ENANTIOSELECTIVE SYNTHESIS OF BIOACTIVE MOLECULES AND ASYMMETRIC OXYFUNCTIONALIZATION OF ALKENES

A THESIS

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IN

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BY

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Dedicated to my beloved parents ...
Sri. K T George
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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Enantioselective synthesis of bioactive molecules and asymmetric oxyfunctionalization of alkenes**" 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.

April 2009 **(Dr. A. Sudalai)**

Pune Research Supervisor

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DECLARATION

I here by declare that the thesis entitled **"Enantioselective synthesis of bioactive molecules and asymmetric oxyfunctionalization of alkenes"** 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.

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ABBREVIATIONS

AD	Asymmetric Dihydroxylation
Ac	Acetyl
Ar	Aryl
bp	Boiling Point
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
n-BuLi	n-Butyl Lithium
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Dichloromethane
$CHCl_3$	Trichloromethane
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DHQ	Dihydoquinine
DHQD	Dihydroquinidine
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
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	Infrared
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NMR	Nuclear Magnetic Resonance

NBS	*N*-Bromosuccinimide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
PhNO	Nitrosobenzene
p-TSA	*p*-Toluene sulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-Butyl hydroperoxide
TBDMSCl	*tert*-Butyldimethylsilyl chloride

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, 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 entitled "**Enantioselective synthesis of bioactive molecules and asymmetric oxyfunctionalization of alkenes**" is divided into four chapters.

The title of the thesis clearly indicates the objective that is to synthesize enantiomerically pure drugs and to interface synthetic organic chemistry for the development of new methodologies. **Chapter 1** deals with a short enantioselective synthesis of (-)-chloramphenicol (**7**) and (+)-thiamphenicol (**15**) using tethered aminohydroxylation. **Chapter 2** describes an organocatalytic route to tarchonanthuslactone (**31**) and atorvastatin side-chain (**42**). The stereogenic center in both of them is introduced *via* proline-catalyzed asymmetric α-aminooxylation of aldehydes. **Chapter 3** describes the enantioselective synthesis of (-)-bestatin (**52**) via L-proline catalyzed α-amination of an aldehyde and asymmetric synthesis of guggultetrol (**63**) using Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation. **Chapter 4** deals with the asymmetric bromohydroxylation of α, β-unsaturated carboxamides with $NaIO_4$ and its application to the enantioselective synthesis of (-)-cytoxazone (**77**) and L-*threo*-DOPS (droxidopa) (**82**).

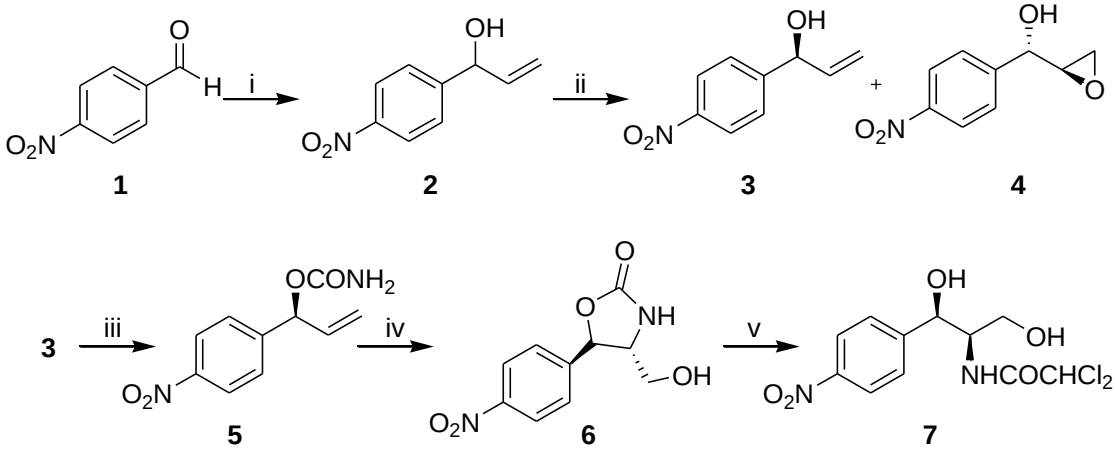
CHAPTER 1

A short enantioselective synthesis of (-)-chloramphenicol and (+)-thiamphenicol using tethered aminohydroxylation

(-)-Chloramphenicol **7** and (+)-thiamphenicol **15** are broad-spectrum antibiotics with a range of biological activities.[1] While chloramphenicol is active only in its D-*threo* configuration and is especially effective in the treatment of typhus, dysentery and ocular bacterial infections,[2] (+)-thiamphenicol **15**, a synthetic analogue of chloramphenicol **1**, is bacteriostatic for both gram-positive and gram-negative aerobes and for some anaerobes.[3] The tethered aminohydroxylation (TA),[4] an intramolecular asymmetric aminohydroxylation of alkenes, has become a reliable method in recent years for achieving excellent levels of *syn* selectivity while providing at the same time complete control over the regio- and chemoselectivity of the oxidation. In this chapter, we describe the application of Sharpless asymmetric epoxidation[5] and the tethered

aminohydroxylation for the stereoselective synthesis of (-)-chloramphenicol **7** and (+)-thiamphenicol **15**.[6]

Our synthesis of (⁻)-chloramphenicol **7** started with the reaction of 4-nitrobenzaldehyde **1** with divinylzinc to give 1-(4-nitrophenyl) allyl alcohol **2** in 68% yield. Allylic alcohol **2** was then subjected to Sharpless asymmetric epoxidation under kinetic resolution conditions using naturally occurring (+)-diisopropyl tartrate to furnish the corresponding chiral allylic alcohol, 1-(***S***)-4-(nitrophenyl)-2-propen-1-ol, **3** in 44% chemical yield and 98% ee (optical purity was determined by ^{1}H NMR analysis of the corresponding Mosher's ester) along with the corresponding epoxide **4** in 49% yield. Both chiral alcohol **3** and epoxide **4** could be easily separated by column chromatographic purification.

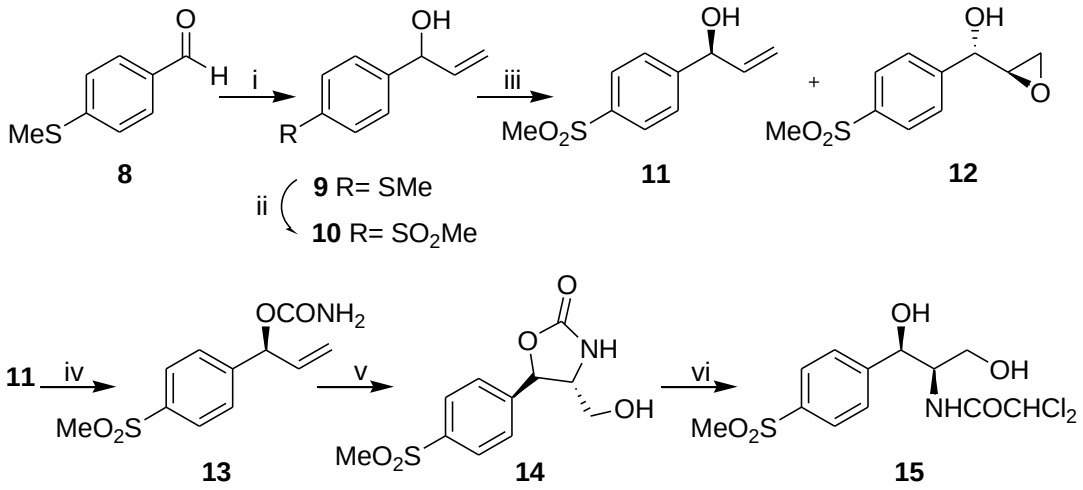


Scheme 1. (i) Divinyl zinc, THF, Et_2O, -78 °C to 25 °C, 10 h, 68%; (ii) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 °C, 14 h, 44%; (iii) (a) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C to 25 °C, 2 h; (b) K_2CO_3, MeOH, H_2O, 0 °C to 25 °C, 18 h, 90%; (iv) $K_2Os(OH)_4O_2$, *t*-BuOCl, NaOH, EtN-*i*-Pr_2,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

Alcohol **3** was then treated with trichloroacetyl isocyanate in CH_2Cl_2 to give the corresponding isocyanate, which on treatment with K_2CO_3 and methanol in presence of H_2O gave the carbamate **5** in 90% yield (**Scheme 1**). The carbamate **5** thus obtained was converted into the oxazolidinone **6** by a tethered aminohydroxylation protocol using *tert*-butyl hypochlorite as the oxidant in the presence of potassium osmate, 0.08M NaOH, diisopropyl ethylamine and propan-1-ol as the solvent. The reaction proceeded smoothly to furnish the protected aminoalcohol **6** as a single isomer with complete regiocontrol and excellent *syn* selectivity (s*yn:anti* >20:1, determined by ^{1}H NMR analysis) giving 69%

yield. The oxazolidinone **6** was then hydrolyzed using 1N NaOH in methanol to furnish the crude amino alcohol, which was then taken in methyl dichloroacetate and heated at 90 ^{o}C for 3 h to give (-)-chloramphenicol **7** in 78% yield.

The same strategy was extended to the synthesis of (+)-thiamphenicol **15** (**Scheme 2**). Commercially available 4-(methylthio)benzaldehyde **8** was converted to the allyl alcohol **9** by treating with vinylmagnesium bromide in THF in 96% yield. The thioether **9** was then oxidized using oxone to give the corresponding sulfonyl ester **10** in 95% yield. Allyl alcohol **10** was then subjected to Sharpless asymmetric epoxidation using (+)-diisopropyl tartrate under kinetic resolution conditions to furnish the chiral alcohol **11** in 43% yield and 98% ee (the optical purity was determined by ^{1}H NMR analysis of the corresponding Mosher's ester) along with the epoxide **12.** Both alcohol **11** and epoxide **12** were readily separated by column chromatography.



Scheme 2. (i) Vinyl magnesium bromide, THF, 0 °C-25 °C, 2 h, 96%; (ii) Oxone, THF/MeOH/H_2O (1:1:1), 0 °C-25 °C, 30 min, 95%; (iii) (+)-DIPT, Ti($O^{i}Pr$)$_4$, TBHP, CH_2Cl_2, -20 °C, 14-24 h, 43%; (iv) (a) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C-25 °C, 2 h; (b) K_2CO_3, MeOH, H_2O, 0 °C-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%.

The carbamate **13** obtained from **11** under the same experimental conditions as explained earlier was converted into the oxazolidinone **14** using tethered aminohydroxylation. The desired isomer of the oxazolidinone **14** was obtained with high stereoselectivity (s*yn:anti* >20:1, determined by ^{1}H NMR analysis) giving 65% yield. Finally, the hydrolysis of **14**

with 1N NaOH in methanol followed the treatment with methyl dichloroacetate gave the final product thiamphenicol **15** in 77% yield.

CHAPTER 2

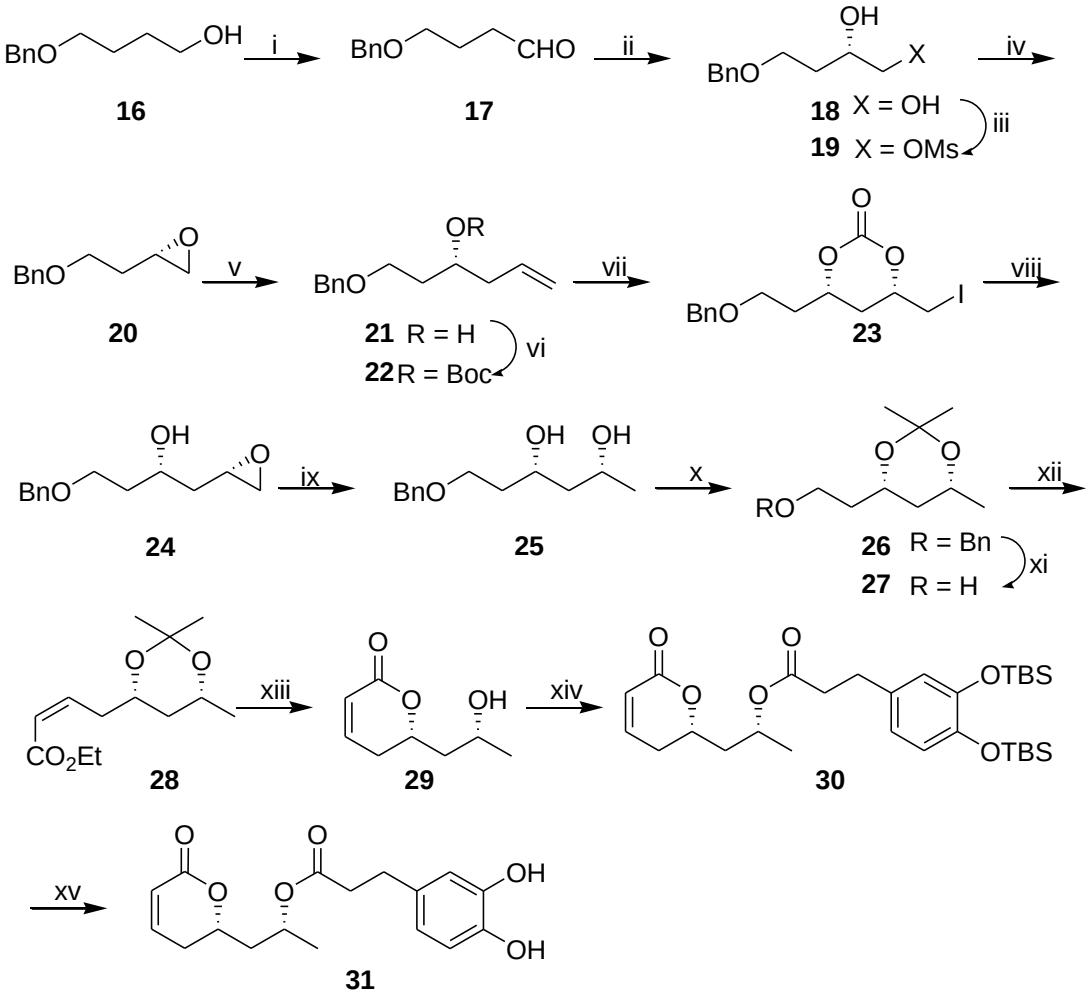
Enantioselective synthesis of tarchonanthuslactone and atorvastatin side-chain using proline-catalyzed asymmetric α-aminooxylation

Asymmetric organocatalysis in organic chemistry has provided several new methods for obtaining chiral compounds in an environmentally benign manner.[7] In this connection, proline, an abundant, inexpensive aminoacid available in both enantiomeric forms has emerged as a practical and versatile organocatalyst.[8] Proline is equally efficient for α-functionalization[9] of aldehydes and ketones. This chapter is divided into two sections. **Section I** deals with the enantioselective synthesis of tarchonanthuslactone **31** and **Section II** describes an organocatalytic route to atorvastatin side-chain **42** using proline-catalyzed α-aminooxylation of aldehydes.

SECTION I: Enantioselective synthesis of tarchonanthuslactone using proline-catalyzed asymmetric α-aminooxylation

Tarchonanthuslactone **31**, was isolated[10] from the leaves of *Tarchonanthus tribolus* in 1979 and it is found to lower the blood plasma level in diabetic rats as an important biological activity.[11] The present section deals an efficient synthesis of tarchonanthuslactone **31**, using proline catalyzed α-aminooxylation of *n*-butyraldehyde as well as iodine-induced electrophilic cyclization as the chiral inducing steps (**Scheme 3**).[12] The synthesis of tarchonanthuslactone **31**, commencing from the monoprotected 1,4-butane diol **16,** is shown in **Scheme 3**. The primary alcohol function in **16** was oxidized under IBX in DMSO to provide the corresponding precursor aldehyde **17.** The proline catalyzed α-asymmetric aminooxylation of aldehyde **17** involves a two-step reaction sequence: (i) reaction of aldehyde **17** with nitrosobenzene as the oxygen source in the presence of D-proline in CH_3CN at -20 °C followed by treatment with $NaBH_4$ in MeOH gave the crude aminooxy alcohol *in situ* and (ii) subsequent reduction of the crude aminoxy product with 30 mol% $CuSO_4$ yielded chiral diol **18** in 86% yield and 97% ee (determined by ^1H NMR analysis of the corresponding Mosher's ester). Selective

mesylation of the primary alcohol in **18** was achieved to afford mesylate **19**, which on treatment with K_2CO_3 in MeOH yielded the terminal epoxide **20**.



Scheme 3: (i) IBX, DMSO, 25 °C, 2 h, 95%; (ii) (a) PhNO, D-proline (25 mol%), CH_3CN, −20 °C, 24 h then MeOH, $NaBH_4$; (b) $CuSO_4$ (30 mol%), MeOH, 0 °C, 10 h, 87% (over two steps); (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 92%; (iv) K_2CO_3, MeOH, 25 °C, 1 h, 95%; (v) vinylmagnesium bromide, THF, CuI, -40 °C, 1 h, 92%; (vi) $(Boc)_2O$, DMAP, CH_3CN, 25 °C, 5 h, 95%; (vii) NIS, CH_3CN, -40 to 0 °C, 12 h, 85%; (viii) K_2CO_3, MeOH, 0 °C to 25 °C, 4 h, 90%; (ix) $LiAlH_4$, THF, 50 °C, 6 h, 90%; (x) 2,2-dimethoxypropane, camphorsulfonic acid, 25 °C, 4 h, 95%; (xi) 10% Pd/C, H_2 (1 atm), MeOH, 12 h, 91%; (xii) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h; (b) ethyl(di-*o*-tolylphosphono)acetate, NaH, THF, -78 to 0 °C, 1.5 h, 80% (over two steps); (xiii) pyridinium-*p*-toluene sulfonate, ethanol, 55 °C, 12 h, 75%; (xiv) TBS-protected dihydrocaffeic acid **,** DCC, DMAP, CH_2Cl_2, 5 h, 81 %; (xv) TBAF, $PhCO_2H$, THF, 25 °C, 88%.

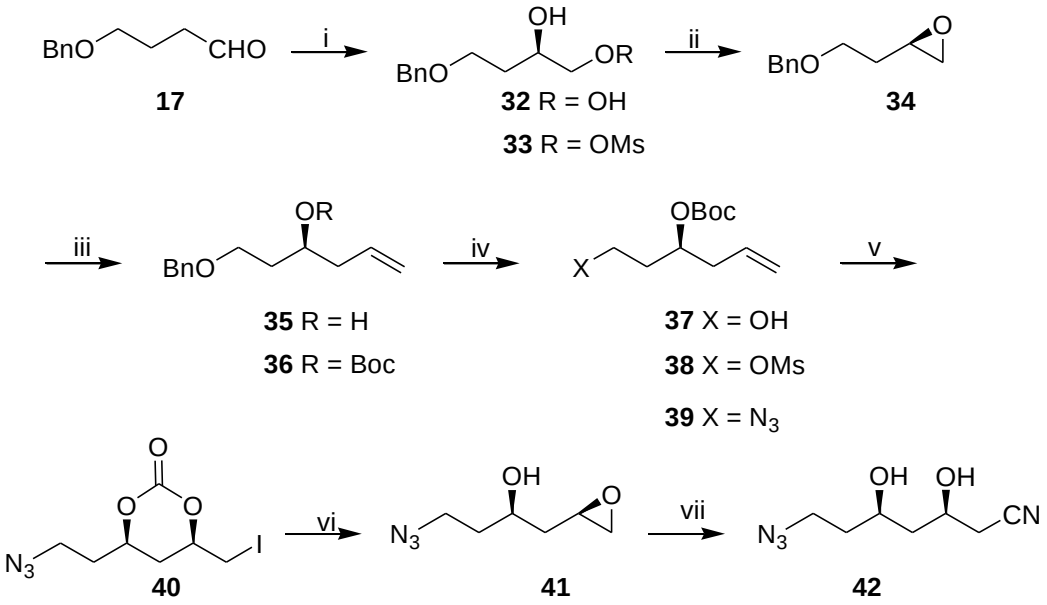
For getting *syn*-1,3-diol with high diastereoselectivity, the iodine-induced carbonate cyclization methodology, was undertaken. Thus, epoxide **20** was first treated with vinylmagnesium bromide in presence of CuI in THF at -40 °C to give the homoallylic

alcohol **21**. The homoallylic *tert*-butyl carbonate **22**, prepared in high yields from the corresponding alcohol **21** on treatment with di-*tert*-butyldicarbonate in the presence of DMAP in CH_3CN, was subjected to the diastereoselective iodolactonization using *N*-iodosuccinimide in CH_3CN at low temperature (-40 to 0 °C) to furnish the cyclic carbonate derivative **23** in 85% yield as a single diastereomer (determined by ^{1}H NMR analysis). The iodocarbonate **23**, upon exposure to basic methanolic solution, gave the desired *syn*-epoxy alcohol **24** in 90% yield. Regioselective reduction of epoxy alcohol **24** using $LiAlH_4$ in THF furnished the *syn*-1,3-diol **25** in 90% yield, which was then protected as its acetonide **26** on treatment with 2,2-dimethoxypropane in the presence of catalytic amounts of camphorsulfonic acid. Deprotection of the benzyl group in **26** under catalytic hydrogenolysis conditions [Pd/C, H_2 (1 atm), MeOH], provided the primary alcohol **27** in 91% yield. Alcohol **27** on Swern oxidation gave the aldehyde *in situ* which was then subjected to Horner-Wittig-Emmons olefination with ethyl (di-*o*-tolylphosphono) acetate and NaH in THF to obtain the *Z*-unsaturated ester **28** (confirmed by ^{1}H NMR analysis) in 80% yield over the two steps. The deprotection of acetonide unit in **28** followed by its cyclization was achieved by treating **28** with pyridinium-*p*-toluene sulfonate (PPTS) in ethanol at 55 °C to give pyranone **29** in 75% yield. Esterification of **29** with TBS-protected dihydrocaffeic acid provided the ester **30** in 85% yield. Finally, desilylation of **30** with tetrabutylammonium fluoride (TBAF) and benzoic acid in THF furnished tarchonanthuslactone **31** in 90% yield.

SECTION II: An efficient organocatalytic route to the atorvastatin side-chain

Statins act by inhibiting HMG-CoA reductase (HMG = 3-hydroxy-3-methylglutaryl), the rate-limiting enzyme in cholesterol biosynthesis.[13] They not only lower the low-density lipoprotein (LDL) cholesterol as well as triglyceride levels but also increase the levels of high-density lipoprotein (HDL). The present section describes an organocatalytic route to atorvastatin side-chain **42** by using proline catalyzed α-aminooxylation of *n*-butyraldehyde and iodine-induced intramolecular electrophilic cyclization (**Scheme 4**).[14] The complete synthetic sequence for statin side-chain **42**, commencing from the precursor aldehyde **17**, is shown in **Scheme 4**. The proline catalyzed α-aminooxylation of aldehyde **17** which involves a two-step reaction sequence as described in the previous section, yielded chiral diol **32** in 86% yield and 97% ee (determined by ^{1}H NMR analysis

of the corresponding Mosher's ester). Selective mesylation of the primary alcohol in **32** with mesyl chloride gave mesylate **33**, which on treatment with K_2CO_3 in MeOH yielded the terminal epoxide **34**. Regioselective ring opening of the epoxide **34** with vinylmagnesium bromide in presence of CuI in THF at −40 °C gave the homoallylic alcohol **35**, which was protected as its *tert*-butyl carbonate **36** in high yields (di-*tert*-butyldicarbonate, DMAP and CH_3CN). Debenzylation of **36** was achieved with DDQ in a 2:1 mixture of CH_2Cl_2 and H_2O to afford the alcohol **37** in 85% yield. Mesylation of the primary alcohol **37** gave mesylate **38**, which on treatment with NaN_3 in DMF at 60 °C yielded the corresponding azide **39** in 83% yield**.**



Scheme 4: (i) (a) PhNO, L-proline (25 mol%), CH_3CN, −20 °C, 24 h then MeOH, $NaBH_4$; (b) $CuSO_4$ (30 mol%), MeOH, 0 °C, 10 h, 87% (over two steps); (ii) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 92%; (b) K_2CO_3, MeOH, 25 °C, 1 h, 95%; (iii) vinylmagnesium bromide, THF, CuI, −40 °C, 1 h, 92%; (iv) (a) $(Boc)_2O$, DMAP, CH_3CN, 25 °C, 5 h, 95%; (b) DDQ, CH_2Cl_2:H_2O (2:1), 25 °C, 20 h, 85%; (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 94%; (b) NaN_3, DMF, 60 °C, 2 h, 83%; (c) NIS, CH_3CN, −40 to 0 °C, 20 h, 87%; (vi) K_2CO_3, MeOH, 0 °C to 25 °C, 2 h, 96%; (vii) NaCN, $Ti(O^iPr)_4$, *n*-Bu_4NI, DMSO, 70 °C, 6 h, 80%.

Diastereoselective iodolactonization of homoallylic *tert*-butyl carbonate **39** using *N*-iodosuccinimide in CH_3CN at low temperature (−40 to 0 °C) furnished the iodo carbonate derivative **40** in 85% yield as a single diastereomer (determined by ^1H NMR analysis). The iodocarbonate **40**, upon exposure to a basic methanolic solution, gave the desired *syn*-epoxy alcohol **41** in 90% yield. Finally, nucleophilic ring opening of the epoxide **41**

using NaCN in presence of titanium tetraisopropoxide and tetrabutylammonium iodide in DMSO gave the corresponding nitrile **42** in 80% yield.

CHAPTER 3

A short enantioselective synthesis of (-)-bestatin via L-proline catalyzed α-amination of an aldehyde and asymmetric synthesis of guggultetrol using Sharpless asymmetric epoxidation and dihydroxylation

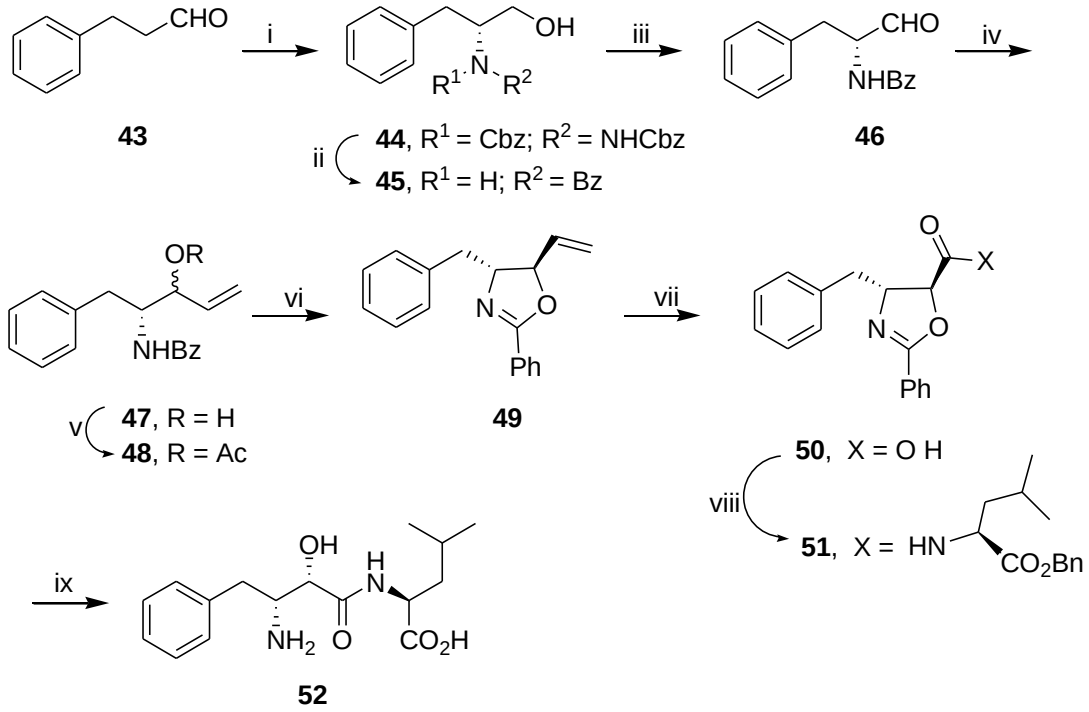
This Chapter is divided into two sections. **Section I** deals with the enantioselective synthesis of (-)-bestatin **52** via L-proline catalyzed α-amination of an aldehyde and **Section II** describes the asymmetric synthesis of guggultetrol **63** using Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation.

SECTION I: A short enantioselective synthesis of (-)-bestatin via L-proline catalyzed α-amination of an aldehyde

(-)-Bestatin **52** is an aminopeptidase inhibitor[15] that exhibits immunostimulatory activity as well as cytotoxic activity. It is used clinically as an oral medication for the treatment of cancer[16] and HIV.[17] Asymmetric α-amination of aldehydes using proline as the catalyst represents[18] a burgeoning field of synthetic efforts towards synthesizing chiral building blocks such as α-amino acids and alcohols. The present section describes the enantioselective synthesis of (-)-bestatin **52** via L-proline catalyzed α-amination of an aldehyde (**Scheme 5**).[19]

Accordingly, 3-phenylpropionaldehyde **43** was subjected to α-amination with dibenzyl azodicarboxylate in the presence of L-proline (10 mol%) to produce an amino aldehyde, which upon *in situ* reduction with $NaBH_4$ afforded the protected amino alcohol **44** in 92% yield and 95% ee. Amino alcohol **44** was then subjected to hydrogenolysis [over Raney nickel, H_2 (60 psi), 25 °C] to give the free amine, which was protected (BzCl, Et_3N, THF, 25 °C) as its benzamide **45** in 70% yield over two steps. Oxidation of alcohol **45** with Dess-Martin periodinane gave the corresponding aldehyde **46**, which on reaction with vinylmagnesium bromide in THF at 0 °C afforded allylic alcohol **47** as a 1.1:1 mixture of *syn*/*anti* isomers (determined by ^1H NMR analysis) in 85% yield. Acetylation of **47** (Ac_2O, Py, DMAP, CH_2Cl_2, 25 °C) gave the secondary allylic acetate **48** in 98% yield. The Pd-catalyzed intramolecular cyclization of allylic acetate **48** using $Pd(PPh_3)_4$ and

K_2CO_3 in CH_3CN proceeded readily to give the desired *trans*-oxazoline **49** as an inseparable mixture of diastereomers (dr >14:1, as determined by ^1H and ^{13}C NMR spectral analysis) in 79% yield. Oxidative degradation of **49** [(i) OsO_4, NMO, (ii) $NaIO_4$ (iii) $NaClO_2$, NaH_2PO_4) gave the acid **50** which on condensation with benzyl ester of L-leucine (DCC, HOBT in THF) provided the amide **51** in 70% yield over the four steps. Finally, catalytic hydrogenolysis [20% $Pd(OH)_2/C$, H_2 (75 psi), MeOH/AcOH (9:1), 25 °C, 36 h] of **51** furnished (-)-bestatin **52** in 72% yield.



Scheme 5: (i) dibenzyl azodicarboxylate, L-proline (10 mol%), CH_3CN, 0 to 25 °C, 3 h then $NaBH_4$, EtOH, 0 °C, 30 min, 92%, 95% ee; (ii) (a) H_2 (60 psi), Raney nickel, MeOH, AcOH, 25 °C, 20 h; (b) benzoyl chloride, Et_3N, THF, 0 to 25 °C, 30 min, 70% (over two steps); (iii) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 2 h; (iv) CH_2=CHMgBr, THF, 0 to 25 °C, 1 h, 85% (over two steps); (v) Ac_2O, Py, DMAP, CH_2Cl_2, 25 °C, 12 h, 98%; (vi) $Pd(PPh_3)_4$ (5 mol%), K_2CO_3, CH_3CN, reflux, 24 h, 79%, dr >14: 1; (vii) (a) OsO_4, 50% aq. NMO, acetone/H_2O (9:1), 25 °C, 12 h; (b) $NaIO_4$, CH_2Cl_2, 25 °C, 10 min; (c) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 25 °C, 2 h; (viii) L-leucine benzyl ester.TsOH, DCC, HOBT, THF, 0 °C to 25 °C, 16 h, 70% (over 4 steps); (ix) 20% $Pd(OH)_2/C$, H_2 (75 psi), MeOH/AcOH (9:1), 25 °C, 36 h, 72%.

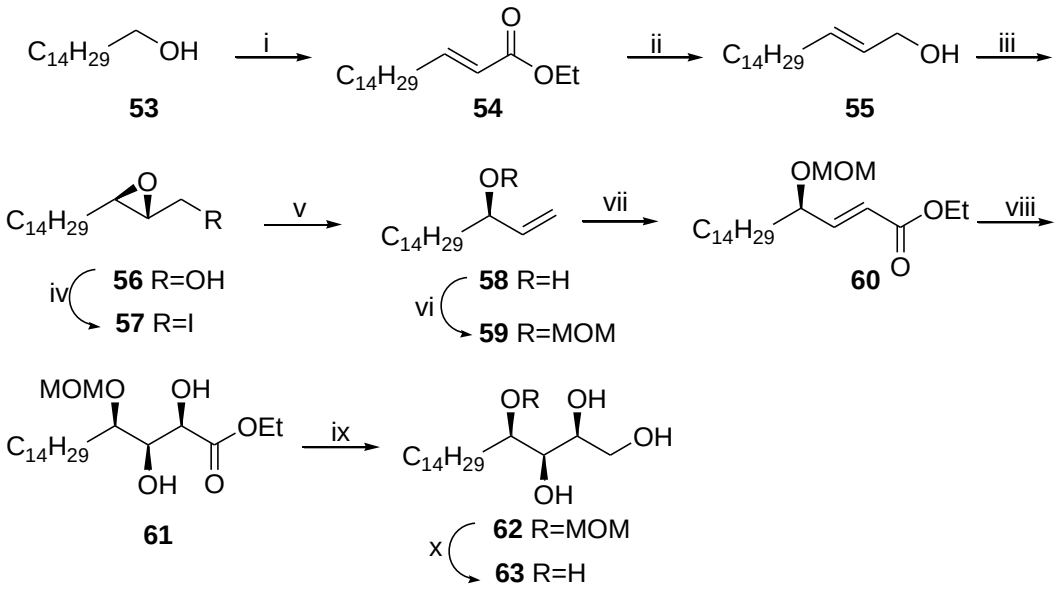
SECTION II: Asymmetric synthesis of guggultetrol using Sharpless asymmetric epoxidation and dihydroxylation

This section illustrates two different routes for the enantioselective synthesis of guggultetrol **63** using Sharpless asymmetric epoxidation (**Scheme 6**) and Sharpless

asymmetric dihydroxylation (**Scheme 7**). Guggultetrol **63**, a naturally occurring lipid isolated from the gum-resin of the tree *Commiphoru mukul (guggul)*,[20] known in Ayurveda, the Indian traditional system of medicine, is used in the treatment of arthritis, inflammation, obesity and disorders of lipid metabolism.[21]

a) Sharpless asymmetric epoxidation approach

In the first route, synthesis of guggultetrol **63** was started from 1-pentadecanol **53** (**Scheme 6**) which on Swern oxidation followed by Wittig olefination gave (*E*)-α,β-unsaturated ester **54** in 90 % yield. DIBALH reduction of the ester **54** gave the allyl alcohol **55** which was then subjected to Sharpless asymmetric epoxidation [(-)-DET, $Ti(O^iPr)_4$ and TBHP][5,22] to give the epoxy alcohol **56** in 89% yield and 98% ee (optical purity was determined by ^1H NMR analysis of the corresponding Mosher's ester). Conversion of epoxy alcohol **56** into epoxy iodide **57** (I_2, PPh_3) followed by its treatment with NaI and Zn gave allylic alcohol **58** which was further protected as its MOM ether **59 (**MOMCl, DIPEA) in 91% yield. Oxidative cleavage of **59** [(i) OsO_4, NMO, (ii) $NaIO_4$] followed by Wittig olefination gave α,β-unsaturated ester **60** which was subjected to

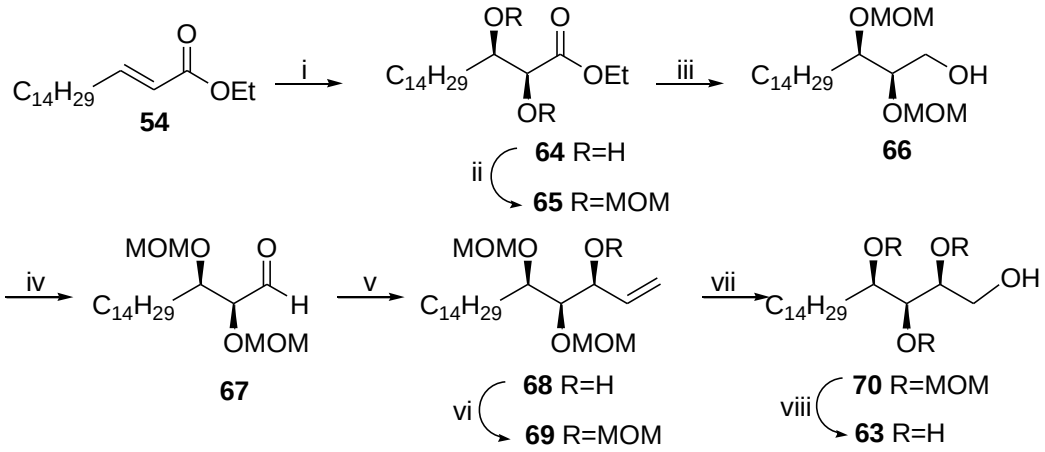


Scheme 6: (i) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 25 °C, 1 h; (b) $PPh_3{=}CHCO_2Et$, benzene, reflux, 12 h, 90%; (ii) DIBALH, CH_2Cl_2, -78 °C, 2 h, 96%; (iii) (-)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 °C, 24 h, 89%; (iv) I_2, PPh_3, imidazole, ether/acetonitrile (3:1), 0 °C, 1 h, 83%; (v) Zn, NaI, MeOH, reflux, 6 h, 80%; (vi) MOMCl, DIPEA, CH_2Cl_2, 0 °C to 25 °C, 12 h, 91%; (vii) (a) OsO_4, 50% aq. NMO, acetone/H_2O (9:1), 25 °C, 12 h; (b) $NaIO_4$, CH_2Cl_2, 25 °C, 10 min.; (c) $PPh_3{=}CHCO_2Et$, benzene, 50 °C, 1 h, 90%; (viii) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/ H_2O (1:1), $K_2OsO_4.H_2O$ (0.2 mol %), 0 °C, 5 h, 86%; (ix) $LiAlH_4$, THF, 0 °C to 25 °C, 5 h, 86%; (x) con. HCl, MeOH, 25 °C, 4 h, 78%.

Sharpless asymmetric dihydroxylation [OsO_4, $K_3Fe(CN)_6$, $(DHQ)_2$-PHAL] to give the diol **61** in 86% yield. The reduction of the ester function in **61** ($LiAlH_4$, THF) followed by deprotection of the MOM group with con. HCl in methanol afforded guggultetrol **63** in 78% yield.

a) Sharpless asymmetric dihydroxylation approach

In the second route, Sharpless asymmetric dihydroxylation[23] of olefins is proved to be a powerful tool for synthesizing chiral vicinal diols with high enantioselectivity. Synthesis of gugultetrol **63** was started from the α,β-unsaturated ester **54** (**Scheme 7**) which was subjected to Sharpless asymmetric dihydroxylation [OsO_4, $K_3Fe(CN)_6$, $(DHQD)_2$-PHAL] to give the diol **64** in 94% yield and 98% ee (the enantiomeric excess was determined by chiral HPLC analysis). Protection of diol **64** as its MOM ether followed by $LiAH_4$ reduction of the MOM ether **65** gave the alcohol **66** in 95% yield. Oxidation of alcohol **66** (IBX, DMSO) followed by chelation controlled vinylation reaction gave the allylic alcohol **68** in 87% yield with excellent diastereoselectivity (>15:1), as determined by ^1H and ^{13}C NMR spectral analysis.



Scheme 7: (i) $(DHQD)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), $K_2OsO_4.H_2O$ (0.2 mol %), 0 °C, 24 h, 94%; (ii) MOMCl, DIPEA, CH_2Cl_2, 0 °C to 25 °C , 12 h, 94%; (iii) $LiAlH_4$, THF, 0 °C to 25 °C, 12 h, 95%; (iv) IBX, DMSO, 25 °C, 3 h; (v) CH_2=$CHMgBr$, $MgBr_2.Et_2O$, CH_2Cl_2, -78 °C, 10 h, 87%, d.r. >15:1; (vi) MOMCl, DIPEA, CH_2Cl_2, 0 °C to 25 °C, 12 h, 92%; (vii) (a) OsO_4, 50% aq NMO, acetone/H_2O (9:1), 25 °C, 12 h; (b) $NaIO_4$, CH_2Cl_2, 25 °C, 10 min; (c) $NaBH_4$, MeOH, 0 °C to 25 °C, 30 min, 88%; (viii) con.HCl, MeOH, 25 °C, 2 h, 79%.

After protection of the hydroxyl group in **68** as its MOM ether, the olefin **69** was oxidatively cleaved [(i) OsO_4, NMO, (ii) $NaIO_4$] and the aldehyde thus formed was

reduced using $NaBH_4$ in methanol to give the alcohol **70** in 88% yield. Eventually the global deprotection of all the MOM groups in compound **70** using con. HCl in methanol afforded guggultetrol **1** in 79% yield.

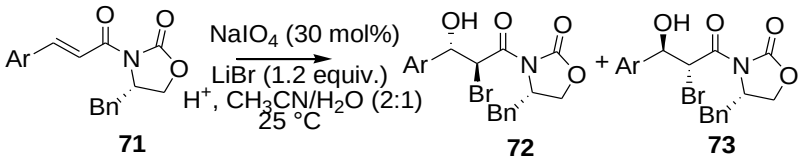
CHAPTER 4

$NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides with high diastereoselectivity: a short route to (-)-cytoxazone and droxidopa

This chapter is divided into three sections. **Section I** deals with the $NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides with high diastereoselectivity. **Section II** describes the application of asymmetric bromohydroxylation for the enantioselective synthesis of (-)-cytoxazone while **Section III** deals with the asymmetric synthesis of L-*threo*-DOPS (droxidopa).[24]

SECTION I: $NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides

In continuation of our interest on $NaIO_4$-mediated oxyfunctionalization of organic compounds,[25] we were interested to carry out a "transition metal-free" procedure for the asymmetric bromohydroxylation of α,β-unsaturated carboxamides with $NaIO_4$ as oxidant and LiBr as the halogen source under ambient conditions. (4***S***)-*N*-cinnamoyl-4-benzyl-2-oxazolidinone (**71a),** readily derived from Evans' chiral auxillary obtainable from (***S***)-phenylalanine, was subjected to oxidative bromination in the presence of 30 mol% $NaIO_4$ in a 2:1 mixture of CH_3CN and water using LiBr (1.2 equiv.) as the bromine source under acidic conditions (aq. HCl), to obtain the corresponding bromohydrins **72a** and **73a** in 81% combined yield and high diastereoselectivity (dr = 5.5:1). Several (4***S***)-*N*-cinnamoyl-4-benzyl-2-oxazolidinones (entries **71a-i**) with electron- donating as well as withdrawing substituents on the aromatic nucleus were subjected to bromohydroxylation to produce the corresponding bromohydrins **72** and **73** in excellent yields and high diastereoselectivity (**Table 1**).

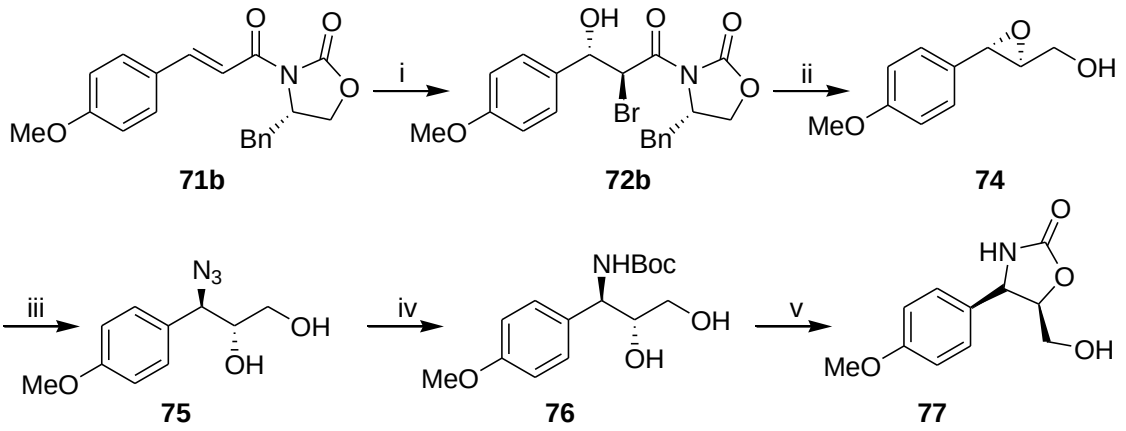


entry	substrate (Ar)	ratio (**72**:**73**)[a]	% yield[b]
a	C_6H_5	5.5:1	81
b	4-OMe-C_6H_4	10:1	90
c	4-CH_3-C_6H_4	9:1	86
d	3,4-dimethoxy-C_6H_3	7:1	82
e	4-Cl-C_6H_4	6:1	77
f	3,4,5-trimethoxy-C_6H_2	6:1	86
g	3,4-O-CH_2-O-C_6H_3	5:1	84
h	3,4-dibenzyloxy-C_6H_3	6:1	87
i	furan	5:1	82

Table 1: [a] Diastereomeric ratios were determined from GC.
[b] Combined isolated yield of **72** and **73**.

SECTION II: Enantioselective synthesis of (-)-cytoxazone using $NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides

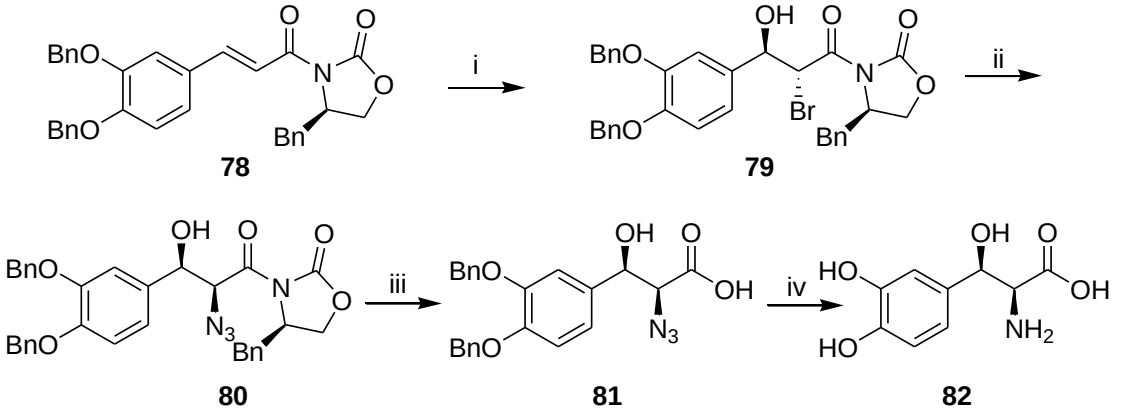
(-)-Cytoxazone **77** exhibits cytokine modulating activity by inhibiting the signalling pathway of Th2 cells.[26] For (-)-cytoxazone **77**, the carboxamide **71b** was subjected to oxidative bromohydroxylation using the procedure developed in our laboratory ($NaIO_4$, LiBr, H^+)[24] to produce the bromohydrin **72b** which was then followed by the reductive removal of chiral auxiliary to yield the epoxide **74**. The regiospecific ring opening of epoxide **74** with azide anion furnished the azidoalcohol **75**. Azido alcohol **75** was converted to (-)-cytoxazone **77** using a standard sequence of reactions *viz*. azide reduction, amine protection followed by cyclization (**Scheme 8**).



Scheme 8: Reagents and conditions: (i) $NaIO_4$ (30 mol%), LiBr, H^+, CH_3CN:H_2O (2:1), 25 °C, 1 h, 82%; (ii) $LiBH_4$, Et_2O, THF, MeOH, 0 °C, 1.5 h then 10% NaOH, 25 °C, 86%; (iii) NaN_3, NH_4Cl, MeOH, H_2O, 80 °C, 3 h, 84%; (iv) (a) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 25 °C, 2 h, 77%; (v) NaH, THF, 25 °C, 2 h, 89%, 99% ee.

SECTION III: Enantioselective synthesis of L-*threo*-DOPS (droxidopa) using $NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides

L-*threo*-DOPS [(2*S*,3*R*)-3,4-dihydroxy phenylserine] **82**, an alternative biological precursor of norepinephrine, is useful in treating disorders of the central and sympatheic nervous systems.[27] For droxidopa **82**, the carboxamide **78**, prepared from (*R*)-phenylalanine was subjected to oxidative bromohydroxylation to produce bromohydrin **79** (**Scheme 9**). The nucleophilic displacement of bromide group in **79** with sodium azide in DMF furnished the azido alcohol **80**. Subsequent removal of the chiral auxiliary with LiOH and 30% H_2O_2 followed by its azide reduction and deprotection of benzyl groups with 10% Pd/C, H_2 (1 atm) in MeOH yielded droxidopa **82** in 94% yield.



Scheme 9: (i) $NaIO_4$ (0.3 equiv.), LiBr, H+, CH_3CN:H_2O (2:1), 25 °C, 1 h, 75%; (ii) NaN_3, DMF, 60 °C, 4 h, 82%; (iii) LiOH, 30% H_2O_2, THF, H_2O, 0 °C, 2 h, 88%; (iv) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h, 94%, 99% ee.

References:

1 Ehrlich, J.; Bartz, Q. R.; Smith, R. M.; Josylyn, D. A.; Burkholder, P. R. *Science* **1947**, *106*, 417.

2 Gillet, A. D.; Abdel-Monem, M. M. *J. Med. Chem.*, **1973**, *16*, 992 and the references cited therein.

3 Cutler, R. A.; Stenger, R. J.; Suter, C. M. *J. Am. Chem. Soc*. **1952**, *74*, 5475.

4 Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *J. Am. Chem. Soc*. **2002**, *124*, 12934; (b) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett*. **2004**, *6*, 2583.

5 Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974.

6 George, S.; Narina, S. V.; Sudalai, A. *Tetrahedron* **2006**, *62*, 10202.

7 List, B.; Seayad, J. *Org. Biomol. Chem.* **2005**, *3*, 719.

8 For a review of proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573.

9 Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293.

10 Bohlmann, F.; Suwita, A. *Phytochemistry* **1979**, *18*, 677.

11 Hsu, F. L.; Chen, Y. C.; Cheng, J. T. *Planta Med*. **2000**, *66*, 228.

12 George, S.; Sudalai, A. *Tetrahedron*: *Asymmetry* **2007**, *18*, 975.

13 Kathawala, F. G. *Med. Res. Review* **1991**, *11*, 121.

14 George, S.; Sudalai, A. *Tetrahedron Lett*. **2007**, *48*, 8544.

15 Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97

16 Abe, F.; Ino, K.; Bierman, P. J.; Talmadge, J. E.; Sawada, H.; Ogino, T.; Ishizuka, M.; Aoyagi, T. *Int. Congr. Ser.* **2001**, *1218*, 155.

17 Pulido-Cejudo, G.; Conway, B.; Proulx, P.; Brown, R.; Izaguirre, C. A. *Antiviral Res.* **1997**, *36*, 167.

18 List, B. *J. Am. Chem. Soc*. **2002**, *124*, 5656.

19 George, S.; Suryavanshi, G. S.; Sudalai, A. *Tetrahedron Lett*. **2008**, *49*, 6791.

20 Howell, A. R.; So, R. C.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327.

21 Patil, V. D.; Nayak, U. R.; Dev, S. *Tetrahedron* **1973**, *29*, 1595.

22 Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B.

J. Am. Chem. Soc. **1987**, *109*, 5765.

23 Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 448

24 George, S.; Narina, S. V.; Sudalai, A. *Tetrahedron Lett.* **2007**, *48*, 1375.

25 Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501.

26 Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126.

27 Tohgi, H.; Abe, T.; Takahashi, S. *J. Neural. Trnasm. [P. D. Sect.]* **1993**, *5*, 27.

Chapter I

A short enantioselective synthesis of (-)-chloramphenicol and (+)-thiamphenicol using tethered aminohydroxylation

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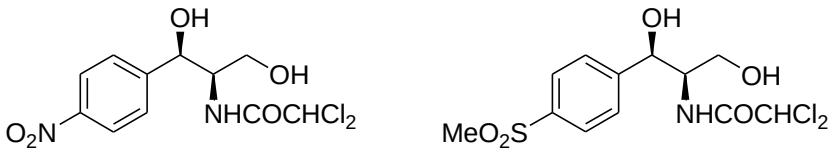
"A short enantioselective synthesis of (-)-chloramphenicol and (+)-thiamphenicol using tethered aminohydroxylation" Shyla George, Srinivasarao V. Narina and Arumugam Sudalai; *Tetrahedron*, **2006**, *62*, 10202.

A short enantioselective synthesis of (-)-chloramphenicol and (+)-thiamphenicol using tethered aminohydroxylation

1.1 Introduction

Optically active amino alcohols with vicinal stereocenters are important as drugs and natural products such as amino sugars,[1] peptides and peptide analogs,[2] enzyme inhibitors, such as glycosphingolipids, antibiotics and alkaloids. (-)-Chloramphenicol (**1a**) and (+)-thiamphenicol (**1b**) (**Fig. 1**) are broad-spectrum antibiotics with a range of biological activities.[3] The antibiotic chloramphenicol is active only in its D-*threo* configuration and is effective in the treatment of typhus, dysentery and ocular bacterial infections.[4] (+)-Thiamphenicol (**1b**), a synthetic analogue of chloramphenicol (**1a**), is bacteriostatic for both gram-positive and gram-negative aerobes and for some anaerobes.[5] Owing to their potential biological activity, a number of syntheses have been described.[6-34]



1a **1b**

Fig. 1: Structure of (-)chloramphenicol (**1a**) and (+)-thiamphenicol (**1b**)

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

Chloramphenicol (**1a**) 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

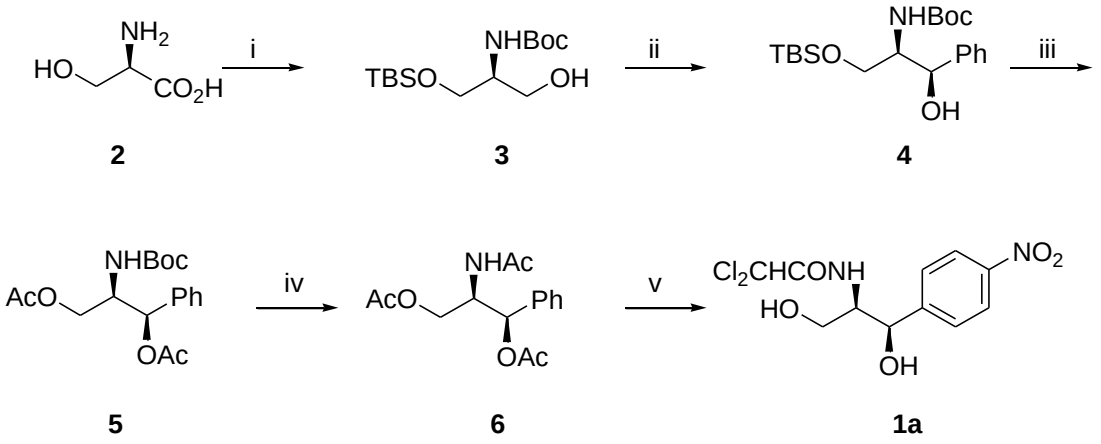
the 3-hydroxy position causes total loss of biological activity and the L(+) isomer lacks antibacterial activity. The simple structure and inherent stability of the intramolecular bonds in chloramphenicol yield a compound that is remarkably resistant to acid or alkaline degradation, autoclaving, oxidation 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 (**1a**) possesses high *in vivo* activity for having a good property of unbinding with glucuronic acid in liver and has been used clinically.

1.3 Review of Literature

Literature search revealed that there are several reports available for the synthesis of (-)-chloramphenicol (**1a**) and (+)-thiamphenicol (**1b**) involving chiral pool, chemo-enzymatic approach or enantioselective syntheses, which are described below.

Datta's approach (1998)[17]

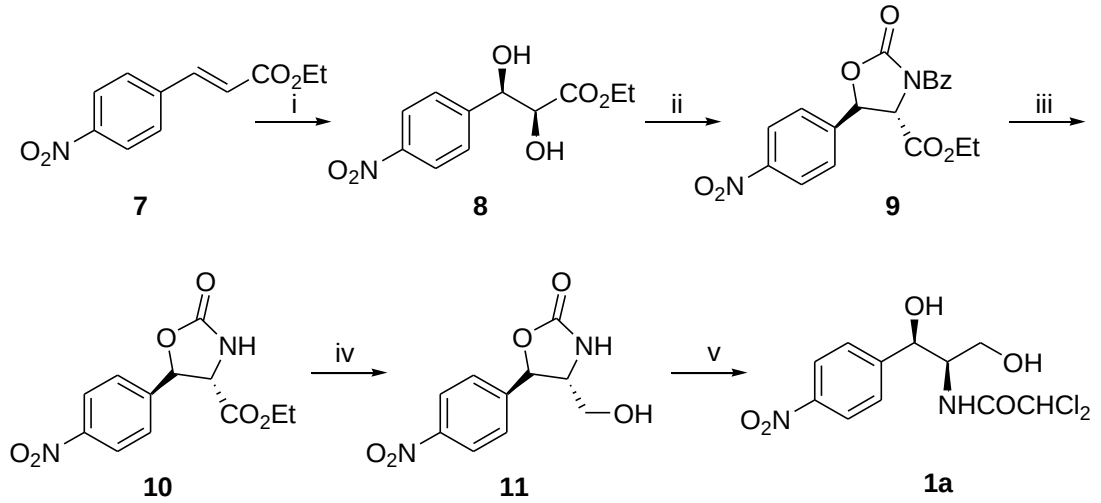
Datta *et al.* have achieved the synthesis of (-)-chloramphenicol (**1a**) using a chiral pool approach starting with D-serine **2**, which was converted into the amino diol derivative **3** in four steps. Swern oxidation of the alcohol **3** followed by Grignard addition with phenyl magnesium bromide afforded the *syn*-amino alcohol **4** with diastereoselectivity >19:1. A stepwise deprotection, acylation sequence of **4** gave the desired product **6**, which on nitration with con. HNO_3-con. H_2SO_4 (1:1) followed by treatment with methyl dichloroacetate gave (-)-chloramphenicol (**1a**) in 73% yield (**Scheme 1**).



Scheme 1: (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, $^{i}Pr_2NEt$, 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%; (iv) (a) CF_3CO_2H, 0 °C; (b) Ac_2O, DMAP, pyridine, 85%; (v) (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)[19]

Ko *et al.* have synthesized (-)-chloramphenicol (**1a**) by employing Sharpless asymmetric dihydroxylation as the key reaction. Thus the ester **7** was subjected to asymmetric dihydroxylation to give the diol **8** in 98% yield which was successively treated with

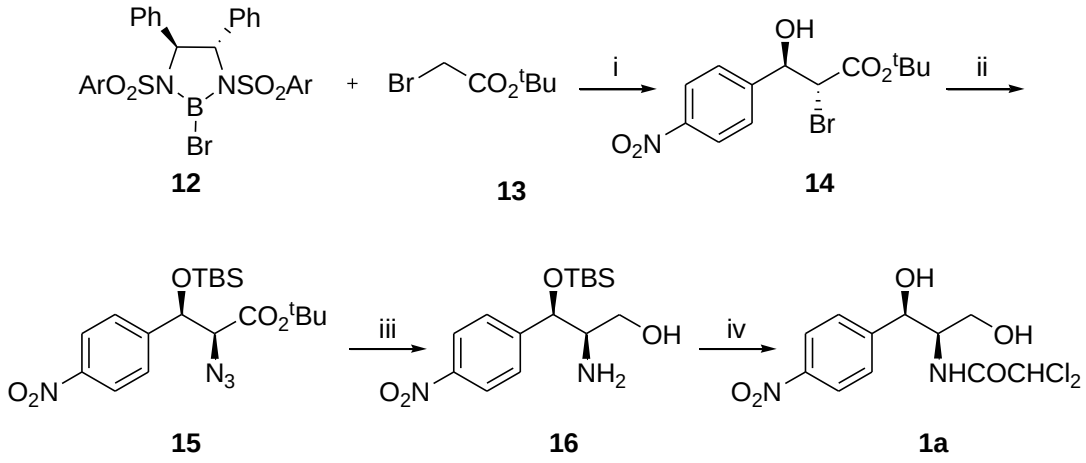


Scheme 2: (i) AD-mix-β, *t*-BuOH:H_2O (1:1), 25 °C, 98%, >99% ee; (ii) (a) Bu_2SnO; (b) BzNCS; (c) Bu_4NBr; (iii) $Ti(O^{i}Pr)_4$, ethanol, 81%; (iv) $NaBH_4$, 92%; (v) (a) 1N NaOH, 92%; (b) Cl_2CHCO_2Me, 74%.

Bu_2SnO, BzNCS and Bu_4NBr to give the protected *syn* amino alcohol **9**. Debenzoylation of **9** with $Ti(O^iPr)_4$ and ethanol afforded **10** which was then treated with $NaBH_4$ to give the alcohol **11** in 92%yield. Hydrolysis of **11** with 1 N NaOH followed by amidation with methyl dichloroacetate gave (-)-chloramphenicol (**1a**) in 74% yield (**Scheme 2**).

Corey's approach (2000)[19]

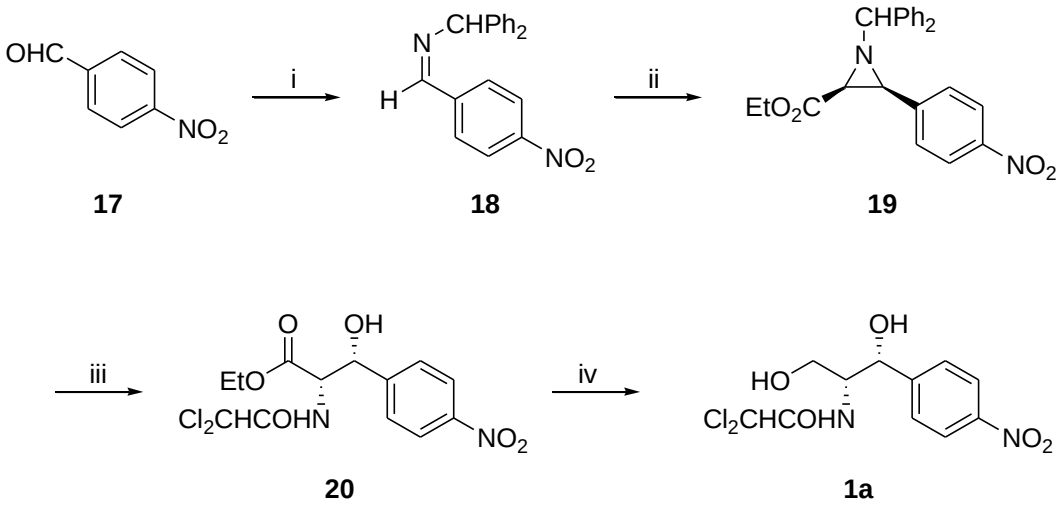
(-)-Chloramphenicol (**1a**) was also synthesized by Corey *et al. via* aldol reaction of *p*-nitrobenzaldehyde and *t*-butyl bromoacetate **13** in the presence of (*S*,*S*)-bromoborane to give the bromohydrin **14** in 99% yield and 93% ee. Protection of the hydroxyl group in **14** as its silyl ether followed by reaction with sodium azide gave **15**. Reduction of the azido ester **15** was performed in two steps with $LiBH_4$ follwed by triphenylphosphine in THF-H_2O to form the alcohol **16**. *N*-acylation of **16** and subsequent desilyaltion with Bu_4NF in THF afforded (-)-chloramphenicol (**1a**) (**Scheme 3**).



Scheme 3: (i) (a) toluene, -78 °C, Et_3N; (b) *p*-nitrobenzaldehyde, -78 °C, 99%, d.r. = 96:4, 93% ee; (ii) (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 96%; (b) NaN_3, DMF, 40 °C, 73%; (iii) (a) $LiBH_4$, Et_2O, 0 °C, 80%; (b) PPh_3, THF-H_2O, 80%; (iv) (a) Cl_2CHCO_2Me, CH_2Cl_2, 0 °C; (b) Bu_4NF, THF.

Wulff's approach (2001)[20]

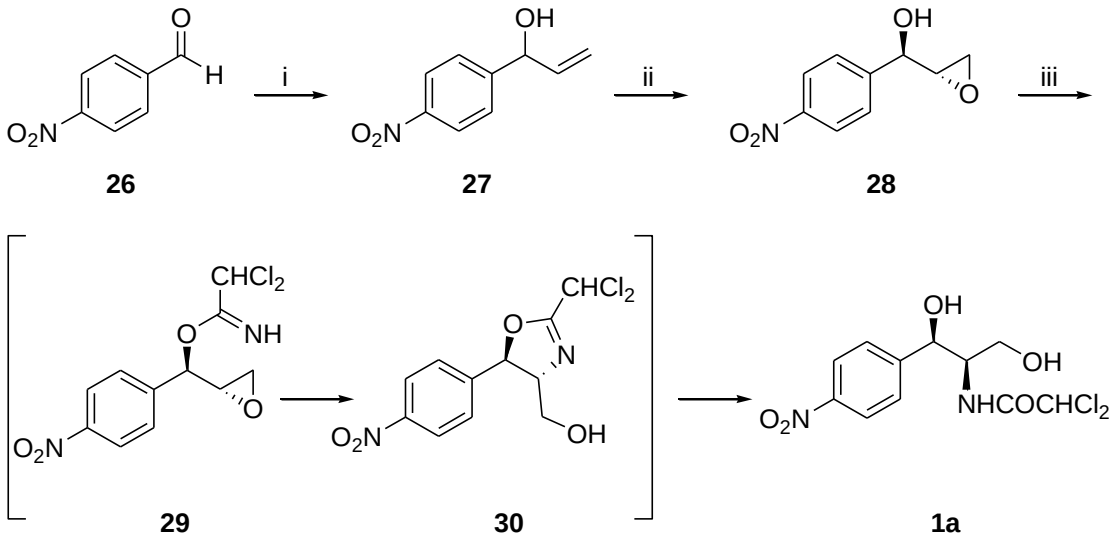
Wulff *et al.* have synthesized (-)-chloramphenicol (**1a**) *via* catalytic aziridination of *p*-nitrobenzaldimine **18** in presence of 10 mol% of a catalyst prepared from triphenylborate and (*S*)-VAPOL to give the aziridine **19** in 80% yield and 96% ee. Treatment of aziridine **19** with 10 equivalent of dichloroacetic acid gave the hydroxyl acetamide **20** which on subsequent reduction with $NaBH_4$ in MeOH afforded (-)-chloramphenicol (**1a**) in 74% yield (**Scheme 4**).



Scheme 4: (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%.

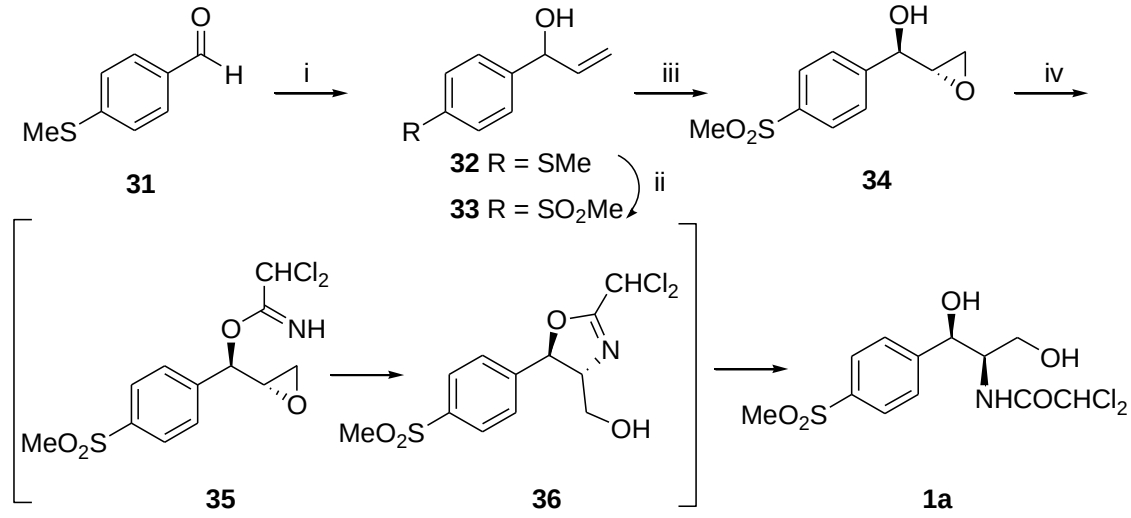
Rao's approach (2004)[21]

Rao *et al.* have achieved the synthesis of (-)-chloramphenicol (**1a)** by employing Sharpless asymmetric epoxidation of the allylic alcohol **27** using (-)-DIPT to afford the chiral epoxyalcohol **28** with 95% ee. Epoxyalcohol **28** was then converted into (-)-chloramphenicol (**1a)** by treatment with dichloroacetonitrile in the presence of NaH followed by an *in situ* opening of the product **29** with $BF_3.Et_2O$ (**Scheme 5**).



Scheme 5: (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%.

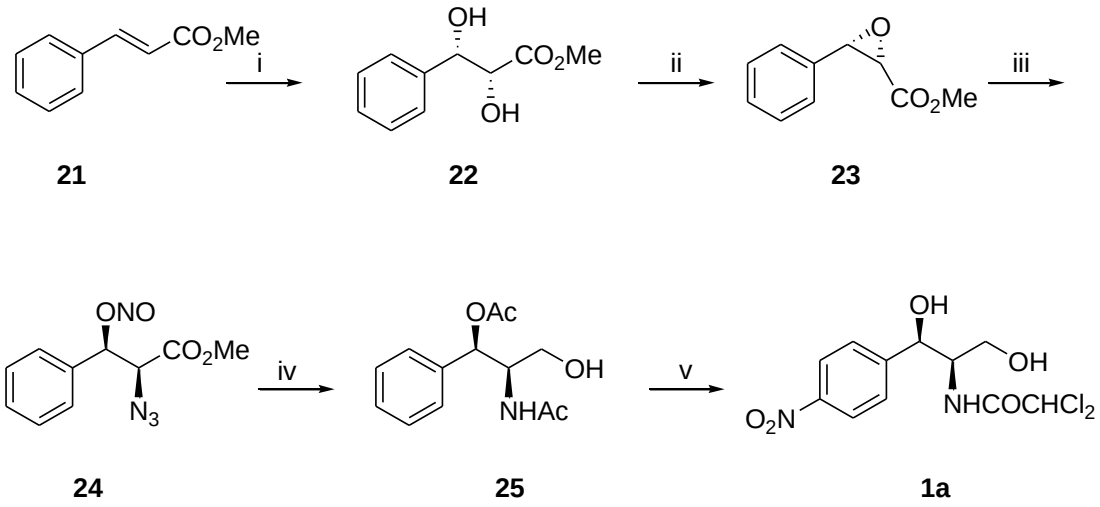
The same group has also synthesized (+)-thiamphenicol (**1b**) by following a similar set of reaction sequences: Sharpless asymmetric epoxidation of allylic alcohol **33** followed by opening of the corresponding chiral epoxyalcohol **34** with Lewis acid (**Scheme 6**).



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

Barua's approach (2005)[22]

(-)-Chloramphenicol (**1a**) was also synthesized by Barua *et al.* using regioselective ring opening of epoxide **23** which was prepared from methyl cinnamate **21** by Sharpless asymmetric dihydroxylation. The epoxide **23** 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 **24**. Catalytic hydrogenation of **24** [10% Pd/C, MeOH, H_2 (1 atm)] followed by acylation with Ac_2O gave the desired product **25**. The synthesis of (-)-chloramphenicol (**1a)** was completed by following the three-step reaction sequence: nitration, hydrolysis and *N*-acylation (**Scheme 7**).

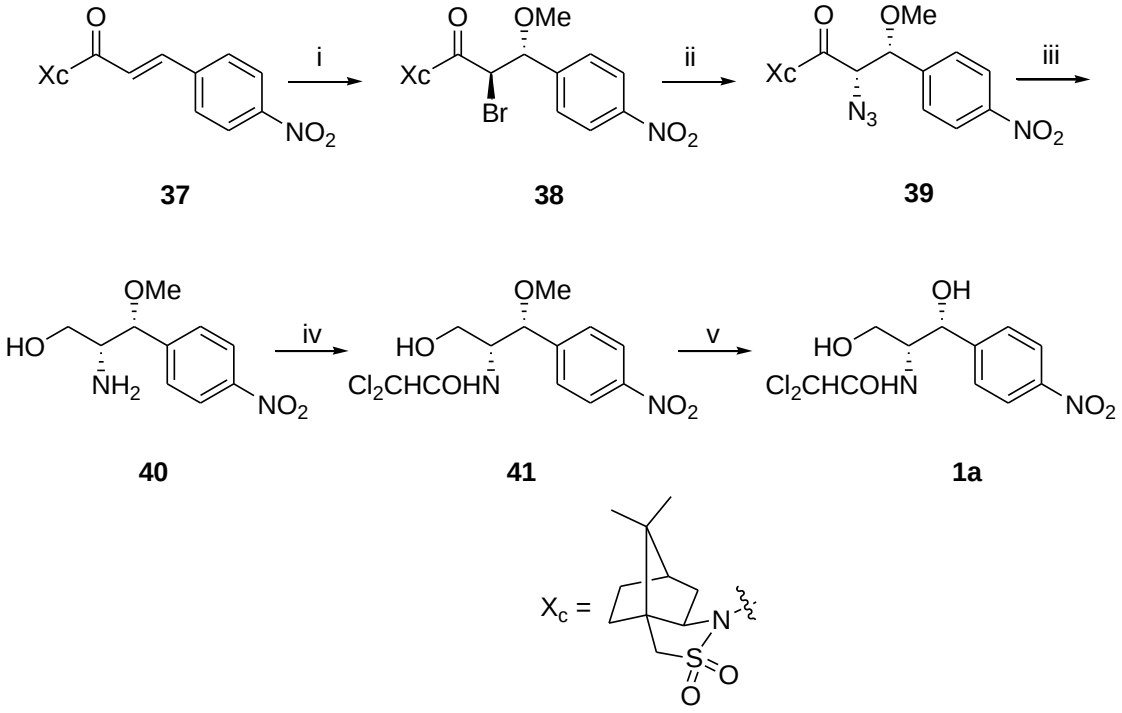


Scheme 7: (i) OsO_4 (cat.), NMO, DHQ-*p*ClBz, acetone, H_2O, 98% ee; (ii) (a) TsCl, pyridine, CH_2Cl_2; (b) K_2CO_3, H_2O, DMF, 86%; (iii) (a) $NaNO_2$, AcOH, H_2O, 0 °C to 25 °C, 2 h, 89%; (b) DPPA, DEAD, PPh_3, THF, 0 °C to 25 °C, 1.5 h, 82%; (iv) (a) 10% Pd/C, MeOH, H_2 (1 atm), 25 °C, 12 h, 97%; (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)[23]

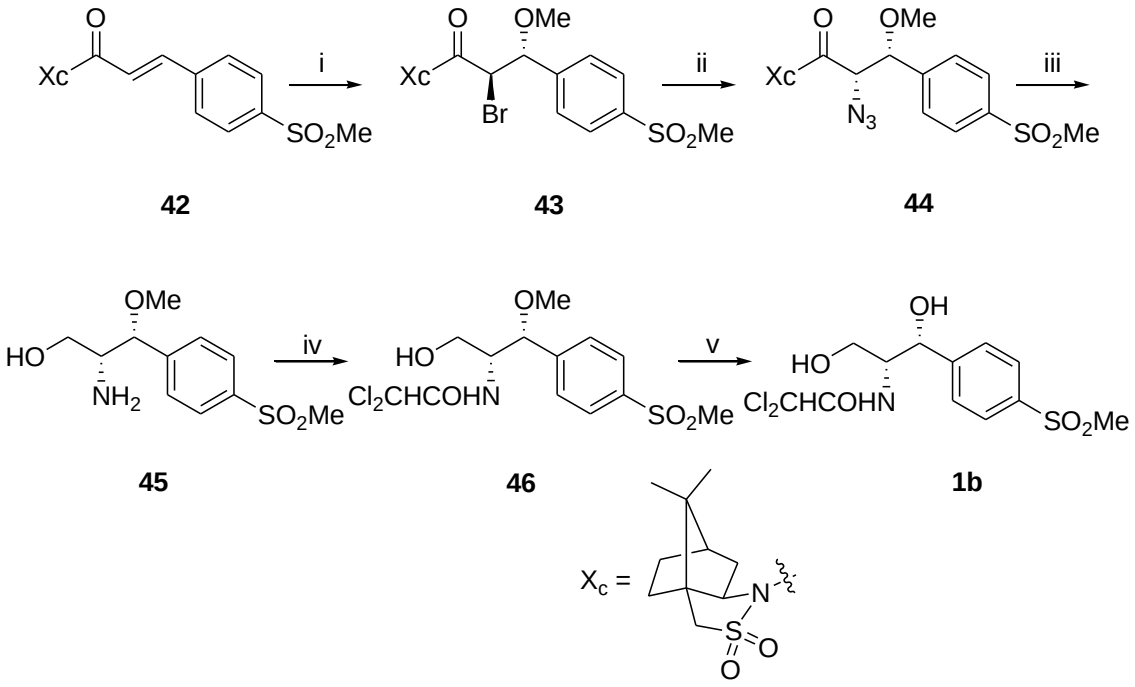
Hajra *et al.* have synthesized (-)-chloramphenicol (**1a**) using silver(I)-promoted asymmetric bromomethoxylation. $AgNO_3$-promoted bromomethoxylation of α, β-

unsaturated carboxamide **37** provided the desired product **38** in 72% yield. Reaction of **38** with NaN_3 in DMF gave the azido product **39** 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 **40**. *N*-acylation of **40** gave **41** which on subsequent demethylation with BBr_3 gave the target molecule **1a** in 80% yield (**Scheme 8**).



Scheme 8: (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%.

(+)-Thiamphenicol (**1b**) was also synthesized by the same group following the same synthetic strategy applied for (-)-chloramphenicol (**1a**) (**Scheme 9**).

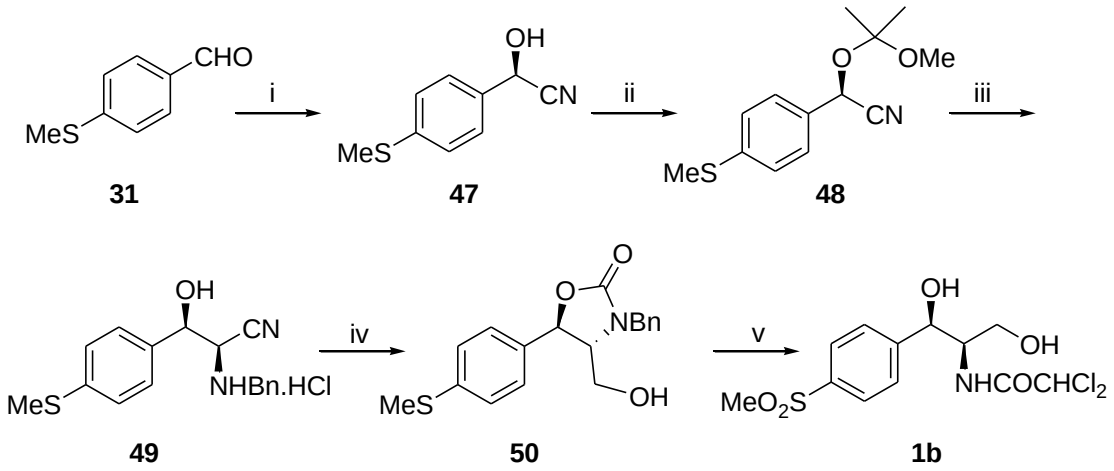


Scheme 9: (i) $AgNO_3$, Br_2, MeOH, 0 ^{0}C, 30 min, 68%, d.r. = 2.5:1; (ii) NaN_3, DMF, 60 ^{0}C, 4 h, 92%; (iii) (a) $LiBH_4$, THF, MeOH; (b) PPh_3, THF-H_2O, 25 ^{0}C, 5 h, 82%; (iv) Cl_2CHCO_2Me, 90 °C, 1 h, 85%; (v) BBr_3, CH_2Cl_2, -78 ^{0}C to -20 ^{0}C, 10 h, 84%.

Lin's approach (2008)[34]

Lin *et al.* have achieved the synthesis of (-)-chloramphenicol (**1a**) by means of a chemo-enzymatic approach. 4-(Thiomethyl)benzaldehyde **31** was treated with (*R*)-hydroxynitrile lyase (HNL) in isopropyl ether to give the product cyanohydrin **47** in 98% yield and 99% ee. Protection of the alcohol in **47** followed by DIBALH reduction, benzylamine addition and hydrocyanation of imine generated the second chiral centre with diastereomeric ratio >20:1. Treatment of **49** with carbonyldiimidazole provided the corresponding oxazolidine derivative which when reacted with K_2CO_3 followed by $NaBH_4$ afforded the alcohol **50**. Oxidation of **50** with *m*CPBA converted the methylsulfanyl group into methylsulfonyl group which was then converted into (+)-thiamphenicol (**1b**) by known sequences of

reactions such as hydrolysis with aq. KOH, catalytic debenzylation and acylation (**Scheme 10**).



31 **47** **48** **49** **50** **1b**

Scheme 10: (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%.

1.4 Present Work:

1.4.1 Objective

Even though several methods are reported for the synthesis of (-)-chloramphenicol (**1a**) and (+)-thiamphenicol (**1b**),[6-34] 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 (**1a**) and (+)-thiamphenicol (**1b**) is highly desirable.

Retrosynthetic analysis for (-)-chloramphenicol (**1a**) reveals that *anti*-oxazolidinone **55** could be visualized as the key intermediate. The *anti*-oxazolidinone **55** could be achieved by means of tethered aminohydroxylation of allyl carbamate **54**. The allylic carabamate **54** could be prepared from the corresponding allylic alcohol **27** by performing Sharpless

asymmetric epoxidation of **27** under kinetic resolution and then conversion into the carbamate **54**. The requisite racemic allylic alcohol fragment **27** could be easily prepared from *p*-nitrobenzaldehyde **26** by the addition of divinylzinc (**Fig. 2**).

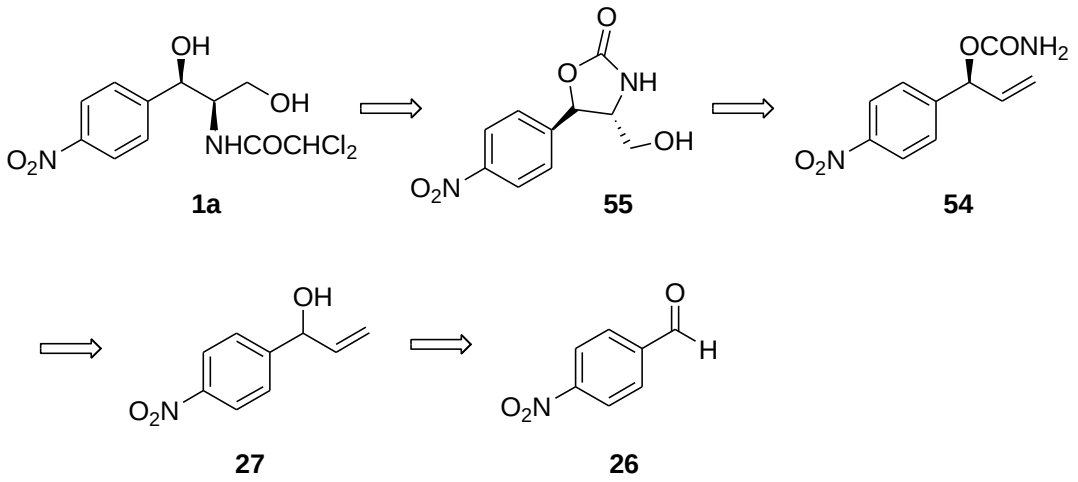


Fig. 2: Retrosynthetic analysis of (-)-chloramphenicol (1a)

In case of (+)-thiamphenicol (**1b**), the retrosynthetic analysis reveals that *anti*-oxazolidinone **60** could be visualized as a key intermediate (**Fig. 3**).

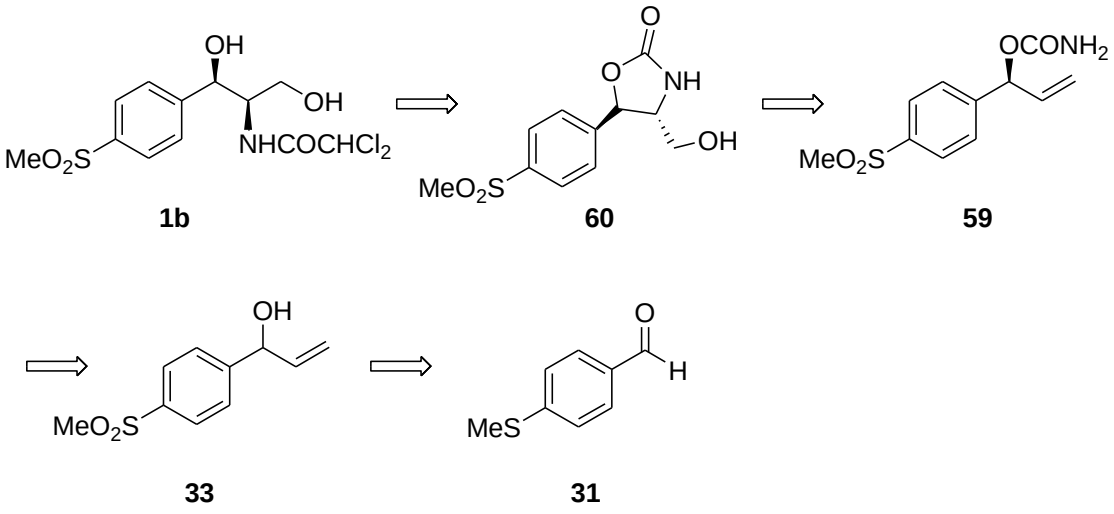


Fig. 3: Retrosynthetic analysis of (+)-thiamphenicol (1b)

The *anti*-oxazolidinone **60** could be achieved from the allylic carbamate **59** by tethered aminohydroxylation, which in turn could be obtained from the allylic alcohol **33** by employing Sharpless asymmetric epoxidation under kinetic resolution followed by conversion of the chiral alcohol into the carbamate **59**. The requisite racemic allylic alcohol fragment **33** would be accessed from 4-(thiomethyl)benzaldehyde **31** by Grignard addition and successive oxidation of the corresponding product with oxone.

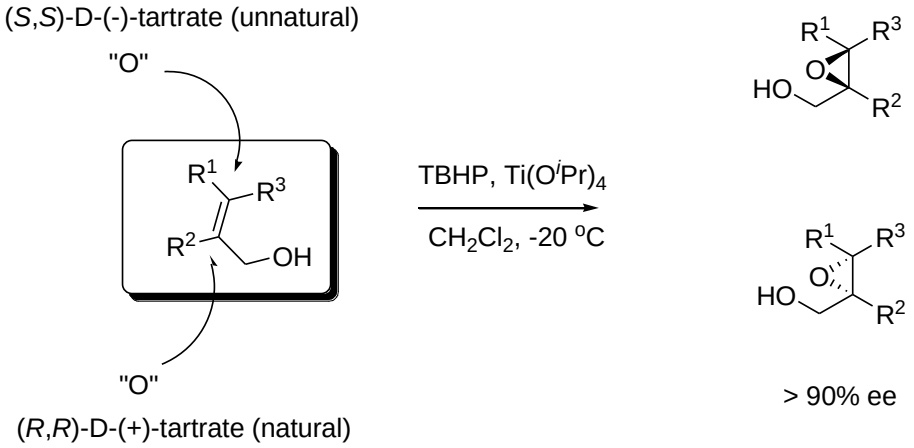
Since this chapter describes novel strategies for the asymmetric synthesis of (-)-chloramphenicol (**1a**) and its structural analogue (+)-thiamphenicol (**1b**) by employing Sharpless asymmetric epoxidation under kinetic resolution[35] and the tethered aminohydroxylation,[36] for introducing stereogenicity into the prochiral molecule, a brief account of each is presented in the following sections.

1.4.2 Sharpless asymmetric epoxidation

Asymmetric epoxidation of allylic alcohols is one of the leading areas of investigation in synthetic organic chemistry, mainly due to the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents. Today, the most successful asymmetric epoxidation reaction is the titanate-mediated epoxidation of allylic alcohols, or Sharpless epoxidation,[35] which enables the achievement of an enantiomeric excess of more than 90% in most cases. The Sharpless epoxidation is a popular laboratory and industrial process due to its both enantioselective and catalytic nature. The reaction mixture includes a titanium tetraalkoxide, a chiral tartrate diester, an allylic alcohol substrate, and an alkyl hydroperoxide as the oxidant. The consistency of the reaction is remarkable, excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. In addition to being

able to asymmetrically oxidize prochiral substrates to products of predictable absolute configuration, the reaction is extremely sensitive to preexisting chirality in selected positions of the allylic alcohols. For example, kinetic resolution of racemic secondary allylic alcohols is very efficient since it can be used for generating chiral allylic alcohols as well as *trans*-epoxyalcohols in high enantiomeric excess.

Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product (**Scheme 11**).



Scheme 11: The Sharpless epoxidation reaction

Since its discovery in 1980, the Sharpless expoxidation of allylic alcohols has become a benchmark classic method in asymmetric synthesis. One factor that simplifies the standard epoxidation reaction is that the active chiral catalyst is generated *in situ*, which means that the pre-preparation of the active catalyst is not required.

It is believed that the species containing equal moles of Ti and tartrate is the most active catalyst. It promotes the reaction much faster than Ti(IV) tetraalkoxide alone and exhibits

selective ligand-accelerated reaction.[37] Sharpless suggested that epoxidation was catalyzed by a single Ti center in a dimeric complex with a C_2 symmetric axis (**Fig. 4**).[38]

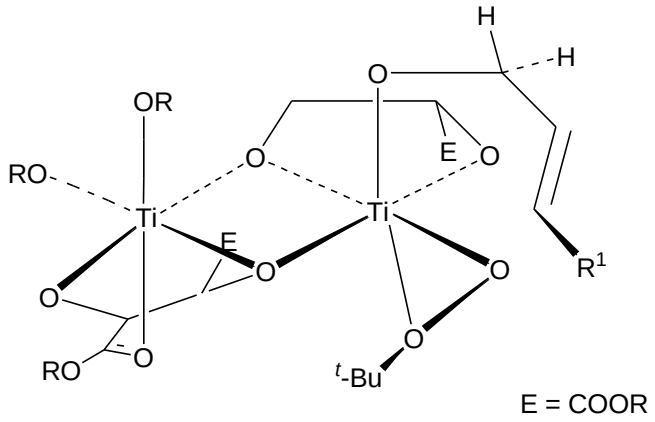
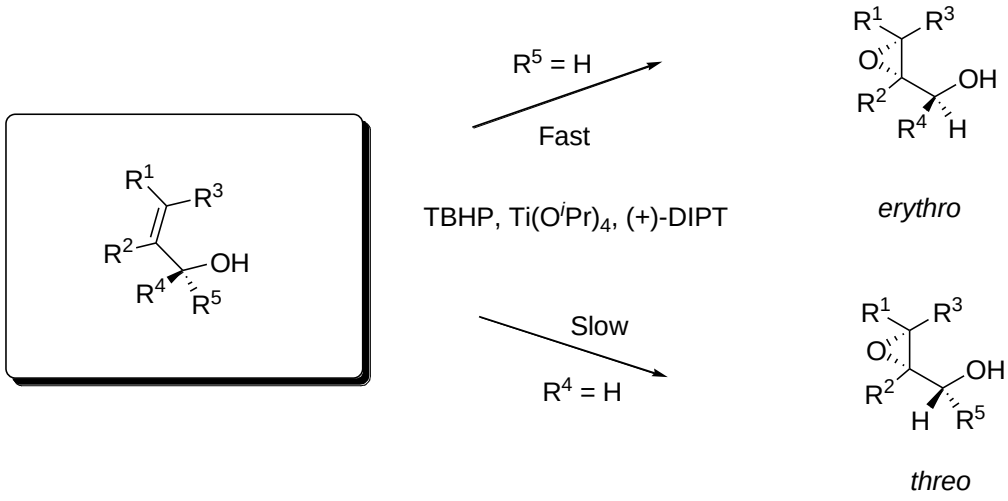


Fig. 4: Structure of dinuclear Ti-tartrate complex

1.4.2.1 Sharpless epoxidation under Kinetic Resolution

The kinetic resolution of secondary allylic alcohols was first reported in 1981,[35b] wherein some examples were performed with as little as 13-25% catalyst and there onwards complete catalytic manner developed, key feature of this catalytic procedure is molecular sieves (zeolites).

With cyclohexyl (*E*)-1-propenyl carbinol as the model ($R^1 = CH_3$, $R^2 = R^3 = R^4 =$ H, $R^5 = C_6H_{11}$ and $R^1 = CH_3$, $R^2 = R^3 =$ H, $R^4 = C_6H_{11}$) (**Scheme 12**), it was found that the (*S*)- enantiomer reacts 74 times faster than the (*R*)-enantiomer at 0 °C when (*R,R*)-(+)-diisopropyl tartrate is used as the chiral auxiliary. As in the epoxidation of primary allylic alcohols, the stereochemical course of the kinetic resolution processes has been highly predictable. When the secondary allylic alcohol is drawn so that the hydroxy group lies in the lower right corner of the plane (**Scheme 12**), the enantiomer that reacts rapidly with (*R,R*)- (+)-dialkyl tartrate is the one in which the substituent (R^4) on C-1 is located above



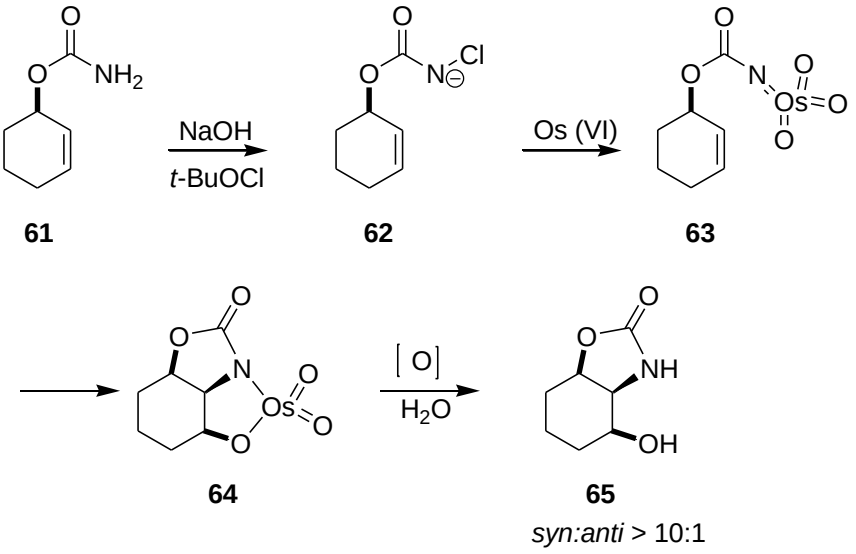
Scheme 12: Kinetic resolution of secondary alcohols

the plane. Epoxidation occurs from the underside to give the usual 2(*S*)-epoxide (*erythro* selectivity, 98:2). The slow-reacting enantiomer is the one in which the C-1 substituent (R^5) is located on the underside, interfering with the 'normal' delivery of the oxygen atom.

1.4.3 Tethered aminohydroxylation

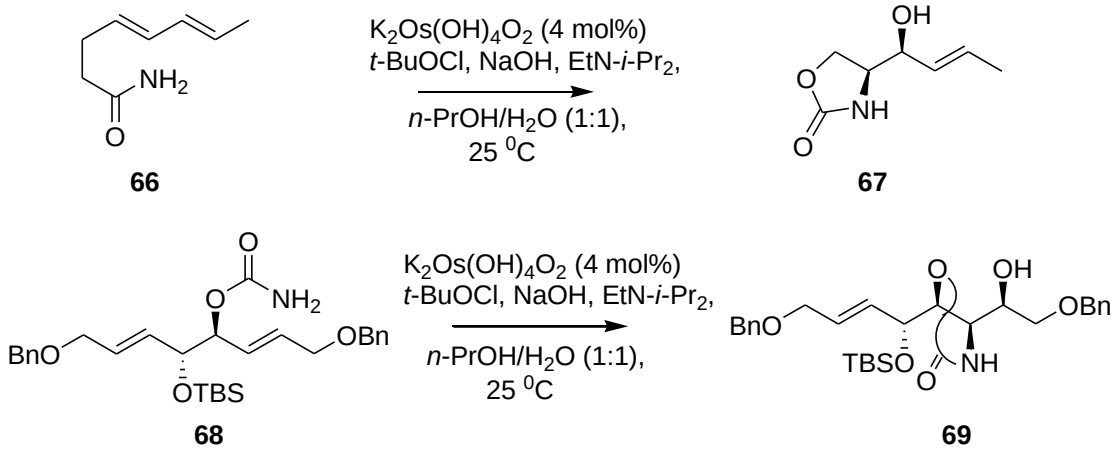
The discovery of asymmetric aminohydroxylation by Sharpless group has evolved and revolutionized the synthesis of protected amino alcohol functionality in a single step. Though it has the advantage of one-pot process, the oxidation of unsymmetrical alkenes is associated with a lack of regiochemistry. Recently, Donohoe *et al.*[36] have demonstrated the complete achievement of regioselectivity through tethering the nitrogen source to both chiral and achiral allylic alcohols (**Scheme 13**).

The complete regioselectivity can be explained by the mechanism shown in **Scheme 13**. This mechanism suggests that *in situ* chlorination and deprotonation of the allylic carbamate gives a species **62** (a nitrene equivalent) that is capable of oxidizing



Scheme 13: The mechanism of tethered aminohydroxylation

potassium osmate [Os (VI)] to the osmium tetroxide analogue **63** [Os (VIII)] which on addition to alkene gives azaglycolate osmate ester [Os (VI)] **64**. It is then oxidized and hydrolyzed *in situ* to give the protected amino alcohol **65**. Representative examples of tethered aminohydroxylation are shown in **Scheme 14**.

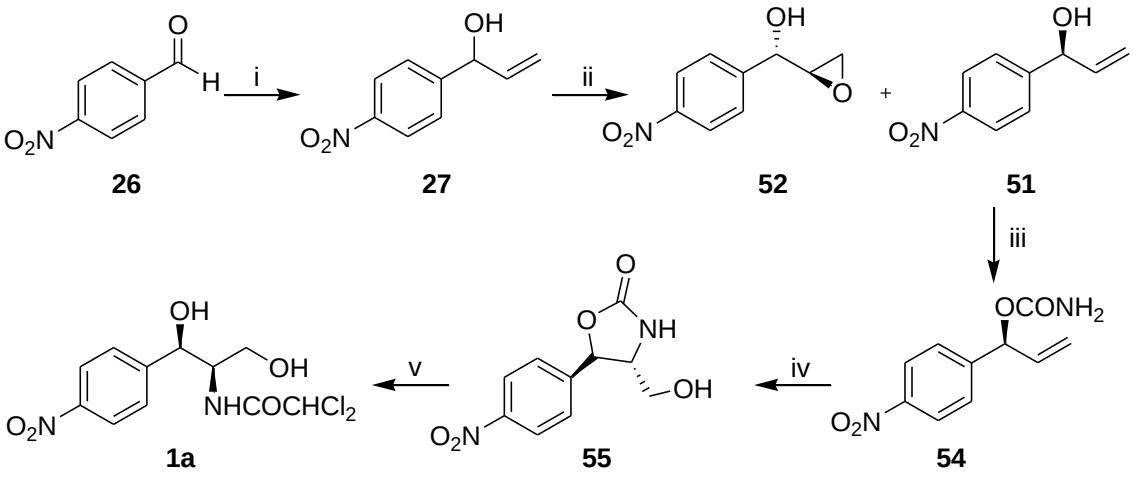


Scheme 14: Representative examples of tethered aminohydroxylation

1.5 Results and Discussion

1.5.1 Enantioselective synthesis (-)-chloramphenicol

The synthesis of (-)-chloramphenicol (**1a**), wherein Sharpless asymmetric epoxidation[35b] constitutes a key step for the introduction of chirality is presented in **Scheme 15**.



Scheme 15: (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.

Our synthesis of (−)-chloramphenicol (**1a**) (**Scheme 15**) was started with the reaction of 4-nitrobenzaldehyde **26** with divinylzinc[39] to give 1-(4-nitrophenyl)allyl alcohol **27** in 68% yield. The formation of allylic alcohol **27** was confirmed by the appearance of multiplets at δ 5.35 integrating for three protons and δ 5.98 integrating for one proton in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed typical signals at δ 74.4, 116.67 & 139.05 corresponding to benzylic and olefinic carbons respectively (**Fig. 5**). Allylic alcohol **27** was then subjected to Sharpless asymmetric epoxidation under kinetic resolution conditions[35b] using the naturally occurring (+)-diisopropyl tartrate [(+)-DIPT]

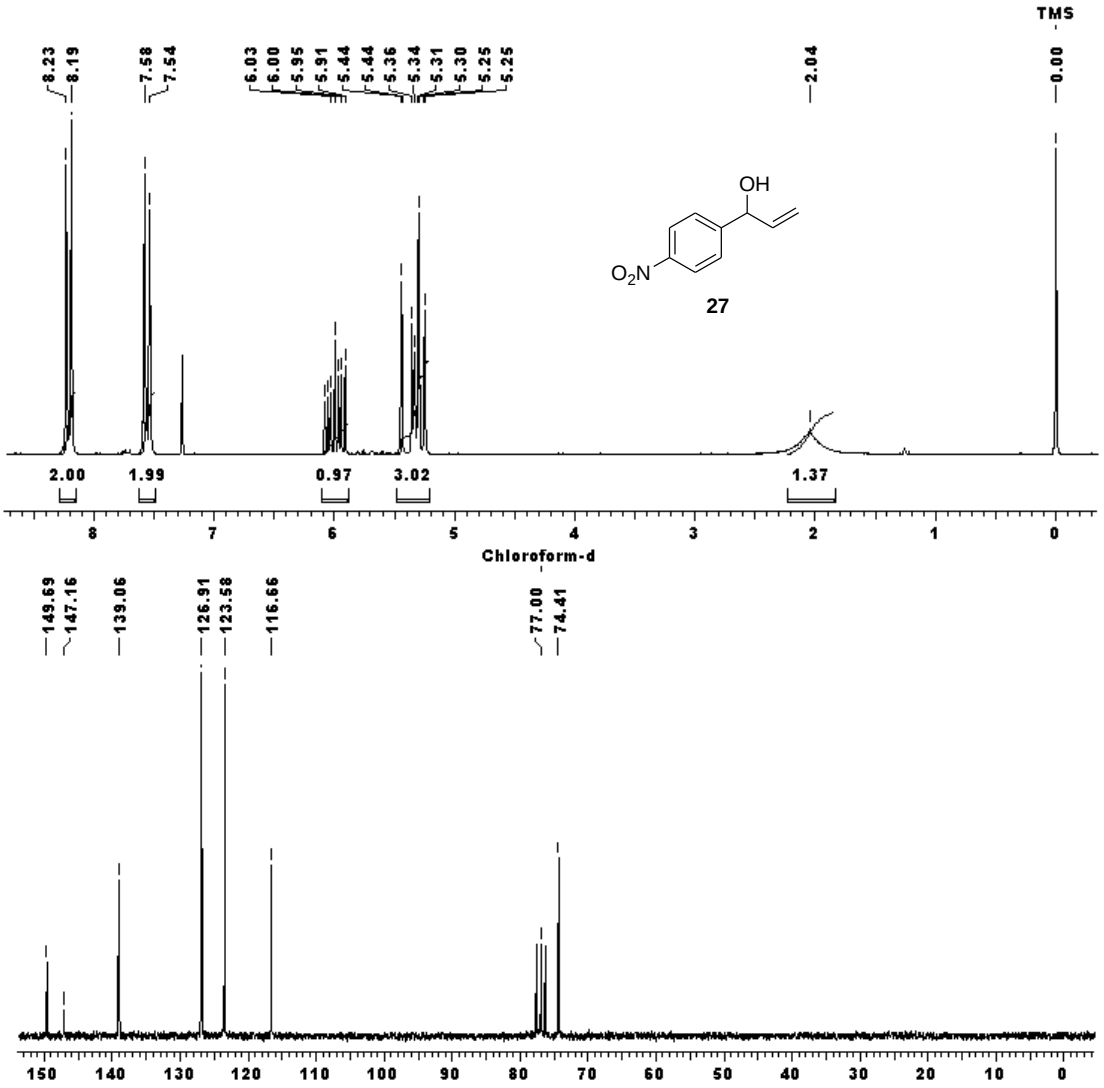


Fig. 5: ^{1}H and ^{13}C NMR spectra of 27

to furnish the corresponding chiral allylic alcohol, 1-(*S*)-4-(nitrophenyl)-2-propen-1-ol, **51** as a pale yellow amorphous solid {mp: 48–49 ºC and $[\alpha]^{25}_{D}$ = +41.3 (*c* 1, $CHCl_3$)} in 44% chemical yield and 98% ee along with the corresponding epoxide **52** in 49% yield. Both alcohol **51** and epoxide **52** were easily separated by column chromatographic purification. The optical purity of **51** was determined by ^{1}H NMR analysis of the corresponding Mosher's ester **53** (**Fig. 6**) (see experimental section for details).

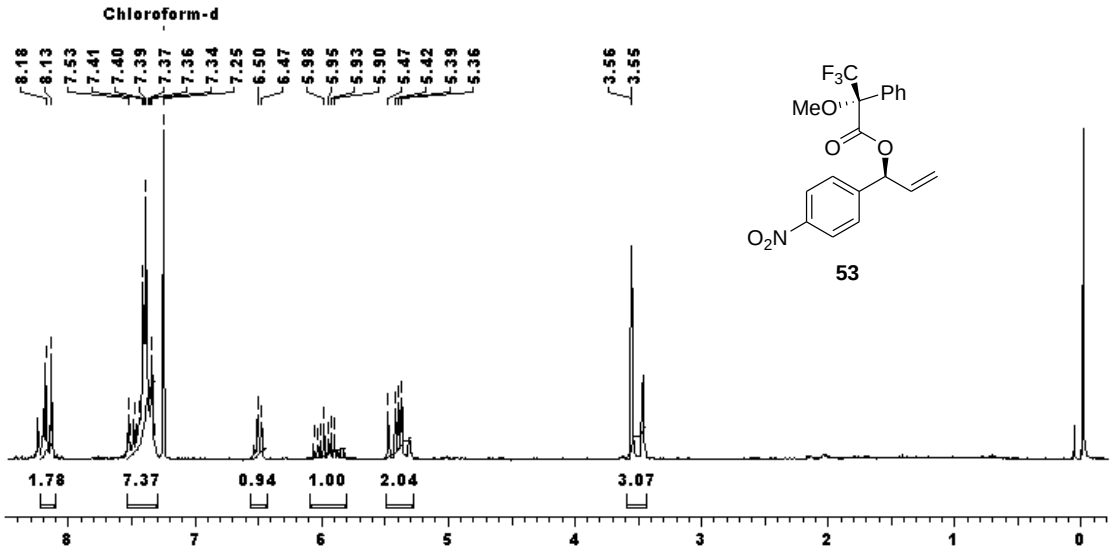


Fig. 6: ^{1}H NMR spectrum of Mosher's ester 53

Alcohol **51** was then treated with trichloroacetyl isocyanate[40] in CH_2Cl_2 to give the corresponding isocyanate, which on treatment with K_2CO_3 and methanol in the presence of H_2O gave the carbamate **54** in 90% yield. The ^{1}H NMR spectrum of carbamate **54** showed signals at δ 5.35 (m), 5.89-6.06 (m), and 6.21-6.24 (m) corresponding to the methine and olefinic protons respectively. Its ^{13}C NMR spectrum displayed typical peaks at δ 75.78, 118.22, 135.20 and 155.59 corresponding to the methine, olefinic and carbonyl carbons respectively (**Fig. 7**). The IR spectrum of **54** showed a characteristic strong band at 1724 cm^{-1} indicative of the presence of carbonyl group.

The carbamate **54** thus obtained was converted into oxazolidinone **55** by a tethered aminohydroxylation protocol[36b] using *tert*-butyl hypochlorite as the oxidant in the presence of potassium osmate, 0.08M NaOH, diisopropyl ethylamine and propan-1-ol as the solvent. The reaction proceeded smoothly to furnish the protected aminoalcohol **55** as a single isomer with complete regiocontrol and excellent *syn* selectivity (*syn:anti* >20:1, determined by ^{1}H NMR analysis) giving 69% yield.

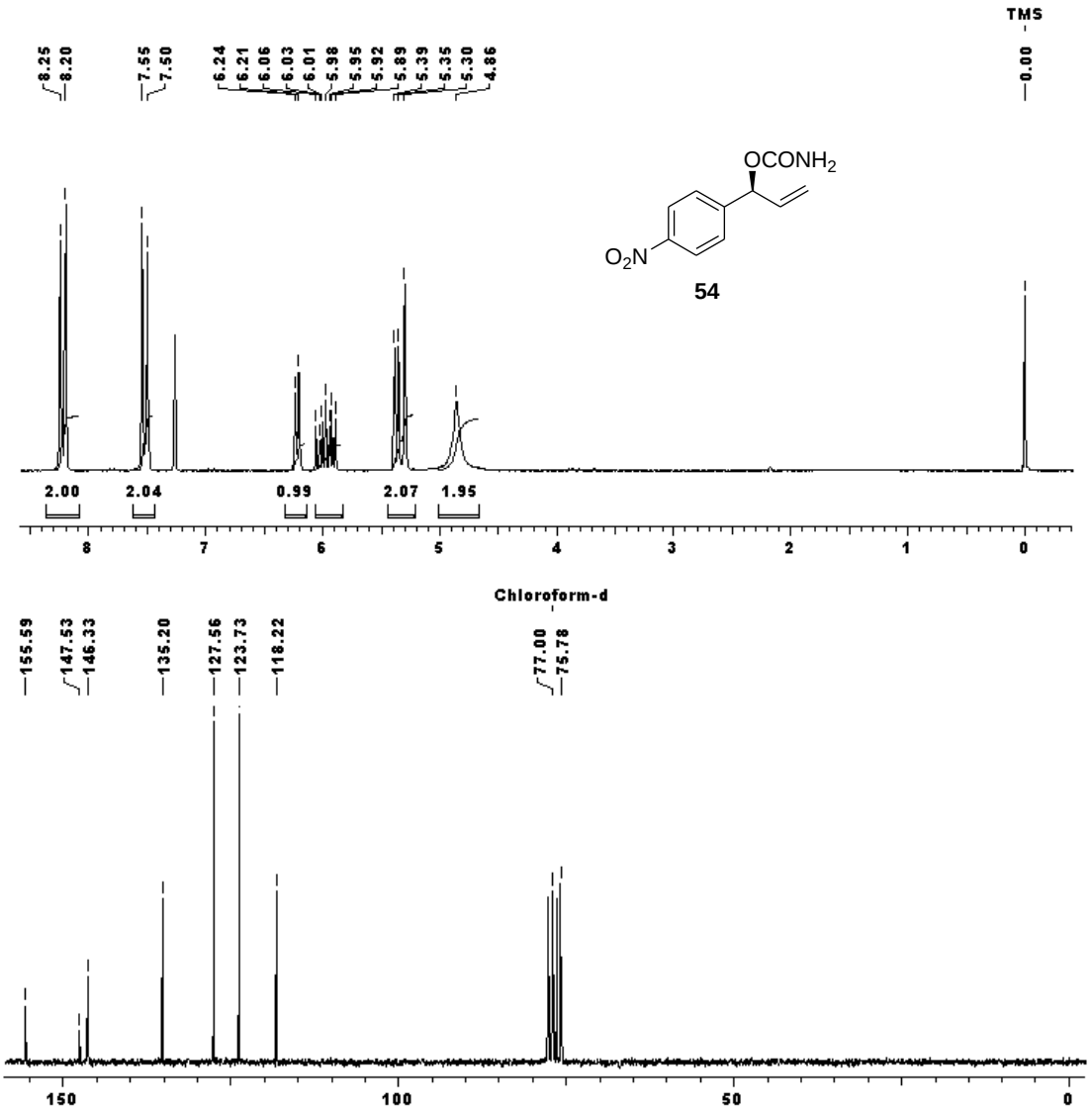


Fig. 7: ^{1}H and ^{13}C NMR spectra of carbamate 54

The formation of oxazolidinone moiety in **55** was confirmed by the appearance of a broad peak at δ 6.97 due to the typical oxazolidinone ring NH proton in its ^{1}H NMR spectrum. A characteristic signal at δ 158.32 confirms the presence of oxazolidinone carbonyl in its ^{13}C NMR spectrum (**Fig. 8**).

The oxazolidinone **55** was then hydrolyzed using 1N NaOH in methanol[18] to furnish the crude amino alcohol, which was taken in methyl dichloroacetate[6,18] and heated at 90 °C

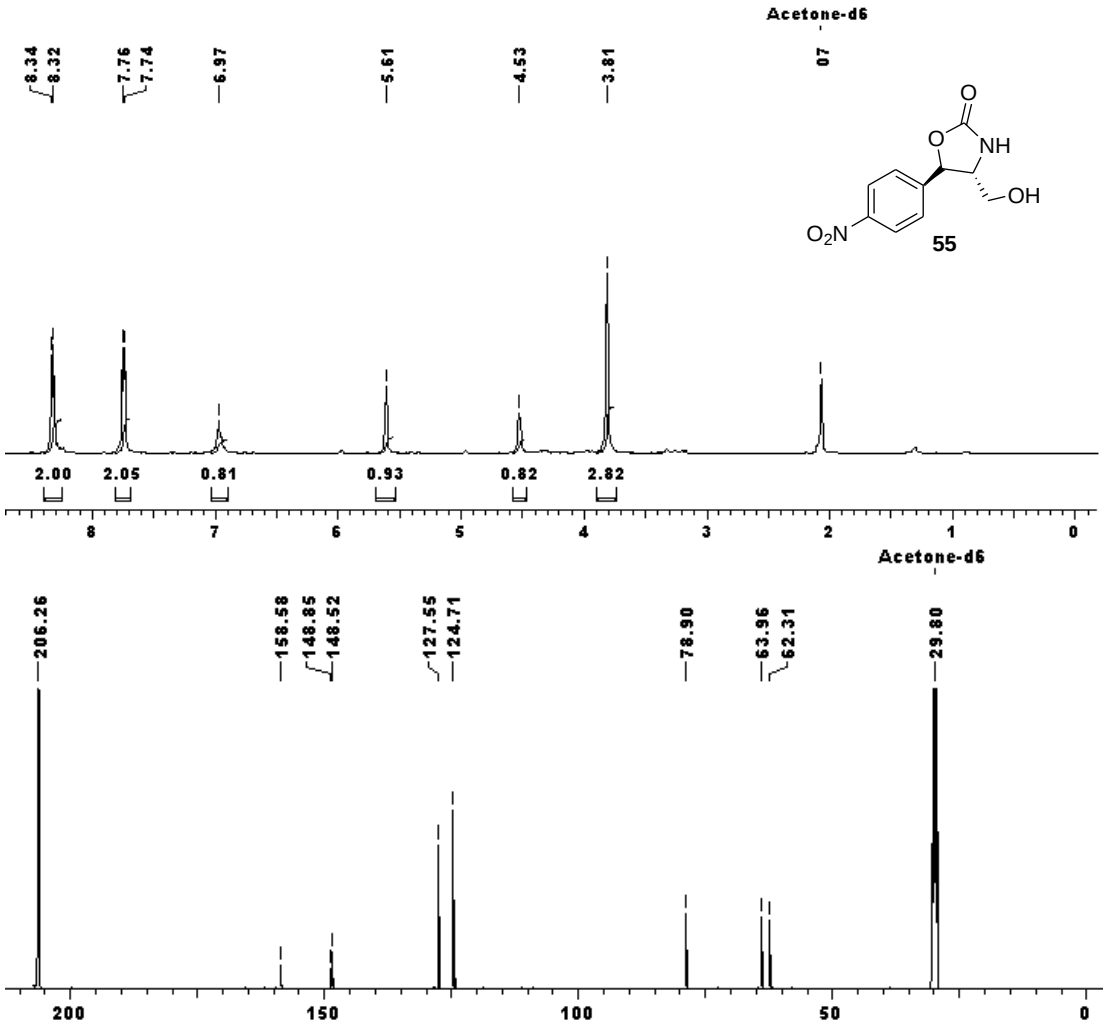


Fig. 8: ^{1}H and ^{13}C NMR spectra of oxazolidinone 55

for 3h to give (-)-chloramphenicol **1a** in 78% yield and 98% ee. The ee of (-)-chloramphenicol (**1a**) 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.[41] $[\alpha]^{23}_{D}$ −25.5 (*c* 1, EtOAc)]}. A singlet at δ 6.47 integrating for one proton indicated the presence of CH of NHCO**CH**Cl_2 which was further ascertained by the presence of 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**OCHCl_2) in its ^{13}C

NMR spectrum. The IR spectrum of **1a** displayed characteristic strong band above 3000 cm^{-1} indicating the presence of -OH and -NH groups.

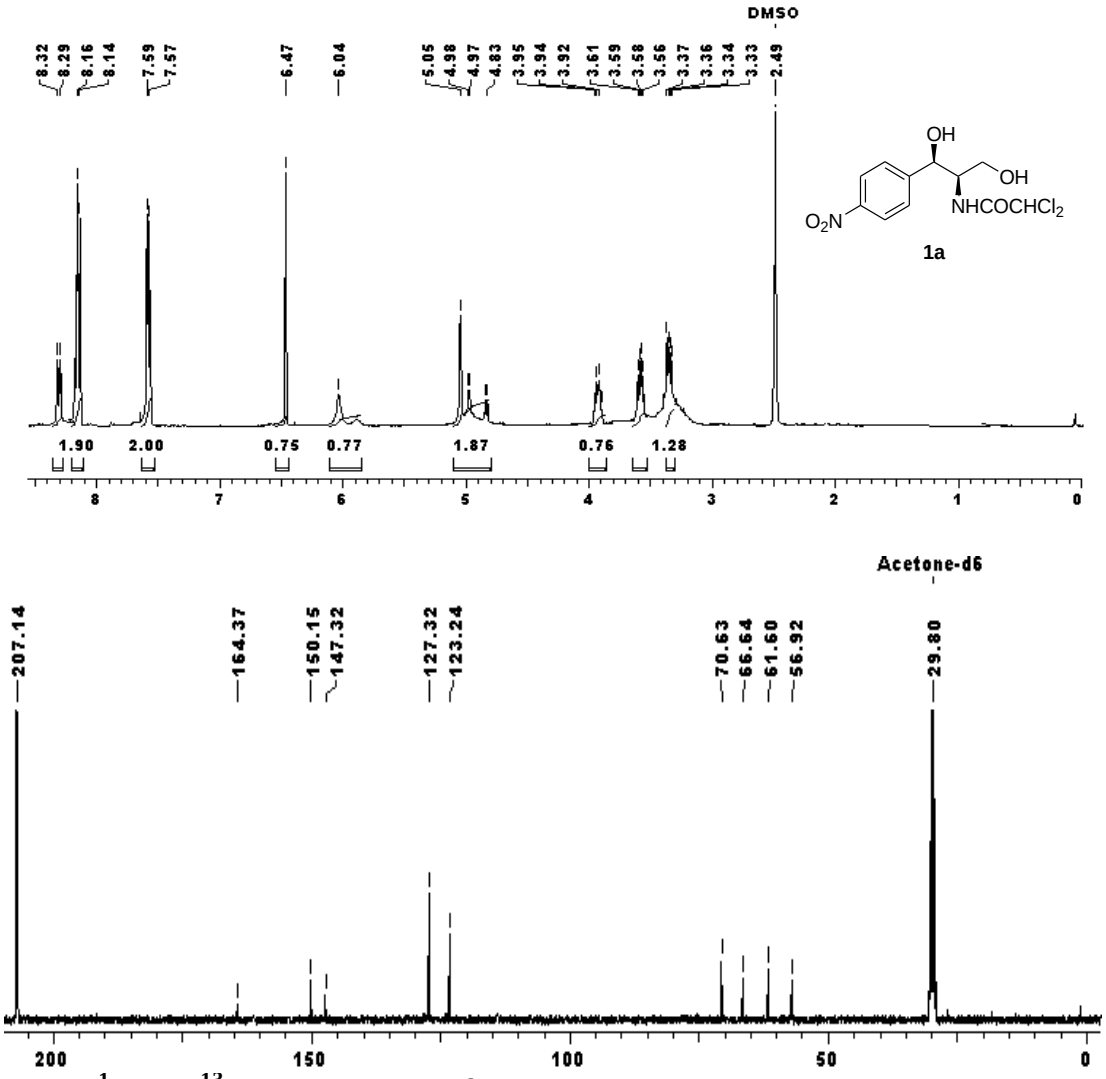
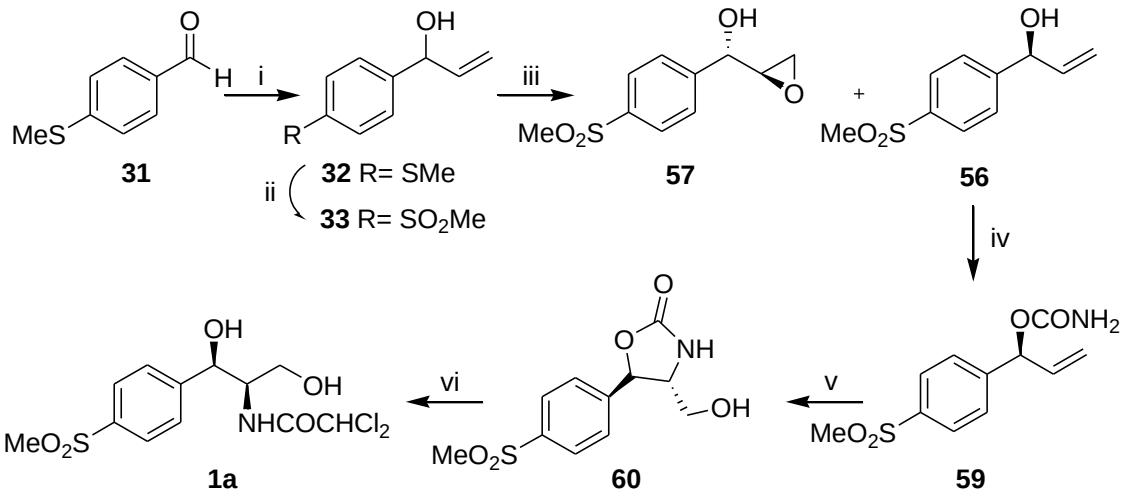


Fig. 9: ^{1}H and ^{13}C NMR spectra of (-)-chloramphenicol 1a

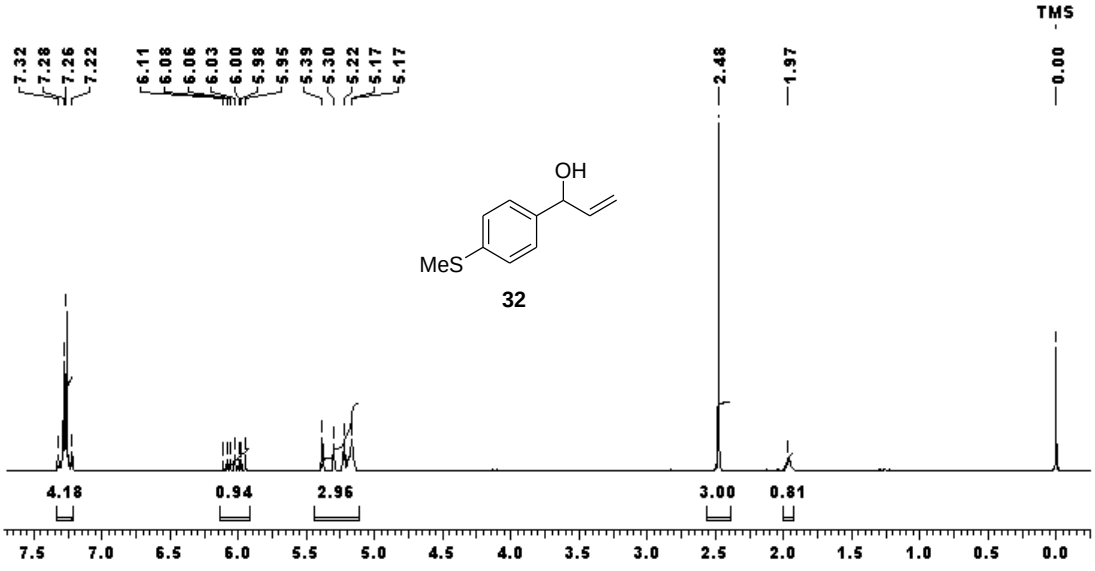
1.5.2 Enantioselective synthesis (+)-thiamphenicol

The synthesis of (+)-thiamphenicol (**1b**), wherein Sharpless asymmetric epoxidation[35b] constitutes a key step for the introduction of chirality is presented in **Scheme 16**. Commercially available 4-(methylthio)benzaldehyde **31** was converted to the allyl alcohol **32** using vinylmagnesium bromide in THF.[21] Two signals at δ 5.17-5.39 (m, 3H)



Scheme 16: (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.

and 5.95-6.11 (m, 1H) in the ^{1}H NMR spectrum of **32** were attributed to the olefinic and benzylic protons. It was further substantiated by the appearance of the corresponding carbon signals at δ 74.60, 114.97 and 139.99 in its ^{13}C NMR spectrum (**Fig. 10**).



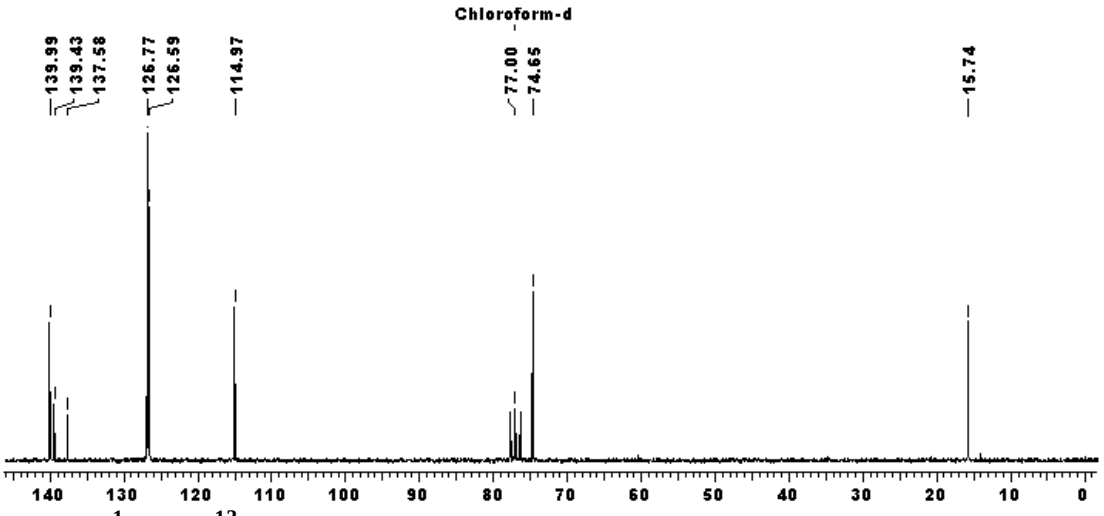
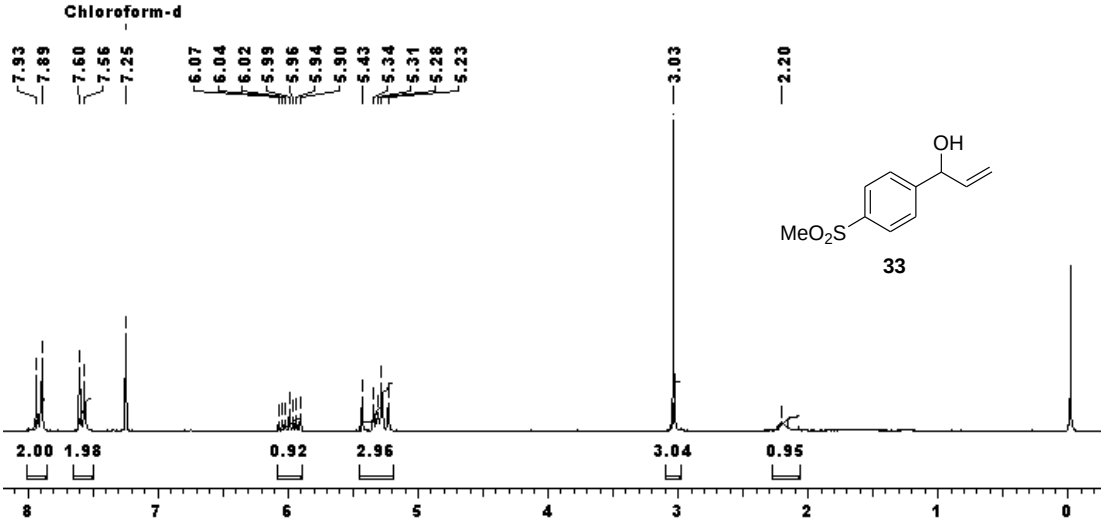


Fig. 10: ^{1}H and ^{13}CNMR spectra of 32

The thioether **32** was then oxidized using oxone[42] to give the corresponding sulfonyl ester **33** in 95% yield. The formation of sulfonyl ester **33** was confirmed by the appearance of a singlet at δ 3.05 integrating for three protons ($-SO_2C\mathbf{H}_3$) in its ^{1}H NMR spectrum and a typical signal corresponding to the methyl carbon ($-SO_2\mathbf{C}H_3$) appeared at δ 44.39 in its ^{13}C NMR spectrum (**Fig. 11**). The IR spectrum of sulfonyl ester **33** displayed typical sulfone absorption bands at 1149 and 1303 cm^{-1}.



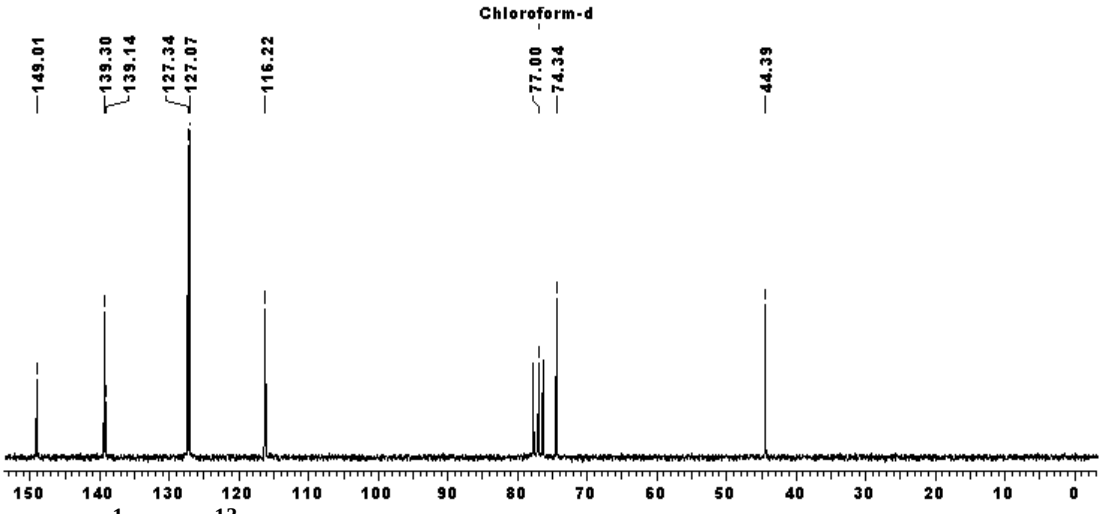


Fig. 11: ^{1}H and ^{13}CNMR spectra of 33

Allylic alcohol **33** was then subjected to Sharpless asymmetric epoxidation using (+)-diisopropyl tartrate under kinetic resolution conditions[35b] to furnish the chiral alcohol **56** in 43% yield and 98% ee along with the epoxide **57** in 48% yield. Both alcohol **56** and epoxide **57** were easily separated by column chromatography. The optical purity of the chiral allylic alcohol **56** was determined by ^{1}H NMR analysis of the corresponding Mosher's ester **58**, (**Fig. 12**) (see experimental section for details)**.**

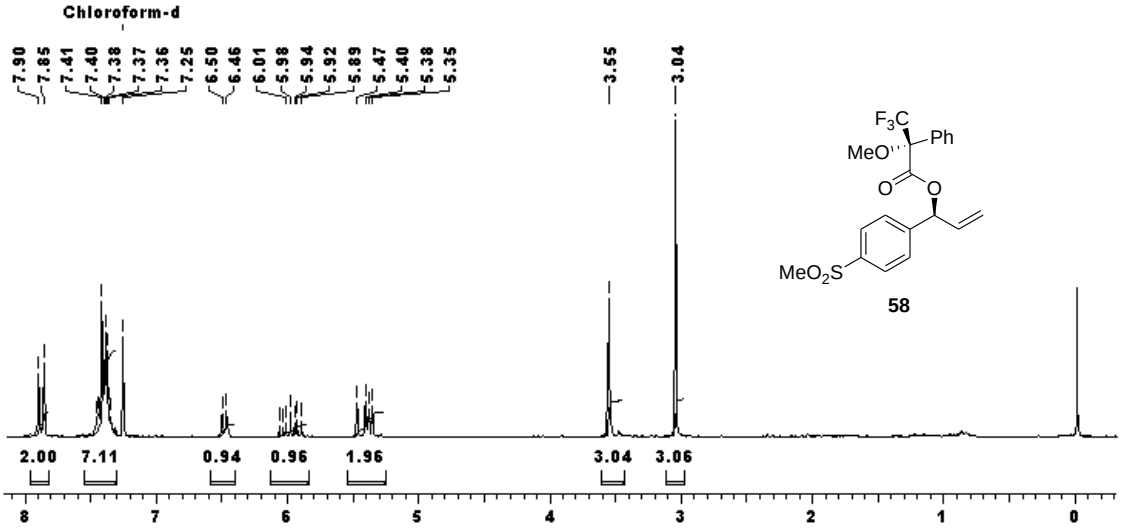


Fig. 12: ^{1}H NMR spectrum of Mosher's ester 58

Alcohol **56** was then treated with trichloroacetyl isocyanate[40] in CH_2Cl_2 to give the corresponding isocyanate, which on treatment with K_2CO_3 and methanol in the presence of H_2O gave the carbamate **59** in 86% yield. Two broad peaks at δ 6.61 and 6.84 integrating for one proton each in its ^1H NMR spectrum confirmed the formation of carbamate **59**. It was further ascertained by the appearance of a typical signal at δ 155.75 corresponding to the carbonyl carbon, while the terminal olefinic carbons have exhibited signals at δ 117.00 and 136.97 in its ^{13}C NMR spectrum (**Fig. 13**).

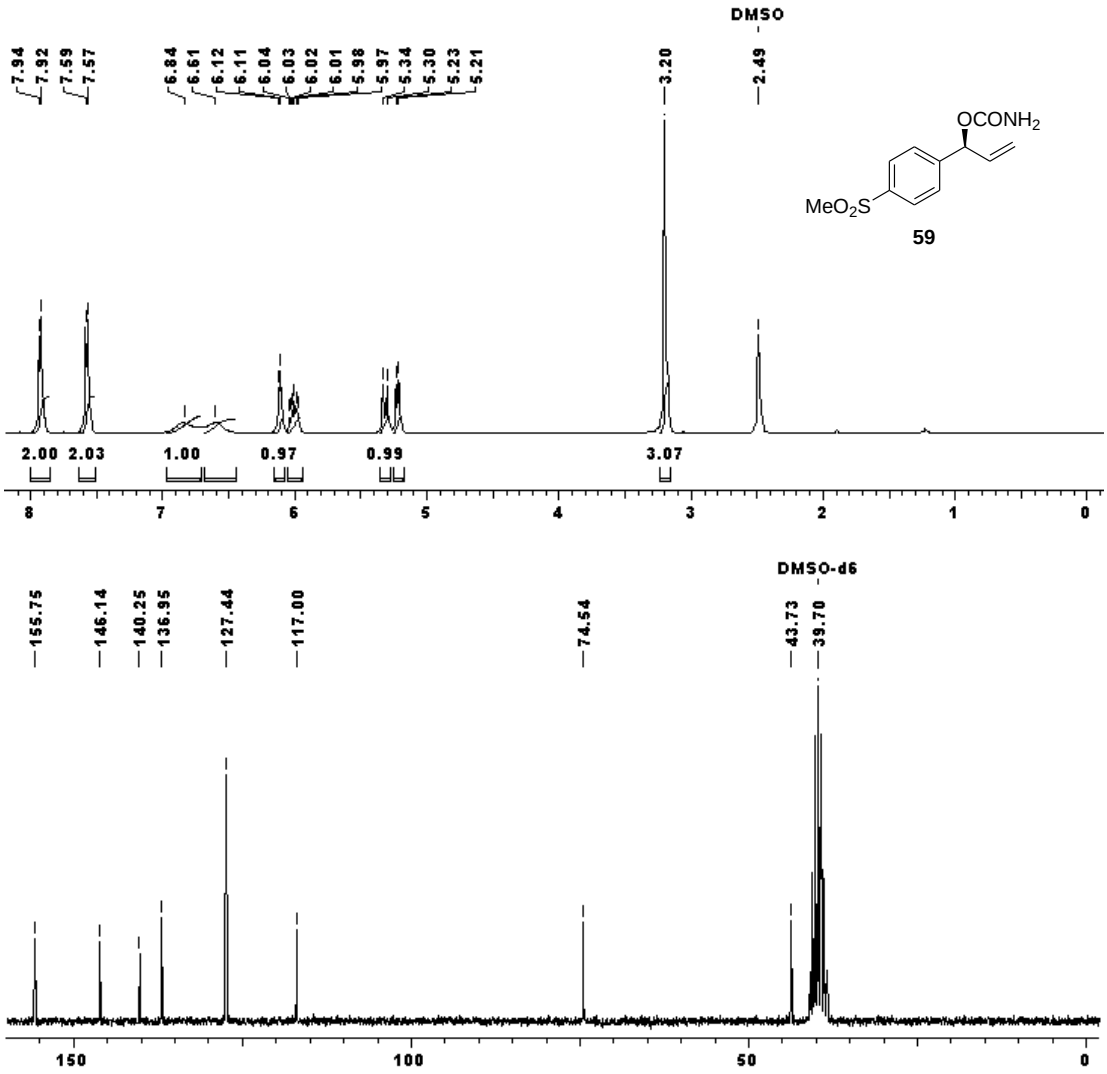


Fig. 13: ^1H and ^{13}C NMR spectra of carbamate 59

Carbamate **59** thus obtained was then converted into oxazolidinone **60** by employing tethered aminohydroxylation protocol[36b] using *tert*-butyl hypochlorite as the oxidant in the presence of potassium osmate, 0.08M NaOH, diisopropyl ethylamine and propan-1-ol as the solvent. The desired isomer of oxazolidinone **60** was obtained with high stereoselectivity (s*yn:anti* >20:1, determined by ^{1}H NMR analysis) giving 65% yield. The ^{1}H and ^{13}C NMR spectra of **60** confirmed the disappearance of olefinic protons and the appearance of oxazolidinone carbonyl moiety, which showed a signal at δ 158.09 in its ^{13}C NMR spectrum (**Fig. 14**).

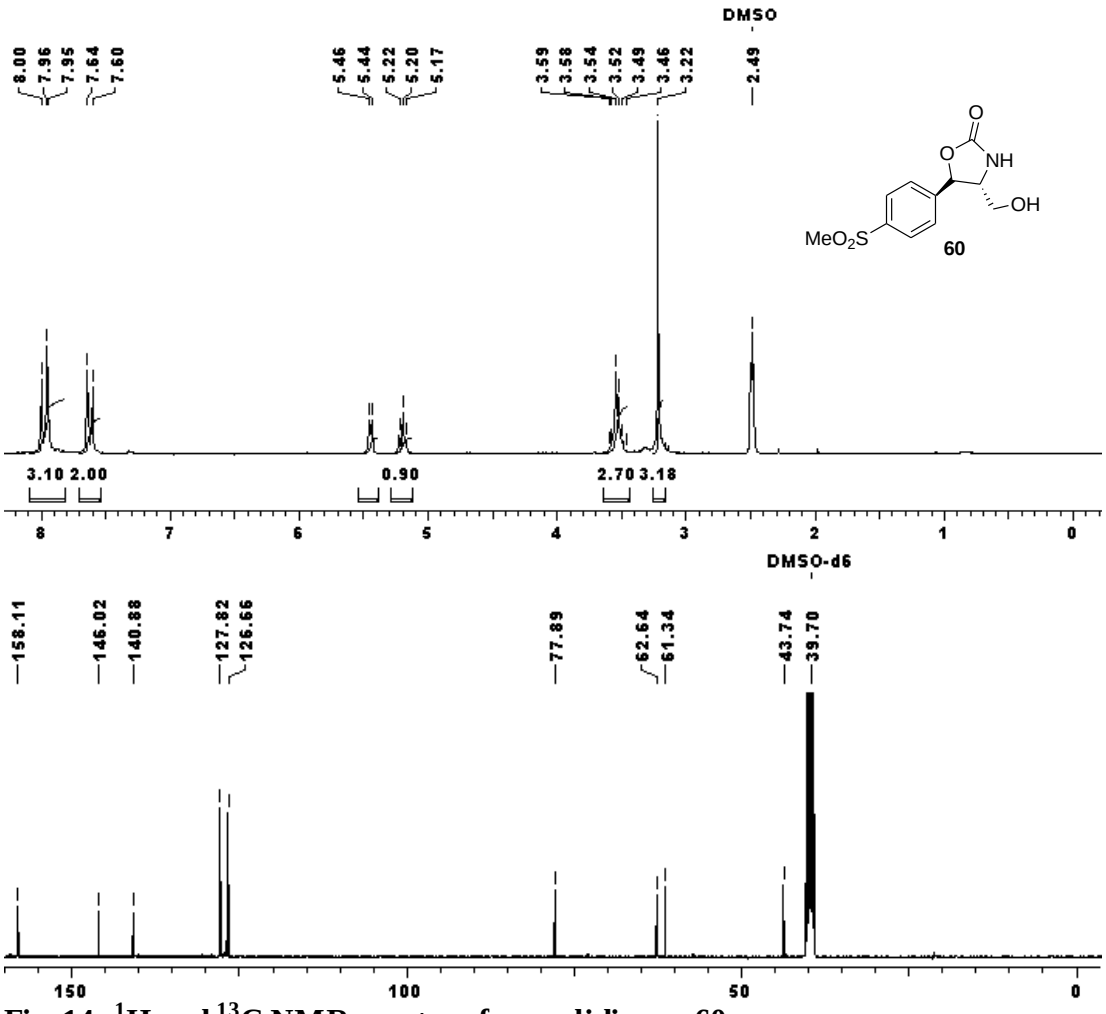


Fig. 14: ^{1}H and ^{13}C NMR spectra of oxazolidinone 60

Finally, hydrolysis of **60** with 1N NaOH in methanol[18] followed by its treatment with methyl dichloroacetate[6,18] gave the final product thiamphenicol **1b** in 77% yield and 98% ee. The ee of (+)-thiamphenicol (**1b**) 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.[5] $[\alpha]^{25}_D$ +12.9 (*c* 1, EtOH)}. A singlet at δ 6.41 integrating for one proton indicated the presence of CH of NHCO**CH**Cl_2 which was further ascertained by the appearance of signals at δ 57.99 (-**C**HNH-), 61.66 (-**C**H_2OH), 66.51 (-CO**C**HCl_2), 70.28(-**C**HOH-) and 164.37 (NH**C**OCHCl_2) in its ^{13}C NMR spectrum (**Fig. 15**). The IR spectrum of **1b** displayed strong absorption band above 3000 cm^{-1} indicating the presence of -OH and -NH groups.

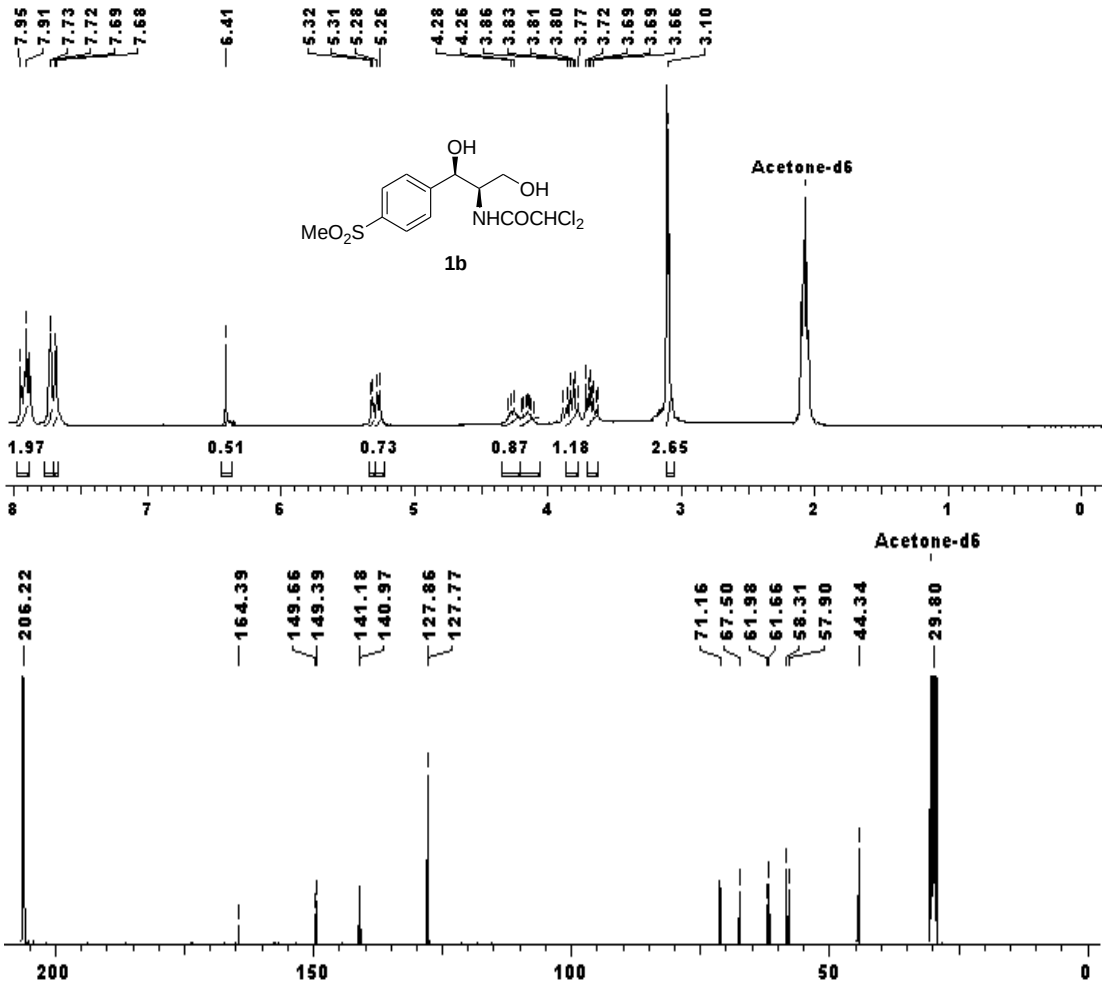


Fig. 15: ^{1}H and ^{13}C NMR spectra of (+)-thiamphenicol 1b

1.6 Conclusion

In conclusion, we have achieved an efficient syntheses of (-)-chloramphenicol (**1a**) (overall yield 29%, 98% ee) and (+)-thiamphenicol (**1b**) (overall yield 34%, 98% ee). Both the syntheses involved tethered aminohydroxylation and Sharpless asymmetric epoxidation as the key chiral inducing reactions. The major advantages of these syntheses are the use of naturally occurring (+)-diisopropyl tartrate for the kinetic resolution and tethered aminohydroxylation for the induction of second chiral centre in the molecule in a highly diastereoselective fashion (dr = 98:2).

1.7 Experimental Section

1-(4-Nitrophenyl)-2-propen-1-ol (27)

To a stirred solution of vinyl magnesium bromide [prepared from vinyl bromide (8.49 g, 79.4 mmol) and magnesium (1.93 g, 79.4 mmol)] in THF (90 mL), freshly fused $ZnCl_2$ (5.40 g, 39.7 mmol) dissolved in THF (30 mL) was added at 0 ºC under nitrogen atmosphere. This solution was stirred at 55 ºC for 18 h, after which it was cooled to 10 ºC and dry ether (150 mL) added and stirred for 10 min. The reaction mixture was allowed to settle for 30 min. The supernatant liquid was transferred through a canula to another flask. This solution was allowed to cool to -78 ºC, then *p*-nitrobenzaldehyde **26** (1.5 g, 9.92 mmol) in THF (20 mL) was added over a period of 15 min. The reaction mixture was allowed to warm to room temperature and stirring continued for 10 h. The reaction mixture was then quenched at -20 ºC by the addition of aq. ammonium chloride. The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic fractions collected and washed with water and brine solution, then dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by

column chromatography using petroleum ether/EtOAc (8:2) to afford the allylic alcohol **27** (1.21 g) as a pale yellow amorphous solid.

Yield: 68%; **mp**: 48-49 ºC; **IR** ($CHCl_3$, cm^{-1}): 3433, 2858, 1606, 1519, 1348, 1217, 1108, 1041, 989, 854, 757; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.04 (br s, 1H), 5.25-5.45 (m, 3H), 5.91-6.05 (m, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 74.41, 116.66, 123.58, 126.91, 139.06, 147.16, 149.69; **Analysis:** **$C_9H_9NO_3$** requires C, 60.33; H, 5.06; N, 7.82; found: C, 60.55; H, 5.21; N, 7.55%.

1-(*S*)-(4-Nitrophenyl)-2-propen-1-ol (51)

To a stirred suspension of powdered 4 Å molecular sieves (1.5 g) in dry CH_2Cl_2 (25 mL), titanium tetraisopropoxide (1.27 g, 4.47 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled to -20 ºC and (+)-diisopropyl tartrate (1.25 g, 5.36 mmol) added and stirred for 10 min, after which nitro allylic alcohol **27** (0.8 g, 4.5 mmol) dissolved in CH_2Cl_2 (20 mL) was added and stirred at –20 ºC for 30 min. To the above solution, *tert*-butyl hydroperoxide (0.22 g, 2.5 mmol) dissolved in toluene was added and stirred at -20 ºC for 14 h. After completion of half of the reaction (monitored by TLC), the reaction mixture was quenched with 10% aqueous solution of tartaric acid (25 mL), after which stirring was continued for 1 h at -20 ºC and 2 h at room temperature. The organic layer was separated, washed with water and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with ether (75 mL) and stirred with 1M NaOH (25 mL) for 1 h at 0 ºC. The organic layer was then separated, washed with brine solution, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum

ether/EtOAc (8:2) to afford the allylic alcohol **51** (0.35 g) as a pale yellow amorphous solid.

Yield: 44%; **mp**: 48-49 ºC; **[α]$^{25}_{D}$**: +41.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3433, 2858, 1606, 1519, 1348, 1217, 1108, 1041, 989, 854, 757; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.04 (br s, 1H), 5.25-5.45 (m, 3H), 5.91-6.05 (m, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 74.41, 116.66, 123.58, 126.91, 139.06, 147.16, 149.69; **M/S**: 179, 162, 150, 132, 115, 105, 91, 77, 55, 51; **Analysis: $C_9H_9NO_3$** requires C, 60.33; H, 5.06; N, 7.82; found: C, 60.55; H, 5.21; N, 7.55%.

(1*R*,2*S*)-1-(4-Nitrophenyl)oxiranemethanol (52)

Yield: 49%; **mp**: 74-75 ºC; **[α]$^{25}_{D}$**: +60.8 (*c* 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45 (br s, 1H), 2.72 (dd, *J* = 4.2, 4.9 Hz, 1H), 2.88 (dd, *J* = 2.6, 4.9 Hz, 1H), 3.20 (ddd, *J* = 2.6, 3.0, 4.2 Hz, 1H), 5.01 (br d, *J* = 3.0 Hz, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J*= 9.0 Hz, 2H).

Mosher's ester of 1-(*S*)-(4-nitrophenyl)-2-propen-1-ol (53)

A two-neck 10 mL flask with septum was charged with (44 mg, 0.21 mmol) *N*,*N*'-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool to 0 ºC for 10 min and a solution of alcohol **51 (**32 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 ºC for additional 1 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over anhyd. Na_2SO_4

and then concentrated under reduced pressure to give Mosher's ester **53** (53 mg) as a thick syrup.

Yield: 70%; **[α]$^{25}_{D}$**: +39.5 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3158, 2952, 2927, 2850, 2250, 1753, 1606, 1519, 1495, 1348, 1268, 1242, 1217, 1153, 1122, 1015, 957, 911, 735, 650; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.55 (s, 3H), 5.36-5.47 (m, 2H), 5.90-6.06 (m, 1H), 6.48 (d, *J* = 6.6 Hz, 1H), 7.32-7.53 (m, 7H), 8.15 (d, *J* = 9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.56, 77.06, 119.95, 123.86, 127.24, 127.68, 128.45, 129.79, 132.04, 133.87, 134.09, 144.53, 147.98, 165.27; **Analysis: $C_{19}H_{16}F_3NO_5$** requires C, 57.72; H, 4.08; N, 3.54; found: C, 57.94; H, 3.82; N, 3.21%.

1-(*S*)-(4-Nitrophenyl)allylcarbamate (54)

To a stirred solution of alcohol **51** (0.45 g, 2.5 mmol) in dichloromethane (12 mL) at 0 ºC was added dropwise trichloroacetyl isocyanate (0.36 mL, 3.0 mmol). The resulting solution was stirred for 2 h and then concentrated *in vacuo*. The residue was diluted with MeOH (13 mL), cooled to 0 ºC and a solution of potassium carbonate (1.04 g, 7.5 mmol) in H_2O (2.4 mL) was added. The resulting suspension was stirred at 0 ºC for 2h, then at room temperature for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with H_2O (50 mL) and brine (50 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography using petroleum ether/EtOAc (6:4) to give **54** (0.5 g) as a pale yellow crystalline solid.

Yield: 90%; **mp**: 101 ºC; **[α]$^{25}_{D}$**: +12.39 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3471, 3280, 3178, 1724, 1620, 1514, 1386, 1346, 1328, 1215, 925, 854, 756; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.86 (br s, 2H), 5.30-5.39 (m, 2H), 5.89-6.06 (m, 1H), 6.21-6.24 (m, 1H), 7.53

(d, *J* = 8.7 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 75.78, 118.22, 123.73, 127.56, 135.20, 146.33, 147.53, 155.59; **Analysis: $C_{10}H_{10}N_2O_4$** requires C, 54.05; H, 4.54; N, 12.62; found: C, 54.16; H, 4.20; N, 12.82%.

(5*R*,6*R*)-4-(Hydroxymethyl)-5-(4-nitrophenyl)-2-oxazolidinone (55)

A fresh aqueous solution of sodium hydroxide (0.08M, 0.9 equiv.) was prepared. All but a few drops of this was added in one portion to a stirred solution of the allylic carbamate **54** (0.22 g, 1.00 mmol) in propan-1-ol (12 mL). The solution was allowed to stir for 5 min, before freshly prepared *tert*-butyl hypochlorite (0.114 mL, 1.00 mmol) was added. The mixture was again allowed to stir for 5 min. To this was added diisopropyl ethylamine (5 mol%) in one portion. The mixture was allowed to stir for a further 5 min before the final addition of a solution of potassium osmate (4 mol%) in the remainder of the sodium hydroxide solution made earlier. The reaction was monitored by TLC and halted when no further change was detected. The reaction was quenched by the addition of sodium sulfite (500 mg), and allowed to stir for 30 mins. The mixture was extracted with ethyl acetate (2 × 50 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica using petroleum ether/EtOAc (4:6) to give oxazolidinone **55** (0.16 g) as a gum.

Yield: 69%; **$[\alpha]^{25}_D$**: -4.08 (*c* 1.1, EtOH); **IR** ($CHCl_3$, cm^{-1}): 3351, 2944, 2832, 2523, 1755, 1607, 1527, 1450, 1416, 1351, 1112, 666; **^{1}H NMR** (200 MHz, acetone-d_6): δ 3.81(m, 3H), 4.53 (s, 1H), 5.61 (m, 1H), 6.97 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 8.33 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.05, 63.70, 78.64, 124.45, 127.29,

148.26, 148.60, 158.32; **Analysis: $C_{10}H_{10}N_2O_5$** requires C, 50.42; H, 4.23; N, 11.77; found: C, 50.26; H, 4.56; N, 11.59%.

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

A solution of 1 N NaOH was prepared in methanol. 10 mL of the above solution was added to oxazolidinone **55** (0.95 g, 0.4 mmol) and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate concentrated in vacuum. The crude compound was taken 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 (3:7) to give the product **1a** (0.1 g) as a white amorphous solid.

Yield: 78%; **mp**: 151-152 ºC [lit.[41] **mp**:149.7-150.7 ºC]; **$[\alpha]^{25}_D$**: -24.9 (*c* 1, EtOAc) [lit.[41] **$[\alpha]^{23}_D$**: -25.5 (*c* 1, EtOAc)]; **IR** ($CHCl_3$, cm^{-1}): 3420, 3020, 2929, 1686, 1604, 1523, 1454, 1403, 1348, 1216, 1049, 850; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.33-3.40 (m, 1H), 3.56-3.61 (m, 1H), 3.90-3.95 (m, 1H), 4.83-5.05 (m, 2H), 6.04 (br s, 1H), 6.47 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 8.15 (d, *J* = 8.3 Hz, 2H), 8.31 (d, *J* = 9 Hz, 1H); **^{13}C NMR** (100 MHz, acetone-d_6): δ 56.92, 61.60, 66.64, 70.63, 123.24, 127.32, 147.32, 150.15, 164.37; **M/S**: 323, 242, 209, 179; **Analysis: $C_{11}H_{12}Cl_2N_2O_5$** requires C, 40.89; H, 3.74; N, 8.68; found: C, 40.98; H, 3.92; N, 8.36%.

1-(4-Methylsulfanylphenyl)-2-propen-1-ol (32)

To a stirred suspension of magnesium (7.1 g, 296 mmol) in THF (75 mL), vinyl bromide (15.82 g, 147.81 mmol) in THF (45 mL) was added at 0 ºC under nitrogen atmosphere over a period of 15 min and the continued stirring at room temperature for a further 30 min. The reaction mixture was cooled to 0 ºC and 4-(methylthio)benzaldehyde **31** (7.5 g,

49.26 mmol) dissolved in THF (75 mL) added over a period of 10 min. After the addition was complete, the reaction mixture was allowed to return to room temperature and stirring continued for another 2 h. The reaction mixture was quenched by the addition of aqueous ammonium chloride and extracted with ethyl acetate (3 × 100 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. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford alcohol **32** (8.5 g) as a thick syrup.

Yield: 96%; **IR** ($CHCl_3$, cm^{-1}): 3398, 3078, 2981, 2920, 1639, 1598, 1492, 1431, 1404, 1219, 1093, 989, 927, 815; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.97 (br s, 1H), 2.48 (s, 3H), 5.17-5.39 (m, 3H), 5.95-6.11 (m, 1H), 7.24 (d, *J* = 8.7Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.74, 74.6, 114.9, 126.5, 126.7, 137.5, 139.4, 139.9; **M/S**: 180, 151, 137, 109, 91, 77, 55, 45; **Analysis: $C_{10}H_{12}OS$** requires C, 66.63; H, 6.71; S, 17.79; found: C, 66.79; H, 6.89; S, 17.55%.

1-(4-Methylsulfonylphenyl)-2-propen-1-ol (33)

To a vigorously stirred solution of sulfide **32** (3.78 g, 21 mmol) in THF (20 mL), MeOH (20 mL), and H_2O (20 mL) at 0 ºC was added oxone (36 g, 59 mmol) portionwise. After 5 min at 0 ºC, the white suspension was warmed to room temperature and stirred for 30 min. The reaction was poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (6:4) to give sulfone **33** (4.25 g) as a white amorphous solid.

Yield: 95%; **mp**: 56.5-57.5 ºC; **IR** ($CHCl_3$, cm^{-1}): 3481, 3020, 2927, 2360, 1639, 1598, 1407, 1303, 1149, 1087, 958, 761; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.20 (br s, 1H), 3.03 (s, 3H), 5.23-5.43 (m, 3H), 5.99 (m, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.39, 74.34, 116.2, 127.1, 127.3, 139.1, 139.3, 149.0; **Analysis: $C_{10}H_{12}O_3$ S** requires C, 56.58; H, 5.69; S, 15.11; found: C, 56.79; H, 5.86; S, 14.89%.

1-(*S*)-(4-Methylsulfonylphenyl)-2-propen-1-ol (56)

To a stirred suspension of powdered 4 Å molecular sieves (7 g) in dry CH_2Cl_2 (75 mL), titanium tetraisopropoxide (3.12 g, 11 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled to -20 ºC and (+)-diisopropyl tartrate (3.1 g, 13.2 mmol) added and stirred for 10 min, after which allyl alcohol **33** (2.3 g, 11 mmol) dissolved in CH_2Cl_2 (60 mL) was added and stirred at -20 ºC for about 30 min. To the above solution *tert*-butyl hydroperoxide (0.59 g, 6.6 mmol) dissolved in toluene was added and stirred at ⁻20 ºC for about 24 h. After completion of half of the reaction (monitored by TLC), the reaction mixture was quenched with 10% aqueous solution of tartaric acid (80 mL), after which stirring was continued for 1 h at -20 ºC and 2 h at room temperature. The organic layer was separated, washed with water and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with ether (250 mL) and stirred with 1M NaOH (100 mL) for about 1 h at 0 ºC. The organic layer was then separated, washed with brine solution, dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (6:4) to afford compound **56** (1 g) as white amorphous solid.

Yield: 43%; **mp**: 56.5-57.5 ºC; **[α]$^{25}_{D}$**: +28.38 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3481, 3020, 2927, 2360, 1639, 1598, 1407, 1303, 1149, 1087, 958, 761; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.20 (br s, 1H), 3.03 (s, 3H), 5.23-5.43 (m, 3H), 5.99 (m, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.39, 74.34, 116.2, 127.1, 127.3, 139.1, 139.3, 149.0; **M/S**: 212, 183, 157, 132, 115, 105, 91, 77, 55, 51; **Analysis: $C_{10}H_{12}O_3$ S** requires C, 56.58; H, 5.69; S, 15.11; found: C, 56.79; H, 5.86; S, 14.89%.

(1*R*,2*S*)-1-(4-Methylsulfonylphenyl)oxiranemethanol (57)

Yield: 48%; **[α]$^{25}_{D}$**: +47.3 (*c* 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.50 (br s, 1H), 2.73 (dd, *J* = 3.7, 5.2 Hz, 1H), 2.88 (dd, *J* = 3.0, 5.2 Hz, 1H), 3.02 (s, 3 H), 3.19 (m, 1H), 4.96 (br d, *J* = 3.0 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 8.3Hz, 2H).

Mosher's ester of 1-(*S*)-(4-methylsulfonylphenyl)-2-propen-1-ol (58)

A two-neck 10 mL flask with septum was charged with (44 mg, 0.21 mmol) *N*,*N*'-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 ºC for 10 min and a solution of alcohol **56** (38 mg, 0.179 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL) was done. This reaction mixture was then stirred at 0 ºC for additional one hour and then at room temperature for overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure to get Mosher's ester **58** (53 mg) as a thick syrup.

Yield: 70%; **[α]$^{25}_{D}$**: +42.5 (*c* 0.4, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3156, 3069, 2951, 2930, 2851, 2255, 1754, 1644, 1601, 1496, 1452, 1410, 1318, 1243, 1154, 1016, 957, 910, 737, 650; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.04 (m, 3H), 3.55 (s, 3H), 5.35-5.47 (m, 2H), 5.89-6.06 (m, 1H), 6.48 (d, *J* = 6.5 Hz, 1H), 7.35-7.45 (m, 7H), 7.87 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 44.44, 55.55, 77.31, 119.84, 127.24, 127.78, 128.43, 129.77, 131.99, 134.17, 140.73, 143.67, 147.44, 165.33; **Analysis: $C_{20}H_{19}F_3O_5S$** requires C, 56.07; H, 4.47; S, 7.48; found: C, 57.24; H, 4.24; S, 7.61.

1-(*S*)-(4-(Methylsulfonyl)phenyl)allylcarbamate (59)

To a stirred solution of alcohol **56** (1 g, 4.7 mmol) in dichloromethane (23 mL) at 0 ºC was added dropwise trichloroacetyl isocyanate (0.71 mL, 5.64 mmol). The resulting solution was stirred for 2 h and then concentrated *in vacuo*. The residue was diluted with MeOH (25 mL), cooled to 0 ºC and a solution of potassium carbonate (1.95 g, 14.1 mmol) in H_2O (5 mL) was added. The resulting suspension was stirred at 0 ºC for 2h, then at room temperature for 16 h. The reaction was concentrated *in vacuo*, diluted with H_2O (50 mL) and brine (50 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography using petroleum ether/EtOAc (4:6) to give carbamate **59** (0.99 g) as a colorless crystalline solid.

Yield: 86%; **mp**: 159 ºC; **[α]$^{25}_{D}$**: -10.23 (*c* 1, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3421, 3265, 2906, 1720, 1608, 1406, 1379, 1298, 1145, 1041, 947, 769; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.20 (s, 3H), 5.22 (d, *J* = 10.1 Hz, 1H), 5.32 (d, *J* = 16.9 Hz, 1H), 5.97-6.04 (m, 1H), 6.10 (d, *J* = 5.5 Hz, 1H), 6.61 (s, 1H), .6.84 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 43.73, 74.54, 117.00, 127.44,

127.50, 136.95, 140.25, 146.14, 155.75; **M/S**: 255, 195, 157, 128, 116; **Analysis:** $\mathbf{C_{11}H_{13}NO_4}$ requires C, 51.75; H, 5.13; N, 5.49; S, 12.56; found: C, 51.89; H, 5.27; N, 5.40; S, 12.29%.

(5*R*,6*R*)-4-(Hydroxymethyl)-5-(4-(methylsulfonyl)phenyl)-2-oxazolidinone (60)

A fresh aqueous solution of sodium hydroxide (0.08M, 0.9 equiv.) was prepared. All but a few drops of this was added in one portion to a stirred solution of the allylic carbamate **59** (0.76 g, 3 mmol) in propan-1-ol (30 mL). The solution was allowed to stir for 5 min, before freshly prepared *tert*-butyl hypochlorite (0.4 mL, 3 mmol) was added. The mixture was again allowed to stir for 5 min. To this was added di*iso*propyl ethylamine (5 mol%) in one portion. The mixture was allowed to stir for a further 5 min before the final addition of a solution of potassium osmate (4 mol%) in the remainder of the sodium hydroxide solution made earlier. The reaction was monitored by TLC and halted when no further change was detected. The reaction was quenched by the addition of sodium sulfite (1.5 g), and allowed to stir for 30 mins. The mixture was extracted with ethyl acetate (2 × 50 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica using petroleum ether/EtOAc (2:8) to give oxazolidinone **60** (0.53 g) as a pale yellow amorphous solid.

Yield: 86%; **mp**: 152 ºC; $\mathbf{[\alpha]^{25}_D}$: +9.74 (*c* 1.16, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3259, 3020, 2929, 2399, 2360, 1716, 1602, 1407, 1299, 1215, 1149, 1089, 1026, 954, 769; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.22 (s, 3H), 3.46-3.59 (m, 3H), 5.20 (t, *J* = 5.3 Hz, 1H), 5.45 (d, *J* = 3.9 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.95 (br s, 1H), 7.98 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 43.74, 61.34, 62.64, 77.89, 126.66, 127.82, 140.88,

146.02, 158.11; **Analysis: $C_{11}H_{13}NO_5S$** requires C, 48.69; H, 4.83; N, 5.17; S, 11.82; found: C, 48.52; H, 4.94; N, 5.33; S, 11.66%.

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

A solution of 1N NaOH was prepared in methanol. 10 mL of the solution is added to oxazolidinone **60** (0.14 g, 0.4 mmol) and stirred overnight at 25 ºC. The reaction mixture was filtered and the filtrate concentrated in vauum. The crude compound was taken 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 **1b** (0.11 g) as a white amorphous solid.

Yield: 77%; **mp**: 164-165 ºC [lit.[5] **mp**: 164.3-166.3 ºC]; **$[\alpha]^{25}_D$**: +12.5 (*c* 1, EtOH) [lit.[5] **$[\alpha]^{23}_D$**: +12.9 (*c* 1, EtOH)]; **IR** ($CHCl_3$, cm^{-1}): 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 3.10 (s, 3H), 3.63-3.72 (m, 1H), 3.77-3.89 (m, 1H), 4.10-4.20 (m, 1H), 4.28 (t, *J* = 4.7 Hz, 1H), 5.27 (d, *J* = 3.8 Hz, 1H), 5.31 (d, *J* = 2.4 Hz, 1H), 6.41 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, acetone-d_6): δ 44.34, 57.99, 62.08, 67.51, 71.21, 127.77, 127.85, 140.95, 149.59, 164.42; **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%.

1.8 References

1. (a) Nakanishi, K.; Goto, T.; Ito, S.; Natoro, S.; Nozoe, S. *Natural Products Chemistry*; Oxford University Press: Oxford, **1983**; Vol. 3; (b) Fuganti, G.; Grasselli, P.; Pedrocchi-Fantoni, G. *J. Org. Chem*. **1983**, *48*, 909; (c) Garner, P.;

Ramkanth, S. *J. Org. Chem*. **1986**, *51*, 2609; (d) Boutin, R. H.; Rapoport, H. *J. Org. Chem*. **1986**, *51*, 5320. (e) Jacobsen, S. *Acta Chem. Scand*. **1988**, *B42*, 605.

2. (a) Groth, U.; Schöllkopf, U.; Tiller, T. *Tetrahedron* **1991**, *47*, 2835 and references cited therein; (b) *Merck Index*; 10th ed.; Merck and Co.: Rahway, NJ, 1983; p. 289; (c) Bennett, R. B.; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580.
3. (a) Ehrlich, J.; Bartz, Q. R.; Smith, R. M.; Josylyn, D. A.; Burkholder, P. R. *Science* **1947**, *106*, 417; (b) Al-Badr, A. A.; El-Obeid, H. A. *Chloramphenicol. In Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic: Orlando, **1986**; Vol. 15, p 701.
4. Gillet, A. D.; Abdel-Monem, M. M. *J. Med. Chem*. **1973**, *16*, 992 and the references cited therein.
5. Cutler, R. A.; Stenger, R. J.; Suter, C. M. *J. Am. Chem. Soc*. **1952**, *74*, 5475.
6. Controulis, J.; Rebstock, M. C.; Crooks, H. M., Jr. *J. Am. Chem. Soc*. **1949**, *71*, 2463.
7. Long, L. M.; Troutman, H. D. *J. Am. Chem. Soc*. **1949**, *71*, 2469.
8. Long, L. M.; Troutman, H. D. *J. Am. Chem. Soc*. **1949**, *71*, 2473.
9. Ehrhart, G.; Siedel, W.; Nahm, H. *Chem. Ber*. **1957**, *90*, 2088.
10. Horak, V.; Moezie, F.; Klein, R. F. X.; Giordano, C. *Synthesis* **1984**, 839.
11. Hazra, B. G.; Pore, V. S.; Maybhate, S. P. *Synth. Commun*. **1997**, *27*, 1857
12. Chenevert, R.; Thiboutot, S. *Synthesis* **1989**, 444.
13. Schollkopf, U.; Beulshausen, T. *Liebigs Ann. Chem*. **1989**, 223.
14. Rao, A. V. R.; Rao, S. P.; Bhanu, M. N. *J. Chem. Soc. Chem. Commun*. **1992**, 859.

15. Lou, B.-L.; Zhang, Y.-Z.; Dai, L.-X. *Chem. Ind*. **1993**, *7*, 249.

16. Easton, C. J.; Hutton, C. A.; Merrett, M. C.; Tiekink, E. R. T. *Tetrahedron* **1996**, *52*, 7025.

17. Veeresa, G.; Datta, A. *Tetrahedron Lett*. **1998**, *39*, 8503.

18. Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett*. **2000**, *41*, 5553.

19. Corey, E. J.; Choi, S. *Tetrahedron Lett*. **2000**, *41*, 2765.

20. Loncaric, C.; Wulff, W. D. *Org. Lett*. **2001**, *3*, 3675.

21. Bhaskar, G.; Kumar, V. S.; Rao, B. V. *Tetrahedron: Asymmetry* **2004**, *15*, 1279.

22. Boruwa, J.; Borah, J. C.; Gogoi, S.; Barua, N. C. *Tetrahedron Lett*. **2005**, *46*, 1743.

23. Hajra, S.; Karmakar, A.; Maji, T.; Medda, A. K. *Tetrahedron* **2006**, *62*, 8959.

24. Horak, V.; Moezie, F.; Klein, R. F. X.; Giordano, C. *Synthesis* **1984**, 839.

25. McCombie, S. W.; Nagabhushan, T. L. *Tetrahedron Lett*. **1987**, *28*, 5395.

26. Giordano, C.; Cavicchioli, S.; Levi, S.; Villa, M. *Tetrahedron Lett*. **1988**, *29*, 5561.

27. Giordano, C.; Cavicchioli, S.; Levi, S.; Villa, M. *J. Org. Chem*. **1991**, *56*, 6114.

28. Davis, F. A.; Zhou, P. *Tetrahedron Lett*. **1994**, *35*, 7525.

29. Wu, G.-Z.; Tormos, W. I. PTC Int. Appl. WO 94/14764, **1994** (to Schering).

30. Gennari, C.; Pain, G. *Tetrahedron Lett*. **1996**, *37*, 3747.

31. Wu, G.-Z.; Schumacher, D. P.; Tormos, W.; Clark, J. E.; Murphy, B. L. *J. Org. Chem*. **1997**, *62*, 2996.

32. Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5909.

33. Kaptein, B.; Dooren, T. J. G. M.; Boesten, W. H. J.; Sonke, T.; Duchateau, A. L. L.; Broxterman, Q. B.; Kamphuis, J. *Org. Process Res. Dev*. **1998**, *2*, 10.

34. Lu, W.; Chen, P.; Lin, G. *Tetrahedron* **2008**, *64*, 7822.

35. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; (b) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

36. (a) Donohoe, T. J.; Johnson, P. D.; Helliwell, M.; Keenan, M. *Chem. Commun.* **2001**, 2078; (b) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934; (c) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2004**, *6*, 2583.

37. Woodward, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106.

38. (a) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113; (b) Potvin, P. G.; Bianchet, S. J. *J. Org. Chem.* **1992**, *57*, 6629.

39. Bartocha, B.; Kaesz, H. D.; Stone, F. G. A. Z. Natueforsch **1959**, *14b*, 352; C. A. **1960**, *54*, 1272h.

40. Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2005**, *7*, 1275.

41. Bartz, Q. R. *J. Biol. Chem.* **1948**, *172*, 445.

42. Voight, E. A.; Roethle, P. A.; Burke, S. D. *J. Org. Chem.* **2004**, *69*, 4534.

Chapter II

Enantioselective synthesis of tarchonanthuslactone and atorvastatin side-chain using proline-catalyzed asymmetric α-aminooxylation

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1. "Enantioselective synthesis of tarchonanthuslactone using proline-catalyzed asymmetric α-aminooxylation" Shyla George and Arumugam Sudalai; *Tetrahedron: Asymmetry,* **2007**, *18*, 975.

2. "An efficient organocatalytic route to the atorvastatin side-chain" Shyla George and Arumugam Sudalai; *Tetrahedron Lett*. **2007**, *48*, 8544.

Section I

Enantioselective synthesis of tarchonanthuslactone using proline-catalyzed asymmetric α-aminooxylation

2.1.1 Introduction

Several natural products with 1,3-polyol/5,6-dihydro-2*H*-pyran-2-one structural units are found to exhibit wide range of biological activities. For instance, they act as plant growth inhibition as well as antifeedant, antifungal, antibacterial and antitumor agents.[1] Some such natural products are tarchonanthuslactone (**1**), strictifolione (**2**),[2a] passifloricin A (**3**),[2b] pironetin (**4**)[2c] and cryptocarya diacetate (**5**).[2d] Tarchonanthuslactone (**1**) was isolated[3] by Bohlmann *et al.* from the leaves of *Tarchonanthustrilobus compositae* in 1979. Subsequently, Hsu *et al.* found that **1** lowers the blood plasma level in diabetic rats as an important biological activity.[4] The important structural feature as well as biological activity of tarchonanthuslactone (**1**) (**Fig. 1**) made it an ideal target to develop new asymmetric synthetic methodology for its construction and thus a number of synthetic methods have been reported in literature.[5-19]

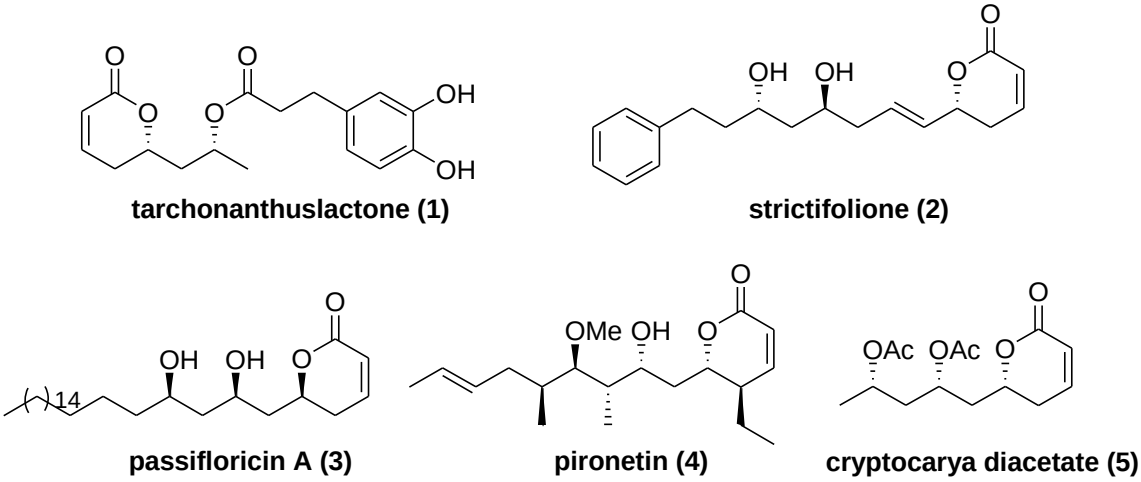


Fig. 1

2.1.2 Pharmacology of tarchonanthuslactone

The main structural features of tarchonanthuslactone (**1**) are a *syn*-1,3-diol and a 6-substituted 5,6-dihydro-α-pyrone subunit, which are also present in various natural products with important biological activities. The absolute and relative stereochemistry of tarchonanthuslactone has been established by a combination of Mosher's ester analysis and Rychnovsky ^{13}C NMR/acetonide analysis.[20] Later Nakata[5] and co-workers confirmed its absolute configuration by carrying out its first asymmetric synthesis. The basic structure of tarchonanthuslactone (a dihydrocaffeic acid ester) consists of a *syn*-1,3-diol unit with one hydroxyl group involved in an unsaturated lactone and the other esterified with 3,4-dihydroxyhydrocinnamic acid. Caffeic acid has been established as an active principle that lowers the plasma glucose levels in diabetic rats and several lactones from the *Compositae* family show significant medicinal properties. The α, β-unsaturated δ-lactone functionality is presumed to be responsible for the biological activities, due to its ability to act as a Michael acceptor, enabling these molecules to bind to a target enzyme.

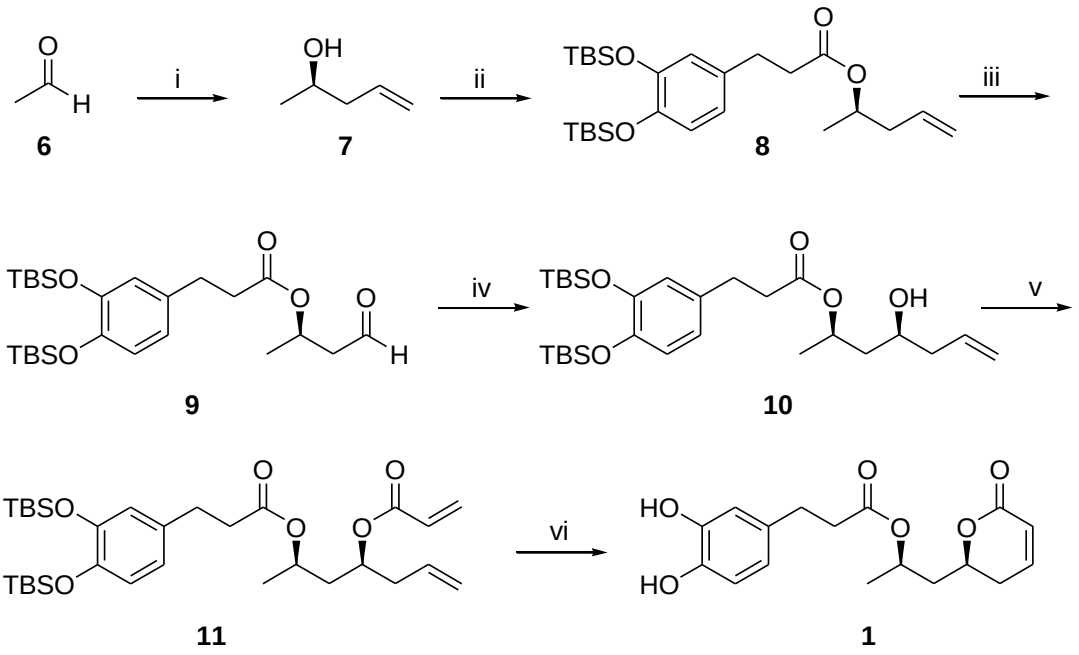
2.1.3 Review of Literature

Literature search revealed that there are several reports available for the synthesis of tarchonanthuslactone (**1**) involving chiral pool, chemo-enzymatic approach or enantioselective syntheses, some of which are described below.

Ramachandran's approach (2001)[9]

Ramachandran *et al.* have achieved the synthesis of tarchonanthuslactone (**1**) using asymmetric allylboration of acetaldehyde **6** with (-)-*B*-allyldiisopinocamphenylborane to furnish the homoallylic alcohol **7** in 71% yield and 99% ee. Alcohol **7** was then coupled with TBS-protected dihydrocaffeic acid to give the ester **8**, which was then subjected to osmylation followed by periodate cleavage to provide the aldehyde **9** in 77% yield. A

second allylation of aldehyde **9** with (-)-*B*-allyldiisopinocamphenylborane furnished the homoallylic alcohol **10** which was then esterified with acryloyl chloride to furnish the diester **11**. The diester **11** was then subjected to ring-closing metathesis using Grubbs' first generation catalyst followed by subsequent deprotection of TBS-group with tetrabutylammonium fluoride in THF to provide tarchonanthuslactone (**1**) in 80% yield (**Scheme 1**).

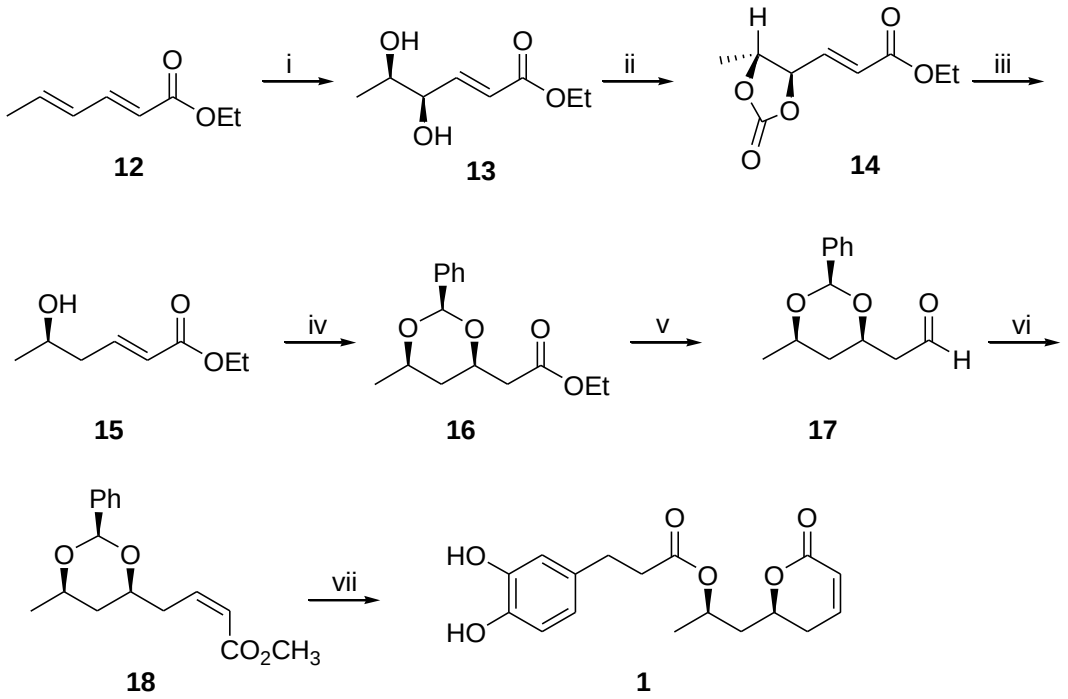


Scheme 1: (i) (-)-*B*-allyldiisopinocamphenylborane, Et_2O-pentane, -100 °C, 1 h, NaOH, H_2O_2, 71%, 99% ee; (ii) TBS-protected dihydrocaffeic acid, DCC, CH_2Cl_2, 6 h, 81%; (iii) OsO_4 (cat.), dioxane:H_2O (3:1), $NaIO_4$, 25 °C, 77%; (iv) (-)-*B*-allyldiisopinocamphenylborane, Et_2O-pentane, -100 °C, 1 h, NaOH, H_2O_2; (v) acryloyl chloride, Et_3N, CH_2Cl_2; (vi) (a) Grubbs' 1st generation catalyst, CH_2Cl_2, reflux, 46% (over 3 steps); (b) TBAF, THF, 25 °C, 80 %.

O'Doherty's approach (2002)[10]

Ko *et al.* have synthesized tarchonanthuslactone (**1**) by employing Sharpless asymmetric dihydroxylation as the key reaction. Thus unsaturated ester **12** was subjected to asymmetric dihydroxylation using AD mix-β to give the diol **13** in 85% yield which was successively treated with triphosgene in presence of pyridine to furnish the cyclic

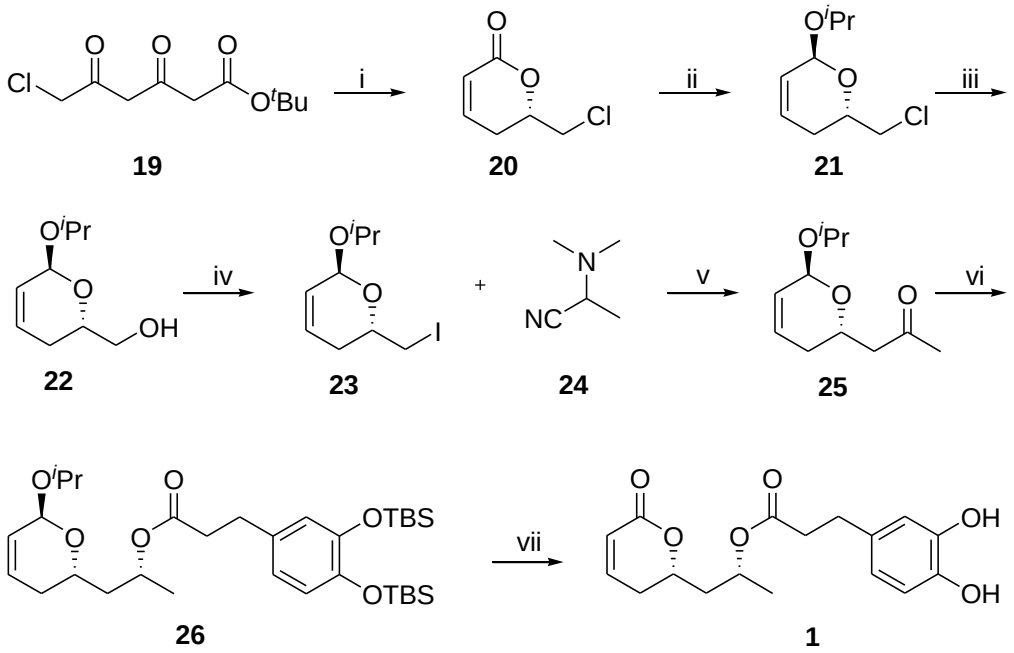
carbonate **14** in 95% yield. Treatment of carbonate **14** with catalytic amount of palladium/triphenylphosphine and a mild hydride source (1:1, Et_3N/HCO_2H) afforded δ-hydroxy ester **15** which when reacted with benzaldehyde in presence of KO^tBu yielded benzylidene protected ester **16** in 64% yield. DIBALH reduction of ester **16** followed by subsequent treatment of the corresponding aldehyde **17** with potassium salt of bis(2,2,2-trifluoroethyl)methoxycarbonylmethylphosphonate provided *cis*-enoate **18** in 72% yield with 9:1 diastereoselectivity. The enoate **18** was then converted into tarchonanthuslactone (**1**) by utilizing the following reaction sequence: treatment of **18** with $AcOH/H_2O$, catalytic amount of TsOH, DCC and TBS-protected dihydrocaffeic acid and finally TBS deprotection using TBAF (**Scheme 2**).



Scheme 2: (i) AD mix-β, 85%; (ii) $(Cl_3CO)_2CO$, pyridine, CH_2Cl_2, 95%; (iii) HCO_2H/Et_3N, 1 mol% $Pd_2(dba)_3.CHCl_3$, 2.5 mol% PPh_3, THF, 66 °C, 92%; (iv) 3.3 equiv PhCHO, KO^tBu, 64%; (v) DIBALH, THF, 95%; (vi) KO^tBu, 18-crown-6, bis(2,2,2-trifluoroethyl)methoxycarbonylmethylphosphonate, -78 °C, 72%; (vii) (a) $AcOH/H_2O$, then TsOH, TBS-protected dihydrocaffeic acid, DCC, 71%; (b) TBAF, $PhCO_2H$, 85%.

Enders' approach (2003)[11]

Enders *et al.* have employed enzyme-catalyzed asymmetric reduction of *tert*-butyl-6-chloro-3,5-dioxohexanoate **19** as the key step followed by a second reduction, cyclization and dehydration to afford the chloro lactone **20**. The lactone moiety was reduced with DIBALH followed by its treatment with catalytic amount of PPTS furnished acetal **21** in 76% yield. Conversion of chloride **21** into alcohol **22** was carried out *via* its acetate. Alcohol **22** was then converted into the corresponding iodide **23** using PPh_3 and iodine in presence of imidazole. Alkylation of acetaldehyde α-amino nitrile **24** with iodide **23** was carried out in presence of LDA followed by its hydrolysis on silica gel afforded **25** in 83% yield.

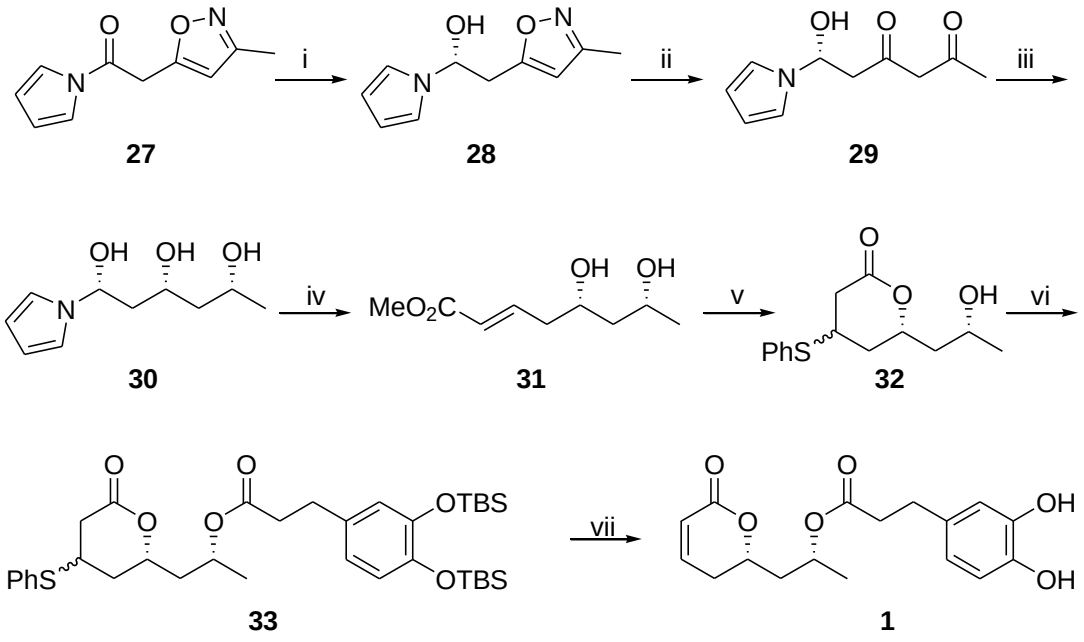


Scheme 3: (i) (a) *rec*LBADH, cat. $NADP^+$, ^{i}PrOH, pH 5.5 buffer; (b) $NaBH_4$, EtOH, 0 °C; (c) cat. *p*TsOH, toluene, 25 °C, 14 h, 120 °C, 4 h, 56%, 99% ee; (ii) (a) DIBALH, CH_2Cl_2, -78 °C, 76%; (b) ^{i}PrOH, PPTS, benzene, 80 °C, 76%; (iii) (a) TBAA, NMP, 85 °C; (b) K_2CO_3, MeOH, 25 °C, 93%; (iv) PPh_3, imidazole, I_2, Et_2O/CH_3CN, 0 °C; (v) LDA, THF, -78 °C to 25 °C, SiO_2, 83%; (vi) (a) L-Selectride, CH_2Cl_2, -100 °C to 25 °C, 72%; (b) DCC, DMAP, TBS-protected dihydrocaffeic acid, CH_2Cl_2, 25 °C, 66%, 85% de; (vii) (a) PCC, CH_2Cl_2, 25 °C; (b) TBAF, benzoic acid, THF, 25 °C, 87%.

The ester **26** was accessed from **25** by employing a two-step reduction sequence: reduction of **25** using L-selectride® and then coupling of the product with TBS-protected dihydrocaffeic acid in presence of DCC as a coupling agent. Eventually, the synthesis was completed by treatment of the ester **26** with pyridinium chlorochromate followed by TBS-deprotection with TBAF in THF (**Scheme 3**).

Dixon's approach (2005)[12]

Dixon *et al.* have achieved the synthesis of tarchonanthuslactone (**1**) using asymmetric reduction of *N*-acyl pyrrole **27** with Me-(*S*)-CBS reagent in presence of $BH_3.SMe_2$ to give the desired product **28** in 99.5% ee. Reductive cleavage of the N-O bond in **28** was achieved with molybdenum hexacarbonyl followed by hydrolysis using aqueous acetic acid gave 1,3-diketone **29**. Treatment of **29** with diethylmethoxy borane and $NaBH_4$

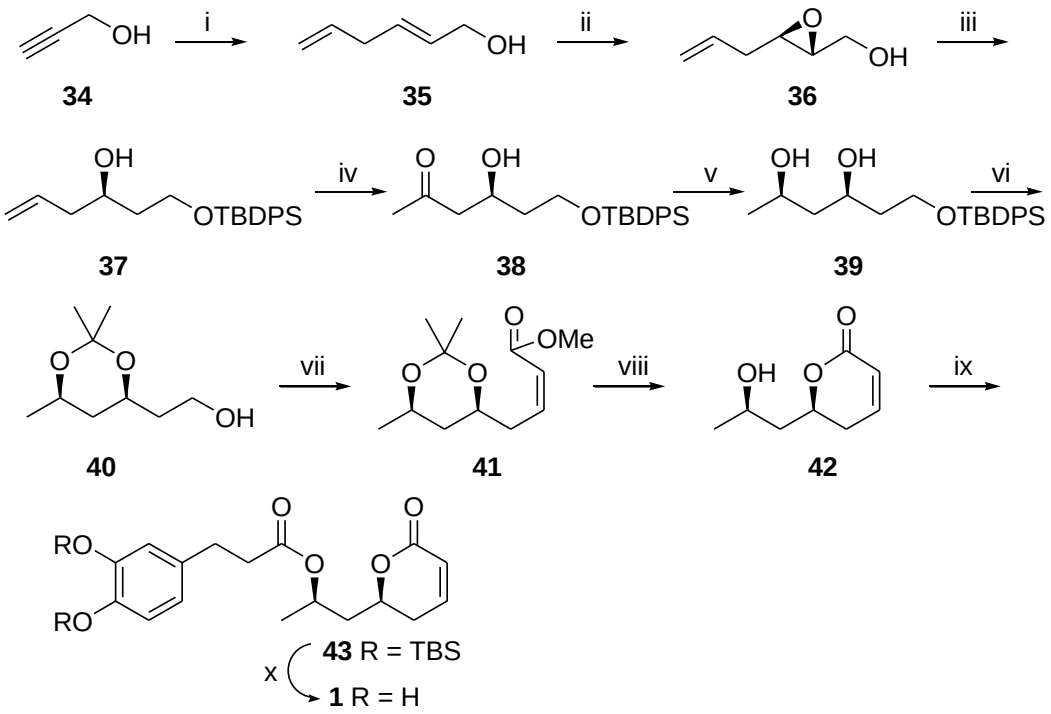


Scheme 4: (i) Me-(*S*)-CBS, $BH_3.SMe_2$ (1.7 equiv), CH_2Cl_2, -78 °C, 92%, 99% ee; (ii) (a) $Mo(CO)_6$, CH_3CN, H_2O, reflux, 25 °C, 69%; (b) CH_3CN:AcOH:H_2O (2:2:1), 99%; (iii) Et_2BOMe, $NaBH_4$, THF:MeOH (3:1), 90%; (iv) $(MeO)_2P(=O)CH_2CO_2Me$, NaH, THF, 0 °C, 97%; (v) (a) PhSH, $^iPr_2NEt$, PhH, 25 °C; (b) Amberlyst A-15, CH_3CN, 25 °C, 71%; (vi) DCC, DMAP, TBS-protected dihydrocaffeic acid, CH_2Cl_2, 25 °C, 77%; (vii) (a) DBU, CH_2Cl_2, 0 °C, 98%; (b) TBAF, $PhCO_2H$, THF, 25 °C, 98%.

produced triol **30** which was then subjected to deprotective HWE conditions to give α,β-unsaturated ester **31**. Base-catalyzed conjugate addition of benzenethiol followed by acid-catalyzed lactonization afforded alcohol **32** in 71% yield. Coupling of alcohol **32** with TBS-protected dihydrocaffeic acid in presence of DCC provided the ester **33** which on subsequent elimination with DBU followed by deprotection with TBAF in THF furnished tarchonanthuslactone (**1**) in 98% yield (**Scheme 4**).

Sabitha's approach (2005)[13]

Sabitha *et al.* have synthesized tarchonanthuslactone (**1**) by utilizing chelation-controlled reduction of β-hydroxy ketone **38**. Propargyl alcohol **34** on alkylation with allyl bromide in presence of Na_2CO_3, TBAI and CuI afforded the alkylated product which was reduced to *trans* allyl alcohol **35** under $LiAlH_4$/THF conditions. Allyl alcohol **35** was subjected to Sharpless asymmetric epoxidation using (-)-DET, $Ti(O^iPr)_4$ and TBHP to afford the epoxide **36**, which on reduction with Red-Al followed by alcohol protection produced the TBDPS ether **37** in 95% yield. The homoallylic alcohol **37** thus obtained was subjected to Wacker oxidation to give ketone **38** which was then reduced under LiI/$LiAlH_4$ protocol to furnish the 1,3-*syn*-diol with *syn:anti* selectivity >99:1. The *syn*-1,3-diol was then protected as its acetonide and the silyl protection was removed using TBAF to produce the free primary alcohol **40**. The aldehyde obtained from alcohol **40** under Dess-Martin periodinane condition was subjected to HWE olefination to produce the *cis*-enoate **41** with 78% yield. Hydrolysis of the acetonide in **41** followed by treatment with $ZnCl_2$ in THF provided the lactenone **42** which was converted to tarchonanthuslactone (**1**) in two-step reaction sequence: coupling with TBS-protected dihydrocaffeic acid in presence of DCC and TBS-deprotection with oxone in aqueous MeOH (**Scheme 5**).

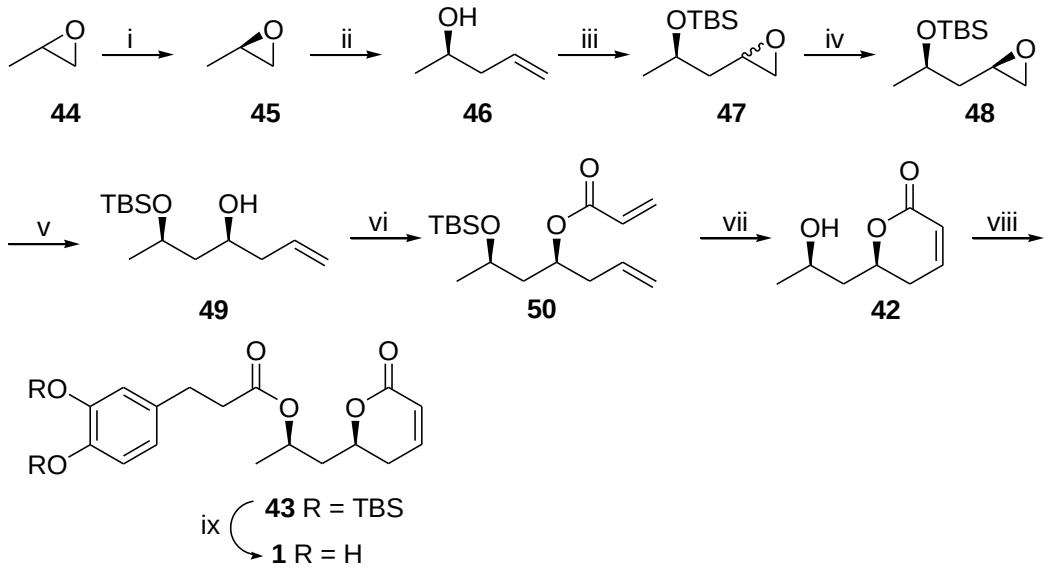


Scheme 5: (i) (a) allyl bromide, Na_2CO_3/TBAI; (b) CuI, DMF, 25 °C, 82%; (c) $LiAlH_4$, THF, 25 °C, 75%; (ii) (-)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 ^{0}C, 4Å MS, 82%; (iii) (a) Red-Al, THF, -15 °C to 25 °C, 90%; (b) TBDPSCl, imidazole, CH_2Cl_2, 0 ^{0}C to 25 °C, 1 h, 95%; (iv) $PdCl_2$, CuCl, O_2, THF–H_2O (10:1), 25 °C, 4 h, 65%; (v) $LiAlH_4$/LiI (1:1), Et_2O, -78 °C to 25 °C, 1 h, 84%; (vi) (a) 2,2-DMP, PPTS, 12 h, 94%; (b) TBAF, THF, 1 h, 90%; (vii) (a) Dess–Martin periodinane, CH_2Cl_2, 25 ^{0}C, 1 h, 88%; (b) $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, NaH, THF, -80 °C, 0.5 h, 78%; (viii) (a) 0.1N HCl, MeOH, 86%; (b) $ZnCl_2$, THF, reflux, 80%; (ix) TBS-protected dihydrocaffeic acid, DCC, DMAP, 82%; (x) oxone, aqueous MeOH, 25 ^{0}C, 24 h, 80%.

Kumar's approach (2005)[14]

Kumar *et al.* have achieved the synthesis of tarchonanthuslactone (**1**) using hydrolytic kinetic resolution as the key step. Propylene oxide **44** was subjected to Jacobsen's HKR using (*R,R*)-salen-Co-(OAc) catalyst to give the epoxide **45** which was further treated with vinylmagnesium bromide in presence of CuI to give the homoallylic alcohol **46** in 89% yield. Protection of the alcohol in **46** as its TBS-ether followed by epoxidation of olefin with *m*CPBA provided epoxide **47** with *syn:anti* selectivity 1.2:1. Epoxide **47** was subjected to HKR using (*R,R*)-salen-Co-(OAc) catalyst to afford **48** which on treatment

with vinylmagnesium bromide in presence of CuI gave the homoallylic alcohol **49** in 86% yield. Alcohol **49** was then esterified with acryloyl chloride to give the ester **50** followed by ring-closing metathesis with Grubbs' 1st generation catalyst and TBS-deprotection with TBAF in THF to provide the lactenone **42** in 86% yield. Finally coupling of the alcohol **42** with TBS-protected dihydrocaffeic acid gave **43** which on silyl deprotection with TBAF furnished tarchonanthuslactone (**1**) in 84% yield (**Scheme 6**).

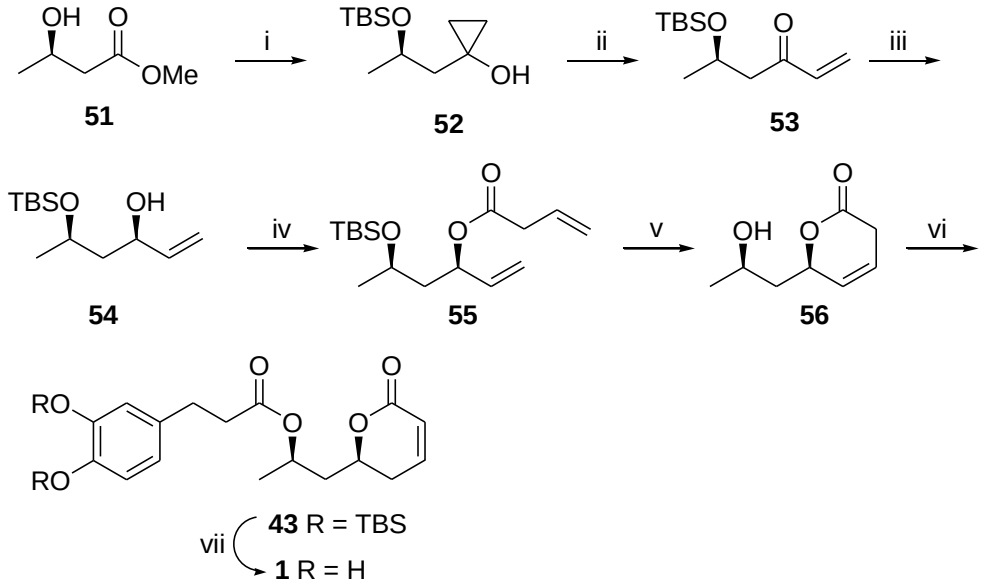


Scheme 6: (i) (*R*,*R*)-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), 0 °C, 14 h, 46%; (ii) vinylmagnesium bromide, THF, CuI, -20 °C, 12 h, 89%; (iii) (a) *m*CPBA, CH_2Cl_2, 0 °C to 25 °C, 10 h, 96%; (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to 25 °C, 4 h, 95%; (iv) (*R*,*R*)-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), 0 °C, 24 h, 45%; (v) vinylmagnesium bromide, THF, CuI, -20 °C, 1 h, 86%; (vi) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to 25 °C, 5 h, 89%; (vii) (a) $(PCy_3)_2Ru(Cl)_2$=CH–Ph (10 mol%), CH_2Cl_2, reflux, 8 h, 87%; (b) TBAF, THF, 25 °C, overnight, 86%; (viii) TBS-protected dihydrocaffeic acid, DCC, DMAP, CH_2Cl_2, 5 h, 85%; (ix) TBAF, THF, 1 h, 84%.

Singh's approach (2005)[15]

Singh *et al.* have commenced their synthesis from (*R*)-3-hydroxybutanoate **51**, which was protected as its TBS ether followed by treatment with ethylmagnesium bromide in presence of $Ti(O^iPr)_4$ to produce substituted cyclopropanol **52** in 87% yield.

Cyclopropanol **52** when reacted with NBS and Et_3N provided the desired ketone **53** which was further subjected to reduction under Luche's condition to produce allylic alcohol **54** with *syn:anti* selectivity 86:14. The allylic alcohol **54** was coupled with vinylacetic acid in presence of DCC and DMAP to provide the RCM precursor **55** which when subjected to RCM using Grubbs' second generation catalyst followed by desilylation under acidic conditions furnished the alcohol **56**. Finally, the synthesis of tarchonanthuslactone (**1**) was achieved by coupling **56** with TBS-protected dihydrocaffeic acid, treatment with DBU and then desilylation using TBAF (**Scheme 7**).

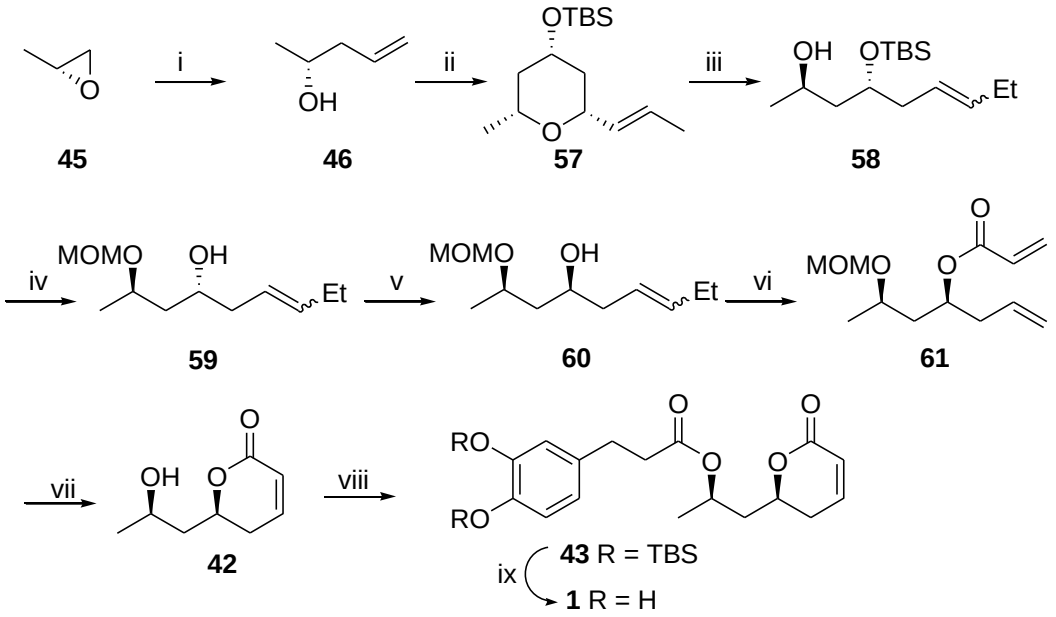


Scheme 7: (i) (a) TBSCl, imidazole, 0 °C; (b) $Ti(O^iPr)_4$, EtMgBr, 20 °C, 87%; (ii) NBS, then Et_3N, 95%; (iii) $NaBH_4$, $CeCl_3$, 91%; (iv) vinylacetic acid, DCC, DMAP, 83%; (v) (a) Grubbs' second generation catalyst, CH_2Cl_2, 40 °C; (b) 5% HF-H_2O/CH_3CN, 99%; (vi) (a) TBS-protected dihydrocaffeic acid, DCC, DMAP; (b) DBU, $CHCl_3$, 65%; (vii) TBAF, $PhCO_2H$, 80%.

Yadav's approach (2007)[17]

Yadav *et al.* have synthesized tarchonanthuslactone (**1**) by Cu-mediated opening of (*R*)-propylene oxide **45** obtained *via* Jacobsen's HKR methodology with vinyl magnesium bromide to yield homoallylic alcohol **46** in 80% yield. The Prins cyclization of **46** with

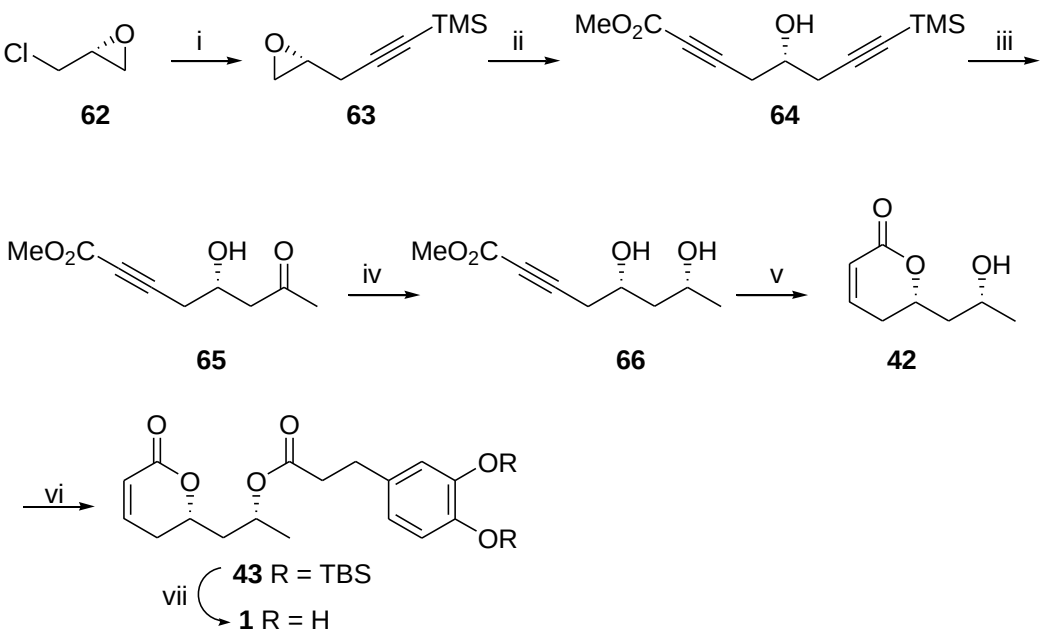
crotonaldehyde in presence of Et_3N followed by hydrolysis of the resulting trifluoroacetate and subsequent protection with TBSCl afforded the silyl ether **57** in 92% yield. Allylic cleavage of pyran **57** was carried out with Na in liquid ammonia to furnish 1,3-diol derivative **58** which was protected as its MOM-ether followed by desilylation with TBAF to provide the alcohol **59**. Mitsunobu inversion of the alcohol **59** afforded **60** which was esterified with acryloyl chloride to give the RCM precursor **61**. The ester **61** was then subjected to ring-closing metathesis with Grubbs' second generation catalyst followed by cleavage of MOM-ether under acidic conditions to produce **42** in 85% yield. Eventually, coupling of **42** with TBS-protected dihydrocaffeic acid and then desilylation afforded tarchonanthuslactone (**1**) in 82% yield (**Scheme 8**).



Scheme 8: (i) CH_2=CHMgBr, CuBr, THF, -78 °C to -40 °C, 6 h, 80%; (ii) (a) crotonaldehyde, TFA, CH_2Cl_2, 25 °C, 4 h, then K_2CO_3, MeOH, 25 °C, 1 h, 70%; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to 25 °C, 4 h, 92%; (iii) Na, liquid NH_3, THF, -33 °C, 45 min, 90%; (iv) (a) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to 25 °C, 4 h, 92%; (b) TBAF, THF, 0 °C to 25 °C, 4 h, 94%; (v) *p*-$NO_2CH_2CO_2H$, DEAD, Ph_3P, THF, 0 °C to 25 °C, 30 min, then K_2CO_3, MeOH, 25 °C, 4 h, 75%; (vi) acryloyl chloride, TEA, DMAP, CH_2Cl_2, 0 °C to 25 °C, 1 h, 84%; (vii) (a) Grubbs' second generation catalyst, CH_2Cl_2, 25 °C, 12 h, 60%; (b) TFA/CH_2Cl_2 (1:5), CH_2Cl_2, 0 °C to 25 °C, 2 h, 85%; (viii) TBS-protected dihydrocaffeic acid, DCC, DMAP, 5 h, 0 °C to 25 °C, 83%; (ix) TBAF, benzoic acid, THF, 25 °C, 1 h, 82%.

Lee's approach (2009)[19]

Lee *et al.* have achieved the synthesis of tarchonanthuslactone (**1**) commencing from chiral epichlorohydrin **62**. This was reacted with lithium salt of TMS-acteylene in the presence of $BF_3.Et_2O$ to produce the corresponding halohydrin which under basic conditions produced epoxide **63**. The epoxide **63** was treated with lithium salt of propanoate to give *bis*-alkynyl ester **64** which was subjected to mercury-mediated hydration reaction to give ketone **65**. The ketone **65** was reduced under chelation-control using diethylmethoxyborane and $NaBH_4$ to furnish *syn*-1,3-diol **66** followed by its partial reduction with Lindlar catalyst and cyclization with PTSA in benzene. The lactenone **42** thus produced was converted to tarchonanthuslactone (**1**) by coupling it with TBS-protected dihydrocaffeic acid and then desilylation with TBAF in THF (**Scheme 9**).



Scheme 9: (i) (a) TMSCCLi, $BF_3.Et2O$, THF, 72%; (b) NaOH, CH_2Cl_2; (ii) LiCCCOOMe, $BF_3.Et_2O$, THF, 67%; (iii) $HgSO_4$, H_2SO_4, THF, 25 °C, 85%; (iv) $NaBH(OAc)_3$, CH_3CN:AcOH (2:1), -40 °C, 92%; (v) (a) H_2, $Pd/CaCO_3$, quinoline, benzene, 25 °C; (b) PTSA, benzene, 70%; (vi) TBS-protected dihydrocaffeic acid, DCC, DMAP, CH_2Cl_2; (vii) TBAF, benzoic acid, THF, 70%.

2.1.4 Present Work:

2.1.4.1 Objective

The stereoselective synthesis of 1,3-polyol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-polyols in various biologically active natural products and drugs. Thus, numerous strategies for their synthesis have been developed with great success. But, most of the methods reported[5-19] for the asymmetric synthesis of **1** involve the use of stoichiometric or exotic reagents including toxic metal catalysts or the inherent loss of 50% yield of chiral materials in the case of hydrolytic kinetic resolution strategies. With the development of an efficient approach to the synthesis of 1,3-polyols using proline catalyzed α-aminooxylation of an aldehyde as well as iodine-induced electophilic cyclization, we became interested in applying this protocol for the synthesis of tarchonanthuslactone (**1**).

Retrosynthetic analysis for tarchonanthuslactone (**1**) is outlined in **Fig. 2**. Evidently, alcohol **42**, the key intermediate, can be visualized to get from the corresponding *cis*-olefinic ester **79**. The iodocarbonate **74** can be prepared from olefin **73** *via* diastereoselective iodolactonization. The key chiral inducing step in the synthesis involves the proline catalyzed α-aminooxylation of readily available *n*-butyraldehyde **68**.

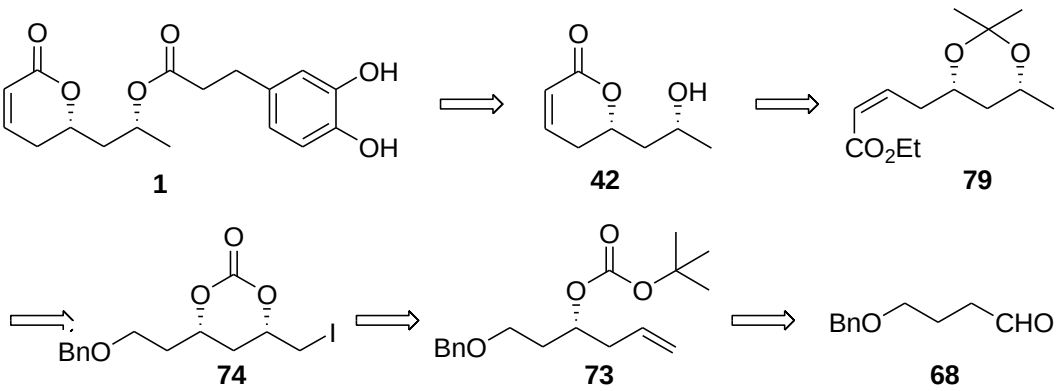


Fig. 2: Retrosynthetic analysis of tarchonanthuslactone (1)

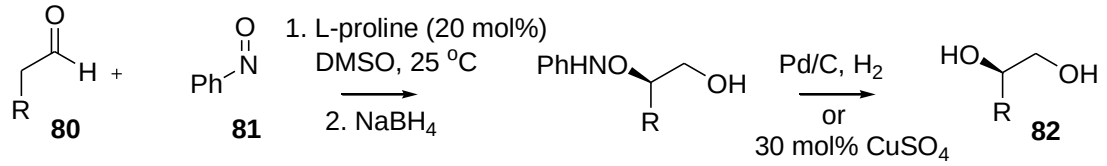
Since this section deals with a highly important and attractive asymmetric reaction i.e., proline-catalyzed *α-aminooxylation*, which introduces stereogenicity into the prochiral molecule, a brief account of the same is described below.

2.1.4.2 Proline-catalyzed α-Aminooxylation

Optically active α-hydroxy aldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[21a] Sharpless dihydroxylation of enol ethers,[21b] manganese-salen epoxidation of enol ethers,[9c] and Shi epoxidation of enol ethers.[21d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[22] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde.

Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur and phosphorus and does not contain any metals. The advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Asymmetric organocatalysis has begun to catch up with the spectacular advancements of enantioselective transition metal catalysis. In this connection, proline, an abundant, inexpensive aminoacid available in both enantiomeric forms has emerged as

a practical and versatile organocatalyst.[23] Proline is equally efficient for α-functionalization[24] of aldehydes and ketones. When an aldehyde **80** without substitution at α-position was reacted with nitrosobenzene **81** in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde takes place at α-position. The aminooxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **82** in very high enantioselectivities (**Scheme 10**).



Scheme 10: α-aminooxylation of aldehydes

The mechanism of the α-aminooxylation reaction is shown in **Fig. 3**. The observed enantioselectivitiy of the catalytic α -aminooxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an *E*-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α -aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one-pot sequential catalytic α -aminooxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

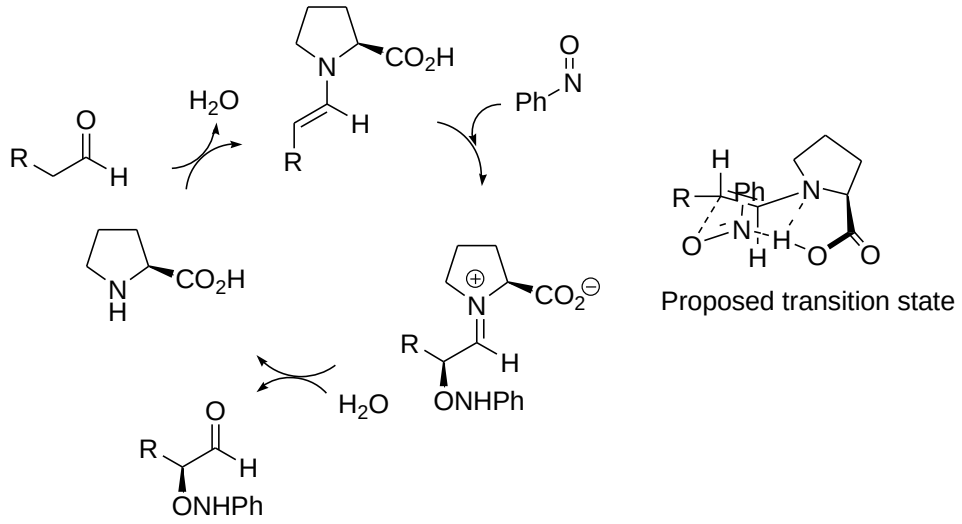
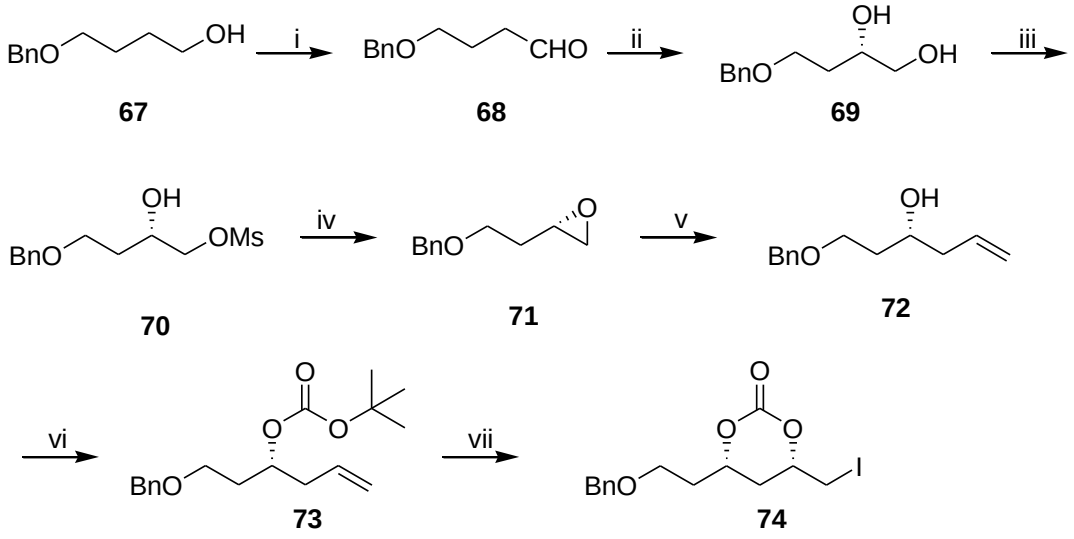


Fig. 3: Proposed mechanism of the α-aminooxylation reaction

2.1.5 Results and Discussion

The complete synthetic sequence for tarchonanthuslactone (**1**), wherein D-proline-catalyzed α-aminooxylation[24] reaction constitutes a key step for the introduction of chirality, is presented in **Schemes 11** & **12**.



Scheme 11: (i) IBX, DMSO, 25 °C, 2h, 95%; (ii) (a) PhNO, D-proline (25 mol%), CH_3CN, -20 °C, 24 h then MeOH, $NaBH_4$; (b) $CuSO_4$ (30 mol%), MeOH, 0 °C, 10 h, 87% (over two steps); (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 92%; (iv) K_2CO_3, MeOH, 25 °C, 1 h, 95%; (v) vinylmagnesium bromide, THF, CuI, -40 °C, 1 h, 92%; (vi) $(Boc)_2O$, DMAP, CH_3CN, 25 °C, 5 h, 95%; (vii) NIS, CH_3CN, -40 to 0 °C, 12 h, 85%.

Our synthesis of tarchonanthuslactone (**1**) was started with commercially available 1,4-butanediol, which was benzylated with BnBr in presence of NaH to give the monoprotected 1,4-butanediol **67**. The characteristic benzyl peak integrating for two protons has appeared at δ 4.50 in its ^{1}H NMR spectrum (**Fig. 4**).

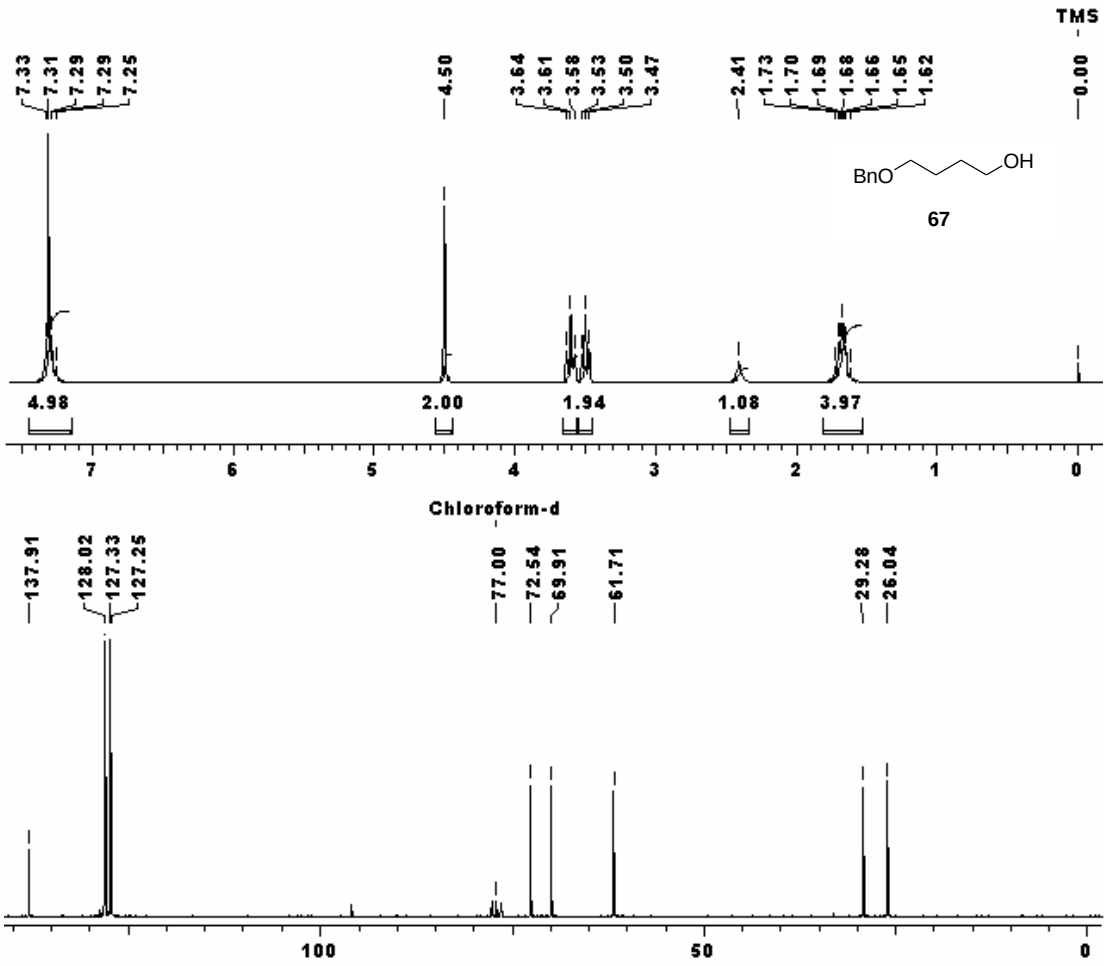


Fig. 4: ^{1}H and ^{13}C NMR spectra of 67

The primary alcohol function in **67** was then oxidized under IBX in DMSO to provide the corresponding precursor aldehyde **68.** The praline-catalyzed asymmetric α-aminooxylation of aldehyde **68** involves a two-step reaction sequence: (i) reaction of aldehyde **68** with nitrosobenzene as the oxygen source in the presence of D-proline in CH_3CN at -20 °C[24a] followed by treatment with $NaBH_4$ in MeOH gave the crude

aminooxy alcohol *in situ* and (ii) subsequent reduction of the crude aminoxy product with 30% $CuSO_4$[25] yielded chiral diol **69** in 86% yield and >95% ee (determined by ^1H NMR analysis of the corresponding Mosher's ester **80** (**Fig. 6**), (see experimental section) with

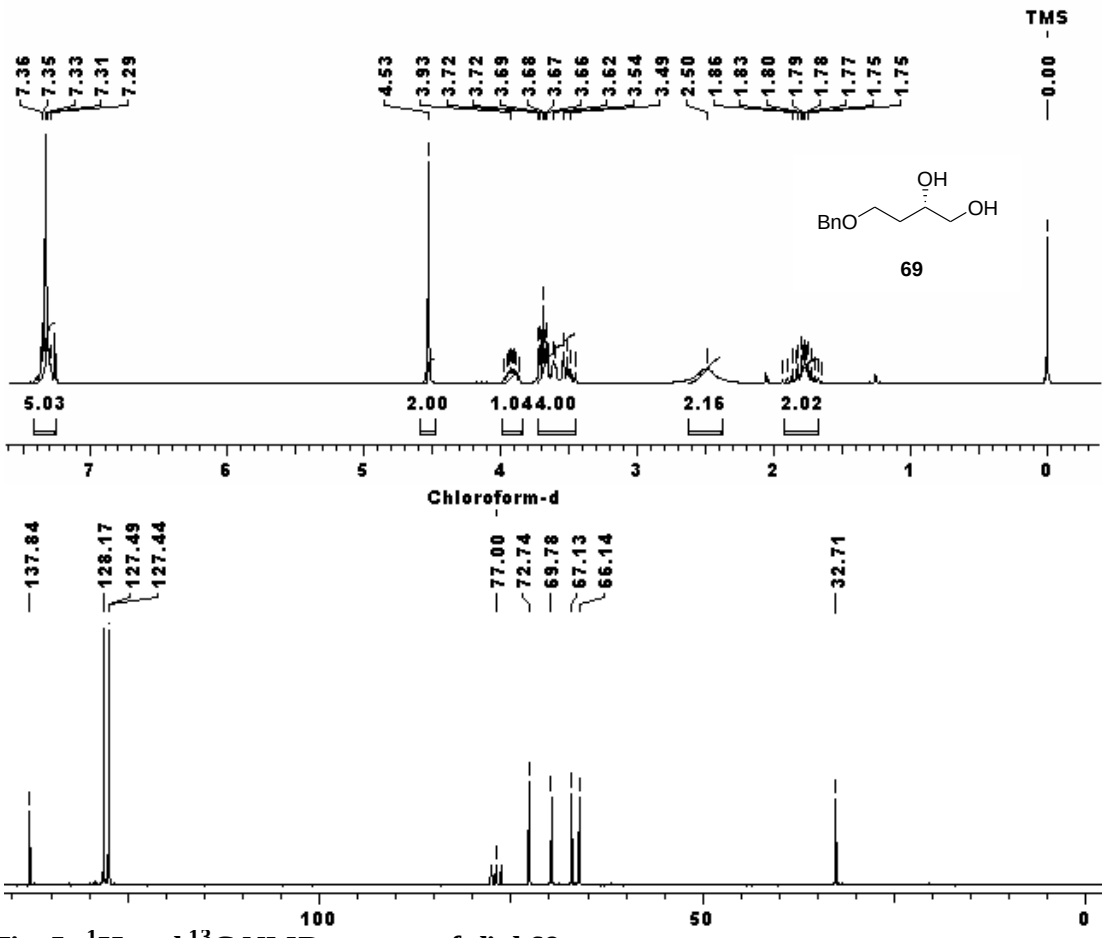


Fig. 5: ^1H and ^{13}C NMR spectra of diol 69

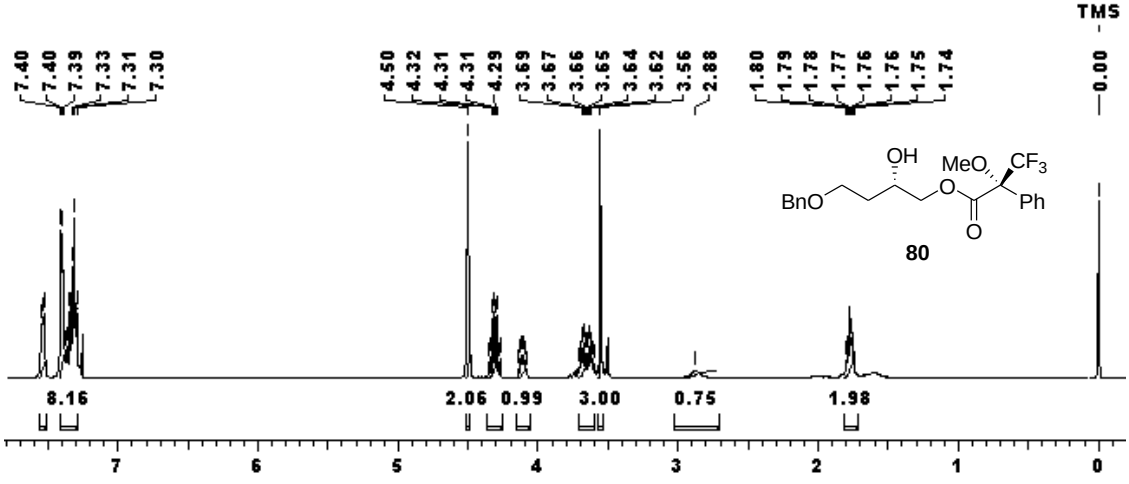


Fig. 6: ^1H NMR spectrum of Mosher's ester 80

$[\alpha]^{25}_D$ = + 5.02 (*c* 1, $CHCl_3$). The formation of diol **69** was confirmed by the appearance of peaks at δ 3.45-3.72 (m, 4H) and 3.87-3.98 (m, 1H) in the ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed signals at δ 66.14, 67.13, 69.78 and 72.74, which correspond to carbons attached to oxygen atoms (**Fig. 5**). Selective mesylation[26] of the primary alcohol in **69** was achieved to afford mesylate **70**, which on treatment with K_2CO_3 in MeOH[26] yielded the terminal epoxide **71**; $[\alpha]^{25}_D$ = -16.2 (*c* 3, $CHCl_3$) { lit.[27] $[\alpha]^{25}_D$ = + 16.9 (*c* 2.51, $CHCl_3$) for its antipode}. The ^{1}H NMR spectrum of **71** showed characteristic proton signals at δ 2.50 (dd, *J* = 2.7, 5.06 Hz, 1H), 2.76 (dd, *J* = 4.06, 4.94 Hz, 1H) and 3.01-3.10 (m, 1H). Its ^{13}C NMR spectrum displayed typical peaks at δ 46.68 and 49.68 corresponding to the methylene and methine carbons of the epoxide (**Fig. 7**).

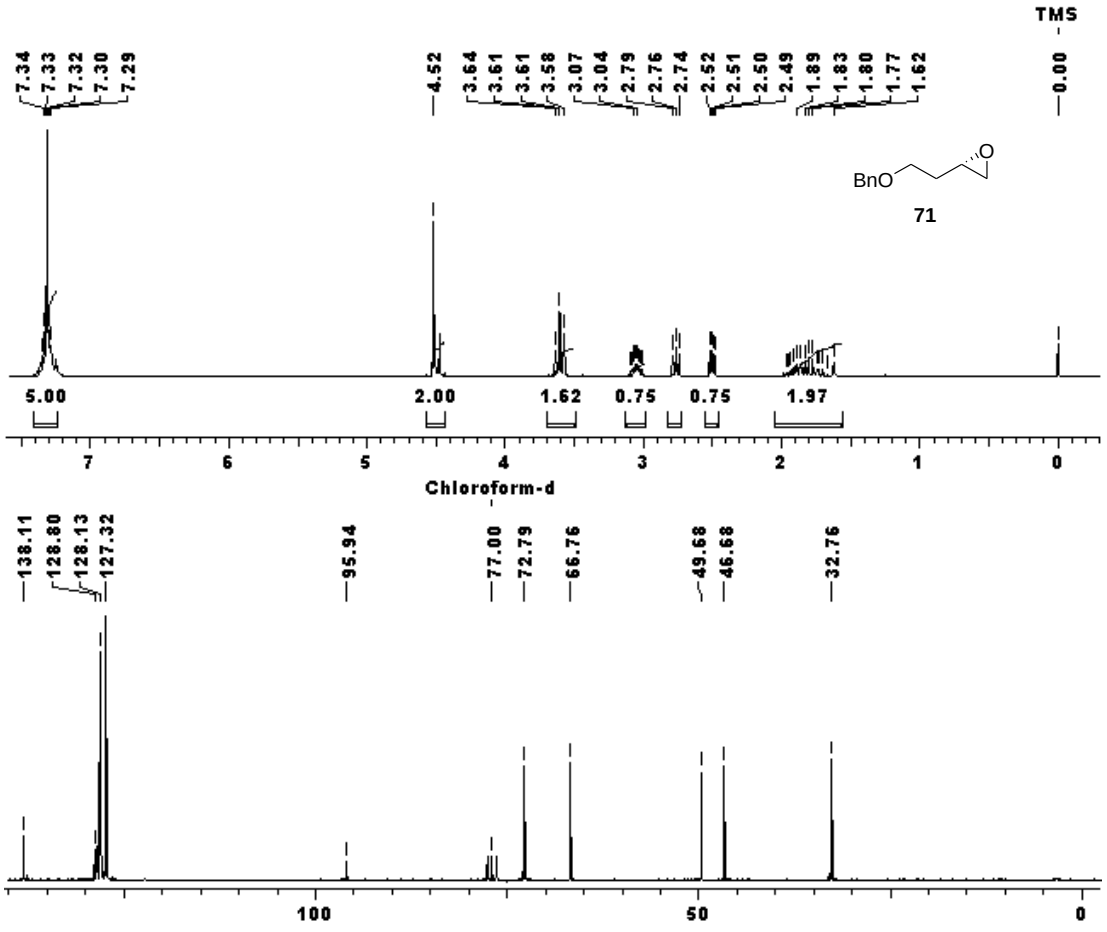


Fig. 7: ^{1}H and ^{13}C NMR spectra of epoxide 71

Our next task was to construct *syn*-1,3-diol moiety from epoxide **71**. In order to achieve this transformation with high diastereoselectivity, the iodine-induced carbonate cyclization methodology, originally published by Bartlett[28a] and later improved by Smith[28b] was undertaken. Thus, epoxide **71** was first treated with vinylmagnesium bromide in presence of CuI[29] in THF at -40 °C to give the homoallylic alcohol **72**. Three multiplets shown at δ 5.05, 5.12 and 5.82, integrating for proton each, in its ^{1}H NMR spectrum were attributed to the olefinic protons which was further substantiated by the appearance of the corresponding signals at δ 117.28 and 134.65 in its ^{13}C NMR spectrum (**Fig. 8**). The IR spectrum of **72** displayed characteristic strong band at 3469 cm^{-1} indicating the presence of -OH group.

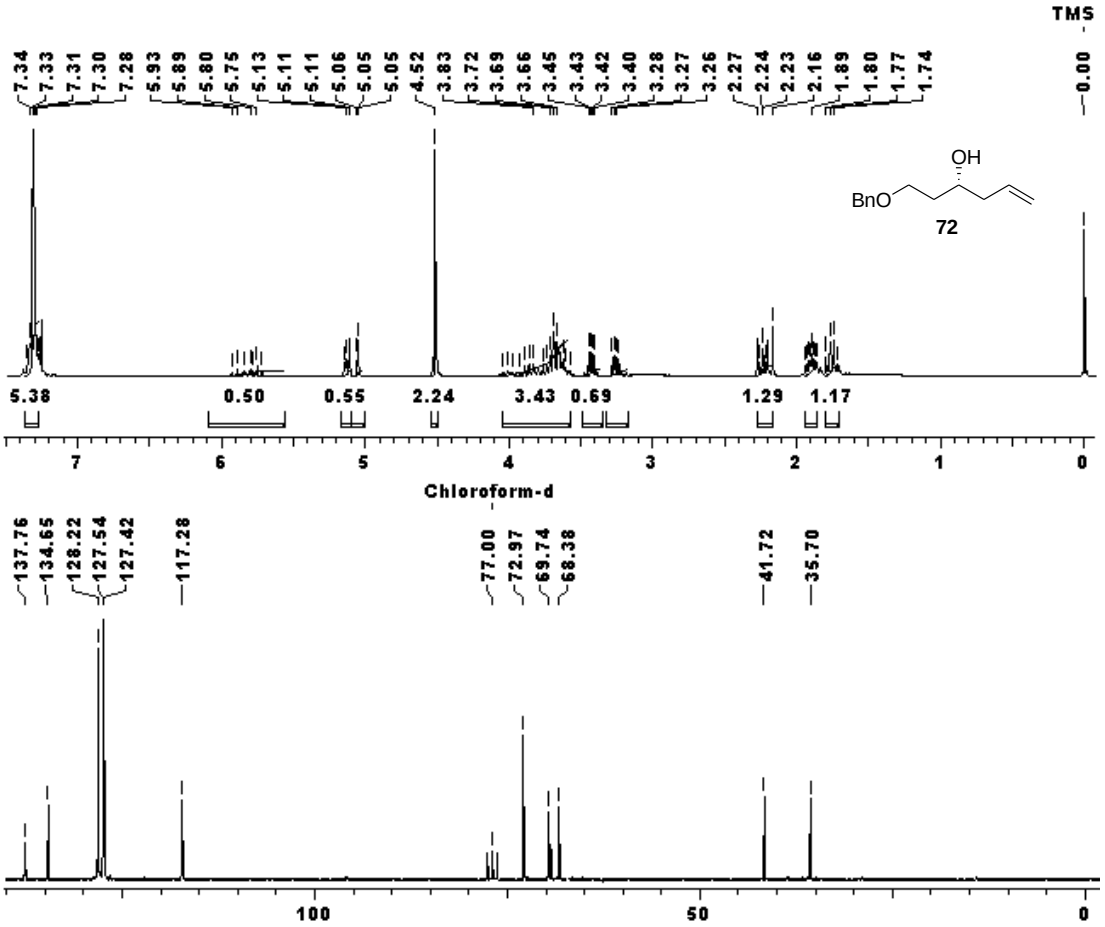


Fig. 8: ^{1}H and ^{13}C NMR spectra of 72

The homoallylic *tert*-butyl carbonate **73**, was prepared in high yields from the corresponding alcohol **72** on treatment with di-*tert*-butyldicarbonate in the presence of DMAP[29] in CH_3CN. The formation of carbonate **73** was confirmed by the appearance of a singlet at δ 1.47 integrating for nine protons [-OC(C**H**$_3$)$_3$] in the ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed typical peaks at δ 27.69 [-OC(**C**H_3)$_3$], 81.43 [-O**C**$(CH_3)_3$] and 153.05 (-O**C**O-) (**Fig. 9**).

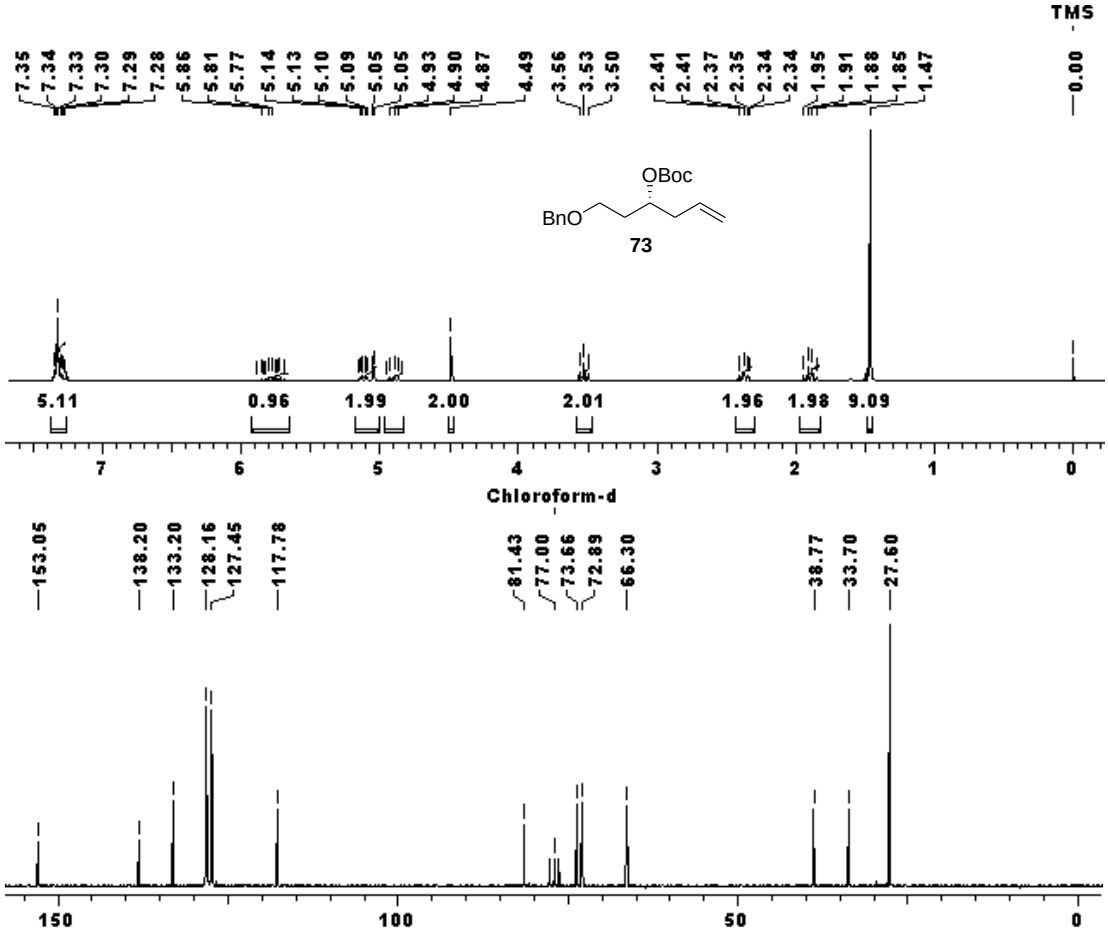


Fig. 9: ^{1}H and ^{13}C NMR spectra of 73

The homoallylic *tert*-butyl carbonate **73** was subjected to the diastereoselective iodolactonization using *N*-iodosuccinimide[30] in CH_3CN at low temperature (-40 to 0 °C) to furnish the cyclic carbonate derivative **74** in 85% yield as a single diastereomer

(determined by ^{1}H NMR analysis). Its ^{1}H NMR spectrum confirmed the disappearance of olefinic protons and the other spectral features displayed are follows: δ 3.25 (dd, *J* = 7.37, 10.53 Hz, 1H), 3.38 (dd, *J* = 4.42, 10.52 Hz, 1H), 3.59-3.64 (m, 1H), 3.67-3.73 (m, 1H), 4.39-4.45 (m, 1H), 4.47-4.55 (m, 2H), 4.64-4.71 (m, 1H). The carbonyl peak of **74** showed an upfield shift from δ 153.05 (in the homoallylic alcohol **73**) to 148.09 in its ^{13}C NMR spectrum (**Fig. 10**). The IR spectrum of **74** exhibited characteristic carbonate carbonyl absorption band at 1751 cm^{-1}.

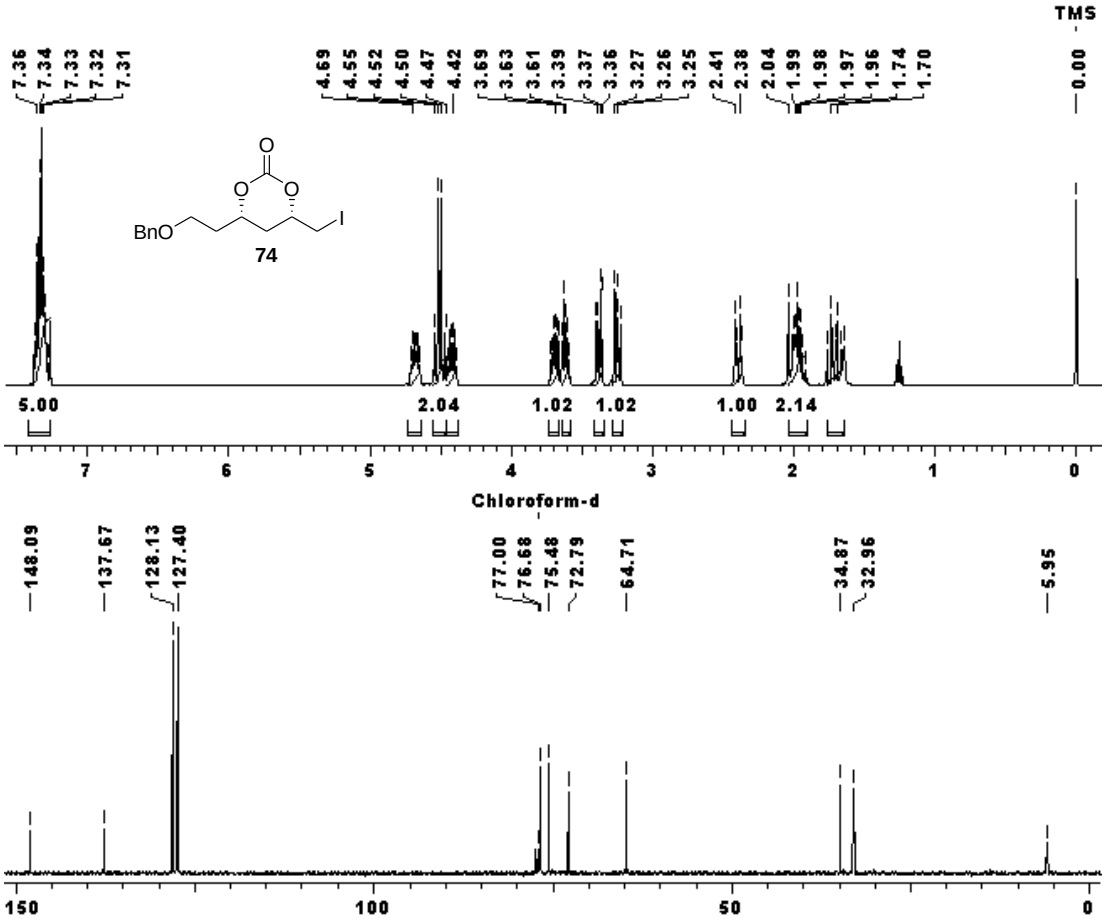
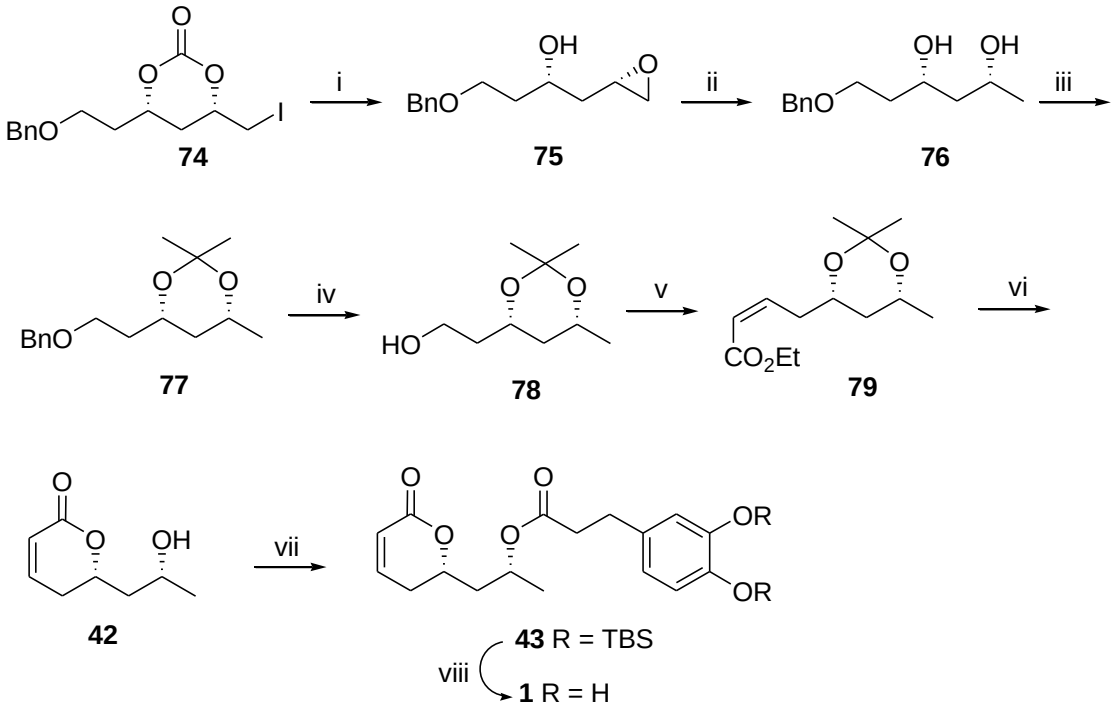


Fig. 10: ^{1}H and ^{13}C NMR spectra of iodocarbonate 74



Scheme 12: (i) K_2CO_3, MeOH, 0 °C to 25 °C, 4 h, 90%; (ii) $LiAlH_4$, THF, 50 °C, 6 h, 90%; (iii) 2,2-dimethoxypropane, camphorsulfonic acid, 25 °C, 4 h, 95%; (iv) 10% Pd/C, H_2 (1 atm), MeOH, 12 h, 91%; (v) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h; (b) ethyl (di-*o*-tolylphosphono)acetate, NaH, THF, -78 °C to 0 °C, 1.5 h, 80% (over two steps); (vi) pyridinium-*p*-toluene sulfonate, ethanol, 55 °C, 12 h, 75%; (vii) TBS-protected dihydrocaffeic acid, DCC, DMAP, CH_2Cl_2, 5 h, 81 %; (viii) TBAF, $PhCO_2H$, THF, 25 °C, 88%.

The iodocarbonate **74**, upon exposure to basic methanolic solution,[30] gave the desired *syn*-epoxy alcohol **75** in 90% yield. The formation of epoxide **75** was confirmed by the

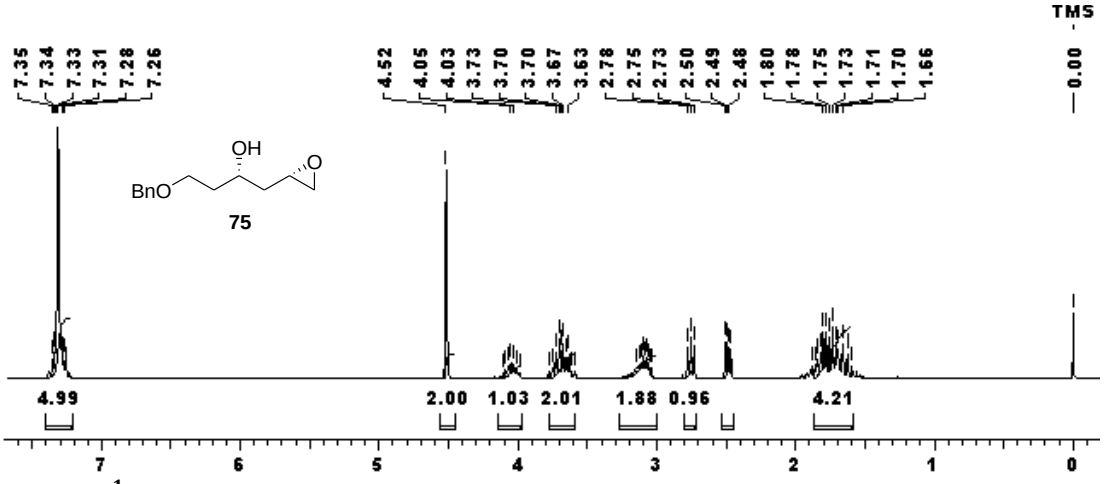


Fig. 11: ^{1}H NMR spectrum of 75

appearance of epoxide proton signals at δ 2.48 (dd), 2.75 (dd) and 3.10 (m) in its ^{1}H NMR spectrum (**Fig. 11**) which was further ascertained by the peaks in its ^{13}C NMR spectrum at δ 46.31 and 49.70 corresponding to the methylene and methine carbons of the epoxide as well as at δ 68.41, 68.82 and 73.11 due to methylene and methine carbons attached to oxygen atoms. Regioselective reduction of epoxy alcohol **75** using $LiAlH_4$[26] in THF furnished the *syn*-1,3-diol **76** in 90% yield. The ^{1}H and ^{13}C NMR spectra were in accordance with the proposed structure of **76**. In its ^{1}H NMR spectrum the newly created methyl protons resonated at δ 1.19 as a doublet (J = 6.53 Hz) (**Fig. 12**) while the corresponding carbon signal was found at δ 23.66 in its ^{13}C NMR spectrum. The IR spectrum of **76** displayed a strong absorption band above 3000 cm^{-1} indicating the presence of hydroxyl groups.

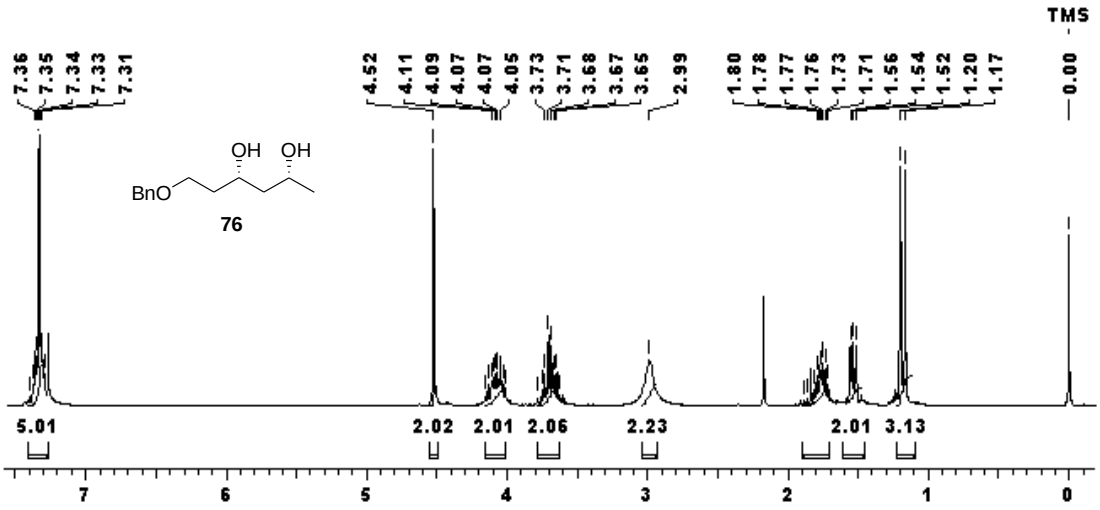


Fig. 12: ^{1}H NMR spectrum of 76

The *syn*-1,3-diol **76** was then protected as its acetonide **77** on treatment with 2,2-dimethoxypropane in the presence of catalytic amounts of camphorsulfonic acid.[31]

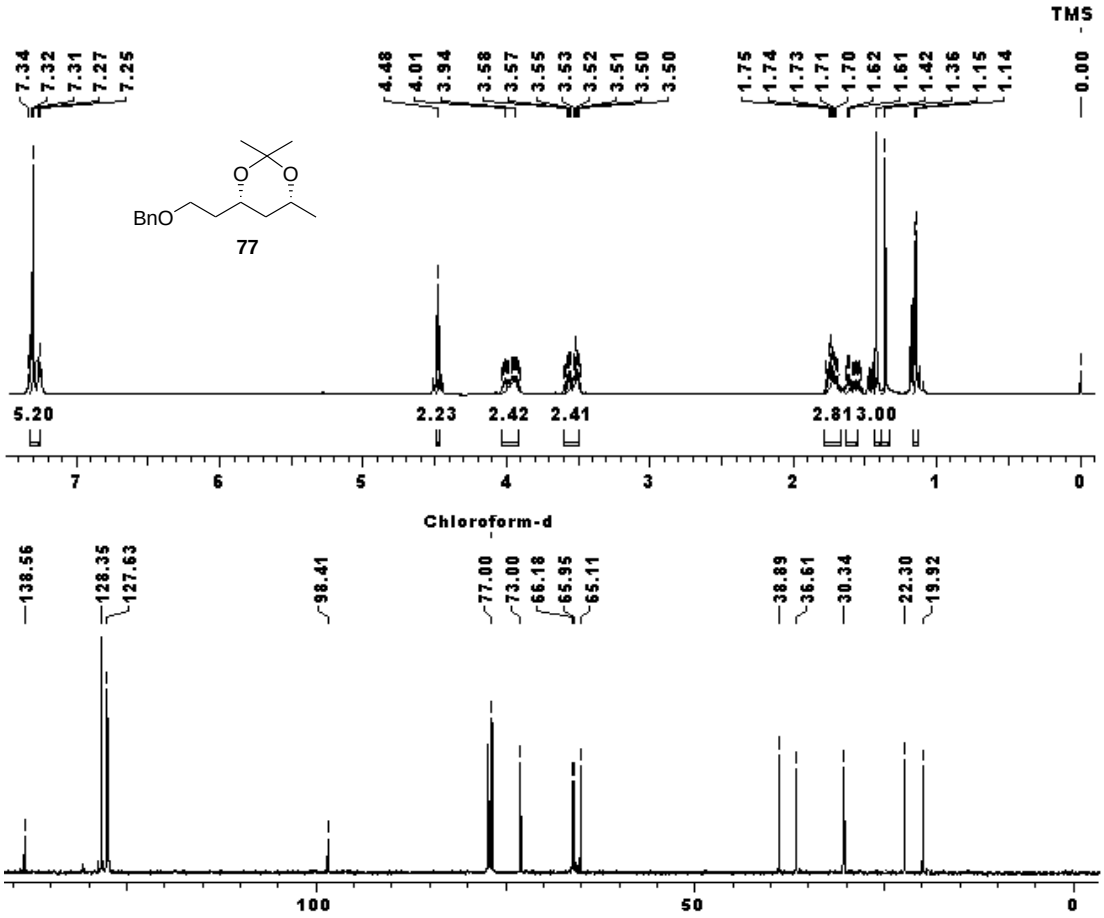


Fig. 13: ^{1}H and ^{13}C NMR spectra of 77

Two singlets at δ 1.36 and 1.42 integrating for three protons each in its ^{1}H NMR spectrum confirmed the formation of acetonide **77**. A typical pattern of *syn*-1,3-diol was evident in its ^{13}C NMR spectrum. It displayed peaks at δ 19.92 & 30.34 (corresponding to the methyl carbons of isopropylidene group) and 98.41 (corresponding to quarternary carbon of isopropylidene group) in its ^{13}C NMR spectrum, substantiating the formation of acetonide **77** (**Fig. 13**). Deprotection of the benzyl group in **77** under catalytic hydrogenolysis conditions[32] [Pd/C, H_2 (1 atm), MeOH], provided the primary alcohol **78** in 91% yield. The ^{1}H and ^{13}C NMR spectra showed the disappearance of benzyl peaks (**Fig. 14**). A broad singlet at δ 3.08 is due to the corresponding -OH proton in its ^{1}H NMR spectrum.

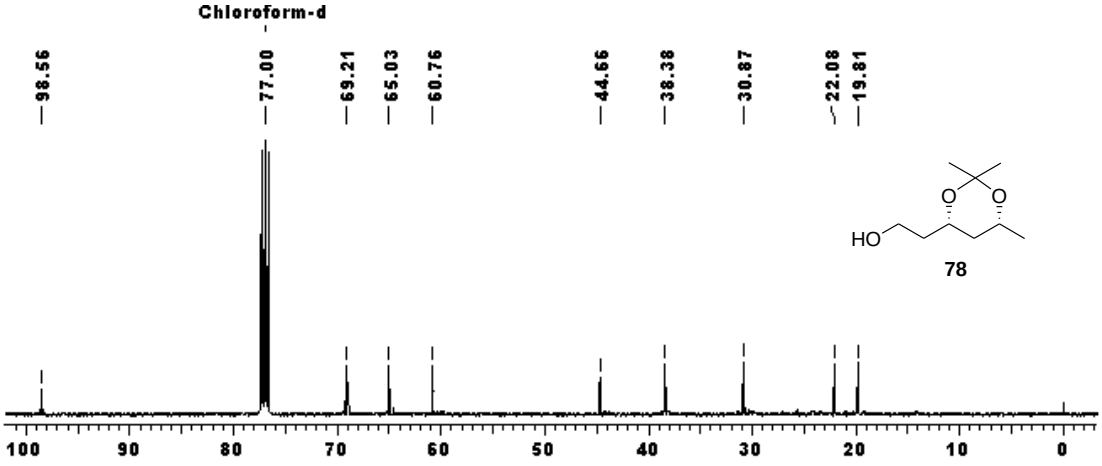
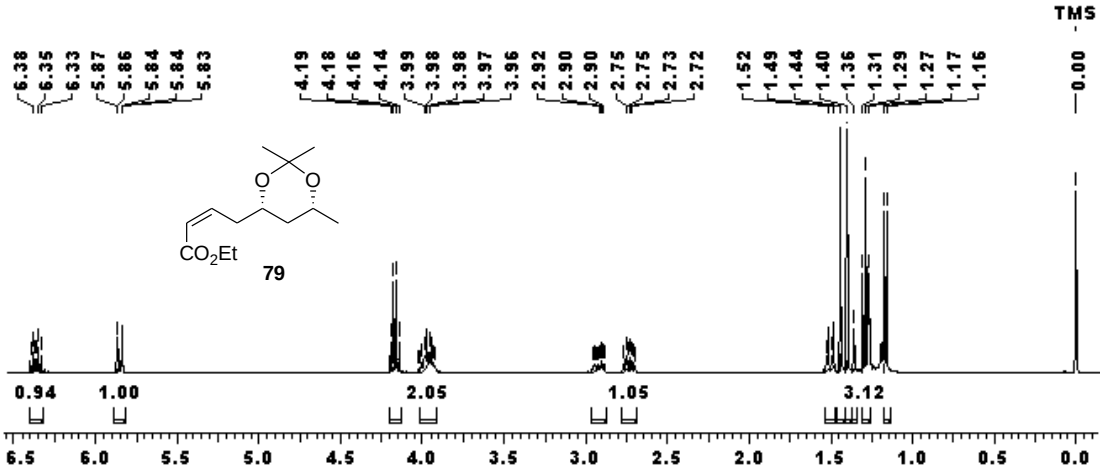


Fig. 14: ^{13}C NMR spectrum of 78

At this stage, we turned our attention to the construction of the pyranone functionality of tarchonanthuslactone (**1**). To achieve this, we converted alcohol **78** into the corresponding *cis*-enoate **79** as follows: alcohol **78** on Swern oxidation gave the aldehyde *in situ* which was then subjected to Horner-Wittig-Emmons olefination with ethyl (di-*o*-tolylphosphono)acetate[33] and NaH in THF to obtain *Z*-unsaturated ester **79** (stereochemistry confirmed by ^{1}H NMR analysis) in 80% yield over the two steps. Two sets of triplet of doublet at δ 5.85 (J = 1.54, 11.49 Hz) and 6.35 (J = 7.25, 11.46 Hz) in the ^{1}H NMR spectrum, corresponding to the olefinic protons confirmed the formation of *Z*-unsaturated ester **79** which was further substantiated by the appearance of olefinic and



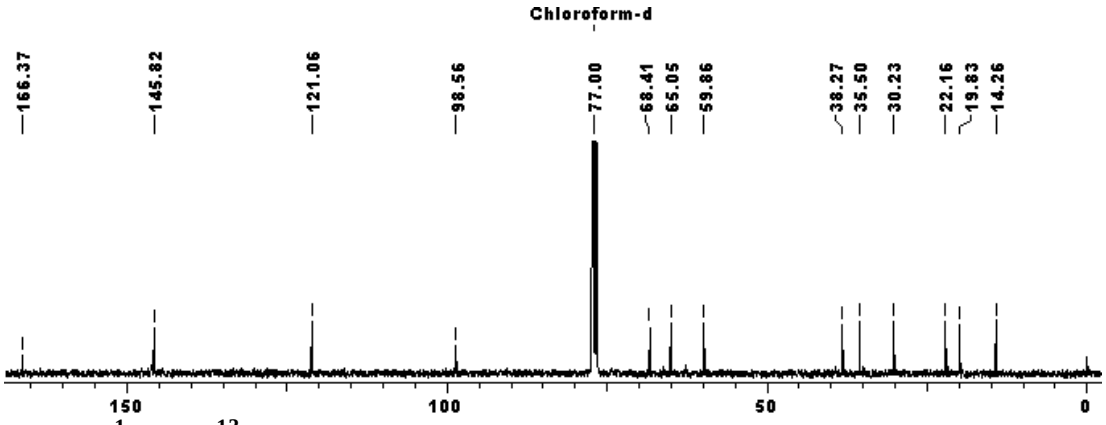
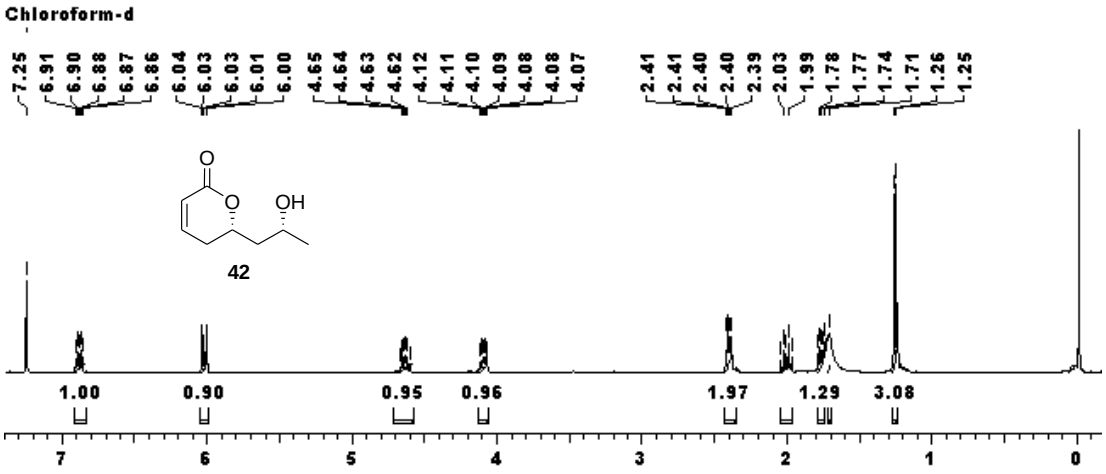


Fig. 15: ^{1}H and ^{13}C NMR spectra of 79

carbonyl carbon peaks at δ 121.06, 145.82 and 166.37 in its ^{13}C NMR spectrum (**Fig. 15**). The formation of unsaturated ester **79** was further confirmed by analyzing its IR spectrum which displayed characteristic carbonyl absorption band at 1713 cm^{-1}.

The deprotection of acetonide unit in **79** followed by its symultaneous cyclization was achieved by treating **79** with pyridinium-*p*-toluene sulfonate (PPTS) in ethanol at 55 °C to give lactenone **42** in 75% yield. The olefinic protons of lactenone **42** have shown as triplet of doublets at δ 6.02 and 6.88 in its ^{1}H NMR spectrum and the carbonyl signal displaying at δ 163.91 in its ^{13}C NMR spectrum confirmed the formation of lactenone **42** (**Fig. 16**). Its IR spectrum showed a broad hydroxyl absorption band at 3550 cm^{-1}.



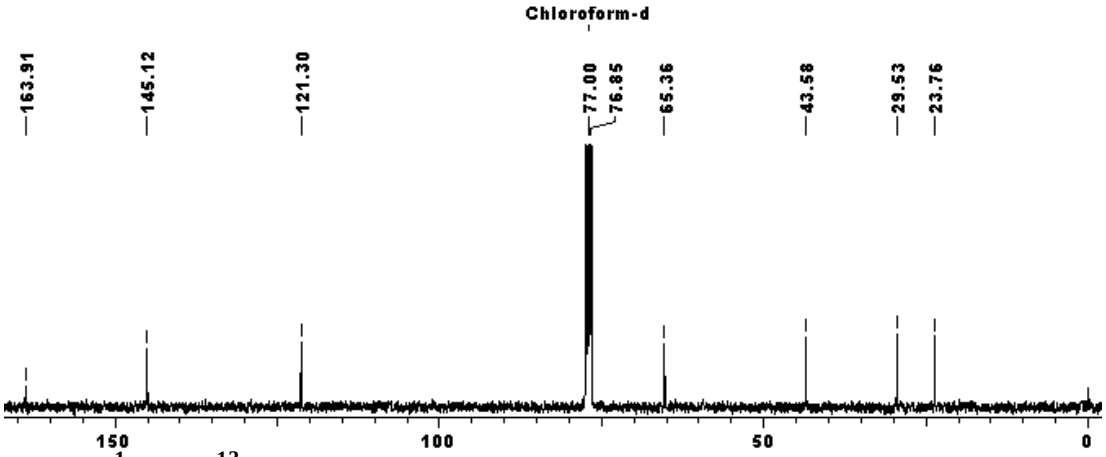


Fig. 16: ^{1}H and ^{13}C NMR spectra of lactenone 42

Esterification of lactenone **42** with TBS-protected dihydrocaffeic acid[4d] in presence of DCC as a coupling agent and catalytic amount of DMAP provided the ester **43** in 85% yield. The ^{1}H and ^{13}C NMR and other analytical data were in accordance with the proposed structure of target molecule **43**. For example, in ^{1}H NMR spectrum of **43**, the characteristic peaks for TBS-group have appeared in the upfield region [δ 0.18 (s, 6H), 0.19 (s, 6H), 0.98 (s, 9H) and 0.99 (s, 9H)] and the corresponding carbon signals appearing at δ -4.23 and 25.82 in its ^{13}C NMR spectrum. The methine carbons which are attached to oxygen atoms have shown signals at δ 67.00 and 74.79 in its ^{13}C NMR spectrum (**Fig. 17**).

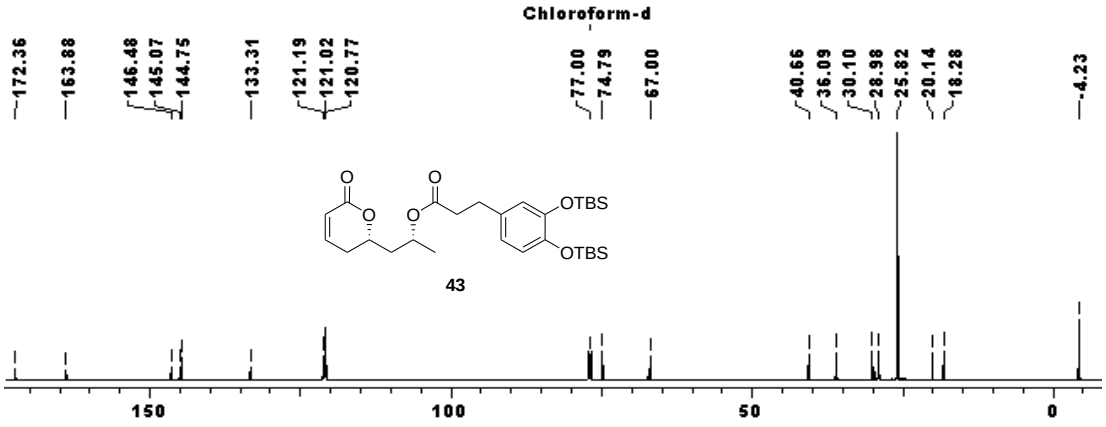


Fig. 17: ^{13}C NMR spectrum of 43

Finally, desilylation of silyl ether **43** with tetrabutylammonium fluoride (TBAF) and benzoic acid[8] in THF furnished tarchonanthuslactone (**1**) in 90% yield. The spectral data of **1** were in complete agreement with the reported values.[8] The ^{1}H NMR spectrum of **1** displayed a doublet at δ 1.22 with J = 5.78 Hz which corresponds to the methyl protons and the olefinic protons have appeared as doublets at δ 5.98 (d, J = 9.42 Hz, 1H) and 6.55 (d, J = 7.17 Hz, 1H). Its ^{13}C NMR spectrum showed the presence of two carbonyl peaks at δ 165.28 and 172.96 and the methine carbons attached to oxygen gave resonance at δ 67.19 and 75.24 (**Fig. 18**).

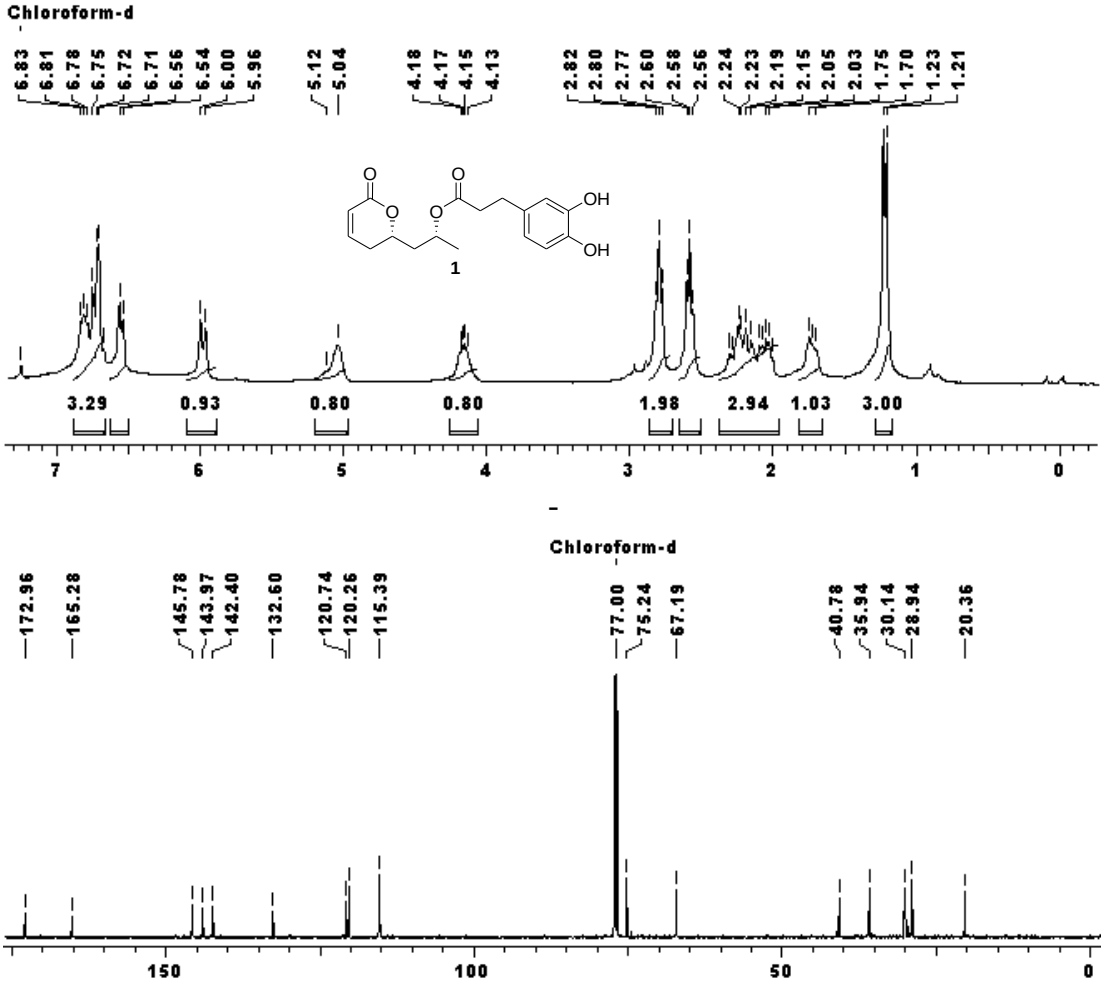


Fig. 18: ^{1}H and ^{13}C NMR spectra of tarchonanthuslactone 1

2.1.6 Conclusion

An efficient and straightforward enantioselective synthesis of polyketide natural product, tarchonanthuslactone (**1**) has been described. The D-proline-catalyzed α-aminooxylation of aldehydes for the introduction of chirality and the subsequent diastereoselective iodine-induced electrophilic cyclization constitute the key reactions for constructing *syn*-1,3-diol moiety. The synthetic strategy described here has significant potential for the synthesis of a variety of other biologically important substituted 1,3-polyol/5,6-dihydropyran-2-one-containing natural products.

2.1.7 Experimental Section

4-(Benzyloxy)butan-1-ol (67)

To a solution of 1,4-butane diol (3.6 g, 40 mmol) in anhydrous DMF was slowly added 60% NaH in oil suspension (1.42 g, 44 mmol) followed by the addition of benzyl bromide (5.25 mL, 44 mmol). The reaction mixture was stirred at 25 °C for 4 h, quenched with cold water, extracted with diethyl ether (3 × 100 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 (7:3) to give benzyl ether **67** (6.8 g) as a colorless oil.

Yield: 95%; **IR** ($CHCl_3$, cm^{-1}): 3624, 3413, 3017, 2941, 2867, 2401, 1952, 1702, 1496, 1455, 1363, 1216, 1099, 957, 932, 850, 771; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.62-1.73 (m, 4H), 2.41 (br s, 1H), 3.50 (t, *J* = 5.61 Hz, 2H), 3.61 (t, *J* = 5.73 Hz, 2H), 4.50 (s, 2H), 7.27-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.04, 29.28, 61.71, 69.91, 72.54, 127.25, 127.33, 128.02, 137.9; **Analysis: $C_{11}H_{16}O_2$** requires C, 73.30, H, 8.95; found: C, 73.01, H, 9.26%.

4-(Benzyloxy)butanal (68)

To a solution of the alcohol **67** (6.48 g, 36 mmol) in DMSO (100 mL) was slowly added IBX (11.09 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 was then extracted with diethyl ether (3 × 100 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 **68** (6.1 g) as a colorless oil.

Yield: 95%; **IR** ($CHCl_3$, cm^{-1}): 3032, 2933, 2864, 1706; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.89 (m, 2H), 2.49 (t, *J* = 7.08 Hz, 2H), 3.45 (t, *J* = 6.01 Hz, 2H), 4.43 (s, 2H), 7.26 (m, 5H), 9.72 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.57, 40.95, 69.13, 72.95, 127.58, 128.36, 128.39, 138.28, 202.17; **Analysis: $C_{11}H_{14}O_2$** requires C, 74.13, H, 7.92; found: C, 74.40, H, 7.61%.

(+)-(*S*)-4-(Benzyloxy)butane-1,2-diol (69)

To a stirred precooled (-20 °C) acetonitrile (50 mL) solution of aldehyde **68** (6.05 g, 34 mmol) and nitrosobenzene (1.82 g, 17 mmol) was added D-proline (0.49 g, 25 mol%). The reaction mixture was allowed to stir at the same temperature for 24 h followed by the addition of MeOH (20 mL) and $NaBH_4$ (1.94 g, 51 mmol) to the reaction mixture, which was stirred for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aminooxy alcohol which was directly taken up for the next step without purification.

To a MeOH (50 mL) solution of the crude aminooxyalcohol was added $CuSO_4.5H_2O$ (1.28 g, 5.1 mmol) at 0 °C and the reaction mixture was allowed to stir for 10 h at that temperature. After addition of phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 × 60 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude diol which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4) to give diol **69** (2.9 g) as a colorless oil.

Yield: 87%; **$[\alpha]^{25}_D$:** +5.02 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3684, 3618, 3470, 3020, 2927, 2400, 2252, 1602, 1521, 1455, 1424, 1216, 1094, 1051, 929, 850, 771, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.65-1.94 (m, 2H), 2.50 (br s, 2H), 3.45-3.72 (m, 4H), 3.87-3.98 (m, 1H), 4.53 (s, 2H), 7.29-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.71, 66.14, 67.13, 69.78, 72.74, 127.44, 127.49, 128.17, 137.84; **Analysis: $C_{11}H_{16}O_3$** requires C, 67.32, H, 8.22; found: C, 67.64, H, 7.95%.

(+)-(*S*)-4-(Benzyloxy)-2-hydroxybutyl methanesulfonate (70)

A solution of diol **69** (2.94 g, 15 mmol) in CH_2Cl_2 (50 mL) was treated with methane sulfonyl chloride (1.75 mL, 22.5 mmol) and Et_3N (4.21 mL, 30 mmol) at 0 °C. After being stirred for 15 min, the mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude mesylate, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4) to give the mesylate **70** (3.78 g) as a colorless oil.

Yield: 92%; **$[\alpha]^{25}_D$**: +0.4 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3407, 3019, 2927, 2400, 1719, 1518, 1454, 1364, 1215, 1176, 1047, 928, 756, 668; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.71-1.75 (m, 2H), 2.94 (s, 3H), 3.16 (br s, 1H), 3.52-3.65 (m, 2H), 3.98-4.07 (m, 2H),

4.11-4.15 (m, 1H), 4.43 (s, 2H), 7.19-7.28 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 32.43, 37.36, 67.59, 68.61, 73.27, 127.68, 127.84, 128.47, 137.64; **Analysis: $C_{12}H_{18}O_5S$** requires C, 52.54, H, 6.61, S, 11.69; found: C, 52.25, H, 6.99, S, 11.77%.

(-)-(*S*)-4-(Benzyloxy)-1,2-epoxybutane (71)

To a solution of mesylate **70** (3.56 g, 13 mmol) in MeOH (50 mL) was added K_2CO_3 (1.79 g, 13 mmol) and the mixture was stirred at 25 °C for 1 h. After the reaction was complete (monitored by TLC), solvent was evaporated and the residue was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give epoxide **71** (2.2 g) as a colorless oil.

Yield: 95%; **$[\alpha]^{25}_D$**: -16.2 (*c* 3, $CHCl_3$) {lit.[27] **$[\alpha]^{23}_D$**: +16.9 (*c* 2.51, $CHCl_3$) for its antipode}; **IR** ($CHCl_3$, cm^{-1}): 3477, 3015, 2925, 2864, 2402, 1725, 1496, 1455, 1362, 1217, 1102, 1028, 910, 831, 766; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.62-1.97 (m, 2H), 2.50 (dd, *J* = 2.7, 5.06 Hz, 1H), 2.76 (dd, *J* = 4.06, 4.94 Hz, 1H), 3.01-3.10 (m, 1H), 3.58-3.64 (m, 2H), 4.52 (s, 2H), 7.29-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.76, 46.68, 49.68, 66.76, 72.79, 127.32, 128.13, 128.80, 138.11; **Analysis: $C_{11}H_{14}O_2$** requires C, 74.13, H, 7.92; found: C, 74.46, H, 7.69%.

(+)-(*R*)-6-(Benzyloxy)-1-hexen-4-ol (72)

Vinyl bromide (6.44 M in THF, 7.76 mL, 50 mmol) was added slowly to magnesium (0.61 g, 25 mmol) in dry THF (25 mL) at 0 °C and the mixture was stirred for 10 min, then cooled to -40 °C and cuprous iodide (0.34 g, 15 mol%) was added. The resulting mixture was stirred for 30 min, at -40 °C and a solution of epoxide **71** (2.14 g, 12 mmol)

in THF (30 mL) was added. After being stirred for 1 h, the mixture was quenched with saturated NH_4Cl solution, extracted with diethyl ether (3 × 100 mL), washed with brine and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give alcohol **72** (2.27 g) as a colorless oil.

Yield: 92%; **$[\alpha]^{25}_D$**: +1.55 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3469, 3067, 3016, 2918, 2866, 2401, 1952, 1811, 1640, 1496, 1455, 1424, 1363, 1216, 1095, 1027, 921, 769; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.71-1.80 (m, 1H), 1.86-1.94 (m, 1H), 2.16-2.28 (m, 1H), 3.26 (dd, *J* = 3.45, 5.05 Hz, 1H), 3.42 (dd, *J* = 2.65, 5.05 Hz, 1H), 3.57-4.04 (m, 3H), 4.52 (s, 2H), 5.05-5.06 (m, 1H), 5.11-5.14 (m, 1H), 5.72-5.93 (m, 1H), 7.27-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.70, 41.72, 68.38, 69.74, 72.97, 117.28, 127.42, 127.54, 128.22, 134.65, 137.76; **Analysis: $C_{13}H_{18}O_2$** requires C, 75.69, H, 8.80; found: C, 75.33, H, 9.01%.

***tert*-Butyl (*R*)-1-(benzyloxy)hex-5-en-3-yl carbonate (73)**

To a solution of alcohol **72** (2.06 g, 15 mmol) in acetonitrile (40 mL) were added $(Boc)_2O$ (3.27 g, 15 mmol) and DMAP (0.48 g, 4 mmol). After stirring for 5 h, the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (30 mL) and imidazole (3.34 g, 49 mmol) was added. The resulting mixture was stirred at 25 °C for 15 minutes and then CH_2Cl_2 was added. The organic phase was washed with 5% HCl solution (3 × 50 mL), dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give carbonate **73** (2.75 g) as a colorless oil.

Yield: 95%; **$[\alpha]^{25}_{D}$**: +33.3 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3686, 3625, 3019, 2983, 2870, 2401, 1737, 1644, 1455, 1395, 1370, 1280, 1216, 1160, 1093, 926, 770; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.90 (dd, *J* = 6.5, 12.89 Hz, 2H), 2.34-2.41 (m, 2H), 3.53 (t, *J* = 6.41 Hz, 2H), 4.49 (s, 2H), 4.83-4.96 (m, 1H), 5.04-5.15 (m, 2H), 5.69-5.86 (m, 1H), 7.28-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.60, 33.70, 38.77, 66.30, 72.89, 73.66, 81.43, 117.78, 127.35, 127.45, 128.16, 133.20, 138.20, 153.05; **Analysis: $C_{18}H_{26}O_4$** requires C, 70.56, H, 8.55; found: C, 70.89, H, 8.29%.

(-)-(4*S*,6*S*)-4-[2-(Benzyloxy)ethyl]-6-(iodomethyl)-1,3-dioxan-2-one (74)

To a stirred solution of **73** (2.76 g, 9 mmol) in acetonitrile (60 mL) was added *N*-iodosuccinimide (4.05 g, 18 mmol) at -40 °C. The mixture was then warmed up and stirred at 0 °C for 12 h. After the reaction was completed (monitored by TLC), 50 mL aq. sodium thiosulfate solution was added, followed by 50 mL of aq. $NaHCO_3$. The reaction mixture was then extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (7:3) to give iodocarbonate **74** (2.87 g) as a colorless oil.

Yield: 85%; **$[\alpha]^{25}_{D}$**: -3.08 (*c* 1.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3019, 2400, 1751, 1523, 1399, 1216, 1104, 988, 770, 669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65-1.76 (m, 1H), 1.92-2.04 (m, 2H), 2.40 (dt, *J* = 3.03, 14.36 Hz, 1H), 3.25 (dd, *J* = 7.37, 10.53 Hz, 1H), 3.38 (dd, *J* = 4.42, 10.52 Hz, 1H), 3.59-3.64 (m, 1H), 3.67-3.73 (m, 1H), 4.39-4.45 (m, 1H), 4.47-4.55 (m, 2H), 4.64-4.71 (m, 1H), 7.28-7.38 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 5.95, 32.96, 34.87, 64.71, 72.79, 75.48, 76.68, 127.40, 127.44, 128.13, 137.67, 148.09; **Analysis: $C_{14}H_{17}IO_4$** requires C, 44.70, H, 4.55; found: C, 44.45, H, 4.77%.

(+)-(2*S*,4*S*)-6-(Benzyloxy)-1,2-epoxyhexan-4-ol (75)

To a stirred solution of **74** (2.6 g, 7 mmol) in MeOH (50 mL) was added K_2CO_3 (4.83 g, 35 mmol) at 0 °C. The mixture was then warmed up and stirred at 25 °C. After the reaction was complete (monitored by TLC), 50 mL of aq. $NaHCO_3$ was added and the reaction mixture was extracted with EtOAc (3 × 60 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (6:4) to give epoxy alcohol, **75** (1.39 g) as a colorless oil.

Yield: 90%; **$[\alpha]^{25}_D$**: +8 (*c* 1.25, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3682, 3491, 3019, 2922, 2400, 2258, 1733, 1479, 1455, 1424, 1362, 1216, 1093, 927, 770, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.59-1.88 (m, 4H), 2.48 (dd, *J* = 2.64, 5.06 Hz, 1H), 2.75 (dd, *J* = 4.22, 4.96 Hz, 1H), 3.04-3.15 (m, 2H), 3.59-3.78 (m, 2H), 3.99-4.11 (m, 1H), 4.52 (m, 2H), 7.26-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.34, 39.70, 46.31, 49.70, 68.41, 68.82, 73.11, 127.49, 127.58, 128.28, 137.78; **Analysis: $C_{13}H_{18}O_3$** requires C, 70.24, H, 8.16; found: C, 70.59, H, 7.89%.

(+)-(2*R*,4*S*)-6-(Benzyloxy)hexane-2,4-diol (76)

A solution of epoxy alcohol **75** (1.33 g, 6 mmol) in THF (30 mL) was added to a stirred slurry of lithium aluminium hydride (0.47 g, 12 mmol). After being stirred for 6 h at 50 °C, the reaction was carefully quenched with water. It was then extracted with EtOAc (3 × 50 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (5:5) to give the diol **76** (1.2 g) as a colorless oil.

Yield: 90%; **[α]$^{25}_{D}$**: +3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3616, 3461, 3019, 2934, 2400, 1519, 1454, 1378, 1215, 1095, 930, 758, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.53 Hz, 3H), 1.54 (t, *J* = 3.62 Hz, 2H), 1.71-1.88 (m, 2H), 2.99 (br s, 2H), 3.62-3.78 (m, 2H), 4.01-4.15 (m, 2H), 4.52 (s, 2H), 7.29-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.66, 36.94, 44.58, 68.31, 71.71, 73.13, 127.57, 127.64, 128.33, 137.72; **Analysis: $C_{13}H_{20}O_3$** requires C, 69.61, H, 8.99; found: C, 69.99, H, 7.54%.

(+)-(4*S*,6*R*)-4-[2-(Benzyloxy)ethyl]-2,2,6-trimethyl-1,3-dioxane (77)

To the solution of diol **76** (0.68 g, 3 mmol) in 2,2-dimethoxypropane (6 mL) was added camphorsulfonic acid (69 mg, 0.3 mmol) and the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was diluted with water, extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give 1,3-dioxane derivative **77** (0.75 g) as a colorless oil.

Yield: 95%; **[α]$^{25}_{D}$**: +4 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3610, 3019, 2400, 1716, 1646, 1523, 1456, 1381, 1215, 1097, 929, 758, 669; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.14 (d, *J* = 5.89 Hz, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 1.53-1.64 (m, 1H), 1.69-1.77 (m, 3H), 3.50-3.60 (m, 2H), 3.92-4.01 (m, 2H), 4.48 (s, 2H), 7.25-7.34 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 19.92, 22.30, 30.34, 36.61, 38.89, 65.11, 65.95, 66.18, 73.00, 98.41, 127.54, 127.63, 128.35, 138.56; **Analysis: $C_{16}H_{24}O_3$** requires C, 72.69, H, 9.15; found: C, 73.01, H, 7.21%.

(-)-(4*S*,6*R*)-2-(2,2,6-Trimethyl-1,3-dioxan-4-yl)ethanol (78)

To a solution of 1,3-dioxane derivative **77** (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 (5:5) to give **78** (0.32 g) as a colorless oil.

Yield: 91%; **$[\alpha]^{25}_{D}$**: -15 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3502, 3054, 2930, 2103, 1734, 1541, 1427, 1382, 1265, 1201, 1111, 1051, 951, 866, 739; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.13-1.23 (m, 4H), 1.37 (s, 3H), 1.44 (s, 3H), 1.53-1.74 (m, 3H), 3.05 (br s, 1H), 3.71-3.81 (m, 2H), 3.96-4.14 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.81, 22.08, 30.87, 38.38, 44.66, 60.76, 65.03, 69.21, 98.56; **Analysis: $C_9H_{18}O_3$** requires C, 62.04, H, 10.41; found: C, 62.36, H, 10.12%.

(-)-(5*S*,7*R*,2*Z*)-Ethyl-5,7-(isopropylidenedioxy)octenoate (79)

To a precooled (-78 °C) solution of $(COCl)_2$ (0.11 mL, 1.2 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.17 mL, 2.4 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at -78 °C for 15 min, then alcohol **78** (0.1 g, 0.6 mmol) was added. The reaction mixture was stirred for 40 min at -78 °C followed by the addition of Et_3N (0.5 mL, 3.6 mmol). The mixture was allowed to warm to 0 °C. After 30 min, the reaction was diluted with water and extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aldehyde, which was immediately used in the next step.

A solution of ethyl (di-*o*-tolylphosphono)acetate (0.23 g, 0.66 mmol) in THF (5 ml) was treated with NaH (17 mg, 0.72 mmol) at -78 °C for 15 minutes. To the above mixture was added a freshly prepared above aldehyde in THF (3 mL) and the resulting mixture

was stirred at -78 °C. After TLC showed completion of the starting material, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 × 20 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give unsaturated ester **79** (0.12 g) as a colorless oil.

Yield: 80%; **$[\alpha]^{25}_D$**: -23.5 (*c* 0.17, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2995, 2940, 2401, 1713, 1645, 1417, 1381, 1216, 1185, 1035, 995, 826, 755, 667; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.09 Hz, 3H), 1.29 (t, *J* = 7.31 Hz, 3H), 1.36 (d, *J* = 1.49 Hz, 1H), 1.40 (s, 3H), 1.44 (s, 3H), 1.50 (dt, *J* = 2.49, 13.05 Hz, 1H), 2.69-2.77 (m, 1H), 2.88-2.96 (m, 1H), 3.92-4.02 (m, 2H), 4.17 (q, *J* = 7.29 Hz, 2H), 5.85 (td, *J* = 1.54, 11.49 Hz, 1H), 6.35 (td, *J* = 7.25, 11.46 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.26, 19.83, 22.16, 30.23, 35.50, 38.27, 59.86, 65.05, 68.41, 98.56, 121.06, 145.82, 166.37; **Analysis: $C_{13}H_{22}O_4$** requires C, 64.44, H, 9.15; found: C, 64.11, H, 9.39%.

(-)-(5*S*,7*R*)-7-Hydroxy-5-(oct-2-enolide) (42)

To a solution of ester **79** (0.11 g, 0.45 mmol) in EtOH (5 mL) was added pyridinium-*p*-toluene sulfonate (10 mg, 10 mol%) and stirred for 12 h at 55 °C. Solvent was evaporated and the residue extracted with EtOAc (3 × 20 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (5:5) to give lactenone **42** (49 mg) as a colorless oil.

Yield: 80%; **$[\alpha]^{25}_D$**: -108 (*c* 0.13, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3550, 2958, 1718, 1472, 1380, 1255, 1216; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.28 Hz, 3H), 1.71 (br s, 1H), 1.74-1.79 (m, 1H), 2.01 (dt, *J* = 8.07, 14.4 Hz, 1H), 2.38-2.41 (m, 2H), 4.06-4.12

(m, 1H), 4.60-4.67 (m, 1H), 6.02 (dt, *J* = 1.73, 9.81 Hz, 1H), 6.88 (dt, *J* = 4.3, 8.52 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.76, 29.53, 43.58, 65.36, 76.85, 121.30, 145.12, 163.91; **Analysis: $C_8H_{12}O_3$** requires C, 61.52, H, 7.74; found: C, 61.85, H, 7.43%.

TBS-protected tarchonanthuslactone (43)

To a solution of alcohol **42** (47 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added TBS-protected hydrocaffeic acid (0.14 g, 0.33 mmol), dicyclohexylcarbodiimide (77 mg, 0.33 mmol) and DMAP (16 mg, 0.13 mmol). The reaction mixture was stirred for 3 h. Ether was added to the solution and the mixture was filtered through a pad of celite. Removal of solvent under reduced pressure provided the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give silyl ether **43** (0.13 g) as a colorless oil.

Yield: 81%; **$[\alpha]^{25}_D$**: -44 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1723, 1505, 1255, 900, 840; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.19 (s, 6H), 0.98 (s, 9H), 0.99 (s, 9H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.78-1.85 (m, 1H), 2.13-2.29 (m, 1H), 2.30-2.35 (m, 2H), 2.52-2.60 (m, 2H), 2.78-2.86 (m, 2H), 4.36-4.50 (m, 1H), 5.06-5.15 (m, 1H), 6.01 (d, *J* = 9.5 Hz, 1H), 6.61-6.85 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ -4.23, 18.28, 20.14, 25.82, 28.98, 30.10, 36.09, 40.66, 67.00, 74.79, 120.77, 120.94, 121.02, 121.19, 133.31, 144.75, 145.07, 146.48, 163.88, 172.36; **Analysis: $C_{29}H_{48}O_6Si_2$** requires C, 63.46, H, 8.81; found: C, 63.74, H, 8.60%.

Tarchonanthuslactone (1)

Benzoic acid (40 mg, 0.33 mmol) was added to a solution of TBS-protected tarchonanthulactone **43** (59 mg, 0.11 mmol) in THF (2 mL). A 1.0 M solution of TBAF in THF (0.25 mL) was added to the solution. The mixture was stirred at 25 °C for 2 h.

Solvent was evaporated and the residue extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4) to give tarchonanthuslactone (**1**) (30 mg) as a colorless oil. **Yield**: 88%; **[α]$^{25}_{D}$**: -76 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3412, 1720, 1600, 1520, 1445, 1380, 1260, 1010; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.22 (d, *J* = 5.78 Hz, 3H), 1.70-1.75 (m, 1H), 2.0-2.10 (m, 1H), 2.15-2.30 (m, 2H) 2.58 (t, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.61 Hz, 2H), 4.13-4.18 (m, 1H), 5.04-5.12 (m, 1H), 5.98 (d, *J* = 9.42 Hz, 1H), 6.55 (d, *J* = 7.17 Hz, 1H), 6.67-6.83 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.36, 28.94, 30.14, 35.94, 40.78, 67.19, 75.24, 115.39, 120.26, 120.74, 132.60, 142.40, 143.97, 145.78, 165.28, 172.96; **Analysis: $C_{17}H_{20}O_6$** requires C, 63.74, H, 6.29; found: C, 63.41, H, 6.52%.

Mosher's ester of (+)-(*S*)-4-(Benzyloxy)butane-1,2-diol (80)

A two-neck 10 mL flask equipped with septum was charged with (49 mg, 0.24 mmol) *N*,*N*'- dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 ºC for 10 min and a solution of diol **69 (**40 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (51 mg, 0.22 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 ºC for additional one hour and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over

anhyd. Na_2SO_4 and then concentrated under reduced pressure to give Mosher's ester **80** (47 mg) as a thick syrup.

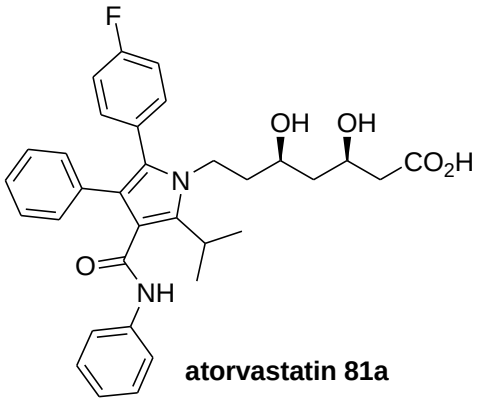
Yield: 75%; **$[\alpha]^{25}_D$**: +36 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3484, 3019, 2856, 2401, 1749, 1496, 1453, 1363, 1266, 1216, 1171, 1106, 1021, 928, 759, 668; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74-1.80 (m, 2H), 2.88 (br s, 1H), 3.56 (s, 3H), 3.60-3.71 (m, 2H), 4.08-4.14 (m, 1H), 4.26-4.35 (m, 2H), 4.50 (s, 2H), 7.29-7.40 (m, 8H), 7.53-7.55 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 32.76, 55.47, 67.87, 68.56, 69.50, 73.34, 84.58, 127.38, 127.69, 127.84, 128.43, 128.49, 129.66, 132.17, 137.72, 166.49; **Analysis: $C_{21}H_{23}F_3O_5$** requires C, 61.16, H, 5.62; found: C, 61.49, H, 5.43%.

Section II

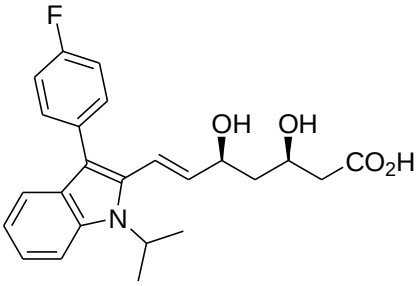
An efficient organocatalytic route to the atorvastatin side-chain

2.2.1 Introduction

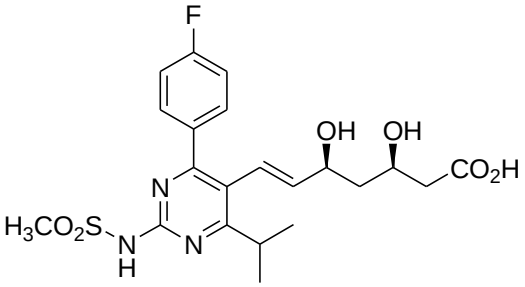
Statins act by inhibiting HMG-CoA reductase (HMG = 3-hydroxy-3-methylglutaryl), the rate-limiting enzyme in cholesterol biosynthesis.[34] They not only lower the low-density lipoprotein (LDL) cholesterol as well as triglyceride levels but also increase the levels of high-density lipoprotein (HDL). Statin drugs like atorvastatin, fluvastatin or rosuvastatin (**Fig. 19**) are composed of large lipophilic residues and a C-7 carboxylic acid side-chain bearing a *syn*-1,3-diol. Atorvastatin (**81a**, lipitor ®), a statin launched in 1997, is now the worlds largest-grossing drug with 2004 sales of $ 12 billion. Due to their biological importance, a number of routes to these statin side-chains have been reported.[35-55]



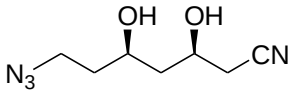
atorvastatin 81a



fluvastatin 82



rosuvastatin 83



atorvastatin side-chain 81b

Fig. 19

2.2.2 Pharmacology of atorvastatin

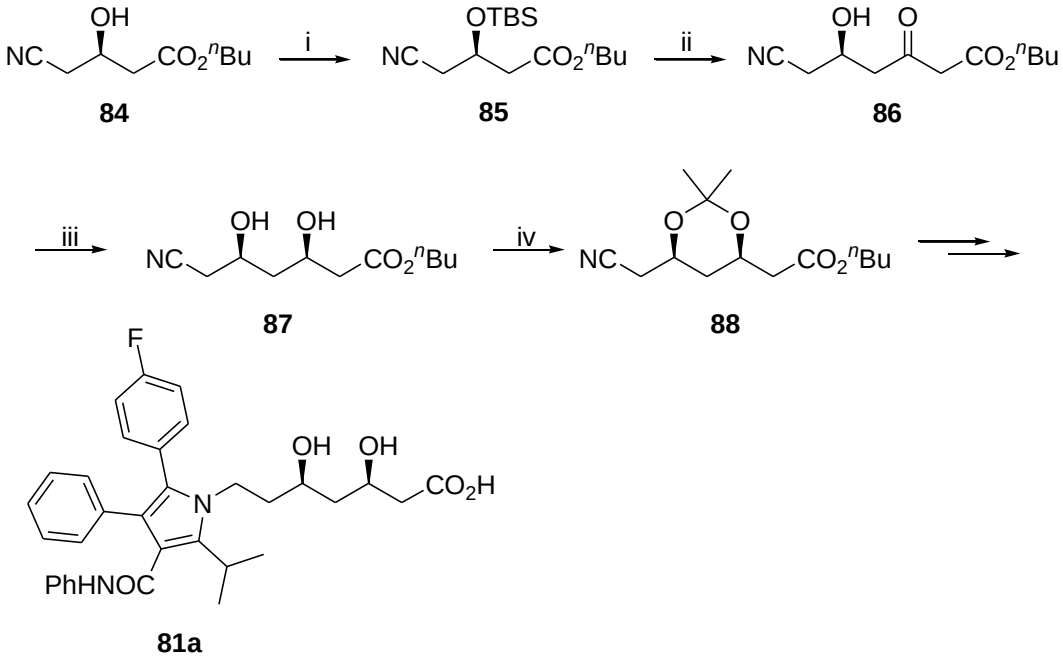
Coronary heart disease (CHD) is a leading cause of death worldwide.[56] Epidemiological evidence indicates that there is a strong link between hypercholesterolemia and the risk of CHD.[57] As a consequence, significant efforts have been undertaken to lower the cholesterol levels in hypercholesterolemic patients to mitigate this risk factor. Currently, the most successful and widely utilized method for treating hypercholesterolemia is the use of HMG-CoA reductase inhibitors, which block the rate limiting step of cholesterol synthesis.[58] As a class, HMG-CoA reductase inhibitors have proven to be well tolerated and remarkably effective. When cholesterol biosynthesis is inhibited, the low density lipoprotein cholesterol (LDL-c) receptor is upregulated and LDL-c is rapidly cleared from the bloodstream.[59] In addition to lowering LDL-c, statins have been shown to lower very low density lipoprotein cholesterol (VLDL-c) and triglycerides, and sometimes raise HDL-c. Furthermore, results from multiple clinical studies have indicated that statins may be beneficial for restoring endothelial function, stimulating bone formation, decreasing vascular inflammation and enhancing the stability of plaques associated with atherosclerosis.[60] An adverse side effect occasionally associated with all statins is myalgia, mild muscle pain or weakness which generally increases with higher doses of the drug.[61]

2.2.3 Review of Literature

Literature search revealed that there are several reports[35-55] available for the synthesis of atorvastatin side-chain (**81b**) involving chiral pool synthesis,[35,36,38] classical resolution of racemates,[42] use of intact cells which secrete the final building block into the culture broth,[43] enzymatic desymmetrization[48,54] and enantioselective syntheses, some of which are described below.

Roth's approach (1992)[38]

Roth *et al.* have achieved a formal synthesis of atorvastatin (**81a**) starting from cyanoester **84** which was protected as its silyl ether using TBSCl to provide **84**. The TBS-protected compound **85** was hydrolyzed and chain extended by activation using *N*,*N*-carbonyldiimidazole followed by reaction with magnesium salt of potassium *t*-butyl malonate. Acidification followed by deprotection with buffered fluoride ion gave **86**, which was subjected to diastereoselective reduction using diethylmethoxy borane and $NaBH_4$ to furnish *syn*-1,3-diol **87**. The 1,3-diol **87** was protected as its acetonide using 2,2-dimethoxypropane under acidic condition to provide atorvastatin side-chain intermediate **88**, thus making a formal synthesis (**Scheme 13**).



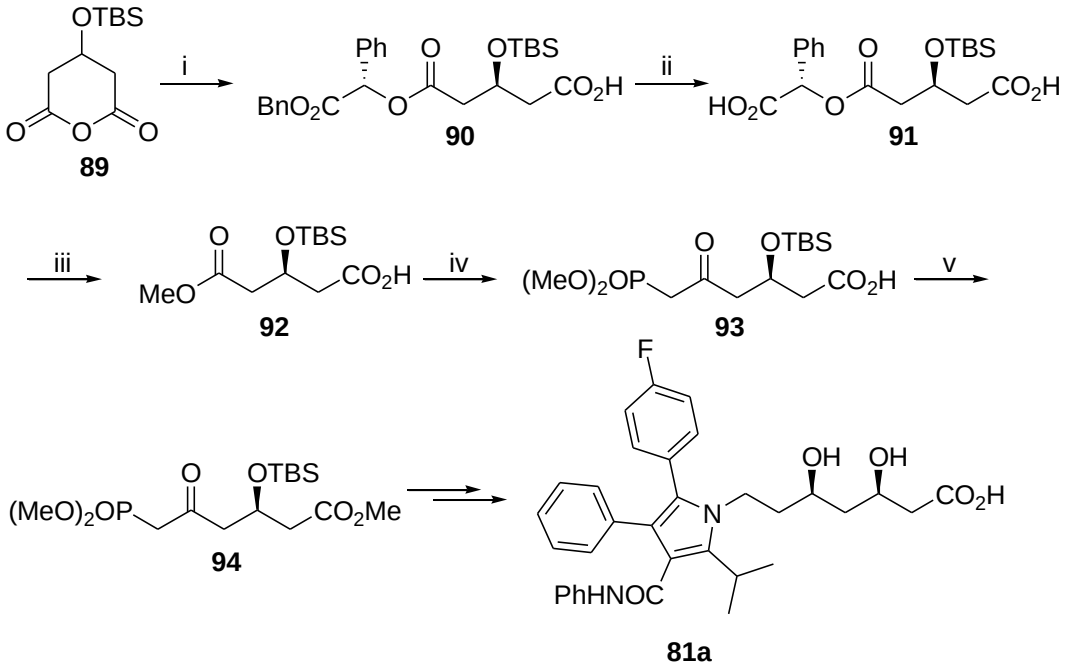
84 85 86 87 88 81a

Scheme 13: (i) TBSCl; (ii) (a) NaOH; (b) carbonyldiimidazole; (c) $Mg(O_2CCH_2CO_2{}^tBu)_2$; (d) Bu_4NF, AcOH, THF; (iii) $NaBH_4$, MeOH, Et_2BOMe, -90 °C; (iv) $(Me)_2C(OMe)_2$, *p*-TsOH, 65%.

Konoike's approach (1994)[40]

Konoike *et al.* have described the synthesis of atorvastatin synthon (**94**) starting from the

prochiral anhydride **89**, which was reacted with lithium salt of benzyl (*R*)-mandelate in THF at -78 °C to give **90** in 99% yield with 9:1 diastereoselectivity. Hydrogenation of benzyl ester **90** with H_2, $Pd(OH)_2/C$ gave **91** which was converted into **92** in 99% yield by ester exchange with excess of NaOMe in MeOH. Wittig ester **93** was prepared from ester **92** by treating it with lithiated methyltriphenylphosphonium bromide in THF. Methyl ester formation from carboxylic acid **93** was accomplished *via* a phosphinyl enol lactone obtained by dehydration of **93** with MsCl, Et_3N followed by treatment with methanol and catalytic amount of sodium methoxide to afford the atorvastatin synthon **94** in 67% yield (**Scheme 14**).

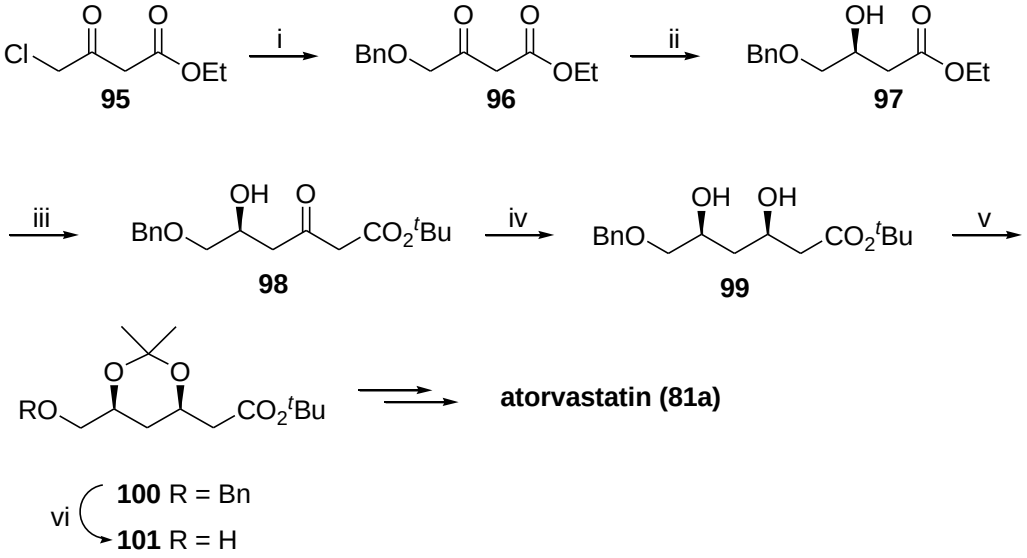


Scheme 14: (i) benzyl (*R*)-mandelate, *n*-BuLi, THF, -78 °C, 99%; (ii) H_2, $Pd(OH)_2/C$, EtOAc, 25 °C; (iii) NaOH, MeOH, <7 °C, 99%; (iv) *n*-BuLi, methyltriphenylphosphonium bromide, THF, -60 °C, 98%; (v) (a) MsCl, Et_3N, CH_2Cl_2, 25 °C, 82%; (b) NaOMe, MeOH, 0 °C, 67%.

Beck's approach (1995)[41]

Beck *et al.* have synthesized atorvastatin side-chain intermediate (**101**) starting from ethyl 4-chloroacetate **95**, which was converted into benzyloxyacetoacetate **96** on treatment

with NaH and BnOH. The asymmetric reduction of β-ketoester **96** with $RuCl(C_6H_6)$(*R*)-BINAP as catalyst under H_2 atmosphere provided alcohol **97** in 96% yield and 97% ee. The alcohol **97** was subjected to Claisen condensation with the enolate prepared from *tert*-butyl acetate and LDA to afford β-ketoester **98** which was diastereoselectively reduced using Et_3B and $NaBH_4$ to give the *syn*-1,3-diol **99**. The *syn*-1,3-diol **99** was then protected as its acetonide using 2,2-dimethoxypropane to provide **100**, which on hydrogenation with H_2 (1 atm) and 10% Pd/C afforded the atorvastatin side-chain **101** in 96% ee (**Scheme 15**).

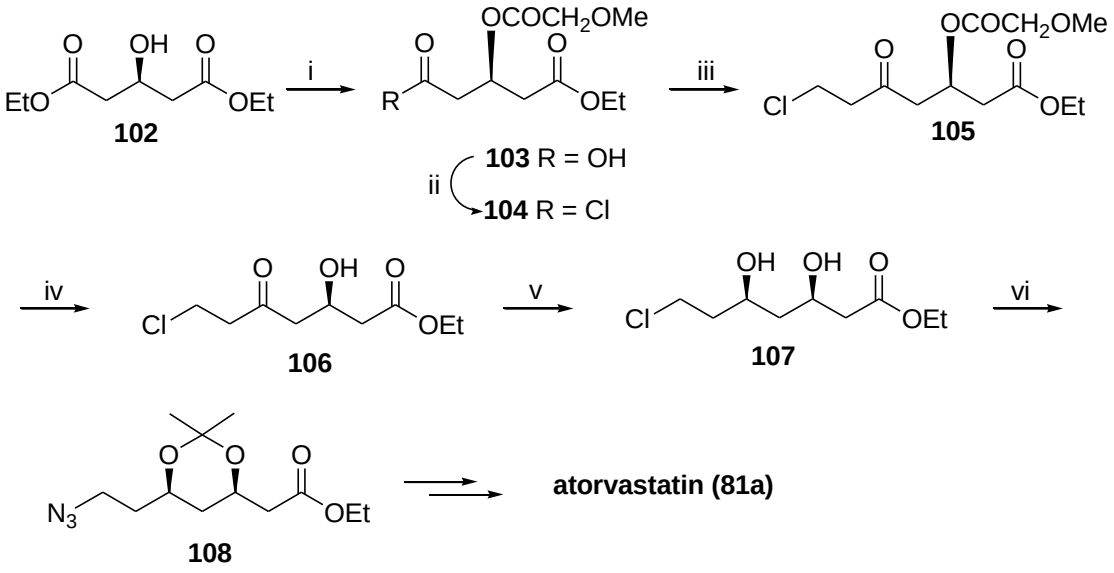


Scheme 15: (i) (a) BnOH, NaH, toluene, 20 °C; (b) high vacuum distillation, 84%; (ii) (a) cat. $RuCl(C_6H_6)$(*R*)-BINAP, EtOH, 100 °C, H_2 (4 atm) 6 h ; (b) high vacuum distillation, 96%; (iii) $CH_2=C(O^tBu)OLi$, THF, -40 °C, 2 h; (iv) (a) Et_3B, $NaBH_4$, CH_3OH/THF, -60 °C, 5 h; (b) H_2O_2, THF/H_2O, 10 °C, 1 h, 80%; (v) (a) 2,2-dimethoxypropane, cat. *p*-TsOH, acetone, 24 °C, 4 h; (b) SiO_2 chromatography, 55%; (vi) H_2 (1 atm), 10% Pd/C, EtOAc, 32 °C, 5 h, 100%.

Ohrlein's approach (2003)[48]

Roth *et al.* have achieved a formal synthesis of atorvastatin (**81a**) starting from the diester **102**, which was acylated with methoxyacetic acid and subsequently desymmetrized to give acid **103** in quantitative yield. Treatment of acid **103** with oxalyl chloride provided

acid chloride **104**, which was subjected to Friedel-Crafts-like chain elongation with gaseous ethylene and aluminium chloride. Deacylation of **105** was carried out with pig liver esterase to give alcohol **106** which was diastereoselectively reduced using Et_3B and $NaBH_4$ to give the *syn*-1,3-diol **107**. Protection of 1,3-*syn*-diol **107** with 2,2-dimethoxypropane under acidic condition followed by displacement of chloride with azide provided the atorvastatin side-chain intermediate (**108**), in 98% yield and 98.1% ee, thus constituting a formal synthesis (**Scheme 16**).

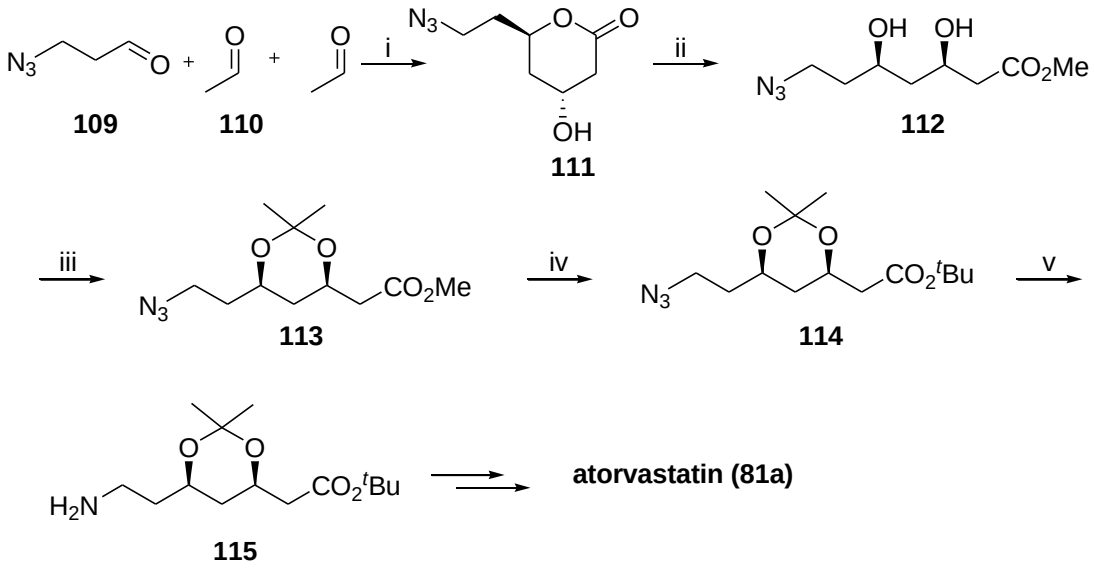


Scheme 16: (i) (a) $ClCOCH_2OMe$, pyridine, 98%; (b) α-chymotrypsin, 0 °C, 100%; (ii) $(COCl)_2$, 0 °C, 100%; (iii) $(CH_2Cl)_2$, 0 °C, ethylene, $AlCl_3$, 89%; (iv) pig liver esterase (PLE), pH = 7.76; (v) BEt_3, $NaBH_4$, -78 °C, 91%; (vi) (a) 2,2-dimethoxypropane, H^+, 98%; (b) NaN_3, DMF, 94%, 98.1% ee, 96.8% de.

Wong's approach (2004)[49]

Wong *et al.* have synthesized atorvastatin synthon (**115**) by using a sequential aldol reaction in which 3-azidopropionaldehyde **109** was treated with acetaldehyde **110** in presence of an enzyme Ser238Asp to give the lactone product **111** in 35%yield. The lactone **111** was then opened under basic conditions to afford *syn*-1,3-diol **112**, which was then protected as its acetonide using 2,2-dimethoxypropane in presence of

camphorsulfonic acid to afford **113** in 76% yield. The methyl ester **113** was then hydrolyzed and subsequently esterified as its *tert*-butyl ester **114** using Boc_2O in presence of DMAP. Reduction of **114** with triphenylphosphine afforded the atorvastatin synthon **115** in 72% yield (**Scheme 17**).

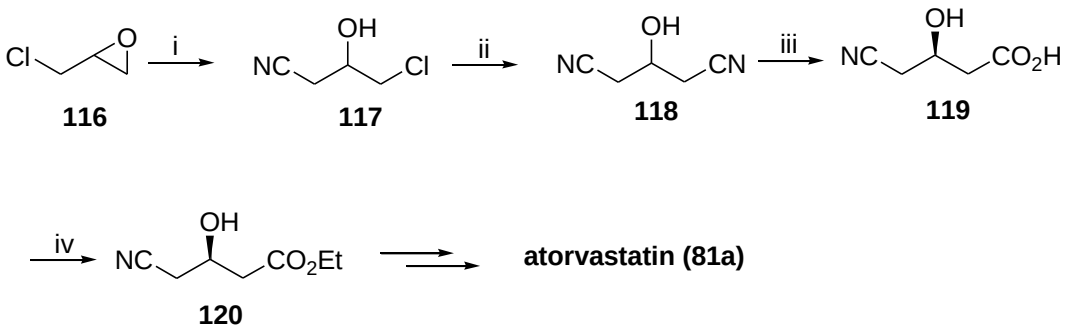


Scheme 17: (i) (a) Ser238Asp; (b) Br_2, $BaCO_3$, 35%; (ii) MeONa, MeOH, 83%; (iii) camphorsulfonic acid, 2,2-dimethoxypropane, 76%; (iv) (a) LiOH, MeOH-H_2O, 83%; (b) Boc_2O, DMAP, 86%; (v) Ph_3P, 3 d, 72%.

Holt-Tiffin's approach (2006)[54]

Konoike *et al.* have described the synthesis of atorvastatin synthon (**120**) starting from epichlorohydrin **116**, which was reacted with HCN in presence of phase transfer catalyst to give 4-chloro-3-hydroxybutyronitrile **117** in 92% yield. Displacement of the chloride function in **117** with cyanide was achieved to give **118** in 68% yield on treatment with aqueous NaCN. The dicyano compound **118** was then subjected to enzyme-catalyzed desymmetrization using nitrilase enzyme (BD9570) at a pH of 7.5 to provide (*R*)-4-cyano-3-hydroxybutyric acid **119** in 81% yield. The esterification of **119** was then

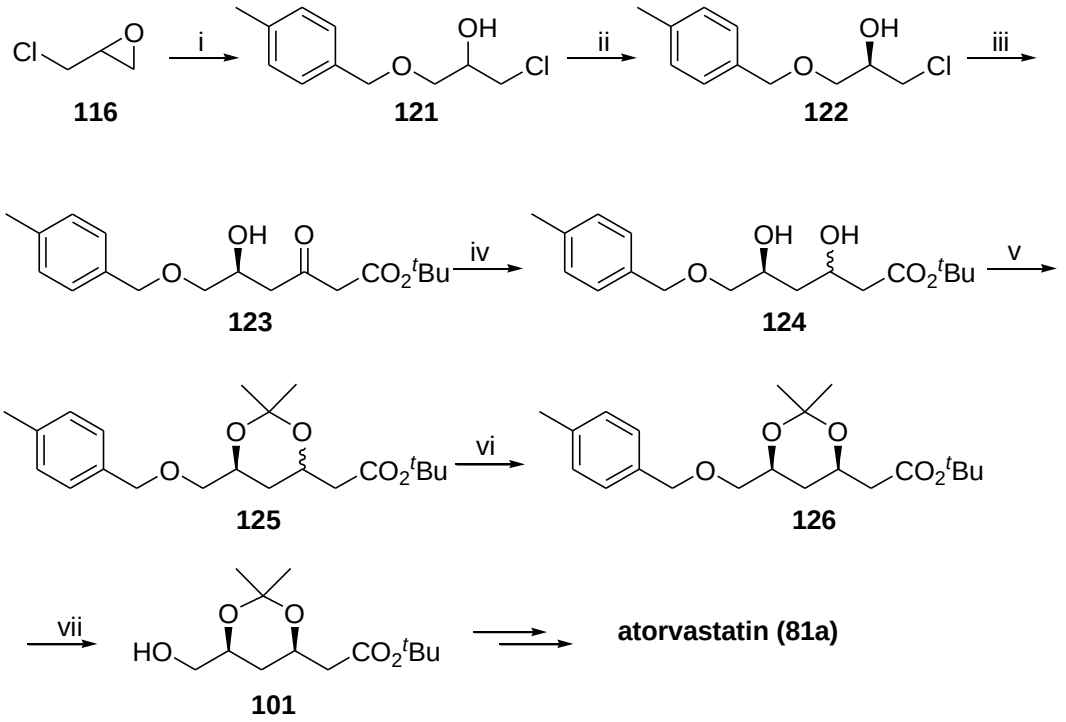
accomplished on treatment with ethanol and sulfuric acid to afford atorvastatin synthon (**120**) in 99% yield and 98.7% ee (**Scheme 18**).



Scheme 18: (i) HCN, triethanolamine, H_2O, 50 °C, 12 h, 92%; (ii) 30% aqueous NaCN, HCl, 50 °C, 4 h, 68%; (iii) pH 7.5 NaH_2PO_4, nitrilase BD9570, 27 °C, 16 h, 81%; (iv) $EtOH/H^+$, 80 °C, 1 h, 99%, 98.7% ee.

Yang's approach (2007)[55]

Yang *et al.* have achieved a formal synthesis of atorvastatin (**81a**) starting from epichlorohydrin **116**, which on treatment with *p*-methylbenzyl alcohol in presence of base gave the corresponding epoxide. It was subsequently opened with NH_4Cl and DMSO to give chloro-3-(4-methylbenzyloxy)-2-propanol **121** in 85% yield. Lipase-catalyzed asymmetric esterification of **121** gave the halohydrin **122** with 98% ee. β-Hydroxy ketone **123** was formed in an overall yield of 58% from **122** by the addition of sodium cyanide, followed by hydroxyl group protection and condensation with *tert*-butyl-2-bromoacetate. β-ketoester **123** was then reduced by sodium borohydride in aqueous isopropyl alcohol giving alcohol **124** with *syn*:*anti* = 4:1. After acid-catalyzed protection of **124** with 2,2-dimethoxypropane, *syn*/*anti*-**125** was treated with aqueous acid to give diastereomeric mixture, which was separable by column chromatography. The resulting protected *syn*-1,3-diol **126** was subjected to hydrogenolysis to afford atorvastatin side-chain (**101**) in 90% yield and 98% de (**Scheme 19**).



Scheme 19: (i) (a) 40% NaOH, *p*-methylbenzyl alcohol, aq. *n*-Bu_4NBr, 10 °C, 24 h, 80%; (b) DMSO, NH_4Cl, 75 °C to 80 °C, 8 h, 85%; (ii) vinyl acetate, the lipase from *Alcaligenes* sp. (PL), a mixed solvent (*n*-hexane/acetonitrile = 3:1, v/v), 30 °C, 25 h, 48%; (iii) (a) NaCN, DMSO, 70 °C, 7 h, 80%; (b) TMSCl, Et_3N, THF, 0 °C, 12 h, 95%; (c) $BrCH_2CO_2{}^tBu$, Zn, $MeSO_3H$, THF, reflux 4 h, then, 3 M HCl, 0 °C, 3 h, 76%; (iv) $NaBH_4$, $^iPrOH/H_2O$, 0 °C, 4 h, 85%; (v) $Me_2C(OMe)_2$, camphorsulfonic acid, 25 °C, 4 h, 95%; (vi) 0.50 M *p*-TsOH, CH_2Cl_2, 25 °C, 10 h, 65%; (vii) H_2 (20 atm), 10% Pd/C, EtOAc, 32 °C, 16 h, 90%.

2.2.4 Present Work:

2.2.4.1 Objective

The stereoselective synthesis of 1,3-polyol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-polyols in various biologically active natural products and drugs and may be utilized for synthesizing HMG-CoA reductase inhibitors, such as atorvastatin (**81a**), fluvastatin (**82**), rosuvastatin (**83**) etc. Due to their biological importance, a number of different routes to statin side-chains have been reported.[35-55] However, all the reported methods of preparation of the statin side-chain

involve several drawbacks such as loss of 50% of starting material in the case of resolution methods, low volume yields and lengthy and tedious processing steps.

Retrosynthetic analysis of atorvastatin shows that 1,3-diol **81b** emerges as the key intermediate, which could be obtained from iodocarbonate **135**. The iodocarbonate **135** can be prepared by an intramolecular diastereoselective iodolactonization of olefin **131**, which in turn could be prepared by the proline catalyzed α-aminooxylation of readily available *n*-butyraldehyde **68** (**Fig. 20**).

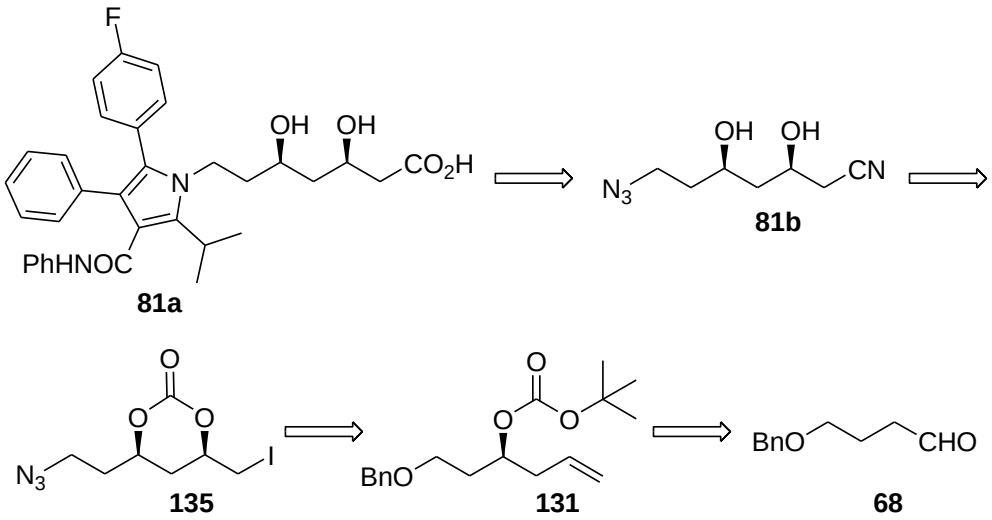
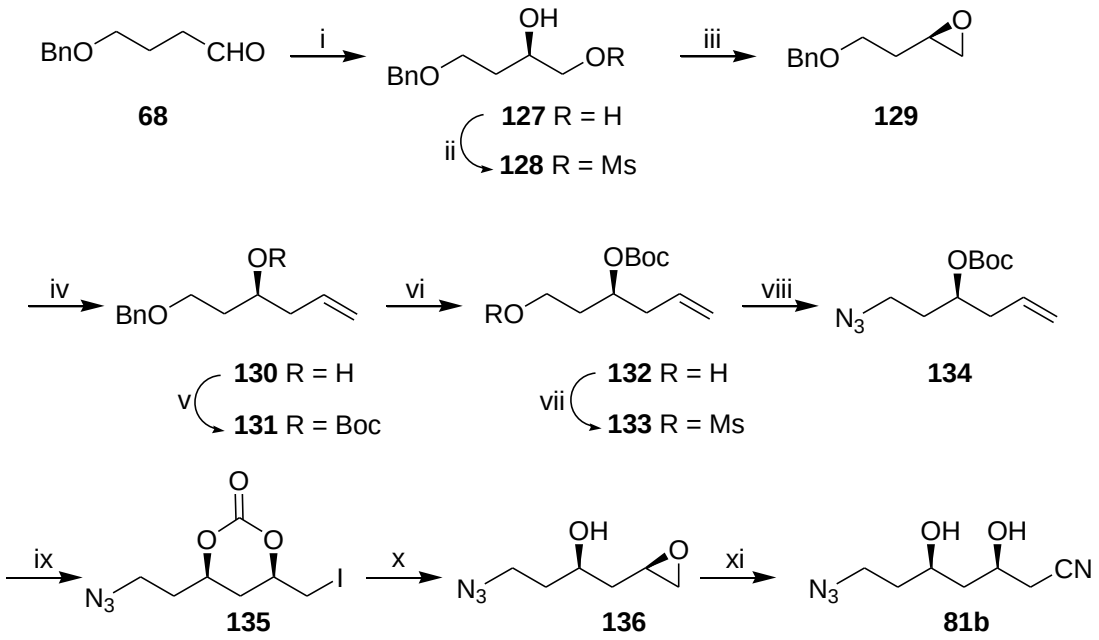


Fig. 20: Retrosynthetic analysis of atorvastatin 81a

2.2.5 Results and Discussion

The complete synthetic sequence for atorvastatin side-chain (**81b**), wherein L-proline-catalyzed α-aminooxylation[24] reaction constitutes a key step for the introduction of chirality, is presented in **Scheme 20**.



Scheme 20: (i) (a) PhNO, L-proline (25 mol%), CH_3CN, -20 °C, 24 h then MeOH, $NaBH_4$; (b) $CuSO_4$ (30 mol%), MeOH, 0 °C, 10 h, 87% (over two steps); (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 92%; (iii) K_2CO_3, MeOH, 25 °C, 1 h, 95%; (iv) vinylmagnesium bromide, THF, CuI, -40 °C, 1 h, 92%; (v) $(Boc)_2O$, DMAP, CH_3CN, 25 °C, 5 h, 95%; (vi) DDQ, CH_2Cl_2:H_2O (2:1), 25 °C, 20 h, 85%; (vii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 94%; (viii) NaN_3, DMF, 60 °C, 2 h, 83%; (ix) NIS, CH_3CN, -40 to 0 °C, 20 h, 87%; (x) K_2CO_3, MeOH, 0 °C to 25 °C, 2 h, 96%; (xi) NaCN, $Ti(O^iPr)_4$, *n*-Bu_4NI, DMSO, 70 °C, 6 h, 80%.

Our synthesis of atorvastatin side-chain (**81b**) was started from the precursor aldehyde **68**, obtained from the corresponding monoprotected 1,4-butanediol **67** by oxidation with IBX in DMSO. The praline-catalyzed α-aminooxylation of aldehyde **68** involves a two-step reaction sequence: (i) reaction of aldehyde **68** with nitrosobenzene as the oxygen source in the presence of 25 mol% L-proline in CH_3CN at -20 °C[24a] followed by treatment with $NaBH_4$ in MeOH to give the crude aminooxy alcohol *in situ* and (ii) subsequent reduction of the crude aminooxy product with 30% $CuSO_4$[25] to yield chiral diol **127** in 86% yield and 97% ee (determined by ^1H NMR analysis of the corresponding Mosher's ester **137** (**Fig. 22**), see experimental section); $[\alpha]^{25}_D$ = -5.02 (*c* 1, $CHCl_3$).

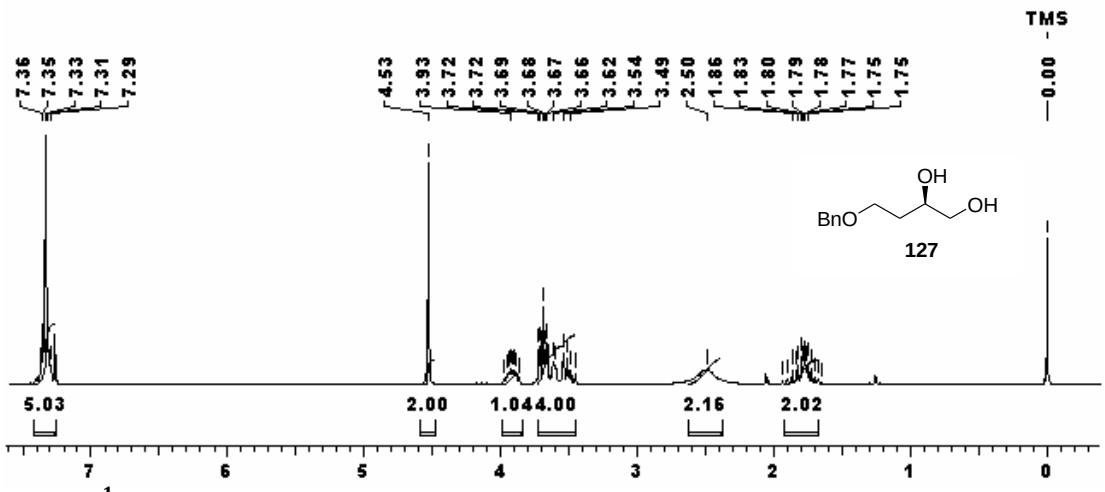


Fig. 21: ^{1}H NMR spectrum of diol 127

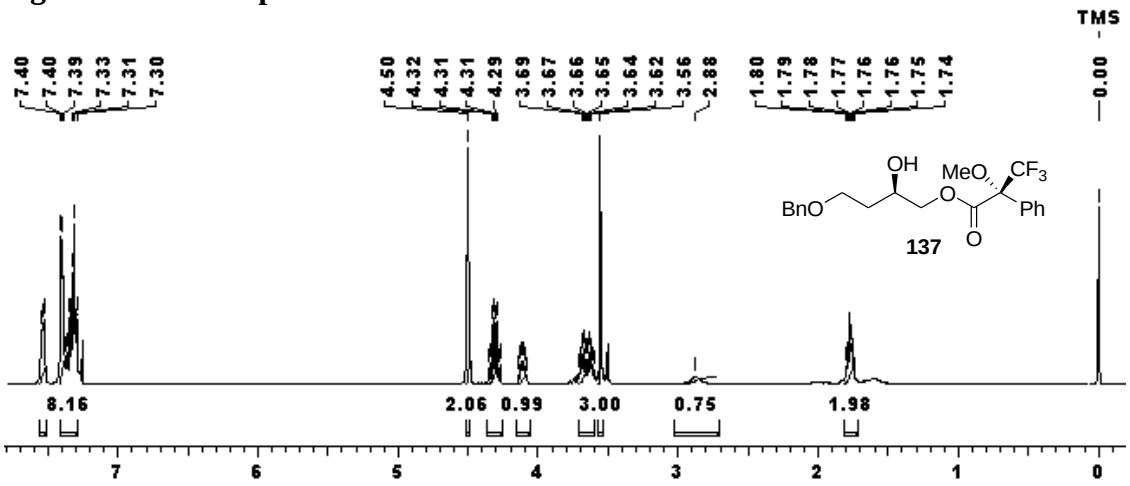


Fig. 22: ^{1}H NMR spectrum of Mosher's ester 137

The formation of the diol **127** was confirmed by the presence of a multiplet at δ 3.93 integrating for one proton (-C**H**OH-) in its ^{1}H NMR spectrum (**Fig. 21**) and further substantiated by the signals in the downfield region of ^{13}C NMR spectrum at δ 66.14, 67.13, 69.78 and 72.74 which correspond to the carbons attached to oxygen atoms. Selective mesylation[26] of the primary alcohol in **127** with mesyl chloride gave mesylate **128**, which on treatment with K_2CO_3 in MeOH yielded the terminal epoxide **129**; $[\alpha]^{25}_{D}$ = +16.4 (*c* 3, $CHCl_3$) {lit.[27] $[\alpha]^{25}_{D}$ = + 16.9 (*c* 2.51, $CHCl_3$)}. The presence of terminal epoxide group was indicated by the ^{1}H NMR signals at δ 2.50 (dd, *J* = 2.7, 5.06 Hz, 1H),

2.76 (dd, *J* = 4.06, 4.94 Hz, 1H) and 3.01-3.10 (m, 1H) and confirmed by characteristic epoxide carbon signals at δ 46.68 (-**C**H_2-O-) and 49.68 (-**C**H-O-) in its ^{13}C NMR spectrum (**Fig. 23**).

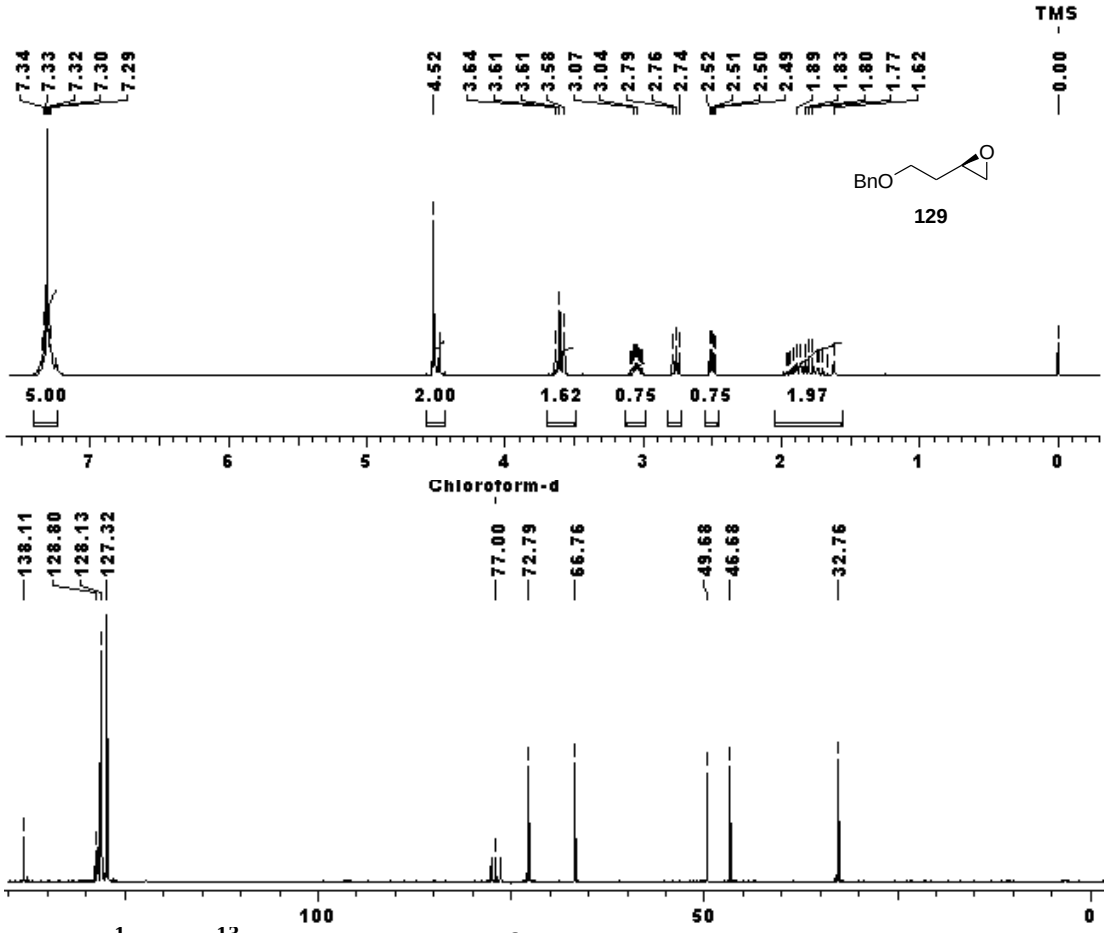


Fig. 23: ^{1}H and ^{13}C NMR spectrum of 129

Regioselective ring opening of the epoxide **129** with vinylmagnesium bromide in presence of CuI[29] in THF at -40 °C afforded the homoallylic alcohol **130** in 92% yield. The ^{1}H and ^{13}C NMR spectral values and other analytical data were in accordance with the proposed structures of **130**. For example, the ^{1}H NMR spectrum of **130** has shown characteristic peaks for olefinic protons at δ 5.05, 5.12 and 5.82 as multiplets which

integrated for one proton each and it was further supported by olefinic signals that appeared at δ 117.28 and 134.65 in its ^{13}C NMR spectrum (**Fig. 24**).

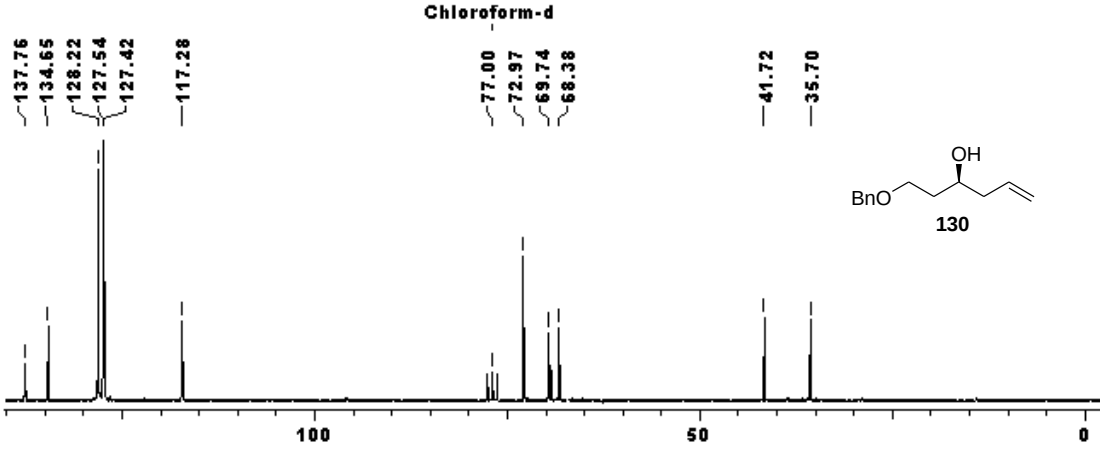


Fig. 24: ^{13}C NMR spectrum of 130

The homoallylic alcohol **130** was protected as its *tert*-butyl carbonate **131** in high yields by treating **130** with di-*tert*-butyldicarbonate and DMAP[29] in CH_3CN. The ^{1}H NMR spectrum of **131** showed a characteristic peak for Boc-group in the upfield region at δ 1.47 integrating for nine protons [-OC(C**H**$_3$)$_3$] (**Fig. 24**) and its ^{13}C NMR spectrum displayed resonances at δ 27.69 [-OC(**C**H$_3$)$_3$], 81.43 [-O**C**(CH$_3$)$_3$] and 153.05 (-O**C**O-).

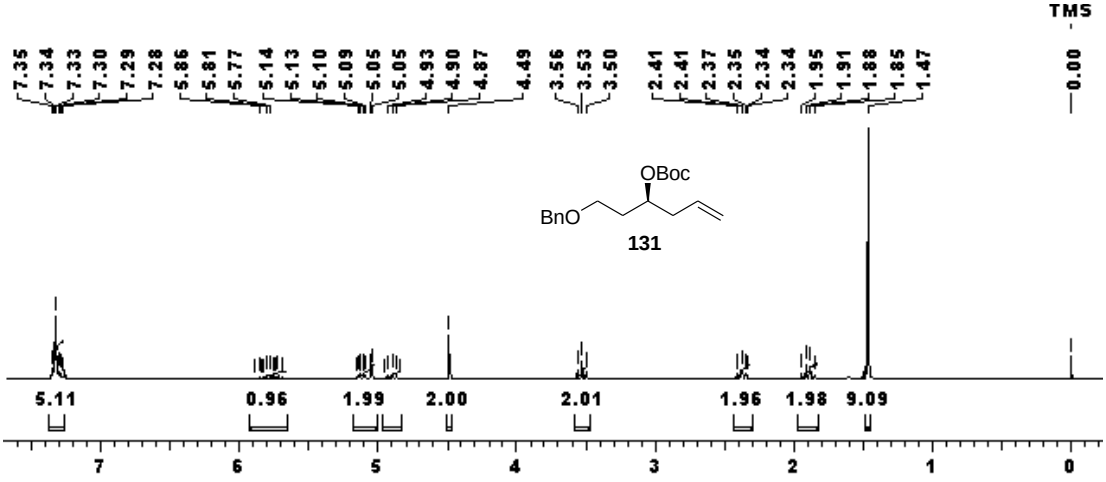


Fig. 25: ^{1}H NMR spectrum of 131

Debenzylation of **131** was achieved with DDQ in a 2:1 mixture of CH_2Cl_2 and H_2O[62] to afford the alcohol **132** in 85% yield. The ^1H and ^{13}C NMR spectra of **132** confirmed the disappearance of benzyl group while a multiplet integrating for two protons has appeared at δ 3.62 in its ^1H NMR spectrum corresponding to the methylene protons (-C**H**$_2$OH). This was further ascertained by the typical signals at δ 58.44 and 73.50 corresponding to the methylene (-**C**H$_2$OH) and methine [-**C**H(OBoc)-] carbons in its ^{13}C NMR spectrum (**Fig. 26**). The IR spectrum of **132** displayed a strong absorption band at 3450 cm^{-1} indicating the presence of hydroxyl group.

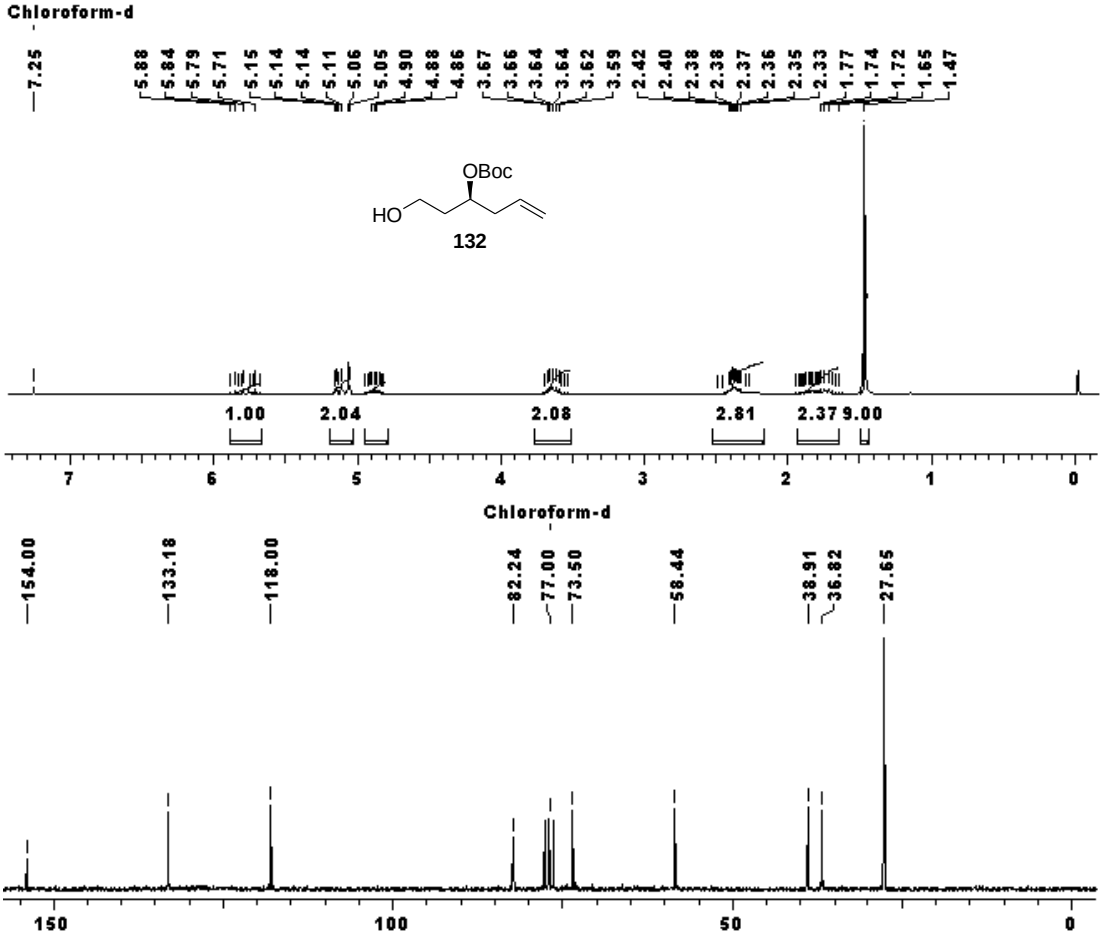


Fig. 26: ^1H and ^{13}C NMR spectra of 132

Mesylation of the primary alcohol **132** was carried out with MsCl and Et_3N in CH_2Cl_2 to give the mesylate **133** in 94% yield. A singlet at δ 3.02 integrating for three protons in its ^{1}H NMR spectrum confirmed the formation of mesyate **133** which was further supported by the appearance of a typical signal at δ 37.29 (-SO_2**C**H_3) in its ^{13}C NMR spectrum (**Fig. 27**).

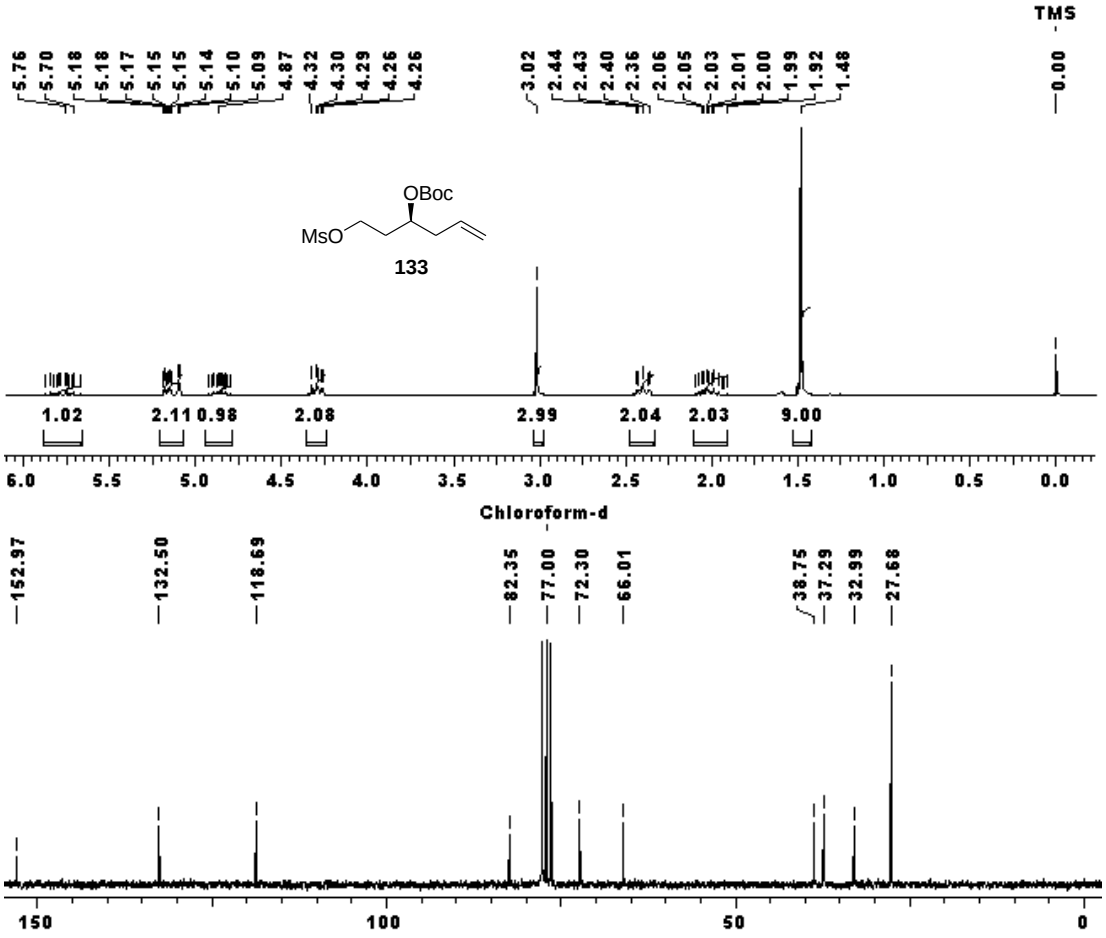


Fig. 27: ^{1}H and ^{13}C NMR spectra of 133

Mesylate **133**, on treatment with NaN_3 in DMF at 60 °C yielded the corresponding azide intermediate **134** in 83% yield. The methylene protons of the carbon attached to azide appeared as a multiplet at δ 3.38 in the ^{1}H NMR spectrum and the corresponding carbon

showed signal at δ 47.65 in the ^{13}C NMR spectrum (**Fig. 28**). The IR spectrum of **134** showed a characteristic azide absorption band at 2101 cm^{-1}.

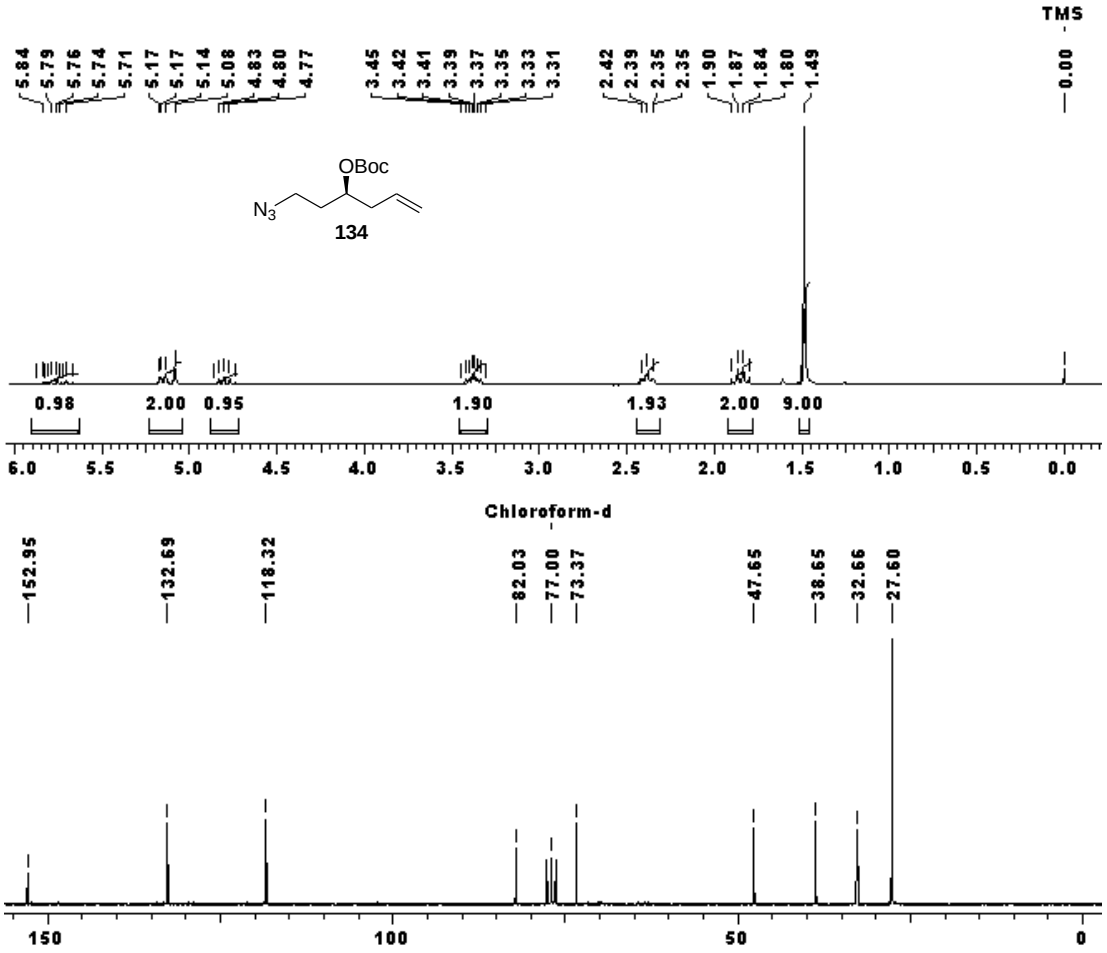


Fig. 28: ^{1}H and ^{13}C NMR spectra of 134

In order to construct the *syn*-1,3-diol moiety from azide **134** with high diastereoselectivity, the iodine-induced carbonate cyclization methodology, originally published by Bartlett[28a] and later improved by Smith[28b] was undertaken. Accordingly, the homoallylic *tert*-butyl carbonate **134** was subjected to the diastereoselective iodolactonization using *N*-iodosuccinimide[30] in CH_3CN at low temperature (-40 to 0 °C) to furnish the iodocarbonate derivative **135** in 85% yield as a single diastereomer (determined by ^{1}H NMR analysis). The ^{1}H and ^{13}C NMR spectra have confirmed the

disappearance of olefin functionality. Its ^{1}H NMR spectrum displayed signals at δ 1.70-1.77 (m, 1H), 1.83-2.02 (m, 2H) 2.35-2.44 (m, 1H), 3.22-3.44 (m, 2H), 3.52-3.59 (m, 2H), 4.39-4.52 (m, 1H), 4.54-4.67 (m, 1H). The carbonyl carbon of the carbonate gave a typical peak at δ 147.86 in the ^{13}C NMR spectrum (**Fig. 29**).

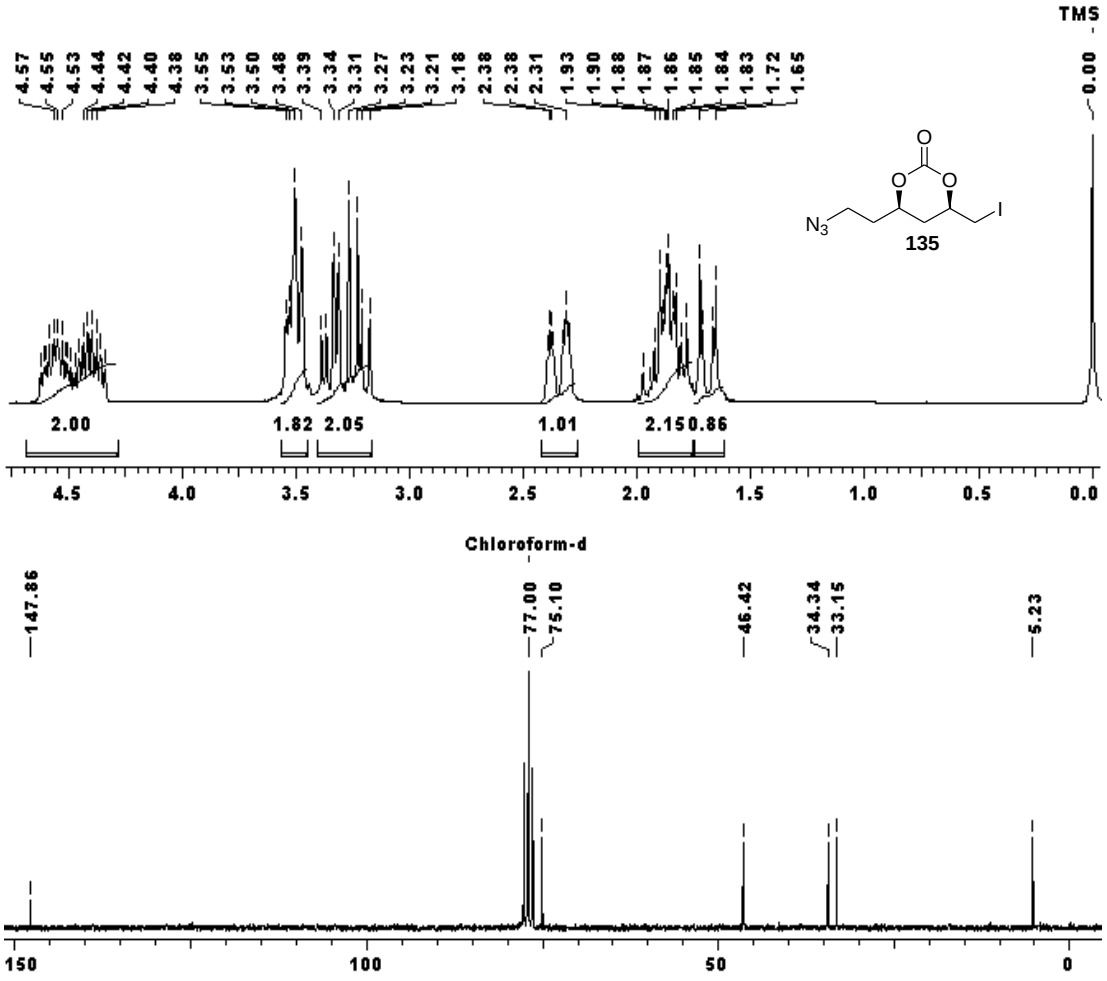


Fig. 29: ^{1}H and ^{13}C NMR spectra of 135

The iodocarbonate **135**, upon exposure to a basic methanolic solution,[30] gave the desired *syn*-epoxy alcohol **136** in 90% yield. The presence of terminal epoxide group was indicated by the ^{1}H NMR signals at δ 2.52 (dd, J = 2.72, 4.83 Hz, 1H), 2.79-2.85 (m, 1H) and 3.07-3.16 (m, 1H) and confirmed by resonances at δ 48.22 and 50.39 corresponding to the methylene and methine carbons of the epoxide in the ^{13}C NMR spectrum (**Fig. 30**).

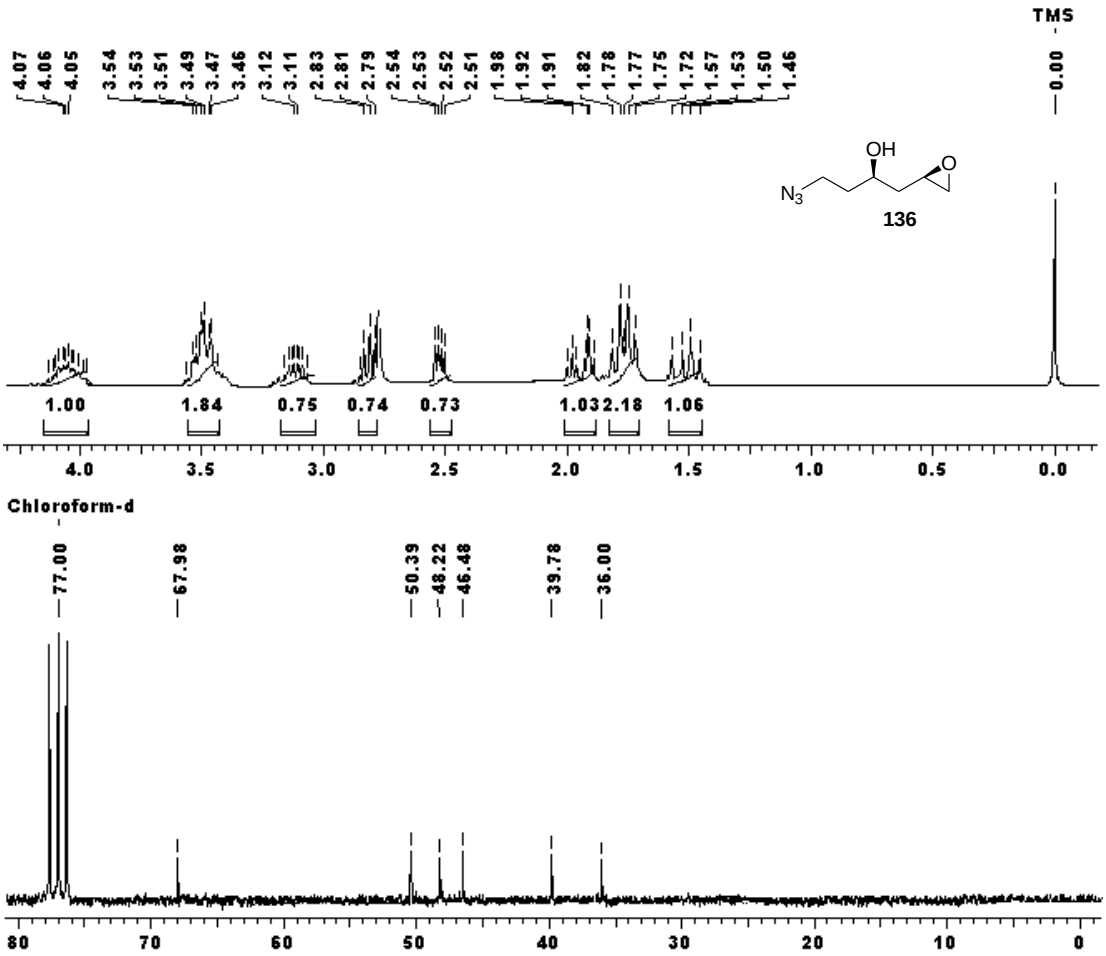


Fig. 30: ^{1}H and ^{13}C NMR spectra of 136

Finally, nucleophilic ring opening of the epoxide **136** using NaCN[62] in presence of titanium tetraisopropoxide and tetrabutylammonium iodide in DMSO gave the corresponding nitrile **81b,** $[\alpha]^{25}_{D}$ = +40.0 (*c* 0.2, $CHCl_3$) in 80% yield. The synthesis of atorvastatin has already been reported from **81b**,[49] thus constituting a formal synthesis. The ^{1}H and ^{13}C NMR spectra were in accordance with the proposed structures of **81b**. Its ^{1}H NMR spectrum displayed all the expected peaks: δ 1.25-1.27 (m, 1H), 1.56-1.59 (m, 1H), 1.70-1.76 (m, 2H), 3.26-3.29 (m, 1H), 3.43-3.49 (m, 2H), 3.58-3.65 (m, 1H) and 3.97-4.05 (m, 2H) while its ^{13}C NMR spectrum showed the cyanide peak at δ 117.13. The

IR spectrum of **81b** showed a characteristic cyanide absorption band at 2237 cm^{-1} and azide band at 2098 cm^{-1} (**Fig. 31**).

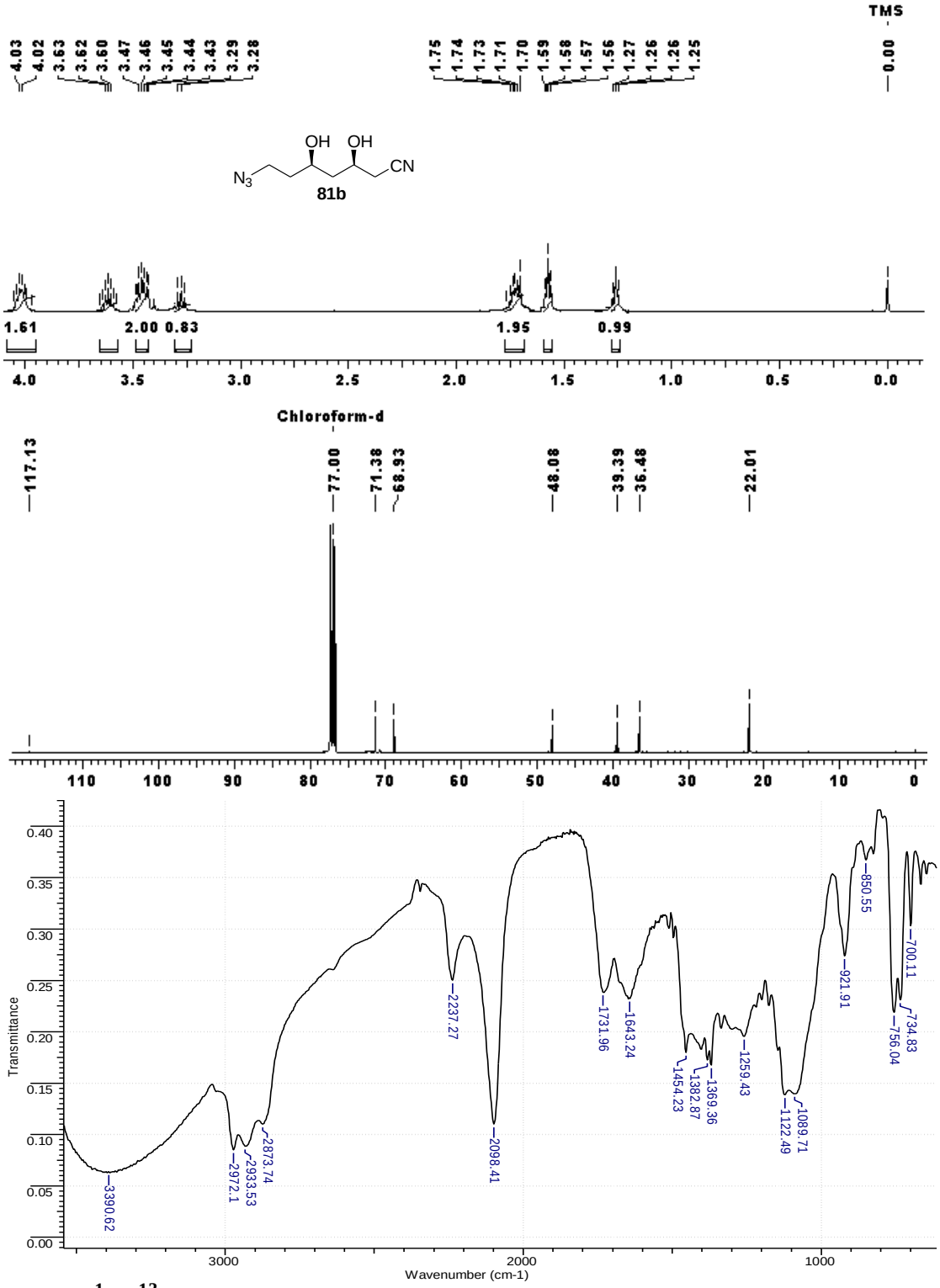


Fig. 31: ^{1}H, ^{13}C NMR and IR spectra of 81b

2.2.6 Conclusion

In conclusion, an enantioselective synthesis of the statin side-chain (**81b**) has been achieved by employing an organocatalytic α-aminooxylation methodology. The synthesis made use of cheaply available, naturally occurring L-proline in catalytic amounts for the induction of chirality, while s*yn*-1,3-diol moeity was introduced in a highly diastereoselective manner using the iodine-induced electophilic cyclization.

2.2.7 Experimental Section

(-)-(*R*)-4-(Benzyloxy)butane-1,2-diol (127)

Yield: 87%; $[\alpha]^{25}_{D}$: -5.02 (*c* 1, $CHCl_3$) (*vide infra* of section I of the same chapter for experimental procedure and spectral details).

(-)-(*R*)-4-(Benzyloxy)-2-hydroxybutyl methanesulfonate (128)

Yield: 92%; $[\alpha]^{25}_{D}$: -0.4 (*c* 0.5, $CHCl_3$) (*vide infra* of section I of the same chapter for experimental procedure and spectral details).

(+)-(*R*)-4-(Benzyloxy)-1,2-epoxybutane (129)

Yield: 95%; $[\alpha]^{25}_{D}$: +16.2 (*c* 3, $CHCl_3$) {lit.[27] $[\alpha]^{23}_{D}$: = +16.9 (*c* 2.51, $CHCl_3$)} (*vide infra* of section I of the same chapter for experimental procedure and spectral details).

(-)-(*S*)-6-(Benzyloxy)-1-hexen-4-ol (130)

Yield: 92%; $[\alpha]^{25}_{D}$: -1.55 (*c* 1.1, $CHCl_3$) (*vide infra* of section I of the same chapter for experimental procedure and spectral details).

***tert*-Butyl (*S*)-1-(benzyloxy)hex-5-en-3-yl carbonate (131)**

Yield: 95%; $[\alpha]^{25}_{D}$: -33.3 (*c* 0.6, $CHCl_3$) (*vide infra* of section I of the same chapter for experimental procedure and spectral details).

***tert*-Butyl (*S*)-1-hydroxyhex-5-en-3-yl carbonate (132)**

To a sample of benzyl ether **131** (2.38 g, 8.0 mmol) was added CH_2Cl_2 (28 mL) and H_2O (16 mL). To this mixture was added DDQ (3.63 g, 16.0 mmol) and the contents were stirred vigorously for 18 h. It was quenched with 5% aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with H_2O, brine, dried over anhyd. Na_2SO_4, filtered and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (7:3) to give **132** (1.41 g) as a colorless oil.

Yield: 85%; **$[\alpha]^{25}_D$**: +24.3 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3450, 1736, 1642, 1476, 1395, 1370, 1281, 1256, 1218, 1161, 1052, 921, 756; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.65-1.95 (m, 2H), 2.27-2.49 (m, 3H), 3.53-3.70 (m, 2H), 4.82-4.94 (m, 1H) 5.05-5.15 (m, 2H), 5.67-5.88 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.65, 36.82, 38.91, 58.44, 73.50, 82.24, 118.00, 133.18, 254.00; **Analysis: $C_{11}H_{20}O_4$** requires C, 61.09, H, 9.32; found: C, 61.41, H, 8.99%.

***tert*-Butyl (*S*)-1-(methylsulfonyloxy)hex-5-en-3-yl carbonate (133)**

A solution of alcohol **132** (1.35 g, 6.5 mmol) in CH_2Cl_2 (20 mL) was treated with methanesulfonyl chloride (0.76 mL, 9.75 mmol) and Et_3N (1.36 mL, 9.75 mmol) at 0 °C. After being stirred for 15 min, the mixture was extracted with CH_2Cl_2 (3 × 20 mL), washed with water and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude mesylate, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4) to give the mesylate **133** (1.75 g) as a colorless oil.

Yield: 94%; **$[\alpha]^{25}_{D}$**: +40 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1739, 1643, 1361, 1280, 1215, 1175, 757,668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.92-2.10 (m, 2H), 2.36-2.44 (m, 2H), 3.02 (s, 3H), 4.26-4.32 (m, 2H), 4.79-4.92 (m, 1H), 5.09-5.29 (m, 2H), 5.67-5.87 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.68, 32.99, 37.29, 38.75, 66.01, 72.30, 82.35, 118.69, 132.50, 152.97; **Analysis: $C_{12}H_{22}O_6S$** requires C, 48.96, H, 7.53, S, 10.89; found: C, 49.31, H, 7.39, S, 10.71%.

***tert*-Butyl (*S*)-1-azidohex-5-en-3-yl carbonate (134)**

To a stirred solution of mesylate **133** (1.72 g, 6 mmol) in DMF (20 mL) was added NaN_3 (1.17g, 18 mmol) and heated at 60 °C for 2 h. The reaction mixture was diluted with water, extracted with EtOAc (3 × 50 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude azide, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give the mesylate **134** (1.75 g) as a colorless gum.

Yield: 83%; **$[\alpha]^{25}_{D}$**: +4 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2101, 1739, 1643, 1480, 1458, 1370, 1280, 1255, 1160, 1090, 919, 756, 667; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.80-1.90 (m, 2H), 2.35-2.42 (m, 2H), 3.31-3.45 (m, 2H), 4.74-4.87 (m, 1H), 5.08-5.17 (m, 2H), 5.67-5.88 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.60, 32.66, 38.65, 47.65, 73.37, 82.03, 118.32, 132.69, 152.95; **Analysis: $C_{11}H_{19}N_3O_3$** requires C, 54.76, H, 7.94, N, 17.41; found: C, 54.99, H, 7.79, N, 17.25%.

(4*R*,6*R*)-4-(2-Azidoethyl)-6-(iodomethyl)-1,3-dioxan-2-one (135)

To a stirred solution of **134** (0.47 g, 2 mmol) in acetonitrile (20 mL) was added *N*-iodo-succinimide (1.35 g, 6 mmol) at -40 °C. The mixture was then warmed up and stirred at 0 °C for 15 h. After the reaction was complete (monitored by TLC), 30 mL aq. sodium

thiosulfate solution was added, followed by 30 mL of aq. $NaHCO_3$. The reaction mixture was then extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (5:5) to give cyclic carbonate **135** (0.54 g) as a colorless oil.

Yield: 87%; **$[\alpha]^{25}_D$**: +25.7 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2103, 1752, 1671, 1459, 1385, 1249, 1186, 1110, 909, 733; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.70-1.77 (m, 1H), 1.83-2.02 (m, 2H), 2.35-2.44 (m, 1H), 3.22-3.44 (m, 2H), 3.52-3.59 (m, 2H), 4.39-4.52 (m, 1H), 4.54-4.67 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.23, 33.15, 34.34, 46.42, 75.10, 77.20, 147.86; **Analysis: $C_{14}H_{17}IO_4$** requires C, 44.70, H, 4.55, I, 33.73; found: C, 44.45, H, 4.77, I, 33.65%.

(*R*)-4-Azido-1-((*R*)-oxiran-2-yl)butan-2-ol (136)

To a stirred solution of cyclic carbonate **135** (0.31 g, 1 mmol) in MeOH (10 mL) was added K_2CO_3 (0.28 g, 2 mmol) at 0 °C. The mixture was then warmed up and stirred at 25 °C. After the reaction was complete (monitored by TLC), 20 mL aqueous $NaHCO_3$ was added and reaction mixture was then extracted with EtOAc (3 × 20 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (4:6) to give epoxide **136** (0.15 g) as a colorless oil.

Yield: 96%; **$[\alpha]^{25}_D$**: +20 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3398, 3018, 2399, 2100, 1739, 1406, 1215, 1083, 757; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.46-1.57 (m, 1H), 1.72-1.82 (m, 2H), 1.89-2.00 (m, 1H), 2.50-2.54 (m, 1H), 2.79-2.85 (m, 1H), 3.07-3.16 (m, 1H), 3.43-3.57 (m, 2H), 3.97-4.13 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.00, 39.78, 46.48,

48.22, 50.39, 67.98; **Analysis: $C_6H_{11}N_3O_2$** requires C, 45.85, H, 7.05, N, 26.74; found: C, 46.17, H, 6.92, N, 26.58%.

(3*S*,5*R*)-7-Azido-3,5-dihydroxyheptanenitrile (81b)

To a stirred solution of epoxide **136** (0.08 g, 0.5 mmol) in DMSO (5 mL) was added titanium tetraisopropoxide (0.21 g, 0.75 mmol), NaCN (0.098 g, 1.5 mmol) and Bu_4NI (0.37 g, 0.5 mmol) and heated at 70 °C for 6 h. After the reaction was complete (monitored by TLC), reaction mixture was diluted with water, extracted with EtOAc (3 × 20 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using petroleum ether/EtOAc (5:5) to give the azidodiol **81b** (0.074 g) as a colorless oil.

Yield: 80%; **$[\alpha]^{25}_D$**: +40 (*c* 0.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3390, 2237, 2098, 1731, 1643, 1454, 1369, 1122, 1089, 921, 756; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.25-1.27 (m, 1H), 1.56-1.59 (m, 1H), 1.70-1.76 (m, 2H), 3.26-3.29 (m, 1H), 3.43-3.49 (m, 2H), 3.58-3.65 (m, 1H), 3.97-4.05 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 22.01, 36.48, 39.39, 48.08, 68.93, 71.38, 117.13; **Analysis: $C_7H_{12}N_4O_2$** requires C, 45.64, H, 6.57, N, 30.42; found: C, 45.98, H, 6.39, N, 30.25%.

Mosher's ester of (+)-(*R*)-4-(benzyloxy)butane-1,2-diol (137)

Yield: 75%; **$[\alpha]^{25}_D$**: -36 (*c* 0.5, $CHCl_3$) (*vide infra* of section I of the same chapter for experimental procedure and spectral details).

2.2.8 References

1. (a) Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med*. **2000**, *66*, 199; (b) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O.

Phytochemistry **1995**, *38*, 1427.

2. (a) Juliawaty, L. D.; Watanabe, Y.; Kitajima, M.; Achmad, S. A.; Takayama, H.; Aimi, N. *Tetrahedron Lett*. **2002**, *48*, 8657; (b) Echeverri, F.; Arango, V.; Quinones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881; (c) Kobayashi, S.; Tsuchiya, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Kobayashi, K. *J. Antibiot*. **1994**, *47*, 697; (d) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry* **1995**, *38*, 1427.
3. Bohlmann, F.; Suwita, A. *Phytochemistry* **1979**, *18*, 677.
4. Hsu, F. L.; Chen, Y. C.; Cheng, J. T. *Planta Med*. **2000**, *66*, 228.
5. Nakata, T.; Hata, N.; Iida, K.; Oishi, T. *Tetrahedron Lett*. **1987**, *28*, 5661.
6. Mori, Y.; Kageyama, H.; Suzuki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2574.
7. Mori, Y.; Suzuki, M. *J. Chem. Soc. Perkin Trans 1* **1990**, 1809.
8. Solladie, G.; Gressot-Kempf, L. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2371.
9. Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem*. **2001**, *66*, 2512.
10. Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem*. **2002**, *67*, 2682.
11. Enders, D.; Steinbusch, D. *Eur. J. Org. Chem*. **2003**, 4450.
12. Scott, M. S.; Luckhurst, C. A.; Dixon, D. J. *Org. Lett*. **2005**, *7*, 5813.
13. Sabitha, S.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett*. **2005**, *46*, 6567.
14. Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett*. **2005**, *46*, 6571.
15. Baktharaman, S.; Selvakumar, S.; Singh, V. K. *Tetrahedron Lett*. **2005**, *46*, 7527.
16. Scott, M. S.; Luckhurst, C. A.; Dixon, D. J. *Synfacts* **2006**, *6*, 543.

17. Yadav, J. S.; Kumar, N. N.; Reddy, M. S.; Prasad, A.R. *Tetrahedron* **2007**, *63*, 2689.

18. Yadav, J. S.; Reddy, P. M. K.; Gupta, M. K.; Chary, C. J. *Synthesis* **2007**, *3639*.

19. Lee, H.-Y.; Sampath, V.; Yoon, Y. *Synlett* **2009**, 249.

20. Collett, L. A.; Cavies-Coleman, M. T.; Rivett, D. E. A.; Drewes, S. E.; Horn, M. M. *Phytochemistry* **1997**, *44*, 935.

21. (a) Davis, F. A.; Bang-Chi, C. *Chem. Rev*. **1992**, *92*, 919; (b) Morikawa, K.; Park, J.; Andersson, P.G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1993**, *115*, 8463; (c) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 708; (d) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 7819.

22. Merino, P.; Tejero, T.*; Angew. Chem. Int. Ed.* **2004**, *43*, 2995.

23. For a review of proline-catalyzed asymmetric reactions, see: (a) List, B. *Tetrahedron* **2002**, *58*, 5573; (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; (c) Marigo, M.; Jorgensen, K. A. *Chem. Commun*. **2006**, 2001.

24. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673.

25. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2003**, *125*, 6038.

26. Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett*. **2003**, *5*, 27.

27. Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, *7*, 621; (b) Liu, C.; Coward, J. K. *J. Org. Chem*. **1991**, *56*, 2262.

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

29. Felpin, F.; Lebreton J. *J. Org. Chem*. **2002**, *67*, 9192.

30. Taylor, R. E.; Jin, M. *Org. Lett*. **2003**, *5*, 4959.

31. Raghavan, S.; Reddy S. R. *J. Org. Chem*. **2003**, *68*, 5754.

32. Bonini, C.; Racioppi, R.; Righi, G.; Viggiani, L. *J. Org. Chem*. **1993**, *58*, 802.

33. Ando, K. *J. Org. Chem*. **1997**, *62*, 1934.

34. Kathawala, F. G. *Med. Res. Review* **1991**, *11*, 121.

35. Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, G.; Kleine, H.; Schnierer, M. *Tetrahedron Lett*. **1990**, *31*, 2545.

36. Jendralla, H.; Granzer, E.; Kerekjarto, B. V.; Krause, R.; Schacht, U.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L. J.; Granata, S.; Herchen, J.; Kleine, H.; Schussler, H.; Wagner, K. *J. Med. Chem*. **1991**, *34*, 2962.

37. Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. *J. Med. Chem*. **1991**, *34*, 357.

38. Brower P. L.; Butler, D. E.; Deering, C. F.; Le, T. V.; Millar, A.; Nanninga, T. N.; Roth, B. D. *Tetrahedron Lett*. **1992**, *33*, 2279.

39. Baumann, K. L.; Butler, D. E.; Deering, C. F.; Mennen, K. E.; Millar, A.; Nanninga, T. N.; Palmer, C. W.; Roth, B. D. *Tetrahedron Lett*. **1992**, *33*, 2283.

40. Konoike, T.; Araki, Y. *J. Org. Chem*. **1994**, *59*, 7849.

41. Beck, G.; Jendralla, H.; Kesseler, K. *Synthesis* **1995**, 1014.

42. Ghosh, A. K.; Lei, H. *J. Org. Chem*. **2000**, *65*, 4779.

43. Patel, R. N.; Banergee, C.; McNamee, C. G.; Brzoowski, D.; Hanson, R. N.; Szarka, L. J. *Enzyme Microb. Technol.* **2001**, *15*, 1014.

44. Kizaki, N.; Yasohara, Y.; Hasegawa, J.; Wada, M.; Kataoka, M.; Shimizu, S. *Appl. Microbiol. Biotechnol.* **2001**, *55*, 590.

45. Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Kitahara, M.; Sakashita, M.; Sakoda, R. *Bioorg. Med. Chem*. **2001**, *9*, 2727.

46. Radl, S.; Stach, J.; Hajicek, J. *Tetrahedron Lett*. **2002**, *43*, 2087.

47. Radl, S. *Synth. Commun.* **2003**, *33*, 2275.

48. Ohrlein, R.; Baisch, G. *Adv. Synth. Catal.* **2003**, *345*, 713.

49. Liu, J.; Hsu, C. C.; Wong, C. H. *Tetrahedron Lett*. **2004**, *45*, 2439.

50. Moen, A. R.; Hoff, B. H.; Hansen, L. K.; Anthonsen, T.; Jacobsen, E. E. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1551.

51. For a compilation of chemoenzymatic approaches to statin side chains, see: Müller, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 362.

52. Tararov, V. I.; Andrushko. N.; Andrushko, V.; Konig, G.; Spannenberg, A.; Borner, A. *Eur. J. Org. Chem*. **2006**, 5543.

53. Sun, F.; Xu, G.; Wu, J.; Yang, L. *Tetrahedron*: *Asymmetry* **2006**, *17*, 2907.

54. Bergeron, S.; Chaplin, D. A.; Edwards, J. H.; Ellis, B. S. W.; Hill, C. L.; Holt-

Tiffin, K.; Knight, J. R.; Mahoney, T.; Osborne, A. P.; Ruecroft, G. *Org. Process Res. Dev*. **2006**, *10*, 661 and the references cited therein.

55. Sun, F.; Xu, G.; Wu, J.; Yang, L. *Tetrahedron*: *Asymmetry* **2007**, *18*, 2454.
56. Grundy, S. M. *J. Intern. Med.* **1997**, *241*, 295.
57. (a) Knopp, R. H. N. *Engl. J. Med.* **1999**, *341*, 498; (b) Castelli, W. P. *Am. J. Med.* **1984**, *76*, 4.
58. For reviews, see: (a) McKenney, J. M. *Clin. Cardiol.* **2003**, *26* (*Suppl. III*), 32; (b) Speidal, K. M.; Hilleman, D. E. *Expert Opin. Pharmacother.* **2006**, *7*, 1291.
59. Watanabe, M.; Koike, H.; Ishiba, T.; Okade, T.; Seo, S.; Hiri, K. *Bioorg. Med. Chem*. **1997**, *5*, 437.
60. (a) Istvan, E. S.; Delsenhofer, J. *Science* **2001**, *292*, 1160; (b) Takemoto, M.; Liao, J. K. *Arterioscler. Thromb. Vasc. Biol.* **2001**, *12*, 1712.
61. (a) Tobert, J. A. *Nat. Rev*. **2003**, *2*, 517; (b) Stein, E. A.; Strutt, K.; Southworth, H.; Diggle, P. J.; Miller, E. *Am. J. Cardiol.* **2003**, *92*, 1287.
62. Langille, N. F.; Panek, J. S. *Org. Lett*. **2004**, *6*, 3203.

Chapter III

A short enantioselective synthesis of (-)-bestatin via L-proline catalyzed α-amination of an aldehyde and asymmetric synthesis of guggultetrol using Sharpless asymmetric epoxidation and dihydroxylation

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"A short enantioselective synthesis of (-)-bestatin via L-proline-catalyzed α-amination of an aldehyde" Shyla George, Gurunath S. Suryavanshi and Arumugam Sudalai; *Tetrahedron Lett*. **2008**, *49*, 6791.

Section I

A short enantioselective synthesis of (-)-bestatin via L-proline catalyzed α-amination of an aldehyde

3.1.1 Introduction

The aminopeptidases are a group of exopeptidases that specifically cleave polypeptide chains at the amino terminus. These enzymes are ubiquitous in nature and are of biochemical and medicinal importance due to their key role in the metabolism of numerous biologically active peptides, for example the enkephalins.[1] (-)-Bestatin (**1**) (**Fig. 1**), a naturally occurring small peptide containing a non-proteinogenic α-hydroxy-β-amino acid at the *N*-terminus of the peptide chain, is an aminopeptidase inhibitor[2] that exhibits immunostimulatory activity as well as cytotoxic activity. It is isolated from the culture filtrates of *Streptomyces olivoreticuli* and is otherwise known as 'ubenimex'. It is used clinically as an oral medication for the treatment of cancer[3] and shows potential as an anti-inflammatory agent and for the treatment of HIV.[4] A variety of stereoselective methods for the formation of β-amino-α-hydroxy acids have been reported, including aminohydroxylation,[5] reduction of α-keto acid derivatives,[6] nucleophilic addition to chiral aminoaldehydes,[7] olefins,[8] imines,[9] ring opening procedures on chiral epoxides,[10] halocyclocarbamation of allylamines[11] and transformation of chiral sugars,[12] β-amino

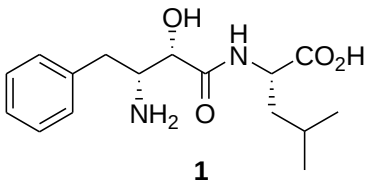

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Fig. 1: Structure of (-)-bestatin (**1**)

acids[13] etc. Due to its promising biological activity and intriguing structure, more than 25 syntheses of bestatin (**1**) have been reported.[6c,7,14-29]

3.1.2 Pharmacology of (-)-bestatin

α-Hydroxy-β-amino acids are common structural units found in many biologically active compounds, including both naturally occurring and synthetic pharmaceuticals.[30] Bestatin (**1**), an anticancer agent launched in Japan, is a peptide mimetic composed of (2*S*,3*R*)-3-amino-2-hydroxy-4-phenyl butyric acid and L-leucine.[2] α-Hydroxy-β-amino acid moiety of bestatin provides a strong interaction with zinc ions at the active site. Its binding mode for the di-zinc aminopeptidases, was elucidated from the X-ray structures of bovine lens aminopeptidase complexed with bestatin.[31] The stereochemistry of the hydroxyl as well as the amino groups in (-)-bestatin (**1**) plays a vital role in the biological activity of the molecule. Thus, controlling the stereochemistry at the C-2 and C-3 stereogenic centres for the introduction of the desired (2*S*, 3*R*) configuration of the *N*-terminal component becomes important. The technologies required to produce the intermediates for this drug economically on an industrial scale are becoming ever more important.

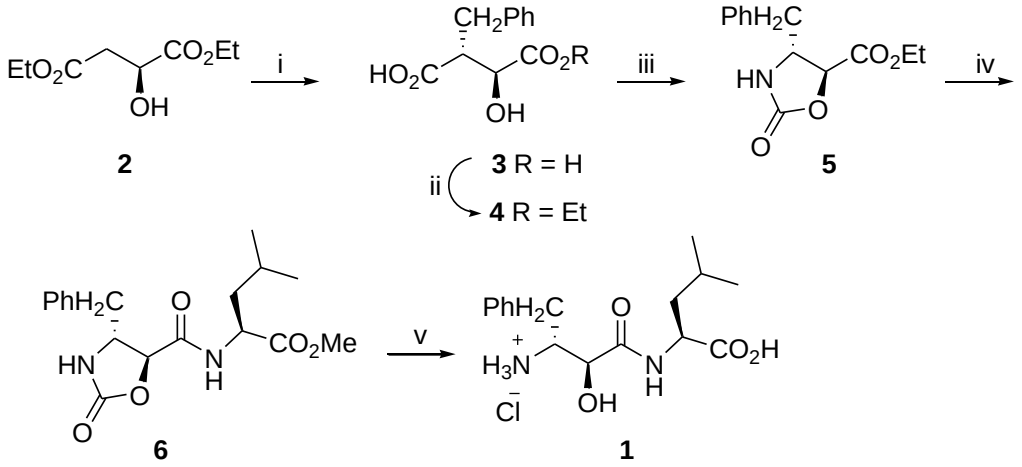
3.1.3 Review of Literature

Literature search revealed that there are several reports available for the synthesis of (-)-bestatin (**1**) involving chiral pool, chemo-enzymatic approach or enantioselective syntheses, some of which are described below.

Norman's approach (1992)[15]

Norman *et al.* have achieved the synthesis of (-)-bestatin (**1**) starting from (-)-diethyl-(*S*)-malate **2** which was subjected to alkylation in presence of LHMDS and benzyl bromide to give the corresponding alkylation product in 70% yield and >35:1 diastereoselectivity. On subsequent saponification with 1N NaOH in dioxane, it gave the diacid **3** in 100%

yield. Treatment of **3** with trifluoroacetic anhydride gave an intermediate cyclic anhydride which was opened with an equivalent of ethanol to afford the monoacid **4**. The monoacid **4** was subjected to Curtius rearrangement with diphenylphosphoryl azide in presence of triethylamine producing an isocyanate intermediate which was trapped by the hydroxyl group to provide oxazolidinone **5** in 65% yield. Saponification of **5** with LiOH gave the corresponding acid, which was coupled with leucine methyl ester in presence of EDC and HOBt followed by treatment of the corresponding amide **6** with NaOH in ethanol to afford (-)-bestatin (**1**) in 100% yield (**Scheme 1**).

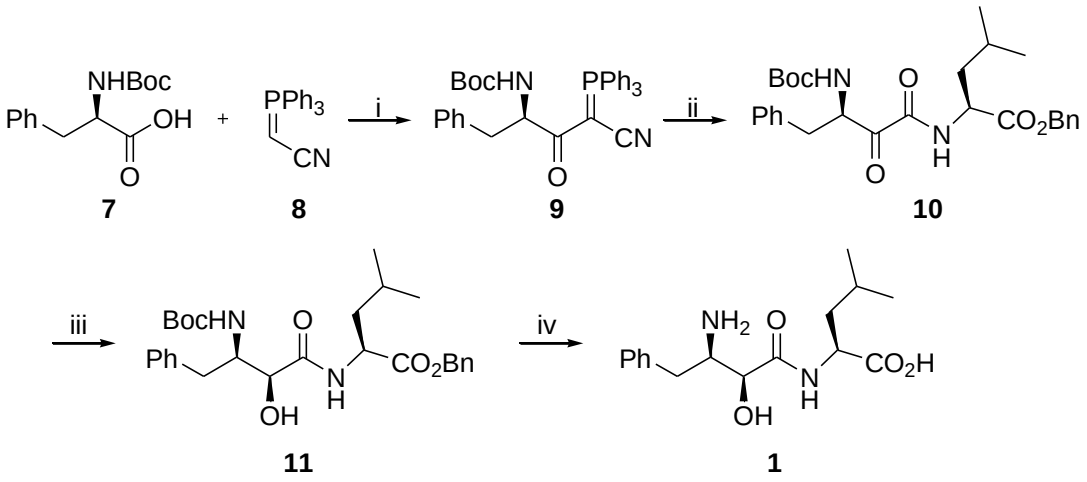


Scheme 1: (i) (a) LHMDS, $PhCH_2Br$, -78 °C to 25°C, 70%; (b) 1N NaOH, dioxane, reflux, 100 %; (ii) (a) TFAA, 0 °C; (b) EtOH, 25 °C, 97 %; (iii) DPPA, Et_3N, toluene, 90 °C, 65 %; (iv) (a) LiOH, THF, H_2O, 100 %; (b) Leu-OCH_3.HCl, NMM, EDC, HOBt, DMF, 64 %; (v) 1N NaOH, EtOH, reflux, 100%.

Wasserman's approach (1999)[27]

Wasserman *et al.* have described the synthesis of (-)-bestatin (**1**) commencing from *N*-Boc-D-phenylalanine **7** which was coupled with triphenylphosphoranylideneacetonitrile **8** to form the acyl cyano ylide **9** in 88% yield. Ozonolysis of **9** was followed by coupling with benzyl ester of L-Leucine to yield the amide **10** which was subjected to reduction with zinc borohydride to give the α-hydroxy amide **11** with diastereoselectivity >93:7.

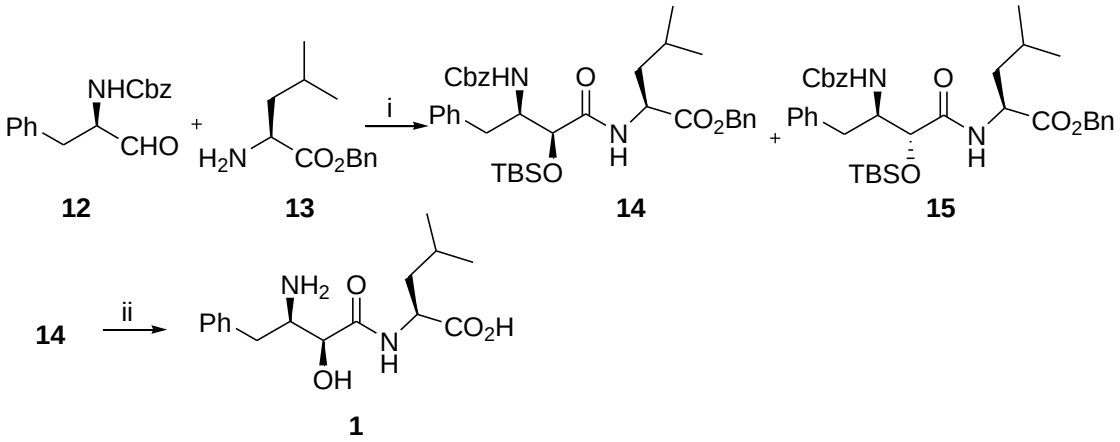
The amide **11** was then acidified with 2M HCl followed by hydrogenation with H_2, Pd/C, MeOH gave (-)-bestatin (**1**) in 92% yield (**Scheme 2**).



Scheme 2: (i) EDCl, DMAP, 88%; (ii) (a) O_3, CH_2Cl_2, -78 °C; (b) L-Leu-OBn, CH_2Cl_2, -78 °C; (iii) $Zn(BH_4)_2$, THF, -78 °C, 85%, d.r. >93:7; (iv) (a) 2M HCl/CH_3CO_2Et; (b) H_2, Pd/C, MeOH, 92%.

Nemato's approach (2000)[29]

Nemato *et al.* have achieved a one-pot method for the synthesis of (-)-bestatin (**1**) by mixing the aldehyde **12** derived from D-phenyl alanine, L-leucine benzyl ester **13** and masked acyl cyanide [H-C$(CN)_2$O-TBS] in presence of 4-prorridinylpyridine to produce

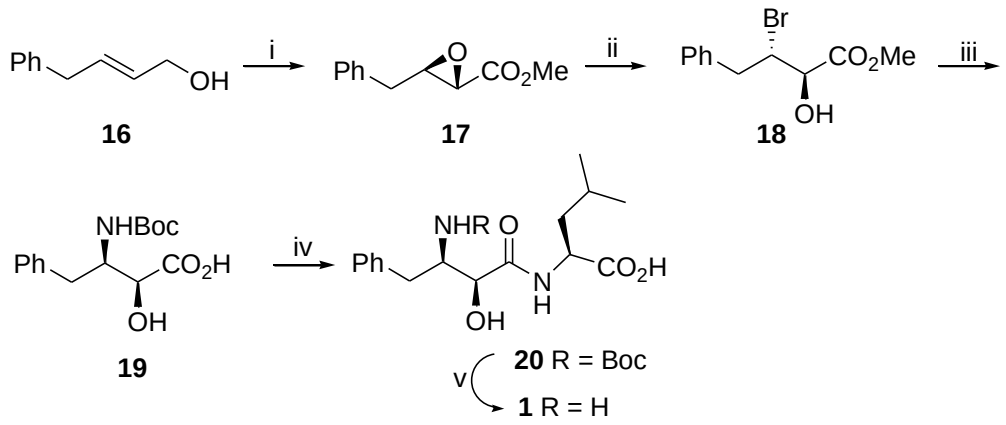


Scheme 3: (i) [H-C$(CN)_2$O-TBS], 4-prorridinylpyridine, ether, 5 h, 80%, d.r. = 79:21; (ii) (a) Bu_4NF, THF; (b) H_2, Pd/C, MeOH, 96%.

a diastereomeric mixture of **14** and **15** (79:21) in 80% yield. The major isomer **14** was then transformed to (-)-bestatin (**1**) in 96% yield by the removal of TBS, Cbz and benzyl groups (**Scheme 3**).

Righi's approach (2003)[17]

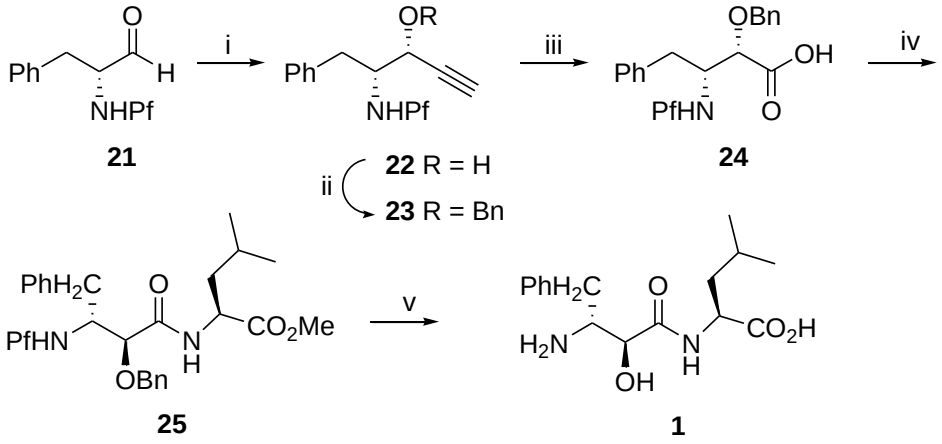
Righi *et al.* have reported the synthesis of (-)-bestatin (**1**) commencing from the epoxide **17**, obtained by the Sharpless asymmetric epoxidation of allyl alcohol **16**, which when subjected to $MgBr_2$-mediated opening afforded the bromohydrin **18** in 92% yield. The bromohydrin **18** was converted to the protected amino acid **19** by following a three-step reaction sequence: nucleophilic displacement of the bromide to azide using NaN_3, hydrogenolysis of the corresponding azide with H_2, Pd/C, EtOAc and subsequent protection of the product amine as its carbamate using $(Boc)_2O$ and hydrolysis of the protected amino ester with Na_2CO_3, H_2O/MeOH. The protected amino acid **19** was then coupled with L-leucine benzyl ester in presence of coupling agents EDAC and HOBt followed by catalytic hydrogenation to give the amide **20** which was transformed to (-)-bestatin (**1**) by acidification with TFA in CH_2Cl_2 (**Scheme 4**).



Scheme 4: (i) (a) Sharpless asymmetric epoxidation; (b) oxidation; (ii) $MgBr_2$, Et_2O, 25 °C, 2 h, 92%; (iii) (a) NaN_3, DMSO, 40°C, 6 h, 73%; (b) H_2, Pd/C, EtOAc, $(Boc)_2O$, 25 °C, 5 h, 95%; (c) Na_2CO_3, H_2O/MeOH, 25 °C, 12 h, 79%; (iv) (a) EDAC, HOBt, DIPEA, L-Leu-OBn.TsOH, DMF, CH_2Cl_2, 25 °C, 12 h, 87%; (b) H_2, Pd/C, MeOH, 25 °C, 3 h, 95%; (v) TFA, CH_2Cl_2, 25 °C, 12 h, 85%.

Park's approach (2003)[7e]

Park *et al.* have achieved the synthesis of (-)-bestatin (**1**) starting from (*R*)-phenylalaninal **21** which was treated with ethynylmagnesium bromide at -40°C to give amino alcohol **22** in 96% yield and 9.5:1 diastereoselectivity. After protection of hydroxyl group in **22** with BnBr, the resulting product **23** was oxidized with $KMnO_4$ to afford the acid **24** which was coupled with L-leucine methyl ester in presence of coupling agents DCC and HOBt to provide the amide **25**. Treatment of the amide **25** with lithium hydroxide followed by exposure of the resulting crude acid to H_2 over Pd/C gave (-)-bestatin (**1**) in 93% yield (**Scheme 5**).

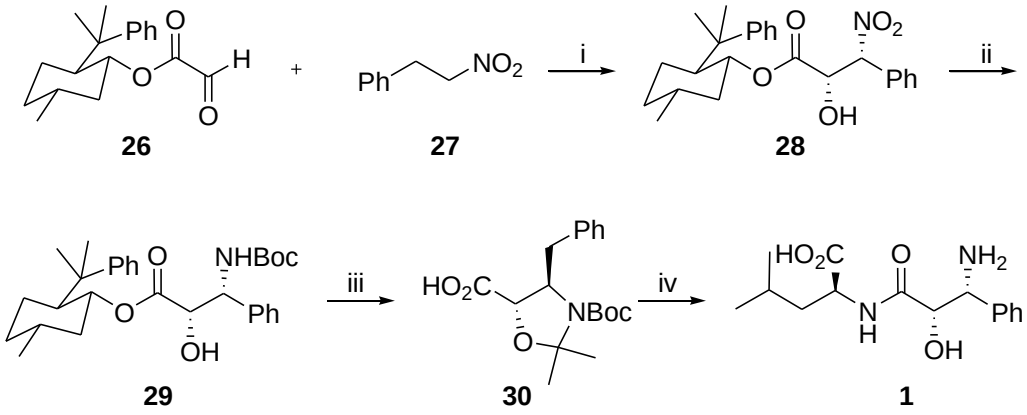


Scheme 5: (i) ethynylmagnesium bromide, -40°C, THF, 96%, d.r. = 9.5:1; (ii) BnBr, NaH, Bu_4NI, THF, 0 °C, 97%; (iii) $KMnO_4$, HOAc, H_2O, pentane, 87%; (iv) L-Leu-OCH_3, DCC, HOBT, TsOH, Et_3N, THF, 0 °C, 91%; (v) (a) LiOH, THF/H_2O, 0°C, 95%; (b) H_2, Pd/C, MeOH, 50°C, 93%.

Jurczak's approach (2003)[18]

Jurczak *et al.* have described the synthesis of (-)-bestatin (**1**) using nitroaldol reaction wherein they treated (*R*)-8-phenylmenthyl glyoxalate **26** was treated with 1-nitro-2-phenylethane **27** in presence of aluminium oxide to afford a mixture (71:19:6:5) of diastereomeric nitroalcohols in 89% yield. The major diastereomer **28** was separated by

column chromatography and hydrogenated to give the corresponding amine, which was subsequently protected as its carbamate **29** using $(Boc)_2O$. Compound **29** was then reacted with 2,2-dimethoxypropane to give, after hydrolysis of the ester functionality, the acid **30** in 78% yield. The acid **30** was then coupled with the methyl ester of L-leucine using mixed anhydride method to afford dipeptide, which was then acidified to give (-)-bestatin (**1**) in 70% yield (**Scheme 6**).

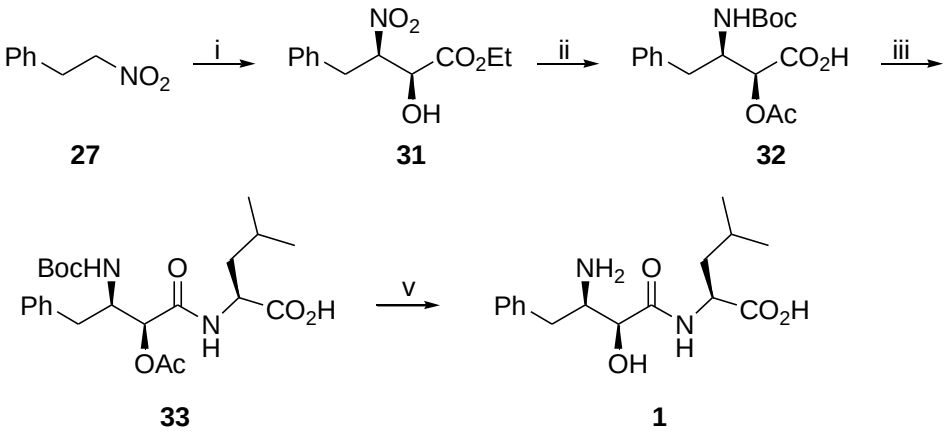


Scheme 6: (i) (a) activated Al_2O_3, dry THF, 25 °C, 7 h; (b) column chromatography; (ii) (a) H_2, catalytic Raney-Ni, MeOH, 25 °C, 16 h; (b) $(Boc)_2O$, saturated aq. $NaHCO_3$, AcOEt, 25 °C, 2 h; (iii) (a) DMP, catalytic TsOH, toluene, 50 °C, 5 h; (b) MeONa, MeOH, 25 °C, 24 h; (iv) (a) *N*-ethylmorpholine, isobutyl chloroformate, L-LeuOMe, THF, -5 °C to 25 °C, 1 h; (b) catalytic TsOH, MeOH, 25 °C, 24 h; (c) 1N HCl, 25 °C, 16 h, 70%.

Barua's approach (2005)[20]

Barua *et al.* have reported the synthesis of (-)-bestatin (**1**) using Shibasaki's asymmetric Henry reaction. Treatment of 2-phenyl-1-nitroethane **27** with ethyl glyoxalate in presence of La-(*R*)-BINOL in THF provided the nitroalcohol **31** in 81% yield and 93% ee. The nitroaldol product **31** was acetylated and the resulting nitroacetate was hydrogenated with H_2 over Pd/C in methanol in presence of $NaBH_4$ to furnish the amino acetate **32** in 60% yield. Coupling of the amino acetate **32** with benzyl ester of L-leucine and subsequent

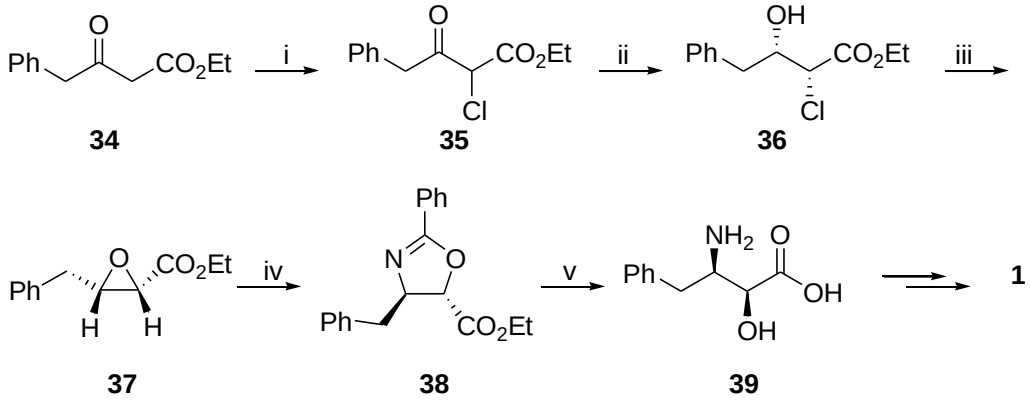
hydrogenation delivered the amide **33** in 77% yield. Finally, deprotection of both the protecting groups in two-steps furnished (-)-bestatin (**1**) in 73% yield (**Scheme 7**).



Scheme 7: (i) ethyl glyoxalate, La-(*R*)-BINOL, THF, -50 °C, 81%; (ii) (a) acetylation, 94%; (b) H_2, Pd/C, MeOH, $NaBH_4$, 60%; (c) $(Boc)_2O$, aq. $NaHCO_3$, AcOEt, 92%; (iii) (a) *N*-ethylmorpholine, isobutyl chloroformate, L-LeuOMe, THF, -10°C; (b) H_2, Pd/C, MeOH, 77%; (iv) (a) K_2CO_3, MeOH; (b) TFA, 73%.

Stewart's approach (2005)[21]

Stewart *et al.* have achieved a formal synthesis of (-)-bestatin (**1**) starting from β-keto ester **34**, prepared from Meldrum's acid by an acylation/decarboxylation strategy, which was chlorinated with SO_2Cl_2 to produce chloro derivative **35**. Treatment of **35** with *E.coli* cells produced chlorohydrin **36** in 41% yield and 98% ee. Ring closure of chlorohydrin

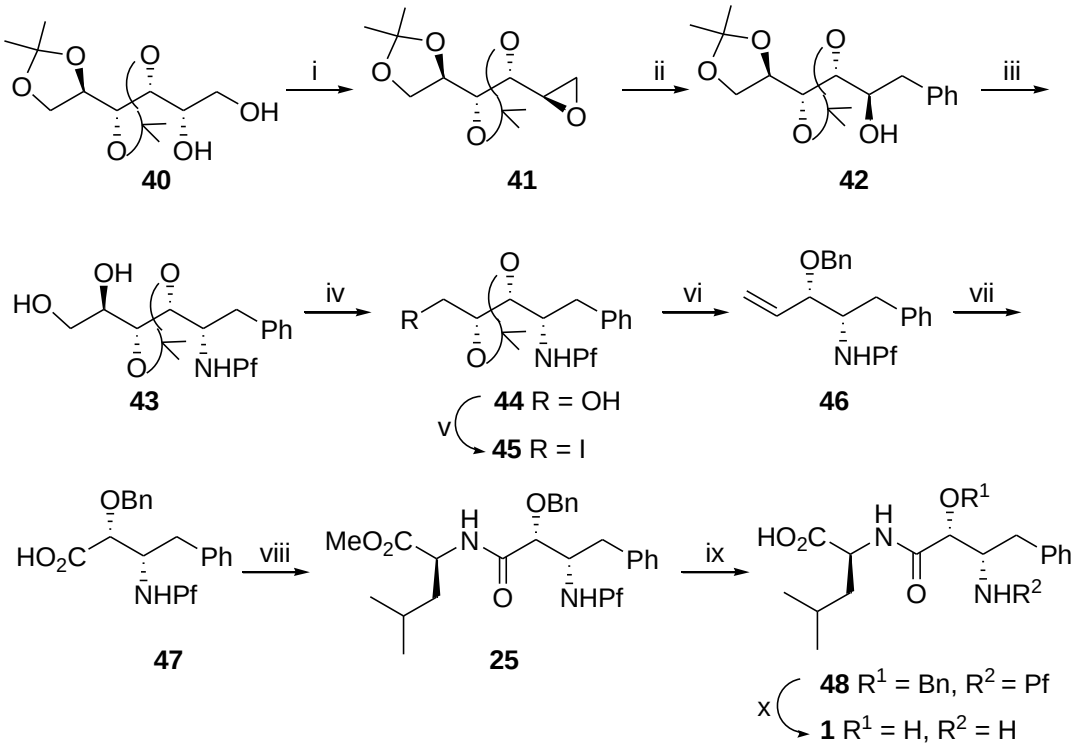


Scheme 8: (i) SO_2Cl_2, (ii) engineered *E.coli* cells, 41%, >98% de, >98% ee; (iii) K_2CO_3; (iv) $BF_3.Et_2O$, PhCN; (v) 6M HCl.

36 with K_2CO_3 followed by treatment of epoxide **37** with benzonitrile in presence of $BF_3.Et_2O$ produced the oxazine **38**. Finally, hydrolysis of oxazine **38** with 6M HCl afforded the bestatin intermediate **39**, thus constituting a formal synthesis (**Scheme 8**).

Park's approach (2006)[23]

Park *et al.* have reported the synthesis of (-)-bestatin (**1**) commencing from glucitol **40**, which was readily accessed *via* reduction of D-glucono-δ-lactone with $NaBH_4$. Selective protection of the primary alcohol function in **40** with TBDMSCl and mesylation of the secondary alcohol followed by subsequent treatment with Bu_4NF enacted desilylation and intramolecular mesylate displacement affording the epoxide **41**. The epoxide **41** was then

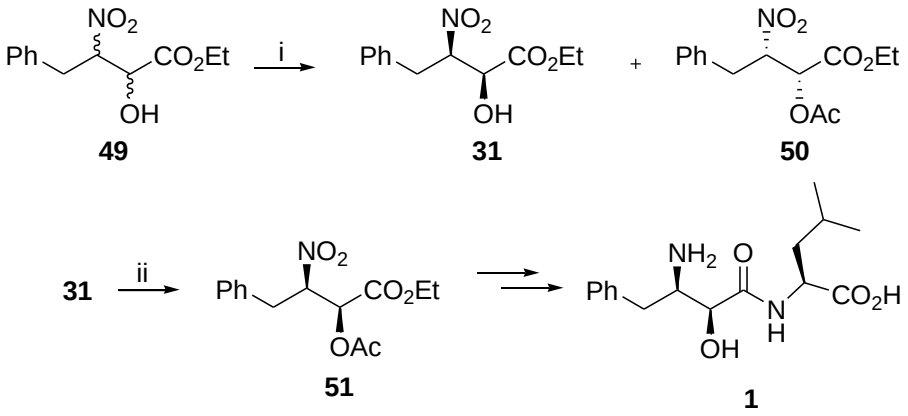


Scheme 9: (i) (a) TBDMSCl, imidazole, CH_2Cl_2, 25 °C, 94%; (b) MsCl, Et_3N, THF, 0 °C, 94%; (c) Bu_4NF, THF, 25 °C, 88%; (ii) PhMgBr, CuI, THF, -40 °C, 94%; (iii) (a) Tf_2O, pyridine, CH_2Cl_2, -10 °C, 96%; (b) NaN_3, DMF, 25 °C, 96%; (c) H_2, Pd/C, EtOAc, 25 °C, 85%; (d) PfBr, $Pb(NO_3)_2$, Et_3N, CH_2Cl_2, 25 °C, 80%; (e) Dowex 50W-X8, MeOH, 25 °C, 92%; (iv) $NaIO_4$, EtOH-H_2O (2:1), 25 °C, $NaBH_4$, 0 °C, 90%; (v) (a) MsCl, Et_3N, THF, 0 °C, 97%; (b) LiI, DMF, 80 °C, 92%; (vi) (a) *n*BuLi, THF, -40 °C, 90%; (b) BnBr, 60% NaH, Bu_4NI, THF, 0 °C, 91%; (vii) O_3, MeOH, -78 °C, 30% H_2O_2, 25 °C, 94%; (viii) (*S*)-Leu-OCH_3, HOBT, TsOH, DCC, Et_3N, THF, 0 °C, 89%; (ix) LiOH, THF-H_2O (2:1), 0 °C, 89%; (x) H_2, 10% Pd/C, MeOH, 70 °C, 89%.

reacted with PhMgBr in presence of CuI at -40 °C to give the alcohol **42** in 94% yield. The *N*-Pf protected amine **43** was prepared from **42** by following a four-step reaction sequence: treatment of **42** with Tf_2O, displacement of the triflate with azide followed by its hydrogenation and subsequent protection of the amine formed with PfBr and acetonide deprotection with Dowex resin. The diol **43** was then oxidatively cleaved using $NaIO_4$ and $NaBH_4$ followed by mesylation of the primary alcohol and its displacement with iodide to give **45** in 92% yield. Treatment of the iodide **45** with *n*BuLi in THF generated the amino alcohol which was protected as its benzyl ether **46** by reacting **45** with BnBr in presence of NaH. Ozonolysis of **46** gave the acid **47** which was coupled with methyl ester of L-leucine in presence of coupling agent HOBt to give the amide **25** in 89% yield. The methyl ester in **25** was hydrolyzed using LiOH to produce acid **48** which was hydrogenated with H_2 over Pd/C in methanol to afford (-)-bestatin (**1**) in 89% yield (**Scheme 9**).

Barua's approach (2007)[24]

Barua *et al.* have achieved the synthesis of (-)-bestatin (**1**) by employing the enzymatic kinetic resolution of niroalcohols. Thus, the nitroalcohol **49** was subjected to kinetic resolution with lipase AK in presence of vinyl acetate which resulted in the acylation of one isomer giving the acetate **50** in 48% yield and 97% ee while the nitro alcohol **31** was obtained in 47% yield and 98.5% ee. Acetylation of the nitro alcohol **31** afforded the acetate **51** from which the synthesis of (-)-bestatin (**1**) was achieved by following a literature procedure (**Scheme 10**).



Scheme 10: (i) Lipase AK, vinyl acetate, hexane:toluene (3:1), 47%, 98.5% ee for **31** (48%, 97% ee for **50**); (ii) Ac_2O, I_2, 94%.

3.1.4 Present Work:

3.1.4.1 Objective

In recent years there has been an increased interest in the synthesis of optically active α-hydroxy-β-amino acids, not only because of their wide-ranging chemical utility, but also for the fact that this functionality is a key fragment in a number of natural products. Notably, the α-hydroxy-β-amino acids have been implicated in the development of supermolecular drugs and conformationally stable oligo and dipeptide species. The presence of this moiety and the stereochemistry of the hydroxy as well as the amino group play a vital role in the biological activity of the molecules containing it. Even though there are many reports in literature[6c,7,14-29] for the synthesis of bestatin (**1**) many of them utilized unnatural D-phenylalanine as a chiral starting material.[6c,7b-e,19,26-29] As part of our research program directed towards expanding the synthetic utility of L-proline catalyzed asymmetric α-amination of aldehydes for the synthesis of α-hydroxy-β-amino acids, we became interested in applying this protocol for the synthesis of (-)-bestatin (**1**).

Retrosynthetic analysis for (-)-bestatin (**1**) is outlined in **Fig. 2**. We believe that, the oxazine **59**, the key intermediate for the synthesis of (-)-bestatin (**1**), can be obtained from the α-amino aldehyde **56** using a Pd-catalyzed intramolecular cyclization of benzamide. Amino aldehyde **56**, in turn, can be visualized to be prepared from 3-phenylpropionaldehyde **52** by utilizing L-proline-catalyzed asymmetric α-amination of aldehyde.

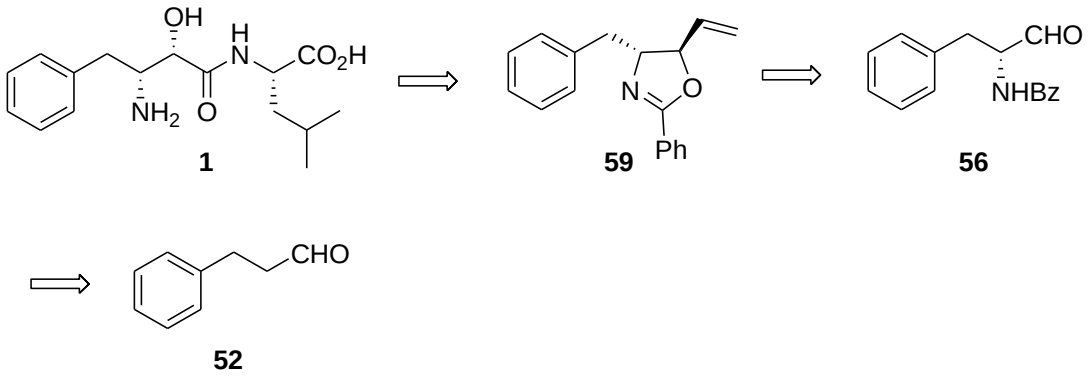


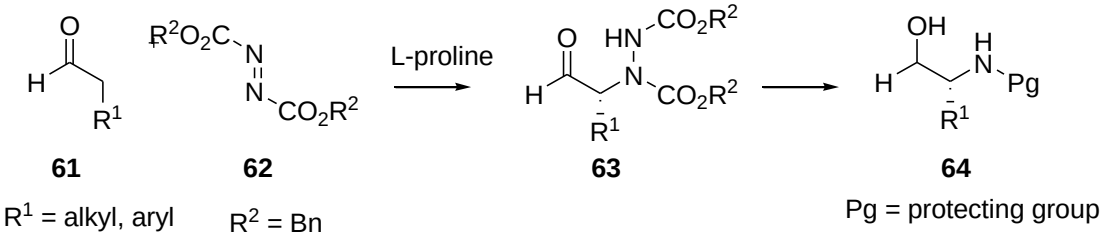
Fig. 2: Retrosynthetic analysis of (-)-bestatin (1)

Since this section deals with a highly important and attractive proline-catalyzed α-amination, which introduces stereogenicity into the prochiral molecule, a brief account of proline-catalyzed α-amination of carbonyl compounds is described.

3.1.4.2 Proline-catalyzed α-Amination

The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the C-C and the C-N bond-forming reactions. The catalytic enantioselective C-C bond-forming reactions include the addition to imines, such as the Strecker and Mannich reactions.[32] The catalytic, enantioselective, direct C-N bond-forming reaction

using aldehydes and a nitrogen source, such as azodicarboxylates, would constitute one of the simplest procedures for the construction of a stereogenic carbon center attached to a nitrogen atom. Asymmetric α-amination of aldehydes using proline as the catalyst represents[33] a burgeoning field of synthetic efforts towards synthesizing chiral building blocks such as α-amino acids and alcohols. Recently, both List[33a] and Jørgensen[33b] disclosed the asymmetric α-amination of aldehydes (**Scheme 11**) using catalytic quantities of proline. The reaction involves the addition of L-proline (10 mol%) to a solution of aldehyde **61** and azodicarboxylate ester **62**. List found that optimal enantiomeric enrichment of alcohol product **64** was obtained when the reaction temperature of 0 °C and in situ reduction with sodium borohydride was employed.



Scheme 11: L-Proline-catalyzed α-amination of aldehydes

The transition states for α-amination reaction is given in **Figure 3**. The highly reactive enamine intermediate formed between aldehydes and proline might serve as nucleophile and add stereoselectively to the diazo functional group. The observed stereochemistry can be explained with a proline-enamine involving transition state (**A**). The proposed model is based on Houk's calculated transition state of the Hajos-Parrish-Eder-Sauer-Wiechert reaction (**B**)[34] and is also consistent with previously proposed transition states for intermolecular aldol and Mannich reactions.[35]

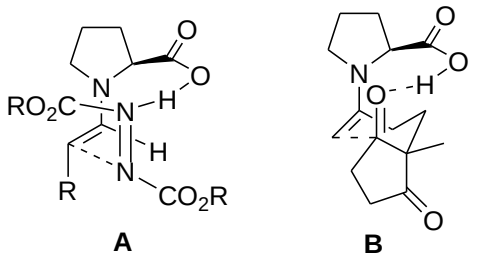
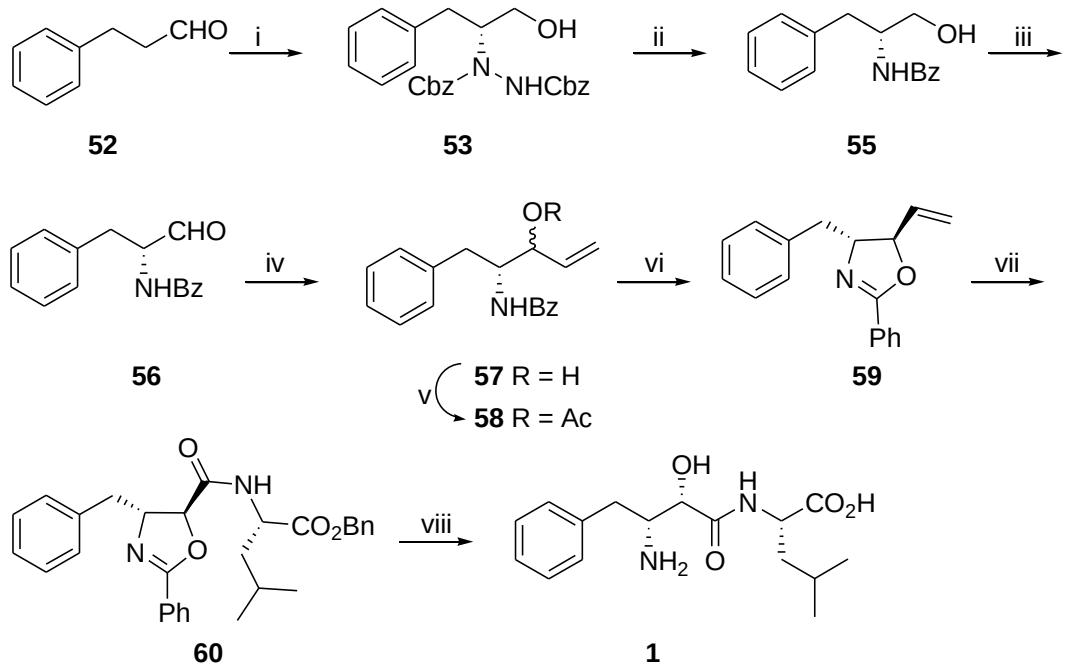


Fig. 3: Transition states for α-amination

3.1.5 Results and Discussion

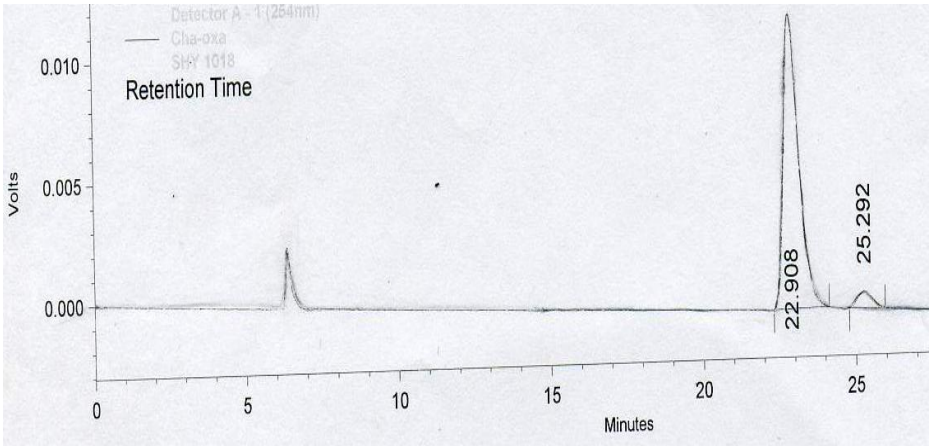
The complete synthetic sequence for (-)-bestatin (**1**), wherein L-proline-catalyzed α-amination[33a] reaction constitutes a key step for the introduction of chirality, is presented in **Scheme 12**.



Scheme 12: (i) dibenzyl azodicarboxylate, L-proline (10 mol%), CH_3CN, 0 °C to 25 °C, 3 h then $NaBH_4$, EtOH, 0 °C, 30 min, 92%, 95% ee; (ii) (a) H_2 (60 psi), Raney Nickel, MeOH, AcOH, 25 °C, 20 h; (b) benzoyl chloride, Et_3N, THF, 0 to 25 °C, 30 min, 70% (over two steps); (iii) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 2 h; (iv) CH_2=CHMgBr, THF, 0 to 25 °C, 1 h, 85% (over two steps); (v) Ac_2O, Py, DMAP, CH_2Cl_2, 25 °C, 12 h, 98%; (vi) $Pd(PPh_3)_4$ (5 mol%), K_2CO_3, CH_3CN, reflux, 24 h, 79%, dr >14: 1; (vii) (a) OsO_4, 50% aq. NMO, acetone/H_2O (9:1), 25 °C, 12 h; (b) $NaIO_4$, CH_2Cl_2, 25 °C, 10 min; (c) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 25 °C, 2 h; (d) L-leucine benzyl ester.TsOH, DCC, HOBT, THF, 0 °C to 25 °C, 16 h, 70% (over 4 steps); (viii) 20% $Pd(OH)_2/C$, H_2 (75 psi), MeOH/AcOH (9:1), 25 °C, 36 h, 72%.

Our synthesis of (-)-bestatin (**1**) was started with the α-amination of 3-phenyl-propionaldehyde using List's protocol.[33a] Accordingly, 3-phenylpropionaldehyde **52** was subjected to α-amination with dibenzyl azodicarboxylate in the presence of L-proline (10 mol%) to produce an amino aldehyde, which upon *in situ* reduction with $NaBH_4$ afforded the protected amino alcohol **53** in 92% yield and 95% ee, mp: 110-116 °C; $[\alpha]^{25}_D$ = +11.43 (*c* 1.8, $CHCl_3$).

The enantiomeric purity of **53** was determined as 95% by chiral HPLC analysis of the corresponding oxazolidinone **54** obtained from the protected amino alcohol **53** by following the literature procedure.[33a] HPLC conditions: Kromasil 5-AmyCoat column (250× 4.6 mm), petroleum ether: *i*-PrOH (90:10), 0.5 mL/min, 254 nm (**Fig. 4**).



Peak No.	Retention Time	Area (µV-sec)	Area (%)
1	22.908	432396	97.764
2	25.292	9890	2.236

Fig. 4: HPLC chromatogram of oxazolidinone 54

The formation of protected amino alcohol was confirmed by the appearance of a characteristic signal at δ 3.65 as a multiplet in its ^{1}H NMR spectrum for the benzyl protons (C_6H_5-C**H**$_2$-CHN-) and the corresponding carbon signal appeared at δ 34.38 in

the ^{13}C NMR spectrum (**Fig. 5**). The IR spectrum of **53** displayed strong absorption band above 3000 cm^{-1} indicating the presence of -OH and -NH groups.

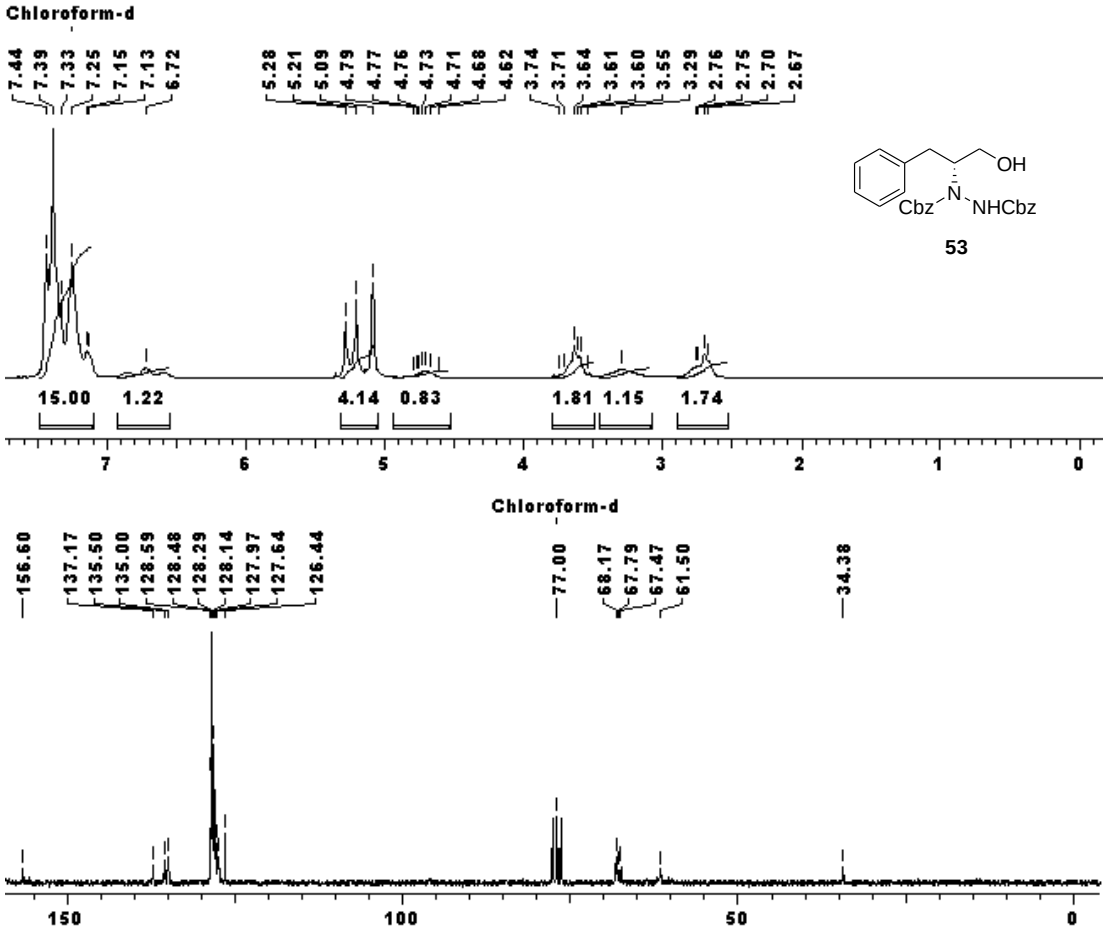


Fig. 5: ^{1}H and ^{13}C NMR spectra of amino alcohol 53

Amino alcohol **53** was then subjected to hydrogenolysis over Raney Nickel[36] and H_2 (60 psi) at 25 °C to give free amine, which was protected as benzamide **55** using BzCl in presence of Et_3N in THF in 70% yield over two steps. The methylene protons of the carbon attached to oxygen resonated at δ 3.59 as a multiplet while the methine proton of the carbon attached to nitrogen gave a multiplet at δ 4.27 in the ^{1}H NMR spectrum. The formation of benzamide **55** was further confirmed by ^{13}C NMR spectrum in which the amide carbonyl exhibited a strong peak at δ 166.33 (**Fig. 6**). Oxidation of alcohol **55** with

Dess-Martin periodinane reagent in CH_2Cl_2 at 25 °C gave the corresponding aldehyde **56**.

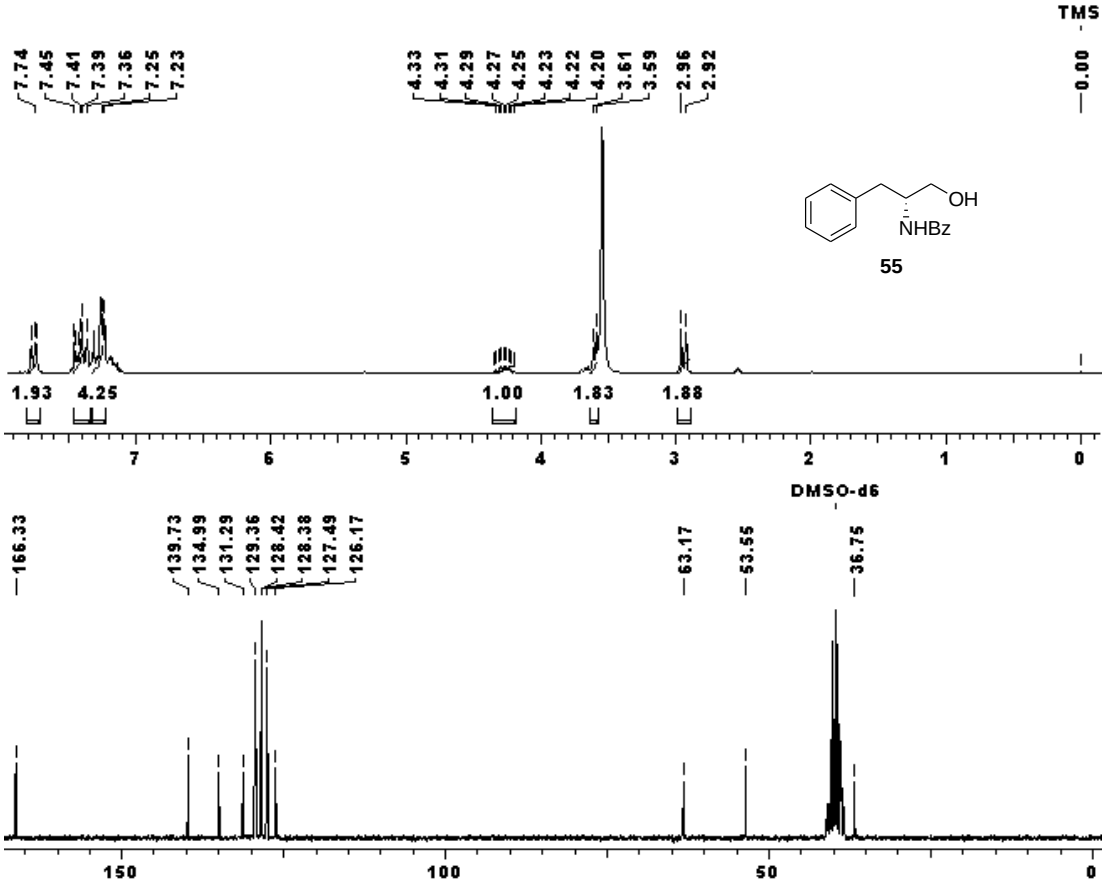


Fig. 6: ^{1}H and ^{13}C NMR spectra of amino alcohol 55

The characteristic aldehydic signal has appeared at δ 9.73 as a singlet in its ^{1}H NMR spectrum, thus confirming the formation of **56** (**Fig. 7**).

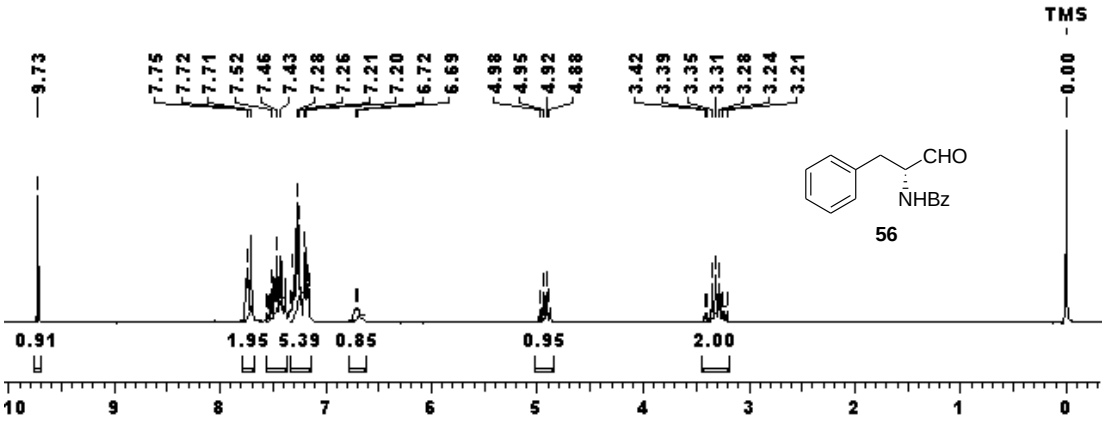


Fig. 7: ^{1}H NMR spectrum of aldehyde 56

The aldehyde **56**, on reaction with vinylmagnesium bromide in THF at 0 °C afforded allylic alcohol **57** as a 1.1:1 mixture of *syn*/*anti* isomers (determined by ^{1}H NMR analysis) in 85% yield. The ^{1}H and ^{13}C NMR spectra were in accordance with the proposed structure of **57**. For example, the characteristic peaks for olefin have appeared as multiplets at δ 5.30 (integrating for two protons) and δ 5.95 (integrating for one proton) in ^{1}H NMR of **57** and it was further supported by two sets of diastereomeric peaks in its ^{13}C NMR spectrum (**Fig. 8**).

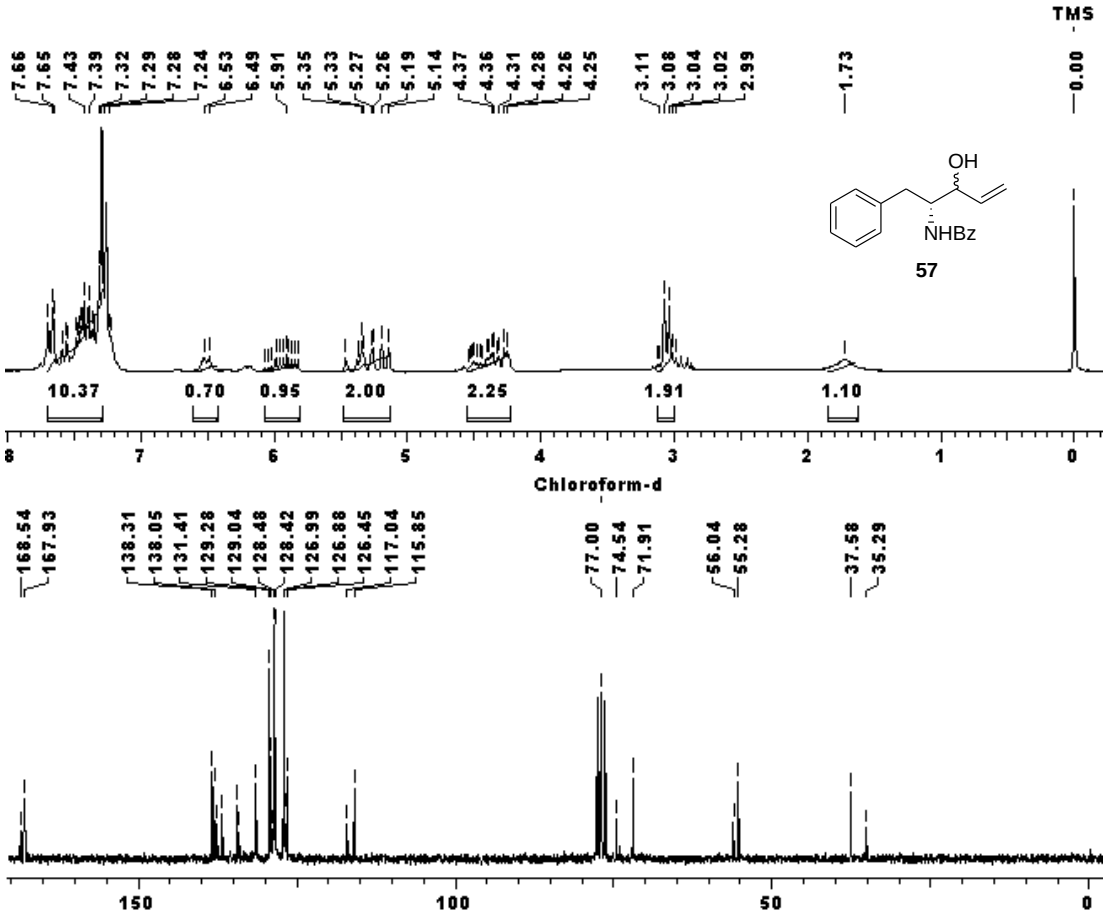


Fig. 8: ^{1}H and ^{13}C NMR spectra of amino alcohol 57

Acetylation of alcohol **57** was carried out with Ac_2O in the presence of pyridine and catalytic amount of DMAP in CH_2Cl_2 to give the secondary allylic acetate **58** in 98%

yield. Two diastereomeric singlets have appeared at δ 2.10 and 2.12 (-OCOC**H**$_3$), integrating for three protons in the ^{1}H NMR spectrum confirmed the formation of acetate **58** which was further substantiated by the appearance of corresponding carbon signals at δ 20.87 and 20.96 (-OCO**C**H$_3$) in the ^{13}C NMR spectrum (**Fig. 9**).

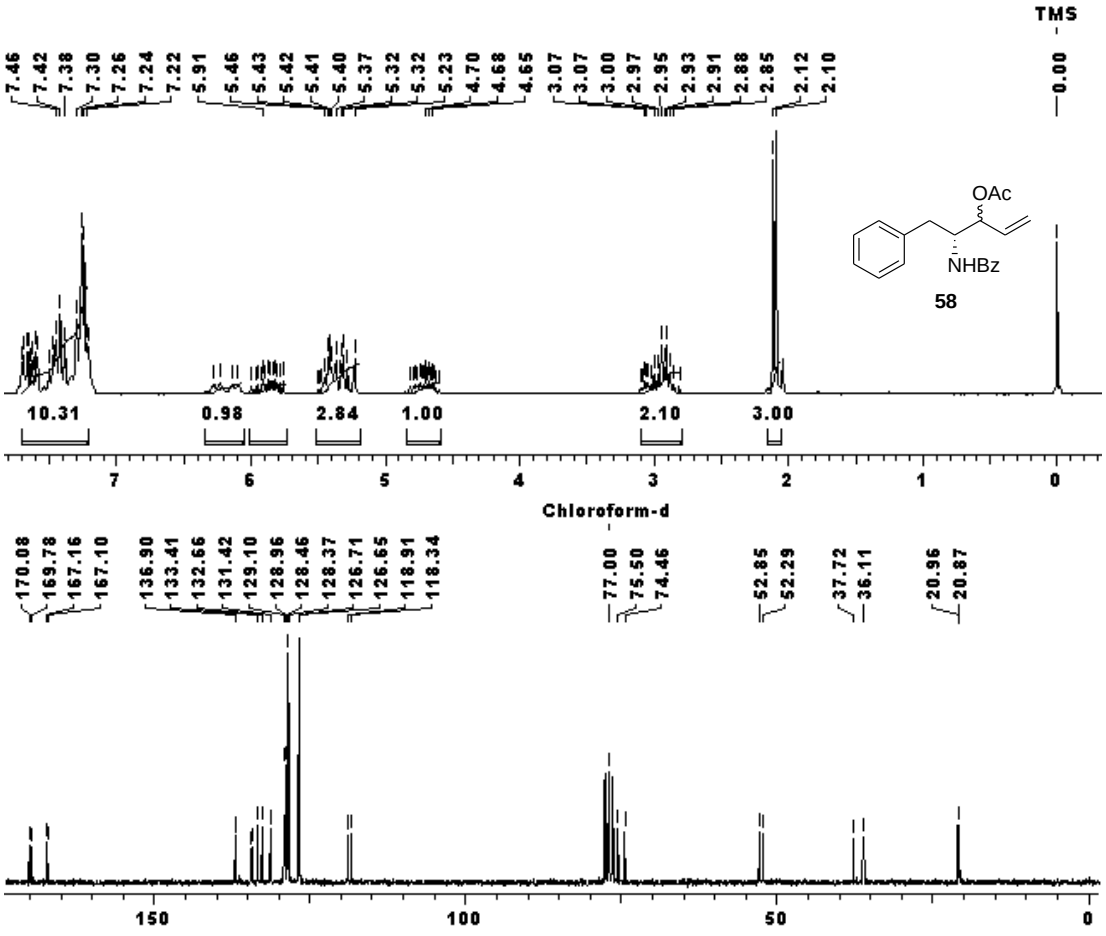


Fig. 9: ^{1}H and ^{13}C NMR spectra of acetate 58

The Pd-catalyzed intramolecular cyclization[37] of allylic acetate **58** using $Pd(PPh_3)_4$ and K_2CO_3 in CH_3CN proceeded smoothly to give the desired *trans*-oxazoline **59** in 79% yield as an inseparable mixture of diastereomers (dr >14:1). The diastereomeric ratio in *trans*-oxazoline **59** was determined by ^{1}H NMR spectral analysis. Two doublet of doublets have appeared at δ 2.85 (dd, *J* = 8.6, 13.7 Hz, 1H) and 3.31 (dd, *J* = 5.3, 13.8

Hz, 1H) accounted for the benzylic protons of **59** while the olefinic peaks resonated at δ 5.08-5.16 (m, 2H) and 5.75 (ddd, J = 6.6, 10.2, 17.0 Hz, 1H) in its ^{1}H NMR spectrum which was further ascertained by the appearance of the oxazine carbon [Ph-**C**(O)=N-] at δ 162.92 in the ^{13}C NMR spectrum (**Fig. 10**).

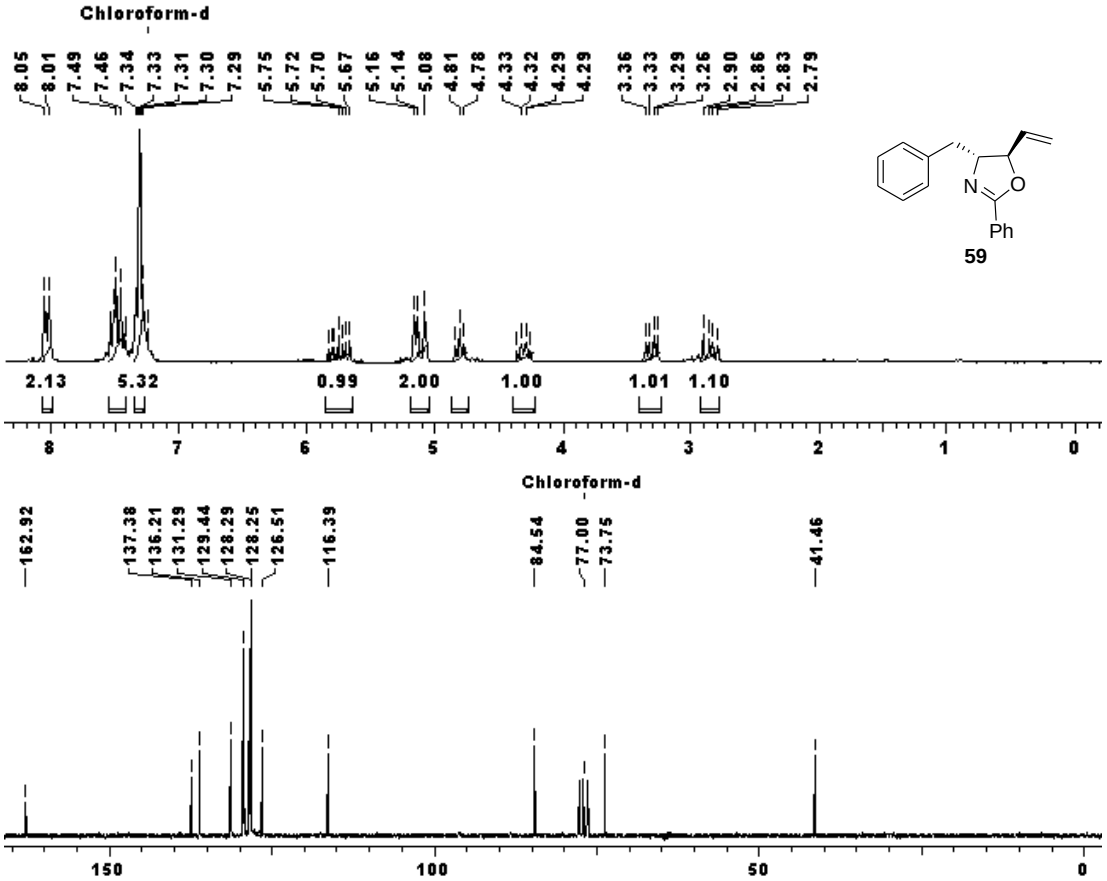


Fig. 10: ^{1}H and ^{13}C NMR spectra of oxazoline 59

Oxidative degradation of the vinylic group in **59** was carried out as indicated in the following sequence of reactions: (i) the olefin function in oxazoline **59** was initially dihydroxylated (OsO_4, NMO); (ii) the diol so formed was subsequently cleaved on treatment with $NaIO_4$[38] which gave the corresponding aldehyde; (iii) the crude aldehyde, being labile, was immediately oxidized ($NaClO_2$, NaH_2PO_4),[39] to the corresponding carboxylic acid without purification; (iv) the acid thus formed (column purification of

acid was found to be difficult giving many decomposed products) was readily condensed with the benzyl ester of L-leucine (DCC, HOBT in THF)[40] to provide the amide **60** in 70% yield over the four steps. The ^{1}H and ^{13}C NMR spectra were in accordance with the proposed structure of **60**. A doublet at δ 5.15 with coupling constant 2.52 Hz, integrating for two protons, accounted for the methylene protons of benzyl ester (-$CO_2C\mathbf{H}_2Ph$) and the amide proton resonated as a doublet at δ 6.52 in the ^{1}H NMR spectrum. The formation of amide **60** was further supported by the appearance of two typical carbonyl peaks at δ 170.09 and 172.13 in its ^{13}C NMR spectrum (**Fig. 11**).

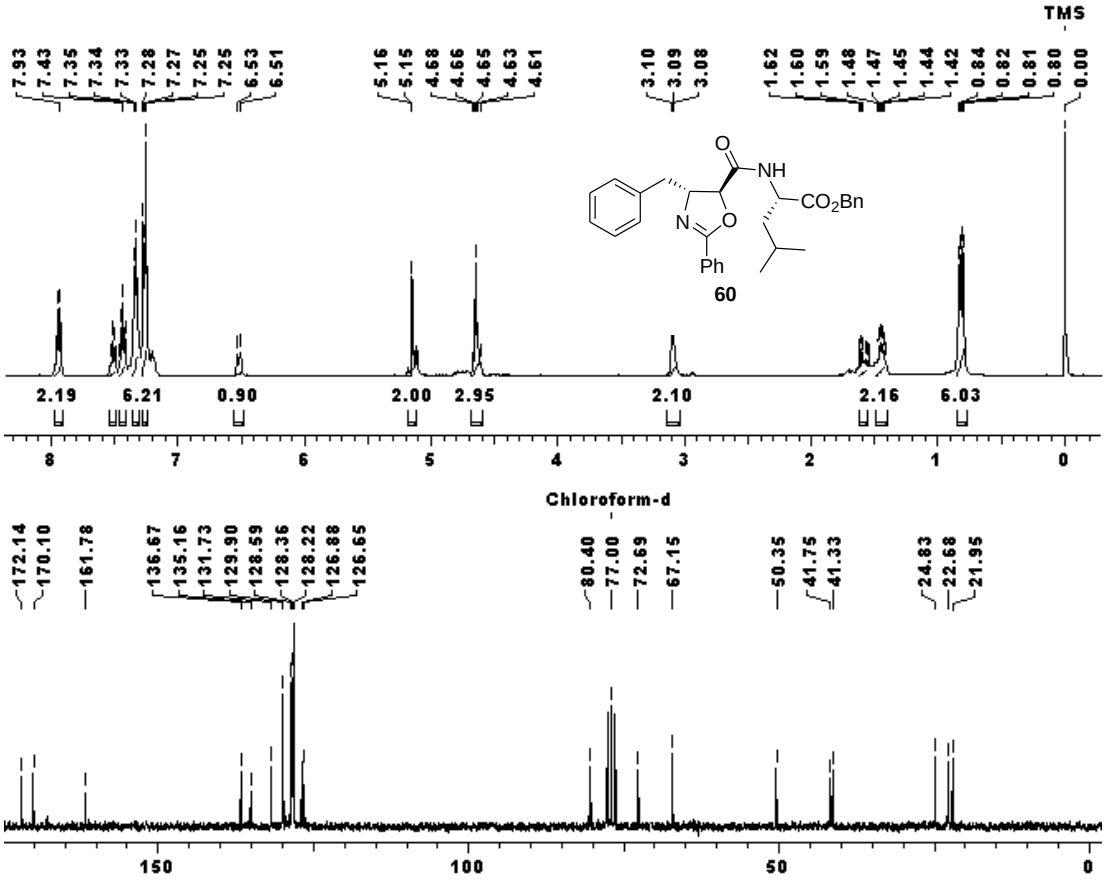


Fig. 11: ^{1}H and ^{13}C NMR spectra of amide 60

Finally, catalytic hydrogenolysis [20% $Pd(OH)_2/C$, H_2 (75 psi), MeOH/AcOH (9:1), 25 °C, 36 h][37c] of amide **60** furnished (-)-bestatin (**1**) in 72% yield, $[\alpha]_D^{25}$ = -13.5 (*c* 0.5, 1 N

HCl); {lit.[40] $[\alpha]_D^{25}$ = -14.3 (*c* 0.5, 1 N HCl)}. The spectroscopic data of **1** was in full agreement with those reported in the literature.[40] The ^{1}H NMR spectrum of **1** displayed spectral pattern as δ 3.08 (dd, *J* = 7.98, 12.24 Hz, 1H), 3.25 (dd, *J* = 5.50, 13.12 Hz, 1H) corresponding to the benzylic protons and δ 4.04 (m, 1H), 4.57 (m, 2H) corresponding to the methine protons of the carbons attached to nitrogen and oxygen atoms. Its ^{13}C NMR spectrum showed the presence of two carbonyl peaks at δ 173.94 and 177.49 and the methine carbons attached to nitrogen and oxygen atoms gave resonances at δ 52.60, 57.31 and 70.58 (**Fig. 12**). The IR spectrum of (-)-bestatin (**1**) displayed characteristic carbonyl absorption bands corresponding to the acid and amide groups at 1713 and 1662 cm^{-1} respectively.

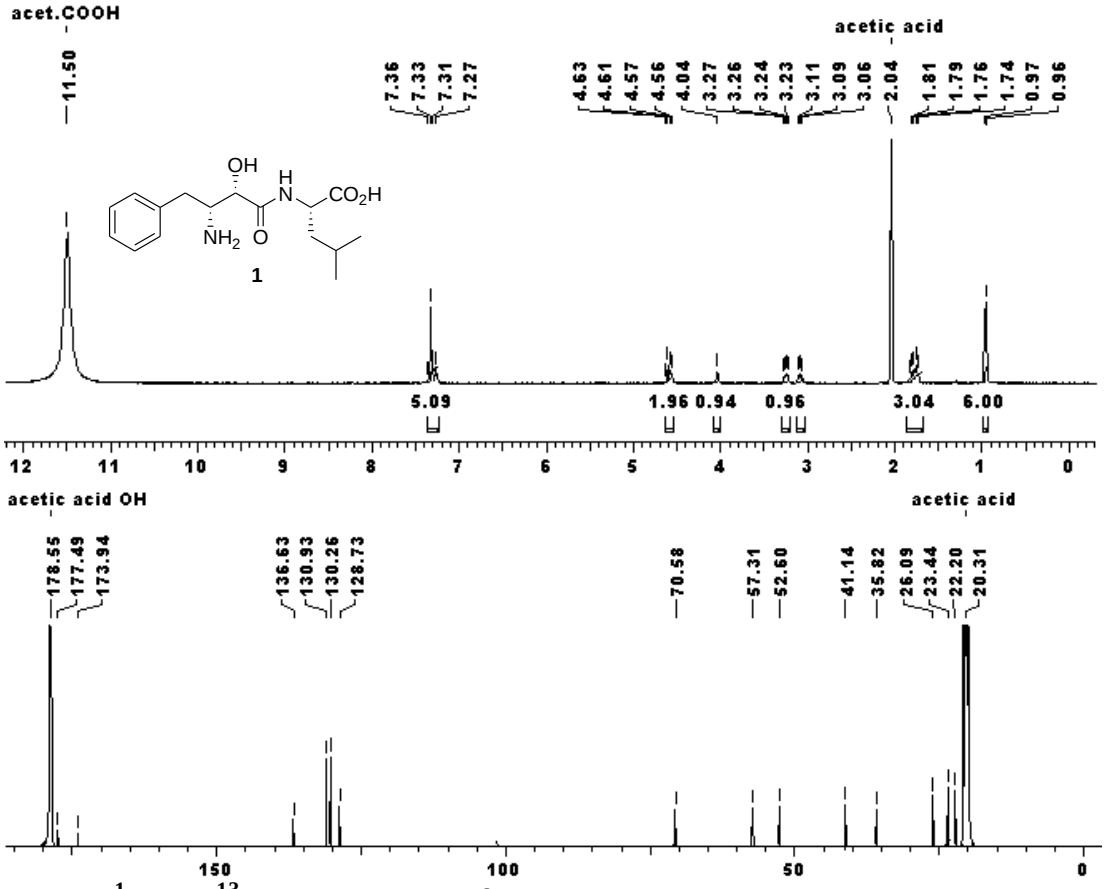


Fig. 12: ^{1}H and ^{13}C NMR spectra of (-)-bestatin (1)

3.1.6 Conclusion

A short synthetic route to (-)-bestatin (**1**) with an overall yield of 22% is described, which includes a successful application of L-proline-catalyzed asymmetric α-amination of an aldehyde to give the corresponding amino alcohol **53** in 95% ee. The protocol also demonstrates the synthetic utility of the Pd-catalyzed intramolecular cyclization of benzamide **58** to give *trans*-oxazoline **59** in a highly diastereoselective fashion.

3.1.7 Experimental Section

(*R*)-2-(1, 2-Dibenzyloxycarbonylhydrazinyl)-3-(phenyl)propan-1-ol (54)

To a mixture of of dibenzyl azodicarboxylate (5.97 g, 20 mmol) and proline (230 mg, 10 mol%) in CH_3CN (100 mL) at 0 ºC was added *n*-butyraldehyde (2.68 g, 20 mmol) and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 20 ºC within 1 h. After the reaction mixture became colorless, it was cooled to 0 ºC again and then treated with EtOH (100 mL) and $NaBH_4$ (1.5 g) for 5 min at 0 ºC. After completion of reaction, it was quenched by adding half-concentrated aq. ammonium chloride solution and extracted with ethyl acetate (3 × 100 mL), 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 (7:3) to give amino alcohol **54** (7.99 g) as a colorless solid.

Yield: 92%; **mp**: 110-116 °C; **$[\alpha]^{25}_D$**: +11.43 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3446, 1716, 1496, 1456, 1409, 1261, 1217, 1134, 729; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.67-2.75 (m, 2H), 3.29 (br s, 1H), 3.55-3.74 (m, 2H), 4.62-4.79 (m, 1H), 5.09-5.08 (m, 4H), 6.72 (br s, 1H), 7.13-7.44 (m, 15H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.38, 61.50, 67.47, 67.79, 68.17, 126.44, 127.42, 127.64, 127.97, 128.14, 128.29, 128.35, 128.48, 128.59,

135.00, 135.50, 137.17, 156.60; **Analysis: $C_{25}H_{26}N_2O_5$** requires C, 69.11; H, 6.03; N, 6.45; found: C, 69.43; H, 5.82; N, 6.26%.

***N*-[(*R*)-1-Hydroxy-3-phenylpropan-2-yl]benzamide (55)**

Alcohol **54** (8.26 g, 19 mmol) was dissolved in MeOH (100 mL), AcOH (10 drops) and treated with Raney Nickel (13.0 g, excess) for 24 h under 12 bar of hydrogen atmosphere. The reaction mixture was filtered over celite and concentrated to give the corresponding amino alcohol which was directly taken for the next step. To a stirred solution of amino alcohol in THF (100 mL) containing Et_3N (3.17 mL, 22.8 mmol) was added benzoyl chloride (3.31 mL, 28.5 mmol) and the mixture was stirred for 30 min. The solvent was evaporated, reaction mixture was diluted with water (150 mL), extracted with ethyl acetate (3 × 150 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 (8:2) to give benzamide **55** (3.4 g) as a colorless solid.

Yield: 70%; **mp**: 175-176 °C; **$[\alpha]^{25}_D$**: +81.3 (*c* 1.5, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3361, 2945, 2833, 2044, 1706, 1637, 1544, 1448, 1415, 1230, 1114, 1057; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.94 (d, *J* = 7.22 Hz, 2H), 3.59-3.61 (m, 2H), 4.20-4.35 (m, 1H), 7.23-7.45 (m, 4H), 7.36-7.45 (m, 4H), 7.73-7.78 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.75, 53.55, 63.17, 126.17, 127.49, 128.38, 128.42, 129.36, 131.29, 134.99, 139.73, 166.33; **Analysis: $C_{16}H_{17}NO_2$** requires C, 75.27; H, 6.71; N, 5.49; found: C, 74.95; H, 6.90; N, 5.63%.

***N*-[(*R*)-1-Formyl-2-phenylethyl]benzamide (56)**

To a solution of Dess-Martin periodinane (8.23 g, 19.5 mmol) in CH_2Cl_2 (50 mL) at 25 °C was added a solution of alcohol **55** (3.3g, 13 mmol) in CH_2Cl_2 (50 mL). The reaction

mixture was stirred for 2 h at 25 °C, after which time TLC analysis indicated complete reaction. The reaction mixture was diluted with ether (150 mL) and extracted with saturated $NaHCO_3$ (150 mL) and with water (150 mL), dried over anhyd. Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give crude aldehyde. This aldehyde was immediately employed in the next step without further purification.

IR ($CHCl_3$, cm^{-1}): 2399, 2252, 1733, 1662, 1658, 1515, 1483, 1215, 908; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.21-3.42 (m, 2H), 4.93 (q, *J* = 6.58 Hz, 1H), 6.70 (d, *J* = 5.58 Hz, 1H), 7.16-7.34 (m, 5H), 7.38-7.56 (m, 3H), 7.71-7.75 (m, 2H).

***N*-[(*R*)-3-Hydroxy-1-phenylpent-4-en-2-yl]benzamide (57)**

To a stirred suspension of magnesium (0.62 g, 26 mmol) in THF (20 mL), vinyl bromide (5.56 g, 52 mmol) in THF (20 mL) was added at 0 ºC under nitrogen atmosphere over a period of 15 min and the continued stirring at room temperature for a further 30 min. The reaction mixture was cooled to 0 ºC and the crude aldehyde **56** dissolved in THF (20 mL) was added over a period of 10 min. After the addition was complete, the reaction mixture was allowed to return to room temperature and stirring continued for another 2 h. The reaction mixture was quenched by the addition of aq. ammonium chloride and extracted with ethyl acetate (3 × 100 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. The crude compound was purified by column chromatography using petroleum ether/EtOAc (5:5) to afford amide **57** (2.95 g) as colorless solid.

Yield: 85%; **mp**: 153-154 °C; **$[\alpha]^{25}_D$**: +73.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3330, 1637, 1625, 1541, 1134, 1029, 727, 694; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.73 (br s, 1H), 3.06 (d, *J* = 7.36 Hz, 2H), 4.25-4.54 (m, 2H), 5.14-5.46 (m, 2H), 5.82-6.07 (m, 1H), 6.51 (d, *J*

= 8.05 Hz, 1H), 7.22-7.69 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.29, 37.58, 55.28, 56.04, 71.91, 74.54, 115.85, 117.04, 126.45, 126.59, 126.88, 126.99, 128.42, 128.48, 128.56, 128.67, 128.75, 129.04, 129.28, 131.41, 131.56, 134.04, 134.34, 136.74, 137.70, 138.05, 138.31, 167.93, 168.54; **Analysis: $C_{18}H_{19}NO_2$** requires C, 76.84; H, 6.81; N, 4.98; found: C, 77.16; H, 6.62; N, 4.79%.

(*R*)-2-(Benzamido)-1-phenylpent-4-en-3-yl acetate (58)

Acetic anhydride (0.83 mL, 8.8 mmol), pyridine (0.72 mL, 8.8 mmol) and DMAP (97 mg, 0.8 mmol) were added to a stirred solution of alcohol **57** (2.14 g, 8 mmol) in CH_2Cl_2 (40 mL) and stirring was allowed to continue for 12 h. The reaction mixture was washed with 1N HCl (3 × 50 mL), saturated aq. $NaHCO_3$ solution (3 × 50 mL), and brine (3 × 50 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (6:4) to afford acetate **58** (2.53 g) as colorless solid.

Yield: 98%; **mp**: 147-148 °C; **$[\alpha]^{25}_D$**: +72.6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3446, 3384, 3024, 1735, 1718, 1650, 1602, 1541, 1533, 1490, 1369, 1234, 1108, 1027, 756; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.10-2.12 (m, 3H), 2.81-3.10 (m, 2H), 4.60-4.82 (m, 1H), 5.23-5.50 (m, 3H), 5.76-6.00 (m, 1H), 6.10-6.28 (m, 1H), 7.20-7.71 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.87, 20.96, 36.11, 37.72, 52.29, 52.85, 74.46, 75.50, 118.34, 118.91, 126.57, 126.65, 126.71, 126.80, 128.37, 128.46, 128.96, 129.10, 131.30, 131.42, 132.66, 133.41, 134.33, 134.45, 136.90, 137.03, 167.10, 167.16, 169.78, 170.08; **Analysis: $C_{20}H_{21}NO_3$** requires C, 74.28; H, 6.55; N, 4.33; found: 73.96; H, 6.73; N, 4.56%.

(4*R*,5*R*)-4-Benzyl-4,5-dihydro-2-phenyl-5-vinyloxazole (59)

Tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] (380 mg, 0.325 mmol), was added

under N_2 to a stirred solution of allyl benzamide **58** (2.09 g, 6.5 mmol) and K_2CO_3 (2.69 g, 19.5 mmol) in 60 mL of CH_3CN. The resulting mixture was refluxed for 24 h, whereupon it was allowed to cool to room temperature and filtered through a pad of silica and the filtrate was then evaporated under reduced pressure to give the crude product. The crude compound was purified by column chromatography using petroleum ether/EtOAc (9:1) to afford ozazoline **59** (1.35 g) as thick liquid.

Yield: 79%; **$[\alpha]^{25}_{D}$**: -35.5 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3353, 2945, 2831, 2596, 2044, 1701, 1650, 1450, 1417, 1114, 1029; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.85 (dd, *J* = 8.6, 13.7 Hz, 1H), 3.31 (dd, *J* = 5.3, 13.8 Hz, 1H), 4.26-4.36 (m, 1H), 4.81 (t, *J* = 6.6 Hz, 1H), 5.08-5.16 (m, 2H), 5.75 (ddd, *J* = 6.6, 10.2, 17.0 Hz, 1H), 7.27-7.35 (m, 5H), 7.41-7.54 (m, 3H), 8.01-8.05 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 41.46, 73.75, 84.54, 116.39, 126.51, 128.25, 128.29, 128.43, 129.44, 131.29, 136.21, 137.38, 162.92; **Analysis: $C_{18}H_{17}NO$** requires C, 82.10; H, 6.51; N, 5.32; found: C, 82.43; H, 6.32; N, 5.11%.

(*S*)-Benzyl-2-[(4*R*,5*S*)-4-benzyl-4,5-dihydro-2-phenyloxazole-5-carboxamido]-4-methylpentanoate (60)

Osmium tetroxide (catalytic amount) and 50% aqueous *N*-methylmorpholine *N*-oxide (0.93 mL, 4 mmol) were added to a solution of oxazine **59** (0.53 g, 2 mmol) in acetone (9.3 mL) at 0 °C. After continuous stirring for 12 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (40 mL), and dried over anhyd. Na_2SO_4 and concentrated to give the crude diol, which was then directly taken for the next step without purification.

To a vigorously stirred suspension of silica gel-supported $NaIO_4$ reagent (4.0 g) in CH_2Cl_2 (7 mL) in a 25 mL round-bottomed flask was added a solution of the crude

vicinal diol in CH_2Cl_2 (5 mL). The reaction was monitored by TLC until disappearance of the starting material. The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated under reduced pressure to give the product aldehyde which was immediately treated with NaH_2PO_4 (0.83 g, 6 mmol) and $NaClO_2$ (0.37, 6 mmol) in $^tBuOH/H_2O$(15/3 mL). After TLC showed the complete disappearance of starting material, the reaction mixture was diluted with EtOAc (10 mL) and dried over anhyd. Na_2SO_4 and concentrated to give the crude acid which was then directly taken for the next step without purification.

BenzylL-leucinate *p*-toluenesulfonic acid salt (0.87 g, 2.2 mmol), 3-hydroxybenzotriazole (0.33 g, 2.4 mmol), and the above acid were all taken up in THF (10 mL) and cooled to 0 °C. Dicyclohexylcarbodiimide (0.496 mg, 2.48 mmol) and triethylamine (0.3 mL, 2.2 mmol) were then added, and the mixture was stirred at room temperature for 12 h. The resulting mixture was diluted with THF (5 mL) and filtered. The filtrate was diluted with Et_2O (30 mL) and extracted with 0.5 N HCl (1 × 20 mL), 5% aq. $NaHCO_3$ (1 × 20 mL), and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (6:4) to afford ester **60** (0.68 g) as a gum.

Yield: 70%; **$[\alpha]^{25}_D$**: -4.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3353, 2945, 2831, 2044, 1701, 1650, 1460, 1417, 1114, 1029; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.82 (m, 6H), 1.41-1.48 (m, 2H), 1.56-1.63 (m, 1H), 3.08-3.10 (m, 2H), 4.61-4.68 (m, 3H), 5.15-5.16 (m, 2H), 6.52 (d, *J* = 8.65 Hz, 1H), 7.25-7.28 (m, 6H), 7.32-7.35 (m, 4H), 7.41-7.46 (m, 2H), 7.50-7.53 (m, 1H), 7.93-7.95 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.94, 22.67, 24.82, 41.32, 41.74, 50.34, 67.14, 72.68, 80.39, 126.64, 126.87, 128.21, 128.35, 128.45, 128.48,

128.58, 129.89, 131.72, 135.15, 136.66, 161.77, 170.09, 172.13; **Analysis: $C_{30}H_{32}N_2O_4$** requires C, 74.36; H, 6.66; N, 5.78; found: C, 74.69; H, 6.47; N, 5.59%.

(-)-Bestatin (1)

To a solution of the amido ester **60** (0.48 g, 1 mmol) in AcOH/MeOH (1/9, 10 mL) was added 150 mg of 20% $Pd(OH)_2$ and was vigorously shaken under 75 psi H_2 for 36 h at ambient temperature. The mixture was then filtered through a pad of silica and concentrated in vacuo to give the final product, (-)-bestatin (**1**) (0.21 g), which was recrystallized from methanol/ethyl acetate to give a colorless solid.

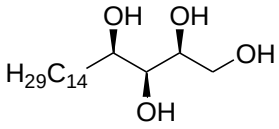
Yield: 72%; **mp**: 230-234 °C [lit.[40] **mp**: 231-236 °C]; **$[\alpha]^{25}_D$**: -13.5 (*c* 0.5, 1N HCl) {lit.[40] **$[\alpha]^{23}_D$**: -14.3 (*c* 0.5, 1 N HCl)}; **IR** ($CHCl_3$, cm^{-1}): 3397, 2961, 1713, 1662, 1539, 1256, 1184, 1158; **^{1}H NMR** (400 MHz, acetic acid-d_4): δ 0.96-0.97 (m, 6H), 1.74-1.83 (m, 3H), 3.08 (dd, *J* = 7.98, 12.24 Hz, 1H), 3.25 (dd, *J* = 5.50, 13.12 Hz, 1H), 4.04 (m, 1H), 4.56-4.63 (m, 2H), 7.27-7.36 (m, 5H); **^{13}C NMR** (100 MHz, acetic acid-d_4): δ 22.20, 23.44, 26.09, 35.82, 41.14, 52.60, 57.31, 70.58, 128.73, 130.26, 130.93, 136.63, 173.94, 177.49; **Analysis: $C_{16}H_{24}N_2O_4$** requires C, 62.32; H, 7.84; N, 9.08; found: C, 61.99; H, 8.01; N, 9.25%.

Section II

Asymmetric synthesis of guggultetrol using Sharpless asymmetric epoxidation and dihydroxylation

3.2.1 Introduction

The asymmetric catalysis has emerged as one of the practical, cost effective and efficient method for the synthesis of biologically active natural products containing multiple stereocenters. Tetrols, in particular, having contiguous stereogenic centers are useful intermediates in the synthesis of a number of biologically active compounds[41] such as phytosphingosines.[42] For instance, guggultetrol (**61)**, a naturally occurring lipid isolated from the gum-resin of the tree *Commiphoru mukul (guggul)*,[43] known in Ayurveda, the Indian traditional system of medicine, is used in the treatment of arthritis, inflammation, obesity and disorders of lipid metabolism.[44] There are only few literature reports[45-47] available for the synthesis of guggultetrol (**61**); all of them have made use of chiral pool approach for its asymmetric synthesis.



guggultetrol (61)

Figure 12

3.2.2 Pharmacology of guggultetrol

The use of plants in the treatment of disease occupies an important place in Ayurveda, the traditional medicine of India. The *Sushruta Samhita* (600 B.C.), a well-known Ayurvedic medical text, describes the usefulness of the gum resin from the tree *Commiphora mukul* in the treatment of a number of ailments, including obesity and disorders of lipid

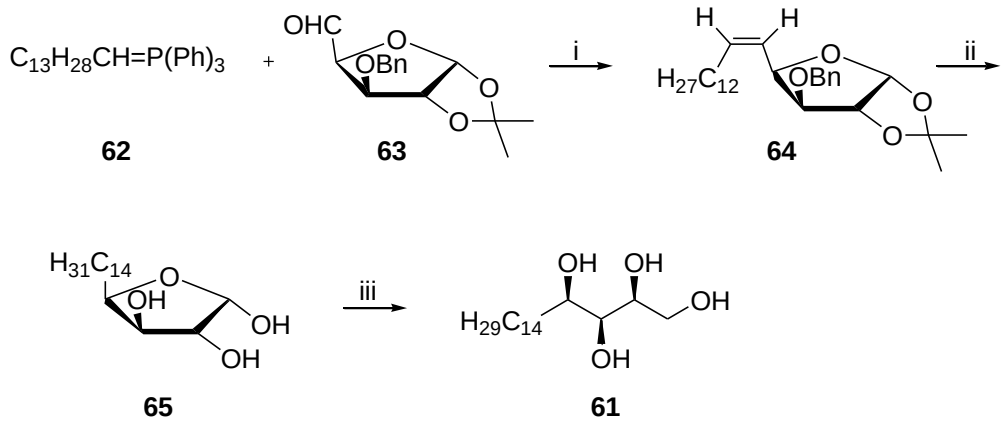
metabolism.[44a] *Commiphora mukul* is a member of the *Burseraceae* family and is found in arid areas of India, Bangladesh, and Pakistan.[44a] On incision, the plant exudes a yellowish gum-resin, which rapidly solidifies to an agglomerate of tears or stalactitic pieces. This product, called 'guggulu' in Sanskrit, is valued in Ayurveda, for the treatment of several diseases, especially rheumatoid arthritis and lipid disorders. Guggultetrol (**61**) was isolated from guggulu after saponification of its ethyl acetate extract.

3.2.3 Review of Literature

Literature search revealed that there are only few reports[45-47] available for the synthesis of guggultetrol (**61**), all of which utilized chiral pool approach for its asymmetric synthesis.

Kjaer's approach (1986)[45]

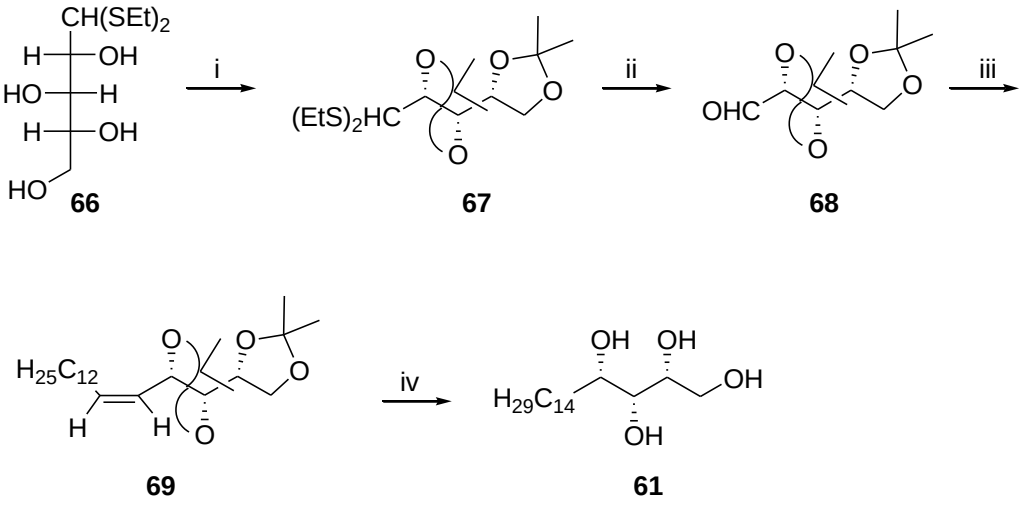
Kjaer *et al.* have achieved the synthesis of guggultetrol (**61**) starting from aldehyde **63** which was subjected to Wittig olefination with **62** in THF and DMSO to give the *Z*-olefin **64**. The olefin **64** was then subjected to hydrogenation over Pd/C followed by acid hydrolysis to afford **65**. The furanoside derivative **65** was then converted to guggultetrol (**61**) by treating it with $NaBH_4$ in EtOH (**Scheme 13**).



Scheme 13: (i) THF, DMSO; (ii) (a) H_2 (1 atm), Pd/C, EtOH; (b) $HClO_4$, dioxane/H_2O; (iii) $NaBH_4$, EtOH.

Sukh Dev's approach (1987)[46]

Sukh Dev *et al.* have described the synthesis of the enantiomer of guggultetrol (**61**) commencing from D-xylose diethyldithioacetal **66** which was protected as its diacetonide **67** on exposure to acetone in presence of catalytic amounts of $FeCl_3$ in 85% yield. Treatment of diacetonide **67** with mercuric chloride and cadmium carbonate gave the aldehyde **68** which was subjected to Wittig olefination using tridecyltriphenylphosphonium bromide to afford the *Z*-olefin **69** in 60% yield. Catalytic hydrogenation of the *Z*-olefin **69** followed by acidification provided the enantiomer of guggultetrol (**61**) in quantitative yield (**Scheme 14**).

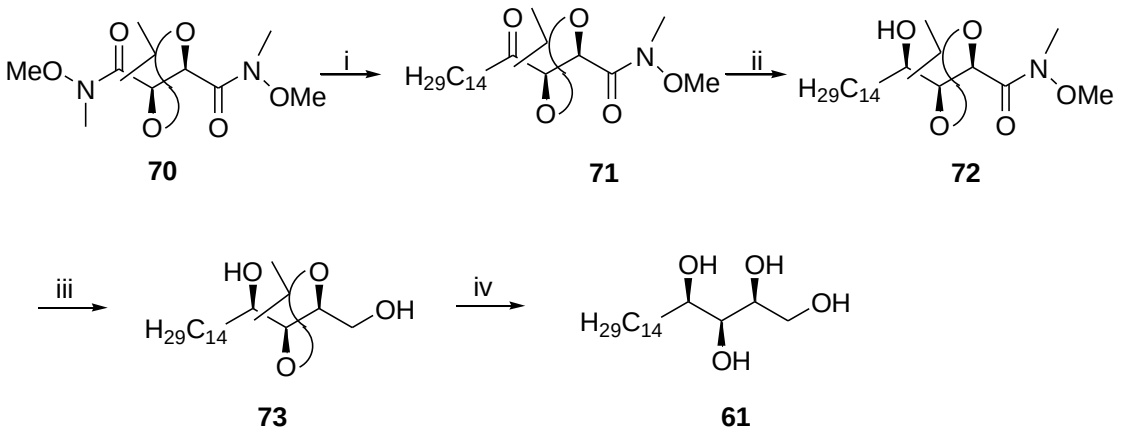


Scheme 14: (i) acetone, $FeCl_3$, 85%; (ii) $HgCl_2$, $CdCO_3$, CH_3CN/H_2O, 70%; (iii) $C_{13}H_{27}PPh_3Br$, PhLi, THF, 60%; (iv) (a) 10% Pd/C, H_2, EtOH; (b) $HClO_4$, dioxane/H_2O, 100%.

Prasad's approach (2007)[47]

Prasad *et al.* have reported the synthesis of guggultetrol (**61**) by the Grignard addition of pentadecanylmagnesium bromide to bis-amide **70** derived from L-(+)-tartaric acid. Reduction of ketoamide **71** with K-selectride provided single diastereomer of alcohol **72** in 98% yield. Alcohol **72** was then converted to guggultetrol (**61**) by the reduction of

amide **72** with $NaBH_4$ followed by deprotection of acetonide using $FeCl_3.6H_2O$ (**Scheme 15**).



Scheme 15: (i) $C_{14}H_{29}MgBr$, THF, -15 °C, 0.5 h; (ii) K-selectride, THF, -78 °C, 2 h, 98%; (iii) $NaBH_4$, MeOH, 0 °C to 25 °C, 2 h, 96%; (iv) $FeCl_3.6H_2O$, CH_2Cl_2, 25 °C, 10 min, 71%.

3.2.4 Present Work:

3.2.4.1 Objective

Acyclic vicinal diols are occasionally encountered as part of many biologically active natural products. Guggultetrol (**61**), a long-chain linear aliphatic tetrol with contiguous steriogenic centers, was isolated by Suk Dev *et al.* in 1973[43] and is used in the treatment of arthritis, inflammation, obesity and disorders of lipid metabolism in ayurveda. In spite of its interesting biological activity, there are not many reports available in literature for its asymmetric synthesis and all of the reported syntheses utilized chiral pool approach for establishing the chiral centers. In this context, a more practical method for the asymmetric synthesis of guggultetrol (**61**) is highly desirable.

Retrosynthetic analysis (**Fig. 13**) for guggultetrol (**61**) reveals that the target molecule can be synthesized by making use of two different approaches. In the first approach

guggultetrol (**61**) could be visualized to be prepared from the α, β-unsaturated ester **82** which in turn can be obtained from the epoxy alcohol **77**, readily accessible from the

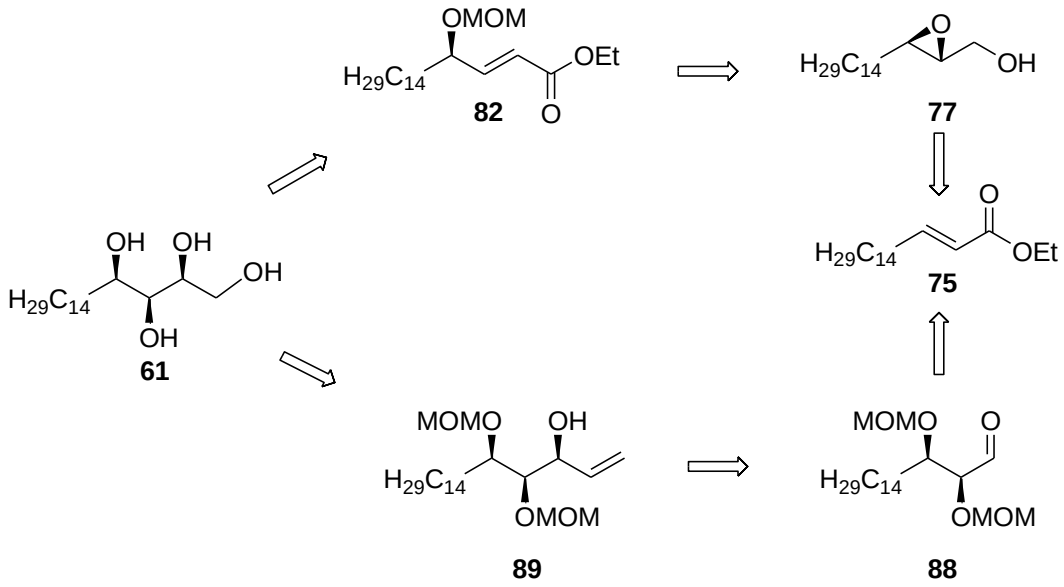


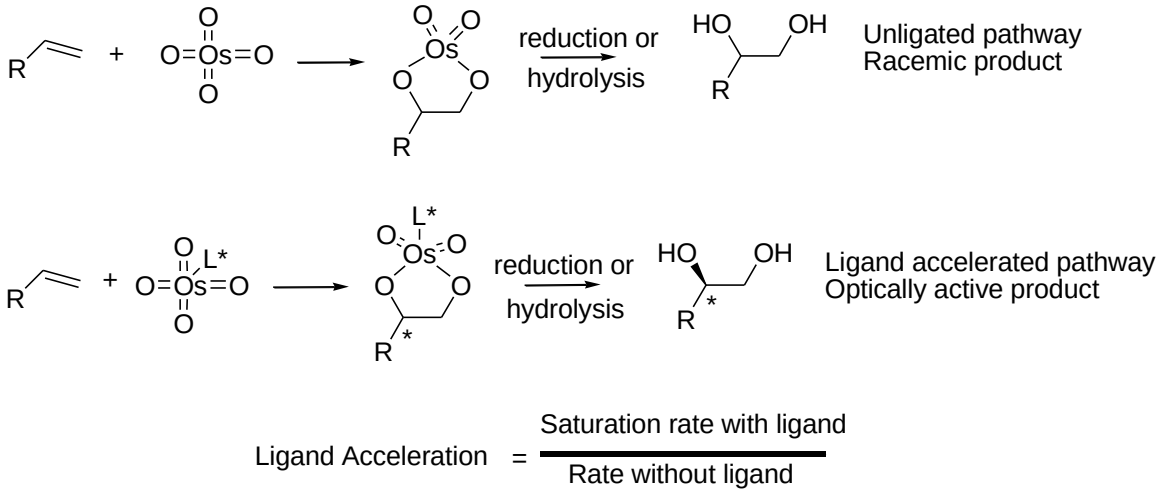
Fig. 13: Retrosynthetic analysis of guggultetrol (61)

α, β-unsaturated ester **75** by employing Sharpless asymmetric epoxidation.[48] In a similar manner, the key intermediate **89** can be prepared from aldehyde **88** by vinyl Grignard addition. This, in turn, can be obtained from the α, β-unsaturated ester **75** by utilizing Sharpless asymmetric dihydroxylation protocol.[49] Since this section utilizes two key reactions namely, Sharpless asymmetric epoxidation and dihydroxylation for introducing stereogenicity into the prochiral molecule, a brief account of Sharpless asymmetric dihydroxylation of olefins is described (a brief account of Sharpless asymmetric epoxidation is already given in Chapter I).

3.2.4.2 Sharpless asymmetric dihydroxylation

In recent years, much attention has been focused on the catalytic asymmetric synthesis. It often has significant economic advantages over stoichiometric asymmetric synthesis for

industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[50] 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 inactivated olefins.[51]



Scheme 16: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless *et al.*[51] demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ) (**Scheme 16**).[52] To improve the enantiomeric excess of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions **(Fig. 14)**. 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

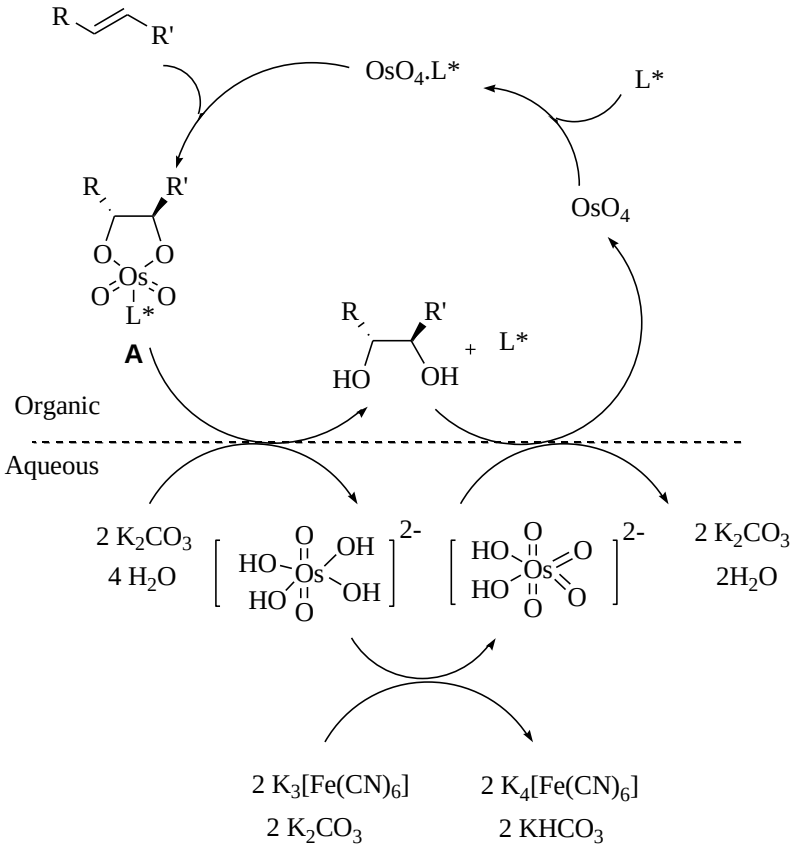


Fig. 14: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant

recycled into the catalytic cycle. Further improvement in the AD was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species **A**, thus facilitating the dihydroxylation smoothly. Addition of methyl sulfonamide also allowed carrying out the reactions of 1,2-di- tri- and 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 **92** or DHQD **93** ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselective diols **(Fig. 15)**. [53]

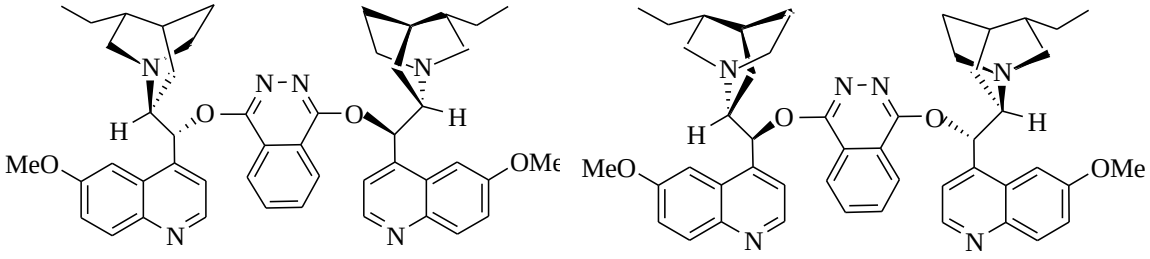


Fig. 15: Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[54] Sharpless *et al.*[51] have shown that the facial selectivity for both ligands **92** and **93** is different, based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model **(Fig. 16)** 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.

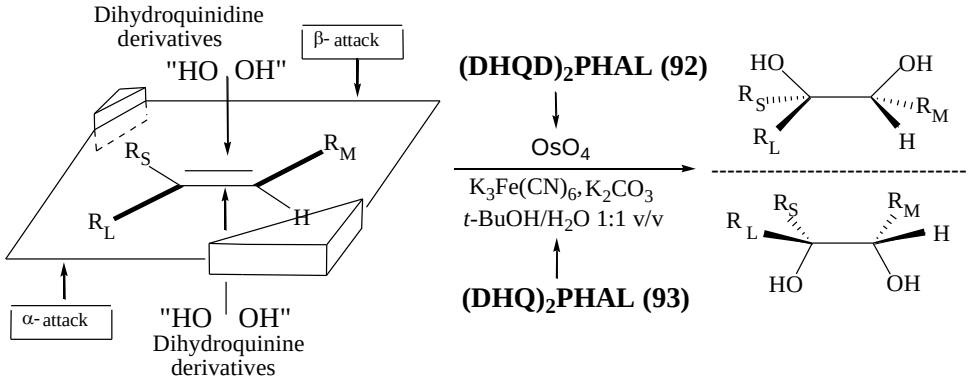


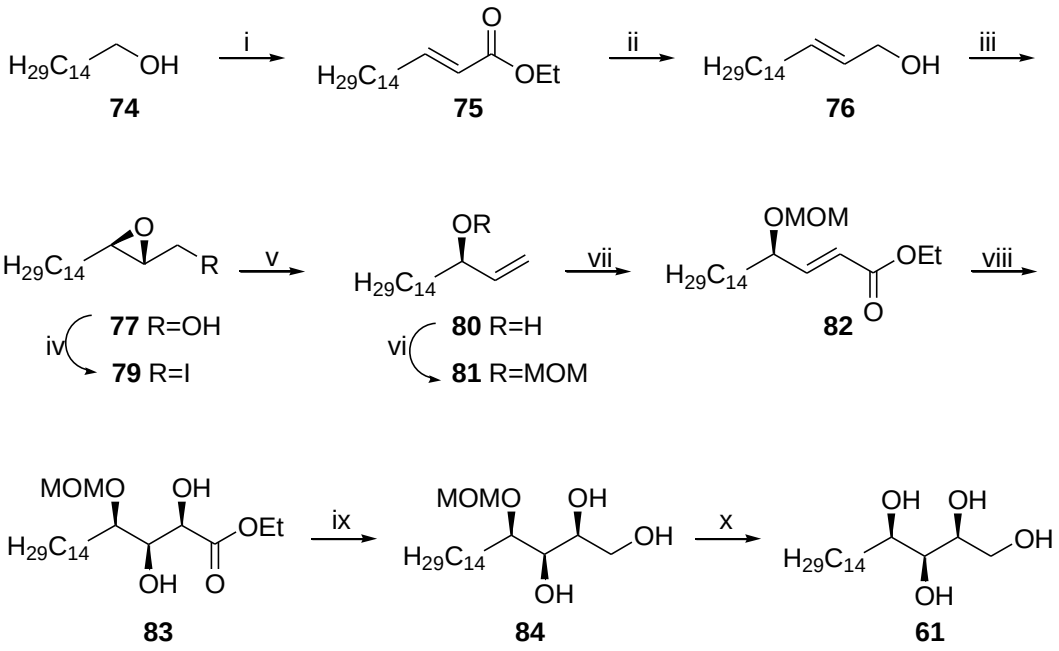
Fig. 16: Enantioselectivity mnemonic scheme

3.2.5 Results and Discussion

The synthesis of guggultetrol (**61**) has been achieved in two routes namely Sharpless epoxidation and dihydroxylation approaches.

Route 1: Sharpless epoxidation approach

A short and effective procedure for the synthesis of guggultetrol (**61**) in high enantiomeric purity from readily available starting materials using Sharpless asymmetric epoxidation[48] is shown in **Scheme 17**.



Scheme 17: (i) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 25 °C, 1 h; (b) $PPh_3{=}CHCO_2Et$, benzene, reflux, 12 h, 90%; (ii) DIBALH, CH_2Cl_2, -78 °C, 2 h, 96%; (iii) (-)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 °C, 24 h, 89%; (iv) I_2, PPh_3, imidazole, ether/acetonitrile (3:1), 0 °C, 1 h, 83%; (v) Zn, NaI, MeOH, reflux, 6 h, 80%; (vi) MOMCl, DIPEA, CH_2Cl_2, 0 °C to 25 °C, 12 h, 91%; (vii) (a) OsO_4, 50% aq. NMO, acetone:H_2O (9:1), 25 °C, 12 h; (b) $NaIO_4$, CH_2Cl_2, 25 °C, 10 min; (c) $PPh_3{=}CHCO_2Et$, benzene, 50 °C, 1 h, 90%; (viii) $(DHQD)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/ H_2O (1:1), $K_2OsO_4.H_2O$ (0.2 mol %), 0 °C, 5 h, 86%; (ix) $LiAlH_4$, THF, 0 °C to 25 °C, 5 h, 86%; (x) con. HCl, MeOH, 25 °C, 4 h, 78%.

Accordingly, the synthesis of guggultetrol, **61** was undertaken starting from 1-pentadecanol **74**. The oxidation of alcohol **74** under Swern conditions,[55] followed by

Wittig olefination of the resulting aldehyde gave (*E*)-α,β-unsaturated ester **75** in 90% yield. Two triplet of doublets integrating for one proton each in the ^{1}H NMR spectrum of **75** at δ 5.79 (td, *J* = 1.6, 15.7 Hz, 1H) and 6.95 (td, *J* = 6.9, 13.8 Hz, 1H) accounted for olefinic protons in **75** which was further supported by the typical carbon signals at δ 121.38 and 149.35 in its ^{13}C NMR spectrum (**Fig. 17**).

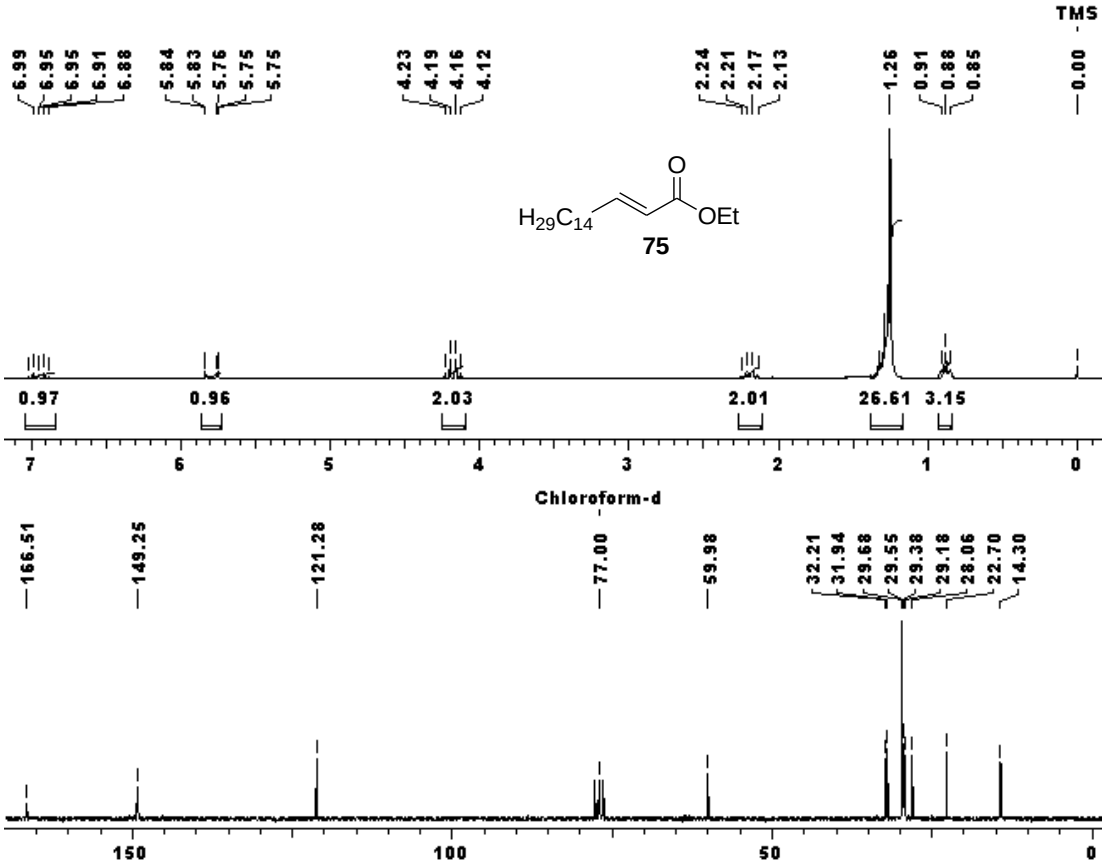


Fig. 17: ^{1}H and ^{13}C NMR spectra of ester 75

The unsaturated ester **75** was then reduced using DIBALH in CH_2Cl_2 to give the allyl alcohol **76** in 96% yield. The formation of the allyl alcohol **76** was confirmed by the appearance of a typical mutiplet at δ 4.06 which correspond to the methylene protons of the carbon attached to oxygen atom (-C**H**$_2$OH) in the ^{1}H NMR spectrum which was

further confirmed by the corresponding carbon signal appearing at δ 63.50 in its ^{13}C NMR spectrum (**Fig. 18**).

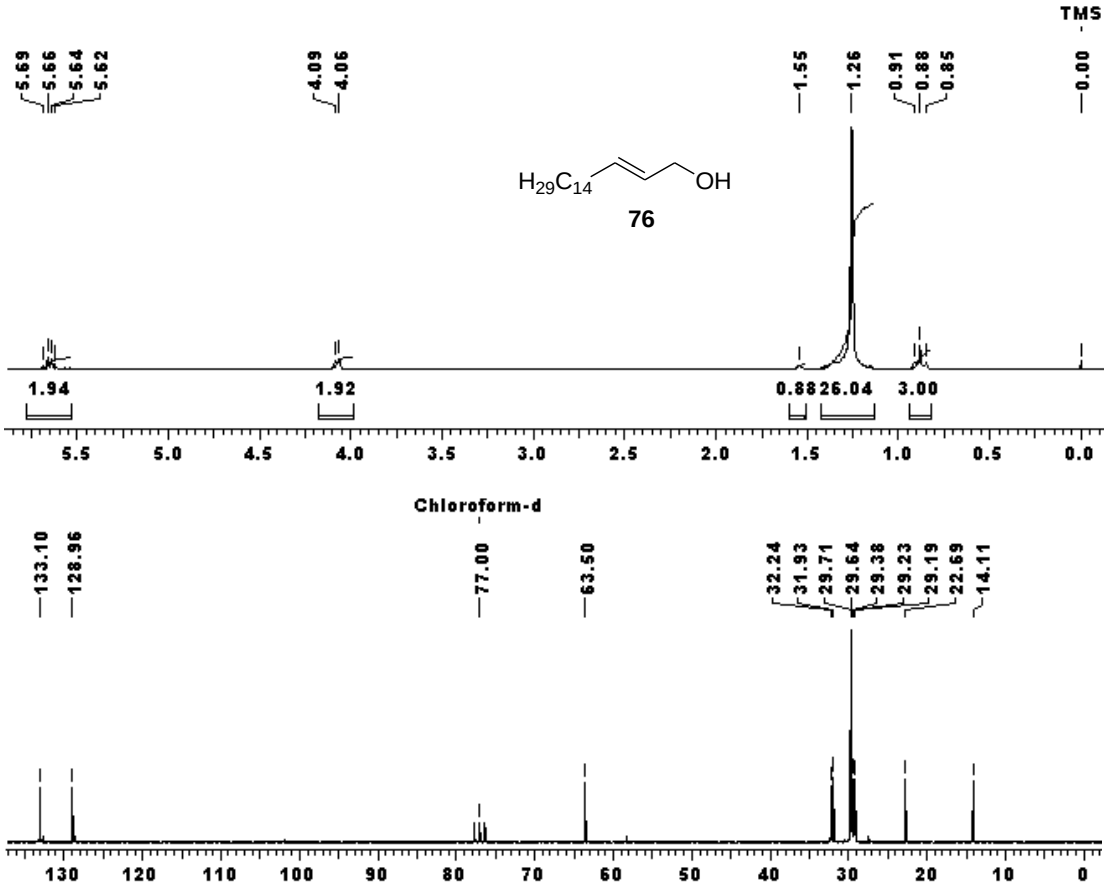


Fig. 18: ^{1}H and ^{13}C NMR spectra of alcohol 76

The allyl alcohol **76** thus obtained after the reduction was subjected to epoxidation using Sharpless' asymmetric epoxidation conditions,[48] with (-)-diethyl tartrate [(-)-DET], $Ti(O^{i}Pr)_4$ and anhydrous TBHP as an oxidant to give the epoxy alcohol **77** in 89% yield and 98% ee; $[\alpha]_D^{25}$ = +10 (*c* 0.6, $CHCl_3$). The optical purity of the epoxy alcohol **77** was determined by the ^{1}H NMR analysis of the corresponding Mosher's ester **78** (**Fig. 20**). The ^{1}H NMR spectrum of **77** displayed a multiplet δ 2.90 integrating for two protons which correspond to the methine protons of the epoxide while the corresponding carbon signals have appeared at δ 55.94 and 58.55 in its ^{13}C NMR spectrum (**Fig. 19**).

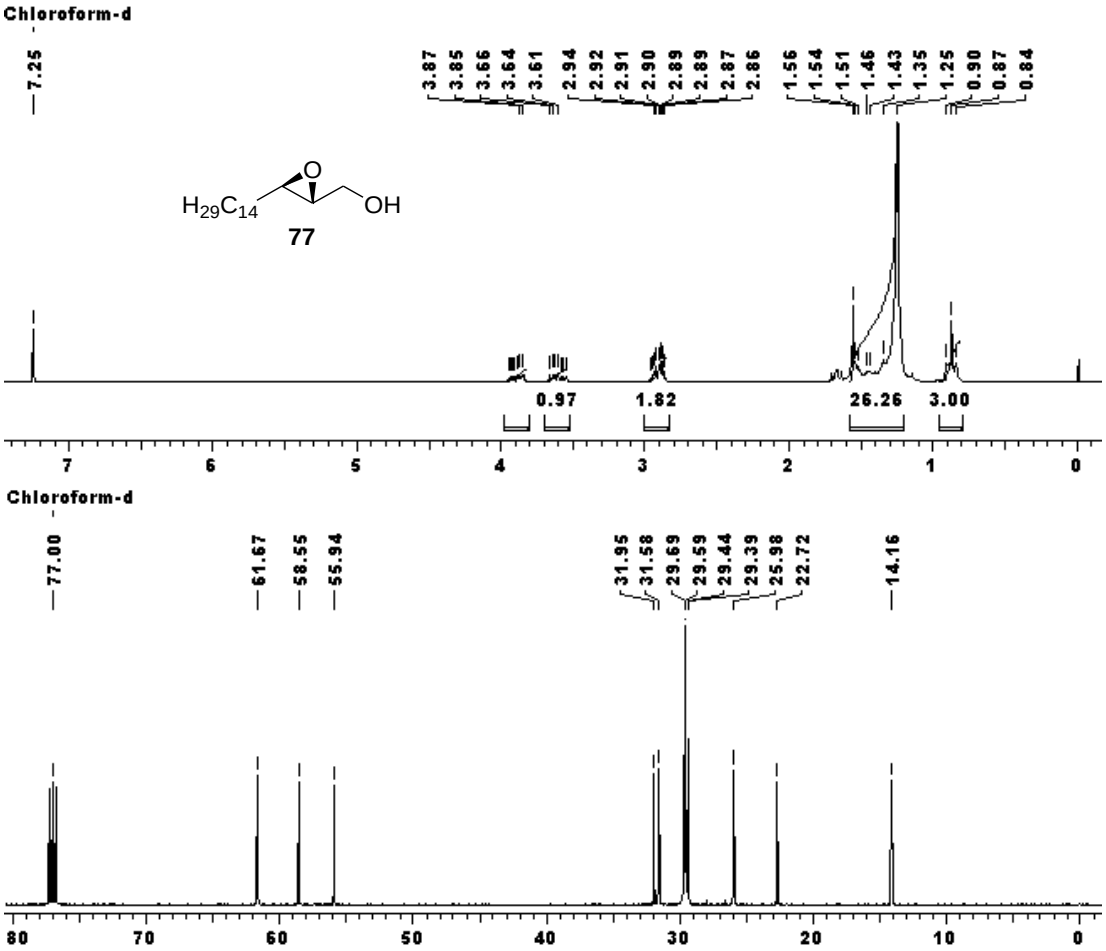


Fig. 19: ^{1}H and ^{13}C NMR spectra of epoxy alcohol 77

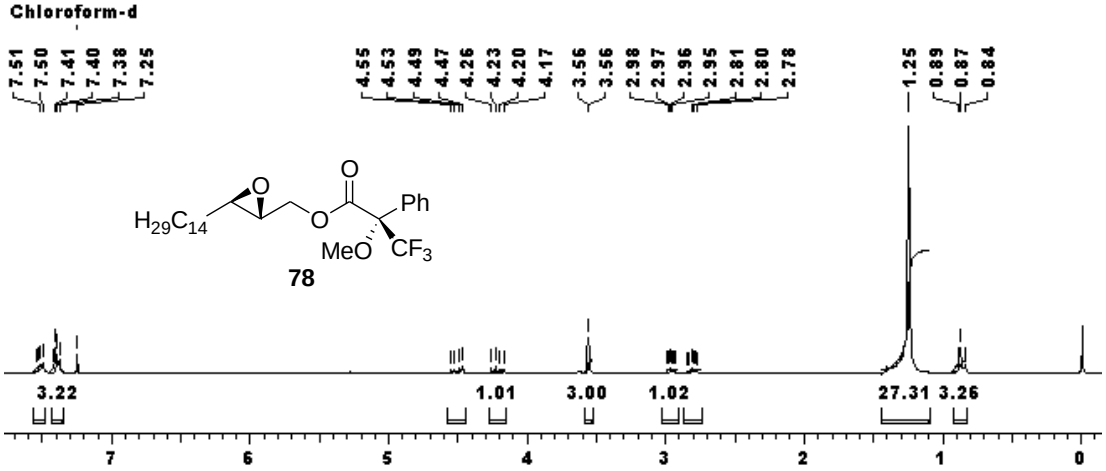


Fig. 20: ^{1}H NMR spectrum of Mosher's ester 78

The treatment of the epoxy alcohol **77** with I_2 and PPh_3[56] gave epoxy iodide **79** in 83% yield whose formation was confirmed by the analysis of its ^1H NMR spectrum which gave the spectral pattern as δ 2.73-2.79 (m, 1H), 2.93-3.03 (m, 2H) and 3.20-3.31 (m, 1H) corresponding to the methine protons of epoxide and methylene protons of the carbon attached to iodine atom respectively. In the ^{13}C NMR spectrum, methylene carbon attached to iodine gave a signal at δ 4.89 (**Fig. 21**).

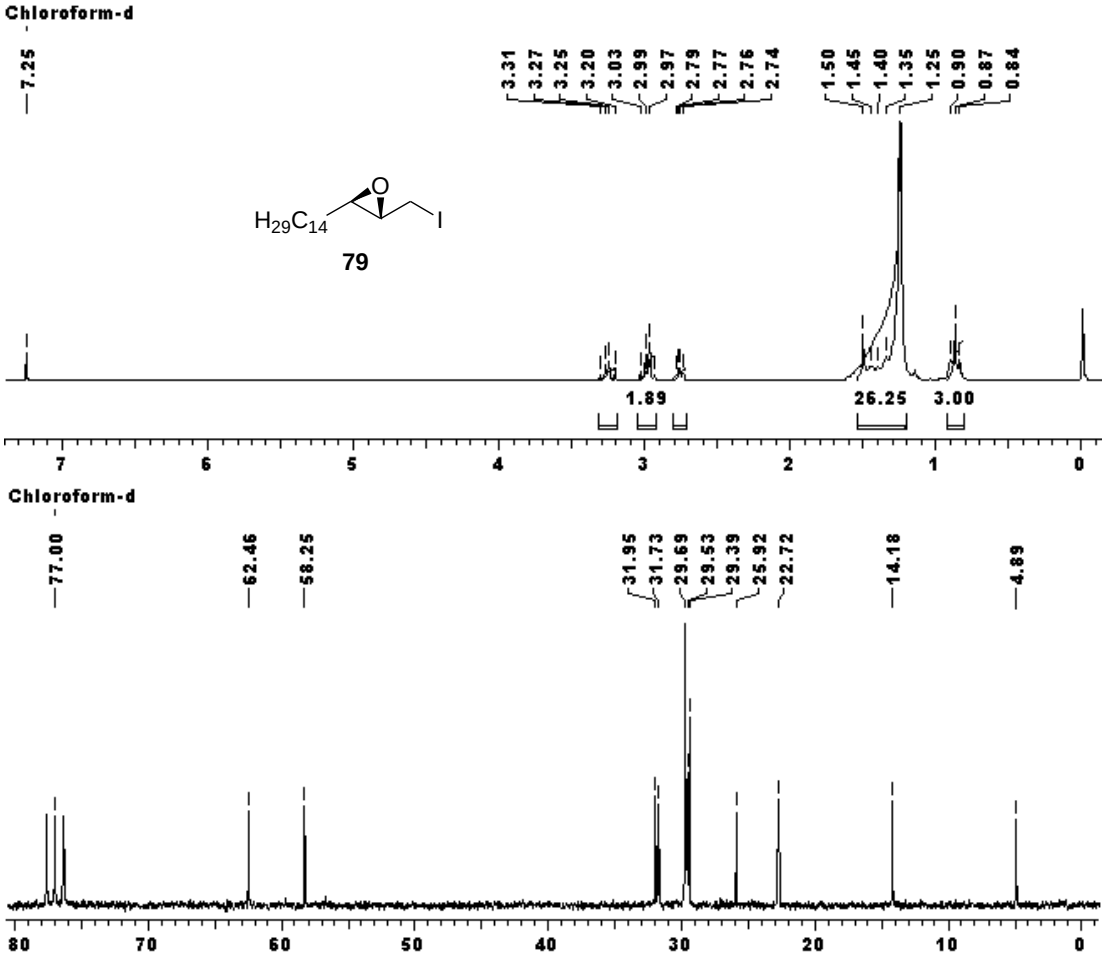


Fig. 21: ^1H and ^{13}C NMR spectra of epoxy iodide 79

The epoxy iodide **79** thus obtained was then converted to the allylic alcohol **80** in 80% yield by refluxing **79** with NaI and Zn[57] in MeOH. The formation of allylic alcohol **80** was confirmed by the appearance of olefinic proton signals at δ 5.07-5.22 (m, 2H) and

5.81-5.89 (m, 1H) whereas the methine proton of the carbon attached to hydroxyl group has appeared as a multiplet at δ 4.07 in its ^{1}H NMR spectrum. The above observation was further supported by ^{13}C NMR spectral analysis wherein the olefinic carbons have shown typical peaks at δ 114.38 and 141.44 (**Fig. 22**). The IR spectrum of **80** displayed strong absorption band above 3000 cm^{-1} indicating the presence of -OH group.

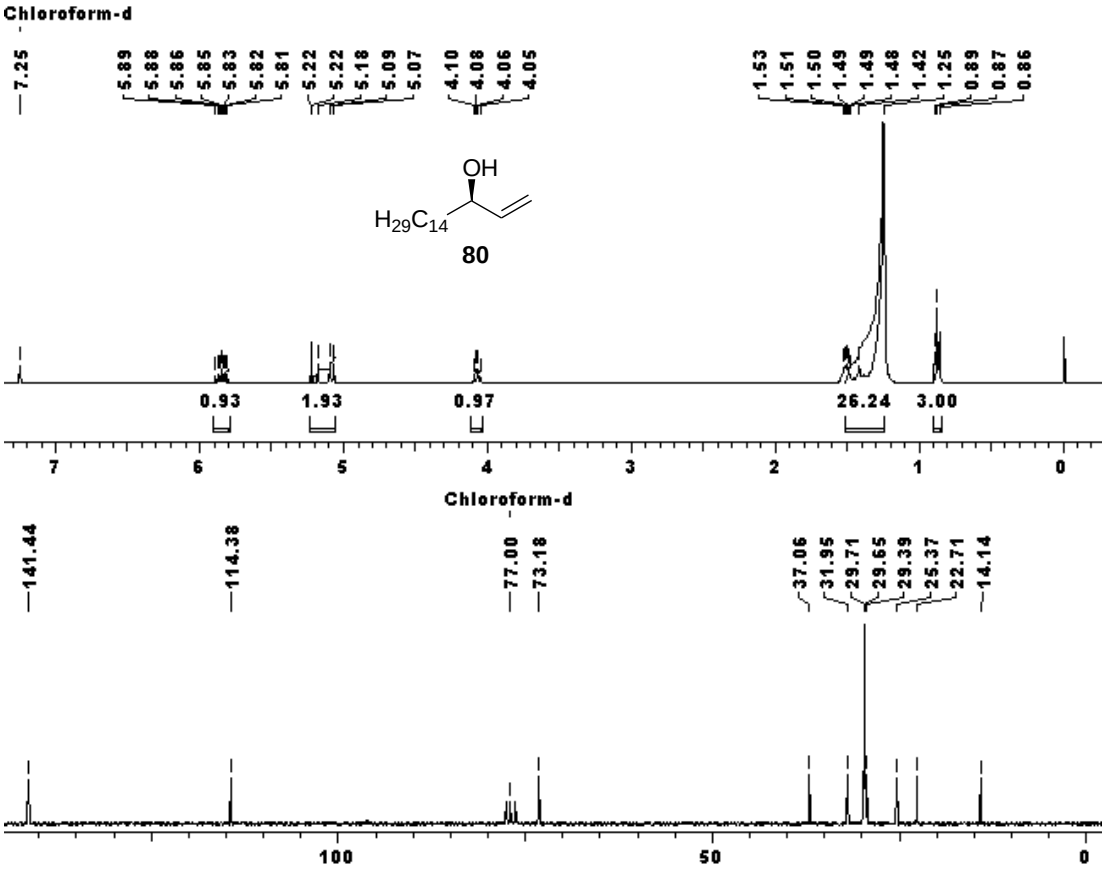


Fig. 22: ^{1}H and ^{13}C NMR spectra of allylic alcohol 80

The allylic alcohol **80** was then protected as its MOM ether **81** in 91% yield by treating it with MOMCl in presence of diisopropylethylamine. Two doublets at δ 4.52 (d, J = 6.74 Hz, 1H) and 4.69 (d, J = 6.74 Hz, 1H) were attributed to the methylene protons of the MOM group while its methyl protons appeared as a singlet at δ 3.36 ppm in its ^{1}H NMR spectrum. The formation of MOM ether **81** was further confirmed by the appearance of

signals at δ 54.96 and 93.33 corresponding to the methyl and methylene carbons respectively of the MOM group in its ^{13}C NMR spectrum (**Fig. 23**).

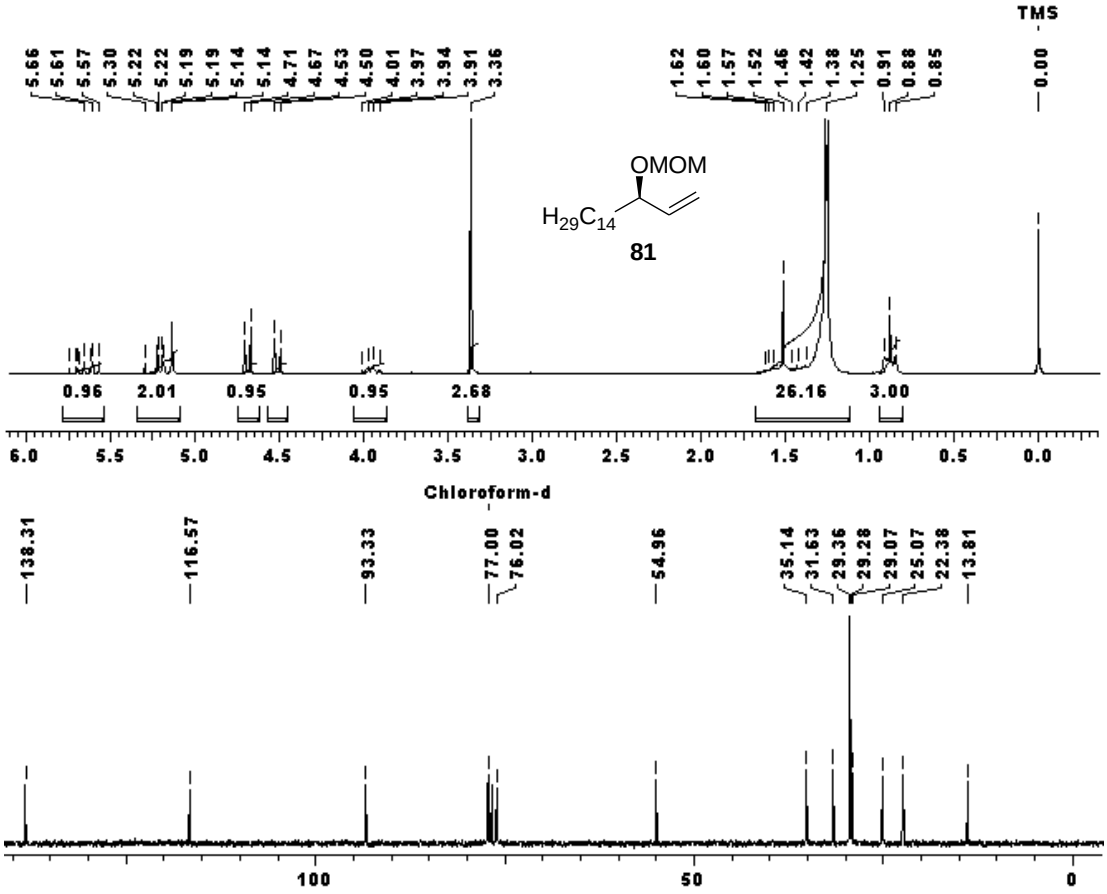


Fig. 23: ^{1}H and ^{13}C NMR spectra of MOM ether 81

The oxidative degradation of the MOM protected allylic alcohol **81** was carried out as indicated in the following sequence of reactions: (i) the olefin function in **81** was initially dihydroxylated using OsO_4 and NMO; (ii) the diol so formed was subsequently cleaved on treatment with $NaIO_4$ which gave the corresponding aldehyde; (iii) the crude aldehyde, being labile, was immediately subjected to Wittig olefination to provide the α, β-unsaturated ester **82** in 90 % yield over three steps. The ^{1}H and ^{13}C NMR spectra confirmed the formation of unsaturated ester **82**. The olefinic protons of **82** resonating as doublet of doublets at δ 5.95 and 6.78 in its ^{1}H NMR spectrum (**Fig. 24**) and the carbonyl

of the ester appearing at δ 166.10 in its ^{13}C NMR spectrum have confirmed the formation of α, β-unsaturated ester **82**. The IR spectrum of **82** exhibited a characteristic α, β-unsaturated ester carbonyl absorption band at 1712 cm^{-1}.

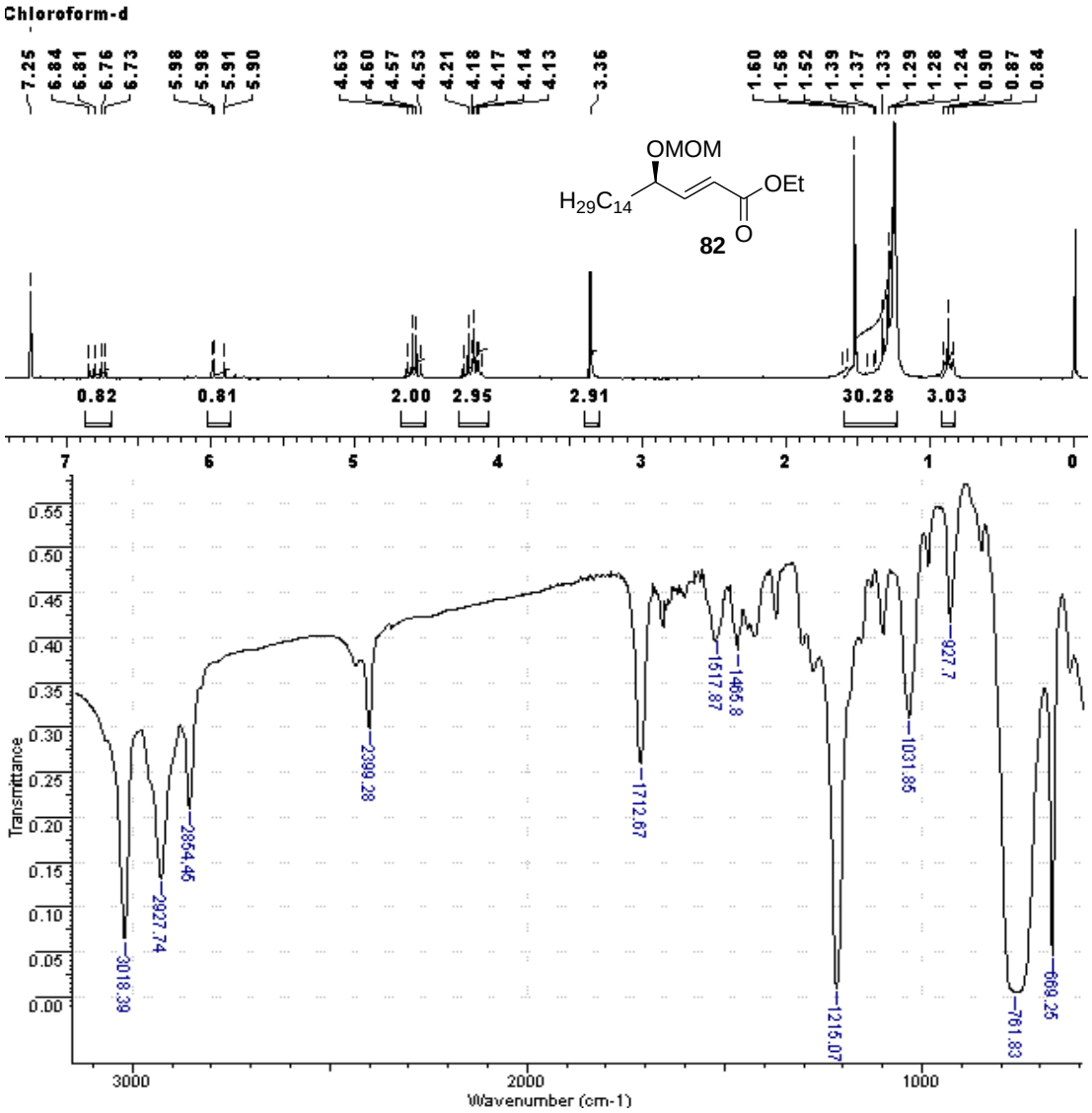


Fig. 24: ^{1}H and IR spectra of unsaturated ester 82

The dihydroxyltion of the α, β-unsaturated ester **82** was carried out under Sharpless asymmetric dihydroxylation (SAD) conditions,[49] using catalytic amount of OsO_4 and $K_3Fe(CN)_6$ as co-oxidant in the presence of $(DHQ)_2$-PHAL ligand to give the dihydroxylated ester **83** in 86% yield. The ^{1}H NMR spectrum of **83** confirmed the

formation of diol **83** as it exhibited peak patterns such as δ 3.42 (s, 3H), 3.55-3.68 (m, 2H), 3.75-3.82 (m, 1H), 4.13-4.18 (m, 1H), 4.29 (q, *J* = 7.20 Hz, 2H) and 4.62-4.76 (m, 2H). The carbonyl peak of diol ester **83** showed a shift from δ 166.10 (in the α, β-unsaturated ester **82**) to 172.99 in its ^{13}C NMR spectrum, confirming the saturation of double bond (**Fig. 25**).

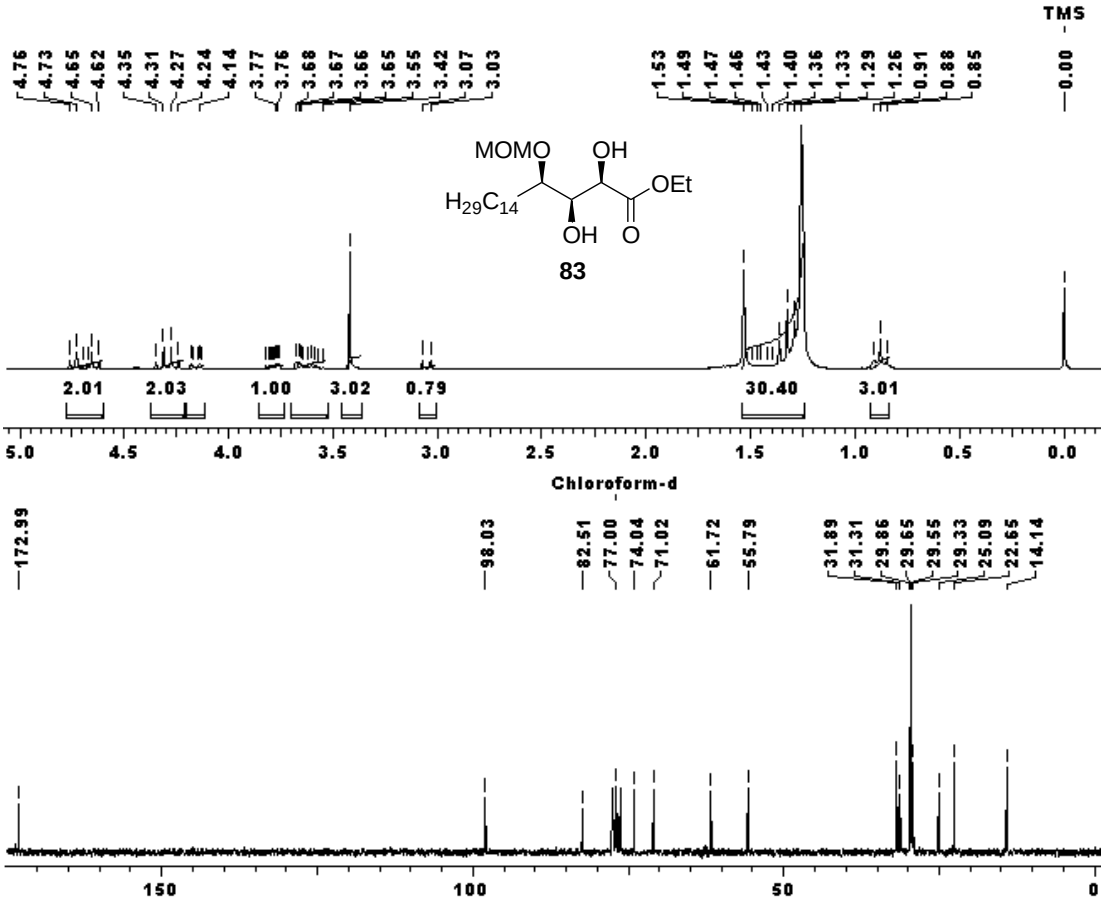


Fig. 25: ^{1}H and ^{13}C NMR spectra of diol ester 83

The reduction of the ester function in ester **83** was achieved by its treatment with $LiAlH_4$ in THF at room temperature to afford the triol **84** in 86% yield. Methyl protons of the MOM-group resonated at δ 3.41 while two multiplets at δ 3.67 (integrating for five protons) and at δ 4.68 (integrating for two protons) respectively accounted for rest of the protons of the carbons attached to oxygen atom in its ^{1}H NMR spectrum. The reduction

of the ester moiety was further ascertained by the disappearance of carbonyl peak in its ^{13}C NMR spectrum (**Fig. 26**).

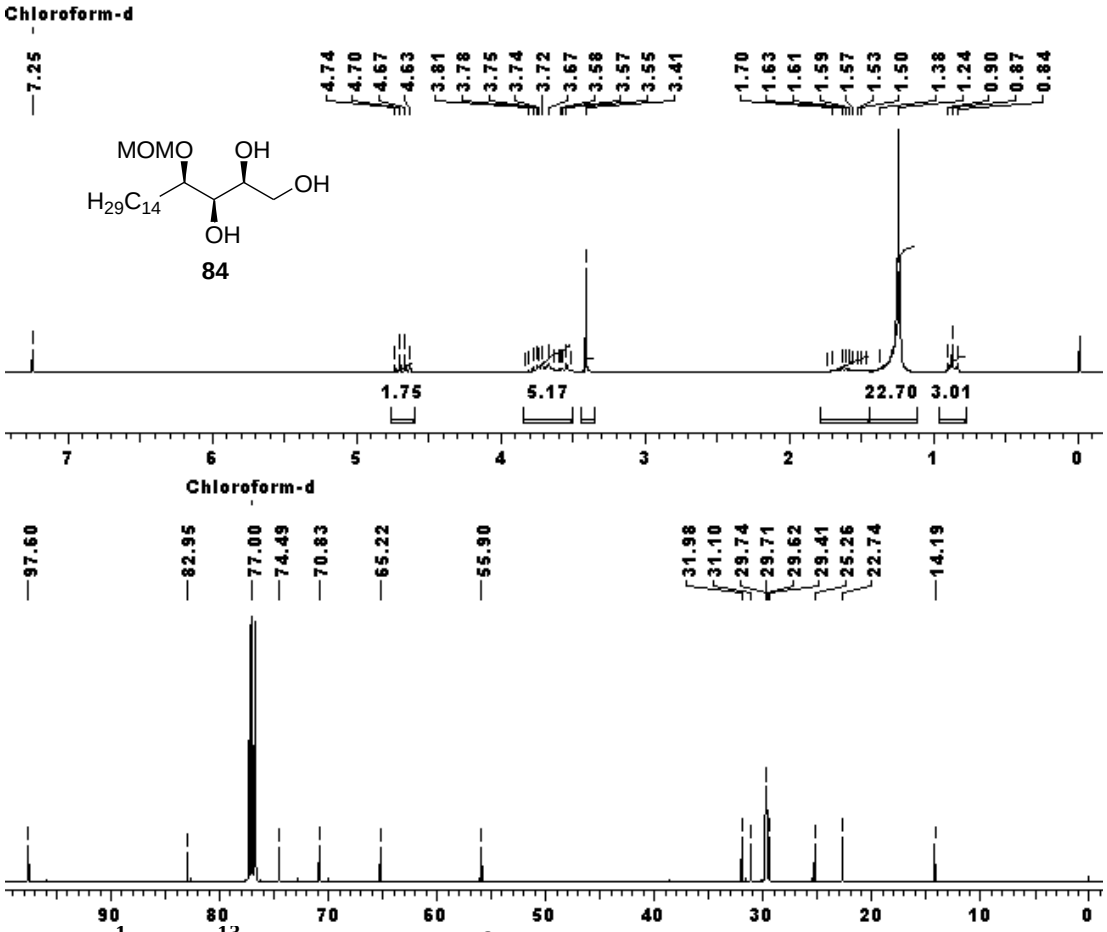


Fig. 26: ^{1}H and ^{13}C NMR spectra of triol 84

Eventually, deprotection of the MOM group with con. HCl in methanol furnished guggultetrol, **61** in 78% yield, $[\alpha]_D$ = +12 (*c* 0.5, EtOH); {lit.[45,46] $[\alpha]_D$ = +11.4 (*c* 0.34, EtOH)}. The ^{1}H NMR spectrum of **61** displayed signals typical of its structural pattern such as δ 0.88 (t, *J* = 6.58 Hz, 3H), 1.28-1.59 (s, 26H), 3.42 (dd, *J* = 3.78, 7.53 Hz, 1H) and 3.50-3.81 (m, 4H) (**Fig. 27**) whereas its ^{13}C NMR spectrum showed peaks at δ 64.4, 73.5, 74.1 and 74.3 for the carbons attached to oxygen atom.

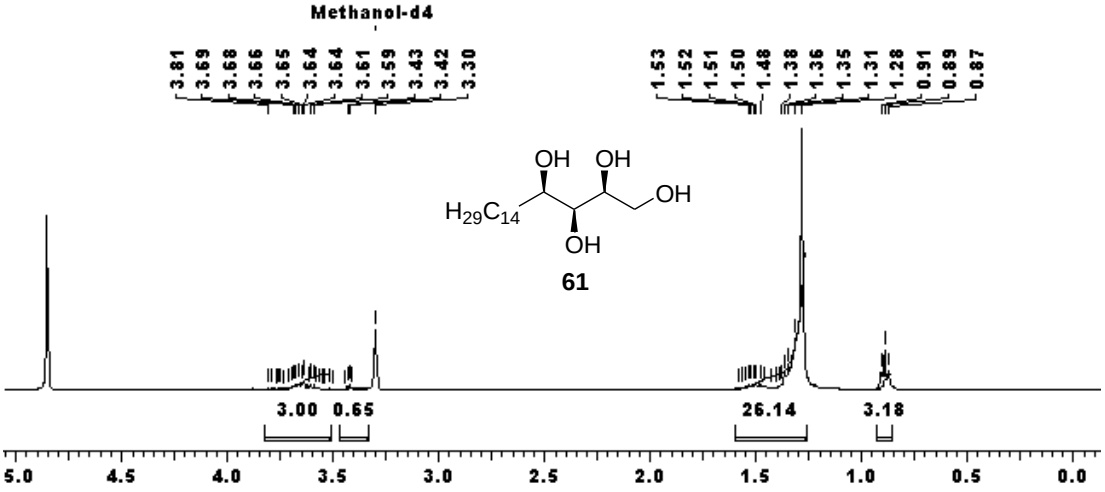
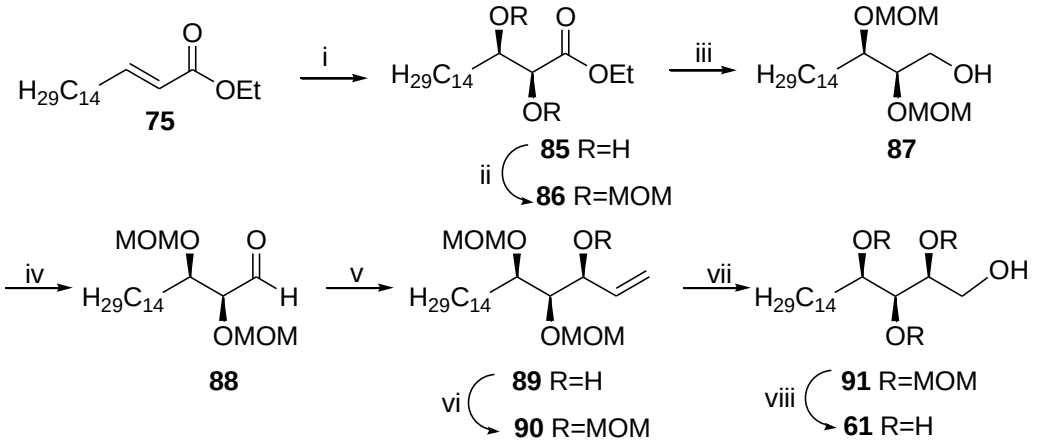


Fig. 27: ^{1}H NMR spectrum of guggultetrol, 61

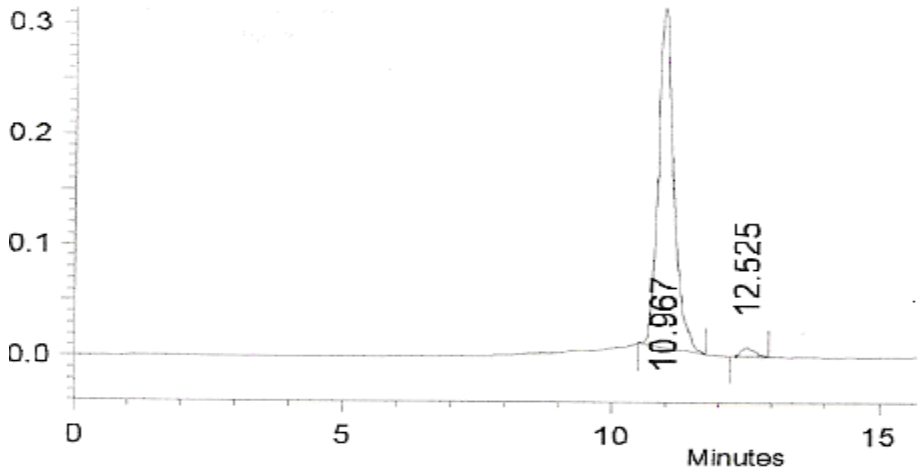
Route 2: Sharpless dihydroxylation approach

The synthesis of guggultetrol, **61** using Sharpless asymmetric dihydroxylation[49] involves less number of steps thus increases the overall yield of the synthesis as compared to Sharpless epoxidation approach (**Scheme 18**).



Scheme 18: (i) $(DHQD)_2$-PHAL, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), $K_2OsO_4.H_2O$ (0.2 mol %), 0 °C, 24 h, 94%; (ii) MOMCl, DIPEA, CH_2Cl_2, 0 °C to 25 °C , 12 h, 94%; (iii) $LiAlH_4$, THF, 0 °C to 25 °C, 12 h, 95%; (iv) IBX, DMSO, 25 °C, 3 h; (v) CH_2=CHMgBr, $MgBr_2.Et_2O$, CH_2Cl_2, -78 °C, 10 h, 87%, d.r. >15:1; (vi) MOMCl, DIPEA, CH_2Cl_2, 0 °C to 25 °C, 12 h, 92%; (vii) (a) OsO_4, 50% aq. NMO, acetone/H_2O (9:1), 25 °C, 12 h; (b) $NaIO_4$, CH_2Cl_2, 25 °C, 10 min; (c) $NaBH_4$, MeOH, 0 °C to 25 °C, 30 min, 88%; (viii) con. HCl, MeOH, 25 °C, 2 h, 79%.

The α, β-unsaturated ester **75** was subjected to asymmetric dihydroxylation (ADH) with catalytic amount of OsO_4 and $K_3Fe(CN)_6$ as co-oxidant in the presence of $(DHQD)_2$-PHAL ligand under Sharpless asymmetric dihydroxylation (SAD) conditions,[49] to give the diol (2*S*,3*R*)-**85** in 94% yield and 98% ee; {$[\alpha]_D$ = +9.9 (*c* 3, $CHCl_3$); lit.[58] $[\alpha]_D$ = -10.13 (*c* 1, $CHCl_3$) for its antipode}. The enantiomeric excess of the diol **85** was determined by chiral HPLC analysis using Chiralcel OJ column (250× 4.6 nm), eluting with petroleum ether/*i*-PrOH (97.5:2.5), 0.5 mL/min, 220 nm (**Fig. 28**).



Peak No.	Retention Time	Area (µV-sec)	Area (%)
1	10.967	6311786	98.988
2	12.525	64513	1.012

Fig. 28: HPLC chromatogram of diol 85

The ^1H and ^{13}C NMR analysis confirmed the formation of diol **85**. The methine protons of the carbons attached to hydroxyl group resonated at δ 3.84 as a multiplet and at δ 4.04 as a doublet of doublet in its ^1H NMR spectrum. Its ^{13}C NMR spectrum showed the corresponding methine carbon peaks at δ 72.56 and 73.21 while the carbonyl carbon of the ester resonated at δ 173.65 (**Fig. 29**).

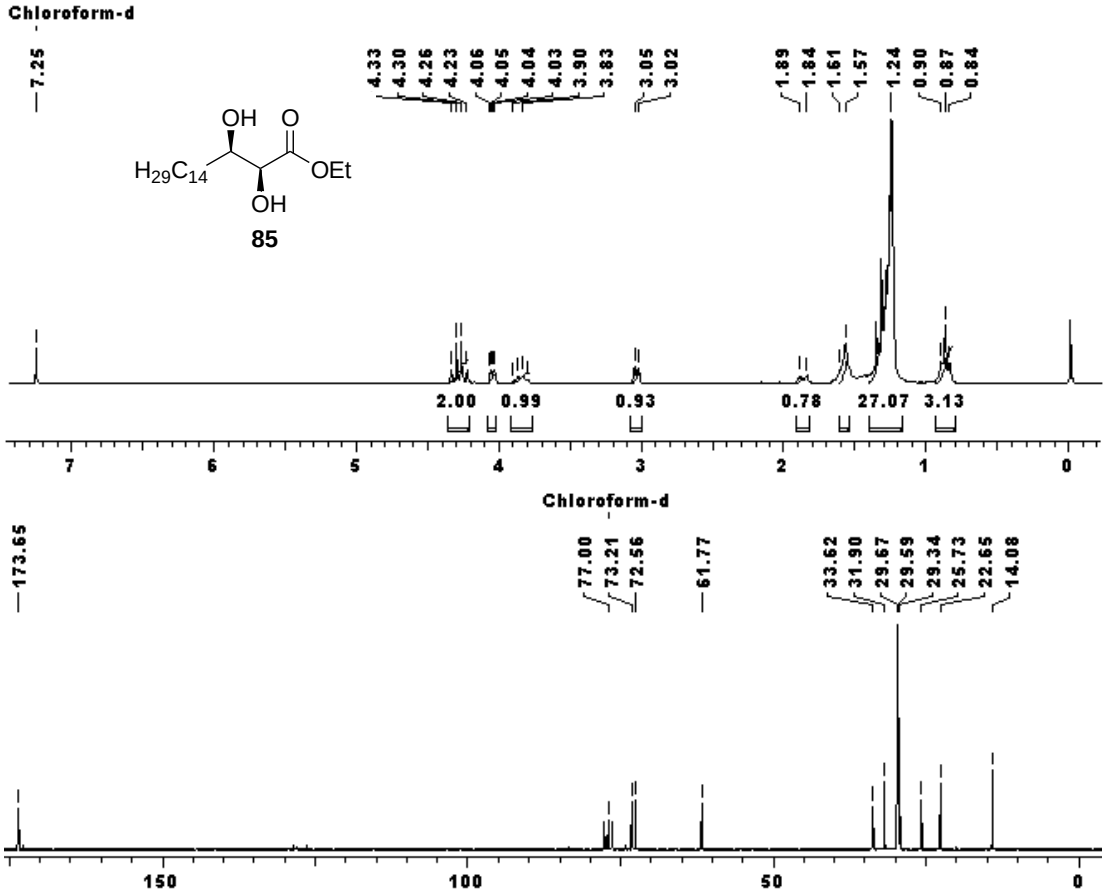


Fig. 29: ^{1}H and ^{13}C NMR spectra of diol 85

In order to have a better *syn* selectivity in the vinylation step at a later stage, it was thought worthwhile to protect diol **85** as its MOM ether. Thus, the diol **85** was treated with MOMCl in the presence of diisopropylethylamine to afford the diprotected dihydroxy ester **86** in 94% yield. Two singlets at δ 3.35 and 3.41 integrating for three protons each accounted for the methyl protons of the MOM groups whereas its methylene protons resonated as mutiplets at δ 4.66 and 4.75 in its ^{1}H NMR spectrum. Methyl carbons of the MOM group gave signals at δ 55.70 and 56.14 and its methylene carbons showed peaks at δ 96.36 and 96.40 in its ^{13}C NMR spectrum (**Fig. 30**). The IR spectrum of **86** showed a characteristic ester carbonyl absorption band at 1747 cm^{-1}.

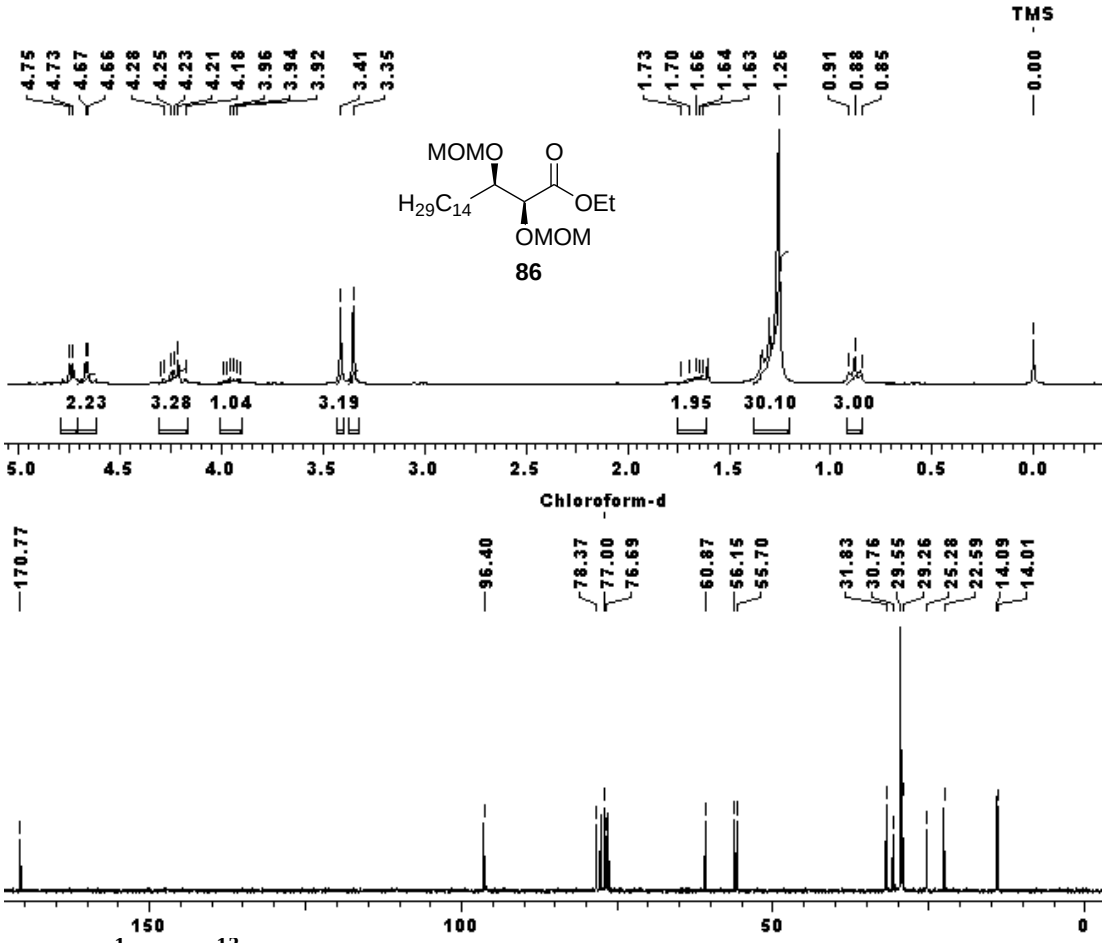


Fig. 30: ^{1}H and ^{13}C NMR spectra of MOM ether 86

Reduction of ester **86** with $LiAlH_4$ in THF at 0 °C furnished the alcohol **87** in 95% yield whose formation was confirmed by ^{1}H and ^{13}C NMR analysis (**Fig. 31**).

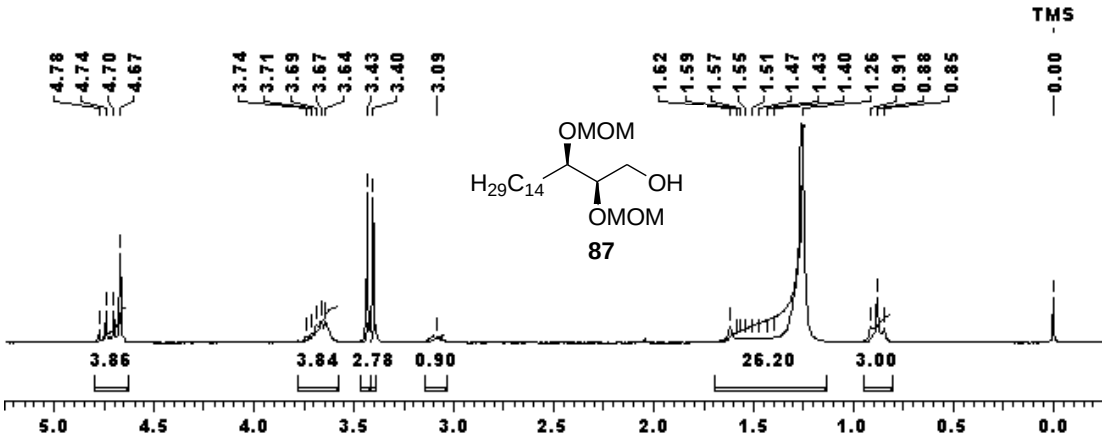


Fig. 31: ^{1}H NMR spectrum of alcohol 87

The alcohol **87** was then oxidized using IBX in DMSO at room temperature to give the corresponding aldehyde **88**, which was directly used in the next reaction without any further purification. The formation of the aldehyde was confirmed by ^{1}H NMR analysis which displayed the aldehydic proton signal at δ 9.74 ppm. When the aldehyde **88** was subjected to chelation controlled vinylation reaction[59] in CH_2Cl_2 at -78 °C catalyzed by $MgBr_2.Et_2O$,[60] allyl alcohol derivative **89** was obtained in 87% yield with excellent diastereoselectivity (>15:1),[61] as determined by ^{1}H and ^{13}C NMR spectral analysis. The formation of the major *syn* isomer can be explained by the extra chelation of magnesium with the MOM protecting group. The diastereomers were not separable at this stage by column chromatographic purification.

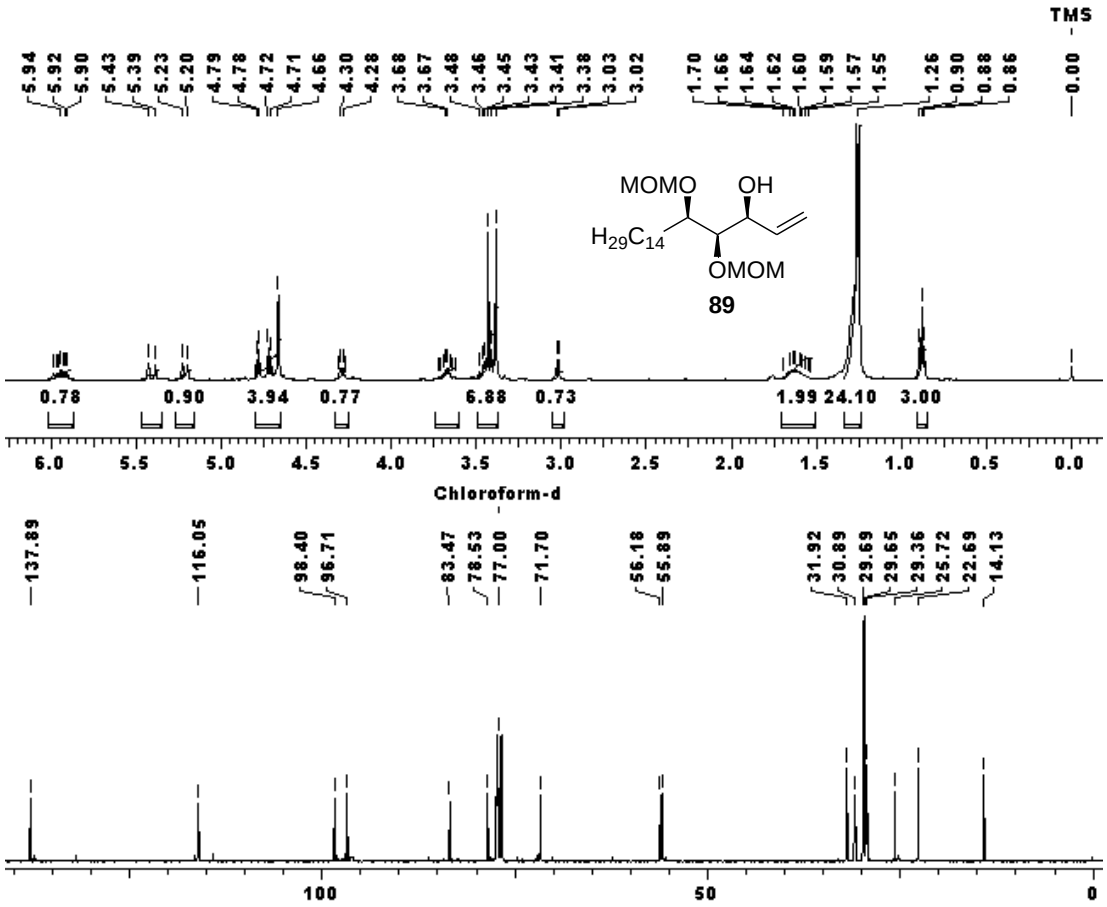


Fig. 32: ^{1}H and ^{13}C NMR spectra of allylic alcohol 89

The ^{1}H, ^{13}C NMR spectral and other analytical data were in accordance with the proposed structure of **89**. For example, the ^{1}H NMR spectrum of **89** the characteristic peaks for olefin appeared at δ 5.22 (d, *J* = 10.68 Hz, 1H), 5.41 (d, *J* = 17.38 Hz, 1H) and 5.95 (m, 1H) and it was further supported by the olefin carbon signals at δ 116.05 and 137.89 in its ^{13}C NMR spectrum (**Fig. 32**). After protection of the hydroxyl group in **89** as its MOM ether, the required *syn* isomer was easily separated by flash column chromatography. A multiplet at δ 3.41 integrating for nine protons accounted for three methyl groups of MOM ethers in the ^{1}H NMR spectrum of olefin **90** (**Fig. 33**).

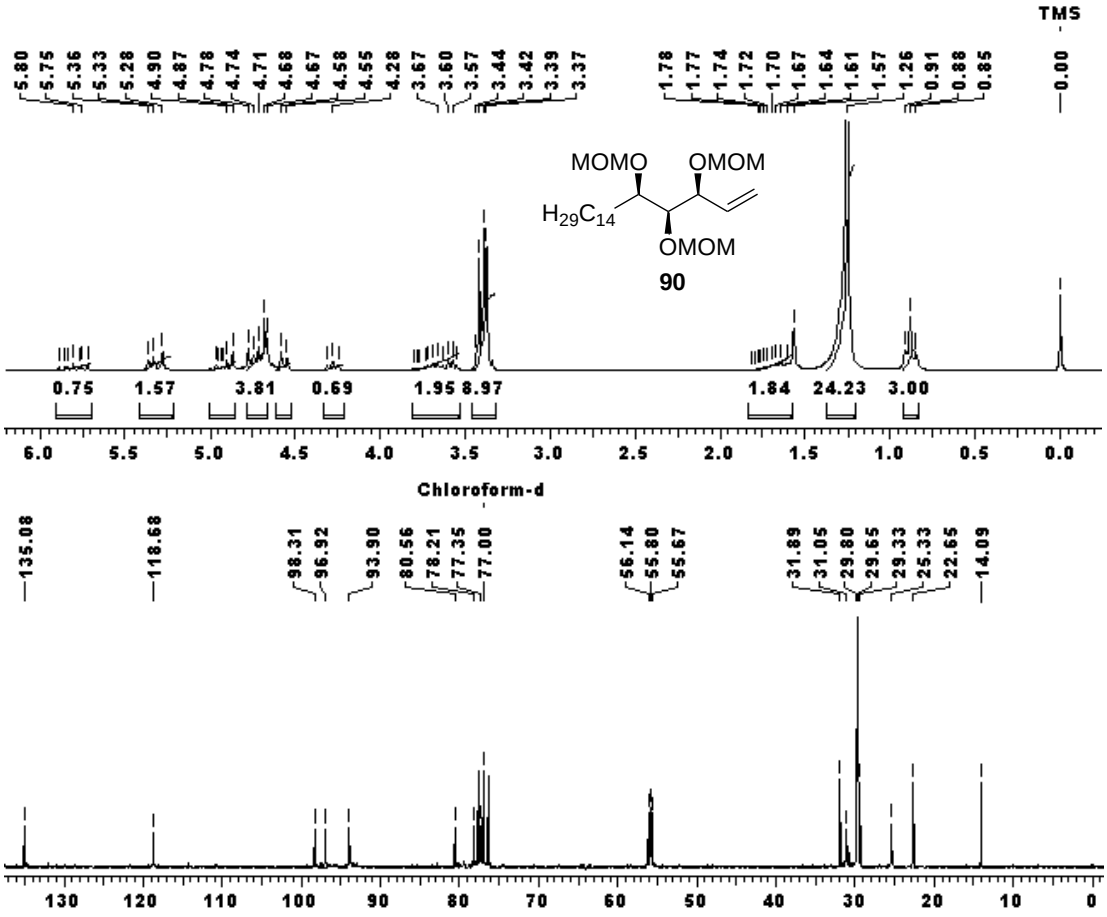


Fig. 33: ^{1}H and ^{13}C NMR spectra of olefin 90

Further, olefin **90** was oxidatively cleaved on treatment with OsO_4, NMO and $NaIO_4$ followed by reduction of the corresponding aldehyde with $NaBH_4$ in methanol gave the

alcohol **91** in 88% yield. The ^{1}H and ^{13}C NMR spectra of **91** confirmed the disappearance of olefin function and the appearance of spectral features as 3.41 (m, 9H), 3.73 (m, 5H) and 4.71 (m, 6H), in support of formation of alcohol **91** (**Fig. 34**).

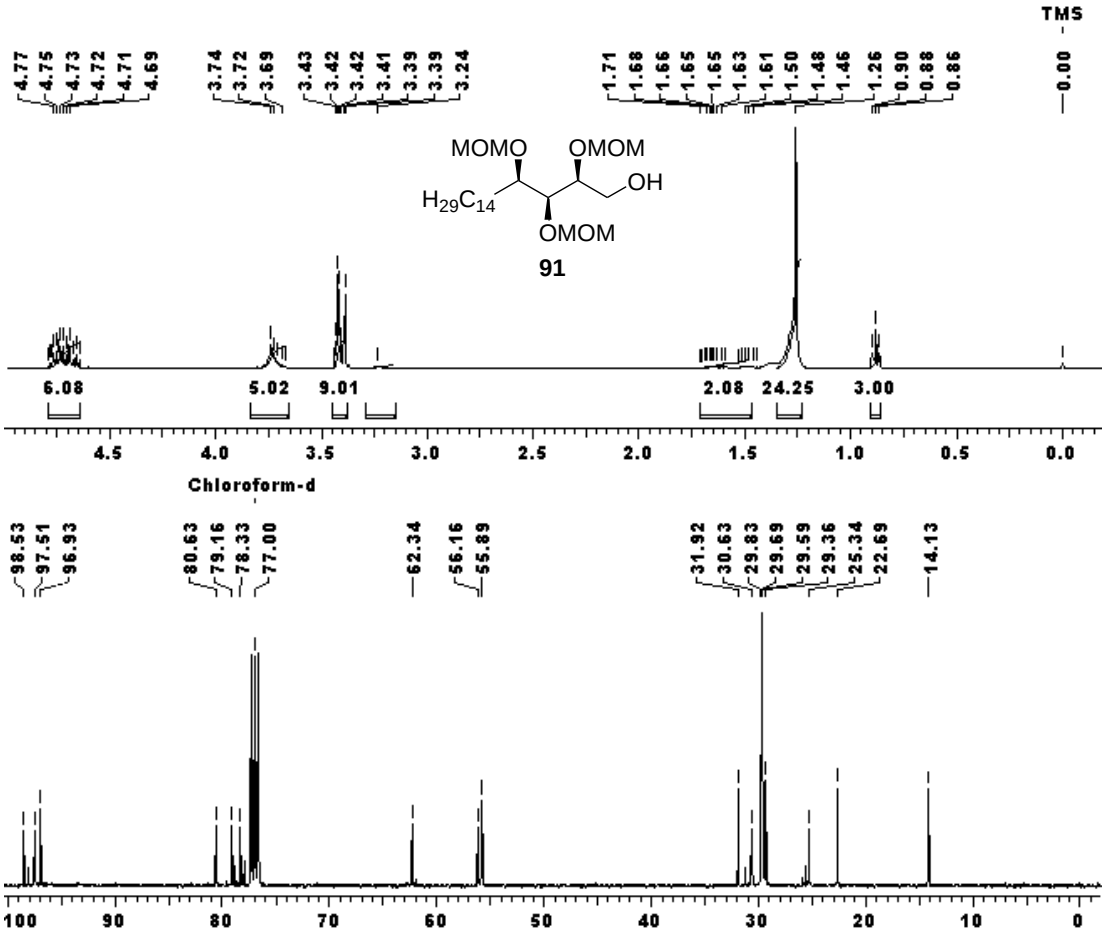


Fig. 34: ^{1}H and ^{13}C NMR spectra of alcohol 91

Eventually, the global deprotection of all the MOM groups in alcohol **91** using con. HCl in methanol afforded guggultetrol, **61** in 79% yield. The spectral data of guggultetrol, **61** were in complete agreement with the reported values.[45-47]

3.2.6 Conclusion

Enantioselective total synthesis of guggultetrol (**61**), a naturally occurring lipid possessing three contiguous stereogenic centers, has been achieved starting from the

readily available 1-pentadecanol **74** using Sharpless epoxidation (10 linear steps, overall yield 24%) and Sharpless dihydroxylation (8 linear steps, overall yield 42%) in two independent routes. Chelation-controlled vinylation reaction gave high diastereoselectivity (>15:1) in two independent routes. The present synthetic work constitutes the first catalytic approaches in the asymmetric synthesis of guggultetrol (**61**).

3.2.7 Experimental Section

(*E*)-Ethylheptadec-2-enoate (75)

To a precooled (-78 °C) solution of $(COCl)_2$ (3.63 mL, 40 mmol) in CH_2Cl_2 (50 mL) was added DMSO (5.68 mL, 80 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at -78 °C for 15 min, then alcohol **74** (4.56 g, 20 mmol) was added in CH_2Cl_2 (30 mL). The reaction mixture was stirred for 40 min at -78 °C followed by the addition of Et_3N (16.67 mL, 120 mmol). The mixture was allowed to warm to 0 °C. After 30 min, it was diluted with water and extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aldehyde, which was immediately used in the next step.

To a solution of the above crude aldehyde in benzene (60 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (7.66 g, 22 mmol) and heated under reflux for 12 h. Removal of solvent under reduced pressure provided the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give **75** (5.3 g) as a colorless oil.

Yield: 90%; **IR** ($CHCl_3$, cm^{-1}): 2924, 2853, 1724, 1655, 1465, 1367, 1309, 1264, 1178, 1045, 981; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.69 Hz, 3H), 1.26-1.33 (m, 27H), 2.13-2.24 (m, 2H), 4.18 (q, *J* = 7.08 Hz, 2H), 5.79 (td, *J* = 1.56, 15.67 Hz, 1H), 6.95 (td, *J*

= 6.95, 13.84 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.14, 14.30, 22.70, 28.06, 29.18, 29.38, 29.43,29.55, 29.68, 31.94, 32.21, 59.98, 121.28, 149.25, 166.51; **Analysis:** **$C_{19}H_{36}O_2$** requires C, 76.97; H, 12.24; found: C, 77.22; H, 12.01%.

(*E*)-Heptadec-2-en-1-ol (76)

To a solution of **75** (2.67 g, 9 mmol) in dry CH_2Cl_2 (60 mL) at -78 °C was added dropwise diisobutylaluminium hydride (22.5 mL, 22.5 mmol, 1 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, recooled to 0 °C, treated with saturated sodium potassium tartrate solution and strirred for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) gave alcohol **76** (2.2 g) as a colorless solid.

Yield: 96%; **mp**: 41.8 °C; **IR** ($CHCl_3$, cm^{-1}): 3433, 3018, 2926, 2864, 1216, 767, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.72 Hz, 3H), 1.25-1.35 (m, 26H), 1.54 (br s, 1H), 4.05-4.08 (m 2H), 5.61-5.68 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.11, 22.69, 29.19, 29.23, 29.38, 29.54, 29.64, 29.71, 31.93, 32.24, 63.50, 128.96, 133.10; **Analysis:** **$C_{17}H_{34}O$** requires C, 76.97; H, 12.24; found: C, 77.22; H, 12.01%.

[(2*R*,3*R*)-3-Tetradecyloxiran-2-yl]methanol (77)

To a stirred suspension of powdered 4 Å molecular sieves (1 g) in dry CH_2Cl_2 (30 mL), titanium tetraisopropoxide (0.12 g, 0.44 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled to −20 ºC and (-)-diethyl tartrate (0.13 g, 0.64 mmol) added and stirred for 10 min, after which allyl alcohol **76** (2.2 g, 8.5 mmol) was dissolved

in CH_2Cl_2 (20 mL) was added and stirred at −20 ºC for 30 min. To the above solution anhyd. *tert*-butyl hydroperoxide (1.5 g, 17 mmol) dissolved in hexane was added and stirred at −20 ºC for 24 h. After completion of the reaction (monitored by TLC), it was quenched with 10% aq. solution of tartaric acid (25 mL), after which stirring was continued for 1 h at −20 ºC and 2 h at room temperature. The organic layer was separated, washed with water and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with ether (75 mL) and stirred with 1M NaOH (25 mL) for 1 h at 0 ºC. The organic layer was then separated, washed with brine solution, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford epoxide **77** (2.0 g) as a colorless solid.

Yield: 89%; **mp**: 74-77 °C; **$[\alpha]^{25}_D$**: +10 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3462, 3020, 2926, 2854, 1710, 1363, 1216, 767, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.67 Hz, 3H), 1.25-1.56 (m, 26H), 2.86-2.96 (m, 2H), 3.54-3.66 (m, 1H), 3.89 (dddd, *J* = 2.37 Hz, 2.61, 5.47, 5.47 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.16, 22.72, 25.98, 29.39, 29.44, 29.57, 29.59, 29.69, 31.58, 31.95, 55.94, 58.55, 61.67; **Analysis: $C_{17}H_{34}O_2$** requires C, 75.50; H, 12.67; found: C, 75.82; H, 12.39%.

(2*S*,3*R*)-2-(Iodomethyl)-3-tetradecyloxirane (79)

To a stirred solution of epoxy alcohol **77** (1.89 g, 7 mmol) in dry ether-acetonitrile (3:1, 40 mL) at 0 °C under nitrogen atmosphere were added imidazole (0.71 g, 10.5 mmol), triphenylphosphine (2.75 g, 10.5 mmol), and iodine (2.67 g, 10.5 mmol) successively. The mixture was stirred for 1 h at the same temperature, diluted with cold ether (20 mL), and filtered through a sintered funnel. The residue was washed with ether (3 × 50 mL)

and concentrated in vacuo. The crude compound was purified by column chromatography using petroleum ether/EtOAc (9:1) to afford epoxy iodide **79** (2.2 g) as a colorless solid.

Yield: 83%; **mp**: 60-61 °C; **[α]$^{25}_{D}$**: −20 (*c* 0.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3018, 2927, 2854, 1216, 767, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.80 Hz, 3H), 1.25-1.50 (m, 26H), 2.73-2.79 (m, 1H), 2.93-3.03 (m, 2H), 3.20-3.31 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.89, 14.18, 22.72, 25.92, 29.39, 29.53, 29.56, 29.69, 31.73, 31.95, 58.25, 62.46; **Analysis: $C_{17}H_{33}IO$** requires C, 53.68; H, 8.75; found: C, 53.99; H, 8.56%.

(*R*)-Heptadec-1-en-3-ol (80)

A mixture of epoxy iodide **79** (2.09 g, 5.5 mmol), NaI (2.06 g, 13.75 mmol), and freshly activated zinc (16.5 g, 1.08 mmol) in dry MeOH (25 mL) was refluxed for 6 h under nitrogen atmosphere. The solution was filtered and the residue was washed with MeOH (2 × 25 mL). The combined filtrates were concentrated and the residue was taken in ethyl acetate (50 mL), washed with water (2 × 30 mL), brine (1 × 20 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (9.5:0.5) to afford the olefinic compound **80** (1.12 g) as a colorless solid.

Yield: 80%; **mp**: 42-44 °C; **[α]$^{25}_{D}$**: −16.7 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3427, 3307, 3018, 2926, 2864, 1465, 1458, 1217, 1018, 993, 927, 769, 669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.79 Hz, 3H), 1.25-1.53 (m, 26H), 4.05-4.10 (m, 1H), 5.07-5.22 (m, 2H), 5.81-5.89 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.14, 22.71, 25.37, 29.39, 29.65, 29.71, 31.95, 37.06, 73.18, 114.38, 141.44; **Analysis: $C_{17}H_{34}O$** requires C, 80.24; H, 13.47; found: C, 79.95; H, 13.79%.

(*R*)-3-(Methoxymethoxy)heptadec-1-ene (81)

To a solution of the allylic alcohol **80** (0.76 g, 3 mmol) and diisopropylethylamine (0.78 g, 1.02 mL, 6 mmol) in dry CH_2Cl_2 (20 mL) was added methoxymethyl chloride (0.36 g, 0.39 mL, 5.5 mmol) under nitrogen over 5 min at 0 °C, and the mixture was allowed to warm to room temperature and stirred overnight. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether gave ether **81** (0.81 g) as a colorless liquid.

Yield: 91%; **$[\alpha]^{25}_D$**: +64 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3018, 2927, 2854, 1216, 1033, 929; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.81 Hz, 3H), 1.25-1.62 (m, 26H), 3.36 (s, 3H), 3.91-4.01 (m, 1H), 4.52 (d, *J* = 6.74 Hz, 1H), 4.69 (d, *J* = 6.74 Hz, 1H), 5.14-5.30 (m, 2H), 5.57-5.74 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.81, 22.38, 25.07, 29.07, 29.28, 29.32, 29.36, 29.39, 31.63, 35.14, 54.96, 76.02, 93.33, 116.57, 138.31; **Analysis: $C_{19}H_{38}O_2$** requires C, 76.45; H, 12.83; found: C, 76.77; H, 12.58%.

(*R*,*E*)-Ethyl-4-(methoxymethoxy)octadec-2-enoate (82)

Osmium tetroxide (catalytic amount) and 50% aqueous *N*-methylmorpholine *N*-oxide (0.66 mL, 2.8 mmol) were added to a solution of MOM ether **81** (0.42 g, 1.4 mmol) in acetone (5 mL) at 0 °C. After continuous stirring for 12 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (30 mL), and dried over anhyd. Na_2SO_4 and concentrated to give the crude diol which was then directly taken for the next step without purification.

To a vigorously stirred suspension of silica gel-supported $NaIO_4$ reagent (3.0 g) in CH_2Cl_2 (5 mL) in a 25 mL round-bottomed flask was added a solution of the crude vicinal diol in CH_2Cl_2 (5 mL). The reaction was monitored by TLC until disappearance of the starting material. The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated under reduced pressure to give the product aldehyde which was immediately treated with (ethoxycarbonylmethylene)triphenylphosphorane (0.48 g, 1.4 mmol) in benzene (10 mL) and stirred at 50 °C for 1 h. Removal of solvent under reduced pressure provided the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9.5:0.5) to give unsaturated ester **82** (0.38 g) as a colorless oil.

Yield: 73%; **$[\alpha]^{25}_{D}$**: +30 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3018, 2927, 2864, 2399, 1712, 1517, 1466, 1216, 1031, 927, 761, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.69 Hz, 3H), 1.24-1.60 (m, 29H), 3.36 (s, 3H), 4.11-4.24 (m, 3H), 4.53-4.63 (m, 2H), 5.95 (dd, *J* = 1.25, 15.80 Hz, 1H), 6.78 (dd, *J* = 6.43, 15.75 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.17, 14.30, 22.73, 25.20, 29.41, 29.57, 29.65, 29.70, 29.73, 31.97, 34.96, 55.56, 60.36, 75.23, 94.58, 121.82, 147.99, 166.10; **Analysis: $C_{22}H_{42}O_4$** requires C, 71.31; H, 11.42; found: C, 71.02; H, 11.73%.

(2*R*,3*R*,4*R*)-Ethyl-2,3-dihydroxy-4-(methoxymethoxy)octadecanoate (83)

To a mixture of $K_3Fe(CN)_6$ (0.59 g, 1.8 mmol), K_2CO_3 (0.25 g, 1.8 mmol) and $(DHQ)_2PHAL$ (5 mg, 1 mol%), in *t*-BuOH/H_2O (1:1, 12 mL) cooled at 0 °C was added $K_2OsO_4.H_2O$ (1 mg, 0.2 mol%) followed by methanesulfonamide (57 mg, 0.6 mmol). After being stirred for 5 min at 0 °C, olefin **82** (0.22 g, 0.6 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 5 h and then quenched with solid

sodium sulfite (1 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (7:3) as eluent gave the diol **83** (0.2 g) as a colorless liquid.

Yield: 86%; **[α]$^{25}_{D}$**: −18 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3417, 3018, 2927, 2854, 2399, 1736, 1216, 1126, 1029, 757, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.81 Hz, 3H), 1.26-1.53 (m, 29H), 3.42 (s, 3H), 3.55-3.68 (m, 2H), 3.75-3.82 (m, 1H), 4.13-4.18 (m, 1H), 4.29 (q, *J* = 7.20 Hz, 2H), 4.62-4.76 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.08, 14.14, 22.65, 25.09, 29.33, 29.55, 29.63, 29.65, 31.31, 31.89, 55.79, 61.72, 71.02, 74.04, 82.51, 98.03, 172.99; **Analysis: $C_{22}H_{44}O_6$** requires C, 65.31; H, 10.96; found: C, 65.62; H, 10.69%.

(2*S*,3*R*,4*R*)-4-(Methoxymethoxy)octadecane-1,2,3-triol (84)

A solution of ester **83** (0.16 g, 0.4 mmol) in THF (5 mL) was added to a stirred slurry of $LiAlH_4$ (47 mg, 1.2 mmol) in THF (5 mL). After being stirred for 5 h at 25 °C, the reaction was carefully quenched with water. The reaction mixture was then extracted with EtOAc (2 × 100 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography using petroleum ether/EtOAc (4:6) to give the triol **84** (125 mg) as a colorless oil.

Yield: 86%; **[α]$^{25}_{D}$**: − 40 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3411, 3018, 2926, 2854, 2399, 1216, 1031, 927, 767, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.70 Hz, 3H), 1.24-1.38 (m, 23H), 1.47-1.74 (m, 3H), 3.41 (s, 3H), 3.51-3.84 (m, 5H), 4.63-4.74 (m,

2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.19, 22.74, 25.26, 29.41, 29.62, 29.65, 29.71, 29.74, 29.77, 31.10, 31.98, 55.90, 65.22, 70.83, 74.49, 82.95, 97.60; **Analysis: $C_{20}H_{42}O_5$** requires C, 66.26; H, 11.68; found: C, 65.95; H, 11.99%.

Guggultetrol (61)

To a stirred solution of the alcohol **84** (72 mg, 0.2 mmol) in methanol (5 mL) was added con. HCl and stirred for 4 h and then extracted with EtOAc (3 × 10 mL), washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (3:7) gave guggultetrol **61** (50 mg) as a colorless solid.

Yield: 78%; **mp**: 80-136 °C (lit.[45] **mp**: 87-135 °C); **$[\alpha]^{25}_D$**: +12 (*c* 0.5, EtOH) {lit.[45,46] **$[\alpha]^{25}_D$**: +11.4 (*c* 0.34, EtOH)}; **IR** (MeOH, cm^{-1}): 3382, 2925, 2833, 1448, 1419, 1116, 1027; **^{1}H NMR** (400 MHz, CD_3OD): δ 0.88 (t, *J* = 6.58 Hz, 3H), 1.28-1.59 (s, 26H), 3.42 (dd, *J* = 3.78, 7.53 Hz, 1H), 3.50-3.81 (m, 4H); **^{13}C NMR** (100 MHz, CD_3OD): δ 14.4, 23.7, 26.9, 30.5, 30.7, 30.8, 33.1, 64.4, 73.5, 74.1, 74.3; **M/S**: 318, 301, 265, 149, 121; **Analysis: $C_{18}H_{38}O_4$** requires C, 67.88; H, 12.03; found: C, 67.59; H, 12.34%.

Mosher's ester of [(2*R*,3*R*)-3-tetradecyloxiran-2-yl]methanol (78)

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.68 Hz, 3H), 1.25 (s, 26H), 2.78-2.84 (m, 1H), 2.93-3.00 (m, 1H), 3.56 (s, 3H), 4.22 (dd, *J* = 6.08, 11.99 Hz, 1H), 4.51 (dd, *J* = 3.54, 12.02 Hz, 1H), 7.38-7.43 (m, 3H), 7.50-7.54 (m, 2H).

(2*S*,3*R*)-Ethyl- 2,3-dihydroxyheptadecanoate (85)

To a mixture of $K_3Fe(CN)_6$ (15.79 g, 48 mmol), K_2CO_3 (6.62 g, 48 mmol) and $(DHQD)_2$-PHAL (124 mg, 1 mol %), in *t*-BuOH/H_2O (1:1, 160 mL) cooled at 0 °C was added $K_2OsO_4.H_2O$ (12 mg, 0.2 mol %) followed by methanesulfonamide (1.52 g, 16 mmol).

After being stirred for 5 min at 0 °C, the olefin **75** (4.74 g, 16 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (22 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (7:3) as eluent gave the diol **85** (4.98 g) as a colourless solid.

Yield: 94%; **mp**: 58-60 °C; **$[\alpha]^{25}_D$**: +9.9 (*c* 3, $CHCl_3$) {lit.[58] **$[\alpha]^{25}_D$**: -10.13 (*c* 1, $CHCl_3$) for its antipode}; **IR** ($CHCl_3$, cm^{-1}): 3392, 2916, 2848, 1735, 1716, 1616, 1598, 1469, 1371, 1217, 1135, 1118, 1085; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.82 Hz, 3H), 1.24-1.35 (m, 27H), 1.57-1.61 (m, 2H), 1.86 (d, *J* = 8.86 Hz, 1H), 3.03 (d, *J* = 5.18 Hz, 1H), 3.79-3.90 (m, 1H), 4.04 (dd, *J* = 1.89, 4.90 Hz, 1H), 4.28 (q, *J* = 7.28 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 14.08, 22.65, 25.73, 29.34, 29.54, 29.59, 29.67, 31.90, 33.62, 61.77, 72.56, 73.21, 173.65; **Analysis: $C_{19}H_{38}O_4$** requires C, 69.05; H, 11.59; found: C, 69.34; H, 11.36%.

(2*S*,3*R*)-Ethyl-2,3-bis(methoxymethoxy)heptadecanoate (86)

To a solution of the diol **85** (3.3 g, 10 mmol) and diisopropylethylamine (4.52 g, 5.99 mL, 35 mmol) in dry CH_2Cl_2 (50 mL) was added methoxymethyl chloride (1.99 g, 2.18 mL, 25 mmol) under nitrogen over 5 min at 0 °C, and the mixture was allowed to warm to room temperature and stirred overnight. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of

the crude product using petroleum ether/EtOAc (8:2) gave **86** (3.93 g) as a colorless liquid.

Yield: 94%; **mp**: 58-60 °C; **$[\alpha]^{25}_{D}$**: -44.1 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3448, 2920, 2850, 1747, 1618, 1604, 1467, 1369, 1217, 1153, 1029, 919, 727; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.15 Hz, 3H), 1.26-1.34 (m, 27H), 1.63-1.73 (m, 2H), 3.35 (s, 3H), 3.41 (s, 3H), 3.91-3.99 (m, 1H), 4.18-4.30 (m, 3H), 4.62-4.70 (m, 2H), 4.71-4.78 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 14.01, 14.09, 22.59, 25.28, 29.26, 29.48, 29.55, 31.76, 31.83, 55.70, 56.15, 60.87, 76.69, 78.37, 96.36, 96.40, 170.77; **Analysis: $C_{23}H_{46}O_6$** requires C, 65.99; H, 11.08; found: C, 66.28; H, 10.78%.

(2*R*,3*R*)-2,3-Bis(methoxymethoxy)heptadecan-1-ol (87)

A solution of ester **86** (3.14 g, 7.5 mmol) in THF (30 mL) was added to a stirred slurry of $LiAlH_4$ (0.88 g, 22.5 mmol) in THF (100 mL). After being stirred for overnight at 25 °C, the reaction was carefully quenched with water. The reaction mixture was then extracted with EtOAc (2 × 100 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography using petroleum ether/EtOAc (7:3) to give the alcohol **87** (2.68 g) as a colorless oil.

Yield: 95%; **$[\alpha]^{25}_{D}$**: +12.3 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3433, 2920, 2850, 1620, 1497; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.69 Hz, 3H), 1.26-1.62 (m, 26H), 3.09 (br s, 1H), 3.40 (s, 3H), 3.43 (m, 3H), 3.64-3,74 (m, 4H), 4.67-4.78 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 14.09, 22.64, 25.75, 29.32, 29.56, 29.62, 29.65, 30.30, 31.88, 55.70, 55.79, 62.41, 78.35, 82.20, 96.76, 97.56; **Analysis: $C_{21}H_{44}O_5$** requires C, 66.98; H, 11.78; found: C, 66.69; H, 11.99%.

(2*S*,3*R*)-2,3-Bis(methoxymethoxy)heptadecanal (88)

To a solution of the alcohol **87** (2.64 g, 7 mmol) in DMSO (50 mL) was slowly added 2-iodoxybenzoic acid (2.35 g, 8.4 mmol). The reaction mixture was stirred for 3 h at 25 °C followed by quenching with cold water. The reaction mixture was filtered and the filtrate was then extracted with diethyl ether (3 × 100 mL) and the combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude aldehyde **88** which was then directly taken up for the next step without purification.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.70 Hz, 3H), 1.25 (s, 24H), 1.60-1.75 (m, 2H), 3.34 (s, 3H), 3.44 (m, 3H), 3.90-4.03 (m, 2H), 4.59-4.81 (m, 4H), 9.74 (s, 1H).

(3*S*,4*R*,5*R*)-4,5-Bis(methoxymethoxy)nonadec-1-en-3-ol (89)

The crude aldehyde **88** dissolved in CH_2Cl_2 (20 mL) was added to a stirred suspension of $MgBr_2.Et_2O$ (2.17 g, 8.4 mmol) in CH_2Cl_2 (50 mL) in a 250 mL round-bottom flask at 0 °C. After stirring for 10 min, the flask was cooled to -78 °C and treated with vinylmagnesium bromide (1 M in THF, 28 mL, 28 mmol); the solvent was removed in *vacuo* and diluted with CH_2Cl_2 three times over 30 min, stirred for 10 hours and allowed to warm to 0 °C. The reaction mixture was diluted with saturated NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with 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 the allylic alcohol **89** (2.45 g) as an inseparable mixture of diastereomers (*syn:anti* = 15:1) as a colorless oil.

Yield: 87%; **$[\alpha]^{25}_D$**: +3.4 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3442, 2918, 2850, 1712, 1618, 1467, 1217, 1151, 1101, 1031, 919, 757; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.04 Hz, 3H), 1.26 (s, 24H), 1.53-1.70 (m, 2H), 3.02 (d, *J* = 5.02 Hz, 1H), 3.38 (s, 3H),

3.41-3.48 (m, 4H), 3.62-3,73 (m, 1H), 4.27-4.31 (m, 1H), 4.66-4.79 (m, 4H), 5.22 (d, *J* = 10.68 Hz, 1H), 5.41 (d, *J* = 17.38 Hz, 1H), 5.90-5.99 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.13, 22.69, 25.72, 29.36, 29.59, 29.65, 29.74, 30.89, 31.92, 55.89, 56.18, 71.70, 78.53, 83.47, 96.71, 97.40, 116.05, 137.89; **Analysis: $C_{23}H_{46}O_5$** requires C, 68.61; H, 11.52; found: C, 68.93; H, 11.29%.

(3*S*,4*S*,5*R*)-3,4,5-Tris(methoxymethoxy)nonadec-1-ene (90)

To a solution of the alcohol **89** (2.01 g, 5 mmol) and diisopropylethylamine (1.29 g, 1.7 mL, 10 mmol) in dry CH_2Cl_2 (40 mL) was added methoxymethyl chloride (0.48 g, 0.52 mL, 6 mmol) under nitrogen over 5 min at 0 °C, and the mixture was allowed to warm to room temperature and stirred overnight. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (7:3) gave **90** (2.05 g) as a colorless liquid.

Yield: 92%; **$[\alpha]^{25}_D$**: +17.0 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2921, 2852, 1618, 1467, 1213, 1151, 1103, 1029, 919, 756; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.72 Hz, 3H), 1.26 (s, 24H), 1.57-1.81 (m, 2H), 3.37-3.44 (m, 9H), 3.55-3.80 (m, 2H), 4.28 (t, *J* = 6.83 Hz, 1H), 4.55-4.58 (m, 1H), 4.67-4.78 (m, 4H), 4.87-4.97 (m, 1H), 5.28-5.36 (m, 2H), 5.72-5.89 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.09, 22.65, 25.33, 29.59, 29.63, 29.65, 29.80, 31.05, 31.89, 55.67, 55.80, 56.14, 77.35, 78.21, 80.56, 93.90, 96.92, 98.31, 118.68, 135.08; **M/S**: 446, 408, 371, 307, 237, 221, 149, 121; **Analysis: $C_{25}H_{50}O_6$** requires C, 67.22; H, 11.28; found: C, 66.92; H, 11.59%.

(2*S*,3*S*,4*R*)-2,3,4-Tris(methoxymethoxy)octadecan-1-ol (91)

Osmium tetroxide (catalytic amount) and 50% aqueous *N*-methylmorpholine *N*-oxide (0.12 mL, 1 mmol) were added to a solution of MOM ether **90** (0.22 g, 0.5 mmol) in acetone (5 mL) at 0 °C. After continuous stirring for 12 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (30 mL), and dried over anhyd. Na_2SO_4 and concentrated to give the crude diol which was then directly taken for the next step without purification.

To a vigorously stirred suspension of silica gel-supported $NaIO_4$ reagent (1.0 g) in CH_2Cl_2 (5 mL) in a 25 mL round-bottomed flask was added a solution of the vicinal diol (0.5 mmol) in CH_2Cl_2 (5 mL). The reaction was monitored by TLC until disappearance of the starting material. The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated under reduced pressure to give the product aldehyde which was further dissolved in methanol (5 mL) and $NaBH_4$ (56 mg) was added to the reaction mixture at 0 °C and stirred for 30 min. The reaction mixture was quenched with water; solvent was evaporated and then extracted with EtOAc (3 × 10 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (6:4) gave **91** (0.2 g) as a colorless liquid. **Yield**: 88%; **$[\alpha]^{25}_D$**: +6.03 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3429, 2920, 2850, 1618, 1465, 1454, 1161, 1106, 1029, 919; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.56 Hz, 3H), 1.26 (s, 24H), 1.45-1.71 (m, 2H), 3,24 (br s, 1H), 3.39-3.43 (m, 9H), 3.67-3.80 (m, 5H), 4.64-4.79 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.13, 22.69, 25.34, 29.36, 29.59, 29.69, 29.83, 30.63, 31.92, 55.89, 56.16, 62.34, 78.33, 79.16, 80.63, 96.93, 97.51, 98.53; **Analysis: $C_{24}H_{50}O_7$** requires C, 63.96; H, 11.18; found: C, 64.27; H, 10.91%.

Guggultetrol (61)

To a stirred solution of the alcohol **91** (45 mg, 0.3 mmol) in methanol (5 mL) was added con. HCl and stirred for 2 h and then extracted with EtOAc (3 × 10 mL), washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (3:7) gave guggultetrol **61** (75 mg, 79%) as a colorless solid; $[\alpha]^{25}_{D}$: +12.2 (*c* 0.5, EtOH) (*vide infra* of the same section for spectral details).

3.2.8 References

1. Giros, B.; Gros, C.; Solhonne, B.; Schwartz, J. C. *Mol. Pharmacol.* 1986, *29*, 281.
2. (a) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot*. **1976**, *29*, 97; (b) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot*. **1976**, *29*, 100; (c) Nakamura, H.; Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H.; Iitaka, Y. *J. Antibiot*. **1976**, *29*, 102.
3. Abe, F.; Ino, K.; Bierman, P. J.; Talmadge, J. E.; Sawada, H.; Ogino, T.; Ishizuka, M.; Aoyagi, T. *Int. Congr. Ser.* **2001**, *1218*, 155.
4. (a) Pulido-Cejudo, G.; Conway, B.; Proulx, P.; Brown, R.; Izaguirre, C. A. *Antiviral Res.* **1997**, *36*, 167; (b) Bourinbaiar, A.; Lee-Huang, S.; Krasinski, K.; Borkowsky, W. *Biomed. Pharmacother.* **1994**, *48*, 55.
5. Rubin, A. E.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2637.
6. (a) Nozaki, K.; Sato, N.; Takaya, H. *Tetrahedron*: *Asymmetry* **1993**, *4*, 2179; (b) Kearns, J.; Kayser, M. M. *Tetrahedron Lett*. **1994**, *35*, 2845; (c) Wasserman, H. H.; Xia, M.; Petersen, A. K. *Tetrahedron* **2003**, *59*, 6771.
7. (a) Herranz, R.; Castro-Pichel, J.; Vinnesa, S.; Garcia Lopez, M. T. *J. Org. Chem.*

1990, *55*, 2232; (b) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Chem. Lett.* **1990**, 723; (c) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939; (d) Manickam, G.; Nogami, H.; Kanai, M.; Groger, H.; Shibasaki, M. *Synlett* **2001**, 617; (e) Lee, B. W.; Lee, H. J.; Jang, K. C.; Kang, J. E.; Kim, J. H.; Park, K.-M.; Park, K. H. *Tetrahedron Lett.* **2003**, *44*, 5905.

8. Raghavan, S.; Rasheed, M. A. *Tetrahedron*: *Asymmetry* **2003**, *14*, 1371.
9. (a) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175; (b) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 529.
10. (a) Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46; (b) Deng, L.; Jacobsen E. N. *J. Org. Chem.* **1992**, *57*, 4320; (c) Commercon, A.; Bezard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185; (d) Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287; (e) Righi, G.; Chionne, A.; D'Achille, R.; Bonini, C. J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 903; (f) Grosjean, F.; Huche, M.; Larcheveque, M.; Legendre, J. J.; Petit, Y. *Tetrahedron* **1994**, *50*, 9325; (g) Pasto, M.; Castejon, P.; Moyano, A.; Pericas, M. A.; Riera, A. J. *J. Org. Chem.* **1996**, *61*, 6033.
11. Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079.
12. Lee, H. J.; Lee, B. W.; Jang, K. C.; Jeong, I. Y.; Yang, M. S.; Lee, S. G.; Park, K. H. *Synthesis* **2003**, 829.
13. (a) Jefford, C. W.; Wang, J. B.; Lu, Z.-H. *Tetrahedron Lett.* **1993**, *34*, 7557; (b) Caputo, R.; Cecere, G.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Eur. J. Org. Chem.* **2002**, 3050.

14. Ocain, T. D.; Rich, D. H. *J. Med. Chem*. **1988**, *31*, 2193.

15. Norman, B. H.; Morris, M. L. *Tetrahedron Lett*. **1992**, *33*, 6803.

16. Liu, Q.; Marchington, A. P.; Rayner, C. M. *Tetrahedron* **1997**, 53, 15729.

17. Righi, G.; D'Achille, C.; Pescatore, G.; Bonini, C. *Tetrahedron Lett*. **2003**, *44*, 6999.

18. Kudyba, I.; Raczko, J.; Jurczak, J. *Tetrahedron Lett*. **2003**, *44*, 8685.

19. Tasic, G.; Matovic, R.; Saicic, R. N. *J. Serb. Chem. Soc.* **2004**, *69*, 981.

20. Gogoi, N.; Boruwa, J.; Barua, N. C. *Tetrahedron Lett*. **2005**, *46*, 7581.

21. Feske, B. D.; Stewart, J. D. *Tetrahedron*: *Asymmetry* **2005**, *16*, 3124.

22. Jung, D. Y.; Kang, S.; Chang, S.; Kim, Y. H. *Synlett* **2006**, 86.

23. Lee, J. H.; Kim, J. H.; Lee, B. W.; Seo, W. D.; Yang, M. S.; Park, K. H. *Bull. Korean Chem. Soc*. **2006**, *27*, 1211.

24. Gogoi, N.; Borah, J. C.; Boruwa, J.; Barua, N. C. *Lett. Org. Chem*. **2007,** *4,* 234.

25. Feske, B. D. *Curr. Org. Chem*. **2007,** *11*, 483 and references cited therein.

26. Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot*, **1976**, *29*, 600.

27. Wasserman, H.; Xia, M.; Peterson, A.; Jorgensen, M.; Curtis, E. *Tetrahedron Lett*. **1999**, *40*, 6163.

28. Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett*. **2000**, *2*, 2769.

29. Nemoto, H.; Ma, R.; Suzuki, I.; Shibuya, M. *Org. Lett*. **2000**, *2*, 4245.

30. Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.

31. Kim, H.; Lipscomb, W. N. *Biochemistry* 1993, *32*, 8465.

32. Bøgevig, A. Juhl, K. Kumaragurubaran, N. Zhuang, W. Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790.

33. (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656; (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254; (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448; (e) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770.

34. Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 9922.

35. List, B. *Synlett* **2001**, 1675.

36. Udodong, U. E.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2103.

37. (a) Lee, K. Y.; Kim, Y. H.; Park, M. S.; Ham, W. H. *Tetrahedron Lett.* **1998**, *39*, 8129; (b) Lee, K. Y.; Kim, Y. H.; Park, M. S.; Ham, W. H. *J. Org. Chem.* **1999**, *64*, 9450; (c) Lee, K. Y.; Kim, Y. H.; Oh, C. Y.; Ham, W. H. *Org. Lett.* **2000**, *2*, 4041; (d) Lee, K. Y.; Oh, C. Y.; Ham, W. H. *Org. Lett.* **2002**, *4*, 4403.

38. Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

39. White, J. D.; Hanselmann, R.; Wardrop, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1106.

40. Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235.

41. For stereoselective synthesis and application of tetrols see: (a) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769; (b) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.

42. For a review on sphingolipid synthesis see: Howell, A. R.; So, R. C.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327.

43. (a) Isolation and assignment of absolute stereochemistry of guggultetrols see: Patil, V. D.; Nayak, U. R.; Dev, S. *Tetrahedron* **1973**, *29*, 1595; (b) For a review of

guggul lipids see: Urizar, N. L.; Moore, D. D. *Annu. Rev. Nutr.* **2003**, *23*, 303.

44. (a) Satyavati, G. V. *Indian J. Med. Res.* **1988**, *87*, 327; (b) Sastry, V. V. S. *Bull. Indian Inst. Hist. Medicine*, **1976**, *6*, 102.
45. Kjaer, A.; Kjaer, D.; Skrydstrup, T. *Tetrahedron* **1986**, *42*, 1439.
46. Kumar, V; Dev, S. *Tetrahedron* **1987**, *43*, 5933.
47. Prasad, K. R.; Chandrakumar, A. *Tetrahedron* **2007**, *63*, 1798.
48. (a) Katasuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
49. (a) Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448; (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
50. (a) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737; (b) Kolb, H. C.; Anderson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K. S.; Kwong, H. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226.
51. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.
52. Gawley, R. A.; Aube, J. *Principles of Asymmetric Synthesis* Elesevier Science (Oxford), **1996**, Vol. 14, (Chap. 8), pp 314.
53. Sharpless K. B.; Amerg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu. D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.
54. Amerg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless K. B. *J. Org. Chem.* **1993**, *58*,

844.

55. For reviews on the Swern oxidation see: (a) Tidwell, T. T. *Synthesis* **1990**, 857; (b) Tidwell, T. T. *Org. React*. **1990**, *39*, 297.

56. Corey, E. J.; Pyne, S. G.; Su, W.-G. *Tetrahedron Lett*. **1983**, *24*, 4883.

57. Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett*. **1984**, *25*, 2069.

58. Fernandes, R. A.; Kumar, P. *Tetrahedron Lett*. **2000**, *41*, 10309.

59. Kumar, P.; Naidu, V. *J. Org. Chem*. **2006**, *71*, 3935.

60. For similar type Grignard additions using $MgBr_2.Et_2O$ see: (a) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem*. **1991**, *56*, 417; (b) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem*. **1994**, *59*, 3113.

61. The *syn* configuration of the newly generated chiral center was further confirmed by the NOE studies of compound **90**, where strong NOE correlations were observed for the protons at the newly generated chiral centre and the adjacent carbon.

Chapter IV

$NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides with high diastereoselectivity: a short route to (-)-cytoxazone and droxidopa

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"$NaIO_4$-mediated Asymmetric Bromohydroxylation of α,β-unsaturated Carboxamides with High Diastereoselectivity: A short route to (-)-Cytoxazone and Droxidopa" Shyla George, Srinivasarao V. Narina and Arumugam Sudalai; *Tetrahedron Lett*. **2007**, *48*, 1375.

Section I

$NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides

4.1.1 Introduction

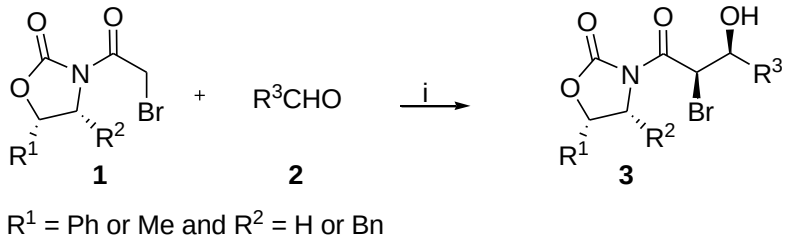
The 1,2-functionalization of electron-deficient olefins (e.g. α, β-unsaturated acid derivatives) by the selective addition of two different functional groups, such as water and halogens (halohydroxylation) in a highly regio- and enantioselective manner, constitutes an important transformation in organic synthesis.[1] The product halohydrins are versatile intermediates for the synthesis of pharmaceuticals, dyes, flame retardants, agrochemicals etc.[2] Also such chiral α-halo-β-hydroxy carboxamides are important precursors which could readily be transformed into epoxides, ketones and unusual β-hydroxy-α-amino acids.[3] The asymmetric bromohydroxylation of alkenes, a potentially straight-forward method to obtain such halohydrins, is scarce and known only for limited chiral substrates.[4]

4.1.2 Review of Literature

Literature search revealed that there are only few reports[5-7] available for asymmetric bromohydroxylation, which involve the use of metal salts (Ag, Yb) and stoichiometric amounts of Br_2/*N*-halosuccinimides, are described below.

Evans' approach (1987)[5]

Evans *et al.* have reported asymmetric bromohydroxylation using aldol reaction of chiral bromoacetate enolates **1** with aromatic or aliphatic aldehydes **2** in presence of Bu_2BOTf and Et_3N yielding bromohydroxylated products **3** with diastereomeric ratio >94:6 and 63-94% yield (**Scheme 1**).

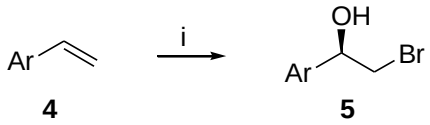


R^1 = Ph or Me and R^2 = H or Bn

Scheme 1: (i) Bu_2BOTf, Et_3N, CH_2Cl_2, -78 °C, 63-94%.

Sudalai's approach (2003)[6]

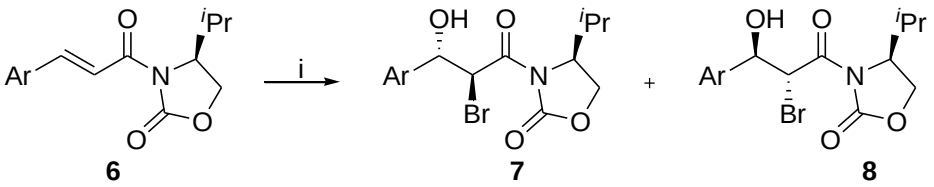
Asymmetric bromohydroxylation of β-cyclodextrin complexes of styrenic substrates has been described with $NaIO_4$ and LiBr in aqueous acetonitrile under acidic conditions to provide bromohydrins with good yield (78-90%) and moderate enantiomeric excess (20-55%) (**Scheme 2**).



Scheme 2: (i) β-cyclodextrin complex of styrene, LiBr (1.2 equiv.), $NaIO_4$ (25 mol%), aq. H_2SO_4, CH_3CN/H_2O (3:1), 25 °C, 12 h, 78-90%, 20-55% ee.

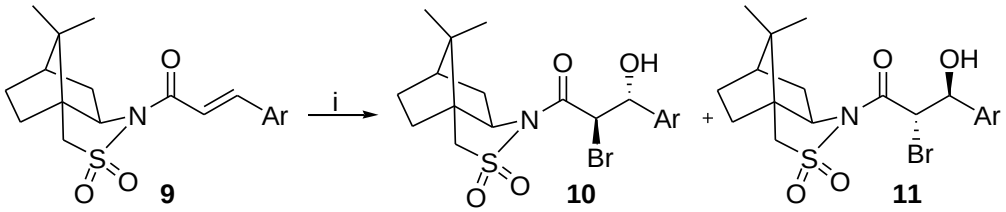
Hajra's approach (2005)[7]

The halohydrin formation of chiral *N*-enoyl-2-oxazolidinones **6** by bromine and water has been reported in presence of silver(I)[7a] to give the product bromohydrins **7** and **8** with moderate diastereoselectivity (upto 4:1) (**Scheme 3**).



Scheme 3: (i) $AgOAc/Ag_2O/AgNO_3$, Br_2, aqueous acetone, 0 to 25 °C, 88-97%.

Same authors have developed Lewis acid-catalyzed asymmetric bromohydroxylation of chiral α, β-unsaturated carboxylic acid derivatives **9** with NBS[7b] and aqueous CH_3CN giving bromohydrins **10** and **11** with diastereoselectivity upto 4:1 (**Scheme 4**).



Scheme 4: (i) $Yb(OTf)_3$, NBS, aqueous CH_3CN, 25 °C.

4.1.3 Present Work:

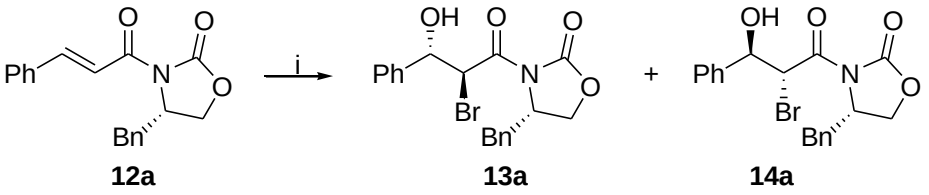
4.1.3.1 Objective

Halohydrins are valuable reaction intermediates that can be transformed into epoxides, ketones and other derivatives. Only few reports on the asymmetric bromohydroxylation are known in literature.[5-7] The asymmetric version of halohydrin reactions suffer from several disadvantages such as low diastereoselectivities, use of expensive metal salts (Ag, Yb), stoichiometric amounts of corrosive Br_2/*N*-halosuccinimides or the formation of large amounts of organic and inorganic waste.[7] In this context, a more practical method for asymmetric brmohydroxylation is highly desirable.

4.1.4 Results and Discussion

In continuation of our interest in $NaIO_4$-mediated oxyfunctionalization of organic compounds,[6] we were interested to carry out a "transition metal-free" procedure for the asymmetric bromohydroxylation of α, β-unsaturated carboxamides with $NaIO_4$ as the oxidant and LiBr as the halogen source under ambient conditions.

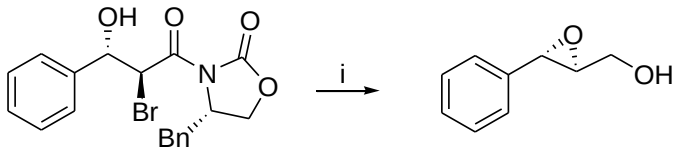
After initial experimentation, (4*S*)-*N*-cinnamoyl-4-benzyl-2-oxazolidinone (**12a),** readily derived from the Evans' chiral auxiliary obtainable from (*S*)-phenylalanine,[8] was subjected to oxidative bromination in the presence of 30 mol% $NaIO_4$ in a 2:1 mixture of CH_3CN and water and LiBr (1.2 equiv.) under acidic conditions (aq. HCl), to afford the corresponding bromohydrins **13a** and **14a** in 81% combined yield and high diastereoselectivity (dr = 5.5:1) (**Scheme 5**).



12a **13a** **14a**

Scheme 5: (i) carboxamide (5 mmol), $NaIO_4$ (30 mol%), LiBr (6 mmol), 35% aq. HCl (0.5 ml), CH_3CN/H_2O (2:1), 25 °C, 3 h, 81%.

A mixture of CH_3CN and H_2O (2:1 ratio) was found to be the best solvent system for the formation of bromohydrins. There was a marginal increase in the diastereomeric ratio (dr = 6.5:1) when bromohydroxylation of **1a** was conducted at 10 °C, however lower conversion resulted. In order to confirm the resulting configuration of the diastereomers obtained, the oxazolidinones **13a** and **14a** were separated by column chromatography and



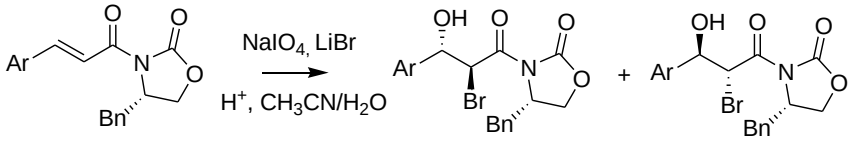
13a **15**

Scheme 6: (i) $LiBH_4$, Et_2O, THF, MeOH, 0 °C, 1.5 h then 10% NaOH, 25 °C, 85%.

subsequently **13a** was subjected to reduction with $LiBH_4$ under basic conditions to give the chiral epoxy alcohol **15** in 99.1% ee (**Scheme 6**). The optical purity of the epoxy alcohol **15** was determined by comparing the specific rotation of **15** with that reported in

literature. $[\alpha]^{25}_D$ = -50.58 (*c* 1, $CHCl_3$) {lit.[9] $[\alpha]^{25}_D$ = -49.6 (*c* 2.4, $CHCl_3$)}. Encouraged by this result, several (4*S*)-*N*-cinnamoyl-4-benzyl-2-oxazolidinones (entries **12a-i**) with electron-donating as well as -withdrawing substituents on the aromatic nucleus were prepared and then subjected to asymmetric bromohydroxylation to produce the corresponding bromohydrins **13** and **14** in excellent yields and high diastereoselectivities (**Table 1**).

Table 1: $NaIO_4$-mediated[a] asymmetric bromohydroxylation [a]of α, β-unsaturated carboxamides with LiBr



12a-i **13a-i** **14a-i**

Entry	Substrate (Ar)	Ratio (**13**:**14**)[b]	% Yield[c]
a	C_6H_5	5.5:1	81
b	4-MeO-C_6H_4	10:1	90
c	4-CH_3-C_6H_4	9:1	86
d	3,4-dimethoxy-C_6H_3	7:1	82
e	4-Cl-C_6H_4	6:1	77
f	3,4,5-trimethoxy-C_6H_2	6:1	86
g	3,4-(O-CH_2-O)-C_6H_3	5:1	84
h	3,4-dibenzyloxy-C_6H_3	6:1	87
i	furan	5:1	82

[a] Reaction conditions: carboxamides **12a-i** (5 mmol), $NaIO_4$ (30 mol%), LiBr (6 mmol), 35% aq. HCl (0.5 ml), CH_3CN/H_2O (2:1), 25 °C, 3 h.
[b] Diastereomeric ratios were determined by GC.
[c] Combined isolated yield of **13** and **14**.

With all the substrates studied, the reaction proceeded in a highly regiospecific manner, the hydroxyl group adding at the benzylic position, exclusively. No traces of dibromide

was observed in all the substrates screened. Mono-substituted electron-donating groups at the *para* position (e.g. OMe, CH_3) gave the maximum diastereoselectivities of 10:1 and 9:1, respectively (**entries b & c, Table 1**).

The structures of both diastereomers were confirmed by ^1H, ^{13}C NMR and mass spectroscopy. For example, compound **13a** showed a doublet of doublet at δ 5.92 (d, J = 8.2 Hz, 1H) for the benzylic proton attached to hydroxyl group in the ^1H NMR spectrum which was further confirmed by the corresponding methine carbon signal at δ 74.82 ppm in its ^{13}C NMR spectrum (**Fig. 1**).

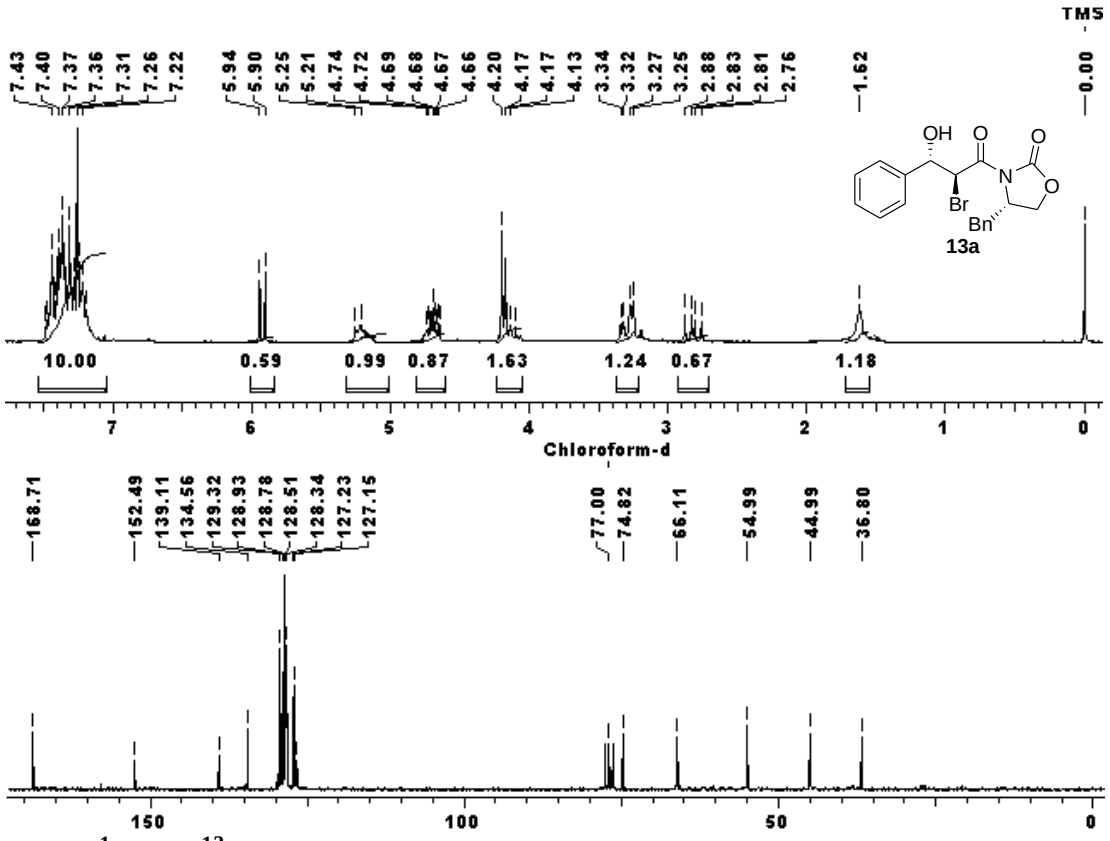


Fig. 1: ^1H and ^{13}C NMR spectra of bromohydrin 13a

4.1.4.1 Mechanism

The bromohydroxylation of carboxamides is believed to follow a mechanistic pathway as shown in **Fig. 2**. It is proposed that H^+-chelated carboxamide **15** will undergo preferred

attack of Br^+ from the *Re*-face of **15** and subsequent *anti*-opening of the bromonium intermediate **16** by nucleophilic attack of hydroxyl group at the β-position to afford the major diastereomer **17**.

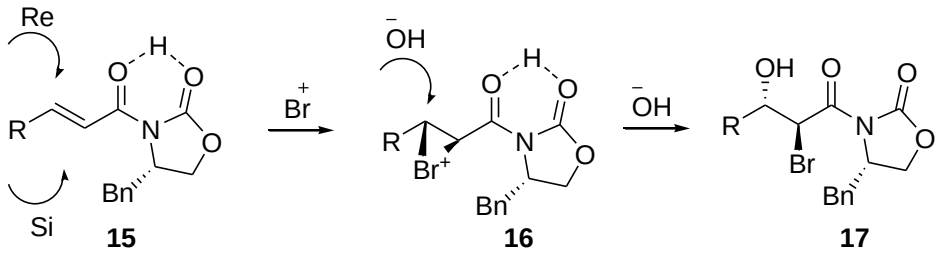


Fig. 2: Plausible mechanism for bromohydroxylation of carboxamides

4.1.5 Conclusion

In conclusion, we have developed an elegant method of $NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides, using Evans' chiral auxiliary and LiBr as the halogen source, which proceeds with high regio- and diastereoselectivity to give the corresponding bromohydrins. The methodology avoids the use of heavy metals and molecular bromine as well as *N*-halosuccinimides as halogen source.

4.1.6 Experimental Section

General experimental procedure for bromoamination

To a stirred solution of olefin (5 mmol), $NaIO_4$ (30 mol%), and 30% aq. HCl (0.5 mL) in CH_3CN/H_2O (2:1, 30 mL) at 25 °C, LiBr (6 mmol) was added portionwise. The reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with ethyl acetate (3 × 50 mL). The organic layers were washed with dilute solution of sodium thiosulfate and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by column

chromatography over silica gel using petroleum ether/ethyl acetate (7:3) as eluent to afford the pure products.

***anti*-(4*S*,2'*S*,3'*S*)-3-(2'-Bromo-3'-hydroxy-3'-phenyl-propionyl)-4-benzyloxazolidin-2-one (13a)**

mp: 97 °C; **$[\alpha]^{25}_{D}$**: +81.66 (*c* 0.8, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3502, 3019, 2926, 2400, 1783, 1707, 1497, 1455, 1385, 1216, 1019, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.82 (dd, *J* = 9.3, 13.5 Hz, 1H), 3.29 (dd, *J* = 3.4, 13.4 Hz, 1H), 4.10-4.20 (m, 2H), 4.65-4.74 (m, 1H), 5.22 (d, *J* = 8.2 Hz, 1H), 5.92 (d, *J* = 8.2 Hz, 1H), 7.19-7.44 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.80, 44.99, 54.99, 66.11, 74.82, 126.67, 127.15, 127.23, 128.34, 128.51, 128.78, 128.93, 129.32, 134.56, 139.11, 152.49, 168.71; **Analysis: $C_{19}H_{18}BrNO_4$** requires C, 56.45; H, 4.49; Br, 19.77; N, 3.46; found: C, 56.16; H, 4.78; Br, 19.51; N, 3.69%.

***anti*-(4*S*,2'*S*,3'*S*)-3-[2'-Bromo-3'-hydroxy-3'-(4-methoxyphenyl)-propionyl]-4-benzyloxazolidin-2-one (13b)**

mp: 103 °C; **$[\alpha]^{25}_{D}$**: +7.76 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3602, 3019, 2927, 2400, 1785, 1701, 1604, 1498, 1384, 1215, 1111, 1021, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.76 (dd, *J* = 9.0, 13.7 Hz, 1H), 3.21 (dd, *J* = 3.6, 13.7 Hz, 1H), 3.37 (d, *J* = 6.3 Hz, 1H), 3.89 (s, 3H), 4.15-4.31 (m, 2H), 4.68-4.74 (m, 1H), 5.12 (d, *J* = 7.6 Hz, 1H), 5.86 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 7.10-7.14 (m, 2H), 7.27-7.40 (m, 4H), 7.65 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.12, 44.56, 55.24, 56.00, 66.02, 74.08, 111.30, 111.50, 127.20, 127.31, 128.72, 129.18, 130.03, 131.86, 132.62, 134.40, 137.17, 152.36, 155.70, 168.75; **Analysis: $C_{20}H_{20}BrNO_5$** requires C, 55.31; H, 4.64; Br, 18.40; N, 3.23; found: C, 55.59; H, 4.48; Br, 18.01; N, 3.54%.

***anti*-(4*S*,2'*S*,3'*S*)-3-[2'-Bromo-3'-hydroxy-3'-(*p*-tolyl)-propionyl]-4-benzyloxazolidin-2-one (13c)**

$[\alpha]^{25}_{D}$: +95.63 (*c* 2.2, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3684, 3598, 3019, 2977, 2925, 2400, 1784, 1707, 1604, 1518, 1479, 1455, 1385, 1215, 1109, 1018, 928, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.82 (dd, *J* = 9.6, 13.8 Hz, 1H), 3.10-3.33 (m, 2H), 4.07-4.20 (m, 2H), 4.65-4.77 (m, 1H), 5.18 (d, *J* = 8.2 Hz, 1H), 5.91 (d, *J* = 8.8 Hz, 1H), 7.07-7.36 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.07, 36.84, 45.03, 55.03, 66.14, 74.73, 126.60, 127.05, 127.26, 128.53, 128.82, 128.96, 129.11, 129.35, 129.52, 134.61, 136.12, 138.39, 152.57, 168.84; **Analysis: $C_{20}H_{20}BrNO_4$** requires C, 57.43; H, 4.82; Br, 19.10; N, 3.35; found: C, 57.16; H, 5.09; Br, 19.41; N, 3.19%.

***anti*-(4*S*,2'*S*,3'*S*)-3-[2'-Bromo-3'-hydroxy-3'-(3,4-dimethoxyphenyl)-propionyl]-4-benzyloxazolidin-2-one (13d)**

$[\alpha]^{25}_{D}$: +97.5 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3502, 3019, 2926, 1785, 1701, 1508, 1384, 1215, 1111, 1029, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.83 (dd, *J* = 9.3, 13.3 Hz, 1H), 3.30 (dd, *J* = 3.3, 13.4 Hz, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 4.10-4.22 (m, 2H), 4.66-4.78 (m, 1H), 5.17 (d, *J* = 8.3 Hz, 1H), 5.93 (d, *J* = 8.2 Hz, 1H), 6.85-7.03 (m, 3H), 7.22-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.96, 45.15, 55.10, 55.79, 55.83, 66.20, 74.93, 109.86, 110.83, 119.61, 127.40, 128.93, 129.38, 131.56, 134.56, 148.93, 149.17, 152.57, 168.98; **Analysis: $C_{21}H_{22}BrNO_6$** requires C, 54.32; H, 4.78; Br, 17.21; N, 3.02; found: C, 54.61; H, 4.45; Br, 17.56; N, 2.75%.

***anti*-(4*S*,2'*S*,3'*S*)-3-[2'-Bromo-3'-hydroxy-3'-(4-chlorophenyl)-propionyl]-4-benzyloxazolidin-2-one (13e)**

$[\alpha]^{25}_{D}$: +1.26 (*c* 2.4, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3677, 3483, 3019, 2923, 1952, 1901,

1783, 1701, 1600, 1496, 1388, 1216, 1093, 1015, 928, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.81 (dd, *J* = 9.15, 13.6 Hz, 1H), 3.26 (dd, *J* = 3.3, 13.3 Hz, 1H), 4.08-4.21 (m, 2H), 4.59-4.76 (m, 1H), 5.19 (d, *J* = 8.4 Hz, 1H), 5.83 (d, *J* = 8.4 Hz, 1H), 7.13-7.37 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.80, 44.75, 55.01, 66.21, 74.11, 126.80, 127.32, 128.34, 128.53, 128.64, 128.84, 129.04, 129.30, 134.31, 134.46, 137.64, 152.54, 168.50; **Analysis: $C_{19}H_{17}BrClNO_4$** requires C, 52.02; H, 3.91; Br, 18.21; Cl, 8.08; N, 3.19; found: C, 51.75; H, 4.29; Br, 18.53; Cl, 8.18; N, 3.01%.

***anti*-(4*S*,2'*S*,3'*S*)-3-[2'-Bromo-3'-hydroxy-3'-(3,4,5-trimethoxyphenyl)-propionyl]-4-benzyloxazolidin-2-one (13f)**

$[\alpha]^{25}_D$: +67.33 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3608, 3019, 2400, 1783, 1701, 1594, 1509, 1463, 1422, 1384, 1327, 1215, 1129, 1046, 928, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.83 (dd, *J* = 9.3, 13.6 Hz, 1H), 3.24-3.41 (m, 2H), 3.84 (s, 3H), 3.88 (s, 6H), 4.19-4.21 (m, 2H), 4.64-4.76 (m, 1H), 5.15 (d, *J* = 7.5 Hz, 1H), 5.95 (d, *J* = 7.9 Hz, 1H), 6.67 (s, 2H), 7.22-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.82, 44.95, 54.99, 55.93, 60.60, 66.12, 75.05, 103.92, 127.29, 128.82, 129.27, 134.43, 134.72, 137.71, 152.51, 152.95, 168.72; **Analysis: $C_{22}H_{24}BrNO_7$** requires C, 53.45; H, 4.89; Br, 16.16; N, 2.83; found: C, 53.16; H, 4.58; Br, 16.42; N, 3.12%.

***anti*-(4*S*,2'*S*,3'*S*)-3-[2'-Bromo-3'-hydroxy-3'-(benzo[*d*][1,3]dioxol-5-yl)-propionyl]-4-benzyloxazolidin-2-one (13g)**

$[\alpha]^{25}_D$: +22.45 (*c* 2.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3503, 3020, 2922, 1784, 1702, 1606, 1504, 1479, 1387, 1216, 1111, 1040, 758, 667; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.86 (dd, *J* = 3.2, 9.6 Hz, 1H), 3.30 (dd, *J* = 3.3, 13.4 Hz, 1H), 4.10-4.24 (m, 2H), 4.66-4.81 (m, 1H), 5.63 (d, *J* = 6.7 Hz, 1H), 5.84 (d, *J* = 8.6 Hz, 1H), 5.98-6.01 (m, 2H), 6.79-7.02 (m,

2H), 7.22-7.36 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.96, 43.80, 45.24, 55.16, 66.26, 75.04, 112.71, 114.57, 121.12, 127.48, 128.29, 129.01, 129.45, 131.34, 132.95, 134.64, 147.88, 148.55, 152.52, 168.67; **Analysis: $C_{20}H_{18}BrNO_6$** requires C, 53.59; H, 4.05; Br, 17.83; N, 3.12; found: C, 53.31; H, 4.35; Br, 17.51; N, 3.45%.

***anti*-(4*S*,2'*S*,3'*S*)-3-[2'-Bromo-3'-hydroxy-3'-(3,4-bis(benzyloxy)phenyl)-propionyl]-4-benzyloxazolidin-2-one (13h)**

$[\alpha]^{25}_D$: +52.75 (*c* 3.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3502, 3019, 2926, 2252, 1787, 1496, 1383, 1250, 1160, 1107, 911, 794, 737; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.77 (dd, *J* = 9.5, 13.5 Hz, 1H), 3.25 (dd, *J* = 3.3, 13.5 Hz, 1H), 3.58 (br s, 1H), 4.03-4.12 (m, 2H), 4.47-4.58 (m, 1H), 5.10 (s, 2H), 5.15 (s, 2H), 5.48 (d, *J* = 7.1 Hz, 1H), 6.02 (d, *J* = 6.1 Hz, 1H), 7.09-7.44 (m, 18H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.82, 43.82, 54.94, 66.03, 71.03, 71.09, 73.32, 114.11, 114.47, 118.11, 127.21, 127.33, 127.49, 127.81, 127.95, 128.38, 128.45, 128.86, 129.37, 130.73, 134.58, 136.23, 136.52, 148.25, 149.52, 152.28, 168.40; **Analysis: $C_{33}H_{30}BrNO_6$** requires C, 64.29; H, 4.90; Br, 12.96; N, 2.27; found: C, 64.01; H, 5.21; Br, 12.69; N, 2.49%.

***anti*-(4*S*,2'*S*,3'*S*)-3-[2'-Bromo-3'-hydroxy-3'-(furan-2-yl)-propionyl]-4-benzyloxazolidin-2-one (13i)**

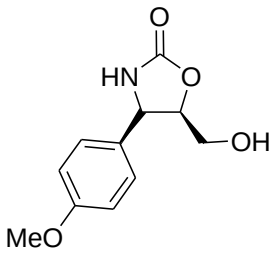
$[\alpha]^{25}_D$: +90.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3601, 3020, 2400, 1782, 1521, 1389, 1215, 1110, 1047, 928, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.79 (dd, *J* = 9.8, 13.5 Hz, 1H), 3.30 (dd, *J* = 3.4, 13.5 Hz, 1H), 4.21-4.25 (m, 2H), 4.62-4.74 (m, 1H), 5.61 (d, *J* = 7.4 Hz, 1H), 6.23 (d, *J* = 5.4 Hz, 1H), 7.26-7.38 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.68, 53.91, 53.98, 64.34, 70.23, 113.76, 122.56, 123.25, 127.96, 128.00, 128.50, 128.65, 128.88, 134.42, 139.25, 150.39, 162.11.

Section II

Enantioselective synthesis of (-)-cytoxazone using $NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides

4.2.1 Introduction

In 1998, Osada and co-workers reported the isolation of (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine-2-one [(–)-**18**, generic name cytoxazone],[1] which was shown to possess high cytokine modulator activity by acting on the Th2 cells.[11] Because of these biological properties, several total syntheses of (-)-cytoxazone (**18**) (**Fig 3)** have been reported.[12-34]



(-)-cytoxazone (18)

Fig. 3

4.2.2 Pharmacology of Cytoxazone

It is well-established that the induction of humoral or cellular response is influenced by the development of distinct subsets of $CD4^+$ T cells.[35] The Th1 cell subset produces predominately IL-2, GM-CSF, INF-γ, and TNF-β, (type 1 cytokines) and is involved in delayed-type hypersensitivity reactions, whereas the Th2 cell subset secretes IL-4, IL-5, IL-6, IL-10, and IL-13 (type 2 cytokines), which are important factors for B cell growth and differentiation to Ig secretion. The imbalance of cytokine production by $CD4^+$ T cells

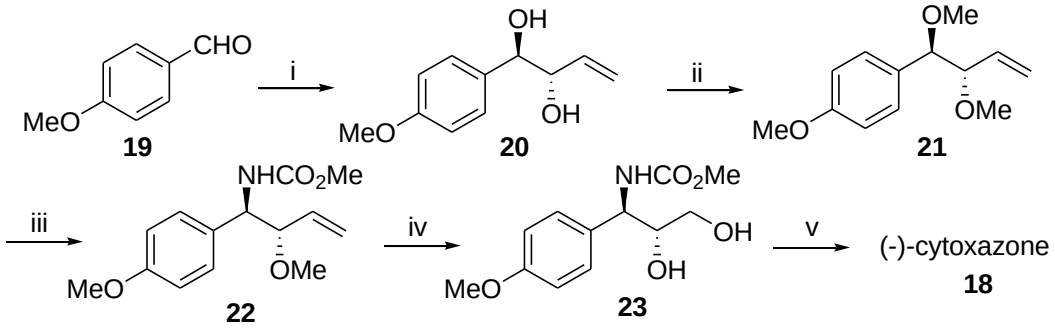
leads to a wide variety of immunological disorders, i.e. allergy, progressive lymphoproliferation, and severe immunodeficiency.[36] Skin and lung biopsies from allergic patients indicate that the pivotal cells in the allergic site are the Th2 cells.[37] Treatments effectively suppressing the function or the differentiation of these allergen-specific Th2 cells will most likely provide efficient ways to intervene in Ig-mediated allergic diseases. In the course of screening for chemical immunomodulators that inhibit the type 2 cytokine production in Th2 cells, it was found that cytoxazone (**18**) containing a 2-oxazolidinone ring, which is rare in microbial metabolites, as a novel cytokine modulator produced by *Streptomyces* sp. Cytoxazone (**18**) shows a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells.[10]

4.2.3 Review of Literature

Literature search showed that several reports are available for the synthesis of cytoxazone (**18**)[12-34] involving resolution, chemo-enzymatic or enantioselective syntheses, some of which are described below.

Jung's approach (2005)[27]

Jung *et al.* have made use of the regio- and diastereoselective introduction of a *N*-protected amine group into the key intermediate **21**. Thus the treatment of compound **21**

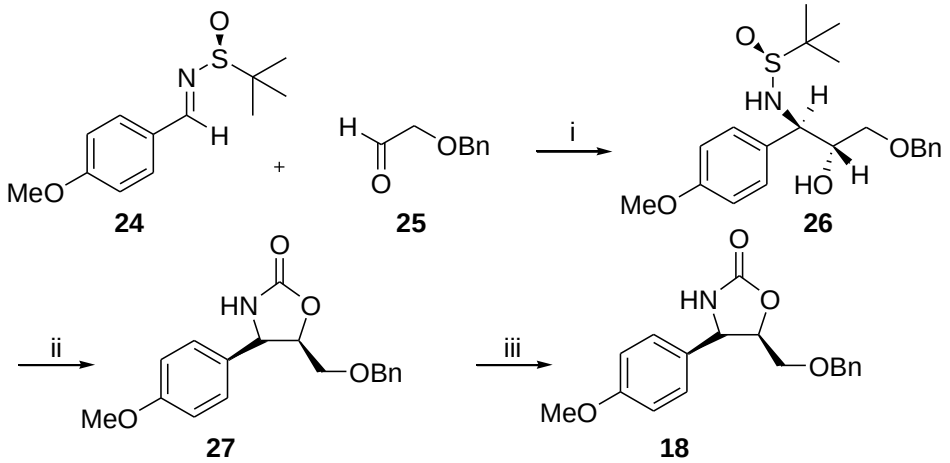


Scheme 7: (i) (a) *B*-[3-((diisopropylamino)dimethylsilyl)allyl]diisopinocampheyl borane, Et_2O, -78 ºC; (b) H_2O_2, KF, $KHCO_3$, THF-MeOH, 25 ºC, 52%; (ii) MeI, NaH, THF, 0 ºC, 96%; (iii) (a) chlorosulfonyl isocyanate, Na_2CO_3, toluene, -78 ºC; (b) Na_2SO_3, KOH, 25 ºC, 95% (dr = 27:1); (iv) (a) O_3, -78 ºC then $NaBH_4$, 0 ºC, CH_2Cl_2-MeOH, 94%; (b) BBr_3, CH_2Cl_2, 0 ºC, 80%; (v) NaH, THF, 0 ºC, 95%.

with chlorosulfonyl isocyanate (CSI) in the presence of sodium carbonate in dry toluene at -78 °C, followed by the reduction of the *N*-chlorosulfonyl group furnished the desired *anti*-1,2-amino alcohol derivative **22** with high diastereoselectivity (27:1). Ozonolysis of the double bond and intramolecular cyclization of **23** using NaH finally gave (-)-cytoxazone (**18**) in 95% yield (**Scheme 7**).

Bentley's approach (2005)[29]

Bentley *et al.* have made use of stereoselective cross-coupling of phenyl imine auxiliary **24** and aldehyde **25** in presence of samarium iodide to obtain the corresponding aminoalcohol **26**. Removal of chiral auxiliary and cyclization using triphosgene gave **27**, which on debenzylation afforded (-)-cytoxazone (**18**) (**Scheme 8**).

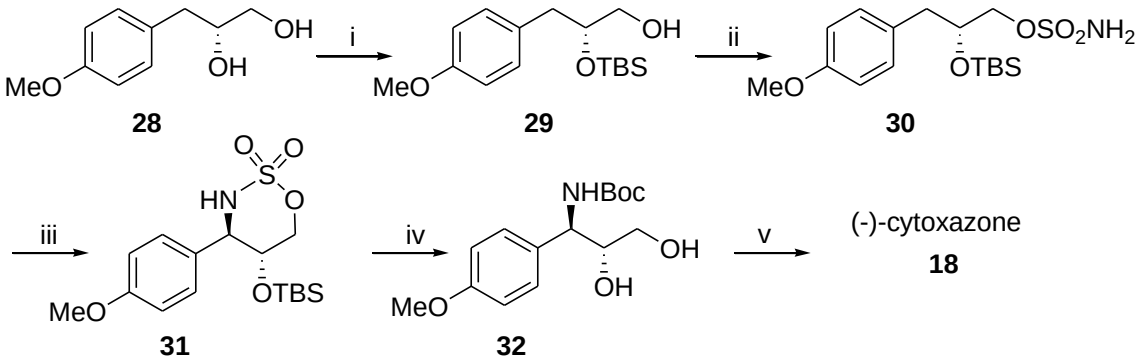


Scheme 8: (i) SmI_2, ^tBuOH, THF, -78 ºC, 83%; (ii) (a) HCl, MeOH, 25 ºC; (b) triphosgene, Et_3N, CH_2Cl_2, 25 ºC, 85%; (iii) $Pd(OH)_2/C$, H_2, MeOH, 86%.

Sudalai's approach (2006)[32]

Sudalai *et al*. have developed a simple method for the enantioselective synthesis of (-)-cytoxazone (**18**) commencing from the diol **28** obtained by two different routes: hydrolytic kinetic resolution and proline-catalyzed α-aminooxylation. Diol **28** was converted to *bis*-TBS-protected silyl ether followed by selective deprotection of the

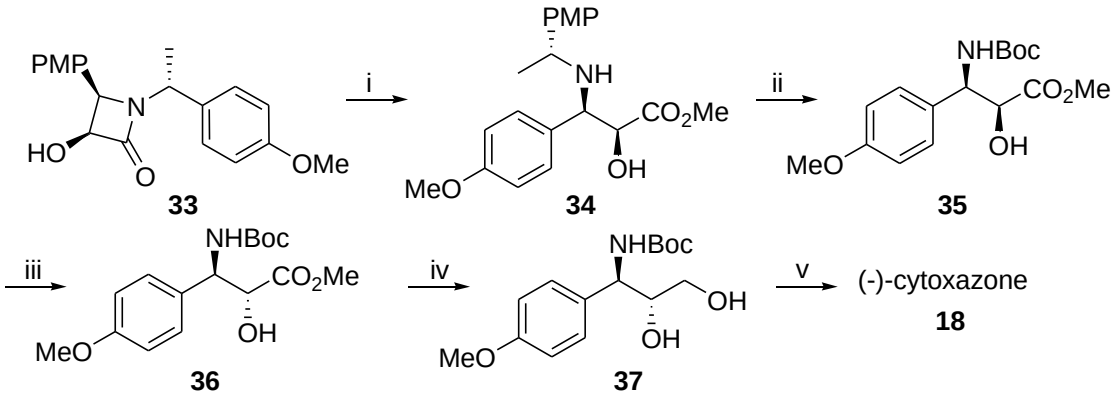
primary OH group with camphorsulfonic acid to afford **29** which was converted into sulfamate ester **30** in 76% yield using HCO_2H and chlorosulfonyl isocyanate. The γ-C-H insertion of **30** was carried out with a catalytic amount of $Rh_2(OAc)_4$ (2 mol%), $PhI(OAc)_2$ and MgO in CH_2Cl_2 to give sulfamate ester **31** with *anti* (10:1) diastereoselectivity. The TBS deprotection, carbamoylation and ring opening of *N*-Boc protected oxathiazinane furnished the *anti*-amino alcohol **32** in 84% which was converted to (-)-cytoxazone (**18**) by intramolecular cyclization using NaH in THF (**Scheme 9**).



Scheme 9: (i) (a) TBSCl, imidazole, DMF, 25 °C, 4 h, 98%; (b) camphorsulfonic acid, MeOH, 95%; (ii) HCO_2H, chlorosulfonyl isocyanate, 0 °C, 76%; (iii) 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 2 h, 82%, *anti*:*syn* (10:1); (iv) (a) camphorsulfonic acid, MeOH, 25 °C, 1 h, 97%; (b) (a) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 25 °C, 1 h; (c) CH_3CN:H_2O (4:3), 60 °C, 4 h, 84%; (v) NaH, THF, 0 °C, 1 h, 96%.

Turos's approach (2007)[33]

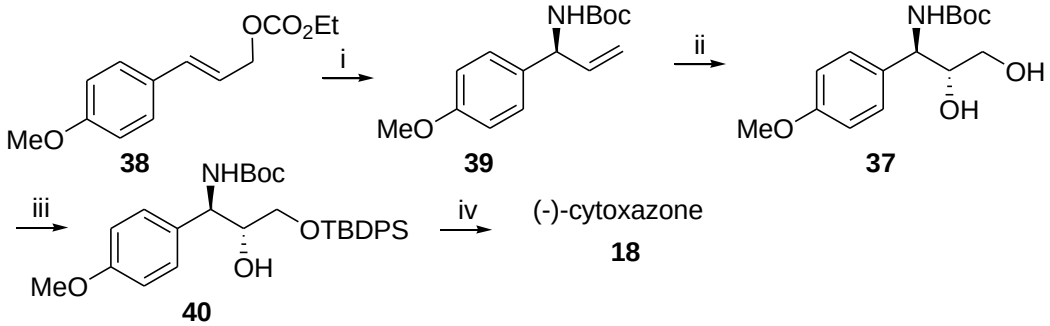
Turos *et. al.* have reported the synthesis of (-)-cytoxazone (**18**) starting with methanolysis of the optically pure hydroxyl lactam **33** with TMSCl and MeOH to give the *syn*-amino alcohol **34**. The amino alcohol **34** was then subjected to catalytic hydrogenation and subsequent protection of the corresponding amine as its carbamate followed by Mitsunobu reaction of the product to give *anti*-amino alcohol **36**. Reduction of **36** using $NaBH_4$ followed by its cyclization under NaH in THF conditions afforded (-)-cytoxazone (**18**) in 92% yield (**Scheme 10**).



Scheme 10: (i) TMSCl, MeOH, reflux, 12 h, 92%; (ii) (a) H_2, $Pd(OH)_2/C$, MeOH, 23 °C, 12 h; (b) Boc_2O, $NaHCO_3$, MeOH, sonication, 23 °C, 6 h, 80%; (iii) (a) PPh_3, DIAD, 4-nitrobenzoic acid, THF, 0 °C to 23 °C, 6 h, 70%; (b) Et_3N, THF, 23 °C, 1 h, 98%; (iv) $NaBH_4$, MeOH, 0 °C to 23 °C, 4 h, 85%; (v) NaH, THF, 0 °C to 23 °C, 2 h, 92%.

Han's approach (2007)[34]

Hans *et. al.* have described the synthesis of (-)-cytoxazone (**18**) by employing the allylic amidation of carbonate **38** with Ir, chiral phosphoramidite and *N*-acetyl *N*-*tert*-butyl carbamate in presence of DBU followed by treatment with K_2CO_3 and MeOH to provide allylation product **39**. The Sharpless dihydroxylation of the allylic amine gave the *anti*/*syn* diols in a ratio 7:3 which were not separable. After protection of the primary alcohol as its silyl ether, the diastereomers were, however, separated followed by its conversion to (-)-cytoxazone (**18**) on cyclization using NaH and THF coupled with silyl deprotection with TBAF (**Scheme 10**).



Scheme 11: (i) (a) Ir (I), phosphoramidite ligand, DBU, *N*-acetyl *N*-*tert*-butyl carbamate, THF, 50 °C; (b) K_2CO_3, MeOH, 25 °C, 0.5 h, 92%, 99% ee; (ii) OsO_4, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH-H_2O, 95%; (iii) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, 97%; (iv) (a) NaH, THF; (b) TBAF, THF, 94%.

4.2.4 Present Work:

4.2.4.1 Objective

Literature search revealed that several methods such as classical resolution, chemo-enzymatic or enantioselective synthesis have been reported for the synthesis of (-)-cytoxazone (**18**).[12-34] However, these methods suffer from many disadvantages such as low overall yields, the need for separation of diastereomers and the use of expensive chiral reagents. The synthetic precursors of (-)-cytoxazone (**18**) is 1,2-aminoalcohols, which have been the subject of thorough synthetic efforts in recent years.[38] Most of the syntheses for cytoxazone (**18**) have made use of indirect methods to establish the *anti*-amino alcohol functionality. In this context, a more practical method for the synthesis of (-)-cytoxazone (**18**) is highly desirable.

Retrosynthetic analysis (**Fig. 4**) for (-)-cytoxazone (**18**) reveals that *anti*-amino alcohol **37** could be visualized as the key intermediate. The *anti*-isomer **37** could be prepared from bromohydrin **13b** obtained by the $NaIO_4$-mediated asymmetric bromohydroxylation of carboxamides (see Section I).

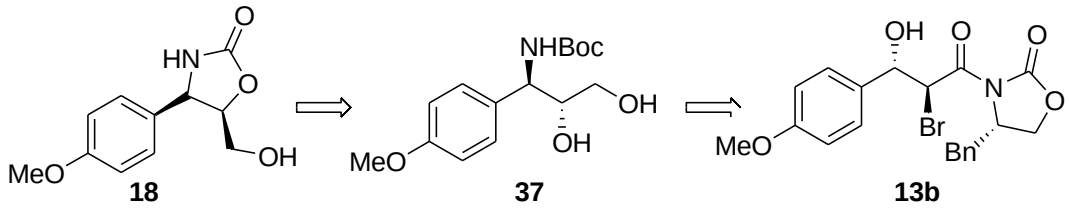
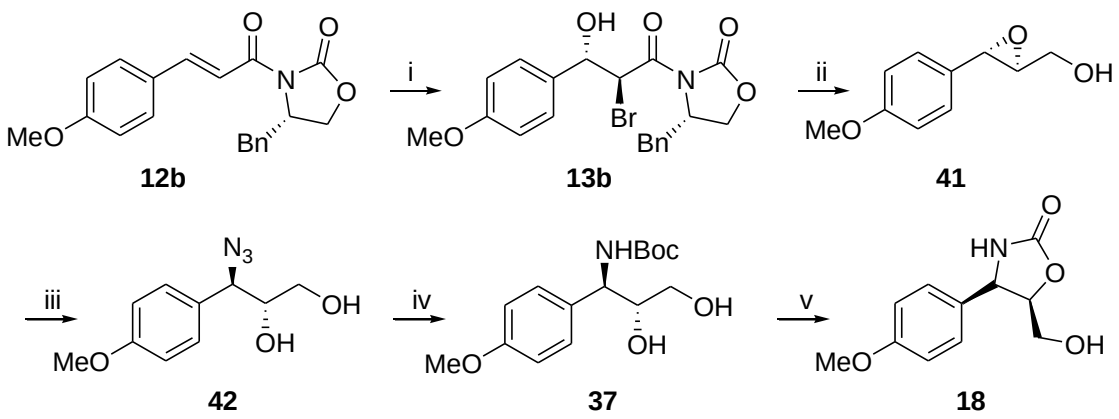


Fig. 4: Retrosynthetic analysis of (-)-cytoxazone (18)

4.2.5 Results and Discussion

The complete synthetic sequence for (-)-cytoxazone (**18**), wherein $NaIO_4$-mediated asymmetric bromohydroxylation of carboxamides constitutes a key step for the introduction of chirality, is presented in **Scheme 12**.



Scheme 12: (i) $NaIO_4$ (30 mol%), LiBr, H^+, CH_3CN:H_2O (2:1), 25 °C, 1 h, 82%; (ii) $LiBH_4$, Et_2O, THF, MeOH, 0 °C, 1.5 h then 10% NaOH, 25 °C, 86%; (iii) NaN_3, NH_4Cl, MeOH, H_2O, 80 °C, 3 h, 84%; (iv) (a) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 25 °C, 2 h, 77% (2 steps); (v) NaH, THF, 25 °C, 2 h, 89%, 99% ee.

Our synthesis of (-)-cytoxazone (**18**) was started with $NaIO_4$-mediated asymmetric bromohydroxylation of carboxamide **12b** with LiBr in acidic medium to produce the bromohydrin **13b** with excellent diastereoselectivity (dr = 10:1) and 82% isolated yield.

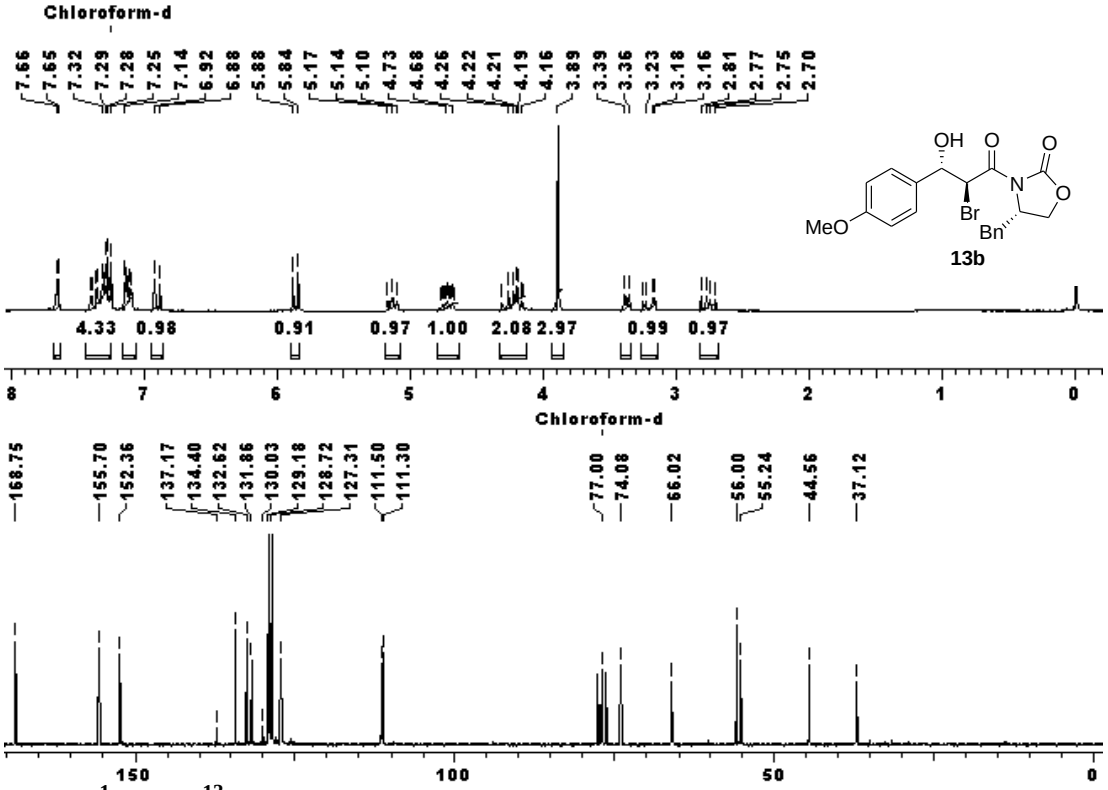


Fig. 5: ^{1}H and ^{13}C NMR spectra of bromohydrin 13b

The ^{1}H and ^{13}C NMR spectra of **13b** were in accordance with its proposed structure (**Fig. 5**). The chiral auxiliary in **13b** was removed by reduction with $LiBH_4$ followed by treatment with 10% NaOH[39] to give the epoxy alcohol **41** in 86% yield; $[\alpha]^{25}_{D}$ = -12.5 (*c* 1.1, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra of **41** confirmed the disappearance of chiral auxiliary. The epoxide carbons have displayed typical signals at δ 56.23 and 62.26 in its ^{13}C NMR spectrum (**Fig. 6**).

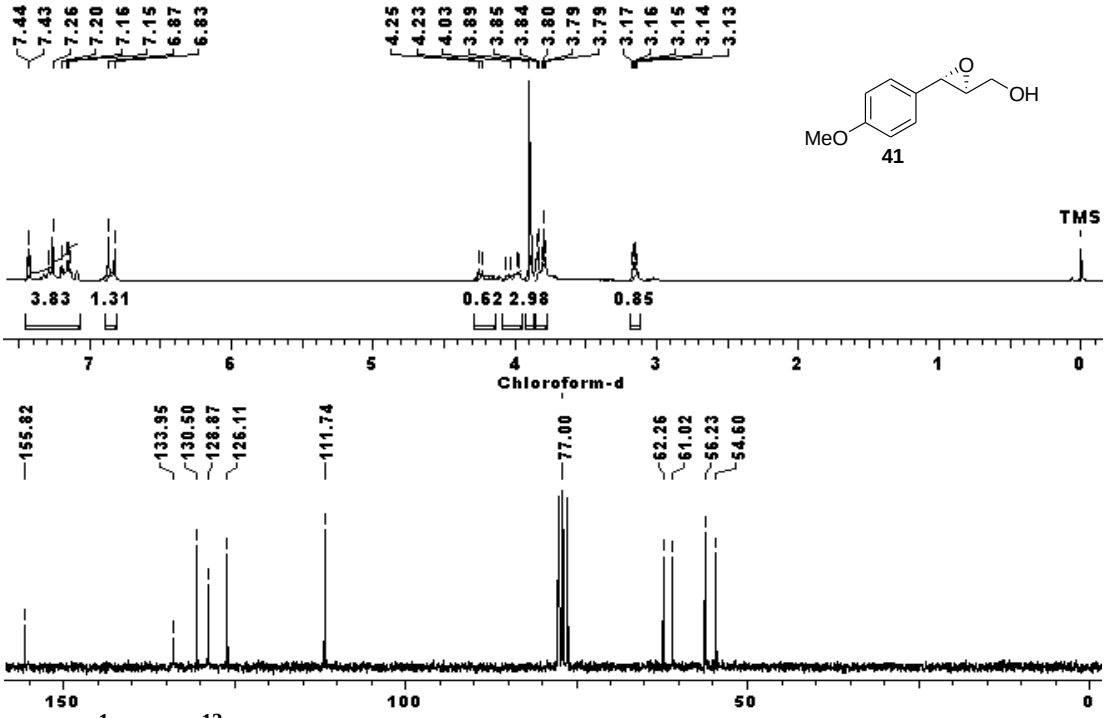


Fig. 6: ^{1}H and ^{13}C NMR spectra of epoxy alcohol 41

The regiospecific opening[40] of epoxide **41** with azide was carried out with NaN_3 and

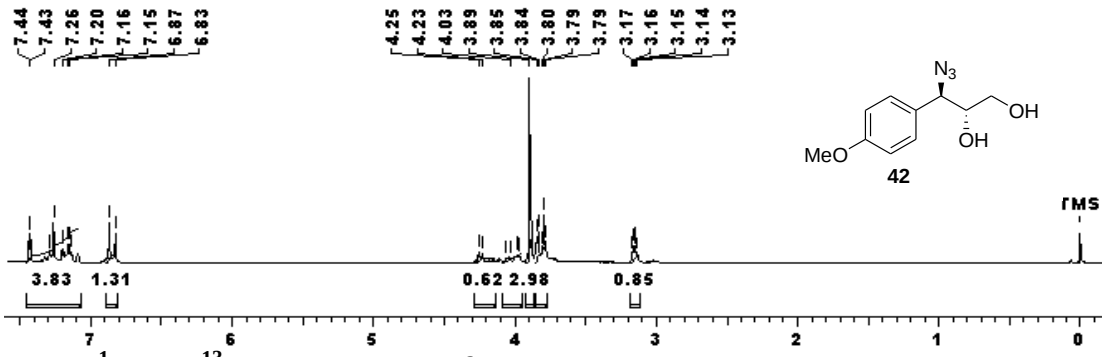


Fig. 7: ^{1}H and ^{13}C NMR spectra of azido diol 42

NH_4Cl in MeOH to produce azido alcohol **42** in 84% yield. The ^1H NMR spectrum confirmed the formation of azido alcohol **42** (**Fig. 7**). Its IR spectrum displayed a characteristic strong azide band at 2107 cm^{-1}. Catalytic hydrogenation of azide **42** gave the corresponding amine which was immediately protected as its carbamate **37** on treatment with $(Boc)_2O$ and Et_3N in CH_2Cl_2. The formation of carbamate **37** was confirmed by the appearance of a singlet at δ 1.41 integrating for nine protons [-NHC(O)OC(C**H**$_3$)$_3$] in its ^1H NMR spectrum which was further supported by the Boc-carbon signals appearing at δ 28.87 [-NHC(O)OC(**C**H_3)$_3$], 80.24 [-NHC(O)O**C**$(CH_3)_3$] and 159.20 [-NH(**C**=O)-] in its ^{13}C NMR spectrum (**Fig. 8**).

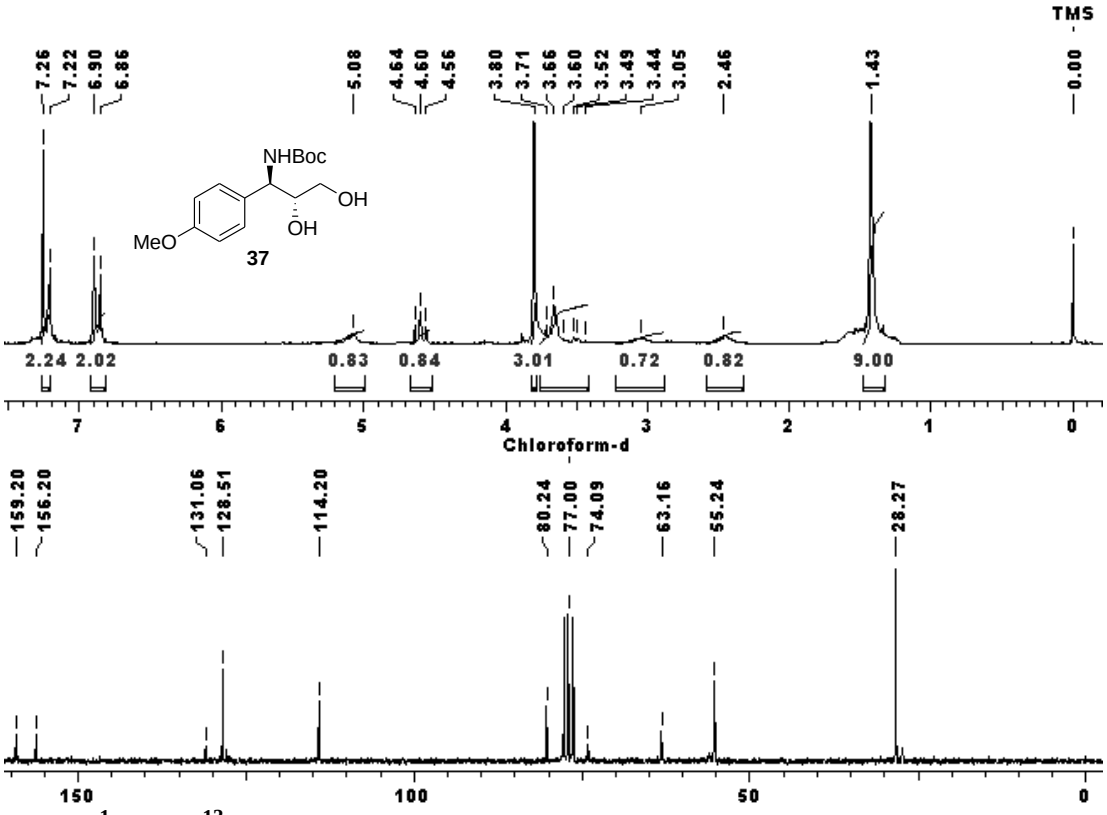
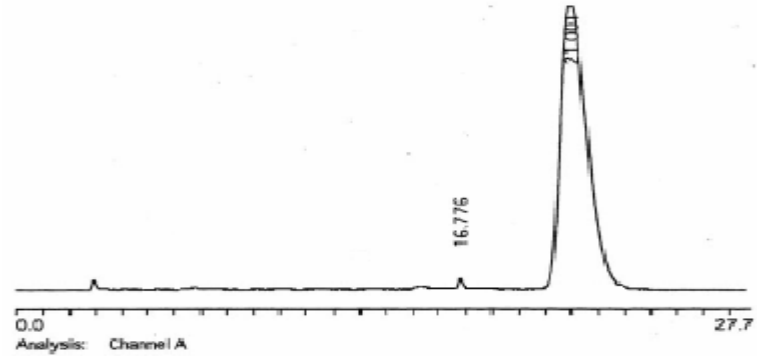


Fig. 8: ^1H and ^{13}C NMR spectra of amino alcohol 37

The carbamate **43** was converted to (-)-cytoxazone (**18**) by treating it with NaH in THF at 25 °C to give the target molecule in 89% yield and 99% ee; $[\alpha]^{25}_D$ = -71 (*c* 1, MeOH);

{lit.[10] $[\alpha]^{25}_{D}$ = -71 (*c* 1, MeOH)}. The optical purity of (-)-cytoxazone, **18** was determined by chiral HPLC analysis using Chirasphere® column (**Fig. 9**).



Peak No.	Retention Time	Area (µV-sec)	Area (%)
1	16.776	10795	0.699
2	21.001	1531408	99.300

Fig. 9: HPLC chromatogram of (-)-cytoxazone (18)

The NH-proton of oxazolidinone in (-)-cytoxazone (**18**) have appeared as a broad peak at δ 7.92 in its ^{1}H NMR spectrum. The signal at δ 160.09 in its ^{13}C NMR spectrum confirmed the presence of oxazolidinone carbonyl moiety (**Fig. 10**).

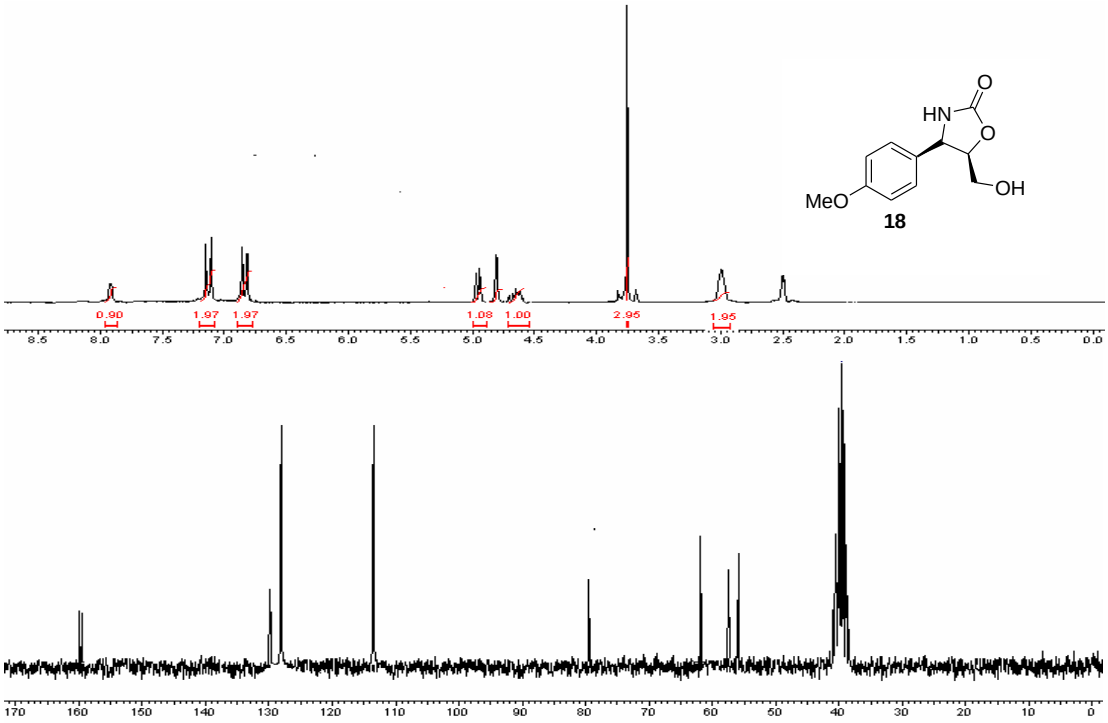


Fig. 10: ^{1}H and ^{13}C NMR spectra of (-)-cytoxazone (18)

4.2.6 Conclusion

A short and efficient enantioselective synthesis of (-)-cytoxazone has been achieved in five linear steps with 41% overall yield and 99% ee. The $NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamide **12b** giving high diastereoselectivity (10:1), constituted a key reaction in this synthesis.

4.2.7 Experimental Section

[(2*S*,3*S*)-3-(4-Methoxyphenyl)oxiran-2-yl]methanol (41)

Oxazolidinone **13b** (1.3 g, 3.5 mmol) and anhydrous methanol (0.17 mL, 4.2 mmol) in 30 mL diethyl ether were stirred and cooled to 0 ºC. Lithium borohydride (2.0 M in THF, 2.2 mL, 4.2 mmol) was added dropwise *via* syringe. After stirring for 1.5 h the reaction was quenched by the dropwise addition of 15 mL of 10% NaOH and warmed to 25 °C. After 20 min, the reaction was extracted with ethyl acetate (2 × 100 mL), combined organic layers were dried over anhyd. Na_2SO_4 and purified by silica gel column chromatography using petroleum ether/ethyl acetate (6:4) to afford the product epoxy alcohol **41** (0.54 g) as a gum.

Yield: 86%; **$[\alpha]^{25}_{D}$**: -12.45 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3488, 3019, 2928, 2400, 1603, 1498, 1440, 1259, 1216, 1055, 928, 757; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.13-3.17 (m, 1H), 3.79-3.85 (m, 2H), 3.89 (s, 3H), 3.97-4.06 (m, 1H), 4.24 (d, *J* = 4.6 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 7.13-7.29 (m, 2H), 7.44 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.60, 56.23, 61.02, 62.26, 111.74, 126.11, 128.87, 130.50, 133.95, 155.82; **Analysis: $C_{10}H_{12}O_3$** requires C, 66.65; H, 6.71; found: C, 66.37; H, 7.01%.

(2*R*,3*R*)-3-Azido-3-(4-methoxyphenyl)propan-1,2-diol (42)

To a solution of NaN_3 (0.29 g, 4.5 mmol) and NH_4Cl (0.16 g, 3 mmol) in H_2O (7 mL)

was added the epoxy alcohol **41** (0.27 g, 1.5 mmol) in MeOH (7 mL). The mixture was stirred at 80 ºC. The reaction was monitored by TLC. After completion of the reaction, solvent was evaporated and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with water, brine, dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. Purification by silica gel column chromatography using petroleum ether/ethyl acetate (6:4) afforded the azido diol **42** (0.28 g) as a gum.

Yield: 84%; **[α]$^{25}_{D}$**: +108.2 (*c* 2.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3685, 3602, 3019, 2929, 2400, 2107, 1603, 1499, 1422, 1264, 1216, 1055, 929, 757, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.61-3.74 (m, 3H), 3.90 (s, 3H), 4.48 (d, *J* = 6.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 7.22-7.28 (m, 2H), 7.54 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.29, 63.16, 66.25, 74.49, 111.90, 128.38, 132.85, 135.94, 156.19; **Analysis: $C_{10}H_{13}O_3N_3$** requires C, 53.80; H, 5.87; N, 18.82; found: C, 53.62; H, 5.76; N, 19.15%.

***tert*-Butyl(1*R*,2*R*)-2,3-dihydroxy-1-(4-methoxyphenyl)propylcarbamate (37)**

The azido alcohol **42** (0.22 g, 1 mmol) was dissolved in methanol (5 mL) and a catalytic amount of 10% Pd/C was added to it. The resulting mixture was stirred overnight under hydrogen atmosphere at 25 °C. The mixture was then filtered through a pad of celite and the solvent was removed under reduced pressure. The crude compound was taken up in CH_2Cl_2 (5 mL), Et_3N was added followed by $(Boc)_2O$ (0.33 g, 1.5 mmol). The reaction mixture was stirred until the starting material disappeared and the mixture extracted with CH_2Cl_2. The organic layer was washed with water, brine, dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. Purification by silica gel column chromatography using petroleum ether/ethyl acetate (4:6) afforded **37** (0.23 g) as a colorless solid.

Yield: 77%; **mp**: 116 ºC; **[α]$^{25}_{D}$**: -51.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3682, 3438, 3019,

2981, 2839, 2400, 1701, 1612, 1585, 1509, 1392, 1368, 1216, 1167, 1035, 927, 831, 757, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.46 (br s, 1H), 3.05 (br s, 1H), 3.44-3.71 (m, 3H), 3.80 (s, 3H), 4.60 (t, *J* = 7.9 Hz, 1H), 5.08 (br s, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.27, 55.24, 63.16, 74.09, 80.24, 114.20, 128.51, 131.06, 156.20, 159.20; **Analysis: $C_{15}H_{23}NO_5$** requires C, 60.59; H, 7.80; N, 4.71; found: C, 60.31; H, 8.09; N, 4.60%.

(4*R*,5*R*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one (18)

To a solution of the amino alcohol **37** (0.15 g, 0.5 mmol) in dry THF (5 mL) was added NaH [0.024 g, 1 mmol (60% w/w in wax)] at room temperature and the mixture was stirred under nitrogen atmosphere for 2 h. The reaction mixture was concentrated, extracted with CH_2Cl_2, washed with saturated NH_4Cl, brine and dried over anhyd. Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography using petroleum ether/ethyl acetate (3:7) to afford (-)-cytoxazone, **18** (0.10 g) as a colorless solid.

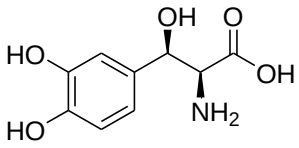
Yield: 89%; **mp**: 118-121 ºC (lit.[10] **mp**: 118-121 ºC); **$[\alpha]^{25}_{D}$**: -71 (*c* 0.5, MeOH) {lit.[10] **$[\alpha]^{25}_{D}$**: -71 (*c* 1, MeOH)}; **HPLC**: 99% ee, Chirasphere®, λ = 254 nm, 5% 2-propanol/hexane, 1 mL/min., Retention time: (*S*,*S*) 16.776 min, (*R*,*R*) 21.001 min; **IR** ($CHCl_3$, cm^{-1}): 3745, 3325, 2975, 1739, 1514, 1400, 1250, 1181, 1050; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.95-2.97 (m, 2H), 3.75 (s, 3H), 4.62–4.73 (m, 1H), 4.82 (t, *J* = 5.1 Hz, 1H), 4.90 (d, *J* = 4.37 Hz, 1H), 6.91 (d, *J* = 8.76 Hz, 2H), 7.15 (d, *J* = 8.46 Hz, 2H), 8.02 (br s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 55.17, 56.82, 61.93, 80.48, 113.79, 128.17, 129.45, 158.81, 160.09; **Analysis: $C_{11}H_{13}NO_4$** requires C, 59.19; H, 5.87; N, 6.27; found: C, 58.88; H, 6.09; N, 6.14%.

Section III

Enantioselective synthesis of L-*threo*-DOPS (droxidopa) using $NaIO_4$-mediated asymmetric bromohydroxylation of α, β-unsaturated carboxamides

4.3.1 Introduction

L-*threo*-DOPS [(2*S*,3*R*)-(3,4-dihydroxyphenyl)-serine) [(**43**), generic name: droxidopa] is beneficial in treating disorders of both the central and sympathetic nervous systems. For example, orthostatic hypotension, characterized by adrenergic deficiency and certain symptoms of Parkinson's disease can be alleviated by treatment with L-*threo*-DOPS.[41] In spite of its important biological activitites a very few reports are available in the literature[42-43] for the asymmetric synthesis of L-*threo*-DOPS (**43**).



droxidopa (43)

Fig. 11

4.3.2 Pharmacology of L-*threo*-DOPS

The final step in the biosynthesis of norepinephrine, an important neurotransmitter of the sympathetic and central nervous systems, is enzymatic side-chain hydroxylation of dopamine. Recently, much attention has been focused on (2*S*,3*R*)-(3,4-dihydroxyphenyl)-serine (L-*threo*-DOPS, **43**) as a possible alternative biological precursor of norepinephrine that would be independent of dopamine biosynthesis, since enzymatic decarboxylation would produce norepinephrine directly. In addition to potential activity

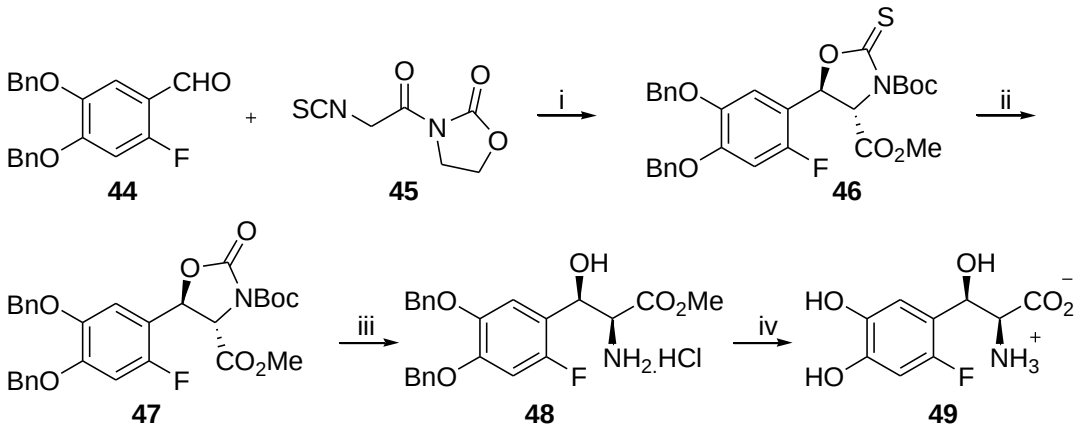
in the periphery,[45] there is substantial evidence that administered L-*threo*-DOPS crosses the blood-brain barrier and is subsequently decarboxylated to produce norepinephrine in the central nervous system.[45,46] In fact, several clinical trials suggest that it is beneficial in treating disorders of both the central and sympathetic nervous systems.

4.2.3 Review of Literature

Literature search showed that there are only few reports available,[42-44] which describe the synthesis of L-*threo*-DOPS (**43**) as detailed below.

Kirk's approach (2001)[43]

Kirk *et. al* have reported the synthesis of fluorinated analogue of L-*threo*-DOPS (**49**) starting from reaction of aldehyde **44** with isothiocyanate **45** in presence of LHMDS and $Sn(OTf)_2$ to give ester **46** with d.r = 8.5:1. Subsequently, removal of chiral auxiliary with methoxymagnesium bromide followed by Boc protection of the thiocarbamate nitrogen was carried out. Thiocarbamate **46** was then converted to oxygen analogue **47** in 96% yield by treating it with $Hg(OAc)_2$. This was followed by subsequent cleavage of **47** using Cs_2CO_3 and its Boc depotection gave the ester **48**. Saponification of ester **48** followed by hydrogenation afforded fluoro analogue of L-*threo*-DOPS (**49**) (**Scheme 13**).



Scheme 13: (i) (a) LiHMDS, $Sn(OTf)_2$, THF -78 °C, 72%, d.r. = 8.5:1; (ii) (b) MeOMgBr, THF, MeOH, 88%; (c) Boc_2O, DMAP, CH_2Cl_2, 86%; (ii) $Hg(OAc)_2$, CH_2Cl_2, 96%; (iii) (a) Cs_2CO_3, MeOH, 83%; (b) HCl, EtOAc, 72%; (iv) (a) NaOH, MeOH, H_2O, 96%; (b) H_2, Pd/C, 94%.

Sang-Ho's approach (2007)[44]

Sang-Ho *et. al* have achieved an enzyme-catalyzed synthesis of L-*threo*-DOPS (**43**) by reacting in one-pot glycine, 3,4-dihydrobenzaldehyde, 2-mercaptoethanol, pyridoxal-5-phosphate solution, sodium sulfite and Triton X-100 in presence of *E.coli* at 15 °C.

4.3.4 Present Work:

4.3.4.1 Objective

Literature search revealed that there are only few reports available for the synthesis of L-*threo*-DOPS (**43**) which mainly involved the synthesis of its analogue or the use of enzymatic methods to prepare the target molecule. Owing to its important biological activity, a more practical and enantioselective method for the synthesis of L-*threo*-DOPS (**43**) is highly desirable.

Retrosynthetic analysis (**Fig. 12**) reveals that β-hydroxy acid (**53**) could be the key intermediate for the synthesis of L-*threo*-DOPS (**43**). The β-hydroxy acid (**53**) can be obtained from bromohydin **51**, easily accessible from the corresponding carboxamide by $NaIO_4$-mediated asymmetric bromohydroxylation.

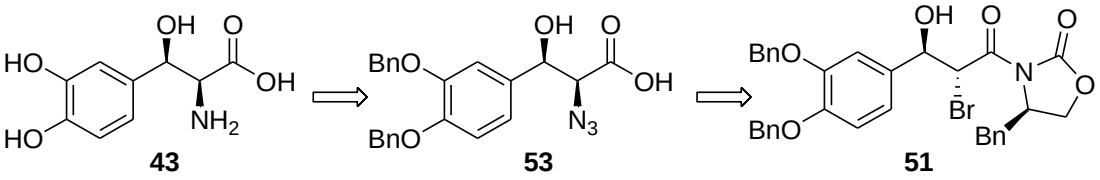
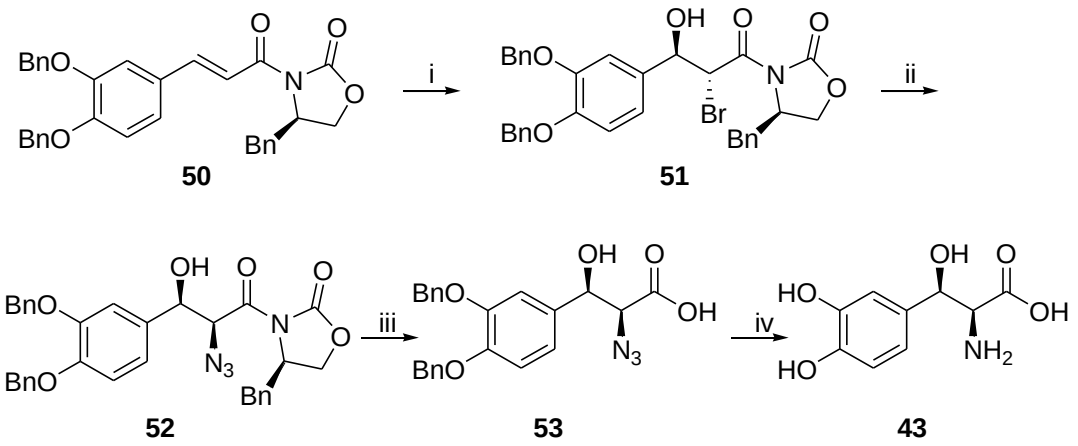


Fig. 12: Retrosynthetic analysis of L-*threo*-DOPS (43)

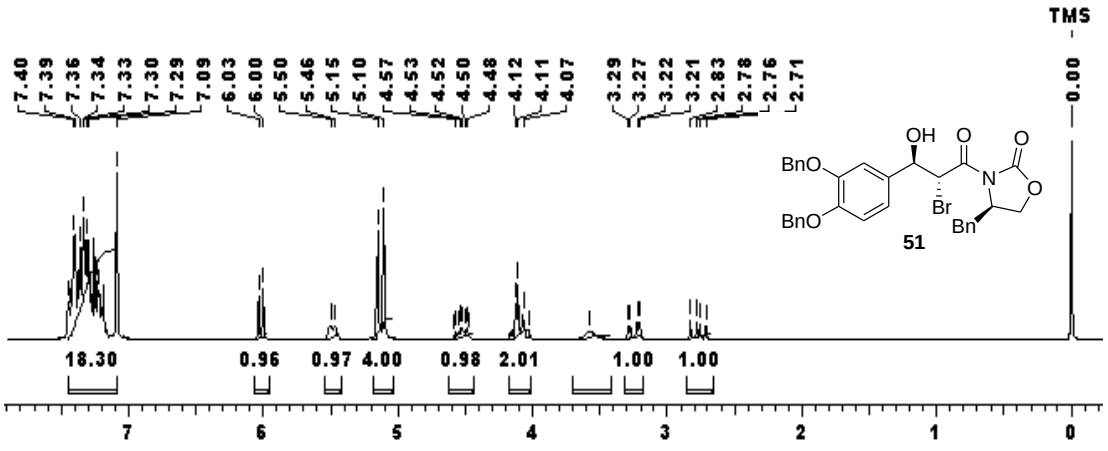
4.3.5 Results and Discussion

The complete synthetic sequence for L-*threo*-DOPS (**43**), wherein $NaIO_4$-mediated asymmetric bromohydroxylation of carboxamides constitutes a key step for the introduction of chirality, is presented in **Scheme 14**.



Scheme 14: (i) $NaIO_4$ (30 mol%), LiBr, H^+, CH_3CN:H_2O (2:1), 25 °C, 1 h, 75%; (ii) NaN_3, DMF, 60 °C, 4 h, 82%; (iii) LiOH, 30% H_2O_2, THF, H_2O, 0 °C, 2 h, 88%; (iv) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h, 94%.

Our synthesis of droxidopa, **43** was started with the carboxamide **50**, prepared from (*R*)-phenylalanine.[8] Carboxamide **50** was subjected to $NaIO_4$-mediated oxidative bromohydroxylation with LiBr under acidic medium to produce bromohydrin **51** with the ratio dr = 6:1 and 82% isolated yield; $[\alpha]^{25}_D$ = -52.75 (*c* 3.0, $CHCl_3$). The ^1H and ^{13}C NMR spectra were in accordance with the proposed structure of **51** (**Fig. 13**).



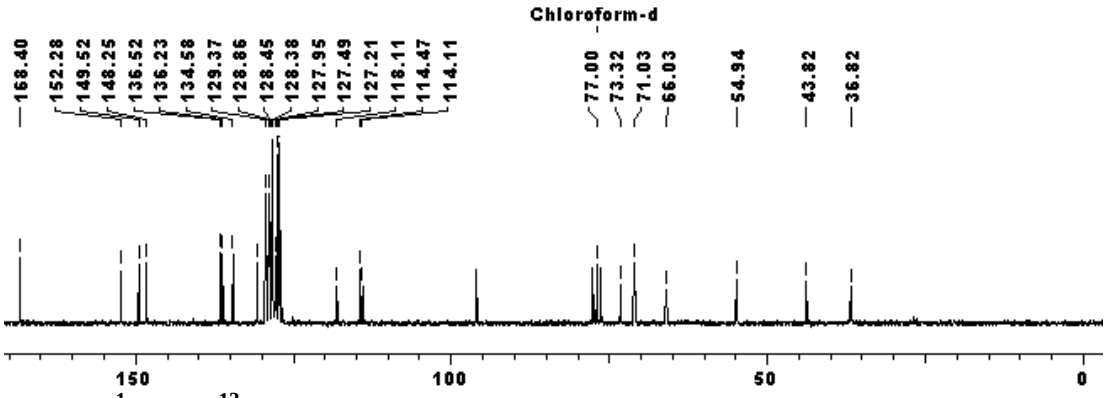


Fig. 13: ^{1}H and ^{13}C NMR spectra of bromohydrin 51

Nucleophilic displacement of bromide group in **51** with sodium azide in DMF furnished the azido alcohol **52** in 82% yield; $[\alpha]^{25}_{D}$ = -17 (*c* 1, $CHCl_3$). The ^{13}C NMR spectrum of **52** displayed two carbonyl peaks at δ 152.46 and 168.70 confirming its structure (**Fig. 14**).

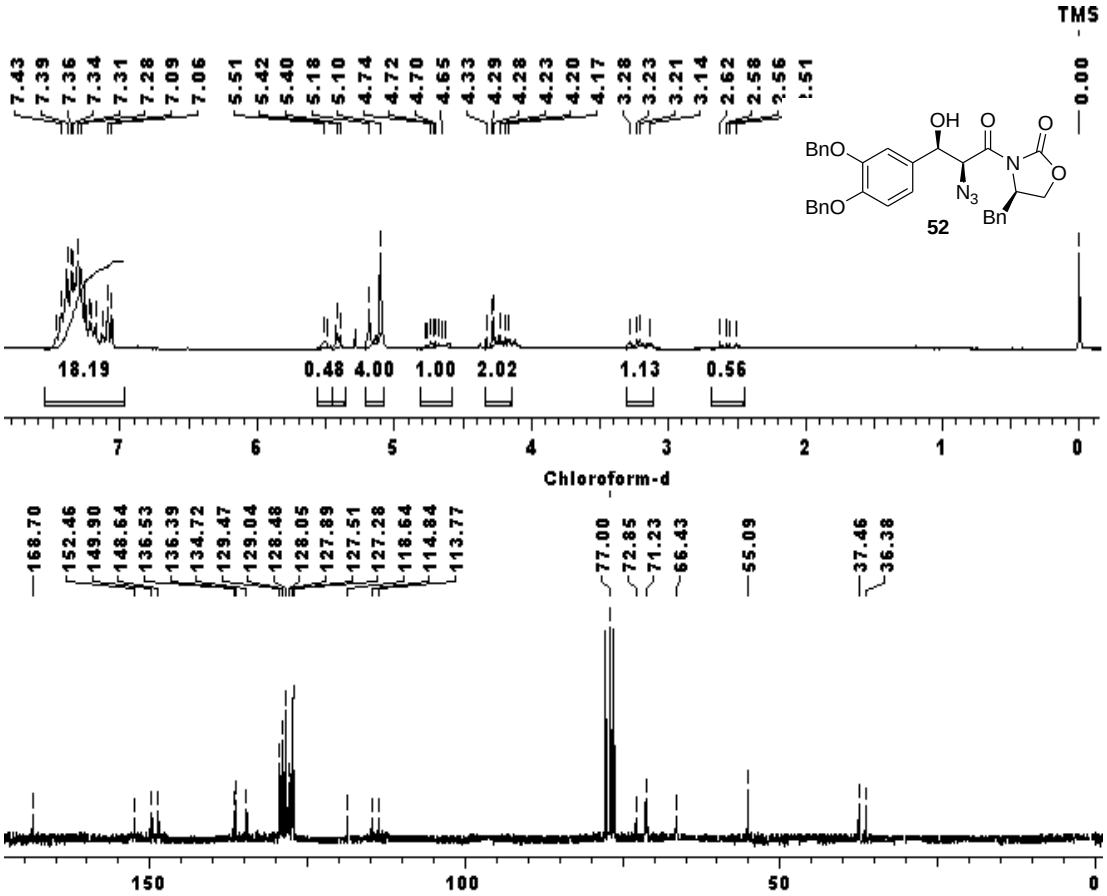


Fig. 14: ^{1}H and ^{13}C NMR spectra of azido alcohol 52

Removal of the chiral auxiliary in **52** was achieved using LiOH and 30% H_2O_2[47] to provide the carboxylic acid **53** in 88% yield. The ^1H and ^{13}C NMR spectra of **53** confirmed the absence of chiral auxiliary (**Fig. 15**). The methine protons attached to azide and hydroxyl group resonated at δ 4.52 (d, *J* = 3.8 Hz, 1H) and 5.27 (m, 1H) respectively in the ^1H NMR spectrum which was further substantiated by the appearance of carbonyl carbon [-(**C**=O)-OH] signal at δ 174.39 in its ^{13}C NMR spectrum.

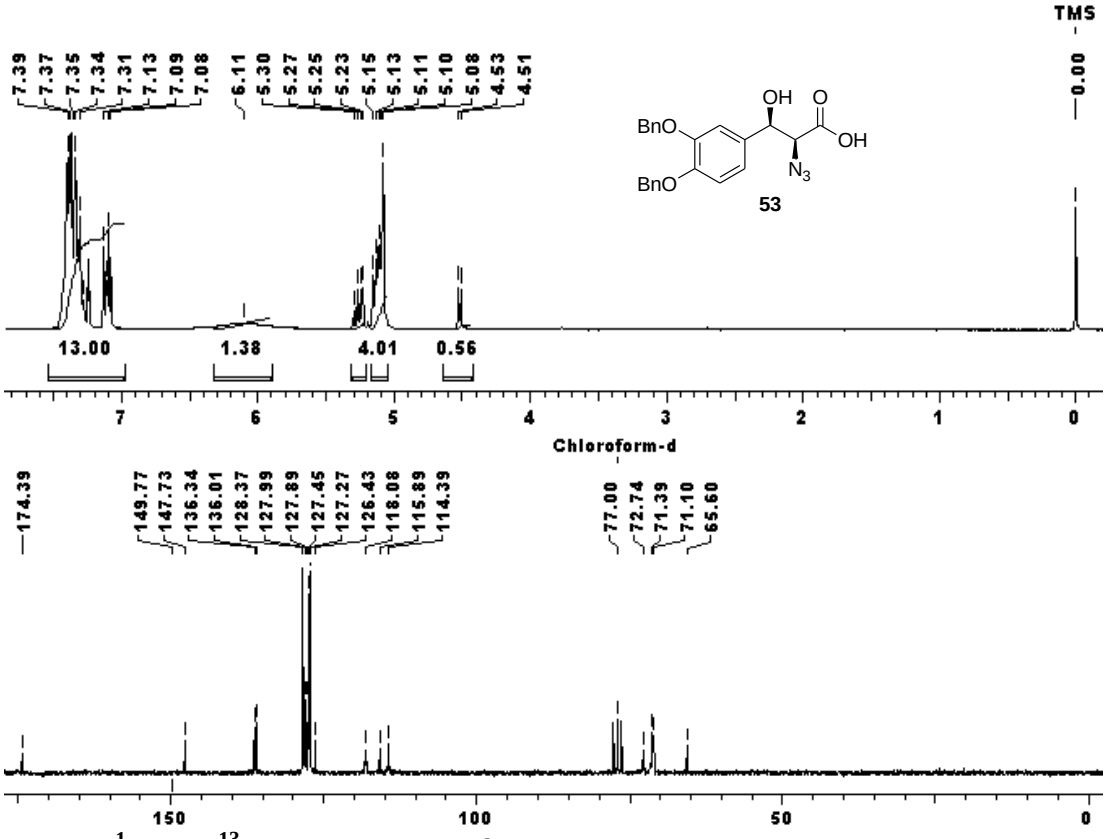


Fig. 15: ^1H and ^{13}C NMR spectra of azido alcohol 53

Azide reduction as well as deprotection of the benzyl groups were done with 10% Pd/C, H_2 (1 atm) in MeOH to afford L-*threo*-DOPS **43** in 94% yield and 99% ee. The enantiomeric excess was calculated by comparing the optical rotation of target molecule with reported value; mp: 232-233 ºC (lit.[42] mp: 232-235 ºC); $[\alpha]^{25}_D$ = -38.7 (*c* 0.4, 1N HCl) {lit.[42] $[\alpha]^{25}_D$ = -39 (*c* 0.4, 1N HCl)}. The formation of L-*threo*-DOPS **43** was

confirmed by the appearance of two doublets at δ 4.23 (d, *J* = 4.3 Hz, 1H) and 5.10 (d, *J* = 3.8 Hz, 1H) corresponding to the homobenzylic and benzylic protons in its ^{1}H NMR spectrum. The corresponding methine carbons resonated at δ 55.41 and 70.70 ppm whereas the carbonyl carbon of the acid **43** gave signal at δ 171.91 ppm in its ^{13}C NMR spectrum (**Fig. 16**).

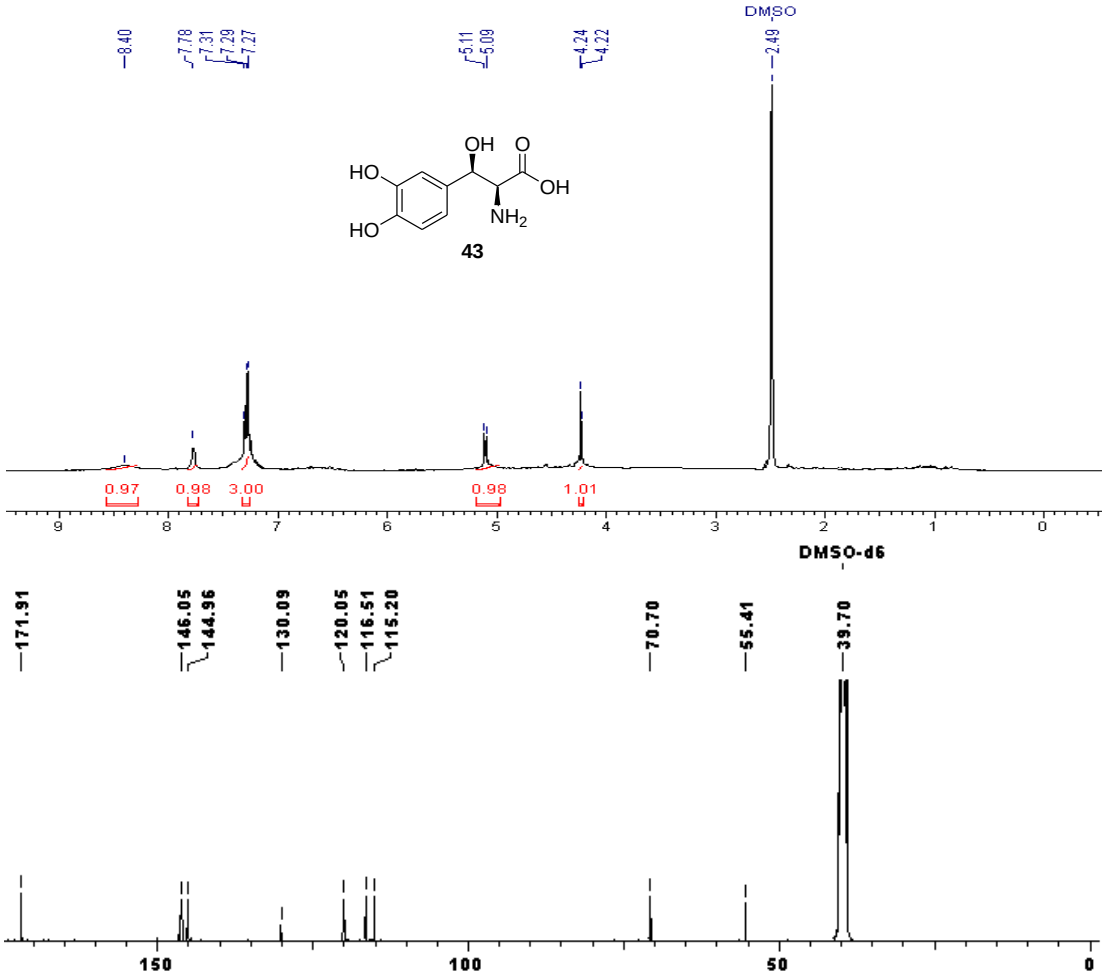


Fig. 16: ^{1}H and ^{13}C NMR spectra of droxidopa, 43

4.3.6 Conclusion

A short and efficient enantioselective synthesis of L-*threo*-DOPS (droxidopa) has been achieved in four linear steps with 51% overall yield and 99% ee. The $NaIO_4$-mediated

asymmetric bromohydroxylation of carboxamide **50** is used as the key reaction which proceeded to give high diastereoselectivity (>6:1), in the formation of bromohydroxylated product **51**.

4.3.7 Experimental Section

***anti*-(4*R*,2'*R*,3'*S*)-3-[2'-Bromo-3'-azido-3'-(3,4-bis(benzyloxy)phenyl)-propionyl]-4-benzyloxazolidin-2-one (52)**

A mixture of bromohydrin **51** (2.12 g, 4.1 mmol) and NaN_3 (0.81 g, 12.3 mmol) in DMF (20 mL) was stirred at 60 °C for 4 h. After completion of the reaction, the reaction mixture was extracted with diethyl ether (100 mL), washed with water, brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification of the crude product by silica gel column chromatography using petroleum ether/ethyl acetate (7:3) afforded the azido alcohol **52** (1.6 g) as a gum.

Yield: 82%; **$[\alpha]^{25}_D$**: -17.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3506, 3020, 2397, 2098, 2112, 1784, 1384, 1216, 769, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.57 (dd, *J* = 9.4, 13.5 Hz, 1H), 3.25 (dd, *J* = 3.5, 13.7 Hz, 1H), 4.17-4.33 (m, 2H), 4.63-4.78 (m, 1H), 5.10-5.18 (m, 4H), 5.41 (d, *J* = 4.5 Hz, 1H), 5.50 (d, *J* = 5.1 Hz, 1H), 7.06-7.47 (m, 18H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.38, 37.46, 55.09, 66.43, 71.23, 71.42, 72.85, 113.77, 114.84, 118.64, 127.28, 127.47, 127.51, 127.89, 128.05, 128.48, 128.56, 129.04, 129.32, 129.47, 134.72, 136.39, 136.53, 148.64, 149.90, 152.46, 168.70; **Analysis: $C_{33}H_{30}N_4O_6$** requires C, 68.50; H, 5.23; N, 9.68; found: C, 68.22; H, 5.51; N, 9.49%.

(2*S*,3*R*)-3-(3,4-Bis(benzyloxy)phenyl)-2-azido-3-hydroxypropanoic acid (53)

To a solution of azido alcohol **52** (0.96 g, 2 mmol) in a mixture of THF (5 mL) and water (3.4 mL) cooled in an ice bath was added a solution of 30% H_2O_2 (0.81 mL, 8 mmol).

After the mixture was stirred for 5 min, a solution of LiOH (0.072 g, 3 mmol) in water (1 mL) was added. The mixture was allowed to stir at 0 °C for 2 h at which time sodium sulfite (1.0 g) was added. Stirring was continued for 30 min. The solution was acidified with 10% citric acid (pH = 3) and extracted with ethyl acetate thrice. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure. Purification by column chromatography using petroleum ether/ethyl acetate (4:6) afforded the carboxylic acid **53** (0.74 g) as a gum.

Yield: 88%; **[α]$^{25}_{D}$**: -15.0 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3018, 2399, 2098, 1652, 1521, 1215, 1018, 929, 757, 669, 626; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.52 (d, *J* = 3.8 Hz, 1H), 5.08-5.15 (m, 4H), 5.23-5.30 (m, 1H), 6.11 (br s, 1H), 7.08-7.39 (m, 13H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 65.60, 71.10, 71.39, 72.74, 114.39, 115.89, 118.08, 126.43, 127.27, 127.45, 127.89, 127.99, 128.37, 128.44, 136.01, 136.09, 136.36, 147.73, 149.77, 174.39; **Analysis: $C_{23}H_{21}N_3O_5$** requires C, 65.86; H, 5.05; N, 10.02; found: C, 65.53; H, 5.19; N, 10.15%.

(2*S*,3*R*)-3,4-Dihydroxyphenylserine (L-*threo*-DOPS, 43)

The carboxylic acid **53** (0.42 g, 1 mmol) was dissolved in methanol (10 mL), and a catalytic amount of 10% Pd/C was added to it. The resulting heterogeneous mixture was stirred overnight under hydrogen atmosphere at room temperature. The reaction mixture was then filtered through a pad of celite and the solvent was removed under reduced pressure to give the product (0.2 g) as a grey coloured solid.

Yield: 94%; **mp**: 230-233 ºC; (lit.[42] **mp**: 232-235 ºC); **[α]$^{25}_{D}$**: -38.7 (*c* 0.4, 1N aq. HCl); {lit.[42] **[α]$^{25}_{D}$**: -39 (*c* 1, 1N HCl)}; **IR** ($CHCl_3$, cm^{-1}): 3018, 2399, 2366, 2345, 1652, 1519, 1215, 1018, 929, 756, 669; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 4.23 (d, *J* = 4.3 Hz, 1H),

5.10 (d, J = 3.8 Hz, 1H), 7.27-7.31 (m, 3H), 7.78 (br s, 1H), 8.40 (br s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 55.41, 70.70, 115.21, 116.51, 120.06, 130.09, 144.96, 146.06, 171.91; **Analysis: $C_9H_{11}NO_5$** requires C, 50.70; H, 5.20; N, 6.57%; found: C, 50.99; H, 5.01; N, 6.33%.

4.3.8 References

1. (a) Tenaglia, A.; Pardigon, O.; Buono, G. *J. Org. Chem.* **1996**, *61*, 1129; (b) Rodriguez, J.; Dulcere, J. P. *Synthesis* **1994**, 1177; (c) Block, E.; Schwan, A. L. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Semmelhack, M. F.; Eds.; Pergamon Press: Oxford, **1991**; Vol. 4, pp 344.
2. Ullmann's Encyclopedia of Industrial Chemistry, 6th ed.; Electronic Release, **1998** Cabanal-Duvillard, I.; Berrier, J. F.; Royer, J.; Husson, H. P. *Tetrahedron Lett*. **1998**, *39*, 5181.
3. (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience, New York, 2001, p.478 and references cited therein; (b) Dolenc, D.; Harej, M. *J. Org. Chem.* **2002**, *67*, 312; (c) Boukhris, S.; Souizi, A. *Tetrahedron Lett*. **2003**, *44*, 3259; (d) Cho, S.; Kang, S.; Keum, G.; Kang, S. B.; Han, S. Y.; Kim, Y. *J. Org. Chem.* **2003**, *68*, 180.
4. (a) Barluenga, J.; Alvarez-Perez, M.; Rodriguez, F.; Fananas, F. J.; Cuesta, J. A.; Garcia-Granda, S. *J. Org. Chem.* **2003**, *68*, 6583; (b) El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem*. **1998**, *63*, 2790; (c) Fu, H.; Kondo, H.; Ichikawa, Y.; Look, G. C.; Wong, C. *J. Org. Chem*. **1992**, *57*, 7265; (d) Niedleman, S. L.; Geigert, J. *Biohalogenation: principles, basic rules and applications*, Ellis Horwood: London, **1986**, pp 1.

5. Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett*. **2005**, *28*, 39.

6. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501.

7. (a) Hajra, S.; Karmakar, A.; Bhowmick, M. *Tetrahedron* **2005**, *61*, 2279; (b) Hajra, S.; Bhowmick, M.; Karmakar, A. *Tetrahedron Lett*. **2005**, *46*, 3073.

8. Gage, J. R.; Evans, D. A. *Org. Synth*. **1989**, *68*, 77.

9. Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

10. Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126.

11. Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052.

12. Sakamoto, Y.; Shiraishi, A.; Seonhee, J.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 4203.

13. Seki, M.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2965.

14. Miyata, O.; Asai, H.; Naito, T. *Synlett* **1999**, 1915.

15. Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett.* **2000**, *41*, 5553.

16. Madhan, A.; Kumar, A. R.; Rao, B. V. *Tetrahedron: Asymmetry* **2001**, *12*, 2009.

17. Hamerak, Z.; Ljubovic, E.; Mercep, M.; Mesic, M.; Sunjic V. *Synthesis* **2001**, 1989.

18. Carda, M.; Gonzalez, F.; Sanchez, R.; Marco, J. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1005.

19. Carter, P. H.; LaPorte, J. R.; Scherle, P. A.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1237.

20. Hamersak, Z.; Sepac, D.; Ziher, D.; Sunjic, V. *Synthesis* **2003**, 375.

21. Miyata, O.; Koizumi, T.; Asai, H.; Iba, R.; Naito, T. *Tetrahedron* **2004**, *60*, 3893.

22. Sugiyama, S.; Arai, S.; Ishii, K. *Tetrahedron: Asymmetry* **2004**, *15*, 3149.

23. Milicevic, S.; Matovic, R.; Saicic, R. N. *Tetrahedron Lett.* **2004**, *45*, 955.

24. Boruwa, J.; Borah, J. C.; Kalita, B.; Barua, N. C. *Tetrahedron Lett.* **2004**, *45*, 7355.

25. Davies, S. G.; Hughes, D. G.; Nicholson, R. T.; Smith, A. D.; Wright, A. J. *Org. Biomol. Chem.* **2004**, *2*, 1549.

26. Tokic-Vujosevic, Z.; Petrovic, G.; Rakic, B.; Matovic, R.; Saicic, R. N. *Synth. Commun.* **2005**, *35*, 435.

27. Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2005**, *7*, 4025.

28. Miyata, O.; Hashimoto. J.; Iba, R.; Naito, T. *Tetrahedron Lett.* **2005**, *46*, 4015.

29. Lin, X.; Bentley, P. A.; Xie, H. *Tetrahedron Lett.* **2005**, *46*, 7849.

30. Asano. M.; Nagasawa, C.; Suzuki, M.; Nishiyama, S.; Sugai, T. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 145.

31. Paraskar, A. S., Sudalai, A. *Tetrahedron* **2006**, *62*, 5756.

32. Narina, S. V.; Talluri, S. K.; George, S.; Sudalai, A. *Tetrahedron Lett.* **2007**, *48*, 65.

33. Mishra, R. K.; Coates, C. M.; Revell, K. D.; Turos, E. *Org. Lett.* **2007**, *9*, 575.

34. Singh, O. V.; Han, H. *Tetrahedron Lett.* **2007**, *48*, 7094.

35. (a) Seder, R. A.; Paul, W. E. *Annu. Rev. Immunol.* **1994**, *12*, 635; (b) Finkelman, F. D.; Shea-Donohue, T.; Goldhill, J.; Sullivan, C. A.; Morris, S. C.; Madden, K. B.; Gause, W. C.; Urban, J. F. *Annu. Rev. Immunol.* **1997**, *15*, 505.

36. (a) Stirling, R. G.; Chung, K. F. *Eur. Respir. J.* **2000**, *16*, 1158; (b) Renauld, J. C. *J. Clin. Pathol.* **2001**, *54*, 577.

37. (a) Gazzinelli, R. T.; Makino, M.; Chattopadhyay, S. K.; Snapper, C. M.; Sher, A.; Hugin, A. W.; Morise, H. C. III *J. Immunol.* **1992**, *148*, 182; (b) Romagnani, S. *Immunol. Today* **1990**, *11*, 316; (c) Secrist, H.; Chelen, C. J.; Wen, Y.; Marshell, J. D.; Umetsu, D. T. *J. Exp. Med.* **1993**, *178*, 2123.

38. (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561; (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (c) Kolb, H. C.; Sharpless, K. B. *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, **1998**; p 243.

39. Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029.

40. McCarthy, J. R.; Wiedeman, P. E.; Schuster, A. J.; Whitten, J.; Barbuch, R. J.; Huffman, J. C. *J. Org. Chem.* **1985**, *50*, 3095.

41. Tohgi, H.; Abe, T.; Takahashi, S. *J. Neural. Trnasm. [P. D. Sect.]* **1993**, *5*, 27.

42. Hegedus, V. B.; Krasso, A. F.; Noack, K.; Zeller, P. *Helv. Chim. Acta* **1975**, *58*, 147.

43. Herbert, B.; Kim, I. H.; Kirk, K. L. *J. Org. Chem.* **2001**, *66*, 4892.

44. Sang-Ho, B.; Yoshioka, H.; Yukawa, H.; Harayama, S. *J. Microbiol. Biotechnol.* **2007**, *17*, 721.

45. Thomas, S. A.; Marck, B. T.; Palmiter, R. D.; Matsumoto, A. M. *J. Neurochem.* **1998**, *70*, 2468.

46. Kikuchi, K.; Nashino, K.; Ohyu, H. *Brain Res.* **2000**, *860*, 130.

47. Xue, C.-B.; He, X.; Roderick, J.; Corbett, R. L.; Decicco,C.P. *J. Org. Chem*. **2002**, *67*, 865.

LIST OF PUBLICATIONS

- "A short enantioselective synthesis of (-)-chloramphenicol and (+)-thiamphenicol using tethered aminohydroxylation" Shyla George, Srinivasarao V. Narina, Arumugam Sudalai; *Tetrahedron* **2006**, *62*, 10202.
- "Enantioselective synthesis of (-)-cytoxazone and (+)-*epi*-cytoxazone via Rh-catalyzed diastereoselective oxidative C-H aminations" Srinivasarao V. Narina, Talluri Siva Kumar, Shyla George, Arumugam Sudalai; *Tetrahedron Lett*. **2007**, *48*, 65.
- "$NaIO_4$-mediated asymmetric bromohydroxylation of α,β-unsaturated carboxamides with high diastereoselectivity: a short route to (-)-cytoxazone and droxidopa" Shyla George, Srinivasarao V. Narina, Arumugam Sudalai; *Tetrahedron Lett*. **2007**, *48*, 1375.
- "Enantioselective synthesis of tarchonanthuslactone using proline-catalyzed asymmetric α-aminooxylation" Shyla George, Arumugam Sudalai; *Tetrahedron: Asymmetry* **2007**, *18*, 975.
- "An efficient organocatalytic route to the atorvastatin side-chain" Shyla George, Arumugam Sudalai; *Tetrahedron Lett*. **2007**, *48*, 8544.
- "A short enantioselective synthesis of (-)-bestatin via L-proline-catalyzed α-amination of an aldehyde" Shyla George, Gurunath S, Suryavanshi, Arumugam Sudalai; *Tetrahedron Lett*. **2008**, *49*, 6791.
- "First enantioselective synthesis of streptopyrrolidine, an angiogenesis inhibitor" Chaithanya Kiran Indukuru, Shyla George, Arumugam Sudalai; Communicated to *Tetrahedron: Asymmetry*, **2009**.
- "Organocatalytic approaches to the asymmetric synthesis of streptopyrrolidine" Shyla George, R. Santhosh Reddy, Chaithanya Kiran Indukuru, Arumugam Sudalai; Communicated to *Tetrahedron Lett*. **2009**.
- "Enantioselective total synthesis of guggultetrol, a naturally occurring lipid" Shyla George, Arumugam Sudalai (Manuscript under preparation).
- "A short and efficient enantioselective synthesis of guggultetrol using Sharpless asymmetric dihydroxylation" Shyla George, Arumugam Sudalai (Manuscript under preparation).