Total Synthesis of Biologically Active Natural Products Involving Asymmetric Induction Using Chiral Catalysis

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 "**Total Synthesis of Biologically Active Natural Products Involving Asymmetric Induction Using Chiral Catalysis**" being submitted by Suraksha in the fulfillment of the requirement for the award of the Degree of Doctor of Philosophy to the School of Chemistry and Biochemistry, Thapar University, Patiala, is a authentic record of candidate's own work carried out by her under my 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 "**Total Synthesis of Biologically Active Natural Products Involving Asymmetric Induction Using Chiral Catalysis**" in partial fulfillment of the requirement for the award of the Degree of Doctor of Philosophy, School of Chemistry and Biochemistry, Thapar University, Patiala, is an authentic record of my own work carried out under the supervision of Dr. Satyendra Kumar Pandey, Associate Professor, School of Chemistry and Biochemistry, Thapar University, 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

Acknowledgements

I humbly prostrate myself before the Almighty God for his grace and enduring blessings which enabled me to complete this work successfully with my full satisfaction.

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Despite all this co-operation rendered generously by one and all, I am solely responsible for any and all the errors and short comings of this dissertation.

Suraksha

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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 "**Total Synthesis of Biologically Active Natural Products Involving Asymmetric Induction Using Chiral Catalysis**" is divided into four chapters.

Chapter 1: A brief account of Trost's dynamic kinetic asymmetric transformation (DYKAT), Jacobsen's hydrolytic kinetic resolution (HKR), Sharpless asymmetric dihydroxylation (AD) and organocatalyzed aldol reactions.

Chapter 2: Stereoselective approaches towards the synthesis of marine natural products (+)-serinolamide A and (-)-haliclamide. This chapter is divided into two sections.

Chapter 3: Stereoselective approaches towards the synthesis of 2,5-disubstituted-3-oxygenated tetrahydrofuran and 2,3,4,6-tetrasubstituted pyran and their applications to the total synthesis of (+)-petromyroxol and (+)-phomonol, respectively. This chapter is divided into two sections.

Chapter 4: Stereoselective general approach towards the synthesis of functionalized *γ*- and *δ*-lactones skeleton and its applications to the total synthesis of (+)-*epi*-muricatacin and (-)-6-acetoxy-hexadecanolide, respectively.

Chapter 1: A brief account of Trost's dynamic kinetic asymmetric transformation (DYKAT), Jacobsen's hydrolytic kinetic resolution (HKR), Sharpless asymmetric dihydroxylation (AD) and organocatalyzed aldol reactions

Asymmetric synthesis is a powerful tool that allows the synthesis of enantio- and diastereomerically pure natural products as well as natural product-like bioactive derivatives. In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents either employing chiral transition-metal complexes or chiral organocatalysts.

A number of transition metal-mediated reactions such as Trost's DYKAT, Sharpless AD and Jacobsen's HKR have emerged as a powerful tool for asymmetric synthesis. A common feature of most of these processes is the phenomenon of ligand acceleration, wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand. This causes the reaction to be funneled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo-, regio- and stereoselectivity of the above reactions in a profound way.

Palladium-catalyzed DYKAT process has proven to be a powerful tool for the construction of stereogenic centers. Asymmetric allylic alkylation (AAA) reaction of butadiene monoepoxide was unambiguously illustrated by Trost[1] in which racemic mixture was converted, in high yield and enantioselectivity, into enantiomerically pure product. This deracemisation of butadiene monoepoxide in highly regio- and enantioselective fashion in presence of palladium catalysed Trost's DYKAT with (*S*,*S*)-DACH(1,2-Diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphino-1-naphthoyl)) and $[\eta^3\text{-}C_3H_5PdCl]_2$, phthalimide and base Na_2CO_3 provided asymmetric allylic alkylation (AAA) derivative phthaloyl alcohol as a single enantiomer with 99% *ee*.

The importance of enantiomerically pure epoxides in organic synthesis arises because the high reactivity of epoxides which allows straightforward elaboration to useful functionality, often with generation of new carbon-carbon bonds with retention of stereochemical integrity. The Jacobsen's HKR[2] of terminal epoxides catalyzed by chiral salen/Co(III)-OAc complex has become a standard method for the preparation of a variety of terminal epoxides and 1,2 diol in enantioenriched form. In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

The osmium tetroxide mediated dihydroxylation of alkenes is a basic organic reaction, and its catalytic asymmetric form *i.e* Sharpless AD[3] has proven to be a powerful method for enantioselective synthesis. $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL are the most commonly used chiral ligands for Sharpless AD.

Organocatalysis is an emerging and fast-moving field in asymmetric synthesis. Proline has been shown to be an effective organocatalyst in many asymmetric transformations such as aldol, Mannich and Michael reactions. MacMillan successfully reported the proline catalysed enantioselective direct aldol reactions of α- oxyaldehydes.[4]

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

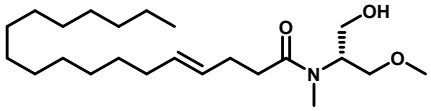
1. Asymmetric total synthesis of bioactive natural product (+)-serinolamide A employing Trost's DYKAT.

2. Asymmetric synthesis of bioactive natural product (+)-petromyroxol employing Sharpless AD, intramolecular S_N2 cyclization and stereoselective Grignard reaction.

3. Asymmetric total synthesis of bioactive natural product employing Jacobsen's HKR.

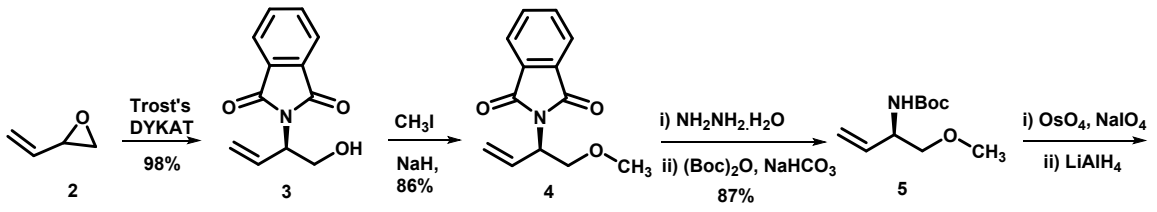
Chapter 2: Stereoselective approaches towards the synthesis of marine natural products (+)-serinolamide A and (-)-haliclamide. This chapter is divided into two sections.

Section A: Enantioselective total synthesis of (+)-serinolamide A, a marine natural product



(+)- Serinolamide 1

The endocannabinoid lipid (+)-serinolamide A **1** was isolated from the marine cyanobacteria *Lyngbya majuscula* collected in Papua New Guinea, and represents the newest addition to the known cannabinomimetic natural products.[5] (+)-Serinolamide A **1** showed selectivity for the CB_1 cannabinoid receptor (K_i = 1.3 μM, >5-fold) and exhibits moderate agonist effect. The synthesis of (+)-serinolamide A **1** started from the commercially available racemic starting material butadiene monoepoxide **2**, which was subjected to regio- and enantioselective epoxide opening with phthalimide in presence of palladium catalysed Trost's DYKAT with (*S*,*S*)-DACH, [η^3-$C_3H_5PdCl]_2$ and base Na_2CO_3 furnished asymmetric allylic alkylation (AAA) derivative phthaloyl alcohol **3** as a single enantiomer.[1]



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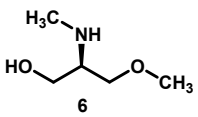
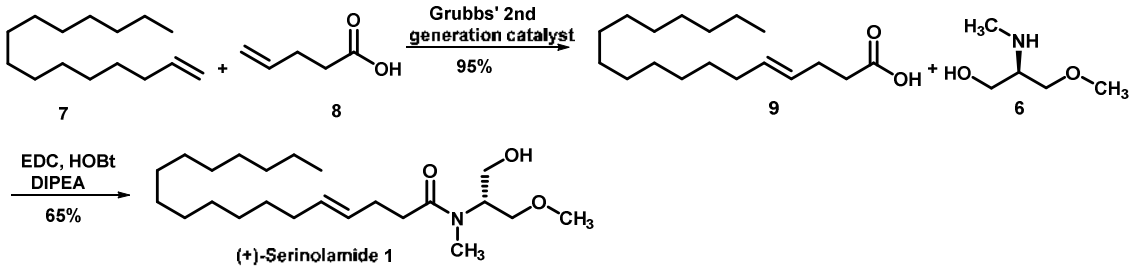


6

With enantiomerically pure alcohol **3** in hand, we then subjected it to *O*-methylation with MeI in presence of NaH which afforded the methyl ether **4.** One pot cleavage of phthalimide group of (*R*)-**4** with hydrazine monohydrate followed by treatment with $(Boc)_2O$ furnished the Boc

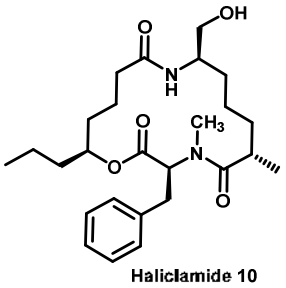
protected derivative (*R*)-**5**. Terminal olefin in **5** was subjected to $OsO_4/NaIO_4$ mediated oxidative cleavage followed by concomitant reduction of aldehyde and *N*-Boc group with $LiAlH_4$ under reflux condition afforded the serinol derivative (*R*)-**6** which was used for coupling with acid **9** without purification.



On the other hand, the cross-metathesis[6] was undertaken with confidence between pentadec-1-ene **7** and 4-pentenoic acid **8** in presence of a small amount (5 mol %) of Grubbs' second generation catalyst to yield *E*-olefin **9**. Finally acid amine coupling was carried out between **6** and **9** in presence of EDC, HOBt and DIPEA which afforded the target compound (+)-serinolamide A **1** in excellent yield.

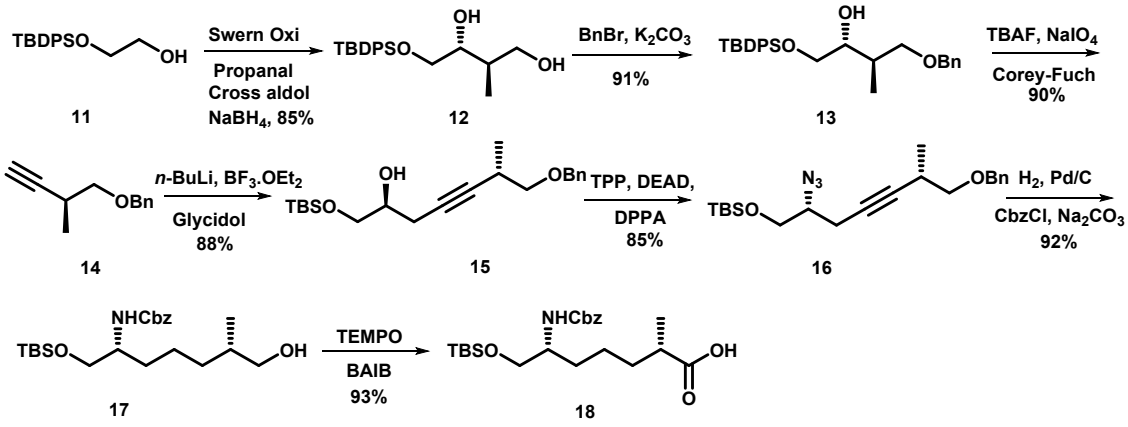
Section B: Total synthesis of haliclamide, a marine natural product

In 2001, Randazzo and co-workers reported the isolation of a novel macrocycle, haliclamide **10** from the marine sponge *Haliclona sp*. collected in the waters off Vanuatu Island.[7] Haliclamide **10** has been shown to possess potent *in vitro* antitumor activity against the human bronchopulmonary non-small cell lung carcinoma cell line NSCLC-N6 {IC_{50} = 4 μg/mL (8.7 μM)}.

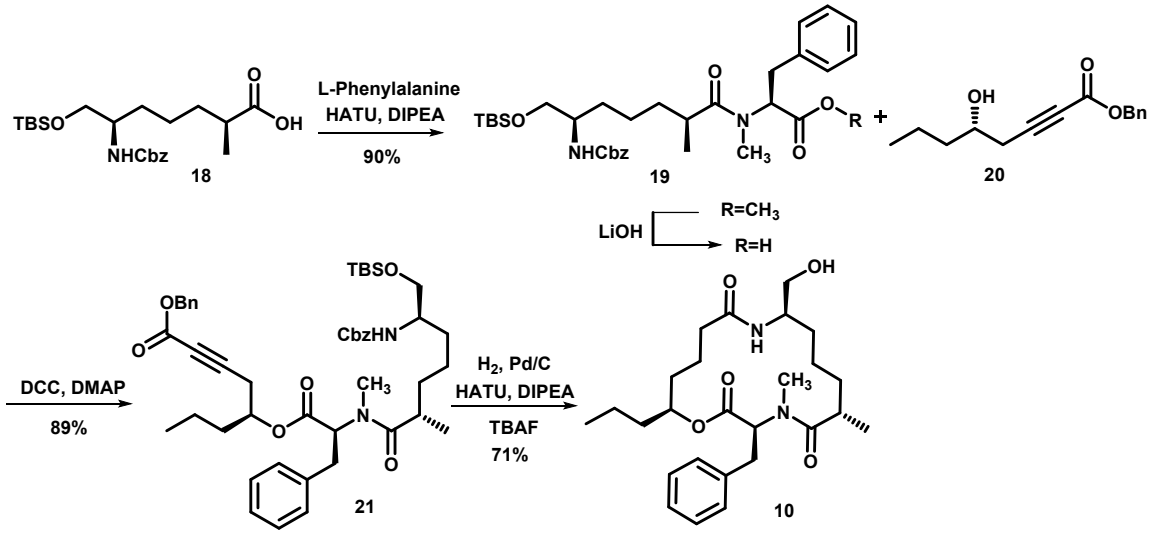


The synthesis of key fragment **18** began with monosilylated ethylene glycol **11** which was subjected to MacMillan cross aldol reaction followed by reduction with $NaBH_4$ to afford 1,3-diol derivative **12**.[4] Treatment of 1,3-diol **12** with K_2CO_3 and BnBr in acetone under reflux condition successfully furnished the monobenzylated derivative **13**. Synthesis of acetylene

derivative **14** from alcohol **13** were carried out by a process including silyl deprotection, $NaIO_4$ mediated oxidative cleavage and Corey-Fuchs protocol[8] in quantitative yield.



The lithium acetylide of acetylene derivative **14** was then treated with (*S*)-glycidol silyl ether[9] under the Yamaguchi-Hirao conditions[10] to deliver the homopropargylic alcohol **15** which was converted into azide **16** under Mitsunobu conditions.[11] The formation of carbamate moiety **17** from azide derivative **16** was rationalized by hydrogenation and subsequent treatment with benzyl chloroformate to afford the compound **17**. Finally, TEMPO/BAIB mediated oxidation of the primary hydroxyl group of **17** provided the key intermediate acid derivative **18** in good yield.

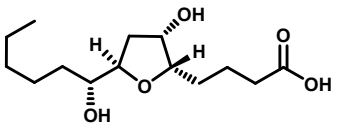


First intermolecular coupling was carried out between acid derivative **18** and *N*-methyl-L-phenylalanine derivative under HATU/DIPEA[12] conditions which afforded the amide **19**. Saponification of the methyl ester **19** with LiOH and subsequent treatment of the acid under

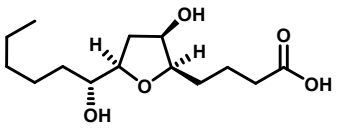
Steglich esterification conditions with alcohol derivative **20** furnished compound **21**. Concomitant deprotectionof Cbz, hydrogenolysis of ester and alkyne reduction of compound **21** were carried out *via* hydrogenation and subsequent macrolactamization[13] using HATU in THF in the presence of the Hunig's base and desilylation afforded haliclamide **10** in good yield.

Chapter 3: Stereoselective approaches towards the synthesis of 2,5-disubstituted-3-oxygenated tetrahydrofuran and 2,3,4,6-tetrasubstituted pyran and their applications to the total synthesis of (+)-petromyroxol and (+)-phomonol, respectively. This chapter is divided into two sections.

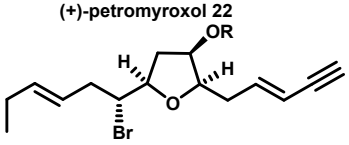
Section A: Enantioselective approach towards the total synthesis of 2,5-disubstituted-3-oxygenated tetrahydrofuran and its application to the total synthesis of (+)-petromyroxol



(+)-petromyroxol 22

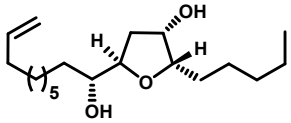


iso-petromyroxol 23



trans-Kumausyne (24, R = Ac)

trans-Deacetylkumausine (25, R = H)

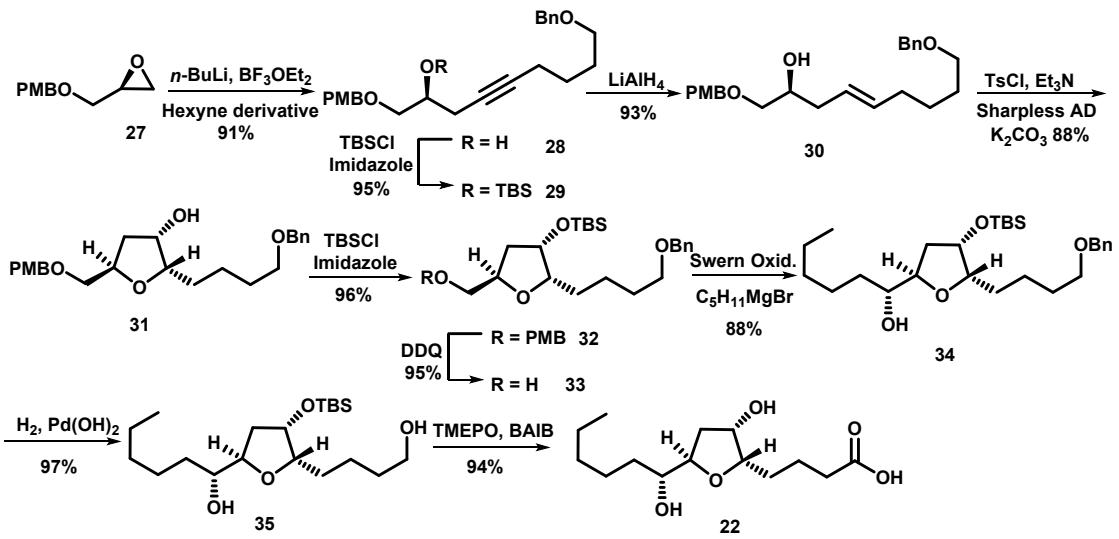


Anthelmintic oxylipid 26

Petromyroxol **22**, *iso*-petromyroxol **23**, *trans*-(-)-kumausyne **24**, *trans*-(+)-deacetylkumausyne **25** and anthelmintic oxylipid **26** marine natural products are few examples of dihydroxytetrahydrofuran from the acetogenin family.[14] The novel dihydroxylated THF enantiomers (+)-petromyroxol **22**[15a] and *iso*-petromyroxol **23**[15b] were recently isolated by Li, W. and co-workers from water conditioned with larvae of the sea lamprey, *Petromyrzon marinus* L. (+)-Petromyroxol **22** has been a synthetic target of considerable interest due to its potent olfactory activity in the concentration range of 0.01-1 μM and with an array of functionalities.

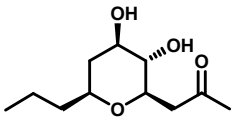
The synthesis of (+)-petromyroxol **22** commenced with conversion of epoxide **27**[16] into alkyne alcohol **28** with lithium acetylide prepared from the benzyl protected alkyne in presence of boron trifluoride etherate. Protection of free alcohol with TBSCl (**28**→**29**), then reduction with $LiAlH_4$ in diglyme proceeded smoothly and concomitant deprotection of silyl ether during acidic work-up furnished the *E*-olefin **30**. The free hydroxyl group of **30** was subjected to *O*-tosylation which

on dihydroxylation with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ under the Sharpless asymmetric conditions[3] afforded the diol, which

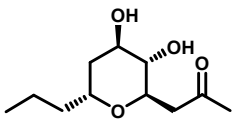


on further treatment with K_2CO_3 in MeOH furnished tetrahydrofuranyl alcohol **31**. With tetrahydrofuranyl alcohol **31** in hand, we then subjected it to imidazole-promoted protection with TBSCl and selective deprotection of the PMB ether with DDQ afforded the tetrahydrofuranyl alcohol **33** in excellent yield. Oxidation of alcohol derivative **33** under Swern conditions and subsequent treatment of aldehyde with *n*-pentyl magnesium bromide afforded **34** as the major product.[17] The desired major isomer **34** was subjected to debenzylation under 1 atm. pressure in presence of catalytic amount of $Pd(OH)_2$ which afforded the diol **35**. Selective oxidation of primary alcohol and concomitant cleavage of the silyl ether was achieved by treatment of diol **35** with a catalytic amount of TEMPO[18] and excess bis(acetoxy)-iodobenzene (BAIB) which furnished the target compound (+)-petromyroxol **22**.

Section B: Enantioselective approach towards the total synthesis of 2,3,4,6-tetrasubstituted pyran and its application to the total synthesis of (+)-phomonol



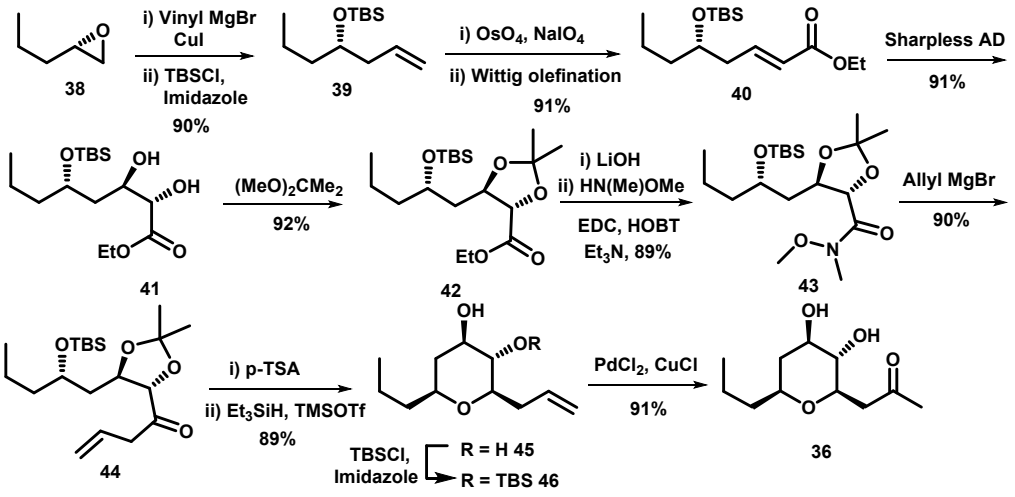
Phomonol 36



6-*epi*-Phomonol 37

In 2010, Shen and co-workers[19] reported the isolation of a novel 2,6-*cis*-disubstituted tetrahydropyran, phomonol **36** from the endophytic fungal strain *Phomopsis* sp. A 123. Synthesis

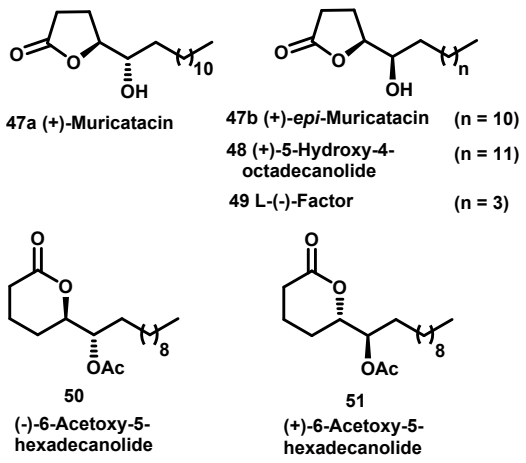
of phomonol **36** commenced with the commercially available (*S*)-1,2-epoxypentane **38** which was regioselectively opened with vinyl magnesium bromide and further treated with TBSCl to furnish silyl ether **39**. A one-pot oxidative degradation of terminal alkene **39** with OsO_4/$NaIO_4$ led to aldehyde which was extended to the unsaturated *E*-ester **40** using the stabilized Wittig reagent ethyl(triphenylphosphoranylidene)acetate. The Sharpless AD[3] of olefin **40** in presence of



$(DHQD)_2PHAL$ furnished vicinal diol **41** which was treated with 2,2- dimethoxy propane in presence of catalytic (±)-CSA successfully furnished the 2,2-*O*-isopropylidene derivative **42**. Saponification of the ethyl ester **42** with LiOH and subsequent treatment with *N,O*-dimethylhydroxylamine hydrochloride generated the Weinreb amide **43**. Indeed, treatment of the Weinreb amide **43** with AllylMgBr furnished the desired product **44**. One pot deprotection of acetonide and silyl ether with *p*-TSA furnished ketotriol which was subjected to stereoselective reductive etherification[20] with Et_3SiH/TMSOTf to produce 2,6-*cis*-disubstituted tetrahydropyran skeleton **45** as a single stereoisomer. The secondary alcohol of **45** was regioselectivly silylated with TBSCl to furnish *tert*-butyldimethylsilyl ether derivative **46** in quantitative yield. Finally, one pot Wacker oxidation[21] of terminal alkene and cleavage of the silyl ether was achieved by treatment of compound **46** with $PdCl_2$, CuCl under oxygen atmosphere and acidic workup which provided the natural product phomonol **36** in excellent yield.

Chapter 4: Stereoselective general approach towards the synthesis of functionalized *γ*- and *δ*-lactones skeleton and its applications to the total syntheses of (+)-*epi*-muricatacin and (-)-6-acetoxy-hexadecanolide, respectively.

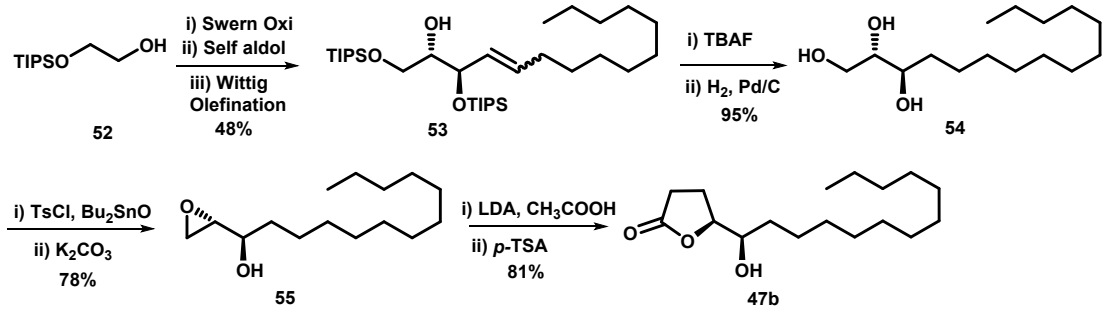
Enantioselective approach to *γ*-and *δ*-lactones: total synthesis of (+)-*epi*-muricatacin and (-)-6-acetoxy-hexadecanolide



In 1991, McLaughlin and co-workers reported the isolation of a novel *γ*-butyrolactone, Muricatacin **47a** from the seeds of *Annona muricate* L. (Annonaceae) commonly known as soursop or guanabana.[22] Interestingly, isomers muricatacin **47a** and (+)-*epi*-muricatacin **47b** have received interest due to their potent cytotoxic activity against certain cell lines.[23] (-)-Muricatacin analogue (+)-5-hydroxy-4-octadecanolide **48** exhibited cytotoxicity against esophageal cancer cells with IC_{50} values of 20 μg/mL.[24] (4*S,*5*R*)-4,5-dihydroxydecanoic acid **49** *γ*-lactone is also a natural compound, named as L-factor, isolated from the cultures of *Streptomyces griseus*, which reveal autoregulatory properties.[25]

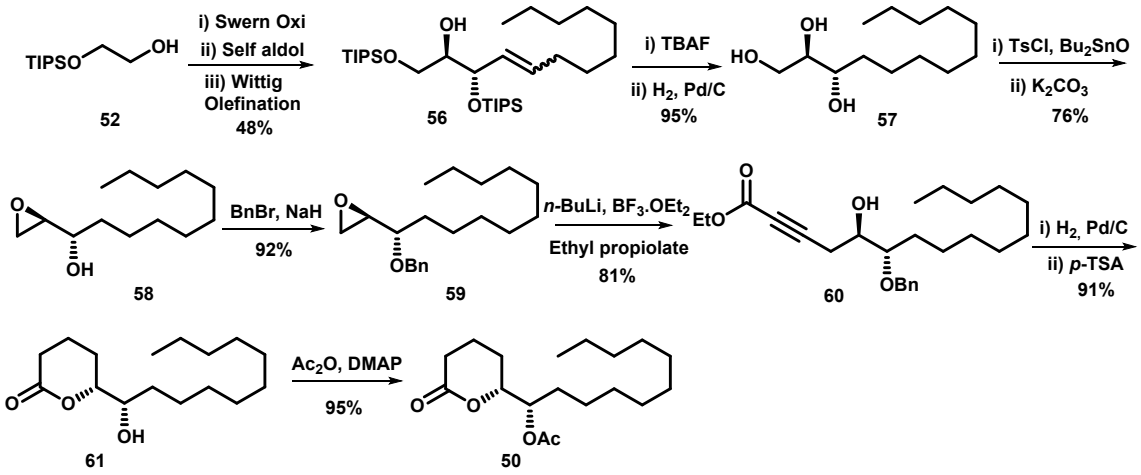
In 1979, Laurence and Pickett isolated the mosquito oviposition attractant pheromone, *erythro-6*-acetoxy-hexadecanolide **50** from apical droplets formed on the egg of the mosquito *Culex pipens*.[26]

Synthesis of (+)-*epi*-muricatacin **47b** began with readily available monosilylated ethylene glycol **52** which was subjected to a three step sequence including Swern oxidation followed by L-proline catalyzed MacMillan's self aldol reaction[4] and Wittig homologation reaction with phosphonium salt (undecyltriphenylphosphonium bromide) afforded olefin derivative **53**. Desilylation of silyl ether in **53** with TBAF and successive hydrogenation in the presence of a catalytic amount of Pd/C (10%) provided desired saturated triol **54**. Sulfonylation of 1,2,3-triol derivative **54** with Et_3N and TsCl in the presence of catalytic amount of Bu_2SnO at room temperature proceeded smoothly to furnish monotosylated derivative, which on treatment with



K_2CO_3 afforded epoxy alcohol derivative **55**. Finally, regioselective ring-opening of the epoxide **55** with dilithioacetate dianion[27] generated from acetic acid was performed smoothly to furnish acid derivative which was subsequently subjected to lactonization *via* catalytic *p*-TSA in benzene under reflux condition to access targeted molecule (+)-*epi*-muricatacin **47b** in good yield.

In another approach for synthesis of (-)-6-acetoxy-hexadecanolide **50**, the synthetic sequence began with monosilylated ethylene glycol **52** which was converted into olefin derivative **56** *via* a process including Swern oxidation, D-proline catalyzed MacMillan's self aldol reaction[28] and



Wittig homologation reaction with phosphonium salt (nonyltriphenylphosphonium bromide). Compound **56** was smoothly transformed into triol **57** *via* removal of silyl ether with TBAF followed by hydrogenation in the presence of 10% Pd/C under 1 atm of hydrogen. Then, treatment of 1,2,3-triol **57** with TsCl and Et_3N in presence of catalytic Bu_2SnO successfully furnished the monotosylated derivative which without further purification treated with K_2CO_3 in MeOH to afford epoxy alcohol derivative **58**. The free hydroxy group of **58** was subjected to *O*-benzylation with BnBr to furnish the benzylated derivative **59**. Next, the epoxide derivative **59** was regioselectively opened with a lithium salt of ethyl propiolate under the Yamaguchi-Hirao

conditions[10] to deliver the homopropargylic alcohol **60**. Subsequently, the lactone **61** was obtained from compound **60** by a two-step process involving hydrogenation and *p*-TSA catalysed lactonization. Finally, acetylation of the alcohol in lactone **61** with Ac_2O and DMAP furnished (-)-*6*-acetoxy-hexadecanolide **50** in good yield.

Characterization:

All the synthesized compounds were characterized by ^1H 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.

Conclusion:

We have described herein enantioselective approaches for the syntheses of (+)-serinolamide A, (-)-haliclamide, (+)-petromyroxol, (+)-phomonol, (+)-*epi*-muricatacin and (-)-6-acetoxy-hexadecanolide employed Trost's DYKAT, MacMillan's organocatalyzed aldol reaction, Sharpless AD and Jacobsen's HKR 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 ^1H-NMR, ^{13}C NMR, HRMS, % *ee* by chiral HPLC and $[\alpha]_D^{25}$ for all new chiral compounds.

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List of Publications

1. Enantioselective total synthesis of (+)-serinolamide A
   Suraksha Gahalawat and Satyendra Kumar Pandey*
   RSC Adv. **2015***, 5*, 41013-41016
2. An enantioselective approach to 2-alkyl substituted tetrahydroquinolines: total synthesis of (+)-angustureine
   Yuvraj Garg, **Suraksha Gahalawat** and Satyendra Kumar Pandey*
   RSC Adv. **2015**, *5*, 38846-38850
3. Total Synthesis of (+)-Petromyroxol, a Marine Natural Product
   Suraksha Gahalawat, Yuvraj Garg and Satyendra Kumar Pandey*
   Asian J. Org. Chem. **2015**, *4*, 1025-1029
4. Total synthesis of haliclamide
   Suraksha Gahalawat and Satyendra Kumar Pandey*
   Org. Biomol. Chem. **2016**, *14*, 9287-9293

5. Asymmetric total synthesis of phomonol

Suraksha Gahalawat and Satyendra Kumar Pandey*

Tetrahedron Letters **2017**, *58*, 2898-2900

6. Enantioselective Approach to *γ*-and *δ*-Lactones: Total Synthesis of (+)-*epi*-Muricatacin and (-)-6-Acetoxy-hexadecanolide

Suraksha Gahalawat and Satyendra Kumar Pandey

(**Manuscript Communicated**)

Conferences

1. Enantioselective total synthesis of (+)-Serinolamide A and (+)-Petromyroxol, marine natural products

   Suraksha Gahalawat and Satyendra kumar Pandey

   Poster presentation, International Conference on NDCS, 2015 at BITS Pilani.

2. Enantioselective total synthesis of (+)-Serinolamide A and (+)-Petromyroxol, marine natural products

   Suraksha Gahalawat and Satyendra Kumar Pandey

   Poster presentations at International conference FCASI 2016, University of Rajasthan, Jaipur, India.

3. Asymmetric Total Synthesis of Biologically Active Natural Products

   Suraksha Gahalawat and Satyendra Kumar Pandey

   Oral and poster presentations at Thematic Conference in Chemical Sciences (TC2S) - 2017, IIT Ropar.

   (Awarded best oral presentation)

CHAPTER 1

A brief account of Trost's dynamic kinetic asymmetric transformation (DYKAT), Sharpless asymmetric dihydroxylation (AD), Jacobsen's hydrolytic kinetic resolution (HKR), organocatalyzed aldol reactions.

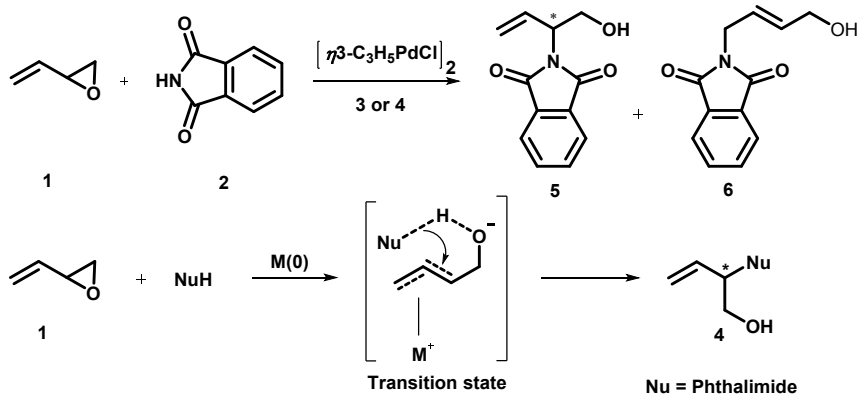
1.1 Trost's dynamic kinetic asymmetric transformation (DYKAT)

1.1.1 Introduction

Over the increasing demand for chiral compounds, as a common motif in biologically active compounds, the development of efficient methods to provide enantiomerically enriched products is of great current interest to both academia and industry.[1] Among the various methods employed for this purpose, asymmetric catalysis provides an especially practical entry into the chiral world in terms of chiral economy and environmental considerations.[2] Recently, B. M. Trost and co-workers have explored palladium catalyzed dynamic kinetic asymmetric transformation (DYKAT) for racemic butadiene monoepoxide,[3] a new approach for asymmetric allylic alkylation (AAA) which helps in the conversion of both the enantiomers of epoxide to a single enantiomeric product. The above strategy is explored in the context of asymmetric synthesis of vinylglycinol from racemic butadiene monoepoxide with phthalimide as the nitrogen source in quantitative yield with >99% *ee*. The asymmetric allylic alkylation of isoprene monoepoxide with phthalimide demonstrates the excellent ability of the newly designed chiral ligands to control both the regio- and enantioselectivity in the generation of a quaternary center asymmetrically.

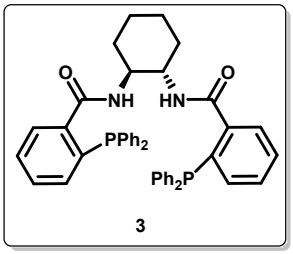
1.1.2 Optimization of experimental conditions

The optimization of the reaction conditions began with treating an equimolar mixture of 2-vinyloxirane **1** and phthalimide **2** with a catalyst synthesized *in situ* from π-allylpalladium chloride dimer and a triphenylphosphine ligand in THF which afforded the phthaloyl alcohol **5** and **6** in 4:1 ratio with 71% yield (Scheme 1). When the reaction was performed with ligand **3** or **4** (Figure 1) in THF gave **5** and **6** in 16:1 ratio with 77% *ee* (er 88.5:11.5), an improved



Scheme 1. Trost's DYKAT (Dynamic Kinetic Asymmetric Transformation)

regioselectivly attack at the more hindered allyl terminus.[3] The enantiomeric excess may be determined by NMR or HPLC methods. Treatment of the primary alcohol with (*S*)-mandelic



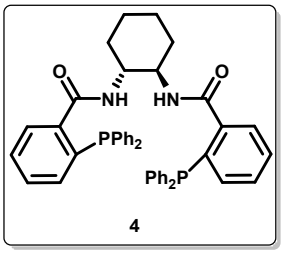
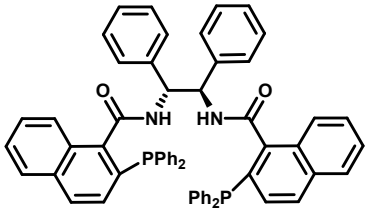
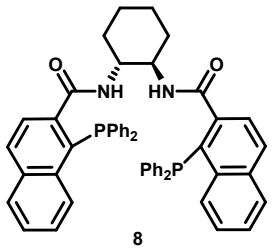
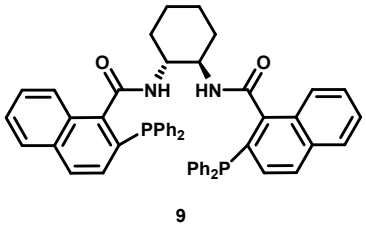


Figure 1: Structures of (*S*,*S*)- and (*R,R*) *N*,*N*'-1,2-Cyclohexanediylbis[2-(diphenylphosphino)-1-benza-amide].

acid furnished (*S*)-*o*-methylmandelate ester which allowed the determination of *de* by both chiral HPLC and ^{1}H NMR methods. In ^{1}H NMR, the doublet of doublet for the methylene group clearly distinguishes between **5** and **6**, at δ 4.387 for compound **4** and δ 4.515 for the compound **5**. However, the HPLC analysis (Dynamax, 15% EtOAc/hexane) first elutes the **6** followed by the compound **5**. On the other hand, HPLC (Chiracel OD, 90:10 heptane/2-propanol) also resolves the two enantiomers of alcohol **5**. Further, switching to another ligand containing diphenyl system **7** significantly improved the regioselectivity of **5** and **6** in the ratio of 19:1 and enantioselectivity of 83% *ee* (er of 91.5:8.5) (Figure 2).







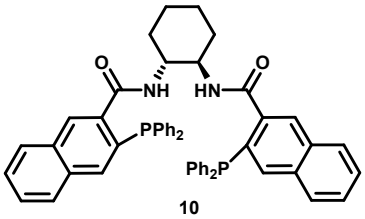


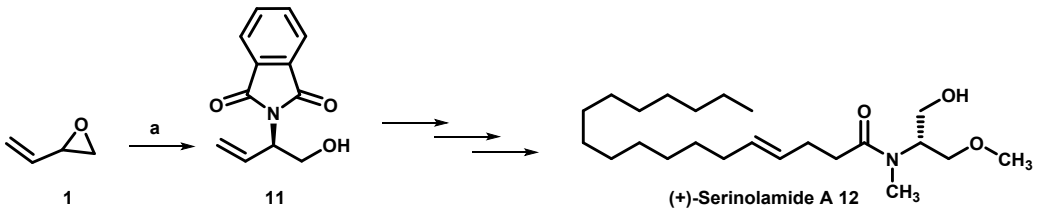
Figure 2. Structures of newly designed chiral ligands **7**-**10**

Also, a set of optimized condition using the palladium complex (2.5 mol %), ligands **8**-**10** (7.5 mol %) and sodium carbonate (5 mol %) as an initiator was selected (Figure 2). Among them, ligand **8** generally provides low enantiomeric excess in all the reactions, so was not used further in this process. The conformationally rigidified ligand **9** furnished alcohol **5** and **6** in 75:1 ratio of regioselectivity, enantioselectivity of 98% *ee* with 99:1 *er*, and with 99%

yield when the reaction was performed in dichloromethane as solvent. On the other side, the ligand **10** furnishes alcohol **5** in low enantioselectivity (55-66% *ee*), although the yield was satisfactorily (94-99%).

1.1.3 Application

We have applied the Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT) for the synthesis of (+)-serinolamide A as shown in Scheme 2. Deracemisation of butadiene monoepoxide **1** in highly regio- and enantioselective fashion in presence of palladium catalysed Trost's DYKAT with 1.2 mol % (*S*,*S*)-DACH and 0.4 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$, phthalimide and base Na_2CO_3 furnished asymmetric allylic alkylation (AAA) derivative phthaloyl alcohol **11** as a single enantiomer in 99% yield with 99% *ee* $\{[\alpha]_D^{25}$ +66.0 (*c* 1, $CHCl_3$) [Lit.[3] +65.9 (c 1, $CHCl_3$)]} which was subjected to functional group transformations to afford (+)-serinolamide A **12** in excellent yield.

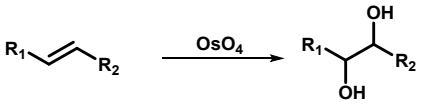


Scheme 2: *Reagents and conditions*: (a) Phthalimide, Na_2CO_3, 1.2 mol % (*S*,*S*)-DACH, 0.4 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$, dry CH_2Cl_2, rt, 14 h, 99%.

1.2 Sharpless asymmetric dihydroxylation (AD)

1.2.1 Introduction

The developments of a number of powerful catalytic asymmetric reactions[4] have always been in front of organic synthetic community due to their application in pharmaceuticals and agrichemicals. The osmium tetroxide-catalyzed Sharpless asymmetric dihydroxylation (AD) of prochiral olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and selective transformations in organic chemistry (Scheme 2). However, cost considerations make the stoichiometric reaction of OsO_4 with olefins uneconomical. The catalytic variants of the reaction, which employ relatively inexpensive reagents for the reoxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility. Inorganic cooxidants, such as sodium or potassium chlorate[5a] or hydrogen peroxide,[5b,c] were the first to be introduced, but these reagents lead to overoxidation. Good results were obtained with alkaline *tert*-butyl hydroperoxide, introduced by Sharpless and Akashi,[6] or *N*-methylmorpholine *N*-oxide known as Upjohn Process.[7] Later, Minato, Yamamoto, and Tsuji[8] introduced $K_3Fe(CN)_6$ and K_2CO_3 which provides a powerful system for the osmium catalyzed dihydroxylation of olefins. Sharpless AD was performed in two-phase conditions and addition of methanesulphonamide (a phase-transfer and general acid catalyst) leads to faster reactions for non-terminal olefins.



Scheme 2: Dihydroxylation of olefin

Initially chiral pyridine derivatives were used to induce enantioselectivity in the dihydroxylation which was failed due to the low affinity of these ligands for OsO_4.[9] Later, quinuclidine derivatives (Figure 3) were used due to their intrinsically higher affinity for

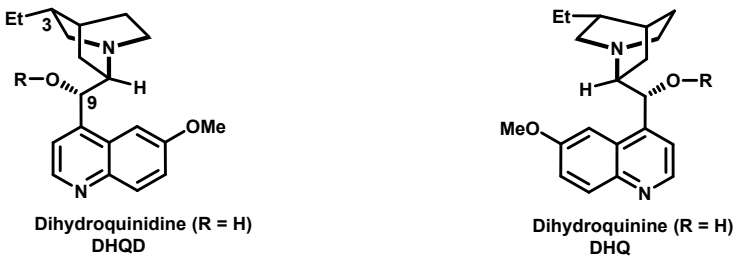
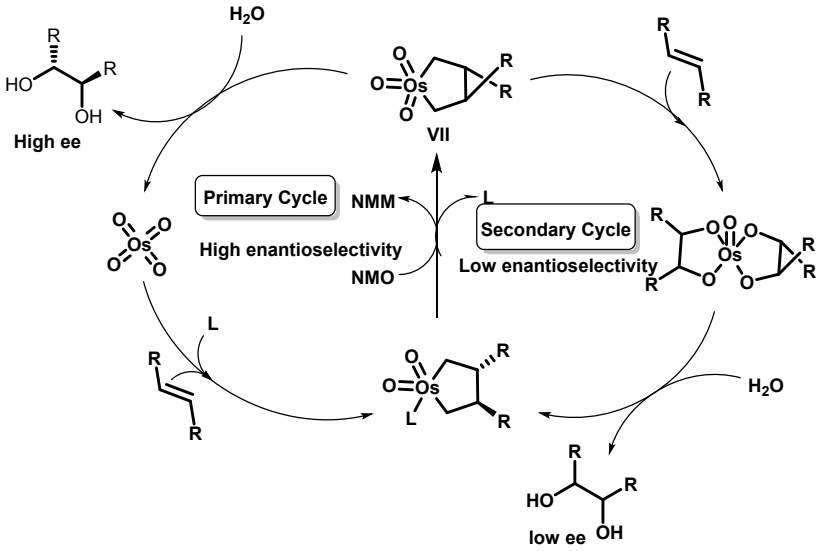


Figure 3: Structure of cinchona alkaloid ligands for AD

OsO_4[10] and moderate to good enantiomeric excess was achieved when acetate esters of cinchona alkaloids were used as chiral ligands.[9] Although, good enantioselectivity of

Sharpless AD was obtained in presence of bidentate diamine ligands,[11] but they form very stable chelate complexes with Os (VI) glycolate products and prevented *in situ* recycling of the Os and the ligand. Thus, OsO_4 and the cinchona alkaloid chiral ligands (Figure 3)[11] were used in stoichiometric amount for all the reactions

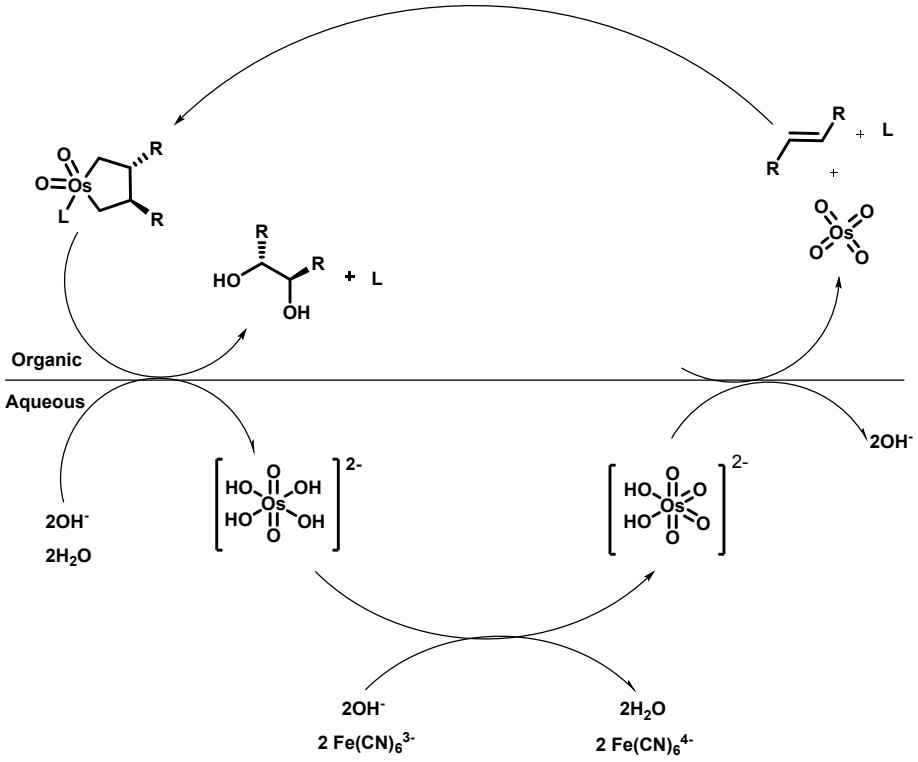
Initially, the asymmetric dihydroxylation was performed stoichiometrically in presence of cinchona alkaloids, later Marko and Sharpless[12] found that the process was catalytic when *N*-methylmorpholine *N*-oxide was used as a cooxidant.



Scheme 3. Two catalytic cycle for the AD reaction using NMO as the Co-oxidant

However, the enantiomeric excesses of the diol products were lower under above catalytic conditions due to the presence of a second catalytic cycle,[13] which exhibited low enantioselectivity (Scheme 3). A partial remedy found by Wai[13] for low enantioselectivity was the slow addition of the alkene while Kwong[14] discovered that second catalytic cycle was eliminated when the reaction was carried out under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant. In these situations there was no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. Since the osmylation of alkene takes place in organic layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os (VI) to the aqueous layer before its regeneration can occur and entry of the osmium glycolate into the second cycle was eliminated (Scheme 4).

Sharpless *et al.*[15] discovered that methanesulphonamide accelerated the hydrolysis of the osmium- (VI) glycolate product. In the presence of above additive, AD was carried out at 0 ^oC which has a beneficial effect on the selectivity and furthermore reaction time was dimished.



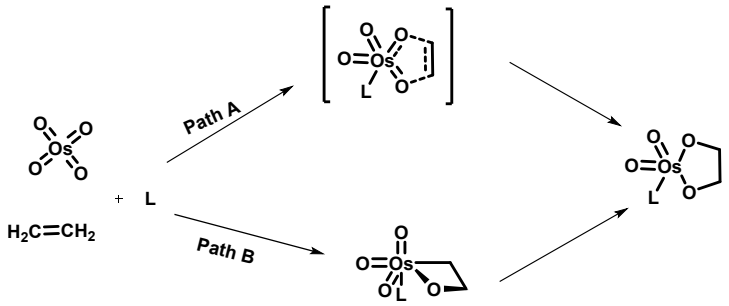
Scheme 4. Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the co-oxidant

Enantioselectivity of Sharpless AD was increased *via* ligands discovered by Hartung[15] (phthalazine core) and Crispino[16] (diphenylpyrimidine core) attached with two independent cinchona alkaloid units by a heterocyclic spacer (Figure 4).

Figure 4. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Figure 4)

1.2.2. The Mechanism of Asymmetric Dihydroxylation (AD)

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken[17a] and Criegee[18] originally proposed a concerted [3+2] pathway, (Scheme 5, Path A) while Sharpless *et al.*[17b] and Jorgensen *et al.*[17c] suggested a stepwise reaction which is initiated by a [2+2] like addition of the olefin across an Os=O bond (Path B), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.

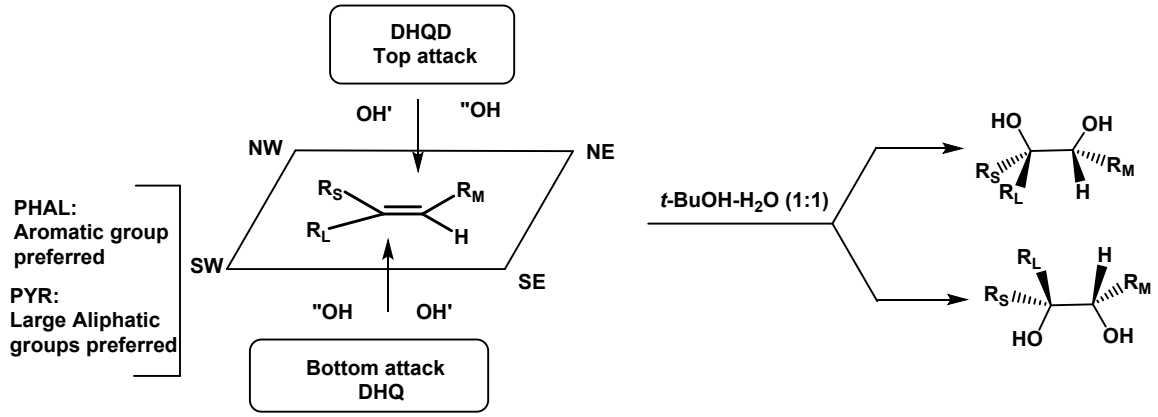


Scheme 5. Schematic presentation of the corrected [3+2] mechanism (Path A) and the stepwise [2+2] osmaoxetane mechanism (Path B).

Recently received support from theoretical studies, based on high activation barriers for formation and ring-expansion of osmaoxetanes, (3 + 2) mechanism was favoured.[19]

1.2.3 Empirical rules for predicting the face selectivity

After the mechanistic investigations, the face selectivity of the dihydroxylation was predicted using a 'mnemonic device' (Scheme 6).[20] According to a simple set of rules, the plane of the alkene was divided into the four quadrants. The SE quadrant is sterically inaccessible and hydrogen and hydrogen like small atom can be placed here. The NW quadrant, lying diagonally to the SE quadrant, is slightly spacious and groups larger than hydrogen can be placed. The NE quadrant appears to be quite spacious and medium group used to placed there. The SW quadrant is preferred for large ligand group, such as PYR ligands and aromatic groups in the case of PHAL ligands. An olefin which was placed according to the above constraints received the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives (Scheme 6).



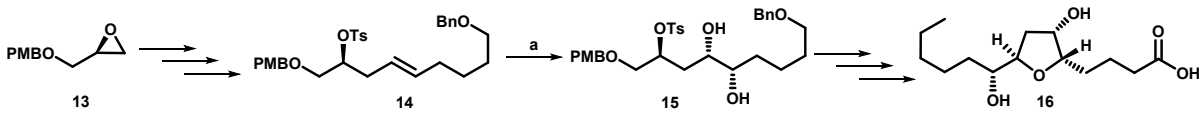
Scheme 6. The mnemonic device for predicting the face selectivity

1.2.4 Reaction Conditions

The Sharpless asymmetric dihydroxylation is performed in a 1:1 mixture of *t*-BuOH and water and the concentration of alkene substrate is usually 0.1 M.[15] The main reagents used in Sharpless AD are 0.2-0.4 mol % osmium tetraoxide, 1 mol % of ligand, 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 1 equivalent of methanesulphonamide and 3 equivalents of potassium carbonate. The combined organic layer is extracted with 3% aq. H_2SO_4 saturated with K_2SO_4 (ca. 40 mL/1g of ligand) and the PHAL ligand enters in the aqueous phase as the hydrogen sulphate salt and the solution can be reused directly for the subsequent AD reaction without further purification.

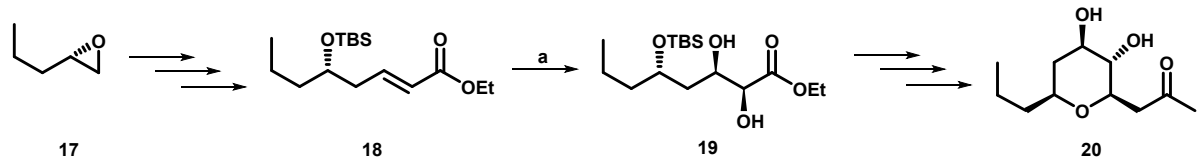
1.2.5 Applications

We have applied Sharpless asymmetric dihydroxylation (AD) for the synthesis of (+)-petromyroxol **16** and phomonol **20**. As depicted in Scheme 7, the synthesis of (+)-petromyroxol **16** commenced with epoxide **13** which was converted into *E*-olefin *via* standard organic transformations. The olefin **14** was subjected to dihydroxylation with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ under the Sharpless asymmetric conditions to afford the diol **15**, which on further functional group transformations furnished (+)-petromyroxol **16**.



Scheme 7: *Reagents and conditions*: (a) 0.5 mol % OsO_4, 1 mol % $(DHQ)_2PHAL$, $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, K_2CO_3, *t*-BuOH:H_2O 1:1 v/v, 0 °C, 24 h.

Synthesis of phomonol **20** as displayed in Scheme 8, commenced with the commercially available (*S*)-1,2-epoxypentane **17** which was converted into alkene derivative **18** *via* a number of organic transformations. The Sharpless AD of olefin **18** with OsO_4 and potassium ferricyanide as co-oxidant in presence of $(DHQD)_2PHAL$ furnished vicinal diol **19** in 91% yield as a single diastereoisomer. The diol **19** on further treatment with a number of standard organic reactions afforded phomonol **20**.

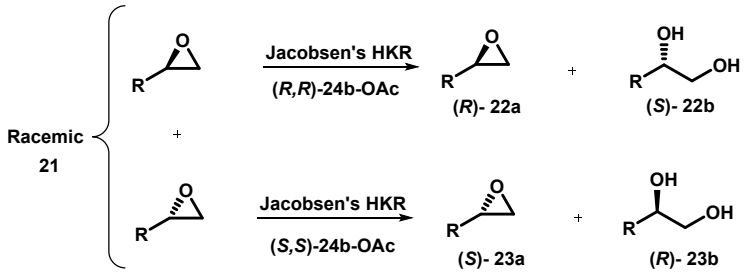


Scheme 8: *Reagents and conditions*: (a) 0.5 mol % OsO_4, 1 mol % $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0 °C, 12 h, 91%.

1.3 Jacobsen's hydrolytic kinetic resolution (HKR)

1.3.1 Introduction

In the last few decades, epoxide, a three-membered strained ring have attracted the synthetic community due to its high reactivity and availability in a large number of naturally occurring bioactive compounds.[21] The enatiopure terminal epoxides are versatile building blocks in organic synthesis, but no general and practical method was available for their synthesis in enantiomerically pure form. Jacobsen's HKR which was first reported in 1997 has emerged as as a powerful tool for the preparation both terminal epoxides and their corresponding diols in enantioenriched form.[22] Racemic epoxides **21** were converted into chiral epoxides **22a** and **23a** along with corresponding chiral 1,2-diols **22b** and **23b** in high enantiomeric excess using Jacobsen (salen) Co complex **24** (Scheme 9).



Scheme 9. Jacobsen's HKR of epoxide.

The Jacobsen's (salen) Co complex **24** (Figure 5) catalyzed the hydrolytic kinetic resolution of a variety of terminal epoxides in a highly efficient manner.[23] Therefore, the commercial synthesis of chiral epoxides such as propylene oxide, glycidyl ether and epichlorohydrin from racemic epoxides has been implemented successfully using Jacobsen's HKR by decreasing the cost of these chiral epoxides for suppliers.

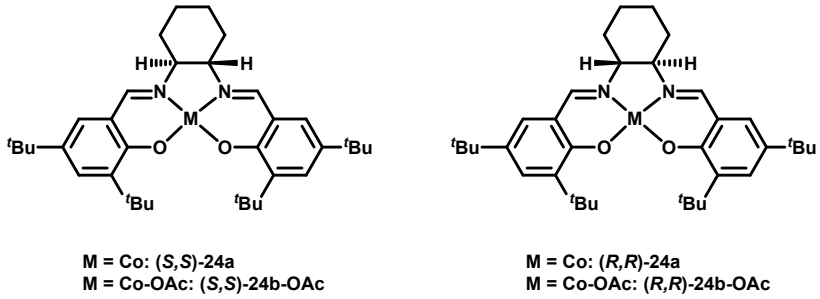


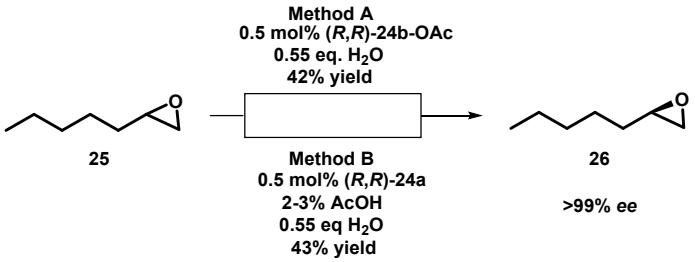
Figure 5. Structure of Jacobsen's catalysts.

1.3.2 Preparation of catalyst and general experimental conditions

Both the enantiomers of (salen)Co-II complex **24** are either commercially available or can be synthesized from the commercially available chiral ligands with $Co(OAc)_2$.[24] The Co(II) complex **24a** and **24b** (Figure 3) are inactive catalytically and requires the +3 oxidation state

of cobalt prior to the HKR *via* one-electron oxidation, produced an anionic ligand (salen)Co-III complex which can be achieved easily by aerobic oxidation using a mild Bronsted acid. Only water was not found to mediate oxidation reaction, but a screen of additives revealed that acetic acid was effective and the corresponding Co(III) precatalyst-**24-**OAc (Figure 5) was found to be efficient in HKR reactions because of its easy preparation and reactivity. Thus, two mole of Co(II) pre-catalyst, two mole of acetic acid and a half mole of oxygen were converted into two mole of Co(III) catalyst and one mole of water.

However, two useful methods for the formation of complex-**24**-OAc (Scheme 8) have been developed. Method A constitutes the isolation of **24**.OAc as crude solid before the HKR. A solution of Co(II) complex **24** in toluene (ca. 1 M solution) was mixed with acetic acid (2 equivalent) and subjected to open air for 30 min at room temperature during which the color of the reaction mixture changed from orange to dark brown. The resulting crude was concentrated *in vacuo* to remove the volatile materials to afford the **24**.OAc as a brown solid which can be used without further purification. Method B constitutes the *in situ* preparation of **24**.OAc using HKR conditions by making a suspension of Co(II) complex **24** and epoxide or with epoxide/solvent followed by addition of AcOH under an aerobic conditions. The catalyst synthesized by above two methods leads to approximately identical results when applied to 1-heptene oxide **25** (Scheme 10). Catalyst prepared by method B is preferable in these situations as it avoids an extra solvent removal step. However with less reactive substrates, catalyst prepared by method A was found to be more effective. Therefore, if HKR



Scheme 10. Development of HKR methods

did not afford epoxide in >99% *ee* with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed as an alternative.

Aside from the procedure for the preparation of **24**.OAc, the other reaction parameters in Jacobsen's HKR for optimization were catalyst loading and choice of solvents for different type of substrates. In most of cases, 0.55 equivalent of H_2O relative to racemic epoxide afforded the epoxide in >99% *ee*. The epoxides with less solubility in water could undergo resolution in high enantiomeric excess without the addition of solvent. While, the HKR of

high lipophilic epoxides provides chiral epoxides in high *ee*'s using water miscible organic solvents such as tetrahydrofuran (THF), isopropyl alcohol (IPA), or hexane-1,2-diol.

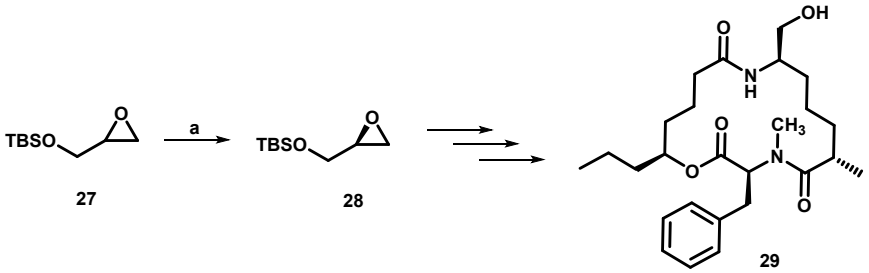
Generally, 1.0 equivalent of solvent relative to racemate was found to be sufficient for Jacobsen's HKR to a variety of substrates. However, the catalyst loadings in the amount of 0.5 mol % or less relative to racemic epoxide were found to be effective for most of the substrates, but saturated sterically hindered or unsaturated epoxides generally required up to 2 mol % of catalyst for achieving the complete resolution. Initially, the reaction generally started at 0 °C followed by stirring at room temperature for 12-18 h.

In the Jacobsen's HKR method a racemic terminal epoxide is treated with Jacobsen's (salen)Co(III)–OAc (**24b**) catalyst (Figure 5) in the presence of approx. half an equivalent of water either neat or with only approx. 10 mol% of a solvent to produce highly enantio-enriched epoxide and 1,2-diol in almost equal amounts (Scheme 9).

Thus, the salient features of the HKR method include the following: the high availability of racemic terminal epoxides; most of which are quite inexpensive; access to highly enantio-enriched products in close to theoretical yields; the low catalyst loading (0.2–2 mol %) and recyclability of HKR catalysts; the use of water as the nucleophile and the ease of Jacobsen's HKR products separation due to large polarity differences. Many chiral building blocks have been developed based on HKR technology such as propylene oxide, epichlorohydrin, methyl glycidate and 3-chloro-1,2-propanediol.[24]

1.3.3 Application

We have applied Jacobsen's hydrolytic kinetic resolution (HKR) for the synthesis of haliclamide **29**. The synthesis of haliclamide **29** as displayed in Scheme 11, commenced with the treatment of (±)-(*tert*-butyldimethylsilyl) glycidyl ether **27** with (*R,R*)-(salen)Co(II) catalyst **24a** under Jacobsen's HKR conditions to afford (*S*)-(*tert*-butyldimethylsilyl) glycidyl ether **28** in 48% yield with > 99% ee which was further subjected to standard organic transformations to furnish haliclamide **29**.



Scheme 11: *Reagents and conditions*: (a) **24a**, acetic acid, THF, H_2O, 0 °C to rt, 14 h, 48%.

1.4 Organocatalyzed aldol reactions

1.4.1 Introduction

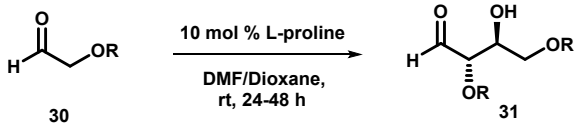
Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound. Recently, organocatalysis is one of the most powerful strtergy for the asymmetric synthesis of chiral molecules. Organocatalysts composed of carbon, hydrogen, nitrogen, phosphorus and sulfur but does not contain a metal atom. Apart from lots of "green" advantage, compared to metal catalysts, it also reduces the organic waste involved in chemical transformation and saves time and cost of manufacturing pharmaceutical leads.

Among various types of organocatalysts, L-proline, a naturally occurring cyclic amino acid, has been most extensively studied and catalyses various powerful asymmetric transformations such as α-functionalization, inter and intramolecular aldol reaction, Michael addition, mannich and Diels-Alder reactions. Proline is referred as a"universal catalyst" due to its diversity of organic transformations and high utility.

In 1971, intramolecular aldol reaction known as Hajos- Parrish-Eder-Sauer-Wiechert reaction was the first reaction where proline was used as a catalyst in organic transformation.[25] Later, Barbas and coworkers synthesized Wieland-Miescher ketone *via* proline catalyzed Robinson annulation reaction.[26]

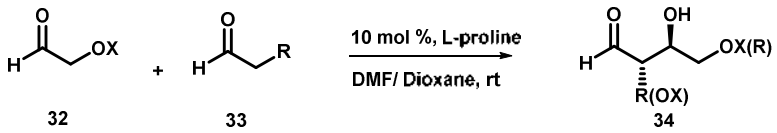
1.4.2 Macmillan's organocatalyzed direct aldol reactions of α-oxyaldehydes

In 2002, Macmillan disclosed an organocatalytic strategy for cross aldol reactions of α-alkyl-bearing aldehydes in a highly regioselective, diastereoselective, and enantioselective manner.[27] An important characteristic of this transformation was that the enantioenriched aldol aldehyde products did not undergo further aldol reactions. In 2004, Macmillan extended the above transformation to the self and cross aldol reaction of α-oxygenated aldehydes[28] as shown in Scheme 12 and 13 respectively. Macmillan examined the organocatalytic self coupling of α-oxyaldehydes **30** in presence of 10 mol % L-proline which provided the desired aldol products **31** with both *anti* aldol selectivity and excellent enantioselectivity (Scheme 12).



Scheme 12: Self-aldol reactions of protected glycoaldehydes. (R= TIPS, TBDPS, Bn, PMB, MOM, Ac, TBS).

Further, MacMillan performed cross-coupling between α-oxyaldehydes **32** and α-alkyl-substituted aldehydes **33** in presence of 10 mol % L-proline in DMF which afforded *anti* cross-aldol products **34** with good enantiomeric excess (Scheme 13).



Scheme 13: Cross-aldol reactions with protected glycoaldehydes. (R= Me, *i*-Pr; OX= OTIPS, OTBDPS, OBn).

1.4.3. The Mechanism of Aldol reaction

A general mechanism of proline catalyzed asymmetric self/cross aldol reaction is explained in Figure 6. The aldehyde **35** on reaction with proline generates enamine intermediate **36** which on nucleophilic addition to same or different aldehyde synthesizes self/cross imine

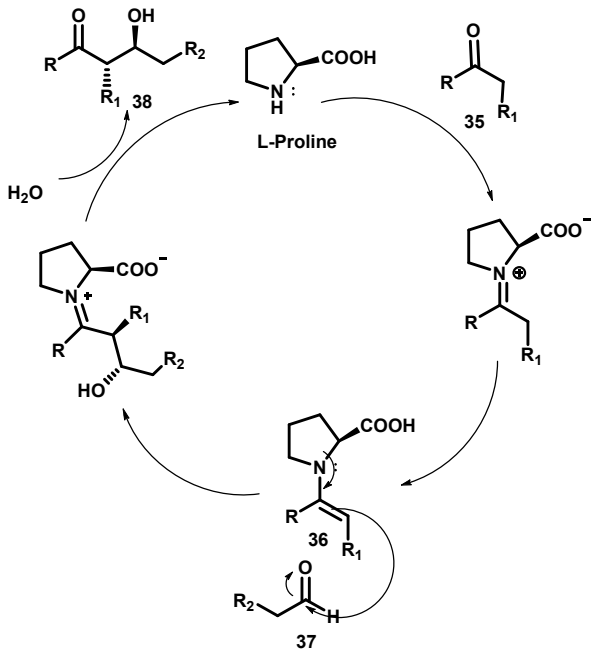


Figure 6. A general mechanism of proline-catalyzed self and cross aldol reactions

intermediate. Finally, the imine intermediate on hydrolysis with water furnish the β-hydroxyaldehyde derivatives **38** with simultaneous release of proline molecule.

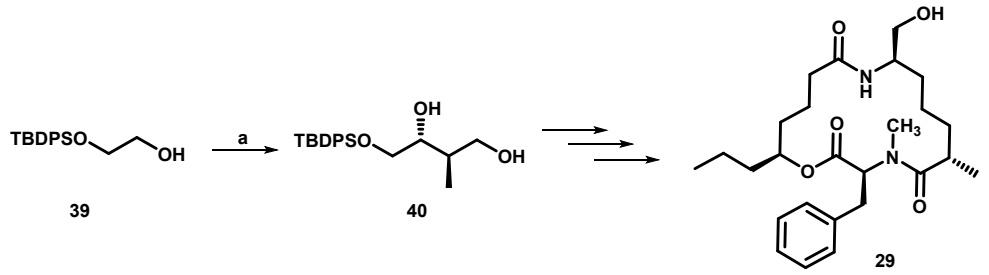
1.4.4 Reaction conditions

In cross aldol reaction, both acceptor (1 equivalent) and donor aldehydes (5 equivalents) in dioxane were kept at 4 ^{o}C. A solution of donor aldehyde in DMF or dioxane was added dropwise *via* syringe pump to a mixture of acceptor aldehyde and L-proline (0.1 equivalent) in DMF or dioxane at 4 ^{o}C and resulting suspension was stirred for 24-48 h at 4 ^{o}C.

Similarly, self aldol reaction of oxyaldehyde (1 equivalent) in presence of 10 mol % L-proline in DMF or dioxane was carried out at room temperature.

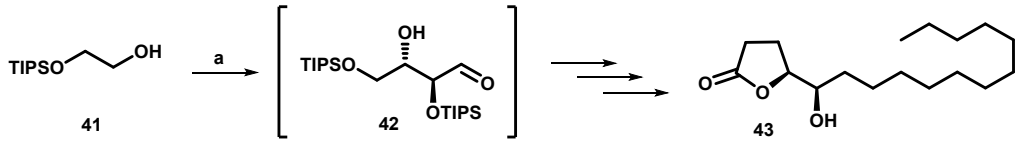
1.4.5 Applications

The synthesis of haliclamide began with readily available monosilylated ethylene glycol **39** which was subjected to a process involving L-proline catalyzed MacMillan's cross aldol reaction and reduction with $NaBH_4$ to afford 1,3 diol derivative **40** which was further subjected to standard organic transformations to furnish the haliclamide **29** (Scheme 14).



Scheme 14. *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC to rt, 2 h; ii) Propionaldehyde, 10 mol% L-Proline, dioxane, 4 ^oC, 48 h; iii) $NaBH_4$, MeOH, 0 ^oC to rt, 30 min, 85% (three steps).

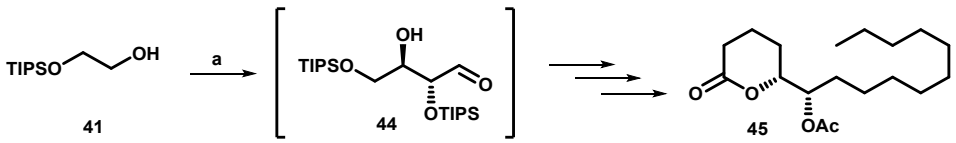
The synthesis of (+)-*epi*-muricatacin **43** (Scheme 15) began with monosilylated ethylene glycol **41** which was subjected to a two step sequence including Swern oxidation followed by L-proline catalyzed MacMillan's self aldol reaction to furnish the *anti*-diastereomer **42** as the



Scheme 15: *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC to rt, 2 h; ii) 10 mol % L-proline, dioxane:DMF (1:1, v/v), rt, 48 h, 72% (over two steps).

major product in 72% isolated yield. Aldehyde intermediate **42** was subjected to functional group manipulation to furnish (+)-*epi*-muricatacin **43**.

As shown in Scheme 16, the synthetic sequence began with **41** which was subjected to a process including Swern oxidation, D-proline catalyzed MacMillan's self aldol reaction to



Scheme 16: *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC to rt, 2 h; ii) 10 mol % D-proline, dioxane:DMF (1:1, v/v), rt, 48 h, 72% (over two steps).

furnish the *anti*-diastereomer **44** as the major product in 72% yield. Aldol aldehyde derivative **44** was converted into (-)-6-acetoxy-5-hexadecanolide **45** *via* a sequence of standard organic reactions.

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CHAPTER 2

Stereoselective approaches towards the synthesis of marine natural products (+)-serinolamide A and (-)-haliclamide. This chapter is divided into two sections.

2.1 Section A

Enantioselective total synthesis of (+)-serinolamide A, a marine natural product

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2.1.1 Introduction:

The endocannabinoid lipid (+)-serinolamide A **1** was isolated from the marine cyanobacteria *Lyngbya majuscula* collected in Papua New Guinea, and represents the newest addition to the known cannabinomimetic natural products.[1] (+)-Serinolamide A **1** showed selectivity for the CB_1 cannabinoid receptor (K_i = 1.3 μM, >5-fold) and exhibits moderate agonist effect (Figure 1). (+)-Serinolamide A **1** has been a synthetic target of considerable interest due to its long chain fatty acid bonded to a chiral serinol derivative with an array of functionalities.

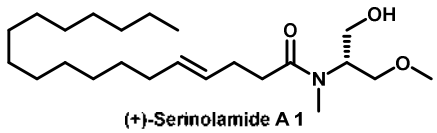


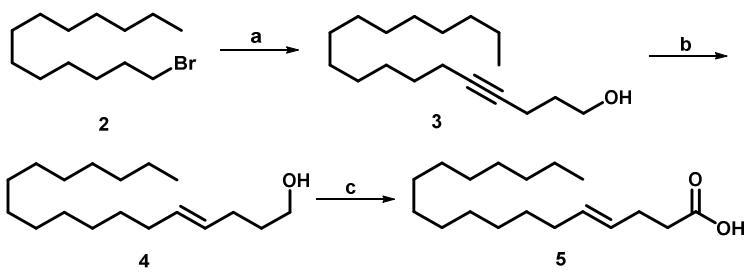
Figure 1. Structure of (+)-serinolamide A **1**.

2.1.2 Review of Literature:

There is only one synthesis of (+)-serinolamide A **1** has been documented in the literature which is described below.

Wang, Y. Q. *et al.* (2011)[2]

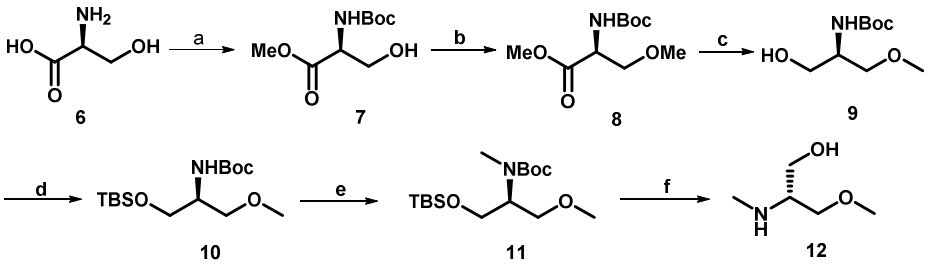
Y. Q. Wang and co-workers reported first total synthesis of (+)-serinolamide A **1** from L-serine in nine steps with 30% overall yield. The synthesis of the requisite coupling partner **5**



Scheme 1. *Reagents and conditions:* (a) Pent-4-yn-1-ol, *n*-BuLi, HMPA, THF, 86%; (b) $LiAlH_4$, diglyme, THF, 96%; (c) PDC, DMF, 92%.

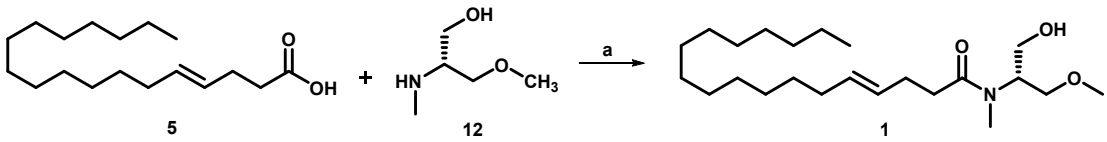
for acid amine coupling is described in Scheme 1. The synthesis began with coupling of pent-4-yn-1-ol and 1-bromotridecane **2** using *n*-BuLi in hexamethylphosphoramide (HMPA) and THF which furnished **3** in 86% yield. Reduction of alkyne **3** with $LiAlH_4$ in diglyme furnished the *E*-olefin **4** in 96% yield. Oxidation of **4** with PDC afforded the fatty acid **5** in 92% yield.

Synthesis of compound **12** as shown in Scheme 2, started from L-serine **6**, which was esterified using acetyl chloride in presence of methanol and subsequently subjected to amine protection with $(Boc)_2O$ to get compound **7** in 90% yield over two steps. Alcohol **7** was subjected to *O*-methylation with MeI in presence of Ag_2O which afforded the methyl ether **8** in 67% yield followed by reduction with $NaBH_4$ gave alcohol **9** in 85% yield. Treatment of alcohol **9** with TBSCl and imidazole produced silyl ether **10** in 91% yield. Next, amine **10** was treated with MeI/NaH to get the corresponding *N*-methylated compound **11** in 99% yield and finally deprotection with TFA furnished amine derivative **12**.



Scheme 2. *Reagents and conditions*: (a) CH_3COCl, CH_3OH; ii) $(Boc)_2O$, Et_3N, CH_3CN, 90%; (b) Ag_2O, CH_3I, acetone, 67% (over two steps); (c) $NaBH_4$, H_2O:CH_3OH 1:1, 85%; (d) TBSCl, imidazole, CH_2Cl_2, 91%; (e) NaH, CH_3I, THF, DMF, 99%; (f) TFA, CH_2Cl_2.

Finally, coupling of the acid **5** with amine **12** in the presence of EDC and HOBt under standard conditions afforded the natural product **1** in 82% yield (Scheme 3).



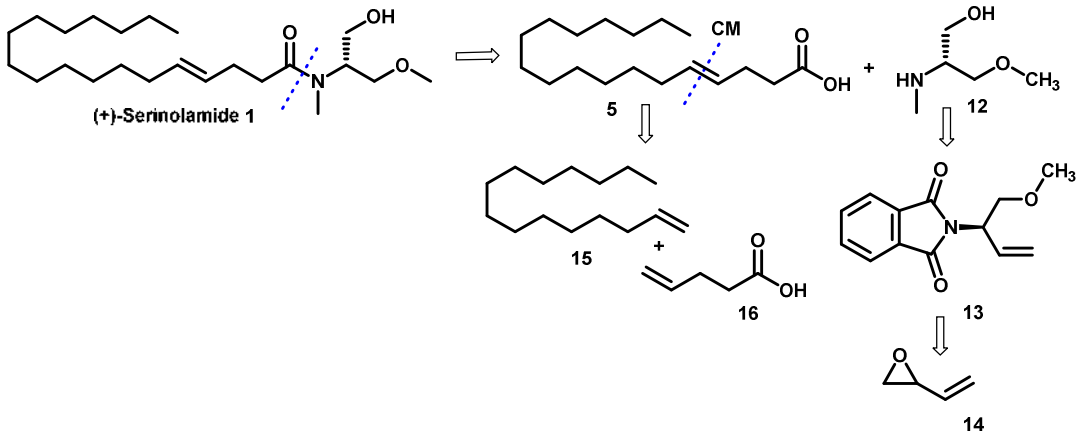
Scheme 3. *Reagents and conditions*: (a) EDC, HOBt, DIPEA, CH_2Cl_2, 82%.

2.1.3 Present Work:

Herein, we are reporting a new, short and highly efficient synthetic strategy for (+)-serinolamide A **1** employing Trost's DYKAT and cross-metathesis as key steps.

2.1.4 Results and Discussion:

Our retrosynthetic approach for the synthesis of (+)-serinolamide A **1** is outlined in Scheme 4. Accordingly, we envisioned that the (+)-serinolamide A **1** could be obtained from the two fragments, the long chain fatty acid **5** and serinol derivative **12**. The fatty acid fragment **5** could be obtained from pentadec-1-ene **15** and pent-4-enoic acid **16** *via* cross-metathesis. The phthalimide derivative **13** was visualized as a synthetic intermediate from which serinol derivative **12** could be synthesized. Terminal double bond of derivative **13** on standard organic transformation *viz.* phthalimide cleavage, oxidative cleavage and reduction could



Scheme 4. Retrosynthetic approach to (+)-serinolamide A **1**.

give the serinol derivative **12**. Enantiopure phthaloyl alcohol derivative **13** in turn could be easily prepared by the racemic butadiene monoepoxide **14** by means of Trost's DYKAT followed by methylation. The (*S*)- and (*R*)-configuration of the derivative **13** could be simply manipulated by changing the chiral ligand (*R*,*R*)-DACH and (*S*,*S*)-DACH (Figure 2), respectively, in the Trost's DYKAT step.

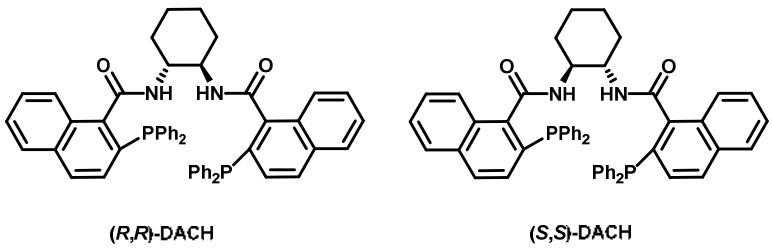
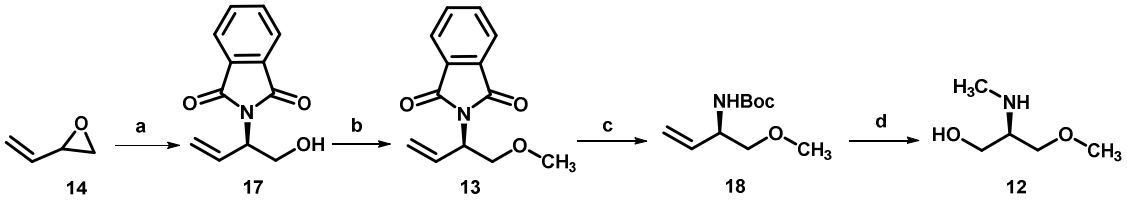


Figure 2. Structures of (*R*,*R*)- and (*S*,*S*)- *N*,*N*'-1,2-Cyclohexanediylbis[2-(diphenylphosphino) -1-naphth-amide].

The synthesis of (+)-serinolamide A **1** started from the commercially available racemic starting material butadiene monoepoxide **14**, which can also easily synthesized from silver-catalyzed oxidation of 1,3-butadiene (Scheme 5).[3] Deracemisation of butadiene monoepoxide **14** in highly regio- and enantioselective fashion in presence of palladium catalysed Trost's DYKAT with 1.2 mol % (*S*,*S*)-DACH and 0.4 mol % [η^3-$C_3H_5PdCl]_2$, phthalimide and base Na_2CO_3 furnished asymmetric allylic alkylation (AAA) derivative phthaloyl alcohol **17** as a single enantiomer in 99% yield with 99% *ee* {$[\alpha]_D^{25}$ +66.0 (*c* 1, $CHCl_3$) [Lit.[4] +65.9 (c 1, $CHCl_3$)]}. The IR spectrum of **17** showed hydroxyl absorption at 3517 cm^{-1} and olefin C=C stretching at 1695 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 6.14 (doublet of doublet of doublet, one proton) and δ 5.27-5.30 (multiplet, two protons).



Scheme 5. *Reagents and conditions:* (a) Phthalimide, Na_2CO_3, 1.2 mol % (*S*,*S*)-DACH, 0.4 mol % [η^3-$C_3H_5PdCl]_2$, dry CH_2Cl_2, rt, 14 h, 99%; (b) MeI, NaH, DMF, 0 ^oC to rt, 6 h, 91%; (c) i) $NH_2NH_2.H_2O$, isopropyl alcohol, 0 ^oC to rt, 2 h; ii) $(Boc)_2O$, $NaHCO_3$, THF:H_2O (1:1) v/v, rt, 12h, 87% (over two steps); (d) i) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane:water 3:1 v/v, 25 ^oC, 2 h ; ii) $LiAlH_4$, dry THF, 0 ^oC to reflux, 12 h.

With enantiomerically pure alcohol **17** in hand, we then subjected it to *O*-methylation with MeI in presence of NaH which furnished the methyl ether **13** in 91% yield. Our next aim was to carry out the alcohol formation at the terminal double bond site and *N*-methylation at 2-aza site. To this end, one pot cleavage of phthalimide group of (*R*)-**13** with hydrazine monohydrate in 2-propanol followed by treatment of the resulting free amine with $(Boc)_2O$ in the presence of $NaHCO_3$ in THF:H_2O (1:1) furnished the Boc protected derivative (*R*)-**18** in 87% yield. Finally, oxidative cleavage of terminal double bond in presence of OsO_4 and sodium periodate[5] followed by concomitant reduction of aldehyde and *N*-Boc group with

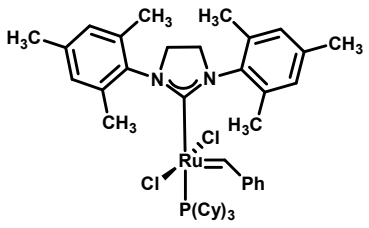
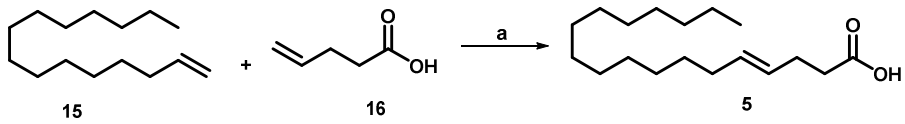


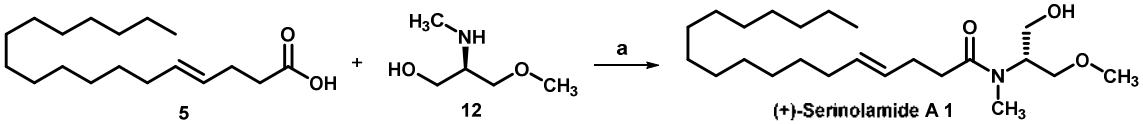
Figure 3. Grubbs' second generation catalyst.

$LiAlH_4$ under reflux condition afforded the serinol derivative (*R*)-**12** which was used for coupling with acid **5** without purification. On the other hand, the cross-metathesis[6] was undertaken with confidence between pentadec-1-ene **15** and 4-pentenoic acid **16** in presence of a small amount (5 mol %) of Grubbs'[7] second generation catalyst (Figure 3). The reaction proceeded smoothly, and the desired coupling product **5** was obtained in 95% yield with an impressive *E*/*Z* ratio (95:5). The ^{1}H NMR spectrum of compound **5** showed olefinic proton at δ 5.44 (triplet of quartet, two protons) with the coupling constant J = 15.1 Hz indicating *trans*-olefin. The homocoupling product of **16** was not observed by ^{1}H NMR. In this case the use of $Ti(O^iPr)_4$ or other additive was not necessary to obtain excellent results (Scheme 6).



Scheme 6. *Reagents and conditions:* (a) 5 mol % Grubbs' second generation catalyst, CH_2Cl_2, 40 ^oC, 12 h, 95%.

With long chain fatty acid **5** and serinol derivative **12** in hand, we then subjected it to acid amine coupling reaction in presence of EDC, HOBt and DIPEA which afforded the target compound (+)-serinolamide A **1** in 65% yield {$[\alpha]_D^{20}$ = +1.97 (*c* 0.18, $CHCl_3$) [Lit.[2]{$[\alpha]_D^{20}$ = +1.98 (*c* 0.18, $CHCl_3$). The physical and spectroscopic data of (+)-serinolamide A **1** were in full agreement with those documented in the literature (Scheme 7).



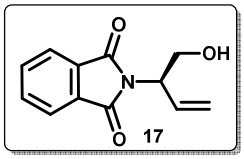
Scheme 7. *Reagents and conditions:* (a) EDC, HOBt, DIPEA, CH_2Cl_2, 0 ^oC to rt, 12 h, 65%.

2.1.5 Conclusion:

In conclusion, a simple, flexible and highly efficient enantioselective total synthesis of (+)-serinolamide A **1** has been developed. The overall yield for (+)-serinolamide A **1** was 51% in five steps. The merits of this synthesis are high regio- and enantioselectivity with high yielding reaction steps. Moreover, the synthetic strategy described has significant potential for stereochemical variations at C-2 position and further extension to other stereoisomers.

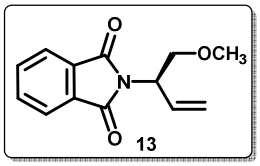
2.1.6 Experimental Section:

(*R*)-2-(Isoindolin-2-yl)but-3-en-1-ol, 17



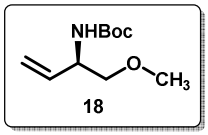
To a mixture of π-allylpalladium chloride dimer 0.4 mol % (14.6 mg, 0.04 mmol), (*S*,*S*)-DACH ligand 1.2 mol % (94.6 mg, 0.12 mmol), Na_2CO_3 (53 mg, 0.50 mmol) and phthalimide (1.47 g, 10 mmol) in 80 mL of dry CH_2Cl_2 was purged with nitrogen for 1 h. The resulting mixture was stirred for 10 min at room temperature to which butadiene monoepoxide **14** (810 μl, 10 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 14 h, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 3:7) furnished (*R*)-**17** (2.16 g, 99%) as a crystalline white solid. Mp 62-63 °C; [R_f = 0.21, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ +66.01 (*c* 1, $CHCl_3$), [Lit.[5] +65.9 (*c* 1, $CHCl_3$)]; IR (KBr) *v*: 3517, 1755, 1695, 1656, 1611, 1475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.85 (dd, *J* = 5.5, 2.8 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.2 Hz, 2H), 6.14 (ddd, *J* = 17.4, 10.6, 6.9 Hz, 1H), 5.30-5.27 (m, 2H), , 4.91-4.96 (m, 1H), 4.15 (ddd, *J* = 16.1, 11.4, 8.2 Hz, 1H), 3.97 (ddd, *J* = 11.9, 7.3, 3.6 Hz, 1H), 2.76 (dd, *J* = 8.2, 3.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.5, 134.2, 131.9, 131.7, 123.4, 118.8, 62.8, 55.9.

(*R*)-2-(1-Methoxybut-3-en-2-yl)isoindoline, 13



To a solution of compound **17** (2.0 g, 9.2 mmol) in dry DMF (25 ml) was added NaH (442 mg, 18.4 mmol, 60% dispersion in mineral oil) at 0 ^oC in one portion. MeI (1.73 ml, 27.6 mmol) was added after stirring the reaction mixture for 15 minutes at above temperature. The resulting mixture was allowed to warm at rt and stirred for 6 h. After completion of reaction monitored by TLC, the reaction mixture was quenched with cold H_2O, extracted with diethyl ether (3 x 20 mL) and dried over anhydrous $MgSO_4$. The organic layer was then concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/hexane 1:9) to furnish (*R*)-**13** (1.94 g, 91%) as a crystalline white solid. [R_f = 0.56, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ +55.17 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 1772, 1711, 1471, 1381 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ:* 7.84 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.72 (dd, *J* = 5.5, 2.8 Hz, 2H), 6.16 (ddd, *J* = 17.4, 10.6, 7.3 Hz, 1H), 5.32 (td, *J* = 17.4, 1.0, 1H), 5.27 (td, *J* = 10.6, 1.4, 1H), 5.01-5.07 (m, 1H), 4.05-4.15 (m, 1H), 3.64 (dd, *J* = 10.08, 5.96 Hz, 1H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 168.1, 133.9, 132.1, 131.9, 123.2, 119.0, 71.3, 58.7, 52.9; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{13}NO_3Na$ $[M + Na]^+$ 254.0793 found 254.0793.

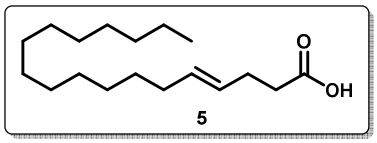
(*R*)-*tert*-Butyl 1-methoxybut-3-en-2-ylcarbamate, 18



18

To a solution of compound (*R*)-**13** (1.0 g, 4.32 mmol) in isopropyl alcohol (10 mL) was added hydrazine monohydrate (0.25 mL, 5.18 mmol) at 0 ^{o}C under nitrogen atmosphere. The reaction mixture was stirred at rt for 2 h. Then 30 ml of 6N aqueous hydrochloric acid was added and the reaction mixture was heated at reflux (80 ^{o}C) for 1 h. After cooling to 0 ^{o}C, the reaction mixture was filtered through glass wool to remove the phthalhydrazide. The crude solution was neutralized by sodium bicarbonate. Then 15 ml THF was added to the resulting solution followed by di-*tert*-butyl dicarbonate (1.89 g, 8.64 mmol), sodium bicarbonate (1.08 g, 12.96 mmol) and stirred for 12 h at rt. The reaction mixture was quenched by addition of water, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. The organic layer was then concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/*n*-hexane 1:9) to furnish (*R*)-**18** (0.75 g, 87%) as a colorless liquid. [R_f = 0.42, EtOAc/hexane 2:8 v/v]; $[\alpha]_D^{25}$ +18.76 (*c* 1.0, $CHCl_3$); IR (KBr) *v*: 2977, 2930, 1685, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.82 (ddd, *J* = 15.6, 10.5, 5.0 Hz, 1H), 5.24 (td, *J* = 17.4, 1.4 Hz, 1H), 5.18 (td, *J* = 10.5, 1.4 Hz, 1H), 4.93 (brs, 1H), 4.29 (brs, 1H), 3.45 (d, *J* = 4.6 Hz, 2H), 3.35 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.2, 136.1, 115.3, 79.1, 74.3, 58.8, 52.1, 28.1; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{19}NO_3Na$ $[M + Na]^+$ 224.1263, found 224.1261.

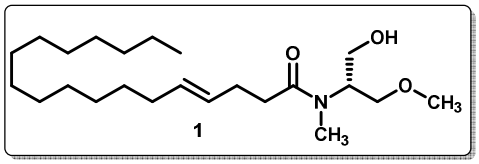
(*E*)-Octadec-4-enoic acid, 5



5

To a solution of pentadec-1-ene **15** (500 mg, 2.38 mmol) and 4-pentenoic acid **16** (48 mg, 48 μL, 0.48 mmol) in dry CH_2Cl_2 (100 mL) was added Grubbs' second generation catalyst (10 mg). The mixture was stirred to 40 ^{o}C for 6 h under argon atmosphere. A second portion of Grubbs' catalyst (11 mg) was then added and the reaction mixture was kept stirred at 40 ^{o}C for 6 h. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane 1:9) to furnish **5** (0.128 g, 95%) as a white solid. [R_f = 0.25, EtOAc/hexane 2:8 v/v]. The homocoupling product of **16** was not observed by proton NMR. IR (KBr) *v*: 3420, 2900, 2820, 1710, 1460, 1280, 1220, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.44 (tq, *J* = 15.1, 6.4 Hz, 2H), 2.42 (t, *J* = 6.9 Hz, 2H), 2.31 (m, 2H), 1.96 (m, 2H), 1.26 (m, 22H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.7, 132.2, 127.4, 32.5, 31.9, 29.7, 29.6, 29.5, 29.4, 29.1, 27.6, 22.7, 14.1.

(+)-Serinolamide A, 1



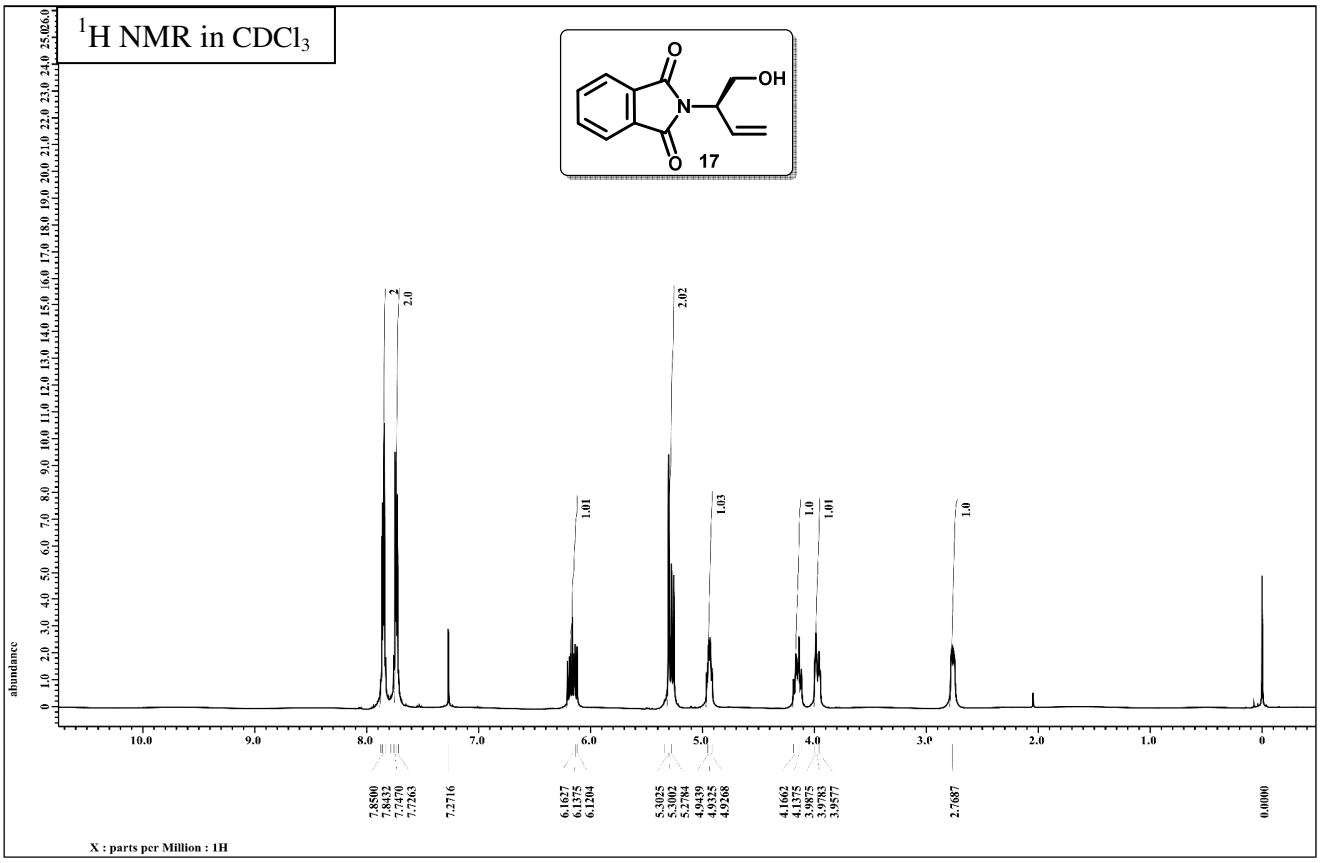
To a solution of compound (*R*)-**8** (0.500 g, 2.49 mmol) in dioxane-water (3:1, 16 mL) was added 2,6-lutidine (0.58 mL, 4.98 mmol), OsO_4 (0.1 M solution in toluene, 0.48 mL, 0.05 mmol) and $NaIO_4$ (1.06 g, 4.98 mmol). The reaction was stirred at 25 ^oC for 2 h. After completion of reaction, water (10 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was separated, and the water layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give crude aldehyde which was used as such for the next step without further purification.

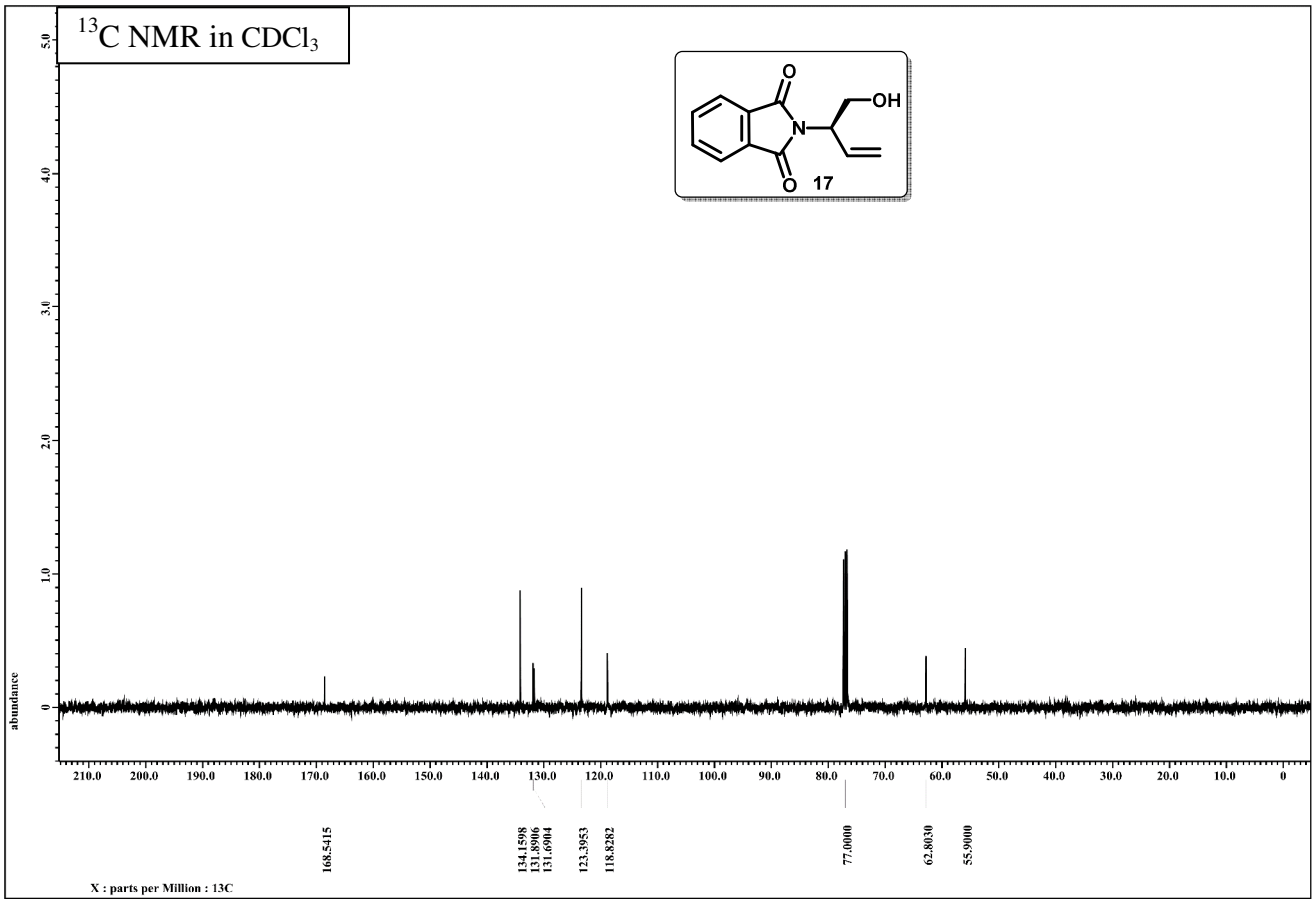
The above aldehyde was dissolved in anhydrous THF (12 mL) and lithium aluminium hydride (560 mg, 14.76 mmol) was added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred at the same temperature under N_2 for additional 1 h, then warmed up to reflux conditions and stirred for 12 h. The solution was quenched with 10% NaOH and extracted with ethyl acetate and dried over anhydrous $MgSO_4$. The organic layer was then concentrated *in vacuo* to afford **12** quantitative without further purification.

The residue **12** obtained above was dissolved in CH_2Cl_2 (5 mL) and added to a solution of (*E*)-octadec-4-enoic acid **5** (396 mg, 1.4 mmol), EDC (726 mg, 3.78 mmol), HOBt (302 mg, 2.24 mmol) and DIPEA (1.9 mL, 11.2 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 12 h. Then CH_2Cl_2 was added and the mixture was washed with water (5 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/hexane 1:1) to furnish (*R*)-**1** (348 mg, 65%) as a yellow liquid. [R_f = 0.42, EtOAc]; {$[\alpha]_D^{25}$ = +1.97 (c 0.18, $CHCl_3$), [Lit.[2]{$[\alpha]_D^{20}$ +1.98 (c 0.18, $CHCl_3$); IR (KBr) *v*: 3421, 2915, 2866, 1631, 1411, 1285, 1125, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ:* 5.43-5.46 (m, 2H), 4.44-4.46 (m, 1H), 3.71-3.77 (m, 2H), 3.62-3.67 (m, 1H), 3.55 (dd, *J* = 10.50, 5.00 Hz, 1H), 3.46 (d, *J* = 6.4 Hz, 1H), 3.33 (s, 3H), 3.01 (s, 3H), 2.39-2.47 (m, 2H), 2.29-2.34 (m, 2H), 1.96 (d, *J* = 5.2Hz, 2H), 1.25-1.45 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) *δ:* 174.3, 131.6, 128.4, 70.9, 61.8, 58.9, 57.1, 34.5, 33.3, 32.5, 31.9, 29.6, 29.5, 29.3, 29.2, 28.3, 22.6, 14.1; HRMS (ESI-TOF) m/z calcd for $C_{23}H_{46}NO_3$ $[M + H]^+$ 384.3472, found 384.3474.

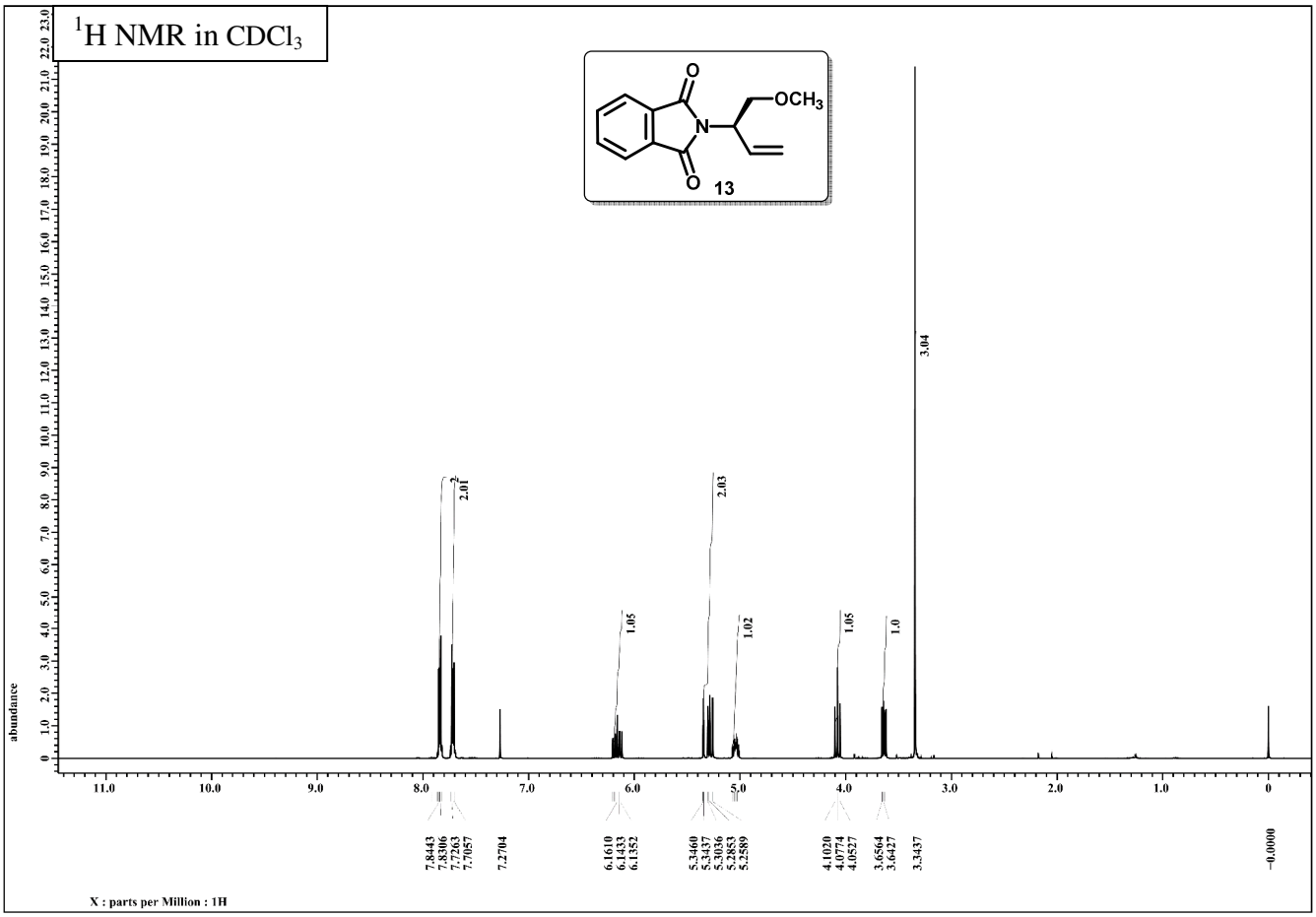
2.1.7 Spectra:

1. ^{1}H and ^{13}C NMR spectra of **17**
2. ^{1}H and ^{13}C NMR spectra of **13**
3. ^{1}H and ^{13}C NMR spectra of **18**
4. ^{1}H and ^{13}C NMR spectra of **5**
5. ^{1}H and ^{13}C NMR spectra of **1**

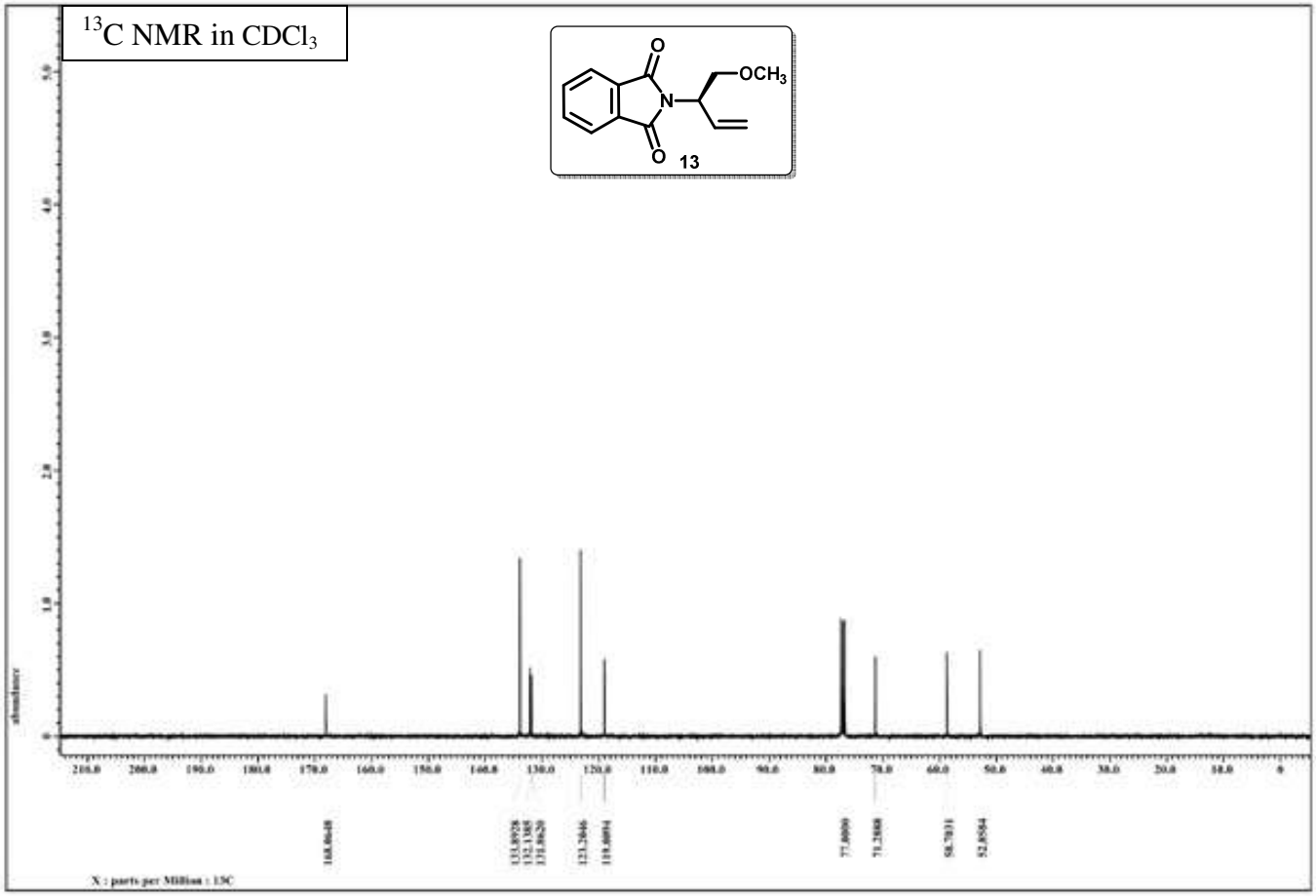

^{1}H NMR in $CDCl_3$
17
abundance
X : parts per Million : 1H

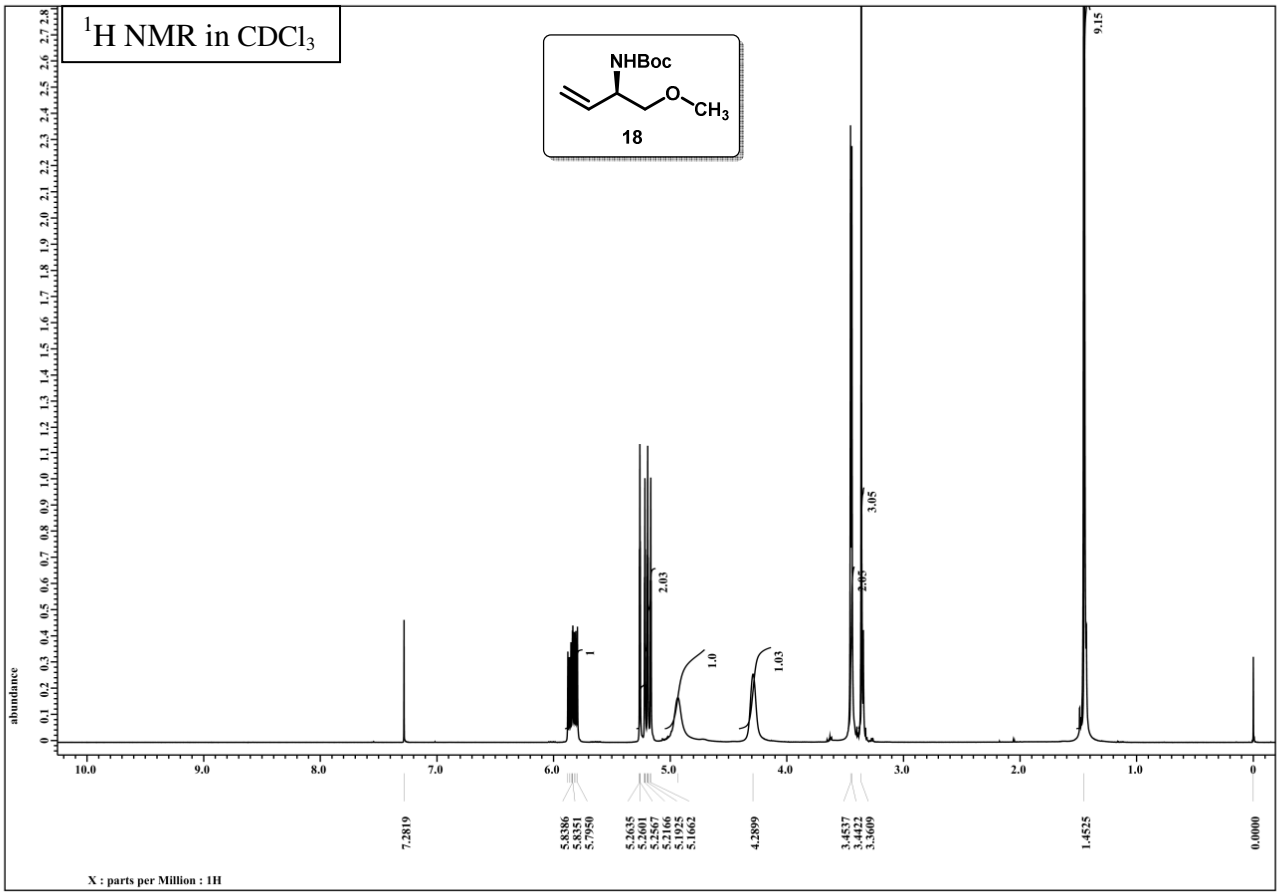

^{13}C NMR in $CDCl_3$
17
abundance
X : parts per Million : 13C

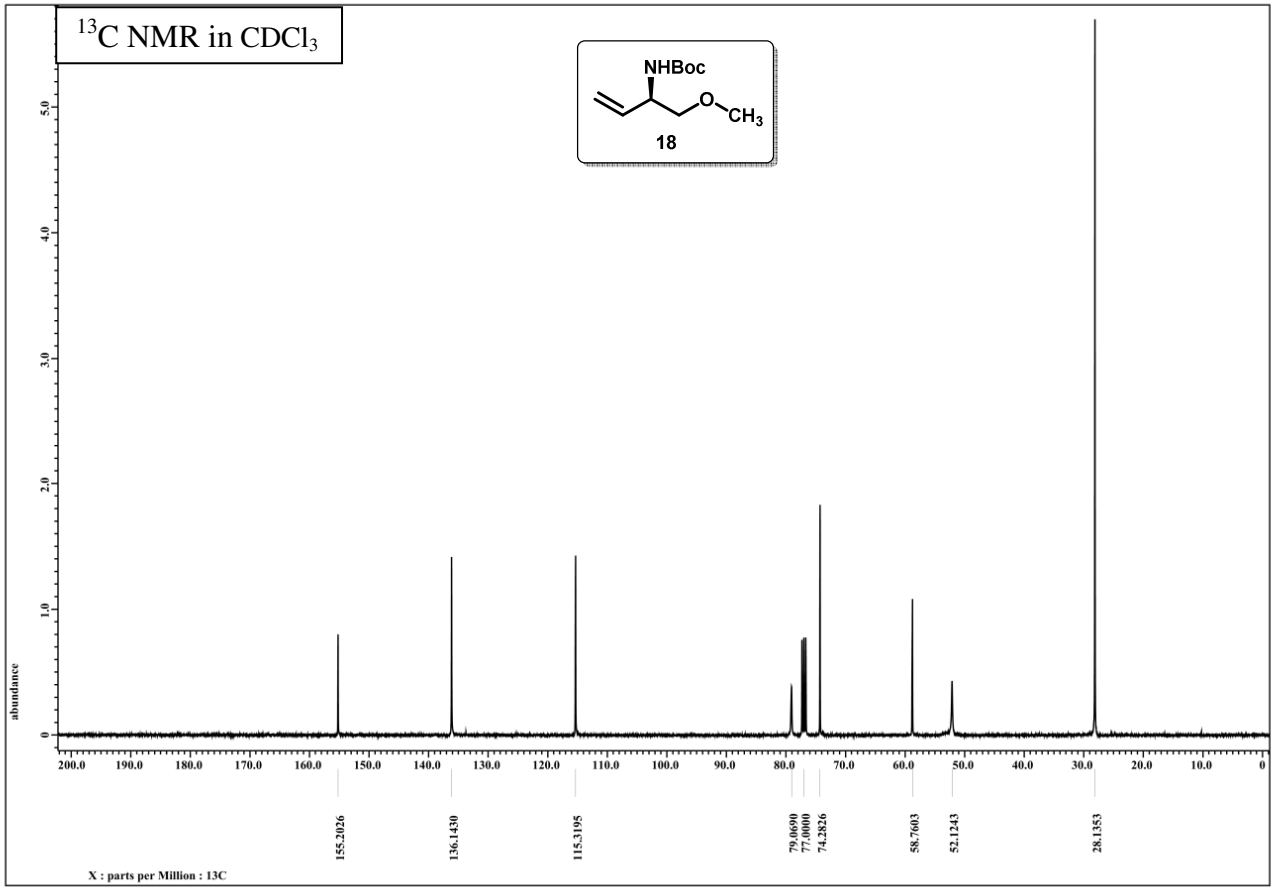
^{1}H NMR in $CDCl_3$

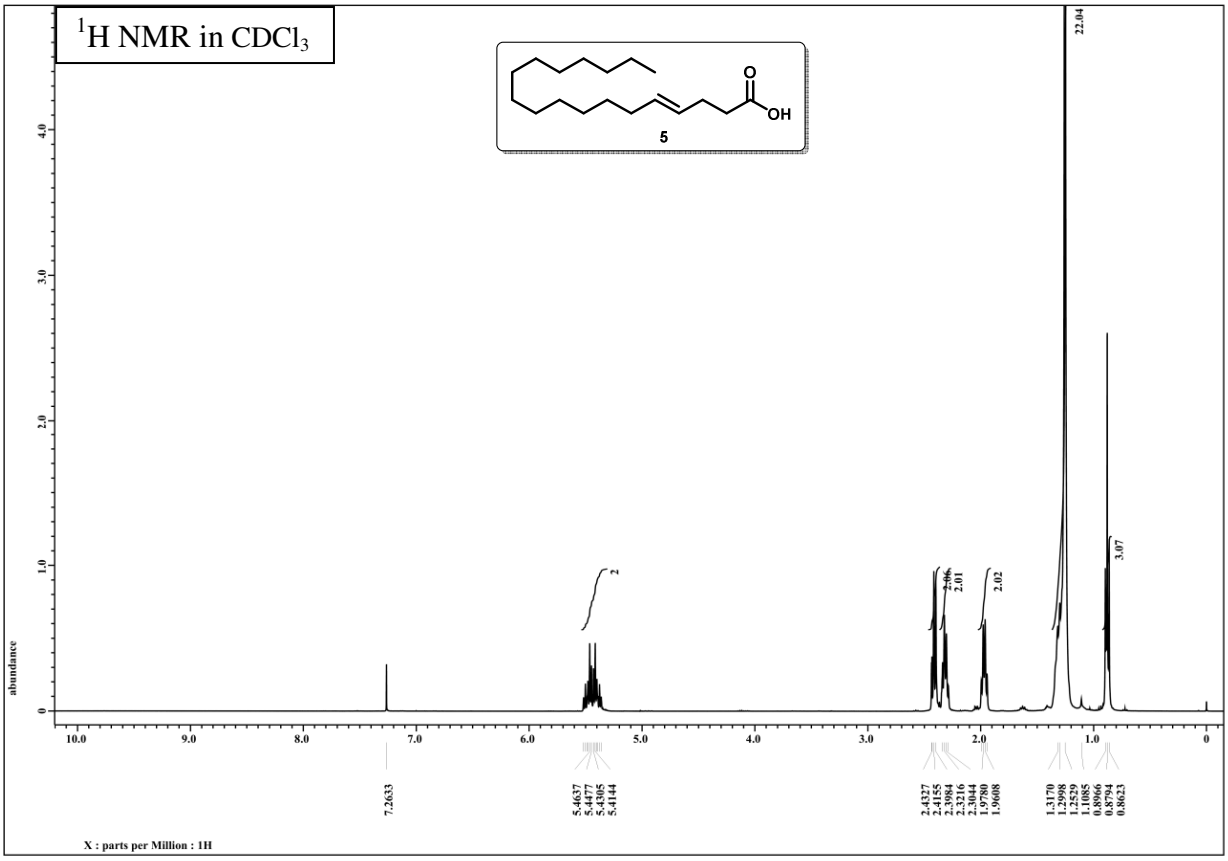


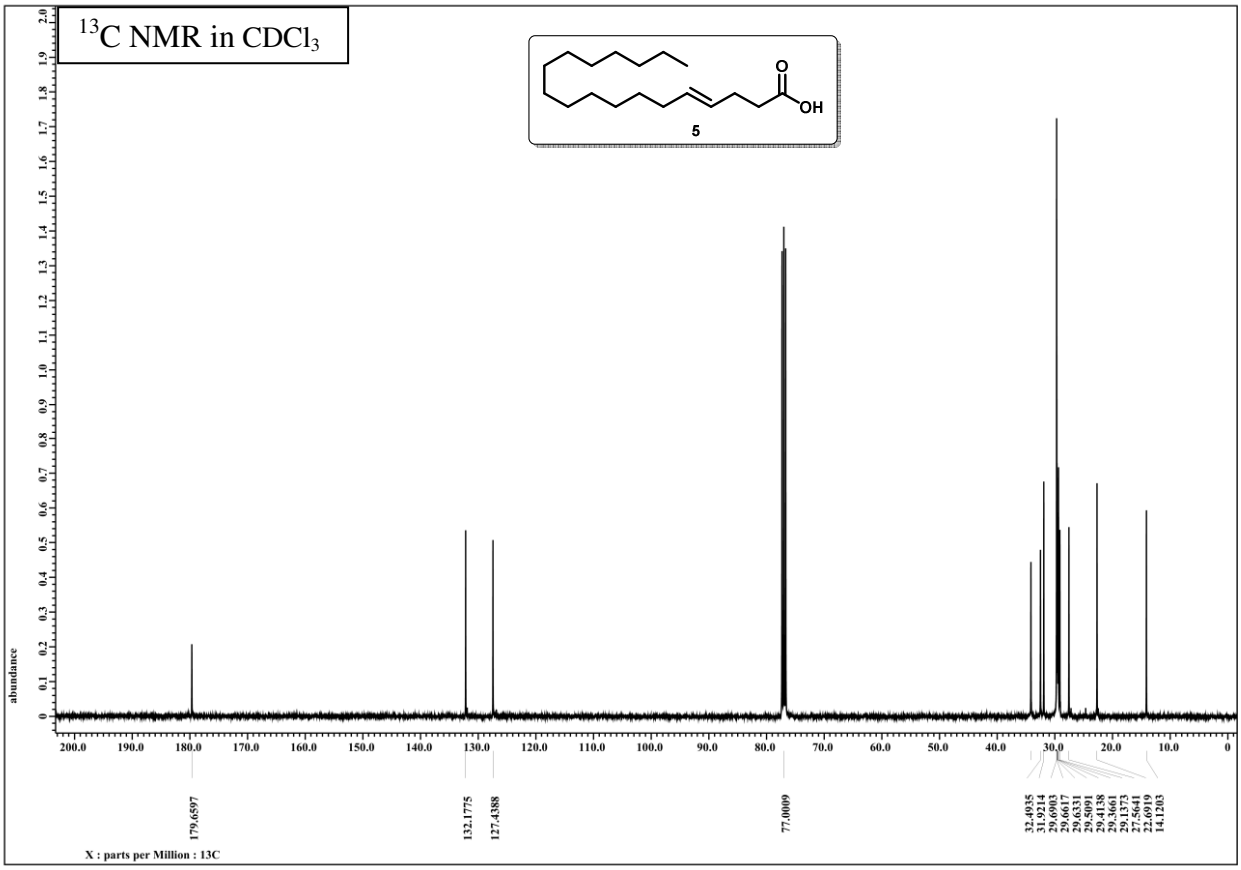
^{13}C NMR in $CDCl_3$

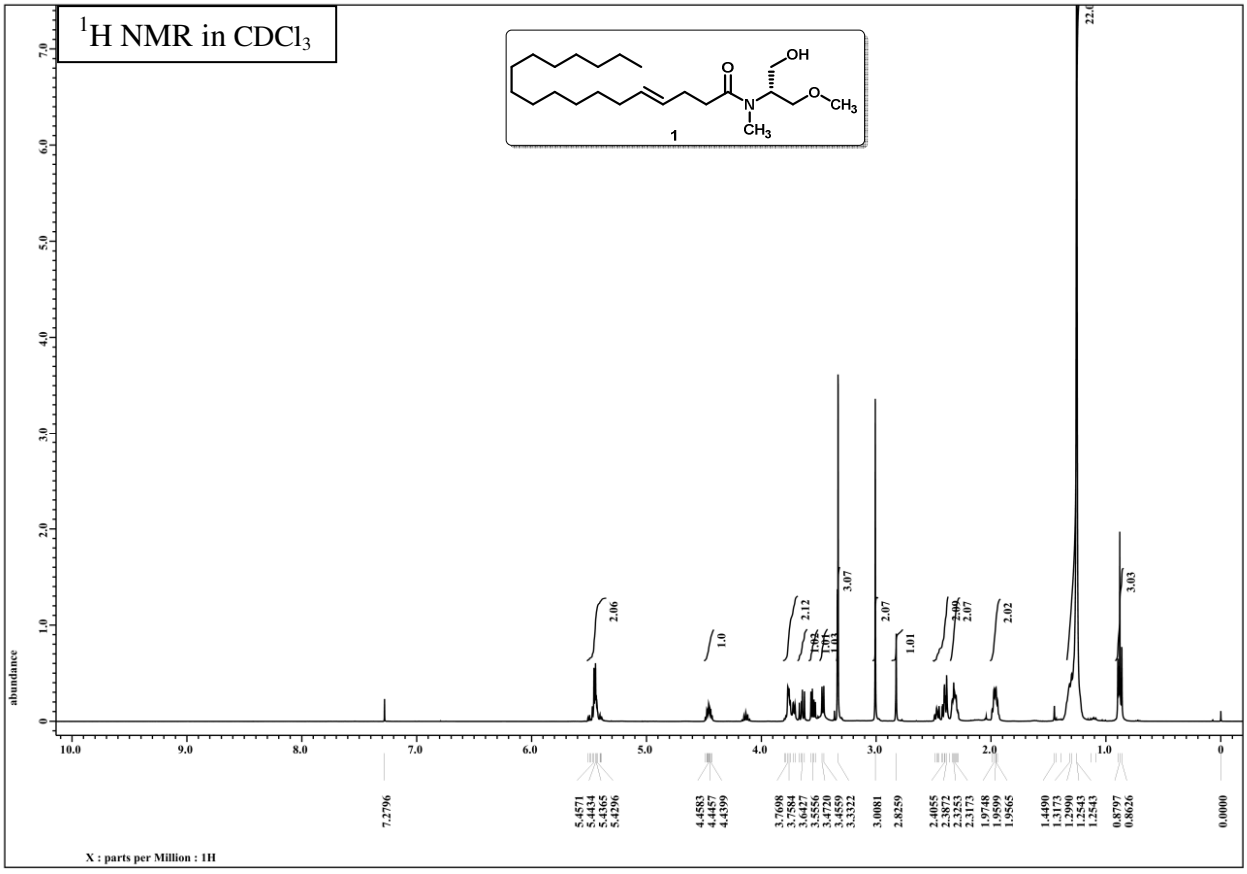


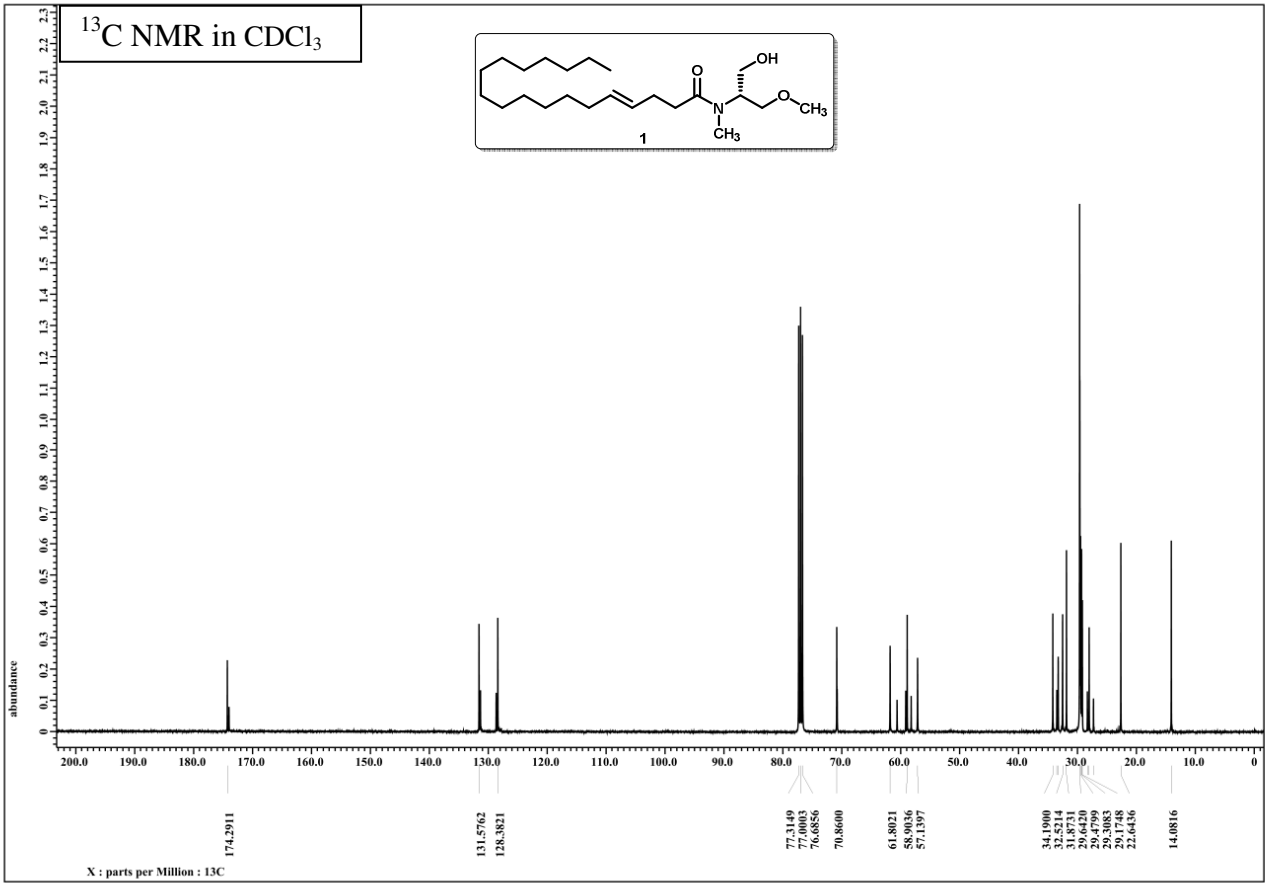

^{1}H NMR in $CDCl_3$
NHBoc
O
CH_3
18
abundance
9.15
3.05
2.03
1.0
1.03
7.2819
5.8386
5.8351
5.7950
5.2635
5.2601
5.2567
5.2166
5.1925
5.1662
4.2899
3.4537
3.4422
3.3609
1.4525
0.0000
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
NHBoc
O
CH_3
18
abundance
155.2026
136.1430
115.3195
79.0690
77.0000
74.2826
58.7603
52.1243
28.1353
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
5
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
5
abundance
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OH
O
N
O
CH_3
CH_3
1
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
O
N
O
CH_3
CH_3
1
abundance
X : parts per Million : 13C

2.2 Section B

Total synthesis of haliclamide, a marine natural product

2.2.1 Introduction:

A large number of natural products containing the cyclodepsipeptide nucleus have been isolated from sponge of marine origin and received considerable attention because of their potent properties such as insecticidal, anthelmintic, antiviral, antimicrobial, antitumor, anti-inflammatory and immunosuppressive activities.[8] In 2001, Randazzo and co-workers reported the isolation of a novel macrocycle, haliclamide **19** from the marine sponge *Haliclona sp*. collected in the waters off Vanuatu Island.[9] Haliclamide **19** has been shown to possess potent *in vitro* antitumor activity against the human bronchopulmonary non-small cell lung carcinoma cell line NSCLC-N6 {IC_{50} = 4 μg/mL (8.7 μM)}. Haliclamide **19** has been a synthetic target of considerable interest due to its potent antitumor activity and with an array of functionalities. Architecturally, haliclamide **19** (Figure 4) is a 16-membered hybrid macrocycle bearing four stereogenic centers and possess modified amino acids including a featured *N*-methyl-L-phenylalanine (*N*-Me-L-Phe), 5-hydroxy-octanoic acid (HOA) and 6-amino-7-hydroxy-2-methylheptanoic acid (AHMA) moieties connected by ester and amide linkages. The absolute configurationof the two chiral centers at C2 and C14 were resolved by Randazzo and co-workers with the help of 2D NMR analysis and Yamaguchi method,[10] however the remaining two centers C9 and C20 were assigned by Altmann and co-workers by chemical synthesis and NMR studies.

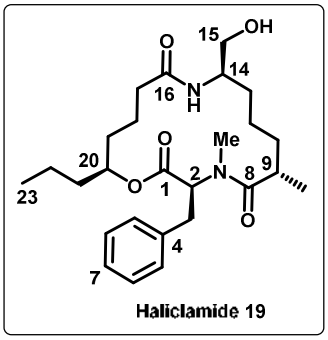


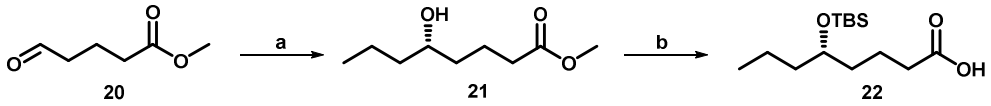
Figure 4. Structure of haliclamide **19**.

2.2.2 Review of Literature:

There is only one synthesis of haliclamide **19**[11] has been documented in the literature which is described below.

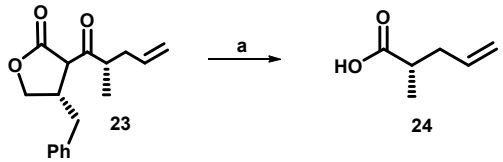
Altmann, K. H. ***et al*. (2013)[11]**

K. H. Altmann and co-workers reported the total synthesis and configurational assignment of the marine natural product haliclamide **19** based on macrocyclization by ring-closing olefin metathesis. The synthesis of fragment **22** is depicted in Scheme 8. Carboxylic acid **22** was obtained from *δ*-valerolactone *via* known aldehyde **20** and ester **21** (er 93:7), silylation of compound **21** followed by saponification furnished acid **22** in 58% overall yield.



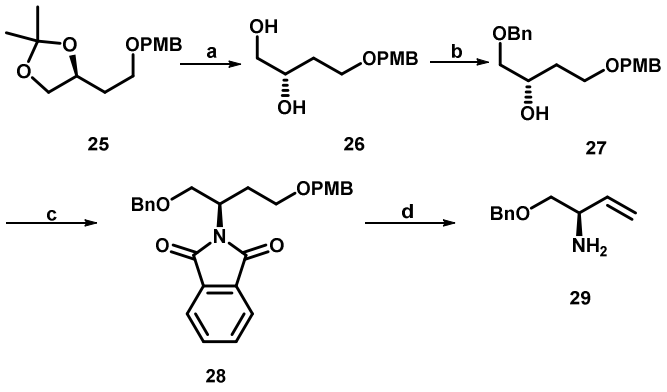
Scheme 8. *Reagents and conditions*: (a) See reference 12 (b) i) TBSCl, imidazole, DCM, 66%; ii) LiOH, THF:H_2O 4:1, 88%.

Oxazolidinone **23** was converted into carboxylic acid **24** *via* hydrolysis of auxiliary with LiOH and H_2O_2 in 76% yield (Scheme 9).



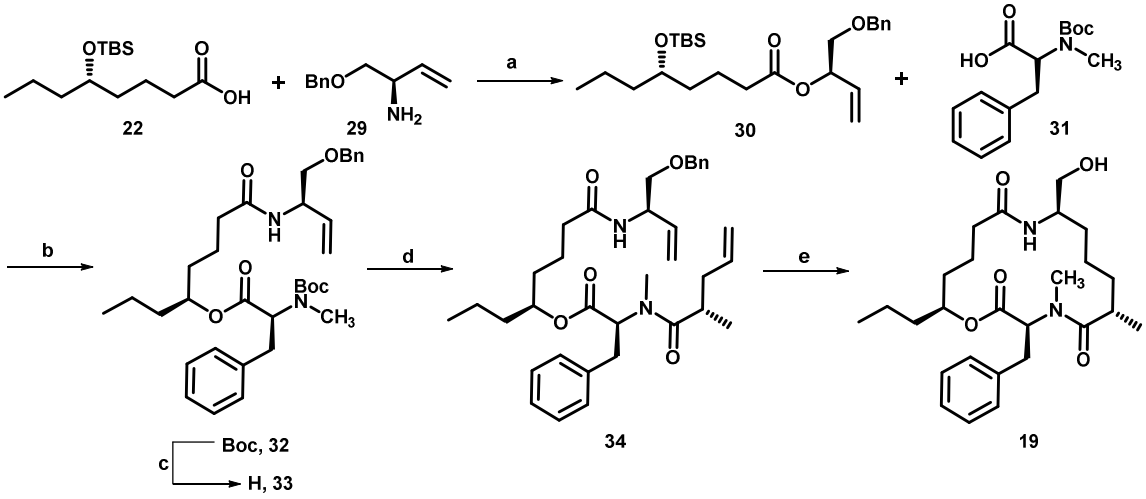
Scheme 9. *Reagents and conditions*: (a) LiOH, H_2O_2, THF:H_2O 4:1, 76%.

The synthesis of fragment **29** commenced with acetonide derivative **25** (Scheme 10), which on treatment with copper (II) chloride dihydrate furnished mono-PMB-protected triol **26** in92% yield. Selective benzylation of diol **26** wth benzyl chloride in presence of dibutyl tin oxide afforded primary benzyl ether **27** in 87% yield. Alcohol **27** was converted into the *N*-substituted phthalimide **28** *via* Mitsunobu reaction in excellent yield. Finally, DDQ-mediated removal of the PMB group in **28** followed by Grieco-Sharpless olefination and phthalimide cleavage provided the desired amine **29** in 39% yield over three steps.



Scheme 10. *Reagents and conditions*: (a) $CuCl_2.H_2O$, MeOH, 92%; (b) Bu_2SnO, BnCl, TBAI, benzene, 87%; (c) DIAD, phthalimide, TPP, THF, 95%; (d) i) DDQ, DCM:H_2O 9:1, 87%; ii) O_2N-PhSeCN,(*n*-Bu)$_3$P, $NaHCO_3$, H_2O_2, THF, 76%; iii) $MeNH_2$, EtOH, 59%.

Finally, first coupling was carried out between acid **22** and amine **29** under HBTU/DIPEA conditions to furnish the amide **30** in 89% yield. DCC/DMAP mediated esterification of acid



Scheme 11. *Reagents and conditions*: (a) i) HOBt, HBTU, DIPEA, DMF, 89%; ii) 20% TFA, DCM, 82%; (b) i) DCC, DMAP, DCM, 99%; (c) 20% TFA, DCM, 98%; (d) **24**, HATU, DIPEA, DMF, 92%; (e) i) Grubb's second generation catalyst, toluene, 49%; ii) H_2, Pd-C, MeOH, 38%.

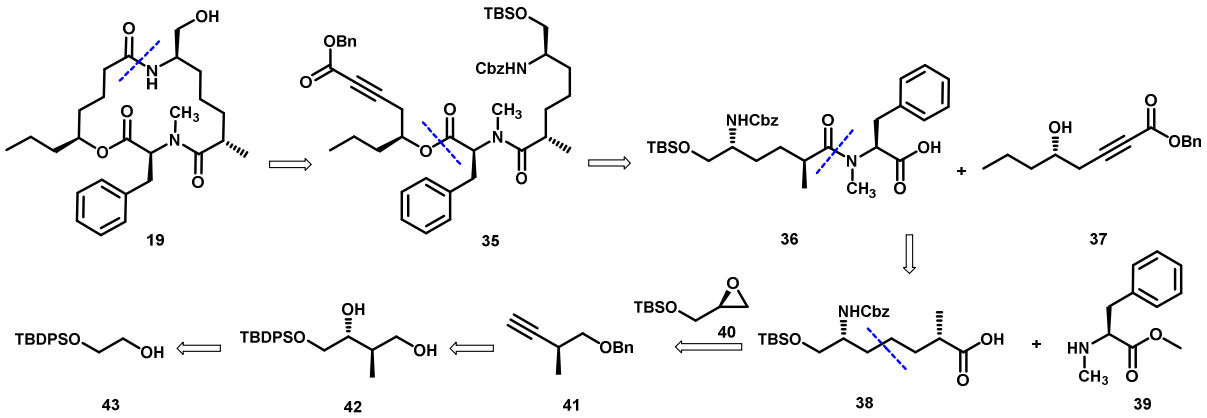
31 with alcohol (obtained from deprotection of TBS ether in compound **30**) furnished ester derivative **32** which was treated with 20% TFA/DCM to give the free amino ester **33** in excellent yield. Compound **33** was coupled with **24** in presence of HATU to furnish amide **34** as the substrate for the key cyclization step. Finally, RCM of **34** was carried out with Grubbs second generation catalyst and subsequent hydrogenation with Pd/C afforded diastereomeric mixture of targeted natural haliclamide **19**.

2.1.3 Present Work:

Herein, we are reporting a new synthesis of haliclamide **19** employing proline catalyzed enantioselective MacMillan's cross aldol reaction of *α*-oxyaldehyde, Yamaguchi-Hirao alkylation of oxirane, Mitsunobu, Corey-Fuchs protocol and Steglich esterification reactions as the key steps.

2.1.4 Results and Discussion:

Our retrosynthetic analysis for the total synthesis of haliclamide **19** is displayed in Scheme 12. We anticipated the construction of targeted molecule **19** from the ester **35** *via* hydrogenolysis followed by intramolecular macrocyclization using amide coupling as one of the key step. The precursor **35** could be accessed from the acid **36** and alcohol **37** by intermolecular Steglich esterification. The alcohol **37** in turn could be synthesized from easily accessible enatiopure (S)-1,2-epoxypentane *via* Yamaguchi-Hirao alkylation. The acid fragment **36** could be assembled from the coupling partners N-Me-L-Phe derivative **39** and fragment **38** *via* peptide coupling. We envisaged that fragment **38** would serve as the key

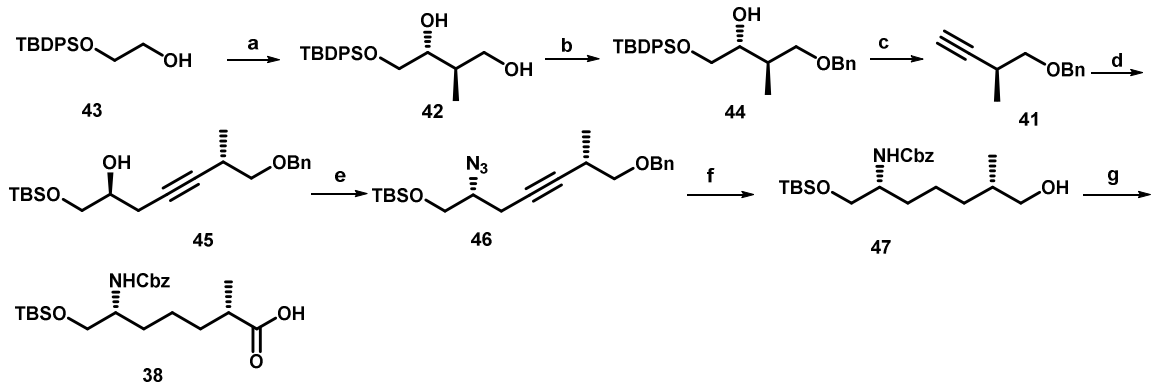


Scheme 12. Retrosynthetic analysis of haliclamide **19**.

synthetic intermediate in this approach and would be prepared by Yamaguchi-Hirao alkylation of (*S*)-silyl protected glycidyl ether **40** with lithioacetylides **41** followed by Mitsunobu inversion allowing the formation of corresponding azide and standard organic transformation. The acetylene derivative **41** in turn could be obtained from diol **42** by oxidative cleavage and Corey-Fuchs protocol which could be easily obtained from monosilylated ethylene glycol **43** *via* asymmetric aldol reaction.

The synthesis of key fragment **38** is depicted in Scheme 13. The 1,3-diol **42** was easily prepared from readily available monosilylated ethylene glycol **43** *via* L-proline catalyzed MacMillan's cross aldol reaction and reduction with $NaBH_4$ following a literature

procedure.[13] The IR spectrum of **42** showed hydroxyl absorption at 3423 cm^{-1}. Treatment of 1,3-diol **42** with K_2CO_3 and BnBr in acetone under reflux condition[14] successfully furnished the monobenzylated derivative **44** in 91% yield. Synthesis of acetylene derivative **41** from alcohol **44** were carried out by a process including silyl deprotection, $NaIO_4$ mediated oxidative cleavage and Corey-Fuchs protocol[15] in 90% yield (95% ee), $[\alpha]_D^{25}$ -5.06 (*c* 1.0,



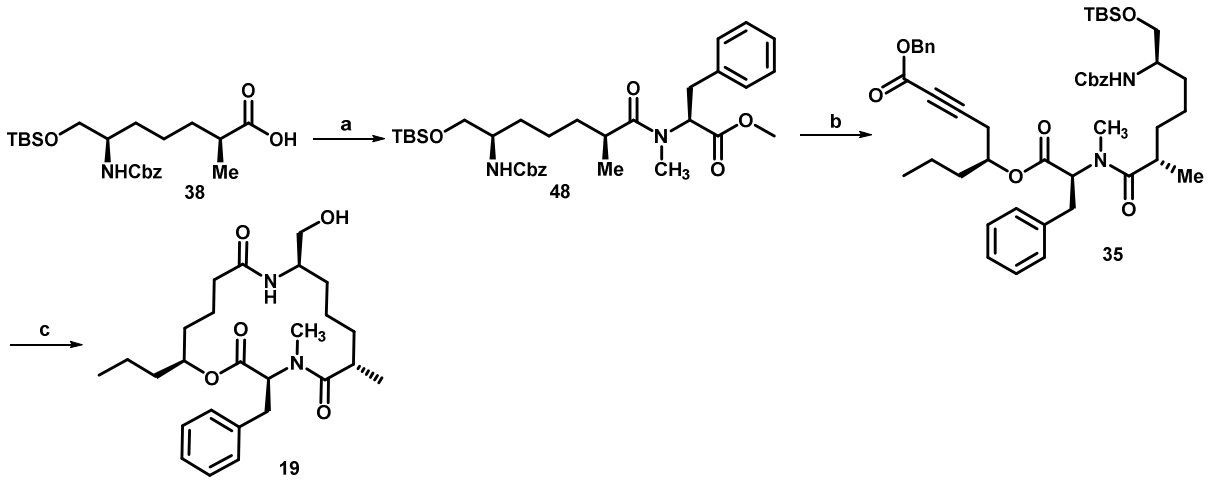
Scheme 13. *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 °C to rt, 2 h; ii) Propionaldehyde, 10 mol% L-Proline, dioxane, 4 °C, 48 h; iii) $NaBH_4$, MeOH, 0 °C to rt, 30 min, 85% (three steps). (b) BnBr, K_2CO_3, acetone, reflux, 16 h, 91%. (c) i) TBAF, THF, rt, 2 h; ii) $NaIO_4$, THF:H_2O (2:1), rt, 20 min; iii) CBr_4, PPh_3, dry DCM, 0 °C, 20 min; iv) *n*-BuLi, dry THF, -78 °C, 30 min, 90% (four steps). (d) *n*-BuLi, $BF_3.OEt_2$, **40**, dry THF, -78 °C, 1 h, 88%. (e) DPPA, DEAD, TPP, THF, rt, 1 h, 85%. (f) i) H_2, Pd/C (10%), MeOH, rt, 24 h; ii) CbzCl, Na_2CO_3, THF, rt, 4 h, 92% (two steps). (g) TEMPO, BAIB, CH_2Cl_2:H_2O (2:1), rt, 18 h, 93%.

$CHCl_3$), {lit[16] $[\alpha]_D^{20}$ -5.1 (*c* 1.0, $CHCl_3$)}. The IR spectrum of **41** showed alkyne absorption at 3301 and 2125 cm^{-1}. The lithium acetylide of acetylene derivative **41** was then treated with (*S*)-glycidol silyl ether **40**[17] under the Yamaguchi-Hirao conditions[18] to deliver the homopropargylic alcohol **45** as a single diastereomer[19] in 88% yield. At this stage an attempt to convert the free hydroxyl group of **45** to azide **46** with *O*-mesylate and subsequent nucleophilic displacement with sodium azide in dry DMF was not very satisfactory. Accordingly the free hydroxyl group of **45** was converted into azide **46** under Mitsunobu conditions[20] with 85% yield. The IR spectrum of **46** showed azide absorption at 2096 cm^{-1}. The azide derivative **46** was subjected to hydrogenation in the presence of a catalytic amount of Pd/C (10%) and subsequent Cbz protection furnished the carbamate moiety **47** in 92% yield.[21] Finally, TEMPO/BAIB mediated oxidation of the primary hydroxyl group provided

the key intermediate **38** in 93% yield. The IR spectrum of **38** showed acid absorption at 3405 and 1715 cm^{-1}.

To access fragment **37**, commercially available (*S*)-1,2-epoxypentane[22] was regioselectively opened with lithium salt of benzyl propiolate in 85% yield.[18] The natural L-phenylalanine was transformed by a two-step sequence[23] into *N*-Me-L-Phe derivative **39.**

After successful constructions of all three skeletons, we moved towards the final coupling reactions to accomplish the total synthesis of haliclamide **19** (Scheme 14). First intermolecular coupling was carried out between fragment **38** and *N*-methyl-L-phenylalanine derivative **39** under HATU/DIPEA[24]conditions which afforded the amide **48** in 90% yield. Saponification of the methyl ester **48** with LiOH in aqueous THF at room temperature and subsequent treatment of the acid under Steglich esterification conditions with fragment **37** furnished compound **35** in 89% yield. Concomitant deprotection of Cbz, hydrogenolysis of



Scheme 14. *Reagents and conditions*: (a) **39**, HATU, DIPEA, DMF, rt, 5 h, 90%. (b) i) LiOH, THF:H_2O, rt, 4 h; ii) **37**, DCC, DMAP, dry DCM, rt, 1 h, 89% (two steps). (c) (i) H_2, Pd/C (10%), MeOH, rt, 24 h; (ii) HATU, DIPEA, dry THF, rt, 12 h; (iii) TBAF, THF, rt, 12 h, 71% (three steps).

ester and alkyne reduction of compound **35** were carried out *via* hydrogenation in the presence of catalytic amount of Pd/C(10%) and subsequent macrolactamization[25] using HATU in DMF (Table 1, entry 1) in the presence of the Hunig's base and desilylation afforded haliclamide **19** with poor yield (15%). Next, we turned our attention to improve the yield *via* EDC/HOBt mediated lactamization reaction which have been used very effectively

for coupling of acid and secondary amine.[2] Macrocyclization of crude with EDC/HOBt in DMF or DCM (Table 1, entry 2, 3) in the presence of the Hunig's base and desilylation afforded haliclamide **19** in moderate 25% and 45% yield, respectively. Further improvement in macrolactamization[25] using HATU and DIPEA was observed when the solvent was switched to THF (Table 1, entry 4), with 71% yield of haliclamide **19** $[\alpha]_D^{25}$ -4.5 (*c* 0.02, $CHCl_3$){ lit.[11] $[\alpha]_D^{24}$ -4.1 (*c* 0.02, $CHCl_3$) (lit.[9] $[\alpha]_D^{24}$ -4.8 (*c* 0.006 g/mL, $CHCl_3$)}. HATU was preferred over other coupling reagents in this step, as it has been shown to provide for optimal coupling efficiency in reactions involving secondary amino groups.[26] The physical and spectroscopic data were in full agreement with those reported in the literature.[9]

Table 1: Reaction conditions for 16-membered lactam formation

Entry	Conditions[a,b]	Yield[c]
1.	HATU, DIPEA, DMF	15%
2.	EDC, HOBt, DIPEA, DMF	25%
3.	EDC, HOBt, DIPEA, DCM	45%
4.	HATU, DIPEA, THF	71%

[a]Stirred at room temperature under argon atmosphere for 12 h. [b]Other conditions are identical. [c]Overall isolated yield of 1 in 3 steps. 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: *N*-hydroxybenzotrizole. DIPEA: *N*, *N*-diisopropylethylamine.

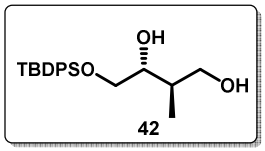
2.1.5 Conclusion:

In conclusion, we have developed a convergent and flexible approach for the total synthesis of bioactive marine natural product haliclamide **19** from readily available starting materials. The synthetic sequence demonstrates the application of organocatalyzed MacMillan cross-aldol reaction, Steglich esterification, Corey-Fuchs protocol, Mitsunobu inversion, Yamaguchi-Hirao alkylation and macrolactamization reactions as the key steps. The synthetic approach described has significant potential for stereochemical variations at all the positions and further extension to other stereoisomers, and analogues.

2.1.6 Experimental Section:

(2*R*,3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methylbutane-1,3-diol, 42

To a solution of oxalyl chloride (2.15 mL, 24.96 mmol) in dry CH_2Cl_2 (20 mL) at -78 ^oC was added dropwise a solution of DMSO (3.65 mL, 51.60 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 30 min at the same temperature, and a solution of the monosilylated ethylene glycol **43** (5.0 g, 16.64 mmol) in CH_2Cl_2 (40 mL) was added slowly, and stirred for another 30 min at -78 ^oC. After Et_3N (10.27 mL, 73.21 mmol) in CH_2Cl_2 (40 mL) was added at -78 ^oC, the stirring was continued for additional 1 h at the room temperature. The mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude aldehyde, which was used for the next step.

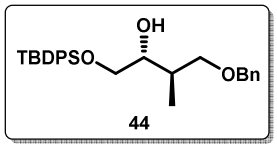


Into a 4 ^oC suspension of crude *tert*-butyldiphenylsilyloxy-acetaldehyde and L-proline (192 mg, 1.66 mmol) in dioxane (17 mL) were added dropwise a precooled (4 ^oC) solution of propionaldehyde (6 mL, 83.2 mmol) in dioxane (17 mL) over 24 h *via* syringe pump. The mixture was allowed to stir for an additional 24 h at the same temperature. Following completion, the reaction was diluted with ethyl acetate and vigorously washed with water and brine. The organics were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude oil was directly used for the next reaction.

To a solution of the above aldehyde in dry MeOH (40 mL) was added $NaBH_4$ (1.26 g, 33.28 mmol) portion wise at 0 ^oC. After 30 min of stirring at room temperature, saturated NH_4Cl solution was poured over the reaction mixture. The organics were extracted with EtOAc (3 x 40 mL), dried over anhydrous Na_2SO_4, and evaporated under vacuum. Silica gel column chromatography (hexane/EtOAc 4:1) of the residue afforded 1,3-diol **42** (5.1 g, 85%) as a thick colorless liquid. [R_f = 0.4, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ +7.26 (*c* 1.5, $CHCl_3$); IR (CH_2Cl_2) ν: 3423, 2929, 1426, 1108, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.65 (m, 4H), 7.46-7.38 (m, 6H), 3.75 (m, 1H), 3.67-3.57 (m, 4H), 3.06 (bs, 1H), 3.00 (d, J = 2.76 Hz, 1H), 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 $C_{21}H_{30}O_3SiNa$ $[M+Na]^+$ 381.1861; found 381.1858.

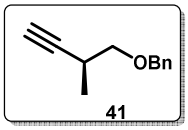
(2*R*,3*R*)-4-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-3-methylbutan-2-ol, 44

To a solution of diol **42** (5.0 g, 13.99 mmol) in acetone (60 mL) were added K_2CO_3 (5.8 g, 41.97 mmol), TBAI (40 mg) and benzyl bromide (1.83 mL, 15.38 mmol). The resulting mixture was heated to reflux for 16 h. The reaction mixture was then concentrated under reduced pressure, the crude was



dissolved in water (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 19:1) to obtain **44** (5.70 g, 91%) as a colourless syrup. [R_f = 0.5, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ +12.6 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 3429, 2929, 2856, 1427, 1105, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.65 (d, *J* = 8.6 Hz, 4H), 7.45-7.25 (m, 11H), 4.46 (s, 2H), 3.74-3.60 (m, 3H), 3.55-3.48 (m, 2H), 3.00 (bs, 1H), 2.02-1.95 (m, 1H), 1.05 (s, 9H), 0.92 (d, *J* = 6.84 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 135.6, 133.2, 129.7, 128.3, 127.7, 127.5, 74.7, 73.2, 73.1, 66.2, 35.7, 26.8, 19.2, 13.9; HRMS (ESI), calcd for $C_{28}H_{36}O_3SiNa$ $[M+Na]^+$ 471.2331; found 471.2327.

(*S*)-((2-Methylbut-3-ynyloxy)methyl)benzene, 41



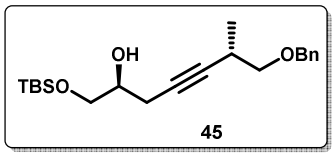
To a solution of *tert*-butyldimethylsilyl ether derivative **44** (5.0 g, 11.16 mmol) in dry THF (50 mL) was added TBAF (1.0 M in THF, 16 mL, 16.74 mmol), and the resulting reaction mixture was stirred for 2 h at room temperature. Aqueous saturated solution of NH_4Cl (30 mL) and EtOAc (40 mL) were added, and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken for the next reaction without further purification.

A suspension of the above 1,2-diol in THF (60 mL) was added to a solution of $NaIO_4$ (3.34 g, 15.62 mmol) in THF-H_2O (1:1, 60 mL) and stirred for 20 min at room temperature. To the reaction mixture water and EtOAc were added, the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. A crude aldehyde was obtained, which was used for the next reaction without further characterizations.

PPh_3 (11.70 g, 44.64 mmol) was added to a solution of CBr_4 (7.40 g, 22.32 mmol) in dry CH_2Cl_2 (80 mL) at 0 ^oC and stirred for 10 min at the same temperature. To the mixture was added a solution of the above aldehyde in dry CH_2Cl_2 (40 mL) at 0 ^oC, and stirred at the same temperature for 10 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl, giving a slurry that was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude dibromo-olefin, which was used as such for the next step without further purification.

To a solution of above crude dibromo-olefin in dry THF (30 mL) was added *n*-BuLi (2.5 M solution in hexane, 9.8 mL, 24.55 mmol) at -78 ^{o}C, the mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl and giving a slurry that was extracted with EtOAc (3 x 3 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane 1:49) of the crude product furnished the corresponding terminal alkynes **41** (1.75 g, 90% over four steps) as a colorless oil. [R_f = 0.65, EtOAc/hexane 1:19 v/v]; $[\alpha]_D^{25}$ -5.06 (*c* 1.0, $CHCl_3$), {lit[9] $[\alpha]_D^{20}$ -5.1 (c 1.0, $CHCl_3$)}; IR (CH_2Cl_2) ν: 3301, 2925, 2854, 2125, 1091, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.25 (m, 5H), 4.57 (dd, *J* = 14.2, 11.88 Hz, 2H), 3.52 (dd, *J* = 9.16, 6.44 Hz, 1H), 3.38 (dd, *J* = 9.16, 7.32 Hz, 1H), 2.78-2.72 (m, 1H), 2.07 (d, *J* = 2.28 Hz, 1H), 1.22 (d, *J* = 6.88 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.1, 128.3, 127.6, 86.4, 73.7, 73.0, 68.9, 26.5, 17.6; HRMS (ESI), calcd for $C_{12}H_{14}ONa$ $[M+Na]^+$ 197.0942; found 197.0944; HPLC: Chiralcel OJ-RH (150 x 4.6 mm), MeOH/H_2O 85:15 v/v, flow rate 0.5 mL/min, λ_{max} = 254 nm, t_R = 17.97 min. and t_R = 18.90 min, 95% ee.

(2*S*,6*S*)-7-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)-6-methylhept-4-yn-2-ol, 45

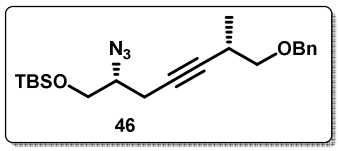


45

Under nitrogen atmosphere, a solution of *n*-butyllithium (2.5 M solution in hexane, 4.12 mL, 10.33 mmol) was added to a solution of acetylene derivative **41** (1.5 g, 8.61 mmol) in dry THF (100 mL) at -78 ^{o}C. The resulting mixture was warmed slowly to 0 ^{o}C and stirred for 30 min at the same temperature. Further to the above reaction mixture boron trifluorideetherate (1.09 mL, 8.60 mmol) was added at -78 ^{o}C. Finally, (*S*)-TBS glycidyl ether **35** (1.47 g, 7.82 mmol) was added to the above reaction mixture and stirred for 1 h at -78 ^{o}C. After completion of reaction, the reaction was quenched by addition of aqueous sodium bicarbonate solution, diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc/hexane 1:19) afforded homopropargylic alcohol derivative **45** (2.5 g, 88%) as a colorless oil. [R_f = 0.4, EtOAc/hexane 1:19 v/v]; $[\alpha]_D^{25}$ -16.8 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 3410, 2921, 2846, 2090, 1253, 1090, 835, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.25 (m, 5H), 4.54 (dd, *J* = 14.64, 12.36 Hz, 2H), 3.76-3.67 (m, 2H), 3.62-3.58 (m, 1H), 3.50-3.46 (m, 1H), 3.35-3.31 (m, 1H), 2.73-2.69 (m, 1H), 2.48 (d, *J* = 5.04 Hz, 1H), 2.41-2.37 (m, 2H), 1.18 (d, *J* = 6.88 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.2, 128.4, 127.6, 84.4,

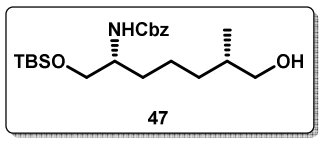
76.8, 74.3, 72.9, 70.4, 65.5, 26.7, 25.9, 23.4, 18.3, 18.0, -5.4; HRMS (ESI), calcd for $C_{21}H_{35}O_3Si$ $[M+H]^+$ 363.2350; found 363.2346.

(2*R*,6*S*)-2-Azido-7-(benzyloxy)-6-methylhept-4-ynyloxy)(*tert*-buty)ldimethylsilane, 46



To a solution of above homopropargylic alcohol **45** (2.4 g, 6.63 mmol) in dry THF (6.0 mL) were added triphenylphosphine (3.47g, 13.26 mmol) and diethyl azodicarboxylate (2.1 mL, 13.26 mmol) sequentially at room temperature. Diphenyl phosphorazidate (2.87 mL, 13.26 mmol) was added dropwise and the resulting mixture was stirred for 1 h. The filtrate was concentrated under reduced pressure. Silica gel chromatography of the crude product (EtOAc/hexane 1:49) afforded the title compound **46** (2.2 g, 85%) as a colorless oil. [R_f = 0.6, EtOAc/hexane 1:19 v/v]; $[\alpha]_D^{25}$ +10.53 (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) ν: 2929, 2856, 2096, 1253, 1090, 835, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.25 (m, 5H), 4.54 (d, *J* = 2.28 Hz, 2H), 3.80-3.77 (m, 1H), 3.72-3.68 (m, 1H), 3.55-3.43 (m, 2H), 3.37- 3.31 (m, 1H), 2.75-2.69 (m, 1H), 2.48-2.35 (m, 2H), 1.18 (d, *J* = 6.88 Hz 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.2, 128.3, 127.6, 84.6, 76.3, 74.1, 72.9, 64.8, 61.8, 26.7, 25.7, 21.1, 18.2, 17.9, -5.5; HRMS (ESI), calcd for $C_{21}H_{34}N_3O_2Si$ $[M+H]^+$ 388.2415; found 388.2432.

Benzyl (2*R*,6*S*)-1-(*tert*-butyldimethylsilyloxy)-7-hydroxy-6-methylheptan-2-ylcarbamate, 47

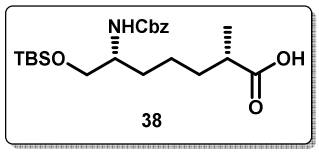


To a solution of azide derivative **46** (2.0 g, 5.16 mmol) in methanol (30 mL) was added a saptula tip of 10 wt % Pd on activated carbon and the resulting mixture was stirred under one atmospheric hydrogen pressure for 24 h at room temperature. After completion of reaction, the catalyst was removed by filtration over Celite and concentrated *in vacuo* to give the amine as a colourless oil which was used as such for the next step.

To a stirred solution of the above amine in THF (25 mL) was added solid Na_2CO_3 (1.53 g, 14.44 mmol) and benzylchloroformate (2.1 mL, 6.19 mmol). The suspension was vigorously stirred for 4 h at room temperature, and the reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, evaporated under vacuum and purified on silica gel (EtOAc/hexane 1:4) to give carbamate moiety **47** (1.94 g, 92%) as a colorless oil. [R_f = 0.3, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ +13.8 (*c* 1.15, $CHCl_3$); IR (CH_2Cl_2) ν: 3441, 2928, 2856,

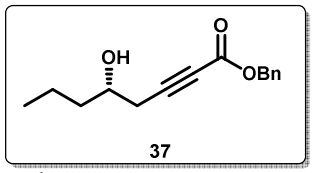
1699, 1251, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.26 (m, 5H), 5.09 (s, 2H), 4.92 (d, J = 9.16 Hz, 1H), 3.87-3.65 (m, 1H), 3.64-3.57 (m, 2H), 3.45-3.40 (m, 2H), 1.67-1.23 (m, 7H), 1.09-1.07 (m, 1H), 0.90 (d, J = 6.88 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.2, 136.6, 128.5, 128.1, 67.8, 66.6, 64.8, 52.0, 35.6, 32.6, 31.9, 25.8, 23.2, 18.3, 16.8, -5.5; HRMS (ESI), calcd for $C_{22}H_{40}NO_4Si$ $[M+H]^+$ 410.2721; found 410.2719.

(2*S*,6*R*)-6-(Benzyloxycarbonylamino)-7-(*tert*butyldimethylsilyloxy)-2-methylheptanoic acid, 38



To a suspension of alcohol **47** (1.0 g, 2.44 mmol) in CH_2Cl_2 (10 mL) and H_2O (5 mL) were added TEMPO (76 mg, 0.48 mmol) and [bis(acetyloxy)iodo]benzene (BAIB; 1.72 g, 5.36 mmol) at room temperature. The mixture was stirred at rt for 18 h. The reaction mixture was quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (2 x 30 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (EtOAc/hexane, 1:4) to furnish acid derivative **38** (961 mg, 93%) as a colorless thick oil. [R_f = 0.3, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ +11.5 (c 1.53, $CHCl_3$); IR (CH_2Cl_2) ν: 3405, 2928, 2856, 1715, 1699, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.25 (m, 5H), 5.09 (s, 2H), 4.93 (d, J = 8.68 Hz, 1H), 3.66-3.52 (m, 3H), 2.45-2.41 (m, 1H), 1.72-1.65 (m, 1H), 1.56-1.25 (m, 5H), 1.16 (d, J = 6.84 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 182.5, 156.0, 136.6, 128.5, 128.0, 66.6, 64.5, 52.2, 39.2, 33.2, 31.4, 25.8, 23.5, 18.2, 16.8, -5.5; HRMS (ESI), calcd for $C_{22}H_{38}NO_5Si$ $[M+H]^+$ 424.2541; found 424.2539.

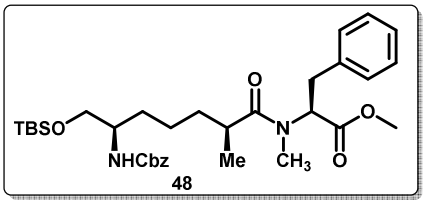
(*S*)-Benzyl-5-hydroxyoct-2-ynoate, 37



n-Butyllithium (2.5 M solution in hexanes, 2.7 mL, 6.96 mmol) was added dropwise to a stirred mixture of the benzyl propiolate (1.02 g, 6.38 mmol) in dry THF (10 mL) at -90 °C under a nitrogen atmosphere. The resulting solution was stirred for 30 min at the same temperature, boron trifluoride/diethyl etherate (0.8 mL, 6.38 mmol) and (*S*)-1,2 epoxypentane (500 mg, 5.80 mmol) in THF (5 mL) was added and stirring was continued for 2 h at -78 °C. Aqueous ammonium chloride was added and the mixture was extracted with ethyl acetate (3 x 10 mL), the combined organic extracts was dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane 1:9) afforded the title compound **37** (1.21 g, 85%) as a colourless oil. [R_f = 0.5, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ +2.34 (c 1.0, $CHCl_3$); IR (CH_2Cl_2)

ν: 3414, 2931, 2850, 2234, 1707, 1238, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.18 (s, 2H), 3.85-3.82 (m, 1H), 2.50 (ddd, J = 22.0, 16.96, 5.04 Hz, 2H), 2.04 (bs, 1H) 1.52-1.25 (m, 4H), 0.93 (t, J = 7.32 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.4, 134.8, 128.6, 86.6, 74.7, 69.2 67.6, 38.5, 27.6, 18.7, 13.8; HRMS (ESI), calcd for $C_{15}H_{18}O_3Na$ $[M+Na]^+$ 269.1153; found 269.1148.

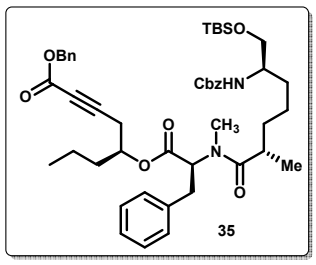
(*S*)-Methyl 2-((2*S*,6*R*)-5-(benzyloxycarbonylamino)-7-(*ter*-butyldimethylsilyoxy)-N, 2-dimethylheptanamido)-3-phenylpropanoate, 48



48

To a solution of acid derivative **38** (500 mg, 1.18 mmol) and HATU (493 mg, 1.29 mmol) in dry DMF (8 mL) was added DIPEA (0.4 mL, 2.36 mmol), and the reaction mixture was then stirred for 5 min at room temperature. *N*-Me-L-Phe derivative **39** (250 mg, 1.29 mmol) was then added portion wise over 5 min. After stirring at room temperature for 5 h, the mixture was diluted with ethyl acetate, washed with water, and brine. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The residue obtained was purified by silica gel column chromatography (EtOAc/hexane 1:4) to furnish coupled product **48** (694 mg, 90%) as a colourless oil. [R_f = 0.35, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ -25.4 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 2956, 2856, 1720, 1641, 1238, 1084, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.11 (m, 10 H), 5.43 (dd, J = 11.92, 5.04 Hz, 1H), 5.07 (s, 2H), 4.96 (d, J = 9.16 Hz, 1H), 3.68 (s, 3H), 3.65-3.48 (m, 3H), 3.39 (dd, J = 15.12, 5.52 Hz, 1H), 2.99 (dd, J = 14.68, 11.0 Hz, 1H), 2.82 (s, 3H), 2.55-2.50 (m, 1H), 1.69-1.66 (m, 2H), 1.54-1.20 (m, 4H), 0.85 (s, 9H), 0.74 (d, J = 6.88 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.0, 171.6, 156.1, 136.9, 136.6, 129.0, 128.7, 128.4, 128.3, 128.0, 126.6, 66.5, 64.6, 57.6, 52.5, 52.2, 35.4, 34.7, 33.6, 32.6, 31.5, 25.8, 23.8, 18.3, 16.9, -5.5; HRMS (ESI), calcd for $C_{33}H_{51}N_2O_6Si$ $[M+H]^+$ 599.3511; found 599.3509.

(*S*)-Benzyl 5-((*S*)-2-((2*S*,6*S*)-6-(benzyloxycarbonylamino)-7-(*ter*-butyldimethylsilyoxy)-N,2 dimethylheptanamido)-3-phenylpropanoyloxy)oct-2-ynoate, 35

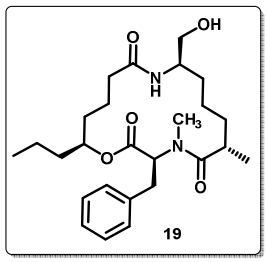


A mixture of methyl ester **48** (500 mg, 0.83 mmol), lithium hydroxide (174 mg, 4.15 mmol), THF (4 mL) and water (1 mL), was stirred at room temperature for 4 h. The organic solvent was removed under reduced pressure, and the residue obtained was then acidified to pH 5 with 1 N HCl, and the mixture was extracted with EtOAc (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered,

and concentrated under reduced pressure to give crude acid as a colorless oil which was used for the next step without further purification.

DMAP (101 mg, 0.83 mmol) and DCC (342 mg, 1.66 mmol) were added to a solution of above crude acid and homopropargylic alcohol derivative **37** (224 mg, 0.91 mmol) in CH_2Cl_2 (10 mL) at room temperature. The suspension was then stirred for 1 h at room temperature, monitoring by TLC. Upon completion, the solvent was evaporated and the residue was purified through silica gel column chromatography (EtOAc/hexane 1:9) to afford **35** as a colorless oil (600 mg, 89%). [R_f = 0.45, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ -16.7 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 2956, 2856, 1725, 1702, 1641, 840cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.08 (m, 15H), 5.28 (dd, *J* = 11.0, 4.16 Hz, 1H), 5.17 (s, 2H), 5.11-5.05 (m, 3H), 5.0-4.9 (m, 1H), 3.61-3.49 (m, 3H), 3.41-3.33 (m, 1H), 3.08-2.90 (m, 1H), 2.76 (s, 3H), 2.69-2.41 (m, 3H), 1.74-1.25 (m, 10H), 0.89-0.86 (m, 12H), 0.75 (d, *J* = 6.88 Hz, 3H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.2, 170.5, 155.9, 153.2, 137.1, 136.6, 134.7, 128.9, 128.7, 128.6, 128.5, 128.3, 128.0, 126.5, 84.9, 74.6, 71.4, 67.5, 66.5, 64.6, 58.2, 52.5, 52.3, 35.4, 34.8, 34.5, 33.5, 33.0, 32.8, 31.4, 25.8, 24.2, 23.8, 18.3, 18.2, 16.8, 13.7, -5.5; HRMS (ESI), calcd for $C_{47}H_{65}N_2O_8Si$ $[M+H]^+$ 813.4505; found 813.4505.

Haliclamide, 19



19

10% Palladium on carbon (20 mg) was added to a solution of **35** (100 mg, 0.12 mmol) in methanol (5 mL), and the mixture was hydrogenolyzed with H_2 (1 atmosphere) for 24 h, at which point TLC indicated the complete consumption of the starting material. The mixture was filtered through a pad of Celite and then the solvent was removed *in vacuo* to give the residue as colorless oil.

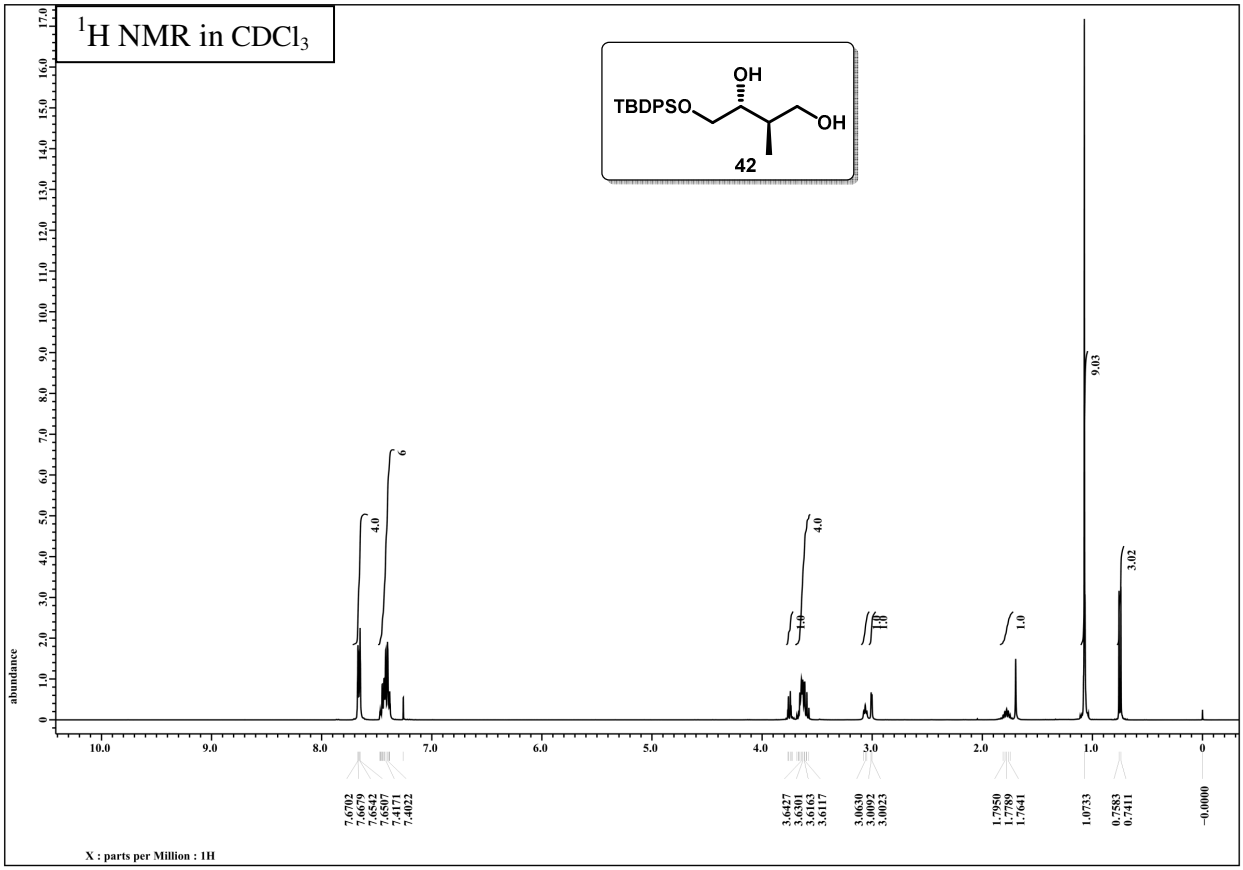
HATU (68 mg, 0.18 mmol) and DIPEA (0.1 mL, 0.6 mmol) were added to a solution of the above residue in THF (10 mL). The resulting suspension was stirred for 12 h at room temperature. After removal of THF, water and ethyl acetate were added and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic extracts were dried over Na_2SO_4, the solvent was evaporated and the crude product was used for silyl group deprotection.

To a solution of above macrocycle in THF (5 mL) was added TBAF (0.2 mL, 0.18 mmol) at room temperature. After stirring at room temperature for 12 h, the mixture was diluted with ethyl acetate washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. Silica gel column chromatography

(MeOH/$CHCl_3$ 1:24) afforded the target compound haliclamide **19** (38 mg, 71% in three step) as a white solid. [R_f = 0.4, MeOH/$CHCl_3$ 1:24 v/v]; $[\alpha]_D^{25}$ -4.5 (*c* 0.02, $CHCl_3$), { lit.[4] $[\alpha]_D^{24}$ -4.1 (*c* 0.02, $CHCl_3$) (lit.[2] $[\alpha]_D^{24}$ -4.8 (*c* 0.006 g/mL, $CHCl_3$)}; IR (CH_2Cl_2) ν: 3310, 1731, 1680, 1626, 1452, 852cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.12 (m, 5H), 6.86 (d, *J* = 5.96 , 1H), 5.90 (dd, *J* = 11.92, 5.06 Hz, 1H), 5.17 (br s, 1H), 5.02−4.95 (m, 1H), 3.87 (d, *J* = 11.88 Hz, 1H), 3.68 (bd, *J* = 4.12 Hz, 1H), 3.51 (dd, *J* = 15.1, 5.04 Hz, 1H), 3.45−3.37 (m, 1H), 2.96 (dd, *J* = 15.5, 12.36 Hz, 1H), 2.84 (s, 3H), 2.65−2.58 (m, 1H), 2.47−2.40 (m, 1H), 2.20−2.10 (m, 2H), 1.87−1.70 (m, 2H), 1.65−1.45 (m, 6H), 1.38−1.20 (m, 4H), 1.11−1.01 (m, 1H), 0.93 (t, *J* = 7.32 Hz, 3H), 0.65 (d, *J* = 6.44 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 174.5, 170.7, 136.5, 128.5, 128.4, 126.8, 77.0, 65.7, 56.2, 53.6, 37.1, 36.4, 36.3, 34.1, 32.7, 31.2, 31.2, 27.7, 23.2, 22.9, 18.5, 18.0, 14.0; HRMS (ESI), calcd for $C_{26}H_{41}N_2O_5$ $[M + H]^+$ 461.3010; found 461.3013.

2.1.7 Spectra:

1. ^1H and ^{13}C NMR spectra of **42**
2. ^1H and ^{13}C NMR spectra of **44**
3. ^1H and ^{13}C NMR spectra of **41**
4. ^1H and ^{13}C NMR spectra of **45**
5. ^1H and ^{13}C NMR spectra of **46**
6. ^1H and ^{13}C NMR spectra of **47**
7. ^1H and ^{13}C NMR spectra of **38**
8. ^1H and ^{13}C NMR spectra of **37**
9. ^1H and ^{13}C NMR spectra of **48**
10. ^1H and ^{13}C NMR spectra of **35**
11. ^1H and ^{13}C NMR spectra of **19**
12. HPLC data for compound **41**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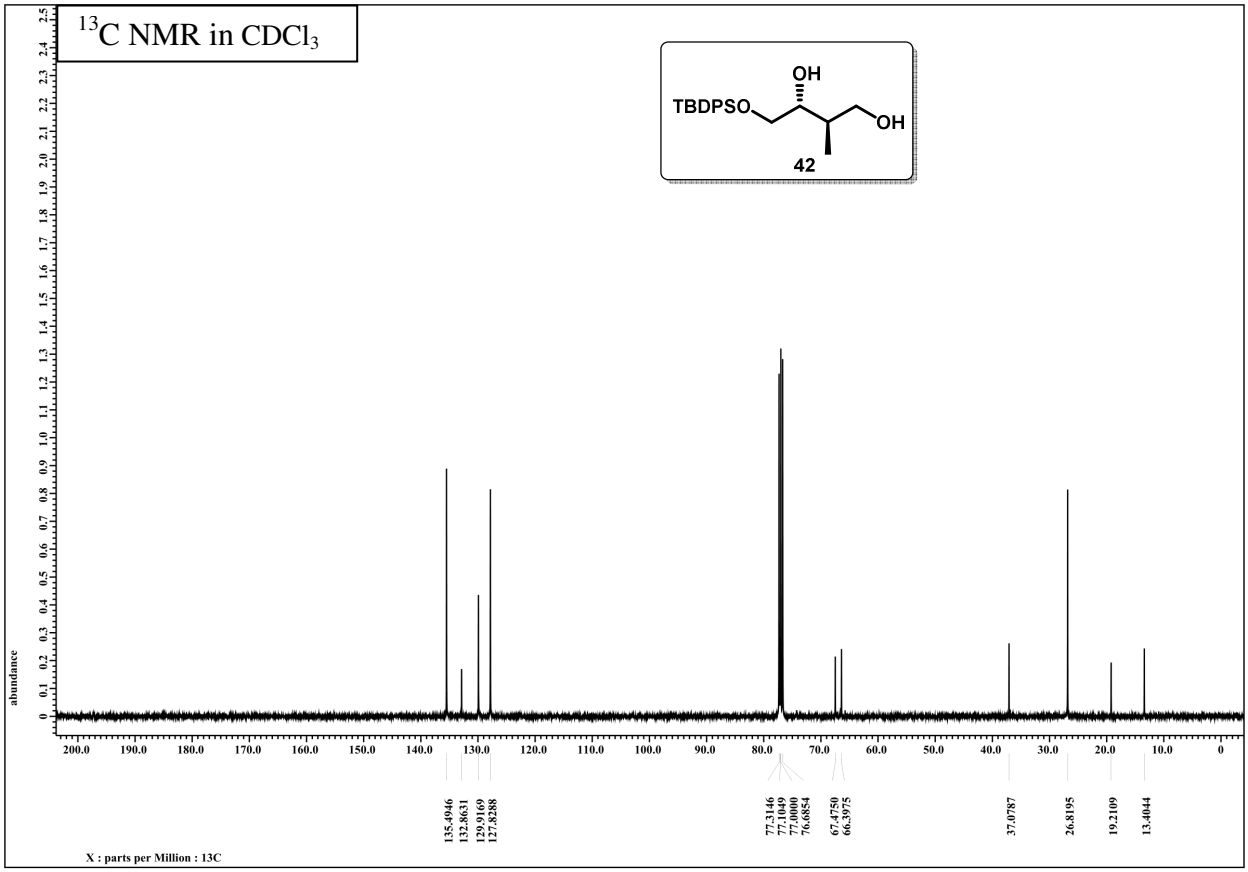
OH
TBDPSO
OH
42
abundance
X : parts per Million : 1H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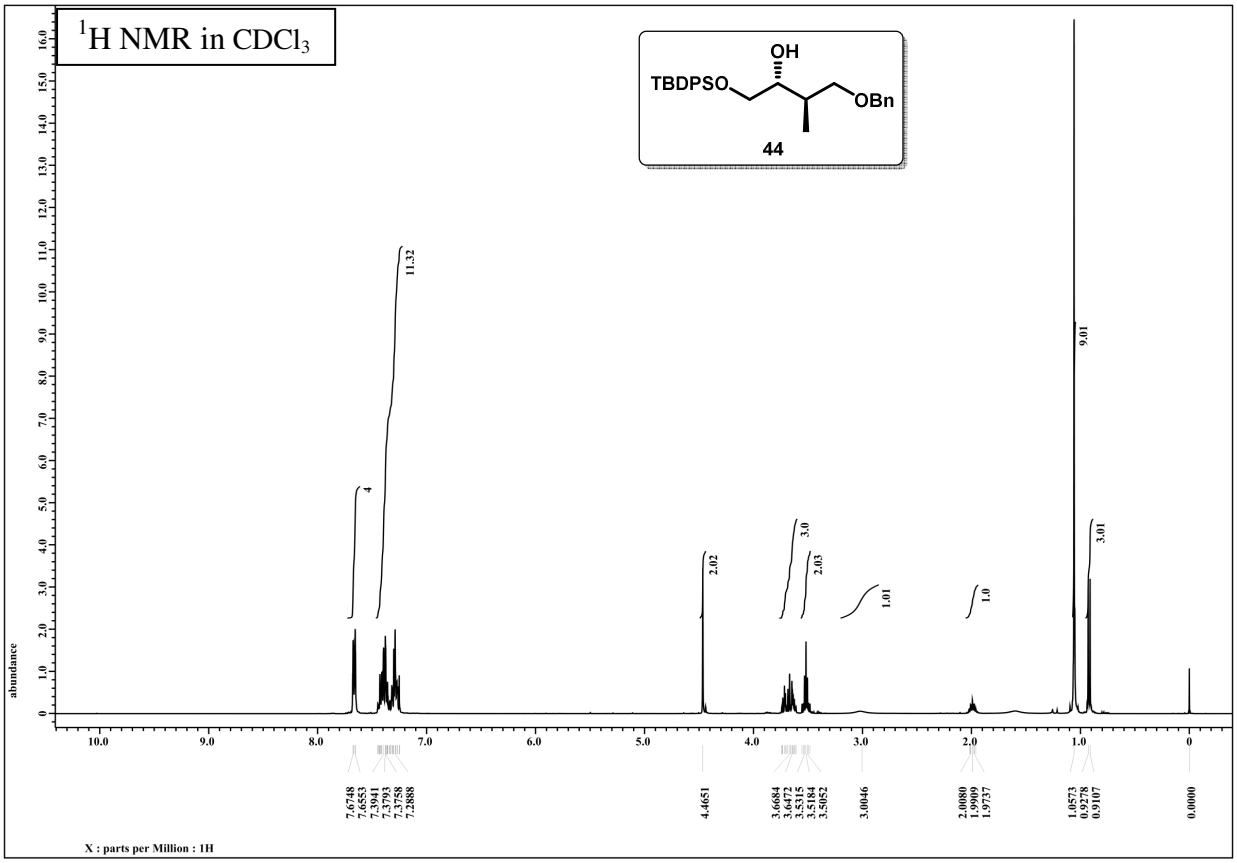
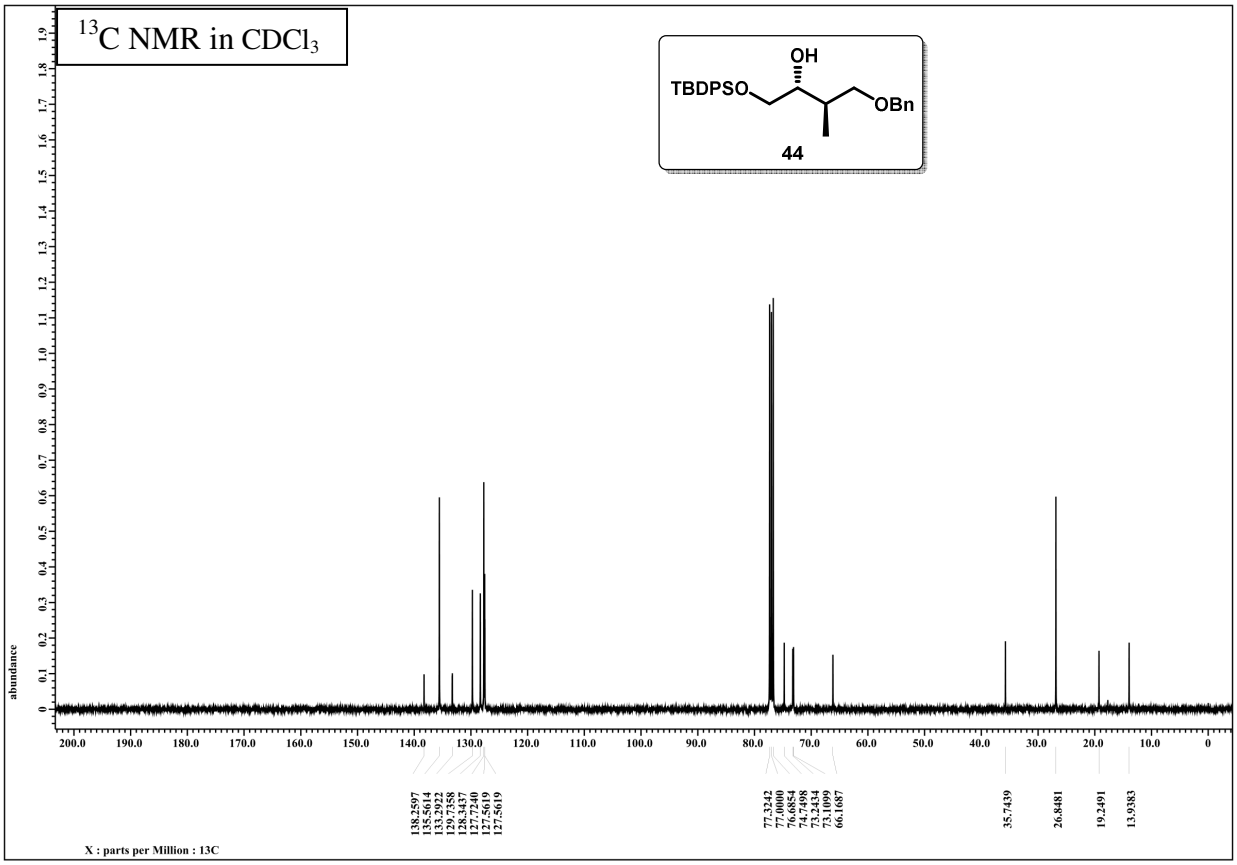
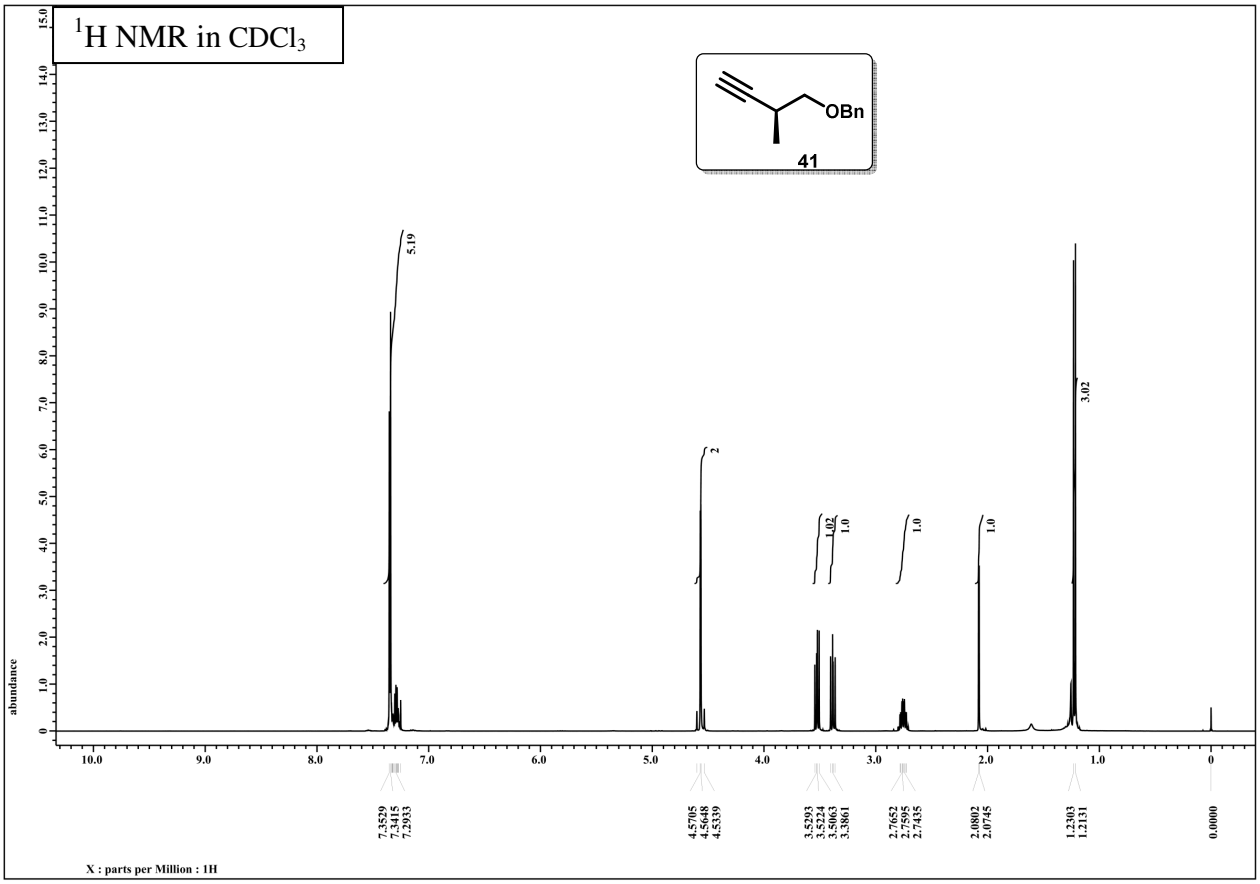
OH
TBDPSO
OH
42
abundance
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OH
TBDPSO
OBn
44
11.32
9.01
4
2.02
3.0
2.03
3.01
1.01
1.0
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
TBDPSO
OBn
44
abundance
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OBn
41
abundance
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1.02
1.0
1.0
1.0
3.02
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.3529
7.3415
7.2933
4.5705
4.5648
4.5339
3.5293
3.5224
3.5063
3.3861
2.7652
2.7595
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2.0802
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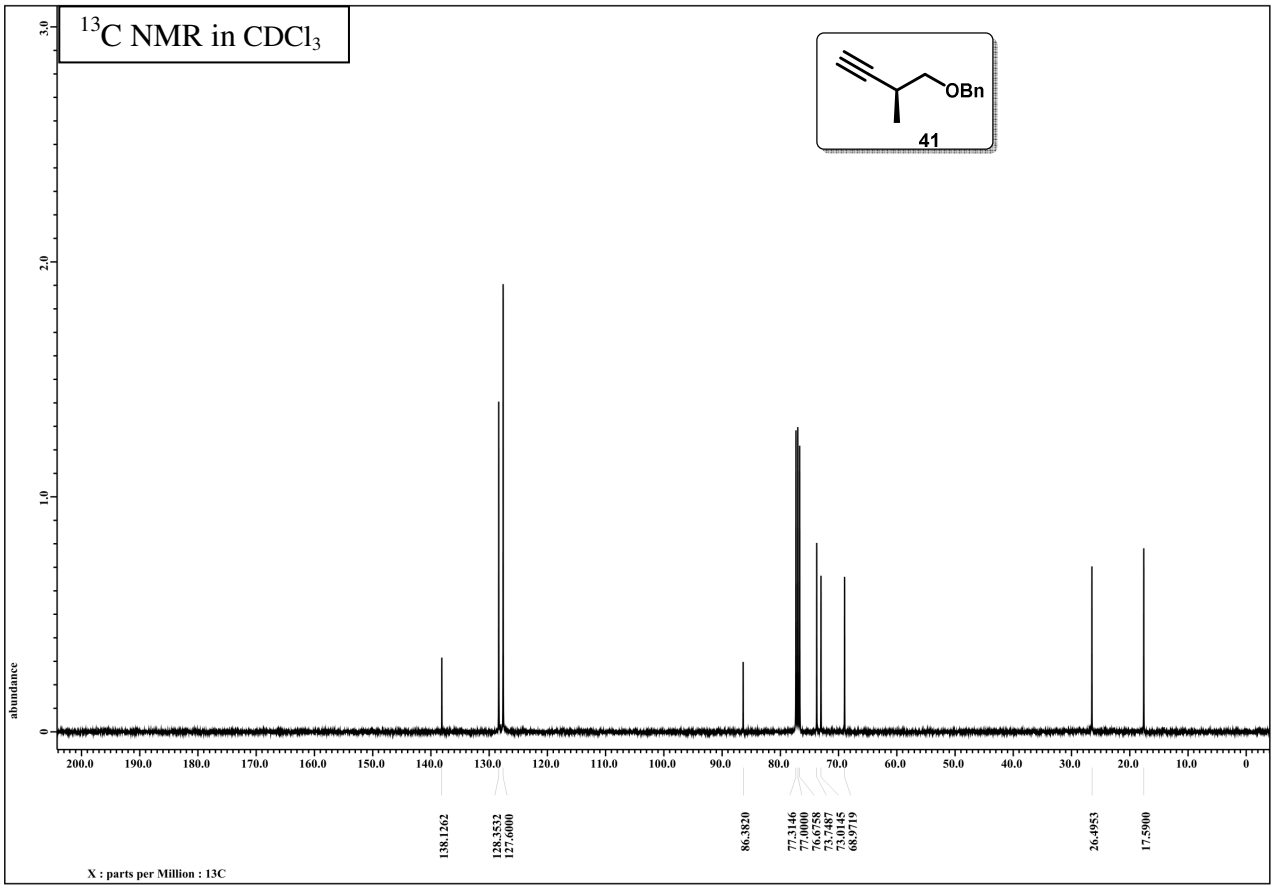
1.2131
0.0000
X : parts per Million : 1H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OBn
41
abundance
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170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
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128.3532
127.6000
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77.0000
76.6758
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73.0145
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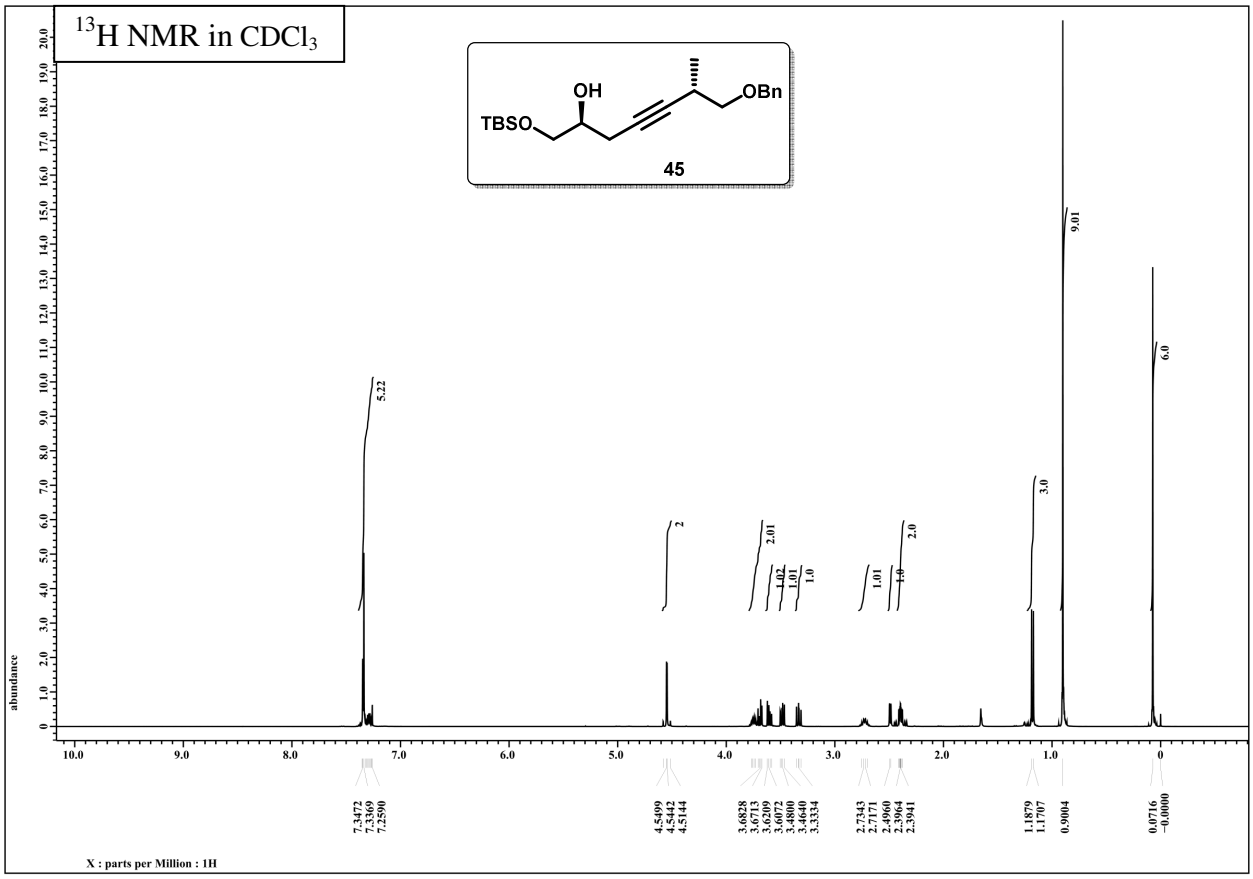
17.5900
X : parts per Million : 13C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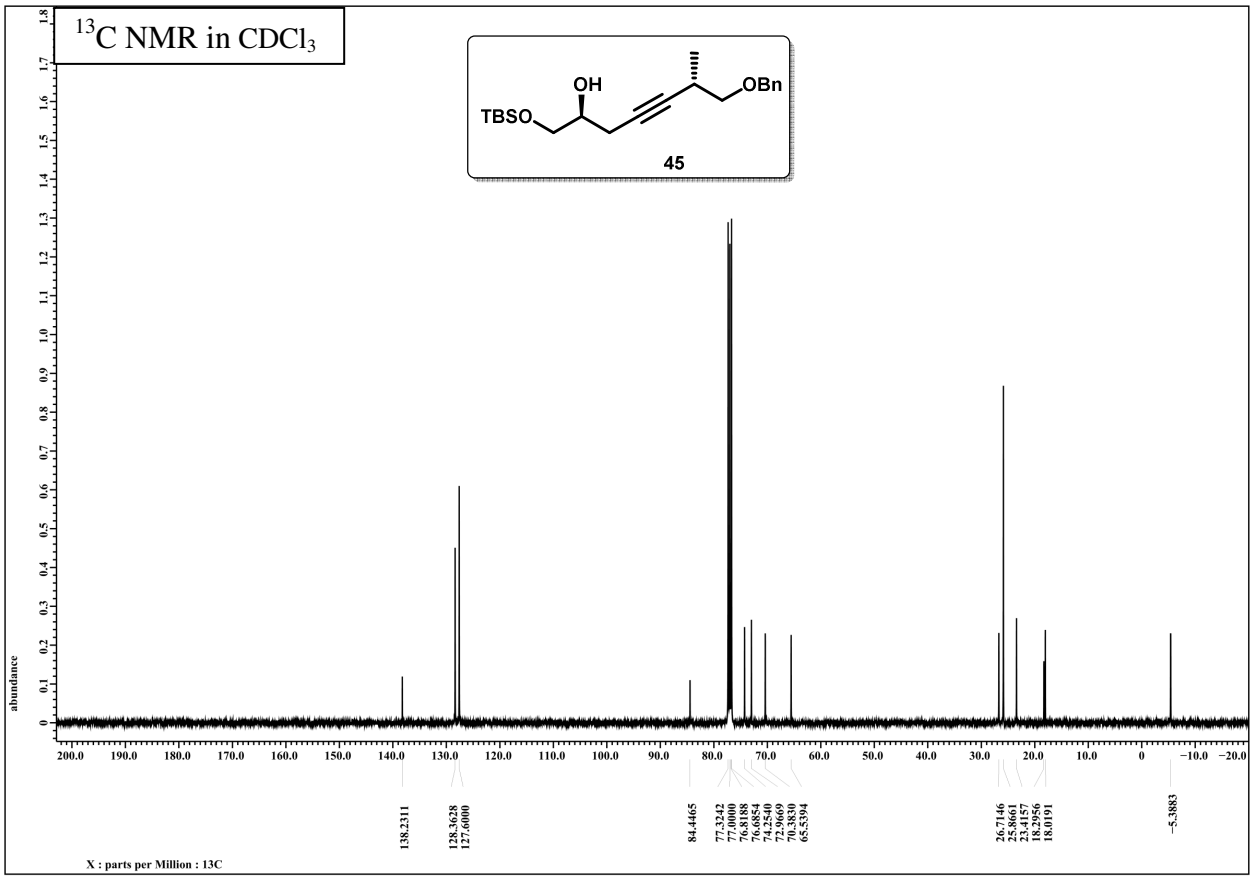
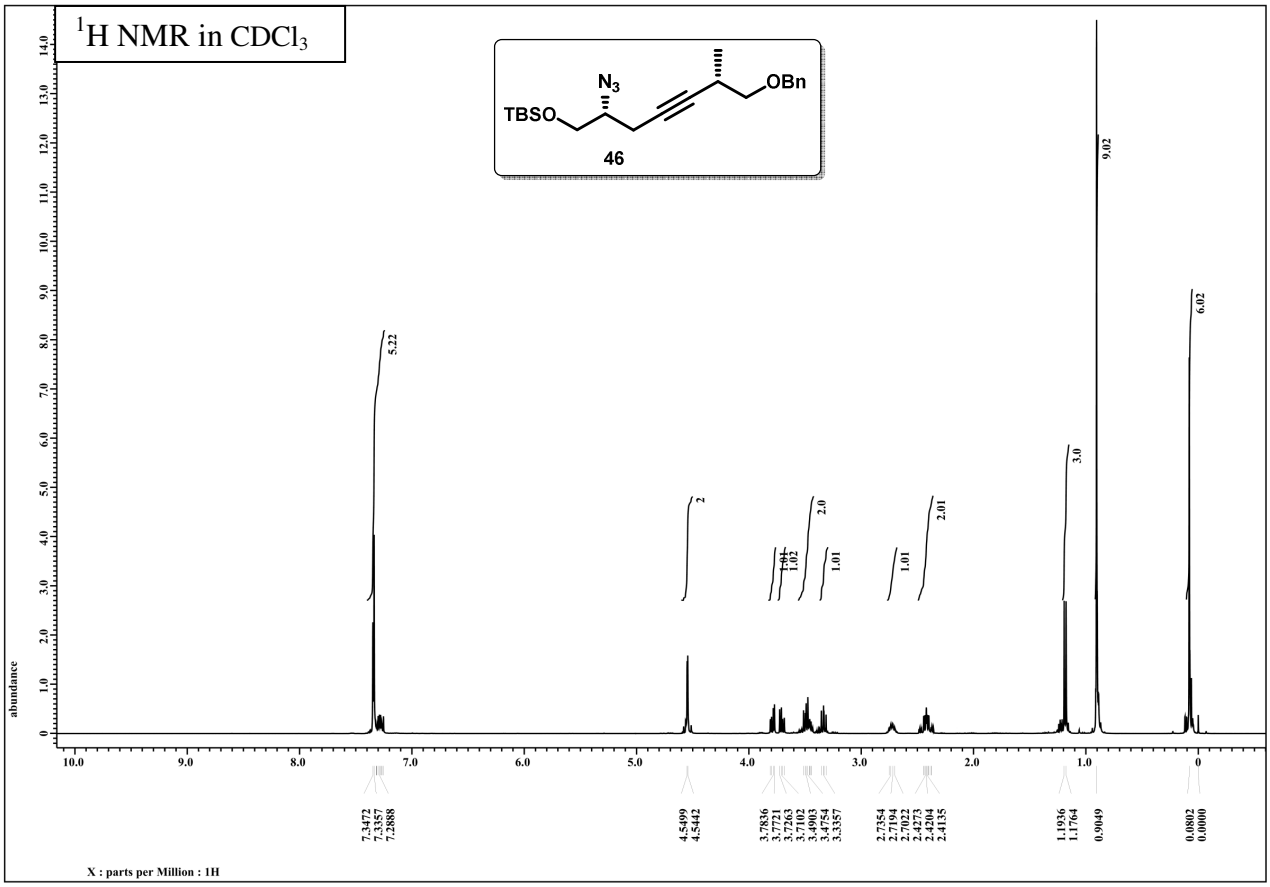
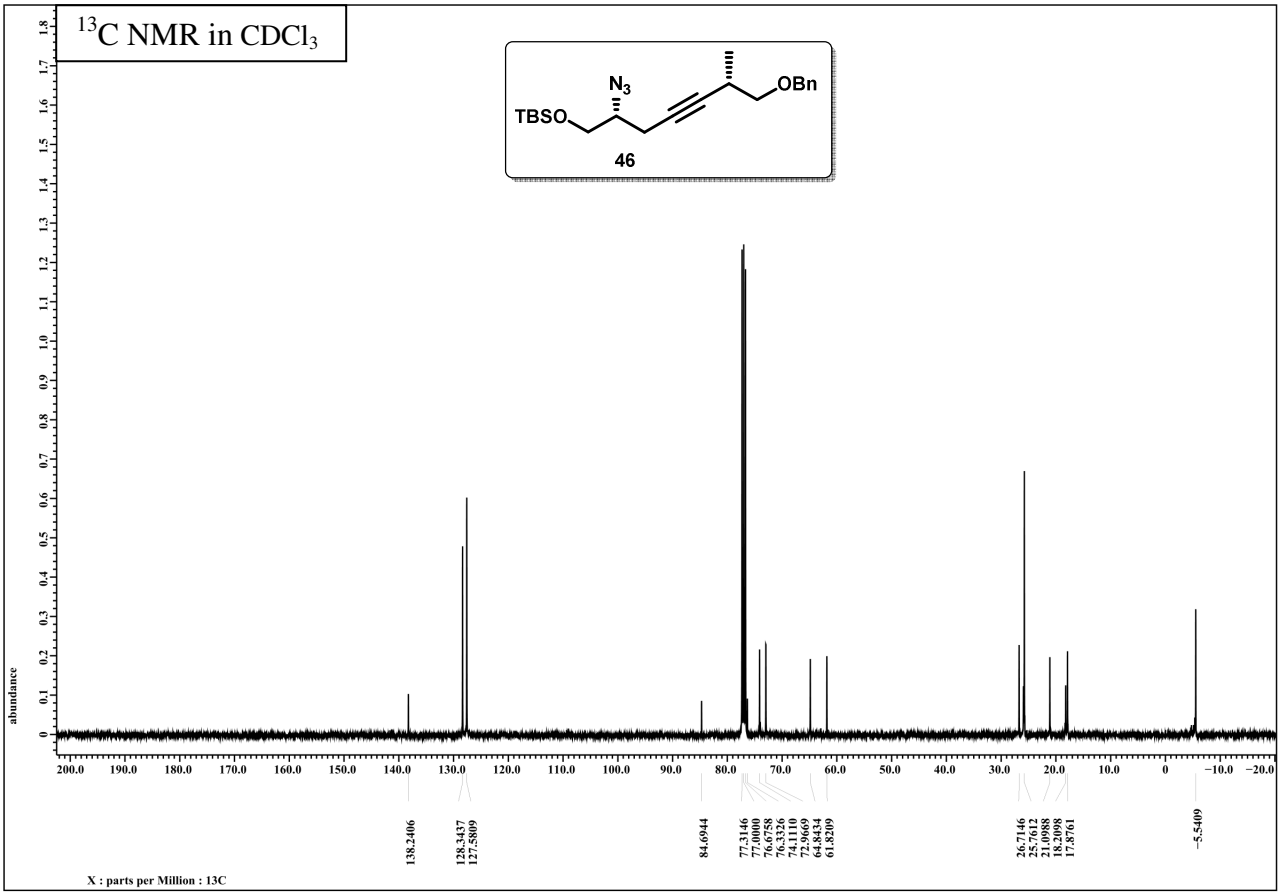
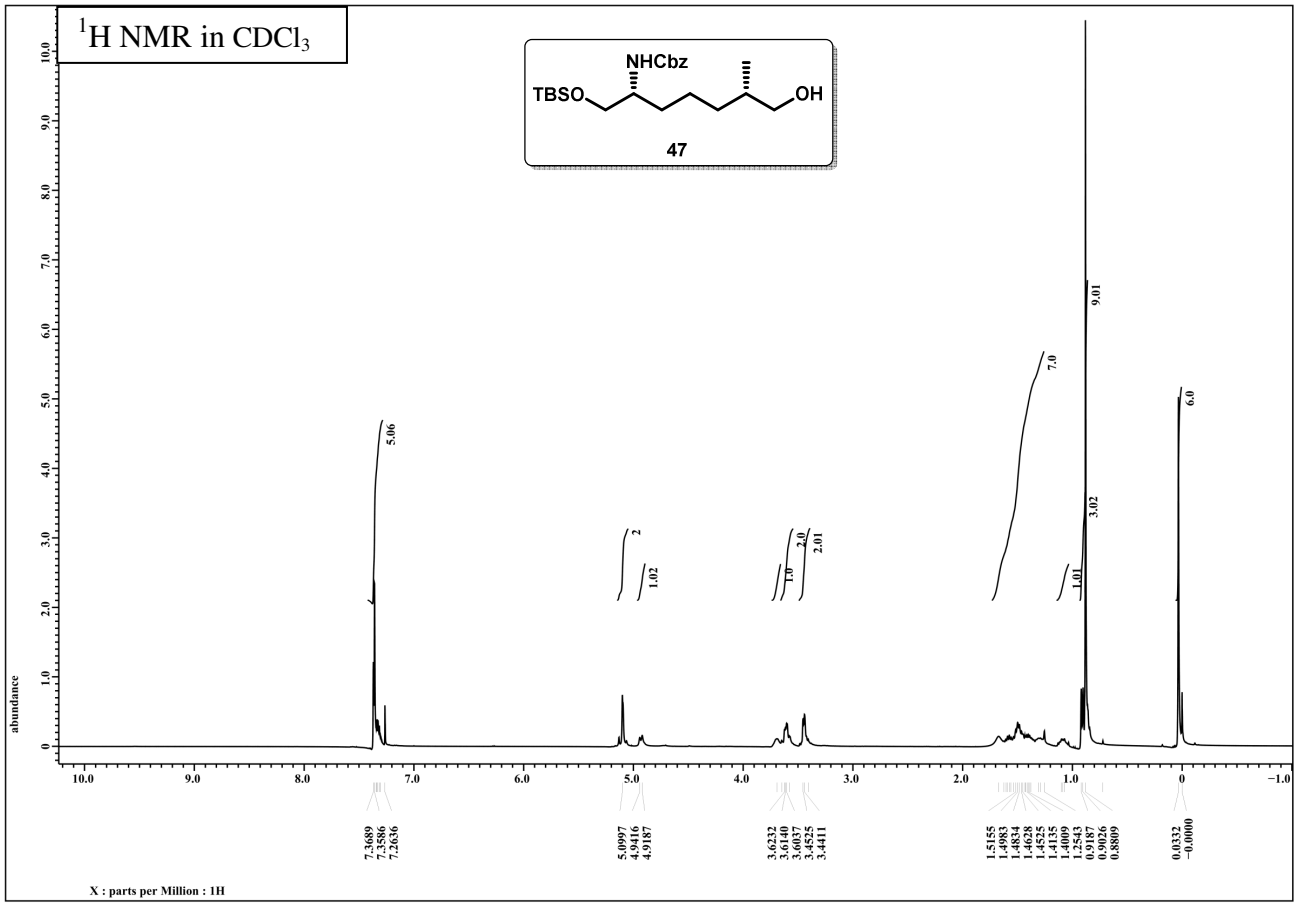
OH
TBSO
OBn
45
abundance
X : parts per Million : 1H


^{13}C NMR in CDCl$_3$
OH
TBSO
OBn
45
abundance
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
N3
OBn
TBSO
46
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
N3
OBn
TBSO
46
abundance
X : parts per Million : 13C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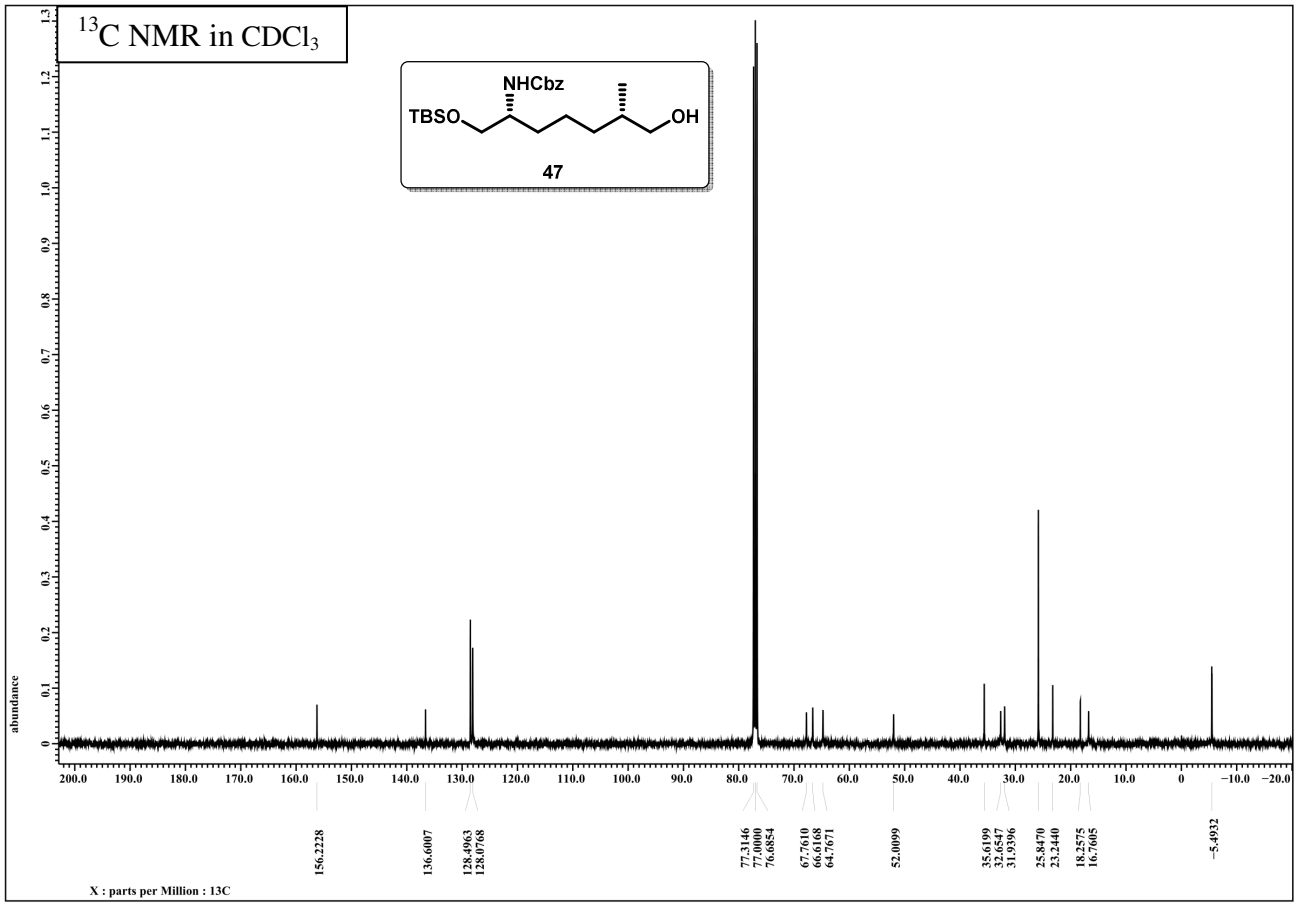
TBSO
OH
47
abundance
X : parts per Million : 1H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NHCbz
TBSO
OH
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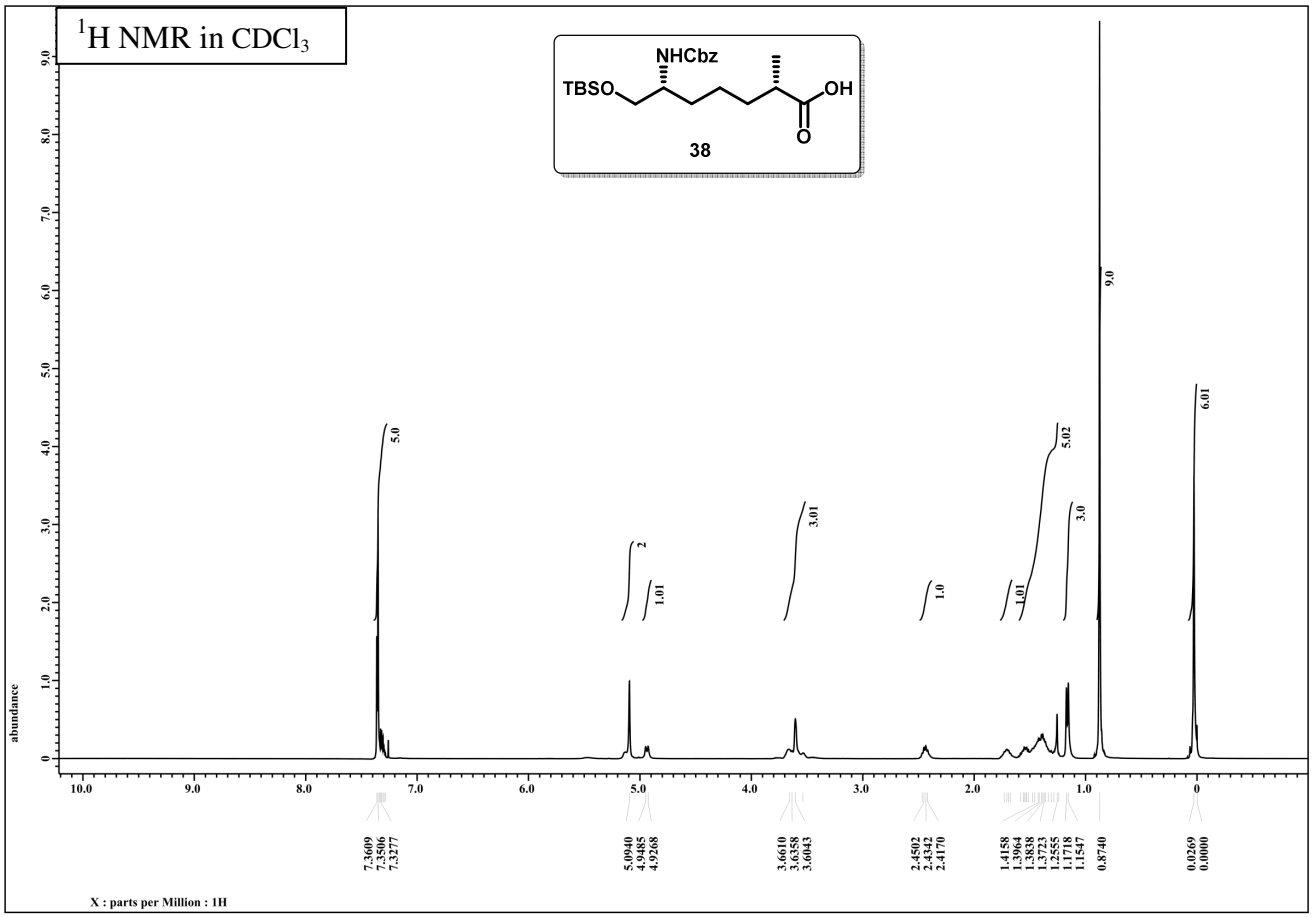
abundance
X : parts per Million : 13C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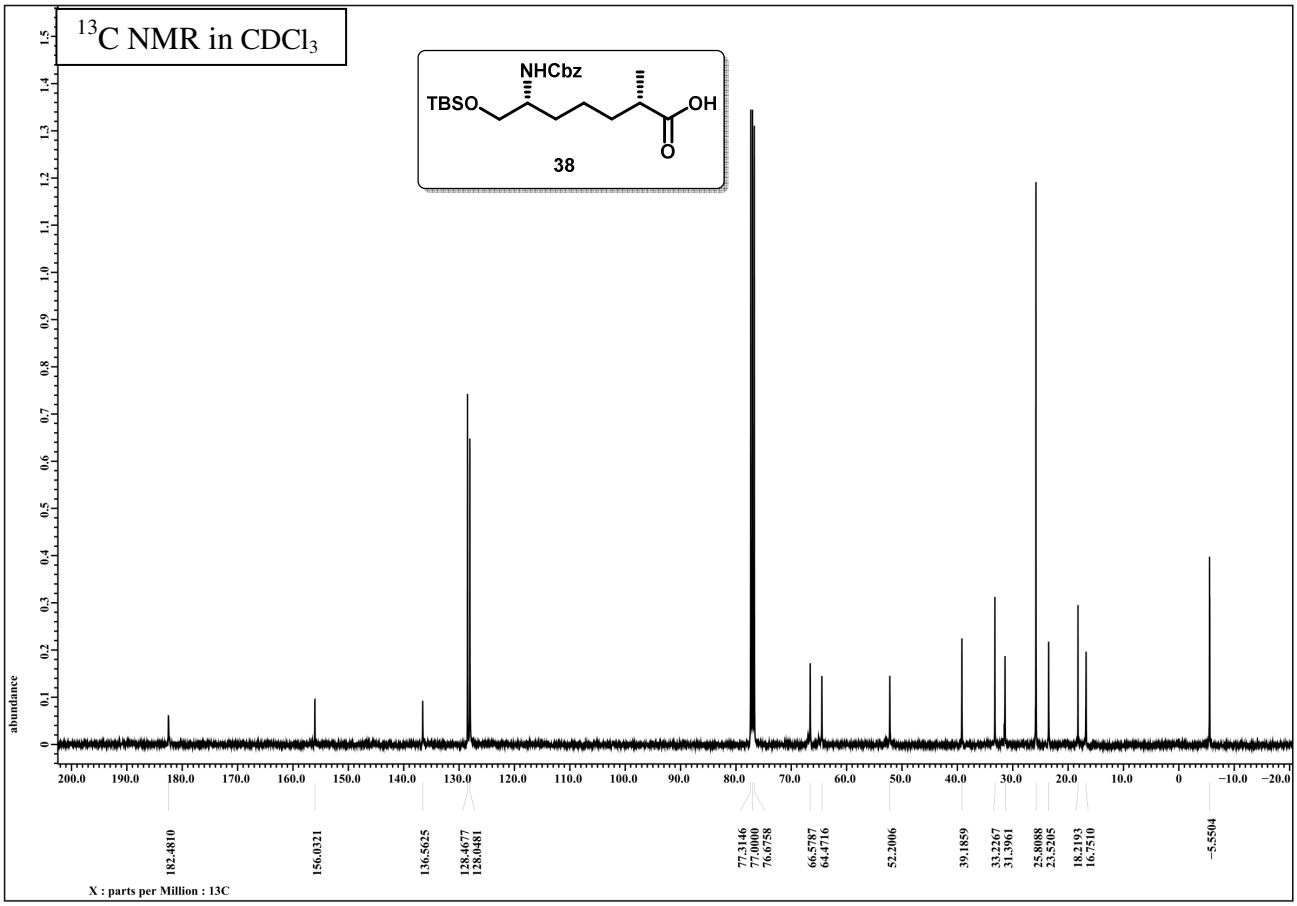
TBSO
OH
O
38
abundance
X : parts per Million : 1H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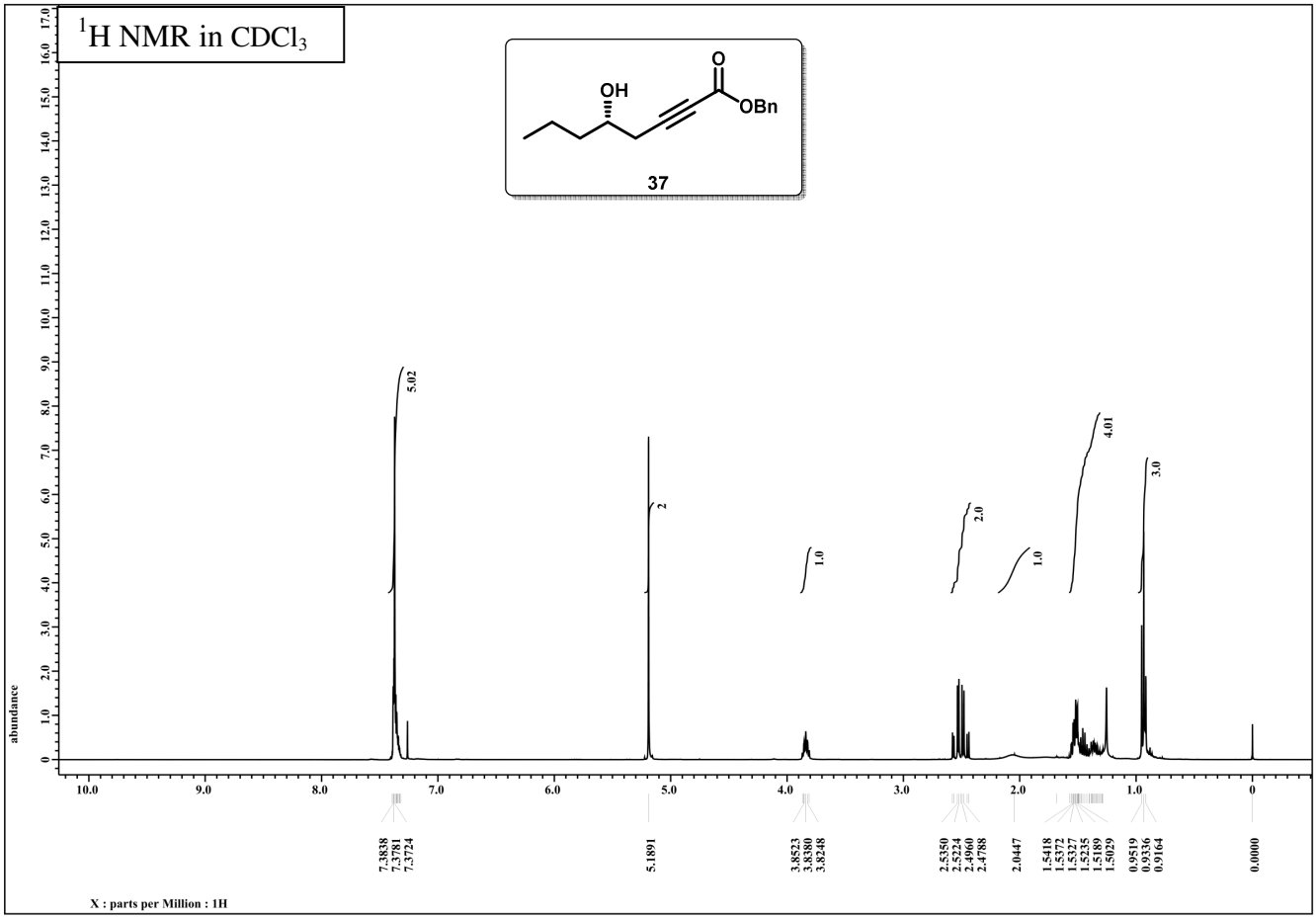
NHCbz
TBSO
OH
O
38
abundance
X : parts per Million : 13C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O
OBn
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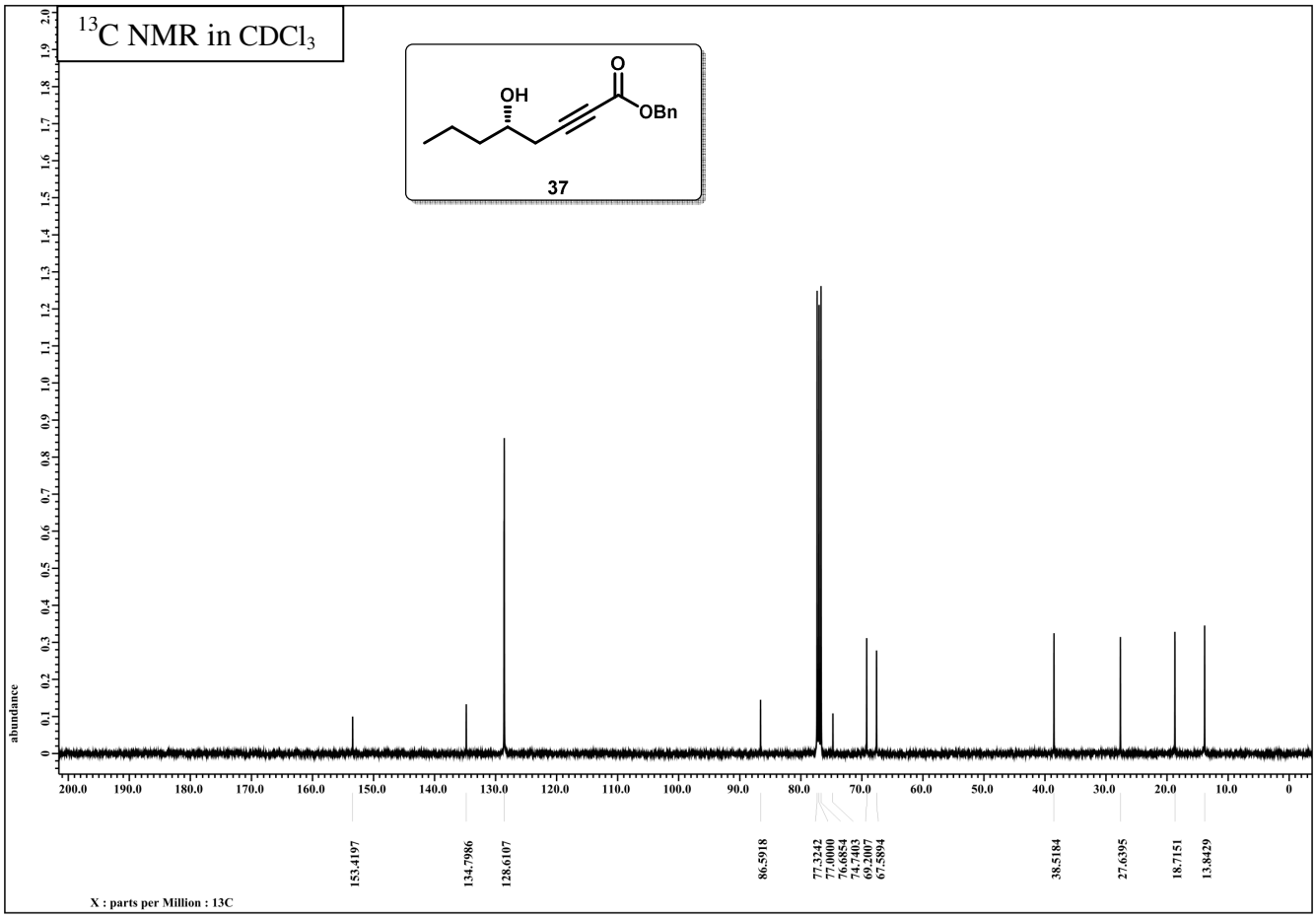
2
1.0
2.0
1.0
4.01
3.0
abundance
X : parts per Million : 1H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OH
O
OBn
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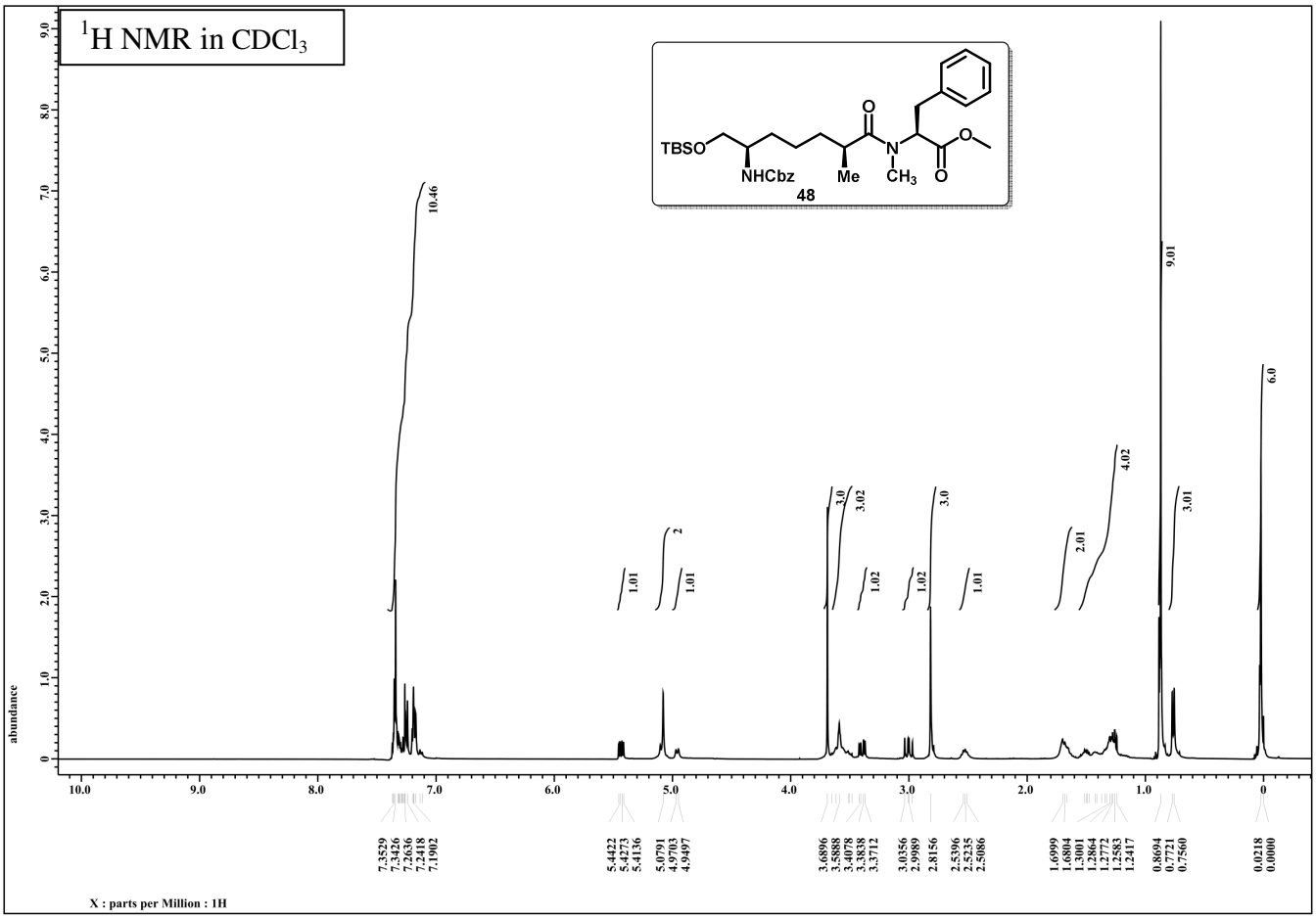
abundance
X : parts per Million : 13C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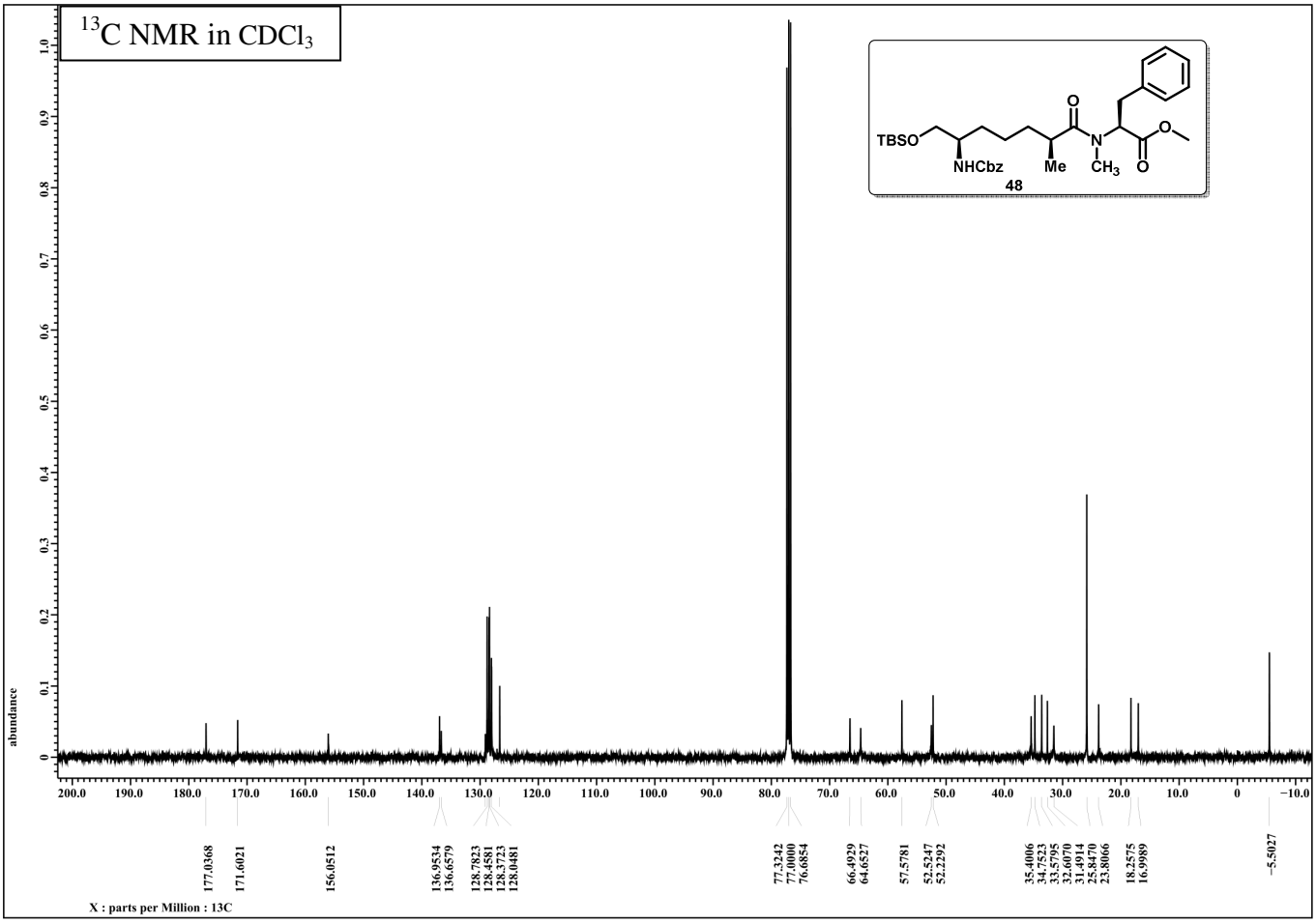
TBSO
NHCbz
Me
CH_3
O
N
O
48
abundance
X : parts per Million : 1H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CH_3
O
N
O
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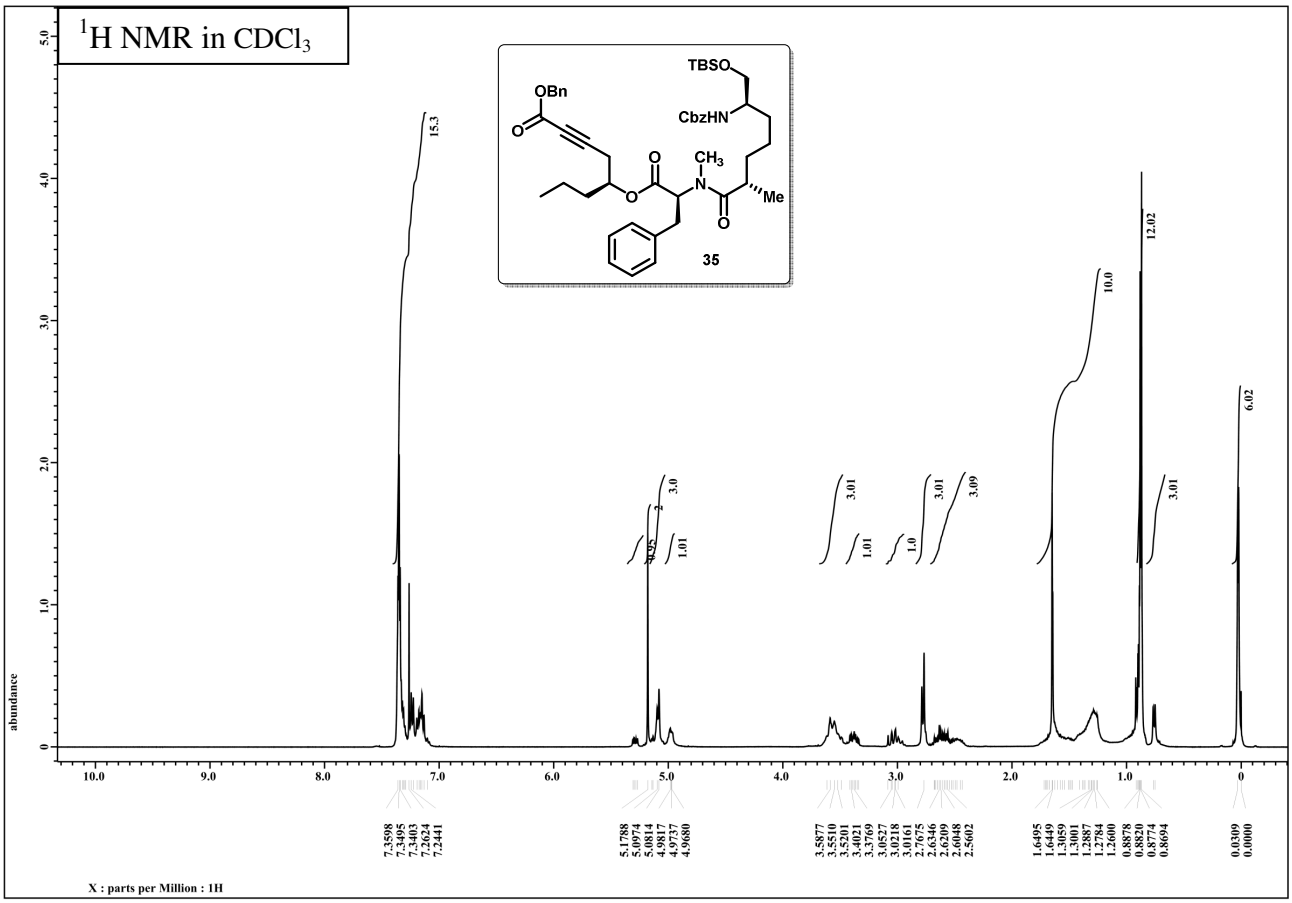
abundance
X : parts per Million : 13C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N
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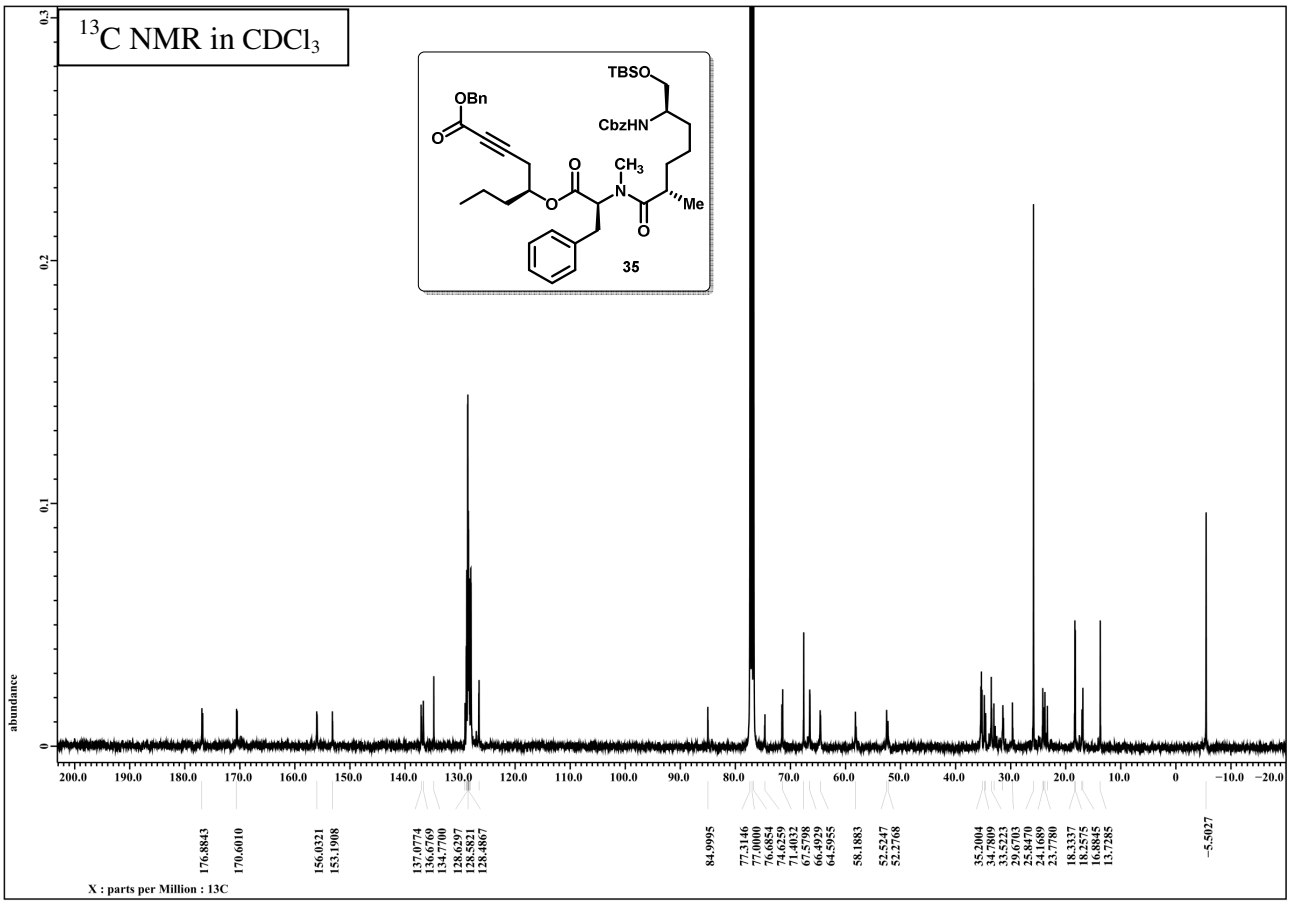
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CbzHN
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N
Me
O
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abundance
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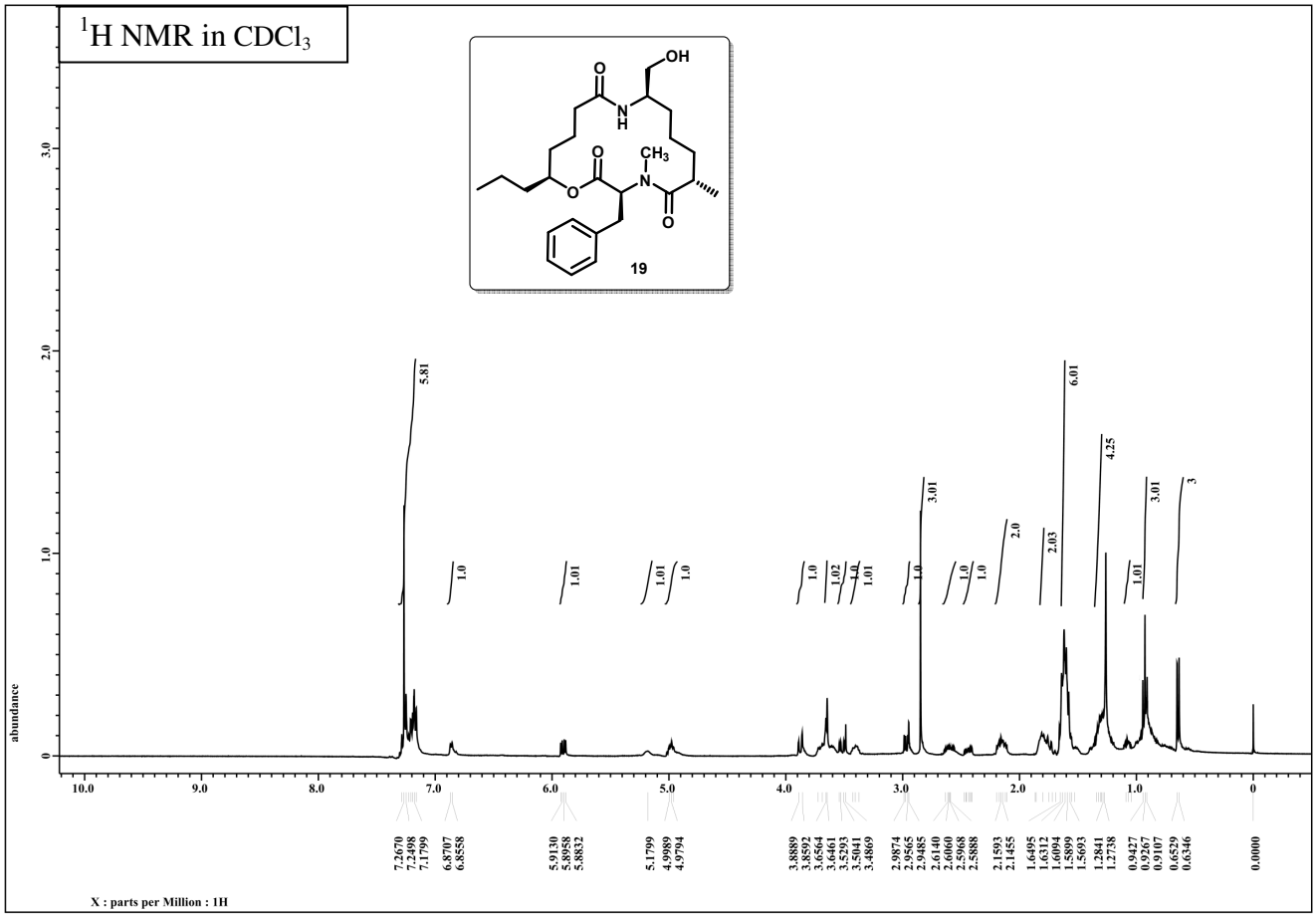
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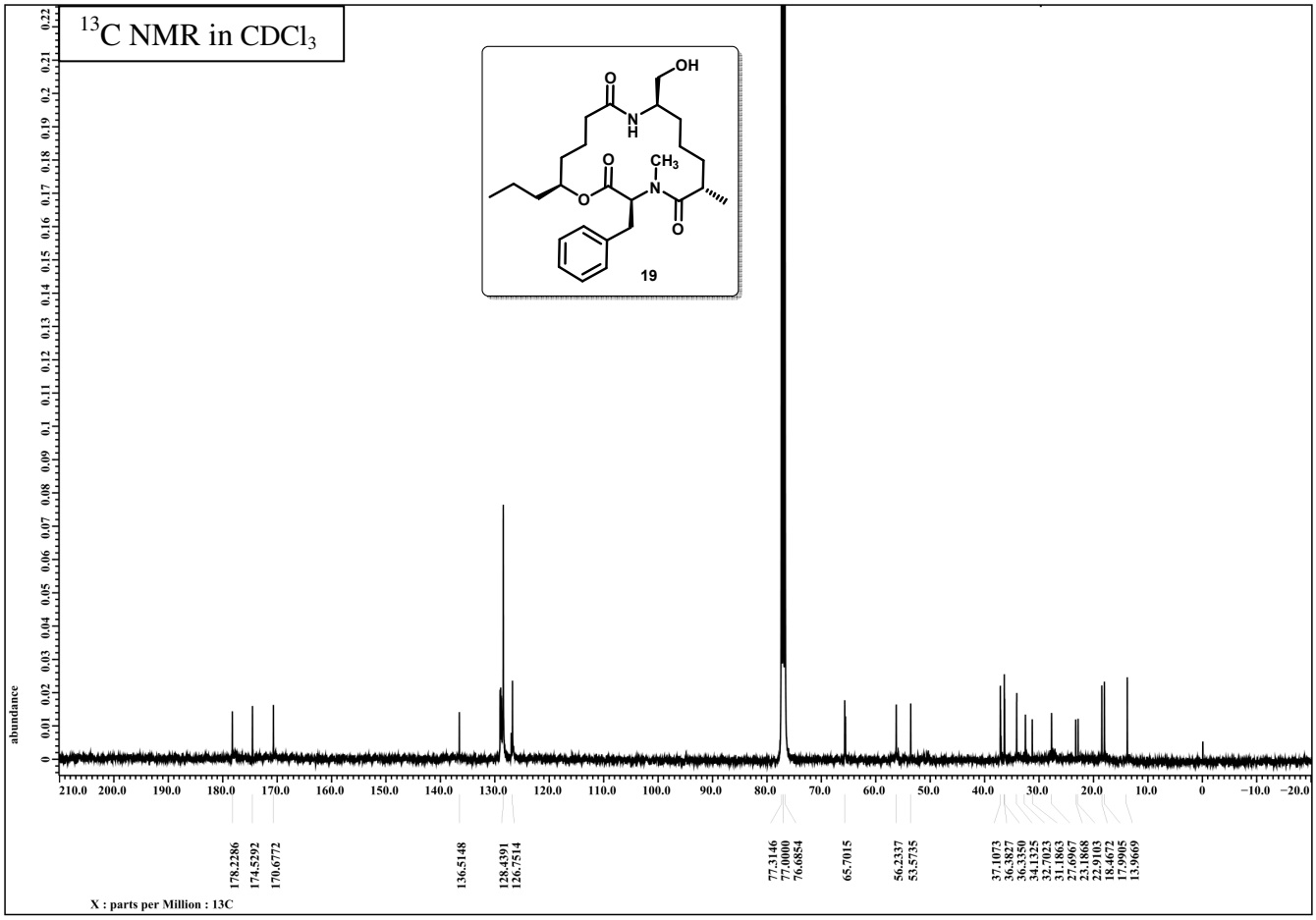
19
abundance
X : parts per Million : 1H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19
abundance
X : parts per Million : 13C

Racemic 41

D-7000 HPLC System Manager Report

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Reported: 07/15/16 01:56 PM
Processed: 07/15/16 01:56 PM

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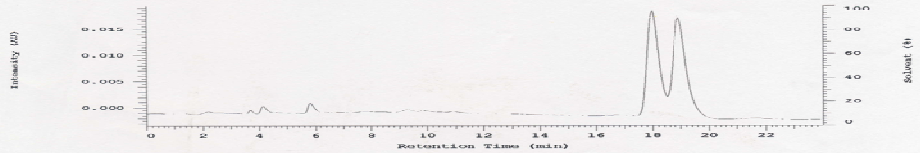
Processing Method: SANTOSHH
System(acquisition): Sys 1
Application: HPLC
Sample Name: BENZYL-Rac
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O (85:15)

Series:8991
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



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		19205	597604	100.000

Peak rejection level: 0

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WAVELENGTH :- 254nm
FLOW RATE :- 0.5 ml/min (880 psi)
SAMPLE CONC :-1 mg/1 ml injection vol: 2 ul

Chiral 41

D-7000 HPLC System Manager Report

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Reported: 07/15/16 01:55 PM
Processed: 07/15/16 01:55 PM

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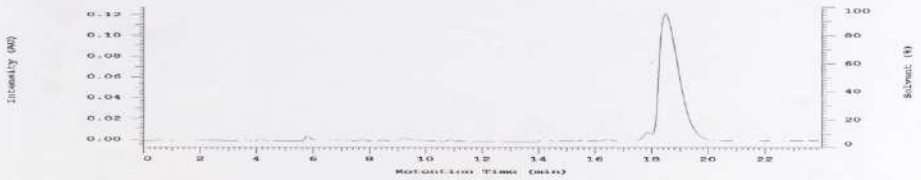
System(acquisition): Sys 1
Application: HPLC
Sample Name: BENZYL-Chiral
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O(85:15)

Series:8992
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



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		64650	2977363	100.000

Peak rejection level: 0

Group Leader :-Dr.P.K.TRIPATHI
COLUMN :chiralcel OJ-RH(150 X 4.6mm)
MOBILE PHASE :-MEOH:H2O(85:15)
WAVELENGTH :- 254nm
FLOW RATE :- 0.5 ml/min (880 psi)
SAMPLE CONC :-1 mg/1 ml injection vol: 2 ul

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CHAPTER 3

Stereoselective approaches towards the synthesis of 2,5-disubstituted-3-oxygenated tetrahydrofuran and 2,3,4,6-tetrasubstituted pyran and their applications to the total synthesis of (+)-petromyroxol and (+)-phomonol, respectively. This chapter is divided into two sections.

3.1 Section A

Enantioselective approach towards the total synthesis of 2,5-disubstituted 3-oxygenated tetrahydrofuran and its application to the total synthesis of (+)-petromyroxol

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3.1.1 Introduction:

The 2,5-disubstituted-3-oxygenated THF motif is found abundantly in biologically active natural products.[1] Petromyroxol **1**, *iso*-petromyroxol **2**,[2] *trans*-(-)-kumausyne **3**, *trans*-(+)-deacetylkumausyne **4**[3] and anthelmintic oxylipid **5**[4] marine natural products are few examples of dihydroxytetrahydrofuran from the acetogenin family[5] (Figure 1).

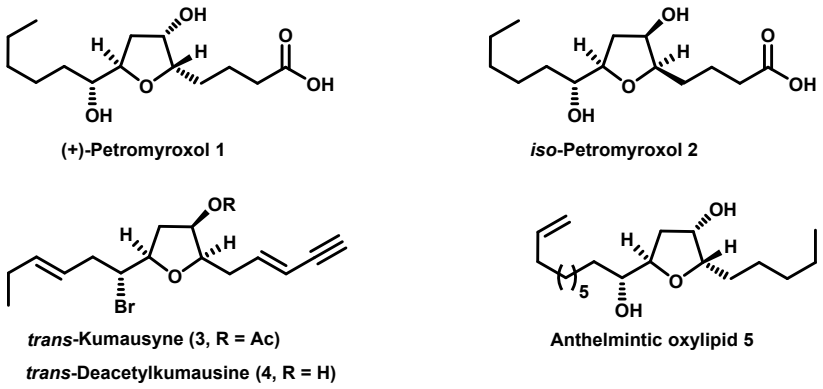


Figure 1. Some structures of acetogenin family natural products.

The novel dihydroxylated THF enantiomers (+)-petromyroxol **1**[2a] and *iso*-petromyroxol **2**[2b] were recently isolated by Li, W. and co-workers from water conditioned with larvae of the sea lamprey, *Petromyrzon marinus* L which represents the first example of dihydroxylated THF-containing metabolites isolated from a vertebrate.[2] The sea lamprey is an aggressive predator of trout populations, and found in the northern Atlantic Ocean along shores of North America and Europe, in the shores of the Great Lakes and in the western Mediterranean Sea.[6] Thus, there has been an extensive investigation on various novel aquatic pest-control and aquatic pheromones are ongoing.[7] (+)-Petromyroxol **1** has been a synthetic target of considerable interest due to its potent olfactory activity in the concentration range of 0.01-1 μM and with an array of functionalities. The absolute configuration of the four stereogenic centers of (+)-petromyroxol **1** and *iso*-petromyroxol **2** were determined by Li, W. and co-workers with the help of 2D NMR studies, compared with known substituted THF, and

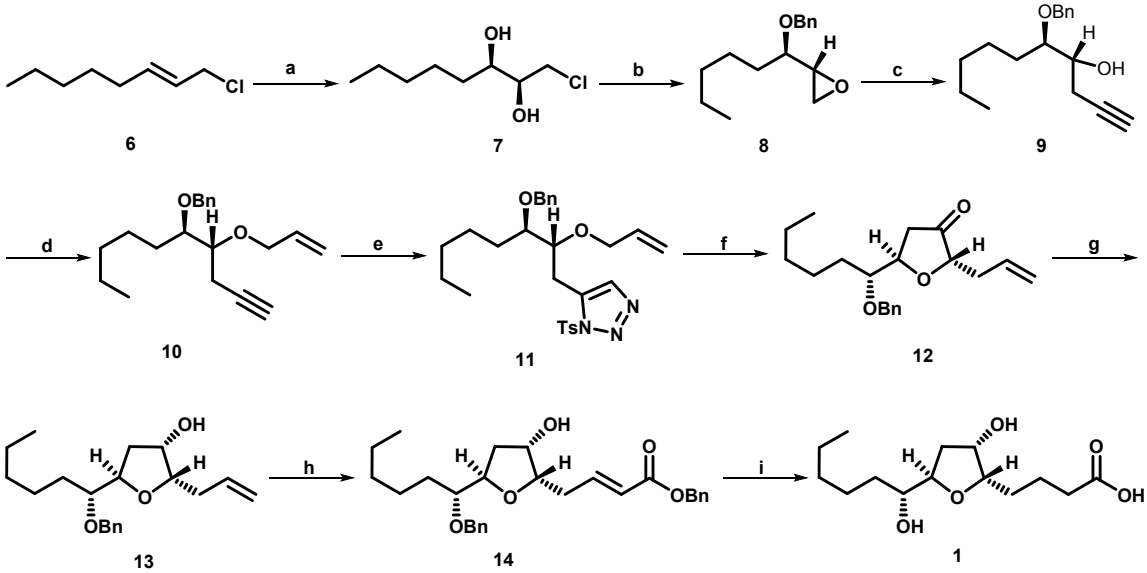
Mosher ester analysis. Therefore, it is highly desirable to develop a general synthetic route that provides a common pivotal intermediate from which 2,5-disubstituted-3-oxygenated THF motif with desired stereochemical variations can be synthesized.

3.1.2 Review of Literature:

Four total synthesis of (+)-petromyroxol **1** have been documented in the literature from academia[8] which are described below.

Boyer, A. (2015)[8a]

Alistair Boyer reported the first synthesis of (+)-petromyroxol **1** from a readily accessible allylic chloride **6** in nine steps using transition-metal-catalyzed denitrogenation rearrangement of 1-sulfonyl-1,2,3-triazoles as a key step (Scheme 1). The synthesis of the (+)-petromyroxol **1** began with the conversion of easily accessible *trans*-1-chloro-2-octene **6** to the 1,2-diol **7** *via* Sharpless AD with excellent yield (95%) and enantioselectivity (>95% *ee*). Diol **7** was converted into epoxide **8** by treatment with base followed by benzyl bromide in 78% yield. Regioselective ring opening of epoxide **8** with an aluminum acetylide led to alkyne derivative **9** in 83% yield. Then, the free hydroxyl group in **9** was subjected to *O*-allylation with allyl bromide in presence of NaHMDS which furnished the allyl ether **10** in 94% yield. Treatment of the terminal alkyne derivative **10** with *n*-BuLi followed by TsN_3, installed triazole moiety successfully resulting formation of compound **11** in 89% yield.



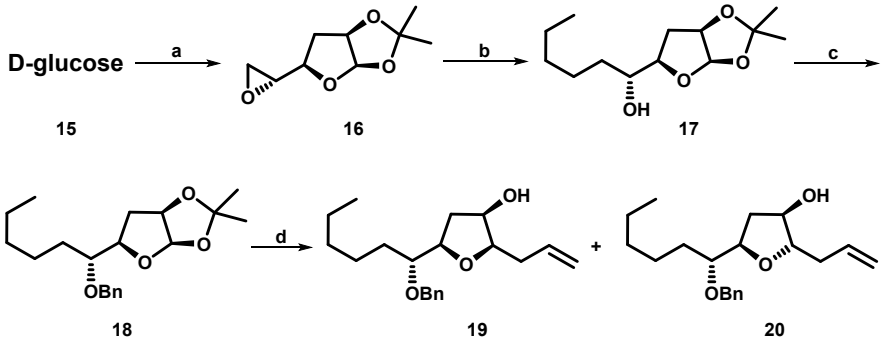
Scheme 1. *Reagents and conditions*: (a) 0.6 mol % OsO_4, 1.3 mol % $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, K_2CO_3, *t*-BuOH:H_2O 1:1 v/v, 0 ^oC, 18 h, 95%; (b) $NaN(SiMe_3)_2$, TBAI, BnBr, DMF, 0 ^oC to rt, 18 h, 78%; (c) Ethynyltrimethylsilane, *n*-BuLi, $AlMe_3$,

$BF_3.OEt_2$, TBAF, -78 °C, 16 h, 83%; (d) $NaN(SiMe_3)_2$, allyl bromide, TBAI, THF, 0 °C to rt, 12 h, 94%; (e) TsN_3, *n*-BuLi, THF, -78 °C, 1 h, 89%; (f) $Rh_2(OAc)_4$, toluene, reflux, basic Al_2O_3, 1 h, 67%; (g) *s*-Bu_3BHLi, THF, -78 °C, 16 h, 79%; (h) Benzyl acrylate, Grubbs' second generation catalyst, DCM, 50 °C, 2.5 h, 82%; (i) H_2, Pd/C, EtOAc, 20 °C, 36 h, 89%.

The conditions developed previously, were used for the conversion of **11** into furanone **12** with the desired *trans*-2,5-configuration. Reduction of the ketone in compound **12** with lithium tri-*sec*-butylborohydride cleanly furnished the THF derivative **13** in 79% yield with >10:1 selectivity. Cross-metathesis was carried out between alkene derivative **13** and benzyl acrylate in presence of a small amount (5 mol %) of Grubbs' second generation catalyst to afford compound **14** in 82% yield. Finally, treatment of the benzyl ester **14** with hydrogenation condition furnished the synthetic (+)-petromyroxol **1** in 89% yield.

Ramana, C. V. *et al.* (2015)[8b]

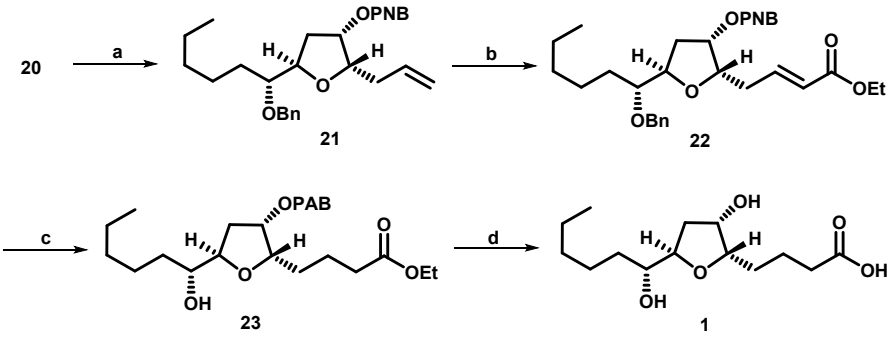
C. V. Ramana and co-workers described the total synthesis of (+)-petromyroxol **1** from easily accessible carbohydrate building block as starting material (Scheme 2). Synthesis of petromyroxol **1** thus began with the preparation of epoxide **16** from D-glucose **15**[9] *via* a known procedure (Scheme 2). Treatment of the epoxide derivative **16** with *n*-BuLi and CuI afforded alcohol derivative **17** in 76% yield. Then, the free hydroxyl group in **17** was subjected to *O*-benzylation with benzyl bromide in presence of NaH to furnish the benzyl ether derivative **18** in 95% yield. Next, acetonide **18** was treated with allyltrimethylsilane and $BF_3.Et_2O$ to give a mixture of *α*- and *β*-C-allylglycosides **20***α*/**19***β* in a ratio of 7 : 3 with 81%



Scheme 2. *Reagents and conditions*: (a) See reference 9; (b) *n*-BuLi, CuI, Et_2O, -40 to 0 °C, 2 h, 76%; (c) NaH, BnBr, THF, 0 °C to rt, 8 h, 95%; (d) allylTMS, $BF_3.OEt_2$, CH_2Cl_2, 3 h, 81%.

yield at 0 °C and a ratio of 1:1 at -40 °C. Free hydroxyl group in THF derivative **20***α* was converted into ester **21** under Mitsunobu conditions in 81% yield (Scheme 3). Then, one pot oxidative cleavage of terminal double bond **21** in presence of OsO_4 and sodium periodate

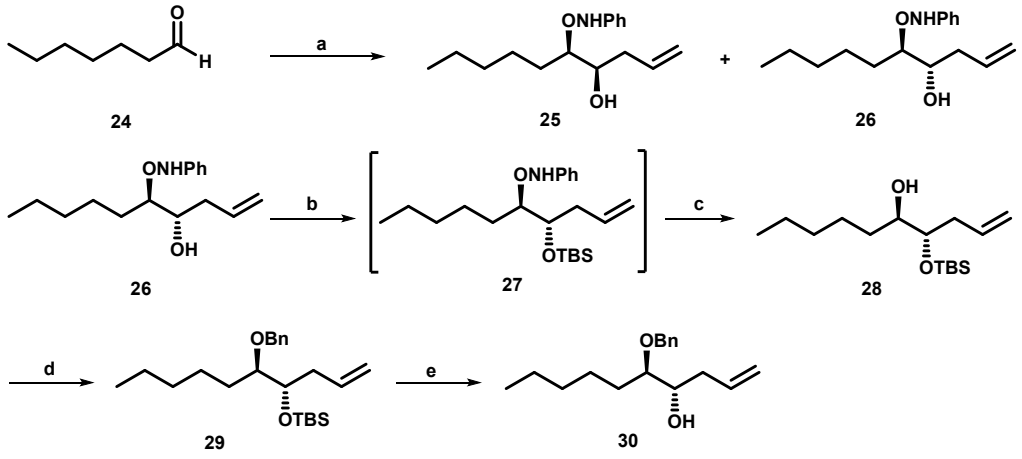
followed by two-carbon Wittig homologation afforded the unsaturated ester **22** in 69% yield. Compound **22** was subjected to hydrogenation using Pearlman catalyst [20% $Pd(OH)_2/C$], which afforded the ester derivative **23** in 89% yield. Finally, KOH mediated saponification of both the ester groups in **23** provided (+)-petromyroxol **1** in 77% yield.



Scheme 3. *Reagents and conditions*: (a) *p*-nitrobenzoic acid, DIAD, PPh_3, THF, 0 °C to rt, 3 h, 81%; (b) i) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, H_2O, 6 h; ii) $Ph_3P{=}CHCO_2Et$, THF, 0 °C to rt, 12 h, 69% (over 2 steps); (c) 1 bar H_2, 20% $Pd(OH)_2/C$, MeOH, rt, 3 h, 89%; (d) aq. KOH, MeOH, rt, 12 h, 77%.

Kumar, P. *et al*. (2015)[8c]

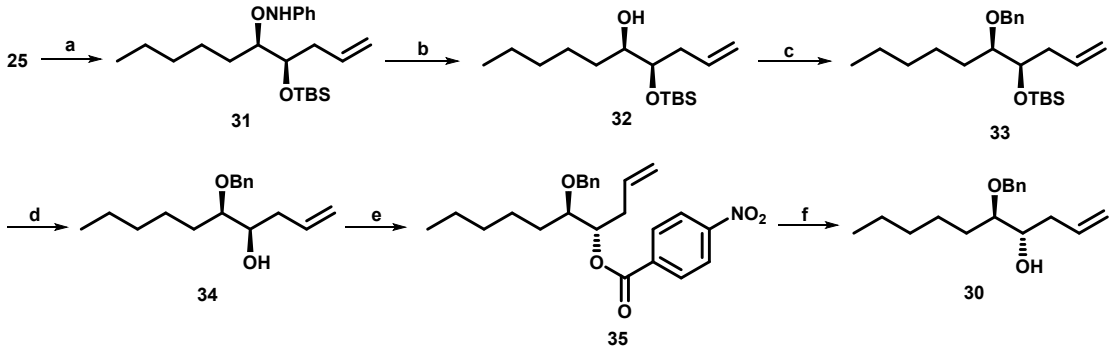
P. Kumar and co-workers described the total synthesis of (+)-petromyroxol **1** employed a tandem *α*-aminoxylation-allylation, cross metathesis and tandem AD-S_N2 cyclization as key



Scheme 4. *Reagents and conditions*: (a) L-Proline, nitrosobenzene, DMSO, rt, 20 min, In powder, allyl bromide, NaI, 30 min, 70%; (b) i) TBSOTf, TEA CH_2Cl_2, 15 min, 0 °C; (c) $Cu(OAc)_2$, MeOH, 12 h, 82% (over two steps); (d) NaHMDS, BnBr, TBAI, THF, 0 °C to rt, 2 h, 92%; (e) TBAF, THF, rt, 12 h, 95%.

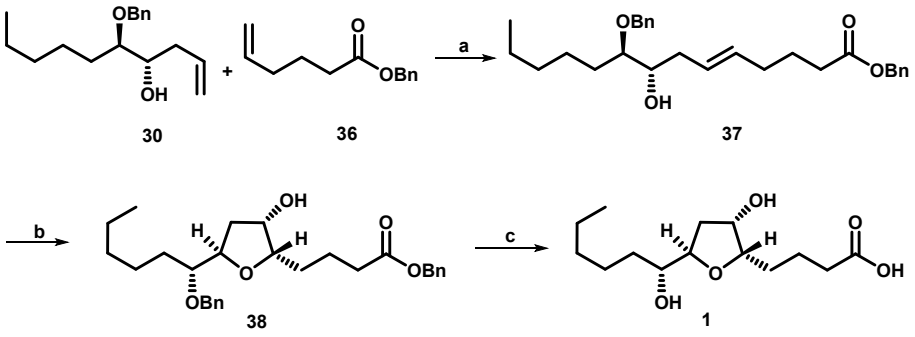
steps (Scheme 4). The synthesis of petromyroxol **1** commenced with commercially available heptanal **24** which was subjected to L-proline catalysed *α*-aminoxylation followed by *in situ*

allylation using indium, allyl bromide and sodium iodide to provide a column separable mixture of *O*-amino-substituted allylic alcohols **25** and **26** with a ratio of 3:2 (*syn*:*anti*) in 70% overall yield. The next step involved the TBS protection of *anti* compound **26** with TBSOTf and Et_3N to provide the silyl ether derivative **27** which was subjected to copper (II) acetate mediated N-O bond cleavage to furnish compound **28** in 82% yield. Further, treatment of the free hydroxyl group in compound **28** with NaHMDS and benzyl bromide provided benzyl ether **29**, which was subjected to TBAF mediated desilylation to afford homo allylic alcohol derivative **30** in 95% yield.



Scheme 5. *Reagents and conditions*: (a) TBSOTf, TEA, CH_2Cl_2, 15 min, 0 °C, 97%; (b) $Cu(OAc)_2$, MeOH, 12 h, 85%; (c) NaHMDS, BnBr, TBAI, THF, 0 °C to rt, 2 h, 92%; (d) TBAF, THF, rt, 12 h, 95%; (e) PNBA, DIAD, Toluene, 0 °C to rt, 97%; (f) $LiOH.H_2O$, THF, MeOH, H_2O, rt, 95%.

Further, compound **25** was converted into the homoallylic alcohol **34** (Scheme 5) following a similar sequence of reactions as described in Scheme 4. Alcohol derivative **34** was smoothly converted to the ester derivative **35** *via* Mitsunobu reaction in 97% yield. Then, saponification of ester **35** with LiOH in aqueous methanolic THF at room temperature furnished compound **30** in 95% yield.



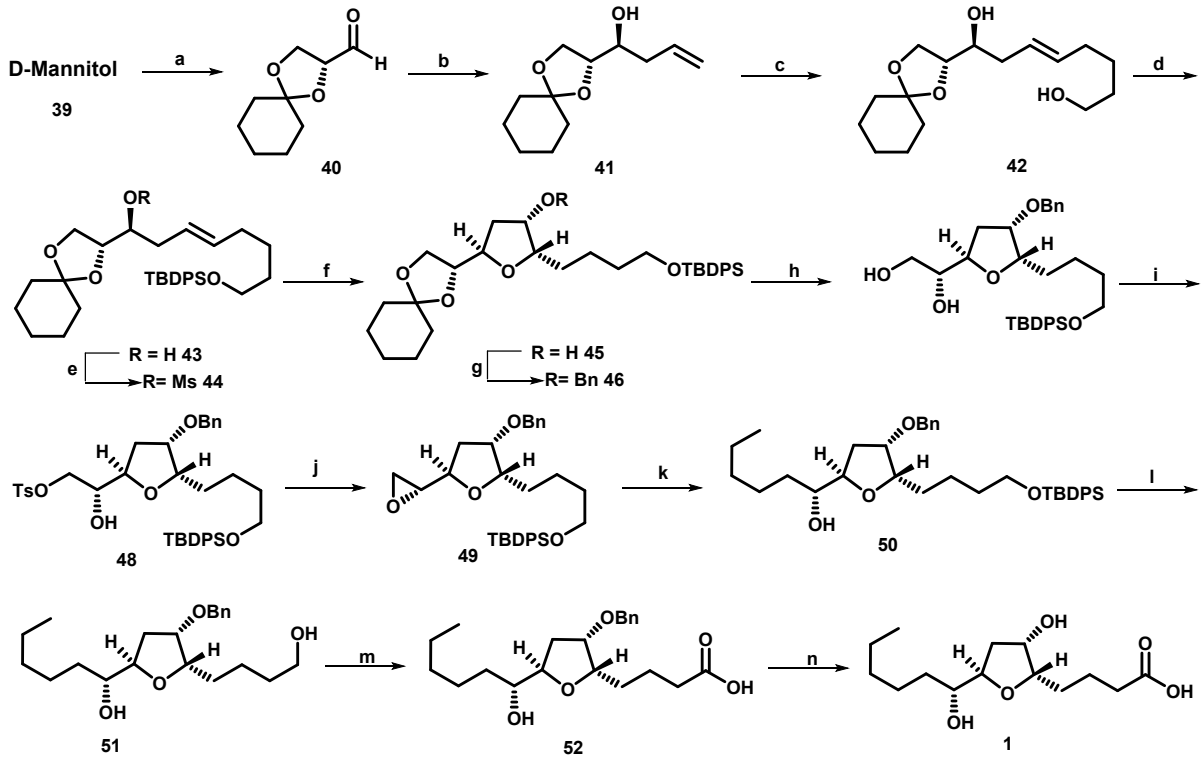
Scheme 6. *Reagents and conditions:* (a) Grubbs' second generation catalyst, CH_2Cl_2, rt, 16 h, 70%; (b) i) MsCl, TEA, CH_2Cl_2, 0 °C, 15 min; ii) OsO_4, $(DHQ)_2PHAL$, $MeSO_2NH_2$,

$K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 0 °C, 24 h; iii) pyridine, reflux, 16 h, 80% (three steps); (c) Pd/C, H_2 Ballon, EtOH, 3 h, 95%.

Cross metathesis[12] reaction was carried out between fragment **30** and **36** in anhydrous CH_2Cl_2 using Grubb's second generation catalyst, resulting *E*-olefin **37** as major product in 70% yield (Scheme 6). Alkene derivative **37** was converted into THF derivative **38** *via* a three step sequence including *O*-mesylation, then Sharpless AD and pyridine mediated cyclization under reflux condition in 80% yield as a single diastereomer, confirmed by ^1H and ^{13}C NMR. Finally debenzylation of **38** using Pd/C (10% wt/wt) under hydrogen atmosphere furnished the target molecule (+)-petromyroxol **1** in 95% yield.

Reddy B. V. S. *et al.* (2016)[8d]

B. V. S. Reddy and co-workers reported the stereoselective total synthesis of (+)-petromyroxol **1** employed the cross-metathesis, tandem Sharpless AD, S_N2 cyclization and



Scheme 7. *Reagents and conditions*: (a) According to reference 10; (b) Zn, allyl bromide, THF, sat. NH_4Cl soln. (cat.), 6 h, 0 °C, 90%; (c) 5-hexene-1-ol, Grubbs' second generation catalyst, CH_2Cl_2, 40 °C, 6 h, 85%; (d) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 2 h, 90%; (e) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 4 h, 87%; (f) AD-mix-*α*, $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 6 h, 78%, 0 °C to rt; (g) NaH, BnBr, DMF, 0 °C, 6 h, 87%; (h) 80% TFA, 0 °C, 3 h, 75%; (i) Bu_2SnO, Et_3N, TsCl, 0 °C to rt, 3 h, 90%; (j) MeONa, MeOH, 0 °C to rt, 2 h, 76%;

(k) C_4H_9Br, Mg, THF, 30 °C, then CuI, 3 h, 73%; (l) TBAF, THF, 0 °C to rt, 2 h, 78%; (m) TEMPO, BAIB, MeCN:H_2O 4:1, 0 °C to rt, 2 h, 80%; (n) 10% Pd/C, H_2, EtOH, rt., 4 h, 86%.

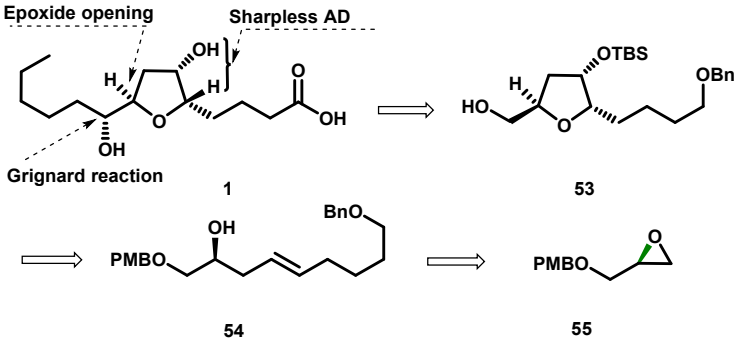
regioselective ring opening of epoxide as the key steps. As depicted in Scheme 7, synthesis of (+)-petromyroxol **1** began with commercially available D-mannitol **39** which was converted into glyceraldehyde derivative **40** *via* a known procedure. Zn mediated reaction of aldehyde **40** with allyl bromide under Luche conditions afforded the homoallylic alcohol derivative **41** in a ratio of 5:95 (syn/anti). Cross-metathesis was carried out between homoallylic alcohol **41** and 5-hexene-1-ol in the presence of second generation Grubbs' catalyst in anhydrous CH_2Cl_2 under reflux conditions to furnish the *E* olefin derivative **42** in 85% yield. Primary alcohol in **42** was selectively protected with TBDPSCl as its silyl ether **43** in 90% followed by *O*-mesylation of secondary alcohol using Et_3N, $MeSO_2Cl$, and catalytic amount of DMAP provided the compound **44** in 87% yield. Now alkene derivative **44** was converted into THF derivative **45** through a sequential Sharpless AD by AD-mix-*α* followed by S_N2 cyclization with diastereomeric ratio of 9:1. Benzylation of the secondary hydroxyl **45** *via* benzyl bromide in the presence of NaH gave the benzyl ether **46** in 87% yield. THF derivative **46** was converted into epoxide derivative **49** *via* a process including removal of the cyclohexylidene group under acidic conditions followed by selective tosylation of **47** using Et_3N, *p*-TsCl, and catalytic amount of Bu_2SnO furnished the tosylate **48**, which was then treated with base to provide the epoxide **49**. Treatment of epoxide **49** with *n*-butyl magnesium bromide at -30 °C afforded **50** in 73% yield. TBAF mediated removal of silyl ether of compound **50** led to the formation of primary alcohol **51** in 78% yield, which was then subjected to TEMPO/BAIB mediated oxidation to furnish the acid **52** in 80% yield. Finally, the removal of benzyl group under hydrogenation condition afforded the (+)-petromyroxol **1** in 86% yield.

3.1.3 Present Work:

As part of our ongoing program towards the syntheses of biologically active natural products, we became interested in developing a general synthetic route that provides a common pivotal intermediate from which 2,5-disubstituted-3-oxygenated THF motif with desired stereochemical variations can be synthesized. Therefore, herein we are reporting a new synthetic approach for the total synthesis of (+)-petromyroxol **1** employing Sharpless AD, intramolecular S_N2 cyclization and stereoselective Grignard reaction as the key steps.

3.1.4 Results and Discussion:

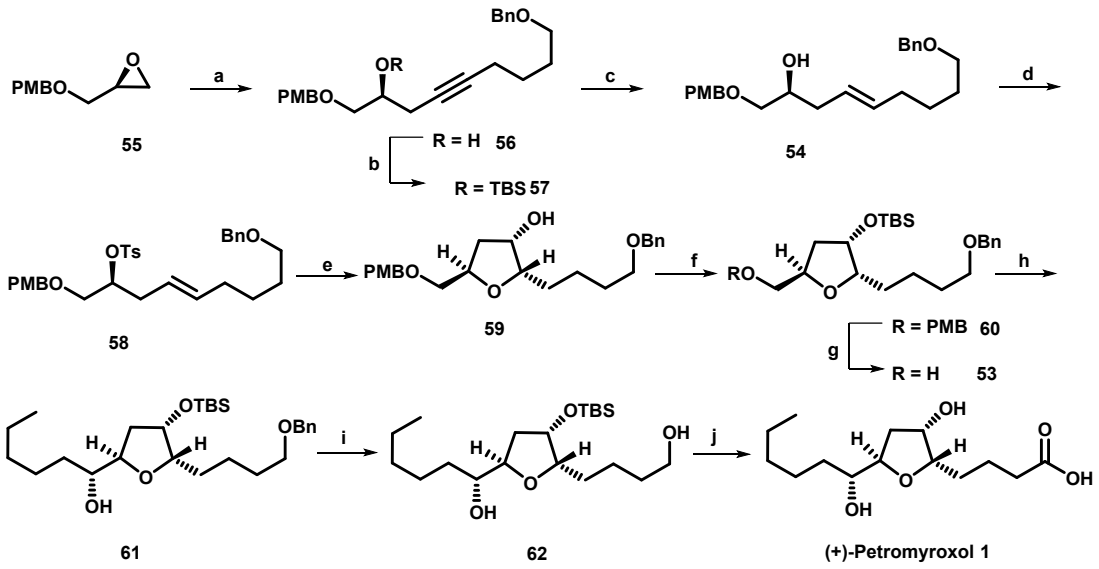
Our synthetic approach for the synthesis of (+)-petromyroxol **1** was envisioned *via* the retrosynthetic route as shown in Scheme 8. The 2,5-disubstituted-3-oxygenated THF derivative **53** was visualized as a synthetic intermediate from which (+)-petromyroxol **1** could be synthesized *via* oxidation of free alcohol followed by stereoselective Grignard reaction and standard organic transformations. The THF derivative **53** in turn could be obtained from the alcohol **54** by tosylation followed by Sharpless AD and base treatment. The alcohol derivative **54** could be easily prepared from the enantiopure terminal epoxide **55** by suitable lithium acetylide in presence of catalytic amount of boron trifluoride etherate. The all (*R*)- and (*S*)- configuration of the target compound **1** could be manipulated by simply stereoselective Grignard reaction, and either changing chiral ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ under Sharpless AD conditions or using *cis*-hydrogenation followed by Sharpless AD, alternatively.



Scheme 8. Retrosynthetic approach for (+)-petromyroxol **1**.

As depicted in Scheme 9, the synthesis of (+)-petromyroxol **1** commenced with conversion of epoxide **55**[11] into alkyne alcohol **56** with lithium acetylide prepared from the benzyl protected alkyne in presence of boron trifluoride etherate at -78 ^oC in 91% yield. The IR spectrum of **56** showed hydroxyl absorption at 3434 cm^{-1}. Reduction of **56** with $LiAlH_4$ in THF solvent at different temperature was sluggish. Considering the low reactivity of compound **56**, we decided to replace THF with diglyme which has a higher boiling point and we found that reaction was still sluggish at different temperature. Therefore, we protected free alcohol with TBSCl (**56**→**57**), and then performed reduction with $LiAlH_4$ in diglyme which proceeded perfectly at the elevated temperature, and concomitant deprotection of silyl ether during work-up[12] furnished the *E*-olefin **54** in 89% yield. The ^1H NMR spectrum of compound **54** showed olefinic proton at δ 5.49 (triplet of doublet, one proton) with the coupling constant J = 21.5, 14.64 Hz and at 5.39 (triplet of doublet, one proton) J = 22, 14.64 Hz indicating *trans*-olefin. The free hydroxyl group of **54** was subjected to *O*-tosylation with tosyl chloride

(TsCl) and Et_3N in presence of catalytic amount of DMAP furnished tosylated olefin which on dihydroxylation with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ under the Sharpless asymmetric conditions[13] afforded the diol, which, without further purification, was subjected to treatment with K_2CO_3 in MeOH to afford tetrahydrofuranyl alcohol **59**[14] in 88% yield as a single diastereoisomer.[15] Compound **59** showed presence of hydroxyl absorption in the IR spectrum at 3440 cm^{-1}. With tetrahydrofuranyl alcohol **59** in hand, we then subjected it to imidazole-promoted protection with TBSCl and selective deprotection of the PMB ether with DDQ afforded the tetrahydrofuranyl alcohol **53** in excellent yield. The IR spectrum of compound **53** showed hydroxyl absorption at 3435 cm^{-1}. Oxidation of alcohol derivative **53** under Swern conditions[16] and subsequent treatment of aldehyde with *n*-pentyl magnesium bromide at



Scheme 9. (a) *n*-BuLi, $BF_3.OEt_2$, hexyne derivative, dry THF, -78 ^oC, 1 h, 91%; (b) TBSCl, Imidazole, DMAP, dry CH_2Cl_2, rt, 12 h, 95%; (c) $LiAlH_4$, diglyme, dry THF, 125 ^oC, 3 h, 93%; (d) TsCl, Et_3N, DMAP, dry CH_2Cl_2, 0 ^oC to rt, 12 h, 95%; (e) i) 0.5 mol % OsO_4, 1 mol % $(DHQ)_2PHAL$, $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, K_2CO_3, *t*-BuOH:H_2O 1:1 v/v, 0 ^oC, 24 h; ii) K_2CO_3, MeOH, rt, 12 h, (88% two steps); (f) TBSCl, Imidazole, DMAP, dry CH_2Cl_2, rt, 12 h, 96%; (g) DDQ, pH 7 buffer solution, CH_2Cl_2, rt, 2 h, 95%; (h) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC to -60 ^oC, 2 h; ii) $C_5H_{11}MgBr$, dry Et_2O, -78 ^oC, 2 h (88% two steps); (i) H_2, $Pd(OH)_2$ (20%), EtOAc, rt, 18 h, 97%; (j) TEMPO, BAIB, CH_2Cl_2:H_2O 2:1 v/v, rt, 12 h, 94%.

-78 ^oC afforded **61** as the major product along with its column separable epimer in a 3:1 ratio and 88% combined yield.[17] The desired major isomer **61** was subjected to debenzylation under 1 atm. pressure in presence of catalytic amount of $Pd(OH)_2$ which afforded the diol **62**

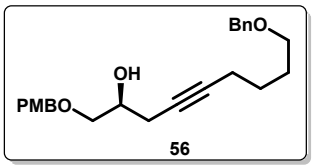
in 97% yield. The ^{1}H NMR spectrum of compound **62** indicated absence of aromatic protons. Selective oxidation of primary alcohol and concomitant cleavage of the silyl ether was achieved by treatment of diol **62** with a catalytic amount of TEMPO[18] and excess bis(acetoxy)-iodobenzene (BAIB) in a mixture of dichloromethane and water (2:1) which furnished the target compound (+)-petromyroxol **1** in 94% yield {$[\alpha]_D^{25}$ +21.2 (*c* 1.7, $CHCl_3$), Lit.[8a] $[\alpha]_D^{19}$ +20.5 (*c* 1.7, $CHCl_3$)}. The physical and spectroscopic data of (+)-petromyroxol **1** were in full agreement with those reported in the literature.

3.1.5 Conclusion:

In conclusion, an efficient approach to the total synthesis of (+)-petromyroxol **1** has been developed employing stereoselective Grignard reaction, Sharpless AD and intramolecular S_N2 cyclization as key steps. The overall yield for (+)-petromyroxol **1** was 39% in nine steps. The synthetic approach described has significant potential for stereochemical variations in all the positions and further extension to other stereoisomers, and analogues.

3.1.6 Experimental Section:

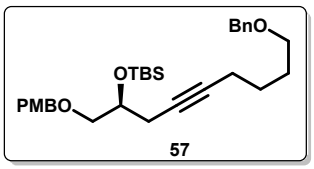
(2*S*)-9-(Benzyloxy)-1-(4-methoxybenzyloxy)non-4-yn-2-ol,56



A flame-dried 250 mL round-bottomed flask was charged with benzyl protected 5-hexyne-1-ol (2.00 g, 10.62 mmol) in THF (100 mL) and cooled to -78 °C. To this solution was added *n*-BuLi (2.5 M in hexane, 5.09 mL, 12.74 mmol) dropwise by syringe. The resulting mixture was warmed slowly to 0 °C. During this time, the reaction mixture turned dark red in color. After 30 min, (*S*)-PMB glycidyl **55** (1.72 g, 8.85 mmol) and boron trifluoride etherate (1.23 mL, 9.73 mmol) were successively added dropwise at -78 °C. After an additional 30 min at -78 °C, the cold bath was removed and the reaction was quenched with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc/hexane 1:4) furnished **56** (3.08 g, 91%) as a colourless oil. [R_f= 0.25, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ +7.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 3434, 2935, 2863, 2360, 2059, 1883, 1612, 1513, 1248, 1101 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.27 (m, 4H), 7.26-7.24 (m, 3H), 6.88 (d, *J* = 8.68 Hz, 2H), 4.49 (d, *J* = 4.12 Hz, 4H), 3.93-3.85 (m, 1H), 3.80 (s, 3H), 3.57-3.54 (m, 1H), 3.49-3.43 (m, 3H), 2.48 (bs, 1H), 2.40-2.38 (m, 2H), 2.23-2.15 (m, 2H), 1.69-1.66 (m, 2H), 1.60-1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 138.4, 129.6, 129.4, 128.3, 127.6, 121.3, 113.8, 82.6, 75.6, 73.1, 70.4, 69.7,

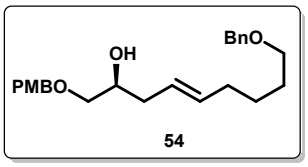
69.3, 68.9, 55.2, 45.9, 28.8, 25.5, 23.8, 18.5; HRMS (ESI), calcd for $C_{24}H_{30}O_4Na$ $[M+Na]^+$ 405.2036, found 405.2037.

(2*S*)-9-(Benzyloxy)-1-(4-methoxybenzyloxy)non-4-yn-2-yloxy)(*tert*-butyl)dimethylsilane 57



To a solution of alkyne alcohol **56** (2.50 g, 6.54 mmol) in CH_2Cl_2 (40 mL) was added imidazole (668 mg, 9.80 mmol) followed by *tert*-butyldimethylsilyl chloride (1.28 g, 8.50 mmol) and DMAP (161 mg, 1.31 mmol) at rt. The reaction was stirred under N_2 for 12 h, after which it was quenched by adding a saturated NH_4Cl (20 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane 1:9) furnished **57** (3.08 g, 95%) as a colourless oil. [R_f= 0.4, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ +16.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 3011, 2951, 2931, 2857, 2401, 1612, 1513, 1362, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ:* 7.34-7.27 (m, 4H), 7.26-7.24 (m, 3H), 6.86 (d, *J* = 8.68 Hz, 2H), 4.48 (d, *J* = 11.44 Hz, 4H), 3.92-3.89 (m, 1H), 3.79 (s, 3H), 3.49-3.39 (m, 4H), 2.45-2.37 (m, 1H), 2.32-2.25 (m, 1H), 2.17-2.13 (m, 2H), 1.74-1.66 (m, 2H), 1.57-1.52 (m, 2H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 158.9, 138.5, 130.5, 129.1, 128.3, 127.5, 127.4, 113.6, 81.3, 77.1, 73.5, 72.9, 72.8, 70.9, 69.8, 55.1, 28.8, 25.8, 25.7, 25.6, 24.9, 18.6, 18.1, -4.60, -4.80; HRMS (ESI), calcd for $C_{30}H_{44}O_4SiNa$ $[M+Na]^+$ 519.2901, found 519.2906.

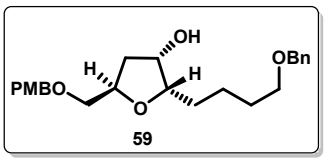
(2*S*,4*E*)-9-(Benzyloxy)-1-(4-methoxybenzyloxy)non-4-en-2-ol 54



To a cold suspension of $LiAlH_4$ (706 mg, 18.60 mmol) in a mixture of diglyme (20 mL) and THF (10 mL) was added a solution of TBS protected alkyne **57** (3.08 g, 6.20 mmol) in diglyme (10 mL). The mixture was heated at 125 ^oC for 3 h. The oil bath was replaced with a salt-ice bath. Water (10 mL) and 10% NaOH (10 mL) was slowly added dropwise until the solid turned gray. After filtration, the solid was washed with ethyl acetate and the combined organic layer was washed with 1.5 N HCl (3 x 10 mL) to remove diglyme from organic layer. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane 1:4) to afford the *trans*-alkene **54** (2.22 g, 93%) as a colourless oil. [R_f= 0.25, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ +29.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 3450, 3100, 2933, 2861, 1637, 1454, 1248, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ:* 7.34-

7.27 (m, 4H), 7.26-7.24 (m, 3H), 6.88 (d, J = 8.24 Hz, 2H), 5.49 (td, J = 21.5, 14.64, 5.96 Hz, 1H), 5.39 (td, J = 22, 14.64, 6.88 Hz, 1H), 4.49 (d, J = 8.28 Hz, 4H), 3.80 (s, 4H), 3.48-3.40 (m, 3H), 3.34-3.30 (m, 1H), 2.33 (bs, 1H), 2.19-2.16 (dd, J = 14.2, 6.88 Hz, 2H), 2.04-1.99 (m, 2H), 1.64-1.56 (m, 2H), 1.47-1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 138.5, 133.6, 130.0, 129.3, 128.3, 127.6, 127.4, 125.5, 113.7, 73.5, 72.9, 71.8, 70.4, 58.9, 55.2, 36.6, 32.3, 29.2, 25.9; HRMS (ESI), calcd for $C_{24}H_{32}O_4Na$ $[M+Na]^+$ 407.2193, found 407.2197.

(2*S*,3*S*,5*R*)-2-(4-Benzyloxy)butyl)-5-((4-methoxybenzyloxy)methyl)-tetrahydrofuran-3-ol 59



59

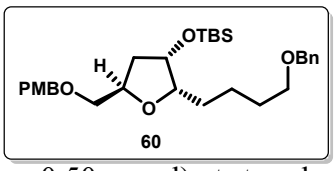
Et_3N (0.72 mL, 5.58 mmol) was added to the solution of alkene **54** (1.45 g, 3.72 mmol) in 40 mL of DCM at 0 °C. After the solution was stirred for 5 min, TsCl (1.42 g, 7.44 mmol) and DMAP (90 mg, 0.74 mmol) were added at the same temperature. After an additional 12 h at room temperature, saturated NH_4Cl (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude tosylated olefin **58**.

To a stirred solution of $K_3Fe(CN)_6$ (3.66 g, 11.13 mmol), K_2CO_3 (1.54 g, 11.13 mmol) and $(DHQ)_2PHAL$ (29 mg, 1 mol %) in *t*-BuOH/H_2O (60 mL 1:1 v/v) at 0 °C was added OsO_4 (0.2 mL, 0.1 M solution in toluene, 0.5 mol %) followed by methanesulfonamide (353 mg, 3.70 mmol). After being stirred for 2 min at 0 °C, the above tosylated olefin **58** was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (4.00 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 x 20 mL) and concentrated *in vacuo*, which was used as such for the next step without further purification.

To a solution of diol in MeOH (20 mL) was added K_2CO_3 (1.54 g, 11.13 mmol) and stirred for 12 h at rt. The MeOH was evaporated under reduced pressure, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 3:7) to give tetrahydrofuran **59** (1.30 g, 88%) as colourless oil. [R_f = 0.35, EtOAc/hexane 2:3 v/v]; $[\alpha]_D^{25}$ +16.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 3440, 1612, 1586, 1513, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.28 (m, 4H), 7.27-7.24 (m, 3H), 6.87 (d, J = 8.68 Hz, 2H), 4.50 (d, J = 4.6 Hz, 4H), 4.41-4.35 (m, 1H), 4.21 (bs, 1H), 3.80-3.77 (m, 4H), 3.51-3.41 (m, 4H), 2.03-1.89 (m, 2H), 1.85 (bs, 1H), 1.74-1.57 (m, 4H), 1.55-1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0, 138.4, 130.3, 129.2, 128.3, 127.6, 127.5, 113.6,

82.5, 75.8, 72.9, 72.8, 72.2, 70.0, 55.2, 37.7, 29.6, 28.4, 22.8; HRMS (ESI), calcd for $C_{24}H_{32}O_5Na$ $[M+Na]^+$ 423.2142, found 423.2142.

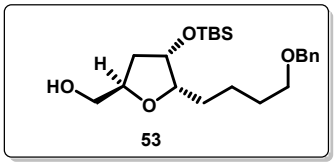
((2*S*,3*S*,5*R*)-2-(4-(Benzyloxy)butyl)-5-((4-methoxybenzyloxy)-methyl)tetrahydrofuran-3-yloxy)(*tert*-butyl)di-methylsilane, 60



60

To a solution of 2,5-disubstituted-3-oxygenated THF derivative **59** (1.00 g, 2.50 mmol) in dry CH_2Cl_2 (20 mL) was added imidazole (255 mg, 3.75 mmol) followed by *tert*-butyldimethylsilyl chloride (490 mg, 3.25 mmol) and DMAP (61 mg, 0.50 mmol) at rt under a nitrogen atmosphere. The reaction mixture was stirred for 12 h at room temperature. After completion, the reaction was quenched with saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane 1:9) furnished the TBS protected THF derivative **60** (1.23 g, 96%) as a colourless oil. [R_f = 0.40, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ +36.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 2950, 2856, 2360, 2061, 1879, 1612, 1512, 1461, 1360, 1249, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 4H), 7.26-7.24 (m, 3H), 6.87 (d, J = 8.72 Hz, 2H), 4.50 (d, J = 6.44 Hz, 4H), 4.38-4.29 (m, 1H), 4.25-4.18 (m, 1H), 3.79 (m, 4H), 3.51-3.38 (m, 4H), 1.92-1.81 (m, 2H), 1.74-1.49 (m, 6H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0, 138.6, 130.4, 129.3, 128.3, 127.6, 127.4, 113.6, 83.2, 76.1, 73.0, 72.8, 72.4, 70.3, 55.2, 38.4, 29.9, 29.6, 29.3, 25.7, 22.9, 18.0, 14.1, -4.5, -5.1; HRMS (ESI), calcd for $C_{30}H_{46}O_5SiNa$ $[M+Na]^+$ 537.3007, found 537.3009.

(2*R*,4*S*,5*S*)-5-(4-Benzyloxy)butyl)-4-(*tert*-butyldimethylsilyloxy)tetrahydrofuran-2-yl) methanol, 53

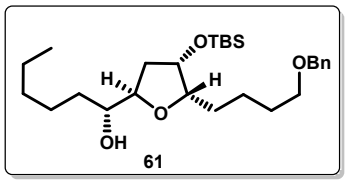


53

To a magnetically stirred solution of compound **60** (1.00 g, 1.94 mmol) in methylene chloride (10 mL) were added pH 7 buffer solution (1.0 mL) and DDQ (528 mg, 2.33 mmol). After TLC indicated no remaining of compound 12, saturated $NaHCO_3$ (5 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to afford the alcohol **53** (727 mg, 95%) as a colourless oil. [R_f= 0.25, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ +39.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 3435, 2929, 2856, 1459, 1361, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.24 (m, 5H), 4.5 (s,

2H), 4.33-4.28 (m, 1H), 4.27-4.22 (m, 1H), 3.82-3.77 (m, 1H), 3.75-3.70 (m, 1H), 3.49-3.47 (m, 3H), 1.95 (bs, 1H), 1.93-1.81 (m, 2H), 1.71-1.54 (m, 6H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 138.6, 128.3, 127.6, 127.5, 83.5, 73.4, 72.8, 70.3, 64.7, 37.3, 29.9, 29.3, 25.7, 22.9, 18.0, -4.5, -5.0; HRMS (ESI), calcd for $C_{22}H_{38}O_4SiNa$ $[M+Na]^+$ 417.2431, found 417.2434.

(*R*)-1-(2*R*,4*S*,5*S*)-5-(4-Benzyloxy)butyl)-4-(*tert*-butyldimethylsilyl-oxy)tetrahydrofuran 2-yl)hexan-1-ol, 61



61

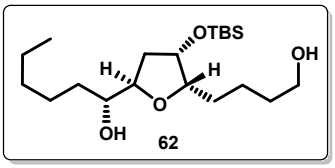
To a solution of oxalyl chloride (290 mg, 0.2 mL, 2.28 mmol) in dry CH_2Cl_2 (2 mL) at -78 °C was added dropwise DMSO (368 mg, 0.33 mL, 4.71 mmol) in CH_2Cl_2 (2 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of alcohol **53** (600 mg, 1.52 mmol) in CH_2Cl_2 (6 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at -78 °C and 30 min at -60 °C and then Et_3N (676 mg, 0.9 mL, 6.68 mmol) was added dropwise and stirred for 1 h. The reaction mixture was poured into cold water (10 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude aldehyde, which was used as such for the next step without further purification.

To a stirred solution of above aldehyde in dry diethyl ether (15 mL) was added *n*-pentylmagnesiumbromide, freshly prepared from *n*-pentyl bromide (505 mg, 3.34 mmol) and magnesium (109 mg, 4.56 mmol) in dry diethyl ether (15 mL). After being stirred for 2 h at -78 °C, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9). The first fraction afforded alcohol **61** (465 mg, 66% yield) as a colourless liquid. [R_f = 0.5, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ +18.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 3452, 2930, 2858, 2360, 1461, 1361, 1254, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.35-7.24 (m, 5H), 4.49 (s, 2H), 4.24-4.20 (m, 1H), 4.03-3.98 (m, 1H), 3.81-3.70 (m, 1H), 3.48 (t, *J* = 6.84 Hz, 2H), 3.38-3.33 (m, 1H), 2.06 (bs, 1H), 1.90-1.77 (m, 2H), 1.69-1.22 (m, 14H), 0.9-0.86 (m, 12H), 0.06 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ:*138.6, 128.3, 127.6, 127.4, 83.1, 80.3, 74.2, 73.6, 72.8, 70.3, 38.4, 33.5, 31.9, 29.9, 29.2, 25.7, 25.3,

22.9, 22.6, 18.0, 14.0, -4.5, -5.0; HRMS (ESI), calcd for $C_{27}H_{48}O_4SiNa$ $[M+Na]^+$ 487.3214, found 487.3216.

The second fraction furnished the minor isomer (155 mg, 22% yield); $[\alpha]_D^{25}$ +15.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 3441, 2925, 2858, 2365, 1454, 1361, 1240, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.34-7.25 (m, 5H), 4.49 (s, 2H), 4.26-4.23 (m, 1H), 4.16-4.10 (m, 1H), 3.87-3.78 (m, 2H), 3.48 (t, *J* = 6.44 Hz, 2H), 2.07 (bs, 1H), 2.04-1.97 (m, 1H), 1.72-1.25 (m, 15H), 0.91-0.84 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ:*138.6, 128.3, 127.6, 127.4, 83.9, 80.2, 73.4, 72.8, 71.7, 70.3, 34.4, 32.2, 31.8, 29.9, 29.5, 25.7, 25.6, 22.9, 22.5, 18.0, 14.0, -4.5, -5.1.

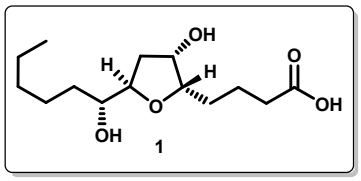
(1*R*)-1-(2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(4-hydroxybutyl)tetrahydrofuran-2 yl)hexan-1-ol, 62



62

To a solution of diol **61** (465 mg, 1.00 mmol) in ethyl acetate (5 mL) was added catalytic amount of $Pd(OH)_2$ (20%) and the resulting mixture was stirred under hydrogen atmosphere for 18 h. After completion of reaction, the catalyst was removed by filtration over Celite and washed with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by silica gel column chromatography (EtOAc/hexane 3:7) to furnish the alcohol **62** (364 mg, 97%) as a colourless oil. [R_f= 0.5, EtOAc/hexane 1:1 v/v]; $[\alpha]_D^{25}$ +34.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v:* 3400, 2956, 2930, 1462, 1388, 1254, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ:* 4.25-4.21 (m, 1H), 4.05-3.99 (m, 1H), 3.78-3.74 (m, 1H), 3.65 (t, *J* = 13.28 Hz, 2H), 3.38-3.36 (m, 1H), 2.36 (bs, 1H), 1.89-1.81 (m, 2H), 1.69-1.21 (m, 15H), 0.89 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 83.2, 80.4, 74.1, 73.6, 62.7, 38.4, 33.5, 32.8, 31.9, 29.1, 25.7, 25.3, 22.6, 22.5, 18.0, 14.0, -4.5, -5.0; HRMS (ESI), calcd for $C_{20}H_{42}O_4SiNa$ $[M+Na]^+$ 397.2744, found 397.2746.

(+)-Petromyroxol, 1



1

To a vigorously stirred solution of alcohol **62** (250 mg, 0.67 mmol) in CH_2Cl_2 (4 mL) and H_2O (2 mL) was added TEMPO (21 mg, 0.13 mmol) and [bis(acetyloxy)iodo]benzene (BAIB; 518 mg, 1.60 mmol). Stirring was continued until TLC indicated complete conversion of the starting material. The reaction was quenched by addition of a saturated $Na_2S_2O_3$ solution (10 mL). The mixture was extracted with CH_2Cl_2 (2 x 10 mL), the combined organic layer was washed with 2 N HCl (3 x 10 mL), dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (AcOH/EtOAc 1:19) afforded the (+) petromyroxol **1** (172 mg, 94%) as a colourless oil. [R_f= 0.74, AcOH/EtOAc 1:9 v/v;] $[\alpha]_D^{25}$ +21.2 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) *v* 3423, 2932, 2860, 1710, 1409, 1290, 1240, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.30 (bs, 3H), 4.28 (dd, *J* = 6.4, 3.2 Hz, 1H), 4.06 (ddd, *J* = 9.16, 6.88, 6.4 Hz, 1H), 3.78 (td, *J* = 6.4, 6.4, 3.2 Hz, 1H), 3.40 (ddd, *J* = 7.32, 6.4, 3.68 Hz, 1H), 2.39 (t, *J* = 14.68, 7.3 Hz, 2H), 2.03 (dd, *J* = 20.0, 6.44 Hz, 1H), 1.86 (ddd, *J* = 13.72, 9.16, 4.56 Hz, 1H), 1.74-1.60 (m, 4H), 1.52-1.49 (m, 1H), 1.41-1.22 (m, 7H), 0.89 (t, *J* = 6.84 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 82.4, 80.6, 74.1, 73.0, 37.4, 33.7, 32.9, 31.8, 28.1, 25.2, 22.6, 21.2, 14.0; HRMS (ESI), calcd for $C_{14}H_{26}O_5Na$ $[M+Na]^+$ 297.1672, found 297.1673.

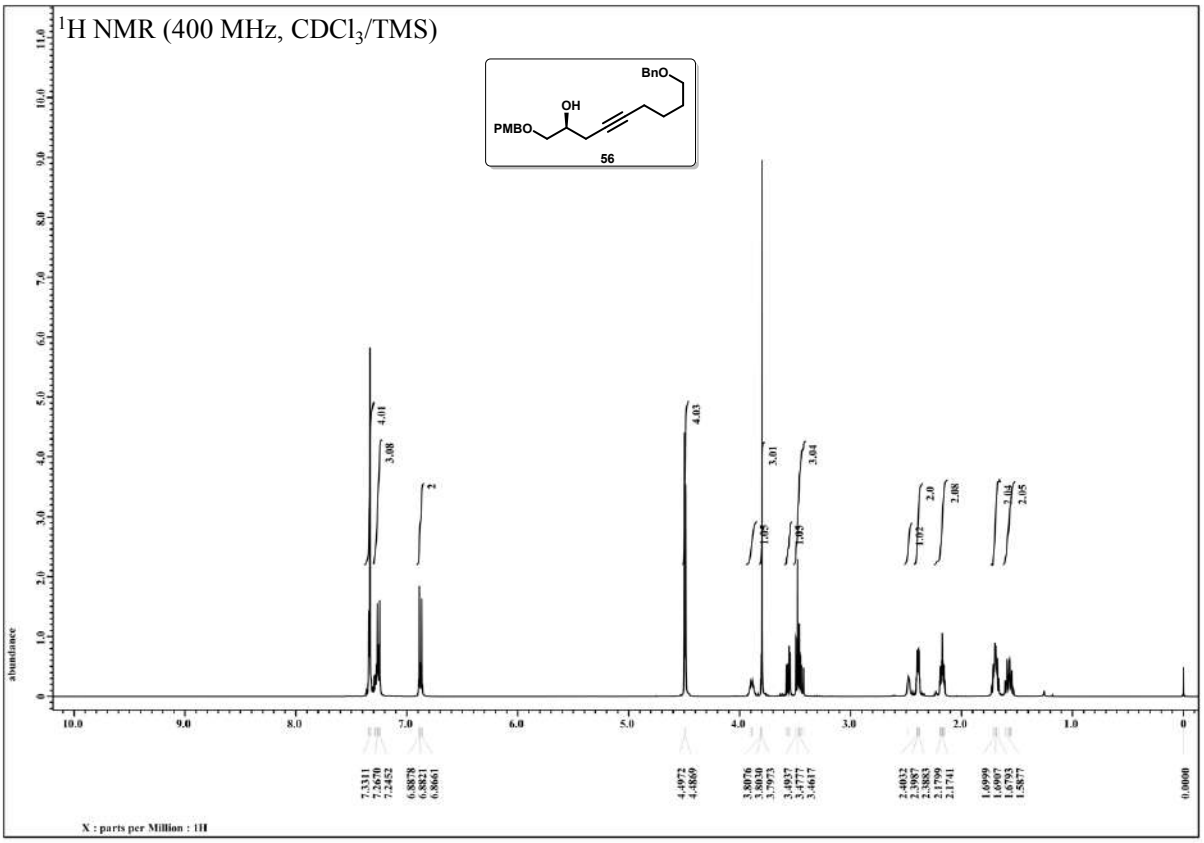
3.1.7 Spectra:

1. ^1H and ^{13}C NMR spectra of **56**
2. ^1H and ^{13}C NMR spectra of **57**
3. ^1H and ^{13}C NMR spectra of **54**
4. ^1H and ^{13}C NMR spectra of **58**
5. ^1H and ^{13}C NMR spectra of **59**
6. ^1H and ^{13}C NMR spectra of **60**

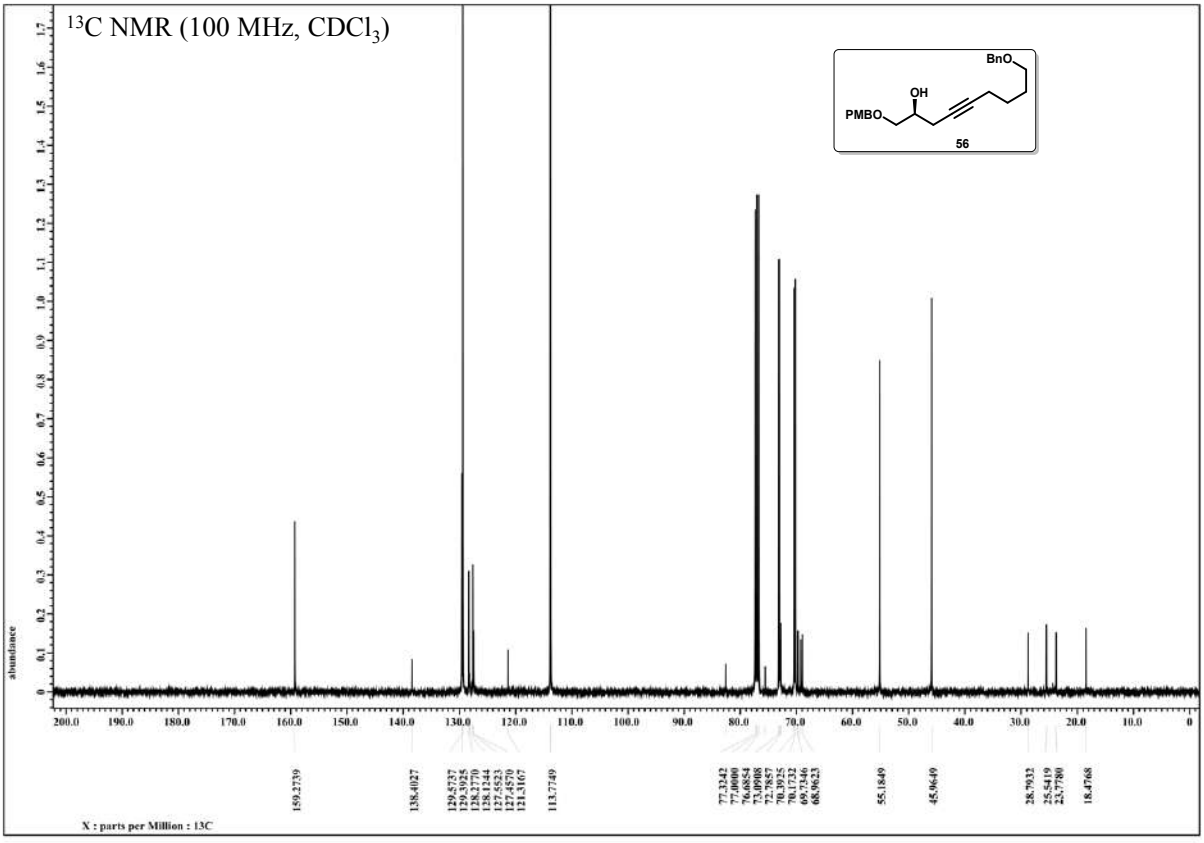
7. ^1H and ^{13}C NMR spectra of **53**

8. ^1H and ^{13}C NMR spectra of **61**
9. ^1H and ^{13}C NMR spectra of **62**
10. ^1H, ^{13}C NMR and Cosy spectra of **1**

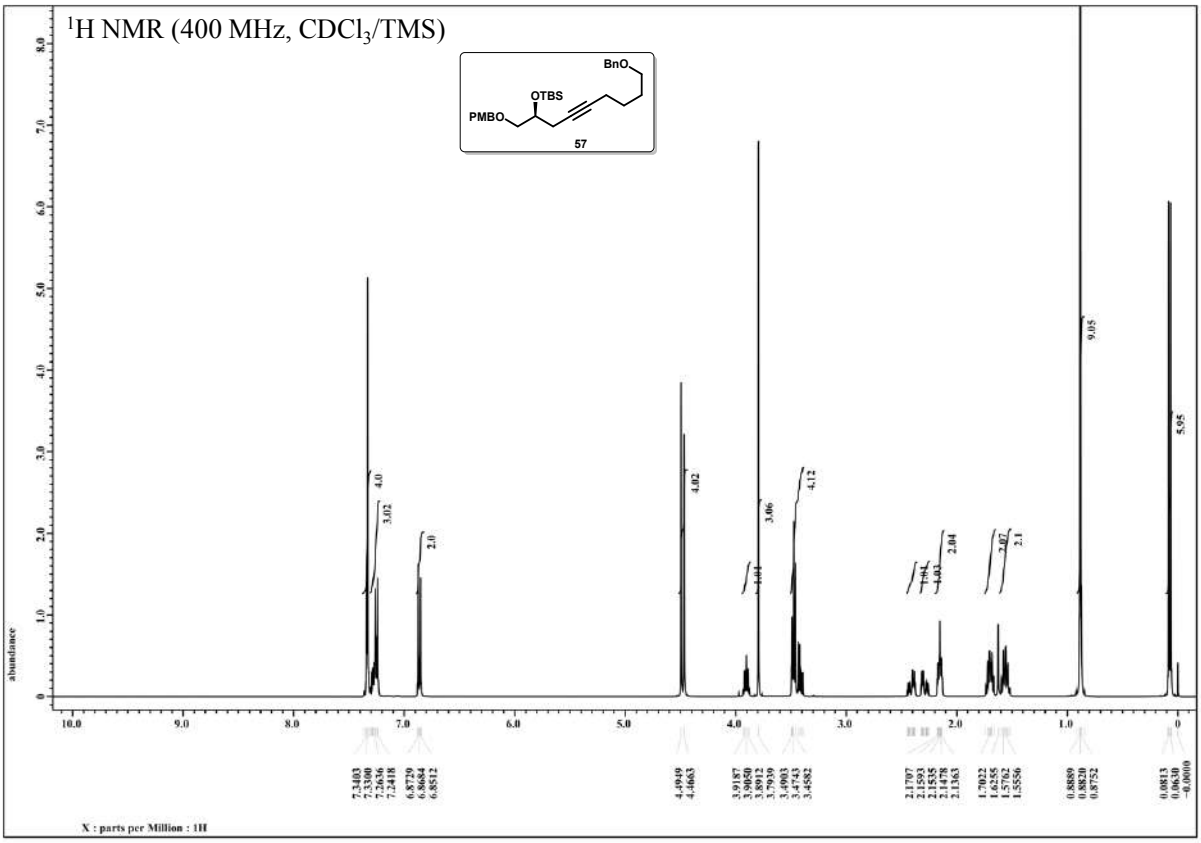
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



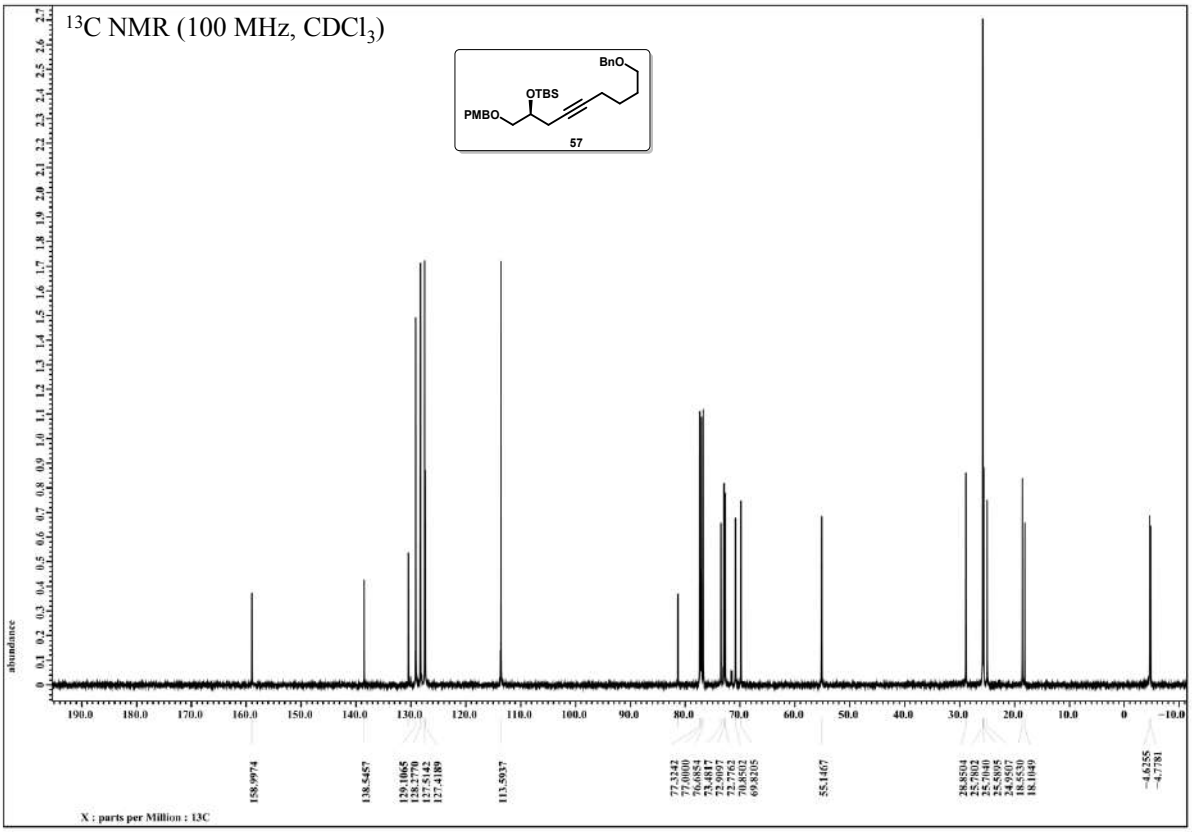
^{13}C NMR (100 MHz, $CDCl_3$)



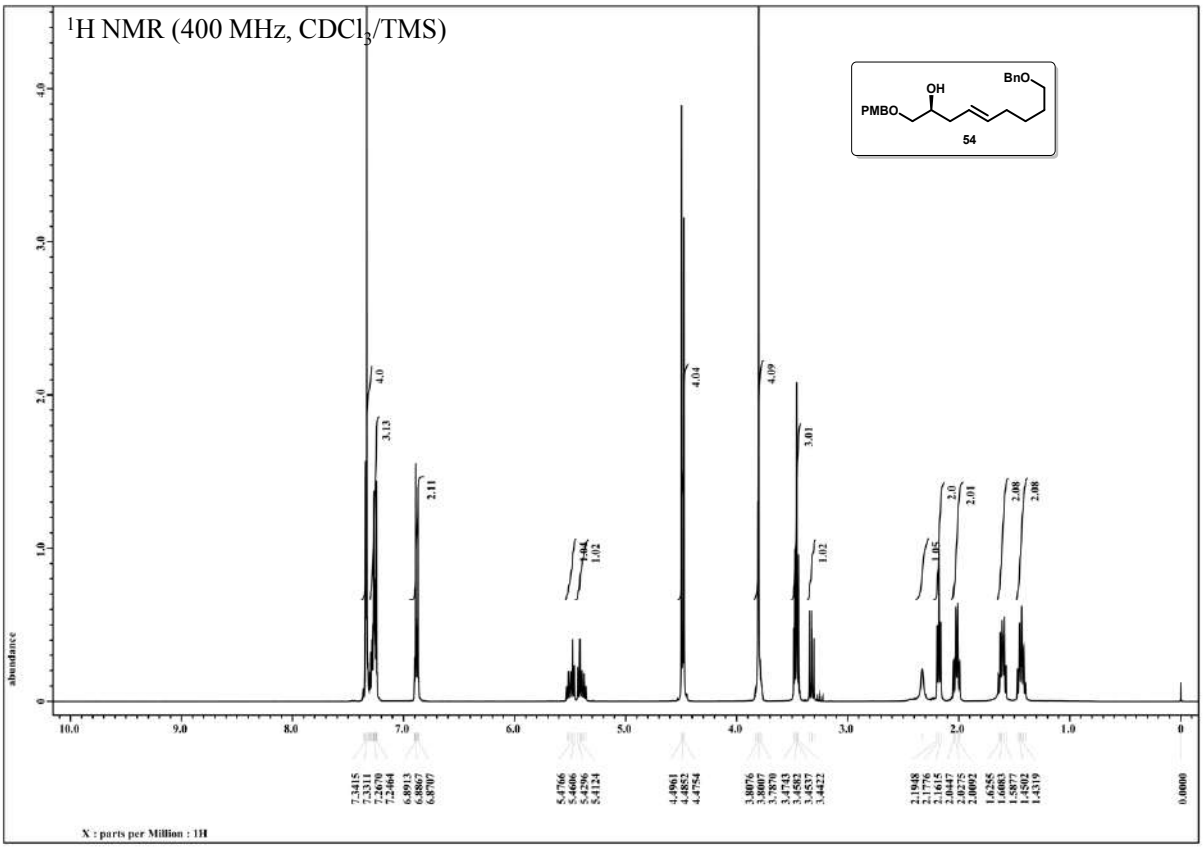
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



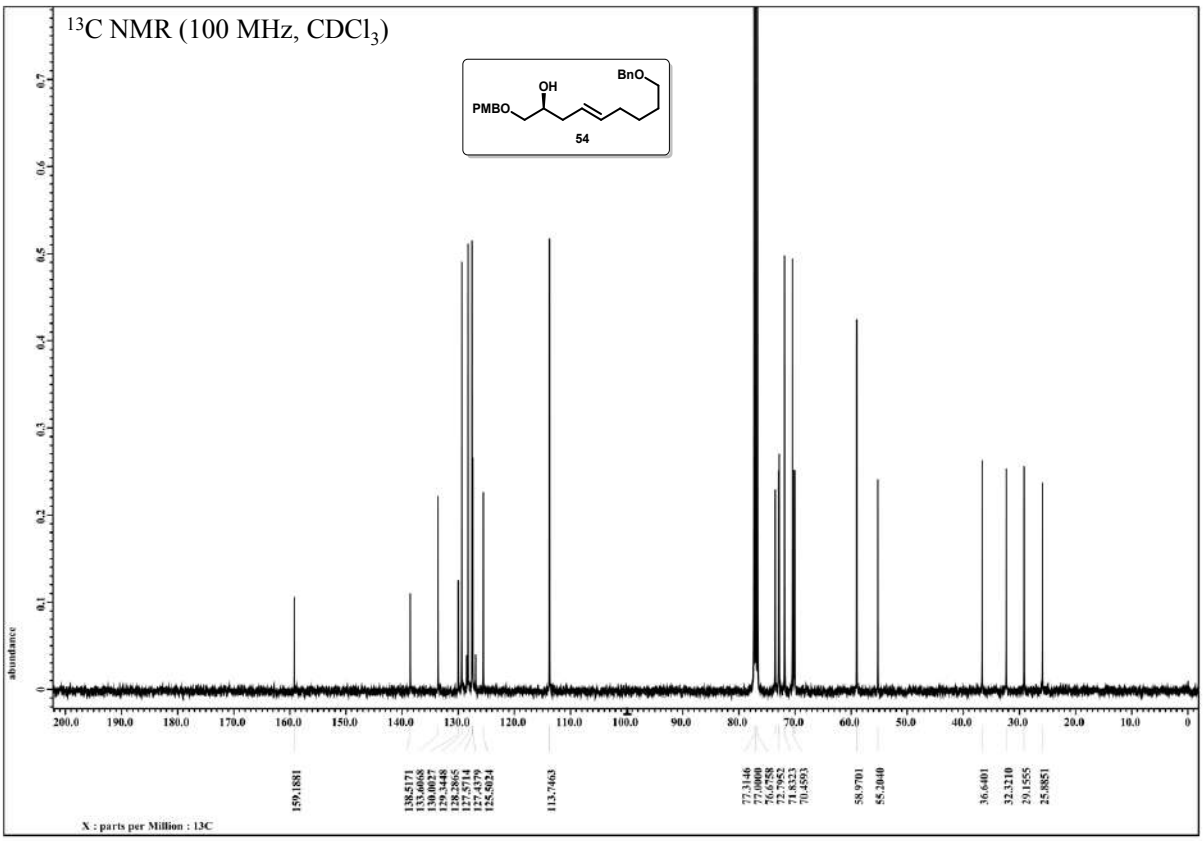
^{13}C NMR (100 MHz, $CDCl_3$)



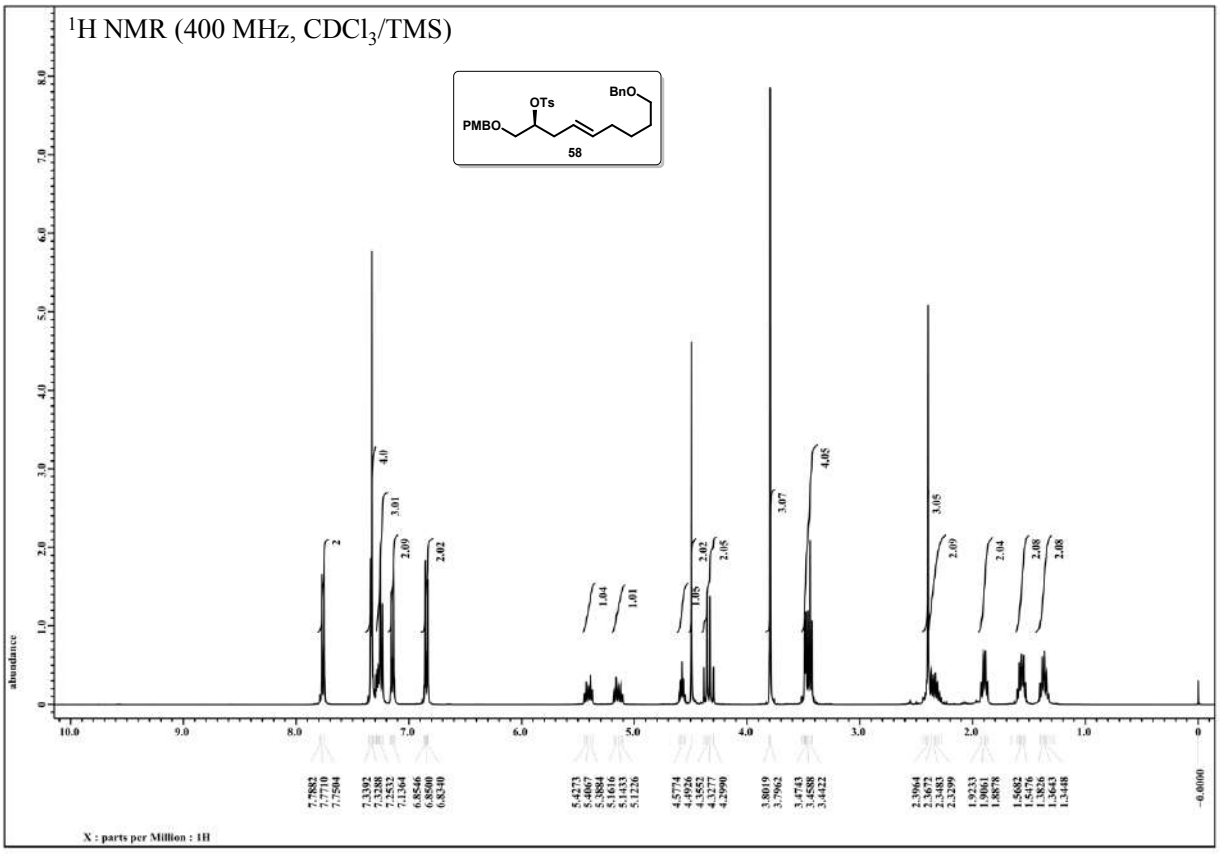
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



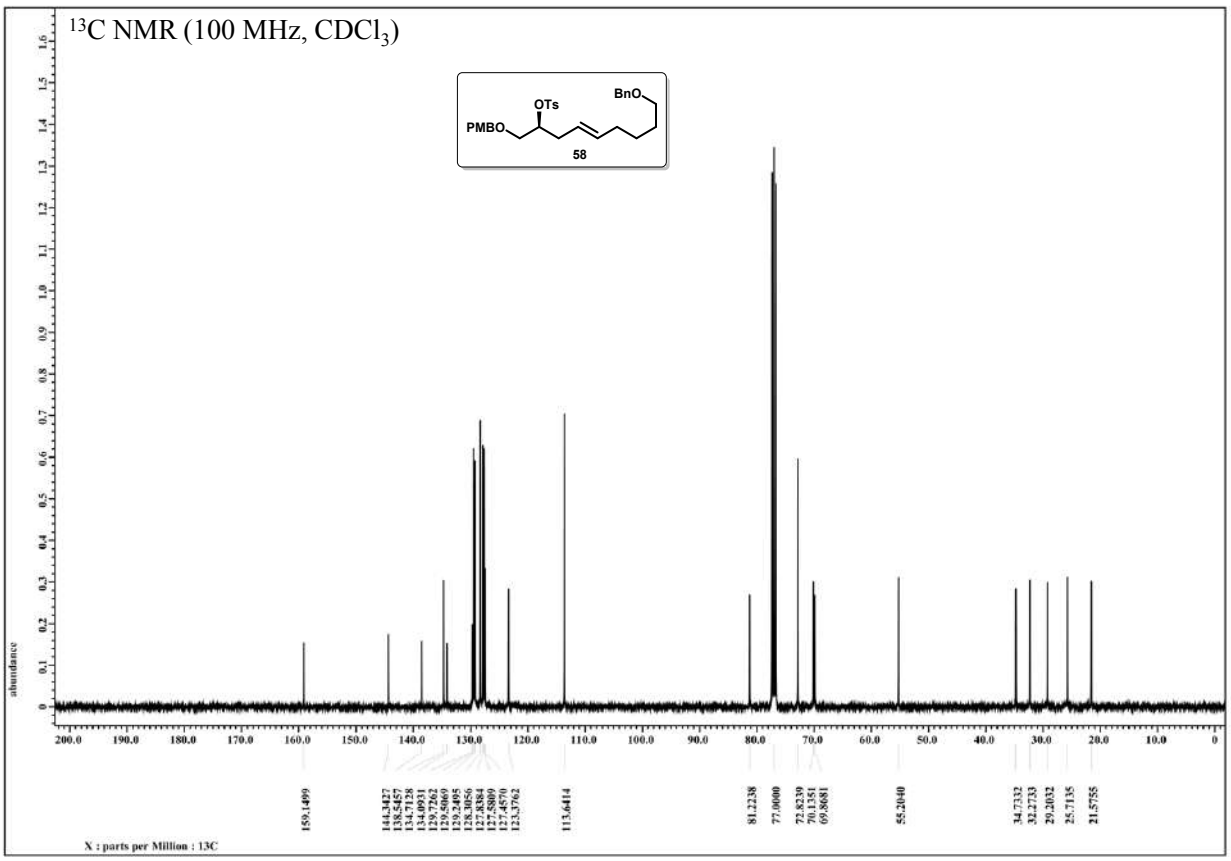
^{13}C NMR (100 MHz, $CDCl_3$)



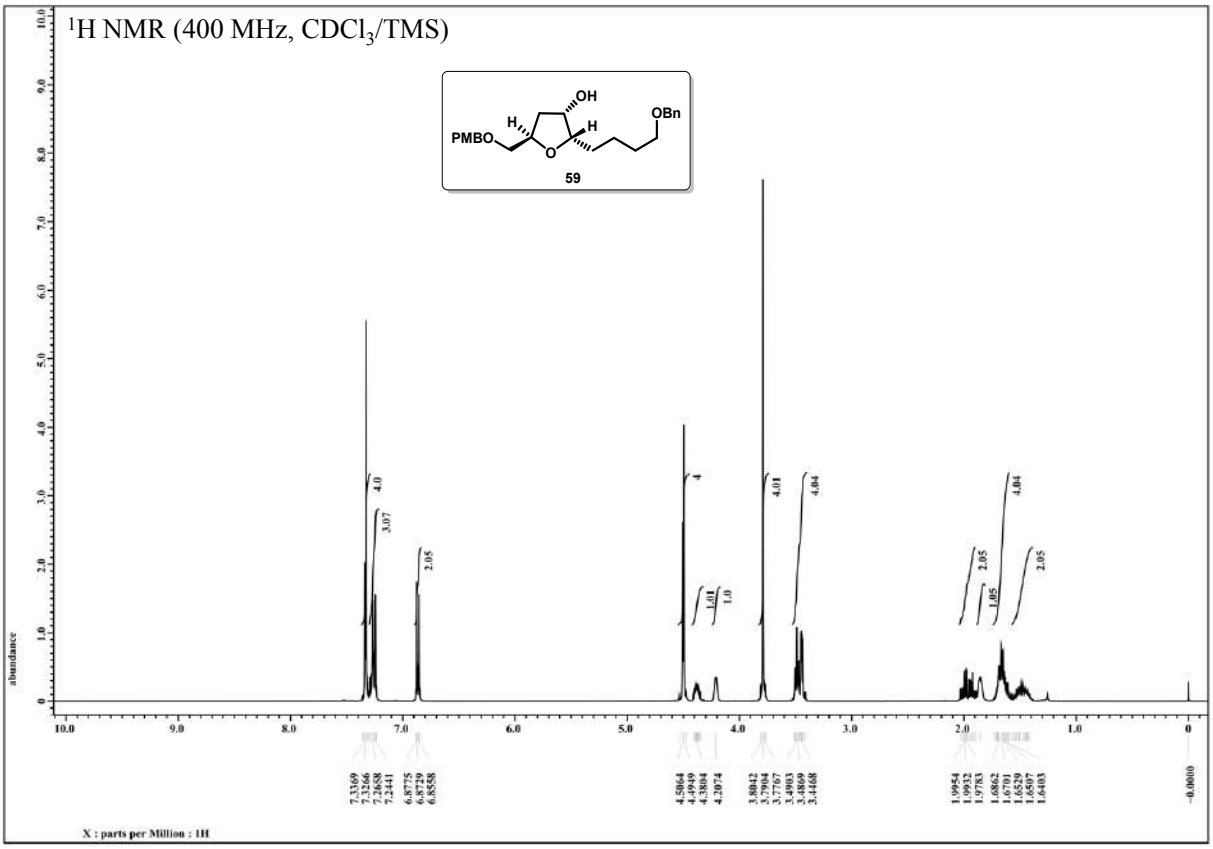
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



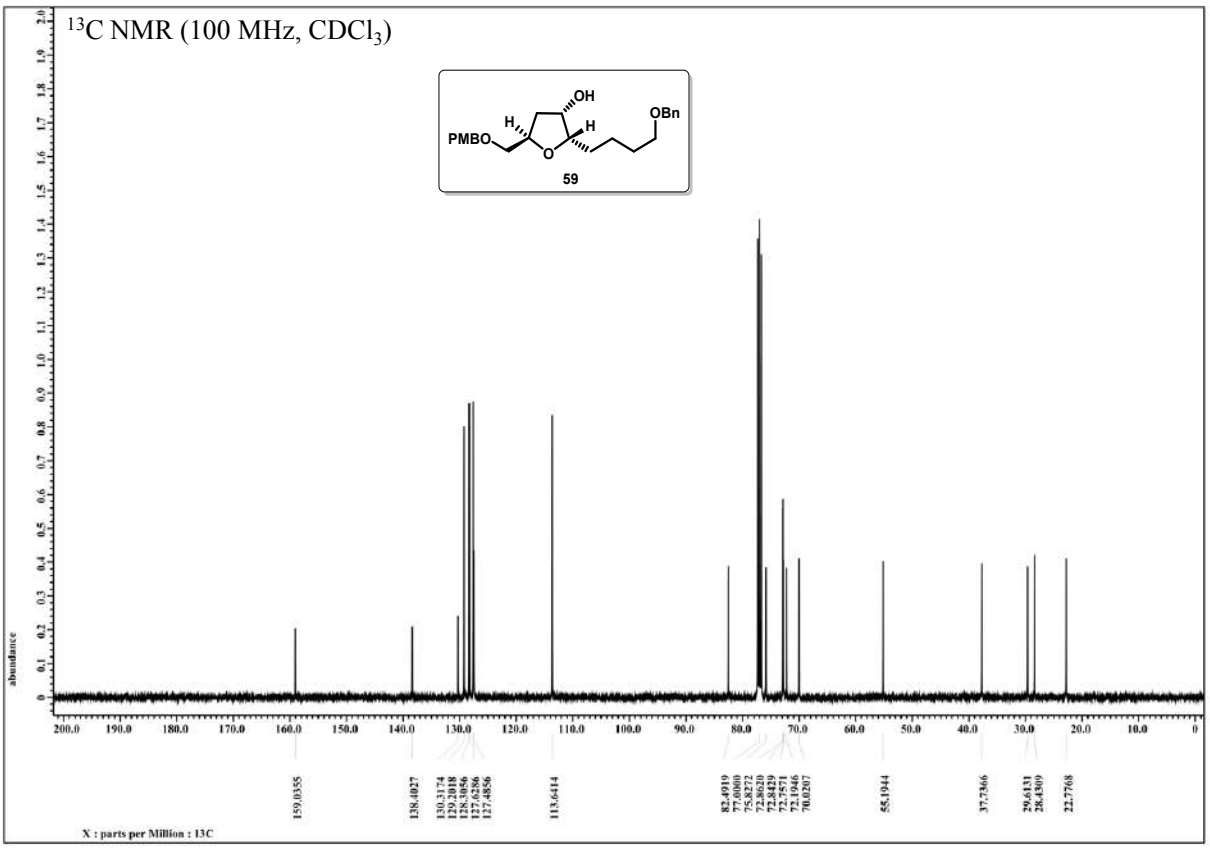
^{13}C NMR (100 MHz, $CDCl_3$)



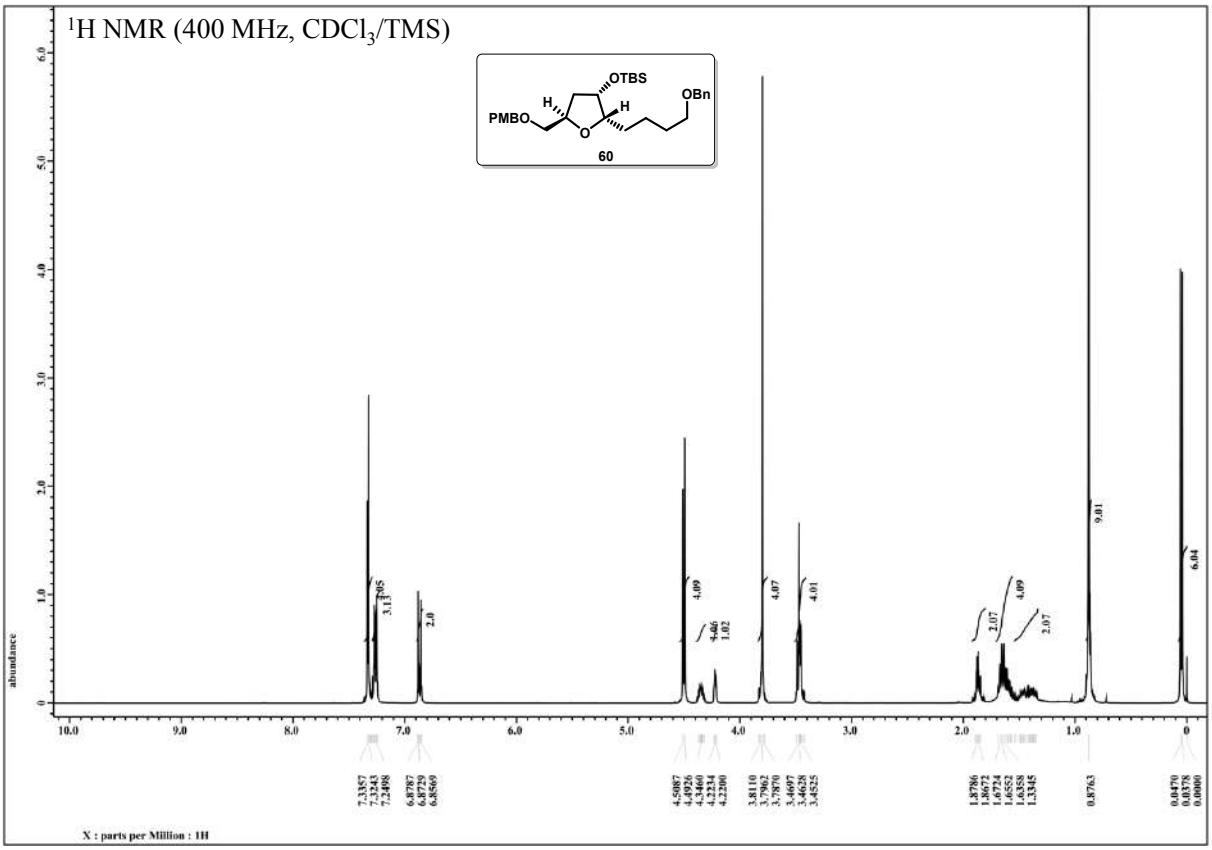
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



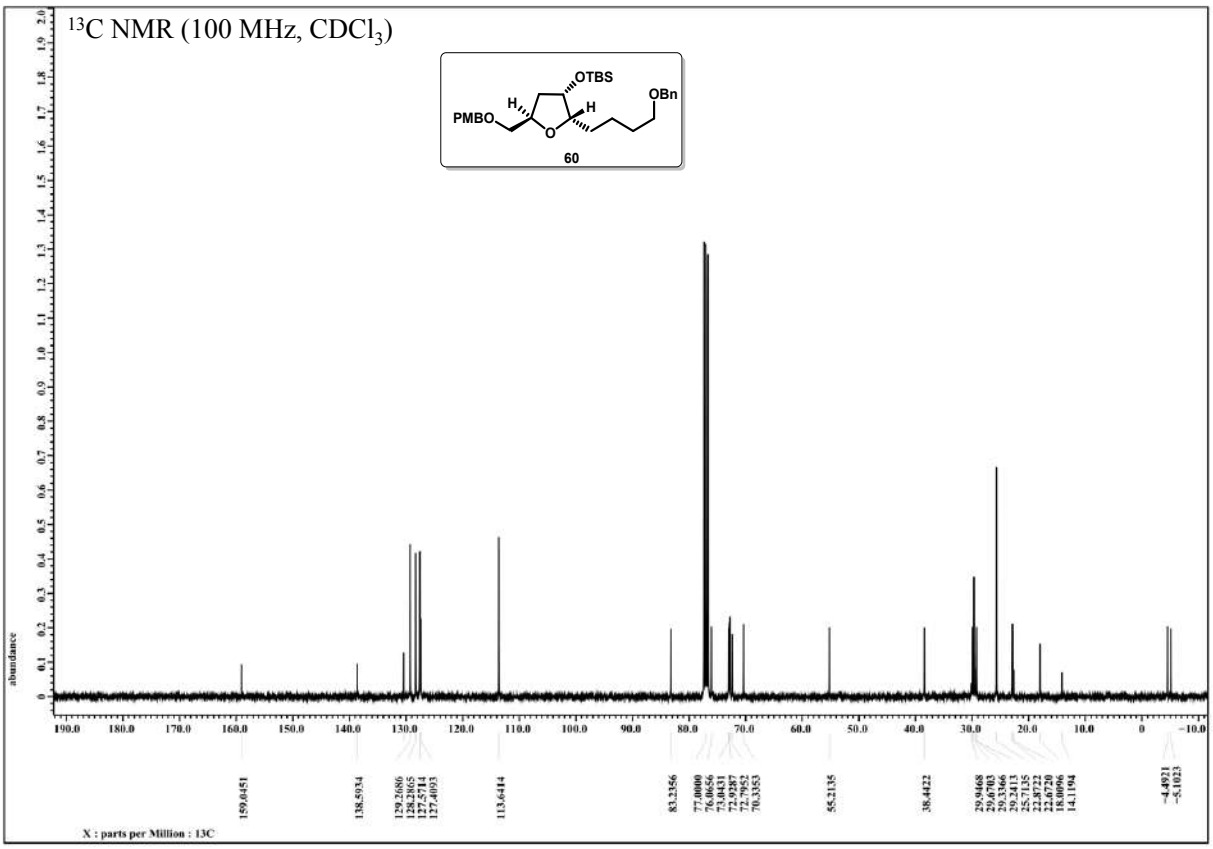
^{13}C NMR (100 MHz, $CDCl_3$)



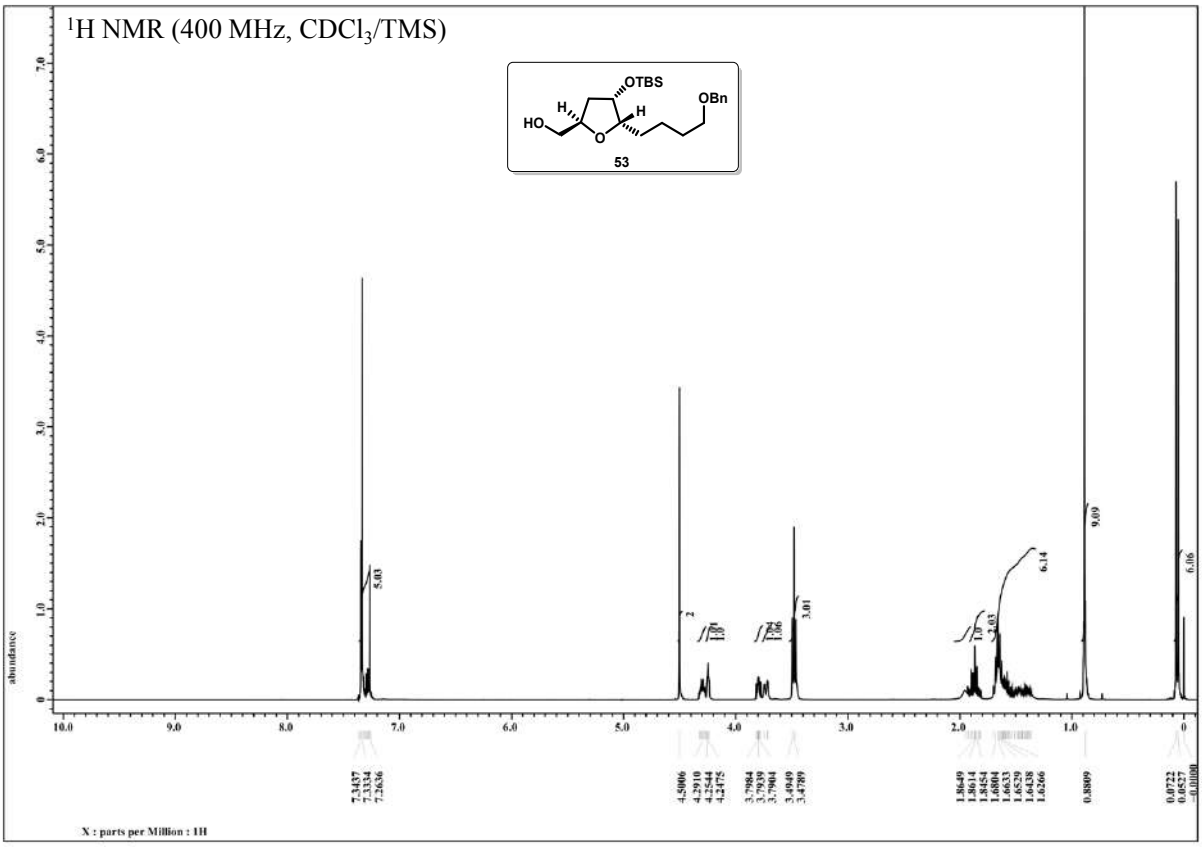
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



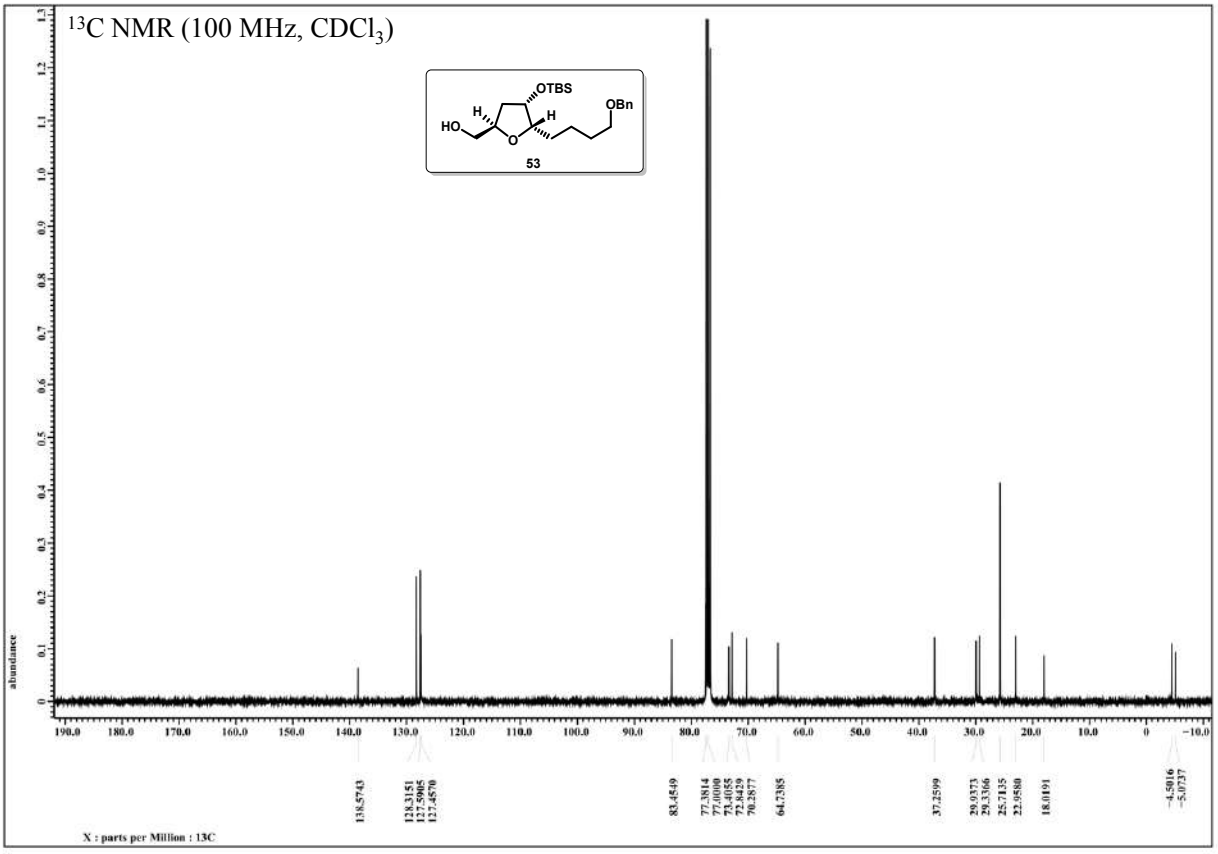
^{13}C NMR (100 MHz, $CDCl_3$)



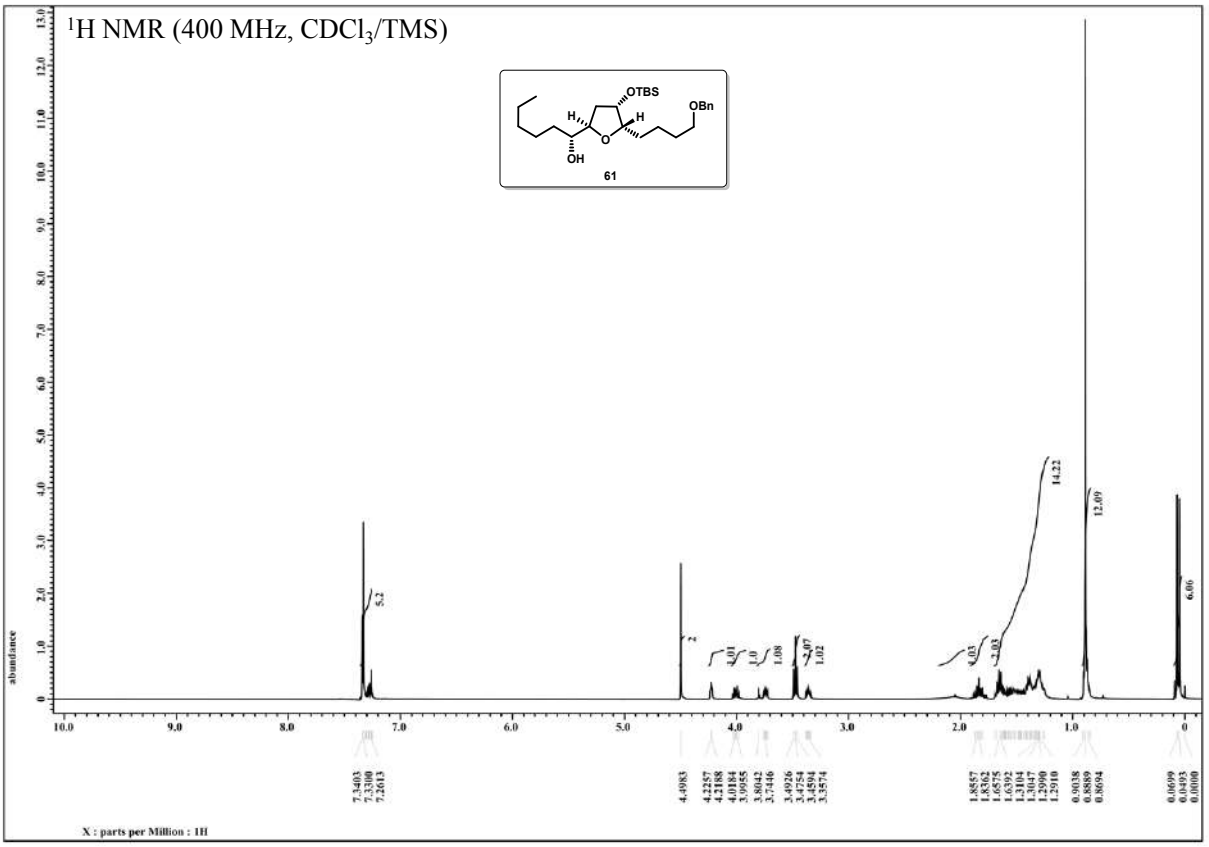
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



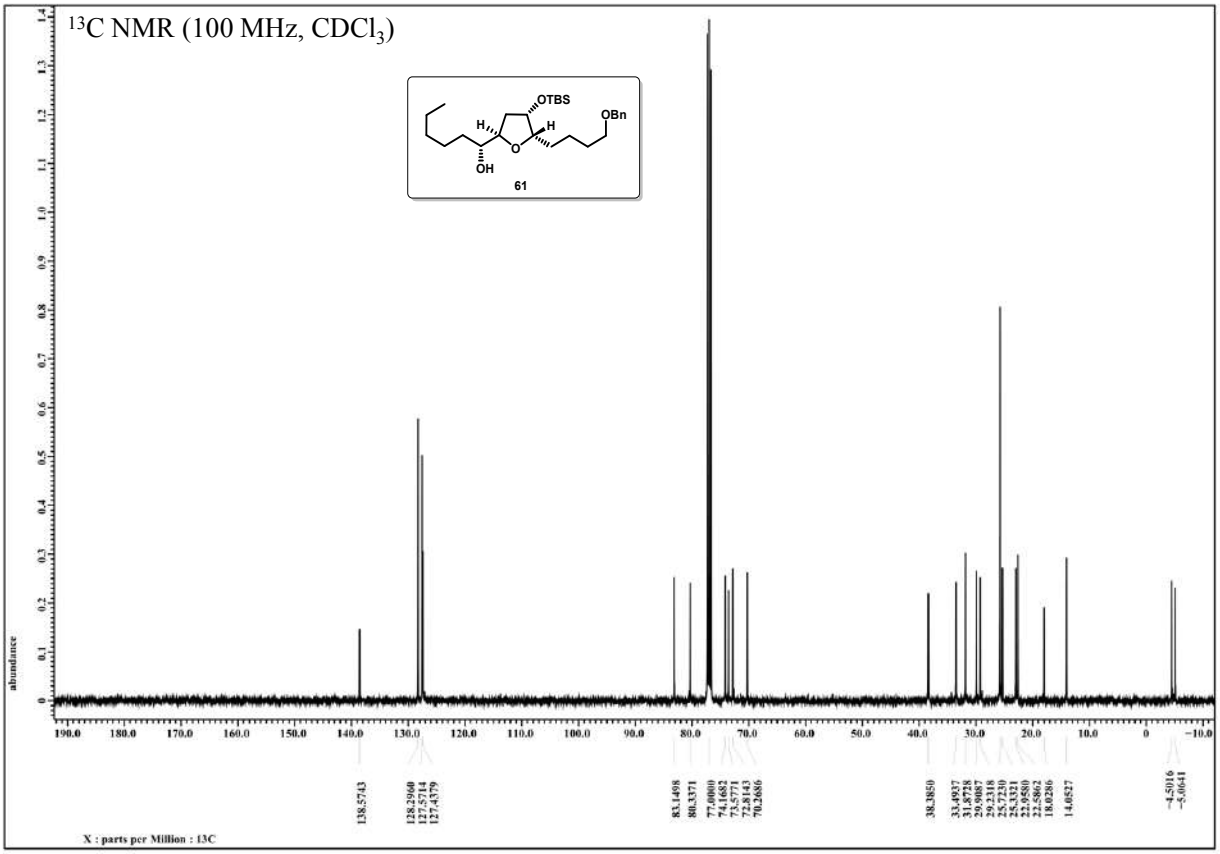
^{13}C NMR (100 MHz, $CDCl_3$)



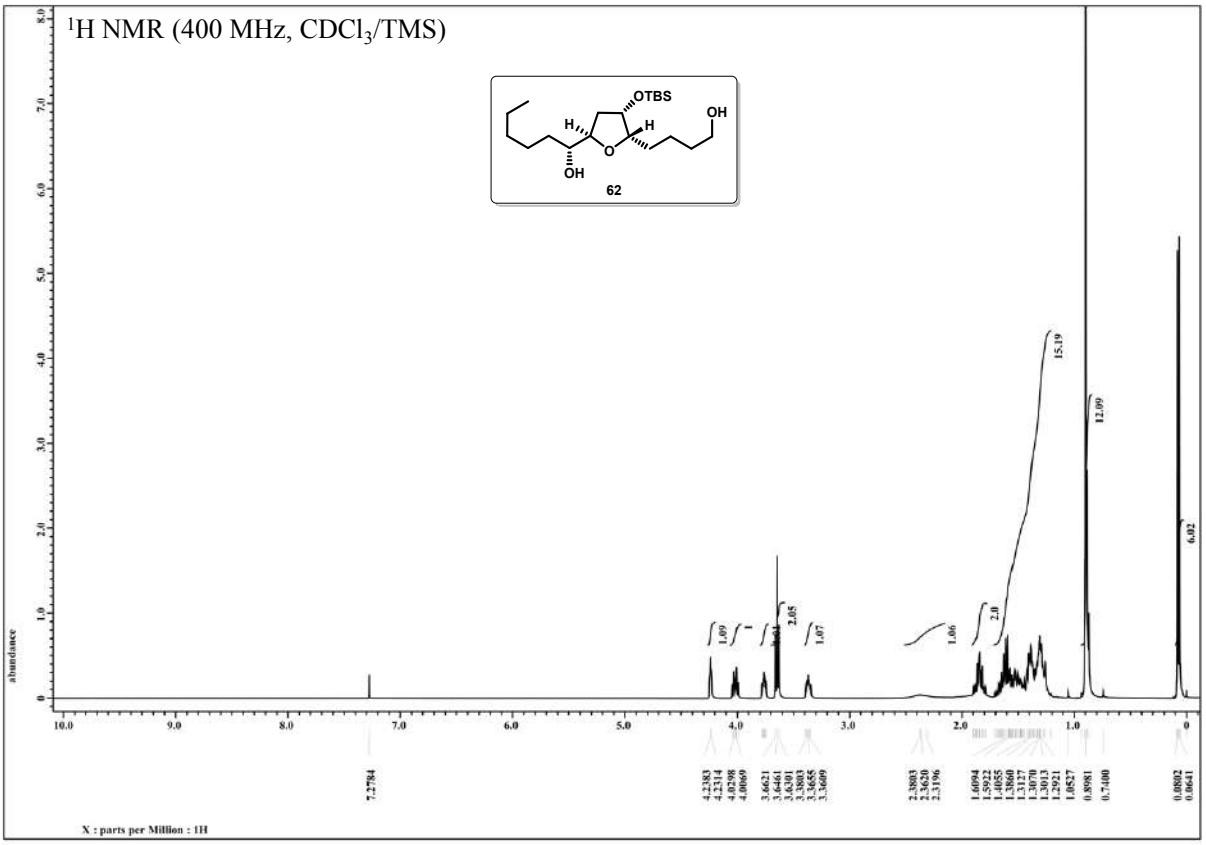
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



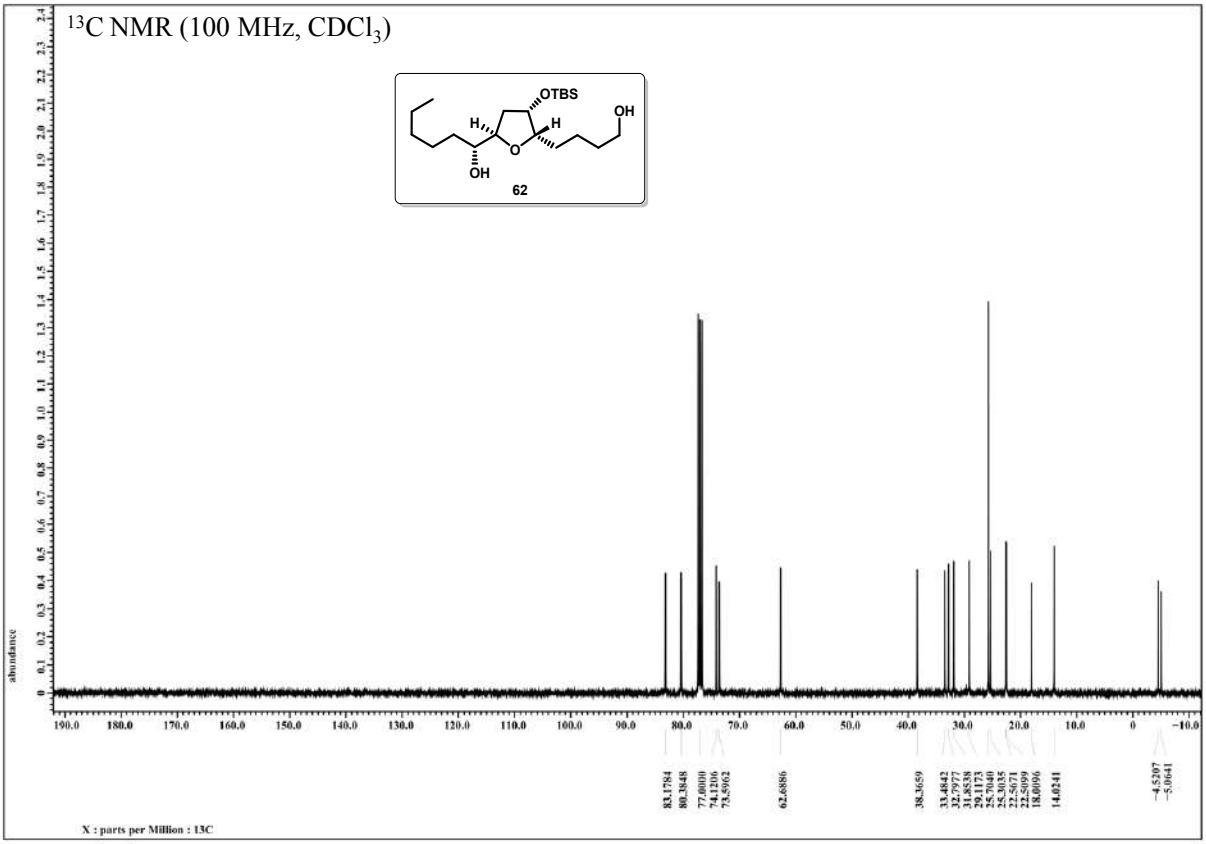
^{13}C NMR (100 MHz, $CDCl_3$)



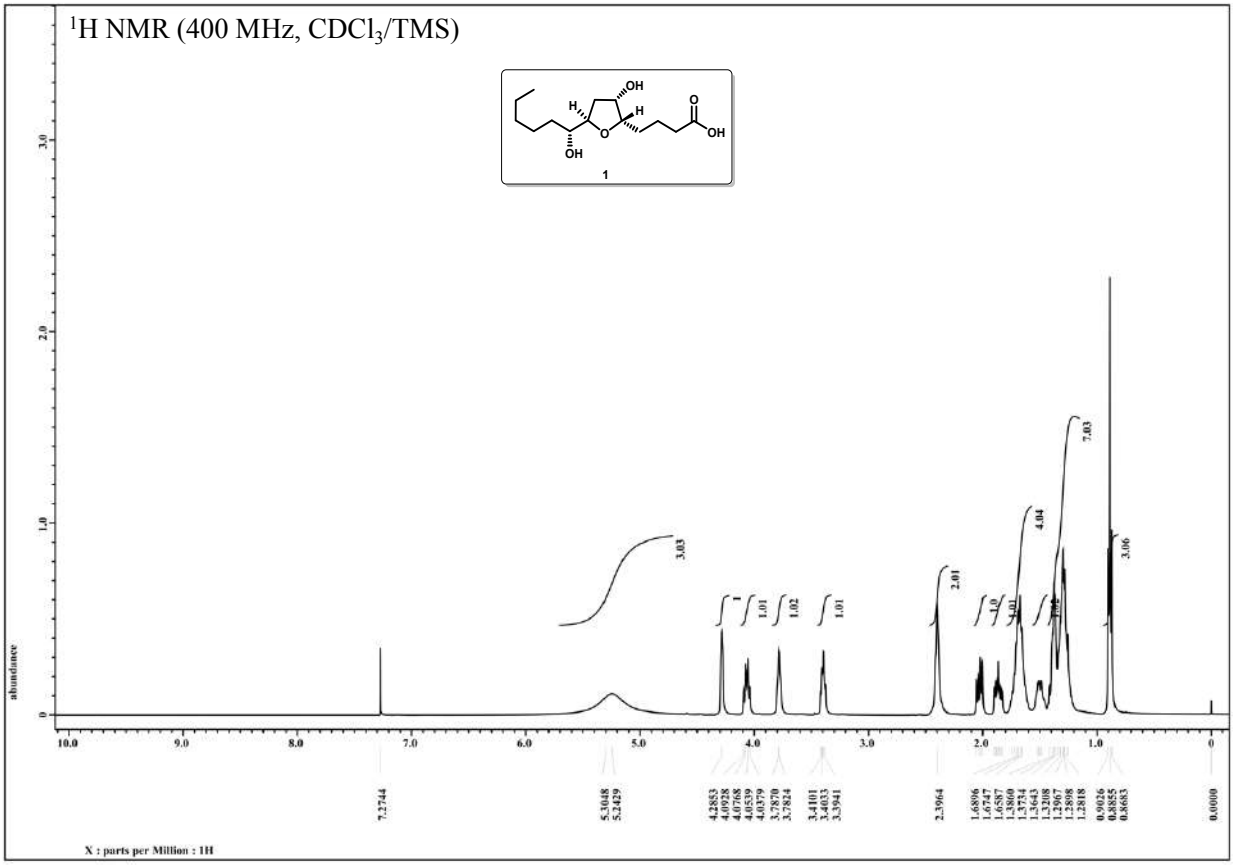
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



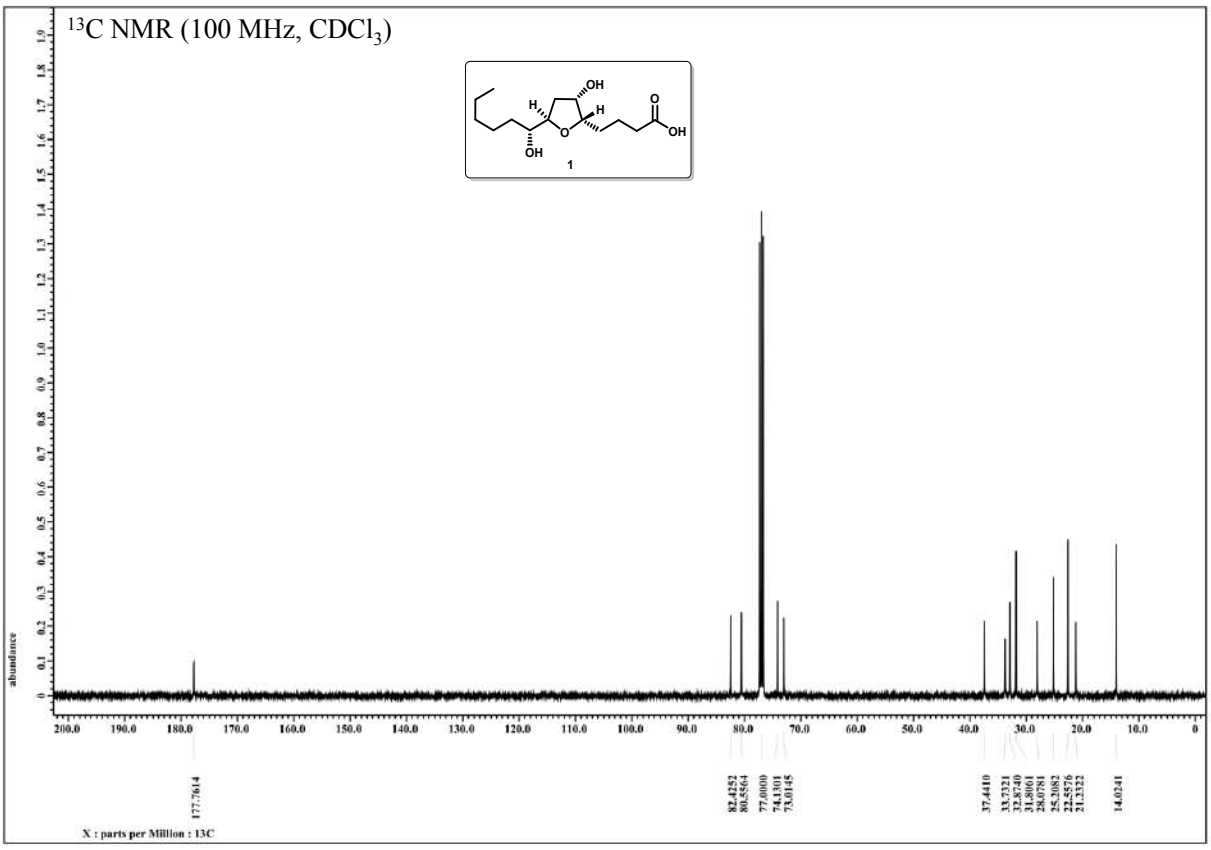
^{13}C NMR (100 MHz, $CDCl_3$)



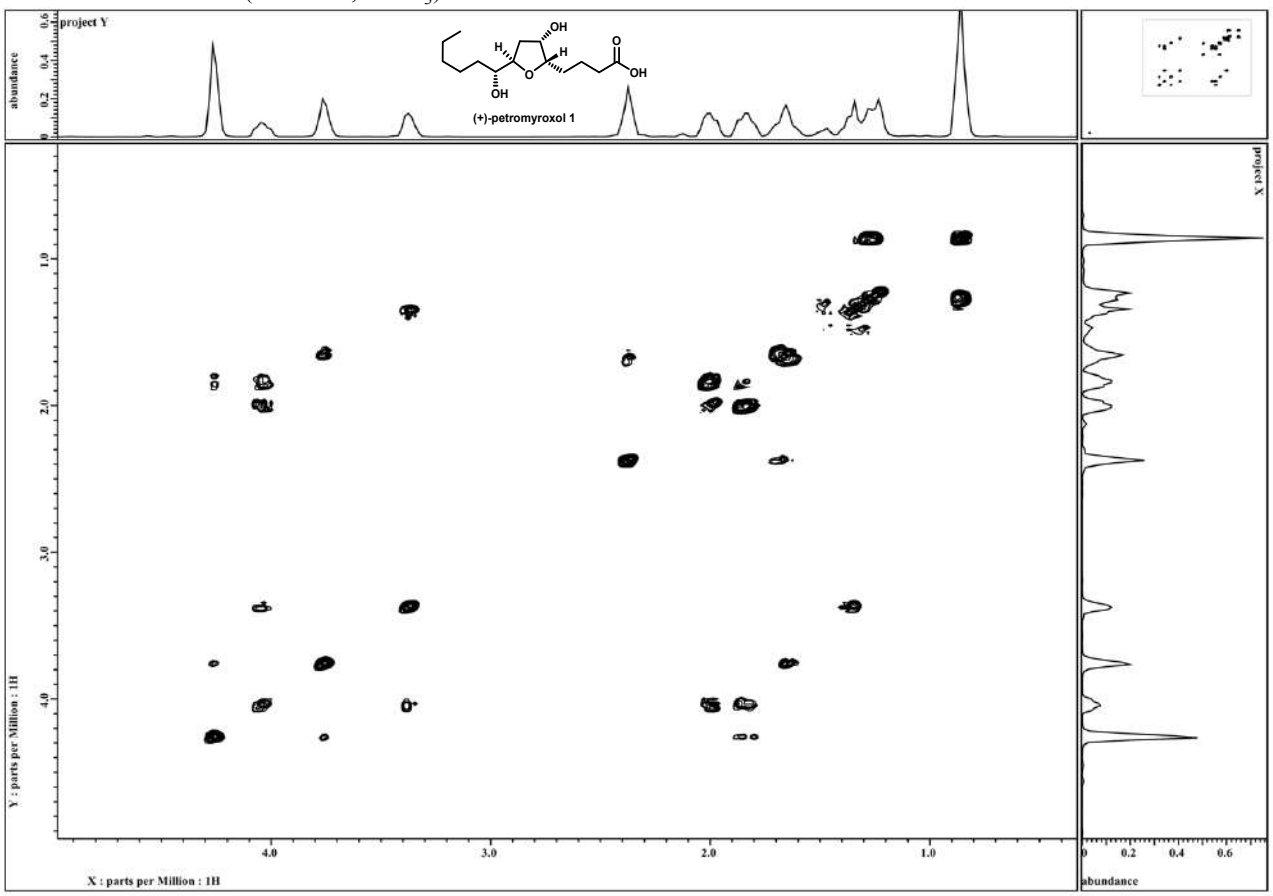
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



^{13}C NMR (100 MHz, $CDCl_3$)



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



3.2 Section B

Enantioselective approach towards the total synthesis of 2,3,4,6-tetrasubstituted pyran and its application to the total synthesis of (+)-phomonol

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3.2.1 Introduction:

The functionalyzed tetrahydropyran moiety is a common motif present in a myriad of bioactive natural products and medicinal compounds.[19] In 2010, Shen and co-workers[20] reported the isolation of a novel 2,6-*cis*-disubstituted tetrahydropyran, phomonol **63** from the endophytic fungal strain *Phomopsis* sp. A 123 (Figure 2). The above specific endophyte fungal strain was obtained from the leaves of the mangrove species *Kandelia candel* collected from the Fugong Mangrove Conservation Area in Fujian, China. Architecturally, phomonol **63** and *epi*-phomonol **64** are 2,3,4,6-tetrasubstituted pyran embedded with four stereogenic centers. Its chemical structure was deduced by a combination of detailed NMR studies including 1D- and 2D-NMR, HR-Q-TOF mass spectrometry and revised structure has been confirmed by total synthesis.[21a]

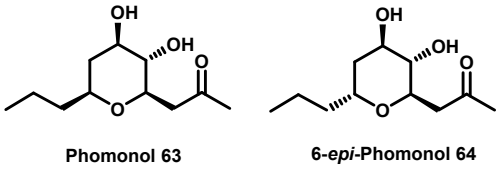


Figure 2: Structures of phomonol **63** and 6-*epi*-phomonol **64**.

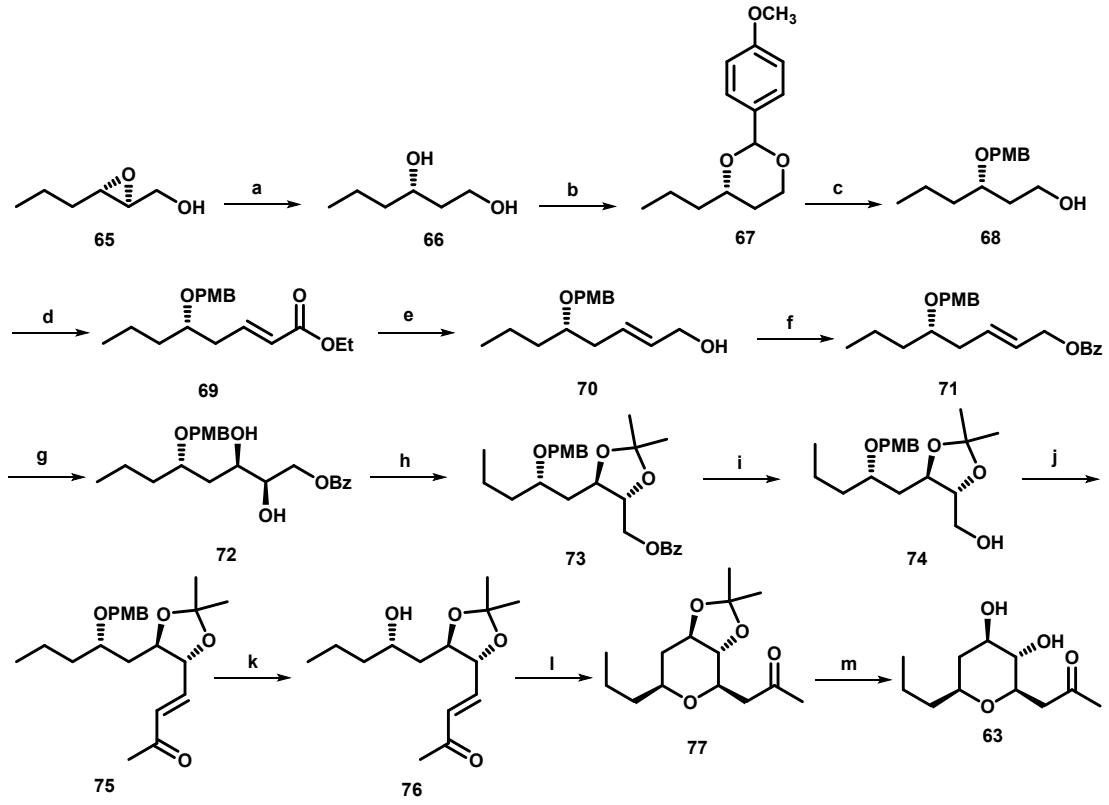
3.2.2 Review of Literature:

There are three total synthesis of (+)-phomonol **63**[21a-c] and one synthesis of 6-*epi*-phomonol **64**[21d] have been documented in the literature. Asymmetric total syntheses of phomonol **63** are described below.

Krishna P. R. *et al*. (2013)[21a]

P. R. Krishna and co-workers described the first stereoselective total synthesis of phomonol **63** employed Sharpless AD and 6-exo-trig oxa-Michael addition as the key steps. As demonstrated in Scheme 10, the synthesis of phomonol **63** commenced with known epoxy alcohol **65**, which was subjected to Red-Al mediated regioselective ring-opening reaction to afford the desired diol **66** as the major isomer with 82% yield. The precursor diol **66** was

protected as its PMB-acetal **67** under acidic condition which was then treated with DIBAL-H to afford the corresponding primary alcohol **68** in 88% yield. Swern oxidation and 2C Wittig olefination reaction under reflux conditions converted **68** into the unsaturated ester **69** in 81% yield. Later, DIBAL-H mediated reduction of the unsaturated ester **69** afforded allylic alcohol **70** in 90% yield. Treatment of allylic alcohol **70** with BzCl, Et_3N and DMAP led to allylic benzoate **71** in 86% yield. Alkene derivative **71** was converted into diol **72** *via* Sharpless AD protocol using AD-mix-*β* as the separable major isomer (dr 95:5) in 76% yield. The diol **72**

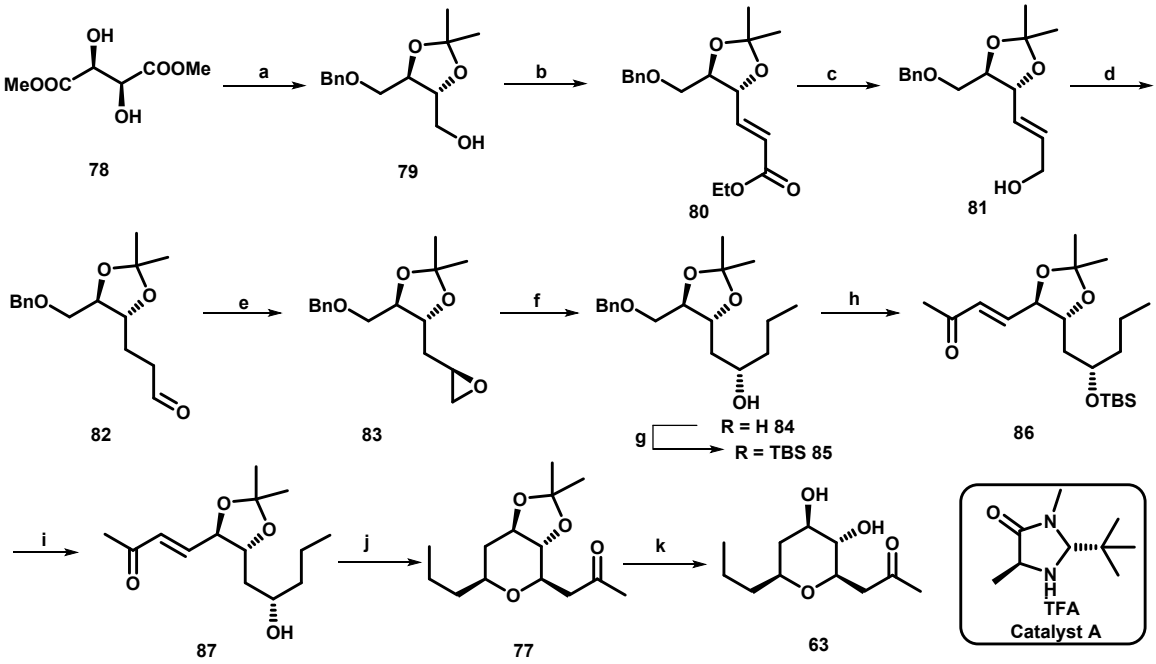


Scheme 10. *Reagents and conditions*: (a) Red-Al, dry THF, 0 °C to rt, 3 h, 82%; (b) anisaldehyde dimethyl acetal, *p*-TSA, dry CH_2Cl_2, 0 °C to rt, 1 h, 94%; (c) DIBAL-H, dry CH_2Cl_2, 0 °C to rt, 1 h, 88%; (d) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, 1 h, ii) Ph_3P= CH_2COOEt, benzene, reflux, 8 h, 81% (over two steps); (e) DIBAL-H, dry CH_2Cl_2, 0 °C, 0.5 h, 90%; (f) BzCl, Et_3N, dry CH_2Cl_2, 0 °C to rt, 1 h, 86%; (g) AD-mix *β*, *t*-BuOH:H_2O, 0 °C to rt, 18 h, 76% (major isomer); (h) 2,2-DMP, PPTS, dry CH_2Cl_2, 0 °C to rt, 1 h, 92%; (i) K_2CO_3, MeOH, 0 °C to rt, 81%; (j) i) TEMPO, BAIB, dry CH_2Cl_2, 0 °C to rt, 1 h, ii) 1-(tri phenyl phosphoranylidene)-2-propanone, dry THF, reflux, 8 h 91% (over two steps); (k) DDQ, CH_2Cl_2:H_2O (19:1), 0 °C to rt, 0.5 h, 81%; (l) NaH, dry THF, 0 °C, 0.5 h, 89%; (m) *p*-TSA, MeOH, 0 °C to rt, 0.5 h, 90%.

was converted to 2,2-*O-iso*-propylidene derivative **73** with 2,2-dimethoxypropane and catalytic PPTS at 0 °C in 92% yield. Benzoyl group in **73** was removed with K_2CO_3 to get **74** in 81% yield. Treatment of the alcohol **74** with TEMPO/BAIB conditions at 0 °C afforded aldehyde which was converted to unsaturated ketone derivative **75** *via* Wittig olefination with 1-(triphenyl phosphoranylidene)-2-propanone ylide under reflux conditions in 91% yield. Deprotection of the PMB ether **75** with DDQ afforded the alcohol **76** in excellent yield. *α,β*-unsaturated ketone **76** was subjected to NaH catalyzed intramolecular 6-exo-trig oxa-Michael addition to afford the tetrahydropyran derivative **77** as an exclusive diastereomer in 89% yield. Finally, treatment of tetrahydropyran **77** with *p*-TSA in methanol afforded target compound phomonol **63** in 90% yield.

Reddy, B. V. S. *et al.* (2014)[21b]

B. V. S Reddy and co-workers reported a stereoselective total synthesis of phomonol **63**, following organocatalytic enantioselective epoxidation and intramolecular oxa-Michael reaction as key steps. Accordingly, the synthetic sequence commenced with the oxidation and



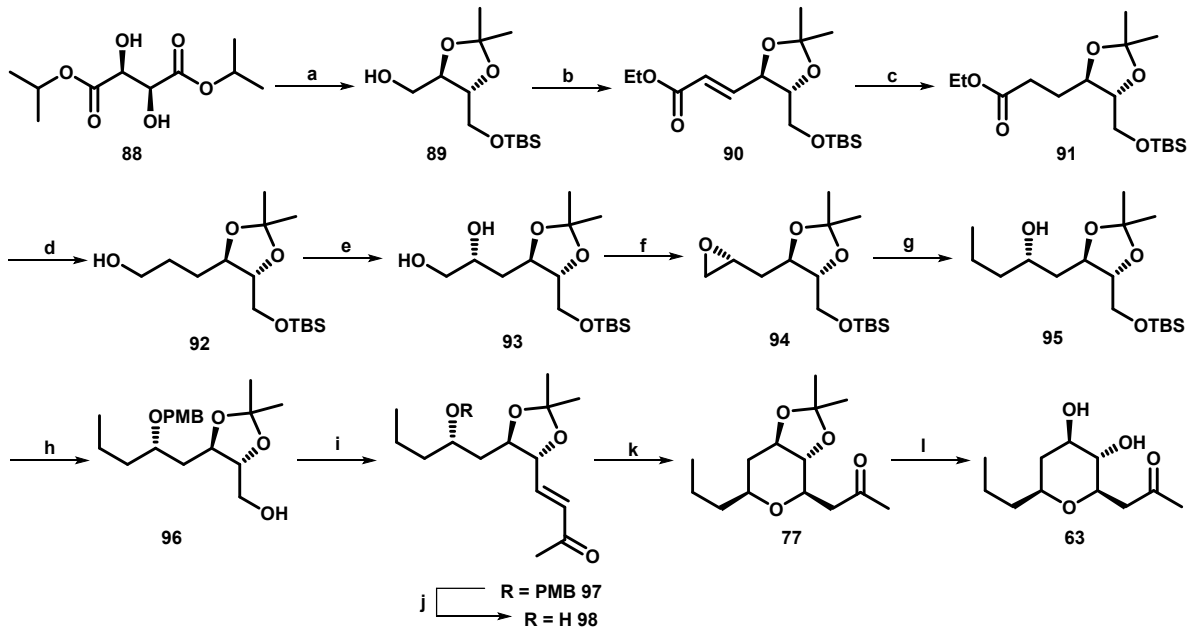
Scheme 11. *Reagents and conditions:* (a) See reference 22; (b) Tetrapropylammonium perruthenate (TPAP), NMO, CH_2Cl_2, Ph_3P=CHCOOEt, 80%; (c) DIBAL-H, CH_2Cl_2, 0 ^oC, 15 min, 85%; (d) $Pd(OH)_2/C$, Et_3N, benzene, 90%; (e) 50 mol-% $Cu(TFA)_2 \cdot H_2O$, 20 mol-% cat. A, LiCl, $Na_2S_2O_8$, MeCN, $NaBH_4$, 0 ^oC, 15 min, KOH, r.t, 30 min, 86%; (f) EtMgBr, CuCN, THF, 0 ^oC, 1 h, 90%; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 91%; (h) i) Li, naphthalene, -20 ^oC, 91%; ii) DMAP, CH_2Cl_2, rt, 3 h; iii) 1-(triphenylphosphoranylidene) propan-2-one,

dry THF, reflux, 8 h, 87%; (i) HF/pyridine, THF, 90%; (j) DBU, LiCl, THF; 90%. (k) $CeCl_3.7H_2O$, MeOH:MeCN 1:1, reflux, 4 h, 66%.

2C-Wittig olefination of alcohol derivative **79** derived from L-tartaric acid **78** to furnish *E*-ester **80** in 80% yield. Reduction of the *α,β*-unsaturated ester under DIBAL-H reduction conditions afforded the allylic alcohol **81** in 85% yield. $Pd(OH)_2/C$ catalysed isomerization of unsaturated alcohol **81** provided corresponding aldehyde **82** in 90% yield which was subjected to asymmetric epoxidation with catalyst A to furnish epoxide **83** (93% de; by HPLC analysis) in 86% yield. Copper catalyzed epoxide ring-opening of **83** with ethyl magnesium bromide led to the corresponding alcohol **84** in 90% yield. Treatment of alchol **84** with TBSOTf and 2,6-lutidine furnished the silylated ether **85** in 91% yield. Subsequent debenzylation of **85** under Li/naphthalene conditions followed by DMP mediated oxidation led to the formation of aldehyde, which was homologated with 1-(triphenylphosphoranylidene)propan-2-one in THF to furnish the *α,β*-unsaturated ketone **86** in 87% yield, which was further reacted with HF/pyridine to get the compound **87** in 90% yield. Intramoleculr 6-exo-trig oxa-Michael reaction of compound **87** with DBU in the presence of LiCl in MeCN at room temperature proceeded smoothly to furnish 2,6-*cis*-tetrasubstituted tetrahydropyran **77** exclusively in 90% yield. Finally, removal of acetonide from compound **77** using $CeCl_3 \cdot 7H_2O$ afforded phomonol **63** in 66% yield.

Bhaskar, K. *et al.* (2015)[21c]

K. Bhaskar and co-workers described the total synthesis of phomonol **63** from optically active L-(-)-diisopropyl tartarate employed Swern oxidation, MacMillan, Grignard and Oxa-Michael addition reactions as key steps. Accordingly, the synthetic sequence began with the monoprotected alchol **89** which was synthesized from commercially available L-(-) diisopropyl tartarate **88** following a literature protocol. Compound **89** was oxidized to the corresponding aldehyde under Swern conditions and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane to furnish *α,β*-unsaturated ester **90** in 83% yield. Reduction of **90** with $NiCl_2.6H_2O/NaBH_4$ yielded the saturated ester **91** in 90% yield, which on further reduction with $LiAlH_4$ afforded alcohol **92** in 97% yield. Swern oxidation of the alcohol in **92** afforded the corresponding aldehyde, which on reaction with L-proline and nitrosobenzene following MacMillan procedure, afforded *α*-aminoxylated aldehyde and subsequent reduction with $NaBH_4/CH_3OH$ followed by benzylamine cleavage with Zn furnished the required diol **93** in 71% yield. Treatment of diol **93** with tosylimidazole in the presence of NaH afforded the epoxide derivative **94** in 91% yield. Regioselective ring



Scheme 12. *Reagents and conditions:* (a) See reference 23; (b) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h; ii) $Ph_3P{=}CH_2CO_2Et$, THF, rt, 8 h, 83% (over two steps); (c) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0 °C to rt, 3 h, 90%; (d) LAH, dry THF, 0 °C to rt, 97%; (e) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt, 1 h; ii) PhNO, L-proline, $CHCl_3$, 0 °C, 2 h then $NaBH_4$, EtOH, 0 °C, 2 h then AcOH, Zn, 12 h, 71%; (f) tosylimidazole, NaH, THF, 0 °C to rt, 2 h, 91%; (g) EtBr, Mg, CuI, THF, -20 °C to rt, 12 h, 84%; (h) i) PMBCl, NaH, THF, 0 °C to rt, 4 h ; ii) TBAF, THF, 0 °C to rt, 3 h, 92% (over two steps) (i) i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 1.5 h; ii) 1-(tri phenyl phosphoranylidene)-2-propanone, dry THF, reflux, 8 h, 91% (over two steps); (j) DDQ, CH_2Cl_2:H_2O 19:1, 0 °C to rt, 1 h, 92%; (k) NaH, dry THF, 0°C, 1 h, 88%; (l) *p*-TSA, MeOH, 0 °C to rt, 1 h, 90%.

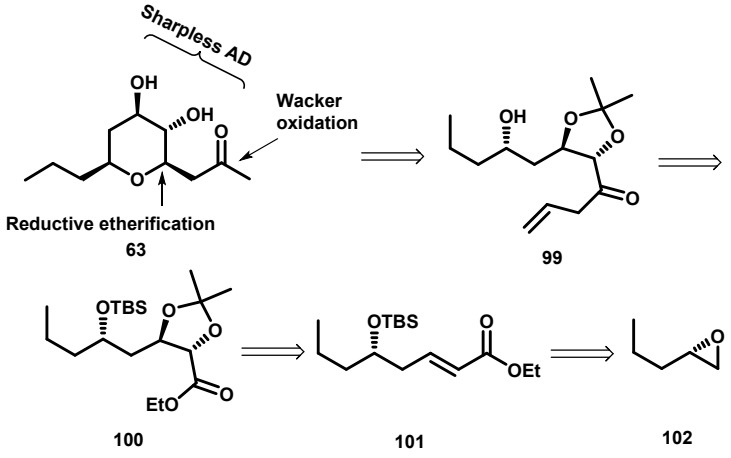
opening of **94** with EtMgBr in the presence of a catalytic amount of CuI furnished the alcohol **95** in 84% yield. Protection of the alcohol **95** with PMBCl followed by removal of silyl ether with TBAF afforded alcohol **96** in 92% yield over two steps. Oxidation of the primary alcohol **96** with IBX followed by Wittig olefination with 1-(triphenylphosphoranylidene)propan-2-one under reflux conditions furnished *α,β*-unsaturated ketone **97** in 91% yield. The *α,β*-unsaturated ketone **97** was converted into 2,6-*cis* tetrasubstituted tetrahydropyran **77** *via* a process including deprotection of the PMB ether with DDQ followed by intramolecular oxa-Michael addition of *α,β*-unsaturated ketone **98** with NaH in 88% yield. Finally, the deprotection of acetonide of compound **77** with *p*-TSA in MeOH furnished phomonol in 90% yield.

3.2.3 Present Work:

As part of our ongoing program towards the syntheses of biologically active natural products, we became interested in developing a simple and flexible route to phomonol **63**. Herein, we are reporting a new, highly efficient synthesis of phomonol **63** that utilizes Sharpless AD, reductive diastereoselective cyclization and Wacker oxidation as key steps.

3.2.4 Results and Discussion:

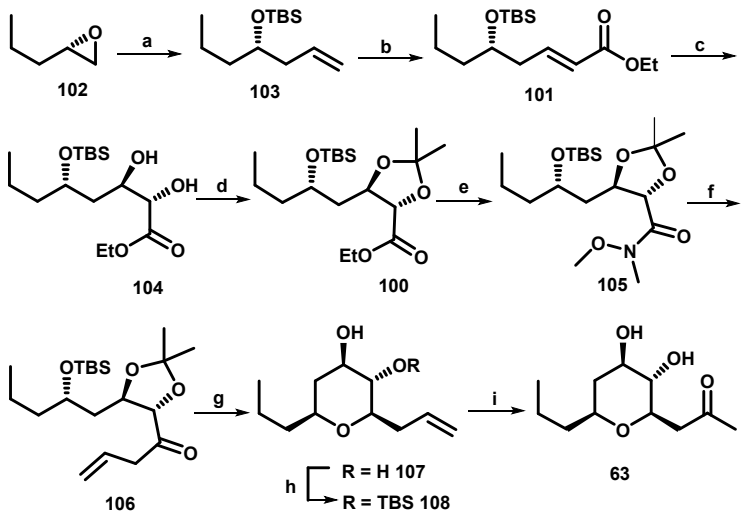
Our retrosynthetic approach to phomonol **63** is depicted in Scheme 13. Retrosynthetically, target molecule **63** was envisioned to be obtained from precursor **99** *via* Et_3SiH/TMSOTf-mediated reductive etherification reaction followed by Wacker oxidation. Allylic ketone derivative **99** was conceived to be derived from ester derivative **100** *via* Weinreb amide formation and subsequent treatment with allyl Grignard reagent. The ester derivative **100** in turn could be obtained from **101** involving Sharpless AD followed by acetonide protection. The *α,β*-unsaturated ester **101** could be constructed from commercially available enantiomerically pure (*S*)-1,2-epoxypentane **102** through regioselective vinyl Grignard reaction, oxidative cleavage followed by 2C-Wittig olefination. Alternatively, epoxide **102** could be obtained by hydrolytic kinetic resolution (HKR) using Jacobsen's methodology.[24]



Scheme 13: Retrosynthetic approach for phomonol **63**.

Synthesis of phomonol **63** as displayed in Scheme 14, commenced with the commercially available (*S*)-1,2-epoxypentane **102** which was regioselectively opened with vinyl magnesium bromide and further treated with TBSCl to furnish silyl ether **103** in 90% yield; {$[\alpha]_D^{25}$ +8.1 (*c* 2.0, $CHCl_3$); lit.[25] $[\alpha]_D^{25}$ +8.0 (*c* 2.0, $CHCl_3$)}. The IR spectrum of **103** showed alkene absorption at 2925 cm^{-1}. The ^1H NMR spectrum of compound **103** showed olefinic proton at *δ* 5.86-5.76 (multiplet, one proton) and at *δ* 5.04-5.00 (multiplet, two

protons). A one-pot oxidative degradation[26] of terminal alkene **103** with $OsO_4/NaIO_4$ led to aldehyde which was extended to the unsaturated *E*-ester **101** using the stabilized Wittig reagent ethyl(triphenylphosphoranylidene)acetate in 91% yield. The IR spectrum of compound **101** showed the ester carbonyl absorption at 1724 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 6.96 (triplet of doublet, one proton) with the coupling constant J = 15.6 Hz and at δ 5.83 (doublet, one proton) with the coupling constant J = 15.6 Hz indicating *trans*-olefin. The Sharpless AD[27] of olefin **101** with OsO_4 and potassium ferricyanide as co-oxidant in presence of $(DHQD)_2PHAL$ furnished vicinal diol **104** in 91% yield as a single diastereoisomer.[28] The IR spectrum of compound **104** showed the hydroxyl absorption at 3410 cm^{-1}. The ^1H NMR indicated absence of olefin protons. Further, treatment of 1,2-diol **104** with 2,2-dimethoxy propane and catalytic (±)-10-camphorsulfonic acid in acetone under reflux conditions successfully furnished the 2,2-*O*-isopropylidene derivative **100** in 92% yield. Saponification of the ethyl ester **100** with LiOH in aqueous methanolic THF at room temperature and subsequent treatment with *N,O*-dimethylhydroxylamine hydrochloride



Scheme 14: *Reagents and conditions*: (a) i) H_2C=CHMgBr, CuI, dry THF, -78 °C, 1 h; ii) TBSCl, imidazole, DMAP, dry CH_2Cl_2, rt, 12 h, 90% (over two step); (b) i) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane:water 3:1, rt, 2 h; ii) Ph_3P=CHCOOEt, THF, rt, 5 h, 91% (over two step); (c) 0.5 mol % OsO_4, 1 mol % $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0 °C, 12 h, 91%; (d) $(MeO)_2CMe_2$, CSA, acetone, reflux, 30 min., 92%; (e) i) LiOH, THF:MeOH:H_2O (4:1:1), rt, 4 h; ii) HN(Me)OMe-HCl, EDC, HOBt, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h, 89% (over two step); (f) H_2C=$CHCH_2MgBr$, dry THF, 0 °C, 10 min., 90%; (g) i) *p*-TSA, MeOH, rt, 1 h; ii) Et_3SiH, TMSOTf, dry CH_2Cl_2, -78 °C, 30 min., 89% (over two step); (h) TBSCl, imidazole, DMAP, dry CH_2Cl_2, rt, 12 h, 95%; (i) $PdCl_2$, CuCl, O_2, DMF:H_2O (1:0.1), rt, 12 h, 91% (over two step).

generated the Weinreb amide **105**[29] in 89% yield. Indeed, treatment of the Weinreb amide **105** with AllylMgBr[29b] at 0 °C, furnished the desired product **106** in 89% yield. The IR spectrum of compound **106** showed the carbonyl absorption at 1720 cm^{-1}. At this stage, to get the intermediate **99** for Et_3SiH/TMSOTf mediated reductive cyclization, initial treatment of silyl ether **105** with TBAF at low temperature afforded a complex mixture of products. To overcome this problem, concomitant deprotection of acetonide and silyl ether with *p*-TSA furnished ketotriol which was subjected to stereoselective reductive etherification[30] with Et_3SiH/TMSOTf (DCM, -78 °C) to produce 2,6-*cis*-disubstituted tetrahydropyran skeleton **107** as a single stereoisomer[28] in 89% yield. The IR spectrum of compound **107** showed the hydroxyl absorption at 3420 cm^{-1}. With cyclised compound **107** in hand, initial attempts to convert the diol **107** to phomonol **63** under standard Wacker oxidation conditions[31] was unsuccessful and led to lactol derivative.[32] Therefore, protection of diol **107** before Wacker oxidation was employed as an alternative. Unfortunately, protection of diol **107** with 2,2-dimethoxy propane in different solvent and at different temperatures was unsuccessful. Therefore, the secondary alcohol of **107** was regioselectivly silylated with TBSCl to furnish *tert*-butyldimethylsilyl ether derivative **108** in quantitative yield. Finally, one pot Wacker oxidation[31] of terminal alkene and cleavage of the silyl ether was achieved by treatment of compound **108** with $PdCl_2$, CuCl under oxygen atmosphere in DMF and acidic workup which provided the natural product phomonol **63** in 91% yield; $[\alpha]_D^{25}$ +5.8 (*c* 0.3, $CHCl_3$) {lit.[21a] $[\alpha]_D^{25}$ +2.3 (*c* 0.36, $CHCl_3$), lit.[20] $[\alpha]_D^{24}$ +6.0 (*c* 0.3, $CHCl_3$)}. The spectroscopic and physical data were identical in all respects with those reported in the literature.[21]

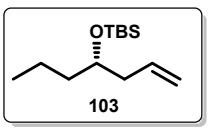
3.2.5 Conclusion:

In conclusion, a facile and efficient asymmetric total synthesis of phomonol **63** was accomplished after nine column chromatographic steps with 42% overall yield. Pivotal reaction sequence includes Wittig olefination, Sharpless AD, reductive etherification (Et_3SiH/TMSOTf) and Wacker oxidation. Moreover, the synthetic strategy described has significant potential for stereochemical variations at C-2,3,4,6 positions and further extension to other stereoisomers.

3.2.6 Experimental Section:

(*S*)-*tert*-Butyl(hept-1-en-4-yloxy)dimethylsilane, 103

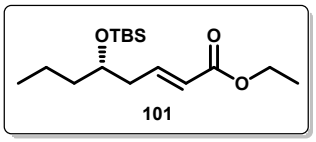
To a stirred solution of (*S*)-1,2-epoxypentane **102** (2.0 g, 23.19 mmol) and CuI (442 mg, 2.32 mmol) in dry THF (30 mL) was added



vinylmagnesium bromide (35 mL, 34.79 mmol, 1M solution in THF) dropwise at -78 °C. After 60 min, the mixture was allowed to warm up to 0 °C before it was quenched with a saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to get the allylic alcohol.

To a solution of above allylic alcohol in dry CH_2Cl_2 (40 mL) was added imidazole (2.36 g, 34.78 mmol), *tert*-butyldimethylsilyl chloride (4.19 g, 27.82 mmol) and a catalytic amount of DMAP (283 mg, 2.32 mmol) at 0 ^oC. The mixture was stirred for 12 h, after which it was quenched by adding a saturated NH_4Cl (20 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL) and combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Silica gel column chromatography of the residue (*n*-hexane) gave **103** (4.76 g, 90%) as a colorless liduid. [R_f = 0.6, *n*-hexane]; [α] $_D^{25}$ +7.5 (*c* 1.0, $CHCl_3$); lit.[6] [α] $_D^{25}$ +8.0 (*c* 2.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 2925, 1640, 1634, 1458, 1244, 1042, 838, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 5.86-5.76 (m, 1H), 5.04-5.00 (m, 2H), 3.70-3.60 (m, 1H), 2.23-2.18 (m, 2H), 1.41-1.21 (m, 4H), 0.89-0.84 (m, 12H), 0.01(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 135.5, 116.5, 71.9, 41.9, 39.4, 25.7, 18.6, 18.5, 14.2, -4.3, -4.5; HRMS (ESI), calcd for $C_{13}H_{27}OSi$ $[M-H]^+$ 228.1909; found 227.1905.

(*S,E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)oct-2-enoate, 101



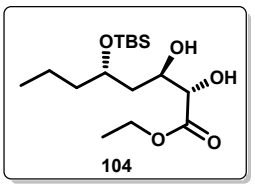
101

To a solution of compound **103** (2.0 g, 8.75 mmol) in dioxane-water (3:1 v/v, 8 mL) were added OsO_4 (0.1 M solution in toluene, 0.12 mL, 0.17 mmol), 2,6-lutidine (2.0 mL, 17.51 mmol) and $NaIO_4$ (7.49 g, 35 mmol). The reaction mixture was stirred at 25 ^oC for 2 h. After completion of reaction, water (10 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was separated, and the water layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give crude aldehyde.

A solution of stabilized ylide ($Ph_3P{=}CHCO_2Et$, 4.58 g, 13.12 mmol) in THF (20 mL) was added slowly to a stirred solution of above crude aldehyde in THF (20 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for 5h after which the reaction mixture was concentrated under reduced pressure. Silica gel chromatography of the crude product (EtOAc/hexane 1:49) afforded (*E*)-alkene ester **101** (2.39 g, 91%) as a colourless liquid. [R_f = 0.5, EtOAc/hexane 1:49 v/v]; [α] $_D^{25}$ + 4.3 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3079, 2935, 2859,

1724, 1659, 1468, 1366, 1261, 1167, 1095, 1045, 975, 914, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.96 (td, J = 15.6, 7.36 Hz, 1H), 5.83 (d, J = 15.6 Hz, 1H), 4.19 (q, J = 14.2 , 6.88 Hz, 2H), 3.78-3.74 (m, 1H), 2.37-2.29 (m, 2H), 1.45-1.27 (m, 7H), 0.91-0.85 (m, 12H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 146.1, 123.1, 71.1, 60.1, 40.2, 39.5, 29.6, 25.8, 18.5, 18.0, 14.2, 14.1, -4.5; HRMS (ESI), calcd for $C_{16}H_{31}O_3Si$ $[M - H]^+$ 301.2194; found 301.2195.

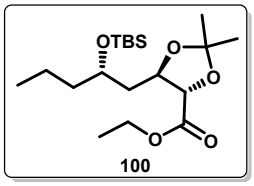
(2*S*,3*R*,5*S*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxyoctanoate, 104



104

To a stirred solution of $K_3Fe(CN)_6$ (3.66 g, 11.13 mmol), K_2CO_3 (1.54 g, 11.13 mmol) and $(DHQD)_2PHAL$ (29 mg, 1 mol%) in *t*-BuOH/H_2O (60 mL 1:1 v/v) at 0 °C was added OsO_4 (0.2 mL, 0.1M solution in toluene, 0.5 mol%) followed by methanesulfonamide (316 mg, 3.32 mmol). After stirring for 2 min at 0 °C, the olefin **101** (1.0 g, 3.32 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 12 h and then quenched with solid sodium sulfite (2.0 g). The stirring was continued for an additional 45 min, then the solution was extracted with EtOAc (3 × 30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane 1:4) afforded diol derivative **104** (1.0 g, 91% yield) as a colorless liquid. [R_f = 0.4, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ + 28.2 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3410, 2957, 2931, 2896, 2858, 1735, 1374, 1360, 1255, 1135, 1091, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.31-4.26 (m, 3H), 4.03-3.90 (m, 1H), 3.97-3.95 (m, 1H), 3.39 (b, 1H), 3.09 (b, 1H), 2.0-1.93 (m, 1H),1.61-1.53 (m, 3H), 1.35-1.25 (m, 5H), 0.94-0.88 (m, 12 H), 0.08 (d, J = 9.64 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 74.0, 70.8, 69.5, 61.8, 38.6, 38.0, 25.8, 18.9, 17.9, 14.2, 14.1, -4.6, -4.8; HRMS (ESI), calcd for $C_{16}H_{35}O_5Si$ $[M + H]^+$ 335.2249; found 335.2249.

Ethyl (4*S*,5*R*)-5-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate, 100

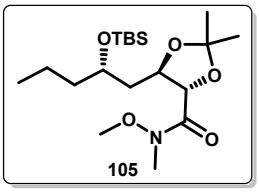


100

To a round bottom flask containing vicinal diol **104** (800 mg, 2.39 mmol) in acetone (15 mL) was added 2,2-dimethoxypropane (3.4 mL, 23.9 mmol) and camphorsulfonic acid (12 mg, 0.05 mmol). The contents were allowed to reflux for 30 minutes, at which time TLC indicated all starting material was consumed. The reaction mixture was then cooled to room temperature and neutralized with $NaHCO_3$. The aqueous layer was then extracted with EtOAc (3 × 30 mL) and the organic layers were combined, washed with brine (1 × 30 mL)

and dried over Na_2SO_4. Evaporation of the solvent and purification by silica gel column chromatography (EtOAc/hexane 1:19) afforded acetonide derivative **100** (820 mg, 92% yield) as a colorless liquid. [R_f = 0.5, EtOAc/hexane 1:9 v/v]; [α] $_D^{25}$ +20.4 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 2957, 2951, 2836, 2858, 1735, 1374, 1330, 1235, 1135, 1050, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.26-4.20 (m, 3H), 4.06-4.04 (m, 1H), 3.89-3.87 (m, 1H), 1.87-1.81(m, 1H), 1.71-1.64 (m, 1H), 1.49-1.43 (m, 8H), 1.37-1.25 (m, 5H), 0.92-0.86 (m, 12H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 170.8, 110.8, 79.2, 75.9, 68.7, 61.2, 40.9, 40.5, 27.2, 25.8, 25.6, 18.0, 17.8, 14.3, 14.2, -4.2, -4.8; HRMS (ESI), calcd for $C_{19}H_{39}O_5Si$ $[M + H]^+$ 375.2562; found 375.2581.

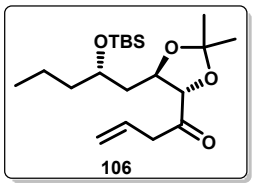
(4*S*,5*R*)-5-((*S*)-2-(*tert*-Butyldimethylsilyloxy)pentyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide, 105



A mixture of ethyl ester **100** (800 mg, 2.13 mmol), lithium hydroxide (448 mg, 10.68 mmol), THF (4 mL), methanol (1 mL) and water (1 mL) was stirred at room temperature for 4 h. The organic solvent was removed under reduced pressure, and the residue obtained was then acidified to pH 5 with 1 N HCl, and the mixture was extracted with EtOAc (3 × 10 mL). The combined extracts was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude acid as a white jelly which was used for the next step without further purification.

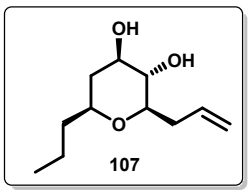
The residue obtained above was dissolved in CH_2Cl_2 (20 mL) and added *N,O*-dimethylhydroxylamine hydrochloride (314 mg, 3.20 mmol), EDC (615 mg, 3.20 mmol), HOBt (432 mg, 3.20 mmol) and Et_3N (0.49 mL, 3.20 mmol) at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 12 h. Then CH_2Cl_2 was added and the mixture was washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography using EtOAc/hexane (EtOAc/hexane 1:9) as eluent to furnish (740 mg, 89%) amide **105** as a colorless oil. [R_f = 0.3, EtOAc/hexane 1:9 v/v]; [α] $_D^{25}$ +12.0 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 2937, 2921, 2873, 2832, 1650, 1464, 1389, 1265, 1136, 1123, 1092, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.45-4.42 (m, 2H), 3.89-3.86 (m, 1H), 3.72 (s, 3H), 3.21 (s, 3H), 1.75-1.67 (m, 2H), 1.48-1.43 (m, 8H), 1.36-1.25 (m, 2H), 0.91-0.88 (m, 12H), 0.06 (d, *J* = 9.64 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 170.5, 110.5, 79.5, 75.7, 68.9, 61.5, 40.6, 40.5, 27.6, 26.1, 25.9, 18.0, 17.9, 14.3, -4.3, -4.7; HRMS (ESI), calcd for $C_{19}H_{40}NO_5Si$ $[M + H]^+$ 390.2670; found 391.2654.

1-((4*S*,5*R*)-5-((*S*)-2-(*tert*-Butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4yl) but-3-en-1-one, 106



Allyl magnesium bromide (1.0 M solution in diethyl ether, 2.3 mL, 2.31 mmol) was added dropwise over 15 min to an ice-cooled solution of Weinreb amide **105** (600 mg, 1.54 mmol) in THF (10 mL). After 10 min, saturated aqueous ammonium chloride solution (20 mL) was added and aqueous layer was extracted with EtOAc (3 × 30 mL). Combined organic layers was concentrated *in vacuo* and subjected to silica gel column chromatography (EtOAc/hexane 1:49) to yield allylic ketone **106** as colorless liquid (513 mg, 90%). [R_f = 0.6, EtOAc/hexane 1:19 v/v]; [α] $_D^{25}$ +16.2 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3067, 1720, 1641, 1361, 1253, 1097, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 5.97-5.87 (m, 1H), 5.21-5.10 (m, 2H), 4.13-4.08 (m, 1H), 3.95-3.93 (m, 1H), 3.88-3.85 (m, 1H), 3.41-3.38 (m, 2H), 1.79-1.73 (m, 1H), 1.65-1.60 (m, 1H), 1.46-1.35 (m, 8H), 1.34-1.25 (m, 2H), 0.91-0.85 (m, 12H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 207.5, 129.7, 119.1, 110.3, 85.3, 74.9, 68.7, 42.9, 40.4, 27.4, 26.3, 25.8, 18.0, 17.8, 14.4, -4.2, -4.8; HRMS (ESI), calcd for $C_{20}H_{39}O_4Si$ $[M + H]^+$ 371.2612; found 371.2620.

(2*R*,3*S*,4*R*,6*S*)-2-allyl-6-propyltetrahydro-2H-pyran-3,4-diol, 107

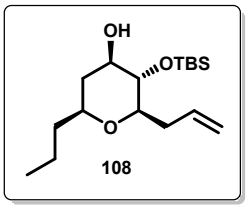


Ketone derivative **106** (500 mg, 1.30 mmol) was dissolved in MeOH (5 mL) and cooled to 0 °C. Monohydrated *p*-TSA (514 mg, 2.70 mmol) was added to it, ice bath was removed, and mixture was stirred for 1 h at room temperature. Reaction was quenched with solid $NaHCO_3$, residue was partitioned between EtOAc (20 mL) and water (10 mL), and two layers were separated. Aqueous layer was extracted with EtOAc (2 × 20 mL). Combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*, which was used as such for the next step without further purification.

To a solution of the above ketotriol intermediate in CH_2Cl_2 at -78 ^oC was added Et_3SiH (0.5 mL, 2.97 mmol) and TMSOTf (0.3 mL, 1.48 mmol). The resultant solution was stirred at -78 ^oC for 30 min before it was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (EtOAc/hexane 1:1) furnished alcohol **107** (240 mg, 89%) as a colorless liquid. [R_f = 0.26, EtOAc/hexane 1:1 v/v]; [α] $_D^{25}$ +8.0 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3420, 3105, 2950, 1641, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ:* 5.96-5.88 (m,

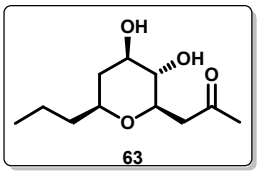
1H), 5.15-5.0 (m, 2H), 3.62-3.56 (m, 1H), 3.37-3.33 (m, 1H), 3.2-3.19 (m, 4H), 2.59-2.53 (m, 1H), 2.30-2.23 (m, 1H), 2.0-1.95 (m, 2H), 1.41-1.35 (m, 4H), 0.90 (t, J = 6.88 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.0, 116.7, 78.4, 76.7, 75.2, 73.2, 39.1, 37.7, 36.4, 18.9, 13.9; HRMS (ESI), calcd for $C_{11}H_{20}O_3Na$ $[M + Na]^+$ 223.1304; found 223.1305.

(2*R*,3*R*,4*R*,6*S*)-2-Allyl-4-(*tert*-butyldimethylsilyloxy)-6-propyltetrahydro-2H-pyran-3-ol, 108



To a stirred solution of diol **107** (100 mg, 0.49 mmol) in dry CH_2Cl_2 (5 mL) was added imidazole (66 mg, 0.97 mmol), followed by *tert*-butyldimethylsilyl chloride (98 mg, 0.65 mmol) and DMAP (6 mg, 10 mol %) at 0 °C. Resulting mixture was allowed to stir at room temperature for 12 h. Saturated NH_4Cl solution (10 mL) was added and organic layer was separated. Aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). Combined organic layers were concentrated *in vacuo*. Crude was purified by silica gel column chromatography (EtOAc/hexane 1:49) to yield **108** (146 mg, 95%) as a colorless oil. [R_f = 0.5, EtOAc/hexane 1:19 v/v]; $[\alpha]_D^{25}$ +7 .4 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3415, 3100, 2933, 1625, 1097, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.97-5.90 (m, 1H), 5.14-5.04 (m, 2H), 3.35-3.30 (m, 1H), 3.22-3.11(m, 2H), 2.62-2.56 (m, 1H), 2.28-2.20 (m, 2H), 1.84-1.79 (m, 1H), 1.57-1.29 (m, 7H), 0.97-0.82 (m, 12H), 0.1 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.2, 116.4, 78.3, 76.1, 75.0, 74.8, 40.2, 37.7, 36.4, 25.8, 18.9, 17.9, 14.0, -4.2, -4.6; HRMS (ESI), calcd for $C_{17}H_{35}O_3Si$ $[M + H]^+$ 315.235; found 315.235.

Phomonol, 63



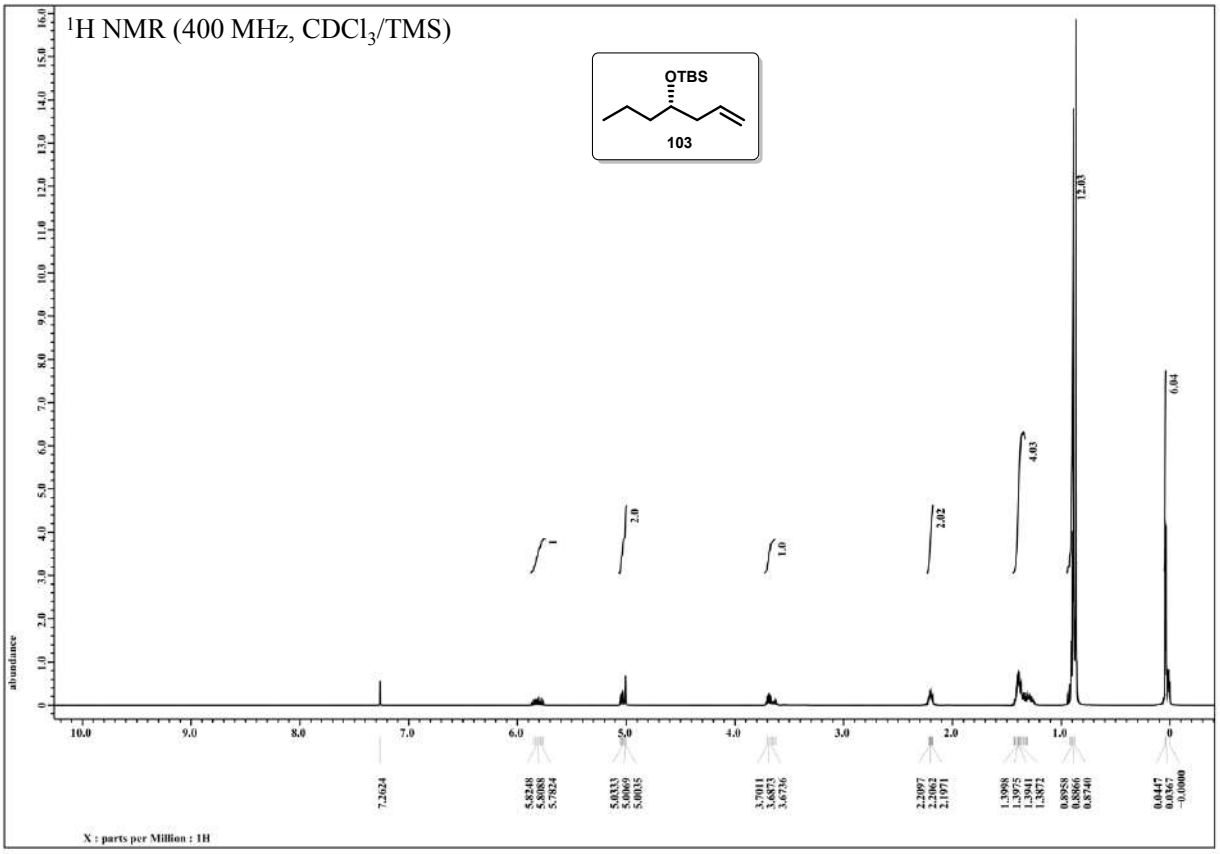
To a stirred solution of alcohol **108** (100 mg, 0.31 mmol) in DMF (3 mL) and water (0.3 mL) were added $PdCl_2$ (11 mg, 20 mol%) and CuCl (34 mg, 0.35 mmol) under an atmosphere of oxygen and the reaction mixture was stirred vigorously at room temperature until consumption of the starting material was complete. Aqueous HCl (3 N, 5 mL) was added to the reaction mixture, and it was extracted with ether (3 × 20 mL). The ether layer was washed with saturated aqueous $NaHCO_3$ solution followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/ hexane, 4:1) to give the phomonol **63** (62 mg, 91%) as a colourless liquid. [R_f = 0.5, EtOAc]; $[\alpha]_D^{25}$ +5.6 (*c* 0.3, $CHCl_3$); IR (CH_2Cl_2) *v*: IR (CH_2Cl_2): 3380, 2964, 2944, 1686, 1365, 1054, 843, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.65-3.59 (m, 2H), 3.45-3.38 (m, 1H), 3.10 (t, J = 9.05 Hz, 1H), 2.87 (dd, J = 15.56, 4.12 Hz, 1H), 2.65 (dd, J = 15.6, 7.8 Hz,

1H), 2.22 (s, 3H), 1.99 (ddd, J = 12.8, 5.04, 1.8 Hz, 1H), 1.89 (br, 2H), 1.54-1.45 (m, 1H), 1.43-1.28 (m, 4H), 0.89 (t, J = 6.88 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.6, 76.3, 75.4, 73.1, 46.2, 39.0, 37.5, 31.0, 18.8, 13.9; HRMS (ESI), calcd for $C_{11}H_{20}O_4Na$ $[M + Na]^+$ 239.1254; found 239.1255.

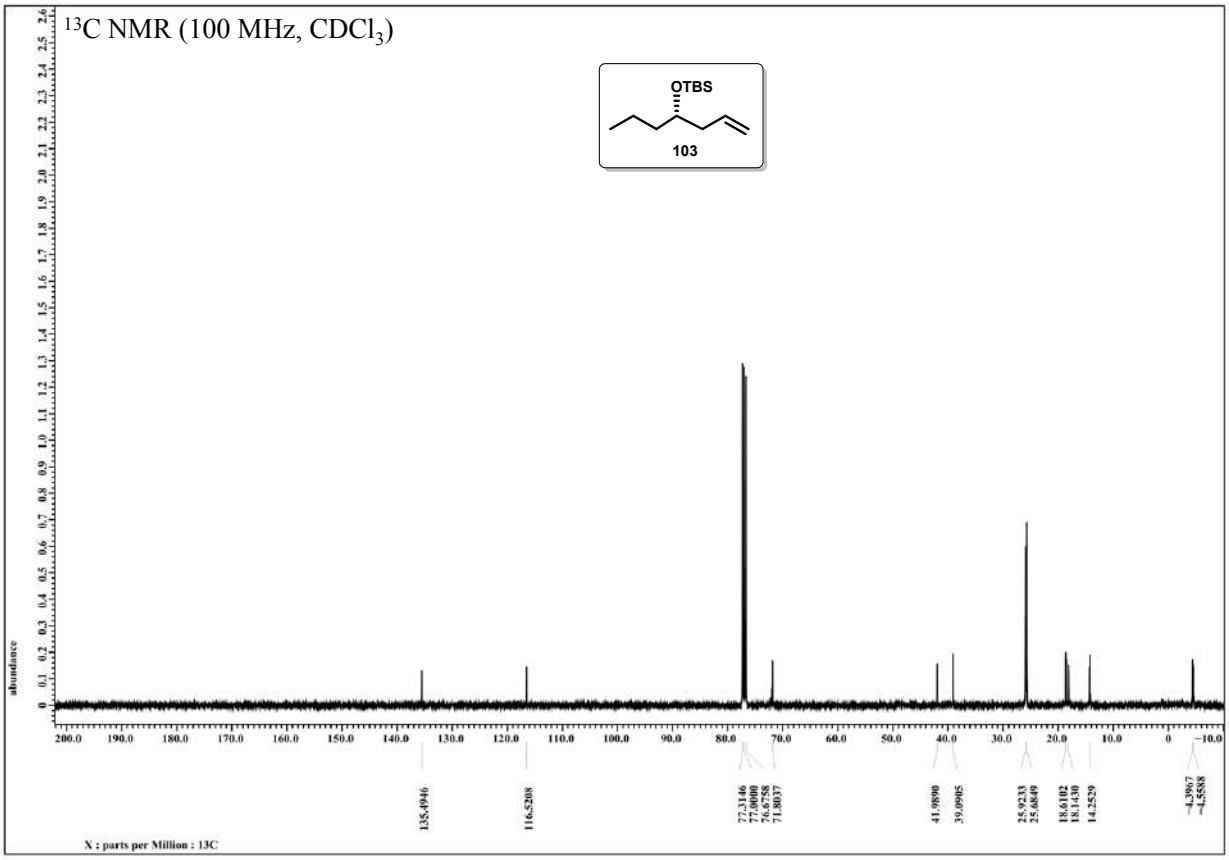
3.2.7 Spectra:

1. ^{1}H and ^{13}C NMR spectra of **103**
2. ^{1}H and ^{13}C NMR spectra of **101**
3. ^{1}H and ^{13}C NMR spectra of **104**
4. ^{1}H and ^{13}C NMR spectra of **100**
5. ^{1}H and ^{13}C NMR spectra of **105**
6. ^{1}H and ^{13}C NMR spectra of **106**
7. ^{1}H and ^{13}C NMR spectra of **107**
8. ^{1}H and ^{13}C NMR spectra of **108**
9. ^{1}H and ^{13}C NMR spectra of **63**

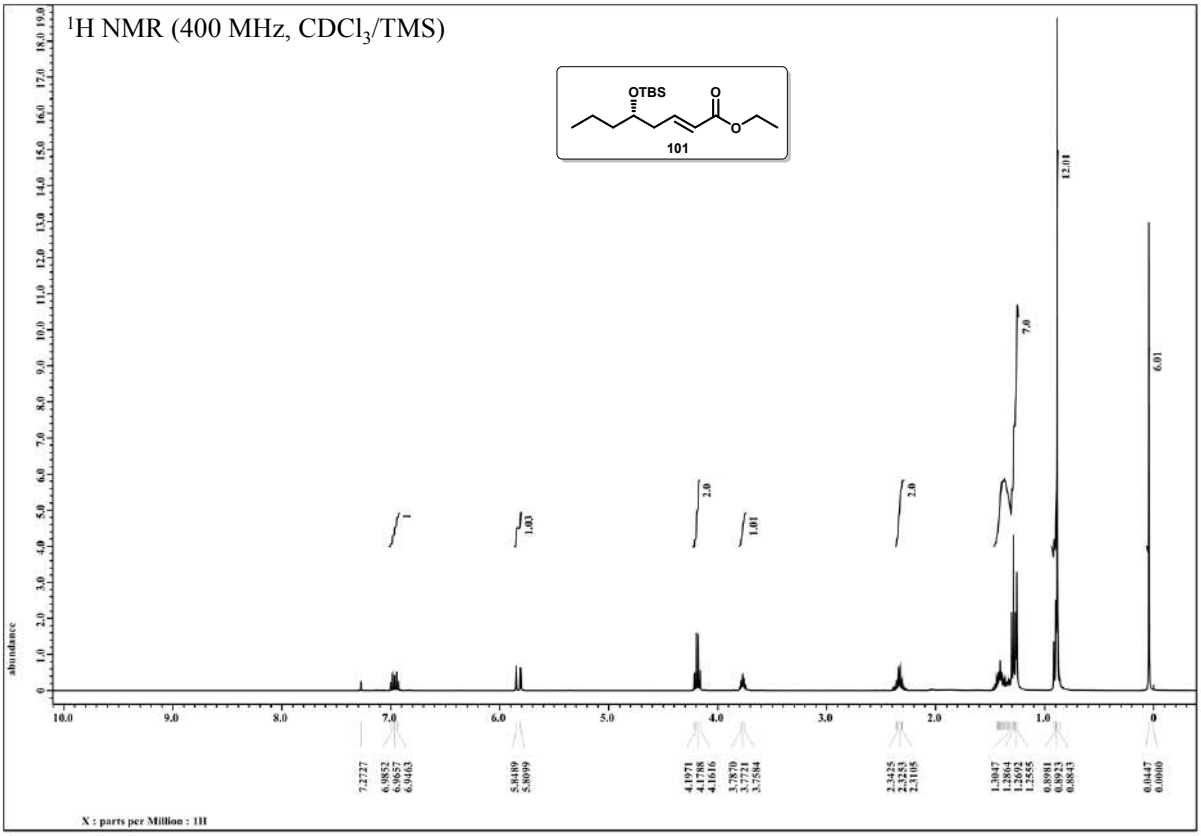
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



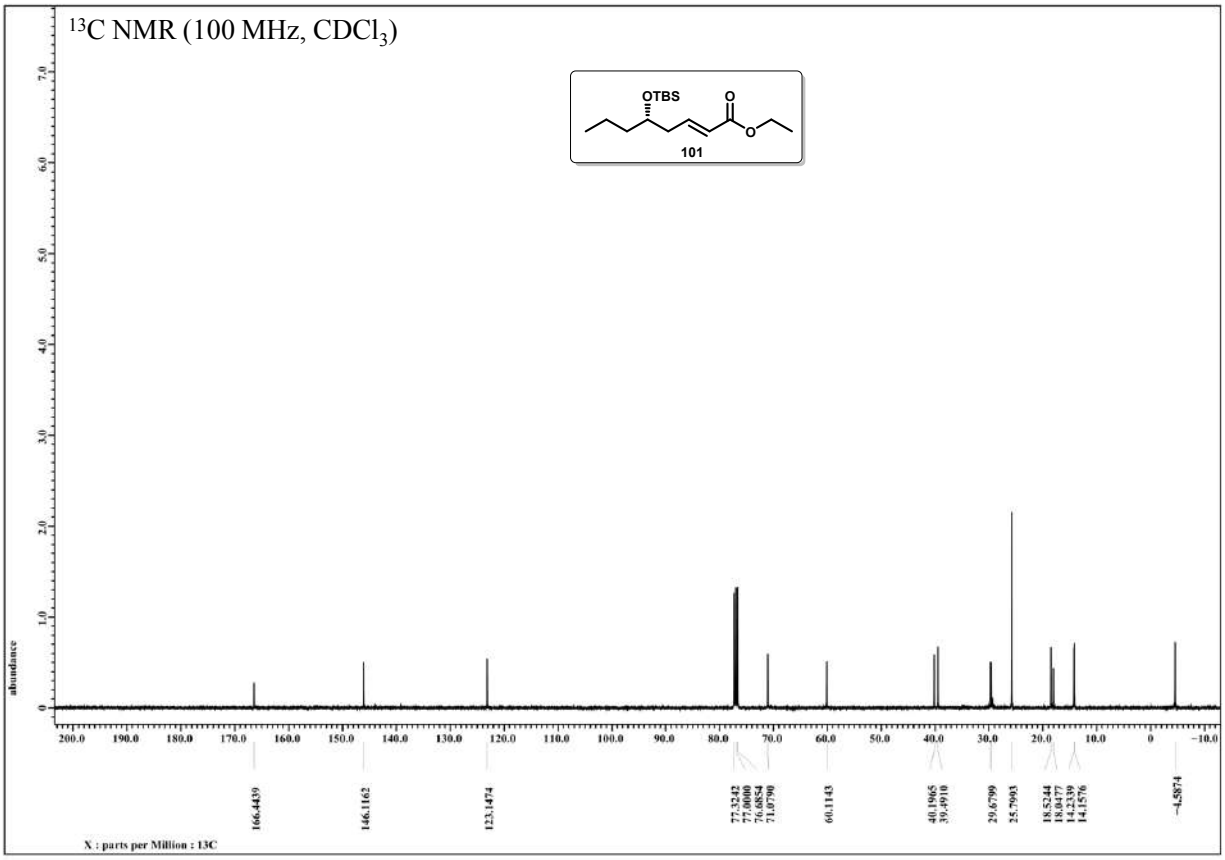
^{13}C NMR (100 MHz, $CDCl_3$)



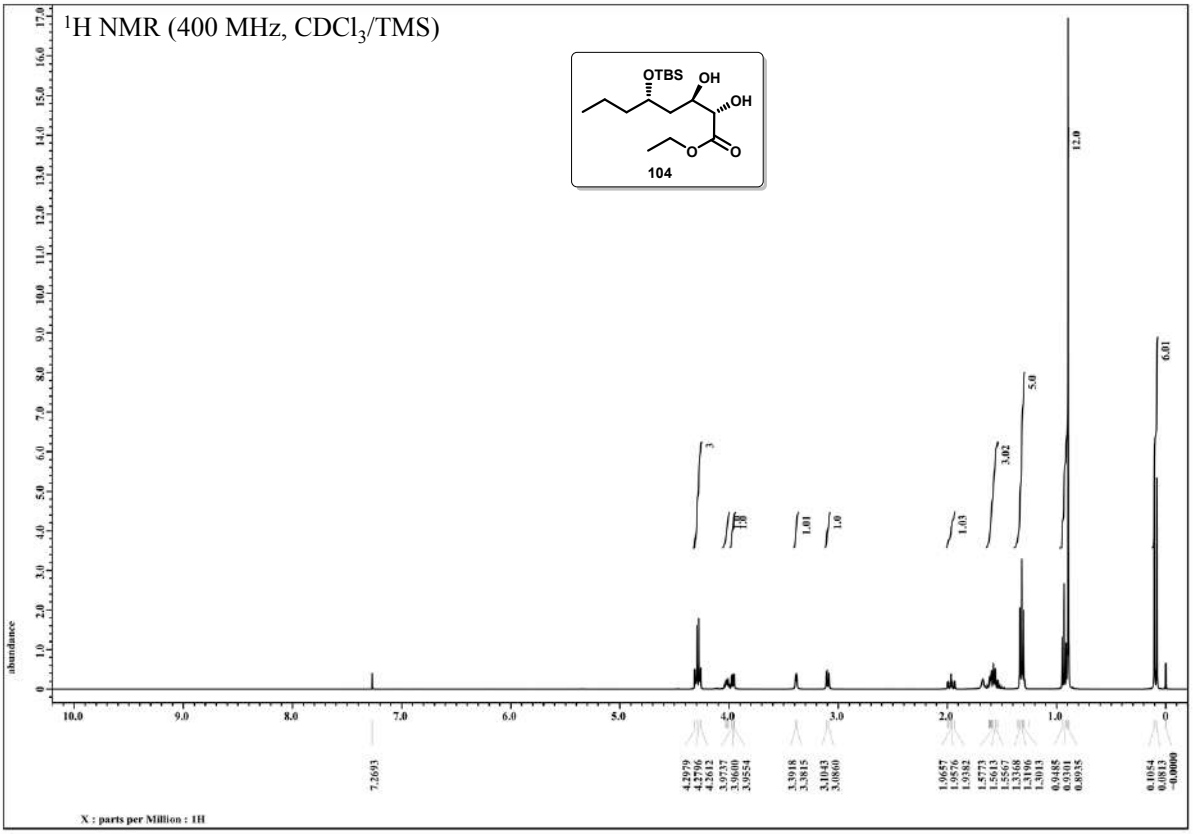
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



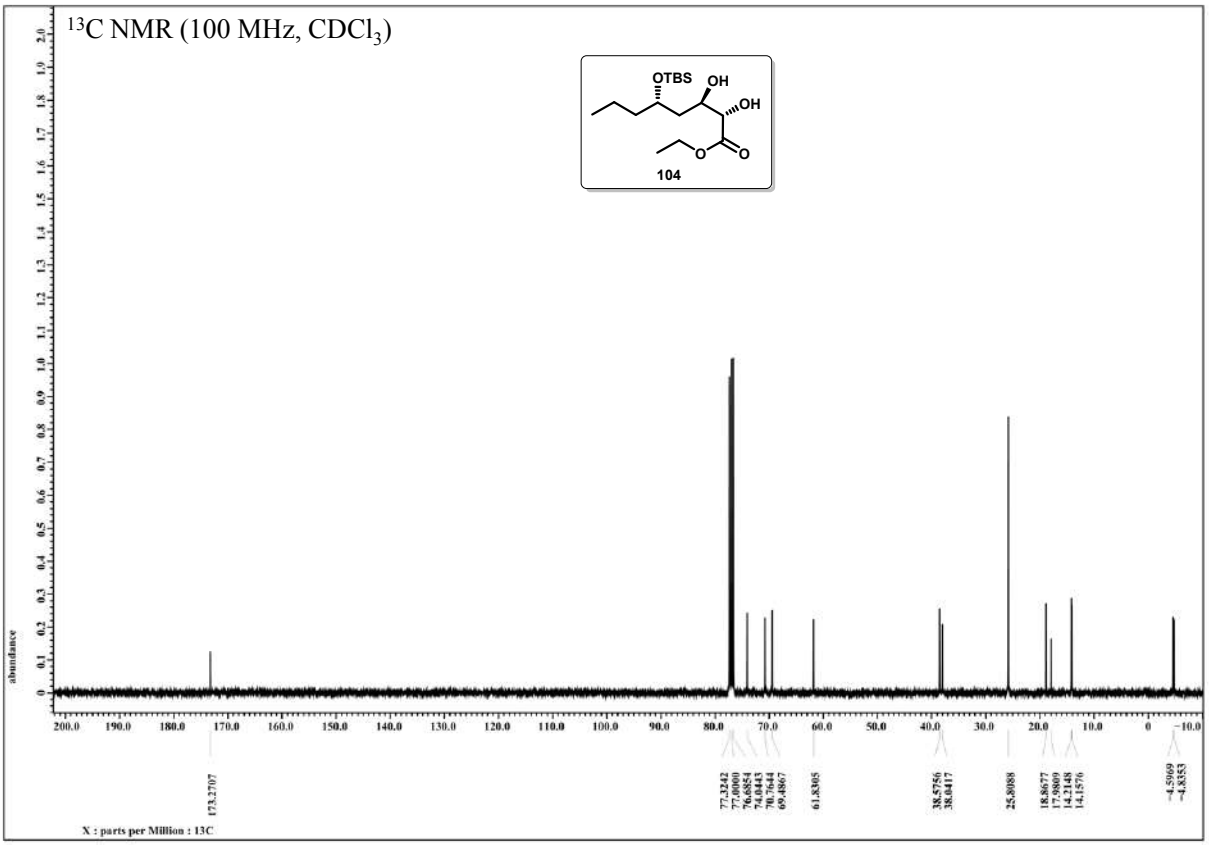
^{13}C NMR (100 MHz, $CDCl_3$)



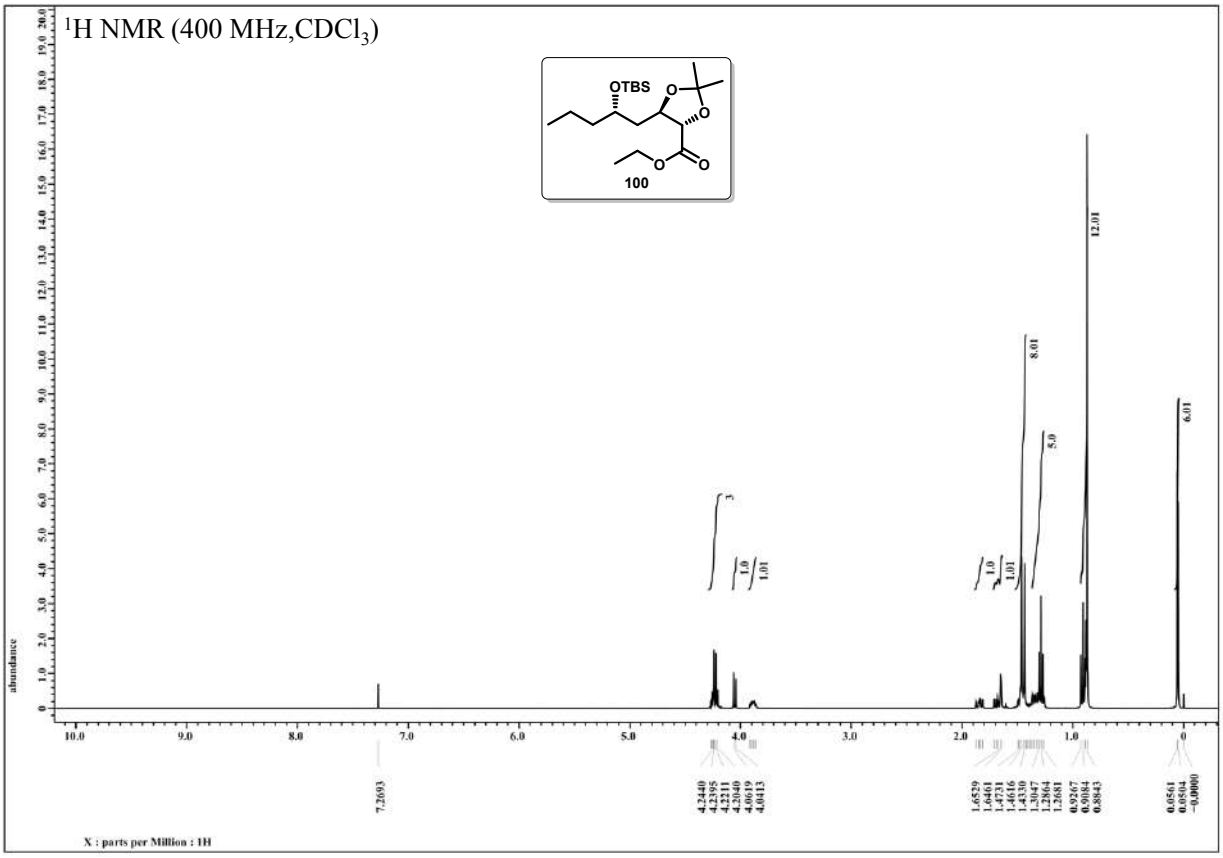
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



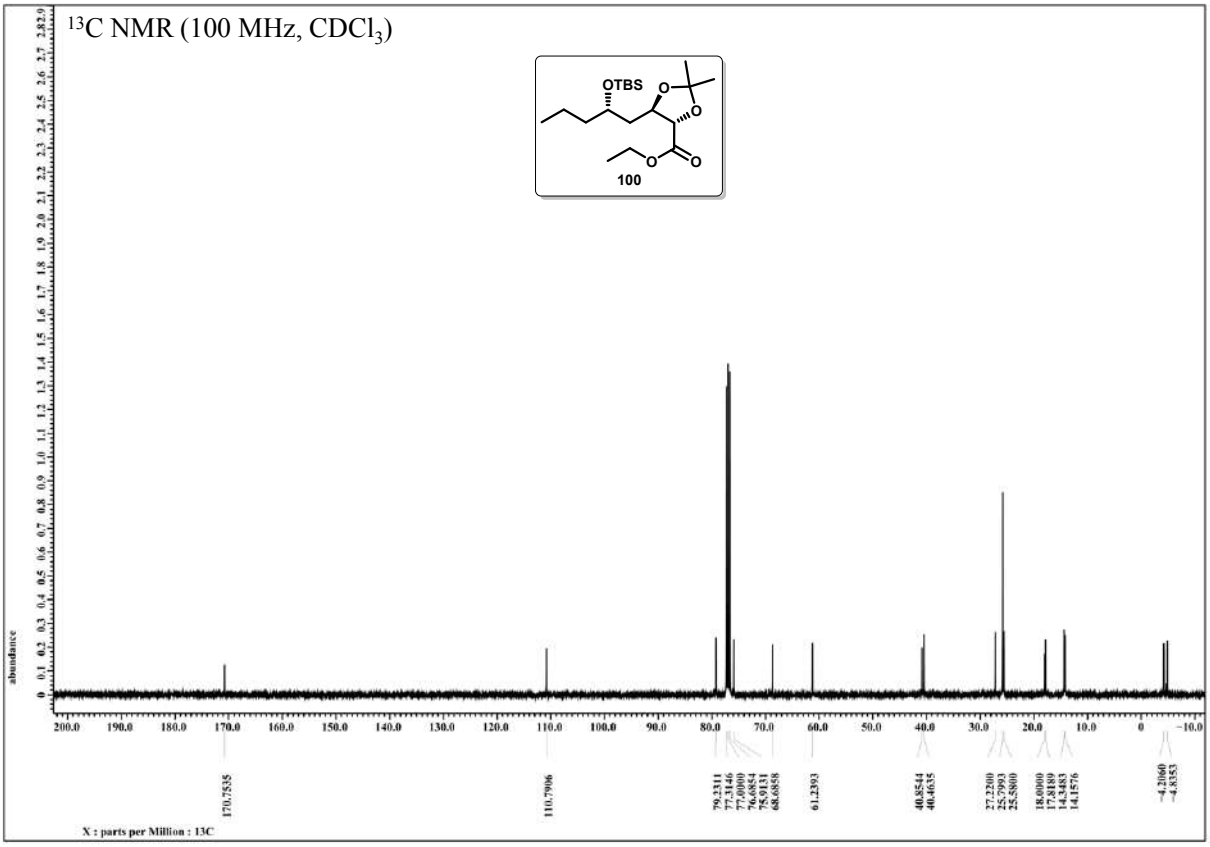
^{13}C NMR (100 MHz, $CDCl_3$)



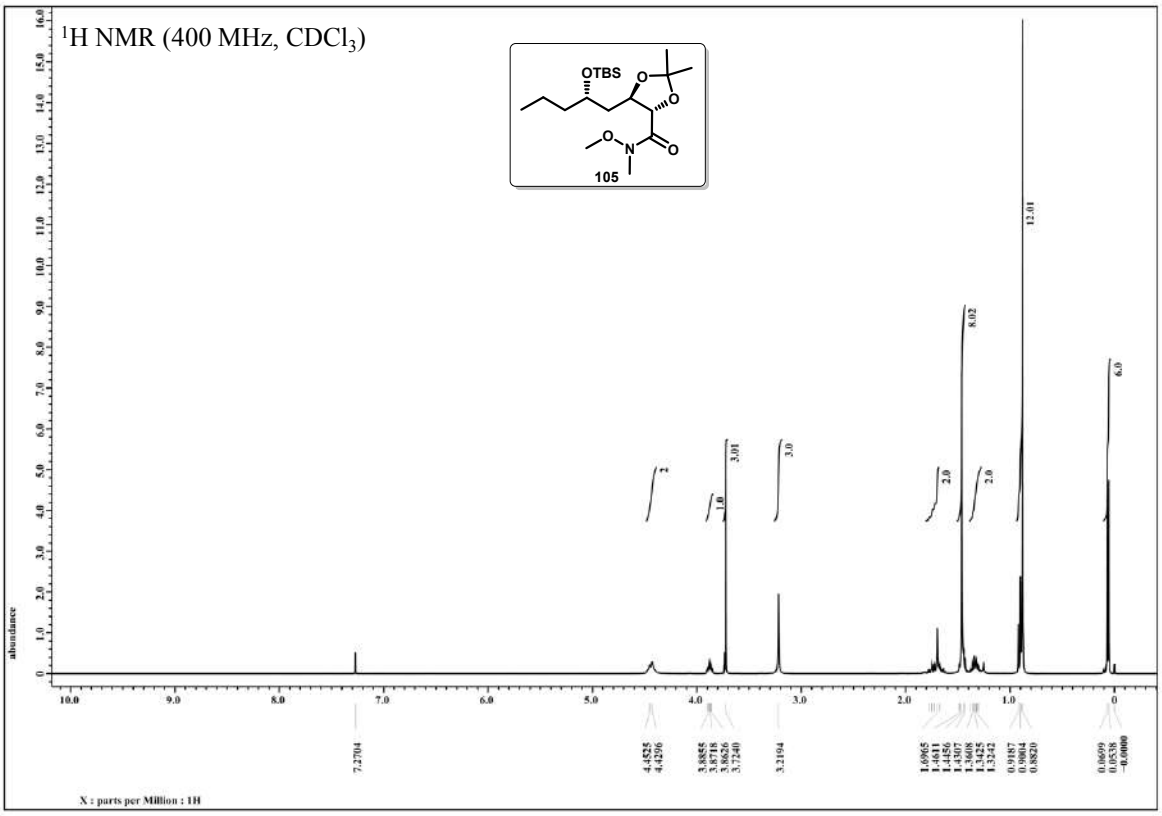
^{1}H NMR (400 MHz,$CDCl_3$)



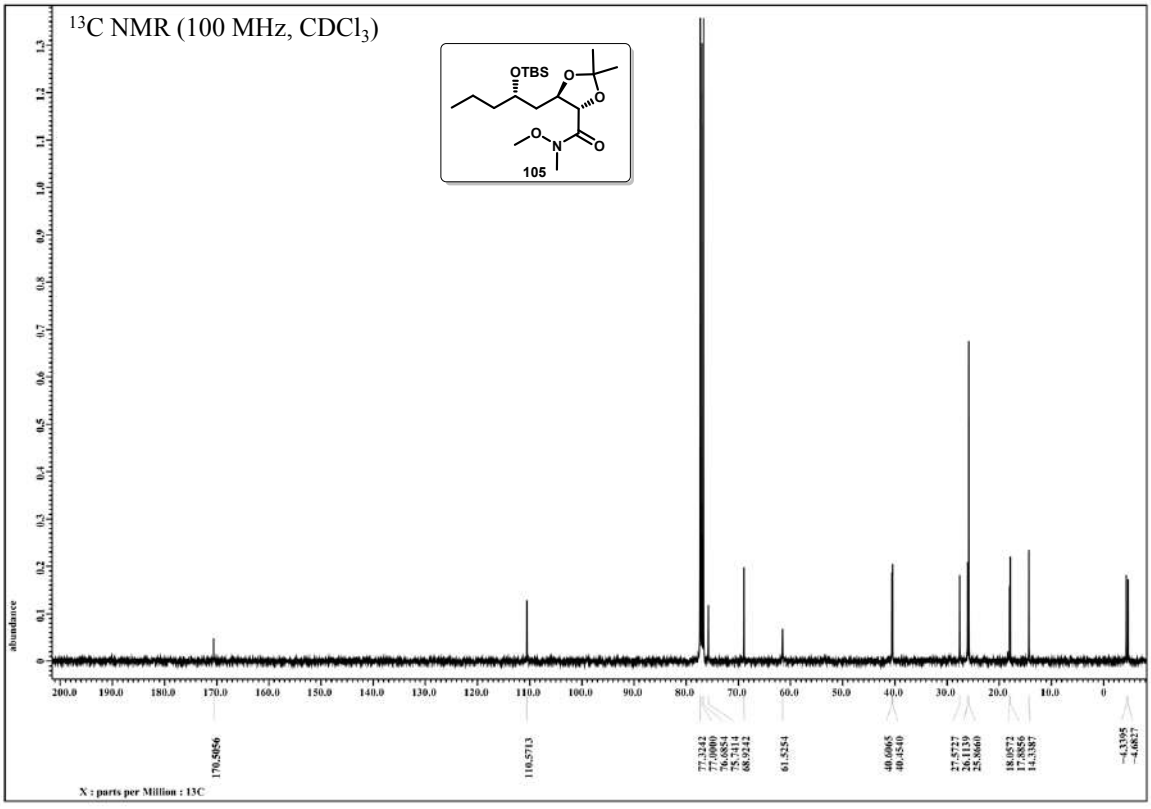
^{13}C NMR (100 MHz, $CDCl_3$)



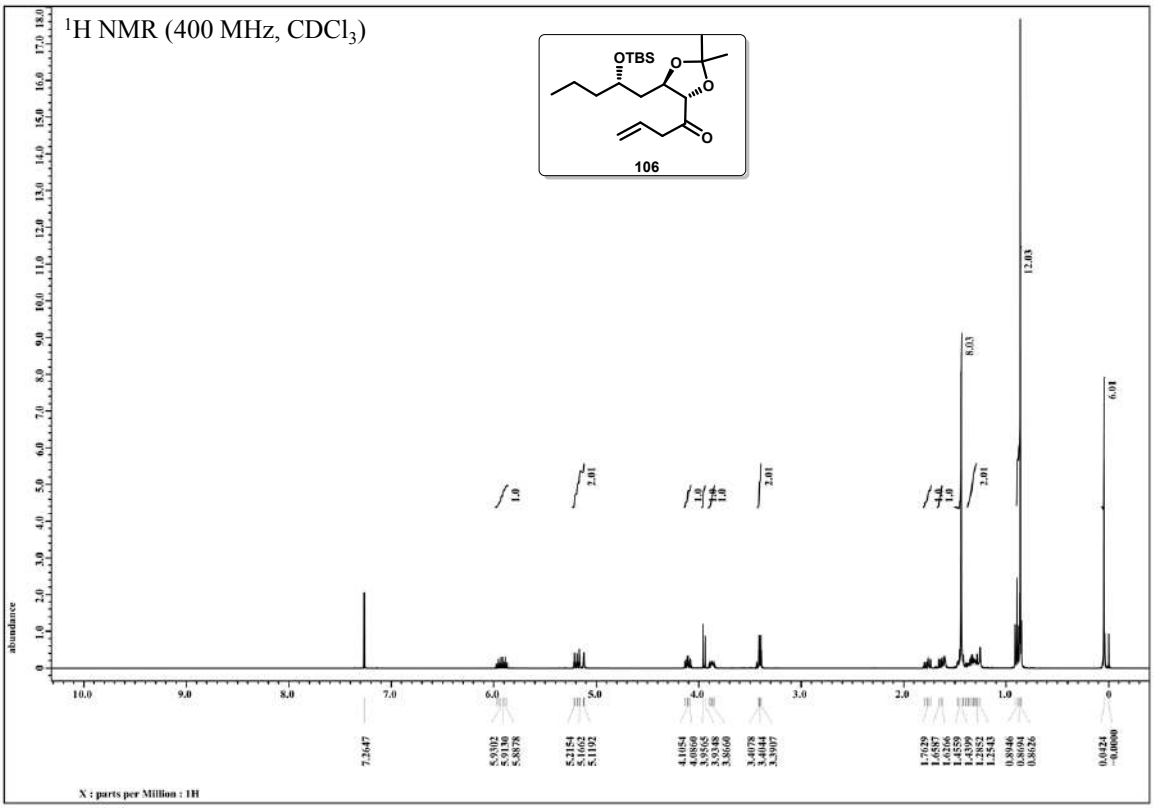
^{1}H NMR (400 MHz, $CDCl_3$)



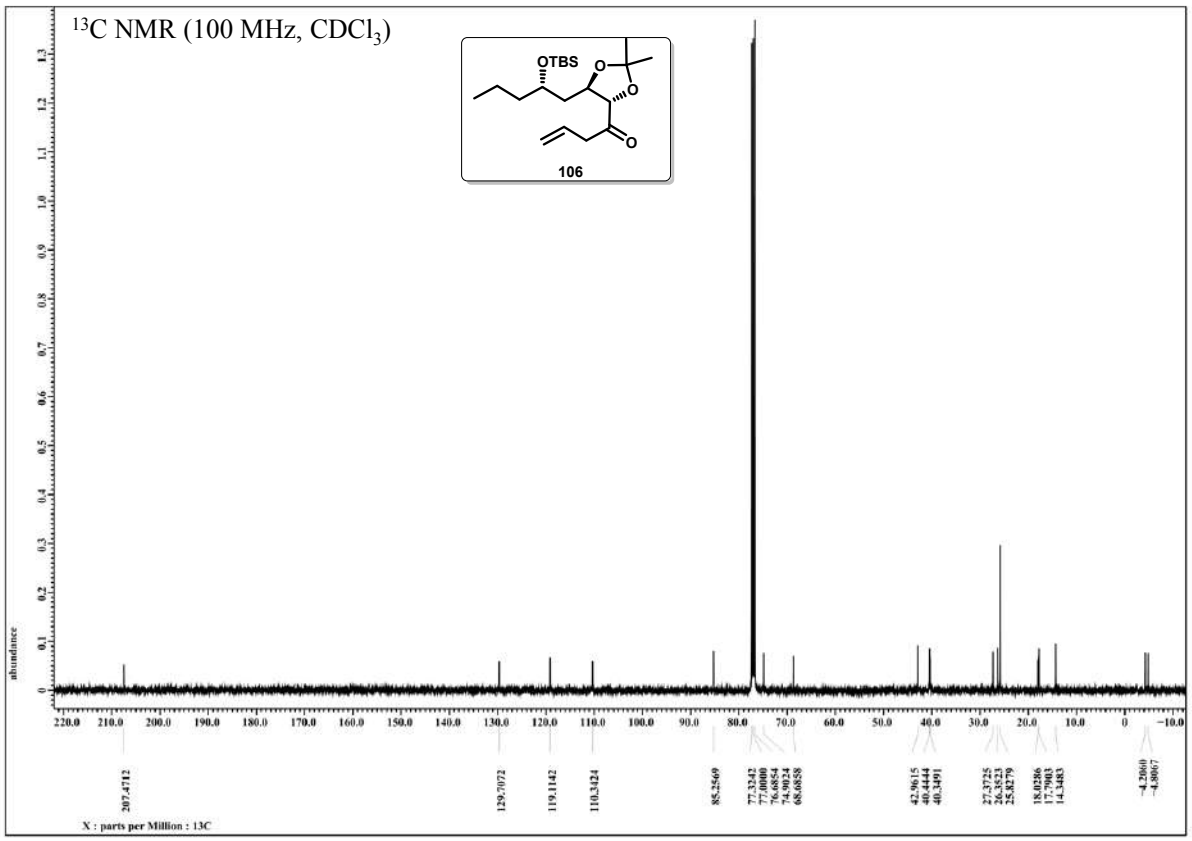
^{13}C NMR (100 MHz, $CDCl_3$)



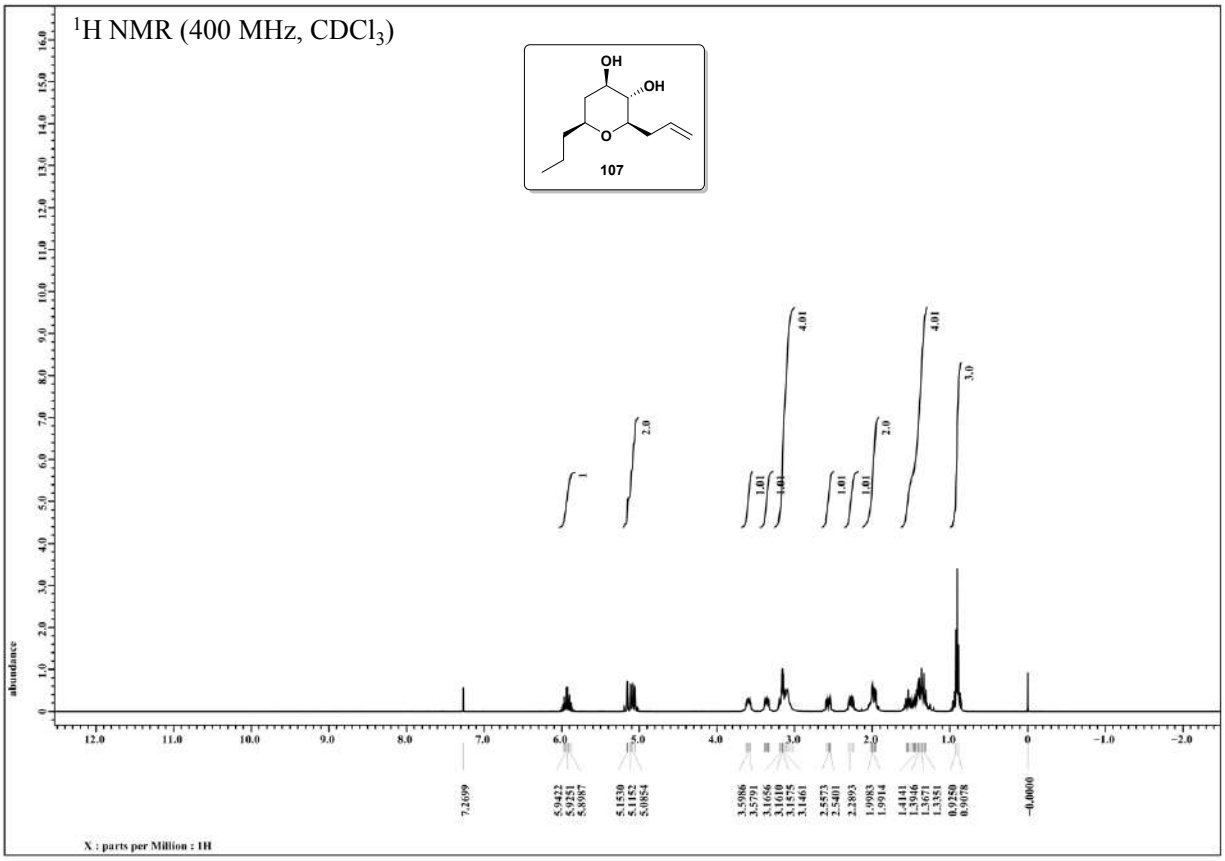
^{1}H NMR (400 MHz, $CDCl_3$)



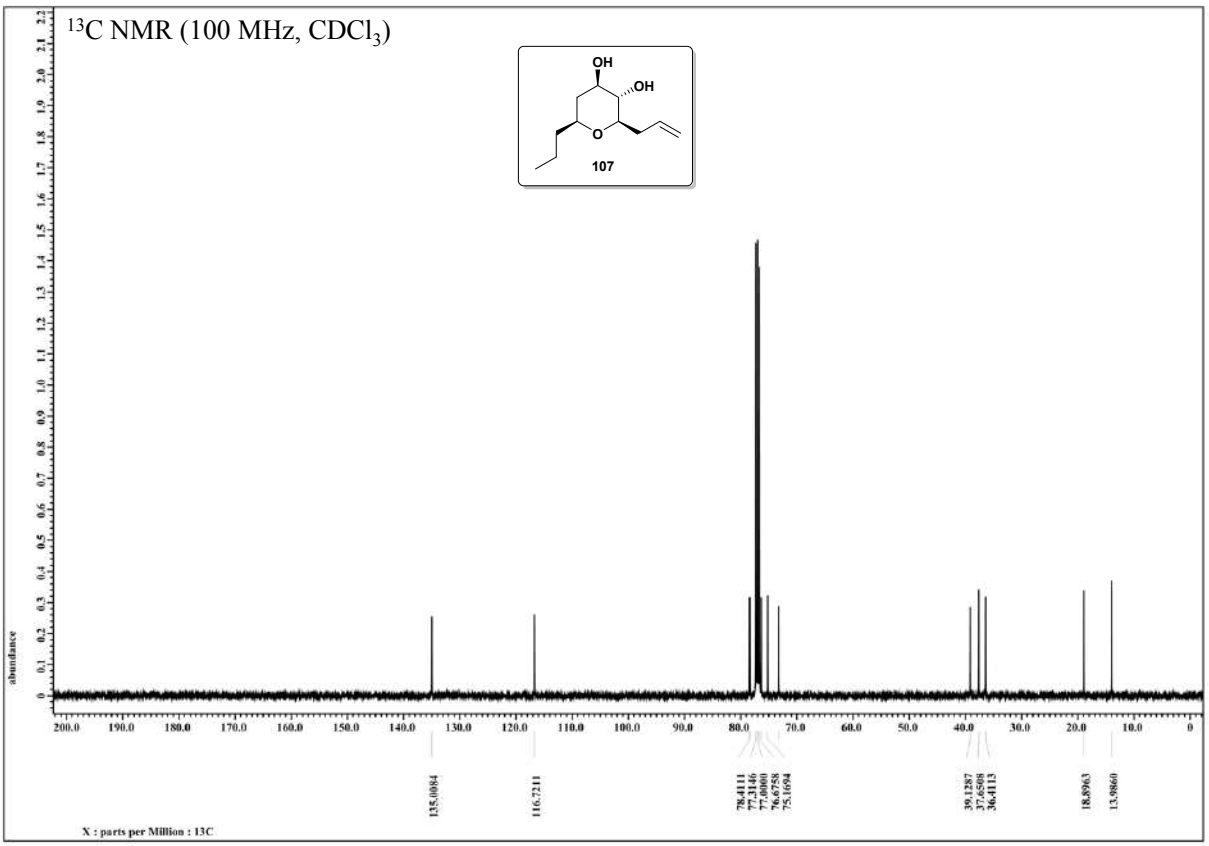
^{13}C NMR (100 MHz, $CDCl_3$)



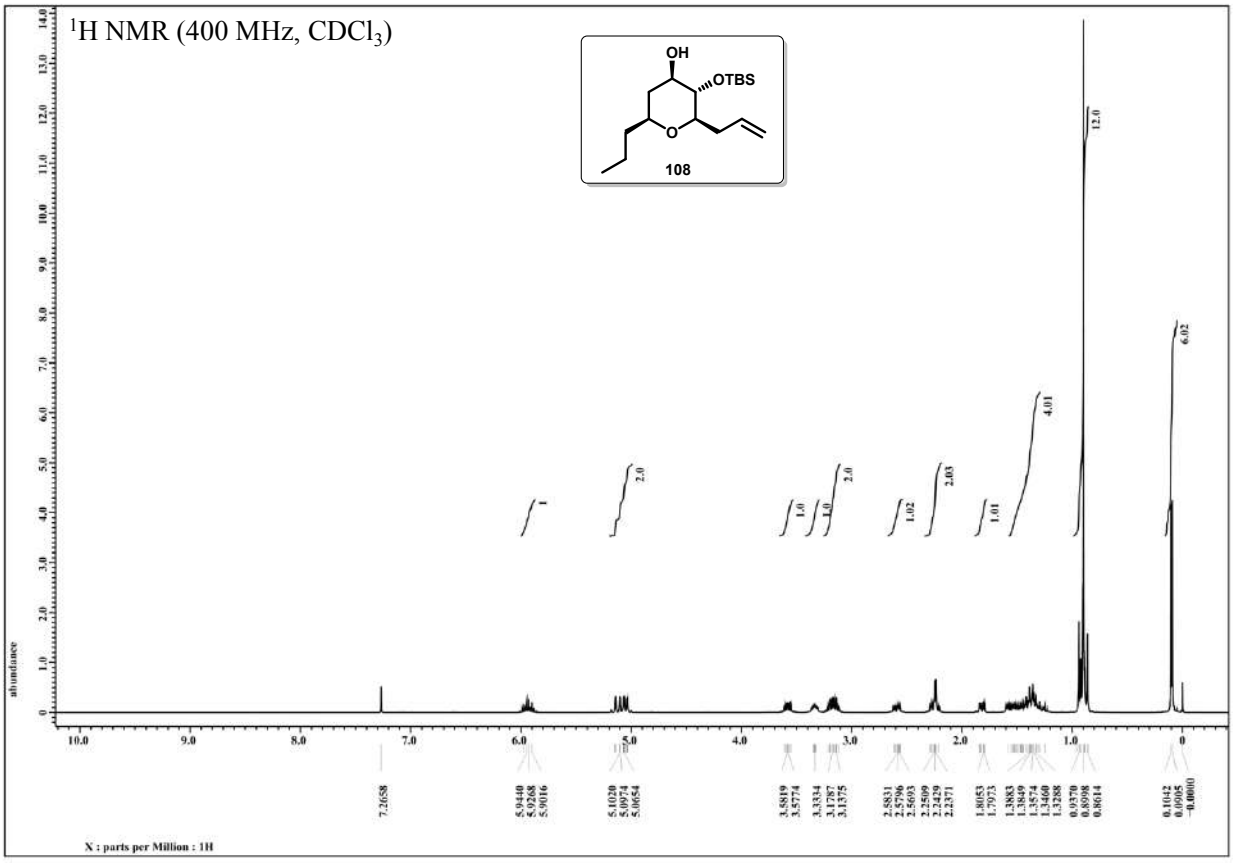
^{1}H NMR (400 MHz, $CDCl_3$)



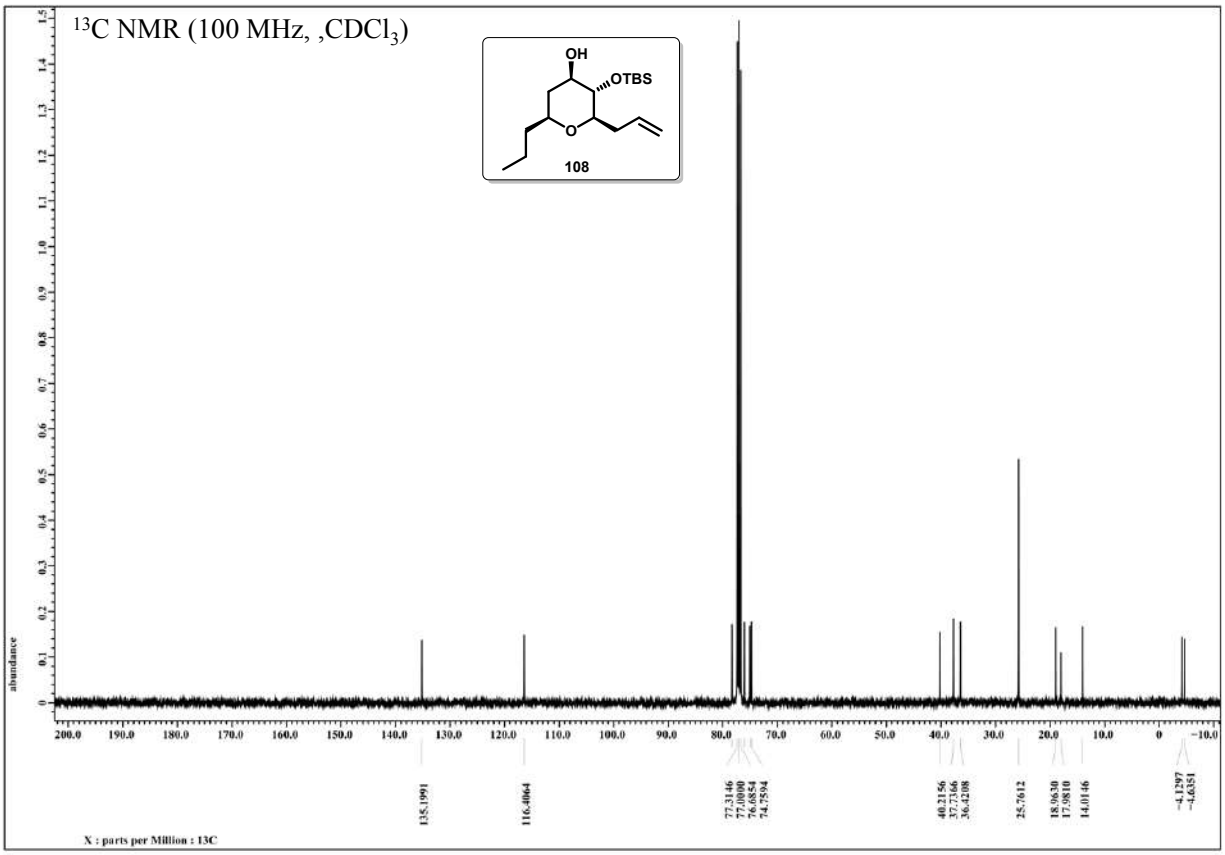
^{13}C NMR (100 MHz, $CDCl_3$)



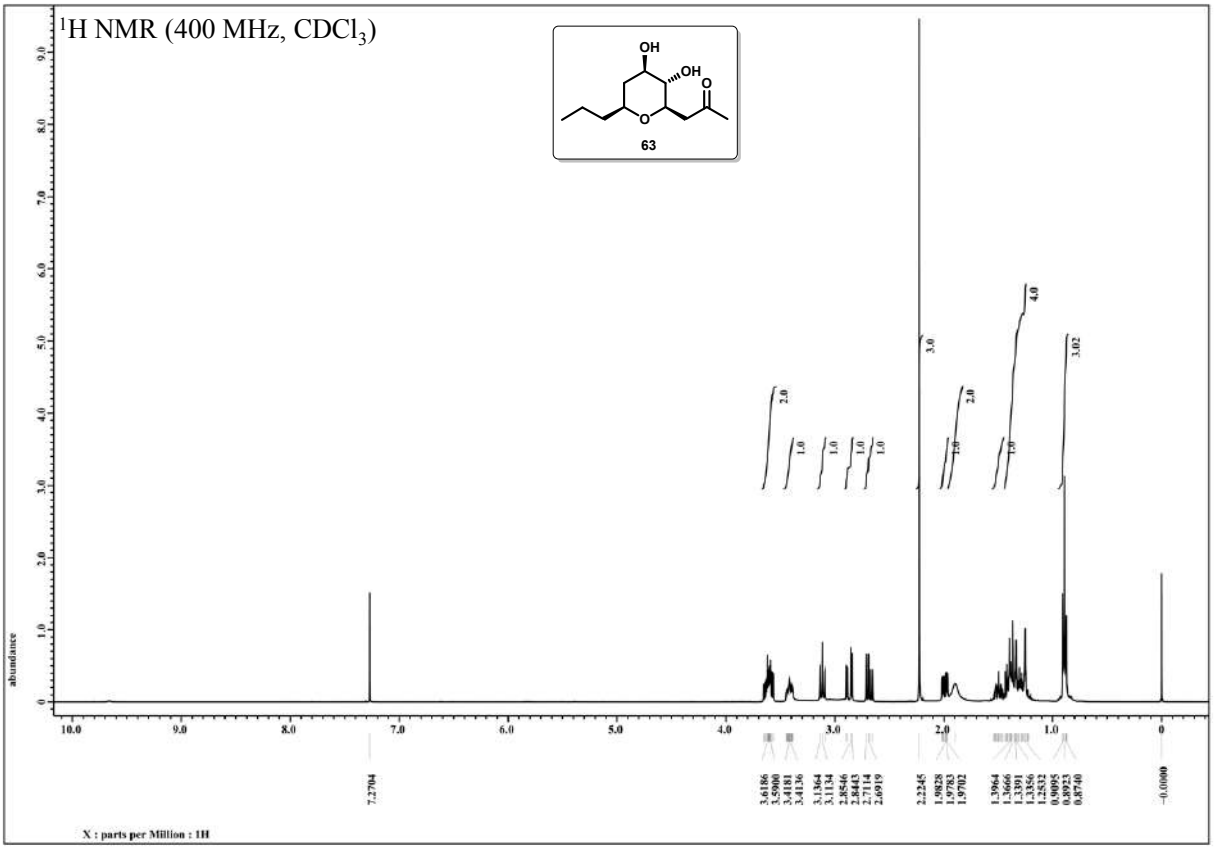
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, ,$CDCl_3$)



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



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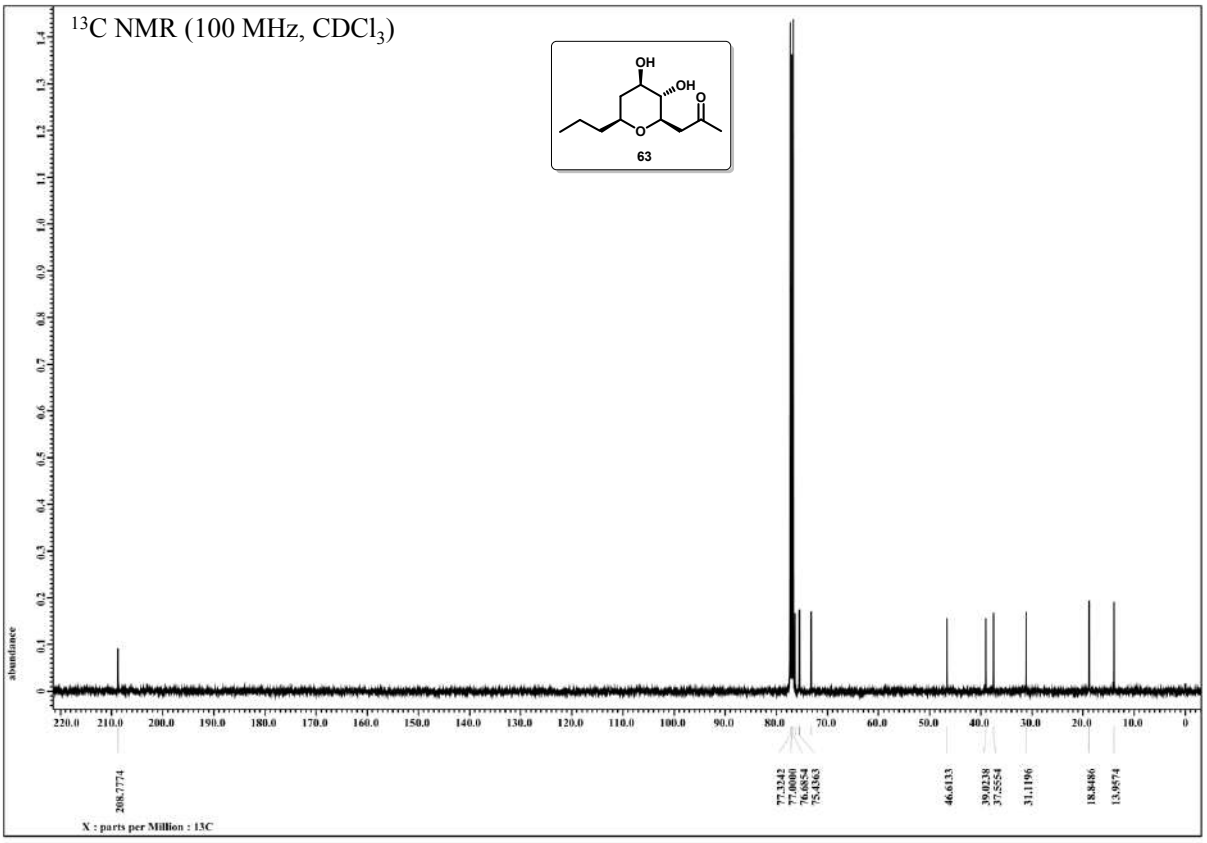

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CHAPTER 4

Stereoselective general approach towards the synthesis of functionalized *γ*- and *δ*-lactones skeleton with their applications to the total synthesis of (+)-*epi*-muricatacin and (-)-6-acetoxy-hexadecanolide, respectively.

4.0 Enantioselective approach to *γ*-and *δ*-lactones: total synthesis of (+)-*epi*-muricatacin and (-)-6-acetoxy-hexadecanolide

4.0.1 Introduction:

Functionalized hydroxy *γ*- and *δ*-lactone motifs possess intriguing biological activities and are important building blocks to synthesize a variety of biologically active natural products,[1] some of which are displayed in figure 1. The *γ*-butyrolactone functional group array is mainly originated from the acetogenins isolated from plant family Annonaceae.[2] In 1991, McLaughlin and co-workers reported the isolation of a novel functionalized 5-hydroxy-*γ*-lactone (+)-muricatacin **1a** from the seeds of *Annona muricate* L. (Annonaceae) commonly known as soursop or guanabana.[3] Interestingly, isomers (+)-muricatacin **1a** and (+)-*epi*-muricatacin **1b** have received interest due to their potent cytotoxic activity against certain cell lines.[4] (-)-Muricatacin analogue (+)-5-hydroxy-4-octadecanolide **2** exhibited cytotoxicity against esophageal cancer cells with IC_{50} values of 20 μg/mL.[5] (4*S*,5*R*)-4,5-dihydroxydecanoic acid **3** *γ*-lactone (Figure 1) is also a natural compound, named as L-factor, isolated from the cultures of *Streptomyces griseus*, which reveal autoregulatory properties.[6]

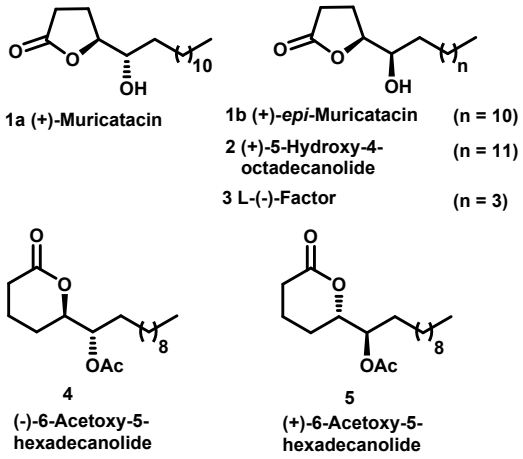


Figure 1. Some natural products containing *γ*- and *δ*- lactones.

In 1979, Laurence and Pickett isolated the mosquito oviposition attractant pheromone, *erythro*-6-acetoxy-hexadecanolide **4**, a functionalized *δ*-lactone from apical droplets formed on the egg of the mosquito *Culex pipens*,[7] which is distributed worldwide and can be a vector for malaria, filarial disease and West Nile virus.[8] Due to the potential of **4** in controlling mosquito populations, it has received considerable attention from the synthetic community and numerous stereoselective syntheses of natural (-)-*erythro*-6-acetoxy-5-hexadecanolide **4** and unnatural isomer, (+)-*threo*-6-acetoxy-5-hexadecanolides **5** have been reported.[11]

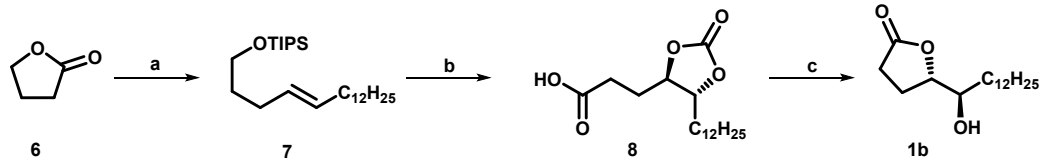
4.0.2 Review of Literature:

Various methods for the syntheses of (+)-*epi*-muricatacin **1b**[9] and (-)-6-acetoxy-hexadecanolide **4**[10] have been documented in the literature. Some of the recent syntheses of (+)-*epi*-muricatacin **1b** and (-)-6-acetoxy-hexadecanolide **4** are described below.

4.0.2.1 Syntheses of (+)-*epi*-muricatacin 1b

Couladouros, E. A. *et al.* (1999)[9r]

E. A. Couladouros and co-workers reported the asymmetric synthesis of (+)-*epi*-muricatacin **1b** featuring Wittig-Schlosser coupling, Sharpess AD, oxidation and lactonization as key steps. The synthesis of (+)-*epi*-murcatacin **1b** as shown in Scheme 1, began with commercially available *γ*-butyrolactone **6**. The required *E*-alkene **7** was prepared from lactone **6** *via* DIBAL-H reduction followed by silylation and Wittig-Schlosser reaction in 87% overall yield over 3 steps. Then, olefin **7** was exposed to Sharpless AD (Ad-mix-*β*) protocol to furnish the diol which was treated with 1,1'-carbonyldiimidazole (CDI) followed by TBAF mediated desilylation and oxidation with $NaIO_4/RuCl_3$ to deliver acid derivative **8** in four steps. Finally, acid **8** was subjected to regio- and stereo-specifically lactonization *via* heating in DMF to furnish targeted compound **1b** in 91% yield.

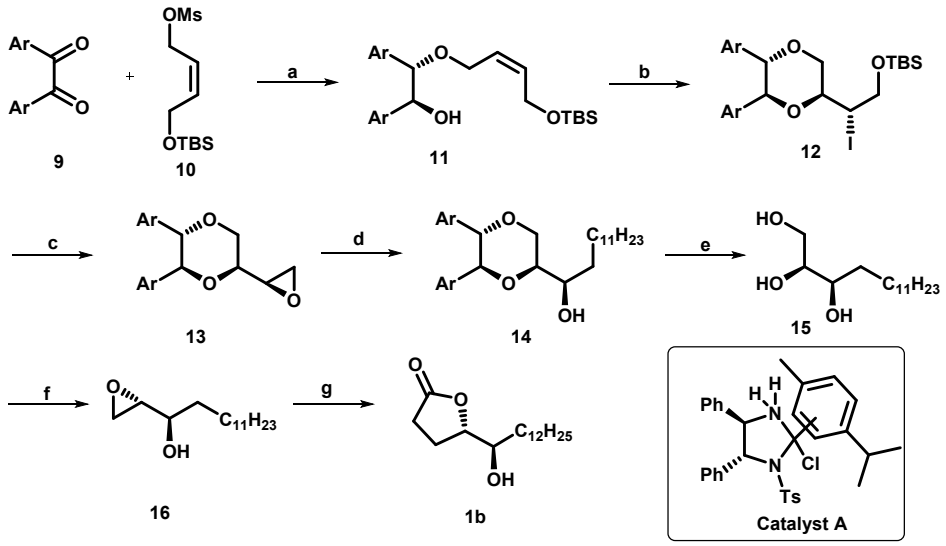


Scheme 1. *Reagents and conditions*: (a) i) DIBAL-H, 93%; ii) TIPSCl, 84%; iii) $Ph_3P^+(Br^-)C_{13}H_{27}$, *sec*-BuLi, 1 h, -78 °C to rt, 3 h, 84%; (b) i) AD-mix-*β*, 92% ii) CDI, 97%; iii) TBAF, THF, rt, 91%; iv) $NaIO_4$, $RuCl_3$, 87%; (c) DMF, 153 °C, 3 h, 91%.

Kumaraswamy, G. *et al.* (2010)[9h]

G. Kumaraswamy and co-workers described enantioselective total synthesis of (+)-*epi*-muricatacin **1b** employed catalytic asymmetric hydrogenation and a chiral auxiliary mediated intramolecular iodoetherification as key steps (Scheme 2). The synthesis commenced with readily available benzil **9** which was converted into alcohol **11** *via* Noyori's catalytic asymmetric hydrogenation in the presence of 0.1 mol % of catalyst **A** followed by NaH mediated nucleophilic substitution reaction with *tert*-butyldimethylsilyloxy *cis*-butene mesylate **10** in 70% yield (dr >97%, 99% *ee*). Treatment of **11** with *N*-iodosuccinimide (NIS) in THF furnished **12** in 9:1 ratio of separable diastereomers in a yield of 90%. Furthermore,

reaction of compound **12** with TBAF afforded epoxide **13** in 85% isolated yield (>99% *ee*). Next, epoxide **13** was regioselectively opened with undecylmagnesium bromide to afford the corresponding alcohol **14** in 89% yield. Next, alcohol **14** was treated with Li/liq. NH_3 at -78 ^oC to furnish triol **15.** The triol **15** was regioselectively converted into epoxy alcohol **16** under Mitsunobu conditions in 90% yield. Finally, substrate **16** was reacted with dilithioacetate dianion followed by *p*-TSA catalysed lactonization furnished the title compound **1b** in 80% yield.

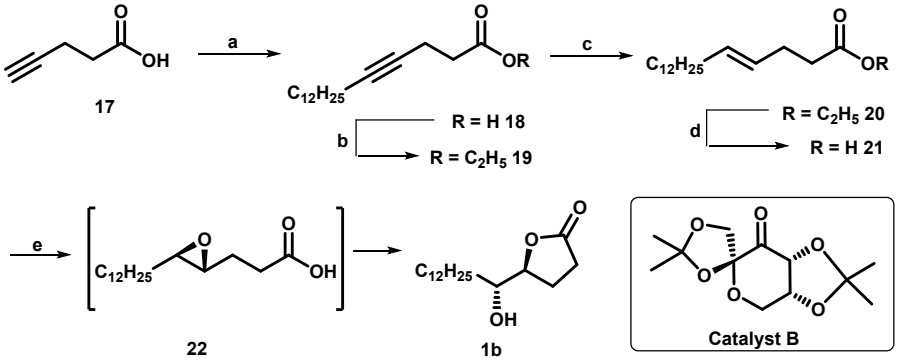


Scheme 2. *Reagents and conditions*: (a) i) 0.1 mol % catalyst **A**, HCOOH/Et_3N, 40 ^oC, 24 h; ii) NaH, THF, 0 ^oC to rt, 12 h, 70% (over two steps); (b) *N*-iodosuccinimide, THF, rt, 6 h, 90%; (c) TBAF, THF, 0 ^oC, 30 min, 85%; (d) $C_{11}H_{23}MgBr$, CuI (10 mol %), THF, 8 h, 85%; (e) Li/liq. NH_3, -78 ^oC, 30 min, 89%; (f) DIAD, PPh_3, benzene, 0 ^oC, 30 min and *in vacuo* 130 ^oC, 20 min, 90%; (g) i) acetic acid, LDA, THF, 0 ^oC to reflux, 12 h; ii) *p*-TSA, benzene, reflux, 1 h, 80% (over two steps).

Wang, M-A. *et al.* (2014)[9c]

M-A. Wang and co-workers accomplished stereoselective total synthesis of (+)-*epi*-muricatacin **1b** from commercially available chemical pent-4-ynoic acid **17** *via* Shi's asymmetric epoxidation as the key step in 26.9% overall yield (Scheme 3). The coupling of 1-bromododecane and pent-4-yn-1-oic acid **17** in presence of *n*-BuLi in hexamethylphosphoramide (HMPA) and THF furnished acid derivative **18** in 77% yield. Fischer esterification of acid **18** with ethanol in presence of sulfuric acid afforded ethyl ester **19** in 96% yield. Red-Al mediated reduction of alkyne **19** furnished *E*-olefin **20** in a moderate yield and further subjected to saponification to afford acid **21** in 74% yield. The key

intermediate **21** was converted into targeted compound **1b** by using Shi epoxidation conditions in 78% yield and 96.2% enantioselectivity.

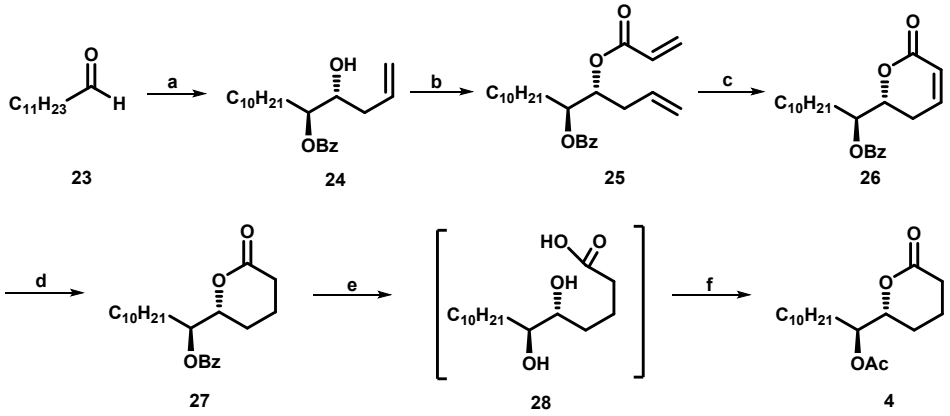


Scheme 3. *Reagents and conditions*: (a) i) *n*-BuLi, THF/HMPA, -78 °C to 0 °C, 2 h; ii) bromododecane, -78 °C to rt, 15 h, 77% (over two steps); (b) C_2H_5OH, H_2SO_4, reflux, 5 h, 96%; (c) red-Al, -40 °C, THF, 63%; (d) NaOH, C_2H_5OH/H_2O, 60 °C, 2.5 h, 74%; (e) $Na_2B_4O_7$, Na_2(EDTA), Bu_4NHSO_4, catalyst **B**, CH_3CN, rt, 12 h, 78% (over two steps).

4.0.2.2 Syntheses of (-)-*6*-acetoxy-hexadecanolide, 4

Tae, J. *et al*. (2010)[10c]

J. Tae and co-workers described total synthesis of (–)-6-acetoxy-5-hexadecanolide employing a seven-step sequence (Scheme 4). The synthesis of (-)-6-acetoxy-5-hexadecanolide **4** commenced with commercially available dodecanal **23** which was converted into homoallylic

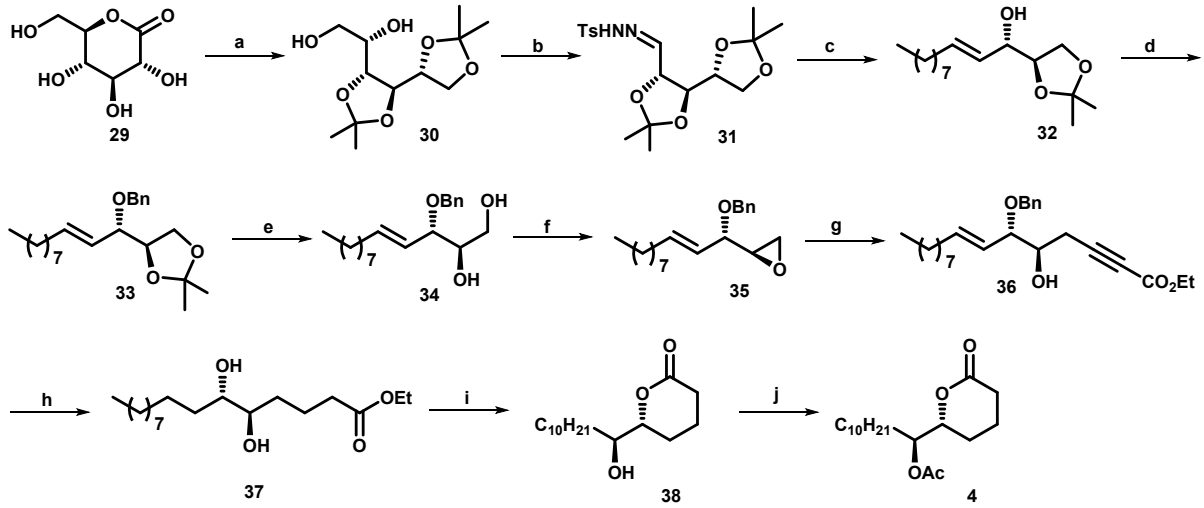


Scheme 4. *Reagents and conditions*: (a) i) BzOOBz, hydroquinone, THF, (*S*)-TMS prolinol; ii) allyl bromide, Indium, THF:H_2O (5:1), rt, 12 h; (b) acrolyl chloride, Et_3N, DMAP, DCM, 0 °C, 5 h, 73%; (c) Grubbs' second generation catalyst, DCM, reflux, 8 h, 77%; (d) H_2, Pd/C, Et_2O, rt, 5 h, 90%; (e) 1M NaOH, EtOH/H_2O, rt, 75%; (f) Ac_2O, pyridine, 0 °C, 5 h, 71%.

alcohol **24** *via* a two step sequence involving organocatalysed α-benzoyloxylation with benzoyl peroxide followed by *in situ* indium mediated allylation in 44% yield. Acryloylation of alcohol **24** with acryloyl chloride afforded the ester **25**, which on ring-closing metathesis (RCM) with Grubbs' second generation catalyst furnished the lactone **26** in 77% yield. Next, hydrogenation of compound **26** using 10% wt/wt Pd/C under hydrogen pressure gave the lactone derivative **27** in excellent yield. Saponifaction of **27** with sodium hydroxide furnished the intermediate **28** which was further reacted with acetic anhydride in pyridine to furnish the title compound **4** in 71% yield.

Yadav, J. S. *et al.* (2012)[10b]

J. S. Yadav and co-workers accomplished the total synthesis of (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide, from a readily available carbohydrate δ-gluconolactone in 18% overall yield. As depicted in Scheme 5, the synthesis of (-)-*6*-acetoxy-hexadecanolide **4** began with a known diol **30** obtained in two steps from commercially available δ-gluconolactone **29** as conditions developed previously. Synthesis of hydrazone derivative **31** from alcohol **30** was carried out by a process including $NaIO_4$ mediated oxidative cleavage and treatment of

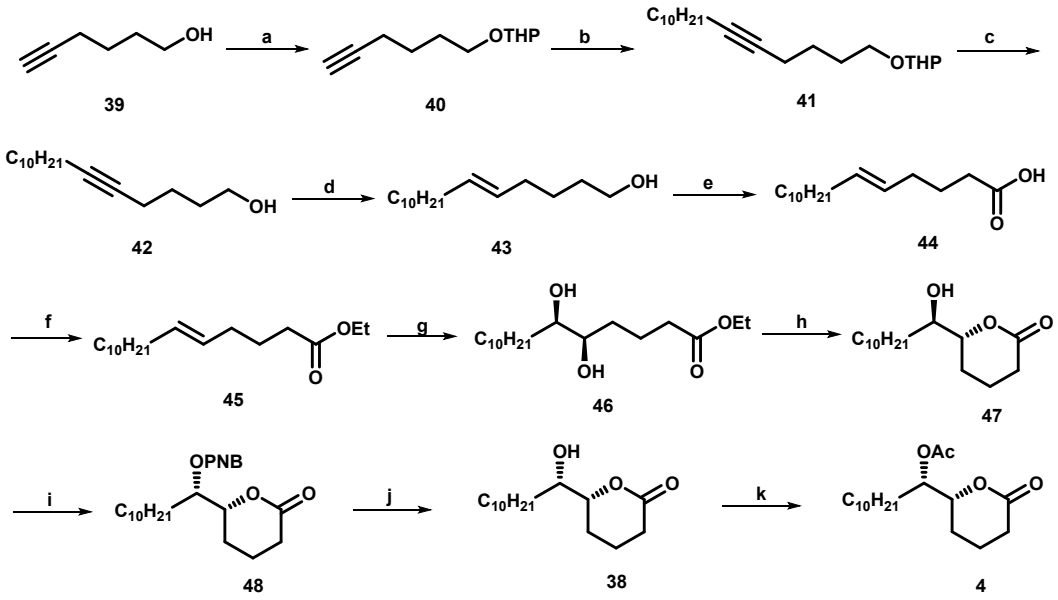


Scheme 5. *Reagents and conditions*: (a) i) 2,2-DMP, *p*-TSA, acetone, MeOH, rt, 12 h, 86%; ii) $LiAlH_4$, THF 0 °C to rt, 4 h, 96%; (b) i) $NaIO_4$, CH_3CN/H_2O (6:1), rt, 5 h; (ii) NH_2NHTs, MeOH, rt, 5 h, 78% (over two steps); (c) *n*-$C_8H_{17}MgBr$, diethyl ether, 0 °C to rt, 3 h, 76%; (d) NaH, BnBr, DMF, 0 °C to rt, 2 h, 98%; (e) *p*-TSA, MeOH, rt, 5 h, 80%; (f) i) TsCl, Et_3N, Bu_2SnO, DCM, 0 °C to rt, 12 h; (ii) NaH, THF, 0 °C 1h, 75% (over two steps); (g) Ethyl propiolate, *n*-BuLi, $BF_3.OEt_2$ THF, -78 °C, 80%; (h) H_2, Pd/C, MeOH, rt, 12 h; (i) *p*-TSA, benzene, rt, 87.2% (over two steps); (j) Ac_2O, DMAP, DCM, 20 °C, 1 h, 90 %

resulting aldehyde with tosylhydrazine in 78% yield. Next, hydrazone derivative **31** was allowed to react with *n*-octylmagnesium bromide to furnish allyl alcohol **32** in satisfactory yield. Free hydroxyl group in **32** was subjected to *O*-benzylation with benzyl bromide in presence of NaH which furnished the benzyl ether **33** in 98% yield. Exposure of compound **33** with catalytic amount of *p*-TSA afforded diol **34** in 80% yield which was further converted into epoxide **35** *via* a two step sequence including regioselective tosylation with TsCl followed by its treatment with base in 75% yield. Now, regioselective opening of epoxide **35** with lithium salt of ethyl propiolate under Yamaguchi-Hirao conditions delivered the alcohol **36** in 80% yield. Compound **36** was converted into *δ*-lactone **38** by hydrogenation followed by acid catalysed lactonization in 87% yield. Finally, acetylation of free hydroxyl group in compound **38** with acetic anhydride afforded title compound **4** in 90% yield.

Wang, M-A. *et al*. (2014)[10a]

M-A. Wang and co-workers reported the stereoselective synthesis of (-)-6-acetoxy-5-hexadecanolide **4** employed Sharpless AD and Mitsunobu reaction as the key steps (Scheme 6). The synthesis of (-)-6-acetoxy-5-hexadecanolide **4** began with commercially available



Scheme 6. *Reagents and conditions*: (a) 3,4-dihydro-2H-pyran, CSA, CH_2Cl_2, rt, 4 h, 98%; (b) *n*-BuLi, 1-iododecane, THF/HMPA, -78 to 0 ^oC, overnight, 73%; (c) *p*-TSA, CH_3OH, rt, 2 h, 83%; (d) $LiAlH_4$, THF/diglyme, 160 ^oC, 13 h, 58%; (e) PDC, DMF, rt, overnight, 58%; (f) H_2SO_4, CH_3CH_2OH, -78 ^oC, 5 h, 84%; (g) AD-mix-*β*, methanesulfonamide, *t*-BuOH/H_2O, 0 ^oC, 60 h; (h) (i) NaOH, H_2O, CH_3CH_2OH, 60 ^oC, 2 h; ii) TsOH, CH_2Cl_2, rt, 2.5 h, 80% (over two steps); (i) Ph_3P, DEAD, PNBA, THF, rt, 4 h, 90%; (j) K_2CO_3, CH_3OH, rt, 10 min, 87%; (k) Ac_2O, DMAP, CH_2Cl_2, rt, 4 h, 90%.

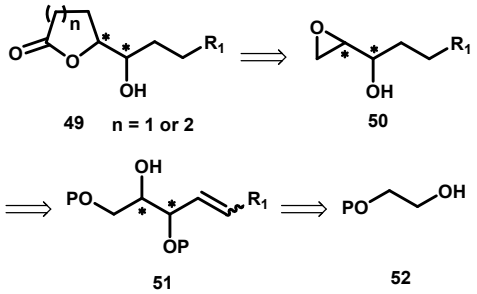
hex-5-yn-1-ol **39** which was protected as THP ether to furnish compound **40**. The coupling of compound **40** with 1-iododecane using *n*-BuLi and HMPA afforded **41** in 86% yield. Accordingly, compound **41** was reacted with *p*-TSA and further subjected to $LiAlH_4$ reduction in diglyme at 160 ^oC to furnish *E*-olefin alcohol **43** in 83% yield. Oxidation of **43** with PDC produced fatty acid **44** in 58% yield. The olefinic acid **44** was subjected to fischer esterification using H_2SO_4/C_2H_5OH to afford the ethyl ester **45** in 84% yield. Treatment of olefin **45** with Sharpless AD using commercially available AD-mix-α in *t*-BuOH-H_2O (1:1) furnished diol **46** in good yield. Saponification of diol **46** with NaOH afforded acid which was furher subjected to cyclization in the presence of *p*-TSA to afford (5*R*,6*R*)-lactone **47** in 84% yield. Next, lactone **47** was smoothly converted to the required compound **38** *via* Mitsunobu inversion. Finally, reaction of (5*R*,6*S*)-lactone **38** with acetic anhydride and DMAP furnished the corresponding natural product *erythro*-(5*R*,6*S*)-6-acetoxy-5-hexadecanolides **4** in 90% yield.

4.0.3 Present Work:

As part of our continuing efforts towards the syntheses of bioactive natural products, we became interested in developing a simple and flexible route to γ- and δ-lactones and its application to the total syntheses of (+)-*epi*-muricatacin **1b** and (-)-6-acetoxy-hexadecanolide **4**, employing organocatalyzed MacMillan's self aldol reaction and Wittig olefination as the key steps.

4.0.4 Results and Discussion:

Our initial retrosynthetic analysis of (+)-*epi*-muricatacin **1b** and (-)-*6*-acetoxy-hexadecanolide **4** are summarized in Scheme 7. The epoxy alcohol derivative **50** was visualized as a synthetic



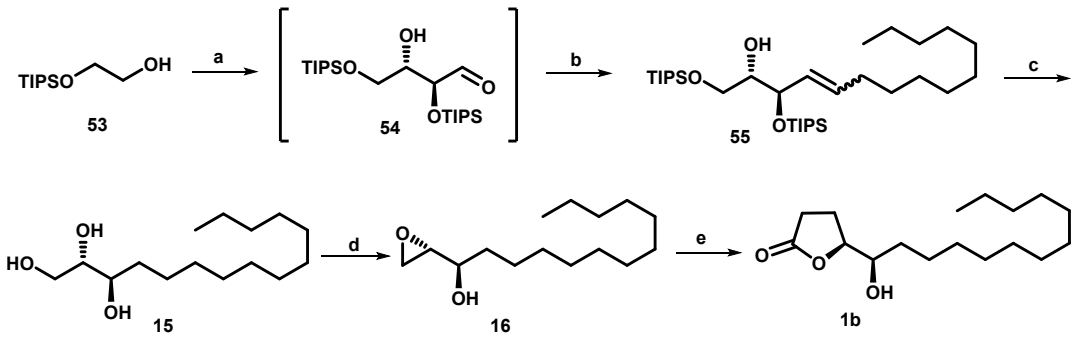
Scheme 7: Retrosynthetic approach to asymmetric synthesis of γ-and δ-lactone motif.

intermediate from which functionalized hydroxyl γ- and δ-lactone **49**, muricatacin's analogues **1b**, **2**, **3** and *6*-acetoxy-hexadecanolide **4-5** could be synthesized *via* Yamaguchi-

Hirao alkylation/dilithioacetate dianion reaction followed by standard organic transformations. The epoxide derivative **50** in turn could be obtained from alcohol derivative **51** in simple steps including deprotection and epoxide formation. Subsequently, compound **51** envisaged from readily available ethylene glycol derivative **52** *via* organocatalyzed Macmillan's self aldol reaction of aldehyde derived from **52** and Wittig homologation reaction to incorporate the appropriate side chain. The all (*R*)- and (*S*)- configuration of the target compounds **1b** and **4** could be manipulated by either changing organocatalyst under MacMillan's self aldol conditions or Mitsunobu inversion.

Our approach for the synthesis of (+)-*epi*-muricatacin **1b** is depicted in Scheme 8. Synthesis of (+)-*epi*-muricatacin **1b** began with readily available monosilylated ethylene glycol **53** which was subjected to a two step sequence including Swern oxidation followed by L-proline catalyzed MacMillan's self aldol reaction to furnish the *anti*-diastereomer **54** as the major product along with its column separable *syn*-diastereomer in 4:1 ratio and 90% combined isolated yield following a literature procedure.[11] Aldehyde intermediate **54** was subjected to Wittig homologation reaction with phosphonium salt (undecyltriphenylphosphonium bromide) which afforded olefin derivative **55** in 67% yield. We did not analyse the olefin geometry of derivative **55**, as the incipient olefin would be eventually hydrogenated for the synthesis of target compound.

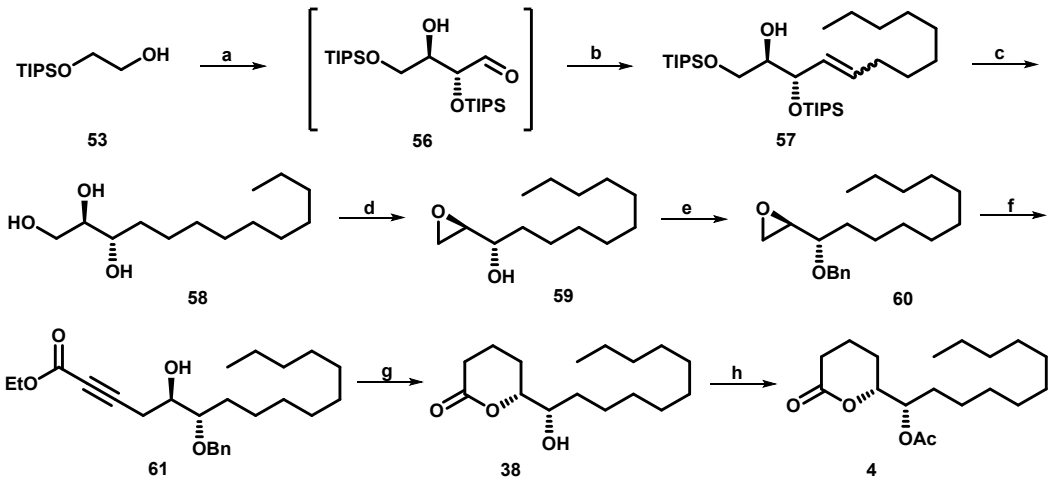
Desilylation of silyl ether in **55** with TBAF and successive hydrogenation in the presence of a catalytic amount of Pd/C (10% w/w) provided desired saturated triol **15** in 95% yield; $[\alpha]_D^{25}$ +5.7 (*c* 1.0, $CHCl_3$), {lit.[9h] $[\alpha]_D^{24}$ +6.0 (*c* 1.0, MeOH)}. The IR spectrum of **15** showed hydroxyl absorption at 3680 cm^{-1}. Regioselective sulfonylation of 1,2,3- triol derivative **15** with Et_3N and TsCl in the presence of catalytic amount of Bu_2SnO at room temperature proceeded smoothly to furnish primary monotosylated alcohol derivative, which on further treatment with K_2CO_3 in MeOH afforded epoxy alcohol derivative **16** in 78% yield $[\alpha]_D^{25}$ -11.4 (*c* 1.0, $CHCl_3$); {lit.[9h] $[\alpha]_D^{24}$ -11.0 (*c* 1.0, $CHCl_3$)}. The epoxide peak appeared at δ 3.03-3.01 (multiplet, one proton), 2.82-2.77 (multiplet, one proton), 2.74-2.72 (multiplet, one proton) in ^1H NMR. Finally, regioselective ring-opening of the epoxide **16** with dilithioacetate dianion[12] generated from acetic acid was performed smoothly to furnish acid derivative which was subsequently subjected to lactonization *via* catalytic *p*-TSA in benzene



Scheme 8: *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC to rt, 2 h; ii) 10 mol % L-proline, dioxane:DMF (1:1, v/v), rt, 48 h, 72% (over two steps); (b) KHMDS, $C_{29}H_{38}PBr$, THF, -78 °C to rt, 3 h, 67%; (c) i) TBAF, THF, rt, 12 h; ii) H_2, Pd/C (10%), MeOH, rt, 24 h, 95% (over two steps); (d) i) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 0 ^oC to rt, 1 h; ii) K_2CO_3, MeOH, rt, 30 min, 78% (over two steps), (e) i) LDA, CH_3CO_2H, THF, reflux, 12 h; ii) *p*-TSA, benzene, reflux, 1 h, 81% (over two steps).

under reflux condition to access targeted molecule (+)-*epi*-muricatacin **1b** in 81% yield; $[\alpha]_D^{25}$ +31.8 (*c* 0.9, $CHCl_3$); {lit.[9h] $[\alpha]_D^{24}$ +32.0 (*c* 0.9, $CHCl_3$)}. The physical and spectroscopic data were in full agreement with those reported in the literature.[9]

The synthesis of (-)-6-acetoxy-5-hexadecanolide **4** is outlined in Scheme 9. Accordingly the synthetic sequence began with monosilylated ethylene glycol **53** which was converted into aldol aldehyde derivative **56** *via* a process including Swern oxidation, D-proline catalyzed MacMillan's self aldol reaction furnished the *anti*-diastereomer **56** as the major product along with its column separable *syn*-diastereomer in 4:1 ratio and 90% combined isolated yield following a literature procedure.[11,13] Treatment of aldehyde **56** with phosphonium salt (nonyltriphenylphosphonium bromide) in presence of KHMDS delivered olefin **57** in 65% yield. Since the incipient olefin would be eventually hydrogenated for the synthesis of the target compound, we did not analyse the geometry of olefin **57**. Compound **57** was smoothly transformed into triol **58** *via* removal of silyl ether with TBAF followed by hydrogenation in the presence of 10% Pd/C under 1 atm of hydrogen. The IR spectrum of **58** showed hydroxyl absorption at 3415 cm^{-1}. Treatment of 1,2,3-triol derivative **58** with TsCl and Et_3N in presence of catalytic Bu_2SnO successfully furnished the primary alcohol monotosylated derivative which without further purification treated with K_2CO_3 in MeOH to afford epoxy alcohol derivative **59** in 76% yield; $[\alpha]_D^{25}$ +16.4 (*c* 1.0, $CHCl_3$); {lit[10n] $[\alpha]_D^{20}$ +15.0 [*c* 2.1, $CHCl_3$]}, {lit[10o] $[\alpha]_D^{20}$ +16.2 [*c* 1.01, $CHCl_3$]}. The epoxide peak appeared at δ 3.01-2.99 (multiplet, one proton), 2.84-2.83 (multiplet, one proton), 2.79-2.77 (multiplet, one proton) in ^1H NMR. The free hydroxy group of **59** was subjected to *O*-benzylation with BnBr and NaH



Scheme 9: *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC to rt, 2 h; ii) 10 mol % D-proline, dioxane:DMF (1:1, v/v), rt, 48 h, 72% (over two steps); (b) KHMDS, $C_{27}H_{34}PBr$, THF, -78 °C to rt, 3 h, 65%; (c) i) TBAF, THF, rt, 12 h; ii) H_2, Pd/C (10%), MeOH, rt, 12 h, 95% (over two steps); (d) i) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 0 ^oC to rt, 1 h; ii) K_2CO_3, MeOH, rt, 30 min, 76% (over two steps); (e) NaH, BnBr, DMF, 0 ^oC, 4 h, 92%; (f) *n*-BuLi, $BF_3.OEt_2$, ethyl propiolate, dry THF, -78 ^oC, 2 h, 81%; (g) i) H_2, Pd/C (10% w/w), MeOH, rt, 12 h; ii) *p*-TSA, benzene, reflux, 1 h, 91% (over two steps); (h) Ac_2O, DMAP, DCM, 30 min, 95%.

in DMF to furnish the benzylated derivative **60** in 92% yield. Next, the epoxide derivative **60** was regioselectively opened with a lithium salt of ethyl propiolate under the Yamaguchi-Hirao conditions[14] to deliver the homopropargylic alcohol **61** in 81% yield. The IR spectrum of compound **61** showed hydroxyl absorption at 3460 cm^{-1} and carbonyl absorption at 1720 cm^{-1}. Subsequently, the lactone **38** was obtained from compound **61** by a two-step process involving hydrogenation in presence of catalytic amount of 10% Pd/C and *p*-TSA catalysed lactonization in 91% yield. Finally, acetylation of the alcohol **38** with Ac_2O and DMAP furnished (-)-*6*-acetoxy-hexadecanolide **4** in 95% yield; $[\alpha]_D^{25}$ -30.0 (*c* 0.4, $CHCl_3$); {lit.[10b] $[\alpha]_D^{32}$ -33.0 (*c* 0.4, $CHCl_3$)}.

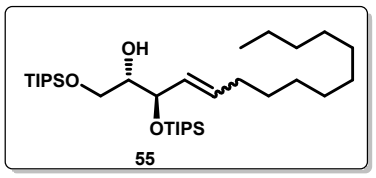
4.0.5 Conclusion:

In summary, we have developed a convergent and flexible approach for *γ*- and *δ*-lactones and its application to the total syntheses of (+)-*epi*-muricatacin **1b** and (-)-*6*-acetoxy-hexadecanolide **4**. The synthetic sequence demonstrates the application of organocatalyzed MacMillan's self-aldol and Wittig olefination as the key steps. The synthetic approach

described has significant potential for stereochemical variations at all the positions and further extension to other stereoisomers and their analogues.

4.0.6 Experimental Section:

(5*R*,6*S*)-5-(dodec-1-en-1-yl)-3,3,9,9-tetraisopropyl-2,10-dimethyl-4,8-dioxa-3,9 disila-undecan-6-ol, 55



55

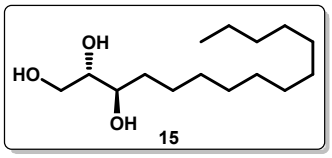
A solution of DMSO (0.7 mL, 10.32 mmol) in CH_2Cl_2 was added slowly to a stirred solution of oxalyl chloride (0.4 mL, 5.0 mmol) in CH_2Cl_2 (10 mL) at -78 °C. The reaction mixture was stirred for 30 min at the same temperature and a solution of the monosilylated ethylene glycol **53** (1.0 g, 3.33 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the resultant solution was stirred for another 30 min at -78 °C. A solution of Et_3N (2.0 mL, 14.65 mmol) in CH_2Cl_2 (10 mL) was added and the resultant mixture was left to warm to rt over 1 h before the addition of H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give (triisopropyl-silanoxy)-acetaldehyde as yellow oil, which was used for the next step directly.

L-Proline (38 mg, 0.33 mmol) was added to a solution of above (triisopropyl-diphenyl-silanoxy)-acetaldehyde in 1,4-dioxane (3 mL) and DMF (3 mL), which was stirred at rt for 48 h. The resulting suspension was diluted with ethyl acetate (50 mL) and washed successively with water (25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to furnish *anti*-/*syn*-diastereomeric aldehyde as yellow oil. The *anti*-/*syn*-diastereomers were then separated by silica gel column chromatography using (EtOAc/hexane 1:49 v/v) as eluent to furnish th e*anti*-diastereomer **54** (500 mg, 72%) and *syn*-diastereomer (125 mg, 18%) as yellow oil.

To a stirred solution of phosphonium salt $C_{11}H_{23}BrPPh_3$ of (650 mg, 1.31 mmol) in THF (10 mL) was added, dropwise KHMDS (1.0 M in hexane, 1.4 mL, 1.42 mmol) at -78 °C and the mixture was left to warm to rt over 1 h before being cooled to -78 °C. To this orange solution was added above aldehyde **54** dissolved in THF (5 mL) *via* syringe and the mixture was stirred under the same conditions for 10 min., then cooling bath was removed and the reaction mixture was left to warm to rt over 2 h before the addition of H_2O (20 mL). The resulting suspension was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica-gel

chromatography (EtOAc/hexane 1:99) to afford alkene **55** (586 mg, 67%) as a colourless liquid.

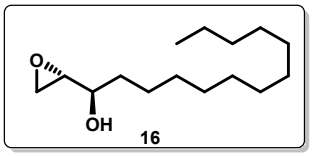
(2*S*,3*R*)-Pentadecane-1,2,3-triol, 15



To a stirred solution of olefin **55** (500 mg, 0.68 mmol) in THF (10 mL) at 0 °C was added TBAF (2.0 mL, 2.04 mmol) in one portion. The resultant suspension was stirred for 5 h atrt and then diluted with saturated aqueous solution of NH_4Cl (20 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give triol which was used for next step**.**

A mixture of crude triol and catalytic amount of Pd/C in MeOH was vigorously stirred for 12 h at rt under hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and concentrated under reduced pressure. Silica gel column chromatography (EtOAc/hexane 4:1 v/v) of the residue yielded **15** (168 mg, 95%) as a white solid. [R_f = 0.4, EtOAc]; $[\alpha]_D^{25}$ +5.7 (*c* 1.0, MeOH),{lit.[7f] $[\alpha]_D^{24}$ +6.0 (*c* 1.0, MeOH)}; IR (CH_2Cl_2) *v*: 3680, 3185, 2923, 2849, 1462, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.90-3.50 (m, 4H) 2.79 (br, 1H), 2.32 (br, 2H), 1.60-1.10 (m, 22H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.9, 65.0, 63.1, 33.7, 32.9, 31.8, 29.5, 29.3, 25.9, 25.5, 22.6, 14.1; HRMS (ESI), m/z calcd for $C_{15}H_{33}O_3$ $[M + H]^+$ 261.2429; found 261.2419.

(*R*)-1-((*S*)-oxiran-2-yl)tridecan-1-ol, 16

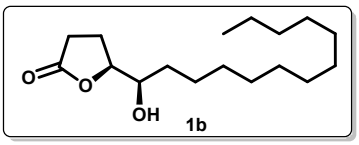


To a mixture of triol **15** (150 mg, 0.58 mmol), dibutyl tin oxide (28 mg, 20 mol %) and Et_3N (0.1 mL, 0.70 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC, was added *p*-TsCl (122 mg, 0.64 mmol) portion-wise and the resulting suspension was stirred for 1 h at rt. Then the reaction mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the residue.

K_2CO_3 (160 mg, 1.16 mmol) was added to a mixture of above crude diol in MeOH (5 mL) and stirred for 30 min at rt. The MeOH was evaporated under reduced pressure and then the residue was diluted with water and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*and purified by silica gel column chromatography (EtOAc/hexane 1:4) to give epoxide **16** (110 mg, 78%) as a white solid. [R_f = 0.3, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$-11.4 (*c* 1.0, $CHCl_3$); {lit.[7f] $[\alpha]_D^{24}$ -11.0 (*c* 1.0, $CHCl_3$)};IR(CH_2Cl_2) *v*: 3405, 2939, 2920, 2863, 1701, 1651, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.87-3.80 (m, 1H), 3.03-3.01

(m, 1H), 2.82-2.77 (m, 1H), 2.74-2.72 (m, 1H), 1.74 (br, 1H), 1.22-1.61 (m, 22H), 0.88 (t,*J* = 6.88 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 68.3, 54.5, 43.3, 33.4, 31.9, 29.6, 29.5, 29.3, 25.3, 22.7, 14.1; HRMS (ESI), m/z calcd for $C_{15}H_{31}O_2$ $[M + H]^+$ 242.2324; found 242.2303

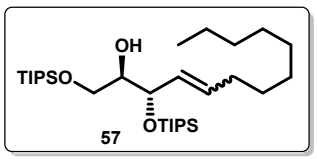
(+)-*epi*-Muricatacin, 1b



Dry acetic acid (57 μL, 1 mmol) was added to a solution of LDA (1.6 M, 2 mmol) in THF (4 mL) at 0 °C. After 30 min, the epoxy alcohol **16** (50 mg, 0.21 mmol) was added and the resulting mixture was refluxed for 12 h. Then, acidified with saturated aqueous solution of sodium hydrogen sulfate and extracted with ether (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 concentrated under reduced pressure to give crude acid which was used for next step without purification.

To a solution of above crude in benzene was added catalytic amount of *p*-toluene sulfonic acid and refluxed for 1 h. Then, the reaction mixture was cooled to rt and washed with an aqueous solution of sodium hydrogen carbonate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc/hexane 3:7) delivered (+)-*epi*-muricatacin **1b** (26 mg, 81%) as a white solid. Mp: 66-67 °C. [R_f = 0.4, EtOAc/hexane 2:3 v/v]; $[\alpha]_D^{25}$+31.8 (*c* 0.9, $CHCl_3$), {lit[7f] $[\alpha]_D^{24}$ +32.0 (*c* 0.9, $CHCl_3$)};IR (CH_2Cl_2) *v*: 3410, 2925, 2846, 1780, 1244, 1042, 838, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.47-4.41(m, 1H), 3.96-3.90 (m, 1H), 2.64-2.47 (m, 2H), 2.32-2.09 (m, 2H), 1.86 (br, 1H), 1.56-1.18 (m, 22H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:177.5, 82.8, 71.3, 31.9, 29.6, 29.5, 29.4, 29.3,28.7, 25.6, 22.7, 21.0, 14.1; HRMS (ESI), m/z calcd for $C_{17}H_{33}O_3$ $[M + H]^+$ 285.2429; found 285.2418.

(5*S*,6*R*)-5-(dec-1-enyl)-3,3,9,9-tetraisopropyl-2,10-dimethyl-4,8-dioxa-3,9disilaundecan 6-ol, 57



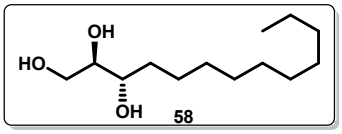
To a solution of oxalyl chloride (0.4 mL, 4.99 mmol) in anhydrous CH_2Cl_2 (5 mL) at -78 °Cwas added dropwise, a solution of DMSO (0.7 mL, 10.32 mmol) in CH_2Cl_2 (5 mL) under N_2 atmosphere. After 30 min, a solution of monosilylated ethylene glycol **53** (1.00 g, 3.33 mmol) in anhydrous CH_2Cl_2 (5 mL) was added, and the resulting mixture was left for an additional 30 min. Then, Et_3N (2.0 mL, 14.65 mmol) was added dropwise and the resulting suspension was vigorously stirred for another 30 min. The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried over Na_2SO_4. The solvent was evaporated *in*

vacuo to afford the crude aldehyde, which was used in the next step without further purification.

D-Proline (38 mg, 0.33 mmol) was added to a solution of crude aldehyde in DMF (3 mL) and dioxane (3 mL) under N_2 atmosphere. After stirring for 48 h atrt, the reaction mixture was diluted with H_2O and EtOAc. The aqueous phase was then extracted with EtOAc (3 × 30 mL), the combined organic phase was successively washed with H_2O. The combined organic phase was dried over Na_2SO_4 and solvent was removed *in vacuo* to give the *anti*-/*syn*-diastereomeric mixture as yellow oil. The *anti*-/*syn*-diastereomers were then separated by silica gel column chromatography using (EtOAc/hexane 1:49 v/v) as eluent to furnish the more quickly eluted *anti*-diastereomer **56** (500 mg, 72%) and the *syn*-diastereomer (125 mg, 18%) as yellow oil. Anti diastereomer was used for next step.

To a round-bottomed flask charged with a suspension of the phosphonium salt $C_9H_{19}BrPPh_3$ (614 mg, 1.27mmol) in anhydrous THF (10 mL) at -78 ^oC, was added KHMDS (1.4 mL, 1.4mmol, 1.0 M in THF) dropwise *via* syringe. The solution was stirred for 1 h atrt and then recooled to -78 °C. A solution of above *anti*-aldehyde **56** in anhydrous THF (5 mL) was added dropwise, and the resulting suspension was stirred vigorously for 3 h at rt. The reaction mixture was quenched by the addition of H_2O (20 mL) and the aqueous layer was extracted with EtOAc (3× 30 mL). The combined organic layer was dried with $Na_2SO_4$and concentrated underreduced pressure. Silica gel column chromatography (EtOAc/hexane 1:99) of the residue furnished olefin derivative **57** (546 mg, 65%) as a colourless liquid.

(2*R*,3*S*)-Tridecane-1,2,3-triol, 58

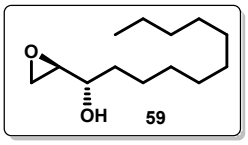


TBAF (3.0 mL, 2.97 mmol) was added to a solution of silyl ether derivative **57** (400 mg, 0.74 mmol) in THF (0.3 mL) at rt under N_2 atmosphere. After 5 h, the reaction mixture was quenched with saturated solution of ammonium chloride. The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried with $Na_2SO_4$and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography to furnish triol derivative as a colourless liquid.

A mixture of above crude and catalytic amount of Pd/C in MeOH (5 mL) was vigorously stirred under H_2 atmosphere at rt for 12 h, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes 4:1 v/v) to give triol **58** (163 mg, 95%) as a white solid. [R_f = 0.4, EtOAc]; $[\alpha]_D^{25}$ -10.4 (*c* 0.8, $CHCl_3$); IR (CH_2Cl_2) *v*: 3415, 2945, 2910, 2863, 1701, 1651 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ: 3.90-3.48 (m, 3H), 2.64 (br, 1H), 2.74 (br, 1H), 2.26 (br, 2H) 1.70-1.10 (m, 18H), 0.93 (t, J= 6.88 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.0, 67.5, 62.8, 33.8, 31.9, 29.6, 29.5, 29.3, 25.3, 22.6, 14.1; HRMS (ESI), m/z calcd for $C_{13}H_{28}O_3$ [M + Na]$^+$ 255.1930; found 255.1929.

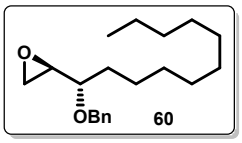
(*S*)-1-((*R*)-Oxiran-2-yl)undecan-1-ol, 59



To a stirred solution of **58** (150 mg, 0.65 mmol) in CH_2Cl_2 (6 mL) were added Et_3N (0.1 ml, 0.78 mmol), catalytic amount of Bu_2SnO (16 mg, 0.06 mmol) and TsCl (136 mg, 0.72 mmol) at 0 °C and the resulting mixture was stirred at rt for 1 h. Then the reaction mixture was quenched with water, extracted with CH_2Cl_2 and dried over Na_2SO_4.The combined organic layer was concentrated *in vacuo* to afford crude tosylate which was used for next step.

K_2CO_3 (179 mg, 1.30 mmol) was added to a solution of above crude in methanol (5 mL) at rt and stirred for 30 minutes. The resulting mixture was diluted with H_2O (10 mL) and EtOAc (30 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give epoxide derivative **59** (105 mg, 76%) as a colorless liquid. [R_f = 0.3, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$ +16.4 (*c* 1.0, $CHCl_3$); {lit.[11n] $[\alpha]_D^{20}$ +15.0 [*c* 2.1, $CHCl_3$]}, {lit.[11o] $[\alpha]_D^{20}$ +16.2 [*c* 1.01, $CHCl_3$]}; IR (CH_2Cl_2) ν: 3453, 2935, 2856, 1256, 1426 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71-3.68 (m, 1H), 3.01-2.99 (m, 1H), 2.84-2.83 (m, 1H), 2.79-2.77 (m, 1H), 1.69-1.66 (m, 2H), 1.50-1.21 (m, 16H), 0.93 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 68.4, 54.5, 43.4, 33.4, 31.9, 29.7, 29.6, 29.5, 29.3, 25.3, 22.7, 14.1; HRMS (ESI), m/z calcd for $C_{13}H_{27}O_2$ [M + H]$^+$ 215.2011; found 215.2012.

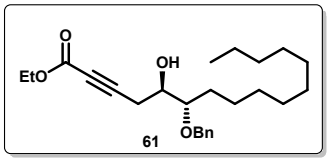
(*R*)-2-((*S*)-1-(Benzyloxy)undecyl)oxirane, 60



NaH (15 mg, 0.56 mmol) was added slowly to a solution of **59** (100 mg, 0.47 mmol) in anhydrous DMF (3 mL) at -20^{o}C under N_2 atmosphere and stirred for 10 minutes. Then a solution of benzyl bromide (72μL, 0.61 mmol) in DMF (1 mL) was added to the reaction mixture at the same temperature. After an additional 1 h, it was warmed to room temperature and stirred for another 2 h. The reaction mixture was then quenched with ice cooled water and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual product was subjected to silica gel column chromatography to furnish epoxide derivative **60** (131 mg, 92%). [R_f = 0.4, EtOAc/hexane 1:9 v/v]; $[\alpha]_D^{25}$ -16.0(*c* 1.0, $CHCl_3$){lit.[11n]$[\alpha]_D^{25}$-17.0 (*c* 1.16, CH_2C1_2)}; IR (CH_2Cl_2) ν: 2921,

2850, 1465, 1053, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.27 (m, 5H), 4.65(d, J = 12.08 Hz, 1H), 4.50(d, J= 11.4 Hz, 1H), 3.28-3.23 (m, 1H), 2.95-2.92 (m, 1H), 2.80-2.77 (m, 1H), 2.73-2.70(m, 1H), 1.68-1.62 (m, 2H), 1.40-1.20 (m, 16H), 0.88(t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.5, 128.3, 127.8, 127.6, 78.0, 72.2, 53.6, 45.6, 32.8, 31.9, 29.6, 29.5, 29.3, 25.2, 22.7, 14.1; HRMS (ESI), m/z calcd for $C_{20}H_{33}O_2$ $[M + H]^+$ 305.2425; found 305.2427.

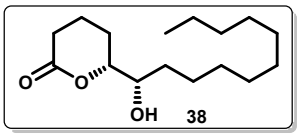
Benzyl (5*R*,6*S*)-6-(benzyloxy)-5-hydroxyhexadec-2-ynoate, 61



61

n-BuLi (2.5 in hexanes, 0.13 mL, 0.66 mmol) was added dropwise *via* syringe to a flame-dried round-bottomed flask charged with ethyl propiolate(66mg, 0.66mmol) in THF (4 mL) at -78 °C. After 1 h, epoxide derivative **60** (100 mg, 0.33 mmol) was added dropwise, followed by $BF_3{\cdot}OEt_2$ (40 μL, 0.66 mmol) at -78 °C and the mixture was stirred for an additional 2 h. Then the reaction was quenched with saturated solution of $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane, 1:3) provided alcohol derivative **61** (107 mg, 81%) as a colourless oil. [R_f = 0.5, EtOAc/hexane 1:1 v/v]; $[\alpha]_D^{25}$ +23 (*c* 1.0, $CHCl_3$), {lit.[11n] $[\alpha]_D$ +23 (*c* 1.21, CH_2C1_2)}; IR (CH_2Cl_2) *v*: 3460, 2914, 2235, 1720, 1460, 1368, 1250, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.27 (m, 5H), 4.58 (q, J = 17.88, 11.48 Hz, 2H), 4.22 (q, J= 14.2, 7.32 Hz, 2H), 3.99-3.93 (m, 1H), 3.53-3.47 (m, 1H), 2.62-2.58 (m, 2H), 2.32 (brd, 1H), 1.70-1.60 (m, 2H), 1.56-1.20 (m, 19H), 0.88(t, J= 6.88 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.5, 138.0, 128.5, 128.4, 127.8, 85.9, 80.7, 74.7, 72.4, 70.4, 61.9, 31.8, 29.7, 29.6, 29.5, 29.3, 25.1, 24.1, 22.7, 22.6,14.1, 14.0; HRMS (ESI), m/z calcd for $C_{25}H_{39}O_4$ $[M + H]^+$ 403.2848; found 403.2825.

(*R*)-6-((*S*)-1-Hydroxyundecyl)tetrahydro-2H-pyran-2-one, 38



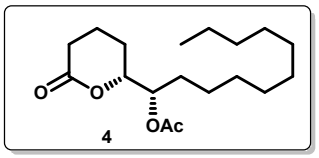
38

To a suspension of **61** (60 mg, 0.15 mmol) in methanol was added palladium on activated carbon 10% Pd/C and the solution was stirred under an atmosphere of hydrogen for 12 h at rt. The Pd catalyst was filtered off through a pad of Celite and the filtrate was concentrated *in vacuo*to provide crude alcohol as a white solid which was used for next step directly.

Catalytic amount of *p*-TSA was added to a stirred solution of above crude in benzene and the mixture was allowed to be refluxed for 1 h at rt. Then, the reaction mixture was quenched by saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The organic

layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, purification by silica-gel column chromatography afforded **38** (36 mg, 91%) as a white solid. [R_f = 0.5, EtOAc/hexane 1:1 v/v]; $[\alpha]_D^{25}$ -10.6 (*c* 0.8, $CHCl_3$), {lit.[11b] $[\alpha]_D^{30}$-11.0 (*c* 0.8, CH_2Cl_2)}; IR (CH_2Cl_2) *v*: 3280, 2935, 2861, 1710, 1468, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.27-4.23 (m, 1H), 3.85-3.80 (m, 1H), 2.65-2.58 (m, 1H), 2.50-2.41 (m, 1H), 2.04-1.71 (m, 4H),1.65-1.40 (m, 4H), 1.38-1.26(m, 15H), 0.88 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 171.7, 83.4, 72.4, 31.9, 31.6, 29.8, 29.6, 29.5, 29.3, 25.9, 22.7, 21.2, 18.3, 14.1; HRMS (ESI), m/z calcd for $C_{16}H_{31}O_3$ $[M + H]^+$ 271.2273; found 271.2269.

(-)-6-Acetoxy-hexadecanolide, 4



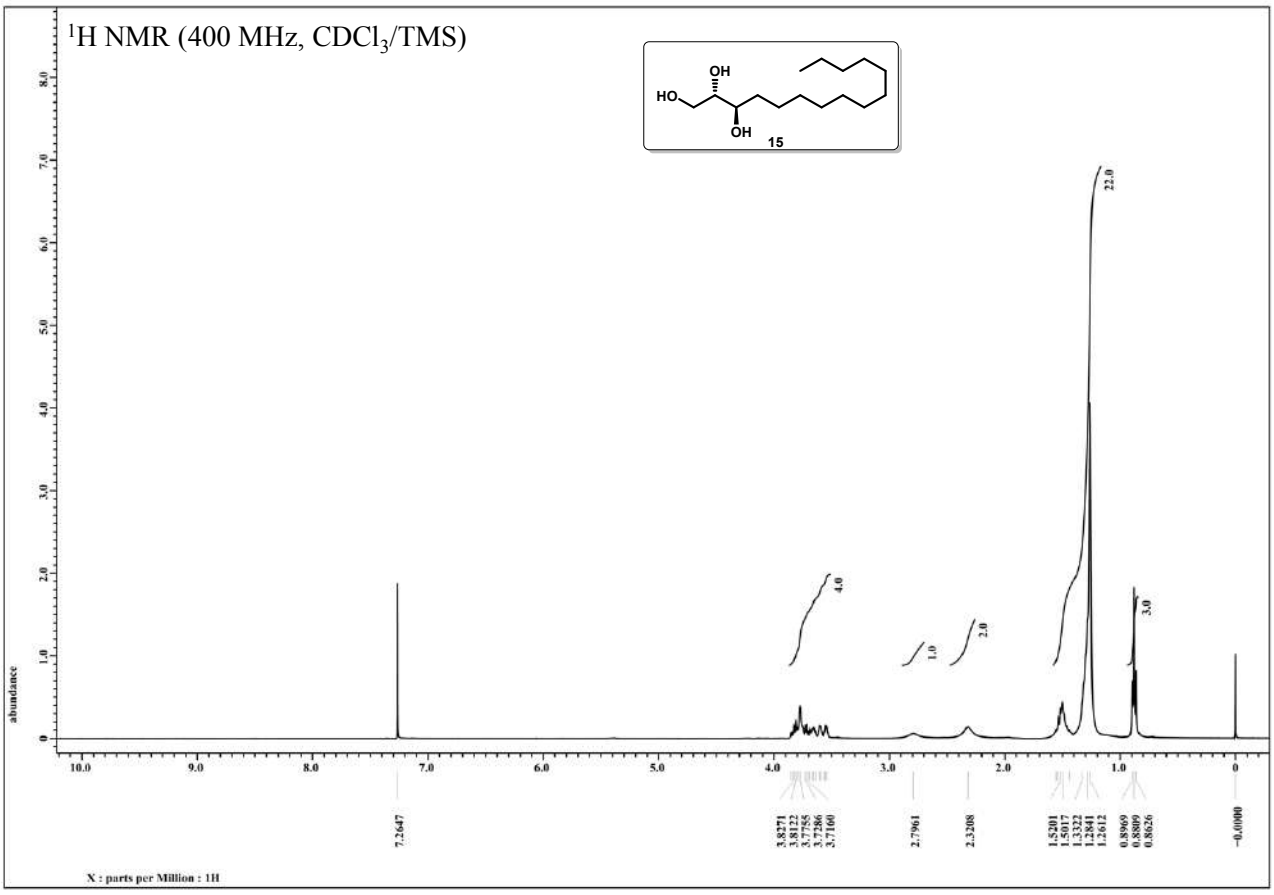
4

To a stirred solution of the alcohol derivative **38** (20 mg, 0.07 mmol) in anhydrous CH_2Cl_2 (3.0 mL) were added DMAP (51 mg, 0.42 mmol) and Ac_2O (43 mg, 0.42 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 minutes. Then, the reaction mixture was quenched by addition of cold water and extracted with EtOAc (3 ×5 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed *in vacuo*. Silica gel column chromatography of the resultant residue furnished **4** (20 mg, 95%) as a colorlessoil. [R_f = 0.4, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{25}$-30.0 (*c* 0.4, $CHCl_3$);{lit.[11b] $[\alpha]_D^{32}$-33.0 (*c* 0.4, $CHCl_3$)}; IR (CH_2Cl_2) *v*:2935, 2844, 1740, 1361, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.99-4.95 (m, 1H), 4.38-4.31 (m, 1H), 2.65-2.57 (m, 1H), 2.50-2.41 (m, 1H), 2.08 (s, 3H), 2.00-1.79 (m, 2H), 1.72-1.56 (m, 4H), 1.38-1.20 (m, 16H), 0.88 (t, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*:170.9, 170.5, 80.5, 74.3, 31.9, 29.8, 29.7, 29.6, 29.5, 25.2, 23.5, 22.7, 21.0, 18.2, 14.1; HRMS (ESI), m/z calcd for $C_{18}H_{33}O_4$[M + H]$^+$ 313.2379; found 313.2395.

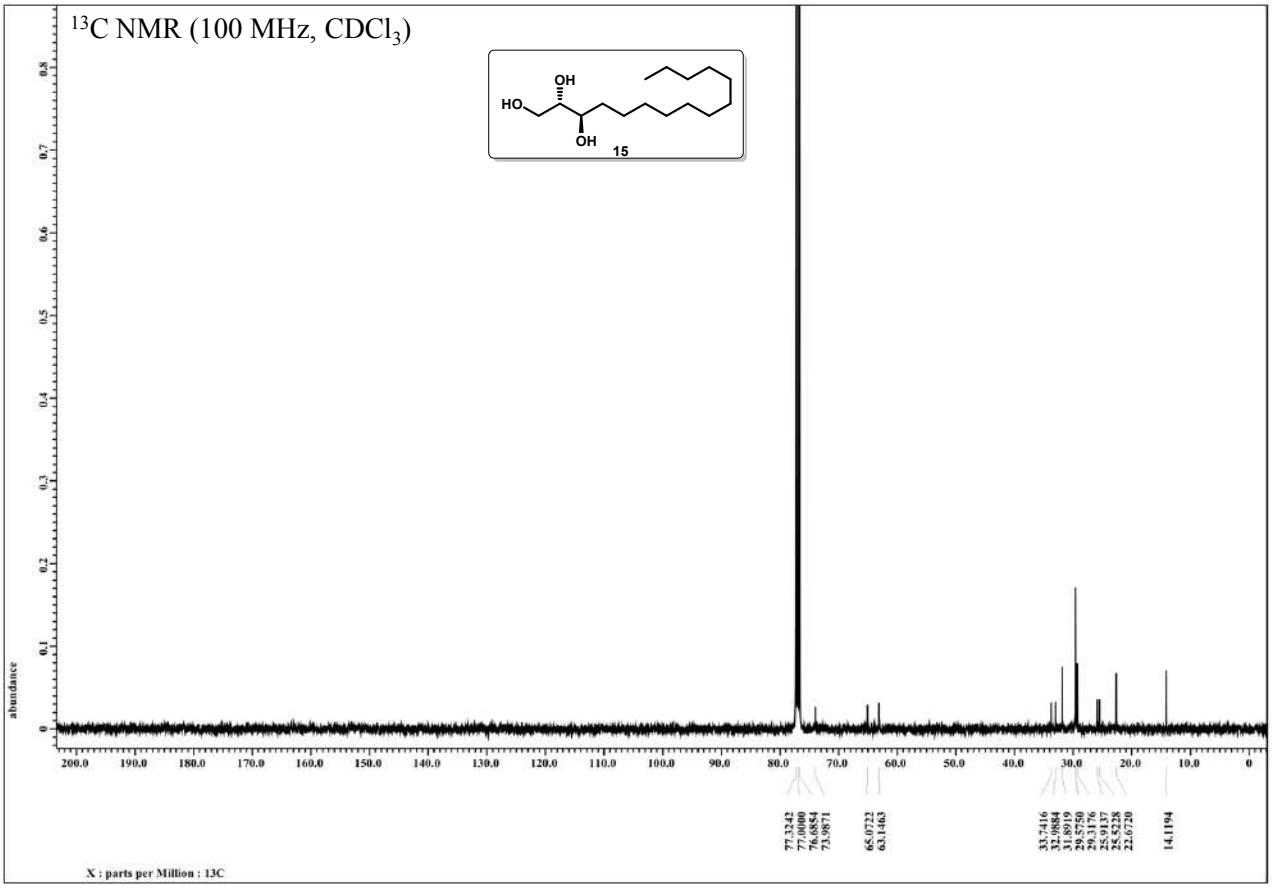
4.0.7 Spectra:

1. ^{1}H and ^{13}C NMR spectra of **15**
2. ^{1}H and ^{13}C NMR spectra of **16**
3. ^{1}H and ^{13}C NMR spectra of **1b**
4. ^{1}H and ^{13}C NMR spectra of **58**
5. ^{1}H and ^{13}C NMR spectra of **59**
6. ^{1}H and ^{13}C NMR spectra of **60**
7. ^{1}H and ^{13}C NMR spectra of **61**
8. ^{1}H and ^{13}C NMR spectra of **38**
9. ^{1}H and ^{13}C NMR spectra of **4**

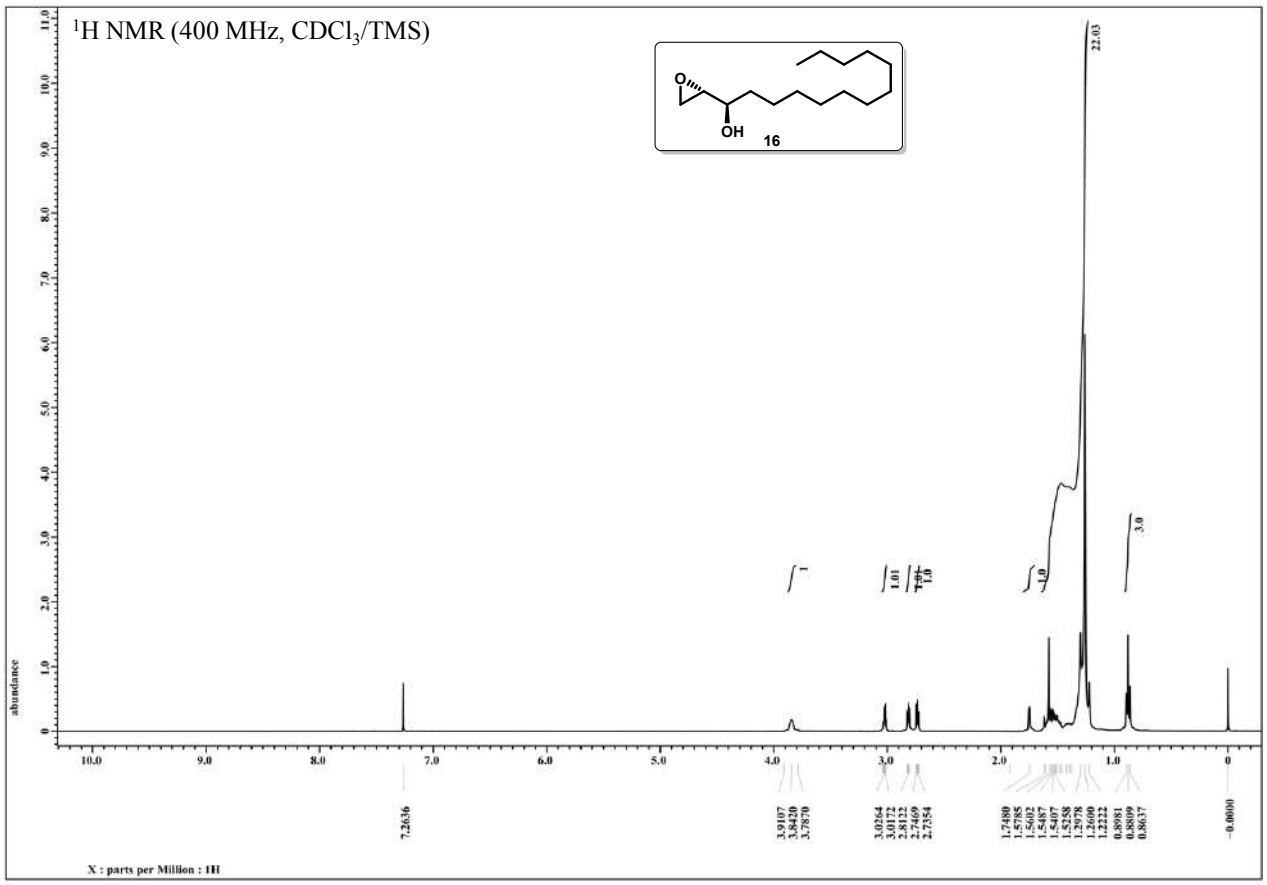
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



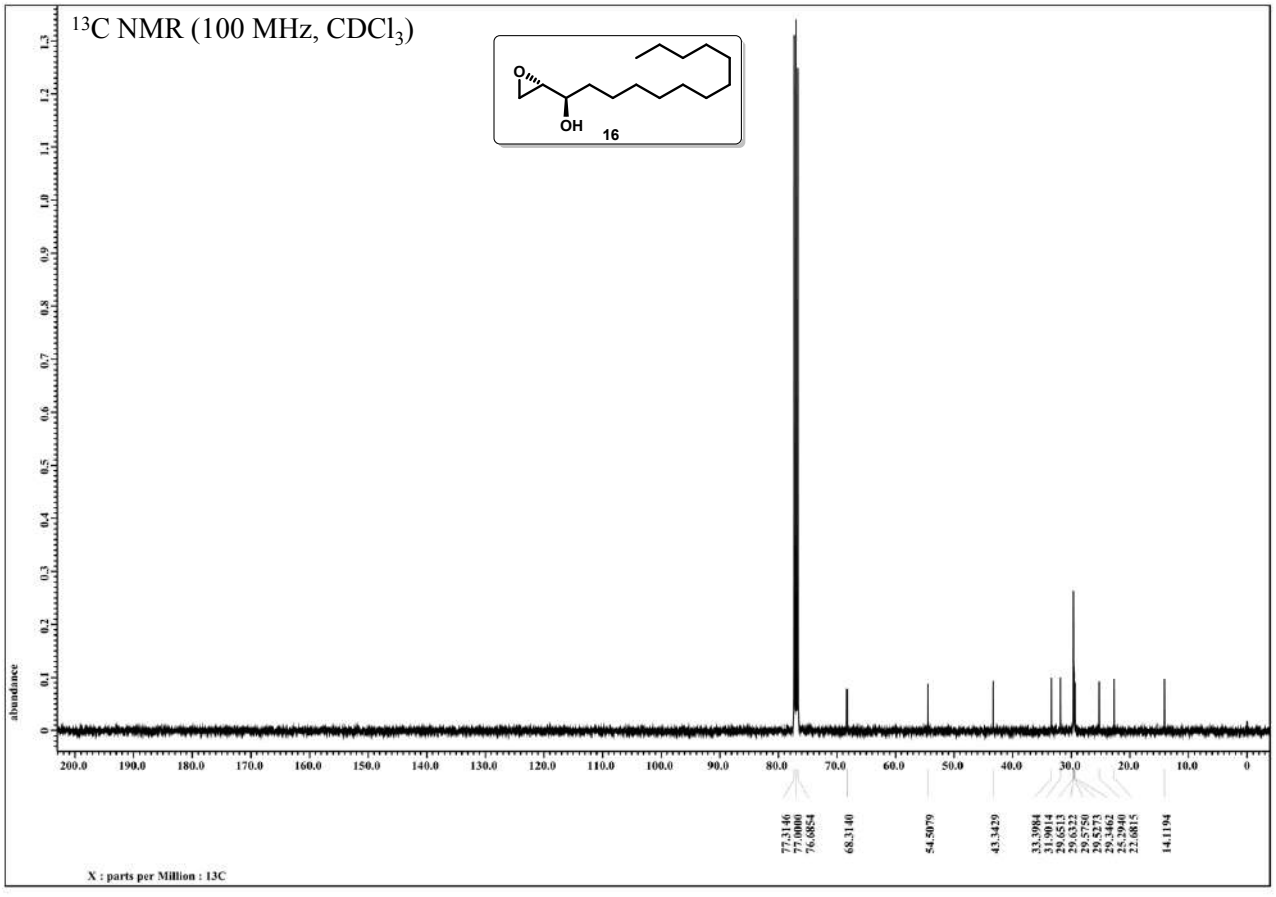
^{13}C NMR (100 MHz, $CDCl_3$)



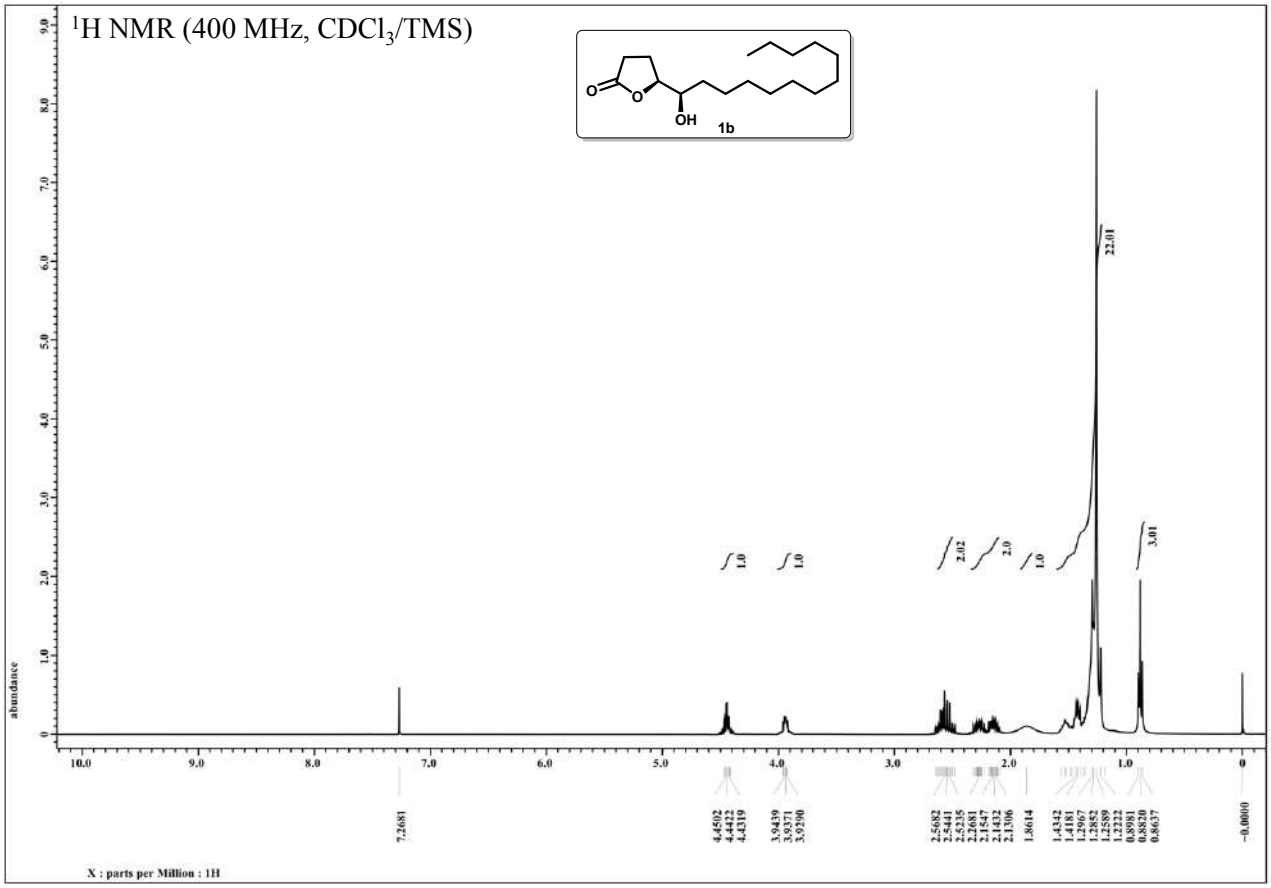
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



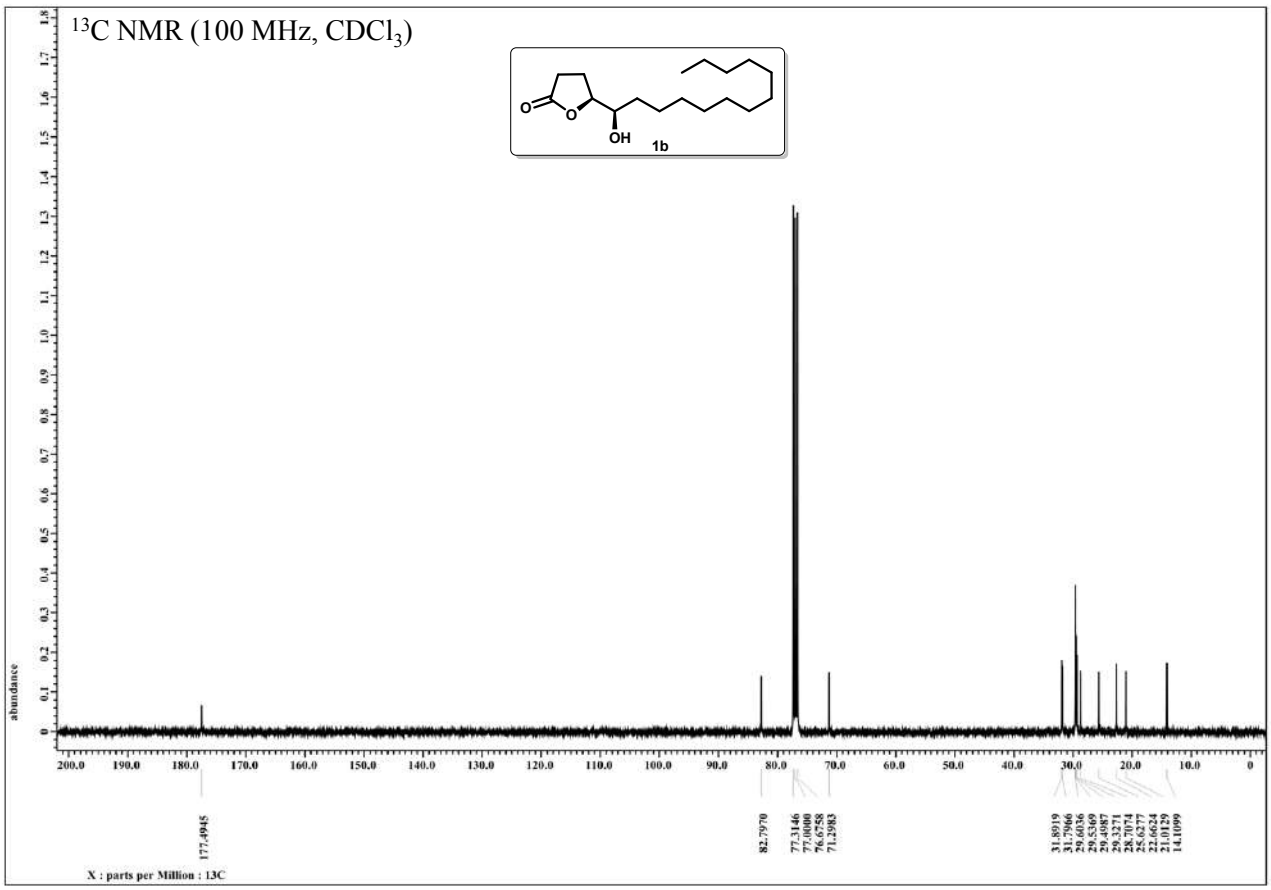
^{13}C NMR (100 MHz, $CDCl_3$)



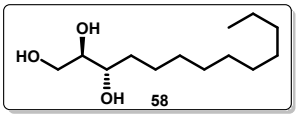
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



^{13}C NMR (100 MHz, $CDCl_3$)



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



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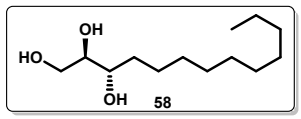
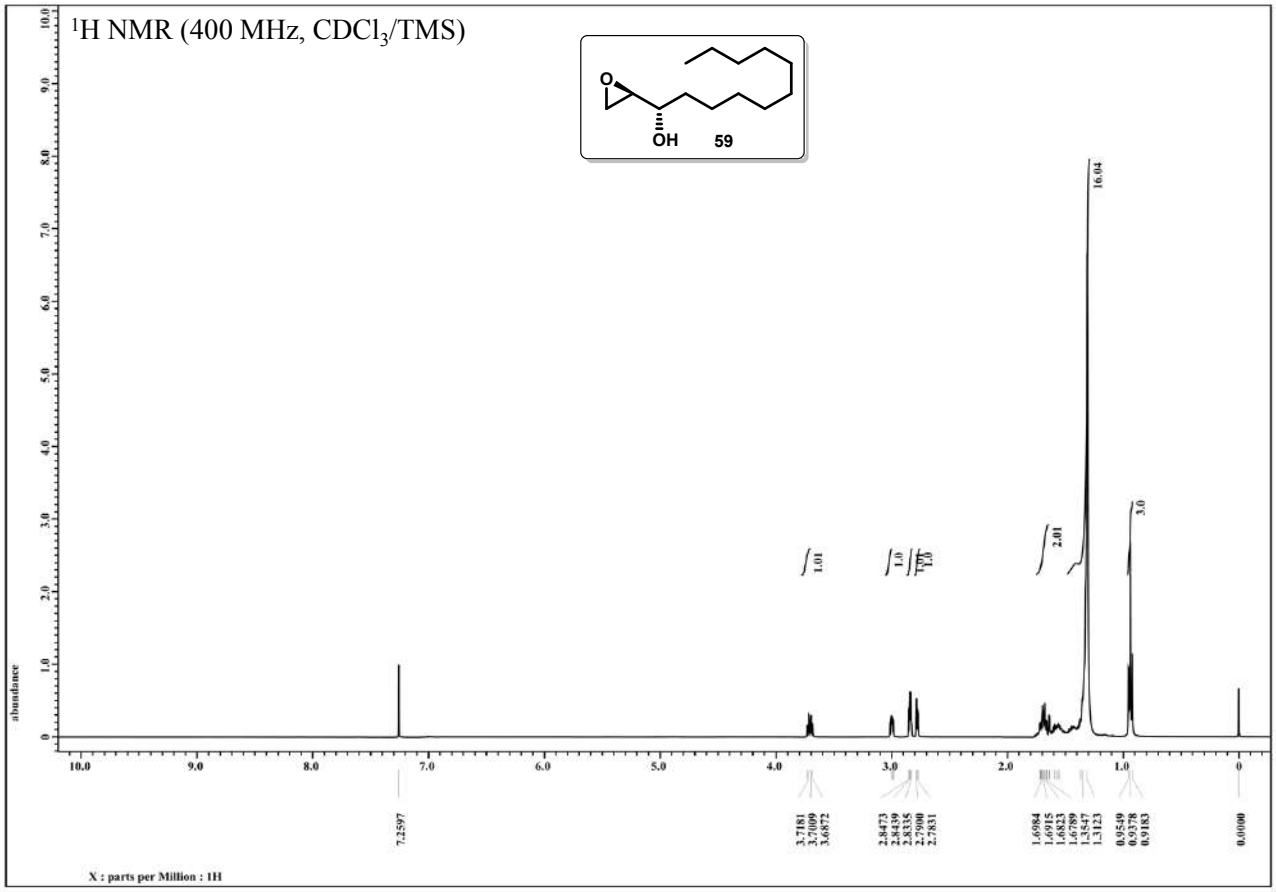


^{1}H NMR (400 MHz, $CDCl_3$/TMS)



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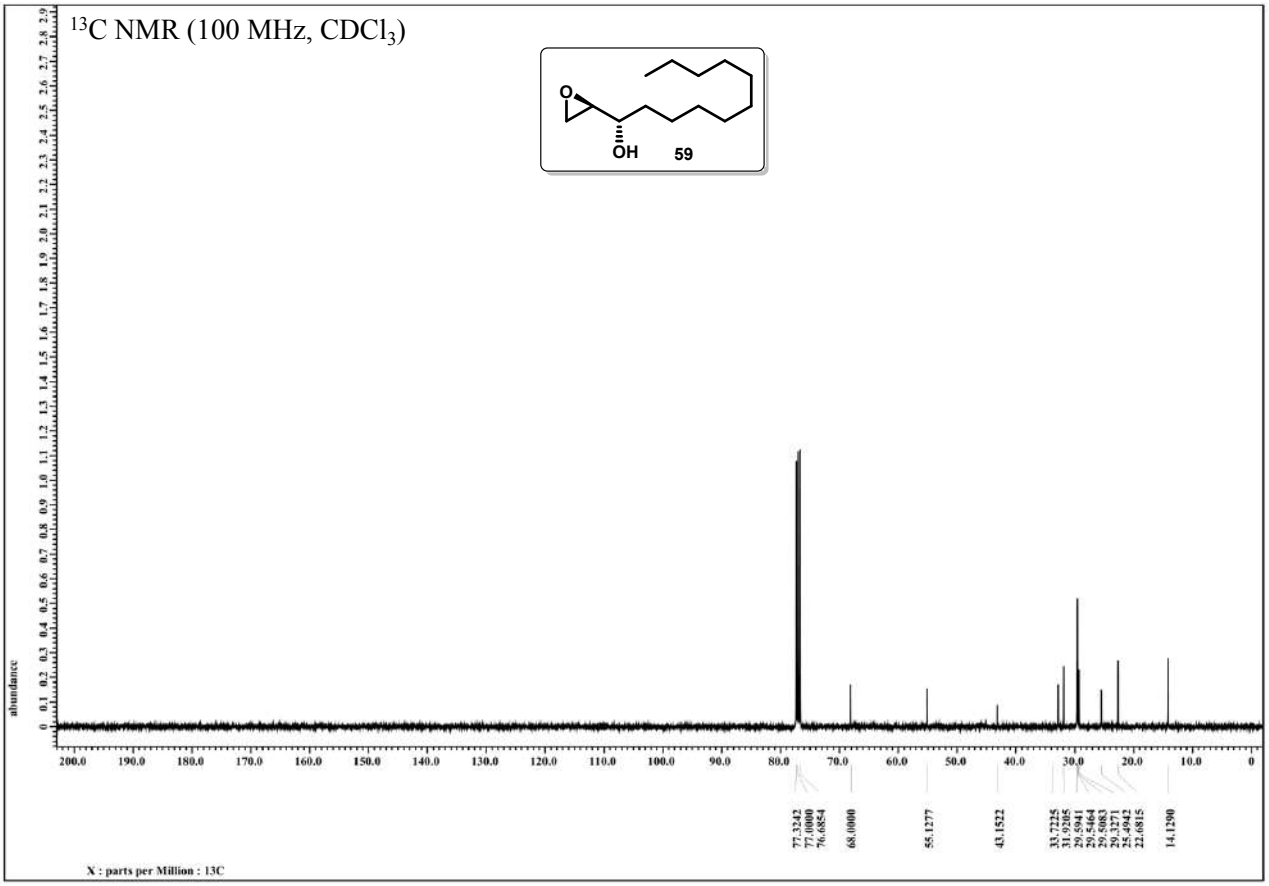

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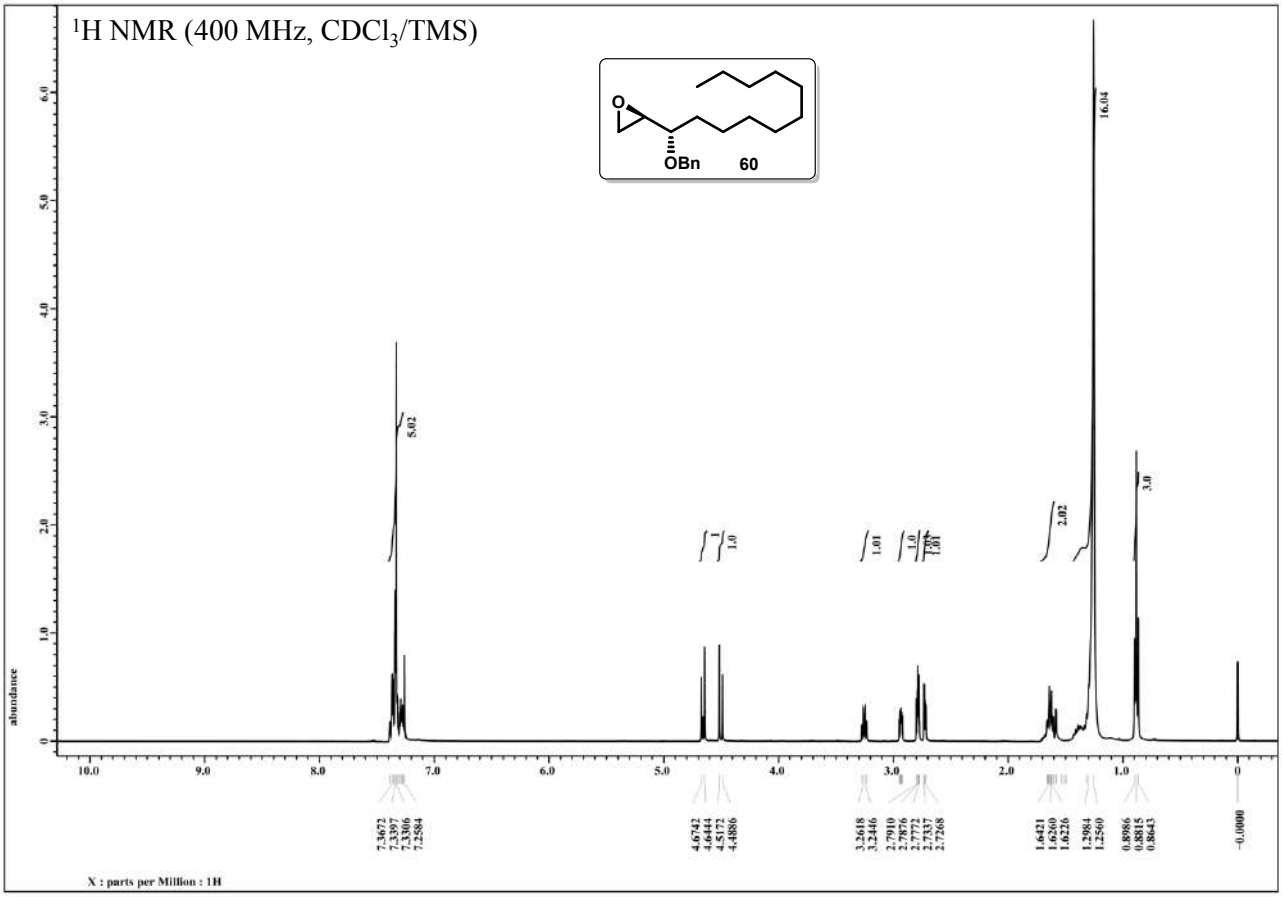
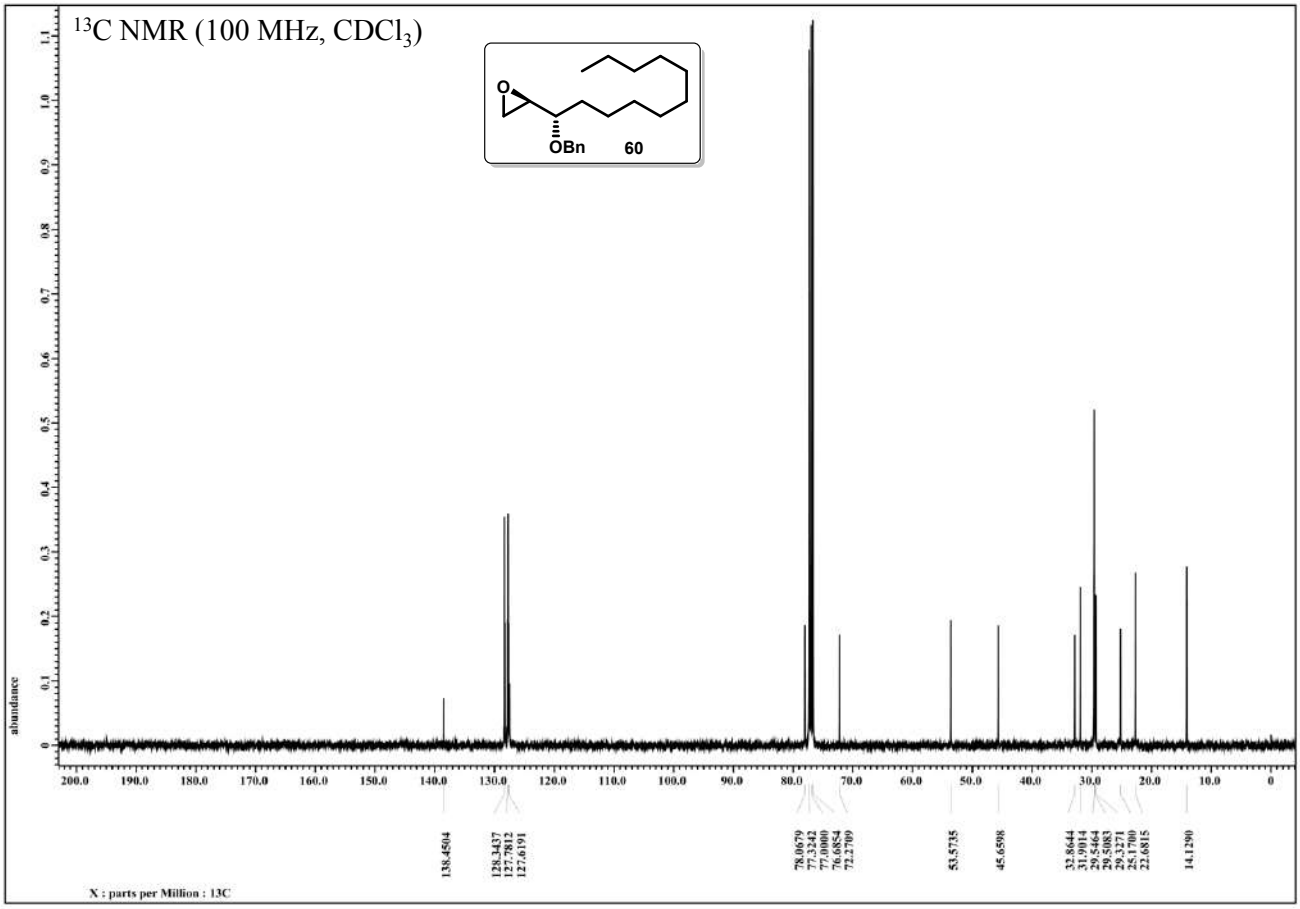
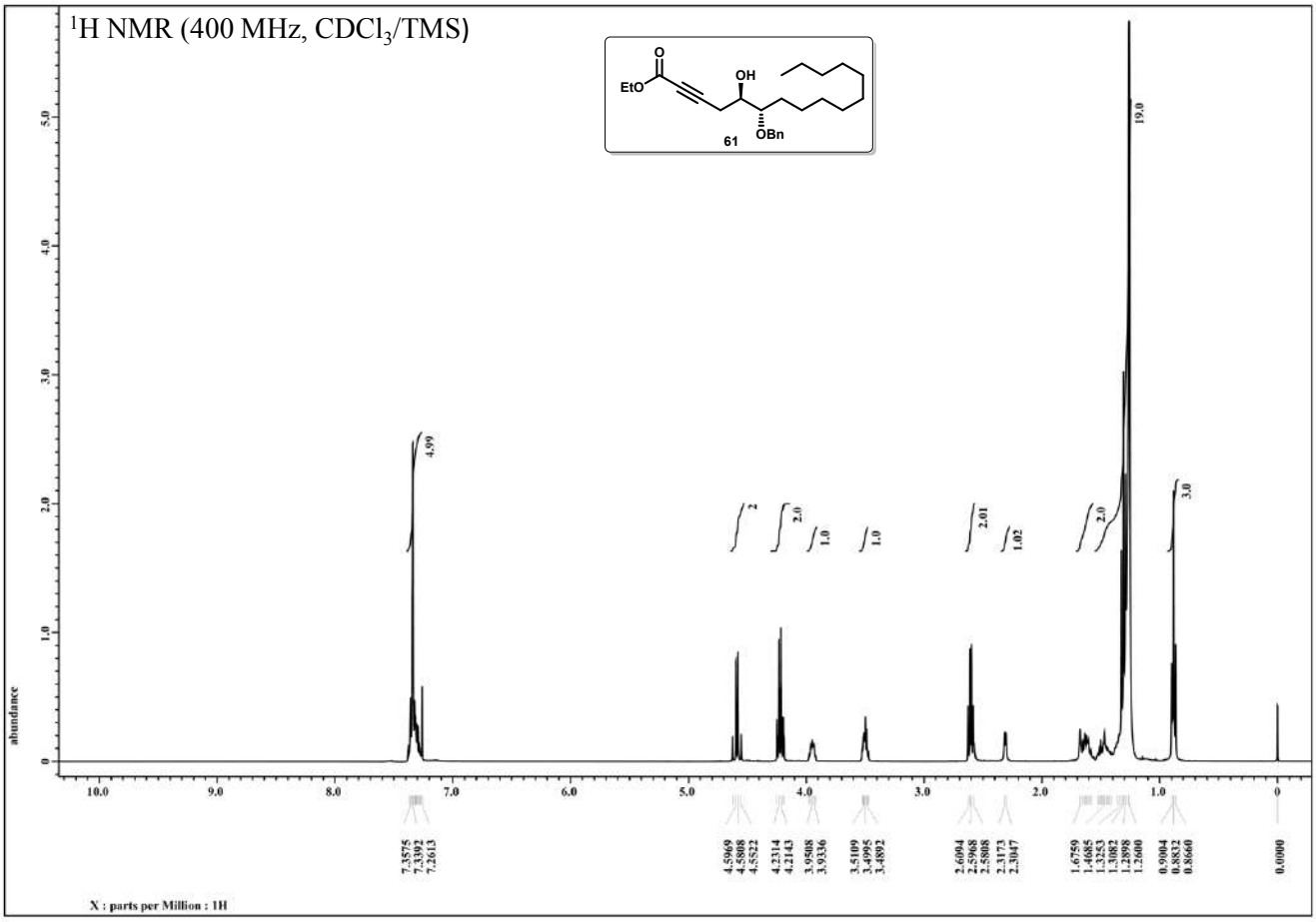


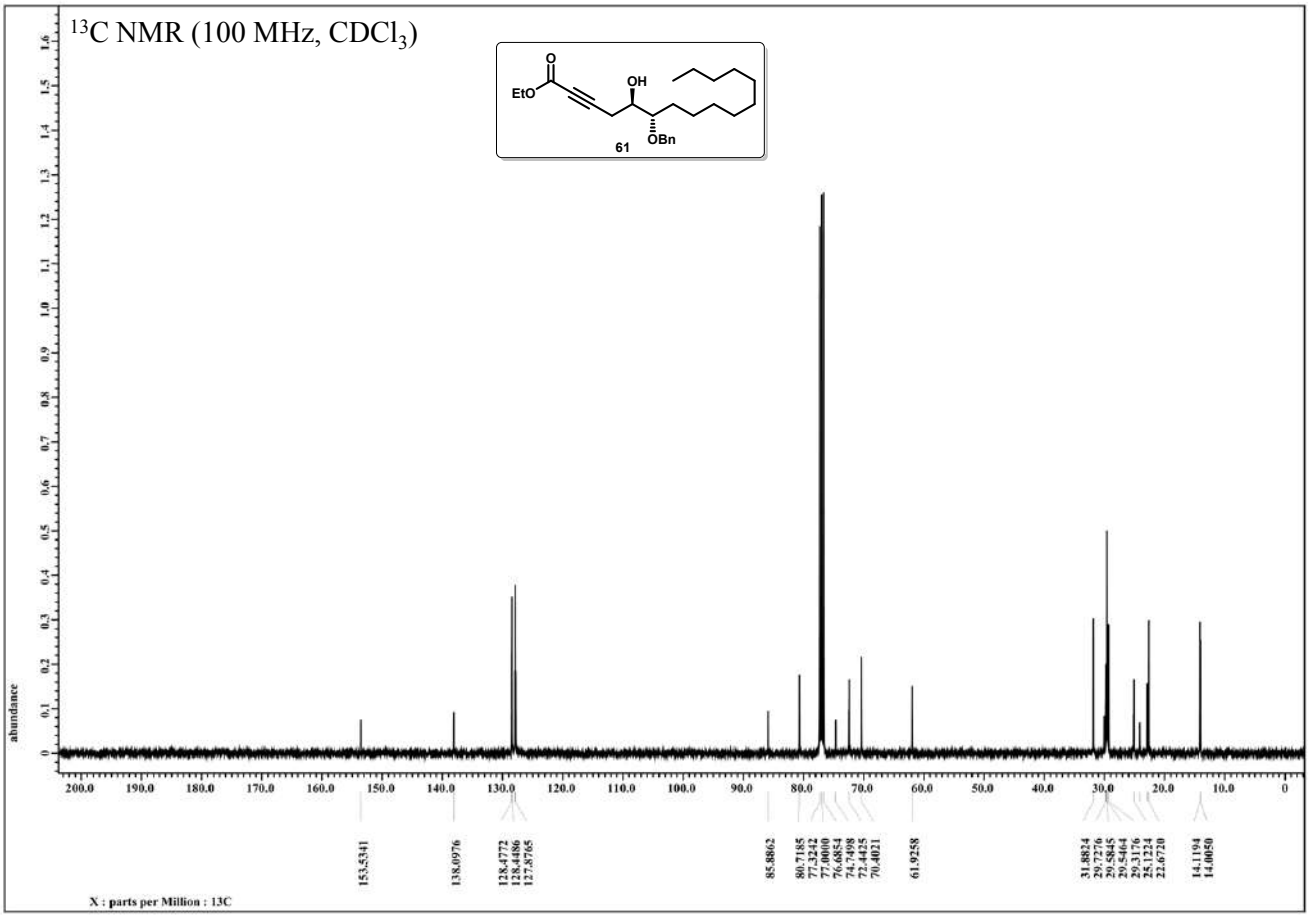
^{13}C NMR (100 MHz, $CDCl_3$)



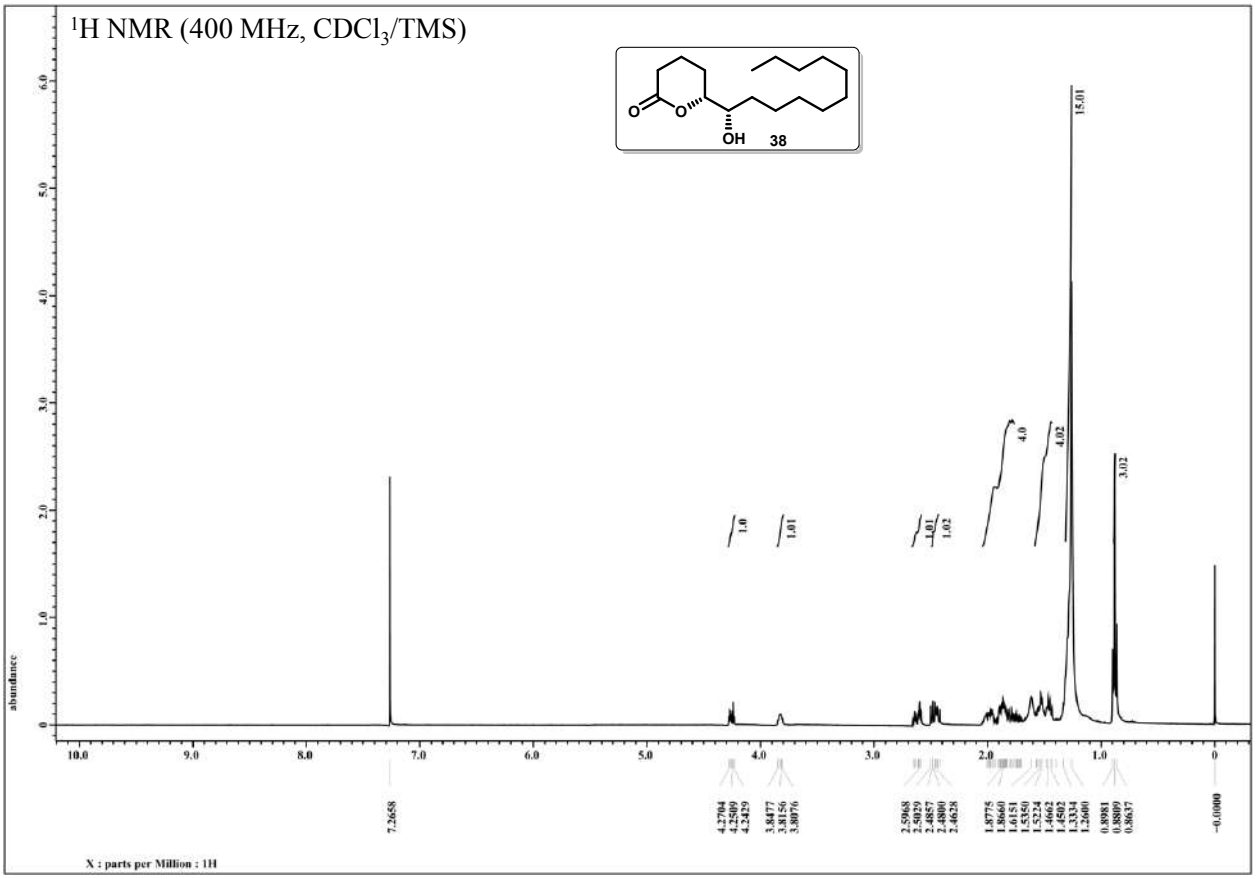
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



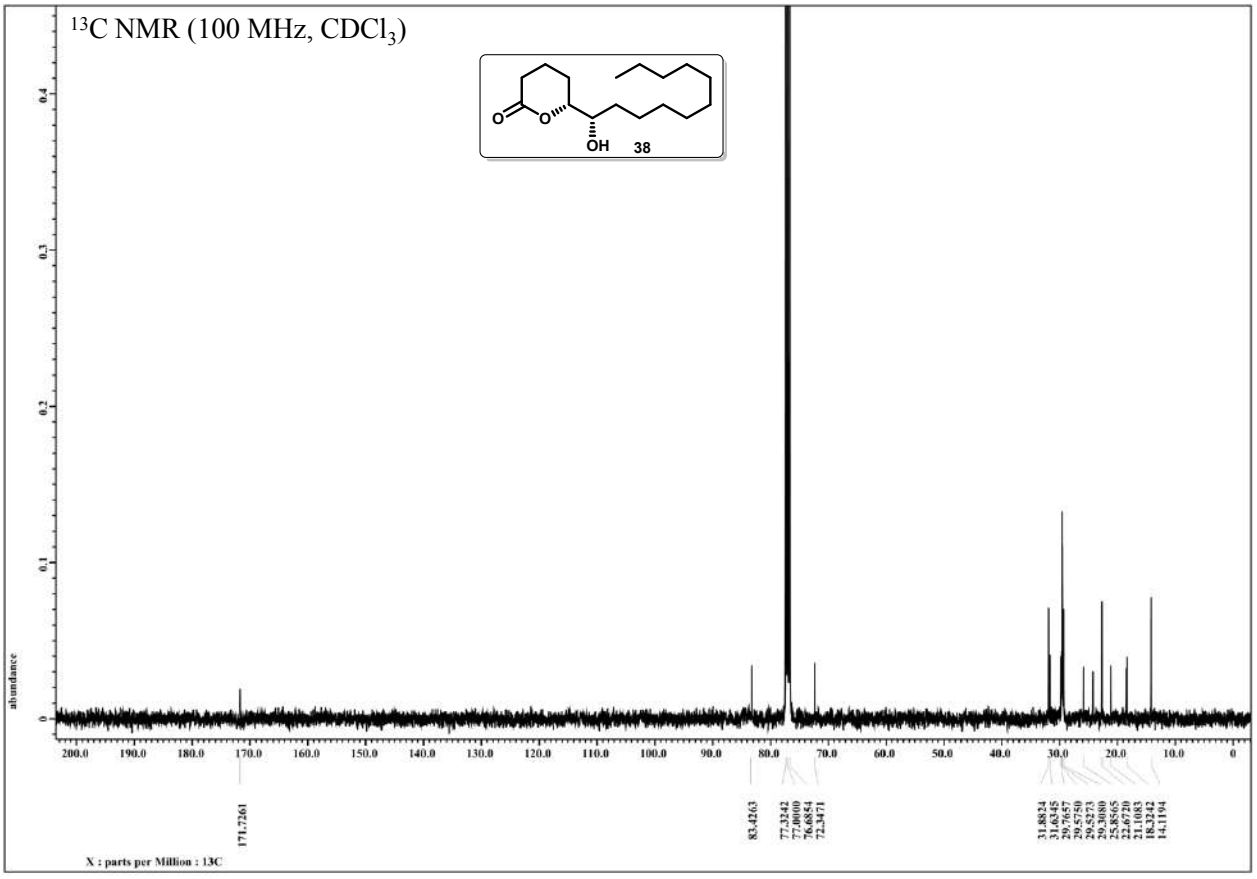
^{13}C NMR (100 MHz, $CDCl_3$)

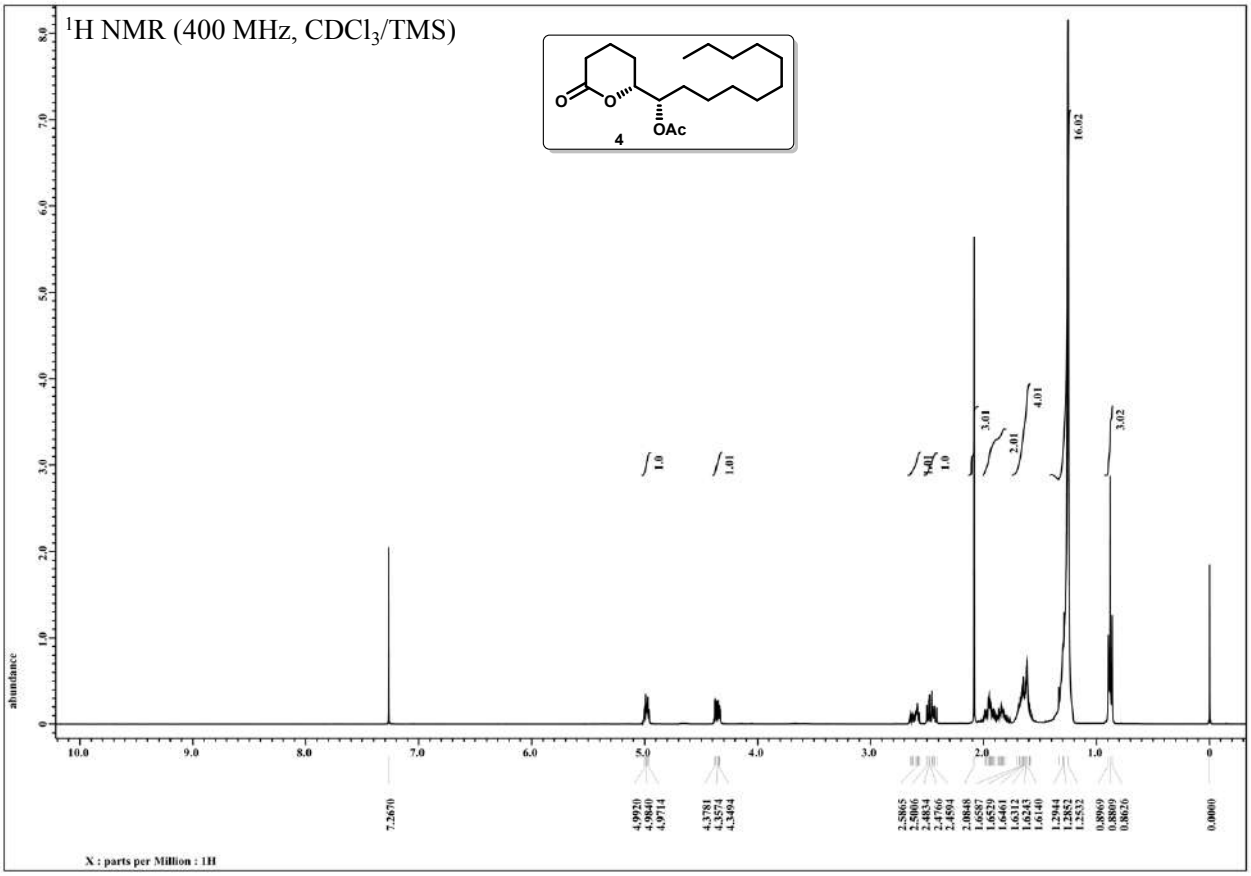


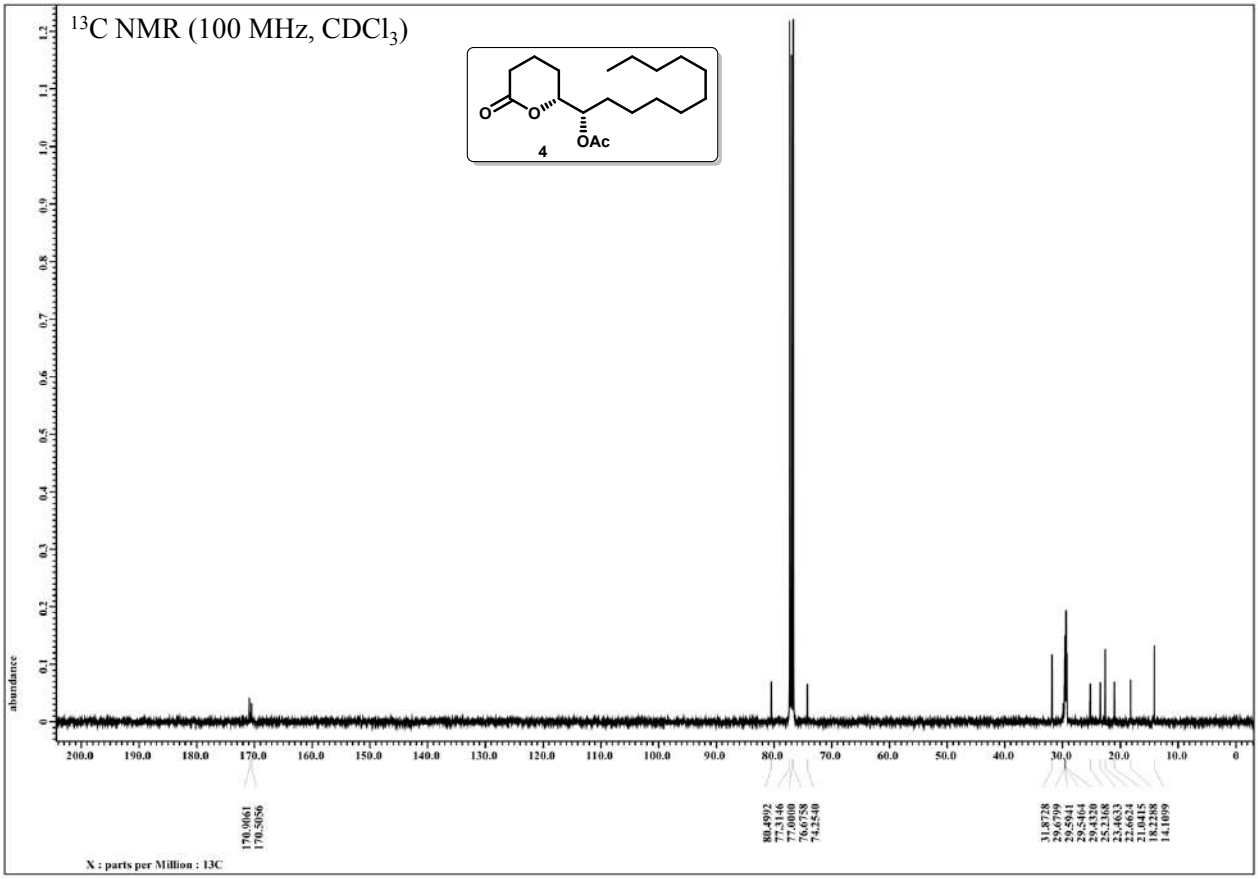
^{1}H NMR (400 MHz, $CDCl_3$/TMS)



^{13}C NMR (100 MHz, $CDCl_3$)




^{1}H NMR (400 MHz, $CDCl_3$/TMS)
4
OAc
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
4
OAc
abundance
X : parts per Million : 13C

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RSC Advances

PAPER

Enantioselective total synthesis of (+)-serinolamide A†‡

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A short and highly efficient enantioselective synthetic approach to (+)-serinolamide A **1** from racemic butadiene monoepoxide as a starting material is described. The synthesis utilizes the palladium catalyzed Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT) and cross-metathesis (CM) as key steps.

Introduction

The endocannabinoid lipid (+)-serinolamide A **1** was isolated from the marine cyanobacteria *Lyngbya majuscula* collected in Papua New Guinea, and represents the newest addition to the known cannabinomimetic natural products.[1] (+)-Serinolamide A **1** showed selectivity for the CB_1 cannabinoid receptor ($K_i = 1.3$ μM, >5-fold) and exhibits moderate agonist effect (Fig. 1).

(+)-Serinolamide A **1** has been a synthetic target of considerable interest due to its long chain fatty acid bonded to a chiral serinol derivative with an array of functionalities. Very recently, Y.-Q. Wang and co-workers reported the first total synthesis of (+)-serinolamide A **1** in nine steps starting from chiral starting material L-serine *via* Kuhn's methylation, Wittig olefination and acid-amine coupling reactions.[2] To avoid possible racemization, Kuhn method[3a] for *O*-methylation reaction is generally performed under neutral conditions involving MeI and Ag_2O, and requires longer reaction time (3–5 days) for better yield.[3b,c] Herein, we wish to report a new, short and highly efficient synthetic strategy for (+)-serinolamide A **1** employing Trost's DYKAT and cross-metathesis as key steps. We have also developed an efficient approach for *O*-methylation employing MeI and NaH as a base which would eliminate the problem of partial racemization and shorten the reaction time.

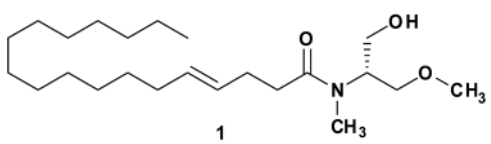
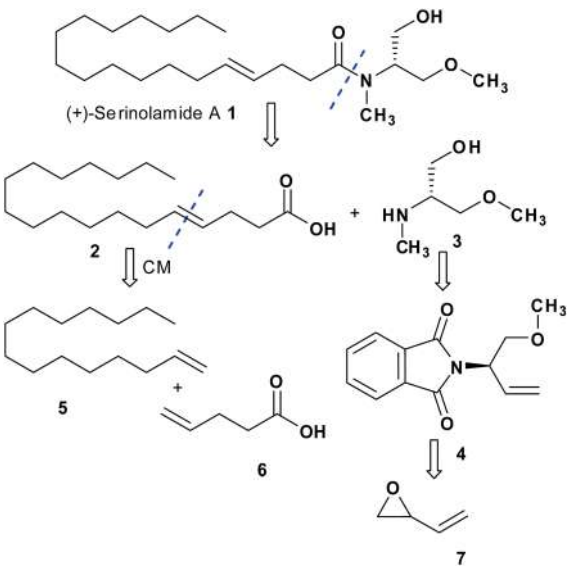


Fig. 1 Structure of (+)-serinolamide A **1**.

Results and discussion

Our retrosynthetic approach for the synthesis of (+)-serinolamide A **1** is outlined in Scheme 1. Accordingly, we envisioned that the (+)-serinolamide A **1** could be obtained from the two fragments, the long chain fatty acid **2** and serinol derivative **3**. The fatty acid fragment **2** could be obtained from pentadec-1-ene **5** and pent-4-enoic acid **6** *via* cross-metathesis. The phthalimide derivative **4** was visualized as a synthetic intermediate from which serinol derivative **3** could be synthesized. Terminal double bond of derivative **4** on standard organic transformation *viz.* phthalimide cleavage, oxidative cleavage and reduction could give the serinol derivative **3**. Enantiopure phthaloyl methyl ether derivative **4** in turn could be easily prepared by the



Scheme 1 Retrosynthetic approach to (+)-serinolamide A **1**.

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† Dedicated to Dr Pradeep Kumar in recognition of his seminal contributions to so many aspects of organic chemistry.

‡ Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra of compounds **1**, **2**, **4** and **8–9**. See DOI: 10.1039/c5ra06609c

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An enantioselective approach to 2-alkyl substituted tetrahydroquinolines: total synthesis of (+)-angustureine†

Yuvraj Garg, Suraksha Gahalawat and Satyendra Kumar Pandey*

A simple and highly efficient synthetic approach to enantiopure 2-alkyl substituted tetrahydroquinoline **1** skeleton from aldehydes as starting materials and its application to the total synthesis of (+)-angustureine **2** is described. Key transformations include proline catalyzed aminoxylation, Corey–Fuchs protocol, Sonogashira coupling and intramolecular Mitsunobu reactions.

Introduction

Quinoline and tetrahydroquinoline alkaloids are found abundantly in nature and most of them exhibit interesting biological activity.[1] Enantiomerically pure 2-alkyl substituted tetrahydroquinoline alkaloids **1** from which angustureine **2**, galipeine **3**, cuspareine **4**, and galipinine **5** were first extracted from the bark of the *Galipea officinalis* Hancock shrub tree found in the mountains of Venezuela (Fig. 1).[2]

These alkaloids exhibits anti-malarial, anti-tuberculous, cytotoxic, and antiplasmodial activities.[3] *Galipea* species have also been used in folk medicine for the treatment of dysentery, dyspepsia, chronic diarrhea, spinal motor nerve problems and fevers.[4] Enantiomerically pure 2-alkyl substituted tetrahydroquinoline alkaloids have synthetic target of considerable interest due to their wide range of important biological activities and with an array of functionalities. Various methods for the synthesis of (+)-angustureine **2** and others **3–5** have been documented in the literature.[5] Very recently, M. Yus and co-workers reported the synthesis of the (+)-angustureine **2** using diastereoselective addition of an allylic indium intermediate to chiral *O*-bromophenyl *N*-*tert*-butylsulfinyl aldimines.[5v] Herein, we wish to report a new, general and highly efficient synthetic approach for enantiopure 2-alkyl substituted tetrahydroquinolines **1** and its application to the total synthesis of (+)-angustureine **2** employing proline catalyzed asymmetric aminoxylation, Corey–Fuchs protocol, palladium catalyzed Sonogashira coupling, and Mitsunobu reaction as key steps.

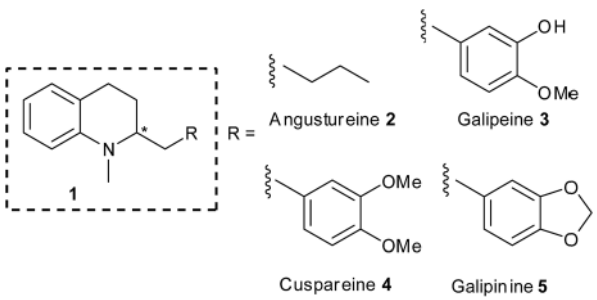

Fig. 1 Some naturally occurring 2-alkyl substituted tetrahydroquinoline alkaloids.

Results and discussion

Our retrosynthetic approach for the synthesis of 2-alkyl substituted tetrahydroquinolines **1** including (+)-angustureine **2** is outlined in Scheme 1. We envisioned that the aryl nitro-alkyne derivative **6** from which 2-alkyl substituted tetrahydroquinolines **1** and (+)-angustureine **2** could be synthesized *via* hydrogenation, Mitsunobu intramolecular ring closer in S_N2 fashion followed by alkylation. The aryl nitro-alkyne derivative **6** could be obtained from the monoprotected alkyne derivative **7** through palladium catalyzed Sonogashira coupling reaction with suitable aromatic nitro-halides. The alkyne derivative **7** in turn could be obtained by means of Corey–Fuchs protocol from the aldehyde synthesized from oxidation of monoprotected alcohol **8**. Enantiomerically pure monoprotected alcohol **8** could be obtained from the commercially available aldehydes **9** *via* proline catalyzed aminoxylation followed by standard organic transformation. The (*S*)- and (*R*)-configuration of the 2-alkyl substituted tetrahydroquinolines **1** and (+)-angustureine **2** could be manipulated by simply changing the D-proline and L-proline, respectively, during organocatalytic step.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **2** and **11–16**. See DOI: 10.1039/c5ra05987a

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ASIAN JOURNAL OF ORGANIC CHEMISTRY Communication

Total synthesis (+)-Petromyroxol

Total Synthesis of (+)-Petromyroxol, a Marine Natural Product

Suraksha Gahalawat, Yuvraj Garg, and Satyendra Kumar Pandey*[a]

Dedicated to Professor Ganesh Pandey in recognition of his seminal contributions to so many aspects of organic chemistry.

Abstract: An efficient total synthesis of (+)-petromyroxol, a marine natural product, is described. The synthesis utilizes the Sharpless asymmetric dihydroxylation (AD), intramolecular S_N2 cyclization and stereoselective Grignard reaction as key steps.

The 2,5-disubstituted-3-oxygenated THF motif is found abundantly in biologically active natural products.[1] Petromyroxol (**1**), *iso*-petromyroxol (**2**),[2] *trans*-(−)-kumausyne (**3**), *trans*-(+)-deacetylkumausyne (**4**),[3] and anthelmintic oxylipid (**5**),[4] marine natural products, are few examples of dihydroxytetrahydrofurans from the acetogenin family[5] (Figure 1).

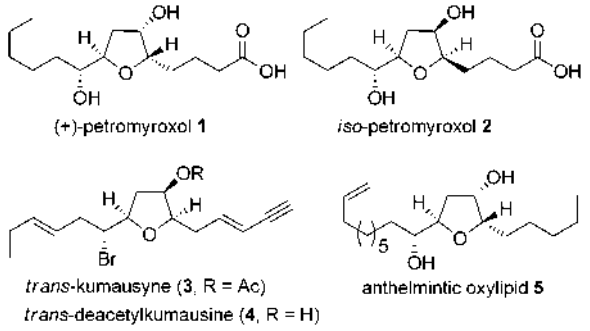
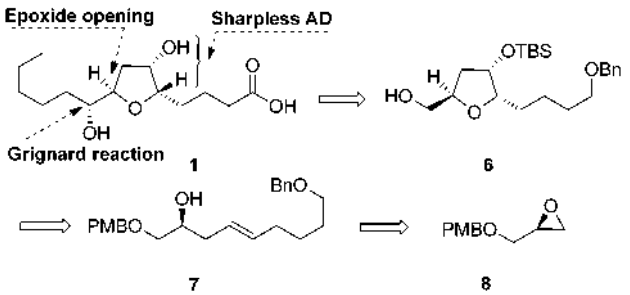


Figure 1. Some structures of the acetogenin family natural products.

The dihydroxylated THF enantiomers (+)-petromyroxol[2a] and *iso*-petromyroxol[2b] were recently isolated by Li and co-workers from water conditioned with larvae of the sea lamprey, *Petromyzon marinus* L., which is the first example of dihydroxylated THF-containing metabolites isolated from a vertebrate.[2] The sea lamprey is an aggressive predator of trout populations, and is found in the northern Atlantic Ocean along shores of North America and Europe, on the shores of the Great Lakes, and in the western Mediterranean Sea.[6] Thus, there has been an extensive investigation on various aquatic pest-control and aquatic pheromones, which is ongoing.[7] (+)-Petromyroxol has been a synthetic target of considerable interest due to its potent olfactory activity in the concentration range of 0.01–1 μM and its array of functionalities. The absolute configuration of the four stereogenic centers of (+)-petromyroxol and *iso*-petromyroxol were determined by Li and co-workers with the help of 2D NMR studies, compared with known substituted THFs, and Mosher ester analysis. To the best of our knowledge, until now only two syntheses of (+)-petromyroxol have been documented in the literature.[8] The first, reported by Boyer, involved the construction of the THF motif via diastereoselective, rhodium-catalyzed denitrogenation and rearrangement of the 1-sulfonyl-1,2,3-triazole into a *trans*-2,5-disubstituted dihydrofuran-3-one as key steps.[8a] More recently, Mullapudi and Ramana disclosed the multistep synthesis of **1** from a chiral pool building block.[8b] Therefore, it is highly desirable to develop a general and enantiopure synthetic route that provides a common pivotal intermediate from which 2,5-disubstituted-3-oxygenated THF motifs with desired stereochemical variations can be synthesized. Herein, we report a synthetic approach for the total synthesis of (+)-petromyroxol employing Sharpless asymmetric dihydroxylation (AD), intramolecular S_N2 cyclization, and stereoselective Grignard reaction as the key steps.

Our synthetic approach for the synthesis of (+)-petromyroxol was envisioned via the retrosynthetic route as shown in Scheme 1. The 2,5-disubstituted-3-oxygenated THF derivative **6** was visualized as a synthetic intermediate from which (+)-petromyroxol could be synthesized via oxidation of the free alcohol followed by stereoselective Grignard reaction and standard organic transformations. The THF derivative **6** in turn could be



Scheme 1. Retrosynthetic approach for (+)-petromyroxol (**1**). Bn = benzyl. TBS = *tert*-butyldimethylsilyl.

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Organic & Biomolecular Chemistry

PAPER

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Total synthesis of haliclamide†

Suraksha Gahalawat and Satyendra Kumar Pandey*

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A stereoselective approach for the synthesis of haliclamide **1**, a marine natural product, has been developed. The notable features of our synthesis include MacMillan cross aldol, Mitsunobu inversion, Yamaguchi–Hirao alkylation, Steglich esterification and macrolactamization reactions and the Corey–Fuchs protocol as the key steps.

Introduction

A large number of natural products containing the cyclodepsipeptide nucleus have been isolated from sponges of marine origin and received considerable attention because of their potent properties such as insecticidal, anthelmintic, antiviral, antimicrobial, antitumor, anti-inflammatory and immunosuppressive activities.[1] In 2001, Randazzo and co-workers reported the isolation of a novel macrocycle, haliclamide **1** from the marine sponge *Haliclona* sp. collected in the waters off the Vanuatu island.[2] Haliclamide **1** has been shown to possess potent *in vitro* antitumor activity against the human bronchopulmonary non-small cell lung carcinoma cell line NSCLC-N6 {IC_{50} = 4 μg mL^{-1} (8.7 μM)}.

Architecturally, haliclamide **1** (Fig. 1) is a 16-membered hybrid macrocycle bearing four stereogenic centers and possesses modified amino acids including the featured *N*-methyl-L-phenylalanine (*N*-Me-L-Phe), 5-hydroxy-octanoic acid (HOA) and 6-amino-7-hydroxy-2-methylheptanoic acid (AHMA) moieties connected by ester and amide linkages. The absolute configuration of the two chiral centers at C2 and C14 was resolved by Randazzo and co-workers with the help of 2D NMR analysis and the Yamaguchi method,[3] however the remaining two centers C9 and C20 were assigned by Altmann and co-workers by chemical synthesis and NMR studies.[4] To the best of our knowledge, until now only one synthesis of haliclamide **1** has been reported by Altmann and co-workers since the time of its isolation, employing ring closing metathesis (RCM), Brown's asymmetric allylboration and asymmetric allylation of oxazolidinone as the key steps. Haliclamide **1** has been a synthetic target of considerable interest due to its potent antitumor activity and with an array of functionalities. As part of our ongoing program towards the syntheses of biologically active natural products,[5] we became interested in developing a simple and flexible route to haliclamide **1**. Herein, we report a new synthesis of haliclamide **1** employing proline catalyzed enantioselective MacMillan's cross aldol reaction of α-oxyaldehyde, Yamaguchi–Hirao alkylation of oxirane, Mitsunobu inversion, and Steglich esterification reactions and the Corey–Fuchs protocol as the key steps.

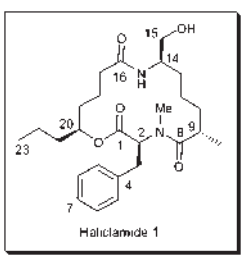

Fig. 1 Structure of haliclamide **1**.

Results and discussion

Our retrosynthetic analysis for the total synthesis of haliclamide **1** is displayed in Scheme 1. We anticipated the construction of the targeted molecule **1** from ester **2** *via* hydrogenolysis followed by intramolecular macrocyclization using amide coupling as one of the key steps. The precursor **2** could be accessed from acid **3** and alcohol **4** by intermolecular Steglich esterification. The alcohol **4** in turn could be synthesized from easily accessible enantiopure (*S*)-1,2-epoxypentane *via* Yamaguchi–Hirao alkylation. The acid fragment **3** could be assembled from the coupling partners *N*-Me-L-Phe derivative **5** and fragment **6** *via* peptide coupling. We envisaged that fragment **6** would serve as the key synthetic intermediate in this approach and would be prepared by the Yamaguchi–Hirao alkylation of (*S*)-silyl protected glycidyl ether **7** with lithioacetylides **8** followed by Mitsunobu inversion allowing the for-

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†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **4**, **6**, **8**, **9** and **12–16**. See DOI: 10.1039/c6ob01775d

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Asymmetric total synthesis of phomonol

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Natural product
Sharpless AD
Reductive etherification
Wacker oxidation

ABSTRACT

An efficient asymmetric total synthesis of phomonol **1** is presented, starting from (*S*)-1,2-epoxypentane. The synthesis features Sharpless asymmetric dihydroxylation (AD), diastereoselective reductive etherification and Wacker oxidation as key steps.

Introduction

The functionalyzed tetrahydropyran moiety is a common motif present in a myriad of bioactive natural products and medicinal compounds.[1] In 2010, Shen and co-workers[2] reported the isolation of a novel 2,6-*cis*-disubstituted tetrahydropyran, phomonol **1** from the endophytic fungal strain *Phomopsis* sp. A 123 (Fig. 1). The above specific endophyte fungal strain was obtained from the leaves of the mangrove species *Kandelia candel* collected from the Fugong Mangrove Conservation Area in Fujian, China. Architecturally, phomonol **1** and *epi*-phomonol **2** are 2,3,4,6-tetrasubstituted pyran embedded with four stereogenic centers. Its chemical structure was deduced by a combination of detailed NMR studies including 1D- and 2D-NMR, HR-Q-TOF mass spectrometry and revised structure has been confirmed by total synthesis.[3d]

Intrigued by the biological activities and unique structural features of tetra substituted tetrahydropyran, hitherto, three total syntheses of phomonol **1**[3b–d] and one total synthesis of *epi*-phomonol **2**[3a] have been documented.[3] All the reported synthesis for phomonol **1** involved intramolecular 6-*exo*-trig oxa-Michael reaction as a common step for the construction of 2,6-*cis*-substituted tetrahydropyran ring. As part of our ongoing program towards the syntheses of biologically active natural products,[4] we became interested in developing a simple and flexible route to phomonol **1**. Herein, we are reporting a new, highly efficient synthesis of phomonol **1** that utilizes Sharpless AD, reductive diastereoselective cyclization and Wacker oxidation as key steps.

Results and discussion

Our retrosynthetic approach to phomonol **1** is depicted in Scheme 1. Retrosynthetically, target molecule **1** was envisioned to be obtained from precursor **3** *via* Et_3SiH/TMSOTf-mediated reductive etherification reaction followed by Wacker oxidation. Allylic ketone derivative **3** was conceived to be derived from ester derivative **4** *via* Weinreb amide formation and subsequent treatment with allyl Grignard reagent. The ester derivative **4** in turn could be obtained from **5** involving Sharpless AD followed by acetonide protection. The α,β-unsaturated ester **5** could be constructed from commercially available enantiomerically pure (*S*)-1,2-epoxypentane **6** through regioselective vinyl Grignard reaction, oxidative cleavage followed by 2C-Wittig olefination. Alternatively, epoxide **6** could be obtained by hydrolytic kinetic resolution (HKR) using Jacobsen's HKR methodology.[5]

Synthesis of phomonol **1** as displayed in Scheme 2, commenced with the commercially available (*S*)-1,2-epoxypentane **6** which was subjected to copper-catalyzed (CuI) regioselective opening with the vinyl magnesium bromide and further treatment of the newly generated secondary alcohol with TBSCl in the presence of

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