Enantioselective Total Synthesis of Bioactive Compounds Employing Transition Metal Based Chiral Ligands and Organocatalysis

Thesis Submitted in fulfillment of the

requirement of the degree of

Doctor of Philosophy

By

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Certificate

This is to certify that thesis entitled "**Enantioselective Total Synthesis of Bioactive Compounds Employing Transition Metal Based Chiral Ligands and Organocatalysis**" being submitted by Amanpreet Kaur in the fulfillment of the requirement for the award of the Degree of Doctor of Philosophy to the School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala, is an authentic record of candidate's own work carried out by her under our supervision and guidance. The matter presented in this thesis has not been submitted in part or full for the award of any degree in any other University or Institute.

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Candidate's Declaration

I, hereby declare that the work presented in the thesis entitled "**Enantioselective Total Synthesis of Bioactive Compounds Employing Transition Metal Based Chiral Ligands and Organocatalysis**" in partial fulfillment of the requirement for the award of the Degree of Doctor of Philosophy, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala, is an authentic record of my own work carried out under the supervision of Dr. Satyendra Kumar Pandey, Professor, Banaras Hindu University and Dr. Ranjana Prakash, Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala, India. The matter embodied in this thesis has not been submitted in part or full to any other University or institute for the award of any degree in India or abroad.

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Dedicated
To My
Beloved
Family

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Above all, I am grateful to GOD, ***Almighty*** who sustain this amazing world and without whos grace and blessings anybody can ever succeed.
May the ***Almighty*** GOD bless all of you.

Amanpreet Kaur

AMANPREET KAUR

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ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
BAIB	-	(Diacetoxyiodo)benzene
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
Cat.	-	Catalytic
DCC	-	*N*,*N′*-Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
DIAD	-	Diisopropyl azodicarboxylate
DEAD	-	Diethyl azodicarboxylate
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-yl)phthalazine
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminium hydride
DIPEA	-	*N*,*N*-Diisopropylethylamine
DMP	-	2,2-Dimethoxypropane
DMF	-	*N*, *N′*-Dimethylformamide
DMAP	-	*N*,*N′*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
DPPA	-	Diphenylphosphoryl azide
EDC	-	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride
ee	-	Enantiomeric excess

de	-	Diastereomeric excess
er	-	Enantiomeric ratio
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Hz	-	Hertz
HATU	-	2-(7-aza-1Hbenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	-	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt	-	1-Hydroxy-1H-benzotriazole
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram
mL	-	Millilitre
mmol	-	Millimole
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TEMPO	-	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR and ^{13}C NMR spectra were recorded on on JEOL ECS spectrometer operating at 400 and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- Mass spectra were obtained by using electron spray ionization (ESI) and mass values are expressed as m/z.
- IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}.
- Optical rotations were measured on Automatic polarimeter AA-65 and concentrations of g/100mL.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2, ninhydrin and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 40 °C.
- Column chromatography were performed on silica gel (60-120, 100-200 and 230-400 mesh) using a mixture of hexane/ethyl acetate and dichloromethane/methanol as eluent.

ABSTRACT

The thesis entitled "**Enantioselective Total Synthesis of Bioactive Compounds Employing Transition Metal Based Chiral Ligands and Organocatalysis**" is divided into five chapters.

Chapter 1: A brief introduction on Sharpless asymmetric dihydroxylation, asymmetric Michael addition and organocatalyzed aldol reaction.

Chapter 2: An efficient approach towards the chiral synthesis of piperidine skeleton: core unit of potent dual orexin receptor antagonist MK-6096.

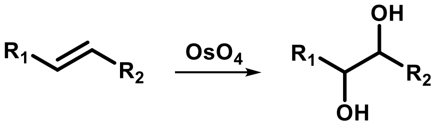
Chapter 3: A stereoselective approach towards the total synthesis of Sacubitril: a prodrug neprilysin inhibitor.

Chapter 4: An enantioselective synthesis of C1-C4 and C5-C14 fragments of Cytospolide D.

Chapter 5: Conclusions and future scope.

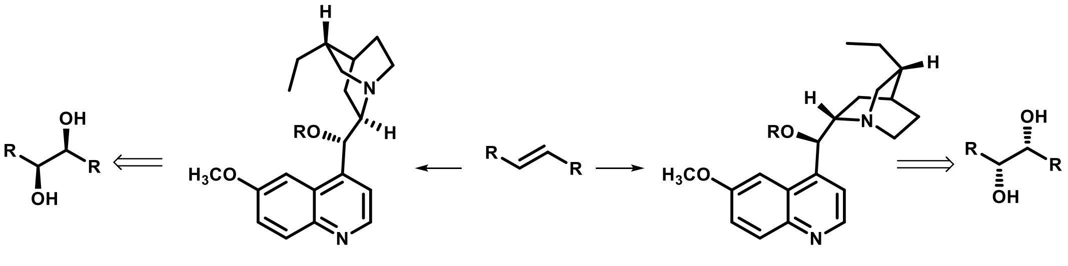
Chapter 1: A brief introduction on Sharpless asymmetric dihydroxylation, asymmetric Michael addition and organocatalyzed aldol reaction.

Natural products have evolved over millions of years, possesses multi-dimensional chemical structures; which results in diversity in their biological activities and drug-like properties. Natural products will undergo continual use towards meeting the urgent need to develop effective drugs, and in turn play a noteworthy part in the discovery of therapeutic agents for curing human diseases.[1] Among the various techniques used to create analogues and derivatives of natural products, asymmetric synthesis by applying chiral auxiliary and new methodologies consisting of fewer steps and lesser cost, are of great significance. Catalytic asymmetric reactions provide a practical entry into the chiral world due to their economical use of asymmetry inducing agents. The osmium tetroxide-catalyzed Sharpless asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the well-grounded and selective transformations in organic chemistry.



The hydroxylation of maleic and fumaric acid using co-oxidant chlorates and catalyst OsO_4 was first studied by Zelikoff and Taylor[2] and Milas *et al* [3a,b] reported the dihydroxylation using OsO_4 and hydrogen peroxide, however these reagent combinations accompanied by lesser yield due to over oxidation. Sharpless and Akashi[4] introduced the use of *tert*-butyl hydrogen peroxide and Upjohn Process[5] that involves *N*-methylmorpholine accomplished the dihydroxylation process with positive results. Much better outcomes were observed with alkaline *t*-BuOOH, introduced by Tsuji *et al.*[6] and Sharpless and Akashi[4] and they demonstrated that use of $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.

Sharpless *et al.*[7] in 1992 after intensive investigation reported the two major modifications in osmium catalyzed AD process. The use of phthalazine class of ligands **1** and **2** and enhances rate of hydrolysis of osmate ester using organic sulphonamides offered a comprehensible procedure that is vital for dihydroxylation of wide range of non-terminal olefins. The use of methane sulphonamide additive compensate the limited turnover of osmium tetraoxide from osmate ester, resulting in decreased reaction time and relatively less loading of ligand (1 mol %) was sufficient to achieve good enantioselctivity (upto 96%).

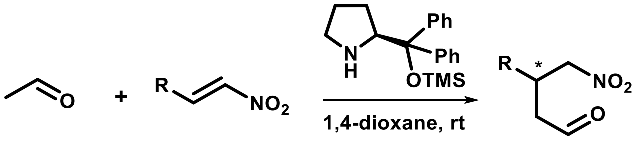


Dihydroquinidine (R = H)
DHQD, 1

Dihydroquinine (R = H)
DHQ, 2

Sharpless AD emerged as a powerful practice as unlike other asymmetric reactions it does not require directing functional groups. Along with this, low loading of osmium as catalyst is required and chincona alkaloids and their derivatives **1** & **2** (at C-9) are readily available. Moreover, cincona alkaloid diasteromers (quinine and quinidine) fulfill enantiomeric functions with excellent enatioselctivity.

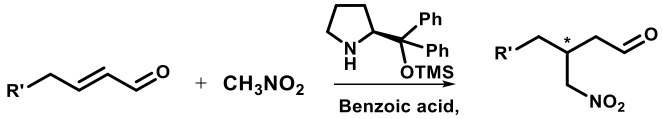
Secondly, asymmetric Michael addition represents the initiating step for more integrated inter- and intramolecular tandem processes. The diphenylprolinol silyl ether catalyzed asymmetric conjugate addition of various carbon and heteroatom nucleophiles to aliphatic and aromatic nitroalkenes or conjugated carbonyl compounds serve as a medium for the construction of highly functionalized synthetic building blocks of natural products. The TMS prolinol catalysed Michael reaction performed by Hayashi *et al.*[8] was selected as a reference for the reaction of aldehdydes with conjugated nitro alkenes for the synthesis of diversified range of biologically active compounds. They performed the diphenylprolinol silyl ether catalysed asymmetric Michael addition reaction of acetaldehyde **3** as nucleophile and nitroalkene **4** as electrophile to furnish the chiral product **5** in pleasant yield.



3 **4** **5**

R = alkyl, aryl

Hayashi *et al*[8b] also investigate the Micheal addition between nitromethane **6** (nucleophile) and *α β*- unsaturated aldehydes **7** as an in the presence of organocatalyst (diphenylprolinol silyl ether) to produce the nitroaldehyde adduct **8** in excellent yield (≥ 90%).

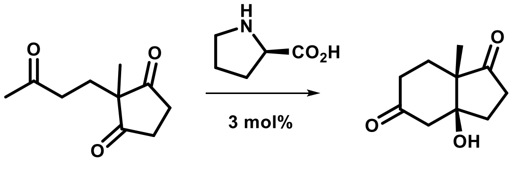


7 **6** **8**

R' = alkyl, aryl

Next, the asymmetric aldol reaction is one of the vital class of reactions among modern catalytic synthetics procedures. Among various asymmetric catalytic methods, the proline catalysed version which proceeds via an *in situ* generated enamine intermediate, has attracted much attention, leading to products with good chemo & stereoselctivity under mild circumstances.

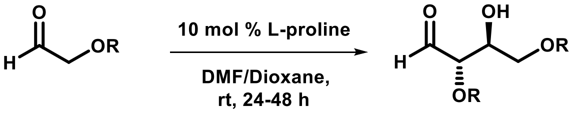
In 1971[9] the first L-proline catalysed intramolecular asymmetric aldol reaction of compound **9** was reported which is known as Hajos-Parrish- Eder- Saucer- Wiechert cyclization.



9

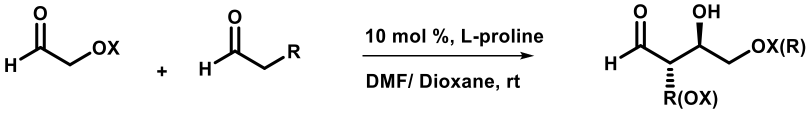
100%, 93% ee

Further, MacMillan successfully outlined the L-proline catalysed enantioselective self and cross aldol reactions of *α*-oxyaldehydes.[10] Organocatalytic self-coupling of *α*-oxyaldehydes **10** in DMF/dioxane in presence of L-proline provided the desired oxyaldehyde dimer **11.**



10 11

Next, L-proline (10 mol%) catalysed cross-coupling between *α*-oxyaldehydes **12** and *α*-alkyl-substituted aldehydes **13** in DMF/dioxane afforded the *syn*-, *anti*- product **14** in 33-84 % with excellent enantiomeric excess.



12 13 14

Keeping in view the above points, the following objectives have been designed:

Objectives:

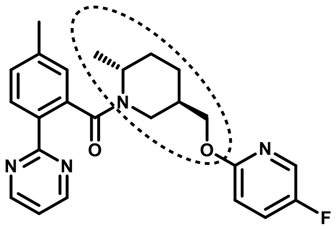
1. Enantioselective synthesis and characterization of cytospolide D using Sharpless asymmetric dihydroxylation and proline catalyzed cross aldol reaction.

2. Synthesis of bioactive natural products and piperidine core unit of orexin receptor antagonist MK 6096 employing Michael addition using trimethylsilyl prolinol as a chiral catalyst.

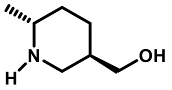
Chapter 2: An efficient approach towards the chiral synthesis of piperidine skeleton: Core unit of potent dual orexin receptor antagonist MK-6096.

Introduction:

The orexins (hypocretins)[11] functions as neurotransmitter and widely participate in sleep regulations.[12] This correlation demonstrated the use of Orexin receptors for the cure of sleep illness in place of sedative hypnotics that may cause unwanted side effects. Campeau and co-workers[13a] discovered a structurally distinct, dual Orexin Receptor Antagonists (DORA) named MK-6096 (Figure 1) that was under evaluation to be used as a potent drug for the treatment of insomnia. MK-6096 **15**, consist of *trans*-2,5 disubstituted piperidinyl core **16,** a biaryl acid and fluoropyridine fragment.



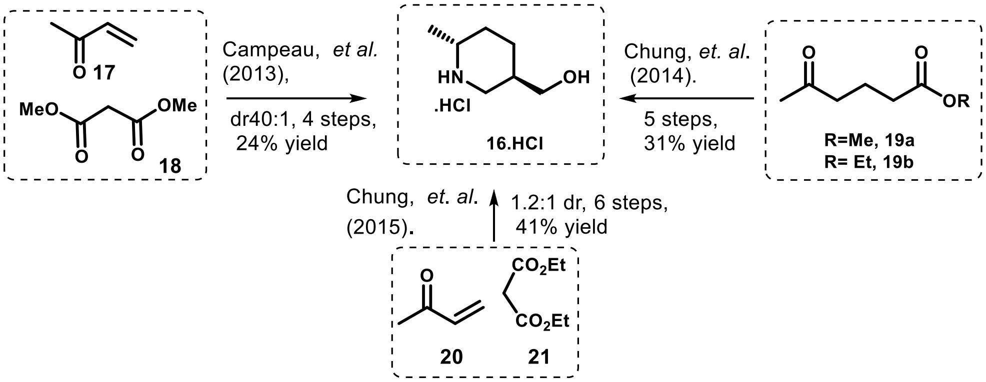
MK-6096, 15



Piperidine Core Unit, 16

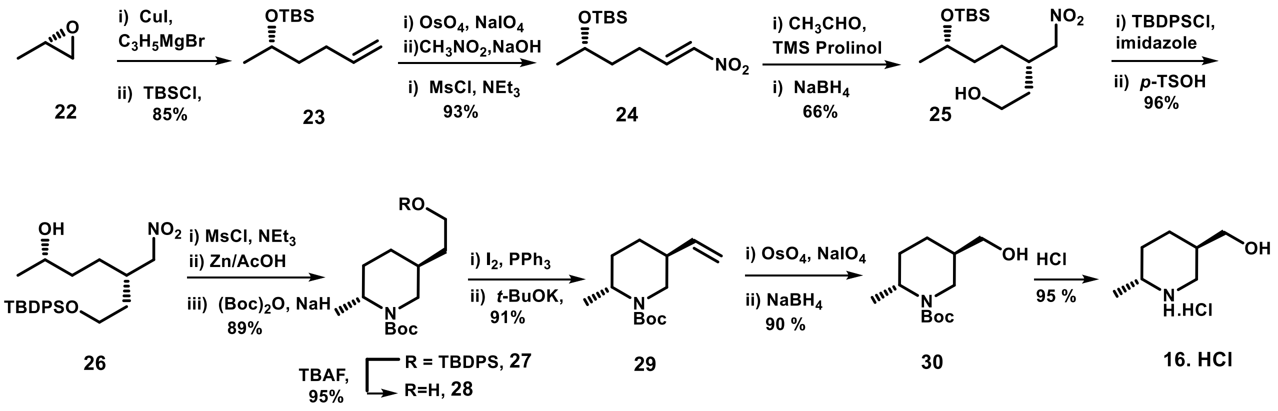
Literature Review:

Campeau, *et. al***.**[13a] reported first multi-gram synthesis of **16** in 2013 using methyl vinyl ketone **17** and dimethyl malonate **18** as starting materials. The key steps involved Michael addition and biocatalysed transamination involving 3 enzymes. Next, in 2014, Chung, *et. al.*[13b] utilize the diketoesters **19a** & **19b** as starting material and employed Mukaiyama aldol and biocatalytic transamination involving one enzymatic system as key step. Chung, *et. al.*[13c] again in 2015 described a modified procedure for the synthesis of **16** from compound **20** & **21** employing crystallization–induced dynamic resolution (CIDR) process for enhancing the diasteroselectivity. Here also one enzyme system was used for transamination process.



Present Work:

The synthesis of *trans*-3,6-disubstituted piperidine unit **16** began from readily available (*S*)-propylene oxide **22** which was subjected to CuI catalyzed regio-selective ring opening with the allyl magnesium bromide and its further treatment with TBSCl using imidazole and catalytic amount of DMAP furnished the alkene derivative[14] **23** in 85% yield. A one-pot oxidative cleavage of olefin **23** with $OsO_4/NaIO_4$ led to aldehyde which under Henry reaction conditions and dehydration yielded α, β-unsaturated nitro alcohol derivative **24** in excellent yield. Asymmetric Michael addition[6] of acetaldehyde with compound **24** in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether furnished the nitro-aldehyde adduct which on reduction with $NaBH_4$ furnished nitroalcohol derivative **25** as a single diastereomer in 66% yield. Next, imidazole mediated hydroxyl protection of **25** with *tert*-butyldiphenylsilyl chloride afforded the silyl ether intermediate which on subsequent selective TBS deprotection in presence of catalytic amount of *p*-TSA afforded the alcohol derivative **26** in good yield.

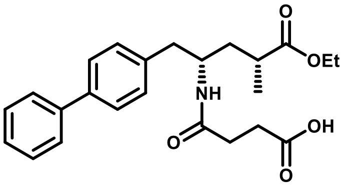


The derivative **26** on *O*-mesylation followed by Zn/AcOH mediated reduction of nitro to amine, nucleophilic SN_2 displacement of *O*-Mesylate and subsequent *N*-Boc protection of cyclized intermediate furnished the piperidine derivative **27** in 89% yield. Further, TBAF mediated TBDPS ether cleavage of compound **27** furnished alcohol derivative **28** in excellent yields. The alcohol **28** was transformed into olefin derivative **29** *via* iodination of hydroxyl group followed by elimination in the presence of excess amount of *t*BuOK.[15] Then, the N-Boc protected derivative **30** was synthesized *via* $NaIO_4$ mediated oxidative cleavage of **29** followed by reduction of intermediate aldehyde using $NaBH_4$, in excellent yield. Finally, treatment of **30** with 6 N HCl in water afforded ((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol **16** as its hydrochloride salt in excellent purity.

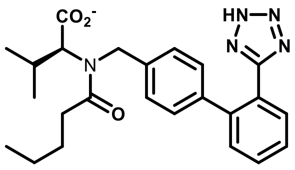
Chapter 3: A stereoselective approach towards the total synthesis of Sacubitril: a prodrug neprilysin inhibitor.

Introduction:

In the early 1990's, Ksander and co-workers developed an active pharmaceutical compound Sacubitril (AUH-377) **31** which is a pro drug neprilysin inhibitor.[16a] Combinations of Sacubitril **31** with the angiotensin II receptor-blocker Valsartan **32** by co-crystallization are known as supramolecular complex LCZ696 which was developed by Novartis for the treatment of heart failure (HF).[17] A first-in-class combination drug LCZ696 (brand name Entresto) was approved by FDA in 2015 and is used to reduce the risk of cardiovascular death and hospitalization for HF in patients with reduced ejection fraction and chronic HF (NYHA Class II−IV).[18]



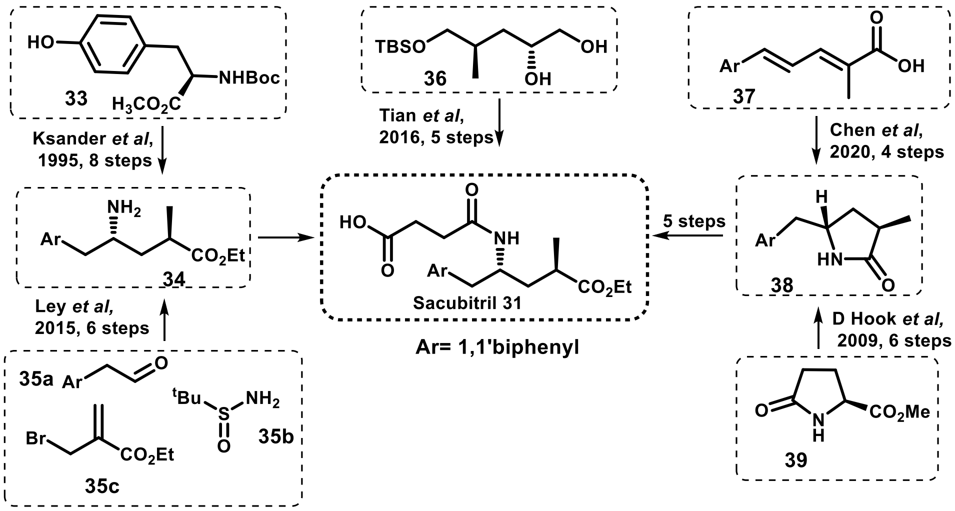
Sacubitril 31



Valsartan 32

Literature Review:

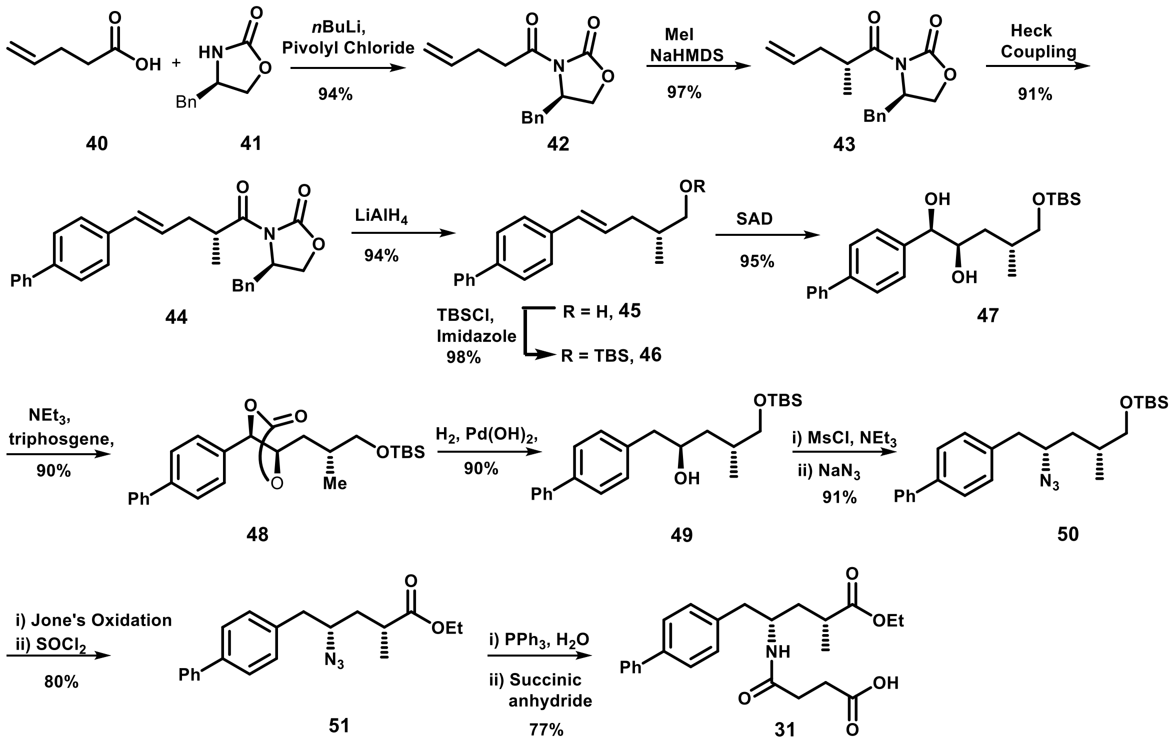
Ksander and co-workers[16a] describe the introductory synthesis of Sacubitril **31** using N-Boc-D-tyrosine methyl ester **33** as starting material in 9 steps. Ley *et al.*[16e] in 2015 also reported the synthesis of **31** from commercially available 4-iodobiphenyl using flow technology. 4-iodobiphenyl was converted into aldehyde **35a** using standard organic transformation which further reacts with **35b** & **35c** to yield **31** in 7 steps. W. S. Tian[16d] and co-workers in 2016 reported synthesis of sacubiril **31** based on chiron approach from mono protected chiral triol **36** in total 7 steps in 41% yield. Hook *et al.*[16c] in 2009 reported the synthesis of **31** from chiral pyrrolidine **39** in total of 11 steps through the chiral intermediate **38**. Recently, Chen and co-workers[16b] disclosed the gram scale synthesis of **31** through the intermediated **38** same as reported by Hook *et al.* in total of 9 steps. They utilized conjugated α-substituted dienoic acid **37** as starting material and Trifer-Rh complex catalysed hydrogenation as key step.



Present Work:

The synthesis of Sacubitril **31** lead off from commercially available pentanoic acid **40** which on treatment with Evan's oxazolidinone chiral auxiliary (*R*)-**41** in the presence of pivaloyl chloride and Et_3N afforded the chiral imides **42** in excellent yield. Stereoselective Evans methylation[19] of **42** with methyl iodide in the presence of NaHMDS, furnished the methylated product **43** in 97% yield (dr = 93/7). The diastereomers were easily separated by column chromatography. Next, Heck cross coupling of olefin derivative **43** with commercially available 4-bromobiphenyl in the presence of $Pd(OAc)_2/Et_3N$/tri-*o*-tolyl phosphine combination in acetonitrile afforded the biphenyl olefin **44** in 91% yield.[20]

The compound **44** was subjected to $LiAlH_4$ reduction which led to the cleavage of chiral auxiliary and furnished the alcohol derivative **45** in excellent yield. Furthermore, the silyl ether protection of alcohol **45** with TBSCl afforded the TBS protected olefin derivative **46** in 98% yield which under Sharpless AD conditions in the presence of $(DHQD)_2PHAL$ catalyst[7] furnished the diol **47** in good yield. The pure diol derivative **47** was treated with triphosgene in the presence of Et_3N to afford the cyclic carbonate derivative **48** which on subsequent hydrogenolysis[21] in the presence of catalytic amount of $Pd(OH)_2$ afforded mono alcohol derivative **49** in 90% yield. Accordingly, the free hydroxy group of compound **49** was transformed into its *o*-mesylate intermediate which on immediate S_N2 displacement reaction with sodium azide afforded compound **50** in good yield.

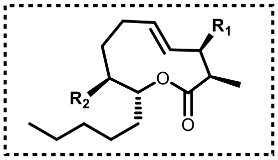


On moving further, concomitant deprotection of the acid-sensitive TBS group of azide **50** and conversion of free alcohol to acid were achieved under Jones oxidation reaction conditions which on subsequent treatment with thionyl chloride afforded the ethyl ester derivative **51** in 80% yield. Finally, the azide of ester derivative **51** under Staudinger reaction conditions[22] afforded the amine intermediate which was subsequently refluxed with succinic anhydride to furnish the Sacubitril **31** in excellent yield.

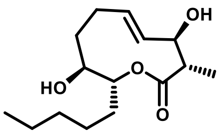
Chapter 4: An enantioselective synthesis of C1-C4 and C5-C14 fragments of cytospolide-D.

Introduction:

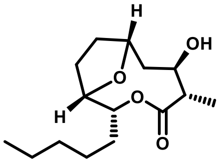
The novel decanolide compounds, cytospolide A-E (**52-60**) along with other thirteen natural product analogues (cytospolides F-Q and decytospolides A and B) were isolated by Zhang and co-workers from leaves of endophytic fungus shrub Ilex canariensis found mainly in the island of Gomera, Spain.[23a,b] A number of cytospolides showed cytotoxic effects to various human carcinoma cell lines. The C-2 methyl group inversion in cytospolide E **56** from 2*R* of **55** to 2*S* of **56** was found to lead to a surprise increase in cytotoxic activity against the A-549 tumor cell lines.[23a]



Cytospolide A 52: R1 = OAc, R2 = OH
Cytospolide B 53: R1 = OH, R2 = OAc
Cytospolide C 54: R1 = R2 = OAc
Cytospolide D 55: R1 = R2 = OH



Cytospolide E 56



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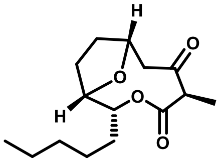
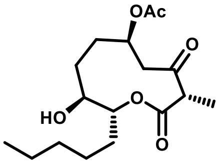
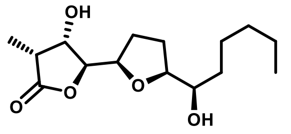


Cytospolide O 58



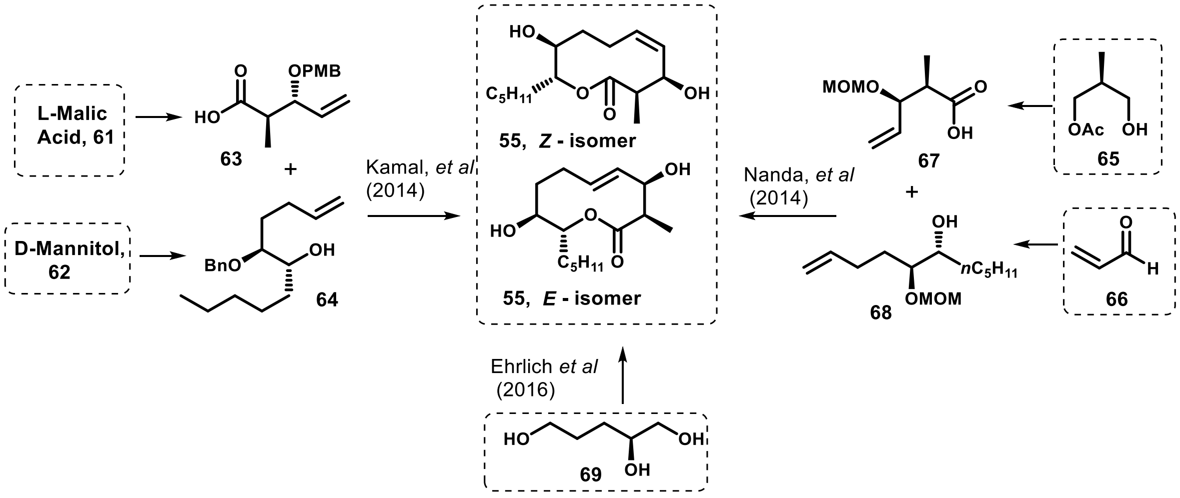
Cytospolide P 59



Cytospolide Q 60

Literature Review:

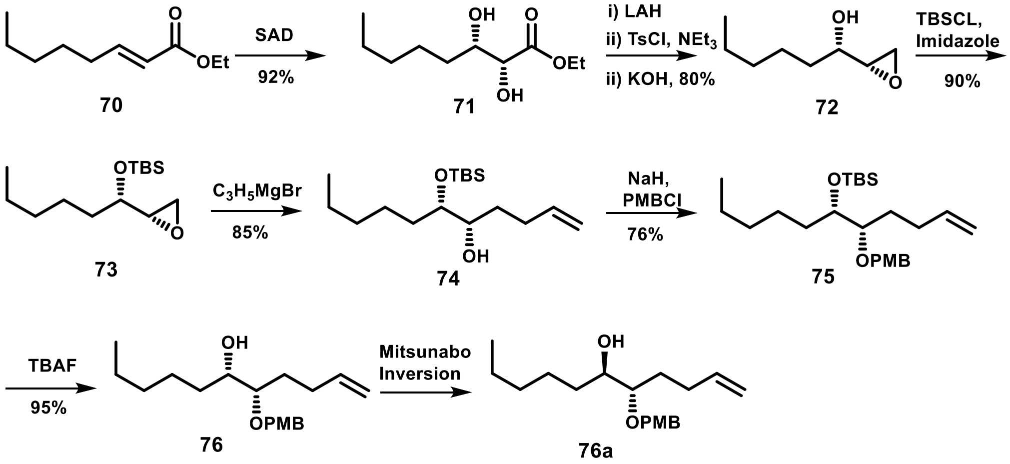
A. Kamal and co-workers[23c] reported the divergent enantioselective synthesis of cytospolide D **55** starting from L-malic acid **61** and D-mannitol **62** which were converted into key acid **63** and alcohol **64** fragments respectively. The fragment **63** & **64** on following different step sequences were converted into both *E* & *Z* isomer of cytospolide D **55** respectively. Next, S. Nanda *et al*[23d] in 2014 reported the enantioselective synthesis of *Z*-isomer of cytospolide D **55** involving chemo enzymatic processes, as the pivotal steps, used for the construction of alcohol **68** and acid **67** fragments from compound **66** & **65** respectively.



Yamaguchi coupling followed by Grubs metathesis afforded the *Z* cytospolide D **55**. Further, Gunnar Ehrlich and Christian B. W. Stark[23e] in 2016 reported the total synthesis of cytospolide D **55** from chiral triol **69** employing *anti* aldol addition, Shina esterification as key step.

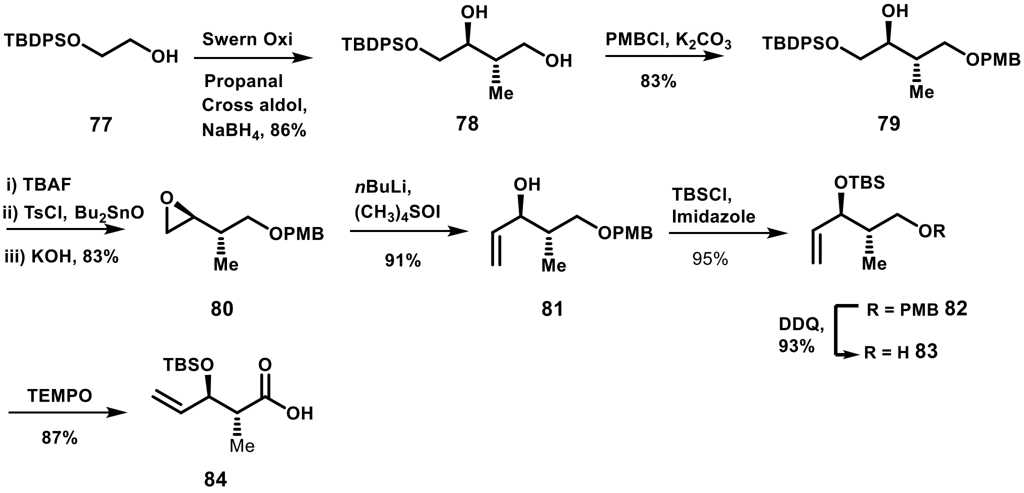
Present Work:

The synthesis started from *α*, *β*-unsaturated ester **70**, which under Sharpless asymmetric conditions[24] in the presence of $(DHQ)_2PHAL$ furnished **71** in 92% yield. The diol derivative **71** on $LiAlH_4$ reduction afforded triol intermediate, which on regioselective primary *o*-tosylation using TsCl and Et_3N in the presence of catalytic amount of Bu_2SnO[25] followed by base treatment afforded the epoxy alcohol derivative **72** in excellent yield. The free secondary hydroxyl group of **72** was protected as its TBS ether **73** in excellent yield. The epoxide **73** on CuI catalyzed regioselective ring opening with AllylMgBr afforded alkenol derivative **74** in excellent yield.

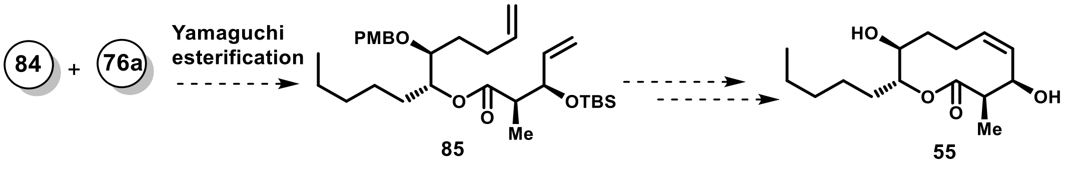


The free hydroxyl group of alkenol derivative **74** on *p*-methoxybenzyl chloride (PMBCl) protection and selective desilylation of the TBS ether with TBAF furnished the alkenol derivative **76** in excellent yield.

The synthesis of 1,3-Diol **78** began from monosilylated ethylene glycol **77** which on MacMillan's crossed aldol[10] reaction followed by subsequent $NaBH_4$ reduction afforded the target compound **78**. Treatment of 1,3-diol **78** with K_2CO_3 and PMBCl in acetone[26] furnished the PMB protected derivative **79** in 83% yield. The synthesis of the epoxide **80** from alcohol **79** was carried out by a process including silyl deprotection and selective primary alcohol tosylation using TsCl and Et_3N in the presence of catalytic amount of Bu_2SnO[22] followed by base treatment. The epoxide derivative **80** on one-carbon homologation furnished the allyl alcohol derivative **81** in 91% yield.[27] Alcohol derivative **81** then subjected to imidazole-promoted hydroxyl group protection with TBSCl and selective deprotection of the PMB ether with DDQ afforded the primary alcohol derivative **83** in excellent yield. Finally, TEMPO/BIAB mediated oxidation of the primary alcohol **83** furnished the key fragment **84** in 87% yield.



Next, the alkenol derivative **76** and acid fragment **84** could be used for the coupling reactions to accomplish the synthesis of key precursor *bis*-olefin derivative **85** which could be employed for the total synthesis of cytospolide D **55.** The ester **85** could be prepared by coupling of alcohol fragment **76** and acid fragment **84** under Mitsunobu conditions. Alternatively, alkenol derivative **76** could be subjected to Mitsunobu inversion to afford required alkenol derivative **76a.** The Yamaguchi esterification[28] of acid fragment **84** and alkenol derivative **76a** could also lead to derivative **85**. The *bis*-olefin derivative **85** could then be converted into the target compound cytospolide D **55** *via* the Grubbs RCM and deprotection of both protecting group following the standard organic transformations.[29]



Chapter 5: Conclusions and future scope

We have described enantioselective synthetic approaches for the synthesis of piperidine skeleton, Sacubitril and C1-C4 and C5-C14 fragments of Cytospolide-D employing Sharpless AD, organocatalzyed Michael addition, proline catalysed MacMillan cross aldol reactions as key steps. The merits of these synthetic approaches are high enantio and diastereoselectivity with high yielding reaction steps. All the new compounds were characterized by ^{1}H-NMR, ^{13}C NMR, HRMS and %*ee* was determined using chiral HPLC and $[\alpha]_D^{25}$ for all new chiral compounds was also taken.

Characterization:

All the synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on JEOL ECS operating at 400 and 100 MHz, respectively. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory. HRMS were recorded using Electron Spray Ionization. Optical rotations were measured on Automatic polarimeter AA-65. Column chromatography was performed on silica gel (60-120 and 100-200 mesh) using a mixture of hexane/ethyl acetate and/or CH_2Cl_2/MeOH. The enantiomeric excess (% ee) of chiral compounds was determined by HPLC on chiral phase OD-H and Chiradex columns

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List of Publications

1. Enantioselective Total synthesis of Sacubitril.
   Amanpreet Kaur, Anju Gehlawat, Ranjana Prakash and Satyendra Kumar Pandey*
   ChemistrySelect., **2021**, *6*, 8928-8930.
2. An Asymmetric Synthesis of ((3*R*,6*R*)-6-Methylpiperidine-3-yl)methanol; A Piperidine Core Unit of Potent Dual Orexin Receptor Antagonist MK-6096.
   Amanpreet Kaur, Ranjana Prakash and Satyendra Kumar Pandey*
   ChemistrySelect **2018,** *3,* 12164-12166.
3. Proton Nuclear Magnetic Resonance-Based Method for the Quantification of Epoxidized Methyl oleate.
   Avneet Kaur, Neha Bhardwaj, **Amanpreet Kaur**, Abida, Tejo Prakash Nagaraja, Amjad Ali and Ranjana Prakash*
   Journal of the American Oil Chemist's Society **2020**, *2*, 139-147.
4. Enantioselective Synthesis of C1-C4 and C5-C14 Fragments of Cytospolide D
   Amanpreet Kaur, Anju Gehlawat, Ranjana Prakash and Satyendra Kumar Pandey*
   Arkivoc **2021**, *partv,* 158-170.

Conferences

1. Total Synthesis of Biologically Active Natural products
   Amanpreet Kaur and Satyendra kumar Pandey.
   Poster presentations at International conference FCASI 2016, University of Rajasthan, Jaipur, India.
2. Enantioselective total synthesis of piperidine skeleton: (Core unit of potent dual orexin receptor antagonist MK-6096).
   Amanpreet Kaur and Satyendra Kumar Pandey.
   Poster presentations at Chemical and Environmental Sciences: Innovation and Advances-2018, Punjabi University Patiala, Punjab, India.

CHAPTER 1

A brief introduction on Sharpless asymmetric dihydroxylation, asymmetric Michael addition and organo catalysed aldol reaction.

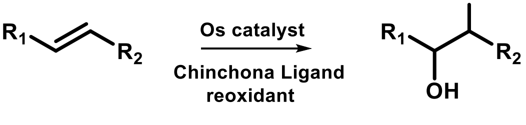
1.1 Sharpless asymmetric dihydroxylation (AD)

1.1.1 Introduction

Asymmetric catalysis[1] emerged as a favourable pathway for the syntheses of intricate organic molecules, having numerous stereo-centres, of biological significance. The carbon-heteroatom bond forming reaction giving rise to optically active adducts, that can be easily altered to produce vital classes of compounds with high enantiomeric purity, are of immense importance.

Although remarkable progress have been made in this direction, however, Sharpless AD used for introducing two chiral hydroxyl groups in prochiral olefin framework catalysed by osmium tetraoxide persists as a reliable organic transformation (Scheme 1). Initially, Criegee carried out the dihydroxylation of double bond using OsO_4 and pyridine. However, this noteworthy method was uneconomical as excess of expensive OsO_4 was used. The hydroxylation of maleic and fumaric acid using co-oxidant chlorates and catalyst OsO_4 was first studied by Zelikoff and Taylor[2]. Milas and co-workers[3a,b] further, reported the dihydroxylation using OsO_4 and hydrogen peroxide, however these reagent combinations accompanied by lesser yield as of over oxidation. Distinguished outcomes were anticipated with *tert*-butyl hydrogen peroxide under alkaline conditions, introduced by Sharpless and Akashi[4] or with the use of *N*-methylmorpholine *N*-oxide familiar as Upjohn Process[5]. Subsequently, Minato, Yamamoto, and Tsuji[6] used $K_3Fe(CN)_6$ and K_2CO_3 combination which facilitated the osmium catalyzed dihydroxylation of alkenes effectively.

Next, Sharpless AD was executed in two-phase conditions and addition of methanesulphonamide (a phase-transfer and basic acid catalyst) promoted rapid occurrence of dihydroxylation of non-terminal olefins.



Scheme 1: Dihydroxylation of olefin.

Further, work was initiated towards the enantioselctive dihydroxylation. For this, in the beginning, Sharpless and Hentges tested chiral pyridine derivatives. However, low enantioselectivity was observed as these ligands showed low binding tedency with OsO_4.[7] Next, chiral quinuclidine derivatives displayed more binding affinity towards OsO_4[8] when employed for asymmetric induction, but later switched with acetate esters of cinchona alkaloids (Figure 1) (dihydroquinine acetate & dihydroquinidine acetate, where R=Ac in Figure 1) as chiral ligands.[7] Interestingly, these ligands showed considerable rise in terms of both enantiomeric excess and yield.

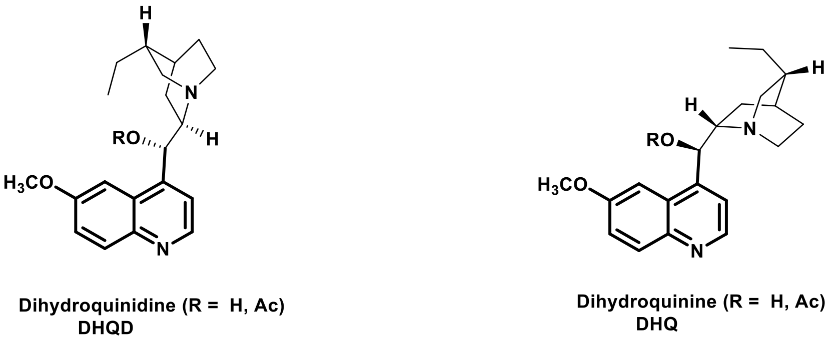
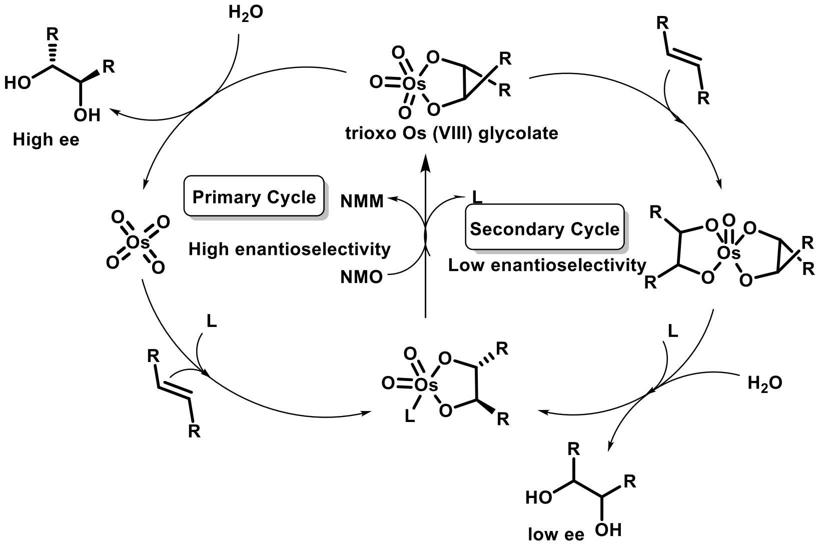


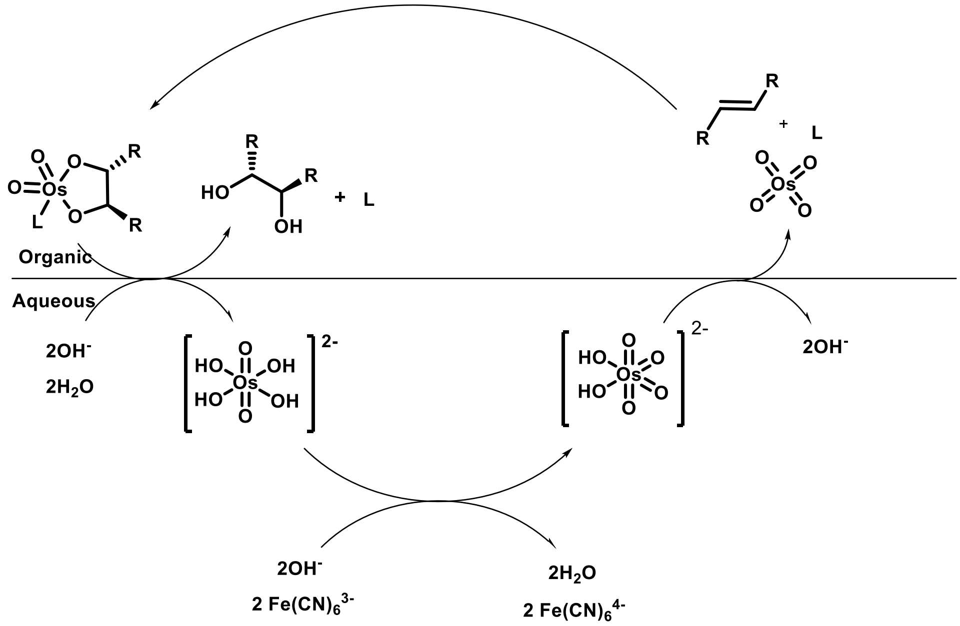
Figure 1: Structure of cinchona alkaloid ligands for AD.

The use of bidentate diamine ligands[9] brought exceptional enantioselctivity during Sharpless AD but their inert chelate complexes with Os (VI) glycolate products and hindered *in situ* recycling of osmium metal and ligands restricted their applications. Therefore, OsO_4 and the cinchona alkaloid based chiral ligands[9] were used in stoichiometric amount in these reactions. Sharpless and Marko[10] pointed out that the use of NMO as co-oxidant makes the asymmetric dihydroxylation more catalytic as compared when cinchona alkaloids are operated alone. Conversely, the enantiomeric excess of the vicinal diol synthesized was moderate utilizing NMO catalytic conditions and is attributed to the occurrence of a secondary catalytic route[11] (Scheme 2).



Scheme 2. Dual catalytic sequences involved in AD reaction employing NMO as co-oxidant.

For the above mentioned disadvantage a partial remedy, that is addition of alkene at slow pace, was proposed by Wa[11] that moderately enhanced the enantioselectivity. Kwong[12] discovered the eradication of secondary catalytic cycle when the AD was carried in two phase conditions using stoichiometric potassium hexaferrocyanate ($K_3Fe(CN)_6$ as co-oxidant. Here, exclusively OsO_4 is used as an oxidant in organic layer, in comparison to the homogeneous NMO conditions as depicted in Scheme 2.



Scheme 3. Catalytic sequence of AD route when $K_3Fe(CN)_6$ functions as co-oxidant.

Mechanistically, the osmylation of olefin took place in organic solvent phase and the formed final osmium monoglycolate ester (VI) underwent hydrolysis to releasing the diol. Next, ligand and Os (VI) were released to the organic phase and aqueous layer respectively. This process restrict the entrance of the osmium glycolate to the another cycle (Scheme 3).

Sharpless *et al.*[13] in 1992 after intensive investigation proposed the two crucial variations in osmium catalyzed AD process. The use of phthalazine class of cincona alkaloid derived ligands and enhances rate of hydrolysis of osmate ester using organic sulphonamides offered a lucid procedure applicable for the dihydroxylation of broad range of non-terminal olefinic substrates. The presence of methane sulphonamide, as an additive, compensates the limited release of OsO_4 from osmate ester and also supports the shorten reaction duration. During this, relatively less loading of ligand (1 mol%) also ensured the achievement of adequate enantioselectivity (upto 96%).

Ligands discovered by Crispino[14] (diphenylpyrimidine core) and Hartung[13] (phthalazine core) attached with two distinct cinchona alkaloid entities through a cyclic spacer, enhanced the enantioselectivity of Sharpless AD (Figure 2). Further, the mixture of $K_2OsO_2(OH)_4$ and inorganic cooxidant $[K_3Fe(CN)_6]$ and PHAL ligands are commercially available in premix form as "AD-mix", which containing all reagents and ligand required for dihydroxylation.

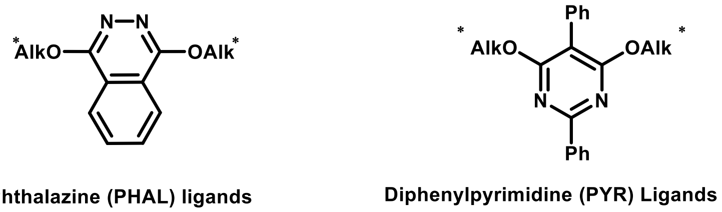
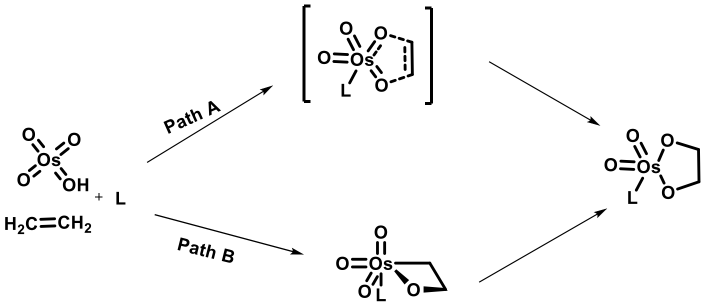


Figure 2. The modern equivalents of "dimeric" PHAL and PYR ligands (Alk* = DHQD or DHQ)

1.1.2. The Mechanism of Asymmetric Dihydroxylation (AD)

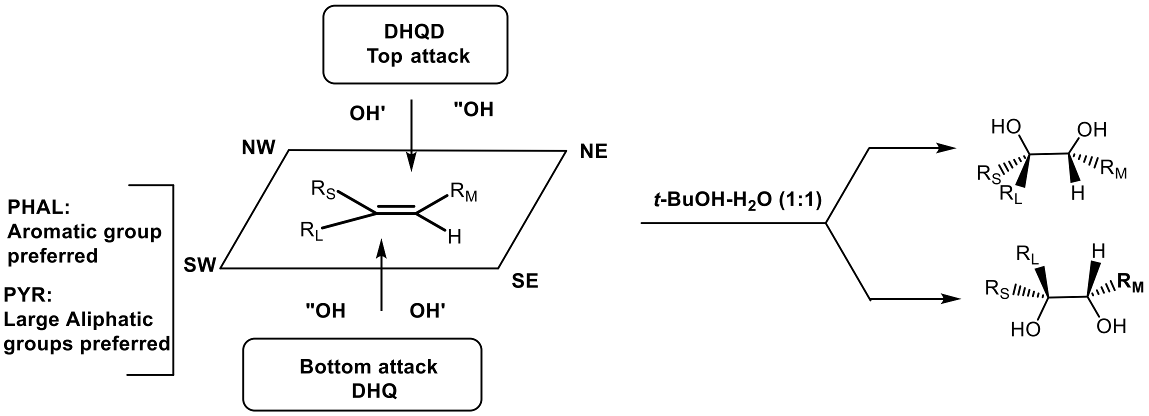
Mechanistically, osmium metal catalyzed dihydroxylation of olefins has been intensively explored and two different set of plausible pathways have been put forward. Boseken[15a] and Criegee[16] originally demonstrated concerted pathway [3+2], (Scheme 4, Path A) whereas Sharpless *et al.*[15b] and Jorgensen *et al.*[15c] independently proposed stepwise process, commenced by a [2+2] analogues addition of the alkene around one Os=O bond demonstrated in Scheme 4 (Path B) resulting into formation of osmaoxetane which further rearranges into the osmylate ester. However, mechanistic investigation and theoretical studies relying upon high activation barrier, favors the [3 + 2] pathway. [17]



Scheme 4. Schematic depiction of the [3+2] (Path A) and stepwise [2+2] (Path B) mechanism.

1.1.3 Empirical rules used for envisaging for the surface selection.

After the plausible mechanistic studies, 'Mnemonic device' was used for understanding the face selection sensitivity involved in the asymmetric dihydroxylation protocol (Scheme 5)[18]. According to basic set of rules, the alkene's plane was split up into four quadrants. In SE, i.e South East quadrant, small atoms like hydrogen can be inserted, as it is sterically inaccessible for bulky molecules. Groups heavier than hydrogen can take position in NW (North West) quadrant as it is little bit more voluminous than SE. In north east, quadrant because of its medium size pocket, moderate sized organic cluster can be placed. The South West (SW) quadrant accommodates massive ligand group (aromatic groups in PHAL ligands and PYR ligand) due to its comparatively large size. After, the placement of alkene according to above instructions, insertion of two hydroxyl group around the double bond take place in two ways; i.e from the above side (the β-face) when the DHQD ligand is used and from beneath (the α-face) when DHQ derived ligands are utilized.



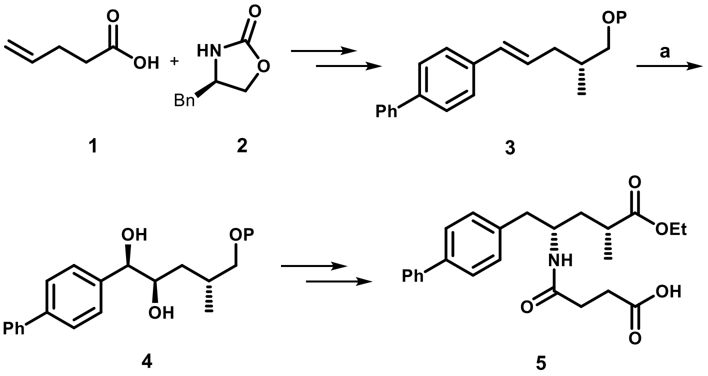
Scheme 5: The recommended mnemonic device used for face selectivity prediction.

1.1.4 Reaction Conditions

The Sharpless AD reaction is executed in 1:1 composition of *t*-BuOH and H_2O as solvent and usually concentration of olefin as substrate is taken around 0.1 M.[13] The pivotal reagents employed in Sharpless AD comprises OsO_4 (0.2-0.4 mol %), ligand (1 mol %), $K_3Fe(CN)_6$ (3 equivalents), methanesulphonamide (1 equivalent) and K_2CO_3 (3 equivalents). Further, the free chiral ligand can be extracted when Sharpless AD is carried out at bulk scale. After successful completion of the reaction, combined organic solvent layer is drawn out with 3% *aq*. sulphuric acid saturated utilizing K_2SO_4 (ca. 40 mL/1g of ligands) and the PHAL ligand go to the water layer as a salt of hydrogen sulphate and subsequent AD reaction could be performed with the recovered solution without further purification.

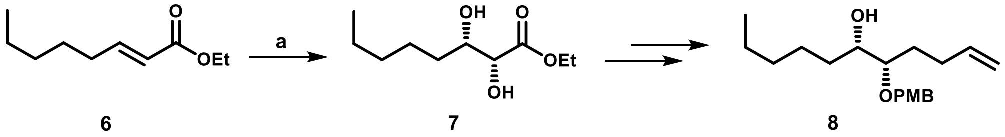
1.1.5 Application

We have utilized the Sharpless AD conditions for the synthesis of intermediate **4** required for the enantioselective formation of Sacubitril **5** as displayed in the Scheme 6. The synthetic route of **4** began from pente noic acid **1** which was converted into mono protected non terminal alkene **3** *via,* Evans methylation, Heck coupling and after following other standard functional group transformations. Next, alkene **3** on OsO_4 catalyzed Sharpless AD in the presence of $(DHQD)_2PHAL$ as ligand afforded the *syn* vicinal diol fragment **4** with good enatioselctivity, which on further organic manipulations furnished the target molecule Sacubitril **5** in excellent yield.



Scheme 6. *Reagents and conditions*: (a) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, $CH_3SO_2NH_2$, *t*-BuOH/Water (1:1), 24 h, 0 ^{o}C, 95%.

Furhter more, $(DHQ)_2PHAL$ ligand mediated Sharpless AD was also employed for the synthesis of the mono protected olefinic alcohol fragment **8** of cytospolide D. As depicted in Scheme 7, the synthesis of olefinic alcohol **8** was initiated with achiral *α*, *β*-unsaturated ester **6.** Next, the Sharpless AD of ester **6** utilizing OsO_4, co-oxidant $K_3[Fe(CN)_6]$ and with catalytic proportion of $(DHQ)_2PHAL$ gave vicinal diol **7** which on further standard organic transformations furnished compound **8** in acceptable yield.



Scheme 7: Reagents and conditions: (a) 0.005 mol% OsO_4, 0.1 mol% $(DHQ)_2PHAL$, $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, potassium carbonate, *t*-BuOH:H_2O 1:1 v/v, 0 ^{o}C, 24 h, 92%.

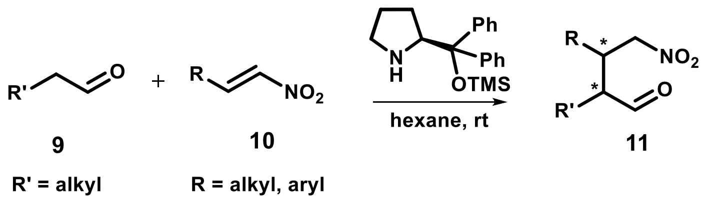
1.2 Organocatalyzed Michael addition reactions

1.2.1 Introduction

Micheal addition reaction also familiar as conjugate addition reaction (1,4 addition) is broadly characterized as addition of nucleophile (enolate) on *β* carbon of an *α, β* unsaturated carbonyl compounds or electro-deficient alkene such as nitro olefins in the presence of catalyst.[19] Among various C-C or C-X (heteroatom(X)=N, S, O) bond forming methodologies, conjugate addition emerged as a versatile reaction and therefore employed in organic synthesis for the construction of enantiomerically pure bioactive skeletons.[20] The participation of large variety of electrophiles (*α, β*-unsaturated carbonyl compounds, esters, phosphonates, cyanoester, nitrostyrene as electrophiles etc.) and nucleophiles (organometallic reagents, Michael donors, other carbanions) enhances utility of this approach. In the recent years, because of high requirement for optically active compounds, tremendous progress has been made in the field of asymmetric version of conjugate addition reaction, which provide the Michael adduct with desired chirality and enantioselectivity. In this direction, organocatalysed asymmetric Michael addition reaction evolves as a promising tool. Numerous reagent systems for this kind of transformation utilizing asymmetric catalysis have been documented in literature.[21]

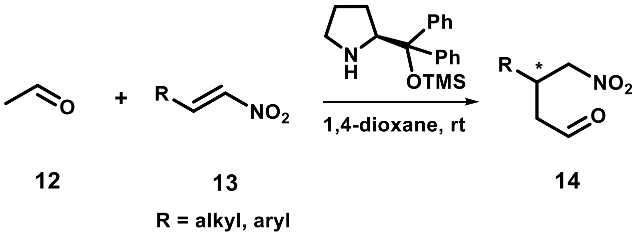
1.2.2 Organocatalysed Michael addition reaction on conjugated nitro alkenes

The utmost synthetic challenge is not only to construct the C-C bond but also to control the configuration of newly generated chiral centre while executing organic synthesis of compounds. The branch of organocatalysis is growing rapidly and several important asymmetric transformations have been cited where reactive chiral enamines and iminum ions controlled the stereochemistry. Michael addition reaction of nitroalkenes with various aldehyde as nucleophiles turned out to be a constructive approach for building *β* -substituted nitro alkanes. These *β* -substituted motifs emerged as crucial synthetic building blocks as aldehyde and nitro functionality could be efficaciously transformed into other functional groups. In this direction, Hayashi and co-workers[22] developed an organocatalysed asymmetric conjugated addition approach where an *α* substituted aldehyde **9** on reaction with nitro-olefins **10** in the presence of catalytic amount of diphenyl prolinolsilyl ether (TMS prolinol) yielded the *α* substituted *γ* nitro aldehydes **11** with excellent enatioselectivity (upto 99% *ee*) and diastereoselectivity (97:3 *syn*:*anti*) with yield of 85%. (Scheme 8).



Scheme 8. Organocatalyzed Michael addition reaction of nitroalkene.

In an another attempt, Hayashi and his team performed the diphenylprolinol silyl ether catalysed asymmetric Michael addition reaction of acetaldehyde **12** as nucleophile and acceptor nitroalkene **13** as electrophile to furnish the chiral product **14** in pleasant yield (upto 77%) with >99 % enantiomeric excess (Scheme 9).[23] The stereochemistry of the chiral centre was controlled using *(R)* or (*S)*- TMS prolinol as catalyst.



Scheme 9. Organocatalyzed Michael addition reaction of acetaldehyde with nitroalkene.

The mechanism proposed for the TMS prolinol catalysed conjugate addition of acetaldehyde to nitroalkene is described in Figure 3. In the first step, an enamine **I** formation takes place when aldehyde **15** is treated with TMS-prolinol catalyst. In the next step, this nucleophile enamine joins with conjugated nitro-olefin **13** to produce the imine intermediate **II,** which upon subsequent hydrolysis afforded the nitroaldehyde **16** and organocatalyst**.**

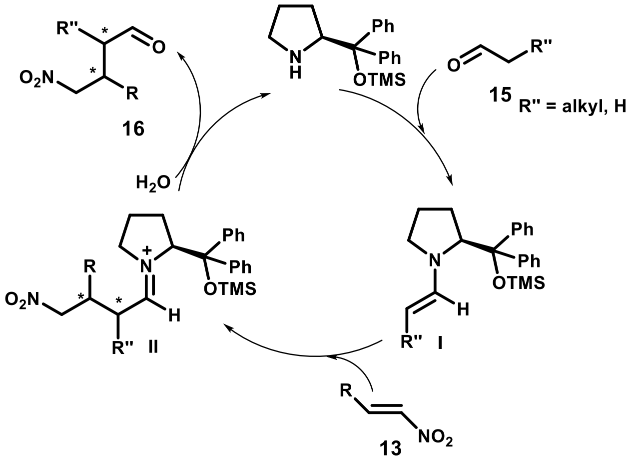
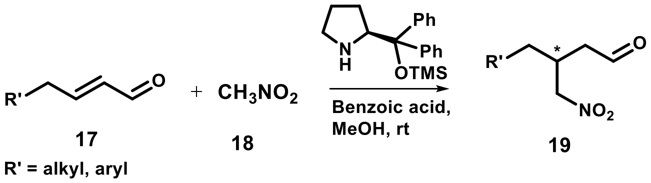


Figure 3. General mechanistic approach for organocatalzyed Michael addition reaction.

1.2.3 Organocatalyzed Michael addition reaction on conjugated aldehydes

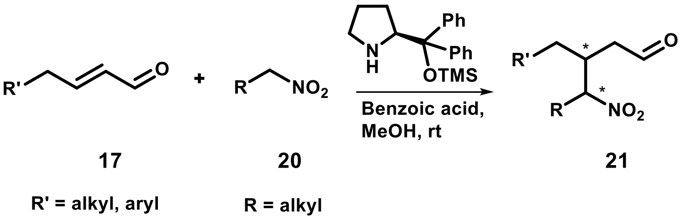
As γ-nitro aldehydes are synthetically valuable chiral intermediates that can be converted into amino carbonyl and amino alkanes utilised for the production of wide range of chiral pharmaceuticals such as Baclofen[24] and Pregabalin.[25,24b] Therefore, for the synthesis of these nitroaldehyde adducts Hayashi and his team[24b] investigated the Micheal addition between nitromethane **18** (nucleophile) and α β-unsaturated aldehydes **17** (as an electrophile). Originally, 1,4 conjugate additions was not favourable due the presence of rapidly occurring competitive 1,2 addition reaction.

The methodology involves the addition of CH_3NO_2 **18** to *trans*-olefinic aldehydes **17** in the presence of organocatalyst diphenylprolinol silyl ether to produce the nitroaldehyde adduct **19** in excellent yield (≥ 90%) and enantioselectivity (upto 95 %ee) (Scheme 10).



Scheme 10. Organocatalyzed Michael addition reaction using nitromethane as nucleophile.

Hayashi and co-workers also carried out the Michael addition of substituted conjugated aldehydes **17** with substituted nitroalkane **20** using substoichiometric concentration of TMS-prolinol for yielding nitroaldehyde adduct **21** in high diastereoselctivity, enantioselectivity (upto 96% ee) and excellent yield (upto 95%) (Scheme 11).[20]



Scheme 11. Organocatalyzed Michael addition reaction with substituted nitromethane.

A plausible mechanism for organocatalyzed Michael addition reaction of nucleophilic nitroalkanes to electrophilic conjugated aldehydes is described in Figure **4**. Here, aldehyde **17** on coupling with TMS-prolinol produces imine intermediate **I** which on reaction with nitroalkane **20** furnishes enamine intermediate **II.** Further, hydrolysis of intermediate **II** generates nitroaldehyde adduct **21** along with subsequent generation of organocatalyst.

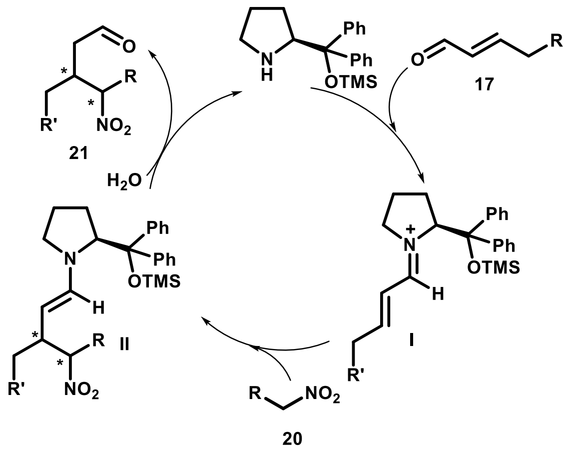


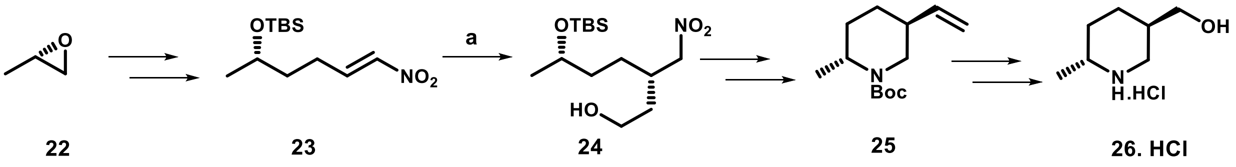
Figure 4. General mechanism for organocatalzyed Michael addition reaction

1.2.4 Reaction conditions

The catalytic organocatalysed direct Micheal addition of nitroolefin with acetaldehyde was carried out in DMF as solvent at ambient temperature. Nitro olefin (1 equivalent) along with organocatalyst (20 mol %) and 2-propanol (10 equivalnet) was taken in sealed tube under argon. Acetaldehyde (5 equivalent) taken in DMF was added drop by drop to the previous mixture and resulting suspension was agitated for 24-48 h at room temperature.

1.2.5 Application

We have successfully implemented organocatalzyed Michael addition strategy for the synthesis of piperidine skeleton **26** (core unit of potent dual orexin receptor antagonist MK-6096). The synthesis of piperidine skeleton **26** started with readily available (*S*)-propylene oxide **22** which was transformed into *α*, *β*-unsaturated nitroolefin **23** *via* standard organic transformations (Scheme 12). The *α*, *β*-unsaturated nitroalkene **23** on successful conjugate Michael addition with acetaldehye in the presence of (*R*)-diphenylprolinol silyl ether (10 mol%) in DMF afforded the nitroaldehyde adduct which on subsequent reduction with NaBH$_4$ furnished the nitro-alcohol derivative **24** in excellent yield. Further, other standard organic functional group manipulations on **24** were carried out to deliver nitro-alkene **25** which further furnished piperidine skeleton **26** as its HCl salt**.**



Scheme 12. *Reagents and conditions*: (a) (i) CH_3CHO, (*R*)-diphenylprolinol silyl ether, *i*-PrOH, DMF, rt, 24 h; (ii) $NaBH_4$, CH_3OH, 0 ^oC, 30 min, 66% (over 2 steps).

1.3 Organocatalyzed aldol reactions

1.3.1 Introduction

The aldol reaction is a carbon-carbon bond making approach, involves linking of two carbonyl compounds that eventually leads to the formation of β-hydroxy carbonyl moieties. Conventionally, aldol reactions were carried out under acidic and basic conditions and products obtained were usually condensed ones. Asymmetric construction of chiral β-hydroxy carbonyl motifs was envisioned by controlling the absolute configuration of newly generated stereocentre during aldol reaction of aldehydes or non-symmetrical ketones. Therefore, asymmetric aldol reactions have been investigated as reliable tool for these tranformations.[26a] Initially, chiral auxiliaries like oxazolidinones and their analogues were favoured for the synthesis of enantiopure β–hydroxy compounds.[26b,c] However, use of stoichiometric ratios of the chiral auxiliaries makes it an inefficient asymmetric protocols, and instead organocatalysed enantioselective aldol procedures emerged as an effective pathways for providing enantiopure products.

Organocatalytic strategies are on the forefront to carry out the chemical reactions for the asymmetric synthesis of complex chiral skeletons employing a sub stoichiometric amount of an organic compound. Organocatalysts are usually enantiomerically pure small molecules devoid of any active inorganic element.

Among several types of organocatalysts, lewis base such as amines dominates the field. L-proline, a naturally occurring amino acid possess a secondary amine functionality, available in both enantiomeric forms, promotes broad diversity of organic transformation such as inter and intramolecular aldol reaction, Mannich, Michael addition and Diels-Alder reactions. Proline, operate as a "micro-aldolase" as it carries nucleophilic amino group and as well as carboxylate that act as an acid/base co-catalyst.

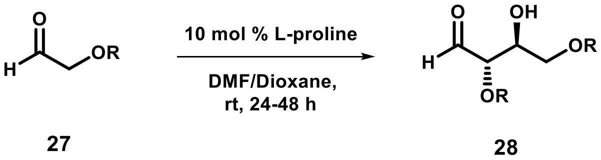
Proline referred as a "universal catalyst", as it is water soluble, eco-friendly, innocuous, easily recoverable and provide high enantioselctivity with in mild reaction conditions. In 1971, Hajos- Parrish-Eder-Sauer-Wiechert reaction was the foremost intramolecular aldol reaction that utilized proline as a catalyst.[27] Later, Barbas and his team synthesized Wieland-Miescher ketone employing proline mediated Robinson annulation reaction.[28]

1.3.2 MacMillan's organocatalyzed self and crossed aldol reactions of *α*-oxyaldehydes

Inter and intra-molecular asymmetric aldol reactions are one of the fundamental carbon-carbon bond formation procedures widely performed in total synthesis of complex organic compounds. In 2002, MacMillan firstly reported highly expedient organocatalytic strategy for cross aldol sequence of *α*-alkyl-bearing aldehydes in a highly regioselective, diastereoselective, and enantioselective manner.[29] Here, interestingly, enantio-enriched aldol aldehyde as a product resist further aldol reactions in the presence of L-proline (10 mol %) as an organocatalyst.

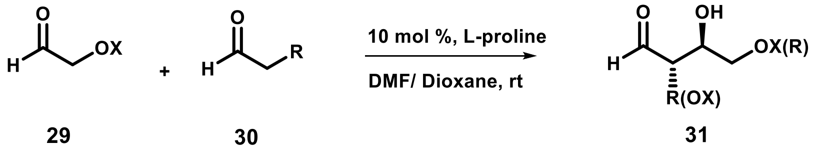
In 2004, MacMillan extended the applicability of proline catalysis to self and cross aldol reaction of *α*-oxygenated aldehydes[30] as depicted in Scheme 13 & Scheme 14 respectively. This protocol provided a pathway for the stereocontrolled construction of polyol fragments required for carbohydrate synthesis. More importantly, the final oxyaldehyde adducts of this reaction were inert to further proline-catalyzed enolization or enamine addition.

Firstly, MacMillan and co-workers explored the organocatalytic self-coupling of *α*-oxyaldehydes **27** in DMF/dioxane in presence of L-proline (10 mol %) which provided the desired oxyaldehyde dimer **28** with *anti* aldol selectivity (88-98% ee) and with 42-92% yield (Scheme 13).



Scheme 13: Self-aldol reactions of protected glycoaldehydes. (R= TIPS, TBDPS, Bn, PMB, MOM, Ac, TBS).

Further, they studied L-proline (10 mol%) catalyzed cross-coupling between *α*-oxyaldehydes **29** and *α*-alkyl-substituted aldehydes **30** in DMF/dioxane**.** Among the both enolizable protons bearing substrates, glycoldehyde reacted as electrophile with respect to the alkyl aldehydes having methylene protons. The final result of this cross coupling afforded the *syn*-, *anti*-product **31** in 33-84% with excellent enantiomeric excess (>94% ee) (Scheme 14).



Scheme 14: Cross-aldol reactions between glycoaldehydes & *α*-alkyl-substituted aldehydes. (R= Me, *i*-Pr; OX= OTIPS, OTBDPS, OBn).

1.3.3. The Mechanism of Aldol reaction

The mechanism involved in proline catalyzed asymmetric self/cross aldol reaction is demonstrated in Figure 5. The aldehyde **32** on reaction with proline leads to the formation of enamine intermediate **33** which upon nucleophilic addition to same or different aldehyde **34** synthesizes self/cross imine intermediate **II**.

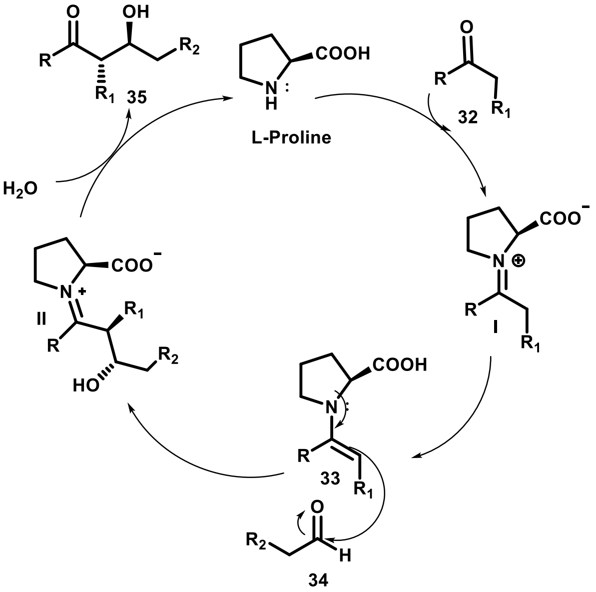


Figure 5. A general mechanism of proline-catalyzed self and cross aldol reactions.

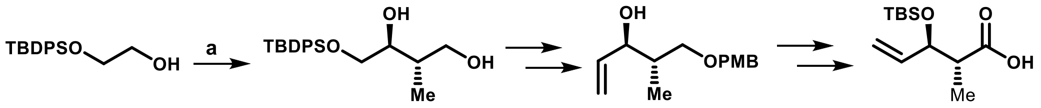
Finally, *in situ* produced imine intermediate **II** on hydrolysis furnish the *β*-hydroxyaldehyde derivatives **35** with concurrent release of proline molecule.

1.3.4 Reaction conditions

The asymmetric cross aldol reaction of oxyaldehyde (1 equivalent) was performed at 4 ^{o}C temperature in presence of L-proline (10 mol %) taken in DMF or dioxane. Both acceptor (1 equivalent) and donor aldehydes (5 equivalents) were kept at 4 ^{o}C. To a mixture of acceptor aldehyde and L-proline (0.1 equivalent) in DMF or dioxane was added drop by drop to a suspension of donor aldehyde dissolved in DMF or dioxane *via* syringe pump and obtained suspension was agitated for 24-48 h at 4 ^{o}C.

1.3.5 Application

We have successfully applied MacMillan's cross-coupling between the aldehyde derived from mono protected ethylene glycol **36** and propionaldehyde for the synthesis of acid **39** fragment **39** of Cytospolide D as displayed in Scheme 15. The cross aldol reaction was catalyzed using D-proline and the intermediate aldehyde upon reduction using $NaBH_4$ afforded the *anti*-alcohol **37**, which was further exposed to set of organic transformations for the synthesis of acid derivative **39** through the intermediate **38**.



36 **37** **38** **39**

Scheme 15. *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, triethylamine, CH_2Cl_2, -78 ^{o}C to rt, 2 h; ii) Propionaldehyde, 10 mol % D-proline, 1,4 dioxane, 4 ^{o}C, 24 h; iii) $NaBH_4$, CH_3OH, 30 min, 86% (three steps).

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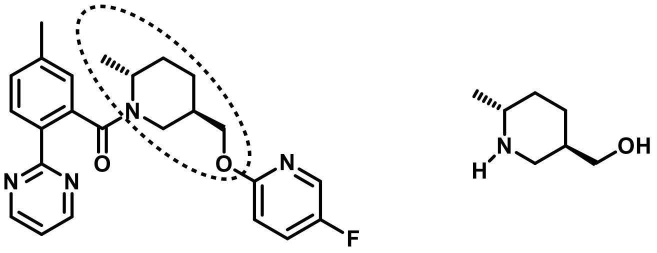
CHAPTER 2

An efficient approach towards the chiral synthesis of piperidine skeleton: Core unit of potent dual orexin receptor antagonist MK-6096.

An efficient approach towards the chiral synthesis of piperidine skeleton: core unit of potent dual orexin receptor antagonist MK-6096

2.1 Introduction:

Insomnia, is a rapidly occurring neuropsychiatric disorders especially affecting 40-60% elder individuals and is closely associated with a host of other diseases like, obesity, cardiovascular disease, depression, cancer and chronic pain.[1] The orexins (hypocretins)[2] functions as neurotransmitter and widely participate in sleep regulations.[3] This correlation explained the use of orexin receptors for the treatment of sleep illness in place of sedative hypnotics that may cause unwanted side effects. Suvorexant and almorexant, are dual orexin receptor antagonists (DORA), and were found to promote sleep in animals and were in the clinical trials for the treatment of initial insomnia. Campeau and co-workers[4a] discovered a structurally distinct, dual Orexin Receptor Antagonists (DORA) named MK-6096 (Figure 6) that was under evaluation to be used as a potent drug for the treatment of insomnia. MK-6096 **40**, consist of *trans*-3,6 disubstituted piperidinyl core **26** (Figure 6)**,** a biaryl acid and fluoropyridine fragment. In functional cell based assays and radioligand binding MK-6096 **40** demonstrated potent antagonism and binding to both human OX1R and OX2R (11 nM in FLIPR, 170 enzymes and receptors. Therefore, it is highly desirable to develop a simple and enantiopure synthetic pathway that enable the synthesis of 3,6-disubstituted piperidine motifs **26** with desired stereochemical variations in good yield.



MK-6096, 40

Piperidine Core Unit, 26

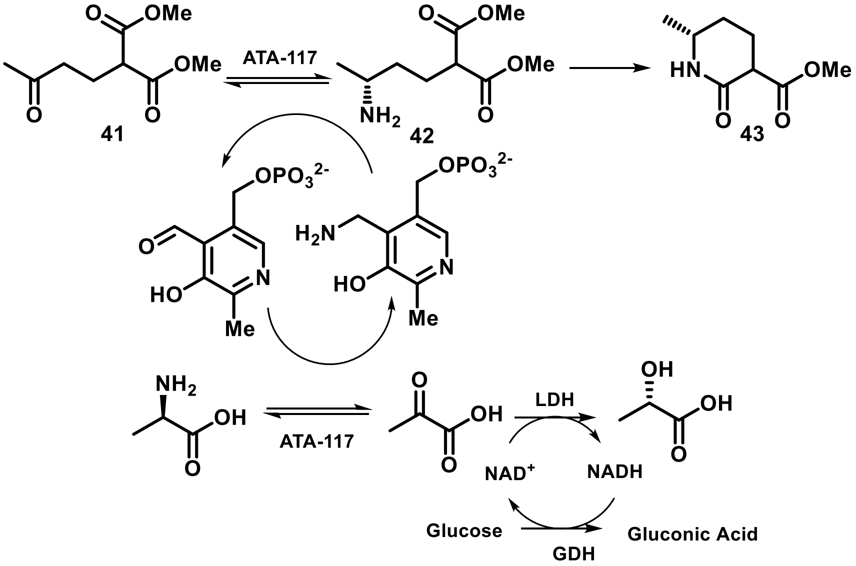
Figure 6: Structure of dual orexin receptor antagonists MK 6096 and ((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol core unit.

2.2 Review of Literature:

Various elegant syntheses of ((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol **26**, core unit of MK6096 **40** have been outlined in literature.[4] All of asymmetric syntheses have utilized complex biocatalytic transamination process for the introduction of *trans* stereochemistry in **26** and are narrated as follow:

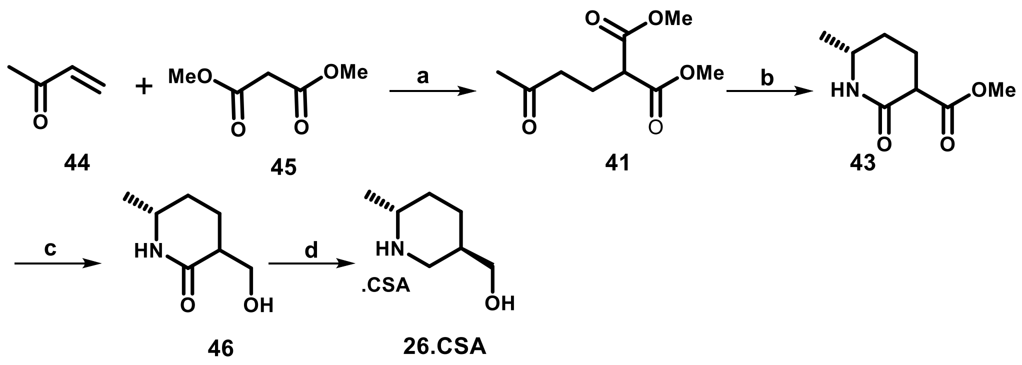
Campeau, L. C. *et al.* (2013)[4a]

Campeau and co-workers put forward the first multigram scale synthesis of dual orexin receptor antagonist **40**, where the chirality in piperidine moiety **26** was incorporated using biocatalyzed process as illustrated in Scheme 16 & Scheme 17. Methyl vinyl ketone **44** and dimethyl malonate **45** served as starting material which under Michael addition condition (K_2CO_3/MeCN) furnished the compound **41** in excellent yield (Scheme 17). The ketone derivative **41** was exposed to biocatalytic transamination process to yield the intermediate amino diester compound **42** as depicted in Scheme 16. For this catalytic process, a combination of ATA-117 enzyme/D-alanine and pyridoxal-5'-phosphate as co-factor were used which successfully enable the transfer of amine group to the compound **42**. In this, the enzyme lactate dehydrogenase (LDH) and glucose dehydrogenase (GDH) were also utilized to ensure the catalytic turnover and NADH recyclability respectively.



Scheme 16: Biocatalytic transamination process of compound 41.

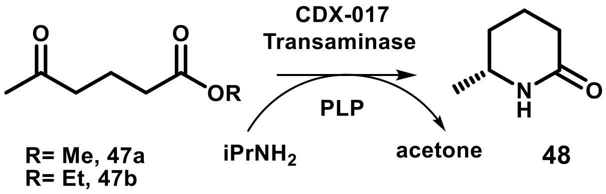
Further, intermediate **42** readily cyclized to furnish the piperidone **43** with desired stereochemistry. Further, the ester group of compound **43** was reduced using a combination of $NaBH_4$ and $CaCl_2$, to furnished cyclic lactam **46** in 94% yield (dr 1.7:1) (Scheme 17). Finally, the reduction of lactam derivative **46** was performed employing $LiAlH_4$ and chiral piperidine core **26** was isolated as its CSA salt with acceptable diastereomeric ratio (dr >40:1) with 24% overall yield



Scheme 17. *Reagents and Conditions*: (a) K_2CO_3, MeCN, 17 ^oC, 21 h, 80%; (b) Na_2HPO_4, D-alanine, glucose, NAD, PLP, ATA-117, LDH, GDH, 42 h, 74% (enzymatic transamination, Scheme 1); (c) $NaBH_4$, $CaCl_2$, EtOH, 21 h, 94%; (d) i) $LiAlH_4$, THF, 50 ^oC, 12 h, 82%; ii) D-(+)-CSA, MTBE, THF, rt, 5 h, 52%.

Chung, J. Y. L. *et. al.* (2014).[4b]

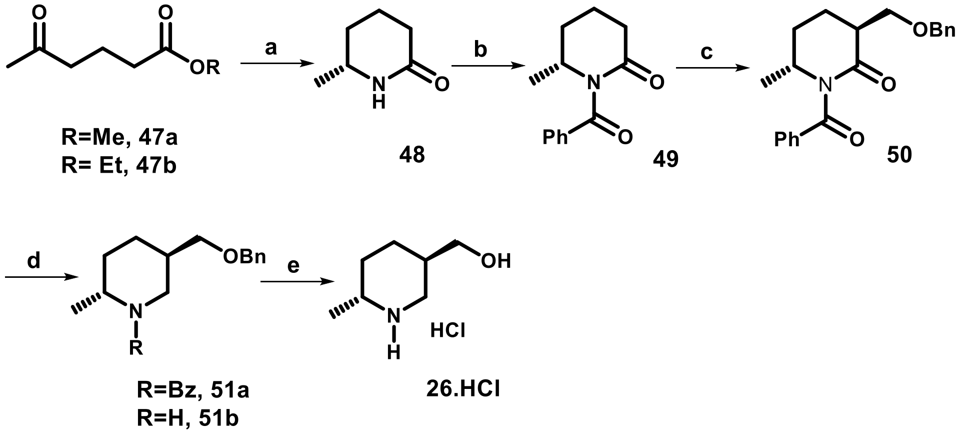
John Y. L. Chung and co-workers described the asymmetric synthesis of piperidone core **26** from keto-ester **47a** & **47b** in total five steps (Scheme 19). The synthesis of **26** began with biocatalytic transamination of substrate **47a** and **47b** using three enzymatic systems as mentioned in Scheme 16 and improved one enzymatic system (scheme 18) to afford the lactam **48** with 99 % ee.



Scheme 18: One enzyme biocatalytic transamination process for the synthesis of compound **48.**

Further, the treatment of cyclic lactam derivative **48** with benzoyl chloride furnished the *N*-benzoyl protected compound **49** in 96% yield. The derivative **49** on Mukaiyama aldol reaction with dibenzyloxymethane afforded the piperidine **50** in excellent yield. Mukaiyama aldol reaction was used for the synthesis of fragment **50** where, in general silyl enol ether on treatment with aldehyde using lewis acid as catalyst afforded the condensed products. Here, TMSOTf solution of lactam **49** and dibenzyloxymethane in the presence of base afforded the fragment **50** in excellent yield and diasteromeric excess. However, the same reaction could be conducted in the presence of $TiCl_4$/Hunigs base but in slight lower diaseteromeric excess

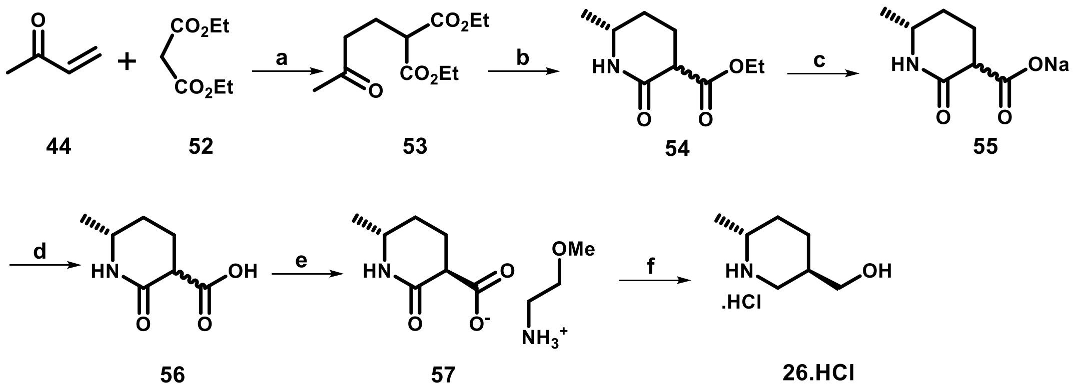
(96:4 *trans*/*cis*). For the current studies, former conditions were utilized. Next, the derivative **50** on reduction with $LiAlH_4$ in dry THF delivered the mixture of benzyloxy piperidine compound **51a** & **52b** in good yield. Subsequently, compound **51a** & **52b** under hydrogenolysis conditions using catalytic amount of $Pd(OH)_2$ and immediate treatment with HCl afforded the target compound hydroxyl methyl piperidine **26** as it HCl salt in 48% yield.



Scheme 19. *Reagents and Conditions*: (a) Sodiumtetraborate decahydrate, isopropylamine, CDX-017, PLP, 25 ^{o}C, 26 h, 76% (Scheme 18); (b) BzCl, Et_3N, DMP, CH_3CN, rt-70 ^{o}C, 18 h, 96%; (c) $(OBn)_2CH_2$, TMS-OTf, TEA, CAN, 0-22 ^{o}C, 2 h, 90%; (d) $LiAlH_4$, THF, 50 ^{o}C, 20 h; (e) H_2, $Pd(OH)_2$, cat. HCl, MeOH, 4 h, 40 ^{o}C, 48%.

Chung, J. Y. L. *et. al.* (2015).[4c]

Chung and his team proposed another method for the construction of *trans*-piperidine core **26** employing crystallization–induced dynamic resolution (CIDR) that resulted in improved diastero-selectivity and excellent yield (Scheme 20). For this, diethyl malonate **52** and methyl vinyl ketone **44** were exposed to solvent free Micheal addition in the presence of 0.25% cesium carbonate (Cs_2CO_3) to afford the ketone derivative **53** in 87% yield. Transaminase reaction of compound **53** was carried out using one enzyme system to afford the lactam ethyl ester **54** in 74% yield with 1.2:1 diastereomeric ratio.



Scheme 20. *Reagents and Conditions*: (a) 0.25% Cs_2CO_3, 15 ^oC, 22 h, 87%; (b) transaminase CDX-010, pyridoxal-5-phosphate, borate buffer, *i*$PrNH_2$, 45 ^oC, 20 h, 74%; (c) 5N NaOH, THF, 15 ^oC, 2 h; (d) HCl, 30 min, 0 ^oC - rt ; (e) 2-methoxyethylamine, 19-23 ^oC, 2-16 h, 91%; (f) BH_3.THF, THF, 70 %.

The derivative **54** on saponification and further careful treatment of the intermediate sodium salt **55** with HCl yielded the acid derivative **56** in good yield (1.1-1.8:1 *cis*:*trans*). With clean lactam acid derivative **56** in hand, crystallization–induced dynamic resolution of compound **56** was performed in the presence of 2-methoxyethylamine (MEA) to furnish *trans* derivative **57** as its MEA salt with 91% yield and 96% diastereomeric excess. The methoxyethylamine salt **57** on treatment with BH_3.THF delivered the desired *trans* piperidinol **26** as its hydrochloride salt in 70% yield.

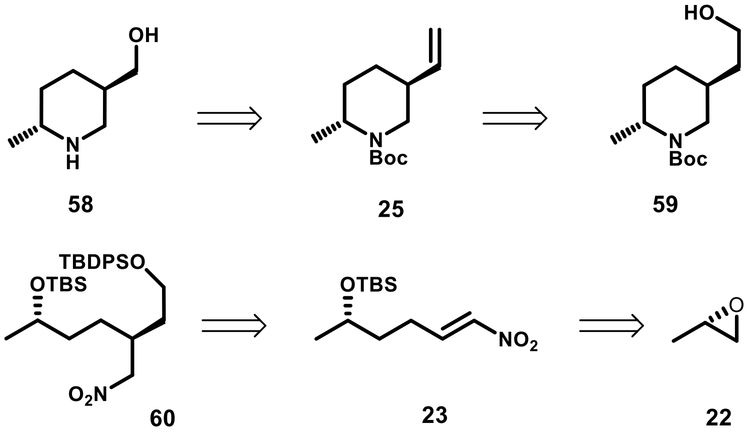
2.3 Present work:

Objective:

As a component of our on-going research plan towards the asymmetric syntheses of medicinally important compounds, herein, we are reporting a flexible approach for the synthesis of ((3*R*, 6*R*)-6-methylpiperidin-3-yl)methanol **26** using commercial available (*S*)-propylene oxide as a starting material and organo-catalyzed asymmetric Michael addition[5] reaction as key step. This route is favourable for sterochemical derivatization at both chiral centres.

2.4 Results and Discussion

The retrosynthetic analysis for the synthesis of *trans*-3,6- disubstituted piperidine unit **26** is depicted in Scheme 21. We anticipated that the alcohol **58** could be accessible from alkene **25** using oxidative cleavage of double bond followed by reduction. The alkene derivative **25** in turn could be derived from *N*-Boc protected piperidine alcohol **59** *via* its conversion to corresponding iodide followed by subsequent thermal elimination. The alcohol derivative **59** could be constructed from silyl group protected nitro-alcohol derivative **60** through selective TBS deprotection, *O*-mesylation and Zn/AcOH mediated reduction of nitro to amine for cyclization and N-Boc protection. We envisaged that, the key intermediate nitro-alcohol derivative **60** could be assimilated from *α*, *β*-conjugated nitro alkene **23** *via* organocatalyzed asymmetric Michael addition reaction. The *α*, *β*-unsaturated nitro alkene derivative **23** in turn could be accessed from chiral (*S*)-propylene oxide **22** *via* allyl Grignard, oxidative cleavage of terminal double bond and Henry reaction following standard organic transformations. The epoxide **22** could be alternatively obtained by using Jacobsen's hydrolytic kinetic resolution (HKR) methodology.[6]

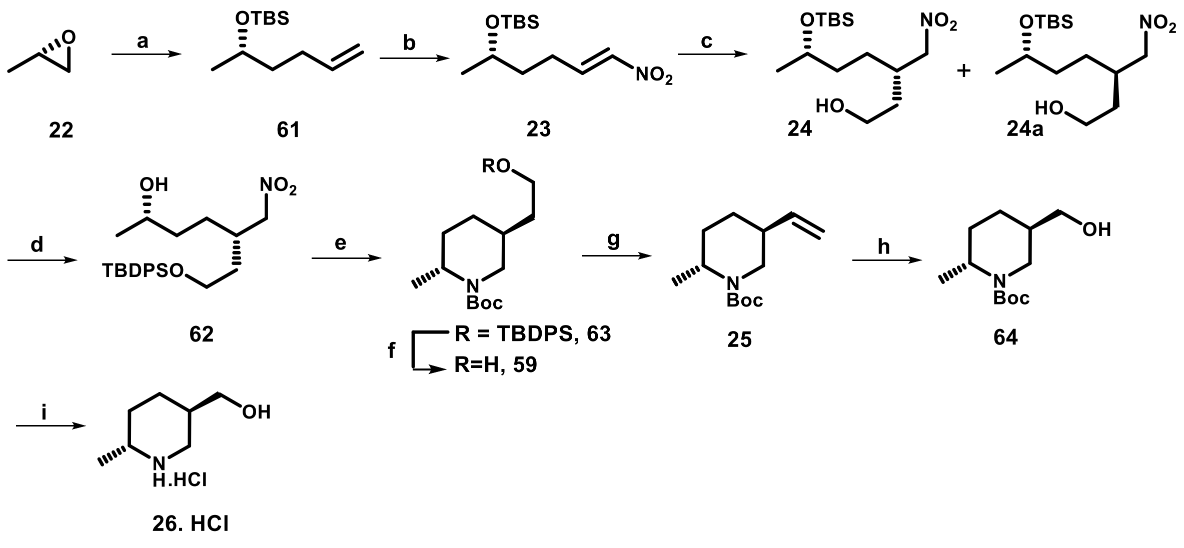


Scheme 21: Reterosynthetic analysis for *trans*-3,6-disubstituted piperidine.

The synthesis of *trans*-3,6-disubstituted piperidine unit **26** commenced from commercially available (*S*)-propylene oxide **22** as outlined in Scheme 22. The (*S*)-propylene oxide **22** was subjected to copper-catalyzed (CuI) regioselective opening with the allyl magnesium bromide and further treatment of the newly generated secondary alcohol with TBSCl in the presence of imidazole and catalytic amount of DMAP furnished the alkene derivative[7] **61** in 85% yield. A one-pot oxidative cleavage of silyl ether **61** with OsO_4/$NaIO_4$ led to aldehyde which under Henry reaction conditions and dehydration afforded *α*, *β*-unsaturated nitro alcohol derivative **23** in 93% yield. In the IR spectrum of compound **23**, NO_2 stretch was found at 1528 and 1340 cm^{-1}. In ^1H NMR spectrum of **23**, olefin protons were found resonating at *δ* 7.35-7.26 as a multiplet (one proton) and at *δ* 7.01 as doublet of triplets (one proton) with coupling constant (*J*) of 13.6 and 1.6 Hz, confirming the formation of **23**.

Our next aim was to carry out the synthesis of *trans*-3,6-disubstituted piperidine moiety **26**. Towards this end, asymmetric Michael addition[5] of acetaldehyde with α, β-unsaturated nitro-olefin alcohol derivative **23** in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether furnished the nitro-aldehyde adduct which on spontaneous reduction with $NaBH_4$ furnished nitroalcohol derivative **24** as a single diastereomer in 66% yield $\{[a]_D^{25}$ +11.8 (c 0.25, CH_3OH)$\}$. The disappearance of olefin protons at δ 7.35-7.26 and at δ 7.01 in ^{1}H NMR spectrum of **24** also supports the utilization of double bond during Michael addition and a doublet was also found resonating at δ 1.72 (3H) with coupling constant value of 6.0 Hz that correspond to terminal methyl group. The IR spectrum of **24** exhibited hydroxy absorption at 3470 cm^{-1} and NO_2 stretching at 1550 and 1348 cm^{-1}.

Further, to elucidate the diastereoselectivity during the Michael addition, conjugate addition of acetaldehyde with α, β-unsaturated nitroalcohol derivative **23** was carried out in the presence of racemic diphenylprolinol silyl ether catalyst (containing equimolar quantities of *R* and *S*-diphylprolinol silyl ether) which on reduction with $NaBH_4$ furnished the *syn*-/*anti*-nitroalcohol diastereomers[8] **24** & **24a** (dr, 1.1:1) with 68% combined yield. On the other side, the conjugate addition of substrate **23** in the presence of catalytic amount of enantiopure (*R*)-diphenylprolinol silyl ether furnished the *syn*-nitroalcoholderivative **24** as a single diastereomer, (dr, > 99%) which is in accordance with the previously proven model in organocatalytic Michael addition reaction.[5] Here, under later reaction conditions no traces of *anti*- diasteromers were found in the reaction mixture.



Scheme 22: *Reagents and conditions*: (a) (i) C_3H_5MgBr, CuI, THF, 40 ^oC, 1 h; (ii) TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 3 h, 85%; (b) (i) OsO_4, 2,6-lutidine, $NaIO_4$, dioxane:H_2O (3:1, v/v), 3 h; (ii) CH_3NO_2, *aq*. NaOH, CH_3OH, 0 ^oC to rt, 20 min; (iii) MsCl, NEt_3, CH_2Cl_2, 0 ^oC to rt, 1.5 h, 93% (over 3 steps); (c) (i) CH_3CHO, (*R*)-diphenylprolinol silyl ether, *i*-PrOH, DMF, rt, 24 h; (ii) $NaBH_4$, CH_3OH, 0 ^oC, 35 min, 66% (over 2 steps); (d) (i) TBDPSCl, imidazole, DMAP, dry CH_2Cl_2, 0 ^oC- rt, 2 h; (ii) *p*-TsOH, CH_3OH, 0 ^oC to rt, 30 min, 96% (over 2 steps); (e) (i) MsCl, Et_3N, CH_2Cl_2, 0 ^oC - rt, 25 min; (ii) Zn, AcOH, CH_2Cl_2, rt, 1 h; (iii) $(Boc)_2O$, NaH, DMAP, DMF, 0 ^oC to rt, 12 h, 89% (over 3 steps); (f) TBAF, THF, 0 ^oC to rt, 2 h, 95%; (g) (i) I_2, PPh_3, Imidazole, DCM, rt, 30 min; (ii) *t*-BuOK, *t*-BuOH, reflux, 83 o C, 1 h, 91%; (h) (i) OsO_4, $NaIO_4$, 2,6- lutidine, dioxane: water 3:1v/ v, rt, 4 h; (ii) $NaBH_4$, CH_3OH, 0 ^oC, 35 min. 90%. (i) 6 N HCl, water, 101 ^oC, 1.5 h, 95%.

Further, hydroxyl protection of **24** with *tert*-butyldiphenylsilyl chloride in the presence of imidazole and catalytic amount of DMAP afforded the silyl ether intermediate which on subsequent selective TBS deprotection in presence of catalytic amount of *p*-TSA afforded the alcohol derivative **62** in 96% yield. In the ^1H NMR, presence of additional set of aromatic protons resonates at δ 7.69-7.60 & at δ 7.48-7.34 (multiplet, four protons) confirmed the primary hydroxyl group protection as its TBDPS ether in compound **62**.

Our next aim was to carry out the cyclization reaction of **62**. To this end, the derivative **62** on *o*-mesylation followed by Zn/AcOH mediated reduction of nitro to amine, nucleophilic S_N2 displacement of *o*-mesylate and subsequent *N*-Boc protection of cyclized intermediate furnished the piperidine derivative **63** in 89% yield. In the IR spectrum of **63,** the disappearance of stretching frequencies corresponding to OH and NO_2 confirms the cyclisation and reduction of nitro to amine.

Further, the cleavage of TBDPS ether of cyclic piperidine derivative **63** with TBAF in dry THF furnished alcohol derivative **59** in excellent yields. In the IR spectrum stretching at 3350 cm^{-1} confirms the existence of primary alcohol group. Additionally, in the ^1H-NMR spectrum of compound **59** no signals were found resonating in the aromatic region also supports the cleavage of TBDPS ether moiety.

Furthermore, the conversion of alcohol **59** into terminal olefin derivative **25** was executed through iodination of free hydroxyl group of **59** followed by subsequent elimination under reflux conditions in the presence of large excess of *t*BuOK in 91% yield.[9] In ^1H NMR spectrum of **25**, the two sets of signals related to the extreme olefinic hydrogens were found resonating at δ 5.90 (one proton) & δ 5.07 (two hydrogen's) in ^{1}H NMR spectrum of olefin **25**. With olefin derivative **25** in hand, we proceeded further to synthesize the N-Boc protected derivative **64** *via* $NaIO_4$ mediated oxidative cleavage followed by reduction of intermediate aldehyde using sodium borohydride in excellent yield. The IR spectrum of **64** showed OH absorption at 3475 cm^{-1}. Finally, treatment of **64** with 6N HCl in water afforded ((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol **26** as its hydrochloride salt in high purity. The physical and spectroscopic data of piperidine **26**.HCl was found in accordance with those reported in literature.[4]

2.5 Conclusion

In conclusion, we have described a novel and efficient asymmetric synthetic approach for ((3*R*,6*R*)-6-methylpiperidin 3-yl) methanol **26**, a piperidine core unit of potent dual Orexin receptor antagonist MK-60961 **40** from readily available (*S*)-propylene oxide as starting compound employing organo-catalysed asymmetric Michael addition reaction as major pathway.

2.5.1 Table 1: Comparison with the previously reported syntheses of Piperidine core unit **26**

Sr. No.	**Syntheses**	**Key Steps**	**Starting Material**	**Overall yield**	**No. of steps**
1.	***ChemistrySelect* 2018,*3*, 12164**	Organo-catalysed asymmetric Michael addition	Propylene oxide	33%	9
2.	*Org. Process Res.Dev.* **2015**,*19*,1418	Crystallization- induced dynamic resolution (CIDR)	Methyl vinyl ketone and diethyl malonate	40 % approximate (with two steps yield is unknown)	6
3.	*Org. Lett.* **2014**,*16* 5890	Biocatalytic trasmaination using three enzymativ system and one enzymatic system	Methyl and ethyl keto esters	31.5 % approximate (with one step yield unknown)	5
4.	*Org. Process Res.Dev.* **2013**,*17*,61	Biocatalytic trasmaination using three enzymativ system and Michael addition	Methyl vinyl ketone and dimethyl malonate	23.7%	Enzymatic process and 4 synthetic steps.

The overall yield for the core unit **26** was 33% in total of 9 steps. The merits of described synthesis are excellent enantio- and diastereoselectivity with high yielding reaction steps. The synthetic approach described, here in, is also reliable for diversification in stereochemistry of freshly installed chiral centres which in turn would be helpful in synthesizing various substituted piperidine core analogues with high enantio- and diastereoselectivity. A comparison of represented synthesis with the previously reported syntheses has been reported in the Table 1.

2.6 Experimental Section

All experiments were performed under Nitrogen, with moisture free, freshly extracted solvents through distillation unless otherwise indicated. All the reagents or chemicals were put in reaction either *via* syringe or cannula. Each distillation was also performed under unreactive conditions. Every reaction was performed at necessary temperatures as narrated in their corresponding schemes. Evaporations of solvents was achieved under reduced pressure using Heidolph rotary evaporator keeping temperature below 40 °C.

Chromatography

Every reaction performed was examined through Thin Layer Chromatography executed on commercially available silica gel plates 60 F_{254} using UV light, then were stained in ninhydrin or in ethanolic solution of anisaldehyde or in aqueous $KMnO_4$ as development reagents follow up by concise heating using a heating gun. Silica gel (60-120 and 100-200 mesh) was employed for column chromatography and different compositions of ethyl acetate/hexane and methanol/ dichloromethane were used as organic eluent.

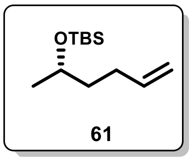
Reagents and solvents

Commercially obtained organic solvents utilized as such unless stated in experimental conditions. Distilled H_2O was consumed for reaction and work-up proceures. For reaction, solvent like DCM was purified using Calcium hydride, and THF was distilled under nitrogen using sodium benzophenone ketyl, straightaway prior to use.

Spectroscopic Measurements

JEOL ECS spectrometer was employed for recording the ^{1}H NMR and ^{13}C NMR respectively. Tetramethylsilane (TMS) utilized as reference. Chemical shifts have been expressed in ppm units (δ). J values are listed in hertz (Hz). Electron spray ionization (ESI) was used for recording HRMS and mass values are expressed as m/z. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}. Yields mentioned referred to isolated combined amount after chromatography.

(*S*)-*tert*-butyl(hex-5-en-2-yloxy)dimethylsilane, 61

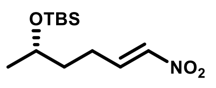


61

To a stirred suspension of 1M allyl magnesium bromide (12.9 mL) in ether at -40 ^{o}C was put CuI (0.163 mg, 0.86 mmol) and resulting solution was agitated for 10 minutes. To it (*S*)-propylene oxide **22** (0.6 mL, 8.6 mmol) in ether (5 mL) was added dropwise and suspension was stirred for 1 hour at same temperature and on completion quenched with saturated solution of NH_4Cl (30 mL). The aqueous phase was extracted with diethylether (3 x 20 mL) washed using brine, dried over $Na_2SO_{4,}$ concentrated in *vacuo,* and obtained compound used as such for subsequent step.

To a suspension of above alcohol taken in dry THF (40 mL), was added imidazole (1.18 g, 17.21 mmol), TBSCl (1.94 g, 12.90 mmol), and DMAP (210 mg, 1.721 mmol) sequentially. The resulting content was stir for 3 hours and 20 mL saturated NH_4Cl was poured into it. The water phase was extracted with ethyl acetate (3 x 25 mL). Collected organic phase was washed using brine, dried utilizing Na_2SO_4**,** and concentrated under vacuum, further the obtained residue on purification using silica gel column chromatography utilizing EtOAc and hexane (0.5: 9.5) as eluent afforded the alkene **61** (1.48 g, 85%) as colourless liquid: [R_f = 0.4, EtOAc/hexane 3 : 7 v/v];]; $[\alpha]_D^{25}$ +20.2 (*c* 1.0, $CHCl_3$). Due to the volatile nature of the compound we proceeded further without characterisation.

(*S*,*E*)-*tert*-Butyldimethyl(6-nitrohex-5-en-2-yloxy)silane, 23



23

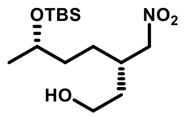
Alkene **61** (1.25 g, 6.18 mmol) dissolved in dioxane:H_2O (3:1) at room temperature and to it was added 2,6-lutidine (1.32 g, 12.35 mmol), OsO_4 (31 mg, 0.12 mmol) and $NaIO_4$ (5.29 g, 24.7 mmol). The reaction content was stir for 3 hour at ambient temperature. After completion, as checked by TLC, H_2O was poured to stop further progess of the reaction. The water phase was extracted using EtOAc (3 x 25 mL), dried utilizing Na_2SO_4, and concentrated to obtain the aldehyde used in next procedure as such.

To the freshly obtained crude aldehyde dissolved in methanol (15 mL) at 0 ^{o}C were added nitromethane (0.5 mL, 6.79 mmol) and aqueous solution of NaOH (297 mg, 7.41mmol). After continuing the stirring for 20 minutes, the organic content was quenched with H_2O. The mixture was isolated using EtOAc (2 x 30 mL), combined organic solvent was washed using brine, upon drying utilizing anhydrous Na_2SO_4**,** concentrated to furnish crude nitro-alcohol for the next protocol.

To a stirred mixture of above obtained nitro-alcohol prepared in DCM (10 mL) at 0 ^oC was added sequentially mesylchloride (0.6 mL, 7.41 mmol) and Et_3N (1.8 mL, 12.36 mmol). Prepared reaction content after stirring for 1.5 h at room temperature was added H_2O (10 mL) and extracted with DCM (3 x 15 mL). The collected organic fractions were dried using anhydrous Na_2SO_4 and concentrated. After performing silica gel column chromatography for purification (EtOAc/Hexane 0.5:9.5 v/v),nitro-olefin **23** was isolated as colourless oil (1.38 g, 93%).[R_f = 0.7, EtOAc/hexane 1 : 19 v/v]; $[\alpha]_D^{25}$ +18.2 (*c* 0.10, $CHCl_3$); IR (CH_2Cl_2) *ν*: 3011, 2880, 1650, 1528, 1340 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.35-7.26 (m, 1H), 7.01 (dt, *J* = 13.6, 1.6 Hz, 1H) 3.89-3.82 (m, 1H), 2.47-2.23 (m, 2H), 1.63-1.58 (m, 2H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.89-0.87 (m, 9H), 0.05 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 143.0, 139.4, 67.4, 37.2, 25.7, 24.7, 23.6, 18.0, 16.3, -4.2, -4.8; HRMS (ESI), calcd for $C_{12}H_{25}NO_3SiNa$ $[M+Na]^+$ 282.1502; found 282.1493.

(3*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-3-(nitromethyl)heptan-1-ol, 24

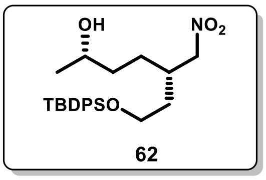
To a stirred suspension of nitro-olefin **23** (1.25 g, 5.09 mmol) taken in DMF (5 mL) in a airtight tube under argon was added drowise 2-propanol (3.8 mL, 50.93 mmol) and a solution of (*R*)-diphenyltrimethylsiloxymethyl pyrrolidine (331 mg, 1.01 mmol, 20 mol %) in anhyrous DMF (2 mL). To the above content, solution of acetaldehyde (1.42 mL, 25.45 mmol) in dry DMF (2 mL) was added drop by drop and agitated for 24 hours at room temperature. After completion of the reaction, as examined by TLC, it was terminated with 1N HCl (10 mL). The watery phase was washed with EtOAc (3 x 16 mL), dried using anhydrous Na_2SO_4 and obtained solution was concentrated under vacuum to deliver the intermediate aldehyde motif.



24

To an ice-cold solution of previously prepared aldehyde in methanol was added sodium borohydride (0.376 mg, 10.18 mmol) and reaction content was agitated for 35 min at same temperature. The reaction was stopped with saturated aqueous NH_4Cl (12 mL), extracted with ethyl acetate (3 x 20 mL), dried using Na_2SO_4 and volatiles were removed under low pressure. Purification through silica gel column chromatography (EtOAc/hexanes 3:7 v/v) furnished the nitro-alcohol derivative **24** as a pale yellow liquid (1.0 g, 66 %). [R_f = 0.4, EtOAc/hexane 1 : 3 v/v]; $[\alpha]_D^{25}$ +11.8 (*c* 0.25, MeOH); IR (CH_2Cl_2) *ν*: 3410, 2921, 2890, 1551, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.48-4.36 (m, 2H), 3.80-3.71 (m, 3H), 2.42-2.34 (m, 1H), 1.71-1.36 (m, 7H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 3.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 79.4, 68.3, 60.1, 36.1, 34.8, 33.9, 27.4, 25.8, 23.7, 18.0, -4.3, -4.7; HRMS (ESI), calcd for $C_{14}H_{31}NO_4$ $[M+1]^+$ 306.2022; found 306.2077.

(2*S*,5*S*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(nitromethyl)heptan-2-ol, 62

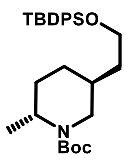


62

To an ice-cold solution of nitro derivative **24** (950 mg, 3.10 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen, imidazole (642 mg, 9.31 mmol), TBDPSCl (1.02 g, 3.73 mmol) and DMAP (76 mg, 0.62 mmol) were put sequentially and content was stirred for 2 hours. After completion reaction was terminated with saturated aqueous NH_4Cl (15 mL). The aqueous part was extracted with CH_2Cl_2 (3 x 20 mL), dried using Na_2SO_4, concentrated under vacuum to furnish TBDPS protected compound which was used as such for subsequent reaction irrespective of conducting any purification.

To a stirred suspension of above TBDPS protected compound in methanol (12 mL) was added *para*-toluene sulfonic acid (155 mg, 0.62 mmol) at 0 ^oC. Resultant content was stirred for 30 min, and quenched using saturated suspension of $NaHCO_3$ and extraction of watery phase was carried out using ethyl acetate (4 x 15 mL). Collected organic solvents were dried over Na_2SO_4, concentrated under vacuum and purified utilizing silica gel column chromatography (ethyl acetate/hexane, 1:9) to yield compound **62** (1.28 g, 96%) as colorless liquid. [R_f = 0.5, EtOAc/hexane, 1:4 v/v]; $[\alpha]_D^{25}$ -12.2 (*c* 0.10, $CHCl_3$); IR (CH_2Cl_2) *ν*: 3470, 2920, 2817, 1550, 1348, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.69-7.60 (m, 4H), 7.48-7.34 (m, 6H), 4.47-4.41 (m, 1H), 4.34-4.24 (m, 1H), 4.15-4.07 (m, 1H), 3.79-3.66 (m, 2H), 2.49-2.40 (m, 1H), 1.69-1.20 (m, 7H), 1.72 (d, *J* = 6.0 Hz, 3H), 1.08-1.01 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*:135.5, 133.3, 129.7, 127.7, 79.3, 67.8, 61.0, 35.6, 34.5, 33.5, 27.4, 26.8, 23.5, 19.0; HRMS (ESI), calcd for $C_{24}H_{35}NO_4SiNa$ $[M+Na]^+$ 452.2233; found 452.2225.

(2*R*,5*S*)-*tert*-butyl5-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-2-methylpiperidine-1 carboxylate, 63



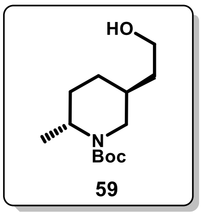
63

To an ice cold solution of nitro alcohol derivative **62** (1.1 g, 2.56 mmol) taken in dry DCM (10 mL) addition of Et_3N (0.74 mL, 5.12 mmol) and MsCl (900 mg, 7.68 mmol) was carried out sequentially. The resulting suspension was agitated for 25 minutes and after quenching with H_2O, the aqueous part was extracted with DCM (3 x 10mL). The collected organic extracts were dried using Na_2SO_4, concentrated under vacuum and mesyl derivative was utilized as such in the following procedure.

To a prepared mixture of above mesyl derivative in DCM (15 mL) were added sequentially Zn (2.5 g, 38.4 mmol) and AcOH (4.4g, 74.28 mmol) at 0 °C. Upon stirring the reaction content for 1 hour at room temperature, reaction was ended on pouring 1N NaOH. Organic materials were isolated using ethyl acetate, and the contents were once washed utilizing brine and dried utilizing anhydrous Na_2SO_4 then concentrated. Amine derivative obtained was used in next procedure without additional purification.

NaH (93 mg, 3.84 mmol) was put into the agitated emulsion of previously synthesized amine derivative in dry DMF (14 mL) at 0 °C. Upon stirring the solution for 30 min, di-*tert*-butyl dicarbonate (838 mg, 3.84 mmol) and DMAP (156 mg, 1.3 mmol) were added sequentially at the same temperature. The combined content was agitated for 12 hours at room temperature. Upon completion, the reaction, as examined using TLC was ended with H_2O and extracted with ethyl acetate (3 x 10 mL). The organic extract after washing brine, dried using anhydrous Na_2SO_4 and concentrated in *vacuo* and purified *via* silica gel column chromatography (EtOAc/hexane 0.5:9.5 v/v) furnished the cyclic motif **63** (1.1 g, 89%) as colorless oil. [R_f = 0.6, EtOAc/hexane 1 : 9 v/v]; $[\alpha]_D^{25}$ -7.2 (*c* 0.10, $CHCl_3$); IR (CH_2Cl_2) ν: 2928, 2865, 1451, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.60 (m, 4H), 7.44-7.33 (m, 6H), 4.38-4.29 (m, 1H), 3.74-3.65 (m, 3H), 2.99 (dd, J = 3.6, 10 Hz, 1H), 1.92-1.90 (m, 1H), 1.78-1.43 (m, 6H), 1.39 (s, 9H), 1.13 (d, J = 6.8 Hz, 3H), 1.041 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:155.3, 135.5, 133.9, 129.5, 127.5, 78.9, 61.8, 46.0, 41.5, 32.8, 29.4, 28.4, 26.8, 25.1, 23.1, 19.2, 16.1; HRMS (ESI), calcd. for $C_{29}H_{43}NO_3Si$ $[M+1]^+$ 482.3012; found 482.3085.

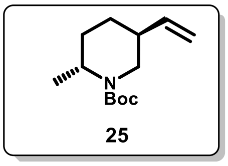
(2*R*,5*S*)-*tert*-Butyl 5-(2-hydroxyethyl)-2-methylpiperidine-1-carboxylate, 59



59

TBAF (1.0 M in THF, 3.2 mL, 3.11 mmol) was gradually put to a suspension of cyclic amine **63** (1.0 g, 2.07 mmol) taken in THF (10 mL) precooled to 0 ^oC and the obtained mixture was agitated for additional 2 h at room temperature. After completion aqueous saturated solutions of NH_4Cl (30 mL) and EtOAc (30 mL) were added, and organics were collected. The watery phase was again extracted utilizing EtOAc (3 × 20 mL). Whole organic part was collected and dried utilizing anhydrous Na_2SO_4, and concentrated to yield the impure residue. Silica gel chromatography (EtOAc/hexane 1 : 19) of crude gave the cyclic amine derivative **59** as a colorless oil. (475 mg, 95%) [R$_f$ = 0.3, EtOAc/hexane 3 : 7 v/v]; $[\alpha]_D^{25}$ -11.2 (*c* 0.10, $CHCl_3$); IR (CH_2Cl_2) *v*: 3350, 2927, 2860, 1450, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 4.40-4.29 (m, 1H), 3.87-3.65 (m, 3H), 3.07-2.96 (m, 1H), 1.88-1.67 (m, 8H), 1.49-1.41 (m, 9H), 1.19-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 155.4, 79.2, 61.2, 46.2, 41.1, 32.9, 30.1, 28.4, 25.1, 23.7, 16.1; HRMS (ESI), calcd for $C_{13}H_{25}NO_3Na$ $[M+Na]^+$ 266.1732; found 266.1740.

(2*R*,5*S*)-*tert*-Butyl 2-methyl-5-vinylpiperidine-1-carboxylate, 25

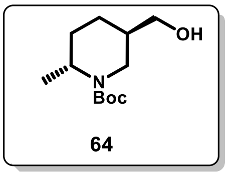


25

Imidazole (557 mg, 8.2 mmol) along with triphenylphosphine (1.72 g, 6.57 mmol) were added to a suspension of cyclic alcohol **59** (400 mg, 1.64 mmol) in dry CH_2Cl_2 (20 mL). After stirring the solution for 15 min, iodine (1.66 g, 6.56 mmol) was added in two parts over 15 min. The resultant content was agitated for further 15 min and reaction was terminated with saturated solution of $Na_2S_2O_3$ after completion. The aqueous layer was washed with CH_2Cl_2 and organic portion was dried using Na_2SO_4, concentrated. Upon performing silica gel chromatography utilizing a combination of EtOAc/hexane (0.5:9.5 v/v) as eluent furnished iodinated compound (550 mg, 94%) as yellow oil.

To an agitated solution of above intermediate iodinated derivative (500 mg, 1.41 mmol) in *tert*-butanol was added *tert*-butoxide (474 mg, 4.23 mmol) and refluxed for 1 hour. After completion, as examined using TLC, reaction was ended using H_2O and aqueous layer was washed with ethyl acetate (3 x 20 mL). Collected organic phase were dried using Na_2SO_4, concentrated under lowered pressure and purified using silica gel column chromatography (ethyl acetate/hexane, 1:9) to deliver alkene derivative **25** (282 mg, 91%) as pale yellow oil. . [R$_f$ = 0.5, EtOAc/hexane 1:19 v/v] $[\alpha]_D^{25}$ +16.2 (*c* 0.10, $CHCl_3$); IR (CH_2Cl_2) *v*: 3029, 2857, 1650, 1451cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 5.94-5.83 (m, 1H), 5.07 (tdd, *J* = 1.6, 10.4, 17.6 Hz, 2H), 4.40-4.27 (m, 1H), 3.99-3.88 (m, 1H), 3.13-3.01 (m, 1H), 2.41-2.29 (m, 1H), 1.92-1.81 (m, 2H), 1.63-1.52 (m, 2H), 1.49-1.36 (m, 9H), 1.17-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 155.3, 139.6, 114.7, 79.1, 45.9, 41.4, 36.6, 31.9, 29.6, 28.4, 22.6; HRMS (ESI), calcd for $C_{13}H_{23}NO_2Na$ $[M+Na]^+$ 248.1627; found 248.1621.

(2*R*,5*R*)-*tert*-Butyl 5-(hydroxymethyl)-2-methylpiperidine-1-carboxylate, 64

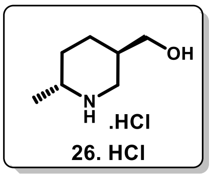


64

Alkene **25** (200 mg, 0.88 mmol) was dissolved in dioxane-water (3:1, 4 mL). 2,6- lutidine (190 mg, 1.77 mmol), OsO_4 (4 mg, 0.02 mmol) along with $NaIO_4$ (760 mg, 3.54 mmol) were added in a stepwise process. The resultant content was agitated at room temperature for 4 h. After completion, H_2O (7 mL) and ethyl acetate (15 mL) were poured into reaction. Organic layer was taken out, and aqueous medium was again extracted with EtOAc (3 x 10 mL). All organic content was collected and after washing with brine and dried using anhydrous Na_2SO_4, concentrated *in vacuo* to deliver aldehyde utilized in next reaction without additional purification.

To a stirred suspension of aldehyde in dry MeOH (10 mL) was put $NaBH_4$ (65 mg, 1.77 mmol) in small fractions at 0 ^oC. After agitating the mixture at room temperature for 35 min, content was quenched with slow addition of saturated NH_4Cl solution. The organics were isolated using EtOAc (2 x 40 mL), dried with anhydrous Na_2SO_4, and evaporated under vacuum. column chromatography (hexane/EtOAc 4:1) of the residue afforded **64** (178 mg, 90%) as a thick colorless liquid. [R_f = 0.4, EtOAc/hexane 3 : 7 v/v]; $[\alpha]_D^{25}$ +8.0 (*c* 0.10, $CHCl_3$); IR (CH_2Cl_2) *v*: 3475, 2954, 2856, 1451, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.34-4.23 (m, 1H), 3.94 (d, J = 14.4 Hz, 1H), 3.59-3.46 (m, 2H), 3.02 (dd, J = 3.2, 14.4 Hz, 1H), 1.88-1.55 (m, 6H), 1.46 (s, 9H), 1.18 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.9, 79.7, 61.9, 47.1, 37.9, 35.6, 28.4, 25.7, 20.2, 16.6; HRMS (ESI), calcd for $C_{12}H_{23}NO_3Na$ $[M+Na]^+$ 252.1576; found 252.1570.

((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol, 26.HCl



26. HCl

To a stirred suspension of **64** (50 mg, 1.023mmol) in water (5 mL) was added 6N HCl (10 mL) and obtained content was refluxed for 1.5 hour. The water was evaporated under lowered pressure and HCl salt of ((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol **26** was obtained in high purity (29 mg, 95%). ^1H NMR (400 MHz, D_2O) δ: 3.38-3.34 (m, 1H), 3.29-3.21 (m, 2H), 2.96 (m, 1H), 2.53 (t, J = 12.4 Hz, 2H), 1.81-1.64 (m, 3H), 1.30-1.27 (m, 1H), 1.10 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, D_2O) δ: 63.3, 52.9, 46.4, 35.3, 29.5, 24.8, 18.3.

2.7 Spectra:

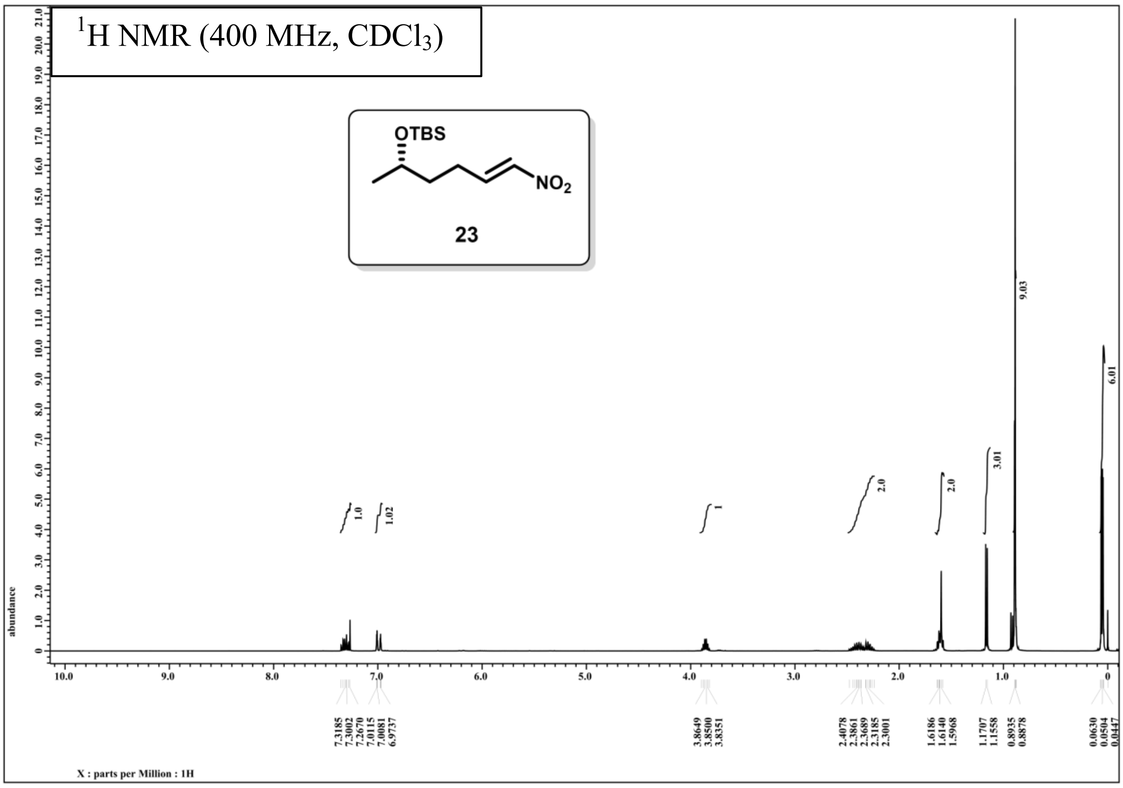
1. ^1H and ^{13}C NMR Spectra of **23**
2. ^1H and ^{13}C NMR Spectra of **24**
3. ^1H and ^{13}C NMR Spectra of mixture (**24 & 24a)**
4. ^1H and ^{13}C NMR Spectra of **62**
5. ^1H and ^{13}C NMR Spectra of **63**
6. ^1H and ^{13}C NMR Spectra of **59**

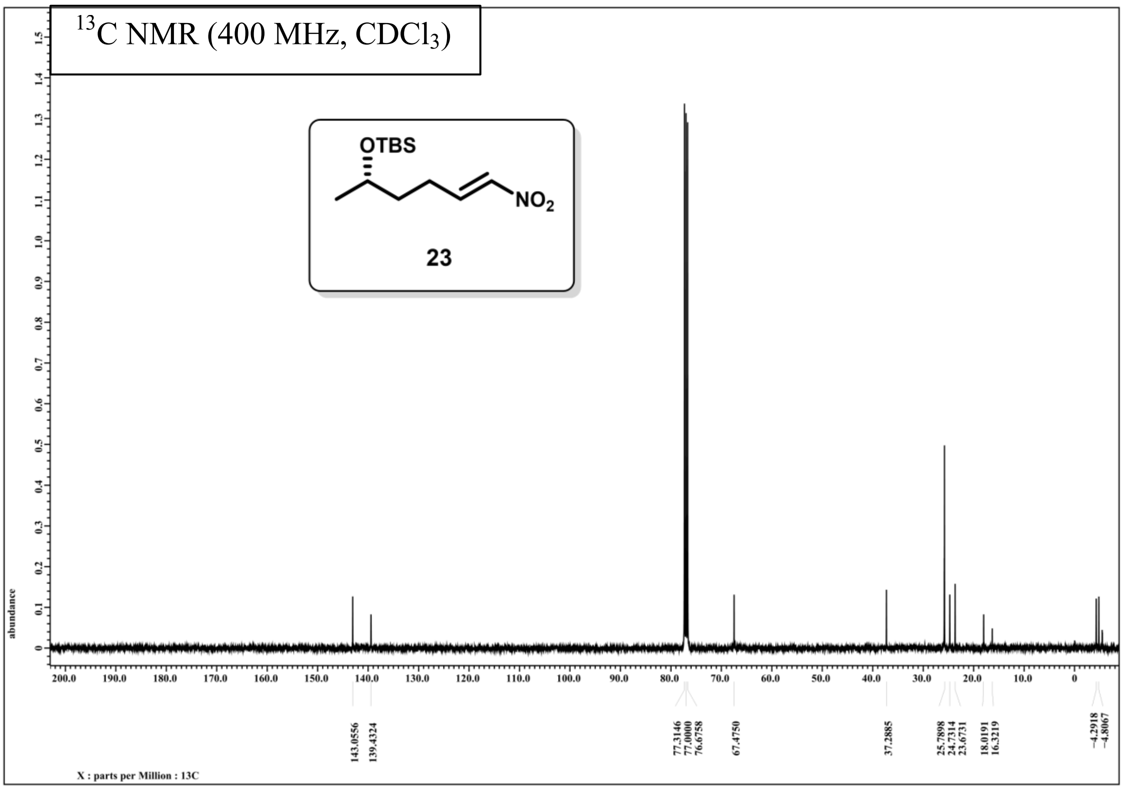
7. ^{1}H and ^{13}C NMR Spectra of **25**

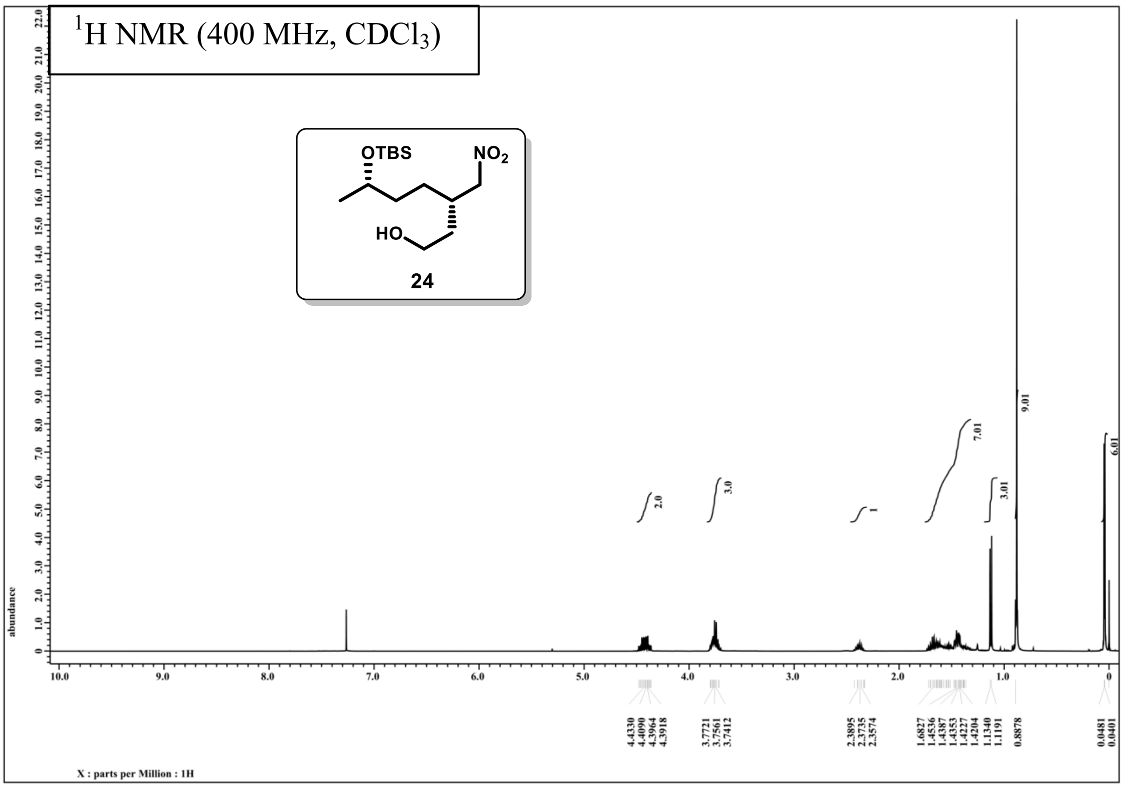
8**.** ^{1}H and ^{13}C NMR Spectra of **64**

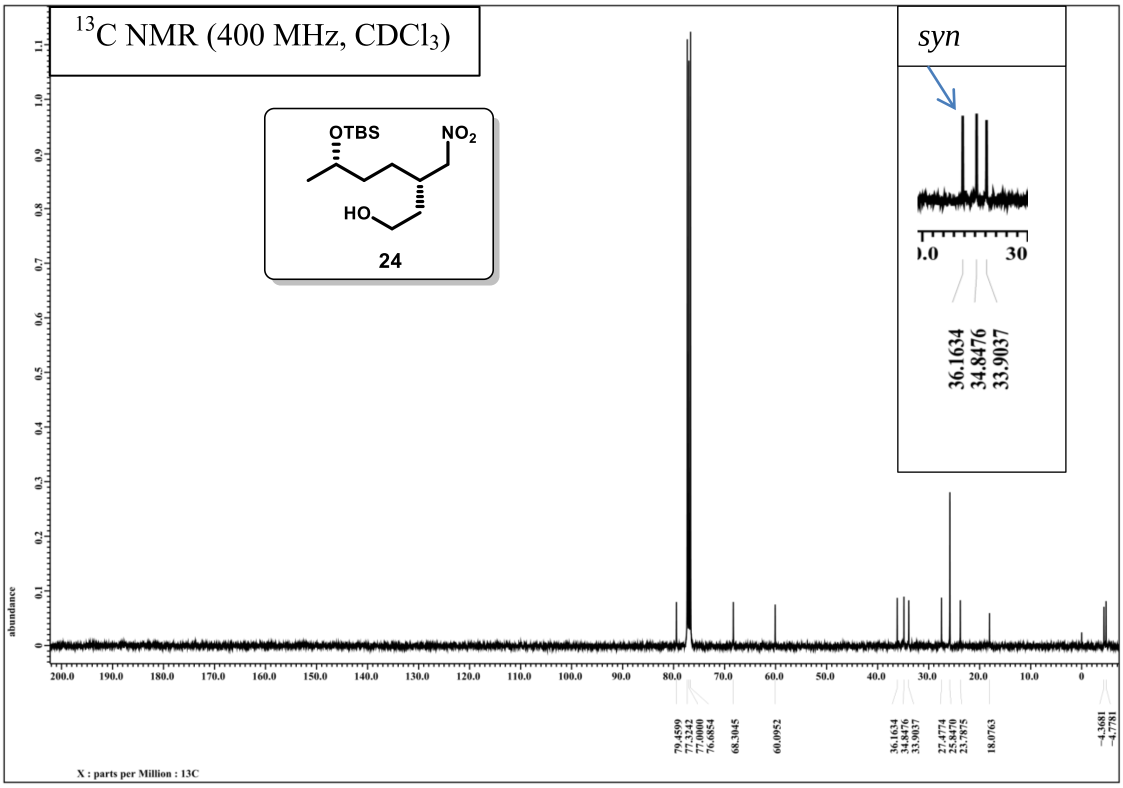
9**.** ^{1}H and ^{13}C NMR Spectra of **26.HCl**

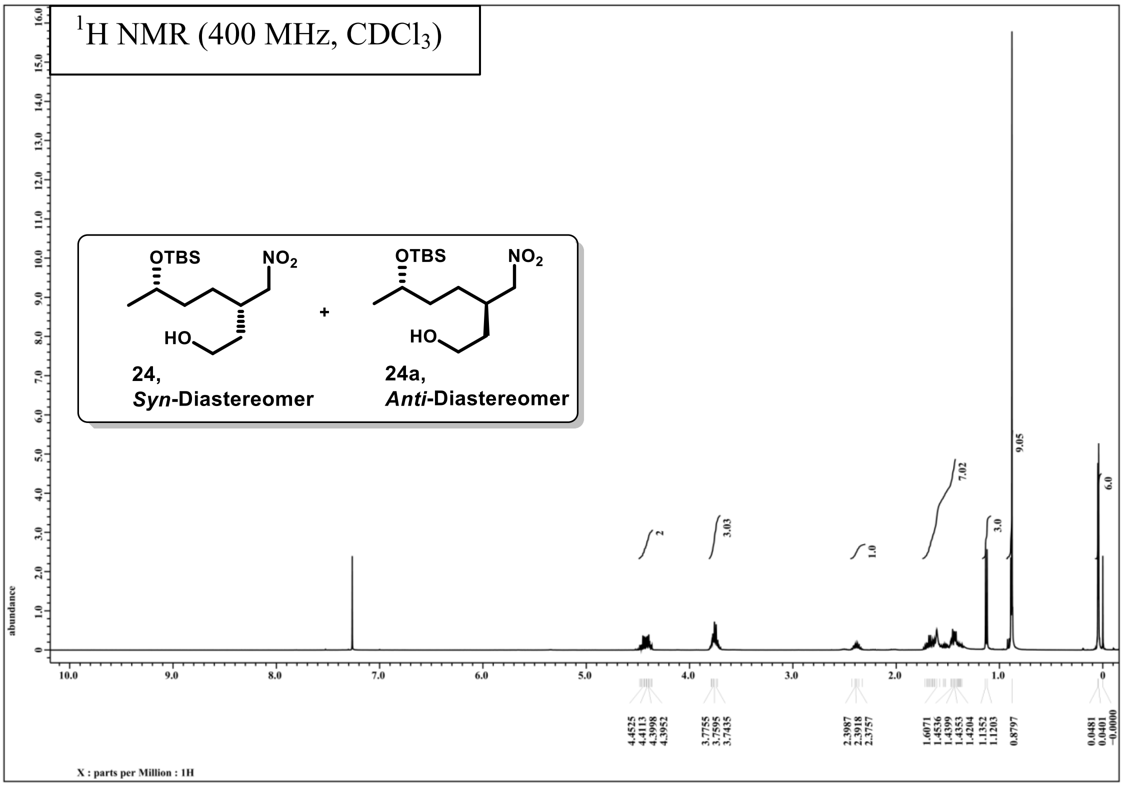
10. HRMS of Compound **64**


^{1}H NMR (400 MHz, $CDCl_3$)
OTBS
NO_2
23
abundance
X : parts per Million : 1H
1.0
1.02
1
2.0
2.0
3.01
9.03
6.01
7.3185
7.3002
7.2670
7.0115
7.0081
6.9737
3.8649
3.8500
3.8351
2.4078
2.3861
2.3689
2.3185
2.3001
1.6186
1.6140
1.5968
1.1707
1.1558
0.8935
0.8878
0.0630
0.0504
0.0447

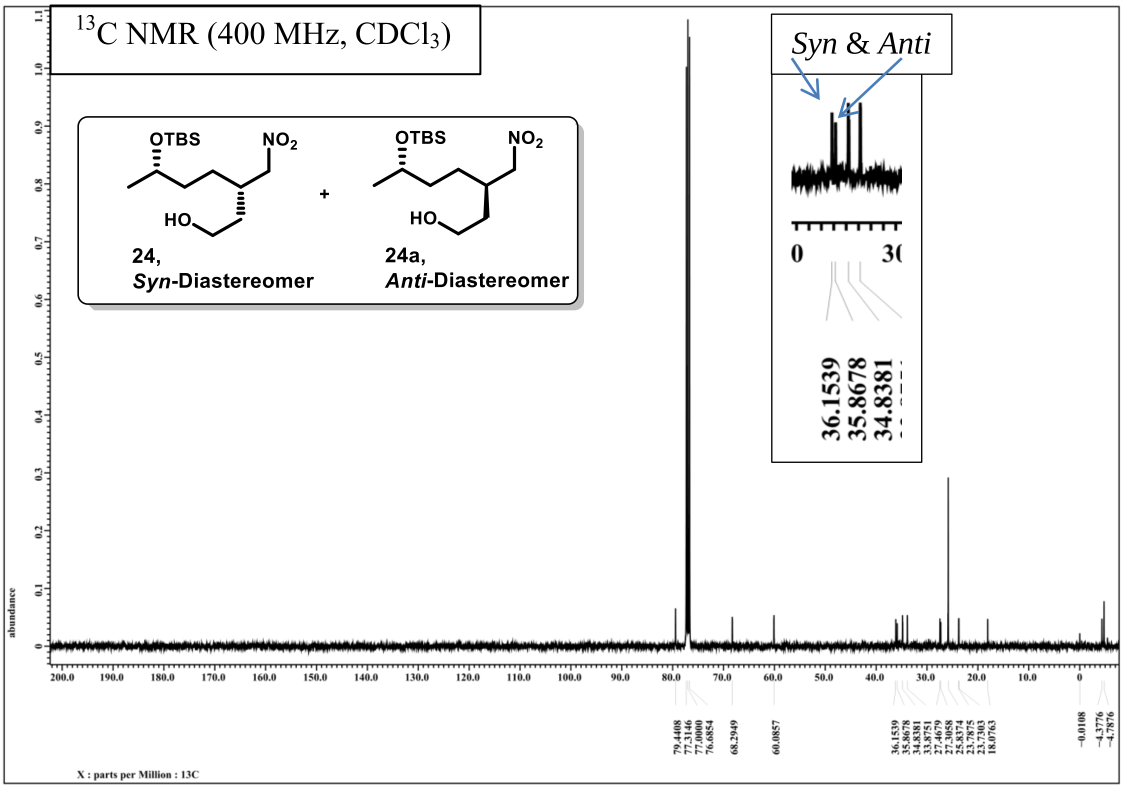

^{13}C NMR (400 MHz, $CDCl_3$)
OTBS
NO_2
23
abundance
X : parts per Million : 13C
143.0556
139.4324
77.3146
77.0000
76.6758
67.4750
37.2885
25.7898
24.7314
23.6731
18.0191
16.3219
−4.2918
−4.8067


^{1}H NMR (400 MHz, CDCl$_3$)
OTBS
NO$_2$
HO
24
abundance
X : parts per Million : 1H
2.0
3.0
1
7.01
3.01
9.01
6.01
4.4330
4.4090
4.3964
4.3918
3.7721
3.7561
3.7412
2.3895
2.3735
2.3574
1.6827
1.4536
1.4387
1.4353
1.4227
1.4204
1.1340
1.1191
0.8878
0.0481
0.0401

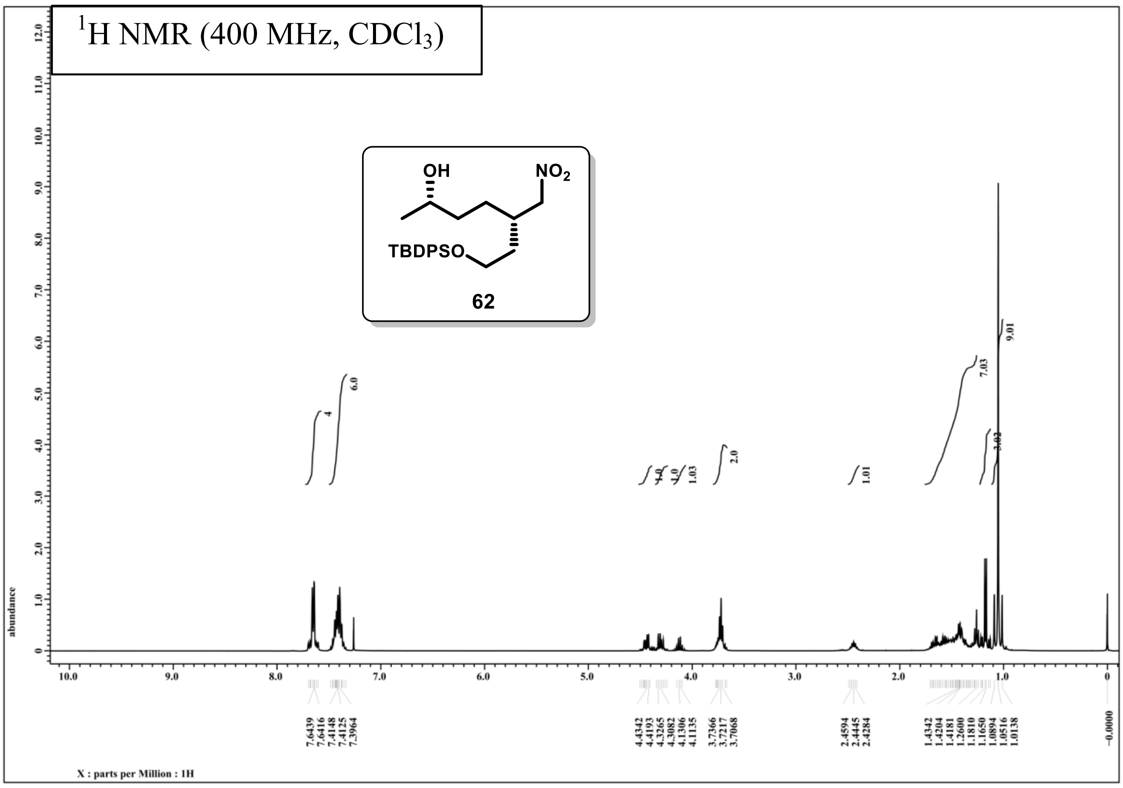

^{13}C NMR (400 MHz, CDCl$_3$)
OTBS
NO$_2$
HO
24
syn
36.1634
34.8476
33.9037
abundance
X : parts per Million : 13C
79.4599
77.3242
77.0000
76.6854
68.3045
60.0952
36.1634
34.8476
33.9037
27.4774
25.8470
23.7875
18.0763
−4.3681
−4.7781



¹H NMR (400 MHz, CDCl₃)
OTBS
NO₂
HO
24,
Syn-Diastereomer
+
OTBS
NO₂
HO
24a,
Anti-Diastereomer
2
3.03
1.0
7.02
3.0
9.05
6.0
4.4525
4.4113
4.3998
4.3952
3.7755
3.7595
3.7435
2.3987
2.3918
2.3757
1.6071
1.4536
1.4399
1.4353
1.4204
1.1352
1.1203
0.8797
0.0481
0.0401
-0.0000
abundance
X : parts per Million : 1H

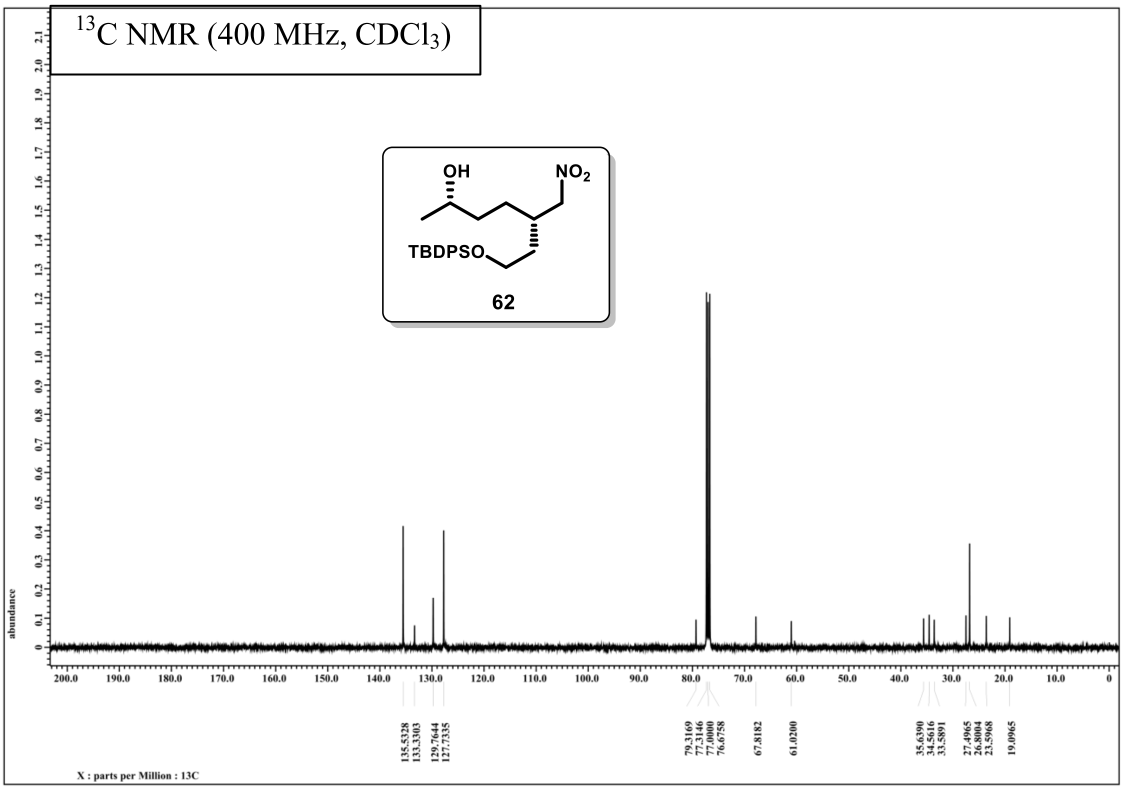


¹³C NMR (400 MHz, CDCl₃)
OTBS
NO₂
HO
24,
Syn-Diastereomer
+
OTBS
NO₂
HO
24a,
Anti-Diastereomer
Syn & Anti
36.1539
35.8678
34.8381
79.4408
77.3146
77.0000
76.6854
68.2949
60.0857
36.1539
35.8678
34.8381
33.8751
27.4679
27.3058
25.8374
23.7875
23.7303
18.0763
-0.0108
-4.3776
-4.7876
abundance
X : parts per Million : 13C



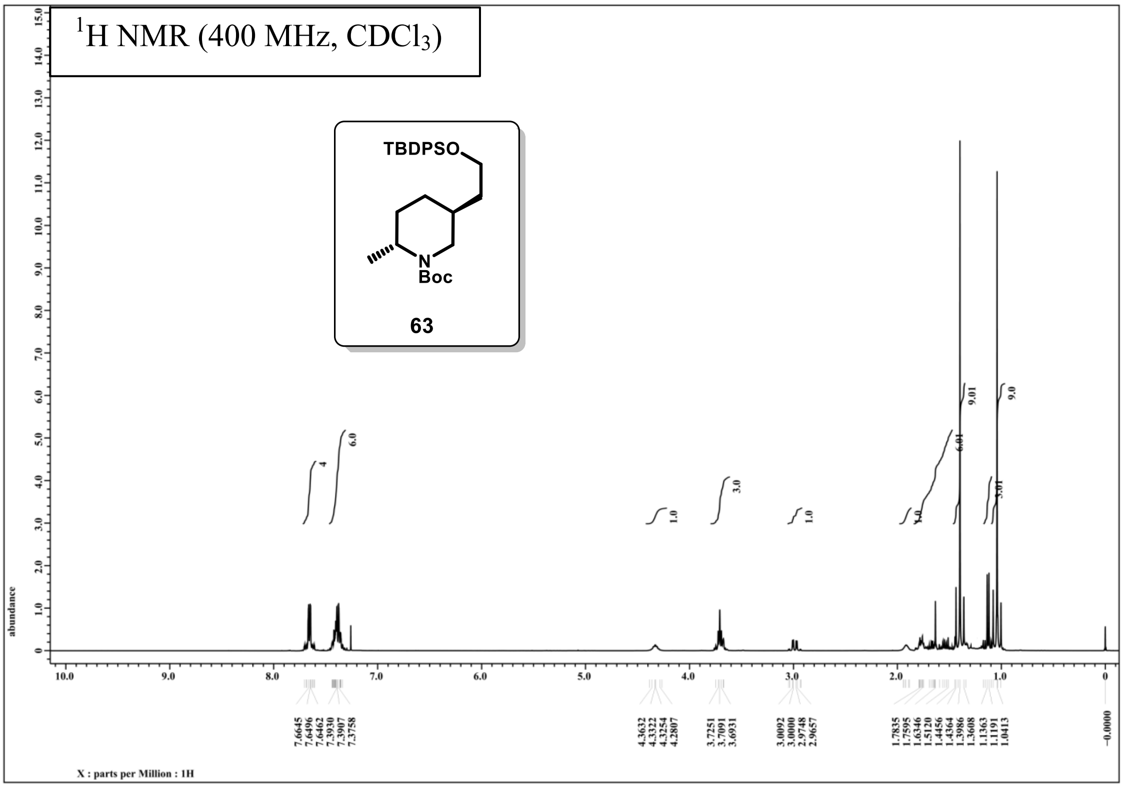
^{1}H NMR (400 MHz, CDCl$_3$)

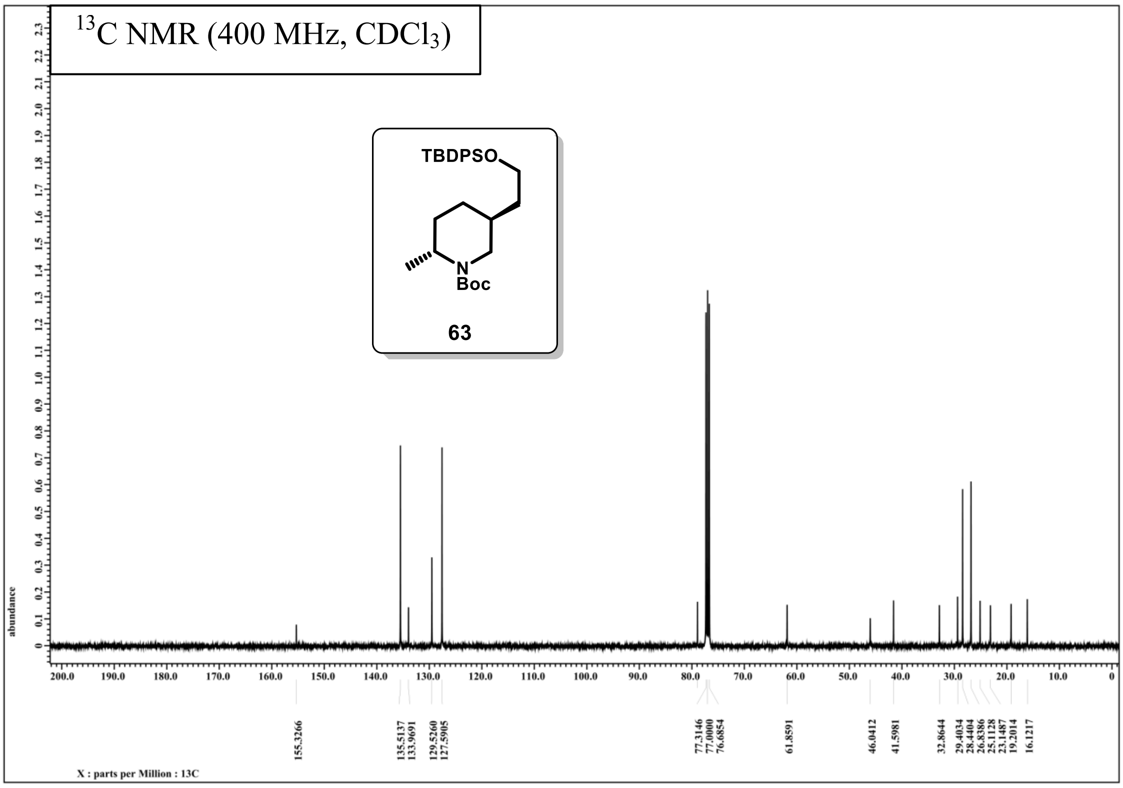
62

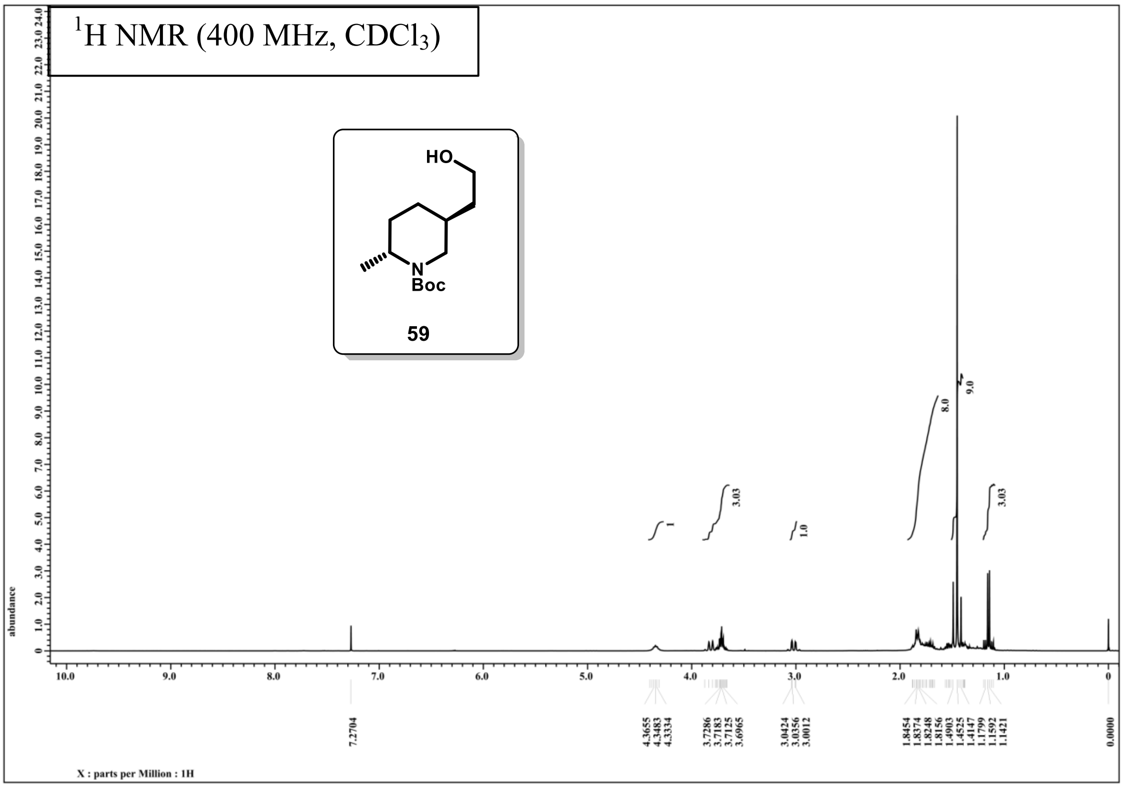


^{13}C NMR (400 MHz, CDCl$_3$)

62


^{1}H NMR (400 MHz, $CDCl_3$)
TBDPSO
N
Boc
63
abundance
X : parts per Million : 1H
4
6.0
1.0
3.0
1.0
1.0
6.01
9.01
3.01
9.0
7.6645
7.6496
7.6462
7.3930
7.3907
7.3758
4.3632
4.3322
4.3254
4.2807
3.7251
3.7091
3.6931
3.0092
3.0000
2.9748
2.9657
1.7835
1.7595
1.6346
1.5120
1.4456
1.4364
1.3986
1.3608
1.1363
1.1191
1.0413
−0.0000


^{13}C NMR (400 MHz, $CDCl_3$)
TBDPSO
N
Boc
63
abundance
X : parts per Million : 13C
155.3266
135.5137
133.9691
129.5260
127.5905
77.3146
77.0000
76.6854
61.8591
46.0412
41.5981
32.8644
29.4034
28.4404
26.8386
25.1128
23.1487
19.2014
16.1217



^{1}H NMR (400 MHz, CDCl$_3$)
HO
N
Boc
59
abundance
X : parts per Million : 1H
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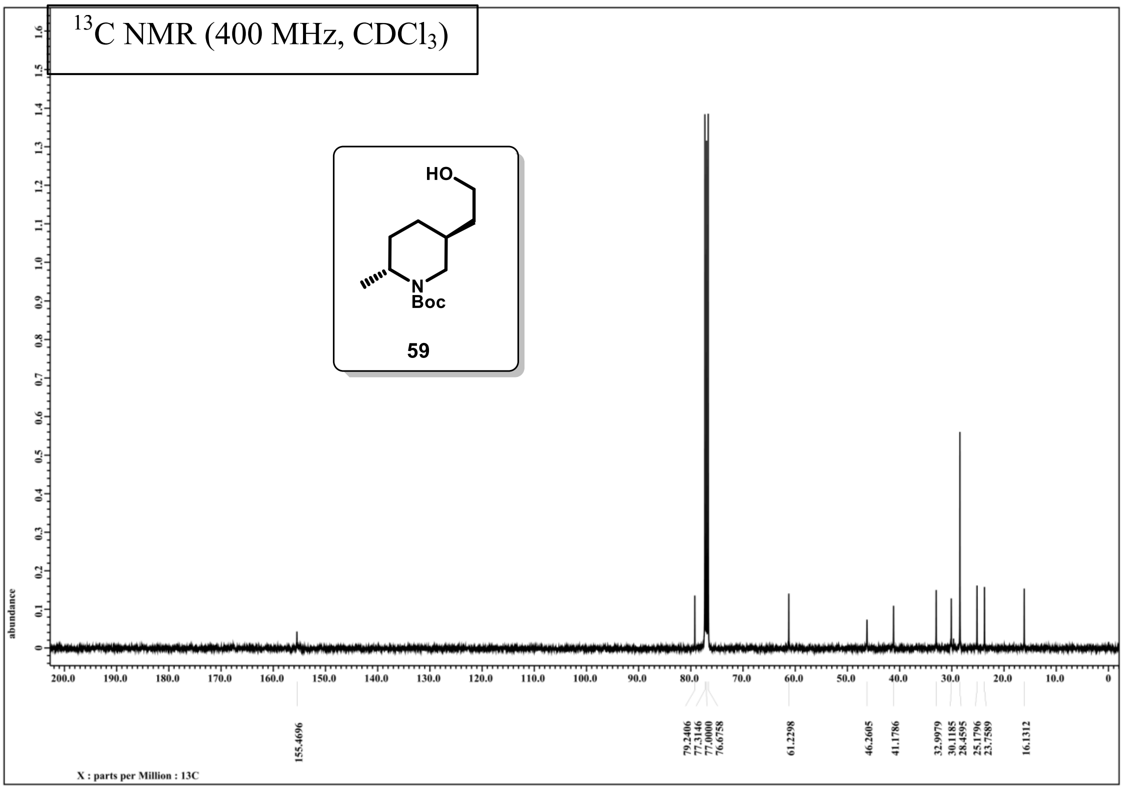
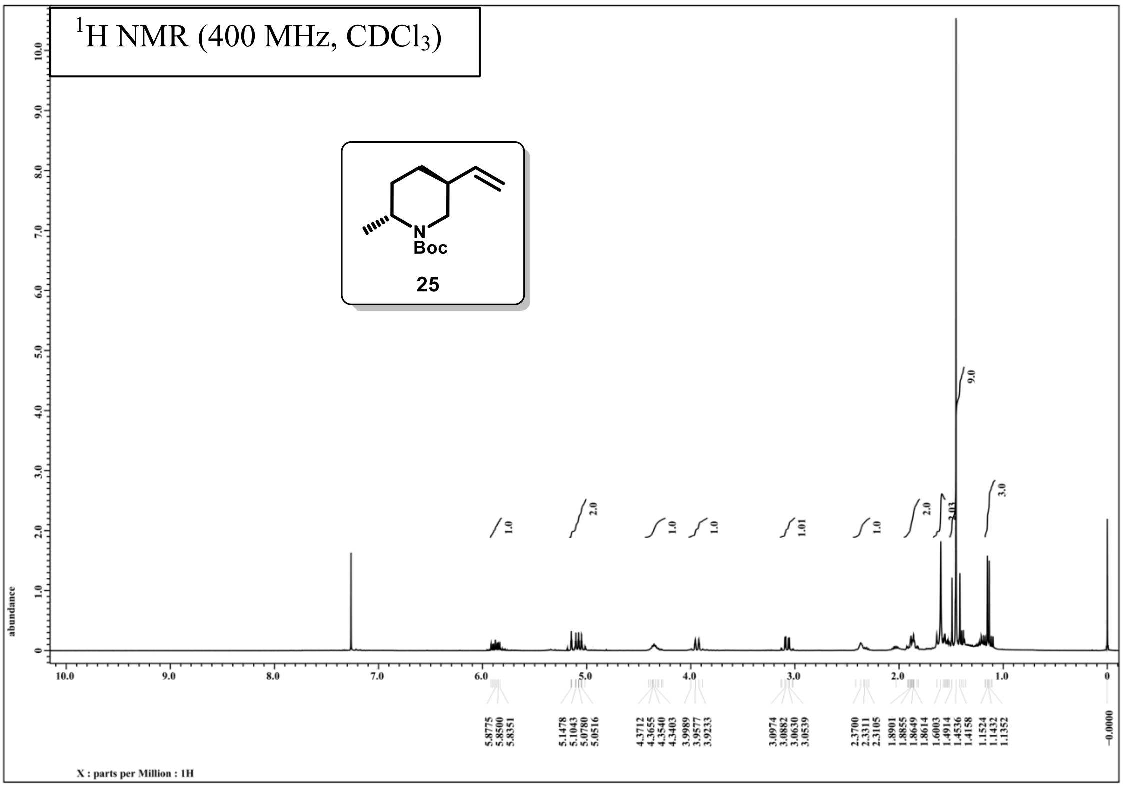
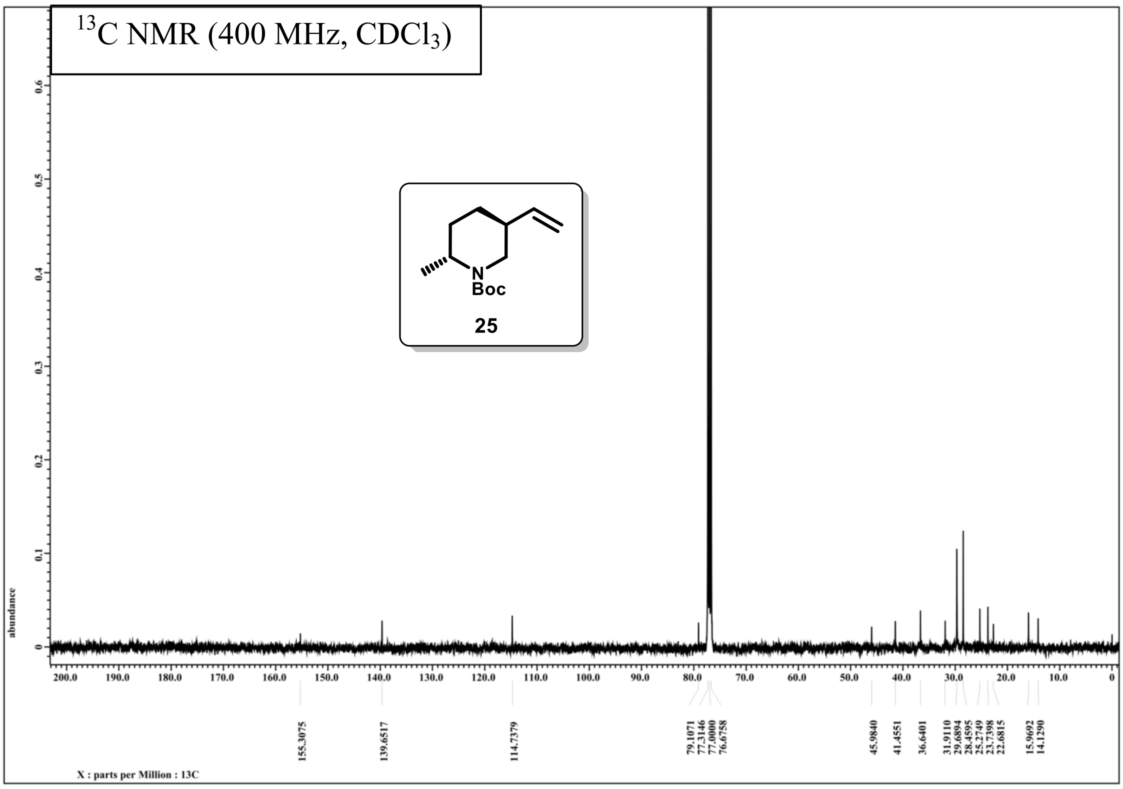
3.03
1.0
8.0
9.0
3.03
7.2704
4.3655
4.3483
4.3334
3.7286
3.7183
3.7125
3.6965
3.0424
3.0356
3.0012
1.8454
1.8374
1.8248
1.8156
1.4903
1.4525
1.4147
1.1799
1.1592
1.1421
0.0000



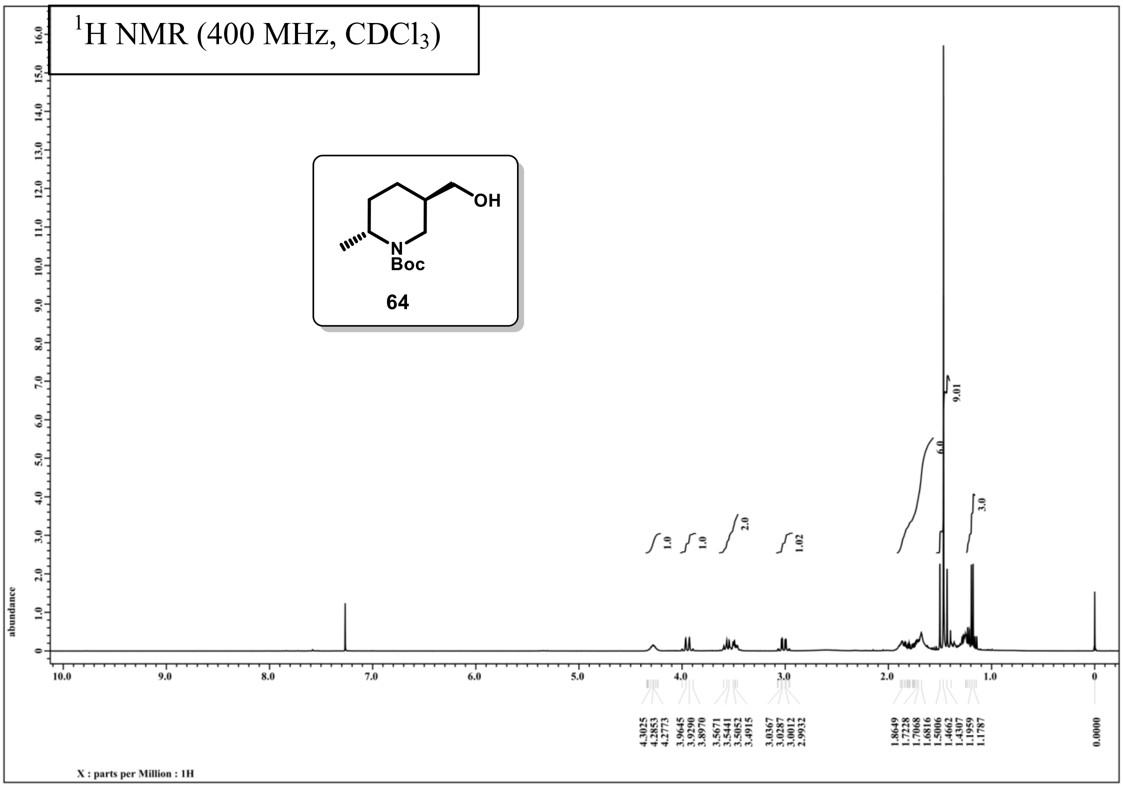
^{13}C NMR (400 MHz, CDCl$_3$)
HO
N
Boc
59
abundance
X : parts per Million : 13C
155.4696
79.2406
77.3146
77.0000
76.6758
61.2298
46.2605
41.1786
32.9979
30.1185
28.4595
25.1796
23.7589
16.1312

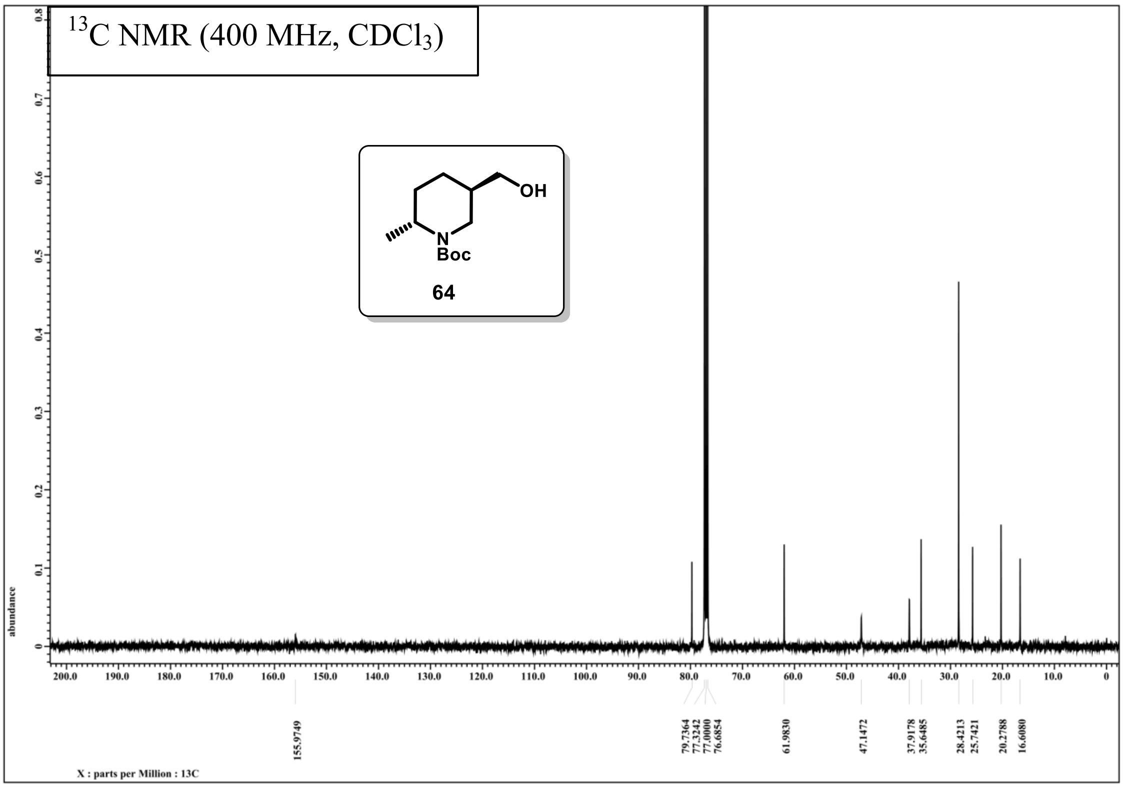

^{1}H NMR (400 MHz, CDCl$_3$)

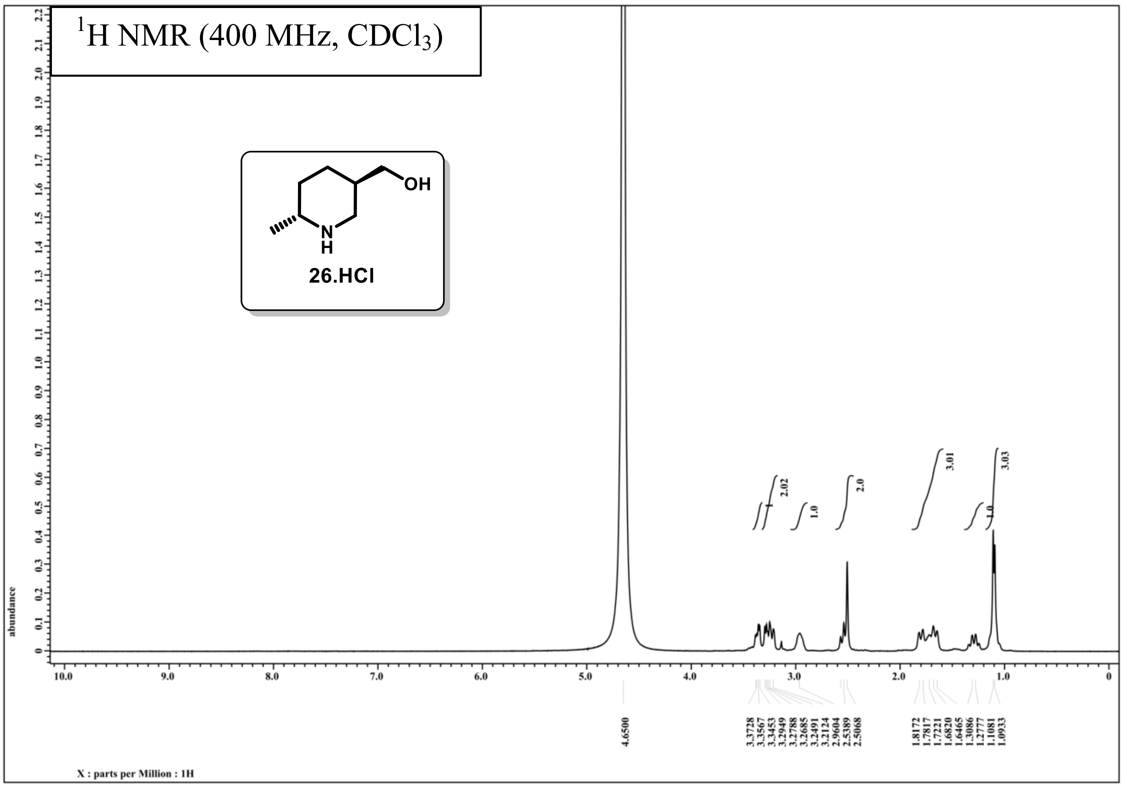
25

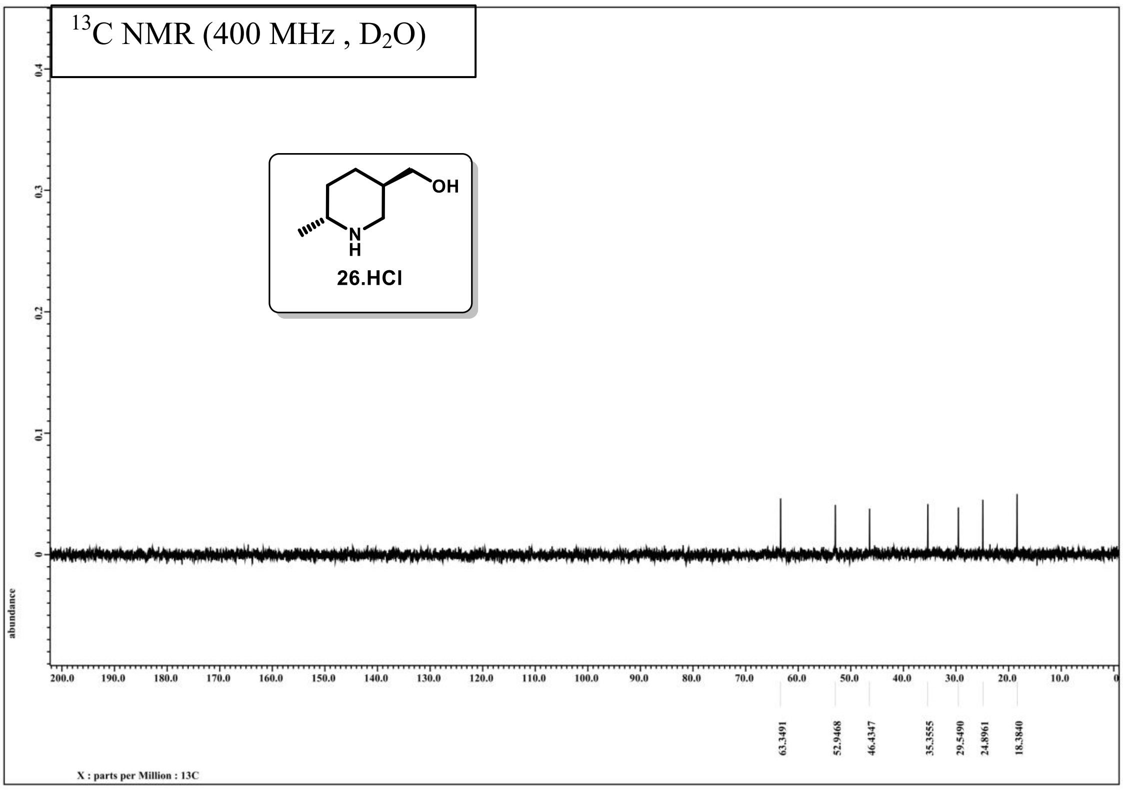

^{13}C NMR (400 MHz, CDCl$_3$)

25

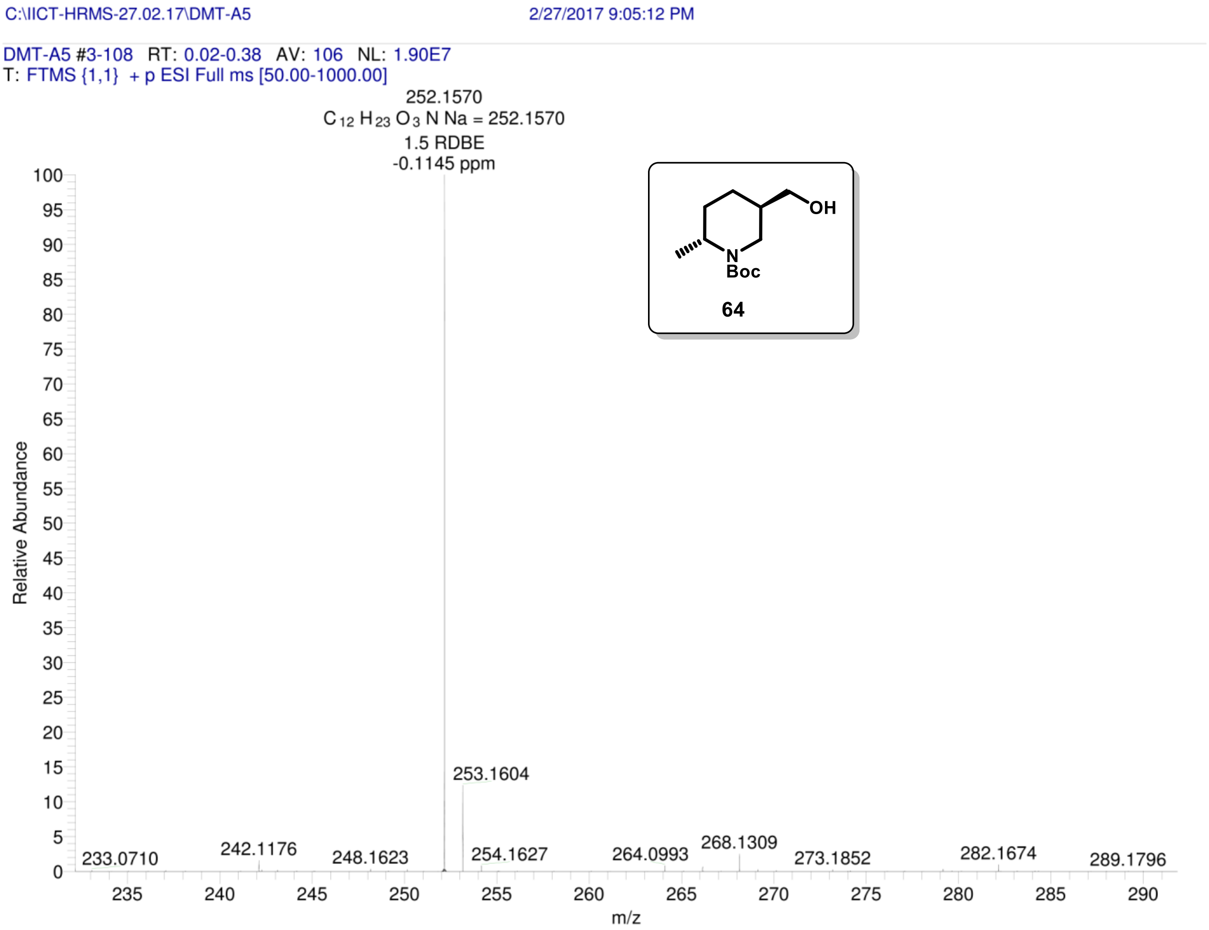

^{1}H NMR (400 MHz, CDCl$_3$)
OH
N
Boc
64
abundance
16.0 15.0 14.0 13.0 12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
1.0
1.0
2.0
1.02
6.0
9.01
3.0
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
4.3025
4.2853
4.2773
3.9645
3.9290
3.8970
3.5671
3.5441
3.5052
3.4915
3.0367
3.0287
3.0012
2.9932
1.8649
1.7228
1.7068
1.6816
1.5006
1.4662
1.4307
1.1959
1.1787
0.0000
X : parts per Million : 1H


^{13}C NMR (400 MHz, CDCl$_3$)
OH
N
Boc
64
abundance
0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
155.9749
79.7364
77.3242
77.0000
76.6854
61.9830
47.1472
37.9178
35.6485
28.4213
25.7421
20.2788
16.6080
X : parts per Million : 13C


^{1}H NMR (400 MHz, CDCl$_3$)
OH
N
H
26.HCl
abundance
2.02
1.0
2.0
3.01
1.0
3.03
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
4.6500
3.3728
3.3567
3.3453
3.2949
3.2788
3.2685
3.2491
3.2124
2.9604
2.5389
2.5068
1.8172
1.7817
1.7221
1.6820
1.6465
1.3086
1.2777
1.1081
1.0933
X : parts per Million : 1H


^{13}C NMR (400 MHz , D$_2$O)
OH
N
H
26.HCl
abundance
0.4
0.3
0.2
0.1
0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
63.3491
52.9468
46.4347
35.3555
29.5490
24.8961
18.3840
X : parts per Million : 13C

HRMS of Compound **64**



C:\IICT-HRMS-27.02.17\DMT-A5 2/27/2017 9:05:12 PM

DMT-A5 #3-108 RT: 0.02-0.38 AV: 106 NL: 1.90E7
T: FTMS {1,1} + p ESI Full ms [50.00-1000.00]

2.8 References:

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8. The diastereomeric ratio (dr) was determined from ^{1}H and ^{13}C-NMR spectral data. ^{13}C-NMR: Compound **23** on treatment with racemic diphenylprolinol silyl ether afforded diasteromers i.e compound **24 & 24a** with two signals at δ 36.15 (*syn*-diasteromer) and δ 35.86 (*anti-* diasteromer). On the other hand, Compound **23** on

treatment with (*R*)-diphenylprolinol silyl ether furnished only one signal at *δ* 36.16 (*syn*-diasteromer, **24**) while no signal corresponding to *anti*-diasteromer of compound **24a** at *δ* 35.86 was observed.

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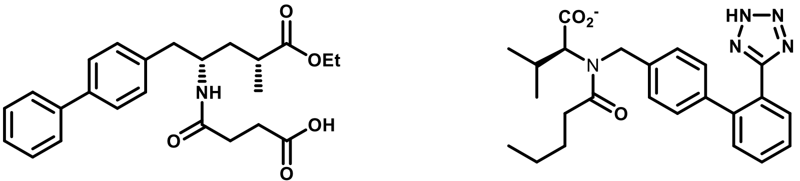
CHAPTER 3

A stereoselective approach towards the total synthesis of Sacubitril: a prodrug neprilysin inhibitor

A stereoselective approach towards the total synthesis of Sacubitril: a prodrug neprilysin inhibitor

3.1 Introduction:

In the early 1990's, Ksander and co-workers developed an active pharmaceutical compound Sacubitril (AUH-377) **5** which is a pro drug neprilysin inhibitor (Figure 7).[1] Combinations of Sacubitril **5** with the angiotensin II receptor-blocker Valsartan **65** by co-crystallization are known as supramolecular complex LCZ696 which was originally established by Novartis for the cure of heart failure (HF).[2] A first-in-class combination drug LCZ696 (brand name Entresto) was approved by FDA in 2015 and is used to lessen the threat of cardiovascular death and hospitalization for HF in patients having reduced ejection fraction and with chronic HF (NYHA Class II−IV).[3] Architecturally, Sacubitril **5** is a α-methyl-γ-amino-δ-biphenyl valeric acid analogue bearing two stereogenic centres. Sacubitril **5** has been a synthetic target of notable interest due to its immense medicinal significance and structural framework along with unique assembly of functionalities.



Sacubitril 5 **Valsartan 65**

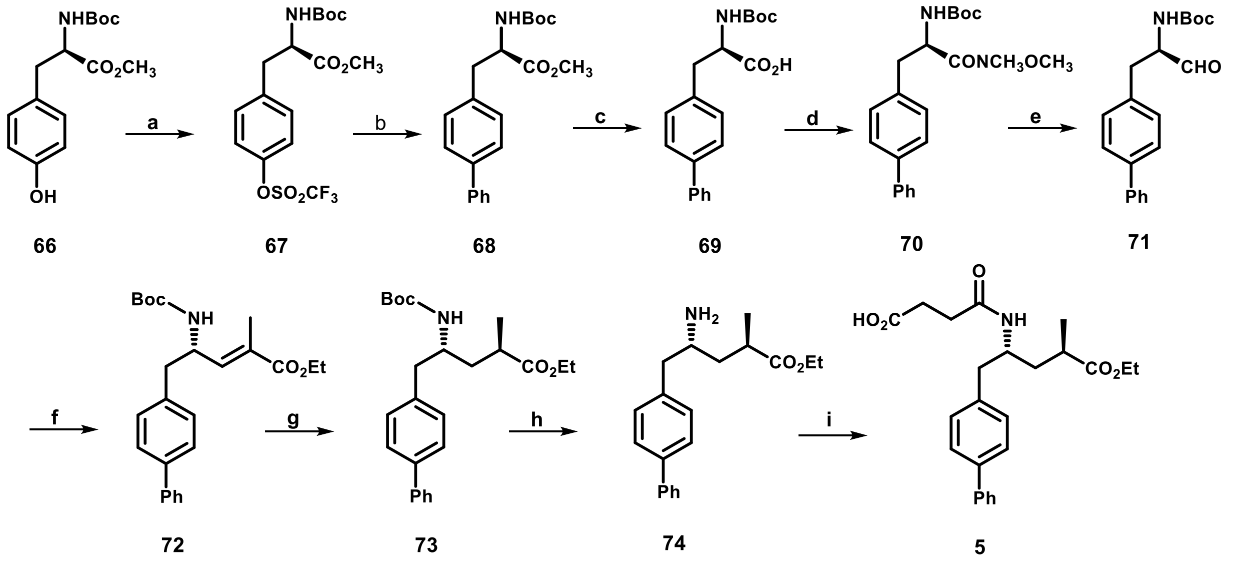
Figure 7. Structures of Sacubitril and Valsartan.

3.2 Review of Literature:

Various elegant asymmetric synthetic approaches of Sacubitril **5** and its precursors utilizing chiral pool starting materials have been illustrated in the literature.[1,4] Some of the recent syntheses of it are described below:

G. M. Ksander *et al.* (1995)[1]

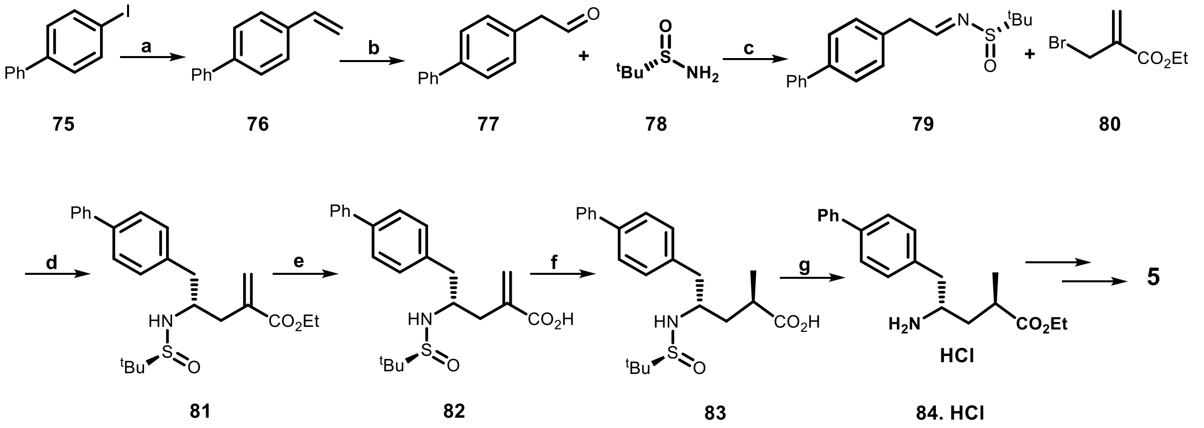
Ksander and co-workers proposed the introductory synthesis of Sacubitril **5** using N-Boc-D-tyrosine methyl ester **66** as starting material in 9 steps. As outlined in Scheme 23, in the opening step, methyl ester **66** was converted into its triflate **67** on treatment with triflic anhydride. Further, Suzuki coupling of triflate **67** was carried out with phenylboric acid to furnish the biphenyl **68** in good yield. Next, biphenyl methyl ester **68** on basic hydrolysis afforded acid **69** which was converted into hydroxymate **70** followed by lithium aluminum hydride reduction that led to the synthesis of aldehyde **71** in excellent yield. Aldehyde **71** on Wittig condensation with carbethoxyethylideneltriphenylphosphorane yielded the olefin **72** in 78 % yield. Then, Pd/C mediated hydrogenation of compound **72** provided the compound **73** as its *threo* & *erythro* mixture (*threo*:*erythro*:: 6:1) in quantitative yield. Further, compound **73** on Boc deprotection using HCl furnished the amino ester derivative **74** in good yield. Finally, the amino ester **74** on condensation with succinic anhydride afforded **5** in diastereomeric form.



Scheme 23. *Reagents and conditions*: (a) Triflic anhydride, pyridine, DCM, -15 ^{o}C, 5 min, 96%; (b) phenylboronic acid, tetrakis(triphenylphosphine)palladium(0), K_2CO_3, toluene, 80 ^{o}C, 2h, quantitative yield; (c) NaOH, CH_3OH, THF, rt, 30 min, 95%; (d) $HNCH_3OCH_3$, EDCl, HOBT, CH_2Cl_2, rt, 16 h, 97%; (e) $LiAlH_4$, dry ether, 0 ^{o}C, 20 min, 100%; (f) (carbethoxyethy1idene)triphenylphosphorane, DCM, rt, 16 h, 78%; (g) H_2/Pd/C, C_2H_5OH, 50 psi, 6 h, (threo:erythro::6:1); (h) HCl, CH_2Cl_2,0 ^{o}C-rt, 5h, 95%; (i) succinic anhydride, pyridine, CH_2Cl_2, rt, 16h,.

Ley, S. V. *et al.* (2015)[4d]

S. V. Ley and his team reported an elegant creation of amino derivative **84** as its HCl salt, that act as a precursor for the total synthesis of Sacubitril **5** from the commercially available 4-iodobiphenyl **75** using flow technology as depicted in Scheme 24. Iodobiphenyl **75** on Heck coupling with ethylene furnished the styrene derivative **76** in 99% yield. Then, compound **76** under *anti*-Markovnikov Wacker Oxidation conditions afforded the aldehyde **77** in 80 % yield. The aldehyde **77** on condensation with (*S*)-*tert*-butanesulfinamide **78**, using catalytic quantity of PPTS yielded the chiral imine **79** in 99% yield with an enantiomeric excess of 99%. Next, Reformatsky-type carbethoxyallylation of imine **79** was performed utilizing bromide derivative **80** in the presence of LiCl to furnish the acrylic ester **81** in 82% yield. Further, acrylic ester **81** on treatment with LiOH furnished the acid derivative **82** in 98% yield, which further on enantioselective hydrogenation afforded the derivative **83** in excellent yield. Finally, compound **83** was esterified in the presence of $SOCl_2$/EtOH to synthesize **84** as its HCl salt. The precursor **84** was further converted into Sacubitril **5** using known procedure.

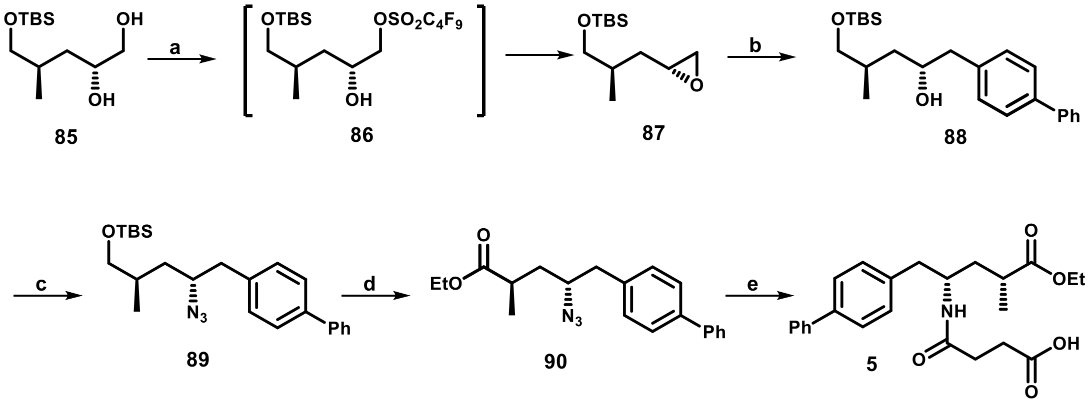


Scheme 24. *Reagents and conditions*: (a) C_2H_4, $Pd(OAc)_2$, $^tBu_3PH.BF_4$, CyNMe,:MeOH (9:1), 120 ^{o}C, 20 min, 99%; (b) $(PhCN)_2PdCl_2$, $CuCl_2$, H_2O:PhMe (1:6), 60 ^{o}C, 1 h, 80%; (c) PPTS, *i*PrOH, 70 ^{o}C, 10 min, 99%, (ee>99%); (d) LiCl, *i*PrOH. 25 ^{o}C, 1 h, 70%; (e) LiOH, THF/H_2O(1:1), 0 ^{o}C, 2 h, 98%; (f) H_2, catASium®(R)Rh, DIPEA, EtOH, 25 bar, 20 ^{o}C, 3 h, 99%; (g) $SOCl_2$, EtOH, 20 ^{o}C, 30 min, 99%.

Tian, W. S *et al.* (2016)[4c]

W. S. Tian and co-workers reported synthesis of Sacubiril **5** based on chiron approach from mono protected chiral triol **85** in total 7 steps as shown in Scheme 25. The alcohol derivative **85** on treatment with $C_4F_9SO_2F$ and DBU afforded the sulfonate intermediate **86**, which was rapidly cyclised to furnished the epoxide **87** with excellent stereoslectivity. Next, regioselective ring opening of epoxide derivative **87** was carried out with (1, 1' biphenyl)-4-yl magnesium bromide to afford the alcohol derivative **88** in 80% yield. Further, the alcohol derivative **88** was subjected to *o*-mesylation and subsequent treatment of mesylated derivative with sodium azide furnished the azide **89** in 92 % yield. Treatment of previously prepared azide **89** with Jones reagent followed by its esterification with thionyl chloride afforded the ester **90** in 80% yield (over two steps). Finally, the compound **90** was exposed to

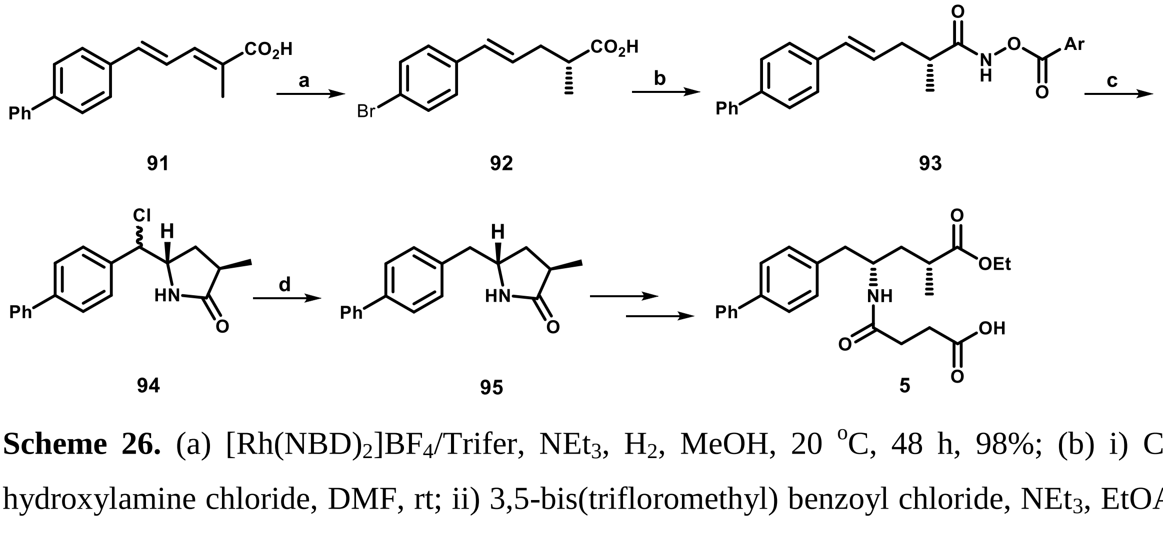
Staudinger reduction to yield the intermediate amine, which on treatment with succinic anhydride under refluxed conditions furnished the Sacubitril **5** in 77% yield.



Scheme 25. *Reagents and conditions*: (a) $C_4F_9SO_2F$, DBU, DCM, 0 °C, 91%; (b) biphenylmagnesium bromide, $CuBr.Me_2S$, 0 °C, 80%; (c) i) MsCl, NEt_3, DMAP, DCM, 0 °C, 3 h, ii) NaN_3, DMF, 60 °C, 6 h, 92% (after two steps); (d) (i) Jones reagent, acetone, 0 °C, 4 h; ii) $SOCl_2$, EtOH, 4 h, rt, 80% (over two steps); (e) (i) PPh_3, $CHCl_3$, rt, 3 h (ii) succinic anhydride, reflux, 4 h, 77% (over two steps)

Chen, W. *et al.* (2020)[4a]

More recently, Chen and co-workers disclosed the gram scale synthesis of **95**, an important precursor for the synthesis of Sacubitril **5** (Scheme 26). They utilized conjugated α-substituted dienoic acid **91** as starting material and Trifer-Rh complex catalysed hydrogenation as pivotal step.



Scheme 26. (a) $[Rh(NBD)_2]BF_4$/Trifer, NEt_3, H_2, MeOH, 20 °C, 48 h, 98%; (b) i) CDI, hydroxylamine chloride, DMF, rt; ii) 3,5-bis(trifloromethyl) benzoyl chloride, NEt_3, EtOAc , 0 °C - rt, 88%; (c) $FeCl_2$, 1,10-phenanthroline, TBAC, DCM, 86%; (d) Pd/C , MeOH, 95%.

Asymmetric hydrogenation of **91** was performed using $[Rh(NBD)_2]BF_4$/Trifer compex in the presence of NEt_3 at 20 ^oC to affored the chiral methylated compound **92** in 98% yield (98% ee). Then, the derivative **92** on sequential treatment with CDI (N,N'-carbonyldiimidazole), hydoxylammonium chloride and 3,5-bis(trifluoromethyl)benzoyl chloride was subsequently converted into hydroxylamine **93** in 88% yield. The compound **93** underwent diastereoselective intramolecular olefin aminochlorination using $FeCl_2$ for affording the motif **94**. Finally, Pd-catalyzed dechlorination of **94** furnished the Sacubitril precursor **95** with desired stereochemistry in good yield and this could be converted into Sacubitril **5** using known procedure.[4e]

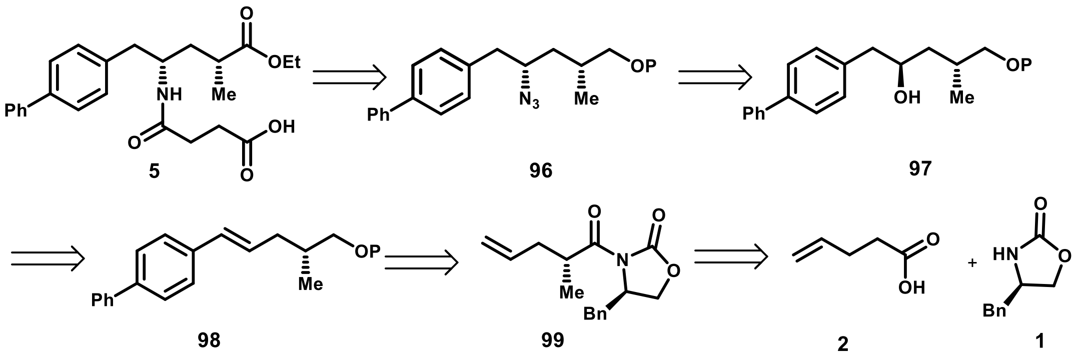
3.3 Present Work:

***Objective*:**

As our research programme is aimed at synthesizing medicinally important molecules. Herein, we are reporting a novel, and efficient synthetic strategy for the synthesis of Sacubitril **5** employing Evan's msethylation and Heck coupling reactions as principal steps.

3.4 Results and Discussions:

Our synthetic route for the asymmetric synthesis of Sacubitril **5** was envisioned *via* the retrosynthetic analysis as displayed in Scheme 27. The azide derivative **96** was envisioned to serve as a synthetic intermediate from which Sacubitril **5** could be synthesized *via* deprotection of primary alcohol followed by ethyl ester formation then reduction of azide and esterification with the succinic anhydride. The azide derivative **96** could be obtained from the hydroxyl derivative **97** via S_N2 displacement reaction of the free alcohol with the sodium azide. The hydroxyl derivative **97** in turn could be obtained from biphenyl derivative **98** employing Sharpless AD followed by regioselective hydrogenolysis of cyclic carbonate. The biphenyl derivative **98** could be accomplished from olefin derivative **99** *via* Heck coupling reaction. The intermediate **99** could be accessed from commercially available pentenoic acid **2** and (*R*)-4-benzyl-2-oxazolidione **1** *via* Evans asymmetric alkylation reaction. The (*S*)- and (*R*)-configuration of Sacubitril **5** at C2 and C4 position could be manipulated by simply changing chiral ligand under Sharpless AD and chiral 4-benzyl-2-oxazolidione involved in the Evans asymmetric alkylation reaction steps.

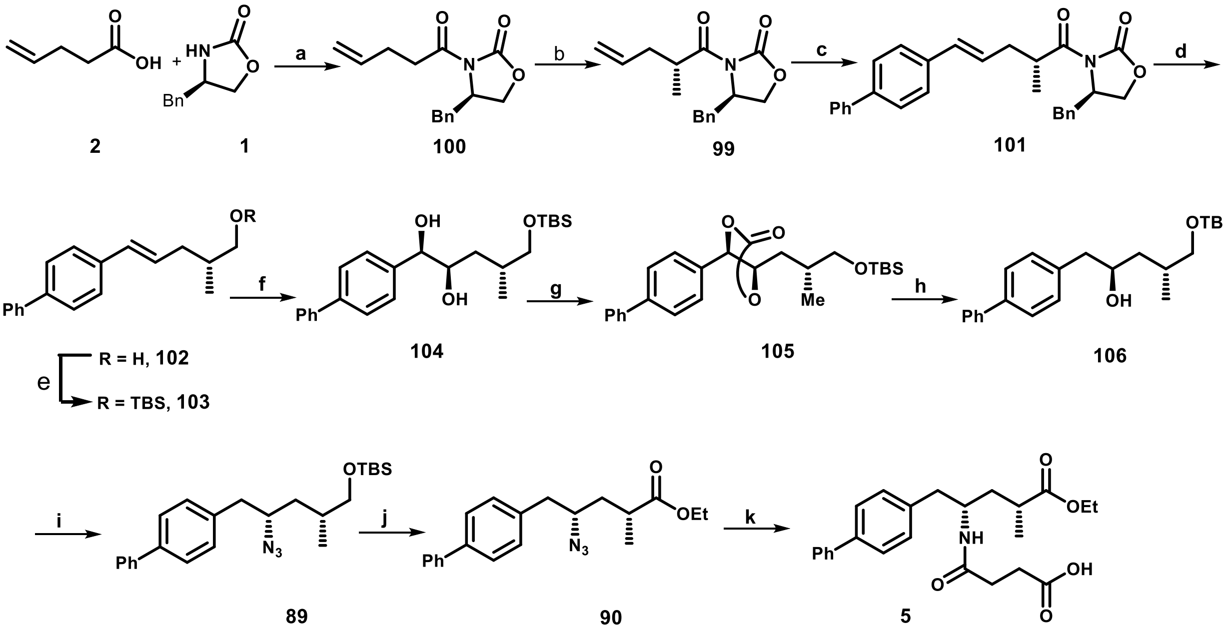


Scheme 27. Planned retrosynthetic approach for the Sacubitril.

As outlined in Scheme 28, the synthesis of Sacubitril **5** commenced from commercially available pentenoic acid **2** which on treatment with Evan's oxazolidinone chiral auxiliary (*R*)-**1** in the presence of pivaloyl chloride and Et_3N afforded the chiral imide **100** in excellent yield {$[\alpha]_D^{25}$ = -52.34 (c 1.0, $CHCl_3$); lit.[5] $[\alpha]_D^{23}$ = -55.00 (c 0.8, $CHCl_3$)}. The IR spectrum revealed C=C vibrations at 2976 cm^{-1} and C=O frequencies at 1777 & 1691 respectively. In the proton NMR spectrum of **100**, terminal olefinic hydrogens were found resonating at δ 5.96-5.82 as a multiplet (one proton), as a doublet of doublet of doublet at δ 5.08 (two hydrogen's) with J value of 13.9, 11.8, & 1.7 Hz respectively.

Stereoselective methylation, according to Evans *et al.*[6] of **100** with sodium NaHMDS (bis(trimethylsilyl)amide) and methyl iodide in THF at -78 °C furnished the methylated product **99** in 97% yield (dr = 93/7).[7] The diastereoisomers were easily separated by column chromatography. Further, a doublet resonating at δ 1.30 corresponding to three protons (J = 6.9 Hz,) in the ^1H NMR spectrum also supports the methylation of substrate **100**. Next, we turn our attention to carry out the Heck cross coupling of methylated olefin derivative **99** with commercially available 4-bromobiphenyl under numerous reagent combinations. However, the tried conditions were sluggish with poor or no yield (Table 1).

In the end, we were delighted to note that the $Pd(OAc)_2$/ Et_3N/ *tri*-o-tolyl phosphine reagent combination in acetonitrile (Table 1, entry 5) was a success to afford biphenyl olefin product **101** in 91% yield.[8] ^1H NMR of biphenyl derivative **101** also confirmed the presence of *trans* olefinic hydrogens resonating at δ 6.47 (doublet, one protons) and at δ 6.24 (dt, one proton) with the coupling constant J = 15.8 & 7.6, 15.6 Hz respectively, as a result of heck coupling. After the successful accomplishment of Heck coupling reaction, the biphenyl olefin derivative **101** was subjected to $LiAlH_4$ reduction which led to the cleavage of chiral auxiliary and furnished the alcohol derivative **102** in 94% yield. The IR spectrum of **102** showed absorption at 3354 cm^{-1} corresponding to alcohol functionality. Furthermore, the silyl ether protection of alcohol **102** with TBSCl afforded the TBS protected olefin derivative **103** in 98% yield.



Scheme 28. *Reagents and conditions*:(a) Pivaloyl chloride, Et_3N, *n*-BuLi, THF, -78 °C, 4 h, 94%; (b) NaHMDS, MeI, THF, -78 °C, 8 h, 97%; (c) $C_{12}H_9Br$, $Pd(OAc)_2$, Et_3N, *tri*-(*o*-tolyl)phosphine, CH_3CN, 100 °C, 5 h, 91%; (d) $LiAlH_4$, THF, 0 °C, 3.5 h, 94%; (e) TBSCl, Imidazole, DCM, rt, 4 h, 98%; (f) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), 24 h, 0 °C, 95%; (g) Triphosgene, Et_3N, CH_2Cl_2, -45 °C, 2 h, 90%; (h) $Pd(OH)_2$, H_2, EtOAc, rt, 18 h, 90%. (i) (i) DMAP, Et_3N, MsCl, 0 °C, 2 h; (ii) NaN_3, DMF, 60 °C, 6 h, 91% (over two steps); (j) (i) Jones reagent, acetone, 0 °C, 4 h; ii) $SOCl_2$, EtOH, 4 h, rt, 80% (over two steps); (k) (i) PPh_3, $CHCl_3$, rt, 3 h (ii) succinic anhydride, reflux, 4 h, 77 % (over two steps)

Next, subsequent treatment of olefin compound **103** with osmium tetraoxide (OsO_4) and potassium ferricyanide as co-oxidant, in the presence of $(DHQD)_2PHAL$ under Sharpless AD conditions [9] furnished the biphenyl diol product **104** in 95% yield as a single diastereomer.[10] The disappearance of olefinic protons in the ^1H NMR also serve as an evidence that substrate **104** underwent dihydroxylation. Additionally, the vibrations corresponding to alcohol functional group were found at frequency 3430 cm^{-1} in the IR spectrum of compound **104**.

With enantiomerically pure diol derivative **104** in hand, we then treated it with triphosgene in the presence of Et_3N as a base to afford the cyclic carbonate derivative **105** which on subsequent hydrogenolysis[11] in the presence of catalytic amount of palladium hydroxide afforded mono alcohol derivative **106** in 90% yield. Attempts were made to convert the free alcohol group of compound **106** to azide in single step employing Mitsunobu conditions and results were not satisfactory.[12] Accordingly, the free alcohol group of compound **106** was converted into its *o*-mesylate intermediate and its subsequent S_N2 displacement with sodium azide in dry DMF afforded compound **89** in 91% yield {$[\alpha]_D^{25}$ +11.10 (c 1.0, $CHCl_3$), lit.[4c] $[\alpha]_D^{25}$ +11.00 (c 1.10, $CHCl_3$)}. The IR spectrum of **89** indicated azide band at 2107 cm^{-1}.

On moving further, concomitant deprotection of the acid-sensitive TBS group of azide **89** and conversion of free alcohol to acid were achieved under Jones oxidation reaction conditions which on subsequent treatment with thionyl chloride in ethanol afforded the ethyl ester derivative **90** in 80% yield.

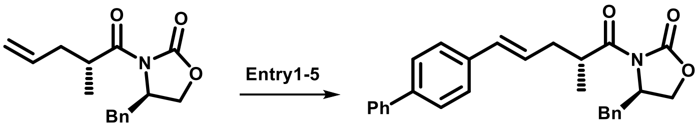
In the end, the azide of ester derivative **90** was reduced with triphenyl phosphine under Staudinger reaction conditions[13] to afford the amine intermediate which was refluxed with succinic anhydride in dichloromethane to afford the target compound Sacubitril **5** in excellent yield {$[\alpha]_D^{25}$ -21.88 (c 0.50, $CHCl_3$), lit.[4c] ($[\alpha]_D^{25}$ -22.00 (c 0.45, $CHCl_3$)}. The spectral and physical properties of the synthesized Sacubitril **5** were in agreement with previously reported values.

3.5 Research and Development (R & D):

3.5.1 Table 2. Heck cross coupling reaction optimization of compound **101**.

Sr. No.	Reagents	Temperature (^oC)	Time (h)	Yield (%)
1.	$Pd(PPh_3)_2Cl_2$, K_2CO_3; DMF:H_2O	100	4	58
2.	$Pd(OAc)_2$, K_2CO_3; Toluene	Reflux	10	45
3.	$Pd(PPh_3)_4$, Cy_2NMe; Toluene	95	24	63
4.	$Pd(OAc)_2$, K_2CO_3; DMF:H_2O	100	3	75
5.	Tri-(o-tolyl)phosphine/$Pd(OAc)_2$, Et_3N; CH_3CN	100	5	91

For the synthesis of olefin derivative **101**, we have optimized a few reaction conditions as described in Table 1. Foremost, compound **99** on treatment with $Pd(PPh_3)_2Cl_2/K_2CO_3$ in DMF:H_2O at 100 ^oC for 4 h furnished desired product **101** in moderate yield (Table 1, entry 1). Secondly, exposure of olefin **99** to a combination of $Pd(OAc)_2/K_2CO_3$ in toluene under refluxed condition was also not satisfactory (Table 1, entry 2). Next, the compound **99** was treated with $Pd(PPh_3)_4/Cy_2NMe$ in toluene and suspension was refluxed overnight at 95 ^oC. In this attempt, biphenyl motif **101** was isolated with 63% yield (Table 1, entry 3). Next, $Pd(OAc)_2/K_2CO_3$ reaction conditions were repeated by varying the solvent from toluene to DMF:H_2O. However, the results were good with 75% yield of **101** (Table 1, entry 4). Finally, treatment of **99** with *tri*-(*o*-tolyl)phosphine/ $Pd(OAc)_2/Et_3N$ in acetonitrile, furnished the anticipated biphenyl derivative **101** in excellent yield (Table 1, entry 5).



99 **101**

3.6 Conclusion:

In summary, we developed an efficient enantioselective approach for the total synthesis of Sacubitril **5** from commercially available pentenoic acid as starting material in 33% overall yield.

3.6.1 Table 3: Comparison with the previously reported syntheses of Sacubitril **5**.

Sr. No.	**Syntheses**	**Key Steps**	**Starting Material**	**Overall yield**	**No. of steps**
1.	***ChemistrySelect*** **2021**,*6*, 8928	Sharpless AD, Heck coupling, Evans Asymmetric alkylation	Pentenoic acid	31%	11
2.	*Org. Lett.* **2020**, *22*, 3149	Trifer-Rh complex catalysed hydrogenation	α-substituted dienoic acid	-	9
3.	*Tetrahedron Lett.* **2016**, *57*, 5 928	Chiron approach	Chiral triol	31.5 % approximate (with one step yield unknown)	7
4.	*Org. Lett.* **2015**, *17*, 5436	*Anti*-Markovniov Wacker oxidation , Reformatsky type carbethoxyallylation	4-iodobiphenyl, (*S*) –*tert*-butanesulfinamide bromo compound	52 %	7
5.	*J. Med. Chem .* **1995**, *38*, 1689.	Suzuki coupling	N-Boc-D tyrosinemethyl ester.	20%	9

Key sequences comprise the Evans methylation as a pivotal step for installing the first chiral centre. Further, the intermolecular Heck coupling was used to construct the required biphenyl backbone for the synthesis of Sacubitril **5,** where a combination of *tri*-(*o*-tolyl)phosphine/Pd$(OAc)_2$ and Et_3N gave fruitful results. For the introduction of second chital centre Sharpless AD conditions were found promising. Moreover, present synthetic route display significant potential for stereo chemical variations and further extension to other stereoisomers. A comparison of represented synthesis with the previously reported syntheses has been reported in the Table **3**.

3.7 Experimental Section

All experiments were performed under Nitrogen, with moisture free, freshly extracted solvents through distillation unless otherwise indicated. All the reagents or chemicals were put in reaction either *via* syringe or cannula. Each distillation was also performed under unreactive conditions. Every reaction was performed at required temperatures as narrated in their corresponding schemes. Evaporations of solvents was achieved under reduced pressure using Heidolph rotary evaporator keeping temperature below 40 °C.

Chromatography

Every reaction performed was examined through Thin Layer Chromatography executed using commercially available silica gel plates 60 F_{254} using UV light, then were stained in ninhydrin or in ethanolic solution of anisaldehyde or in aqueous $KMnO_4$ as development reagents follow up by concise heating using a heating gun. Silica gel (60-120 and 100-200 mesh) was employed for column chromatography and different compositions of ethyl acetate/hexane and methanol/ dichloromethane were used as organic eluent.

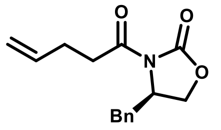
Reagents and solvents

Commercially obtained Organic solvents utilized as such unless stated in experimental conditions. Distilled H_2O was utilized for each aqueous reaction and work-up procedures. For reaction, solvent like DCM was purified using Calcium hydride, and THF was distilled under nitrogen using sodium benzophenone ketyl, straightaway prior to use.

Spectroscopic Measurements

JEOL ECS spectrometer was employed for recording the ^{1}H NMR and ^{13}C NMR respectively. Tetramethylsilane (TMS) utilized as reference. Chemical shifts have been expressed in ppm units (δ) downfield from TMS. J values are listed in hertz (Hz). Electron spray ionization (ESI) were used for recording HRMS and mass values are expressed as m/z. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}. Yields mentioned referred to isolated combined amount after chromatography.

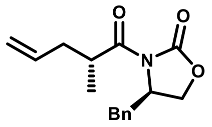
(*R*)-4-Benzyl-3-(pent-4-enoyl)oxazolidin-2-one, 100



100

The compound was synthesized in a similar way to the reported procedure.[14] Briefly, to a solution of 4-pentenoic acid **2** (1.00 g, 10.0 mmol) and triethyl amine (1.53 mL, 11.0 mmol) at -78 °C taken in dry THF (25mL) was added pivaloyl chloride (1.22 mL,10.0 mmol) over 5 min, and suspension was agitated at 0 °C for 1h. Then, (*R*)-4-benzyloxazolidin-2-one **1** (1.77 g, 10.0 mmol) was mixed with anhydrous THF (25.0 mL) under N_2 atmosphere. The resulting solution was chilled to -78 °C followed by drop by drop addition of *n*-BuLi (1.6 M in *n*-hexane, 6.56 mL, 10.5 mmol) over 5 min. The final suspension was agitated for next 30 min. To this resultant suspension was added the previously prepared mixture of 4-pentenoic acid dropwise and stirring was continued for additional 20 min at -78 °C and then warmed to 0 °C. Next, reaction was stopped by addition of saturated $NaHCO_3$ aqueous solution. The obtained solution was isolated using ethyl acetate (3 x 30 mL) and the collected organic phases were washed with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated using vacuum. Colum chromatography (eluent, hexane/AcOEt = 3/1) of crude furnished desired product **100** as colorless oil (2.46 g, 94% yield). $[\alpha]_D^{25} = -52.34$ (c 1.0, $CHCl_3$) {lit.[14] $[\alpha]_D^{23} = -55.00$ (c 0.8, $CHCl_3$)}; IR (neat) 2976, 1777, 1691, 1382, 1353, 1207 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.20 (m, 5H), 5.96-5.82 (m, 1H), 5.08 (ddd, J = 13.9, 11.8, 1.7 Hz, 2H), 4.68 (ddd, J = 13.2, 6.9, 3.4 Hz, 1H), 4.23-4.14 (m, 2H), 3.30 (dd, J = 13.4, 3.3 Hz, 1H), 3.14-2.99 (m, 2H), 2.76 (dd, J = 13.4, 9.7 Hz, 1H), 2.51–2.42 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.7, 153.5, 136.8, 135.4, 129.6, 129.1, 127.5, 115.9, 66.3, 55.3, 38.0, 34.9, 28.3.

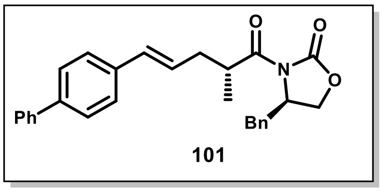
(*R*)-4-Benzyl-3-((*R*)-2-methylpent-4-enoyl)oxazolidin-2-one, 99



99

To a mixture of compound **100** (2.0 g, 7.70 mmol) in dry tetrahydro furan (20 mL) at -78 °C was added slowly NaHMDS (1.1 M in THF, 10.5 mL, 11.56 mmol) over 5 min. After stirring the reaction mixture for 1 h at same conditions, drop wise addition of MeI (1.92 mL, 30.84 mmol) over 5 min was carried out. The resultant mixture was continued to agitate at -78 °C for 7 h. Then on quenching the reaction with saturated NH_4Cl aqueous solution (50 mL), product was collected with ethyl acetate (3 x 50 mL). The collected organic extracts were washed with brine (60 mL) and dried out using anhydrous Na_2SO_4. Organic phase was concentrated in *vacuo*, and crude was purified by silica gel column chromatography and gave the desired alkene **99** (2.04 g, 97% yield) as a colorless syrupy liquid. $[\alpha]_D^{25}$ = - 69.17 (c 1.0, $CHCl_3$); IR (neat) 2978, 2952, 1777, 1704, 1383, 1320, 1199, 1043, 700 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.39-7.21 (m, 5H), 5.78 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.12-5.00 (m, 2H), 4.67 (ddt, *J* =10.0, 6.8, 3.4 Hz, 1H), 4.23-4.15 (m, 2H), 3.82 (dt, *J* = 14.1, 7.1 Hz, 1H), 3.26 (dt, *J* = 13.2, 6.6 Hz, 1H), 2.82-2.73 (m, 1H), 2.48 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.20 (dt, *J* = 14.0, 7.0 Hz, 1H), 1.23 (t, *J* = 7.5 Hz , 3H); ^{13}C NMR (101MHz, $CDCl_3$) δ = 176.6, 153.2, 135.6 (2C), 135.4, 129.6, 129.1(4C), 129.0, 127.5, 117.2, 66.2, 55.5, 38.0, 37.7, 37.6, 17.2; HRMS (ESI-TOF) m/z 296.1261 $[M + Na]^+$ (calcd for $C_{16}H_{19}NO_3Na$, 296.1257).

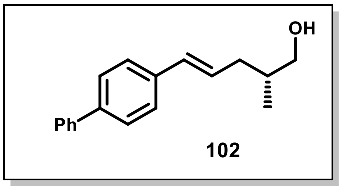
(*R*)-3-((*R*,*E*)-5-([1,1'-Biphenyl]-4-yl)-2-methylpent-4-enoyl)-4-benzyloxazolidin-2-one, 101



101

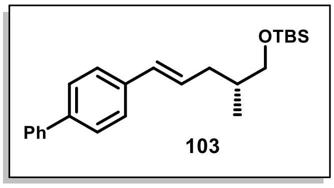
Mixture of compound **99** (1.80 g, 6.58 mmol), biphenyl bromide (1.91 g, 8.23 mmol), *tri*-o-tolylphosphine (400 mg, 0.20 mol%), Palladium (II) acetate (73 mg, 5 mol%) and triethytlamine (1.10 mL,8.23 mmol) in 15 mL of acetonitrile was purged with nitrogen gas for 15 minutes and heated in a closed tube at 100 °C for 5 h. The suspension was then chilled to room temperature and the residue was taken up in 50 mL of DCM. Further, washing of the same twice with H_2O (50 mL) followed by drying (Na_2SO_4), filtration and on concentrating in *vacuo* afforded the crude solid. Column chromatography of the collected crude furnished the olefin derivative **101** (2.55 g, 91%) as a colourless solid. Recrystallization from ethyl acetate-hexanes (hot filtration) afforded the analytical sample of **101** as shiny colorless needles. $[\alpha]_D^{25}$ -41.28 (c 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 2985, 2964, 1769, 1718, 1325, 1207, 1047, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60-7.52 (m, 4H), 7.46-7.40 (m, 4H), 7.36-7.27 (m, 4H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.24 (dt, *J* = 15.6, 7.6 Hz, 1H), 4.65 (ddt, *J* = 10.4, 7.4, 3.0 Hz, 1H), 4.16-4.07 (m, 2H), 3.93(dt, *J* = 13.9, 6.9 Hz, 1H), 3.27 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.78 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.64 (dt, *J* = 21.4, 7.5 Hz, 1H), 2.43-2.35 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.5, 153.3, 140.8, 140.1, 136.4, 135.3, 131.8, 129.7, 129.0, 128.9, 127.4, 127.3, 127.0, 126.6, 66.2, 55.4, 38.0, 37.3, 17.3; HRMS (ESI-TOF) m/z 448.1881 $[M + Na]^+$ (calcd for $C_{28}H_{27}NO_3Na$, 448.1883).

(***R***,***E***)-5-([1,1'-Biphenyl]-4-yl)-2-methylpent-4-en-1-ol, 102



Biphenyl olefin derivative **101** (2.0 g, 4.70 mmol) dissolved in anhydrous THF (20 mL) was dropwise added to a emulsion of $LiAlH_4$ (392 mg, 10.34 mmol) taken in anhydrous THF (10 mL) and stirred for 30 minutes at room temperature. Further, the resultant suspension was refluxed for 3 hours until the completion as observed by using thin layer chromatography. The solution was allowed to cool at room temperature and after that 100 mL of ether and celite (10 g) was added to it. Drop wise addition of water was carried out until hydrogen development stopped. The obtained residue after filtered was washed with ether. The solvent was concentrated and obtained crude upon silica gel column chromatography delivered the biphenyl olefin alcohol derivative **102** as thick oil (1.10 g, 94%). $[\alpha]_D^{25}$-29.71 (c 1.0, $CHCl_3$); IR (CH_2Cl_2) *ν*: 3354, 3019, 2961, 2919, 1602, 1489, 1215, 1072, 1029, 963, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (dd, *J* = 19.7, 8.0 Hz, 4H), 7.44 (t, *J* = 7.8 Hz, 4H), 7.34 (t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.33-6.23 (m, 1H), 3.55(qd, *J* = 10.6, 6.2 Hz, 2H), 2.37 (dt, *J* = 13.3, 6.6 Hz, 1H), 2.18-2.08 (m, 1H), 1.85 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.40 (brs, 1H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.8, 139.7, 136.6, 130.9, 128.9, 128.7, 127.2, 126.9, 126.4, 67.9, 37.0, 36.1, 16.5; HRMS (ESI-TOF) m/z 275.1411 $[M + Na]^+$ (calcd. for $C_{18}H_{20}ONa$, 275.1406).

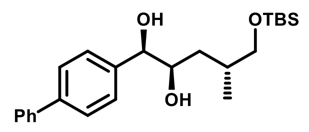
(***R***,***E***)-((5-([1,1'-Biphenyl]-4-yl)-2-methylpent-4-en-1-yl)oxy)(***tert***-butyl)dimethylsilane, 103



Biphenyl olefin alcohol derivative **102** (1.00 g, 3.96 mmol) was taken in anhydrous CH_2Cl_2 (20 mL). To it, imidazole (408 mg, 5.94 mmol), TBSCl (775 mg, 5.15 mmol) and DMAP (96 mg, 0.792 mmol) were added sequentially at 25 ^oC under argon atmosphere. The reacting solution was agitated for additional 4 hours under same conditions. After completion, the resultant solution was quenched with NH_4Cl (10 mL). After extraction with CH_2Cl_2 (3 x 10 mL), combined organic phase was washed away using brine and dehydrated with the help of anhydrous Na_2SO_4. The collected organic phase was concentrated under vacuum and crude collected upon purification using silica gel column chromatography furnished the TBS-protected biphenyl motif **103** as colorless oil (1.50 g, 98%). $[\alpha]_D^{25}$- 18.20 (c 1.0, $CHCl_3$); IR (neat) *ν* 2961, 2931, 2861, 1256,1112, 963, 741, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63-7.54 (m, 4H), 7.49 – 7.41 (m, 4H), 7.34 (dt, *J* = 3.9, 1.5 Hz, 1H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.31-6.21 (m, 1H), 3.48 (d, *J* = 5.9 Hz, 2H), 2.38

(dt, J = 13.8, 6.9 Hz, 1H), 2.03 (dd, J = 21.5, 0.9 Hz, 1H), 1.80 (dt, J = 13.4, 6.5 Hz, 1H), 0.91 (d, J = 4.8 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, CDCl3) δ = 140.8, 139.5, 136.9, 130.6, 129.6, 128.7, 127.12, 127.1, 126.9, 126.3, 67.7, 36.8, 36.2, 25.9, 18.4, 16.5, -5.3; HRMS (ESI-TOF) m/z 389.2270 [M+Na]$^+$ (calcd for $C_{24}H_{34}OSiNa$, 389.2271).

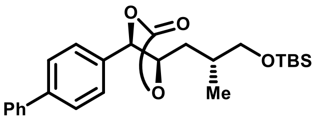
(1*R*,2*R*,4*R*)-1-([1,1'-Biphenyl]-4-yl)-5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentane-1,2-diol, 104



104

To a solution of *tert*-butyl alcohol and water (40 mL, 1:1) at room temperature, $K_3Fe(CN)_6$ (2.69 g, 8.16 mmol), potassium carbonate (0.41 g, 8.16 mmol) and $(DHQD)_2PHAL$ (21 mg, 0.027 mmol, 0.01 mol %) were added sequentially. The generated reagent blend was cooled to 0 ^{o}C followed by addition of OsO_4 (0.12 mL, 0.1 M solution in toluene, 0.005 mol%) and methanesulfonamide (258 mg, 2.72 mmol). After being agitated for 5 min at 0 ^{o}C, TBS-protected biphenyl olefin derivative **103** (1.0 g, 2.72 mmol) was put in one lot and resulting solution was further stirred at 0 ^{o}C overnight. The reaction was quenched using sodium sulfite (2.0 g) and stirring was sustained for extra 45 min, and the suspension was extracted with EtOAc (3 x 30 mL), dried over Na_2SO_3 and concentrated in *vacuo*. Silica gel column chromatography of residue afforded diol derivative **104** (1.03 g, 95%). [R_f = 0.4, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ -12.2 (c 1.0, $CHCl_3$); IR (CH_2Cl_2) v: 3430, 3050, 3020, 2950, 2870, 1650, 1600, 1580, 1495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (dd, J = 11.7, 4.6 Hz, 4H), 7.47-7.42 (m, 4H), 7.34 (t, J = 7.4 Hz, 1H), 4.44 (d, J = 7.2 Hz, 1H), 3.7-3.72 (m, 1H), 3.56 (dd, J = 10.1, 4.4 Hz, 1H), 3.37 (dd, J = 10.0, 8.3 Hz, 1H), 1.88-1.84 (m, 1H), 1.67 (brs, 2H) 1.44-1.35 (m, 2H), 0.91 (s, 9H), 0.80 (d, J = 6.9 Hz, 3H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.0, 140.8, 140.4, 128.9, 127.8, 127.4, 127.2, 78.4, 75.0, 69.6, 39.1, 34.3, 26.0, 18.4, 18.1, -5.3, -5.4; HRMS (ESI-TOF) m/z 423.2321 [M+Na]$^+$ (calcd for $C_{24}H_{36}O_3SiNa$, 423.2326).

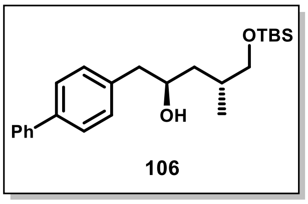
(4*R*,5*R*)-4-([1,1'-Biphenyl]-4-yl)-5-((*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-1,3-dioxolan- 2-one, 105



105

Diol derivative **104** (900 mg, 2.24 mmol) and triethyl amine (2.42 mL, 18 mmol) was mixed with anhydrous CH_2Cl_2 (20 mL) and temperature of resultant reacting suspension was lowered to -45 °C. A solution of triphosgene (4.63 g, 17.18 mmol) taken in CH_2Cl_2 (30 mL) was added to the above stirred solution, *via* cannula over a period of 10 minute. A salty slurry was obtained and temperature of resultant slurry was raised to 30 °C over 30 min. and agitation was carried out for extra 1.5 hour. Next, TLC was examined and after completion $NaHCO_3$ (20 mL, saturated solution) was added. Further, the slurry was concentrated under reduced pressure in order to exterminate dichloromethane. The slurry was taken up in a mixture of diethylether (15 mL) and saturated $NaHCO_3$ (15 mL) and transferred to a separatory funnel. Layers were parted, and water layer was re-extracted using Et_2O (2 x 15 mL). The organic portions were collected, washed using brine (15 mL), and moisture was removed with anhydrous Na_2SO_4. Additional Et_2O (15 mL) was used to extract any remaining product. Silica gel column chromatography of the residue afforded white coloured cyclic derivative **105** (0.83 g, 90%) in solid state. $[\alpha]_D^{25}$ -6.38 (c 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 3069, 3017, 2962, 2868, 1650, 1797, 1605, 1586, 1502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.57 (m, 4H), 7.50-7.38 (m, 5H), 5.22 (d, J = 7.6 Hz, 1H), 4.67 (ddd, J = 9.6, 7.8, 3.6 Hz, 1H), 3.50 (dd, J = 9.9, 5.2 Hz, 1H), 3.43-3.37 (m, 1H), 2.06 (ddd, J = 14.2, 9.5, 4.6 Hz, 1H), 1.98-1.90 (m, 1H), 1.65-1.60 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.4, 142.7, 140.0, 134.2, 128.9, 127.9, 127.8, 127.1, 126.9, 83.7, 82.6, 67.7, 36.8, 32.1, 25.8, 25.7, 18.2, 16.1, -5.46, -5.51; HRMS (ESI-TOF) m/z 449.2121 $[M + Na]^+$ (calcd for $C_{25}H_{34}O_4SiNa$, 449.2119).

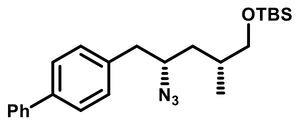
(2*R*,4*R*)-1-([1,1'-Biphenyl]-4-yl)-5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentan-2-ol, 106



106

To the cyclic carbonate intermediate **105** (800 mg, 1.87 mmol) obtained in the above reaction taken in ethyl acetate (5 mL) was added $Pd(OH)_2$ (20 mol%) and resulting suspension was agitated under H_2 ballon for 18 h. After completion of reaction, the catalyst was taken out by filtration over celite and washed using EtOAc. Collected organic phase was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Remaining residue on purification by silica gel column chromatography (EtOAc/hexane 3:7) furnished the mono alcohol **106** (648 mg, 90%) as a colorless oil. $[\alpha]_D^{25}$ +7.8 (c 1.0, $CHCl_3$){ lit.[4c] $[\alpha]_D^{24}$ +7.6 (c 1.24, $CHCl_3$)}; IR (CH_2Cl_2) ν: 3428, 2949, 2861, 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.61-7.57 (m, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.32 (dd, J = 16.0, 7.7 Hz, 3H), 3.94 (d, J = 2.8 Hz, 1H), 3.54 (dd, J = 10.0, 4.9 Hz, 1H), 3.42 (dd, J = 9.9, 7.5 Hz, 1H), 3.22 (d, J = 2.6 Hz, 1H), 2.81 (ddd, J = 19.3, 13.5, 6.3 Hz, 2H), 1.82 (td, J = 13.5, 6.7 Hz, 1H), 1.48 (t, J = 6.2 Hz, 2H), 0.91 (s, 9H), 0.88 (d, J = 6.8 Hz, 3H), 0.07 (s, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.2, 139.2, 138.2, 130.1, 128.9, 127.2 (2C), 127.1, 71.5, 69.5, 44.4, 42.4, 34.2, 26.1, 18.50, 17.86, -5.2, -5.3; HRMS (ESI-TOF) m/z 385.2557 $[M + H]^+$ (calcd for $C_{24}H_{36}O_2Si$, 385.2557).

(((2*R*,4*S*)-5-([1,1'-Biphenyl]-4-yl)-4-azido-2-methylpentyl)oxy)(*tert*-butyl)dimethylsilane, 89

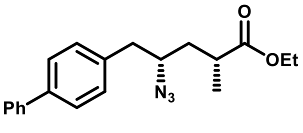


89

Methanesulfonyl chloride (0.06 mL, 0.77mmol), NEt_3 (0.28 mL, 1.55 mmol) and DMAP (catalytic) (6 mg, 0.051 mmol) were added sequentially to a stirred suspension of alcohol derivative **106** (201 mg, 1.29 mmol) taken in moisture free DCM (10 mL). The stirring was continued for 2 h at 0 °C, after completion as checked using TLC the reaction was terminated with saturated solution of Na_2CO_3, and layers were segregated with brine and CH_2Cl_2. The organic extract was dried over Na_2SO_4, and concentrated in *vacuo*. The mesylated derivative thus formed was further used in next reaction without purification.

The above mesylated derivative and NaN_3 (134 mg, 2.07 mmol) was mixed with dry DMF (10 mL) and the resultant solution was agitated at 60 °C for 6 h. As the reaction completes, monitored using thin layer chromatography, mixture was diluted with the addition of EtOAc, washed with H_2O and brine, dried above Na_2SO_4, and concentrated in vacuum. The crude product was purified by silica gel chromatography (petroleum/EtOAc: 30/1) to afford **89** as a colorless oil (400 mg, 91 %). [R_f = 0.4, EtOAc/hexane 3 : 7 v/v]; $[\alpha]_D^{25}$ +11.10 (c1.10, $CHCl_3$) {lit.2 $[\alpha]_D^{25}$ +11.00 (c 1.10, $CHCl_3$)}; IR (CH_2Cl_2) *v*: 2953, 2931, 2856, 2107, 1491, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60-7.534 (m, 4 H),7.43 (t, *J* = 7.6 Hz, 2H), 7.35-7.27 (m, 3H), 3.70- 3.63 (m, 1H), 3.50 (dd, *J* = 5.2, 9.8 Hz, 1H), 3.42 (dd, *J* = 5.6, 9.6 Hz, 1H), 2.84 (t, *J* = 5.6 Hz, 2H), 1.89-1.82 (m, 1H), 1.74-1.67 (m, 1H), 1.41-1.33 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.018 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.0, 139.7, 137.0, 129.8, 128.9, 127.4, 127.3, 127.1, 67.5, 62.5, 41.0, 37.9, 32.9, 26.0, 18.4, 17.7, -5.3.

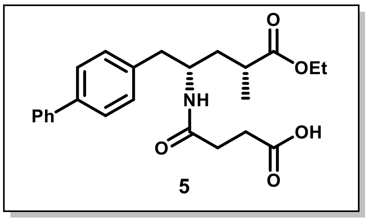
Ethyl (2*R*,4*S*)-5-([1,1'-biphenyl]-4-yl)-4-azido-2-methylpentanoate, 90



90

]]./;/A dropwise addition of Jones reagent (0.26 mL, 2.6 M, 0.64 mmol) was carried out to a stirred solution of **89** (0.1 g, 0.24 mmol) in acetone (4 mL) maintained at 0 °C and suspension obtained was stirred for four hours. The reaction after completion, as checked by TLC, was terminated with *i*- PrOH, and filtered. The obtained filtrate was concentrated in vacuum. The resultant compound was simultaneously dissolved in EtOH (15 mL) and to its stirred solution was added $SOCl_2$ (0.04 mL, 0.5 mmol). After additionally stirring the mixture for 4 hours at 25 ^{o}C, TLC was checked and after completion the reaction was ended with saturated aqueous Na_2CO_3. The residue was extracted with EtOAc, washed with water and brine, and concentrated in *vacuo*. Purification of crude was perfomed using silica gel chromatography and the azide derivative **90** was collected as colorless oil (65 mg, 80%). $[\alpha]_D^{25}$ -31.89 (c 1.00, $CHCl_3$) {Lit.[4c] $[\alpha]_D^{26}$ -33.00 (c 1.24, $CHCl_3$)}; IR (CH_2Cl_2) *v*: 2988, 2943, 2105, 1733, 1267 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50 (dd, *J* = 17.9, 7.7 Hz, 4H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.28-7.18 (m, 3H), 4.07 (q, *J* = 7.4 Hz, 2H), 3.59-3.51 (m, 1H), 2.80 (d, *J* = 6.8 Hz, 2H), 2.70-2.61 (m, 1H), 1.92-1.83 (m, 1H), 1.47-1.40 (m, 1H), 1.17 (t, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz,) δ: 176.1, 140.9, 139.9, 136.6, 129.8, 128.9, 127.5, 127.4, 127.2, 62.6, 60.7, 41.2, 38.6, 36.8, 18.2, 14.4.

Sacubitril, 5



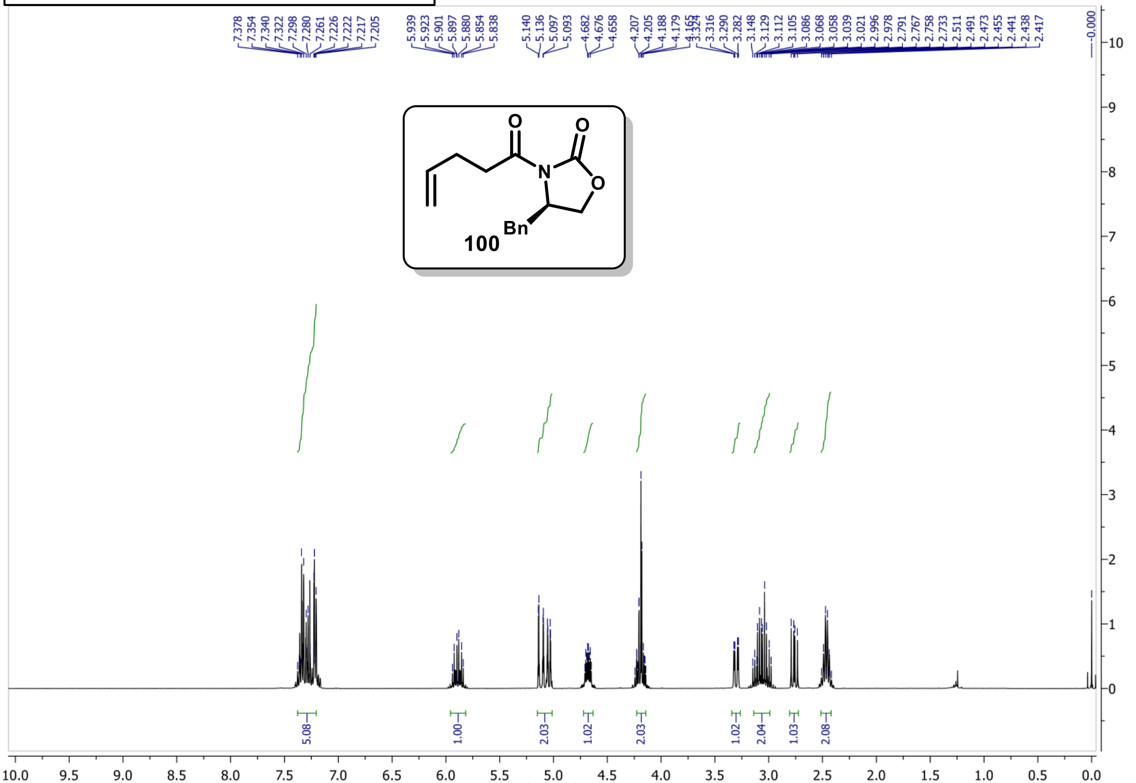
5

To a stirred mixture of azide **90** (35 mg, 0.10 mmol) in $CHCl_3$ (7 mL) triphenylphosphine was added (0.10 g, 0.31 mmol) and reaction mixture stirred at 25 ^{o}C for 3 h. Triethyl amine (0.07 mL, 0.56 mmol) and succinic anhydride (31 mg, 0.31 mmol) were put into the above mixture sequentially and obtained suspension was refluxed for 4h. After completion, indicated by TLC, was diluted with CH_2Cl_2, and concentrated under reduce pressure. The crude was purified through silica gel chromatography to furnish the target compound Sacubitril **5** as a pale yellow gum (32 mg, 77%). $[\alpha]_D^{25}$ -21.88 (c 0.50, $CHCl_3$) {Lit.[4c] $[\alpha]_D^{26}$ -22 (c 0.45, $CHCl_3$)}; IR (CH_2Cl_2) *v*: 3548, 3259, 3064, 2981, 1728, 1644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (dd, *J* = 19.8, 8.5 Hz, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.81 (d, *J* = 8.6 Hz, 1H), 4.33-4.21 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.85 (dd, *J* = 6.3, 3.3 Hz, 2H), 2.64 (t, *J* = 6.5 Hz, 2H), 2.59 – 2.51 (m, 1H), 2.45 (t, *J* = 6.8 Hz, 2H), 1.98 –1.92 (m, 1H), 1.5 – 1.52 (m, 1H), 1.23 (t, *J* = 7.8 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.6, 172.2, 140.8, 139.6, 136.5, 130.0, 128.9, 127.4, 127.3, 127.1, 60.9, 48.9, 40.5, 37.2, 36.6, 30.9, 29.8, 17.7, 14.3; HRMS (ESI-TOF) m/z 412.2123 $[M+H]^+$ (calcd for $C_{24}H_{29}NO_5$, 412.2118).

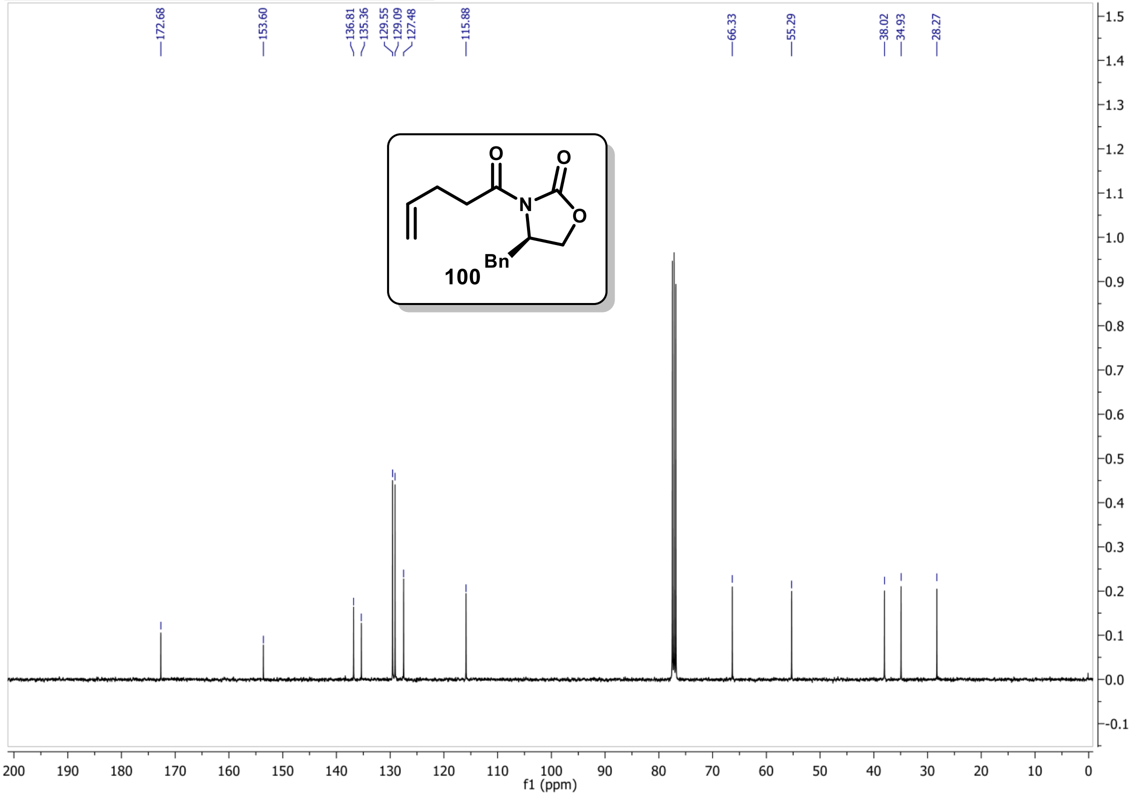
3.8 Spectra

1. ^{1}H and ^{13}C NMR Spectra of **100**
2. ^{1}H and ^{13}C NMR Spectra of **99**
3. ^{1}H and ^{13}C NMR Spectra of **101**
4. ^{1}H and ^{13}C NMR Spectra of **102**
5. ^{1}H and ^{13}C NMR Spectra of **103**
6. ^{1}H and ^{13}C NMR Spectra of **104**
7. ^{1}H and ^{13}C NMR Spectra of **105**
8. ^{1}H and ^{13}C NMR Spectra of **106**
9. ^{1}H and ^{13}C NMR Spectra of **89**
10. ^{1}H and ^{13}C NMR Spectra of **90**
11. ^{1}H and ^{13}C NMR Spectra of **5**

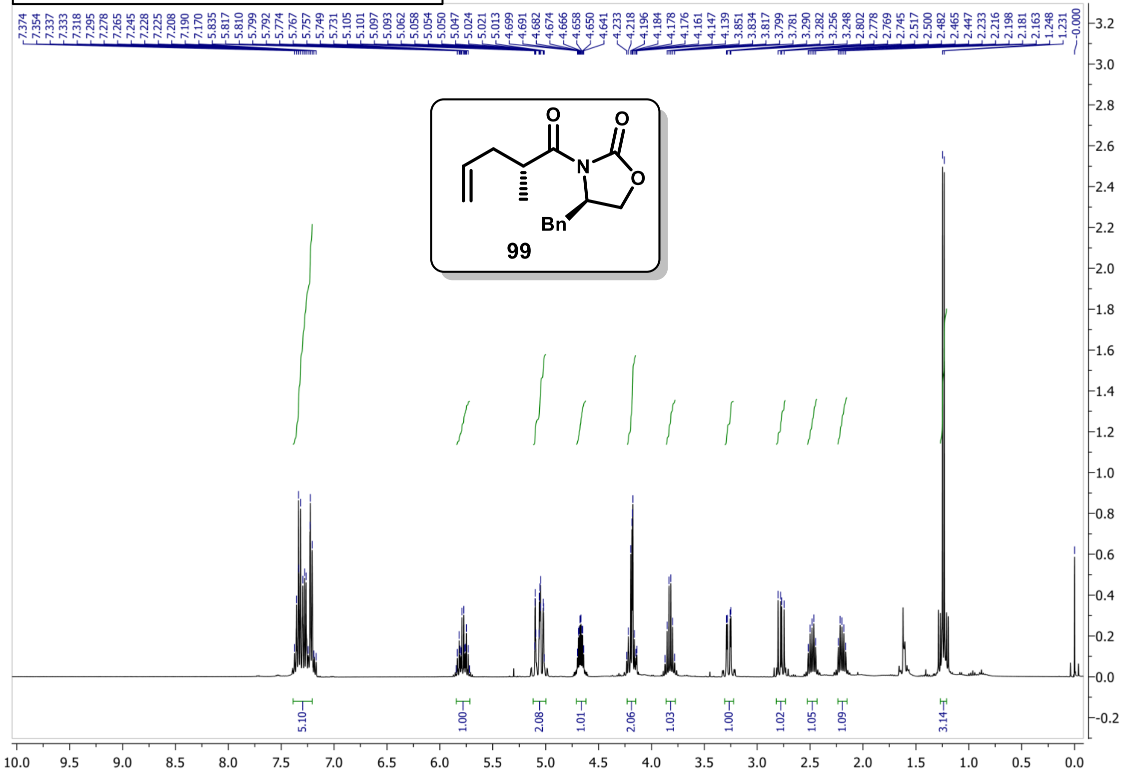
^{1}H NMR (400 MHz, CDCl$_3$)



^{13}C NMR (400 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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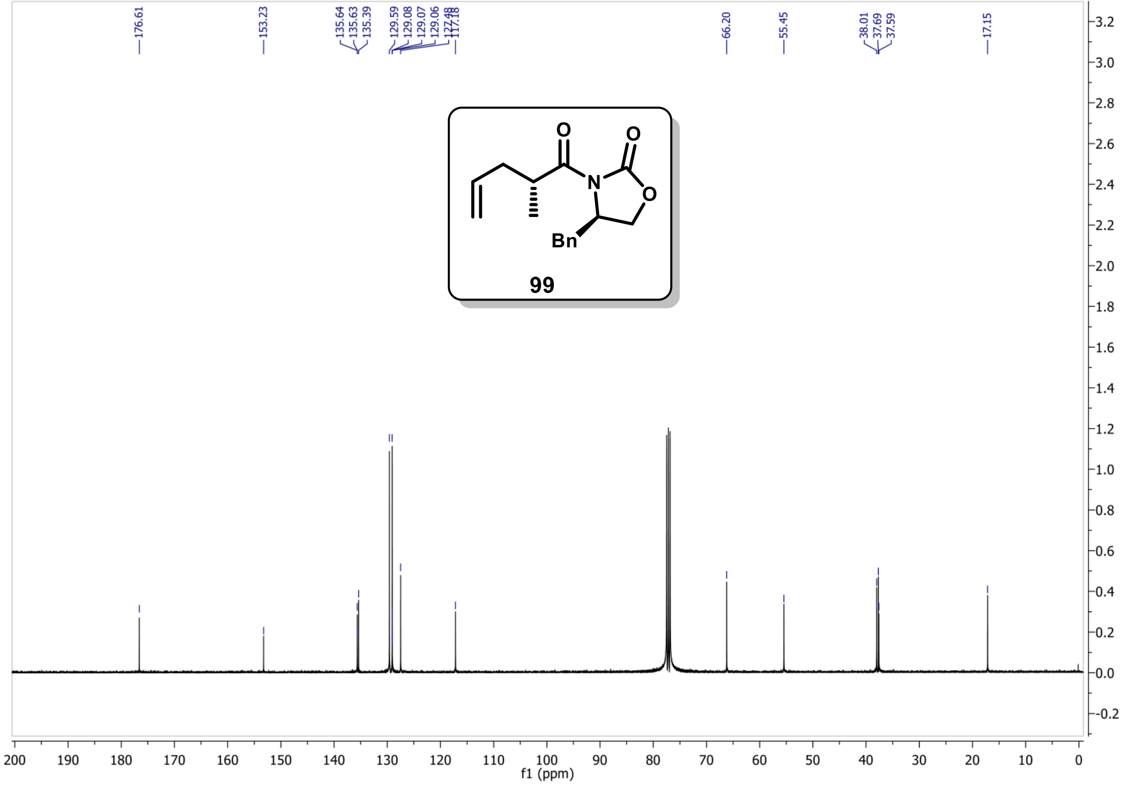

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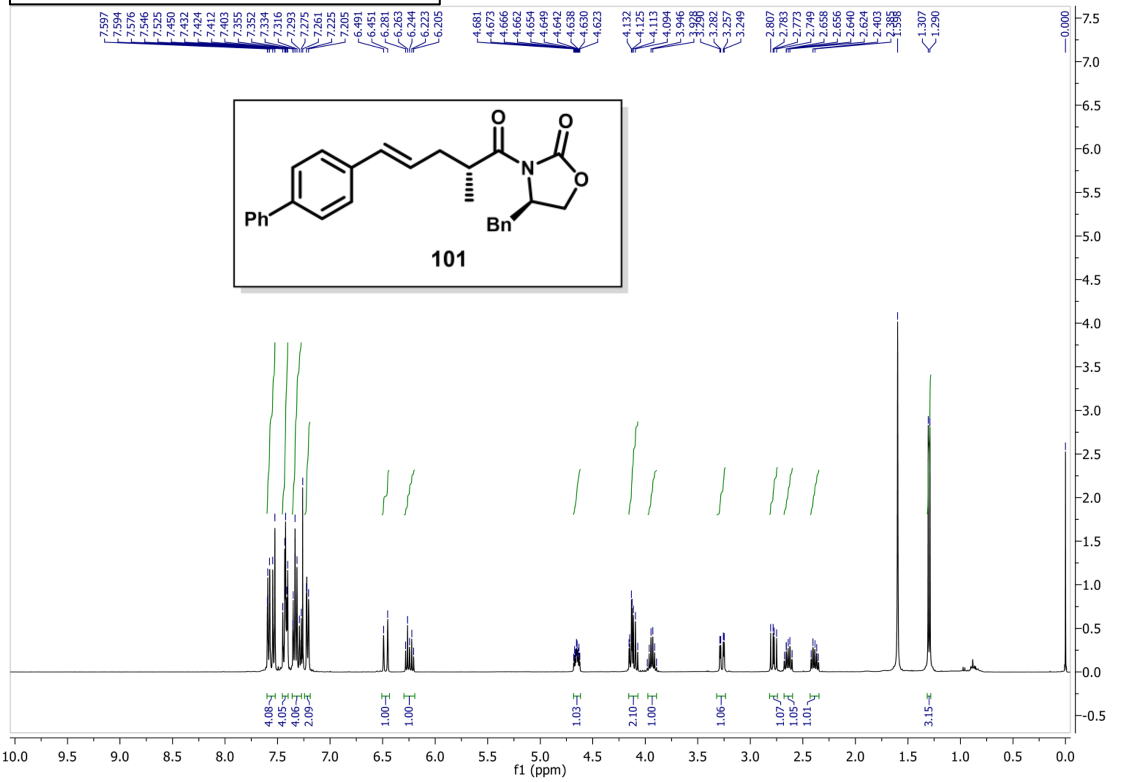

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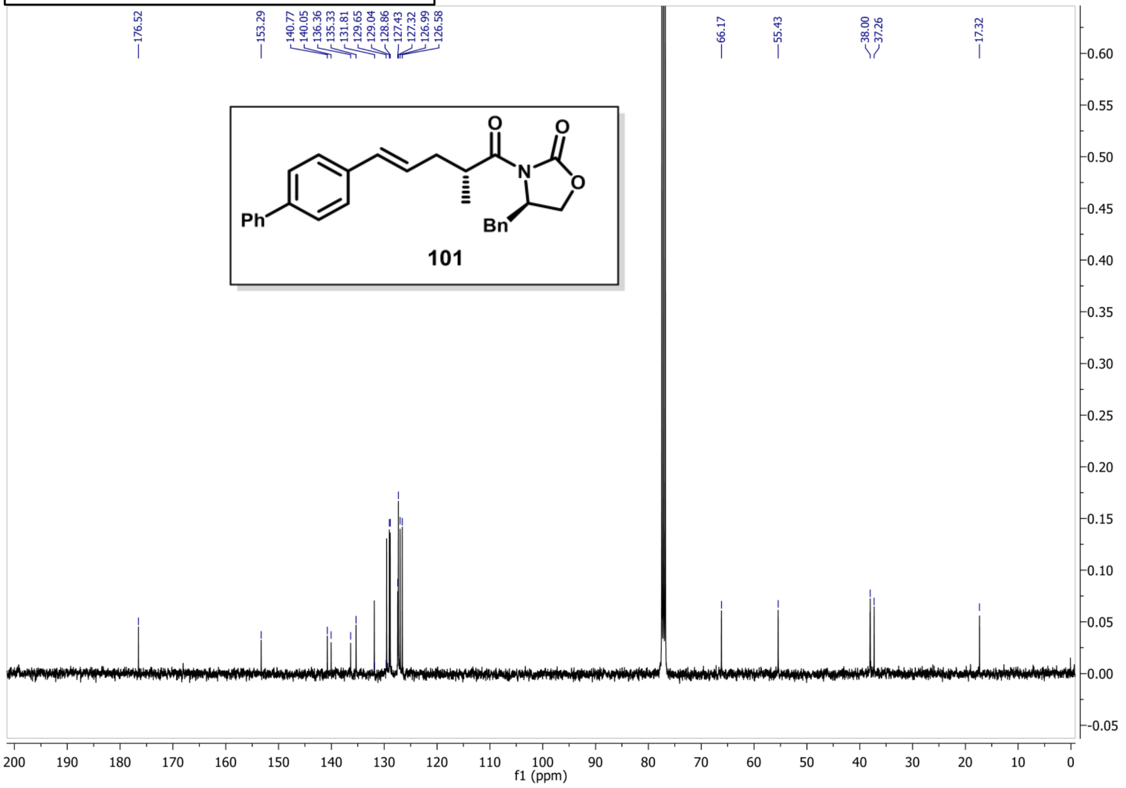

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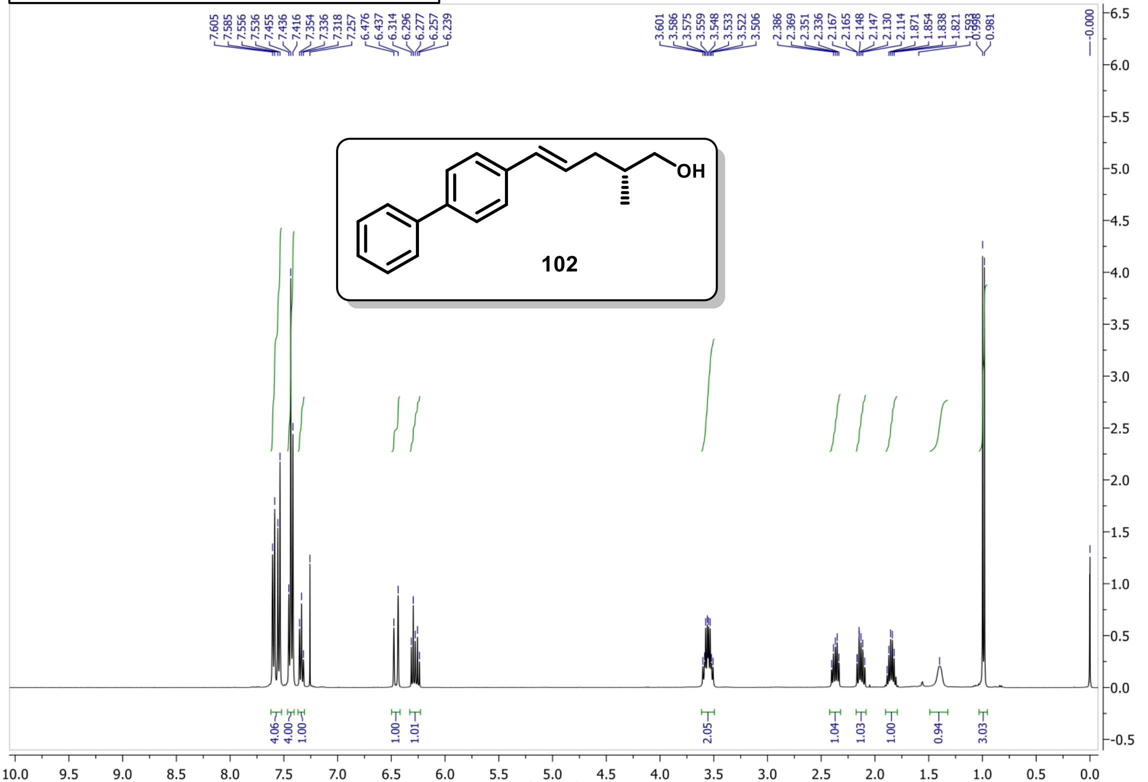

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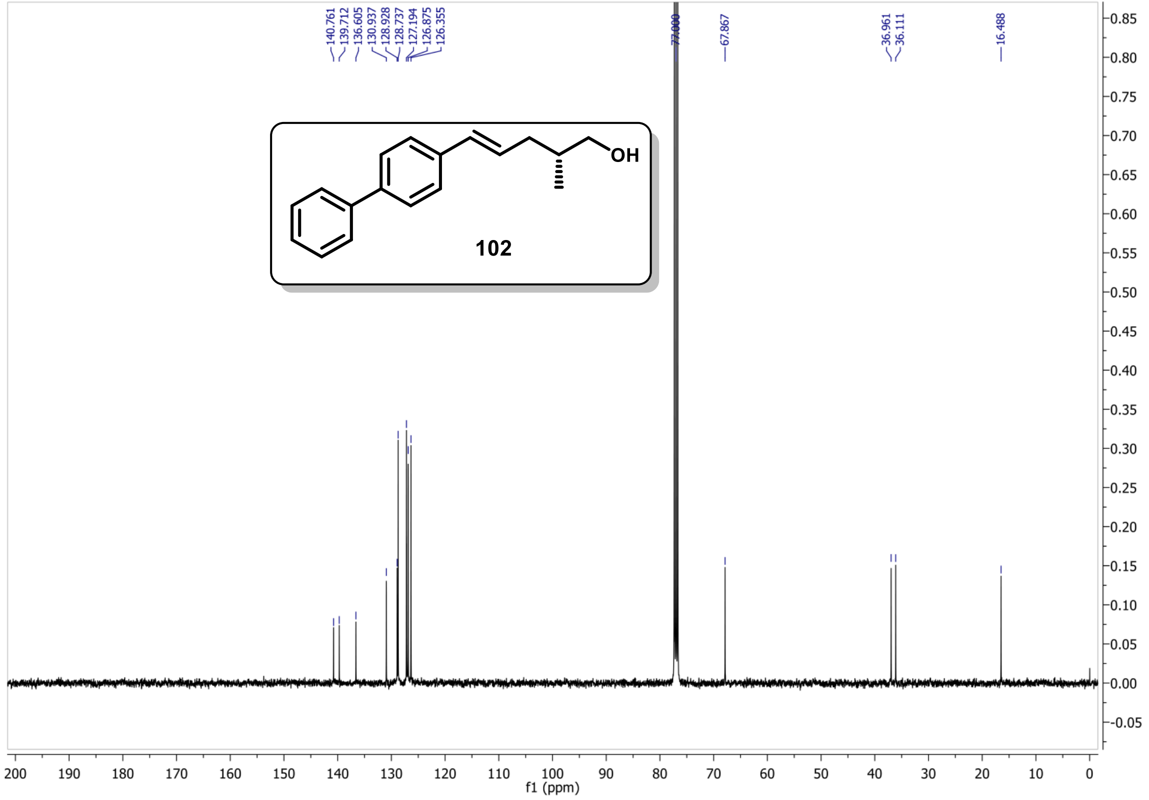

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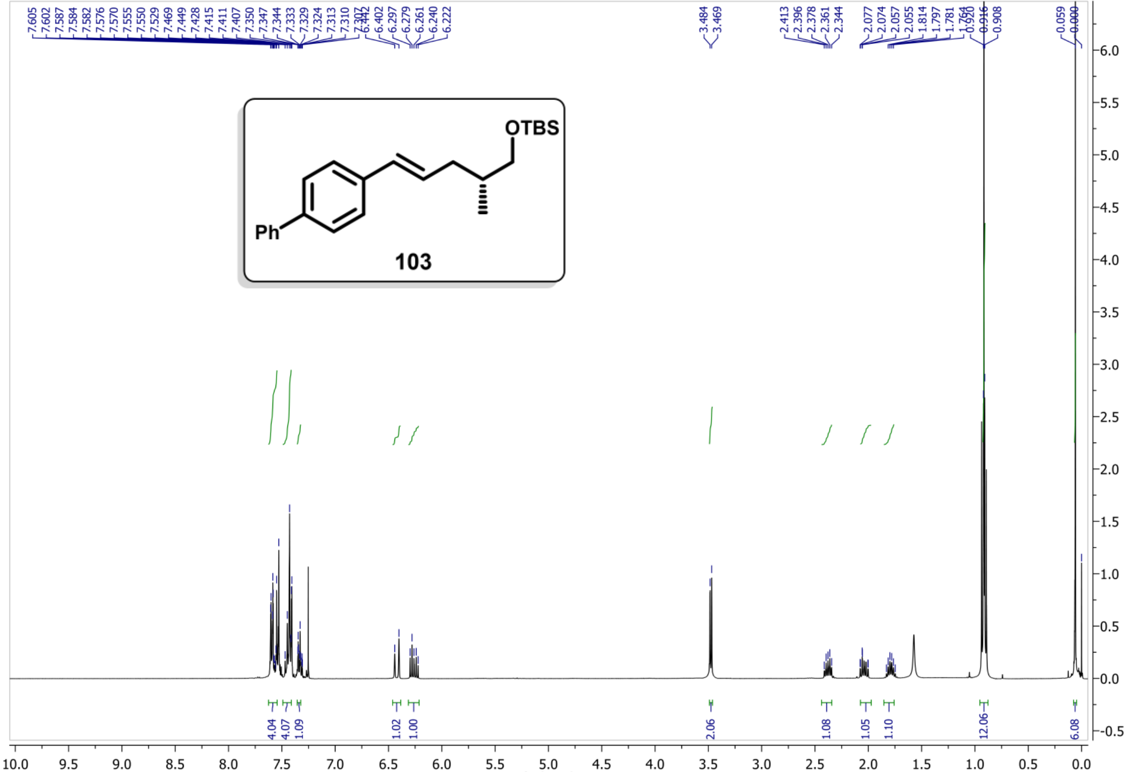

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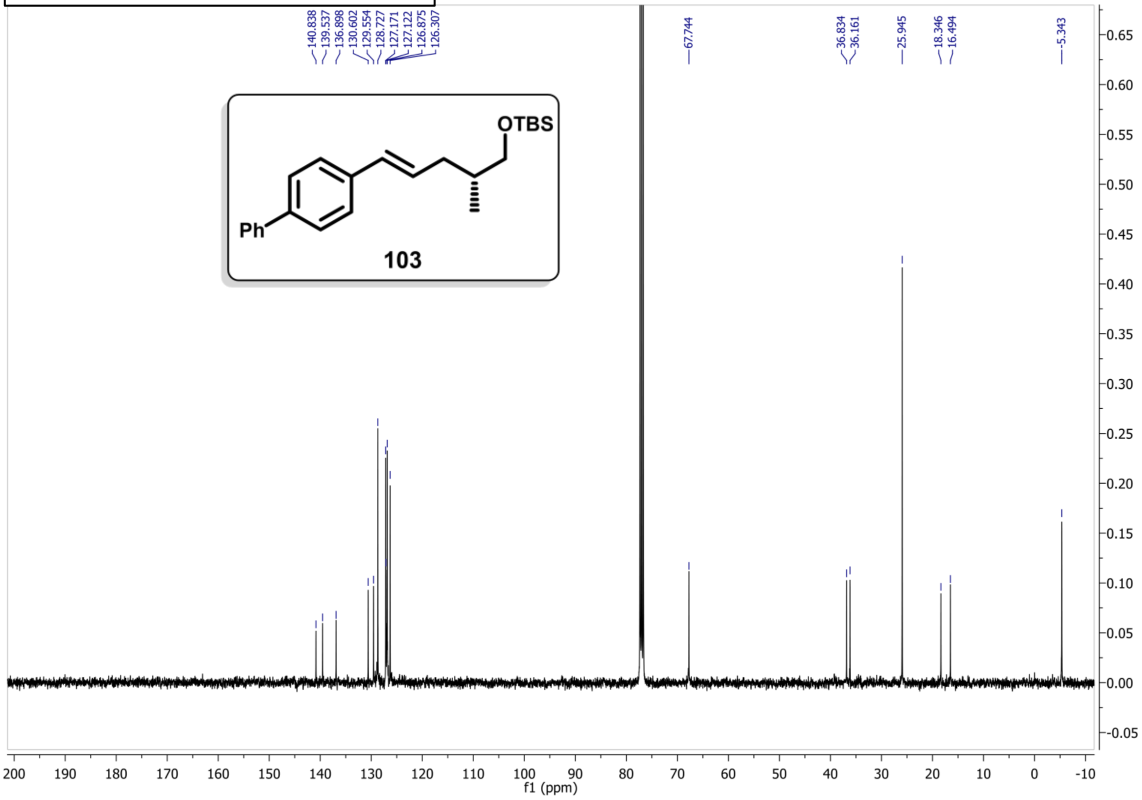

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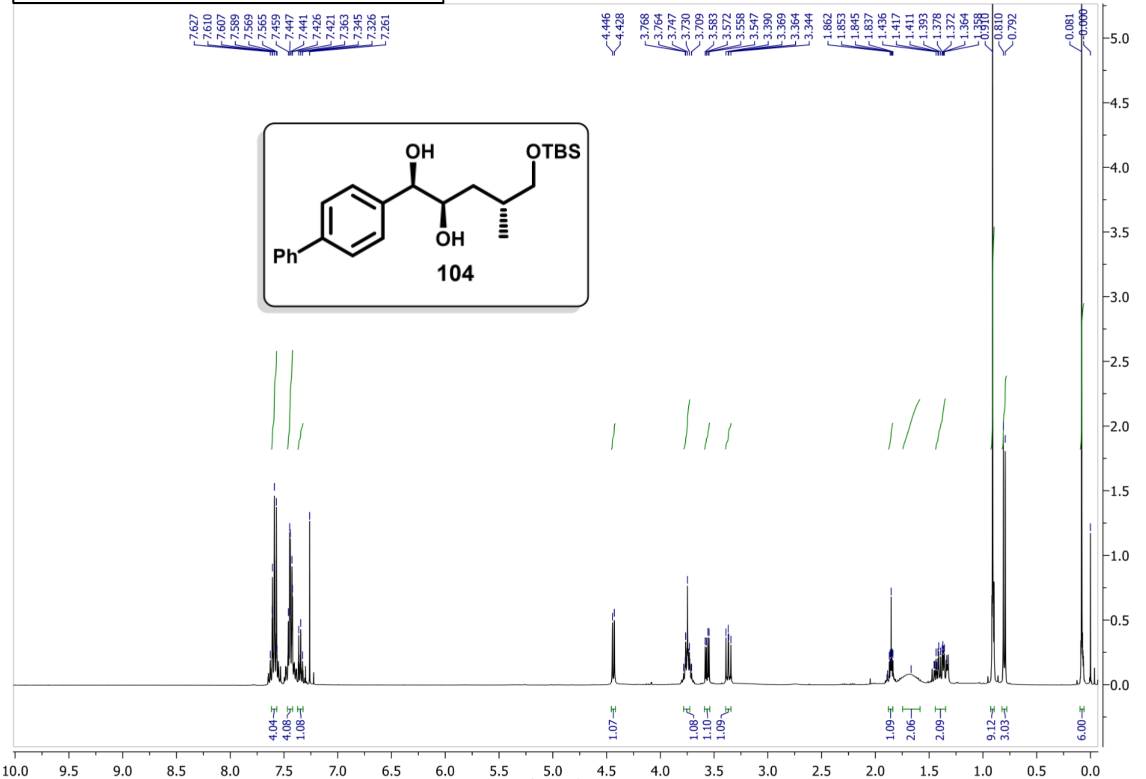

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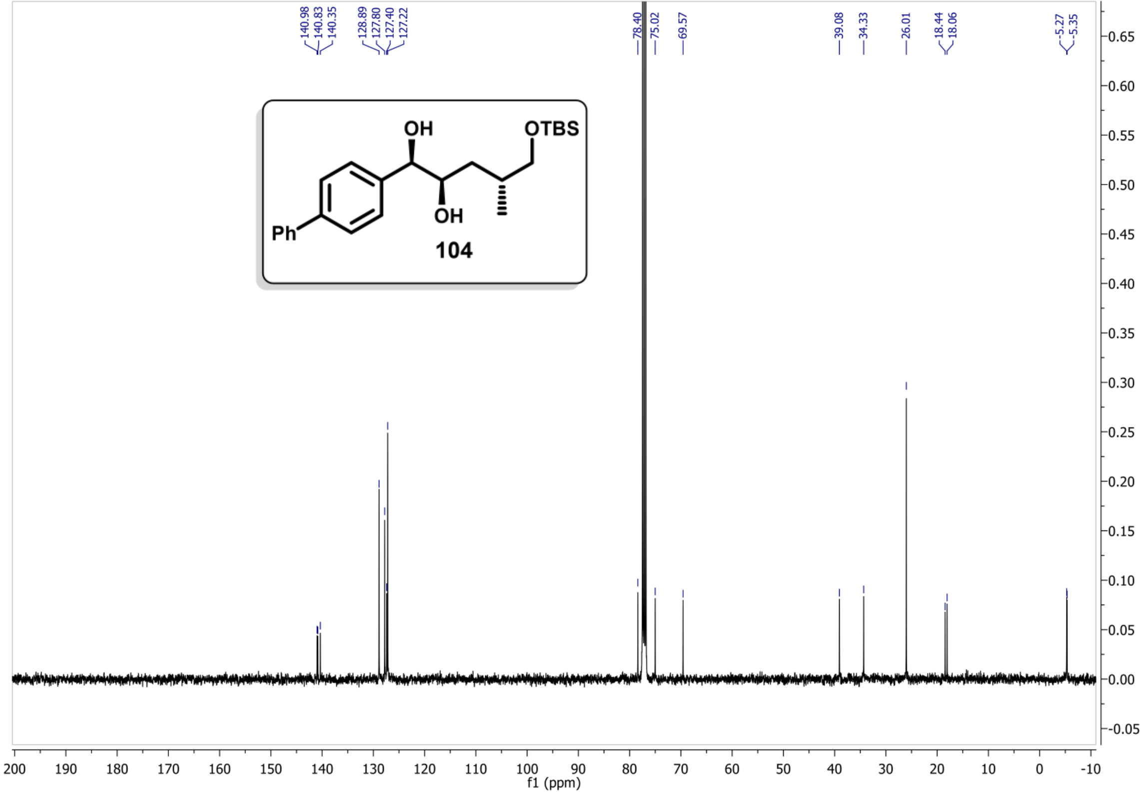
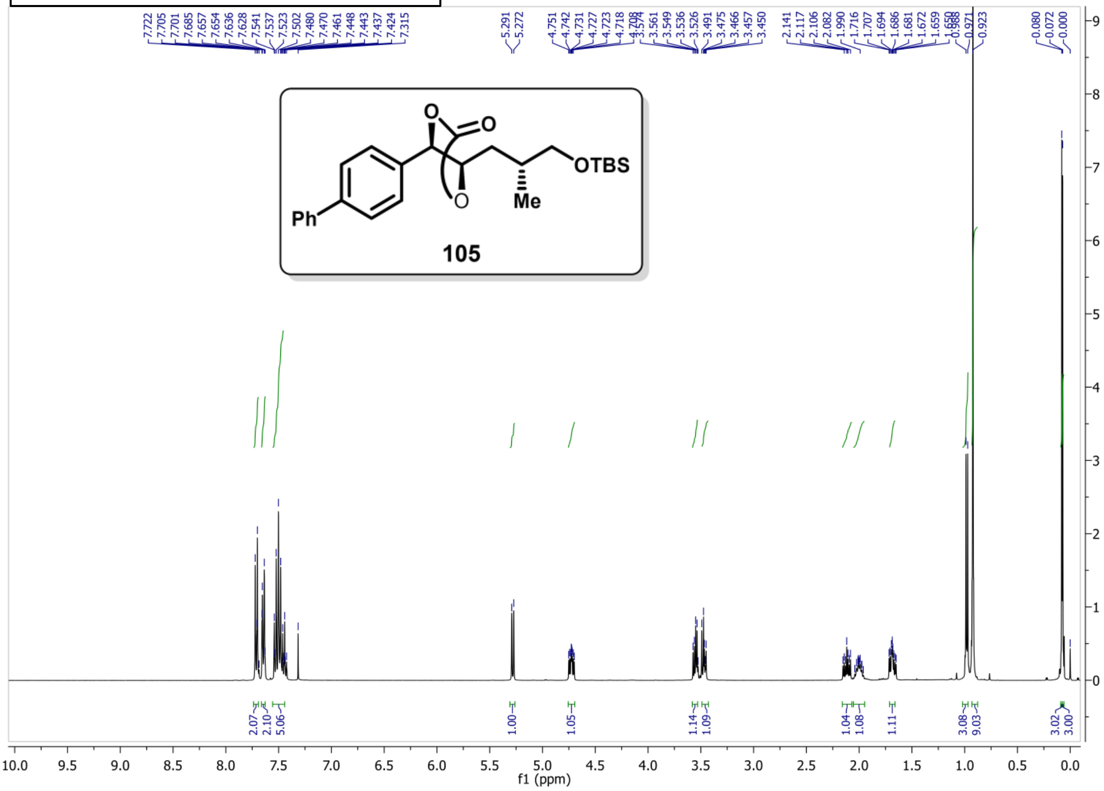
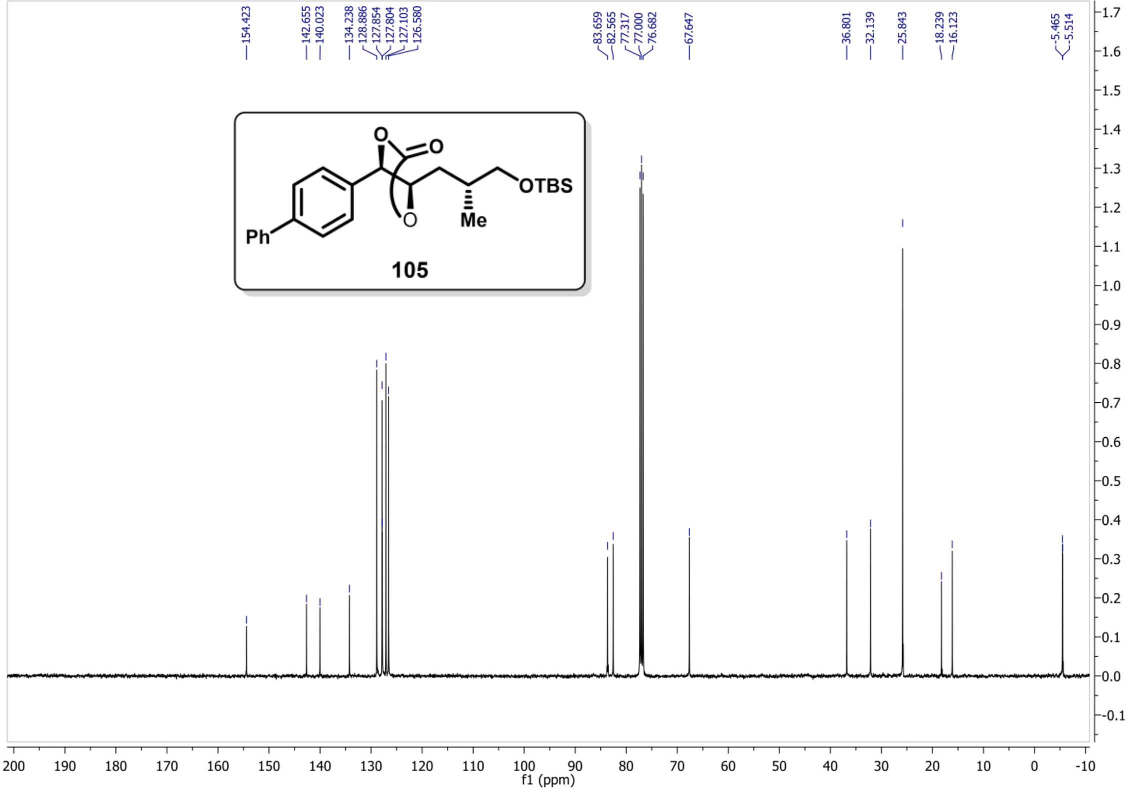


^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (400 MHz, $CDCl_3$)



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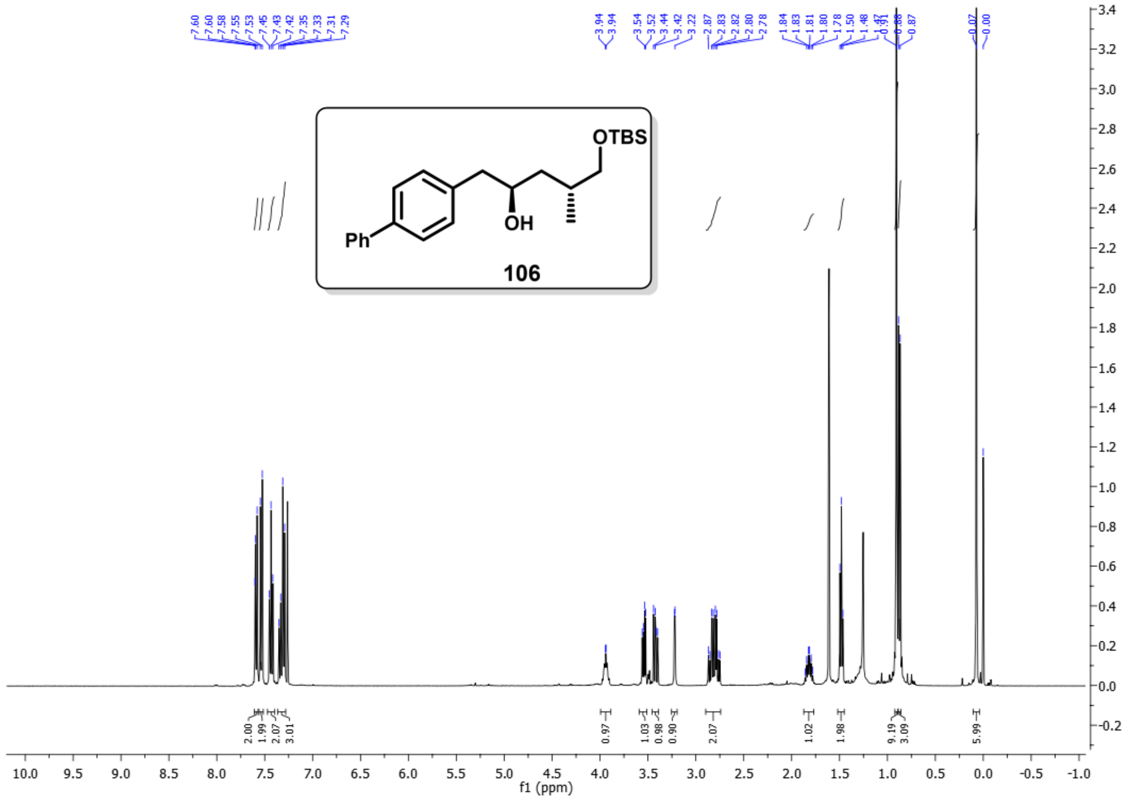
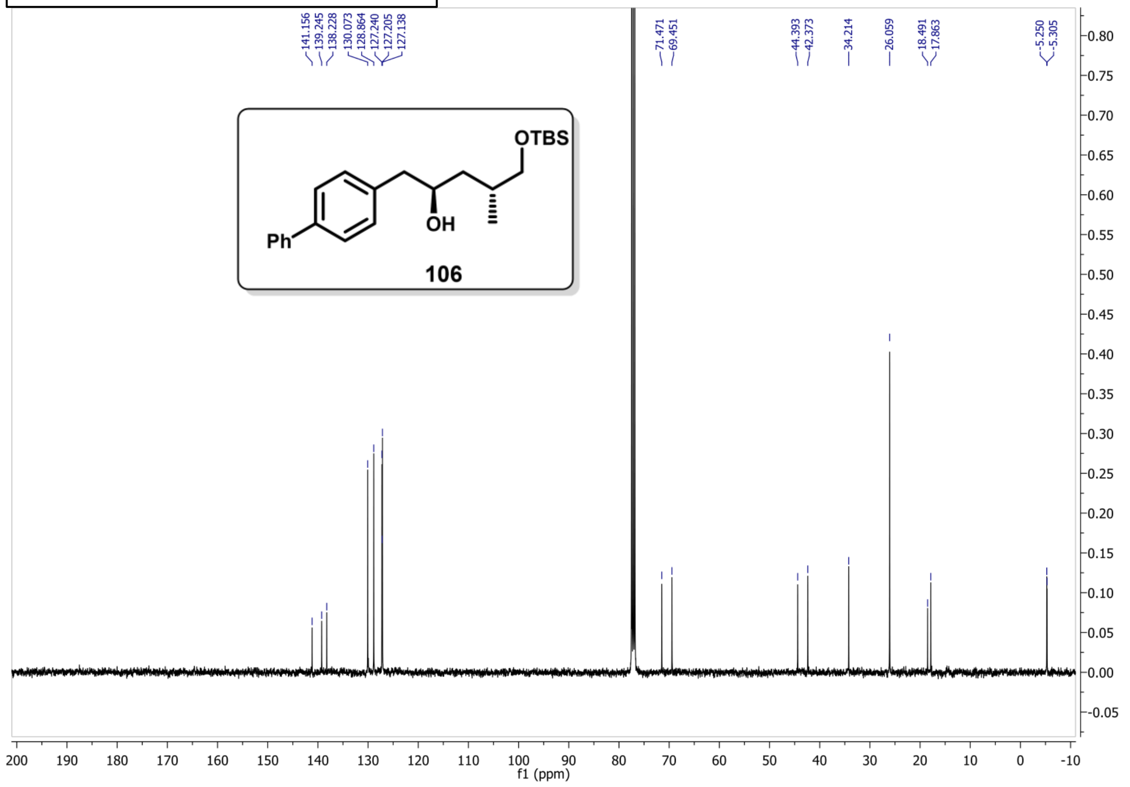


^{13}C NMR (400 MHz, CDCl$_3$)



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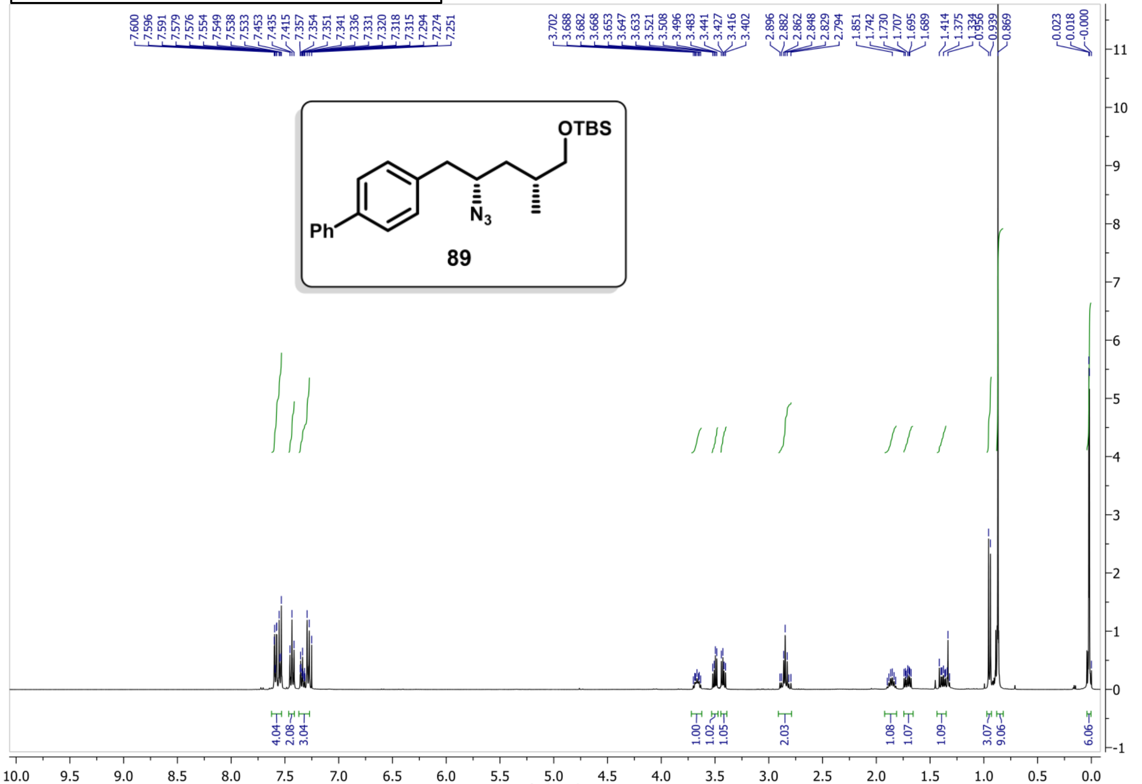
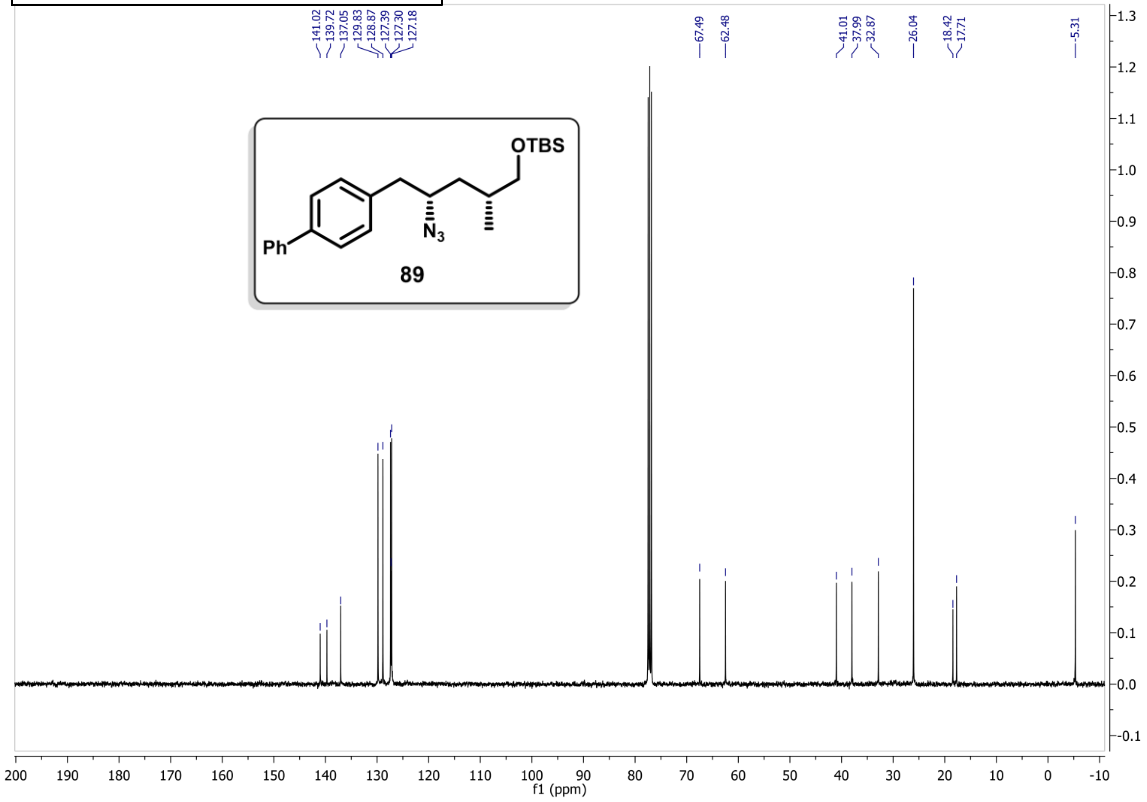
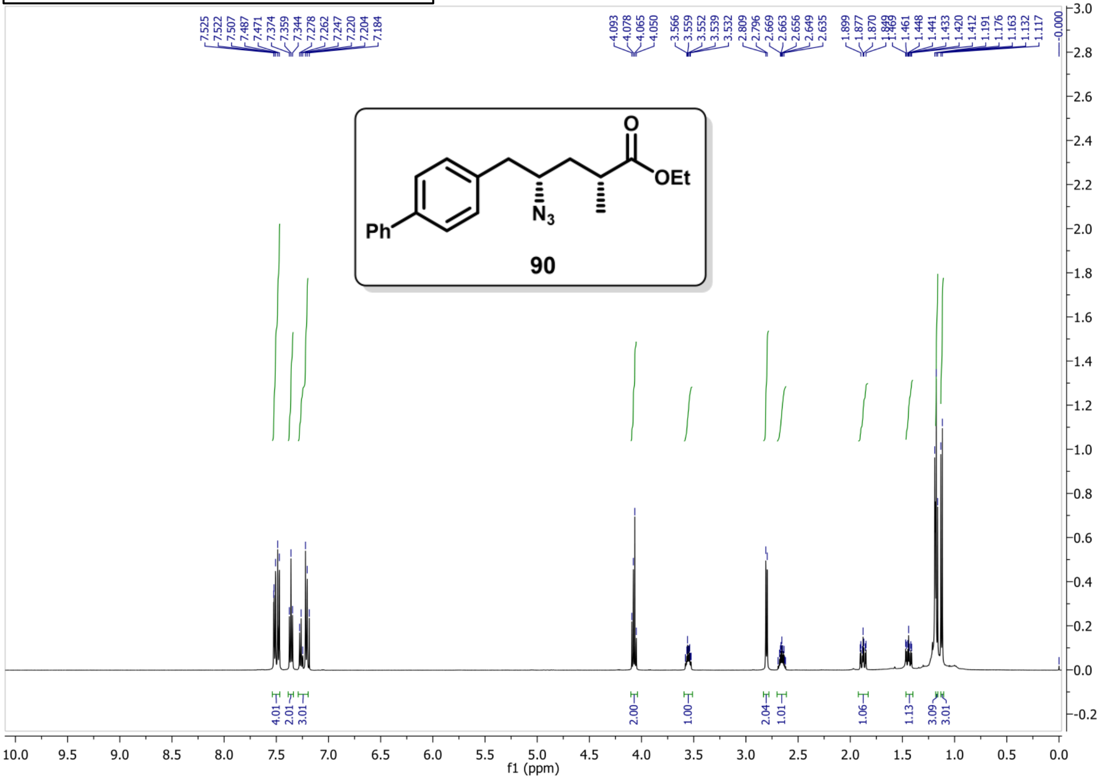


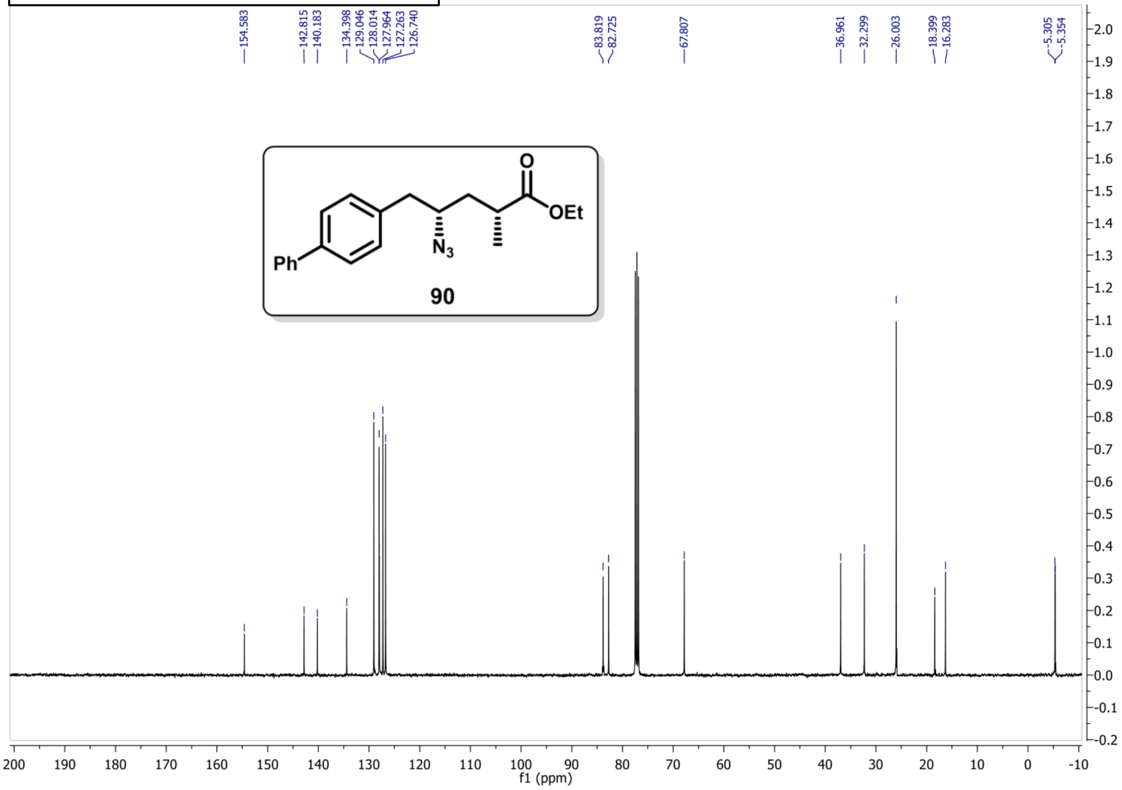
^{13}C NMR (400 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



^{13}C NMR (400 MHz, CDCl$_3$)



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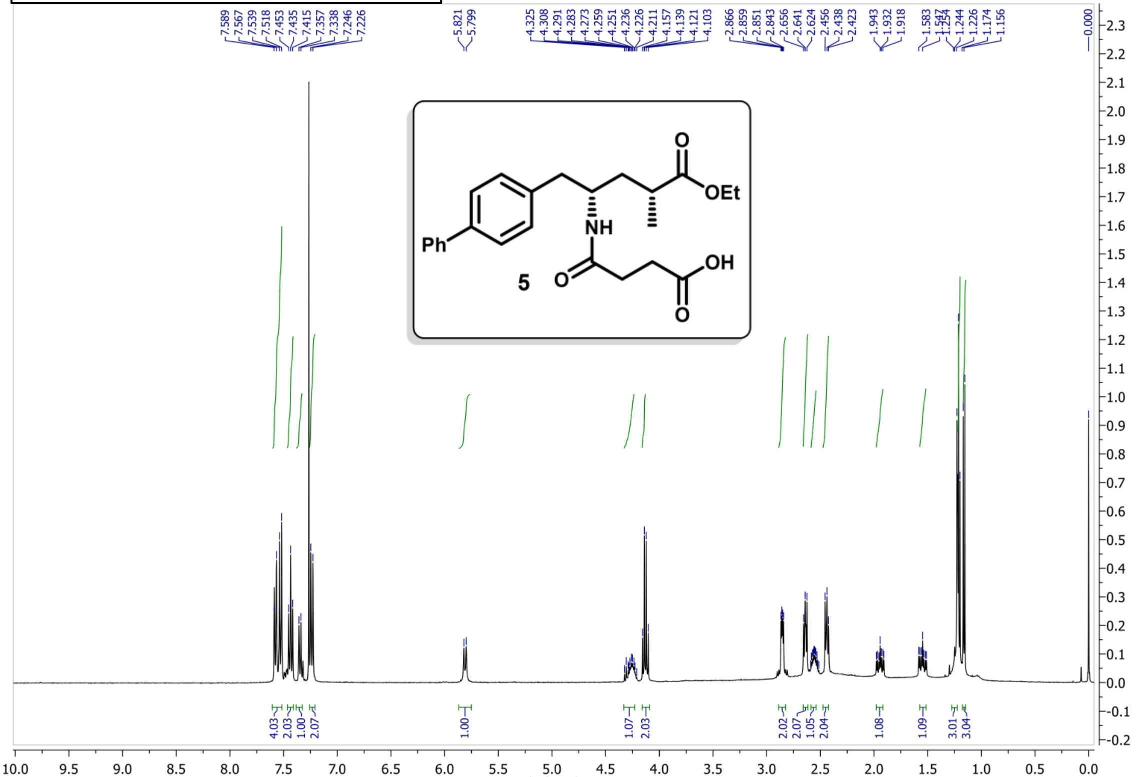
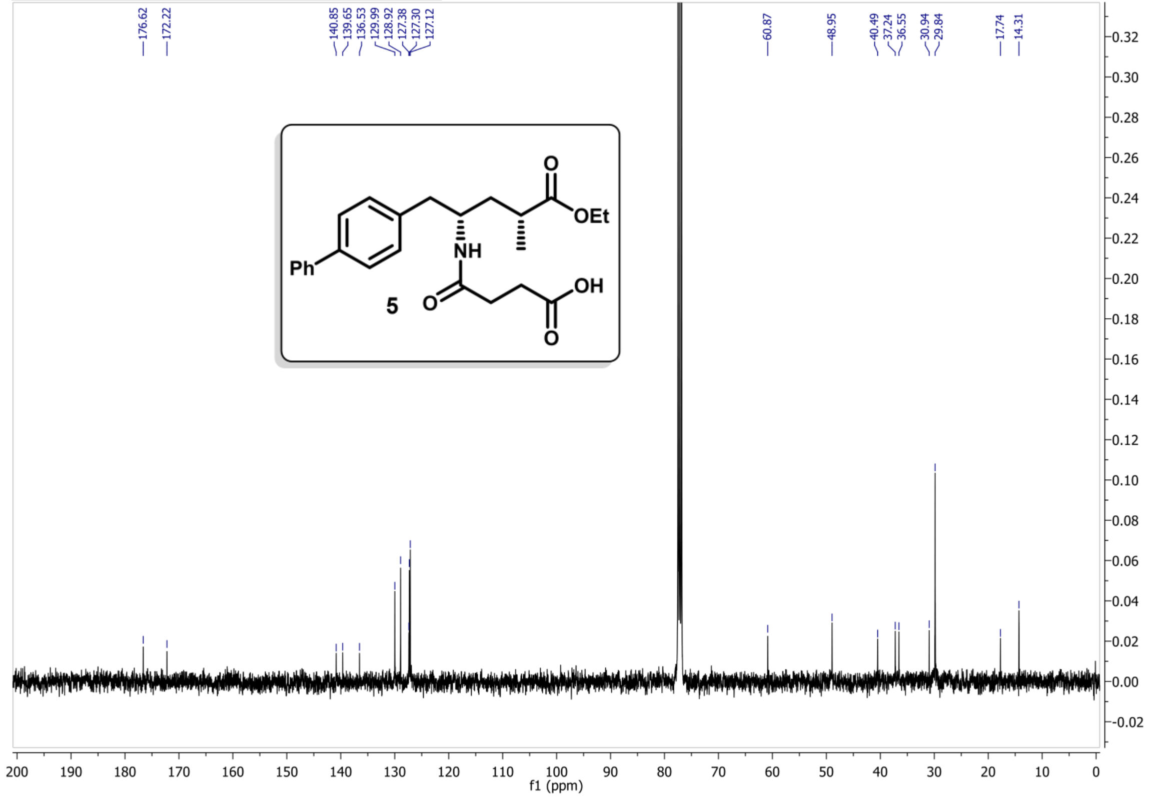


^{13}C NMR (400 MHz, CDCl$_3$)



3.9 References:

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CHAPTER 4

An enantioselective synthesis of C1-C4 and C5-C14 fragments of cytospolide- D.

An enantioselective synthesis of C1-C4 and C5-C14 fragments of cytospolide-D

4.1 Introduction:

Over the recent years, decanolides have been acknowledged as a rich source of bioactive natural products with fascinating chemical structures.[1] The novel decanolide, cytospolide A-E (**107-111**) (Figure 7) along with other thirteen natural product analogues (cytospolides F-Q and decytospolides A and B) were isolated by Zhang and co-workers from leaves of endophytic fungus shrub Ilex canariensis found prominently in the island of Gomera, Spain (Figure 8).[2] A number of cytospolides exhibited cytotoxic effects to innumerable human carcinoma cell lines. The C-2 methyl group inversion in cytospolide E **111** from 2*R* of **110** to 2*S* of **111** was found to lead to a surprise upsurge in cytotoxic activity towards the A-549 tumor cell lines.[2a] The structures of all the cytospolides were deduced through extensive exploration of the chemical, spectroscopic and single crystal X-ray analysis.[2b] Therefore, cytospolide D **110** has been a synthetic target of substantial attention due to its bioactivities and distinctive structure having wide range of functionalities.

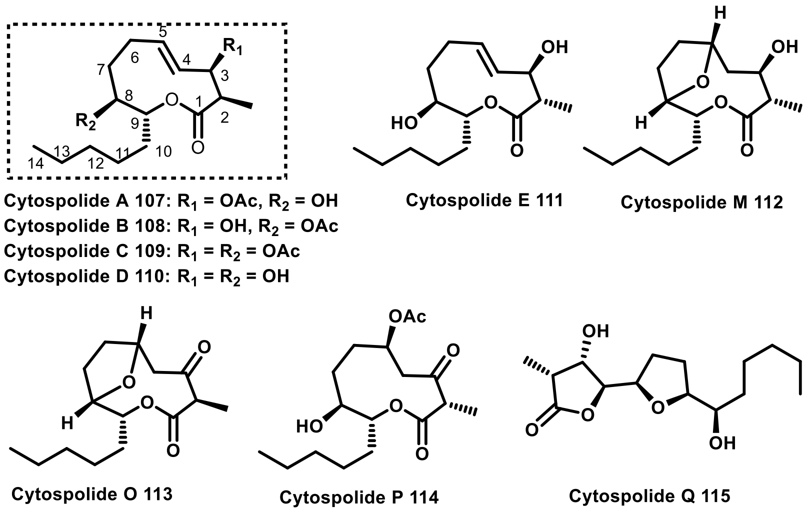


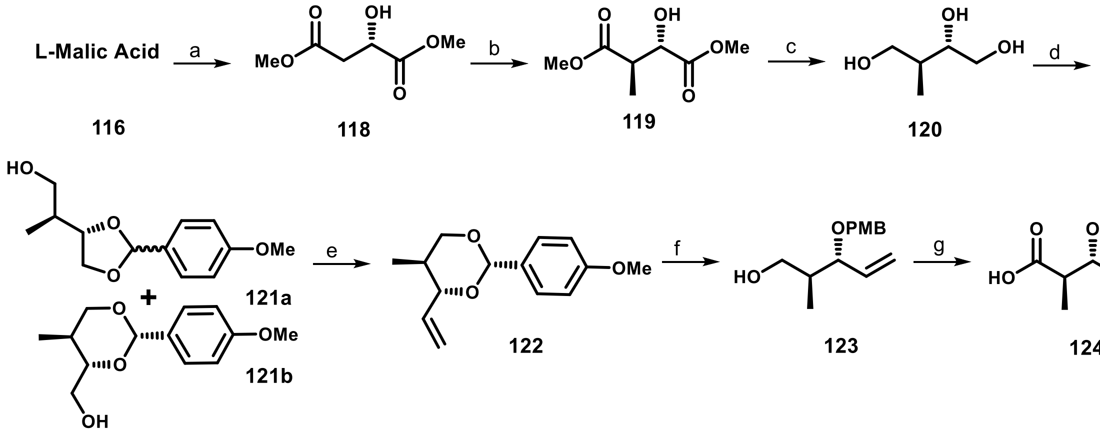
Figure 8. Structures of cytospolide D **110** and its isomers.`

4.2 Review of Literature:

Numerous elegant studies and syntheses of cytospolide D **110** have been listed in the literature.[3] Majority of syntheses reported employed cross metathesis using Grubb’s reagents, Shina esterification, *anti*-aldol addition and Yamaguchi protocol as fundamental steps.

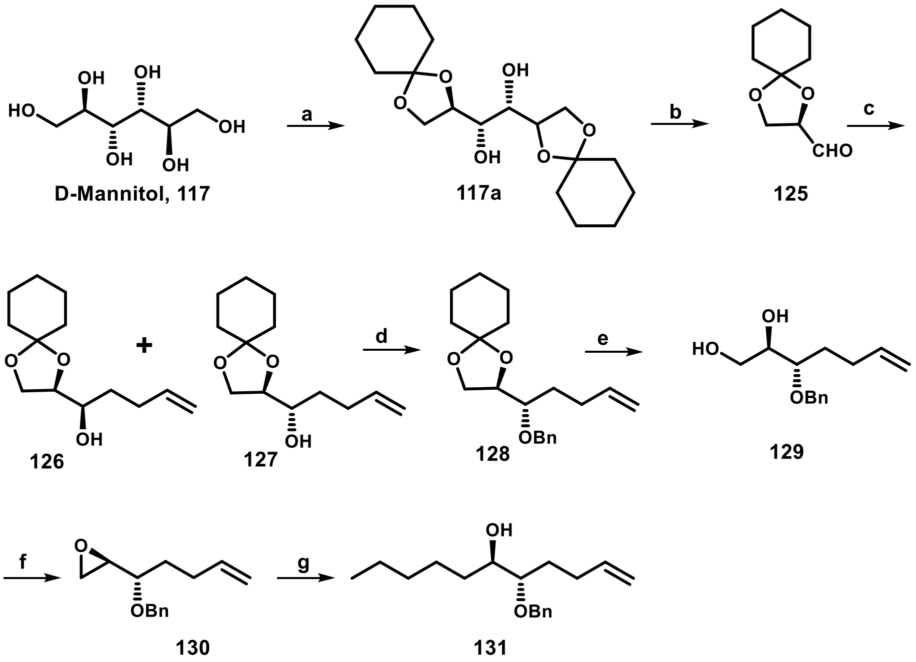
Kamal, A. *et. al.* (2014)[3a]

A. Kamal and co-workers reported the convergent enantioselective synthesis of cytospolide D **110** starting from L-malic acid **116** and D-mannitol **117** as shown in Scheme 29 & 30 respectively**.** Principal sequences performed to synthesize the acid **124** and fragment **131** included stereoselective methylation, olefin cross-metathesis, and Yamaguchi reaction. Firstly, esterification of L-malic acid **116** was accomplished using BF_3/OEt_2 for the quantitative synthesis of ester **118.** Next, the ester **118** on treatment with methyl iodide in the presence of LiHMDS afforded methylated diester **119** in diasteromeric form (*anti*/*syn* 10:1), which on further reduction with $LiAlH_4$ gave the triol **120** in 78% yield**.** Further, triol **120** on treatment with *p*-methoxybenzaldehyde dimethylacetal using CSA (camphor sulphonic acid) delivered a mixture of 1,3-protected acetal **121b** as major, and 1,2-protected acetal **121a** as minor product. Next, compound **121b** on Swern oxidation yielded the intermediate aldehyde which on Witting olefination with MeTPPBr afforded alkene **122** in 60% yield. Furthermore, region-selective ring opening of compound **122** followed by oxidation with sodium perchlorite generated the acid fragment **124** in 74% yield.



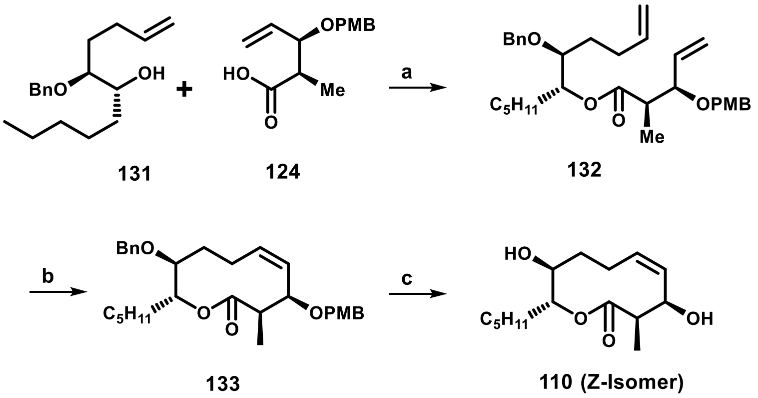
Scheme 29. *Reagents and conditions*: (a) BF_3OEt_2, MeOH, 6 h, 98%; (b) LiHMDS, MeI, THF, 78 ^{o}C, 6 h, 71%; (c) LAH, THF, 55 ^{o}C, 12 h, 78%; (d) $PMB(OMe)_2$, CSA, DCM, 0 ^{o}C, 2 h, 82%; (e) (i) oxalylchloride, DMSO, Et_3N, DCM, 78 ^{o}C, 1 h; (ii) MeTPPBr, *t*-BuOK, THF, 78 ^{o}C, 6 h, 60% over two steps; (f) DIBAL-H, CH_2Cl_2, 78 ^{o}C to 0 ^{o}C, 1 h, 87%; (g) (i) DMP, CH_2Cl_2, 0 ^{o}C, 1 h; (ii) $NaClO_2$, NaH_2PO_4, DMSO, H_2O, 0 ^{o}C to rt, 10 h, 74% over two steps.

The synthesis of second fragment **131** commenced from the D-mannitol **117** (Scheme 30), where the vicinal terminal diols of **117** were protected using cyclohexanone to afford the diacetal **117a** in excellent yield. Next, the compound **117a**, on first stage was converted into its aldehyde **125** using periodate cleavage and then its subsequent treatment of aldehyde**125** with Grignard reagent afforded the alcohol derivative **126** & **127** {*syn* (18%): *anti* (66%)}. *Anti*-alcohol **127**, on treatment with benzyl bromide using NaH, was transformed into its benzyl ether **128**. Further, TFA catalyzed removal of the cyclohexylidene group in **128** provided the 1,2 diol **129** in 80% yield. Selective primary *o*-tosylation of primary alcohol of compound **129** with *p*-toluenesulfonyl chloride (TsCl) utilizing dibutyl tin oxide followed by exposure with potassium carbonate afforded the *o*-Benzyl protected epoxide derivative **130** good yield. Next, epoxide **130** on CuI catalysed ring opening with *n*-butylmagnesiumbromide furnished the second crucial fragment **131** in 81% yield.



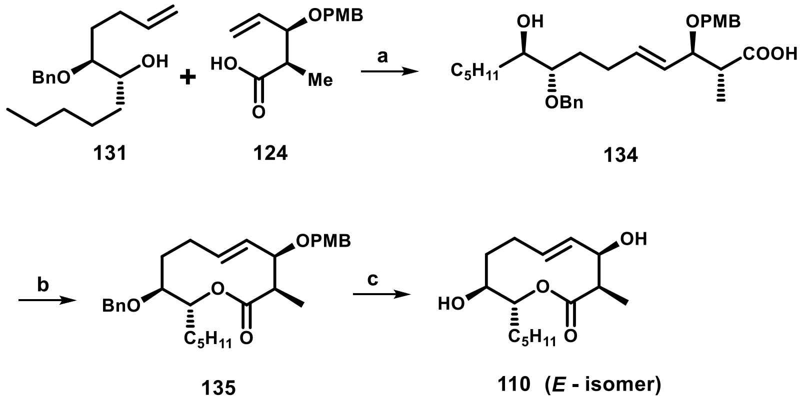
Scheme 30. *Reagents and conditions*: (a) cyclohexanone, 5h, 0 ^{o}C, 88%; (b) NaIO$_4$, acetonitrile (60%), 2h, 0 ^{o}C, 95%; (c) Mg, homoallyl bromide, THF, 0 ^{o}C to rt, 2 h, 66%; (d) NaH, BnBr, THF, 0 ^{o}C, 4 h, 87%; (e) TFA (THF/H$_2$O 9:1) 0 ^{o}C, 6 h, 80%; (f) i) TsCl, Bu$_2$SnO, Et$_3$N, CH$_2$Cl$_2$, 0 ^{o}C, 5 h; ii) K$_2$CO$_3$, MeOH, 0 ^{o}C, 1 h, 79% (over two steps); (g) C$_5$H$_{11}$MgBr, CuI (cat), THF, 35 ^{o}C, 3 h, 81%.

Further, compound **131** was combined with acid **124** in presence of DCC and DMAP to furnish the diene **132** which turned out as substrate for the chief cyclization step (Scheme 31). Finally, RCM of derivative **132** was carried out using Grubbs catalyst (First & Second generation, Hoveyda Grubbs) to afford the macrolactone **133** having *cis*-geometry. Finally concomitant deprotection of benzyl and PMB ether of **133** using $TiCl_4$ yielded the *Z*-Cytospolide **110** in 84% yield.



Scheme 31. *Reagents and conditions*: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 3 h, 82%; (b) Grubb's metathesis, DCM; (c) $TiCl_4$, CH_2Cl_2, 0 °C, 15 min, 84%.

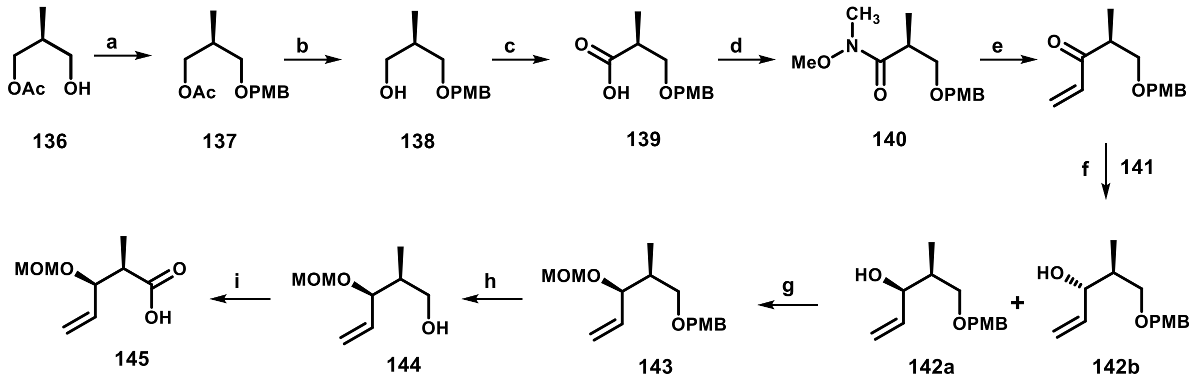
Alternatively, compound **131** and acid **124** were exposed to olefin cross metathesis using Grubb's catalyst (II^{nd} generation) to afford the alkene **134** with *trans*-geometry in 70% yield (Scheme 32). Next, olefin **134** underwent macrolactonization under Yamaguchi conditions to furnish the lactone **135** which subsequently on treatment with $TiCl_4$ yielded the final product **110** with *E*- geometry.



Scheme 32. *Reagents and conditions*: (a) Grubb's-II, dry CH_2Cl_2, reflux, 12 h, 70%; (b) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 1 h; ii) DMAP, toluene,12 h, 90 °C, 40%; (c) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 15 min, 82%.

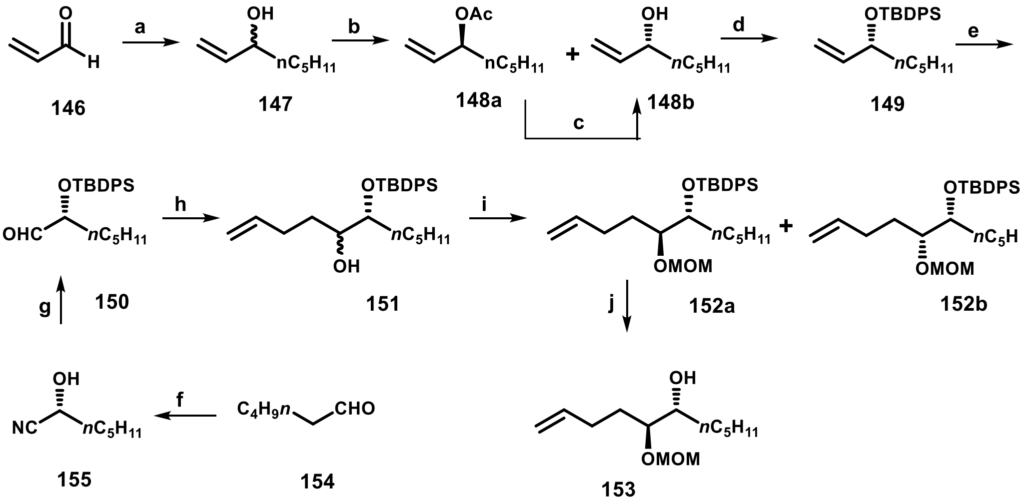
Nanda, S. *et al.* (2014)[3b]

S. Nanda and R. K. Rej repoted the enantioselective synthesis of *Z*-isomer of cytospolide D **110** involving chemo enzymatic processes as the pivotal steps, used for the construction of chiral acid **145 (**Scheme 33**)** and alcohol **153** (Scheme 34). Herein, formation of acid fragment **145** began from the mono protected chiral alcohol **136**, which on treatment with PMB imidate afforded the compound **137** in 82% yield. Next, deacetylation of **137** using K_2CO_3 in methanol furnished the alcohol **138**, which subsequently on Anelli oxidation in the presence of BAIB and TEMPO furnished the acid derivative **139** 88% yield. Further, compound **139** on coupling with *N,O* dimethylhydroxylamine utilizing EDC and trietylamine afforded the required Weinreb amide **140** in quantitative yield. Addition of vinyl magnesium bromide on compound **140** led to formation of conjugate ketone derivative **141** which was reduced using *S*-CBS catalyst and furnished diasteromeric alcohol derivative **142a** (2*R*, 3*S*) & **142b** (2*R*, 3*R*) respectively. Then, the free OH group of **142a** was protected as MOM ether **143** and compound **143** on DDQ facilitated OPMB deprotection yielded the alcohol derivative **144** which further on TEMPO/BAIB mediated oxidation furnished the first acid fragment **145** in quantitative yield.



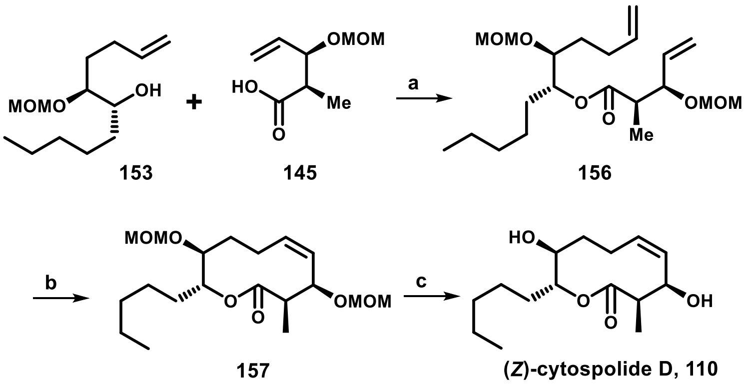
Scheme 33. *Reagents and conditions*: (a) (C=NH)CCl_3, PMBO, CSA, CH_2Cl_2/cyclohexane (2:1), rt., 82%; (b) K_2CO_3, methanol, rt, 1 h, 90%; (c) BAIB, TEMPO, CH_2Cl_2/H_2O (1:1), 88%; (d) MeNH- (OMe)·HCl, Et_3N, EDCI·HCl, rt., 6 h, 90%; (e) CH_2=CHMgBr, THF, -78 °C, 80%; (f) (*S*)-CBS (10 mol-%), BH_3/THF, THF, -78 °C to rt. 6 h, 72%; (g) MOM-Cl, DIPEA, CH_2Cl_2, reflux, 4 h, 82%; (h) DDQ, CH_2Cl_2/H_2O (19:1), 80%; (i) BAIB, TEMPO, CH_2Cl_2/H_2O (1:1), 86%.

As displayed in Scheme 34, for the synthesis of the alcohol fragment **153,** acrolein **146** was reacted with *n*-pentylmagnesium bromide to yield racemic alcohol derivative **147** in 85% yield. The compound **147** underwent enzymatic kinetic resolution (EKR) with CAL-B and acetate to produce a mixture of *S*-acetate **148a** and *R*-alcohol **148b** in 96% & 95% yield respectively. Further, compound **148a** was also converted into alcohol **148b** *via* Mitsunobu inversion. The protection of free OH of compound **148b** was carried out using TBDPSCl to yield alkene **149** which on Lemieux-Johnson oxidative cleavage furnished the aldehyde **150** in quantitative yield. The aldehyde **150** was also synthesized from *n*-hexanal **154** using hydroxynitrile lyase followed by hydrocynation through the cyanoalcohol derivative **155**. Next, compound **150** on treatment with 1-butene magnesium bromide furnished diasteromeric alcohol derivative **151** in 80% yield. The free OH of compound **151** was protected as its MOM ether and resultant crude was separated into olefin derivative **152a** and **152b** via column chromatography. Further, TBAF mediated desilylation of compound **152a** afforded the second required alcohol fragment **153** with desired stereochemistry and in reasonable yield.



Scheme 34. *Reagents and conditions*: (a) $nC_5H_{11}MgBr$, Et_2O, 0 °C, 2.5 h, 85%; (b) i) CAL-B, vinyl acetate, Et_2O, MS 4 Å, 1 h; (c) i) K_2CO_3, Methanol, room temp, 2 h; ii) Triphenyl phosphine, DIAD, CH_3CO_2H, rt. 8 h; iii) K_2CO_3, CH_3OH, room temp., 1 h, 90% in two steps; (d) $C_3N_2H_4$, TBDPSCl, room temp., 6 h, 88%; (e) OsO_4, NMO, THF/Water (3:1), $NaIO_4$, rt, 2 h, 80%; (f) ParsHNL, HCN, DIPE, 25 °C, citrate buffer (pH 4.0), 4 h, 82%; (g) i) Imidazole, TBDPSCl, Dichloromethane, 12 h, 88 %; ii) DIBAL-H, -45 °C, 1 h, 90%; (h) $CH_2=CH(CH_2)_2MgI$, Et_2O, -78 °C, 80%; (i) MOMCl, DIPEA, NaI (cat.), CH_2Cl_2, reflux, 12 h, 84%; (j) TBAF, THF, 4 h, 90%.

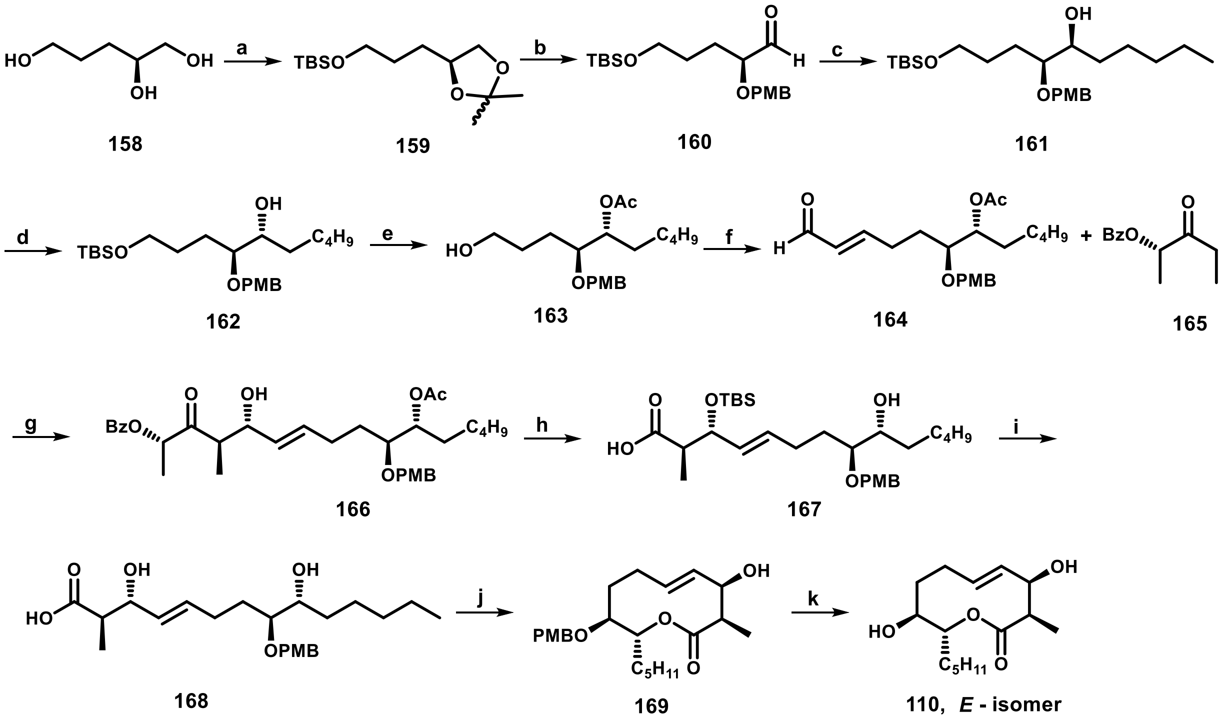
Further, compound **153** was co-joined with acid **145** via Yamaguchi coupling to afford the diene **156** which on metathesis reaction in the presence of Grubbs II catalyst afforded the lactone **157** as showed in Scheme 35. The compound **157** on global deprotection using HCl yielded the *Z*-isomer of cytospolide D **110.**



Scheme 35. *Reagents and conditions*:(a) DCC, DMAP, CH_2Cl_2, 0 ^oC to rt, 3 h, 82%; (b) Grubb's metathesis, DCM; (c) $TiCl_4$, CH_2Cl_2, 0^oC, 15 min, 84%.

Ehrlich G. (2016)[3c]

Gunnar Ehrlich* and Christian B. W. Stark reported the total synthesis of *E*-isomer of Cytospolide D **110** employing *anti* aldol addition, Shina esterification as important steps, indicated in Scheme 36. Here, the triol **158** was converted into 1,2 *p*-methoxybenzylidine acetal **159** on treatment with $PMPCH(OMe)_2$ in the presence of *p*-TSA as catalyst and the remaining primary alcohol functionality group was masked as its TBS ether.



Scheme 36. *Reagents and conditions*: (a) $PMPCH(OMe)_2$, *p*-TsOH, THF, rt, 16 h, 49%; ii) TBSCL, imidazole, CH_2Cl_2, rt, 30 min, 93%; (b) DIBAL-H, toluene, 0^oC, 24 h, 75%; ii) Dess-Martin Periodinane, CH_2Cl_2, 0 ^oC, 2 h, 76%; (c) $C_5H_{11}MgBr$, Et_2O, 0 ^oC, 24 h; (d) i)

Dess-Martin Periodinane, CH_2Cl_2, rt, 2 h, 85%; ii) $Zn(BH_4)_2$, Et_2O, -50 ^oC, 1 h; (e) Ac_2O, DIPEA, DMAP, CH_2Cl_2, rt, 24 h, 89%; ii) TBAF, THF, rt, 4 h, 89%; (f) i) Dess Martin periodinane, CH_2Cl_2, rt, 30 min, 93%; ii) $Ph_3P=CCHO$, $CDCl_3$, 50 ^oC, 3 d, 82%; (g) Cy_2BCl, Me_2NEt, Et_2O, -78 ^oC to 0 ^oC 4 h; ii) **166**, -78 ^oC, 1h, then -20 ^oC, 16 h, 80%; (h) i) TBSCl, imidazole, CH_2Cl_2, rt, 16 h, 89%; ii) $NaBH_4$, MeOH, rt, 30 min, then Na, rt, 16 h, 93%; iii) $NaIO_4$on silica, CH_2Cl_2, rt, 3 h; iv) $NaClO_4$, 2-Me-2-butene, ^{t}BuOH, Saturated NaH_2PO_4, rt, 30 min, 96%; (i) TBAF, THF, rt, 3h; (j) 2-methyl-6-nitrobenzoic anhydride, DMAP, toluene, rt, 44 h, 21%; (k) DDQ, CH_2Cl_2/H_2O (6:1), rt, 4 h, 86%.

The acetal **159** on regioselective opening using DIBAL and resultant intermediate on treatment with DMP produced the aldehyde **160** in 76% yield. This aldehyde derivative **160** on Grignard reagent opening with *n*-pentylmagnesium bromide furnished the 4,5 *syn*-diol **161** exclusively in quantitative yield.

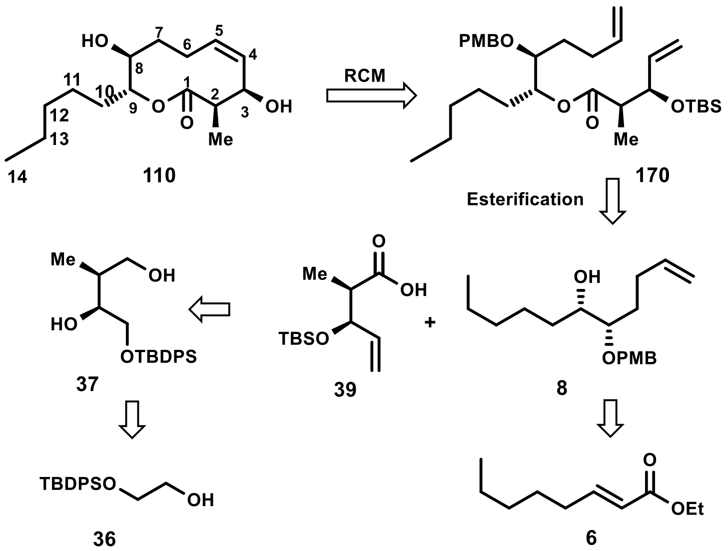
Further, the *syn*-diol **161** was exposed to a sequence of oxidation-reduction reaction where compound **161** firstly underwent DMP oxidation followed by Zn-borohydride mediated reduction to furnish the *anti*-alcohol **162** with high diastero-selectivity (94:6). Next, the free hydroxy group of compound **162** was protected as acetate, which on TBS ether cleavage using TBAF afforded the alcohol derivative **163.** The compound **163** on oxidation followed by Wittig olifination using triphenylphosphoranylidene-acetaldehyde furnished the conjugated aldehyde **164** in 82 % yield. The compound **164** on Peterson *anti*-aldol addition with **165** in the presence of Cy_2BCl and Me_2NEt furnished the derivative **166** in excellent yield. Furhter, aldol adduct **166** was exposed to a set of sequence of reaction that involved TBS protection, removal of chiral auxiliary and saponification followed by glycol cleavage to furnished the seco acid derivative **167**. The seco-acid **167** on removal of TBS ether as protecting group afforded the dihydroxy acid **168** in 90% yield which further underwent Shina cyclization using 2-methyl-6-nitrobenzoic anhydride to produce the macrolactone **169** in moderate yield**.** Finally, the PMB protecting group of compound **169** was removed using DDQ to yield cytospolide D **110** as its *E* isomer in a good yield.

4.3 Present Work:

As part of our research programme directed towards the asymmetric synthesis of biologically active compounds, we became interested in synthesizing crucial fragments of Cytospolide D **110** employing Sharpless AD, D-proline catalyzed MacMillan’s crossed aldol reaction, Wittig olefination, Mitsunabo inversion and one carbon homologation as major transformations.

4.4 Results and Discussion:

Our retrosynthetic analysis for the syntheses of important fragments **8** and **39** of cytospolide D **110** is displayed in Scheme 37. We envisaged that the cytospolide D **110** in its *E*-form could be synthesized from the key precursor *bis*-olefin derivative **170** *via* Grubbs RCM reaction followed by deprotection of protecting groups. The *bis*-olefin derivative **170** could be accessed from the olefinic alcohol fragment **8** (C5-C14) and acid fragments **39** (C1-C4) by intermolecular Mitsunobu esterification. The alcohol derivative **8** in turn could be synthesized from easily accessible *trans*-olefinic ester **6** *via* Sharpless AD followed by standard organic transformation. The olefinic acid fragment **39** could be assembled from alcohol derivative **37** by employing PMB protection of primary alcohol, silyl ether cleavage, regioselective primary hydroxyl *o*-tosylation, base treatment to get terminal epoxide, one carbon homologation, TBS protection and PMB deprotection followed by oxidation. The 1,3-diol derivative **37** in turn could be achieved from the aldehyde intermediate of monosilylated ethylene glycol derivative **36** *via* asymmetric MacMillan's crossed aldol reaction followed by *in situ* aldehyde reduction.

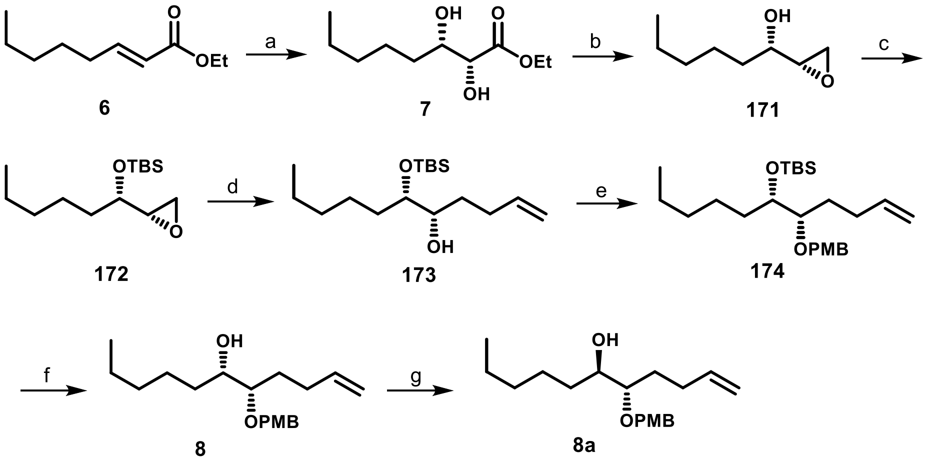


Scheme 37. Retrosynthesis of cytospolide D.

Synthesis of the C5-C14 Fragment (8a)

The synthesis of olefinic alcohol **8** is depicted in Scheme 38. The synthesis started from readily accessible *α*, *β*-unsaturated ester **6** which on reaction with osmium tetroxide and $K_3Fe(CN)_6$ as co-oxidant with $(DHQ)_2PHAL$ employing Sharpless asymmetric conditions[4] furnished the diol **7** in 92% yield with >97% ee {$[\alpha]^{25}$ -14.37 (*c* 1.00, EtOH), Lit[5a] -14.0 (*c* 1.00, EtOH)}. The IR spectrum of **7** showed OH stretching at 3470 cm^{-1}. The diol derivative **7** on LiAlH$_4$ reduction afforded triol intermediate, which on regioselective primary alcohol *o*-tosylation by TsCl and Et$_3$N employing Bu$_2$SnO[6] catalytically followed by base exposure afforded the epoxy alcohol derivative **171** as the sole product in 80% yield.

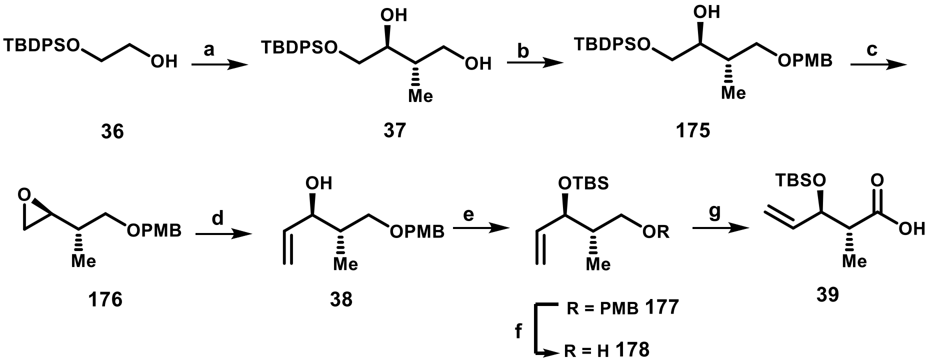
The free secondary hydroxyl group of **171** was subjected to imidazole-promoted protection with TBSCl which furnished the TBS protected epoxide **172** in 90% yield. The protected epoxide derivative **172** was then subjected to copper-catalyzed (CuI) regioselective ring opening with allyl magnesium bromide to give the alkenol derivative **173** in excellent yield. In the ^{1}H NMR of compound **173**, olefin protons as a multiplet were found resonating at δ 5.89-5.79 (one proton) and δ 5.04 (doublet of doublet of double, one proton) with the coupling constants J = 17.2, 3.5 and 1.7 Hz, respectively. The free hydroxyl group of alkenol derivative **173** on (PMBCl) with NaH and selective desilylation of the TBS ether with TBAF furnished the alkenol derivative **8** in excellent yield. Further, alkenol derivative **8** was subjected to Mitsunobu inversion in the presence of *p*-nitrobenzoic acid, Ph$_3$P, and DIAD followed by K$_2$CO$_3$ treatment in MeOH to afford required alkenol derivative **8a** with *anti*-sterochemistry in 82% yield (Scheme 38).[11]



Scheme 38: Reagents and conditions: (a) 0.005 mol% OsO$_4$, K$_3$[Fe(CN)$_6$], 0.1 mol% (DHQ)$_2$PHAL, CH$_3$SO$_2$NH$_2$, potassium carbonate, *t*-BuOH:H$_2$O 1:1 v/v, 0 ^{o}C, 24 h, 92%; (b) i) LiAlH$_4$, dry THF, 0 ^{o}C, 2 h; ii) TsCl, Et$_3$N, Bu$_2$SnO (cat), dry CH$_2$Cl$_2$, 0 ^{o}C to rt, 30 min; iii) KOH, Et$_2$O, 0 ^{o}C to rt, 2 h, 80% (over three steps); (c) TBSCl, imidazole, DMAP, CH$_2$Cl$_2$, 0 ^{o}C to rt, 2 h, 90%; (d) C$_3$H$_5$MgBr, CuI (cat.), dry THF, 0 ^{o}C, 2.5 h, 85%; (e) PMBCl, NaH, TBAI (cat.), THF, 0 ^{o}C to rt, 3 h, 76%; (f) TBAF, THF, 0 ^{o}C to rt, 1 h, 95%; (g) (i) *p*-nitrobenzoic acid, DIAD, Ph$_3$P, toluene, 0 ^{o}C, 2.5 h; (ii) K$_2$CO$_3$, MeOH, 0 ^{o}C, 45 min, 82%.

Synthesis of the C1-C4 Fragment (39)

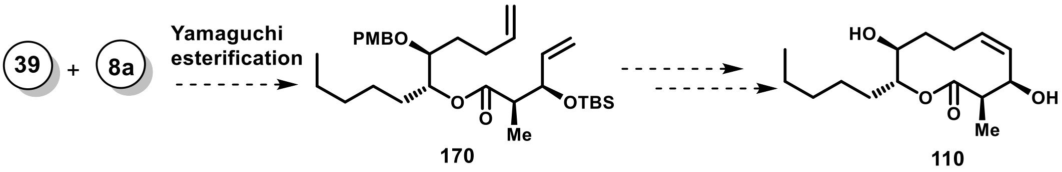
The construction of olefinic acid part **39** (C1-C4) is illustrated in Scheme 39. The 1,3-Diol **37** was synthesized from readily available monosilylated ethylene glycol derivative **36** *via* MacMillan's crossed aldol[7a] reaction with propanal catalyzed by D-proline and subsequent $NaBH_4$ reduction in 86% yield with >99% ee and *anti*:*syn* 98:2 ratio.[7b] The IR spectrum of **37** exhibited hydroxyl absorption at 3423 cm^{-1}. Next, treatment of 1,3-diol **37** with K_2CO_3 and PMBCl in acetone under reflux conditions[8] successfully furnished the regioselective primary alcohol PMB protected derivative **175** in 83% yield. In the ^1H NMR of compound **175** appearance of extra signals in the aromatic region and a triplet at δ 3.79 as singlet corresponding to three protons confirms the PMB protection of primary alcohol.



Scheme 39. *Reagents and conditions*: (a) i) Oxalyl chloride, DMSO, Et_3N, dry DCM, -78 °C to rt, 2 h; ii) Propionaldehyde, 10 mol % D-proline, 1,4 dioxane, 4 °C, 24 h; iii) $NaBH_4$, CH_3OH, 35 min, 86% (three steps); (b) PMBCl, K_2CO_3, TBAI, acetone, 70 °C, 18 h, 84%; (c) i) TBAF, THF, rt, 90 min; ii) TsCl, Bu_2SnO, Et_3N, dry DCM, 0 °C to rt, 50 min; iii) KOH, Et_2O, rt, 2 h, 89% (three steps); (d) trimethylsulphonium iodide, *n*-BuLi, dry THF, -10 to 0 °C, 3 h, 91%; (e) TBSCl, imidazole, DMAP, dry CH_2Cl_2, 0 °C to rt, 2.5 h, 95%; (f) DDQ, dry CH_2Cl_2, rt, 45 min, 93%; (g) TEMPO, (diacetoxyiodo)benzene, CH_2Cl_2: H_2O, 3:1, 28 °C, 24 h, 87%.

On moving forward, the synthesis of the epoxide derivative **176** from alcohol **175** was performed through a process including silyl deprotection and selective primary alcohol tosylation using TsCl and Et_3N and catalytic proportion of Bu_2SnO[6] followed by base exposure in 89% yield (over three steps). The epoxide derivative **176** on one-carbon homologation with dimethylsulfonium methylide in the presence of *n*-BuLi furnished the allyl alcohol derivative **38** in 91% yield.[9] In the ^1H NMR of compound **38,** the additional set of protons resonating at *δ* 5.83 as double of doublet with coupling constant (*J*) of 17.1, 10.4, 6.6 Hz, at *δ* 5.25 as doublet of triplets (one proton) with coupling constant of 17.2 & 1.6 Hz and at *δ* 5.16-5.13 as a multiplet (one proton) confirms the formation of terminal double bond. The IR spectrum of **38** displayed hydroxyl vibration at 3450 cm^{-1}. With allyl alcohol derivative **38** in hand, we then subjected it to imidazole-promoted protection with TBSCl and selective deprotection of the PMB ether with DDQ to afford the primary alcohol derivative **178** in excellent yield. Finally, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and bis(acetoxy)iodobenzene (BAIB) facilitated oxidation of the primary alcohol **178** furnished the acid **39** in 87% yield. The IR spectrum of **39** showed C=O stretching at 1719 cm^{-1}.

Next, the fragments alkenol derivative **8** and acid fragment **39** could be used for the coupling reactions to accomplish the synthesis of key precursor *bis*-olefin derivative **170** which could be used for the chiral synthesis of cytospolide D **110** as shown in Scheme 40. Ester derivative **170** could be prepared by coupling of alcohol fragment **8** and acid fragment **39** under Mitsunobu conditions. Alternatively, to access the key precursor *bis*-olefin **170**, the Yamaguchi esterification[10] could be attempted. The Yamaguchi esterification of acid fragment **39** and alkenol derivative **8a** could also lead to the required *bis*-olefin derivative **170**. The *bis*-olefin derivative **170** could then be converted into the target compound cytospolide D **110** *via* the Grubbs RCM and deprotection of both protecting group following the standard organic transformations. Here, we have reported the synthesis of two fragments of cytospolide D. However, the final coupling steps were not performed as the similar coupling steps were already reported in the literature.



Scheme 40: Proposed pathway for cytospolide -D

4.5 Conclusion:

We have anticipated a new and effective enantioselective approach for the construction of the two vital motifs (C1-C4 and C5-C14) of cytospolide D employing MacMillan's crossed aldol, Sharpless AD and Mitsunobu inversion reactions as key steps. The suggested synthetic protocol described has substantial potential for stereo chemical variations in all the positions and further extension to other stereoisomers and analogues. Currently, the efforts are in progress and the results will be disclosed in due course.

4.6 Experimental Section:

All experiments were performed under Nitrogen, with moisture free, freshly extracted solvents through distillation unless otherwise indicated. All the reagents or chemicals were put in reaction either *via* syringe or cannula. Each distillation was also performed under unreactive conditions. Every reaction was performed at required temperatures as narrated in their corresponding schemes. Evaporations of solvents was achieved under reduced pressure using Heidolph rotary evaporator keeping temperature below 40 °C.

Chromatography

Every reaction performed was examined through Thin Layer Chromatography executed using commercially available silica gel plates 60 F_{254} using UV light, then were stained in ninhydrin or in ethanolic solution of anisaldehyde or in aqueous $KMnO_4$ as development reagents follow up by concise heating using a heating gun. Silica gel (60-120 and 100-200 mesh) was employed for column chromatography and different compositions of ethyl acetate/hexane and methanol/ dichloromethane were used as organic eluent.

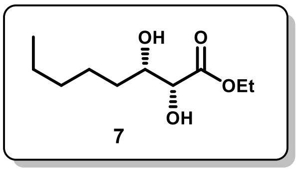
Reagents and solvents

Commercially obtained Organic solvents utilized as such unless stated in experimental conditions. Distilled H_2O was consumed for each aqueous reaction and work-up procedures. For reaction, solvent like DCM was purified using Calcium hydride, and THF was distilled under nitrogen using sodium benzophenone ketyl, straightaway prior to use.

Spectroscopic Measurements

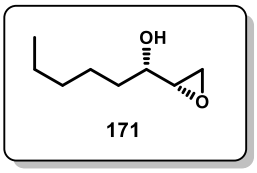
JEOL ECS spectrometer was employed for recording the ^{1}H NMR and ^{13}C NMR respectively. Tetramethylsilane (TMS) utilized as reference. Chemical shifts have been expressed in ppm units (δ) downfield from TMS. *J* values are listed in hertz (Hz). Electron spray ionization (ESI) were used for recording HRMS and mass values are expressed as m/z. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}. Yields mentioned referred to isolated combined amount after chromatography.

(2*R*,3*S*)-Ethyl 2,3-dihydroxyoctanoate, 7


7

To a solution of *tert*-butyl alcohol and water (1:1, 160 mL) at room temperature, $K_3Fe(CN)_6$ (23.26 g, 70.58 mmol), K_2CO_3 (9.79 g, 70.58 mmol) and ligand $(DHQ)_2PHAL$ (183 mg, 0.23 mmol or 0.1 mol %) were added sequentially. The resulting suspension was chilled to 0 °C and immediate addition of OsO_4 (1.16 mL, 0.1 M solution in toluene, 0.005 mol%) and $CH_3SO_2NH_2$ (2.23 g, 23.52 mmol) was performed. After stirring for 2 min at 0 °C, the substrate **6** (4.0 g, 23.52 mmol) was added in single lot and resulting suspension was further agitated at 0 °C overnight. The reaction was stopped by adding sodium sulfite (8.0 g) and stirring was sustained for extra 45 minutes. After completion, solution was extracted with EtOAc (3 x 30 mL), dried over Na_2SO_3 and concentrated in *vacuo*. Silica gel column chromatography (C_6H_{14}/EtOAc 3:1 v/v) of the residue liberated the diol **7** (4.4 g, 92%) as a white solid. [R_f = 0.4, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ -12.2 (c 0.10, $CHCl_3$); IR (CH_2Cl_2) ν: 3470, 2875, 1736, 1482, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.36-4.27 (m, 2H), 4.09 (d, J = 2.0 Hz, 1H), 3.89 (td, J = 7.4, 1.7, 1H), 3.09 (brs, 1H), 1.66-1.54 (m, 5H), 1.53-1.31 (m, 8H), 0.90 (t, J = 7.0, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9, 73.1, 72.7, 62.3, 34.0, 31.8, 25.6, 22.7, 14.3, 14.2; HRMS (ESI), calcd for $C_{10}H_{20}O_4Na$ $[M+Na]^+$ 227.1254; found 227.1262.

(*S*)-1-((*S*)-Oxiran-2-yl)hexan-1-ol, 171

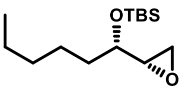

171

Solution of $LiAlH_4$ (1.56 g, 41.12 mmol) prepared in anhydrous THF (20 mL) was maintained at 0 °C. To it, dropwise addition of suspension of **7** (4.2 g, 20.56 mmol) in dry THF (40 mL) was performed. Resulting mixture was agitated at 0 °C for 2 h. Afterwards, 10% *aq*. NaOH (20 mL) solution was dispensed slowly to quench the reaction. The mixture was washed with EtOH (2 x 30 mL), the collected organic phase was dried using Na_2SO_4 and concentrated in *vacuo* to get triol intermediate which is used as such for the next phase.

Above triol was dissolved in dry DCM (40 mL), and to it addition of Et_3N (2.9 mL, 20.56 mmol), TsCl (3.91 g, 20.56 mmol), and Bu_2SnO (1.02 g, 4.11 mmol) was done sequentially. The subsequent solution was agitated for 30 min and stopped using water (20 mL). The organic content of aqueous portion was taken out using DCM (3 x 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum*. Monotosylated derivative formed was collected and used in next phase.

To a solution of monotosylated derivative formed in the above reaction in ether (40 mL) at 0 ^{o}C was added KOH (3.46 g, 61.68 mmol). The derived turbid suspension was agitated for 2 hours at room temperature and after which the reaction was ended with H_2O (20 mL). The compound in aqueous layer was taken out with ether (3 x 20 mL), organic layers were combined and solvent was evaporated at low pressure. Purification by silica gel chromatography (hexane/EtOAc 3:1 v/v) afforded the epoxide **171** as a liquid (2.36 g, 80%). [R_f = 0.5, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ +6.70 (c 1.5, $CHCl_3$); IR (CH_2Cl_2) ν: 3446, 2931, 2878, 1108, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49- 3.39 (m, 1H), 2.99 (ddd, *J* = 4.9, 4.2, 2.8, 1H), 2.83 (t, *J* = 4.8 Hz, 1H), 2.72 (dd, *J* = 4.9, 2.8, 1H), 1.93 (brs, 1H), 1.71-1.59 (m, 2H), 1.53-1.25 (m, 6H), 0.90 (t, *J* = 6.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 71.8, 55.5, 45.3, 34.5, 31.9, 25.1, 22.6, 14.1; HRMS (ESI), calcd for $C_8H_{16}O_2Na$ $[M+Na]^+$ 167.1042; found 167.1039.

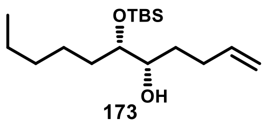
***tert*-Butyldimethyl((*S*)-1-((*S*)-oxiran-2-yl)hexyloxy)silane, 172**



172

To an ice-cold solution of **171** (2.0 g, 13.8 mmol) in CH_2Cl_2 (25 mL) under nitrogen at 0 ^{o}C, $C_3N_2H_4$ (1.42 g, 20.70 mmol), TBSCl (2.71 g, 18.02 mmol) and DMAP (337 mg, 2.76 mmol) were added consecutively and content was agitated for 2 hours before quenching with saturated NH_4Cl (20 mL). The water layer was extracted with CH_2Cl_2, washed using brine and dried with Na_2SO_4, concentrated in vacuo and purified on silica gel (hexane/EtOAc 19:1 v/v) to deliver TBS protected epoxide **172** (3.2 g, 90%) as oil. [R_f = 0.7, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ + 6.60 (c 1.5, $CHCl_3$); IR (CH_2Cl_2) ν: 3449, 2935, 2861, 1070, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.25 (dd, *J* = 12.4, 6.8, 1H), 2.91 (ddd, *J* = 6.8, 4.1, 2.8, 1H), 2.77 (t, *J* = 5.12 Hz, 1H), 2.55 (dd, *J* = 5.0, 2.7, 1H), 1.61-1.45 (m, 2H), 1.42-1.20 (m, 6H), 0.90 (s, 9H), 0.87 (t, *J* = 7.0, 3H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 74.8, 56.2, 45.1, 34.8, 32.0, 26.0, 25.1, 22.7, 18.3, 14.2, -4.2, -4.9; HRMS (ESI), calcd for $C_{14}H_{30}O_2Si$ $[M+H]^+$ 259.2088; found 259.2091.

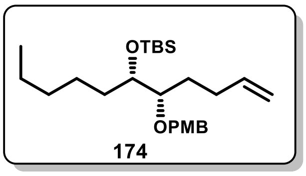
(5*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)undec-1-en-5-ol, 173



173

TBS protected epoxide **172** (3.0 g, 11.60 mmol) was dissolved in dry THF (30 mL) at 0 ^{o}C. Further, addition of CuI (110 mg, 0.58 mmol) was done. Then, gentle drop wise addition of 17.4 mL of 1.0 M solution of allylMgBr in diethylether to the prepared solution was carried out. After addition was complete, the mixture was agitated for 2.5 hours and after completion ended by pouring a saturated solution of NH_4Cl (30 mL). Stirring was again done for extra 20 minutes at 0 ^oC to separate the phases. After extraction performed with ethyl acetate (3 x 30 mL), combined organic extracts were dried over Na_2SO_4, organic layer was concentrated under vacuum. Purification of the crude using silica gel column chromatography (hexane/EtOAc 9:1 v/v) yielded secondary alcohol **173** (2.95 g, 85%) as pale yellow oil. [R_f = 0.6, EtOAc/hexane, 1:9 v/v]; $[\alpha]_D^{25}$ = 3.67 (c 0.5, CH_2Cl_2); IR (CH_2Cl_2) ν: 3423, 2929, 2850, 1435, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.89-5.79 (m, 1H), 5.04 (ddd, J = 17.2, 3.5, 1.7, 1H), 4.96 (ddd, J = 2.9, 2.4, 1.2, 1H), 3.52-3.43 (m, 2H), 2.31-2.19 (m, 1H), 2.17-2.07 (m, 2H), 1.55-1.38 (m, 3H), 1.33-1.22 (m, 7H), 0.90 (s, 9H), 0.87 (t, J = 7.1, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.7, 114.8, 75.3, 72.1, 34.0, 33.6, 32.2, 30.4, 26.0, 24.8, 22.8, 18.3, 14.2, -4.0, -4.46; HRMS (ESI), calcd for $C_{17}H_{36}O_2SiNa$ $[M+Na]^+$ 323.2377; found 323.2386.

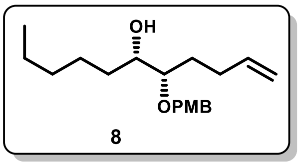
***tert*-Butyl((5*S*,6*S*)-5-(4-methoxybenzyloxy)undec-1-en-6-yloxy)dimethylsilane, 174**



174

To an agitated suspension of NaH (431 mg, 17.96 mmol) in dry THF (15 mL) was added dropwise a solution of secondary alcohol **173** (2.7 g, 8.98 mmol) taken in dry THF (20 mL) in 15 min at 0 ^oC. The reaction mixture was agitated for 1 hour at same temperature then *p*-methoxybenzyl chloride (1.46 mL, 10.77 mmol) was put into it at 0 ^oC over a period of 10 minute along with TBAI (164 mg, 0.44 mmol). The obtained solution was warmed to room temperature and stirred for another 2 hours and afterword's cold water (15 mL) was utilized to end the reaction. Aqueous layer was extracted with EtOAc (2 x 30 mL), collected organic extracts were dried over Na_2SO_4 concentrated in *vaccuo* and purified *via* silica gel column chromatography (hexane/EtOAc 97:3 v/v) to afford *p*-methoxybenzyl ether compound **174** (2.86 g, 76%) as colorless liquid. [R_f = 0.5, EtOAc/hexane 1:19 v/v]; $[\alpha]_D^{25}$ -18.0 (c 2.5, $CHCl_3$); IR (CH_2Cl_2) ν: 2956, 2857, 1653, 1429, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, J = 7.9 Hz, 2H), 6.87 (dd, J = 8.6, 0.7, 2H), 5.88-5.72 (m, 1H), 5.04-4.91 (m, 2H), 4.47 (dd, J =33.7, 11.3, 2H), 3.80 (s, 3H), 3.76-3.71 (m, 1H), 3.31-3.28 (m, 1H), 2.25-2.13 (m, 1H), 2.07-1.95 (m, 1H), 1.76-1.62 (m, 1H), 1.51-1.39 (m, 2H), 1.32-1.15 (m, 7H), 0.05 (s, 12H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 139.1, 131.2, 129.5, 114.7, 114.4, 113.9, 81.9, 81.2, 72.0, 55.4, 32.1, 31.1, 30.7, 30.5, 28.7, 28.1, 26.0, 22.8, 18.2, 14.2, -4.14, -4.43; HRMS (ESI), calcd for $C_{25}H_{44}O_3SiNa$ $[M+Na]^+$ 443.2952; found 443.2950.

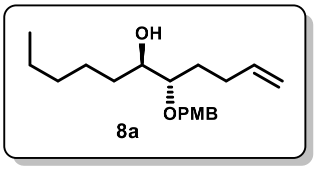
(5*S*,6*S*)-5-(4-Methoxybenzyloxy)undec-1-en-6-ol, 8



8

Compound **174** (2.5 g, 5.94 mmol) firstly dissolved in dry THF (20 mL) at 0 ^{o}C followed by the addition of TBAF (1.0 M in THF, 8.91 mL, 8.91 mmol) and obtained suspension was agitated for 1 hour at 25 ^{o}C. Saturated solution of NH_4Cl was poured to it to terminate the reaction. The aqueous phase was extracted with EtOAc (3 x 30 mL). The organic phase was dried over anhydrous $Na_2SO_4$and concentrated. Silica gel column chromatography ($n$$C_6H_{14}$/EtOAc 18:1) of the residue furnished **8** (1.72 g, 95%) as a colourless liquid. [R_f = 0.4, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ +20.2 (c 2.0, $CHCl_3$); IR (CH_2Cl_2) ν: 3460, 2922, 2850 1656, 1447, 1079 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, *J* = 8.5, 2H), 6.94 (d, *J* = 7.8, 2H), 5.88-5.77 (m, 1H), 5.05-4.94 (m, 2H), 4.58 (d, *J* = 11 Hz, 1H), 4.42 (dd, *J* = 11.0, 6.4 Hz, 1H), 3.80 (s, 3H), 3.56-3.46 (m, 1H), 3.30-3.22 (m, 1H), 2.30-2.04 (m, 3H), 1.77-1.64 (m, 1H), 1.58-1.26 (m, 9H), 0.89 (td, *J* = 6.8, 1.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 138.7, 138.6, 130.6 (d), 129.7, 114.9, 114.0, 82.1, 81.5, 72.8, 72.4, 72.2, 55.4, 33.6, 32.9, 32.3, 32.1, 30.4, 30.2, 29.8, 29.5, 25.6, 24.9, 22.8, 22.8, 14.2; HRMS (ESI), calcd for $C_{19}H_{30}O_3Na$ $[M+Na]^+$ 329.2087 found 329.2088.

(5*S*,6*R*)-5-(4-Methoxybenzyloxy)undec-1-en-6-ol, 8a



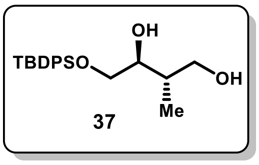
8a

To a stirred combination of alcohol **8** (1.5 g, 4.89 mmol) in toluene (25 mL) under argon, triphenylphosphine (5.13 g, 19.57 mmol) and *p*-nitrobenzoic acid (3.27 g, 19.57 mmol) were added sequentially. The mixture was cooled to 0 °C and treated with DIAD (3.95 g, 19.57 mmol) and stirred for 2.5 hours with slow warming to room temperature. Volatiles were separated under low pressure to afford the corresponding *p*-nitrobenzoate ester intermediate quantitatively, which was taken to the next step as such.

To a solution of above ester in methanol (20 mL) was put K_2CO_3 (1.01 g, 7.33 mmol) at 0 °C and agitated for 45 min with slow warming to room temperature. Water was poured to end the reaction and aqueous phase was extracted using EtOAc (2 × 30 mL), washed with brine, dried (Na_2SO_4). The volatiles were evaporated using vaccum and crude obtained on column chromatography (hexane/EtOAc 17:3 v/v) gave **8a** (2.2 g, 82%) as a colorless oil: [R_f = 0.40 (EtOAc/hexane, 1:9, v/v)]; $[\alpha]_D^{25}$ +35.5 (c 2.7, $CHCl_3$); IR (CH_2Cl_2) ν: 3463, 2928, 2860, 1658, 1475, 1066, 698 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, *J* = 8.5, 2H), 6.88 (d, *J* = 8.6, 2H), 5.90-5.75 (m, 1H), 5.08-4.93 (m, 2H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.43 (dd, *J* =

10.9, 5.3, 1H), 3.80 (s, 3H), 3.53 (ddd, *J* = 10.6, 5.3, 2.3, 1H), 3.32-3.21 (m, 1H), 2.34-2.25 (m, 1H), 2.25- 2.03 (m, 2H), 1.79-1.65 (m, 1H), 1.57-1.26 (m, 9H), 0.89 (td, *J* = 6.7, 1.7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 138.4, 138.3, 130.3, 129.3, 114.7, 114.6, 113.7, 81.8, 81.2, 72.5, 72.1, 71.9, 55.1, 33.3, 32.6, 32.0, 31.7, 30.1, 29.9, 29.5, 29.2, 25.3, 24.6, 22.5 (d), 13.91.

(2*S*, 3*S*)-4-(*tert*-Butyldiphenysilyloxy)-2-methylbutane-1,3diol, 37

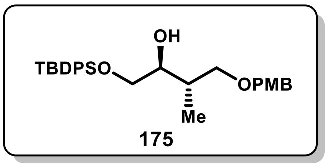


A suspension of DMSO (3.66 mL, 51.6 mmol) in CH_2Cl_2 (20 mL) was added at slower pace to a precooled (-78 °C) combination of oxalyl chloride (2.11 mL, 24.96 mmol) and dry CH_2Cl_2 (20 mL). After stirring the content at the at-78 °C for 30 min, a mixture of the monosilylated ethylene glycol **36** (5.0 g, 16.64 mmol) and DCM (40 mL) was put slowly into it and stirred for next 30 min at -78 ^{o}C. Next, Addition of Et_3N (10.18 mL, 73.21 mmol) dissolved in CH_2Cl_2 (40 mL) was done at -78 ^{o}C and whole content was agitated further for 1 hour at the room temperature. The obtained slurry was separated into layers using water and CH_2Cl_2 and the collected H_2O phase was extracted with CH_2Cl_2 (3 x 50 mL). The collective organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to give the intermediate aldehyde, which was utilized in next part.

To a prepared suspension of above aldehyde and D-proline (192 mg, 1.66 mmol) taken in dioxane (17 mL) at 4 ^{o}C was added dropwise a precooled (4 ^{o}C) solution of propionaldehyde (6 mL, 83.2 mmol) in dioxane (17 mL) over 24 hours *via* syringe pump. The content was continuously stirred overnight at the same temperature. After completion, ethyl acetate and H_2O was poured into it. Separate layers were obtained and whole organic phase was after treatment with brine and Na_2SO_4 was concentrated. The prepared aldehyde obtained was directly put into next reaction.

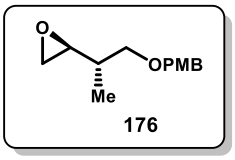
A gradual addition of $NaBH_4$ (1.26 g, 33.28 mmol) in small lots was done to a stirred suspension of above prepared aldehyde taken in dry MeOH (40 mL) at 0 ^{o}C. After stirring the mixture at room temperature for 35 min, reaction was quenched with slow addition of saturated NH_4Cl solution. The organic phase was extracted using EtOAc (3 x 40 mL), dried with anhydrous Na_2SO_4, and evaporated through vacuum. Silica column chromatography (hexane/EtOAc 4:1 v/v) of the residue afforded 1,3-diol **37** (5.1 g, 86%) as a thick colorless liquid. [R_f = 0.4, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ -1.9 (c 0.25, MeOH); IR (CH_2Cl_2) ν: 3458, 2935, 1452, 1110, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.65 (m, 4H), 7.46-7.37 (m, 6H), 3.95-3.71 (m, 1H), 3.67-3.57 (m, 4H), 3.06-3.00 (brs, 2H), 1.81-1.74 (m, 1H), 1.07 (s, 9H), 0.75 (d, *J* = 6.88 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 135.5, 132.9, 129.9, 127.8, 77.1, 67.5, 66.4, 37.1, 26.8, 19.2, 13.4; HRMS (ESI), calcd for $C_{21}H_{30}O_3SiNa$ $[M+Na]^+$ 381.1856; found 381.1857; HPLC: Chiralcel OD-H (250 x 45 mm), EtOH:PE (01:99) v/v, flow rate 1.0 ml/min, λ_{max}= 220 nm, t_R= 10.83,t_R= 12.05, t_R= 13.55 and t_R= 14.91, > 99% ee, *anti*:*syn* 98:2.7.

(2*S*,3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)-3-methylbutan-2-ol, 175



To a solution of diol **37** (5.0 g, 13.99 mmol) prepared in acetone (60 mL) were put K_2CO_3 (5.8 g, 41.82 mmol), TBAI (50 mg) and *p*-methoxy benzyl chloride (2.3 mL, 16.73 mmol) sequentially. After refluxing the content for 18 hours, the reaction was stopped and volatiles were evaporated. The crude was dissolved in water (40 mL) and extracted with EtOAc (3 x 40 mL). The whole organic layer was dried using Na_2SO_4, and once more concentrated under reduced pressure. Crude product was purified by silica gel column chromatography (hexane/EtOAc 9:1 v/v) to obtain **175** (5.5 g, 84%) as a colourless liquid. [R_f = 0.6, EtOAc/hexane 3:17 v/v]; $[\alpha]_D^{25}$ +7.26 (c 1.5, $CHCl_3$); IR (CH_2Cl_2) *ν*: 3433, 2932, 2860, 1430, 1105, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.66 (dt, *J* = 8.0, 1.2, 4H), 7.46-7.31 (m, 6H), 7.20 (d, *J* = 8.6, 2H), 6.85 (d, *J* = 8.6, 2H) 4.39 (s, 2H), 3.79 (s, 3H), 3.75-3.58 (m, 3H), 3.51-3.34 (m, 2H), 3.06 (d, *J* = 3.4 Hz, 1H), 2.06-1.86 (m, 1H), 1.05 (s, 9H), 0.91 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 159.3, 135.7, 133.4, 130.5, 129.9, 129.4, 127.9, 113.9, 75.0, 73.0, 66.3, 55.4, 35.8, 27.0, 19.4, 14.1; HRMS (ESI), calcd for $C_{29}H_{38}O_4SiNa$ $[M+Na]^+$ 501.2431; found 501.2432.

3(*S*)-2((*S*)-1-(4-Methoxybenzyloxy)propan-2-yl)oxirane, 176

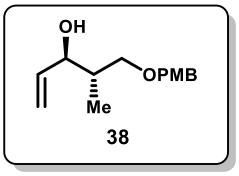


Compound **175** (5.0 g, 10.4 mmol) dissolved in 45 mL of dry THF and to it drowise gradual addition of TBAF (1.0 M in THF, 16 ml, 15.6 mmol) was executed, and resulting solution was agitated for 1.5 hours at room temperature. Saturated solution of NH_4Cl was added to terminate the reaction. Aqueous phase was extracted with EtOAc (3 x 50 mL). The collected organic phase was washed with brine, dried with anhydrous Na_2SO_4 and concentrated in *vaccuo* to get the diol. The crude residue was utilized further as such.

Above diol was dissolved in 20 mL of dry DCM and stirred at 0 ^{o}C. A sequential addition of Et_3N (1.73 mL, 12.48 mmol), TsCl (2.37 g, 12.48 mmol) and Bu_2SnO (517 mg, 2.08 mmol) was performed. The resulting solution was stirred for 50 min at room temperature and reaction was terminated with water (20 mL). The aqueous layer was extracted trice using DCM (18 mL). The whole organic phase was washed with brine, dried using anhydrous Na_2SO_4 and concentrated under vacuum. The monotosylated derivative formed was utilized as such in the next procedure.

Monotosylated derivative obtained in the above reaction was dissolved in 25 mL of ether and to it was added KOH (1.75 g, 31.2 mmol). The whole content was stirred for 2 hours at room temperature and after H_2O was poured into the turbid solution to dilute it. The organic compound was extracted with ether (3 x 20 mL), organic layer separated, washed using brine, and volatiles were removed. Purification by silica gel chromatography (hexane/EtOAc 19:1 v/v) afforded the epoxide **176** (2.05 g, 89%) as transparent liquid. [R_f = 0.7, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ +4.30 (c 1.5, $CHCl_3$); IR (CH_2Cl_2) ν: 2899, 1431, 1106, 1071, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 8.6, 2H), 6.88 (d, *J* = 8.7, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.52-3.38 (m, 2H), 2.90-2.84 (m, 1H), 2.77-2.72 (m, 1H), 2.54 (dd, *J* = 5.2, 2.8 Hz, 1H), 1.72-1.66 (m, 1H), 0.99 (d, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 130.7, 129.3, 113.9, 72.9, 72.5, 55.4, 54.4, 45.9, 36.7, 13.3; HRMS (ESI), calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$ 245.1148; found 245.1157.

(3*R*,4*S*)-5-(4-Methoxybenzyloxy)-4-methylpent-1-en-3-ol, 38

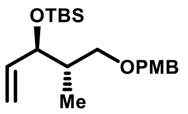


38

To a -10 ^{o}C suspension of trimethylsulphonium iodide (7.33 g, 35.96 mmol) in THF (70 mL) was added gradually *n*-BuLi (2.5 M hexane solution, 13 mL, 33.26 mmol). After 25 min, ice-cold solution of epoxide **176** (2.0 g, 8.99 mmol) prepared using THF (20 mL) was added dropwise and the reaction stirring sustained at 0 ^{o}C for 1 hour and extended for 1.5 hours at normal temperature. The reaction was quenched using water and content was extracted with ethyl acetate. The whole extract was washed with brine, dried using sodium sulfate, filtered, and concentrated under vacuum. Residues were purified on silica gel coloumn chromatography (hexane/EtOH 1:4 v/v) to give the desired allylic alcohol (2.0 g, 91%) **38** as colourles liquid. [R_f = 0.4, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ 18.3 (c 0.125, MeOH); IR (CH_2Cl_2) ν: 3450, 2930, 2858, 1612, 1246, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (dt, *J* = 0.8, 6.4 Hz, 2H), 6.88 (dt, *J* = 6.8, 2.8 Hz, 2H), 5.83 (ddd, *J* = 17.1, 10.4, 6.6, 1H), 5.25

(dt, *J* = 17.2, 1.6, 1H), 5.16-5.13 (m, 1H), 4.45 (s, 2H), 3.99 (td, *J* = 7.2, 3.2 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.48-3.41 (m, 2H), 1.93- 1.83 (m, 1H), 0.88 (d, *J* = 6.8 Hz , 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 159.4, 139.6, 1230, 129.5, 115.9, 114.0, 77.9, 74.5, 73.2, 55.4, 38.6, 13.9; HRMS (ESI), calcd. for $C_{14}H_{20}O_3Na$ $[M+Na]^+$ 259.1304; found 259.1309.

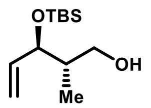
***tert*-Butyl((3*R*,4*S*)-5-(4-methoxybenzyloxy)-4-methylpent-1-en-3-yloxy)dimethylsilane, 177**



177

To an ice-cold mixture of **38** (1.7 g, 7.19 mmol) and CH_2Cl_2 (20 mL) under nitrogen, imidazole (741 mg, 10.78 mmol), TBSCl (1.46 g, 9.3 mmol) and DMAP (175 mg, 0.20 mmol) were put sequentially and mixture was agitated for 2.5 hours before quenching of the reaction content with NH_4Cl (10 mL). The organic content was extracted using CH_2Cl_2 and dried wwith Na_2SO_4, concentrated under *vaccum* and purified on silica gel (C_6H_{14}/EtOAc, 24:1 v/v) to furnish TBS protected compound **177** as transparent oil (2.4 g, 95%). [R_f = 0.6, EtOAc/hexane 1:19 v/v]; $[\alpha]_D^{25}$ -30.2 (c 1.5, CH_2Cl_2); IR (CH_2Cl_2) ν: 2929, 2856, 1615, 1511, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.25 (td, *J* = 6.4, 2.8 Hz, 2H), 6.87 (d, *J* = 8.7, 2H), 5.76 (ddd, *J* = 17.1, 7.4, 4.1, 1H), 5.17-5.02 (m, 2H), 4.41 (q, *J* = 21.2, 11.6, 2H), 4.17 (q, *J* = 7.2 , 4.0 Hz , 1H), 3.80 (s, 3H), 3.43 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.31-3.21 (m, 1H), 1.92-1.79 (m, 1H), 0.95-0.87 (m, 12H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 159.2, 139.6, 131.0, 129.3, 115.3, 113.8, 75.4, 72.8, 72.2, 55.4, 40.1, 26.01, 18.3, 13.2, -4.1, -4.8; HRMS (ESI), calcd for $C_{20}H_{34}O_3SiNa$ $[M+Na]^+$ 373.2169; found 373.2170.

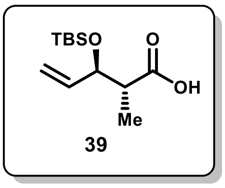
(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpent-4-en-1-ol, 178



178

To an ice-cold solution of compound **177** (1.5 g, 4.27 mmol) prepared using CH_2Cl_2 (15 mL) 0 ^{o}C was put DDQ (1.2 g, 5.13 mmol) and aqueous pH 7.0 buffer (5 mL). After stirring for 45 minutes room temperature, the reaction was stopped using saturated $NaHCO_3$ (10 mL) solution. Excess DCM was poured into it to separate the phases and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). Collected organic layers were washed using brine, dried with Na_2SO_4, filtered and volatiles were evaporated. The residue on purification using silica gel chromatography (hexane/EtOAc 19:3 v/v) furnished a pale yellow liquid **178** (918 mg, 93%); [R_f = 0.5, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ +7.26 (c 1.5, $CHCl_3$); IR (CH_2Cl_2) ν: 3458, 2929, 2858, 1462, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.83 (ddd, *J* = 17.1, 10.4, 6.7, 1H), 5.23-5.11 (m, 2H), 4.07 (t, *J* = 8.0, 1H), 3.73 (d, *J* = 10.9, 1H), 3.61-3.54 (m, 1H), 2.72 (brs, 1H), 1.76-1.67 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.3, 115.7, 79.6, 66.0, 40.8, 26.0, 18.2, 14.3, -3.9, -4.8; HRMS (ESI), calcd for $C_{12}H_{26}O_2SiNa$ $[M+Na]^+$ 253.1594; found 253.1597.

(2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpent-4-enoic acid, 39



39

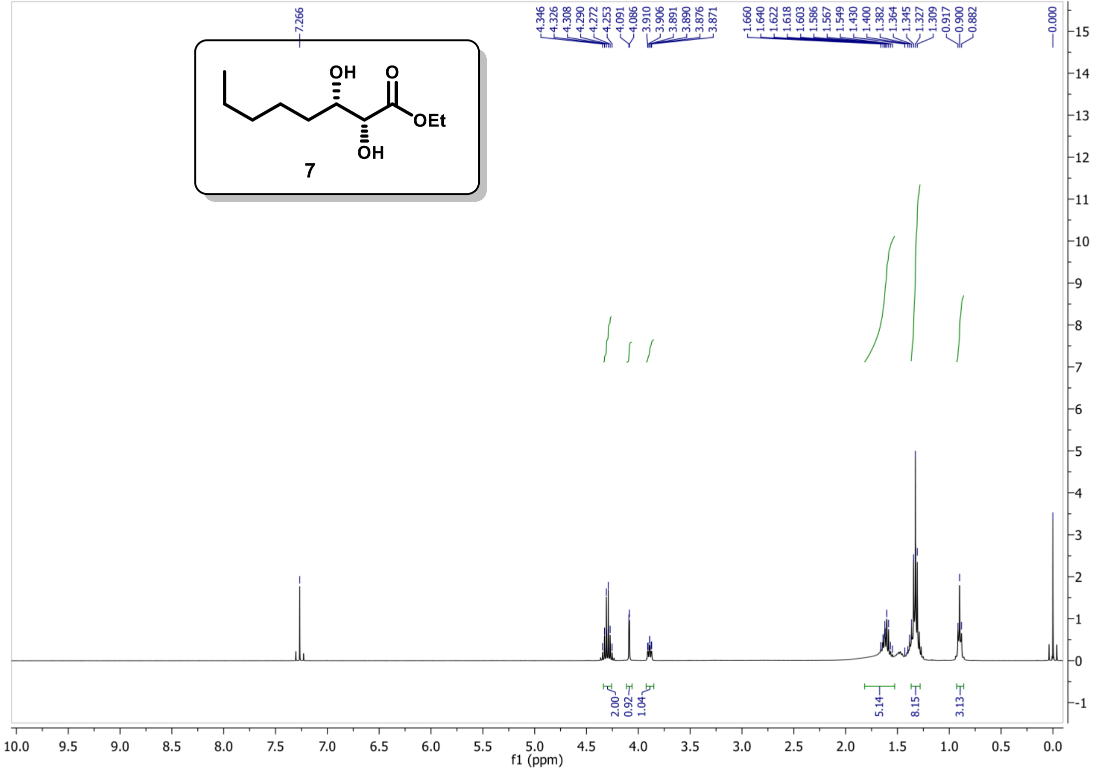
The alcohol **178** (900 mg, 3.90 mmol) was taken in 12 mL DCM:H_2O (2:1). TEMPO (121 mg, 0.78 mmol) and bis(acetoxy)iodobenzene (BAIB) (2.7 g, 8.58 mmol) were put sequentially to the previous solution. The resulting content was agitated at 28 °C for 24 hours and quenched by addition of saturated solution of $Na_2S_2O_3$. The content was diluted suing EtOAc (15 mL) to separate the layers. The watery phase was extracted with EtOAc (3×15 mL). Collected organic layer was washed using brine and dried out using Na_2SO_4, and volatiles were removed. Silica gel column chromatography (hexane/EtOAc, 4:1 v/v) of the residue afforded acid **39** (830 mg, 87%) as a yellow solid.; [R_f = 0.5, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ -59.3 (c 0.06, $CHCl_3$); IR (CH_2Cl_2) ν: 2929, 2857, 1719, 1461, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 (ddd, *J* = 17.3, 10.4, 7.2, 1H), 5.21 (ddt, *J* = 12.6, 10.5, 1.3, 2H), 4.25 (t, *J* = 6.96 Hz, 1H), 2.59-2.55 (m, 1H), 1.13 (d, *J* = 6.80 Hz, 3H), 0.91-0.84 (s, 9H), 0.075 (s, 3H), 0.049 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.2, 138.3, 117.3, 76.2, 46.7, 25.8, 18.2, 13.5, -4.1, -5.1; HRMS (ESI), calcd for $C_{12}H_{24}O_3SiNa$ $[M+Na]^+$ 267.1387; found 267.1395.

4.1Speactra

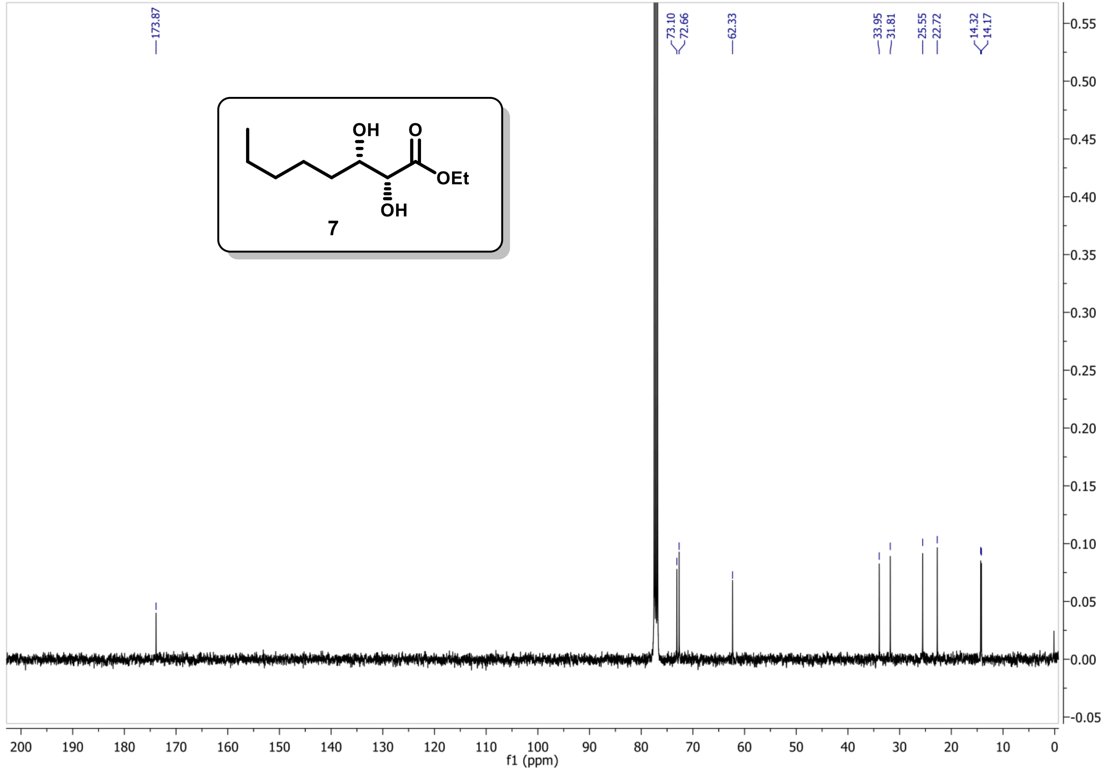
1. ^{1}H and ^{13}C Spectra of **7**
2. ^{1}H and ^{13}C Spectra of **171**
3. ^{1}H and ^{13}C Spectra of **172**
4. ^{1}H and ^{13}C Spectra of **173**
5. ^{1}H and ^{13}C Spectra of **174**
6. ^{1}H and ^{13}C Spectra of **8**
7. ^{1}H and ^{13}C Spectra of **8a**
8. ^{1}H and ^{13}C Spectra of **37**
9. ^{1}H and ^{13}C Spectra of **175**
10. ^{1}H and ^{13}C Spectra of **176**

11. ^{1}H and ^{13}C Spectra of **38**
12. ^{1}H and ^{13}C Spectra of **177**
13. ^{1}H and ^{13}C Spectra of **178**
14. ^{1}H and ^{13}C Spectra of **39**
15. HPLC data Spectra of **37**

^{1}H NMR (400 MHz, CDCl$_3$)



^{13}C NMR (400 MHz, CDCl$_3$)



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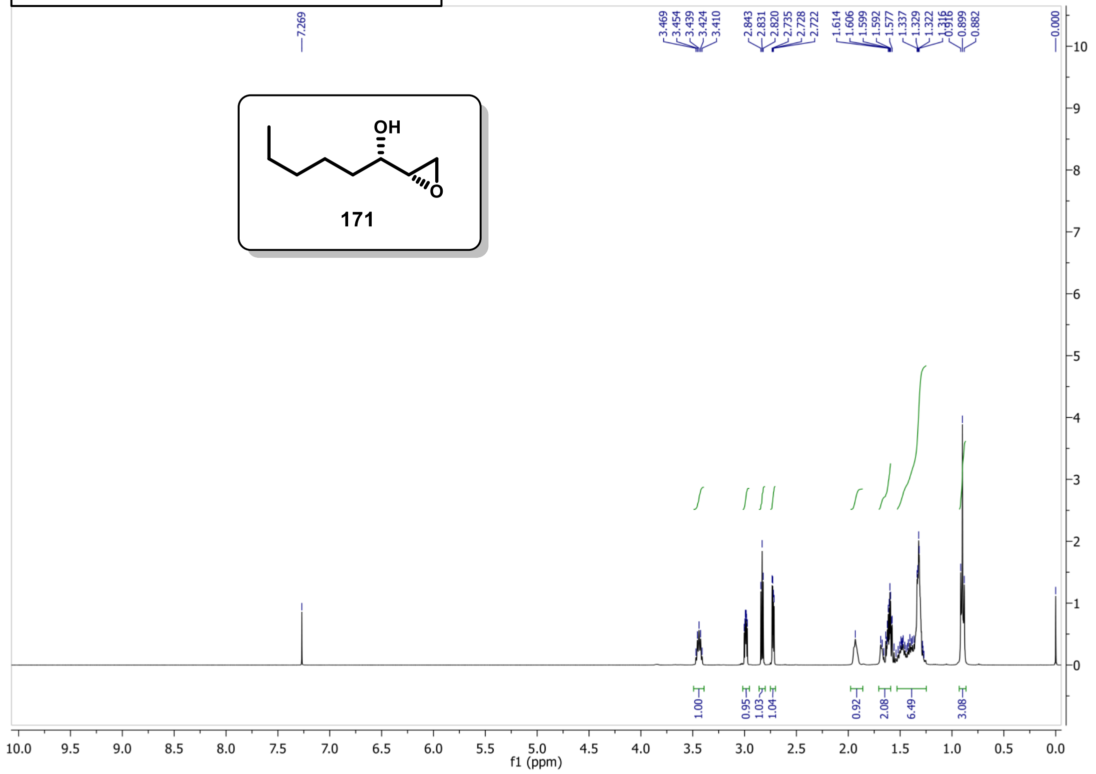

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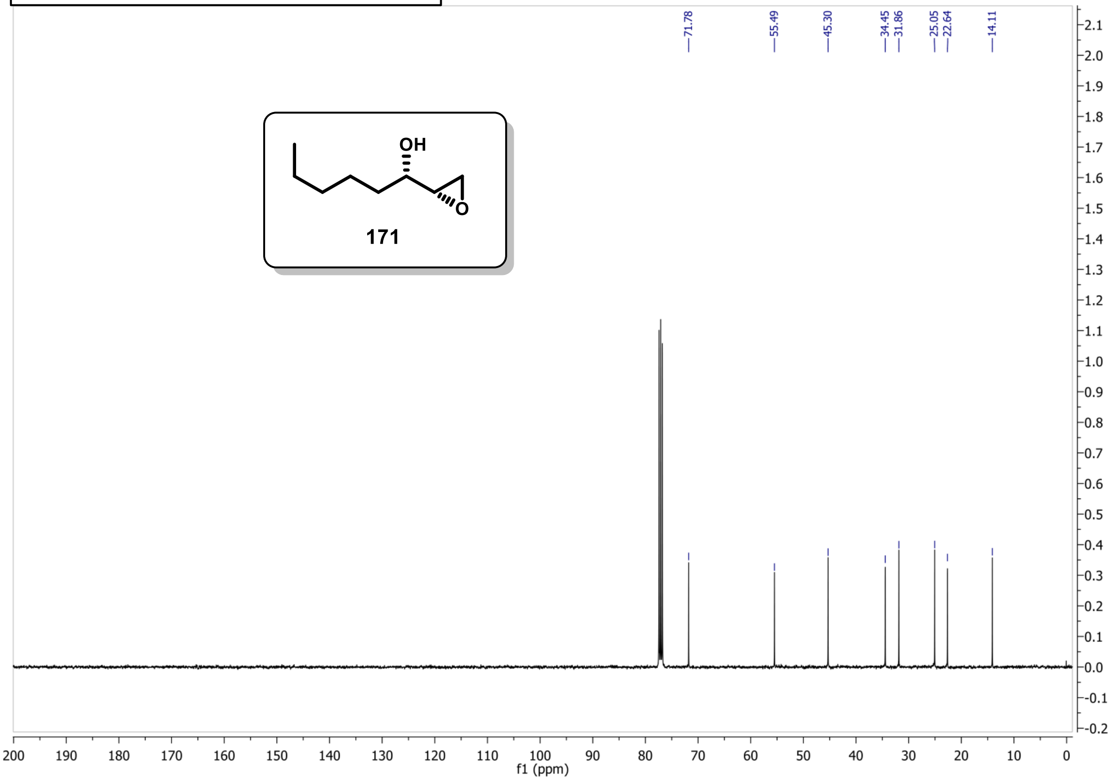

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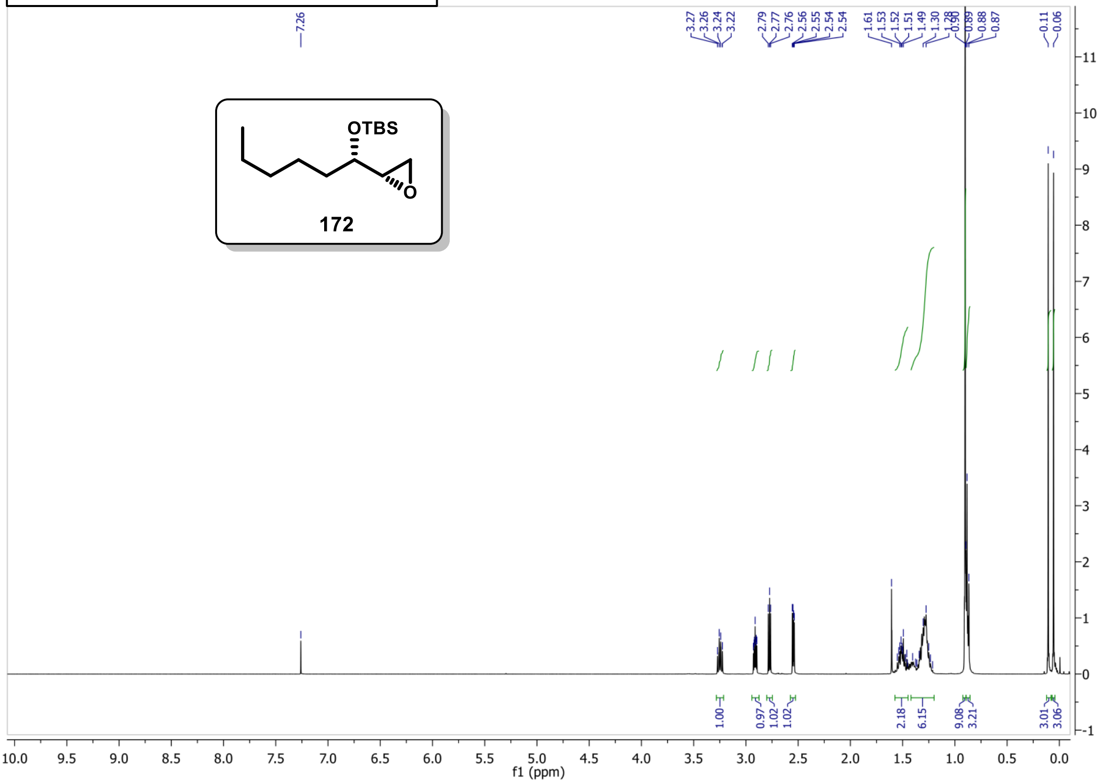

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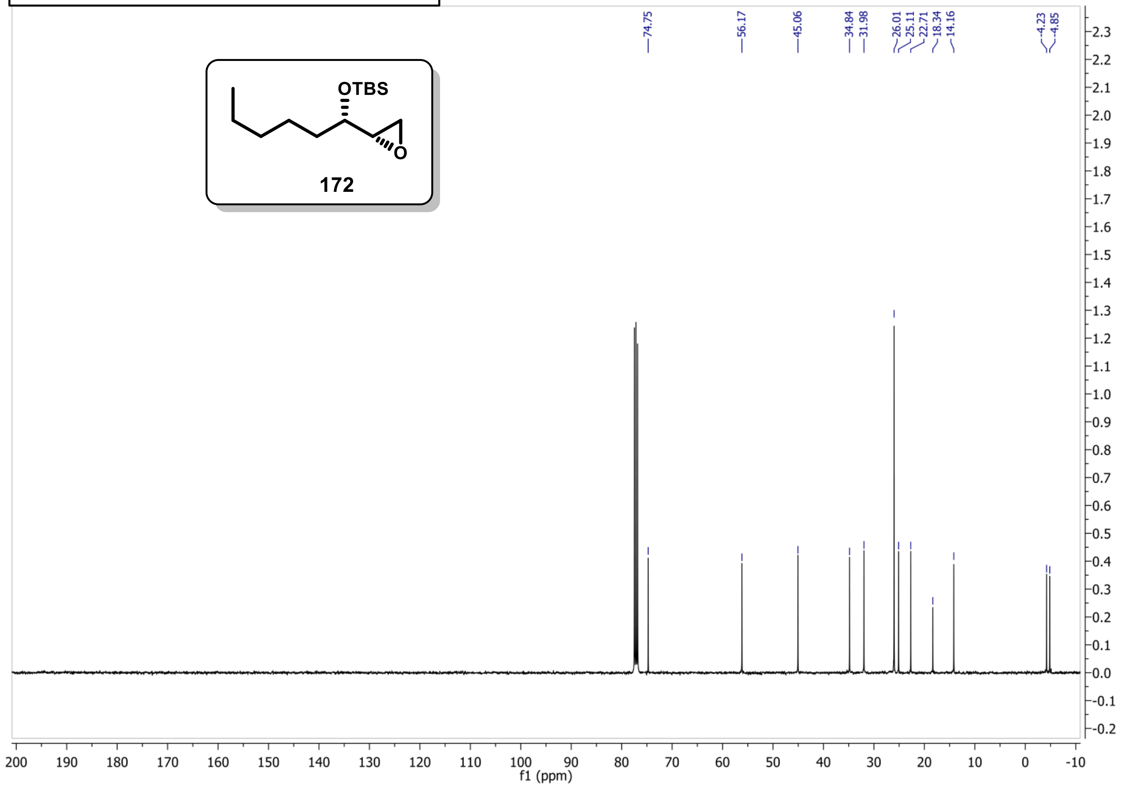

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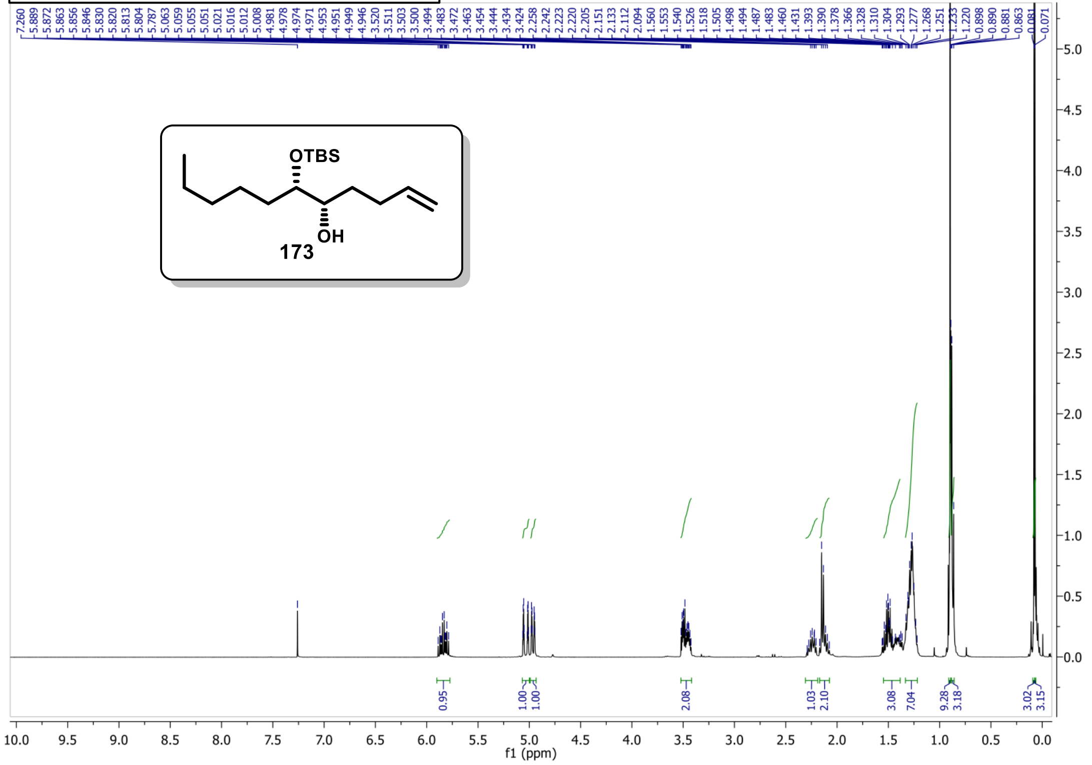

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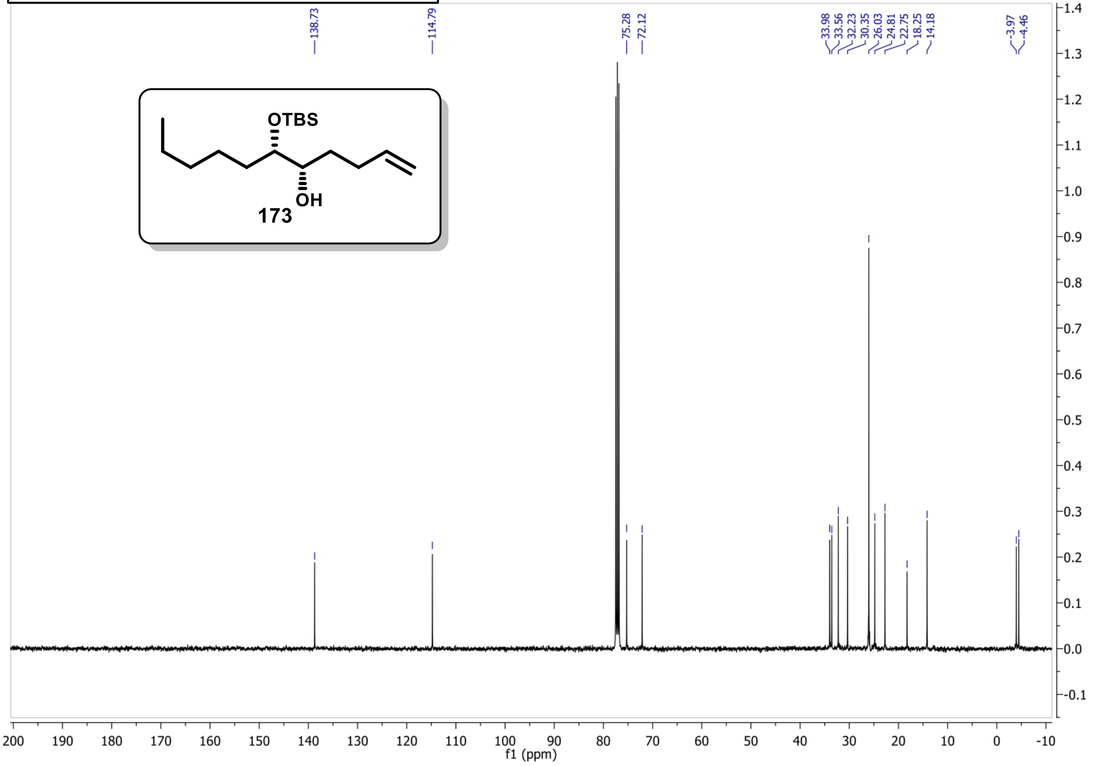
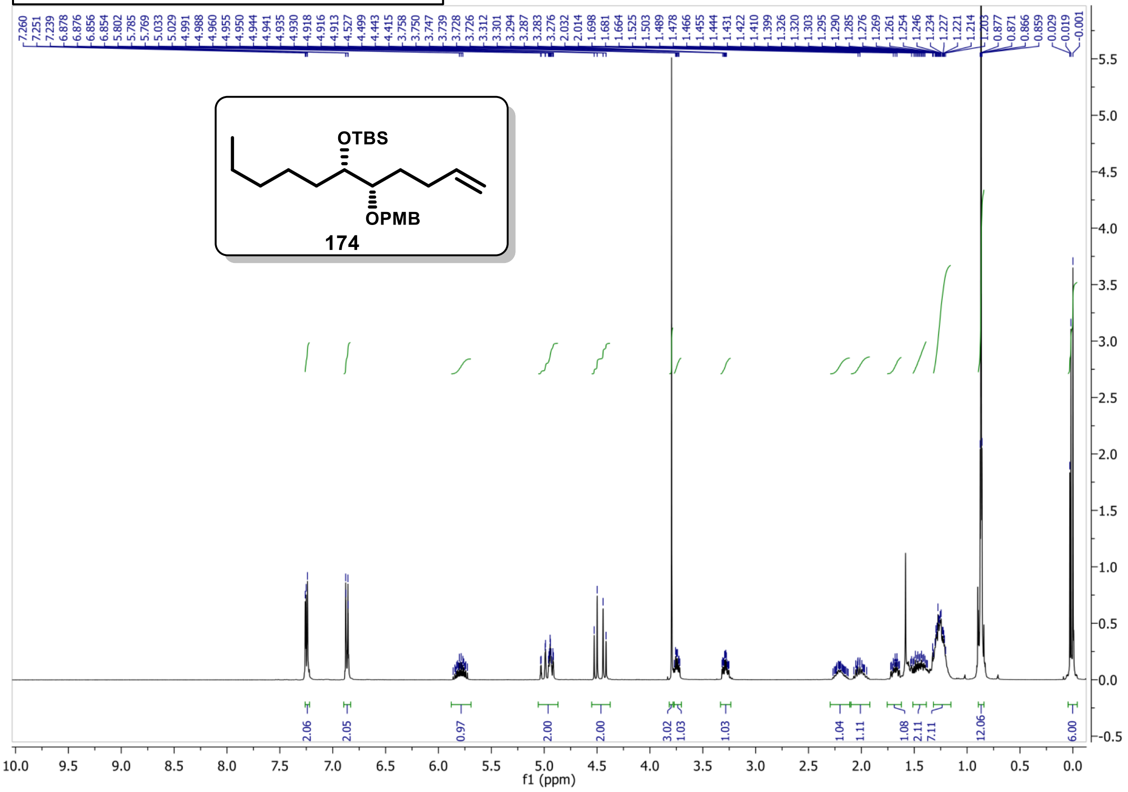


^{1}H NMR (400 MHz, $CDCl_3$)



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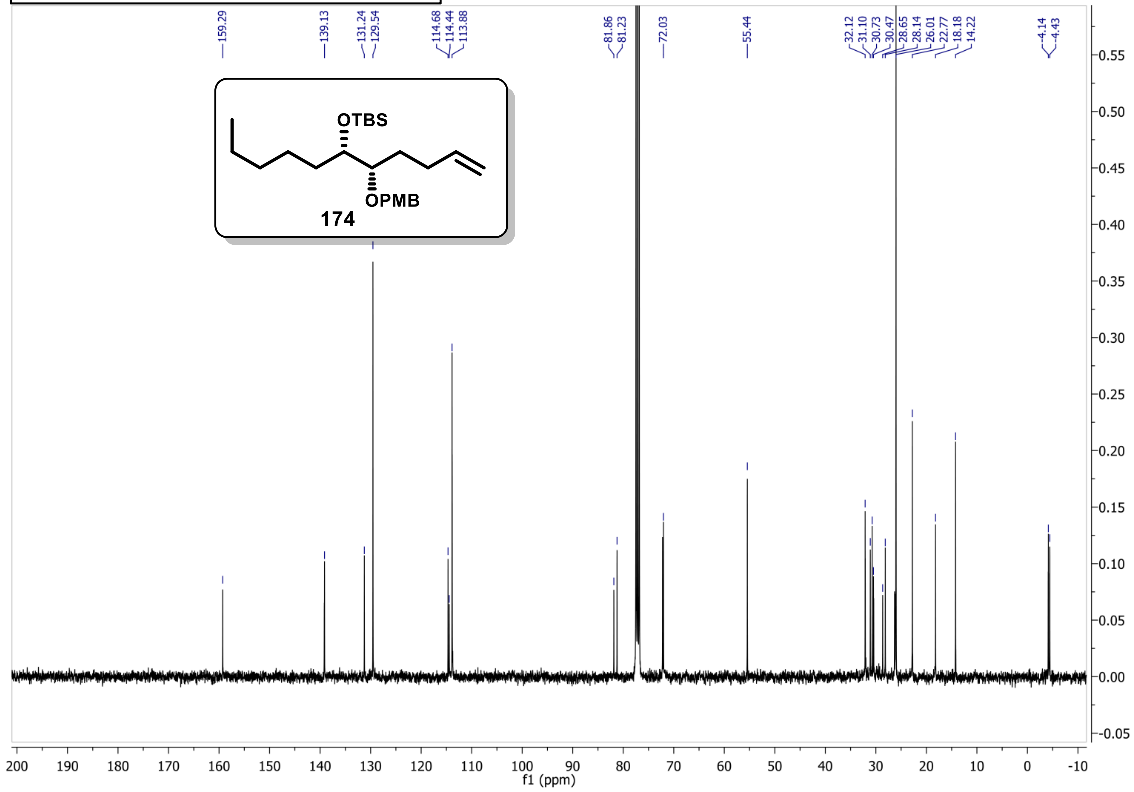

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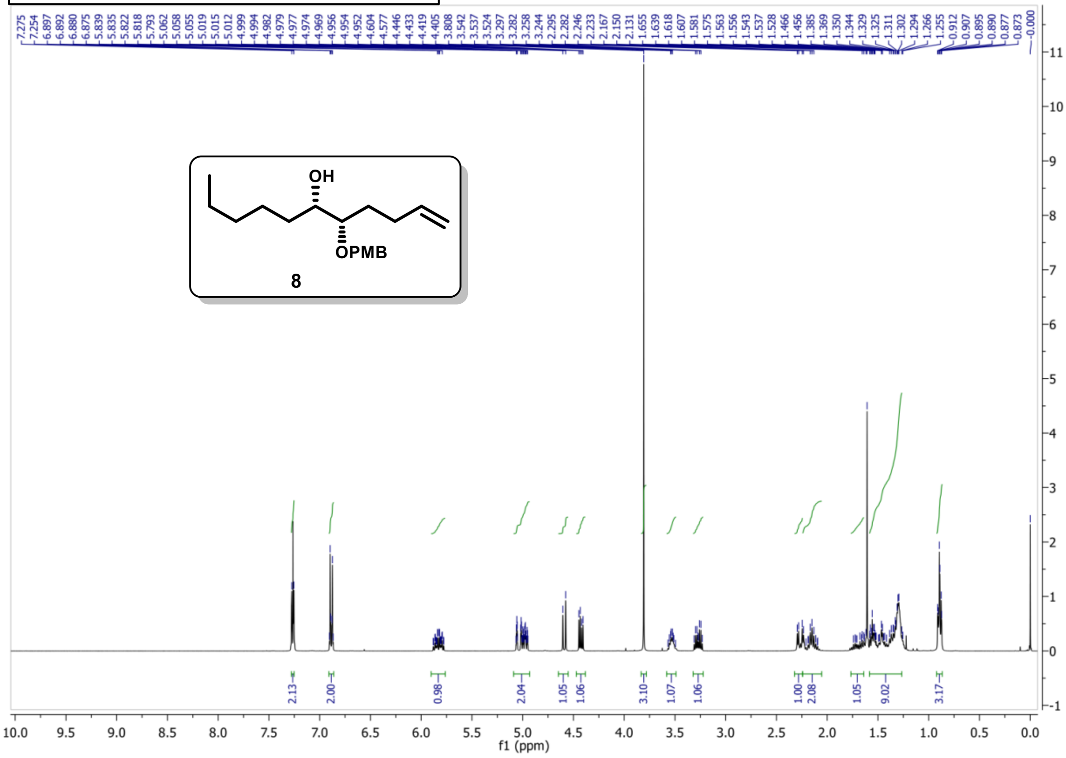

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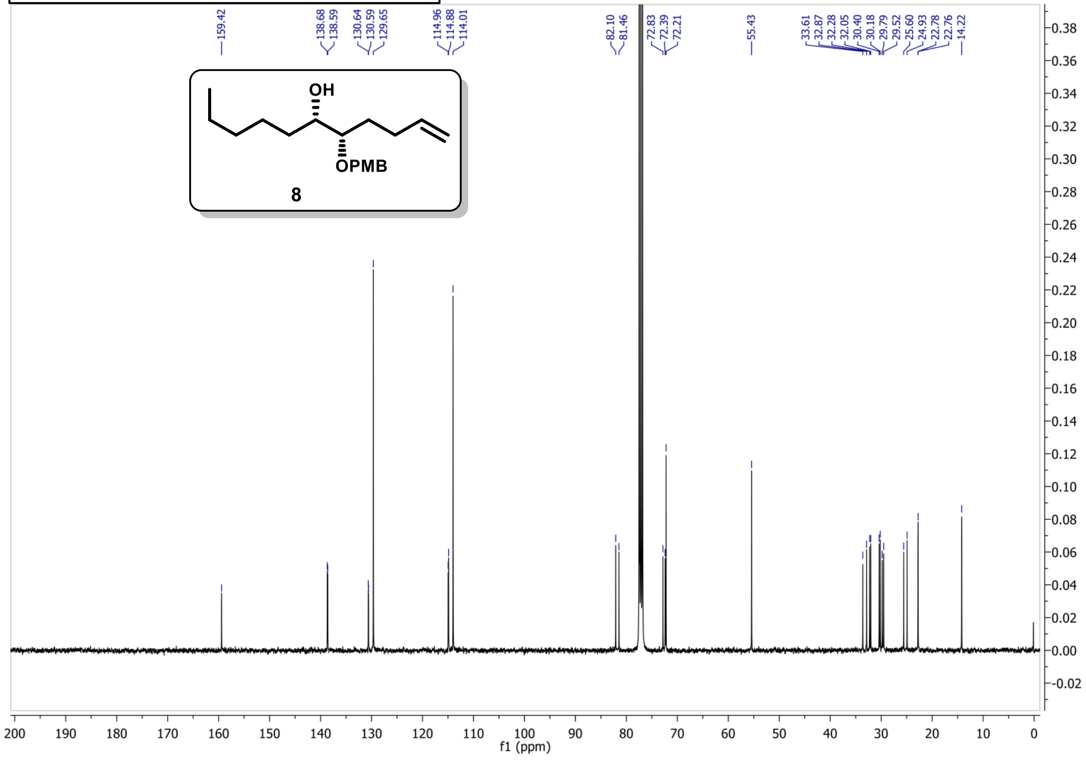
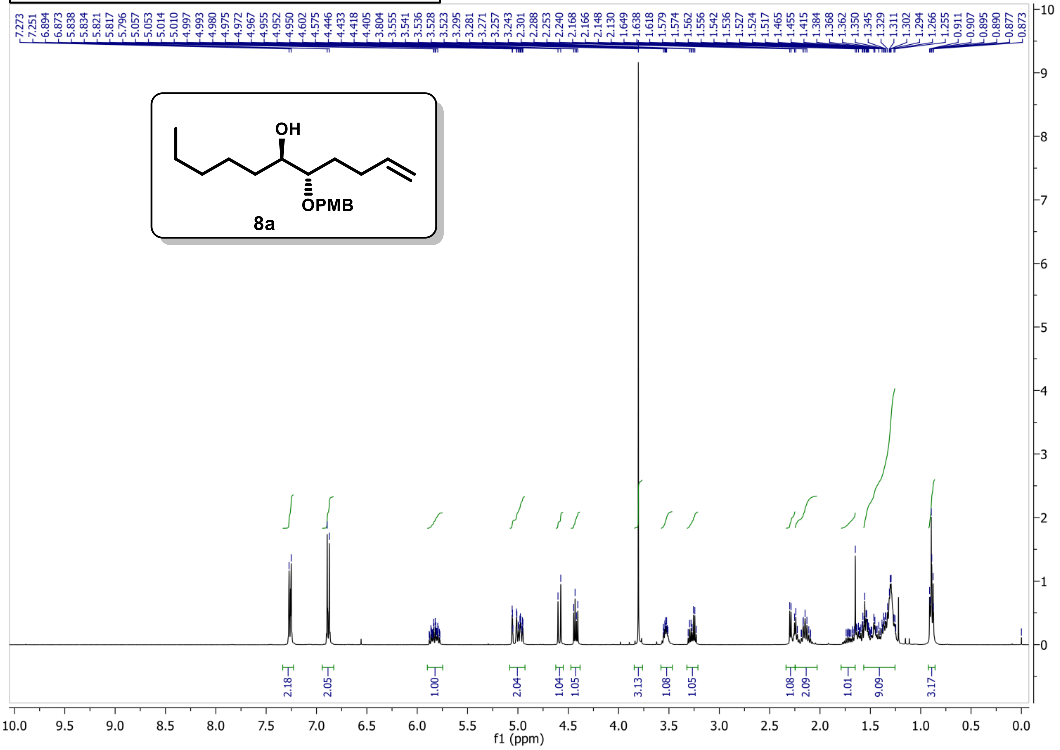


^{1}H NMR (400 MHz, $CDCl_3$)



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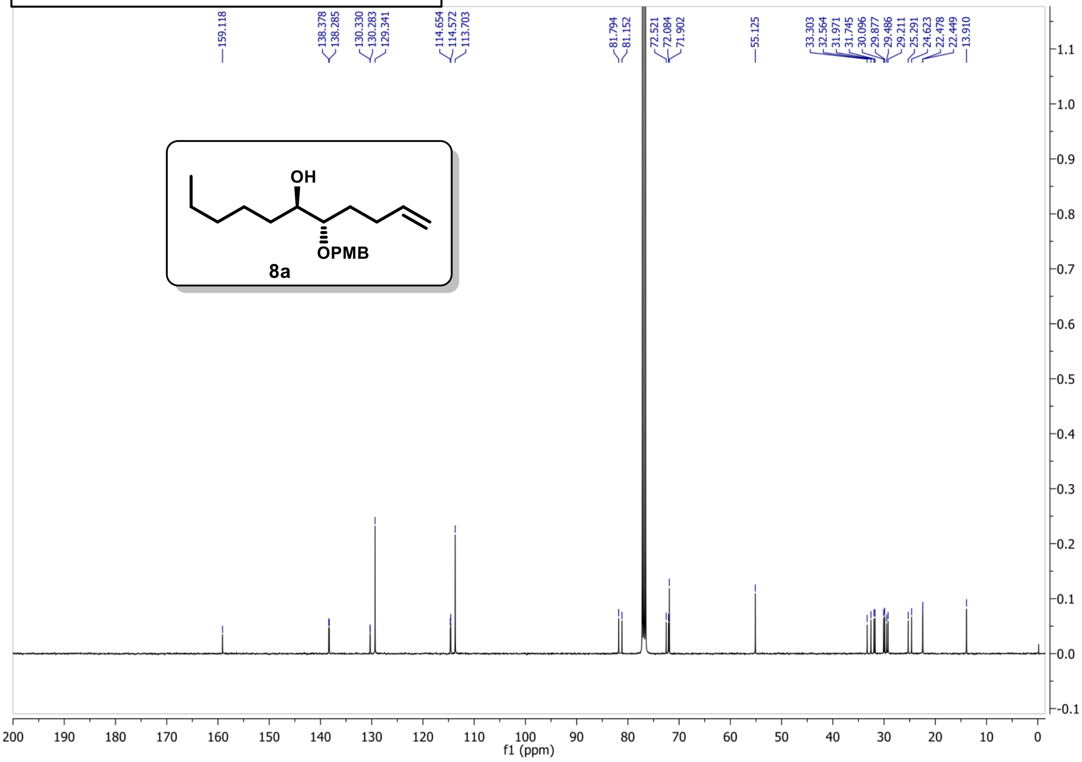

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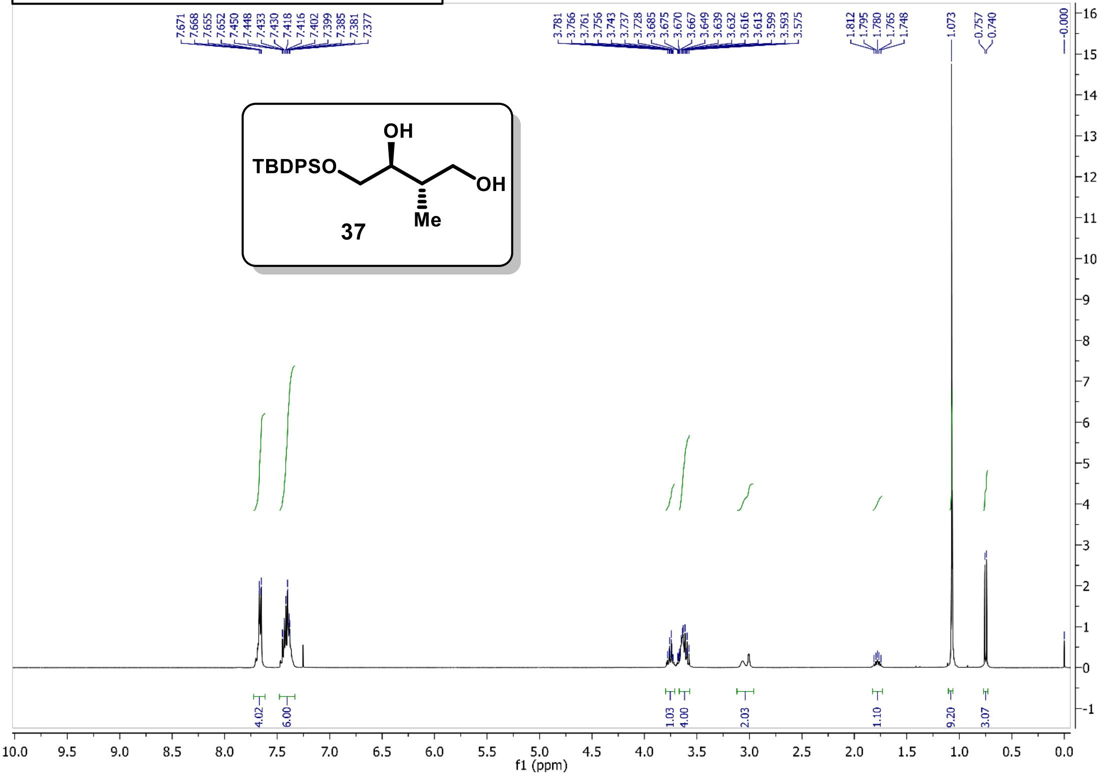

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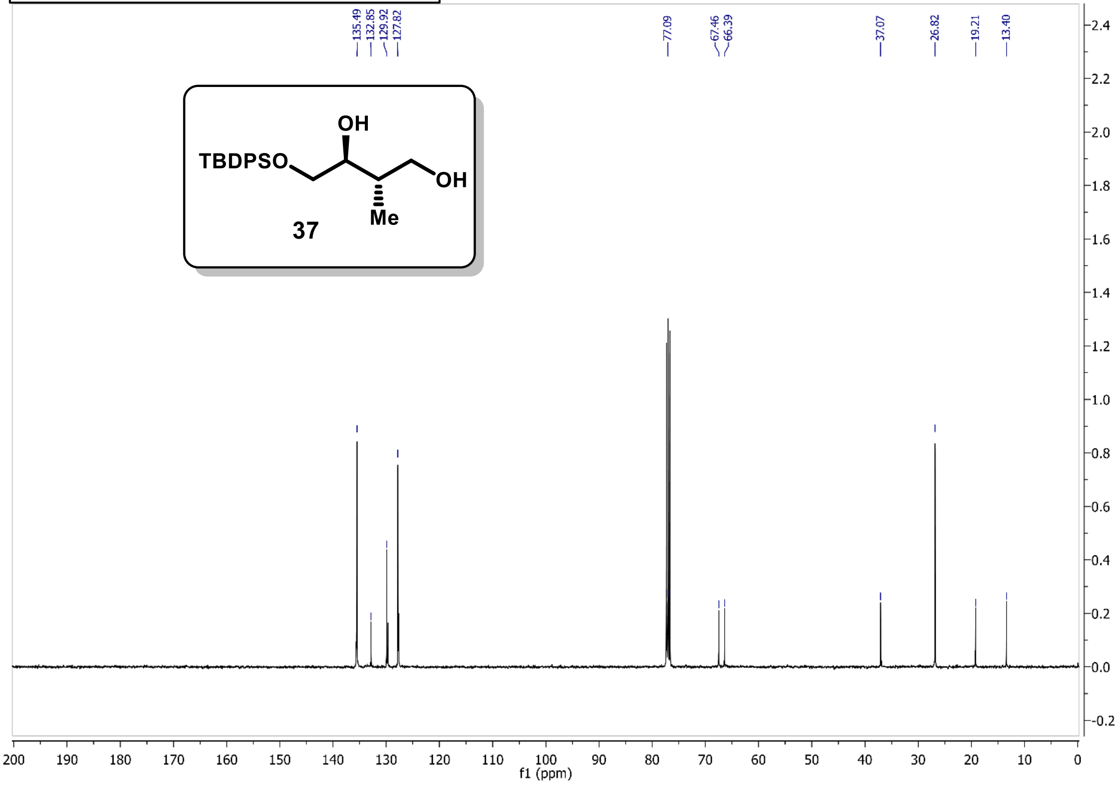

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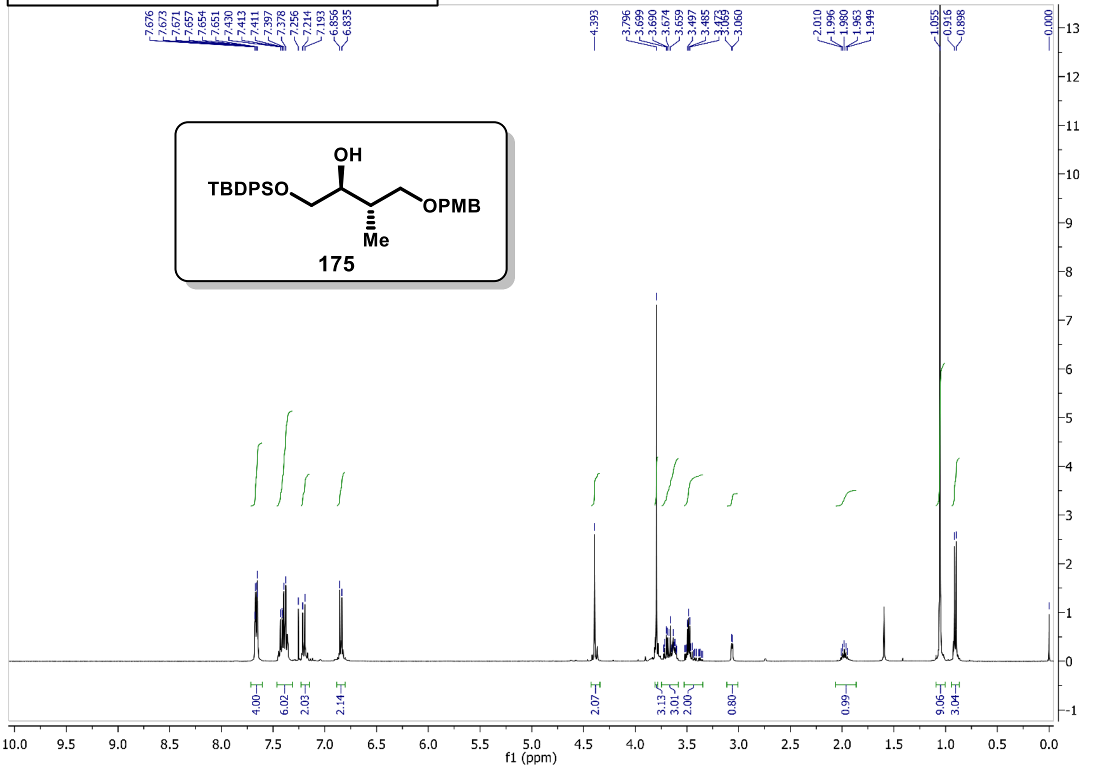

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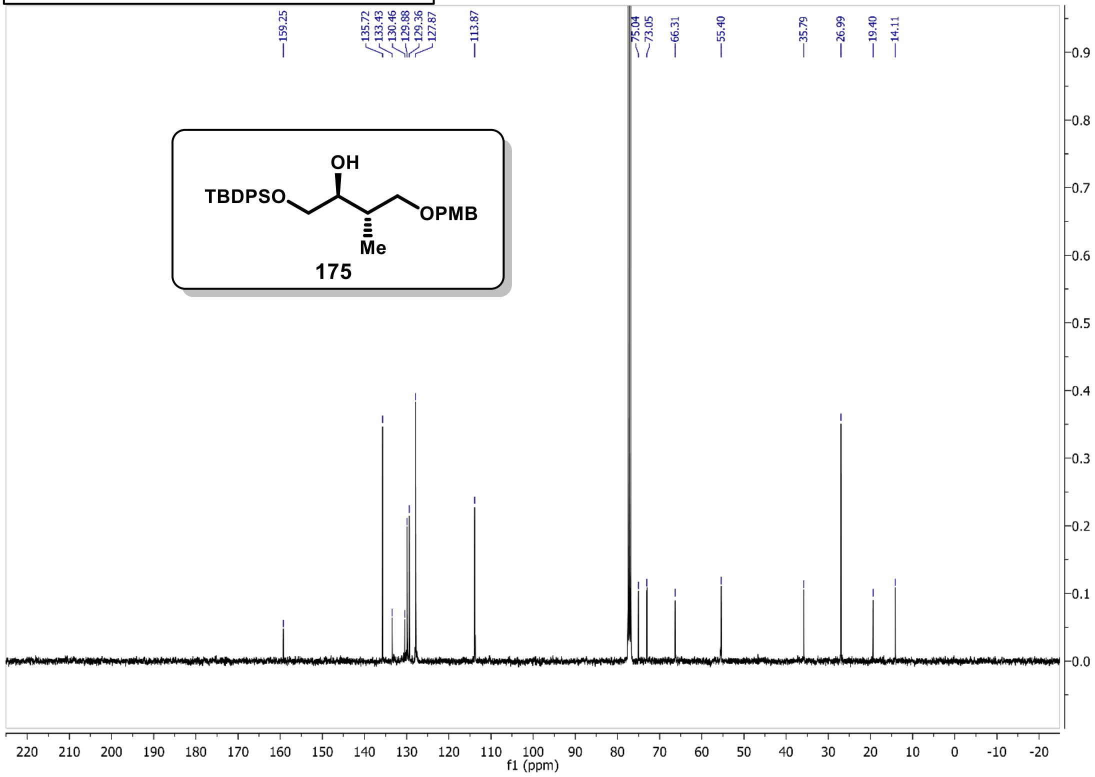
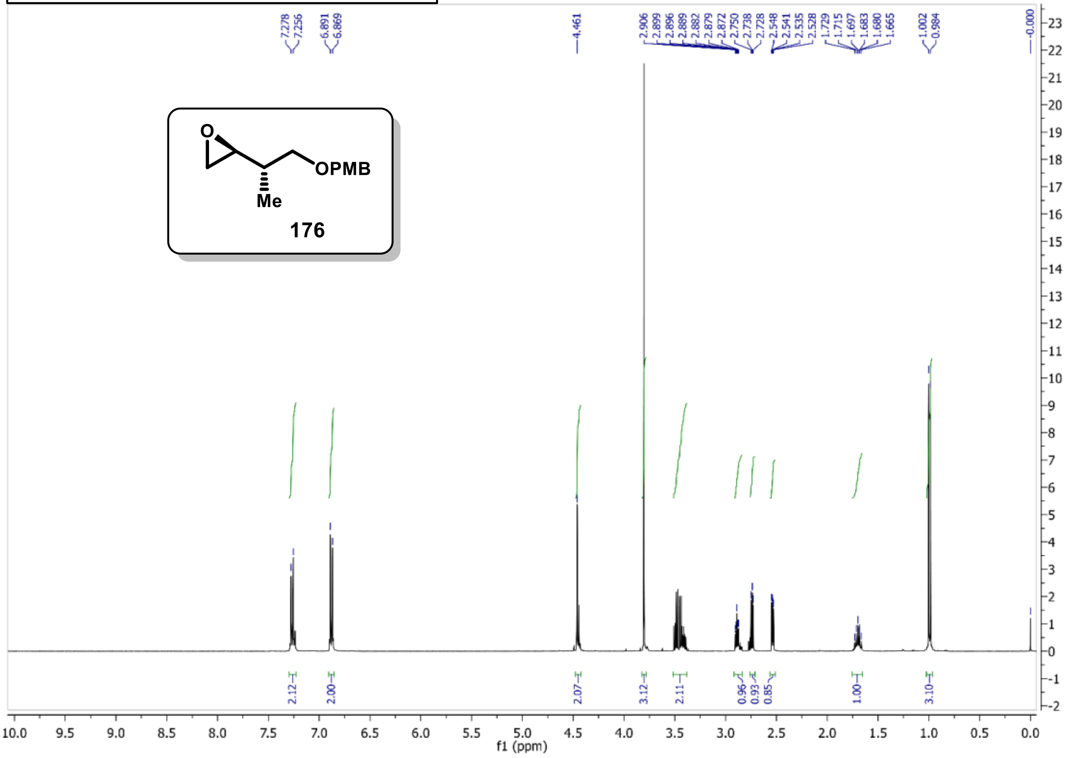


^{1}H NMR (400 MHz, CDCl$_3$)



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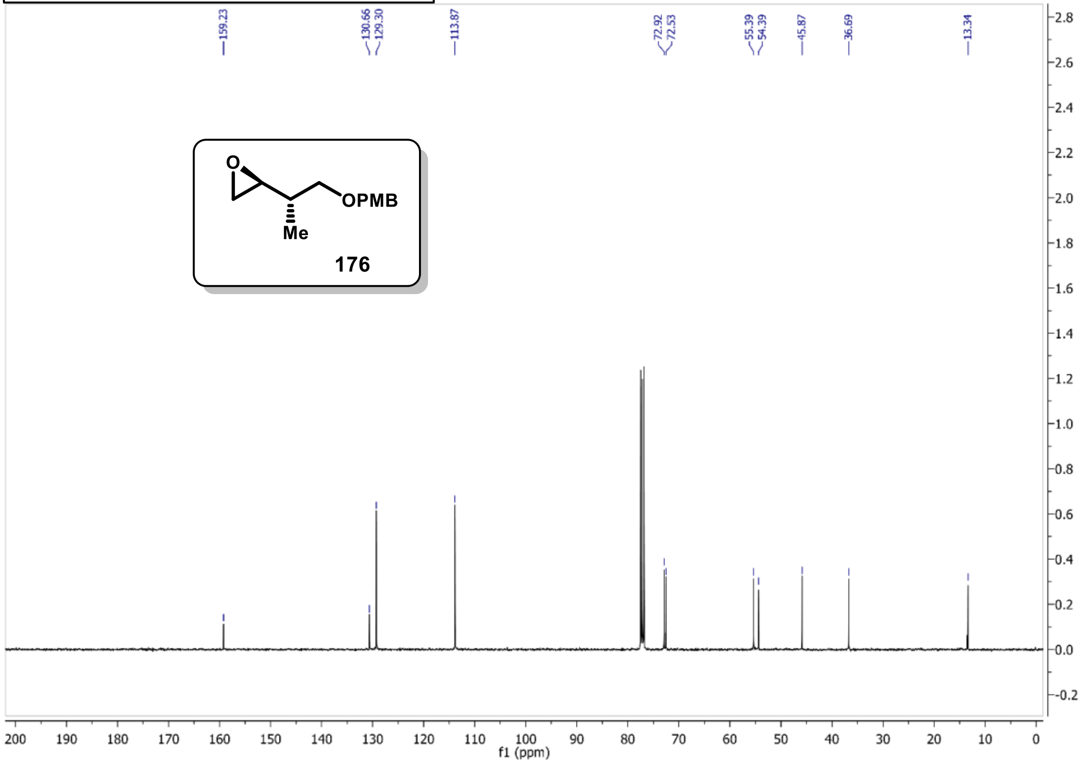

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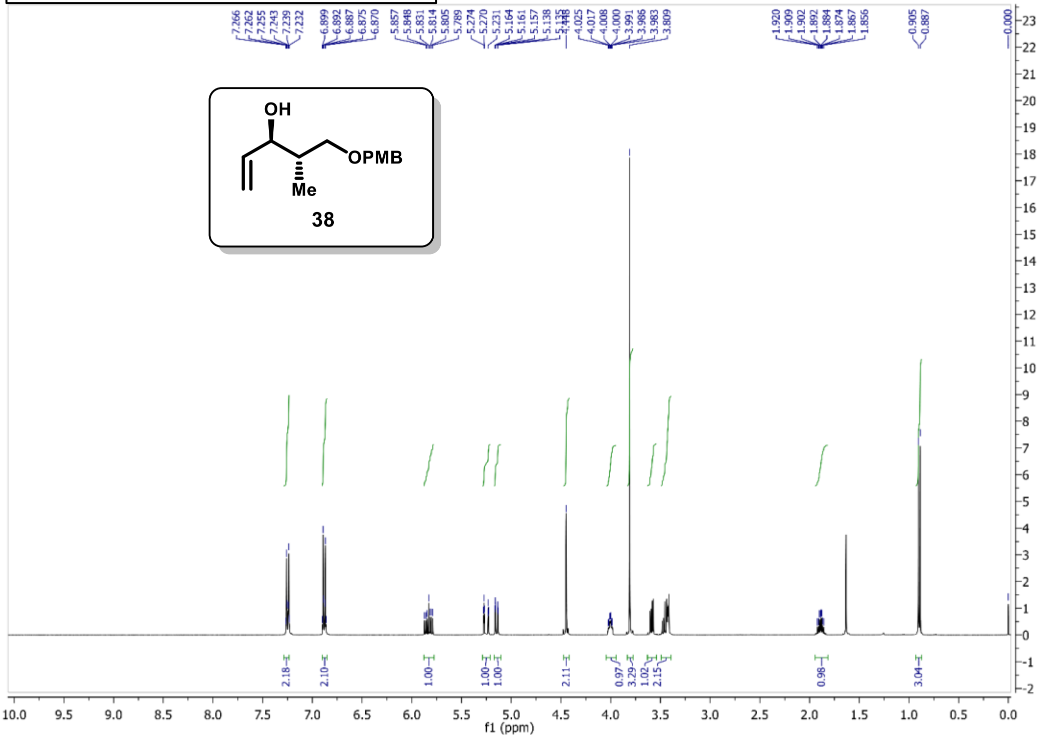

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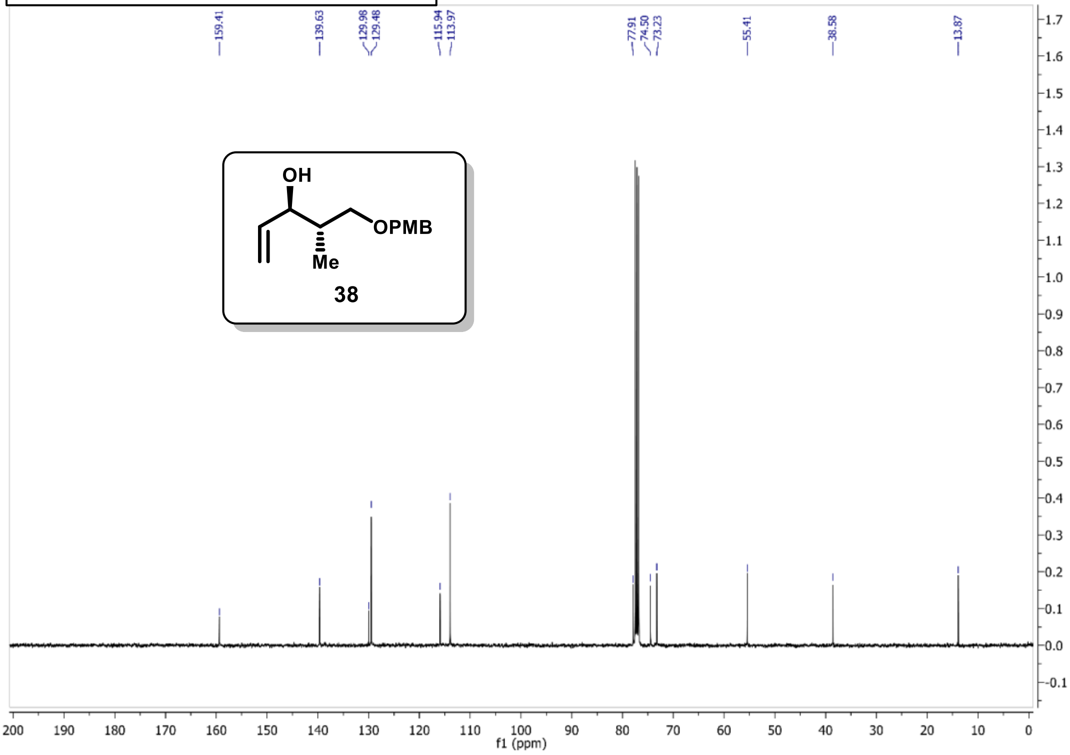

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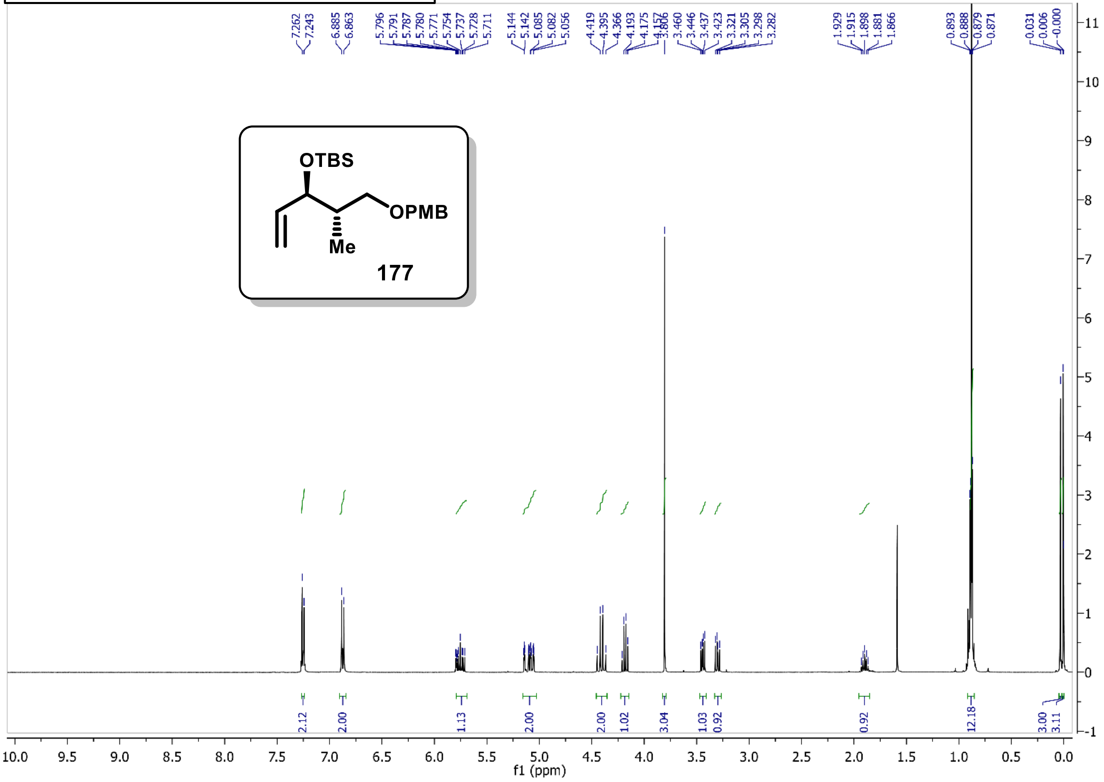

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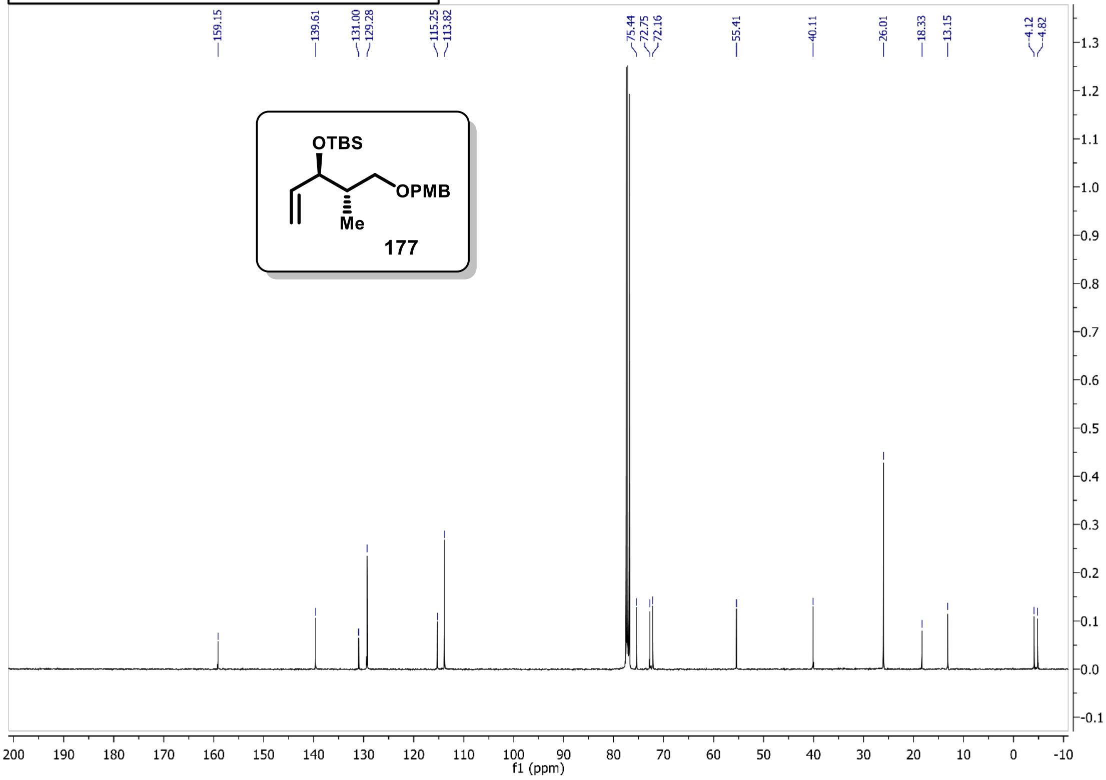

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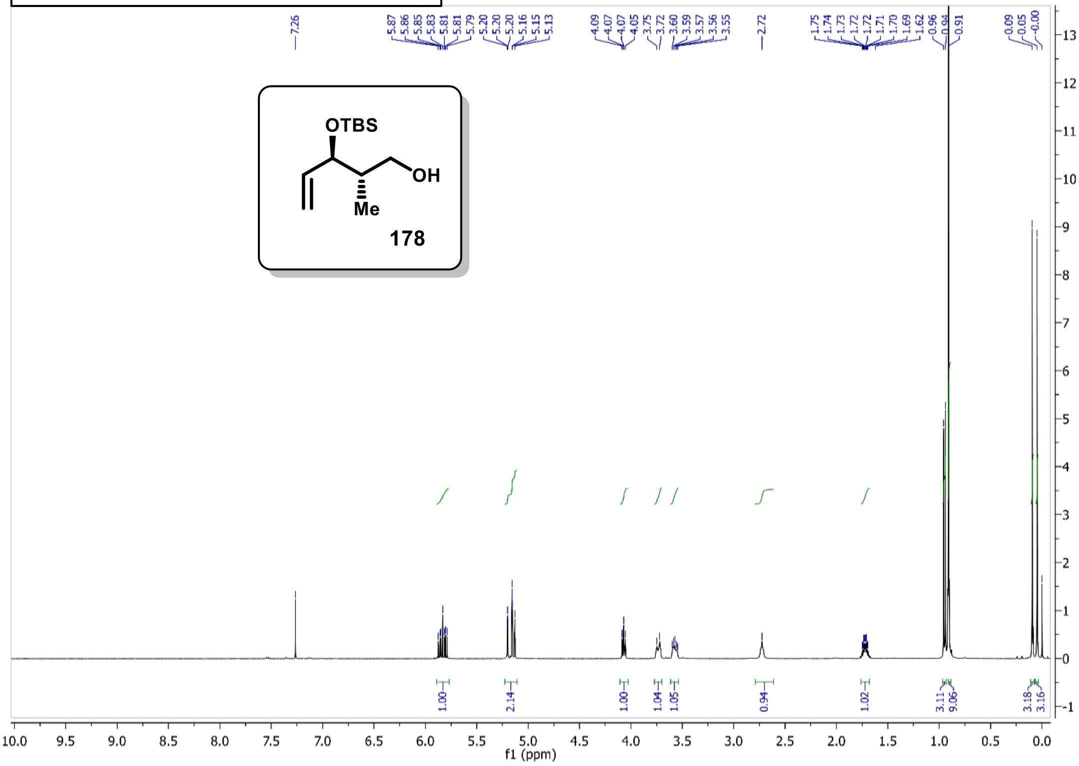

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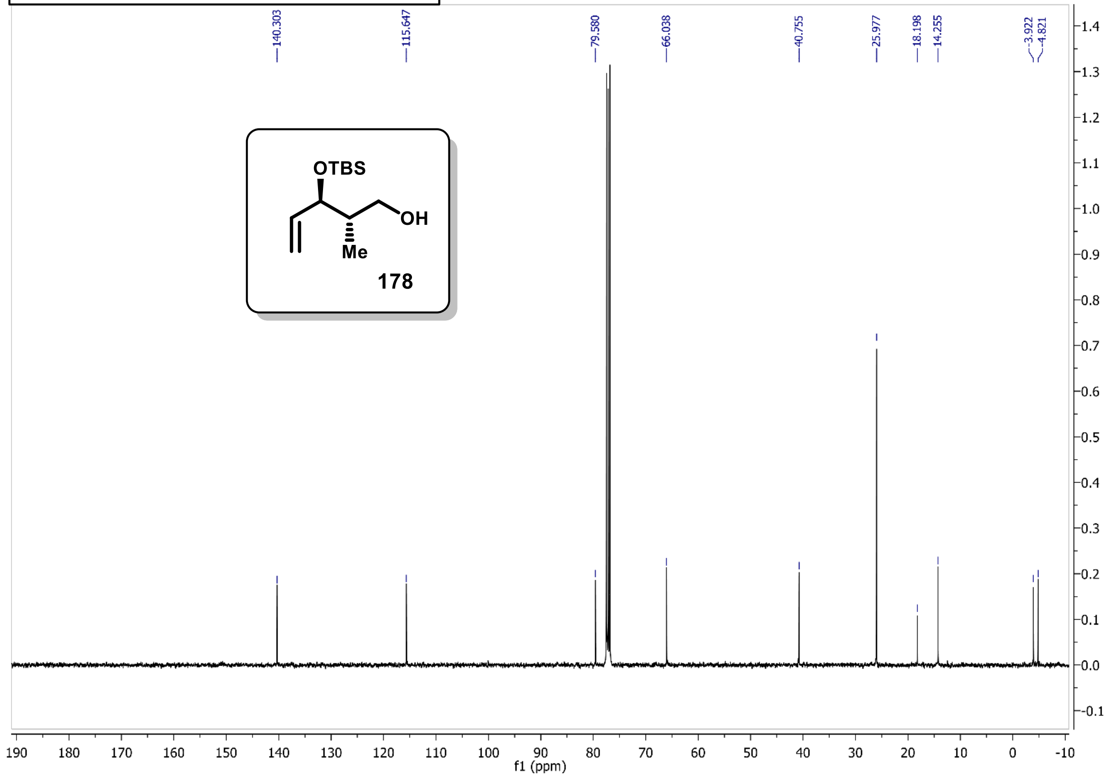

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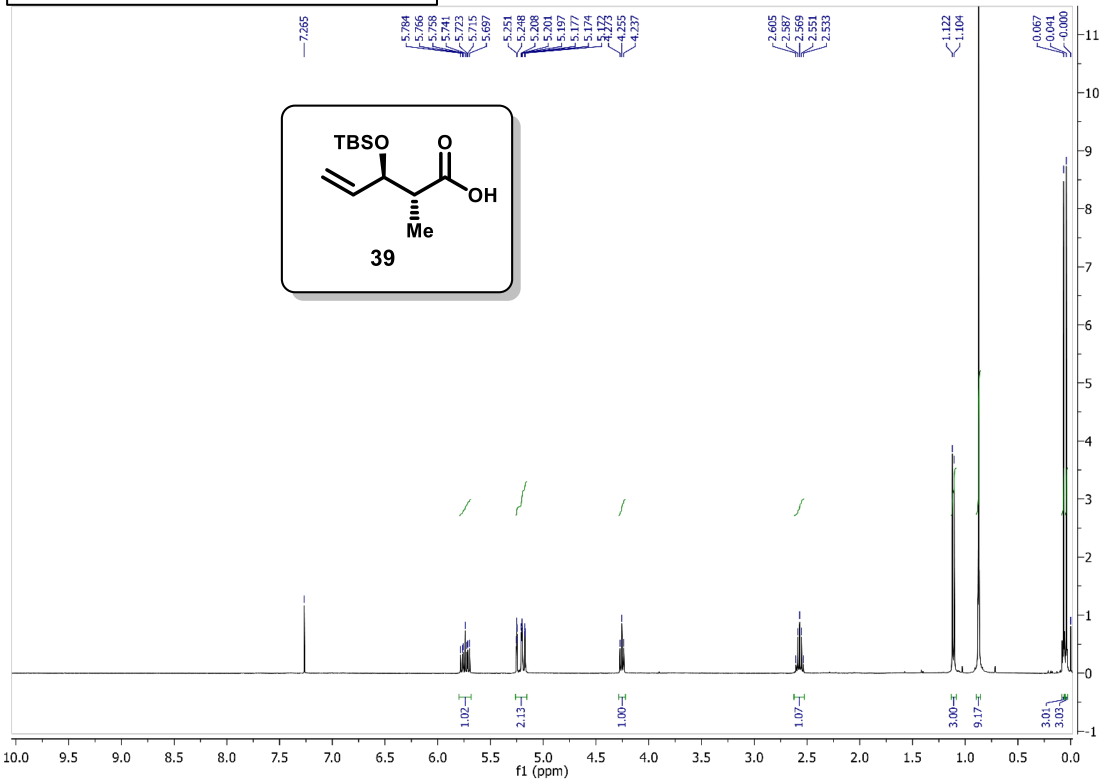

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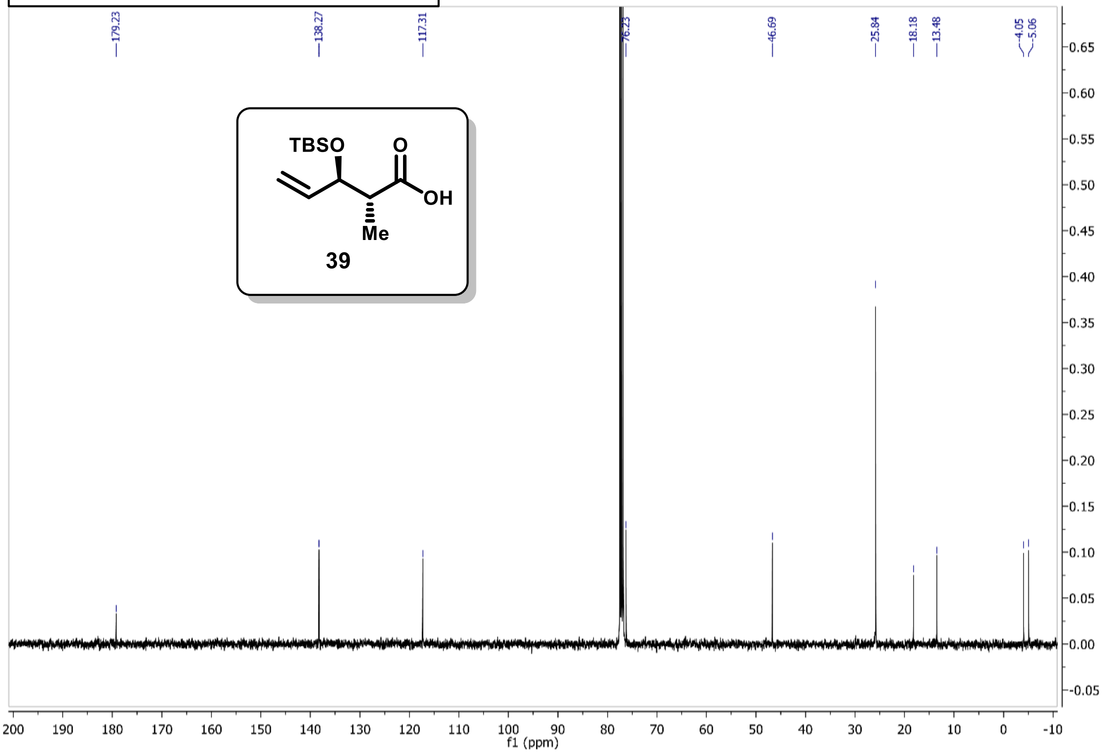
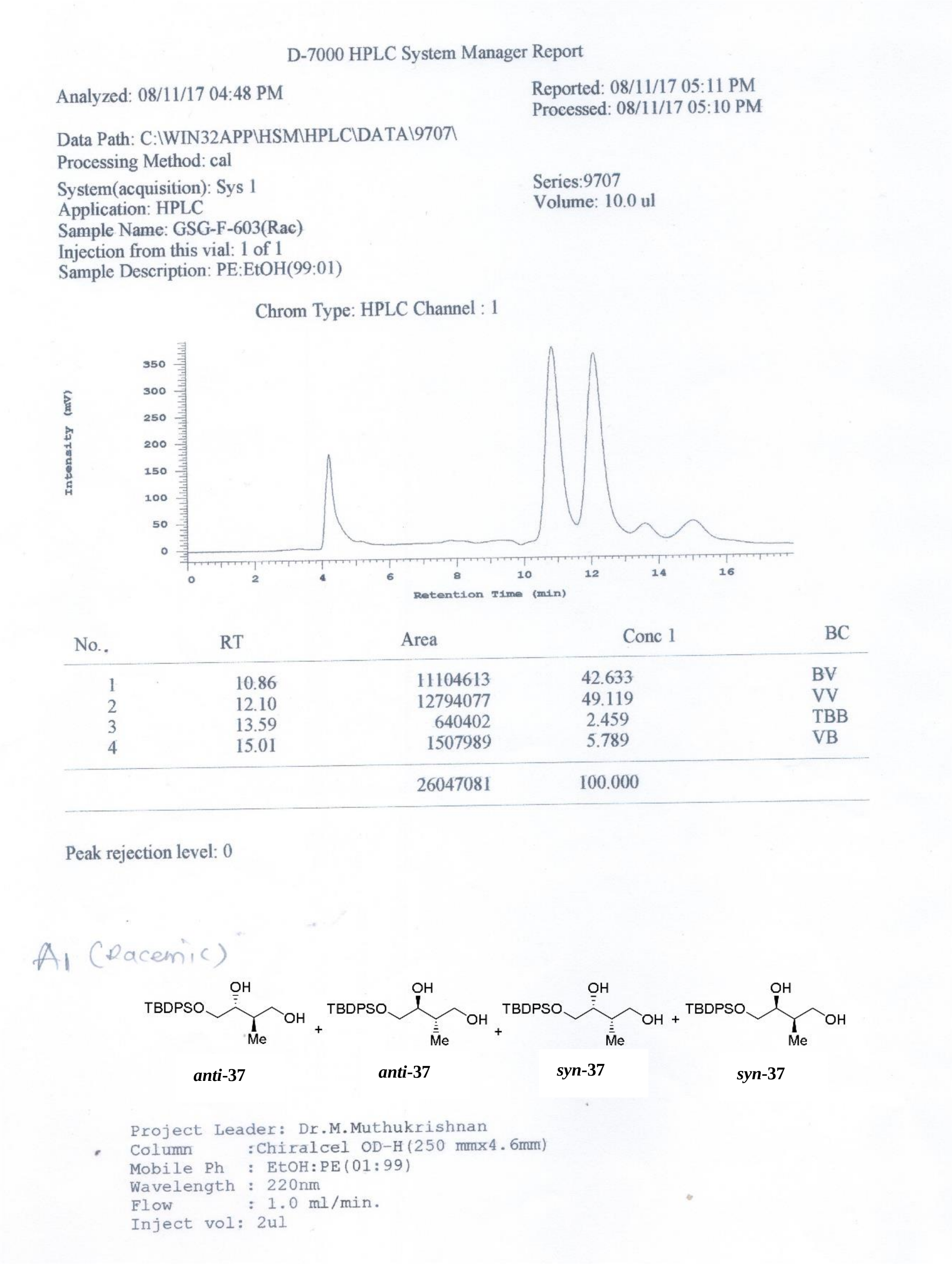


HPLC Data of compound **37**, (Racemic)



D-7000 HPLC System Manager Report

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Reported: 08/11/17 05:11 PM
Processed: 08/11/17 05:10 PM

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Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: GSG-F-603(Rac)
Injection from this vial: 1 of 1
Sample Description: PE:EtOH(99:01)

Series:9707
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1

No.	RT	Area	Conc 1	BC
1	10.86	11104613	42.633	BV
2	12.10	12794077	49.119	VV
3	13.59	640402	2.459	TBB
4	15.01	1507989	5.789	VB
		26047081	100.000	

Peak rejection level: 0

A1 (Racemic)

anti-**37** *anti*-**37** *syn*-**37** *syn*-**37**

Project Leader: Dr.M.Muthukrishnan
Column :Chiralcel OD-H(250 mmx4.6mm)
Mobile Ph : EtOH:PE(01:99)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 2ul

HPLC Data of compound **37**, (Chiral)

D-7000 HPLC System Manager Report

Analyzed: 08/11/17 04:29 PM

Reported: 08/11/17 04:58 PM
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Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: GSG-F-607(Chiral)
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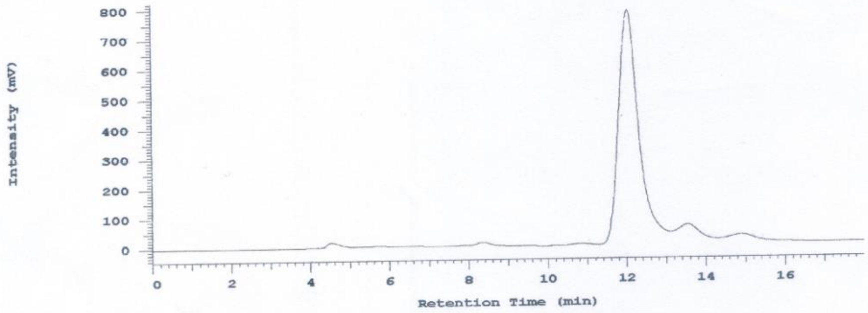
Sample Description: PE:EtOH(99:01)

Series:9706
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
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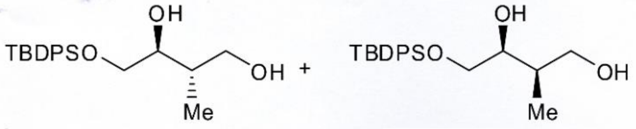
2	12.05	29892393	94.986	BV
3	13.55	993184	3.156	TBB
4	14.91	552776	1.757	TBB
		31470240	100.000	

Peak rejection level: 0

A1 (chiral)



anti-37 *syn*-37

```
Project Leader: Dr.M.Muthukrishnan
Column      :Chiralcel OD-H(250 mmx4.6mm)
Mobile Ph   : EtOH:PE(01:99)
Wavelength  : 220nm
Flow        : 1.0 ml/min.
Inject vol: 2ul
```

4.8 References:

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CHAPTER 5

Conclusions and Future scope.

Conclusions and Scope

5.1 Conclusions

In conclusion, we have demonstrated the total syntheses of ((3*R*,6*R*)-6-methylpiperidin 3-yl) methanol **26**, Sacubitril **5** and key acid **39** (C1-C4) and alkenol **8a** (C5-C14) fragments of cytospolide D **110.** Herein, elaborated biocatalytic transaminase free divergent approach for the synthesis of *trans* piperdine **26** framework have been described. (*S*)-propylene oxide was used as starting material and TMS prolinol catalysed Michael addition reaction was effectively utilized for the insertion of second chiral centre. The overall yield of core unit **26** was 33%. The benefits of proposed synthesis involved excellent enantio- and diastereoselectivity with high yielding reaction steps. The synthetic approach presented here, is also reliable for variation in stereochemistry of newly created chiral centres. In comparison to the previously reported synthesis the current synthesis is enzymatic free which was utilized for the generation of chiral centers.

Next, we have also developed an efficient enantioselective approach for the total synthesis of Sacubitril **5** from commercially available pentenoic acid as starting material in excellent yield. Fundamental transformations comprise the Evans methylation, used for installing the first chiral methyl group. Further, the intermolecular Heck coupling was implemented to construct the vital biphenyl backbone, where a reagent combination of *tri*-(*o*-tolyl)phosphine/Pd$(OAc)_2$ and Et_3N gave promising results. For the introduction of second chital centre Sharpless AD conditions were found fruitful. Moreover, present synthetic route also display significant potential for stereo chemical variations and further extension to other stereoisomers which was not feasible in the previously reported syntheses. The starting materials utilized for the synthesis are commercially available and scale up process for the synthesis could be easily carried out.

Furthermore, lastly we established a new and competent enantioselective approach to the synthesis of the two key fragments i.e acid **39** (C1-C4) and alkenol **8a** (C5-C14) of cytospolide D **110** in good yield. For the construction of chiral acid fragment **39** organocatalysed MacMillan’s crossed aldol was employed and one-carbon homologation reaction was also effectively used. Here, also the starting material used is commercially available and the synthetic step sequence is high yielding. The target synthesis was achieved with excellent diasteroselctivity. On the other side, the second major fragment **8a** was synthesized using $(DHQ)_2$PHAL mediated Sharpless AD and Mitsunobu inversion reaction. The starting material utilised, ethylene glycol is inexpensive and commercially available.

Here also, the synthetic approach illustrated has noteworthy potential to perform stereochemical manipulations at all the chiral centres and thus allows the synthesis of other analogues of cytospolide D. The merits of this synthesis are high regio- and enantioselectivity with high yielding reaction steps. All novel compounds were identified utilizing ^{1}H-NMR, ^{13}C-NMR, HRMS, %*ee* by chiral HPLC and $[\alpha]_D^{25}$ values.

5.2 Future scope

Few futuristic suggestions related with the present work are listed below:

1. The synthetic approach described in chapter 2, has significant potential for the syntheses of other derivatives of piperidine and the present synthesis is also free from complex enzymatic procedures. Here, the target compound was prepared with excellent diasteromeric excess.
2. The described synthetic strategy in chapter 3, started from non-chiral starting materials and organic transformations utilized herein, are applicable for further stereochemical variations at all the possible positions by simply altering the use of *R* or *S*- oxazolidinone during Evans methylation and $(DHQ)_2$PHAL or $(DHQD)_2$PHAL in Sharpless AD.
3. The synthetic approach described in chapter 4, also has significant potential for the variation at possible four chiral sites both in acid and alcohol fragment. The different analogues of cytospolide D could be easily accessed by using D or L - proline while performing cross aldol reaction and ligands during Sharpless AD.

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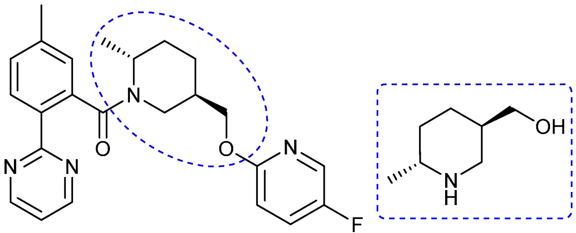
ChemistrySELECT Communications

Organic & Supramolecular Chemistry

An Asymmetric Synthesis of ((3*R*,6*R*)-6-Methylpiperidine-3-yl)methanol; A Piperidine Core Unit of Potent Dual Orexin Receptor Antagonist MK-6096

Amanpreet Kaur,[a] Ranjana Prakash,[a] and Satyendra Kumar Pandey*[a, b]

An asymmetric synthesis of ((3*R*,6*R*)-6-methylpiperidin-3-yl) methanol **2**, a potent dual orexin receptor antagonist MK-6096 **1** piperidine core unit, is described. The synthesis utilizes commercial available (*S*)-propylene oxide as a starting material and organocatalyzed asymmetric Michael addition reaction as key step.



MK-6096 **1**

2

Figure 1. Structure of Orexin receptor antagonists MK-6096 **1** and ((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol core unit **2**.

MK-6096 **1** is a potent, reversible, orally bioavailable and structurally distinct piperidine core unit **2** derived dual Orexin receptor antagonist (DORA) of Orexin 1 Receptor (OX$_1$R) and Orexin 2 Receptor (OX$_2$R), and currently in clinical trial III for treatment of insomnia.[1] Insomnia is the most common neuropsychiatric disorders and closely linked with a host of other diseases including obesity, depression, cardiovascular disease, chronic pain and cancer.[2] Current discovery of Orexin (hypocretin) neuropeptides promoting wakefulness by signaling through OX$_1$R and OX$_2$R receptors has opened up new avenues for the treatment of sleep disorders.[3] In functional cell based assays and radioligand binding MK-6096 **1** demonstrated potent antagonism and binding to both human OX$_1$R and OX$_2$R (11 nM in FLIPR, <3 nM in binding), with no significant off-target activities against a panel of >170 enzymes and receptors.

The asymmetric synthesis of piperidine core unit ((3*R*,6*R*)-6-methylpiperidin-3-yl) **2** is of considerable interest for pharmaceutical industries due to their utility in MK-6096 **1** used for treatment of insomnia and with an array of functionalities. Various methods for the synthesis ((3*R*,6*R*)-6-methylpiperidin-3-yl) **2** have been documented in the literature.[4–5] Campeau and co-workers[4] reported an enantioselective transamination reaction for the preparation of chiral α-methylpiperidines, and a diastereomeric purity upgrade provided by the crystallization of 2•CSA salt, and a chemoselective SN$_2$ reaction which is allowed for the facile preparation of the chiral piperidine core of MK-6096 **1**. More recently, Chung and co-workers[5] reported the total synthesis of MK-6096 **1** and its *trans*-3,6-disubstituted piperidine unit **2** employing a biotransamination[5a] and a *trans*-selective Mukaiyama aldol reaction[5b] as key steps. Therefore, it is highly desirable to develop a general and enantiopure synthetic route that provides a common pivotal intermediate from which 3,6-disubstituted piperidine motifs with desired stereochemical variations could be synthesized. As part of our ongoing research programme towards the asymmetric syntheses of bioactive compounds,[6] we became interested in developing a flexible approach to 3,6-disubstituted piperidine **2** skeleton having the diversity for derivatization. Herein, we are reporting an asymmetric synthetic approach for the ((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol **2** employing commercial available (*S*)-propylene oxide as a starting material and organocatalyzed asymmetric Michael addition[7] reaction as key step.

The retrosynthetic analysis for the synthesis of *trans*-3,6-disubstituted piperidine unit **2** is depicted in Scheme 1. We anticipated that the alcohol **2** could be accessible from alkene **3** using oxidative cleavage of double bond followed by reduction. The alkene derivative **3** in turn could be derived from N-Boc protected piperidine alcohol **4** via its conversion to corresponding iodide followed by subsequent thermal elimination. The alcohol derivative **4** could be constructed from silyl group protected nitro-alcohol derivative **5** through selective TBS deprotection, *O*-mesylation and Zn/AcOHmediated reduction of nitro to amine for cyclization and N-Boc protection. We envisaged that, the key intermediate nitro-alcohol derivative **5**

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J Am Oil Chem Soc (2020)
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ORIGINAL ARTICLE

Proton Nuclear Magnetic Resonance-Based Method for the Quantification of Epoxidized Methyl Oleate

Avneet Kaur[1] · **Neha Bhardwaj**[1] · **Amanpreet Kaur**[1] · **Km Abida**[1] · **Tejo Prakash Nagaraja**[1] · **Amjad Ali**[1] · **Ranjana Prakash**[1]

Received: 3 December 2019 / Accepted: 9 October 2020

Abstract Epoxidized methyl esters (EMO) with their high oxirane ring reactivity, acts as a raw material in the synthesis of various industrial chemicals including polymers, stabilizers, plasticizers, glycols, polyols, carbonyl compounds, biolubricants etc. EMO has been generally quantified by the gas chromatography (GC) and high-performance liquid chromatography (HPLC) techniques. Taking into the account of the limitations of these techniques, two qHNMR-based equations have been proposed for the quantification of EMO in the mixture of EMO and methylesters (MO). The validity of the proposed method was determined using standard mixtures of MO and EMO having different molar concentrations. The developed equations have been applied on the samples of EMO prepared from oleic acid in two-step process viz., esterification followed by epoxidation. The qHNMR-based EMO quantification showed acceptable agreement with the results obtained from HPLC analysis.

Keywords Oleic acid · Methyl oleate · Epoxidized methyl oleate · ^{1}H NMR quantification · Epoxidation · Fatty acid methyl esters

J Am Oil Chem Soc (2020).

Supporting information Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Introduction

^{1}H Nuclear Magnetic Resonance (NMR) spectroscopy is one of the most commonly used spectroscopy technique for the structure elucidation of the synthetic and natural organic compounds (Elyashberg, 2015). ^{1}H NMR has conjointly been applied as a quantitative analytical tool for the quantification owing to the fact that the signal intensity in ^{1}H NMR corresponds directly to the number of proton nuclei responsible for that signal (Rizzo and Pinciroli, 2005). Quantitative ^{1}H NMR (qHNMR) has emerged as an effective analytical tool for quality analysis in various fields such as natural drugs (Yan et al., 2016), food, and beverages (Cao et al., 2014), PLGA-based microspheres (Zhang et al., 2017), medicinal components (Göğer et al., 1999; Hollis, 1963), and dietary supplements (Phansalkar et al., 2017). Apart from qHNMR, HPLC and GC are widely used chromatographic techniques for the quantification of the molecules (Gelbard et al., 1995). GC with its destructive nature required complex operational procedures including handling of explosive H_2 gas, volatile substances, and mass spectra for product conformation (Monteiro et al., 2008). On the other hand, in the case of HPLC, requirement of reference standards, HPLC grade solvents, specific detector for the compound of interest, and equilibration of the columns have made the technique costly and time consuming (Sun et al., 2017). The limitations of both the chromatographic techniques can be overcome by qHNMR as it is rapid technique with no specific requirement of reference standard and offers recovery of the analyte after analysis (Cerceau et al., 2016). Moreover, the amount of solvent (deuterated $CDCl_3$, DMSO, D_2O) required for each qHNMR analysis is minimum (~0.5 mL) as compared to that for HPLC and GC methods.

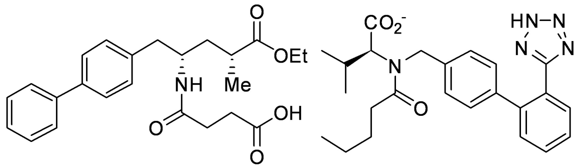
Organic & Supramolecular Chemistry

Enantioselective Total Synthesis of Sacubitril

Amanpreet Kaur,[a] Anju Gehlawat,[a] Ranjana Prakash,[a] and Satyendra Kumar Pandey*[a, b]

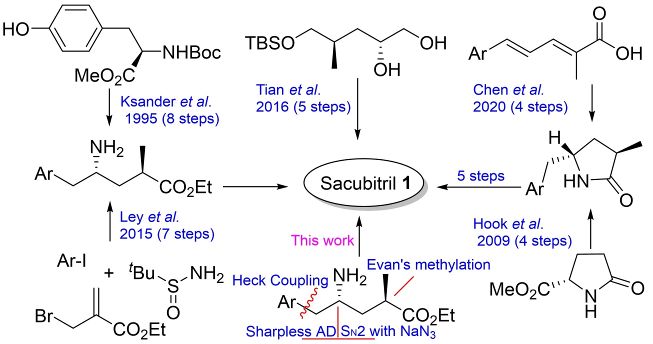
An efficient enantioselective approach of Sacubitril **1** (a NEP inhibitor) which is used as a combination drug with Valsartan to treat heart failure, is described. The synthesis features the Evan's asymmetric alkylation, Sharpless asymmetric diydroxylation (AD) and Heck coupling reactions as key steps.

In the early 1990s, Ksander and co-workers developed an active pharmaceutical compound Sacubitril (AUH-377) **1** which is a pro drug neprilysin inhibitor (Figure 1).[1] Combinations of Sacubitril **1** with the angiotensin II receptor-blocker Valsartan **2** by co-crystallization are known as supramolecular complex LCZ696 which was developed by Novartis for the treatment of heart failure (HF).[2] A first-in-class combination drug LCZ696 (brand name Entresto) was approved by FDA in 2015 and is used to reduce the risk of cardiovascular death and hospitalization for HF in patients with reduced ejection fraction and chronic HF (NYHA Class II–IV).[3] Sacubitril **1** has been a synthetic target of significant interest due to its immense medicinal importance and unique structure with an array of functionalities. Architecturally, it is a α-methyl-γ-amino-δ-biphenyl valeric acid derivative bearing two stereogenic centers. Fascinated by the biological activities, several asymmetric syntheses of Sacubitril **1** have been known in the literature (Scheme 1).[1,4] Most of the synthetic approaches employed chiral pool starting materials. More recently, Chen and co-workers disclosed the highly regio- and enantioselective hydrogenation of conjugated α-substituted dienoic acids using Trifer-Rh complex for the synthesis of chiral α-substituted γ,δ-unsaturated acids and its successful application to the total synthesis of sacubitril.[4a] In continuation of our ongoing research work intending towards the asymmetric syntheses of bioactive compounds,[5] we became interested in developing a novel and efficient approach towards the synthesis of Sacubitril **1** employing Evan's asymmetric alkylation, Sharpless AD and Heck coupling as key reaction steps.



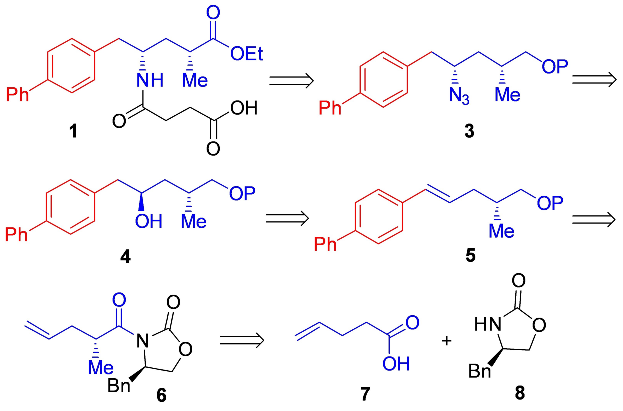
Sacubitril **1**   Valsartan **2**

Figure 1. Structure of Sacubitril **1** and Valsartan **2**.



Scheme 1. Previous and our work on the synthesis of sacubitril.

Our synthetic route for the asymmetric synthesis of Sacubitril **1** was envisioned *via* the retrosynthetic analysis as displayed in Scheme 2. The azide derivative **3** was envisioned to serve as a synthetic intermediate from which Sacubitril **1** could be synthesized *via* deprotection of primary alcohol followed by ethyl ester formation, reduction of azide and



Scheme 2. Retrosynthetic approach for Sacubitril **1**.

---

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Enantioselective synthesis of C1-C4 and C5-C14 fragments of cytospolide D

Amanpreet Kaur,[a] Anju Gehlawat,[a] Ranjana Prakash,[a] and Satyendra Kumar Pandey*[a,b]

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[b]*Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi-221 005, India*
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Dedicated to Prof. Peter Alan Jacobi in recognition of his seminal contributions to so many aspects of organic chemistry

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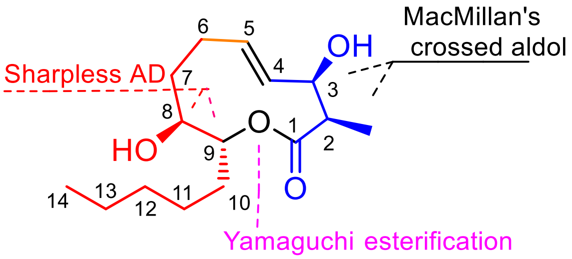
Abstract

A convergent approach for the synthesis of the two key fragments (C1-C4 and C5-C14) of cytospolide D is described. Key transformations include MacMillan's crossed aldol, Sharpless asymmetric dihydroxylation (AD) and Mitsunobu inversion reactions.



Cytospolide D

Keywords: Cytospolide, Sharpless AD, MacMillan's crossed aldol, Mitsunobu inversion, Yamaguchi esterification.