Enantioselective Synthesis of Bioactive Molecules *via* Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and CuCN-Mediated Annulations in C-C, C-O Bond Formation

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To

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By

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UNDER THE GUIDANCE OF

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July 2012

DEDICATED TO

MY BELOVED FAMILY

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Enantioselective Synthesis of Bioactive Molecules *via* Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and CuCN-Mediated Annulations in C-C, C-O Bond Formation**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

July 2012 **(Dr. A. Sudalai)**

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DECLARATION

I here by declare that the thesis entitled **"Enantioselective Synthesis of Bioactive Molecules *via* Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and CuCN-Mediated Annulations in C-C, C-O Bond Formation"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

July 2012
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CONTENTS

		Page No.
Acknowledgements		i
Abbreviations		iii
General Remarks		v
Abstract		vi
Chapter I	**Enantioselective Synthesis of Bioactive Molecules *via* Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and CuCN-Mediated Annulations in C-C, C-O Bond Formation**	
Section I	**Cobalt-catalyzed Hydrolytic Kinetic Resolution of Alkoxy Epoxides**	
1.1.1	Introduction	1
1.1.2	Hydrolytic kinetic resolution (HKR)	1
1.1.3	Review of Literature	5
1.1.4	Present Work	7
1.1.4.1	Objective	7
1.1.5	Results and Discussion	8
1.1.5.1	Synthesis of racemic alkoxy epoxides	8
1.1.5.2	HKR of racemic alkoxy epoxides	15
1.1.6	Conclusion	21
1.1.7	Experimental Section	22
Section II	**Enantioselective Synthesis of (*S*,*S*)-Reboxetine**	
1.2.1	Introduction	36
1.2.2	Pharmacology of (*S*,*S*)-Reboxetine	38
1.2.3	Review of Literature	39
1.2.4	Present Work	47
1.2.4.1	Objective	47
1.2.5	Results and Discussion	48
1.2.6	Conclusion	56
1.2.7	Experimental Section	57

Section III	**Enantioselective Synthesis of (-)-Chloramphenicol and (+)-Thiamphenicol**	
1.3.1	Introduction	62
1.3.2	Pharmacology of (-)-Chloramphenicol and (+)-Thiamphenicol	62
1.3.3	Review of Literature	63
1.3.4	Present Work	73
1.3.4.1	Objective	73
1.3.5	Results and Discussion	74
1.3.5.1	Enantioselective synthesis of (-)-chloramphenicol	74
1.3.5.2	Enantioselective synthesis of (+)-thiamphenicol	80
1.3.6	Conclusion	84
1.3.7	Experimental Section	85
1.3.8	References	92
Chapter II	**Asymmetric Synthesis of Tetrahydroquinolin-3-ols, Anachelin H Chromophore and 1-((*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-yl)propan-1-one**	
Section I	**A New Route to the Synthesis of *(R)*-Tetrahydroquinolin-3-ols *via* $CoCl_2$-catalyzed Reductive Cyclization of Cyclic Sulphites with $NaBH_4$**	
2.1.1	Introduction	95
2.1.2	Review of Literature	96
2.1.3	Present Work	109
2.1.3.1	Objective	109
2.1.3.2	Asymmetric Dihydroxylation (AD)	110
2.1.3.3	Transition metal boride catalyzed reduction	113
2.1.4	Results and Discussion	115
2.1.5	Conclusion	126
2.1.6	Experimental Section	126
Section II	**Asymmetric Formal Synthesis of Anachelin H Chromophore**	
2.2.1	Introduction	143
2.2.2	Review of Literature	144
2.2.3.	Present Work	146

2.2.3.1	Objective	146
2.2.4	Results and Discussion	147
2.2.5	Conclusion	153
2.2.6	Experimental Section	153
Section III	**Asymmetric Synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one**	
2.3.1	Introduction	157
2.3.2	Review of Literature	157
2.3.3.	Present Work	159
2.3.3.1	Objective	159
2.3.4	Results and Discussion	160
2.3.5	Conclusion	163
2.3.6	Experimental Section	164
2.3.7	References	169
Chapter III	**CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-substituted Chiral Phthalides and its Application to the Synthesis of (-)-Matteucen C, Isocoumarins and Alkylidenephthalides**	
Section I	**CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-Substituted Chiral Phthalides**	
3.1.1	Introduction	172
3.1.2	Review of Literature	173
3.1.3	Present Work	180
3.1.3.1	Objective	180
3.1.4	Results and Discussion	181
3.1.5	Conclusion	194
3.1.6	Experimental Section	195
Section II	**First Enantioselective Synthesis of (-)-Matteucen C**	
3.2.1	Introduction	219
3.2.2	Review of Literature	219
3.2.3	Present Work	219
3.2.3.1	Objective	219

3.2.4	Results and Discussion	220
3.2.5	Conclusion	225
3.2.6	Experimental Section	225
Section III	**A Novel Approach to Isocoumarins and Alkylidenephthalides**	
3.3.1	Introduction	229
3.3.2	Review of Literature	230
3.3.3	Present Work	235
3.3.3.1	Objective	235
3.3.4	Results and Discussion	236
3.3.5	Mechanism	241
3.3.6	Conclusion	242
3.3.7	Experimental Section	243
3.3.8	References	248
Chapter IV	**CuCN-Mediated "One-pot" Route to 1-Amino-2-naphthalenecarboxylic acid Derivatives and 3-Substituted Phthalides: Enantioslective Synthesis of Colletotrialide**	
Section I	**CuCN-Mediated "One-pot" Cascade Route to 1-Amino-2-naphthalenecarboxylic Acid Derivatives**	
4.1.1	Introduction	252
4.1.2	Review of Literature	252
4.1.3	Present Work	253
4.1.3.1	Objective	254
4.1.4	Results and Discussion	254
4.1.5	Conclusion	261
4.1.6	Experimental Section	262
Section II	**CuCN-Mediated "One-pot" Synthesis of 3-Substituted Phthalides**	
4.2.1	Introduction	272
4.2.2	Review of Literature	272
4.2.3	Present Work	274
4.2.3.1	Objective	274
4.2.4	Results and Discussions	274

4.2.5	Conclusion	278
4.2.6	Experimental Section	279
Section III	**Enantioselective Synthesis of Colletotrialide**	
4.3.1	Introduction	289
4.3.2	Review of Literature	289
4.3.3	Present Work	289
4.3.3.1	Objective	289
4.3.4	Results and Discussions	290
4.3.5	Conclusion	297
4.3.6	Experimental Section	297
4.3.7	References	304
	List of Publications	306

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ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl Lithium
CAN	Cerric ammonium nitrate
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DIBAL-H	Diisobutyl alulinum hydride
DET	Diethyl Tartarate
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
ee	Enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
IR	Infra red
IBX	2-Iodoxybenzoic acid
KHMDS	potassium hexamethyl disilazide
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
LiHMDS	Lithium hexamethyl disilazide
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
MOM	Methoxymethyl
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride

$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
Red-Al	Bis(2-methoxyethoxy)aluminum hydride
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
TMSCN	Trimethylsilyl cyanide
Ts	Tosyl

GENERAL REMARKS

1. All solvents were distilled and dried before use.

2. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.

3. Organic layers after every extraction were dried over anhydrous sodium sulfate.

4. Column Chromatography was performed over silica gel (60-120 and 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 Bruker FT AV-200, AV-400 and AV-500 MHz 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, td = triplet of doublet and dd = doublet of doublet.

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

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

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

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

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

13. The ligands $(DHQD)_2$-PHAL, $(DHQ)_2$-PHAL, $(DHQD)_2$-AQN were purchased from Aldrich.

ABSTRACT

The thesis entitiled "**Enantioselective Synthesis of Bioactive Molecules *via* Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and CuCN-Mediated Annulations in C-C, C-O Bond Formation**" is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and to develop useful synthetic methodologies. **Chapter 1** describes the cobalt-catalyzed hydrolytic kinetic resolution of alkoxy epoxides and their application in the asymmetric synthesis of (*S*,*S*)-reboxetine, (-)-chloramphenicol and (+)-thiamphenicol. **Chapter 2** deals with the $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulphites using $NaBH_4$ to give the corresponding tetrahydroquinolin-3-ol and its application in the asymmetric synthesis of anachelin H chromophore and 1-[(*S*)-3-(dimethylamino)-3,4- dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one (*S*-903). **Chapter 3** presents the synthesis of 3-substituted chiral phthalides using CN-assisted oxidative cyclization of cyano cinnamates and styrene derivatives and its application in the synthesis of (-)-Matteucen C, isocoumarins and alkylidenephthalides. **Chapter 4** describes the CuCN-mediated "one-pot" route to 1-amino-2-naphthalenecarboxylic acid derivatives, 3-substituted phthalides and its application in the enantioslective synthesis of Colletotrialide.

CHAPTER 1

Cobalt-catalyzed Hydrolytic Kinetic Resolution of Alkoxy Epoxides: A Short Enantioselective Synthesis of (*S*,*S*)-Reboxetine, (-)-Chloramphenicol and (+)-Thiamphenicol

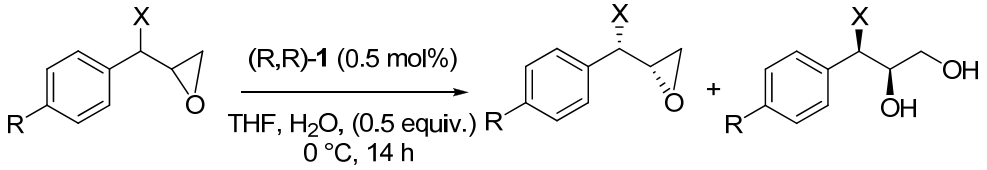
Jacobsen's Hydrolytic Kinetic Resolution (HKR) has emerged as an effective method for obtaining chiral epoxides and 1,2-diols in a highly enantioenriched forms.[1] These compounds are important intermediates in the synthesis of various bioactive molecules.[2] In view of easy availability of chiral ligands and the simplicity of the reaction conditions with water being used as the nucleophile, HKR is being used extensively for providing several chiral building blocks in the synthesis of biologically active compounds.[3] This chapter deals with the development of a novel method in which HKR of two stereocenters in alkoxy epoxides catalyzed by chiral Co(III)(salen)OAc complex can

produce chiral alkoxy epoxides and alkoxy diols. This method is also applied in the asymmetric synthesis of (S,S)-Reboxetine, (-)-Chloramphenicol and (+)-Thiamphenicol. This chapter is divided into three sections.

Section I: Cobalt-catalyzed Hydrolytic Kinetic Resolution of Alkoxy Epoxides

For the first time, HKR of racemic *syn*- or *anti*- alkoxy epoxide derivatives was carried out. In this strategy, the relative stereochemistry between the alkoxy and the epoxide functions is established prior to the HKR step and thus a single asymmetric reaction is employed to form compounds with two asymmetric centres.[4]

Table 1: Co-catalyzed HKR of *syn*-alkoxy epoxides



1a-k (2*SR*, 3*SR*) **2a-k** (2*S*,3*S*) **3a-k**

Sr.No	Alkoxy epoxide (±)-1a-k		Alkoxy Epoxide 2a-k		Alkoxy Diol 3a-k	
	R	X	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b,c]
a	H	OMe	48	97	47	98
b	OMe	OMe	47	98	46	97
c	Me	OMe	44	97	45	98
d	Br	OMe	45	97	42	98
e	SMe	OMe	47	98	46	97
f	H	OBn	45	98	44	98
g	OMe	OBn	49	96	47	98
h	Me	OBn	48	96	45	96
i	Cl	OBn	45	95	42	98
j	Br	OBn	44	98	47	98
k	SMe	OBn	48	96	47	97

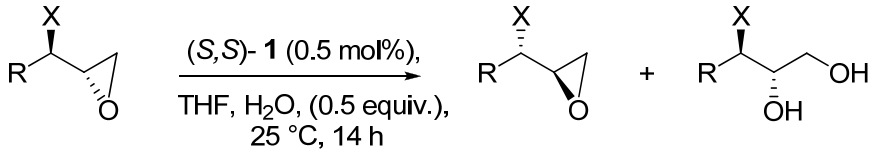
[a] Isolated yield after column chromatographic purification. [b]ee determined by chiral HPLC
[c] ee determined by Mosher's ester analysis.

The racemic *syn*- and *anti*- alkoxy epoxides, the substrates for HKR, were efficiently prepared in highly diastereoselective manner[5] from the corresponding (*E*)- and (*Z*)-allylic alcohols respectively, involving essentially a two-step reaction sequence of NBS-

bromination in the presence of MeOH or BnOH, as the case may be, followed by treatment with base to form the corresponding racemic epoxides. In this section, we have described a flexible, novel method that employs HKR of racemic alkoxy epoxides to generate two stereocentres of high optical purities in a single step. Thus, when HKR of racemic *syn*-alkoxy epoxides **1a-k** was performed with (*R,R*)-Co(III)(salen)OAc complex (0.5 mol%) and H_2O (0.48 equiv.), the corresponding chiral epoxides **2a-k** and diols **3a-k** were isolated in high yields and optical purity (**Table 1**).

Similarly, *anti*-alkoxy epoxides **4a-b** when subjected to (*S,S*)-Co(III)(salen)OAc-catalyzed HKR, produced chiral *anti*-alkoxy epoxides **5a-b** and corresponding diols **6a-b** with high enantio purity (**Table 2)**.

Table 2: Co-catalyzed HKR of *anti*-alkoxy epoxides



4a-b (2SR, 3RS) **5a-b** (2S, 3R) **6a-b**

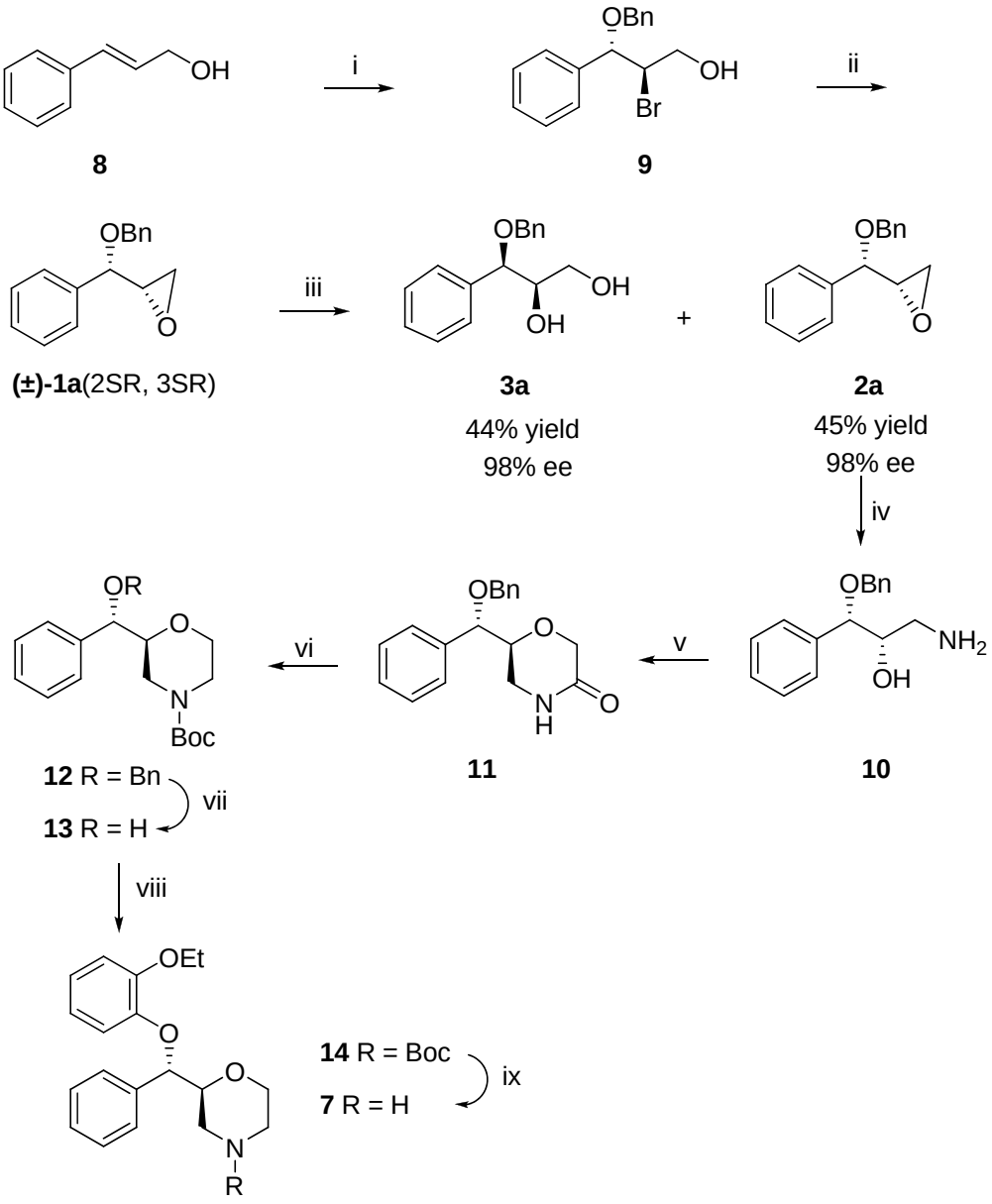
No.	Alkoxy epoxide (±)-**4a-b**		Alkoxy epoxide **5a-b**		Alkoxy diol **6a-b**	
	R	X	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
a	CH_2OTBS	OBn	47	96	49	97
b	Ph	OMe	48	96[c]	47	98[c]

[a] Isolated yield after column chromatographic purification; [b] ee determined by Mosher's ester analysis; [c] ee determined by chiral HPLC analysis.

Section II: Enantioselective Synthesis of (*S, S*)-Reboxetine

Reboxetine, 2-[α-(2-ethoxyphenoxy) phenylmethyl]morpholine **7** is a specific norepinephrine reuptake inhibitor (NRI) widely studied for its pharmacological properties.[5] In this section, we describe a concise enantioselective synthesis of (*S,S*)-reboxetine **7** using two stereocentered HKR of alkoxy epoxide. Our synthesis of (*S,S*)-reboxetine **7** started with the benzyloxy bromination of cinnamyl alcohol **8** using NBS and BnOH to give benzyloxy bromoalcohol **9** in 85% yield. Benzyloxy bromoalcohol **9** on treatment with NaOH powder, in THF afforded racemic *syn*-benzyloxy epoxide **1a** in

88% yield, which was then subjected to HKR using (*R,R)*-Co(III)(salen)OAc to furnish the chiral benzyloxy epoxide **2a** in 45% chemical yield and 98% ee along with the corresponding benzyloxy diol **3a** in 44% yield and 98% ee.

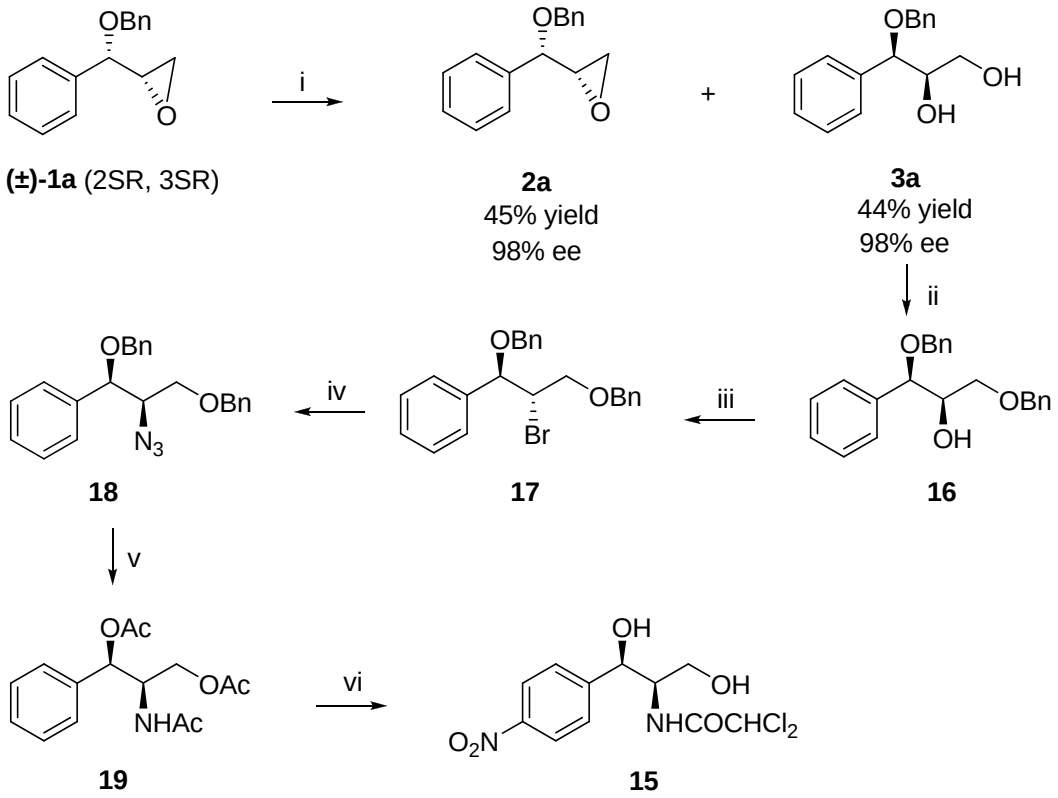


Scheme 1: (i) NBS, BnOH, CH_3CN, 25 °C, 3 h, 85%; (ii) NaOH powder, THF, 25 °C, 2 h, 88%; (iii) *(R,R)*-Co(III)(salen)OAc (1 mol%), THF, H_2O (0.48 equiv.), 0 ºC, 12 h; (iv) 30% NH_4OH, MeOH, 25 °C, 12 h, 83%; (v) (a) $ClCH_2COCl$, Et_3N, CH_2Cl_2, -10 °C; (b) KO^tBu, t-BuOH, 3 h, , 72% ; (vi) (a) Red-Al, dry toluene, 25 °C, then 2N NaOH; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 85%; (vii) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h, 92%; (viii) (a) CBr_4, PPh_3, imid., CH_2Cl_2, 25 °C, 2 h; (b) 2-ethoxyphenol, NaH, DMF, 3 h, 72%; (ix) TFA, CH_2Cl_2, 0 °C, 1 h, 96%.

Both chiral benzyloxy epoxide **2a** and azido diol **3a** could be readily separated by column chromatographic purification. Regiospecific opening of epoxide **2a** with 30% NH_4OH gave amino alcohol **10** in 83% yield, which was condensed with chloroacetyl chloride under basic conditions to afford imide **11** in 72% yield. Imide **11** was reduced to the morpholine derivative *in situ* which was protected as carbamate **12** in 85% yield using $(Boc)_2O$. Deprotection of benzyl group in **12** gave the alcohol **13** in 88% yield. The transformation of **13** to (*S*,*S*)-reboxetine **7** in 98% ee was achieved in 2-steps (i) conversion of alcohol to bromo derivative followed by nucleophilic displacement with sodium salt of *o*-ethoxy phenol affording N-Boc protected reboxetine **14** (ii) deprotection of N-Boc with trifluoroacetic acid (**Scheme 1**).

Section III: Enantioselective Synthesis of (-)-Chloramphenicol and (+)-Thiamphenicol

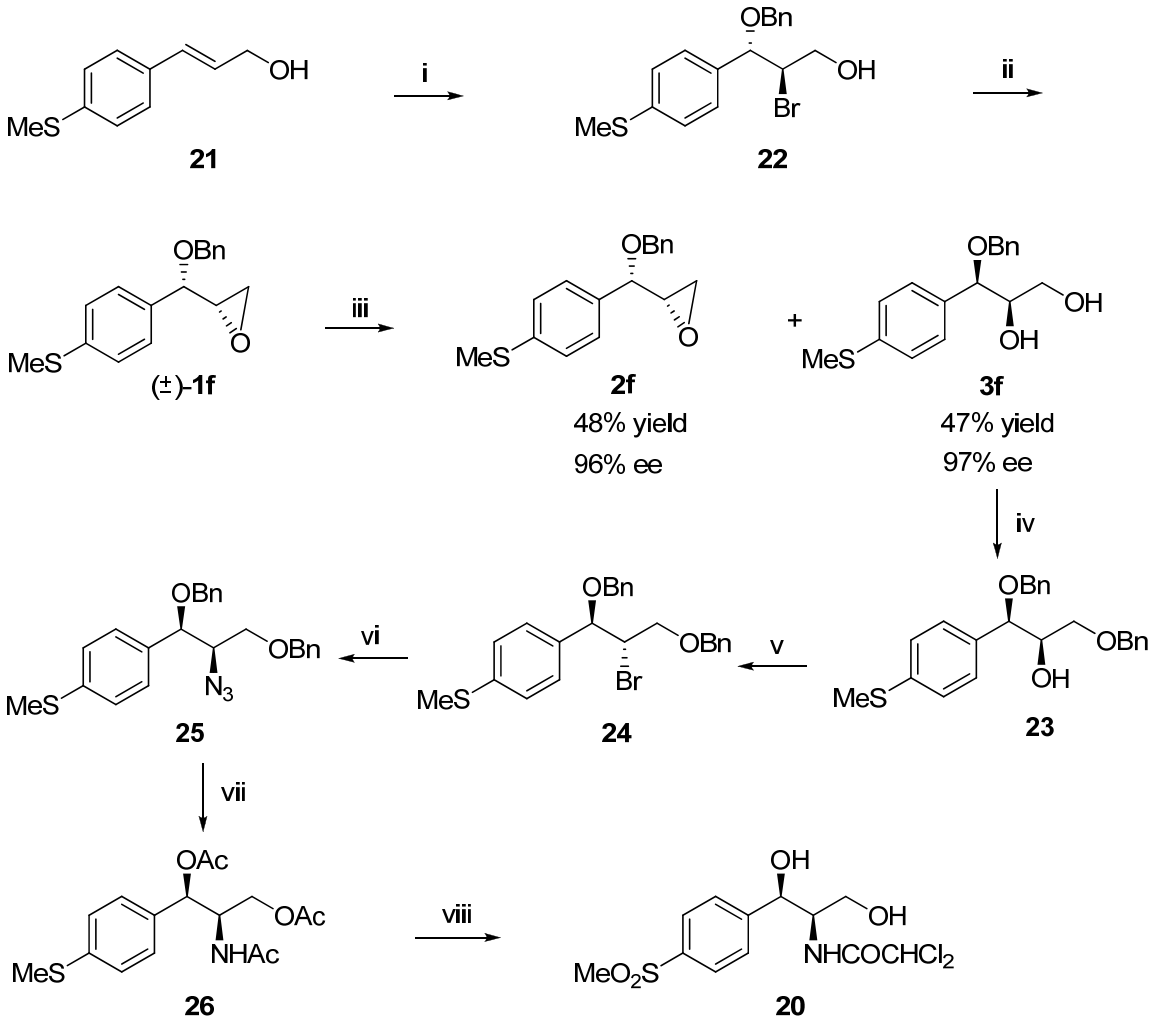
(-)-Chloramphenicol **15** and (+)-thiamphenicol **20** are broad-spectrum antibiotics with a range of biological activities.[6] While chloramphenicol **15** is active only in its D-*threo* configuration and is especially effective in the treatment of typhus, dysentery and ocular bacterial infections,[7] (+)-thiamphenicol **20**, a synthetic analogue of chloramphenicol **15**, is bacteriostatic for both gram-positive and gram-negative aerobes and for some anaerobes.[8] In this section, we describe the application of two stereocentered HKR for the stereoselective synthesis of (-)-chloramphenicol **15** and (+)-thiamphenicol **20**. Racemic *syn*-benzyloxy epoxide **1a** was subjected to HKR using (*R,R)*-Co(III)(salen)OAc to furnish the required chiral benzyloxy diol **3a** in 44% chemical yield and 98% ee. Selective protection of primary alcohol in diol **3a** was achieved using Bu_2SnO and benzyl bromide in 82% yield. Alcohol **16** was then subjected to Appel reaction condition to give *anti*-benzyloxybromo compound **17**, nucleophilic displacement of bromide in **17** to azide **18** was achieved in 80% yield. Deprotection of benzyl ethers and reduction of azide proceeded smoothly under catalytic hydrogenation of **18** followed by acylation with Ac_2O gave triacetate **19**. The synthesis of (–)-chloramphenicol (**15**) was completed by sequences of reactions such as nitration, acid mediated hydrolysis and N-acylation with 76% yield over three steps with 98%ee (**Scheme 2**).



Scheme 2: (i) (*R,R)*-Co**(**III**)**(salen)OAc (1mol%), THF, H_2O (0.48 equiv.), 0 ºC, 12 h; (ii) Bu_2SnO, toluene, reflux, 12 h. then BnBr, TBAB, reflux, 20h, 82%; (iii) CBr_4, imid., PPh_3, CH_2Cl_2, 0 °C, 3h, 76%; (iv) NaN_3, DMF, 60 °C, 12h, 80%; (v) (a) 20% $Pd(OH)_2$/C, MeOH, H_2 (1atm), 25 ^oC, 12h; (b) Ac_2O, DMAP, pyridine, 94% (for 2 steps); (vi) (a) conc. HNO_3-conc. H_2SO_4, -20^{o}C to 25^{o}C; 1.5 h; (b) aq. 5% HCl, 90 ^oC; (c) Cl_2CHCO_2Me, 90 ^oC, 1 h, 76% (for 3 steps).

The same strategy was extended to the synthesis of (+)-thiamphenicol **20**. Our synthesis started with the benzyloxy bromination of 4-(methythio)cinnamyl alcohol **21** using NBS and BnOH to give benzyloxy bromoalcohol **22** in 84% yield. Racemic *syn*-benzyloxy epoxide **1f** was obtained in 86% yield by subjecting benzyloxy bromoalcohol **22** with NaOH powder in THF, which was then subjected to HKR using (*R,R)*-Co(III)(salen)OAc to furnish the chiral benzyloxy epoxide **2f** in 48% chemical yield and 96% ee along with the corresponding benzyloxy diol **3f** in 47% yield and 97% ee. Selective protection of primary alcohol in diol **3f** was achieved using Bu_2SnO and benzyl bromide in 82%. Alcohol **23** was then subjected to Appel reaction condition to give *anti*-benzyloxybromo compound **24**, nucleophilic displacement of bromo in **24** to azide **25** was achieved with 78% yield. Deprotection of benzyl ethers and reduction of azide proceeded smoothly under catalytic hydrogenation of **25**, followed by acylation with AC_2O gave triacetate **19**.

Oxidation of **26** with mCPBA converted the methylsulfanyl group into methyl sulfonyl group which was then subjected to the known reaction sequences such as acid mediated hydrolysis and N-acylation with 78% yield over three steps with 97%ee (**Scheme 3**).



Scheme 3: (i) NBS, BnOH, CH_3CN, 25 °C, 3 h, 84%; (ii) NaOH powder, THF, 25 °C, 2 h, 86%; (iii) (*R,R*)-Co(III)(salen)OAc (1 mol%), THF, H_2O (0.48 equiv.), 0 ºC, 12 h; (iv) Bu_2SnO, toluene, reflux, 12 h. then BnBr, TBAB, reflux, 18 h, 84%; (v) CBr_4, imidazole, PPh_3, CH_2Cl_2, 0 °C, 4 h, 76%; (vi) NaN_3, DMF, 60 °C, 12 h, 78%; (vii) (a) 10% Pd/C, MeOH, H_2 (1atm), 25 ^oC, 12 h; (b) Ac_2O, DMAP, pyridine, 94%; (viii) (a) *m*CPBA, CH_2Cl_2; (b) aq. 5% HCl, 90 ^0C; (c) Cl_2CHCO_2Me, 90 ^oC, 1 h, 78% (for 3steps).

CHAPTER 2

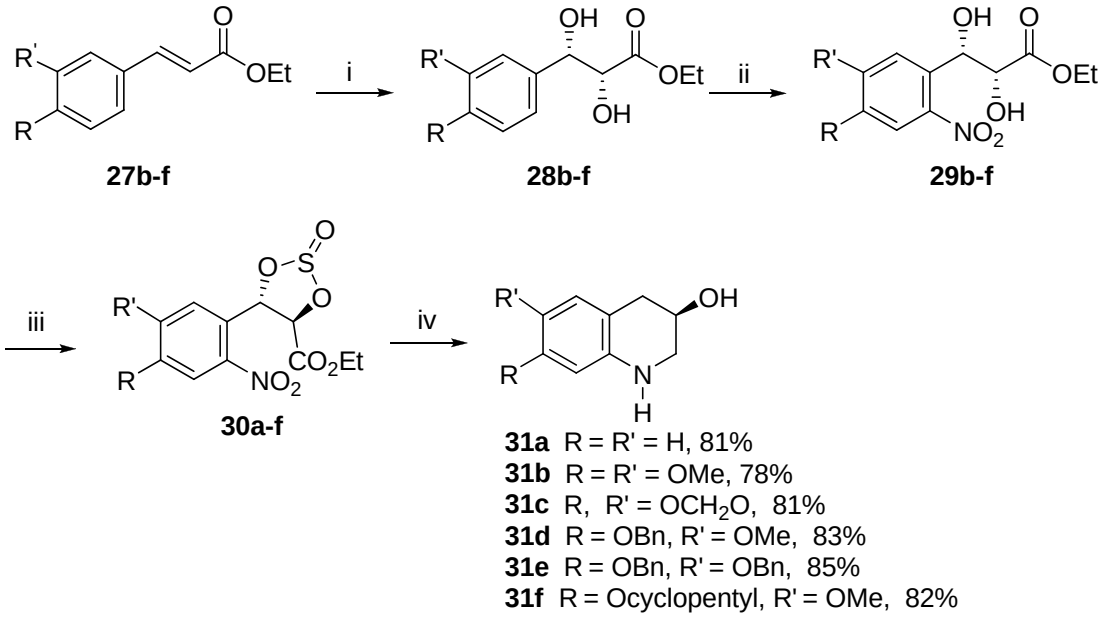
Asymmetric Synthesis of Tetrahydroquinolin-3-ols, Anachelin H Chromophore and 1-((*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-yl)propan-1-one

$CoCl_2$–$NaBH_4$ combination is one of the most effective reducing systems, capable of selectively reducing a variety of functional groups including alkene, N_3, CN, etc. when

present alone. This chapter deals with development of a novel method for the synthesis of tetrahydroquinolin-3-ols **31a-e** *via* $CoCl_2$-catalyzed reductive cyclization of cyclic sulphites followed by its application in the synthesis of anachelin H chromophore and 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one (*S*-903). This chapter is divided into three sections.

Section I: A New Route to the Synthesis of *(R)*-Tetrahydroquinolin-3-ols *via* $CoCl_2$-catalyzed Reductive Cyclization of Cyclic Sulphites with $NaBH_4$

Substituted tetrahydroquinolines display a wide range of physiological activities[9] such as analgesic, antiarrhythmic, cardiovascular, immuno-suppresent, antitumor, antiallergenic, anticonvulsant antifertility and NMDA antagonist activities.[10] This section describes a novel methodology for the synthesis of substituted tetrahydroquinolin-3-ols **31a-f** *via* $CoCl_2$-catalyzed one-pot reduction of cyclic sulphites **30a-f** using $NaBH_4$ as reducing agent.



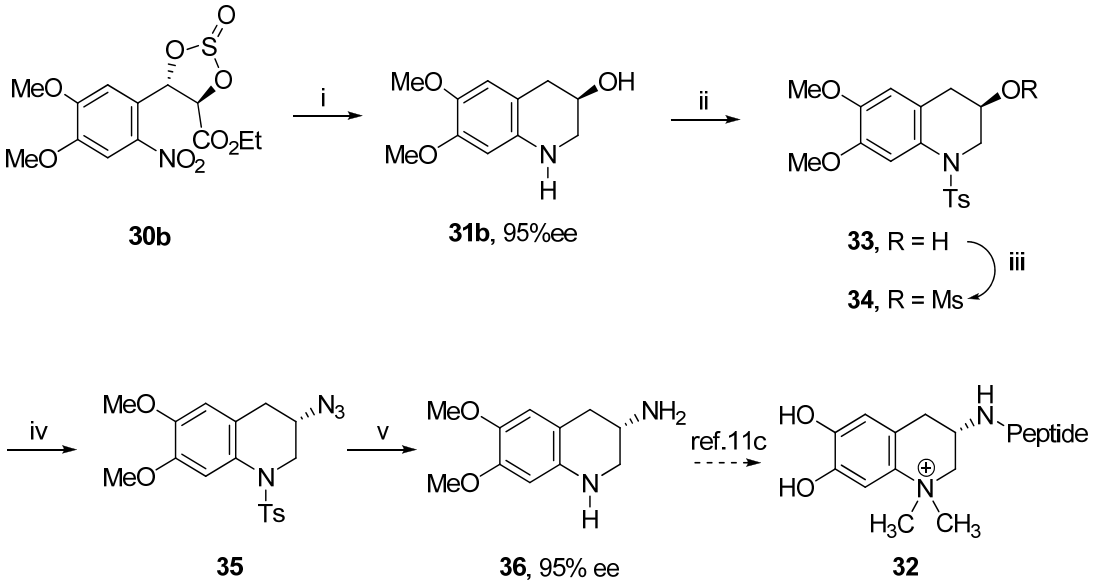
Scheme 4: (i) OsO_4 (0.5 mol%), $(DHQ)_2$-PHAL (1 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (1 equiv.), *tert*-BuOH:H_2O (1:1), 25 °C, 24 h, 80-95%; (ii) conc. HNO_3,CH_2Cl_2, 1 h, 25 °C, 70-81%; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 91-95%; (iv) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$ (4 equiv.), EtOH, 0 -25 °C.

α,β-Unsaturated esters **27b-f**, prepared readily from Wittig olefination of the corresponding benzaldehydes, were subjected to Os-catalyzed asymmetric dihydroxylation (ADH) using $(DHQ)_2$-PHAL as ligand to give the corresponding *α*-diols

28b-f, which on nitration using conc. HNO_3 in CH_2Cl_2 at 25 ºC gave the nitro derivatives **29b-f** in high yields. Nitrodiols **29a-f** were then smoothly converted into the corresponding cyclic sulphites **30b-f** ($SOCl_2$, Et_3N in CH_2Cl_2) in excellent yields. These cyclic sulphites **30a-f**, when subjected to $CoCl_2$-catalyzed reduction with $NaBH_4$, the corresponding tetrahydroquinoline derivatives **31a-f** were obtained in 78-83% yields. In this reaction, we observed the reduction of multifunctional groups and cyclization, all occurring in a single step (**Scheme 4**).

Section II: Asymmetric Formal Synthesis of Anachelin H Chromophore

Anachelin H intermediate **32**, a secondary metabolite recently isolated from cyanobacterium *Anabaena cylindrica*, which serves as a ligand for iron (siderophores) mediating iron uptake.[11a,b] In this section, we describe a short formal synthesis of anachelin H chromophore **32**, by employing $CoCl_2$-catalyzed one-pot reductive cyclization of the corresponding cyclic sulphite **30b** as the key step (**Scheme 5**)**.**



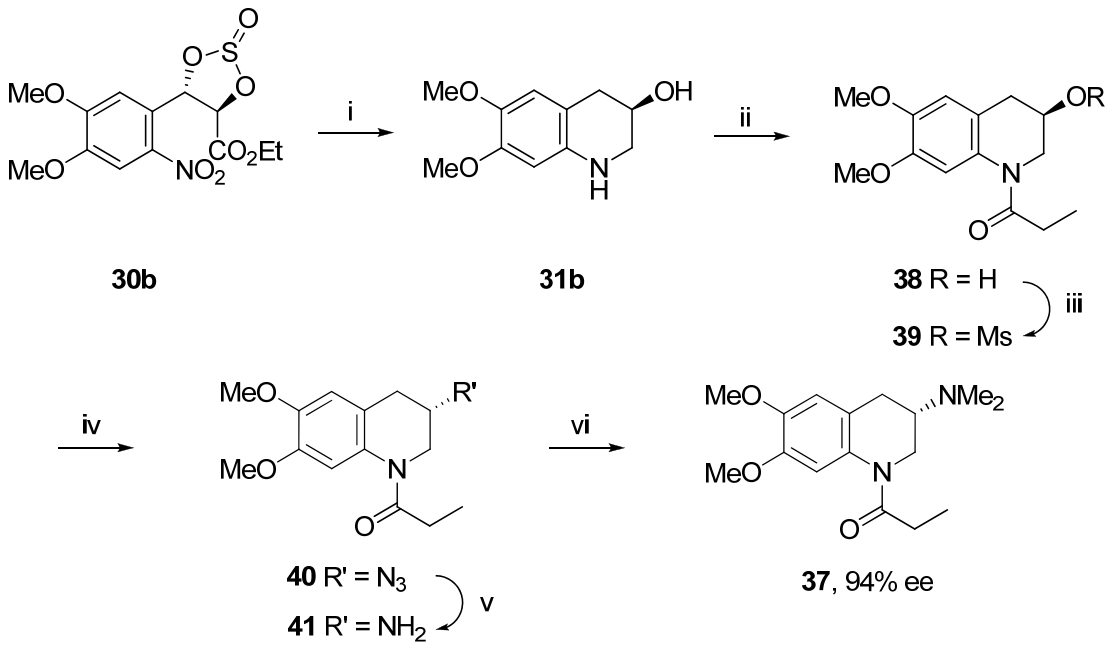
Scheme 5: (i) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$ (4 equiv.), EtOH, 0-25 °C, 6 h, 78%; (ii) TsCl, Et_3N, CH_2Cl_2, 25 °C, 82%; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (iv) NaN_3, DMF, 80 °C, 12 h, 91%; (v) Na(Hg), NaH_2PO_4, MeOH, 25 °C, 76%.

Catalytic one-pot reduction of cyclic sulphite **30b** using $CoCl_2 \cdot 6H_2O$ (1 mol%) and $NaBH_4$ (5 equiv.)**,** gave the tetrahydroquinoline derivative **31b** in 78% yield and 95% ee. Selective amine protection in **31b** was achieved with TsCl to give amide **33** in 82% yield. Chiral amido alcohol **33** was then mesylated (MsCl, Et_3N in CH_2Cl_2) to give **34** and

subsequent displacement of the mesylate with azide anion (NaN_3, DMF) gave azide **35**. Finally, azide **35** was subjected to reduction with sodium amalgam in NaH_2PO_4 whereby reduction of both azide and tosylate functions took place efficiently to afford the known intermediate (*S*)-3-aminotetrahydroquinoline **36** in 76% yield and 95% ee. The conversion of (*S*)-3-aminotetrahydroquinoline **36** to anachelin H chromophore **32**[11c] has been reported in the literature.

Section III: Asymmetric Synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one

Asymmetric synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one (**37),** a positive inotropic agent,[12] is described in this section.



Scheme 6: (i) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$, EtOH, 0-25 °C, 78%; (ii) $(CH_3CH_2CO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 91%; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (iv) NaN_3, DMF, 80 °C, 12 h, 91%; (v) H_2 (1 atm) 10% Pd/C, MeOH, 25 °C, 12 h; (vi) HCHO (40 % aq. solution), HCO_2H, 80 °C, 3 h, 73%.

Tetrahydroquinolinol **31b,** prepared by the $CoCl_2$-catalyzed reduction of the corresponding cyclic sulphite **30b,** was treated with propionic anhydride to give amido alcohol **38** in 93% yield and 95.5% ee. Alcohol **38** on mesylation (MsCl, Et_3N in CH_2Cl_2) followed by its displacement with azide (NaN_3 in DMF) gave azide **40** in 91% yield**.**

Finally, azide **40** was reduced to amine **41** [H_2 (1 atm), 10% Pd/C]. The *N, N'*-dimethylation of amine **41** was achieved by its treatment with formic acid and formaldehyde solution under reflux condition to afford **37** in 73% yield and 94% ee (**Scheme 6**).

CHAPTER 3

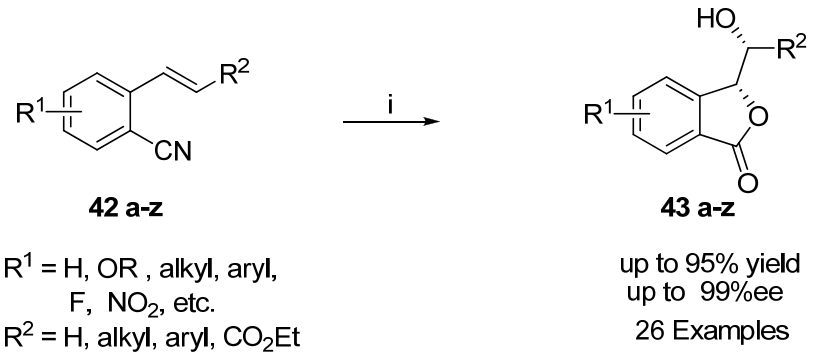
CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-substituted Chiral Phthalides and its Application to the Synthesis of (-)-Matteucen C, Isocoumarins and Alkylidenephthalides

Sharpless asymmetric dihydroxylation (ADH) is one of the most effective methods for the preparation of chiral diols, which are important intermediates for the synthesis of various bioactive compounds. This chapter deals with development of a novel method for the synthesis of chiral phthalides (**43a-z**) *via* CN-assisted oxidative cyclization of cyano cinnamates followed by its application to the synthesis of (-)-matteucen C, isocoumarins and alkylidenephthalides. This chapter is divided into three sections.

Section I: CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-Substituted Chiral Phthalides

Chiral phthalides [isobenzofuran-1(3*H*)-ones] comprising of 5-membered lactones are found in a large number of plant products displaying broad and potent biological activities such as anticonvulsant, anesthesia, antiischemic, antiHIV, anticancer and antibiotics.[13] The Sharpless' asymmetric dihydroxylation (AD) of alkenes has emerged as a most reliable method for the preparation of chiral 1,2-diols, widely found in bioactive compounds and pharmaceuticals. Ligand acceleration is central to the efficiency and selectivity of AD catalytic process.[14] In this section, we describe a single-step oxidative cyclization of cyanocinnamates and styrene substrates that affords 3-substituted phthalides in high yields *via* synergetic acceleration of CN and osmate ester groups present in proximity positions. From the course of our study on the construction of 3-substituted tetrahydroquinolin-3-ols *via* AD process and Co-catalyzed "one-pot" reductive cyclization ($CoCl_2$-$NaBH_4$) of nitro cyclic sulfites, we reasoned that subjecting *cyano* cyclic sulfites to the same reaction conditions should afford synthetically useful benzazepines. To our surprise, when ethyl 2-cyanocinnamate **42a** was subjected to a typical AD-mix-β process for 7 h, with THF as co-solvent for better solubility, the

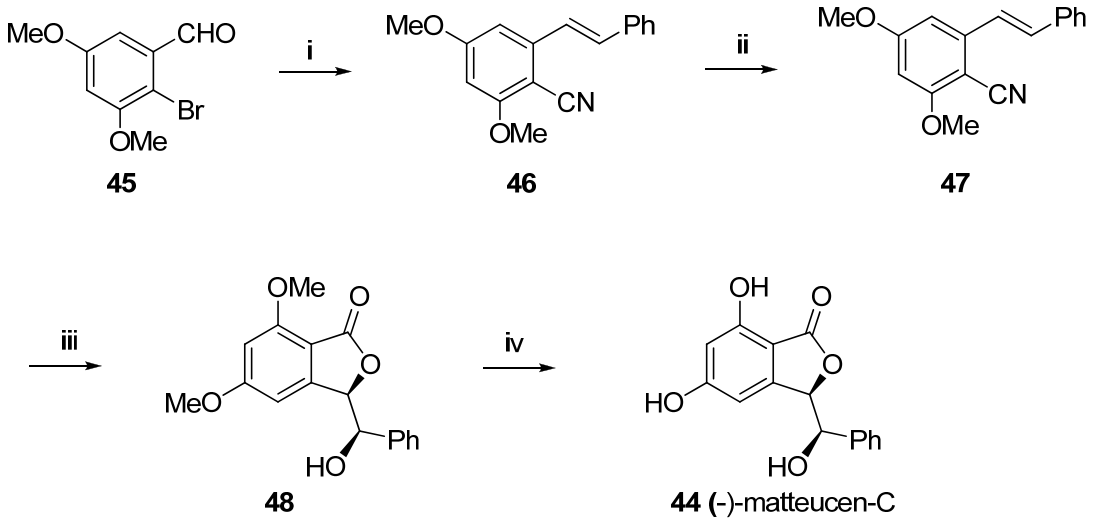
corresponding chiral phthalide **43a** was obtained exclusively in 99%ee. Encouraged by this result, we examined the scope of the reaction with other cyano cinnamate esters and styrene derivatives **42b-z**. In every case, the reaction proceeded rapidly in 3 to 7 h giving the desired phthalides **43b-z** in excellent yields and ees (up to 99%). For instance, substrates having halogen, highly electron-rich or electron-deficient substituents on the aromatic ring including 2-naphthyl nuclear system underwent this oxidative cyclization smoothly affording the corresponding phthalides in excellent yields (**Scheme 7**).



Scheme 7: (i) AD-mix-β, $MeSO_2NH_2$, t-BuOH:THF:H_2O (0.5:0.5:1), 25 °C, 3 to 7 h.

Section II: First Enantioselective Synthesis of (-)-Matteucen C

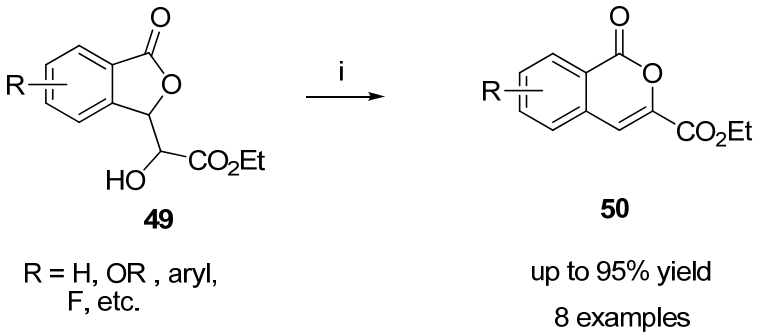
Matteucen C (**44**), isolated from Chinese medicinal herb, is used in the treatment of hemostatics and relieving ostalgia. [15] This section illustrates a practical, first enantioselective synthesis of (-)-matteucen C **44**, by employing CN-assisted oxidative cyclization of the corresponding *o*-cyano styrene derivative **47** as the key step. Our approach to the synthesis of (-)-matteucen C **47** commenced with 2-bromo-3,5-dimethoxybenzaldehyde **45**, which was subjected to Wittig reaction to afford *trans*-stilbene **46** in 82% yield. Rosenmund-von Braun reaction was carried out for conversion of bromo stilbene **46** to cyano stilbene **47** using CuCN under reflux condition in DMF. Cyano stilbene **47** was then subjected to AD-mix-β process to give chiral phthalide **48** in 93% yield and 99%ee *via* CN-assisted "one-pot" oxidative cyclization. Finally, demethylation of chiral phthalide **48** with BBr_3 in CH_2Cl_2 gave (-)-matteucen C in 69% yield and 99% ee (**Scheme 8**). Thus, an efficient enantioselective synthesis of (-)-matteucen C has been achieved for the first time, confirming its structural and stereochemical assignments using CN-assisted one-pot oxidative cyclization.



Scheme 8: (i) $PhCH_2PPh_3^+I^-$, *n*BuLi, THF, 0-25 °C, 3 h, 82%; (ii) CuCN (3.5 equiv.), DMF, reflux, 14 h, 83%; (iii) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH:THF:H_2O (0.5:0.5:1), 25 °C, 7 h, 93%; (iv) BBr_3, CH_2Cl_2, 25 °C, 12 h, 69%.

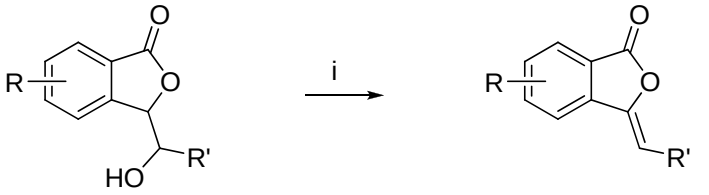
SECTION III: A Novel Approach to Isocoumarins and Alkylidenephthalides

Isocoumarins are important secondary metabolities obtained from various fungi and possess a wide range of biological activities.[16] The alkylidenephthalides have antispasmodic, herbicidal, and insecticidal activities.[17]In view of the biological activity and synthetic utility as intermediates, we have developed a novel route to synthesize these compounds at ambient conditions using PPh_3 and DEAD. We observed that hydroxyphthalides **49,** on treatment with DEAD (1.5 equiv.) and PPh_3 (1.5 equiv.) gave isocoumarins **50** in 84-95% yields. In the case of both electron-donating as well as electron withdrawing substituents on aromatic ring of hydroxyphthalides gave the corresponding isocoumarins in one-pot with excellent yields (**Scheme 9**).



Scheme 9: (i) PPh_3 (1.5 equiv.), DEAD (1.5 equiv.), THF, 25 °C, 30 min.

During the course of our investigation on synthesis of isocoumarins, we observed that simple variation in hydroxyl phthalides **51**, led to the formation of biologically active alkylidenephthalides **52** in one-pot up to 92% yield. This transformation holds good for both electron-donating as well as electron withdrawing substituents on aromatic ring of hydroxyphthalides **51** (**Scheme 10**).



51 **52**

R = H, OR, etc.
R' = H, alkyl

up to 95% yield
9 examples

Scheme 10: (i) PPh_3 (1.5 equiv.), DEAD (1.5 equiv.), THF, 25 °C, 5 h.

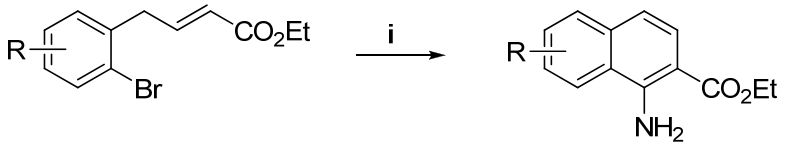
CHAPTER 4

CuCN-Mediated "One-pot" Route to 1-Amino-2-naphthalenecarboxylic acid Derivatives and 3-Substituted Phthalides: Enantioslective Synthesis of Colletotrialide

Copper(I) cyanide (CuCN) is a versatile reagent employed in many organic transformations. For example (i) aryl nitriles can be prepared by the cyanation of aryl halides with an excess of CuCN in polar high-boiling solvent such as DMF, nitrobenzene, or pyridine at reflux temperature (Rosenmund-von Braun Reaction) (ii) in the regioselective and stereoselective allylation and conjugate additions (iii) in the palladium coupling of α-lithio amines and aryl iodides. This chapter deals with development of a novel "one-pot" route to 1-amino-2-naphthalenecarboxylic acid derivatives **54** from the corresponding bromo derivatives **53** and 3-substituted phthalides **56** from the corresponding bromo alcohols **55** *via* CuCN-mediated cascade and tandem reactions respectively. Also included is its application to the enantioselective synthesis of colletotrialide. This chapter is divided into three sections.

Section I: CuCN-Mediated "One-pot" Cascade Route to 1-Amino-2-naphthalenecarboxylic Acid Derivatives

1-Amino-2-naphthalenecarboxylic acid derivatives **54** are the key intermediates of dyes and pigments useful in peptide synthesis.[18] There are very few methods available in the literature for the direct synthesis of 1-amino-2-naphthalenecarboxylic acid derivatives. Moreover, known methods involve multiple-step sequences and also the process requires consumption of large quantities of hazardous chemicals with longer reaction time constituting less efficiency and narrow substrate scope. During the course of our investigation on Rosenmund-von Braun Reaction (Br – CN exchange) of **53** with CuCN, we observed an annulation strategy to 1-amino-2-naphthalenecarboxylic acid derivatives **54**. This prompted us to explore the effectiveness of this "cascade" reaction using CuCN. We thus found that several 1-(2-bromo-phenyl) but-2-ene derivatives **53** when treated with CuCN (3.5 equiv.) in DMF at reflux condition, produced the corresponding 1-amino-2-naphthalenecarboxylic acid derivatives **54** in 78-86% yields (**Scheme 11**).



53 **54**

R = H, alkyl, alkoxy, halo, NO_2, CN, etc.

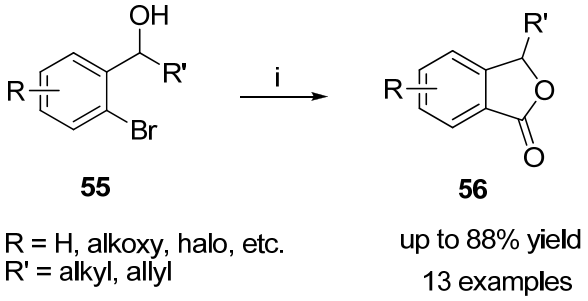
up to 86% yield
9 examples

Scheme 11: (i) CuCN (3.5 equiv.), DMF, 150 °C, 12 h.

SECTION II: CuCN-Mediated "One-pot" Synthesis of 3-Substituted Phthalides

Phthalides are versatile building blocks for the synthesis of biologically active compounds and have been proven to be useful in the treatment of circulatory and heart diseases.[16] In particular, 3-substituted phthalides are useful intermediates for the synthesis of tri- and tetracyclic natural products, such as anthracycline antibiotics.[17] Therefore, significant effort has been focused on synthesizing these organic frameworks. However, known methods involve multiple step sequences and require consumption of large quantities of costly chemicals with narrow substrate scope. During the course of our

investigation on Rosenmund-von Braun Reaction using CuCN, we observed that one-pot conversion of *o*-bromobenzyl alcohol derivatives **55** to 3-substituted phthalides **56** (CuCN (3.5 equiv.), DMF**,** reflux) (**Scheme 12**) took place. Thus, several *o*-bromobenzyl alcohol derivatives **55** with electron-donating as well as electron withdrawing substituents on aromatic ring underwent "one-pot" tandem cyclization and 3-substituted phthalides **56** were produced in high yields.



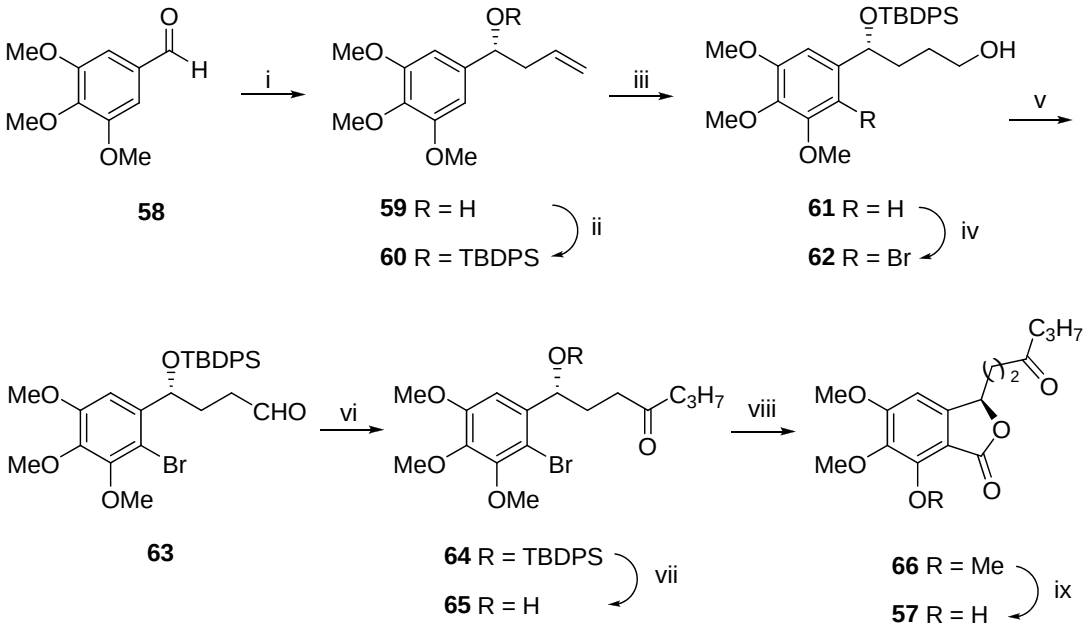
Scheme 12: (i) CuCN (3.5 equiv.), DMF, 150 °C, 10 h.

Section III: Enantioselective Synthesis of Colletotrialide

Recently a new phthalide, colletotrialide **57** was isolated from the endophytic fungus *Colletotrichum* sp. 2 which exhibited cytotoxic activity toward the HepG2 cell line.[19] This section describes the enantioselective synthesis of colletotrialide **57** via "one-pot" tandem cyclization of *o*-bromobenzyl alcohol derivatives **65**.

Our complete synthetic sequence for colletotrialide **57**, commencing from the precursor aldehyde **58**, is shown in **Scheme 14**. Aldehyde **58** was subjected to Brown allylation using (+)-Ipc_2B(allyl)borane at -78 ºC to afford homoallylic alcohol **59** in 89% yield and 95% ee, which was protected as its silyl ether **60** in 96% yield. Regioselective hydroboration and oxidation of olefin **60** resulted in primary alcohol **61** in 84% yield. Aromatic electrophilic bromination of alcohol **61** (NBS, CH_2Cl_2) provided brominated alcohol **62** in 94% yield, which was further converted to the desired ketone **64** in three-step sequence: (i) the primary alcohol function in **62** was oxidized (IBX, DMSO) to provide the corresponding aldehyde **63**; (ii) subsequent *n*-propyl Grignard addition yielded the corresponding secondary alcohol; (iii) secondary alcohol was oxidized to give ketone **64** using Swern oxidation ($(COCl)_2$, Et_3N, CH_2Cl_2). Deprotection of the silyl group in **64 (**TBAF, THF) provided alcohol **65** with 88% yield. Alcohol **65** was subjected

to one-pot tandem cyclization to afford chiral phthalide **66** in 86% yield. Finally selective deprotection of mono methyl ether ($AlCl_3$) furnished colletotrialide **57** in 74% yield (**Scheme 14**).



Scheme 13: (i) (+)-Ipc_2B(allyl)borane, Et_2O, -78 ºC, 1 h then 1N NaOH, 30% H_2O_2, 89%, 95% ee; (ii) TBDPSCl, Et_3N, DMF, 25 °C, 8 h, 96%; (iii) BH_3.DMS, THF, 25 °C, 2h then 1N NaOH, 30% H_2O_2, 84%; (iv) NBS, CH_2Cl_2, 25 °C, 2 h, 94%; (v) IBX, DMSO, 25 °C, 2 h, 93%; (vi) (a) C_3H_7MgI, Et_2O, 25 °C, 3 h; (b) $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C, 1 h, 92%; (vii) TBAF, THF, 25 °C, 10 h, 88%; (viii) CuCN (3.5 equiv.), DMF, reflux, 12 h, 86%; (ix) $AlCl_3$, C_2H_5SH, CH_2Cl_2, 74%.

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CHAPTER I

Cobalt-catalyzed Hydrolytic Kinetic Resolution of Alkoxy Epoxides: A Short Enantioselective Synthesis of (*S*,*S*)-Reboxetine, (-)-Chloramphenicol and (+)-Thiamphenicol

Section I:

Cobalt-catalyzed hydrolytic kinetic resolution of alkoxy epoxides

1.1.1 Introduction

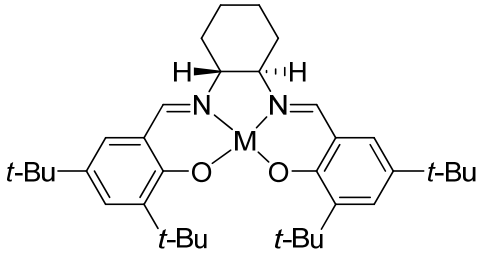
The enantiomerically pure *syn*- or *anti*-alkoxy epoxides and the corresponding diols are valuable 'building blocks' for asymmetric synthesis of bioactive pharmaceuticals and ligands.[1] In principle, access to these building blocks may be provided by several routes including Sharpless' methods of epoxidation and dihydroxylation, and other tedious methods. However, they generally lead to multi-step reaction sequences including protection/deprotection of various functional groups, thereby limiting the overall yield and the enantioselectivity of the process particularly unsuitable for atom economic synthesis. Jacobsen's Hydrolytic Kinetic Resolution (HKR) that uses readily accessible Co-based chiral salen complexes as catalyst and water as the only reagent to afford chiral epoxides and diols of high ee in excellent yields, has been comprehensively studied in recent years to reveal its mechanistic and synthetic aspects.[2] In the present section, we have described a flexible, novel method that employs HKR of racemic alkoxy epoxides to generate two stereocentres of high optical purities in a single step for the first time.

1.1.2 Hydrolytic kinetic resolution (HKR)

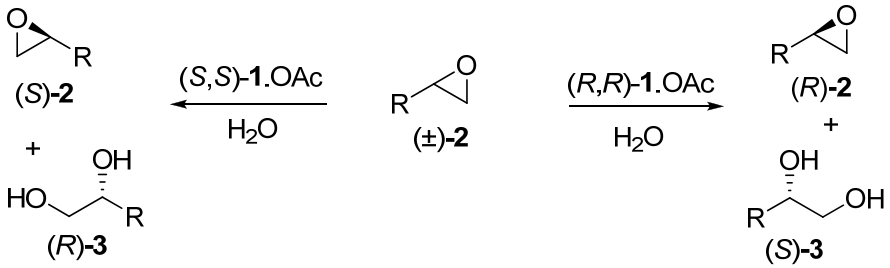
The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[3] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[4] Thus epoxides

are versatile building blocks for organic synthesis. However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomerically pure form. Terminal epoxides are available very inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, given an economical and operationally simple method. Readily accessible synthetic catalysts (for example: chiral cobalt-salen complexes, **1**)[5] have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent, no added solvent, and low loadings of a recyclable catalyst (0.5 mol%), and it affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric enrichment. One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions. This is an important consideration in the present case, since low-molecular weight terminal epoxides are typically liquids at room temperature and are not readily derivatized as salts, and therefore it is not a straightforward matter to upgrade their enantiomeric composition by crystallization. However, in the absence of straightforward substrate racemization protocols, kinetic resolutions have the significant disadvantage of a 50% maximum yield of substrate recovery. With a specific interest in devising a practical method for obtaining highly enantioenriched terminal epoxides, the following criteria must be met in order for a kinetic resolution approach to be viable[6]: (1) The racemic epoxides must be inexpensive or easily accessible from inexpensive commercial starting materials. (2) The catalyst for the resolution must be readily

available in both enantiomeric forms. In the optimal case, the catalyst would be used in small quantities in the resolution and would be recyclable. (3) The nucleophile used for the ring opening should be inexpensive and easily handled. (4) The resolved epoxides must be obtained in good yield and very high enantiopurity and must be easily separated from the ring-opened products. (5) Ideally, although not necessarily, the ring-opened byproducts should also be valuable chiral building blocks and be obtainable in high enantiomeric excess.



1, M = Co



Scheme 1: Jacobsen's Hydrolytic Kinetic Resolution (HKR) of racemic epoxide (±)-**2**

The (salen)Co complex **1** has been well-established to catalyze the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 1**).[7] This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above. First, racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes.

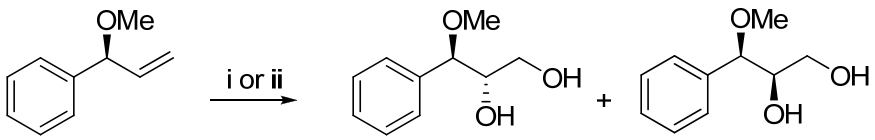
In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[8] The cobalt analogues (*R*,*R*)-**1** and (*S*,*S*)-**1** proved equally accessible, and these are also now available in bulk. Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture. Fourth, for those examples that were described in the preliminary report, highly enantioenriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantioenriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[9] Two useful methods for the generation of complex **1.**OAc have been developed. Method A involves isolation of **1.**OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate ~ 1 M solution, and acetic acid (2 equiv.) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed *in vacuo*, affording **1.**OAc as a brown solid residue that can be used without further purification. Method B involves *in situ* generation of **1.**OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere.

1.1.3 Review of Literature

Several syntheses of enantiomerically pure *syn*- or *anti*-alkoxy epoxides and the corresponding diols have been reported in the literature by two important routes: Sharpless' methods of epoxidation and dihydroxylation; which are described below.

Smith's approach (1995)[10]

Smith *et al.* have synthesized *syn*-methoxy diol **5a** and *anti*-methoxy diol **4b** by employing Sharpless asymmetric dihydroxylation as the key reaction. Thus, methyl protected allyl alcohol **6** was subjected to *AD-mix-β* to give *anti* methoxy diol **4b** and *syn* methoxy diol **5a** in 81% overall yield with dr = 5:1. Similarly, when allyl alcohol **6** was subjected to *AD-mix-α anti*-methoxy diol **4b** and *syn*-methoxy diol **5a** were obtained in 87% yield with dr = 1.4:1 (**Scheme 2**).

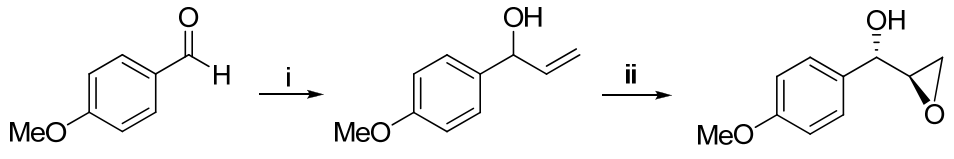


6 **4b** **5a**

Scheme 2: (i) AD-mix-β, *t*-BuOH:H_2O (1:1), 0 °C, 81%, dr = 5:1; (ii) AD-mix-α, *t*-BuOH:H_2O (1:1), 0 °C, 87%, dr = 1.4:1.

Reddy's approach (2005)[11]

Reddy *et al*. have reported synthesis of chiral epoxy alcohol **7** starting from anisaldehyde **9**; the treatment of which with vinyl magnesium bromide gave allyl alcohol **8**.



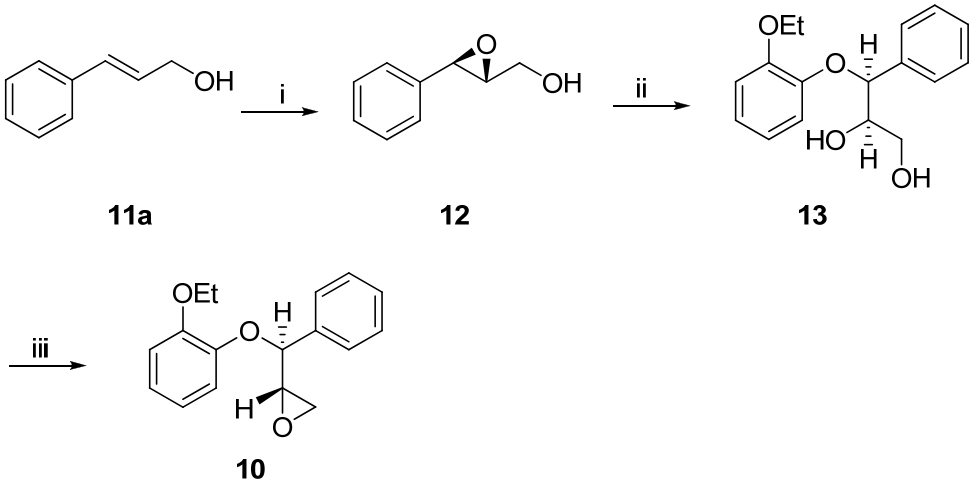
9 **8** **7**

Scheme 3: (i) 1M vinyl magnesium bromide in THF, dry ether, 0 °C, 4 h, 96%; (ii) (+)-DIPT, $Ti(O^iPr)_4$, *t*BuOOH, CH_2Cl_2, -20 °C, 14 h, 46%.

The enantioselective epoxidation of the racemic allyl alcohol **8** in the presence of L-diisopropyl tartarate gave epoxy alcohol **7** in 46% yield with 98%ee (**Scheme 3**).

Henegar's approach (2007)[12]

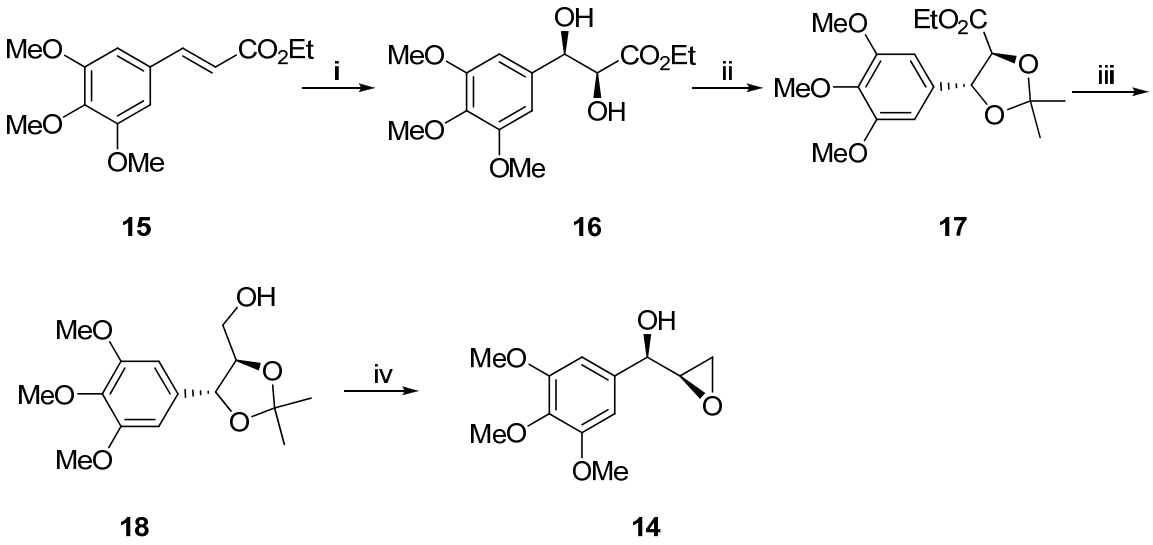
Henegar *et al*. have described the synthesis of chiral *anti*-aryloxy diol **13** and *syn*-aryloxy epoxide **10,** starting from commercially available cinnamyl alcohol **11a**, which was subjected to Sharpless asymmetric epoxidation to furnish epoxide **12** with >99% ee. The regioselective ring opening of epoxide **12** with 2-ethoxy phenol gave a single regioisomer *anti*-aryloxy diol **13** in 52% yield. In order to establish the desired *syn*-configuration, these authors have performed a three-step reaction sequence: (i) chemoselective TMS protection of primary alcohol in diol **13**; (ii) mesylation of secondary hydroxyl function using MsCl; (iii) treatment of crude mesylate with NaOH in THF to furnish the appropriately oriented *syn*-aryloxy epoxide **10** in 95% yield (**Scheme 4**).



Scheme 4: (i) (-)-DIPT, $Ti(O^iPr)_4$, *t*BuOOH in toluene, CH_2Cl_2, -20 – 25 °C; (ii) 2-ethoxyphenol, NaOH, H_2O, 70 °C, 2.5 h, 52% (for 2 steps); (iii) (a) TMSCI, Et_3N, CH_2Cl_2, 25 °C; iv) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (v) 2N NaOH, THF, 25 °C, 4 h, 95%.

Panda's approach (2010)[13]

Panda *et al.* have synthesized *syn*-epoxy alcohol **14** by employing Sharpless asymmetric dihydroxylation as the key reaction. Thus, unsaturated ester **15** was subjected to asymmetric dihydroxylation to give the diol **16** in 98% yield, which was protected as its acetonide **17** in almost quantitative yield (97%). Further, acetonide-protected ester **17** was subjected to $LiAlH_4$-mediated reduction in dry THF to furnish alcohol **18** in 94% yield; which was then protected as its mesylate by treatment with $MsCl/Et_3N$ in dry CH_2Cl_2 at 0 °C. Further, acetonide cleavage of mesylate was achieved with *p*TSA and CH_3OH to give diol, which on treatment with K_2CO_3 gave epoxy alcohol **14** in 93% yield **(Scheme 5**).



Scheme 5: (i) AD-mix-β, $CH_3SO_2NH_2$, 0°C, 30 h, 91%; (ii) 2,2-dimethoxy propane, dry acetone, $BF_3.OEt_2$, 0°C, 30 min., 97%; (iii) $LiAlH_4$, dry THF, 0°C, 30 min., 94%; (iv) (a) MsCl, Et_3N, CH_2Cl_2, 0°C, 20 min., 96%; (b) cat. pTSA, CH_3OH, 0°C, 15min. quant.; (c) K_2CO_3, dry MeOH, 0°C, 2h, 93%.

1.1.4 Present Work

1.1.4.1 Objective

As can be seen from the above discussion, the literature methods for the synthesis of enantiomerically pure *syn*- or *anti*-alkoxy epoxides **20a-k** and the corresponding diols **5a-k** employ either chiral starting materials, or involve multi-step reaction sequences

including protection/deprotection of various functional groups, thereby limiting the overall yield and the enantioselectivity of the process. This is particularly unsuitable for atom economic synthesis. Despite achievements, HKR has only been applied to the resolution of simple terminal epoxides with one stereocentre.[14] To the best our knowledge, study related to HKR of functionalized epoxides (at 3-position) with two stereocentres is rare.[15]

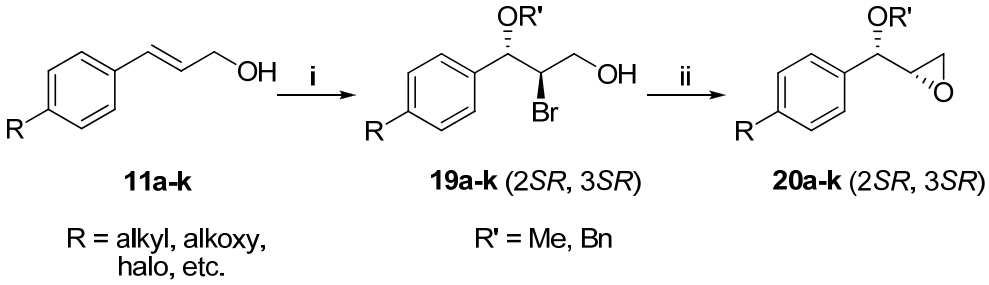
1.1.5 Results and Discussion

In the present work, we have extended the scope of substrates for HKR in order to obtain multi-functionalized molecules with two stereocentres. The aim of such an investigation is to access enantiomerically enriched alkoxy epoxides **20a-k** and diols **5a-k** by a direct and simple method from the racemic materials; thus complementing the other tedious routes. Due to their importance as 'building-blocks' for the synthesis of highly functionalized molecules, racemic alkoxy epoxides (±)-**20a-k** are chosen for the study of HKR with chiral Co-catalysts. In this section, we have described a flexible, novel method that employs HKR of racemic alkoxy epoxides (±)-**20a-k** to generate alkoxy diols **5a-k** and alkoxy epoxides **20a-k** with two stereocentres of high optical purities in a single step (**Table 1**).

1.1.5.1 Synthesis of racemic alkoxy epoxides

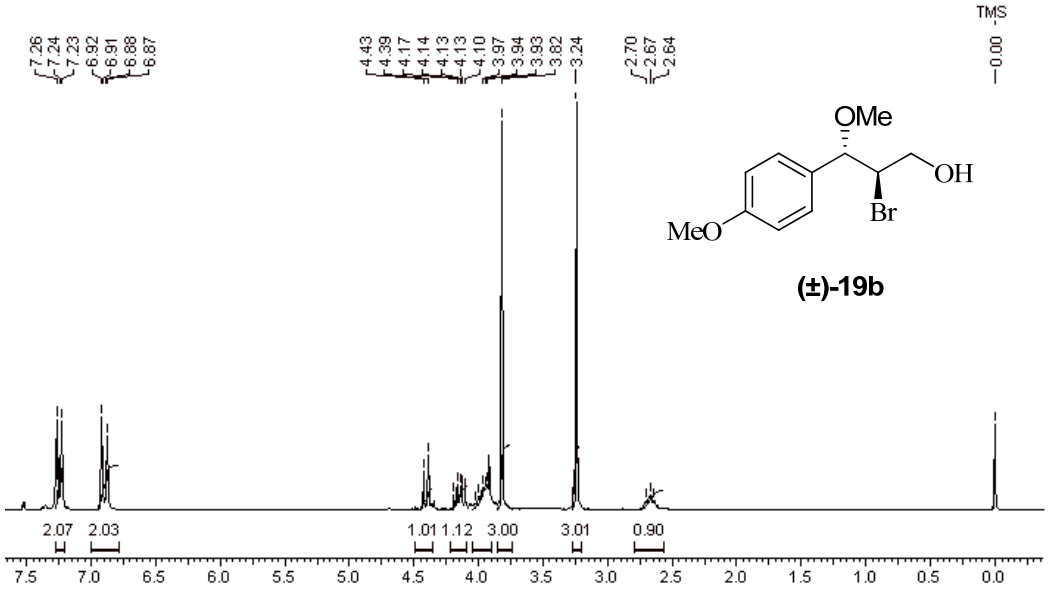
The racemic *syn*-alkoxy epoxides (±)-**20a-k**, the substrates for HKR, were efficiently prepared in two step sequence, in a highly diastereoselective manner starting from the corresponding (E)-allylic alcohols **11a-k**. Thus, cinnamyl alcohols **11a-k** were subjected to methoxy or benzyloxy bromination in presence of NBS and MeOH or BnOH, as the case may be, to give *anti*-methoxy or benzyloxy bromides **19a-k**, which were then

subjected to alkali treatment [NaOH powder, THF] that gave the *syn*-methoxy or benzyloxy epoxides, (±)-**20a-k** in 80-86% yield (**Schemes 6**).



Scheme 6: (i) NBS (1.2 equiv), MeOH or BnOH (1 equiv), CH_3CN, 25 °C, 2-3 h; 80-82% (b) NaOH powder (1.2 equiv), THF, 2-3 h, 80-86%.

The formation of *anti*-methoxy or benzyloxy bromides **19a-k** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. For example, compound (±)-**19b** showed a doublet at δ 4.41 (J = 7.4 Hz) for the benzylic proton attached to oxygen atom in the ^{1}H-NMR spectrum which was further confirmed by the corresponding methine carbon signal appearing at δ 85.3 in its ^{13}C-NMR spectrum (**Fig. 1**).



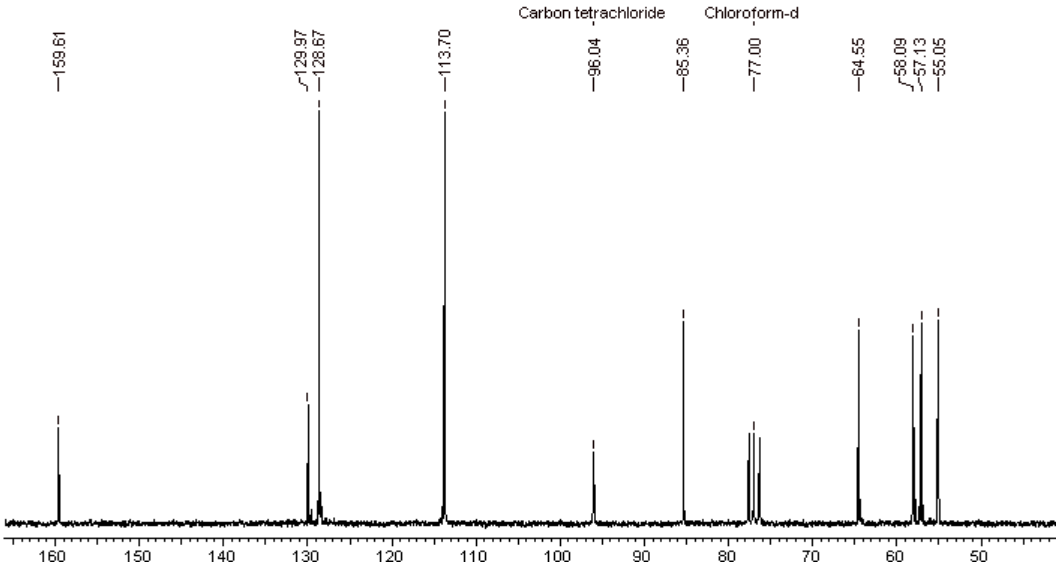
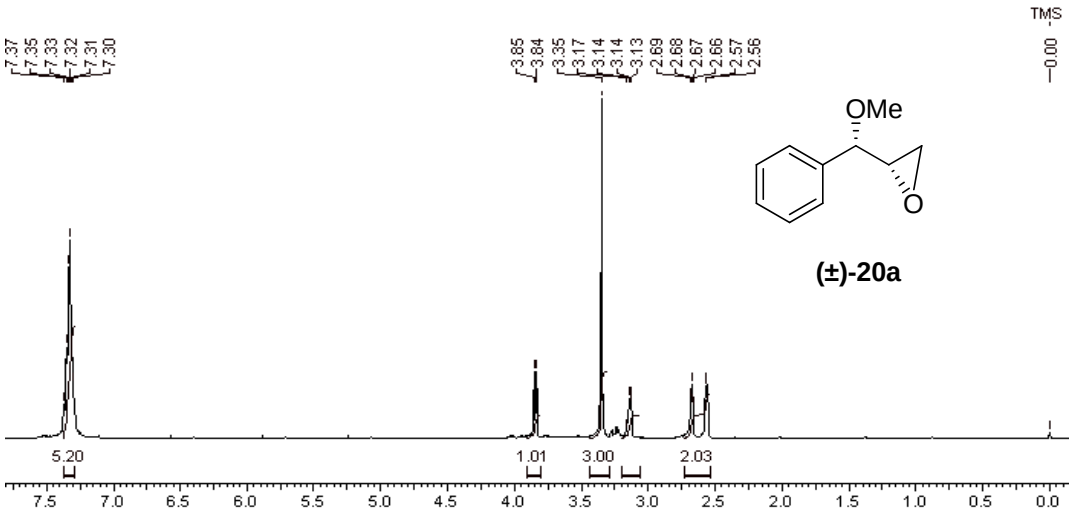


Fig. 1: ^{1}H and ^{13}C-NMR spectra of *anti*-methoxy bromide **(±)-19b**

The formation of *syn*-methoxy epoxides, (±)-**20a-e** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. For example, the ^{1}H-NMR spectrum of *syn*-methoxy epoxide, (±)-**20a** showed typical signals at δ 2.56-2.69 (m, 2H) and δ 3.13-3.17 (m, 1H) corresponding to methylene and methine protons respectively. Its ^{13}C-NMR spectrum showed characteristic signals at δ 43.8 and 55.0 due to carbons of the epoxide moiety (**Fig. 2)**.



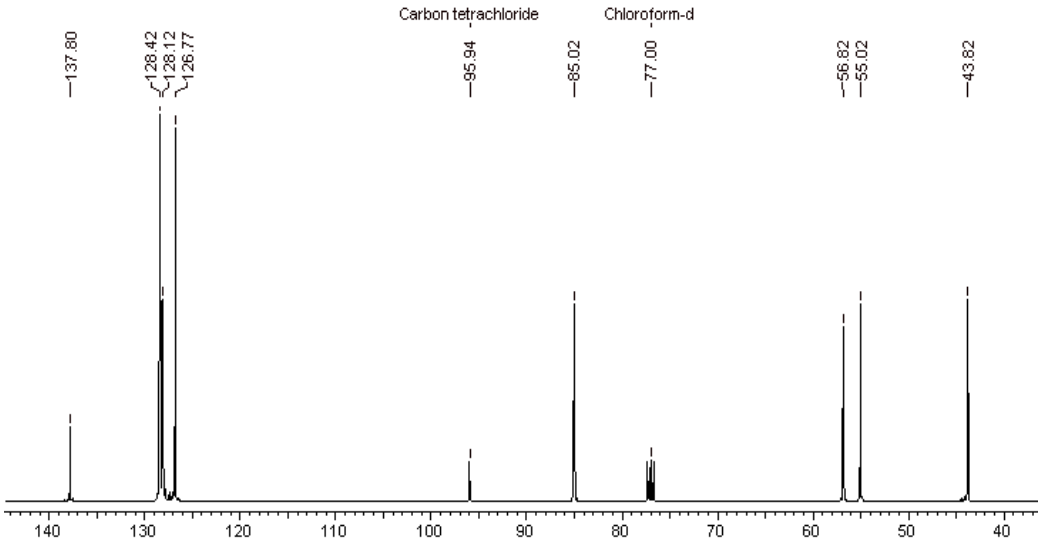
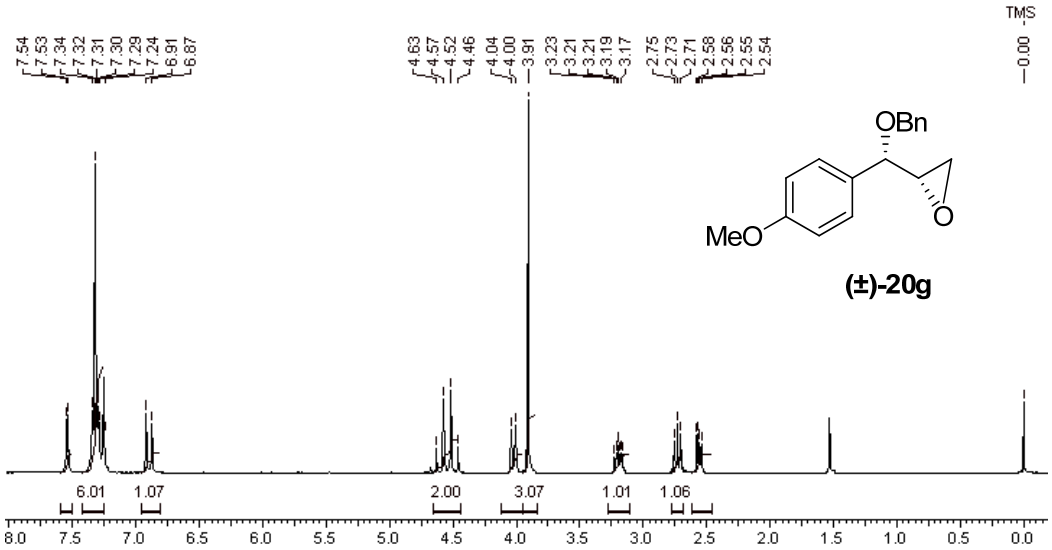


Fig. 2: ^{1}H and ^{13}C-NMR spectra of *syn*-methoxy epoxide **(±)-20a**

Similarly, the formation of *syn*-benzyloxy epoxides, (±)-**20f-k** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. The ^{1}H-NMR spectrum of *syn*-benzyloxy epoxide, (±)-**20g** showed typical signals at δ 2.54-2.75 (m, 2H) and δ 3.17-3.23 (m, 1H) corresponding to methylene and methine protons respectively. Its ^{13}C-NMR showed characteristic signals at δ 43.9 and 55.0 due to carbons of the epoxide ring (**Fig. 3)**.



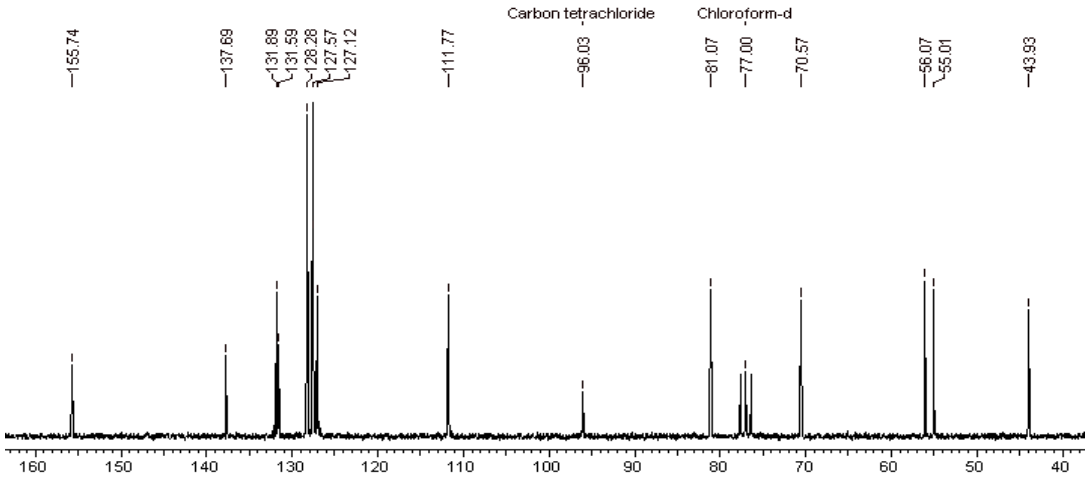
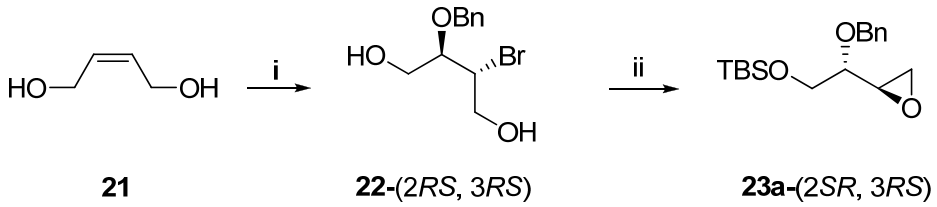


Fig. 3: ^{1}H and ^{13}C NMR spectra of *syn*-benzyloxy epoxide **(±)-20g**

In a similar fashion, *anti*-benzyloxy epoxide, (±)-**23a** was readily prepared from *cis*- 1,4-butenediol **21** in two steps. Thus, diol **21** was subjected to benzyloxybromination in presence of NBS and BnOH to give benzyloxy bromide, (±)-**22** in 82% yield (**Scheme 7**).



21 **22-**(2*RS*, 3*RS*) **23a-**(2*SR*, 3*RS*)

Scheme 7: (i) NBS (1.2 equiv), BnOH (1 equiv), CH_3CN, 25 °C, 3 h, 82%; (ii) (a) NaOH powder (1.2 equiv), THF, 2 h; (b) TBSCl, imid., CH_2Cl_2, 25 °C, 2.5 h, 84%.

The ^{1}H-NMR spectrum of (±)-**22** showed a typical signal at δ 4.69 (s, 2H) for methylene (-O-CH_2-) protons. Its ^{13}C-NMR showed a typical carbon signal at δ 72.93 corresponding to benzylic carbon attached to oxygen group (**Fig. 4).**

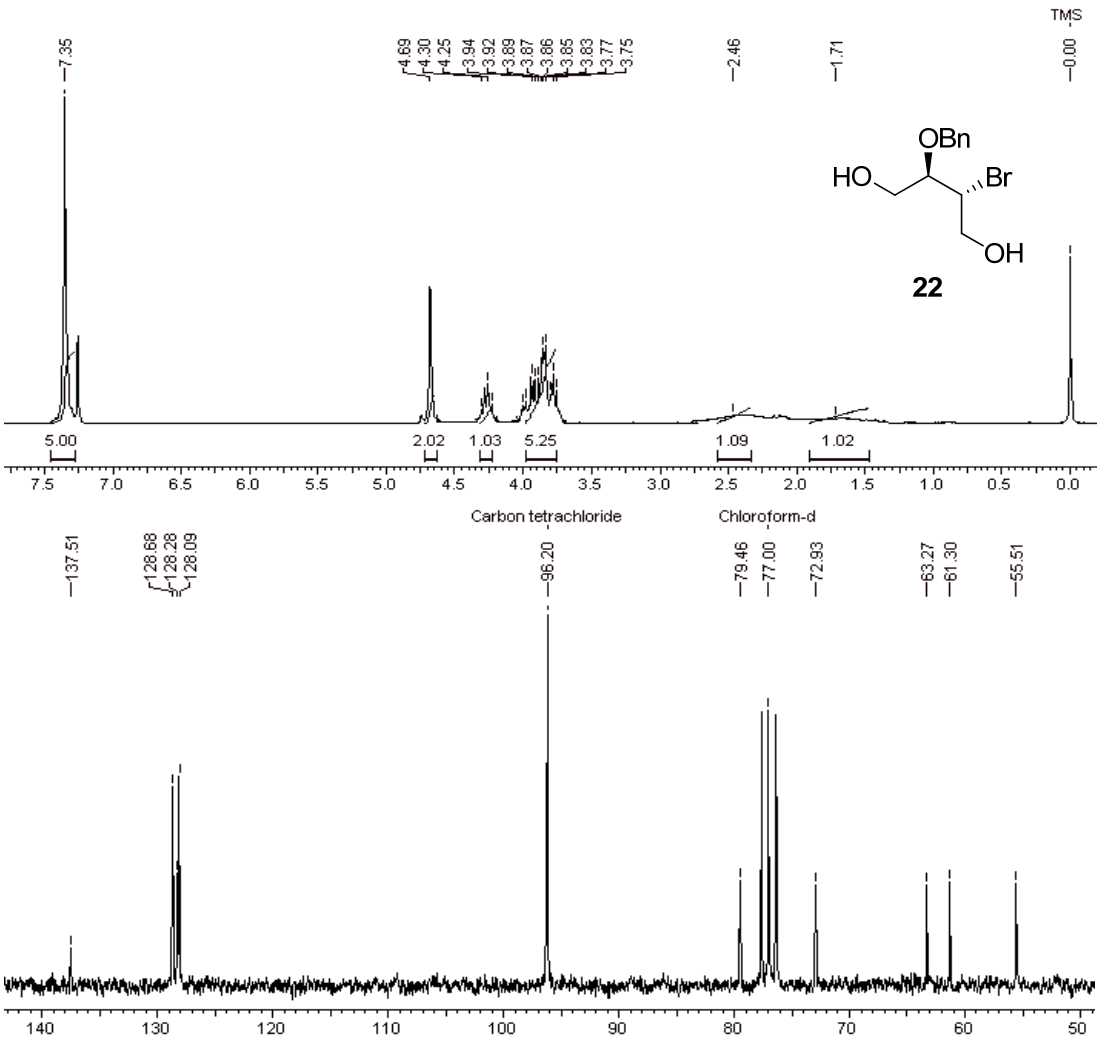


Fig. 4: ^{1}H and ^{13}C NMR spectra of benzyloxy bromo diol **(±)-22**

Benzyloxy bromide (±)-**22** was then subjected to alkali treatment (NaOH, THF) to give epoxide, which was followed by the protection of primary alcohol with TBS to give TBS-protected *anti*-benzyloxy epoxide, (±)-**23a** in 84% yield. The ^{1}H-NMR spectrum of (±)-**23a** showed signals at δ 2.69-2.74 (m, 2H) and δ 3.03-3.08 (m, 1H) corresponding to methylene and methine protons respectively. Its ^{13}C-NMR showed typical signals at δ 44.9 and 51.4 due to carbons of the epoxide ring (**Fig. 5).**

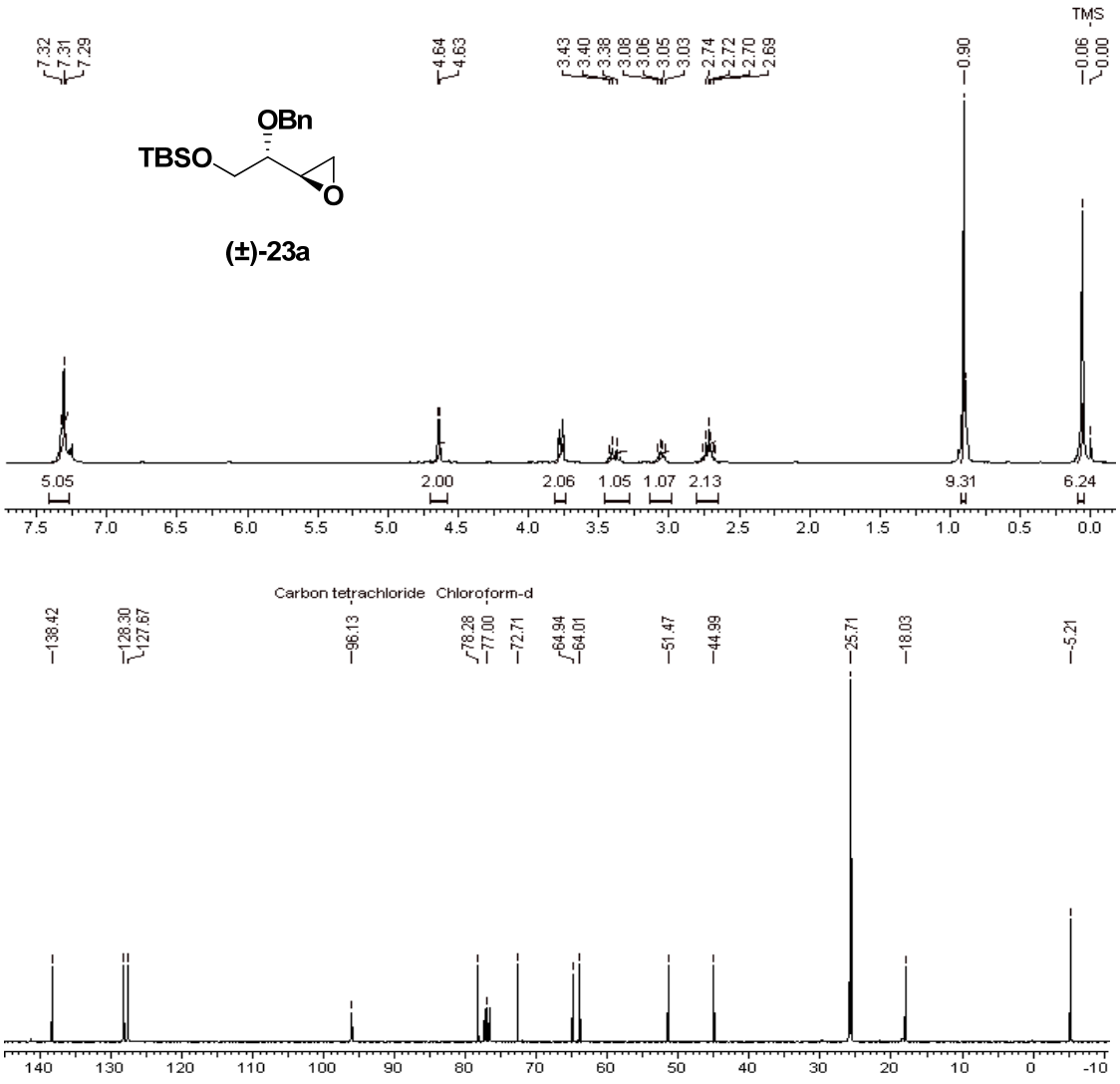


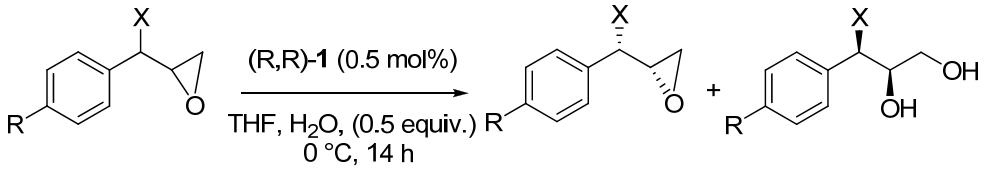
Fig. 5: ^{1}H and ^{13}C NMR spectra of *anti*-benzyloxy epoxide **(±)-23a**

The synthesis of *anti*-methoxy epoxide, (±)-**23b** was achieved following a reported procedure from racemic epoxy alcohol.[12] **12,** which involved selective ring opening with MeOH followed by its mesylation and treatment with base. Thus, in this strategy, the relative stereochemistry between the alkoxy and epoxide groups is established prior to the HKR step itself and in this way a simple asymmetric reaction can be carried out to form the key enantiomerically pure alkoxy epoxides **20a-k** with two stereocentres.

1.1.5.2 HKR of racemic alkoxy epoxides, (±)-20a-k & (±)-23a-b

Initially, when HKR of racemic syn-benzyloxy epoxide (**20a**) was performed with (*R*,*R*)-salen Co(OAc) complex (**1**) (0.5 mol%) and H_2O (0.5 equiv), the corresponding chiral *syn*-epoxide **20a** (48%, 97% ee) and *syn*-diol (**5a**) (47%, 98% ee) were isolated in high yields and optical purity (**Table 1**).

Table 1: Co-catalyzed HKR of *syn*-alkoxy epoxides



20a-k (2SR, 3SR) **20a-k** (2S,3S) **5a-k**

Sr.No	Alkoxy epoxide (±)-20a-k		Alkoxy Epoxide 20a-k		Alkoxy Diol 5a-k	
	R	X	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b,c]
a	H	OMe	48	97	47	98
b	OMe	OMe	47	98	46	97
c	Me	OMe	44	97	45	98
d	Br	OMe	45	97	42	98
e	SMe	OMe	47	98	46	97
f	H	OBn	45	98	44	98
g	OMe	OBn	49	96	47	98
h	Me	OBn	48	96	45	96
i	Cl	OBn	45	95	42	98
j	Br	OBn	44	98	47	98
k	SMe	OBn	48	96	47	97

[a] Isolated yield after column chromatographic purification. [b]ee determined by chiral HPLC
[c] ee determined by Mosher's ester analysis.

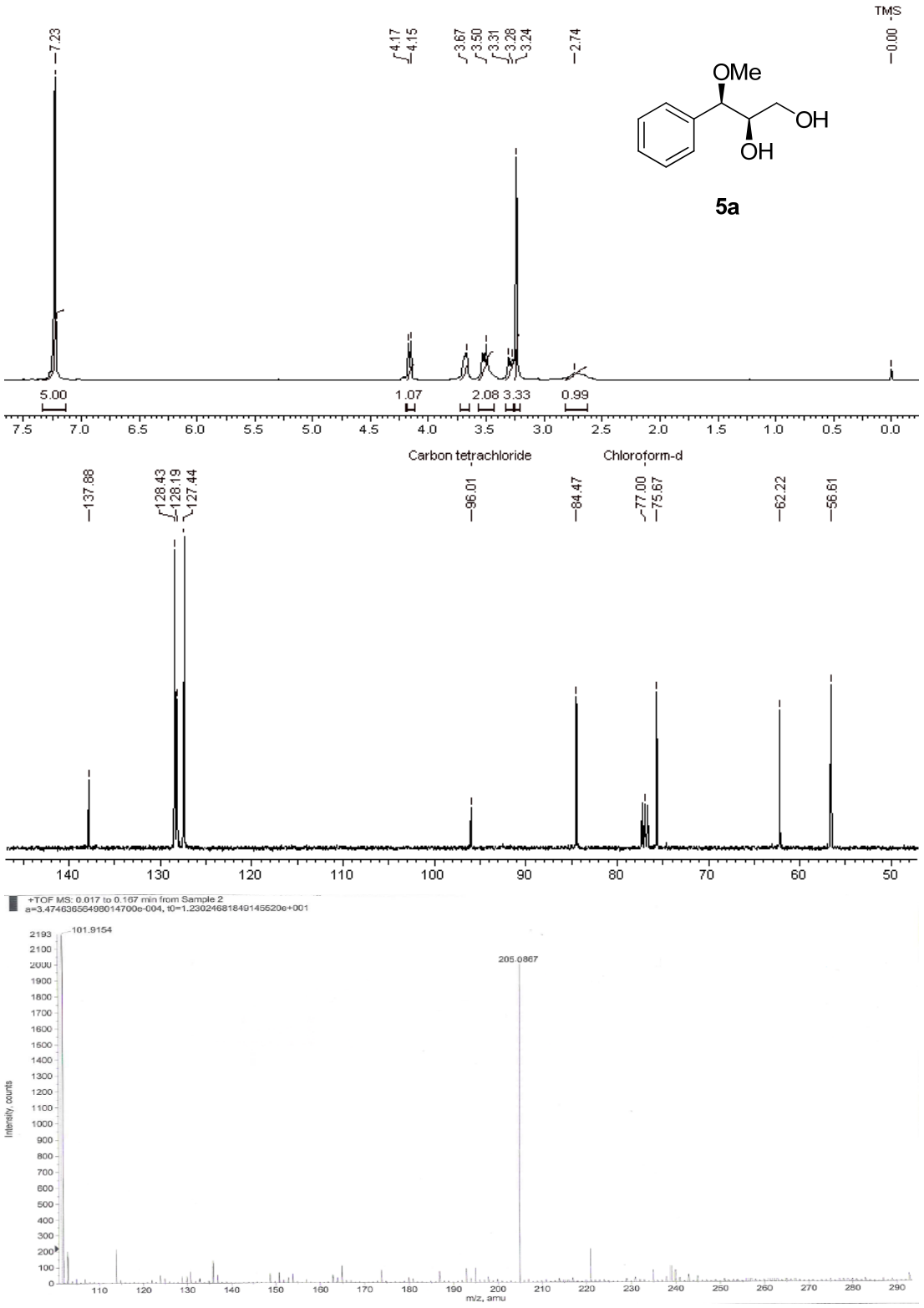


Fig. 6: ^{1}H, ^{13}C NMR and mass spectra of *syn*-methoxy diol **5a**

Encouraged by the observation of high enantioselectivity in this reaction, we examined its scope by subjecting several racemic *syn*-alkoxy epoxides (**20a–k**) to HKR, which indeed proceeded smoothly, with complete regiocontrol, to give the respective enantiopure epoxides (**20a-k**) and diols (**5a-k**) in excellent yields and ees. **Table 1** shows the results of such a study. The reaction exhibited extraordinary generality with respect to the degree of functionalization of epoxides. The configuration of both chiral alkoxy epoxides (**20a-k**) and -diols (**5a-k**) was ascertained by comparing their optical rotations with those reported in the literature.[10-13]

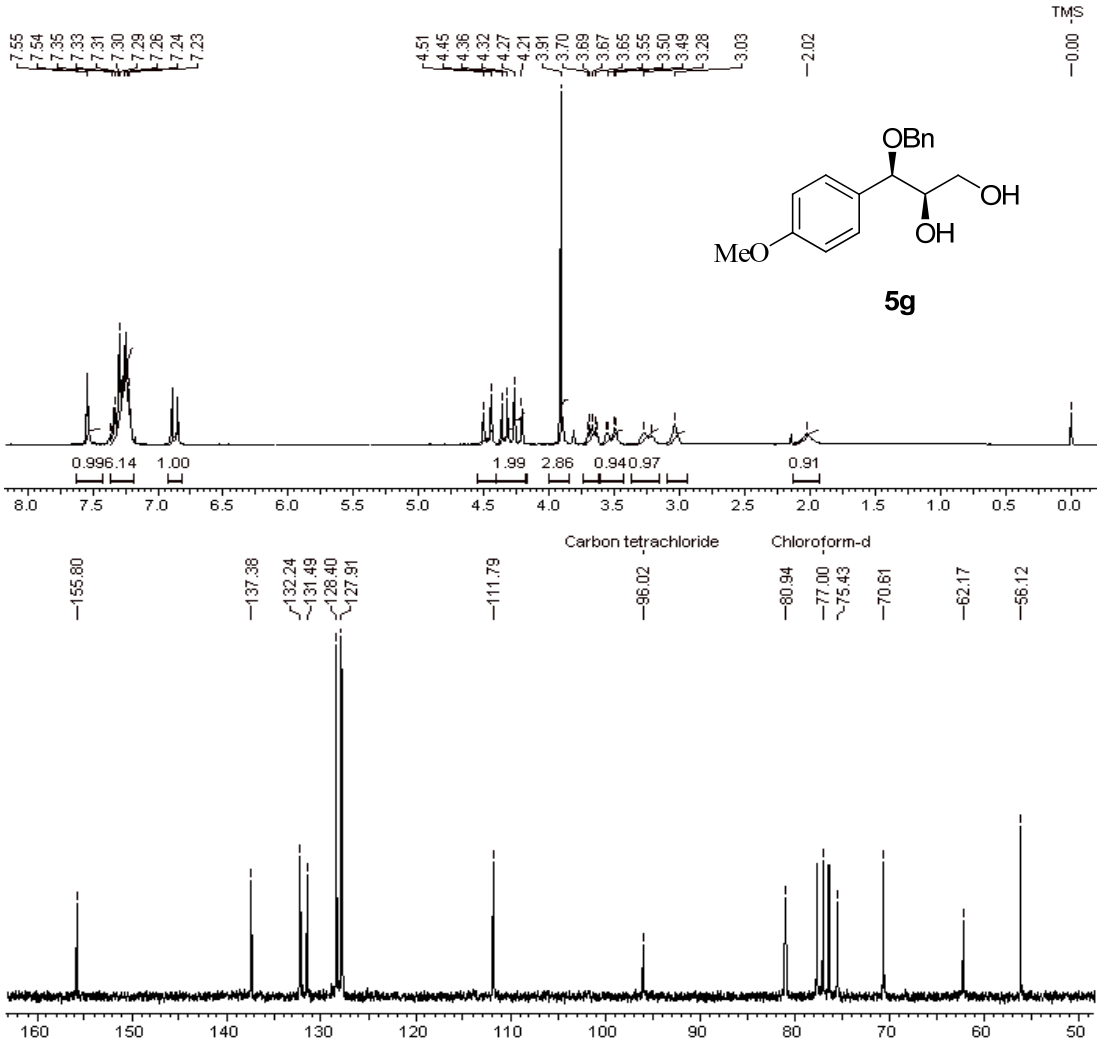
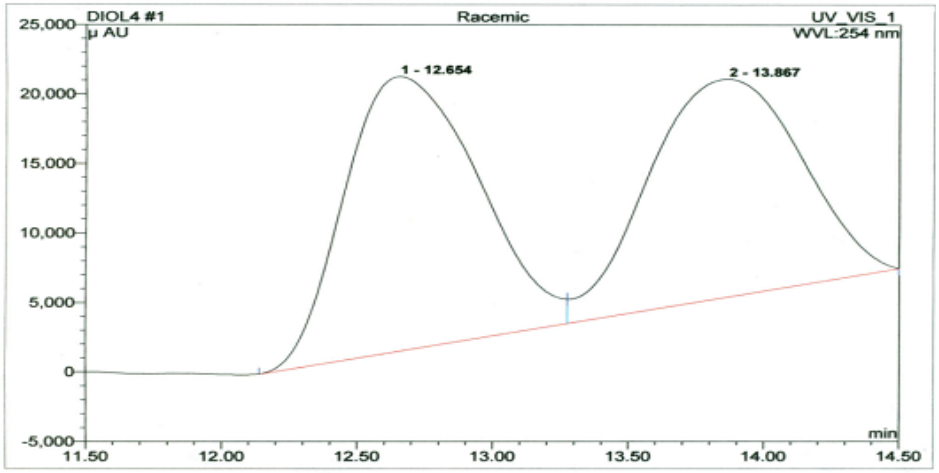


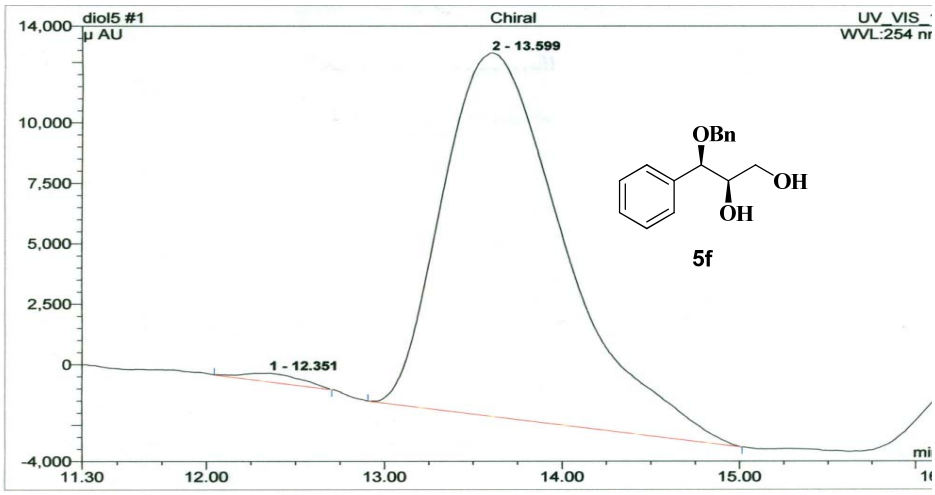
Fig. 6: ^{1}H and ^{13}C NMR spectra of diol **5g**

The formation of *syn*-alkoxy diols **5a-k** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. Example 1: The ^{1}H-NMR spectrum of **5a** showed typical signal at δ 3.29-3.40 (m, 2H) corresponding to methylene (-C**H$_2$**-OH) protons. Its ^{13}C-NMR spectrum showed characteristic signals at δ 62.2 and 75.6 due to the methine and methylene carbons attached to hydroxyl groups respectively (**Fig. 6)**.

Example 2: The ^{1}H-NMR spectrum of benzyloxy diol **5g** has shown signals at δ 3.25 (dd, *J* = 12.7, 2.2 Hz, 1H) and 3.53 (dd, *J* = 12.6, 2.2 Hz, 1H) due to methylene (-C**H$_2$**-OH) protons. Its ^{13}C-NMR spectrum showed characteristic signals at δ 62.1 and 75.4 corresponding to the methine (-**C**H-OH) and methylene (-**C**H$_2$-OH) carbons attached to hydroxyl groups respectively (**Fig. 7)**. The enantiomeric excess of *syn*-benzyloxy diol **5f** was determined by chiral HPLC analysis: Chiralpak OD-H (**Fig**.**8**).

Similarly, *anti*-alkoxy epoxides (±)-**23a-b**, when subjected to (*S,S*)-Co(salen)OAc-catalyzed HKR, produced chiral *anti*-alkoxy epoxides (+)-**23a-b** (47%, 96% ee) and the corresponding diols **4a-b** (49%, 97% ee) with excellent isolated yields and enantio purity (**Table 2)**.

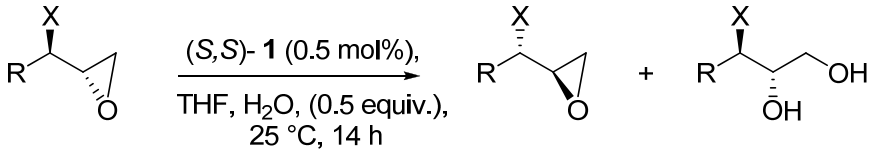




No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %
1	12.35	349.879	130.443	1.08
2	13.60	15012.384	11932.889	98.92

Fig. 8: HPLC chromatogram of diol **5f**

Table 2: Co-catalyzed HKR of *anti*-alkoxy epoxides



23a-b (2SR, 3RS) **23a-b** (2S, 3R) **4a-b**

No.	Alkoxy epoxide (±)-**23a-b**		Alkoxy epoxide **23a-b**		Alkoxy diol **4a-b**	
	R	X	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
a	CH_2OTBS	OBn	47	96	49	97
b	Ph	OMe	48	96[c]	47	98[c]

[a] Isolated yield after column chromatographic purification; [b] ee determined by Mosher's ester analysis; [c] ee determined by chiral HPLC analysis.

The formation of *anti*-alkoxy diols **4a-b** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. Example 1: The ^{1}H-NMR spectrum of *anti*-benzyloxy diol **4a** showed a

typical signal at δ 3.70-3.88 (m, 2H) for methylene (-CH_2-OH) protons. Its ^{13}C-NMR spectrum showed a characteristic signal at δ 72.6 due to the methine carbons (**C**H-OH) attached to hydroxyl group (**Fig. 9).**

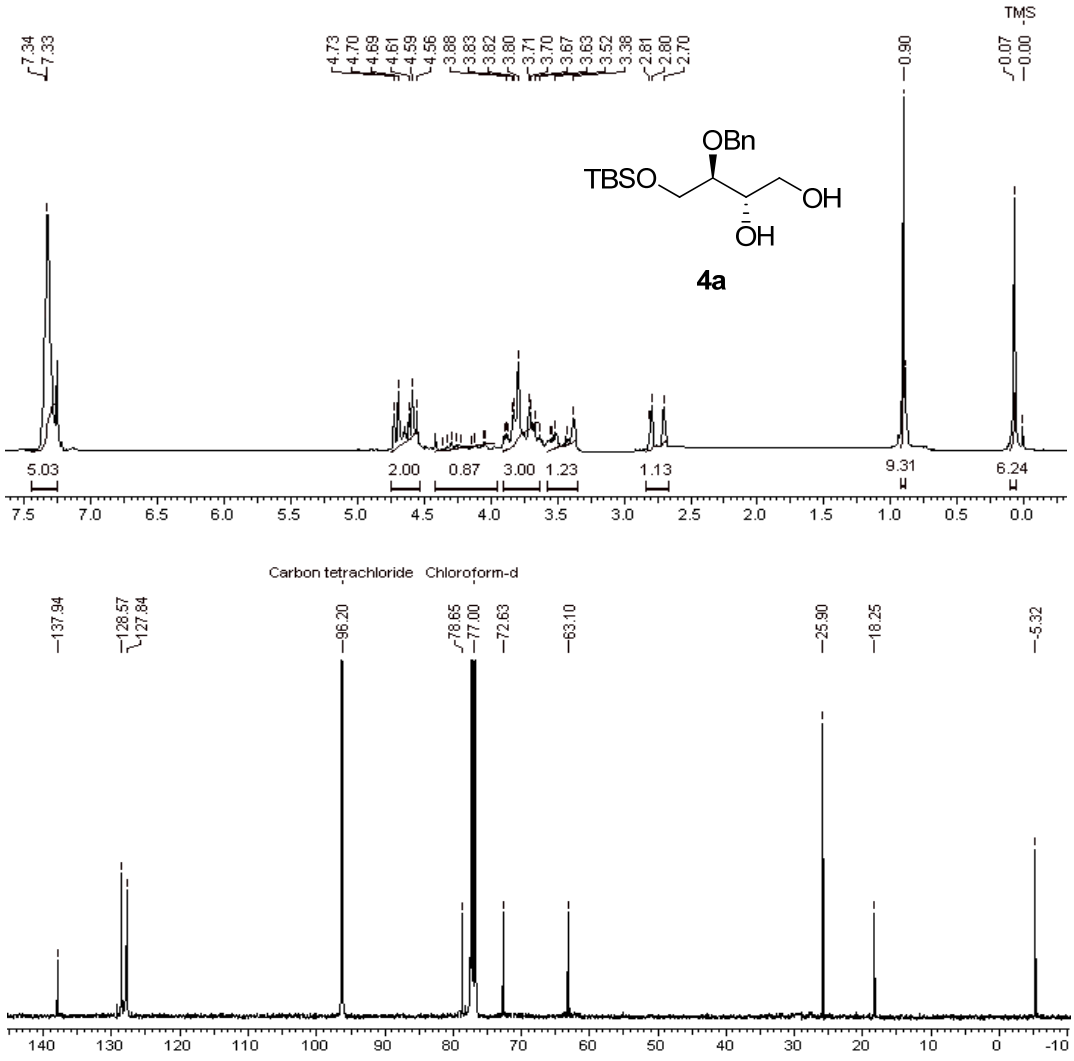


Fig. 9: ^{1}H and ^{13}C NMR spectra of diol **4a**

Example 2: The ^{1}H-NMR spectrum of *anti*-methoxy diol **4b** showed characteristic signals at δ 3.30-3.73 (m, 2H) for methylene (-CH_2-OH) protons. Its ^{13}C-NMR spectrum showed characteristic signals at δ 62.9 and 74.5 due to the methine and methylene carbons attached to hydroxyl groups respectively (**Fig. 10).**

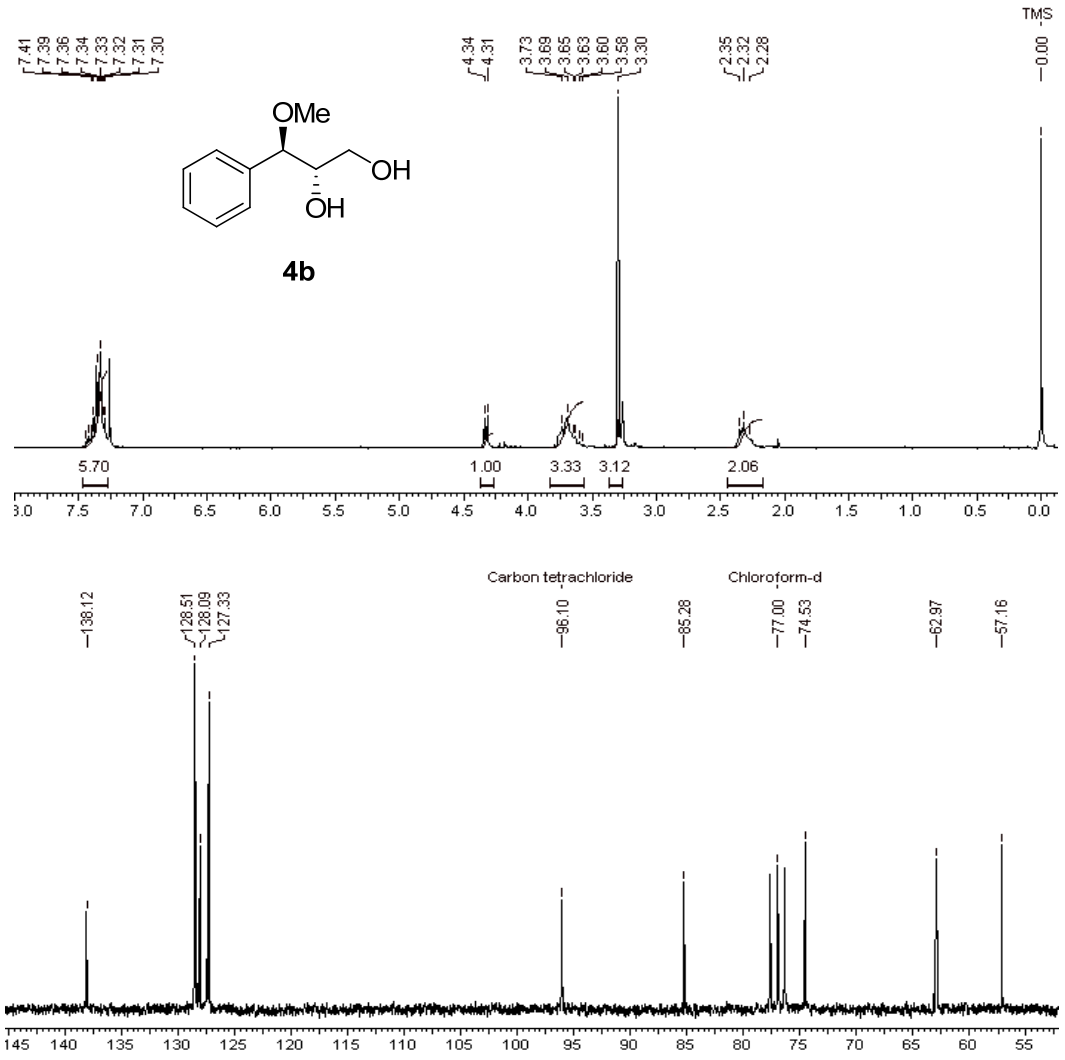


Fig. 10: ^{1}H and ^{13}C NMR spectra of *anti*-methoxy diol **4b**

1.1.6 Conclusion

In conclusion, (salen) Co(III)-catalyzed HKR of racemic alkoxy epoxides provides a highly practical route to enantiopure *syn*- or *anti*-alkoxy epoxides, as the case may be, and the corresponding 1,2-diols in a single step. The reaction is convenient to carry out under mild conditions. We believe that this HKR strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of synthesis of racemic alkoxy epoxides and the ready availability of cobalt salen catalysts in both enantiomeric forms.

1.1.7 Experimental section

General experimental procedure for the preparation of racemic *syn*-alkoxy epoxides ((±)-20a-k):

A mixture of allyl alcohol (13 mmol), BnOH or MeOH (1.4 g, 13 mmol) was taken in CH_3CN (30 mL) and NBS (2.3 g, 15.6 mmol) was added slowly *via* solid addition funnel, with stirring at 25 °C and the progress of reaction was monitored by TLC. After completion of the reaction, it was diluted with EtOAc (30 ml) and washed with water and brine. The organic layer was separated and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (80:20) as an eluent] to afford pure product alkoxy bromides **(±)-19a-k**.

2-Bromo-3-methoxy-3-phenylpropan-1-ol (19a)

Yield: 82%; Colorless viscous liquid; IR ($CHCl_3$, cm^{-1}): υ_{max} 740, 1109, 1265, 1380, 1471, 2931, 3390; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.67 (t, *J* = 6.2 Hz, 1H), 3.27 (s, 1H), 3.87-4.01 (m, 2H), 4.13-4.22 (m, 1H), 4.47 (d, *J* = 7.3 Hz, 1H), 7.31-7.41 (m, 5H); **Analysis**: $C_{10}H_{13}BrO_2$ requires: C, 49.00; H, 5.35; found: C, 48.89; H, 5.23 %.

2-Bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-ol (19b)

Yield: 80%; Colorless viscous liquid; IR ($CHCl_3$, cm^{-1}): υ_{max} 760, 1135, 1285, 1365, 1460, 2925, 3386; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.67 (t, *J* = 6.2 Hz, 1H), 3.24 (s, 3H), 3.82 (s, 3H), 3.93-4.03 (m, 2H), 4.10-4.19 (m, 1H), 4.41 (d, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H); **Analysis**: $C_{11}H_{15}BrO_3$ requires: C, 48.02; H, 5.50; found: C, 48.13; H, 5.61 %.

2-Bromo-3-methoxy-3-p-tolylpropan-1-ol (19c)

Yield: 80%; gum; IR ($CHCl_3$, cm^{-1}): υ_{max} 820, 1090, 1275, 1324, 1472, 2918, 3390; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.71 (t, *J* = 6.2 Hz, 1H), 3.26 (s, 3H), 3.85-4.01 (m, 2H), 4.14-4.23 (m, 1H), 4.45 (d, *J* = 7.4 Hz, 1H), 7.17-7.22 (m, 4H); **Analysis**: $C_{11}H_{15}BrO_2$ requires: C, 50.98; H, 5.83; found: C, 50.88; H, 5.69 %.

2-Bromo-3-(4-bromophenyl)-3-methoxypropan-1-ol (19d)

Yield: 80%; Colorless viscous liquid; IR ($CHCl_3$, cm^{-1}): υ_{max} 780, 1129, 1265, 1360, 1478, 2930, 3382; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.53 (br s, 3H), 3.26 (s, 3H), 3.88-3.99 (m, 2H), 4.07-4.16 (m, 1H), 4.42 (d, *J* = 8.1 Hz, 1H), 7.18-7.25 (m, 4H), 7.46-7.52 (m, 2H); **Analysis**: $C_{11}H_{15}BrO_2$ requires: C, 50.98; H, 5.83; found: C, 50.88; H, 5.69 %.

2-Bromo-3-methoxy-3-(4-(methylthio)phenyl)propan-1-ol (19e)

Yield: 82%; Colorless viscous liquid; IR ($CHCl_3$, cm^{-1}): υ_{max} 815, 1030, 1268, 1355, 1445, 2918, 3390; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.50 (s, 3H); 2.60 (t, *J* = 6.6 Hz, 1H), 3.26 (s, 3H), 3.84-4.03 (m, 2H), 4.09-4.18 (m, 1H), 4.42 (d, *J* = 7.5 Hz, 1H), 7.25 (s, 4H); **Analysis**: $C_{11}H_{15}BrO_2S$ requires: C, 45.37; H, 5.19; S, 11.01 found: C, 45.26; H, 5.09; S, 10.88 %.

3-(Benzyloxy)-2-bromo-3-phenylpropan-1-ol (19f)

Yield: 81%; gum; IR ($CHCl_3$, cm^{-1}): υ_{max} 740, 1109, 1265, 1380, 1471, 2931, 3390; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.59 (t, *J* = 5.6 Hz, 1H), 3.88-4.10 (m, 2H), 4.17-4.23 (m, 1H), 4.28 (d, *J* = 8.8 Hz, 1H), 4.56 (dd, *J* = 10.1, 11.9 Hz, 2H), 7.29-7.39 (m, 10H); **Analysis**: $C_{16}H_{17}BrO_2$ requires: C, 59.83; H, 5.33; found: C, 59.76; H, 5.22 %.

3-(Benzyloxy)-2-bromo-3-(4-methoxyphenyl)propan-1-ol (19g)

Yield: 82%; gum; IR ($CHCl_3$, cm^{-1}): υ_{max} 765, 954, 1106, 1263, 1473, 2931, 3393; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.61 (br s, 1H), 3.91 (s, 3H), 3.94-4.04 (m, 1H), 4.10-4.19

(m, 1H), 4.26 (d, *J* = 7.8 Hz, 1H), 4.44-4.67 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 1H), 7.22-7.36 (m, 7H), 7.62 (d, *J* = 2.8 Hz, 1H); **Analysis**: $C_{17}H_{19}BrO_3$ requires: C, 58.13; H, 5.45; found: C, 58.03; H, 5.34 %.

3-(Benzyloxy)-2-bromo-3-p-tolylpropan-1-ol (19h)

Yield: 80%; gum; IR ($CHCl_3$, cm^{-1}): υ_{max} 720, 930, 1115, 1245, 1480, 2928, 3390; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.15 (br s, 1H), 2.39 (s, 3H), 3.88-4.08 (m, 1H), 4.18-4.24 (m, 1H), 4.45 (d, *J* = 7.8 Hz, 1H), 4.54 (dd, *J* = 10.12, 11.9 Hz, 2H), 7.24-7.32 (m, 9H); **Analysis**: $C_{17}H_{19}BrO_2$ requires: C, 60.91; H, 5.71; found: C, 60.84; H, 5.63 %.

3-(Benzyloxy)-2-bromo-3-(4-chlorophenyl)propan-1-ol (19i)

Yield: 82%; gum; IR ($CHCl_3$, cm^{-1}): υ_{max} 780, 1060, 1120, 1250, 1464, 2930, 3395; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.10 (br s, 1H), 3.90-4.02 (m, 2H), 4.11-4.19 (m, 1H), 4.47 (d, *J* = 8.5 Hz, 1H), 4.69 (s, 2H), 7.30-7.41 (m, 9H); **Analysis**: $C_{16}H_{16}BrClO_2$ requires: C, 54.03; H, 4.53; found: 54.16; H, 4.67 %.

3-(Benzyloxy)-2-bromo-3-(4-bromophenyl)propan-1-ol (19j)

Yield: 81%; Colorless viscous liquid; IR ($CHCl_3$, cm^{-1}): υ_{max} 750, 942, 1074, 1118, 1264, 1480, 2924, 3390; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.21 (br s, 1H), 3.85-4.05 (m, 2H), 4.08-4.18 (m, 1H), 4.45 (d, *J* = 8.5 Hz, 1H), 4.48-4.59 (m, 2H), 7.18-7.24 (m, 1H), 7.21-7.30 (m, 5H), 7.44-7.49 (m, 2H); **Analysis**: $C_{16}H_{16}Br_2O_2$ requires: C, 48.03; H, 4.03; found: 48.16; H, 4.24 %.

3-(Benzyloxy)-2-bromo-3-(4-(methylthio)phenyl)propan-1-ol (19k)

Yield: 81%; gum; IR ($CHCl_3$, cm^{-1}): υ_{max} 768, 1068, 1120, 1270, 1460, 2930, 3395; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.51 (s, 3H), 3.97-4.01 (m, 1H), 4.13-4.19 (m, 1H), 4.27 (d, *J* = 8.9 Hz, 1H), 4.47 (d, *J* = 8.9 Hz, 1H), 4.58 (d, *J* = 8.0 Hz, 1H), 4.69 (s, 2H), 7.28-

7.37 (m, 9H); **Analysis**: $C_{17}H_{19}BrO_2S$ requires: C, 55.59; H, 5.21; S, 8.73; found: C, 55.68; H, 5.09; S, 8.62 %.

Alkoxy bromides **19a-k** was taken in THF (20 mL) and NaOH powder (624 mg, 15.6 mmol) was added slowly with stirring at 0 °C for 2h (monitored by TLC). The reaction mixture was diluted with EtOAc (25 mL) and water (30 mL). The organic layer separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (90:10) as an eluent] to afford pure products **(±)-20a-k**.

General experimental procedure for the preparation of racemic *anti*-alkoxy epoxide (23a):

Alkoxy bromide **22** was prepared in 82% yield from *cis*-butene diol **21** by following the above procedure. Alkoxy bromide **22** (10 mmol) was taken in THF (20 mL) and NaOH powder (0.4 g, 10 mmol) was added slowly with stirring at 0 °C for 2 h (monitored by TLC). The reaction mixture was diluted with EtOAc (25 mL) and water (30 mL). The organic layer was separated and the aq. layer extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. This was subjected to TBS protection without purification [dry CH_2Cl_2 (20 mL), imidazole (10 mmol) and TBSCl (10 mmol)]. It was stirred for 0.5 h and quenched with aq. $NaHCO_3$ solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (2 × 30 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column

chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (90:10) as an eluent] to give **23a** in 84% yield.

General experimental procedure for the Hydrolytic Kinetic Resolution (HKR) of racemic alkoxy epoxides, (±)-20a-k or (±)-23a-b

To a solution of (*R,R*)-**1** or (S,S)-**1** (0.043 g, 0.07 mmol) in toluene (2.0 mL) was added gl. acetic acid (0.04 g, 7.3 mmol). It was allowed to stir at 25 °C in open air for 30 min. over which time the color was changed from orange-red to a dark-brown. It was then concentrated *in vaccuo* to get the Co-salen complex as brown colored solid.

To a stirred solution of (*R,R*)-salen Co(OAc) complex (**1)** (0.004 g, 0.5 mol%) and alkoxy epoxide (1.41 mmol) in THF (0.5 mL) at 0 °C was added H_2O (0.012 g, 0.5 mmol) dropwise over 5 min. The reaction was allowed to warm to 25 °C and stirred for 14 h. After completion of reaction (monitored by TLC), solvent was removed *in vaccuo*. The crude product was purified by column chromatography over silica gel to give chiral alkoxy epoxides **20a-k,** (solvent system; pet ether: EtOAc = 80:20) and chiral alkoxy diols **5a-k** (solvent system; pet ether: EtOAc = 60:40) in pure form.

(*S*)-2-((*S*)-Methoxy(phenyl)methyl)oxirane (20a)

Yield: 48%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ +59.68 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 685, 757, 1035, 1215, 1620, 2978, 3018, 3069; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.57 (dd, *J* = 2.2, 2.9 Hz, 1H), 2.68 (t, *J* = 4.7 Hz, 1H), 3.14-3.15 (m, 1H), 3.35 (s,3H), 3.85 (d, *J* = 7.6 Hz, 1H), 7.29-7.37 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 43.8, 55.0, 55.8, 85.0, 126.8, 128.1, 128.4, 137.8; ESI-MS: *m/z* 187.08 $[M+Na]^+$; **Analysis**: $C_{10}H_{12}O_2$ requires: C, 73.15; H, 7.37; found: C, 73.08; H, 7.21%.

(*S*)-2-((*S*)-Methoxy(4-methoxyphenyl)methyl)oxirane (20b)

Yield: 47%; gum; $[\alpha]^{D}_{25}$ +58.72 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 735, 845, 1065, 1120, 1215, 1620, 2980, 3010, 3098; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.57 (dd, *J* = 2.5, 2.8 Hz, 1H), 2.73 (t, *J* = 5.0 Hz,1H), 3.09-3.16 (m, 1H), 3.36 (s,3H), 3.80 (d, *J* = 6.2 Hz, 1H), 3.91 (s, 3H), 6.89 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 2.2 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 2.2 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 43.8, 54.8, 56.0, 56.9, 83.7, 111.7, 126.9, 131.4, 131.7, 155.7; **Analysis**: $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.27; found: C, 67.94; H, 7.19%.

(*S*)-2-((*S*)-Methoxy(*p*-tolyl)methyl)oxirane (20c)

Yield: 44%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ +59.21 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 635, 764, 865, 1075, 1125, 1253, 1358, 1624, 2998, 3018, 3089; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.60 (dd, *J* = 2.1, 3.0 Hz, 1H), 2.73 (t, *J* = 4.7 Hz, 1H), 3.15-3.22 (m, 1H), 3.35 (s, 3H), 3.84 (d, *J* = 6.6 Hz, 1H), 7.17-7.26 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.9, 43.9, 55.0, 56.7, 84.9, 126.7, 129.1, 134.7, 137.8; **Analysis**: $C_{11}H_{14}O_2$ requires: C, 74.13; H, 7.92; found: C, 74.09; H, 7.84%.

(*S*)-2-((*S*)-(4-Bromophenyl)(methoxy)methyl)oxirane (20d)

Yield: 45%; gum; $[\alpha]^{D}_{25}$ +58.43 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 668, 750, 850, 1055, 1235, 1275, 1480, 1635, 2988, 3018, 3098; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.56 (dd, *J* = 2.2, 2.6 Hz, 1H), 2.72 (t, *J* = 4.4 Hz, 1H), 3.08-3.15 (m, 1H), 3.37 (s, 3H), 3.87 (d, *J* = 7.0 Hz, 1H), 7.19-7.23 (m, 2H), 7.48-7.52 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 43.7, 54.7, 57.0, 84.1, 122.1, 128.5, 131.6, 136.9; **Analysis**: $C_{10}H_{11}BrO_2$ requires: C, 49.41; H, 4.56; found: C, 49.39; H, 4.38%.

(*S*)-2-((*S*)-Methoxy(4-(methylthio)phenyl)methyl)oxirane (20e)

Yield: 47%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ +57.85 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 680, 785, 850, 1055, 1130, 1260, 1496, 1634, 2918, 2998, 3018, 3080; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.49 (s, 3H), 2.57 (dd, *J* = 2.1, 2.7 Hz, 1H), 2.72 (t, *J* = 4.4 Hz, 1H), 3.10-3.17 (m, 1H), 3.36 (s, 3H), 3.83 (d, *J* = 6.7 Hz, 1H), 7..24 (s, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.5, 43.8, 54.9, 56.8, 84.5, 126.4, 127.3, 134.5, 138.6; **Analysis**: $C_{11}H_{14}O_2S$ requires: C, 62.83; H, 6.71; S, 15.25; found: C, 62.56; H, 6.59; S, 15.19%.

(*S*)-2-((*S*)-(Benzyloxy)(phenyl)methyl)oxirane (20f)

Yield: 45%; gum; $[\alpha]^{D}_{25}$ +59.72 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 628, 757, 1043, 1242, 1654, 2989, 3094; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.58 (dd, *J* = 2.5, 2.2 Hz, 1H), 2.73 (dd, *J* = 0.8, 4.2 Hz, 1H), 3.22-3.27 (m, 1H), 4.8 (d, *J* = 6.7 Hz, 1H), 4.56 (dd, *J* = 10.0, 11.9 Hz, 2H), 7.30-7.38 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 43.6, 54.9, 70.3, 82.2, 126.7, 127.2, 127.3, 128.0, 128.3, 137.9; ESI-MS: *m*/*z* 263.2 $[M+Na]^+$; **Analysis**: $C_{16}H_{16}O_2$ requires: C, 79.97; H, 6.71; found: C, 79.58; H, 6.63 %.

(*S*)-2-((*S*)-(Benzyloxy)(4-methoxyphenyl)methyl)oxirane (20g)

Yield: 49%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ +57.25 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 756, 1155, 1215, 1278, 1371, 1496, 1608, 2980, 2999, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.55 (dd, *J* = 2.2, 2.7 Hz, 1H), 2.73 (t, *J* = 4.2 Hz, 1H), 3.16-3.23 (m, 1H), 3.91 (s, 3H), 4.02 (d, *J* = 6.2 Hz, 1H), 4.55 (dd, *J* = 11.0, 11.9 Hz, 2H), 6.89(d, *J* = 8.6 Hz, 1H), 7.24-7.34 (m, 7H), 7.53 (d, *J* = 2.8 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 43.9, 55.0, 56.0, 70.5, 81.0, 111.7, 127.1, 127.5, 127.6, 128.2, 131.5, 131.8, 137.6, 155.7; **Analysis**: $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71; found: C, 75.45; H, 6.57%.

(*S*)-2-((*S*)-(Benzyloxy)(p-tolyl)methyl)oxirane (20h)

Yield: 48%; gum; $[\alpha]^{D}_{25}$ +58..28 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 850, 1155, 1208, 1273, 1329, 1453, 1614, 2985, 3018, 3085; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.37(s, 3H), 2.59 (dd, *J* = 2.1, 3.0 Hz, 1H), 2.73 (t, *J* = 4.9 Hz, 1H), 3.22-3.29 (m, 1H), 4.07 (d, *J* = 7.4 Hz, 1H), 4.55 (dd, *J* = 11.1, 11.6 Hz, 2H), 7.12-7.22 (m, 4H), 7.30-7.36 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.1, 44.1, 55.2, 70.4, 82.3, 126.8, 127.0, 127.4, 127.6, 128.2, 128.6, 129.2, 134.9, 138.0; **Analysis**: $C_{17}H_{18}O_2$ requires: C, 80.28; H, 7.13; found: C, 80.19; H, 7.05%.

(*S*)-2-((*S*)-(Benzyloxy)(4-chlorophenyl)methyl)oxirane (20i)

Yield: 45%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ +58.48 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 721, 848, 1124, 1210, 1278, 1496, 1630, 2988, 3018, 3089; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.54-2.58 (m, 1H), 2.73 (t, *J* = 4.4 Hz, 1H), 3.16-3.22 (m, 1H), 4.09 (d, *J* = 5.4 Hz, 1H), 4.55 (dd, *J* = 9.1, 11.4 Hz, 2H), 7.28-7.45 (m, 9H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 43.9, 55.0, 70.8, 81.4, 127.7, 128.4, 128.4, 128.8, 129.0, 129.2, 134.2, 136.5, 137.7; **Analysis**: $C_{16}H_{15}ClO_2$ requires: C, 69.95; H, 5.50; Cl, 12.90; found: C, 69.86; H, 5.35; Cl, 12.79%.

(*S*)-2-((*S*)-(Benzyloxy)(4-bromophenyl)methyl)oxirane (20j)

Yield: 44%; gum; $[\alpha]^{D}_{25}$ +58.02 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 756, 850, 1125, 1215, 1253, 1325, 1608, 2950, 2998, 3018, 3051; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.56 (dd, *J* = 2.2, 2.4 Hz, 1H), 2.72 (t, *J* = 4.2 Hz, 1H), 3.18-3.22 (m, 1H), 4.09 (d, *J* = 7.9 Hz, 1H), 4.47-4.63 (m, 2H), 7.23-7.27 (m, 2H), 7.31-7.34 (m, 5H), 7.49-7.53 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 43.9, 54.9, 70.8, 81.4, 122.3, 127.7, 128.4, 128.7, 131.7, 137.0, 137.6; **Analysis**: $C_{16}H_{15}BrO_2$ requires: C, 60.21; H, 4.74, Br, 25.03; found: C, 49.39; H, 4.38; Br, 24.98%.

(*S*)-2-((*S*)-(Benzyloxy)(4-(methylthio)phenyl)methyl)oxirane (20k)

Yield: 48%; gum; $[\alpha]^{D}_{25}$ +58.84 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 628, 765, 848, 1015, 1150, 1263, 1357, 1640, 2946, 2998, 3018, 3068; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.49 (s, 3H), 2.55 (dd, *J* = 2.0, 2.8 Hz, 1H), 2.71 (t, *J* = 4.4 Hz, 1H), 3.17-3.24 (m, 1H), 4.05 (d, *J* = 6.7 Hz, 1H), 4.55 (dd, *J* = 10.7, 12.3 Hz, 2H), 7.22-7.27 (m, 5H), 7.30-7.34 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.2, 43.6, 54.8, 70.2, 81.6, 126.2, 127.2, 127.3, 128.0, 134.5, 137.7, 138.4; **Analysis**: $C_{17}H_{18}O_2S$ requires: C, 71.30; H, 6.34; S, 11.20; found: C, 71.26; H, 6.29; S, 11.12%.

(2*R*,3*R*)-3-Methoxy-3-phenylpropane-1,2-diol (5a)

Yield: 47%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ -89.68 (*c* 1.2, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 11.168 (0.99%) and 11.963 (99.01%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 675, 745, 865, 1045, 1145, 1278, 1371, 1485, 1608, 2960, 3018, 3085, 3458; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.50 (br s, 1H), 3.26 (s, 3H), 3.29-3.40 (m, 2H), 3.52-3.61 (m, 1H), 3.71-3.75 (m, 1H), 4.20 (d, *J* = 9.1 Hz, 1H), 7.33-7.36 (m, 5H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 56.6, 62.2, 75.6, 84.4, 127.4, 128.1, 128.4, 137.8; ESI-MS: *m*/*z* 205.09 $[M+Na]^+$; **Analysis**: $C_{10}H_{14}O_3$ requires: C, 65.91; H, 7.74; found: C, 65.88; H, 7.35%.

(2*R*,3*R*)-3-Methoxy-3-(4-methoxyphenyl)propane-1,2-diol (5b)

Yield: 46%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ -89.58 (*c* 0.8, $CHCl_3$); 97% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 16.629 (1.88%) and 18.290 (98.90%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 670, 748, 840, 1075, 1275, 1278, 1385, 1494, 1644, 2920, 3018, 3088, 3458; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.18 (br s, 1H), 3.14 (br s, 1H), 3.25 (s, 4H), 3.51-3.64 (m, 2H), 3.90 (s, 3H), 4.13 (d, *J* = 7.8

Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 7.19-7.24 (m, 2H), 7.49 (d, *J* = 2.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.3, 56.8, 62.3, 75.6, 83.4, 111.9, 127.9, 131.4, 132.2, 155.9; **Analysis**: $C_{11}H_{16}O_4$ requires: C, 62.25; H, 7.60; found: C, 62.18; H, 7.45%.

(2*R*,3*R*)-3-Methoxy-3-p-tolylpropane-1,2-diol (5c)

Yield: 45%; Colorless viscous liquid; $[\alpha]^D_{25}$ -89.25 (*c* 1.2, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.572 (1.06%) and 13.690 (98.94%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 650, 785, 850, 1055, 1215, 1371, 1496, 1645, 2925, 3018, 3098, 3450; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.27 (br s, 1H), 2.36 (s, 3H), 3.24 (s, 4H), 3.30-3.36 (m, 1H), 3.47-3.57 (m, 1H), 3.65-3.74 (m, 1H), 4.15 (d, *J* = 8.4 Hz, 1H), 7.18-7.22 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.1, 56.4, 62.2, 75.6, 84.3, 127.4, 129.1, 134.8, 137.8; **Analysis**: $C_{11}H_{16}O_3$ requires: C, 67.32; H, 8.22; found: C, 67.25; H, 8.17%.

(2*R*,3*R*)-3-(4-Bromophenyl)-3-methoxypropane-1,2-diol (5d)

Yield: 42%; Colorless viscous liquid; $[\alpha]^D_{25}$ -89.44 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 620, 750, 850, 1040, 1275, 1375, 1494, 1645, 2910, 3018, 3440; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.26 (br s, 1H), 3.20 (br s, 1H), 3.25 (s, 3H), 3.32 (m, 1H), 3.52-3.68 (m, 2H), 4.20 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 56.8, 62.1, 75.5, 83.8, 122.3, 129.2, 131.7, 136.9; **Analysis**: $C_{10}H_{13}BrO_3$ requires: C, 46.00; H, 5.02; Br, 30.60; found: C, 45.85; H, 4.95; Br, 30.54%.

(2*R*,3*R*)-3-Methoxy-3-(4-(methylthio)phenyl)propane-1,2-diol (5e)

Yield: 46%; Colorless viscous liquid; $[\alpha]^D_{25}$ -89.32 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 650, 765, 850, 1055, 1260, 1275, 1374, 1496, 1645, 2950, 3018, 3098, 3446; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.12 (brs, 1H), 3.25 (s, 3H), 3.34 (brs, 1H), 3.52-3.71

(m, 2H), 4.17 (d, *J* = 10.0 Hz, 1H), 7.23-7.25 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.6, 56.7, 62.2, 75.6, 84.0, 126.5, 128.0, 134.4, 138.8; **Analysis**: $C_{11}H_{16}O_3S$ requires: C, 57.87; H, 7.06; found: C, 57.78; H, 6.95%.

(2*R*,3*R*)-3-(Benzyloxy)-3-phenylpropane-1,2-diol (5f)

Yield: 44%; gum; $[\alpha]^D_{25}$ -89.65 (*c* 1, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.351 (1.08%) and 13.599 (98.92%); IR ($CHCl_3$, cm^{-1}): υ_{max} 720, 845, 1045, 1125, 1654, 2985, 3085, 3465; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.13 (br s, 1H), 3.16 (br s, 1H), 3.34 (dd, *J* = 4.3, 6.0 Hz, 1H), 3.54 (dd, *J* = 2.8, 9.0 Hz, 1H), 3.73-3.83 (m, 1H), 4.27 (d, *J* = 12.4 Hz, 1H), 4.41-4.52 (m, 2H), 7.29-7.38 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 62.2, 70.6, 75.6, 82.0, 127.6, 127.9, 128.4, 128.6, 137.6, 137.9; ESI-MS: *m*/*z* 281.13 $[M+Na]^+$; **Analysis**: $C_{16}H_{18}O_3$ requires: C, 74.39; H, 7.02; found: C, 74.28; H, 6.97 %.

(2*R*,3*R*)-3-(Benzyloxy)-3-(4-methoxyphenyl)propane-1,2-diol (5g)

Yield: 47%; gum; $[\alpha]^D_{25}$ -89.45 (*c* 1.2, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 17.624 (1.05%) and 19.298 (98.89%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 635, 765, 840, 1045, 1215, 1353, 1371, 1496, 1634, 2980, 3068, 3446; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.02 (br s, 1H), 3.03 (br s, 1H), 3.25 (dd, *J* = 12.7, 2.1 Hz, 1H), 3.53 (dd, *J* = 12.6, 2.1 Hz, 1H), 3.63-3.70 (m, 1H), 3.91 (s, 3H), 4.21-4.36 (m, 2H), 4.47 (d, *J* = 11.9 Hz, 1H), 6.87(d, *J* = 8.0 Hz, 1H), 7.22-7.35 (m, 7H), 7.55 (d, *J* = 2.1 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.1, 62.1, 70.6, 75.4, 80.9, 111.7, 127.8, 127.9, 128.4, 131.4, 132.2, 137.3, 155.8; **Analysis**: $C_{17}H_{20}O_4$ requires: C, 70.81; H, 6.99; found: C, 70.57; H, 6.78%.

(2*R*,3*R*)-3-(Benzyloxy)-3-p-tolylpropane-1,2-diol (5h)

Yield: 45%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ -89..2 (*c* 1.2, $CHCl_3$); 96% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.570 (2.10%) and 13.692 (98.24%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 650, 756, 850, 1055, 1230, 1360, 1485, 1644, 2958, 3058, 3425; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.18 (br s, 1H), 2.36 (s, 3H), 3.35 (br s, 1H), 3.55-3.66 (m, 2H), 3.74-3.84 (m, 1H), 3.90 (dd, *J* = 3.43, 5.54 Hz, 1H), 4.18-4.31 (m, 1H), 4.35-4.47 (m, 2H), 7.28-7.36 (m, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 21.0, 62.1, 69.9, 75.5, 84.5, 127.4, 127.5, 127.6, 128.3, 128.4, 128.6, 137.5, 137.8, 138.2; **Analysis**: $C_{17}H_{20}O_3$ requires: C, 74.97; H, 7.40; found: C, 74.89; H, 7.31%.

(2*R*,3*R*)-3-(Benzyloxy)-3-(4-chlorophenyl)propane-1,2-diol (5i)

Yield: 42%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ -89.25 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 665, 720, 850, 1044, 1215, 1253, 1371, 1498, 1638, 2990, 3078, 3454; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.16 (br s, 1H), 3.12 (br s, 1H), 3.29 (dd, *J* = 4.9, 8.8 Hz, 1H), 3.54 (dd, *J* = 3.8, 8.8 Hz, 1H), 3.68 (m, 1H), 4.26 (d, *J* = 11.5 Hz, 1H), 4.42-4.48 (m, 2H), 7.25-7.38 (m, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 62.2, 70.9, 75.5, 81.3, 128.0, 128.6, 129.0, 134.4, 136.5, 137.3; **Analysis**: $C_{16}H_{17}ClO_3$ requires: C, 65.64; H, 5.85; Cl, 12.11; found: C, 65.56; H, 5.77; Cl, 12.05%.

(2*R*,3*R*)-3-(Benzyloxy)-3-(4-bromophenyl)propane-1,2-diol (5j)

Yield: 47%; gum; $[\alpha]^{D}_{25}$ -89.08 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 658, 780, 810, 1055, 1155, 1278, 1371, 1496, 1638, 2998, 3018, 3450; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.72 (br s, 1H), 3.24-3.27 (m, 2H), 3.49-3.52 (m, 2H), 3.67-3.69 (m, 2H), 4.24 (d, *J* = 8.9 Hz, 1H), 4.38-4.46 (m, 2H), 7.23-7.34 (m, 7H), 7.50 (d, *J* = 8.8 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 62.1, 70.8, 75.4, 81.3, 122.4, 128.0, 128.5, 129.3, 131.8, 137.0, 137.3;

Analysis: $C_{16}H_{17}BrO_3$ requires: C, 56.99; H, 5.08; Br, 23.70; found: C, 56.79; H, 4.99; Br, 23.62%.

(2*R*,3*R*)-3-(Benzyloxy)-3-(4-(methylthio)phenyl)propane-1,2-diol (5k)

Yield: 47%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ -88.92 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 685, 780, 885, 1065, 1075, 1265, 1371, 1485, 1638, 2940, 3018, 3089, 3456; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.12 (br s, 1H), 2.50 (s, 3H), 3.13 (br s, 1H), 3.24-3.36 (m, 1H), 3.49-3.58 (m, 1H), 3.71-3.75 (m, 1H), 4.26 (d, *J* = 11.6 Hz, 1H), 4.37-4.51 (m, 2H), 7.23-7.38 (m, 9H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.5, 62.2, 70.6, 75.5, 81.6, 126.5, 127.8, 127.9, 128.1, 128.4, 134.6, 137.5, 138.8; **Analysis**: $C_{17}H_{23}O_3S$ requires: C, 67.08; H, 6.62; S, 10.53; found: C, 66.98; H, 6.58; S, 10.45%.

2-(Benzyloxy)-3-bromobutane-1,4-diol (22)

Yield: 82%; Colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 760, 860, 1065, 1085, 1270, 1378, 1468, 1625, 2940, 3393; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.71 (br s, 1H), 2.46 (br s, 1H), 3.73-3.94 (m, 5H), 4.23-4.30 (m, 1H), 4.29 (s, 2H), 7.35 (s, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.5, 61.3, 63.3, 72.9, 79.5, 126.1, 126.2, 128.6, 137.5; **Analysis**: $C_{11}H_{15}BrO_3$ requires: C, 48.02; H, 5.50; found: C, 47.98; H, 5.43%.

((*R*)-2-(Benzyloxy)-2-((*S*)-oxiran-2-yl)ethoxy)(tert-butyl)dimethylsilane (23a)

Yield: 47%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ +28.25 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 645, 785, 828, 1085, 1145, 1253, 1496, 1608, 2925, 2996, 3016, 3088; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.94 (s, 9H), 2.72-2.75 (m, 2H), 3.05-3.07 (m, 1H), 3.39-3.41 (m, 1H), 3.74-3.76 (m, 2H), 4.62-4.67 (m, 2H), 7.29-7.32 (m, 5H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ -5.2, 18.0, 25.7, 44.9, 51.4, 64.0, 64.9, 72.7, 78.2, 127.6, 128.3, 138.4; **Analysis**: $C_{17}H_{28}O_3Si$ requires: C, 66.19; H, 9.15; found: C, 66.09; H, 8.98%.

2-(Methoxy(phenyl)methyl)oxirane (23b)

Yield: 47%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ -58.25 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 685, 757, 1035, 1215, 1620, 2978, 3018, 3069; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.57 (dd, *J* = 2.2, 2.9 Hz, 1H), 2.68 (t, *J* = 4.7 Hz, 1H), 3.14-3.15 (m, 1H), 3.35 (s, 3H), 3.85 (d, *J* = 7.6 Hz, 1H), 7.29-7.37 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 43.8, 55.0, 55.8, 85.0, 126.7, 128.1, 128.4, 137.8; **Analysis**: $C_{10}H_{12}O_2$ requires: C, 73.15; H, 7.37; found: C, 73.08; H, 7.21%.

(2*R*,3*S*)-3-(Benzyloxy)-4-tert-butyl) dimethylsilyloxybutane-1,2-diol (4a)

Yield: 49%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ -29.24 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 640, 750, 850, 1040,1075, 1238, 1375, 1485, 1640, 2980, 3018, 3089, 3445; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.90 (s, 9H), 2.65 (br s, 1H), 2.33 (br s, 1H), 2.69-2.81 (m, 1H), 3.37-3.53 (m, 1H), 3.57-3.88 (m, 3H), 4.04-4.30 (m, 2H), 4.56-4.73 (m, 2H), 7.34 (m, 5H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ -5.3, 18.2, 25.9, 63.1, 71.2, 72.2, 72.6, 78.6, 127.9, 128.5, 137.9; **Analysis**: $C_{17}H_{30}O_4Si$ requires: C, 62.54; H, 9.26; found: C, 62.38; H, 9.12%.

(2*S*, 3*R*)-3-Methoxy-3-phenylpropane-1, 2-diol (4b)

Yield: 47%; Colorless viscous liquid; $[\alpha]^{D}_{25}$ +113.95 (*c* 1.16, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralcel OJ-H, *n*-hexane/*i*PrOH, 86:14, 0.5 mL/min) retention time 24.15 (98.92%) and 25.50 (1.08%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 720, 845, 1065, 1125, 1654, 2985, 3085, 3465; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.32 (br s, 1H), 3.30 (s, 3H), 3.52-3.78 (m, 3H), 4.32(d, *J* = 9.1 Hz, 1H), 7.33-7.36 (m, 5H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 57.1, 62.9, 74.5, 85.2, 127.3, 128.1, 128.5, 137.1; **Analysis**: $C_{10}H_{14}O_3$ requires: C, 65.91; H, 7.74; found: C, 65.89; H, 7.37%.

Section II:

Enantioselective Synthesis of (*S,S*)-Reboxetine

1.2.1 Depression

Depression is a common and disabling disorder. The World Health Organization has ranked depression fourth in a list of the most urgent health problems world wide.[16] Depression has major effects on economic productivity, individual well-being and social functioning around the globe. It is a huge burden on individuals, families and society. The lifetime risk for major depression has been estimated to be 7-12% for men and 20-25% for women.[16] Medical treatment for depression favors prescription of antidepressant drugs that work by increasing neurotransmission for one or more of the monoamines-serotonin, norepinephrine, or dopamine. Before 1980, antidepressant treatment consisted primarily of the tricyclics antidepressants (TCADs), monoamine oxidase inhibitors (MAOI) and lithium. The antidepressant properties of these medications are attributed to modulation of noradrenergic and serotonergic function, but they also have many side effects due to binding to multiple unrelated receptors. The tricyclics antagonize muscarinic, H1 histaminic, and A1 adrenergic receptors causing constipation, urinary retention, dry mouth, sedation, and postural hypotension.[17] In addition to these, the monoamine oxidase inhibitors have the added risk of potentially severe hypertensive crisis due to pressor effects of dietary tyramine, which requires dietary restrictions. Both the tricyclics and the monoamine oxidase inhibitors can be lethal in overdose; the monoamine oxidase inhibitors interact dangerously with several over the counter and prescription drugs. In the late 1980's, an important class of antidepressant was introduced, the selective serotonin reuptake inhibitors (SSRIs), which includes sertraline

(**24**), fluoxetine (**25**), paroxetine (**26**) and citalopram (**27**) (**Fig. 11**). This class has become a mainstay of antidepressant treatment because of substantial advantages over the tricyclics and monoamine oxidase inhibitors in safety, tolerability and ease of dosing.

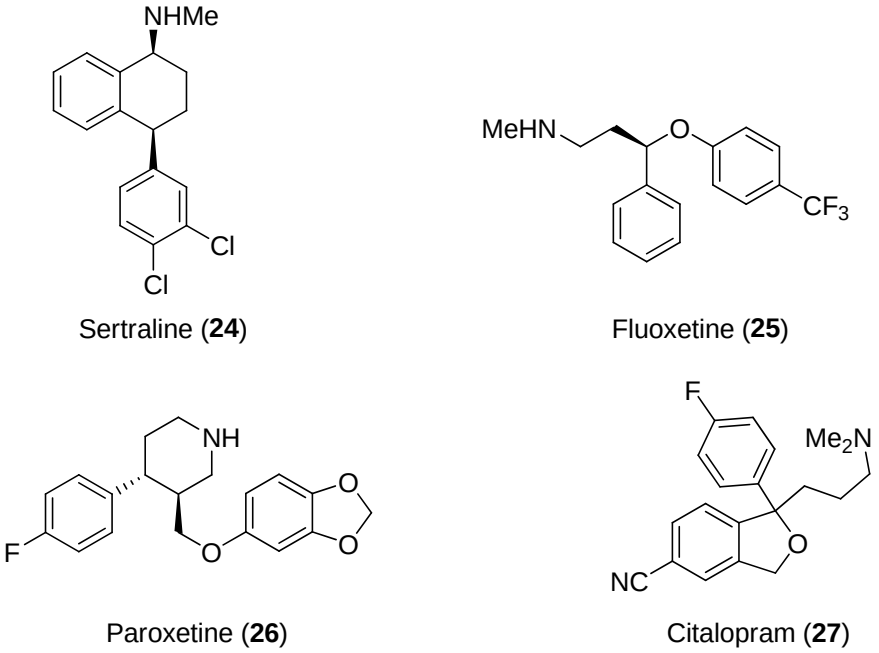
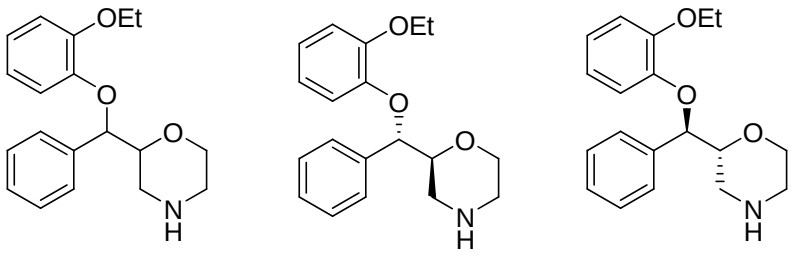


Fig. 11: Selective serotonin reuptake inhibitors (SSRIs)

The SSRIs also have limitations, especially response failure in many of those most severely affected. Many patients experience side effects like gastrointestinal complaints, nervousness and agitation, sexual dysfunction and weight gain with long term use.[17] All these lead to difficulty in long term treatment and non compliance. Hence, one of the most important goals in the pharmacological treatment of depression is to provide the patients with highly efficacious drugs that have few side effects, low or no toxicity and a high level of tolerability.

1.2.2 Reboxetine and pharmacology

Reboxetine (**29**) is a selective noradrenaline reuptake inhibitor (NaRI), the first drug of new antidepressant class introduced in 1997 (**Fig. 12**). It is α- aryloxybenzyl derivative of morpholine and its mesylate (*i.e.* methanesulfonate) salt is sold under trade names such as Edronax®, Norebox®, Prolift®, Solvex® or Vestra®. Reboxetine (**29**) is a selective inhibitor of noradrenaline reuptake. It inhibits noradrenaline reuptake *in vitro* to a similar extent to the tricyclic antidepressant desmethylimipramine. Reboxetine (**29**) does not affect dopamine or serotonin reuptake and has low *in vivo* and *in vitro* affinity for adrenergic, cholinergic, histaminergic, dopaminergic and serotonergic receptors.[18]



(±)-28 **(*S*,*S*)-29** **(*R*,*R*)-30**

Fig. 12: Structures of reboxetine

Due to selectivity of reboxetine (**29**) for norepinephrine, it is generally well tolerated with a benign side effect profile.[16,17] Against comparator antidepressants, reboxetine is at least as effective in the treatment of patients with major depressive disorder in the adult and the elderly population and offers a significant advantage over imipramine in the treatment of melancholic patients. It has a significantly improved adverse event profile compared with TCADs. In severely depressed patients, reboxetine (**29**) was significantly more effective than fluoxetine (**25**). Reboxetine (**29**), the first selective NaRI, with its selective

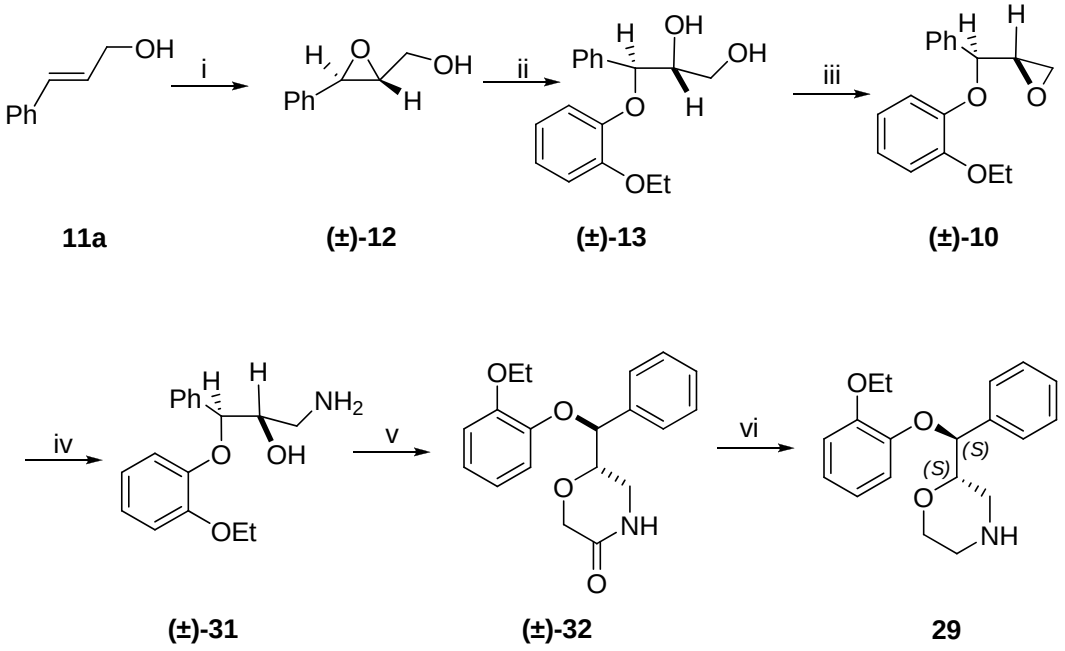
mechanism of action, offering even better efficacy in certain patient groups and acceptable tolerability profile is a valuable addition to the existing armamentarium of drugs used for the treatment of depression.

1.2.3 Review of Literature

Owing to its high biological importance, the synthesis of reboxetine in its optically pure form was reported by many groups world wide as described below.

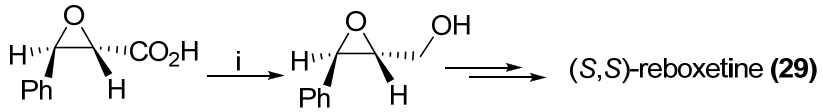
Melloni's approach (1985)[19]

In this approach, cinnamyl alcohol (**11a**) was subjected to diastereoselective epoxidation to give the (2*RS*,3*RS*) epoxide **(±)-12**. The epoxide **(±)-12** was then opened selectively at the benzylic position to give the diol **(±)-13** which was converted to epoxide **(±)-10** (**Scheme 8**).



Scheme 8: (i) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h, then 25 °C, 24 h, 94%; (ii) 2-ethoxyphenol, NaOH, H_2O, 70 °C, 2.5 h, 83%; (iii) (a) 4-nitrobenzoyl chloride, pyridine, -10 °C, 2 h, 61%; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, 84%; (c) 2N NaOH, dioxane, 25 °C, 100%; (iv) 32% NH_4OH, MeOH, 6 h, 75%; (v) (a) $ClCH_2COCl$, Et_3N, CH_2Cl_2, -10 °C, 0.5 h, 98%; (b) *t*-BuOK, *t*-BuOH, 25 °C, 2 h, 86%; (vi) (a) Red-Al, toluene, 4 h, 72%; (b) L-(+)-mandelic acid, EtOH.

The epoxide **(±)-10** was opened at the primary position by NH_4OH to give the corresponding amino alcohol **(±)-31**. The amino alcohol **(±)-31** was treated first with chloroacetyl chloride and then with base to give the corresponding lactam **(±)-32**. Lactam **(±)-32** was reduced to the corresponding morpholine derivative using Red-Al and the (*S*,*S*)-isomer was separated by resolution that involves recrystallizing with L-(+)-mandelic acid in ethanol to give (*S*,*S*)-reboxetine (**29**). Melloni *et al*. also carried out the synthesis of (*S*,*S*)-reboxetine (**29**) using chiral (2*R*,3*R*)-epoxide **12** obtained from chiral glycidic acid **33** (**Scheme 9**).

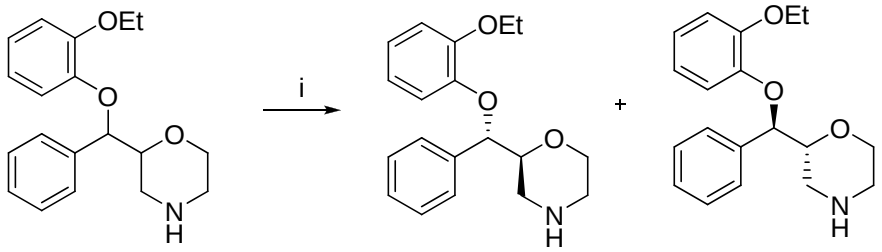


33 **12**

Scheme 9: (i) ethyl chlorocarbonate, Et_3N, CH_2Cl_2, 0 °C, 3 h, then $NaBH_4$, EtOH, 0 °C, 0.5 h, then 25 °C, 12 h, 31%.

Raggi's approach (2002)[20]

In this approach, Raggi *et al*. have made use of capillary electrophoresis method to separate the enantiomers of racemic mixture of (*R*,*R*)-reboxetine **30** and (*S*,*S*)-reboxetine **29**. Sulfobutyl ether-β-cyclodextrin was chosen as the chiral selector using an uncoated fused silica capillary (**Scheme 10**).

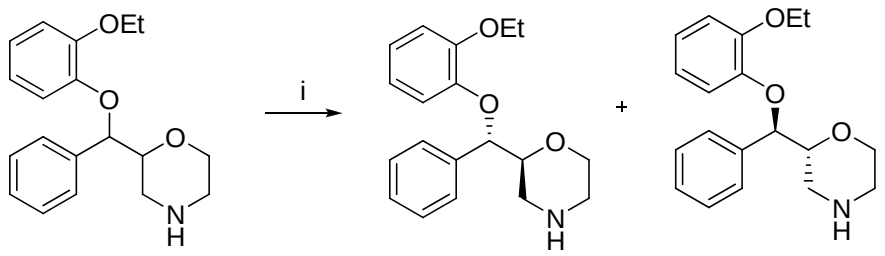


(±)-28 **(*S*,*S*)-29** **(*R*,*R*)-30**

Scheme 10: (i) fused silica capillary (internal diameter 50 μm, total length 48.5 cm, effective length 40.0 cm), electrolyte pH 3.0, 100 mM phosphate buffer, 1.25 mM Sulfobutyl ether-β-cyclodextrin, 20 kV.

Öhman's approach (2002)[21]

In this approach, the separation of the racemic mixture of reboxetine **(±)-28** was done by reverse-phase high-performance liquid chromatography using three different chiral columns (Chiral-AGP, Chiral Grom 2 and Chiral-CBH) (**Scheme 4**).

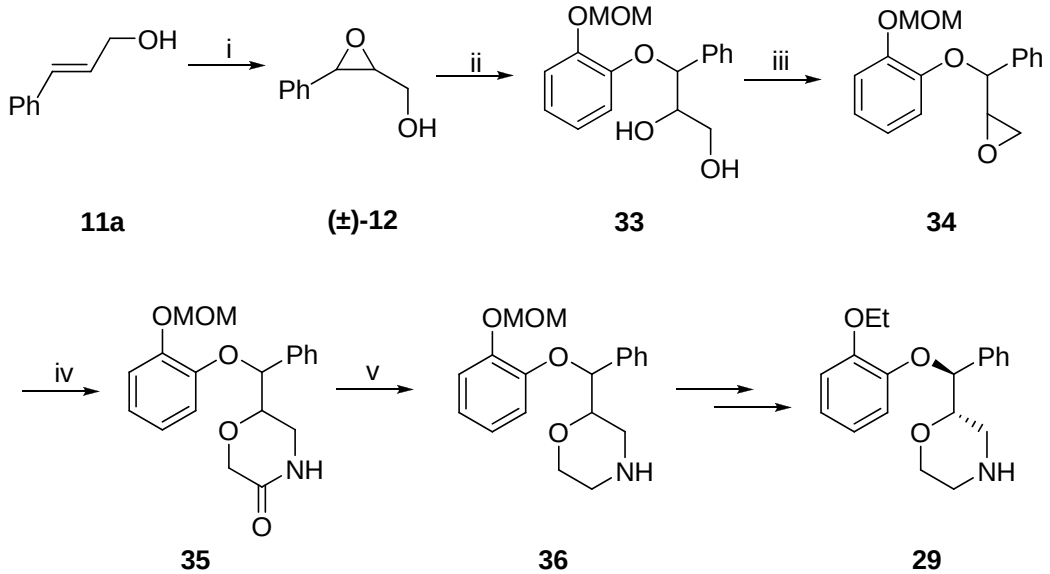


(±)-28 **(*S*,*S*)-29** **(*R*,*R*)-30**

Scheme 11: (i) separation *via* chiral HPLC

Kumar's approach (2004)[22]

This approach is very much similar to the one repoted by Melloni *et al*. involving the epoxidation of cinnamyl alcohol (**11a**) and opening the epoxide **(±)-12** at benzylic position with mono MOM-protected catechol (**Scheme 12**).



11a **(±)-12** **33** **34**

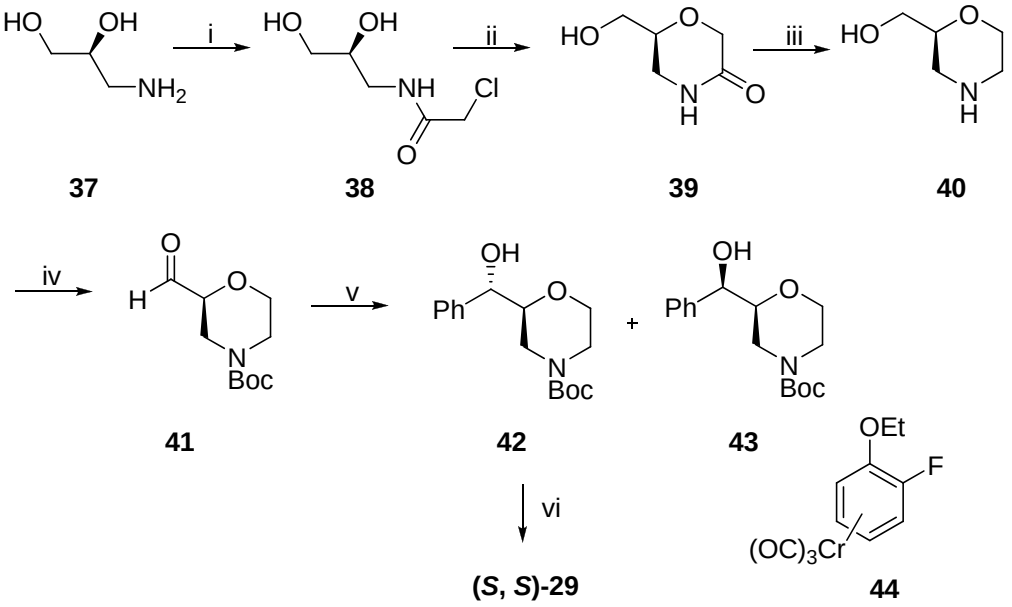
35 **36** **29**

Scheme 12: (i) *m*-CPBA, CH_2Cl_2, 80%; (ii) 2-methoxy methyl phenol, aq. NaOH, 64%; (iii) (a) 4-nitrobenzoyl chloride, pyridine, 65%; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 90%; (c) 2N NaOH, 25 °C, 4 h, 95%; (iv) (a) 30% NH_4OH, MeOH, 88%; (b) $ClCH_2COCl$, Et_3N, CH_2Cl_2, (c) *t*-BuOK, *t*-BuOH, 64%; (v) (a) Red-Al, toluene, 88%; (b) L-(+)-Mandelic acid, EtOH.

Lactam **35** was reduced to the corresponding secondary amine, which was resolved with (+)-mandelic acid and protected to give the corresponding chiral morpholine **36**. Morpholine **36** was converted to (*S*,*S*)-reboxetine (**29**) using simple transformations.

Tamagnan's approach (2005)[23]

Tamagnan's aim was to build the chiral morpholine moiety first before introducing the phenyl and aryloxy groups.



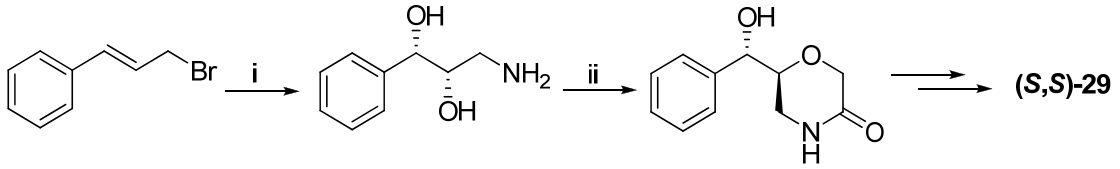
Scheme 13: (i) $ClCH_2COCl$, Et_3N, CH_3CN, MeOH, -10 °C to 25 °C, 16 h, 94%; (ii) *t*-BuOK, *t*-AmOH, 25 °C, 3 h, 92%; (iii) Red-Al, THF, 0 °C to 25 °C, 16 h, 85%; (iv) (a) $(Boc)_2O$, NaOH, CH_2Cl_2/H_2O, 0 °C to 25 °C, 4 h, 83%, (b) TEMPO, TCIA, $NaHCO_3$, EtOAc, -5 °C, 2 h, 89%; (v) Ph_2Zn, THF, -10 °C to 25 °C, 18 h, **42** (60 %), **43** (19%); (vi) (a) **44**, NaH, DMF, 25 °C, 2h, (b) I_2 in THF, 0 ^{0}C to 25 °C, 1 h, 95%; (c) TFA, CH_2Cl_2, 0 °C to 25 °C, 1.5 h, 98%.

Chiral aminoalcohol **37** was thus converted to morpholine **40** using simple transformations. Aldehyde **41** was obtained from morpholine **40** in 2 steps: (i) protection of amine with $(Boc)_2O$ and (ii) oxidation of alcohol with trichloroisocyanuric acid (TCIA) and TEMPO in EtOAc. Aldehyde **41** was treated with excess Ph_2Zn to give the diastereomers (2*S*,3*S*)-**42** and (2*S*,3*R*)-**43** in 60 and 19% yields respectively. Sodium

alkoxide of **42** was reacted with arylchromium **44** to provide two chromium complexes, which led to phenol moiety in 95% yields after oxidative dechromination with iodine. Finally, treatment of phenol moiety with excess TFA provided (*S*,*S*)-reboxetine (**29**) in 98% yield (**Scheme 13**).

Srinivasan's approach (2006)[24]

Srinivasan *et al*. have made use of Sharpless asymmetric dihydroxylation approach for the asymmetric synthesis of (*S*,*S*)-**29**. *trans*-Cinnamyl bromide (**45**) on asymmetric dihydroxylation afforded diol. Nucleophilic displacement of the bromo group with sodium azide furnished the azido alcohol, which was converted to amine **46** using 10% Pd/C and H_2. The free amine **46** was then treated with chloroacetyl chloride to furnish amide, which was readily cyclized to lactam **47**. lactam **47** was converted to (*S*,*S*)-reboxetine (**29**) using simple transformations (**Scheme 14**).



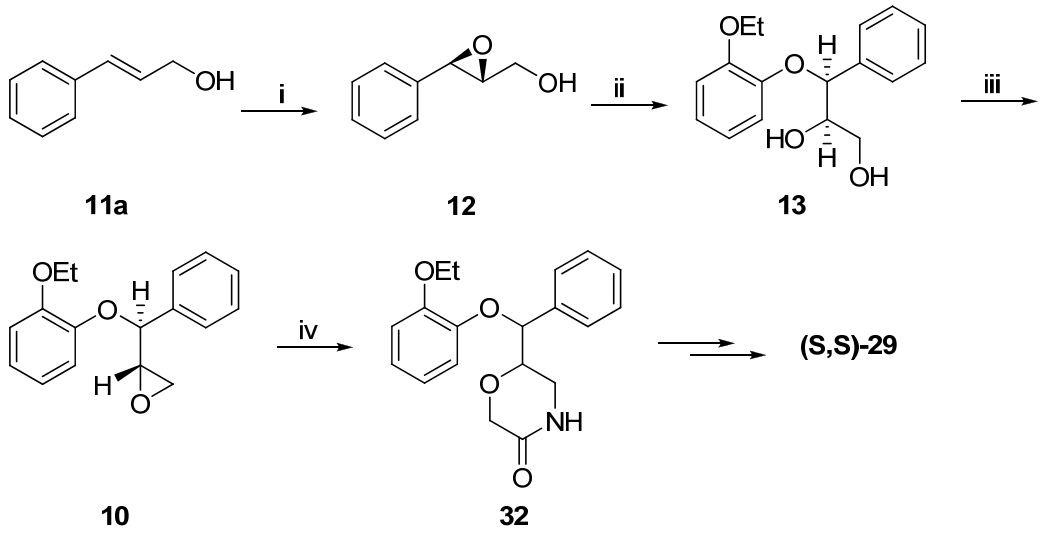
45 **46** **47**

Scheme 14: (i) (a) $(DHQ)_2$-PHAL, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, H_2O:*t*-BuOH (1:1), 0 °C, 24 h, 84%; (b) NaN_3, DMF, 68 °C, 16 h, 80%, (c) 10% Pd/C, H_2 (1 atm), 25 °C, 12 h, 90%; (iii) (a) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2 at –10 °C to 25 °C, 6 h, 70%; (b) *t*-BuOK, *t*-BuOH, 25 °C, 4 h, 80%.

Henegar's approach (2007)[12]

Henegar et al. have described the synthesis of (*S*,*S*) reboxetine **29** *via* Sharpless asymmetric epoxidation as the key step Thus, Sharpless asymmetric epoxidation of commercially available cinnamyl alcohol **11a** furnished epoxide **12** with >99% ee. The regioselective ring opening of epoxide **12** with 2-ethoxyphenol gave a single regioisomer *anti*-aryloxy diol **13** in good yield. In order to establish the desired *syn* configuration,

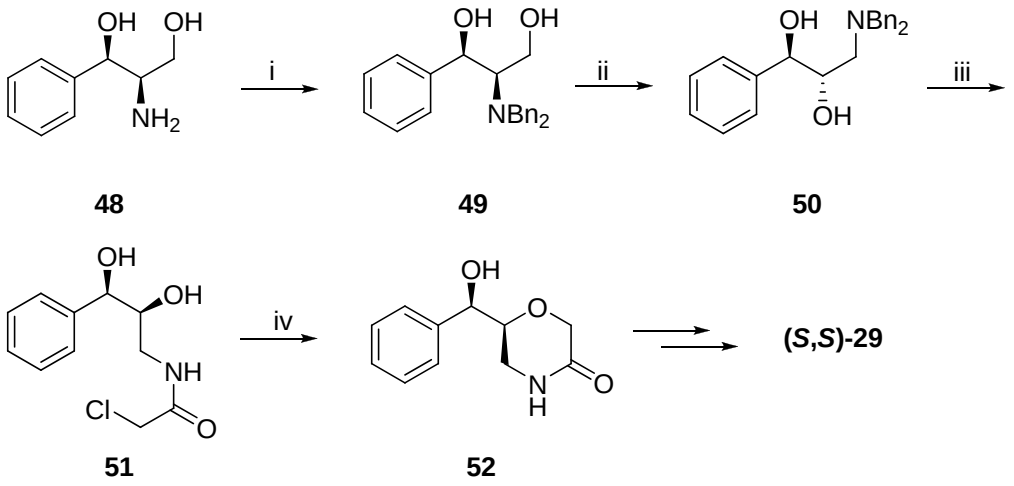
authors had carries out a three-step reaction sequence: (i) chemoselective TMS protection of diol **13**; (ii) mesylation of secondary hydroxyl using MsCl; (iii) final treatment of crude mesylate with NaOH in THF to furnish the appropriately oriented *syn* aryloxy epoxide **10** in 95% yield. Epoxide **10** was converted to (*S*,*S*)-reboxetine (**29**) using simple transformations (**Scheme 15**).



Scheme 15: (i) (-)-DIPT, Ti(O*i*Pr)$_4$, *t*BuOOH in toluene, CH_2Cl_2, -20–25 °C; (ii) 2-ethoxyphenol, NaOH, H_2O, 70 °C, 2.5 h, 52% (for 2 steps); (iii) (a) TMSCI, Et_3N, CH_2Cl_2, 25 °C; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (c) 2N NaOH, THF, 25 °C, 4 h, 95%; (iv) 30% NH_4OH, MeOH, 88%; (v) (a) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2 at –10 °C to 25 °C, 6 h, 70%; (b) *t*-BuOK, *t*-BuOH, 25 °C, 4 h, 80%.

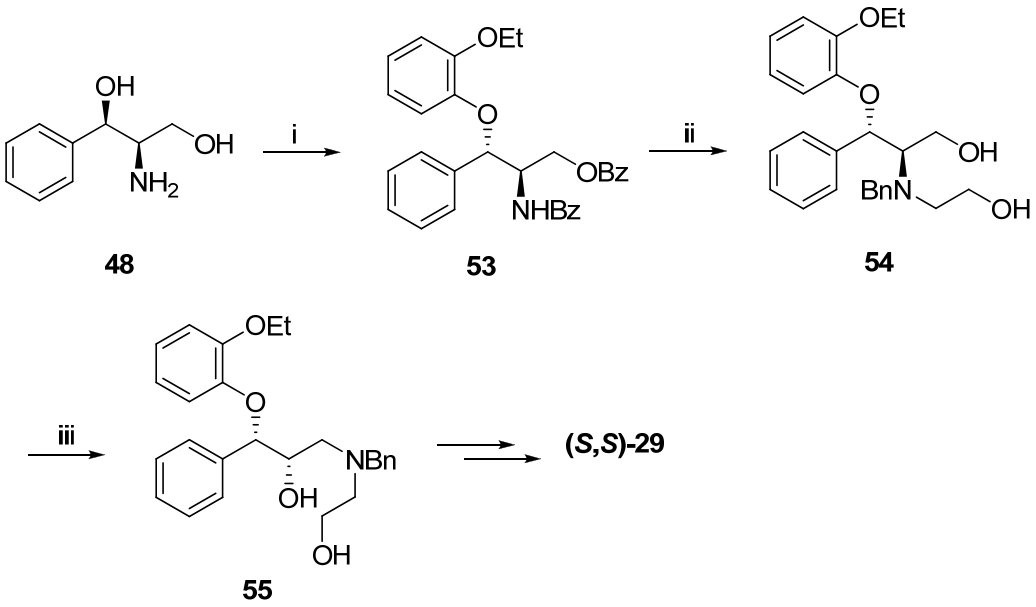
Pardo's approach (2007)[25]

Pardo's *et al*. have made use of rearrangement of *N*,*N*-dialkyl-*α*-amino alcohols **49** in the presence of a catalytic amount of TFAA as the key step. Commercially available (-)-(1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol **48** was converted to the corresponding tertiary amine **49** by *N*,*N*-dibenzylation, which was the precursor for the key step. Then **49** was treated with $(CF_3CO)_2O$ (0.4 equiv) in refluxing toluene for 5 h followed by a NaOH treatment to furnish the rearranged amino alcohol **50**. Amino alcohol **50** was converted to (*S*,*S*)-reboxetine (**29**) using reactions reported in the literature (**Scheme 16**).



Scheme 16: (i) BnBr, K_2CO_3, MeCN, reflux, 8 h, 98%; (ii) (a) $(CF_3CO)_2O$, toluene, reflux, 5 h; (b) NaOH, 25 °C, 2 h, 78%; (iii) (a) $Pd(OH)_2$, H_2 (1 atm), MeOH, 25 °C, 26 h, 71%; (b) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2/MeCN (9:1), 25 °C, 45 min, 89%; (iv) *t*-BuOK, *i*PrOH, 25 °C, 2 h, 62%.

In their second approach, chiral aminodiol **48** was protected as benzoylated amino alcohol**,** which was then converted to aryloxy amino alcohol **53** *via* Mitsunobu reaction on the benzylic alcohol with 2-ethoxyphenol.

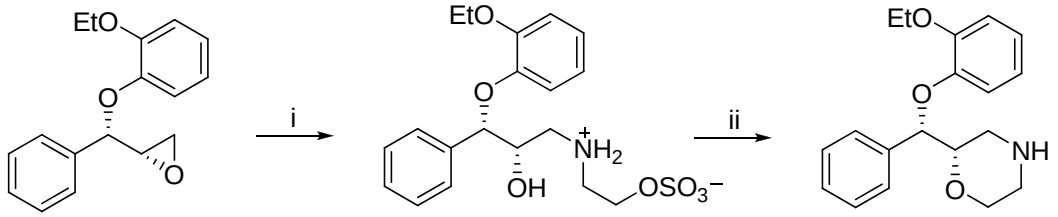


Scheme 17: (i) (a) BzCl, Et_3N, CH_2Cl_2, 25 °C, 24 h, 96%; (b) PPh_3, 2-Ethoxyphenol, DIAD, THF, 25 °C, 2 h, 76%; (ii) (a) BH_3.THF, THF, reflux, 3 h, 92%; (b) $BrCH_2CO_2Me$, K_2CO_3, DMF, 25 °C, 7days; (c) $LiAlH_4$, THF, 25 °C, 2 h, 70%; (iii) $(CF_3CO)_2O$, THF, 120 °C, 18 h, MW, 36%.

Further, *N*,*N*-dialkylamino alcohol **54** was obtained from amino alcohol **53** in three steps: (i) reduction of N/O benzoyl moiety with BH_3.THF (ii) *N*-alkylation using methyl bromoacetate (iii) reduction of the crude material by $LiAlH_4$. The *N*,*N*-dialkylamino alcohol **54** was then subjected to rearrangement by treatment with $(CF_3CO)_2O$ (under microwave irradiation) that afforded the rearranged aminodiol **55** in a modest yield of 36%. Amino diol **55** was finally converted to (*S*,*S*)-reboxetine (**29**) by following the known sequence of reactions (**Scheme 17**).

Assaf's approach (2010)[26]

In this approach, Assaf's *et al*. were able to convert a four-step morpholine synthesis into a more efficient two-step process. In this approach synthesis of (*S*,*S*)-reboxetine (**29**) was achieved starting from aryloxy epoxide **10** using a two-step reaction process: (i) opening of epoxide with (2-amino ethyl hydrogen sulfate) 2-AEHS to afford amino alcohol **56**; (ii) base-mediated ring-closure using a typical solid NaOH/THF/EtOH system. The combined transformations delivered (S,S)-reboxetine in more than 60% overall yield (**Scheme 18**).



10 **56** **(*S*,*S*)-29**

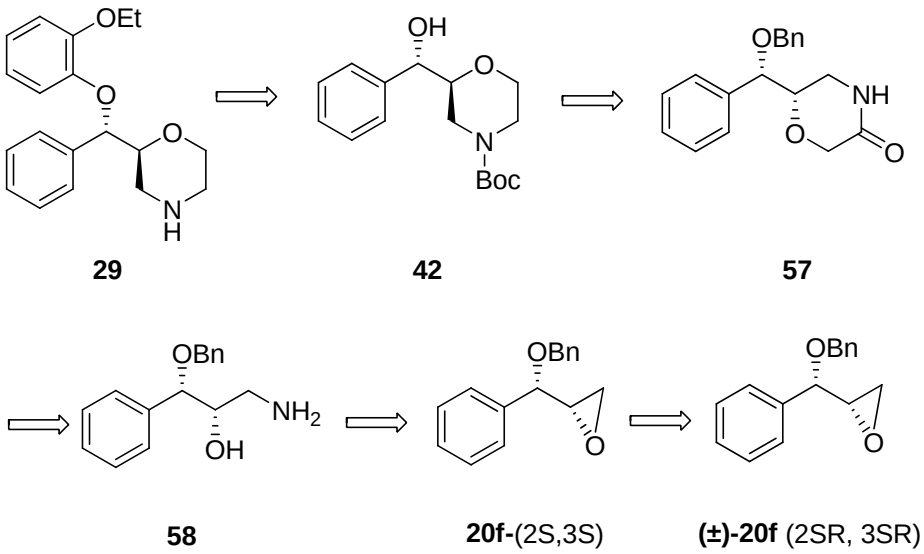
Scheme 18: (i) $H_2NCH_2CH_2OSO_3H$, DBU, PhMe, EtOH, 86%; (ii) NaOH, THF, EtOH, 78%.

1.2.4 Present Work

1.2.4.1 Objective

(*S*,*S*)-Reboxetine (**29**) exhibits the best affinity and selectivity for norepinephrine transporter. The methods described so far in the literature for the synthesis of (*S*,*S*)-reboxetine (**29**) suffer from the following: they involve separation of reboxetine enantiomers by classical resolution, capillary electrophoresis, or chiral HPLC and are specific to the reboxetine structure. In this section, we describe a new approach to the asymmetric synthesis of (*S*,*S*)-reboxetine (**29** using two stereocentred HKR of racemic benzyloxy epoxide **20f**.

The retrosynthesis of (*S*,*S*)-reboxetine (**29**) is presented in **Scheme 19**. Where in (*S*,*S*)-reboxetine (**29**) can be obtained from morpholine **42** which can be realized through the lactam **57**. The lactam **57** can be obtained from the corresponding key intermediate, aminoalcohol **65,** which in turn can be obtained from chiral benzyloxy epoxide **20f.** The benzyloxy epoxide **20f** could be prepared from racemic benzyloxy epoxide (±)**-20f** employing by the two-stereocentred cobalt-catalyzed HKR.



29 **42** **57**

58 **20f-**(2S,3S) **(±)-20f** (2SR, 3SR)

Scheme 19: Retrosynthetic analysis of (*S*,*S*)-reboxetine (**29**)

1.2.5 Results and Discussion

Our synthesis of (*S*,*S*)-reboxetine **29** has started from cinnamyl alcohol **11a,** which was transformed into *syn*-benzyloxy epoxide (±)-**20f** in two steps: (i) benzyloxybromination to give bromo derivative **59** (ii) the formation of epoxide to give *syn*-benzyloxy epoxide (±)-**20b** in 84% yield, which was confirmed by ^{1}H and ^{13}C-NMR spectroscopy.

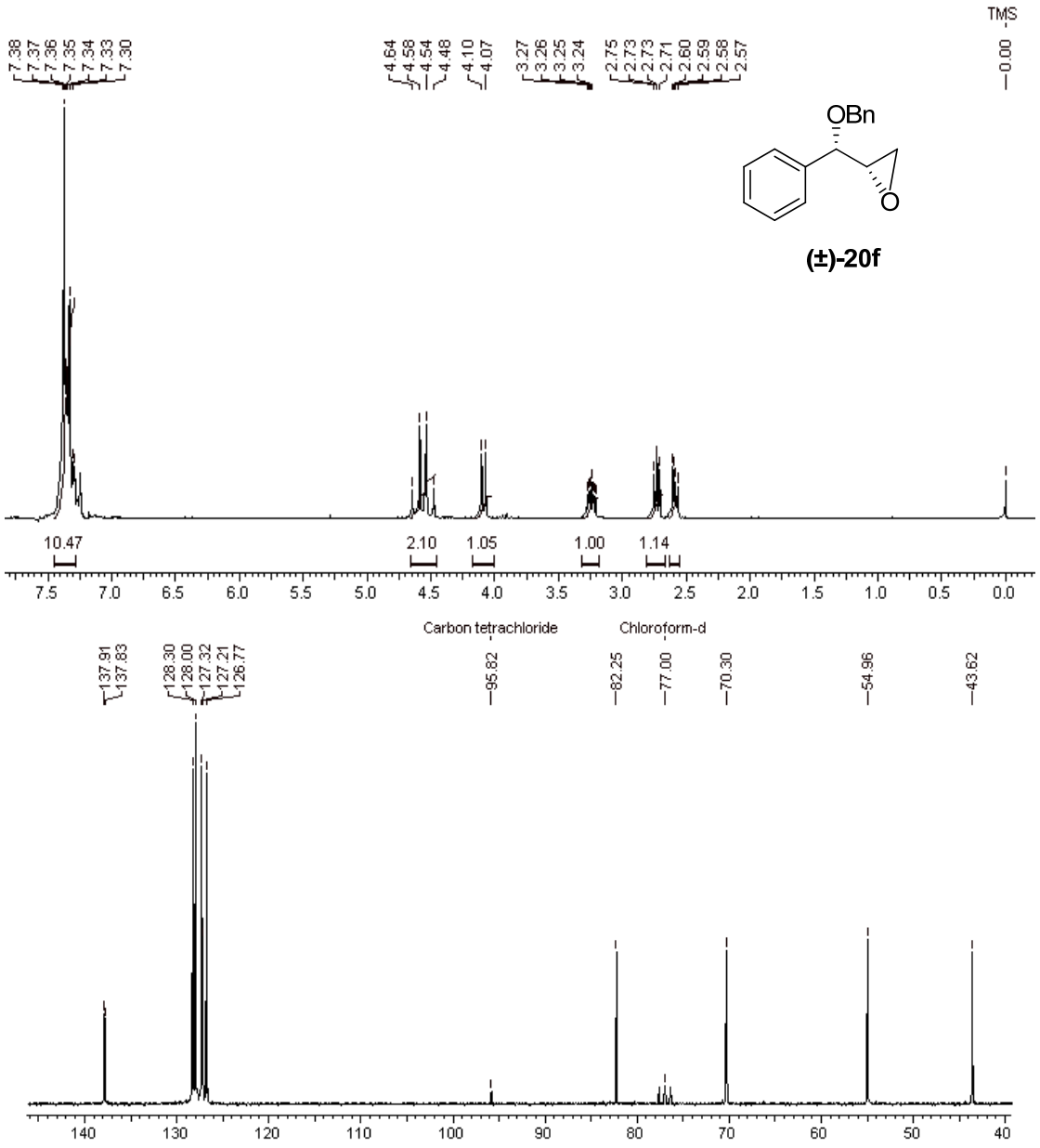
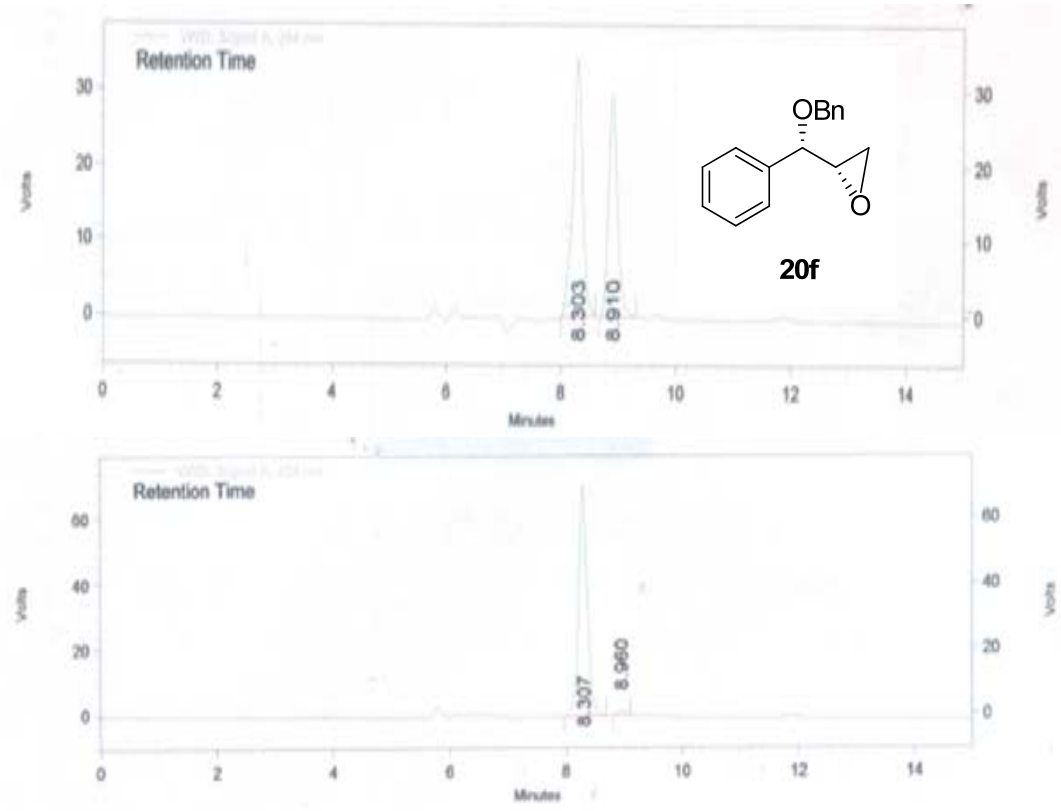


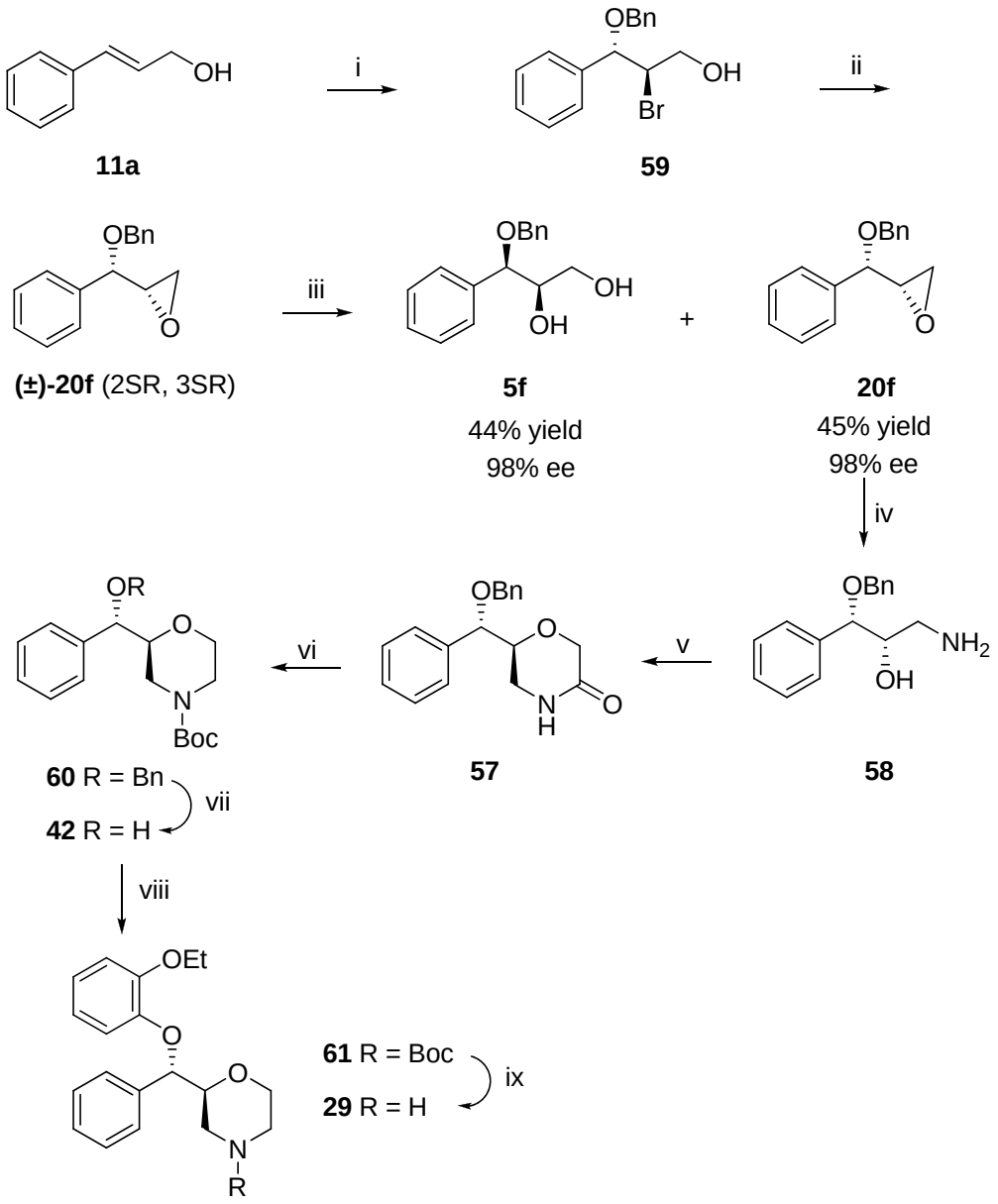
Fig. 13: ^{1}H and ^{13}C-NMR spectra of benzyloxy epoxide (±)-**20f**

The ^{1}H-NMR spectrum of *syn*-benzyloxy epoxide, (±)-**20f** showed typical signals at δ 2.57-2.75 (m, 2H) and δ 3.24-3.27 (m, 1H) for methylene and methine protons respectively. Its ^{13}C-NMR showed characteristic signals at δ 43.62 and 54.96 due to carbons of the epoxide ring (**Fig. 13).** The *syn*-benzyloxy epoxide (±)-**20f** was then subjected to HKR using (*R,R)*-Co(salen)OAc (**1**) to give chiral *syn*-benzyloxy diol **5f** in 44% yield with 98% ee along with chiral *syn*-benzyloxy epoxide **20f** in 45% yield with 98% ee (**Scheme 20)**. The compounds **20f** and **5f** were then readily separated by column chromatographic purification. The enantiomeric excess of *syn*-benzyloxy epoxide **20f** was determined by chiral HPLC analysis; (Chirapalk OD-H, Fig. **14).**



No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %
1	8.30	1184534	12563112	98.48
2	8.96	18485	194031	1.52

Fig. 14: HPLC chromatogram of epoxide **5f**



Scheme 20: (i) NBS, BnOH, CH_3CN, 25 °C, 3 h, 85%; (ii) NaOH powder, THF, 25 °C, 2 h, 88%; (iii) *(R,R)*-Co(III)(salen)OAc (1 mol%), THF, H_2O (0.48 equiv.), 0 ºC, 12 h; (iv) 30% NH_4OH, MeOH, 25 °C, 12 h, 83%; (v) (a) $ClCH_2COCl$, Et_3N, CH_2Cl_2, -10 °C; (b) KO^tBu, t-BuOH, 3 h, , 72% ; (vi) (a) Red-Al, dry toluene, 25 °C, then 2N NaOH; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 85%; (vii) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h, 92%; (viii) (a) CBr_4, PPh_3, imid., CH_2Cl_2, 25 °C, 2 h; (b) 2-ethoxy phenol, NaH, DMF, 3 h, 72%; (ix) TFA, CH_2Cl_2, 0 °C, 1 h, 96%.

The chiral epoxide **20f** was then subjected to regioselective ring opening at the terminal position with aqueous 30% NH_4OH to give the corresponding aminoalcohol **58** in 83%

yield; $[\alpha]^{25}_{D}$: +48.99 (*c* 1.0, $CHCl_3$). The ^{1}H-NMR spectrum of the aminoalcohol **58** showed signals at δ 2.53-2.69 (m, 2H) and 3.86-3.96 (m, 1H) corresponding to the methylene and methine protons attached to C**H**-OH and C**H**-NH_2 protons respectively. Its ^{13}C-NMR spectrum showed peaks at δ 70.61 and 70.88 corresponding to the methylene (-O-**C**H_2-Ph) and methine (-**C**H-OH) carbons respectively. The other carbon signals at 41.64 and 82.48 correspond to methylene (-**C**H_2NH_2) and methine (-**C**H-OBn) carbons respectively (**Fig. 15**).

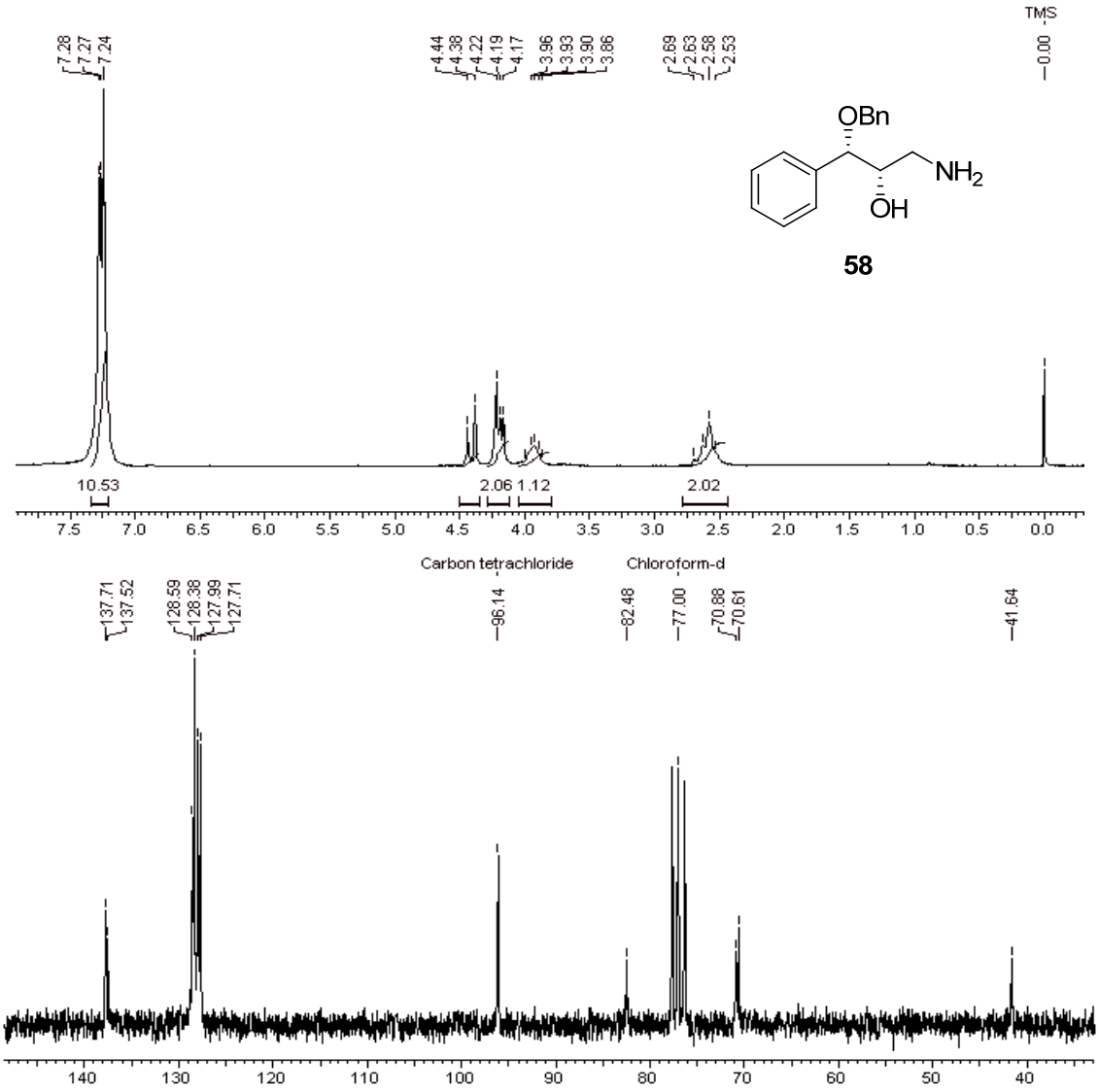


Fig. 15: ^{1}H and ^{13}C-NMR spectra of amino alcohol **58**

The amino alcohol **58** was reacted with chloroacetyl choride in the presence of Et_3N as base at -10 °C to give the corresponding amide *in situ*, which was readily converted to the corresponding lactam **57** using *t*-BuOK as the base; $[\alpha]^{25}_{D}$: +36.34 (*c* 1.0, $CHCl_3$).

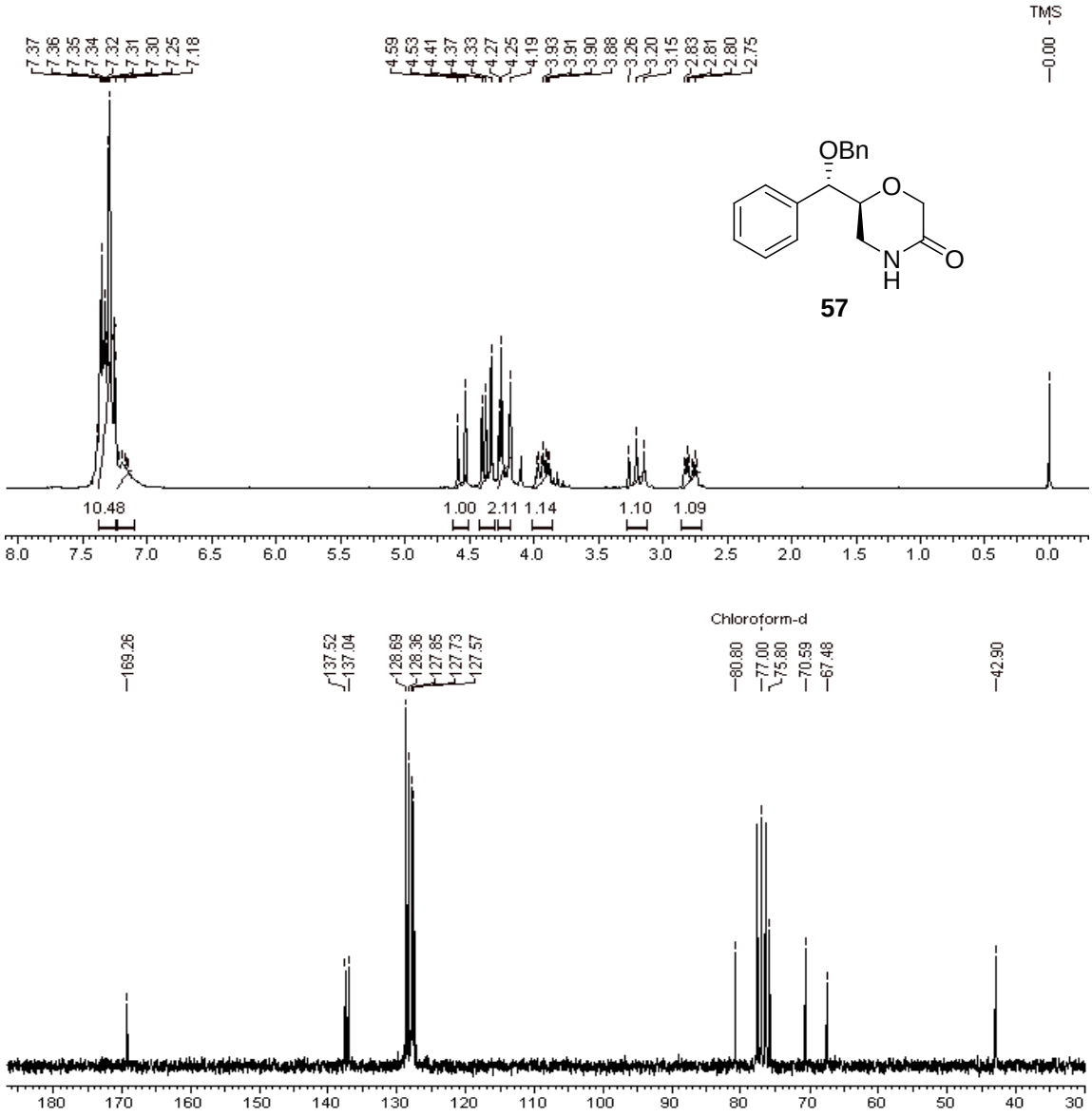


Fig. 16: ^{1}H and ^{13}C-NMR spectra of lactam **57**

The ^{1}H-NMR spectrum of lactam **57** showed typical signals at δ 2.79 (td, *J* = 3.6, 12.0 Hz, 1H); 3.20 (t, *J* = 13.0 Hz, 1H); 3.88-3.98 (m, 1H) (-C**H**C**H₂**NHC=O-), and 4.19-4.27 (m, 2H) (-OC**H₂**C=ONH-) corresponding to the diastereotopic methylene protons present

in the lactam moiety. Its ^{13}C-NMR spectrum showed characteristic carbon signals at δ 42.90 (-CH**C**$\mathbf{H_2}$NHC=O-) and 67.43 (-O**C**$\mathbf{H_2}$C=ONH-) corresponding to methylene carbons present in the lactam moiety. The amide carbonyl in the lactam moiety showed a characteristic peak at δ 169.26 (**Fig. 16**). Its IR spectrum showed a characteristic strong band at 1686 cm^{-1} indicating the presence of amide carbonyl function.

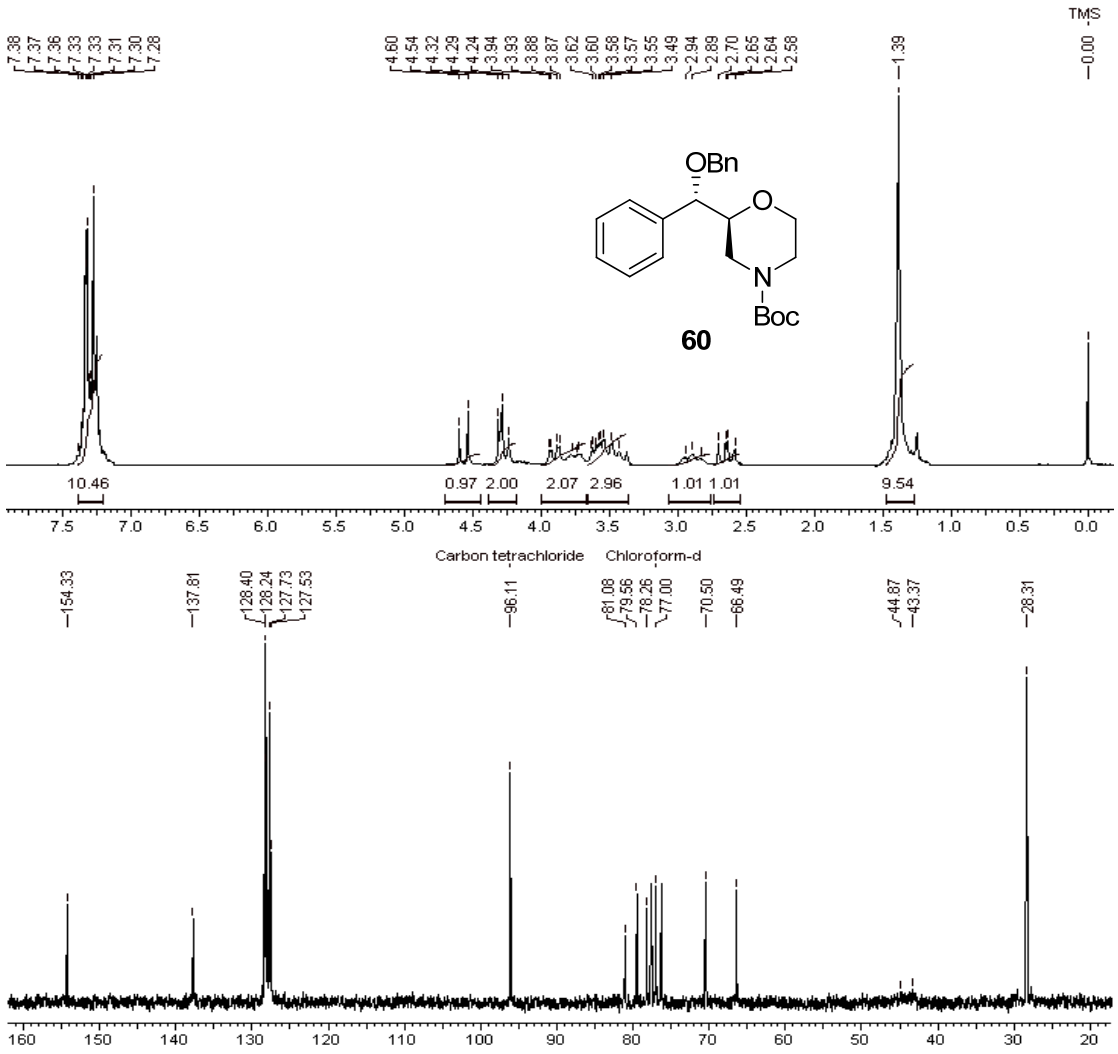


Fig. 17: ^{1}H and ^{13}C-NMR spectra of morpholine **60**

The lactam carbonyl group in **57** was then reduced with Red-Al in toluene to give the corresponding amine *in situ*, which was subsequently protected as its carbamate using

$(Boc)_2O$ to give morpholine **60** in 85% yield; $[\alpha]^{25}_D$: +36.34 (*c* 1.0, $CHCl_3$). The ^{1}H-NMR spectrum of the morpholine **60** showed signals at δ 2.58-2.94 (m, 2H) and 3.49-3.94 (m, 5H) corresponding to the methylene and methine protons present in the morpholine moiety. The signals at δ 4.24-4.31 (m, 2H) and 4.57 (d, *J* = 12.0 Hz, 1H) are due to the benzylic methylene (-O-C**H₂**-Ph) and the benzylic methine (-C**H**-OBn) protons respectively. Its ^{13}C-NMR spectrum showed characteristic carbon signals at δ 43.37 (-OCH_2**C**H_2N(Boc)-), 44.87 (-CH**C**H_2N(Boc)-) and 66.49 (-O**C**H_2CH_2N(Boc)-), corresponding to the three methylene carbons present in the morpholine moiety (**Fig. 17**).

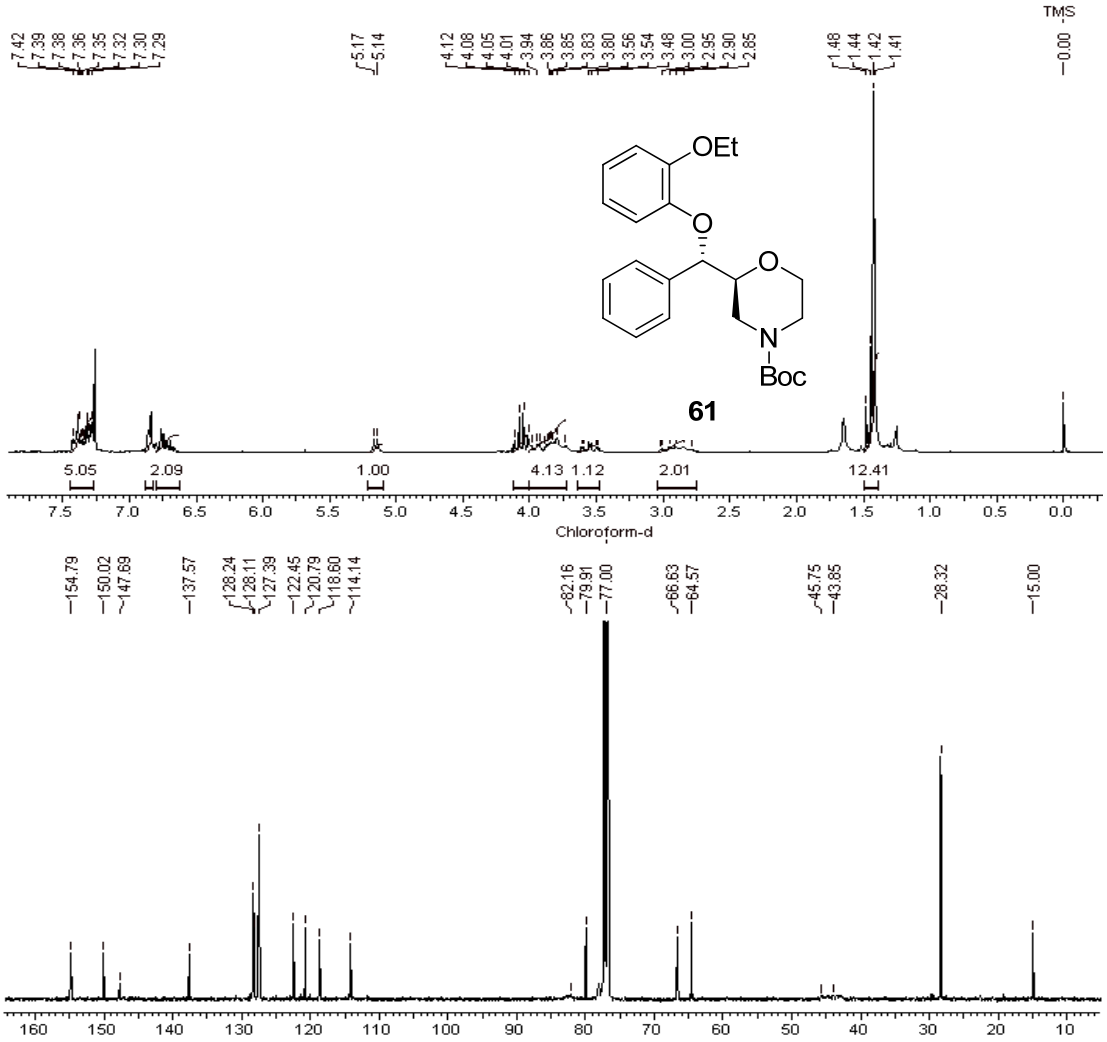


Fig. 18: ^{1}H and ^{13}C NMR spectrum of *N*-Boc amide **61**

The Benzyl group in morpholine **60** was deprotected under catalytic hydrogenation (10% Pd/C in MeOH) to give the corresponding secondary alcohol **42** in 93% yield; $[\alpha]^{25}_{D}$: +33.62 (*c* 1, $CHCl_3$); {lit.[23] $[\alpha]^{20}_{D}$: +34.0 (*c* 1.24, $CHCl_3$)}. Alcohol **42** was then converted to *N*-Boc protected reboxetine **61** in two steps (72% overall yield): (i) conversion of alcohol **42** to its bromo derivative; (ii) followed by nucleophilic displacement of bromo derivative with sodium salt of *o*-ethoxyphenol. This afforded N-Boc protected reboxetine **61;** $[\alpha]^{25}_{D}$: +50.4 (*c* 1, $CHCl_3$); {lit.[23] $[\alpha]^{20}_{D}$: +51.0 (*c* 1.01, $CHCl_3$)}. The ^{1}H-NMR spectrum of the *N*-Boc protected reboxetine **61** showed signals at δ 1.48 (m, 12H) and 5.15 (d, *J* = 3.5 Hz, 1H)) corresponding to methyl, and benzylic (-O-C**H$_2$**-) protons respectively. Its ^{13}C-NMR spectrum displayed characteristic broad signals at 43.85 (br, N**C**H_2CH_2), 45.75 (br, N**C**H_2CH_2) and 82.16 (br, **-**O-CH-) corresponding to the methylene and the methine carbons present in the morpholine moiety (**Fig. 18**).

Finally, treatment of *N*-Boc reboxetine (**61**) with excess CF_3CO_2H in CH_2Cl_2 afforded (*S*,*S*)-reboxetine (**29**) in 98% yield; $[\alpha]^{25}_{D}$: +12.6 (*c* 1.1, MeOH); {lit.[23] $[\alpha]^{20}_{D}$: +13.0 (*c* 1.03, MeOH)}. The ^{1}H-NMR spectrum of (*S*,*S*)-reboxetine (**29**) showed signals at δ 1.44 (t, *J* = 7.5 Hz 3H) and 5.13 (d, *J* = 5.5 Hz, 1H) corresponding to the methyl protons in the ethoxyl moiety and the benzylic proton respectively. Its ^{13}C-NMR spectrum displayed carbon signals at δ 45.1 (N**C**H_2CH_2) and 46.8 (NCH_2**C**H_2) corresponding to the methylene groups in the morpholine moiety (**Fig. 19**). Thus, the spectral data obtained for (*S*,*S*)-reboxetine (**29**) were in full agreement with the values reported in the literature.[12]

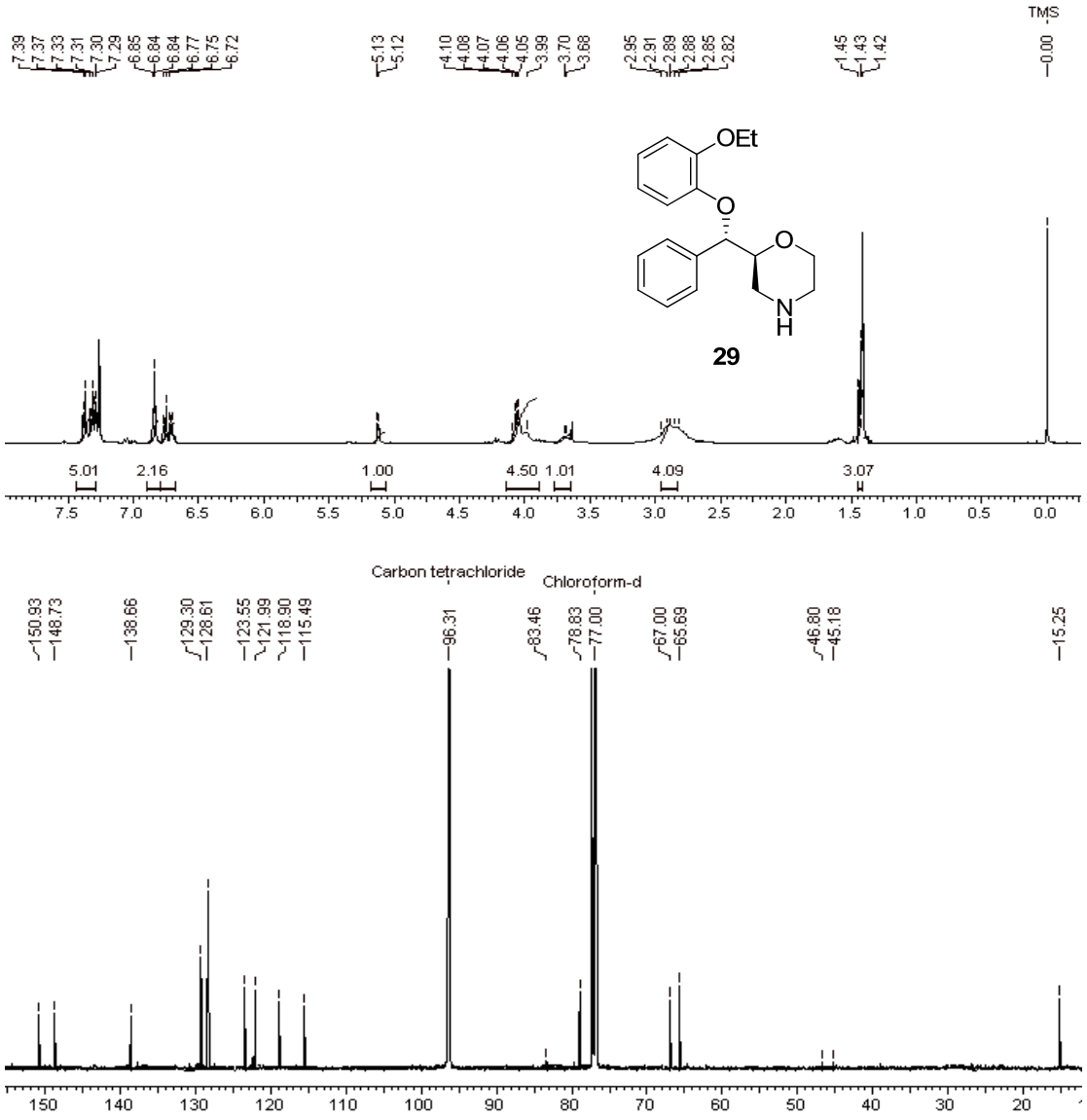


Fig. 19: ^{1}H and ^{13} C-NMR spectrum of (*S*,*S*)-reboxetine (**29**)

1.2.6 Conclusion

In conclusion, we have achieved the asymmetric synthesis of (*S*,*S*)-reboxetine (**29**) (overall yield 11%, 98% ee) *via* two stereocentred HKR of racemic benzyloxy epoxide as the key step. The high enantiomeric excess obtained in this method render our approach a good alternative to the known methods.

1.2.7 Experimental Section

For the preparation of **20f** and **5f** see Section I of this Chapter.

(1*S*,2*S*)-3-Amino-1-(benzyloxy)-1-phenylpropan-2-ol (58)

To a stirred solution of epoxide **20f** (793 mg, 3 mmol) in MeOH (10 mL) was added 30% NH_4OH (15 mL) and the mixture was stirred at 25 °C for 12 h. After completion of the reaction, solvent was distilled off under reduced pressure and the crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (70:30) to give amino alcohol **58** in 83% yield.

Yield: 83%; gum; $[\alpha]^{25}_{D}$ +48.99 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 735, 837, 910, 1097, 1256, 1389, 1472, 1605, 1655, 2929, 3371, 3410, 3426; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 2.53-2.69 (m, 2H), 3.86-4.00 (m, 1H), 4.16-4.22 (m, 2H), 4.41 (d, *J* = 11.0 Hz, 1H) 7.24-7.28 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 41.6, 70.6, 70.8, 82.4, 127.7, 127.9, 128.3, 128.5, 137.5, 137.7; **Analysis:** $C_{16}H_{19}NO_2$ requires C, 74.68; H, 7.44; N, 5.44; found C, 74.58; H, 7.39; N, 5.35%.

(*S*)-6-((*S*)-(Benzyloxy)(phenyl)methyl)morpholin-3-one (57)

To a stirred solution of amine **58** (1.47g, 5.24 mmol) and Et_3N (1.60 mL, 11.5 mmol) in CH_2Cl_2 (40 mL), was added drop-wise at –10 °C, a solution of chloroacetylchloride (0.45 mL, 5.66 mmol) in CH_2Cl_2 (10 mL). After stirring for 0.5 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water followed by saturated brine. The combined organic phase was dried over anhyd. Na_2SO_4 and solvent distilled off under reduced pressure to give the crude product which was dissolved in *t*-BuOH (20 mL) and added to a stirred solution of KO^{t}Bu (1.18 g, 10.44 mmol) in *t*-BuOH (6 mL). The reaction mixture was stirred for 3 h at 25 °C and quenched by the addition of water. The

organic phase was separated and the aqueous phase extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with water and brine, dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (25:75) to give the lactam **57** in 72% yield.

Yield: 72% for 2 steps; gum; $[\alpha]^{25}_{D}$ +36.34 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 700, 777, 860, 1029, 1105, 1251, 1362, 1462, 1541, 1667, 2856, 2885, 2927, 2954, 3440; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 2.79 (td, *J*=12.0, 3.6 Hz, 1H), 3.20 (t, *J*=13.0 Hz, 1H), 3.88-3.98 (m, 1H), 4.19-4.27 (m, 2H), 4.33-4.41 (m, 2H), 4.77 (d, *J* = 12.5 Hz, 1H), 7.56 (br s, 1H), 7.28-7.40 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 42.9, 67.4, 70.5, 75.8, 80.8, 127.5, 127.8, 128.3, 128.6, 137.0, 137.5, 169.2; **Analysis:** $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.44; N, 4.71; found C, 72.59; H, 6.39; N, 4.62%.

(S)-tert-Butyl 2-((S)-(benzyloxy)(phenyl)methyl)morpholine-4-carboxylate (60)

A solution of Red Al (3.5 mL, 10.48 mmol) in dry toluene (10 mL) was slowly added to a stirred solution of amide **57** (964 mg, 3 mmol) in dry toluene (40 mL) at 25 °C. The reaction mixture was stirred for 4 h and the excess Red Al was quenched by the addition of 2N NaOH (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product obtained was dissolved in CH_2Cl_2 (15 mL). The mixture was cooled to 0 °C and Et_3N (460 µL, 3 mmol) and $(Boc)_2O$ (654 mg, 3 mmol) were added to it. After 1 h the reaction mixture was quenched by the addition of aqueous $NaHCO_3$ (10%). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL).

The combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using Pet. Ether/EtOAc as eluent (85:15) to give morpholine derivative **60** in 75% yield.

Yield: 92%; **$[\alpha]^{25}_D$**: +35.45 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 721, 862, 1068, 1114, 1181, 1241, 1323, 1456, 1610, 1699, 2861, 3014; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 1.39 (s, 9H), 2.58-2.94 (m, 2H), 3.49-3.62 (m, 3H), 3.87-3.94 (m, 2H), 4.24-4.32 (m, 2H), 4.57 (d, *J* = 12.0 Hz, 1H), 7.28-7.38 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 28.3, 43.3, 44.8, 66.4, 70.5, 78.2, 79.5, 81.0, 127.5, 127.7, 128.2, 128.4, 137.8, 154.33; **Analysis**: $C_{16}H_{23}NO_4$ requires C, 72.04; H, 7.62; N, 3.65%; found C, 71.98; H, 7.56; N, 3.61%.

(*S*)-tert-Butyl 2-((*S*)-hydroxy(phenyl)methyl)morpholine-4-carboxylate (42)

To a stirred solution of morpholine derivative **60** (0.53 g, 2 mmol) in MeOH (20 mL) was added catalytic amount of 10% Pd/C and the resulting heterogeneous mixture was stirred 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 over silica gel using petroleum ether/EtOAc (80:20) to give **42**.

Yield: 88%; **mp:** 105-106 °C; **$[\alpha]^{25}_D$**: +33.62 (*c* 1, $CHCl_3$); {lit.[23] **$[\alpha]^{20}_D$**: +34.0 (*c* 1.24, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 721, 862, 1068, 1114, 1181, 1241, 1323, 1456, 1610, 1701, 2861, 3214; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.67 (br s, 1H), 2.87-2.99 (m, 2H), 3.37-3.61 (m, 3H), 3.79 (d, *J* = 13.9 Hz, 1H), 3.94 (d, *J* = 12.19 Hz, 1H), 4.49 (d, *J* = 6.9 Hz, 1H), 7.27-7.34 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 28.3,

43.9, 44.6, 66.4, 75.0, 79.4, 79.8, 126.9, 128.3, 128.4, 139.3, 154.3; **Analysis**: $C_{16}H_{23}NO_4$ requires C, 65.51; H, 7.90; N, 4.77%; found C, 65.46; H, 7.79; N, 4.72%.

(*S*)-2-((*S*)-(2-Ethoxyphenoxy)(phenyl)methyl)morpholine (61)

To a stirred solution of morpholine **42** (300 mg, 1.13 mmol), PPh_3 (449 mg, 1.356 mmol) and imidazole (355 mg, 1.356 mmol) in CH_2Cl_2 was added CBr_4 (449 mg, 1.356 mmol) at 0 °C and the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by the addition of 10% $Na_2S_2O_3$ solution and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using Pet. ether/EtOAc as eluent (90:10) to give bromo derivative as colorless solid in 81% yield.

To a stirred suspension of sodium hydride (60% oil dispersion, 60 mg, 1.5 mmol) and 2-ethoxyphenol (50.5 mg, 0.356 mmol) in DMF (5 mL) at 0 °C, the above bromo derivative (100 mg, 0.305 mmol) in DMF (4 mL) was added drop-wise and the mixture was stirred at 25 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using Pet. ether/EtOAc as eluent (90:10) to provide *N*-Boc amide **61** as colorless oil.

Yield: 72%; gum; $\mathbf{[\alpha]^{25}_D}$: +50.4 (*c* 1, $CHCl_3$); {lit.[23] $[\alpha]^{20}_D$: +51.0 (*c* 1.01, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 761, 986, 1123, 1134, 1251, 1456, 1499, 1543, 1690, 2915, 2923; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 1.45 (s, 12H), 2.79-3.00 (m, 2H), 3.50-3.56 (m, 1H),

3.70-3.90 (m, 4H), 4.01-4.12 (m, 2H), 5.16 (d, J = 3.5 Hz, 1H), 6.67-6.87 (m, 4H), 7.29-7.43 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 15.0, 28.3, 43.8, 45.7, 64.5, 66.8, 74.9, 79.9, 82.1, 114.1, 118.6, 120.7, 122.4, 127.3, 128.2, 137.5, 147.8, 150.0, 154.7; **Analysis**: **$C_{24}H_{31}NO_5$** requires C, 69.71; H, 7.56; N, 3.39 found C, 69.64; H, 7.61; N, 3.34%.

(*S,S*)-Reboxetine (29)

To a stirred solution of *N*-Boc amide **46** (100 mg, 0.242 mmol) in CH_2Cl_2 (4 mL), trifluoroacetic acid (0.74 mL, 3.6 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to reach 25 °C and stirred for 1.5 h. It was then cooled to 0 °C and quenched by the addition of 1M NaOH solution (15 mL). The organic phase was separated and the aqueous phase extracted with EtOAc/MeOH (95:5, 3 x 30 mL). The combined organic phase was dried over anhyd. Na_2SO_4, solvent evaporated under reduced pressure and the crude product purified by column chromatography over silica gel using MeOH/$CHCl_3$ (10:90) as eluent to provide (*S,S*)-reboxetine **29** as colorless oil.

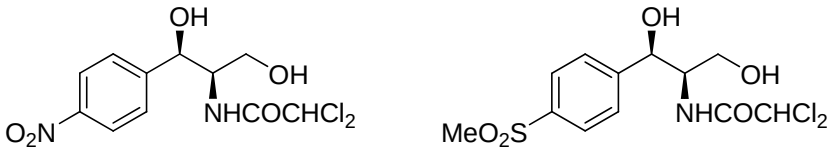
Yield: 98%; gum; **$[\alpha]^{25}_D$**: +12.59 (*c* 1.1, MeOH); {lit.[23] $[\alpha]^{20}_D$: +13.0 (*c* 1.03, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 750, 997, 1119, 1154, 1251, 1453, 1499, 1593, 2915, 3031; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.44 (t, J = 7.5 Hz, 3H), 2.98-2.80 (m, 4H), 3.77-3.68 (m, 1H), 4.13-3.97 (m, 4H), 5.26 (d, J = 5.5 Hz, 1H), 6.71-6.79 (m, 2H), 6.84-6.97 (m, 2H), 7.27-7.43 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.3, 45.1, 46.8, 65.7, 67.0, 78.8, 83.4, 115.5, 118.9, 121.9, 123.5, 128.6, 129.3, 138.6, 148.7, 150.9; **Analysis**: **$C_{19}H_{23}NO_3$** requires C, 72.82; H, 7.40; N, 4.47; found C, 72.69; H, 7.37; N, 4.44%.

Section III:

Enantioselective synthesis of (-)-chloramphenicol and (+)-thiamphenicol

1.3.1 Introduction

Optically active amino alcohols with vicinal stereocenters are important as drugs and natural products such as amino sugars,[27] peptides and peptide analogs,[28] enzyme inhibitors, such as glycosphingolipids, antibiotics and alkaloids. (-)-Chloramphenicol (**62**) and (+)-thiamphenicol (**63**) (**Fig. 20**) are broad-spectrum antibiotics with a range of biological activities.[29] The antibiotic chloramphenicol is active only in its D-*threo* configuration and is effective in the treatment of typhus, dysentery and ocular bacterial infections.[30] Thiamphenicol (**63**), a synthetic analogue of chloramphenicol (**62**), is bacteriostatic for both gram-positive and gram-negative aerobes and for some anaerobes as well.[31]



62 **63**

Fig. 20: Structures of (-)-chloramphenicol (**62**) and (+)-thiamphenicol (**63**)

1.3.2 Pharmacology of (-)-chloramphenicol and (+)-thiamphenicol

Chloramphenicol (**62**) 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, the nitro group can be substituted by a methyl sulfonyl (which is thiamphenicol). In the parent compound, substitution at the 3-hydroxy position causes total loss of biological activity and the L(+) isomer lacks antibacterial activity. The simple structure and inherent stability of the intramolecular bonds in chloramphenicol yield a compound that is remarkably resistant to acid or alkaline degradation, autoclaving, oxidation by light, and decomposition by extremes of temperature. 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. Thiamphenicol (**63**) possesses high *in vivo* activity for having a good property of unbinding with glucuronic acid in liver and has been used clinically.

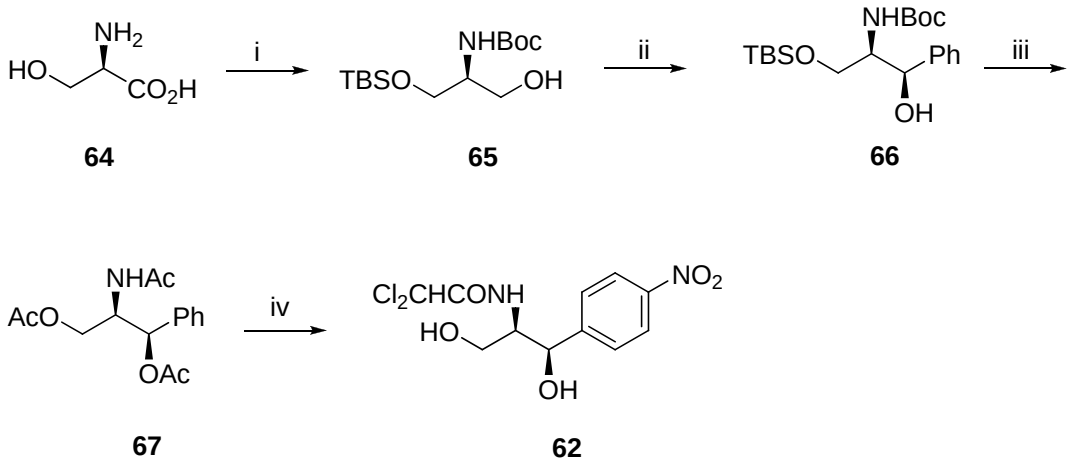
1.3.3 Review of Literature

Literature search revealed that there are several reports available for the synthesis of (-)-chloramphenicol (**62**) and (+)-thiamphenicol (**63**) involving chiral pool, chemo-enzymatic approach or enantioselective syntheses, which are described below.

Datta's approach (1998)[32]

Datta *et al.* have achieved the synthesis of (-)-chloramphenicol (**62**) using a chiral pool approach starting with D-serine **64**, which was converted into the amino diol derivative **65** in four steps. Swern oxidation of the alcohol **65** followed by Grignard addition with phenyl magnesium bromide afforded the *syn*-amino alcohol **66** with diastereoselectivity >19:1. A stepwise deprotection, acylation sequence of **67** gave the desired product

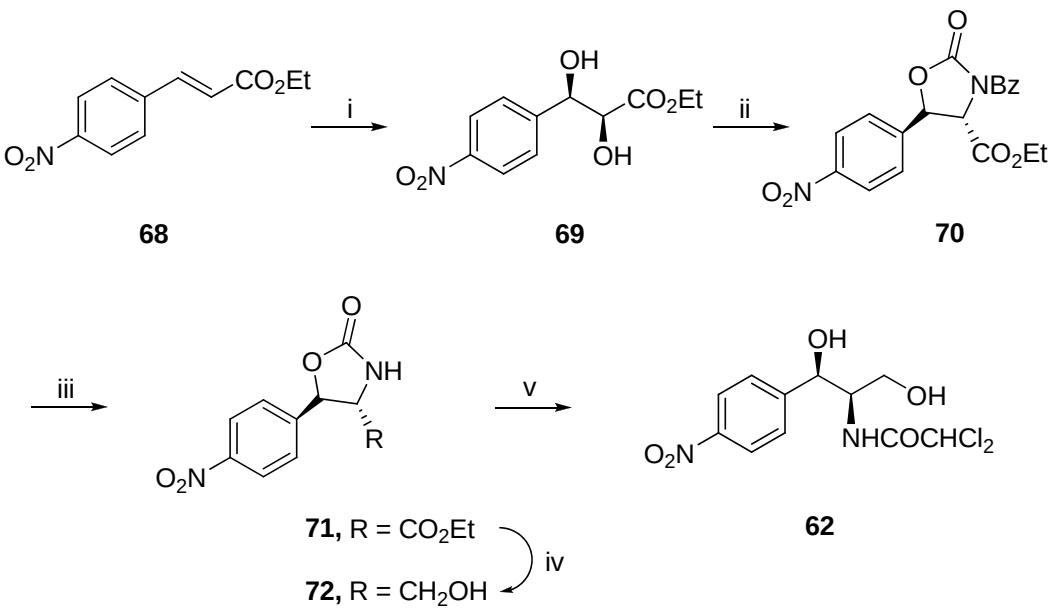
triacetate, which on nitration with con. HNO_3- con. H_2SO_4 (1:1) followed by treatment with methyl dichloroacetate gave (-)-chloramphenicol (**62**) in 73% yield (**Scheme 21**).



Scheme 21: (i) (a) MeOH, HCl; (b) $(Boc)_2O$, Et_3N, THF; (c) TBSCl, imidazole, 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, pyridine, 92%; (c) CF_3CO_2H, 0 °C; (d) Ac_2O, DMAP, pyridine, 85%; (iv) (a) con. HNO_3-con. H_2SO_4 (1:1), -20 °C to 25 °C; (b) aq. 5% HCl, 90 °C, 66%; (c) Cl_2CHCO_2Me, 90 °C, 73%.

Ko's approach (2000)[33]

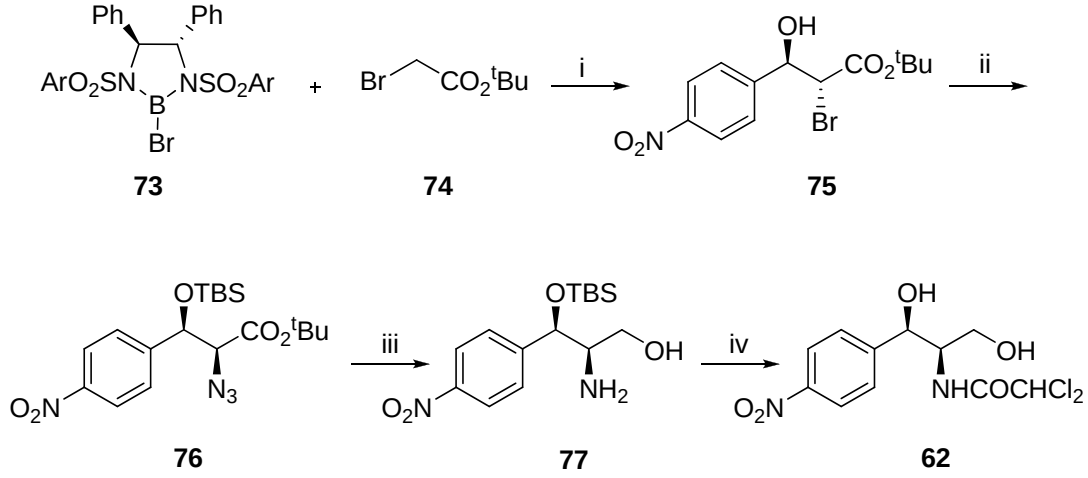
Ko *et al.* have synthesized (-)-chloramphenicol (**62**) by employing Sharpless asymmetric dihydroxylation as the key reaction. Thus, ester **68** was subjected to asymmetric dihydroxylation to give the diol **69** in 98% yield, which was successively treated with Bu_2SnO, BzNCS and Bu_4NBr to give the protected *syn* amino alcohol **70**. Debenzoylation of **70** with $Ti(O^iPr)_4$ and ethanol afforded amine **71**, which was then treated with $NaBH_4$ to give the alcohol **72** in 92%yield. Hydrolysis of **72** with 1 N NaOH followed by amidation with methyl dichloroacetate gave (-)-chloramphenicol (**62**) in 74% yield (**Scheme 22**).



Scheme 22: (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)[34]

(-)-Chloramphenicol (**62**) was also synthesized by Corey *et al. via* aldol reaction of *p*-nitrobenzaldehyde and *t*-butyl bromoacetate **74** in the presence of (*S*,*S*)-bromoborane **73** to give the bromohydrin **75** in 99% yield and 93%ee (**Scheme 23**).

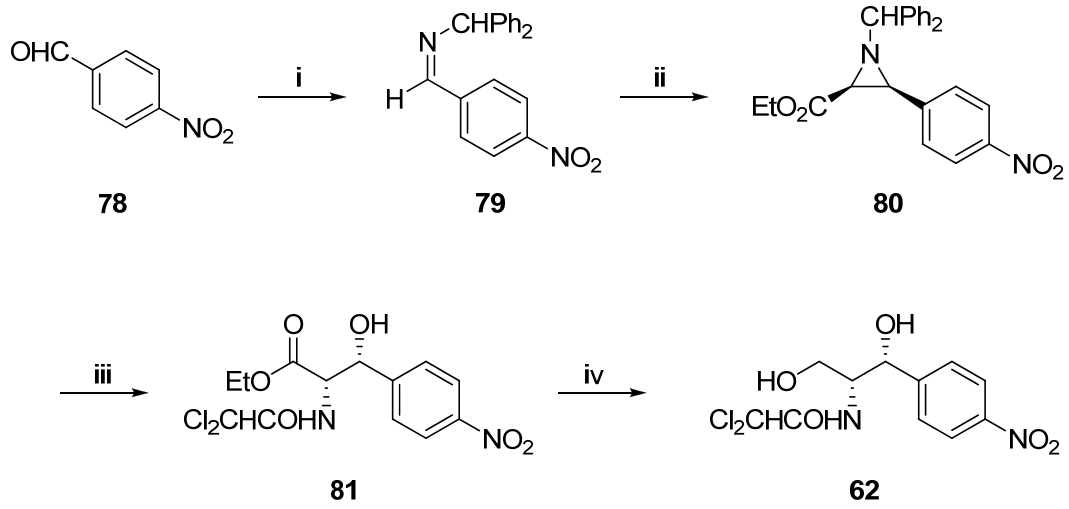


Scheme 23: (i) (a) toluene, -78 °C, Et_3N; (b) *p*-nitrobenzaldehyde, -78 °C, 99%, d.r. = 96:4, 93% ee; (ii) (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 96%; (b) NaN_3, DMF, 40 °C, 73%; (iii) (a) $LiBH_4$, Et_2O, 0 °C, 80%; (b) PPh_3, THF-H_2O, 80%; (iv) (a) Cl_2CHCO_2Me, CH_2Cl_2, 0 °C; (b) Bu_4NF, THF.

Protection of the hydroxyl group in **75** as its silyl ether followed by reaction with sodium azide gave **76**. Reduction of the azido ester **76** was performed in two steps: $LiBH_4$ reduction followed by triphenylphosphine in THF-H_2O to form the alcohol **77**. *N*-Acylation of **77** and subsequent desilyaltion with Bu_4NF in THF afforded (-)-chloramphenicol (**62**).

Wulff's approach (2001)[35]

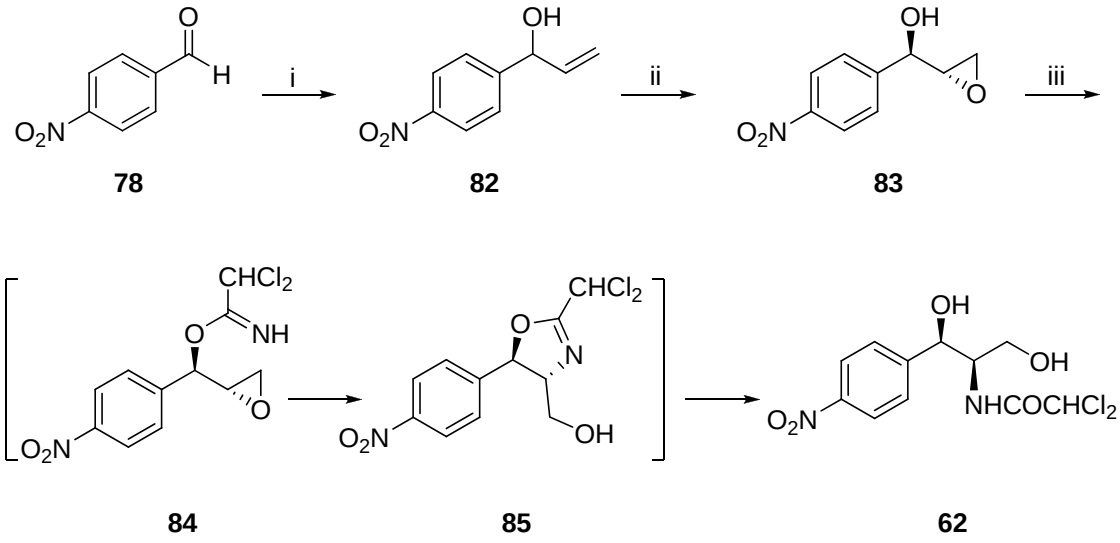
Wulff *et al.* have synthesized (-)-chloramphenicol (**62**) *via* catalytic aziridination of *p*-nitrobenzaldimine **79** in presence of 10 mol% of a catalyst prepared from triphenylborate and (*S*)-VAPOL to give aziridine **80** in 80% yield and 96% ee. Treatment of aziridine **80** with 10 equivalent of dichloroacetic acid gave the hydroxyl acetamide **81** which on subsequent reduction with $NaBH_4$ in MeOH afforded (-)-chloramphenicol (**62**) in 74% yield (**Scheme 24**).



Scheme 24: (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, 1,2-$C_2H_4Cl_2$, reflux, 1 h, 80%; (iv) $NaBH_4$, MeOH, 0 °C, 0.5 h, 74%.

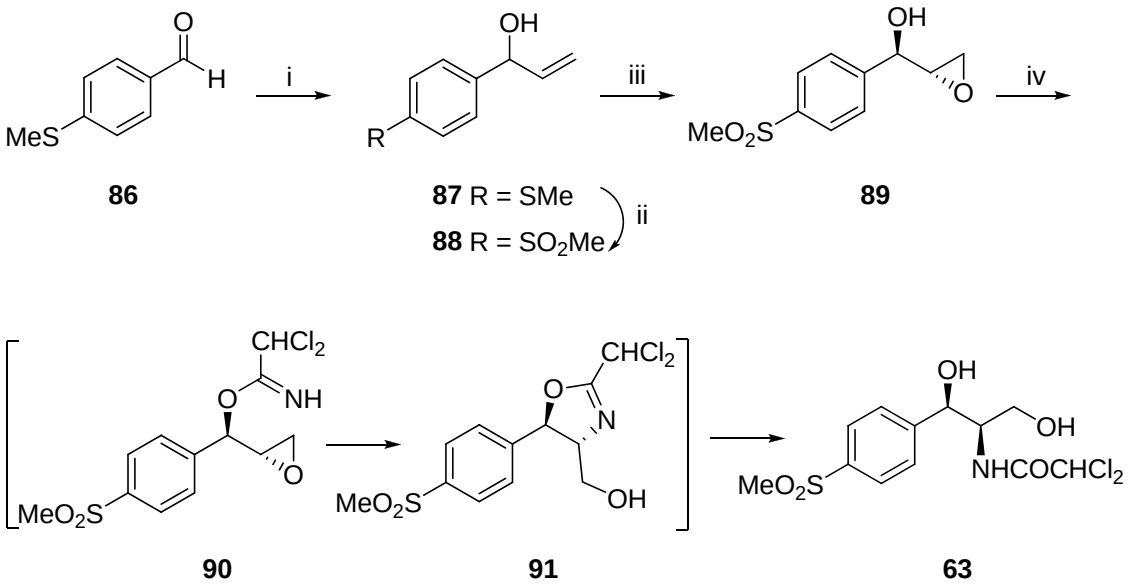
Rao's approach (2004)[36]

Rao *et al*. have achieved the synthesis of (-)-chloramphenicol (**62)** by employing Sharpless asymmetric epoxidation of the allylic alcohol **82** using (-)-DIPT to afford the chiral epoxyalcohol **83** with 95%ee. Epoxyalcohol **83** was then converted into (-)-chloramphenicol (**62)** by treatment with dichloroacetonitrile in the presence of NaH followed by an *in situ* opening of the product **85** with $BF_3.Et_2O$ (**Scheme 25**).



Scheme 25: (i) Divinyl zinc, THF, Et_2O, -78 ^{0}C to 25 ^{0}C, 10 h, 72%; (ii) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 ^{0}C, 14 h, 45%; (iii) NaH, dichloroacetonitrile, CH_2Cl_2, 0 ^{0}C to 25 ^{0}C, 1 h, then $BF_3.OEt_2$, -78 ^{0}C to 25 ^{0}C, 3 h, 71%.

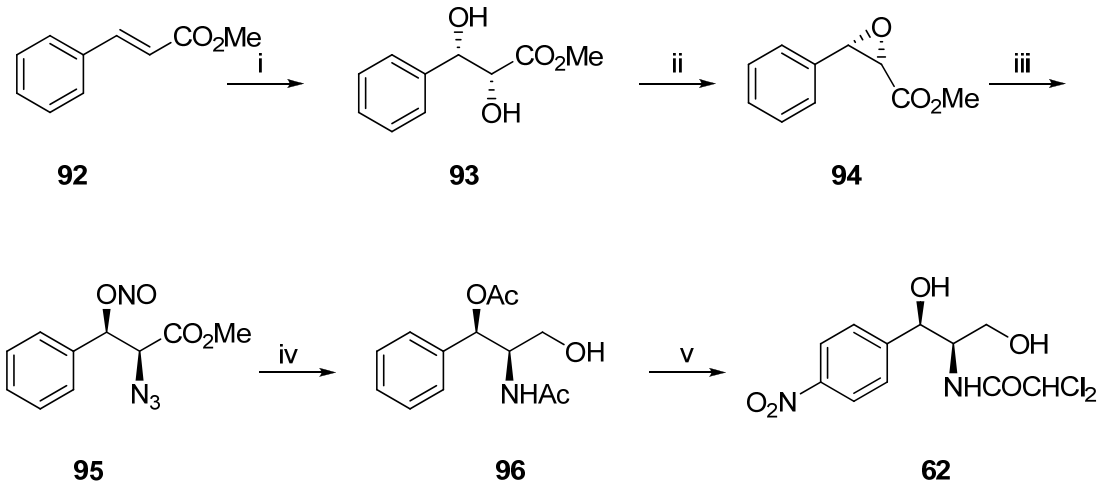
The same group has also synthesized (+)-thiamphenicol (**63**) by following a similar set of reaction sequences: Sharpless asymmetric epoxidation of allylic alcohol **88** followed by opening of the corresponding chiral epoxyalcohol **89** with Lewis acid (**Scheme 26**).



Scheme 26: (i) Vinyl magnesium bromide, THF, 0 °C to 25 °C, 2 h, 88%; (ii) Oxone, THF/MeOH/H_2O (1:1:2), 0 °C to 25 ^{0}C, 6 min, 87%; (iii) (-)-DIPT, Ti(O^iPr)$_4$, TBHP, CH_2Cl_2, -20 °C, 24 h, 42%; (iv) NaH, dichloroacetonitrile, CH_2Cl_2, 0 °C to 25 ^{0}C, 1 h, then $BF_3.OEt_2$, -78 °C to 25 °C, 4 h, 64%.

Barua's approach (2005)[37]

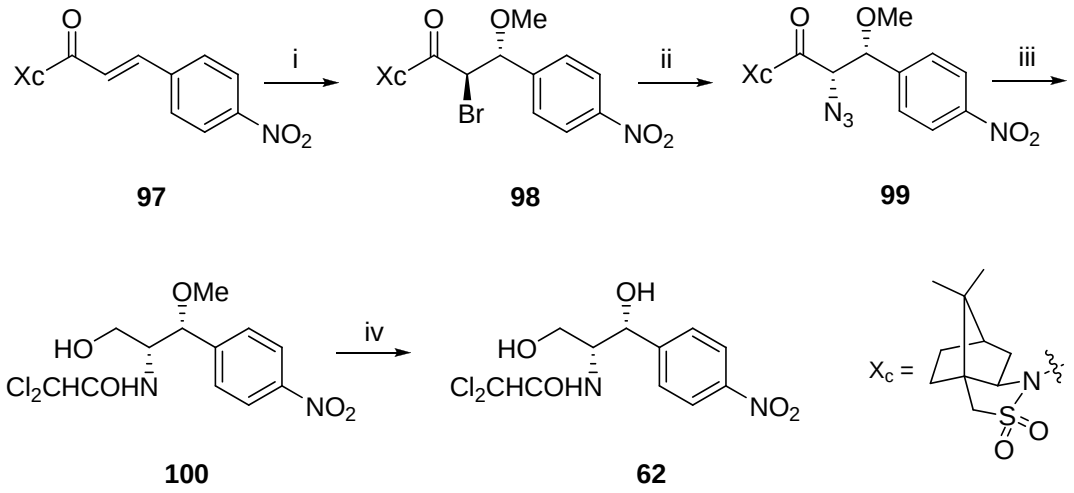
(-)-Chloramphenicol (**62**) was also synthesized by Barua *et al.* using regioselective ring opening of epoxide **94**, which was prepared from methyl cinnamate **92** by Sharpless asymmetric dihydroxylation. The epoxide **94** was exposed to $NaNO_2$ and acetic acid in water followed by treatment with diphenyl phosphorylazide (DPPA), DEAD and PPh_3 to afford the azide **95**. Catalytic hydrogenation of **95** [10% Pd/C, MeOH, H_2 (1 atm)] followed by acylation with Ac_2O gave the desired product **96**. The synthesis of (-)-chloramphenicol (**62)** was completed by following the three-step reaction sequence: nitration, hydrolysis and *N*-acylation (**Scheme 27**).



Scheme 27: (i) OsO_4 (cat.), NMO, DHQ-*p*ClBz, acetone, H_2O, 98% ee; (ii) (a) TsCl, pyridine, 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, pyridine; (v) (a) Con. HNO_3-con. H_2SO_4, -20 °C to 25 °C; (b) aq. 5% HCI, 90 °C, 69%; (c) Cl_2CHCO_2Me, 90 °C, 1 h, 80%.

Hajra's approach (2006)[38]

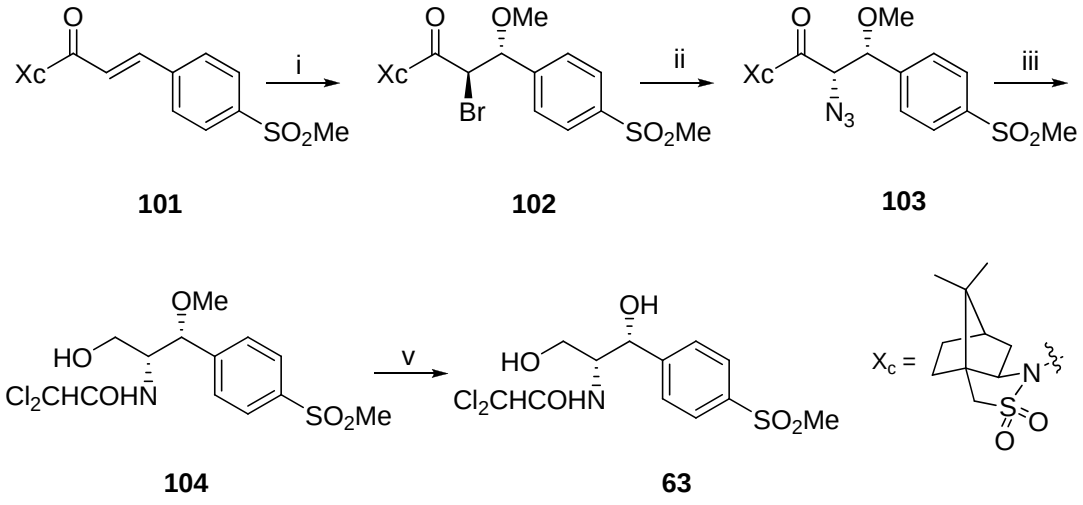
Hajra *et al.* have synthesized (-)-chloramphenicol (**62**) using silver(I)-promoted asymmetric bromomethoxylation.



Scheme 28: (i) $AgNO_3$, Br_2, MeOH, 0 ^{0}C, 30 min, 72%, d.r. = 3:1; (ii) NaN_3, DMF, 60 ^{0}C, 4 h, 92%; (iii) (a) $LiBH_4$, THF, MeOH; (b) PPh_3, THF-H_2O, 25 ^{0}C, 5 h, 82%; (iv) Cl_2CHCO_2Me, 90 °C, 1 h, 87%; (v) BBr_3, CH_2Cl_2, -78 ^{0}C to -20 ^{0}C, 10 h, 80%.

$AgNO_3$-promoted bromomethoxylation of α, β-unsaturated carboxamide **97** provided the desired product **98** in 72% yield. Reaction of **98** with NaN_3 in DMF gave the azido product **99**, which was subjected to a two-step reduction process with $LiBH_4$ followed by PPh_3 in THF-H_2O to furnish the amino alcohol, *N*-acylation of amino alcohol gave **100** which on subsequent demethylation with BBr_3 gave the target molecule **62** in 80% yield (**Scheme 28**).

(+)-Thiamphenicol (**63**) was also synthesized by the same group following the same synthetic strategy applied for (-)-chloramphenicol (**62**) (**Scheme 29**).



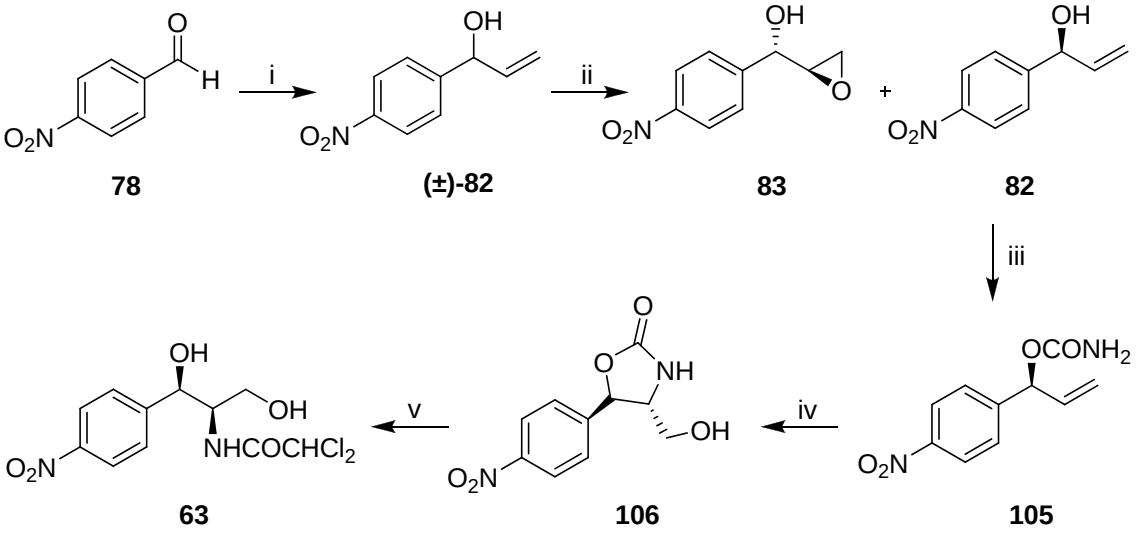
104 63

Scheme 29: (i) $AgNO_3$, Br_2, MeOH, 0 ^{0}C, 30 min, 68%, d.r. = 2.5:1; (ii) NaN_3, DMF, 60 ^{0}C, 4 h, 92%; (iii) (a) $LiBH_4$, THF, MeOH; (b) PPh_3, THF-H_2O, 25 ^{0}C, 5 h, 82%; (iv) Cl_2CHCO_2Me, 90 °C, 1 h, 85%; (v) BBr_3, CH_2Cl_2, -78 ^{0}C to -20 ^{0}C, 10 h, 84%.

Sudalai's approach (2006)[39]

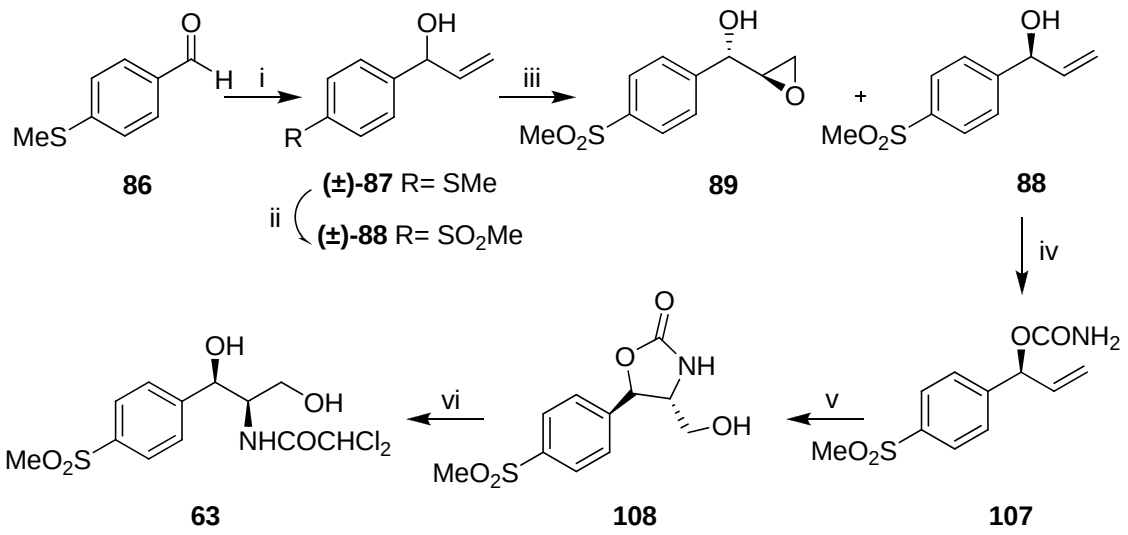
Sudalai *et al*. have developed a simple method for the enantioselective synthesis of (-)-chloramphenicol (**62**) and (+)-thiamphenicol (**63**) using Sharpless asymmetric epoxidation and tethered aminohydroxylation as the key steps. For (-)-chloramphenicol (**62**), the reaction of 4-nitrobenzaldehyde **78** with divinylzinc was carried out to give allyl alcohol **82**, which was then subjected to Sharpless asymmetric epoxidation under kinetic

resolution conditions to furnish the corresponding chiral allylic alcohol **82** in 44% yield and 98% ee along with the corresponding epoxide **83** in 49% yield. Alcohol **82** was then treated with trichloroacetyl isocyanate to give the corresponding isocyanate, which on treatment with base gave the carbamate **105** in 90% yield. The carbamate **105** thus obtained was converted into the oxazolidinone **106** by a tethered aminohydroxylation protocol to furnish the protected aminoalcohol **106** as a single isomer with complete regiocontrol and excellent *syn* selectivity (s*yn:anti* >20:1) giving 69% yield. The oxazolidinone **106** was then hydrolyzed and amine was protected with methyl dichloroacetate to give (-)-chloramphenicol **62** in 78% yield (**Scheme 30**).



Scheme 30: (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.

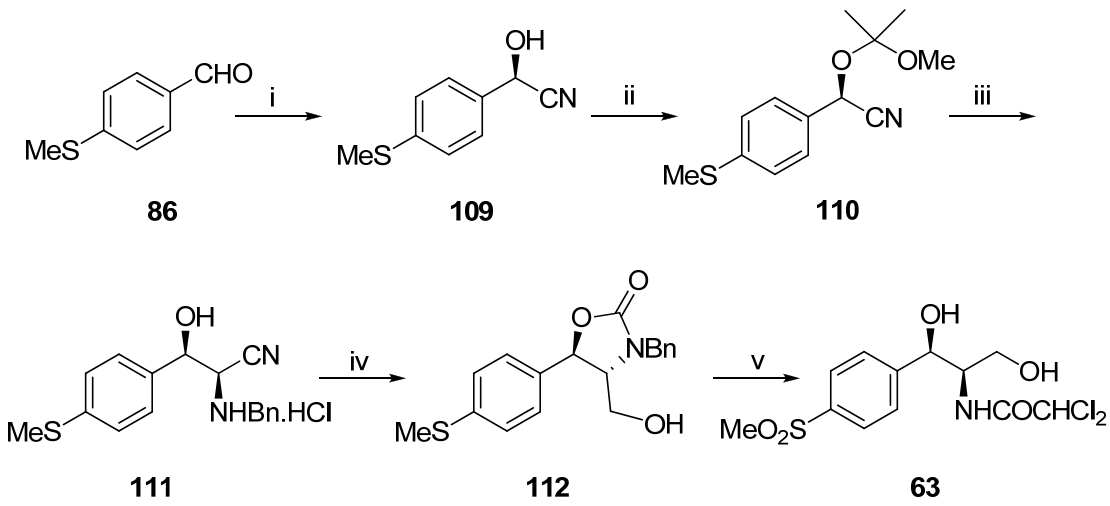
The same group has also synthesized (+)-thiamphenicol (**63**) by following a similar set of reaction sequences: Sharpless asymmetric kinetic resolution of allylic alcohol **88** followed by tethered aminohydroxylation of the corresponding carbamate 1**07** (**Scheme 31**).



Scheme 31: (i) Vinyl magnesium bromide, THF, 0 °C to 25 °C, 2 h, 96%; (ii) Oxone, THF/MeOH/H_2O (1:1:1), 0 °C to 25 °C, 30 min., 95%; (iii) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 °C, 14 to 24 h, 43%; (iv) (a) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C-25 °C, 2 h; (b) K_2CO_3, MeOH, H_2O, 0 °C to 25 °C, 18 h, 86%; (v) $K_2Os(OH)_4O_2$, *t*-BuOCl, NaOH, EtN-*i*-Pr_2, *n*-PrOH/H_2O (1:1), 25 °C, 3 h, 65%; (vi) (a) 1N NaOH, MeOH, 25 °C, overnight; (b) methyl dichloroacetate, 90 °C, 3 h, 77%, 98% ee.

Lin's approach (2008)[40]

Lin *et al*. have achieved the synthesis of (-)-chloramphenicol (**62**) by means of a chemo-enzymatic approach. 4-(Thiomethyl)benzaldehyde **86** was treated with (*R*)-hydroxynitrile lyase (HNL) in isopropyl ether to give product cyanohydrin **109** in 98% yield and 99% ee. Protection of alcohol **110** followed by DIBALH reduction, benzylamine addition and hydrocyanation of imine generated the second chiral centre with diastereomeric ratio >20:1. Treatment of **111** with carbonyldiimidazole provided the corresponding oxazolidine derivative which when reacted with K_2CO_3 followed by $NaBH_4$ afforded the alcohol **112**. Oxidation of **112** with *m*CPBA converted the methylsulfanyl group into methylsulfonyl group which was then converted into (+)-thiamphenicol (**63**) by the known sequences of reactions such as hydrolysis with aq. KOH, catalytic debenzylation and acylation (**Scheme 32**).



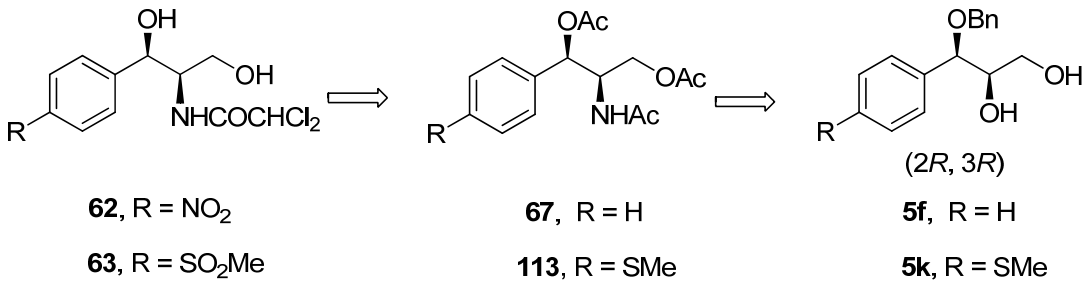
Scheme 32: (i) HCN/HNL, 98%, 99% ee; (ii) 2-methoxypropene, $POCl_3$, 95%; (iii) (a) DIBALH; (b) $BnNH_2$; (c) NH_4Br, NaCN; (d) HCl, H_2O, ethanol, 75%; (iv) (a) $(im)_2CO$, Et_3N, 82%; (b) K_2CO_3, ethanol; then 1 N HCl, 91%; (c) $NaBH_4$, methanol, 85%; (v) (a) *m*CPBA, 90%; (b) 2 N NaOH, reflux, 85%; (c) 10% Pd/C, H_2 (1 atm), MeOH, 90%, $CHCl_2CO_2Et$, Et_3N, 100%.

1.3.4 Present Work:

1.3.4.1 Objective

Even though several methods are reported for the synthesis of (-)-chloramphenicol (**62**) and (+)-thiamphenicol (**63**), most of these methods suffer from the fact that they make use of chiral starting materials, expensive and hazardous reagents, low overall yields, low diastereomeric ratios and also the use of unnatural ligands for the introduction of chirality. In this context, a more practical method for the synthesis of (-)-chloramphenicol (**62**) and (+)-thiamphenicol (**63**) is highly desirable. In this section, we describe a concise enantioselective synthesis of (-)-chloramphenicol (**62**) and (+)-thiamphenicol (**63**) using HKR of benzyloxy epoxides.

Retrosynthetic analysis of (-)-chloramphenicol (**62**) and (+)-thiamphenicol (**63**) reveals that *syn*-amino alcohols **75 & 123** could be visualized as the key intermediates respectively (**Scheme 33**).

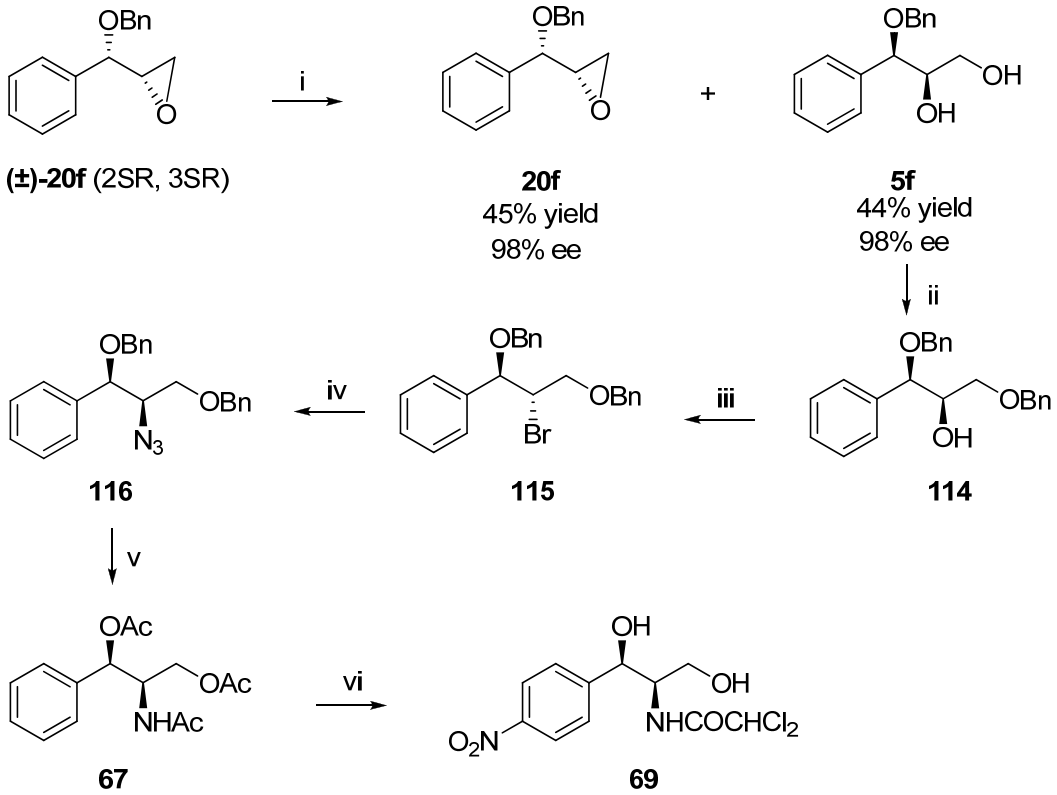


Scheme 33: Retrosynthetic analysis of (-)-chloramphenicol (**62**) and (+)-thiamphenicol (**63**)

1.3.5 Results and Discussion

1.3.5.1 Enantioselective synthesis of (-)-chloramphenicol

Our synthesis of (-)-chloramphenicol (**62**) has started from cinnamyl alcohol 1**5b,** which was transformed into *syn*-benzyloxy epoxide (±)-**20f** in two steps:



Scheme 34: (i) (*R,R*)-Co(III)(salen)OAc (1mol%), THF, H_2O (0.48 equiv.), 0 ºC, 12 h; (ii) Bu_2SnO, toluene, reflux, 12 h. then BnBr, TBAB, reflux, 20h, 82%; (iii) CBr_4, imid., PPh_3, CH_2Cl_2, 0 °C, 3h, 76%; (iv) NaN_3, DMF, 60 °C, 12h, 80%; (v) (a) 20% $Pd(OH)_2$/C, MeOH, H_2 (1atm), 25 °C, 12h; (b) Ac_2O, DMAP, pyridine, 94% (for 2 steps); (vi) (a) conc. HNO_3-conc. H_2SO_4, -20°C to 25°C; 1.5 h; (b) aq. 5% HCl, 90 °C; (c) Cl_2CHCO_2Me, 90 °C, 1 h, 76% (for 3 steps).

(i) benzyloxybromination; (ii) the formation of epoxide to give *syn*-benzyloxy epoxide (±)-**20f** in 84% yield (see **Section-I**). The *syn*-benzyloxy epoxide (±)-**20f** was then subjected to HKR using (*R,R)*-Co(salen)OAc (**1**) to give chiral *syn*-benzyloxy diol **5f** in 44% yield with 98% ee along with chiral *syn*-benzyloxy epoxide **20f** in 45% yield with 98% ee (**Scheme 34)**. The compounds **20f** and **5f** were then readily separated by column chromatographic purification. The enantiomeric excess of *syn*-azido diol in **5f** was determined from chiral HPLC analysis; (Chirapalk OD-H, see **Section I).**

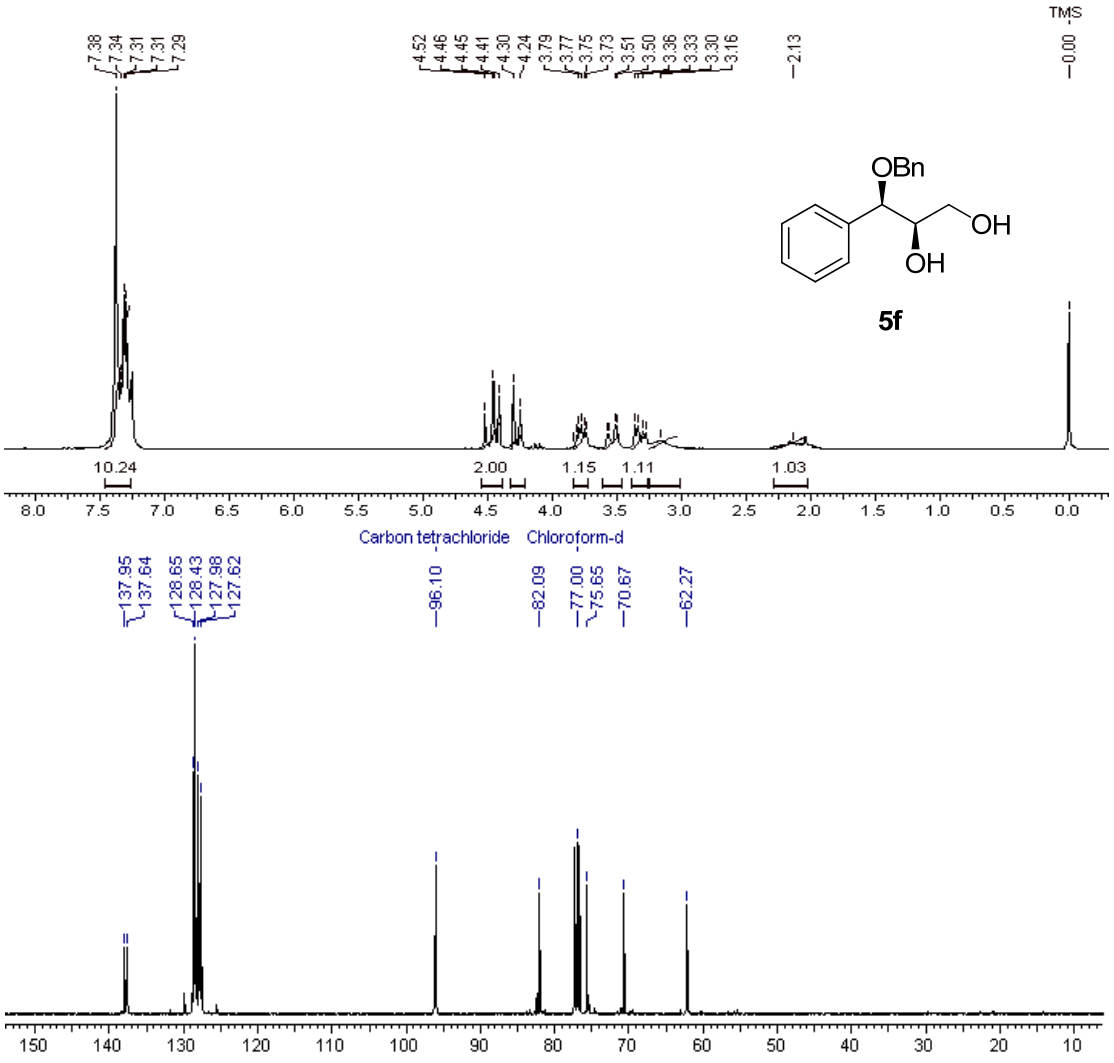
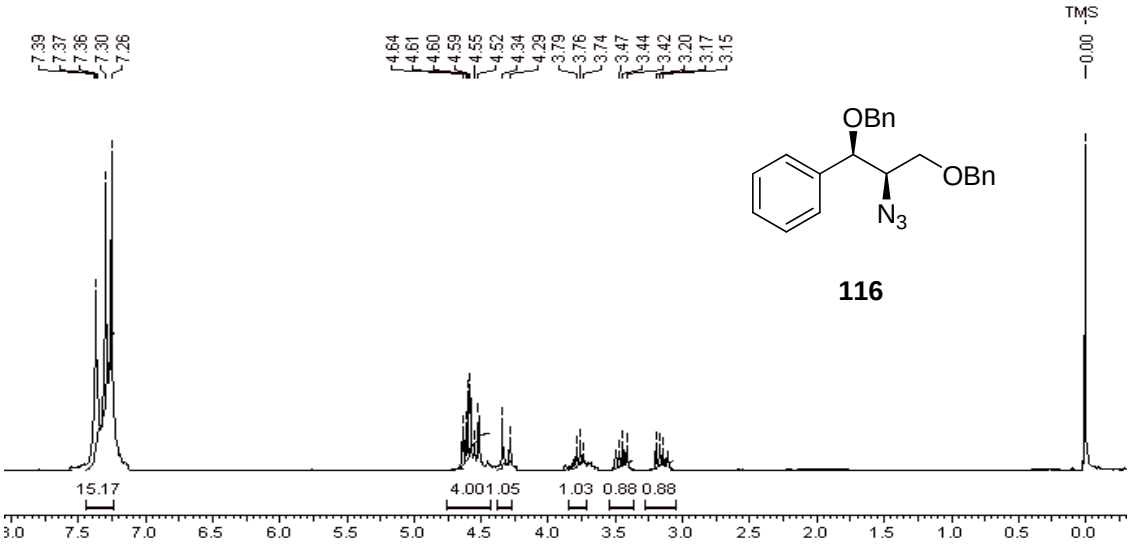


Fig. 21: ^{1}H and ^{13}C NMR spectra of diol **5f**

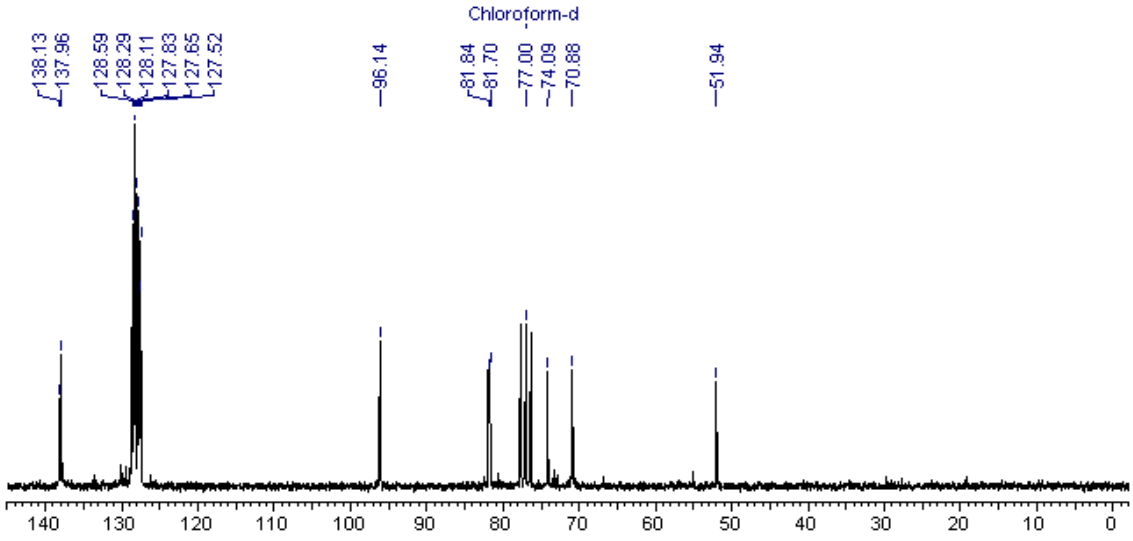
The formation of chiral *syn*-benzyloxy diol **5f** was confirmed by the appearance of multiplets at δ 3.30-3.51 integrating for two protons and δ 3.73-3.79 integrating for one proton in its ^{1}H-NMR spectrum. Further, its ^{13}C-NMR spectrum showed characteristic signals at δ 62.27 and 70.67 corresponding to carbons of the hydroxyl groups (**Fig. 21).** The enantiomeric excess of *syn*-alkoxy diol **5f** was determined from chiral HPLC analysis; (Chirapak OD-H, see **Section I)**.

Chiral diol **5f** was then subjected to selective benzyl protection [Bu_2SnO, BnBr and TBAB in toluene][41] to give mono benzylated alcohol **114** in 82% yield. The alcohol **114** thus obtained was converted into *anti*-benzyloxybromo derivative **115** by Appel reaction condition[42] (CBr_4 and PPh_3 in CH_2Cl_2). Compound **115** was then subjected to nucleophilic displacement with azide that proceeded smoothly to furnish the *syn*-azide **116** in 80% yield. The ^{1}H-NMR spectrum of azide **116** showed a typical signal at δ 3.74-3.78 (m, 1H) for methine (-**CH**-N_3) proton. Its ^{13}C NMR spectrum displayed a typical peak at δ 51.9 corresponding to methine (-**CH**-N_3) carbon (**Fig. 22).** Its IR spectrum showed a characteristic strong band at 2101 cm^{-1} confirming the presence of azide functional group (**Fig. 22)**.

The azide **116** was then subjected to catalytic hydrogenation [10% Pd/C, H_2 (1 atm) and Ac_2O] that produced triacetate **67** (94% yield) in a single step. Three signals at δ 1.95 (s, 3H), 2.01 (s, 3H) and 2.04 (s, 3H) in the ^{1}H-NMR spectrum of **67** were attributed to the three acetate methyl protons. It was further substantiated by the appearance of the corresponding carbon signals at δ 20.3 and 22.5 in its ^{13}C-NMR spectrum (**Fig. 23).**


TMS
7.39
7.37
7.36
7.30
7.26
4.64
4.61
4.60
4.59
4.55
4.52
4.34
4.29
3.79
3.76
3.74
3.47
3.44
3.42
3.20
3.17
3.15
0.00
OBn
OBn
N3
15.17
4.00
1.05
1.03
0.88
0.88

116


Chloroform-d
138.13
137.96
128.59
128.29
128.11
127.83
127.65
127.52
96.14
81.84
81.70
77.00
74.09
70.88
51.94

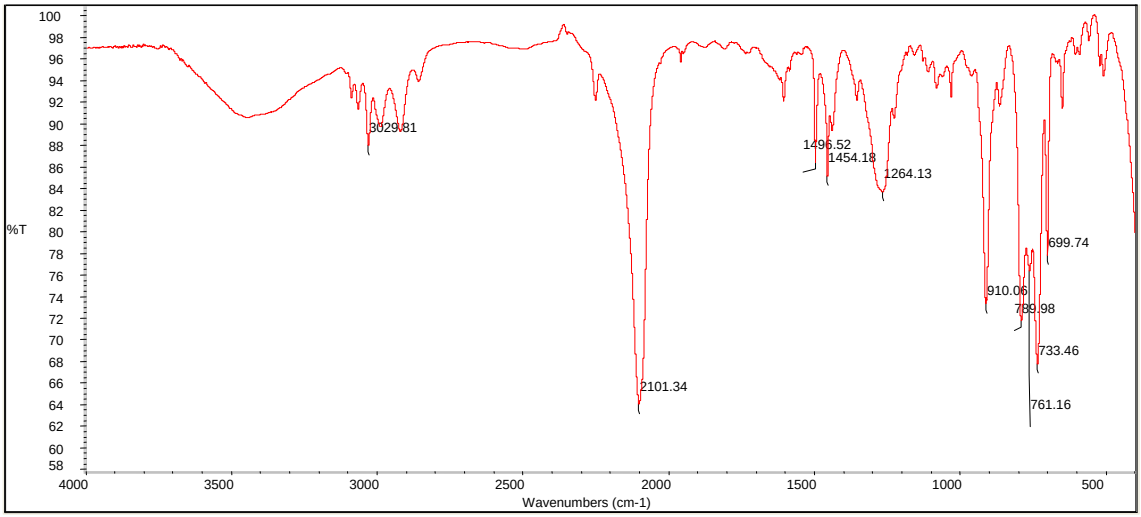

%T
3029.81
2101.34
1496.52
1454.18
1264.13
910.06
789.98
761.16
733.46
699.74
Wavenumbers (cm-1)

Fig. 22: ^{1}H, ^{13}C-NMR and IR spectra of azide **116**

Finally, triacetate **67** was converted to (-)-chloramphenicol (**62)** in three steps using known reaction sequence:[33] (i) nitration of triacetate **67** using mixed acids (ii) hydrolysis of triacetate using 5% HCl and (iii) protection of amine with dichloroacetate; that afforded (-)-chloramphenicol **62** in 76% yield and 98% ee. The ee of (-)-chloramphenicol (**62**) was found to be 98% based on comparison of its optical rotation with the reported value {$[\alpha]^{25}_{D}$ –25.4 (*c* 1, EtOAc); [lit.[43] $[\alpha]^{23}_{D}$ –25.5 (*c* 1, EtOAc)]}.

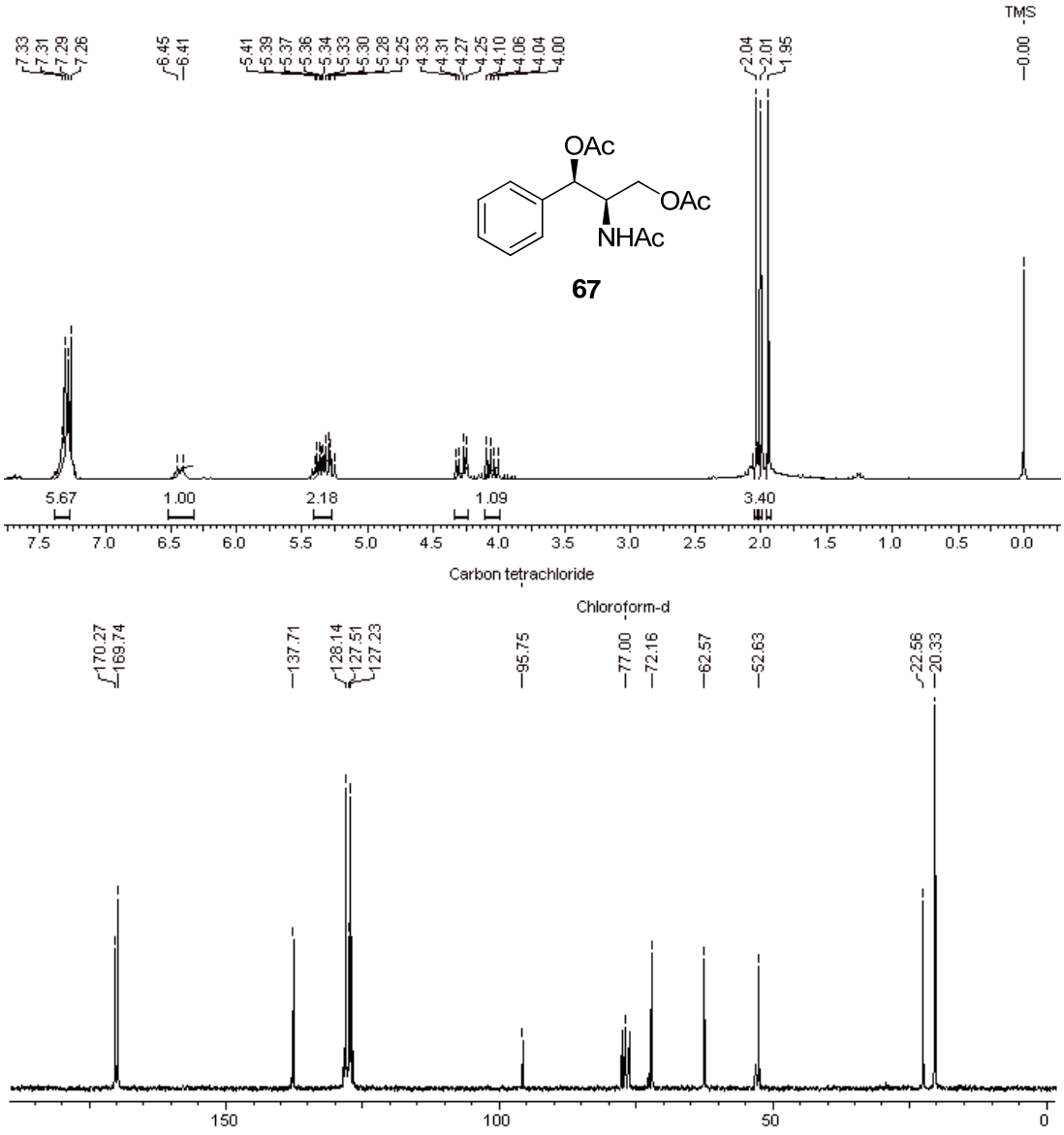


Fig. 23: ^{1}H and ^{13}C-NMR spectra of triacetate **67**

A singlet at δ 6.48 integrating for one proton indicated the presence of CH proton (NHCO**CH**Cl_2) in its ^{1}H-NMR spectrum, which was further ascertained by the presence of typical carbon signals at δ 56.92 (-**C**HNH-), 61.60 (-**C**H_2OH), 66.64 (-CO**C**HCl_2), 70.63(-**C**HOH-) and 164.37 (NH**C**O$CHCl_2$) in its ^{13}C-NMR spectrum (**Fig. 24).** The IR spectrum of **62** displayed characteristic strong broad band at 3000 cm^{-1} indicating the presence of -OH and -NH groups.

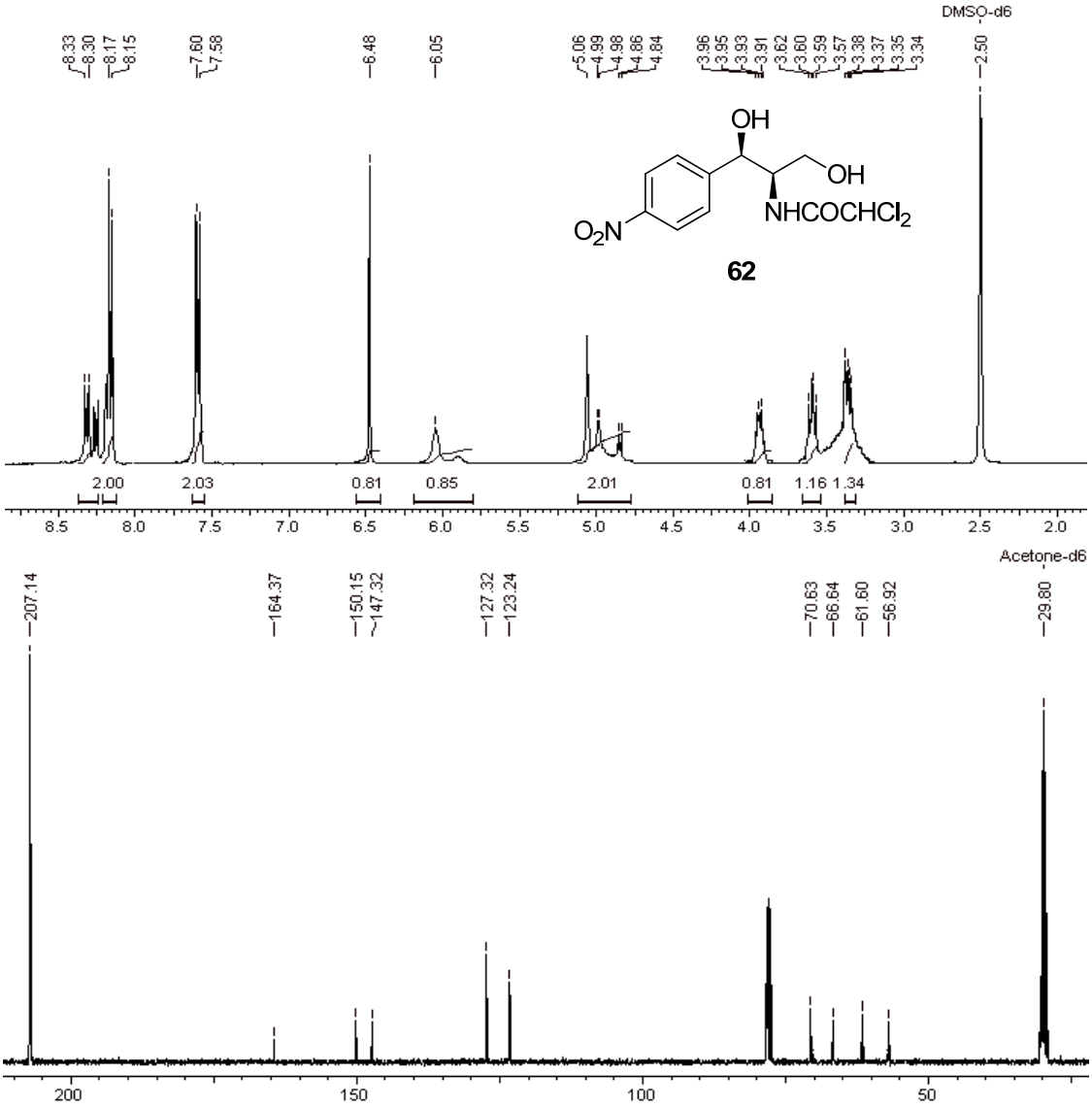
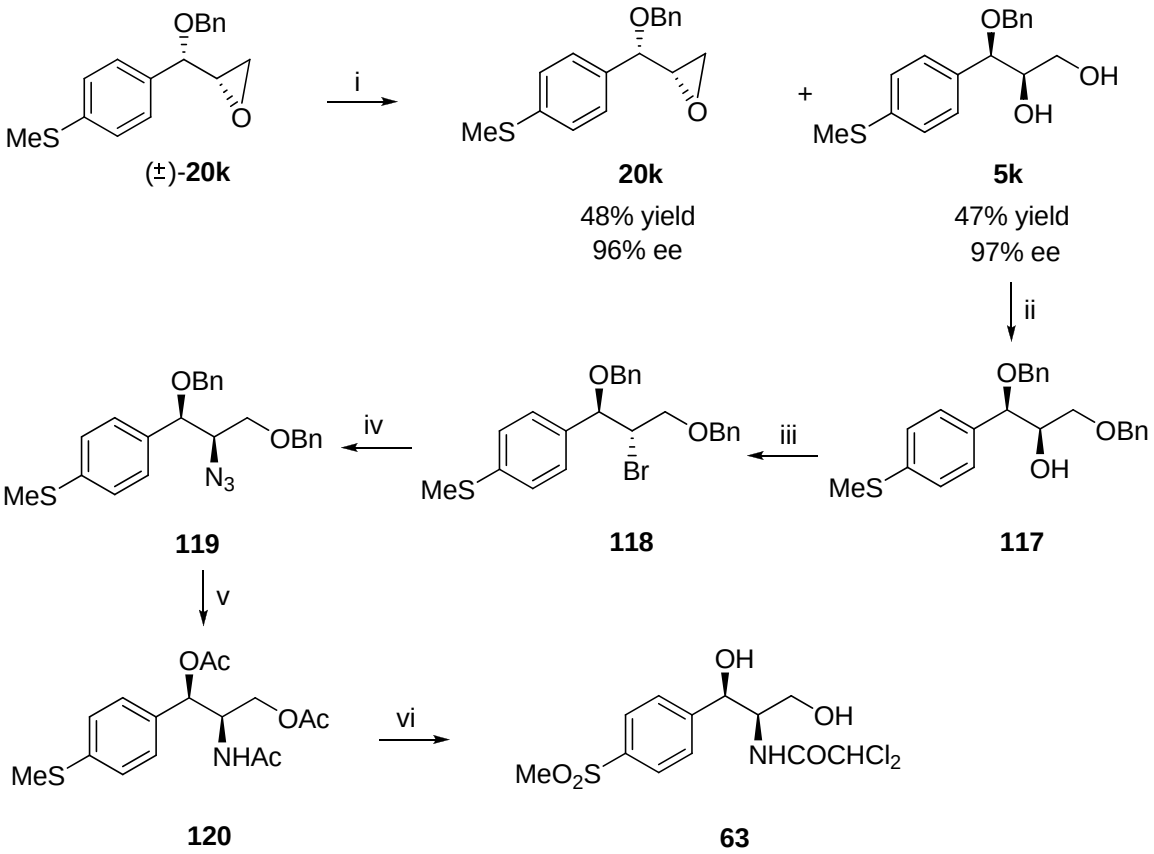


Fig. 24: ^{1}H and ^{13}C NMR spectra of (-)-chloramphenicol (**62**)

1.3.5.2 Enantioselective synthesis of (+)-thiamphenicol

By following a similar strategy, the synthesis of (+)-thiamphenicol (**63**) has been achieved starting from 4-thiomethyl cinnamyl alcohol 1**5k**.



Scheme 35: (i) (*R,R)*-Co(III)(salen)OAc (1 mol%), THF, H_2O (0.48 equiv.), 0 ºC, 12 h; (ii) Bu_2SnO, toluene, reflux, 12 h. then BnBr, TBAB, reflux, 18 h, 84%; (iii) CBr_4, imidazole, PPh_3, CH_2Cl_2, 0 °C, 4 h, 76%; (iv) NaN_3, DMF, 60 °C, 12 h, 78%; (v) (a) 20% $Pd(OH)_2/C$, MeOH, H_2 (1 atm), 25 ^oC, 12 h; (b) Ac_2O, DMAP, pyridine, 94% (for 2 steps); (vi) (a) *m*CPBA, CH_2Cl_2; (b) aq. 5% HCl, 90 °C; (c) Cl_2CHCO_2Me, 90 ^oC, 1 h, 78% (for 3 steps).

The 4-thiomethyl cinnamyl alcohol 1**5k** was transformed into *syn*-benzyloxy epoxide (±)-**20k** in two steps: (i) benzyloxybromination; (ii) the formation of epoxide to give *syn*-benzyloxy epoxide (±)-**20k (**84% yield), which was confirmed by ^1H and ^{13}C-NMR spectroscopy (see **Section-I**). The *syn*-benzyloxy epoxide (±)-**20k** was then subjected to HKR using (*R,R)*-Co(salen)OAc (**1**) to give chiral *syn*-benzyloxy diol **5k** (47% yield with 97% ee) along with chiral epoxide **20k** (48% yield with 96% ee) (**Scheme 35)**.

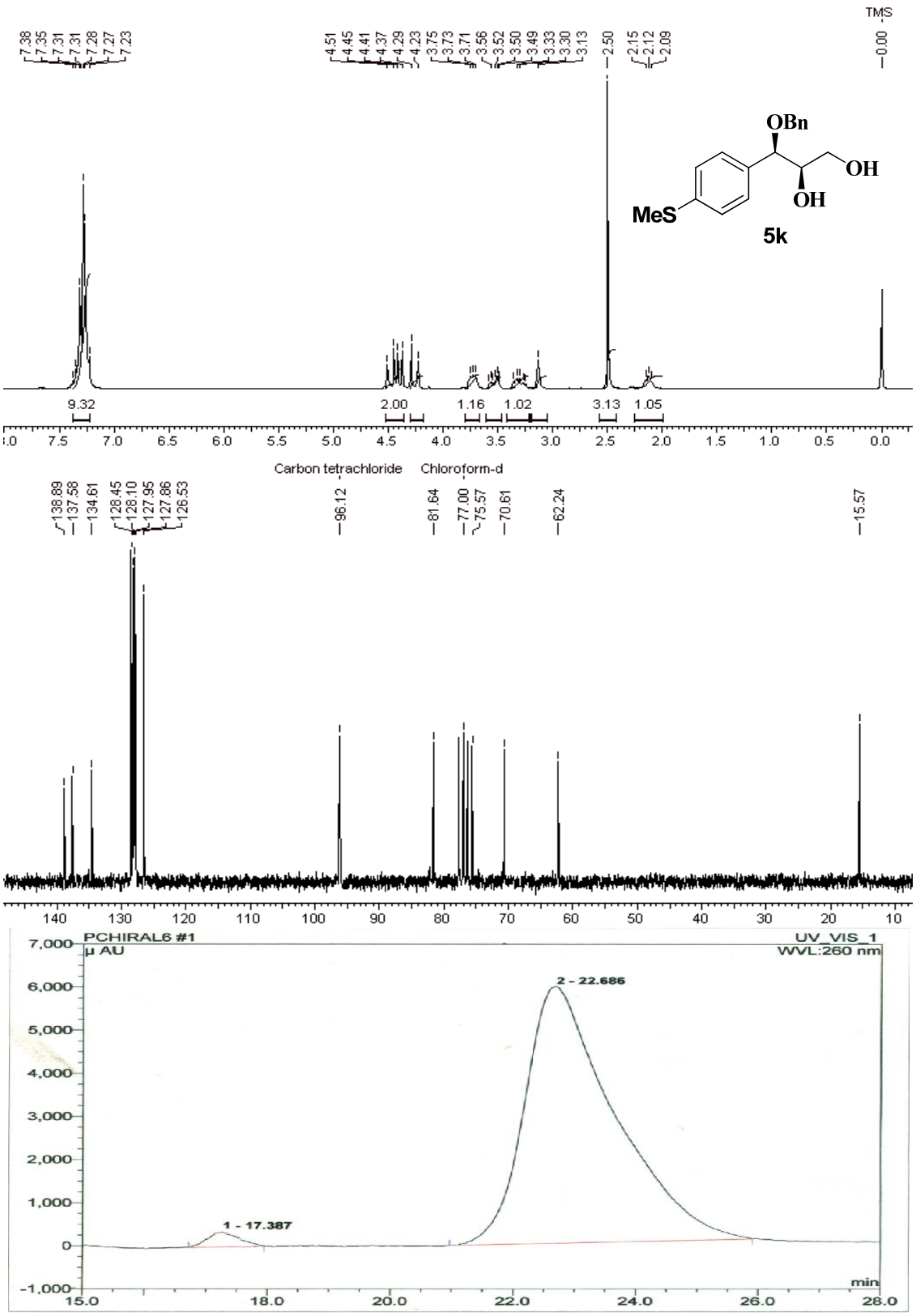
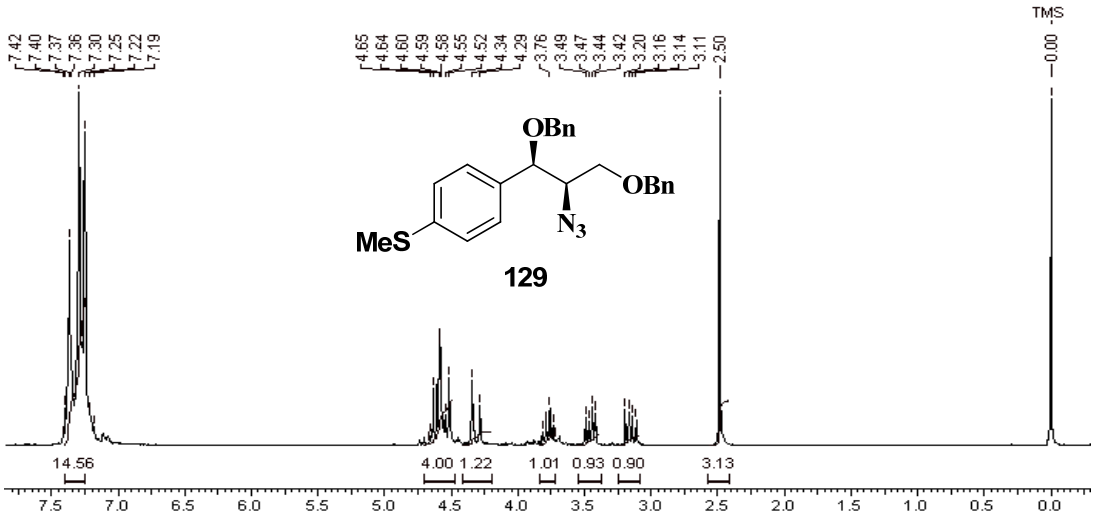


Fig. 25: ^{1}H, ^{13}C NMR spectra and HPLC chromatogram of diol **5k**

The compounds **20k** and **5k** were then readily separated by column chromatographic purification. The enantiomeric excess of *syn*-benzyloxy diol **5k** was determined by chiral HPLC analysis; Chirapalk OD-H (**Fig.25**). The formation of *syn*-benzyloxy diol **5k** was confirmed by the appearance of peaks at δ 3.30-3.33 (m, 1H) and 3.49-3.56 (m, 1H) in its ^{1}H-NMR spectrum. Further, its ^{13}C-NMR spectrum showed characteristic signals at δ 62.2 and 75.5, which correspond to carbons attached to oxygen atoms (**Fig. 25)**.

Chiral diol **5k** was then subjected to selective benzyl protection [Bu_2SnO, BnBr and TBAB in toluene][41] to give mono dibenzyl ether **117** in 82% yield. The alcohol **117** thus obtained was converted into *anti*-benzyloxybromo compound **118** by Appel reaction condition[42] (CBr_4 and PPh_3 in CH_2Cl_2), which was then subjected to nucleophilic displacement with azide that furnished azide **119** in 60% yield. The formation of azide **119** was confirmed by the appearance of multiplets at δ 3.71-3.79 integrating for one proton (-**CH**-N_3) in its ^{1}H-NMR spectrum and a typical signal corresponding to the methine carbon (-**CH**-N_3) appearing at δ 63.2 in its ^{13}C-NMR spectrum (**Fig. 26**). The IR spectrum of **119** showed a characteristic strong stretching vibration at 2115 cm^{-1} confirming the presence of azide functional group.



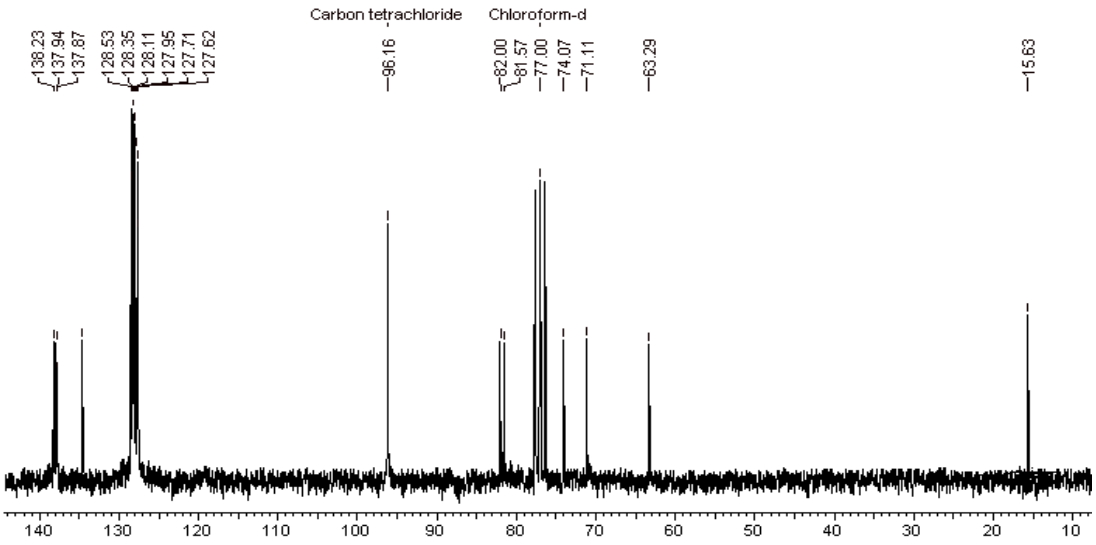


Fig. 26: ^{1}H and ^{13}C NMR spectra of azide **119**

Azide **119** was then subjected to catalytic hydrogenation [10% Pd/C, H_2 (1atm) and Ac_2O] to give triacetate **120** (94% yield) in a single step. Finally, the thioether moiety in triacetate **120** was oxidized with *m*CPBA, and hydrolyzed using aq. 5% HCl followed by its treatment with methyl dichloroacetate[6,18] gave the final product thiamphenicol (**63**) in 78% yield and 98% ee. The ee of (+)-thiamphenicol (**63**) was found to be 98% based on comparison of its optical rotation with the reported value {$[\alpha]^{25}_{D}$ +12.7 (*c* 1, EtOH) [lit.[31] $[\alpha]^{25}_{D}$ +12.9 (*c* 1, EtOH)}. The ^{1}HNMR spectrum showed a typical singlet at δ 6.41 corresponding to CH of NHCO**CH**Cl_2, which was further ascertained by the appearance of signals at δ 57.9 (-**C**HNH-), 61.6 (-**C**H_2OH), 67.5 (-CO**C**HCl_2), 71.1 (-**C**HOH-) and 164.3 (NH**C**O$CHCl_2$) in its ^{13}C-NMR spectrum (**Fig. 27**). The IR spectrum of **63** displayed a strong absorption band above 3000 cm^{-1} indicating the presence of -OH and -NH groups.

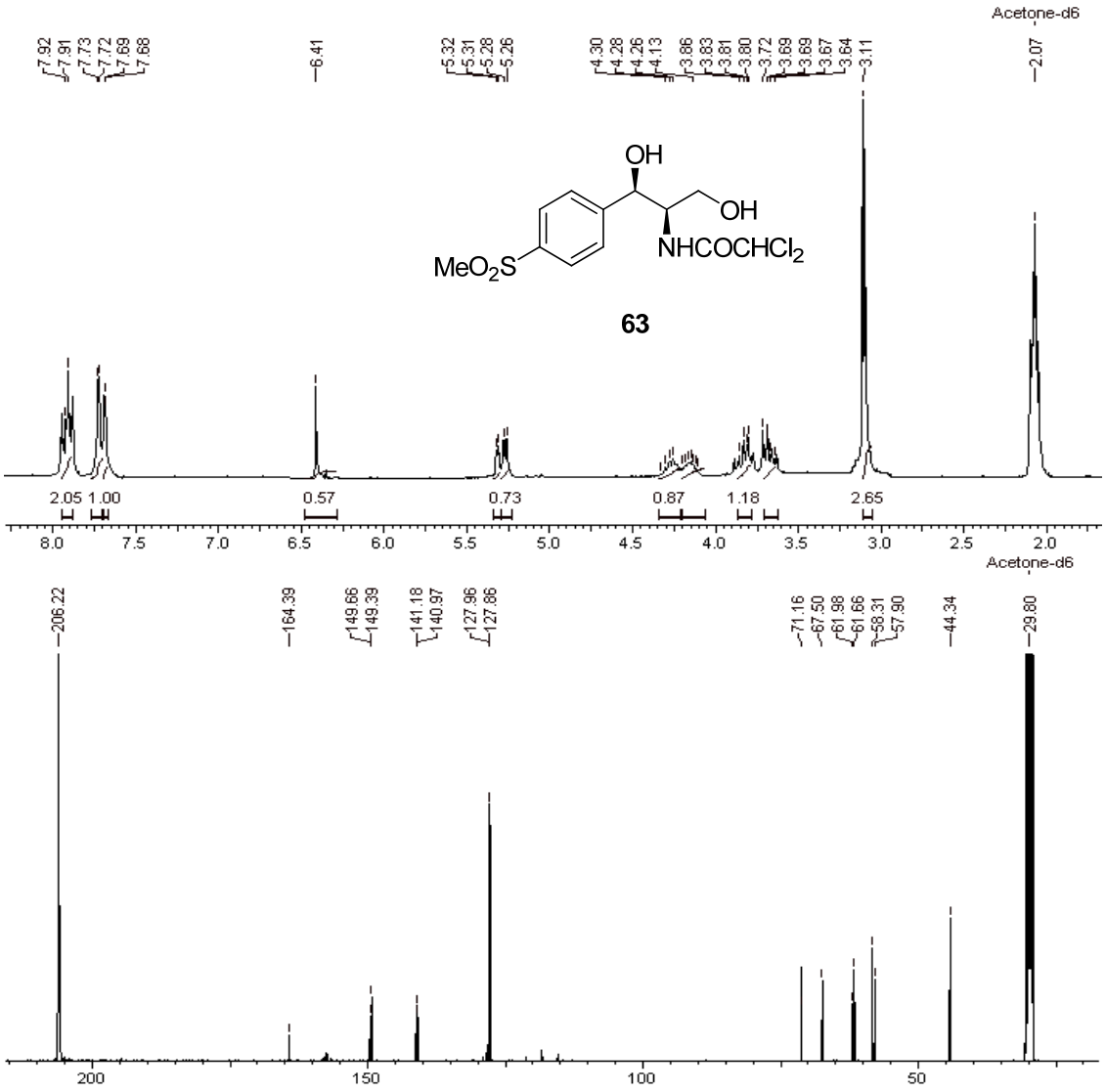


Fig. 27: ^{1}H and ^{13}C NMR spectra of (+)-thiamphenicol (**63**)

1.3.6 Conclusion

The enantioselective syntheses of (-)-chloramphenicol (**62**) (15% overall yield and 98% ee) and (+)-thiamphenicol (**63**) (14% overall yield and 97% ee) have been achieved, starting from the respective racemic benzyloxy epoxides **20f** and **20k**. Both the synthesis involved a cobalt-catalyzed two-stereocentred hydrolytic kinetic resolution of benzyloxy epoxides as the key chiral inducing reaction.

1.3.7 Experimental Section

For the preparation of compounds **20f**, **20k**, **5f** and **5k**, see Section I of this Chapter

(1*R*, 2*R*)-1,3-bis(Benzyloxy)-1-phenylpropan-2-ol (114)

A mixture of chiral diol **5f** (1.8 g, 7 mmol) and Bu_2SnO (2.09 g, 8.4 mmol) in toluene (50 mL) was refluxed for 12 h with azeotropic removal of water. Then TBAB (1.13 g, 3.5 mmol) and BnBr (0.83 mL, 7 mmol) were added and the mixture was refluxed for 20 h. After the completion of the reaction as monitored by TLC, it was concentrated under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/EtOAc (7:3) to afford the benzyloxy ether **114** (1.99 g) as a gum.

Yield: 82%; **$[\alpha]^{D}_{25}$**: -67.58 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 720, 845, 1045, 1220, 1315, 1654, 2985, 3085, 3350; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.97-3.24 (m, 2H), 3.43-3.49 (m, 1H), 3.87 (d, *J* = 8.5 Hz, 1H), 4.43-4.54 (m, 4H), 7.29-7.37 (m, 15H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 69.9, 70.7, 73.4, 74.7, 81.8, 127.5, 127.7, 127.9, 128.2, 128.3, 137.7, 137.9, 138.3; **Analysis:** $C_{23}H_{24}O_3$ requires C, 79.28; H, 6.94; found: C, 69.98; H, 6.75%.

1-(((1R,2S)-3-(Benzyloxy)-2-bromo-1-phenylpropoxy)methyl)benzene (115)

To a stirred solution of chiral dibenzyloxyalcohol **114** (1.4 g, 4 mmol), PPh_3 (1.3 g, 4.8 mmol) and imidazole (324 mg, 4.8 mmol) in dichloromethane (60 mL) at 0 ºC was added CBr_4 (1.6 g, 4.8 mmol). The resulting solution was stirred at 25 °C for 6 h and then concentrated *in vacuo*. The crude compound was purified by column chromatography using petroleum ether/EtOAc (9:1) to afford the bromo benzyloxy ether **115** (1.25 g) as a yellow liquid.

Yield: 76%; **$[\alpha]^{25}_{D}$**: -58.56 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 870, 1150, 1245, 1340, 1645, 2980, 3075; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.86-3.42 (m, 2H), 3.86-3.95

(m, 1H), 4.24 (d, *J* = 8.9 Hz, 1H), 4.48-4.59 (m, 4H), 7.26-7.42 (m, 15H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 70.3, 72.8, 73.5, 75.6, 81.5, 127.3, 127.7, 127.9, 128.4, 128.8, 137.8, 137.9, 138.5; **Analysis:** $C_{23}H_{23}BrO_2$ requires C, 67.16; H, 5.64; found: C, 66.95; H, 5.48%.

1-(((1*R*,2*R*)-2-Azido-3-(benzyloxy)-1-phenylpropoxy)methyl)benzene (116)

To a stirred solution of bromo benzyloxy ether **115** (1.0 g, 2.43 mmol) in DMF (5 mL) was added sodium azide (455 mg, 7 mmol) and the reaction mixture was heated at 60 ^oC for 12 h. After the completion of the reaction as monitored by TLC, it was extracted with EtOAc (3x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure and the residue was purified by column chromatography using petroleum ether: ethyl acetate (8:2) to obtain pure dibenzyloxy azide **116** (0.72g) as colorless oil.

Yield: 80%; **$[\alpha]^{25}_D$**: -84.08 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 733, 789, 910, 1264, 1450, 1496, 2101, 3029; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.15-3.20 (m, 1H), 3.42-3.47 (m, 1H), 3.74-3.79 (m, 1H), 4.31 (d, *J* = 8.6 Hz, 1H), 4.52-4.64 (m, 4H), 7.26-7.39 (m, 15H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.9, 70.8, 74.0, 81.7, 81.8, 127.5, 127.6, 127.8, 128.1, 128.2, 128.5, 137.9, 138.1; **Analysis:** $C_{23}H_{23}N_3O_2$ requires C, 73.97; H, 6.21; N, 11.25; found: C, 73.78; H, 6.08; N, 11.09%.

(1*R*,2*R*)-2-Acetamido-1-phenylpropane-1,3-diyl diacetate (67)

To a stirred solution of azide **116** (600 mg, 1.6 mmol) in methanol (10 mL) was added 20% $Pd(OH)_2/C$ (265 mg, 50 wt %) carefully at room temperature and a hydrogen balloon was kept to provide hydrogen atmosphere. After the completion of the reaction as monitored by TLC, it was filtered over celite and the filtrate was concentrated under

reduced pressure to provide the aminodiol, which was directly taken for the next step. To a stirred solution of amino diol in pyridine (10 mL) was added acetic anhydride (0.83 mL, 8.8 mmol), DMAP (97 mg, 0.8 mmol) and the mixture was stirred for 4 h. After the completion of the reaction as monitored by TLC, the solvent was evaporated, reaction mixture was diluted with water (10 mL), extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material it was then purified by column chromatography on silica gel using petroleum ether/EtOAc (5:5) to give triacetate **67** (443 mg) as a colorless liquid.

Yield: 94%; **$[\alpha]^{25}_D$**: -32.18 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 675, 780, 950, 1250, 1365, 1475, 1720, 2815, 3029, 3325; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.01 (s, 3H), 2.04 (s, 3H), 4.0-4.10 (m, 1H), 4.25-4.33 (m, 1H), 5.25-5.41 (m, 2H), 6.43 (d, *J* = 2.2 Hz, 1H), 7.26-7.33 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.3, 22.5, 52.8, 62.5, 72.1, 127.2, 127.5, 128.1, 137.7, 169.7, 170.2; ESI-MS: *m*/*z* 316.115 $[M+Na]^+$; **Analysis:** $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.78; found: C, 61.28; H, 6.28; N, 4.66%.

(1*R*,2*R*)-2-(Dichloroacetamido)-1-[(4-nitro)phenyl)-1,3-propanediol (62)

To a stirred solution of conc. HNO_3: conc. H_2SO_4 (1:1) (2 mL) was added triacetate **67** (150 mg, 1.02 mmol) at -20 ^oC, the resulting solution was stirred for 1.5 h at 25 °C. After the completion of the reaction as monitored by TLC, it was poured into water (5 mL) and extracted with diethyl ether (3 x 10 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give nitro triacetate, which was directly taken up for the next step. A solution of aq 5% HCl was prepared in methanol, 2 mL of the above solution was added to nitro triacetate

(0.95 g, 0.4 mmol) and stirred overnight at 90 ^{o}C. The reaction mixture was poured into 2N NaOH solution and extracted with diethyl ether (3x 5 mL), washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give crude *p*-nitrophenyl substituted aminodiol. The *p*-nitrophenyl substituted aminodiol was taken in methyl dichloroacetate (1 mL) and heated at 90 ºC for 1h. The excess ester was removed under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/ EtOAc (3:7) to give the product **62** (125 mg) as a colorless amorphous solid.

Yield: 76%; **mp**: 151-152 ºC [lit.[43] **mp**:149.7-150.7 ºC]; **[α]$^{25}_{D}$**: -24.9 (*c* 1, EtOAc) [lit.[43] **[α]$^{25}_{D}$**: -25.5 (*c* 1, EtOAc)]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3420, 3020, 2929, 1686, 1604, 1523, 1454, 1403, 1348, 1216, 1049, 850; **^{1}H-NMR** (400 MHz, DMSO-d_6): δ 3.34-3.38 (m, 1H), 3.57-3.62 (m, 1H), 3.91-3.96 (m, 1H), 4.84-5.06 (m, 2H), 6.05 (br s, 1H), 6.48 (s, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 8.15 (d, *J* = 8.7 Hz, 2H), 8.31 (d, *J* = 9.2 Hz, 1H); **^{13}C-NMR** (100 MHz, acetone-d_6): δ 56.9, 61.6, 66.6, 70.6, 123.2, 127.3, 147.3, 150.1, 164.3; **Analysis:** $C_{11}H_{12}Cl_2N_2O_5$ requires C, 40.89; H, 3.74; N, 8.68; found: C, 40.98; H, 3.65; N, 8.34%.

(1*R*,2*R*)-1,3-bis(Benzyloxy)-1-(4-(methylthio)phenyl)propan-2-ol (117)

A mixture of chiral diol **5k** (2.7 g, 10.5 mmol) and Bu_2SnO (3.13 g, 12.8 mmol) in toluene (70 mL) was refluxed for 12 h with azeotropic removal of water. Then tetra butyl ammonium bromide TBAB (1.68 g, 7.8 mmol) and BnBr (1.23 mL, 10.5 mmol) were added and the mixture was refluxed for 18 h. After the completion of the reaction as monitored by TLC, it was concentrated under reduced pressure and the crude compound

was purified by column chromatography using petroleum ether/EtOAc (6:4) to afford the benzyloxy ether **117** (3.0 g) as a gum.

Yield: 84%; **$[\alpha]^{D}_{25}$**: -74.15 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 830, 1020, 1280, 1360, 1635, 2990, 3070, 3350; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.0 (br s, 1H), 3.24-3.26 (m, 1H), 3.44-3.51 (m, 1H), 3.78-3.94 (m, 1H), 4.27-4.38 (m, 1H), 4.44-4.55 (m, 4H), 7.26-7.42 (m, 14H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.9, 70.5, 72.4, 74.5, 75.5, 82.1, 126.4, 127.7, 127.9, 128.1, 128.4, 134.7, 137.5, 137.7, 138.6; **Analysis:** $C_{24}H_{26}O_3S$ requires C, 73.06; H, 6.64; S, 8.13; found: C, 72.86; H, 6.53; S, 8.03%.

(4-((1*R*,2*S*)-1,3-bis(Benzyloxy)-2-bromopropyl)phenyl)(methyl)sulfane (118)

To a stirred solution of chiral dibenzyloxy alcohol **117** (2.1 g, 6 mmol), PPh_3 (2.0 g, 7.2 mmol) and imidazole (486 mg, 7.2 mmol) in dichloromethane (80 mL) at 0 ºC was added CBr_4 (2.4 g, 7.2 mmol). The resulting solution was stirred for 4 h at 25 °C and then concentrated *in vacuo*. The crude compound was purified by column chromatography using petroleum ether/EtOAc (9:1) to afford the bromo benzyloxy ether **118** (1.85 g) as a yellow liquid.

Yield: 76%; **$[\alpha]^{25}_{D}$**: -66.12 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 870, 1125, 1260, 1340, 1420, 2980, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.62-2.84 (m, 1H), 3.21-3.58 (m, 1H), 3.82-3.89 (m, 1H), 4.28 (d, *J* = 8.5 Hz, 1H), 4.42-4.59 (m, 4H), 7.24-7.40 (m, 15H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.6, 68.3, 71.5, 74.5, 75.8, 81.2, 127.4, 127.7, 127.8, 128.5, 128.6, 134.78, 137.8, 137.9, 138.3; **Analysis:** $C_{24}H_{25}BrO_2S$ requires C, 63.02; H, 5.51; S, 7.01; found: C, 66.92; H, 5.38; S, 6.89%.

(4-((1*R*,2*R*)-2-Azido-1,3-bis(benzyloxy)propyl)phenyl)(methyl)sulfane (119)

To a stirred solution of bromo benzyloxy ether **118** (1.5 g, 3.6 mmol) in DMF (7.5 mL) was added sodium azide (682 mg, 10.5 mmol) and the reaction mixture was heated at 60 ^{o}C for 12 h. After the completion of the reaction as monitored by TLC, it was extracted with EtOAc (3 x 50 mL), washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure and the residue was purified by column chromatography using petroleum ether: ethyl acetate (7:3) to obtain pure dibenzyloxy azide **119** (1.05 g) as yellow liquid.

Yield: 78%; **$[\alpha]^{25}_{D}$**: -96.24 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 733, 789, 910, 1264, 1450, 1496, 2185, 3015; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.5 (s, 3H), 3.11-3.20 (m, 1H), 3.42-3.49 (m, 1H), 3.60-3.79 (m, 1H), 4.31 (d, *J* = 8.8 Hz, 1H), 4.52-4.65 (m, 4H), 7.19-7.42 (m, 14H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.6, 63.2, 71.1, 74.0, 81.5, 82.0, 127.6, 127.7, 127.9, 128.1, 128.3, 128.5, 134.8, 137.8, 137.9, 138.2; **Analysis:** $C_{24}H_{25}N_3O_2S$ requires C, 68.71; H, 6.01; N, 10.02; S, 7.64; found: C, 68.58; H, 5.88; N, 9.94; S, 7.72%.

(1*R*,2*R*)-2-Acetamido-1-(4-(methylthio)phenyl)propane-1,3-diyl diacetate (120)

To a stirred solution of azide **119** (900 mg, 2.4 mmol) in methanol (15 mL) was added 20% $Pd(OH)_2/C$ (398 mg, 50 wt%) carefully at room temperature and a hydrogen balloon was kept to provide hydrogen atmosphere. After the completion of the reaction as monitored by TLC, it was filtered over celite and the filtrate was concentrated under reduced pressure to provide aminodiol, which was directly taken up for the next step. To a stirred solution of amino diol in pyridine (10 mL) was added acetic anhydride (0.3 mL, 2.9 mmol), DMAP (32 mg, 0.26 mmol) and the mixture was stirred for 4 h. After the completion of the reaction as monitored by TLC, the solvent was evaporated, reaction

mixture was diluted with water (10 mL), extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material which was then purified by column chromatography on silica gel using petroleum ether/EtOAc (5:5) to give triacetate **120** (664 mg) as a colorless liquid.

Yield: 94%; $[\alpha]^{25}_{D}$: -38.25 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 675, 760, 985, 1265, 1380, 1475, 1724, 2890, 3015, 3330; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 3.9-4.15 (m, 1H), 4.22-4.35 (m, 1H), 5.228-5.40 (m, 2H), 6.39 (d, *J* = 2.3 Hz, 1H), 7.18-7.34 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.6, 21.5, 22.4, 52.8, 62.4, 72.5, 127.4, 127.6, 128.5, 134.8, 137.6, 169.5, 170.4; ESI-MS: *m*/*z* 362.101 $[M+Na]^+$; **Analysis:** $C_{16}H_{21}NO_5S$ requires C, 56.62; H, 6.24; N, 4.13; S, 9.45; found: C, 56.54; H, 6.13; N, 3.98; S, 9.34%.

(1*R*,2*R*)-2-(Dichloroacetamido)-1-[(4-methylsulfonyl)phenyl)-1,3-propanediol (63)

To a stirred solution of triacetate **120** (350 mg, 1.03 mmol) in CH_2Cl_2 (10 mL), *m*CPBA (356 mg, 2.06 mmol) was added at room temperature. After the completion of the reaction as monitored by TLC, it was poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give sulfone, which was directly taken for the next step. A solution of aq 5% HCl was prepared in methanol, 2 mL of the above solution was added to sulfone triacetate and stirred overnight at 90 ^oC. The reaction mixture was poured into 2N NaOH solution, and extracted with diethyl ether (3x 5 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give crude *p*-methylsulfonyl substituted

aminodiol. The crude compound was taken up further in methyl dichloroacetate (2 mL) and heated at 90 ºC for 3h. The excess ester was removed under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/ EtOAc (1:9) to give the product **63** (280 mg) as a colorless amorphous solid.

Yield: 77%; **mp**: 164-165 ºC [lit.[31] **mp**: 164.3-166.3 °C]; $[\alpha]^{25}_{D}$: +12.5 (*c* 1, EtOH) [lit.[5] $[\alpha]^{23}_{D}$: +12.9 (*c* 1, EtOH)]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3481, 3407, 3242, 3082, 3020, 2925, 1699, 1562, 1406, 1282, 1215, 1145, 1033, 906, 806, 767; **^{1}H-NMR** (200 MHz, acetone-d_6): δ 3.11 (s, 3H), 3.64-3.72 (m, 1H), 3.80-3.86 (m, 1H), 4.13-4.30 (m, 1H), 4.28 (t, *J* = 4.8 Hz, 1H), 5.28 (d, *J* = 3.8 Hz, 1H), 5.30 (d, *J* = 2.4 Hz, 1H), 6.41 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR** (100 MHz, acetone-d_6): δ 44.3, 57.9, 58.3, 61.6, 61.9, 67.5, 71.1, 127.7, 127.8, 140.9, 141.1, 149.3, 149.5, 164.4, 206.2; **Analysis:** $C_{12}H_{15}Cl_2NO_5S$ requires C, 40.46; H, 4.24; N, 3.93, S, 9.0; found: C, 40.59; H, 4.35; N, 4.05, S, 8.86%.

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CHAPTER II

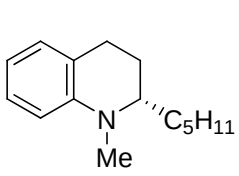
Asymmetric Synthesis of Tetrahydroquinolin-3-ols, Anachelin H Chromophore and 1-((*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl)propan-1-one

Section I:

A New Route to the Synthesis of *(R)*-Tetrahydroquinolin-3-ols *via* $CoCl_2$-catalyzed Reductive Cyclization of Cyclic Sulfites with $NaBH_4$

2.1.1 Introduction

Substituted tetrahydroquinoline derivatives (THQs) bearing various simple and complex substituents are of medicinal and industrial importance due to their pronounced activity in many physiological processes.[1] These heterocycles along with their core structures are present in numerous pharmacological agents. For example, (-)-Angustureine (**1**) is used in folk medicine as a bitter tonic in dyspepsia, dysentery, chronic diarrhoea and for the treatment of fever and also been reported to exhibit anti-malarial and cytotoxic activities.[2] Others include L-689560 (**2**) which is one of the most potent NMDA antagonists;[3] Virantmycin (**3**) showing antibiotic activity.[4]



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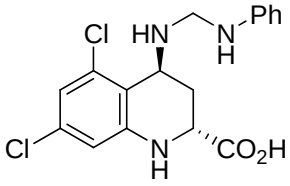
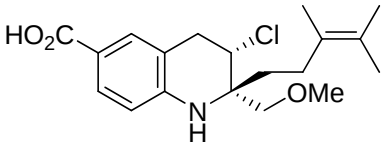
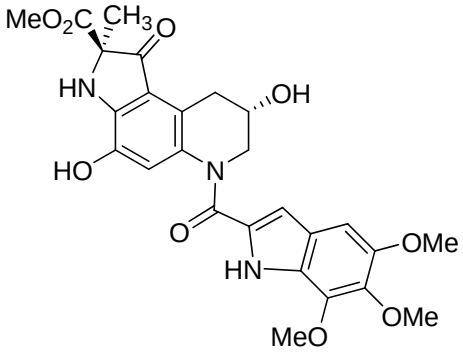


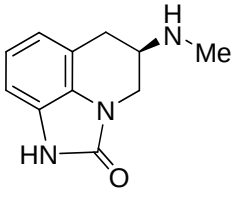
2, L-689560



3, Virantmycin



4, (+)-Duocarmycin D_1



5, PNU 95666-E

Fig. 1 Some of the examples of tetrahydroquinoline derivatives

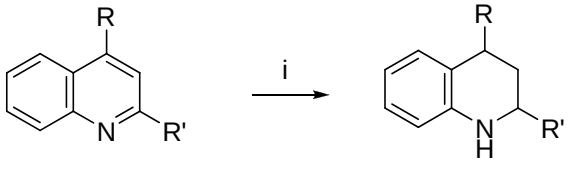
Further, (+)-Duocarmycin D_1 (**4**), having chiral 3-hydroxytetrahydroquinoline system in its structure shows potential cytotoxic activity.[5] Also, sumanirole maleate (PNU9566 E) (**5**)[6] is a selective and high affinity agonist at the dopamine D_2 receptor subtype and a potential agent for the treatment of Parkinson's disease (**Fig. 1**). Many relatively simple 1,2,3,4-tetrahydroquinolines are already proven as potential drugs.[7] Moreover, besides pharmaceutical applications, tetrahydroquinoline derivatives are useful as pesticides,[8] antioxidants,[9] and corrosion inhibitors.[10] Additionally, tetrahydroquinolines are widely used as active components of dyes[11] and photosensitizers in photography.[12] Tetrahydroquinoline based inhibitors are also shown as one of the most potent protein farnesyl transferase inhibitors.

2.1.2 Review of literature

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

Murahashi's Approach (1987)[13]

Murahashi *et al*. have described the synthesis of tetrahydroquinolines **7a-d** *via* hexarhodiumhexadecacarbonyl complex catalyzed selective reduction of pyridine nucleus in quinolines **6a-d** using carbon monoxide and water as efficient reducing agent (**Scheme 1**).



6a-d **7a-d**

7a, R, R' = H, 97%

7b, R, R' = CH_3, 89%

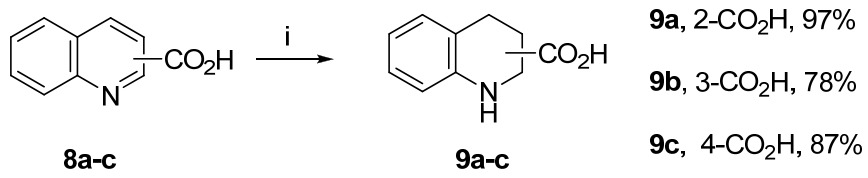
7c, R = CH_3, R' = H, 91%

7d, R = H, R' = CH_3, 87%

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

Gracheva's Approach (1988)[14]

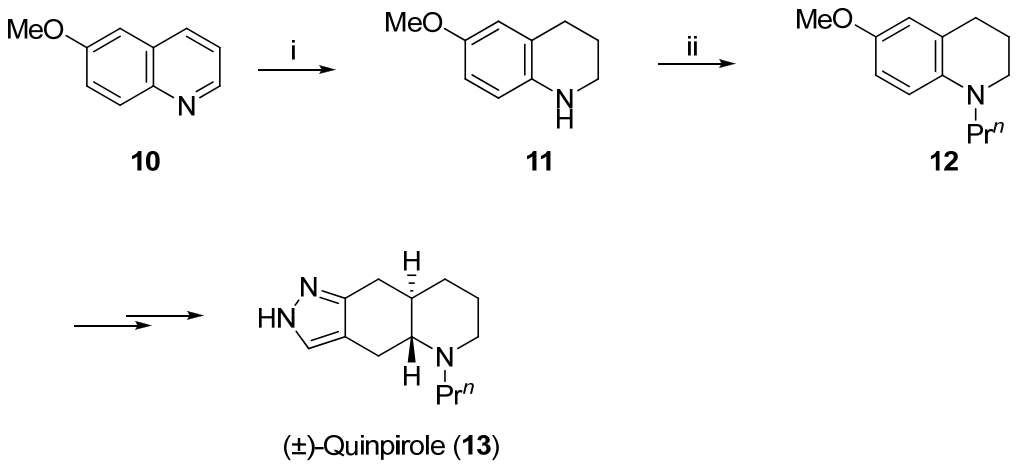
Gracheva *et al.* have reported the use of Ni-Al alloy for the reduction of quinolinecarboxylic acid **8a-c** to obtain tetrahydroquinoline carboxylic acid **9a-c** in high yields (**Scheme 2**).



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

Schaus's Approach (1990)[15]

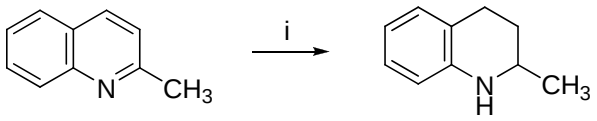
Schaus *et al.* have reported the synthesis of (±)-quinpirole (**13**) using hydrogenation [catalytic PtO_2, H_2 (60 psig)] of 6-methoxyquinoline (**10**), which afforded 6-methoxy-l,2,3,4-tetrahydroquinoline (**11**). Reductive alkylation of **11** [propanaldehyde, 15% Pd/C, H_2 (60 psig)] furnished tetrahydroquinoline **12** in 36 % yield over two steps. Further, **12** was converted into (±)-quinpirole (**13**) by employing a sequence of reactions (**Scheme 3**).



Scheme 3: (i) PtO_2 (10 wt%), H_2 (60 psig), 50 °C, 12 h, MeOH, 65%; (ii) 15% Pd/C, H_2 (60 psig), EtCHO, EtOH, 50 °C, 12 h, 54%.

Bouyssou's Approach (1992)[16]

Bouyssou *et al.* had employed transfer hydrogenation (10% Pd/C, HCO_2H/Et_3N) as a method for reducing quinoline **6d** to afford the corresponding tetrahydroquinoline **7d** in 85 % yield (**Scheme 4**).

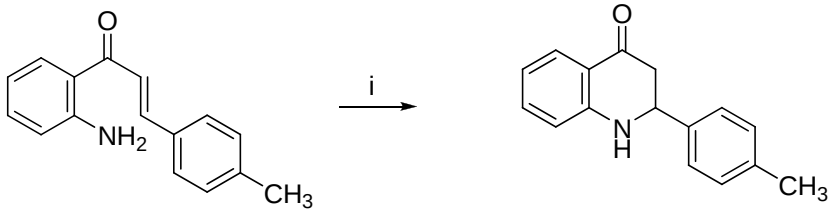


6d **7d**

Scheme 4: (i) 10% Pd/C, HCO_2H (5 equiv.), Et_3N (2 equiv.), 50 °C, 12 h.

Szilagyi's approach (1992)[17]

Szilagyi *et al.* have reported an intramolecular Michael addition of amine functionality onto a *α,β*-unsaturated ketone **14** catalyzed by phosphoric acid to give 2-aryl-4-oxo-1,2,3,4-tetrahydroquinoline **15** in 85% yield (**Scheme 5**).



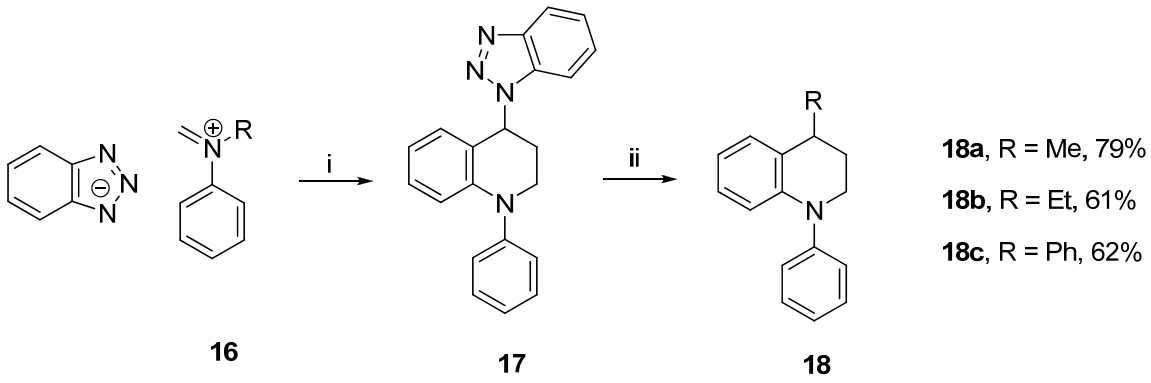
14 **15**

Scheme 5: (i) H_3PO_4, AcOH, 80 ºC, 1 h, 85%.

Katritzky's approach (1995)[18]

Katritzky *et al.* have reported acid catalyzed Diels-Alder reaction of *N*-methylaniline derivative **16** with ethyl vinyl ether to give reactive intermediate 4-ethoxy-1,2,3,4-tetrahydroquinoline, which underwent *in situ* substitution by benzotriazol to provide 4-(benzotriazolyl)-1,2,3,4-tetrahydroquinoline (**17**) in 48% yield. At elevated temperatures,

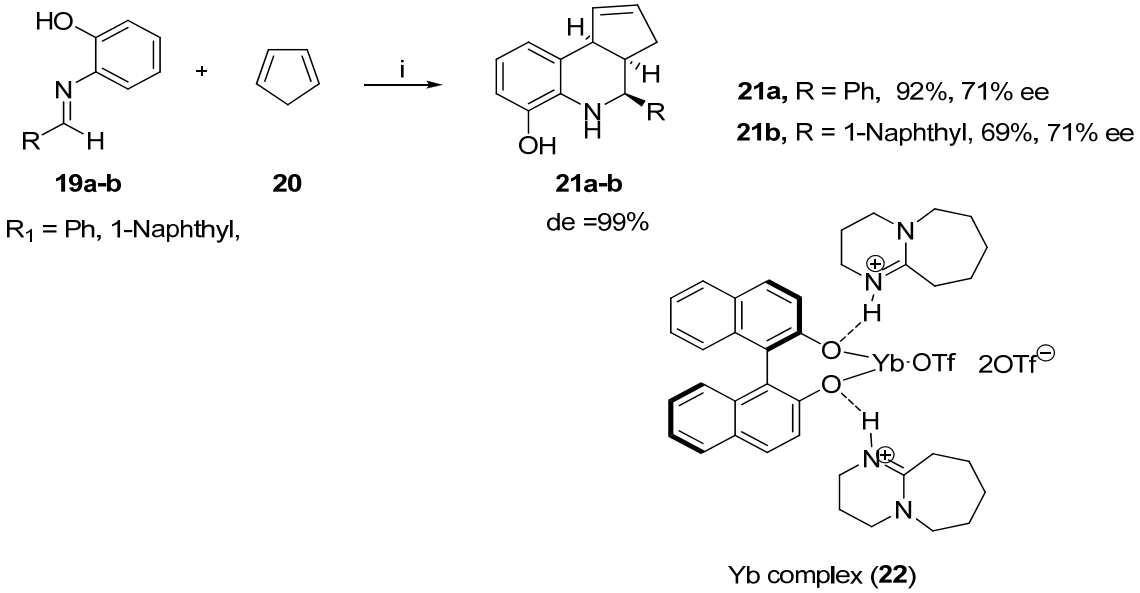
ionization of **17** gives immonium cation which can be trapped *in situ* by Grignard reagent to provide 4-substituted tetrahydroquinolines **18** in good yields (**Scheme 6**).



Scheme 6: (i) ethyl vinyl ether (1.2 mL, 12 mmol), *p*-toluenesulfonic acid monohydrate (10 mg), 22 ºC, 30 min. then 120 ºC, 10 min; (ii) RMgX (25 mmol, Et_2O (25mL) reflux, 1 h.

Kobayashi'Approach (1996)[19]

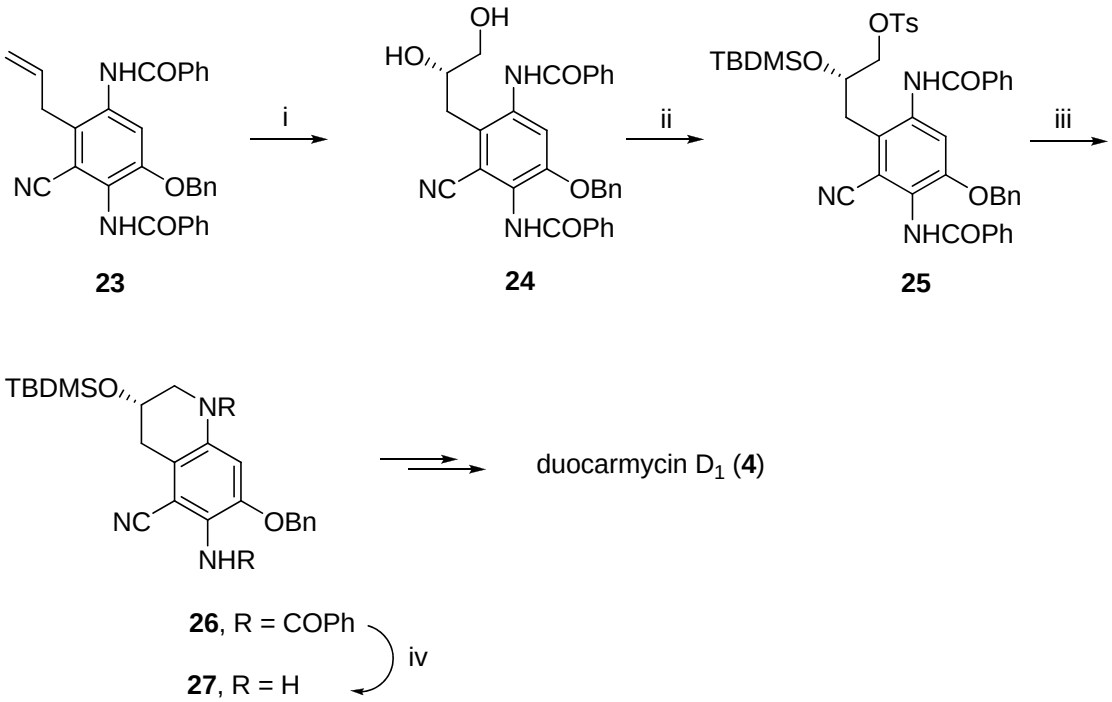
Kobayashi *et al*. have used asymmetric Aza Diels-Alder reactions of imine **19a-b** with cyclopentadiene (**20)** catalysed by $Yb(OTf)_3$·(*R*)-BINOL (**22**) complex that provided tetrahydroquinoline derivatives **21a-b** in 69-92% yields and 71% ee (**Scheme 7**).



Scheme 7: (i) $Yb(OTf)_3$:(*R*)-BINOL:DBU (20 mol%) **22**, 2,6-di-^{t}butylpyridine (1 equiv.), CH_2Cl_2, MS 4 A^o, -15-0 ºC, 20 h.

Boger's approach (1997)[20]

Boger *et al.* have used asymmetric dihydroxylation as the key step for the synthesis of duocarmycin-D_1 (**4**). Asymmetric dihydroxylation of olefin **23** gave diol **24** in 95 % yield. Tosylation of primary alcohol and protection of secondary alcohol as silyl ether in **24** gave **25**. Intramolecular nucleophilic displacement of tosylate **25** with amide anion provided key intermediate **26** which on hydrolysis (N_2H_4, sealed tube, 140 ºC) gave diamine **27**. By sequential transformations, **27** was further converted to duocarmycin A (**4**) (**Scheme 8**).

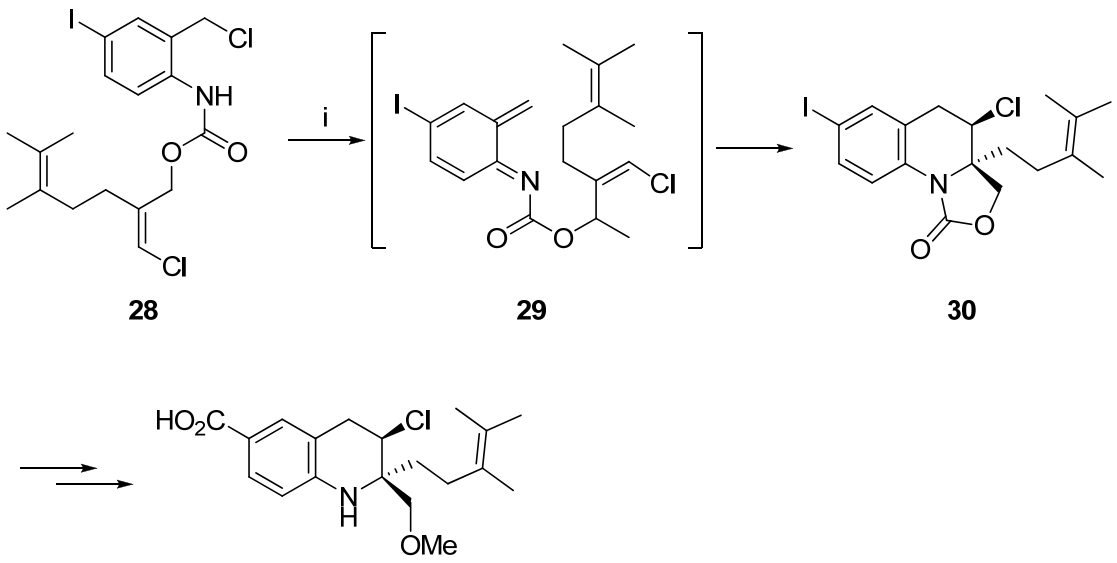


Scheme 8: (i) OsO_4 (1 mol%), $(DHQD)_2$-PHAL (10 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (40 mol%), THF:H_2O (4:1), 0-25 °C, 24 h, 92%; (ii) (a) Bu_2SnO, toluene-THF (10:1), reflux, 6 h; (b) TsCl, Et_3N, CH_2Cl_2, 25 °C, 12 h, 89%; (c) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 67%; (iii) NaH, THF, 0 °C, 2 h, 92%; (iv) NH_2NH_2, EtOH, 140 ºC, 12 h, sealed tube, 85%.

Corey's approach (1999)[21]

Corey *et al.* have reported the synthesis of (±)-virantmycin (**3**) *via* intramolecular Diels-Alder reaction of *o*-azaxylylene **29** which was prepared by elimination reaction of chloro carbamate **28**. Compound **29** underwent intramolecular [4+2] cycloaddition reaction in

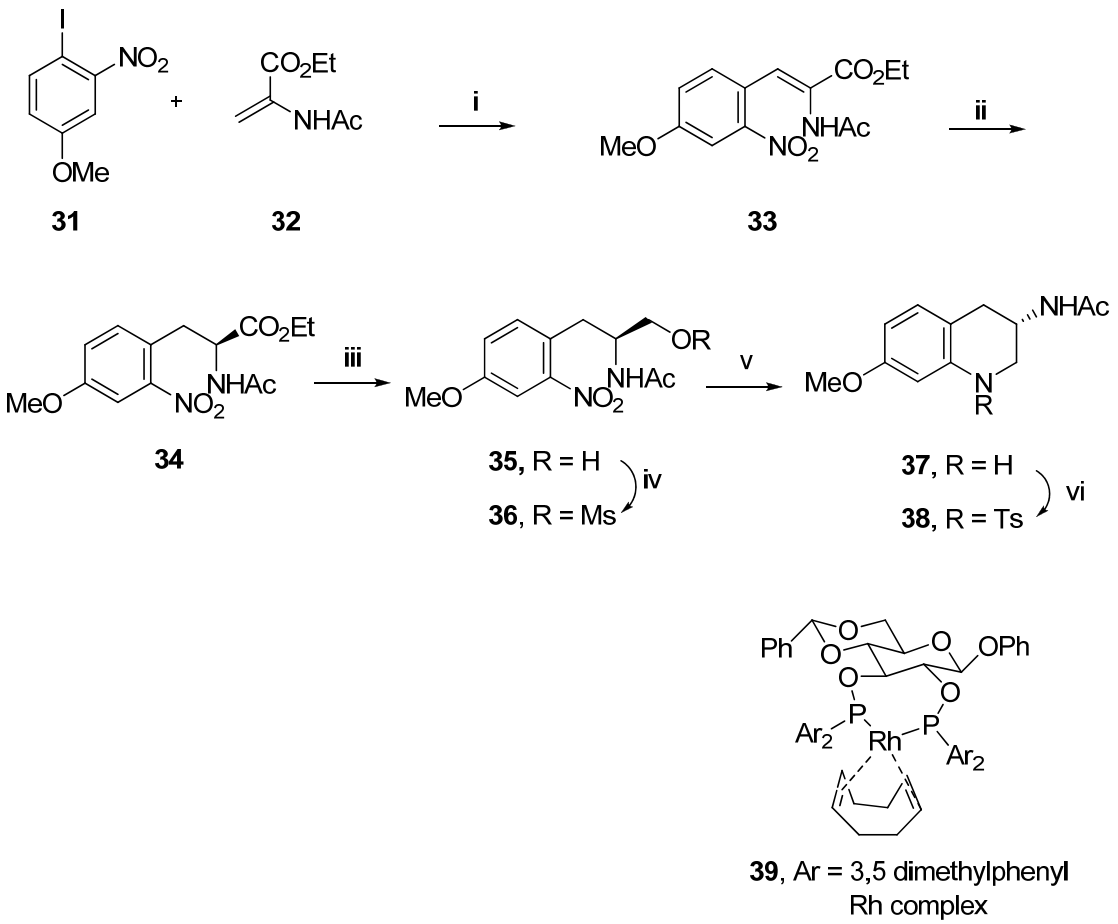
high stereoselectivity to furnish tetrahydroquinoline derivative **30** in 90% yield. Further (±)-virantmycin (**3**) was synthesized by sequential reactions (**Scheme 9**).



Scheme 9: (i) Cs_2CO_3 (5 equiv.), CH_2Cl_2, 23 ºC, 48 h, 90%.

Rajan Babu's approach (2001)[22]

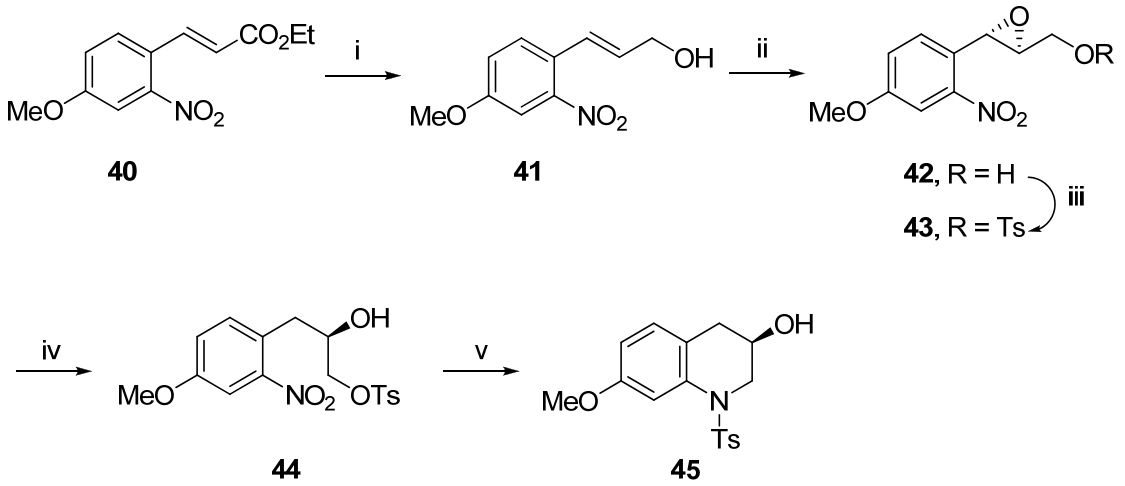
Rajan Babu *et al.* have used Rh-catalyzed asymmetric hydrogenation as a key reaction for the synthesis of aminotetrahydroquinoline **38**. Rh-catalyzed asymmetric hydrogenation of α-acetamido-2 nitrocinnamate ester (**33**) gave α-acetamido ester **34** in 96% yield and 98% ee. Further reduction of ester functionality with super hydride afforded the corresponding alcohol **35** which was subsequently transformed into its mesylate **36**. Reduction (H_2, 10% Pd/C) of nitro in **36** to amine followed by cyclization provided 3-aminotetrahydroquinoline **37** which was transformed (TsCl/ Et_3N) as its tosylamide **38** (**Scheme 10**).



39, Ar = 3,5 dimethylphenyl Rh complex

Scheme 10: (i) $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, sealed tube, 80 ºC, 24 h, 80%; (ii) Rh catalyst **39**, H_2 (40 psig.), THF, 96%, 98%ee; (iii) super hydride, 0 ºC; (iv) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 30 min; (v) H_2, Pd/C, 1 h, 25 ºC; (vi) TsCl, Et_3N, CH_2Cl_2, 0 ºC.

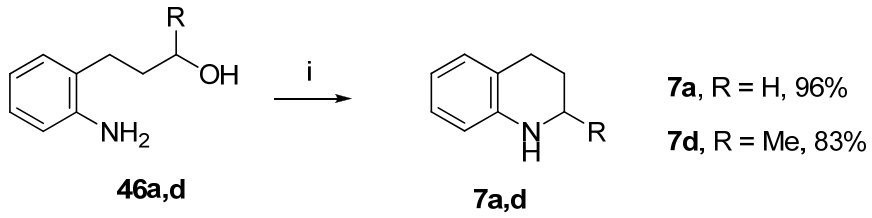
In another approach, 2-nitrocinnamate **40** was reduced to the corresponding allyl alcohol **41** using DIBAL-H. Sharplesss asymmetric epoxidation of allyl alcohol **41** gave the chiral epoxy alcohol **42,** which was further transformed into tosylate **43.** Reductive opening of epoxide **43** over PtO_2 furnished secondary alcohol **44** in 70 % yield. Finally reduction (Fe/HCl, H_2O and DMF) of nitro functionality to amine which displaces tosylate to afford 3-hydroxy tetrahydoquinoline followed by its protection as tosylamide gave **45** in 66% yield (**Scheme 11**).



Scheme 11: (i) DIBAL-H, toluene, 0 ºC, 75%; (ii) $Ti(O^iPr)_4$ (10 mol%), (+)-DIPT (14 mol%), ^{t}BuOOH, CH_2Cl_2, -30 ºC, 6 days, 60%, >90% ee; (iii) TsCl, Et_3N, CH_2Cl_2, DMAP, 0 ºC, 80%; (iv) (a) MgI_2, toluene, -55 ºC; (b) PtO_2, H_2 (40 psig), Et_3N, THF, 70% over two steps; (v) (a) Fe, HCl, H_2O, DMF, 70 ºC; (b) TsCl, Et_3N, CH_2Cl_2, 66% over two steps.

Fujita's approach (2002)[23]

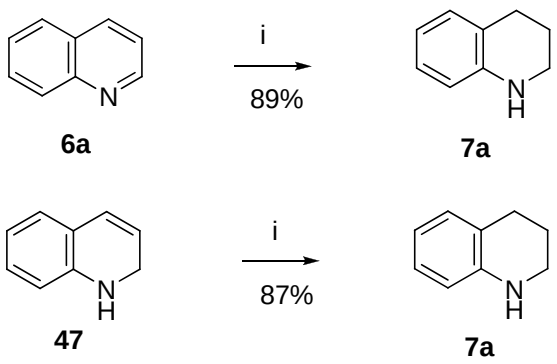
Fujita *et al.* had employed $[CpIrCl_2]_2/K_2CO_3$ catalyzed cyclization of 3-(2-aminophenyl)propanol (**46a,d**) to give tetrahydroquinoline (**7a,d**) in high yields (**Scheme 12**).



Scheme 12: (i) $[CpIrCl_2]_2$ (5.0 mol%), K_2CO_3 (10 mol%), toluene, 111 °C, 20 h.

Fujita's approach (2004)[24]

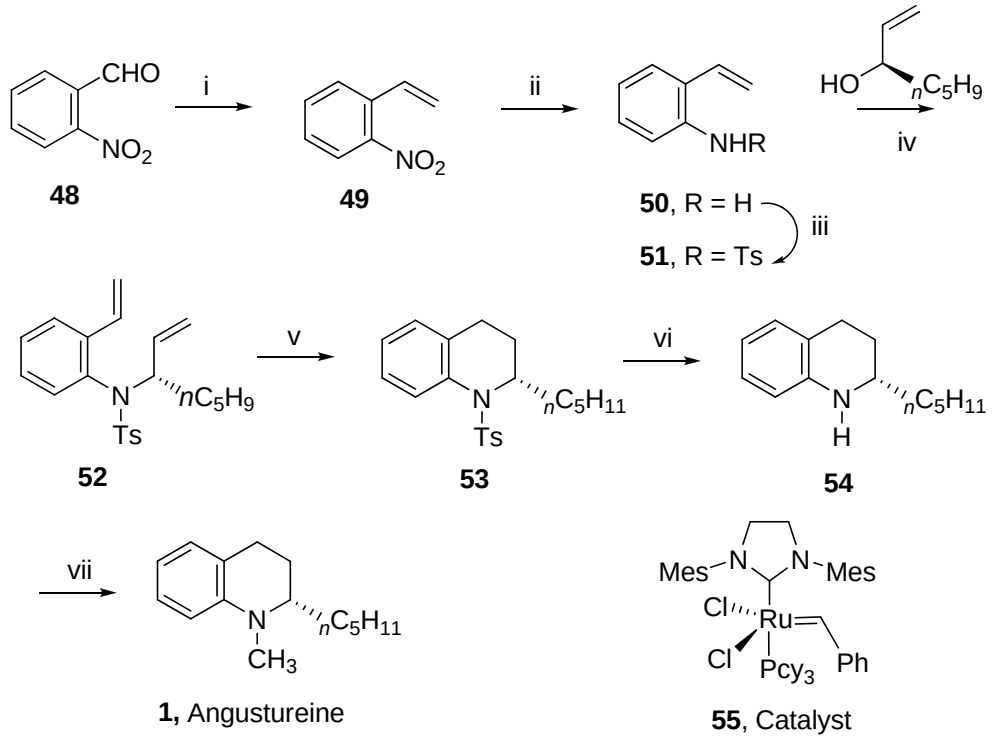
Fujita *et al.* have used Ir-catalyzed transfer hydrogenation of quinoline **6a** and dihydroquinoline **47** to provide tetrahydroquinoline **7a** in high yields. Addition of acid (CF_3CO_2H or $HClO_4$) considerably accelerates the rate of the reaction, whereas addition of water minimizes the formation of byproducts (**Scheme 13**).



Scheme 13: (i) $[CpIrCl_2]_2$ (1 mol%), aq.$HClO_4$ (0.20 mmol) 2-propanol (9.5 mL), H_2O (0.5 mL), reflux, 17 h.

Nishida's approach (2005)[25]

This approach utilized Ru-catalyzed ring closing metathesis (RCM) to construct dihydroquinoline core (**Scheme 14**).

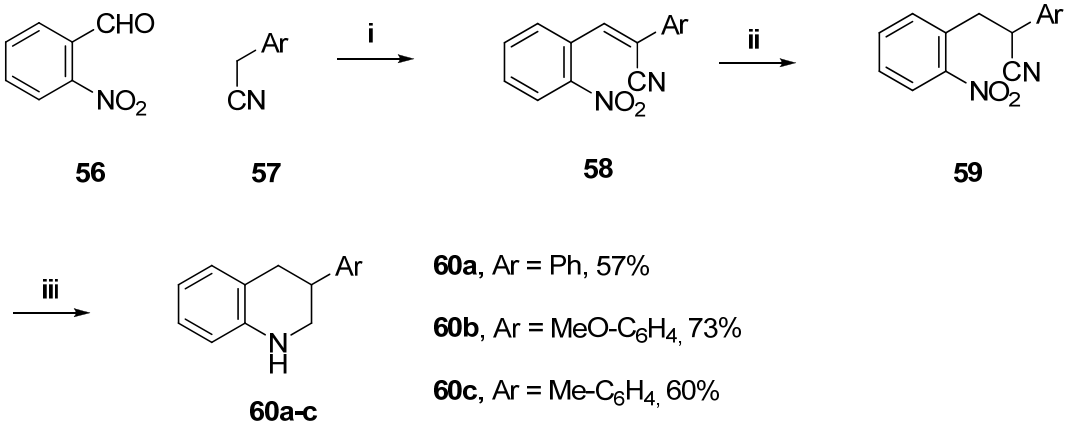


Scheme 14: (i) (a) Ph_3PMeBr, $KN(TMS)_2$, THF, 25 ºC, 1 h, 90%; (ii) Zn powder, AcOH, 25 ºC, overnight, 72%; (iii) TsCl, pyridine, CH_2Cl_2, 25 ºC, 1 h, 86%; (iv) DEAD, PPh_3, THF, 25 ºC, 2 h, 78%; (v) (a) Ru catalyst **55**, CH_2Cl_2 (0.01 M), 50 ºC, 1 h, 92%; (b) PtO_2, H_2, MeOH, 25 ºC, 12 h, 94%; (vi) anthracene sodium, DME, -65 ºC, 10 min, 99%; (vii) MeI, K_2CO_3, THF, reflux, 10 h, 80%.

Wittig olefination of *o*-nitro benzaldehyde (**48**) gave nitrostyrene (**49**), which was subjected to reduction (Zn/AcOH) to give the corresponding *o*-aminostyrene **50**. Protection of amine in **50** as tosamide **51** (TsCl, Py, CH_2Cl_2), followed by Mitsunobu reaction with (*R*)-oct-1-en-3-ol (99% ee) [DEAD and PPh_3] provided the desired *α,ω*-diene **52** in 78% yield. The diene was subjected to ring closing metathesis (RCM) with Grubbs' catalyst **55** gave the corresponding 1,2-dihydroquinoline in 92% yield, which was subsequently hydrogenated over Adam's catalyst in MeOH to provide tetrahydroquinoline **53** in 94% yield and 99.7% ee. Finally detosylation of **53** to free amine **54** and subsequent methylation of the free nitrogen gave (+)-(*S*)-angustureine (**1**) in 80% yield.

Yang's approach (2006)[26]

Yang *et al*. have reported the reductive cyclization of **59** using H_2 over Pd/C to give 3-aryl tetrahydroquinoline **60a-c** (**Scheme 15**).



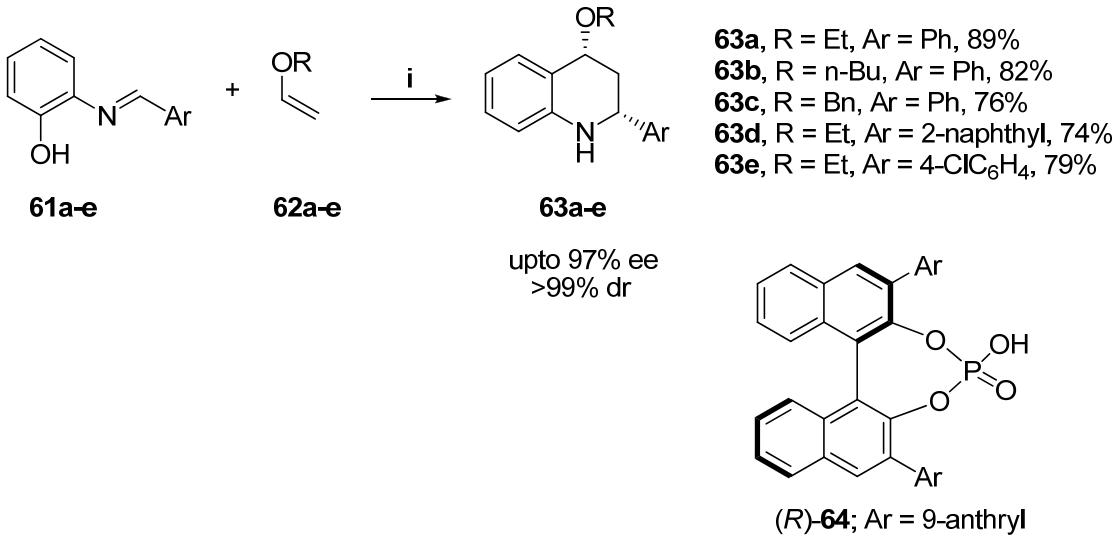
Scheme 15: (i) Na, C_2H_5OH, 5 h; (ii) $NaBH_4$, THF, CH_3OH; (iii) H_2 (1 atm), 30%Pd/C, THF, CH_3OH.

Condensation of 2-nitrobenzaldehyde (**56**) with aryl propionitrile **57** and subsequent reduction of double bond with $NaBH_4$ provided **59,** which was subjected to reduction

with H_2 over 20% Pd/C followed by reductive cyclization with cyano group afforded 3-aryltetrahydroquinoline **60a-c** in 57-73% yields.

Akiyama's approach (2006)[27]

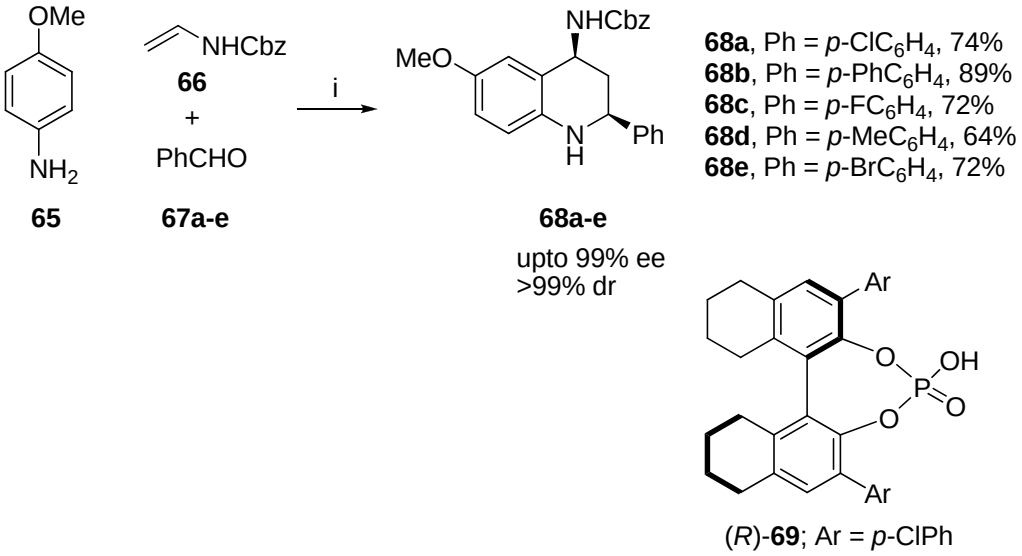
Akiyama's *et al.* have described inverse electron-demand aza Diels-Alder reaction of aldimines **61a-e** with electron-rich alkene enol ethers **62a-e** catalyzed by a chiral Brønsted acid **64** to provide tetrahydroquinoline derivatives **63a-e** in 74-89% yields and upto 97% ee (**Scheme 16**).



Scheme 16: (i) catalyst (R)-**64** (10 mol%), toluene, 10 - 55 h, 25 ºC

Zhu's approach (2009)[28]

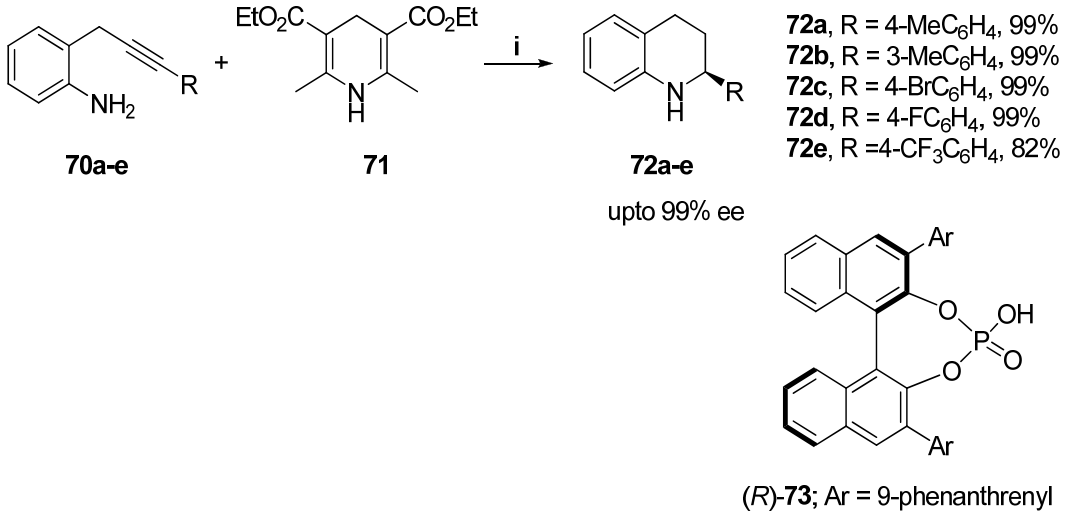
This approach utilized the first catalytic three-component Povarov reaction of aldehydes **67a-e**, aniline **65** and benzyl N-vinylcarbamate **66** in the presence of 0.1 equiv of chiral phosphoric acid **69** afforded *cis*-2,4-disubstituted tetrahydroquinolines **68a-e** in good yields and enantiomeric excesses (upto 99% ee) (**Scheme 17)**.



Scheme 17: (i) catalyst (*R*)-**69** (0.1 equiv.), CH_2Cl_2, 1 h, 0 ºC.

Gong's approach (2009)[29]

Gong *et al.* have developed a new protocol which directly transformed 2-(2-propynyl)aniline **70a-e** derivatives into tetrahydroquinolines **72a-e** in one operation with excellent enantioselectivity under the relay catalysis of an achiral Au complex and a chiral phosphoric acid **73** (**Scheme 18**).



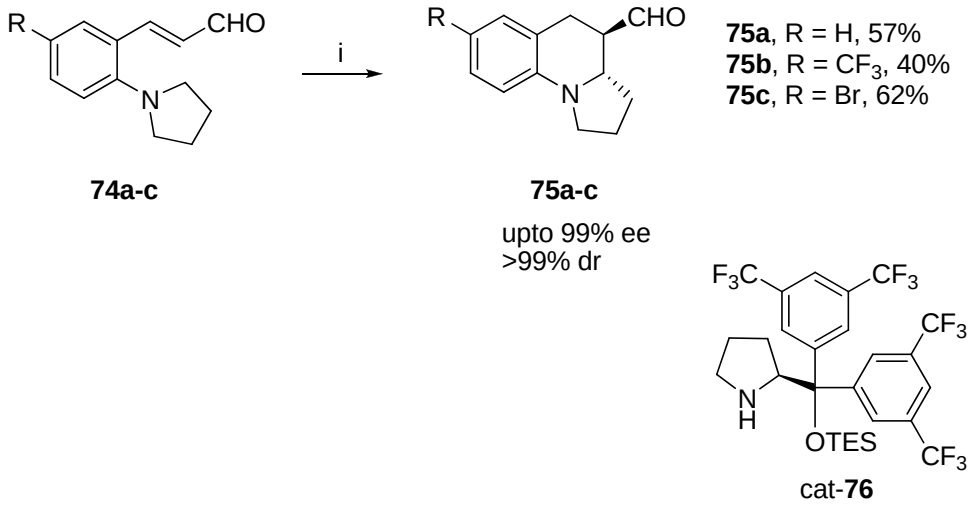
Scheme 18: (i) catalyst (*R*)-**73** (15 mol%.), Ph_3PAuCH_3 (5 mol%), toluene, 25 ºC 16 h

This reaction was considered a consecutive catalytic process consisting of Au-catalyzed intramolecular hydroamination of a C-C triple bond and a Brønsted acid catalyzed enantioselective transfer hydrogenation to provide tetrahydroquinolines **72a-d** in 99% yield with 99% ee.

Kim's approach (2010)[30]

Kim et al. have reported the first enantioselective intramolecular 1,5-hydride transfer/ring closure reaction cascade. In this organocatalytic redox neutral reaction, *o*-dialkylaminosubstituted cinnamaldehydes **74a-c** were reacted in the presence of prolinol derivative **76** (30 mol%) as an organocatalyst and (-)-CSA (30 mol%) as an additive in TCE provided tetrahydroquinolines **75a-c** in high enantioselectivities with moderate yield.

(**Scheme 19**).

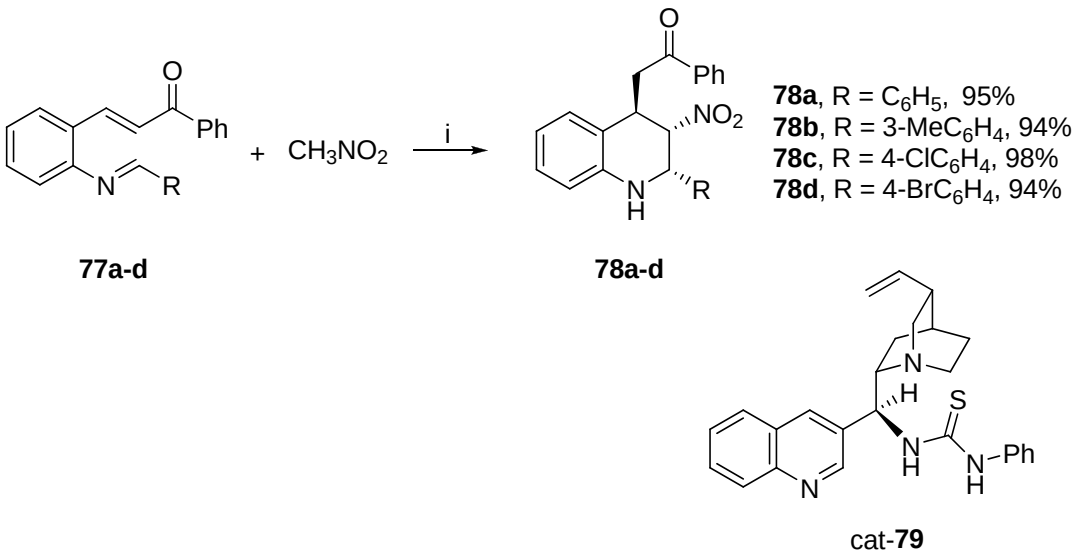


Scheme 19: (i) cat-**76** (30 mol%), (-)-CSA (30 mol%), TCE, 5 - 9 d, 25 ºC.

Xu's approach (2011)[31]

Xu *et al.* have described a novel synthetic method for polysubstituted tetrahydroquinoline derivatives **78a-d** *via* organocatalytic asymmetric tandem Michael addition and the aza-

Henry reaction, in which chalcone **77a-d** and nitromethane were employed as the starting materials. The reaction yields were high (94%-98%), and highly diastereo- and enantioenriched tetrahydroquinoline derivatives **78a-d** with a substantial substitution diversity were smoothly delivered (up to >99% ee, dr up to 20:1) (**Scheme 20**).



Scheme 20: (i) cat-**79** (20 mol%), Ph_3PAuCH_3 (5 mol%), toluene, 25 ºC, 4 h.

2.1.3 Present Work

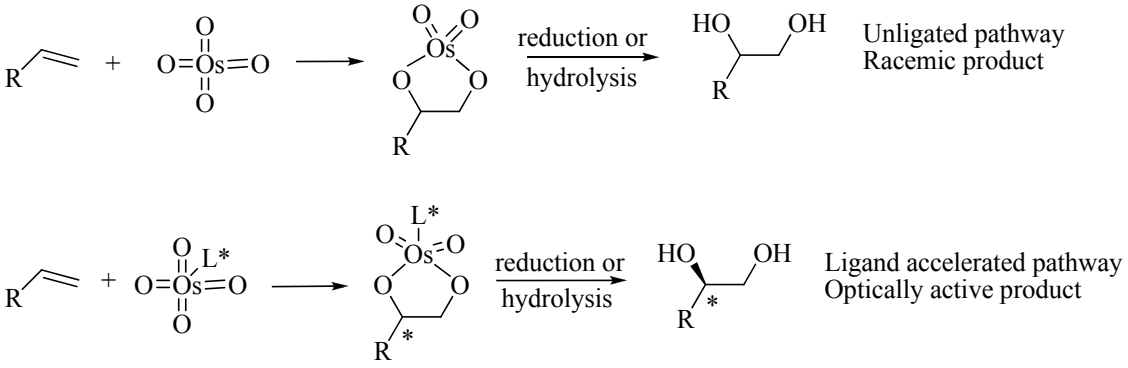
2.1.3.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of tetrahydroquinoline core mainly deal with racemic synthesis. Other disadvantages include use of chiral starting materials, lengthy reaction sequences, need of protection and deprotection of functional groups, low overall yield and use of expensive reagents. In this context, a more practical and efficient synthesis of functionalized tetrahydroquinoline derivatives is highly desirable. In this section, we describe a novel method for efficient synthesis of tetrahydroquinoline derivatives which make use of cobalt catalyzed reduction of cyclic sulfites. Since this chapter deals with two potentially important

reactions [asymmetric dihydroxylation (AD) and $CoCl_2 \cdot 6H_2O$ catalyzed reduction with $NaBH_4$], a brief account of both of them below.

2.1.3.2 Asymmetric Dihydroxylation (AD)

In recent years, much attention has been focused on the catalytic asymmetric synthesis. It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[32] Among all these reactions, Sharpless catalytic Asymmetric Dihydroxylation (AD) is one of the most important practical and widely used reaction in organic synthesis. It has become the most general method for the preparation of optically active *vicinal-syn*-diols from activated as well as unactivated olefins.[33]



$$\text{Ligand Acceleration} = \frac{\text{Saturation rate with ligand}}{\text{Rate without ligand}}$$

Scheme 21: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

In 1936, Criegee *et al.*[34] have found that addition of pyridine or any other tertiary amine to osmylation of olefins, accelerates the rate of reaction considerably. A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless *et al*.[33b] demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands

screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, namely dihydroquinidine (DHQD) and dihydroquinine (DHQ) (**Scheme 21**).[35]

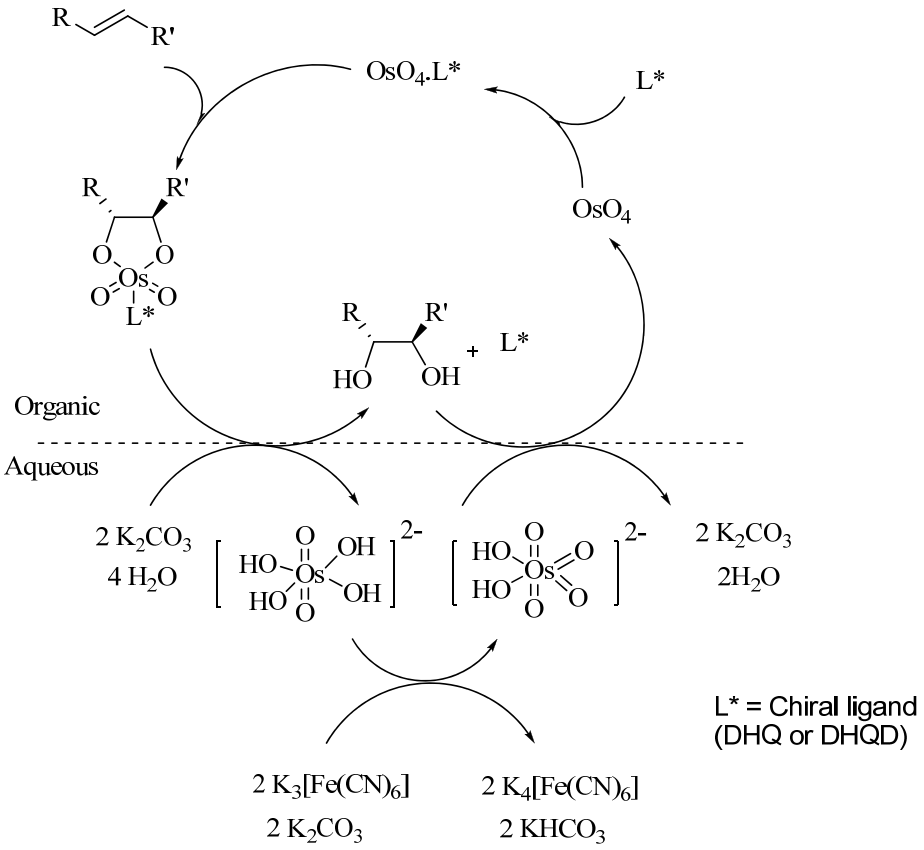


Fig. 2: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant

To improve the %ee of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions **(Fig. 2)**. These conditions helped in protecting the organic osmate-(VI) monoglycolate ester from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) obtains reoxidized and recycled into the catalytic cycle. Further improvement in the AD was realized by the addition of methyl sulfonamide

($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis, thus facilitating the dihydroxylation smoothly. Addition of methyl sulfonamide also allowed carrying out the reactions of 1,2-di- tri- and tetra- substituted olefins at 0 ºC, which improved the selectivity as well as enantiomeric excess. In order to develop the asymmetric version of the Os-catalyzed AD reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the *bis*-DHQ or DHQD ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselective diols[36] **(Fig. 3)**.

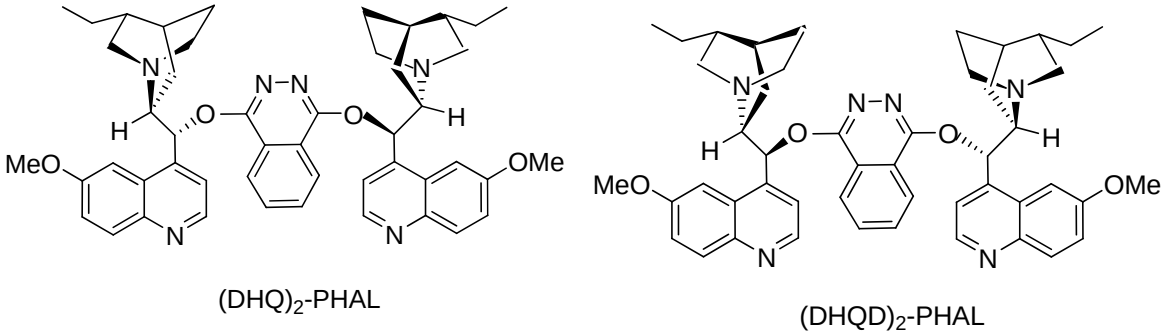


Fig. 3: Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[37] Sharpless *et al*.[33] have shown that the facial selectivity for both ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ is different, based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model **(Fig. 4)** in which olefin with the constraints will be attacked either from the top (i.e. β) face in the presence of dihydroquinidine (DHQD)

derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

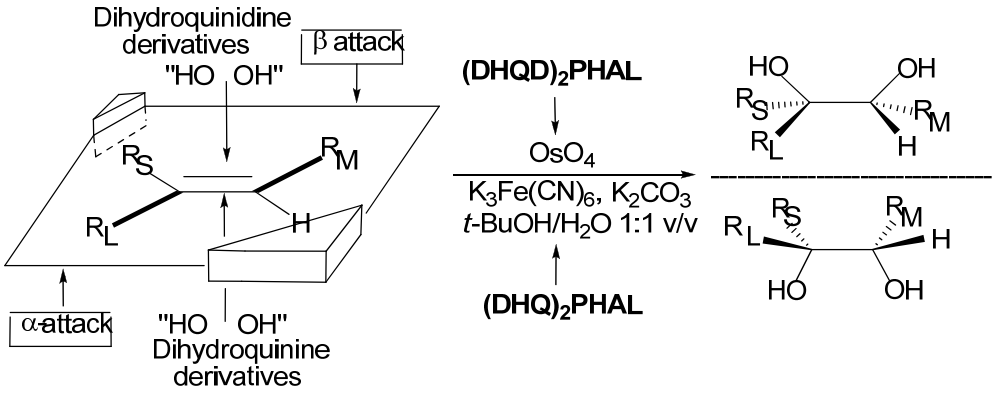


Fig. 4: Enantioselectivity mnemonic scheme

2.1.3.3 Transition metal boride catalyzed reduction

Since the pioneering discovery of nickel-catalyzed hydrogenation by Paul Sabatier, organic chemists have been fascinated with transition metals and their compounds as promoters for other synthetically important reductions. In the last 40 years, metal hydrides, particularly sodium borohydride and lithium aluminum hydride, have emerged as preeminent reducing agents in modern organic chemistry.[38] These are extraordinarily versatile reagents capable of reducing most functional groups. Moreover by attaching organic ligands at boron or aluminum or changing the metal counter ion, one can modulate the scope, regio and stereoselectivity of such reductions. Literally hundreds of substituted boron and aluminum hydrides have been described in the chemical literature and dozens are now commercially available.[39]

More recently, transition metal salts have been used as catalysts or additives in combination with $NaBH_4$ and $LiAlH_4$, to modify or enhance the properties of these reagents. Nearly every conceivable combination of salt and hydride has been investigated

with the concomitant development of many useful new synthetic methods.[40] The resulting systems are complex, however, and in most cases virtually nothing is known about mechanism or reactive intermediates. Boron and aluminum hydrides may combine with metal halides in several different ways: (1) simple metathesis (e.g., LiCl + $NaBH_4$, $LiBH_4$, + NaCl), (2) reduction of the metal halide to the metal, (3) conversion of metal halide to metal hydride: (4) some combination of (2) and (3), viz., $FeC1_3$, + $LiBH_4$ = $Fe(BH_4)_2$, or (5) formation of a boride or aluminide.[41] Furthermore, it is often unclear whether the metal salt serves a true catalytic function or whether some transient, metalloidal complex formed *in situ* is the actual reducing agent.

Historically, borides were first produced by the combination of boron with metallic or metalloidal elements less electronegative than itself. For the most part, borides are very hard, high-melting, refractory substances whose structures and stoichiometries do not conform to the ordinary concepts of valence. H. I. Schlessinger discovered a much simpler synthesis in his pioneering work on borohydrides. Combinations of cobalt or nickel (or other metal salts) with aqueous $NaBH_4$ deposit finely divided black precipitates of Co_2B and Ni_2B (eq 1).

$$4NaBH_4 + 2CoC1_2 + 9H_2O = Co_2B + 3H_3BO_3 + 4NaC1 + 12.5H_2 \quad (1)$$

Because they actively catalyzed the decomposition of borohydride, these borides have been commonly used as a practical, controlled source of hydrogen (eq 2).

$$NaBH_4 + 2H_2O = NaBO_2 + 4H_2 \quad (2)$$

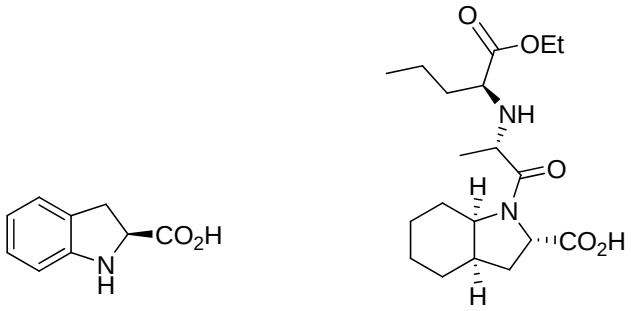
The actual composition of borides prepared from inorganic salts depends to a great extent on the specific mode of preparation. Maybury, Mitchell, and Hawthorne analyzed nickel

and cobalt borides prepared in ethanol under N_2 using excess $NaBH_4$, and concluded that the stoichiometries Ni_2B and Co_2B inadequately represented their constitution.[42]

In dimethylformamide (DMF) reduction of $CoC1_2$ or $NiC1_2$ with $NaBH_4$, produced dark brown/black solutions[43] which comprised quite efficient systems for hydrogenation of alkenes, alkynes, azides, nitriles, alkyl halides, nitro compounds, amides, oximes, etc.[44] Simple reaction procedures and excellent yields of products coupled with high catalytic efficiency makes this method much more impressive and practical.

2.1.3.2 Results and Discussion

We envisaged to provide a new synthetic route to (*S*)-indoline-2-carboxylic acid (**80**), a key intermediate in the synthesis of perindopril **81**, which is an orally active pharmaceutical used for the treatment of hypertension[45] (**Fig. 5**).



80, (*S*)-Indole-2-carboxylic acid **81,** Perindopril

Fig. 5: Structures of (*S*)-indoline-2-carboxylic acid and perindopril

In order to synthesize (*S*)-indoline-2-carboxylic acid (**80**), we visualized a strategy in which simultaneous reduction[46] of nitro cyclic sulfite **84** could probably lead to the cyclized product **80**. Thus, *o*-nitrocinnamate **82**, prepared from Wittig olefination of *o*-nitrobenzaldehyde, was converted to the corresponding nitro diol **83** in 82% yield *via* Os-catalyzed asymmetric dihydroxylation (AD) using $(DHQ)_2$-PHAL as the chiral ligand. Its

^{1}H-NMR spectrum showed methine protons (C**H**OH) for the carbons attached to hydroxyl group as doublets, each resonating at δ 4.48 (*J* = 2.1 Hz, 1H) and 5.67 (*J* = 2.1 Hz, 1H). Its ^{13}C-NMR spectrum showed the corresponding methine carbon signals at δ 69.7 and 73.4 (**Fig. 6**).

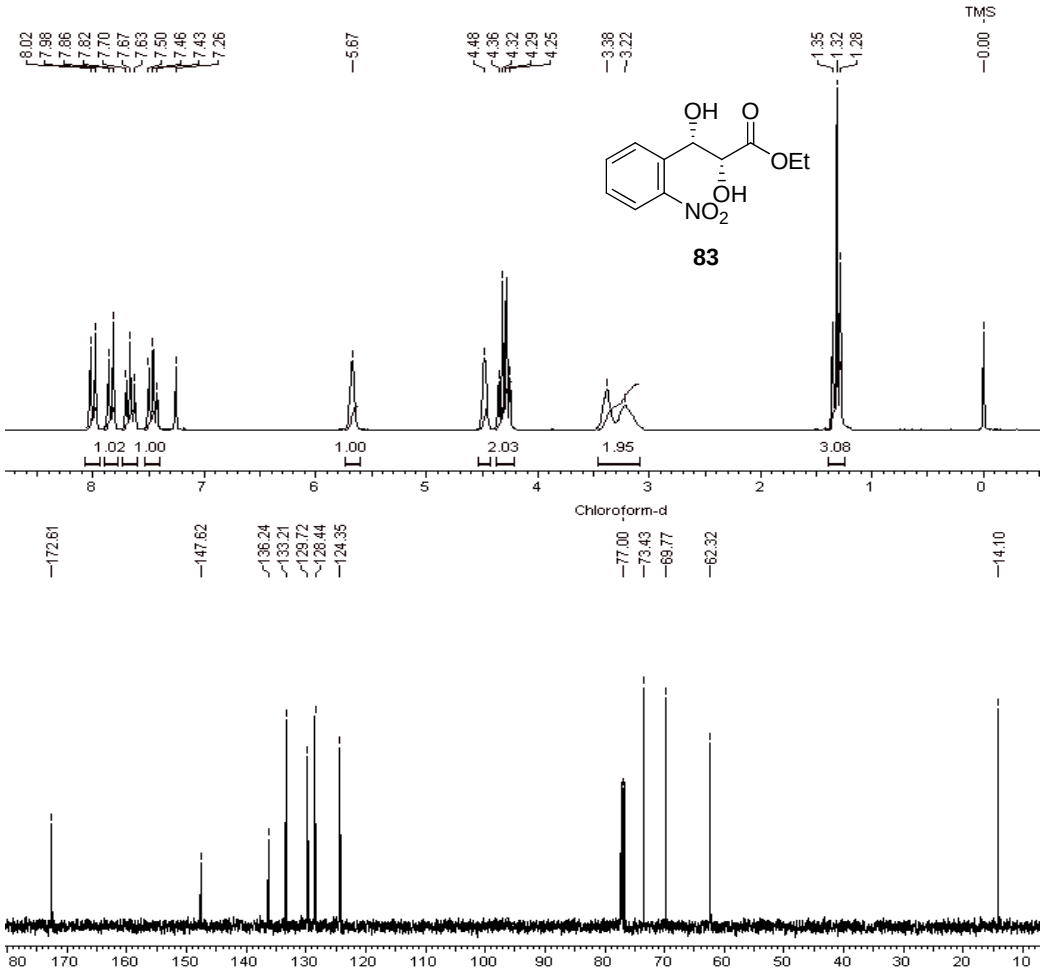
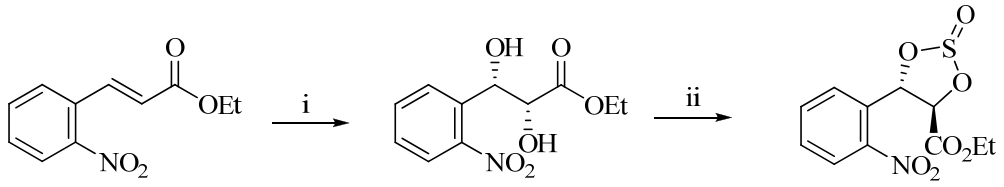


Fig. 6: ^{1}H and ^{13}C-NMR spectra of diol **83**



82 **83** **84**

Scheme 21: (a) K_2OsO_4 (0.2 mol%), $(DHQ)_2$-PHAL (1 mol%), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), $MeSO_2NH_2$ (1 equiv), *tert*-BuOH:H_2O (1:1), 25 °C, 24 h, 82%; (b) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 95%.

The nitro diol **83** was then readily transformed into the corresponding precursor nitro cyclic sulfite **84** ($SOCl_2$, Et_3N and CH_2Cl_2) in 95% yield (**Scheme 21**). Two doublets at δ 4.97 (J = 4.7 Hz) and 6.93 (J = 4.7 Hz) integrating for one proton each accounted for the methine protons of the cyclic sulfite in its ^{1}H-NMR spectrum. Methine carbons of the cyclic sulfite gave signals at δ 83.21 and 83.11 in its ^{13}C NMR spectrum (**Fig. 7**).

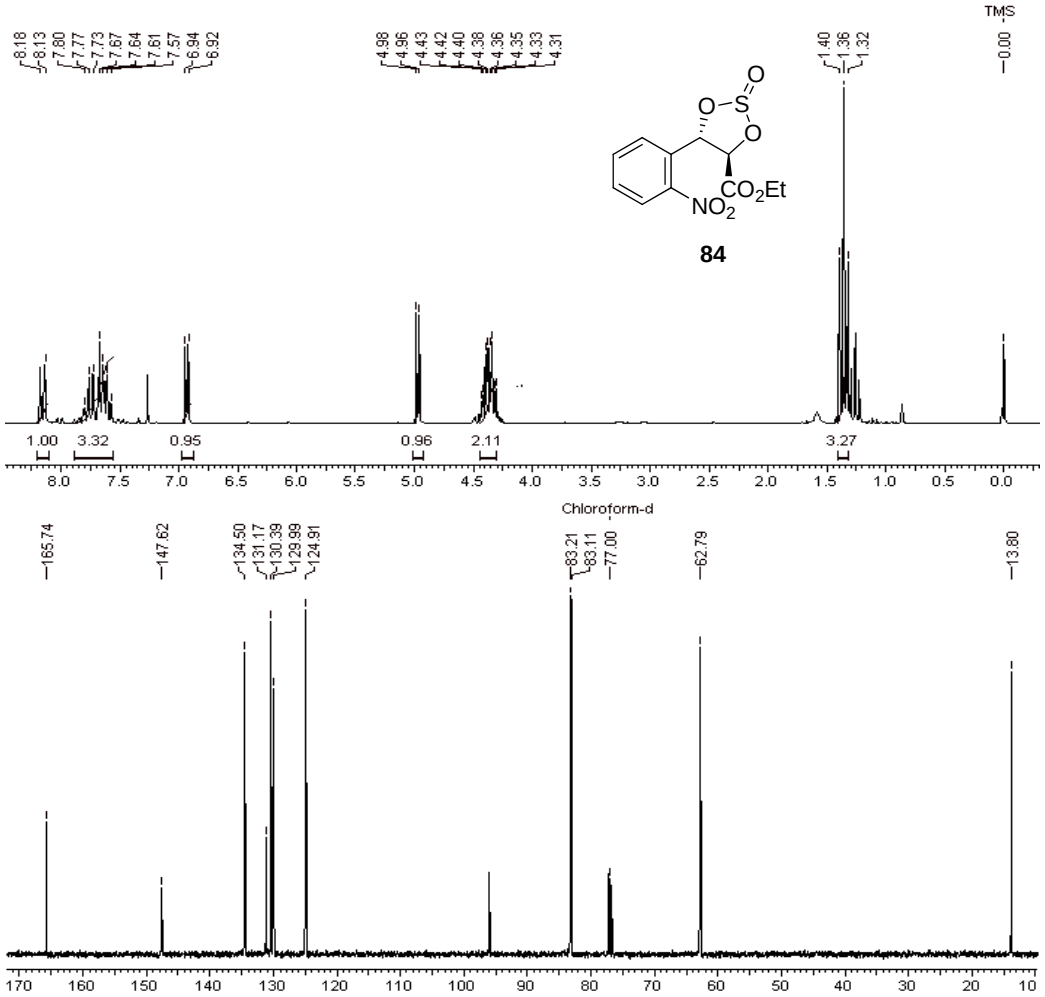
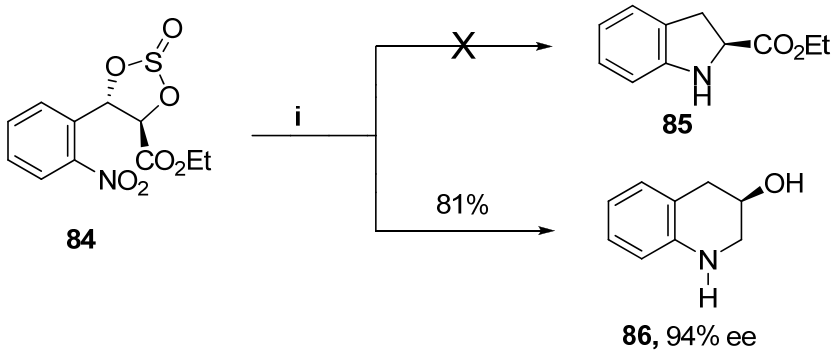


Fig. 7: ^{1}H and ^{13}C-NMR spectra of cyclic sulfite **84**

In order to validate our hypothesis, nitro cyclic sulfite **84** was then subjected to reduction with 4 equivalents of $NaBH_4$ catalyzed by $CoCl_2 \cdot 6H_2O$. Surprisingly, the reaction took

altogether a different course to give the cyclized 3-hydroxytetrahydroquinoline **86**, in a single step, as the only product in 81% isolated yield, instead of the expected cyclized ester **85**. Under the reaction conditions, it was thus observed that a simultaneous reduction of multifunctional groups took place, all occurring in a single step (**Scheme 22**). However, when nitro diol **83** was subjected to reduction under identical conditions, nitro group was unaffected. It was further observed that, nitro functionality was reduced only when nitro diol **83** was converted into its cyclic sulfite **84**.



Scheme 22: (a) $CoCl_2.6H_2O$ (1 mol%), $NaBH_4$ (4 equiv.), EtOH, 0-25 °C, 12 h.

The formation of the tetrahydroquinolin-3-ol **86** was confirmed by their ^{1}H and ^{13}C-NMR spectra, which showed characteristic signals at δ 2.73-2.83 (dd, J = 3.5, 16.8 Hz, 1H), 2.99-3.09 (dd, J = 3.5, 16.8 Hz, 1H), 3.19-3.36 (m, 2H) in its ^{1}H-NMR spectrum corresponding to the benzylic methylene (Bn-C**H**$_2$) and methylene attached to nitrogen (C**H**$_2$N) protons respectively. Also signal at δ 4.19-4.27 (m) due to methine proton (C**H**OH) confirms the formation of 3-hydroxytetrahydroquinoline. Its ^{13}C NMR spectrum showed typical signals at δ 35.3 and 47.6 and 63.2 for two methylene carbons (Ar**C**H$_2$, N**C**H$_2$) and one methine carbon (**C**HOH) respectively. Disappearance of carbonyl

frequency in its IR and ^{13}C-NMR signal establishes the structure of 3-hydroxyquinoline **86** (**Fig. 8).**

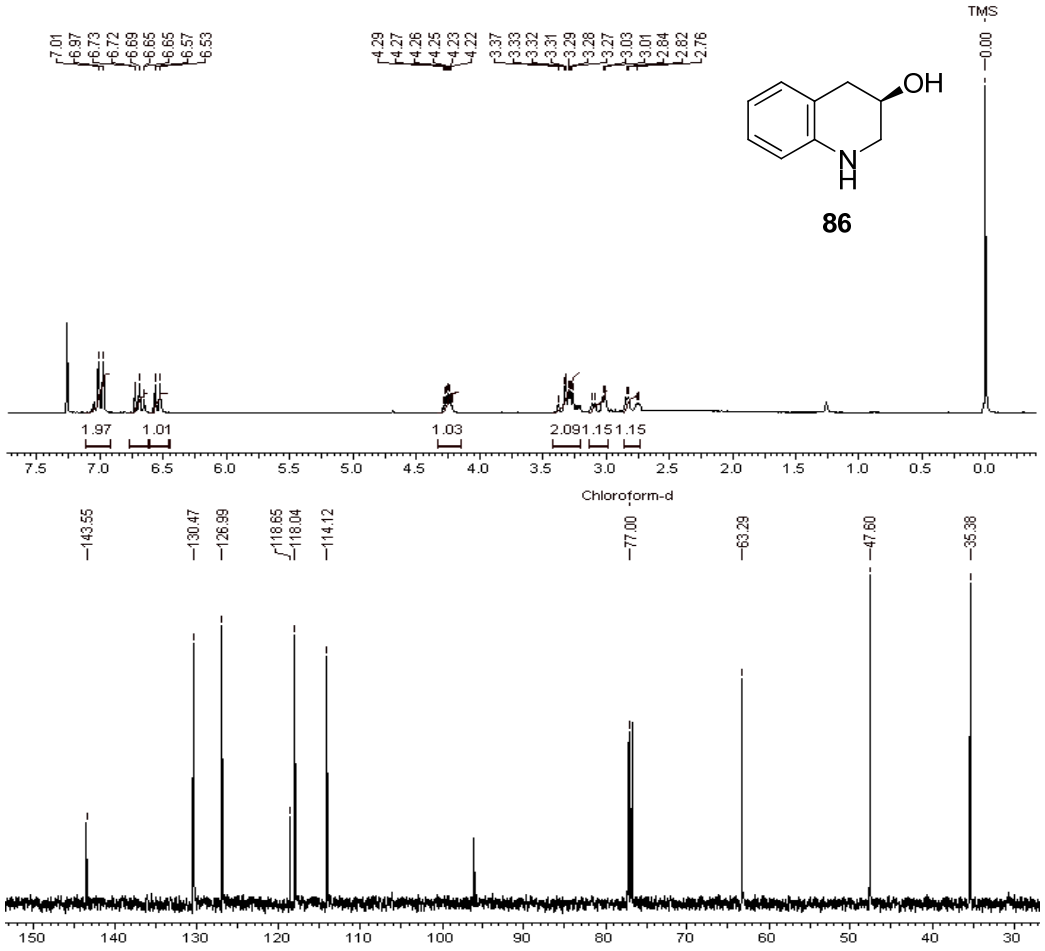
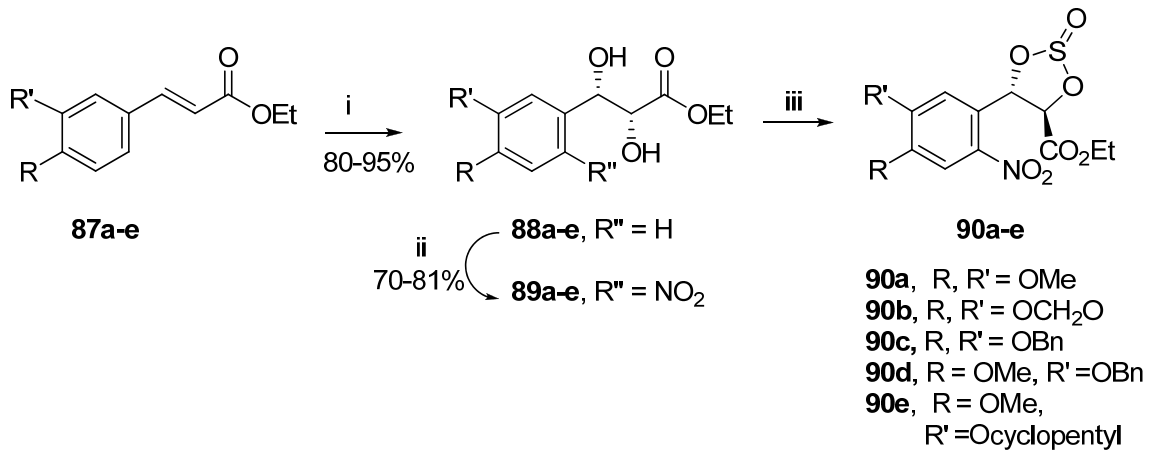


Fig. 8: ^{1}H and ^{13}C NMR spectra of 3-hydroxyquinoline **86**

Encouraged by the result, we became interested in carrying out the reduction of several nitro cyclic sulfites **90a-e**. To start with, the precursors (**90a-e**) were readily prepared in three steps starting from the corresponding *α,β*-unsaturated esters **87a-e.** Firstly, 3,4-disubstituted cinnamates **87a-e** were prepared in high yields by Wittig olefination of the corresponding benzaldehydes.The Os-catalyzed asymmetric dihydroxylation (AD) of the *α,β*-unsaturated esters **87a-e** using $(DHQ)_2$-PHAL as the chiral ligand gave the corresponding chiral diols, **88a-e** in 80-95% yields. Then initially, nitration of diol **88a-e**

in acetic acid was carried out to afford nitrodiols **89a-e** in low yields, as considerable amount of byproducts were formed. However, when direct aromatic nitration of **88a-e** was carried out in biphasic medium (HNO_3, CH_2Cl_2), the corresponding nitro diols **89a-e** were obtained in good yields with excellent regioselectivity. Nitro diols **89a-e** were then readily transformed to the corresponding nitro cyclic sulfites **90a-e** ($SOCl_2$, Et_3N and CH_2Cl_2) in quantitative yields (**Scheme 23**).

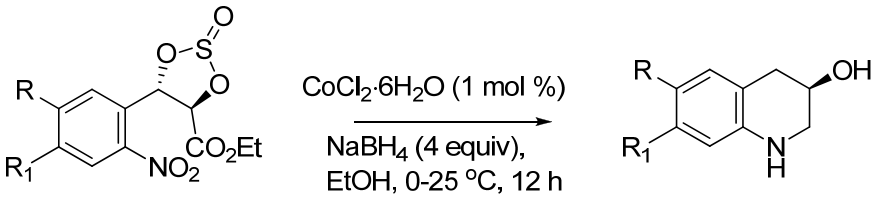


Scheme 23: (i) K_2OsO_4 (0.1 mol%), $(DHQ)_2$-PHAL (0.5 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (1 equiv.), *tert*-BuOH:H_2O (1:1), 25 °C, 24 h; (ii) conc. HNO_3, CH_2Cl_2, 0-25 °C, 30 min.; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 30 min.

When subjected to the $CoCl_2$-catalyzed reduction[15] with 4 equiv. of $NaBH_4$, chiral nitro cyclic sulfites **90a-e** gave the corresponding (*R*)-3-hydroxytetrahydroquinoline derivatives **91a-e** in 78-85% yields with excellent enantioselectivities. Results of such studies are presented in **Table 1**. As can be seen, various cyclic sulfites underwent reductive cyclization smoothly, at ambient conditions, to provide **91a-e** in a one-pot reaction, which comprises several transformations taking place in a single step with a variety of substituted nitro cyclic sulfites **90a-e** using cheaply available reagents. The formation of (*R*)-3-hydroxytetrahydroquinoline derivatives **91a-e** was confirmed by the

^{1}H and ^{13}C-NMR spectroscopy (see the experimental section) and also the mass spectra of **91a-e** (**Fig. 9**).

Table 1: Co–Catalyzed Reductive Cyclization of Nitro Cyclic Sulfites with $NaBH_4$



90a-e **91a-e**

Entry	Substrates (**90a-f**)	Products **91a-f**	
		Yield (%)[a]	ee (%)[b]
a	R = R^1 = OMe	78	96
b	R = R^1 = OBn	85	96
c	R = OBn; R^1 = OMe	83	95
d	R, R^1 = -O-CH_2-O-	81	96
e	R = O-pentyl ; R^1 = OMe	82	94

[a]isolated yield after column chromatographic purification [b]determined from chiral HPLC or Mosher's ester analysis

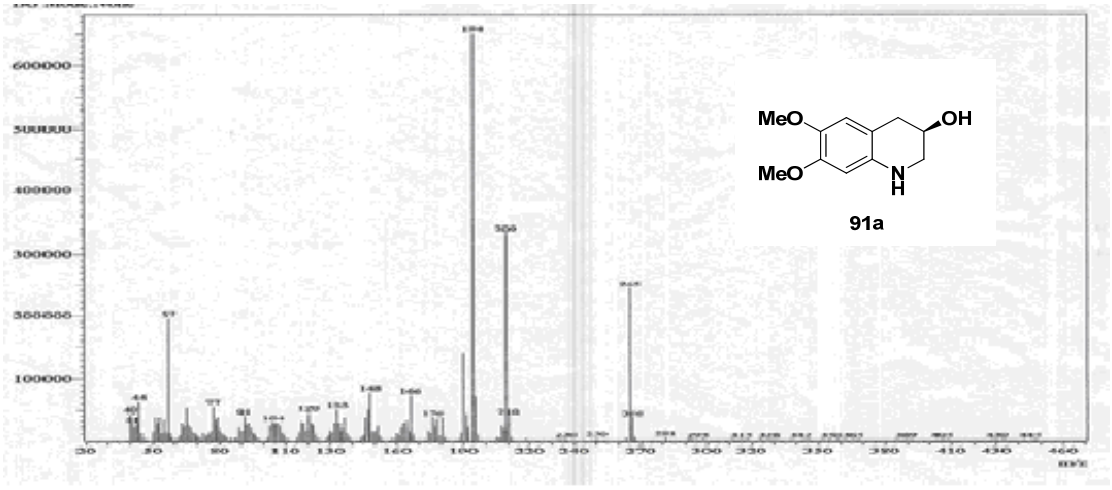
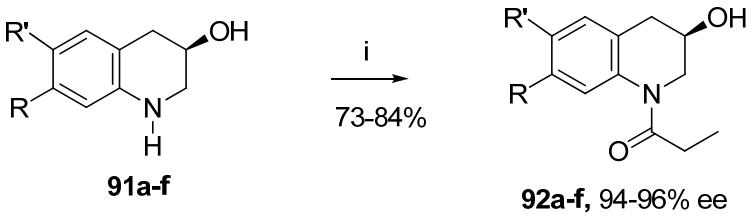


Fig. 9: Mass spectrum of tetrahydroquinoline **91a**

The optimization showed that a mixture of products were obtained with lower equiv of $NaBH_4$, thus requiring a minimum of 4 equiv. of $NaBH_4$ to achieve excellent yields; ethanol or a combination of EtOH and DMF could be used as solvent. However, other metal catalysts such as $NiCl_2$ and MnO_2 were indeed found to show catalytic activity under the reduction conditions although in poor yields (33% and 21% respectively).



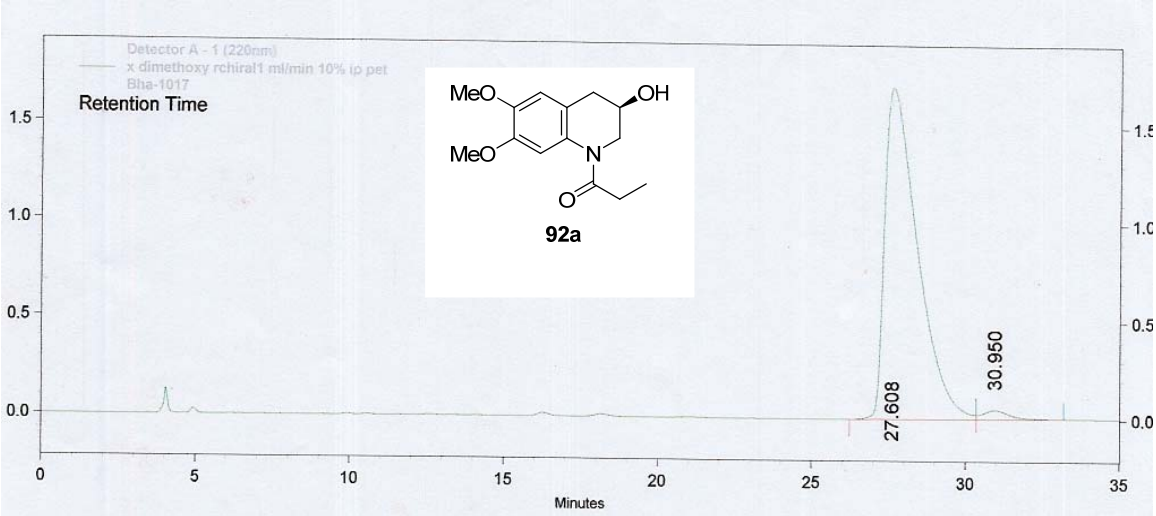
91a-f **92a-f,** 94-96% ee

Scheme 24: (i) $(EtCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 6 h.

Since the optical purities of the tetrahydroquinol-3-ol derivatives **86** and **91a-e** could not be established by HPLC due to their difficulty in separation, the protection of amine function in **86** and **91a-e** as propyl amides (propionic anhydride, Et_3N in CH_2Cl_2) was carried out to give the respective amido alcohols **92a-f** in high yields (**Scheme 24**), which facilitated their easy characterization by HPLC analysis. For example, chiral HPLC chromatogram of **92b** showed 95.5% ee (**Fig. 10).**

Enantiomeric excess of **86** and **91a-e** was also determined by recording ^{1}H-NMR spectra of their Mosher's ester analysis. Thus, free hydroxyl moiety in amido alcohols **92a-e** was subjected to esterification (catalytic DMAP, DCC in CH_2Cl_2) with Mosher's acid [(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid] and the resulting Mosher's esters **100a-e** were analyzed by ^{1}H-NMR spectra to determine their %ee. For example, ^{1}H

NMR spectrum of **100a** showed methyl proton signals at δ 3.38 (2.95H) for *R* isomer (*dr* = 32:1, 94% ee) (**Fig. 11**).



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	27.608	126448551	97.767
2	30.950	2887981	2.233
Totals		129336532	100.000

Fig. 10: HPLC Chromatogram of tetrahydroquinoline **92a**

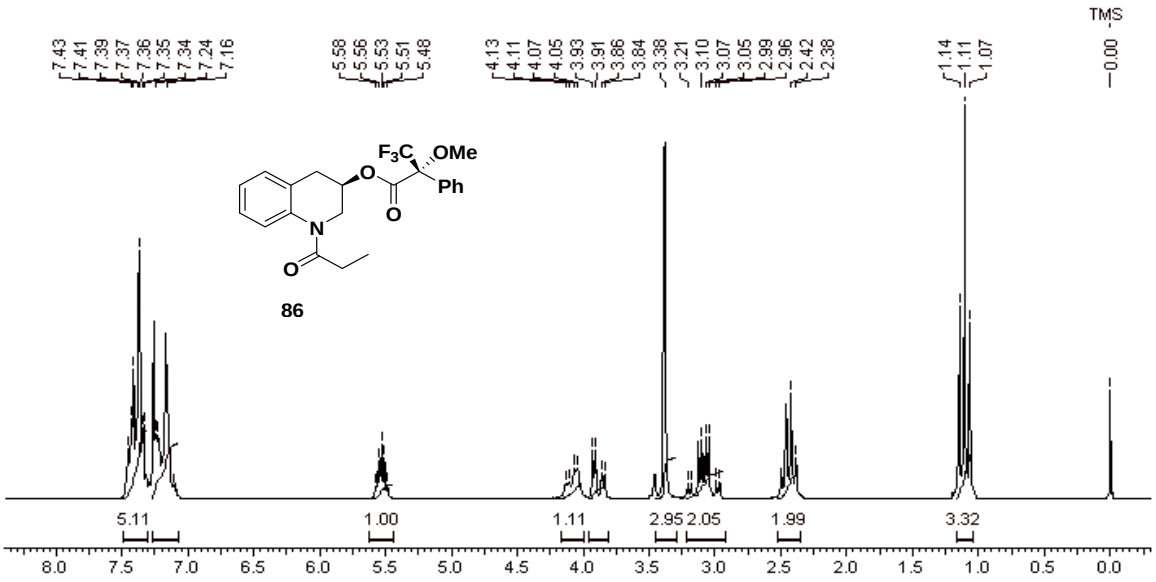
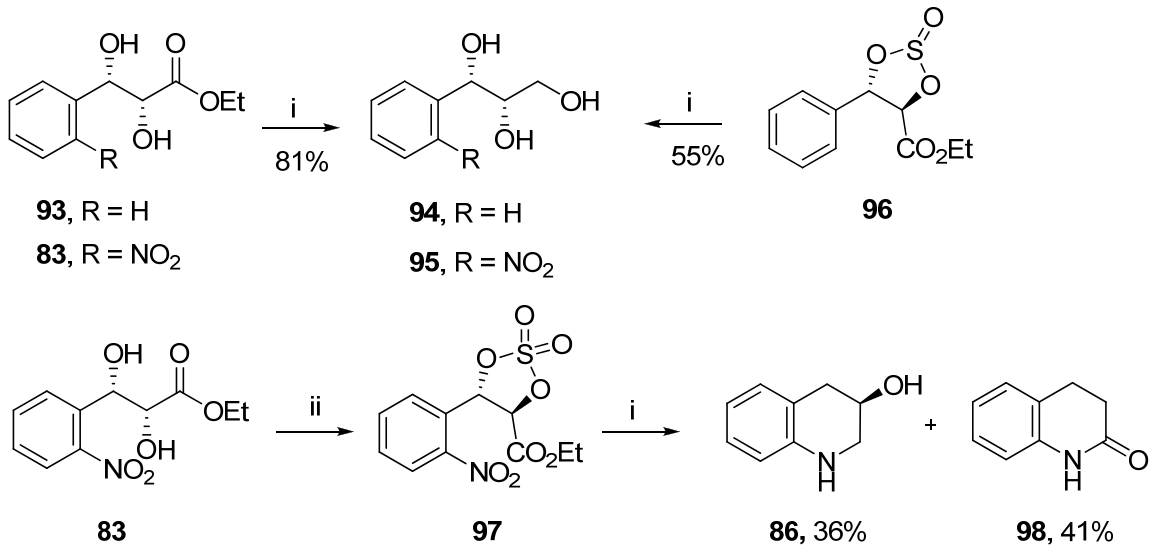


Fig. 11: ^{1}H NMR spectrum of Mosher's ester of **86**

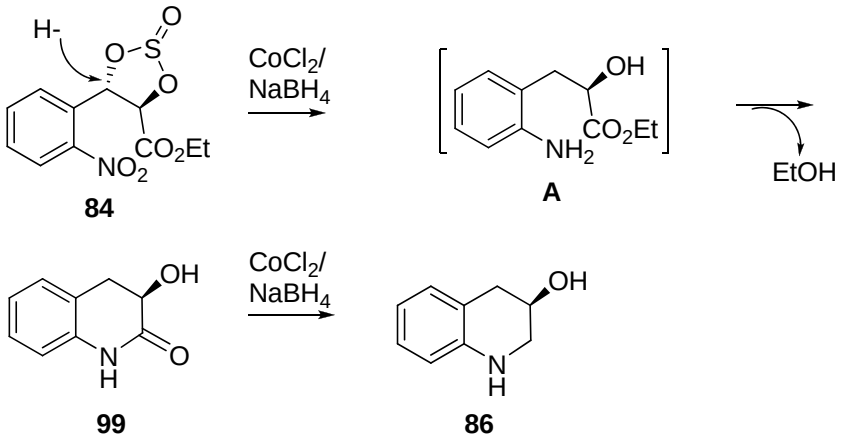
Mechanism:

To have a better understanding of the reaction mechanism, we have subjected diols **93** and **83** to Co-catalyzed reduction that proceeded to give high yields of the corresponding triols **94** and **95** respectively (**Scheme 25**).



Scheme 25: (i) $CoCl_2.6H_2O$ (1 mol%), $NaBH_4$ (4 equiv.), EtOH, 0-25 °C, 12 h; (ii) (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 30 min; (b) $RuCl_3.H_2O$ (cat), $NaIO_4$, $CH_3CN:CCl_4:H_2O$ (1:1:1), 1 h, 88%.

Also, when nitro cyclic sulfate **97**, obtained from **83** in two steps, was subjected to reduction, a mixture of **86** (36%) and **98** (41%) was obtained. However, cyclic sulfite **96**, under the reduction condition, gave only triol **94** in 55% yield. This indicates that both nitro and cyclic sulfite moieties are required in the Co-catalyzed reductions of **84** and **91a-e**. Thus, we believe that simultaneous reduction of both nitro and cyclic sulfite groups takes place to give the unstable species **A**, which underwent cyclization to afford hydroxylactam **99**. Compound **99** was indeed isolated and characterized when the reaction was terminated before completion.



Scheme 26: Mechanistic Pathway for the Co-catalyzed Reduction of Nitro Cyclic Sulfite

The ^{1}H NMR spectrum of hydroxyl amide **99** showed two typical signals at δ 2.85-3.15 (m, 2H)) and 4.24 (dd, *J* = 2.3 Hz, 1H) due to methylene (-C**H**$_2$CHOH-) and methine protons (-CH$_2$C**H**OH-) respectively (**Fig. 12**). Finally, the reduction of the lactam carbonyl in **99**, assisted by the α-hydroxyl group, resulted in the formation of THQs (**86** & **92a-e**) (**Scheme 26**).

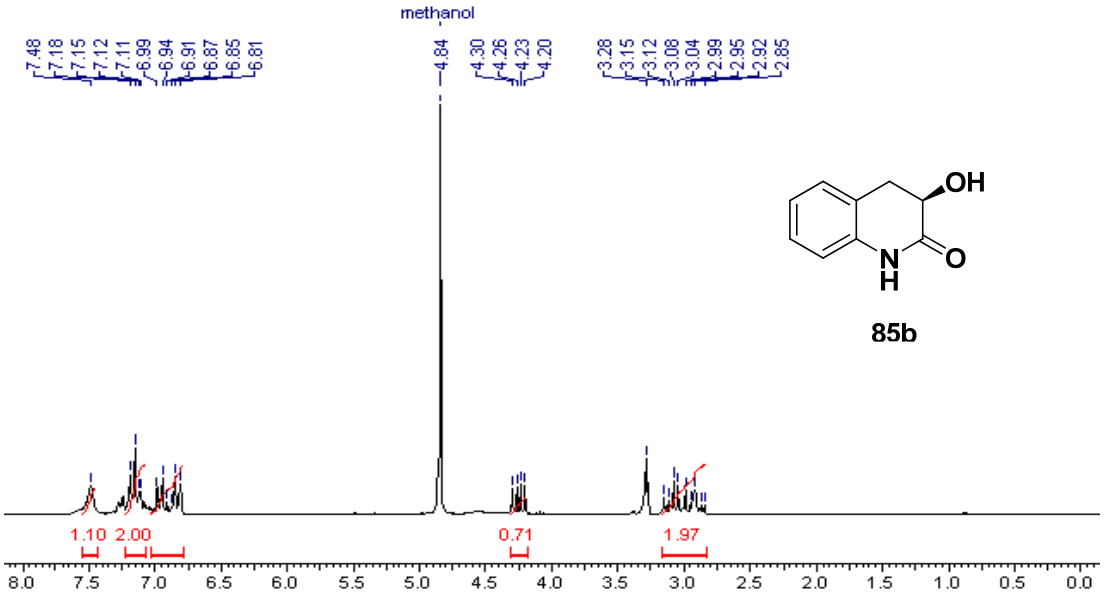


Fig. 12: ^{1}H NMR spectrum of hydroxy amide **85b**

2.1.4 Conclusion

In conclusion, we have developed a simple methodology involving a single-step multifunctional reduction of cyclic sulfites **84** & **90a-e,** which gave the corresponding 3-hydroxytetrahydroquinolines **86** & **91a-e** in high yields. Use of inexpensive, yet powerful reducing agent $NaBH_4$ in combination with catalytic amount of $CoCl_2$ makes our synthesis more attractive. This method has been found very effective in the asymmetric synthesis of several bioactive compounds having tetrahydrquinoline core.

2.1.5 Experimental Section:

Typical experimental procedure for the preparation of (*E*)-ethyl 3-(2-nitrophenyl)acrylate (82)

To a stirred solution of 2-nitrobenzaldehyde (7.55 g, 50 mmol) in benzene (100 mL), $Ph_3P{=}CHCO_2Et$ (19.25 g, 55 mmol) was added. It was then refluxed for 4 h under N_2 atmosphere. After the completion of reaction, benzene was distilled out to give the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petrolium ether: Ethyl acetate (90:10) as eluent] afforded nitro cinnamate **82** (10.5 g). **Yield:** 95%**,** gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 857, 974, 1037, 1095, 1184, 1202, 1216, 1251, 1275, 1291, 1319, 1347, 1368, 1393, 1444, 1477, 1573, 1607, 1640, 1716, 2984, 3023, 3415; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.3 Hz, 3H), 4.29 (q, *J* = 7.3 Hz, 2H), 6.35 (d, *J* = 16 Hz, 1H), 7.50 – 7.66 (m, 3H), 8.02 (d, *J* = 8 Hz, 1H), 8.10 (d, *J* = 16 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 60.7, 123.3, 124.8, 129.0, 130.1, 133.3, 139.7, 148.3, 165.4; **Analysis**: $C_{11}H_{11}NO_2$ requires C 59.63, H 5.01, N 6.33, found C 59.50, H 4.91, N 6.34%.

Typical experimental procedure for the preparation of (2*R*,3*S*)-ethyl 2,3-dihydroxy-3-(2-nitrophenyl)propanoate (83)

To a stirred solution of $K_3Fe(CN)_6$ (39.48 g, 120 mmol), K_2CO_3 (16.56 g, 120 mmol), and $MeSO_2NH_2$ (3.8 g, 40 mmol) in *tert*-BuOH (200 mL) and H_2O (200 mL), $(DHQ)_2$-PHAL (354 mg, 1 mol%) and K_2OsO_4 (19 mg, 0.2 mol%) were added and stirred for 30 min. Then, (*E*)-ethyl 3-(2-nitrophenyl)acrylate **(82)** (8.84g, 40 mmol) was added to the reaction mixture and allowed to stir for 24 h at 25 ºC. After completion of the reaction, sodium bisulfite (10 g) was added slowly at 0 ºC. The organic layer was separated and aqueous layer extracted with ethyl acetate (3 x 300 ml); the combined organic layers were washed with brine (2 x 400 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification using silica gel (230-400 mesh) and petroleum ether: ethyl acetate (60:40) as an eluent afforded pure **83** (8.37g).

Yield: 82%; $[\alpha]^{D}_{25}$ +126.0 (*c* 1, $CHCl_3$); yellow solid, **mp**: 86 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 668, 757, 860, 1055, 1108, 1216, 1263, 1347, 1527, 1733, 3020, 3485; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 8.0 Hz, 3H), 3.22 (bs, 1H), 3.38 (bs, 1H), 4.30 (q, *J* = 8.0 Hz, 2H), 4.48 (d, *J* = 2.1 Hz, 1H), 5.67 (d, *J* = 2.1 Hz, 1H), 7.46 (t, *J* = 6 Hz, 1H,), 7.67 (t, *J* = 6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 62.3, 69.7, 73.4, 124.3, 128.4, 129.7, 133.2, 136.2, 147.6, 172.6; **Analysis** for $C_{11}H_{13}NO_6$ requires C 51.77, H 5.13, N 5.49; found C 51.65, H 5.33, N 5.54%.

Typical experimental procedure for the preparation of nitro cyclic sulfite (84)

To a stirred solution of diol **83** (2.55g, 10 mmol) and triethylamine (4.2 ml, 30 mmol) in CH_2Cl_2 (50 mL) at 0 ºC, freshly distilled $SOCl_2$ (1.0 ml, 12 mmol) was added drop-wise under nitrogen atmosphere. It was further stirred at 0 ºC for 30 min (progress of the

reaction was monitored by TLC). The reaction mixture was quenched by the addition of cold water (20 mL) and a saturated solution of aq. $NaHCO_3$ (20 ml). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extract was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification using silica gel (230-400 mesh) and petroleum ether: ethyl acetate (70:30) as an eluent afforded pure **84.**

Yield: 95%; Gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 757, 962, 1045, 1217, 1350, 1531, 1610,1747, 2985, 3022, 3519; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.97 (d, *J* = 4.7 Hz, 1H), 6.93 (d, *J* = 4.7 Hz, 1H), 7.57-7.80 (m, 3H), 8.13-8.18 (dd, *J* = 1.2, 7.9 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.8, 62.7, 83.1, 83.2, 124.9, 129.9, 130.9, 131.1, 134.5, 147.6, 165.7.

Typical experimental procedure for the preparation (*R*)-1,2,3,4-tetrahydroquinolin-3-ol (86)

To a stirred solution of nitro cyclic sulfite **84** (10 mmol) and $CoCl_2 \cdot 6H_2O$ (23.8 mg, 1 mol %) in 95% ethanol (30 mL), $NaBH_4$ (24 mmol) was added at 0 ºC and the reaction mixture was allowed to stir for 12 h at 25 ºC. After the completion of reaction, it was poured into ice cold water that formed black precipitate. To the aqueous layer, ethyl acetate (100 mL) was added and combined mixture was passed through celite. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 50mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product using silica gel (230-400 mesh) and petroleum ether: ethyl acetate: Et_3N (60: 40:2) gave pure **86** (1.22g).

Yield: 82%; gum, $[\alpha]^{D}_{25}$ +11.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 756, 850, 1155, 1215, 1253, 1278, 1371, 1496, 1608, 1735, 2935, 2983, 3018, 3446; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.73-2.83 (dd, *J* = 3.5, 16.8 Hz, 1H), 2.99-3.09 (dd, *J* = 3.5, 16.8 Hz, 1H), 3.19-3.36 (m, 2H), 4.19-4.27 (m, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 6.67 (dt, *J* = 1.1, 7.5 Hz, 1H), 6.95-7.02 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 35.3, 47.6, 63.2, 114.1, 118.0, 118.6, 126.9, 130.4, 143.5; **Analysis** for $C_9H_{11}NO$ requires C, 72.46; H, 7.43; N, 9.39; found C, 72.22; H, 7.21; N, 9.49%.

General experimental procedure for the preparation of (2*R*,3*S*)-ethyl 2,3-dihydroxy-3-(3,4-dialkyloxyphenyl)propanoate (88a-e)

A 500 mL RB flask was charged with $K_3Fe(CN)_6$ (45 mmol), K_2CO_3 (45 mmol), $MeSO_2NH_2$ (15 mmol), *tert*-BuOH (75 mL) and H_2O (75 mL). This combined reaction mixture was stirred for 10 min and $(DHQ)_2$-PHAL (1 mol%) and K_2OsO_4 (0.2 mol%) were added and stirred for additional 30 min. To the reaction mixture **87a-e** unsaturated esters were added separately was added and allowed to stir for 24 h at 25 ºC. After completion of reaction, sodium bisulfite (5 g) was added slowly at 0 ºC. Organic layer was separated and aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with brine (200 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield the crude products, Flash column chromatographic purification [silica gel (230-400 mesh) and petroleum ether : EtOAc (60:40) as an eluent] afforded diols **88a-e** in pure form.

(2*R*,3*S*)-Ethyl 2,3-dihydroxy-3-(3,4-dimethoxyphenyl)propanoate (88a)

Yield: 95%; colorless solid; **mp:** 78 ºC; $[\alpha]^{D}_{25}$ +3.533 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 848, 939, 1047, 1240, 1373, 1446, 1517, 1737, 2983, 3500; **^{1}H-NMR** (200 MHz,

$CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.35 (d, *J* = 3.1 Hz, 1H), 4.95 (d, *J* = 3.1 Hz, 1H), 6.84-6.98 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.8, 55.6, 55.7, 61.7, 74.2, 74.8, 109.4, 110.6, 118.4, 132.4, 148.4, 148.6, 172.6; **Analysis** for $C_{13}H_{18}O_6$ requires C, 57.77; H, 6.71; found C, 57.47; H, 6.63%.

(2*R*,3*S*)-Ethyl 3-(benzo[*d*][1,3]dioxol-6-yl)-2,3-dihydroxypropanoate (88b)

Yield: 92%; colorless solid; **mp:** 62 ºC; $[\alpha]^{D}_{25}$ +1.5 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 846, 937, 1047, 1244, 1373, 1246, 1745, 2983, 3519; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.1 Hz, 3H), 2.91 (bs, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 3.1 Hz, 1H), 4.89 (d, *J* = 3.1 Hz, 1H), 5.94 (s, 2H), 6.77 (d, *J* = 8.0 Hz , 1H), 6.82-6.87 (dd, *J* =1.5, 8.0 Hz, 1H), 6.92 (d, *J* = 1.5 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 61.8, 74.32, 74.9, 100.9, 106.9, 107.8, 119.6, 133.8, 147.1, 147.5, 172.5; **Analysis** for $C_{12}H_{14}O_6$ requires C, 56.69; H, 5.55; found C, 56.73; H, 5.53%.

(2*R*,3*S*)-Ethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-2,3-dihydroxypropanoate (88c)

Yield: 80%; colorless solid; **mp:** 77 ºC; $[\alpha]^{D}_{25}$ + 1.2 (*c* 1, $CHCl_3$): **IR** ($CHCl_3$, cm^{-1}): υ_{max} 846, 837, 1049, 1244, 1361, 1479, 1751, 2985, 3519; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.2 Hz, 3H), 3.48 (bs, 2H), 3.84 (s, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.27 (d, *J* = 3.4 Hz, 1H), 4.87 (d, *J* = 3.4 Hz, 1H), 5.10 (s, 2H), 6.81 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 7.26-7.43 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.8, 55.7, 61.7, 70.7, 74.7, 74.8, 110.0, 113.4, 118.4, 127.0, 127.6, 128.3, 132.9, 136.8, 147.5, 147.3, 172.5; **Analysis** for $C_{19}H_{22}O_6$ requires C, 65.88; H, 6.40; found , 65.84; H, 6.37%.

(2*R*,3*S*)-Ethyl 3-(3,4-bis(benzyloxy)phenyl)-2,3-dihydroxypropanoate (88d)

Yield: 85%; colorless solid; **mp:** 101 ºC; $[\alpha]^{D}_{25}$ +0.84 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 848, 1045, 1245, 1373, 1514, 1593, 1745, 2981, 3465; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.1 Hz, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.25 (d, *J* = 2.9 Hz, 1H), 4.82 (d, *J* = 2.9 Hz, 1H), 5.14 (s, 2H), 5.15 (s, 2H), 6.89 (m, 2H), 7.04 (m, 1H), 7.28-7.48 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 61.8, 71.1, 71.1, 74.2, 74.7, 113.3, 114.6, 119.3, 127.1, 127.3, 127.6, 127.6, 128.3, 133.2, 137.0, 137.1, 148.5, 148.7, 172.5; **Analysis** for $C_{25}H_{26}O_6$ requires C, 71.07; H, 6.20; found C, 71.01; H, 6.17%.

(2*R*,3*S*)-Ethyl-3-[4-(cyclopentyloxy)-3-methoxyphenyl]-2,3-dihydroxypropanoate (88e)

Yield: 81%; colorless solid; **mp:** 105 ºC; $[\alpha]^{D}_{25}$ +1.50 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 848, 1045, 1245, 1373, 1514, 1593, 1745, 2981, 3465; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.57-1.94 (m, 8H), 2.62 (bs, 1H), 3.07 (bs, 1H), 3.83 (s, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.74-4.81(m, 1H), 4.88 (d, *J* = 2.9 Hz, 1H), 6.80-6.98 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 23.9, 32.6, 55.8, 61.7, 74.3, 74.9, 80.1, 111.4, 113.2, 118.5, 132.3, 147.3, 149.59, 172.6; **Analysis** for $C_{17}H_{24}O_6$ requires C, 62.95; H, 7.46; found C, 62.90; H, 7.44%.

General experimental procedure for the preparation of (2*R*,3*S*)-ethyl 2,3-dihydroxy-3-(4,5-dialkyloxy-2-nitrophenyl) propanoate (**89a-e**)

To a stirred solution of diol **88a-e** (10 mmol) in CH_2Cl_2 (40 mL), conc. HNO_3 (2 mL) was added dropwise at 0 °C. Reaction mixture was stirred for 30 min and progress of the reaction was monitored by TLC. After completion of reaction, 50 mL of water was added. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were washed with brine (50 mL), dried over anhyd.

Na_2SO_4 and concentrated under reduced pressure to give the crude product which was purified by column chromatography [silica gel (230-400 mesh) and petroleum ether:EtOAc (60:40) as an eluent] to give pure **89a-e** in pure form.

(2*R*,3*S*)-Ethyl-2,3-dihydroxy-3-(4,5-dimethoxy-2-nitrophenyl)propanoate (89a)

Yield: 70%; yellow solid; **mp:** 131 ºC; $[\alpha]^{D}_{25}$ +105.23 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 787, 848, 937, 1049, 1240, 1371, 1747, 2985, 3460, 3640; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.1 Hz, 3H), 3.95 (s, 3H), 4.01 (s, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.51(d, *J* = 2.2 Hz, 1H), 5.85 (d, *J* = 2.2 Hz, 1H), 7.33 (s, 1H), 7.65 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.3, 55.1, 55.3, 60.1, 69.0, 72.7, 106.1, 111.0, 132.3, 138.3, 146.6, 152.1, 171.6; **Analysis** for $C_{13}H_{17}NO_8$ requires C, 49.52; H, 5.43; N, 4.44; found C, 49.65; H, 5.23; N, 4.55%.

(2*R*,3*S*)-Ethyl-2,3-dihydroxy-3-(5-nitrobenzo[*d*][1,3]dioxol-6-yl)propanoate (89b)

Yield: 81%; yellow solid; **mp:** 138 ºC; $[\alpha]^{D}_{25}$ +138.5 (*c*1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 786, 846, 937, 1049, 1240, 1373, 1747, 2985, 3463, 3643; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.46 (d, *J* = 2.3 Hz, 1H), 5.68 (d, *J* = 2.3 Hz, 1H), 6.11-6.14 (dd, *J* = 1.1, 4.4 Hz, 2H), 7.33 (s, 1H), 7.53 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.2, 60.0, 68.8, 72.7, 101.9, 103.3, 108.4, 134.8, 140.0, 145.9, 150.8, 171.3; **Analysis** for $C_{12}H_{13}NO_8$ requires C, 48.17; H, 4.38; N, 4.68; found C, 48.01; H, 4.23; N, 4.76%.

(2*R*,3*S*)-Ethyl-3-(4,5-bis(benzyloxy)-2-nitrophenyl)-2,3-dihydroxypropanoate (89c)

Yield: 73%, yellow solid; **mp:** 141 ºC; $[\alpha]^{D}_{25}$ +105.34 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 763, 1132, 1215, 1683, 3388; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.1 Hz, 3H), 2.84 (bs, 1H), 3.19 (bs, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.45 (d, *J* = 1.5 Hz, 1H), 5.21

(s, 2H), 5.28 (s, 2H), 5.78 (d, *J* = 1.5 Hz, 1H), 7.30-7.47 (m, 11H), 7.72 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$+ DMSO-d_6): δ 12.5, 58.9, 68.0, 68.9, 69.1, 71.9, 108.0, 112.7, 125.7, 126.0, 126.3, 126.4, 126.8, 131.9, 134.4, 134.6, 137.7, 145.1, 150.9, 170.6; **Analysis** for $C_{25}H_{25}NO_8$ requires C, 64.23; H, 5.39; N, 3.00; found C, 64.02; H, 5.49; N, 2.87%.

(2*R*,3*S*)-Ethyl-3-(4-(benzyloxy)-5-methoxy-2-nitrophenyl)-2,3-dihydroxypropanoate (89d)

Yield: 75%; yellow solid; **mp:** 138 ºC; $[\alpha]^{D}_{25}$ +102.25 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1215, 1620, 2780, 3400; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3H), 1.65 (bs, 1H), 2.97 (bs, 1H), 4.00 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.49 (d, *J* = 3.4 Hz, 1H), 5.20 (s, 2H), 5.83 (d, *J* = 3.4 Hz, 1H), 7.32 (s, 1H), 7.35-7.48 (m, 5H), 7.70 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 55.9, 61.0, 69.5, 70.6, 73.2, 108.9, 111.4, 127.0, 127.7, 128.1, 132.8, 135.3, 138.7; **Analysis** for $C_{19}H_{21}NO_8$ requires C, 58.31; H, 5.41; N, 3.58; found C, 58.16; H, 5.28; N, 3.51%.

(2*R*,3*S*)-Ethyl-3-(4-(cyclopentyloxy)-5-methoxy-2-nitrophenyl)-2,3-dihydroxy-propanoate (81e)

Yield: 81%; yellow solid; **mp:** 142 ºC; $[\alpha]^{D}_{25}$ +99.72 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 757, 1215, 1620, 3465; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.1 Hz, 3H), 1.58-2.08 (m, 10H), 3.91 (s, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.47 (d, *J* = 2.1 Hz, 1H), 4.87-4.99 (m, 1H), 5.81 (d, *J* = 2.1 Hz, 1H), 7.28 (s, 1H), 7.62 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$+ DMSO-d_6): δ 13.3, 23.0, 31.6, 31.7, 55.1, 60.2, 69.0, 72.8, 79.7, 106.5, 113.1, 132.0, 137.8, 147.3, 151.1, 171.7; **Analysis** for $C_{17}H_{23}NO_8$ requires C, 55.28; H, 6.28; N, 3.79; found C, 55.12; H, 6.13; N, 3.83%.

General experimental procedure for the preparation of nitro cyclic sulfite (90a-e)

To a stirred solution of nitro diol **89a-e** (6.0 mmol) and triethylamine (3.00 ml, 18 mmol) in CH_2Cl_2 (20 mL), was added freshly distilled thionyl chloride (0.5 ml, 7 mmol) drop-wise under nitrogen atmosphere at 0 ºC and allowed to stir at 0 ºC for 30-45 min (monitored by TLC). The reaction mixture was quenched by the addition of cold water (20 mL) and a saturated solution of $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with brine and 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 petroleum ether:EtOAc (70:30) as an eluent] to give pure **90a-e** in pure form.

Nitro cyclic sulfite (90a)

Yield: 92%; Gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 648, 771, 914, 1066, 1278, 1340, 1525, 1585,1748, 2976, 3028; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3H), 3.09 (s, 6H), 4.30-3.41 (q, *J* = 7.2 Hz, 2H), 6.12 (d, *J* = 5.9 Hz, 1H), 6.50 (d, *J* = 5.9 Hz, 1H), 7.28 (s, 1H), 7.68 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.5, 56.0, 56.2, 62.5, 83.5, 105.9, 109.6, 125.9, 139.3, 148.6, 153.7, 166.1; **Analysis** for $C_{13}H_{15}NO_9S$ requires C, 43.21; H, 4.18; N, 3.88; found C, 43.14; H, 4.09; N, 3.81%.

Nitro cyclic sulfite (90b)

Yield: 97%; Gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 737, 1062, 1211, 1281, 1336, 1522, 1578,1749, 2979, 3011; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3H), 4.27-4.38 (q, *J* = 7.2 Hz, 2H), 5.23 (s, 4H), 6.44 (d, *J* = 5.8 Hz, 1H), 7.33-7.47 (m, 10H), 7.60 (s, 1H), 7.75 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.8, 62.9, 71.0, 71.2, 83.6, 83.8,

110.4, 113.3, 126.2, 127.2, 127.6, 128.3, 128.5, 135.2, 135.4, 139.6, 148.3, 153.7, 166.2; **Analysis** for $C_{12}H_{11}NO_9S$ requires C, 41.74; H, 3.21; N, 4.06; found C, 41.68; H, 3.14; N, 3.98%.

Nitro cyclic sulfite (90c)

Yield: 91%; Gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 630, 733, 1043 1217, 1324, 1464, 1525, 1575, 1673,1748, 2983; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.2 Hz, 3H), 4.0 (s, 3H), 4.29-4.40 (q, *J* = 7.2 Hz, 2H), 5.14 (d, *J* = 5.8 Hz, 1H), 5.23 (s, 2H), 6.50 (d, *J* = 5.8 Hz, 1H), 7.36-7.44 (m, 5H), 7.56 (s, 1H), 7.75 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 56.4, 62.8, 71.0, 83.1, 109.5, 111.6, 126.4, 127.3, 128.2, 128.5, 135.1, 139.3, 147.8, 154.5, 166.2; **Analysis** for $C_{25}H_{23}NO_9S$ requires C, 58.47; H, 4.51; N, 2.73; found C, 58.39; H, 4.43; N, 2.66%.

Nitro cyclic sulfite (90d)

Yield: 92%; Gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 662, 756, 947, 1036, 1202, 1269, 1336, 1526, 1616,1752, 2917, 2981; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 5.10 (d, *J* = 6.8 Hz, 1H), 6.19 (d, *J* = 2.0 Hz, 2H), 6.40 (d, *J* = 6.2 Hz, 1H), 7.48 (s, 1H), 7.61 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 62.9, 82.9, 83.6, 103.5, 105.4, 108.9, 128.0, 142.0, 148.5, 153.0, 165.8; **Analysis** for $C_{19}H_{19}NO_9S$ requires C, 52.17; H, 4.38; N, 3.20; found C, 52.09; H, 4.29; N, 3.12%.

Nitro cyclic sulfite (90e)

Yield: 94%; Gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 659, 746, 975, 1068, 1215, 1370, 1575, 1674,1748, 2978, 3010; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3H), 1.66-2.13 (m, 8H), 3.44 (s, 3H), 4.30-4.40 (q, *J* = 7.2 Hz, 2H), 4.82-4.94 (m, 2H), 5.10 (d, *J* =

6.1 Hz, 1H), 6.49 (d, *J* = 6.1 Hz, 2H), 7.50 (s, 1H), 7.60 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.6, 23.7, 23.9, 32.3, 32.4, 55.9, 62.4, 81.2, 83.4, 83.6, 107.6, 112.9, 125.7, 138.8, 149.2, 152.9, 165.9; **Analysis** for $C_{17}H_{21}NO_9S$ requires C, 49.15; H, 5.10; N, 3.37; found C, 49.08; H, 5.01; N, 3.29%.

General experimental procedure for the preparation of (*R*)-1,2,3,4-tetrahydro-6,7-dialkyloxyquinolin-3-ol (91a-e)

To the stirred solution of nitro cyclic sulfite **90a-e** (6 mmol) and $CoCl_2 \cdot 6H_2O$ (1 mol %) in 95% ethanol (30 mL), $NaBH_4$ (24 mmol) was added at 0 ºC and allowed to stir for 12 h at 25 ºC. After completion of reaction, it was poured into ice cold water to form black precipitate. To the aqueous layer, 100 mL of ethyl acetate was added and combined mixture was passed through celite. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 50 mL). Combined organic layers were washed with brine (2 x 50 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product [flash silica gel (230-400 mesh) and petroleum ether:ethyl acetate:Et_3N (60: 38:2)] gave pure tetrahydroquinolin-3-ol (**91a-e**) .

(*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxyquinolin-3-ol (91a)

Yield: 78%; Gum; $[\alpha]^{D}_{25}$ +25.4 (*c* 1.26, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 769, 1215, 1423, 1647, 3456; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.63-2.73 (dd, *J* = 3.9, 16.5 Hz, 1H), 2.85 (bs, 2H), 2.92-3.02 (dd, *J* = 4.3, 16.5 Hz, 1H),3.19-3.29 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 4.15-4.23 (m, 1H), 6.12 (s, 1H), 6.50 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 34.2, 47.6, 55.5, 56.3, 63.3, 99.3, 110.1, 113.9, 137.2, 141.6, 148.0; **MS**: m/z (% rel. Intensity): 209 (M^+, 20), 194 (100), 176 (10), 166 (12), 148 (8), 133 (7), 120 (4), 103 (2), 91 (4);

Analysis for $C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.23; N, 6.69; found C, 63.09; H, 7.17; N, 6.61%.

(*R*)-5,6,7,8-Tetrahydro-[1,3]dioxolo[4,5-*g*]quinolin-7-ol (91b):

Yield: 81%; Gum, $[\alpha]^{D}_{25}$ +28.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 1045, 1247, 1456, 2985, 3450; **^{1}H-NMR (**200 MHz, $CDCl_3$): δ 2.18 (bs, 2H), 2.63-2.73 (dd, *J* = 3.5, 16.5 Hz, 1H), 2.92-3.03 (dd, *J* = 3.9, 16.5 Hz, 1H), 3.20-3.23 (dd, *J* = 1.4, 4.3 Hz, 2H), 4.17-4.25 (m, 1H), 5.82 (s, 2H), 6.15 (s, 1H), 6.48 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 35.1, 47.5, 63.1, 96.4, 100.1, 109.5, 110.1, 137.9, 139.9, 146.1; **Analysis** for $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25; found C, 62.11; H, 5.76; N, 7.21%.

(*R*)-6,7-Bis(benzyloxy)-1,2,3,4-tetrahydroquinolin-3-ol (91c)

Yield: 83%; Gum, $[\alpha]^{D}_{25}$ +30.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 767, 1217, 1504, 2927, 3016, 3402; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.74 (bs, 2H), 2.60-2.70 (dd, *J* = 3.4, 16.5 Hz, 1H), 2.89-2.99 (dd, *J* = 4.9, 16.5 Hz, 1H), 3.12-3.24 (m, 2H), 4.14-4.24 (m, 1H), 5.03 (s, 2H), 5.09 (s, 2H), 6.19 (s, 1H), 6.63 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 34.9, 47.5, 63.4, 71.2, 73.0, 102.2, 111.1, 119.3, 127.2, 127.5, 127.6, 127.6, 128.3, 128.4, 137.3, 138.4, 141.7, 148.7; **Analysis** for $C_{23}H_{23}NO_3$ requires C, 76.43; H, 6.41; N, 3.88; found C, 76.38; H, 6.37; N, 3.82%.

(*R*)-7-(Benzyloxy)-1,2,3,4-tetrahydro-6-methoxyquinolin-3-ol (91d)

Yield: 85%; Gum, $[\alpha]^{D}_{25}$ +25.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 1217, 1404, 2927, 3405; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.64 (dd, *J* = 3.8, 16.5 Hz, 1H), 2.92-3.02 (dd, *J* = 4.2, 16.5 Hz, 1H), 3.17-3.18 (d, *J* = 3.0 Hz, 2H), 3.80 (s,3H), 4.16-4.24 (m, 1H), 5.07 (s, 2H), 6.13 (s, 1H), 6.56 (s, 1H), 7.30-7.44 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 34.7, 47.4, 56.7, 63.2, 70.2, 101.8, 110.8, 114.9, 126.9, 127.4, 128.2, 137.3, 142.3,

147.3; **Analysis** for $C_{17}H_{19}NO_3$ requires C, 71.56; H, 6.71; N, 4.91; found C, 71.52; H, 6.75; N, 4.88%.

(*R*)-7-(Cyclopentyloxy)-1,2,3,4-tetrahydro-6-methoxyquinolin-3-ol (91e):

Yield: 82%; Gum; $[\alpha]^{D}_{25}$ +22.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 767, 1217, 1504, 2927, 3016, 3402; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.55-1.83 (m, 8H), 2.62-2.72 (dd, *J* = 4.1, 16.5 Hz, 1H), 2.91-3.01 (dd, *J* = 3.7, 16.5 Hz, 1H), 3.21-3.23 (d, *J* = 3.7 Hz, 2H), 3.76 (s, 3H), 4.16-4.23 (m, 1H), 4.54-4.65 (m, 1H), 6.11 (s, 1H), 6.52 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.5, 32.3, 34.6, 47.6, 55.5, 63.2, 81.4, 99.7, 110.3, 119.1, 137.7, 139.7, 149.5; **Analysis** for $C_{15}H_{21}NO_3$ requires C, 68.42; H, 8.04; N, 5.32; found C, 68.38; H, 8.01; N, 5.37%.

General experimental procedure for the preparation of amido alcohol (92a-e)

To the stirred solution of tetrahydroquinolin-3-ol (**91a-e**) (4 mmol) and Et_3N (1.4 mL, 10 mmol) in 20 mL of CH_2Cl_2, propionic anhydride (6.5 mL, 5 mmol) was added at 25 ºC. Reaction mixture was stirred for 3 h. Progress of reaction was monitored by TLC and after completion of reaction, saturated aq. $NaHCO_3$ (30 mL) was added. Organic layer was separated; aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products. Chromatographic purification [silica gel (230-400 mesh) and petroleum ether:ethyl acetate: (60: 40:)] gave amide **92a-e** in pure form.

1-[(*R*)-3,4-Dihydro-3-hydroxy-6,7-dimethoxyquinolin-1(2H)-yl]propan-1-one (92a)

Yield: 82%; Gum; $[\alpha]^{D}_{25}$ +8.69 (*c* 1.15, $CHCl_3$); Chiral Column: Cromasil 5-CelluCoat column, Length 250 mm, i.d. 4.6 mm, wavelength: 220 nm, flow rate 0.8 mL per min.

Mobile phase10% IPA in hexane. Retention time 27.608 (97.7%) and 30.850 (2.2%). ee = 95.5%; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 846, 937, 1240, 1388, 1514, 1660, 1751, 2983, 3529; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.56 (q, *J* = 7.3 Hz, 2H), 2.67-2.78 (dd, *J* = 4.6, 16.5 Hz, 1H), 2.98-3.09 (dd, *J* = 5.4, 16.5 Hz, 1H), 3.86 (s, 6H), 3.74-3.95 (m, 2H), 4.32 (m, 1H), 6.63 (bs, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 8.6, 27.4, 35.0, 49.7, 55.6, 65.0, 108.0, 111.1, 122.4, 130.7, 146.3, 174.3; **MS: MS**: m/z (% rel. Intensity): 265 (M^+, 20), 209 (100), 194 (14), 176 (18), 166 (10), 148 (10), 133(8), 120 (6), 104 (8), 91 (8), 77 (6), 57 (4); **Analysis** for $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28; found C, 63.43; H, 7.19; N, 5.22%.

1-[(*R*)-7,8-Dihydro-7-hydroxy-[1,3]dioxolo[4,5-g]quinolin-5(6H)-yl]propan-1-one (92b)

Yield: 85%; Gum; $[\alpha]^{D}_{25}$ +12.7 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 847, 1242, 1515, 1650, 1753, 2983, 3530; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.11 (t, *J* = 7.3 Hz, 3H), 2.30 (q, *J* = 7.3 Hz, 2H), 2.66-2.77 (dd, *J* = 4.6, 16.6 Hz, 1H), 2.92-3.02 (dd, *J* = 6.4, 15.6 Hz, 1H), 3.75-4.09 (m, 2H), 5.24 (m, 1H), 5.96 (s, 2H), 6.60 (s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 8.9, 27.3, 35.5, 49.1, 65.9, 98.0, 108.2, 111.5, 122.1, 131.7, 145.2, 174.1; **Analysis** $C_{13}H_{15}NO_4$ requires C, 62.64; H, 6.07; N, 5.62; found C, 62.61; H, 6.01; N, 5.55%.

1-[(*R*)-6,7-Bis(benzyloxy)-3,4-dihydro-3-hydroxyquinolin-1(2H)-yl]propan-1-one (92c)

Yield: 77%; Gum; $[\alpha]^{D}_{25}$ +15.1 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 847, 1242, 1515, 1650, 1753, 2983, 3530; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.3 Hz, 3H), 2,18 (bs, 1H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.58-2.69 (dd, *J* = 4.9, 16.4Hz, 1H), 2.87-3.00 (dd, *J* =

5.6, 16.5 Hz, 1H), 3.69-3.88 (m, 2H), 4.23 (m, 1H), 5.12 (s, 2H), 5.15 (s, 2H), 6.68 (bs, 2H), 7.30-7.45 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 9.5, 27.1, 35.1, 49.2, 65.8, 71.2, 73.0, 102.2, 111.1, 119.3, 127.2, 127.5, 127.6, 127.6, 128.3, 128.4, 137.3, 138.4, 141.7, 148.7, 173.2; **Analysis** for $C_{26}H_{27}NO_4$ requires C, 74.80; H, 6.52; N, 3.35; found C, 74.82; H, 6.57; N, 3.31%.

1-[(*R*)-6-(Cyclopentyloxy)-3,4-dihydro-3-hydroxy-7-methoxyquinolin-1(2H)-yl]propan-1-one (92e)

Yield: 73%; Gum; $[\alpha]^{D}_{25}$ +15.1 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 849, 1243, 1515, 1650, 1753, 2983, 3530; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.4 Hz, 3H), 1.17-1.88 (m, 8H), 2.54 (q, *J* = 7.4 Hz, 2H), 2.64-2.74 (dd, *J* = 5.0, 16.3 Hz, 1H), 2.95-3.06 (dd, *J* = 5.3, 16.6 Hz, 1H), 3.81 (s, 3H), 3.72-3.90 (m, 2H), 4.27 (m, 1H), 4.73 (m, 1H), 6.60 (bs, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 10.1, 23.5, 27.5, 32.1, 35.1, 47.1, 55.4, 63.1, 81.3, 99.8, 110.1, 119.5, 137.4, 139.2, 149.5; 172.9; **Analysis** for $C_{18}H_{25}NO_4$ requires C, 67.69; H, 7.89; N, 4.39; found C, 67.62; H, 7.82; N, 4.32%.

General experimental procedure for the preparation of Mosher's ester (100b-e)

To the stirred solution of alcohol (0.1 mmol), *N,N′*-Dicyclohexylcarbodiimide (DCC) (41 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) Mosher's acid (26 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added at 0 ºC and allowed to stir for 12 h at 25 °C. After the completion of reaction (monitored by TLC), solvent was distilled under reduced pressure and crude product was purified by column chromatography to give pure **100b-e**.

(2*R*)-(*R*)-5,6,7,8-Tetrahydro-5-propionyl-[1,3]dioxolo[4,5-g]quinolin-7-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (100b)

Yield: 35 mg, 75%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.09 (t, *J* = 7.3 Hz, 3H), 2.41 (q, *J* = 7.3 Hz, 2H), 2.68-2.70 (dd, *J* = 5.0, 16.3 Hz, 1H), 2.92-3.02 (dd, *J* = 5.3, 16.6 Hz, 1H), 3.48 (s, 3H), 3.88-4.10 (m, 2H), 5.49 (m, 1H), 5.94 (s, 2H), 6.52 (s, 1H), 6.60 (s, 1H), 7.35-7.46 (m, 5H).

(2*R*)-(*R*)-6,7-Bis(benzyloxy)-1,2,3,4-tetrahydro-1-propionylquinolin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (100c)

Yield: 42 mg, 66%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.3 Hz, 3H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.58-2.69 (dd, *J* = 4.9, 16.4 Hz, 1H), 2.87-3.00 (dd, *J* = 5.6, 16.5 Hz, 1H), 3.47 (s, 2.90 H), 3.54 (s, 0.1H) 3.69-3.88 (m, 2H), 3.97 (m, 1H), 5.12 (s, 2H), 5.15 (s, 2H), 6.68 (bs, 2H), 7.30-7.45 (m, 10H).

(2*R*)-(*R)*-6-(Cyclopentyloxy)-1,2,3,4-tetrahydro-7-methoxy-1-propionylquinolin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (100e)

Yield: 39 mg, 73%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.3 Hz, 3H), 1.60-1.94 (m, 8H), 2.42 (q, *J* = 7.3 Hz, 2H), 2.90-2.94 (dd, *J* = 3.9, 16.5 Hz, 1H), 3.07 (m, 1H), 3.43 (s, 2.91H), 3.47 (s, 0.09H), 3.81 (s, 3H), 4.11 (m, 1H), 4.70 (m, 1H), 5.46 (s, 1H), 6.66 (s, 1H), 7.34-7.46 (m, 5H).

(1*S*, 2*S*)-1-phenylpropane-1,2,3-triol (94)

Yield: 55%; IR ($CHCl_3$, cm^{-1}): υ_{max} 695, 1125, 1220, 1511, 2983, 3518; **^{1}H-NMR** (200 MHz, $CDCl_3$, D_2O): δ 3.48-5.01 (m, 4H), 7.3-7.50 (m, 5H); **^{13}C-NMR (**50 MHz, $CDCl_3$): δ 63.11, 65.19, 75.78, 127.62, 128.05, 128.13, 128.54, 128.66, 140.58.

1-(2-Nitrophenyl)propane-1,2,3-triol (95)

Yield: 81%; IR ($CHCl_3$, cm^{-1}): υ_{max} 895, 1243, 1518, 1628, 2983, 3480; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.25 (br s, 2H), 1.69 (bs, 1H), 3.84 (d, *J* = 3.9 Hz, 2H) 3.87-3.94 (m,

1H), 5.40 (d, *J* = 2.8 Hz, 1H), 7.42-7.50 (dt, *J* = 1.3, 7.2 Hz, 1H), 7.67 (dt, *J* = 1.0, 7.8 Hz, 1H), 7.84 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.98 (dd, *J* = 1.0, 8.0 Hz, 1H); **^{13}C-NMR(**50 MHz, $CDCl_3$): δ 64.9, 69.6, 73.8, 124.6, 128.4, 129.1, 133.4, 136.5, 148.6.

General experimental procedure for the preparation of cyclic sulfate (97)

A solution of nitro cyclic sulfite (**84**) was cooled with an ice-water bath and diluted with CH_3CN (8 mL) and CCl_4 (8 mL). $RuCl_3.H_2O$ (3.9 mg, 0.013 mmol) and $NaIO_4$ (1.6 g, 7.2 mmol) were added followed by water (8 mL). The resulting orange mixture was stirred at 25 ºC for 1 h. The mixture was then diluted with ether (15 mL) and the two phases separated. The organic layer was washed with water (10 mL), saturated aq. $NaHCO_3$ (10 mL), brine, dried over anhyd. Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **97** as a colorless liquid (0.6 g).

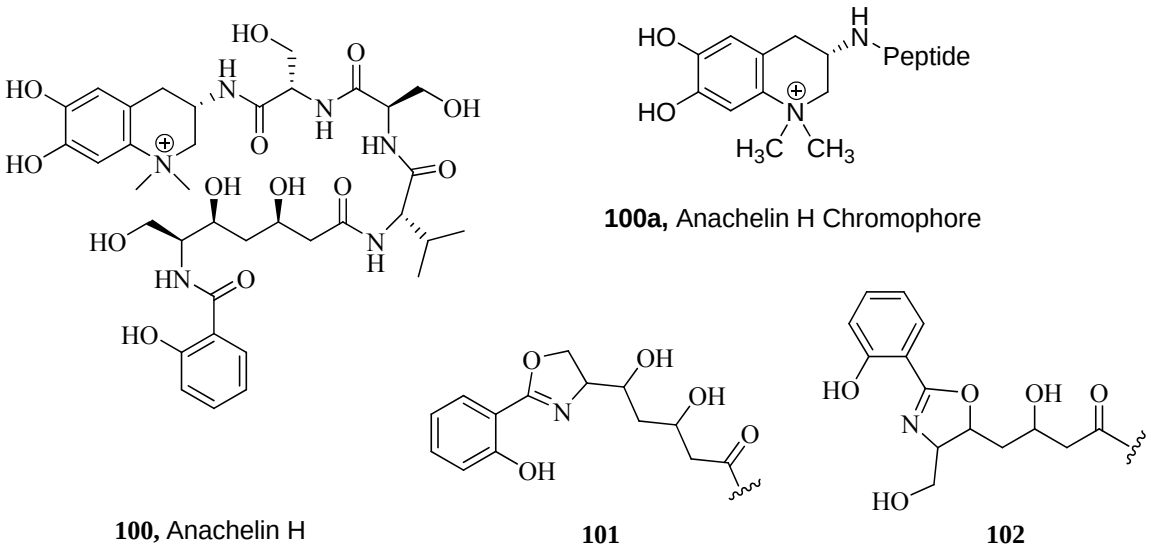
Yield: 88%; liquid, **IR** (neat, cm^{-1}): υ_{max} 713, 1204, 1261, 1529, 1628, 1678, 1740, 2938, 3015; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ1.37 (t, *J* = 6.6 Hz, 3H), 4.4 (q, *J* = 6.9 Hz, 2H), 5.15 (d, *J* = 4.8 Hz, 1H), 7.7 (t, *J* = 8.4, 1.76 Hz, 1H), 7.7 (t, *J* = 8.4 Hz, 1H), 7.88 (t, *J* = 7.4 Hz, 1H), 7.8 (d, *J* = 8.4 1H), 8.25 (d, *J* = 7.8 Hz); **^{13} C-NMR** (125 MHz, $CDCl_3$): δ 13.8, 63.6, 80.7, 82.3, 125.7, 128.16, 129.7, 131.05, 135.2, 146.5, 163.8; **Analysis:** $C_{11}H_{11}NO_8S$ requires: C, 41.64; H, 3.49; N, 4.41 found C, 41.42; H, 3.28; N, 4.37%.

Section II:

Asymmetric Formal Synthesis of Anachelin H Chromophore

2.2.1. Introduction:

Cyanobacteria (or blue-green algae) are considered to be among the oldest life forms still present on earth, populating this planet since 3.5 billion years.[47] These species are thought to have modified the atmosphere of earth by performing oxygenic photosynthesis.[48] The release of oxygen caused a dramatic threat for all life forms present, and those unable to cope became extinct. In addition, the oxidative atmosphere resulted in the conversion of soluble Fe(II) ions to Fe(III) salts, of which the dominant iron oxide hydrates are insoluble at physiological pH (poor bioavailability).[49] Therefore, iron acquisition became crucial for every organism, and many sophisticated strategies were developed by evolution. It is interesting to note that although cyanobacteria probably caused this shortage of iron by performing oxygenic photosynthesis,[50] little was known concerning their mechanism of iron uptake.



100, Anachelin H

100a, Anachelin H Chromophore

101

102

Fig. 13: Structures of anachelins **100-102**

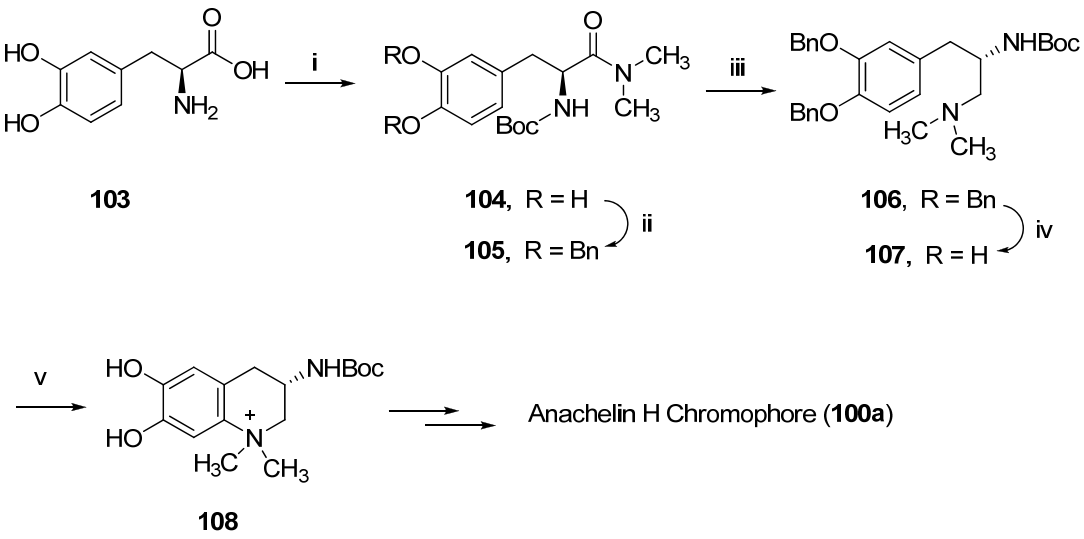
In particular, no complex siderophores, that is, small molecules secreted for iron binding, transport, and uptake, have been isolated from cyanobacteria until recently. In 2000, the first complex metabolites postulated to serve as siderophores from the freshwater bacterium *Anabaena cylindrica* were isolated: Budzikiewicz, Walsby, and co-workers[51a] have isolated mixtures of anachelin H (**100**) and anachelin-1 (**101**) and determined the constitution of the former. Later, Murakami and co-workers reported the isolation and constitution of anachelin-1 and anachelin-2 (**102**) together with two related esters (**Fig. 13**).[51] In these isolation reports, the absolute and relative configuration of four stereogenic centers could not be determined; however, tetrahydroquinolin-3-ol a common (anachelin H chromophore) moiety is present in anachelins (**100**-**102**).[52]

2.2.2 Review of literature

Literature search revealed that there is only one report available for the synthesis of Anachelin H chromophore (**100a**) which is described below.

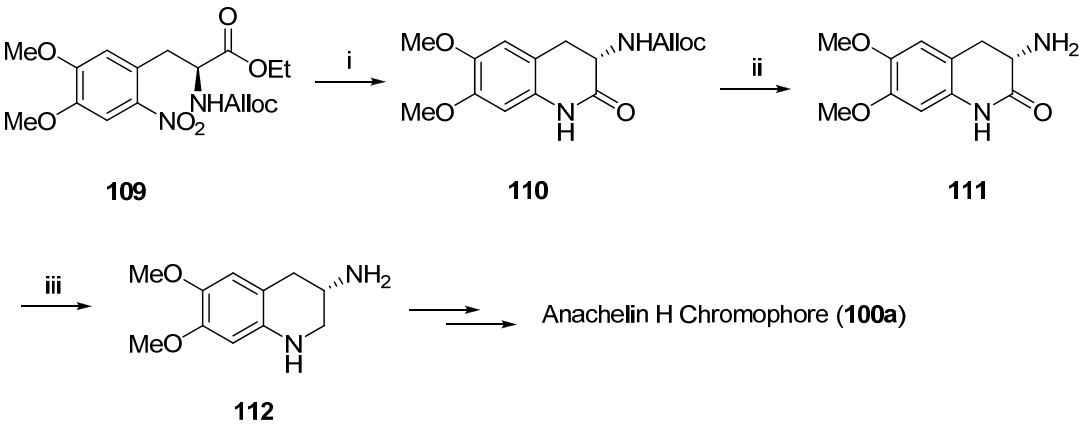
Gademann's approach (2004)[53]

Gademann *et al.* have described oxidative aza-annulation of amine **107** using dianisyltellurium oxide as the key step(**Scheme 27**). *N*-Boc-protection followed by amidation of amino acid **103** gave amide **104** in 61% yields. Further protection of phenol as its benzyl ether **105** and followed by its reduction (BH_3·THF) gave amine **106.** Deprotection of benzyl ether and subsequent oxidative cyclization with dianisyltellurium oxide provided the key intermediate **108** in the synthesis of Anachelin H chromophore (**100a**).



Scheme 27: (i) (a) Boc_2O, aq. NaOH, dioxane; (b) BuOCOCl, THF; (c) $HN(CH_3)_2$; (ii) Cs_2CO_3, BnBr, acetone, reflux; (iii) BH_3·THF; (16% over three steps); (iv) Pd/C (10%), H_2 (1 atm), MeOH, AcOH, 99%; (v) dianisyltellurium oxide, CH_2Cl_2, 69%.

The second approach has started from protected nitro-DOPA derivative **109**. The nitro group in **109** was reduced using iron powder in acetic acid to give the resulting lactam **110** in 90% yield. The Alloc group in lactam **110** was first removed using catalytic amount of Pd(0) to give the amino lactam **111**. The key intermediate, tetrahydroquinoline derivative **112,** was then obtained after subsequent reduction with BH_3.THF complex in 95% yield (**Scheme 28**).



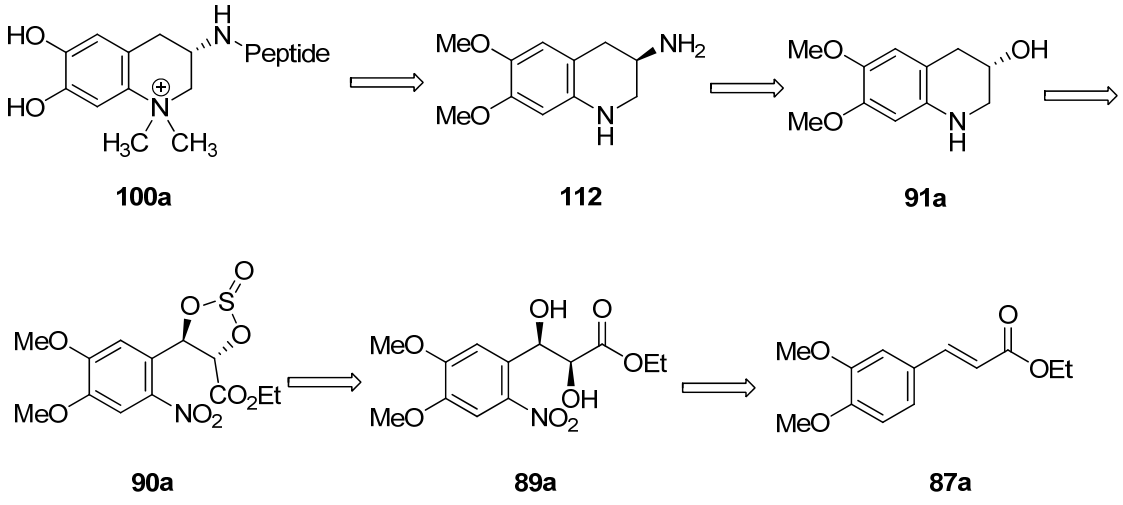
Scheme 28: (i) Fe (s), AcOH, 90%; (ii) $Pd(PPh_3)_4$, barbituric acid, 78%; (iii) BH_3·THF, THF, 95%.

2.2.3 Present work

2.2.3.1 Objective

Literature search reveals that only strategys relating to chiral pool approach is available for the synthesis of Anachelin H chromophore (**100a**). In section I of this Chapter, we have described a short and efficient synthesis of tetrahydroquinolin-3-ol (**91a**). In continuation of the work on Co-catalyzed reduction of nitro cyclic sulphite, a formal synthesis of Anachelin H chromophore (**100a**) is described in this section.

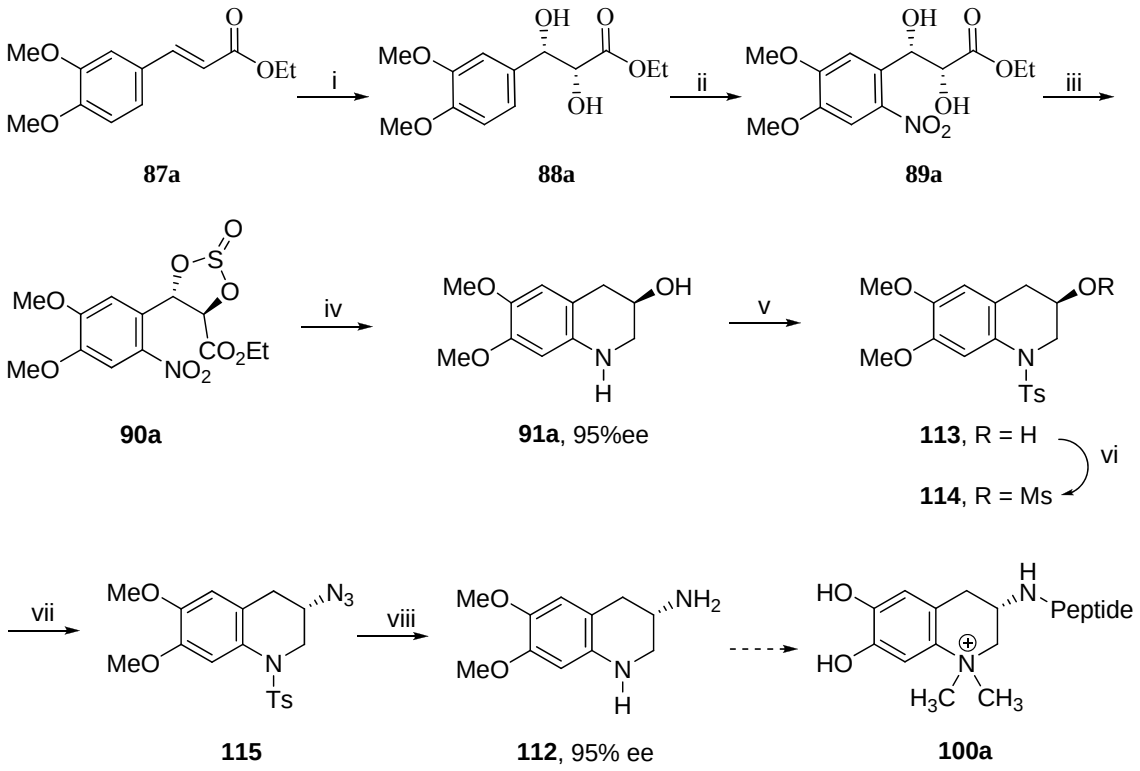
Retrosynthetic analysis of **100a** reveals that, diamine (**112**) turns out to be the key intermediate, which could be easily prepared from (*R*)- tetrahydroquinolin-3-ol (**91a**). We further visualized that amino alcohol **91a** could be prepared from Co-catalyzed reduction of the precursor nitro cyclic sulphite **90a**, which in turn could be obtained from nitro diol **89a**. Compound **89a** can be prepared from **87a** *via* nitration and asymmetric dihydroxylation (AD) (**Scheme 29**).



Scheme 29: Retrosynthetic analysis of Anachelin H chromophore (**100a**)

2.2.4 Results and Discussion

The present synthetic route employed for the synthesis of Anachelin H chromophore (**100a**) is shown in **Scheme 30**. *α,β*-Unsaturated ester **87a**, prepared from Wittig olefination of the corresponding benzaldehyde was converted to the corresponding diol **88a** in 95% yield *via* Os-catalyzed asymmetric dihydroxylation using $(DHQD)_2$-PHAL as the chiral ligand. Then, nitration of diol **88a** was carried out in biphasic medium (HNO_3, CH_2Cl_2) to obtain the corresponding nitro diol **89a** was formed in good yields with excellent regioselectivity. The diol **89a** which was readily transformed into the corresponding nitro cyclic sulfite **90a** ($SOCl_2$ and Et_3N in CH_2Cl_2) in 95% yield.



Scheme 30: (i) K_2OsO_4 (0.1 mol%), $(DHQ)_2$-PHAL (0.5 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (1 equiv.), *tert*-BuOH:H_2O (1:1), 25 °C, 24 h, 95%; (ii) conc. HNO_3, CH_2Cl_2, 0-25 °C, 30 min, 70%; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 30 min, 92%; (iv) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$ (4 equiv.), EtOH, 0-25 °C, 6 h, 78%; (v) TsCl, Et_3N, CH_2Cl_2, 25 °C, 82%; (vi) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min, 88%; (vii) NaN_3, DMF, 80 °C, 12 h, 91%; (viii) Na(Hg), NaH_2PO_4, MeOH, 25 °C, 76%.

Nitro cyclic sulfite **90a** was then subjected to one-pot reduction using $CoCl_2$ (1 mol%) and 4 equivalents of $NaBH_4$ to give tetrahydroquinolin-3-ol **91a,** in 81% yield. The formation of **91a** was confirmed by spectral data. The ^{1}H-NMR spectrum of **91a** showed typical signals at δ 2.63-2.73 (dd, *J* = 3.9, 16.5 Hz, 1H) and 2.92-3.02 (dd, *J* = 4.3, 16.5 Hz, 1H) corresponding to benzylic methylene protons. Also signals at δ 3.19-3.29 (m) and 4.15-4.23 (m) correspond to methylene (*N*-C**H**$_2$) and methine (C**H**OH) protons respectively. Its ^{13}C-NMR showed two methylene and one methine (**C**HOH) carbon signals at δ 34.7, 47.6 and 63.3 respectively (**Fig. 14**).

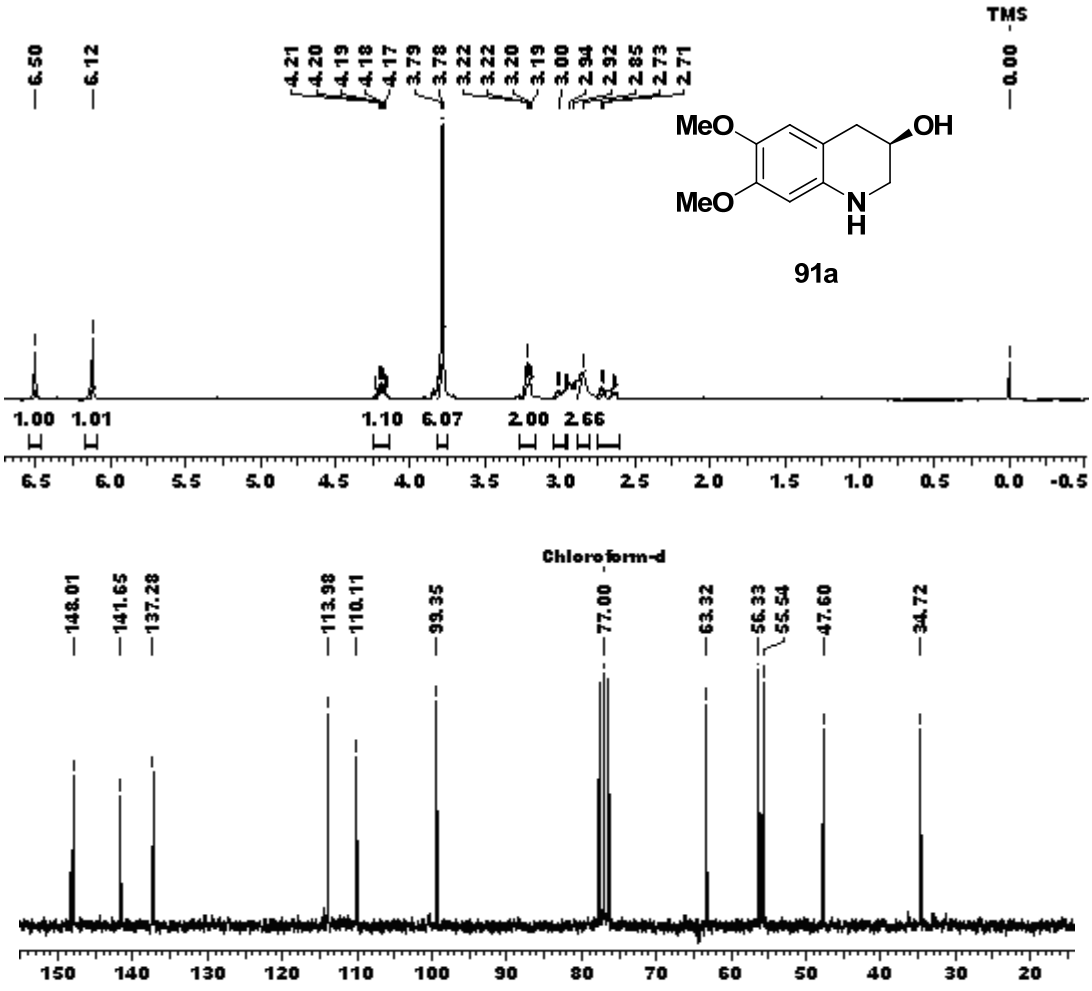
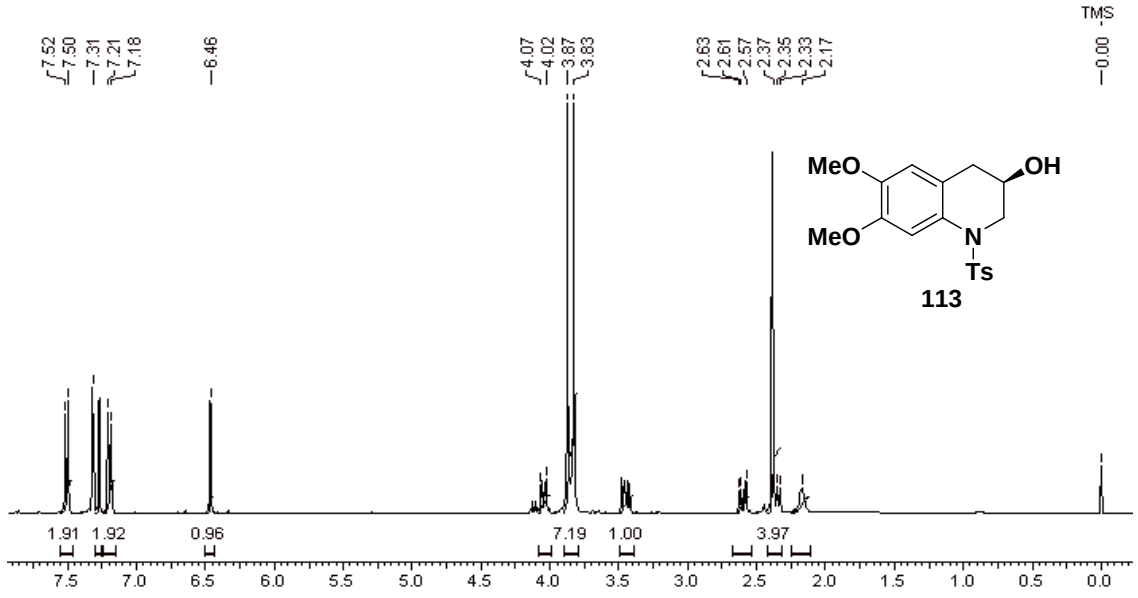


Fig. 14: ^{1}H and ^{13}C NMR spectra of amino alcohol **91a**

Initially, amine function in **91a** was protected as *tert*-butyl carbamate [(*tert*-BuOCO)$_2$O, Et_3N and CH_2Cl_2], followed by protection of the free hydroxyl group as its mesylate (MsCl, Et_3N and CH_2Cl_2)**.** However, nucleophilic displacement of mesylate with azide anion under various conditions failed to give the required azido product probably due to interference shown by the bulky nature of *tert*-butyl group. We observed that protection of amine **91a** as its amide **113** [TsCl, Et_3N and CH_2Cl_2] was found to be useful in subsequent steps, as described below.

The ^{1}H and ^{13}C NMR spectra of **113** confirmed the tosyl protection while a doublet of doublet integrating for one proton each has appeared at δ 2.34 (*J* = 7.91, 10.5 Hz) and 2.6 (*J* = 6.8, 10.25 Hz) in its ^{1}H-NMR spectrum corresponding to the benzylic methylene protons (-C**H**$_2$CH-). This was further ascertained by the typical signals at δ 35.4, 52.1 and 63.8 corresponding to the two methylene and one methine (**C**HOH) carbons in its ^{13}C-NMR spectrum (**Fig. 15**).



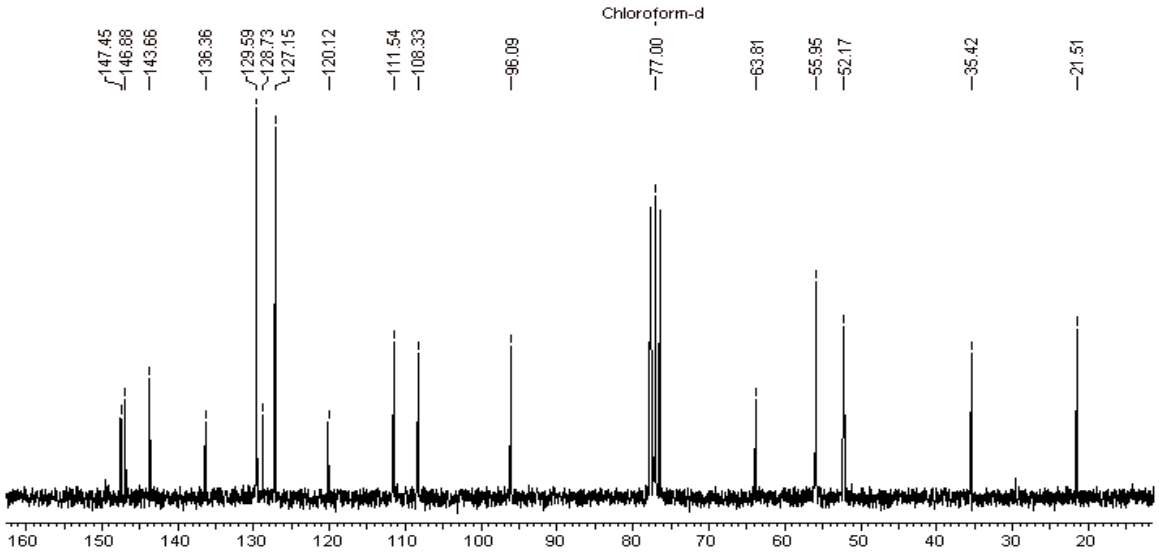


Fig. 15: ^{1}H NMR spectrum of tosylalcohol **113**

At this stage, enantiomeric excess of **113** was determined by Mosher's ester analysis. Thus, free hydroxyl moiety in N-tosyl alcohol **113** was esterified (catalytic DMAP, DCC in CH_2Cl_2) with Mosher's acid [(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid] and the resulting Mosher's ester **116** was analyzed by ^{1}H-NMR spectrum. The enantiomeric excess of **116** was found to be 95 % (**Fig. 16**).

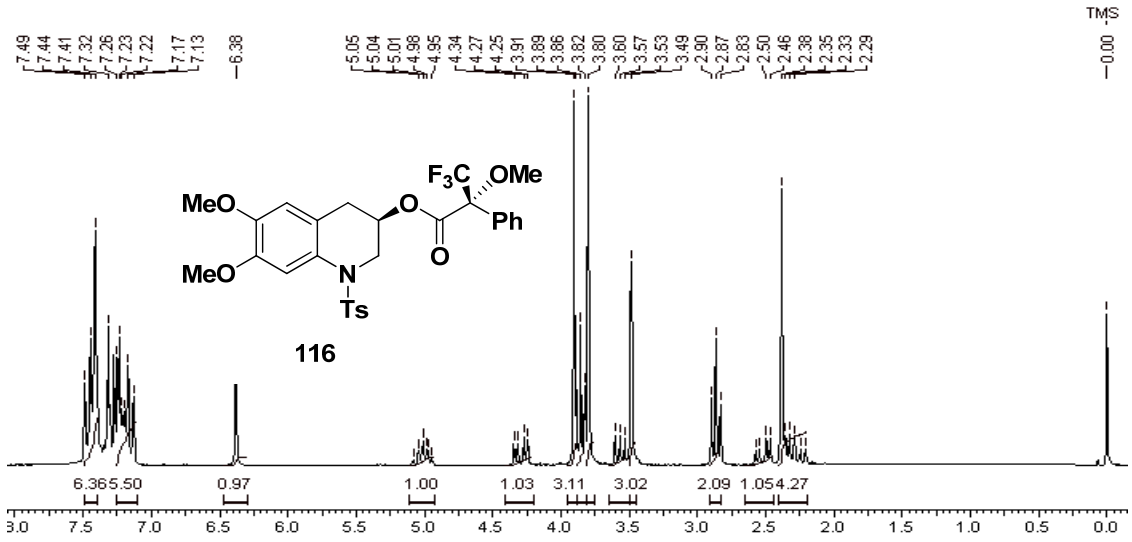


Fig. 16: ^{1}H NMR spectrum of Mosher's ester **116**

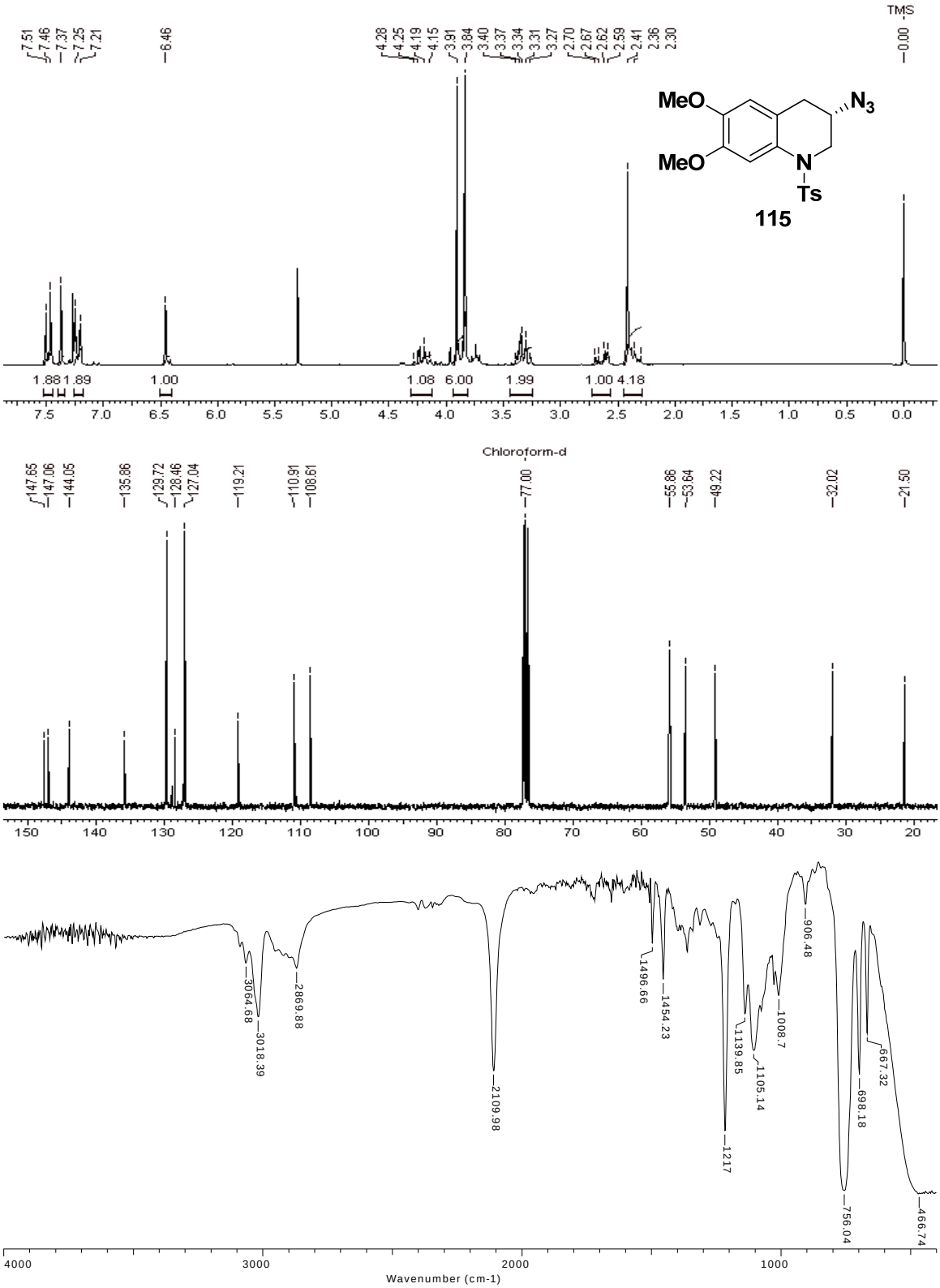
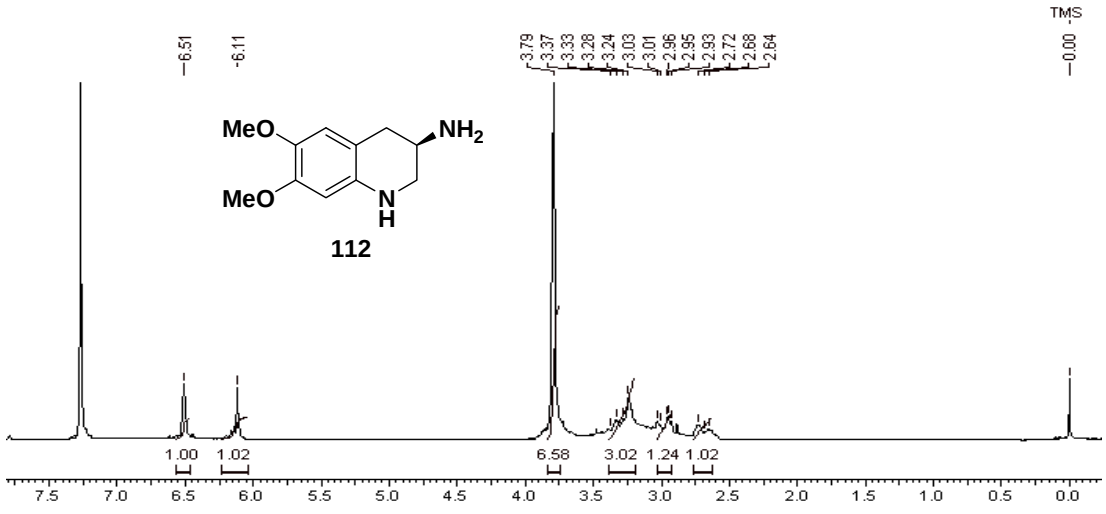


Fig. 17: ^{1}H, ^{13}C NMR and IR spectra of azide **115**

Alcohol **113** was then mesylated readily, which was subjected to nucleophilic displacement with azide anion giving azide **115** in 93% yield. Presence of azide functionality was confirmed from IR spectroscopy, which showed a strong absorption band at 2109 cm^{-1}. Its ^{1}H-NMR spectrum showed typical signals at δ 4.15-4.28 (m) due to the methine proton (C**H**N_3) confirming the formation of azide **115.** Its ^{13}C NMR spectrum showed a characteristic methine (**C**HN_3) carbon signal at δ 53.6 (**Fig. 17**).

N-Tosyl azide **115** was then subjected to reduction with sodium amalgam in NaH_2PO_4 whereby reduction of both azide and tosylate functions took place efficiently to afford (*S*)-3-aminotetrahydroquinoline **112** in 76% yield and 95% ee.[18c] Its ^{1}H-NMR spectrum showed typical signals at δ 2.64-2.72 (m, 1H) and 2.93-3.03 (m, 1H) corresponding to benzylic methylene protons. Also signals at δ 3.24-3.37 (m, 3H) correspond to methylene (*N*-C**H**$_2$) and methine (C**H**OH) protons (**Fig. 18**). Its ^{13}C-NMR spectrum showed typical carbon signals at δ 34.6, 45.4 and 47.6 corresponding to the methylene (-**C**H_2-CH), methine (-**C**H-NH_2) and methylene (*N*-**C**H_2) carbons respectively. Further, synthesis of Anachelin H chromophore (**100a)** from **112** has been reported in the literature.[53]



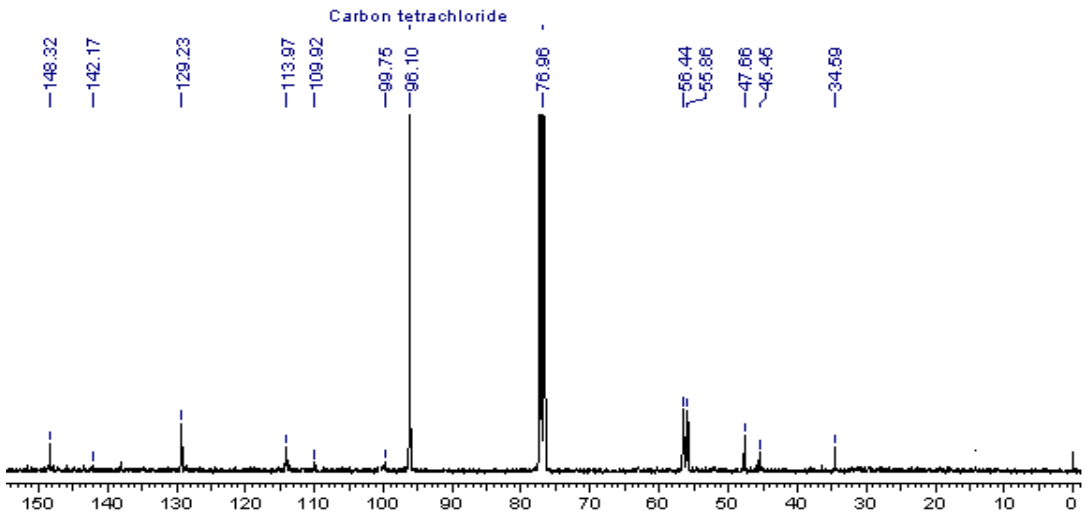


Fig. 18: ^{1}H and $^{13}CNMR$ spectra of diamine **112**

2.2.5 Conclusion

In conclusion, we have achieved the formal synthesis of Anachelin H chromophore **(100a**), which was obtained in 24% overall yield and 95% ee. We have successfully applied asymmetric dihydroxylation and Co-catalyzed multifunctional reduction as key steps to achieve the formal synthesis of Anachelin H chromophore (**100a).**

2.2.6 Experimental section

For the preparation of (**88a**, **89a, 90a, 91a**) see Section I of this chapter

(*R*)-6,7-Dimethoxy-1-tosyl-1,2,3,4-tetrahydroquinolin-3-ol (113)

To a stirred solution of tetrahydroquinolin-3-ol (**91a**) (0.63 g, 3 mmol) and Et_3N (0.5 mL, 3 mmol) in CH_2Cl_2 (10 mL), TsCl (0.55g, 3 mmol) was added at 25 ºC. The mixture was stirred for 3 h. Progress of the reaction was monitored by TLC and after completion of reaction, saturated aq. $NaHCO_3$ (30 mL) was added. Organic layer was separated; aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude tosamide product. Chromatographic purification [silica

gel (230-400 mesh) and petroleum ether:ethyl acetate: (60: 40:)] gave 0.9 g of **113** in pure form.

Yield: 82%; $[\alpha]^{D}_{25}$ +74 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 567, 754, 862, 1055, 1108, 1216, 1268, 1347, 1598, 1707, 3020, 3504; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.17 (br s, 1H), 2.34 (d, *J* = 7.9 Hz, 1H), 2.37 (s, 1H), 2.6 (dd, *J* = 6.8, 10.2 Hz, 1H), 3.45 (dd, *J* = 5.8, 7.5 Hz, 1H), 3.87 (m, 7H), 4.04 (dd, *J* = 4.2, 9.3Hz), 6.46 (s, 1H,), 7.20 (d, *J* = 8.3 Hz, 2H), 7.31 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.5, 35.4, 52.1, 55.9, 63.6, 96.0, 108.3, 111.5, 120.1, 127.1, 128.7, 129.5, 136.3, 143.6, 146.8, 147.4; ESI-MS: m/z 386.115 $[M+Na]^+$; **Analysis**: $C_{18}H_{21}NO_5S$ requires: C 59.49, H 5.82, N 3.85 found: C 59.65, H 5.98, N 3.92%.

(*S*)-3-Azido-6,7-dimethoxy-1-tosyl-1,2,3,4-tetrahydroquinoline (115)

To a stirred solution of alcohol **113** (0.6 g, 1.6 mmol) and triethylamine (0.5 mL, 2 mmol) in CH_2Cl_2 (8 mL), was added mesyl chloride (2 mmol, 0.2 mL) at 0 ºC. It was then stirred for 15 min. After completion of the reaction (monitored by TLC), a saturated solution of $NaHCO_3$ (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with (2 x 20 mL CH_2Cl_2). The combined organic layers were washed with brine (2 x 10 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product **114**.

To the stirred solution of mesylate **114** (0.7 g, 1.6 mmol) in dry DMF (8 mL), NaN_3 (400 mg, 6 mmol) was added. The reaction mixture was stirred for 16 h at 80 ºC. After completion of reaction (monitored by TLC), it was poured into 50 mL of ice cold water and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced

pressure to give the crude product **115**. Chromatographic purification of crude product using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate: (70: 30) gave pure of azide **115** (544 mg).

Yield: 91%; $[\alpha]^{D}_{25}$ +5.5 (*c* 0.36, $CHCl_3$); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 566, 755, 861, 1275, 1598, 1723, 2103; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.33 (d, *J* = 8.4 Hz, 1H), 2.41 (s, 3H), 2.59-2.70 (dd, *J* = 5.5, 10.6 Hz, 1H), 3.27-3.40 (m, 2H), 3.85-3.91 (d, *J* = 14.4 Hz, 6H), 4.15-4.28 (m, 1H), 6.46 (s, 1H), 7.21-7.25 (d, *J* = 7.9 Hz, 2H), 7.46-7.51 (d, *J* = 8.3 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.2, 32.0, 49.3, 53.9, 55.9, 108.7, 111.0, 119.3, 127.1, 128.5, 129.8, 135.9, 147.1, 147.7; **Analysis**: $C_{12}H_{14}N_4O$ requires: C 55.66; H 5.19;

(2*R*)-(*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-tosylquinolin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (116)

To a stirred solution of alcohol **113** (0.1 mmol), DCC (41 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) Mosher's acid (26 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added at 0 ºC and allowed to stir for 12 h at 25 °C. After the completion of reaction (monitored by TLC), solvent was distilled under reduced pressure and crude product was purified by column chromatography to give pure Mosher's ester of amido alcohol **116.**

Yield: 33 mg, 77%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.21-2.35 (m, 1H), 2.38 (s, 3H), 2.52 (dd, *J* = 6.3, 16.8 Hz, 1H), 2.87 (t, *J* = 6.3 Hz, 2H), 3.49 (s, 3H), 3.53-3.60 (m, 1H), 3.80 (s, 3H), 3.86 (t, *J* = 6.3 Hz, 1H), 3.91 (s, 3H), 4.29 (dd, *J* = 6.3, 16.8 Hz, 1H), 4.95-5.08 (m, 3H), 6.38 (s, 1H), 7.13-7.26 (m, 5H), 7.32-7.49 (m, 6H).

N 14.42 found: C 55.92; H 5.67; N 14.81%.

(*S*)-6,7-Dimethoxy-1,2,3,4-tetrahydroquinolin-3-amine (112)

To a solution of azide **115** (0.4 g, 1 mmol) and NaH_2PO_4 (1.148 g, 8.3mmol) in dry MeOH (10 mL) was added Na(Hg) (6%, 3g) at 25 ºC and the mixture was allowed to stir for 4 h. After completion of reaction (monitored by TLC), filtered through celite and the filter cake rinsed with ethyl acetate, and the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product using flash silica gel (230-400 mesh) and chloroform: methanol: (90: 10) gave the pure diamine **112** (160 mg).

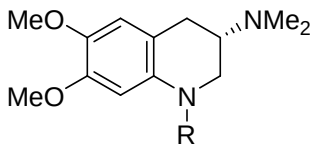
Yield: 76%; colorless solid, **mp**: 120 - 122 °C; $[\alpha]^{D}_{25}$ +20.0 (*c* 0.2, $CHCl_3$); Lit:[18c] $[\alpha]^{D}_{25}$ +20.6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 666, 754, 1225, 1519, 1620, 2933, 3016, 3407, 3661; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2. 65 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.94 (dd, *J* = 4.2, 14.0 Hz, 1H), 3.2-3.5 (m, 3H), 3.7 (s, 6H), 6.1 (s, 1H), 6.5 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 34.5, 45.4, 47.6, 55.8, 56.5, 99.7, 109.9, 113.9, 129.2, 142.1, 148.3; **Analysis**: $C_{11}H_{16}N_2O_2$ requires: C 63.44; H 7.74; N 13.45 found: C 63.92; H 7.87; N 13.81%.

Section III:

Asymmetric synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones

2.3.1 Introduction

Although excellent diuretics and ACE inhibitors are available for the treatment of congestive heart failures, the only current approach that relies on the stimulation of cardiac contractility is the use of cardiac glycosides with a variety of therapeutic limitations. 1-[(*S*)-3-(Dimethylamino)-6,7-dimethoxytetrahydroquinoline alkanones (**117** and **118)** have recently been identified as potentially interesting positive inotropic agents (**Fig 19**).[54]



117, R = COEt

118, R = COPr^{i}

Fig. 19: Positive inotropic agents **117** and **118**

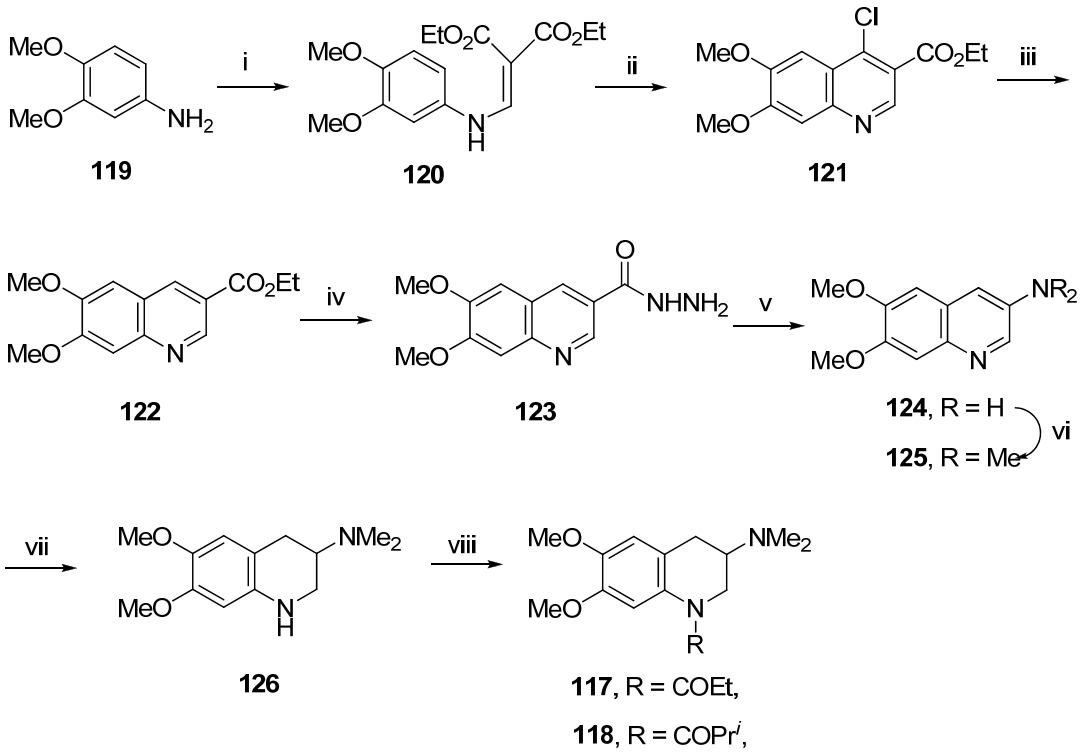
2.3.2 Review of literature

Literature search revealed that there is only one report available for the synthesis of 1-[(*S*)-3-(dimethylamino)-6,7-dimethoxytetrahydroquinoline derivatives **(117** and **118**), which is described below.

Vecchietti's Approach (1994)[54]

Vecchietti *et al.* have reported racemic synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**117** and **118**). Diethyl 2-[(3,4-dimethoxyphenylamino)methylene]malonate **120,** obtained by the condensation of ethoxymethylene malonate with 3,4-dimethoxyaniline (**119**), was cyclized ($POCl_3$ and

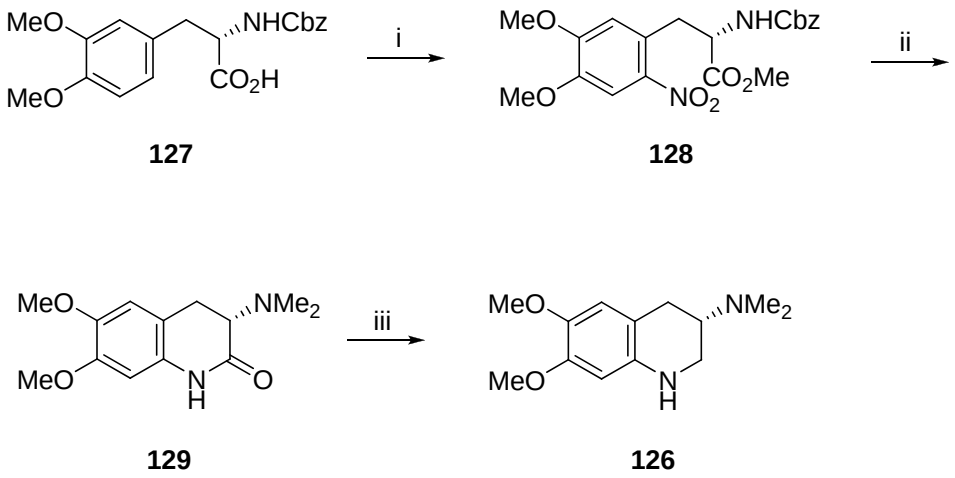
DMF) to give chloro tetrahydroquinoline derivative **121**. Subsequent dechlorination (10% Pd/C, H_2 and AcOH) was achieved to give quinoline derivative **122.** This was subjected to Curtius rearrangement *via* hydrazine amide **123** to provide 3-aminoquionoline **124** in good yields. Subsequently, its reductive amination (HCHO and HCO_2H) gave **125,** which was subjected to ionic hydrogenation under high pressure (10%Pd/C, H_2 and AcOH) to give *N,N*-dimethyl amino tetrahydroquinoline **126.** Finally, acylation of amine **127** (acid chloride and CH_2Cl_2) furnished amides **117** and **118** in good yields (**Scheme 31**).



Scheme 31: (i) $C_2H_5OCH{=}C(COOC_2H_5)_2$, heat; (ii) $POCl_3/PCl_5$; (iii) H_2, 10% Pd/C, acetic acid; (iv) $NH,NH_2{\cdot}H_2O$; (v) $NaNO_2$; (vi) HCHO/HCOOH; (vii) H_2, 10% Pd/C, acetic acid, 80%; (viii) acyl chloride, CH_2Cl_2.

In another approach, the same authors have described the asymmetric synthesis of diamine intermediate **126** starting from chiral starting material. *N*-Cbz protected L–DOPA derivative **127** was esterified to give methyl ester**,** which was regioselectively

nitrated (conc. HNO_3 and AcOH) to give nitro derivative **128**. Nitro ester **128** was reduced (10% Pd/C, H_2 (4 atm) and AcOH) to give (*S*)-3-amino-3,4-dihydro-6,7-dimethoxyquinolin-2(1*H*)-one**,** on reductive amination (10% Pd/C, HCHO and MeOH) gave *N, N*-dimethylaminoquinolin-2-one **129.** Finally, $LiAlH_4$ reduction of **129** gave very low yield of 3-**(***N, N*-dimethylamino)quinoline **126** in 28% (**Scheme 32**).



Scheme 32: (i) (a) CH_3I, K_2,CO_3, acetone, 60 °C, 6 h, 73%; (b) HNO_3, CH_3CO_2H, 15 °C, 3 h 76%; (ii) (a) 10% Pd/C, H_2 (4 atm), CH_3CO_2H, 91%; (b) 10% Pd/C, HCHO, 2N HCl, Et_2O, 40-50 °C, 90%; (iii) $LiAlH_4$, DME, reflux, 24 h, 28%.

2.3.3 Present work

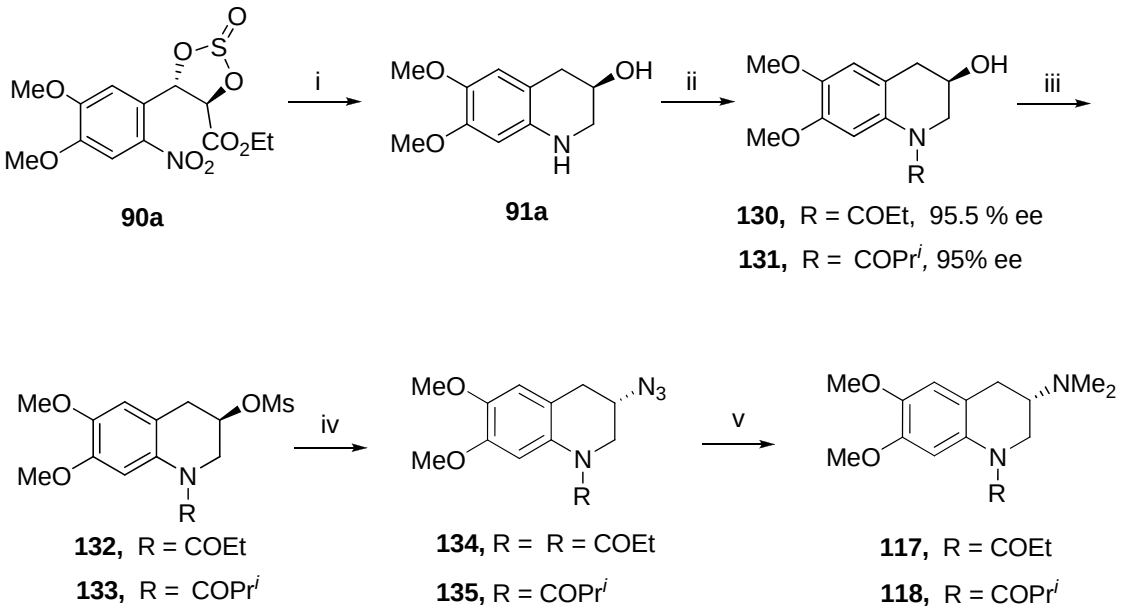
2.3.3.1 Objective

Review of literature reveals that only one report is available for the synthesis of 1-[(*S*)-3-(dimethylamino)3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**117** and **118**). However, use of chiral starting material as well as the need of several protecting groups in the synthesis, make the existing method uneconomical. In section I of this Chapter, we have described an elegant method for the synthesis of 3-hydroxy tetrahydroquinoline derivatives **91a-e**. As an another application on Co-catalyzed reduction of nitro cyclic

sulphites, we describe a short synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**117** and **118**) in this section.

2.3.4 Results and Discussion

A general synthetic scheme for the synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]alkanones (**117** and **118**) is shown in **Scheme 33**. The synthetic route for the tetrahydroquinolin-3-ol **91a** has been described in Section I. Amine function in **91a** was protected as its amides **130** and **131** [RCOCl or $(RCO)_2O$, Et_3N and CH_2Cl_2] in >90% yields.



90a **91a**

130, R = COEt, 95.5 % ee

131, R = $COPr^i$, 95% ee

132, R = COEt

133, R = $COPr^i$

134, R = R = COEt

135, R = $COPr^i$

117, R = COEt

118, R = $COPr^i$

Scheme 33: (i) $(RCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 91%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (iii) NaN_3, DMF, 80 °C, 12 h, 91% over two steps; (iv) H_2 (1 atm) 10% Pd/C, MeOH, 25 °C, 12 h; (v) HCHO, HCO_2H, 80 °C, 3 h, 73% over two steps.

The ^{1}H-NMR spectrum of **131** showed two typical proton signals at δ 1.13 (dd) and 2.38-2.52 (m) corresponding to the methyl (C**H**$_3$) and methine (C**H**) protons present in isopropyl unit respectively. Also proton signals for benzylic methylene (ArC**H**$_2$), aminomethylene (*N*-C**H**$_2$) and methine (C**H**OH) protons have appeared at δ 2.76 (dd), 3.09 (dd), 3.74-4.11 (m) and 5.22-5.31 (m) respectively. Its ^{13}C-NMR spectrum showed

characteristic carbon signals at δ 19.7, 19.9 and 30.8 due to the methyl (CH_3) and methine carbons (**C**H) of isopropyl group. Also its carbonyl signal at δ 178.0 confirms the formation of amide carbonyl group (**Fig. 20**).

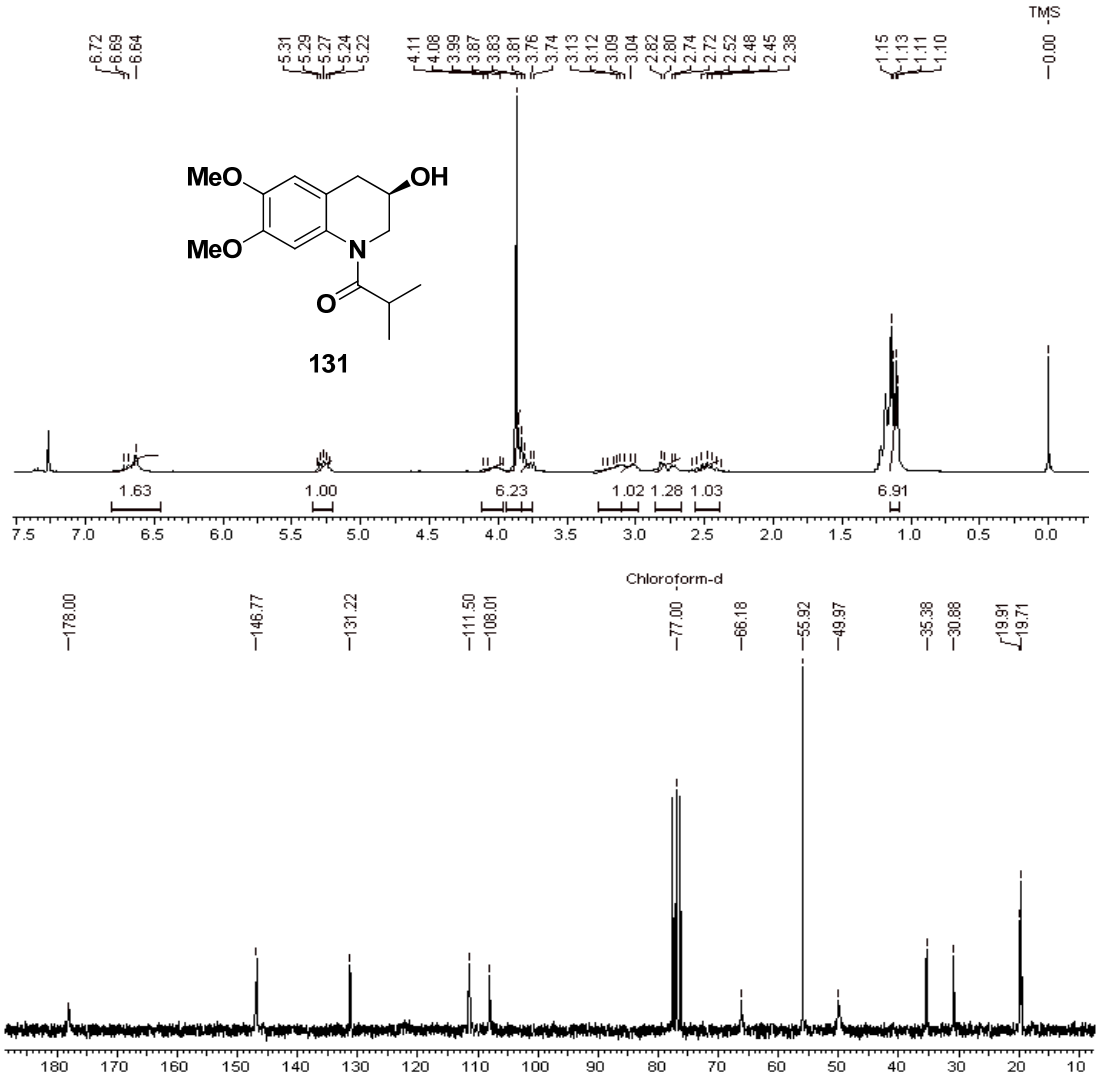


Fig. 20: ^{1}H and ^{13}C-NMR spectra of alcohol **131**

Enantiomeric excess of chiral alcohol **130** and **131** was determined by chiral HPLC and found to be 95%. Free hydroxyl moiety in **130** and **131** was then protected as their mesylates **132** and **133** (MsCl, Et_3N and CH_2Cl_2) followed by their displacement with azide anion (NaN_3, DMF) to give azido quinolines **134** and **135** in 90-91% yields. The

^{1}H-NMR spectrum of azide **135** showed a characteristic signal at δ 4.0-4.09 (m) due to methine (C**H**N_3) proton. Its ^{13}C-NMR spectrum also showed a downfield shift for methine (**C**HN_3) carbon signal at δ 56.7. Its IR spectrum showed a characteristic absorption band at 2110 cm^{-1} for azide group confirming the formation of azide (**Fig. 21**).

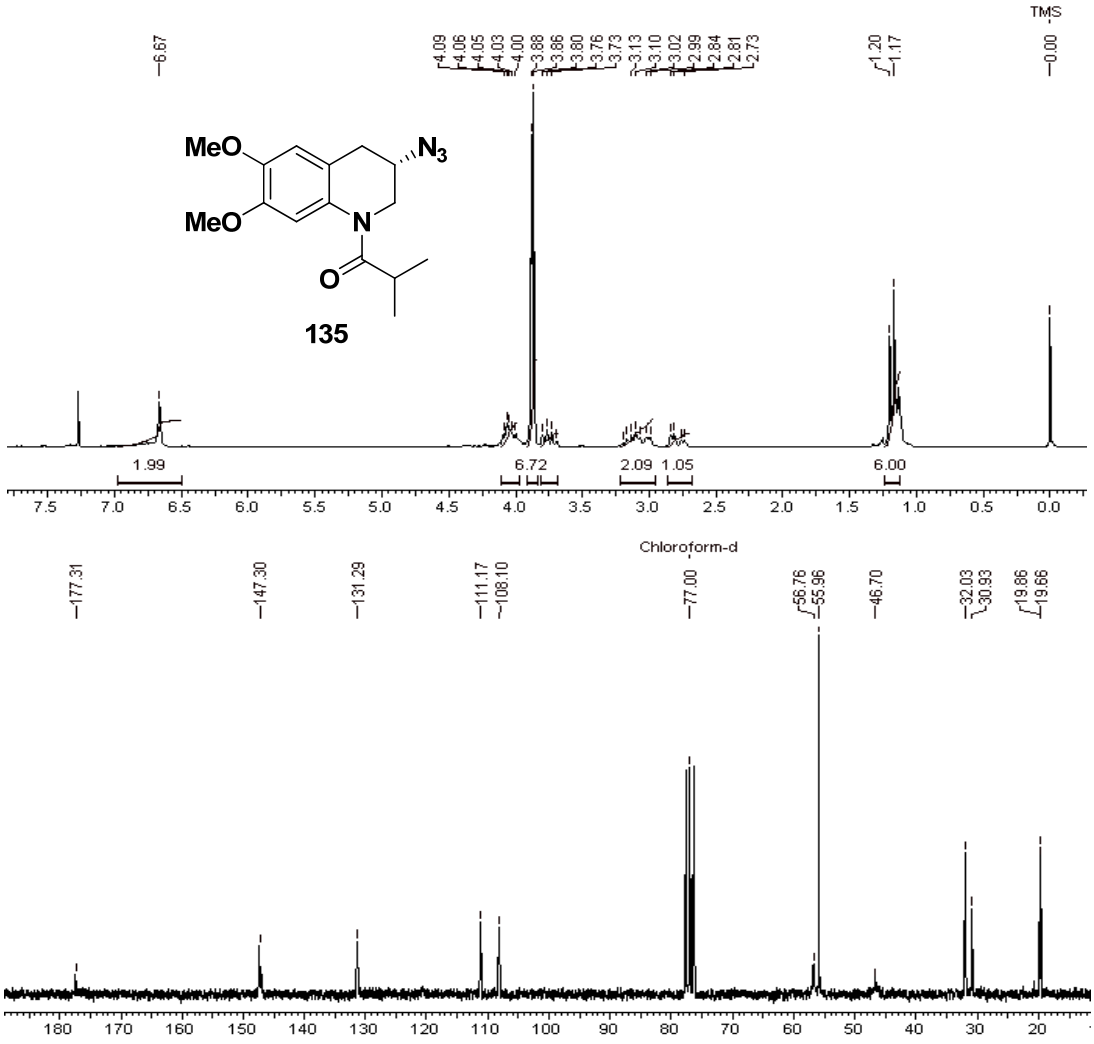


Fig. 21: ^{1}H and ^{13}C-NMR spectra of azide **135**

Catalytic hydrogenation of azide function in **134** and **135** was carried out to give the corresponding amines followed by their reductive aminations (HCHO, HCO_2H) produced 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**117**

and **118**). The ^{1}H-NMR spectrum of **117** showed a typical singlet at δ 2.35 corresponding to methyl amine protons [$N(CH_3)_2$]. Also signals at δ 41.33 and 41.46 in its ^{13}C-NMR spectrum due to methyl amine carbons confirmed the formation of **117** (**Fig. 22**).

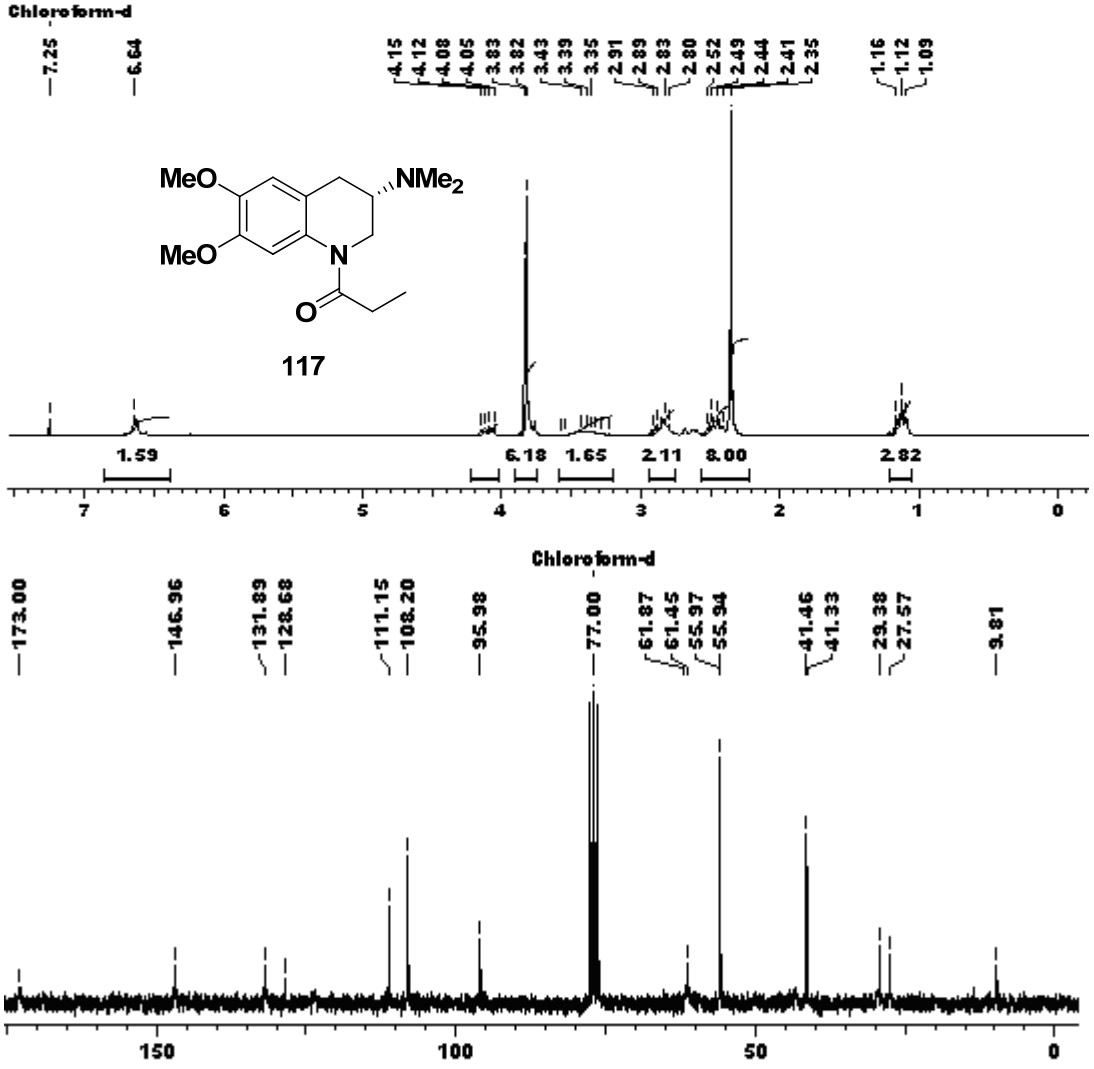


Fig. 22: ^{1}H and ^{13}C-NMR spectra of **117**

2.3.5 Conclusion

In conclusion, synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]alkanones (**117** and **118)** have been achieved in 9 steps with 94% ee. We have utilized asymmetric dihydroxylation and Co-catalyzed multifunctional

reduction, as the key steps in the asymmetric synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]alkanones (**117** and **118)**.

2.3.6 Experimental Section

General experimental procedure for the preparation of amide 130 and 131

To a stirred solution of tetrahydroquinolin-3-ol **91a** (0.83 g, 4 mmol) and triethylamine (1.4 mL, 10 mmol) in CH_2Cl_2 (20 mL), was added the respective anhydride or acid chloride (5 mmol) at 25 ºC. Reaction mixture was stirred for 3 h. Progress of the reaction was monitored by TLC. After the reaction was complete, a saturated solution of $NaHCO_3$ (30 mL) was added. The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give a crude mass. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: (60: 40) as eluent] gave amide **130** and **131** in pure form.

1-[(*R*)-3,4-Dihydro-3-hydroxy-6,7-dimethoxyquinolin-1(2H)-yl]propan-1-one (130)

Yield: 82%; Gum; $[\alpha]^{D}_{25}$ +8.69 (*c* 1.15, $CHCl_3$); Chiral Column: Cromasil 5-CelluCoat column, Length 250 mm, i.d. 4.6 mm, wavelength: 220 nm, flow rate 0.8 mL per min. Mobile phase10% IPA in hexane. Retention time 27.608 (97.7%) and 30.850 (2.2%). ee = 95.5%; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 846, 1047, 1240, 1392, 1514, 1747, 2983, 3514; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.56 (q, *J* = 7.3 Hz, 2H), 2.67-2.78 (dd, *J* = 4.6, 16.5 Hz, 1H), 2.98-3.09 (dd, *J* = 5.4, 16.5 Hz, 1H), 3.86 (s, 6H), 3.74-3.95 (m, 2H), 4.32 (m, 1H), 6.63 (br s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 8.6, 27.4, 35.0, 49.7, 55.6, 65.0, 108.0, 111.1, 122.4, 130.7, 146.3, 174.3; **Analysis:** $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28; found C, 63.53; H, 7.19; N, 5.22%.

1-[(*S*)-3,4-Dihydro-3-hydroxy-6,7-dimethoxyquinolin-1(2H)-yl]-2-methylpropan-1-one (131)

Yield: 91%; Gum; $[\alpha]^{D}_{25}$ +9.5 (*c* 1, $CHCl_3$); Chiral Column: Cromasil 5-CelluCoat column, Length 250 mm, i.d. 4.6 mm, wavelength: 220 nm, flow rate 0.8 mL per min. Mobile phase10% IPA in hexane. Retention time 25.560 (97.5%) and 28.732 (2.5%). ee = 95%; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 846, 1049, 1238, 1514, 1660, 1737, 2979, 3463; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.10-1.15 (dd, *J* = 2.8, 7.1 Hz, 6H), 2.41-2.63 (m, *J* = 7.0 Hz, 1H), 2.71-2.82 (dd, *J* = 4.8, 16.5 Hz, 1H), 3.01-3.12 (dd, *J* = 5.3, 16.5 Hz, 1H), 3.12 (br s, 1H), 3.74-3.83 (dd, *J* = 5.0, 14.0 Hz, 1H), 3.96-4.12 (m, 1H), 3.87 (s, 6H), 5.22-5.32 (m, *J* = 5.4 Hz, 1H), 6.64 (br s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.7, 19.9, 30.8, 35.3, 49.9, 55.9, 66.1, 108.0, 111.5, 131.2, 146.7, 146.9, 178.0; ESI-MS: m/z 302.135 $[M+Na]^+$; **Analysis:** $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01; found C, 64.37; H, 7.41; N, 5.08%**.**

General experimental procedure for the preparation of mesylate 132 and **133**

To a stirred solution of amides **130** and **131** (4 mmol) and triethyl amine (1.4 mL, 10 mmol) in 20 mL of CH_2Cl_2, mesyl chloride (5 mmol, 0.5 mL) was added at 0 ºC. It was then stirred for 15 min. After completion of the reaction (monitored by TLC), a saturated solution of $NaHCO_3$ (30 mL) was added, organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude mesylate. Attempts to purify mesylates were unsuccessful as they undergo elimination readily. Since the mesylates were difficult to purify, it was converted to the

respective azides without purification. The formation of mesylates was confirmed by ^{1}H-NMR analysis of crude mesylates **132** and **133.**

(*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-propionylquinolin-3-yl methanesulfonate (132)

Yield: 83%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.52 (q, *J* = 7.3 Hz, 2H), 3.04 (s, 3H), 2.95-3.22 (m, 2H), 3.72-3.82 (m, 1H) 3.86 (s, 6H), 3.81-3.92 (m, 1H), 4.06-4.33 (m, 1H), 5.22 (m, 1H), 6.63 (br s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 9.6, 27.4, 33.0, 38.3, 46.4, 55.8, 74.3, 108.2, 111.0, 128.5, 130.9, 147.1, 173.6.

(*R*)-1,2,3,4-Tetrahydro-1-(isobutyryl)-6,7-dimethoxyquinolin-3-yl methanesulfonate (133)

Yield: 84%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.6 Hz, 3H), 2.97-3.23 (m, 3H), 3.06 (s, 3H), 3.72-3.82 (m, 1H) 3.87 (s, 6H), 4.07-4.31 (m, 2H), 5.25 (m, 1H), 6.67 (br s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.5, 20.0, 30.8, 33.2, 38.5, 46.8, 75.9, 108.1, 111.3, 120.17, 131.3, 147.4, 177.5.

General procedure for the preparation of 1-[(*S*)-3-azido-3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-yl]alkanones 134 and 135

To the stirred solution of mesylate **132** and **133** in dry DMF (10 mL), was added NaN_3 (1.30 g, 20 mmol). It was then stirred for 16 h at 80 ºC. After completion of the reaction (monitored by TLC), it was poured into 50 mL of ice cold water and extracted with ethyl acetate (3 x 50mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: (70: 30)] gave azide **134** and **135** in pure form.

1-[(*R*)-3-Azido-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propan-1-one (134)

Yield: 91%; gum; $[\alpha]^{D}_{25}$ +38.2 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1043, 1217, 1514, 1650, 1735, 2110, 3018 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.3 Hz, 3H), 2.57 (q, *J* = 7.3 Hz, 2H), 2.78-2.88 (dd, *J* = 5.5, 16.0 Hz, 1H), 3.04-3.15 (dd, *J* = 5.4, 16.6 Hz, 1H), 3.72-3.82 (m, 1H) 3.89 (s, 3H), 3.90 (s, 3H), 3.99-4.13 (m, 2H), 6.68 (br s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 9.5, 27.4, 31.7, 46.5, 55.7, 55.7, 56.1, 108.1, 110.9, 119.8, 130.8, 146.8,146.9, 173.3; **Analysis** for $C_{14}H_{18}N_4O_3$ requires C, 57.92; H, 6.25; N, 19.30; found C, 57.88; H, 6.20; N, 19.33%.

1-[(*R*)-3-Azido-3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-yl]-2-methylpropan-1-one (135)

Yield: 91%; gum; $[\alpha]^{D}_{25}$ +39.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 759, 1047, 1218, 1510, 1647, 1745, 2106, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 6.8 Hz, 6H), 2.73-2.84 (dd, *J* = 4.9, 15.7 Hz, 1H), 2.99-3.09 (dd, *J* = 4.9, 15.9 Hz, 1H), 3.10-3.20 (q, *J* = 6.8 Hz, 1H), 3.69-3.80 (m, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.00-4.09 (m, 2H), 6.67 (br s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.6, 19.8, 30.9, 32.0, 46.7, 55.9, 56.7, 108.1, 111.1, 131.2, 147.0, 147.3, 177.3; **Analysis**: $C_{15}H_{20}N_4O_3$ requires C, 59.20; H, 6.62; N, 18.41; found C, 59.14; H, 6.69; N, 18.44.

General procedure for the synthesis of 1-[(*S*)-3-(Dimethylamino)-6,7-dimethoxytetrahydroquinoline alkanones 117 and 118

To a solution of azide **134** and **135** (2 mmol) in methanol (10 mL), was added 10% Pd/C (40 mg). It was stirred under H_2 atmosphere (1 atm; balloon pressure) for 12 h. After the completion of reaction (monitored by TLC), it was passed through celite and concentrated under reduced pressure that afforded crude amine. To the crude amine 40%

aq. solution HCHO (1 mL) and HCO_2H (2 mL) was added, and the resulting mixture was refluxed for 3 h. After completion of reaction, saturated aq. $NaHCO_3$ solution (10 mL) was added and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhyd. Na_2SO_4, concentrated under reduced pressure. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: triethyl amine (60:38:2) as eluent] gave pure **117** and **118**.

1-[(*R*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-yl]propan-1-one (117)

Yield: 91%; Colorless soild; **mp** 136 °C, [lit.[54]135-137 °C]; $[\alpha]^{D}_{25}$ –3.2 (*c* 1, EtOH) {lit.[54] $[\alpha]^{D}_{25}$ –3.3 (*c* 1, EtOH)}[54]; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 760, 1049, 1211, 1511, 1647, 1743, 3018, 3450; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.3 Hz, 3H), 2.35 (s, 6H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.80-2.91 (m, 2H), 3.23-3.54 (m, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 6.64 (bs, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 9.8, 27.5, 29.5, 41.3, 41.4, 55.9, 55.9, 61.4, 61.8, 108.2, 111.1, 128.6, 131.8, 146.9, 173.0; **Analysis** for $C_{15}H_{21}N_2O_3$ requires C, 64.96; H, 7.63; N, 10.10; found C, 64.82; H, 7.60; N, 10.27%.

1-[(*R*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-yl]-2-methylpropan-1-one (118)

Yield: 91%; Colorless soild; **mp** 119-120 °C; [lit.[54] 120-122 °C]; $[\alpha]^{D}_{25}$ –2.2 (*c* 1, EtOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 759, 1047, 1215, 1510, 1640, 1747, 3010, 3459; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.12 (d, *J* = 6.7 Hz, 6H), 2.76 (s, 6H), 2.90-3.12 (m, 1H) 3.10-3.18 (m, 2H), 3.38 (m, 1H), 3.75-3.83 (m, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 6.90 (s,1H), 6.98 (s, lH); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.9, 26.5, 32.5, 41.9, 42.1, 56.1, 56.9, 61.1, 107.2,

111.1, 126.6, 131.4, 146.0, 175.1; **Analysis** for $C_{17}H_{26}N_2O_3$ requires C, 66.64; H, 8.55; N, 9.14; Found C, 66.61; H, 8.40; N, 9.02%.

2.3.7 References

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CHAPTER III

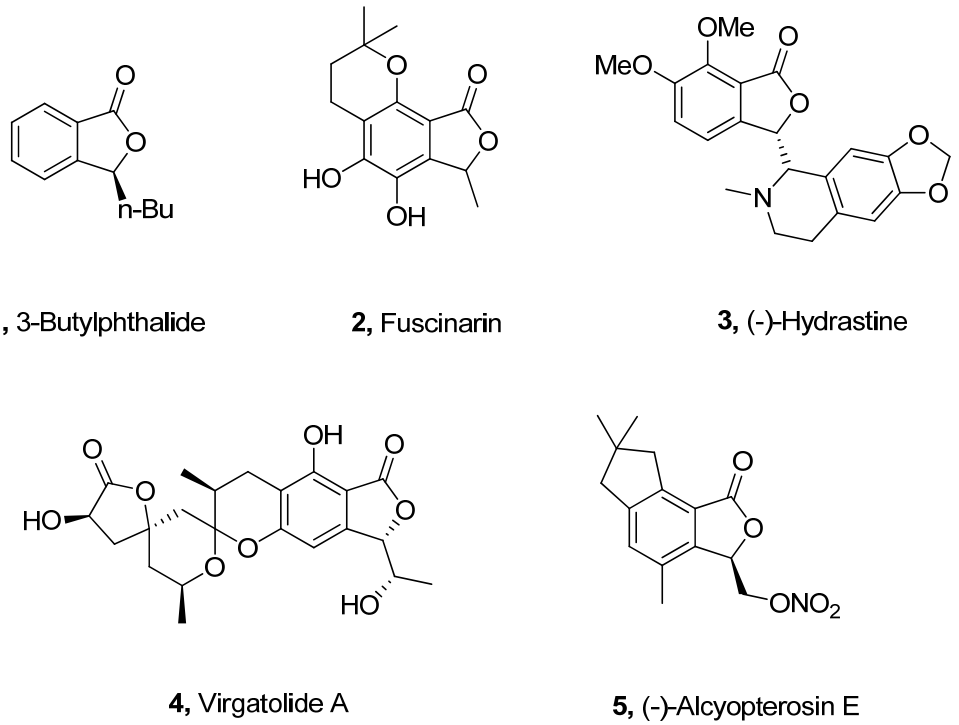
CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-substituted Chiral Phthalides and its Application to the Synthesis of (-)-Matteucen C, Isocoumarins and Alkylidenephthalides

Section I:

CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-Substituted Chiral Phthalides

3.1.1 Introduction

Chiral phthalides [isobenzofuran-1(3H)-ones] comprising of 5-membered lactones are found in a large number of plant products displaying broad and potent biological activities.[1] Some representative examples are shown in **Fig. 1**. 3-Butylphthalide (**1**), a component in the Chinese folk medicine extracted from celery seed oil,[2a] is in phase II clinical trials in China and potentially can be used for the treatment of stroke.[2b] Moreover, it is employed for seasoning and flavoring purposes, shows anticonvulsant action,[2c] increases the duration of anesthesia,[2d] and exhibits cerebral antiischemic action.[2e]



1, 3-Butylphthalide **2,** Fuscinarin **3,** (-)-Hydrastine

4, Virgatolide A **5,** (-)-Alcyopterosin E

Fig. 1: Some of the examples of chiral phthalides

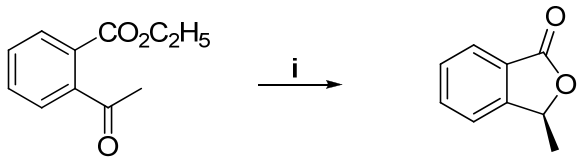
Fuscinarin (**2**) is a potent human CCR5 antagonist, used effectively for blocking HIV entry into host cells.[3] (-)-Hydrastine (**3**) is active at the opioid receptor.[4] In addition, it possesses antipaclitaxel-resistant human ovarian cancer activity through c-Jun kinasemediated apoptosis and is in phase I clinical trials.[5] Virgatolide A (**4**) and (-)-Alcyopterosin E (**5**) which show cytotoxic activity against HeLa cells.[6] Due to the biological importance of 3-substituted phthalides **1–5** (**Fig. 1**), their molecular architectures have become a platform for new synthetic methodology development.[7]

3.1.2 Review of literature

Literature search revealed that there are various methods available for the synthesis of 3-substituted phthalide derivatives which are described below.

Noyori's approach (1990)[8]

Noyori *et al*. have described the synthesis of chiral phthalide ((*S*)-3-methylisobenzofuran-1(3H)-one) **7** *via* asymmetric hydrogenation of ethyl o-acetylbenzoate (**6**) in ethanol with 0.4 mol% of the (S)-BINAP-Ru catalyst at 100 atm in 97% ee and 97% yield (**Scheme 1**).



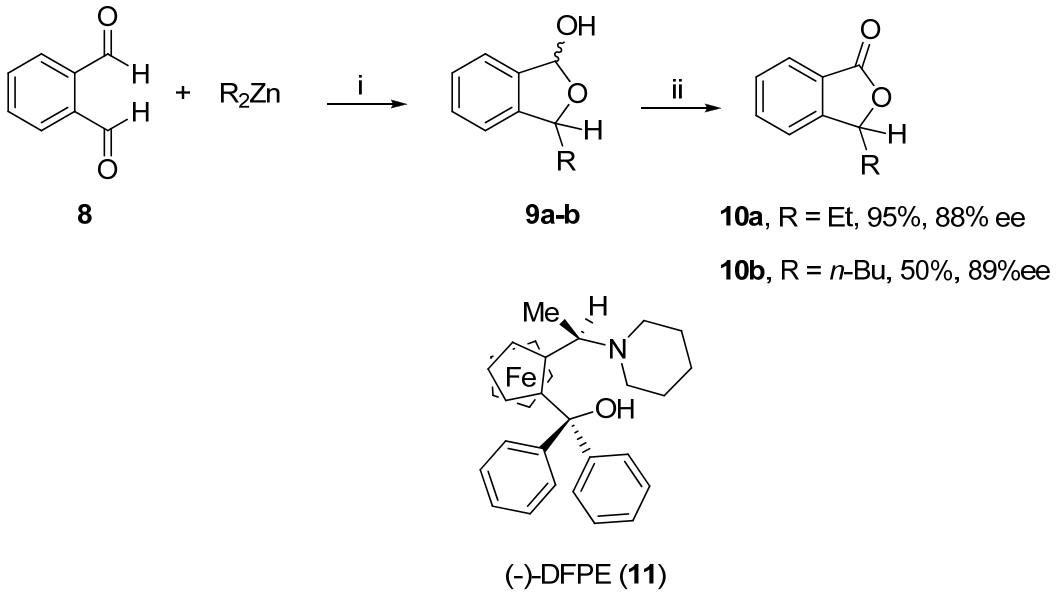
6 **7;** 97% ee

Scheme 1: (i) $Ru(OCOCH_3)_2$[(*S*)-BINAP] (0.4 mol%), H_2 (100 atm), EtOH, 0.5N HCl, 35 °C, 165 h, 97%.

Butsugan's approach (1992)[9]

Butsugan *et al.* have reported the synthesis of optically active 3-ethyl- and 3-*n*-butylphthalides using enantioselective addition of dialkylzinc reagents. Thus, *o*-phthalaldehyde (**8**) is subjected to asymmetric addition of dialkyl reagents, catalyzed by

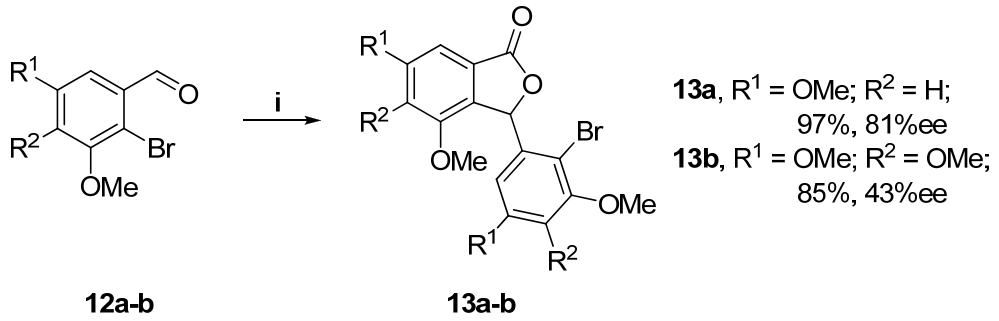
chiral 1,2-disubstituted ferrocenyl amino alcohol **11**, followed by oxidation of the resulting lactols **9a-b** to provide phthalides **10a-b** in 88-89%ee (**Scheme 2**).



Scheme 2: (i) (-)-DFPE (5 mol%), 25 °C, 1-3 h, (ii) 1N HCl, 0 °C.

Lin's approach (2002)[10]

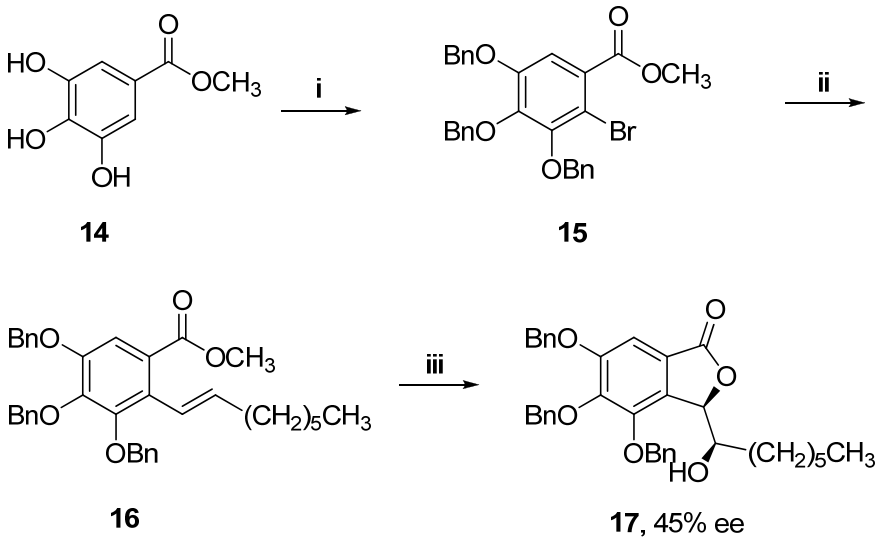
Nickel-catalyzed tandem homo addition of *o*-bromoaldehydes **12a-b** *via in situ* cyclization was developed in presence of (*S*)-BINAP and zinc that provided optically active phthalides **13a-b** in good yields with moderate enantiomeric excess (**Scheme 3**).



Scheme 3: (i) $NiCl_2(PPh_3)_2$ (0.2 equiv). (*S*)-BINAP, zinc, toluene, 90 °C.

Mori's approach (2003)[11]

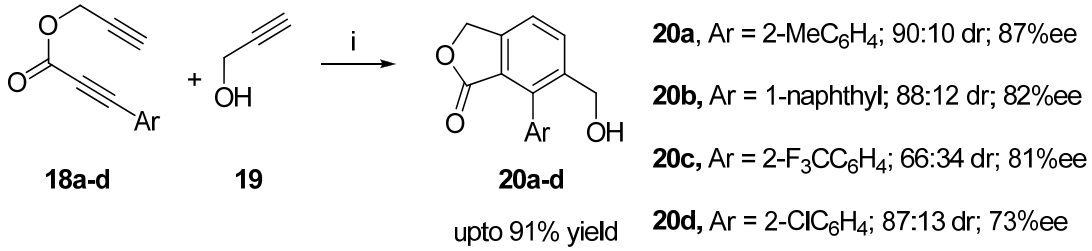
Mori *et al.* have used Sharpless asymmetric dihydroxylation as the key reaction. Thus, commercially available methyl 3,4,5-trihydroxybenzoate (**14**) was benzylated and subsequently subjected to bromination to afford bromo compound **15** in 96% yield. The bromo compound **15** was subjected to Miyaura-Suzuki coupling with (*E*)-1-octeneboronic acid to give olefin **16.** Asymmetric dihydroxylation of olefin **16** with AD-mix-β proceeded to furnish phthalide **17** in 54% yield with 45% ee (**Scheme 4**).



Scheme 4: (i) (a) BnBr, K_2CO_3, 96%; (b) NBS, DMF, 96%; (ii) (*E*)-$CH_3(CH_2)_5CH{=}CHB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, C_6H_6/EtOH (5:1) 71%; (iii) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), 54%.

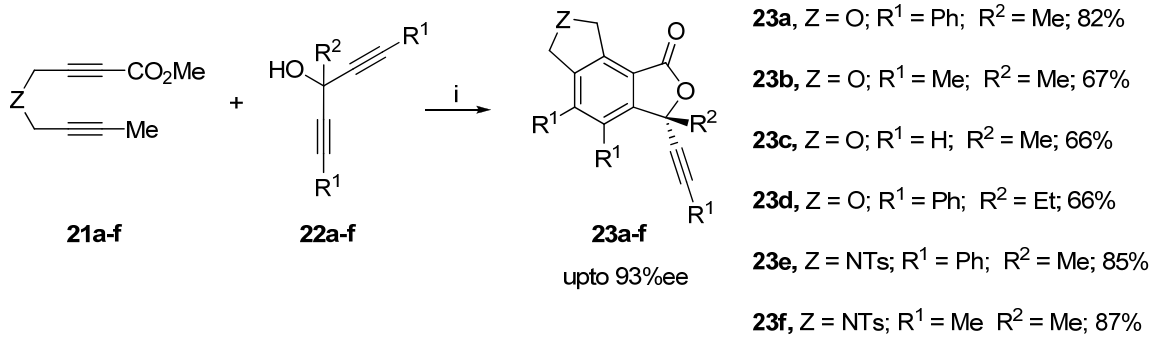
Tanaka's Approach (2004)[12]

Tanaka *et al.* have described the enantioselective synthesis of axially chiral phthalides by the cationic [$Rh^I(H_8$-binap)] complex catalyzed alkyne cyclotrimerization. The reaction of aryl-substituted 1,6-diyne **18a-d** with terminal monoynes **19** in the presence of the cationic complex [$Rh^I(H_8$-binap)] provided axially chiral phthalides **20a-d** in high yields with moderate enantioselectivity (**Scheme 5**).



Scheme 5: (i) 5% [Rh{(*S*)-H_8-BINAP}]BF_4 (1 mol%), CH_2Cl_2, 25 °C, 3 h.

Same authors have developed a cationic rhodium(I)/Solphos complex-catalyzed asymmetric one-pot transesterification and [2 + 2 + 2] cycloaddition of 1,6-diyne esters **21a-f** with tertiary propargylic alcohols **22a-f** leading to enantioenriched tricyclic 3,3-disubstituted phthalides **23a-f** in good yields (66-87%) with moderate enantioselectivity (**Scheme 6**).

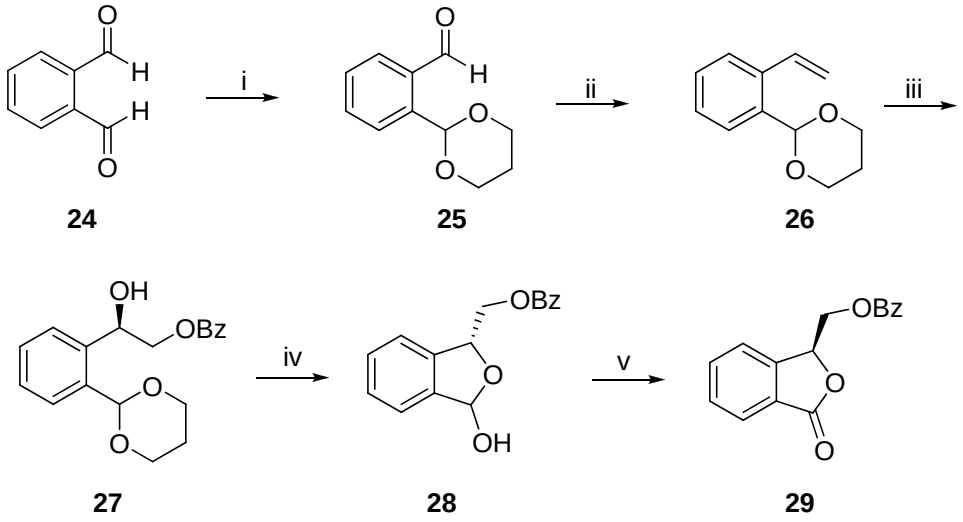


Scheme 6: (i) 5% [Rh(cod)$_2$]BF_4/(R)-Solphos (1 mol%), CH_2Cl_2, 25 °C, 1-3 h.

Vaccher's approach (2005)[13]

Vaccher *et al*. have reported the synthesis of 3-benzoyloxy methylisobenzofuranone (**29**) using Sharpless asymmetric dihydroxylation as the key step. Thus, phthalaldehyde **24** was firstly protected using propane-1,3-diol to give the benzaldehyde derivative **25**, which was subjected to Witting reaction to afford the styrene derivative, **26**. Asymmetric dihydroxylation using AD-mix-β gave diol, which was protected with benzoyl chloride to

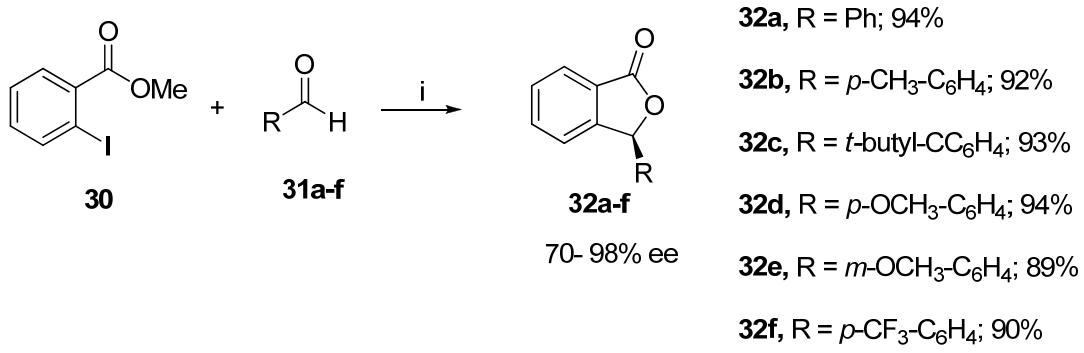
afford compound **27** with a free secondary hydroxyl group. Removal of the acetal from **27** in acidic medium gave benzo[c]furan **28,** which was converted to phthalide **29** in 50% yield using $RuCl_3$-$NaIO_4$ (**Scheme 7**).



Scheme 7: (i) PTSA, propan-1,3-diol, toluene, 5 h, 82%; (ii) *t*-BuOK, $CH_3(C_6H_5)_3PBr$, toluene, 3 h, 78%; (iii) (a) AD-mix-β, *t*-BuOH, H_2O; 12 h, 72%; (b) BzCl, $(C_2H_5)_3N$, toluene, 5 h, 78%; (iv) PTSA, acetone, H_2O, 1 h, 82%; (v) $NaIO_4$, $RuCl_3$, CH_3CN, EtOAc, H_2O, 50%.

Cheng's approach (2007)[14]

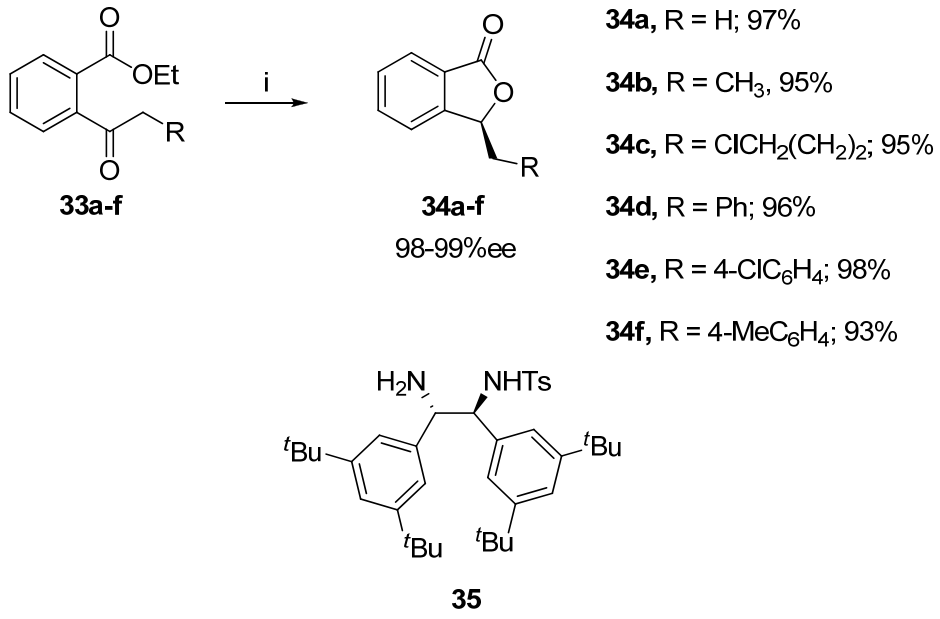
Cheng *et al.* have reported Cobalt bidentate phosphine complex catalyzed synthesis of phthalides **32a-f**. Thus, methyl 2-iodobenzoates **30** underwent cyclization reactions with various aromatic aldehydes **31a–f** in the presence of [CoI_2(dppe)] (5 mol%) and Zn powder in dry THF at 75 ºC for 24 h to give the corresponding phthalide derivatives **32a-f** in 89-94% yields with 70-98%ee (**Scheme 8**).



Scheme 8: (i) $[CoI_2(dppe)]$ (5 mol%), Zn, THF, 75 ºC, 24 h.

Xu's approach (2009)[15]

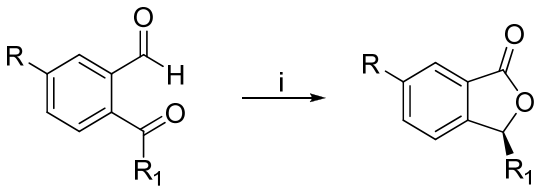
Xu *et al.* have reported a new diamine ligand **35** for asymmetric transfer hydrogenation (ATH) to synthesize 3-substituted phthalides. The reductive cyclization of 2-acylarylcarboxylates **33a-f** *via* the new $[RuCl_2(p\text{-cymene})]_2$/**35**-catalyzed ATH and subsequent *in situ* lactonization under aqueous conditions proceeded to give a variety of 3-substituted phthalides **34a-f** in high yields (93-97%) with high ee (98-99%) (**Scheme 9**).



Scheme 9: (i) $[RuCl_2(p\text{-cymene})]_2$/**35** (1 mol%), HCO_2Na, 4% CTAB, H_2O/CH_2Cl_2, 40 ºC, 24 h.

Dong's approach (2009)[16]

Dong *et al.* have employed $[Rh(cod)Cl]_2$-catalyzed hydroacylation of ketones **36a-f** in presence of duanphos **38** (10 mol%), and $AgNO_3$ (10 mol%) to give chiral phthalides **37a-f** in 81-94% yields with 92-98% ee (**Scheme 10**).



36a-f → **37a-f**

92-98% ee

37a, R = H; R_1 = Et; 94%

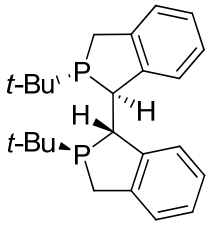
37b, R = H; R_1 = *i*-Pr; 83%

37c, R = H; R_1 = C_6H_5; 81%

37d, R = H; R_1 = 4-$CH_3C_6H_5$; 48%

37e, R = Me; R_1 = Me; 91%

37f, R = *t*-Bu; R_1 = Me; 84%

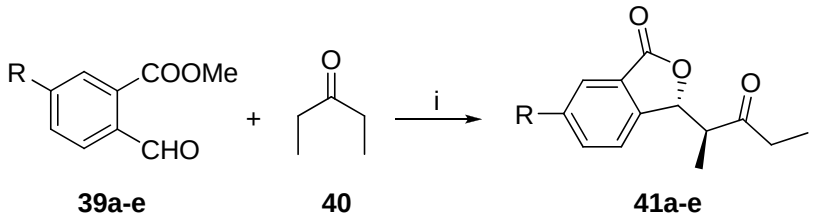


(*S*,*S*,*R*,*R*)-Duanphos (**38**)

Scheme 10: (i) $[Rh(cod)Cl]_2$ (10 mol%), duanphos (**42**) (10 mol%), $AgNO_3$ (10 mol%), toluene, 90 °C, 3-3.5 h.

Wang's approach (2010)[17]

Wang *et al*. have described the synthesis of chiral phthalides **41a-e** by employing organocatalytic asymmetric aldol-lactonization as the key reaction. Thus, 2-formylbenzoic esters **39a-e** and ketone **40** were subjected to aldol reaction using L-prolinamide alcohol **42** as catalyst and $PhCO_2H$ as an additive to give 3-substituted phthalides **41a-e** in 77-91% yield with 74-97%ee (**Scheme 11**).



39a-e **40** **41a-e**

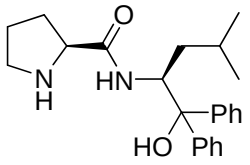
41a, R = H; 91%; 96%ee

41b, R = F; 83%; 97%ee

41c, R = Cl; 77%; 90%ee

41d, R = Br; 84%; 93%ee

41e, R = Ph; 78%; 74%ee

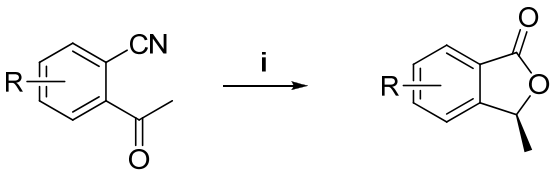


42

Scheme 11: (i) (a) **42** (2.5 mol%), $PhCO_2H$ (2.5 mol%), -40 ºC, 12-24 h; (b) K_2CO_3, acetone/methanol (10:1), 15 min

Gotor's approach (2012)[18]

Gotor *et al.* have described Baker's yeast-catalyzed bioreduction of 2-acetylbenzonitriles **43a-e** followed by aqueous HCl that provided access to enantiopure (S)-3-methylphthalides **44a-e** in moderate to excellent yields (42-99%) with >98% ee (**Scheme 12**).



43a-e **44a-e** >98%ee

44a, R = H; 99%

44b, R = 6-Me; 61%

44c, R = 5-Me; 81%

44d, R = 5-OMe; 42%

44e, R = 5-F; 92%

44f, R = 5-Cl; 72%

Scheme 12: (i) (a) Baker's yeast, glucose, H_2O (IPA), 25 °C, 16-72 h; (b) HCl 1M, 25 °C, 48 h, 50->97% conversion.

3.1.3 Present Work

3.1.3.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of 3-substituted phthalides employ either chiral auxiliaries or expensive organometallic reagents in stoichiometric amounts and often lack in broad substrate scope and higher reaction stereoselectivity; only a few are atom economical. In this context, a more practical and efficient synthesis of functionalized 3-substituted phthalide derivatives is highly desirable. In this section, we present a single-step oxidative cyclization of cyanocinnamates and styrenic substrates that affords 3-substituted phthalides in high yields *via* synergetic acceleration of CN and osmate ester groups present in proximity positions.

3.1.4 Results and Discussion

In Chapter 2, we have presented a novel protocol of AD process and Co-catalyzed "one-pot" reductive cyclization ($CoCl_2$-$NaBH_4$) of *nitro* cyclic sulfites that led to the construction of 3-substituted tetrahydroquinolin-3-ols.[19] In analogy with this, we reasoned that subjecting *cyano* cyclic sulfites to the same reaction conditions should afford synthetically useful benzazepines.[20] In order to synthesize cyano cyclic sulfite, we visualized a strategy in which cyano diol **48** could probably lead to the *cyano* cyclic sulfite. Thus, *o*-cyano benzaldehyde **45** was subjected to Wittig olefination to afford (*E*)-α,β-unsaturated ester **46a** in 88% yield (**Scheme 13**). Two doublets at δ 6.60 (d, J = 16 Hz, 1H) and 7.96 (d, J = 16 Hz, 1H) integrating for one proton each in the ^{1}H-NMR spectrum of **46a** accounted for olefinic protons in **46a.** It was further supported by typical carbon signals at δ 122.9 and 139.0 in its ^{13}C-NMR spectrum (**Fig. 2**).

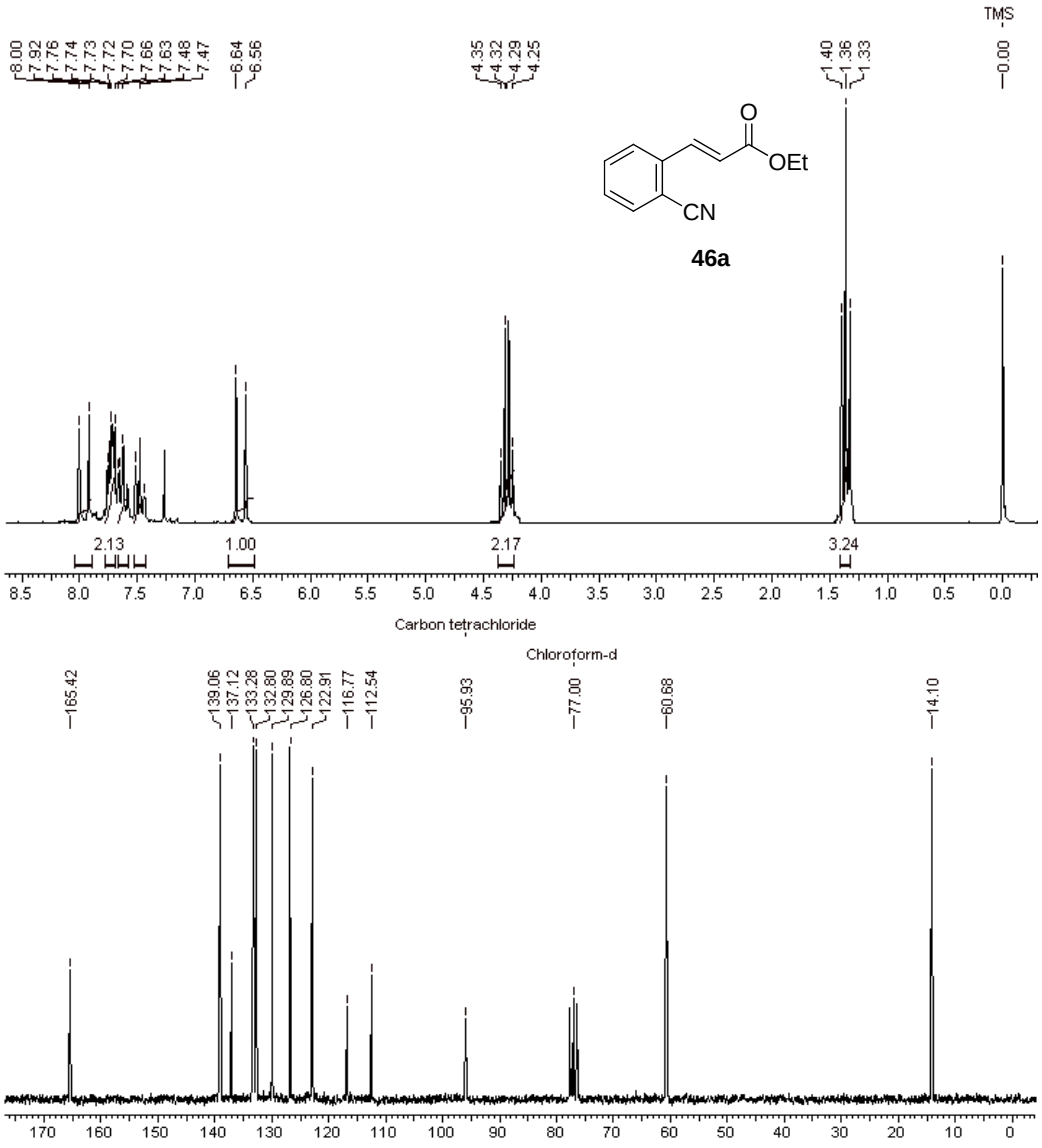
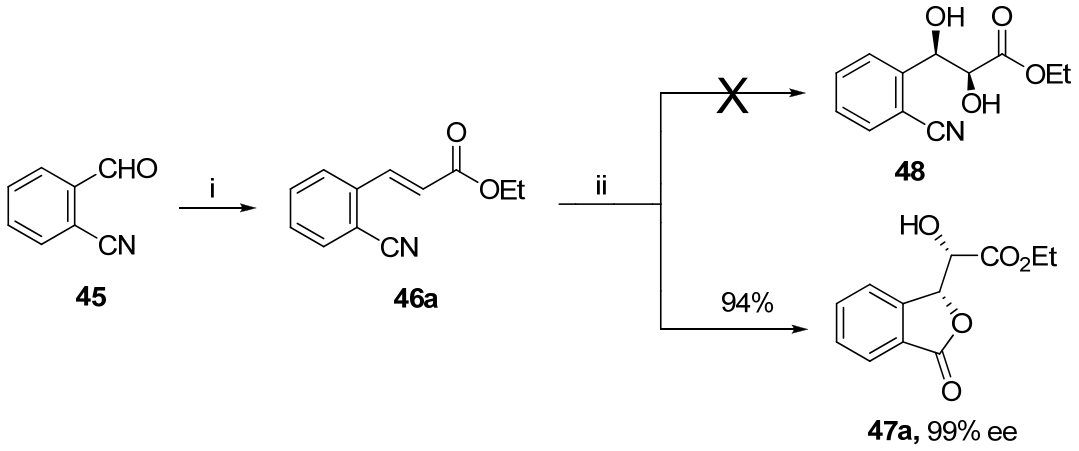


Fig. 2: ^{1}H and ^{13}C NMR spectra of o-cyano cinnamate **46a**

In order to validate our hypothesis, ethyl 2-cyanocinnamate **46a** was subjected to Sharpless asymmetric dihydroxylation using $(DHQD)_2$-PHAL as the chiral ligand for 7 h, with THF as co-solvent for better solubility. Surprisingly, the reaction took altogether a different course to give the cyclized chiral phthalide **47a** exclusively with 99%ee in a single step, instead of the expected cyano diol **48** (**Scheme 13**). This unexpected transformation is characterized by high rate, excellent yield and enantioselectivity which

is attributed to coordination assistance provided by the neighboring CN group to osmate ester, leading to faster hydrolysis of osmate ester in the catalytic cycle. Incidentally, the rate of AD process for electron-deficient *o*-substituted cinnamates is generally reported to be sluggish (48 h to 7 days) giving products invariably with moderate enantioselectivity (88%ee).[21]



Scheme 13: (i) PPh_3=$CHCO_2Et$, benzene, reflux,12 h, 88%; (ii) $K_2[OsO_2(OH)_4]$ (0.1 mol%), $(DHQD)_2$-PHAL (0.5 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), *tert*-BuOH:THF:H_2O (1:1:2), 25 °C, 7 h.

The formation of chiral phthalide **47a** was confirmed by the presence of a doublet of doublet at δ 4.66 (dd, J = 2.1, 5.8 Hz) integrating for one proton (-C**H**-OH) and also a doublet at δ 5.79 (d, J = 2.1 Hz, 1H) integrating for one proton (-C**H**-O-CO-) in its ^{1}H-NMR spectrum. It was further substantiated by the signals at δ 70.3 and 80.3 in ^{13}C-NMR which correspond to carbons attached to oxygen atoms of hydroxyl and carbonyl group respectively (**Fig. 3**). The IR spectrum of phthalide **47a** displayed a strong absorption bands at 1720 and 1768 cm^{-1} confirming the presence of ester and γ-lactone carbonyl groups respectively.

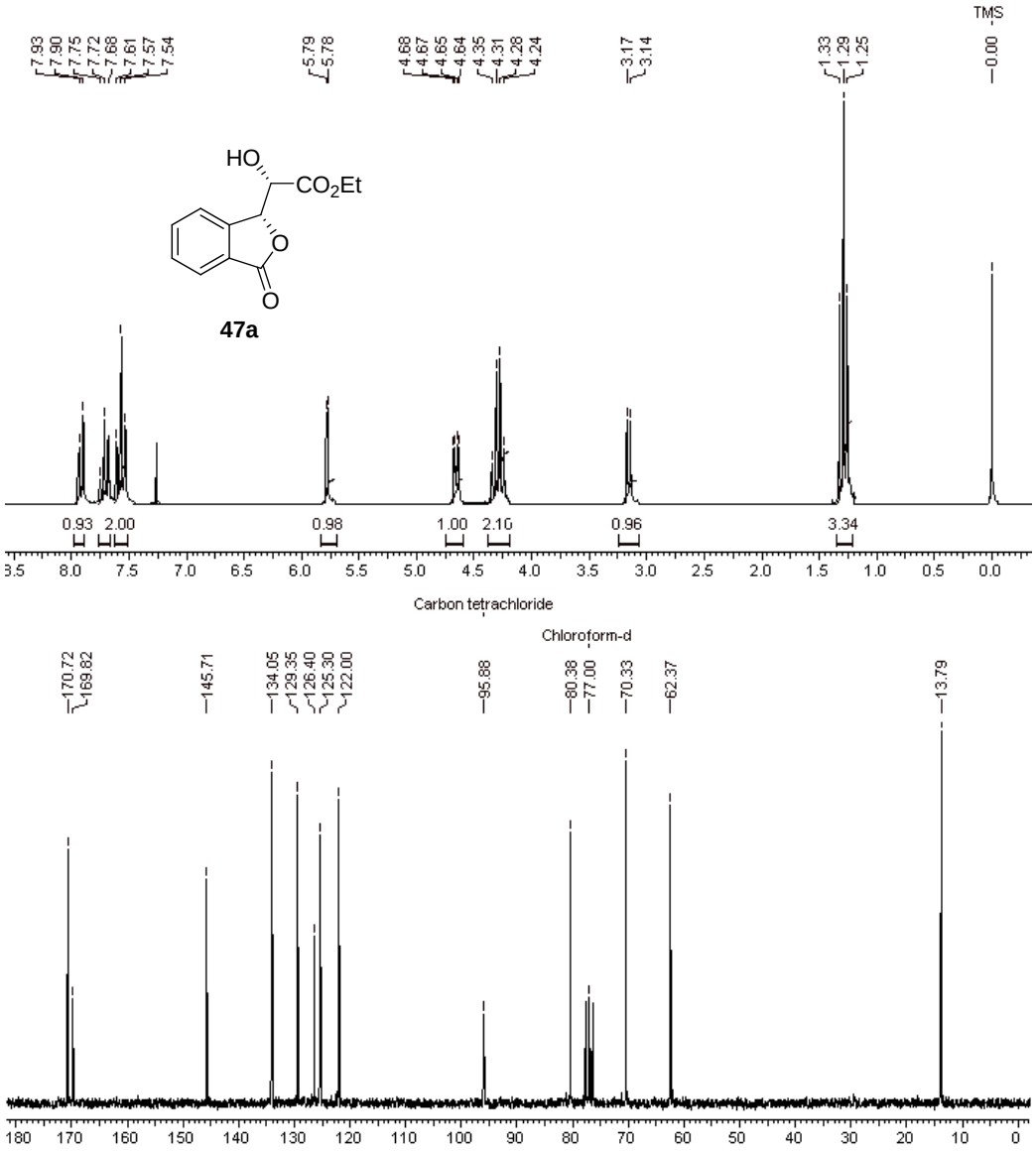


Fig. 3: ^{1}H, and ^{13}C-NMR spectra of phthalide **47a**

Further, the formation of chiral phthalide **47a** was confirmed by COSY and mass spectrum (**Fig. 4**)

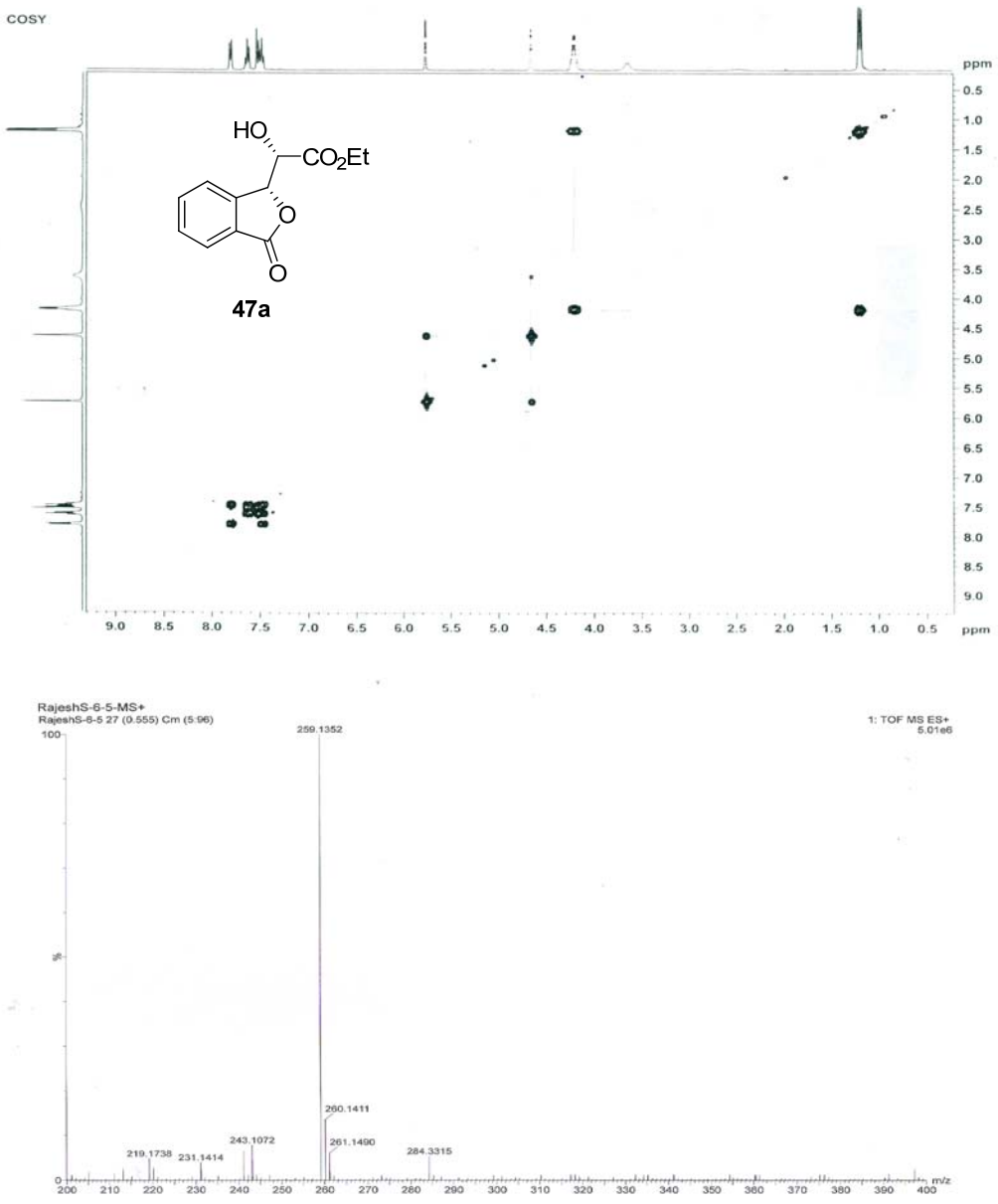
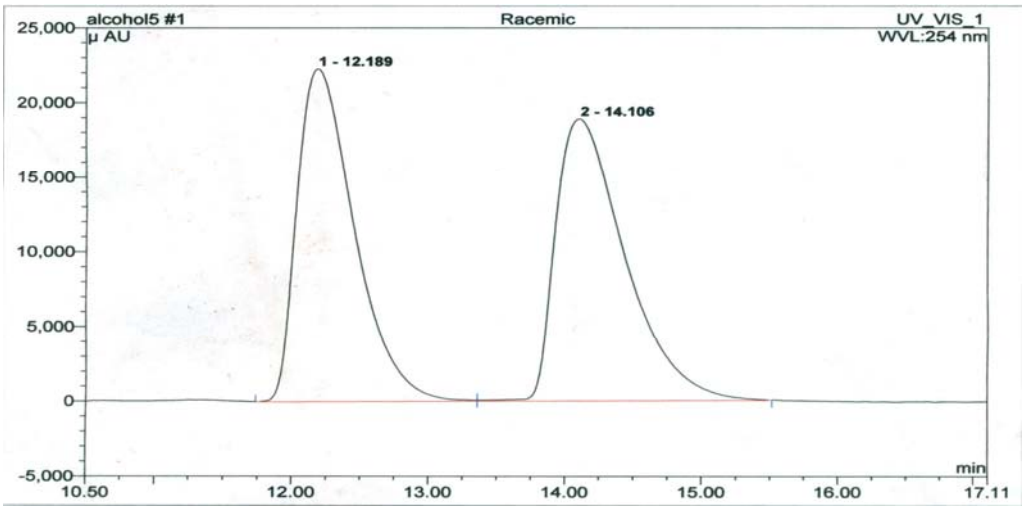
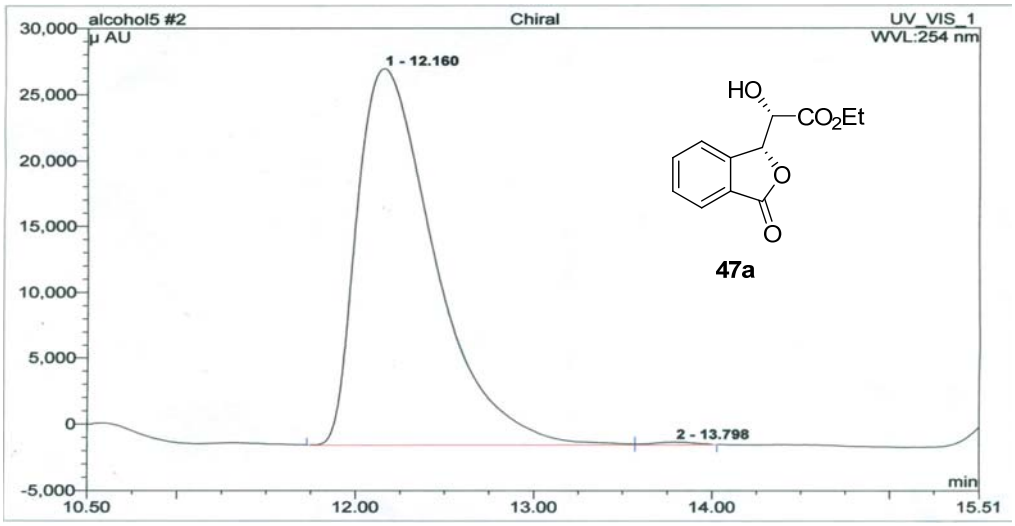


Fig. 4: COSY and mass spectra of phthalide **47a**

The enantiomeric excess of chiral phthalide **47a** was determined as 99% by chiral HPLC analysis (Chiracel OJ-H, **Fig. 5**).





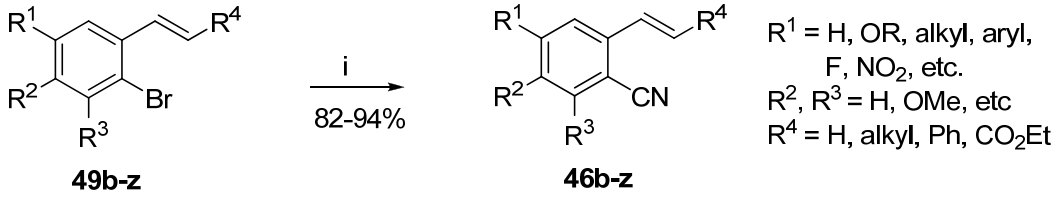
47a

No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %	Amount	Type
1	12.16	28495.075	14410.126	99.65	n. a.	BMB
2	13.80	189.662	50.523	0.35	n. a.	BMB

Fig. 5: HPLC chromatogram of **47b**

Encouraged by the result, we became interested in the scope of the reaction by subjecting other *o*-cyano alkenes **46b-z**. *o*-Cyano alkenes **46b-z** were prepared in a single step, starting from the corresponding *o*-bromo alkene derivatives **49b-z** *via* Rosenmund-von Braun reaction using CuCN (3 equiv) and DMF as solvent at 150 °C in 76-84% yield (**Scheme 14**). *o*-Bromo alkene derivatives **49b-z** were prepared in high yields using

Wittig or Julia olefination of the respective benzaldehydes by following the literature procedures.[22]



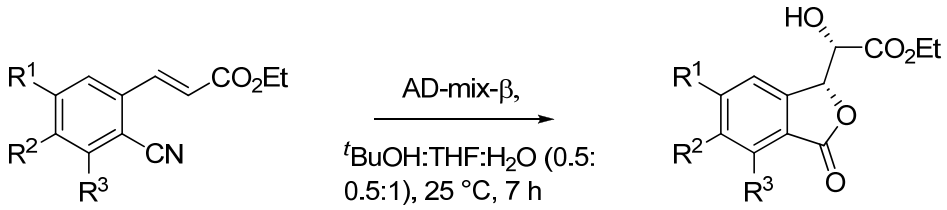
Scheme 14: (i) CuCN (3 equiv), DMF, reflux, 18 h.

When subjected to Os-catalyzed asymmetric dihydroxylation (AD) using $(DHQD)_2$-PHAL as the chiral ligand, *o*-cyano *α,β*-unsaturated esters **46b-l** gave the corresponding chiral phthalide derivatives **47b-l** in 92-95% yields with excellent enantioselectivities (98-99%). Results of such studies are presented in **Table 1**. As can be seen, in every case, the reaction proceeded rapidly with in 7 h giving the desired phthalides **46b-l** in excellent yields and ees (up to 99%) at ambient conditions. For instance, substrates having halogen (entry i), highly electron-rich (entry f) or electron-deficient (entry j) groups on the aromatic nucleus including 2-naphthyl system (entry l) underwent this oxidative cyclization smoothly affording the corresponding phthalides **46b-l** with excellent yields in single step.

Subsequently, we extended our study to include other styrene derivatives **46m-z** bearing different functionalities on the aromatic nucleus as well as on the *β*-position of the styrene derivative side chain (R^4) (**Table 2**). It was again found that this AD process displayed a wide substrate scope tolerating alkyl, aryl, alkoxy, fluoro or tosyl groups. Excellent yields of phthalide derivatives **47m-z** (93-95%) and enantioselectivities (97-

99%ee) were indeed realized in all the cases studied. The stereochemistry of the cyclized products was assigned according to the previously established absolute configuration of phthalides as well as in accordance with AD rules.[23]

Table 1: CN-assisted Os-catalyzed Oxidative Cyclization of Cyano Ethyl Cinnamates

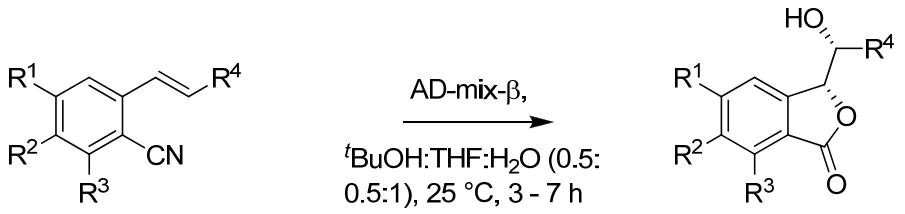


46a-l **47a-l**

Entry	R^1	R^2	R^3	Yield (%)[a]	ee (%)[b,c]
a	H	H	H	94	99
b	OMe	H	H	95	99
c	OMe	OMe	H	94	99
d	H	OMe	OMe	94	99
e	OMe	H	OMe	94	99
f	OMe	OMe	OMe	92	99
g	OTs	OMe	H	93	99
h	OBn	OMe	H	94	99
i	F	H	H	94	99
j	NO_2	H	H	93	99
k	-O-CH_2-O-		H	95	98
l	(E)-ethyl 3-(1-cyanonaphthalen-2-yl)acrylate			94	98

[a] Isolated yield after column chromatographic purification. [b]ee determined by chiral HPLC analysis. [c]ee determined by Mosher's ester analysis for entries h, i & l.

Table 2: CN-assisted Os-catalyzed Oxidative Cyclization of Cyano Styrene Derivatives



46m-z **47m-z**

Entry	R^1	R^2	R^3	R^4	Yield (%)[a]	ee (%)[b,c,d]
m	H	H	H	H	95	99
n	OMe	H	H	H	95	99
o	OMe	OMe	H	H	93	99
p	H	OMe	OMe	H	94	99
q	OMe	H	OMe	H	94	99
r	OMe	OMe	OMe	H	92	99
s	OTs	OMe	H	H	93	99
t	OBn	OMe	H	H	94	99
u	F	H	H	H	94	99
v	-O-CH_2-O-		H	H	93	99
w	H	H	H	C_3H_7	93	97
x	OMe	OMe	H	CH_2OTBS	94	97
y	OMe	OMe	H	Ph	94	97
z	OMe	OMe	H	n-C_6H_{13}	92	98

[a] Isolated yield after column chromatographic purification. [b]ee determined by chiral HPLC analysis. [c]ee determined by Mosher's ester analysis for entries t, u, w-z.[d]reaction completed in 3 h for entries m-v.

The formation of phthalide derivatives **47m-z** were confirmed by ^{1}H and ^{13}C-NMR spectroscopy. For example: The formation of phthalide **47m** was confirmed by the appearance of peaks at δ 3.90 (d, *J* = 11.80 Hz, 1H), 4.14 (d, *J* = 11.80 Hz, 1H) and 5.54-5.59 (m, 1H) in its ^{1}H-NMR spectrum. Further, its ^{13}C-NMR spectrum showed signals at

δ 61.7, 81.5 and 170.6, which correspond to carbons attached to oxygen atoms and carbonyl carbon of lactone respectively (**Fig. 6**). Its IR spectrum displayed characteristic IR absorption 1756 cm^{-1} indicating the presence of carbonyl group in lactone.

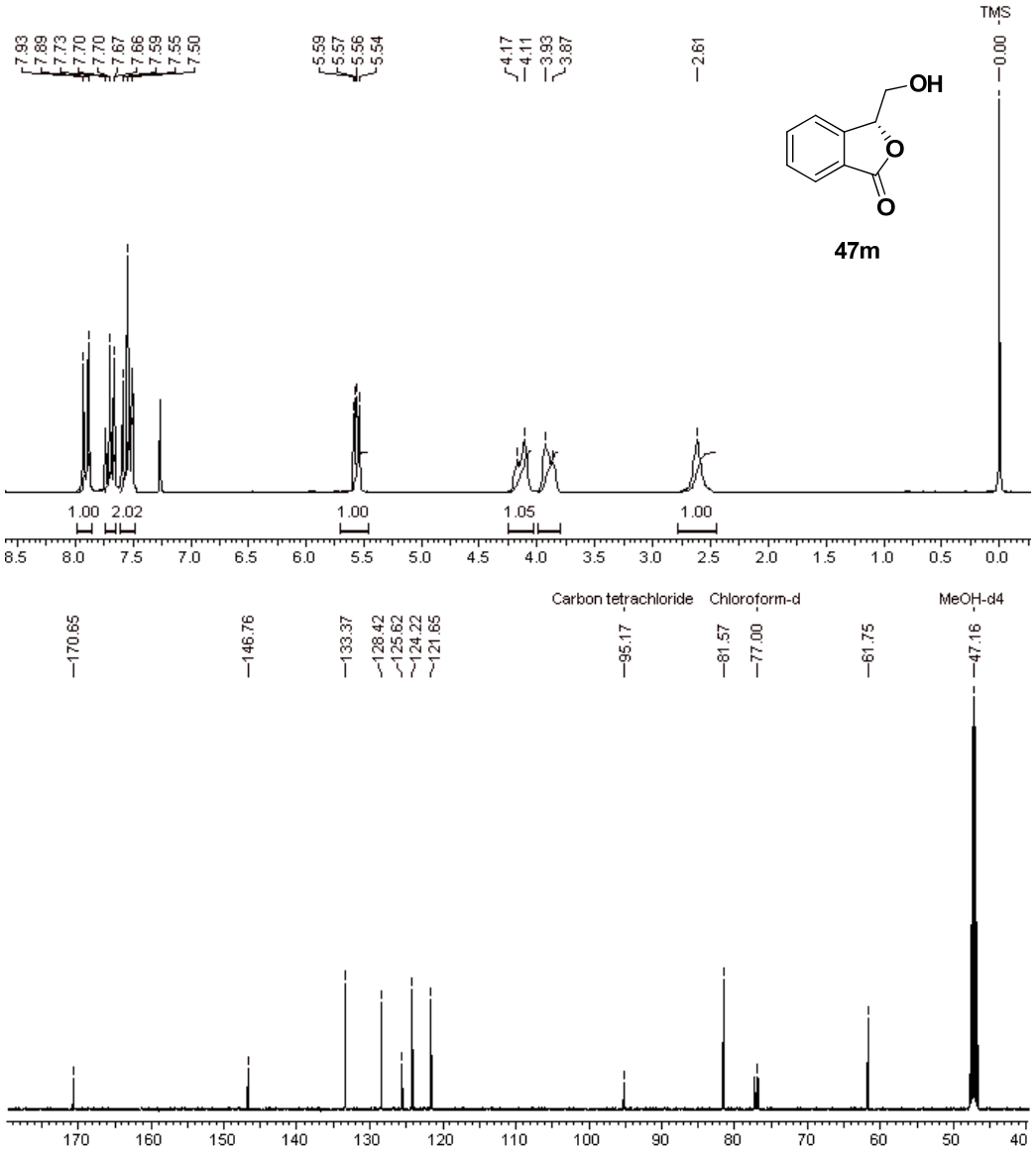
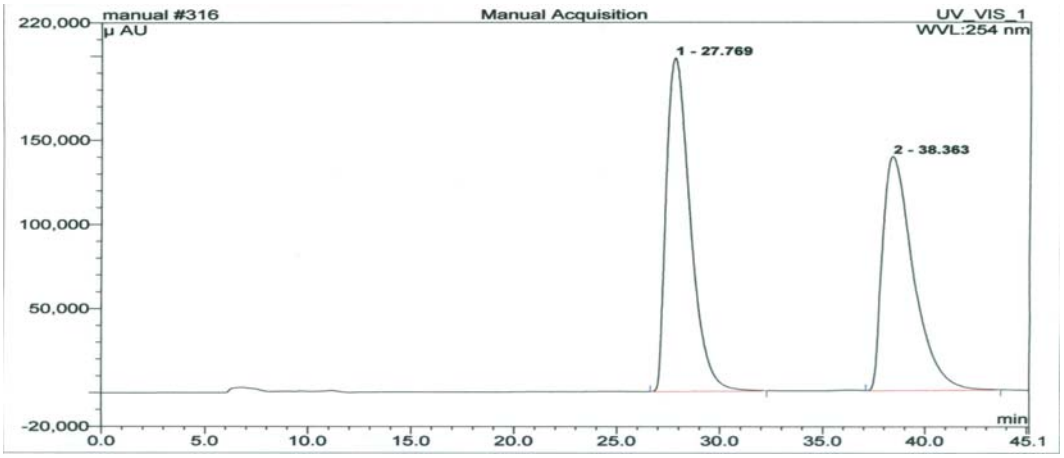


Fig. 6: ^{1}H and ^{13}C NMR spectra of phthalide **47m**

The enantiomeric excess of chiral phthalides **47m-z** was determined by chiral HPLC analysis and also by Mosher's ester analysis. For example: The enantiomeric excess of

chiral phthalide **47n** was determined as 99% by chiral HPLC analysis (Chiracel OJ-H, **Fig. 7**).



No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %	Amount	Type
1	27.19	2066521.172	26133.285	99.36	n. a.	BMB
2	39.72	10209.799	168.309	0.64	n. a.	BMB

Fig. 7: HPLC chromatogram of **47n**

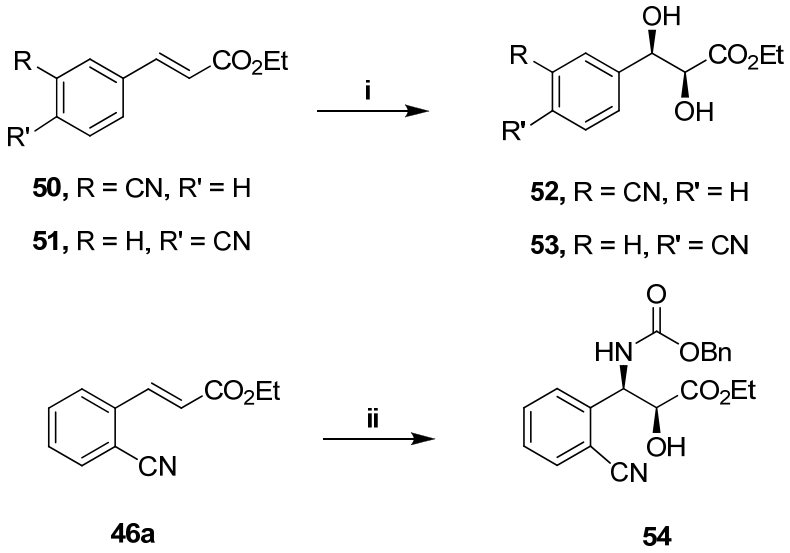
The higher reactivity of cyano substituted cinnamates and styrenes **46a-z** were substantiated by carrying out several competitive experiments involving 1:1 molar equivalents of aromatic substrates with and without cyano substitution; the results of which are presented in **Table 3**. The results clearly show that cyano substituted substrates

react almost 10-12 times faster than the one without cyano substitution, giving excellent yields of phthalides (92-94%).

Table 3: Competitive experiments[a]

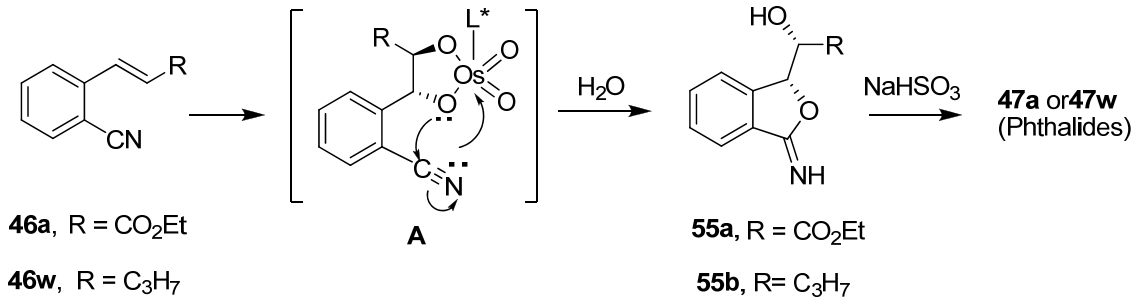
Entry	Substrates	Product	Yield (%)[b,c]
1	**46a** + ethyl cinnamate	47a	92
2	**46e** + 3, 5 dimethoxy ethyl cinnamate	47e	93
3	**46m** + styrene	47m	94
4	**46o** + 3, 5 dimethoxystyrene	47o	92
5	**46r** + 3, 4, 5 trimethoxystyrene	47r	92

[a]1:1 Molar equivalents of aromatics substrates with and without cyano substitution (1 mmol each) AD-mix-β (0.5 mol%), *t*BuOH:THF:H_2O (0.5: 0.5:1), 25 °C, 3 h for entries 3-5 and 7 h for entries 1 and 2. [b]Isolated yields after column chromatographic purification. [c]5–8 % of 1, 2-diol from the corresponding substrates without cyano substitution was indeed isolated.



Scheme 15: (i) $K_2[OsO_2(OH)_4]$ (0.1 mol%), $(DHQD)_2$-PHAL (0.5 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), *tert*-BuOH:THF:H_2O (1:1:2), 36 h, 25 °C, 94-95%; (ii) $BnOCONH_2$, aq. NaOH, $K_2[OsO_2(OH)_4]$, $(DHQD)_2$PHAL, *t*-BuOCl, n-PrOH/H_2O, 3 h, 64%, dr = 6:1.

In order to account for the mechanistic course of the reaction, the following experiments (**Scheme 15**) were conducted: (i) AD-mix-β of substrates **50** & **51** for 36 h gave the corresponding cyanodiols **52** & **53** respectively, indicating that both CN and C=C groups must be positioned in proximity for CN coordination assistance to take place; (ii) asymmetric *aminohydroxylation*[24] of **46a** gave the expected amino alcohol **54** (64%) with no phthalide formation, suggesting that coordination of CN onto imino osmate ester is thermodynamically less favorable, due to its reduced Lewis acid character;[25] (iii) in addition, imino intermediates **55a-b** were indeed isolated in 20% yield during the AD-mix-β of substrates **46a** and **46w.** This study clearly excludes the hydrolysis of CN to CO_2H followed by cyclization route, (iv) addition of benzonitrile as an external source of CN-assistance resulted in no rate enhancement for the AD process. On the basis of these results, a mechanistic model is presented in species **A** in which a synergism involving co-ordination of CN to Os(VI) and concurrent attack of osmate ester onto electropositive carbon of CN is shown that probably helps to accelerate the hydrolysis of osmate ester. These results indicate the 5-*exo*-*dig* type cyclization[26]to afford iminoesters **55a-b**, which finally lead to the formation of phthalides **47a** or **47w** (**Scheme 16).**



Scheme 16: Mechanism of CN-assisted Os-catalyzed oxidative cyclization

This formation of iminoester **55b** was clearly demonstrated by IR data of the nonsubstituted imidate C=NH band (around 1687 cm^{-1}) and the phthalide (**47w**) C=O band (around 1752 cm^{-1}) (**Fig. 8**).

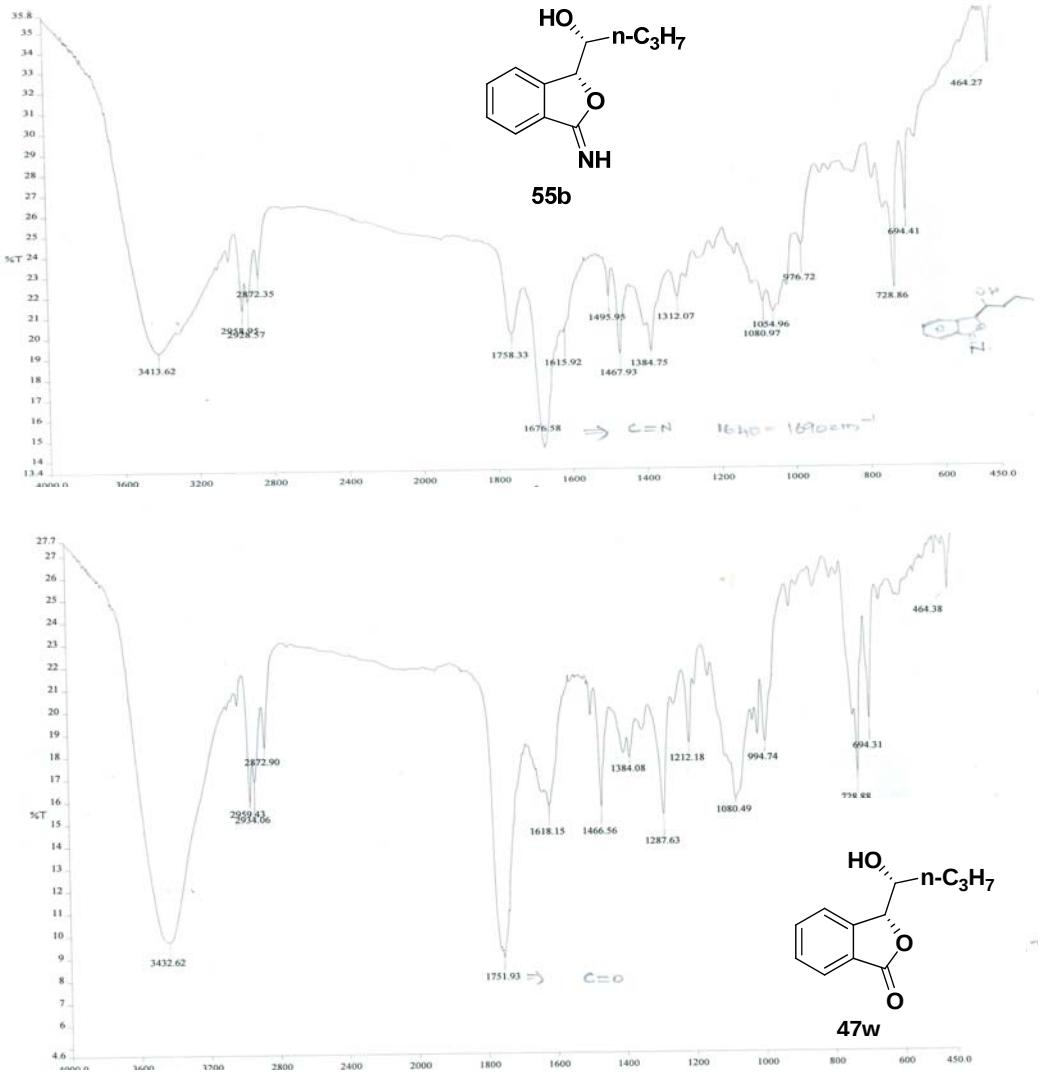


Fig. 8: IR spectra of phthalides **55b** and **47w**

3.1.5 Conclusion

We have demonstrated a novel CN-assisted oxidative cyclization for the synthesis of a wide variety of 3-substituted phthalides and their structural analogues *via* AD process of cyano cinnamates and styrene derivatives. This reaction is highly practical in the sense that the products were obtained in excellent yields and optical purities (97-99%ee) and

shows broad substrate scope and good functional group tolerance. The synergism shown by CN and osmate groups in proximity helps to enhance the rate of this reaction. We believe that this oxidative intramolecular cyclization AD strategy should find wide applications in the total synthesis of other bioactive phthalide frameworks.

3.1.6 Experimental Section

Typical experimental procedure for the preparation of (*E*)-Ethyl 3-(2-cyanophenyl)acrylate (46a)

To a stirred solution of 2-cyanobenzaldehyde **45** (2 g, 7.9 mmol) in benzene (40 mL), $Ph_3P{=}CHCO_2Et$ (3.1 g, 8.6 mmol) was added. It was then refluxed for 12 h under N_2 atmosphere. After the completion of reaction, benzene was distilled out to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (90:10) as eluent] afforded the cyano cinnamate **46a** (1.4 g yield).

Yield: 88%**,** colorless solid; **mp** 60–62 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 784, 1031, 1184, 1318, 1447, 1480, 1594, 1640, 1712, 2225, 2938, 2983; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.3 Hz, 3H), 4.31 (q, *J* = 7.3 Hz, 2H), 6.60 (d, *J* = 16 Hz, 1H), 7.47 (td, *J* = 1.4, 7.5 Hz, 1H), 7.62 (td, *J* = 1.4, 7.5 Hz, 1H), 7.70-7.76 (m, 2H), 7.96 (d, *J* = 16 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 60.7, 112.5, 116.8, 122.9, 126.8, 129.9, 132.8, 133.3, 137.1, 139.1, 165.4; **Analysis**: $C_{12}H_{11}NO_2$ requires C 71.63, H 5.51, N 6.96 found C 71.59, H 5.56, N 6.93%.

Typical experimental procedure for the preparation of (*S*)-Ethyl-2-((*R*)-1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47a)

A 50 mL RB flask was charged with $K_3Fe(CN)_6$ (1 g, 3 mmol), K_2CO_3 (414 mg, 3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and H_2O (5 mL) and stirred for 10 min. Subsequently, $(DHQD)_2PHAL$ (8 mg, 1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (2 mg, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, (*E*)-ethyl 3-(2-cyanophenyl)acrylate (**46a**) (200 mg, 1 mmol) was added and allowed to stir for 7 h at 25 ºC. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 ºC. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and petroleum ether/EtOAc (7:3) as an eluent] gave **47a** (221 mg).

Yield: 94%; colorless solid; **mp** 146–148 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.16 (99.65%) and 13.80 (0.35%); $[\alpha]^{D}_{25}$ -95.65 (*c* 1.24, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 762, 856, 968, 1027, 1068, 1078, 1210, 1298, 1349, 1467, 1611, 1652, 1720, 1768, 2924, 3014, 3440; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 3H), 3.16 (d, *J* = 5.7 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.66 (dd, *J* = 2.1, 5.8 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 7.57 (t, *J* = 7.0 Hz, 2H), 7.68-7.75 (m, 1H), 7.90-7.93 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 62.3, 70.3, 80.3, 122.0, 125.3, 126.4, 129.3, 134.0, 145.7, 169.8, 170.7; ESI-MS: *m*/*z* 259.1352 $[M+Na]^+$; **Analysis**: $C_{12}H_{12}O_5$ requires C 61.01, H 5.12 found C 60.96, H 5.07%.

General experimental procedure for the preparation of *o*-cyano alkenes (46b-z)

o-Bromo alkenes **49b-z** (1 mmol) were taken in dry DMF (10 mL) and CuCN (3 mmol) was added and refluxed under N_2 for 18 h (monitored by TLC). The reaction mixture was

then cooled to room temperature, and then 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 and 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 give *o*-cyanoalkenes **46b-z** in 76-84% yield.

(E)-Ethyl 3-(2-cyano-5-methoxyphenyl)acrylate (46b)

Yield: 86%**,** colorless solid; **mp** 130–132 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 728, 868, 1026, 1256, 1490, 1594, 1607, 1640, 1712, 2228, 2853, 2923 3023; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7 Hz, 3H), 3.90 (s, 3H), 4.29 (q, *J* = 7 Hz, 2H), 6.56 (d, *J* = 16 Hz, 1H), 6.97 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 16 Hz, 1H) ; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 55.6, 60.8, 104.6, 112.1, 116.0, 117.3, 123.1, 135.0, 139.4, 162.7, 165.5; **Analysis**: $C_{13}H_{13}NO_3$ requires C 67.52, H 5.67, N 6.06 found C 67.49, H 5.61, N 6.01%.

(E)-Ethyl 3-(2-cyano-4,5-dimethoxyphenyl)acrylate (46c)

Yield: 87%, colorless solid; mp 159–161 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 761, 848, 1094, 1149, 1204, 1326, 1462, 1571, 1594, 1709, 2222, 2984, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.3 Hz, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.29 (q, *J* = 7.3 Hz, 2H), 6.47 (d, *J* = 16 Hz, 1H), 7.07 (s, 1H), 7.11 (s, 1H), 7.89 (d, *J* = 16 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 55.9, 56.2, 60.7, 105.2, 108.2, 114.2, 117.1, 120.7, 131.5, 139.2, 150.5, 152.6, 165.8; **Analysis**: $C_{14}H_{15}NO_4$ requires C 64.36, H 5.79, N 5.36 found C 64.32, H 5.71, N 5.34%.

(E)-Ethyl 3-(2-cyano-3,4-dimethoxyphenyl)acrylate (46d)

Yield: 88%**,** colorless solid; **mp** 145–147 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 894, 1078, 1138, 1208, 1318, 1326, 1462, 1571, 1594, 1608, 1710, 2222, 2984, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.0 Hz, 3H), 3.93 (s, 3H), 4.03 (s, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 6.48 (d, *J* = 16 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 16 Hz, 1H) ; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 56.1, 60.6, 61.6, 107.9, 114.1, 116.4, 120.7, 122.9, 129.7, 139.2, 152.1, 153.5, 165.9; **Analysis**: $C_{14}H_{15}NO_4$ requires C 64.36, H 5.79, N 5.36 found C 64.34, H 5.71, N 5.32%.

(E)-Ethyl 3-(2-cyano-3,5-dimethoxyphenyl)acrylate (46e)

Yield: 87%**,** colorless solid; **mp** 119–122 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 734, 876, 1069, 1128, 1208, 1326, 1326, 1478, 1568, 1594, 1608, 1712, 2228, 2958, 3082; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.1 Hz, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.55 (d, *J* = 16 Hz, 1H), 6.73 (d, *J* = 2.1 Hz, 1H), 7.86 (d, *J* = 16 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 55.7, 56.1, 60.8, 94.9, 96.1 99.4, 103.4, 114.8, 123.3, 139.6, 140.1, 163.4, 163.9, 165.6; **Analysis**: $C_{14}H_{15}NO_4$ requires C 64.36, H 5.79, N 5.36 found C 64.32, H 5.71, N 5.34%.

(E)-Ethyl 3-(2-cyano-3,4,5-trimethoxyphenyl)acrylate (46f)

Yield: 88%**,** colorless solid; **mp** 150–152 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 703, 749, 940, 1260, 1311, 1573, 1607, 1640, 1708, 2210, 2979, 3016; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.1 Hz, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 4.06 (s, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 6.50 (d, *J* = 16 Hz, 1H), 6.91 (s, 1H), 7.84 (d, *J* = 16 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 55.8, 60.3, 109.1, 115.4, 117.0, 118.5, 126.2, 142.5, 148.5, 151.1, 161.2; **Analysis**: $C_{15}H_{17}NO_5$ requires C 61.85, H 5.88, N 4.81 found C 61.82, H 5.79, N 4.75%.

5-((E)-2-(Ethoxycarbonyl)vinyl)-4-cyano-2-methoxyphenyl 4-methylbenzene sulfonate (46g)

Yield: 87%, colorless solid; **mp** 150–151 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 742, 865, 1030, 1128, 1232, 1318, 1329, 1478, 1571, 1594, 1608, 1708, 2225, 2982, 3025; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 6.9 Hz, 3H), 2.48 (s, 3H), 3.73 (s, 3H), 4.30 (q, *J* = 6.9 Hz, 2H), 6.54 (d, *J* = 16 Hz, 1H), 7.09 (s, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.39 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 16 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 21.7, 56.0, 61.0, 104.5, 110.3, 116.0, 123.8, 128.3, 129.7, 132.6, 137.9, 138.4, 139.1, 145.8, 155.6, 165.2; **Analysis**: $C_{20}H_{19}NO_6S$ requires C 59.84, H 4.77, N 3.49 found C 59.78, H 4.69, N 3.42%.

(E)-Ethyl 3-(5-(benzyloxy)-2-cyano-4-methoxyphenyl)acrylate (46h)

Yield: 86%**,** colorless solid; **mp** 146–148 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 738, 825, 1031, 1098, 1234, 1334, 1380, 1467, 1568, 1575, 1608, 1710, 2228, 2982, 3034; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3H), 3.93 (s, 3H), 4.28 (q, *J* = 7.3 Hz, 2H), 5.20 (s, 2H), 6.34 (d, *J* = 15.4 Hz, 1H), 7.08 (s, 2H), 7.34-7.43 (m, 5H), 7.84 (d, *J* = 15.4 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 56.2, 60.8, 71.0, 105.5, 110.5, 114.7, 117.2, 120.9, 127.3, 128.8, 131.5, 135.4, 139.3, 151.1, 151.8, 165.9; **Analysis**: $C_{20}H_{19}NO_4$ requires C 71.20, H 5.68, N 4.15 found C 71.14, H 5.61, N 4.09%.

(E)-Ethyl 3-(2-cyano-5-fluorophenyl)acrylate (46i)

Yield: 85%**,** colorless solid; **mp** 72–74 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 828, 866, 981, 1030, 1186, 1226, 1276, 1325, 1370, 1480, 1574, 1603, 1640, 1693, 2984, 3012; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 6.58 (d, *J* = 15.9 Hz, 1H), 7.19 ((td, *J* = 2.8, 8.4 Hz, 1H), 7.41 (dd, *J* = 2.6, 9.1 Hz, 1H), 7.74 (dd, *J*

= 5.4, 8.4 Hz, 1H), 7.91 (d, *J* = 15.9 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 60.9, 108.8, 133.9 (d, *J* = 23.6 Hz), 116.0, 117.6 (d, *J* = 23.6 Hz), 124.2, 135.7 (d, *J* = 9.8 Hz), 140.2 (d, *J* = 8.8 Hz), 164.5 (d, *J* = 257.7 Hz), 164.9; **Analysis**: $C_{12}H_{10}FNO_2$ requires C 65.75, H 4.60, N 6.39 found C 65.68, H 4.56, N 6.36%.

(E)-Ethyl 3-(2-cyano-5-nitrophenyl)acrylate (46j)

Yield: 87%**,** colorless solid; **mp** 105–107 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 739, 830, 968, 1032, 1106, 1346, 1540, 1708, 2233, 2980, 3087; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.0 Hz, 3H), 4.33 (q, *J* = 7.0 Hz, 2H), 6.78 (d, *J* = 15.8 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.98 (d, *J* = 15.8 Hz, 1H), 8.33 (dd, *J* = 2.0, 8.4 Hz, 1H) 8.59 (d, *J* = 2.0 Hz, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 14.2, 61.3, 115.2, 117.8, 121.7, 124.1, 125.9, 134.7, 136.9, 139.5, 150.2, 164.8; **Analysis**: $C_{12}H_{10}N2O_4$ requires C 58.54, H 4.09, N 11.38 found C 58.48, H 4.02, N 11.31%.

(E)-Ethyl 3-(5-cyanobenzo[d][1,3]dioxol-6-yl)acrylate (46k)

Yield: 86%, colorless solid; **mp** 148–149 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 728, 878, 1042, 1134, 1256, 1366, 1382, 1478, 1568, 1594, 1608, 1712, 2218, 2958, 3082; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7 Hz, 3H), 4.28 (q, *J* = 7 Hz, 2H), 6.12 (s, 2H), 6.41 (d, *J* = 15.8 Hz, 1H), 7.05 (s, 1H), 7.13 (s, 1H), 7.90 (d, *J* = 15.8 Hz, 1H) ; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 60.8, 102.8, 105.9, 106.8, 111.8, 116.9, 121.4, 133.9, 138.9, 149.2, 151.9, 165.7; **Analysis**: $C_{13}H_{11}NO_4$ requires C 63.67, H 4.52, N 5.71 found C 63.59, H 4.48, N 5.65%.

(E)-Ethyl 3-(1-cyanonaphthalen-2-yl)acrylate (46l)

Yield: 88%**,** colorless solid; **mp** 118–119 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 784, 865, 989, 1030, 1106, 1210, 1275, 1291, 1319, 1368, 1573, 1607, 1712, 2218, 2978, 3084; **^{1}H-**

NMR (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.0 Hz, 3H), 4.32 (q, *J* = 7.0 Hz, 2H), 6.68 (d, *J* = 16 Hz, 1H), 7.59-7.78 (m, 3H), 7.90 (d, *J* = 7.7 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 8.19 (d, *J* = 16 Hz, 1H), 8.28 (d, *J* = 8.7 Hz, 1H) ; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 60.8, 110.8, 115.5, 122.1, 123.5, 125.8, 128.3, 129.1, 132.5, 132.9, 137.0, 139.5, 165.5; **Analysis**: $C_{16}H_{13}NO_2$ requires C 76.48, H 5.21, N 5.57 found C 76.42, H 5.19, N 5.52%.

2-Vinylbenzonitrile (46m)

Yield: 86%, gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 839, 962, 1014, 1072, 1118, 1202, 1308, 1347, 1368, 1444, 1573, 1607, 1625, 1675, 2215, 2889, 2923, 3012; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 5.54 (d, *J* = 10.6 Hz, 1H), 5.95 (d, *J* = 17.8 Hz, 1H), 7.08 (dd, *J* = 10.6, 17.8 Hz, 1H), 7.34 (td, *J* = 1.2, 7.5 Hz, 1H), 7.51-7.70 (m, 3H) ; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 111.0, 117.4, 118.7, 125.2, 127.8, 132.5, 132.7, 140.4; **Analysis**: C_9H_7N requires C 83.69, H 5.46, N 10.84 found C 83.62, H 5.41, N 10.78%.

4-Methoxy-2-vinylbenzonitrile (46n)

Yield: 84%**,** gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 839, 1030, 1083, 1119, 1256, 1308, 1347, 1368, 1456, 1573, 1607, 1625, 1668, 2208, 2923, 3081; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.88 (s, 3H), 5.53 (d, *J* = 11.1 Hz, 1H), 5.92 (d, *J* = 17.7 Hz, 1H), 6.85 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.03 (dd, *J* = 11.1, 17.7 Hz, 1H), 7.11 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.4, 103.2, 110.4, 114.1, 117.9, 118.7, 132.9, 134.4, 142.5, 162.7; **Analysis**: $C_{10}H_9NO$ requires C 75.45, H 5.70, N 8.80 found C 75.41, H 5.67, N 8.73%.

4,5-Dimethoxy-2-vinylbenzonitrile (46o)

Yield: 88%**,** colorless solid; **mp** 106–107 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 839, 936, 1031, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2210, 2923,

3052; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.97 (s, 3H), 5.45 (d, *J* = 11.0 Hz, 1H), 5.80 (d, *J* = 17.2 Hz, 1H), 6.94-7.08 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.7, 55.9, 102.7, 106.9, 113.5, 116.5, 117.7, 132.5, 134.9, 148.7, 152.5; **Analysis**: $C_{11}H_{11}NO_2$ requires C 69.83, H 5.86, N 7.40 found C 69.75, H 5.75, N 7.39%.

2,3-Dimethoxy-6-vinylbenzonitrile (46p)

Yield: 86%, colorless solid; **mp** 108–110 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 748, 840, 936, 1028, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2202, 2981, 3029; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.90 (s, 3H), 5.53 (d, *J* = 10.9 Hz, 1H), 5.90 (d, *J* = 17.3 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 6.69 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 10.9, 17.3 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.1, 61.5, 106.7, 114.7, 116.7, 120.8, 132.4, 133.4, 151.5, 151.7; **Analysis**: $C_{11}H_{11}NO_2$ requires C 69.83, H 5.86, N 7.40 found C 69.73, H 5.78, N 7.39%.

2,4-Dimethoxy-6-vinylbenzonitrile (46q)

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

2,3,4-Trimethoxy-6-vinylbenzonitrile (46r)

Yield: 87%, colorless solid; **mp** 102–103 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 771, 867, 1051, 1105, 1204, 1238, 1257, 1580, 1609, 1753, 2228, 2979, 3013; **^{1}H-NMR** (200 MHz,

$CDCl_3$): δ 3.86 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 5.48 (d, *J* = 11.2 Hz, 1H), 5.83 (d, *J* = 17.3 Hz, 1H), 6.85 (s, 1H), 6.97 (dd, *J* = 11.2, 17.3 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.9, 60.8, 61.5, 98.7, 103.4, 114.8, 117.8, 132.6, 137.2, 141.1, 155.4, 157.2; **Analysis**: $C_{12}H_{13}NO_3$ requires C 65.74, H 5.98, N 6.39 found C 65.72, H 5.91, N 6.37%.

4-Cyano-2-methoxy-5-vinylphenyl 4-methylbenzenesulfonate (46s)

Yield: 82%, colorless solid; **mp** 149–150 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 746, 845, 938, 1034, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2220, 2978, 3075; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.48 (s, 3H), 3.74 (s, 3H), 5.57 (d, *J* = 10.9 Hz, 1H), 5.86 (d, *J* = 17.6 Hz, 1H), 6.93-7.08 (m, 2H), 7.28 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.7, 55.8, 102.9, 108.9, 116.6, 119.7, 127.7, 128.5, 129.6, 132.3, 132.7, 137.7, 141.4, 145.6, 155.5; **Analysis**: $C_{17}H_{15}NO_4S$ requires C 61.99, H 4.59, N 4.25 found C 61.89, H 4.53, N 4.23%.

4-(Benzyloxy)-5-methoxy-2-vinylbenzonitrile (46t):

Yield: 84%**,** colorless solid; **mp** 111–113 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 747, 858, 934, 1028, 1065, 1119, 1232, 1308, 1394, 1389, 1456, 1574, 1612, 1631, 1656, 2220, 2988, 3086; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 5.21 (s, 2H), 5.39 (d, *J* = 11.1 Hz, 1H), 5.66 (d, *J* = 17.4 Hz, 1H), 6.89-7.04 (m, 2H), 7.10 (s, 1H), 7.32-7.47 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.0, 70.8, 103.1, 109.2, 114.0, 116.6, 117.8, 127.2, 128.2, 128.6, 132.6, 134.9, 135.7, 149.3, 151.8; **Analysis**: $C_{17}H_{15}NO_2$ requires C 76.96, H 5.70, N 5.28 found C 76.91, H 5.67, N 5.27%.

4-Fluoro-2-vinylbenzonitrile (46u):

Yield: 86%**,** colorless solid; **mp** 105–107 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 839, 962, 1014, 1072, 1118, 1202, 1308, 1347, 1368, 1444, 1573, 1607, 1625, 1675, 2853, 2923,

3012; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 5.62 (d, *J* = 11.0 Hz, 1H), 5.96 (d, *J* = 17.3 Hz, 1H), 7.02-7.08 (m, 2H), 7.34 (dd, *J* = 2.2, 9.4 Hz, 1H), 7.64 (dd, *J* = 5.5, 8.5 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 107.6, 112.6 (d, *J* = 23.7 Hz), 115.8 (d, *J* = 23.7 Hz), 116.8, 120.2, 132.2, 143.8 (d, *J* = 9.5 Hz), 165.1 (d, *J* = 243.8 Hz); **Analysis**: C_9H_6FN requires C 73.46, H 4.11, N 9.52 found C 73.44, H 4.08, N 9.49%.

6-Vinylbenzo[*d*][1,3]dioxole-5-carbonitrile (46v)

Yield: 88%, colorless solid; **mp** 88–91 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 868, 930, 1038, 1162, 1263, 1359, 1486, 1505, 1604, 1615, 2219, 2916, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.44 (d, *J* = 11.1 Hz, 1H), 5.77 (d, *J* = 17.3 Hz, 1H), 6.07 (s, 2H), 6.95-7.04 (m, 2H), 7.09 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 102.3, 104.0, 104.8, 110.9, 117.2, 117.7, 132.5, 137.5, 147.4, 151.8; **Analysis**: $C_{10}H_7NO_2$ requires C 69.36, H 4.07, N 8.09 found C 69.34, H 4.02, N 7.99%.

2-((E)-Pent-1-enyl)benzonitrile (46w)

Yield: 87%, colorless solid; **mp** 126–128 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 857, 974, 1037, 1095, 1184, 1202, 1216, 1251, 1275, 1291, 1319, 1347, 1368, 1393, 1444, 1477, 1573, 1607, 1640, 1716, 2984, 3023; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.45-1.63 (m, 2H), 2.22-2.33 (m, 2H), 6.43 (dt, *J* = 15.3, 6.8 Hz, 1H), 6.74 (d, *J* = 15.3 Hz, 1H), 7.25 (dd, *J* = 15.3, 1.4 Hz, 1H), 7.45-7.62 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 22.2, 35.2, 110.5, 117.9, 125.2, 126.0, 126.8, 132.5, 132.7, 136.4, 141.1; **Analysis**: $C_{12}H_{13}N$ requires C 84.17, H 7.65, N 8.18 found C 84.14, H 7.61, N 8.15%.

4,5-Dimethoxy-2-((E)-3-*tert*-butyldimethylsilyloxyprop-1-enyl)benzonitrile (46x)

Yield: 85%**,** Gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 748, 876, 932, 1032, 1098, 1276, 1339, 1486, 1505, 1604, 1615, 2220, 2989, 3054; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.94

(s, 9H), 3.88 (s, 3H), 3.94 (s, 3H), 4.39 (dd, *J* = 1.7, 4.7 Hz, 2H), 6.27-6.39 (m, 1H), 6.89 (d, *J* = 15.5 Hz, 1H), 6.98 (s, 1H), 7.00 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 25.9, 55.8, 55.9, 63.3, 102.6, 107.4, 113.7, 117.9, 124.9, 132.4, 134.8, 148.4, 152.5; **Analysis**: $C_{18}H_{27}NO_3Si$ requires C 64.83, H 8.16, N 4.20 found C 64.79, H 8.09, N 4.13%.

4,5-Dimethoxy-2-styrylbenzonitrile (46y)

Yield: 83%, colorless solid; **mp** 158–159 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 761, 1149, 1204, 1326, 1462, 1571, 1594, 2215, 2984, 3023; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.01 (s, 3H), 7.01-7.17 (m, 3H), 7.26-7.42 (m, 4H), 7.54 (d, *J* = 6.9 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.9, 102.9, 106.8, 113.6, 118.0, 123.8, 126.7, 128.7, 128.6, 131.2, 134.9, 136.1, 148.5, 152.6; **Analysis**: $C_{17}H_{15}NO_2$ requires C 76.96, H 5.70, N 5.28 found C 76.89, H 5.57, N 5.19%.

2,3,4-Trimethoxy-6-((E)-oct-1-enyl)benzonitrile (46z)

Yield: 86%**,** colorless solid; **mp** 172–174 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 755, 878, 969, 989, 1097, 1216, 1271, 1452, 1464, 1513, 1600, 2220, 2970, 3025, 3059; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.87-0.93 (m, 3H), 1.26-1.46 (m, 8H), 2.21-2.31 (m, 2H), 3.85 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 6.23-6.36 (m, 1H), 6.63 (d, *J* = 15.6 Hz, 1H), 6.78 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 28.9, 29.0, 31.6, 33.1, 56.0, 61.1, 61.6, 98.3, 103.3, 115.4, 125.8, 135.9, 138.1, 140.5, 155.6, 157.2; **Analysis**: $C_{18}H_{25}NO_3$ requires C 71.26, H 8.31, N 4.62 found C 71.22, H 8.28, N 4.58%.

(E)-Ethyl 3-(3-cyanophenyl)acrylate (50)

Yield: 93%; colorless solid; **mp** 62–65 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 710, 765, 977, 1032, 1185, 1278, 1318, 1447, 1480, 1640, 1712, 2225, 2938, 2983; **^{1}H-NMR** (200 MHz,

$CDCl_3$): δ 1.35 (d, *J* = 7 Hz, 3H), 4.28 (d, *J* = 7 Hz, 2H), 6.48 (d, *J* = 16.1 Hz, 1H), 7.48-7.80 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 60.5, 113.2, 117.8, 120.8, 129.6, 131.1, 131.6, 132.8, 135.5, 141.5, 165.7; **Analysis**: $C_{12}H_{11}NO_2$ requires C 71.63, H 5.51, N 6.96 found C 71.59, H 5.45, N 6.85%.

(E)-Ethyl 3-(4-cyanophenyl)acrylate (51)

Yield: 93%; colorless solid; **mp** 68–70 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 730, 795, 955, 1065, 1194, 1268, 1375, 1445, 1495, 1652, 1721, 2226, 2983; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.35 (d, *J* = 7.1 Hz, 3H), 4.28 (d, *J* = 7.1 Hz, 2H), 6.51 (d, *J* = 15.8 Hz, 1H), 7.59-7.71 (m, 5H); **^{13}C-NMR** ($CDCl_3$): δ 14.1, 60.6, 113.2, 117.9, 121.6, 128.2, 132.4, 138.5, 141.8, 165.7; **Analysis**: $C_{12}H_{11}NO_2$ requires C 71.63, H 5.51, N 6.96 found C 71.58, H 5.48, N 6.88%.

General experimental procedure for the preparation of chiral phthalides (47b-z)

A 50 mL RB flask was charged with $K_3Fe(CN)_6$ (3 mmol), K_2CO_3 (3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and H_2O (5 mL) and stirred for 10 min. Subsequently, $(DHQD)_2PHAL$ (1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, *o*-cyanoalkene(s) **46b-z** (1 mmol) was added and allowed to stir for 3-7 h at 25 ºC. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 ºC. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and petroleum ether/EtOAc (7:3) as an eluent] gave phthalides **47b-z** in 92-95% yield.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47b)

Yield: 95%; colorless solid; **mp** 121 – 122 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 1 mL/min) retention time 25.80 min (99.55%) and 30.33 min (0.45%); $[\alpha]^{D}_{25}$ -94.49 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 724, 876, , 1031, 1084, 1191, 1212, 1278, 1295, 1357, 1398, 1445, 1486, 1578, 1607, 1721, 1765, 2984, 3023, 3415; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz, 3H), 3.14 (br s, 3H), 3.91 (s, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.63 (d, *J* = 1.7 Hz, 1H), 5.69 (d, *J* = 2.2 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 7.05 (dd, *J* = 2.1, 8.6 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H) ; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.0, 55.7, 62.6, 70.5, 79.6, 106.0, 116.9, 118.9, 127.0, 148.5, 164.7, 169.5, 170.8; ESI-MS: *m*/*z* 266.04 $[M+Na]^+$; **Analysis**: $C_{13}H_{14}O_6$ requires C 58.64, H 5.30 found C 58.62, H 5.19%.

(*S*)-Ethyl-2-((*R*)-1,3-dihydro-5,6-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47c)

Yield: 94%; colorless solid; **mp** 144–146 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 23.18 min (99.36%) and 27.60 min (0.64%); $[\alpha]^{D}_{25}$ -95.12 (*c* 1.12, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 945, 1125, 1297, 1507, 1722, 1764, 2925, 3010, 3341; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 3.20 (d, *J* = 6.2 Hz, 1H), 3.94 (s, 3H), 3.98 (s, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.62 (dd, *J* = 2.4, 6.1 Hz, 1H), 5.66 (d, *J* = 2.2 Hz, 1H), 6.93 (s, 1H), 7.27 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 14.3, 56.1, 56.3, 61.1, 70.1, 81.1, 105.2, 105.7, 118.2, 141.6, 150.4, 154.7, 170.2, 171.3; ESI-MS: *m*/*z* 296.15 $[M+Na]^+$; **Analysis**: $C_{14}H_{16}O_7$ requires C 64.36, H 5.79, N 5.36 found C 64.32, H 5.71, N 5.34%.

(*S*)-Ethyl-2-((*R*)-1,3-dihydro-6,7-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47d)

Yield: 94%**,** colorless solid; **mp** 110–112 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 23.90 min (99.44%) and 27.87 min (0.56%); $[\alpha]^{D}_{25}$ -95.28 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 762, 946, 1132, 1298, 1518, 1728, 1764, 2985, 3034, 3425; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.1 Hz, 3H), 3.19 (br s, 1H), 3.91 (s, 3H), 4.10 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.57 (s, 1H), 5.65 (d, J = 2.0 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H); **^{13}C- NMR** (50 MHz, $CDCl_3$): δ 14.0, 56.6, 62.2, 62.6, 70.7, 79.0, 116.4, 118.7, 119.2, 138.5, 148.3, 152.9, 167.2, 170.9; **Analysis**: $C_{14}H_{16}O_7$ requires C 64.36, H 5.79 found C 64.34, H 5.71%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5,7-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47e)

Yield: 94%**,** colorless solid; **mp** 154–156 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.37 min (99.60%) and 21.74 min (0.40%); $[\alpha]^{D}_{25}$ -96.29 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 746, 985, 1130, 1287, 1514, 1723, 1762, 2954, 3085, 3414; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 3H), 3.37 (br s, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.61 (s, 1H), 5.67 (s, 1H), 6.47 (s, 1H), 6.59 (s, 1H); **^{13}C-NMR** (50 MHz, CD_3OD): δ 14.5, 56.5, 56.8, 62.9, 71.9, 82.1, 99.8, 100.2, 108.0, 153.0, 160.9, 168.9, 170.6, 172.4; **Analysis**: $C_{14}H_{16}O_7$ requires C 64.36, H 5.79 found C 64.34, H 5.76%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5,6,7-trimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47f)

Yield: 92%**,** colorless solid; **mp** 111–112 ºC; $[\alpha]^{D}_{25}$ -94.65 (*c* 1.23, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1012, 1094, 1140, 1254, 1350, 1475, 1602, 1765, 2954, 3085, 3408 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3H), 3.09 (s,1H), 3.86 (s, 3H), 3.96 (s, 3H), 4.13 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.58 (d, *J* = 2.1 Hz, 1H), 5.58 (d, *J* = 2.1 Hz, 1H), 6.70 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 56.3, 61.1, 62.0, 62.4, 79.1, 99.5, 111.0, 141.9, 143.5, 152.1, 159.6, 167.3, 176.7; ESI-MS: *m*/*z* 326.21 $[M+Na]^+$; **Analysis**: $C_{15}H_{18}O_8$ requires C 55.21, H 5.56 found C 55.18, H 5.53%.

(*S*)-Ethyl 2-((*R*)-5-(*p*-toluenesulfonoyloxy)-1,3-dihydro-6-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47g)

Yield: 93%**,** colorless solid; **mp** 107–108 ºC; $[\alpha]^{D}_{25}$ -94.89 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 768, 819, 1025, 1050, 1120, 1180, 1190, 1330, 1374, 1494, 1614, 1767, 2924, 3012, 3371; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.48 (s, 3H), 3.07 (s, 1H), 3.78 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.63 (d, *J* = 2.1 Hz, 1H), 5.67 (d, *J* = 2.1 Hz, 1H), 6.99 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.49 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 2H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 14.4, 21.7, 56.6, 61.4, 70.3, 71.6, 81.3, 107.3, 118.6, 119.7, 128.6, 130.0, 132.5, 139.5, 145.9, 147.9, 156.9, 168.8, 170.9; **Analysis**: $C_{20}H_{20}O_9S$ requires C 55.04, H 4.62 found C 55.01, H 4.59%.

(*S*)-Ethyl 2-((*R*)-5-(benzyloxy)-1,3-dihydro-6-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47h)

Yield: 94%**,** colorless solid; **mp** 138–140 ºC; $[\alpha]^{D}_{25}$ -96.04 (*c* 1.21, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 738, 856, 1025, 1078, 1130, 1184, 1195, 1336, 1395, 1494, 1645, 1765, 2942,

3035, 3413; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 3.04 (d, *J* = 5.9 Hz, 1H), 3.94 (s, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 4.55 (dd, *J* = 2.5, 5.9 Hz, 1H), 5.22 (d, *J* = 3.5 Hz, 2H), 5.61 (d, *J* = 2.0 Hz, 1H), 6.94 (s, 1H), 7.26 (s,1H), 7.29-7.45 (m, 5H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 13.7, 55.7, 61.4, 70.3, 70.6, 79.9, 105.2, 105.8, 118.5, 127.0, 127.8, 128.2, 135.3, 139.9, 150.7, 153.5, 169.6, 170.4; **Analysis**: $C_{20}H_{20}O_7$ requires C 64.51, H 5.41 found C 64.39, H 5.36%.

(*S*)-Ethyl-2-((*R*)-5-fluoro-1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47i)

Yield: 94%**,** colorless solid; **mp** 108–109 ºC; $[\alpha]^D_{25}$ -95.41 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 891, 1052, 1097, 1130, 1190, 1325, 1374, 1485, 1629, 1765, 2928, 3015, 3351; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 3.17 (d, *J* = 6.7 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.62 (dd, *J* = 2.2, 5.8 Hz, 1H), 5.74 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.91 (dd, *J* = 5.8, 8.3 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 62.2, 70.2, 79.7, 109.5 (d, *J* = 24.6 Hz), 117.6 (d, *J* = 24.6 Hz), 122.7, 127.7, 148.6 (d, *J* = 10.3 Hz), 166.3 (d, *J* = 256.3 Hz), 168.5, 170.5; **Analysis**: $C_{12}H_{11}FO_5$ requires C 56.70, H 4.36 found C 56.67, H 4.33%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5-nitro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47j)

Yield: 93%**,** colorless solid; **mp** 146–148 ºC; $[\alpha]^D_{25}$ -95.28 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 738, 829, 967, 1037, 1106, 1346, 1540, 1740, 1779, 2853, 2918, 3009, 3444; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3H), 3.21 (d, *J* = 6.1 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.71 (d, *J* = 3.6 Hz, 1H), 5.90 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.42-8.46 (m, 2H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 14.1, 63.2, 70.1, 80.1, 117.8, 125.3, 127.0,

131.8, 146.8, 151.7, 167.3, 170.2; **Analysis**: $C_{12}H_{11}NO_7$ requires C 51.25, H 3.94, N 4.98 found C 51.24, H 3.85, N 4.93%.

(*S*)-Ethyl 2-((*R*)-5-1,3-dihydro-5, 6-dioxomethyl-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (47k)

Yield: 95%**,** colorless solid; **mp** 150–153 ºC; $[\alpha]^{D}_{25}$ -95.74 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 786, 891, 1015, 1054, 1122, 1183, 1196, 1356, 1395, 1489, 1618, 1755, 2942, 3021, 3410; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.1 Hz, 3H), 3.10 (br s, 1H), 4.30 (qd, *J* = 1.4, 7.1 Hz, 2H), 4.56 (s, 1H), 5.62 (d, *J* = 2.1 Hz, 1H), 6.14 (dd, *J* = 1.4, 4.4 Hz, 2H), 6.89 (s, 1H), 7.20 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.0, 62.6, 70.4, 79.6, 101.8, 102.7, 104.2, 120.4, 142.2, 149.6, 153.7, 169.2, 170.8; **Analysis**: $C_{13}H_{12}O_7$ requires C 55.72, H 4.32 found C 55.65, H 4.29%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-1-oxonaphtho[2,1-c]furan-3-yl)-2-hydroxyacetate (47l)

Yield: 94%**,** colorless solid; **mp** 107–109 ºC; $[\alpha]^{D}_{25}$ -95.69 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 784, 865, 989, 1010, 1106, 1210, 1275, 1291, 1319, 1368, 1573, 1607, 1750, 2978, 3084, 3457; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.4 Hz, 3H), 3.14 (d, *J* = 6.0 Hz, 1H), 4.31 (q, *J* = 7.4 Hz, 2H), 4.74 (dd, *J* = 2.1, 6.0 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.63-7.78 (m, 2H), 7.97 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H) 8.97 (d, *J* = 8.5 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$+ CD_3OD): δ 13.2, 61.4, 69.8, 80.3, 118.1, 118.6, 120.2, 122.4, 126.7, 128.0, 128.3, 133.0, 135.2, 147.6, 170.3; **Analysis**: $C_{16}H_{14}O_5$ requires C 67.13, H 4.93 found C 67.11, H 4.89%.

(*R*)-3-(Hydroxymethyl)isobenzofuran-1(3*H*)-one (47m)

Yield: 95%**,** colorless solid; **mp** 101–104 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 8.03 (99.36%) and 9.24

(0.64%); $[\alpha]^{D}_{25}$ -78.12 (*c* 1.23, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 744, 847, 968, 1025, 1067, 1089, 1211, 1288, 1349, 1467, 1607, 1640, 1756, 2924, 3012, 3440; **^{1}H-NMR** (200 MHz, $CDCl_3$): 2.61 (s, 1H), 3.90 (d, *J* = 11.8 Hz, 1H), 4.14 (d, *J* = 11.8 Hz, 1H), 5.54-5.59 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.70 (td, *J* = 1.1, 7.4 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 61.7, 81.5, 121.6, 124.2, 125.6, 128.4, 133.3, 146.7, 170.6; **Analysis**: $C_9H_8O_3$ requires C 65.85, H 4.91 found C 65.83, H 4.85%.

(*R*)-3-(Hydroxymethyl)-5-methoxyisobenzofuran-1(3*H*)-one (47n)

Yield: 95%**,** colorless solid; mp 137–140 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 1 mL/min) retention time 27.19 min (99.36%) and 39.72 min (0.64%); $[\alpha]^{D}_{25}$ -78.36 (*c* 1.12, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 728, 868, 1026, 1256, 1490, 1607, 1640, 1749, 2853, 2923, 3440; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.31 (br s, 1H), 3.84-3.91 (m, 4H), 4.06-4.14 (m, 1H), 5.46 (t, *J* = 5.3 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 7.04 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 54.8, 62.1, 81.0, 105.5, 116.3, 117.7, 126.0, 149.8, 164.5, 170.8; **Analysis**: $C_{10}H_{10}O_4$ requires C 61.85, H 5.19 found C 61.79, H 5.12%.

(*R*)-3-(Hydroxymethyl)-5,6-dimethoxyisobenzofuran-1(3*H*)-one (47o)

Yield: 93%**,** colorless solid; **mp** 165–167 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 23.18 min (99.36%) and 27.60 min (0.64%); $[\alpha]^{D}_{25}$ -77.89 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 828, 956, 1027, 1056, 1225, 1266, 1309, 1335, 1474, 1508, 1612, 1752, 2922, 3023, 3358; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.71 (t, *J* = 6.4 Hz, 1H), 3.81-3.90 (m, 1H), 3.93 (s, 3H), 3.99 (s, 3H), 4.04-4.15 (m, 1H), 5.42-5.47 (m, 1H), 6.93 (s, 1H), 7.25 (s, 1H); **^{13}C-NMR** (50

MHz, DMSO-d_6): δ 56.1, 56.3, 62.4, 81.6, 105.0, 105.8, 117.9, 142.4, 150.3, 154.6, 170.5; **Analysis**: $C_{11}H_{12}O_5$ requires C 58.93, H 5.39 found C C 58.85, H 5.37%.

(*R*)-3-(Hydroxymethyl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one (47p)

Yield: 94%**,** colorless solid; **mp** 85–88 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.35 min (99.35%) and 20.85 min (0.56%); $[\alpha]^{D}_{25}$ -78.21 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 798, 956, 1030, 1067, 1220, 1328, 1339, 1458, 1605, 1745, 2976, 3012, 3457; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.24 (brs, 1H), 3.79-3.85 (m, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 4.03-4.09 (m, 1H), 5.35-5.39 (m, 1H), 6.42 (s, 1H), 6.48(s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.6, 62.0, 63.7, 80.7, 116.8, 118.4, 119.4, 139.6, 148.0, 152.5, 168.2; **Analysis**: $C_{11}H_{12}O_5$ requires C 58.93, H 5.39 found C 58.83, H 5.36%.

(*R*)-3-(Hydroxymethyl)-5,7-dimethoxyisobenzofuran-1(3*H*)-one (47q)

Yield: 94%**,** colorless solid; **mp** 152–153 ºC; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.27 min (99.36%) and 20.40 min (0.64%); $[\alpha]^{D}_{25}$ -78.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 765, 950, 1030, 1058, 1232, 1331, 1365, 1463, 1615, 1751, 2982, 3010, 3443; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.53 (br s, 1H), 3.77-3.88 (m, 3H), 3.91 (s, 3H), 3.99-4.04 (m, 3H), 4.10 (s, 1H), 5.40-5.45 (m, 1H), 7.09 (dd, *J* = 8.4, 8.2 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 54.6, 54.9, 62.2, 80.4, 97.6, 98.2, 105.8, 151.7, 158.9, 166.6, 168.9; **Analysis**: $C_{11}H_{12}O_5$ requires C 58.93, H 5.39 found C C 58.89, H 5.37%.

(*R*)-3-(Hydroxymethyl)-5,6,7-trimethoxyisobenzofuran-1(3H)-one (47r)

Yield: 93%**,** colorless solid; **mp** 178–180 ºC; $[\alpha]^{D}_{25}$ -78.05 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1014, 1097, 1254, 1345, 1483, 1600, 1754, 2947, 3017, 3444; **^{1}H-NMR** (200

MHz, $CDCl_3$): δ 2.62 (br s, 1H), 3.84-3.90 (m, 4H), 3.96 (s, 3H), 4.03-4.09 (m, 1H), 4.13(s, 3H), 5.35-5.39 (m, 1H), 6.69 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 56.3, 61.1, 62.0, 63.7, 80.6, 99.9, 110.6, 141.8, 144.8, 152.1, 159.7, 168.3; **Analysis**: $C_{12}H_{14}O_6$ requires C 56.09, H 5.55 found C 56.05, H 5.53%.

(*R*)-1,3-Dihydro-1-(hydroxymethyl)-5-methoxy-3-oxoisobenzofuran-6-yl 4-methylbenzenesulfonate (47s)

Yield: 95%**,** colorless solid; **mp** 152–154 ºC; $[\alpha]^{D}_{25}$ -77.79 (*c* 1.18, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 734, 849, 973, 103, 1053, 1178, 1345, 1372, 1494, 1614, 1755, 2919, 3018, 3437; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.24 (br s, 1H), 2.48 (s, 3H), 3.80 (s, 3H), 3.92 (dd, *J* = 4.6, 12.3 Hz, 1H), 4.03 (dd, *J* = 4.7, 12.3 Hz, 1H), 5.44 (t, *J* = 4.6 Hz, 1H), 6.97 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.48 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 20.0, 55.0, 61.4, 80.9, 105.3, 117.4, 119.3, 127.6, 128.8, 131.9, 138.9, 145.1, 147.7, 156.6, 169.5; **Analysis**: $C_{17}H_{16}O_7S$ requires C 56.04, H 4.43 found C 55.97, H 4.37%.

(*R*)-5-(Benzyloxy)-3-(hydroxymethyl)-6-methoxyisobenzofuran-1(3*H*)-one (47t)

Yield: 94%**,** colorless solid; **mp** 126–128 ºC; $[\alpha]^{D}_{25}$ -78.22 (*c* 1.10, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 689, 825, 975, 1025, 1076, 1223, 1268, 1312, 1334, 1494, 1528, 1621, 1752, 2924, 3032, 3385; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.31 (br s, 1H), 3.75-3.85 (m, 1H), 3.92 (s, 3H), 3.98-4.06 (m, 1H), 5.22 (s, 2H), 5.36-5.41 (m, 1H), 6.92 (s, 1H), 7.28 (s, 1H), 7.32-7.45 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.2, 64.1, 71.1, 81.0, 105.4, 106.6, 118.6, 127.3, 128.3, 128.7, 135.6, 140.9, 151.2, 154.0, 170.5; **Analysis**: $C_{17}H_{16}O_5$ requires C 67.99, H 5.37 found C 67.91, H 5.35%.

(*R*)-5-Fluoro-3-(hydroxymethyl)isobenzofuran-1(3*H*)-one (47u)

Yield: 93%**,** Gum; $[\alpha]^{D}_{25}$ -77.21 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 689, 825, 975, 1025, 1076, 1223, 1268, 1312, 1334, 1494, 1528, 1621, 1752, 2924, 3032, 3385; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 2.87 (br s, 1H), 3.93 (dd, *J* = 4.0, 12.5 Hz, 1H), 4.11 (dd, *J* = 4.0, 12.5 Hz, 1H), 5.51-5.53 (t, *J* = 4.0 Hz, 1H), 7.21-7.27 (m, 2H), 7.88-7.91 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 63.4, 80.9, 109.7 (d, *J* = 24.6 Hz), 117.7 (d, *J* = 24.6 Hz), 122.6, 128.2 (d, *J* = 9.4 Hz), 149.7 (d, *J* = 9.4 Hz), 167.3 (d, *J* = 398.5 Hz), 167.9; **Analysis**: $C_9H_7FO_3$ requires C 59.35, H 3.87 found C 73.44, H 4.08%.

(*R*)-3-(Hydroxymethyl)-5, 6-dioxomethylisobenzofuran-1(3*H*)-one (47v)

Yield: 94%**,** colorless solid; **mp** 144–145 ºC; $[\alpha]^{D}_{25}$ -78.11 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 852, 957, 1024, 1067, 1232, 1286, 1319, 1343, 1484, 1582, 1612, 1766, 2942, 3054, 3389; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.40 (br s, 1H), 3.84 (dd, *J* = 4.0, 12.4 Hz, 1H), 4.06 (dd, *J* = 4.0, 12.4 Hz, 1H), 5.41 (m, 1H), 6.13 (d, *J* = 2.3 Hz, 2H), 6.87 (s, 1H), 7.20 (s, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 62.1, 81.3, 102.8, 103.3, 119.7, 144.5, 149.0, 153.2, 169.6; **Analysis**: $C_{10}H_8O_5$ requires C 57.70, H 3.87 found C 57.68, H 3.85%.

(*R*)-3-((*R*)-1-Hydroxybutyl)isobenzofuran-1(3*H*)-one (47w)

Yield: 93%; colorless solid; **mp** 103–109 ºC; $[\alpha]^{D}_{25}$ -76.89 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 728, 1080, 1212, 1287, 1467, 1618, 1752, 2873, 2959, 3433; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.8 Hz, 3H), 1.44-1.72 (m, 4H), 1.97 (br s, 1H), 3.99 (br s, 1H), 5.40 (d, *J* = 3.6 Hz, 1H), 7.51-7.57 (m, 2H), 7.65-7.73 (m, 1H), 7.87-7.92 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 18.8, 34.9, 71.9, 83.2, 122.4, 125.6, 126.6, 129.2, 134.0, 147.2, 170.5; **Analysis**: $C_{12}H_{14}O_3$ requires C 69.88, H 6.84 found C 69.82, H 6.81%.

(*R*)-3-((*R*)-1-Hydroxy-2-tertiarybutyldimethylsilylethyl)-5,6-dimethoxy isobenzofuran-1(3*H*)-one (47x)

Yield: 94%**,** colorless solid; **mp** 166–168 ºC; $[\alpha]^{D}_{25}$ -79.24 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 775, 837, 1060, 1137, 1471, 1503, 1740, 2855, 2926, 3406; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.08 (d, *J* = 5.4 Hz, 6H), 0.90 (s, 9H), 2.30 (d, *J* = 5.5 Hz, 1H), 3.62-3.82 (m, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 4.05-4.12 (m, 1H), 5.51 (d, *J* = 3.4 Hz, 1H), 6.98 (s, 1H), 7.28 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ -5.0, -4.5, 17.8, 25.5, 56.2, 63.1, 73.3, 80.1, 104.2, 106.0, 118.9, 141.5, 150.6, 154.6, 170.6; **Analysis**: $C_{18}H_{28}O_6Si$ requires C 58.67, H 7.66 found C 58.65, H 7.56%.

(R)-3-((R)-Hydroxy(phenyl)methyl)-5,6-dimethoxyisobenzofuran-1(3*H*)-one (47y)

Yield: 94%**,** colorless solid; **mp** 113–115 ºC; $[\alpha]^{D}_{25}$ -79.23 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 857, 974, 1026, 1064, 1158, 1216, 1334, 1604, 1743, 2858, 2928, 3430 ; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.05 (br s, 1H), 3.64 (s, 3H), 3.90 (s, 3H), 4.69 (d, *J* = 7.4 Hz, 1H), 5.47 (d, *J* = 7.4 Hz, 1H), 5.85 (s, 1H), 7.20 (s, 1H), 7.34-7.41 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 54.7, 74.3, 83.0, 104.3, 117.4, 126.6, 127.4, 138.1, 140.6, 149.8, 153.5, 170.6; **Analysis**: $C_{17}H_{16}O_5$ requires C 67.99, H 5.37 found C 67.92, H 5.29%.

(*R*)-3-((*R*)-1-Hydroxyheptyl)-5,6,7-trimethoxyisobenzofuran-1(3*H*)-one (47z)

Yield: 92%**,** colorless solid; **mp** 113–115 ºC; $[\alpha]^{D}_{25}$ -78.36 (*c* 1.08, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 796, 1089, 1130, 1254, 1326, 1465, 1543, 1749, 2898, 2974, 3988 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.87-0.93 (m, 3H), 1.26-1.37 (m, 8H), 1.64-1.78 (m, 2H), 3.87 (s, 3H), 3.94-3.96 (m, 4H), 4.13 (s, 3H), 5.23 (d, *J* = 3.0 Hz, 1H), 6.68 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.5, 25.7, 29.1, 31.7, 32.8, 56.3, 61.2, 62.1, 72.1, 81.7,

99.8, 111.1, 141.8, 145.3, 152.2, 159.6, 168.1; **Analysis**: $C_{18}H_{26}O_6$ requires C 63.89, H 7.74 found C 63.81, H 7.68%.

(2*S*,3*R*)-Ethyl 3-(3-cyanophenyl)-2,3-dihydroxypropanoate (52)

Yield: 93%; Gum; $[\alpha]^{D}_{25}$ -36.06 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 680, 725, 954, 1057, 1118, 1214, 1291, 1734, 2229, 2985, 3443; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (d, *J* = 7.1 Hz, 3H), 3.26 (d, *J* = 7.5 Hz, 1H), 3.43 (d, *J* = 5.8 Hz, 1H), 4.24-4.34 (m, 3H), 5.02 (dd, *J* = 2.3, 7.5 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.57-7.67 (m, 2H), 7.72 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 62.3, 73.5, 74.5, 112.2, 118.6, 129.0, 130.2, 130.9, 131.3, 141.9, 172.3; **Analysis**: $C_{12}H_{13}NO_4$ requires C 61.27, H 5.57, N 5.95 found C 61.26, H 5.54, N 5.89.

(2*S*,3*R*)-Ethyl 3-(4-cyanophenyl)-2,3-dihydroxypropanoate (53)

Yield: 93%; colorless solid; **mp** 102 – 103 ºC; $[\alpha]^{D}_{25}$ -36.42 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 685, 765, 1017, 1050, 1105, 1204, 1257, 1752, 2228, 2978, 3332; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (d, *J* = 7.0 Hz, 3H), 3.03 (d, *J* = 7.6 Hz, 1H), 3.27 (d, *J* = 5.3 Hz, 1H), 4.24-4.35 (m, 3H), 5.05 (dd, *J* = 2.3, 7.5 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.57-7.67 (m, 2H), 7.72 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 12.9, 60.6, 73.2, 74.2, 110.0, 117.9, 126.7, 131.0, 146.2, 171.4; **Analysis**: $C_{12}H_{13}NO_4$ requires C 61.27, H 5.57, N 5.95 found C 61.23, H 5.52, N 5.84%.

Benzyl(1*R*,2*S*)-2-(ethoxycarbonyl)-1-(2-cyanophenyl)-2-hydroxyethylcarbamate (54)

Sodium hydroxide (60 mg, 1.5 mmol) was dissolved in water (4 mL), and 0.5 mL of this NaOH solution was transferred to a small vial containing $K_2OsO_2(OH)_4$ (0.02 mmol for 4 mol %) for later use. To the remainder of the NaOH solution were added the carbamate (1.55 mmol) and *n*-PrOH (2 mL). The mixture was stirred for 2-3 min and placed in a

water bath before *tert*-butylhypochlorite 16 (175 μL, 1.52 mmol) was slowly added with vigorous stirring. Then, the resulting solution was sequentially treated with a solution of $(DHQD)_2PHAL$ (0.025 mmol for 5 mol %) in *n*-PrOH (1 mL), the o-cyano ethylcinnamate (0.50 mmol), the previously prepared solution of $K_2OsO_2(OH)_4$, and *n*-PrOH (1 mL). The reaction mixture was monitored by TLC to establish completion, quenched by the addition of saturated aqueous sodium sulfite (4 mL) while being cooled in an ice-water bath, and stirred for an additional 30 min. The separated aqueous phase was extracted with EtOAc (3 X 5 mL), and the combined organic extracts were washed with water (3 mL) followed by brine (5 mL), dried over anhyd.Na_2SO_4, and concentrated under reduced pressure to give the crude products which were purified by column chromatography [silica gel (230-400 mesh) and petroleum ether: EtOAc (60:40) as an eluent] to give product **54** in 64% yield with dr 6:1.

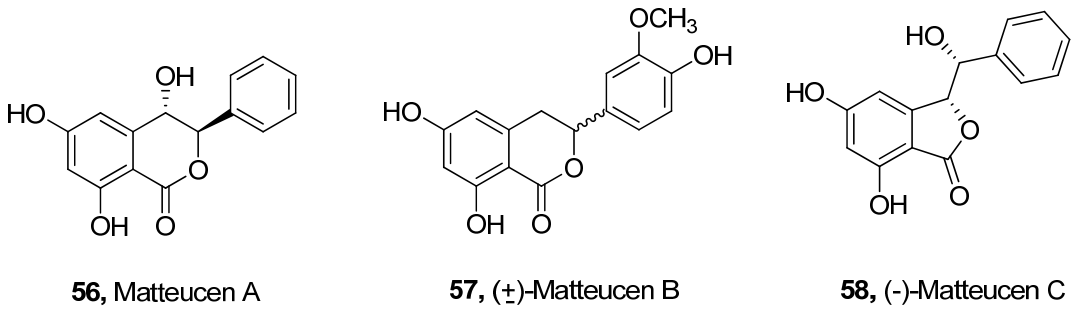
Gum; $[\alpha]^D_{25}$ -36.06 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 857, 974, 1037, 1095, 1184, 1202, 1275, 1291, 1319, 1347, 1368, 1393, 1477, 1573, 1607, 1640, 1716, 2219, 2984, 3023, 3415; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.34 (d, *J* = 7.5 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.50 (s, 1H), 5.06 (dd, *J* = 2.3, 7.5 Hz, 1H), 5.62 (d, *J* = 8.9 Hz, 1H), 5.85 (d, *J* = 8.9 Hz, 1H), 7.32-7.36 (m, 5H), 7.39-7.56 (m, 3H), 7.66-7.77 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 55.3, 60.3, 62.8, 72.5, 111.1, 117.0, 122.0, 128.4, 132.8, 133.2, 142.9, 145.8, 155.3, 172.0; **Analysis**: $C_{12}H_{13}NO_4$ requires C 61.27, H 5.57, N 5.95 found C 61.26, H 5.54, N 5.89.

Section II:

First Enantioselective Synthesis of (-)-Matteucen C

3.2.1 Introduction

Matteuccia orientalis (HOOK.) TREV (Onocleaceae), mainly distributed in Southern China, is a Chinese medicinal herb used for the treatment of hemostatics and reliving ostalgia.[27] A new bioactive constituents from the rhizomes of this plant led to the isolation of three new isocourmarin derivatives, Matteucen A (**56**), *racemic*-Matteucen B (**57**) and two new phthalide derivatives, (-)-Matteucen C (**58**).[28]



56, Matteucen A **57,** (±)-Matteucen B **58,** (-)-Matteucen C

Fig. 9: Structures of Matteucen A-C (**56**-**58**)

3.2.2 Review of Literature

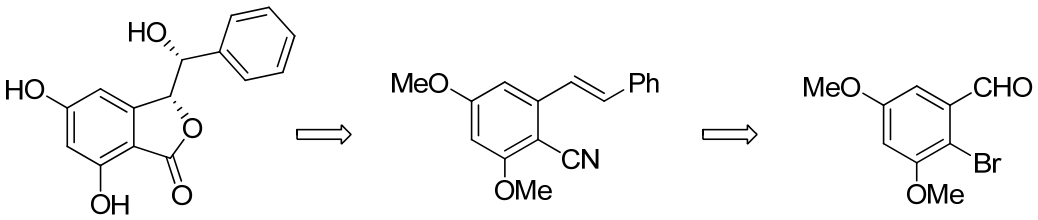
Literature search revealed that there is no report available for the synthesis of (-)-Matteucen C (**58**).

3.2.3 Present Work

3.2.3.1 Objective

In section I of this Chapter, we have described an elegant method for the synthesis of 3-substituted chiral phthalide derivatives **47a**-**z**. In continuation of the work on Os-catalyzed oxidative cyclization of *o*-cyano alkenes, we describe in this section a short and first synthesis of (-)-Matteucen C (**58**).[29]

Retrosynthetic analysis of **58** (**Fig. 10**) reveals that *o*-cyanostilbene (**59**) could be the key intermediate for the oxidative cyclization leading to the synthesis of (-)-Matteucen C (**58**). *o*-cyanostilbene (**59**) can in turn be obtained from *o*-bromobenzaldehyde **60**.

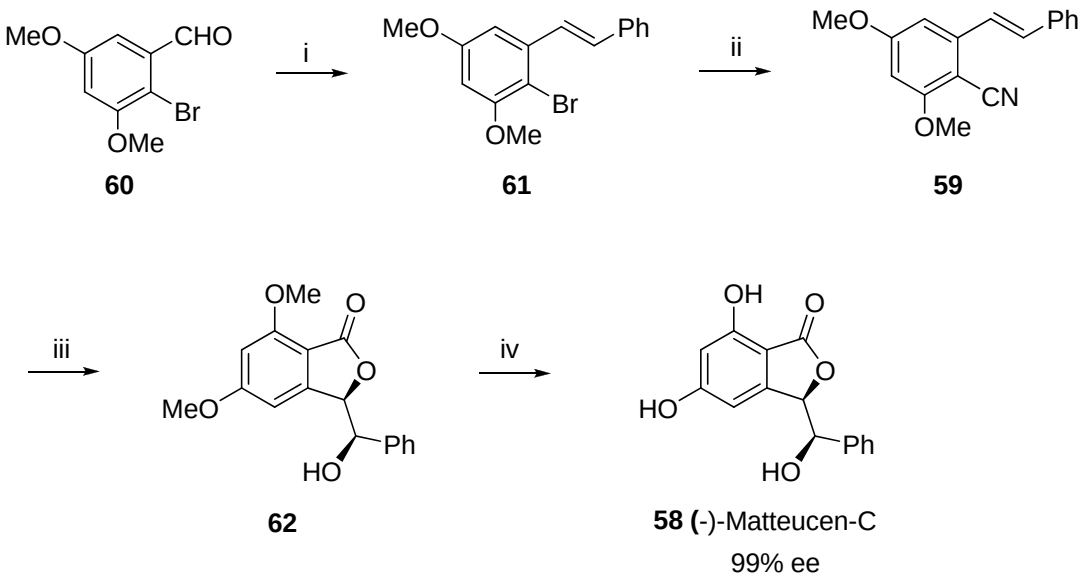


58 **59** **60**

Fig. 10: Retrosynthetic analysis of (-)-Matteucen C (**58**)

3.2.4 Results and Discussion

The complete synthetic sequence for (-)-Matteucen C (**58**), wherein Os-catalyzed CN-assisted oxidative cyclization of *o*-cyano stilbene (**59**) constitutes a key step for the introduction of chirality, is presented in **Scheme 17**.



60 **61** **59**

62 **58 (-)-Matteucen-C**
99% ee

Scheme 17: (i) $PhCH_2PPh_3^+I^-$, nBuLi, THF, 0-25 °C, 3 h, 82%; (ii) CuCN (3.5 equiv), DMF, reflux, 14 h, 83%; (iii) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH:THF:H_2O (0.5:0.5:1), 25 °C, 7 h, 93%; (iv) BBr_3, CH_2Cl_2, 25 °C, 12 h, 69%.

Accordingly, the synthesis of (-)-Matteucen C, **58** was undertaken starting from *o*-bromobenzaldehyde **60**, which on subjecting to Wittig olefination [$PhCH_2PPh_3^+I^-$, nBuLi, THF] gave *o*-bromostilbene **61** in 82% yield. Two doublets at δ 6.99 (d, *J* = 16.1 Hz, 1H) and 7.52 (d, *J* = 16.1 Hz, 1H) integrating for one proton each in the ^{1}H-NMR spectrum of **61** accounted for olefinic protons, which was further supported by the typical carbon signals at δ 127.9 and 128.0 in its ^{13}C NMR spectrum (**Fig. 11**).

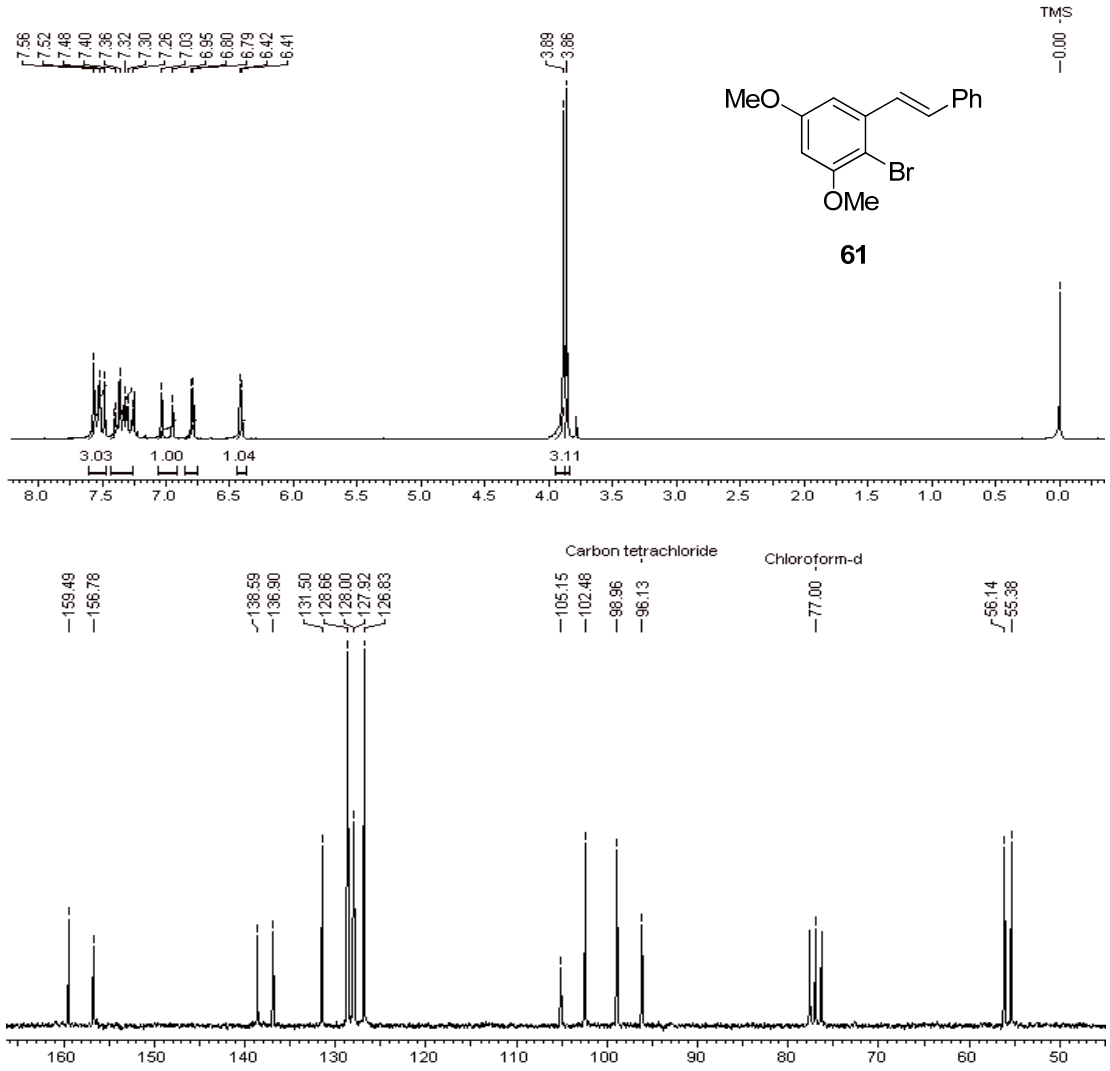


Fig. 11: ^{1}H and ^{13}C NMR spectra of o-bromostilbene **61**

o-Bromo stilbene **61** was then converted to *o*-cyanostilbene **59** using Rosenmund-von Braun reaction [CuCN, DMF and reflux] in 83%. The formation of the *o*-cyano stilbene **59** was confirmed by the appearance of CN carbon at δ 115.7 in its ^{13}C-NMR spectrum (**Fig. 12**). The IR spectrum of **59** displayed a characteristic CN stretching vibration at 2216 cm^{-1}.

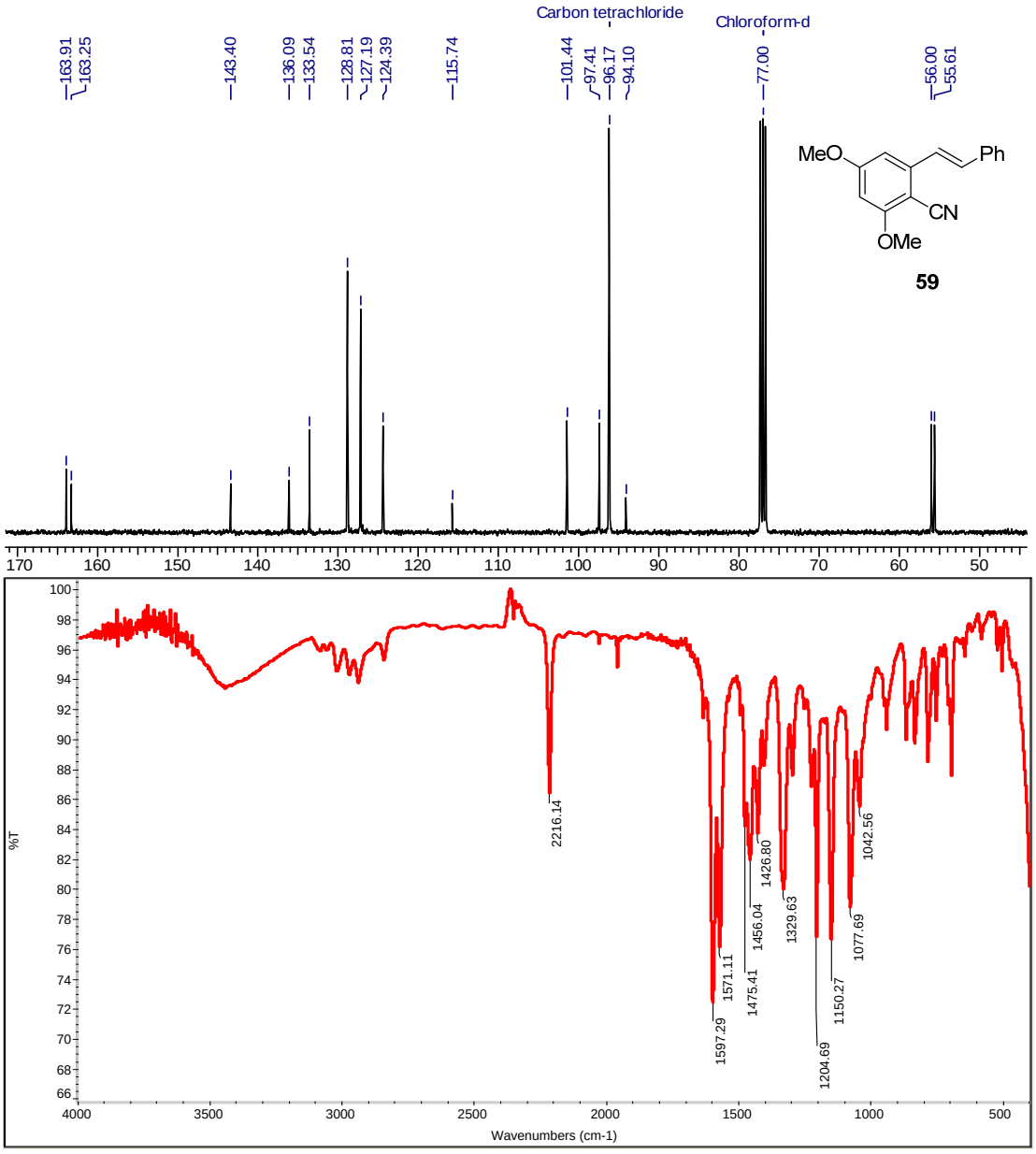
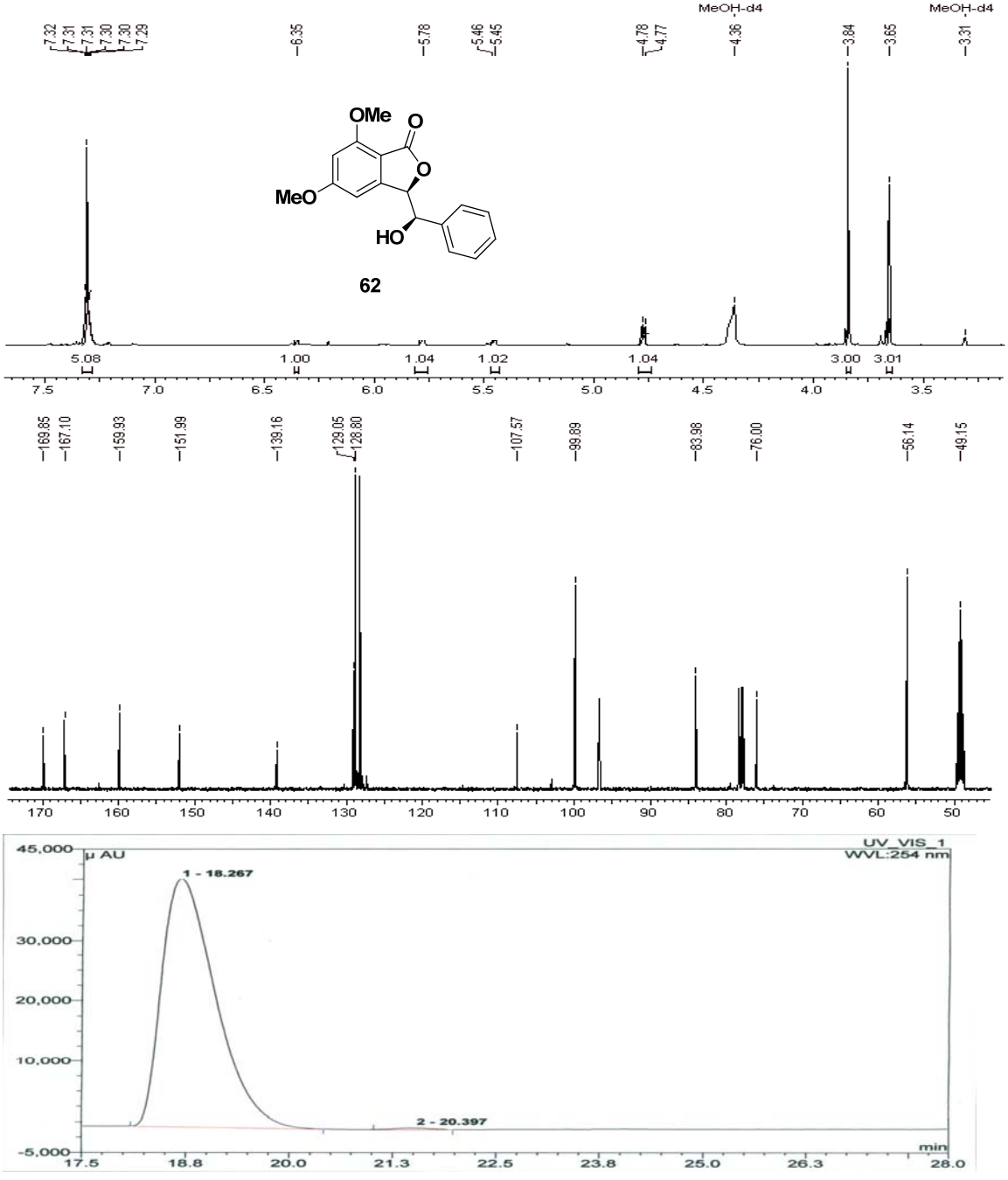


Fig. 12: ^{13}C NMR and IR spectra of *o*-cyanostilbene **59**

Cyanostilbene **59** was then subjected to CN-assisted one-pot oxidative cyclization using AD-mix-β process to give chiral phthalide **62** in 93% yield and 99%ee.



No	Ret. Time min	Height μ AU	Area μ AU* min	Rel. Area %	Amount	Type
1	18.27	40895.238	30456.124	99.36	n. a.	BMB
2	20.40	2196.930	195.138	0.64	n. a.	BMB

Fig. 13: ^{1}H ^{13}C NMR spectrum and HPLC chromatogram of phthalide **62**

The ^{1}H, ^{13}C-NMR and IR spectra of **62** confirmed the formation of phthalide (**Fig. 13**). The methine protons attached to lactone and hydroxyl group resonated at δ 4.77 (d, J = 6.41 Hz, 1H) and 5.45 (d, J = 6.41 Hz, 1H) respectively in the ^{1}H-NMR spectrum, which was further substantiated by the appearance of carbonyl carbon [-(**C**=O)-O-] signal at δ 169.8 in its ^{13}C-NMR spectrum. Its IR spectrum exhibited a characteristic γ-lactone carbonyl absorption band at 1752 cm^{-1}. The enantiomeric excess of chiral phthalide **62** was determined to be 99% by chiral HPLC analysis (Chiracel OJ-H, **Fig. 13**).

Finally, demethylation of chiral phthalide **62** with BBr_3 in CH_2Cl_2 gave (-)-Matteucen C (**58**) in 69% yield with 99%ee and the optical rotation of the target molecule was found to be $[\alpha]^{D}_{25}$ -54.16 (*c* 1.0, MeOH). The formation of (-)-Matteucen C (**58**) was confirmed by the appearance of two doublets at δ 5.45 (d, J = 4.0 Hz, 1H) and 5.73 (d, J = 4.8 Hz, 1H) corresponding to the homobenzylic and benzylic protons respectively in its ^{1}H-NMR spectrum. The corresponding methine carbons resonated at δ 72.6 and 81.7 in its ^{13}C-NMR spectrum (**Fig. 14**).

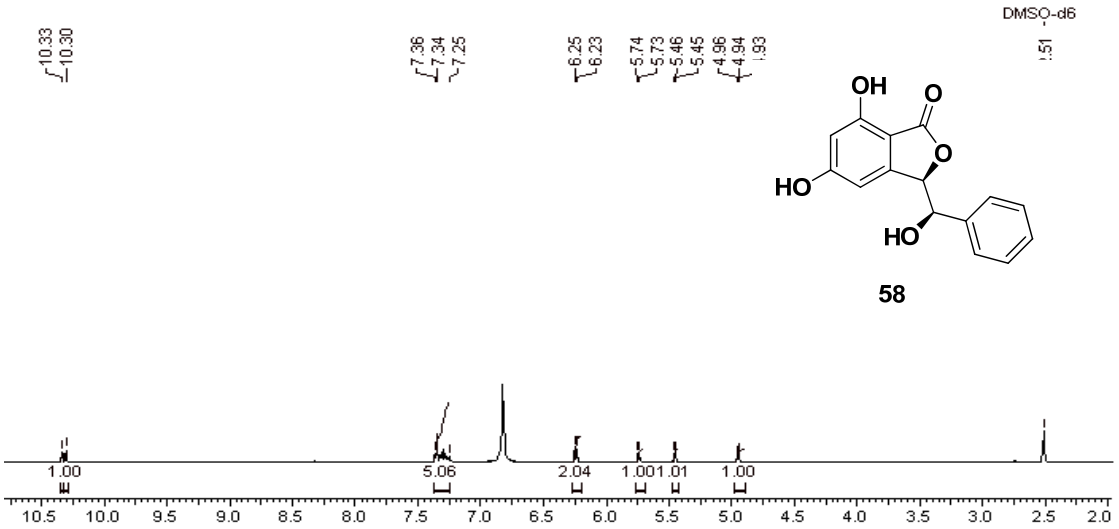


Fig. 14: ^{1}H NMR spectrum of (-)-matteucen C (**58**)

3.2.5 Conclusion

A short and an efficient enantioselective synthesis of (-)-Matteucen C (**58**) has been achieved in four linear steps with 44% overall yield and 99%ee for the first time, confirming its structural and stereochemical assignments. The CN-assisted one-pot oxidative cyclization of *o*-cyanostilbene **59** is used as the key reaction, which proceeded to give high enantioselectivity.

3.2.6 Experimental Section

2-Bromo-1,5-dimethoxy-3-styrylbenzene (61)

To a stirred solution of benzyltriphenylphosphonium iodide (2.1 g, 4.5 mmol) in THF was added *n*-butyllithium in hexane (2.8 mL, 4.5 mmol). The solution was stirred for 30 min at 0 °C and 2-bromobenzaldehyde (**60**) (1 g, 4.1 mmol) in THF was added dropwise *via* syringe at the same temperature and the reaction mixture was allowed to stir for 90 min at room temperature (monitored by TLC). It was then cooled to 0 °C, diluted with sat. NH_4Cl (25mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and 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 petroleum ether:EtOAc (90:10) as an eluent] affording the 2-bromostyrene **61** (1.12 g) as a gum.

Yield: 86%; **IR** ($CHCl_3$, cm^{-1}): 669, 769, 1216, 1384, 1468, 1580, 2098, 3020; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.89 (s, 3H), 6.42 (d, *J* = 2.7 Hz, 1H), 6.99 (d, *J* = 16.1 Hz, 1H), 7.26-7.40 (m, 3H), 7.52 (d, *J* = 16.1 Hz, 1H), 7.53-7.55 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.3, 56.1, 98.9, 102.4, 105.1, 126.8, 127.9, 128.0, 128.6, 131.5,

136.9, 138.5, 156.7, 159.4; **Analysis:** $C_{16}H_{15}BrO_2$ requires C, 60.21; H, 4.74; found: C, 60.08; H, 4.59%.

2, 4-Dimethoxy-6-styrylbenzonitrile (59)

o-Bromostilbene **61** (1 g, 3.1mmol) was taken in dry DMF (10 mL) and CuCN (0.83 g, 9.3 mmol) was added and refluxed under N_2 for 18 h (monitored by TLC). The reaction mixture was then cooled to room temperature, and then 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 and 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 petroleum ether: EtOAc (7:3) as an eluent] to give *o*-cyanostilbene **59** 0.7 g.

Yield: 83%; colorless solid; **mp** 147–148 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 831, 953, 1045, 1073, 1150, 1203, 1326, 1460, 1570, 1595, 2216; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 3.90 (s, 6H), 6.34 (d, *J* = 2.3 Hz, 1H), 6.80 (d, *J* = 2.3 Hz, 1H), 7.20 (d, *J* = 16.4 Hz, 1H), 7.26-7.30 (m, 1H), 7.32-7.38 (m, 3H), 7.55 (d, *J* = 7.38 Hz, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 55.6, 56.0, 94.1, 97.4, 101.4, 115.7, 124.4, 127.2, 128.8, 133.5, 136.1, 143.4, 163.2, 163.9; **Analysis**: $C_{17}H_{15}NO_2$ requires C 76.96, H 5.70, N 5.28 found C 76.92, H 5.68, N 5.24%.

(*R*)-3-((*R*)-Hydroxy(phenyl)methyl)-5,7-dimethoxyisobenzofuran-1-(3*H*)-one (62)

A 50 mL RB flask was charged with $K_3Fe(CN)_6$ (1 g, 3 mmol), K_2CO_3 (414 mg, 3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and H_2O (5 mL) and stirred for 10 min. Subsequently, $(DHQD)_2PHAL$ (8 mg, 1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (2 mg, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, *o*-

cyanostilbene **59** (265 mg, 1 mmol) was added and allowed to stir for 7 h at 25 ºC. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 ºC. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and petroleum ether/EtOAc (7:3) as an eluent] gave **62** (221 mg).

Yield: 93%; colorless solid; **mp** 170 –172 ºC; $[\alpha]^{D}_{25}$ -77.56 (*c* 1.15, $CHCl_3$); 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.27 min (99.36%) and 20.40 min (0.64%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 759, 947, 1041, 1077, 1204, 1336, 1461, 1625, 1754, 2981, 3018, 3444; **^{1}H-NMR** (500 MHz, CD_3OD): δ 3.61 (s, 3H), 3.84 (s, 3H), 4.77 (d, *J* = 6.41 Hz, 1H), 5.45 (d, *J* = 6.41 Hz, 1H), 5.78(d, *J* = 1.7 Hz, 1H), 6.35 (d, *J* = 1.7 Hz, 1H), 7.29-7.32 (m, 5H); **^{13}C-NMR** (125 MHz, $CDCl_3$+CD_3OD): δ 56.1, 76.0, 83.9, 99.9, 102.9, 107.6, 128.2, 128.8, 129.0, 139.2, 152.0, 159.9, 167.1, 169.8; ESI-MS: *m*/*z* 323.085 $[M+Na]^+$;**Analysis**: $C_{17}H_{16}O_5$ requires C 67.99, H 5.37, found C 67.85, H 5.29%.

(-) Matteucen C (58)

To a solution of phthalide **62** (0.17 mmol, 50 mg) in CH_2Cl_2 (5 mL) at - 78 ^{o}C was added BBr_3 (1.36 mL, 1.36 mmol, 1 M in CH_2Cl_2) over 10min. The reaction mixure was allowed to warm to room temperature and then stirred for 24 h. It was quenched with sat. aq. sodium bicarbonate (5 mL). The aqueous layer washed with CH_2Cl_2 and extracted with ethyl acetate (3 x10 mL). The combined organic layers were washed with brine (10

mL) and dried over anhyd. Na_2SO_4. After concentration, the crude product was purified by silica gel column chromatography to give **58** in 31 mg.

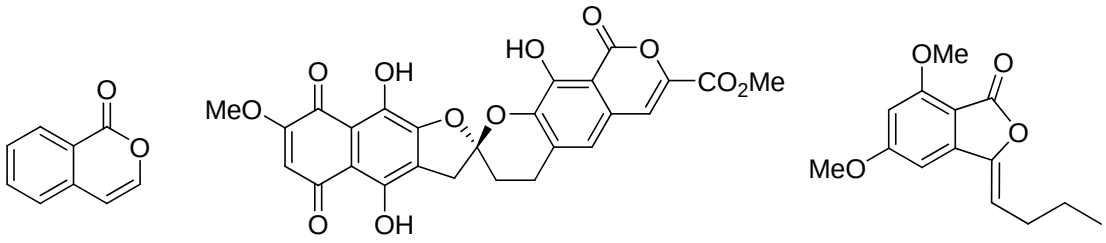
Yield: 68%; colorless powder; $[\alpha]^{D}_{25}$ -54.16 (*c* 1.0, MeOH); **IR** ($CHCl_3$): 691, 710, 1169, 1615, 1684, 1725, 3364 cm^{-1}; **^{1}H-NMR** (500 MHz, DMSO-d_6): δ 4.94 (t, *J* = 4.8 Hz, 1H), 5.44 (d, *J* = 4.0 Hz, 1H), 5.73 (d, *J* = 4.8 Hz, 1H), 6.23 (d, *J* = 1.8 Hz, 1H), 6.25 (d, *J* = 1.8 Hz, 1H), 7.27-7.36 (m, 5H), 10.30 (s, 1H), 10.33 (s, 1H) ; **^{13}C-NMR** ($CDCl_3$): δ 72.6, 81.7, 101.1, 102.3, 104.2, 126.9, 127.3, 127.6, 140.7, 151.5, 157.6, 163.9, 167.7; **Analysis**: $C_{15}H_{12}O_5$ requires C 66.17, H 4.44, found C 66.09, H 4.39%.

Section III:

A Novel Approach to Isocoumarins and Alkylidenephthalides

3.3.1 Introduction

A number of 3-substituted isocoumarins(**63**-**64**) and 3-alkylidenephthalides(**65**) have been isolated from natural sources.[30,31] The 3-substituted isocoumarins, natural structures found in many natural products, exhibit a broad range of biological activities such as antiallergic and antimicrobial,[32,33] immunomodulatory,[34] cytotoxic,[35] antifungal,[36] antiinflammatory,[37] antiangiogenic[38] and antimalarial.[39] The alkylidenephthalides have antispasmodic, herbicidal, and insecticidal activities,[40] and are also attractive intermediates[41] for the synthesis of a variety of heterocyclic and carbocyclic compounds including some aromatic 1,4-dicarbonyl compounds.



63 Bergenin

64 γ–Rubromycin

65 (Z)-3-Butylidne-5,7-dimethoxyphthalide

Fig. 15 Some of the examples of isocoumarins and alkylidenephthalides

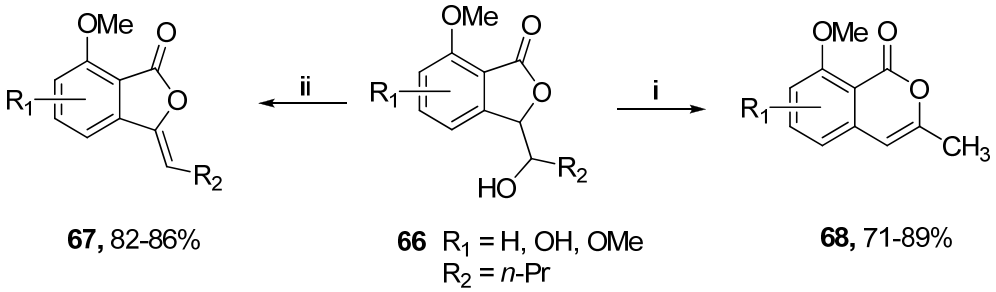
The alkylidenephthalides are also useful intermediates[42] for the synthesis of various natural products such as Bergenin (**63**), γ-Rubromycin (**64**), (*Z*)-3-Butylidne-5-7-dimethoxyphthalide (**65**), cytogenin etc. (**Fig. 15**) including some isoquinoline alkaloids.[43]

3.3.2 Review of literature

Literature search revealed that there are various routes available for the synthesis of isocoumarins and alkylidenephthalide derivatives which are described below.

Mali's approach (1998)[44]

Mali *et al* have described acid-catalyzed dehydration method for the synthesis of both (*Z*)-3-butylidenephthalides **67** and 3-alkyl-8-hydroxy/methoxyisocoumarins **68** from phthalides **66** (**Scheme 19**).

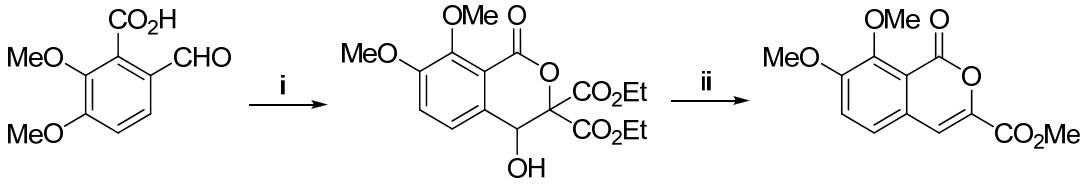


67, 82-86% **66** R_1 = H, OH, OMe; R_2 = *n*-Pr **68,** 71-89%

Scheme 19: (i) *p*-TsOH, dry toluene, reflux; (ii) 1N HCl, 0 °C; (ii) HCO_2H, H_3PO_4, 80 °C, 8 h.

Behar's approach (2000)[45]

In this approach, readily accessible phthaldehydic acid **69** was subjected to a slight excess of NaH in DMPU, followed by addition of diethyl bromomalonate gave a 90% yield of cyclized intermediate **70**. The excess sodium hydride presumably facilitates a base-catalyzed aldol closure to **69** *via* malonate ester of **70**. Decarboxylative elimination afforded acid, which on Fischer esterification gave ester **71** in 85% yield (**Scheme 20**).

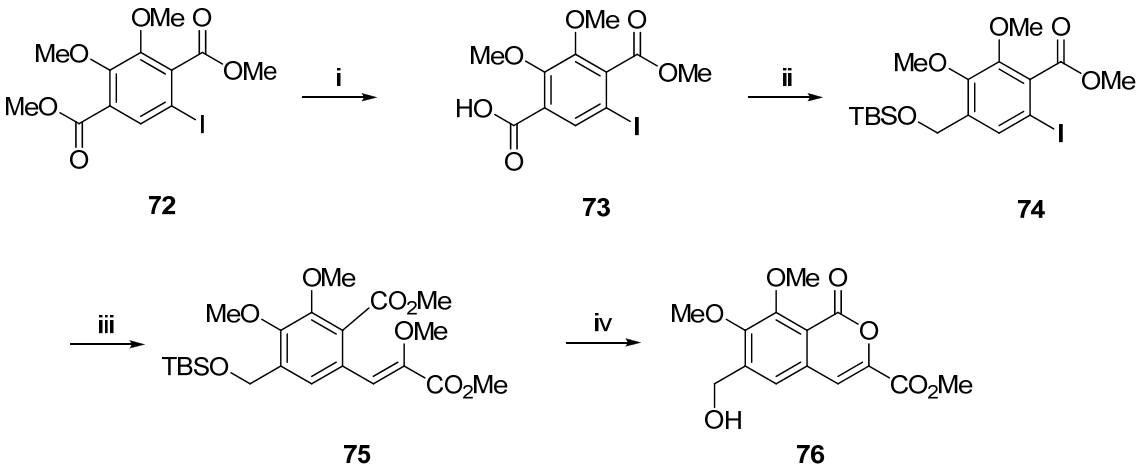


69 **70** **71**

Scheme 20: (i) NaH, DMPU, then diethyl bromomalonate, 25 ºC, 90%; (ii) (a) conc HCl/gl.AcOH, reflux; (b) cat. H_2SO_4, MeOH, reflux, 85%.

Kozlowski's approach (2001)[46]

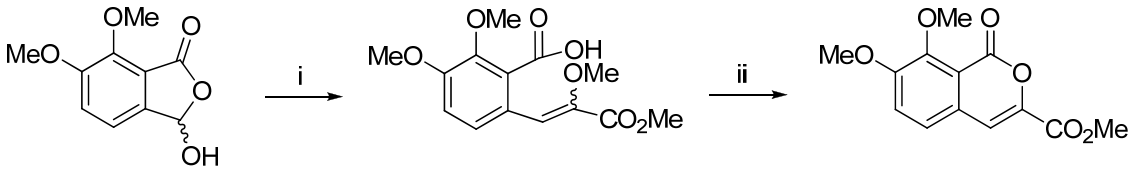
Kozlowski *et al* have synthesized isocoumarin fragment **76** as part of their rubramycin synthesis. The synthesis was started from regioselective saponification of less hindered methyl ester (*meta* to the iodide) of **72** using LiOH to generate acid **73**. This on chemoselective reduction gave the corresponding alcohol which was protected as its silyl ether **74** in 87% yield. The Heck coupling of **74** with α-methoxy methyl pyruvate gave the coupled product **75** in 71% yield. Acid catalyzed intramolecular condensation of **74** in 5% HCl/MeOH resulted in the formation of isocoumarin along with concomitant removal of silyl ether to provide isocoumarin precursor **76** directly in 83% yield (**Scheme 21**).



Scheme 21: (i) LiOH, THF/H_2O; (ii) (a) BH_3.THF, THF; (b) TBSCl, imid., 87%; (iii) $Pd(PPh_3)_4$, K_2CO_3, **21**, 71% (iv) 5% HCl/MeOH, 83%.

Danishefsky's approach (2001)[47]

Danishefsky *et al* have described an elegant synthesis of isocoumarin fragment **79** as part of their rubramycin synthesis, which commenced with commercially available opianic acid **77**. Subjecting **77** with modified Horner-Emmons reaction using phosphonate ester afforded **78** as a mixture of stereoisomers (98%, 1:1). Cyclization under acidic conditions afforded isocoumarin derivative **79** in 83% yield (**Scheme 22**).

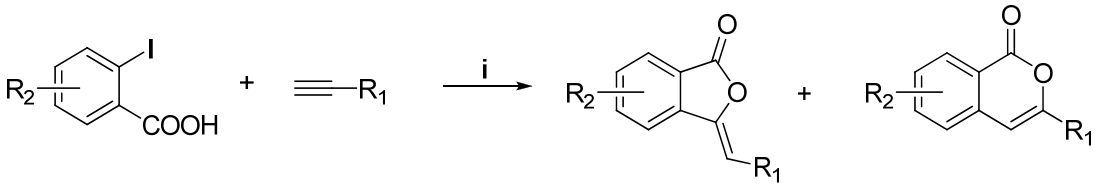


77 **78** **79**

Scheme 22: (i) $(OMe)_2POCH(OMe)CO_2Me$, NaH, THF, 0 ºC, 98% (1:1); (ii) 3N H_2SO_4, MeOH, reflux, 83%.

Bellina's approach (2003)[48]

Bellina *et al.* have found $Pd(PPh_3)_4$/CuI/Et_3N combination as an efficient reagent system for the reaction of *o*-iodobenzoic acids **80** with alkynes **81** to produce (*Z*)-3-butylidenephthalides **82** as the major and 3-alkylisocoumarins **83** as the minor products (**Scheme 23**).



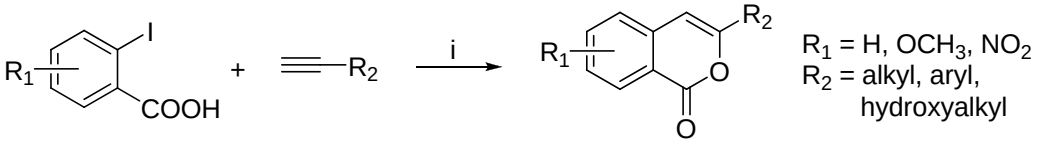
80 **81** **82** major **83** minor

R_1 = alkyl, alkoxy
R_2 = OH, OMe, H

Scheme 23: (i) $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 25 °C, 24 h, 61-82%.

Pal's approach (2005)[49]

In this approach the coupling reaction of *o*-iodobenzoic acids **84** with terminal alkynes **85** by using a catalyst system of 10% Pd/C-Et_3N-CuI-PPh_3 in EtOH provided 3-substituted isocoumarins **86** in 40-75% yield (**Scheme 24**).

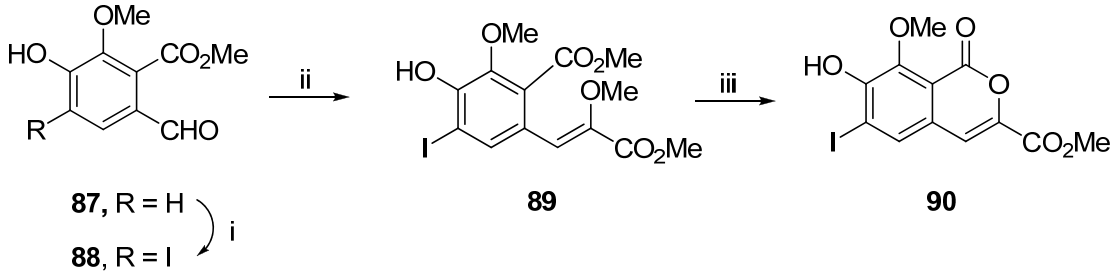


84 **85** **86,** 40-75%

Scheme 24: (i) 10% Pd/C, PPh_3, CuI, Et_3N, EtOH, 80 °C, 16 h

Brasholz's approach (2005)[50]

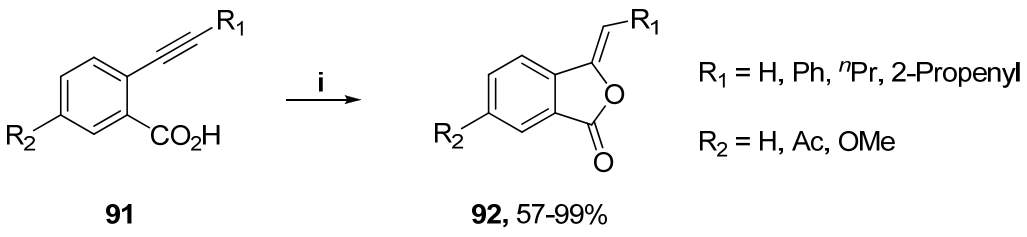
Brasholz *et al* also have described synthesis of isocoumarin fragment **90** as part of their rubramycin synthesis. Thus, Iodination of **87** with tetramethylammonium dichloroiodate gave iodinated aldehyde **88**. Which was subjected to Horner–Wadsworth–Emmons reaction with phosphonate ester to give enol ether **89** as a mixture of diastereoisomers (*E*/*Z* = 35:65) in 82% yield. Subsequently, intramolecular condensation of **89** in the presence of aq. HBr solution provided isocoumarin **90** in 68% yield (**Scheme 25**).



Scheme 25: (i) Me_4NICl_2, $NaHCO_3$, CH_2Cl_2, 25 °C, 4 h, 91 %; (ii)Phosphonate ester, NaHMDS, THF, -78 to 25 °C, 82%; (iii) HBr (47%, aq)-MeOH, 1:1, reflux, 12 h, 68%.

Terada's approach (2007)[51]

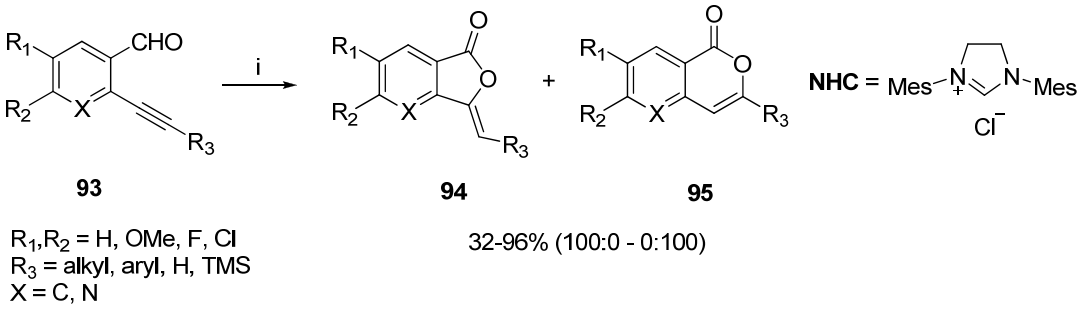
In this approach, the authors have employed organic-base such as DBU in catalytic amount for effecting 5-exo intramolecular cyclization in *o*-alkynylbenzoic acids **91,** which produced the corresponding phthalides **92** regioselectively in 57-99% yields (**Scheme 26**).



Scheme 26: (i) DBU (5 mol%), MeCN, 80 ºC, 2 h.

Youn's approach (2011)[52]

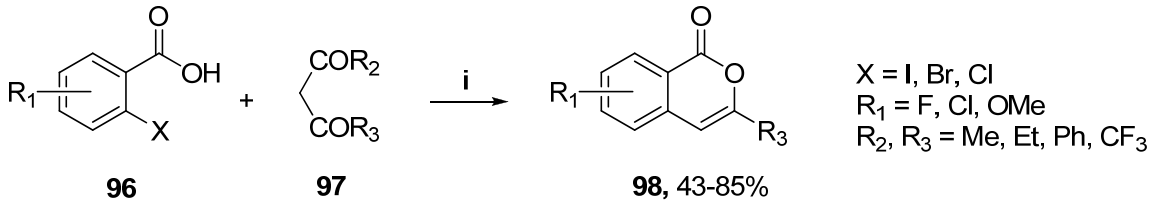
Youn *et al*. have developed an NHC-catalyzed oxidative cyclization of *o*-alkynylbenzaldehydes **93** bearing an unactivated alkyne moiety as an internal electrophile to afford O-heterocycles **94** & **95** in 32-96% yield. The duality of DBU renders its ability to generate the active NHC catalytic species and concomitantly, to activate the alkyne moiety. In this strategy, molecular oxygen in air is utilized as a source of an oxygen for the oxidation of various benzaldehydes to the corresponding benzoic acids (**Scheme 27**).



Scheme 27: (i) **NHC** (20 mol%), DBU (40 mol%), MeCN, air, 80 °C, 2-24 h.

Xi's approach (2012)[53]

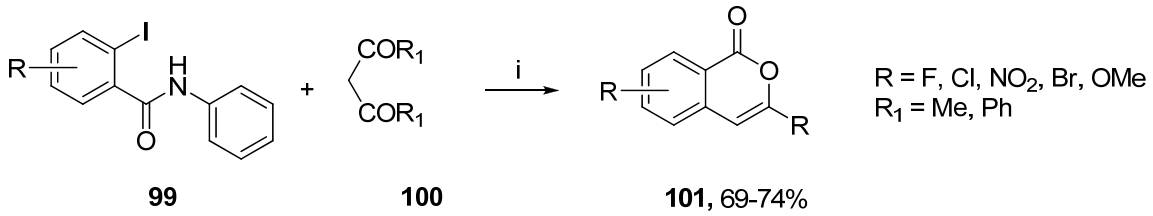
Xi *et al.* have prepared 3-substituted isocoumarin derivatives **98** from o-halobenzoic acids **96** and 1,3-diketones **97** *via* a copper(I)-catalyzed domino reaction in DMF under the action of K_3PO_4 at 90−120 °C without a ligand in 43-85% yields (**Scheme 28**).



Scheme 28: (i) CuI (10 mol%), K_3PO_4, DMF, 90-120 °C, 24-36 h.

Yao's approach (2012)[54]

Vaccher *et al*. have reported the synthesis of isocoumarins **101** by employing copper-catalyzed tandem C−C/C−O coupling transformation as the key step. Thus, 2-iodo-N-phenylbenzamides **99** were subjected to reaction with various 1,3-diketones **100** *via* copper (I)-catalyzed tandem reaction in DMSO under the action of Cs_2CO_3 at 100 °C to afford isocoumarins **101** in 69-74% yield (**Scheme 29**).



Scheme 29: (i) CuI (10 mol%), Cs_2CO_3, DMSO, 100 °C, N_2, 5-60 h.

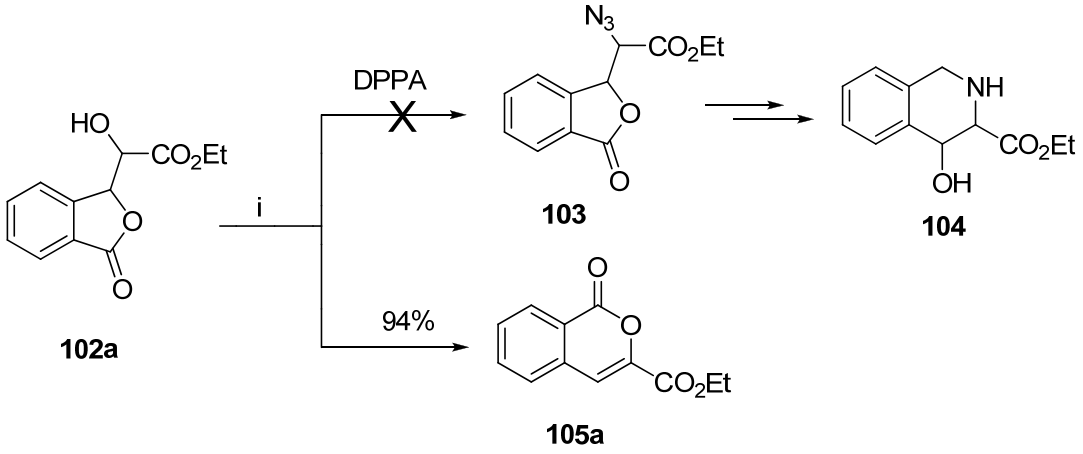
3.3.3 Present Work

3.3.3.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of 3-substituted isocoumarins and alkylidenephthalides employ either acid medium or expensive organometallic reagents involving longer reaction sequences and often lack in broad substrate scope and higher reaction stereoselectivity. In this context, a more practical and efficient synthesis of functionalized 3-substituted isocoumarins and 3-alkylidenephthalides is highly desirable. In this section, we present a single-step strategy in which PPh_3 DEAD promote the ring expansion or elimination of 3-substituted phthalides that affords 3-substituted isocoumarins or 3-alkylidenephthalides in high yields (**Scheme 30**).

3.3.4 Results and Discussion

In Section-I, we have presented a novel protocol of CN-assisted oxidative cyclization for the synthesis of a wide variety of 3-substituted phthalides and their structural analogues *via* AD process of cyano cinnamates and styrene derivatives. In continuation of this methodology, we have planned to synthesize the bioactive tetrahydroisoquinoline **104** directly from 3-substituted phthalide **102a** *via* a two-step sequence: (i) Mitsunobu reaction of phthalide **102a** [PPh_3, diethyl azodicarboxylate (DEAD) and diphenylphosphoryl azide (DPPA)] and (ii) the reduction of the corresponding azide **103** with $LiAlH_4$. To our surprise, when 3-substituted phthalide **102a** was subjected to a typical Mitsunobu reaction using PPh_3 and DEAD (with DPPA or without DPPA), the corresponding ring expansion product, i.e. isocoumarin derivative **105a** was obtained exclusively in 94% yield.



Scheme 30: (i) PPh_3 (1.5equiv.), DEAD (1.5 equiv.), THF, 25 °C, 30 min.

The formation of isocoumarin derivative **105a** was confirmed by the presence of olefinic proton at δ 7.48 as singlet in its ^{1}H-NMR spectrum. The carbonyl signal and olefinic carbons showed signals at δ 160.4, 111.9 and 143.5 respectively in its ^{13}C-NMR spectrum

(**Fig. 16**). Its IR spectrum displayed strong absorption bands at 1718 and 1737 cm^{-1} indicating the presence of ester and lactone carbonyl groups repectively.

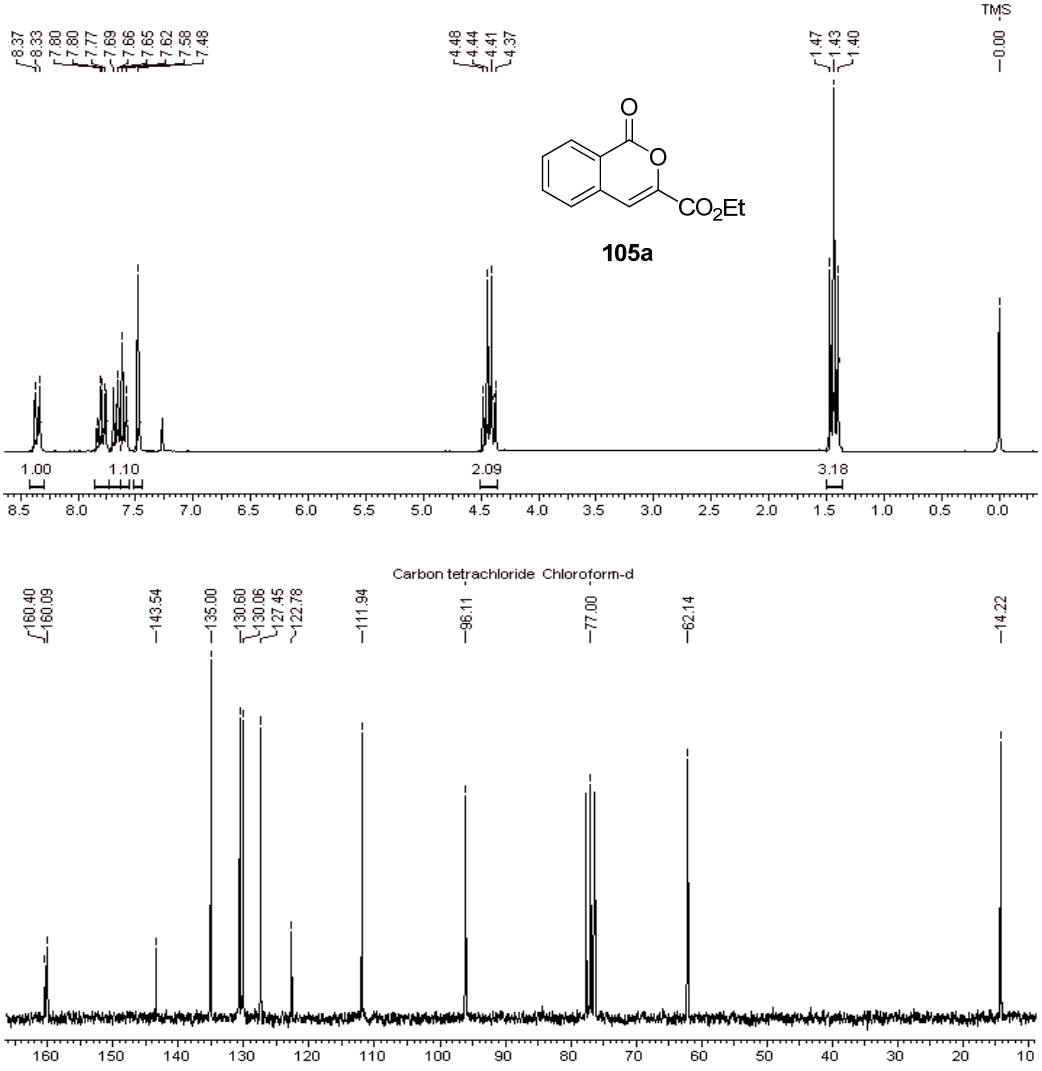
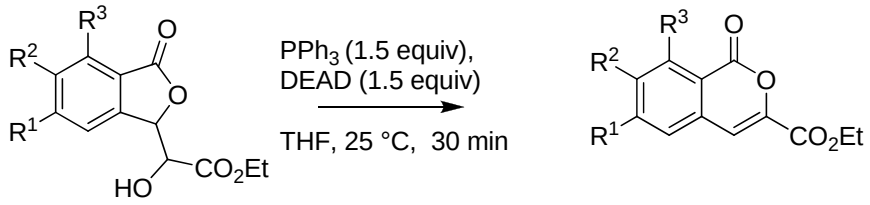


Fig. 16: ^{1}H and ^{13}C NMR spectra of isocoumarin derivative **105a**

Encouraged by this result, we examined the scope of the reaction with other 3-substituted phthalides **102a-h** (**Table 1**). In every case, the reaction proceeded rapidly in 30 min giving the desired isocoumarin derivatives **105a-h** in excellent yields. For instance, substrates having halogen (entry f), methoxy (entry d) or substituents on the aromatic ring including 2-naphthyl nuclear system (entry h) underwent this ring expansion smoothly

affording the corresponding isocoumarin derivatives **105a-h** in excellent yields (90-95%) in a single step.

Table 1: PPh_3-DEAD Promoted Synthesis of Isocoumarins



102 a-h **105 a-h**

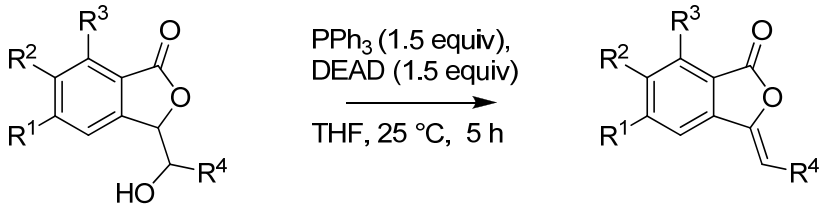
Entry	R^1	R^2	R^3	Yield (%)[a]
a	H	H	H	94
b	OMe	H	H	93
c	H	OMe	OMe	92
d	OMe	OMe	OMe	90
e	OBn	OMe	H	92
f	F	H	H	95
g	-O-CH_2-O-		H	95
h	(E)-ethyl 3-(1-cyanonaphthalen-2-yl)acrylate			93

[a] Isolated yield after column chromatographic purification

During the course of our investigation on synthesis of isocoumarins, we observed that simple variation of R^4 in phthalides **106a-i**, led to the formation of biologically active alkylidenephthalides **107a-i** in yields up to 92% yield (**Table 2**). It was again found that this novel method displayed a wide substrate scope tolerating both alkyl and alkoxy groups. The confirmation of alkylidenephthalides **107a-h** and configuaration of (Z)-3-

ethylidne-5-7-dimethoxyphthalide (**107i**) was ascertained by comparing their spectral data with those reported in the literature.[44,48,52]

Table 2: PPh_3-DEAD Promoted Synthesis of Alkylidenephthalides



106a-i **107a-i**

Entry	R^1	R^2	R^3	R^4	Yield (%)[a]
a	H	H	H	H	95
b	OMe	H	H	H	95
c	OMe	OMe	H	H	93
d	H	OMe	OMe	H	94
e	OMe	H	OMe	H	94
f	OMe	OMe	OMe	H	92
g	OBn	OMe	H	H	94
h	-O-CH_2-O-		H	H	93
i	OMe	H	OMe	Me	94

[a] Isolated yield after column chromatographic purification

Further, the formation of alkylidenephthalide derivatives **107a-i** were confirmed by ^{1}H and ^{13}C-NMR spectroscopy. Example 1: Two doublets have appeared at δ 5.16 (d, J = 3.0 Hz, 1H) and 5.19 (d, J = 3.0 Hz, 1H) accounting for olefinic protons of **107b** in its ^{1}H-NMR spectrum which was further ascertained by the appearence of carbonyl and olefinic carbons at δ 166.2, 90.7 and 117.7 respectively in the ^{13}C-NMR spectrum (**Fig. 17**). The

IR spectrum of **107b** displayed a characteristic strong band at 1774 cm^{-1} indicating the presence of carbonyl group in lactone.

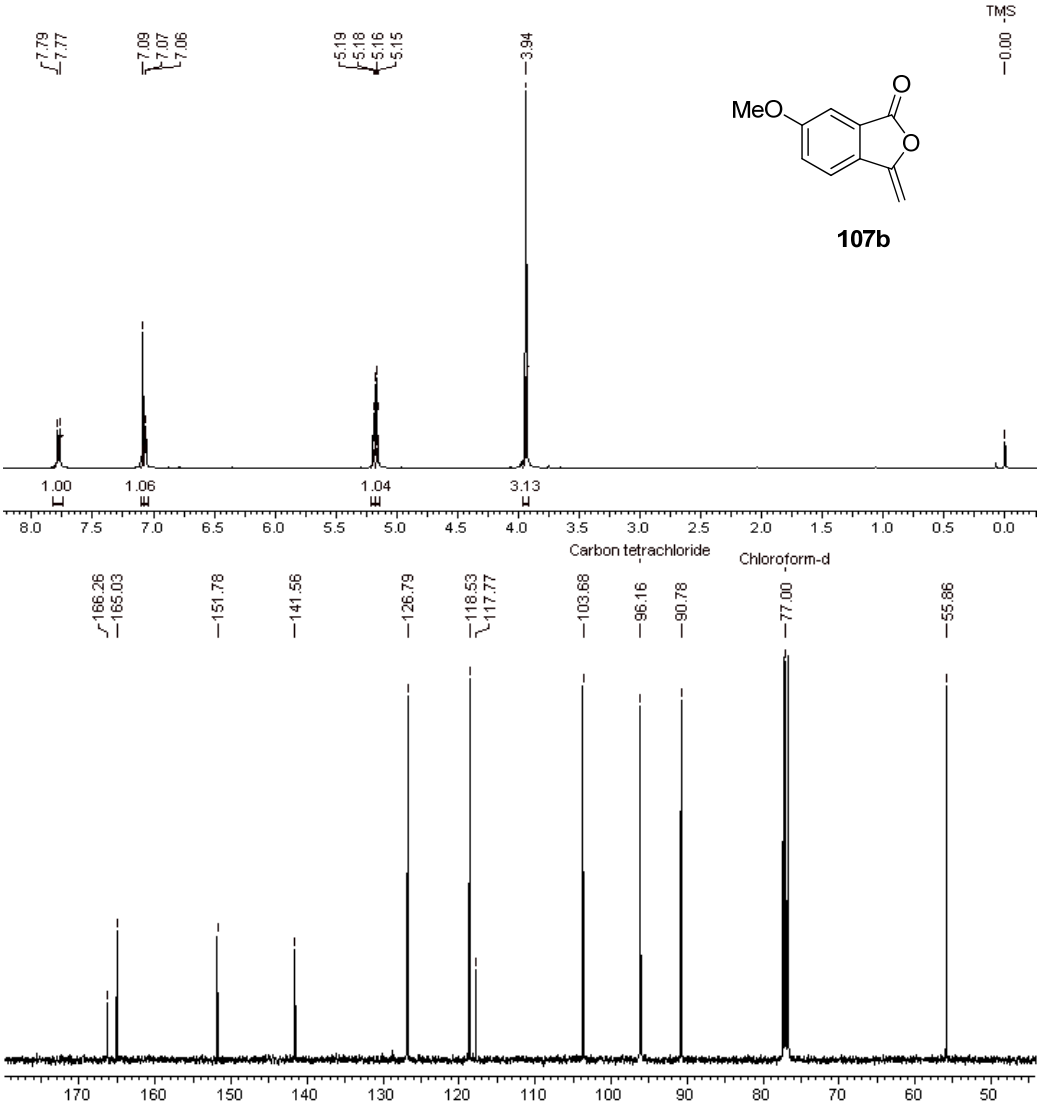


Fig. 17: ^{1}H and ^{13}C NMR spectra of methylidenephthalides **107b**

Example 2: The formation of (Z)-3-ethylidene-5-7-dimethoxyphthalide **107h** is confirmed by the appearance of characteristic signals at δ 1.99 (d, *J* = 7.1 Hz, 3H) and δ 5.57 (d, *J* = 7.1 Hz, 1H) for the methyl (=CH-C**H**$_3$) and olefinic (=C**H**-CH_3) protons respectively in its ^{1}H-NMR spectrum. Further it is supported by the signals at δ 11.2, 94.4

and 164.5 which corresponds to the methyl (=CH-C**H$_3$**), olefinic (=C**H**-CH$_3$) and carbonyl carbons respectively in the ^{13}C-NMR spectrum (**Fig. 18)**.

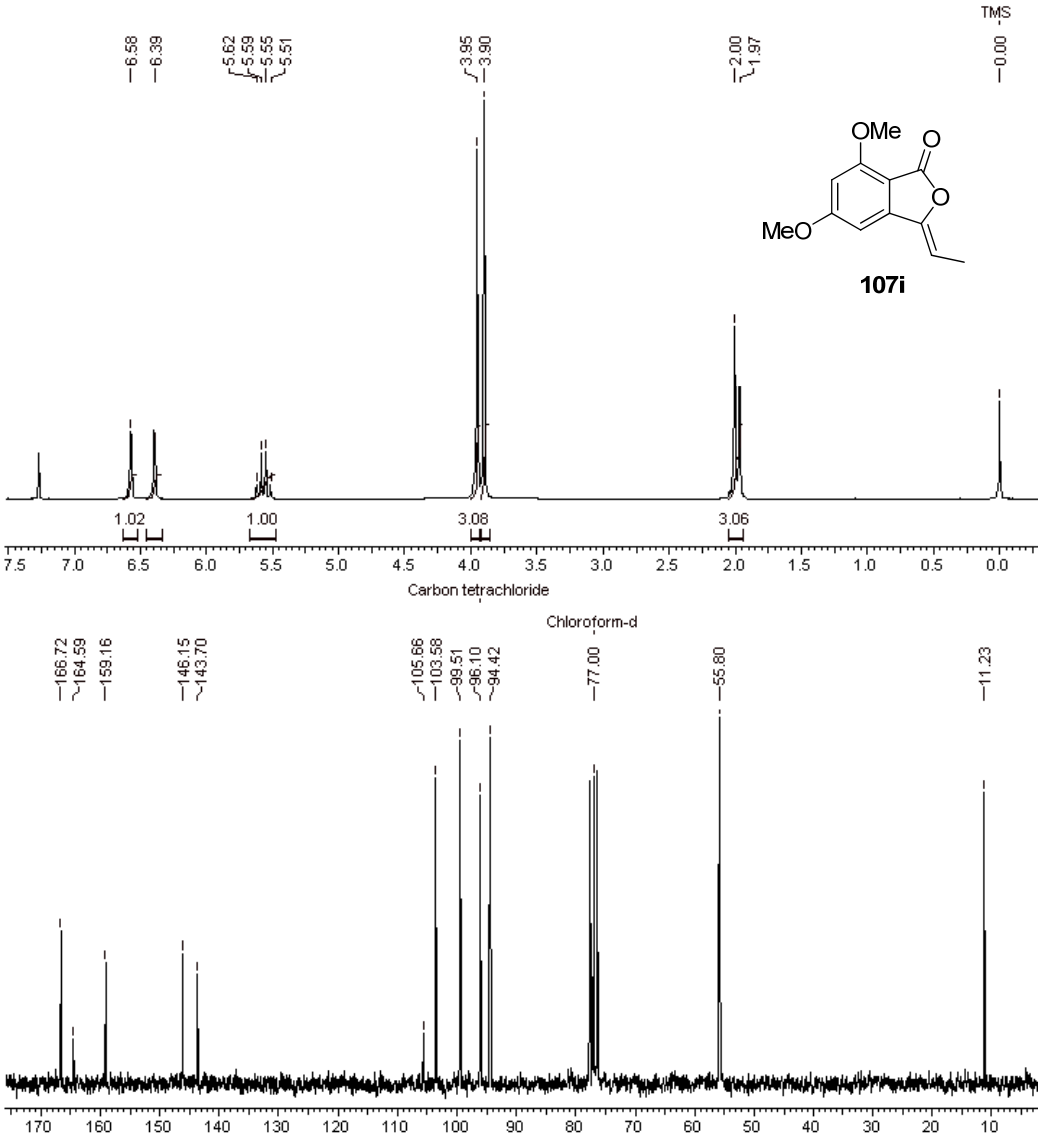
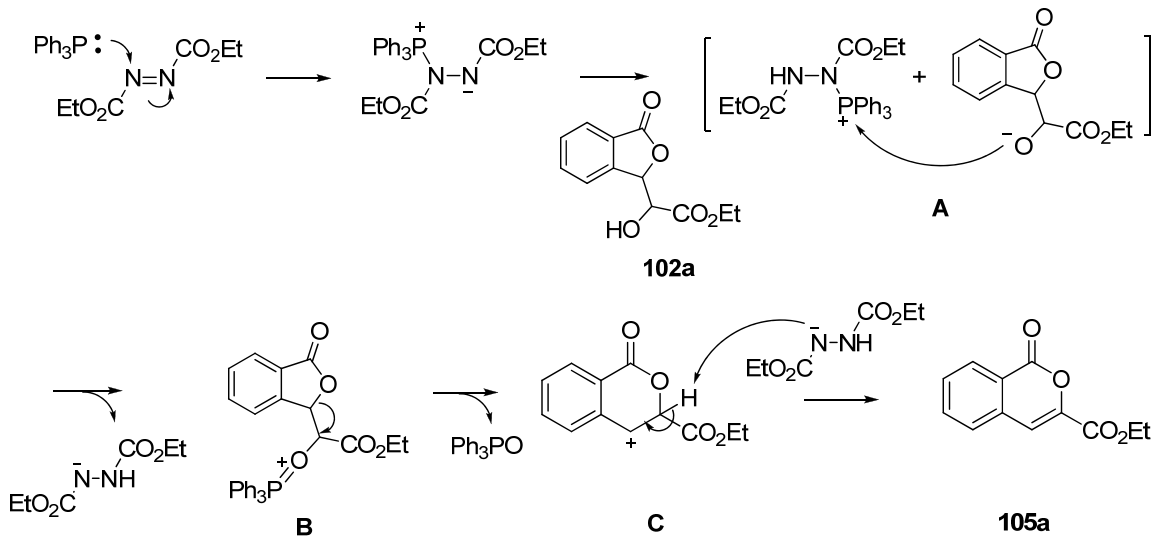


Fig. 18: ^{1}H and ^{13}C NMR spectra of ethylidenephthalide **107h**

3.3.5 Mechanism

A probable mechanistic pathway for the formation of isocoumarin derivative is shown in **Scheme 31**, which is similar to the Mitsunobu reaction mechanism.[55] Firstly, PPh_3 adds onto DEAD to generate a phosphonium betaine intermediate, which readily deprotonates alcoholic proton in α-hydroxy ester **102a** to provide the ion pair **A**. Further, alkoxide

oxygen in **A** binds to the phosphonium intermediate, activating it as a better leaving group to form phosphoxonium intermediate **B**, which undergoes Wagner-Meerwein-type rearrangement resulting in ring expansion, thereby providing a more stable benzylic carbocation **C**. Aromatization of **C** produces isocoumarin derivatives **105a** (**Scheme 31**).



Scheme 31: Possible reaction pathway

3.3.6 Conclusion

In summary, we have developed a novel one-pot procedure for the preparation of 3-substituted isocoumarins **105a-h** and 3-substituted alkylidenephthalides **107a-i** from 3-substituted phthalides *via* PPh_3-DEAD promoted ring expansion and elimination processes. This reaction is highly practical in the sense that the products were obtained in excellent yields and shows broad substrate scope and good functional group tolerance. This methodology also can be performed in the presence of acid sensitive groups. A remarkable feature of this novel method is that neither an acid medium nor a metal complex is required.

3.3.7 Experimental Section

General experimental procedure for the preparation of 3-substituted isocoumarins (105a-h) and alkylidenephthalides (107a-i)

To a stirred solution of 3-substituted phthalide derivatives **102a-h** or **106a-i** (1 mmol) in THF (10 mL) was added diethyl azodicarboxylate (1.5 mmol), PPh_3 (1.5 mmol) and allowed to stir for 0.5-5 h at 25 ºC. After the completion of reaction (as monitored by TLC), THF was distilled out to give crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (70:30) as eluent] afforded 3-substituted isocoumarins (**105a-h**) or 3-substituted alkylidenephthalides (**107a-i**) in high yields.

Ethyl 1-oxo-1H-isochromene-3-carboxylate (105a)

Yield: 94%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 684, 751, 815, 1070, 1237, 1482, 1509, 1626, 1718, 1737, 3068, 2919; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.3 Hz, 3H), 4.42 (q, *J* = 7.3 Hz, 2H), 7.48 (s, 1H), 7.58-7.70 (m, 2H), 7.80 (td, *J* = 7.5, 1.4 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 62.1, 111.9, 122.7, 127.4, 130.0, 130.6, 135.0, 143.5, 160.0, 160.4; ESI-MS: *m*/*z* 241.036 $[M+Na]^+$; **Analysis**: $C_{12}H_{10}O_4$ requires C 66.05, H 4.62 found C 65.89, H 4.49%.

Ethyl 6-methoxy-1-oxo-1H-isochromene-3-carboxylate (105b)

Yield: 93%**,** gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 749, 785, 827, 1072, 1257, 1510, 1601, 1720, 1736, 2934, 3067; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 3.94 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 7.16 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.4 (s, 1H), 8.26 (d, *J* = 9.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 55.7, 62.2, 109.7,

112.0, 115.8, 118.6, 132.3, 137.4, 144.2, 160.2, 164.9; ESI-MS: *m*/*z* 271.045 $[M+Na]^+$; **Analysis**: $C_{13}H_{12}O_5$ requires C, 62.90; H, 4.87. Found: C, 63.04; H, 5.01%.

Ethyl 5,6-dimethoxy-1-oxo-1H-isochromene-3-carboxylate (105c)

Yield: 92%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 686, 785, 835, 1056, 1278, 1545, 1634, 1718, 1728, 2928, 3025; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.40 (t, *J* = 7.2 Hz, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 6.95 (d, *J* = 2.5 Hz, 1H), 6.85 (m, 1H), 7.18 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.6, 55.4, 61.2, 62.6, 105.3, 110.8, 127.7, 133.4, 134.5, 144.8, 154.3, 157.6, 159.7, 161.5; **Analysis**: $C_{14}H_{14}O_6$ requires C, 60.43; H, 5.07. Found: C, 60.34; H, 4.96%.

Ethyl 6,7,8-trimethoxy-1-oxo-1H-isochromene-3-carboxylate (105d)

Yield: 90%**,** brown solid; **mp** 122–123 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 721, 997, 1018, 1119, 1194, 1261, 1360, 1437, 1473, 1592, 1655, 1719, 1728, 2943; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.8 Hz, 3H), 3.96 (s, 1H), 3.97 (s, 1H), 3.98 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 6.83 (s, 1H), 7.17 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 55.9, 61.2, 62.1, 105.0, 110.2, 127.6, 133.6, 134.5, 144.6, 154.8, 157.3, 159.3, 161.2; **Analysis**: $C_{13}H_{10}O_6$ requires C, 59.55; H, 3.84 Found: C, 59.48; H, 3.72%.

Ethyl 6-(benzyloxy)-7-methoxy-1-oxo-1H-isochromene-3-carboxylate (105e)

Yield: 92%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 689, 765, 844, 1062, 1234, 1341, 1485, 1643, 1718, 1731, 2959, 3068; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.2 Hz, 3H), 4.01 (s, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 5.24 (s, 2H), 6.95 (s, 1H), 7.32-7.49 (m, 6H), 7.78 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 56.3, 62.0, 71.1, 108.0, 111.7, 112.0, 116.5, 127.7, 128.4, 128.8, 130.5, 135.6, 142.7, 150.8, 155.6, 160.5; **Analysis**: $C_{20}H_{18}O_6$ requires C, 67.79; H, 5.12. Found: C, 67.91; H, 5.27%.

Ethyl 6-fluoro-1-oxo-1H-isochromene-3-carboxylate (105f)

Yield: 95%**,** amorphous white solid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 892, 1026, 1256, 1371, 1439, 1573, 1640, 1715, 1726, 2930, 3048; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.2 Hz, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 7.22-7.39 (m, 2H), 7.42 (s, 1H), 8.35-8.42 (dd, *J* = 5.3, 8.5 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 62.3, 111.0 (d, *J* = 2.6 Hz), 113.2 (d, *J* = 22.5 Hz), 118.6 (d, *J* = 22.5 Hz), 119.0 (d, *J* = 2.6 Hz), 133.3 (d, *J* = 10.2 Hz), 137.6 (d, *J* = 10.2 Hz), 144.5, 159.5, 159.8, 166.5 (d, *J* = 256.3 Hz); **Analysis**: $C_{20}H_{18}O_6$ requires C, 67.79; H, 5.12. Found: C, 67.91; H, 5.27%.

Ethyl 5-oxo-5H-[1,3]dioxolo[4,5-g]isochromene-7-carboxylate (105g)

Yield: 95%**,** colorless solid; **mp** 162–163 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 832, 895, 955, 1065, 1160, 1341, 1482, 1643, 1718, 1724, 2928, 3054; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.8 Hz, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 6.16 (s, 2H), 6.93 (s, 1H), 7.36 (s, 1H), 7.68 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 62.0, 102.7, 105.7, 108.1, 111.9, 118.2, 132.3, 142.6, 150.3, 153.7, 160.1; **Analysis**: $C_{13}H_{10}O_6$ requires C, 59.55; H, 3.84. Found: C, 59.68; H, 3.98%.

Ethyl 1-oxo-1H-benzo[h]isochromene-3-carboxylate (105h)

Yield: 93%**,** colorless solid; **mp** 164–165 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 680, 748, 819, 852, 1065, 1185, 1368, 1488, 1632, 1718, 1732, 2935, 3054; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.46 (t, *J* = 7.3 Hz, 3H), 4.45 (q, *J* = 7.5 Hz, 2H), 7.54-7.57 (m, 2H), 7.68 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.79 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H); 8.18 (d, *J* = 8.9 Hz, 1H), 9.74 (d, *J* = 8.6 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 62.3, 112.4, 117.3, 124.3, 127.1, 128.0, 128.8, 129.9, 131.5, 134.1, 136.7, 137.5, 144.8, 159.8, 160.0; **Analysis**: $C_{16}H_{12}O_4$ requires C, 71.64; H, 4.51. Found: C, 71.56; H, 4.39%.

3-Methyleneisobenzofuran-1(3H)-one (107a)

Yield: 95%**,** brown solid; **mp** 57–58 ºC {lit.[52] 57 ºC}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 956, 1018, 1278, 1478, 1665, 1784, 2930; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 5.24 (dd, *J* = 3.0, 6.2 Hz, 2H), 7.57-7.62 (m, 1H), 7.72 (d, *J* = 4.0 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 91.2, 120.6, 125.1, 125.2, 130.4, 134.4, 139.0, 151.8, 166.8. ESI-MS: *m*/*z* 169.015 $[M+Na]^+$; **Analysis**: $C_9H_6O_2$ requires C, 73.97; H, 4.14. Found: C, 74.09; H, 4.06%.

5-Methyl-3-methyleneisobenzofuran-1(3H)-one (107b)

Yield: 95%**,** yellow solid; **mp** 87-88 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 1026, 1100, 1180, 1240, 1303, 1346, 1456, 1491, 1606, 1660, 1774, 2943, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.94 (s, 3H), 5.15 (d, *J* = 3.0 Hz, 1H), 5.18 (d, *J* = 2.9 Hz, 1H), 7.06-7.09 (m, 2H), 7.79 (dd, *J* = 7.9, 1.2 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.9, 90.8, 103.7, 117.8, 118.5, 126.8, 141.6, 151.8, 165.0, 166.2; ESI-MS: *m*/*z* 199.035 $[M+Na]^+$; **Analysis**: $C_{10}H_8O_3$ requires C, 68.18; H, 4.58 Found: C, 68.04; H, 4.48%.

5,6-Dimethoxy-3-methyleneisobenzofuran-1(3H)-one (107c)

Yield: 93%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1022, 1104, 1229, 1278, 1321, 1369, 1466, 1504, 1764, 2919; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.01 (s, 3H), 5.06 (d, *J* = 2.8 Hz, 1H), 5.06 (d, *J* = 2.9 Hz, 1H), 7.05 (s, 1H), 7.25 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.2, 56.7, 89.5, 101.3, 105.3, 117.8, 133.4, 151.8, 151.9, 155.1, 166.7; **Analysis**: $C_{11}H_{10}O_4$ requires C, 64.07; H, 4.89 Found: C, 64.18; H, 4.78%.

6,7-Dimethoxy-3-methyleneisobenzofuran-1(3H)-one (107d)

Yield: 94%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1024, 1275, 1458, 1499, 1719, 1773, 2943; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.94 (s, 3H), 4.14 (s, 3H), 5.03 (d, *J* = 2.8 Hz, 1H), 5.03 (d, *J*

= 2.9 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.34 (s, *J* = 8.2 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.4, 89.5, 101.5, 105.4, 118.0, 133.5, 151.9, 152.0, 155.1, 166.7; **Analysis**: $C_{11}H_{10}O_4$ requires C, 64.07; H, 4.89 Found: C, 64.16; H, 4.81%.

5,7-Dimethoxy-3-methyleneisobenzofuran-1(3H)-one (107e)

Yield: 94%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 779, 856, 1025, 1104, 1222, 1254, 1323, 1499, 1663, 1762, 2919; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.96 (s, 3H), 3.01 (s, 3H), 5.09 (d, *J* = 7.1 Hz, 2H), 7.05 (s, 1H), 7.24 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.4, 89.5, 101.5, 105.4, 118.0, 133.5, 151.9, 152.0, 155.1, 166.7; **Analysis**: $C_{11}H_{10}O_4$ requires C, 64.07; H, 4.89 Found: C, 64.18; H, 4.78%.

5,6,7-Trimethoxy-3-methyleneisobenzofuran-1(3H)-one (107f)

Yield: 92%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1019, 1112, 1199, 1262, 1345, 1418, 1480, 1597, 1771, 2853, 2942; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.99 (s, 3H), 4.16 (s, 3H), 5.06 (d, *J* = 2.9 Hz, 1H), 5.12 (d, *J* = 3.2 Hz, 1H), 6.85 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.4, 61.4, 62.2, 89.6, 97.7, 109.9, 136.3, 151.5, 151.9, 159.8; **Analysis**: $C_{12}H_{12}O_5$ requires C, 61.01; H, 5.12 Found: C, 60.92; H, 5.03%.

5-(Benzyloxy)-6-methoxy-3-methyleneisobenzofuran-1(3H)-one (107g)

Yield: 94%**,** yellow solid; **mp** 232-233 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 980, 1035, 1136, 1182, 1273, 1352, 1415, 1482, 1588, 1775, 2953, 3040; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.01 (s, 3H), 5.0 (d, *J* = 2.9 Hz, 1H), 5.1 (d, *J* = 2.9 Hz, 1H), 5.20 (s, 2H) 7.1 (s, 1H), 7.28-7.5 (m, 7H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 56.3, 71.0, 89.5, 101.8, 107.2, 117.8, 127.4, 128.3, 128.7, 133.7, 135.6, 151.0, 151.8, 155.6, 166.6; **Analysis**: $C_{17}H_{15}O_4$ requires C, 64.07; H, 4.89 Found: C, 72.07; H, 5.34%.

7-Methyleneisobenzofuro[5,6-d][1,3]dioxol-5(7H)-one (107h)

Yield: 93%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 956, 1024, 1168, 1192, 1278, 1370, 1460, 1490, 1590, 1772, 2934, 3026; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 5.02 (d, *J* = 3.0 Hz, 1H), 5.12 (d, *J* = 2.9 Hz, 1H), 6.15 (s, 2H), 7.01 (s, 1H), 7.2 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 90.1, 99.9, 102.4, 103.4, 119.7, 135.6, 150.5, 151.6, 153.9, 166.1; **Analysis**: $C_{10}H_6O_4$ requires C, 63.16; H, 3.18 Found: C, 63.08; H, 3.09%.

(*Z*)-3-ethylidene-5,7-dimethoxyisobenzofuran-1(3H)-one (107i)

Yield: 94%**,** colorless solid; **mp** 147-148 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 668, 756, 1032, 1052, 1160, 1215, 1342, 1496, 1691, 1763, 3020; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.98 (d, *J* = 7.1 Hz, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 5.56 (q, *J* = 7.1 Hz, 1H), 6.40 (s, 1H), 6.58 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 11.2, 55.7, 55.8, 94.4, 99.5, 103.6, 105.7, 143.7, 146.1, 159.1, 164.6, 166.8; **Analysis**: $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.49. Found: C, 65.32; H, 5.35 %.

3.3.8 References

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CHAPTER IV

CuCN-Mediated “One-pot” Route to 1-Amino-2-naphthalenecarboxylic acid Derivatives and 3-Substituted Phthalides: Enantioslective Synthesis of Colletotrialide

Section I:

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

4.1.1 Introduction

Highly substituted bicyclic and polycyclic aromatic compounds are common structural motifs present in natural products and pharmaceuticals.[1] In recent years such aromatic systems have attracted considerable attention for the construction of organic light emiting diodes, organic semiconductors and luminescent materials.[2] 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.[3] 2-Aminobenzoic acid derivatives are also known as useful starting materials for the synthesis of heterocyclic compounds.[3] The synthetic utility of 1(or 3)-amino-2-naphthalenecarboxylic acid derivatives, which are the benzoanalogues of 2-aminobenzoic acid derivatives, is also well documented.[4] Therefore, the development of efficient methods for constructing polycyclic aromatic compounds have been a longstanding objective of synthetic organic chemist.

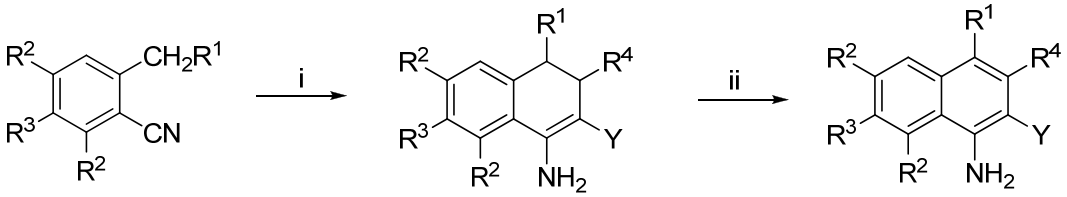
4.1.2 Review of literature

Literature search revealed that there are only two reports available for the synthesis of 1-amino-2-naphthalenecarboxylic acid derivatives, which are described below.

Kobayashi's Approach (1997)[5,6]

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

produced 1-amino-3,4-dihydro-2-naphthalenecarboxylates and carbonitriles **2** 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 **2** were converted to the corresponding 1-amino-2-naphthalenecarboxylic acid derivatives **3** in 43-99% yields on dehydrogenation with Pd/C in refluxing *p*-cymene (**Scheme 1**).

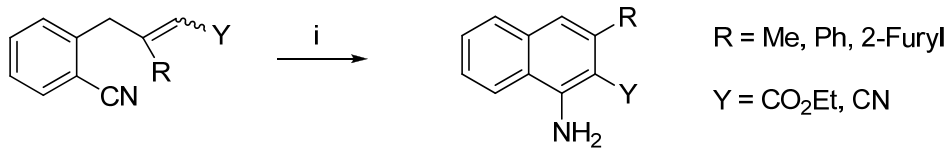


1 **2** **3;** 43-99%

$R^1 = R^2 = R^3$ = H, Ph, Me, OMe
R^4 = Me, Ph
Y = CO_2Et, $CO_2{}^tBu$, CN

Scheme 1: (i) (a) LDA, diglyme, -78 °C; (b) $R^4CH{=}CHY$, -78 °C; (ii) (a) ZnI_2, -78 °C to 25 °C, 54-98%; (b) 10% Pd/C, *p*-cymene, reflux.

The same group has also synthesized 1-amino-2-naphthalenecarboxylic acid derivatives **5** by treating (2-cyano-phenyl)butenoic acid derivatives **4** with NaH in DMF at 0 °C in 75-88% yield (**Scheme 2**).



4 **5;** 75-88%

Scheme 2: (i) NaH, DMF, 0 °C, 1 h.

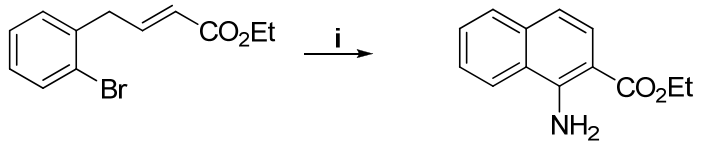
4.1.3 Present Work

4.1.3.1 Objective

There are only two methods available in the literature for the synthesis of 1-amino-2-naphthalenecarboxylic acid derivatives. However, these known methods involve multi-step reaction sequences and also the process requires consumption of large quantities of hazardous chemicals with longer reaction time, thus constituting less efficiency and narrow substrate scope. 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 **7a** directly from 4-(2-bromo-phenyl)-2-butenoates **6a** (**Scheme 3**).

4.1.4 Results and Discussion

It has been well-documented in the 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.[7] We found however, that when the same reaction was carried out under identical conditions with ethyl 4-(2-bromophenyl)-2-butenoate **6a** as the 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 **7a** in excellent yield (**Scheme 3**).



6a **7a**

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

The formation of ethyl 1-amino-2-naphthalenecarboxylate **7a** was confirmed by the presence of two doublets at δ 7.05 (J = 8.8 Hz) and 7.87 (J = 8.8 Hz) corresponding to the newly formed aromatic ring protons integrating for one proton each in its ^{1}H-NMR spectrum. It is further substantiated by the typical aromatic carbon signals at δ 104.2, 115.7, 125.1 and 148.9 in the down field region of ^{13}C-NMR corresponding to carbons of newly formed aromatic ring (**Fig. 1**). The IR spectrum of **7a** displayed strong N-H stretching frequencies at 3335 and 3346 cm^{-1} indicating the presence of primary aminefunctional group.

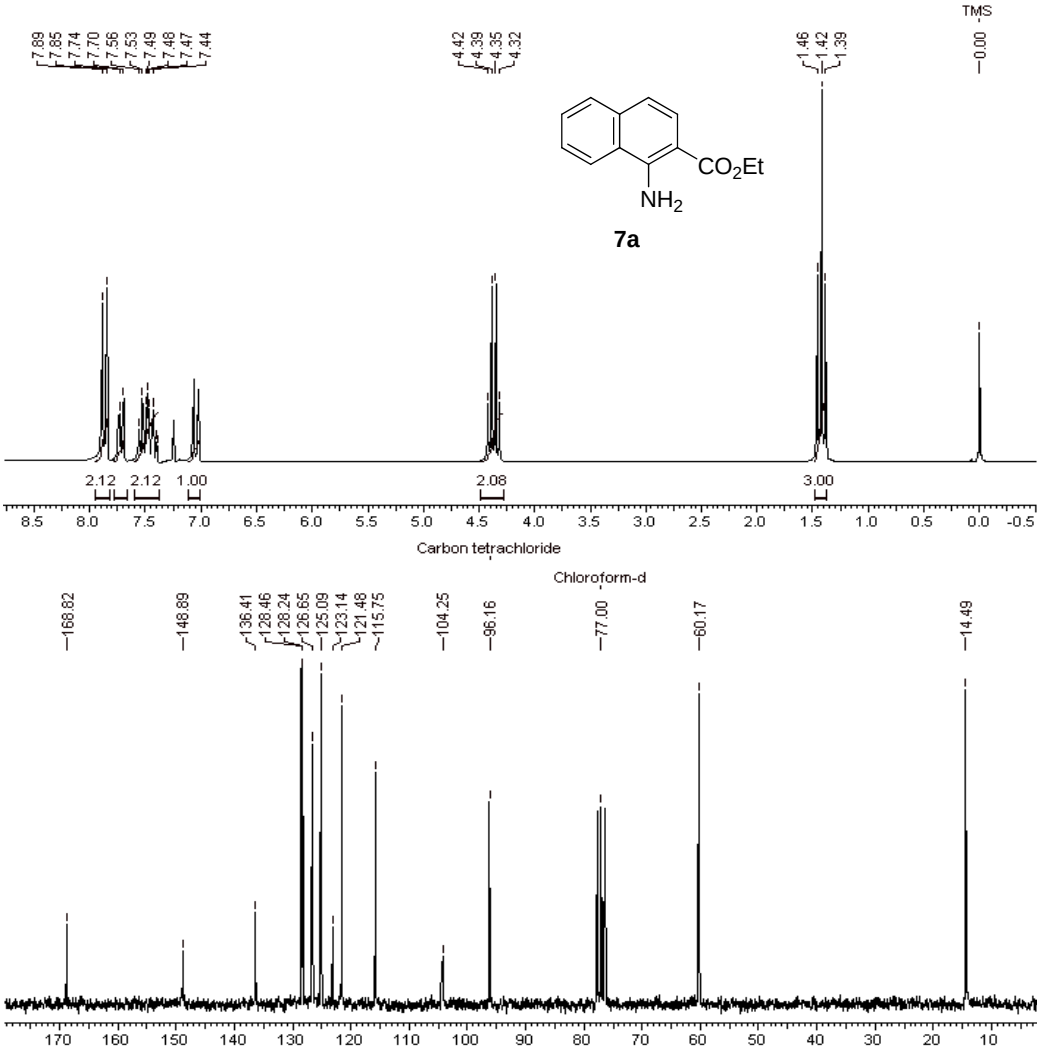
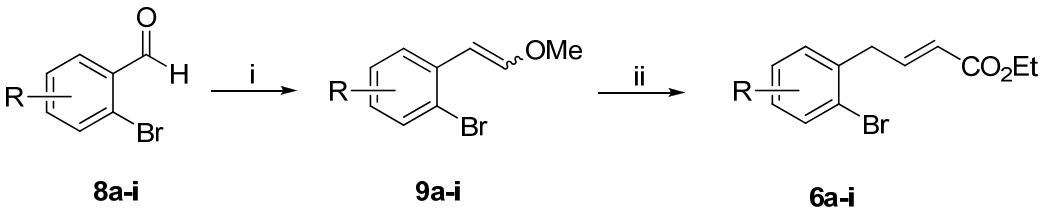


Fig. 1: ^{1}H and ^{13}C NMR spectra of naphthylamine derivative **7a**

Encouraged by the result, we became interested in its scope by subjecting other ethyl 4-(2-bromophenyl)-2-butenoate derivatives **6a-i**. Compounds **6a-i** were prepared in three steps starting from the corresponding *o*-bromobenzaldehydes **8a-i** using reported procedures.[8] Accordingly, Wittig olefination of *o*-bromobenzaldehydes **8a-i** using $MeOCH_2PPh_3Cl$ and KO^tBu in THF gave the corresponding methylethers **9a-i** in 84-92% yield with mixtures of E/Z isomers (1:1). However, acid hydrolysis of methyl ethers **9a-i** afforded the corresponding phenylacetaldehydes in good yields, which was then immediately subjected to Horner-Wadsworth-Emmons reaction using triethylphosphinoacetate and NaH in THF that afforded ethyl 4-(2-bromophenyl)-2-butenoate derivatives **6a-i** in 84-93% yield (**Scheme 4**).



8a-i **9a-i** **6a-i**

R = H, alkoxy, alkyl, F, NO_2, etc.

Scheme 4: (i) $MeOCH_2PPh_3Cl$, KO^tBu, THF, 0-25 °C, 0.5 h, 84-92%; (ii) (a) 2N HCl, THF, reflux, 3 h; (b) $(OEt)_2POCH_2CO_2Et$, NaH, THF, 0 °C, 3 h, 82-89%.

The formation of compounds **6a-i** was confirmed by ^1H & ^{13}C-NMR and IR spectroscopy. For example, compound **6d** showed a triplet of doublet and a multiplet at δ 5.76 (J = 1.5, 15.7 Hz) and 7.02-7.13 respectively integrating for one proton each in the ^1H-NMR spectrum, which accounts for the olefinic protons. It was further supported by the typical carbon signals at δ 120.3 and 145.8 in its ^{13}C-NMR spectrum (**Fig. 2**).

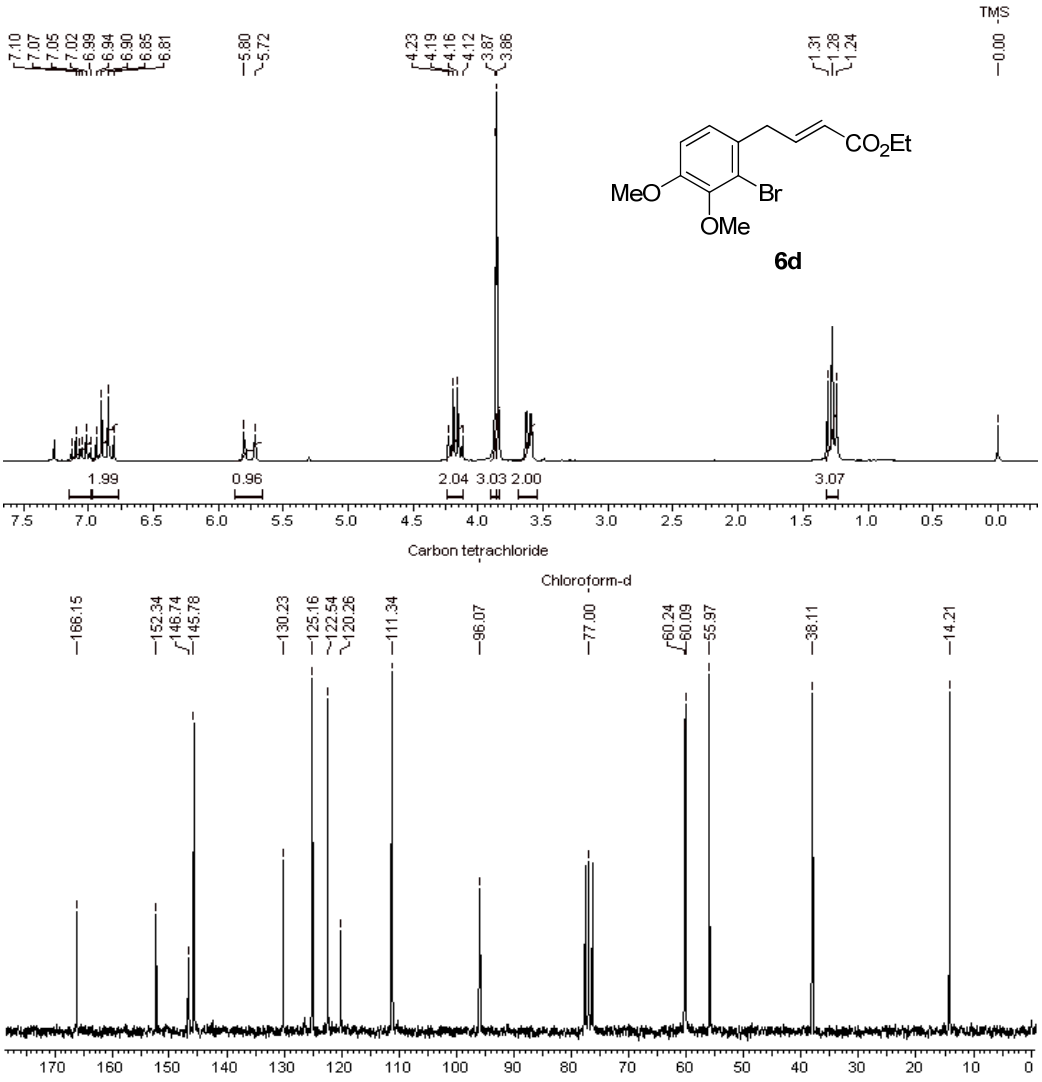
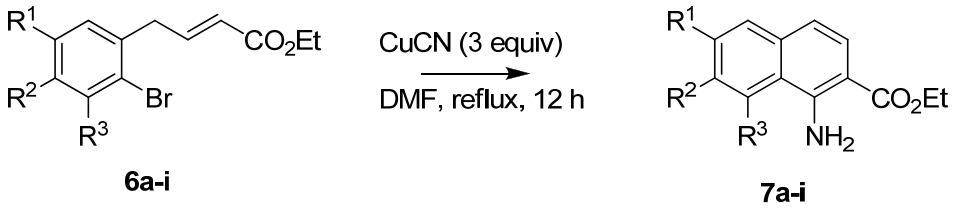


Fig. 2: ^{1}H and ^{13}C NMR spectra of ethyl 4-(2-bromophenyl)-2-butenoate **6d**

When subjected to CuCN-mediated one-pot cascade reaction with 3 equiv of CuCN, several ethyl 4-(2-bromo-phenyl)-2-butenoate derivatives **6a-i** gave the corresponding annulated napthalene derivatives **7a-i** in 73-91% yields. Results of such studies are presented in **Table 1**. As can be seen, this cascade cyclization took place smoothly to provide **7a-i** in a "one-pot" reaction, which comprises several transformations taking place, all occurring in a single step, with a variety of substituted ethyl 4-(2-bromo-phenyl)-2-butenoates **6a-i** and cheaply available reagent, CuCN. For instance, substrates

having halogen (entry g), methyl (entry f), highly electron rich (entry c & d) or electron defficient (entry h) substrates on the aromatic ring underwent this cascade cyclization smoothly affording the corresponding cyclized products **7a-i** 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.

Table 1: CuCN–Promoted Synthesis of Ethyl 1-Amino-2-Naphthalenecarboxylates



6a-i **7a-i**

Entry	R^1	R^2	R^3	Yield (%)[a]
a	H	H	H	85
b	OMe	H	H	78
c	OMe	OMe	H	74
d	H	OMe	OMe	73
e	OBn	OMe	H	76
f	H	Me	H	81
g	F	H	H	88
h	NO_2	H	H	91
i	-O-CH_2-O-		H	82

[a] Isolated yield after column chromatographic purification.

Fig. 3. shows the mass and IR spectra of **7g**. During the optimization studies, we found that, a mixture of products was obtained with lower equiv of CuCN, thus requiring a minimum of 3 equiv of CuCN to achieve excellent conversion.

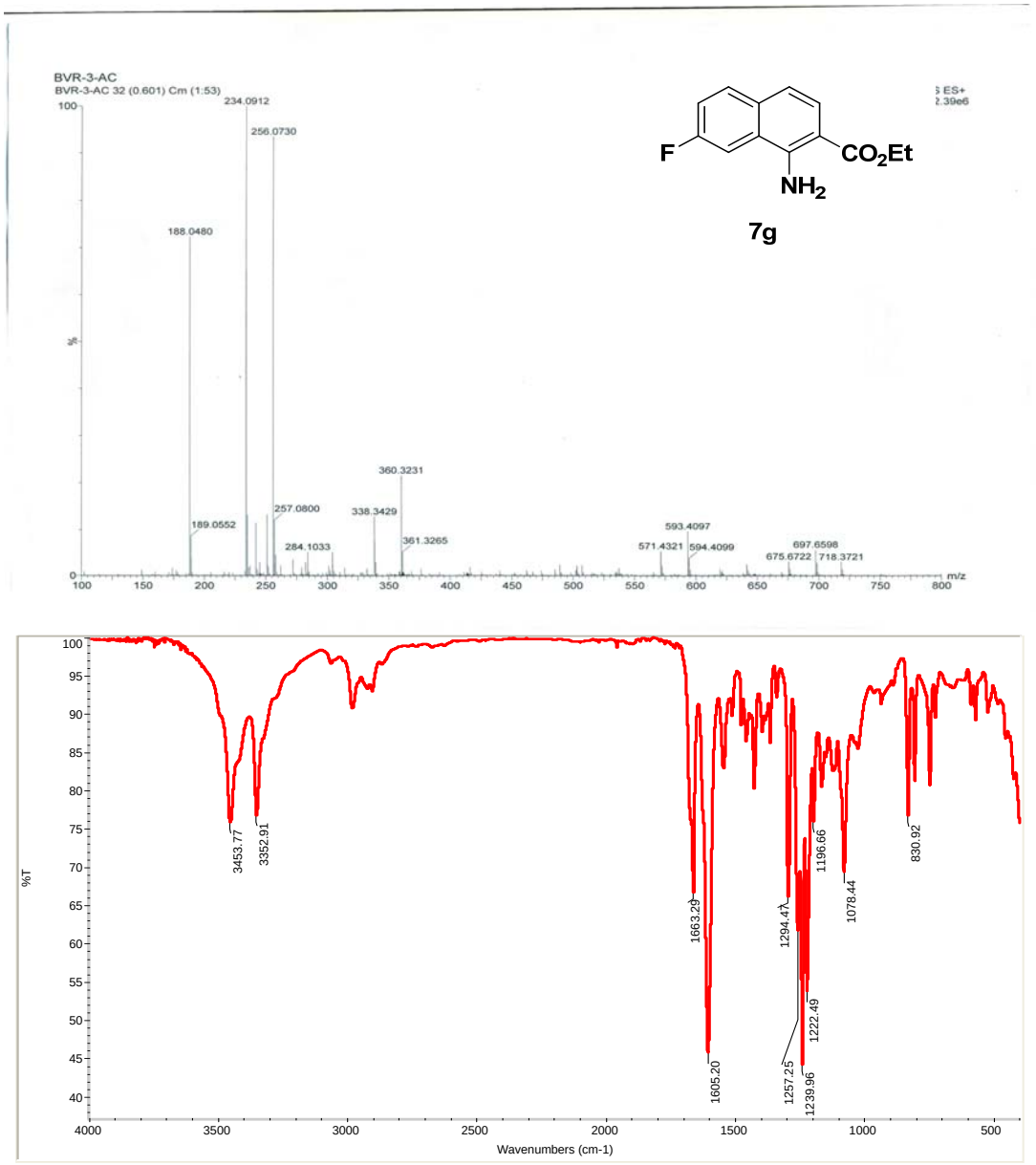
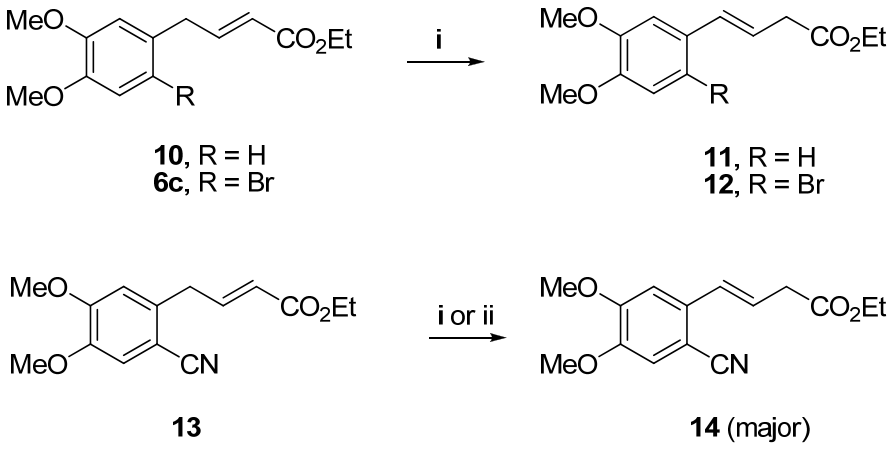


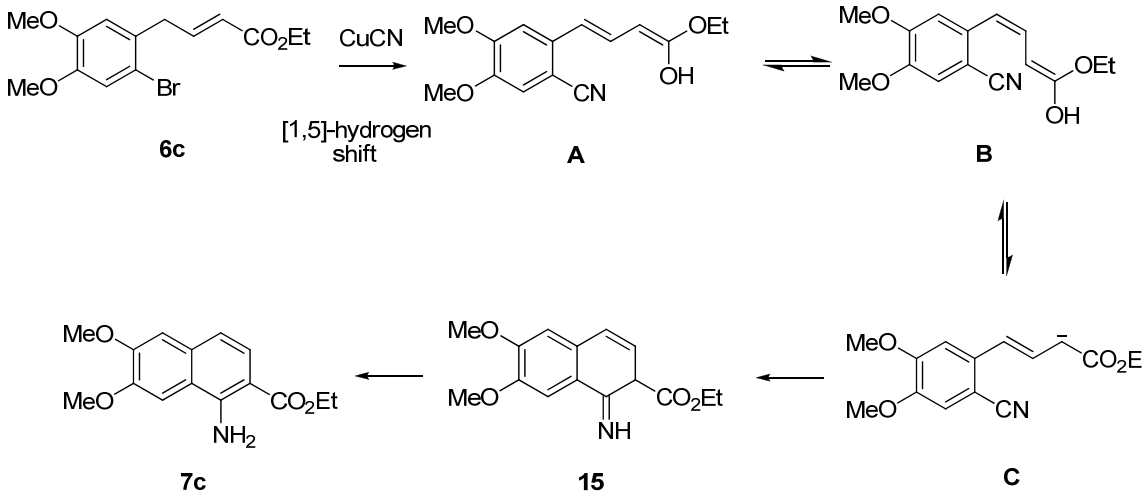
Fig. 3: Mass and IR spectra of ethyl 1-amino-2-naphthalenecarboxylate **7g**

To have a better understanding of the reaction mechanism, we have subjected both alkenes **10** and **6a** in the absence of CuCN, in DMF under reflux conditions that

proceeded to give the corresponding isomerised alkenes **11** and **12** respectively as the major isomers (**Scheme 5**). Also, when the corresponding CN-derivative **13** was subjected to the present reaction condition (with or without CuCN) the isomerised alkene **14** was formed as the major product.



Scheme 5: (i) DMF, reflux, 12 h, 84-92%; (ii) CuCN (3 equiv), DMF, reflux 12 h, 76%.



Scheme 6: Probable reaction pathway

This indicates that the reaction proceeds through 1,5-hydrogen transfer pathway to give species **A**, which is believed to be in equilibrium with species **B** & **C** under thermal

conditions.[9] We strongly believe that both isomerization and C-C bond formation take place simultaneously to give the cyclized unstable species **15**, which undergoes tautomerization[5] to form ethyl1-amino-2-naphthalenecarboxylate (**7c**) (**Scheme 6**). Protonated species **C** (compound **14**) was indeed isolated and characterized when the reaction was terminated before completion. The ^{1}H NMR spectrum of cyano alkene **14** showed a typical signal at δ 3.30-3.34 (m, 2H) corresponding to methylene (=CH-C**H$_2$**-) (**Fig. 4**). The IR spectrum of isomerized cyano alkene **14** displayed a strong absorption band at 2226 cm^{-1} indicating the presence of cyano group.

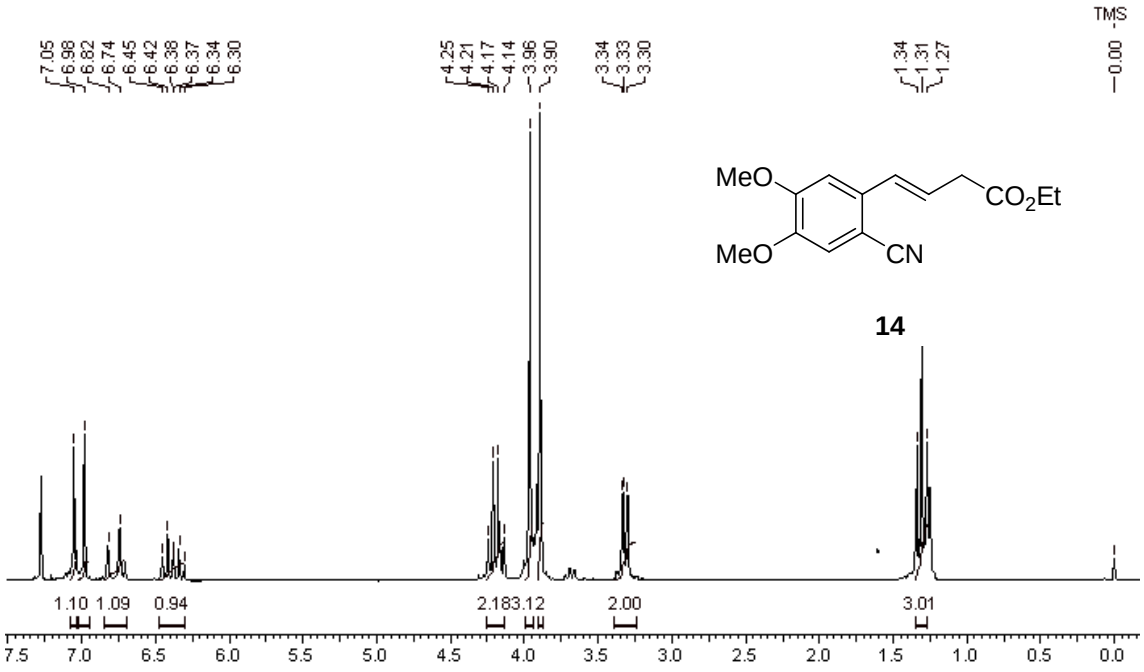


Fig. 4: ^{1}H NMR spectrum of cyano alkene **14**

4.1.5 Conclusion

In conclusion, we have developed a simple annulation strategy for the synthesis of ethyl1-amino-2-naphthalene carboxylate derivatives **7a-i** from the corresponding ethyl 4-(2-bromo-phenyl)-2-butenoate derivatives **6a-i** in high yields *via* CuCN-mediated

cyclizations. Use of inexpensive CuCN and the high purity of the annulated products make our synthesis more attractive. This method has been found very effective in the asymmetric synthesis of bioactive compounds possessing 1-amino-2-naphthalene core.

4.1.6 Experimental Section

General experimental procedure for the preparation methyl vinyl ethers 9a-i

To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (6.5 mmol) in THF (25 mL) was added *n*-BuLi (3.7 mL, 1.6 M solution in hexane, 5.75 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h. A solution of 2-bromo aldehydes **8a-i** (5.0 mmol) in THF (5 mL) was added to the reaction mixture, and the resulting mixture stirred at room temperature. After 30 min, it was quenched with water, and diluted with EtOAc. The organic layer was separated and aqueous layer extracted with ethyl acetate (3 x 20 ml); the combined organic layers were washed with brine (2 x 20 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate (90:10) as an eluent afforded methyl vinyl ethers **9a-i** as the pure product.

1-Bromo-2-(2-methoxyvinyl)benzene (9a)

Yield: 89%**,** gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 875, 924, 1056, 1135, 1255, 1330, 1476, 1502, 1645, 2928, 3010; **^{1}H-NMR** (200 MHz, $CDCl_3$) ***E*-isomer**: δ 3.72 (s, 3H), 6.06 (d, *J* = 12.9 Hz, 1H), 6.98 (d, *J* = 12.9 Hz, 1H), 7.16-7.34 (m, 4H); ***Z*-isomer**: δ 3.75 (s, 3H), 5.49 (d, *J* = 7.2 Hz, 1H), 6.12 (d, *J* = 7.2 Hz, 1H), 7.18-7.35 (m, 4H); **Analysis**: C_9H_9BrO requires C, 50.73; H, 4.26 found C, 50.67; H, 4.19 %.

1-Bromo-4-fluoro-2-(2-methoxyvinyl)benzene (9g)

Yield: 89%**,** gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 875, 960, 1034, 1180, 1269, 1358, 1483, 1574, 1636, 2916, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$) ***E*-isomer**: δ 3.73 (s, 3H), 6.01 (d, *J* = 12.8 Hz, 1H), 6.92 (d, *J* = 12.8 Hz, 1H), 6.7-6.9 (m, 1H), 7.41-7.43 (m, 2H); ***Z*-isomer**: δ 3.82 (s, 3H), 5.56 (d, *J* = 7.2 Hz, 1H), 6.27 (d, *J* = 7.2 Hz, 1H), 7.0-7.1 (m, 1H), 7.44-7.83 (m, 2H); **Analysis**: C_9H_8BrFO requires C, 46.78; H, 3.49 found C ,46.71; H 3.49 %.

1-Bromo-2-(2-methoxyvinyl)-4-nitrobenzene (9h)

Yield: 92%**,** gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 788, 865, 897, 968, 1056, 1087, 1133, 1262, 1334, 1426, 1475, 1514, 1652, 2928, 3012; **^{1}H-NMR** (200 MHz, $CDCl_3$) ***E*-isomer**: δ 3.90 (s, 3H), 5.62 (d, *J* = 12.8 Hz, 1H), 6.40 (d, *J* = 12.9 Hz, 1H), 7.69-7.82 (m, 2H), 8.95 (d, *J* = 3.4 Hz, 1H); ***Z*-isomer**: δ 3.79 (s, 3H), 6.07 (d, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.65-7.86 (m, 2H), 8.18 (d, *J* = 3.2 Hz, 1H); **Analysis**: $C_9H_8BrNO_3$ requires C, 41.89; H, 3.12 found C, 41.78; H 3.08 %.

5-Bromo-6-(2-methoxyvinyl)benzo[d][1,3]dioxole (9i)

Yield: 92%**,** gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 839, 869, 933, 1039, 1090, 1121, 1231, 1289, 1324, 1418, 1476, 1502, 1647, 2897, 2935, 3006; **^{1}H-NMR** (200 MHz, $CDCl_3$) ***Z*-isomer**: δ 3.75 (s, 3H), 5.51 (d, *J* = 7.3 Hz, 1H), 5.93 (s, 2H), 6.14 (d, *J* = 7.3 Hz, 1H), 6.99 (s, 1H), 7.62 (s, 1H); **^{13}C-NMR** (50 MHz, CDCl3): δ 56.5, 101.5, 103.9, 109.7, 112.4, 113.4, 128.6, 146.1, 147.0, 148.0; **^{1}H NMR** (200 MHz, $CDCl_3$) ***E*-isomer**: δ 3.70 (s, 3H), 5.93 (s, 2H), 6.01 (d, *J* = 12.9 Hz, 1H), 6.81 (s, 1H), 6.86 (d, *J* = 12.9 Hz, 1H), 6.98 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 60.7, 101.6, 104.6, 105.2, 112.7, 113.3, 129.5, 146.6, 147.6, 149.5; **Analysis**: $C_{10}H_9BrO_3$ requires C, 46.72; H, 3.53; found C, 46.66; H, 3.48 %.

General experimental procedure for the preparation of ethyl 4-(2-bromophenyl)-2-butenoate derivatives, 6a-i

To a stirred solution of crude methyl vinyl ether derivatives **9a-i** (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 organic solvent *in vacuo*, water was added to the mixture, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with brine, 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 the above crude aldehydes in CH_2Cl_2 (5 mL) at room temperature was added a Wittig reagent (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 petroleum ether: ethyl acetate (80:20) as eluent] afforded the unsaturated esters **6a-i** in pure form.

(E)-Ethyl 4-(2-bromophenyl)but-2-enoate (6a)

Yield: 86%; Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 750, 981, 1024, 1155, 1194, 1266, 1653, 1713, 2980; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H,), 3.66 (dd, *J* = 1.6, 6.6 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.76 (td, *J* = 1.6, 15.7 Hz, 2H), 7.56 (dd, *J* = 1.0, 7.8 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.5, 60.3, 122.8, 124.5, 127.7, 128.4, 130.7, 132.9, 137.3, 145.4, 166.3; **Analysis**: $C_{12}H_{13}BrO_2$ requires C, 53.55; H, 4.87; Br, 29.69 Found: C, 53.46; H, 4.79; Br, 29.61%.

(E)-Ethyl 4-(2-bromo-5-methoxyphenyl)but-2-enoate (6b)

Yield: 89%; Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 803, 983, 1016, 1040, 1131, 1199, 1239, 1267, 1472, 1713, 2979; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.56 (dd, *J* = 1.5, 6.6 Hz, 2H), 3.85 (s, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.1 (s, 2H), 5.75 (td, *J* = 1.5, 15.7 Hz, 1H), 6.88 (s, 1H), 7.02-7.10 (m, 2H), 7.30-7.44 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.7, 55.4, 60.3, 113.9, 114.9, 116.4, 122.9, 133.4, 138.2, 145.2, 159.1, 166.3; **Analysis**: $C_{13}H_{15}BrO_3$ requires C, 52.19; H, 5.05; Br, 26.71 Found: C, 52.25; H, 5.14; Br, 26.82%.

(E)-Ethyl 4-(2-bromo-4,5-dimethoxyphenyl)but-2-enoate (6c)

Yield: 82%; 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 1.30 (t, *J* = 7.2 Hz, 3H), 3.27 (dd, *J* = 1.3, 7.1 Hz, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 6.13 (td, *J* = 7.1, 15.8 Hz, 1H), 6.73 (td, *J* = 1.5, 15.8 Hz, 1H), 6.97 (s, 1H), 7.00 (s, 1H); **^{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, 50.98; H, 5.14; Br, 24.32%.

(E)-Ethyl 4-(2-bromo-3,4-dimethoxyphenyl)but-2-enoate (6d)

Yield: 84%; 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 14.2, 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, 50.95; H, 5.13; Br, 24.34%.

(E)-Ethyl 4-(5-(benzyloxy)-2-bromo-4-methoxyphenyl)but-2-enoate (6e)

Yield: 84%; 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-methylphenyl)but-2-enoate (6f)

Yield: 86%; Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 768, 874, 1028, 1098, 1180, 1195, 1265, 1245, 1465, 1716, 2965; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.52 (s, 3H), 3.50 (dd, *J* = 1.5, 7.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 6.12 (td, J = 3.5, 15.7 Hz, 1H), 7.08(s, 1H), 7.32-7.38 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 22.1, 60.5, 113.3, 114.6, 115.7, 122.4, 128.8, 136.6, 138.2, 148.4, 167.2; **Analysis**: $C_{13}H_{15}BrO_2$ requires C, 55.14; H, 5.34; Br, 28.22 Found: C, 55.05; H, 5.28; Br, 28.16%.

(E)-Ethyl 4-(2-bromo-5-fluorophenyl)but-2-enoate (6g)

Yield: 88%; Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 806, 1024, 1161, 1240, 1295, 1473, 1573, 1719, 2036; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.61 (dd, *J* = 1.5, 6.6 Hz, 2H), 3.85 (s, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.78 (td, *J* = 1.5, 15.7 Hz, 2H), 6.80-7.08 (m, 3H), 7.51 (dd, *J* = 5.3, 8.7 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.5, 60.4, 115.6 (d, *J* = 22.9 Hz), 117.6 (d, *J* = 22.9 Hz), 118.6 (d, *J* = 3.8 Hz), 123.4, 134.1 (d, *J* = 8.6 Hz), 139.4 (d, *J* = 7.6 Hz), 144.3, 162.0 (d, *J* = 246.0 Hz), 166.1; **Analysis**: $C_{12}H_{12}BrFO_2$ requires C, 50.20; H, 4.21; Br, 27.83; F, 6.62; Found: C, 50.13; H, 4.12; Br, 27.76; F, 6.53%.

(E)-Ethyl 4-(2-bromo-4-nitrophenyl)but-2-enoate (6h)

Yield: 84%; 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 1.31 (t, *J* = 7.2 Hz, 3H), 3.33 (dd, *J* = 1.3, 7.1 Hz, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 6.38 (td, J = 3.8, 15.7 Hz, 1H), 7.5 (m, 1H), 7.70 (td, J = 3.8, 15.7 Hz, 1H), 7.75-7.82 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 38.1, 60.2, 113.3, 114.6, 115.8, 122.4, 127.6, 129.6, 148.4, 166.0; **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-(5-bromobenzo[d][1,3]dioxol-6-yl)but-2-enoate (6i)

Yield: 86%; Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 858, 929, 982, 1034, 1113, 1157, 1228, 1268, 1475, 1712, 2980; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.2 Hz, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 6.04 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 7.00 (s, 1H), 7.15(s, 1H), 7.75(d, *J* = 8.8 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 38.4, 60.2, 101.7, 110.2, 112.9, 114.7, 122.7, 130.1, 145.5, 147.4, 147.6, 166.2; **Analysis**: $C_{13}H_{13}BrO_4$ requires C, 49.86; H, 4.18; Br, 25.52 Found: C, 49.78; H, 4.09; Br, 25.44%.

General experimental procedure for the preparation of ethyl1-amino-2-naphthalene carboxylate derivatives (7a-i)

The alkenes **6a-i** (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 for 12 h (monitored by TLC). 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 and 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 petroleum ether: EtOAc (7:3) as an eluent] to give ethyl1-amino-2-naphthalene carboxylate derivatives (**7a-i**) in 73-91% yield.

Ethyl 1-aminonaphthalene-2-carboxylate (7a)

Yield: 85%; 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), 4.36 (q, *J* = 7.1 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 1H), 7.40-7.56 (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; **Analysis**: $C_{13}H_{13}NO_2$ requires C, 72.54 ; H, 6.09 ; N, 6.51; found: C, 73.08; H, 6.34; N, 6.67 %.

Ethyl 1-amino-6-methoxynaphthalene-2-carboxylate (7b)

Yield: 78%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 870, 1076, 1245, 1340, 1599, 1672, 3346, 3457; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, 3H, *J* = 7.0 Hz), 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 = 9.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.5, 55.2, 60.0, 103.1, 107.0, 115.0, 118.0, 123.2, 127.5, 138.3, 148.9, 159.5, 168.8; HRMS (ESI+, *m/z*): calcd for $(C_{14}H_{15}NO_3)^+$ $[(M+Na)^+]$ 268.0944; found: 268.0938; **Analysis**: $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71; found: C, 68.18; H, 5.99; N, 5.45 %.

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

Yield: 74%; 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), 4.36 (q, 2H, *J* = 7.1 Hz), 7.05 (d, *J* = 8.9 Hz, 1H), 7.40-7.56 (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; **Analysis**: $C_{15}H_{17}NO_4$ requires C, 65.44 ; H, 6.22 ; N, 5.09 found: C, 65.69 ; H, 6.18 ; N, 5.11%.

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

Yield: 73%; 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 14.2, 56.6, 59.6, 61.2, 102.5, 113.8, 116.6, 117.8, 124.2, 125.1, 132.9, 146.8, 148.4, 150.9, 168.6; **Analysis**: $C_{15}H_{17}NO_4$ requires C, 65.44 ; H, 6.22 ; N, 5.09 found: C, 65.34 ; H, 6.31 ; N, 5.12%.

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

Yield: 76%; 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, 2H, *J* = 7.1 Hz), 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, 6H), 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, 1136.7, 147.5, 147.9, 151.8, 168.9; **Analysis**: $C_{21}H_{21}NO_4$ requires C, 71.68; H, 6.02; N, 3.99; found: C, 71.63; H, 5.95; N, 3.89%.

Ethyl 1-amino-6-methylnaphthalene-2-carboxylate (7f)

Yield: 81%; 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 1.42 (t, *J* = 7.1 Hz, 3H), 2.55 (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+, *m/z*):

calcd for $(C_{14}H_{15}NO_2)^+$ [$(M+Na)^+$] 252.0995; found: 252.0989; **Analysis**: $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11; found: C, 73.26; H, 6.52; N, 6.01%.

Ethyl 1-amino-6-fluoronaphthalene-2-carboxylate (7g)

Yield: 88%; 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* = 7.1 Hz, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 7.15-7.24 (m, 1H), 7.34 (dd, *J* = 2.5, 7.1 Hz, 1H), 7.84-7.92 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.5, 62.3, 104.1, 111.9, 114.9, 120.0, 124.3, 128.1, 138.1, 148.8, 161.1, 163.6, 168.7; HRMS (ESI+, *m/z*): calcd for $(C_{13}H_{12}FNO_2)^+$ [$(M+Na)^+$] 256.0744; found: 256.0730; **Analysis**: $C_{13}H_{12}FNO_2$ requires C, 66.94; H, 5.19; N, 6.01; found: C, 67.03; H, 5.13; N, 5.89%.

Ethyl 1-amino-6-nitronaphthalene-2-carboxylate (7h)

Yield: 91%; 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 (s, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 8.02 (t, *J* = 8.8 Hz, 1H), 8.18 (d, *J* = 2.26 Hz, 1H), 8.20 (d, *J* = 2.26, 1H), 8.64 (d, *J* = 2.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.7, 107.1, 116.8, 118.2, 123.4, 124.4, 125.6, 129.0, 135.6, 147.0, 148.2, 168.2; HRMS (ESI+, *m/z*): calcd for $(C_{13}H_{12}N_2O_4)^+$ [$(M+Na)^+$] 283.0689; found: 283.0682; **Analysis**: $C_{13}H_{12}N_2O_4$ requires C, 60.00; H, 4.65; N, 10.76; found: C, 59.95; H, 4.51; N, 10.65%.

Ethyl 5-aminonaphtho[2,3-d][1,3]dioxole-6-carboxylate (7i)

Yield: 82%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1243, 1345, 1602, 1674, 3352, 3446; **^{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 14.4, 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; **Analysis**: $C_{13}H_{12}N_2O_4$ requires C, 64.86; H, 5.05; N, 5.40; found: C, 64.79; H, 5.12; N, 5.46%.

(E)-Ethyl 4-(2-cyano-4,5-dimethoxyphenyl)but-3-enoate (14)

Yield: 67%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 780, 884, 1028, 1243, 1345, 1545, 1626, 1720, 2226, 2980, 3010; **^{1}H-NMR** (200MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.0, 3H), 3.31 (dd, *J* = 1.26, 6.95 Hz, 2H), 3.90 (s, 3H), 3.96 (s, 3H), 4.19 (q, *J* = 7.0 Hz, 2H), 6.30-6.45 (m, 1H), 6.78 (d, *J* = 15.7 Hz, 1H), 6.98 (s, 1H), 7.05 (s, 1H); **Analysis**: $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09; found: C, 65.36; H, 6.16; N, 4.98 %.

Section II:

CuCN-Mediated "One-pot" Synthesis of 3-Substituted Phthalides

4.2.1 Introduction

Phthalide (1(3*H*)-isobenzofuranone) frameworks (**Fig. 5)** are not only present in a large number of natural products and biologically active compounds,[10] but also are useful intermediates for the synthesis of tri- and tetracyclic natural products.[11] Thus, significant efforts have been focused on synthesizing phthalides in the past few decades.[12] The ability of a single reagent to promote a desired cascade of reaction events in a single reaction flask with high yields represents an efficient strategy for assembling complex synthetic targets, such as phthalides.[13] However, the development of a simple and efficient method to access 3-substituted phthalides still remains a highly desirable goal in synthetic chemistry.

Fig. 5: Some of the examples of chiral phthalides

4.2.2 Review of literature

Literature search revealed that there are two reports available for the synthesis of 3-substituted phthalide derivatives from 2-bromobenzyl alcohol derivatives, which are described below.

Trost's approach (2007)[14]

Trost *et al*. have described the synthesis of phthalide fragment as part of their spirolaxine methyl ether synthesis. Thus, bromo alcohol **19** is treated with *n*BuLi (2.2 equiv) at -78 °C for one min, then rapidly flushing the reaction with CO_2 gas to trap the aryl lithium species to provide phthalide **20** in 90% yield (**Scheme 7**).

Scheme 7: (i) *n*BuLi, THF, -78 °C then CO_2, HCl/H_2O, 90%.

Brimble's approach (2005)[15,16]

Brimbles *et al.* have reported the synthesis of phthalide **23** in two steps starting from bromo alcohol **21**, which was converted to diethyl carbamate **22.** This on with subsequent lithium-halogen exchange followed by intramolecular acylation and lactonization provided phthalide **23** in 76% yield (**Scheme 8**).

Scheme 8: (i) NaH, THF, 0 °C then N,N-diethylcarbamoylchloride, 82%; (ii) *t*-BuLi, THF, -78 °C, 45 min then PTSA, 20 °C, 12 h, 76%.

In another approach, same authors have described the synthesis of phthalide fragment as as part of their herbaric acid synthesis. Thus, bromo alcohol **24** was treated with 1,10-carbonyldiimidazole and diethylamine to furnish carbamate **25** in 90% yield, which upon

treatment with *n*-BuLi led to intramolecular acylation and subsequent acid-mediated lactonization to deliver vinylphthalide **26** in 74% yield (**Scheme 9**).

Scheme 9: (i) Carbonyl diimidazole, $HNEt_2$, 90%; (ii) (a) n-BuLi, THF (b) HCl, dioxane, 74% (2 steps).

4.2.3 Present Work

4.2.3.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of 3-substituted phthalides employ either lithiation followed by carboxylation or carbamate formation followed by lithiation. This limits the broad substrate scope and higher reaction stereoselectivity. The great challenges are remaining since the cyano group is inert to the insertion of metal species in comparison with C=O, partly due to its low polarity.[17] Moreover, the aromatic nitriles may also have good affinity to transition-metals, resulting in the deactivation of the catalyst.[18] In this context, a more practical and efficient synthesis of functionalized 3-substituted phthalide derivatives is highly desirable using less number of reagents *via* CN activation. In this section, we present a CuCN- mediated single-step cyclization of 2-bromo benzyl alcohol derivatives that afford 3-substituted phthalides in high yields *via in situ* formation of nitriles.

4.2.4 Results and Discussion

In continuation of our interest on development of new methodologies for the synthesis of bioactive intermediates, we were interested to carry out a “one-pot” cost-effective

procedure for the synthesis of 3-substituted phthalides **28a-m** from the corresponding *o*-bromobenzylalcohol derivatives **27a-m**. When, *o*-bromobenzylalcohol **27c**, readily derived from 2-bromo-3,5-dimethoxybenzaldehyde *via* Barbier allylation, was subjected to Rosenmund-von Braun reaction in the presence of CuCN (3 equiv) in DMF under reflux condition, the corresponding phthalide **28c** was formed in 86% yield (**Scheme 10**).

Scheme 10: (i) CuCN (3.0 equiv.), DMF, 150 °C, 10 h, 86%.

Encouraged by the result, we became interested in the scope of the reaction by subjecting other *o*-bromobenzyl alcohols **27a-m.** 2-Bromobenzyl alcohols **27a-m** were prepared in one step, starting from the corresponding *o*-bromoaldehydes *via* Barbier allylation or Grignard reaction using allylbromide or alkyl halides in 79-88% yield (see experimental section). When subjected to CuCN- mediated "one-pot" cyclization with CuCN (3 equiv) in DMF at 150 °C, *o*-bromobenzyl alcohols **27a-m** gave the corresponding phthalide derivatives **28a-m** in 82-88% yields. Results of such studies are presented in **Table 2**. As can be seen, in every case, the reaction proceeded smoothly within 10-12 h giving the desired phthalides **28a-m** in excellent yields. For instance, substrates having halogen (entry g), highly electron-rich groups (entry d) and different alkyl groups at R_4 (entries i-m) underwent this cyclization smoothly affording the corresponding phthalides **28a-m** in excellent yields.

Table 2: CuCN-Mediated One-pot Synthesis of 3-Substituted Phthalides

Entry	R^1	R^2	R^3	R^4	Yield (%)[a]
a	H	H	H	H	88
b	OMe	H	H	H	86
c	OMe	H	OMe	H	86
d	OMe	OMe	OMe	H	85
e	OTs	OMe	H	H	88
f	OBn	OMe	H	H	82
g	F	H	H	H	88
h		-O-CH_2-O-	H	H	84
i	H	H	H	Me	88
j	H	H	H	*n*-C_2H_5	88
k	H	H	H	*n*-C_3H_7	86
l	H	H	H	*n*-C_4H_9	85
m	H	H	H	*n*-C_7H_{15}	86

[a] Isolated yield after column chromatographic purification.

The formation of phthalide derivatives **28a-m** was confirmed by ^{1}H, ^{13}C-NMR and IR spectroscopy. Example 1: The formation of allylphthalide **28c** was confirmed by the presence of a triplet at δ 5.32 (J = 5.8 Hz) integrating for one proton (-C**H**-O-CO-) and also multiplets at δ 5.13, 5.20 and 5.77 integrating for one proton each, which corresponds to olefinic proton in its ^{1}H-NMR spectrum. This is further substantiated by the signals at δ 78.5 and 167.9 corresponding to carbon attached to oxygen atom and carbonyl group of lactone respectively in its ^{13}C NMR spectrum (**Fig. 6**). Its IR spectrum

displayed a strong stretching frequency at 1752 cm^{-1}, indicating the presence of γ-lactone group (**Fig. 6**).

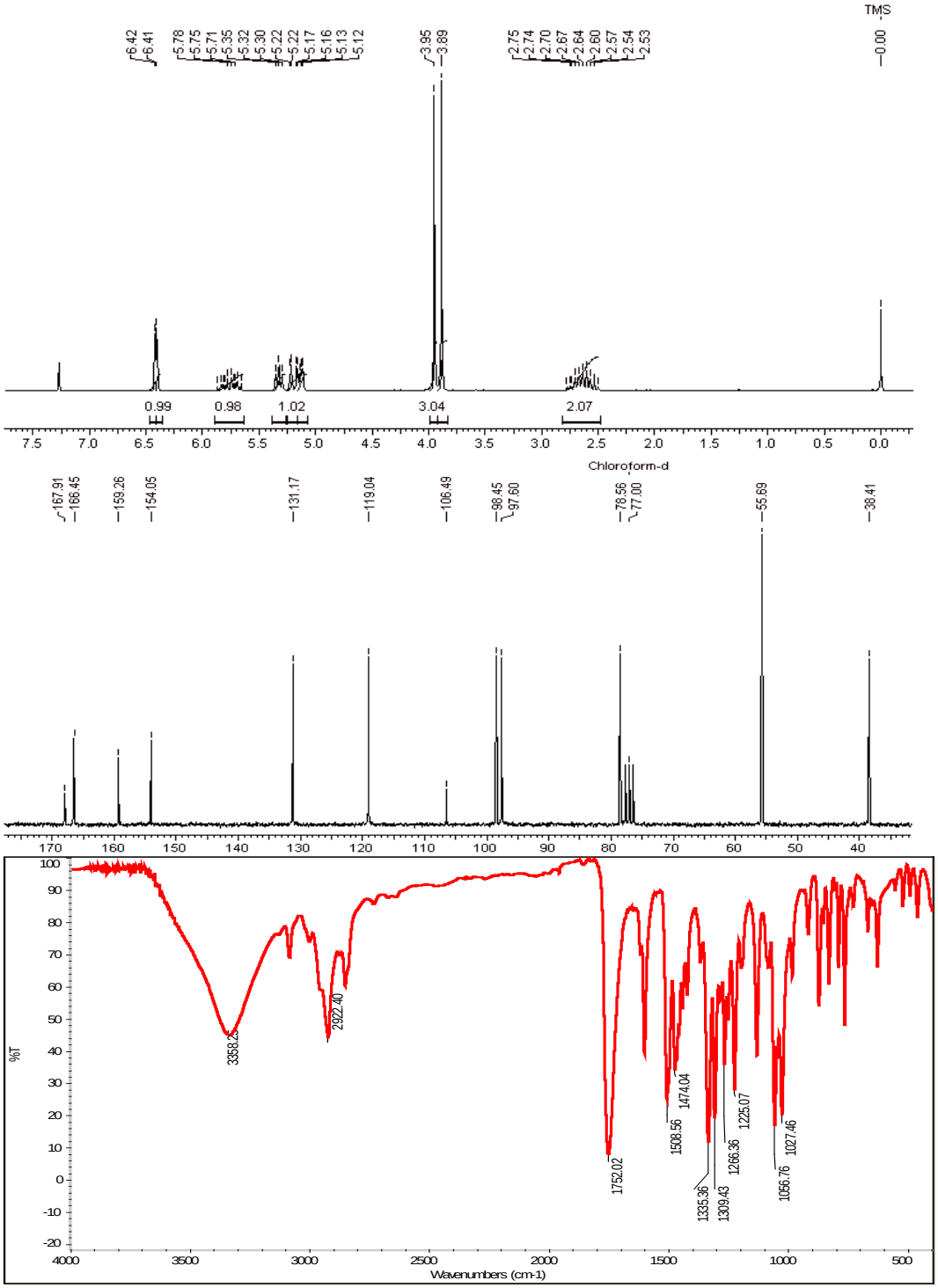


Fig. 6: ^{1}H, ^{13}C NMR and IR spectra of phthalide **28c**

Example 2: The formation of butylphthalide **28l** was confirmed by the presence of a doublet of doublet at δ 5.46 integrating for one proton (-C**H**-O-) in its ^{1}H-NMR spectrum and further substantiated by the carbonyl signal at δ 170.0 its ^{13}C-NMR spectrum. Its IR spectrum displayed a strong absorption band at 1759 cm^{-1} indicating the presence of γ-lactone function (**Fig. 7)**.

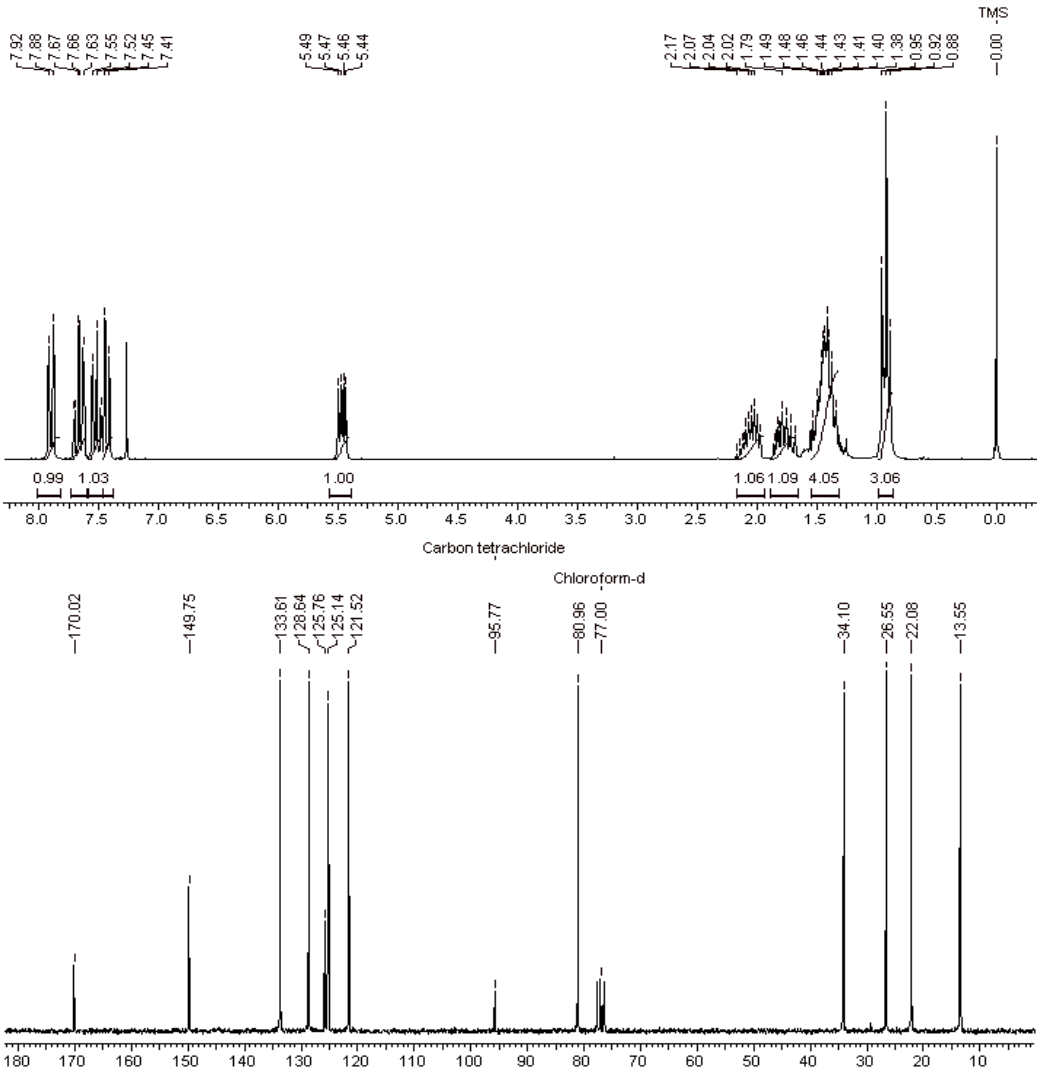


Fig. 7: ^{1}H and ^{13}C NMR spectra of phthalide **28l**

4.2.5 Conclusion

We have developed a novel one-pot tandem route for the synthesis of a wide variety of 3-substituted phthalides and their structural analogues *via* Rosenmund-von Braun reaction.

This reaction is highly practical in the sense that the products were obtained in excellent yields. It also shows broad substrate scope and good functional group tolerance. We believe that this intramolecular cyclization strategy should find wide applications in the total synthesis of bioactive phthalide frameworks.

4.2.6 Experimental Section

General experimental procedure for the preparation of allyl alcohols (27a-m)

To a pre-cooled (0 °C), well stirred mixture of 2-bromo aldehydes (1 mmol), Zn dust (2 mmol) and allyl bromide (1.8 mmol) in 10 mL of CH_3CN was added a saturated solution of NH_4Cl (1 mL). The mixture was stirred for 10 h at ambient temperature until the aldehyde was totally consumed (monitored by TLC). The mixture was filtered and the precipitate was washed thoroughly with EtOAc (3 x 10 mL). The organic layer is then washed with brine and dried over anhyd. Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on chromatographic separation with petroleum ether/EtOAc (7:3 v/v) gave 3-substituted phthalides **27a-m** in pure form.

1-(2-Bromophenyl)but-3-en-1-ol (27a)

Yield: 88%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 792, 865, 985, 1015, 1134, 1323, 1386, 1432, 1476, 1565, 2934, 3425; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.14 (d, *J* = 4.1 Hz, 1H), 2.25-2.41 (m, 1H), 2.63-2.70 (m, 1H), 5.05-5.14 (m, 2H), 5.22-5.25(m, 1H), 5.77-5.98(m, 1H), 7.07-7.16 (m, 1H), 7.28-7.36 (m, 1H), 7.48-7.57 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 42.0, 71.7, 118.5, 121.7, 127.3, 127.6, 128.7, 132.5, 134.2, 142.7; **Analysis**: $C_{10}H_{11}BrO_1$ requires C, 52.89; H, 4.88 Found: C, 52.76; H, 4.72%.

1-(2-Bromo-5-methoxyphenyl)but-3-en-1-ol (27b)

Yield: 80%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 680, 858, 976, 1025, 1148, 1350, 1386, 1472, 1488, 1575, 2928, 3414; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.37-2.39 (m, 2H), 2.62-

2.68 (m, 1H), 3.83 (s, 3H), 5.04-5.08 (m, 1H), 5.19-5.25 (m, 2H), 5.84-5.97 (m, 1H), 7.71 (dd, *J* = 3.1, 8.9 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H). 7.27 (d, *J* = 8.1 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 42.0, 55.5, 71.9, 112.0, 114.9, 118.5, 133.2, 134.3, 143.9, 145.1, 159.2; **Analysis**: $C_{11}H_{13}BrO_2$ requires C, 51.38; H, 5.10 Found: C, 51.29; H, 5.01%.

1-(2-Bromo-3,5-dimethoxyphenyl)but-3-en-1-ol (27c)

Yield: 82%**,** yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 723, 798, 846, 975 1056, 1345, 1392, 1476, 1492, 1568, 2945, 3014, 3398; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.14 (br s, 1H), 2.22-2.37 (m, 1H), 2.57-2.70 (m, 1H), 3.82 (s, 3H), 3.87 (s, 3H), 5.09-5.24 (m, 3H), 5.22 5.79-6.0 (m, 1H), 6.39 (d, *J* = 2.9 Hz, 1H), 6.70 (d, *J* = 2.9 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 41.7, 55.3, 56.0, 71.9, 102.8, 108.1, 134.4, 144.9, 156.0, 159.7; **Analysis**: $C_{12}H_{15}BrO_3$ requires C, 50.19; H, 5.27 Found: C, 50.12; H, 5.20%.

1-(2-Bromo-3,4,5-trimethoxyphenyl)but-3-en-1-ol (27d)

Yield: 79%, gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1009, 1105, 1162, 1195, 1324, 1394, 1426, 1481, 1569, 2938, 3435; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.17 (d, *J* = 4.1 Hz, 1H), 2.24-2.35 (m, 1H), 2.56-2.68 (m, 1H), 3.87 (s, 3H), 3.89 (s, 6H), 5.02-5.10 (m, 1H), 5.14-5.18 (s 1H), 5.21-5.27 (m, 1H), 5.79-6.00 (m, 1H), 6.95 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 42.2, 56.1, 61.0, 61.1, 71.8, 105.8, 107.8, 118.9, 134.5, 138.5, 142.1, 150.4, 153.0; **Analysis**: $C_{12}H_{15}BrO_4$ requires C, 59.23; H, 5.40 Found: C, 59.13; H, 5.29%.

4-Bromo-5-(1-hydroxybut-3-enyl)-2-methoxyphenyl-4-methylbenzenesulfonate (27e)

Yield: 84%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 790, 826, 888, 986, 1185, 1278, 1384, 1436, 1545, 2927, 3419; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.16-2.30 (m, 2H), 2.46 (s, 3H), 2.57-2.68(m, 1H), 3.69 (s, 3H), 4.95-5.02 (m, 1H), 5.13-5.17 (m, 1H), 5.22-5.24 (m, 1H), 5.76-5.97 (m, 1H), 7.09 (s, 1H), 7.29-7.33 (m, 3H), 7.77 (d, *J* = 8.2 Hz, 2H);

Analysis: $C_{18}H_{19}BrO_5S$ requires C, 50. 59; H, 4.48; S, 7.50 Found: C, 50. 43; H, 4.40; S, 7.42%.

1-(2-Bromo-4-methoxy-5-phenoxyphenyl)but-3-en-1-ol (27f)

Yield: 86%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 756, 852, 894, 974, 1085, 1124, 1267, 1358, 1457, 1542, 2934, 3032, 3424; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.09 (brs, 1H), 2.22-2.38 (m, 1H), 2.52-2.68 (m, 1H), 3.88 (s, 3H), 4.96-5.02 (m, 1H), 5.02 (s, 2H), 5.12-5.14 (m, 1H), 5.18-5.23 (m, 1H), 5.77-5.98 (m, 1H), 7.00 (s, 1H), 7.08 (s, 1H), 7.34-7.45 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 42.4, 56.2, 71.2.9, 71.7, 110.3, 111.2, 118.5, 127.4, 128.0, 128.6, 134.4, 135.5, 136.4, 147.8,149.4; **Analysis**: $C_{17}H_{17}BrO_3$ requires C, 58.47; H, 4.91 Found: C, 58.36; H, 4.82%.

1-(2-Bromo-5-fluorophenyl)but-3-en-1-ol (27g)

Yield: 82%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 774, 826, 878, 989, 1167, 1265, 1376, 1435, 1564, 2985, 3420; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.20 (br s, 1H), 2.25-2.36 (m, 1H), 2.58-2.71 (m, 1H), 4.99-5.05 (m, 1H), 5.16-5.18 (m, 1H), 5.23-5.27 (m, 1H), 5.77-5.97 (m, 1H), 6.81-6.91 (m, 1H), 7.30 (dd, *J* = 4.1,4.3 Hz, 1H), 7.46 (dd, *J* = 4 ,4.4 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 41.9, 71.6, 114.6 (d, *J* = 26 Hz), 115.3, 115.8 (d, *J* = 26 Hz), 119.1, 133.7, 133.8, 145.9, 162.8 (d, *J* = 250 Hz); **Analysis**: $C_{10}H_{10}BrFO$ requires C, 49.01; H, 4.11 Found: C, 48.96; H, 4.01%.

1-(6-Bromobenzo[d][1,3]dioxol-5-yl)but-3-en-1-ol (27h)

Yield: 85%, gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 678, 760, 874, 899, 965, 1084, 1167, 1278, 1339, 1465, 1564, 2928, 3016, 3418; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.22-2.38 (m, 1H), 2.49-2.61 (m, 1H), 5.01-5.06 (m, 1H), 5.12-5.15 (m, 1H), 5.75-5.87 (m, 1H), 5.96(s, 2H), 6.95 (s, 1H), 7.04 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 42.2, 71.7, 101.6, 107.2, 111.8,

118.5, 134.2, 136.2, 147.5; **Analysis**: $C_{11}H_{11}BrO_3$ requires C, 48.73; H, 4.09 Found: C, 48.62; H, 4.01%.

1-(2-Bromophenyl)ethanol (27i)

Yield: 82%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 775, 798, 874, 974, 1072, 1189, 1458, 2916, 3025, 3424; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.40 (d, *J* = 6.79 Hz, 3H), 3.19 (br s, 1H), 5.16 (q, *J* = 6.04, 6.79 Hz, 1H), 7.04-7.09 (m, 1H), 7.25-7.30 (m, 1H), 7.44-7.54 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.5, 68.9, 121.5, 126.6, 127.7, 128.5, 132.4, 144.5; **Analysis**: C_8H_9BrO requires C, 47.79; H, 4.51 Found: C, 47.69; H, 4.43%.

1-(2-Bromophenyl)-1-propanol (27j)

Yield: 84%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 741, 894, 1020, 1466, 2967, 3385; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.0 (t, *J* = 7.5 Hz, 3H), 1.94–1.59 (m, 2H), 2.09 (br s, 1H), 7.35-7.52 (m, 2H), 5.0 (dd, *J* = 4.8, 7.5 Hz, 1H), 7.11 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H) 7.42-7.53 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 10.1, 30.5, 74.2, 122.1, 127.3, 127.6, 128.7, 132.6, 143.5; **Analysis**: $C_9H_{11}BrO$ requires C, 50.26; H, 5.15 Found: C, 50.36; H, 5.09%.

1-(2-Bromophenyl)butan-1-ol (27k)

Yield: 79%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 723, 876, 1054, 1485, 2956, 3012, 3340; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.9 (t, *J* = 7.6 Hz, 3H), 1.34-1.56 (m, 2H), 1.94–2.0 (m, 2H), 2.07 (br s, 1H), 7.35-7.52 (m, 2H), 5.0 (dd, *J* = 4.8, 7.5 Hz, 1H), 7.12 (dt, *J* = 1.5, 7.3 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.42-7.53 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 10.1, 30.5, 74.2, 122.1, 127.3, 127.6, 128.7, 132.6, 143.5; **Analysis**: $C_{10}H_{13}BrO$ requires C, 52.42; H, 5.72 Found: C, 50.36; H, 5.12 %.

1-(2-Bromophenyl)pentan-1-ol (27l)

Yield: 79%, light yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 834, 1037, 1123, 1468, 2918, 3018, 3323; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.38 (m, 3H), 1.51 (m, 1H), 1.69 (m, 1H), 1.80 (m, 1H), 2.08 (br s, 1H), 5.07 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.12 (td, *J* = 8.0, 1.5 Hz, 1H), 7.34 (td, *J* = 7.5, 1.0 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 22.7, 28.2, 37.6, 73.1, 122.2, 127.5, 128.9, 132.8, 144.1; **Analysis**: $C_{11}H_{15}BrO$ requires C, 54.34; H, 6.22 Found: C, 54.26; H, 6.16%.

1-(2-Bromophenyl)octan-1-ol (27m)

Yield: 84%**,** yellow oil**; IR** ($CHCl_3$, cm^{-1}): υ_{max} 686, 785, 876, 1056, 1278, 1443, 2927, 3025, 3345; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.84-0.90 (m, 3H), 1.24-1.34 (m, 10H), 1.62-1.78 (m, 2H), 1.87-1.92 (m, 1H), 5.01-5.08 (m, 1H), 7.10-7.14 (m, 1H), 7.28-7.35 (m, 1H), 7.47-7.56 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 25.7, 29.2, 29.4, 31.8, 37.7, 72.6, 121.8, 127.3, 127.4, 128.3, 132.3, 144.1; **Analysis**: $C_{14}H_{21}BrO$ requires C, 58.95; H, 7.42 Found: C, 58.88; H, 7.36%.

General experimental procedure for the preparation of 3-substituted phthalides (28a-m)

Bromo alcohols **27a-m** (1 mmol) were taken in dry DMF (10 mL) and CuCN (3 mmol) was added to it and the entire solution refluxed under N_2 for 12 h (monitored by TLC). The reaction mixture was then cooled to 25 ^oC, 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 and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude products, which were purified by column chromatography [silica gel (230-400 mesh) and

petroleum ether: EtOAc (7:3) as an eluent] to give 3-substituted phthalide derivatives **28a-m** in 82-88% yield.

3-Allylisobenzofuran-1-one (28a)

Yield: 88%**,** yellow oil**; IR** ($CHCl_3$, cm^{-1}): υ_{max} 739, 999, 1060, 1282, 1460, 1597, 1616, 1764, 2982, 3058; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.60-2.81 (m, 2H), 5.13-5.24 (m, 2H), 5.50 (t, *J* = 7.1 Hz, 1H), 5.65-5.86 (m, 1H), 7.43-7.55 (m, 2H), 7.61-7.69 (m, 1H), 7.87-7.91 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.8, 80.3, 119.8, 122.1, 125.8, 126.4, 129.3, 131.3, 134.1, 149.5, 170.4; ESI-MS: *m*/*z* 197.0491 $[M+Na]^+$; **Analysis**: $C_{11}H_{10}O_2$ requires C, 75.84; H, 5.79 Found: C, 75.72; H, 5.68.

3-Allyl-5-methoxyisobenzofuran-1-one (28b)

Yield: 86%**,** yellow oil**; IR** ($CHCl_3$, cm^{-1}): υ_{max} 785, 835, 886, 1064, 1282, 1340, 1562, 1645, 1759, 2968, 3032; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.55-2.80 (m, 2H), 3.90 (s, 3H), 5.12-5.16 (m, 1H), 5.17-5.25 (m, 1H), 5.41 (t, *J* = 5.92 Hz, 1H), 5.67-5.88 (m, 1H), 6.86-6.88 (m, 1H), 6.99-7.04 (m, 1H), 7.77-7.81 (d, *J* = 8.43 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.8, 55.7, 79.4, 106.1, 116.3, 118.7, 127.2, 131.3, 152.0, 164.5, 169.8; ESI-MS: *m*/*z* 227.0614 $[M+Na]^+$; **Analysis**: $C_{12}H_{12}O_3$ requires C, 70.57; H, 5.92. Found: C, 70.50; H, 5.84%.

3-Allyl-5,7-dimethoxyisobenzofuran-1-one (28c)

Yield: 86%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 684, 740, 835, 890, 1027, 1255, 1266, 1335, 1474, 1508, 1752, 2922, 3015; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.53-2.75 (m, 2H), 3.89 (s, 3H), 3.95 (s, 3H), 5.12-5.17 (m, 1H), 5.16-5.22 (m, 1H), 5.31 (t, *J* = 5.8 Hz, 1H), 5.61-5.85 (m, 1H), 6.39-6.44 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.4, 55.7, 78.6, 98.5,

106.5, 119.0, 131.2, 154.1, 159.3, 166.5, 167.9; **Analysis**: $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.02. Found: C, 66.58; H, 5.96%.

3-Allyl-4,5,6-trimethoxyisobenzofuran-1-one (28d)

Yield: 85%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 686, 788, 852, 1028, 1278, 1345, 1566, 1634, 1758, 2928, 3025; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.54-2.69 (m, 2H), 3.86 (s, 3H), 3.93 (s, 3H), 4.13 (s, 3H), 5.13-5.24 (m, 2H), 5.30 (t, *J* = 6.2 Hz, 1H), 5.68-5.89 (m, 1H), 6.60 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.9, 56.3, 61.2, 62.2, 78.7, 99.3, 110.7, 119.4, 131.4, 141.8, 147.1, 152.3, 159.4, 167.5; **Analysis**: $C_{14}H_{16}O_5$ requires C, 63.63; H, 6.10Found: C, 63.52.76; H, 6.01%.

1-Allyl-1,3-dihydro-5-methoxy-3-oxoisobenzofuran-6-yl4-methylbenzenesulfonate (28e)

Yield: 78%**,** gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 764, 835, 873, 925, 1038, 1136, 1265, 1340, 1565, 1628, 1758, 2948, 3016; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.47 (s, 3H), 2.61-2.72 (m, 2H), 3.78 (s, 3H), 5.15 (s, 1H), 5.21-5.25 (m, 1H), 5.41 (t, *J* = 4.2 Hz, 1H), 5.68-5.87 (m, 1H), 6.88 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.47 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.6, 38.4, 56.2, 79.4, 105.2, 118.1, 119.7, 120.3, 128.3, 129.6, 131.0, 132.8, 139.6, 145.5, 149.8, 157.2, 168.8; **Analysis**: $C_{19}H_{18}O_6S$ requires C, 60.95; H, 4.85; S, 8.56 Found: C, 60.83; H, 4.76; S, 8.42%.

3-Allyl-6-methoxy-5-phenoxyisobenzofuran-1-one (28f)

Yield: 82%**,** yellow oil**; IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 785, 824, 855, 982, 1023, 1109, 1268, 1348, 1538, 1628, 1756, 2928, 3045; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.54-2.69 (m, 2H), 3.86 (s, 3H), 3.93 (s, 3H), 4.13 (s, 3H), 5.13-5.24 (m, 2H), 5.30 (t, *J* = 6.2 Hz, 1H), 5.68-5.89 (m, 1H), 6.60 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.9, 56.3, 61.2, 62.2,

78.7, 99.3, 110.7, 119.4, 131.4, 141.8, 147.1, 152.3, 159.4, 167.5; **Analysis**: $C_{18}H_{16}O_4$ requires C, 72.96; H, 5.44 Found: C, 72.83; H, 5.36%.

3-Allyl-5-fluoroisobenzofuran-1(3H)-one (28g)

Yield: 88%**,** yellow oil**; IR** ($CHCl_3$, cm^{-1}): υ_{max} 665, 774, 836, 992, 1034, 1128, 1269, 1568, 1628, 1762, 2980, 3014; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.62-2.78 (m, 2H), 5.15(brs, 1H), 5.21-5.25 (m, 1H), 5.48 (t, *J* = 5.9 Hz, 1H), 5.65-5.86 (m, 1H), 7.12-7.28 (m, 2H), 7.89 (dd, *J* = 4.1, 4.3 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ38.2, 79.2, 109.3 (d, *J* = 25 Hz), 117.2 (d, *J* = 25 Hz), 119.8, 122.2, 127.7 (d, *J* = 11 Hz), 130.6, 151.9, 165.2 (d, *J* = 251 Hz) ; **Analysis**: $C_{11}H_9FO_2$ requires C, 68.74; H, 4.72 Found: C, 68.63; H, 4.66%.

7-Allylisobenzofuro[5,6-d][1,3]dioxol-5(7H)-one (28h)

Yield: 84%, gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 742, 785, 839, 1056, 1278, 1578, 1629, 1762, 2935, 3035; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.59-2.68 (m, 2H), 5.11-5.15 (m, 1H), 5.17-5.22(m, 1H), 5.35 (t, *J* = 6.2 Hz, 1H), 6.11(s, 2H), 6.79 (s, 1H), 7.18 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.7, 79.3, 102.5, 104.3, 120.0, 131.1, 145.8, 149.2, 153.4, 169.5; **Analysis**: $C_{12}H_{10}O_4$ requires C, 66.05; H, 4.62 Found: C, 65.92; H, 4.51%.

3-Methyl-3H-isobenzofuran-1-one (28i)

Yield: 88%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 739, 755, 967, 1060, 1282, 1460, 1597, 1597, 1615, 1759, 2932, 2982; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.65 (d, *J* = 6.6 Hz, 3H), 5.58 (q, *J* = 6.6 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.66-7.73 (m, 1H), 7.89 (d, *J* = 7.8 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.3, 77.7, 121.5, 125.6, 125.7, 129.0, 134.0, 151.1, 170.4; ESI-MS: *m/z* 171.039 $[M+Na]^+$; **Analysis**: $C_9H_8O_2$ requires C, 72.96; H, 5.44 Found: C, 72.83; H, 5.36%.

3-Ethyl-3H-isobenzofuran-1-one (28j)

Yield: 88%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 737, 754, 965, 1062, 1285, 1460, 1761, 2880, 2940, 2970; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.6 Hz, 3H), 1.78-1.88 (m, 1H), 2.09-2.18 (m, 1H), 5.47 (dd, *J* = 5.1, 6.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 8.7, 27.5, 82.2, 121.7, 125.4, 126.1, 128.9, 133.9, 149.6, 170.6; **Analysis**: $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21 Found: C, 73.98; H, 6.16%.

3-Propyl-3*H*-isobenzofuran-1-one (28k):

Yield: 86%, yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 678, 764, 828, 988, 1078, 1125, 1275, 1562, 1628, 1765, 2935, 3060; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.9 (t, *J* = 7.6 Hz, 3H), 1.56-1.35 (m, 2H), 1.77-1.68 (m, 1H), 2.01-1.95 (m, 1H), 5.46 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.41 (d, *J*= 7.2 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 18.4, 34.0, 81.4, 121.9, 125.9, 126.3, 129.2, 133.1, 150.3, 170.8; **Analysis**: $C_{11}H_{12}O_2$ requires C, 74.98; H, 6.86 Found: C, 74.89; H, 6.75%.

3-Butylisobenzofuran-1(3H)-one (28l)

Yield: 92%, yellow 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 0.87-0.94 (m, 3H), 1.26-1.50 (m, 4H), 1.66-1.84 (m, 1H), 1.96-2.12 (m, 1H), 5.42-5.48 (dd, *J* = 4, 8 Hz, 1H), 7.39-7.50 (m, 2H), 7.61-7.69 (m, 1H), 7.88 (d, *J* = 7.4 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.5, 22.1, 26.5, 34.1, 80.9, 121.1, 125.8, 128.6, 133.6, 149.7, 170.0; ESI-MS: *m*/*z* 213.0813 $[M+Na]^+$; **Analysis**: $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42. Found: C, 75.70; H, 7.34%.

3-Heptylisobenzofuran-1(3H)-one (28m)

Yield: 86%**,** yellow 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 0.83-0.90 (m, 3H), 1.26-1.38 (m, 10H), 1.73-1.81 (m, 1H), 1.94-2.09 (m, 1H), 5.42-5.48 (m, 1H), 7.39-7.54 (m, 2H), 7.61-7.69 (m, 1H), 7.88 (d, *J* = 7.4 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 22.4, 24.7, 28.9, 31.5, 34.6, 81.1, 121.6, 125.4, 126.0, 128.8, 133.7, 149.9, 170.2; **Analysis**: $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68. Found: C, 77.48; H, 8.59%.

Section III:

Enantioselective Synthesis of Colletotrialide

4.3.1 Introduction

Endophytic fungi are a rich source of bioactive compounds.[19] A particular endophytic fungi can produce pharmaceutically important substances; for example, paclitaxel (Taxol),[20] podophyllotoxin,[21] camptothecin,[22] and hypericin.[23] Recently Kittakoop *et al* have isolated and identified a new phthalide namely colletotrialide (**29**) from the endophytic fungus *Colletotrichum* sp. CRI535-02, which exihibited cytotoxic, radical scavenging, and antioxidant activities.[24]

Fig. 9: Structure of colletotrialide (**29**)

4.3.2 Review of Literature

Literature search revealed that there is no report available for the synthesis of colletotrialide (**29**).

4.3.3 Present Work

4.3.3.1 Objective

In section II of this Chapter, we have described an elegant method for the synthesis of 3-substituted phthalide derivatives **28a-m**. In continuation of the work on CuCN-promoted

one-pot cyclization of *o*-bromobenzyl alcohol derivatives **27a-m**, we describe a short and first synthesis of colletotrialide (**29**) in this section.

Retrosynthetic analysis for colletotrialide (**29**) is outlined in **Fig. 10.** Evidently, *o*-bromoketone **30**, the key intermediate, can be visualized to obtain from the corresponding bromoaldehyde **31.** The alcohol **32** can be prepared from homoallylic alcohol **33** *via* hydroboration and oxidation. The key chiral inducing step in the synthesis involves the asymmetric Brown allylation of commercially available 3,4,5-trimethoxybenzaldehyde (**34**).

Fig. 10: Retrosynthetic analysis of colletotrialide (**29**)

4.3.4 Results and Discussion

The complete synthetic sequence for colletotrialide methyl ether (**29**), wherein CuCN-mediated "one-pot" synthesis of 3-substituted phthalide and asymmetric Brown allylation reaction constitute key steps, is presented in **Scheme 11**.

Scheme 11: (i) (+)-Ipc_2B(allyl)borane, Et_2O, -78 ºC, 1 h then 1N NaOH, 30% H_2O_2, 89%, 95% ee; (ii) TBDPSCl, Et_3N, DMF, 25 °C, 8 h, 96%; (iii) BH_3.DMS, THF, 25 °C, 2 h then 1N NaOH, 30% H_2O_2, 84%; (iv) NBS, CH_2Cl_2, 25 °C, 2 h, 94%; (v) IBX, DMSO, 25 °C, 2 h, 93%; (vi) (a) C_3H_7MgI, Et_2O, 25 °C, 3 h; (b) $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C, 1 h, 92%; (vii) TBAF, THF, 25 °C, 10 h, 88%; (viii) CuCN (3.5 equiv.), DMF, reflux, 12 h, 86%; (ix) $AlCl_3$, C_2H_5SH, CH_2Cl_2, 74%.

Our synthesis of colletotrialide (**29**) has started with the asymmetric allylation of commercially available 3,4,5-trimethoxybenzaldehyde (**34**) using Brown's protocol. Accordingly, 3,4,5-trimethoxybenzaldehyde (**34**) was subjected to asymmetric allylation[25] with (+)-Ipc_2B(allyl)borane, followed by oxidation to produce homoallylic alcohol **33** in 89% yield {$[\alpha]^D_{25}$ +35.11 (*c* 1.0, $CHCl_3$); lit.[26] $[\alpha]^D_{25}$ +32.2 (*c* 2.9, $CHCl_3$) for 87%ee}. The enantiomeric purity of **33** was determined as 95% by comparing its optical rotation with the reported value.[26] Three multiplets shown at δ 5.14, 5.20 and 5.84 integrating for one proton each and a multiplet at δ 4.85 integrating for one proton in its ^{1}H-NMR spectrum were attributed to the olefinic and benzylic methine protons respectively. It was further substantiated by the appearance of the corresponding carbon

signals at δ 117.9, 134.3 and 71.8 in its ^{13}C-NMR spectrum (**Fig. 11**). Its IR spectrum displayed a characteristic strong band at 3468 cm^{-1} indicating the presence of –OH group.

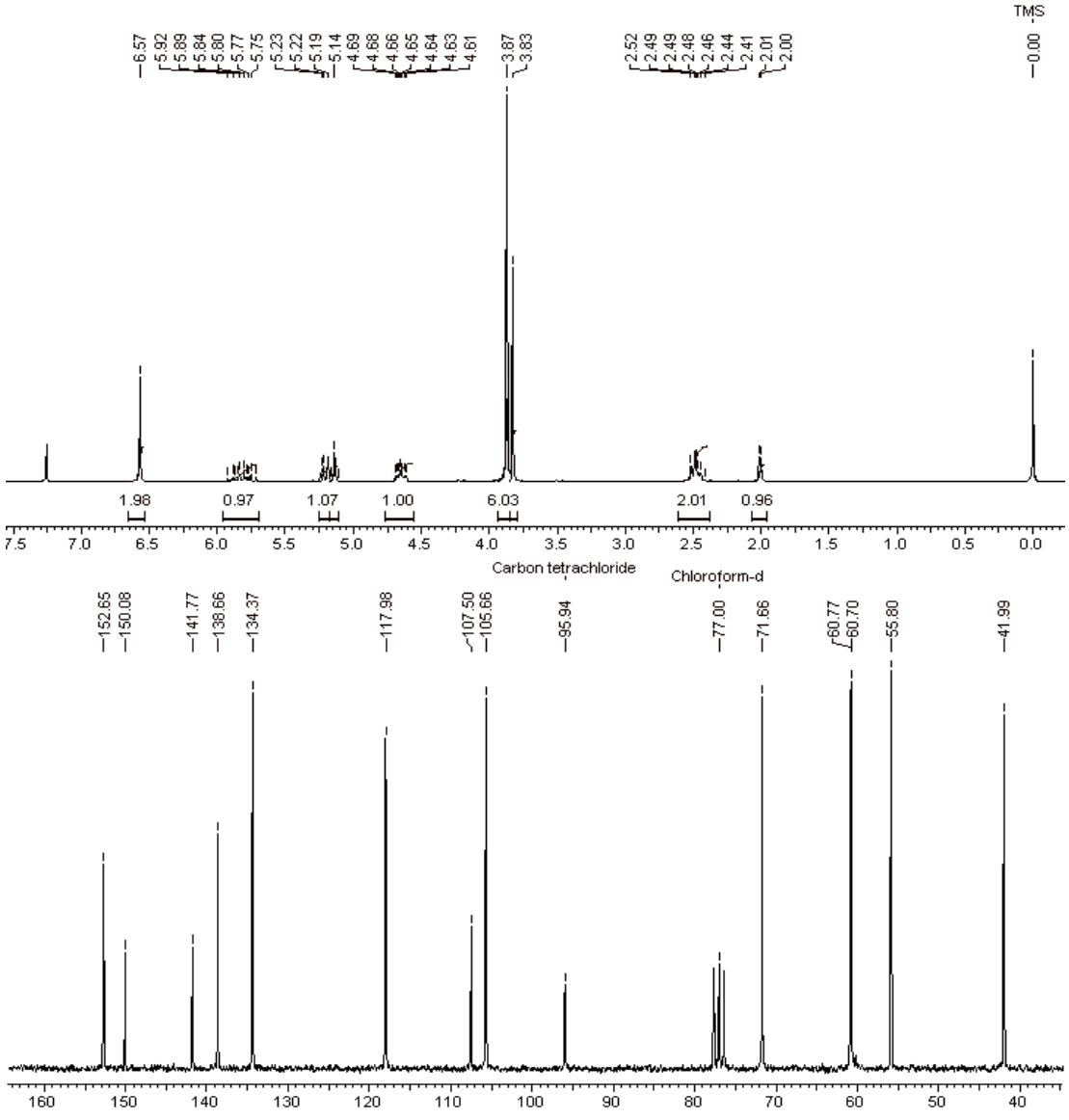


Fig. 11: ^{1}H and ^{13}C NMR spectra of homo allylalcohol **33**

The homoallylic alcohol **33** was protected as its TBDPS ether **35** (TBDPSCl and Et_3N in DMF). The regioselective hydroboration and oxidation of olefin **35** was achieved with BH_3.DMS in THF to afford primary alcohol **32** in 84% yield. The ^{1}H and ^{13}C-NMR spectra of **32** confirmed the disappearance of olefinic function while a multiplet, and a

triplet integrating for two protons each has appeared at δ 1.45 (-C**H₂**-CH_2-OH), and 3.50 (J = 6.4 Hz) (-CH_2-C**H₂**-OH) in its ^{1}H-NMR spectrum corresponding to the methylene protons. This was further ascertained by the typical carbon signals at δ 28.0 and 62.6 corresponding to the methylene (-C**H₂**-CH_2-OH) and methylene (-CH_2-C**H₂**-OH) carbons in its ^{13}C-NMR spectrum (**Fig. 12**). Its IR spectrum displayed a characteristic strong absorption band at 3375 cm^{-1} indicating the presence of –OH group.

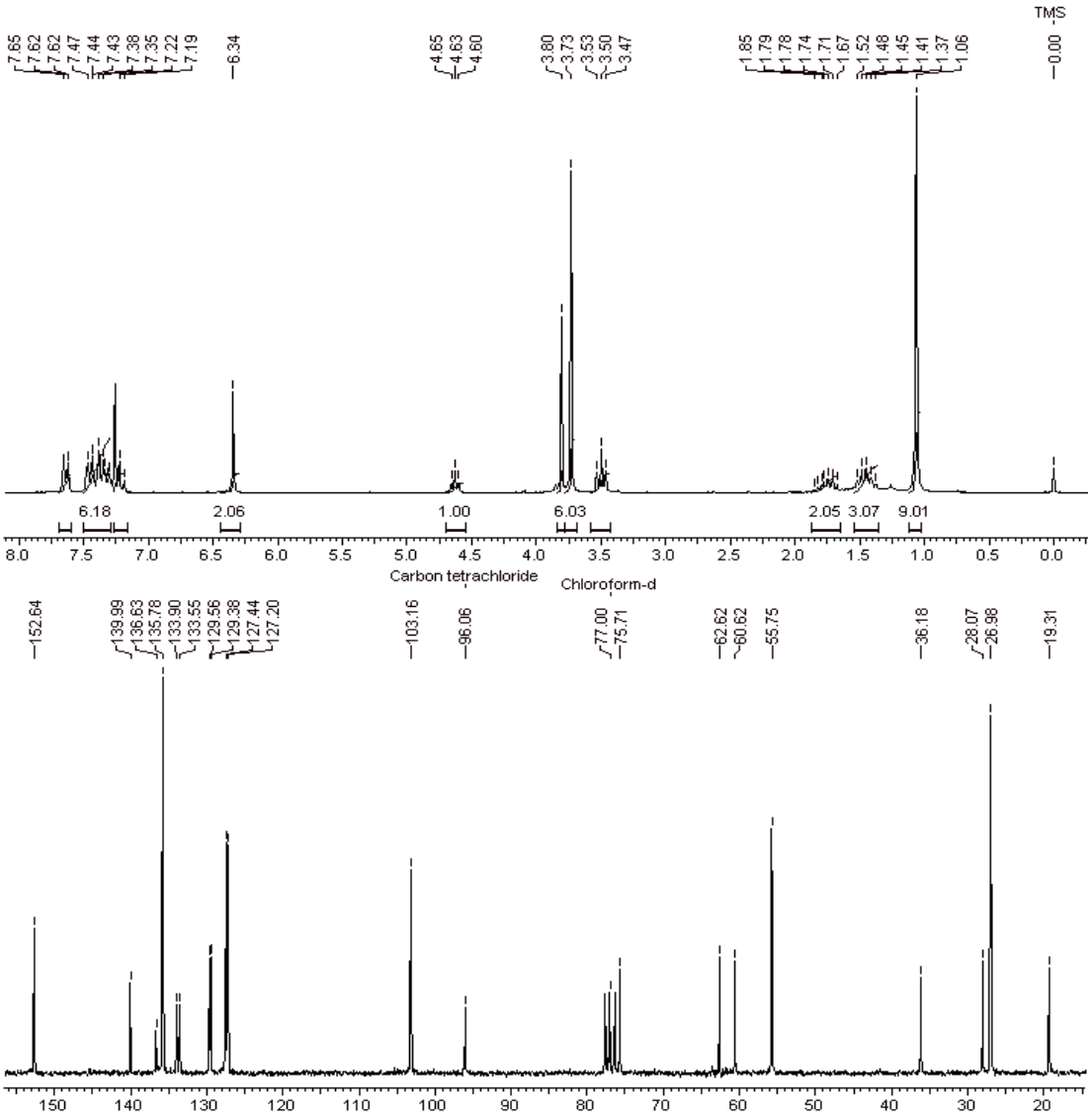


Fig. 12: ^{1}H and ^{13}C NMR spectra of alcohol **32**

Aromatic electrophilic bromination of alcohol **32** was achieved with NBS in CH_2Cl_2 to give the brominated alcohol **36** in 94% yield. The primary alcohol function in **36** was then oxidized under IBX in DMSO to provide the corresponding precursor aldehyde **31**. Further, aldehyde **31** was subjected to Grignard addition with *n*-C_3H_7I and Mg in Et_2O which gave the corresponding secondary alcohol, which was subsequently oxidized under Swern oxidation condition $(COCl)_2$, Et_3N, CH_2Cl_2) to give ketone **37** in 92% yield {$[\alpha]^D_{25}$ +18.5 (*c* 1.0, $CHCl_3$)}.

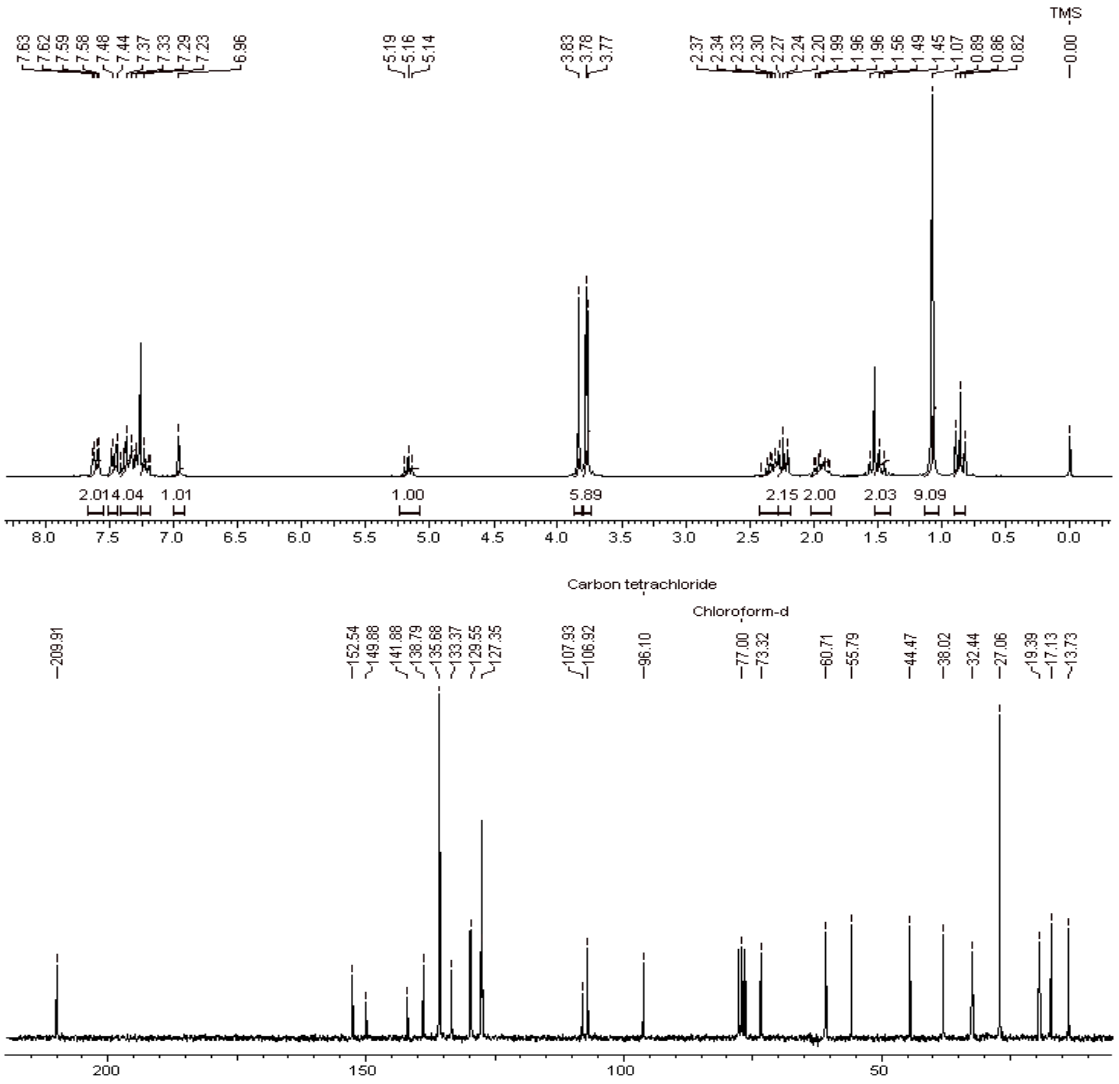


Fig. 13: ^1H and ^{13}C NMR spectra of ketone (**58**)

The ^{1}H and ^{13}C-NMR spectra have confirmed the disappearance of hydroxyl functionality and the other special features displayed are follows: δ 0.86 (t, *J* = 7.5 Hz, 3H), 1.45-1.56 (m, 2H), 1.88-2.0 (m, 2H), 2.20-2.27 (m, 2H), 2.30-2.41 (m, 2H). The carbonyl peak of **37** has appeared at δ 209.9 in its ^{13}C-NMR spectrum (**Fig. 13**). Its IR spectrum exhibited a characteristic ketone carbonyl absorption at 1718 cm^{-1}.

The TBDPS group in **37** was deprotected (TBAF in THF) to give alcohol **30** in 88% yield. Finally, alcohol **30** underwent "one-pot" tandem cyclization with CuCN (3 equiv) in DMF to afford colletotrialide methyl ether (**38**) in 86% yield with {$[\alpha]^{D}_{25}$ +14.68 (*c* 1.0, $CHCl_3$)}; The ^{1}H-NMR spectrum of **38** displayed signals typical of its structural pattern such as δ 0.91 (t, *J* = 7.5 Hz, 3H), 1.54-1.65 (m, 2H), 1.73-1.89 (m, 1H), 2.35-2.46 (m, 3H), 2.51-2.59-2.82 (m, 1H) and 5.26-5.32 (dd, *J* = 2.8, 9.0 Hz, 1H), whereas its ^{13}C-NMR spectrum showed typical peaks at δ 78.6 and 209.4 for the carbons attached to oxygen atom and ketone carbonyl respectively (**Fig. 14**). Its IR spectrum exhibited characteristic ketone and lactone carbonyl absorptions at 1713 and 1756 cm^{-1} respectively.

Finally, the selective deprotection of mono methyl ether of **38** ($AlCl_3$, C_2H_5SH) provided colletotrialide **29** in 74% yield. Its ^{1}H, ^{13}C NMR spectral values and optical rotation were in complete agreement with the reported values.[24]

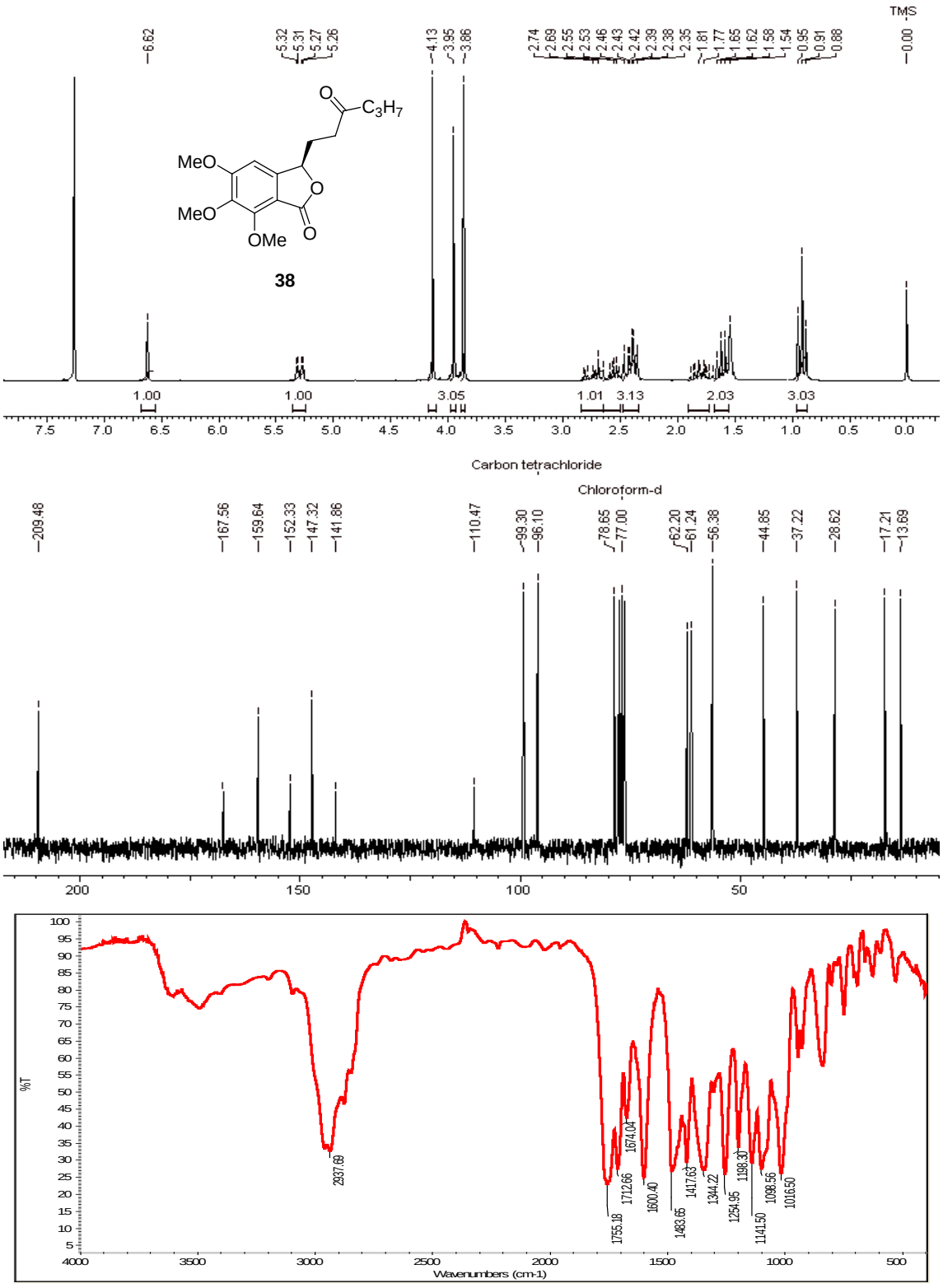


Fig. 14: ^{1}H, ^{13}C NMR and IR spectra of colletotrialide methyl ether (**38**)

4.3.5 Conclusion

A short and first synthetic route to colletotrialide (**29**) with an overall yield of 33% has been described, which includes a successful application of our methodology of CuCN-mediated "one-pot" synthesis of 3-substituted phthalides. The protocol also demonstrates the asymmetric brown allylation as the key feature in the synthesis of colletotrialide **29**.

4.3.6 Experimental Section

(*R*)-1-(3,4,5-Trimethoxyphenyl)but-3-en-1-ol (33)

To a stirred solution of (+)-B-allyl diisopinocamphenyl borane (6 g, 18.3 mmol) in ether (35 mL) at -78 °C was slowly added a solution of benzaldehyde **34** (3 g, 15 mmol) in ether (30 mL). After 1 h of stirring at -78 °C, the reaction mixture was quenched with methanol (2 mL). The resulting mixture was then allowed to warm to room temperature and diluted with 30% NaOH, H_2O_2 and EtOAc (25 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and 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 petroleum ether:EtOAc (9:1) as an eluent] to afforded homoallyl alcohol **33** (3.2 g) as gum.

Yield: 89%; $[\alpha]^{D}_{25}$ +35.11 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 852, 892, 974, 1083, 1129, 1267, 1358, 1457, 1542, 2934, 3032, 3424; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.01 (d, *J* = 2.8 Hz, 1H) 2.41-2.52 (m, 2H), 3.83 (s, 3H), 3.87 (s, 6H), 4.61 -4.69 (m, 1H), 5.12-5.15 (m, 1H), 5.19-5.23 (m, 1H), 5.72-5.92 (m, 1H), 6.57 (s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 41.9, 55.8, 60.7, 71.6, 105.6, 107.5, 117.9, 134.3, 138.6, 141.7, 150.0, 152.6; **Analysis: $C_{13}H_{18}O_4$** requires C, 65.53; H, 7.61 found: C, 65.42; H, 7.49%.

((*R*)-1-(3,4,5-Trimethoxyphenyl)but-3-enyloxy)(*tert*-butyl)diphenylsilane (35)

To a stirred solution of alcohol **33** (3.0 g, 12.6 mmol) in DMF was added Et_3N (1.4 g, 13.9 mmol) followed by *t*-butyldiphenyl silyl chloride (3.8 g, 13.9 mmol) and the mixture stirred for 8 h at 25 ^oC. After completion of the reaction it was diluted with water and EtOAc (20 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and 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 petroleum ether:EtOAc (9:1) as an eluent] that afforded silyl ether **35** (5.7 g) as colourless liquid.

Yield: 96%; $[\alpha]^D_{25}$ +24.06 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 826, 888, 986, 1168, 1274, 1384, 1436, 1545, 2927, 3034; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 2.38-2.53 (m, 2H), 3.72 (s, 6H), 3.80 (s, 3H), 4.60 (t, *J* = 6.0 Hz, 1H), 4.87-4.96 (m, 2H), 5.52-5.73 (m, 1H), 6.33 (s, 2H), 7.18-5.22 (m, 2H), 7.30-7.47 (m, 6H), 7.62-7.65 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.3, 26.8, 41.8, 55.8, 60.7, 60.8, 75.5, 103.8, 107.5, 117.8, 127.1, 127.3, 128.9, 129.4, 133.9, 134.2, 135.6, 136.8, 139.5, 141.5, 150.2, 152.5; **Analysis: $C_{29}H_{36}O_4Si$** requires C, 73.07; H, 7.61 found: C, 72.93; H, 7.52%.

(*R*)-4-(*tert*-Butyldiphenylsilyloxy)-4-(3,4,5-trimethoxyphenyl)butan-1-ol (32)

To a stirred solution of homoallyl alcohol **35** (4.5 g, 9.4 mmol) in THF at 0 °C was added $BH_3.SMe_2$ (5.8 mL, 4.5 mmol) and the reaction mixture was stirred at 25 °C for 2 h. After dilution with THF/MeOH (14 mL, 1:1) and addition of 3 M solution of NaOH (4 mL) and an aq. solution 30% H_2O_2 (4 mL), the reaction was stirred for 1 h and quenched with a saturated solution of Na_2SO_3 (20 mL). The reaction mixture was then cooled to 0 °C, diluted with sat. $NaHCO_3$ (35mL) and Et_2O (35 mL). The organic layer was

separated and the aqueous layer extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine and 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 petroleum ether:EtOAc (7:3) as an eluent] that afforded alcohol **32** (3.94 g) as gum.

Yield: 84%; $[\alpha]^{D}_{25}$ +58.5 (*c* 0.48, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 689, 765, 834, 1075, 1178, 1254, 1365,1480, 1529, 3015, 3416; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.37-1.52 (m, 2H), 1.67-1.85 (m, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 3.73 (s, 6H), 3.80 (s, 3H), 4.63 (t, *J* = 5.8 Hz, 2H), 6.34 (s, 2H), 7.19-7.22 (m, 2H), 7.30-7.47 (m, 6H), 7.62-7.66 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.3, 26.9, 28.0, 36.1, 55.7, 60.5, 62.6, 75.7, 103.1, 127.2, 127.4, 129.3, 129.5, 133.5, 133.9, 135.7, 136.6, 139.9, 152.6; **Analysis:** $C_{29}H_{38}O_5Si$ requires C, 70.41; H, 7.74 found: C, 70.53; H, 7.63%.

(*R*)-4-(2-Bromo-3,4,5-trimethoxyphenyl)-4-(*tert*-butyldiphenylsilyloxy)butan-1-ol (36)

To a solution of alcohol **32** (3.5 g, 7.1 mmol) in CH_2Cl_2 (30 mL) was added NBS (1.4 g, 7.8 mmol) and the mixture was stirred at 25 °C for 2 h. After the reaction was complete (monitored by TLC), it was quenched with sat. $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 25 mL), washed with water and combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude bromo compound, which was then purified by column chromatography over silica gel (230-400 mesh) using petroleum ether:EtOAc (7:3) to give the brominated alcohol **36** (3.8 g) as a colorless oil.

Yield: 94%; $[\alpha]^{D}_{25}$ +23.82 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 769, 1038, 1156, 1216, 1384,1468, 1580, 3020, 3412; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.52-

1.62 (m, 3H), 1.67-1.79 (m, 2H), 3.51 (t, *J* = 6.5 Hz, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 3.8 (s, 3H), 5.18 (t, *J* = 5.1 Hz, 1H), 6.98 (s, 1H), 7.19-7.23 (m, 2H), 7.28-7.41 (m, 4H), 7.46-7.51 (m, 2H), 7.59-7.64 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.3, 27.0, 28.8, 34.7, 55.7, 60.6, 60.8, 62.6, 73.7, 106.9, 107.6, 127.3, 127.4, 129.4, 129.6, 133.3, 135.7, 139.1, 141.6, 149.7, 152.4; **Analysis:** $C_{29}H_{37}BrO_5Si$ requires C, 60.72; H, 6.50 found: C, 60.59; H, 6.43%.

(*R*)-4-(2-Bromo-3,4,5-trimethoxyphenyl)-4-(tert-butyldiphenylsilyloxy)butanal (31)

To a solution of alcohol **36** (3.5 g, 6.1 mmol) in DMSO (30 mL) was slowly added IBX (2.05 g, 39.6 mmol). The reaction mixture was stirred for 2 h at 25 °C followed by quenching with cold water. The reaction mixture was filtered and the filtrate then extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude aldehyde which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give aldehyde **31** (3.2 g) as colorless oil.

Yield: 93%; $[\alpha]^{D}_{25}$ +22.4 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 768, 859, 1089, 1124, 1256, 1367, 1484, 1512, 1715, 2812, 2954, 3012; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.97-2.08 (m, 2H), 2.34-2.42 (m, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 5.22 (t, *J* = 5.2 Hz, 1H), 6.94 (s, 1H), 7.19-7.23 (m, 2H), 7.28-7.41 (m, 4H), 7.44-7.49 (m, 2H), 7.57-7.61 (m, 2H), 9.65 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.3, 27.0, 30.5, 39.1, 55.8, 60.7, 60.9, 73.1, 107.1, 107.7, 127.4, 127.6, 129.6, 129.8, 133.1, 135.7, 138.1, 141.9, 150.0, 152.5; **Analysis:** $C_{29}H_{35}BrO_5Si$ requires C, 60.94; H, 6.17; Br, 13.98 found: C, 60.82; H, 6.09; Br, 13.89%.

(*R*)-1-(2-Bromo-3,4,5-trimethoxyphenyl)-1-(*tert*-butyldiphenylsilyloxy)heptan-4-one (37)

To a stirred suspension of magnesium (0.386 g, 15.9 mmol) in Et_2O (5 mL), *n*-propyliodide (2.7 g, 15.9 mmol) was added at 0 ºC under nitrogen atmosphere over a period of 15 min and continued stirring at room temperature for a further 15 min. The reaction mixture was cooled to 0 ºC and aldehyde **31** (3.0 g, 5.3 mmol) dissolved in Et_2O (20 mL) added over a period of 10 min. After the addition was complete, the reaction mixture was allowed to return to room temperature and the stirring continued for another 2 h. The reaction mixture was quenched by the addition of aq. NH_4Cl and extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were collected and washed with water and brine solution, then dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude mixture of alcohol.

To a stirred solution of oxalyl chloride (0.9 mL, 9.4 mmol) in CH_2Cl_2 (20 mL) at -78 °C, was added a solution of dry DMSO (1.3 mL, 18.8 mmol). The reaction mixture was stirred for 20 min followed by the addition of crude alcohol solution (2.9 g, 4.7 mmol) in CH_2Cl_2 (40 mL). After stirring for 1 h at -78 °C, the reaction was quenched with Et_3N (2.6 mL, 18.8 mmol). It was then stirred for 30 min followed by the addition of water (20 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with water (3 x 20 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding ketone **37** (2.7g) as colorless oil.

Yield: 92%; $[\alpha]^{D}_{25}$ +18.5 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 680, 798, 844, 1046, 1128, 1298, 1323, 1475, 1538, 1718, 2936, 3024; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.86 (t,

J = 7.5 Hz, 3H), 1.07 (s, 9H), 1.45-1.56 (m, 2H), 1.88-2.0 (m, 2H), 2.20-2.27 (m, 2H), 2.30-2.41 (m, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 5.16 (t, *J* = 5.5 Hz, 1H), 6.96 (s, 1H), 7.19-7.23 (m, 2H), 7.29-7.41 (m, 4H), 7.44-7.49 (m, 2H), 7.58-7.63 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 17.1, 19.4, 27.0, 32.4, 38.0, 44.4, 55.7, 60.7, 60.8, 73.3, 106.9, 107.9, 127.3, 127.5, 129.7, 133.3, 135.6, 138.8, 141.8, 149.8, 152.5, 209.9; ESI-MS: *m*/*z* 635.176 $[M+Na]^+$; **Analysis:** $C_{32}H_{41}BrO_5Si$ requires C, 62.63; H, 6.73; Br, 13.02; found: C, 62.54; H, 6.66; Br, 12.93%.

(*R*)-1-(2-Bromo-3,4,5-trimethoxyphenyl)-1-hydroxyheptan-4-one (30)

To a stirred solution of TBS ether **37** (2 g, 3.3 mmol) in THF was added a solution of tetrabutylammonium fluoride (TBAF) (0.9 g, 1M in THF, 3.3 mmol) at 0 °C and the mixture stirred for 10 h. It was quenched by the addition of water and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4. The solvent was distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using pet. ether:EtOAc (7:3) as eluent to give alcohol **30** (1.0 g) as gum.

Yield: 88%; $[\alpha]^D_{25}$ +38.52 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 764, 896, 1023, 1186, 1272, 1368, 1446, 1580, 1715, 2928, 3018, 3435; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.56-1.68 (m, 2H), 1.90-2.07 (m, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.59-2.67 (m, 2H), 3.20 (d, *J* = 3.6 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 4.97-5.04 (m, 1H), 6.95 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 17.2, 31.2, 39.4, 44.6, 55.9, 60.8, 72.3, 105.8, 107.7, 139.1, 142.0, 150.3, 152.9, 212.0; **Analysis:** $C_{16}H_{23}BrO_5$ requires C, 51.21; H, 6.18; Br, 21.29; found: C, 51.13; H, 6.09; Br, 21.18%.

(*R*)-5,6,7-Trimethoxy-3-(3-oxohexyl)isobenzofuran-1-one (38)

Bromo alcohol **30** (0.7 g, 1.8 mmol) was taken in dry DMF (10 mL) and CuCN (3 mmol) was added to it. The entire solution was refluxed under N_2 for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature, and diluted with water (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 and 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 petroleum ether: EtOAc (7:3) as an eluent] to give phthalide **38** (0.6 g) as yellow oil. **Yield:** 86%; $[\alpha]^{D}_{25}$ +14.68 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 780, 853, 1016, 1098, 1198, 1254, 1344, 1483, 1600, 1713, 1756, 2937, 3020; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.91(t, *J* = 7.4 Hz, 3H), 1.54-1.65 (m, 2H), 1.73-1.89 (m, 1H), 2.35-2.46 (m, 3H), 2.51-2.59 (m, 1H), 3.86 (s, 3H), 3.95 (s, 3H), 4.13 (s, 3H), 5.26-5.32 (dd, J = 2.8, 9.1 Hz, 1H), 6.62 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.6, 17.2, 28.6, 37.2, 44.8, 56.4, 61.2, 62.2, 78.6, 99.3, 110.4, 141.8, 147.3, 152.3, 159.6, 167.5, 209.4; ESI-MS: *m/z* 345.1281 $[M+Na]^+$; **Analysis:** $C_{17}H_{22}O_6$ requires C, 63.34; H, 6.88; found: C, 63.24; H, 6.79%.

Colletotrialide (29)

To a mixture of dry ethanethiol (2 mL) and dichloromethane (2 mL) was added aluminum chloride (0.40 g, 1.0 mmol) at 0 °C. The resulting solution was warmed to room temperature and trimethoxyphthalide **38** (0.322 g, 1.0 mmol) was added with stirring. After being stirred for 1.5 h, the reaction mixture was poured into water, acidified with dilute HC1, and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine and 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 petroleum ether: EtOAc (6:4) as an eluent] to give mono deprotected phthalide **29** (0.28 g) as yellow colored oil.

Yield: 74%; $[\alpha]^{D}_{25}$ +16.5 (*c* 1.0, MeOH) {lit.$^{24}[\alpha]^{D}_{28}$ +16.8 (*c* 0.47, MeOH)} **IR** ($CHCl_3$, cm^{-1}): υ_{max} 826, 930, 1007, 1098, 1133, 1258, 1316, 1364, 1465, 1607, 1711, 1730, 2935, 3406; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.53-1.64 (m, 2H), 1.83 (m, 1H), 2.39 (q, *J* = 7.4 Hz, 2H), 2.36-2.42 (m, 1H), 2.51-2.56 (m, 1H), 2.68-2.73 (m, 1H), 3.90 (s, 3H), 3.94 (s, 3H), 5.41 (d, *J* = 6.7 Hz, 1H), 6.49(s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 17.3, 28.5, 37.2, 45.0, 56.6, 60.9, 80.9, 97.0, 105.4, 136.2, 145.5, 148.9, 159.9, 171.0, 209.8; **Analysis:** $C_{16}H_{20}O_6$ requires C, 62.33; H, 6.54; found: C, 62.24; H, 6.62%.

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