyloxylation of Alkenes with Carboxylic Acid:Syntheses of (+)-Tanikolide & (-)-Malyngolide

1. I_2-Catalyzed Regioselective Oxo- and Hydroxy-acyloxylation of Alkenes and Enol Ethers: A Facile Access to α-Acyloxyketones, Esters, and Diol Derivatives Rambabu N. Reddi, **Pragati Kishore Prasad**, Arumugam Sudalai; *Org. Lett.* **2014**, *16*, 5674-77.

Section I

I_2-Catalyzed Regioselective Oxo- and Hydroxy-Acyloxylation of Alkenes and Enol ethers: Access to α-Acyloxyketones, Esters and Diol Derivatives

2.1.1 Introduction

In organic synthesis, molecular iodine has been used extensively in various reactions. It can act as a mild oxidizing reagent and can be used in many functional group transformations and C-C bond formation reactions. The unique property of this element, in direct comparison with the other halogens, is summarized as follows:

(a) Iodide anions are easily oxidized by inorganic and organic peroxides into molecular iodine (I_2) or the corresponding oxy acids (in particular hypoiodite $[IO]^-$, iodite $[IO_2]^-$ and iodate $[IO_3]^-$). The oxy acids themselves can also be interconverted by terminal oxidants or by disproportionation.

(b) Molecular iodine has the lowest homolytic dissociation energy among the non-radioactive halogens (151 kJ/mol), which makes one-electron-transfer processes attractive. This is one of two possible modes of activation for oxidation catalysis.

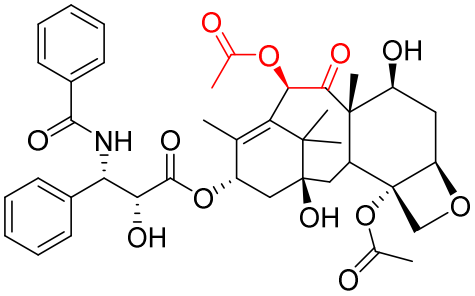
(c) After astatine, iodine has the lowest electronegativity (2.2) among the halogens. Therefore it is much easier to generate the monocationic iodine species ('I^+') *in situ* than monocationic bromine or chlorine species.

(d) Lastly, iodine and its salts have low toxicity and are non-hazardous compared to other halogen atoms and transition-metal-based oxidation catalysts. Thus, they are ideal candidates as catalysts in environmentally benign processes. Based on these properties, two different reaction types can be formulated in iodine-mediated oxidative couplings: (i)

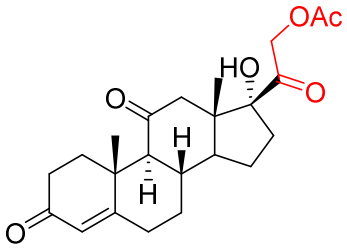
A 'radical'-based oxidative coupling pathway, and (ii) an '*in situ* iodination' based oxidative coupling pathway and comproportionation reactions. This easy conversion of different oxidation states is mandatory in oxidation catalysis.

Even though, stoichiometric iodine was used in many organic transformations, its catalytic version was developed more than four decades later (1998). Komatsu and co-workers reported first iodine catalyzed aziridination of olefins using chloramine-T as the co-oxidant.[1] In recent times, I_2 catalysis, in combination with either aq. H_2O_2 or *tert*-butyl hydroperoxide as water soluble co-oxidants, has been increasingly explored as environmentally benign and inexpensive oxidation reagents in place of rare or toxic heavy metal oxidants.[2]

α-Acyloxy ketones and esters are significant building blocks present in a variety of biologically interesting natural products, pharmaceuticals and synthetic intermediates of broad utility (**Fig. 1**).[3] Further, these compounds can be transformed to mono protected diols (by reduction of carbonyl group), protected amino alcohols (by reductive amination of ketone moity) and acyloins (by hydrolysis of acyloxy group).



Taxol (**6**)



Cortisone (**7**)

Fig 1: Natural products with α-acyloxy ketone moiety

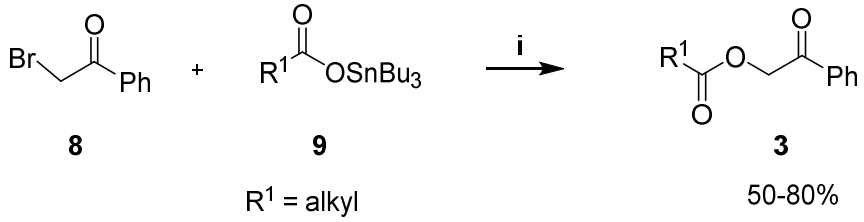
2.1.2. Review of Literature

2.1.2.1 α-Acyloxy Ketones and α-Acyloxy Esters

In the literature, α-acyloxy ketones are prepared either by the substitution of α–halo carbonyl compounds[4] as well as insertion reaction of α-diazoketones[5] with alkaline carboxylates or the direct oxidative coupling of ketones with toxic heavy metal oxidants (e.g. $Pb(OAc)_4$, $Tl(OAc)_3$, $Mn(OAc)_3$, etc).[6] Recently, hypervalent iodine catalyzed oxidative coupling of ketones with carboxylic acids has been reported to give α-acyloxy ketones.[7] More atom economical method have been reported by the addition of carboxylic acids on to the alkynes using Ru catalysis.[8] These developments are discussed below.

Balasubramanian's approach (1985)[9]

Balasubramanian *et al.* have developed a facile method for the synthesis of phenacyl esters **3** using phenacyl bromides **8** and organostannyl carboxylates **9** using quaternary ammonium salt. In the absence of the quaternary ammonium salt, the yields are poor and the reaction does not proceed to completion (**Scheme 1**).

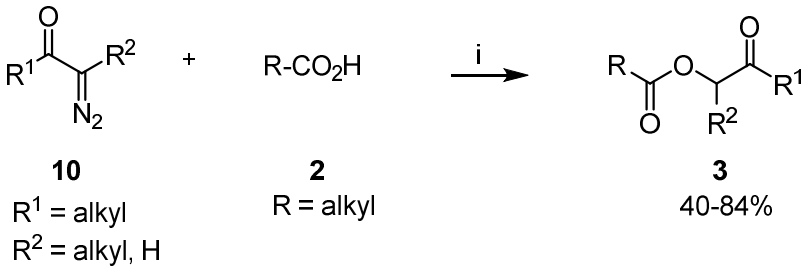


Scheme 1: (i) $Bu_4N^+Br^-$, benzene, 25 °C, 1 h, 50-80%.

Ohfune's approach (1998)[10]

Ohfune *et al*. have reported insertion reaction of α-diazoketone **10** to various carboxylic acids using Cu(acac) as catalyst. Treatment of the diazo compound with carboxylic acid **2** (1.2 equiv) in the presence of Cu(acac) (10 mol %) at room temperature afforded the

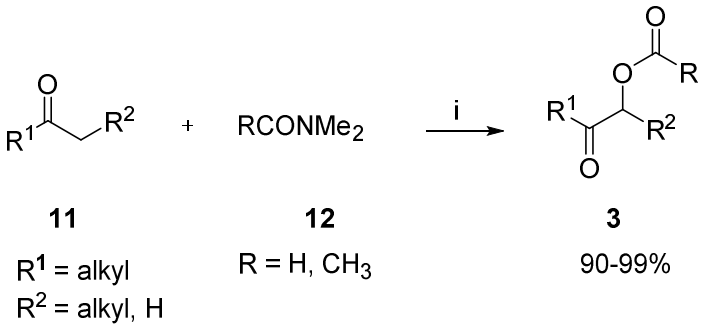
corresponding ketoester **3** in good yields. Various kinds of functional groups were tolerated (**Scheme 2**).



Scheme 2: (i) $Cu(acac)_2$, toluene, 25 °C, 1 h, 40-84%.

Lee's approach (2001)[11]

In Lee's protocol, treatment of ketones **11** with thallium (III) triflate (formed by the reaction of thallium acetate and trifloromethane sulfonic acid) in amide **12** as solvent at 60 °C for 30 min followed by addition of small amount of H_2O provided the corresponding α-acyloxy ketones **3** in very high yields (**Scheme 3**).

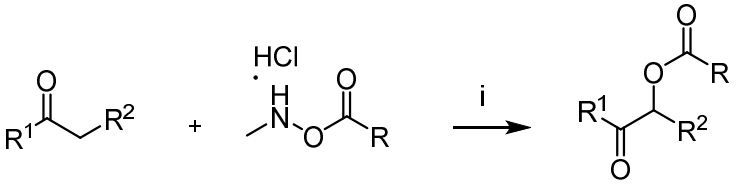


Scheme 3: (i) Thallium (III) acetate, CF_3SO_3H, DMF, 60 °C, 0.5 h then H_2O.

Tomkinson's approach (2005)[7]

Tomkinson *et al.* have developed a "one-pot" method for α-acyloxylation of carbonyl compounds at room temperature in the presence of both moisture and air. Treatment of a variety of aldehydes and both cyclic and acyclic ketones **11** with *N*-methyl-*O*-

benzoylhydroxylamine hydrochloride **13** afforded α-functionalized product **3** in 69-92% isolated yields. The transformation proved to be tolerant to a wide range of functional groups and also regiospecific in the discrimination of secondary over primary centers in the case of nonsymmetrical substrates (**Scheme 4**).



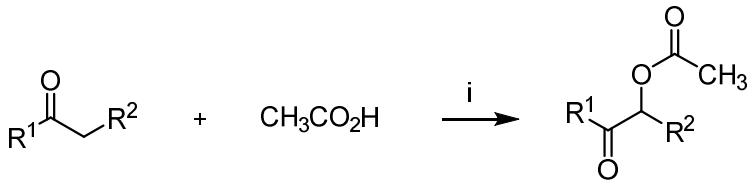
11 **13** **3**

R^1 = alkyl, R^2 = alkyl, H; R = Me, Ph, *t*-Bu, *p*-MeOPh; 69-92%

Scheme 4: (i) DMSO, 25-50 °C, 8 h, 69-92%.

Ochiai's approach (2005)[12]

Ochiai *et al.* have developed iodobenzene-catalyzed α-oxidation of ketones **11**, in which diacyloxy(phenyl)-λ^3-iodanes generated *in situ* acted as real oxidants of ketones while *m*-chloroperbenzoic acid served as a terminal oxidant. However, the use of water and $BF_3{\cdot}Et_2O$ proved to be crucial for the success of this α-acetoxylation process (**Scheme 5**).



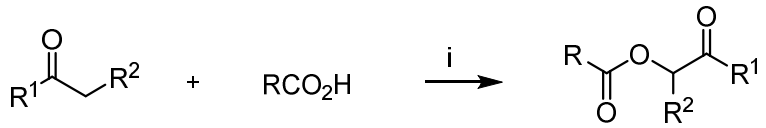
11 **2** **3**

$R^1 = R^2$ = alkyl, aryl; 43-79 %

Scheme 5: (i) *m*CPBA, PhI, H_2O, $BF_3.Et_2O$ (3 equiv), 25-30 °C, 20- 48 h, 43-79%.

Ishihara's approach (2011)[13]

Ishihara *et al.* have developed both intra- and intermolecular tetrabutyl ammonium iodide (TBAI) catalyzed oxidative coupling of carbonyl compounds **11** with carboxylic acids **2** using either H_2O_2 or TBHP as co-oxidant. A large number of substrates were screened. However, aliphatic ketones produced very low yields of α-acyloxy ketones **3** (**Scheme 6**).



11 **2** **3**

R^1 = alkyl
R^2 = alkyl, H

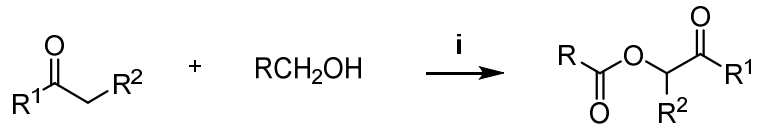
R = alkyl, aryl

40-90 %

Scheme 6: (i) ^{n}Bu$_4$NI, TBHP or H_2O_2, 25 to 30 °C, 20-48 h, 40-90%.

Cheng's approach (2014)[14]

Cheng *et al*. have achieved Bu_4NI-catalyzed reaction of ketones **11** with benzylic alcohols **14**, leading to α-acyloxy carbonyl compounds in moderate to good yields. This metal-free procedure featured the employment of facilely and commercially available starting materials and TBHP as a clean oxidant with high atom economy (**Scheme 7**).



11 **14** **3**

R^1 = aryl
R^2 = alkyl, H

R = alkyl, aryl

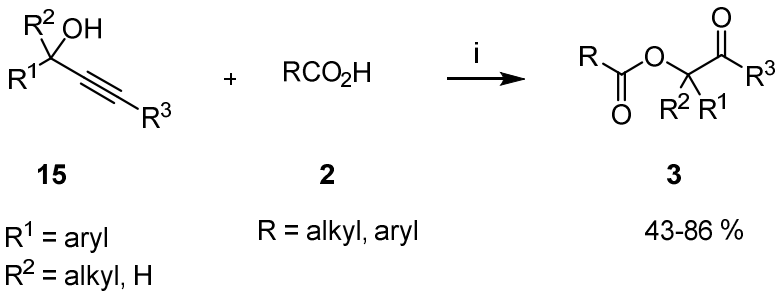
33-90%

Scheme 7: (i) ^{n}Bu$_4$NI, TBHP or H_2O_2, PhCN, air, 90 °C, 20 to 68 h, 33-90%.

Bauer's approach (2008)[15]

Bauer *et al.* have developed a novel protocol for addition of carboxylic acids **2** onto the

propargylic alcohols **15** for the synthesis of α-acyloxycarbonyl compounds **3**. The method is practical as no additives are required and the exclusion of oxygen and moisture is not needed (**Scheme 8**).



Scheme 8: (i) Ru cat. (1.5 mol %), cyclohexane, 90 °C, 8 h, 43-86%.

2.1.2.2 Diol derivatives

Some of the recent developments for the synthesis of diol derivatives have been discussed below. There are several reports available for the preparation of racemic as well as chiral 1,2-diols. Despite these methods, the dihydroxylation of alkenes is the best method as it needs no pre-functionalization of starting materials. Based on the reagents used, the dihydroxylation methods can be divided into the following categories.

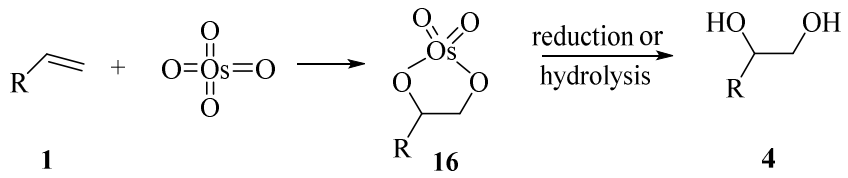
1. Metal oxide addition to olefin
2. Prevost-Woodward type reaction

The above types of dihydroxylation are briefly discussed below:

Metal oxide addition to olefin

OsO_4 catalyzes the *cis*-dihydroxylation of alkenes by hydrogen peroxide or related sources of

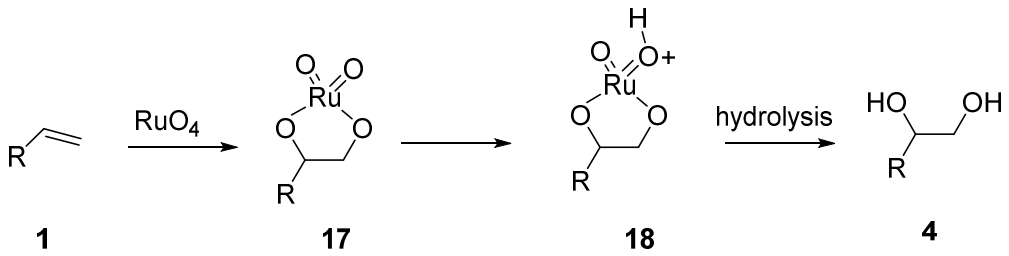
oxygen atoms in the presence of water. In terms of mechanism, OsO_4 adds to alkenes to afford cyclic osmate esters **16**, which undergo hydrolysis to give the *vic* diols **4** (**Scheme 9**).[16]



Scheme 9: OsO_4-catalyzed dihydroxylation of olefins.

Lewis bases such as tertiary amines and pyridines have been found to increase the rate of the reaction. This "ligand-acceleration" arises *via* the formation of adduct OsO_4-L, which adds more rapidly to the alkene. If the amine is chiral, then the dihydroxylation can proceed with enantioselectivity (see Sharpless' asymmetric dihydroxylation).[17] Since OsO_4 is toxic and expensive, it is used in catalytic amounts. The osmium catalyst is regenerated by oxidizing agents, such as H_2O_2, *N*-methylmorpholine *N*-oxide (NMO) and $K_3Fe(CN)_6$. These oxidizing reagents do not react with the alkenes on their own. Other sources of osmium tetroxide include potassium osmate (VI) dihydrate ($K_2OsO_4 \cdot 2H_2O$) and osmium (III) chloride hydrate ($OsCl_3.xH_2O$) which oxidize osmium (VI) to osmium (VIII) in the presence of above mentioned oxidants. Despite its success, some problems still need to be solved. The oxidation is limited to electron-rich or mono-, di-, and in some cases, trisubstituted olefins. Furthermore, the osmium catalyst is toxic and very expensive. RuO_4, as a dihydroxylation catalyst, is most promising. In 1954, Djerassi introduced RuO_4 in organic chemistry. Since then, it has mainly been used for the degradation of unsaturated organic compounds. In ethyl acetate/acetonitrile/water very rapid dihydroxylation of olefins using 7 mol % of RuO_4 was observed (**Scheme 10**).

However, longer reaction times resulted in the formation of fission products. Treatment of olefin **1** with catalytic $RuCl_3$, $NaIO_4$ as reoxidant in ethyl acetate/acetonitrile/water solvent system in the presence of acid produced the corresponding diols **4** in excellent yields. The reaction proceeds *via* the cyclic ruthenium ester **17**. [18]

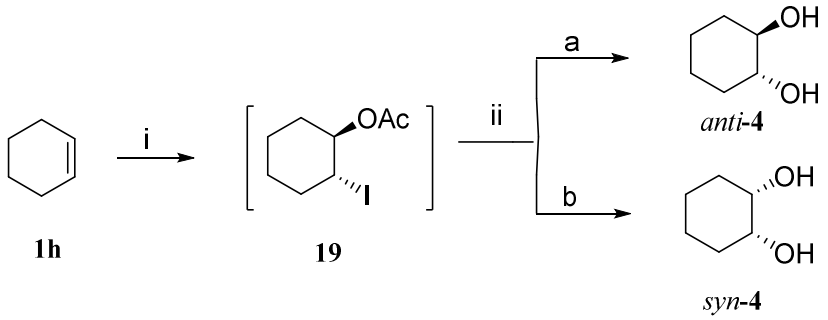


Scheme 10: RuO_4-catalyzed dihydroxylation of olefins.

Prevost-Woodward type reaction

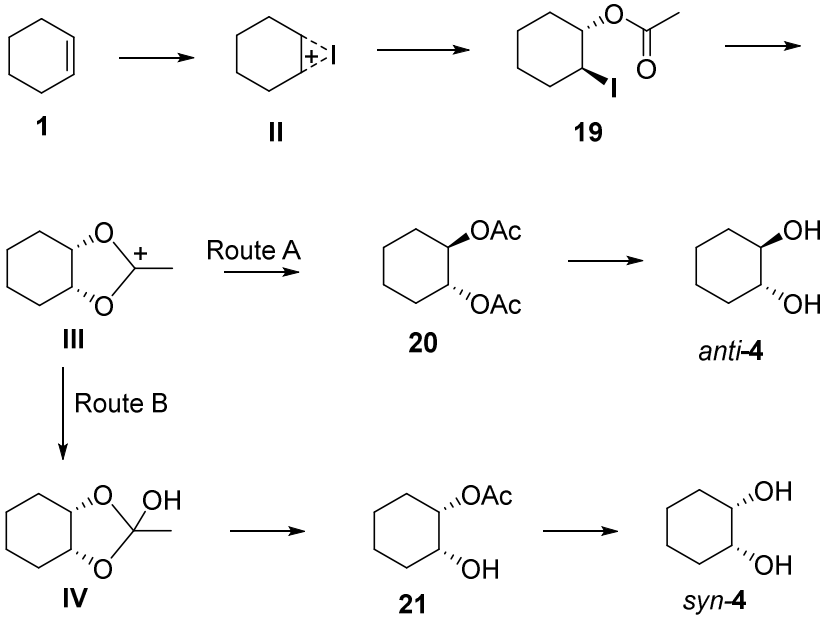
Prevost-Woodward reaction

The Prevost reaction[19] and its Woodward modification[20] are important methods for the preparation of *anti* and *syn* 1,2-diols respectively with excellent yields. These reactions involve the treatment of an alkene with iodine and silver (I) carboxylate. Both reactions are considered to proceed through *trans* iodocarboxylate **19**, which by interaction of neighbouring acyloxy group and displacement with water or acetoxy group results in the formation of *syn* or *anti* diol derivatives depending upon the reaction conditions (**Scheme 11**). The alkaline hydrolysis of these diol derivatives gives the corresponding *anti* and *syn* **4** diols respectively.



Scheme 11: (i) (a) I_2, $PhCO_2Ag$ (2 equiv), AcOH, 85 ºC; (b) K_2CO_3, MeOH, 25 °C; (ii) (a) I_2, $PhCO_2Ag$ (1 equiv), AcOH, H_2O, 85 ºC; (b) K_2CO_3, MeOH, 25 °C.

Mechanistically, in the first step of the reaction iodine adds to cyclohexene (**1h)** to form iodonium ion **I**, which is opened with nucleophilic silver (I) carboxylate to give *trans* 2-iodocyclohexyl acetate (**19, Scheme 12**). Iodo acetate **19** can be isolated in quantitative yield from the reaction by conducting the reaction at lower temperature and lesser equivalent of metal carboxylate. Neighboring group participation of the acetate group displaces the iodine to produce 1,3-dioxolan-2-ylium intermediate **III**. Under anhydrous condition



Scheme 12: Mechanism of Prevost-Woodward reaction

(Prevost condition), acetate ion attacks the cyclic intermediate at C-4 position to furnish *trans* diacetate (**20**, Route **A**). On the other hand, in the presence of water (Woodward condition), the intermediate is attacked by the water molecule at C-2 position to produce hydroxy acetate (**21**) with *syn* stereochemistry (Route **B**).

However, Prevost-Woodward reaction suffers from the following disadvantages

(i) Woodward reaction affords only low yields of *cis* diols with tri- or tetra substituted olefins.

(ii) Highly activated aromatic rings like 2-allyl phenol undergo aromatic iodination to give 2-allyl 6-iodophenol.

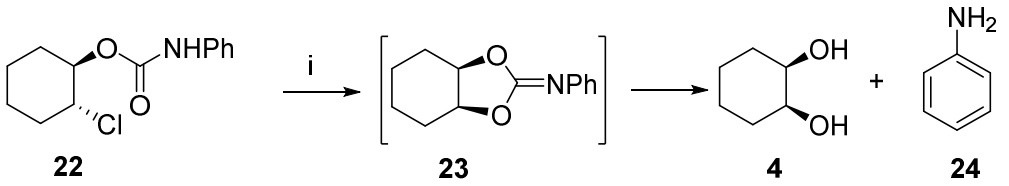
(iii) The deactivated olefins like alkyl cinnamates are less reactive or unreactive under these reaction conditions.

(iv) Often, sterically hindered olefins fail to produce the desired diol derivatives.

Despite the aforementioned drawbacks, Prevost-Woodward reaction serves as a mild and efficient method to prepare diols and thus several modifications in the reagent system have been attempted. Several metal carboxylates like Cu, Bi, Hg (II) were employed as acetate sources and *N*-bromoacetamide, I_2, Br_2, *N*-bromosuccinamide were screened as halogen sources. Some of the modifications are briefly discussed below.

Fenton's approach (1970)[21]

Fenton *et al.* found that when *trans* 2-*N*-phenylurethane cyclohexyl chloride (**22**) was heated in aqueous ethanol for 70 h in a sealed tube, *cis*-1,2-cyclohexane diol (**4**) was formed in 95% *via* dioxan intermediate **23**. Aniline (**24**) was also separated as the by-product (**Scheme 13**).

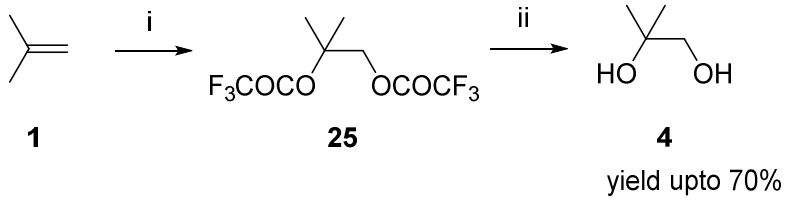


22 **23** **4** **24**

Scheme 13: (i) aq. EtOH, 90 °C, sealed tube, 70 h, 95%.

Buddrus' approach (1973)[22]

Buddrus *et al.* have reported the formation of *vic*-diol **4** in 50-70% yields through addition of olefin **1** to a solution of iodine tris(trifluoroacetate) in pentane followed by hydrolysis proceeding *via* diacetate **25** (**Scheme 14**).



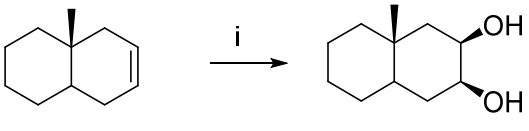
1 **25** **4**

yield upto 70%

Scheme 14: (i) $I(OCOCF_3)_3$, pentane, 25 °C; (ii) K_2CO_3, MeOH, 25 °C.

Granger's approach (1976)[23]

Granger *et al.* have employed *N*-bromoacetamide (NBA) as the halogen source to obtain bromoacetoxy derivative. Decalin derivative **26** when treated with NBA and silver (I) benzoate in wet acetic acid produced *syn* diol derivatives, which on hydrolysis produced *cis*-diol **27** (**Scheme 15**).

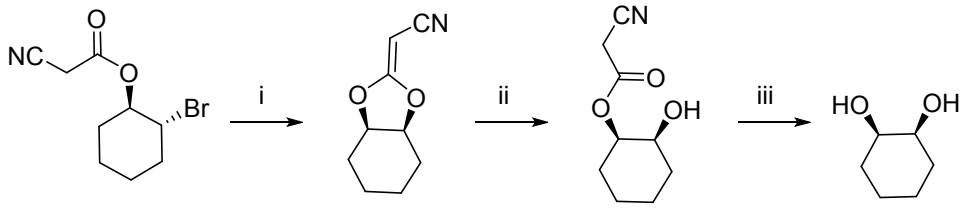


26 **27**

Scheme 15: (i) (a) NBA, $PhCO_2Ag$ (1 equiv), AcOH, H_2O, 85 ºC; (b) K_2CO_3, MeOH, 25 °C.

Corey's approach (1976)[24]

Corey *et al.* have reported the synthesis of *syn* diols involving cyano acetic ester as the intermediate. Accordingly, reaction of the cyanoacetate ester **28** with excess of NaH generated the corresponding enolate, which underwent intramolecular nucleophilic displacement to form cyanoketone acetal **29**. Hydrolysis using 1N HCl produced the mono cyanoacetate **30**, which upon alkaline ester hydrolysis afforded *cis* diol **4** (**Scheme 16**).

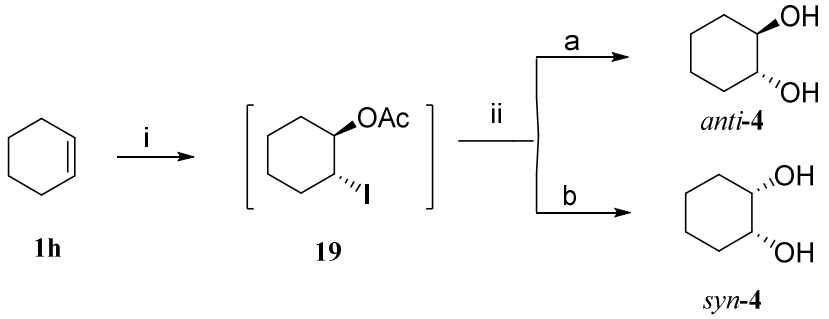


28 **29** **30** **4**

Scheme 16: (i) NaH (excess), THF, 0 °C; (ii) 1N HCl, 25 °C; (iii) aq. KOH, 80 °C, 79%.

Trainor's approach (1992)[25]

Trainor *et al.* have developed a synthetic method for the preparation of *syn* and *anti* cyclohexane 1,2-diols **4** from cyclohexene (**1h**) by reaction with I_2 and bismuth (III) acetate in wet and dry acetic acid respectively. Reaction using lesser amounts of $Bi(OAc)_3$ under dry conditions gave the intermediate *i.e trans* 2-iodocyclohexyl acetate (**19**), (**Scheme 17**).

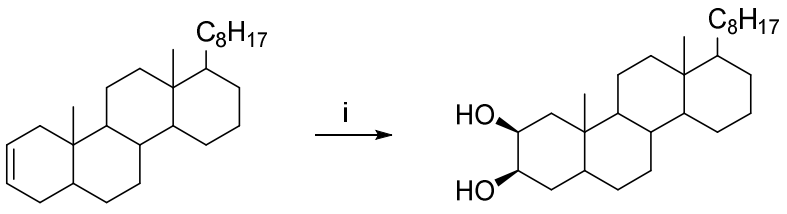


1h **19** *anti*-**4** *syn*-**4**

Scheme 17: (i) (a) I_2, $Bi(OAc)_3$ (2 equiv), AcOH, 85 ºC; (b) K_2CO_3, MeOH, 25 °C; (ii) (a) I_2, $Bi(OAc)_3$ (1 equiv), AcOH, H_2O, 85 ºC; (b) K_2CO_3, MeOH, 25 °C.

Welzel's approach (2000)[26]

Welzel *et al.* have reported the synthesis of diol derivatives even in hindered cholest-2-ene (**31**) by replacing silver (I) benzoate or acetate with mercuric (II) acetate. **31** when treated with mercuric (II) acetate and iodine in wet acetic acid at 85 °C, afforded *syn* diol derivatives, which were further hydrolyzed under basic conditions to afford the diol **32** (**Scheme 18**).

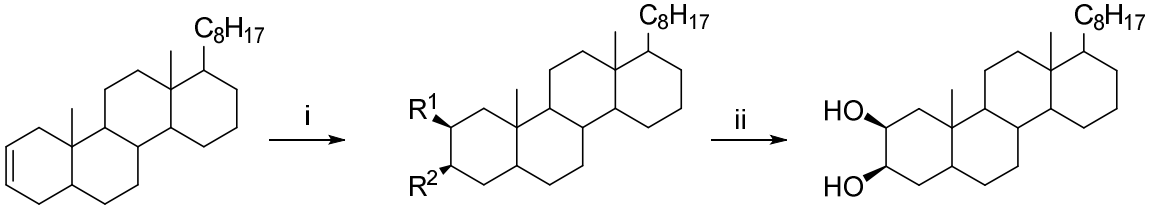


31 **32**

Scheme 18: (i) (a) I_2, $Hg(OAc)_2$ (1 equiv), AcOH, H_2O, 85 °C; (b) aq. KOH, 50 °C.

Horiuch's approach (2006)[27]

Horiuch *et al.* used copper(II) acetate as a better alternative to silver(I) benzoate. The reaction of cholest-2-ene (**31**) with iodine and copper (II) acetate in acetic acid under reflux conditions yielded diol derivatives **33** and **34**, which upon hydrolysis furnished diol **32** (**Scheme 19**).



31

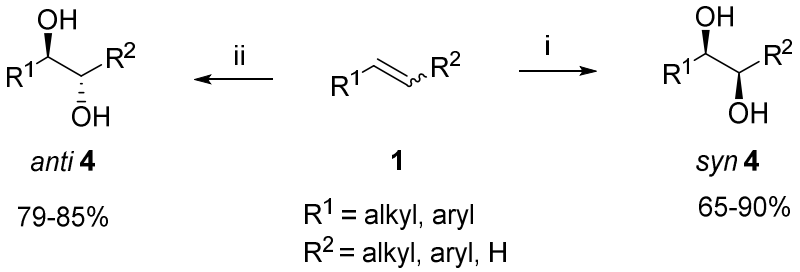
33, $R^1 = OH$; $R^2 = OCOCH_2I$
34, $R^1 = OCOCH_2I$; $R^2 = OH$

32

Scheme 19: (i) I_2, $Cu(OAc)_2$ (1 equiv), AcOH, H_2O, 85 °C; (ii) K_2CO_3, MeOH, 25 °C.

Sudalai's approach (2006)[28]

Sudalai *et al*. have reported a catalytic version for Woodward-Prevost dihydroxylation. LiBr has been used to catalyze efficiently the dihydroxylation of alkenes to afford *syn*- and *anti* diols with excellent diastereoselectivity depending upon the use of $NaIO_4$ (30 mol %) or $PhI(OAc)_2$ (1 equiv) as oxidants respectively (**Scheme 20**).

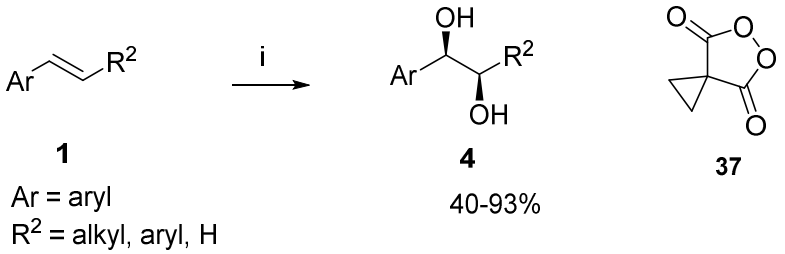


Scheme 20: (i) $NaIO_4$ (30 mol %), LiBr (20 mol %), AcOH, 95 °C, 18 h then K_2CO_3, MeOH, 25 °C, 24 h; (ii) $PhI(OAc)_2$ (1 equiv), LiBr (20 mol %), AcOH, 95 °C, 18 h then K_2CO_3, MeOH, 25 °C, 24 h.

Tomkinson's approach (2010)[29, 30]

Tomkinson *et al.* have reported[29] cyclopropyl malonyl peroxide **37** (prepared in single step from commercially available diacid) as an effective reagent for the dihydroxylation of alkenes. Reaction of **37** with alkenes **1** in the presence of 1 equiv of water at 40 °C followed by alkaline hydrolysis leads to the corresponding diol (40-93%). With 1,2-disubstituted alkenes, the reaction proceeds with *syn* selectivity (3:1 to >50:1) (**Scheme 21**). In yet another approach (2012),[30] they have described the effect of fluorinated alcohols on the dihydroxylation of alkenes using cyclopropyl malonyl peroxide. Addition of perfluoro-*tert*-butyl alcohol to a solution of alkene and peroxide **37** in toluene (instead of $CHCl_3$) increases the rate of product formation and its stereoselectivity thus, providing a simple and effective method for acceleration of this important class of reaction. Basic

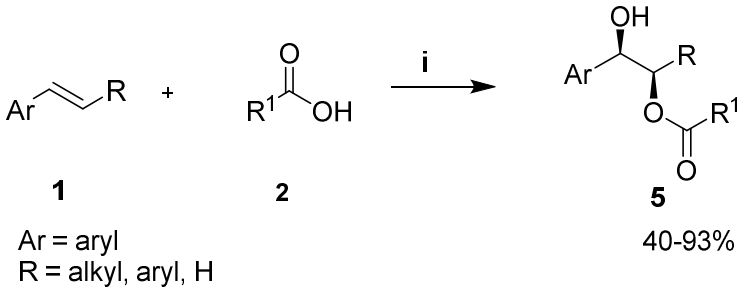
hydrolysis of the crude reaction mixture affords *syn*-diols in high yield and stereoselectivity.



Scheme 21: (i) Malonyl peroxide (**37**) (1.2 equiv), H_2O (1 equiv), $CHCl_3$, 40 °C, then aq. NaOH, 60 °C, 4 h, 40-93%.

Zhu approach (2013)[31]

Zhu *et al.* have developed a new synthetic approach towards difunctionalization of alkenes under metal-free conditions. Various carboxylic acids and amines could react smoothly with alkenes to give dioxygenation and oxyamidation products respectively. This organocatalytic process delivered 2-hydroxy alcohols directly from simple alkenes with high levels of regio-control (**Scheme 22**).



Scheme 22: (i) TBAI (10 mol %), 70% aq. TBHP, *n*-hexane, 120 °C, 4 h, 40-93%.

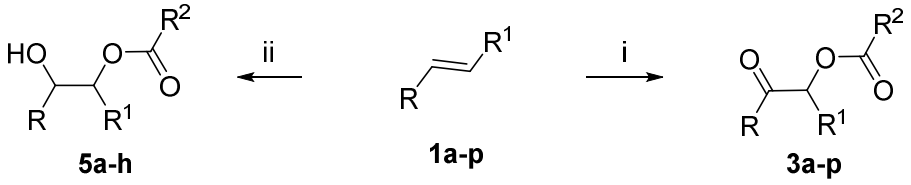
2.1.3 Present Work

2.1.3.1 Objective

As can be seen, there are numerous methods available in literature for the synthesis of diol derivatives. However, many of them suffer from certain drawbacks like low yields, cumbersome experimental procedures and use of expensive air and moisture sensitive or highly toxic catalysts. Hence, there arises a necessity to develop an efficient procedure for the synthesis of commercially available starting materials under ambient conditions.

2.1.3.2 Results and Discussion

In this section, we describe, for the first time, catalytic electrophilic iodination for dioxygenation using I_2/TBHP catalyzed oxo-acyloxylation of alkenes[32] and enol ethers with carboxylic acids **2** in DMSO as solvent and Et_3N as base, giving α-acyloxyketones and esters **3a-p** in high yields and excellent regioselectivity (up to 99%). In addition, one-pot "hydroxy-acyloxylation" has also been developed by sequential addition of $BH_3.SMe_2$ in the reaction mixture that produces mono protected diol derivatives (**5a-h**) in excellent yields (**Scheme 23**).

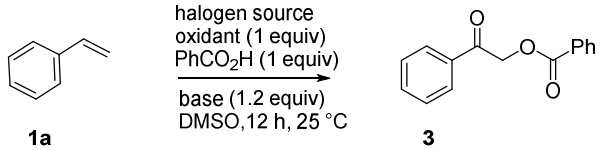


Scheme 23: Reaction conditions (i) I_2 (10 mol %), TBHP (1 equiv), R^2CO_2H (1 equiv), Et_3N (1.2 mmol), DMSO, 25 °C, 12 h, 76-89%; (ii)) I_2 (10 mol %), TBHP (1 equiv), R^2CO_2H (1 equiv), Et_3N (1.2 mmol), DMSO, 25 °C, 12 h then $BH_3.SMe_2$ (0.5 mmol), 0 °C, 5 min, 72-87%.

Initially, when styrene (1 mmol) was treated with a mixture containing benzoic acid (**2a**)

(1 mmol), NBS (1 mmol) and Et_3N (1.2 mmol) at 25 °C in DMSO, the corresponding α-benzyloxyketone **3a** was obtained in 89% isolated yield with excellent regioselectivity (>99%) (**Table 1**). When *stoichiometric* amount of I_2 was used as halogen source, **3a** (90% yield) was indeed obtained with perfect regioselectivity. Encouraged by the result, it was of interest to develop a *catalytic* version of this useful oxo-acyloxylation process**.**

Table 1: I_2-catalyzed oxo-acyloxylation of styrene with carboxylic acids: optimization studies[a]



1a **3**

entry	halogen (10 mol %)	oxidant (1 equiv)	base	yield of **3**[b]
1	NBS[c]	-	Et_3N	89
2	I_2[c]	-	Et_3N	90
3	I_2	50% H_2O_2	Et_3N	13
4	I_2	$NaIO_4$	Et_3N	15
5	I_2	Oxone	Et_3N	8
6	NaI	TBHP	Et_3N	trace
7	nBu$_4$NI	TBHP	Et_3N	11
8	I_2	TBHP	Et_3N	88 (53)[d] (89)[e]
9	I_2	TBHP	NaH	39
10	I_2	TBHP	KO^{t}Bu	72
11	I_2	TBHP	DBU	67
12	I_2	TBHP	K_2CO_3	47

[a]Reaction conditions: styrene (1 mmol), carboxylic acid (1 mmol), halogen source (10 mol %), base (1.2 mmol), TBHP (5-6 M in decane) (1 mmol); in 8 ml DMSO, 25 °C, 12 h; [b]isolated yield after column chromatographic purification; [c]1 equiv of halogen source was used; [d]5 mol % of I_2 was used; [e]20 mol % of I_2 was used.

Thus, a series of experiments were conducted employing I_2 in catalytic amounts (10 mol %) along with other stoichiometric oxidants like aq. H_2O_2, $NaIO_4$, Oxone or TBHP, which gave **3a** in 13, 15, 8 and 88% yields respectively. With 5 mol % of I_2, a lowered yield of **3a** (53%) was however observed. Further modification in iodine source, base or solvent system (DMSO in combination with other solvents) did not show any significant improvement in the product yield (**Table 1**).

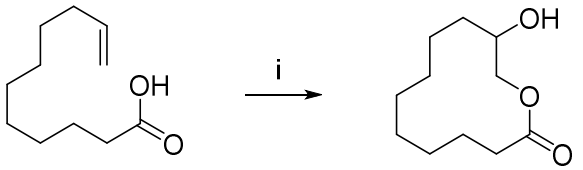
The scope of the study was extended to substituted styrenics and alkenes; the results of which are subsequently displayed in **Table 2**. Several olefins with varied functional groups were found compatible in the reaction. Electron neutral (4-CH_3), electron-deficient (4-CN), and electron-rich (-OAc) groups on the aromatic nucleus were compatible and provided the corresponding products in excellent yields (82-85%, **3b**, **3c** and **3d**). Similarly, aliphatic olefins were found compatible under the optimal conditions and provided (**3f-h**) in good yields (83-89%). Moreover, disubstituted alkene, indene (**1e**) underwent this oxo-acyloxylation process smoothly providing 1-oxo-2,3-dihydro-1*H*-inden-2-yl benzoate (**3e**) in high yields with excellent regioselectivity (>99%, i.e. ketone group at the benzylic position). We envisioned that addition of $BH_3.SMe_2$ to the reaction mixture would enable us to obtain the corresponding diol derivatives **5a-h** (**Table 2**). To our delight, we indeed found that several styrenes and aliphatic alkenes underwent this "oxo-acyloxylation-reduction" process smoothly affording diol derivatives **5a-h** in 72-87% yields and excellent chemoselectivity (99%). Notably, use of excess of $BH_3.SMe_2$ (2 equiv) to the reaction mixture afforded the corresponding diol in 82% yield (entry 6). Remarkably, internal alkenes gave the desired products in moderate diastereomeric ratio (3:1) with high yield (entry 5). Further, intramolecular version of hydroxy-acyloxylation

Table 2: I_2-catalyzed oxo- and hydroxyl benzoyloxylation of alkenes with benzoic acid: substrate scope[a]

entry	alkenes (**1a-h**)	product yields (%)[b] **3a-h**	**5a-h**[c]
1	styrene (**1a**)	88	86
2	4-CH_3-styrene (**1b**)	85	84
3	4-CN-styrene (**1c**)	82	79
4	4-OAc- styrene (**1d**)	84	83
5	indene (**1e**)	76	72 (3:1)[d]
6	PMBO-CH-CH=CH_2 (**1f**)	83	82[e]
7	1-decene (**1g**)	89	87
8	1-tridecene (**1h**)	86	84

[a]see foot-note [*a*] under Table 1; [b]isolated yields after column chromatographic purification; [c]*in situ* addition of anhydrous Na_2SO_4 and $BH_3.SMe_2$ (0.5 equiv) to conditions in foot-note [*a*], in Table 1; [d]*anti:syn* ratio; [e]diol was obtained after excess of $BH_3.SMe_2$ (2 equiv) was added.

was demonstrated in the macrolactonization of undec-10-enoic acid (**1q**), which gave 12-membered hydroxy lactone **5i** in 82% yield (**Scheme 24**).



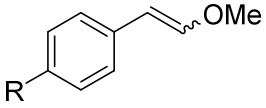
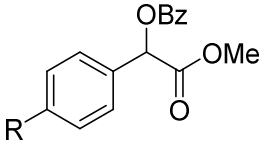
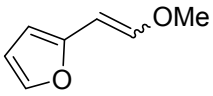
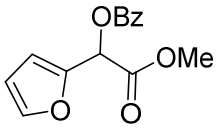
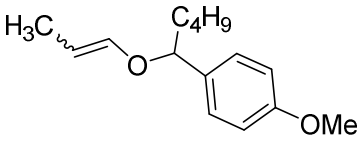
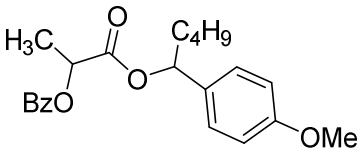
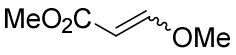
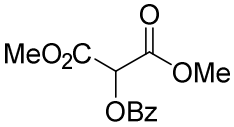
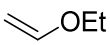
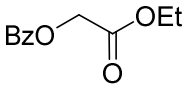
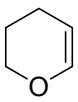
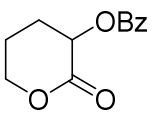
1q **5i**

Scheme 24: (i) I_2 (10 mol %), TBHP (1 equiv), Et_3N (1.2 equiv), DMSO, 25 °C, 8 h, then $BH_3.SMe_2$ (0.5 equiv), 82%.

Table 3 summarizes the application of the optimized reaction conditions to a range of enol ethers in an effort to expand the scope of this oxo-acyloxylation reaction. Enol ethers with *p*-substituted electron-rich or -poor groups and furan substitutions proved to be good substrates for this transformation, affording the corresponding mandelic and lactic acid derivatives **3i-p** in high isolated yields (74-82%). The formation of all α-

acyloxycarbonyls and diol derivatives were confirmed from their corresponding ^{1}H, ^{13}C NMR and IR spectral data.

Table 3: I_2-catalyzed oxo-benzoyloxylation of enol ethers with benzoic acid: substrate scope[a]

substrates (**1i-p**)	products with yields (**3i-p**)
	
1i : R = Br	**3i** : R = Br : 78%
1j : R = CN	**3j** : R = CN : 81%
1k : R = NO_2	**3k** : R = NO_2 : 82%
	
1l	**3l** : 78%
	
1m	**3m** : 74%
	
1n	**3n** : 83%
	
1o	**3o** : 89 %
	
1p	**3p** : 84%

[a] for reaction conditions, see foot-note under Table 1: Bz = benzoyl

Example 1: The ^{1}H NMR spectrum of 2-(4-acetoxyphenyl)-2-oxoethyl benzoate (**3d)** showed a typical singlet at δ 2.34 (s, 3H) corresponding to the acetyl protons (C**H$_3$**CO-); further, signal for the methylene protons (-C**H$_2$**) attached to benzoate group appeared at δ 5.55 (s, 2H). The formation of product **3d** was further substantiated by the presence of carbonyl carbon signals in the ^{13}C NMR spectrum at δ 190.6, 168.2 and 165.6 corresponding to the ketone, acetate and benzoate carbonyl carbons respectively (**Fig. 2**).

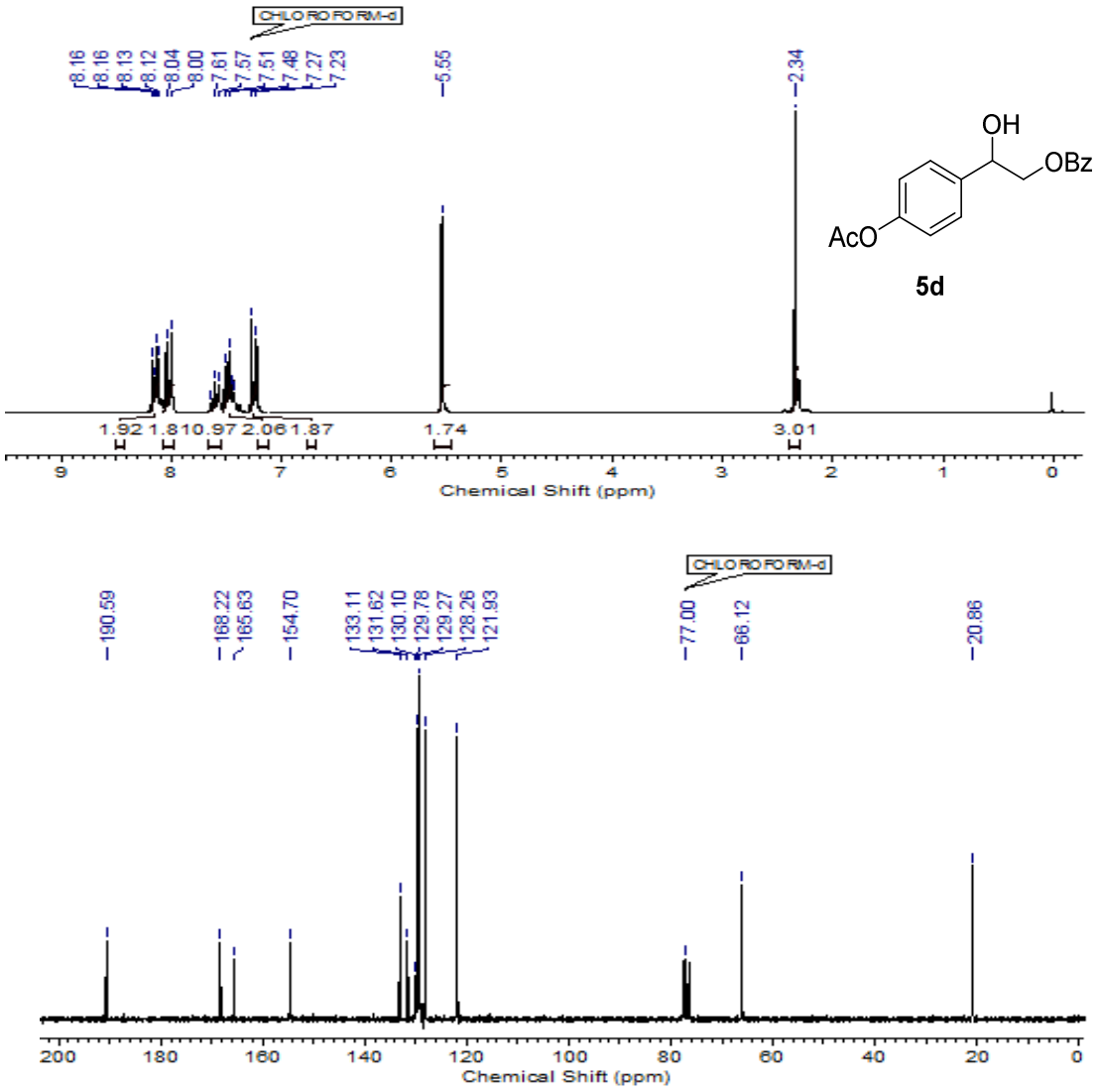


Fig. 2: ^{1}H and ^{13}C NMR spectra of **3d**

Example 2: The proton NMR spectrum of 2-(4-acetoxyphenyl)-2-hydroxyethyl benzoate **(5d)** showed a benzylic proton signal at δ 5.11 (dd, J = 8.0, 3.3 Hz, 1H). The structure was further confirmed by its ^{13}C NMR spectrum showing the corresponding benzylic methine carbon (-**C**H) and methylene carbon (-**C**H_2) signals at δ 72.0 and 69.7 respectively (**Fig. 3**).

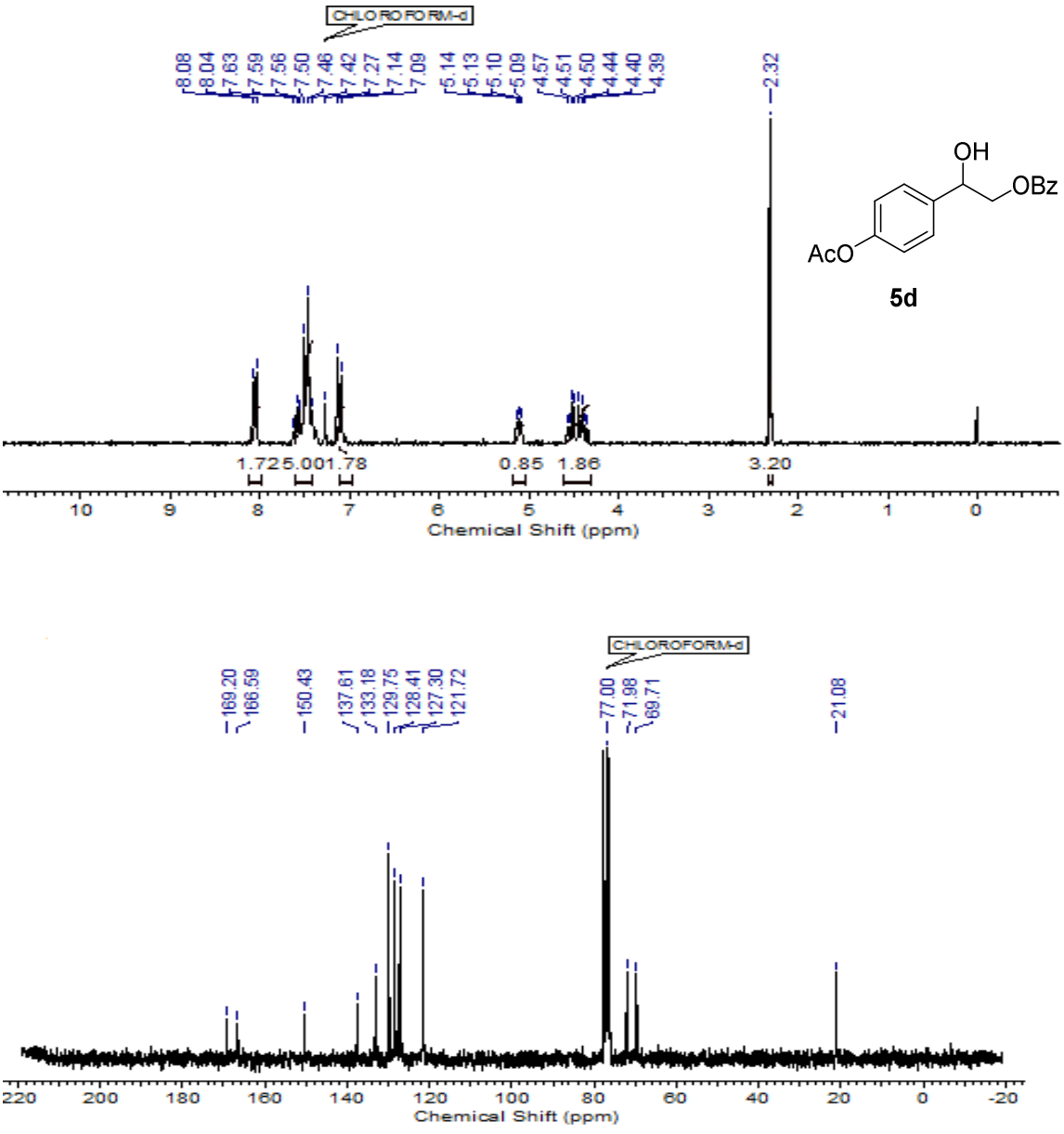


Fig. 3: ^{1}H and ^{13}C NMR spectra of **5d**

Example 3: The ^{1}H NMR spectrum of 2-ethoxy-2-oxoethyl benzoate (**3o**) showed a characteristic –C**H**$_2$ proton (attached to benzoate group) signal at δ 4.84 (s, 2H), while, incorporation of the benzoate group was marked by the aromatic proton signals at δ 7.46-7.50 (m, 2H), 7.56-7.60 (m, 1H) and 8.08-8.13 (m, 2H) corresponding to the benzoate group. In its ^{13}C NMR spectrum the two ester carbonyl carbon peaks appeared at δ 165.5 and 167.4 while the -O**C**H$_2$ group showed two typical signals at δ 60.9 and 61.0 (**Fig. 4**).

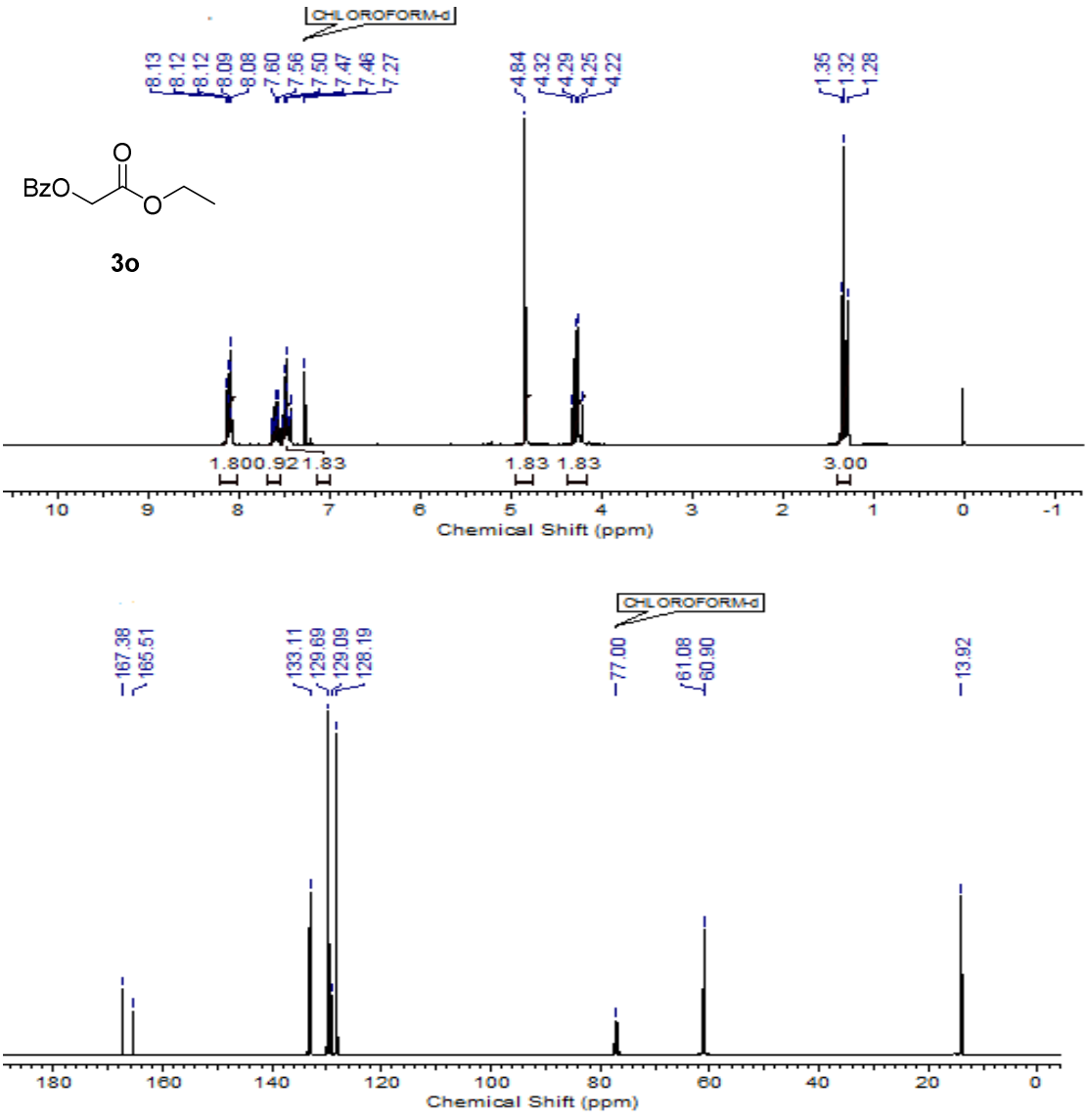
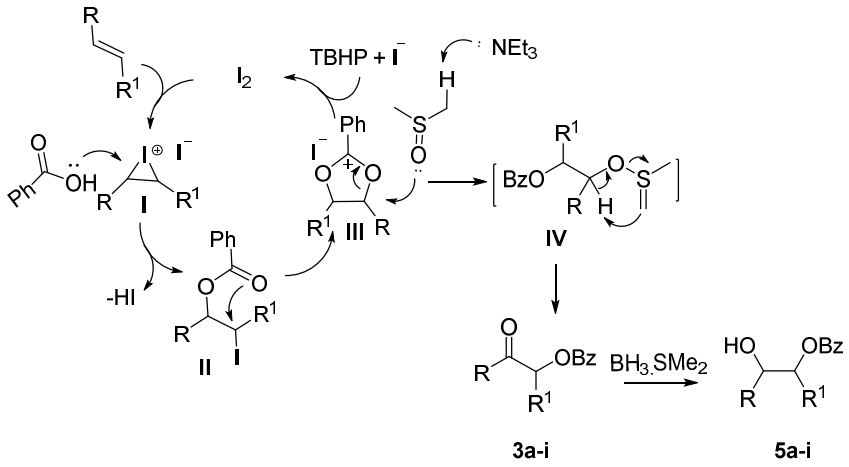


Fig. 4: ^{1}H & ^{13}C NMR spectra of **3o**

2.1.3.3 Mechanistic Discussion

In order to gain insight into mechanism of the reaction, several control experiments were performed, the observations/inferences of which are given below: (i) No reaction was observed in the absence of either benzoic acid or Et_3N; (ii) in the case of styrene, the iodo compound **II** was isolated (20% yield after 2 h) and characterized completely (GCMS, ^1H and ^{13}C NMR) which eliminates the role of hypervalent iodine the in mechanism; (iii) further treatment of compound **II** with DMSO and Et_3N afforded the desired product **3a** in 62% yield; (iv) **Table 1** (entry 2 and 8) suggests that TBHP is mere co-oxidant in the reaction for regeneration of I_2.



Scheme 25: Catalytic cycle for oxo- and hydroxyacyloxylation of alkenes.

According to the aforementioned information and based on previous reports, a proposed mechanism for the I_2-catalyzed oxidative functionalization of alkenes is outlined in **Scheme 25**. Initially, the substrate alkene reacts with I_2 to form the iodonium ion intermediate **I**, which undergoes regioselective ring opening with benzoic acid giving the iodo compound **II**. The proposed key intermediate species **III**[33] formed from **II** by the anchimeric assistance shown by the benzoate group, reacts with DMSO in regioselective

manner to give hydroxy ylide **IV** with the liberation of iodide ion. Iodide ion is then reoxidized with TBHP to regenerate I_2 while elimination (-Me_2S) from **IV** could then be undertaken to provide the desired products **3a-i**, which on reduction with borane gave diol derivatives **5a-i**.

2.1.4 Conclusion

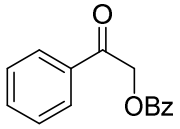
To summarize, we have demonstrated that the oxo- and hydroxyacyloxylation process of alkenes and enol ethers with carboxylic acids can be achieved using metal-free catalytic systems. This operationally simple and efficient method provides a new approach to the synthesis of α-acyloxyketones, esters (**3a-p**) and diol derivatives (**5a-h**) showing good functional group tolerance. We believe that the macrolactonization process directly from unactivated carboxylic acid would serve as a competent method and find tremendous applications in the synthesis of widely occurring macrolides. More importantly, this inexpensive I_2/TBHP system provides for a single step, metal-free dihydroxylation process directly from alkenes, thereby complimenting OsO_4 catalyzed dihydroxylation of alkenes.

2.1.5 Experimental section

General experimental procedure for the preparation of compounds 3a-p

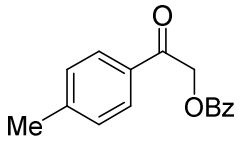
To a stirred solution of alkene (1 mmol) in dry DMSO (8 mL) at 0 °C was added I_2 (10 mol %), Et_3N (1.2 mmol), TBHP (1 mmol) and carboxylic acid (1 mmol) and the reaction mixture was then stirred at 25 °C under air. After completion of the reaction (as monitored by TLC), it was diluted with H_2O (5 mL) at 0 °C. It was then extracted with EtOAc (3 x 20 mL) followed by washing with brine (3 x 25 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Concentration of the organic solvent under reduced pressure gave the crude product, which was then purified by column chromatography over silica gel using Pet. ether:EtOAc (9:1) as eluent to obtain α-acyloxy carbonyl compounds **3a-p** in high purity.

2-Oxo-2-phenylethyl benzoate (3a)



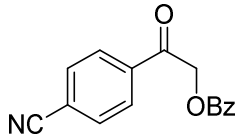
Yield: 88% (210 mg), colorless solid, **mp**: 115-116 °C, (lit.[13] **mp**: 114-115 °C); **IR** (Nujol, cm^{-1}): ν_{max} 705, 1015, 1374, 1459, 1596, 1714, 1750, 2851, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.58 (s, 2H), 7.48-7.61 (m, 6H), 7.97-8.13 (m, 2H), 8.14-8.17 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.2, 127.7, 128.2, 128.73, 129.9, 130.1, 133.1, 133.7, 134.2, 165.7, 191.7; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{15}H_{12}O_3$+Na: 263.0683; found: 263.0692.

2-Oxo-2-(p-tolyl)ethyl benzoate (3b)



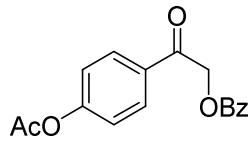
Yield: 85% (216 mg), colorless solid, **mp**: 105-106 °C, (lit.[13] **mp**: 107-108 ºC); **IR** (Nujol, cm^{-1}): ν_{max} 713, 1135, 1231, 1289, 1459, 1604, 1698, 1732, 2840, 2923; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.47 (s, 3H), 5.57 (s, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.61-7.63 (m, 1H), 7.90 (d, *J* = 7.9 Hz, 2H), 8.17 (d, *J* = 7.3 Hz, 2H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 66.9, 123.5, 127.8, 129.6, 131.1, 131.5, 134.8, 145.1, 150.7, 164.1, 190.6; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{14}O_3$+Na: 277.0840; found: 277.0848.

2-(4-Cyanophenyl)-2-oxoethyl benzoate (3c)



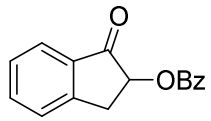
Yield: 82% (217 mg), colorless solid, **mp**: 89-91 °C, (lit.[14] **mp**: 87-88 ºC); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 717, 871, 1131, 1155, 1231, 1595, 1698, 1722, 1746, 2250, 2940; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.53 (s, 2H), 7.48 (s, 2H), 7.60-7.61 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 8.06 (s, 2H), 8.12 (br. s., 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 66.3, 117.4, 117.4, 128.3, 128.6, 129.1, 130.0, 132.7, 133.6, 137.3, 165.7, 190.9; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{11}NO_3$+Na: 288.0637; found: 288.0646.

2-(4-Acetoxyphenyl)-2-oxoethyl benzoate (3d)



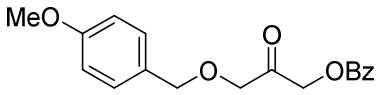
Yield: 84% (250 mg), colorless solid, **mp**: 106-107 °C, (lit.[13] **mp**: 107-108 ºC); **IR** (Nujol, cm^{-1}): ν_{max} 716, 1166, 1212, 1294, 1460, 1593, 1690, 1717, 1753, 2846, 2917; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 5.55 (s, 2H), 7.23 (s, 2H), 7.48-7.51 (m, 2H), 7.61-7.66 (m, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 8.12-8.16 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.9, 66.1, 121.9, 128.3, 129.2, 129.8, 131.6, 133.1, 154.7, 165.6, 168.2, 190.6; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{14}O_5$+Na: 321.0739; found: 321.0748.

1-Oxo-2,3-dihydro-1*H*-inden-2-yl benzoate (3e)



Yield: 76% (191 mg), colorless solid, **mp**: 141-143 °C, (lit.[7] **mp**: 142-144 ºC); **IR** (Nujol, cm^{-1}): ν_{max} 714, 1126, 1275, 1379, 1373, 1582, 1634, 1749, 1822, 2896, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.20 (dd, *J* = 17.0, 4.8 Hz, 1H), 3.79 (dd, *J* = 17.0, 8.0 Hz, 1H), 5.64 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.42-7.49 (m, 5H), 7.59-7.71 (m, 2H), 7.85 (d, *J* = 7.5 Hz, 1H), 8.08-8.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.7, 74.5, 124.6, 126.7, 128.2, 128.5, 129.4, 130.1, 133.4, 134.8, 135.9, 150.4, 166.0, 200.2; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{12}O_3$+Na: 275.0684; found: 275.0672.

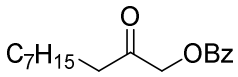
3-((4-Methoxybenzyl)oxy)-2-oxopropyl benzoate (3f)



Yield: 83% (260 mg), oily viscous liquid; **IR** (Nujol, cm^{-1}): ν_{max} 718, 1063, 1263, 1375, 1457, 1567, 1725, 1749, 2861, 2893; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.83 (s, 3H), 4.19 (s, 2H), 4.57 (s, 2H), 5.13 (s, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.31 (s, 2H), 7.43-7.50 (m, 2H), 7.56-7.60 (m, 1H), 8.09 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.2,

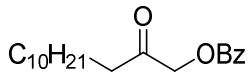
67.3, 73.4, 73.5, 114.0, 128.4, 129.7, 129.9, 133.3, 159.7, 165.7, 201.8; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{18}H_{18}O_5$+Na: 337.1052; found: 337.1074.

2-Oxodecyl benzoate (3g)



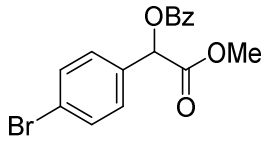
Yield: 89% (245 mg), colorless viscous liquid; **IR** (Nujol, cm^{-1}): ν_{max} 745, 1179, 1250, 1314, 1469, 1571, 1650, 1725, 1747, 2856, 2928; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.85-0.92 (m, 3H), 1.22-1.36 (m, 9H), 1.57-1.64 (m, 3H), 2.49 (t, *J* = 7.3 Hz, 2H), 4.86 (s, 1H), 7.40-7.52 (m, 2H), 7.53-7.65 (m, 1H), 8.03-8.14 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.0, 22.6, 25.5, 29.1, 29.4, 31.8, 35.0, 40.5, 71.0, 128.4, 129.2, 129.8, 133.3, 165.8, 198.5; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{24}O_3$+Na: 299.1623; found: 299.1623.

2-Oxotridecyl benzoate (3h)



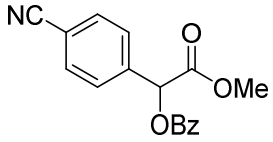
Yield: 86% (273 mg), colorless viscous liquid; **IR** (Nujol, cm^{-1}) ν_{max} 742, 1065, 1314, 1469, 1506, 1724, 1740, 2812, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86-0.92 (t, 3H), 1.17-1.35 (m, 17H), 1.51-1.68 (m, 2H), 2.31 (s, 1H), 2.49 (t, *J* = 7.3 Hz, 1H), 4.86 (s, 1H), 7.41-7.49 (m, 2 H), 8.07-8.08 (m, 1H), 8.11-8.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.0, 22.6, 25.5, 29.1, 31.8, 35.0, 38.8, 40.5, 71.0, 128.4, 129.2, 129.8, 133.3, 165.8, 198.5; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{20}H_{30}O_3$+Na: 341.2093; found: 341.2086.

1-(4-Bromophenyl)-2-methoxy-2-oxoethyl benzoate (3i)



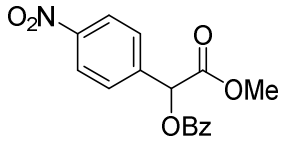
Yield: 78% (273 mg), colorless viscous liquid: **IR** (Nujol, cm^{-1}): ν_{max} 724, 1089, 1277, 1462, 1523, 1600, 1718, 1732, 2855, 2926; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.76 (s, 3H), 6.10 (s, 1H), 7.43-7.49 (m, 4H), 7.50-7.59 (m, 3H), 8.08-8.13 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 52.8, 74.2, 128.4, 128.5, 129.3, 129.8, 130.0, 132.1, 133.1, 133.6, 161.9, 164.6; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{13}BrO_4$+Na: 370.9895; found: 370.9885.

1-(4-Cyanophenyl)-2-methoxy-2-oxoethyl benzoate (3j)



Yield: 81% (238 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 718, 1101, 1167, 1269, 1348, 1508, 1606, 1731, 1760, 2210, 2856, 2953; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.21 (s, 1H), 7.57-7.73 (m, 7H), 8.12 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 53.0, 73.9, 100.2, 127.0, 128.2, 128.6, 130.0, 132.1, 132.6, 133.8, 148.2, 165.3, 168.1; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{13}$ NO_4+Na: 318.0742; found: 318.0742.

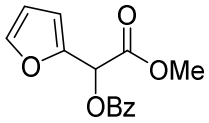
1-(4-Nitrophenyl)-2-methoxy-2-oxoethyl benzoate (3k)



Yield: 82% (258 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 718, 1101, 1169, 1269, 1346, 1366, 1508, 1527, 1696, 1731, 1760; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.28 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 8.7 Hz,

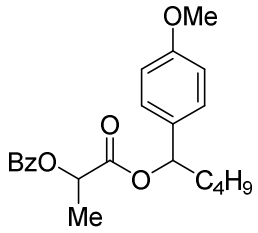
2H), 8.13 (m, *J* = 8.5 Hz, 2H), 8.31 (m, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 53.1, 73.7, 124.1, 128.4, 128.6, 130.0, 133.8, 140.8, 165.3, 168.1; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{13}NO_6$+Na: 338.0641; found: 338.0661.

1-(Furan-2-yl)-2-methoxy-2-oxoethyl benzoate (3l)



Yield: 78% (203 mg), colorless solid, **mp**: 100-102 °C; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 722, 1126, 1270, 1373, 1568, 1613, 1743, 1757, 2863, 2912; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.31 (s, 1H), 6.42 (dd, 1H), 6.55 (d, 1H), 7.38-7.51 (m, 3H), 7.55 (d, 1H), 8.02-8.15 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.7, 67.8, 110.7, 111.1, 128.3, 128.9, 130.0, 133.4, 143.8, 146.8, 165.3, 166.9; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{14}H_{12}O_5$+Na: 283.0582; found: 283.0577.

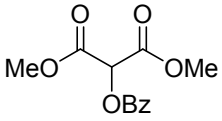
1-((1-(4-Methoxyphenyl)pentyl)oxy)-1-oxopropan-2-yl benzoate (3m)



Yield: 74% (275 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 728, 1131, 1269, 1349, 1376, 1558, 1696, 1745, 1760, 2845, 2905; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.26-1.41 (m, 4H), 1.53-1.57 (m, 3H), 1.70-1.82 (m, 2H), 3.81 (s, 3H), 4.56-4.68 (m, 1H), 5.25-5.35 (m, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.58-7.65 (m, 1H), 8.08-8.13 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 28.1, 38.7, 55.1, 74.2, 75.1, 77.4, 113.7, 127.1, 128.2, 128.5, 129.7,

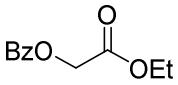
129.9, 132.9, 133.5, 137.2, 158.9, 159.1, 165.8; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{22}H_{26}O_5$+Na: 393.1678; found: 393.1634.

Dimethyl 2-(benzoyloxy)malonate (3n)



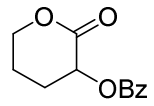
Yield: 83% (210 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1176, 1591, 1695, 1726, 1766, 2854, 2870, 2923; **^{1}H NMR** (400 MHz $CDCl_3$): δ 3.87 (s, 6H), 5.83 (s, 1H), 7.49-7.54 (m, 2H), 7.59-7.65 (m, 1H), 8.15-8.18 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.6, 53.3, 85.2, 128.4, 128.6, 130.4, 134.0, 159.4, 164.1; **HRMS** (ESI): $[M+H]^+$ calcd for $C_{12}H_{13}O_6$+H: 253.0712; found: 253.0746.

2-Ethoxy-2-oxoethyl benzoate (3o)



Yield: 89% (185 mg), colorless oily liquid; **IR** (neat, cm^{-1}): ν_{max} 1121 1285, 1738, 1759, 1732, 2983, 2926; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 4.27 (q, J = 7.2 Hz, 2H), 4.84 (s, 2H), 7.40-7.52 (m, 2H), 7.54-7.67 (m, 1H), 7.92-8.19 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.9, 60.9, 128.2, 129.7, 133.1, 165.5, 167.4; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{11}H_{12}O_4$+Na: 231.0633; found: 231.0653.

2-Oxotetrahydro-2H-pyran-3-yl benzoate (3p)

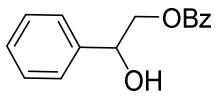


Yield: 84% (185 mg), colorless viscous liquid; **IR** (Nujol, cm^{-1}): ν_{max} 858, 1124, 1273, 1377, 1456, 1511, 1602, 1725, 1753, 2857, 2912; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.61-1.75 (m, 1H), 1.77-1.88 (m, 2H), 1.90-2.15 (m, 1H), 3.57-3.64 (m, 1H), 4.01-4.06 (m, 1H), 4.90-4.94 (m, 1H), 7.39-7.56 (m, 3H), 8.06 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.3, 25.2, 62.3, 71.1, 128.4, 129.9, 130.2, 133.1, 166.1, 166.1; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{12}H_{12}O_4$+Na: 243.0663; found: 243.0665.

General experimental procedure for preparation of compounds 5a-h

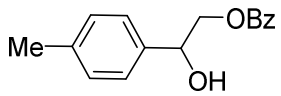
To a stirred solution of alkene (1 mmol) in dry DMSO (8 mL), I_2 (10 mol %), TBHP (1 mmol), Et_3N (1.2 mmol) and benzoic acid (1 mmol) were added and the resulting reaction mixture was then stirred at 25 °C under air. Once α-benzyloxy ketone (**3a-h**) was formed (monitored by TLC), Na_2SO_4 (10 mmol) and $BH_3.SMe_2$ (0.5 mmol) were added to the reaction mixture sequentially at 0° C. After completion of the reaction (monitored by TLC after 5 min), it was quenched with ice at 0 °C. It was then extracted with EtOAc (3 x 50 mL) followed by washing with brine (3 x 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to give the crude product, which was then purified by column chromatography over silica gel using Pet. ether:EtOAc (8:2) as eluent to obtain diol derivative **5a-h** in high purity.

2-Hydroxy-2-phenylethyl benzoate (5a)



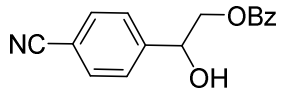
Yield: 86% (208 mg), colorless solid; **mp**: 66-67 °C, (lit.[31] **mp**: 65-67 ºC); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 709, 1023, 1365, 1467, 1598, 1755, 2849, 2921, 3325; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.67 (br.s, 1H), 4.42-4.51 (m, 1H), 4.52-4.55 (m, 1H), 5.10 (dd, *J* = 8.2, 3.2 Hz, 1H), 7.35-7.47 (m, 7H), 7.53-7.56 (m, 1H), 8.06 (d, *J* = 9.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 69.7, 72.4, 126.2, 126.9, 128.1, 128.3, 128.5, 129.7, 133.1, 140.0, 166.6; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{15}H_{14}O_3$+Na: 265.0835; found: 265.0839.

2-Hydroxy-2-(*p*-tolyl)ethyl benzoate (5b)



Yield: 84% (215 mg), colorless solid, **mp**: 79-80 °C, (lit.[31] **mp**: 77-78 ºC); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 716, 1134, 1228, 1283, 1465, 1601, 1756, 2840, 2923, 3315; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.66 (br. s., 1H), 4.35-4.49 (m, 2H), 5.07 (dd, *J* = 8.0, 3.5 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.41-7.49 (m, 2H), 7.55-7.58 (m, 1H), 8.06 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.2, 69.8, 72.4, 126.1, 128.4, 129.3, 129.8, 133.1, 137.1, 137.8, 166.6; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{16}O_3$+Na: 256.1099; found: 256.1094.

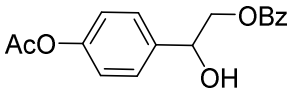
2-(4-Cyanophenyl)-2-hydroxyethyl benzoate (5c)



Yield: 79% (210 mg), colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 717, 871, 1134, 1157, 1238, 1567, 1698, 1746, 2235, 2865, 2940, 3315; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.51-3.55 (m, 1H), 3.63-3.68 (m, 1H), 3.98 (d, *J* = 7.3 Hz, 1H), 4.91-5.01 (m, 1H), 7.32-7.39 (m, 2H), 7.50-7.57 (m, 3H), 7.63-7.65 (m, 1H), 7.71-7.79 (m, 2H), 7.96-8.16 (m, 1H); **^{13}C**

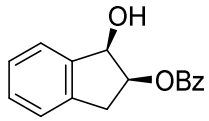
NMR (50 MHz, $CDCl_3$): δ 67.5, 71.5, 111.5, 118.6, 126.3, 128.6, 129.9, 130.1, 132.4, 133.0, 144.9, 165.9; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{13}NO_3$+Na: 290.0788; found: 290.0789.

2-(4-Acetoxyphenyl)-2-hydroxyethyl benzoate (5d)



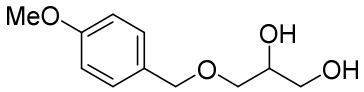
Yield: 83% (250 mg), colorless solid, **mp**: 115-117 °C, (lit.[31] **mp**: 116-117 ºC); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 732, 1164, 1217, 1293, 1460, 1593, 1690, 1753, 2846, 2917, 3280; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.68 (br. s., 1H), 4.39-4.55 (m, 2H), 5.11 (dd, *J* = 8.0, 3.3 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.46-7.63 (m, 5H), 8.03-8.07 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 69.7, 72.0, 121.7, 127.3, 128.4, 129.8, 133.2, 137.6, 150.4, 166.6, 169.2; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{16}O_5$+Na: 300.0998; found: 300.0992.

1-Hydroxy-2,3-dihydro-1*H*-inden-2-yl benzoate (5e)



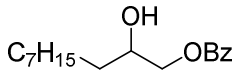
Yield: 72% (182 mg), colorless solid, **mp**: 169-170 °C, (lit.[31] **mp**: 168-169 ºC); **IR** (Nujol, cm^{-1}): ν_{max} 721, 1113, 1278, 1365, 1373, 1582, 1749, 2896, 2943, 3387; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.63 (br. s., 1H), 3.12-3.26 (m, 1H), 3.55 (dd, *J* = 16.3, 8.0 Hz, 1H), 5.30-5.43 (m, 2H), 7.25-7.30 (m, 3H), 7.44-7.46 (m, 3H), 7.49-8.04 (m, 1H), 8.05-8.09 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 36.0, 76.8, 77.1, 77.4, 80.5, 84.8, 96.2, 124.7, 124.8, 127.6, 128.4, 128.5, 128.9, 129.8, 129.8, 129.9, 133.4, 138.5, 141.3, 167.7; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{14}O_3$+Na: 277.0835; found: 277.0840.

3-((4-Methoxybenzyl)oxy)propane-1,2-diol (5f)



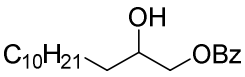
Yield: 84% (173 mg), colorless oily liquid; **IR** (Nujol, cm^{-1}): ν_{max} 718, 1063, 1263, 1375, 1457, 1567, 1749, 2861, 2893, 3300; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.43-3.51 (m, 1H), 3.56 (d, *J* = 5.1 Hz, 1H), 3.76 (d, *J* = 6.4 Hz, 2H), 3.80 (s, 3H), 3.88 (t, *J* = 4.8 Hz, 2H), 4.16 (quintet, *J* = 5.7 Hz, 1H), 4.49-4.51 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.25 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.4, 55.0, 64.4, 70.9, 72.9, 113.7, 128.2, 129.2, 159.2; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{11}H_{16}O_4$+Na: 235.0946; found: 235.0985.

2-Hydroxydecyl benzoate (5g)



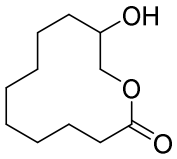
Yield: 87% (240 mg), colorless oily liquid; **IR** (Nujol, cm^{-1}): ν_{max} 745, 1169, 1247, 1360, 1470, 1582, 1747, 2856, 2928, 3289; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86-0.92 (t, *J* = 7.3, 3H), 1.28 (br. s., 13H), 2.09 (br. s., 1H), 3.99 (br. s., 1H), 4.23 (dd, *J* = 11.4, 7.1 Hz, 1 H), 4.41 (dd, *J* = 11.4, 3.2 Hz, 1H), 7.27-7.62 (m, 3H), 8.06 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.5, 29.3, 29.5, 29.6, 31.9, 33.5, 69.3, 70.2, 128.4, 129.7, 130.0, 133.1, 166.7; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{26}O_3$+Na: 301.1774; found: 301.1778.

2-Hydroxytridecyl benzoate (5h)



Yield: 84% (268 mg), colorless oily liquid; **IR** (Nujol, cm^{-1}) ν_{max} 738, 1063, 1360, 1469, 1506, 1753, 2812, 2943, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.85-0.91 (m, 3H), 1.26 (s, 18H), 1.45-1.60 (m, 2H), 2.14 (br. s., 1H), 3.98 (br. s., 1H), 4.17-4.43 (m, 2H), 7.41-7.61 (m, 3H), 8.05 (d, *J* = 6.9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 22.7, 25.5, 29.4, 29.6, 29.7, 31.9, 33.5, 69.3, 70.2, 128.4, 129.7, 130.0, 133.1, 166.6; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{20}H_{32}O_3$+Na: 343.2244; found: 343.2239.

11-Hydroxyoxacyclododecan-2-one (5i)



Yield: 82% (165 mg), colorless gum; **IR** (Nujol, cm^{-1}): ν_{max} 705, 1017, 1312, 1735, 2851, 2923, 3367; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (br. s., 10H), 1.53-1.56 (m, 4H), 1.72-1.84 (m, 1H), 2.06-2.21 (m, 1H), 3.59-3.66 (m, 2H), 3.81-3.88 (m, 1H), 4.09-4.20 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.6, 26.7, 28.7, 29.2, 29.4, 32.6, 35.9, 36.3, 53.1, 63.0, 153.7; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{11}H_{20}O_3$+Na: 223.1310; found: 223.1398.

Section II

Enantioselective Syntheses of (+)-Tanikolide and (-)-Malyngolide *via* I_2-Catalyzed Oxo-acyloxylation Strategy

2.2.1 Introduction

Cyanobacteria (blue-green algae) are an exciting source of novel bioactive natural products.[34] Many structurally diverse metabolites have been isolated from this group of photosynthetic microorganisms, and exhibit a rich variety of biological activities. Of all the marine cyanobacteria, *Lyngbya majuscula* Gomont (Oscillatoriaceae) has been the richest source, yielding more than 100 different secondary metabolites, nearly half of which are of a lipopeptide nature. For example, from a single collection of *L. majuscula*, led to the isolation of curacin A (**38a**),[35] malyngamide H (**38b**),[36] barbamide (**38c**),[37] antillatoxin (**38d**),[38] and the carmabins.[39] Later, from the fractionated lipid extract of *L. majuscula* collected from Madagascar was isolated biologically potent δ-lactones (+)-tanikolide[40] (**38e**) and (-)-malyngolide[41] (**38f**) each bearing chiral quaternary carbon center with a hydroxymethyl group and a multicarbon chain (**Fig. 5**).

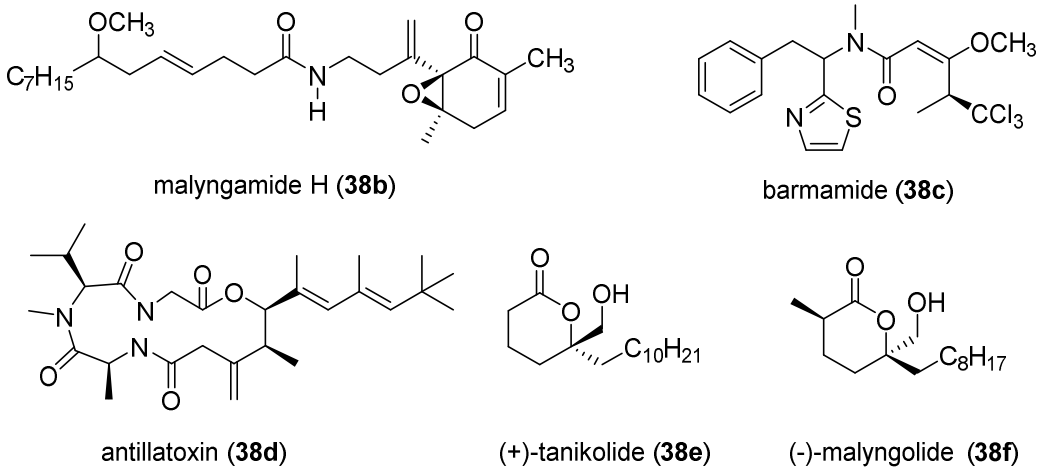


Fig. 5: Select molecules isolated from *L. majuscula*

2.2.2 Pharmacology

(+)-Tanikolide (**38e**) exhibits brine shrimp toxicity, it is molluscicidal, ichthyocidal and antifungal. It shows LD_{50} of 3.6 μg/mL against brine shrimp and 9.0 μg/mL against the snail. Narcotic effect was observed at 10 μg/mL. It is also known to inhibit the growth of *Candida albicans*.[40] Interestingly, tanikolide dimer was found to be a potent inhibitor of SIRT2 (IC_{50} = 176 nM in one assay format) as well as active in a sodium channel blocking assay (54% inhibition at 5.2 μM).[42] (-)-Malyngolide (**38f**) is an antibiotic active against *Mycobacterium smegmatis* and *Strepococcus pyogenes*.[41] Recent studies have shown that malyngolide dimer possesses antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* strain and it is also found to be cytotoxic against human lung tumor cells.[43]

2.2.3 Review of Literature

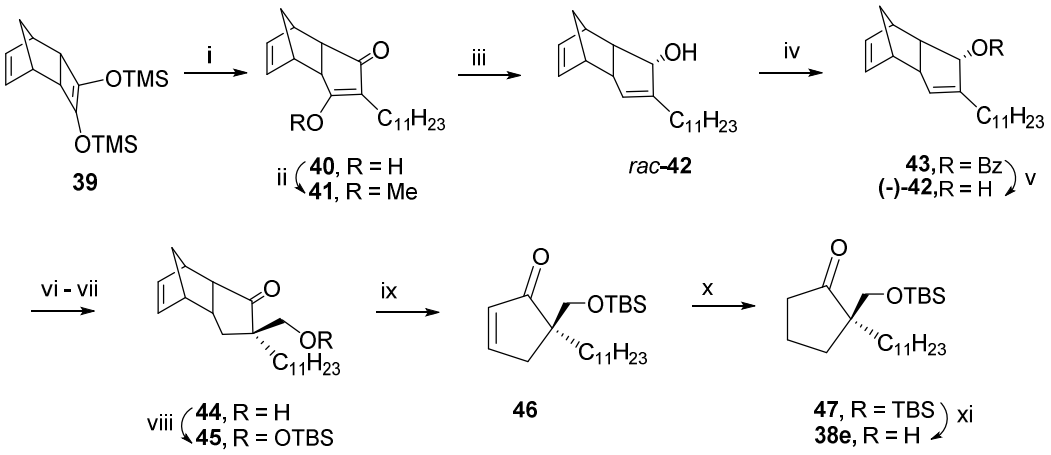
2.2.3.1 Review of Literature for (+)-Tanikolide

In literature there are quite a number of reports available for the synthesis of δ-lactone (+)-tanikolide (**38e**) perhaps due to its interesting biological activity. A few of them have been discussed as follows:

Ogasawara's approach (2000)[44]

Ogaswara *et al*. have reported the first enantioselective synthesis of (+)-tanikolide **38e** by employing catalytic asymmetric hydrogen transfer reaction as the key step. This synthesis confirmed the validity of the proposed structure concluded on the basis of spectroscopic data. The synthesis commenced with enantiomerically pure alcohol derivative **(-)-42** (prepared in five steps from **39** following reported procedure) in order to confirm the absolute structure. Thus, (-)-**42** was subjected to PCC mediated oxidation followed by treatment with diisobutylaluminum hydride (DIBAL-H) in THF in the presence of CuI followed by treatment with gaseous formaldehyde

afforded **44** in excellent yield as a single diastereomer. After protection of alcohol as its TBS ether, it was heated in refluxing diphenyl ether to initiate *retro*-Diels-Alder reaction to give rise to cyclopentenone **46**. Catalytic hydrogenation followed by Baeyer-Villiger rearrangement furnished (+)-tanikolide (**Scheme 26**).

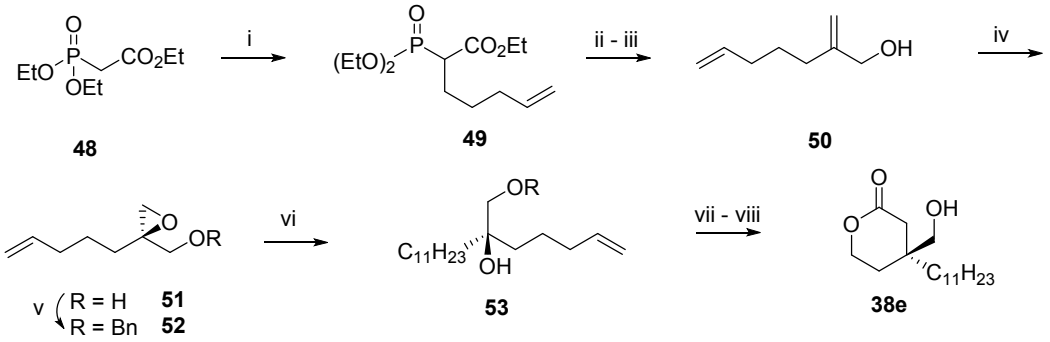


Scheme 26: (i) dodecanal dimethyl acetal, $BF_3.OEt_2$, CH_2Cl_2, - 78 °C then 25 °C, TFA, 4 h, 85%; (ii) MeI (1 equiv), K_2CO_3 (1.2 equiv), MeOH, 2 h, 96%; (iii) $LiAlH_4$, ether, 35 °C, 3 h, 93%; (iv) Ru^{II}[p^6cymene]-(1S,2S)TsDPN[3] (3 mol %), acetone, 25 °C, 20 h then BzCl, DMAP (cat.), 36%, 99% ee; (v) Li_2CO_3, MeOH, 25 °C, 3 h, 96%; (vi) PCC, CH_2Cl_2, 25 °C; (vii) DIBAL-H, CuI (10 mol %), HCHO (gas), THF, 0 °C, 5 h, 95%; (viii) TBSCl, imid., CH_2Cl_2, 25 °C, 3 h, 99%; (ix) diphenyl ether, 260 °C, 5 h, 98%; (x) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 3 h, 97%; (xi) *m*-CPBA, TfOH, CH_2Cl_2, 0 °C, 5 h, 81%.

Borhan's approach (2004)[45]

In Borhan's approach, the key step in the synthesis involves tandem oxidative cleavage-lactonization of a precursor alkenol to deliver the lactone moiety. Synthesis commenced with Wittig olefination of formaldehyde and Wittig ylide precursor **49,** the formed product was reduced under DIBAL-H conditions to afford allylic alcohol derivative **50**. Compound **50** was then subjected to standard Sharpless' epoxidation protocol to afford epoxide **51** which was regioselectively opened using decylmagnesium bromide furnishing alcohol **53**. The final lactonisation was carried

out using Oxone affording the target compound (+)-tanikolide (**38e**) in 8 linear steps with 31% overall yield (**Scheme 27**).

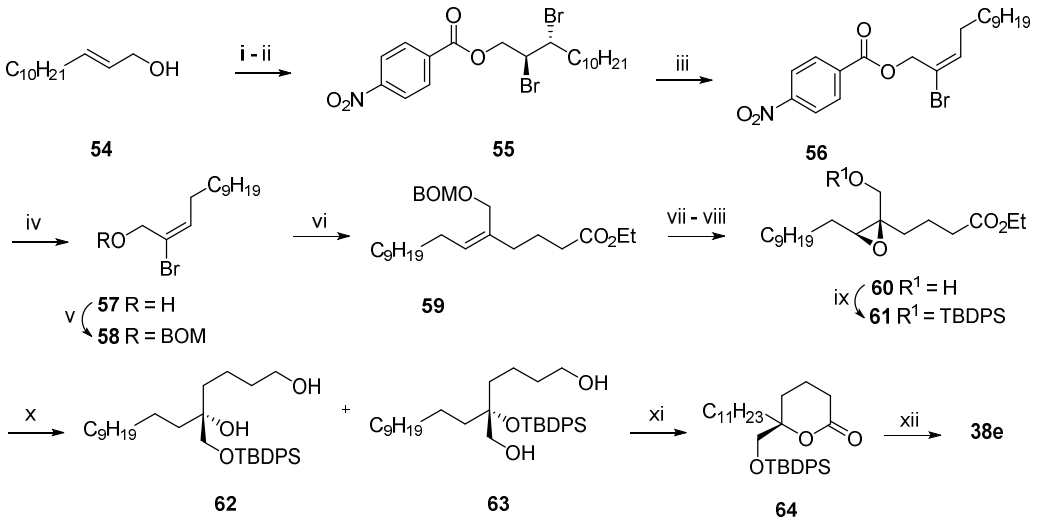


Scheme 27: (i) NaH (1 equiv), 5-bromopent-1-ene (1.1 equiv), THF, 0 °C, 88%; (ii) aq. HCHO (1 equiv), K_2CO_3 (1.5 equiv), 81%; (iii) DIBAL-H (2 equiv), THF, -20 °C, 93%; (iv) $Ti(O^iPr)_4$, (-)-DET, *t*BuOOH (1 equiv), CH_2Cl_2, 4 A° MS, 94%, 94 % ee; (v) BnBr (1.1 equiv), NaH (1.5 equiv), THF, 0 °C, 89%; (vi) decylmagnesium bromide (1 equiv), Li_2CuCl_4, THF, 88%; (vii) nBu_4NHSO_5, OsO_4 (1 mol %), THF, 25 °C, 73%; (viii) H_2 (1 atm), $Pd(OH)_2$ (10 mol %), EtOAc, 25 °C, 87%.

Nishiyama's approach (2004)[46]

In Nishiyama's approach, stereoselective total synthesis of (+)-tanikolide was successfully accomplished by using regioselective HBr elimination reaction of 3-acyloxy-1,2-dibromoalkanes, Pd-mediated coupling reaction and Sharpless asymmetric epoxidation as the key steps. Synthesis of (+)-tanikolide **(38e)** commenced with acylation of **54** which was subjected to bromination with $Py.HBr_3$ to yield the (±)-*anti*-dibromide **55** in 95% yield followed by regioselective *trans*-elimination afforded bromoalkene **56**. The *p*-nitrobenzoate group was hydrolyzed followed by protection of free hydroxyl group as its BOM ether gave **58**. The bromoalkene derivative **58** was then coupled using $Pd(dppf)Cl_2$ catalyzed coupling reaction to give **59** in 73% yield. In the following steps, cleavage of the BOM ether and Sharpless asymmetric epoxidation for the construction of chiral quaternary carbon centre was carried out. Reductive ring opening of the epoxide **61** was achieved with

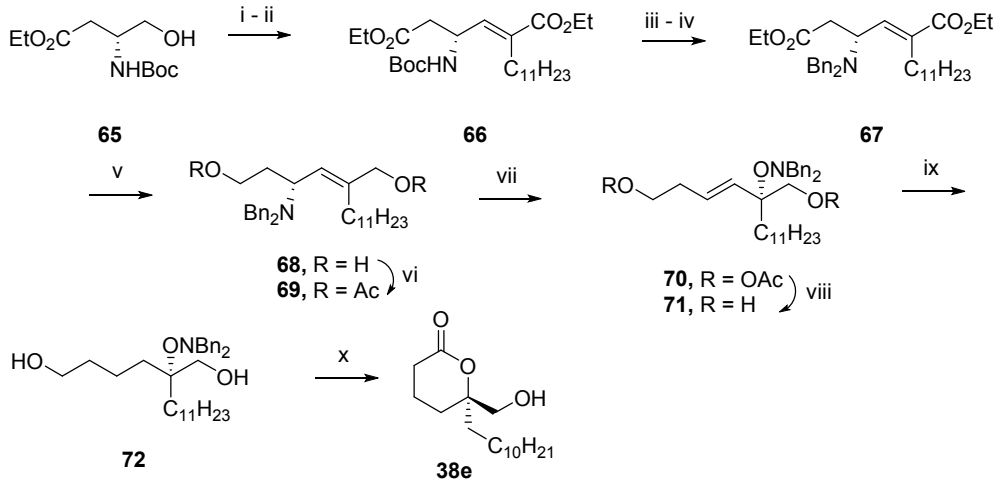
$LiEt_3BH$ at 60 °C which, underwent lactonization with PCC to give δ-lactone **64** and finally treatment with TBAF afforded (+)-tanikolide (**38e**) (**Scheme 28**).



Scheme 28: (i) *p*-$NO_2C_6H_4COCl$, Py., CH_2Cl_2, 25 °C, 100%; (ii) $Py.HBr_3$, AcOH, 25 °C, 95%; (iii) DBU, DMF, 50 °C, 94%; (iv) LiOH, dioxan, 0 °C, 94%; (v) BOMCl, *i*Pr_2NEt, CH_2Cl_2, 25 °C, 95%; (vi) 5 mol % $Pd(dppf)Cl_2$, $BrZn(CH_2)_3CO_2Et$, THF, PhMe, 90 °C, 73%; (vii) conc. HCl, EtOH, 50 °C, 80%; (viii) (-)-DET, TBHP, $Ti(OiPr)_4$, CH_2Cl_2, -30 °C, 90%; (ix) TBDPSCl, imid., DMF, 25 °C, 100%; (x) $LiEt_3BH$, THF, 60 °C, 94%, **62**:**63** = 1:1; (xi) PCC, MS 4A°, CH_2Cl_2, 0 °C, 60%; (xii) TBAF, THF, 25 °C, 87%.

Yang's approach (2013)[47]

Yang *et al.* have reported enantiospecific total synthesis of (+)-tanikolide (**38e**) using [2, 3]-Meisenheimer rearrangement as the key reaction. Synthesis commenced with Wittig reaction of the amino acid derived chiral starting material **65**, to afford **66.** The *Boc*- deprotection and subsequent protection of amine functionality as its dibenzyl amine was carried out to afford **67**. The acetyl protected diol **69** was subjected to the stereoselective [2,3]-Meisenheimer rearrangement reaction *via in situ* formation of *N*-oxide using *m*CPBA. The formed compound **70** was then subjected to deprotection-reduction and lactonisation sequence to afford the target molecule (**Scheme 29**).



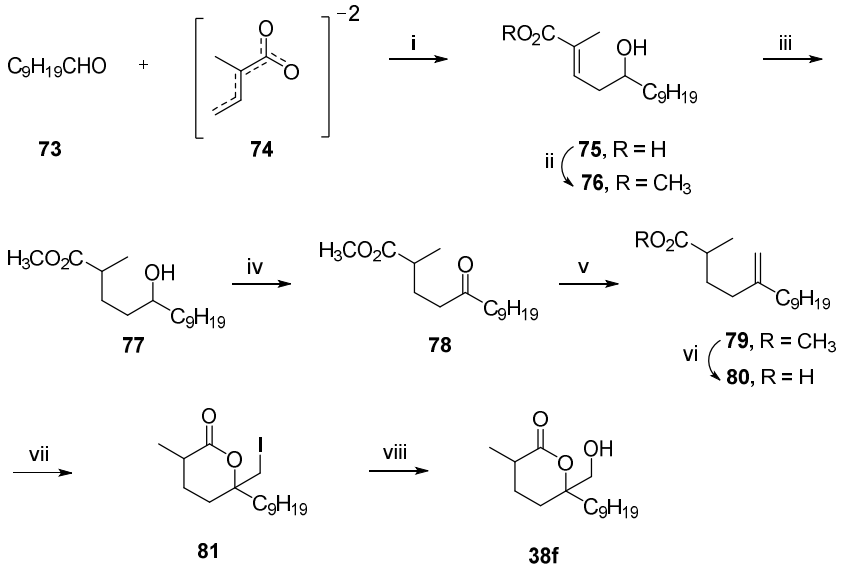
Scheme 29: (i) $Py.SO_3$, DMSO: CH_2Cl_2 (1:1), -5 °C, 5 h; (ii) ethyl 2-(triphenyl-□^{5}phosphanylidene) tri-decanoate, $CHCl_3$, 0.5 h, 93% (over two steps); (iii) TFA, CH_2Cl_2, 25 °C, 5 h; (iv) BnBr, K_2CO_3, CH_3CN, 25 °C, 10 h, 91% (two steps); (v) $LiAlH_4$, ether, 0 °C, 3 h, 95%; (vi) Ac_2O, DMAP (cat.), pyridine, 25 °C, 100%; (vii) *m*CPBA (1 equiv), CH_2Cl_2, 35 °C, 2 h, 83%; (viii) K_2CO_3 (2 equiv), MeOH, 25 °C, 3 h, 95%; (ix) H_2 (60 psi), Pd/C, 25 to 60 °C, 5 h, 93%; (x) NaClO, $NaClO_2$, TEMPO, CH_2Cl_2, CH_3CN, 35 °C, 3 h, 30%.

2.2.3.2 Review of Literature for (-)-Malyngolide

In literature there are a few methods available for the synthesis of (-)-malyngolide owing to its isolation decades back in 1979. Some of the elegant synthetic approaches have been discussed below.

Cardillo's approach (1981)[48]

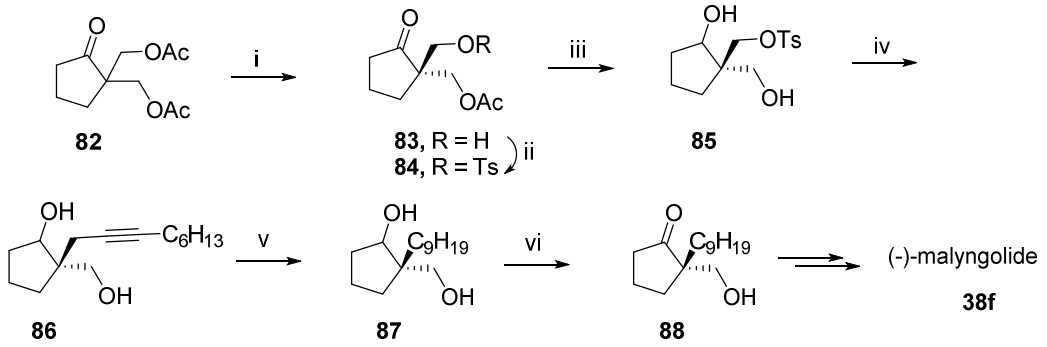
In Cardillo's approach, iodolactonisation reaction has been used as the key step for the synthesis of δ-lactone core. (-)-Malyngolide (**38f**) was synthesized, commencing from the condensation of decanal **73** and dianion **74** (obtained by metalation of sodium salt of tiglic acid with LDA). Successive esterification of **75** followed by oxidation of **77** with Jones' reagent afforded **78** in good yield. Olefination of **78** with methylenemagnesium iodide gave **79**, which was subjected to iodolactonization to afford iodolactone **81**. Hydrolysis of **81** to (-)-malyngolide (**38f**) was accomplished by $Hg(ClO_4)_2$ in dimethoxyethane/water **(Scheme 30).**



Scheme 30: (i) HMPA:THF (9:1), 25 °C, 12 h, 70%; (ii) CH_2N_2, diethyl ether, 0 °C, 4 h, 95%; (iii) H_2 (1 atm), 10% Pd/C, MeOH, 5 h, 100%; (iv) Jones' reagent, acetone, 0 °C, 3 h, 85%; (v) $CH_2(MgI)_2$, KOH, 0 °C, 80%; (vii) I_2, CH_3CN, 25 °C, 3 h, 90%; (viii) $Hg(ClO_4)_2$, dimethoxyethane:water (9:1), 50 °C, 0.5 h, 91%.

Sakai's approach (1988)[49]

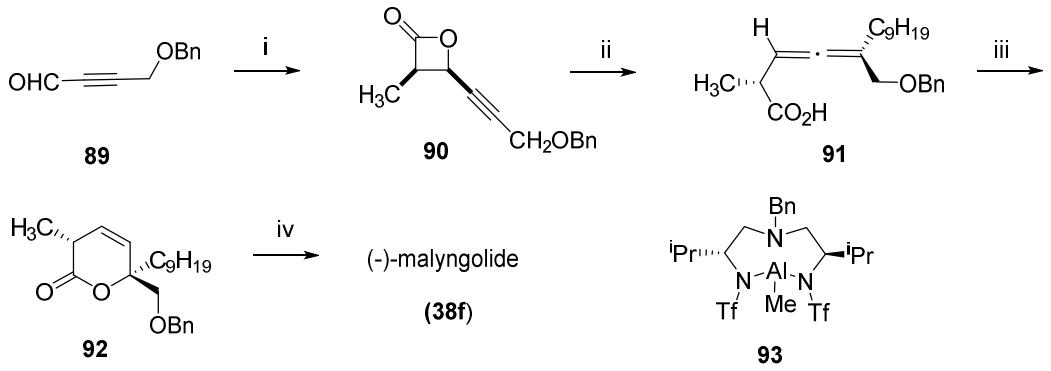
In Sakai's approach, asymmetric hydrolysis of 2,2-bis(acetoxymethylisopentanone) using a biocatalyst followed by its application to the formal synthesis of (-)-malyngolide has been described. Synthesis commenced with chiral cyclopentanone derivative **83** obtained by chiral hydrolysis using cholinesterase enzyme under ambient conditions. Primary tosylate compound **85** was substituted with lithium 1-octylide to afford alkyne derivative **86** which was reduced to **87** *via* catalytic hydrogenation. The subsequent oxidation with bromine and aqueous $NaHCO_3$ afforded **88**, a known intermediate in the synthesis of (-)-malyngolide (**Scheme 31**).



Scheme 31: (i) Cholinesterase enzyme (0.0125 mg/ mL in water), 25 °C, 0.5 h, 36%, 90% ee; (ii) *p*TsCl (1.1 equiv), pyridine, 0 – 25 °C, 3 h, 88%; (iii) $NaBH_4$ (2.0 equiv), MeOH, 25 °C, 2 h, 75%; (iv) Lithium octylide, THF, -20 – 0 °C, 4 h, 84%; (v) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 75%; (vi) Br_2 (in CH_2Cl_2), HMPA, aq. $NaHCO_3$, 5 °C, 1.5 h, 71%.

Nelson's approach (2000)[50]

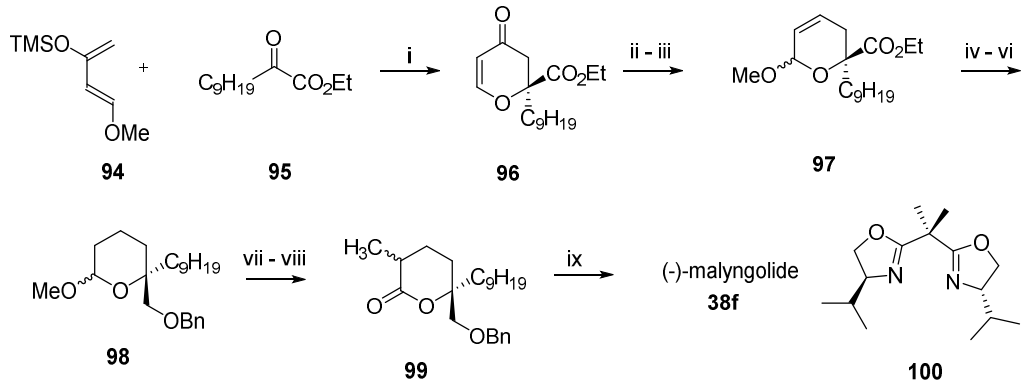
Nelson *et al.* have synthesized (-)-malyngolide in just four steps using asymmetric acyl halide aldehyde cyclocondensation (AAC) as the key chiral inducing step in the synthetic sequence. Synthesis commenced with the asymmetric AAC reaction of propionyl bromide and 4-benzyloxybutynal (**89**) catalyzed by the Al(triamine) complex **93** (10 mol %) to provide the *cis*-3,4-disubstituted-2-oxetanone **90** in 85% yield (94% ee). Copper-catalyzed ring opening of butyrolactone **90** with nonyl Grignard delivered the optically active trisubstituted allene **91**. Further, Ag(I)-catalyzed electrophilic activation of the trisubstituted allene led to the *δ*-lactone **92**, thereby establishing the requisite tertiary carbinol stereocenter. Ensuing Pd(0)-catalyzed alkene dihydrogenation proceeded with concomitant hydrogenolysis of the benzyl ether to afford synthetic (-)-malyngolide (**38f**) in 87% yield (94% ee, 100% de, **Scheme 32**).



Scheme 32: (i) Catalyst **93** (10 mol %), EtCOBr, *i*Pr_2NEt, CH_2Cl_2, -50 °C, 85%, 94% ee, *cis:trans* = 91:9; (ii) *n*C_9H_{19}MgBr, CuBr (10 mol %), THF, -78 °C, 92%; (iii) $AgNO_3$ (10 mol %), *i*Pr_2NEt (5 mol %), 80 °C, CH_3CN, 82%; (iv) H_2, Pd/C, 87%.

Ghosh's approach (2001)[51]

Ghosh *et al*. have made use of asymmetric hetero Diels–Alder reaction for the establishment of quaternary centre in their approach. The chiral cycloadduct pyranone derivative **96** [derived from ethyl 2-oxoundecanate (**95**)] was subjected to Luche's reduction protocol followed by treatment of the resulting 1,2-reduction product with K-10 and methanol thus, furnishing the Ferrier rearrangement product **97** as a 1:1 mixture of diastereomer. Ethyl ester **97** was then converted to its benzyl ether **98** in a three-step sequence involving reduction of ester functionality, hydrogenation of the olefin and protection of the formed hydroxyl group as its benzyl ether. Jones' oxidation of **98** furnished δ-lactone **99** which was methylated following a modified Mukaiyama procedure. Finally, debenzylation of **99** afforded (-)-malyngolide (**38f**) (**Scheme 33**).



Scheme 33: (i) Ligand **100** (10 mol %), CH_2Cl_2, -78 °C, TFA, CH_2Cl_2, 0 °C, 12 h, 73%, 56% ee; (ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH/H_2O, 0 °C; (iii) K-10, CH_3OH, 0 - 23 °C, 56% (three steps); (iv) $LiAlH_4$, Et_2O, 0 °C; (v) H_2, Pd/C, CH_3OH, 23 °C; (vi) BnBr, NaH, DMF, 0 °C, 56% (three steps); (vii) Jones' reagent, acetone, 23°C, 60%; (viii) LHMDS, HMPA, CH_3I, THF, −78 °C, 96%; (ix) H_2, Pd/C, CH_3OH, 23 °C, 93%.

2.2.4 Present Work

2.2.4.1 Objective

As can be seen, the reported methods for the synthesis of (+)-tanikolide (**38e**) and (-)-malyngolide (**38f**) rely on either enzyme catalyzed resolution techniques (in which one of the enantiomers remains unutilised in the synthesis), chiral starting materials or Sharpless asymmetric epoxidation reaction of preformed allylic alcohol for chirality induction. Again, the formation of lactone core generally warrants the use of strongly acidic reaction conditions. In most of the cases the long aliphatic carbon chain is incorporated utilising strongly basic Grignard reaction. Thus, there is a need for efficient and mild syntheses of the (+)-tanikolide and (-)-malyngolide in lesser number of steps, circumventing some of the disadvantages associated with the reported methods. Also no method is available so far for their syntheses using asymmetric allylation reactions. In this section, we describe enantioselective synthesis of (+)-tanikolide (**38e**) and (-)-malyngolide (**38f**) using asymmetric Keck's allylation[52] protocol for chirality induction and I_2-catalyzed oxo-acyloxylation strategy for the installation of α-benzoyloxy ketone moiety.

Retrosynthetic analysis (**Fig. 6**) of (+)-tanikolide (**38e)** reveals that it can be synthesized from δ-hydroxy ester **104** by lactonisation reaction. The conjugated ester **104** can be envisioned through a cross metathesis reaction between homoallylic alcohol **103** and methyl acrylate. The chiral alcohol **103** can be obtained by asymmetric allylation reaction of α-acyloxy ketone **102** which in turn can easily be formed from commercially available 1-tridecene (**101**) using our highly regioselective I_2-catalyzed oxo-acyloxylation protocol. A Similar strategy can be applied for (-)-malyngolide (**38f**), which can be envisioned from homoallylic alcohol **108** *via* esterification with methacroyl chloride followed by Grubbs' ring closing metathesis

reaction to afford unsaturated lactone derivative **109**. The chiral alcohol **108** in turn can be synthesized by asymmetric Keck allylation of α-acyloxy ketone **107,** which can be envisioned by oxo-acyloxylation reaction from 1-undecene (**106**).

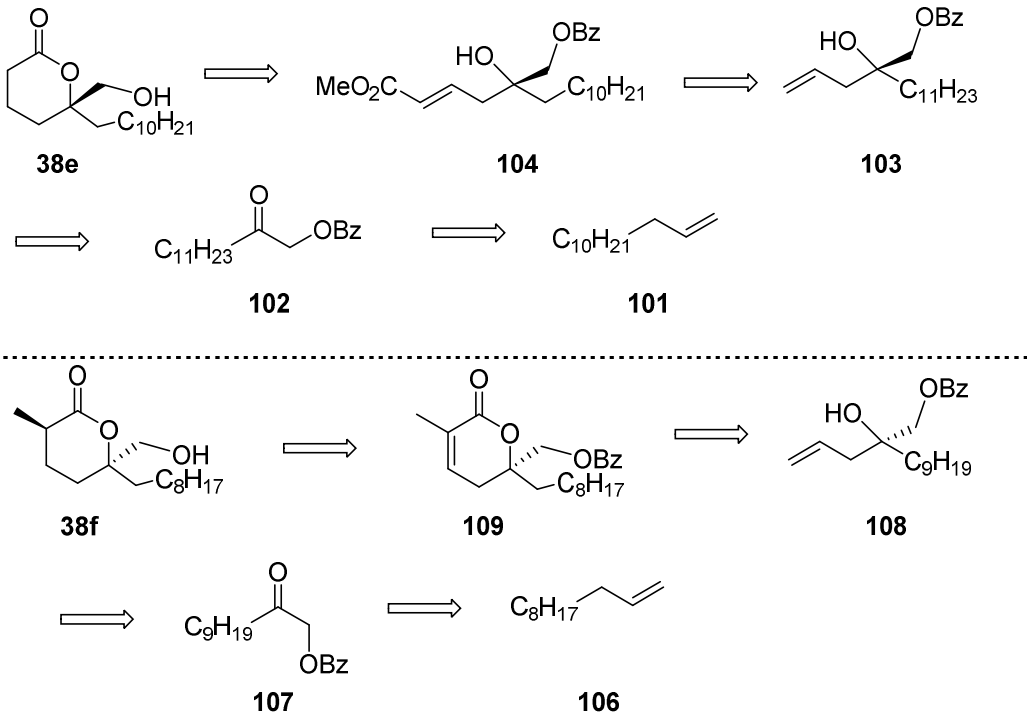
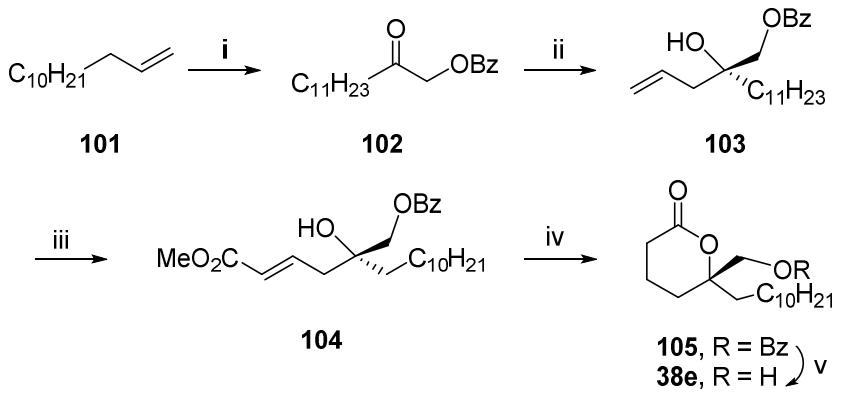


Fig. 6: Retrosynthetic analysis of (+)-tanikolide (**38e**) and (-)-malyngolide (**38f**)

2.2.5 Results and Discussion

2.2.5.1 Synthesis of (+)-Tanikolide

The complete synthetic sequence for (+)-tanikolide (**38e**) wherein I_2 catalyzed oxo-acyloxylation, asymmetric Keck allylation and Grubb's metathesis reaction constitute the key steps is presented in **Scheme 34**. Our synthesis of (-)-tanikolide commenced with oxo-acyloxylation of tridec-1-ene under mildly basic conditions to afford α-benzoyloxy ketone **102** in 86% yield and good regioselectivity. The formation of product **102** was confirmed by NMR, HRMS and IR spectral data.



Scheme 34: (i) I_2 (10 mol %), TBHP (5.5 M in decane, 1 equiv), $PhCO_2H$ (1 equiv), Et_3N (1.2 equiv), DMSO, 0 - 25 °C, 12 h, 86%; (ii) $Ti(O^iPr)_4$ (10 mol %), (*R*)-BINOL (10 mol %), 4 Å° MS, allylSn^nBu_3 (1.1 equiv), CH_2Cl_2, -78° C to -20° C, 72 h, 81%, 81% ee; (iii) methyl acrylate (5 equiv), Grubbs' II (5 mol %), CH_2Cl_2, 25° C, 4 h, 88%; (iv) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h, 96%; (v) K_2CO_3 (1.5 equiv), MeOH, 25 °C, 6 h, 85%.

The ^{1}H NMR spectrum of compound **102** showed typical aromatic signals due to benzoate group appearing at δ 7.39-7.52 (m, 2H), 7.52-7.66 (m, 1H) and 8.00-8.14 (m, 2H) confirming the olefin functionalization with benzoate group. Further methylene protons (-C**H**$_2$) attached to the benzoate group appeared as a singlet at δ 4.86 (s, 2H). The long aliphatic chain showed typical broad methylene envelop at δ 1.26 integrating for 16 protons. The structure of compound **102** was further corroborated by its ^{13}C NMR spectrum which showed characteristic carbonyl carbon signal at δ 203.5 and 165.6 due to ketone and benzoate ester functionality respectively. A typical signal for methylene carbon (-**C**H$_2$) attached to benzoate group appeared at δ 68.3 (**Fig. 7**). Further, its IR spectrum displayed strong absorption bands at 1724 and 1740 cm^{-1} characteristic of -C=O stretching frequency for ketone and ester functionalities respectively. Keto derivative **102** was then subjected to asymmetric allylation protocol under standard Keck allylation conditions to afford chiral alcohol **103** in 81% yield and 81% ee (determined by chiral HPLC analysis). The formed product was thoroughly characterised by NMR, IR, HRMS and HPLC analysis.

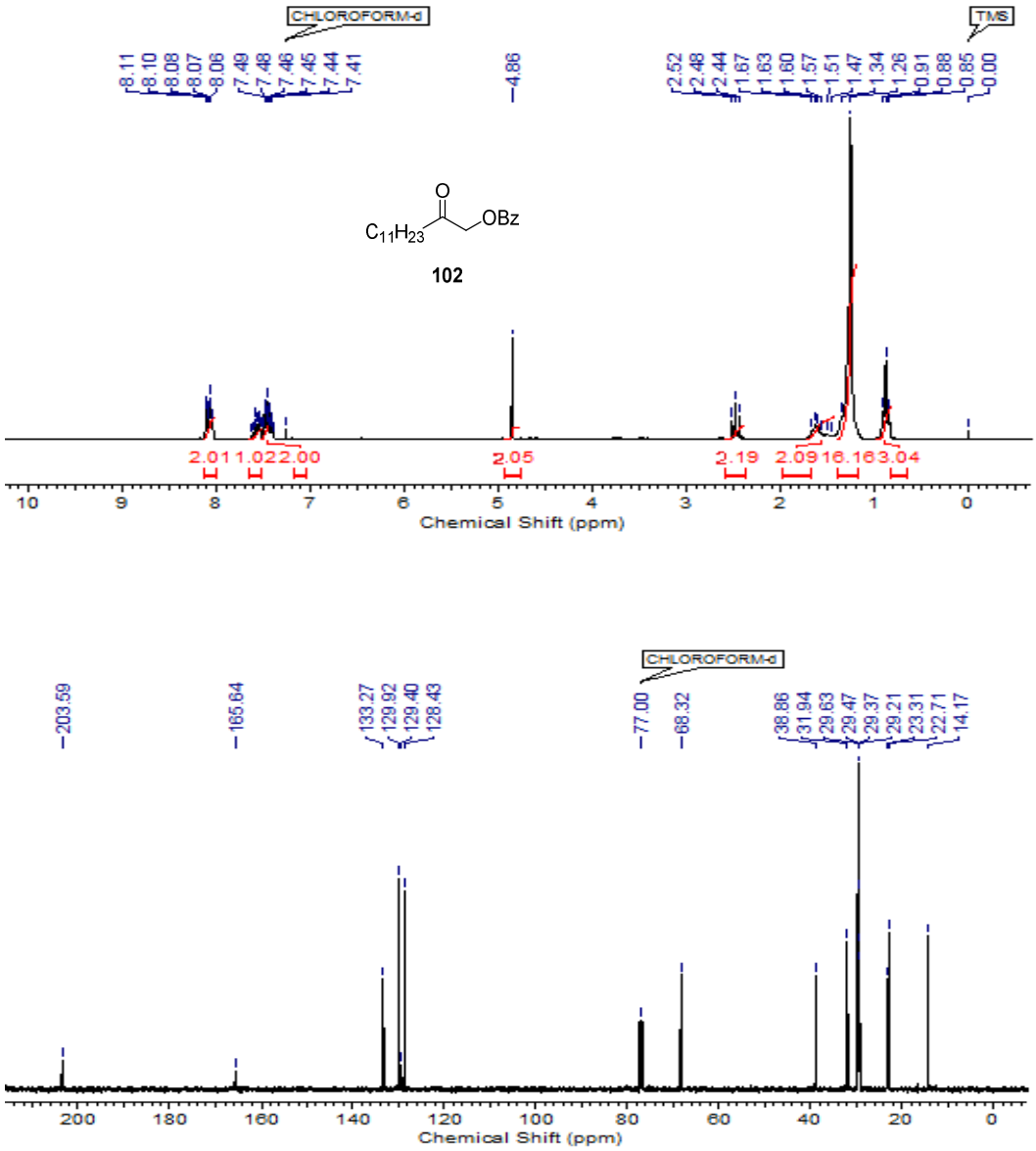
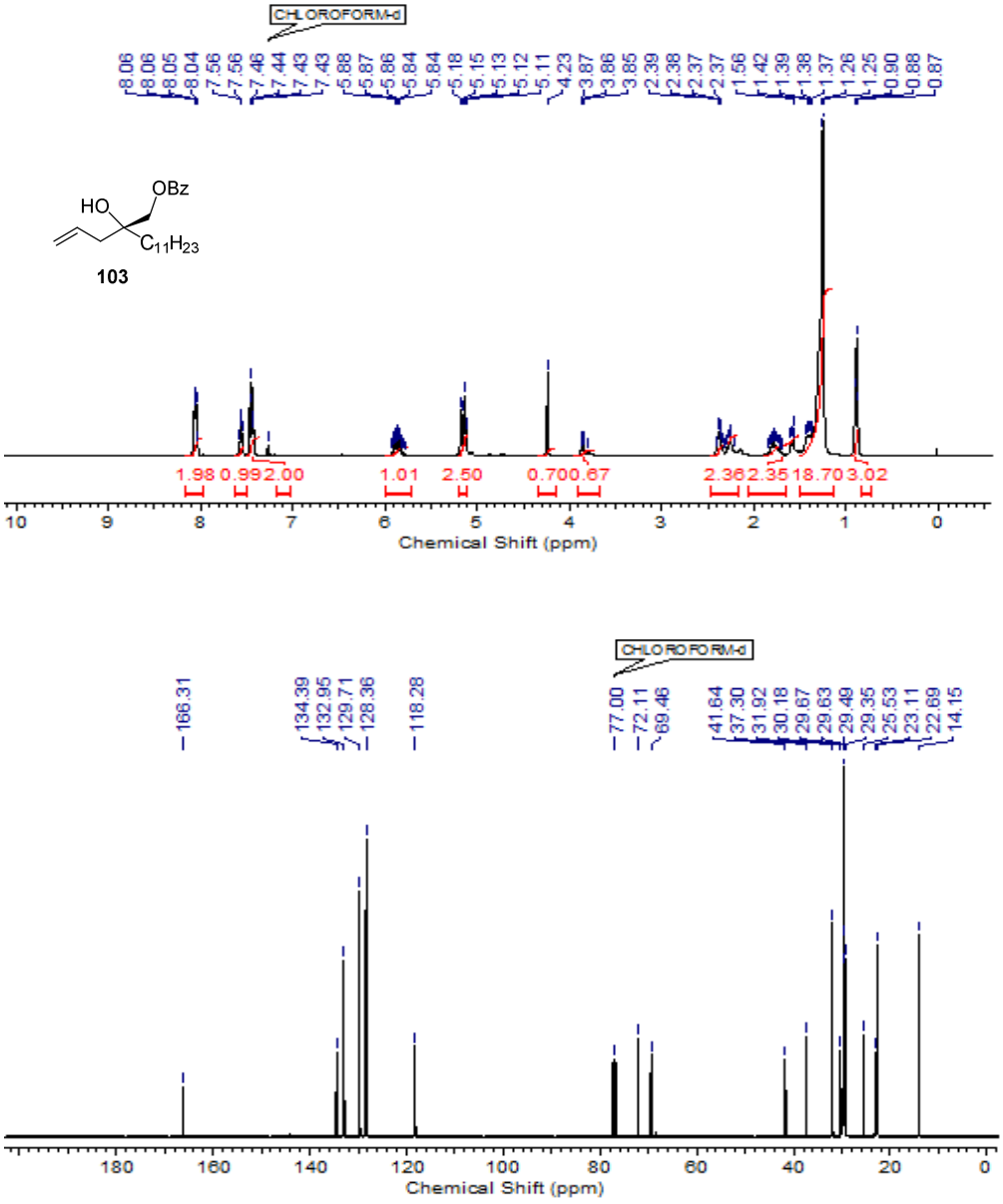
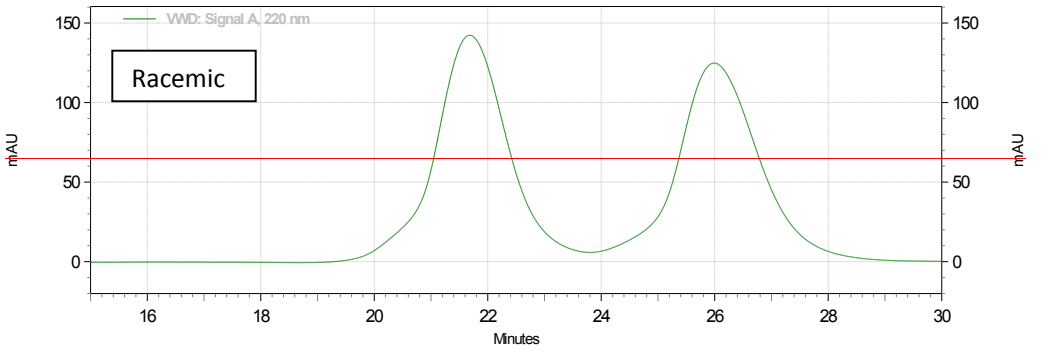


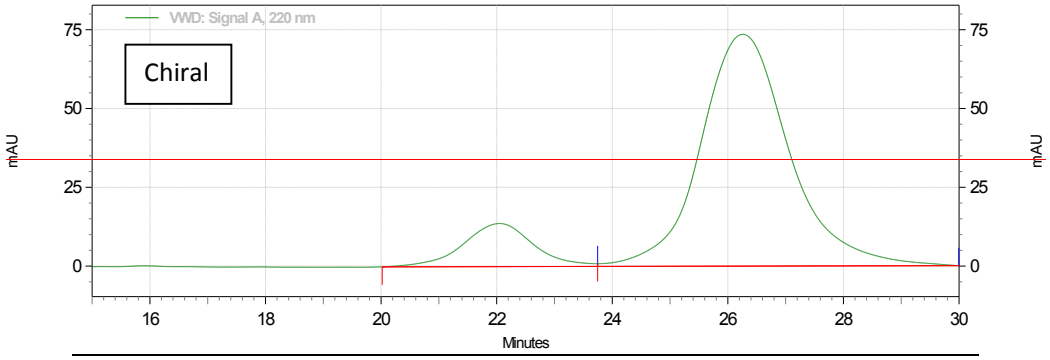
Fig. 7: ^{1}H and ^{13}C NMR spectra of **102**

The ^{1}H NMR spectrum of alcohol **103** showed characteristic olefinic protons at δ 5.11-5.18 (m, 2H) and δ 5.84-5.88 (m, 1H) and diastereotopic methylene protons attached to benzoate group appearing as multiplet at δ 3.85-4.23 (m, 2H). The disappearance of ketone carbonyl carbon signal in its ^{13}C NMR spectrum further confirmed the occurrence of allylation reaction. The quaternary carbon signal

appeared at δ 72.1 while the ester carbonyl carbon of the benzoate group showed a typical signal at δ 166.3 (**Fig. 8**). The enantiomeric excess of the homoallylic alcohol **103** was found using chiral HPLC analysis [Chiracel OD-H column (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 22.05 (minor) and 26.2 (major)].







Retention Time (min)	Area	Area %
22.050	13755964	9.14
26.257	136746919	90.86
Total	150502883	100.00

Fig. 8: ^{1}H, ^{13}C NMR spectra and HPLC chromatogram of **103**

Compound **103** was then subjected to Grubbs' cross metathesis reaction with methyl acrylate to afford α,β-unsaturated ester derivative **104**. The product formation was confirmed by the appearance of typical methoxy proton signal at δ 3.71 (s, 3H) in its ^{1}H NMR spectrum. The olefinic protons appeared at δ 5.90 (d, J = 15.6 Hz, 1H) and δ 6.96-7.09 (m, 1H) suggesting the formation of *trans*- olefin. In its ^{13}C NMR spectrum, two typical carbonyl carbon signals appeared at δ 163.3 and 163.4 (**Fig. 9**).

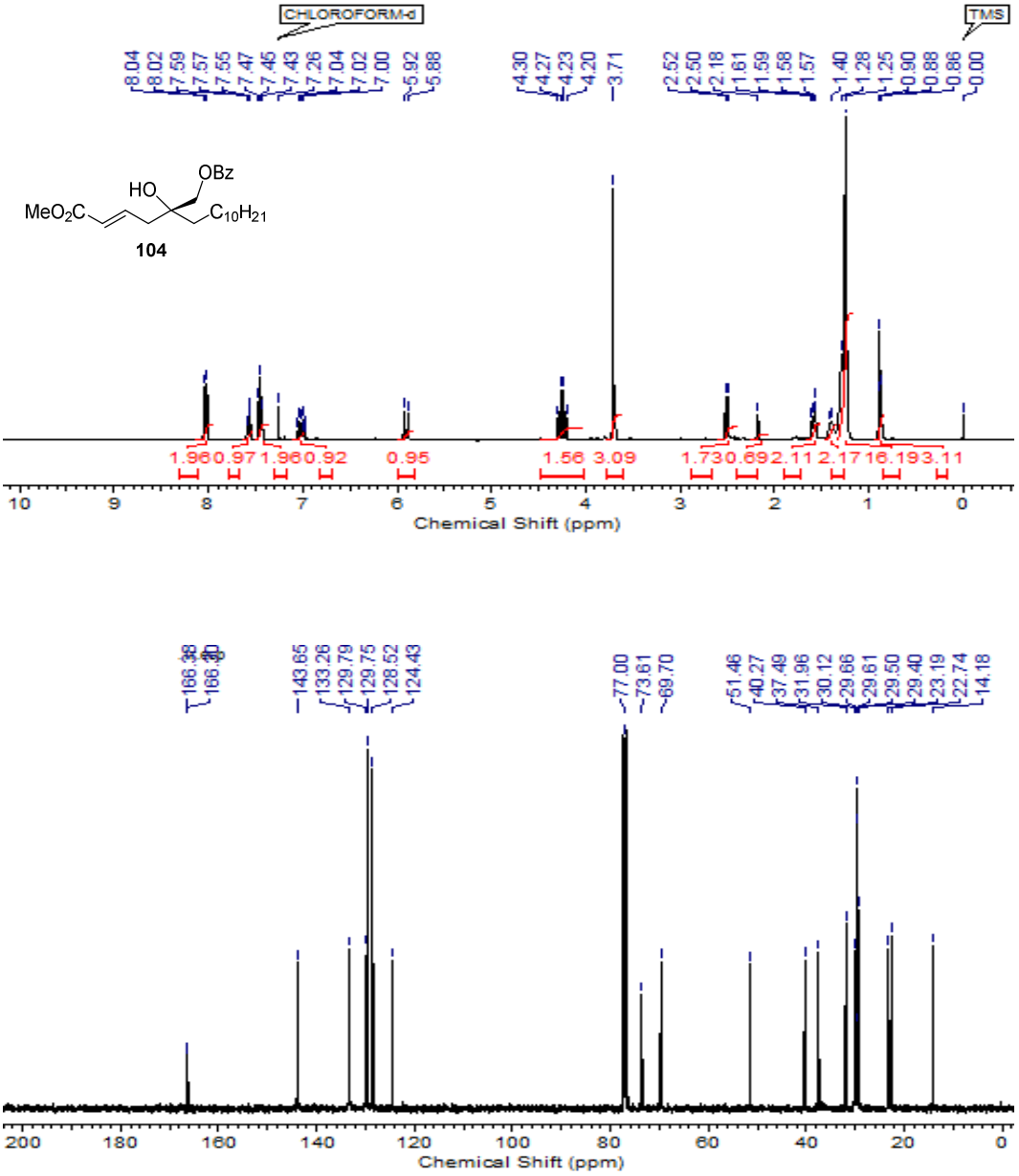


Fig. 9: ^{1}H and ^{13}C NMR spectra of **104**

On subjecting unsaturated compound **104** to catalytic hydrogenation, it underwent concomitant lactonization to afford the desired lactone **105** in 96% isolated yield, which was characterized by the disappearance of typical olefinic and methoxyl proton signals in its proton NMR spectrum. The ^{13}C NMR spectrum featured lactone

carbonyl carbon signal at δ 173.6 and quaternary carbon at δ 73.6 (**Fig. 10**). Finally, hydrolysis of the benzoate ester under mildly basic reaction conditions afforded (+)-tanikolide (**38e**). The

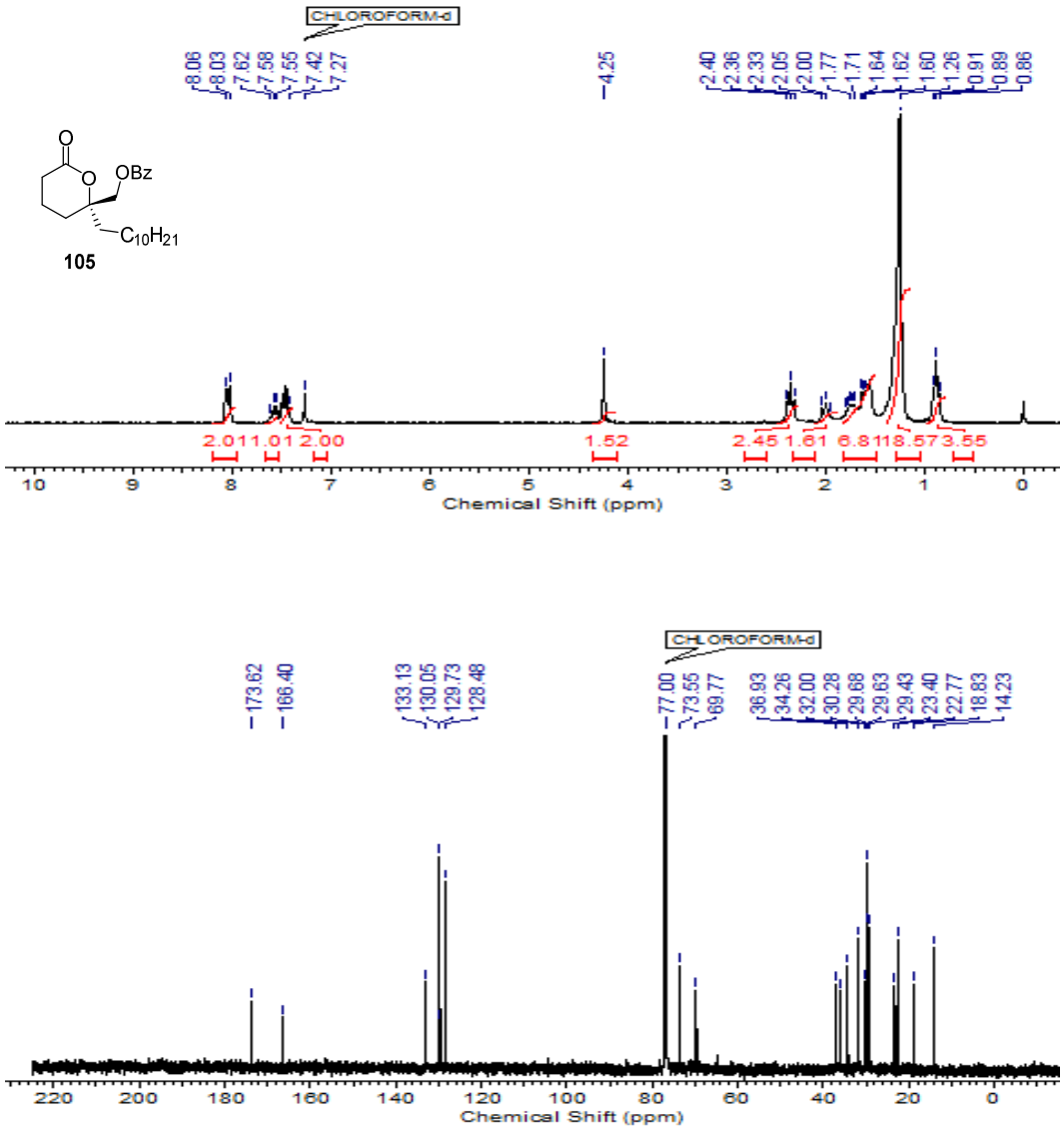


Fig. 10: ^{1}H and ^{13}C NMR spectra of **105**

product formation was confirmed by single ester carbonyl carbon signal in the ^{13}C NMR spectrum at δ 173.6 (**Fig. 11**). The specific rotation value of (+)-tanikolide (**38e**)

was in well agreement with the value reported literature $[\alpha]^{D}_{25}$ = +1.91 (*c* = 0.72, $CHCl_3$) {lit.[44] $[\alpha]^{D}_{20}$ = +2.3 (*c* = 0.65, $CHCl_3$)}.

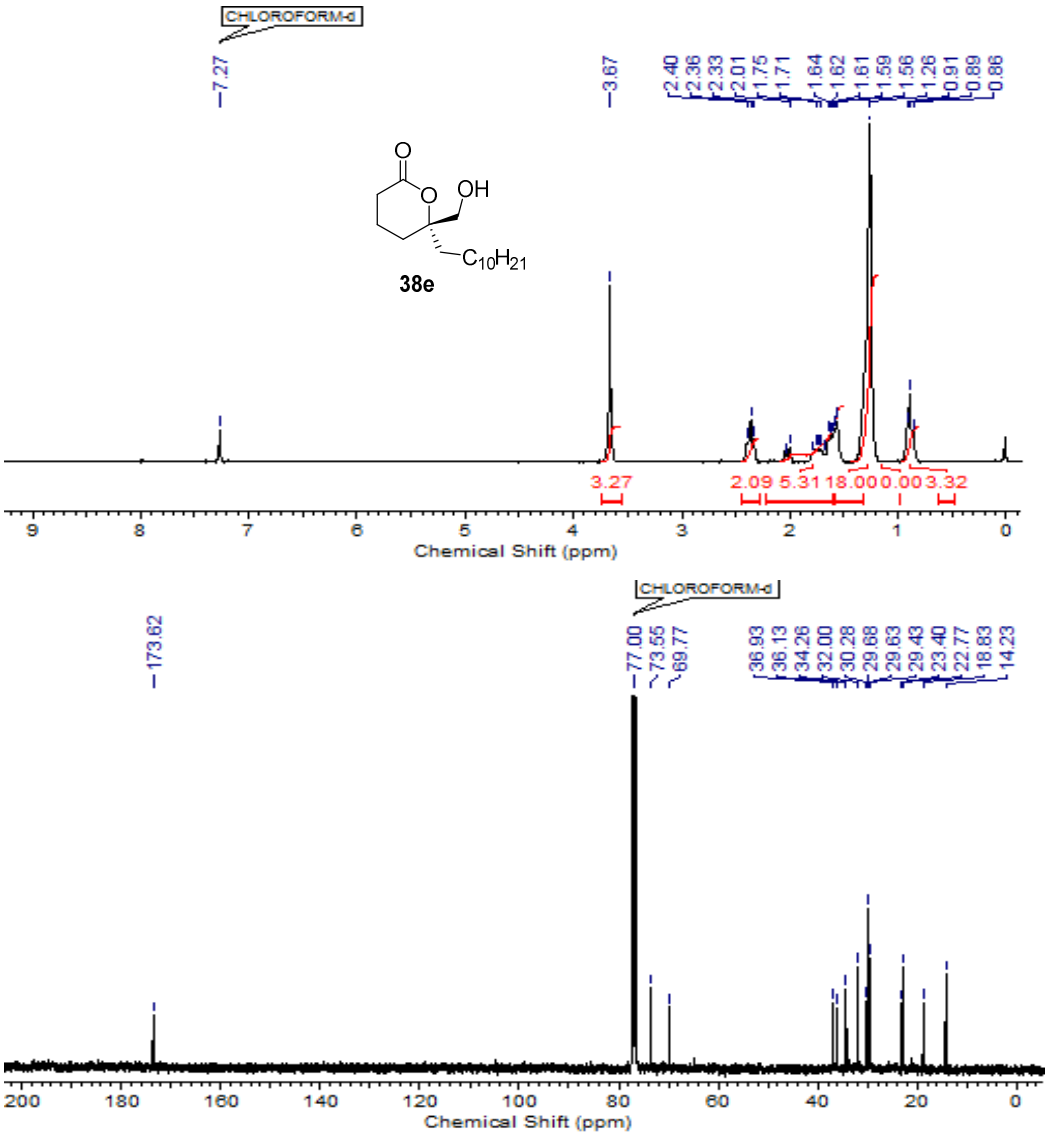
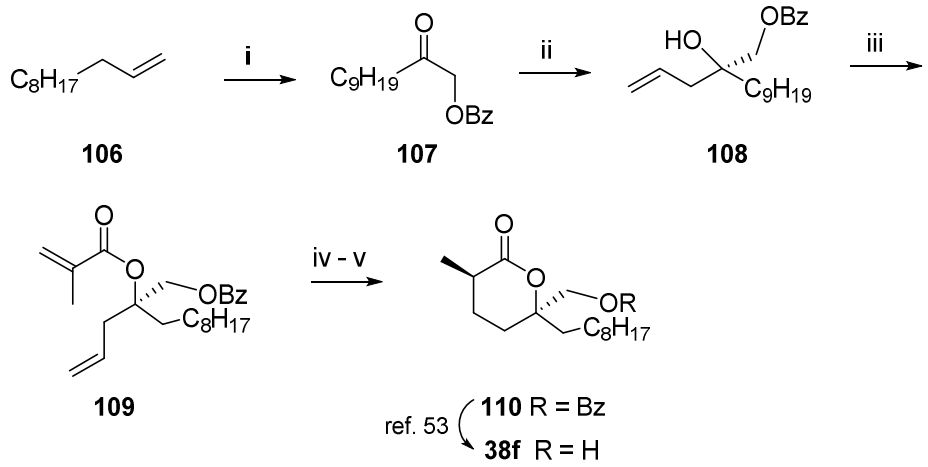


Fig. 11: ^{1}H & ^{13}C NMR spectra of (+)-tanikolide (**38e**)

2.2.5.2 Synthesis of (-)-Malyngolide

The complete synthetic sequence for (-)-malyngolide (**38f**) wherein I_2 catalyzed oxo-acyloxylation reaction, asymmetric Keck allylation reaction and Grubbs' ring closing metathesis reaction constitute the key steps is presented in **Scheme 35**. A similar synthetic route as of (+)-tanikolide (**38e**) was followed for the synthesis of (-)-

malyngolide. Thus, our synthesis commenced with the I_2- catalysed oxo-acyloxylation reaction of undec-1-ene (**106**) to afford α-benzoyloxy ketone compound **107** in 83% yield and



Scheme 35: (i) I_2 (10 mol %), TBHP (5.5 M in decane, 1 equiv), $PhCO_2H$ (1 equiv), Et_3N (1.2 equiv), DMSO, 0 to 25 °C, 12 h, 83%; (ii) $Ti(O^iPr)_4$ (10 mol %), (*S*)-BINOL (10 mol %), allylSn^nBu_3 (1.1 equiv), CH_2Cl_2, -78° C to -20° C, 72 h, 84%, 80% ee; (iii) Methacroyl chloride (1.2 equiv), Et_3N, CH_2Cl_2, 25° C, 3 h, 88%; (iv) Grubbs' II (1 mol %), CH_2Cl_2, 40 °C, 4h; (v) 10% Pd/C, H_2 (1 atm), MeOH, 25° C, 4 h, 71% (2 steps), dr = 3:1.

excellent regioselectivity. Its formation of product was confirmed by the appearance of typical aromatic signals of benzoate group at δ 7.46-7.50 (m, 2H), δ 7.56-7.60 (m, 1H) and δ 8.08-8.12 (m, 2H) in the ^1H NMR spectrum. The product formation was further substantiated by the appearance of carbonyl carbon signals for ketone and ester at δ 204.2 and 165.8 respectively in its ^{13}C NMR spectrum (**Fig. 12**). Its IR spectrum showed strong absorption bands at 1725 and 1747 cm^{-1} characteristics of C=O stretching frequency for keto & ester functionalities respectively. The formed ketone was subjected to asymmetric

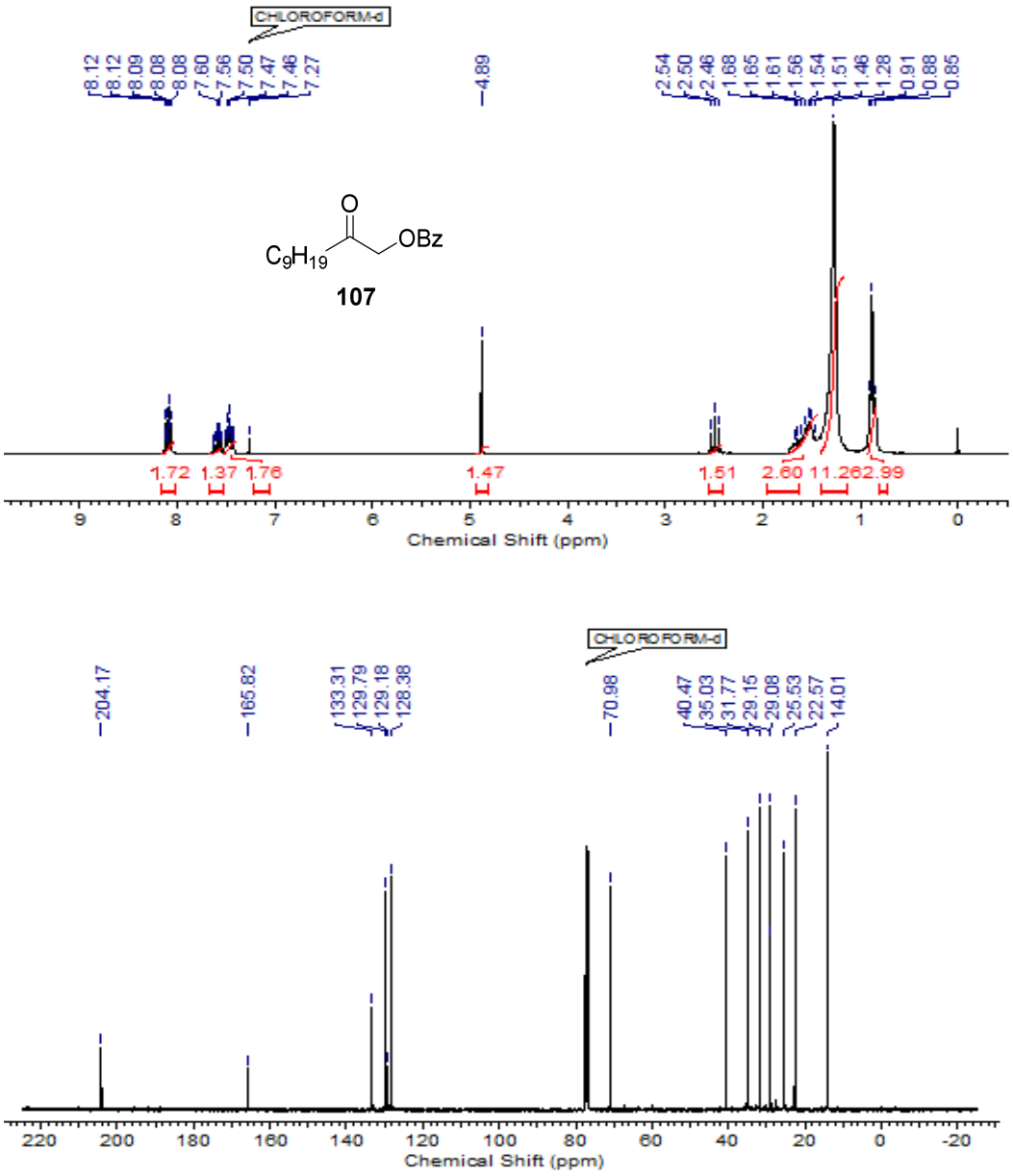


Fig. 12: ^{1}H and ^{13}C NMR spectra of **107**

Keck allylation reaction at lowered temperature thus affording chiral alcohol **108** in 84% yield with 80% ee (determined by chiral HPLC analysis). The formed product showed characteristic olefinic protons at δ 5.10-5.19 (m, 2H) and δ 5.81-5.90 (m, 1H) in its proton NMR spectrum, while the methylene protons attached to benzoate group appeared as singlet at δ 4.13 (s, 2H). Its ^{13}C NMR spectrum showed quaternary

carbon signal at δ 73.2 while ester carbonyl carbon of the benzoate group appeared at δ 166.3 (**Fig. 13**). The alcohol **108** was then esterified with methacroyl chloride using Et_3N in CH_2Cl_2 to afford diene **109** which was easily identifiable from its proton

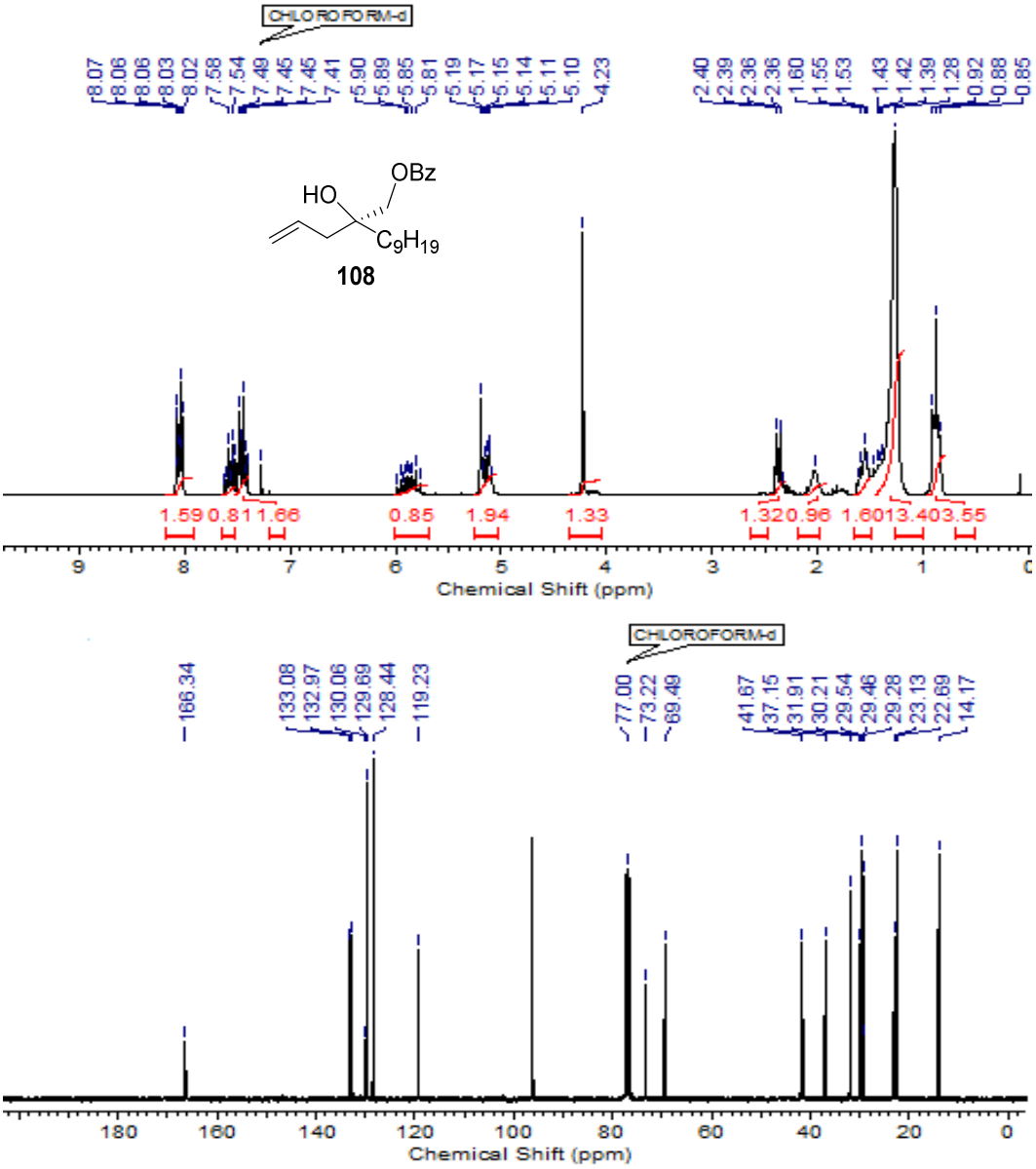


Fig. 13: ^{1}H and ^{13}C NMR spectra of **108**

NMR spectrum due to appearance of typical olefinic signals δ 4.73-5.28 integrating for five protons while its IR spectrum featured a strong absorption band at 1751 cm^{-1}

corresponding to C=O stretching frequency for ester functionality (**Fig. 14**). The diene **109** was then subjected to Grubbs' ring closing metathesis reaction in CH_2Cl_2 followed by catalytic hydrogenation to form **110** in high yield *albeit* in moderate

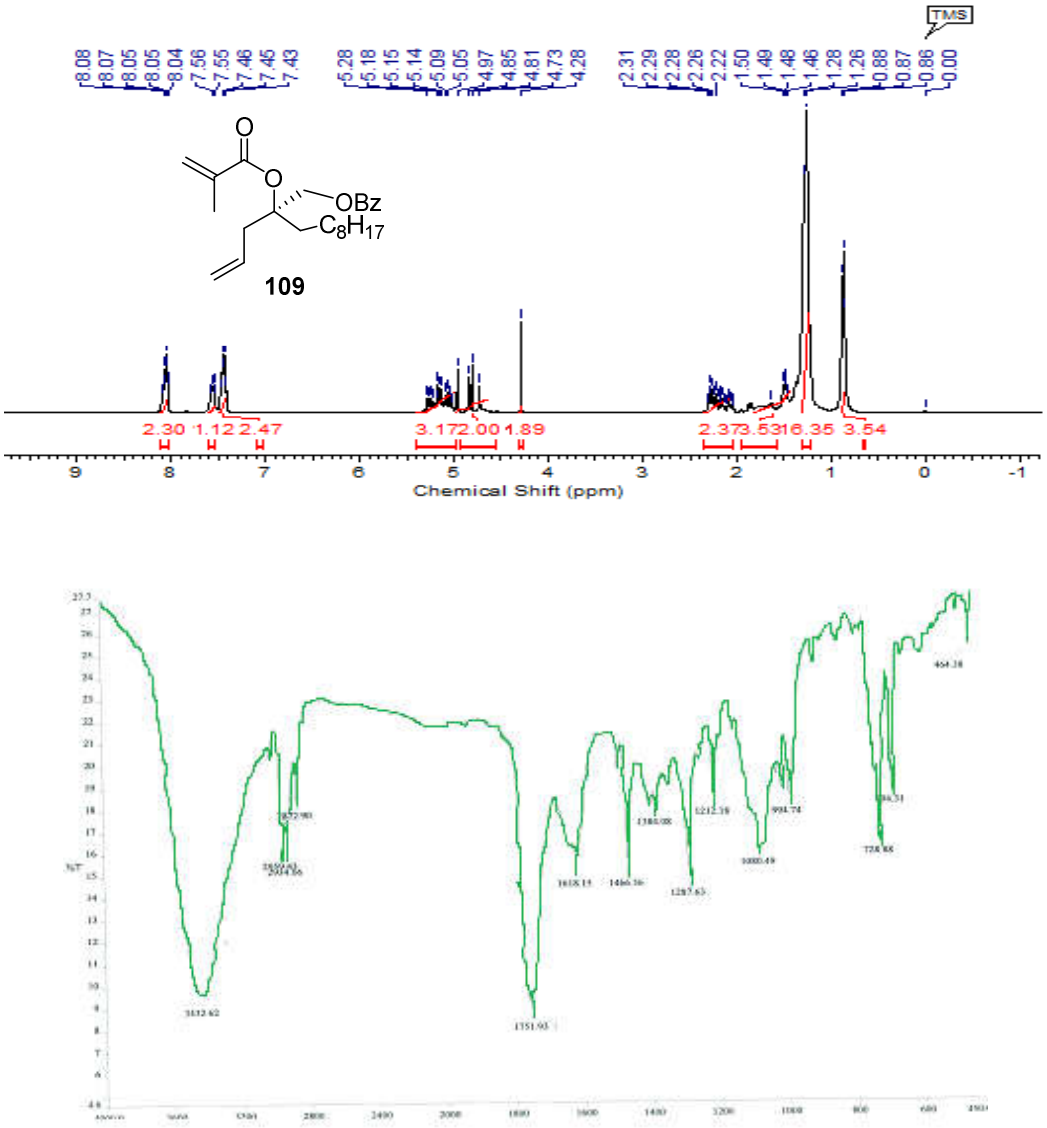


Fig.14: ^{1}H NMR and IR spectra of **109**

diastereoselectivity (3:1) in favour of desired product. The product **110** was confirmed by the disappearance of olefinic proton signals in its ^{1}H NMR spectrum and presence of typical signal at δ 172.9 corresponding to the carbonyl carbon of δ-lactone in its ^{13}C NMR spectrum (**Fig. 15**).

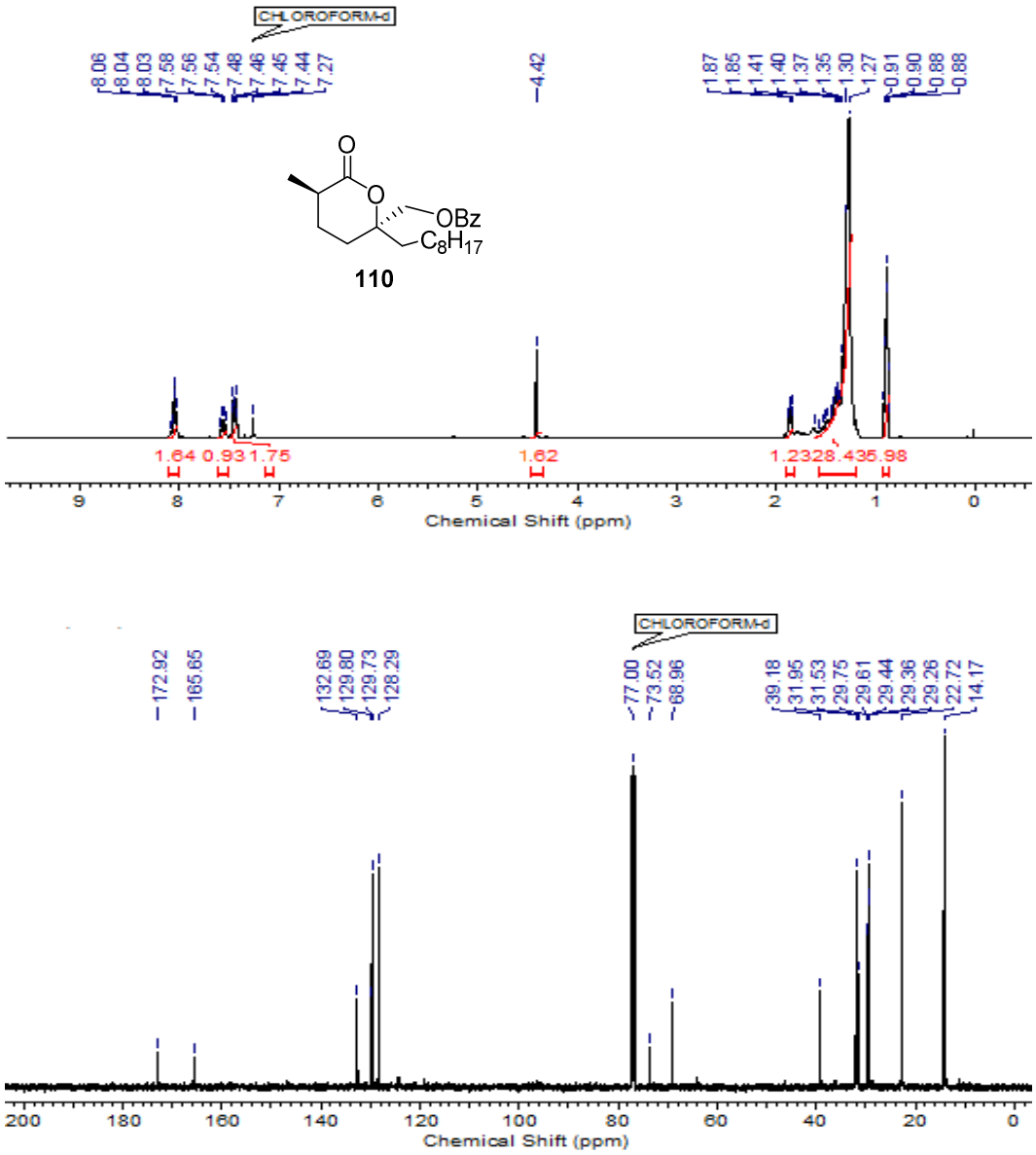


Fig. 15: ^{1}H and ^{13}C NMR spectra of **110**

The final step involves basic hydrolysis of its benzoate group using reported procedure, that would afford (-)-malyngolide (**38f**). This completes the formal synthesis of (-)-malyngolide.

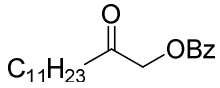
2.2.6 Conclusion

To summarize, our I_2-catalyzed oxo-acyloxylation strategy has successfully been employed to the short and enantioselective syntheses of (+)-tanikolide (**38e**) and (-)-malyngolide (**38f**). The synthesis involves asymmetric Keck's allylation and Grubbs' ring closing metathesis (RCM) reaction as the other key steps. The overall yields of **38e** and **110** were found to be 52% and 43.5% respectively. The present protocol comprises of lesser number of steps, higher overall yields and avoids the use of harsh acidic conditions contrary to the reported methods. Again, we believe that this will be a flexible synthetic route in arriving at δ-lactones with a chiral quaternary carbon center bearing a carbinol moiety.

2.2.7 Experimental section

2.2.7.1 Synthesis of (+)-Tanikolide (38e)

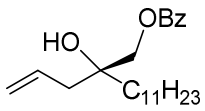
2-Oxotridecyl benzoate (102)



To a stirred solution of tridec-1-1ene (3.0 g, 16.48 mmol) in dry DMSO (50 mL) at 0 ºC was added I_2 (0.421 g, 1.65 mmol), Et_3N (2.8 mL, 19.78 mmol), 5.5 M solution of TBHP in decane (3.6 mL, 16.48 mmol) and benzoic acid (2.2 g, 18.13 mmol) and the resulting reaction mixture was stirred at 25 °C under air. After completion of the reaction (as monitored by TLC after 12 h), it was quenched with H_2O (50 mL) at 0 °C. It was then extracted with EtOAc (3 x 75 mL) followed by washing with brine (3 x 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Concentration of solvent under reduced pressure gave the crude product, which was then purified by column chromatography over silica gel using Pet. Ether:EtOAc (9:1) as eluent to obtain α-acyloxy carbonyl compound **102** in 86% yield.

Yield: 86% (4.5 g, 14.2 mmol), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 742, 1065, 1314, 1469, 1506, 1724, 1740, 2812, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.3, 3H), 1.17-1.35 (m, 17H), 1.51-1.68 (m, 2H), 2.31 (s, 1H), 2.49 (t, *J* = 7.3 Hz, 1H), 4.86 (s, 1H), 7.41-7.49 (m, 2H), 8.07-8.08 (m, 1H), 8.11-8.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0, 22.6, 25.5, 29.1, 31.8, 35.0, 38.8, 40.5, 71.0, 128.4, 129.2, 129.8, 133.3, 165.8, 198.5; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{20}H_{30}O_3$+Na: 341.2093; found: 341.2086.

2-Allyl-2-hydroxytridecyl benzoate (103)

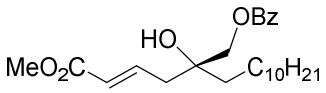


A solution of (*R*)-BINOL (0.233 g, 0.817 mmol) and $Ti(O^iPr)_4$ (0.230 g, 0.817 mmol) in CH_2Cl_2 (60 mL) in the presence of 4 Å molecular sieves (MS) (4 g) was stirred under reflux conditions. After 1 h, the reaction mixture was cooled to room temperature and to it was added ketone **102** (2.6 g, 8.176 mmol) in dry CH_2Cl_2 and the resulting mixture was stirred for 10 min. The reaction mixture was then cooled to -78 °C and allyl tributylstannane (3.82 g, 10.22 mmol) was added and stirring was continued at -20 °C for 36 h. After completion of the reaction as monitored by TLC, it was quenched with saturated $NaHCO_3$ solution (10 mL) and the reaction mixture was stirred for an additional 30 min and extracted into CH_2Cl_2 (40 mL). The organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was concentrated under reduced pressure to give crude residue which was purified over silica gel column chromatography using Pet. ether:EtOAc (8:2) to afford homoallylic alcohol **103** in 81% yield as a clear liquid with 81% ee.

Yield: 81% (2.61 g), colorless oily liquid; $\mathbf{[\alpha]^D_{25}}$ = +2.61 (*c* = 1, $CHCl_3$); **HPLC analysis**: 81% ee, [Chiracel OD-H column (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 22.05 (minor) and 26.2 (major)]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 745, 1181, 1240, 1317, 1459, 1570, 1650, 1747, 2856, 2928, 3315; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.25-1.59 (m, 19H), 1.67-1.86 (m, 1H), 2.37-2.38 (m, 2H), 4.23 (s, 1H), 5.11-5.18 (m, 2H), 5.84-5.89 (m, 1H), 7.43-7.44 (m, 2H), 7.54-7.58 (m, 1H), 8.04-8.06 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 22.7, 23.1, 25.5, 29.4, 29.6, 29.7, 30.2, 31.9, 37.1, 37.3, 41.6, 69.5,

72.1, 118.3, 119.1, 128.4, 129.7, 133.0, 134.4, 166.3; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{23}H_{36}O_3$+Na: 383.2557; found: 383.2552.

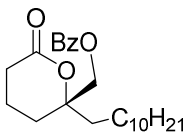
(*E*)-2-Hydroxy-2-(4-methoxy-4-oxobut-2-en-1-yl)tridecyl benzoate (104)



To a solution of homoallylic alcohol **103** (1.5 g, 4.17 mmol) in degassed CH_2Cl_2 (20.0 mL) were added methyl acrylate (3.58 g, 41.67 mmol) and a solution of Grubbs-IInd generation catalyst (160 mg, 0.208 mmol) in degassed CH_2Cl_2 (2.0 mL) dropwise and the resultant solution was stirred at room temperature for 3 h. The reaction mixture was then stirred at room temperature under air to destroy the ruthenium catalyst. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using Pet. ether:EtOAc (80:20) to give α,β-unsaturated ester **104** in pure form.

Yield: 88% (1.54 g), colorless oil; $[\alpha]^{D}_{25}$ = +3.1 (*c* = 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 755, 1162, 1255, 1324, 1450, 1523, 1556, 1650, 1739, 1747, 2856, 2928, 3325; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86-0.91 (m, 3H), 1.26 (s, 16H), 1.56-1.64 (m, 2H), 2.21 (s, 1H), 2.52 (dd, *J* = 7.7, 1.0 Hz, 2H), 3.72 (s, 3H), 4.19-4.33 (m, 2H), 5.88-5.96 (m, 1H), 6.96-7.12 (m, 1H), 7.42-7.50 (m, 2H), 7.55-7.64 (m, 1H), 8.01-8.06 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 22.7, 23.2, 29.4, 29.5, 29.6, 29.6, 29.7, 30.1, 32.0, 37.5, 40.3, 51.5, 69.7, 73.6, 124.4, 128.5, 129.8, 133.3, 143.6, 166.3, 166.4; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{25}H_{38}O_5$+Na: 441.2617; found: 441.2619.

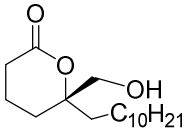
(*R*)-(6-Oxo-2-undecyltetrahydro-2H-pyran-2-yl)methyl benzoate (105)



To a solution of α,β-unsaturated ester **104** (1.0 g, 2.39 mmol**)** in methanol was added 10% Pd/C (20 mg) and the resultant suspension was stirred at room temperature under an atmosphere of H_2 (1 atm) overnight. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford crude product, which was purified by flash column chromatography pet. ether:EtOAc (80:20) to afford purified product **105** in 96% yield.

Yield: 96% (0.950 g); colorless oil; $\mathbf{[\alpha]^{D}_{25}}$ = +8.01 (*c* = 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 753, 1178, 1245, 1312, 1467, 1570, 1754, 2852, 2920; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.26 (br. s., 18H), 1.52-1.85 (m, 6H), 2.03 (d, *J* = 9.1 Hz, 1H), 2.36 (t, *J* = 7.0 Hz, 2H), 4.25 (s, 2H), 7.40-7.51 (m, 2H), 7.57 (d, *J* = 7.1 Hz, 1H), 8.05 (d, *J* = 7.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 18.8, 22.8, 23.4, 29.4, 29.6, 29.6, 29.7, 30.3, 32.0, 34.3, 36.9, 69.8 73.5, 128.5, 129.7, 129.7, 133.1, 166.4, 173.6; **HRMS** (ESI): [M+Na]+ calcd for $C_{24}H_{36}O_4$+Na: 411.2506; found: 411.2513.

(+)-Tanikolide (38e)

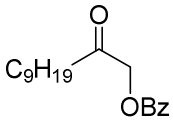


To a stirred solution of lactone derivative **105** (0.5 g, 1.28 mmol) was added K_2CO_3 (0.215 g, 1.55 mmol). The reaction mixture was then allowed to stir at room temperature for 3 h. After completion (as monitored by TLC), the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel Pet. ether:EtOAc (60:40) gave (+)-tanikolide (0.310 g, 85%) as colorless oil. The spectroscopic data of (+)-tanikolide was in full agreement with the literature values.

Yield: 85%, (0.310 g), colorless oil; $[\alpha]^{D}_{25}$ = +1.91 (*c* = 0.72, $CHCl_3$) {lit.[44] $[\alpha]^{D}_{20}$ = +2.3 (*c* = 0.65, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 931, 1051, 1245, 1504, 1685, 1754, 3348; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.26 (br. s., 18H), 1.56- 1.62 (m, 2H), 1.72-1.79 (br. s., 2H), 2.00 (br. s., 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 3.67 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 18.8, 22.8, 23.4, 29.4, 29.6, 29.7, 29.7, 29.7, 30.3, 32.0, 34.3, 36.1, 36.9, 69.8, 73.5, 173.6; **HRMS** (ESI): [M+Na]+ calcd for $C_{17}H_{32}O_3$+Na: 307.2249; found: 307.2213.

2.2.7.2 Synthesis of (-)-Malyngolide (38f)

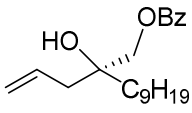
2-Oxoundecyl benzoate (**107**)



The same procedure is followed as described for compound **102**.

Yield: 83% (4.7 g, 16.2 mmol), colorless oily liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 745, 1179, 1250, 1314, 1469, 1571, 1650, 1725, 1747, 2856, 2928; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.28 (br. s., 12H), 1.45-1.76 (m, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 4.89 (s, 2H), 7.29-7.54 (m, 2H), 7.55-7.69 (m, 1H), 8.02-8.15 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0, 22.6, 25.5, 29.1, 29.2, 31.8, 35.0, 38.8, 40.5, 71.0, 128.4, 129.2, 129.8, 133.3, 165.8, 204.2; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{18}H_{26}O_3$+Na: 313.1780; found: 313.1782.

(*S*)-2-Allyl-2-hydroxyundecyl benzoate (108)

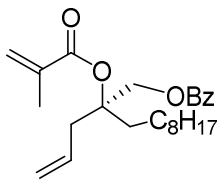


A solution of (*S*)-BINOL (0.255 g, 0.893 mmol) and $Ti(O^iPr)_4$ (0.255 g, 0.893 mmol) in CH_2Cl_2 (60 mL) in the presence of 4 Å molecular sieves (MS) (4 g) was stirred

under reflux conditions. After 1 h, the reaction mixture was cooled to room temperature and to it was added ketone **107** (2.6 g, 8.93 mmol) in dry CH_2Cl_2 and the resulting mixture was stirred for 10 min. The reaction mixture was then cooled to -78 °C and allyl tributylstannane (3.56 g, 10.72 mmol) was added to the reaction mixture and the stirring was continued at -20 °C for 36 h. After completion of the reaction as monitored by TLC, it was quenched with saturated $NaHCO_3$ solution (10 mL) and the reaction mixture was stirred for an additional 30 min and extracted into CH_2Cl_2 (40 mL). The organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give crude residue, which was purified over silica gel column chromatography using Pet. ether:EtOAc (80:20) to afford homoallylic alcohol **108** in 84% yield.

Yield: 84% (2.5 g), colorless liquid; $[\alpha]^{D}_{25}$ = -2.01 (*c* = 1, $CHCl_3$); **HPLC analysis**: 80% ee, [Chiracel OD-H column (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 21.05 (major) and 24.2 (minor)]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 748, 1183, 1247, 1315, 1460, 1573, 1648, 1749, 2854, 2921, 3317; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.6 Hz, 3H), 1.28-1.43 (m, 12H), 1.53-1.60 (m, 2H), 2.36-2.40 (m, 2H), 4.23 (s, 2H), 5.10-5.19 (m, 2H), 5.81-5.90 (m, 1H), 7.41-7.49 (m, 2H), 7.54-7.58 (m, 1H), 8.02-8.07 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 22.7, 23.1, 29.4, 29.5, 29.7, 30.2, 31.9, 37.2, 41.6, 69.5, 73.2, 119.2, 128.4, 129.7, 130.0, 132.9, 133.1, 166.3; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{21}H_{32}O_3$+Na: 355.2249; found: 355.2248.

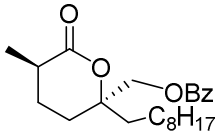
(*S*)-2-Allyl-2-(methacryloyloxy)undecyl benzoate (109)



To a stirred solution of alcohol derivative **108** (1.5 g**,** 4.52 mmol) in dry CH_2Cl_2 was added Et_3N (0.750 mL, 5.42 mmol) at 0 °C, followed by slow addition of methacroyl chloride (0.566 g, 5.42 mmol). The reaction mixture was allowed to stir at room temperature under inert atmosphere till completion of the reaction (monitored by TLC) after which reaction mixture was quenched with ice and work-up was carried out with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product. It was then purified by flash column chromatography using Pet. ether:EtOAc (80:20) as eluent to afford unsaturated ester derivative **109** in 88% yield.

Yield: 88% (1.45 g), colorless oil; $[\alpha]^{D}_{25}$ = -7.01 (*c* = 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 634, 726, 994, 1200, 1212, 1292, 1388, 1466, 1635, 1751, 2893, 2985; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.87 (t, *J* = 4.7 Hz, 3H), 1.23-1.31 (m, 16H), 1.42-1.57 (m, 3H), 2.13-2.31 (m, 2H), 4.28 (s, 2H), 4.73-4.97 (m, 2H), 5.03-5.28 (m, 3H), 7.41-7.48 (m, 2H), 7.53-7.59 (m, 1H), 8.03-8.11 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.1, 17.9, 22.7, 25.2, 29.3, 29.6, 29.7, 29.9, 31.9, 33.7, 37.4, 69.2, 75.0, 118.4, 125.2, 128.6, 129.9, 130.1, 133.0, 134.0, 136.0, 165.4, 167.2; **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{25}H_{36}O_4$+Na: 423.2511; found: 423.2519.

((2*S*,5*R*)-5-Methyl-2-nonyl-6-oxotetrahydro-2*H*-pyran-2-yl)methylbenzoate (110)



To a stirred solution of unsaturated ester derivative **109** (1.0 g, 2.5 mmol) in degassed CH_2Cl_2 (20.0 mL) was added a solution of Grubbs-IInd generation catalyst (0.021 g, 0.025 mmol) was added. The reaction mixture was allowed to stir at 25 ^{0}C until completion of the reaction (monitored by TLC), the organic layer was concentrated

and to the formed crude product was added MeOH (25 mL) and 10% Pd/C (cat.) and the resulting mixture was allowed to stir at 25 °C under H_2 atmosphere (balloon pressure). After completion of the reaction (as monitored by TLC), the reaction mixture was filtered over celite bed and the filtrate was purified by flash column chromatography using Pet. ether:EtOAc (70:30) as eluent to afford **110** in 71% yield.

Yield: 71% (0.660 g), colorless oil; $[\alpha]^{D}_{25}$ = -12.1 (*c* = 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 759, 1173, 1240, 1313, 1466, 1578, 1756, 2854, 2927; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.86-0.93 (m, 6H), 1.27-1.41 (m, 20H), 1.86 (d, *J* = 4.2 Hz, 1H), 4.42 (s, 2H), 7.44-7.48 (m, 2H), 7.54-7.58 (m, 1H), 8.04-8.06 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 14.2, 22.7, 29.2, 29.3, 29.4, 29.6, 29.7, 29.8, 31.5, 39.2, 68.9, 73.5, 128.3, 129.7, 129.8, 132.7, 165.6, 172.9; **HRMS** (ESI): [M+Na]+ calcd for $C_{23}H_{34}O_4$+Na: 397.2355; found: 397.2357.

2.2.8 References

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CHAPTER III

I_2 Catalyzed Azidohydroxylation of Alkenes and Syntheses of Chloramphenicol & Cytoxazone

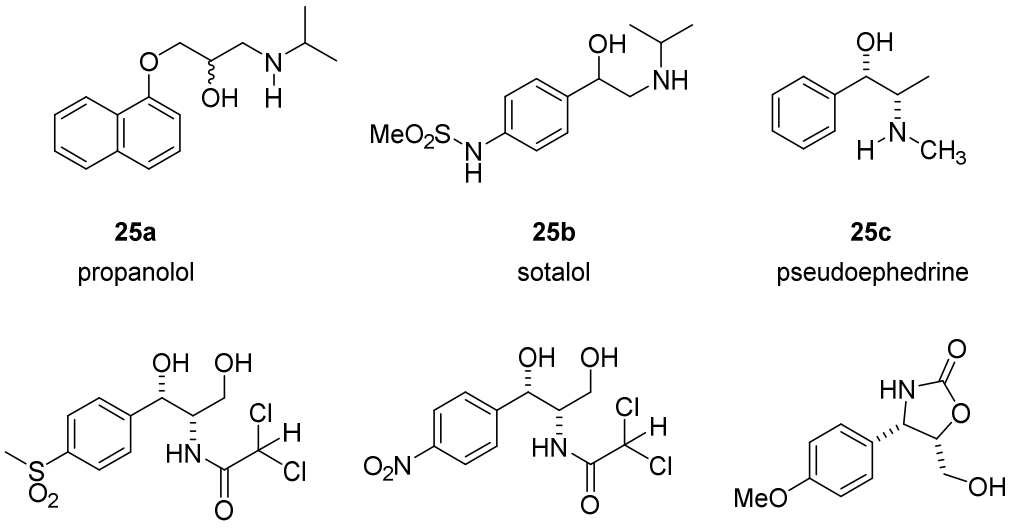
1. Oxidant Controlled Regio- and Stereodivergent Azidohydroxylation of Alkenes *via* I_2 Catalysis; **Pragati Kishore Prasad**, Rambabu N. Reddi, Arumugam Sudalai; *Chem. Commun.* **2015**, *51*, 10276-79 (inside front cover).

Section I

Oxidant Controlled Regio- and Stereodivergent Azidohydroxylation of Alkenes *via* I_2 Catalysis

3.1.1 Introduction

Vicinal difunctionalization of alkenes is an attractive strategy for the assembly of hetero-functionalized organic compounds. In this context, dioxygenation,[1] dinitrogenation[2] and oxy-nitrogenation[3] across the alkenes are well studied. However, the direct vicinal azidohydroxylation across unsymmetrical alkenes in requisite regio- and diastereoselective fashion is rare.[4] The structural units comprising of vicinal azidohydroxy functional groups are important intermediates in the syntheses of drugs, natural products and synthetic materials[5] (**Fig. 1**) and find tremendous utility in the synthesis of biologically active amino sugars,[6] nucleosides,[7] lactams,[8] triazoles,[9] oxazolines[10] and in the chemistry of peptidomimetics[11] and pseudopeptides[12].



25a propanolol

25b sotalol

25c pseudoephedrine

25d thiamphenicol

25e chloramphenicol

26 cytoxazone

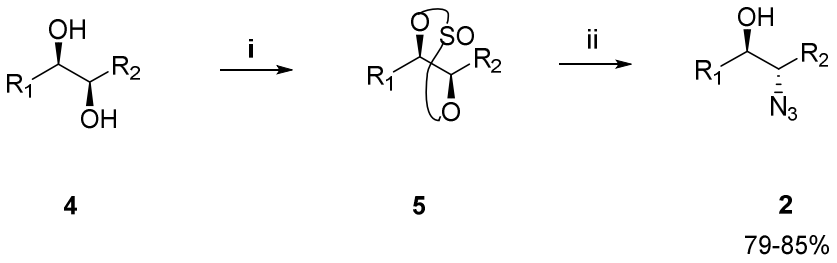
Fig. 1: Indispensable drugs containing vicinal amino alcohol moiety

3.1.2 Review of the Literature

Literature search revealed that synthesis of vicinal azidoalcohol is of prime interest to synthetic organic chemists. Many of the reported methods mainly rely on azidolysis of epoxides using varied conditions and different azide sources. These methods however end up affording *anti*-azido alcohols as the major product with quaky regioselectivity. The unconventional methods available in literature for the synthesis of vicinal azido alcohols are summarized as follows.

Lohray's approach (1991)[13]

Lohray *et al.* have reported reaction of vicinal diols with thionyl chloride to give 1,2-cyclic sulphites **5** in quantitative yield, which undergo facile ring opening by lithium azide in dimethylformamide to yield azido alcohols (**Scheme 1**).



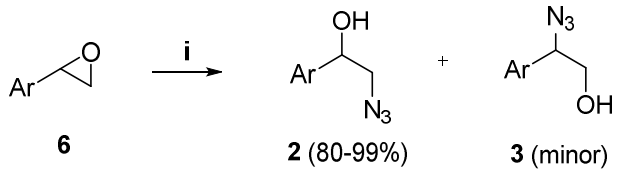
4 **5** **2**

79-85%

Scheme 1: (i) $SOCl_2$, CCl_4, 80 °C, quant.; (ii) LiN_3, DMF, 120 °C, 79-85%.

Guy's approach (1992)[14]

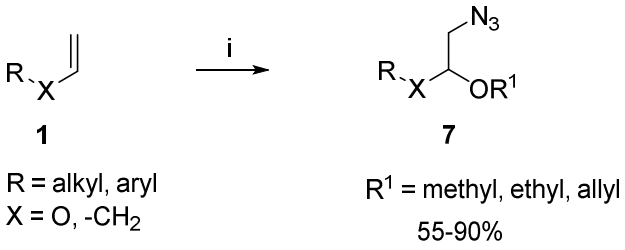
Guy *et al.* have reported the azidolysis of epoxide using a combination of LiN_3/HMPA which allowed for the regioselective ring opening of epoxides **6** from the non-benzylic position leading to the formation of 1-aryl-2-azidoethanol **2** as the major product in the reaction (**Scheme 2**).



Scheme 2: (i) LiN_3/ HMPA, 60 °C, 15 min, 80-99% of **2**.

Chavan's approach (1999)[4a]

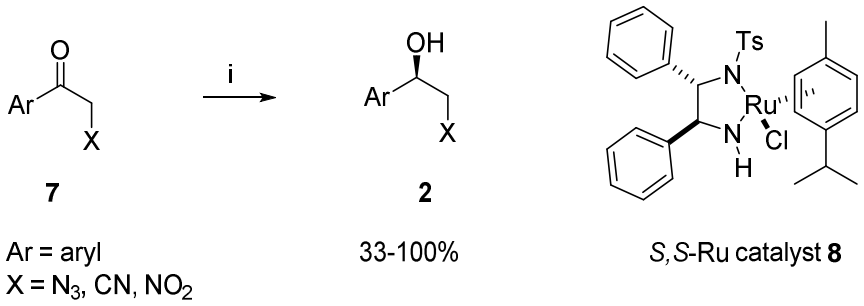
In Chavan's approach, azido alkoxylation of alkenes **1** using ceric ammonium nitrate (CAN) and sodium azide in presence of various alcohols has been described (**Scheme 3**). However, this reaction fails with electron-deficient olefins and requires the use of excessive amount of the alcohol partner.



Scheme 3: (i) NaN_3 (1 equiv), R^1OH (5 equiv), CAN (2 equiv), CH_3CN, 0-25 °C, 12 h, 55-90%.

Ikariya's approach (2002)[15]

In 2002, Ikariya *et al.* have reported a practical synthesis of optically active vicinal azido alcohols *via* asymmetric transfer hydrogenation of α-azido aromatic ketones **7** using chiral Ru- catalyst **8**. The method was also extended to other α-functionalised ketones like 2-cyano- and 2-nitroacetophenones; those were further elaborated to produce amino alcohols (**Scheme 4**). However, this method is limited to aromatic ketones only.



7 **2**

Ar = aryl
X = N_3, CN, NO_2

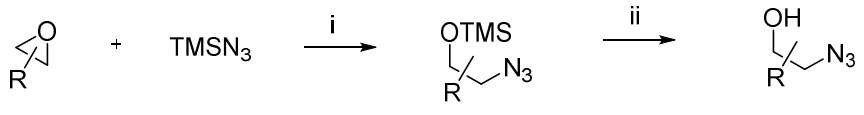
33-100%

S,S-Ru catalyst **8**

Scheme 4: (i) *S,S*-Ru cat. **8** (1-0.1 mol %), HCO_2H/Et_3N, 30-40 °C, 24 h, 33- 100%, 91-99% ee.

Kazemi's approach (2006)[16]

Kazemi *et al*. have reported regioselective conversion of epoxides **6** to vicinal azidoalcohols **3** using NaN_3 in wet *t*-butanol, in the presence of catalytic amount of lithium tetrafluoroborate ($LiBF_4$) in excellent yields under comparatively milder reaction conditions (**Scheme 5**). The $LiBF_4$ catalyst probably acts as a slow BF_3 releasing source.



6 **9** **3**

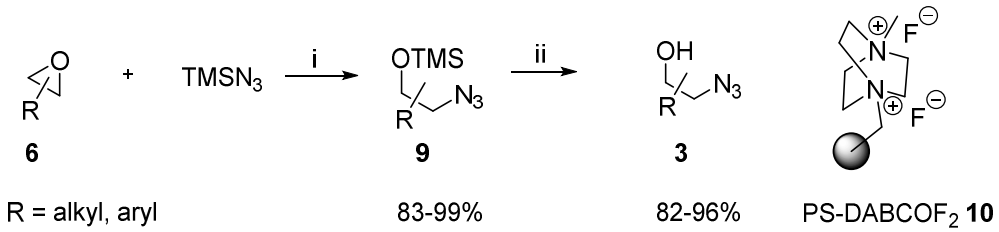
R = alkyl, aryl

89-96%

Scheme 5: (i) $LiBF_4$ (20 mol %), NaN_3 (2 equiv), *t*-BuOH: H_2O (30:1), 82 °C, 10- 255 min, 89-96%; (ii) TBAF (1 equiv), THF, 25 °C, 4 h.

Vaccaro's approach (2013)[17]

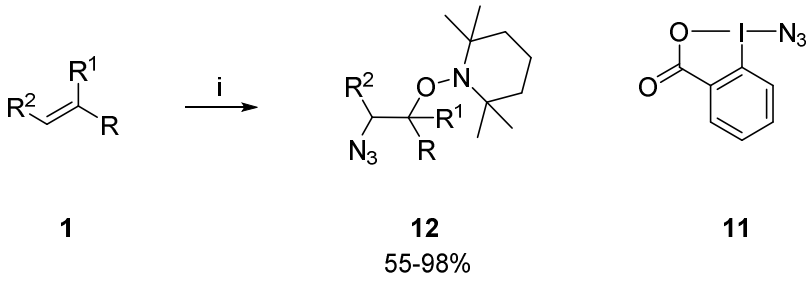
Vaccaro *et al.* have reported polystyryl-supported fluoride (PS-DABCOF_2) **10** catalyzed reaction of epoxides **6** with $TMSN_3$ under solvent-free conditions for the preparation of the corresponding O-TMS protected 1,2-azido alcohols **9** (83-89%) which on treatment with Dowex-H, gave the related 1,2-azido alcohols **3** in excellent yields (82-96%). The use of a flow procedure allowed the authors to significantly minimize waste in the preparation of representative 1,2-azido alcohols (**Scheme 6**).



Scheme 6: (i) $TMSN_3$ (1.1 equiv), PS-DABCOF$_2$ **10** (10 mol %), 60-80 °C, 18- 120 h, 83- 99% (combined yield of both regioisomers); (ii) Dowex-H (20 mol %), EtOAc, 30 °C, 5 h, 82-96 %.

Studer's approach (2013)[18]

Studer *et al.* have recently described a method of radical azido-oxygenation of various alkenes **1**. Freshly prepared N_3-iodine(III) reagent **11** was used as N_3-radical precursor. Radical generation was achieved with TEMPONa acting as a mild organic reducing reagent. The C-radical generated after N_3-radical addition was trapped by *in situ* generated TEMPO (**Scheme 7**). Additional steps are however required to obtain vicinal azido alcohol.



1 **12** **11**

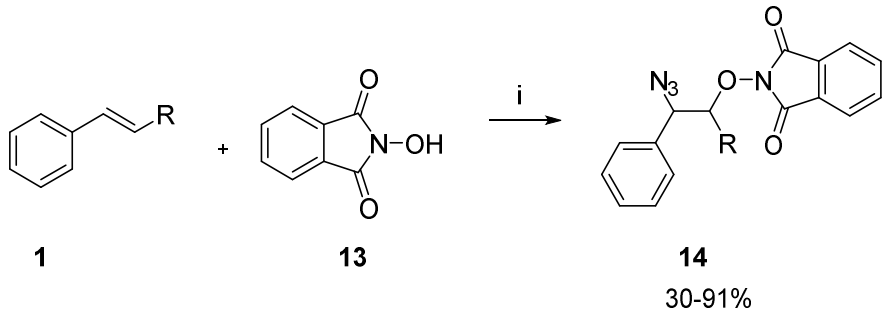
55-98%

Scheme 7: (i) **11** (3 equiv), TEMPONa (3 equiv), CH_2Cl_2, 25 °C, 6 h, 55-98%.

Xia's approach (2015)[4b]

Xia *et al.* have very recently developed oxy-azidation of alkenes **1** under metal-free conditions. *N*-Hydroxyphthalimide **13** and $TMSN_3$ have been used as oxygen-radical precursor and azide sources respectively. Variously substituted aromatic alkenes were compatible under the reaction conditions (**Scheme 8**). The transformation could not be applied to aliphatic alkenes; again, additional steps are required to obtain

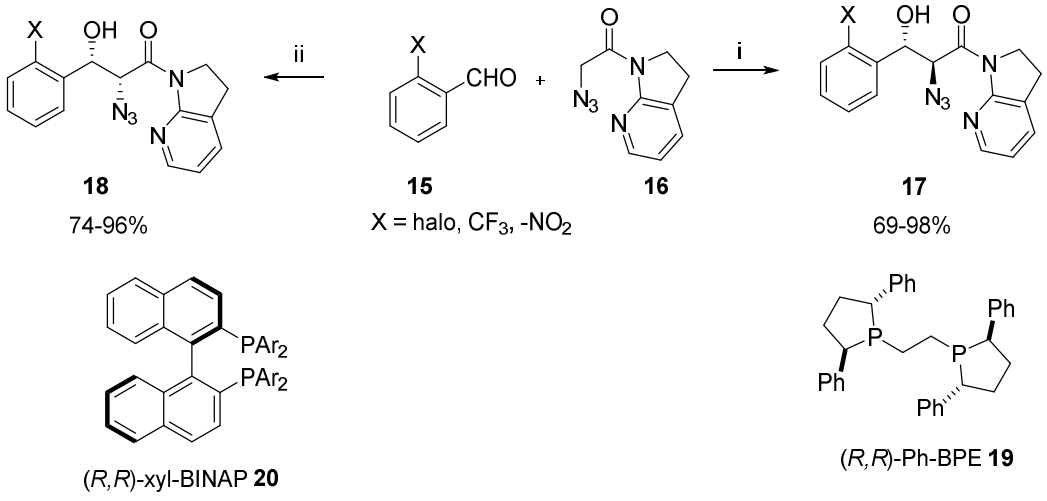
azidohydroxy products, thus reducing the overall yield.



Scheme 8: (i) $TMSN_3$ (3 equiv), $PhI(OAc)_2$ (2 equiv), 1,2- dichloroethane, 25 °C, 12 h, 30-91%.

Shibasaki's approach (2015)[19]

In Shibasaki's approach, aldol reaction of aromatic aldehydes **15** (bearing an *ortho* substituent) and α-azido-7-azaindolinylamide **16** as an aldol donor (promoted by mesityl copper catalyst/chiral bisphosphine ligands) exhibiting diastereodivergency depending on the nature of chiral ligands used has been explored. A vicinal azido alcohol unit in the products **17** or **18** was further elaborated to the corresponding aziridine derivatives (**Scheme 9**).



Scheme 9: (i) Mesityl copper/(*R,R*)-Ph-BPE (5-10 mol %) **19**, THF, -60 °C, 24 h, 69- 98% dr up to 85:15; (ii) mesityl copper/*R,R*-xyl-BINAP (5-10 mol %) **20**, THF, - 60 °C, 24 h, 74-96%, dr up to 98:2.

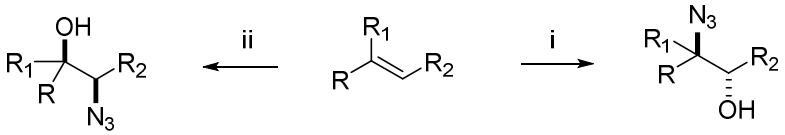
3.1.3 Present Work

3.1.3.1 Objective

Although there are many reports available for the synthesis of 1,2-azido alcohol, the direct vicinal azidohydroxylation across unsymmetrical alkenes in requisite regio- and diastereoselective fashion is rare. The literature reports, as discussed earlier, suffer from disadvantages such as use of pre-functionalized starting materials leading to reduced atom economy, harsh reaction conditions accompanied with low functional group tolerance and often poor regio- and diastereoselectivity. Thus, a mild synthetic procedure that employs readily available starting materials and overcomes the above difficulties is desirable for regio- and stereodivergent synthesis of 1,2-azidoalcohols.

3.1.3.2 Results and Discussion

This section describes, for the first time, I_2-catalyzed controlled synthesis of either regioisomers of 1,2-azidoalcohols with high diastereomeric ratios using DMF as *O*-nucleophile and NaN_3 as *N*-nucleophile (**Scheme 10**).[20]



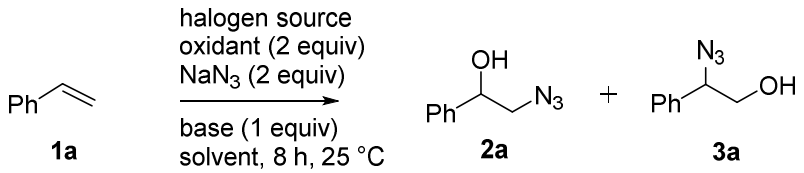
2a-n 74-90% **1a-n** **3a-n** 76-92%

Scheme 10 : (i) I_2 (10 mol %), 50% aq. H_2O_2 (2 equiv), Et_3N (1 equiv), NaN_3 (2 equiv) DMSO: DMF (v/v = 1:1), 0 °C to 25 °C, 8 h, 76-92%; (ii) I_2 (10 mol %), 5-6 M TBHP in decane (2 equiv), Et_3N (1 equiv), NaN_3 (2 equiv) DMSO:DMF (v/v = 1:1), 0 °C to 25 °C, 8 h, 74-90%.

Initially, when styrene (**1a**) (1 mmol) was treated with a mixture of I_2 (10 mol %) and TBHP (2 mmol) followed by addition of Et_3N (1 mmol) and sodium azide (2 mmol) at 0 °C in DMF, to our delight we obtained 2-azido-1-phenylethan-1-ol (**2a)** as exclusive regioisomer *albeit* in moderate yield 53% (Table 1). Encouraged by this

result, it was of interest to optimize the reaction conditions in order to obtain improved yield without affecting its regioselectivity.

Table 1: I_2-catalyzed regiodivergent azidohydroxylation of styrene: optimization studies[a]



no.	halogen 10 mol %	oxidant	base	Solvent v/v = 1:1	yield of **2a**[b]
1	I_2	TBHP	Et_3N	DMF	53
2	I_2	TBHP	Et_3N	THF:DMF	10
3	I_2	TBHP	Et_3N	CH_3CN:DMF	48
4	I_2	TBHP	Et_3N	CH_2Cl_2:DMF	18
5	I_2	TBHP	Et_3N	DMSO:DMF	90, 38[c]
6	I_2	TBHP	K_2CO_3	DMSO:DMF	18
7	I_2	TBHP	K^{t}OBu	DMSO:DMF	44
8	I_2	TBHP	NaH	DMSO:DMF	32
9	I_2	TBHP	DBU	DMSO:DMF	65
10	^{n}Bu$_4$NI	TBHP	Et_3N	DMSO:DMF	5
11	NaI	TBHP	Et_3N	DMSO:DMF	11
12	KI	TBHP	Et_3N	DMSO:DMF	14
13[d]	I_2	50% aq. H_2O_2	Et_3N	DMSO:DMF	82, 78[e]

[a]Reaction conditions: styrene (1 mmol), NaN_3 (2 mmol), halogen source (10 mol %), base (1 mmol), oxidant (2 mmol), 8 mL of solvent (1:1), 25 °C, 8 h; [b]Isolated yields after column chromatographic purification; [c]5 mol % of I_2 was used; [d]**3a** was formed as major product; [e]30% aq. H_2O_2 was used.

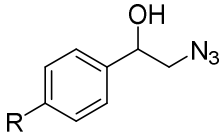
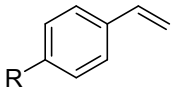
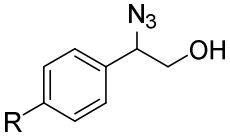
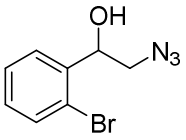
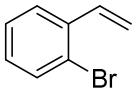
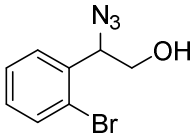
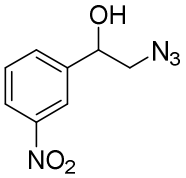
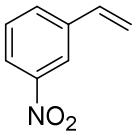
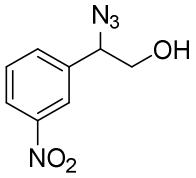
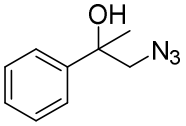
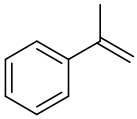
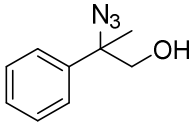
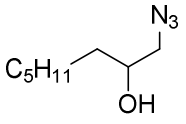
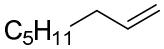
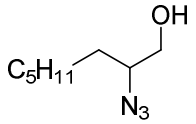
Thus, other solvents like THF, CH_3CN and CH_2Cl_2 were screened and found to be unsuitable for this reaction. Hence, we found that DMF was crucial in obtaining the desired azidoalcohol **2a**. Surprisingly, out of solvent combinations screened (entries 2-5), DMSO:DMF (v/v = 1:1) mixture resulted in excellent yield (90%) of the desired product **2a**. Decrease in I_2 catalyst loading to 5 mol % however had a deleterious effect on yield (38%) (entry 5). Further modification, either in iodine source or base

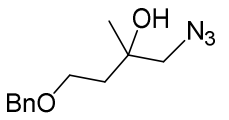
did not show any significant improvement in the product yield (entries 6-12). On the contrary, when 50% aq. H_2O_2 was used as oxidant instead of TBHP, a complete reversal in product regioselectivity was observed affording 2-azido-2-phenylethan-1-ol (**3a**) in 82% yield (entry 13). Even, 30% aq. H_2O_2 can be employed that afforded **3a** in good yield (78%). Furthermore, with 70% aq. TBHP, it gave a 3:1 mixture of **2a** and **3a** in 78% combined yield. Thus, the preliminary studies established an oxidant-directed switch to either regioisomers **2a** or **3a** in excellent yields directly from styrene in a single step.

In order to determine its scope, a variety of olefins were evaluated under the optimized reaction conditions and the results are summarized in **Table 2**. When styrenes, with $–CH_3$ (**1b**), -OH (**1c**), -Br (**1d**), $-NO_2$ (**1e**) groups on aromatic ring were treated with I_2 (10 mol %), anhyd. TBHP (2 equiv), NaN_3 (2 equiv) and Et_3N (1 equiv) in DMF:DMSO (1:1) at 25 °C, the corresponding 1,2-azido alcohols **2a**–**e** were obtained in 76-90% yields with excellent regioselectivity (>95%). In the case of disubstituted α-methyl styrene (**1f**), the azidohydroxylation product **2f** was obtained in high regioselectivity consistent with our initial findings. Also, 1-octene (**1g)** gave the desired products **2g** in high yield (79%) with high regioselectivity (>19:1). Interestingly, sterically congested and abundantly available isoprenol and prenol derivatives **1h** and **1i** too afforded **2h** and **2i** respectively in high yields with excellent regioselectivity. Cyclohexene (**1j)** and indene **(1k)** also participated in azidohydroxylation reaction affording the respective products **2j** and **2k** in predicted regioselectivity accompanied with high diastereoselectivity (**Table 2**) in favour of *syn* isomer. Interestingly, other open chain internal alkene **1l** gave the corresponding 1,2-azido alcohol **2l** in excellent diastereomeric ratio which is the key intermediate for the synthesis of the psychostimulant drug, norpseudoephedrine as well as the anti-

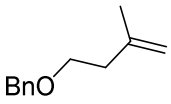
depressant drug, cathinone.[21] Other allylic alcohol **1m** and **1n** were also tested and the diastereoselectivity obtained in each case remained high. Specifically, substrate with free hydroxyl group was also found tolerant under this mild protocol. The products were characterized by their ^{1}H NMR, ^{13}C NMR, NOESY, IR and HRMS analysis.

Table 2: I_2-catalyzed regio- and stereodivergent azidohydroxylation of alkenes: substrate scope

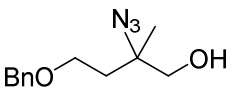
products[b] **(2a-n)**	substrates **(1a-n)**	products[a, c] **(3a-n)**
		
2a; 90%	**1a** R = H	**3a;** 82% (12:1)
2b; 88%	**1b** R = CH_3	**3b;** 89% (9:1)
2c; 76%	**1c** R = OH	**---**
		
2d; 82%	**1d**	**3d;** 86% (10:1)
		
2e; 77%	**1e**	**3e;** 76% (10:1)
		
2f; 78%	**1f**	**3f;** 83% (9:1)
		
2g; 79%	**1g**	**3g;** 83% (9:1)



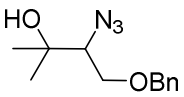
2h; 84%



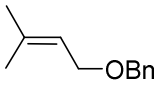
1h



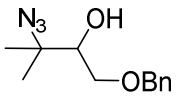
3h; 74% (8:1)



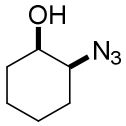
2i; 74%



1i

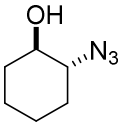


3i; 78% (5:1)

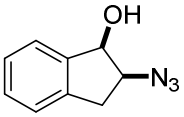


2j; 87% dr = 95:5

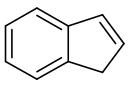
1j



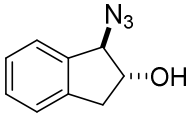
3j; 92% dr = 95:5[d]



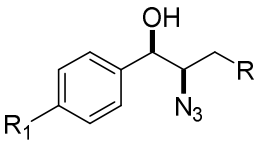
2k; 87% dr = 98:2



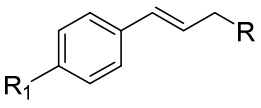
1k



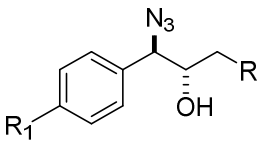
3k; 82% dr = 92:8



2l; 88% dr = 93:7



1l R = H, R_1= H



3l; 86% dr = 97:3

2m; 80% dr = 92:8 **1m** R = OH R_1 = H **3m;** 78% dr = 94:6

2n; 82% dr = 96:4 **1n** R = OH, R_1 = OMe **3n;** 80% dr = 98:2

[a]Alkene (1 equiv), I_2 (10 mol %), Et_3N (1 equiv), 50% aq. H_2O_2 (2 equiv), NaN_3 (2 equiv) DMSO:DMF (1:1), 0 °C to 25 °C, 8 h; [b]alkene (1 equiv), I_2 (10 mol %), Et_3N (1 equiv), 5-6 M TBHP in decane (2 equiv), NaN_3 (2 equiv) DMSO: DMF (1:1), 0 °C to 25 °C, 8 h; [c]ratio of **3**:**2**; [d]diastereomeric ratios were determined using ^{1}H NMR and HPLC analysis.

Example 1: ^{1}H NMR spectrum of *syn*-2-azido-2,3-dihydro-1H-inden-1-ol (**2k**) displayed the benzylic methine proton attached to hydroxyl group at δ 5.12 (dd, *J* = 8.3, 5.0 Hz, 1H) while signal for methine proton attached to azide group appeared at δ 4.31 (q, *J* = 5.0 Hz, 1H). Its ^{13}C NMR spectrum showed benzylic methine carbon (-**C**HOH) at δ 76.4 while methine carbon attached to azide functionality appeared at δ 65.7 (**Fig. 2**). The incorporation of the azide functionality was further confirmed by its

IR spectrum, which showed strong absorption band at 2097 cm^{-1}.

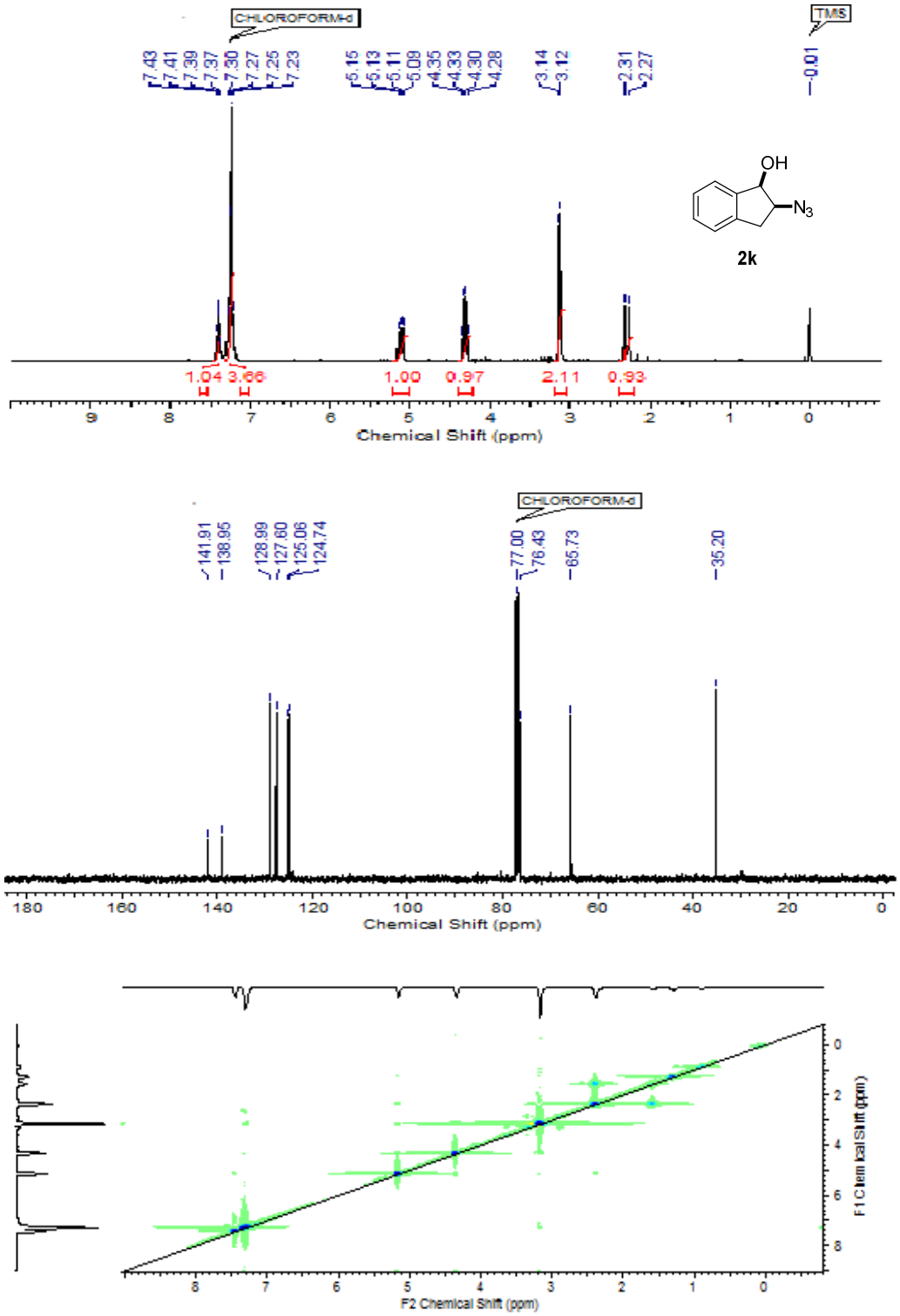


Fig. 2: ^{1}H, ^{13}C and NOESY spectra of **2k**

The *syn*-diastereoselective olefin difunctionalisation was confirmed by NOESY spectrum showing cross peaks between δ 4.3 and δ 5.1 thus proving spacial proximity between the methine protons in this region (**Fig. 2**) while the diastereomeric ratio of 98:2 (*syn:anti*) was calculated from HPLC analysis.

On the contrary, when 50% aqueous H_2O_2 was used as co-oxidant in the reaction, azidoalcohols with complementary regioselectivity were obtained. Here again, substituted styrenes **1a-f** afforded **3a-f** in high yields (76-89%) and regioselectivities (88-95%). Also, electronically unbiased aliphatic alkenes such as octene **1g**, terminal disubstituted alkene **1h** and trisubstituted alkene **1i** smoothly underwent this transformation affording the respective azido alcohols **3g, 3h** and **3i** in high yields (74-84%) *albeit* in moderate regioselectivity (5:1). Remarkably, when symmetrical and unsymmetrical disubstituted alkenes **1j** and **1k** were tested for their diastereoselectivity under the present conditions, 1,2-azidoalcohols **3j** and **3k** were obtained with major *anti* isomer. No discrepancy in *anti*-diastereoselectivity was observed in substrates **1l, 1m** and **1n** thus affording **3l, 3m** and **3n** in high yields (78-86%). However, electron deficient conjugated alkenes failed to undergo catalytic azidohydroxylation under either condition. All the products were thoroughly characterized by their spectroscopic data.

Example 2: *anti*-2-Azido-2,3-dihydro-1*H*-inden-1-ol (**3k**) product formed under aq. H_2O_2 condition showed typical benzylic methine proton (-C**H**N_3) signal at δ 4.68 (d, *J* = 4.9 Hz, 1H) in its ^{1}H NMR spectrum. On the other hand, methine proton (-C**H**OH) appeared at δ 4.48 (q, *J* = 5.7 Hz, 1H). The ^{13}C NMR spectrum for the compound showed typical sp^3-methine carbon signals at δ 78.6 and 71.8 corresponding to the benzylic and internal carbons respectively (**Fig. 3**). The incorporation of the azide functionality was further confirmed by its IR spectrum, which showed strong

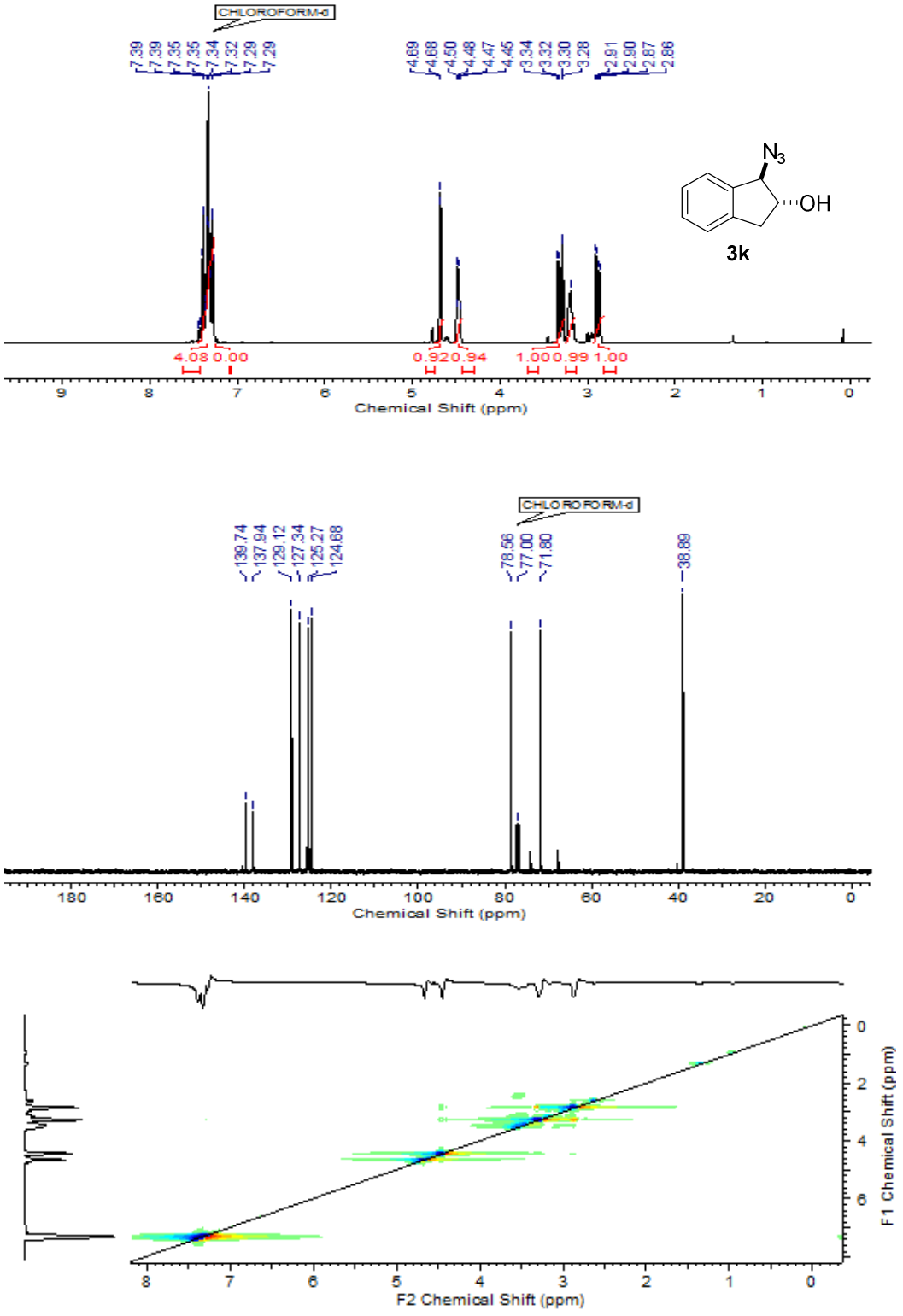


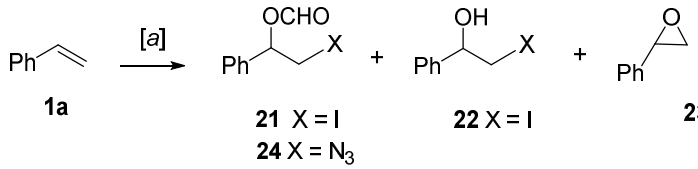
Fig. 3: ^{1}H, ^{13}C & NOESY spectra of **3k**

absorption band at 2098 cm^{-1}. The *anti*-diastereoselectivity in this case was authenticated by NOE spectrum wherein the absence of cross peaks between δ 4.48-4.68 rules out the possibility of spacial proximity between the methine protons in this region while the diastereomeric ratio of 92:8 (*anti:syn*) was calculated from HPLC analysis.

3.1.3.3 Mechanistic Discussion

The results of experiments for the mechanistic studies are summarized in **Table 3**:

Table 3: *Stoichiometric* control experiments for azidohydroxylation of styrene[a]



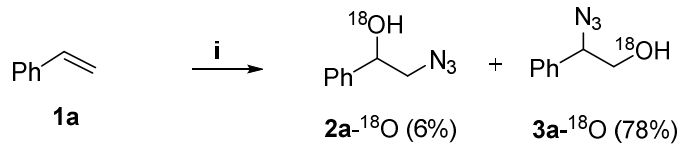
1a **21** X = I, **24** X = N_3 **22** X = I **23**

no.	solvent	base	oxidant	azide	products [b]
1	DMF	---	---	---	**21**(72%)
2	DMF	Et_3N	---	---	**21** (38%) + **22** (42%)
3	DMF:DMSO	Et_3N	anhyd TBHP	---	**21** (34%) + **22** (22%) + **23** (11%)
4	DMF:DMSO	Et_3N	aq. H_2O_2	---	**21** (32%) +**22** (26%) + **23** (18%)
5	DMF:DMSO	Et_3N	---	NaN_3	**24** (22%) + **22** (18%) + **2a** (48%)
6	DMF:DMSO:H_2O	Et_3N	---	NaN_3	**21** (35%) + **3a** (48%)

[a]Reaction condition: styrene (1 mmol), I_2 (1 mmol), oxidant (2 mmol), NaN_3 (2 mmol), base (2 mmol), solvent, 25 °C, 3 h; [b] Isolated yields after column chromatographic purification.

(i) *DMF as oxygen source and role of Et_3N in hydrolysis*: When styrene was treated with I_2 (1 equiv) in DMF, the corresponding iodoformate **21** was isolated in 72% yield. In the presence of Et_3N, iodoalcohol **22** was obtained along with **21** which suggest the role of Et_3N in hydrolysis of formate **21** (entries 1 and 2). (ii) *Co-oxidants*

do not compete with DMF as O-nucleophile: In the presence of co-oxidants (entries 3 and 4), iodoformate **21** was still formed. Further, when ^{18}O labelled DMF was used in the reaction, styrene gave 6% yield of **2a**-^{18}O and 78% of **3a**-^{18}O under aqueous conditions (**Scheme 11**). This clearly establishes that DMF serves as a source of oxygen and thus proves it to be more potent *O*-nucleophile as compared to TBHP, H_2O_2, H_2O or DMSO under present reaction condition. (iii) *Possibility of formation of hypervalent iodine is ruled out:* Further, on adding NaN_3 in the absence of co-oxidants (entry 5), azido alcohol product **2a** was indeed obtained in 48% yield. Therefore, reaction pathway does not involve the formation of hypervalent iodine species to yield **2** or **3** and TBHP/H_2O_2 is solely used for regeneration of I_2. (iv)



Scheme 11: (i) I_2 (10 mol %), H_2O_2 (2 equiv), Et_3N (1 equiv), NaN_3 (2 equiv), DMSO:DMF-^{18}O (1:1), 25 ºC, 8 h.

Account for reversal in regio and stereoselectivity of the product: However, when the above reaction was performed under aqueous conditions (DMSO:DMF:H_2O = 1:1:0.4), iodoformate **5** and product **3a** were isolated (entry 6). Further reaction of iodo formate **21** with NaN_3 (2 equiv) and Et_3N (1 equiv) in DMF:DMSO:H_2O (1:1:0.4) gave **3a** in 54% yield suggesting the formation of cyclic intermediate **III,** which can account for the reversal in regio- and stereoselectivity of azidohydroxylation under aqueous conditions.

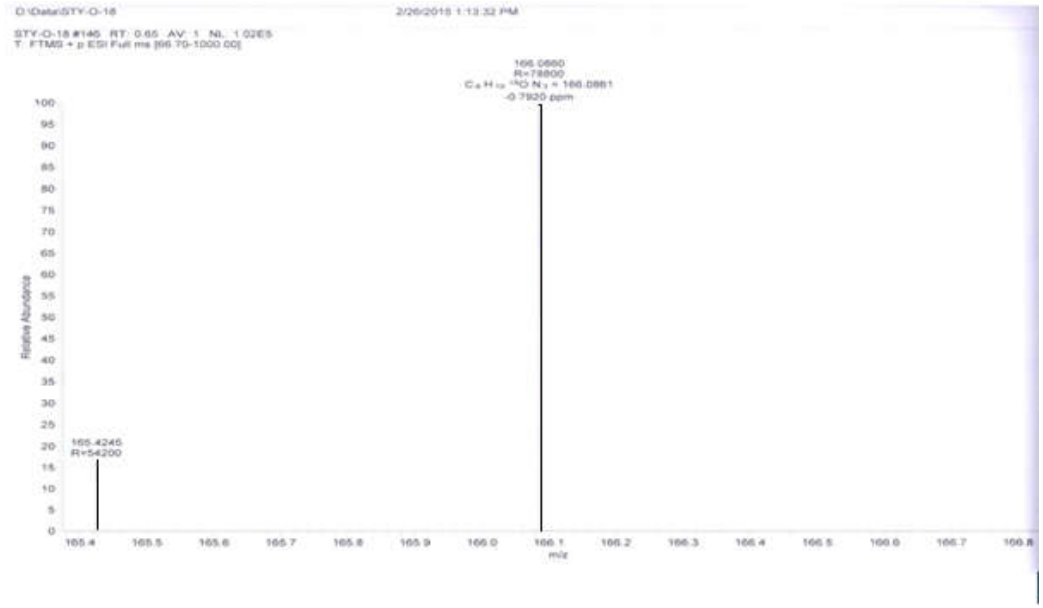
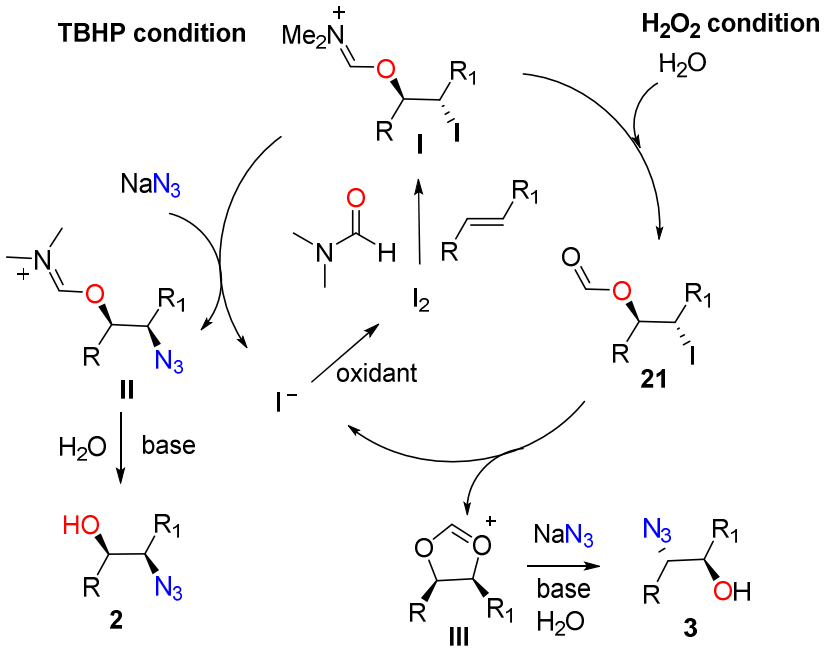


Fig. 4: HRMS spectrum of **3a**-^{18}**O**

Based on the above experiments and literature precedence,[22, 23] the following mechanism has been proposed (**Scheme 12**). Initially, alkene reacts with iodine to form iodonium ion which undergoes regioselective ring opening with DMF to give the corresponding iodo intermediate **I** followed by subsequent stereoselective displacement with azide ion to form species **II.** This on hydrolysis affords *syn* azido alcohols **2**. On the other hand, under aq. H_2O_2 condition, the iodo intermediate **I** is hydrolyzed *in situ* to form iodoformate **21**. The proposed species **III** formed from **21** by the anchimeric assistance shown by the formate group, reacts with azide anion in a regioselective manner to give *anti* azido alcohol **3** with the liberation of iodide ion, which is then reoxidized with TBHP/H_2O_2 to regenerate I_2 in the catalytic cycle.



Scheme 12: Plausible catalytic cycle for azidohydroxylation of alkenes

3.1.4 Conclusion

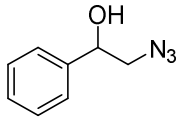
To summarize, we have developed, for the first time, I_2-catalyzed regio- and diastereoselective azidohydroxylation of alkenes to give vicinal azidoalcohols in high yields. The regio- and stereodivergence observed in the process is driven by the nature of oxidants chosen. Extensive mechanistic studies revealed that DMF is crucial for regiodivergence and acts as an *O*-source which was unequivocally proven by ^{18}O-labelling experiments. We believe that this mild, environmentally benign and operationally simple method would find tremendous application in syntheses of drugs and synthetically useful intermediates.

3.1.5 Experimental Section

3.1.5.1 General Experimental Procedure for the Preparation of (2a-n):

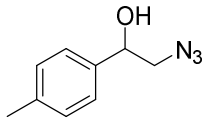
To a stirred solution of alkene (1 mmol) in DMSO:DMF (4 mL:4 mL) at 0 °C was added I_2 (10 mol %) followed by dropwise addition of 5-6 M TBHP in decane (2 mmol). The addition of Et_3N (1 mmol) was then done slowly (slow decolorisation of reaction mixture was observed) and finally sodium azide (2 mmol) was added pinchwise. The reaction mixture was then allowed to stir at room temperature for 8 hours (monitored by TLC). After completion, the reaction mixture was then cooled to 0 °C and excess sodium azide was quenched with water. Organic layer was diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were repeatedly washed with saturated brine solution, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (230-400 mesh)] using Pet. ether:EtOAc (8:2) as an eluent to afford corresponding vicinal azido alcohol (**2a-n)** in 74-90% yield.

2-Azido-1-phenylethan-1-ol (2a)[24]



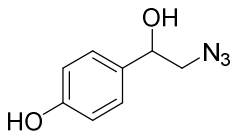
Yield: 90% (146 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1031, 1101, 1247, 2103, 2847, 2933, 3356; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.61 (br. s, 1H), 3.41 (dd, *J* = 3.7, 12.4 Hz, 1H), 3.47 (dd, *J* = 8.2, 12.4 Hz, 1H,), 4.85 (dd, *J* = 8.2, 3.9 Hz, 1H), 7.30-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 58.1, 73.4, 125.9, 128.3, 128.7, 140.6; **HRMS** calcd for [$(C_8H_9N_3O+Na)^+$] 186.0638; found: 186.0640.

2-Azido-1-(p-tolyl)ethan-1-ol (2b)[24]



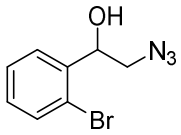
Yield: 88% (155 mg), colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 750, 1222, 2095, 2950, 3020, 3412; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.63 (br. s., 1H), 3.32-3.51 (m, 2H), 4.81 (dd, *J* = 7.6, 4.4 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 58.0, 73.2, 125.8, 129.3, 137.6, 138.1; **HRMS** calcd for $[(C_9H_{11}N_3O+Na)^+]$: 200.0794; found: 200.0793.

4-(2-Azido-1-hydroxyethyl)phenol (2c)



Yield: 76% (135 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1247, 1607, 2103, 2923, 3356; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.41-3.46 (m, 2H), 4.32-4.36 (m, 1H), 4.81 (dd, *J* = 7.7, 4.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.97 (s, D_2O exchangeable, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 58.1, 73.1, 115.6, 127.5, 128.6, 155.8; **HRMS** calcd for $[(C_8H_9N_3O_2+Na)^+]$ 202.0587 found 202.0579.

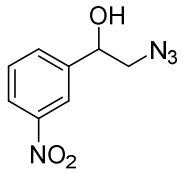
2-Azido-1-(2-bromophenyl)ethan-1-ol (2d)



Yield: 82% (196 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 761, 1012, 1214, 2103, 2724, 3018; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.46 (d, *J* = 3.4 Hz, 1H),

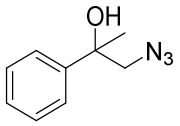
3.35 (dd, *J* = 12.6, 8.2 Hz, 1H), 3.60 (dd, *J* = 12.6, 2.9 Hz, 1H), 5.26 (dt, 3.0 Hz, 1H), 7.19 (t, *J* = 8.5 Hz, 1H), 7.38 (t, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 9.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 56.5, 72.4, 121.7, 127.8, 127.9, 129.7, 132.8, 139.5; **HRMS** calcd for [$(C_8H_8BrN_3O+Na)^+$] 263.9743 found 263.9738.

2-Azido-1-(3-nitrophenyl)ethan-1-ol (2e)[30]



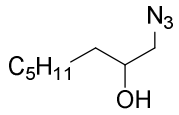
Yield: 77% (160 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1211, 1350, 1531, 2104, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.59 (s, 1H), 3.52-3.56 (m, 2H), 5.01 (t, *J* = 5.9 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 8.19-8.30 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 57.9, 72.3, 121.0, 123.2, 129.6, 132.0, 142.6, 148.4; **HRMS** calcd for [$(C_8H_8N_4O_4+H)^+$] 209.0674 found 209.0673.

1-Azido-2-phenylpropan-2-ol (2f)[25]



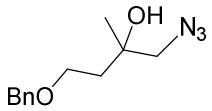
Yield: 78% (140 mg), colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 761, 1272, 2096, 2828, 2950, 3020, 3422; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.61 (s, 3H), 2.36 (s, 1H), 3.45 (d, *J* = 12.3 Hz, 1H), 3.61 (d, *J* = 12.3 Hz, 1H), 7.29-7.32 (m, 1H), 7.37–7.40 (m, 2H), 7.45-7.47 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 27.1, 62.2, 74.5, 124.8, 127.5, 128.5, 144.7; **HRMS** calcd for [$(C_9H_{11}N_3O+Na)^+$] 200.0794; found: 200.0794.

1-Azidooctan-2-ol (2g)[26]



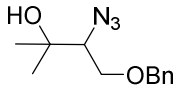
Yield: 79% (135 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 759, 1261, 2104, 2937, 3404; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.82 (t, *J* = 6.2 Hz, 3H), 1.23 (br. s., 7H), 1.38 (br. s., 3H), 1.97 (br. s., 1H), 3.18-3.34 (m, 2H), 3.67 (br. s., 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 25.4, 29.2, 31.8, 34.3, 57.2, 70.8; **HRMS** calcd for $[(C_8H_{17}N_3O+Na)^+]$ 194.1264; found:194.1263.

1-Azido-4-(benzyloxy)-2-methylbutan-2-ol (2h)



Yield: 84% (196 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}) ν_{max} 705, 1082, 1274, 1717, 2106, 2926, 2974, 3412; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.82–1.99 (m, 2H), 2.59 (d, *J* = 4.9 Hz, 1H), 2.70 (d, *J* = 4.9 Hz, 1H), 3.53-3.62 (m, 2H), 4.50 (s, 2H), 7.28-7.37 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 36.6, 53.9, 55.4, 66.6, 73.0, 127.6, 128.4, 138.3; **HRMS** calcd for $[(C_{12}H_{17}N_3O_2+Na)^+]$ 258.1213; found: 258.1209.

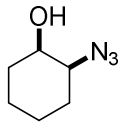
3-Azido-4-(benzyloxy)-2-methylbutan-2-ol (2i)



Yield: 74% (175 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 705, 765, 1082, 1274, 1377, 1612, 1717, 2106, 2926, 2974, 3412; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.35 (s, 3H), 2.98 (t, *J* = 5.4 Hz, 1H), 3.51-3.69 (m, 2H), 4.49- 4.67 (m, 2H), 7.30-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.9, 24.7, 57.5, 61.9, 68.8,

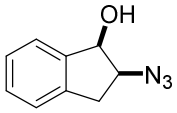
73.2, 127.8, 128.4, 137.9; **HRMS** calcd for [($C_{12}H_{17}N_3O_2$+Na)$^+$] 258.1213; found: 258.1210.

***syn*-2-Azidocyclohexan-1-ol (2j)**



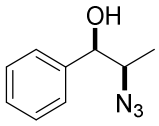
Yield: 87% (122 mg); colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 760, 1259, 2102, 2937, 3403; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.28-1.34 (m, 3H), 1.37-1.56 (m, 1H), 1.83-1.90 (m, 1H), 2.00-2.16 (m, 2H), 2.34 (d, *J* = 2.3 Hz, 1H), 2.45-2.51 (m, 1H), 3.66 (td, *J* = 9.8, 3.9 Hz, 1H), 4.05 (ddd, *J* = 12.4, 9.8, 4.4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.4, 28.0, 33.6, 38.6, 43.5, 76.0; **HRMS** calcd for [($C_6H_{11}N_3O$+Na)$^+$] 164.0794; found: 164.0794.

***syn*-2-Azido-2,3-dihydro-1*H*-inden-1-ol (2k)**[27]



Yield: 87% (152 mg); colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 770, 1219, 2097, 2916, 3356; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.39 (d, *J* = 5.2 Hz, 1H), 3.14-3.22 (m, 2H), 4.35 (q, *J* = 5.2 Hz, 1H), 5.16 (s, 1H), 7.28-7.34 (m, 3H), 7.45-7.47 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 35.2, 65.7, 76.4, 124.7, 125.1, 127.6, 129.0, 139.0, 141.9; **HRMS** calcd for [($C_9H_9N_3O$+Na)$^+$] 198.0638; found:198.0640.

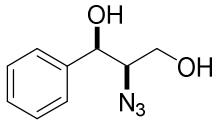
***syn*-2-Azido-1-phenylpropan-1-ol (2l)**[28]



Yield: 88% (155 mg), colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 771, 1229, 1605, 2101, 2926, 3013, 3346; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.58 (d, *J* = 6.1 Hz, 3H), 4.56-4.66

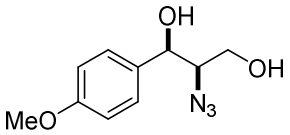
(m, 1H), 5.12 (d, J = 7.8 Hz, 1H), 7.31-7.45 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.4, 80.6, 84.8, 126.0, 129.2, 129.8, 135.2; **HRMS** calcd for [$(C_9H_{11}N_3O+Na)^+$] 200.0794; found: 200.0788.

***syn*-2-Azido-1-phenylpropane-1,3-diol (2m)**[29]



Yield: 80% (115 mg), colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 761, 1219, 1605, 2105, 2893, 2933, 3013, 3416; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.64 (br. s., 1H), 2.70 (br. s, 1H), 3.51-3.73 (m, 2H), 3.83 (d, J = 4.7 Hz, 1H), 4.85 (t, J = 6.5 Hz, 1H), 7.34-7.43 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 62.8, 67.0, 74.0, 126.5, 127.8, 128.9, 136.2; **HRMS** calcd for [$(C_9H_{11}N_3O_2+Na)^+$] 216.0749 found: 216.0736.

***syn*-2-Azido-1-(4-methoxyphenyl)propane-1,3-diol (2n)**

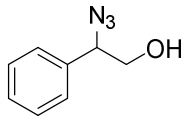


Yield: 82% (182 mg), colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 754, 1222, 2103, 2822, 2937, 3397; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.51-3.90 (m, 6H), 4.78 (t, J = 5.6 Hz, 1H), 6.88-6.95 (m, 2H), 7.29-7.35 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.3, 62.7, 69.1, 74.4, 114.1, 127.6, 132.2, 159.7; **HRMS** calcd for [$(C_{10}H_{13}N_3O_3+H)^+$] 224.1035 found: 224.1033.

1.3.5.2 General Experimental Procedure for the Preparation of (3a-n):

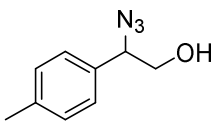
To a stirred solution of alkene (1 mmol) in DMSO:DMF (4 mL:4 mL) at 0 °C was added I_2 (10 mol %) followed by dropwise addition of 50% aqueous H_2O_2 (2 mmol, 0.140 mL). The addition of Et_3N (1 mmol, 0.140 mL) was then done slowly (vigorous decolorisation of reaction mixture was observed) and finally sodium azide (2 mmol, 130 mg) was added portionwise. The reaction mixture was then allowed to stir at room temperature for 8 h (monitored by TLC). Organic layer was diluted with EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were repeatedly washed with saturated brine solution, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified by column chromatography [silica gel (230-400 mesh)] using petroleum ether:EtOAc (8:2) as an eluent to afford the corresponding vicinal azido alcohols (**3a-n**) in 74-92% yield.

2-Azido-2-phenylethan-1-ol (3a)[24]



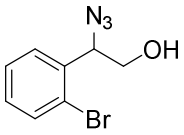
Yield: 82% (150 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1026, 1105, 1227, 2106, 2847, 2933, 3416; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.02 (s, 1H), 3.74 (t, *J* = 5.6 Hz, 2H), 4.68 (t, *J* = 6.4 Hz, 1H), 7.33-7.41 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.3, 67.7, 127.1, 128.6, 128.8, 136.2; **HRMS** calcd for [$(C_8H_9N_3O+Na)^+$] 186.0638; found: 186.0640.

2-Azido-2-(p-tolyl)ethan-1-ol (3b)[24]



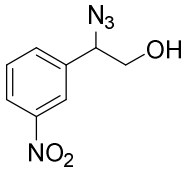
Yield: 89% (158 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 752, 1232, 2104, 2893, 2950, 3021, 3382; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.69 (d, *J* = 6.4 Hz, 2H), 4.60 (t, *J* = 6.4 Hz, 1H), 7.19 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 66.3, 67.6, 127.1, 129.5, 133.2, 138.4; **HRMS** calcd for [$(C_9H_{11}N_3O + Na)^+$] 200.0794; found: 200.0793;

2-Azido-2-(2-bromophenyl)ethan-1-ol (3d)



Yield: 86% (205 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 761, 1032, 1255, 2103, 2931, 3367; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.24 (br. s., 1H), 3.63 (t, *J* = 9.6 Hz, 1H), 3.87 (d, *J* = 11.0 Hz, 1H), 5.18 (dd, *J* = 8.1, 3.7 Hz, 1H), 7.19-7.22 (m, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 65.4, 66.7, 123.1, 128.0, 128.5, 129.9, 133.1, 135.8; **HRMS** calcd for [$(C_8H_8BrN_3O + Na)^+$] 263.9743; found: 263.9739.

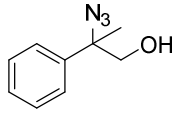
2-Azido-2-(3-nitrophenyl)ethan-1-ol (3e)



Yield: 76% (158 mg); colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 757, 1350, 1530, 1631, 2107, 2925, 3085, 3413; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.81 (dd, *J* = 5.4, 2.5 Hz, 1H), 3.24 (dd, *J* = 5.4, 4.0 Hz, 1H), 3.98 (dd, *J* = 3.9, 2.5 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 8.17-8.19 (m, 2H); **^{13}C NMR** (125 MHz,

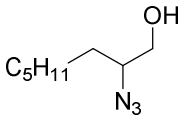
$CDCl_3$): δ 51.4, 76, 120.7, 123.1, 129.6, 131.4, 140.1; **HRMS** calcd for $[(C_8H_8N_4O_4+H)^+]$ 209.0674 found 209.0670.

2-Azido-2-phenylpropan-1-ol (3f)[25]



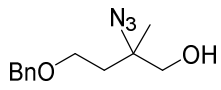
Yield: 83% (146 mg); colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 755, 1122, 1299, 2100, 2897, 2986, 3450; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (s, 3H), 2.32 (s, 1H), 3.50 (d, *J* = 11.3 Hz, 1H), 3.67 (d, *J* = 11.3 Hz, 1H), 7.21-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.0, 70.9, 74.8, 125.1, 127.1, 128.4, 145.0; **HRMS** calcd for $[(C_9H_{11}N_3O+Na)^+]$ 200.0794; found: 200.0794.

2-Azidooctan-1-ol (3g)[26]



Yield: 83% (142 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 745, 1114, 1282, 2101, 2868, 2929, 3465; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87-0.93 (m, 3H), 1.30 (br. s., 8H), 1.50 (d, *J* = 5.2 Hz, 2H), 1.95 (br. s., 1H), 3.41-3.60 (m, 2H), 3.62-3.76 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 26.0, 29.1, 30.6, 31.7, 64.5, 65.2; **HRMS** calcd for $[(C_8H_{17}N_3O+Na)^+]$ 194.1264; found:194.1263.

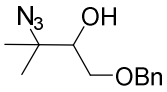
2-Azido-4-(benzyloxy)-2-methylbutan-1-ol (3h)



Yield: 74% (172 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 744, 1104, 1292, 2102, 2867, 2926, 3460; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.64 (s,

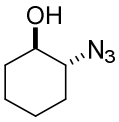
1H), 1.74-1.81 (m, 1H), 1.92-1.99 (m, 1H), 3.24 (s, 2H), 3.58 (s, 1H), 3.70-3.76 (m, 2H), 4.55 (s, 2H), 7.31-7.40 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.0, 37.5, 60.5, 66.9, 72.8, 73.4, 127.8, 127.9, 128.5, 137.4; **HRMS** calcd for $[(C_{12}H_{17}N_3O_2+Na)^+]$ 258.1213; found: 258.1209.

3-Azido-1-(benzyloxy)-3-methylbutan-2-ol (3i)



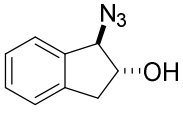
Yield: 78% (185 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 771, 1077, 1456, 2121, 2924, 3416; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.17 (s, 3H), 1.23 (s, 3H), 2.16 (s, 1H), 3.55-3.59 (m, 2H), 3.64 (d, *J* = 8.2 Hz, 1H), 4.54 (dd, *J* = 12.2, 4.6 Hz, 2H), 7.31-7.38 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 25.2, 26.6, 71.5, 71.8, 73.7, 75.6, 127.8, 128.0, 128.5, 137.5; **HRMS** calcd for $[(C_{12}H_{17}N_3O_2+Na)^+]$ 258.1213; found: 258.1210.

***anti*-2-Azidocyclohexan-1-ol (3j)**



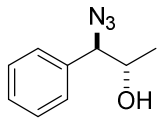
Yield: 92% (130 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 764, 1285, 1455, 2100, 3410; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25-1.33 (m, 4H), 1.65-1.80 (br. s, 2H), 1.97-2.04 (m, 2H), 2.76 (br. s., 1H), 3.12-3.18 (m, 1H), 3.35 (dt, *J* = 9.6, 4.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.8, 24.1, 29.7, 33.0, 66.9, 73.4; **HRMS** calcd for $[(C_6H_{11}N_3O+Na)^+]$ 164.0794; found: 164.0794.

***anti*-2-Azido-2,3-dihydro-1H-inden-1-ol (3k)**[27]



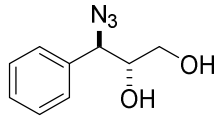
Yield: 82% (144 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 761, 1219, 2098, 2844, 2926, 3366; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.86 (dd, *J* = 16.0, 5.9 Hz, 1H), 3.28 (dd, *J* = 16.0, 6.7 Hz, 1H), 3.44 (br. s, 1H), 4.46 (q, *J* = 5.9 Hz, 1H), 4.65 (d, *J* = 4.9 Hz, 1H), 7.29-7.39 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 35.2, 65.7, 76.4, 124.7, 125.1, 127.6, 129.0, 139.0, 141.9; **HRMS** calcd for [$(C_9H_9N_3O+Na)^+$] 198.0638; found:198.0640.

***anti*-1-Azido-1-phenylpropan-2-ol (3l)**[28]



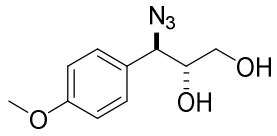
Yield: 86% (152 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 759, 1269, 2109, 2829, 2950, 3020, 3322; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.11 (d, *J* = 6.2 Hz, 3H), 1.63 (br. s., 1H), 3.88 (quin, *J* = 6.1 Hz, 1H), 4.38 (d, *J* = 5.8 Hz, 1H), 7.23-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.6, 70.6, 71.6, 127.8, 128.6, 128.9, 136.3; **HRMS** calcd for [$(C_9H_{11}N_3O+Na)^+$] 200.0794; found: 200.0794.

***anti*-3-Azido-3-phenylpropane-1,2-diol (3m)**[29]



Yield: 78% (112 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 777, 1309, 1604, 2107, 2933, 3014, 3389; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.68 (br. s., 2H), 3.61-3.71 (m, 2H), 3.80 (td, *J* = 6.4, 3.3 Hz, 1H), 4.59 (d, *J* = 7.1 Hz, 1H), 7.34-7.44 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 62.8, 67.1, 74.0, 127.8, 128.8, 129.0, 136.2; **HRMS** calcd for [$(C_9H_{11}N_3O_2+Na)^+$] 216.0749 found: 216.0745.

***anti*-3-Azido-3-(4-methoxyphenyl)propane-1,2-diol (3n)**



Yield: 80% (890 mg), colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1035, 1195, 1513, 1616, 2100, 2920, 3050, 3368 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.73 (br. s., 1H), 3.21-3.68 (m, 2H), 3.74-3.82 (m, 4H), 4.52 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.2, 63.0, 66.4, 73.9, 114.3, 128.0, 129.1, 159.8; **HRMS** calcd for $[(C_{10}H_{13}N_3O_3+H)^+]$ 224.1035 found: 224.1036.

2-Azido-2phenylethan-1-ol (^{18}**O-3a):**

To a stirred solution of styrene (0.5 mmol) in DMSO: ^{18}O-DMF (which was prepared by dimethylaminomethylene)dimethylammonium chloride and ^{18}O-H_2O (>97%-^{18}O) heating in 110 °C for 12 hours) (0.5 mL: 0.5 mL) at 0 °C was added I_2 (10 mol %) followed by dropwise addition of 50% aqueous H_2O_2 (1 mmol). The addition of Et_3N (0.5 mmol) was then done slowly (vigorous decolorisation of reaction mixture was observed) and finally sodium azide (1 mmol) was added pinchwise. The reaction mixture was then allowed to stir at room temperature for 8 h (monitored by TLC). Organic layer was diluted with EtOAc and separated while the aqueous layer was extracted with EtOAc (3 x 8 mL). The combined organic extracts were repeatedly washed with saturated brine solution, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography [silica gel (230-400 mesh)] using Pet. ether:EtOAc (8:2) as an eluent to afford the corresponding vicinal azido alcohol (**^{18}O-3a)** in 78% yield and (**^{18}O-2a**)

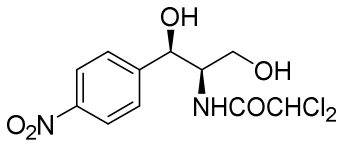
in 6% yield. The ^{1}H NMR and ^{13}C NMR data were in well-agreement with that of compounds **3a** and **2a**. **HRMS** calcd for $[(C_8H_9N_3O+H)^+]$ 166.086; found: 166.0860.

Section II

Concise Diastereoselective Synthesis of (±)-Chloramphenicol and (±)-Cytoxazone *via* I_2-Catalyzed Azidohydroxylation of Alkenes

3.2.1 Introduction

Amino alcohols with vicinal stereocenters are important as drugs and natural products such as amino sugars,[31] peptides and peptide analogs,[32] enzyme inhibitors, such as glycosphingolipids, antibiotics and alkaloids. Chloramphenicol (**25e**) is broad-spectrum antibiotic with a range of biological activities.[33] The antibiotic chloramphenicol is active only in its D-*threo* configuration and is effective in the treatment of typhus, dysentery and ocular bacterial infections.[34] In 1998, Osada and co-workers reported the isolation of another vicinal amino alcohol (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine-2-one [(-)-**26** , generic name cytoxazone],[35] which possesses high cytokine modulator activity by acting on the Th2 cells (**Fig. 5**).[36] Owing to their potent biological activity, a number of syntheses have been described.



25e

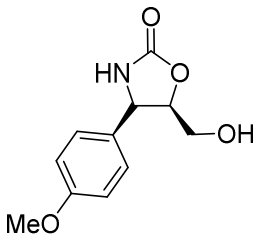


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Fig. 5: Structures of (-)-chloramphenicol (**25e**) and (-)-cytoxazone (**26**)

3.2.2 Pharmacology of (-)-Chloramphenicol and (-)-Cytoxazone

Chloramphenicol (**25**) is a lipid-soluble compound consisting of an aromatic nitro moiety and an aliphatic side chain {(1*R*,2*R*)-2-(dichloroacetamido)-1-[(4-

nitro)phenyl]-1,3-propanediol}. Considerable modification can be performed at the *para* position without a marked loss in its antimicrobial activity. For example, nitro group can be substituted by a methyl sulfonyl (which is thiamphenicol). Chloramphenicol works by binding to the 50S subunit of the bacterial ribosome. It then prevents attachment of amino acyl tRNA to the ribosome. At this time, it is not known if it prevents attachment of the tRNA to the A-site or the P-site. It prevents peptide formation and elongation, and is therefore bacteriostatic. An important aspect of chloramphenicol's distribution is that it is able to penetrate the CSF, lymph, and ganglions, making it a treatment option for paratyphoid, typhoid fever, and meningitis. Cytoxazone containing a 2-oxazolidinone ring, which is rare in microbial metabolites, is a novel cytokine modulator produced by *Streptomyces*. Cytoxazone and its epimers show a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells. It is well established that the induction of humoral or cellular response is influenced by the development of distinct subsets of $CD4^+$ T cells.[37] The Th1 cell subset produces predominantly IL-2, GM-CSF, INF-γ, and TNF-β, (type 1 cytokines) and is involved in delayed-type hypersensitivity reactions, whereas the Th2 cell subset secretes IL-4, IL-5, IL-6, IL-10, and IL-13 (type 2 cytokines), which are important factors for β cell growth and differentiation to Ig secretion. The imbalance of cytokine production by $CD4^+$ T cells leads to a wide variety of immunological disorders *i.e.* allergy, progressive lymphoproliferation, and severe immunodeficiency.[38] Skin and lung biopsies from allergic patients indicate that the pivotal cells in the allergic site are the Th2 cells.[39] Treatments effectively suppressing the function or the differentiation of these allergen-specific Th2 cells will most likely provide efficient ways to intervene in Ig-mediated allergic diseases. In this regard, cytoxazone is exhibits immunomodulatory activity.

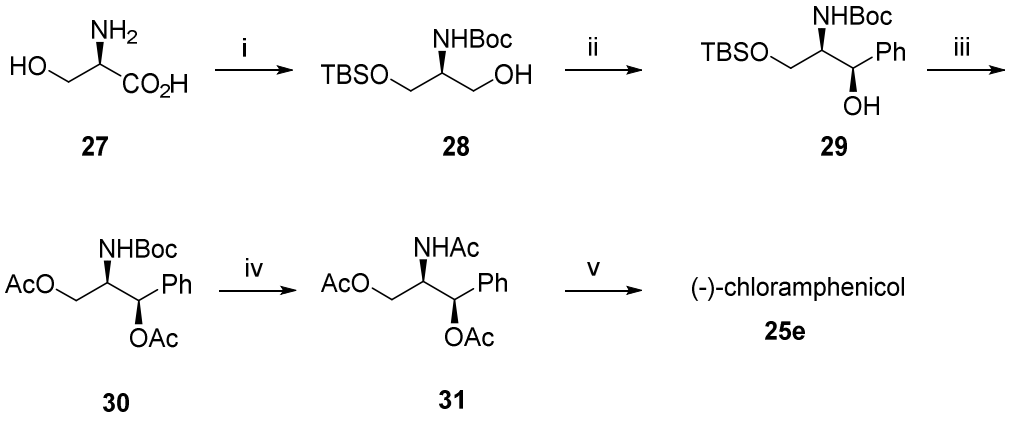
3.2.3 Review of Literature

3.2.3.1 Synthesis of (-)-Chloramphenicol

There are several reports available for the synthesis of (-)-chloramphenicol (**25e**) involving chiral pool, chemo-enzymatic approach or enantioselective syntheses, Some of them are described below.

Datta's approach (1998)[40]

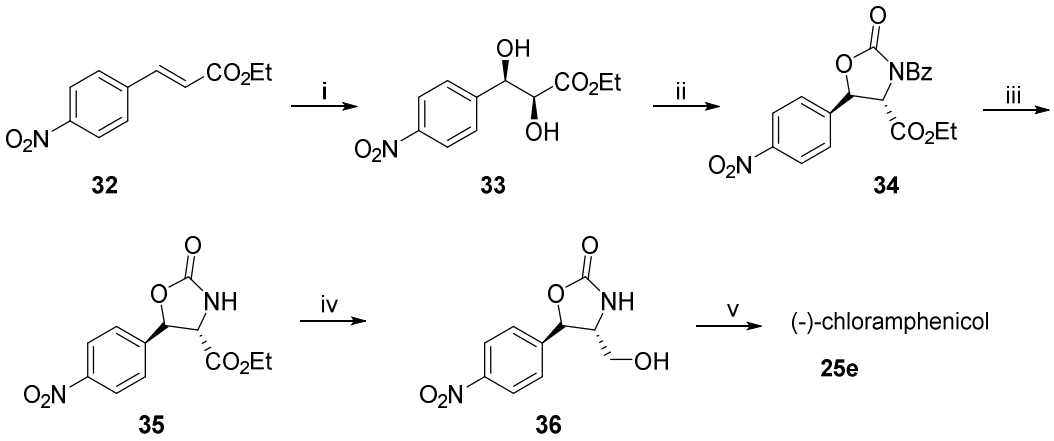
Datta *et al.* have achieved the synthesis of (-)-chloramphenicol (**25e**) using a chiral pool approach starting with D-serine **27**, which was converted into the amino diol derivative **28** in four steps. Swern oxidation of the alcohol **28** followed by Grignard addition with phenyl magnesium bromide afforded the *syn*-amino alcohol **29** with diastereoselectivity >19:1. Stepwise deprotection, acylation sequence of **29** gave the desired product **31**, which on nitration with conc. HNO_3 & conc. H_2SO_4 (1:1) followed by treatment with methyl dichloroacetate gave (-)-chloramphenicol (**25e**) in 73% yield (**Scheme 13**).



Scheme 13: (i) (a) MeOH, HCl; (b) $(Boc)_2O$, Et_3N, THF; (c) TBSCl, imid., CH_2Cl_2; (d) $LiBH_4$, THF, 80%; (ii) $(COCl)_2$, DMSO, $^iPr_2NEt$, CH_2Cl_2, -78 °C then PhMgBr, THF, 25 °C, 69%; (iii) (a) Bu_4NF, THF, 0°C to 25°C; (b) Ac_2O, DMAP, Py., 92%; (iv) (a) CF_3CO_2H, 0 °C; (b) Ac_2O, DMAP, Py., 85%; (v) (a) conc. HNO_3:conc. H_2SO_4 (1:1), -20 °C to 25 °C; (b) aq. 5% HCl, 90 °C, 66%; (c) Cl_2CHCO_2Me, 90 °C, 73%.

Koh's approach (2000)[41]

Koh *et al.* have synthesized (-)-chloramphenicol (**25e**) by employing Sharpless asymmetric dihydroxylation as the key reaction. The ester **32** was subjected to asymmetric dihydroxylation to give the diol **33** in 98% yield, which was successively treated with Bu_2SnO, BzNCS and Bu_4NBr to give the protected *syn* amino alcohol derivative **34**. Debenzoylation of **34** with $Ti(O^iPr)_4$ in ethanol afforded **35** which was reduced with $NaBH_4$ to give the alcohol **36** in 92% yield. Hydrolysis of **36** with aq. NaOH solution followed by amidation with methyl dichloroacetate gave (-)-chloramphenicol (**25e**) in 74% yield (**Scheme 14**).

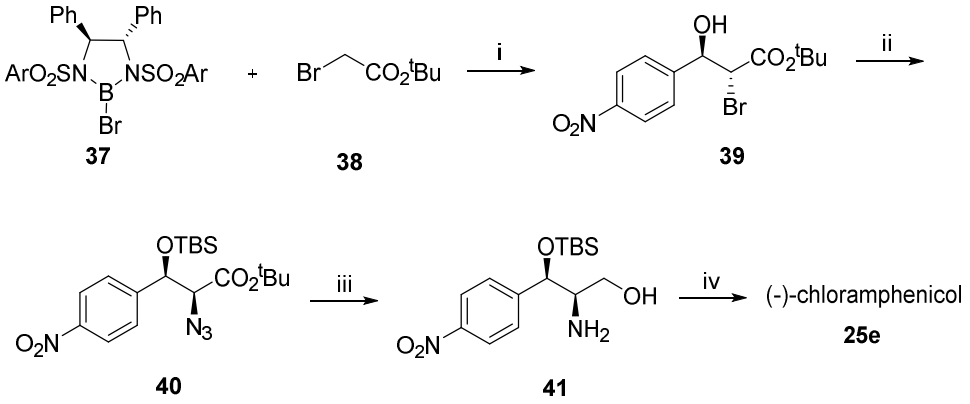


Scheme 14: (i) AD-mix-β, *t*-BuOH:H_2O (1:1), 25 °C, 98%, >99% ee; (ii) (a) Bu_2SnO; (b) BzNCS; (c) Bu_4NBr; (iii) $Ti(O^iPr)_4$, ethanol, 81%; (iv) $NaBH_4$, 92%; (v) (a) 1N NaOH, 92%; (b) Cl_2CHCO_2Me, 74%.

Corey's approach (2000)[42]

Corey *et al.* have synthesized (-)-chloramphenicol (**25e**) *via* aldol reaction of *p*-nitrobenzaldehyde and *t*-butyl bromoacetate **38** in the presence of (*S*,*S*)-bromoborane to give the bromohydrin **37** in 99% yield and 93% ee. Protection of the hydroxyl group in **39** as its silyl ether followed by reaction with sodium azide gave **40**. Reduction of azido ester **40** was performed in two steps with $LiBH_4$ followed by PPh_3 in THF-H_2O to form alcohol **41**. *N*-acylation of **41** and subsequent desilylation with

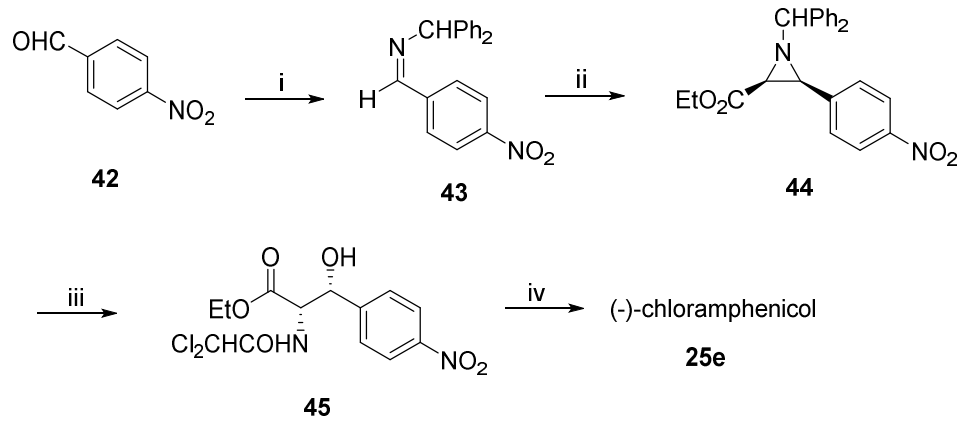
Bu_4NF in THF afforded (-)-chloramphenicol (**Scheme 15**).



Scheme 15: (i) (a) toluene, -78 °C, Et_3N; (b) *p*-nitrobenzaldehyde, -78 °C, 99%, d.r. = 96:4, 93% ee; (ii) (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 96%; (b) NaN_3, DMF, 40 °C, 73%; (iii) (a) $LiBH_4$, Et_2O, 0 °C, 80%; (b) PPh_3, THF-H_2O, 80%; (iv) (a) Cl_2CHCO_2Me, CH_2Cl_2, 0 °C; (b) Bu_4NF, THF.

Wulff's approach (2001)[43]

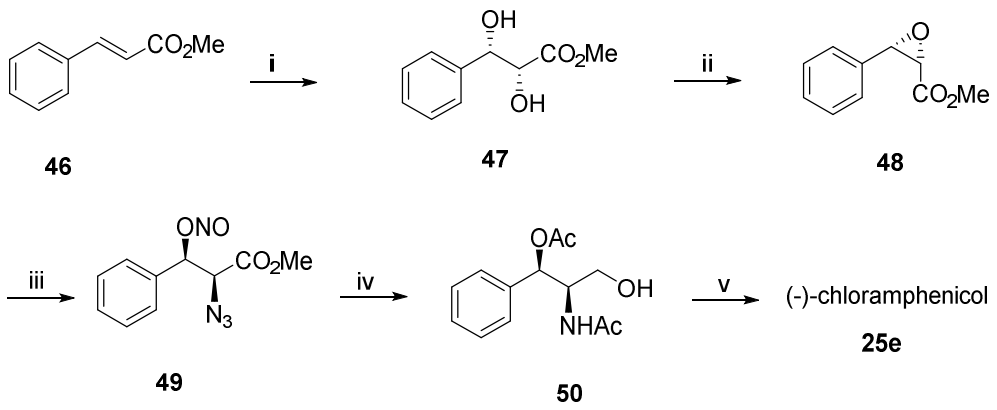
Wulff *et al.* have synthesized (-)-chloramphenicol (**25e**) *via* catalytic aziridination of *p*-nitrobenzaldimine **43** in presence of triphenylborate and (*S*)-VAPOL to give the aziridine **44** in 80% yield and 96% ee. Treatment of aziridine **44** with 10 equivalents of dichloroacetic acid gave hydroxyl acetamide **45** which on subsequent reduction with $NaBH_4$ in MeOH afforded (-)-chloramphenicol (**25e**) in 74% yield (**Scheme 16**).



Scheme 16: (i) Ph_2CHNH_2, $MgSO_4$, CH_2Cl_2, 25 °C, 10 h, 80%;(ii) N_2CHCO_2Et, triphenylborate and (*S*)-VAPOL (10 mol %), toluene, 0 °C, 20 h, 80%, *cis*:*trans* = 30:1, 96% ee; (iii) Cl_2CHCO_2H, EDC, reflux, 1 h, 80%; (iv) $NaBH_4$, MeOH, 0 °C, 0.5 h, 74%.

Boruwa's approach (2005)[44]

Boruwa *et al.* have reported the synthesis of (-)-chloramphenicol (**25e**) by using regioselective ring opening of epoxide **48** which in turn was prepared from methyl cinnamate **46** by Sharpless' asymmetric dihydroxylation. The epoxide **48** was further exposed to $NaNO_2$ and acetic acid in water followed by treatment with diphenyl phosphorylazide (DPPA), DEAD and PPh_3 to afford the azide **49**. Catalytic hydrogenation of **49** [10% Pd/C, MeOH, H_2 (1 atm)] followed by acylation with Ac_2O gave the desired product **50**. The synthesis of (-)-chloramphenicol (**25e)** was then completed by following the three-step reaction sequence: nitration, hydrolysis and *N*-acylation (**Scheme 17**).

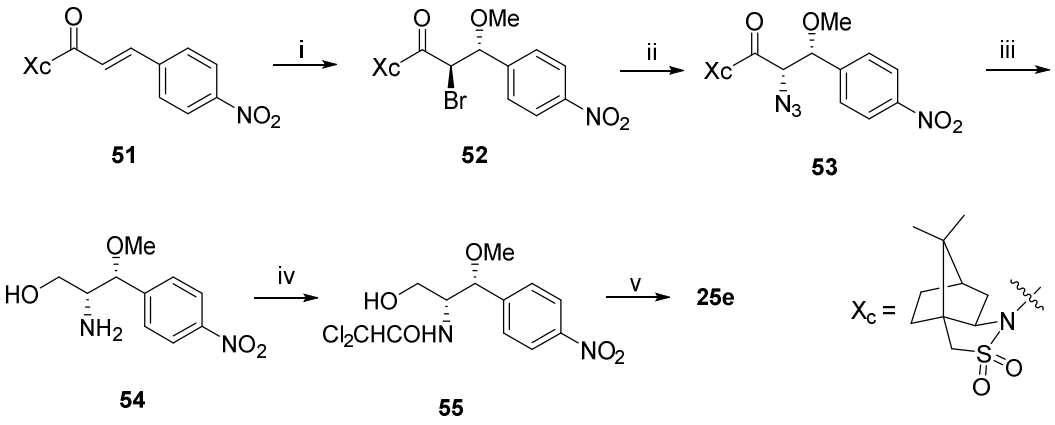


Scheme 17: (i) OsO_4 (cat.), NMO, DHQ-*p*ClBz, acetone, H_2O, 98% ee; (ii) (a) TsCl, Py., CH_2Cl_2; (b) K_2CO_3, H_2O, DMF, 86%; (iii) (a) $NaNO_2$, AcOH, H_2O, 0 °C to 25 °C, 2 h, 89%; (b) DPPA, DEAD, PPh_3, THF, 0 °C to 25 °C, 1.5 h, 82%; (iv) (a) 10% Pd/C, MeOH, H_2 (1 atm), 25 °C, 12 h, 97%; (b) Ac_2O, DMAP, Py.; (v) (a) conc. HNO_3: conc. H_2SO_4, -20 °C to 25 °C; (b) aq. 5% HCl, 90 °C, 69%; (c) Cl_2CHCO_2Me, 90 °C, 1 h, 80%.

Hajra's approach (2006)[45]

Hajra *et al.* have synthesized (-)-chloramphenicol (**25e)** using silver (I)-promoted asymmetric bromomethoxylation. $AgNO_3$-promoted bromomethoxylation of α,β-unsaturated carboxamide **51** provided the desired product **52** in 72% yield. Reaction of **52** with NaN_3 in DMF gave the azido product **53,** which was subjected to two-step

reduction process with $LiBH_4$ followed by PPh_3 in THF-H_2O to furnish the amino alcohol **54**. *N*-Acylation of **54** gave **55** which on subsequent demethylation with BBr_3 gave the target molecule **25e** in 80% yield (**Scheme 18**).

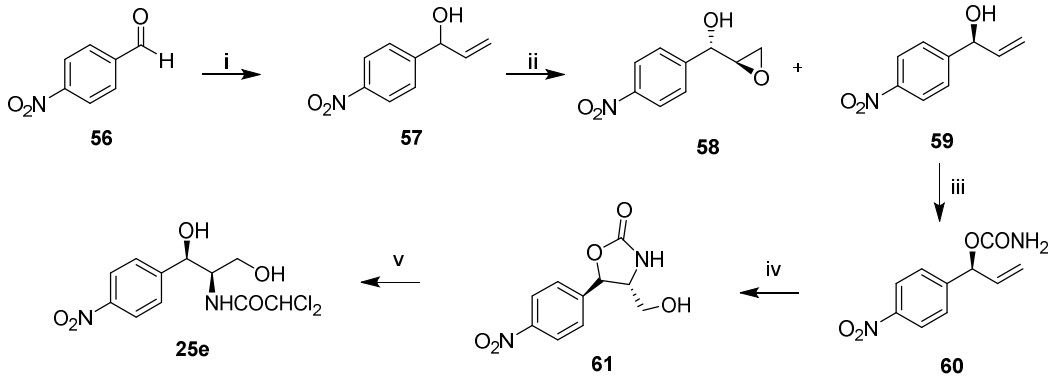


Scheme 18: (i) $AgNO_3$, Br_2, MeOH, 0 ^{0}C, 30 min, 72%, d.r. = 3:1; (ii) NaN_3, DMF, 60 °C, 4 h, 92%; (iii) (a) $LiBH_4$, THF, MeOH; (b) PPh_3, THF-H_2O, 25 °C, 5 h, 82%; (iv) Cl_2CHCO_2Me, 90 °C, 1 h, 87%; (v) BBr_3, CH_2Cl_2, -78 °C to -20 °C, 10 h, 80%.

Sudalai's approach (2006)[46]

In Sudalai's approach, synthesis of (–)-chloramphenicol (**25e**) commenced with the reaction of 4-nitrobenzaldehyde **56** with divinylzinc to give 1-(4-nitrophenyl)allyl alcohol **57** in 68% yield. Allylic alcohol **57** was then subjected to Sharpless' asymmetric epoxidation under kinetic resolution conditions to furnish the corresponding chiral allylic alcohol **59** along with the corresponding epoxide **58** in 49% yield. Alcohol **59** was then converted to the corresponding isocyanate, which on treatment with K_2CO_3 and methanol in the presence of H_2O gave the carbamate **60** in 90% yield. The carbamate **60** thus obtained was converted into oxazolidinone **61** by a tethered aminohydroxylation protocol to furnish the protected aminoalcohol **61** as a single isomer with complete regiocontrol and *syn* selectivity. The oxazolidinone **61** was then hydrolyzed using 1N NaOH in methanol to furnish the crude amino alcohol,

which was protected with methyl dichloroacetate at elevated temperature to give (-)-chloramphenicol **25e** in 78% yield and 98% ee.



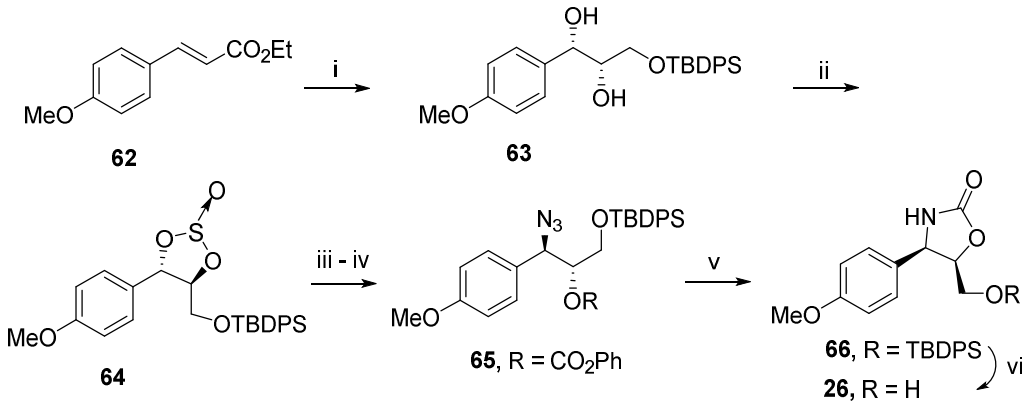
Scheme 19: (i) Divinyl zinc, THF, Et_2O, -78 °C to 25 °C, 10 h, 68%; (ii) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 °C, 14 h, 44%; (iii) (a) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C to 25 °C, 2 h; (b) K_2CO_3, MeOH, H_2O, 0 °C to 25 °C, 18 h, 90%; (iv) $K_2Os(OH)_4O_2$, *t*-BuOCl, NaOH, EtN*i*-Pr_2, *n*PrOH:H_2O (1:1), 25 °C, 3 h, 69%; (v) (a) 1N NaOH, MeOH, 25 °C, overnight; (b) methyl dichloroacetate, 90 °C, 3 h, 78%, 98% ee.

3.2.3.2 Synthesis of (-)-Cytoxazone

Literature search revealed that there are several reports available for the synthesis of (-)-cytoxazone (**26**), which are described below.

Nakata's approach (1999)[47]

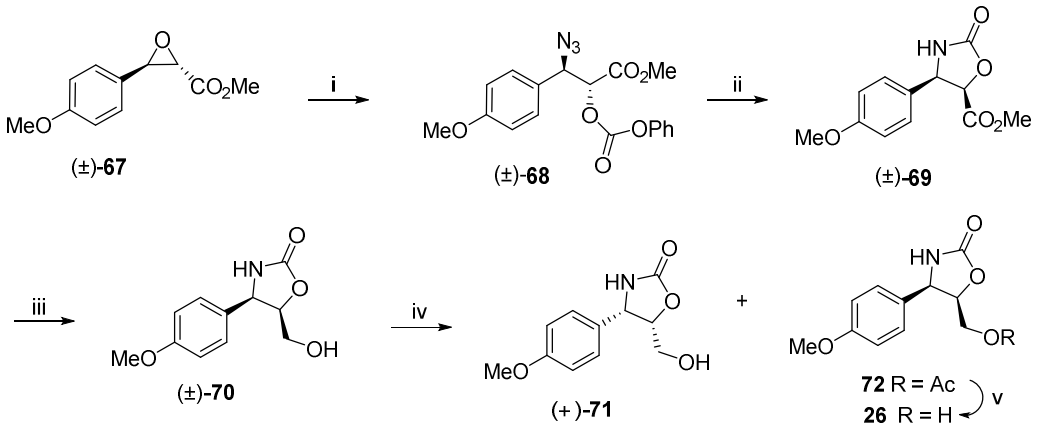
Nakata *et al.* have achieved the synthesis of (-)-cytoxazone (**26)** using Sharpless asymmetric dihydroxylation protocol. Ethyl *p*-methoxycinnamate **62** was converted to cyclic sulfite **64** (in 99% yield and 97% ee) by a two-step process involving the Sharpless catalytic asymmetric dihydroxylation followed by treatment with $SOCl_2$. The cyclic sulfite **64** was then opened regioselectively using LiN_3 and the alcohol thus obtained was protected as its carbonate **65**. Intramolecular cyclization of carbonate **65** with PPh_3 followed by the deprotection of TBDPS group gave (-)-cytoxazone (**26**) in 89% ee and 96% yield (**Scheme 20**).



Scheme 20: (i) (a) AD-mix-α, ^{t}BuOH:H_2O (1:1), 25 °C, 93 %, 99% ee; (b) $NaBH_4$, THF, 0 °C, 66%; (c) TBDPSCI, imid., DMF, 0 °C, 99%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 99%; (iii) LiN_3, DMF, 70 °C, 74 %; (iv) $ClCO_2Ph$, Py., CH_2Cl_2, 25 ºC, 96%; (v) PPh_3, THF/H_2O, 50 °C, 90%; (vi) $^{n}Bu_4NF$, THF, 0 °C, 89% ee, 96%.

Sunjic's approach (2001)[48]

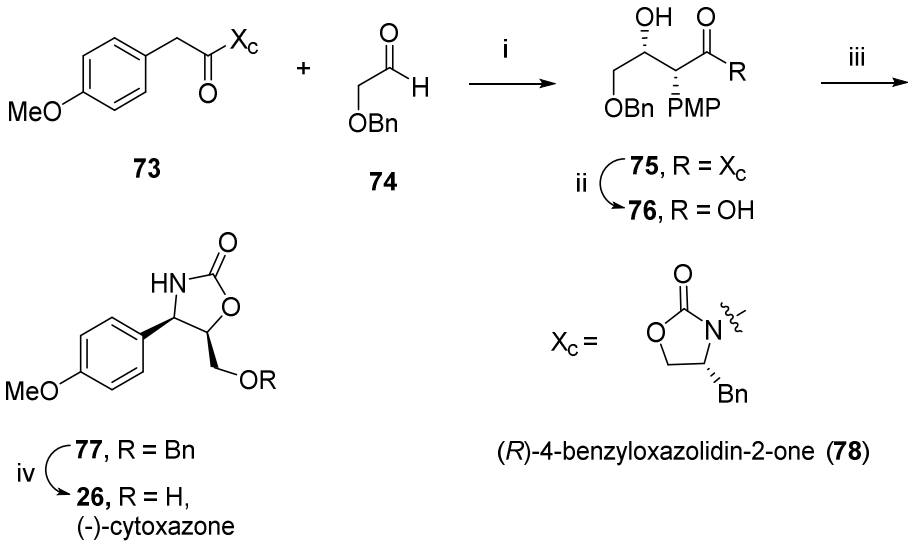
In this approach, synthesis of cytoxazone (**26**) was achieved starting from the glycidic ester **67** using enzymatic kinetic resolution. Nucleophilic ring opening of the epoxide **67** with NaN_3, followed by protection of the alcohol and intramolecular cyclization gave ester **69**. Reduction of the ester **69** and the subsequent kinetic resolution of racemic compound **70** using *Penicillium camemberti* lipase (PcamL) afforded (-)-cytoxazone (**26**) in 33% overall yield and 88.2% ee (**Scheme 21**).



Scheme 21: (i) NaN_3, dioxan, 50 °C, 3 h, 56%; (ii) $ClCO_2Ph$, CH_2Cl_2, -5 °C, 1 h, 100%; (iii) (a) Ph_3P, aq. THF, 50 °C, 1.5 h, 88%; (b) $NaBH_4$, $CoCl_2$, absolute EtOH, 25 ºC, 20 min, 79%; (iv) PcamL, vinyl acetate, 30 °C; (v) KOH, MeOH, 25 ºC, 1 h.

Carter's approach (2003)[49]

Carter *et al*. have made use of Evans' *anti*-selective aldol approach as the key reaction for the synthesis of (-)-cytoxazone (**26**). Thus, acylation of the commercially available (*R*)-oxazolidin-2-one **78** with 4-methoxyphenylacetic acid afforded imide **73**. The reaction of dibutylboryl enolate of **73** with benzyloxyacetaldehyde **74** provided the *syn*-aldol **75** (dr = 3:1). Hydrolysis of the chiral auxiliary from **75** provided the corresponding acid **76**, which was transformed into the oxazolidinone **77** in a one-pot 3-step procedure: (i) acyl azide formation, (ii) Curtius rearrangement and (iii) isocyanate trapping. Oxazolidinone **77** was debenzylated using Pearlman's catalyst to provide (-)-cytoxazone (**26**) (**Scheme 22**).

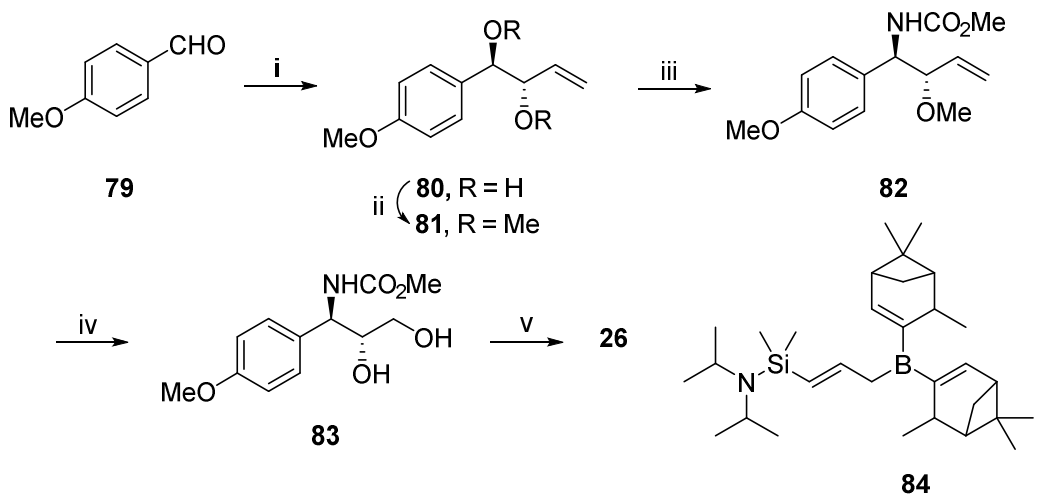


Scheme 22: (i) Bu_2BOTf, $^iPr_2EtN$, 0 °C, 30 min, then $BnOCH_2CHO$ pre-complexed with 0.5 equiv $SnCl_4$, -78 °C, 3 h, 64%; (ii) H_2O_2, LiOH, THF:H_2O (4:1), 0 °C, 1 h, 99%; (iii) $(PhO)_2PON_3$, CH_2Cl_2, 23 °C, 40 min, 45 °C, 12 h, 61%; (iv) H_2 (1 atm), $Pd(OH)_2$, CH_3OH, 23 °C, 24 h, 84%.

Jung's approach (2005)[50]

Jung *et al.* have made use of the regio- and diastereoselective introduction of *N*-protected amine group into the key intermediate **81**. Thus the treatment of ether **81** with chlorosulfonyl isocyanate (CSI) in the presence of sodium carbonate in dry

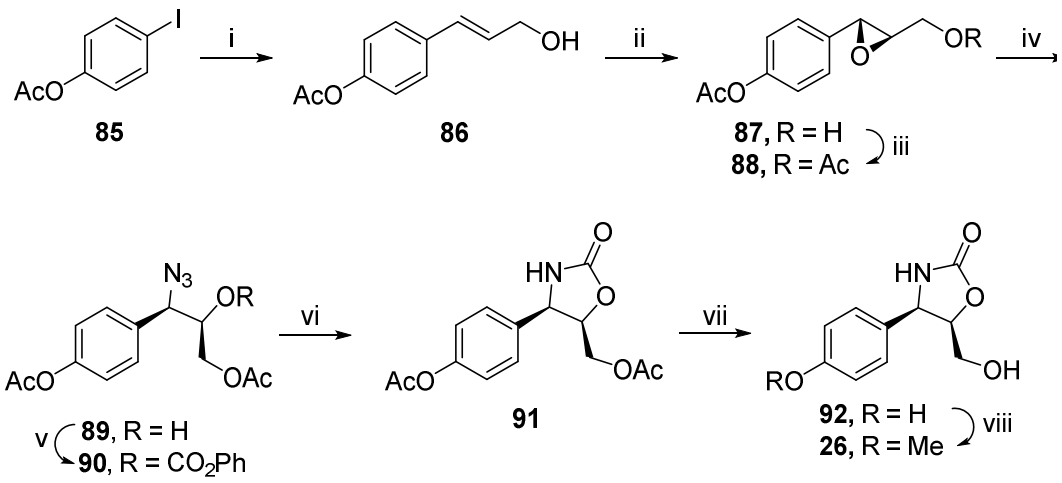
toluene at -78 °C, followed by the reduction of the *N*-chlorosulfonyl group furnished the desired *anti*-1,2-amino alcohol derivative **83** with high diastereoselectivity (27:1). Ozonolysis of the double bond and intramolecular cyclization of **83** using NaH finally gave (-)-cytoxazone (**26**) in 95% yield (**Scheme 23**).



Scheme 23: (i) (a) *β*-[3-((diisopropylamino)dimethylsilyl)allyl]diisopinocamphenyl borane **84**, Et_2O, -78 ºC; (b) H_2O_2, KF, $KHCO_3$, THF-MeOH, 25 ºC, 52%; (ii) MeI, NaH, THF, 0 ºC, 96%; (iii) (a) chlorosulfonyl isocyanate, Na_2CO_3, toluene, -78 ºC; (b) Na_2SO_3, KOH, 25 ºC, 95% (dr = 27:1); (iv) (a) O_3, -78 ºC then $NaBH_4$, 0 ºC, CH_2Cl_2-MeOH, 94%; (b) BBr_3, CH_2Cl_2, 0 ºC, 80%; (v) NaH, THF, 0 ºC, 95%.

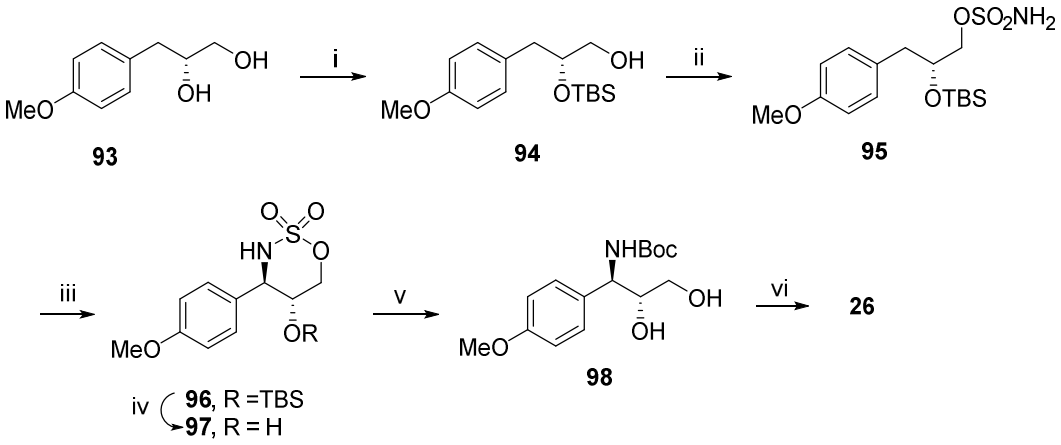
Sudalai's approach (2006, 2007 & 2015)[51]

Sudalai *et al*. have developed a simple method for the enantioselective synthesis of (-)-cytoxazone **26** using Sharpless asymmetric epoxidation as the key step. Thus, asymmetric epoxidation of allyl alcohol **86** gave chiral epoxide **87**, which was further acylated to give acetate **88**. The nucleophilic opening of the epoxide **88** at the benzylic position with NaN_3 gave azido alcohol **89** in 88% yield. The protection of the alcohol followed by reductive cyclization with PPh_3 and deprotection of acetate group gave oxazolidinone **91**, which was directly subjected to methylation with methyl iodide in the presence of NaH to afford (-)-cytoxazone (**26**) in 65% yield and 83% ee (**Scheme 24**).



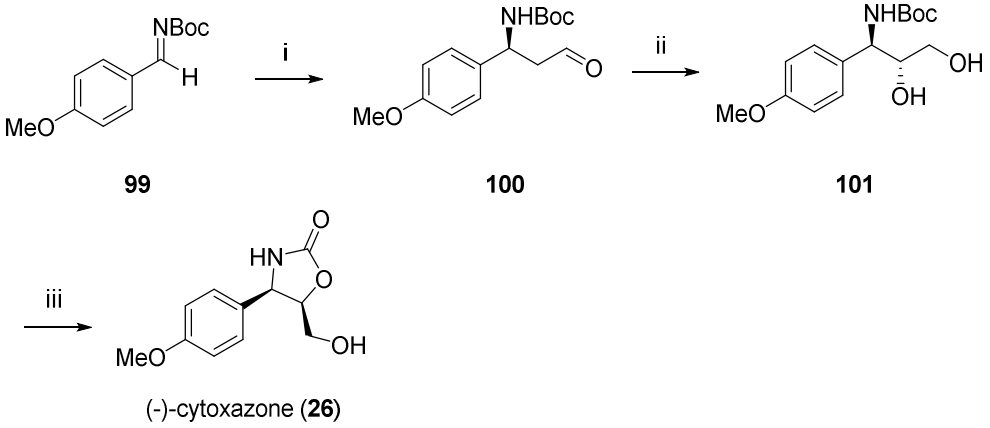
Scheme 24: (i) Allyl alcohol, AgOAc, $Pd(OAc)_2$, PPh_3, DMF, 70 ºC, 16 h, 81%; (ii) anhyd. 5.4 M TBHP in CH_2Cl_2, 4 Å MS, $Ti(O^iPr)_4$, (+)-DIPT, CH_2Cl_2, -20 ºC, 20 h, 78%; (iii) AcCl, Et_3N, DMAP, CH_2Cl_2, 25 ºC, 87%; (iv) NaN_3, NH_4Cl, THF:H_2O (2:1), 50 ºC, 3 h, 79%; (v) PhOCOCl, Py., CH_2Cl_2, -5 to 25 ºC, 1 h, 93%; (vi) PPh_3, THF:H_2O (10:1), 50 ºC, 2 h, 87%; (vii) aq $NaHCO_3$, MeOH, reflux, 1 h; (viii) NaH, MeI, THF, 0-25 ºC, 3 h, 69%, 83% ee.

In the second approach, Sudalai *et al*. have commenced from the diol **93** obtained by two different routes: hydrolytic kinetic resolution and proline-catalyzed α-aminooxylation. Diol **93** was converted to *bis*-TBS-protected silyl ether followed by selective deprotection of the primary hydroxyl group with camphorsulfonic acid to afford **95.** γ-C-H insertion of **95** was carried out with catalytic amount of $Rh_2(OAc)_4$ (2 mol %), $PhI(OAc)_2$ and MgO in CH_2Cl_2 to afford sulfamate ester **96** in 76% yield with *anti* (10:1) diastereoselectivity. The TBS deprotection, carbamoylation and ring opening of *N*-Boc protected oxathiazinane furnished the *anti*-amino alcohol **98** in 84% yield, which was converted to (-)-cytoxazone (**26**) by intramolecular cyclization using NaH in THF (**Scheme 25**).



Scheme 25: (i) (a) TBSCl, imid., DMF, 25 °C, 4 h, 98%; (b) CSA, MeOH, 95%; (ii) HCO_2H, chlorosulfonyl isocyanate, 0 °C, 76%; (iii) $Rh_2(OAc)_4$ (2 mol %), $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 2 h, 82%, *anti*:*syn* (10:1); (iv) (a) CSA, MeOH, 25 °C, 1 h, 97%; (b) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 25 °C, 1 h; (v) CH_3CN:H_2O (4:3), 60 °C, 4 h, 84%; (vi) NaH, THF, 0 °C, 1 h, 96%.

In yet another approach, Sudalai *et al.* have achieved the synthesis of (-)-cytoxazone (**26**) commencing from *L*-proline catalyzed Mannich reaction of arylaldimine **99** with acetaldehyde affording β-aminoaldehyde **100** in 56% yield. β-Aminoaldehyde **100** was then subjected to α-aminoxylation reaction giving α-aminoxyaldehyde, which was *in situ* reduced with $NaBH_4$, followed by subsequent reduction of the crude aminoxy product with $Cu(OAc)_2.H_2O$ that provided a single diastereomer of *anti*-



Scheme 26: (i) CH_3CHO, *L*-proline (20 mol %), CH_3CN, 0 °C, 3 h, 56%; (ii) (a) PhNO (0.8 equiv), *L*-proline (20 mol %), CH_3CN, -10 °C, 18 h; then $NaBH_4$, CH_3OH, 0 °C, 10 min; (b) $Cu(OAc)_2.H_2O$, CH_3OH, 25 °C, 16 h, 68% (over two steps); (iii) NaH, dry THF, 25 °C, 3 h, 90%.

-3-amino-1,2-diol **101** in 68% yield and 92% ee. Finally, the regioselective intramolecular cyclization of **101** using NaH in THF gave (-)-cytoxazone (**26**) in 90% yield and 95% ee (**Scheme 26**).

3.2.4 Present Work

3.2.4.1 Objective

Even though several methods are reported for the synthesis of chloramphenicol (**25e**) and cytoxazone (**26**), an economical method is yet desirable which would effectively produce the target molecules in lesser number of steps, higher overall yields and high diastereoselectivity. In this context, we envisioned to utilize our I_2-catalyzed diastereoselective azidohydroxylation strategy for forming the key 1,2-azido alcohol unit.

Retrosynthetic analysis (**Fig. 6**) for (±)-chloramphenicol (**25e**) reveals that it can be obtained from *syn* azido diol derivative **2m** following a reduction-protection-nitration sequence. The *syn* azido diol **2m** can be envisioned from cinnamyl alcohol (**1m**) through our regio- and diastereoselective I_2-catalyzed azidohydroxylation strategy. A similar retrosynthetic plan can be designed for (±)-cytoxazone (**26**) which can be envisioned from *anti* azido diol **3n** following a reduction-protection sequence and *anti* azido diol **3n** can in turn be obtained by I_2-catalyzed azidohydroxylation reaction of 4-methoxycinnamyl alcohol (**1n**).

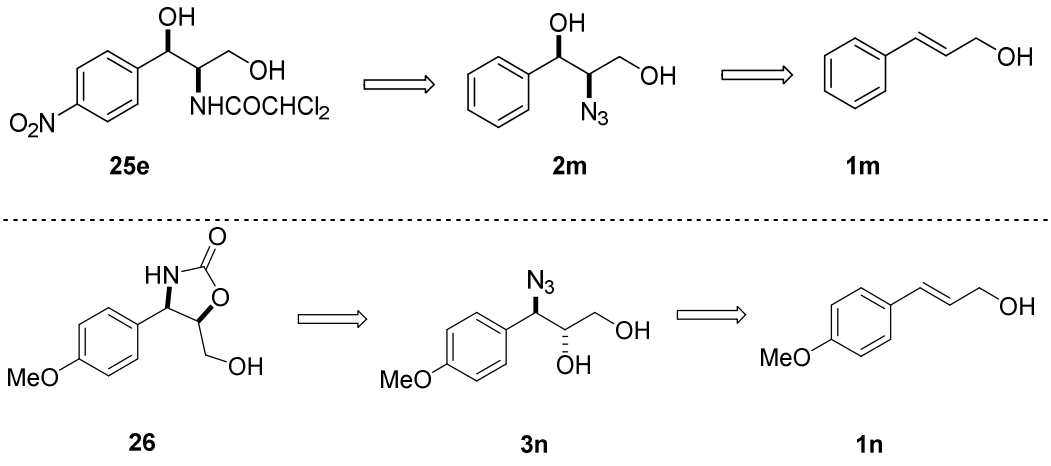
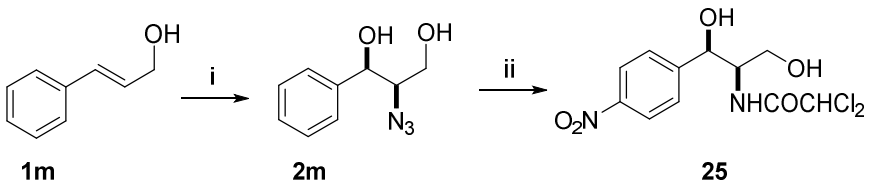


Fig. 6: Retrosynthetic analysis of (±)-chloramphenicol (**25e**) and (±)-cytoxazone (**26**)

3.2.5 Results and Discussion

3.2.5.1 Synthesis of (±)-Chloramphenicol

Complete synthetic sequence for chloramphenicol (**25e**) wherein I_2-catalyzed azidohydroxylation constitutes the key reaction is outlined in **Scheme 27**. Our synthesis of chloramphenicol (**25e**) commenced with *syn*-diastereoselective azidohydroxylation of commercially available cinnamyl alcohol (**1m**) to afford azido diol **2m** in 80% yield and high diastereoselectivity (*syn*:*anti* = 98:2). The formed product **2m** was thoroughly characterized by NMR spectroscopic techniques, HRMS,



Scheme 27: (i) I_2 (10 mol %), Et_3N (1 equiv), 5-6 M TBHP in decane (2 equiv), NaN_3 (2 equiv), DMSO:DMF (1:1), 0 °C to 25 °C, 8 h, 80%, dr = 98:2 (*syn:anti*); (ii) (a) H_2 (1.1 atm), 10% Pd/C, MeOH, 25 °C, 4 h; (b) Cl_2CHCO_2Me (1 equiv), MeOH, 25 °C; (c) conc. HNO_3: conc. H_2SO_4 (1:1), - 20 to 0 °C, 2 h, 70% (3 steps).

IR and HPLC analysis. The proton NMR spectrum of **2m** showed a characteristic signal for benzylic methine proton at δ 4.85 (t, *J* = 6.5 Hz, 1H) while diastereotopic methylene protons attached to hydroxyl group (-C**H**$_2$OH) appeared as multiplet between δ 3.46-3.75 (m, 2H) integrating for two protons. The structure was further substantiated by its ^{13}C NMR spectrum, which featured benzylic methine carbon signal at δ 74.8 while the aromatic carbon signals appeared in the deshielded region at δ 126.4, 128.5, 128.8 and 140.2 (**Fig. 7**). The formed product **2m** was then subjected to a reduction-protection and nitration sequence in that order. Thus, catalytic hydrogenation of **2m** in MeOH afforded amino diol. The formed crude product was filtered to remove Pd/C catalyst and the filtrate was treated with methyl 2,2-dichloroacetate to obtain selectively protected amino diol which was concentrated and

the crude product was regioselectively nitrated at *para* position at low temperature to afford the target molecule chloramphenicol (**25e**). The formed product was confirmed

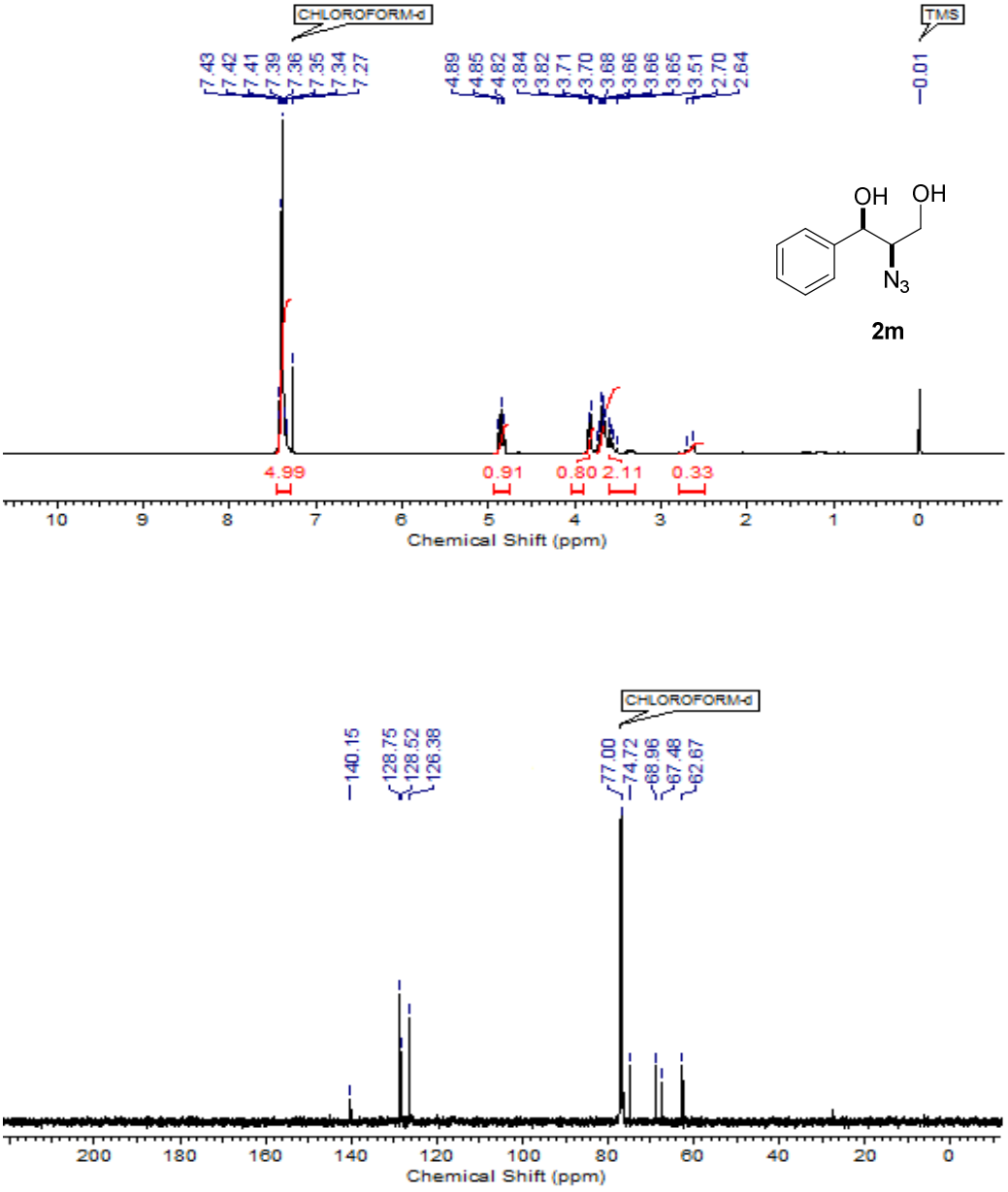


Fig. 7: ^{1}H and ^{13}C NMR spectra of **2m**

by spectroscopic techniques. Its ^{1}H NMR spectrum showed two doublets at δ 7.60 (d, J = 8.5 Hz, 2H) and 8.09 (d, J = 8.5 Hz, 2H) typical of a *para* disubstituted benzene ring. Further, methine proton bearing geminal dichloro groups (-C**H**Cl_2) appeared as a

singlet at δ 6.10. Its ^{13}C NMR spectrum displayed a typical amide carbonyl carbon signal at δ 164.4 and a signal for methine carbon (attached to the germinal dichloro groups) appeared at δ 70.6 (**Fig. 8**).

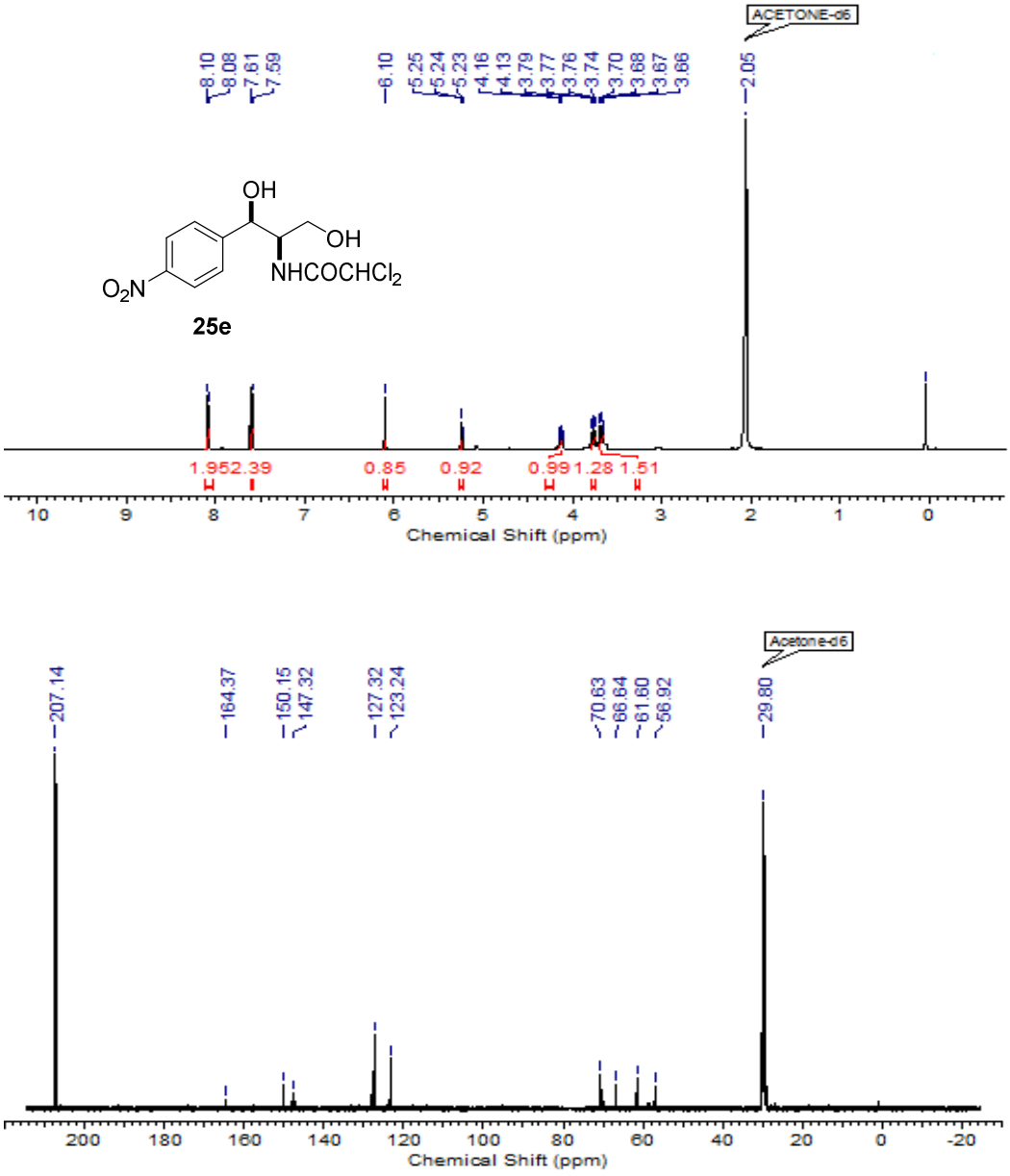
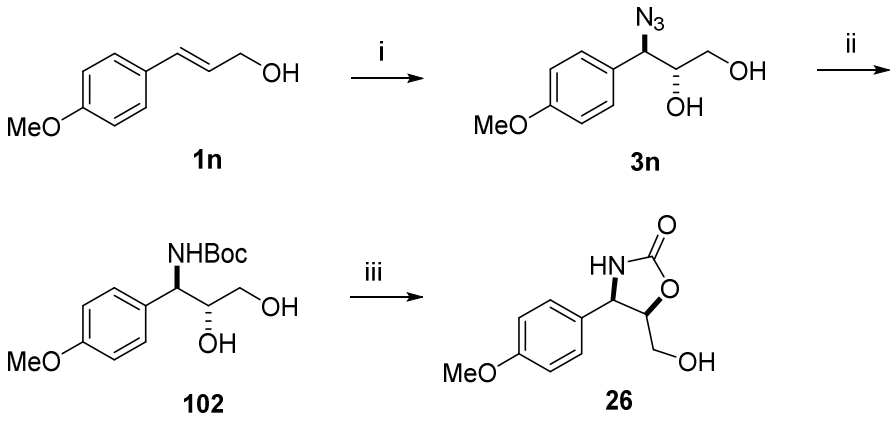


Fig. 8: ^{1}H and ^{13}C NMR spectra of **25e**

3.2.5.2 Synthesis of (±)-Cytoxazone

Our synthesis of cytoxazone (**26**), wherein I_2-catalyzed azidohydroxylation constitutes the key step of the synthesis is outlined in **Scheme 28**. The synthesis commenced with regio- and diastereoselective azidohydroxylation of allylic alcohol derivative 4-methoxycinnamyl alcohol (**1n)** to afford *anti*-azido diol **3n** (*anti:syn* = 92:8) which was thoroughly characterized by NMR spectroscopy, HRMS, HPLC and IR. Compound **3n** showed typical doublets in the aromatic region corresponding to the



Scheme 28: (i) **:** (i) I_2 (10 mol %), Et_3N (1 equiv), 50% aq. H_2O_2 (2 equiv), NaN_3 (2 equiv), DMSO:DMF (1:1), 0 °C to 25 °C, 8 h, 80%, dr = 92:8 (*anti:syn*); (ii) (a) H_2 (1.1 atm), 10% Pd/C, MeOH, 25 °C, 12 h; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 25 °C, 2 h, 76% (2 steps); (iii) NaH (2 equiv), THF, 0 to 25 °C, 3 h, 90%.

para disubstituted aromatic ring at δ 6.92 (d, J = 8.7 Hz, 2H) and 7.27 (d, J = 8.7 Hz, 2H) in its proton NMR spectrum. The signal corresponding to the benzylic methine proton appeared at δ 4.52 (d, J = 7.2 Hz, 1H). The product formation was further corroborated by studying its ^{13}C NMR spectrum, which featured signal at δ 73.9 corresponding to the benzylic carbon (-**C**HN_3) while methoxyl carbon displayed a typical signal at δ 55.2 (**Fig. 9**). The value of diastereomeric ratio was obtained by ^{13}C NMR spectrum and HPLC analysis. The product **3n** was then subjected to catalytic hydrogenation conditions to afford amino diol, followed by *in situ* protection of

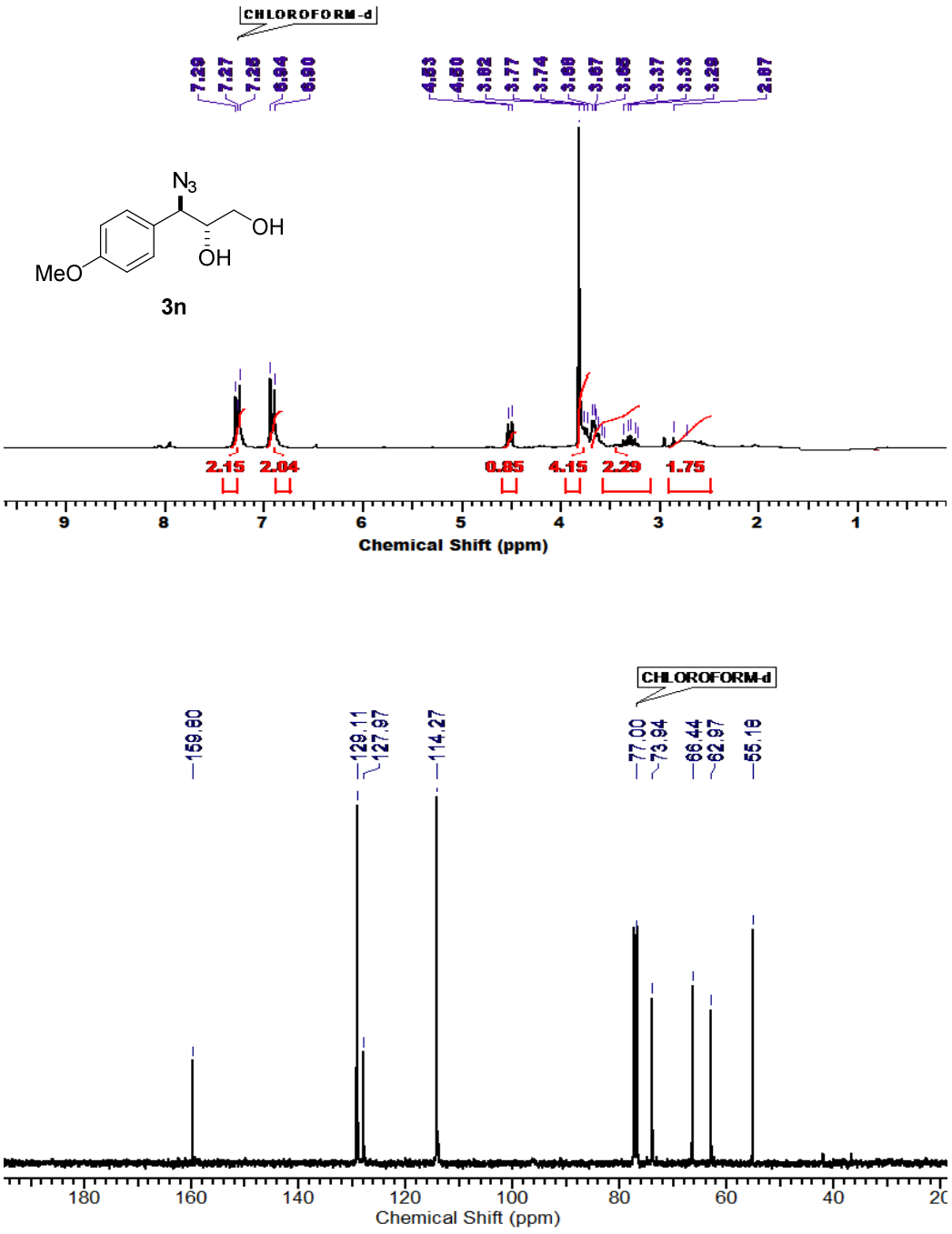


Fig. 9: ^{1}H and ^{13}C NMR spectra of **3n**

-NH_2 functionality with Boc anhydride to produce **102**. Product **102** featured typical singlet corresponding to methyl protons of the Boc group at δ 1.34 in its proton NMR spectrum. While its ^{13}C NMR spectrum displayed a typical carbon signal at δ 159.2 corresponding to Boc carbonyl carbon (**Fig. 10**).

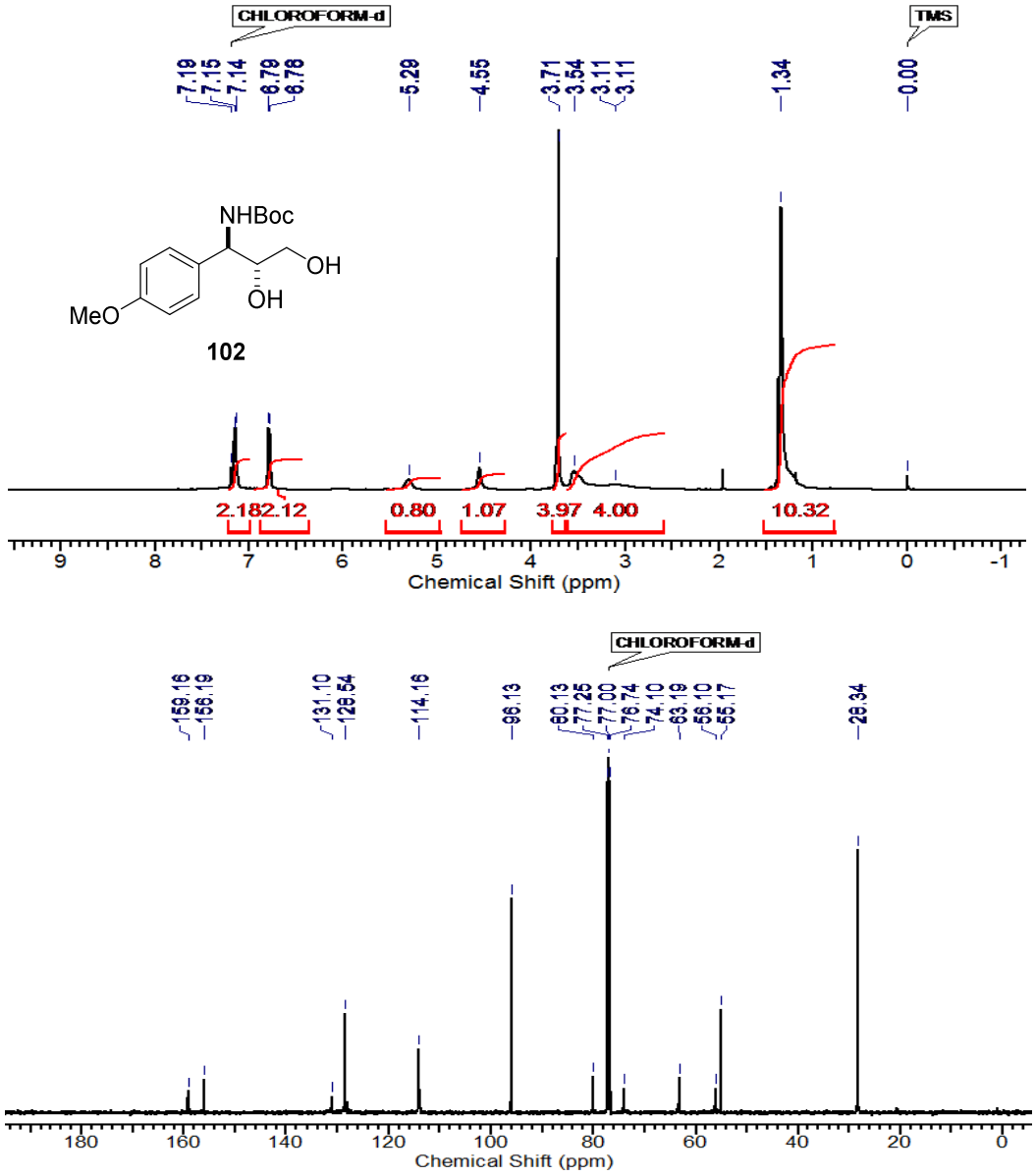


Fig. 10: ^{1}H and ^{13}C NMR spectra of **102**

Finally, NaH-mediated cyclization in THF gave (±)-cytoxazone (**26**) in 90% yield. The ^{1}H NMR spectrum of (-)-cytoxazone (**26**) showed a typical singlet at δ 7.98 for (N-**H**) proton of oxazolidinone ring. Its ^{13}C NMR spectrum showed a characteristic signal at δ 158.9 due to the carbonyl carbon of oxazolidinone ring (**Fig. 11**). The

spectral data of (-)-cytoxazone (**26**) were in complete agreement with that of the reported values.[51]

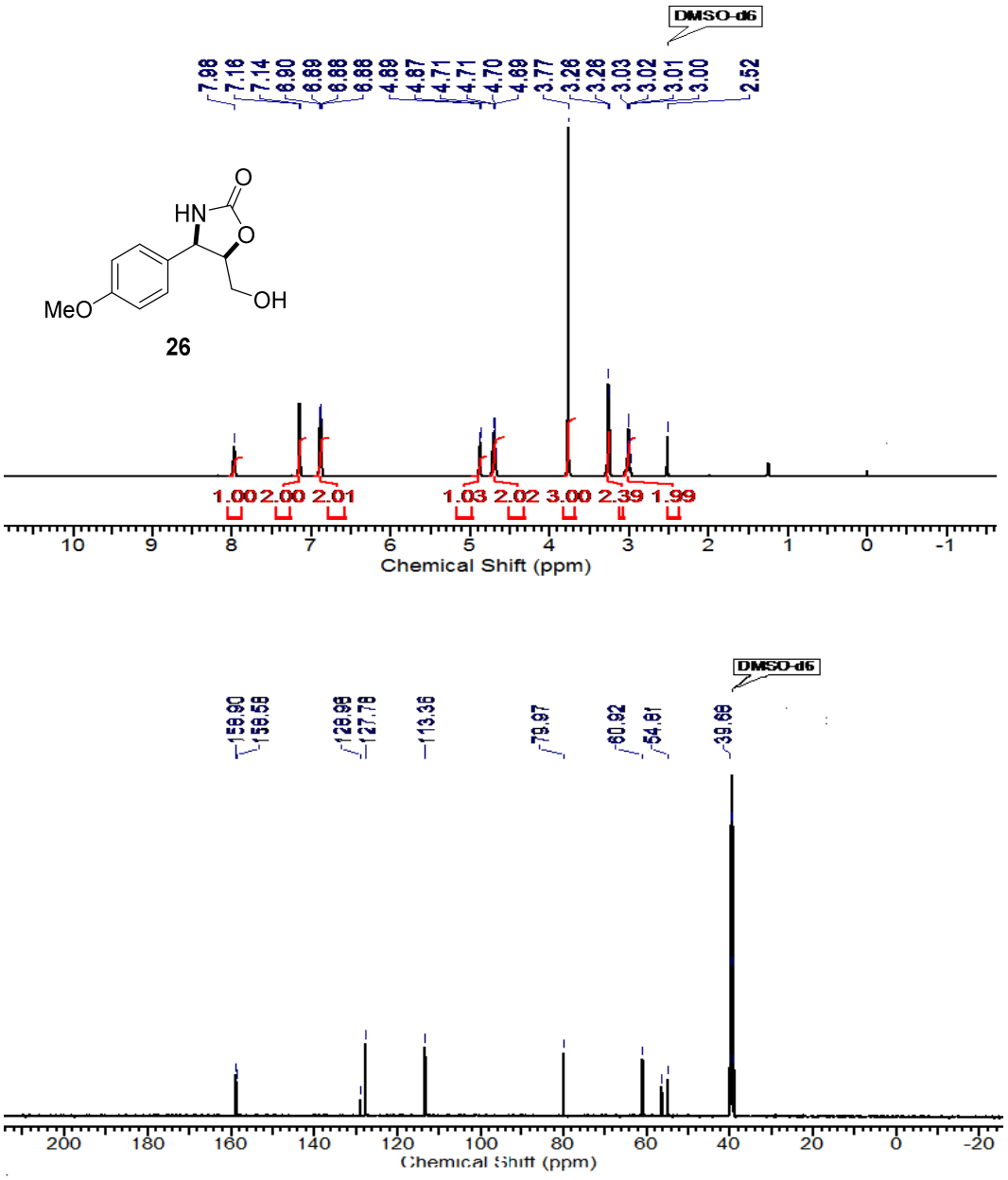


Fig. 11: ^{1}H and ^{13}C NMR spectra of **26**

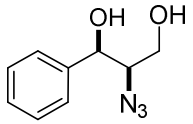
3.2.6 Conclusion

To summarize, I_2-catalyzed azidohydroxylation strategy has successfully been employed to the concise and highly diastereoselective syntheses of (±)-chloramphenicol (**25e**) and (±)-cytoxazone (**26**). The target molecules, chloramphenicol and cytoxazone have been synthesized in four simple steps each with an overall yield of 56.4% and 54.7% respectively. The present protocol comprises of lesser number of steps and higher overall yields contrary to the reported methods. Again, we believe that this will be a flexible and economically viable synthetic route for the synthesis of other amino alcohols containing drugs and natural products.

3.2.7 Experimental section

3.2.7.1 Synthesis of Chloramphenicol (25e)

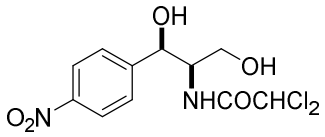
***syn*-2-Azido-1-phenylpropane-1,3-diol (2m)**



To a stirred solution of cinnamyl alcohol (10 mmol, 1.34 g) in DMSO:DMF (40 mL:40 mL) at 0 °C was added I_2 (10 mol %, 0.253 g) followed by dropwise addition of 5-6 M TBHP in decane (20 mmol, 3.60 mL). The addition of Et_3N (10 mmol, 1.3 mL) was then done slowly (slow decolorisation of reaction mixture was observed) and finally sodium azide (20 mmol, 1.28 g) was added portionwise. The reaction mixture was then allowed to stir at room temperature for 8 h (monitored by TLC). After completion, the reaction mixture was cooled to 0 °C and excess sodium azide was quenched with water. Organic layer was diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were repeatedly washed with saturated brine solution, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography [silica gel (230-400 mesh)] using Pet. ether:EtOAc (8:2) as an eluent to afford the corresponding vicinal azido alcohol (**2m**) in 80% yield.

Yield: 80% (1.7 g), colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 761, 1219, 1605, 2105, 2893, 2933, 3013, 3416; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.64 (br. s., 1H), 2.70 (br. s, 1H), 3.51-3.73 (m, 2H), 3.83 (d, *J* = 4.7 Hz, 1H), 4.85 (t, *J* = 6.5 Hz, 1H), 7.34-7.43 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 62.8, 67.0, 74.0, 126.5, 127.8, 128.9, 136.2; **HRMS** calcd for [$(C_9H_{11}N_3O_2+Na)^+$] 216.0749 found: 216.0736.

(±)-Chloramphenicol (25e)

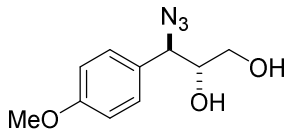


To a stirred solution of azidoalcohol (**2m**) (1.5 g, 7.7 mmol) in methanol (40 mL) was added 20% $Pd(OH)_2/C$ (~50 mg) carefully at room temperature and the reaction mixture was stirred under H_2 atmosphere (balloon pressure). After the completion of the reaction as monitored by TLC, it was filtered over celite and the filtrate was concentrated under reduced pressure to give aminodiol, to which was added methyl dichloroacetate (3 mL) and heated at 90 °C for 1 h. The excess ester was removed under reduced pressure to give the crude product. To a stirred solution of conc. HNO_3: conc. H_2SO_4 (1:1) (5 mL) was added the crude product at -20 °C, the resulting solution was stirred for 1.5 h at 0 °C. After the completion of the reaction as monitored by TLC, it was poured into water and extracted with diethylether (3 x 50 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by flash column chromatography [silica gel (230-400 mesh)] using Pet. ether:EtOAc (6:4) as an eluent to afford chloramphenicol (**25e**) in 71% yield (over the three steps).

Yield: 71% (1.8 g), colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 850, 1049, 1216, 1348, 1416, 1454, 1523, 1604, 1686, 2929, 3020, 3420; **^{1}H NMR** (400 MHz, acetone-d_6): δ 3.58-3.88 (m, 2H), 4.09-4.17 (m, 1H), 4.52 (br. s., 3H), 5.25 (s, 1H), 6.10 (s, 1H), 7.60 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, acetone-d_6): δ 55.9, 60.6, 65.7, 69.6, 122.3, 126.3, 146.3, 149.2, 163.4; **HRMS** calcd for $[(C_{11}H_{12}Cl_2N_2O_5+Na)^+]$ 345.0015; found: 345.0009.

3.2.7.2 Synthesis of (±)-Cytoxazone (26)

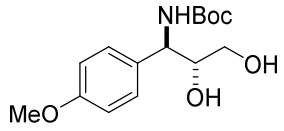
***anti*-3-Azido-3-(4-methoxyphenyl)propane-1,2-diol (3n)**



To a stirred solution of 4-methoxycinnamyl alcohol (1.0 g, 6 mmol) in DMSO:DMF (20 mL:20 mL) at 0 °C was added I_2 (10 mol %) followed by dropwise addition of 50% aqueous H_2O_2 (12 mmol, 0.816 mL). The addition of Et_3N (6 mmol, 0.833 mL) was then done slowly (vigorous decolorisation of reaction mixture was observed) and finally sodium azide (12 mmol, 780 mg) was added pinchwise which was then allowed to stir at room temperature for 8 h (monitored by TLC). Organic layer was diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were repeatedly washed with saturated brine solution, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography [silica gel (230-400 mesh)] using Pet. ether:EtOAc (8:2) as an eluent to afford corresponding vicinal azido alcohol **3n** in 80% yield.

Yield: 80% (1.08 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1035, 1195, 1513, 1616, 2100, 2920, 3050, 3368 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.73 (br. s., 1H), 3.21-3.68 (m, 2H), 3.74-3.82 (m, 4H), 4.52 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.2, 63.0, 66.4, 73.9, 114.3, 128.0, 129.1, 159.8; **HRMS** calcd for [$(C_{10}H_{13}N_3O_3+H)^+$] 224.1035 found: 224.1036.

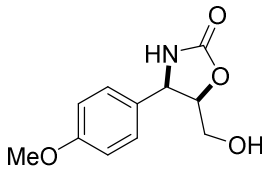
***tert*-Butyl-*anti*-2,3-dihydroxy-1-(4-methoxyphenyl)propyl)carbamate (102)**



To a stirred solution of azido alcohol **3n** (0.5 g, 2.2 mmol) in MeOH (20 mL) was added 20% $Pd(OH)_2/C$ (25 mg) carefully at room temperature and was stirred under hydrogen atmosphere. After completion of the reaction (as monitored by TLC), it was filtered over celite and the filtrate was concentrated under reduced pressure to give aminodiol which was dissolved in CH_2Cl_2. To it was added $(Boc)_2O$ (2.4 m mol, 0.487 g) and Et_3N (4.4 mmol, 0.44 g) and the resulting mixture was allowed to stir at 25 °C for 2 h. After the completion of the reaction (as monitored by TLC), it was poured into water and extracted with diethylether (3 x 50 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography [silica gel (230-400 mesh)] using Pet. ether:EtOAc (6:4) as an eluent to afford compound **102** in 76% yield.

Yield: 76% (496 mg), colorless solid, **mp:** 114-116 ºC; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 669, 757, 831, 927, 1035, 1167, 1216, 1368, 1585, 1612, 1701, 2400, 2839, 2981, 3019, 3438, 3682; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.34 (br. s., 9H), 3.01-3.25 (m, 1H), 3.54 (br. s., 2H), 3.71 (s, 4H), 4.55 (br. s., 1H), 5.29 (br. s., 1H), 6.78 (d, *J* = 5.5 Hz, 2H), 7.15 (d, *J* = 6.7 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 28.3, 55.2, 56.1, 63.2, 74.1, 76.7, 77.3, 80.1, 96.1, 114.2, 128.5, 131.1, 156.2, 159.2; **HRMS** calcd for $[(C_{15}H_{24}NO_5+H)^+]$ 298.1654 found: 298.1650.

(±)-Cytoxazone (26)



To a solution of *anti*-3-amino-1,2-diol **102** (0.3 g, 1.0 mmol) in dry THF (10 mL) was added NaH (0.05 g, 60% w/w, 2.0 mmol) at 25 ºC and the resulting mixture was stirred under inert atmosphere for 3 h. After completion of the reaction (monitored by TLC), excess base was quenched slowly with ice and THF was concentrated under reduced pressure. The crude reaction mixture was worked-up with EtOAc (3 x 10 mL), washed with saturated aq. NH_4Cl (5 mL) and brine solution (5 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using Pet. ether: EtOAc (60:40) as an eluent to give **26** (0.2 g) as a colorless solid.

Yield: 90% (0.2 g), colorless solid, **mp:** 116-118 °C, (lit.[51] **mp**: 115-117 ºC); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 769, 843, 1028, 1248, 1395, 1513, 1610, 1733, 2580, 2924, 3272; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.00-3.03 (m, 2H), 3.26 (t, *J* = 3.7 Hz, 2H), 3.77 (s, 3H), 4.69-4.71 (m, 2H), 4.88 (d, *J* = 8.2 Hz, 1H), 6.89 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.98 (br. s., 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 54.8, 56.3, 60.9, 80.0, 113.4, 127.8, 129.0, 158.6, 158.9; **HRMS** calcd for $[(C_{11}H_{13}NO_4+H)^+]$ 224.0922; found: 224.0920.

3.2.8 References

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CHAPTER IV

Synthesis of α-Ketoesters and Regioselective Azidation of Indoles Assisted by Iodine

1. I_2-Catalyzed Oxidation of Enol Ethers to α-Keto Esters; **Pragati Kishore Prasad** and Arumugam Sudalai; (manuscript under preparation).

2. I_2-Mediated Regioselective Azidation of Indoles; **Pragati Kishore Prasad** and Arumugam Sudalai; (manuscript under preparation).

Section I

I_2-Catalyzed Oxidation of Enol Ethers to α-Keto Esters

4.1.1 Introduction

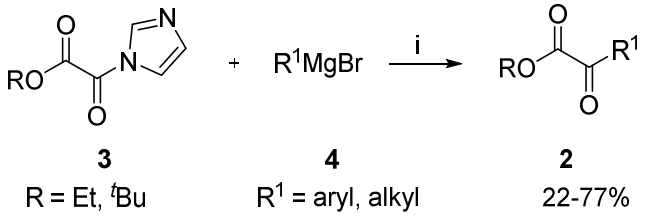
α-Keto esters play a vital role in biological processes. They serve as backbone in natural products, such as the 3-deoxy-2-ulosonic acids and their derivatives.[1] In addition, aryl α-keto esters are also used as key intermediates for the synthesis of bioactive compounds such as potent inhibitors of proteolytic enzymes,[2] inhibitors of leukotriene A4 hydrolase,[3] photopolymerization initiators[4] and precursors in the asymmetric synthesis of α-hydroxy carboxylic acids.[5] α-Keto esters also show antisunburn effects.[6] In the past several decades, considerable attention has been laid on the synthesis of α-keto esters since Berzelius synthesized first α-keto acid, pyruvic acid in 1835.[7] α-Keto acid analogues of the naturally occurring amino acids, are of major importance in intermediary metabolism. For instance, pyruvic acid is a metabolite involved in a number of enzyme catalyzed intracellular phenomena and oxaloacetic acid, α-ketoglutaric acid and oxalosuccinic acid are intermediates in the tricarboxylic acid cycle. The α-keto acid analogues of the protein amino acids are often the penultimate products formed in the biosynthesis of amino acids and are commonly the first product formed in the degradative metabolism of amino acids. Certain α-keto acids accumulate in the blood and tissues in pathological conditions. Recently, α-keto acid derivatives have been used in the therapy of certain conditions *e.g.* uremia and nitrogen accumulation disorders. They are of continuing interest as intermediates in chemical synthesis, in the development of enzyme inhibitors and drugs, as model substrates of enzymes etc.

4.1.2 Review of Literature

There are quite a number of reports available for the synthesis of α-keto esters. Typical ones are described below:

Mosher's approach (1981)[8]

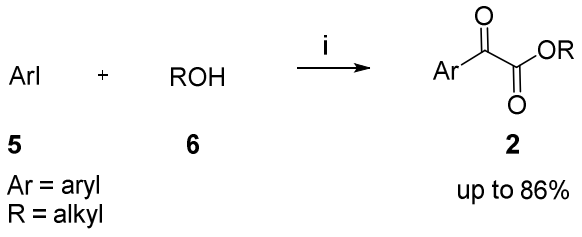
Mosher *et al.* have reported the synthesis of α-keto esters **2** directly from the reaction of acylimidazolides **3** and Grignard reagents **4** to yield ketones without any significant further reaction to give tertiary alcohols. However, products were obtained in low yields (22-26%) in case of aliphatic Grignard reagents (**Scheme 1**).



Scheme 1: (i) R^1MgBr (1 equiv), imidazole (1.5 equiv), THF, 1 h, 25 °C, 3 h, 22-77%.

Tanaka's approach (1987)[9]

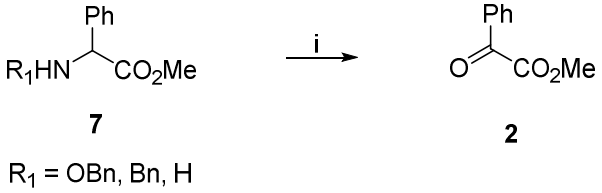
Tanaka *et al.* have applied the first successful double carbonylation approach to yield α-keto esters **2** from aryl iodides *via* Pd catalysis. A three component matrix comprising of aryl iodide **5**, CO gas and alcohol **6** were used in the synthetic preparation (**Scheme 2**). However, the process warranted the use of CO at huge pressure (150-300 atm).



Scheme 2: (i) $PdCl_2[(P(Et)_3]_2$ (1 mol %), $Ca(OH)_2$ (1.25 equiv), CO (300 atm), ROH (2.5 equiv), 100 °C, 12 h, up to 86%.

Miller's approach (1988)[10]

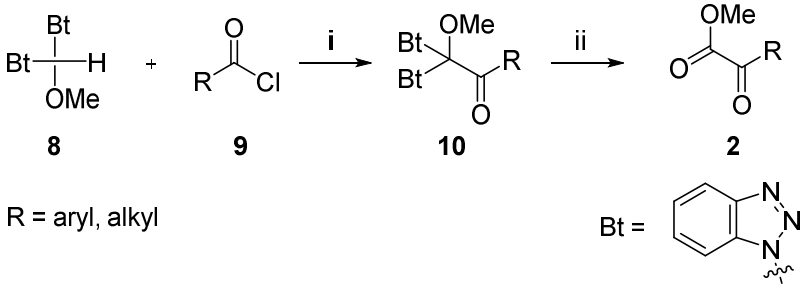
Miller *et al.* have described the reactions of α-amino acid derivatives **7** with azodicarboxylates and PPh_3 that resulted in the oxidation of α-carbon. *N*-acyl or carbamoyl amino acid esters gave azodicarboxylate adducts, whereas free α-amino acid esters were converted to the corresponding α-keto esters **2** in quantitative yields (**Scheme 3**).



Scheme 3: (i) PPh_3 (1.5 equiv), DIAD (2.5 equiv), THF, 25 °C, 12 h, quant.

Katritzky's approach (1995)[11]

Katritzky *et al.* have described a two step sequence to obtain α-ketoesters **2** starting from lithiation of 1,1-di-(benzotriazo-1-yl)-1-methoxymethane (**8**) and acyl chloride **9** followed by acidic hydrolysis in presence of amberlite resin (**Scheme 4**).

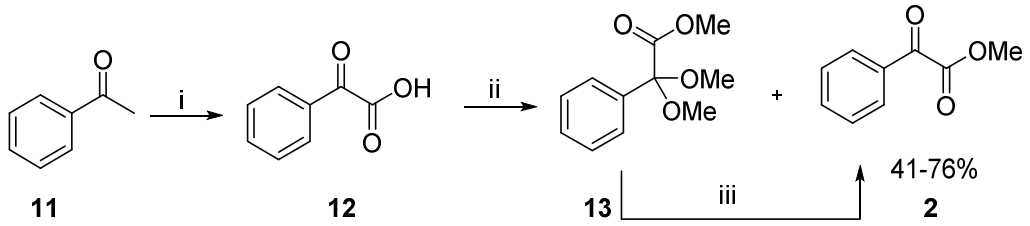


Scheme 4: (i) LDA (2 equiv), **8** (1 equiv), THF, -78 to -25 °C, 12 h, 95%; (ii) Amberlite (proton exchange resin), MeOH:H_2O (15% w/w), 80 °C, 12 h, 79-92%.

Zhang's approach (2009)[12]

Zhang *et al.* have reported a novel "one-pot" synthesis of aryl α-keto esters **2** through oxidation of aryl ketones **11** using selenium dioxide; esterification accompanied by

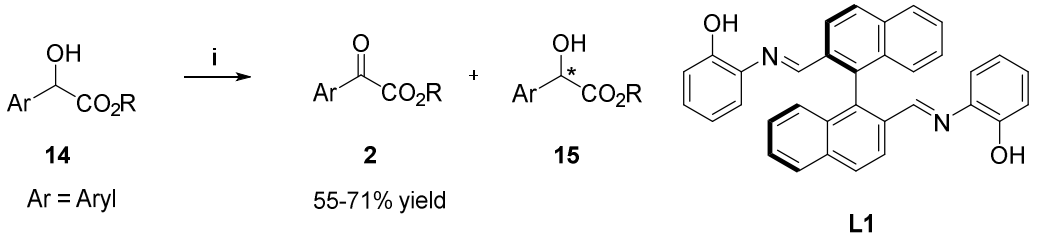
ketalization and hydrolysis. Both aromatics and heteroaromatics afforded α-ketoesters in good yields by this "one-pot" method (**Scheme 5**).



Scheme 5: (i) SeO_2, Py., 120 °C, 18 h; (ii) $SOCl_2$, MeOH, 25 °C, 12 h; (iii) $HClO_4$, CH_3CN, H_2O, 25 °C, 0.5 h, 41-76% (for 3 steps).

Sekar's approach (2010)[13]

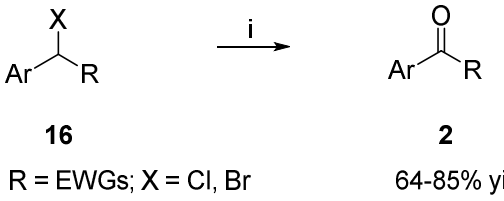
Sekar *et al.* have reported the conversion of α-hydroxy esters **14** to α-keto esters **2** under aerial conditions. The reaction focuses on the Co-catalyzed enantioselective kinetic resolution of α-hydroxy esters to afford chiral alcohol **15** in presence of chiral ligand **L1**. Nevertheless, in the process, keto esters are produced in moderate to good yields (**Scheme 6**).



Scheme 6: (i) **L1**-$Co(OAc)_2$ (10 mol %), TEMPO (5 mol %), O_2, toluene, 90 °C, 6 to 40 h, 55-71%.

Jiao's approach (2011)[14]

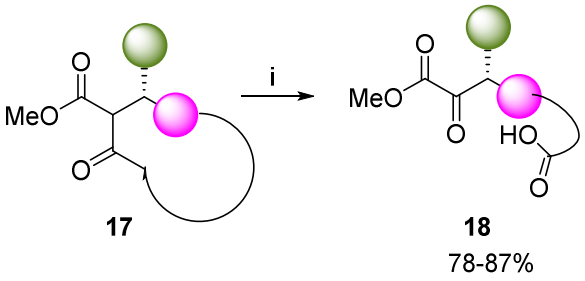
Jiao *et al.* have reported an efficient oxidation of α-halo esters **16** to the corresponding α-ketoesters **2** at room temperature. Natural sunlight and air were successfully utilized in this approach through the combination of photocatalysis and organocatalysis (**Scheme 7**).



Scheme 7: (i) $Ru(bpy)_3Cl_2$ (0.5 mol %), $LiCO_3$ (1 equiv), 4-methoxy-pyridine (20 mol %), O_2, hν, DMA, 25 °C, 24 h.

Johnson's approach (2011)[15]

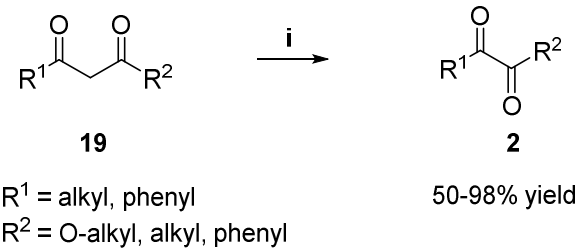
Johnson *et al.* have disclosed a simple method for the preparation of β-stereogenic α-keto esters **18** using a copper(II)-catalyzed aerobic deacylation of substituted acetoacetate esters **17**. The substrates for this process were synthesized from catalytic, enantioselective conjugate additions and alkylation reactions of acetoacetate esters. The reaction conditions do not induce racemization of the incipient enolizable α-keto ester (**Scheme 8**).



Scheme 8: (i) $Cu(NO_3)_2.3H_2O$ (20 mol %), O_2, (balloon pressure), CH_3CN, 25 °C, 78-87%.

Smonou's approach (2013)[16]

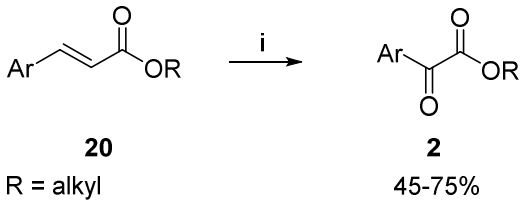
Smonou *et al*. have developed a versatile method for the direct synthesis of α-keto esters **2**. In this approach the oxidative cleavage of a variety of β-keto esters/1,3-diketones **19** mediated by an Oxone/aluminum trichloride system has been described. The one-step oxidation reaction proceeded selectively in aqueous media to afford products in good yields under environmentally benign conditions (**Scheme 9**).



Scheme 9: (i) Oxone (1.0-6.4 equiv), $AlCl_3$ (1.2-4.6 equiv), H_2O, 25 °C, 10 min to 3 h, 50-98%.

Zhao's approach (2014)[17]

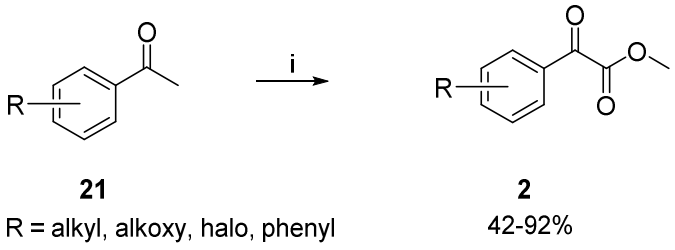
Zhao *et al.* have recently reported a tandem metal-free oxidative aryl migration/ C−C bond cleavage reaction, mediated by hypervalent iodine reagent. The transformation provided straightforward access to important aromatic α-ketoester derivatives **2** from readily available cinnamic acid derivatives derivatives **20** *via* a concerted process of 1,2-aryl shift concomitant with C−C bond cleavage (**Scheme 10**).



Scheme 10: (i) PIDA (3 equiv), conc. H_2SO_4 (1 equiv), EtOAc, 78 °C, O_2, 10 h.

Wang's approach (2013)[18]

Wang *et al.* have developed an anodic oxidation of acetophenones **21** by dioxygen activation under mild conditions, affording α-ketoesters in good yields (**Scheme 11**).

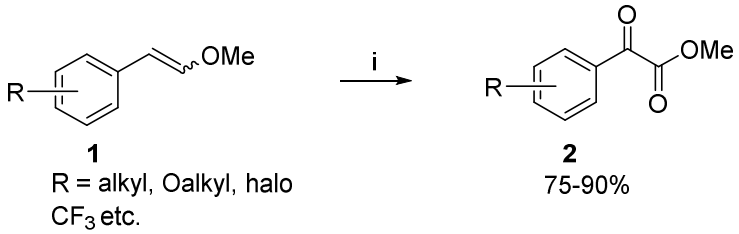


Scheme 11: (i) 2,2,6,6-tetramethylpiperidine (2 equiv), KI (2 equiv), 4-nitrophenol (2 equiv), O_2, MeOH, Pt anode & cathode, 40 mA, 1.5 h, 42-92%.

4.1.3 Present Work

4.1.3.1 Objective

There are quite a number of methods available in literature for the synthesis of α-keto esters. These known methods require highly functionalized starting materials (β-keto esters, enolisable ketones, α,β-unsaturated ketones *etc*.) involving multiple steps. In this context, a more practical and efficient synthesis of α-keto ester derivatives is highly desirable. In this section, a novel I_2-catalyzed oxidation of enol ethers **1** to α-keto esters **2** in high yields is described (**Scheme 12**).



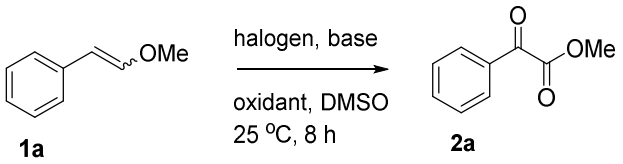
Scheme 12: (i) I_2 (10 mol %), 5-6 M TBHP (2 equiv), Et_3N (2 equiv), DMSO, 25 °C, 8 h, 75-90%.

4.1.3.2 Results and Discussion

Initially, when (2-methoxyvinyl)benzene (**1a**) (1 mmol) was treated with a mixture containing NBS (1 mmol) and Et_3N (2 mmol) at 25 °C in DMSO, the corresponding methyl 2-oxo-2-phenylacetate (**2a**) was obtained in 86% isolated yield (**Table 1**). Encouraged by the result, it was of interest to develop a catalytic version of this useful oxidation process. Thus, a series of experiments were conducted employing I_2 in catalytic amounts (10 mol %) along with other stoichiometric oxidants like aq. H_2O_2, $NaIO_4$, Oxone or TBHP that afforded **2a** in 24, 15, 18 and 76% yields respectively. With 2 mmol of oxidant (TBHP), an enhanced yield (82%) of product was obtained while 5 mol % of I_2 afforded **2a** in a lowered yield (69%). Further modification in iodine source, base or solvent system (DMSO in combination with other solvents) did

not show any improvement in the product yield (**Table 1**). Thus, entry 8[d] was chosen as the best optimised conditions for screening of substrates.

Table 1: I_2-catalyzed oxidation of (2-methoxyvinyl) benzene: optimization studies[a]



1a **2a**

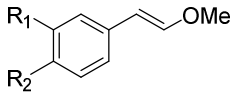
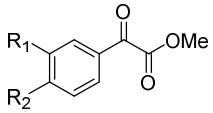
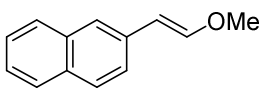
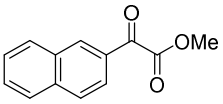
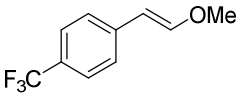
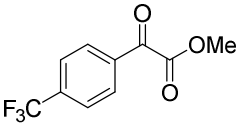
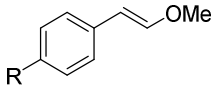
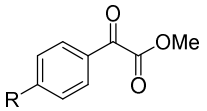
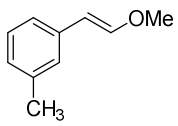
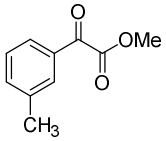
s.no.	halogen source (10 mol %)	oxidant (1 equiv)	base (2 equiv)	yield of **2a**[b] (%)
1	NBS[c]	-	Et_3N	86
2	I_2[c]	-	Et_3N	85
3	I_2	50% aq. H_2O_2	Et_3N	24
4	I_2	$NaIO_4$	Et_3N	15
5	I_2	Oxone	Et_3N	18
6	NaI	TBHP	Et_3N	trace
7	nBu$_4$NI	TBHP	Et_3N	11
8	I_2	TBHP	Et_3N	76 (82)[d] (69)[e]
9	I_2	TBHP	NaH	45
10	I_2	TBHP	DBU	63
11	I_2	TBHP	K_2CO_3	44

[a] Reaction conditions: enol ether (1 mmol), halogen source (10 mol %), base (2 mmol), TBHP (5-6 M in decane) (1 mmol), 8 mL DMSO, 25 °C, 8 h; [b] isolated yield after column chromatographic purification; [c] 1 equiv of halogen source was used; [d] 2 mmol of TBHP was used; [e] 5 mol % of I_2 was used.

The scope of the study was then extended to variously substituted styrenics; the results of which are displayed in **Table 2**. Several methyl vinyl ethers **1a-i** with varied functional groups were found to be compatible under the reaction conditions. Electron neutral (3-CH_3), electron-deficient (4-CF_3) and electron-rich (-OCH_3) groups on the aromatic nucleus smoothly underwent the transformation providing the corresponding products in excellent yields (75-90%). It was observed that substrates with electron-

rich substitution on aromatic ring afforded products in better yields (entries 2&3) than substrates having electron-withdrawing substituents (entries 5&7).

Table 2: I_2-catalyzed oxidation of (2-methoxyvinyl) benzene derivatives: substrate scope[a]

Substrates (**1a-i**)	products (**2a-i**)[b]
	
1a : $R_1 = R_2 = H$	**2a** : $R_1 = R_2 = H$; 82%
1b : $R_1 = R_2 = OCH_3$	**2b** : $R_1 = R_2 = OCH_3$; 88%
1c : $R_1 = R_2 =$ -O-CH_2-O-	**2c** : $R_1 = R_2 =$ -O-CH_2-O-; 90%
	
1d	**2d** : 76%
	
1e	**2e** : 75%
	
1f : R = Br	**2f** : R = Br; 80%
1g : R = F	**2g** : R = F; 79%
1h : R = Cl	**2h** : R = Cl; 82%
	
1i	**2i** : 81%

[a] For reaction conditions, see footnote under Table 1; [b] isolated yield after chromatographic purification.

The formation of all α-keto esters were confirmed unambiguously from their corresponding HRMS, ^1H, ^{13}C NMR and IR spectral data.

Example 1: Methyl 2-(3,4-dimethoxyphenyl)-2-oxoacetate (**2b**) showed three typical singlets in its proton NMR spectrum for the methoxyl protons (3 x -OC**H**$_3$) at chemical shifts of δ 3.91 3.93 and 3.97 integrating for 9 protons. The absence of

signal for the olefinic protons in the region of δ 5-6.5 further confirmed the olefin functionalisation. Its IR spectrum showed two typical absorption bands at 1715 and 1752 cm^{-1} corresponding to ketone and ester C=O stretching frequencies respectively. Its ^{13}C NMR spectrum displayed two characteristic signals at δ 183.9 and δ 164.1 corresponding to the carbonyl carbon of the benzylic ketone and ester carbonyl carbon respectively (**Fig. 1**).

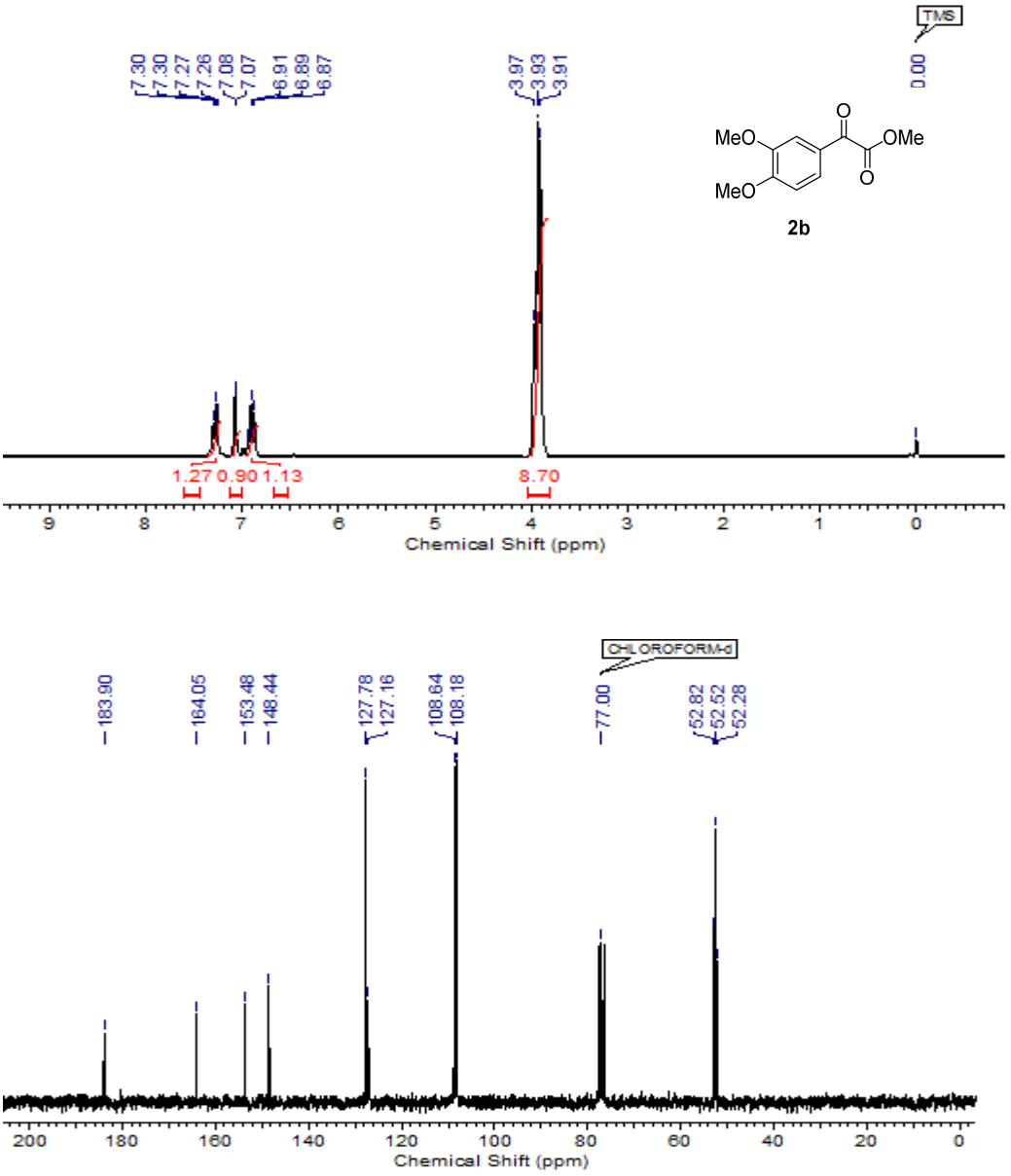
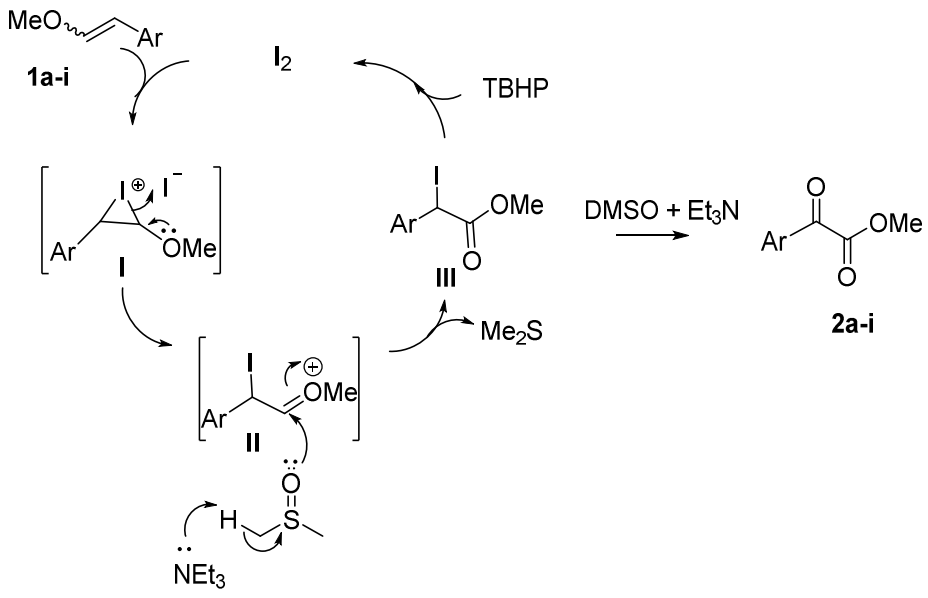


Fig. 1: ^{1}H & ^{13}C NMR spectra of **2b**

To gain an insight into the mechanism of the reaction, the following experiments were performed: (i) No reaction was observed in the absence of either DMSO or Et_3N; (ii) in case of (2-methoxyvinyl)benzene, the iodo compound **III** was isolated (15% yield after 1 h with 1 equiv of I_2 and Et_3N) and characterized. This result eliminates the role of hypervalent iodine in mechanism; (iii) further treatment of **III** with DMSO and another equivalent of Et_3N afforded the desired product **2a** in 62% yield; (iv) **Table 1** (entry 2) suggests that TBHP is a mere co-oxidant in the reaction for regeneration of I_2 and not an *O*-source in the reaction.

According to the aforementioned information and literature precedence,[19] a plausible mechanism for this I_2-catalyzed oxidative functionalization of enol ethers is outlined in **Scheme 13**. Initially, the enol ether substrate **1** reacts with I_2 to afford the iodonium ion intermediate **I**, which undergoes regioselective ring opening by ethereal oxygen lone pair



Scheme 13: Proposed catalytic cycle for α-ketoester synthesis

followed by oxidation with DMSO/Et_3N system to afford iodo intermediate **III** (isolated and characterised by spectroscopic techniques). The proposed key intermediate species **III** is further oxidized at the benzylic position under DMSO/Et_3N conditions[19] to afford α-keto ester by eliminating dimethyl sulphide. Iodide ion is then oxidized with TBHP to regenerate I_2 in the catalytic cycle.

4.1.4 Conclusion

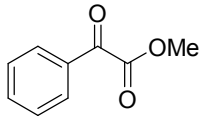
To summarize, we have disclosed for the first time, I_2-catalyzed oxidation of enol ethers leading to the formation of α-ketoesters in high yields (75-90%). This operationally simple method is metal-free, catalytic and can be carried out at room temperature in open flask. A plausible mechanistic cycle has also been proposed based on control experiments and isolated intermediates. We believe that this environmentally benign protocol will find tremendous applications in industrial processes.

4.1.5 Experimental Section

General experimental procedure for the preparation of compounds 2a-i

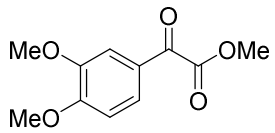
To a stirred solution of enol ether (3 mmol) in dry DMSO (25 mL) at 0 °C was added I_2 (10 mol %), TBHP (6 mmol) and Et_3N (6 mmol). The reaction mixture was then stirred at 25 °C under air for 6 to 8 h. After completion of the reaction (as monitored by TLC), it was diluted with H_2O (20 mL) and EtOAc (20 mL) at 0 °C. The organic layer was separated while the aqueous layer was extracted with EtOAc (3 x 50 mL) followed by washing with brine (3 x 50 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product which was then purified by column chromatography over silica gel using Pet. ether/EtOAc (9:1) as eluent to obtain α-keto ester derivatives **2a-i** in high purity.

Methyl 2-oxo-2-phenylacetate (2a)[12]



Yield: 82% (0.403 g); yellow oil; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 769, 843, 1028, 1248, 1395, 1513, 1610, 1733, 1757, 2580, 2924, 3272; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 52.7, 128.9, 130.1, 132.5, 134.9, 164.0, 186.0; **HRMS** (ESI): calcd for $C_9H_8NaO_3$ + [M + Na^+] 187.0366, found 187.0365.

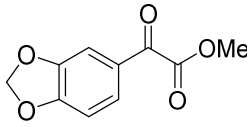
Methyl 2-(3,4-dimethoxyphenyl)-2-oxoacetate (2b)



Yield: 88% (0.590 g); yellow oil; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 775, 1030, 1221, 1396, 1545, 1616, 1722, 1749, 2582, 2925, 3276; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.78-4.04

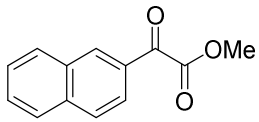
(m, 9H), 6.89 (d, *J* = 8.3 Hz, 1H), 7.02-7.13 (m, 1H), 7.20-7.36 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.3, 52.5, 52.8, 108.2, 108.6, 127.2, 127.8, 148.4, 153.5, 164.1, 183.9; **HRMS** (ESI): calcd for $C_{11}H_{12}NaO_5$ + [M + Na^+] 247.0582, found 247.0585.

Methyl 2-(benzo[*d*][1.3]dioxol-5-yl)-2-oxoacetate (2c)



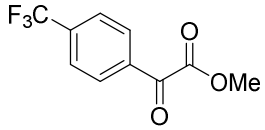
Yield: 90% (0.560 g); colorless oil; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 777, 1076, 139522, 1555, 1633, 1725, 1751, 2582, 2926, 3270; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.33 (s, 1H), 6.85-6.94 (m, 2H), 7.00 (s, 3H), 7.38-7.45 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.5, 96.1, 102.2, 108.2, 108.6, 127.2, 127.8, 148.4, 153.5, 164.1, 183.9; **HRMS** (ESI): calcd for $C_{10}H_8NaO_5$ [M +Na] 231.0269, found 231.0269.

Methyl 2-(naphthalen-2-yl)-2-oxoacetate (2d)[12]



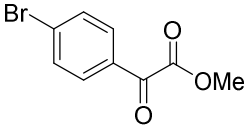
Yield: 76% (0.485 g); yellow oil; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 710, 1015, 1376, 1453, 1596, 1717, 1746, 2851, 2923; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.04 (s, 3H), 7.61-7.56 (m, 1H), 7.67-7.63 (m, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 8.05 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.57 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 52.9, 124.0, 127.2, 128.0, 129.0, 129.6, 129.8, 130.1, 132.3, 133.6, 136.4, 164.2, 186.0; **HRMS** (ESI): calcd for $C_{13}H_{10}NaO_3^+$ [M + Na]$^+$ 237.0528, found 237.0525.

Methyl 2-oxo-2-(4-(trifluoromethyl)phenyl)acetate (2e)



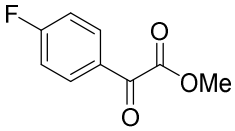
Yield:75% (0.520 g); yellow oil; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 713, 1012, 1203, 1317, 1432, 1598, 1725, 1754, 2862, 2919; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.00 (s, 3H), 7.78 (d, *J* = 8.4 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H), **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 53.0, 121.9, 124.6, 125.8, 125.8, 125.9, 125.9, 128.9, 130.4, 135.2, 135.7, 136.1, 163.0, 184.5; **HRMS** (ESI): calcd for $C_{10}H_7F_3O_3Na$ $[M + Na]^+$ 255.0245, found 255.0247.

Methyl 2-(4-bromophenyl)-2-oxoacetate (2f)[12]



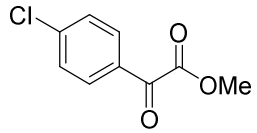
Yield: 80% (0.580 g); colorless solid, **mp**: 50-51 ºC, (lit.[12] **mp**: 49-51 ºC); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 661,745, 840, 1022, 1249, 1399, 1514, 1608, 1725, 1765, 2924, 3217; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.98 (s, 3H), 7.66 (m, 2H), 7.91 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 52.9, 130.6, 131.3, 131.4, 132.3, 163.3, 184.6; **HRMS** (ESI): calcd for $C_9H_7O_3BrNa^+$ $[M + Na^+]$ 264.9476, found 264.9476.

Methyl 2-(4-fluorophenyl)-2-oxoacetate (2g)[12]



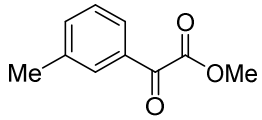
Yield: 79% (0.430 g); yellow oil; **IR** ($CHCl_3$, cm^{-1}) ν_{max} 838, 1015, 1286, 1378, 1519, 1620, 1716, 1765, 2924, 3030; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.99 (s, 3H), 7.20 (t, *J* = 8.0 Hz, 2H), 8.16 – 8.06 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 52.9, 116.3 (d, *J* C-F = 22.2 Hz), 128.9 (d, *J* C-F = 2.8 Hz), 133.1(d, *J* C-F = 9.8 Hz), 163.63, 166.9 (d, *J* C-F = 257.1 Hz), 184.2; **HRMS** (ESI): calcd for $C_9H_7FNaO_3^+$ $[M + Na^+]$ 205.0277, found 205.0276.

Methyl 2-(4-chlorophenyl)-2-oxoacetate (2h)[11]



Yield: 81% (0.480 g); colorless solid, **mp**: 58-59 ºC, (lit.[11] **mp**: 58-60 ºC); **IR** ($CHCl_3$, cm^{-1}) ν_{max} 716, 915, 1028, 1248, 1395, 1513, 1610, 1733, 2580, 2924, 3272; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 52.9, 129.3, 130.9, 131.5, 141.7, 163.4, 184.5; **HRMS** (ESI): calcd for $C_9H_7ClNaO_3^+$ $[M + Na]^+$ 220.9981, found 220.9982.

Methyl 2-oxo-2-(*m*-tolyl)acetate (2i)



Yield: 82% (0.438 g); yellow oil; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1028, 1248, 1395, 1513, 1610, 1733, 1778, 2924, 3272; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.98 (s, 3H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.81 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.3 52.7, 127.4, 128.8, 130.4, 132.4, 135.9, 138.9, 164.2, 186.3; **HRMS** (ESI): calcd for $C_{10}H_{10}NaO_3^+$ [M + Na] 201.0528, found 201.0526.

Section II

I_2-Mediated Regioselective Azidation of Indoles

4.2.1 Introduction

Indole is one of the most popular heterocyclic scaffolds in nature.[20] The challenging molecular architectures of polycyclic, naturally occurring indolyl compounds constitute a continuous stimulus for development in organic synthesis. The field had a formidable boom across the new millennium when catalysis started revolutionizing the chemistry of indole, providing always more sustainable solutions to the selective functionalization of this pharmacophore. A common guideline of these approaches relies on the intrinsic over expression of electron density of the indole core. However, in nature, it is common to encounter indolyl-containing species featuring specific interatomic connections that would be difficult to be obtained *via* "conventional" indole reactivity. In this direction, the availability of efficient synthetic methodologies for the treatment of "electrophilic" indoles will allow to significantly improve the current synthetic portfolio for indole manipulation.[21] The "electrophilic-side" of indole chemistry was first investigated by Szmuszkovicz in the early 1960s,[22] by disclosing the regioselective condensation of phenylmagnesium bromide with 3-benzoylindole derivatives. "Enamine" reactivity property of the pyrrolyl N(1)–C(2)–C(3) framework can be reversed to a Michael acceptor character when an electron-withdrawing group (EWG) is located at the β-carbon of the indole ring.[23] Interestingly, this work was substantially expanded by Liu *et al.* with a range of Grignard reagents and 3-acylindoles in a highly diastereoselective manner.[24] Currently, two distinct synthetic approaches are known for the nucleophilic manipulation of indoles:

1. **Direct approach**: These protocols generally involve a classic electrophilic attack at the C(3)-position, leading to a transient, highly electrophilic iminium intermediate that can conveniently be trapped by an external nucleophile thus, preventing a final rearomatization.[25] This methodology has been extensively investigated also in enantioselective variants and both metal-based and metal-free catalysis has been reported (**Fig. 2**).

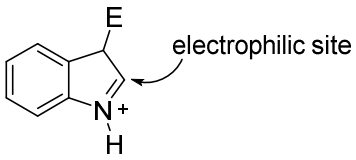


Fig. 2: Direct approaches to umpolung indole reactivity

2. Indirect approach: The methodology involves the direct nucleophilic attack at properly functionalized neutral indole cores, in inter- or intramolecular fashion (**Fig. 3**). The indole functionalizations can broadly be classified into three categories as under:

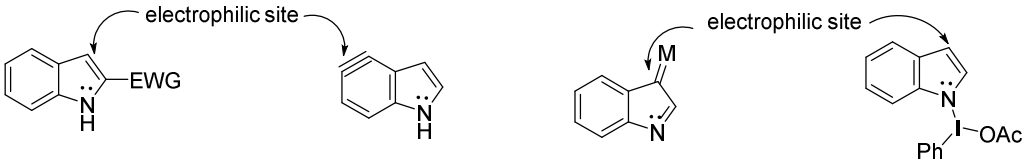


Fig. 3: Indirect approaches to umpolung indole reactivity

(i) **Indole carrying EWG or aryl substituents and LG at the N(1)-position**:

The introduction of electron-deficient groups or aryl substituents at the pyrrolyl unit (both C(2)- and C(3)-positions) has been documented to reverse the natural bias of the heterocyclic core towards electrophilic substitutions.[26] Certainly, introducing the EWG at the C(3)-site will confer on the C(2)-carbon a Michael acceptor-like

behaviour and *vice versa*. In combination with EWGs, the introduction of suitable leaving groups (i.e. halogens, OMe, OH, SO_2Ar etc.) at the nitrogen atom completes the molecular architecture to facilitate a formal S_N2'attack on the pyrrole ring.

(ii) **Au(I)-catalyzed carbene formation at C(3)-indole from *ortho*-azido phenylalkynes**:

Umpolung reactivity on indole chemistry has recently been developed also under the metal-catalyzed regime. Au (I) catalysis offered a valuable opportunity to develop a "one-pot" synthesis and concomitant nucleophilic functionalization of the indolyl core starting from ortho-azidophenylalkyne.[27]

(iii) **Indolyne formation:**

Aryne derivatives of indoles are generally referred to as indolynes and represent highly reactive intermediates that reverse the paradigm of the indole reactivity.[28]

From activity point of view, indolyl C-3 guanidines are known to bind with a putative I3 receptor (a 3rd imidazoline binding site distinct from two imidazoline receptors I1 and I2) in pancreatic β-cells and thereby regulate insulin secretion (**Fig. 4**).[29-31] In continuation to our studies on olefin functionalizations *via* I_2 catalysis for C-C, C-O and C-N bond formations, we rationalized that indole (containing an enamine moiety) could be chosen as test substrate for bringing about C-N bond formations as well and would provide easy access to these indolyl C-3 guanidines.

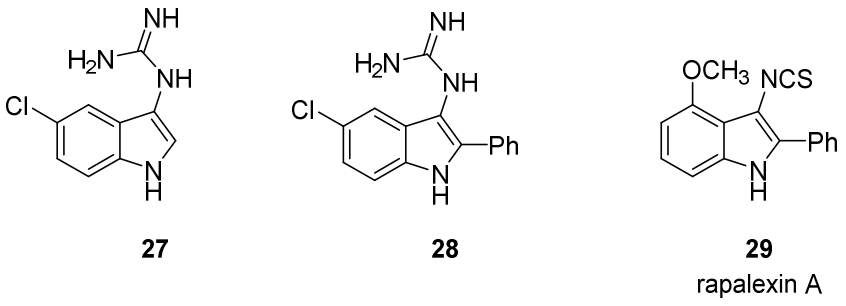


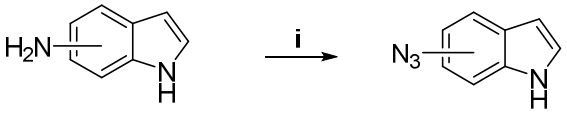
Fig. 4: Biologically active indolyl C-3 guanidines.

4.2.1 Review of Literature

There is no method available in literature for the direct azidation of indole at C-3. Azidation of pre-functionalised indoles under various conditions have been reported and are summarized as follows:

Leonard's approach (1983)[32]

Leonard *et al*. have reported azidation of aminoindoles **30** following a diazotisation-azidation procedure in presence of sodium nitrite at 0 °C. Synthesis of amino indole is a pre-requisite of the reaction which usually involves nitration-reduction sequence. The title compounds **31** were obtained in 47-88% (**Scheme 14**).



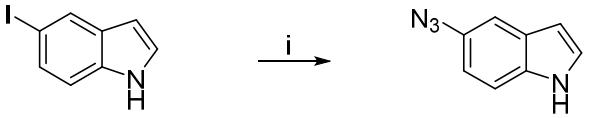
30 **31**

47-88%

Scheme 14: (i) $NaNO_2$, NaN_3, AcOH, 0 °C, 47-88%.

Bhanage's approach (2013)[33]

Bhanage *et al.* have recently reported azidation of iodoaryls **32** using NaN_3 using Cu(II) catalysis at elevated temperature to obtain title compounds **33** in high yields (67-85%) (**Scheme 15**).



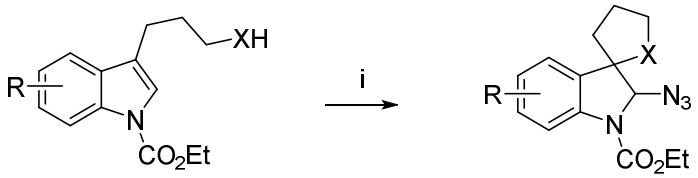
67-85%

32 **33**

Scheme 15: (i) $Cu(TMHD)_2$ (25 mol %), NaN_3 (1.2 equiv), DMF, 120 °C, 10 h, 67-85%.

Shi's approach (2014)[34]

Shi *et al.* have described azidation of indole derivatives **34** with NaN_3 and ceric ammonium nitrate (CAN), giving a variety of spirocyclic 2-azidoindolines **35** in good yields and moderate diastereoselectivities (**Scheme 16**). The reaction is believed to follow a radical mechanism where CAN acts as a single electron oxidant. The aromaticity of indole is lost in the process.



34

X = NTs, O

35

54-81%

Scheme 16: (i) $TMSN_3$ (1.5 equiv), CAN (3 equiv), CH_3CN, 0 °C, 2 h, 54-81%.

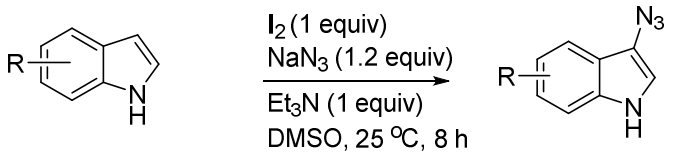
4.2.3 Present Work

4.2.3.1 Objective

In the reported methods of indole azidation, a prior functionalization is essential which in turn requires additional steps. Further, there is no report available for direct C-3 azidation of indoles. Hence, there arises a necessity to develop an efficient procedure for direct C-3 azidation of indoles from commercially available indole substrates under ambient conditions. We envisioned that, this could be made possible through indirect umpolung in reactivity of indoles by N-1 activation. On probing into the literature, we found that hypervalent iodine is known to be effective for N-1 activation. However, its scope has not been explored either with other iodine sources like I_2, NaI, TBAI, etc or with several nucleophiles.

4.2.3.2 Results and Discussion

In this section, we wish to describe for the first time, I_2-mediated protocol for C-3 azidation of indoles **36a-h** to afford 3-azidoindoles **37a-h** in excellent yields and as exclusive regioisomers under transition metal-free conditions (**Scheme 17**).



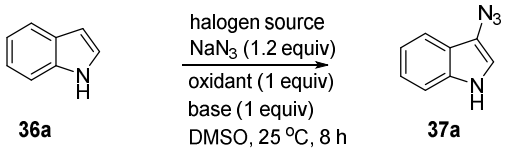
36a-h
R = H, Me, OMe, halo, NO_2, etc

37a-h
88-96%

Scheme 17: (i) I_2 (1 equiv), NaN_3 (1.2 equiv), Et_3N (1 equiv), DMSO, 25 °C, 8 h, 84-96%.

Initially, when indole (1 mmol) was treated with a mixture containing NaN_3 (1.2 mmol), NBS (1 mmol) and Et_3N (1 mmol) at 25 °C in DMSO; 3-azidoindole (**37a**) was obtained in 52% isolated yield with excellent regioselectivity (>99%) (**Table 3**).

Table 3: I_2-mediated azidation of indole with sodium azide: optimization studies[a]



36a **37a**

s.no.	halogen (1 equiv)	oxidant (1 equiv)	base	% yield of **37a**[b]
1	NBS	-	Et_3N	52
2	I_2	-	Et_3N	94
3	I_2[c]	TBHP	Et_3N	NR
4	I_2[c]	50% aq. H_2O_2	Et_3N	NR
5	I_2[c]	Oxone	Et_3N	NR
6	I_2[c]	CHP	Et_3N	NR (56%)[d]
7	NaI	-	Et_3N	54
8	$^nBu_4NI$	-	Et_3N	34
9	KI	-	Et_3N	62
10	I_2	-	NaH	66
11	I_2	-	K_2CO_3	54
12	I_2	-	DBU	47

[a]Reaction conditions: indole (1 mmol), sodium azide (1.2 mmol), halogen source (1 equiv), base (1 mmol), 8 mL DMSO, 25 °C, 8 h; [b]isolated yield after column chromatographic purification; [c]10 mol % of halogen source was used; [d]yield of *N*-Me oxindole obtained when *N*-Me indole was used as substrate.

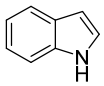
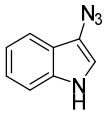
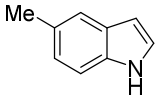
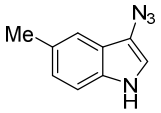
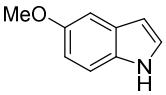
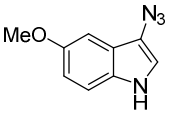
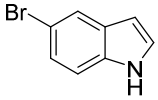
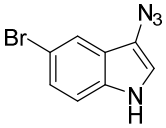
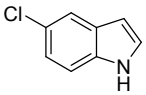
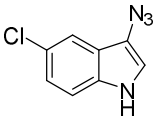
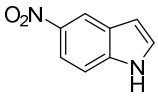
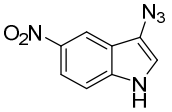
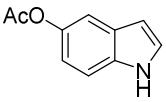
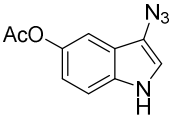
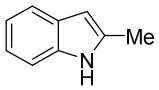
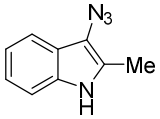
When stoichiometric amount of I_2 was used as halogen source, **37a** (94% yield) was indeed obtained with perfect regioselectivity. Encouraged by the result, it was of interest to develop a catalytic version of this useful azidation process**.** However, with stoichiometric peroxy oxidants like TBHP, aq. H_2O_2, Oxone and cumene hydroperoxide (CHP) used in combination with catalytic amount of I_2 (10 mol %) decomposition of the starting material was observed probably due to the free N-H group in the indole moiety (entries 3-6). Using *N*-Me indole as the starting material

under the reaction conditions resulted in formation of *N*-Me oxiindole as the major product (56% of isolated yield).

Various trials under other oxidative conditions oxidized indole to either oxiindole or isatin. Oxidation of indole was not our objective of undertaking this work. Hence, we proceeded with stoichiometric amount of other iodine sources like NaI, TBAI and KI only to end up with 54, 34 and 62% yields of **37a** respectively (entries 7-9). Other bases like NaH, K_2CO_3 and DBU were not effective in improving the yield of the azido indole any further. Hence, entry 2 was chosen as the best optimised condition for screening of substrates.

The scope of the study was then extended to substituted indoles; the results of which are displayed in **Table 4**. Several indoles with varied functional groups on the aromatic ring afforded products in high yields (88-96%). Indoles substituted with electron neutral groups like 5-Me, 2-Me, 5-Cl and 5-Br were found to be compatible under the reaction conditions affording C-3 azidation product in 95, 88, 91 and 96% yields respectively. The reaction was then tried with electron-withdrawing substituent i.e. 5-nitroindole (**36f**) and to our delight, 3-azido-5-nitro-indole (**37f**) was indeed obtained in 89% yield.

Table 4: I_2-mediated regioselective azidation of indoles: substrate scope[a]

Substrates (**36a-h**)	products (**37a-h**)[b]
 **36a**	 **37a**; 94%
 **36b**	 **37b**; 95%
 **36c**	 **37c**; 92%
 **36d**	 **37d**; 96%
 **36e**	 **37e**; 91%
 **36f**	 **37f**; 89%
 **36g**	 **37g**; 90%
 **36h**	 **37h**; 88%

[a] for reaction conditions, see foot-note under Table 3; [b] isolated yield after column chromatographic purification

The formed products were thoroughly characterized by ^1H and ^{13}C NMR spectroscopy, IR and MALDI-MS analysis.

Example 1: 3-Azido-1*H*-indole (**37a**) showed a typical N-**H** proton signal at δ 11.5 (br. s, 1H) in its ^1H NMR spectrum. Further, the aromatic (C-**H**) proton in the pyrrole

ring appeared as a singlet at δ 7.54 (s, 1H). The structure was further corroborated by its ^{13}C NMR spectrum showing fully substituted carbon signal for indole C-3 at δ 88.7. The azidation of indole was substantiated by its IR spectrum (taken in DMSO-

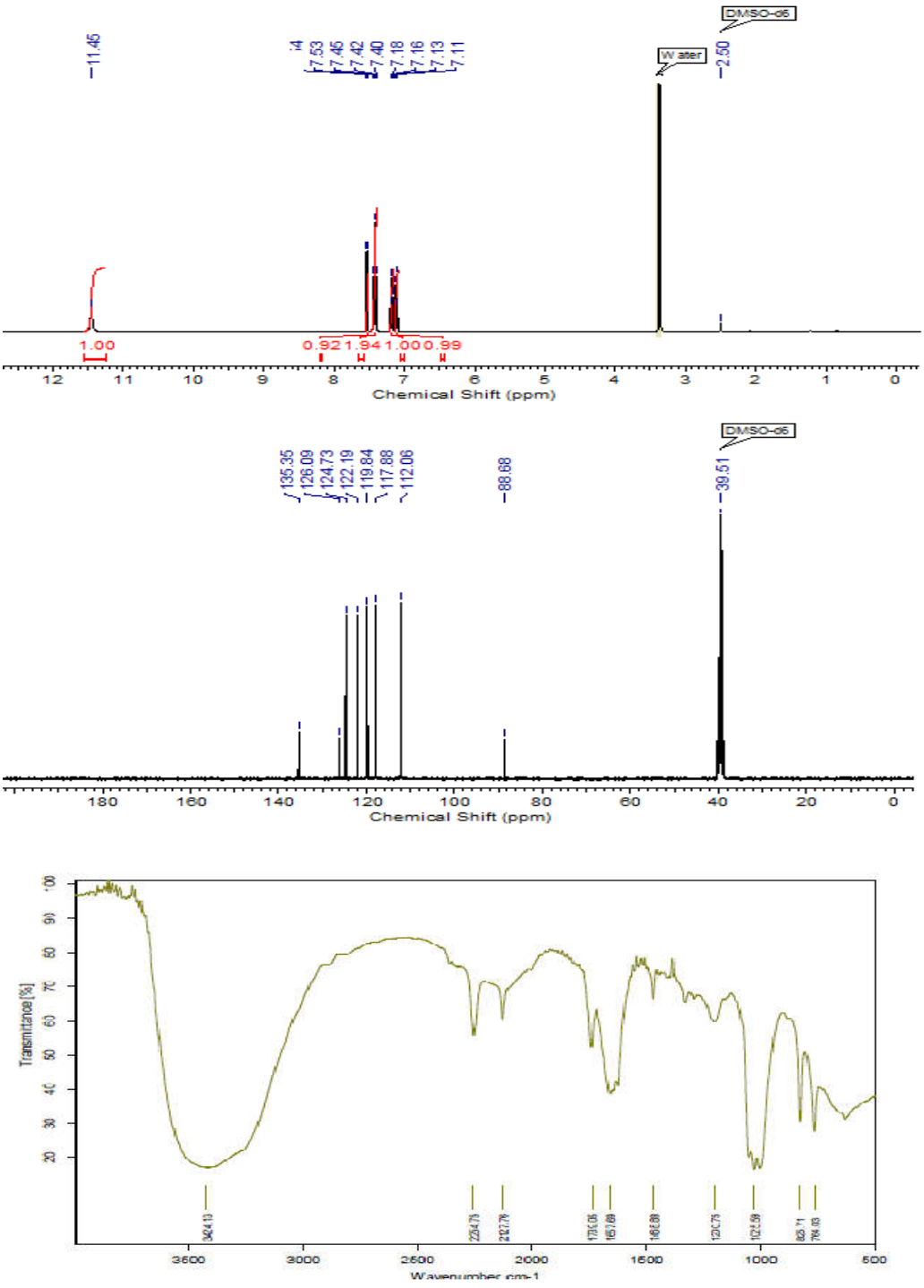


Fig. 5: ^{1}H, ^{13}C NMR and IR spectra for **37a**

d_6, due to instability of the product under air) which showed a typical absorption band of –N=N=N group at a stretching frequency of 2127 cm^{-1} (**Fig. 5**).

Example 2: 3-Azido-5-chloro-1*H*-indole (**37e**) displayed a typical N-**H** proton signal at δ 11.7 (br. s, 1H) in its ^{1}H NMR spectrum. Further, the aromatic (C-**H**) proton in the pyrrole ring appeared as a singlet at δ 7.40 (s, 1H). The structure was further corroborated by its ^{13}C NMR showing fully substituted carbon signal for indole C-3 at δ 88.0 (**Fig. 6**).

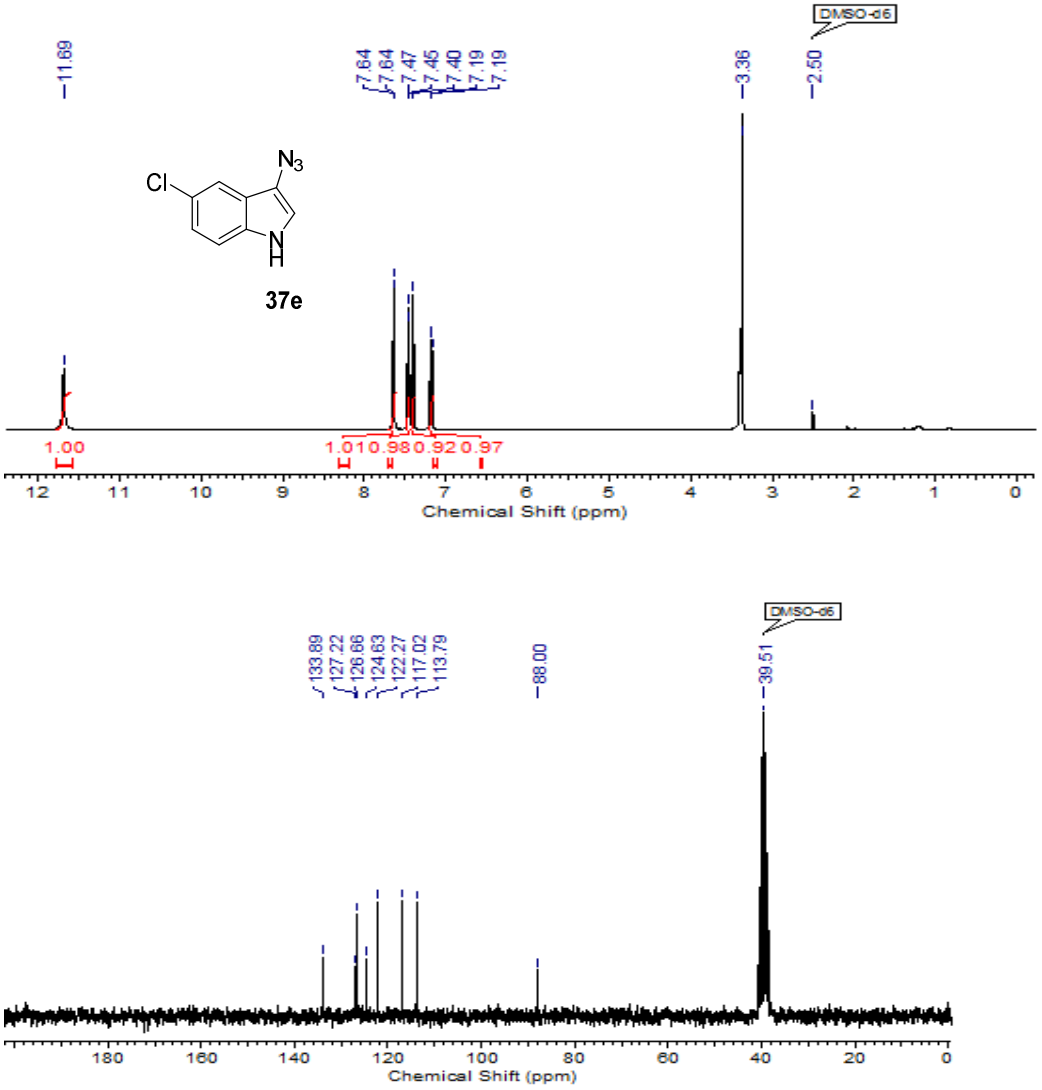


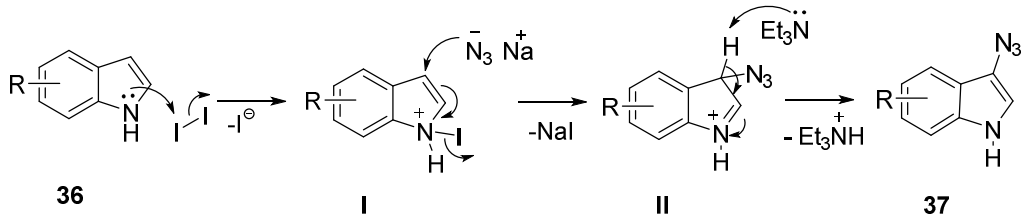
Fig. 6: ^{1}H and ^{13}C NMR spectra of **37e**

4.2.3.3 Stability of 3-Azidoindoles

3-Azido indoles were found to be unstable under air, to heat and also to chlorinated solvents ($CHCl_3$, CH_2Cl_2, etc). These brightly colored solids turned black (in 30 min-1 h) when stored in open flask (even at low temperature). The compounds **37a-h** after column chromatographic purification, were however conveniently stored at room temperature for weeks (slow degradation observed) by dissolving it in DMSO.

4.2.3.4 Mechanistic Discussion

A plausible mechanistic course of the reaction is presented in **Scheme 18**. Indole first undergoes N-1 activation with I_2 to form indolinium iodide intermediate **I** which is further facilitated by the attack of azide nucleophile in S_N2' fashion from C-3 position to form intermediate **II**. This is followed by the process of re-aromatization by eliminating a proton to give the desired product.



Scheme 18: Plausible mechanistic pathway for azidation of indoles

4.2.4 Conclusion

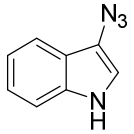
To summarize, we have disclosed for the first time, a regioselective C-3 azidation of indoles mediated by simple molecular iodine. The azidoindole products have been obtained in excellent yields (88-96%) under mild reaction conditions. The umpolung in reactivity has been achieved by N-1 activation of indoles with iodine. We believe that this protocol can be utilized for streamlining the synthesis of various indole-derived therapeutics and can be applied for azidation of other heteroaromatics as well.

4.2.5 Experimental Section

General experimental procedure for the preparation of compounds **37a-h**:

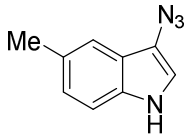
To a stirred solution of indole (3 mmol) in dry DMSO (25 mL) at 0 °C was added I_2 (3 mmol) and Et_3N (3 mmol) dropwise. After 5 min, NaN_3 (3.6 mmol) was added portionwise. The reaction mixture was then stirred at 25 °C under an inert atmosphere for 6-8 h. After completion of the reaction (as monitored by TLC), it was quenched with H_2O (20 mL) at 0 °C. It was then extracted with EtOAc (3 x 50 mL) followed by washing with brine (3 x 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Concentration of organic solvent under reduced pressure gave the crude product, which was further purified by column chromatography over silica gel using Pet. ether: EtOAc (9:1) as eluent to obtain 3-azidoindole derivatives **37a-h** in high purity. Due to instability of the products, they were stored in DMSO-d_6 and hence MALDI-MS technique was used for its mass analysis.

3-Azido-1*H*-indole (37a)



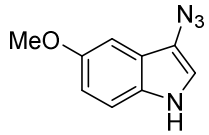
Yield: 94% (0.445 g); yellow colored solid; **mp:** 30 °C (decomposes); **IR** (DMSO-d_6, cm^{-1}): ν_{max} 764, 825, 1025, 1468, 1657, 2127, 2254, 3424; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.09-7.14 (m, 1H), 7.15-7.21 (m, 1H), 7.42 (t, J = 8.6 Hz, 2H), 7.54 (s, 1H), 11.45 (br. s., 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 88.7, 112.1, 117.9, 119.8, 122.2, 124.7, 126.1, 135.4; **MALDI-MS**: calcd for $C_8H_6NaN_4^+$ [M + Na^+] 181.0485, found 181.0478.

3-Azido-5-methyl-1*H*-indole (37b)



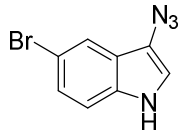
Yield: 95% (0.490 g); orange colored solid; **mp:** 30 °C (decomposes); **IR** (DMSO-d_6, cm^{-1}): ν_{max} 767, 821, 1024, 1468, 1654, 2123, 2252, 3426; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.24 (s, 3H), 6.88 (s, 1H), 7.12-7.18 (m, 1H), 7.37 (d, *J* = 6.8 Hz, 1H), 7.40-7.45 (m, 1H), 10.95 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 21.5, 92.4, 109.2, 123.7, 123.9, 124.1, 127.3, 131.8, 142.8; **MALDI-MS**: calcd for $C_9H_8N_4Na^+$ [M + Na^+] 195.0641, found 195.0644.

3-Azido-5-methoxy-1*H*-indole (37c)



Yield: 92% (0.520 g); colorless solid; **mp:** 30 °C (decomposes); **IR** (DMSO-d_6, cm^{-1}): ν_{max} 762, 824, 1026, 1206, 1490, 1658, 1737, 2125, 2251, 3425; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.43 (s, 3H), 6.76-6.89 (m, 2H), 7.26-7.38 (m, 1H), 7.48 (d, *J* = 2.7 Hz, 1H), 11.31 (br. s., 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 55.3, 88.3, 99.1, 112.7, 113.0, 125.1, 126.4, 130.4, 154.1; **MALDI-MS:** calcd for $C_9H_8N_4ONa^+$ [M + Na^+] 211.0590, found 211.0588.

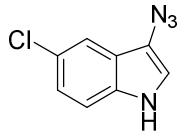
3-Azido-5-bromo-1*H*-indole (37d)



Yield: 96% (0.680 g); red colored solid; **mp:** 30 °C (decomposes); **IR** (DMSO-d_6, cm^{-1}): ν_{max} 624, 760, 822, 1028, 1248, 1659, 2123, 2250, 3438; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 7.29 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 2.5

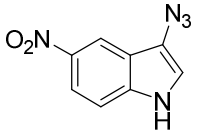
Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 11.68 (br. s., 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 87.8, 112.4, 114.2, 120.1, 124.8, 126.5, 127.9, 134.1; **MALDI-MS**: calcd for $C_8H_5N_4BrNa^+$ [M + Na^+] 258.9590, found 258.9592.

3-Azido-5-chloro-1*H*-indole (37e)



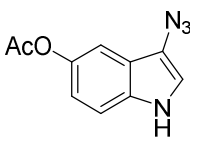
Yield: 91% (0.525 g); yellow colored solid; **mp:** 30 °C (decomposes); **IR** (DMSO-d_6, cm^{-1}): ν_{max} 624, 760, 822, 1027, 1659, 2124, 2250, 3438; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.16-7.21 (m, 1H), 7.40 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.59-7.71 (m, 1H), 11.69 (br. s., 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 88.0, 113.8, 117.0, 122.3, 124.6, 126.7, 127.2, 133.9; **MALDI-MS**: calcd for $C_8H_5ClN_4Na^+$ [M + Na^+] 215.0095, found 215.0097.

3-Azido-5-nitro-1*H*-indole (37f)



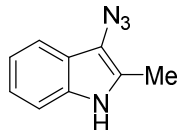
Yield: 89% (0.540 g); red colored solid; **mp:** 30 °C (decomposes); **IR** (DMSO-d_6, cm^{-1}): ν_{max} 763, 825, 1025, 1338, 1531, 1658, 1733, 2127, 2254, 3424; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.60-7.67 (m, 1H), 7.87 (d, *J* = 1.4 Hz, 1H), 8.03-8.12 (m, 1H), 8.28-8.38 (m, 1H), 12.21 (br. s., 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 91.0, 113.0, 115.0, 117.5, 125.7, 129.1, 138.6, 141.4; **MALDI-MS**: calcd for $C_8H_5N_5O_2Na^+$ [M + Na^+] 226.0335, found 226.0336.

3-Azido-1*H*-indol-5-yl acetate (37g)



Yield: 90% (0.582 g); colorless solid; **mp:** 30 °C (decomposes); **IR** (DMSO-d_6, cm^{-1}): ν_{max} 766, 823, 1021, 1650, 1733, 2121, 2252, 3429; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.32 (s, 3H), 6.98 (s, 1H), 7.12 (m, 2H), 7.44 (d, J = 2.6 Hz, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): 21.1, 91.2, 109.3, 111.5, 119.1, 123.8, 126.9, 135.6, 145.2, 169.2; **MALDI-MS**: calcd for $C_{10}H_8N_4O_2Na^+$ [M + Na^+] 239.0539, found 239.0537.

3-Azido-2-methyl-1*H*-indole (37h)



Yield: 88% (0.455 g); colorless solid; **mp:** 30 °C (decomposes); **IR** (DMSO-d_6, cm^{-1}): ν_{max} 761, 822, 1021, 1463, 1651, 2125, 2251, 3427; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.28 (s, 3H), 7.12-7.26 (m, 2H), 7.37-7.56 (m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 20.3, 91.7, 109.5, 123.3, 123.6, 124.5, 127.1, 131.6, 142.1; **MALDI-MS**: calcd for $C_9H_8N_4Na^+$ [M + Na^+] 195.0641, found 195.0640.

4.2.6 References

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