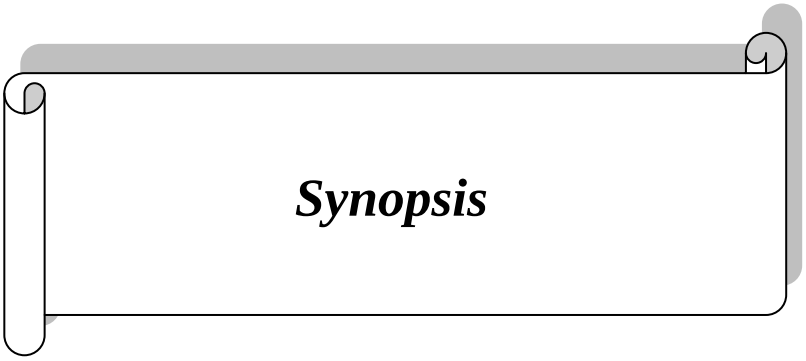

Synopsis

SYNOPSIS

The thesis entitled "**New approaches for the synthesis of bio-active piperidine alkaloids**" has been divided into four chapters.

CHAPTER-I : Chapter **I** describes a brief introduction to bioactive natural alkaloids and importance of piperidine ring containing alkaloids.

CHAPTER-II : Chapter **II** describes the "Synthesis of (-)-dihydropinidine, (2*S*,6*R*)-isosolenopsin and (+)-monomorine *via* a chiral synthon from *L*-aspartic acid".

CHAPTER-III : Chapter **III** describes the "Enantioselective access to (-)-indolizidines 167B, 209D, 239AB, 195B and (-)-monomorine from a common chiral synthon".

CHAPTER-IV : Chapter **IV** describes the "Total synthesis of piperidine alkaloids, microcosamine A and microgrewiapine A".

CHAPTER I: This chapter describes **a brief introduction to bioactive natural alkaloids and focused importance of piperidine ring containing alkaloids.**

CHAPTER-II : This chapter describes **the synthesis of (-)-dihydropinidine, (2*S*,6*R*)-isosolenopsin and (+)-monomorine *via* a chiral synthon from *L*-aspartic acid.**

A good biological profile offered by piperidine and indolizidine class of alkaloids, their natural scarcity and as a part of our ongoing project on synthesizing them as backbone, a practical and enantioselective total synthesis of (-)-dihydropinidine, (2*S*,6*R*)-isosolenopsin and (+)-monomorine is described. Dihydropinidine (**1**) is a *cis*-2,6-disubstituted piperidine alkaloid isolated from various species, such as, needles of *Picea pungens*, pine (*Pinus*) and spruce (*Picea*) trees, mexican bean beetle, *Epilachna varivestis*. Isosolenopsin (**2**) also falls under the class of *cis*-2,6-disubstituted piperidine alkaloids isolated from the ants venom of the genus *Solenopsis saeuissima*. Monomorine (**3**) is an indolizidine based alkaloid identified as

a pheromone of the pharaoh ant *Monomorium pharaonis* and from the skin of amphibians *melanophryniscus stlezneri* (Figure 1). The *cis*-2,6-disubstituted piperidine alkaloids displayed various antibacterial, antifungal, phytotoxic and insecticidal properties. In this chapter, a general strategy for the synthesis of alkaloids **1**, **2** and **3** was discussed through a common intermediate, *cis*-2-hydroxy methyl-6-methyl piperidine unit, synthesized *via* a chiral synthon derived from *L*-aspartic acid. The key steps involved in this synthetic approach are Wittig reaction, palladium catalyzed hydrogenation (reductive cyclization) and Julia olefination.

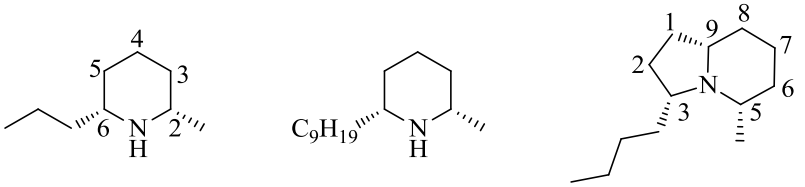
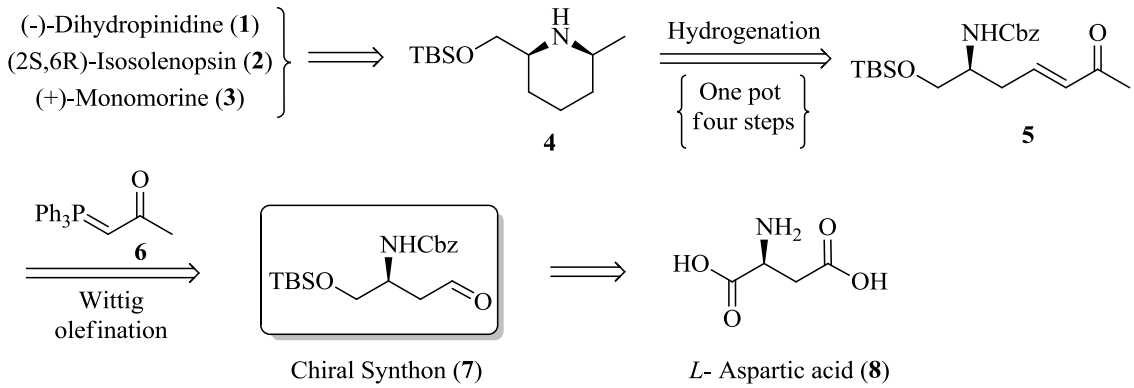


Figure 1

Retrosynthetic analysis

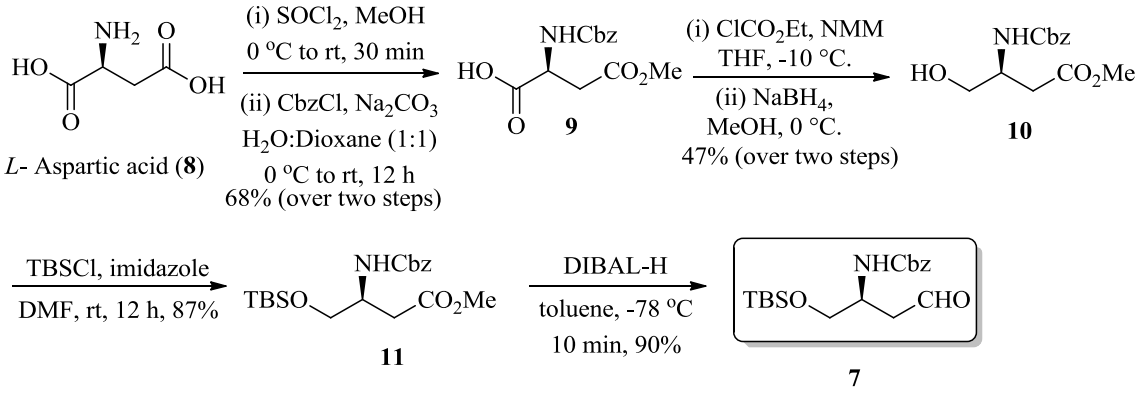
Retrosynthetic approach for the synthesis of alkaloids **1**, **2** and **3** is shown in scheme 1. The synthesis was planned from a common chiral intermediate **4** *via* deprotection, oxidation followed by subsequent olefination reaction sequence. The key fragment **4** involved in the synthesis was expected through palladium catalyzed reductive cyclization of its precursor **5**, which could be obtained by using Wittig reaction of chiral synthon **7** with a stable ylide **6**. The chiral synthon **7** inturn can be obtained from commercially available *L*-aspartic acid **8**.



Scheme 1

Synthesis of chiral synthon 7 from *L*-aspartic acid (8)

The synthesis started with the conversion of commercially available *L*-aspartic acid (**8**) to its β-carboxylic ester using thionyl chloride ($SOCl_2$) in MeOH at 0 ^oC to rt for 30 min., followed by protection of the free amine with benzyl chloroformate (CbzCl) in the presence of Na_2CO_3 in dioxane/water (1:1) system to provide *N*-protected acid **9** in 68% yield (over two steps). Acid **9** was then subjected to reduction through a mixed anhydride procedure by treatment with ethyl chloroformate ($ClCO_2Et$), *N*-methyl morpholine (NMM) in THF at -10 °C for 20 min and the resulted mixed anhydride was reduced with $NaBH_4$ in MeOH at 0 °C for 15 min. to give alcohol **10** in 47% yield (Scheme 2). The hydroxy functionality of **10** was protected as *tert*-butyldimethylsilyl (TBS) ether using TBSCl/imidazole in DMF to obtain the fully protected ester **11** in 87% yield. Exposure of compound **11** to DiBAL-H (di-isobutyl aluminium hydride) at -78 ^oC in anhydrous toluene as solvent for 10 min. yielded stable β-amino aldehyde **7** in a 90% yield (5 g of **7** was prepared in 25% overall yield from *L*-aspartic acid **8**).



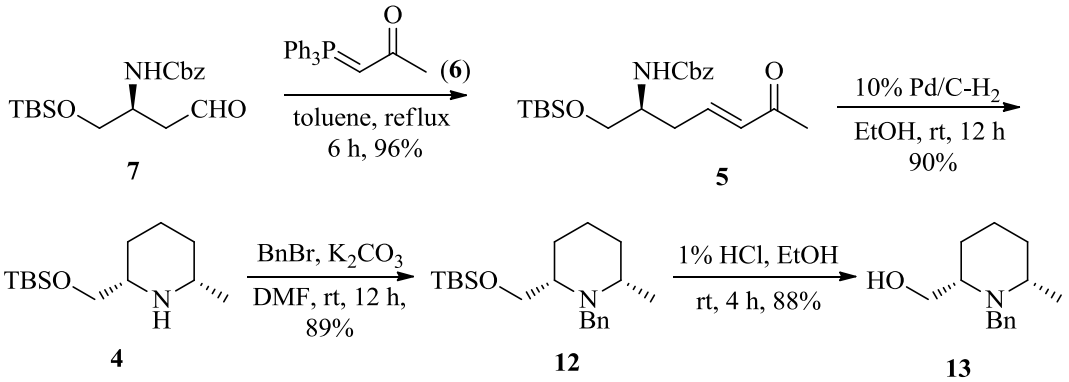
Scheme 2

Synthesis of *cis*-2-hydroxymethyl-6-methyl piperidine skeleton (13)

Chiral synthon **7** was first subjected to Wittig reaction with commercially available and stable ylide, methyl-(triphenylphosphoranylidene)-2-propanone (PPh_3=CHCOMe) **6** in toluene under refluxing conditions to give α,β-unsaturated-δ-amino ketone **5**, a key precursor for the reductive cyclization (Scheme 3). Hydrogenolysis of compound **5** in presence of 10% palladium charcoal under hydrogen atmosphere in ethanol for overnight at room temperature liberated free amine, which underwent a smooth intramolecular cyclization with carbonyl group to

generate six-membered piperidinyl imine, followed by *in situ* stereoselective reduction gave the piperidine skeleton **4** in 90% yield.

The *cis*-configuration of the 2,6-substituents was confirmed at a later stage (compound **13**) by 2D NOESY studies. Next, protection of the amine group in piperidine **4** with benzyl bromide using K_2CO_3 in DMF at room temperature for 12 h yielded compound **12** in 89% yield. Desilylation of **12** with 1% HCl in EtOH at rt for 4 h afforded piperidinol **13** in an 88% yield, an advanced common intermediate for all three alkaloid targets: (-)-dihydropinidine hydrochloride **(-)-1**, (2*S*,6*R*)-isosolenopsin hydrochloride (2*S*,6*R*)-**2**, and (+)-monomorine **(+)-3**.



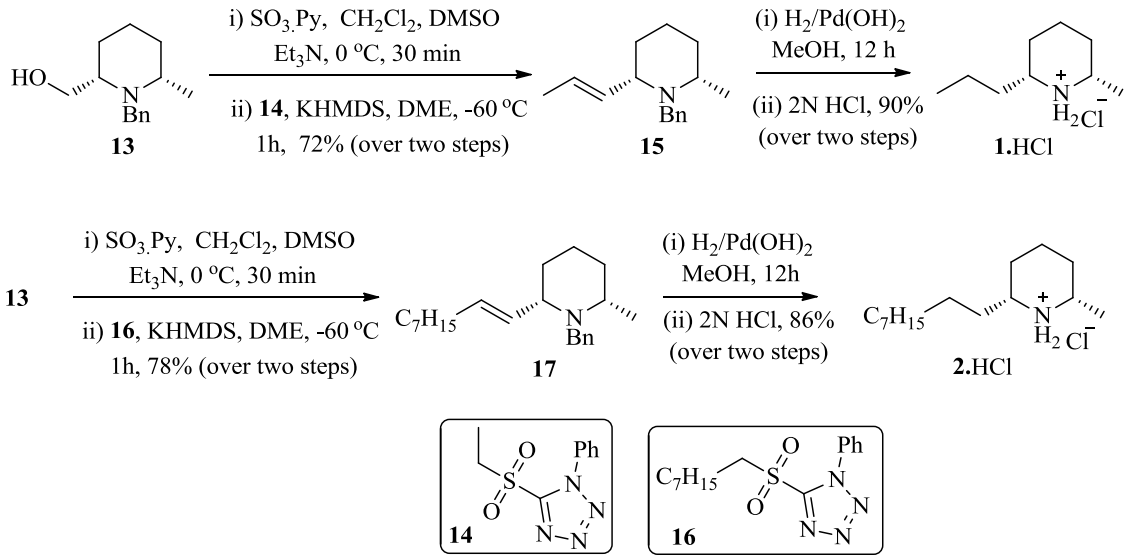
Scheme 3

Completion of synthesis of piperidine alkaloids 1 and 2

The primary hydroxy functionality of **13** was oxidized by Parikh–Doering oxidation using SO_3-Py in CH_2Cl_2:DMSO:Et_3N solvent system at 0 ^oC to give highly unstable aldehyde, which was immediately subjected to Julia-Kocienski olefination with 5-(ethylsulfonyl)-1-phenyl-1*H*-tetrazole **14** using potassium bis(trimethylsilyl)amide (KHMDS) in dry dimethoxy ethane (DME) as solvent at -60 ^oC for 1 h, afforded olefin **15** in 72% yield over two steps, with *E*-selectivity (>20:1) at newly formed double bond. Further, exposure of **15** to 20% $Pd(OH)_2$ under hydrogen atmosphere in EtOH, for saturation of the double bond as well as debenzylation in a one-pot reaction and subsequent treatment with 2N HCl provided the desired (-)-dihydropinidine hydrochloride **1**.**HCl** in a 90% yield.

A similar sequence of reactions was carried out on alcohol **13** involving; (i) oxidation of alcohol **13** using Parikh–Doering oxidation, followed by Julia-Kocienski olefination with 5-(octylsulfonyl)-1-phenyl-1*H*-tetrazole **16** using KHMDS to result olefin **17** in 78% yield over two steps, and (ii) hydrogenation of **17** using 20%

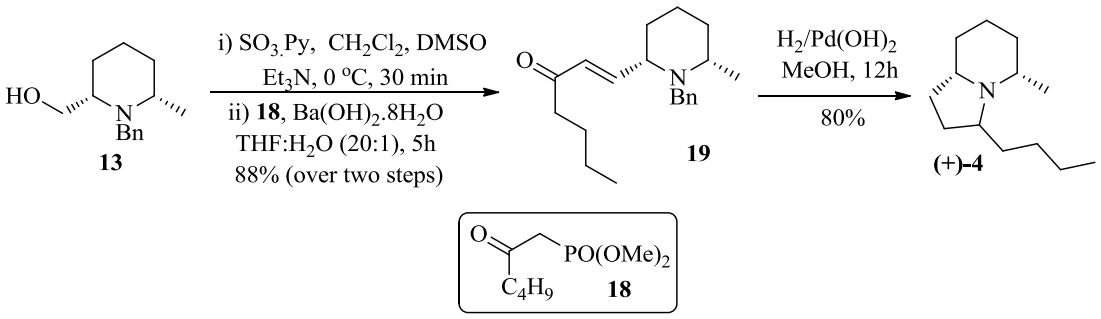
$Pd(OH)_2/C$ in MeOH for 12 h, followed by treatment with 2M HCl, formed (2*S*,6*R*)-isosolenopsin as its hydrochloride salt **3.HCl** in 86% yield over two steps (Scheme 4).



Scheme 4

Completion of synthesis of monomorine 3

After successful completion of the synthesis of (-)-dihydropinidine (-)-**1** and (2S,6R)-isosolenopsin **2** from common intermediate **13**, the synthesis of an indolizidine alkaloid, (+)-monomorine was also achieved (Scheme 5). Thus, alcohol **13** was oxidized to aldehyde under similar conditions as in scheme 4, which upon Horner-Wodsworth-Emmons olefination (HWE Olefination) with β-keto phosphorane **18** using $Ba(OH)_2 \cdot 8H_2O$ in THF:H_2O (20:1) for 5 h, afforded α,β- unsaturated ketone **19** in an 88% yield over two steps.



Scheme 5

Finally, exposure of enone **19** to reductive cyclization involving four transformations; (i) benzyl deprotection, (ii) double bond reduction, (iii) imine formation, and (iv) imine reduction, in one-pot under hydrogenation reaction

conditions using 20% $Pd(OH)_2$ on charcoal in MeOH, furnished the target indolizidine alkaloid, (+)-monomorine **4** in 80% yield.

In conclusion, a general strategy for the syntheses of *cis*-2-alkyl-6-methyl piperidine based alkaloids has been achieved using a handy chiral synthon from *L*-aspartic acid *via* a Wittig followed by hydrogenation reaction sequence. Using this strategy, asymmetric syntheses of (-)-dihydropinidine, (*2S, 6R*)-isosolenopsin and (+)-monomorine have been accomplished.

CHAPTER-III : This chapter describes **the enantioselective access to (-)-indolizidines 167B, 209D, 239AB, 195B and (-)-monomorine from a common chiral synthon.**

Our research group has a focus on total synthesis of natural products of scarce availability. Undoubtedly, indolizidine based alkaloids (IBAs) have been a natural choice for this effort owing to their broad range of biological activities. Towards this, full details pertaining to asymmetric total synthesis of IBAs, such as, (-)-indolizidines 167B (**20**), 209D (**21**), 239AB (**22**), 195B (**23**) and (-)-monomorine (**24**) from a chiral synthon is reported (Figure 2).

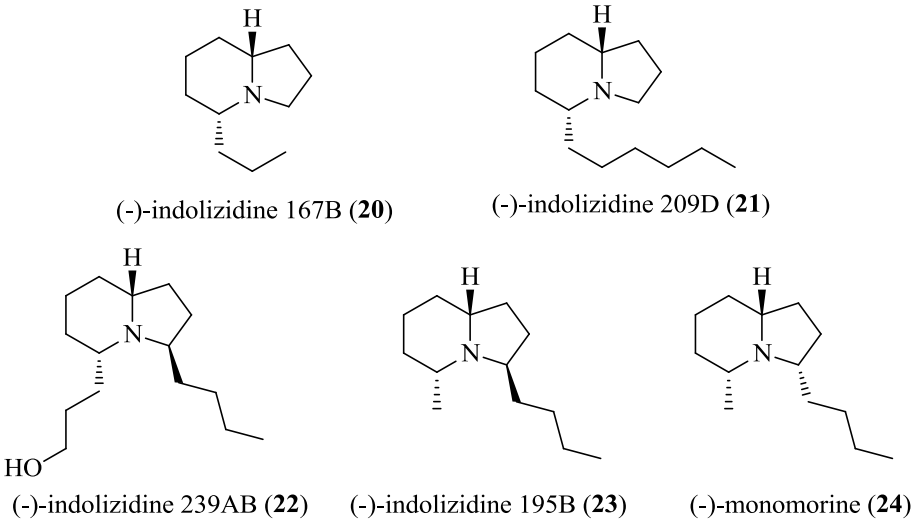


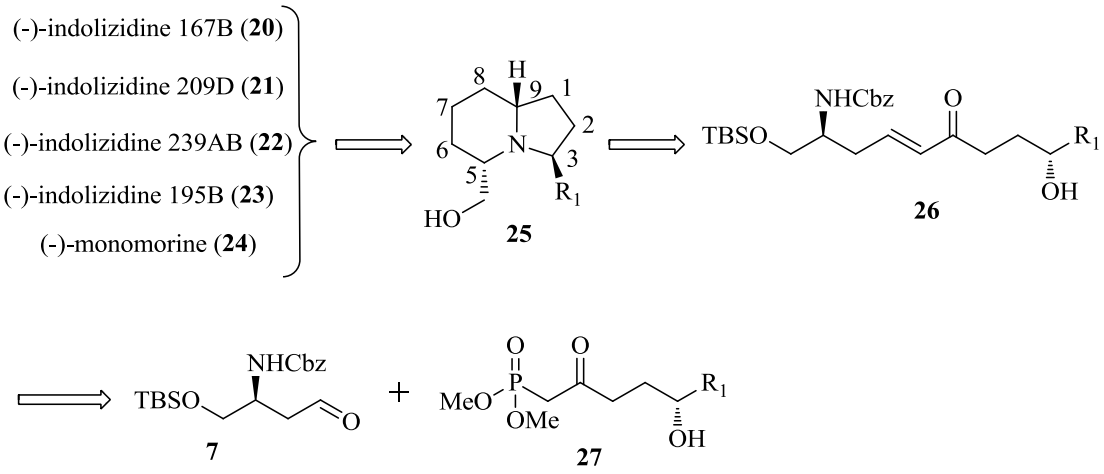
Figure 2

(-)-Indolizidine 167B (**20**) and 209D (**21**) are the unnatural alkaloids shown to function as noncompetitive blockers of neuromuscular transmission. Initially, the structures of these two alkaloids were tentatively proposed for two natural alkaloids isolated from unidentified dendrobatid frogs in minute quantities instead of 3,5-

disubstituted pyrrolizidine skeleton. (-)-Indolizidine 239AB (**22**), a 3,5-disubstituted indolizidine, isolated from poison-frogs of the *Dendrobatidae* family. (-)-Monomorine (**23**) is an unnatural enantiomer of (+)-monomorine I (**3**), a trail pheromone of the widespread pharaoh's ant *Monomorium pharaonis L.*, whereas, (-)-Indolizidine 195B (**24**), one of the diastereomer of (-)-monomorine (**23**), isolated from the source of *Dendrobatidae* neotropical poison frogs.

Retrosynthetic analysis

The retrosynthetic approach for the synthesis of target alkaloids was depicted in scheme 6. The (*S*)-3-(Cbz-amino)-4-(*tert*-butyldimethylsilyloxy) butanal **7** derived from *L*-aspartic acid, considered to be a suitable chiral synthon having an aldehyde functionality for accessing 5-substituted and 3,5-disubstituted indolizidines *via* a Horner-Wadsworth-Emmons (HWE) reaction followed by reductive cyclization as the key steps.

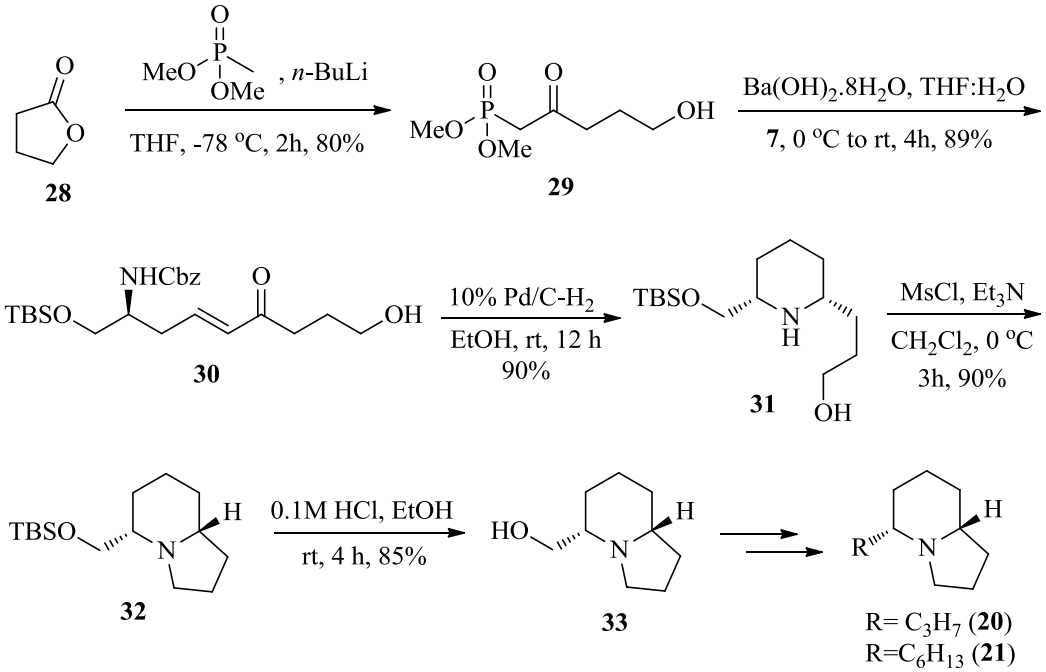


Scheme 6

The C-5 stereocenter of indolizidine scaffold **25** was carried from the chirality of the synthon, the C-9 configuration can be created through the reductive amination and the C-3 chirality was obtained by proline-catalyzed α-hydroxylation. Further, the choice of benzyloxy carbonyl (Cbz) protection would allow its removal during the reductive cyclization step and the *tert*-butyldimethyl silyl (TBS) group was expected to be stable throughout the sequence of reactions and can then be removed after the construction of indolizidine frame work for further structural elaboration.

Synthesis of (-)-indolizidine 167B (20) and 209D (21)

As shown in chapter 1 (Scheme 1), chiral synthon **7** was prepared in four steps from *L*-aspartic acid through a known ester **11**. Initially, the construction of indolizidine ring was studied with the syntheses of 5-substituted indolizidine alkaloids 167B (**20**) and 209D (**21**). HWE olefination of synthon **7** in the presence of $Ba(OH)_2.7H_2O$ with dimethyl (5-hydroxy-2-oxopentyl)phosphonate **29** (which was easily prepared in one-step from γ-butyrolactone **28** by treating with lithium dimethyl methylphosphonate in dry THF at -78 ^oC for 2h) furnished the α,β-unsaturated enone **30** in 89% yield. The adduct **30**, a precursor for reductive cyclization when exposed to 10% Pd/C under hydrogen atmosphere in EtOH at rt for 12 h, provided hydroxy piperidine **31** exclusively as *cis*-isomer in 90% yield. This hydrogenation reaction involves four transformations in single step: (a) olefin reduction, (b) Cbz-removal, (c) intramolecular cyclic imine formation, and (d) stereoselective reduction of the imine to give piperidine **31**. The formation of *cis*-**31** was confirmed at later stage (converting alcohol **33** to known acetyl derivative) by NOE experiments.



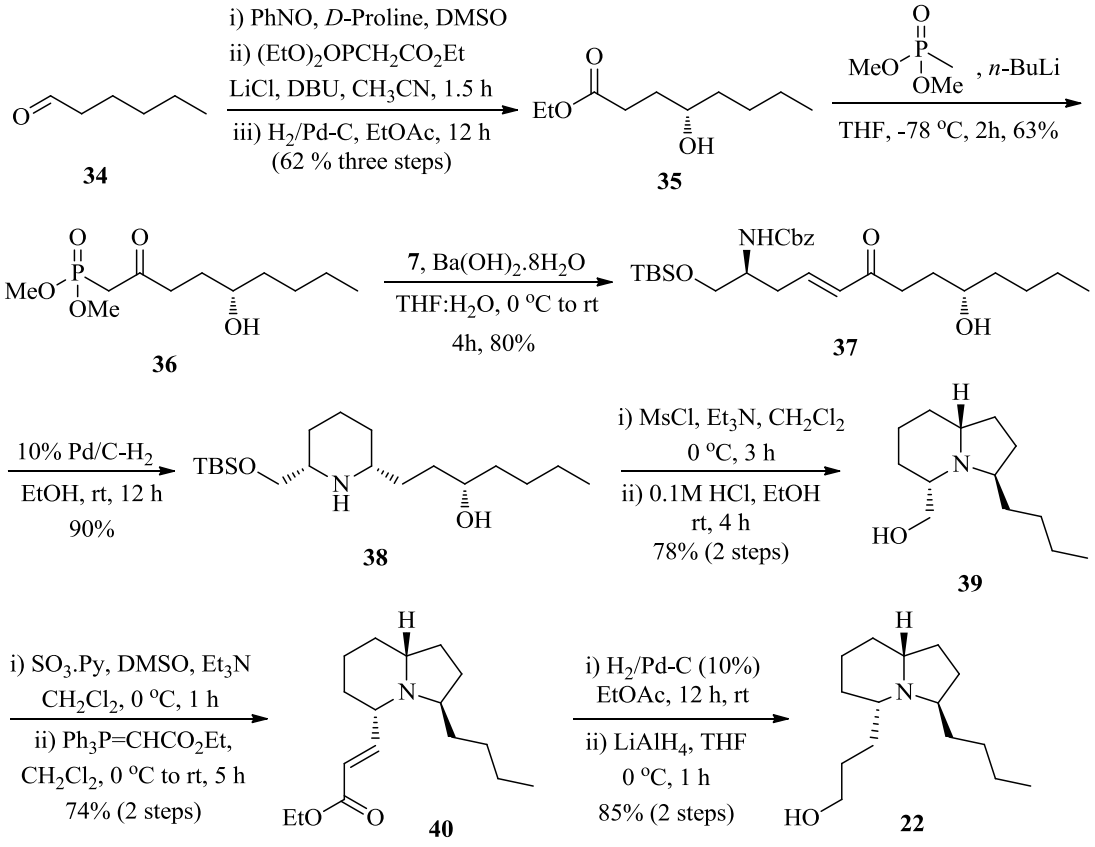
Scheme 7

Further, to achieve the indolizidine scaffold, compound **31** was treated with Et_3N/MsCl in CH_2Cl_2 at 0 ^oC, under which the free hydroxyl group was mesylated followed by in situ cyclization furnishing the indolizidine **32** in 90% yield. TBS deprotection of **32** using 0.1 M HCl in EtOH provided compound **33** in 85% yield,

which has previously been converted to (-)-indolizidine 167B (**20**) and 209D (**21**) in a known two step sequence.

Synthesis of (-)-indolizidine 239AB (22), 195B (23)

For the synthesis of 3,5-disubstituted indolizidine alkaloids, (-)-indolizidine 239AB (**22**) and 195B (**23**) from synthon **7**, a chiral Wittig partner was chosen to install the C-3 centre of indolizidine skeleton. The chiral Wittig partner was prepared from commercially available *n*-hexanal (**34**) by subjecting to proline catalysed α-aminoxylation in the presence of PhNO in DMSO followed by HWE olefination with ethyl-2-(diethoxyphosphoryl)acetate (DBU/LiCl/ CH_3CN) in one-pot operation to produce γ-aminoxy-α,β-unsaturated ester, which was subsequently exposed to hydrogenation conditions (10% Pd/C-H_2 in EtOAc) to provide 3-hydroxy ethyl octanoate in 62% yield with 94% ee (over three operations). The stereochemistry of hydroxy group depends on the proline (*L*/*D*) used in the reaction.

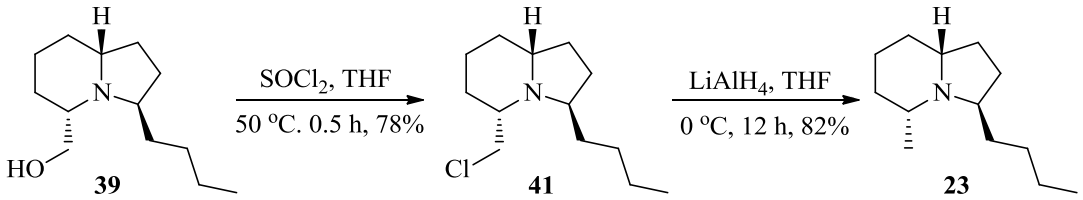


Scheme 8

Thus, hydroxy ester **35** was prepared by *D*-proline catalyzed α-aminoxylation and treated with dimethyl methylphosphonate in the presence of *n*-BuLi in THF at -78 ^{o}C to provide the β-keto phosphonate **36** in 63% yield, which was exist as a mixture of keto and lactol form, confimed by ^{1}H NMR. The HWE olefination of phosphonate **36** with aldehyde **7** in the presence of $Ba(OH)_2.7H_2O$ in THF:H_2O solvent system provided α,β-unsaturated enone **37** in 87% yield. The concomitant one-pot hydrogenation-cyclization reaction of α,β-unsaturated enone **37** gave 2,6-disubstituted piperidine **38** in 83% yield.

Compound **38** underwent a second cyclization in the presence of Et_3N/MsCl followed by TBS deprotection to afford 3,5-disubstituted indolizidine skeleton **39** in 78% yield (over two steps) with excellent stereoselectivity. Next, alcohol **39** was oxidized to the corresponding aldehyde using Parikh-Doering conditions (SO_3.Py, Et_3N, DMSO/CH_2Cl_2), which upon exposure to (ethoxycarbonylmethylene) triphenyl phosphorane gave the α,β-unsaturated ester **40** in 74% yield over two steps (Scheme 8). Saturation of olefin in **40** under atmospheric pressure of hydrogen in the presence of 10% Pd/C and subsequent reduction of the ester functionality using $LiAlH_4$ in THF completed the total synthesis of (-)-indolizidine 239AB (**22**).

Similarly, compound **39** was subjected to a two step sequence of transformations involving (i) conversion of alcohol **39** to chloride **41** using thionyl chloride (ii) reduction of chloro methyl to methyl group using lithium aluminum hydride, to obtain (-)-indolizidine 195B (**23**).

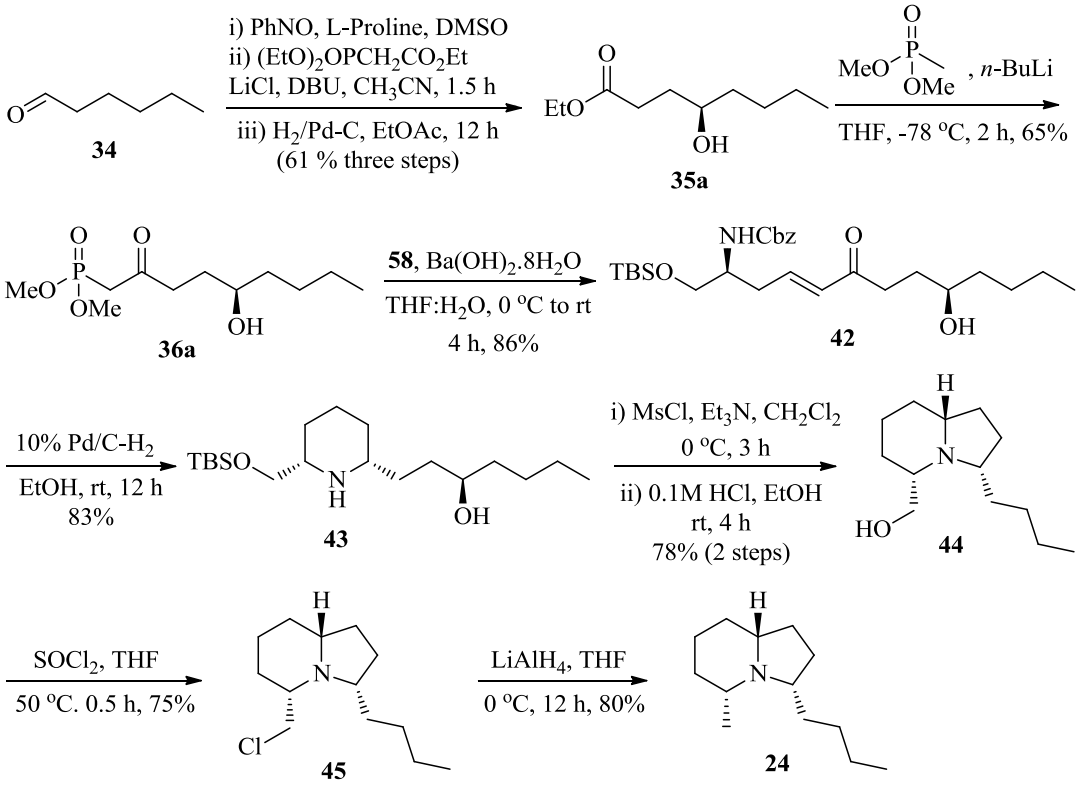


Scheme 9

Synthesis of (-)-monomorine (24)

After successful synthesis of 3,5-disubstituted indolizidines (-)-239AB, and (-)-195B, the stereoselective synthesis of unnatural (-)-monomorine, C3-epimer of (-)-indolizidine 195B, was also attempted (Scheme 10).

The desired γ-hydroxy ester **35a** was obtained from *n*-hexanal **34** using *L*-proline (94% ee). The ester **35a** was then converted to ε-hydroxy-β-keto phosphonate **36a**, which was subjected to HWE olefination to give enone **42**, followed by hydrogenation provided the piperidine **43**. Further, compound **43** was converted to indolizidine skeleton **44** by mesylation and in situ cyclization followed by desilylation. The primary hydroxy group of **44** was converted to chloride **45** and subsequent reduction resulted (-)-monomorine **24** (same sequence of reactions carried out for (-)-indolizidine 195B (**23**)).

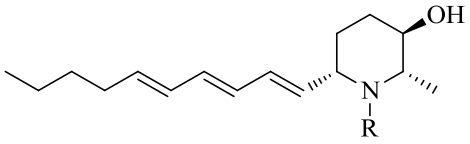


Scheme 10

In conclusion, an efficient and general route for the stereoselective synthesis of indolizidine alkaloids has been developed using a stable and scalable chiral synthon, obtained from *L*-aspartic acid. The formal synthesis of (-)-indolizidine 167B, 209D and total synthesis of (-)-indolizidine 239AB, 195B and (-)-monomorine have been successfully accomplished in good yield.

CHAPTER-IV: This chapter describes **the total synthesis of piperidine alkaloids, microcosamine A and microgrewiapine A**

As part of a programme aimed at building a natural product library with alkaloid scaffolds as backbone, we desired to develop an efficient route to larger quantities of key natural products and also their intermediates. With this programme in mind, we developed a practical and enantioselective synthesis of 3-hydroxy-2,6-disubstituted piperidine alkaloids microcosamine A and microgrewiapine A. In general, 3-hydroxy-2,6-disubstituted piperidines have attracted much attention due to their interesting structural features and potent biological activities. Microcosamine A and microgrewiapine A, are two 2-methyl-3-piperidinol ring alkaloids having deca-1*E*,3*E*,5*E*-trienyl group with a *cis*-relationship between C2-methyl and C6-sidechain units, were recently isolated from *Microcos paniculata*. The only difference is that compound **47** has *N*-methyl, while **46** without *N*-methyl group (Figure 3). The plant *Microcos paniculata*, a large shrub or small tree that grows in South and Southeast Asia countries, is found to be rich source of bio-active compounds. Several parts of this plant such as roots, stem bark, leaves and fruits are used in the local system of medicine for the treatment of diarrhea and fever, as herbal tea to treat cold, enteritis, and skin rash. The crude alkaloidal mixture show activity in various biological tests and also as insecticidal.



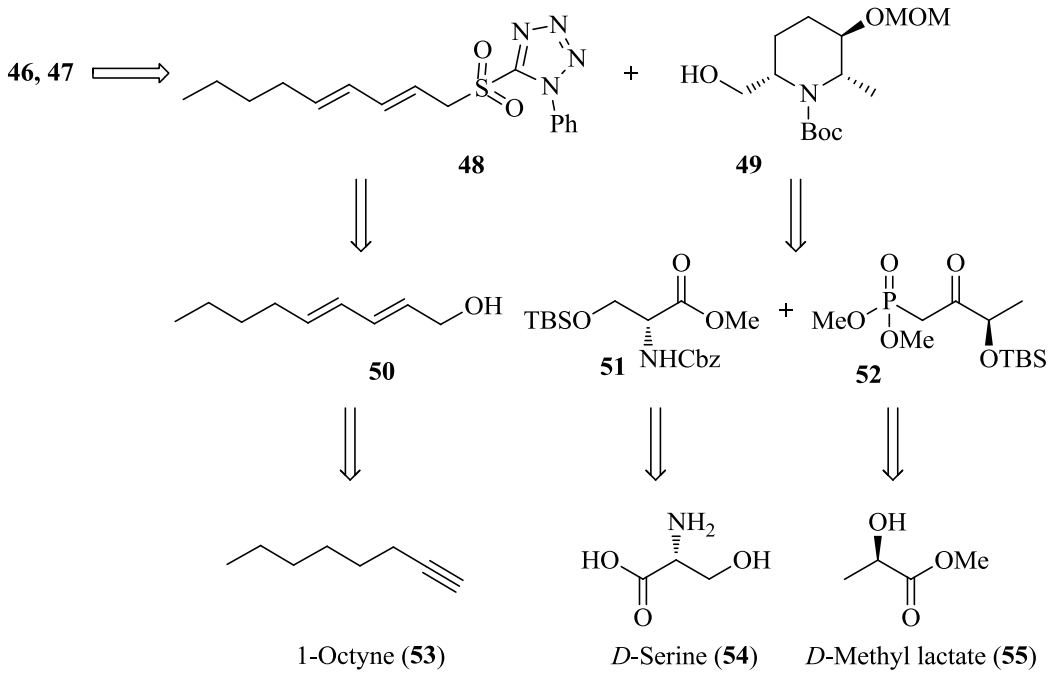
R = H, Microcosamine A (**46**)
R = CH_3, Microgrewiapine A (**47**)

Figure 3

In 2008, microcosamine A (**46**), was isolated from the chloroform extract of the leaves of *Microcos paniculata* exhibiting insecticidal activity. Recently in 2013, microgrewiapine A (**47**), was isolated from the chloroform extract of stem bark of the same plant along with some other piperidine alkaloids including **46** from leaves. Microgrewiapine A was found to have cytotoxic acvity against HT-29 human colon cancer cells. Both the compounds **46** and **47** exhibited neuronal nicotinic acetylcholine receptor (nAChR) activity.

Retrosynthetic analysis

The retrosynthetic outlook for the synthesis of alkaloids, microcosamine A (**46**) and microgrewiapine A (**47**) was shown in Scheme 11. The triene-side chain at C6 position of hydroxy piperidine ring **49** was installed at later stage by using **48** *via* oxidation followed by Julia-Kocienski olefination. Piperidine **49** could be achieved through the intramolecular amide alkylation of its precursor, which inturn can be obtained from *N*,*O*-protected *D*-serine ester **51** and β-keto phosphonate **52** using Horner-Wadsworth-Emmons (HWE) olefination as the key reaction.



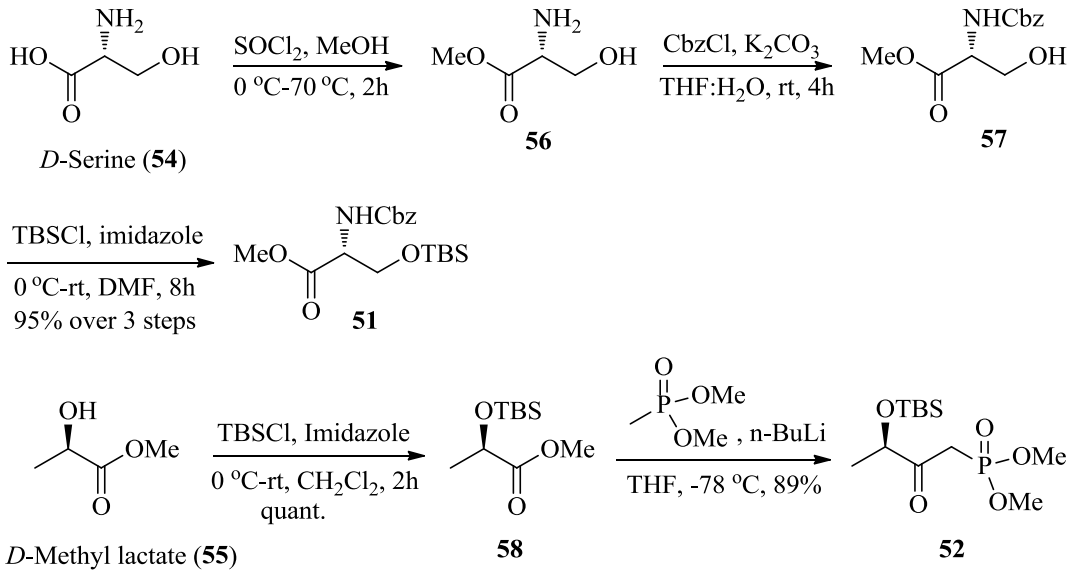
Scheme 11

The sulfone fragment **48** was projected from 1-octyne (**53**) by way of a known conjugated alcohol **50**. Ester **51** and phosphonate **52** were planned from the commercially available chiral starting materials, *D*-serine (**54**) and *D*-methyl lactate (**55**), respectively. The C2 and C6 stereochemistry is expected to achieve from **54** and C3 stereochemistry envisaged from **55** using diastereoselective Luche reduction.

Synthesis of chiral intermediates 51 and 52

Our synthesis commenced with commercially available starting material, *D*-serine **54**. In the very first step, esterification of **54** was carried out using acetyl chloride in MeOH at reflux for 2h to get *D*-serine methylester **56**. Further, the free amine group of serine ester **56** was protected as Cbz carbamate **57** by using Cbz-

Cl/K_2CO_3 in THF:Water at room temperature for 4h, followed by TBS protection of hydroxy group using TBSCl/imidazole in DMF provided TBS ether **51**. Other desired β-keto phosphonate **52** was also smoothly obtained in two steps from *D*-methyl lactate (**55**). TBS protection of secondary hydroxyl group of **55** using TBSCl/imidazole in CH_2Cl_2 gave compound **58**, which on treatment with lithiated anion of methyl dimethyl phosphonate in THF at -78 ^oC afforded desired β-keto phosphonate **52** in 89% yield (Scheme 12).

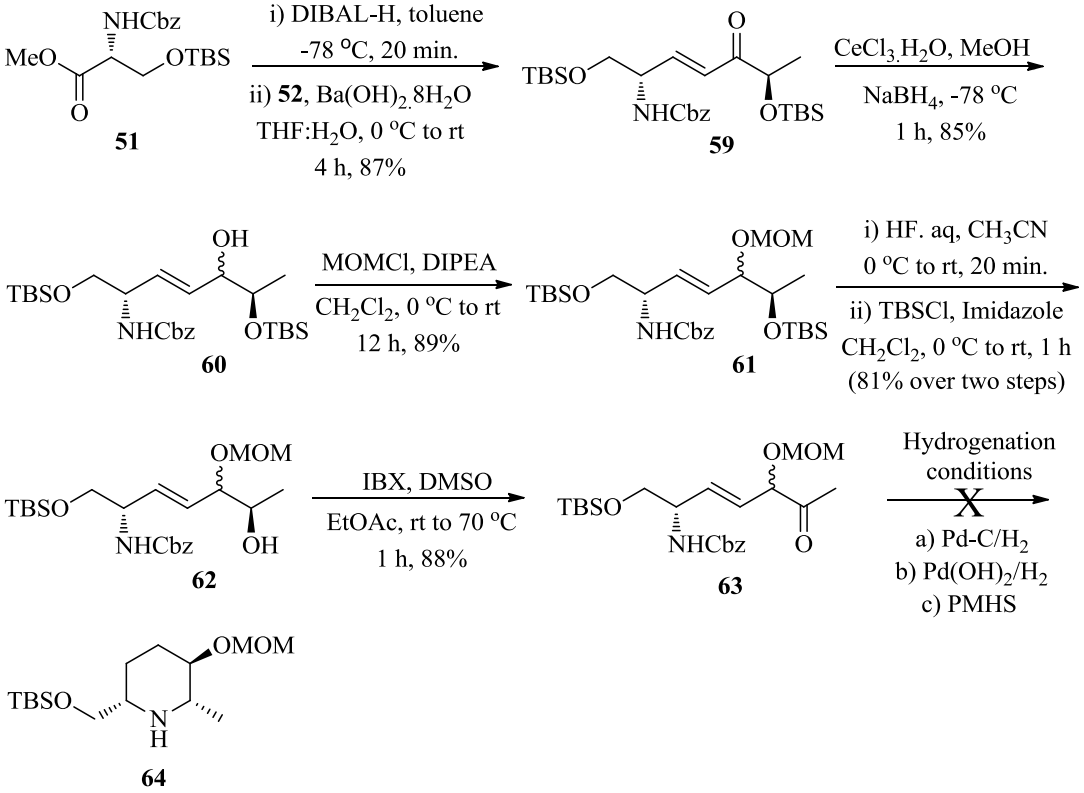


Scheme 12

Synthesis of piperidine skeleton 49

For the synthesis of carbo-*tert*-butyloxy protected piperidine fragment **49**, initially, the ester functionality of **51** was reduced with DIBAL-H in toluene at -78 ^oC to aldehyde, which was immediately subjected to Horner-Wadsworth-Emmons olefination with β-keto phosphonate **52** in the presence of $Ba(OH)_2.8H_2O$ in THF/H_2O to afford the enone **59**. γ-Amino benzyloxycarbonyl α,β-unsaturated ketone **59** was subjected to reduction under Luche conditions with $NaBH_4$ in the presence of $CeCl_3.H_2O$ in MeOH for 30 min. at -78 ^oC provided the allylic alcohol **60** with a little diastereomeric mixture [dr >90% based on the diastereomers separated (**67** and **68**) in cyclization step]. These diastereomers were inseparable either by column or by HPLC (In ^1H NMR also the diastereomeric signals were not separated to check the diastereomeric ratio) and hence, moved for further transformations with the mixture. Thus, the hydroxyl group of **60** was protected as methoxy methyl (MOM) ether **61**

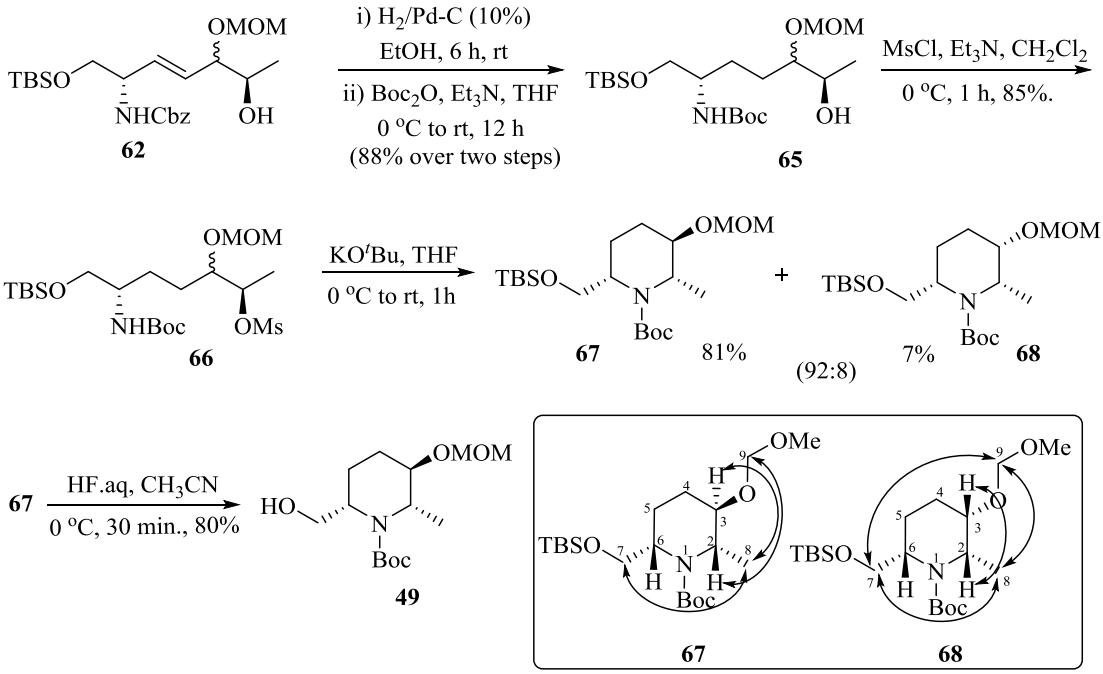
using MOMCl/diisopropylethyl amine in CH_2Cl_2. To obtain free secondary hydroxyl compound **62**, both the *tert*-butyldimethyl silyl groups of **61** were deprotected under HF (40% in water), CH_3CN conditions followed by selective protection of the primary hydroxyl group with TBSCl provided the required alcohol **62**. Oxidation of free hydroxy group of **62** with IBX in DMSO:EtOAc solvent system provided the ketone **63**. Disappointingly, attempts to achieve the piperidine **64** from **63** through hydrogenation was unsuccessful (Scheme 13).



Scheme 13

Hence, an alternative sequence was chosen. Hydrogenation reaction of **62** using 10% Pd/C in EtOH was carried out intially, which involves the olefin reduction as well as Cbz-deprotection to free amine, and the free amine was subsequently treated with di-*tert*-butyl-dicarbonate (Boc_2O)/Et_3N to get Boc-protected amino alcohol **65** in 88% yield. The hydroxy group of **65** was protected with methanesulfonyl chloride in presence of triethyl amine in CH_2Cl_2 as mesylate **66**, which was successfully converted into 2,3,6-trisubstituted piperidine *via* intramolecular amide alkylation (SN reaction) using potassium *tert*-butoxide in THF (88%). At this point, the diastereomers formed during the Luche reduction of **59** were separated by column chromatography (dr 92:8) (Scheme 14). The major isomer **67**

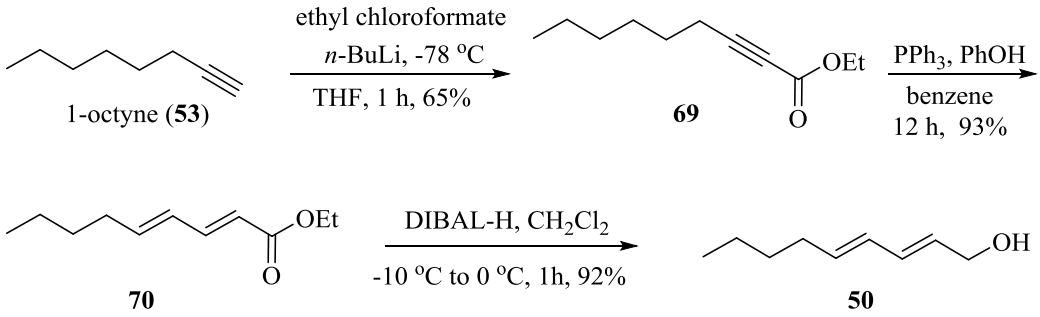
was found to the desired one and the minor isomer **68** was undesired, which were charecterized by 2D COSY and NOESY experiments. Desilylation of **67** using HF (40% in water) in CH_3CN resulted the piperidinol **49** in 80% yield.



Scheme 14

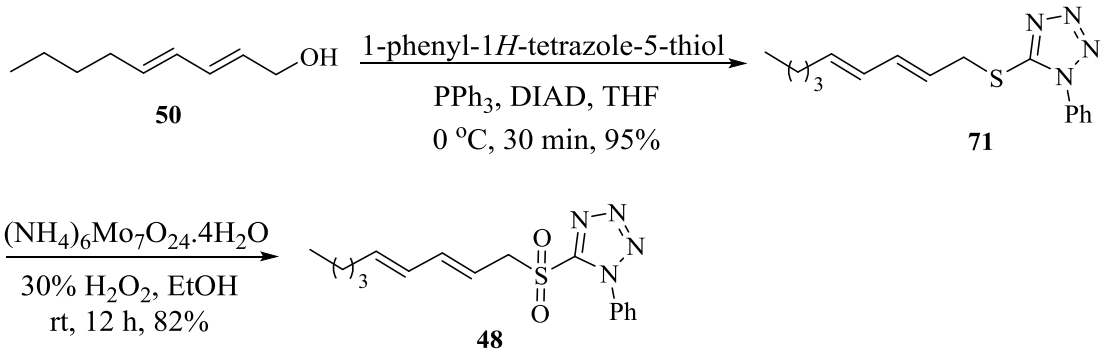
Synthesis of sulfone 48

The sulfone **48** required for Julia olefination was synthesised through dienol **50**, obtained from 1-octyne (**53**) as shown in scheme 15. Carboxylation of terminal alkyne **53** using *n*-BuLi and ethyl chloroformate in THF provided ynoate **69**, which on exposing to the Rychnovsky modified condition of the Trost isomerization (Ph_3P/PhOH, rt, 12 h) cleanly gave *E,E*-dienoate **70**. Reduction of the dienoate **70** with DIBAL-H in CH_2Cl_2 at -10 °C to 0 °C accessed the required conjugated alcohol **50** (Scheme 15).



Scheme 15

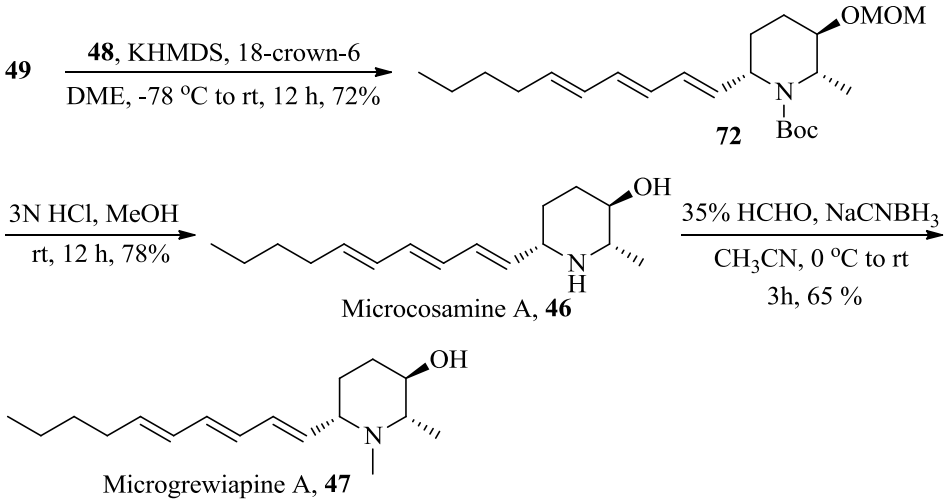
Mitsunobu reaction of the alcohol **50** with 1-phenyl-1*H*-tetrazole-5-thiol to thio-tetrazole **71** followed by ammonium molybdate catalyzed oxidation using hydrogen peroxide in EtOH provided the sulfone **48** in 82% yield (Scheme 16).



Scheme 16

Completion of synthesis microcosamine A (46) and microgrewiapine A (47)

Now, the stage was set for the conversion of **49** to microcosamine A (**46**) and microgrewiapine A (**47**) by connecting the side chain (Scheme 17). Accordingly, the alcohol **49** was oxidized with IBX (2-iodoxybenzoic acid) to the corresponding aldehyde followed by Julia-Kocienski olefination with the trienyl sulfone **48** by treating with KHDMS in the presence of 18-crown-6 in DME provided the trienyl-piperidine **72** exclusively as *Z*-isomer in 72% yield over two steps.



Scheme 17

Deprotection of MOM and Boc groups was accomplished in one step by treating **72** with 3N HCl in MeOH to give the desired microcosamine A (**46**) in 78% yield. Further, compound **46** was converted to microgrewiapine A (**47**) through

reductive *N*-methylation (HCHO, $NaCNBH_3$) in 65% yield. The spectral data (^1H, ^{13}C NMR and mass) and optical rotation of our synthetic microcosamine A were in full agreement to those reported for natural product. However, in the case of microgrewiapine A, the spectral data (^1H, ^{13}C NMR and mass) of synthetic **47** is in full agreement with natural product data, but the specific rotation was observed with opposite sign.

In summary, the first asymmetric total synthesis of natural piperidine alkaloids, microcosamine A and microgrewiapine A was accomplished using HWE-olefination, intramolecular amide cyclization and Julia-Kocienski olefination from commercially available *D*-serine, *D*-methyl lactate and 1-octyne as starting materials. The approach is handy for the synthesis of analogues having different side chains.