DEVELOPMENT OF NEW SYNTHETIC APPROACHES TOWARDS THE TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS

A thesis submitted in fulfillment of the

requirement of the degree of

Doctor of Philosophy

By

Anju

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Under the supervision of

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Certificate

This is to certify that thesis entitled "**DEVELOPMENT OF NEW SYNTHETIC APPROACHES TOWARDS THE TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS**" being submitted by Anju in the fulfillment of the requirement for the award of the Degree of Doctor of Philosophy to the School of Chemistry and Biochemistry, Thapar Institute of Engineering & Technology, 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 "**DEVELOPMENT OF NEW SYNTHETIC APPROACHES TOWARDS THE TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS**" in partial fulfillment of the requirement for the award of the Degree of Doctor of Philosophy, School of Chemistry and Biochemistry, Thapar Institute of Engineering & Technology, Patiala is an authentic record of my own work carried out under the supervision of Dr. Satyendra Kumar Pandey, Professor, Department of chemistry, Banaras Hindu University, Varanasi, Uttar Pardesh and Dr. Ranjana Parkash, Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering & Technology, Patiala, India. The matter embodied in this thesis has not been submitted in part or full to any other university or institute for the award of any degree in India or abroad.

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Dedicated
To My
Beloved
Family

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Anju

Anju

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CONCLUSIONS AND FUTURE SCOPE.

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
DCM	-	Dichloromethane
$(DHQ)_2PHAL$	-	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
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N, N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
de	-	Diastereomeric excess
er	-	Enantiomeric ratio
eq.	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl

Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
g	-	Grams
h	-	Hours
Hz	-	Hertz
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmol	-	Millimole
Ms	-	Methanesulfonyl
Me	-	Methyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
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 "**DEVELOPMENT OF NEW SYNTHETIC APPROACHES TOWARDS THE TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS**" is divided into five chapters.

Chapter 1: A brief account of Sharpless asymmetric dihydroxylation (AD) and organocatalyzed Michael addition reactions.

Chapter 2: Enantioselective general approach for the synthesis of muscarine alkaloid and its application to the asymmetric synthesis of *epi*-muscarine.

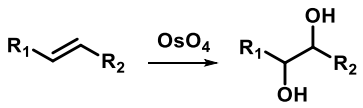
Chapter 3: Enantioselective novel approach for multi-functionalized γ-butyrolactone paraconic acids and its application to the total synthesis of (+)-nephrosteranic acid.

Chapter 4: An attempt towards the total synthesis of (-)-trachelanthamidine.

Chapter 5: Conclusions and future scope.

Chapter 1: A brief account of Sharpless asymmetric dihydroxylation (AD) and organocatalyzed Michael addition reactions.

Nature stands as an inexhaustible source of novel chemotypes & pharmacophores and has been a source of medicinal agents for thousands of years. Moreover, an impressive number of modern drugs find their origin in natural products. Nature provides an enormous number of enantiomerically pure compounds, but again a few of them is either not easily isolated or not available in useful amounts. Asymmetric syntheses evolve as a key process in modern chemistry and are particularly important in the field of pharmaceuticals, as it allows the synthesis of enantio- and diastereomerically pure natural products.

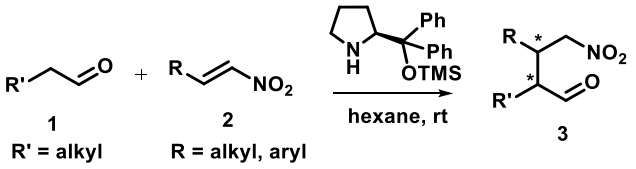


The osmium tetroxide metal-mediated Sharpless AD[1] has emerged as a powerful tool for asymmetric synthesis. Here a coordinating ligand fastened the metal catalyzed process and

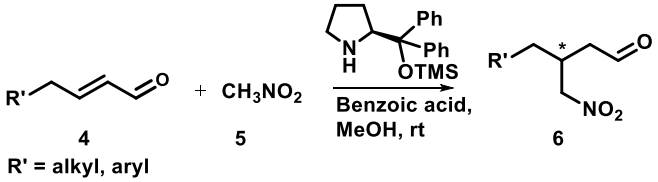
ligand acceleration. This causes the reaction to be funneled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo-, regio- and stereoselectivity of the above reaction in a profound way. Most commonly used chiral ligands for Sharpless AD are $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL.

Organocatalysis is an arising and most powerful field in asymmetric synthesis. Proline catalysed Michael addition[2] reaction is a key organic transformation to generate the chiral centre.

Hayashi and co-workers carried out organocatalyzed asymmetric Michael addition reaction of aldehydes **1** with nitroalkenes **2** using the catalyst diphenylprolinol silyl ether to afford the nitro aldehydes **3** with good enantiopurity.[2a]



Hayashi and co-workers described a synthetic methodology to form nitroaldehyde adduct **6** in the presence of catalytic amount of TMS-prolinol from reaction of nitromethane **5** to acceptor *trans*-olefinic aldehydes **4** in great yield (up to 94%) and high enantioselectivity (up to 95% *ee*).[2b]



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

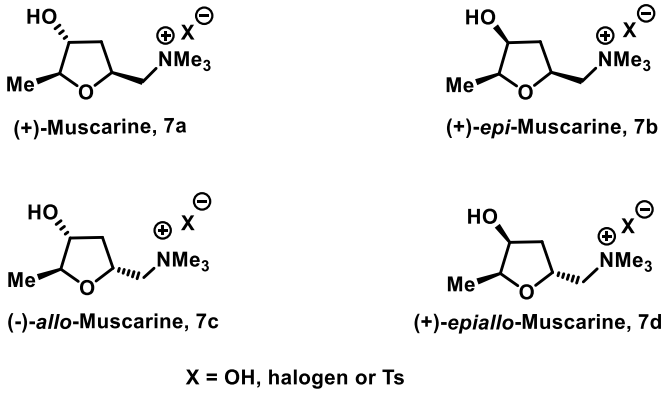
Objectives:

1. Enantioselective total synthesis of *epi*-muscarine employing Sharpless AD.
2. Organocatalysed and chiral catalyst based total synthesis of bioactive natural products.
3. Characterization of compounds using ^{1}H, ^{13}C NMR, IR optical rotation and HRMS analysis.

Chapter 2: Enantioselective general approach for the synthesis of muscarine alkaloid and its application to the asymmetric synthesis of *epi*-muscarine.

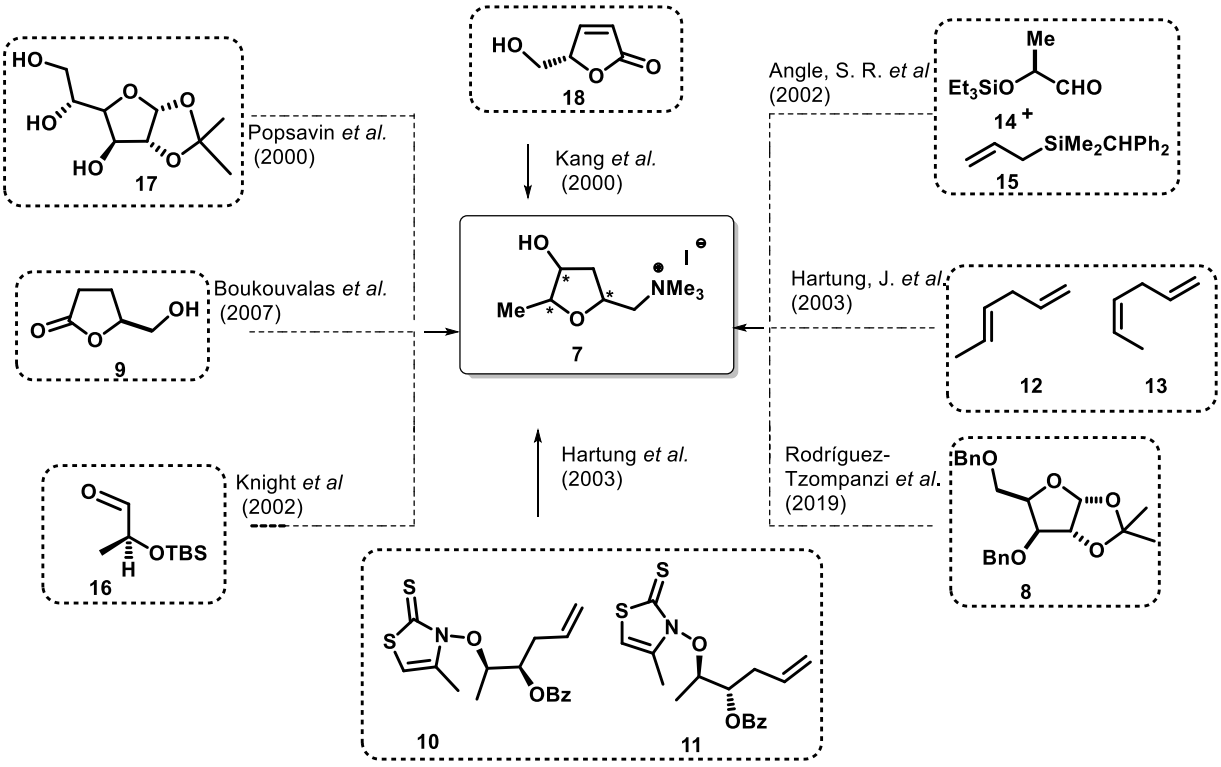
Introduction:

The venomous alkaloids (+)-(2*S*,3*R*,5*S*)-Muscarine **7a**, (+)-(-2*S*,3*S*,5*S*)-*epi*-Muscarine **7b**, (+)-(2*S*,3*S*,5*R*)-*epiallo* muscarine **7c** and (-)-(2*S*,3*R*,5*R*)-*allo*-muscarine **7d** were isolated from numerous species of mushrooms, e.g. *Amanita muscaria* (fly agaric) and certain species of *Clitocybes* and *Inocybes*.[3a] Muscarine acts as a selective agonist of the acetylcholine receptor (muscarinic acetylcholine receptors) on smooth muscles of the eye exocrine glands, gastrointestinal tract, heart and have a wide range of other therapeutic properties.



Literature Review:

In 2019 Rodríguez-Tzompanzi and co-workers[3a] reported the total synthesis of (+)-muscarine **7a** from 1,2-*O*-isopropylidene-D-xylofuranose derivative **8** employing blue light photoredox decarboxylation and tin-free Barton-McCombie reactions as key steps.

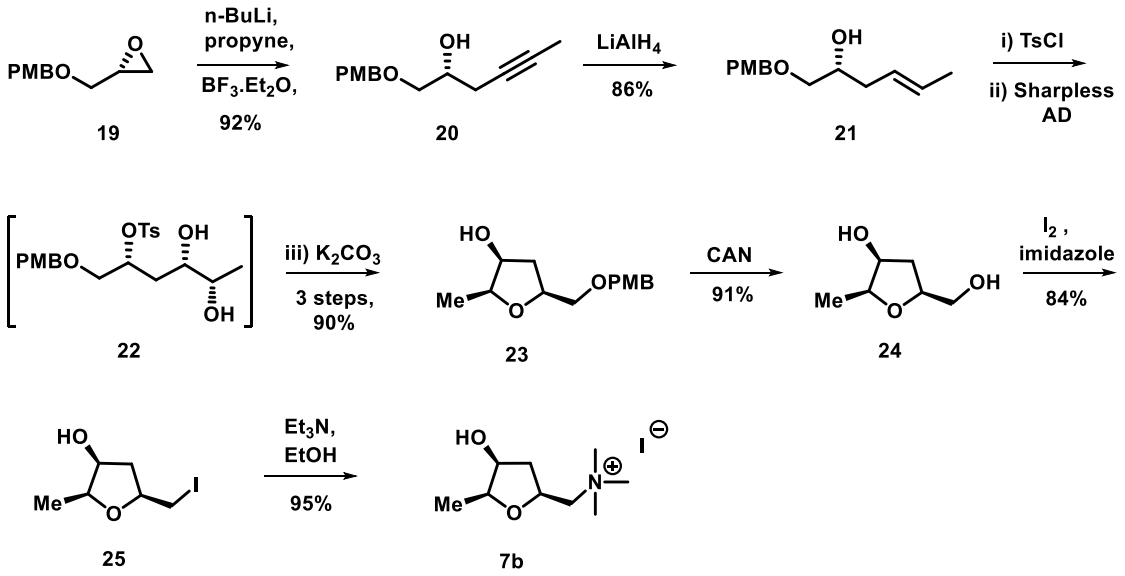


J. Boukouvalas *et al.* [3b] in 2007 described the stereoselective synthesis of (+)-muscarine iodide **7a** from (*S*)-γ-hydroxymethyl-γ-butyro lactone **9** employing hydroboration oxidation reaction as principal step. In 2003 Hartung and co-workers[3c] disclosed an elegant synthesis of (+)-*epi*-muscarine **7b** and its analogues (+)-muscarine **7a**, (+)-*epiallo* muscarine **7c** and (-)-*allo*-muscarine **7d** employing alkoxyl radical cyclization reaction as pivotal step and (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **10** and its (2*R*,3*R*)-diastereomer **11** as starting materials. Again, Hartung *et al* [3d] put forward the enantioselective synthesis of muscarine alkaloids (+)-muscarine **7a**, (+)-*epi*-muscarine **7b**, (+)-*epiallo* muscarine **7c** and (-)-*allo*-muscarine **7d** in 2003 from (*Z*)-1,4-hexadiene **13** and its (*E*)-configured isomer **12** using asymmetric dihydroxylation and diastereoselective bromoetherification as major steps. Further Angle and co-workers[3e] in 2002 reported the formal stereoselective synthesis of (-)-*allo*-muscarine **7c** and (+)-*epi*-muscarine **7b** using [3+2]-cycloaddition as the key step employing *R*-triethylsilyloxy aldehyde **14** and allylsilanes **15** as starting material. D. W. Knight and co-workers[3f] described the formal synthesis of muscarine **7a** employing 5-*endo*-trig iodocyclisation as the pivotal step in 2002. For this synthesis *O*-silyl aldehyde **16** was used as starting material. V. Popsavin and co-workers[3g] described the total synthesis of (+)-*epi*-muscarine **7b** and (+)-muscarine **7a** from a chiral precursor D-glucose **17** employing S_N2 cyclization and hydrogenation as key steps in 2000. K. Kang *et* al.[3h] in 2000 disclosed the synthesis of (+)-muscarine **7a** from (*S*)-(−)-5-hydroxy-2(5*H*)-furanone **18** using a long pathway to give an easy access to wide variety of its analogues.

Present work:

The synthesis of *epi*-muscarine **7b** started from the readily available (*R*)-PMB (*p*-methoxybenzyl) glycidyl ether **19** which was prepared by known literature procedure in 95% yield ($[\alpha]_D^{25}$ +3.18 (*c*, 1.50 in $CHCl_3$) {lit.[4] $[a]_D^{25}$= + 3.2 (*c*, 1.50, $CHCl_3$)}. The (*R*)-PMB glycidyl ether **19** on treatment with propynyl lithium in the presence of $BF_3.Et_2O$ at -78 °C furnished the alkyne alcohol **20** in 92% yield. Our initial attempt to reduce the alkyne derivative **20** with $LiAlH_4$ in THF as solvent at various temperatures was found to be sluggish. In view of the less reactivity of alkyne derivative **20** we decided to take diglyme and THF as solvents due to their higher boiling point and then carried out the $LiAlH_4$ reduction at higher temperature which proceeded well and afforded the *trans*-olefin **21** in 88 % yield.[5] With *E*-olefin **21** in hand, we then subjected it to treatment with TsCl (tosyl chloride) and triethylamine in the presence of catalytic amount of DMAP (4-dimethylaminopyridine) to afford the tosylated *E*-olefin, which was subsequently on dihydroxylation under Shrapless AD conditions using OsO_4

(osmium tetroxide) and co-oxidant $K_3[Fe(CN)_6]$ (potassium ferricyanide) in the presence of $(DHQ)_2PHAL$ ligand furnished the *o*-tosylated diol intermediate **22**.[6] Further, the *o*-tosylated diol intermediate **22** without purification on treatment with K_2CO_3 in methanol underwent cyclisation in S_N2 fashion and afforded PMB protected tetrahydrofuranyl hydroxyl derivative **23** as a single diastereoisomer in excellent yield. The PMB ether deprotection of tetrahydrofuranyl hydroxy derivative **23** with CAN (ceric ammonium nitrate) furnished the tetrahydrofuranyl hydroxy derivative **24** in 91% yield. Regioselective iodination of primary hydroxyl group of tetrahydrofuranyl alcohol derivative **24** with iodine and triphenylphosphine in the presence of imidazole as base under refluxed conditions furnished iodo derivative **25** in 84% yield.[3b] Finally, the desired product *epi*-muscarine iodide salt **7b** was obtained on treatment of iodo derivative **25** with ethanolic solution of trimethylamine in 95% yield.

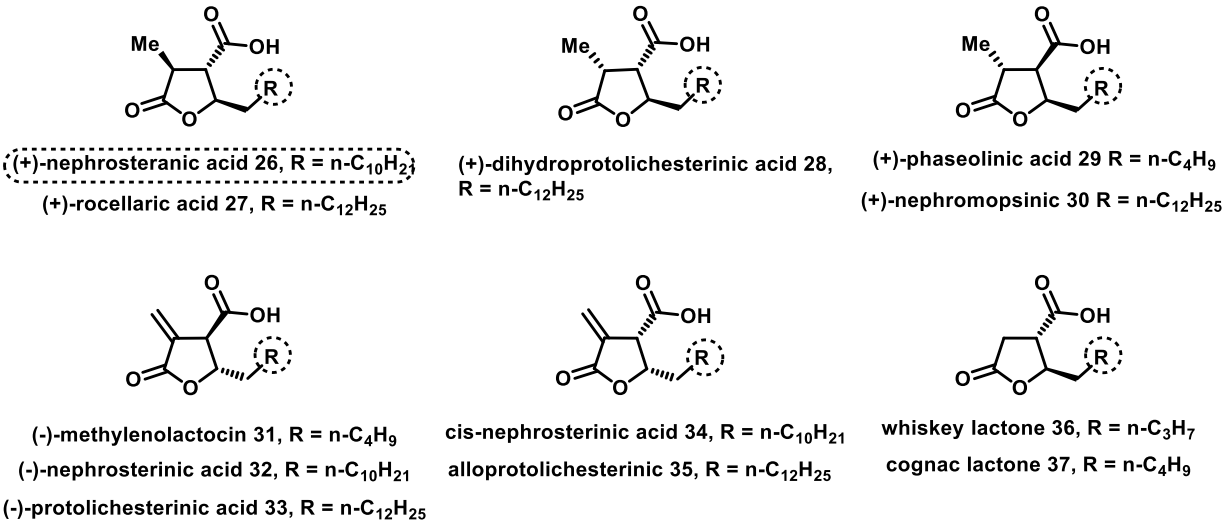


Chapter 3: Enantioselective novel approach for multifunctionalized γ-butyrolactone paraconic acids and its application to the total synthesis of (+)-nephrosteranic acid.

Introduction:

The paraconic acids (**26**-**37**) containing multifunctionalized *γ*-butyrolactone were isolated from various species of lichens, fungi, moss and cultures of *Penicillium sp.*[7] These acids possess interesting biological activities such as antitumor, antibacterial, antibiotic, antifungal/antiviral and growth regulatory properties.[8] The whiskey lactone **36** and cognac lactone **37** are having great commercial interest because they are used as potential key components in flavor of aged alcoholic beverages.[9] Architecturally, paraconic acids family comprises a variable length of

alkyl chain at C5 position, C4 carboxyl group and methyl or methylene substituents at C3 position which plays an important role in the biological activities of the paraconic acids.

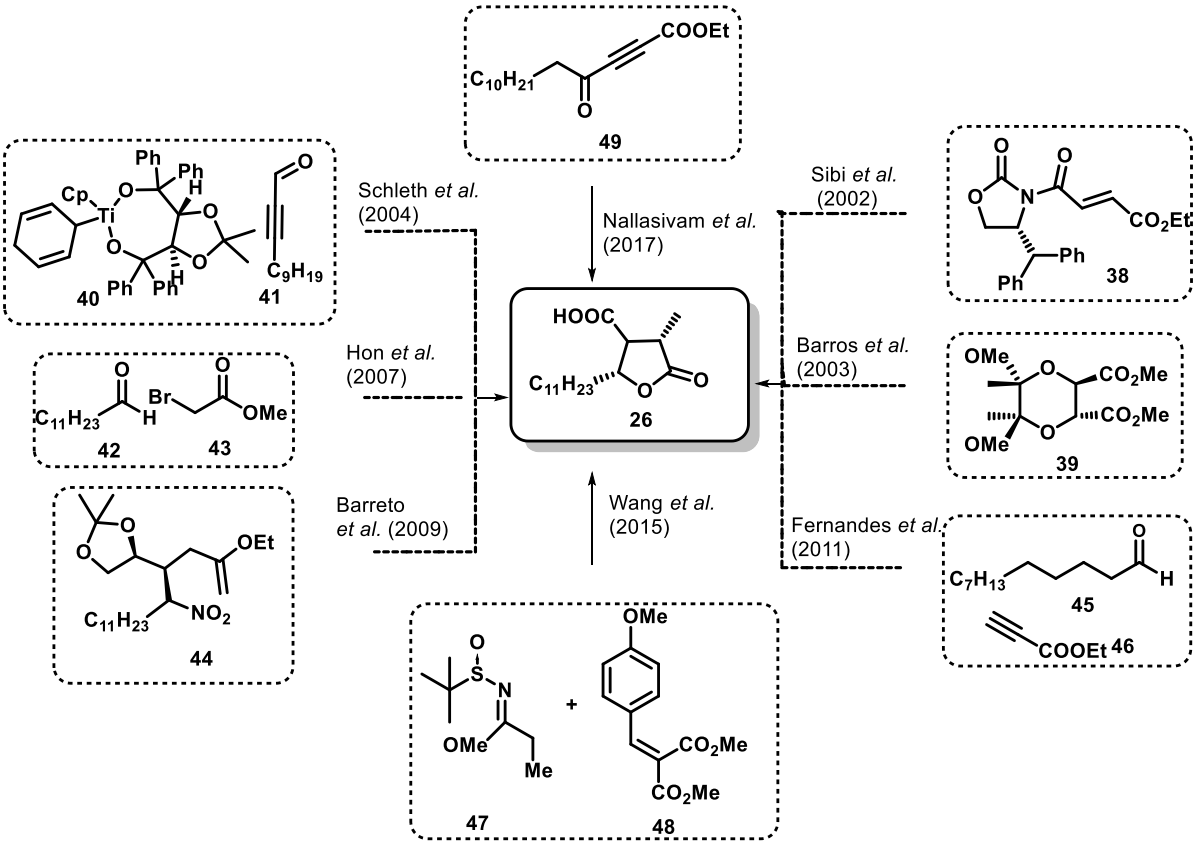


Review of Literature:

Numerous syntheses for the synthesis of target molecule **26** have been reported in the literature and few of them are described below. In 2002, M. P. Sibi and co-workers[10a] reported the enantioselective synthesis of (-)-nephrosteranic acid **26** from desymmetrized fumarate **38** in 53% overall yield over four synthetic steps employing high stereo and regioselective methodology for incorporation of radicals to a desymmetrized fumarate. Barros *et al*[10b] described the enantioselective synthesis of natural (+)-nephrosteranic acid **26** using highly stereoselective aldol reaction as key step and tartaric acid derivative **39** as starting material. F. Schleth and co-workers[10c] in 2004 proposed the introductory synthesis of (+)-nephrosteranic acid **26** where the chirality in alkynal **41** was incorporated using cyclohexadienyl Ti derivative **40** in excellent diastereo- and enantioselectivities. Y.-S. Hon and team[10d] in 2007 reported the formal synthesis of (+)-nephrosteranic acid starting from n-decanal **42** methyl bromoacetate **43** in eleven steps with 7.2% overall yield. The main strategy employed here is the incorporation of α-methylene group by ozonolysis of alkenes and subsequent reaction with mixture of CH_2Br_2 – Et_2NH. C. B. Barreto and co-workers[10e] in 2009 described the formal synthesis of (+)-nephrosteranic acid **26** employing Nef reaction, lactonization and reduction as key steps employing nitro derivative **44** as starting material obtained from D-(+)-mannitol *via* a chiron approach. R A. Fernandes and co-workers[10f] in 2011 reported the elegant synthesis of (+)-nephrosteranic acid **26** employing asymmetric dihydroxylation and Johnson–Claisen

rearrangment as key steps and utilized dodecanal **45** and ethyl propiolate **46** as starting materials.

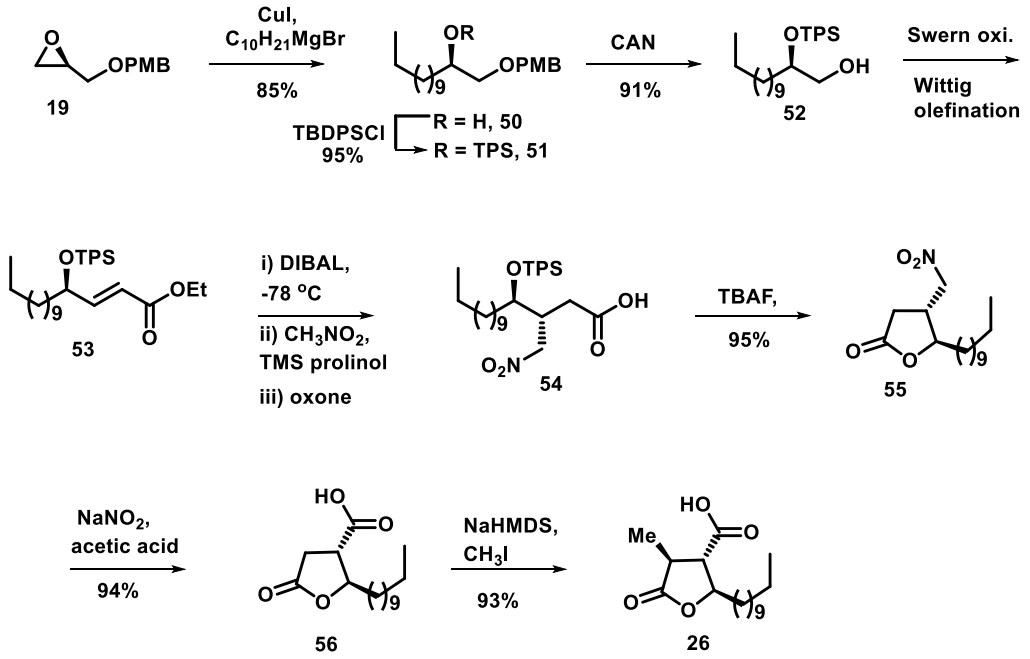
H. Wang and team[10g] in 2015 demonstrated the total synthesis of (−)-nephrosteranic acid **26** using three-step cascade reaction that involves highly stereoselective Michael addition, anion-oxidative hydroxylation and cyclization as key step employing methoxy derivative **47** and olefinic ester **48** as starting material. J. L. Nallasivam and co-workers[10h] reported the synthesis of (+)-nephrosteranic acid **26** and other paraconic acids *via* protecting group free approach employing Pd catalyzed Suzuki–Miyaura cross coupling and Ru-catalyzed Sharpless oxidation as key steps. Here, acetylenic ketones **49** served as starting material.



Present Work:

The synthesis of (+)-nephrosteranic acid **26** as a representative target compound of paraconic acids commenced from readily available PMB (*R*)-glycidyl ether **19**[4] which was subjected to copper-catalyzed (CuI) regioselective ring opening with the Grignard reagent, derived from decyl bromide to furnish the alcohol derivative **50** in 85% yield. The alcohol derivative **50** on silyl protection with *tert*-butyldiphenylsilyl chloride (TBDPSCl) with imidazole with DMAP

in catalytic amount afforded the silyl ether derivative **51** in 95% yield which on PMB ether cleavage using CAN at 0 ^{o}C furnished the terminal alcohol derivative **52** in 91% yield. The alcohol derivative **52** on oxidation under Swern conditions[11] followed by treatment with (ethoxycarbonyl-methylene) triphenylphosphorane in THF afforded the *trans*-olefinic ester derivative **53** in 92% yield. Our next goal was to carry out the synthesis of multifunctionalized γ-butyrolactone. Towards this end, *trans*-olefinic ester **53** on controlled reduction with DIBAL-H at -78 ^{o}C was converted into to α, β-unsaturated aldehyde intermediate which further upon successive conjugate Michael addition[12] of nitro-methane in the presence of (*S*)-diphenylprolinol silylether (10 mol%) afforded the nitroaldehyde adduct which on subsequent oxidation with oxone[13] furnished the nitro-acid derivative **54** in excellent yield.



Further to demonstrate the stereochemistry during the conjugate Michael addition of nitromethane to α, β-unsaturated aldehyde intermediate we carried out the reaction with racemic catalyst (±)-diphenylprolinol silyl ether to get the nitro-aldehyde adduct which on subsequent oxidation with oxone afforded the *anti*/*syn*-nitro-acid diastereomers of **54** (dr, 1:1) in 81% combined yield. However, on the other hand, in the presence of (*S*)-diphenylprolinol silyl ether catalyst the conjugate addition of nitromethane on α, β-unsaturated aldehyde intermediate followed by oxidation with oxone furnished the *anti*-nitro acid derivative **54** as a single diastereomer in 84% yield.

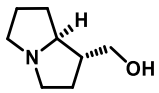
Further, the *anti*-nitro acid derivative **54** on TPS deprotection and concomitant cyclisation with TBAF (tetra-*n*-butylammonium fluoride) furnished the γ-butyrolactone derivative **55** in 95%

yield. The nitro-γ-butyrolactone derivative **55** was subjected to treatment with sodium nitrite and acetic acid under Nef reaction conditions[14] to afford the γ-butyrolactone acid derivative **56** in 94% yield. Finally, stereoselective methylation at α-position of acid derivative **56** was carried out with methyl iodide and NaHMDS in THF to furnish the (+)-nephrosteranic acid **26** in 93% yield.

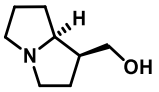
Chapter 4: An attempt towards the total synthesis of (-)-trachelanthamidine.

Introduction:

Pyrrolizidine alkaloids are found maily in Phalaenopsis *hybrids*[15] and gain immense recognition because of their numerous therapeutic properties.[16] (-)-trachelanthamidine **57** (also known as laburnine), a pyrrolizidine (necine) base is the simplest bicyclic compound of this family and gain considerable interest among synthetic chemists due to its unique structural features. Isoretronecanol **58** also contain substituted pyrrolizidine core unit and shared common structural features as of (-)-trachelanthamidine.



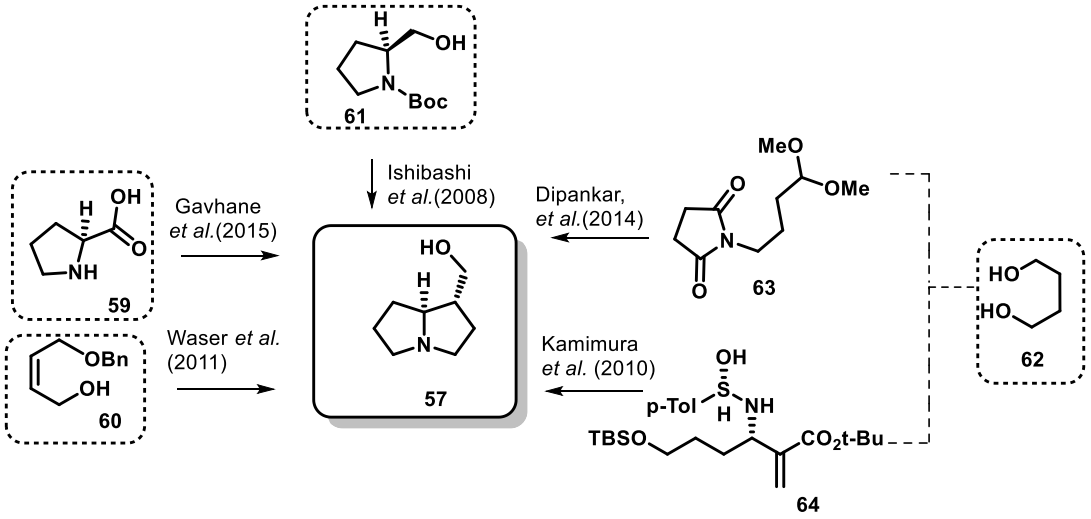
Trachelanthamidine 57



Isoretronecano 58

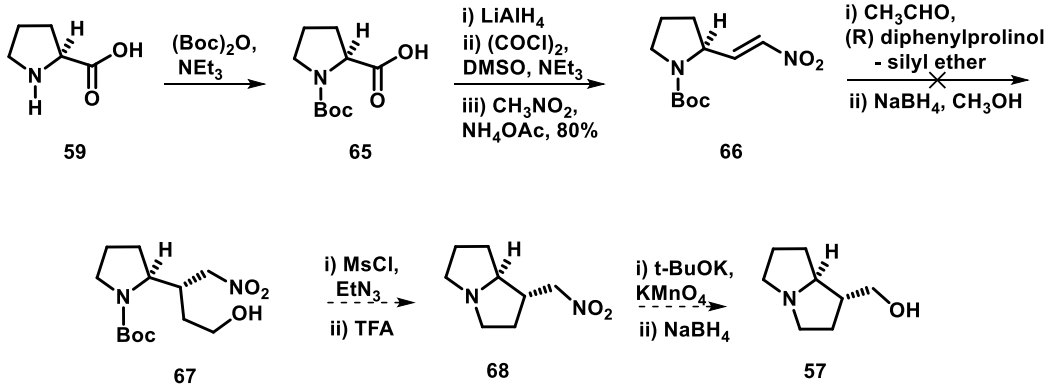
Review of Literature:

Gavhane and co-workers[16c] in 2015 described the synthesis of (-)-trachelanthamidine **57** through the successful implementation of Wittig olefination–Claisen rearrangement as the key step using L-proline **59** as starting material. Jerome Waser *et al* [16d] in 2011, reported the synthesis of (+/-)-trachelanthamidine **57** using palladium catalyzed aminoalkynylation methodology as principle step. The synthesis of **57** commenced from mono protected butene diol **60**. Hiroyuki Ishibashi and his team[16e] reported the synthesis of (-)-trachelanthamidine **57** employing single electron transfer (SET) methodology as key steps using chiral Boc protected prolinol **61** as starting material. Dipankar Koley *et al.*[16f] reported an elegant asymmetric synthesis of (-)-trachelanthamidine **57** *via* one pot organo-catalysed Mannich cyclization using commercially available 1,4-butanediol **62** as starting material and *N*-alkylated imide **63** as key intermediate. Kamimura and his team[16g] disclosed the formal preparation of (-)-trachelanthamidine **57** using preparation of Aza Baylis Hillman adducts and ring closing metathesis as key step. They have also utilized 1,4-butanediol **62** as stating material and involve compound **64** as key intermediate.



Present Work:

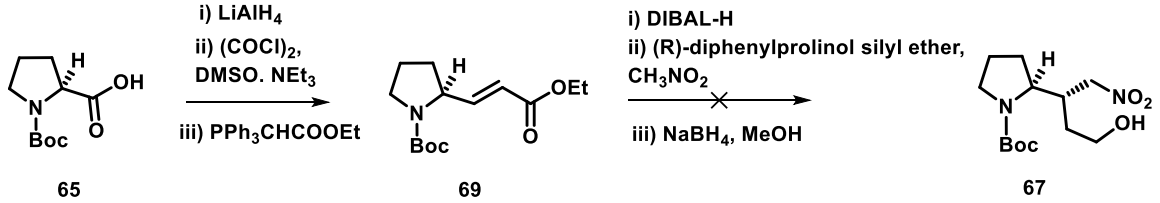
We envisioned the synthesis of trachelanthamidine **57** from commercially available L-proline **59** which on treatment with $(Boc)_2O$ furnished the Boc protected derivative[17] **65**. Reduction of N-Boc protected proline derivative **65** was carried out in the presence of $LiAlH_4$ to afford the terminal alcohol, which under Swern oxidation conditons afforded the intermediate aldehyde which upon treatment with nitromethane furnished the nitroalkene derivative **66**.



Further, attempts were made to synthesize compound **67** by subjecting the nitroalkene **66** to asymmetric Michael addition[18] reaction with acetaldehyde in the presence of catalytic amount of (*R*)-diphenylprolinolsilyl ether followed by reduction with $NaBH_4$. However, no desired product formation was observed under these conditions.

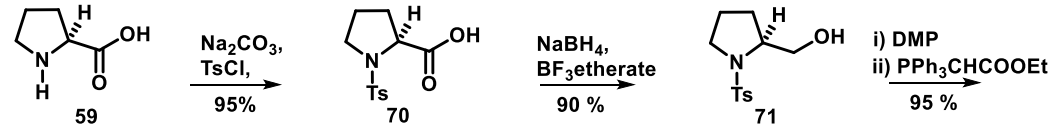
Alternatively, to tackle this issue different route was attempted to synthesize compound **67**. To this direction, compound **65** was first converted into ester **69** by following standard series of organic transformations**.** Further**,** olefinic ester **69**, on reduction with DIBAL-H, was converted into conjugated aldehyde and was exposed to asymmetric Michael addition[18]conditions with

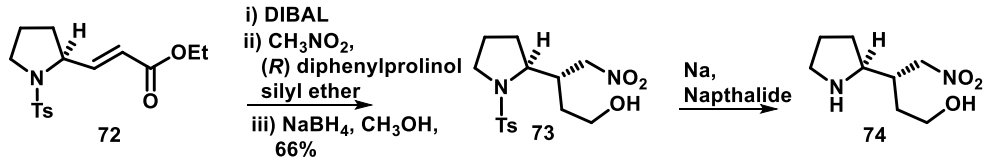
nitromethane in the presence of catalytic amount of (*R*)-diphenylprolinolsilyl ether followed by subsequent reduction with $NaBH_4$ to synthesize the compound **67**. Again, this route was not successful. Therefore, it was assumed that the Boc anhydride may be acting as an obstacle in the completion of the reaction due to its bulky size.

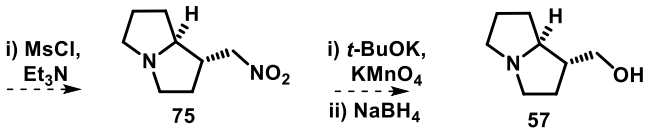


Next, we explored the effect of changing the protecting group of L-proline **59** and then decided to carry out the Michael addition reaction. In this regard, we protected the L-proline **59** as its *N*-benzyl and *N*-tosyl derivative. To our surprise *N*-tosyl proline derivative showed some promising results that are discussed as follows.

Further, the synthesis of **57** was commenced from commercially available L-proline **59** and was first converted into its N-tosyl derivative **70**, on treatment with TsCl in the presence of sodium carbonate.[19] The alcohol derivative **71** was obtained on exposing compound **70** with $NaBH_4$ reduction in the presence of BF_3. etherate[19], in excellent yield. The compound **71** on oxidation with Dess Martin periodinane (DMP) afforded the intermediate aldehyde which on subsequent treatment with (ethoxycarbonylmethylene)-triphenylphosphorane (2C-Wittig reagent) furnished the ester **72**







Interestingly, we successfully converted the *N*-tosyl olefin **72** to the nitro-alcohol compound **73** *via* selective reduction with DIBAl-H to aldehyde intermediate followed by Michael addition of acetaldehyde in the presence of (*R*)-diphenylprolinolsilyl ether followed by subsequent reduction with $NaBH_4$. Therefore, here we concluded that protecting group was playing an important role in the feasibility of Michael addition. Our next challenge was to synthesize the compound **74.** On proceeding in this direction, compound **73** was treated with various tosyl deprotecting agents and then it was successfully cleaved with Na, Naphthalide solution.[20] However at the end no desired product **74** was obtained.

Characterization:

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

Chapter 5: Conclusions and Future Scope:

We have developed enantioselective approaches for the synthesis of (+)-(2*S*,3*S*,5*S*)-*epi*-muscarine, (+)-nephrosteranic acid employing Sharpless AD and organocatalzyed Michael addition reactions as key steps. We have also attempted the synthesis of (-)-trachelanthamidine. The merits of these synthetic approaches are high enantio- and diastereoselectivity with high yielding reaction steps.

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List of Publications

1. Enantioselective Total synthesis of Sacubitril
   Amanpreet kaur**,** **Anju Gehlawat**, Ranjana Prakash and Satyendra Kumar Pandey* *ChemistrySelect,* **2021**, *6,* 1-4.
2. An efficient enantioselective approach to multifunctionalized γ-butyrolactone: concise synthesis of (+)-nephrosteranic acid.
   Anju Gehlawat, Ranjana Prakash and Satyendra Kumar Pandey*
   RSC Adv., **2020**, *10,* 19655–19658.
3. A Short and Efficient Enantioselective Synthesis of (+)-(2*S*,3*S*,5*S*)-*epi*-Muscarine
   Anju Gehlawat , Ranjana Prakash and Satyendra Kumar Pandey*
   ChemistrySelect **2020**, *5*, 1– 4.

4. Enantioselective total syntheses of (−)-clavaminol A and deacetyl (+)-clavaminol H. Rachana Pandey**,** **Anju Gehlawat**, Ranjana Prakash and Satyendra Kumar Pandey* *Synthetic Communication* **2018**, *48*, 2280-2287.
5. Enantioselective Synthesis of C1-C4 and C5-C14 Fragments of Cytospolide D Amanpreet kaur**,** **Anju Gehlawat**, Ranjana Prakash and Satyendra Kumar Pandey* *Arkivoc* **2021**, *v*, 158-170.

Conferences

1. Total Synthesis of Biologically Active Natural products
   Anju Gehlawat and Satyendra Kumar Pandey
   Poster presentations at International conference FCASI 2016, University of Rajasthan, Jaipur, India.

CHAPTER 1

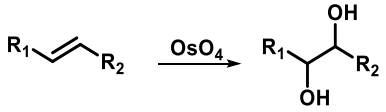
A brief account of Sharpless asymmetric dihydroxylation (AD) and organocatalyzed Michael addition reactions.

1.1 Sharpless asymmetric dihydroxylation (AD)

1.1.1 Introduction

The development of innovative and efficient methods for the synthesis of optically pure molecules has been a focus of organic synthesis because of their application in agrichemicals and pharmaceuticals.[1] Particularly helpful is the carbon-heteroatom bonds formation reaction, because the functionality that results can be manipulated to deliver wide range of bioactive compounds. Asymmetric dihydroxylation, inserting 1,2-dihydroxy groups to an olefinic framework, catalysed by osmium tetroxide is the most assured and selective transformations in chiral synthesis (Scheme 1). Olefinic compounds reaction with OsO_4 is uneconomical due to cost consideration. Firstly introduced inorganic co-oxidants such as $Na/KClO_3$[2a] or H_2O_2,[2b, c] resulted in lessened yield in some cases because of over oxidation. Great outcomes were got with alkaline *tert*-BuOOH, presented by Sharpless and Akashi[3] or with 4-methylmorpholine 4-oxide (NMO) named as Upjohn Process.[4] Afterward, Yamamoto, Minato and Tsuji[5] presented $K_3Fe(CN)_6$ and K_2CO_3 which gives an amazing framework to the osmium catalysed asymmetric dihydroxylation of alkene.

Next, two-phase conditions were used to carry out Sharpless AD, with the addition of $CH_3SO_2NH_2$ (methanesulphonamide) which act as a co-solvent and universal acid catalyst, resulting in quicker reaction for internal olefins.



Scheme 1. Dihydroxylation of olefin.

At first, Sharpless and Hentges tested chiral pyridine subordinates to actuate enantioselectivity in AD that floundered on account of low proclivity of these ligands for OsO_4.[6] Then, ligands having high affinity for OsO_4[7], quinuclidine derivatives were used and later on average to adequate enantiomeric excess was given by cinchona alkaloids ligands[6] (Figure 1).

Despite the great enantioselectivity of bidentatediamine ligands in Sharpless AD, a serious disadvantage comes from their bidentate nature,[8] they produce inert chelate complexes with Osmium (VI) glycolate compounds that leads to prevention of in *situ* recycling of Osmium metal

and the ligand. So, stoichiometric amount of both cinchona alkaloid chiral ligands and OsO_4 are used in all reactions (Figure 1).

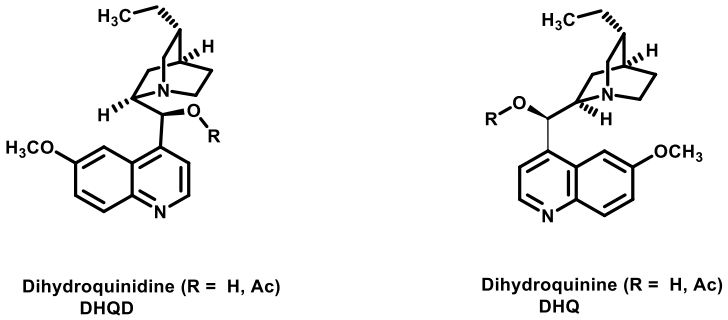
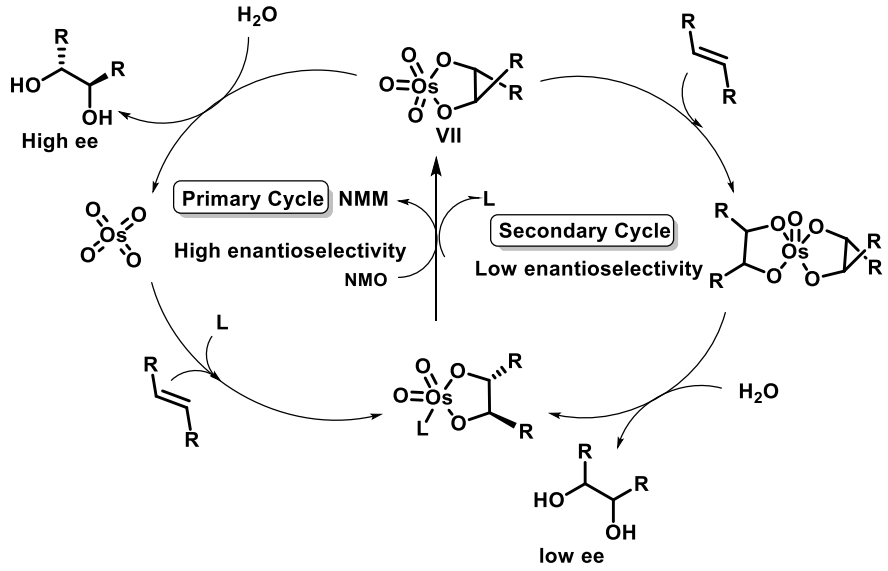


Figure 1. Framework of cinchona alkaloid complexing agent for AD.

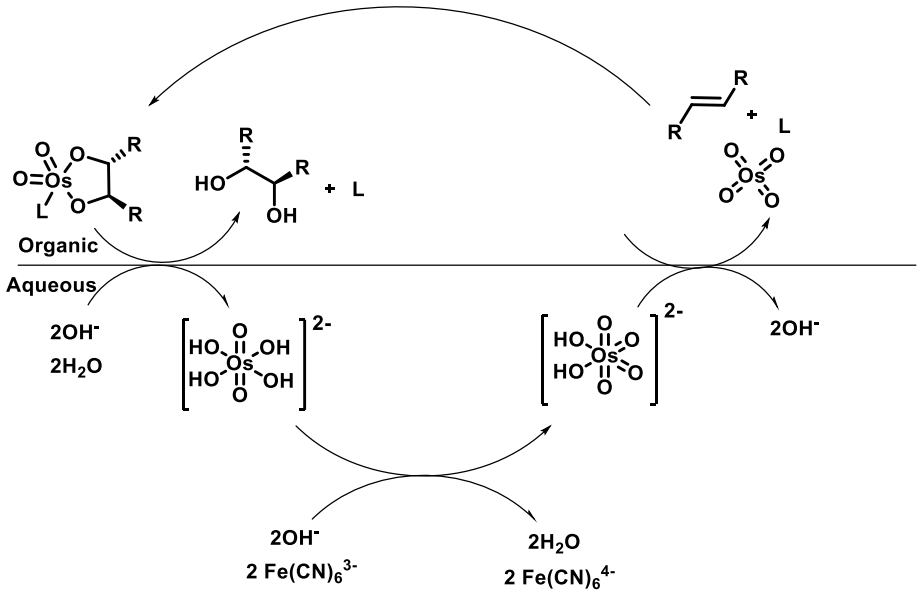
Sharpless and Marko[9] researched out that the use of *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant makes the AD more catalytic as compared when cinchona alkaloids were operated alone.



Scheme 2. Pair of catalytic series involved in AD reaction employing an co-oxidant, NMO.

In catalytic conditions the enantiomeric excess of 1,2 dihydroxy products were low because of the low enantioselectivity of second catalytic cycle.[10] Slow addition of the alkene is the temporary solution for low enantioselectivity given by Wai[10] and the complete elimination of second catalytic cycle took place on carrying out the reaction in two phase conditions along with

stoichiometric co-oxidant $K_3Fe(CN)_6$, discovered by Kwong.[11] Here, in organic phase only OsO_4 oxidant was used in comparison to the NMO conditions (Scheme 2).



Scheme 3. Catalytic sequence of the AD reaction using $K_3Fe(CN)_6$ as the co-oxidant.

As the olefin was osmylated in organic solvent phase, the freshly generated osmium (VI) monoglycolate ester underwent hydrolysis, both ligand and diol were released in the organic solvent phase and Os (VI) to the watery layer and thus approach of the osmium(VI) glycolate osmium glycolate in the another loop was removed as depicted in Scheme 3.

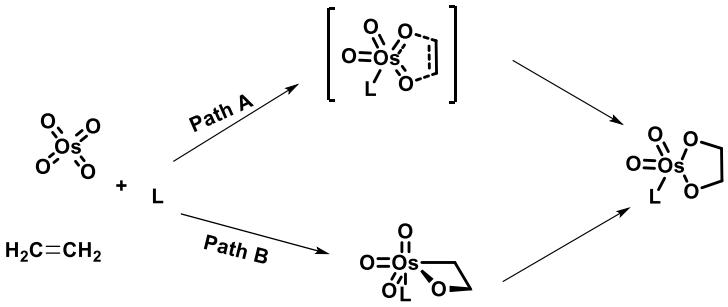
Sharpless *et al*.[12] investigated that use of methane sulphonamide enhanced the hydrolysis of Os (VI) glycolate. Within the sight of above added substance, asymmetric dihdroxylation was performed at 0 ^oC which beneficially affects the selectivity and moreover reaction time was decreased. However, $MeSO_2NH_2$ presence make the terminal olefins react slowly.

Ligands found by Crispino[13] (diphenylpyrimidine core) and Hartung[12] (phthalazine core) connected with two individual cinchona alkaloid units through a cyclic spacer, increase the enantioselectivity of Sharpless asymmetric dihydroxylation (Figure 2). Combination of $K_2OsO_2(OH)_4$ and cooxidant $[K_3Fe(CN)_6]$ permitted us to form a premix, commercially available as “AD-mix”, containing all reagents and ligand.

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

1.1.2 The mechanism of asymmetric dihydroxylation (AD)

Two dissimilar mechanisms have been recommended for AD, one is concerted [3+2] pathway (Scheme 4, Path A) suggested by Boseken[14a] and Criegee[15] and second is a stepwise reaction, started by a [2+2] like addition of OsO_4 across the olefin (Path B), trailed by migratory insertion of the resulting osmaoxetane intermediate to osmylate ester suggested by Sharpless *et al.*[14b] and Jorgensen *et al.*[14c]



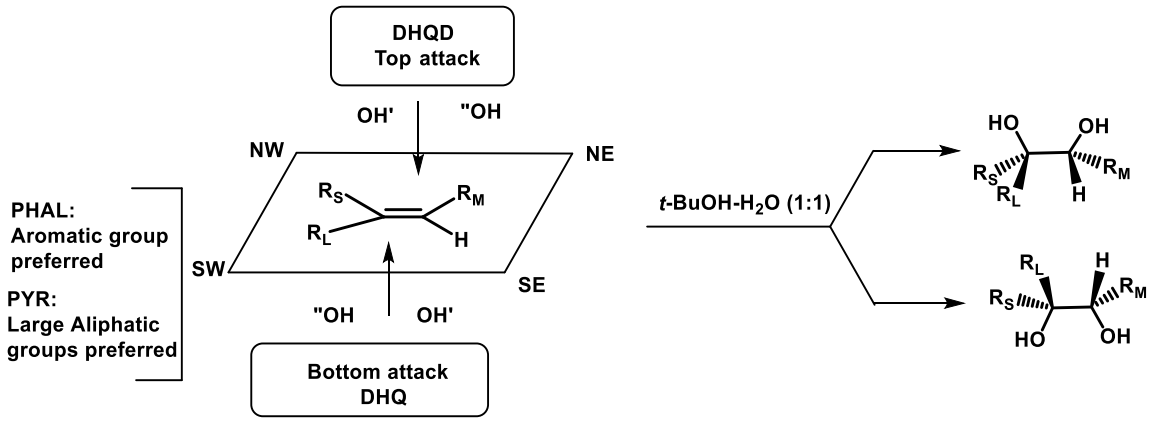
Scheme 4. Schematic delineation of [3+2] mechanism (Path A) and [2+2] mechanism (Path B).

In current (3+2) mechanism[16] was favoured by a academic study, relying upon high activation barrier needed for osmaoxetanes's formation and ring-extension.

1.1.3 Empirical rules for envisioning face selectivity

'Mnemonic device' (Scheme 5)[17] was used for estimating the face selectivity of the asymmetric dihydroxylation, even after mechanistic investigations. According to a straightforward arrangement of rules, the alkene's plane was split up into four quadrants. In SE (south east) quadrant, small atom (H & H like) can be put, as it is sterically inaccessible. In NW quadrant, groups larger than hydrogen can take position due to more space, it lies cater-cornered to SE quadrant. In NE (north east) quadrant, medium group can be placed because it is roomier. In SW quadrant, big ligand group (aromatic groups in PHAL ligands and PYR ligands) used to put. An

olefin aligned by the above limitations got the two hydroxy groups from the upward (the β-face) in DHQD derived ligands and another from beneath (the α-face) in DHQ derived ligands.



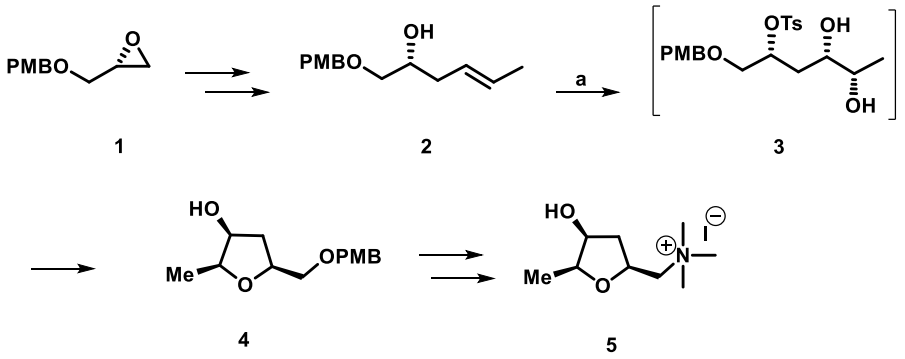
Scheme 5. The recommended mnemonic device for envisioning the face selectivity in AD.

1.1.4 Reaction conditions

The Sharpless AD reaction is carried out in 1:1 combination of *tert*-butanol and H_2O and commonly used concentration of the olefinic compound is 0.1 M.[12] In Sharpless AD the majorly utilised reagents are OsO_4 (0.2-0.4 mol%), ligand (1 mol%), $K_3Fe(CN)_6$ (3 equivalents), methanesulphonamide (1 equivalent) and K_2CO_3 (3 equivalents). When asymmetric dihydroxylation is performed at mass scale, chiral ligands could be recovered. The integrated organic layer is processed with 3% aq. H_2SO_4 saturated with K_2SO_4 and the PHAL ligand released into water layer as a salt of hydrogen sulphate and subsequent reaction could be executed with recovered solution directly by skipping the further purification step.

1.1.5 Application

We have employed Sharpless AD conditions for the synthesis of (+)-(-2*S*,3*S*,5*S*)-*epi*-muscarine **5**. As depicted in Scheme 6. The synthesis began with readily available (*R*)- (*p*-methoxybenzyl) glycidyl ether **1** which was transformed in *trans*-olefin **2** *via* standard organic transformations. Free hydroxyl group of *E*-olefin **2** was first tosylated on treatment with TsCl and triethylamine to afford the tosylated *E*-olefin, which was subsequently on dihydroxylation under Sharpless AD conditions using OsO_4 (osmium tetroxide) and co-oxidant $K_3[Fe(CN)_6]$ (potassium ferricyanide)



Scheme 6. (a) i) TsCl, DMAP, Et_3N, dry DCM, 0 ^oC to rt, 6 h; ii) OsO_4 (0.5 mol %), $K_3[Fe(CN)_6]$, $(DHQ)_2PHAL$ (1 mol %), K_2CO_3, $CH_3SO_2NH_2$, *t*-BuOH/water (1:1 v/v), 0 ^oC, 25 h; iii) K_2CO_3, methanol, rt, 4 h, (3 steps, 90%).

in the presence of $(DHQ)_2PHAL$ ligand furnished the *o*-tosylated diol intermediate **3** which on base treatment afforded PMB protected tetrahydrofuranyl hydroxyl derivative **4**. Compound **4** on further functional group manipulations delivered the target molecule **5**.

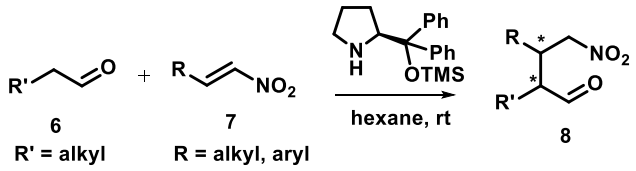
1.2 Organocatalzyed Michael addition reactions

1.2.1 Introduction

Asymmetric organocatalysis has been shown a useful asset for carrying out stereoselective transformations. The Michael addition reaction has emerged as one of the major C-C bond forming methodology in asymmetric synthesis. Organocatalyzed Michael is a conjugate addition reactions with a various combination of Michael donors (active methylene compounds like Malonates, β-keto esters) and acceptors (substituent groups on the activated olefinic compounds like α,β-unsaturated ketones; ester; nitriles; sulfones, nitro). While the demand of environmentally-safe reaction without using the metal based catalyst brought the organocatalyst substitute for conjugate addition reaction.

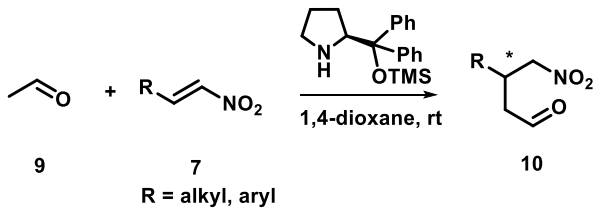
1.2.2 Organocatalzyed Michael addition reaction on conjugated nitro-alkenes

Michael addition reaction of unsaturated nitro compound with various aldehyde as nucleophiles turned out to be a constructive approach for building β -substituted nitro alkanes. Hayashi and his team explored an Michael addition reaction of *α*-substituted aldehydes **6** with nitroalkenes **7** using the organocatalyst diphenylprolinolsilyl ether to afford the *α*-substituted-*γ*-nitro aldehydes **8** with 85% yield and excellent enantio and diastereoselectivity upto 99%*ee* and 97:3 *syn*:*anti* respectively. (Scheme 7).[18]



Scheme 7. Michael addition reaction among aldehydes and nitroalkenes using organocatalyst.

Next, Hayashi and collaborators illustrated the diphenylprolinolsilyl ether catalysed asymmetric



Scheme 8. Organocatalyzed Michael addition reaction of acetaldehyde with nitroalkene.

Michael addition reaction of Michel donor acetaldehyde **9** and acceptor nitroalkene **7** to furnish the chiral product **10** with 77% yield and incredible enantiomeric excess (upto 99%*ee*) (Scheme 8).[19]

The feasible mechanism put forward for the TMS prolinol catalzyed Michael addition reaction of aldehyde and nitro-alkene is represented in Figure 3. At first, an enamine intermediate **I** is produced on treatment of aldehyde **11** with TMS-prolinol which act as Michael donor and underwent nucleophilic addition with nitroalkene **7** to afford the imine intermediate **II**. Hydrolysis of imine intermediate **II** produces nitro aldehyde adduct **12** with subsequent release of organocatalyst.

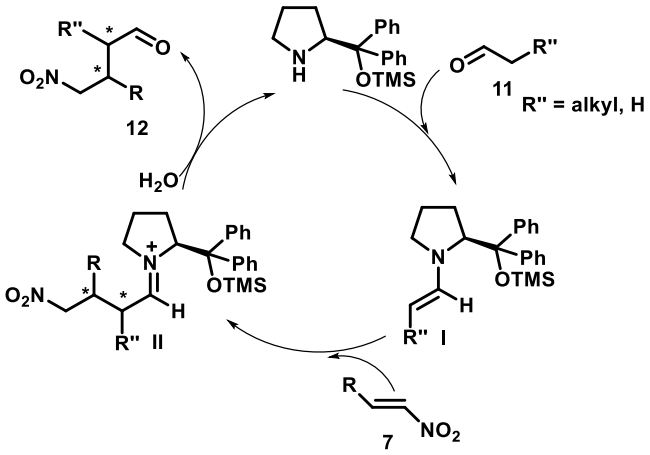
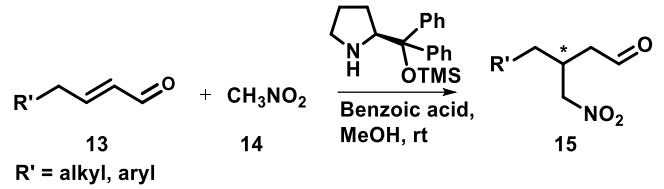


Figure 3. General mechanism for organocatalzyed Michael addition reaction.

1.2.3 Organocatalyzed Michael addition reaction on conjugated aldehydes

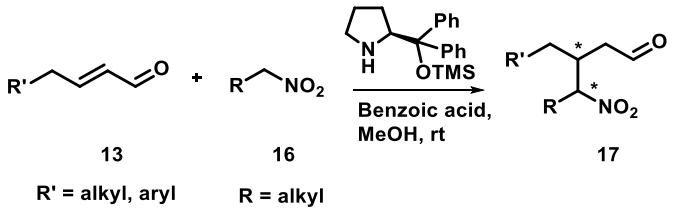
γ-Nitro aldehydes are synthetically important chiral intermediates that can be transformed into amino carbonyl and amino alkanes used for the formation of wide range of chiral pharmaceuticals and natural compounds.

Hayashi and his team explored a strategy to form nitroaldehyde adduct **15** using the Michael addition of CH_3NO_2 **14** and *α,β*-unsaturated aldehydes **13** employing the organocatalyst TMS-prolinol in 94% yield and 95% enantiomeric excess (Scheme 9).[20]



Scheme 9. Michael addition reaction of CH_3NO_2 and conjugated aldehydes, catalysed by TMS-prolinol.

Hayashi and his team also used the organocatalyst TMS-prolinol to perform the Michael addition of conjugated aldehydes **13** and substituted nitroalkane **16** for producing nitroaldehyde derivative **17** in plentiful diastereo 1:1 (*syn*:*anti*) and enantioselectivity (upto 96% ee) and excellent yield (upto 95%) (Scheme 10).[20]



Scheme 10. Michael addition reaction of nitroalkanes and conjugated aldehydes, catalysed by TMS-prolinol.

A predominantly methodology for TMS prolinol catalyzed Michael addition reaction of substituted nucleophilic nitroalkanes to electrophilic enone is outlined in Figure 4. Imine intermediate **I** is produced on incorporation of aldehyde **13** with catalyst TMS-prolinol

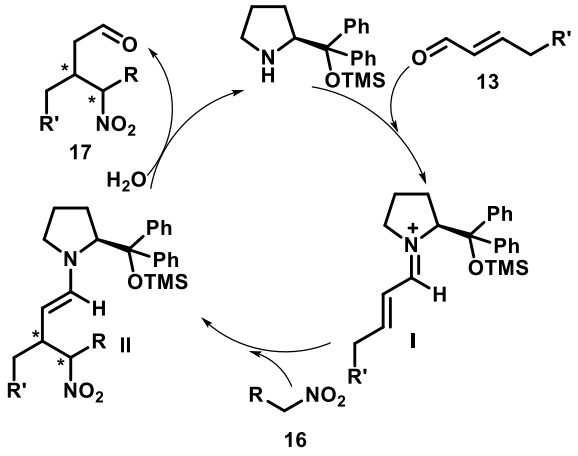
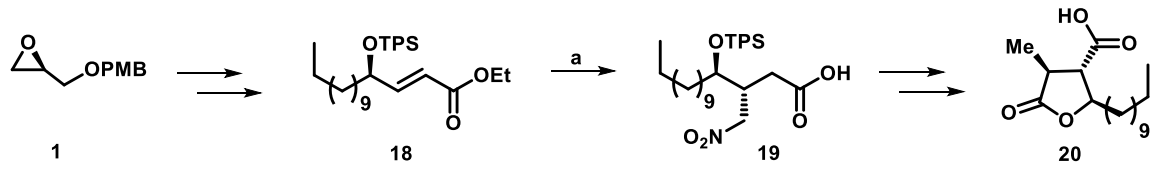


Figure 4. General mechanism for organocatalzyed Michael addition reaction.

Imine intermediate **I** on conjugate addition with nitroalkane **16** furnished the enamine intermediate **II**. Hydrolysis of intermediate **II** results in the formation of nitroaldehyde adduct **17** with subsequent delivery of organocatalyst.

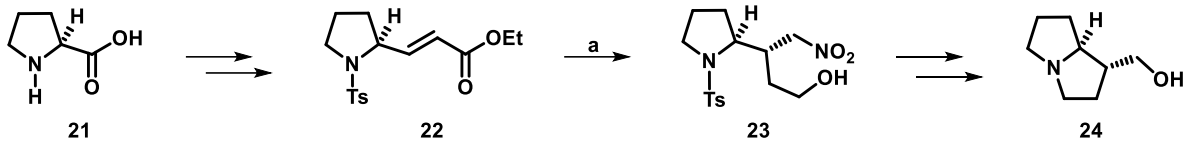
1.2.4 Application

We have applied the organocatalzyed Michael addition reactions for the synthesis of (+)-nephrosteranic acid. The synthesis of (+)-nephrosteranic acid **20** started with easily available PMB (*R*)-glycidyl ether **1** which was transformed into ester **18** *via* standard organic transformations as shown in Scheme 11. *Trans*-olefinic ester **18** on controlled reduction with DIBAL-H at -78 ^{o}C gave *α, β*-unsaturated aldehyde intermediate and successive conjugate Michael addition of nitromethane in the presence of (*S*)-diphenylprolinolsilyl ether (10 mol%) afforded the nitroaldehyde adduct which on subsequent oxidation with oxone furnished the nitro-acid derivative **19** in excellent yield. Further, functional group manipulations of **19** furnished (+)-nephrosteranic acid **20** in plentiful yield.



Scheme 11. *Reagents and conditions*: (a) i) DIBAL-H, CH_2Cl_2, -78 ^{o}C, 1h; ii) (*S*)-diphenylprolinolsilyl ether (10 mol%), CH_3NO_2, benzoic acid, MeOH, rt, 16 h; iii) oxone, DMF, rt, 12 h, 84% (over 3 steps).

Further, organocatalzyed Michael addition strategy was successfully implemented for the synthesis of (-)-trachelanthamidine **24**. The synthesis of (-)-trachelanthamidine **24** started with commercially available L-proline **21** which was transformed into *α, β*-unsaturated ester **22** *via* standard organic transformations (Scheme 12). The *N*-tosyl ester **22,** after converting into an aldehyde with DIBAl, was subjected to asymmetric Michael addition using acetaldehyde employing the catalyst (*R*)-diphenylprolinol silyl ether succeeding by reduction with $NaBH_4$, to obtain the compound **23.** Further, work is in progress for other standard organic functional group manipulations on **23** to furnish (-)-trachelanthamidine **24.**



Scheme 12. *Reagents and conditions*: (a) i) DIBAL-H, CH_2Cl_2, -78 ^oC, 1h; ii) (*R*)-diphenylprolinolsilyl ether, CH_3NO_2, benzoic acid, methanol, rt, 16 h; iii) $NaBH_4$, CH_3OH, 0 ^oC, 1 h, 66%.

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CHAPTER 2

Enantioselective general approach for the synthesis of muscarine alkaloid and its application to the asymmetric synthesis of *epi*-muscarine.

Enantioselective general approach for the synthesis of muscarine alkaloid and its application to the asymmetric synthesis of *epi*-muscarine.

2.1 Introduction:

Bioactive natural products containing multifunctionalized tetrahydrofuran moiety are found abundantly in nature.[1] The venomous alkaloids (+)-(-2*S*,3*S*,5*S*)-*epi*-muscarine **5**, (+)-(2*S*,3*R*,5*S*)-muscarine **5a**, (-)-(2*S*,3*R*,5*R*)-*allo*-muscarine **5b** and (+)-(2*S*,3*S*,5*R*)-*epiallo* muscarine **5c** were isolated from numerous species of mushrooms, e.g. *Amanita muscaria* (fly agaric) and certain species of *Clitocybes* and *Inocybes* (Figure 5).[2] Muscarine acts as a selective agonist of the acetylcholine receptor (muscarinic acetylcholine receptors) on smooth muscles of the eye exocrine glands, gastrointestinal tract, heart and have a wide range of other therapeutic properties.[3] More recently, pharmacological studies with selective antagonists confirmed distinct subtypes of muscarinic receptors.[4]

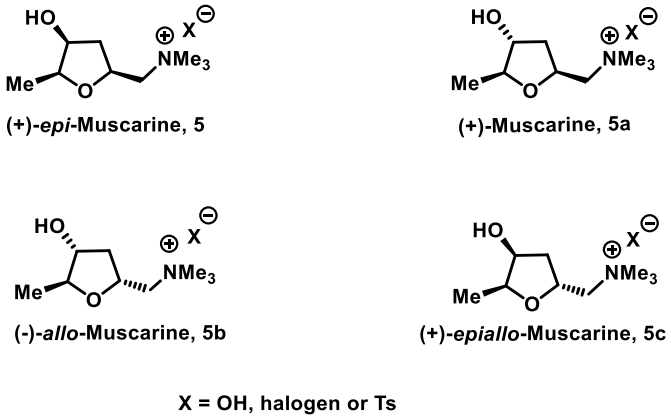


Figure 5. Structure of muscarine and its stereoisomers.

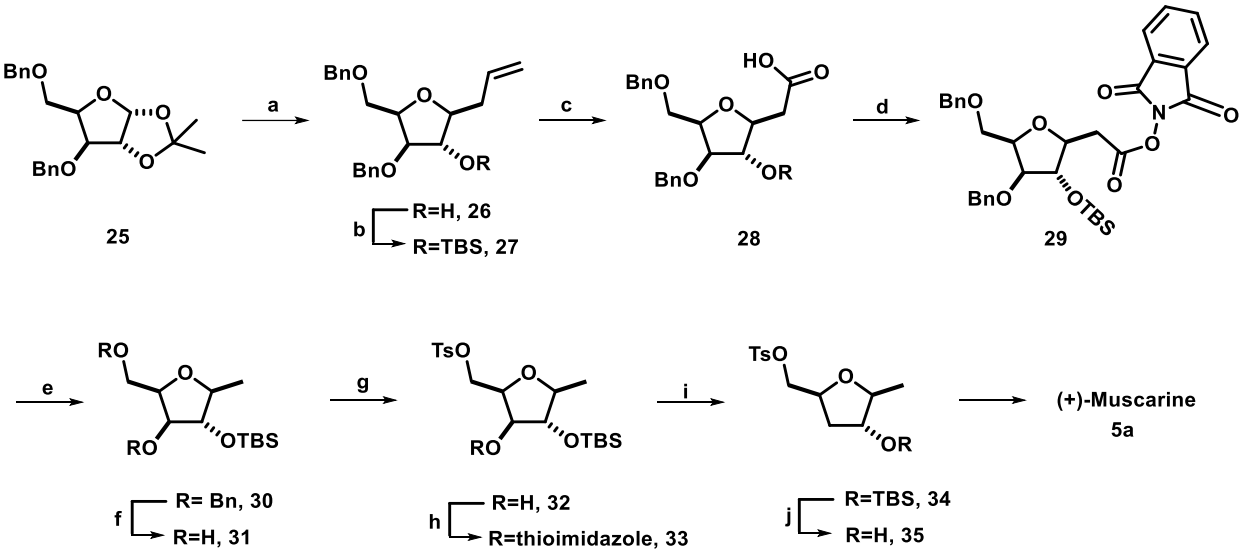
Further, muscarinic field studies developed new interest after the discovery of relationship between cholinergenic deficiency in hippocampal areas, neurodegenerative diseases and the pathology of Alzheimer.[5]

2.2 Review of Literature:

Intrigued by the unique structural features and biological activities of tri-substituted tetrahydropyran, hitherto, numerous syntheses of muscarine and its enantiomers **5-5c** are reported in literature.[6,7] The followings are some of the latest syntheses of (+)-(-2*S*,3*S*,5*S*)-*epi*-muscarine.

Rodríguez-Tzompanzi, V. *et al*. (2019)[6a]

Rodríguez-Tzompanzi and co-workers demonstrated the total synthesis of (+)-muscarine **5**a employing decarboxylation in the presence of blue light and tin-free Barton-McCombie reactions as key steps from xylofuranose derivative **25** via stereoselective nucleophilic substitution at the anomeric position approach (Scheme 13).



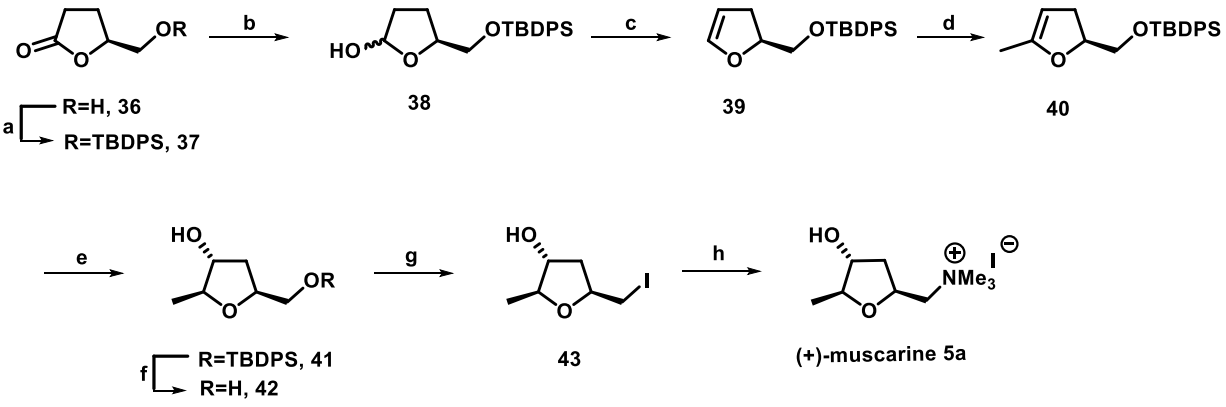
Scheme 13. *Reagents and conditions*: (a) allyltrimethylsilane, BF_3OEt_2, DCM, 0 ^oC-rt, 4 h, 88% (b) TBSCl, imidazole, DCM, 0 ^oC-rt, 12 h, 95%; (c) O_3, $NaClO_2$, H_2O/CH_3CN, *t*-butanol/ H_2O, 5.5 h, -15-0 ^oC, 80%; (d) N-hydroxyphthalimide, DCC, DMAP, $CHCl_3$, 4 h, rt, 82%; (e) $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, Hantzsch ester, blue-LEDs, $CHCl_3$, 70%; (f) H_2 and $Pd(OH)_2$, AcOEt, 12h, rt, 99% (g) TsCl, NEt_3, DMAP, 20 h, 0 ^oC-50 ^oC, 82%; (h) TCDl, DMAP, CH_2Cl_2, 18 h, rt, 94%; (i) Et_3B, H_2O/i-PrOH, over night, rt, 65%; (j) $BF_3.OEt_2$, CH_3CN, 30 min., 0 ^oC, 70%.

Stereoselective allylation of dibenzylated D-xylofuranose derivative **25** at anomeric position was carried out *via* NSAP approach with trimethylallylsilane to furnish *C*-glycoside derivative **26** in excellent yield. Compound **26** on silyl ether protection of free alcohol group followed by ozonolysis/Pinnick at the terminal double bond afforded carboxylic acid derivative **28** in 80% yield. Compound **28** on treatment with *N*-hydroxy phthalimide, DCC and DMAP furnished *N*-acyloxyphthalimida **29** in 82% yield. Further, the derivative **29** was subjected to blue light photoredox decarboxylation at rt employing Hantzsch ester and catalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ to get the desired product **30** in good yield. The compound **30** on H_2 and palladium hydroxide mediated debenzylation gave hydroxy derivative **31** in 99% yield.

Furthermore, selective tosylation of diol **31** was carried out using tosyl chloride which furnished tosylate **32** in 82% yield. The free alcoholic functional group of tosyl derivative **32** was treated with 1,10-thiocarbonyldiimidazole (TCDI) and DMAP and provided the acyclic thiocarbonate **33** which was subjected to radical deoxygenation employing the Oshima´s radical conditions to furnish deoxygenated product **34**. Elimination of silyl ether of compound **34** was carried out using $BF_3.OEt_2$ to produce the primary hydroxy derivative **35** in 70% yield. Finally, the synthesis of (+)-muscarine **5a** was accomplished by replacement of tosyl group with $N(CH_3)$ with known literature procedure.[7d]

Boukouvalas, J. *et al.* (2007)[6e]

Boukouvalas and his team disclosed the stereoselective synthesis of (+)-muscarine iodide **5a** from (*S*)-*γ*-hydroxymethyl-γ-butyro lactone **36** employing hydroboration oxidation reaction as principal step (Scheme 14). (*S*)-*γ*-hydroxymethyl-γ-butyro lactone **36** on silyl protection followed by DIBAL reduction furnished tetrahydrofuran **38** in 86% yield. The free alcohol group of derivative **38** on mesylation in the presence of mesyl chloride and NEt_3 and subsequent *β*-elimination afforded the dihydrofuran derivative **39** in 77% yield. Compound **39** underwent methylation on treatment with *t*-BuLi and excess of MeI in the presence of tetramethylethylenediamine (TMEDA) yielded compound **40** in 85% yield. Hydroboration of vinyl ether **40** was carried out using the hydrating reagent thexylborane ($ThxBH_2$) which furnished hydroxy derivative **41** in 59% yield.



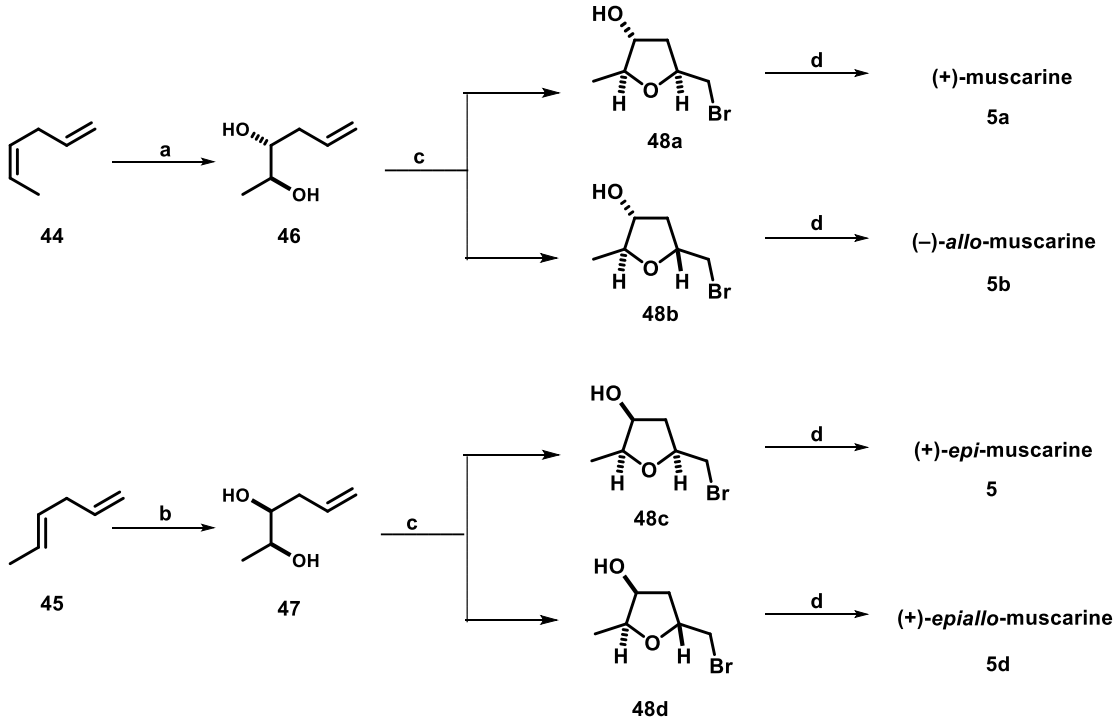
Scheme 14. *Reagents and conditions*: (a) *tert*-Butyldiphenylsilylchloride, triethylamine, 4-Dimethylaminopyridine, DCM, 0 ^oC , rt, 3 h, 86%; (b) $(i\text{-}Bu_2AlH)_2$, DCM, -78 ^oC, 2 h, 95%; (c) Mesyl chloride, triethylamine, DCM, -20 ^oC to -40 ^oC, 2.5 h, 77%; (d) *tert*-butyllithium, MeI, TMEDA, THF, -78 ^oC - rt, 13 h, 85%; (e) $ThxBH_2$, THF, *aq*. NaOH/*aq*. H_2O_2, 0 ^oC - rt,

22h, 59%; (f) n-Bu_4NF, oxolane, rt, 2.5 h, 93%; (g) $P(C_6H_5)_3$, iodine, 1,3-diazole, toluene, 70 ^oC, 2.5 h, 74%; (h) $N(CH_3)_3$, CH_3CH_2OH, reflux, 2.5 h, 92%.

Next, the derivative **41** on TBAF mediated silyl ether cleavage furnished the diol **42** which on subsequent treatment with iodine and PPh_3 at high temperature yielded iodide derivative **43** in excellent yield. Finally, the iodo-alcohol derivative **43** on refluxing with ethanolic solution of trimethylamine was converted into target compound (+)-muscarine **5a.**

Hartung, J. ***et al***. **(2003)**[6k]

Hartung and co-workers put forward the enantioselective synthesis of muscarine alkaloids (+)-*epi*-muscarine **5**, (+)-muscarine **5a**, (-)-*allo*-muscarine **5b** and (+)-*epiallo* muscarine **5c** from cis-1,4-hexadiene **44** and its trans isomer **45** using asymmetric dihydroxylation and diastereoselective bromoetherification as major steps as shown in Scheme 15. The cis isomer of 1,4-hexadiene **44** on exposure to AD-mix-beta at 0 °C afforded (2*S*,3*R*)-5- hexene-1,2-diol **46** in 51% yield and 40% ee. On the other hand trans isomer of 1,4-hexadiene **45** on treatment with AD-mix-alpha furnished (2*S*,3*S*)-5-hexene-2,3-diol **47** in 59% yield and 90% enantiomeric excess.



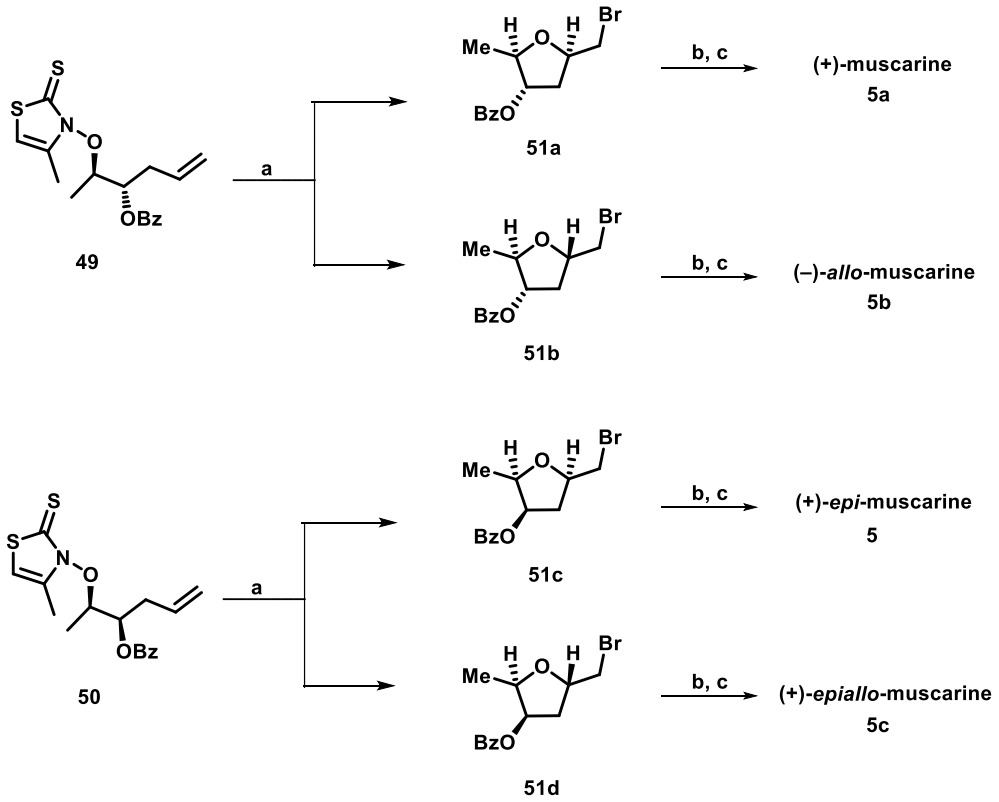
Scheme 15. *Reagents and conditions*: (a) AD-mix-alpha, *tert*-Butanol/water, $CH_3SO_2NH_2$, 0 ^oC, 52% (b) AD-mix-alpha, *tert*-Butanol/water, $CH_3SO_2NH_2$, 0 ^oC, 60% (c) *tert*-Butylhydroperoxide, pyHBr, chloroform, 10 mol% of VOL(OEt)(EtOH), 20 °C, 5.5 h, 59%

from **46**, 58% from **47**; (d) NMe_3, EtOH, 7 d, 60 °C, 63% from **48a**, 56% from **48b**, 52% from **48c**, 79% from **48d**.

Next, bromoetherifications of (2*S*,3*R*)-configured diol **46** was carried out using *tert*-butyl hydroperoxide (TBHP) and "oxovandium(V) complex [VOL(OEt)(EtOH)] [L = *N*-(2-hydroxyphenyl) salicylideneimine dianion]" as catalyst which afforded pure diastereomers 3,5-*trans*-substituted tetrahydrofuran **48a** in 35% yield and its cis isomer **48b** in 24% yield.
Further, bromocyclization of (2*S*,3*S*)-substituted hexenediol **47** employing the identical reagents and conditions gave pure diastereomers, 3,5-*cis*-configured and 3,5-*trans*-substituted bromomethyl tetrahydrofuran **48c** and **48d** respectively. Finally, muscarine alkaloids **5-5c** were prepared by treating bromomethyl-substituted tetrahydofurans **48a**, **48b**, **48c** and **48d** with 4.2 M solution of trimethyamine at 60 °C in ethanol respectively.

Hartung, J. *et al*. (2003)[6g]

Hartung and co-workers disclosed an elegant synthesis of (+)-*epi*-muscarine **5** and its analogues (+)-muscarine **5a**, (-)-*allo*-muscarine **5b** and (+)-*epiallo* muscarine **5c** employing alkoxyl radical cyclization reaction as pivotal step and (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **49** and its (2*R*,3*R*)-diastereomer **50** as starting materials (Scheme 16).



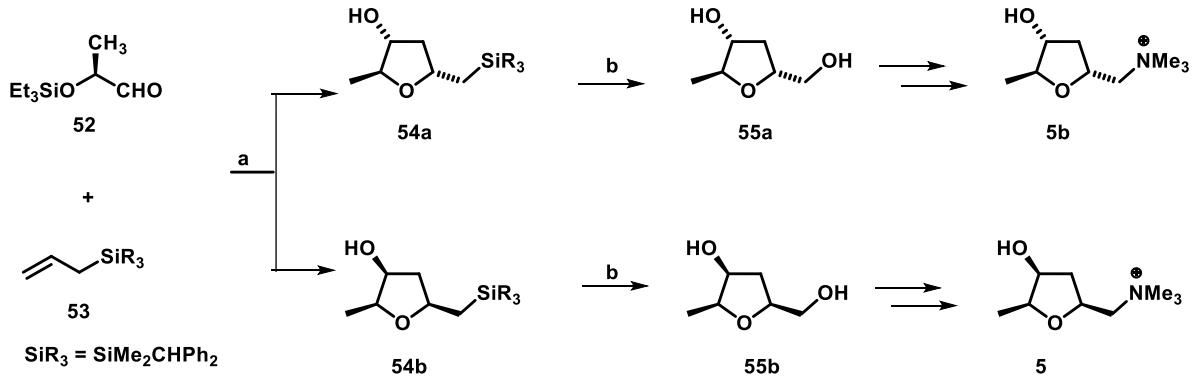
Scheme 16. *Reagents and conditions*: (a) $CBrCl_3$, *hv*, Hexane, 20 °C, 79%; (b) Caustic Soda, methanol, 20 °C, (92% from **51a**, 66% from **51b**, 84% from **51c**, 78% from **51d**); (c) Trimethylamine, Ethanol, 60 °C (89% for **51a**, 73% for **51b**, 65% for **51c**, 68% for **51d**).

The synthesis commenced with photolysis of thiazolethione derivative **49** with $BrCCl_3$ at 20°C in UV light to furnish (2*R*,3*S*,5*R*)-tetrahydrofuran **51a** and (2*R*,3*S*,5*S*)-diastereomer **51b** in 79% overall yield. Further saponification of benzoates **51a** and **51b** was carried out utilizing methanolic solution of NaOH which furnished diastereomers of 5-bromomethyl-2-methyltetrahydrofuran-2-ols, followed by treatment with ethanolic solution of trimethylamine for seven days to afford (-)-muscarine **5a** and (+)-*allo*-muscarine **5b** in in 89% and 73% yield, respectively.

Thiazolethione **50** was photolysed in the presence of near UV light and 8 equiv. of $BrCCl_3$ which furnished (2*R*,3*R*,5*R*)-3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofuran **51c** and its (2*R*,3*R*,5*S*)-stereoisomer **51d** in an equimolar ratio and in 79% yield. Column chromatography was used to separate **51c** and **51d** and simultaneously reacted with sodium hydroxide in methanol to afford the respective heterocycles which were treated with ethanolic solution of trimethylamine to furnish (-)-*epi*-muscarine **5** and (−)-*epiallo*-muscarine **5c**.

Angle, S. R. *et al* (2002)[6h]

Angle and his research group reported the formal stereoselective synthesis of muscarine alkaloids, (+)-*epi*-muscarine **5** and its stereo isomer (-)-*allo*-muscarine **5b** using [3+2]-cycloaddition as the key step and *R*-triethylsilyloxy aldehyde **52** and allylsilanes **53** as starting material (Scheme 17).

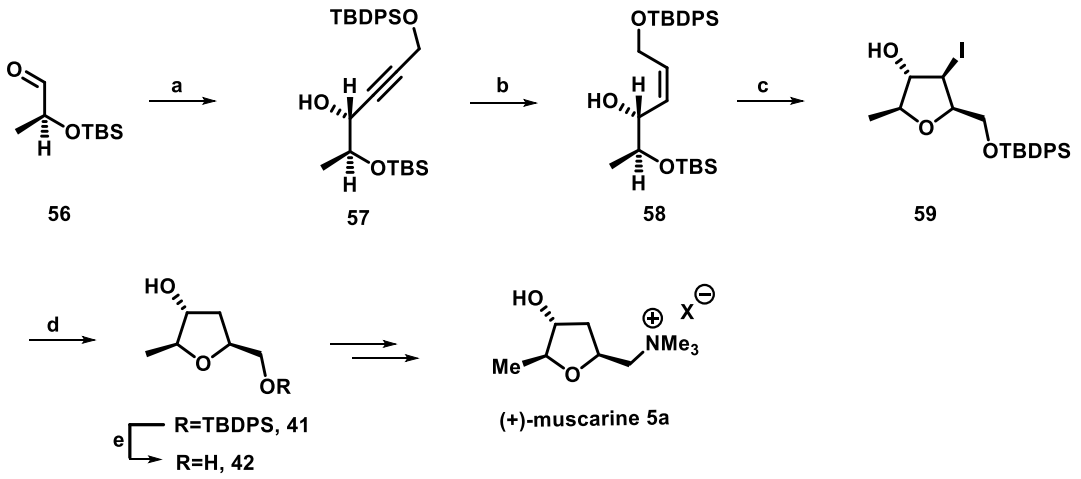


Scheme 17. *Reagents and conditions*: (a) $(Me_3C)_2C_5H_3N$, BF_3, CH_2Cl_2, -78 °C, 80%; (b) TBAF, H_2O_2, $KHCO_3$, 83% from **54a**, 88% from **54b**.

The cycloaddition reaction between allylsilane **53** and aldehyde **52** using dibutylpyridine afforded tetrahydrofuran diastereomers **54a** and **54b** (2.2:1) in 80% yield. Fleming-Tamao oxidation of compounds **54a** and **54b** with TBAF in the presence of $H_2O_2/KHCO_3$ furnished the diol **55a** with 83% yield (92% ee) and **55b** with 88% yield (96% ee) respectively. Further target compounds **5b** and **5** were obtained from diol **55a** and **55b** on reaction with TsCl and Me_3N following a known literature procedure.[7g]

Knight, D. W. *et al*. (2002)[6i]

D. W. Knight and his team described the formal synthesis of muscarine **5a** employing 5-*endo*-trig iodocyclisation as the pivotal step as displayed in Scheme 18. For muscarine **5a** synthesis *O*-silyl aldehyde **56** is used as starting material which could be obtained from commercially available methyl (*S*)-lactate *via* sequential silyl protection and DIBAL-H reduction.



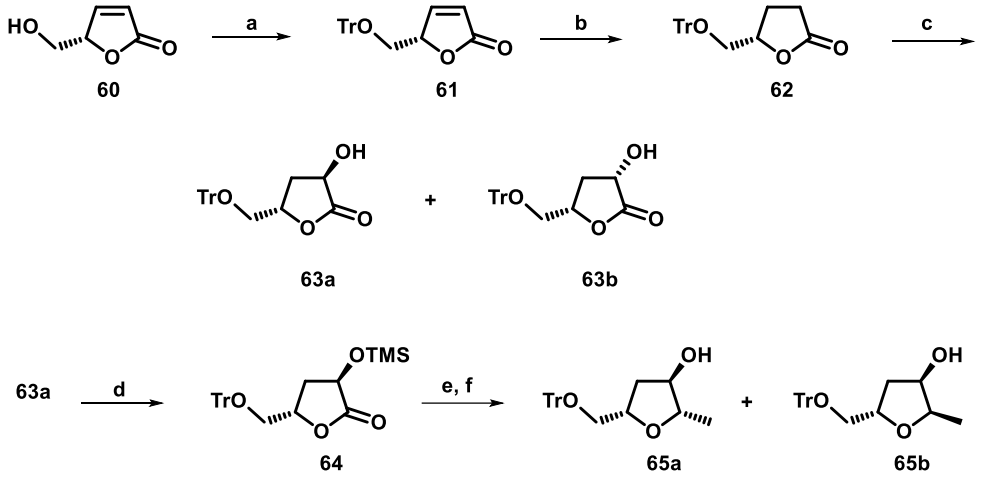
Scheme 18. "*Reagents and conditions*:" (a) Butyllithium, lithium ionophore, -78 °C, 4.5 h, 60% (b) H_2, 5% Pd-$CaCO_3$, benzopyridine, methanol, 20 °C, 1 h, 90%; (c) IBr, acetonitrile, −10 °C, 5 h, 70%; (d) i) H_2, 5% Pd-C, Et_3N, methanol, 20 °C, 4.5 h; ii) NH_4F, methanol, 20 °C, 12.5 h, 91%.

Anti-Selective incorporation of *O*-TBDPS protected propynol was performed to the *O*-silyl aldehyde **56** utilizing BuLi and 12-crown-4 which afforded alkyne-diol **57** as a single enantiomer in 60% yield. Then compound **57** was exposed to Lindlar reduction conditions; 5% Pd–$CaCO_3$, MeOH, quinoline under 1 atm pressure of H_2 which furnished *anti*-(*Z*) cyclisation precursor **58** in 90% yield. *O*-silyl derivative **58** was subjected to cyclisation in the presence of iodine monobromide in acetonitrile which afforded iodo-tetrahydrofuran **59** in 70% yield. Next, iodine of compound **59** was removed by hydrogenolysis to give tetrahydrofuran

derivative **41** which on silyl deprotection using TBAF in methanol led to formation of diol derivative **42**. This was the formal synthesis of muscarine **5a**. The final product could be obtained by tosyl protection of the primary alcoholic group succeeded by thermolysis using methanolic solution of trimethylamine at 80°C following known literature procedure.[7d]

Kang, K. H. *et al.* (2000)[6n]

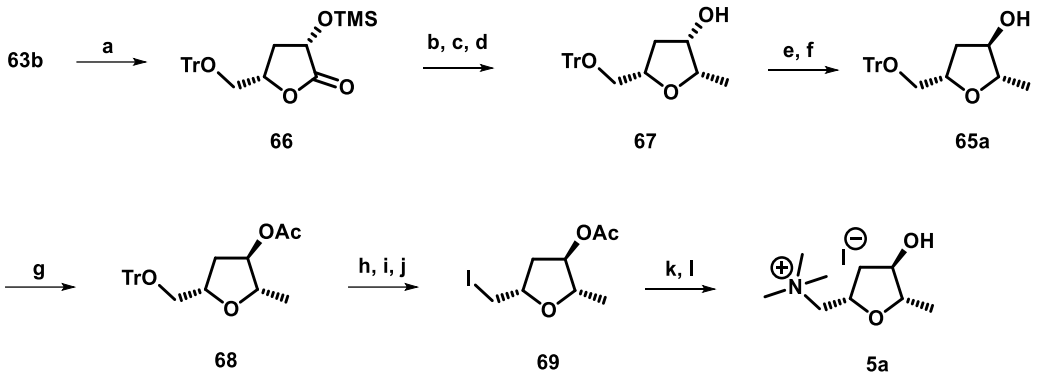
Kang and co-workers disclosed the synthesis of (+)-muscarine **5a** from (*S*)-(−)-5-hydroxy-2(5*H*)-furanone **60** using a lengthy strategy to give an straightforward way to achieve great variety of its isomers. As outlined in Scheme 19 synthesis started from furanone derivative **60**, which on tritylation with trityl chloride in azabenzene for 16 h afforded tritylated protected butanolactones **61** in 83% yield.



Scheme 19. *Reagents and conditions*: (a) $(C_6H_5)_3CCl$, azabenzene, 70 °C, 83%; (b) H_2, $Pd/CaCO_3$, $(CH_2)_3CH_2O$, 96%; (c) $C_{13}H_{26}LiNSi_2$, , MoOPH, -78 °C to −25 °C, ½ h, 71% (**63a**:**63b** 12:1); (d) $(CH_3)_3SiCl$, azabenzene, 0 °C–rt, 86%; (e) Tebbe reagent, oxolane /methylbenzene (1:3), azabenzene, -40 °C; (f) Spongy Ni/H_2, oxolane, 78% (**65a**:**65b** 44:56) (two steps).

α, *β*-Unsaturated lactone **61** on H_2/Pd mediated hydrogenation furnished the lactone **62** in 96% yield. Further lactone **62** was *α*-hydroxlated on treatment with 1.0 M LiHMDS and MoOPH **(**oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)) to furnish diastereomeric alcohols **63a** and **63b** in 12:1 ratio. Alcohol **63a** after flash column chromatography separation, was protected with TMS which furnished silyl ether **64** in 86% yield. Lactone **64** was subjected to *exo*-methylation using 0.5 M Tebbe reagent in

methylbenzene followed by palladium catalysed hydrogenation and deprotection of silyl group to furnish **65a** and **65b** in a ratio of 1:11.



Scheme 20. *Reagents and Conditions*: (a) $(C_6H_5)_3CCl$, Pyridine, 0 °C-rt, 85%; (b) Tebbe reagent (0.5 M), THF/methyl benzene (1/3), Pyridine, −40 °C; (c) H_2, $Pd/CaCO_3$, oxolane; (d) K_2CO_3 in methanol, 67% (three steps); (e) diethyl azodicarboxylate, $C_6H_5CO_2H$, $P(C_6H_5)_3$, THF, 0 °C; (f) methanolic solution of aq. K_2CO_3, 67% (two steps) (g) $(CH_3CO)_2O$, sodium acetate, 60 °C, 70%; (h) Ferric chloride hexahydrate, DCM; (i) TsCl, C_5H_5N, −20 °C; (j) NaI, $CH_3C(O)CH_2CH_3$, 80 °C, 56% (three steps); (k) MeOH solution of aq. K_2CO_3, 72%; (l) NMe_3 in CH_3CH_2OH, reflux, 92%.

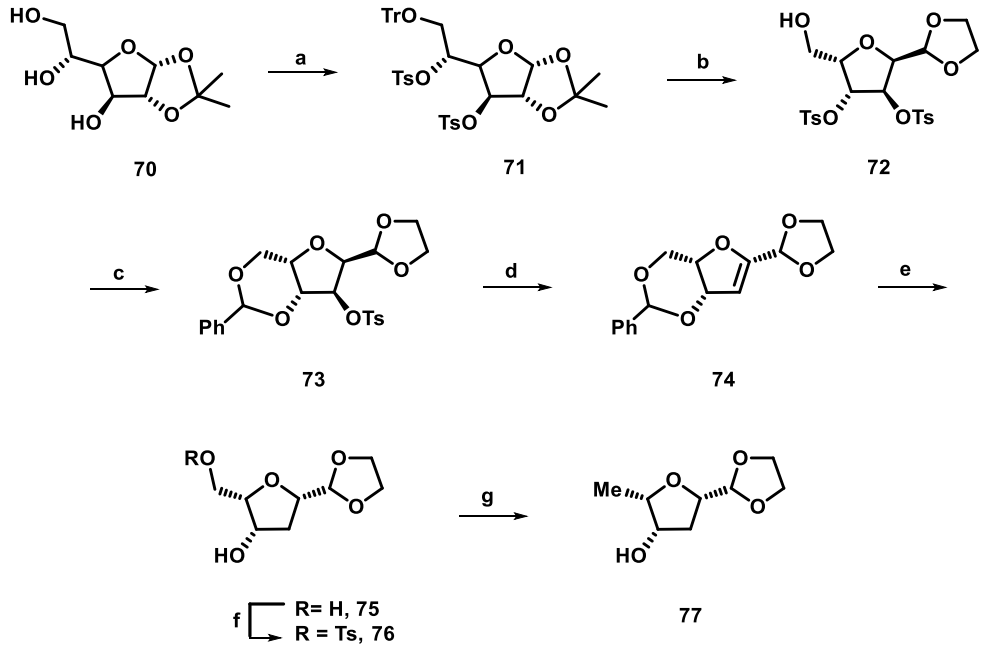
(3*S*,5*S*)-buytyrolactone **63b** could be transformed to **65a** (Scheme 20) *via* standard organic transformation *viz.* silyl protection, exo methylation followed by deprotection of silyl and subsequent Mitsunobu inversion of hydroxy group at C-3 following known literature procedure.

The free hydroxyl group of **65a** was esterified using ethanoic anhydride and NaOAc at 60 °C to furnish the acetate **68** in 70% yield. Iodide **69** was obtained by detritylation, tosylation and subsequent iodination on treatment with sodium iodide in methyl ethyl ketone at 80 °C in 56% overall yield. Finally, the compound **69** was exposed to deacetylation to yield hydroxy intermediate, which on reaction with ethanolic solution of $N(Me)_3$ furnished (+)-muscarine iodide **5a**.

Popsavin, V. *et al.* (2000)[6m]

Popsavin and his team described the total synthesis of (+)-*epi*-muscarine **5** and (+)-muscarine **5a** from chiral precursor D-glucose **70** employing S_N2 cyclization and hydrogenation as key steps (Scheme 21). The synthesis started with tritylation and subsequent tosylation of monoacetone glucose **70** in single-pot reaction to yield the respective 3,5-di-*O*-tosyl-6-*O*-trityl

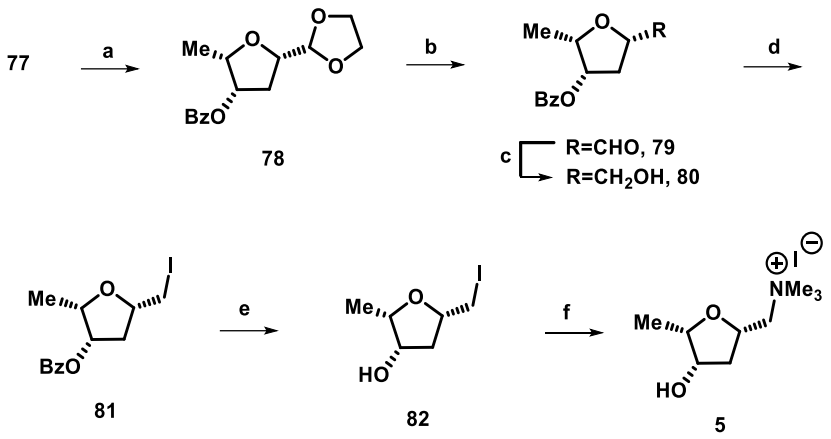
structural analog **71** in appreciable yield. 3,5-Di-*O*-tosyl ester **71** was reacted with ethane-1,2-diol using a catalyst *p*-toluenesulfonic acid which afforded 3-*O*-tosyl derivative **72** in 54% overall yield. Condensation reaction of compound **72** with *α*,*α*-dimethoxytoluene in DMF furnished 4,6-*O*-benzylidene derivative **73** which on subsequent treatment with tetrabutylammonium fluoride afforded olefin **74** in 74% overall yield. Hydroxy derivative **75** was obtained from olefin **74** by one-pot procedures of catalytic hydrogenation and debenzylation using 10% Pd/C. Compound **75** on monotosylation produced tosyl analog **76** in 80% yield. Lithium aluminum hydride mediated detosylation in hot tetrahydrofuran yielded chiral intermediate **77** in 90% yield. Compound **77** act as an intermediate to produce the muscarine alkaloids *epi*-muscarine **5** and muscarine **5a**.



Scheme 21. (a) TrCl, Pyridine, TsCl, 13 days, rt, 100%; (b) Ethane-1,2-diol, PTSA, 80 ^{o}C, 5 h, 54%; (c) $C_6H_5CH(OCH_3)_2$, PTSA, DMF $(CH_3)_2NC(O)H$, 70 ^{o}C, 20 h, 86%; (d) Bu_4NF, MeCN, N_2, reflux, 48 h, 86%; (e) H_2, 10% Pd/C, CH_3CH_2OH, CH_3COOH, rt, 16 h, 83%; (f) $H_3C(C_6H_4)SO_2Cl$, Pyridine, rt, 6 days, 80%; (g)LAH, tetrahydrofuran, N_2, reflux, 4 h, 90%.

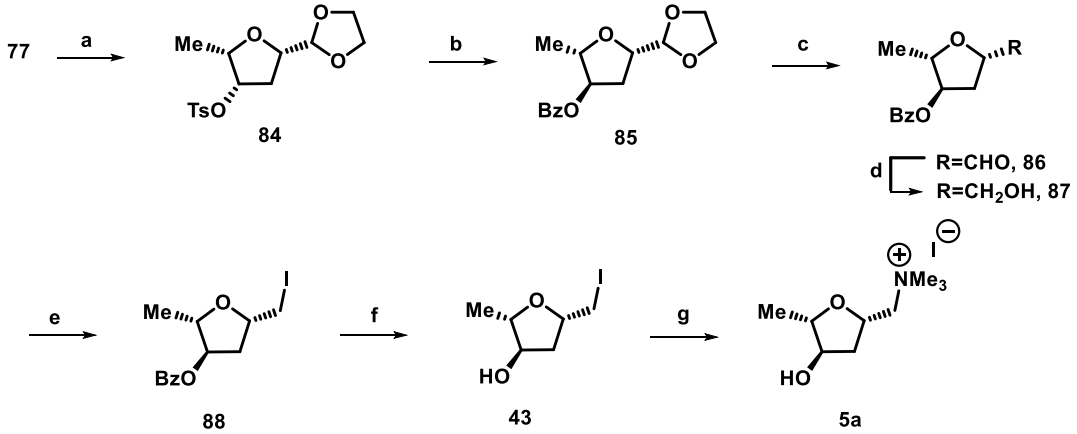
Intermediate **77** was *O*-benzoylated using benzyl chloride and pyridine to get benzoyl analog **78** in 86% yield. Dioxolane moiety was removed to give readily decomposable aldehyde **79** which was subsequently reduced with $NaBH_4$ to furnish primary alcohol **80** in 59% yield as shown in Scheme 22. Compound **80** on iodination in the presence of iodine and

triphenylphosphine furnished iodo derivative **81** in 84% yield which on subsequent debenzylation using potassium carbonate furnished iodo alcohol **82** in 83% yield.



Scheme 22. (a) BzCl, Py, rt, 24 h, 86%; (b) TFA, 6 M HCl, rt, 24 h; (c) $NaBH_4$, MeOH, rt, 2 h, 59%; (d) imidazole, Ph_3P, I_2, toluene, N_2, reflux, 3 h, 90%; (e) K_2CO_3, MeOH, THF, rt, 2 h, 65%; (f) Me_3N, CH_3CH_2OH, 80 ^oC, 3.5 h, 95%.

Final *epi*-muscarine iodide **5** was obtained by reaction of **82** with trimethylamine in ethanol.



Scheme 23. (a) TsCl, Pyridine, rt, 48.5 h, 80%; (b) C_6H_5COOK, $(CH_3)_2NC(O)H$, 100 ^oC, 24 h, 66%; (c) TFA, 6 M HCl, 14 ^oC, 24 h; (d) $NaBH_4$, MeOH, rt, 2 h, 27%; (e) Imidazole, Ph_3P, I_2, toluene, N_2, reflux, 3 h, 84%; (f) K_2CO_3, CH_3OH, oxolane, rt, 2 h, 83%; (g) Me_3N, CH_3CH_2OH, 80 ^oC, 3 h, 93%.

For the synthesis of (+)-muscarine as illustrated in Scheme 23, hydroxy group of intermediate **77** was tosylated using TsCl in pyridine which furnished the 4-*O*-tosyl derivative **84** in 80% yield. Tosyl derivative **84** was exposed with potassium salt of benzoic acid to afford the inverse configured chiral product **85** in 66% yield. Thus, the reaction of compound **85** with a mixture

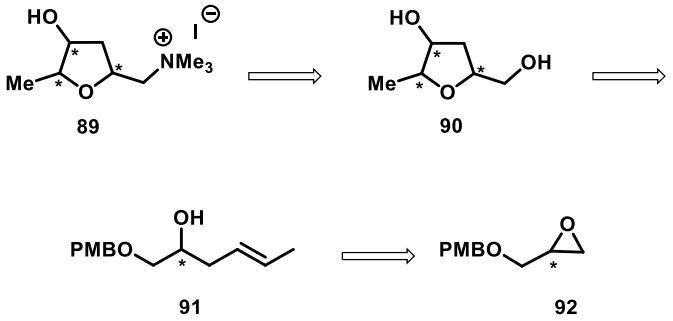
of trifluoroacetic acid and 6 M HCl (4:1) afforded the fickle aldehyde **86**, which on treatment with $NaBH_4$ yielded hydroxy derivative **87**. Iodo derivative **88** was obtained by treatment of **87** with iodine, triphenylphosphine and imidazole in 84% yield. Compound **88** was reacted with K_2CO_3 which furnished iodo alcohol **43** in 83% yield. Finally, (+)-muscarine iodide **5a** was obtained from compound **43** by treatment with ethanolic solution of trimethylamine.

2.3 Present Work:

We represent a new, productive and novel approach for the muscarine alkaloids and its application to the enantioselective synthesis of (+)-(-2*S*,3*S*,5*S*)-*epi*-muscarine **5** employing Sharpless AD, regioselective epoxide ring opening and intramolecular S_N2 cyclization as initial measures.

2.4 Results and Discussion:

We envisioned our synthetic route for the muscarine including *epi*-muscarine **5** *via* general retrosynthetic approach as displayed in Scheme 24. We envisioned that the 2,5-disubstituted-4-hydroxy tetrahydrofuran **90** was a key intermediate compound from which *epi*-muscarine **5** and muscarine **5a** could be prepared *via* regioselective iodination of primary hydroxyl group followed by nucleophilic substitution reaction with trimethylamine. The THF derivative **90** could be derived from the alkene derivative **91** by tosylation of free hydroxy group followed by asymmetric dihydroxylation and treatment with base.

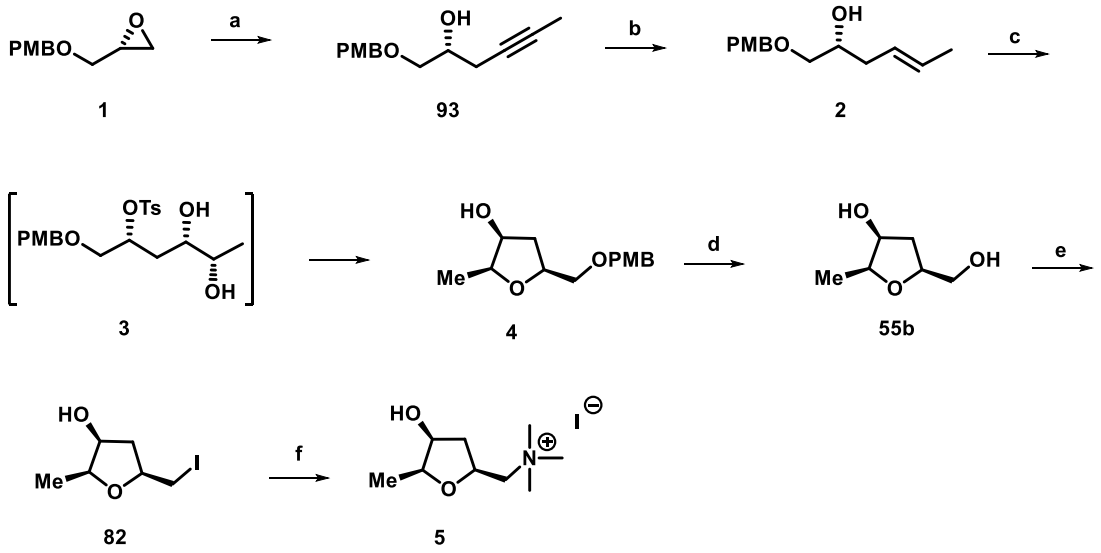


Scheme 24. Retrosynthetic general approach for muscarine alkaloids.

The alkene **91** in turn could be accessed from enantiomerically pure PMB protected glycidol **92** using propynyllithium in presence of boron trifluoride etherate ($BF_3.OEt_2$) to get the alkyne intermediate followed by selective reduction. The *R* / *S* configurations to all chiral centers of muscarine **89** enantiomers could be simply achieved by either changing chiral ligands $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ in Sharpless AD reaction step or alternatively with *Z*-olefin

of intermediate **91** followed by Sharpless AD. The synthesis of *epi*-muscarine **5** started from the readily available (*R*)-PMB (p-methoxybenzyl) glycidyl ether **1** which was prepared by known literature procedure in 95% yield ($[\alpha]_D^{25}$ +3.18 (*c*, 1.50 in $CHCl_3$) {lit.[8] $[a]_D^{25}$ = +3.2 (*c*, 1.50, $CHCl_3$}). The (*R*)-PMB glycidyl ether **1** on treatment with propynyllithium employing boron trifluoride etherate at -78 ^oC furnished the alkyne alcohol **93** in 92% yield (Scheme 25). The IR spectrum of **93** revealed hydroxyl absorption at 3436 cm^{-1}.

Our initial attempt to reduce the alkyne derivative **93** with $LiAlH_4$ in THF solvent at various temperature was found to be sluggish. In view of the less reactivity of alkyne derivative **93** we decided to take diglyme[9] and THF solvents due to higher boiling point and then carried out the $LiAlH_4$ reduction at higher temperature, which proceeded well, and afforded the *trans*-olefin **2** in 88% yield.



Scheme 25. *Reagents and conditions*. (a) *n*-BuLi, propyne, $BF_3.Et_2O$, dry THF, -78 ^oC, 3 h, 92%; (b) $LiAlH_4$, diglyme, dry THF, 125 ^oC, 4 h, 86%; (c) i) TsCl, DMAP, Et_3N, dry DCM, 0 ^oC to rt, 6 h; ii) OsO_4 (0.5 mol %), $K_3[Fe(CN)_6]$, $(DHQ)_2PHAL$ (1 mol %), K_2CO_3, $CH_3SO_2NH_2$, *t*-BuOH/water (1:1 v/v), 0 ^oC, 25 h; iii) K_2CO_3, methanol, rt, 4 h, (3 steps, 90%); (d) CAN, CH_3CN/H_2O (4:1v/v), 0 ^oC, 1.5 h, 91%; (e) I_2, imidazole, Ph_3P, toluene, reflux, 3 h, 84%; (f) Et_3N, EtOH, reflux, 3 h, 95%.

The ^1H NMR spectrum of **2** revealed alkene proton at δ 5.51 (td, one proton) with J-coupling = 21.52, 15.12, 6.40 Hz and at δ 5.43 (td, one proton) with *J* = 22, 15.12, 6.88 Hz indicating *trans*-olefin.

With *E*-olefin **2** in hand, we then subjected it to treatment with TsCl (tosyl chloride) and triethylamine in the presence of DMAP (4-dimethylaminopyridine) to furnish the tosylated *E*-

olefin, which was subsequently on dihydroxylation under Sharpless AD conditions[10] using OsO_4 (osmium tetroxide) and co-oxidant $K_3[Fe(CN)_6]$ (potassium ferricyanide) in the presence of $(DHQ)_2PHAL$ ligand furnished the *o*-tosylated diol intermediate **3**. Further, the *o*-tosylated diol intermediate **3** without purification on treatment with K_2CO_3 in methanol underwent cyclisation in S_N2 fashion and afforded PMB protected tetrahydrofuranyl hydroxyl derivative **4** as a single diastereoisomer in excellent yield.[11] In the infrared spectrum of derivative **4**, -OH absorption was detected at 3442 cm^{-1}.

The PMB ether deprotection of tetrahydrofuranyl hydroxy derivative **4** with CAN (ceric ammonium nitrate) furnished the tetrahydrofuranyl hydroxy derivative **55b** in 91% yield. The hydroxyl group IR absorption was identified at 3408 cm^{-1}. Furthermore, the absence of signals resonating in the aromatic region in the ^{1}H-NMR spectrum of compound **55b** supports the cleavage of the PMB ether moiety.

Regioselective iodination of primary hydroxyl group of tetrahydrofuranyl alcohol derivative **55b** with iodine and triphenylphosphine in the presence of imidazole as base under refluxed conditions furnished iodo derivative **82** in 84% yield.[6j] In the IR spectrum stretching at 3619 cm^{-1} confirms the existence of primary alcohol group and appearance of new absorption peak at 496 cm^{-1} shows the presence of alkyl iodine group.

Finally, the desired product *epi*-muscarine **5** was obtained as its iodide salt on treatment of iodo derivative **82** with ethanolic solution of trimethylamine in 95% yield ($[\alpha]_D^{25}$ +31.8 (*c*, 0.50 in H_2O) {lit.[6m] $[a]_D^{25}$ = +32 (*c*, 0.55, H_2O}). The spectral and physical properties of target compound **5** were in full agreement with reported values.[6m]

2.5 Conclusion:

To sum up, we described a short and efficient enantioselective general synthesis of muscarine alkaloid and its application to the asymmetric synthesis of *epi*-muscarine iodide salt **5** from readily available (*R*)-PMB glycidyl ether as starting material and employing Sharpless AD, intramolecular S_N2 cyclization and regioselective epoxide ring opening as fundamental steps. The *epi*-muscarine iodide salt **5** was produced in overall yield of 52%. The synthetic route presented has further capabilities for the stereochemical modifications in all the cyclic ring positions and advancement to other stereoisomers.

2.6 Experimental Section:

All experiments were performed under Nitrogen, with moisture free, freshly extracted solvents through distillation unless otherwise indicated. All the reagents or chemicals were put in

reaction either via syringe or cannula. Each distillation was also performed under unreactive conditions. Every reaction was performed at their respective temperatures as narrated within their respective schemes. Solvent evaporation was performed utilising a Heidolph rotary evaporator at reduced pressure and at less than 40 °C temperature.

Chromatography

Every reaction performed was examined through Thin Layer Chromatography executed using commercially available silica gel plates 60 F_{254} using UV light, then were stained in ninhydrin or in ethanolic solution of anisaldehyde or in aqueous KMnO4 as development reagents follow up by concise heating using a heating gun. For column chromatography, silica gel of mesh size 60-120 and 100-200 was employed and different compositions of ethyl acetate/hexane and methanol/ dichloromethane were used as organic eluent.

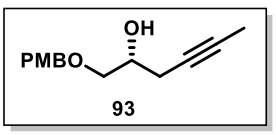
Reagents and solvents

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

Spectroscopic Measurements

JEOL ECS spectrometer was employed for recording the ^{1}H NMR and ^{13}C NMR respectively. Tetramethylsilane (TMS) utilized as reference. The measuring unit for chemical shifts (δ) is parts per million (ppm). J values (Coupling constants) are listed in hertz (Hz). Electron spray ionization (ESI) were used for recording HRMS and mass data were presented as m/z. The IR spectra were captured on an Agilent resolution Pro 600 FT-IR spectrometer with a beam-condensing ATR attachment, and the peaks were measured in centimeter inverse. Yields mentioned referred to isolated combined amount after chromatography.

(*R*)-1-((4-Methoxybenzyl)oxy)hex-4-yn-2-ol, 93

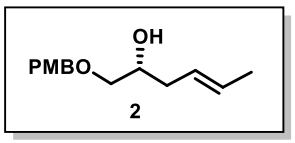


93

A round-bottomed (RB) flask of 100mL was charged with propyne (0.247g, 6.17 mmol) in dry THF (10 mL) and temperature was reduced to -78 °C. A solution of *n*- butyllithium (2.5 M in hexane, 2.87 mL, 7.19 mmol) was added drip by drip *via* syringe and agitated under inert atmosphere. The cooling bath was set to rest to reach the 0 °C over 30 min. Meanwhile, the organic suspension became dark red in colour. The bath was cooled again to -78 °C before a solution of PMB-

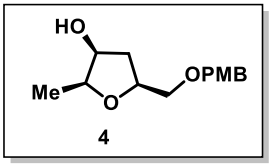
glycidyl ether (1.0 g, 5.14 mmol) and $BF_3 \cdot OEt_2$ (0.716 mL, 5.65 mmol) were introduced. The resultant organic suspension was agitated at -78 °C for 2.5 hours, after that cold bath was removed and saturated aqueous $NaHCO_3$ solution was poured to terminate the reaction. The organic layer was extracted with EtOAc (3 x 15 mL) and the collected organic phases were rinsed with brine and moisture was removed employing Na_2SO_4. Excess solvent was distilled under *vacuo* and purified using silica gel chromatography (EtOAc/hexane 1:4) to furnish the alkyne alcohol derivative **93** (1.09 g, 91%) as a colourless oil. R_f = 0.45 (EtOAc/hexane 1:4); $[\alpha]_D^{25}$ = -9.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3436, 3223, 2937, 2873, 2238, 1879, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.26 (d, *J* = 8.70Hz, 2H), 6.88 (d, *J* = 8.70 Hz, 2H), 4.49, (s, 2H), 3.92-3.86 (m, 1H), 3.81 (s, 3H), 3.56 (dd, J = 9.4, 3.7Hz, 1H), 3.44 (dd, *J* = 9.4, 6.6 Hz,1H), 2.45 (br s, 1H), 2.39-2.35 (m, 2H), 1.78 (t, *J* = 2.28 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 159.2, 130.0, 129.4, 113.8, 78.0, 74.7, 73.0, 72.7, 69.0, 55.2, 23.8, 3.5; HRMS (ESI), calcd for $C_{14}H_{18}O_3$ $[M+H]^+$: 235.1329; found: 235.1334.

(*R, E*)-1-(4-Methoxybenzyloxy)hex-4-en-2-ol, 2



To the above alkyne alcohol derivative **93** (1.0 g, 4.27 mmol) in diglyme (10 mL) was added dropwise a cold suspension of $LiAlH_4$ (486 mg, 12.80 mmole) in a mixture of diglyme (10 mL) and dry THF (5 mL). The reaction miscellany was refluxed for 4 h at 125 °C. As the reaction completed, shown by TLC, the reaction mixture was cooled to 0 °C and terminated by the careful addition of water (5 mL), 10% NaOH solution (5 mL), until the solid turned whitish grey. Then the quenched solid was rinsed with EtOAc (3x 10 mL) and organic fractions were collected and rinsed with 1.5 N HCl (3 x 10 ml) to remove the diglyme. Now whole organic portion was dried over anhydrous Na_2SO_4 and after that solvent was vaporized using rotary evaporator to get the crude product. Further purification was carried out using silica gel column chromatography (EtOAc/hexane 3:7) to furnish the olefin derivative **2** (868 mg, 86%) as a colorless oil. R_f = 0.37 (EtOAc/hexane 3:7); $[\alpha]_D^{25}$ = -5.80 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) *v*: 3452, 3103, 2935, 2863, 1630, 1459, 1245, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.26 (d, *J* = 8.72, 2H), 6.88 (d, *J* = 8.72, 2H), 5.51 (td, *J* = 21.52, 15.12, 6.40 Hz, 1 H), 5.43 (td, *J* = 22.0, 15.12, 6.88 Hz, 1 H), 4.48 (s, 2H), 3.57(dd, *J* = 6.88, 4.16 Hz, 1 H), 3.48 (dd, *J* = 9.64, 3.24 Hz, 1 H),2.35 (brs, 1H), 2.17 (t, *J* = 6.88 2H), 1.67 (dd, *J* = 0.92, 5.90 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 159.2, 130.0, 129.4, 128.4, 126.5, 113.8, 73.6, 72.9, 55.2, 36.6, 18.0; HRMS (ESI), calcd for $C_{14}H_{20}O_3$ $[M+H]^+$237.1485; found 237.1481.

(2*S*,3*S*,5*S*)-5-((4-Methoxybenzyloxy)methyl)-2- methyltetrahydrofuran-3-ol, 4



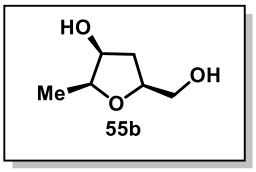
4

To a solution of alkene alcohol derivative **2** (400 mg, 1.69 mmol) and trimethylamine (257 mg, 0.35 mL, 2.54 mmol) in dry CH_2Cl_2 (10 mL) at 0 ^oC were added tosyl chloride (355 mg, 1.86 mmol) and DMAP (41 mg, 0.20 mmol) sequentially. The reaction mixture was put at rest to attain the rt, and then stirred for 6 hours, saturated aqueous NH_4Cl solution was added to quench the reaction. After extraction with CH_2Cl_2 (3 x 10 mL) the collected organic portion was combined and rinsed with salt water, dried over anhydrous sodium sulphate, concentrated in *vacuo*, and used for the next step after filtration column.

To a agitated solution of K_2CO_3 (702 mg, 5.08 mmol), $K_3Fe(CN)_6$ (1.67 g, 5.08 mmol), and $(DHQ)_2PHAL$ (14 mg, 1 mol %) in *t*-BuOH/H_2O (16 mL 1:1 v/v) at 0 ^oC was added osmium tetroxide (0.08 mL, 0.1m solution in toluene, 0.5 mol %) followed by methane sulfonamide (160 mg, 1.69 mmol) and stirred the reaction mixture at 0 ^oC for 5 min. The above synthesized tosylated alkene intermediate was poured entirely and stirred the organic suspension for 24 h at 0 ^oC and then solid sodium sulfite (800 mg) was added to quench the reaction. The mixture was agitated for another 1 hour, after which the solution was extracted with organic solvent ethyl ethanoate (3 x 10 mL) and concentrated under pressure, which was used directlty without purification.

To a stirred solution of the above synthesized diol precursor in MeOH (10 mL) K_2CO_3 (467 mg, 3.38 mmol) was added and the mixture was agitated for 4 h at room temperature. Under low pressure MeOH was evaporated, then water was poured and collected with ethyl acetate (3 x 10 ml). The organic fractions were rinsed with brine (salt water), dried over anhydrous Na_2SO_4, concentrated on rotary evaporator, and purified by silica gel column chromatography (EtOAc/hexane 3:7) to furnish the tetrahydrofuran hydroxy derivative **4** (0.384 mg, 90%) as a colourless oil. R_f = 0.37 (EtOAc/hexane 3:7); $[a]_D^{25}$+13.02 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) *v*: 3442, 1616, 1588, 1515, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.27 (d, *J* = 8.72, 2H), 6.88 (d, *J* = 8.72, 2H), 4.63 (d, *J* = 11.48, 1H), 4.46 (d, *J* = 11.44, 1H), 3.90-3.87 (m, 1H), 3.83-3.74 (m, 5H), 3.67 (dd, *J* = 10.52, 2.28, 1H), 3.38 (dd, *J* = 10.08, 1.84, 1H), 2.37-2.30 (m, 1H), 1.91 (dd, *J* = 13.72, 2.76, 1H), 1.83 (brs, 1H), 1.27 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.4, 129.5, 129.2, 113.9, 80.0, 76.2, 73.2, 72.6, 71.4, 55.2, 37.5, 14.1; HRMS (ESI), calcd for $C_{14}H_{20}O_4$ $[M+ H]^+$253.1434; found 253.1433.

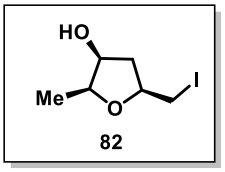
(2*S*,3*S*,5*S*)-5-(Hydroxymethyl)-2-methyltetrhydrofuran-3-ol, 55b



55b

To a solution of PMB protected tetrahydrofuranyl hydroxyl derivative **4** (250 mg, 0.99 mmol) in $CH_3CN:H_2O$= 4:1 (8 mL) at 0 ºC, CAN (1.31 g, 2.39 mmol) was added. After agitating organic suspension for 1.5 h, it was quenched with brine solution (10 mL) and the organic portion was extracted with ethyl acetate (3 x 5 mL). The combined organic portion of solvent was dried over anhydrous Na_2SO_4 and distilled using rotary evaporator. The remnant was purified by silica gel based column chromatography (EtOAc/hexane 1:1) to afford the tetrahydrofuranyl hydroxy derivative **55b** (119 mg) in 91% yield as a white solid, mp 67 °C{lit.[1], R_f = 0.5 (EtOAc/hexane 3:1); $[a]_D^{25}$+48.5 (*c* 1.0 in $CHCl_3$) {lit.[1] $[a]_D^{25}$= +47.0 (*c*, 0.90, $CHCl_3$)}; IR ($CDCl_3$) *v*: 3408, 2946, 2876, 2590, 1441, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.22-4.17 (m, 1H), 4.00 (dd,*J* = 5.52, 2.76Hz, 1H), 3.88-3.83 (m, 2H), 3.53 (dd, *J* = 11.92, 2.20 Hz, 1H), 3.11 (brs, 1H), 2.41 (ddd, *J* = 14.2, 10.0, 5.4 Hz, 1H), 1.92 (dd, *J* = 3.2, 14.2 Hz, IH), 1.29 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 80.0, 77.1, 72.6, 64.1, 37.5, 13.9; HRMS (ESI), calcd for $C_6H_{12}O_3$ $[M+H]^+$133.0859; found 133.0862.

2*S*,3*S*,5*S*)-5-(Iodomethyl)-2-methyltetrahydrofuran-3-ol, 82

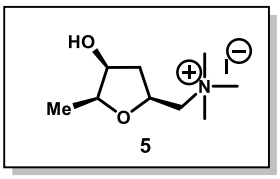


82

To a solution of tetrahydrofuranyl hydroxy derivative **55b** (60 mg, 0.45 mmol) in dry toluene (5 mL) were added successively imidazole (93 mg, 1.36 mmol), Ph_3P (178 mg, 0.68 mmol) and iodine (161 mg, 0.63 mmol). The reaction mixture was refluxed while agitationg in an inert atmosphere for 3 h. The toluene was evaporated under *vacuo*. Column chromatographyof silica gel of the remnant furnished the pure iodo compound **82** (93 mg, 84%) which was recrystallized from *n*-hexane to afford colourless needles crystal, R_f = 0.4 (EtOAc/hexane 1:3); m.p. 63.0 ºC {lit.[2]63.5ºC}; $[a]_D^{25}$ = -1.46 (*c* 1.0 in $CHCl_3$) {lit.[2]$[a]_D^{25}$ = -1.50 (*c* 1.13, $CHCl_3$)};IR ($CDCl_3$) 3619, 2935, 2882, 2677, 2533, 496 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.18 (brs, 1H), 3.97-3.84 (m, 2H), 3.43 (dd,*J* = 10.08, 6.00 Hz, 1H), 3.33 (dd,*J* = 10.08, 4.60 Hz, 1H), 2.42 (ddd,*J* = 14.44, 8.24, 5.96 Hz, 1H), 1.80 (ddd, *J* = 14.20, 5.04, 1.4 Hz, 2H), 1.67 (brs, 1H) 1.31 (d, *J* =6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 79.9, 73.4, 41.4, 14.0, 11.9; HRMS (ESI), calcd for $C_6H_{11}O_2I$ $[M+H]^+$242.9876; found 242.9870.

***epi*-Muscarine iodide, 5**

The iodo compound **82** (30 mg, 0.12 mmol) was refluxed at 80 ^{o}C in 40% ethanolic solution of trimethyamine in a airtight tube for 3 h. After the evaporation of volatiles, the viscous residue was parted between distilled H_2O (4 mL) and ethyl acetate (3 ml). Watery layer was collected and the organic layer was washed with H_2O (2 mL). The combined aqueous phases were evaporated by co-distillation with toluene, to afford the pure *epi*-Muscarine iodide alkaloid **5** (35 mg, 95%) as a yellow thick syrup. After recrystallisation using 2-propanol afforded pale yellow needles: m.p. 173 ^{o}C {lit.[2]m.p. 172-173^{o}C}; $[\alpha]_D^{25}$+31.8 (*c*, 0.50 in H_2O) {lit.[2] $[a]_D^{25}$ = +32 (*c* 0.55, H_2O)}; IR(KBr) *v*: 3419, 2976, 2883, 1655, 1561, 1462, 1059, 1012 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz) δ: 4.32 (q, *J* = 15.12, 7.32 1H), 4.10 (ddd, *J* = 7.80, 4.12, 1.84 Hz, 1H), 3.81(ddd, *J* = 8.24, 3.20, 1.84 Hz, 1H), , 3.46-3.36 (m, 2H), 3.05 (s, 9H), 2.48 (ddd, *J* = 20.60, 6.40, 2.28 Hz, 1H), 1.48 (ddd, *J* = 14.20, 5.52, 1.84 Hz, 2H), 1.09 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) δ: 80.7, 71.4, 71.2, 70.1, 54.0, 39.2, 13.3.

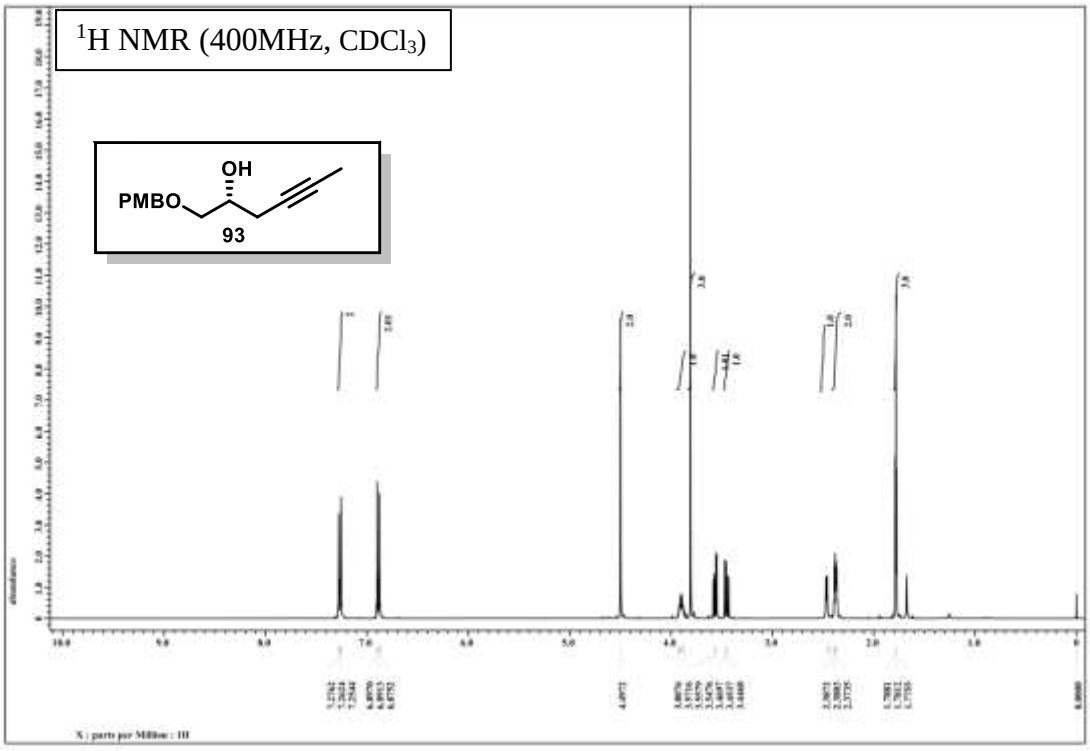


5

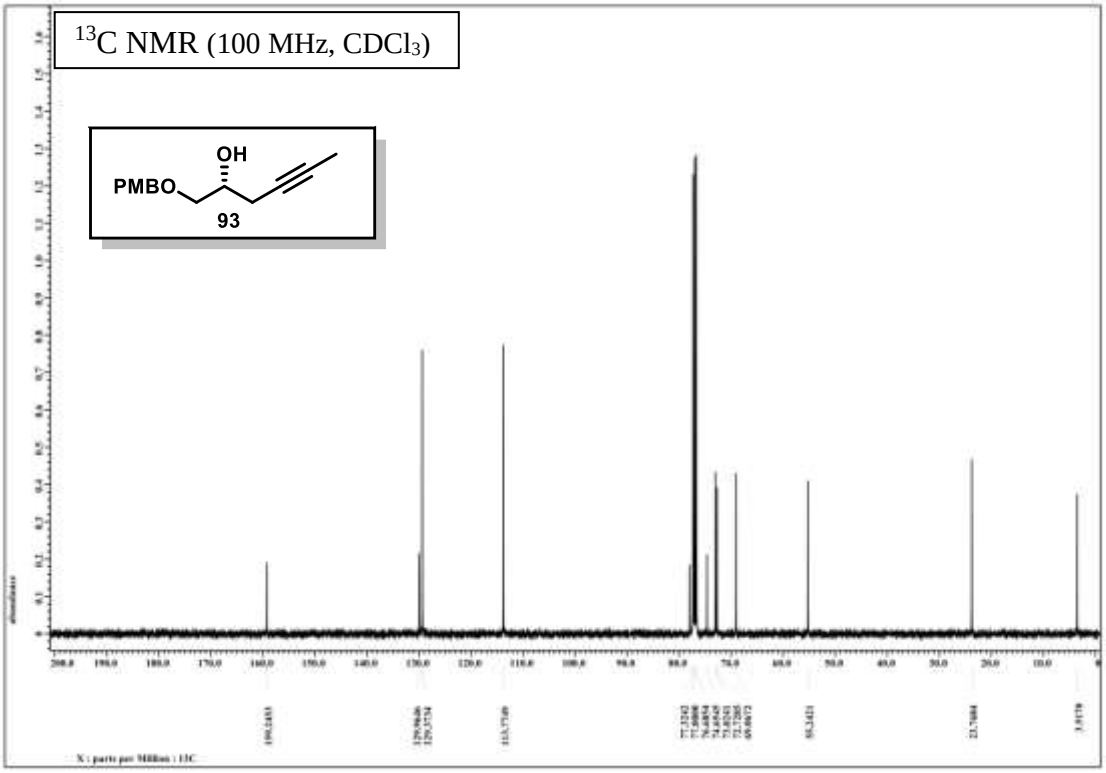
2.7 Spectra:

1. ^{1}H spectrum for compound **93**
2. ^{13}C spectrum for compound **93**
3. ^{1}H spectrum for compound **2**
4. ^{13}C spectrum for compound **2**
5. ^{1}H spectrum for compound **4**
6. ^{13}C spectrum for compound **4**
7. ^{1}H spectrum for compound **55b**
8. ^{13}C spectrum for compound **55b**
9. ^{1}H spectrum for compound **82**
10. ^{13}C spectrum for compound **82**
11. HRMS of compound **82**
12. ^{1}H spectrum for compound **5**
13. ^{13}C spectrum for compound **5**

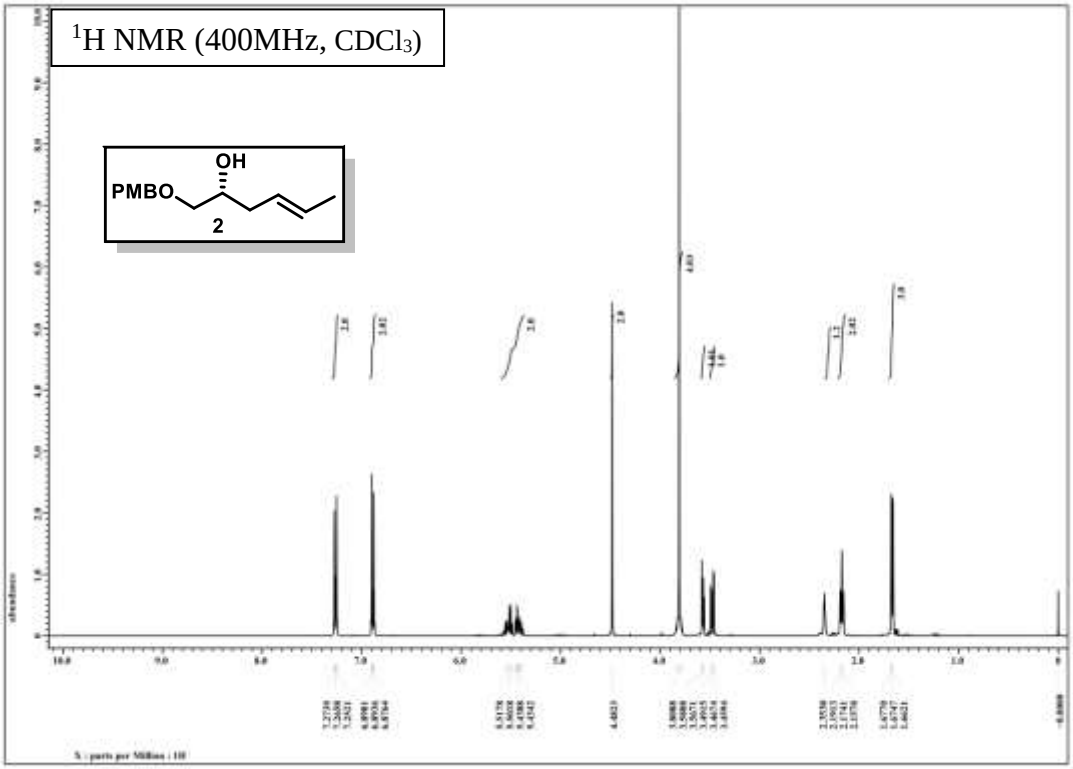
^{1}H NMR (400MHz, $CDCl_3$)



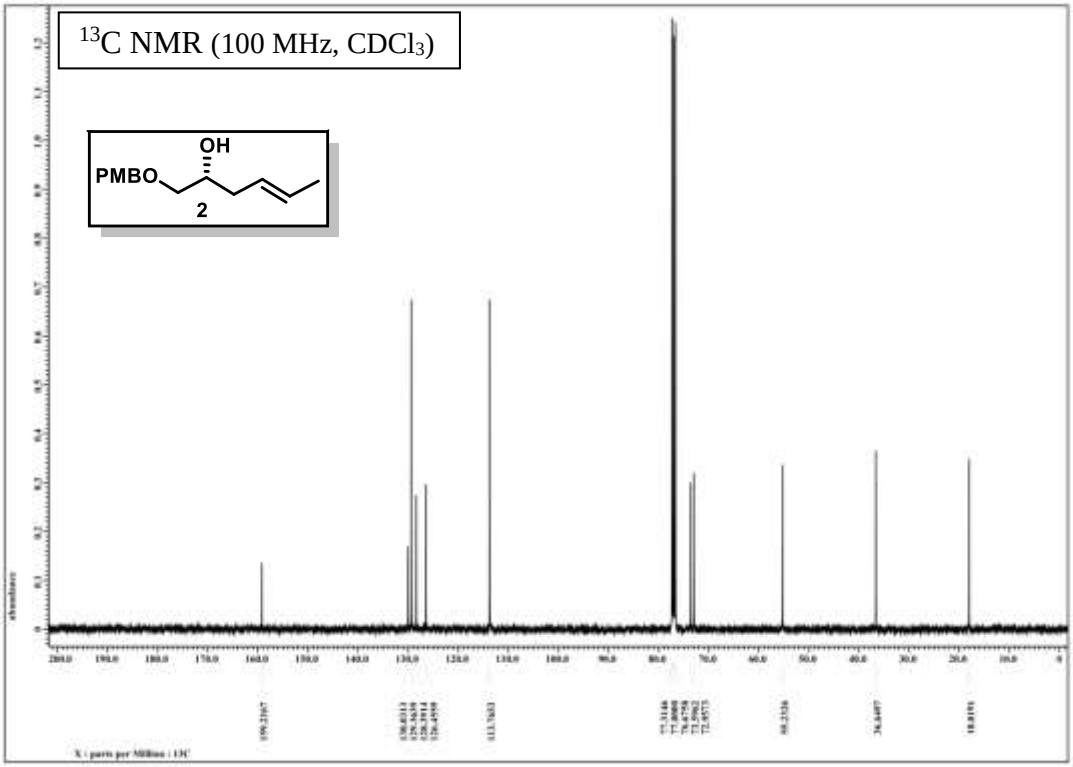
^{13}C NMR (100 MHz, $CDCl_3$)



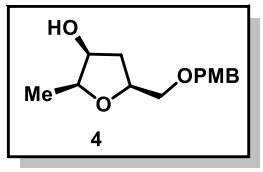
^{1}H NMR (400MHz, $CDCl_3$)



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

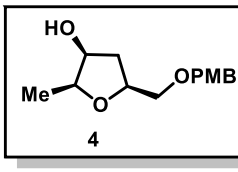


^{1}H NMR (400MHz, $CDCl_3$)



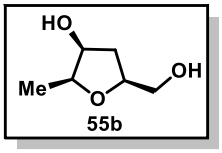
4

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



4

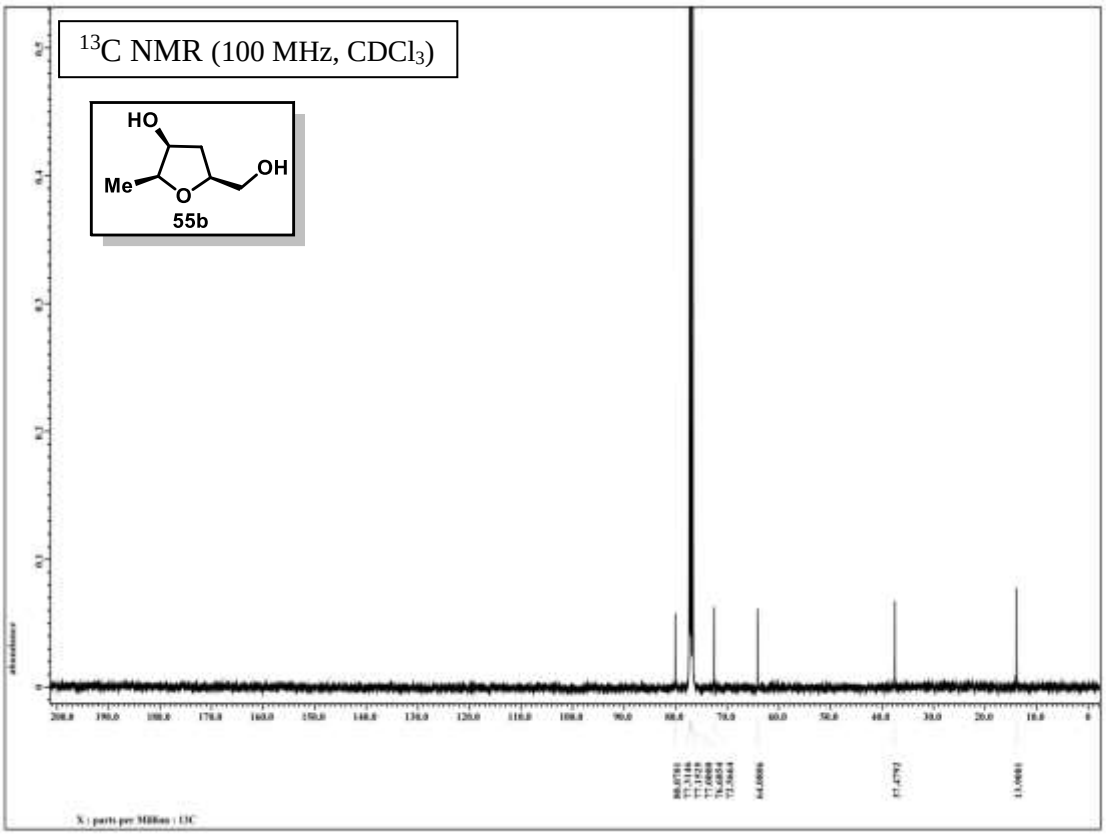
^{1}H NMR (400MHz, $CDCl_3$)



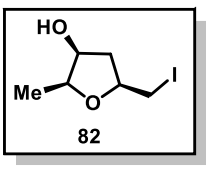
55b

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

55b

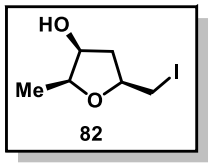


^{1}H NMR (400MHz, $CDCl_3$)



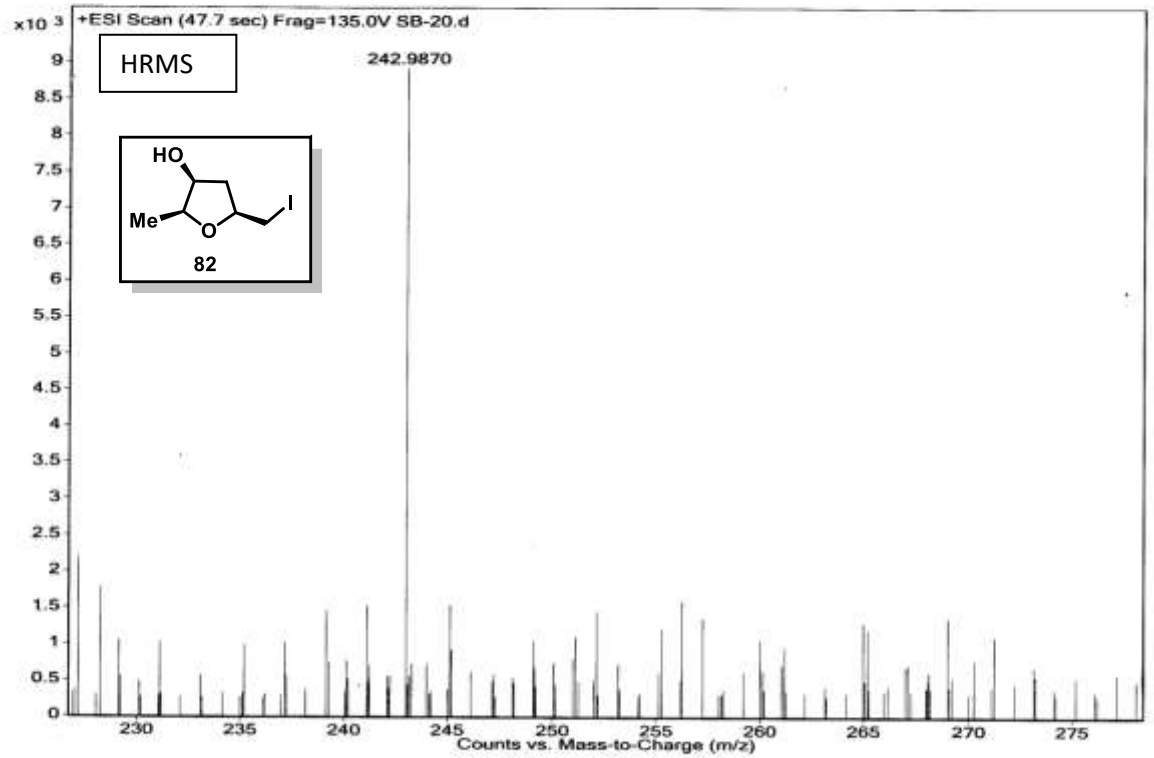
82

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

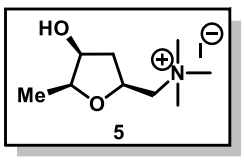


82

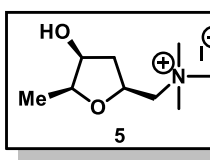
Sample Name	SB-20	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	SB-20.d	**ACQ Method**		**Comment**		**Acquired Time**	11/21/2016 4:29:27 PM



^{1}H NMR (400MHz, D_2O)



^{13}C NMR (100 MHz, D_2O)



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CHAPTER 3

Enantioselective novel approach for multi-functionalized γ-butyrolactone paraconic acids and its application to the total synthesis of (+)-nephrosteranic acid.

Enantioselective novel approach for multi-functionalized *γ*-butyrolactone paraconic acids and its application to the total synthesis of (+)-nephrosteranic acid.

3.1 Introduction:

Bioactive natural products containing multifunctionalized γ-butyrolactone moiety are found abundantly in nature.[1] The paraconic acids (**20, 94-104**) containing multifunctionalized γ-butyrolactone were isolated from various species of lichens, fungi, moss and cultures of *Penicillium sp.*[2] These acids possess interesting biological activities such as antitumor, antibacterial, antibiotic, antifungal/antiviral and growth regulatory properties.[3] The whiskey lactone **103** and cognac lactone **104** are having great commercial interest because they are used as potential key components in flavor of aged alcoholic beverages.[4] Architecturally, paraconic acids family comprises a variable length of alkyl chain at C5 position, C4 carboxyl group and methyl or methylene substituents at C3 position which plays an important role in the biological activities of the paraconic acids (Figure 6).

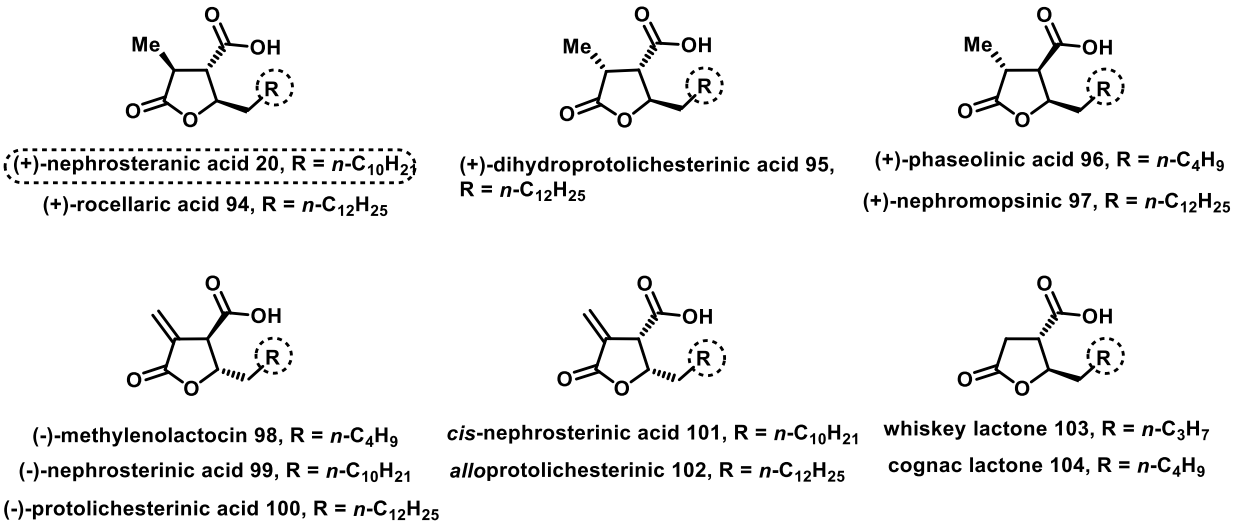


Figure 6. Representative structures of *γ*-butyrolactone based paraconic acids and lactones.

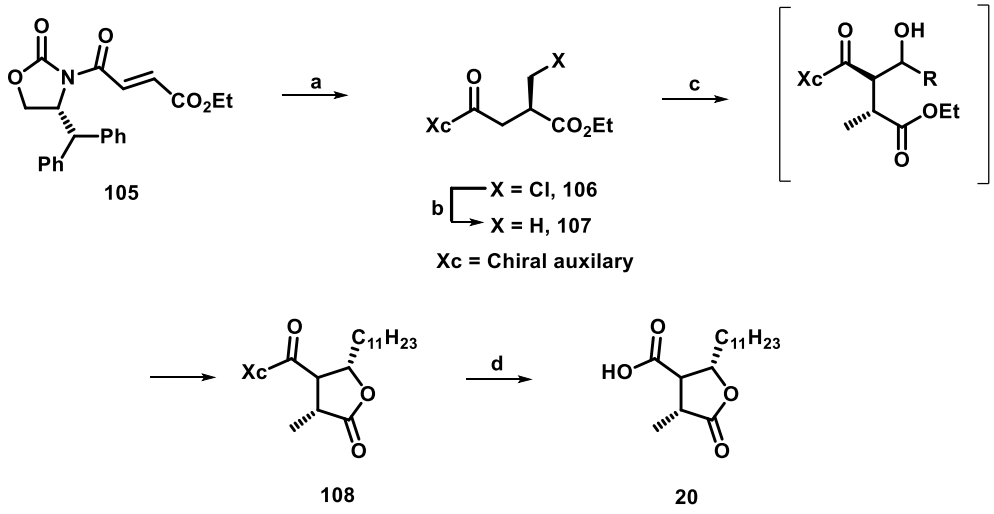
3.2 Review of Literature:

Intrigued by the unique structural features and biological activities of paraconic acids, hitherto,

several total[5] and formal[6] synthesis of paraconic acids such as (+)-nephrosteranic acid **20** are given in literature. The following are some of the most recent syntheses of (+)-nephrosteranic acid **20**.

Sibi, M. P. *et al.* (2002)[5t]

Sibi and co-workers delineated the enantioselective synthesis of (-)-nephrosteranic acid **20** from desymmetrized fumarate **105** in 53% overall yield over four synthetic steps employing free-radical-mediated conjugate addition strategy for incorporation of radicals to a desymmetrized fumarate as shown in Scheme 26. The synthesis began with the regioselective combination of chloromethyl radical to the fumarate **105** using $ClCH_2I$ in the presence of reagent Bu_3-SnH and samarium triflate, yielding chloromethyl derivative **106** as a only possible diastereomer in 91% yield. Next, chlorine substituent of compound **106** was reduced using freshly prepared Bu_3SnH to afford methyl derivative **107** in 76% yield. The compound **107** on aldol reaction with lauraldehyde employing dibutylboron triflate and triethylamine furnished an intermediate which on subsequent cyclization afforded the lactone **108** in excellent yield. Finally chiral auxiliary was selectively removed with $LiOH/H_2O_2$ to produce (-)-nephrosteranic acid **20** in 92% yield.

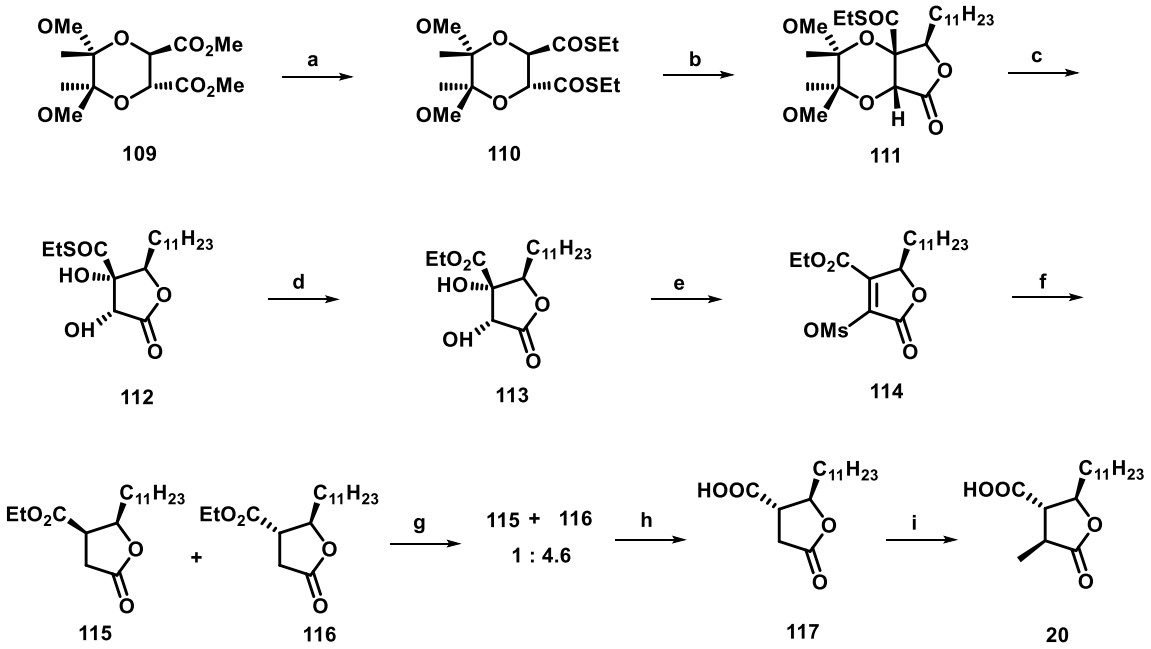


Scheme 26. *Reagents and conditions*: (a) Samarium triflate, chloroiodomethane, Bu_3SnH, Et_3B/O_2, DCM/THF, -78 °C, 60 min., 91%; (b) $(C_4H_9)_3SnH$, $[(CH_3)_2C(CN)]_2N_2$, methylbenzene, reflux, 12 h, 76%; (c) lauraldehyde, Bu_2BOTf, DCM, Et_3N, -78 to 0 °C, 12 h, 84%; (d) LiOH, H_2O_2, THF/H_2O, rt, 1 h, 92%.

Barros, M. T. *et al.* (2003)[5s]

Barros and his team described the total synthesis of natural (+)-nephrosteranic acid **20** employing highly stereoselective aldol reaction as a main step and tartaric acid derivative **109** as starting material as sketched in Scheme 27. Treatment of tartaric acid derivative **109** with ethanethiol and trimethylaluminum afforded dithioester **110** in 75% yield. Lactone **111** was obtained on reaction of **110** with of lithium diisopropylamide (2.2 equiv) followed by quenching of dienolate of dioxane **110** with a suitable aldehyde in good yield.

Dioxane acetal of product **111** on hydrolysis using ethanedithiol and BF_3OEt_2 yielded the diol **112** in 94% yield. Compound **112** on *trans* esterification employing sodium ethoxide yielded the ethyl ester **113** in excellent yield. Further, mesylation and spontaneous elimination, resulting in an 85% yield of the labile enol mesylate **114**. Then, Pd/C mediated hydrogenation of compound **114** in the presence of NaOAc provided the two *cis*/*trans* (5.2:1) isomers **115** and **116** in 89% yield. Isomerization was achieved (1:4.6 **115**/**116**) on treatment of diastereomeric mixture of **115** and **116** with diazabicycloundecene (DBU).

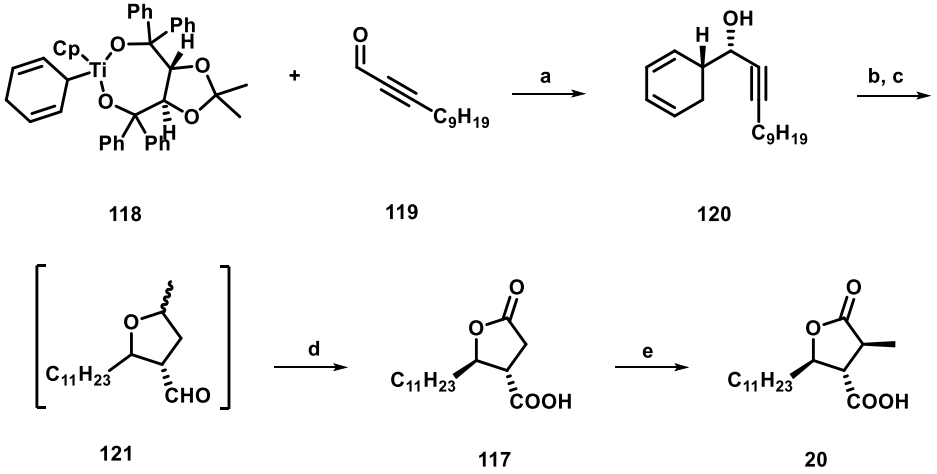


Scheme 27. *Reagents and conditions:* (a) EtSH, CH_2Cl_2, Me_3Al, 0 °C-rt, 99%; (b) LDA, THF, RCHO, -78 °C, 75%; (c) BF_3,OEt_2, $HS(CH_2)_2SH$, CH_2Cl_2, 80 °C, 94%; (d) NaOEt, EtOH, THF, 0 °C, 96%; (e) CH_3SO_2Cl, DIPEA, DCM, 0 °C, 85%; (f) H_2, Pd/C, CH_3COONa, CH_3OH, ETAC, rt, 89%; (g) DBU, DCM, rt, 99%; (h) HCl, 1,4-dioxane, 110 °C, 90%; (i) NaHMDS, CH_3I, oxolane, -78 °C, 96%.

Further, diastereomers **115** and **116** on acid-catalyzed hydrolysis produced acid derivative **117** in 90% yield, leaving the *cis* content **115** unreacted. α-Alkylation with MeI and NaHMDS as the base produced (+)-nephrosteranic acid **20** in good yield.

Schleth, F. *et al*. (2004)[5o]

Schleth and his team proposed the introductory synthesis of (+)-nephrosteranic acid **20** where a special strategy of chirality incorporation in aldehydes using cyclohexadienyl titanium was explored in excellent diastereo- and enantioselectivities. As illustrated in Scheme 28, treatment of Titanium cyclohexadienyl compound **118** with alkynal **119** provided homoallylic alcohol **120** in excellent yields with high stereoselectivity. Next, ozonolysis of **120** in dichloromethane was carried out, which subsequently on hydrogenation using H_2 and Pd/C afforded the lactol derivative **121**. Under Jones conditions, crude **121** was oxidized to γ-butyrolactone **117** in overall 21% yield. Further, methylation of compound **117** under known literature procedure yielded (+)-nephrosteranic acid **20** in 89% yield.[5t]

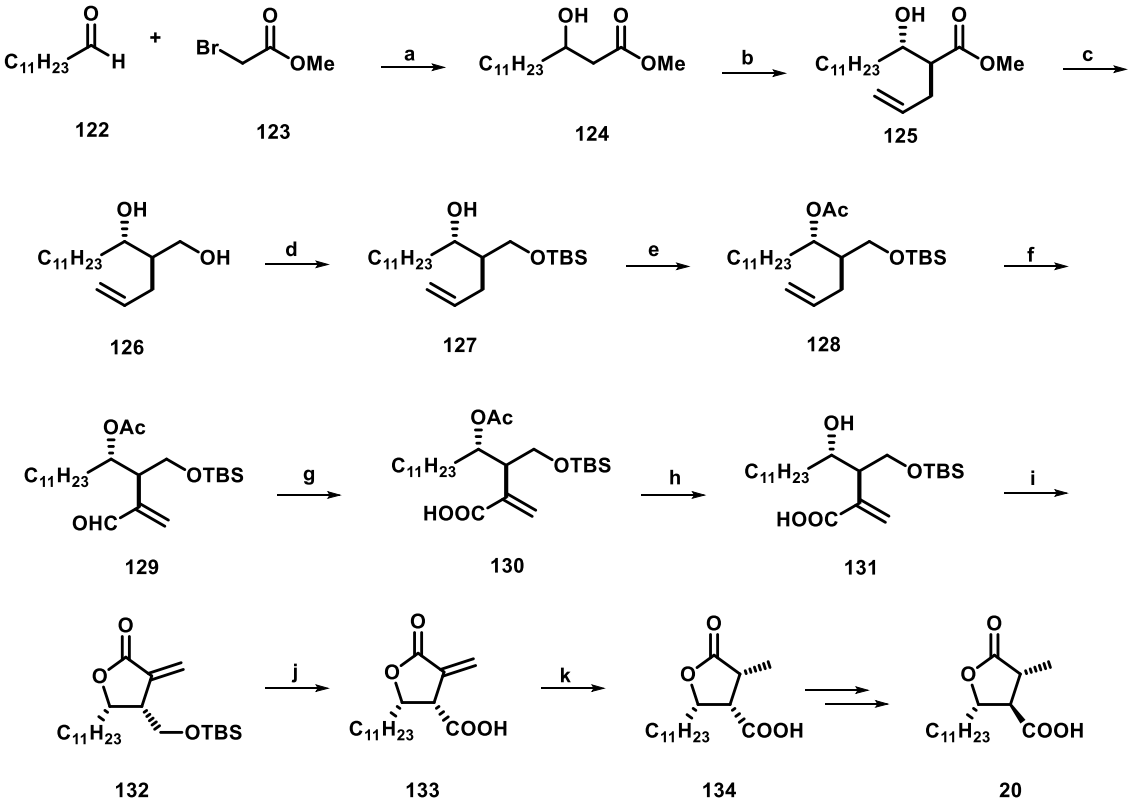


Scheme 28. *Reagents and conditions:* (a) Et_2O/THF, -100 °C to -110 °C, 1.5 h, 92%; (b) O_3, Me_2S, CH_2Cl_2, -78 °C to 0 °C, all-night; (c) H_2, Pd/C, CH_3CH_2OH, rt, all-night; (d) CrO_3/H_2SO_4, CH_3COCH_3, 0 °C, 3.5 h, 21% (over b-d steps); (e) $((CH_3)_3Si)_2NNa$, MeI, oxolane, -78 °C to 20 °C, overnight, 89%.

Hon, Y. S. *et al*. (2007)[6b]

Hon and his team described an elegant creation of lactone derivative **134** that act as precursor for the synthesis of (+)-nephrosteranic acid **20** starting from *n*-decanal **122** and methyl bromoacetate

123 in eleven steps and 7.2% overall yield (Scheme 29). The main strategy employed here was the incorporation of *α*-methylene group, *via* ozonolysis of olefins and subsequently treatment with mixture of dibromomethane and diethylamine. The synthesis began with reaction of starting material *n*-decanal **122** with methyl bromoacetate **123** using the activated zinc to furnish *ß*-hydroxy ester **124** in 82% yield. Methyl 3-hydroxytridecanoate **124** on allylation using allyl bromide in the presence of lithium diisopropyl amide yielded the anti *β*-hydroxy ester derivative **125** in 62% yield. DIBALH reduction of the hydroxy ester **125** with gave the corresponding diol **126** in 68% yield.

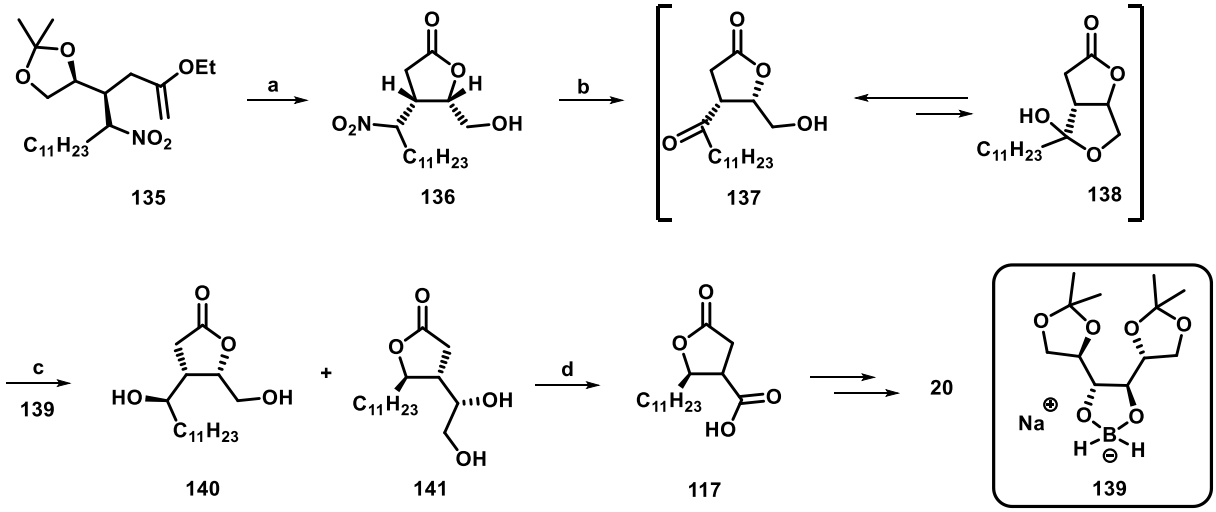


Scheme 29. *Reagents and conditions:* (a) Zn, PhH, reflux, 3h, 82%; (b) LDA, $H_2C{=}CHCH_2Br$, THF, -78 ^oC to rt, 2 h, 62%; (c) DIBAL-H, DCM, 0 ^oC to rt, 2h, 68%; (d) TBSCl, imidazole, DMAP, DCM, 3 h, 76%; (e) $(CH_3CO)_2O$, DMAP, Et_3N, DCM, 2 h, 91%; (f) Ozone, DCM, -78 ^oC, $(C_2H_5)_2NH$, CH_2Br_2, 1.5 h, 78%; (g) $ClNaO_2$, $(CH_3)_3COH$, $H_2NaO_4P.2H_2O$, $CH_3CH{=}C(CH_3)_2$, 2 h, 72%; (h) KOH, 0 ^oC to rt, CH_3OH, 1.5 h; (i) $C_6H_4ClNO_4S$, Na_2CO_3, DCM, 0.5 h, 73% for 2 steps; (j) CrO_3/H_2SO_4, CH_3COCH_3, 40 ^oC, 5 min, 87%; (k) H_2, 10% Pd/C, $CH_3COOC_2H_5$, 4 h, 85%.

Next, selective silyl ether protection of primary alcohol **126** with TBSCl furnished the silyl protected olefin derivative **127** in 98% yield. The acetate **128** was obtained by acetylation of **127** using acetic anhydride in excellent yield. Olefin **128** on ozonolysis and subsequent addition of mixture of dibromomethane and diethylamine led to the generation of acrolein **129** in 78 % yield. Further, compound **129** on oxidation using sodium chlorite furnished acrylic acid **130** in good yield. Acrylic acid **130** on deacetylation with KOH in methanol afforded the hydroxy derivative **131** which on treatment with *o*-nitro phenylsulfonyl chloride in the presence of sodium carbonate gave 2-methylenebutyrolactone **132** in 72% yield. Compound **132** was oxidized in the presence of Jones reagent to afford γ-butyrolactone acid derivative **133** in 87% yield. Compound **133** on Pd catalysed hydrogenation furnished the all-*cis* isomer of lactone derivative **134** in 85% yield. The precursor **134** was converted into **20** using known literature procedure.[7]

Barreto, C. B. *et al*. (2009)[6a]

Barreto and his team described the formal synthesis of (+)-nephrosteranic acid **20** employing Nef reaction, lactonization and reduction as key steps and a nitro derivative **135** as starting material obtained from D-(+)-mannitol *via* a chiron approach.

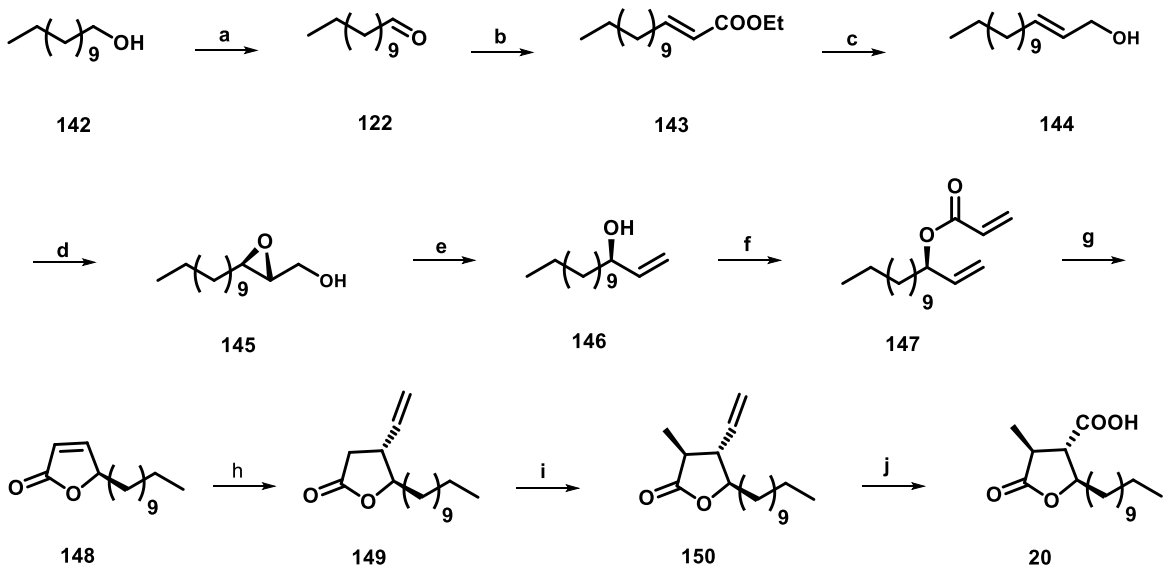


Scheme 30. *Reagents and conditions:* (a) 20%, HCl, 1 h, rt, 98%; (b) $NaNO_2$, DMSO/H_2O (7:1), 60 °C, 12 h, 77%; (c) chiral hydride $NaBH_2$ (mannitol diacetonide), THF, H_3O^+, 0 °C, 2h, 90%; (d) H_5IO_6, CH_3CN, PCC, 2 h, rt, 75%.

As outlined in Scheme 30, nitro derivative **135** on lactonization in acidic medium furnished butyrolactone **136** in excellent yield. Then, compound **136** under Nef reaction conditions afforded the two equilibrium derivatives, keto- butyrolactone **137** and its furanosidic form **138** in 95% diastereoisomeric excess and 77% yield. Further, to reduce the keto group of compound **137**, diastereomeric mixture of **137** and**138** was treated with chiral hydride $NaBH_2$ **139** to furnish the butyrolactone derivatives **140** and **141** in 90% yield. The butyrolactone **140** and **141** was exposed to H_5IO_6 and then subsequently with pyridinium chlorochromate in one pot to yield the nephrosteranic acid precursor **117** in 75% yield. Finally, (+)-nephrosteranic acid **20** was obtained from **117** by known literature procedure.[5i]

Perepogu, A. K. *et al.* (2010)[5e]

Perepogu and his research team described the asymmetric synthesis of the (+)-nephrosteranic acid **20** utilizing Sharpless epoxidation, ring-closing metathesis (RCM) and Gilman addition as key steps and dodecanol **142** as starting material (Scheme 31). Pyridinium chlorochromate oxidation of dodecanol **142** was performed to furnish dodecanal **122** in 95% yield. Compound **122** underwent a two-carbon Wittig homologation using ethoxycarbonylmethylenetriphenylphosphorane to afford *trans* olefin compound **143** which on chemoselective reduction in anhydrous ether with LAH/$AlCl_3$ furnished allyl alcohol **144** in 86% yield.



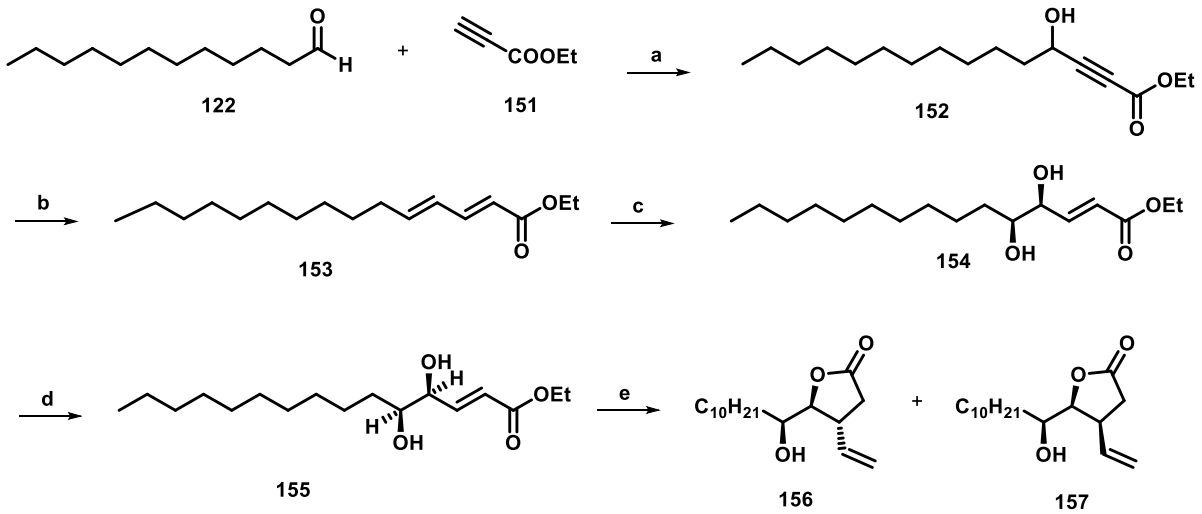
Scheme 31. *Reagents and conditions:* (a) PCC, CH_2Cl_2, rt, 3 h, 95%; (b) Wittig reagent ($Ph_3P{=}CHCO_2Et$), C_6H_6, reflux, 2 h, 90%; (c) $LiAH_4/AlCl_3$, THF, 0 ^oC, 0.5 h, 86%; (d)

$Ti[OCH(CH_3)_2]_4$, (-)DET, $C_6H_5CMe_2OOH$, CH_2Cl_2, -20 ^oC, 3 h, 85%; (e) $P(C_6H_5)_3$, py, I_2, $(CH_3CH_2)_2O$:CH_3CN (5:3), 0 ^oC, water, reflux, 6h, 95%; (f) CH_2=CHCOCl, $N(CH_2CH_3)_3$, $(CH_3)_2NC_5H_4N$, 5 h, 75%; (g) Grubbs First generation catalyst, $Ti(OPr^i)_4$, DCM, 40 ^oC, 36 h, 79%; (h) CuI, CH_3Li, C_2H_3BrMg, -78 ^oC, 81%; (i) $((CH_3)_3Si)_2NNa$, MeI, -78 ^oC, THF, 76%; (j) $RuCl_3$, sodium periodate, CCl_4, CH_3CN, H_2O, 80%.

Further, compound **144** on Sharpless asymmetric epoxidation with D-(-)-DET (diethyl tartrate) afforded 2,3- epoxy alcohol **145** in 85% yield. Allyl alcohol **146** was formed by reduction of epoxy iodide of compound **145** (*in situ* generated) in 95% yield. The acrylate ester **147** was obtained in 75% yield by reacting **146** with acryloyl chloride and Et_3N in the presence of dimethylaminopyridine. Following normal RCM protocol, compound **147** was treated with Grubbs first-generation catalyst in CH_2Cl_2 for 24 hours which afforded lactone **148** in excellent yield. 1, 4-conjugate addition of a vinyl cuprate to **148** afforded the lactone **149** in 81% yield. Lactone **149** on treatment with excess of methyl iodide and $NaN(SiMe_3)_2$ as base furnished methylated lactone **150** in 76% yield. Finally, methylated lactone **150** on oxidation with RuO_4 furnished the target compound **20.**

Fernandes, R. A. *et al*. (2011)[8]

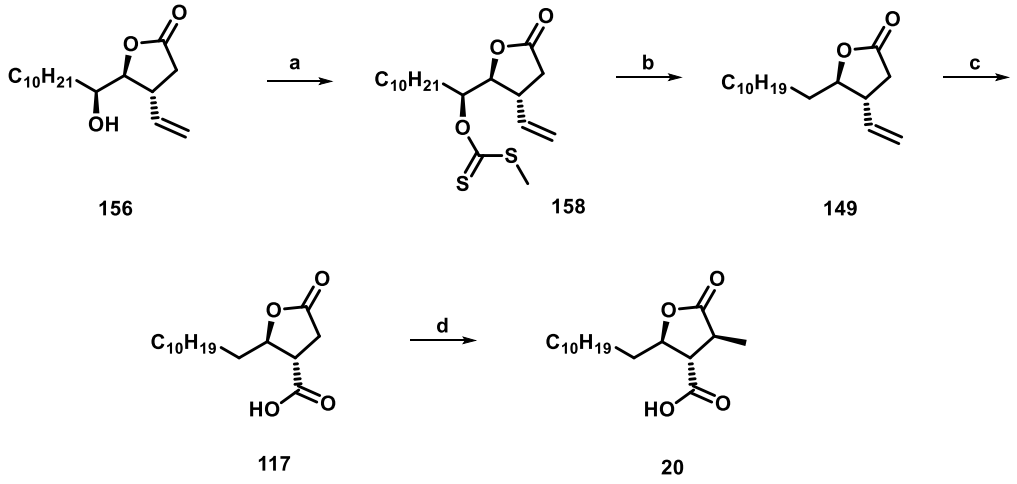
Fernandes and his team documented the elegant synthesis of (+)-nephrosteranic acid **20** employing Sharpless AD and Johnson–Claisen rearrangment as key steps and utilized dodecanal **122** and ethyl propiolate **151** as starting materials.



Scheme 32. *Reagents and conditions:* (a) LiHMDS, THF, –78 °C, 1.5 h, 86% (b) Ph_3P, PhH, rt., 6 h, 70%; (c) $K_3Fe(CN)_6$, $(DHQ)_2$-PHAL (1.0 mol%), $K_2OsO_4 \cdot 2H_2O$, $MeSO_2NH_2$, *tert*-BuOH/H_2O (1:1), 0 °C, 12 h, 62% (d) i) $Me_2C(OMe)_2$, Me_2CO, pTsOH, rt., 12 h, 98%; ii) (*i*-$Bu_2AlH)_2$, CH_2Cl_2, 0 °C, 2.5 h, 89% (e) $(MeO)_3CMe$, toluene, $EtCO_2H$, reflux, 24 h, rt., 4 n HCl, MeOH, 12 h, 58%.

The synthesis started with formation of hydroxy alkynoate **152** on incorporation of lithiated ethyl propiolate **151** to aldehyde **122** as shown in Scheme 32. Treatment of **152** with 1.2 equiv. of Ph_3P, "allene"-type re-arrangement took place which resulted in *trans* diene **153** in 70% yield. Dihydroxylation of distant double bond of compound **153** under Sharpless AD conditions produced diol **154** in 62% yield (96% ee). Diol **154** on acetonide protection and subsequent reduction of ester group furnished the protected compound **155** in 89% yield. Next, Johnson–Claisen rearrangement of compound **155** was executed with trimethylorthoacetate utilizing propionic acid and subsequent acetonide hydrolysis afforded diastereomeric lactones **156** and **157** in 2:1 ratio.

The hydroxy group in **156** was transformed to xanthate group to yield **158** in 64% yield as illustrated in Scheme 33.



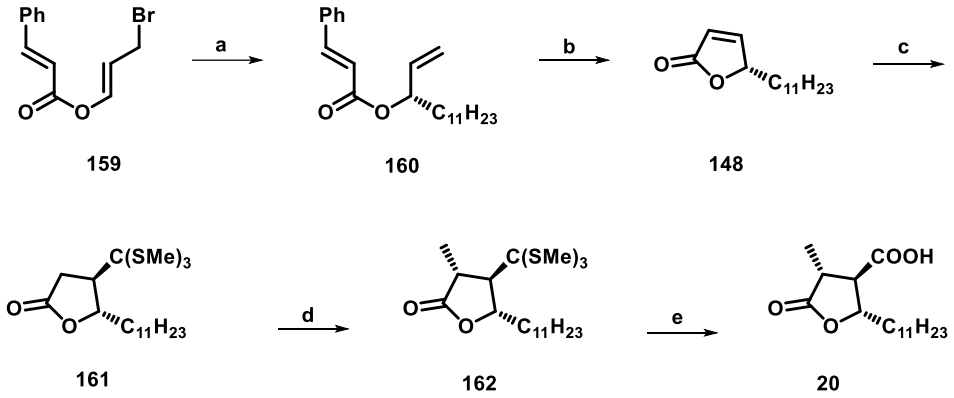
156 158 149 117 20

Scheme 33. *Reagents and conditions:* (a) CS_2, NaH, THF, MeI, 0 °C to rt., 3 h, 62%; (b) Bu_3SnH, AIBN, toluene, reflux, 6 h; (c) i) O_3, CH_2Cl_2, Me_2S, –78 °C, 90 min., rt., 2 h; ii) CrO_3, H_2SO_4, acetone, 0 °C, 20 min, 95%; (d) NaHMDS, MeI, THF, –78 °C, 3 h, 99%.

The removal of the xanthate group by AIBN/ nBu_3SnH yielded β-vinyl γ-lactone **149** in quantitative yield. The required β-carboxylic acid group was efficiently positioned by ozonolytic cleavage of the vinyl bond of compound **149** and further oxidation, yielded **117** in 95% yield. Using NaHMDS/MeI, the α-methyl group in **117** was stereoselectively incorporated, to afford (+)-nephrosteranic acid **20** in 99% yield.

Mao, B. *et al*. (2011)[5d]

Mao and co-workers gave an efficient method for the synthesis of (-)-nephrosteranic acid **20** from cinnamyl ester **159** employing hetero-allylic asymmetric alkylation and ring closing metathesis as key steps (Scheme 34).

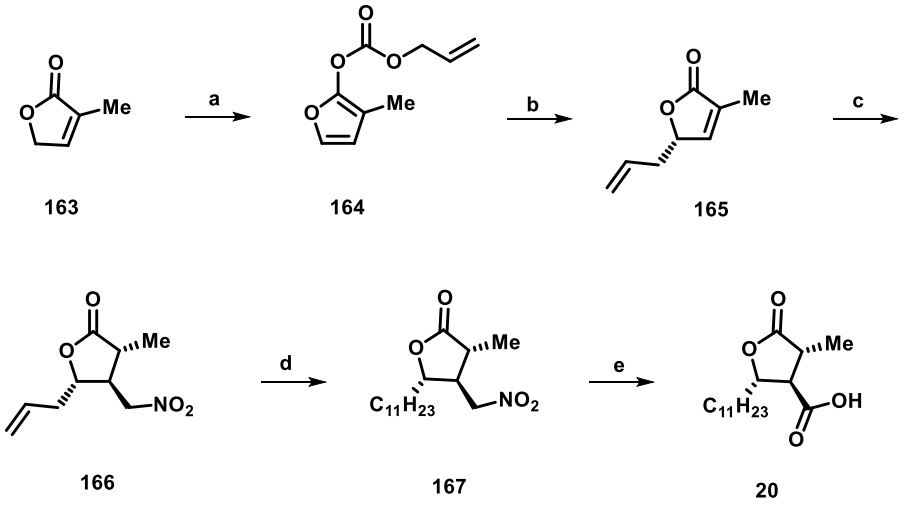


Scheme 34. *Reagents and conditions*: (a) $CuBr_3$ SMe_2, (*R*,*R*)-(+)-Taniaphos, $C_{11}H_{23}MgBr$, CH_2Cl_2, -75 ^oC to -55 ^oC, 84%; (b) CH_2Cl_2, Hoveyda-Grubbs II catalyst, 40 ^oC, 40 h, 84%; (c) HC $(SMe)_3$, n-BuLi, THF, -78^oC, 2h; (d) NaHMDS, MeI THF, -78 ^oC to -20 ^oC, 86% (over two steps); (e) THF/H_2O (4:1), HgO, BF_3. Et_2O, rt, 97%.

Copper-catalyzed hetero-allylic asymmetric alkylation (h-AAA) reaction of cinnamyl substrate **159** was performed using Grignard reagent undecyl magnesium bromide in the presence of (*R*,*R*)-(+)-Taniaphos to afford **160** in good enantio (97% ee) and regioselectivity (>99:1). Ring closing metathesis of diolefinic esters **160** was carried out using Hoveyda-Grubbs II catalyst (6 mol %), which furnished furanone **148** in 84% yield. The disubstituted product **161** was produced by treatment of **148** with lithiated tris(methylthio)methane and quenching of reaction with *aq*. NH_4Cl solution. Further, compound **161** on treatment with NaHMDS and MeI at -78 ^oC, furnished trisubstituted trans product **162** in 86% yield. Target product (-)-nephrosteranic acid **20** was obtained by efficient hydrolysis of **162** in 97% yield.

Fournier, J. *et al*. (2013)[5c]

Fournier and his team developed a asymmetric synthesis of (-)-nephrosteranic acid **20** using 3-methyl-2(5H)-furanone **163** as starting material. They employed Pd catalyzed asymmetric allylic alkylation as pivotal step for the formation of *αlpha*-quaternary butenolides as outlined in Scheme 35.

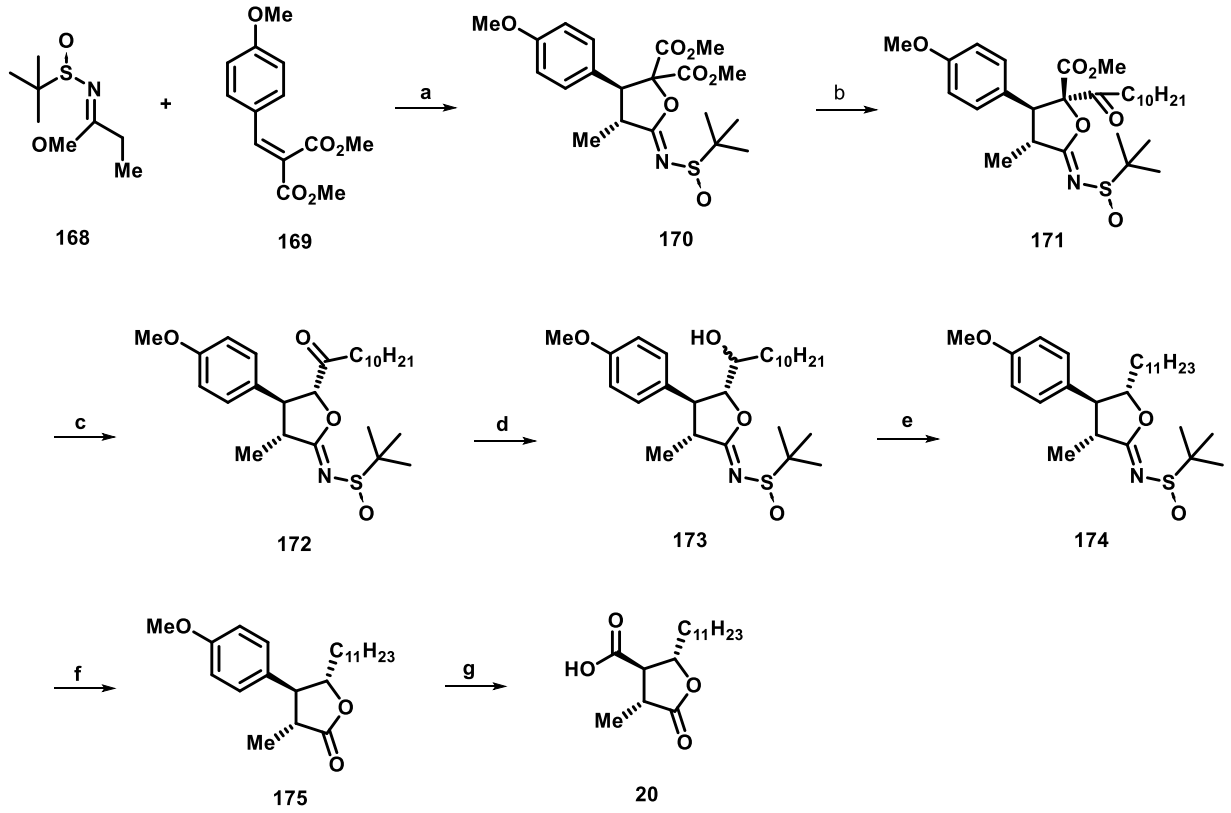


Scheme 35. *Reagents and conditions:* (a) NaHMDS, allyl chloroformate, THF, -60 ^{o}C, 94%; (b) i) (R,R)-DACH-phenyl Trost ligand, [Pd_2-$(dba)_3$·$CHCl_3$], NMP, -20 ^{o}C, 80%; ii) MW, CH_3CN, 180 ^{o}C, 1 h, 80%; (c) CH_3NO_2, DBU, CH_2Cl_2, 40%; (d) i) decene, [HG]-II, CH_2Cl_2, MW, 100 ^{o}C ii) H_2, Pd/C, MeOH, 47%; (e) $NaNO_2$, AcOH, DMSO, 45 ^{o}C, 70%.

The synthesis started with reaction of 3-methyl-2(5H)-furanone **163** with NaHMDS and allyl chloroformate in THF to afford allyl dienol carbonate **164** in 94% yield. Then, Pd-catalysed asymmetric allylic alkylation of compound **164** was carried out in the presence of Trost ligand (*R,R*)-DACH-phenyl and [Pd_2-$(dba)_3$·$CHCl_3$] to furnish α-quaternary butanolide which on stereospecific Cope rearrangement afforded γ-tertiary furanone **165** in 80 % yield. Compound **165** on conjugate addition of nitromethane in the presence of DBU resulted nitro derivative **166** in 40% yield. Compound **166** was subjected to cross metathesis with decene using [HG]-II and subsequent Pd/C mediated hydrogenation yielded the precursor **167** in 47% yield. Precursor **167** on Kornblum oxidation in the presence of $NaNO_2$ and AcOH afforded target compound **20** in 70% yield.

Wang, H. *et al*. (2015)[5b]

Wang and his team demonstrated the total synthesis of (−)-nephrosteranic acid **20** using three-step cascade reaction that involves stereoselective Michael addition, anion-oxidative hydroxylation, and cyclization. (Scheme 36).



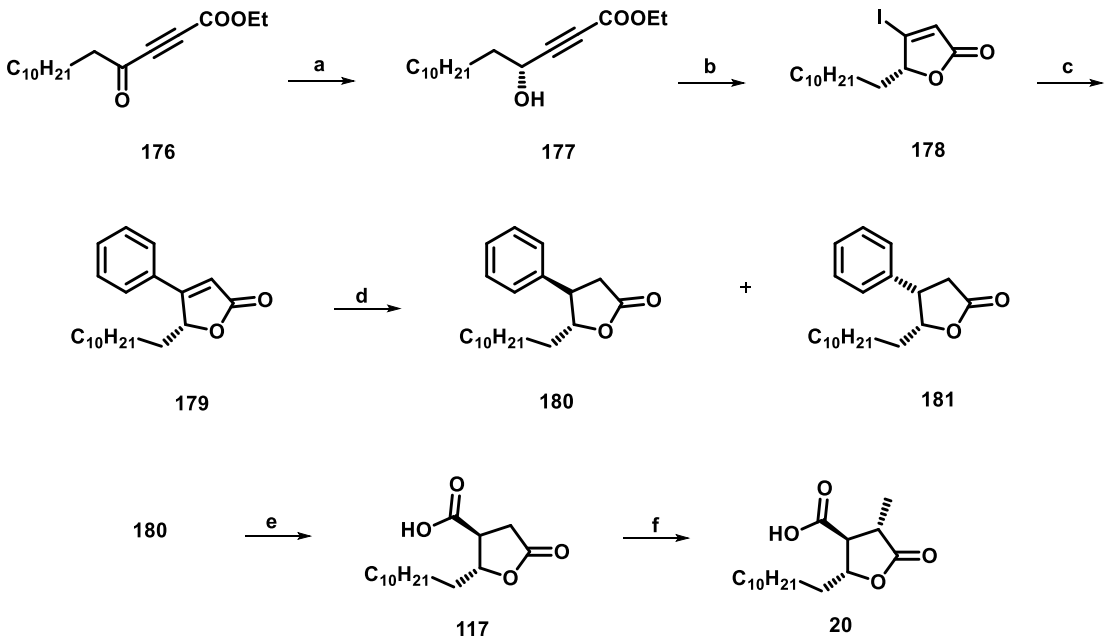
Scheme 36. *Reagents and conditions:* (a) N_2, LiHMDS, Cu $(OTf)_2$, -78 to 50 ^oC, 51 h, 75%; (b) $C_{10}H_{21}MgBr$, -40 ^oC, 1h, THF, 53%; (c) LiCl, DMF, 100 ^oC. 1h, 60%; (d) $NaBH_4$, MeOH, rt, 1h, 92%; (e) i) $(imidazolyl)_2CS$, DMAP, $ClCH_2CH_2Cl$, rt-80 ^oC, Overnight; ii) BuSnH, AIBN, PhMe, 40 ^oC, 5h, 48%; (f) TFA, CH_2Cl_2, rt, 24h, 92%, (g) $NalO_4$, $RuCl_3$, H_2O:CCl_4:MeCN (3:2:2), rt, Overnight, 65%.

Synthesis of butyrolactonimidate **170** commenced from methoxy derivative **168** and olefinic ester **169** *via* one pot three consecutive reactions, Michael addition, anion-oxidative hydroxylation, and oxygen anion cyclization using ideal conditions of LiHMDS (4.2 equiv), THF (0.01 M) and of $Cu(OTf)_2$ (3.0 equiv) in 75% yield. Compound **170** on treatment with Grignard reagent decylmagnesium bromide in THF yielded the ketone derivative **171** in 53% yield. Compound **171** on decarbonylation in presence of LiCl/DMF yielded a single diastereomer **172**. Reduction of compound **172** using $NaBH_4$ in MeOH furnished inseparable diastereomers **173** in 92% yield and

2:1 diastereomeric ratio. Compound **173** on Barton-McCombie deoxygenation yielded alkyl derivative **174** in 48 % yield. Next, extraction of *tert*-butylsulfinyl group was carried out under acidic conditions, provided lactone **175** in 96% yield. Compound **175** on oxidation of phenyl ring employing NalO4 and ruthenium(III)chloride delivered the desired target (-)-nephrosteranic acid **20** in 65%.

Nallasivam, J. L. *et al*. (2017)[5a]

Nallasivam and co-workers proposed an elegant synthesis of (+)-nephrosteranic acid **20** and other paraconic acids *via* protecting group free approach employing Suzuki–Miyaura cross coupling catalyzed by Pd and Sharpless oxidation catalyzed by Ru as key steps as shown in Scheme 37.



Scheme 37. *Reagents and conditions*: (a) (*R*)-alpine borane, rt, 48h, 68%; (b) i) $Pd(PPh_3)_4$, nBu_3SnH, THF, rt, 20 min; ii) I_2, CH_2Cl_2, KF, rt, 18h, 53%; (c) $PhB(OH)_2$, K_2CO_3, $Pd(O_2CCH_3)_2$, Ligand L, C_2H_5OH:H_2O (4:1), rt, 15 min., quant yield; (d) Pd-C, H_2, EtOH, rt, 1h, **180** in 45%, **181** in 45% ; (e) $RuCl_3.3H_2O$, $NaIO_4$, CCl_4:CH_3CN: H_2O (1:1:2), rt, 48h, quant; (f) NaHMDS, THF, 1.5 h, 2h, -70 ^oC, quant.

Acetylenic ketones **176** served as starting material which under Midland reduction condition in the presence of (*R*)-alpine borane furnished the compound **177** in excellent yield. Next, the hydrostannylation of alkynol **177** with *n*Bu_3SnH in the presence of $Pd(P(C_6H_5)_3)_4$ and subsequent

iodination gave regioisomers *β*-stannane **178** in 53% over all yield. Compound **178** underwent Suzuki–Miyaura coupling with phenylboronic acid in the presence of palladium acetate and ligand L (unimolecular tetrakis-4-hydroxypiperidinol) furnished *β*–phenylbutenolides **179** in quantitative yields. Compound **179** on hydrogenation employing Pd–C and H_2 (1 atm), yielded diastereomeric mixture of β–phenylbutyrolactones **180** and **181** (*anti*:*syn* = 1:1.2–2) in quantitative yields. Upon chromatographic separation of diastereomeric mixture, Sharpless oxidation was performed to oxidize the phenyl group of compound **180** using $RuCl_3 \cdot 3H_2O/NaIO_4$ to afford *β*-CO_2H-*γ*-butyrolactones **117** in quantitative yields. Finally, *α*-methylation of **117** was carried out using NaHMDS and MeI to furnish (+)-nephrosteranic acid **20** in good yield.

3.3 Present Work:

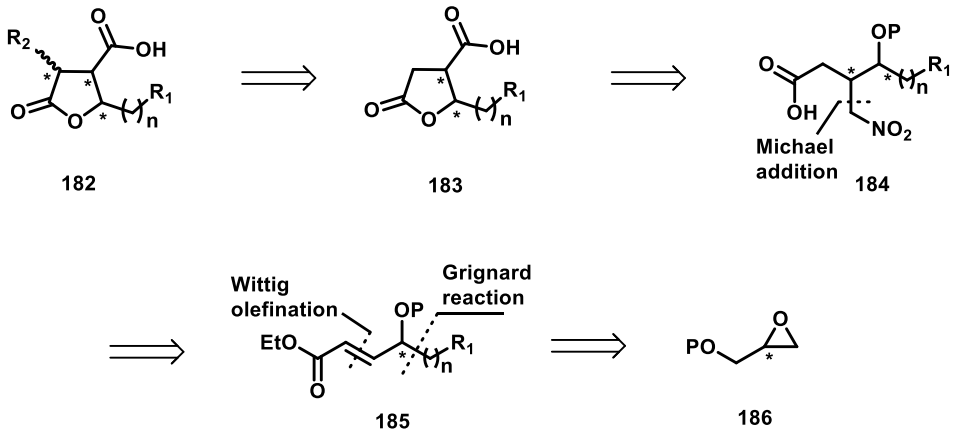
We present a short, efficient, and novel framework for the synthesis of paraconic acids and its application to the enantioselective synthesis of (+)-nephrosteranic acid **20** using organocatalyzed Michael addition reaction as key step.

3.4 Results and Discussion:

Our general retrosynthetic route for asymmetric synthesis of *γ*-butyrolactone based paraconic acids and its application to enantioselective synthesis of (+)-nephrosteranic acid **20** was envisaged *via* the retrosynthetic approach as displayed in Scheme 38. We envisioned that the *γ*-butyrolactone **183** could be used as a key intermediate from which paraconic acids **94**-**104** including (+)-nephrosteranic acid **20** would be synthesized *via* methylenation or stereoselective methylation at the C3 centre. The *γ*-butyrolactone **183** could be achieved from protected nitro-acid derivative **184** via deprotection and in situ lactonization followed by Nef reaction. The nitro-acid derivative **184** in turn could be synthesized from (*R*)- or (*S*)-diphenylprolinol silyl ether catalyzed Michael addition of CH_3NO_2 to *α*, *β*-unsaturated aldehyde intermediate obtained from the controlled DIBAL-H reduction of olefinic ester derivative **185** followed by oxidation.

The *α*,*β*-unsaturated ester **185** could be obtained from protected (*R*)- or (*S*)-glycidol **186** by treatment with suitable Grignard reagents, secondary alcohol protection, primary alcohol deprotection and oxidation followed by 2C-Wittig olefination reaction. The desired stereochemistry of (+)-nephrosteranic acid **20** and other paraconic acids **94**-**104** could be achieved by simply altering the (*R*)- and (*S*)-configuration of glycidyl ether and/or by using catalyst (*R*)- or

(*S*)-diphenylprolinol silyl ether during Michael addition reaction. Thus, in principle, C3, C4 and C5 chiral centers in paraconic acids could be easily manipulated and accessed by this approach.



Scheme 38. Retrosynthetic general approach of *γ*-butyrolactone based some paraconic acids and lactones.

The *α,β*-unsaturated ester **185** could be obtained from protected (*R*)- or (*S*)-glycidol **186** by treatment with suitable Grignard reagents, secondary alcohol protection, primary alcohol deprotection and oxidation followed by 2C-Wittig olefination reaction. The desired stereochemistry of (+)-nephrosteranic acid **20** and other paraconic acids **94**-**104** could be achieved by simply altering the (*R*)- and (*S*)-configuration of glycidyl ether and/or by using catalyst (*R*)- or (*S*)-diphenylprolinol silyl ether during Michael addition reaction. Thus, in principle, C3, C4 and C5 chiral centers in paraconic acids could be easily manipulated and accessed by this approach.

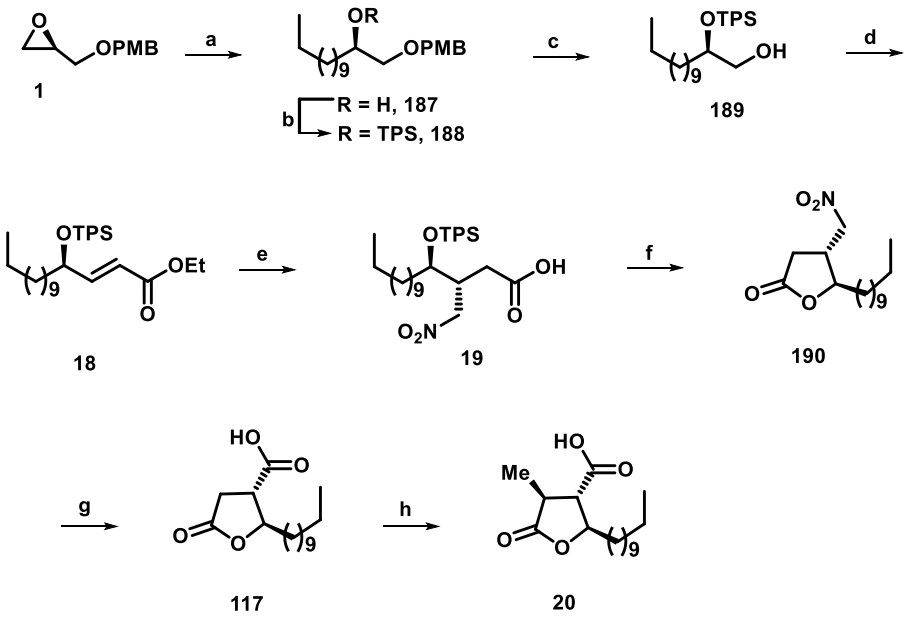
As depicted in Scheme 39, the synthesis of (+)-nephrosteranic acid **20** as a representative target compound of paraconic acids commenced from readily available PMB (*R*)-glycidyl ether **1**[9] which was subjected to regioselective ring opening (copper-catalyzed, CuI) with the Grignard reagent, derived from decyl bromide to furnish the alcohol derivative **187** in 85% yield. The -OH group of **187** revealed the IR absorption at 3460 cm^{-1}.

The alcohol derivative **187** on silyl protection with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole with DMAP in catalytic amount afforded the silyl ether derivative **188** in 95% yield which on PMB ether cleavage using CAN (ceric ammonium nitrate) at 0 ^{o}C-rt furnished the terminal alcohol derivative **189** in 91% yield. The hydroxyl absorption peak was found at 3329 cm^{-1} in the IR spectra of compound **102**.

The alcohol derivative **189** on oxidation under Swern conditions[10] followed by treatment with (ethoxycarbonyl-methylene)triphenylphosphorane in THF afforded the *trans*-olefinic ester derivative **18** in 92% yield. The ester carbonyl absorption was found at 1728 cm^{-1} in the IR spectrum of **18** and the olefin C=C stretching was at 1655 cm^{-1}. The ^1H NMR spectrum revealed double bond protons at δ 6.86 (dd, one proton, J = 15.56, 5.04 Hz) and at δ 5.90 (dd, one proton, J = 15.56, 1.36 Hz) intimating *trans*-alkene.

Our next goal was to carry out the synthesis of multifunctionalized γ-butyrolactone. Towards this end, *trans*-olefinic ester **18** on controlled reduction with DIBAL-H at -78 ^oC to α, β-unsaturated aldehyde intermediate and successive conjugate Michael addition[11] of nitromethane in the presence of (*S*)-diphenylprolinol silyl ether (10 mol%) afforded the nitroaldehyde adduct which on subsequent oxidation with oxone[12] furnished the nitro-acid derivative **19** in excellent yield.

At 3152 cm^{-1}, hydroxy absorption was detected in the IR spectra of compound **19**. The disappearance of olefin protons at δ 6.86 and at δ 5.90 in the ^1H NMR spectrum of compound **19** supports the consumption of double bond during Michael addition.



Scheme 39. *Reagents and conditions*: (a) $C_{10}H_{21}MgBr$, CuI, dry THF, -30 ^oC, 6 h, 85%; (b) TBDPSCl, Imidazole, cat. DMAP, CH_2Cl_2, 0 ^oC-rt, 8 h, 95%; (c) CAN, CH_3CN:H_2O (4:1, v/v), 0 ^oC-rt, 2h, 91%; (d) i) Oxalyl chloride, $(CH_3)_2SO$, Et_3N, DCM, -78 ^oC to -60 ^oC, 3 h; ii)

$PPh_3CHCOOEt$, THF, rt, 20 h, 92% (over two steps); (e) i) DIBAL-H, CH_2Cl_2, -78 ^oC, 1h; ii) (*S*)-diphenylprolinol silyl ether (10 mol%), CH_3NO_2, benzoic acid, MeOH, rt, 16 h; iii) oxone, DMF, rt, 12 h, 84% (over 3 steps); (f) TBAF, dry THF, rt, 2 h, 95%; (g) $NaNO_2$, acetic acid, DMSO, rt, 24 h, 94%; (h) NaHMDS, CH_3I, dry THF, -78 ^oC, 3 h, 93%.

Further to demonstrate the stereochemistry during the conjugate Michael addition of nitromethane to *α, β*-unsaturated aldehyde intermediate we carried out the reaction with racemic catalyst (±)-diphenylprolinol silyl ether to get the nitro-aldehyde adduct which on subsequent oxidation with oxone afforded the *anti*-/*syn*-nitroacid diastereomers (dr, 1:1) in 83% combined yield. However, on the other hand, in the presence of (*S*)-diphenylprolinol silyl ether catalyst the conjugate addition of nitromethane on *α, β*-unsaturated aldehyde intermediate obtained from **18** followed by oxidation with O_3 gave the *anti*-nitro acid derivative **19** as a single diastereomer[13] in 84% yield.

The *anti*-nitro acid derivative **19** on TPS deprotection and concomitant cyclisation with TBAF (tetra-*n*-butylammonium fluoride) furnished the γ-butyrolactone derivative **190** in 95% yield. In the IR spectrum of **190**, the disappearance of stretching frequencies corresponding to OH and in ^1H NMR spectrum disappearance of aromatic protons from δ 7.65-7.36 confirms the cyclisation.

The nitro-γ-butyrolactone derivative **190** was subjected to treatment with sodium nitrite and acetic acid under Nef reaction conditions[14] to afford the γ-butyrolactone acid derivative **117** in 94% yield. Finally, stereoselective methylation at *α*-position of acid derivative **117** was carried out with methyl iodide and NaHMDS in THF to furnish the (+)-nephrosteranic acid **20** in 93% yield ($[\alpha]_D^{25}$+27.18 (*c* 1.50, $CHCl_3$), {lit.[5r] $[\alpha]_D^{27}$ +27.2 (*c* 1.45, $CHCl_3$). The spectral and physical properties of the (+)-nephrosteranic acid **20** were completely consistent with previously reported values.[5a]

3.5 Conclusion:

To sum up we have developed an efficient and enantioselective route to multifunctionalized γ-butyrolactone paraconic acids and its application to the synthesis of (+)-nephrosteranic acid **20** from readily accessible PMB (*R*)-glycidyl ether starting material. Pivotal reaction sequence comprises asymmetric Michael addition catalyzed by (*S*)-diphenylprolinol silyl ether and stereoselective *α*-methylation. The overall yield for the (+)-nephrosteranic acid **20** was 50%. The

synthetic route presented has further capabilities for the stereochemical variations in all the ring positions and extension to other stereoisomers and analogues.

3.6 Experimental Section:

All experiments were performed under Nitrogen, with moisture free, freshly extracted solvents through distillation unless otherwise indicated. All the reagents or chemicals were put in reaction either via syringe or cannula. Each distillation was also performed under unreactive conditions. Every reaction was performed at their respective temperatures as narrated within their respective schemes. Solvent evaporation was performed utilising a Heidolph rotary evaporator at reduced pressure and at less than 40 °C temperature

Chromatography

Every reaction performed was examined through Thin Layer Chromatography executed using commercially available silica gel plates 60 F_{254} using UV light, then were stained in ninhydrin or in ethanolic solution of anisaldehyde or in aqueous KMnO4 as development reagents follow up by concise heating using a heating gun. For column chromatography, silica gel of mesh size 60-120 and 100-200 was employed and different compositions of ethyl acetate/hexane and methanol/ dichloromethane were used as organic eluent.

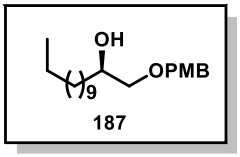
Reagents and solvents

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

Spectroscopic Measurements

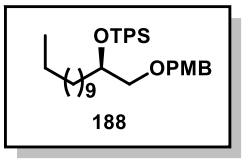
JEOL ECS spectrometer was employed for recording the ^{1}H NMR and ^{13}C NMR respectively. Tetramethylsilane (TMS) utilized as reference. The measuring unit for chemical shifts (δ) is parts per million (ppm). J values (Coupling constants) are listed in hertz (Hz). Electron spray ionization (ESI) were used for recording mass spectra and mass data were presented as m/z. The IR spectra were captured on an Agilent resolution Pro 600 FT-IR spectrometer with a beam-condensing ATR attachment, and the peaks were measured in centimeter inverse Yields mentioned referred to isolated combined amount after chromatography.

(*R*)-1-((4-methoxybenzyl)oxy)tridecan-2-ol, 187



A solution of decylmagnesium bromide freshly prepared from Mg turnings (0.493 g, 20.58 mmol) and decylbromide (3.40 g, 15.43 mmol) in anhydrous THF, was added drop by drop to a stirred solution of (*R*)-PMB- glycidyl ether **1** (2.0 g, 10.29 mmol) and CuI (195 mg, 1.029 mmol) in anhydrous THF (20 mL) at -30 °C. At the same temperature, the agitating was continued for 6 hours. As the TLC gave the indication of reaction completion, saturated aq. NH_4Cl was poured to quench the reaction. The organic suspension was extracted with ethyl acetate (3 x 20 mL), moisture was absorbed over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography to afford the (*R*)-alcohol derivative **187** (2.95 g, 85%) as white solid. R_f = 0.4 (hexane/EtOAc, 9.8:0.2, v/v); m.p. 186-187 ^oC; $[\alpha]_D^{25}$= - 2.78 (*c* = 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3460, 2980, 1662, 1595, 1516, 1057, 937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, *J* = 8.72 Hz, 2H), 6.89(d, *J* = 8.72 Hz, 2H), 4.47 (s, 2H), 3.80 (s, 3H), 3.75-3.81 (m, 1H), 3.47 (dd, *J* = 9.64, 3.24 Hz, 1H), 3.28 (dd, *J* = 9.60, 8.24 Hz, 1H), 2.41 (brs, 1H), 1.33-1.47 (m, 2H), 1.25-1.32 (m, 18H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 130.0, 129.4, 113.8, 74.3, 72.9, 70.4, 55.2, 33.1, 31.9, 29.63, 29.59, 29.32, 25.5, 22.7, 14.1; HRMS (ESI), calcd for $C_{21}H_{36}O_3$ $[M+H]^+$: 337.2737, found 337.2741

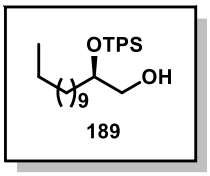
(*R*)-*tert*-butyl((1-((4-methoxybenzyl)oxy)tridecan-2-yl)oxy)diphenylsilane, 188



To a agitated solution of alcohol derivative **187** (2.0 g, 5.94 mmol) in dry CH_2Cl_2 (30 mL) sequentially imidazole (606 mg, 8.91 mmol), *tert*-butyl chlorodiphenylsilane (1.95 g, 7.12 mmol) and DMAP (108 mg, 0.89 mmole) added at 0 ^oC and further the organic suspension was continued to be agitated at rt for 8 hours. Reaction progress was monitored by thin layer chromatography and as the reaction completed, quenched with saturated aq. NH_4Cl. The organic fraction was taken out with DCM (3 x 20 mL). The collected organic portion was washed using brine, moisture was removed over anhydrous Na_2SO_4 and solvent was evaporated employing rotary evaporator. After purifying the crude product *via* silica gel column chromatography (EtOAc/hexane, 0.1:9.9) the silyl ether derivative **188** (3.24 g) was obtained in 95% yield as colorless oil. R_f = 0.5 (EtOAc/hexane 0.1:9.9); $[\alpha]_D^{25}$ = +8.91 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66 (tt, *J* = 5.96, 1.34 Hz, 4H), 7.31-7.41(

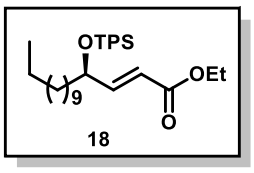
m, 6H), 7.08(d, *J* = 8.72 Hz, 2H), 6.81(d, *J* = 8.72 Hz, 2H), 4.25 (q, *J* = 18.80, 11.44 Hz, 2H), 3.82-3.86 (m, 1H), 3.79 (s,3H), 3.30-3.37 (m, 2H), 1.11-1.50 (m, 2H), 1.19-1.31 (m, 18H), 1.03 (s, 9H), 0.88 (t, *J*=7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9, 136.0, 135.9, 134.6, 134.1, 130.5, 129.5, 129.3, 129.2, 127.3, 127.2, 113.5, 73.6, 72.6, 72.2, 55.2, 34.3, 31.9, 29.7, 29.6, 29.5, 29.4, 27.0, 24.7, 22.7, 19.4, 14.1; HRMS (ESI), calcd for $C_{37}H_{54}O_3Si$ $[M+Na]^+$: 597.3734, found 597.3737.

(*R*)-2-((*tert*-butyldiphenylsilyl)oxy)tridecan-1-ol, 189



To a agitated solution of **188** (2.50 g, 4.34 mmol) in acetonitrile: water (4:1 = v/v, 30 mL) at 0 ºC CAN (5.76 g, 10.52 mmol) was added and the organic suspension was stirred at rt for 2.0 hours. As the TLC gave the indication of reaction completion, brine (5 mL) solution was poured to quench the reaction and the organic solution was extracted with EtOAc (3 x 15 mL). Moisture of organic fraction was absorbed by anhydrous Na_2SO_4 and concentrated in *vacuo*. The remnant was purified by silica gel column chromatography (EtOAc/hexane 0.5:9.5) to furnish the primary alcohol derivative **189** (1.79g) in 91% yield as a white solid. R_f = 0.5 (EtOAc/hexane 0.5:9.5); m.p. 147-148 ºC; $[\alpha]_D^{25}$ = -29.21 (*c* = 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3329, 2755,1660, 1589, 1581, 1509, 1161, 910 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (dt, *J* = 8.04, 1.64Hz, 4H), 7.38-7.45 (m, 6H), 3.73-3.79 (m, 1H), 3.45-3.57 (m, 2H), 1.84 (brs, 1H),1.39-1.49 (m, 2H), 1.11-1.33 (m, 18H), 1.07 (s, 9H), 0.88 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.9, 135.7, 133.9, 133.8, 129.8, 129.7, 127.7, 127.6, 74.1, 65.9, 33.5, 31.9, 29.6, 29.5, 29.4, 29.3, 27.0, 25.1, 22.7, 19.3, 14.1; HRMS (ESI), calcd for $C_{29}H_{46}O_2Si$ $[M+Na]^+$: 477.3159, found: 477.3161.

ethyl (*R*,*E*)-4-((*tert*-butyldiphenylsilyl)oxy)pentadec-2-enoate, 18

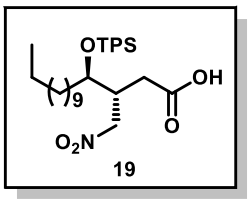


To a agitated solution of $(COCl)_2$ (628 mg, 0.427 mL, 4.95 mmol) in anhydrous CH_2Cl_2 (2 mL) at -78 ºC was added dropwise dimethylsulfoxide (798 mg, 0.725 mL, 10.24 mmol) in dry CH_2Cl_2 (2 mL) and stirred the reaction mixture. After 30 min. a solution of silyl protected hydroxy derivative **189** (1.50 g, 1.52 mmol) in dry CH_2Cl_2 (10 mL) was drop by drop added in 15 min at the previously maintained temperature. The organic suspension was agitated at -78 °C for ½ h and at slightly increased, -60 °C for 1 h and then Et_3N (1.46 g, 2.02 mL, 14.54 mmol) was added

dropwise at the same temperature and stirred for another 1 hour. The organic suspension was put at rest to attain the rt and diluted with water and DCM. Two layers were partitioned and organic portion was extracted with DCM (3 x15 mL), washed with brine, sodium sulphate was added to absorbed moisture, and concentrated with rotary evaporator to hand the crude aldehyde, which was utilized in the succeeding step following filter column purification.

A solution of (ethoxycarbonylmethylene)triphenylphosphorane (1.73 g, 4.95 mmol) in THF was added to a solution of the above aldehyde in THF (10 mL) (20 mL). The reaction mixture was continuously stirred for 20 h at room temperature. TLC was checked and after completion, concentrated under reduced pressure. Silica gel column chromatography (EtOAc/hexane, 1:9, v/v) was employed to purify the crude (EtOAc/hexane, 1:9, v/v) which afforded the *α*, *β*-unsaturated ester derivative **18** (1.58 g, 92% over two steps) as a colorless thick syrupy liquid. R_f = 0.35 (EtOAc/hexane 1:9); $[\alpha]_D^{25}$ = +7.29 (*c* = 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 2952, 2861, 1728, 1655, 1356, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.68 (dd, *J* = 8.24, 1.36Hz,2H), 7.61 (dd, *J* = 7.80, 1.36Hz, 2H), 7.35-7.45 (m, 6H), 6.86 (dd, *J* = 15.56, 5.04 Hz, 1H), 5.90 (dd, *J* = 15.56,1.36Hz,1H), 4.34 (q, *J* = 6.44 Hz, 1H), 4.18 (dq, *J* = 14.20, 6.88, 2.33Hz, 2H), 1.35-1.49 (m, 2H), 1.29 (t, *J* = 7.32, 3H), 1.11-1.29 (m, 18H), 1.08 (s, 9H), 0.88(t, *J* = 6.88, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*:166.7, 150.3, 135.8, 134.0, 133.5, 129.7, 129.6, 127.6, 120.0, 72.4, 60.3, 36.7, 31.9, 29.7, 29.6, 29.5, 29.4, 27.0, 26.9, 23.9, 22.7, 19.3, 14.2, 14.1; HRMS (ESI), calcd for $C_{33}H_{50}O_3Si$ $[M+H]^+$: 523.3602; found: 523.3599.

(3*R*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-(nitromethyl)pentadecanoic acid, 19

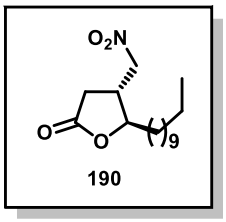


To a stirred solution of *α*, *β*-unsaturated ester derivative **18** (1.0 g, 1.92 mmol) in dry DCM (15 mL) was added DIBAL-H (2.30 mL, 2.30 mmol, 1 M in hexane) under inert atmosphere at -78 °C. After stirring the reaction mixture for 1 hour under the above maintained conditions, the reaction was ended with addition of sodium potassium tartrate (saturated aq. solution) and stirred for additional 30 min. The two phases were separated and organic suspension was extracted with DCM (3 x 15 mL). The combined organic extract was dried over anhydrous sodium sulphate and concentrated *in vacuo* to yield *α*,*β*-unsaturated aldehyde which was utilized as such for the future action after filtration column using Celite.

To the above *α, β*-unsaturated aldehyde intermediate in dry methanol was added nitromethane (0.31 mL, 5.76 mmol), (*S*)-diphenyltrimethylsiloxymethylpyrrolidine (62 mg, 0.19 mmol) and C_6H_5COOH (23 mg, 0.19 mmol) sequentially at room temperature. The suspension was agitated for 16 h at rt. After completion (confirmed by TLC) the reaction was ended with addition of saturated aqueous $NaHCO_3$ solution. The organic fraction was extracted with EtOAc (3 x 10 mL), dried over anhydrous Na_2SO_4 and distilled with rotary evaporator to furnish nitro-aldehyde intermediate which was used directly for the next stage lacking purification.

To a stirred solution of above nitro-aldehyde intermediate in DMF (10 mL) solvent oxone (2.30 g, 7.68 mmol) was put on and the organic suspension was stirred at rt for 12 hours. As the TLC gave the indication of reaction completion, the reaction mixture was diluted with water and extracted with EtOAc (3 x15 mL). The collected organic portion was combined, rinsed using brine, and moisture was removed over anhydrous sodium sulphate, concentrated *in vacuo* and crude was purified by silica gel column chromatography (EtOAc/hexane 2:8, v/v) to furnish the nitro-acid derivative **19** (870 mg, 84%, over three steps) as colorless solid. R_f = 0.4 (EtOAc/hexane, 1:4); m.p. 161-162 ^oC; $[\alpha]_D^{25}$ = + 16.52 (*c* = 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3152, 2831, 1728, 1527, 1362 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.65 (t, *J* = 1.36 Hz, 2H), 7.63 (t, *J* = 1.40 Hz, 2H), 7.46-7.36 (m, 6H), 4.62 (dd, *J* = 13.28, 7.32Hz,1H), 4.49 (dd, *J* = 12.84,6.44Hz,1H), 3.72 (dt, *J* = 5.48, 2.28 Hz, 1H), 2.83-2.92 (m, 1H), 2.67 (dd, *J* = 16.96, 5.04Hz, 1H), 2.47 (dd, *J* = 16.92, 8.24Hz, 1H), 1.11-1.45 (m, 20H), 1.04 (s, 9H), 0.88 (t, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.4, 135.8, 135.7, 134.8, 133.7, 132.4, 130.1, 129.7, 127.9, 127.7, 127.5, 76.4, 72.8, 38.1, 33.8, 31.9, 31.0, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 27.0, 25.3, 22.7, 19.4, 14.1; HRMS (ESI), calcd for $C_{32}H_{49}NO_5Si$ $[M+H]^+$: 556.3453, found: 556.3455.

(4*R*,5*R*)-4-(nitromethyl)-5-undecyldihydrofuran-2(3H)-one, 190

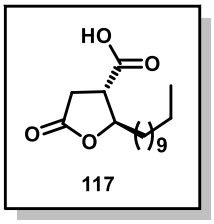


190

To a stirred solution of compound **19** (600 mg, 1.07 mmol) in dry THF (15 mL) TBAF (1.29 mL, 1.0 M in THF, 1.29 mmol) was added drip by drip *via* syringe and the reacting solution was agitated at rt for 2 hours. After completion, the reaction was quenched with saturated aqueous NH_4Cl solution and organic residue was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and distilled with rotary evaporator to get the crude product. The residue was purified by silica gel column chromatography

(EtOAc/hexane,3:2v/v) to afford the nitro γ-butyrolactone derivative **190** (315 mg, 95%) as a colorless solid. R_f = 0.4 (EtOAc/hexane 1.5:8.5); m.p. 137-138 ^oC; $[\alpha]_D^{25}$ = +28.26 (*c* = 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 1768, 1534, 1514, 1056, 937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.53 (dd, *J* = 13.28, 6.88 Hz, 1H), 4.45 (dd, *J* = 13.28, 7.44Hz, 1H), 4.28 (q, *J* = 12.84, 5.96Hz, 1H), 2.90 (dd, *J* = 17.88, 9.16 Hz, 2H), 2.43 (dd, *J* = 17.88, 6.44 Hz, 1H), 1.72-1.66 (m, 2H), 1.26-1.45 (m, 18 H), 0.88 (t, *J*=6.44, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 174.1, 82.1, 76.4, 38.7, 34.7, 32.5, 31.9, 29.6, 29.5, 29.3, 29.3, 29.2, 25.2, 22.7, 14.1; HRMS (ESI), calcd for $C_{16}H_{29}NO_4$ $[M+H]^+$: 300.2169, found 300.2159

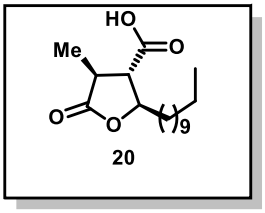
(2*R*,3*S*)-5-oxo-2-undecyltetrahydrofuran-3-carboxylic acid, 117



117

To a stirred solution of nitro γ-butyrolactone derivative **190** (150 mg, 0.40 mmol) in dimethyl sulfoxide (5 mL) sodium nitrite (83mg, 1.20 mmol) and acetic acid (0.22 mL, 4.00 mmol) were added and the resultant suspension was agitated at room temperature for 24 hours. TLC was tracked, as the reaction completed, organic extract was suspended with water, acidified with HCl (10% aq. solution, 2 mL). Organic portion was extracted with ether (3 x 10 mL), moisture was absorbed over anhydrous Na_2SO_4, distilled *in vacuo*, and purified by column chromatography of silica gel (EtOAc/hexane, 1:1v/v) to yield the γ-butyrolactone acid derivative **117** (134 mg, 94%) as a white solid. R_f = 0.4 (EtOAc/hexane 7:3); m.p. 117-118 ^oC; $[\alpha]_D^{25}$ = +45.11 (*c* = 0.25, $CHCl_3$) {lit.[SI-1] $[\alpha]_D^{25}$ +44.8 (*c* = 0.25, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.60-4.65 (m, 1H), 3.06-3.13 (m, 1H), 2.94 (dd, *J* = 17.88, 8.24Hz, 1H), 2.82 (dd, *J* = 17.88, 9.64 Hz, 1H), 1.69-1.89 (m, 2H), 1.18-1.59 (m, 18 H), 0.88 (t, *J* = 6.88, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 175.4, 174.4, 81.8, 45.4, 35.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.2, 22.7, 14.1; HRMS (ESI), calcd for $C_{16}H_{28}O_4$ $[M+H]^+$: 285.2060, found 285.2064.

(+)-Nephrosteranic acid, 20



20

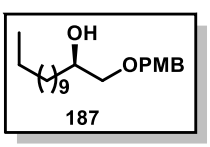
To a stirred solution of γ-butyrolactone acid derivative **117** (60 mg, 0.21 mmol) in dry THF (2 mL) was added NaHMDS (0.46 mL,1.0 M solution in THF, 0.46 mmol) at -78 °C in drop wise fashion and stirred the reaction mixture for 1 hour. Further, MeI (281 mg, 0.13 mL, 2.00 mmol) was added and the reaction was allowed to agitate at -78 °C for additional 2 hours.

Then TLC was examined and after completion the suspension was put at rest to attain the -20 ^{o}C. The HCl (2N, 1.0 mL) was added to the above solution and extracted with organic solvent EtOAc (3 x 5mL). The collected organic portion was combined and anhydrous Na_2SO_4 was added to dry and were concentrated using rotary evaporator. The residue obtained was purified by preparative TLC (EtOAc/hexane, 1:1 v/v) to furnish the (+)-nephrosteranic acid **20** (58mg, 93%) as white solid. R_f = 0.4 (EtOAc/hexane, 1:1); m.p. 96-97 ^{o}C; $[\alpha]_D^{25}$ +27.18 (*c* = 1.50, $CHCl_3$), {lit.[SI-1] $[\alpha]_D^{25}$ +27.2 (*c* = 1.45, $CHCl_3$), lit.[SI-2] $[\alpha]_D^{25}$+26.9 (*c* 0.14, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.48 (dt, *J* = 8.72, 3.68 Hz, 1H), 2.95-3.04 (m, 1H), 2.71 (dd, *J* = 11.48, 9.64 Hz, 1H), 1.66-1.87 (m, 2H), 1.37 (d, *J* = 7.32 Hz, 3 H), 1.02-1.61 (m, 18H), 0.88 (t, *J* = 6.40, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.7, 175.7, 79.4, 53.9, 39.8, 34.9, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.3, 22.7, 14.5, 14.1; HRMS (ESI), calcd for $C_{17}H_{30}O_4$ $[M+H]^+$: 299.2217; found: 299.2219.

3.7 Spectra:

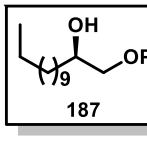
1. ^{1}H spectrum for compound **187**
2. ^{13}C spectrum for compound **187**
3. ^{1}H spectrum for compound **188**
4. ^{13}C spectrum for compound **188**
5. ^{1}H spectrum for compound **189**
6. ^{13}C spectrum for compound **189**
7. ^{1}H spectrum for compound **18**
8. ^{13}C spectrum for compound **18**
9. ^{1}H spectrum for *anti*-/*syn*-diastereomeric mixture
10. ^{13}C spectrum for *anti*-/*syn*-diastereomeric mixture
11. ^{1}H spectrum for compound **19**
12. ^{13}C spectrum for compound **19**
13. ^{1}H spectrum for compound**190**
14. ^{13}C spectrum for compound **190**
15. ^{1}H spectrum for compound **117**
16. ^{13}C spectrum for compound **117**
17. ^{1}H spectrum for compound **20**
18. ^{13}C spectrum for compound **20**

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



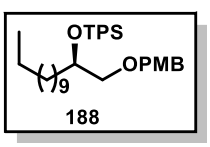
187

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



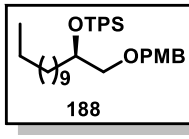
187

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



188

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



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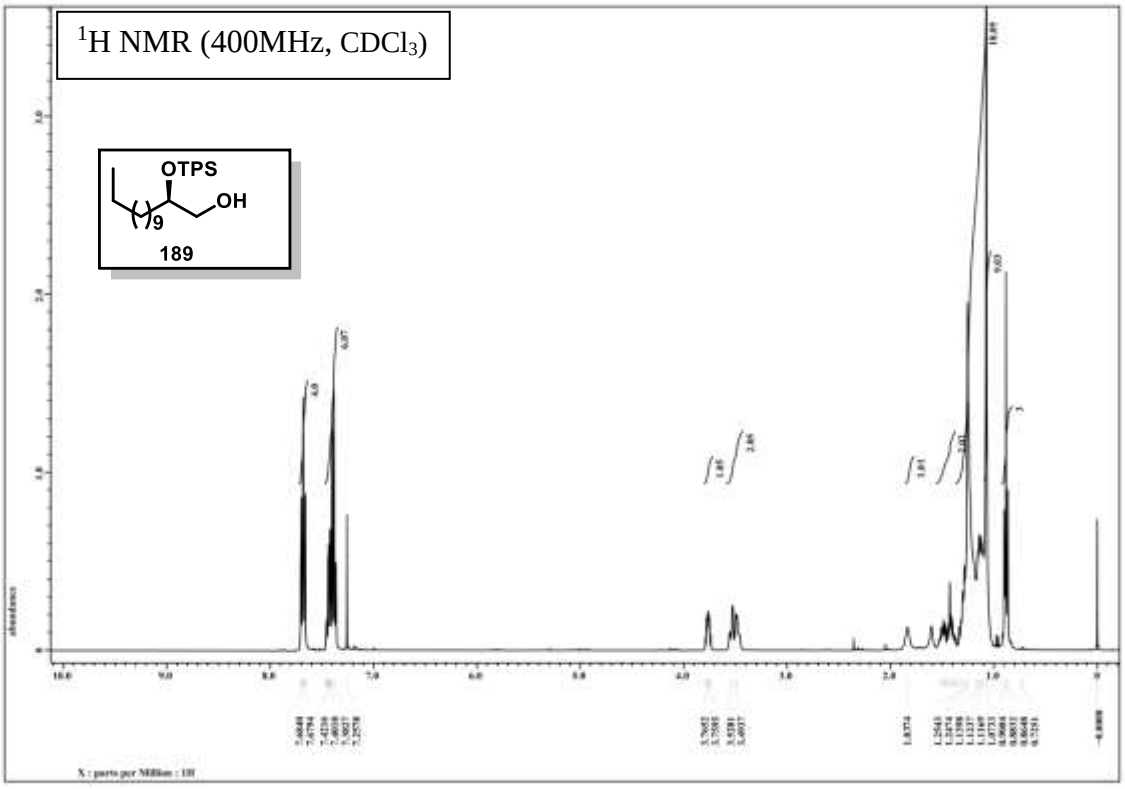
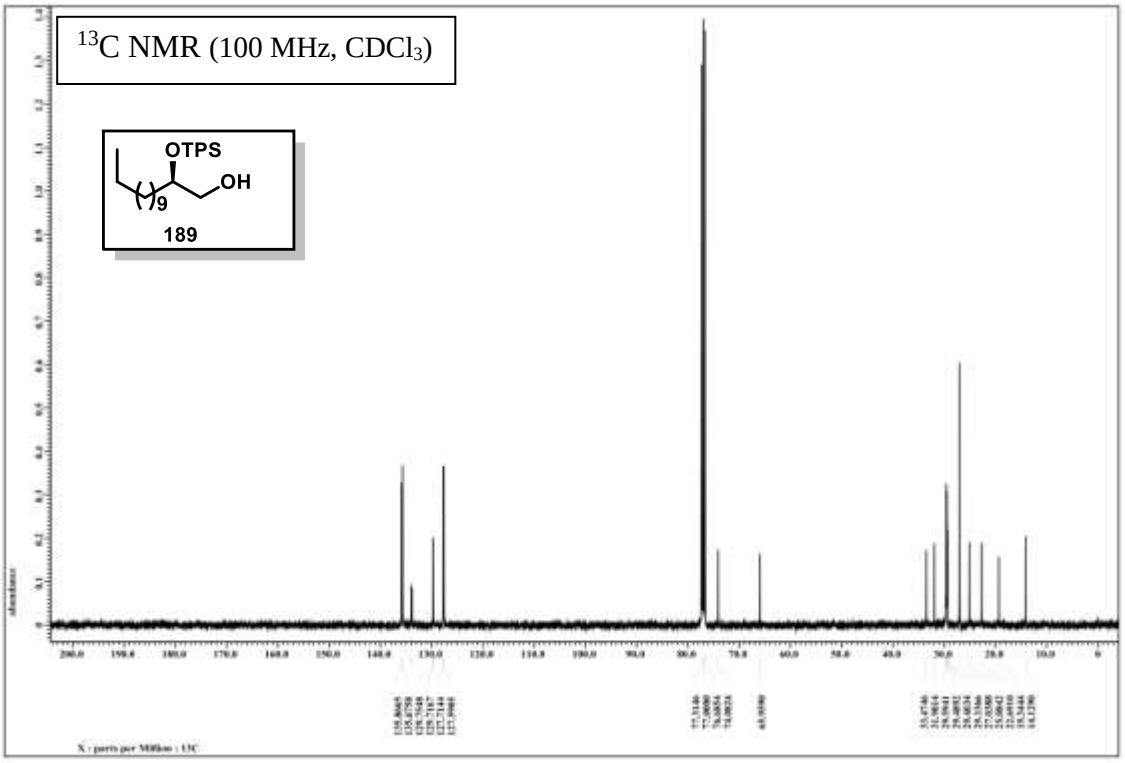
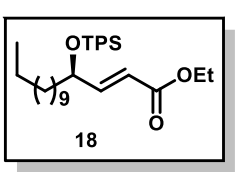
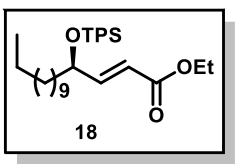

^{1}H NMR (400MHz, $CDCl_3$)
OTPS
OH
9
189

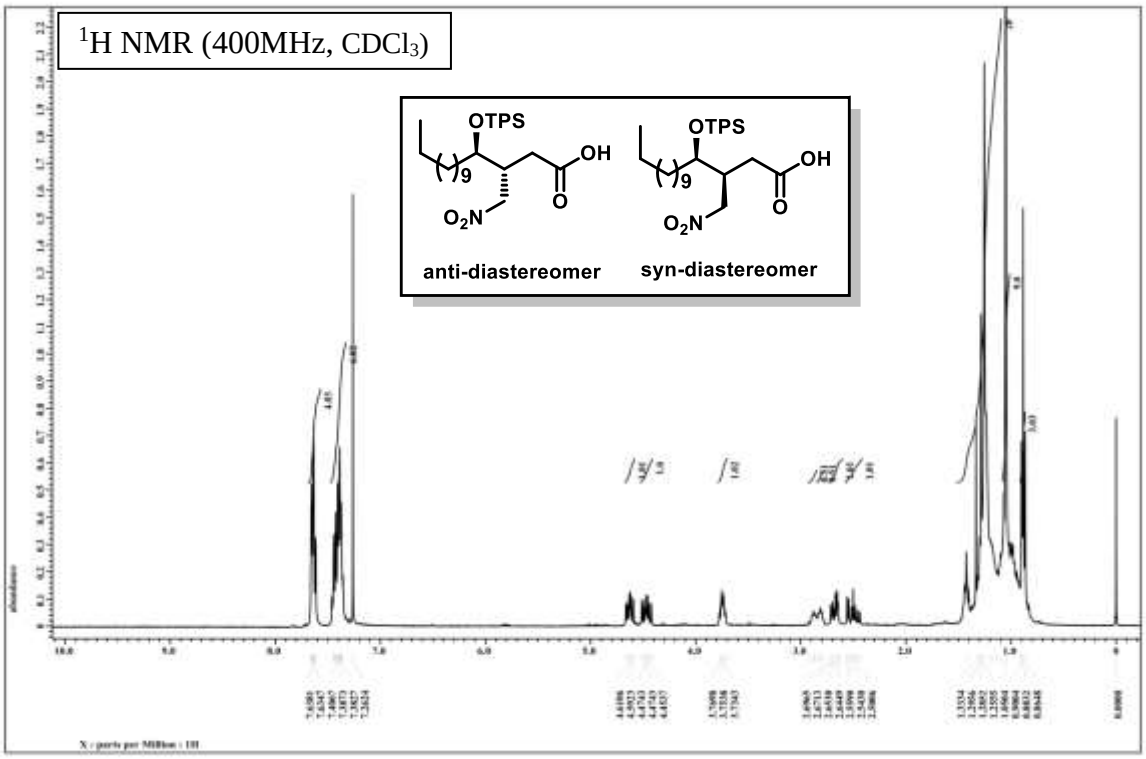

^{13}C NMR (100 MHz, $CDCl_3$)
OTPS
OH
9
189

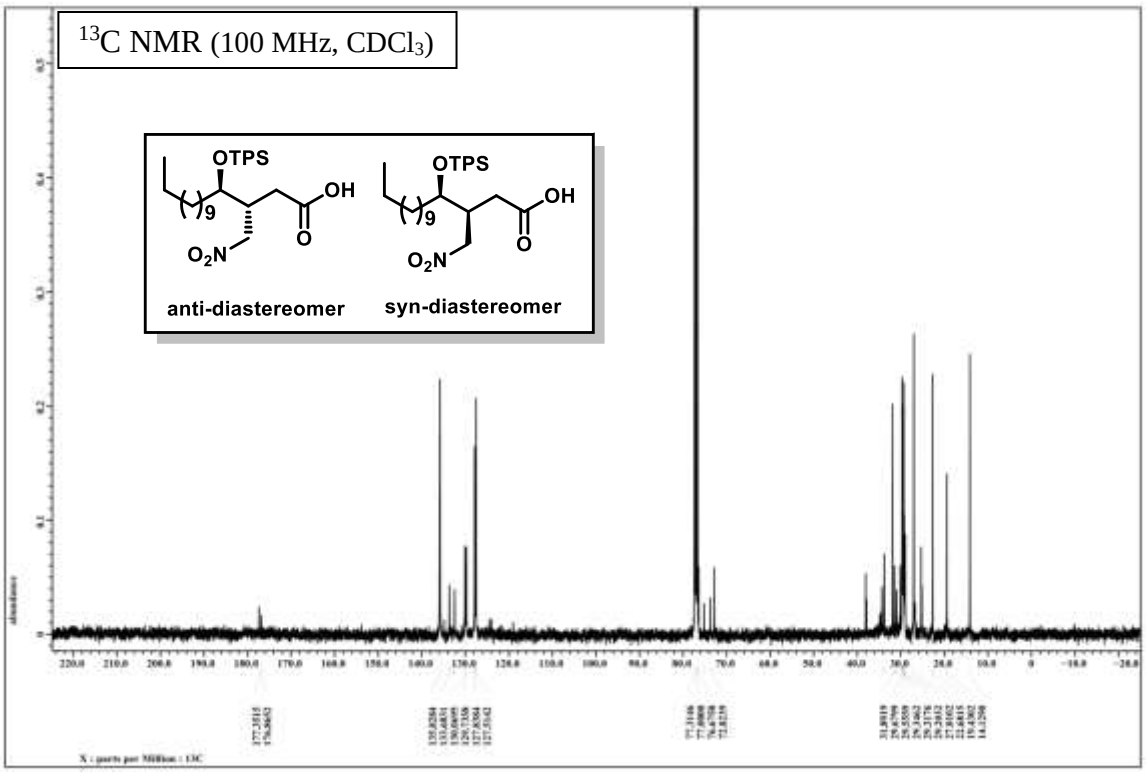
^{1}H NMR (400MHz, $CDCl_3$)

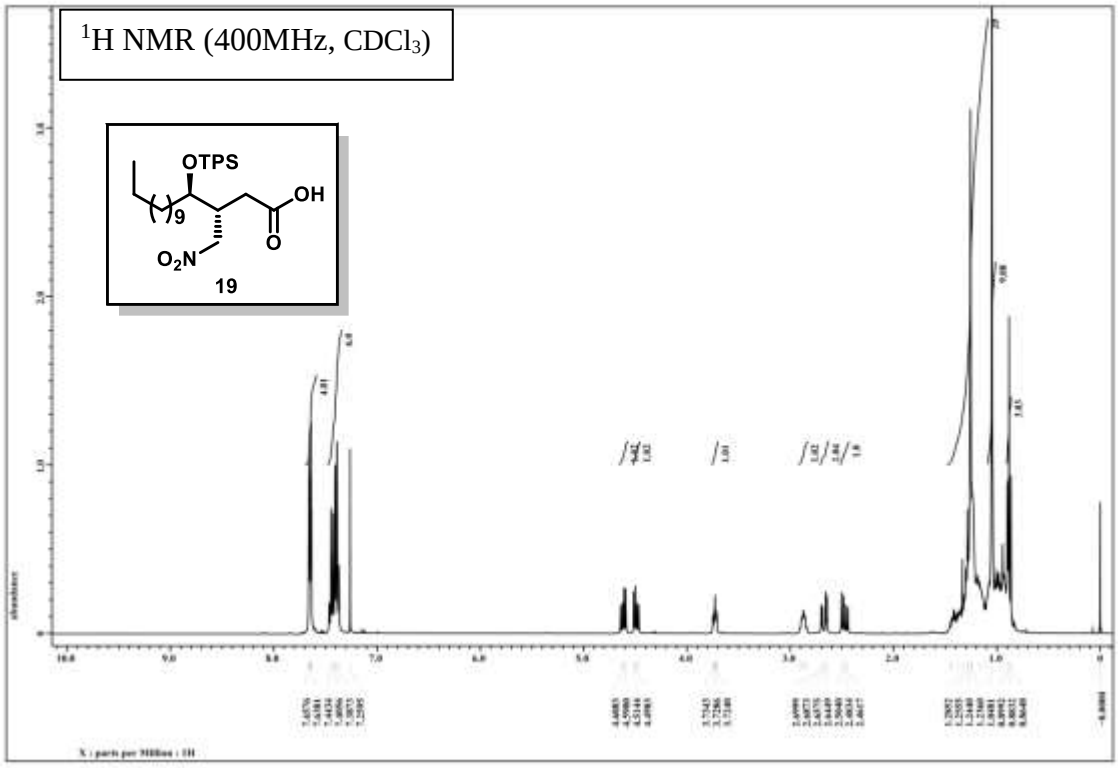


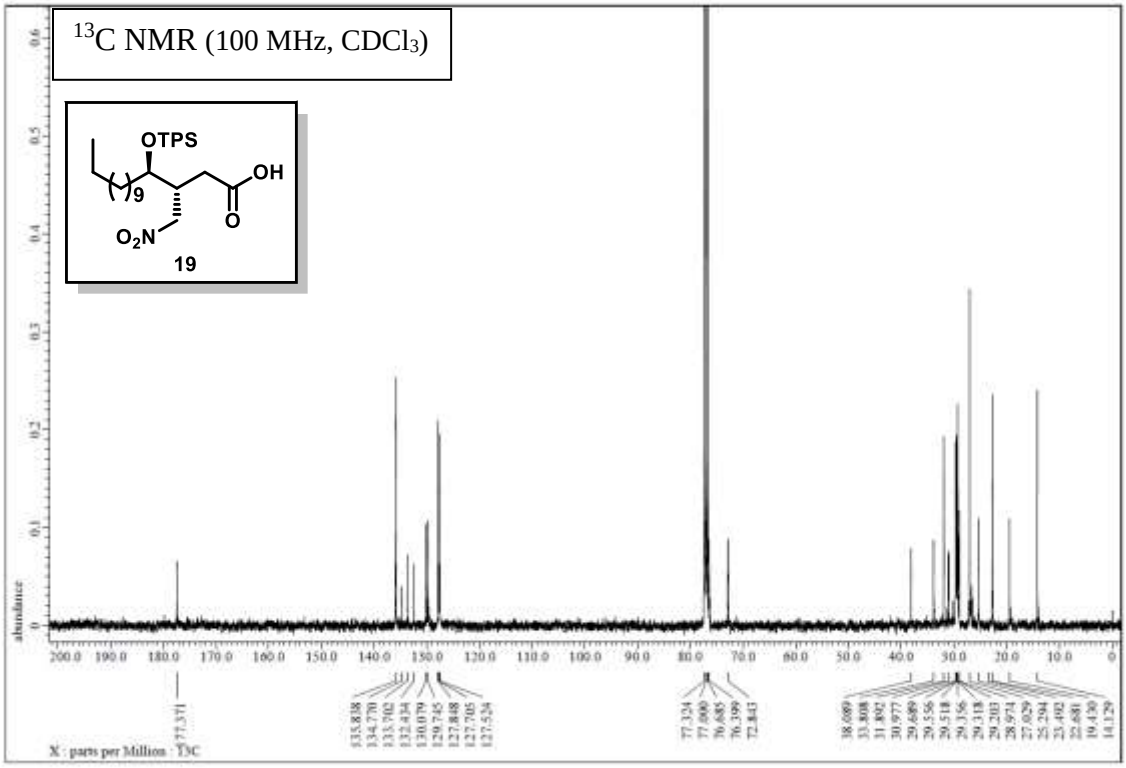
^{13}C NMR (100 MHz, $CDCl_3$)



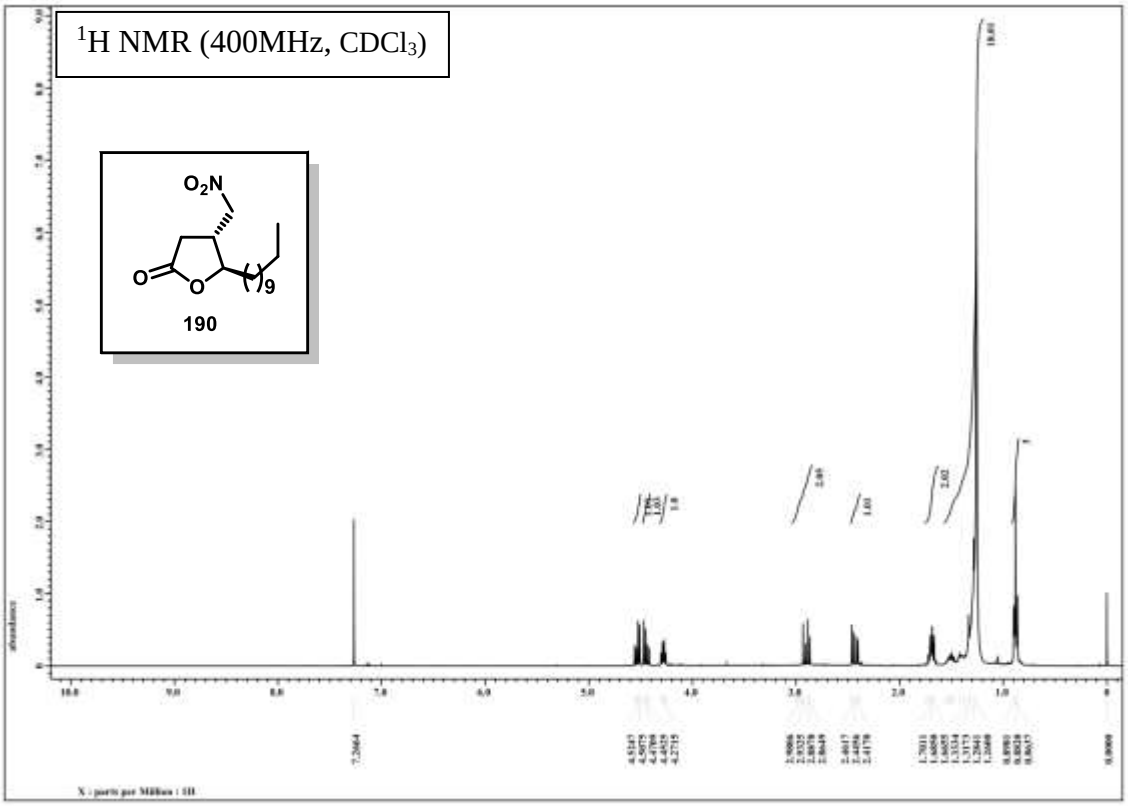

^{1}H NMR (400MHz, $CDCl_3$)
OTPS
OH
O
O_2N
9
anti-diastereomer
syn-diastereomer


^{13}C NMR (100 MHz, $CDCl_3$)
OTPS
OH
O
O_2N
9
anti-diastereomer
syn-diastereomer


^{1}H NMR (400MHz, $CDCl_3$)
OTPS
OH
O
9
O_2N
19


^{13}C NMR (100 MHz, $CDCl_3$)
OTPS
OH
O
9
O_2N
19

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



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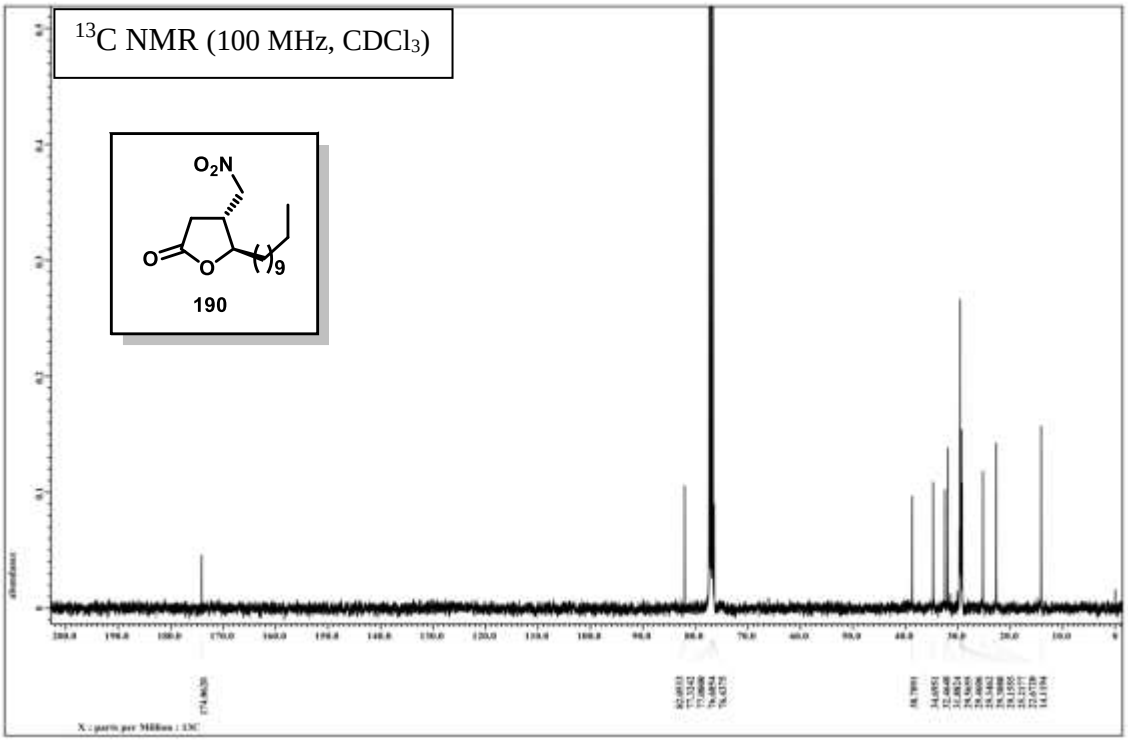
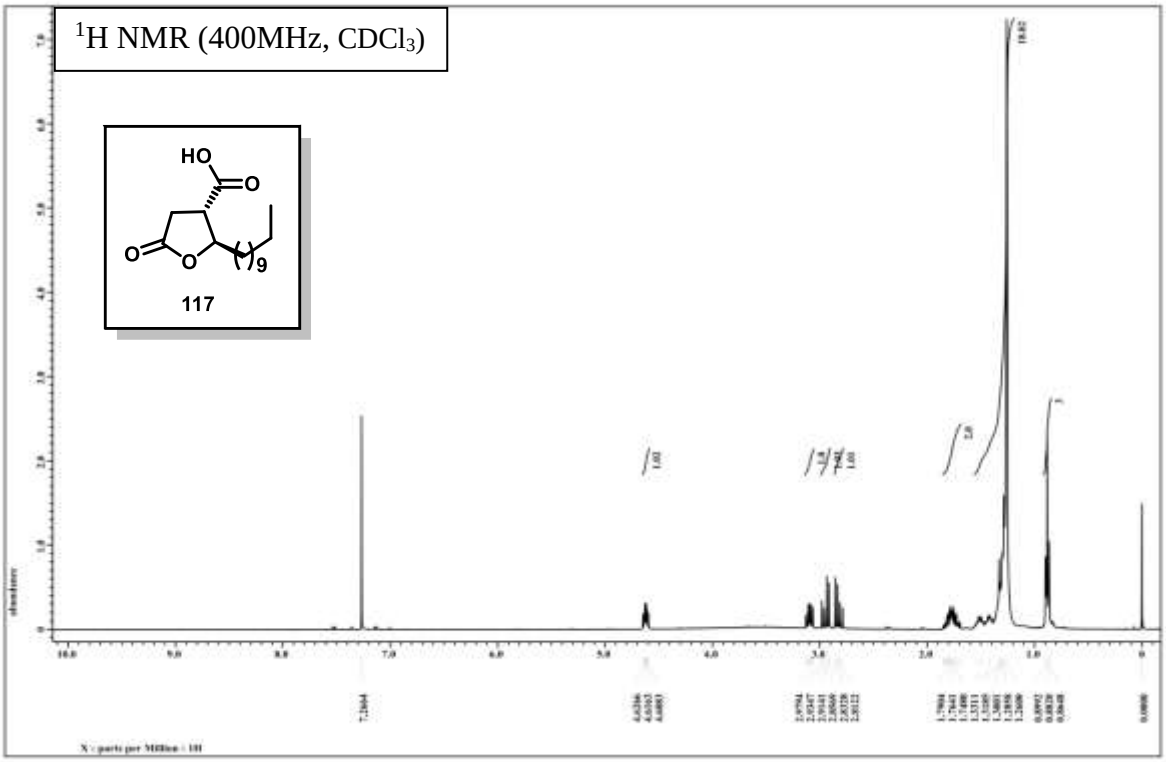
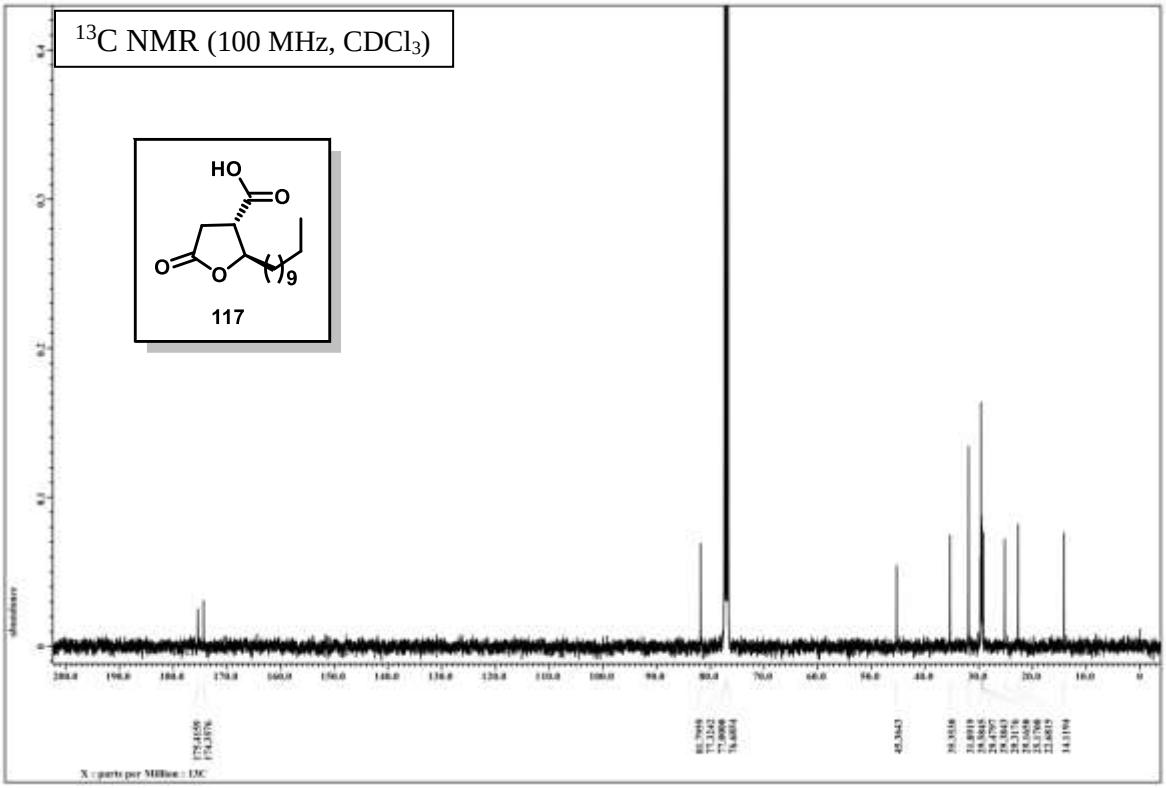


^{1}H NMR (400MHz, $CDCl_3$)



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



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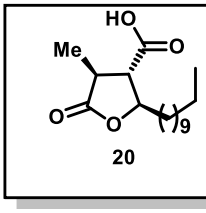
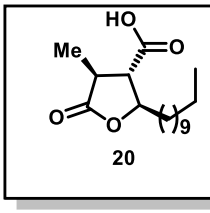


20

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



20

3.8 References:

1. For reviews on synthesis and isolation of plant lignans, see: (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426; (b) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43; (c) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, 22, 696; (d) Koch, S. S. C.; Chamberlin, A. R. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, **1995**; Vol. 16, p 687.
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CHAPTER 4

An attempt towards the total synthesis of (-)-trachelanthamidine.

An attempt towards the total synthesis of (-)-Trachelanthamidine

4.1 Introduction:

Pyrrolizidine alkaloids are found mainly in phalaenopsis hybrids[1] and gain immense recognition because of their numerous therapeutic properties.[2] (-)-Trachelanthamidine **24** (also called laburnine), a pyrrolizidine (necine) base is the simplest bicyclic compound of this family and gain considerable interest among synthetic chemists due to its unique structural features. Isoretronecanol **191** also contain substituted pyrrolizidine core unit and shared common structural features as of (-)-trachelanthamidine (Figure 7).

Trachelanthamidine 24 Isoretronecano 191

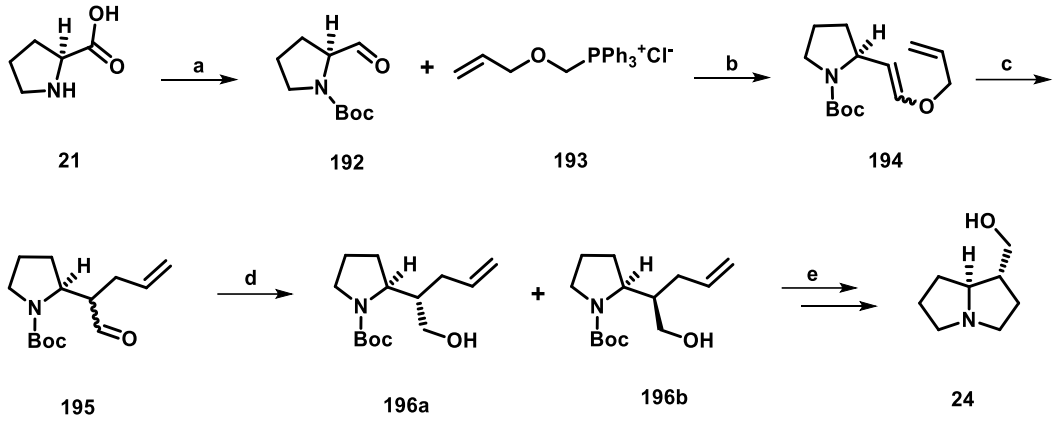
Figure 7. Structures of (-)-trachelanthamidine and isoretronecanol.

4.2 Review of Literature:

Various elegant asymmetric synthetic approaches of (-)-trachelanthamidine **24** have been reported in the literature[3] and some of the latest syntheses are discussed below.

Gavhane K. B. *et al.* (2015)[3a]

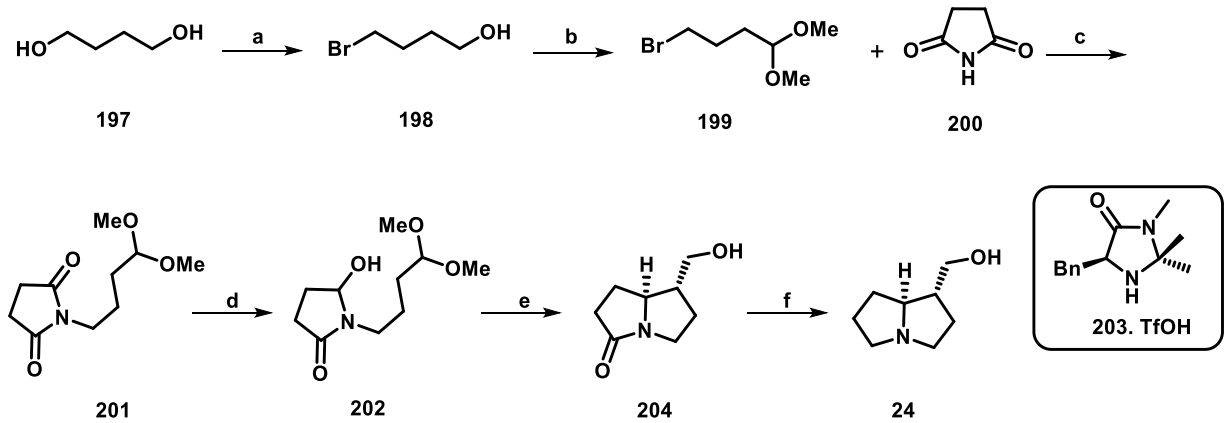
Gavhane and co-workers described the synthesis of (-)-trachelanthamidine **24** through the successful implementation of Wittig olefination and Claisen rearrangement (Scheme 40). The synthesis started from L-proline **21** which was initially transformed into *N*-Boc-prolinal **192** which upon Wittig olefination with allyloxymethylenetriphenylphosphonium chloride **193** yielded **194** (*E*:*Z* :: 5:1) in 74% yield. Next, allyl derivative **194** underwent Claisen rearrangement to furnish the inseparable mixture of aldehyde derivative **195**, which further on reduction with $NaBH_4$ in MeOH afforded the diastereomeric alcohol **196a** and **196b** (de, 6.92:1). The *anti*-alcohol **196b** was further utilized for the formal synthesis of **24** using a step of sequences reported earlier.[4]



Scheme 40. *Reagents and conditions*: (a) i) di-*tert*-butylcarbonate, Na_2CO_3, H_2O, 24 h, ii) $BH_3.SMe_2$, THF, 5h, 98%; iii) $(COCl)_2$, DMSO, *i*Pr_2NEt, -78 ^oC, rt , 2 h, 94%; (b) $K^+(CH_3)_3CO^-$, toluene, 0 ^oC, 2 h, 74%; (c) benzene, 80 ^oC, 48 h; (d) MeOH, $NaBH_4$, 0 ^oC, ½ h, 90% (over last two steps); (e) ref 4.

Dipankar, K. *et al.* (2014)[3b]

Koley and his team reported an elegant asymmetric synthesis of (-)-trachelanthamidine **24** *via* one pot organo-catalysed Mannich cyclization between hydroxylactam **202** and acetal as a pivotal step (Scheme 41). The synthesis commenced from the commercially available 1,4-butanediol **197** which on treatment with HBr in toluene under refluxed conditions afforded the bromoalcohol **198** in 92% yield. The hydroxy group of compound **198** was transformed into aldehydic group under Swern oxidation conditions followed by reaction with trimethyl orthoformate employing *p*-TSA to derive the derivative **199** in 82% yield.

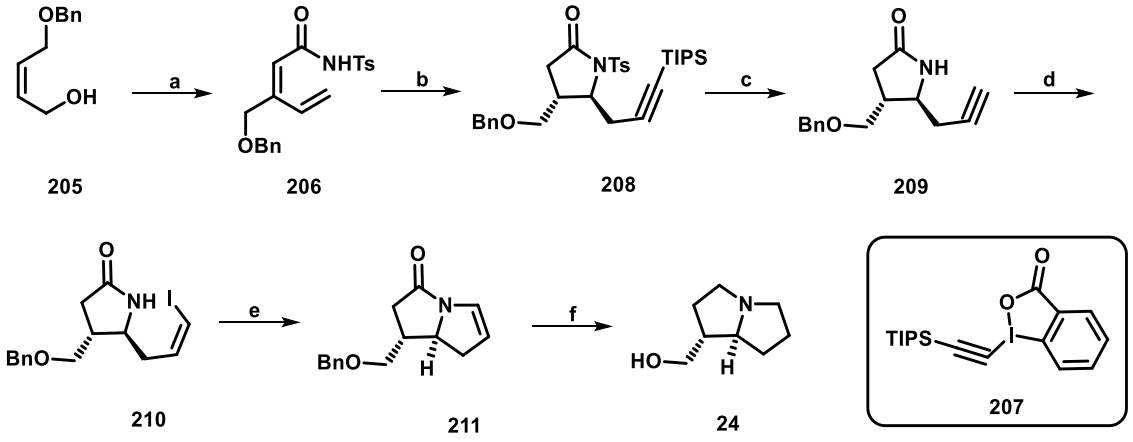


Scheme 41. *Reagents and conditions*: (a) 47% HBr in H_2O, toluene, reflux, 4 h, 92%; (b) i) oxalyl chloride, $(CH_3)_2SO$, NEt_3, DCM, -78 ^oC, 2 h; ii) $HC(OMe)_3$, *p*-TSA, MeOH, 0 ^oC 82%; (c) succiniamide, K_2CO_3, DMF, 60 ^oC, 3h, 99%; (d) $NaBH_4$, THF:MeOH (2:1), -15 ^oC, 6 h, 99%; (e) i) **15**. TfOH, acetone, 18 ^oC; ii) $NaBH_4$, MeOH, 0 ^oC, 79%; (f) $LiAlH_4$, THF, reflux, 2 h, 74%.

Next, the bromoacetal **199** on treatment with succinimide **200** in the presence of K_2CO_3 furnished the N-alkylated imide **201** which on reduction with $NaBH_4$ affored the hydroxy lactam **202**. The derivative **202** on cyclization with acetone in the presence of organocatalyst **203**, furnished the intermediate which upon reduction with $NaBH_4$ using MeOH yielded the fused bicycle compound **204**. Finally bicycle derivative **204** on treatment with $LiAlH_4$ yielded the target compound **24** in 6 steps with 52% overall yield (dr,7:1).

Waser, J. *et al*. (2011)[3c]

Waser and his team explored the synthesis of (+/-)-trachelanthamidine **24** using Palladium catalysed aminoalkynylation methodology as principal step as mentioned in Scheme 42. The synthesis of target **24** commenced from mono protected butene diol **205** which underwent Johnson-Claisen rearrangement to furnish the intermediate which upon subsequent hydrolysis and tosylation with *p*-tosylisocyanate furnished the amide **206** in appreciable yield.



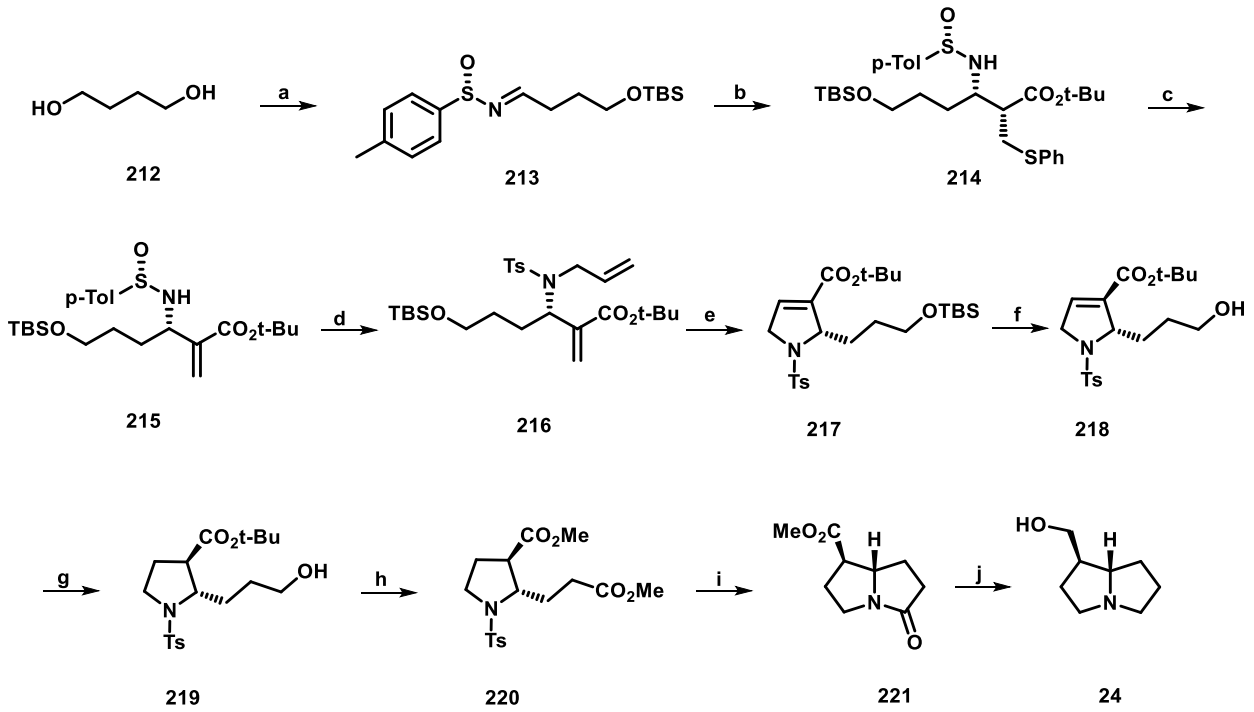
Scheme 42. *Reagents and conditions*: (a) i) $CH_3C(OEt)_3$, $EtCO_2H$, 100 ^oC to 160 ^oC; then KOH, MeOH, reflux, 80%; ii) *p*-TsNCO, Et_3N, THF, rt, 80%; (b) 5 mol% of $PdCl_2$, LiCl, TIPS-EBX (**19**), EtOH, rt, 72%; (dr,83:17); (c) i) Na/naphthalene, tetrahydrofuran, -78 ^oC, 77%; ii) *n*-Bu_4NF, tetrahydrofuran, 0 ^oC to rt, 98%; d) i) $InCl_3$, DIBALH; ii) Et_3B; iii) I_2, tetrahydrofuran, -50 ^oC,

95%; e) 40 mol% CuI, Cs_2CO_3, *N*,*N*'-dimethylethylenediamine, toluene, 85 ^oC, 73%; (f) i) H_2, Pd/C, CH_3OH, rt; ii) LAH, THF, reflux, 94%.

Next, aminoalkyaltion of amide derivative **206** was carried out using a combimation of $PdCl_2$ and LiCl, as a catalyst employing TIPS-EBX **207** to afford the derivative **208** in 72% yield with good diasteroselctivity (dr, 83:17). Further, the cleavage of tosyl and silyl protecting groups using TBAF and Na-naphthalide afforded the alkyne derivative **209** which transformed into iodo derivative **210** through a set of standard organic transfomations. The iodo compound **210** on treatment with CuI employing Cs_2CO_3 underwent cyclisation to produce the bicyclic derivative **211** in 73% yield. Compound **211** on Pd/C catalysed hydrogenation followed by amide group reduction using $LiAlH_4$ afforded the racemic (+/-)- trachelanthamidine **24** in 22% overall yield.

Kamimura, A. *et al*. (2010)[4d]

Akio Kamimura and his team disclosed the formal synthesis of (-)-trachelanthamidine **24** using Aza Baylis Hillman adducts and ring closing metathesis as key steps (Scheme 43). The synthetic route began with the preparation of chiral sulfinimine **213** from 1,4-butenediol **212** through a sequence of steps involving selective TBS protection, oxidation followed by treatment with (-)-*p*-Toluenesulfinamide as depicted in Scheme 43. The optically active sulfinimine **213** underwent Michael/imino-aldol Domino reaction to furnish a ester derivatives **214** in 85% yield (dr, 85:15). The compound **214** on treatment with *m*-CPBA resulted into sulfoxide intermediate which on refluxing in the presence of toluene yielded olefin derivative **215** in 76% yield. Next, compound **215** underwent oxidation using *m*-CPBA followed by N-allylation resulted into compound **216** in moderate yield. The compound **216** on reaction with ring-closing Grubbs metathesis afforded 2,5-dihydropyrrole **217** in 90% yield (ee > 94%). Further, CSA mediated deprotection of TBS ether of **217** yielded the compound **218** which on subsequent stereoselective hydrogenation utilizing Pd/C gave alcohol **219** in 88% yield (dr, 86:14). The alcohol derivative **219** on PDC catalysed oxidation afforded the acid derivative, which further on esterification yielded diester **220** in moderate yield. Finally, cleavage of tosyl group was carried out with Mg metal to afford an intermediate which on cyclisation followed by reduction[5] gave (-)-trachelanthamidine **24**.



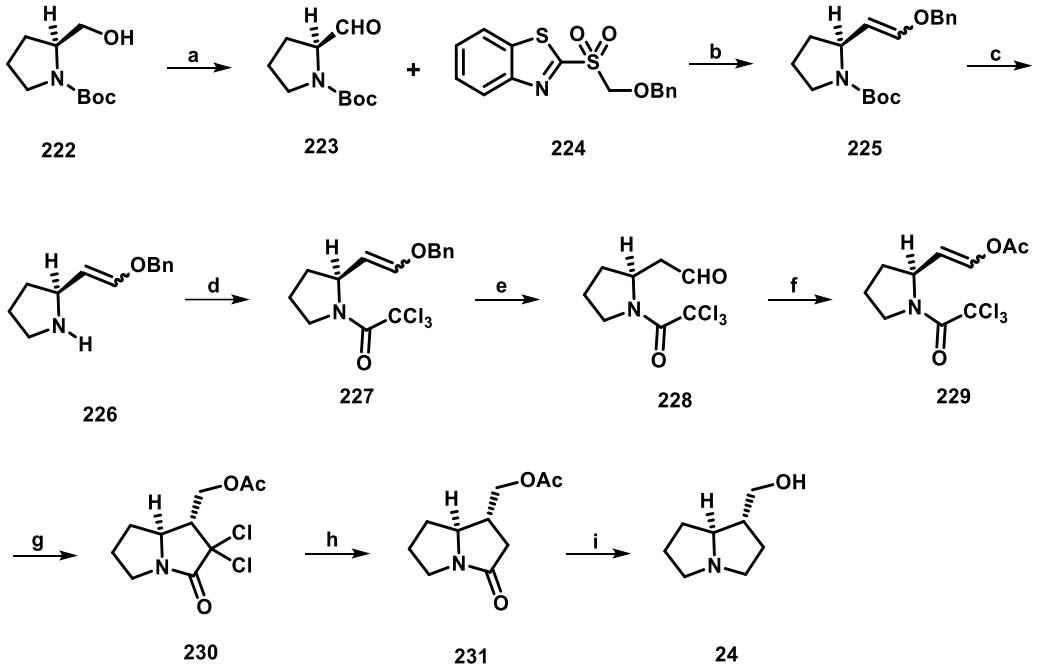
Scheme 43. (a) i) TBSCl, *t*-BuOK, CPME, 0 ^{o}C, 7 h, 83%; ii) oxalyl chloride, $(CH_3)_2SO$, Et_3N, DCM, -50 ^{o}C to rt, 2.5 h, 96%; iii) (-)-sulfinamide, $Ti(OEt)_4$, DCM, reflux, 24 h, 64%; (b) PhSMgBr, $C_2H_3CO_2tBu$, -50 ^{o}C, 37 h, 85% (*syn*/*anti* = 85:15); (c) i) *m*CPBA, DCM, 1 h; ii) toluene, 110 ^{o}C, 76% (after two steps); (d) i) *m*CPBA, CH_2Cl_2, 2.5 h; ii) allyl bromide, K_2CO_3, DMF, 27 h, 78% (94% ee); (e) Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, 15 h, 90%; (f) CSA, CH_2Cl_2:MeOH (1:1), 1 h, rt; (g) H_2, Pd/C, CH_3OH, rt, 48 h, 98% (over 3 steps); (h) i) PDC, DMF, rt, 24 h; ii) $SOCl_2$, MeOH, reflux, 12 h; 75%; (i) Mg, MeOH, rt-reflux, 6 h, 76%; (j) ref 5.

Ishibashi, H. *et al*. (2008)[3e]

Hiroyuki Ishibashi and his team reported the synthtesis of (-)-trachelanthamidine **24** employing single electron transfer (SET) methodology as key steps (Scheme 44). The synthesis pathway began with the chiral *N*-boc protected prolinol **222** which upon oxidation under Swern conditions afforded the intermediate aldehyde **223** which further on subsequent treatment with *α*-benzylsulfone **224** in the presence of LiHMDS afforded the olefin derivative **225.**

Next, TMSOTf mediated cleavage of Boc protecting group of **225** furnished the cyclic amine **226** and the obtained amine derivative **226** on subsequent *N*-trichloroacetylation gave the derivative

227 in 95% yield. Compound **227** upon acid hydrolysis yielded the aldehyde **228** which on treatment with acetic anhydride afforded the acetoxy alkene derivative **229** (*E*:*Z*,1;1). Next, compound **229** underwent cyclisation on heating with 1,4-dimethylpiperazine yielding desired product **230** in 52% yield. Dichlorine cleavage of **230** through catalytic hydrogenolysis followed by $LiAlH_4$ mediated reduction of acetoxy and carbonyl group of compound **231** furnished (-)-trachelanthamidine **24** in 86% yield.



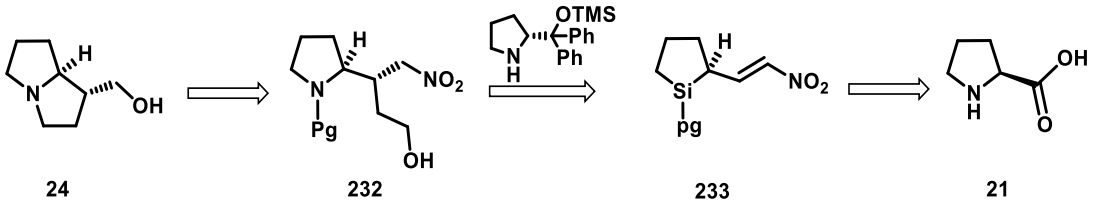
Scheme 44. (a) i) $(COCl)_2$, DMSO. NEt_3, DCM, -78 ^oC, 2 h; (b) LiHMDS, TBS, 0 ^oC, 61% ; (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 ^oC, 92%; (d) CCl_3COCl, Et_3N, CH_2Cl_2, 0 ^oC, 95%; (e) 1% HCl, THF, rt, 96%; (f) Ac_2O, KOAc, Et_3N, 120 ^oC, 59%; (g) 1,4-dimethylpiperazine, reflux, 52%; (h) H_2, Pd/C, NaOAc, ethanol, rt; (i) $LiAlH_4$, THF, reflux, 86%.

4.3 Present Work:

As our research programme is aimed at synthesizing medicinally important molecules. Herein, we made an attempt towards the shortest possible route for the synthesis of (-)-trachelanthamidine **24** from L-proline and employing Michael addition as pivotal step.

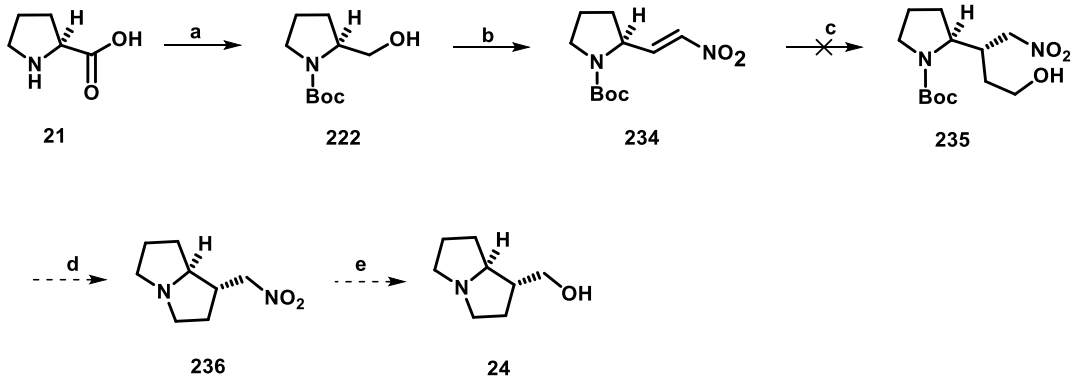
4.4 Results and Discussions:

Proposed synthetic route for the asymmetric synthesis of (-)-trachelanthamidine **24** is elucidated in Scheme 45. The target compound was envisioned to be obtained from the nitro-alcohol intermediate **232** *via* reduction of nitro group to alcohol followed by cyclization. The nitro-alcohol derivative **232** was found to be key precursor for the synthesis and could be synthesized from *α*, *β*-unsaturated nitroalkene **233** through *R*-TMS prolinol catalysed Michael addition reaction with acetaldehyde. The *α*, *β*-unsaturated nitroalkene derivative **233** in turned could be accomplished from L-proline **21** *via* reduction, Henry reaction followed by other standard organic transformations.



Scheme 45. Proposed biosynthetic approach for (-)-trachelanthamidine.

The synthesis of (-)-trachelanthamidine **24** started from commercially available proline **21** which on treatment with $(Boc)_2O$ furnished the *N*-Boc protected Proline[6] intermediate and its subsequent reduction in the presence of $LiAlH_4$ afforded the *N*-Boc Prolinol **222**. The alcohol derivative **222** under Swern oxidation conditions afforded the intermediate aldehyde which upon treatment with nitromethane followed by base induced *O*-mesylation and elimination furnished the nitro-olefin derivative **234**. Compound **234** displayed the C=C stretching of double bond at 1650 cm^{-1} in IR spectrum.

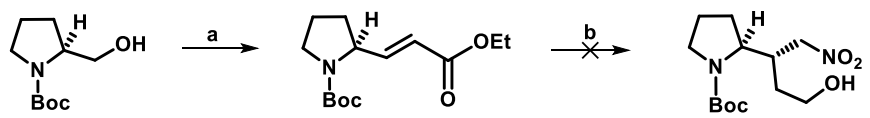


Scheme 46. (a) i) di-*tert*-butylcarbonate, NaOH, THF:H_2O (2:1) , 24 h, 96%; ii) $LiAlH_4$, THF, 0 ^oC - rt, 2 h, 96%; (b) i) $(COCl)_2$, $(CH_3)_2SO$, NEt_3, DCM, -78 ^oC, 2 h; ii) CH_3NO_2, *aq*. NaOH, CH_3OH, 0 ^oC to rt, 25 min; (iii) MsCl, NEt_3, DCM, 0 ^oC to rt, 1 h, 95% (over 3 steps); (c) i) CH_3CHO, (*R*)-diphenylprolinolsilyl ether, 1,4-dioxane, 4 ^oC to rt, 18 h; ii) $NaBH_4$, MeOH, 0 ^oC rt, 2 h.

The ^1H NMR spectrum of **234** gave signals of olefinic protons resonating at δ 7.13 (doublet, one proton) and at δ 6.99 (dd, one proton) with *J*=12.8 and 5.2 & 12.4 Hz, respectively indicating *trans*-olefin. Further, attempts were made to synthesize compound **235** by subjecting the nitroalkene **234** to asymmetric Michael addition[7] reaction with acetaldehyde using the (*R*)-diphenylprolinol silyl ether succeeded by $NaBH_4$ reduction. However, no desired product formation was seen under these conditions and starting material was restored.

Alternatively, to tackle this issue different route was proposed to synthesize compound **235**. To this direction, compound **222** was first converted into aldehyde intermediate under Swern oxidation conditions which on 2C-Wittig olefination with (ethoxycarbonylmethylene)-triphenylphosphorane in THF gave the *trans*-olefinic ester **237** in 92% yield (Scheme 47). The IR spectrum of **237** showed C=O stretching vibration at 1750 cm^{-1}. The ^1H NMR spectrum of **237** displayed signals corresponding to alkene protons at δ 6.83 (td, one proton) and at δ 5.82 (doublet, one proton) with *J* = 15.6 and 15.2 Hz, respectively specifying *trans*-alkene.

Further**,** olefinic ester **237**, on reduction with DIBAL-H, was converted into conjugated aldehyde intermediate at -78^oC and was exposed to asymmetric Michael addition[7] conditions with CH_3NO_2 employing (*R*)-diphenylprolinol silyl ether succeeded by reduction with $NaBH_4$ to synthesize the compound **235**. Again, this route was not successful. Therefore, it was assumed that the Boc protection may be acting as an obstacle in the completion of the reaction due to its bulky size.



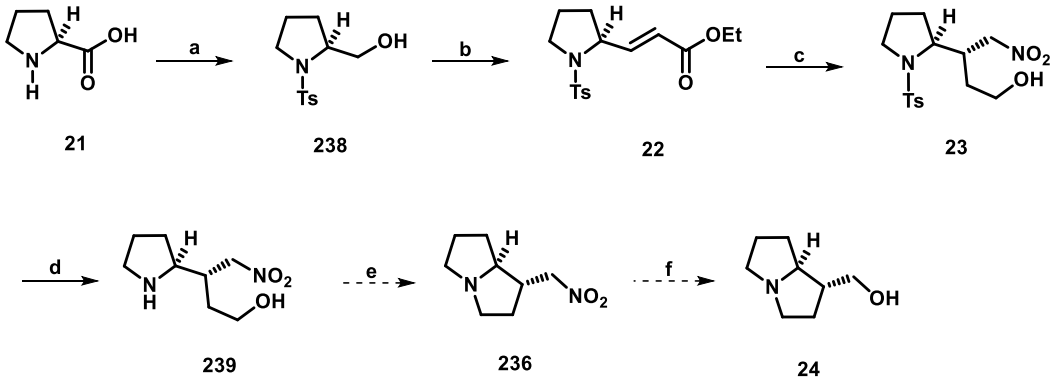
222 237 235

Scheme 47. (a) i) $(COCl)_2$, DMSO. NEt_3, DCM, -78 ^oC, 2 h; ii) $PPh_3CHCOOEt$, THF, rt, 10 h, 92% (over two steps); (b) i) $[(CH_3)_2CHCH_2]_2AlH$, DCM, -78 ^oC, 1 h; ii) (*R*)-diphenylprolinol silyl ether, CH_3NO_2, C_6H_5COOH, CH_3OH, 16 h, rt; iii) $NaBH_4$, MeOH, 0 ^oC, 1 h.

Next, we proposed to change the protecting group of proline and then decided to carry out the Michael addition reaction. In this regard, we protected the proline as its *N*-benzyl and *N*-tosyl derivative. No successful results were obtained in case of *N*-Benzyl protected proline. However, to our surprise *N*-tosyl proline derivative showed some promising results.

Further, the synthesis of **24** was commenced from commercially available L-proline **21** and was first treated with TsCl in the presence of sodium carbonate.[8] and the resultant N-tosyl proline on further reduction with $NaBH_4$ in the presence of BF_3. etherate[8] was successfully converted into N-tosyl prolinol alcohol derivative **238** in excellent yield. $[\alpha]_D^{20}$ -62.4 (c 1.00, $CHCl_3$) {Lit.[8] $[\alpha]_D^{20}$ -62.7 (c 1.00, $CHCl_3$)} (Scheme 48). The hydroxyl derivative **238** on oxidation with Dess Martin Periodinane (DMP) afforded the intermediate aldehyde which on subsequent treatment with (ethoxycarbonylmethylene)-triphenylphosphorane (two carbon Wittig reagent) furnished the ester **22**. In the ^1H NMR the olefinic protons were found resonating at δ 6.83 (dd, one protons) and at δ 6.08 (dd, one protons) with mutual coupling constant (*J*) of 15.6 Hz indicating *trans*- geometry.

Next, we proceed further to carry out Michael addition[7] of acetaldehyde on *N*-tosyl ester substrate **22**. For this, the *N*-tosyl ester derivative **22**, was transformed into an aldehyde intermediate using DIBAL and then the obtained aldehyde was exposed to asymmetric Michael addition with nitromethane employing (*R*)-diphenylprolinol silyl ether and its subsequent reduction with $NaBH_4$ furnished the compound **23**.



The signals corresponding to olefin vanished in the ^{1}H NMR of compound **23** confirmed the occurrence of Michael addition on ester substrate **22** and rest of the protons were found resonating at their respective positions.

Scheme 48. (a) i) TsCl, Na_2CO_3, H_2O, rt, 48 h, 99% ; ii) $NaBH_4/BF_3.Et_2O$, THF, rt, 17 h, 89%; (b) i) DMP, DCM, 0 ^{o}C, 2 h; ii) $PPh_3CHCOOEt$, THF, rt, 10 h, 92% (over two steps); (c)) i) DIBAL-H, CH_2Cl_2, -78 ^{o}C, 1 h; ii) (*R*)-diphenylprolinol silyl ether, CH_3NO_2, benzoic acid, MeOH, 16 h, rt; iii) $NaBH_4$, CH_3OH, 0 ^{o}C, 1 h, 66%; (d) Na, naphthalide, THF, -78 ^{o}C; (e) MsCl, NEt_3, DCM; (f) i) *t*-BuOK, $KMnO_4$, 0 ^{o}C; ii) $NaBH_4$, MeOH.

Therefore, here we concluded that protecting group was playing vital role in the feasibility of Micheal addition. Our next challenge was to synthesize the compound **239.** On proceeding in this direction, compound **239** was treated with various tosyl deprotecting agents and then it was successfully cleaved with Na, naphthalide solution prepared in dry THF[9] and it led to formation of complex inseparable reaction mixture.

4.5 Conclusion

In conclusion, we made an attempt towards the shortest possible route for the synthesis of (-)-trachelanthamidine **24** from L-proline and employing Michael addition as key step. We have optimized the reaction conditions up to the intermediate **23** and the work is currently ongoing and will be reported as soon as possible.

4.6 Experimental section

All experiments were performed under Nitrogen, with moisture free, freshly extracted solvents through distillation unless otherwise indicated. All the reagents or chemicals were put in reaction either via syringe or cannula. Each distillation was also performed under unreactive conditions. Every reaction was performed at their respective temperatures as narrated within their respective schemes. Solvent evaporation was performed utilising a Heidolph rotary evaporator at reduced pressure and at less than 40 °C temperature.

Chromatography

Every reaction performed was examined through Thin Layer Chromatography (TLC) executed using commercially available silica gel plates 60 F_{254} using UV light, then were stained in ninhydrin or in ethanolic solution of anisaldehyde or in aqueous KMnO4 as development reagents follow up by concise heating using a heating gun. For column chromatography, silica gel of mesh size 60-120 and 100-200 was employed and different compositions of ethyl acetate/hexane and methanol/ dichloromethane were used as organic eluent

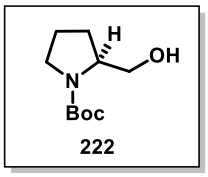
Reagents and solvents

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

Spectroscopic Measurements

JEOL ECS spectrometer was employed for recording the ^{1}H NMR and ^{13}C NMR respectively. Tetramethylsilane (TMS) utilized as reference. The measuring unit for chemical shifts (δ) is parts per million (ppm). J values (Coupling constants) are listed in Hertz (Hz). Electron spray ionization (ESI) were used for recording mass spectra and mass data were presented as m/z. The IR spectra were captured on an Agilent resolution Pro 600 FT-IR spectrometer with a beam-condensing ATR attachment, and the peaks were measured in centimeter inverse Yields mentioned referred to isolated combined amount after chromatography.

***tert*-Butyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate, 222**



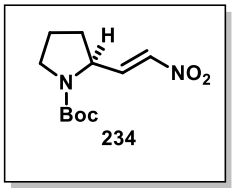
222

L-proline **21** was converted into N-Boc proline synthesized in a similar way to the reported procedure.[6] Briefly, to a agitated solution of L-Proline **21** (1.00 g, 8.69 mmol) taken in THF/H_2O (20 ml, 2:1) was added 10% aq NaOH (4ml) and di-*tert*-butylcarbonate (2.78 g, 12.78 mmol) sequentially. The resultant solution was agitated at rt for 24 h. After completion the solvent was removed in vacuo. The pH of the remaining solution was adjusted to the value of 2 with the dropwise addition of *aq.* $KHSO_4$ (10%). The obtained solution was extracted with EtOAc (3 x 30 mL) and the collected organic portion was combined and rinsed with water and brine, and anhydrous Na_2SO_4 was added to absorb the

moisture and concentrated under vacuum to furnish N-Boc Proline (1.80 g, 96%) as a syrup, which was used directly without purification for the future step.

To a stirred solution of above N-Boc proline (1.80 g, 8.36 mmol) taken in dry THF at 0 ^{o}C was added $LiAlH_4$ (635 mg, 16.73 mmol). The stirring was continued 2 h and the reaction was quenched using 10% *aq.* NaOH solution. The product was extracted with ethyl acetate (3 x 50 mL). The combined extracts were rinsed with brine (60 mL) and dried over anhydrous Na_2SO_4. The organic phase was concentrated in *vacuo*, and crude product was purified by silica gel column chromatography to afford the desired product **222** (1.60 g, 95 % yield). $[\alpha]_D^{21}$ = -48.3 (c 1.3, $CHCl_3$) {lit.[10] $[\alpha]_D^{21}$ = -48.0 (c 1.3, $CHCl_3$)}; IR (neat) 3305, 2976, 1832, 1735, 1143, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.86 (1H, brs), 3.98 (d, *J* = 7.2 Hz, 1H), 3.55-3.65 (m, 2H), 3.48-3.42 (m, 1H), 3.33-3.27 (m, 1H), 2.05-1.98 (m, 1H), 1.86-1.77 (m, 3H), 1.47 (s, 9 H).

***tert*-Butyl (*S*,*E*)-2-(2-nitrovinyl)pyrrolidine-1-carboxylate, 234**



234

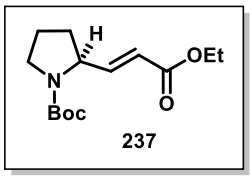
To a solution of oxalyl chloride (0.65 mL, 7.45 mmol) in dry DCM (10 mL) taken at -78 ^{o}C was added drop by drop a solution of DMSO (1.09 mL, 15.42 mmol) in CH_2Cl_2 (10 mL). The organic suspension was agitated for 30 min at the same degrees, and a solution of the compound **222** (1.0 g, 4.97 mmol) in dichloromethane (10 mL) was added steadily, and stirred for additional 30 min. at -78 ^{o}C. After a solution of Et_3N (3.13 mL, 22.36 mmol) in DCM (10 mL) was added at -78 ^{o}C, the stirring was carried out for additional 1 h at the rt. The mixture was partitioned between water and DCM and the organic portion was extracted with DCM (3 x 10 mL). The collected organic layers were combined and done waterless over anhydrous Na_2SO_4 and excess solvent was evaporated *in vacuo* to give the crude aldehyde, which was used directly for the next step without purifying.

To the above synthesized crude aldehyde taken in CH_3OH (10 mL) at 0 ^{o}C was added nitro-methane (0.3 mL, 5.46 mmol) followed by pouring of aqueous solution of NaOH (238 mg, 1.2 mmol). The stirring was carried on for next 25 minutes and after completion the reaction was quenched with H_2O. The cude was extracted with EtOAc (2 x 15 mL), the collected organic portion was washed with brine, dried over anhydrous Na_2SO_4**,** and concentrated under vacuum. The crude nitro-alcohol was further used as it is in the next reaction.

To a stirred solution of above nitro-alcohol taken in DCM (10 mL) at 0 ^{o}C was added sequentially MsCl (0.48 mL, 5.96 mmol) and Et_3N (1.5 mL, 9.88 mmol). The resulting solution was stirred at

ambient temperature for 1 hour and quenched with water (10 mL) and extracted with DCM (3 x 15 mL). The organic fractions were combined and dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The crude was purified by silica gel column chromatography (EtOAc/Hexane 1:9.v/v) to afford N-tosyl nitro alkene **234** (1.1 g, 95%) as colourless oil. [R_f = 0.75, EtOAc/hexane 1 : 9 v/v]; IR (CH_2Cl_2) *v*: 3011, 2880, 1650, 1528, 1340 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.139 (d, *J* =12.8 Hz, 1H), 6.98 (dd, *J* = 5.2. 12.4 Hz, 1H), 4.66-4.40 (m,1H), 3.55-3.38 (m, 2H), 2.25-2.09 (m, 2H), 1.96-1.85 (m, 2H), 1.46 (s, 9H).

***tert*-Butyl (*S*,*E*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)pyrrolidine-1-carboxylate, 237**

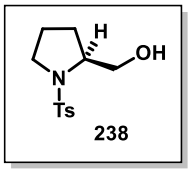


237

The aldehyde obtained from alcohol **222** by following the same procedure was taken further to synthesize the **237** via following procedure:

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (2.60 g, 7.455 mmol) in dry THF (10 mL) was added drop wise a solution of aldehyde obtained from alcohol **222** in THF (5 mL) and stirred for 10 h at ambient temperature. The reaction miscellany was then concentrated *in vacuo* and purified by silica gel column chromatography using (EtOAc/hexane 1:9 v/v) as eluent to furnish the *trans*-olefin **237** (1.20 g, 92%) as a thick liquid. IR (CH_2Cl_2) *v*: 3021, 2880, 1750, 1650, 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.83 (td, *J* = 15.6, 4.8 Hz, 1H), 5.82 (d, *J* = 15.2 Hz, 1H), 4.50-4.36 (m, 1H), 4.20-4.09 (m, 2H), 3.48-3.26 (m, 2H), 2.13-2.02 (m, 1H), 1.97-1.74 (m, 3H), 1.45 (s, 9H), 1.28 (t, *J* = 6.4 Hz, 3H).

(*S*)-(1-Tosylpyrrolidin-2-yl)methanol, 238



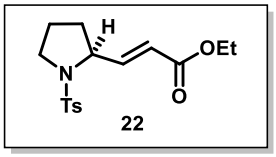
238

To a solution of L-proline **21** (1.0 g, 8.69 mmol) in water (10 mL) were added Na_2CO_3 (184 mg, 17.38 mmol) and 4-toluenesulfonyl chloride (TsCl) (1.98 g, 10.43 mmol) at 0 ^oC. The resultant mixture was agitated at rt for 48 h. After completion, the pH of the reaction mixture was attained at the value of 2 using conc. HC1. The product was filtered and obtained solid washed with pH 2 buffer and dried in a vacuum oven to obtained N-Ts proline (2.30 g, 99%) which was used in next reaction without purification.

Sodium borohydride (274 mg, 7.43 mmol) was taken in 15 mL of dry THF and the mixture was cooled to 10 °C. To the above resultant mixture borontrifluoride etherate (3.4 mL, 22.76, 50 %)

was added dropwise over a period of 1 h. Then a solution of N-(4-tolylsulfonyl)- L-proline(1 g, 3.71mmol) in THF (10 mL)obtained in above reaction was added carefully and the mixture was allowed to stir for 16 h. After completion, the reaction was ended up with methanol, a 10% aqueous hydrochloric acid solution was added, and the mixture was steadily warmed to 60 °C for 1 h. The reaction mixture's pH was adjusted to neutral using 50% aqueous NaOH solution, and the volatiles were removed using rotary evaporator. The crude residue was purified by silica gel chromatography to furnish tosyl derivative **238** (850 mg, 89%) a white solid. $[\alpha]_D^{20}$ -62.4 (c 1.00, $CHCl_3$) {Lit.[8] $[\alpha]_D^{20}$ -62.7 (c 1.00, $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$) δ:7.72 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 4.77 (dd, J = 5.2, 12.8 Hz, 1H), 4.42 (dd, J = 8.4, 12.8 Hz, 1H), 3.42-3.36 (m, 1H), 3.32-3.26 (m, 1H), 3.06-2.98 (m, 1H), 2.44 (s, 3H), 1.99-1.57 (m, 5H).

Ethyl (*S*,*E*)-3-(1-tosylpyrrolidin-2-yl)acrylate, 22



22

N-Tosyl derivative **238** (600 mg, 2.35 mmol) was dissolved in anhydrous dichloromethane (20 mL) at 0 ^{o}C. To the above solution DMP salt (1.14 g, 2.70 mmol) was added and mixture was agitated for 30 min. After the completion of the reaction, as monitored using thin layer chromatography, reaction was quenched utilizing saturated solution of sodiumthiosulphate (5mL) and sodiumbiocarbonate (5 mL). Further, the resulting suspension was transferred to a separatory funnel, layers were separated, and the water layer was re-extracted with DCM (2 x 15 mL). The organic portions were combined and rinsed with brine (20 mL), and moisture was absorbed over anhydrous Na_2SO_4. The intermediate aldehyde obtained was used as it is for the succeeding step.

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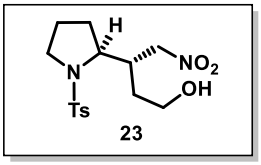
The aldehyde obtained above was dissolved in dry THF (15mL) and 2-carbon Wittig Ylide (984 mg, 2.82 mmol) was added. The resultant organic mixture was stirred for 10 hours and after completion the reaction mixture was distilled by rotary evaporator and purified by silica gel column chromatography (EtOAc/hexane 1:9 v/v) to furnish the *trans*-olefin ester **22** (725 g, 95%) as a white solid. IR (DCM) v: 3069, 2962, 1735, 1650, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.715 (d, J = 8.4 Hz, 2H), 7.732 (d, J =8.0 Hz, 2H), 6.835 (dd, J = 5.6, 15.6 Hz, 1H), 6.08 (dd, J = 1.2, 15.2 Hz, 1 H), 4.32-4.28 (m, 1H), 4.191 (q, J = 7.6 Hz, 2 H), 3.51-3.45 (m, 1 H), 3.26-3.20 (m, 1H), 2.439 (s, 3H), 1.87-1.67 (m, 4 H), 1.30 (td, J = 1.6, 7.2 Hz, 3 H).

(*S*)-4-Nitro-3-((*S*)-1-tosylpyrrolidin-2-yl)butan-1-ol, 23



23

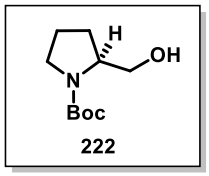
To a CH_2Cl_2 (10 mL) solution of N-tosyl ester **22** (500 mg, 1.54 mmol) was added DIBAL-H (1.32 mL, 2.32 mmol, 1.75 M in toluene) at -78 ^oC and agitated for 1 h at the -78 ^oC. The reacting suspension was quenched with saturated aqueous solution of sodium potassium tartrate and stirred for additional 30 min. The organic layer was parted and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The organic fractions were combined and moisture was removed over anhydrous Na_2SO_4 and concentrated *in vacuo* to give intermediate *α,β*-unsaturated aldehyde as a yellow liquid, which was used as such for the following step without further purifcation.

To a CH_3OH (10 mL) solution of above aldehyde was added nitromethane (0.2 mL, 4.62 mmol), (*R*)-diphenyltrimethylsiloxymethylpyrrolidine (50 mg, 0.154 mmol) and benzoic acid (18 mg, 0.154 mmol) at rt. After stirring the mixture for 16 h, organic suspension was then cooled to 0 °C, $NaBH_4$ (113 mg, 3.08 mmol) was added and strirred for additional 1 hour. H_2O was added to quench the reaction. The organic solution was extracted with EtOAc (3 x 30 mL), moisture was absorbed over Na_2SO_4 and distilled in *vacuo*. The crude product was purified by silica gel column chromatography using (EtOAc/hexane 1.5:8.5 v/v) as eluent furnished the nitro-alcohol **23** (350 mg, 66%) as pale yellow liquid. IR (CH_2Cl_2) *v*: 3404, 3069, 3017, 2962, 2868, 1586, 1320, 1797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.718 (d, *J* = 6.8 Hz, 2H), 7.325 (d, *J* = 6.0 Hz, 2H), 4.755 (dd, *J* = 4.0, 10.0 Hz, 1H), 4.41 (dd, *J* = 6.0, 10.4 Hz, 1 H), 3.89-3.86 (m, 1 H), 3.775 (td, *J* = 1.6, 4.8 Hz, 2 H), 3.41-3.36 (m, 1H), 3.31-3.36 (m, 1 H), 2.89-3.05 (m, 1 H), 2.43 (s, 3H), 1.81-1.56 (m, 6 H), 1.343- 1.348 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.9, 134.1, 129.9, 127.7, 76.3,61.1, 60.5, 50.1, 39.2, 31.7, 28.2, 24.4, 21.5.

4.6 Spectra

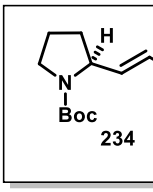
1. ^1H spectrum for **222**
2. ^1H spectrum for **234**
3. ^1H spectrum for **237**
4. ^1H spectrum for **238**
5. ^1H spectrum for **22**
6. ^1H spectrum for **23**
7. ^{13}C NMR spectrum for **23**

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



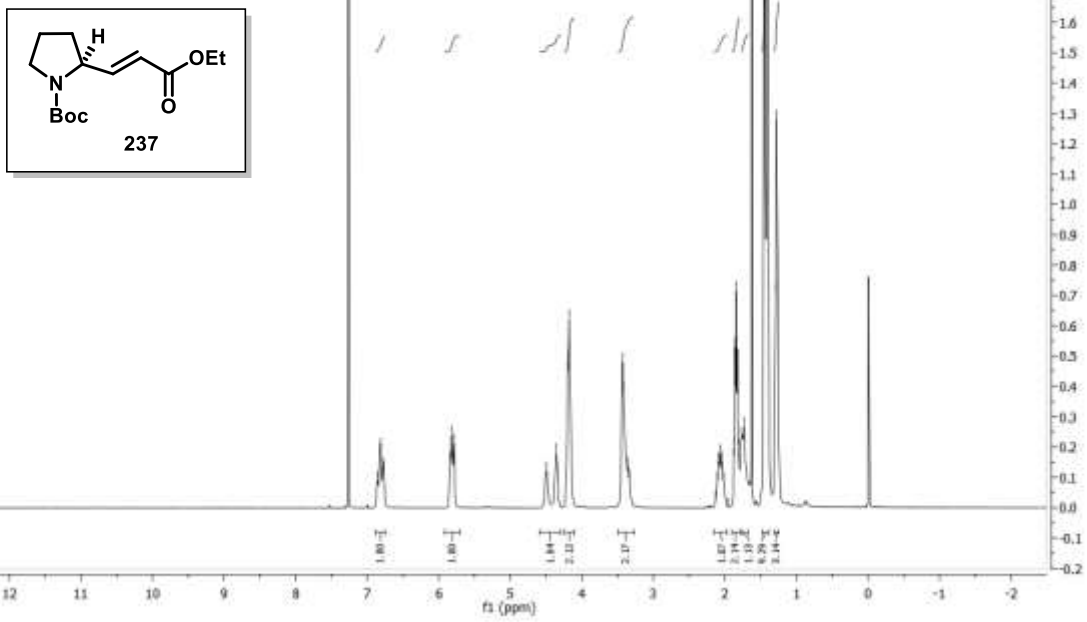
222

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

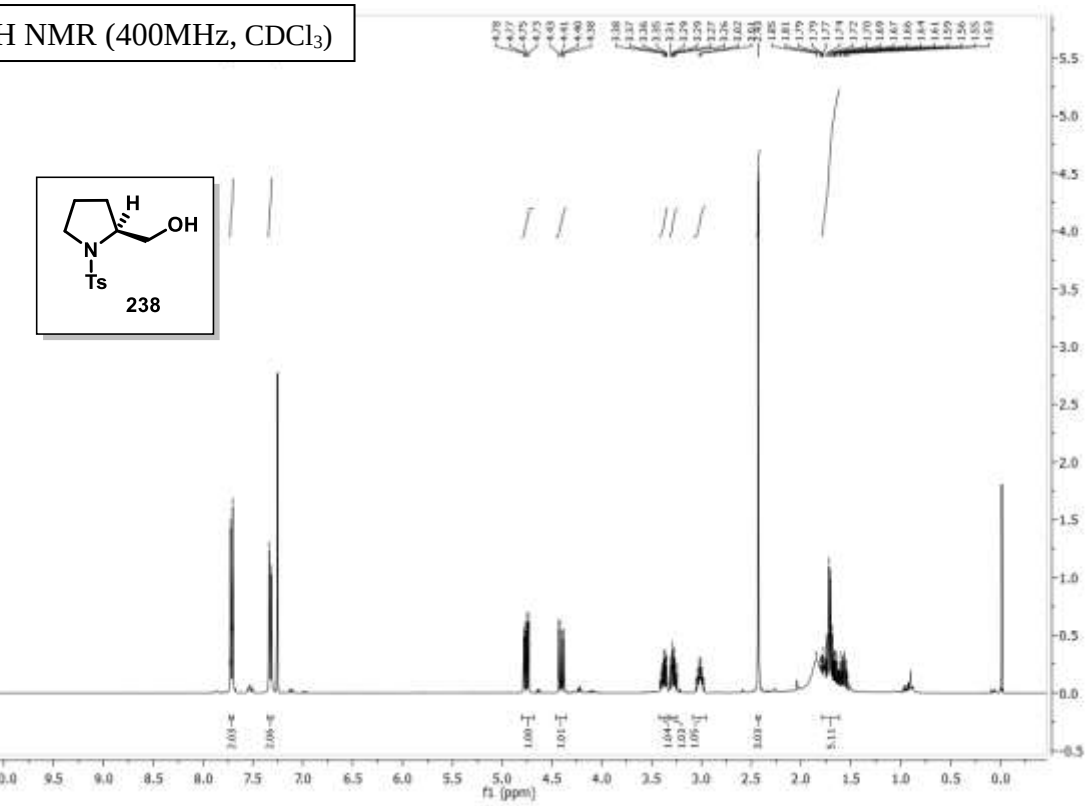


234

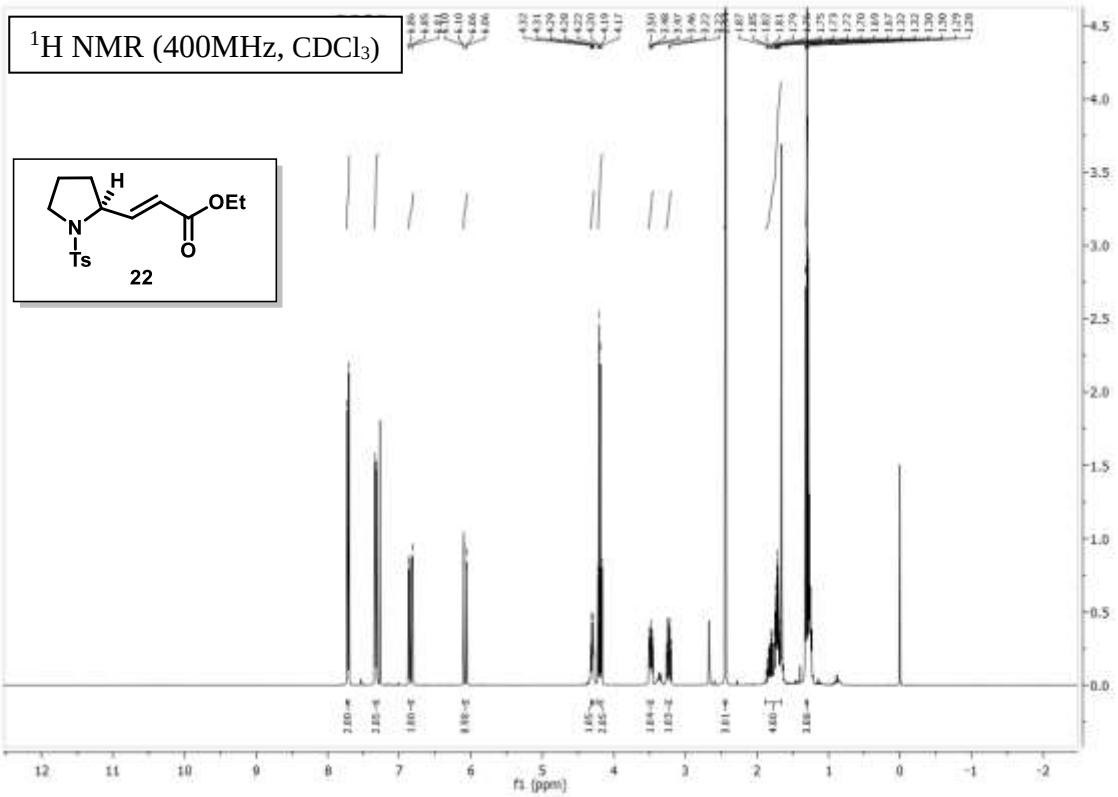
^{1}H NMR (400MHz, $CDCl_3$)



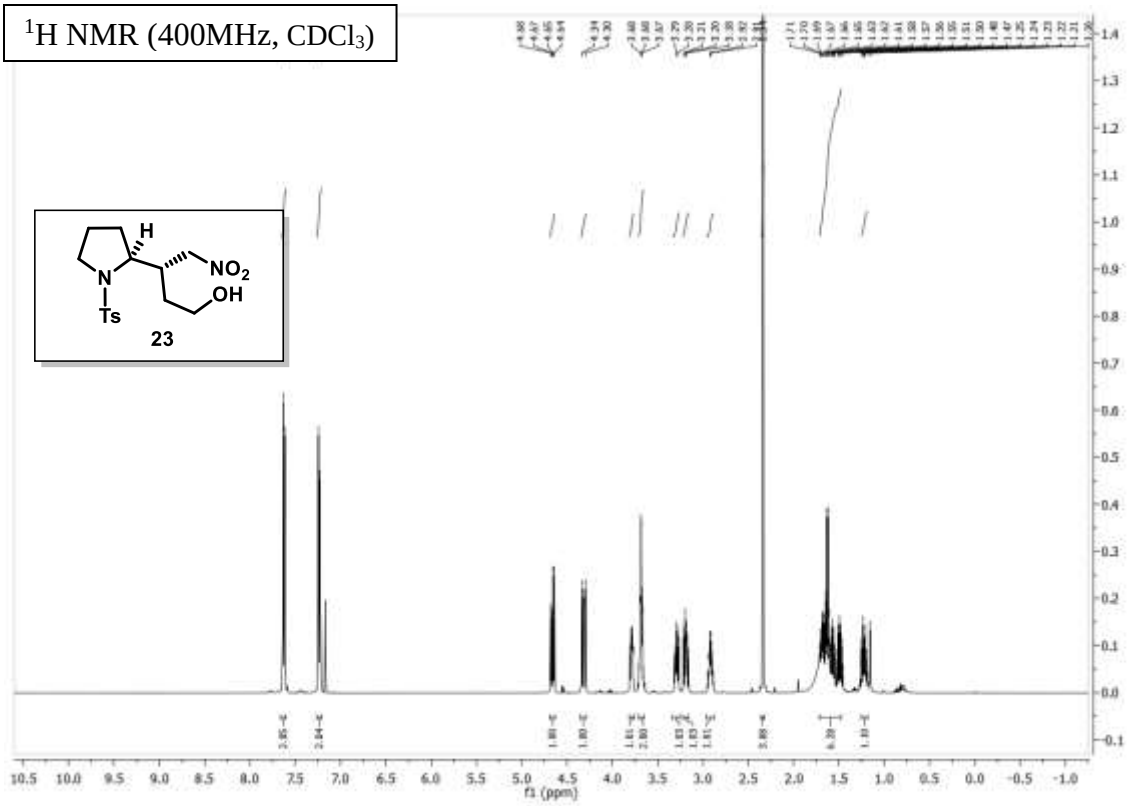
^{1}H NMR (400MHz, $CDCl_3$)



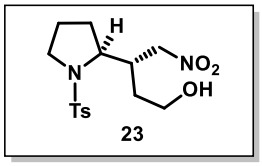
^{1}H NMR (400MHz, $CDCl_3$)



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



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



23

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CHAPTER 5

Conclusions and future scope.

5.1 Conclusions

In conclusion, we have developed the total synthesis of *epi*-muscarine iodide salt **5**, synthesis of (+)-nephrosteranic acid **20** and also made an attempt to synthesize (-)-trachelanthamidine **24.** Herein, we have developed a short and efficient enantioselective general approach for the synthesis of muscarine alkaloid and its application to the asymmetric synthesis of *epi*-muscarine iodide salt from readily available (*R*)-PMB glycidyl ether as starting material and employing Sharpless AD, intramolecular S_N2 cyclization and regioselective epoxide ring opening as key steps. The overall yield for the *epi*-muscarine iodide salt **5** was 52%. The synthetic route presented has further potential for the stereochemical variations in all the positions of the ring and extension to other analogues. Next, we have also developed an efficient enantioselective approach for the synthesis of multifunctionalized γ-butyrolactone paraconic acids and its application to the synthesis of (+)-nephrosteranic acid **20** using accessible PMB (*R*)-glycidyl ether as starting material. Pivotal reaction sequence comprises copper-catalyzed (CuI) regioselective ring opening with the Grignard reagent, Swern oxidation, Wittig olefination, asymmetric Michael addition reaction catalyzed by (*R*)-diphenylprolinol silyl ether, Nef oxidation reaction and stereoselective *α*-methylation. The overall yield for the (+)-nephrosteranic acid **20** was 50%. Moreover, synthetic route presented has further potential for the stereochemical variations in all the positions of the ring and extension to other analogues. Also, an attempt towards the shortest possible route for the synthesis of (-)-trachelanthamidine **24** was made from L-proline and employing 2C-Wittig olefination and Michael addition reaction as key steps. The merits of these syntheses are high regio- and enantioselectivity with high yielding reaction steps. All the noval compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, %ee by chiral HPLC and $[\alpha]_D$ ^{25}.

5.2. Future scope of the work

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

1. The synthetic route described in chapter 2, has further potential for the stereochemical variations in all the positions of the ring and extension to other analogues of muscarine alkaloids with interesting pharmacological activities. The *R*/*S* configurations to all chiral

centers of muscarine enantiomers could be simply achieved by either changing chiral ligands $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ in Sharpless AD reaction step or alternatively with changing the Z/E configuration of olefin intermediate followed by Sharpless AD.

2. The synthetic approach described in chapter 3, has potential for syntheses of the desired stereochemistry of paraconic acids by simply altering the (*R*)- and (*S*)-configuration of glycidyl ether and/or by using catalyst (*R*)- or (*S*)-diphenylprolinol silyl ether during Michael addition reaction. Thus, in principle, C3, C4 and C5 chiral centres in paraconic acids could be easily manipulated and accessed by this approach.

3. The synthetic strategy explained in chapter 4 has potential for the construction of (-) trachelanthamidine and its isomers. We have successfully implemented the organocalatysed Michael addition reaction for the synthesis of chiral key fragments. Work is still in progress to complete synthesis of the target molecules along with its sterochemical analogues through same or alternative pathway.

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Enantioselective total syntheses of (−)-clavaminol A and deacetyl (+)-clavaminol H

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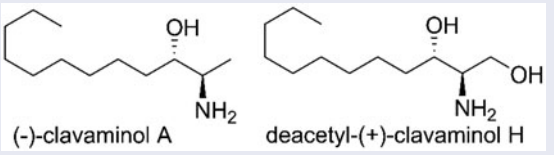
ABSTRACT

An efficient enantioselective approach to the syntheses of (−)-clavaminol A and deacetyl (+)-clavaminol H is presented, starting from *n*-decanol. The synthesis features Sharpless asymmetric dihydroxylation (AD), regioselective epoxide formation/opening and α-tosylation as key steps.

GRAPHICAL ABSTRACT



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KEYWORDS
2-amino-3-alkanols; clavaminols; cytotoxic; Sharpless AD; regioselective

Introduction

Long chain *anti*-2-amino-3-alkanols sphingoid bases **1**–**7** are important functional motifs possess intriguing biological activities and are important building blocks to synthesize a variety of biologically active natural products and medicinal compounds.[1] Architecturally, these molecules are correlated to the sphingosine derivatives, well known as central core unit of sphingolipids, which are important components of the cell membranes lipid portion in living organisms. Among these sphingoids, clavaminols A–N were isolated from marine Mediterranean ascidian *Clavelina phlegraea*[2] and display cytotoxic activities against various cancer cell lines, namely AGS (gastric carcinoma), A549 (lung carcinoma) and T47D (breast carcinoma), by activation of apoptosis. Among clavaminols A–N, (−)-clavaminol A **1** was found to be the most active member.[3] Deacetyl (+)-clavaminol H **3** was found to be active against AGS-gastric carcinoma, although (+)-clavaminol H **4** showed no substantial activity (Figure 1).

Fascinated by the biological activities and unique structural features of *anti*-2-amino-3-alkanols, hitherto, various asymmetric syntheses for clavaminols have been reported.[4]

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Supplemental data for this article can be accessed on the publisher's website.

Organic & Supramolecular Chemistry

A Short and Efficient Enantioselective Synthesis of (+)-(2*S*,3*S*,5*S*)-*epi*-Muscarine

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

A short, efficient and novel enantioselective general approach for the synthesis of muscarine alkaloid and its application to the asymmetric synthesis of *epi*-muscarine from readily available (*R*)-PMB glycidyl ether as starting material is described. Key transformations include Sharpless asymmetric dihydroxylation (AD), regioselective epoxide ring opening and intramolecular S_N2 cyclization.

Bioactive natural products containing multifunctionalized tetrahydrofuran moiety are found abundantly in nature.[1] The venomous alkaloids (+)-(2*S*,3*R*,5*S*)-muscarine **1 a**, (+)-(2*S*,3*S*,5*S*)-*epi*-muscarine **1 b**, (+)-(2*S*,3*S*,5*R*)-*epiallo* muscarine **1 c** and (-)-(2*S*,3*R*,5*R*)-*allo*-muscarine **1 d** were isolated from numerous species of mushrooms, e.g. *Amanita muscaria* (fly agaric) and certain species of *Clitocybes* and *Inocybes* (Figure 1).[2] Muscarine acts as a selective agonist of the acetylcholine receptor (muscarinic acetylcholine receptors) on smooth muscles of the eye exocrine glands, gastrointestinal tract, heart and have a wide range of other therapeutic properties.[3] More recently, pharmacological studies with selective antagonists confirmed distinct subtypes of muscarinic receptors.[4] Further, muscarinic field studies developed new interest after the discovery of relationship between cholinergenic deficiency in hippocampal areas and neurodegenerative diseases, and the pathology of Alzheimer.[5] Intrigued by the unique structural features and biological activities of tri-substituted tetrahydropyran, hitherto, numerous syntheses of muscarine and its enantiomers **1 a**–**d** are reported in literature.[6,7] As part of our research program aimed at developing the asymmetric synthesis of bioactive natural molecules,[8] we became attentive in developing a general route for muscarine and it's all enantiomers **1 a**–**d**. Herein, we are reporting a new short, efficient and novel general approach for the muscarine alkaloids and its application to the enantioselective synthesis of (+)-(2*S*,3*S*,5*S*)-*epi*-muscarine **1 b** employing Sharpless AD, regioselective epoxide ring opening and intramolecular S_N2 cyclization as key steps.

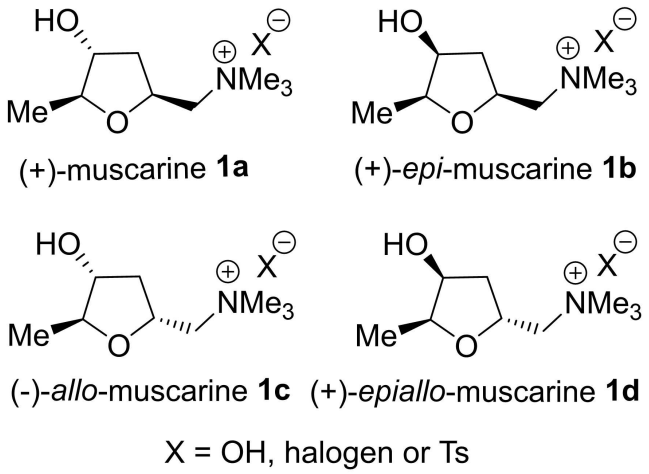
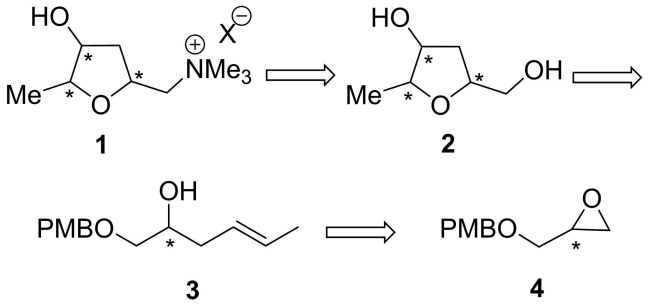


Figure 1. Structure of muscarine and its stereoisomers.

We envisioned our synthetic route for the muscarine including *epi*-muscarine **1 b** *via* general retrosynthetic approach as displayed in Scheme 1. We envisioned that the 2,5-disubstituted-4-hydroxy tetrahydrofuran **2** was a key intermediate compound from which muscarine and *epi*-muscarine **1 b** could be prepared *via* regioselective iodination of primary hydroxyl group followed by nucleophilic substitution reaction with trimethylamine. The THF derivative **2** could be derived from the alkene derivative **3** by tosylation of free hydroxy group followed by asymmetric dihydroxylation and treatment with base. The alkene **2** in turn could be accessed from enantiomerically pure PMB protected glycidol **4** using propy-



Scheme 1. Retrosynthetic general approach for muscarine alkaloids.

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An efficient enantioselective approach to multifunctionalized γ-butyrolactone: concise synthesis of (+)-nephrosteranic acid†

Anju Gehlawat,[a] Ranjana Prakash[a] and Satyendra Kumar Pandey *[ab]

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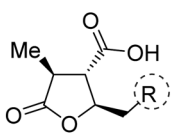
A short, efficient and novel approach for multifunctionalized γ-butyrolactone paraconic acids and its application to the total synthesis of (+)-nephrosteranic acid from readily available PMB (*R*)-glycidyl ether as a starting material are described. Key transformations include asymmetric Michael addition catalyzed by chiral diphenylprolinol silyl ether and stereoselective α-methylation.

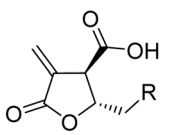
Bioactive natural products containing a multifunctionalized γ-butyrolactone moiety are found abundantly in nature.[1] The paraconic acids (**1–10**) containing multifunctionalized γ-butyrolactone were isolated from various species of lichens, fungi, moss and cultures of *Penicillium* sp.[2] These acids possess interesting biological activities such as antitumor, antibacterial, antibiotic, antifungal/antiviral and growth regulatory properties.[3] The whiskey lactone **11** and cognac lactone **12** have great commercial interest because they are potential key components in the flavor of aged alcoholic beverages.[4] Architecturally, the paraconic acid family comprises a variable length alkyl chain at the C5 position, a C4 carboxyl group and methyl or methylene substituents at the C3 position, which play an important role in the biological activities of the paraconic acids (Fig. 1).

Intrigued by the unique structural features and biological activities of paraconic acids, hitherto, several total[5] and formal[6] synthesis of paraconic acids such as (+)-nephrosteranic acid are documented in literature. More recently, Appayee and co-workers disclosed an elegant approach for the stereodivergent synthesis of chiral paraconic acids *via* dynamic kinetic resolution of 3-acylsuccinimides.[7] As part of our research program aimed at developing the asymmetric synthesis of bioactive natural molecules,[8] we became attentive in developing a flexible and general approach for the synthesis of multifunctionalised γ-butyrolactone paraconic acids. Herein, we are reporting a short, efficient and novel general approach for the synthesis of paraconic acids and its application to the enantioselective synthesis of (+)-nephrosteranic acid **1** using organocatalyzed Michael addition reaction as key step.

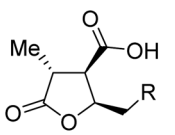
Our general retrosynthetic route for asymmetric synthesis of γ-butyrolactone based paraconic acids and its application to enantioselective synthesis of (+)-nephrosteranic acid **1** was envisaged *via* the retrosynthetic approach as displayed Scheme 1. We envisioned that the γ-butyrolactone **13** could be used as a key intermediate from which paraconic acids **1–10** including



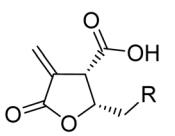
(+)-nephrosteranic acid **1**, R = *n*-$C_{10}H_{21}$
(+)-rocellaric acid **2**, R = *n*-$C_{12}H_{25}$



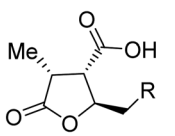
(-)-methylenolactocin **3** R = *n*-C_4H_9
(-)-nephrosterinic acid **4**, R = *n*-$C_{10}H_{21}$
(-)-protolichesterinic acid **5**, R = *n*-$C_{12}H_{25}$



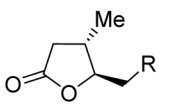
(+)-phaseolinic acid **6**, R = *n*-C_4H_9
(+)-nephromopsinic **7**, R = *n*-$C_{12}H_{25}$



cis-nephrosterinic acid **8**, R = *n*-$C_{10}H_{21}$
alloprotolichesterinic **9**, R = *n*-$C_{12}H_{25}$



(+)-dihydroprotolichesterinic acid **10**,
R = *n*-$C_{12}H_{25}$



whiskey lactone **11**, R = *n*-C_3H_7
cognac lactone **12**, R = *n*-C_4H_9

Fig. 1 Representative structures of γ-butyrolactone based paraconic acids and lactones.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra04267f

Organic & Supramolecular Chemistry

Enantioselective Total Synthesis of Sacubitril

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

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

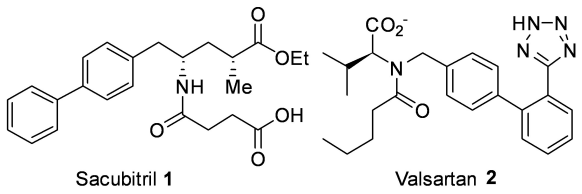
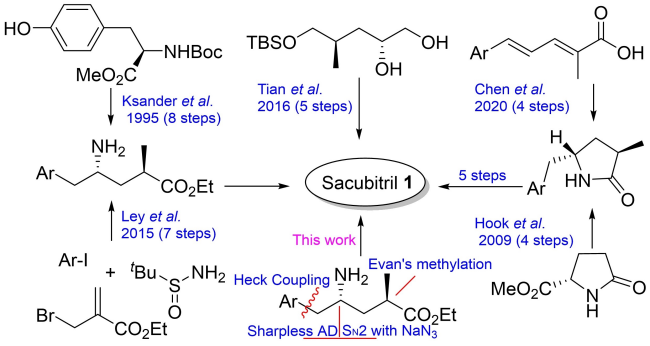
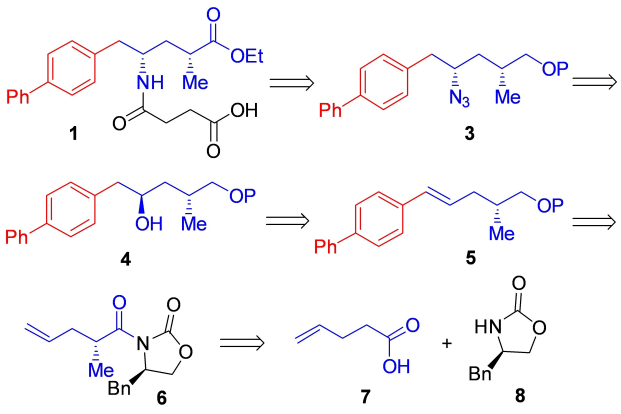


Figure 1. Structure of Sacubitril **1** and Valsartan **2**.



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

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



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

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

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Dedicated to Prof. Peter Alan Jacobi in recognition of his seminal contributions to so many aspects of organic chemistry

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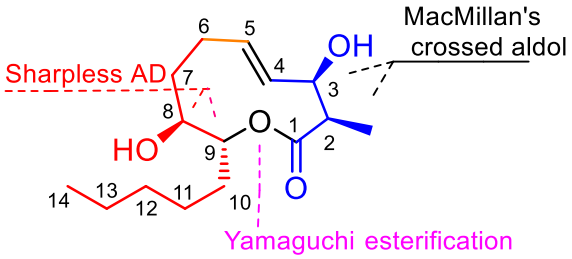
Abstract

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



Cytospolide D

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

