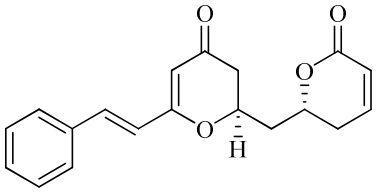
The thesis entitled **"Stereoselective total synthesis of obolactone and PF1163A; diastereoselective allylation of iminium ion protocol for the total synthesis of (+)-deoxoprosopinine and studies towards total synthesis of (+)-deoxoprosophylline"** is divided into three chapters.

Chapter I: Brønsted acid catalysed tandem cyclization protocol for the stereoselective total synthesis of obolactone

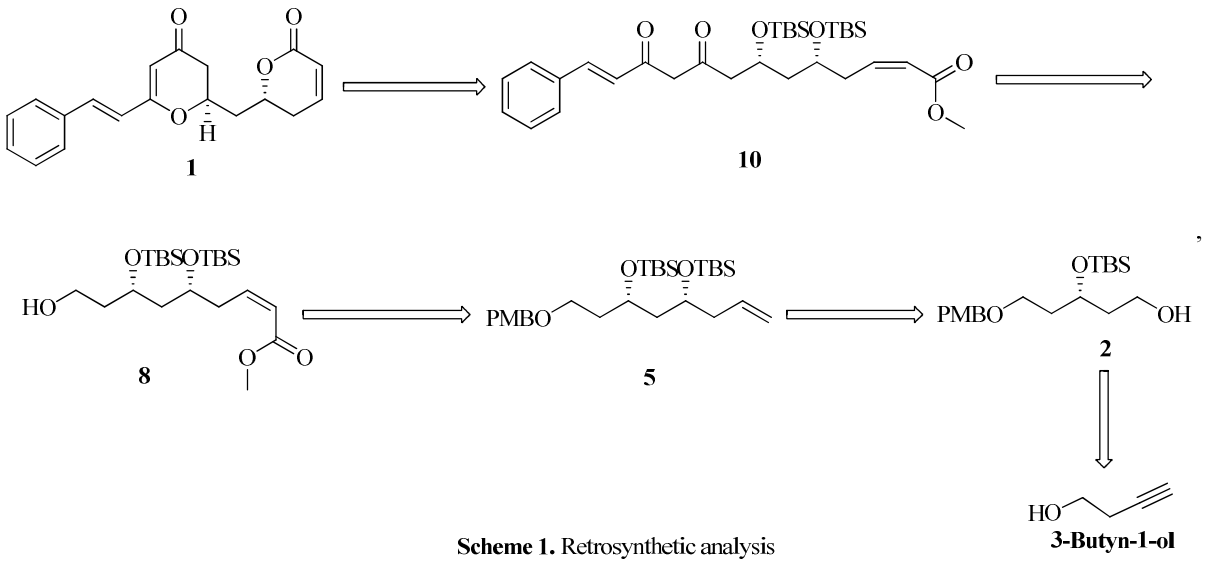
This chapter deals with stereoselective total synthesis of obolactone

Lactone rings are a common structural feature of many natural products.[1] As a matter of fact, 5,6-dihydropyran-2-ones of both natural and non-natural origin have been found to be cytotoxic.[2] In addition, they inhibit HIV protease,[3] induce apoptosis,[4,5] and have even proven to be antileukemic,[6] along with having many other relevant pharmacological properties.[7] At least some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor.[1a,8]

Recently, pyrone containing natural product, obolactone **1** (Figure 1) was isolated by Guéritte and co-workers from *Cryptocarya obovata*.[9] Obolactone **1** is unique in the sense that two dihydropyrones, namely a γ-pyrone and α-pyrone are linked through a methylene bridge thus presenting a rare structural motif. Our group interested in the total synthesis of α-pyrone containing natural products due to their structural diversity, substitution pattern on the side-chain, their ubiquitous presence coupled with varied biological activity[10] and reported the synthesis of some 6-alkyl α-pyrone containing natural products earlier.[11] Recently Pan and co-workers reported the first asymmetric total synthesis of **1** *via* RCM protocol.[12] Attracted by its structural elegance and complexity, alternative strategy was explored that allows far simpler and efficient access to such skeleton containing natural products. Herein this chapter, the stereoselective total synthesis of **1** will be discussed in detail by the Brønsted acid mediated tandem cyclization of the diketone **10** in one-pot.



Obolactone 1
Figure 1

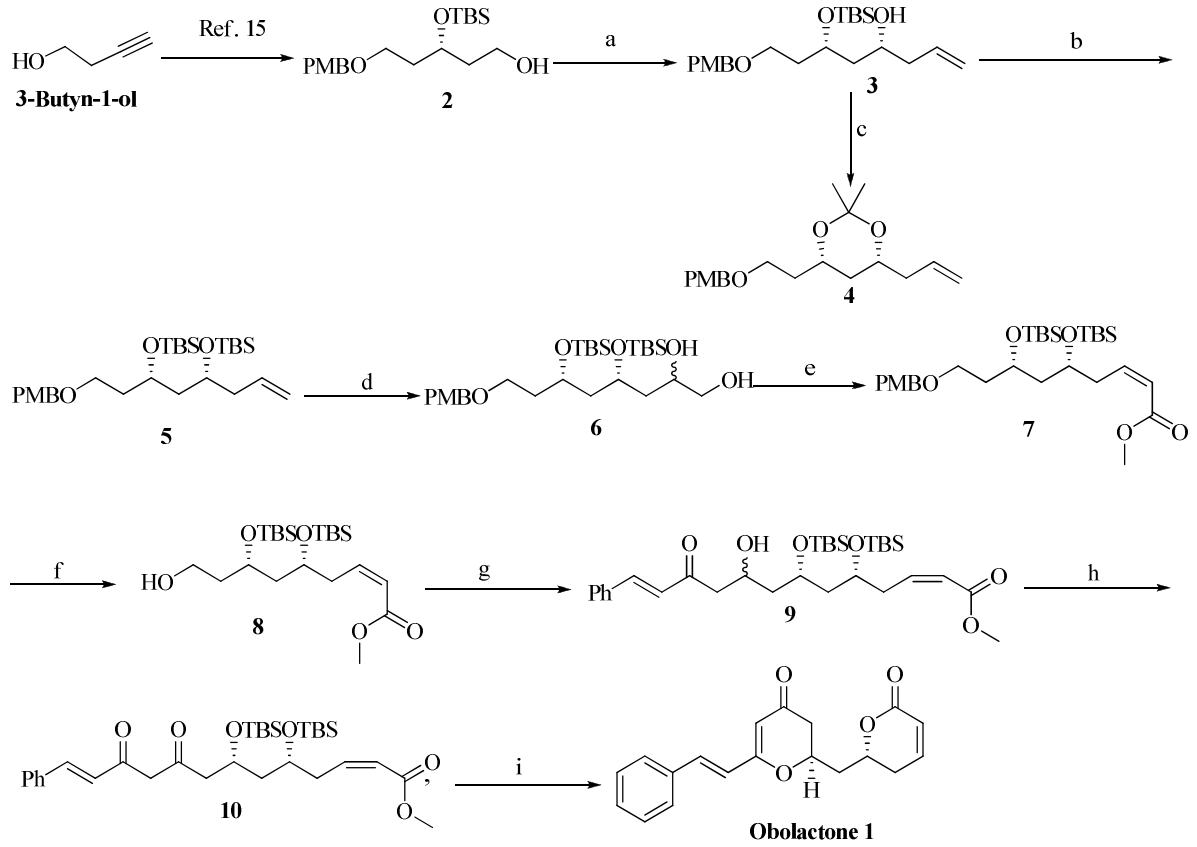


Scheme 1. Retrosynthetic analysis

The Retrosynthetic analysis (Scheme 1) revealed that Brønsted acid (PTSA) mediated tandem cyclization of the appropriately substituted diketone **10** to result in the target **1**. Diketone **10** in turn could be synthesized from compound **8** by Swern oxidation followed by aldol addition with benzylideneacetone and oxidation of resulting secondary hydroxyl group by Dess-Martin periodinane. Compound **8** was obtained from **5** in series of reactions such as oxidative cleavage of terminal double bond, subsequently thus obtained aldehyde was utilized for *cis*-Wittig olefination and deprotection of PMB protecting group. The compound **5**, in turn obtained from compound **2** by Swern oxidation, Keck asymmetric allylation and silylation reactions. To realise the compound **2**, 3-butyn-1-ol was chosen as starting material upon which several transformations such as formylation, stereospecific hydride reduction of propargylic alcohol to *'E'* allylic alcohol, Sharpless asymmetric epoxidation, reductive ring opening of epoxy alcohol, protections and deprotections were carried out to lead to the compound **2** (Scheme 1).

Accordingly, the synthesis (Scheme 2) commenced from the commercially available 3-butyn-1-ol and its transformations to a known alcohol **2**.[13] Next, **2** was oxidized to aldehyde under Swern conditions and was immediately subjected to Keck asymmetric allylation[14] reaction {(*R*,*R*)-Binol/Ti(O^iPr)$_4$/allyltri-*n*-butyltin/CH_2Cl_2/-78 to -20 ^oC) to afford homoallyl alcohol **3** in good yield (75%, over two steps) and diastereoselectivity (dr 9:1). The absolute stereochemistry of the newly created stereogenic center was assigned based on the Rychnovsky's analogy of the corresponding acetonide **4**.[15] For instance, the ^{13}C NMR of **4** revealed the carbon atoms of the acetonide methyls at δ 19.8 and at δ 30.1 ppm characteristic of the acetonide derivative of a *syn*-1,3-diol moiety. Thus the relative

stereochemistry of the newly created stereogenic center was unequivocally assigned as *syn* to the existing one and its absolute stereochemistry as *'R'*. Having obtained the 1,3-diol **3** that is differently functionalized at both the ends, the free hydroxyl group was protected as its silyl ether under the conventional reaction conditions to afford **5** (90%). Since the terminal olefin present in **5** was conceived as the masked carbonyl group, its dihydroxylation {OsO_4/NMO/acetone:H_2O (4:1)} and oxidative cleavage ($NaIO_4$/sat. aq. $NaHCO_3$/CH_2Cl_2/rt) gave the corresponding aldehyde which on a Wittig olefination reaction[16] {$(CF_3CH_2O)_2POCH_2COOCH_3$/KHMDS/18-Crown-6/THF/-78 °C-rt/12h}



Scheme 2. *Reagents and Conditions*: a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1h, 90%, (ii) (*R,R*)-BINOL, 4 Å MS, $Ti(O^iPr)_4$, allyltributyl tin, CH_2Cl_2, -78 to -20 °C , 12h, 75%; b) TBSCl, imidazole, DMAP, CH_2Cl_2, 3h, 90%; c) (i) HF.Py., THF, 0 °C-rt, 12h, (ii) 2,2-DMP, PPTS, CH_2Cl_2, rt, 2h, (85% over two steps); d) OsO_4, NMO, acetone: water (4:1), 12h; (e) (i) $NaIO_4$, sat. $NaHCO_3$, CH_2Cl_2, 0 °C to rt , 12h, (ii) $(CF_3CH_2O)_2POCH_2COOCH_3$, KHMDS, 18-Crown-6, dry THF, -78 °C-rt; 12h, 70%, (70% over three steps); f) DDQ, CH_2Cl_2:H_2O (19: 1), 0 °C to rt, 30 min, 90%; g) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1h, 90%, (ii) Benzylideneacetone, LHMDS, dry THF, -78 °C, 2h, 65%; h) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C-rt, 1h, 80%; i) PTSA, benzene, rt, 4h, 75%.

furnished the α,β-unsaturated ester **7** (70%, over three steps) predominantly as the (*Z*)-isomer, as characterized by ^1H and ^{13}C NMR spectroscopy. The coupling constant (J = 11.7 Hz) and the chemical shift values (δ 6.35-6.26 ppm as a multiplet and at δ 5.80 ppm as a

doublet) confirmed the (*Z*)-geometry of the olefin. Later the PMB group was deblocked (DDQ/CH_2Cl_2:H_2O/rt/0.5h) to afford compound **8** (90%).

The alcohol **8** was oxidized to aldehyde under Swern reaction conditions which on crucial aldol reaction with the *in situ* generated anion of benzylideneacetone (LHMDS/THF/-78 ^oC) furnished compound **9** (65%) as a 1:1 diastereomeric mixture. The diastereomeric mixture was taken up for the next reaction without any purification since the alcohol transforms into ketone functionality in the next step. Accordingly, the alcohol was oxidized (DMP/$NaHCO_3$/CH_2Cl_2/0 ^oC-rt/1h) to afford the diketone **10** (80%) which was earlier identified as the crucial intermediate. The diketone **10** was characterized by its spectral data. For instance, ^1H NMR spectrum revealed the protons due to characteristic methylene flanked by two ketone groups at δ 3.10-2.90 as a multiplet integrating for one proton while the other proton showed at δ 2.78-2.67 as a multiplet. The same protons were present at δ 2.89-2.64 as a multiplet in compound **9**. Later the tandem PTSA catalyzed cyclization of **10** to result in **1** was effected by the literature inspired report for the γ-pyrone ring construction.[17] Thus, **10** on exposure to PTSA in benzene at room temperature for 4h afforded the target natural product **1** (75%) through a multiple reaction set; namely silyl deprotection-tandem ring-closing reactions in an unprecedented single step. The physical and spectroscopic data of synthetic **1** is consistent with the reported values.[9,12] The HRMS spectrum displayed the $[M+Na]^+$ 333.1109, calculated 333.1102 for the molecular formula $C_{19}H_{18}O_4Na$.

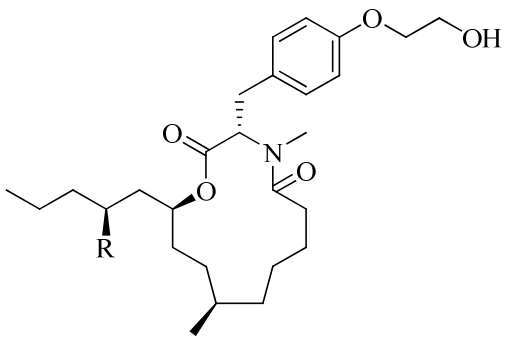
In conclusion, the total synthesis of obolactone **1** was accomplished *via* Brønsted acid mediated tandem cyclization protocol as the key reaction to realize a methylene bridged bis-dihydropyrone ring skeleton in one-pot in a highly efficient manner. This strategy may be adopted for the synthesis of similar ring-containing natural products.

Chapter II: Stereoselecive total synthesis of antifungal antibiotic PF1163A

This chapter deals with stereoselective total synthesis of PF1163A

People who are infected by HIV and those who have undergone chemotherapy for cancer are susceptible to infections caused by yeast and fungi. Most prevalently used antifungal agents like polyenes and azoles are less potent, toxic and develops resistance over a period of usage. Hence development of novel antifungal antibiotic is necessary. Recently two novel antifungal antibiotics PF1163A **11** and PF1163B **12** (Figure 2) were isolated from fermentation broth of *Penicillium sp*.[18a] Both **11** and **12** exhibit potent growth inhibitory activity against pathogenic fungal strain *Candida albicans* and were shown to

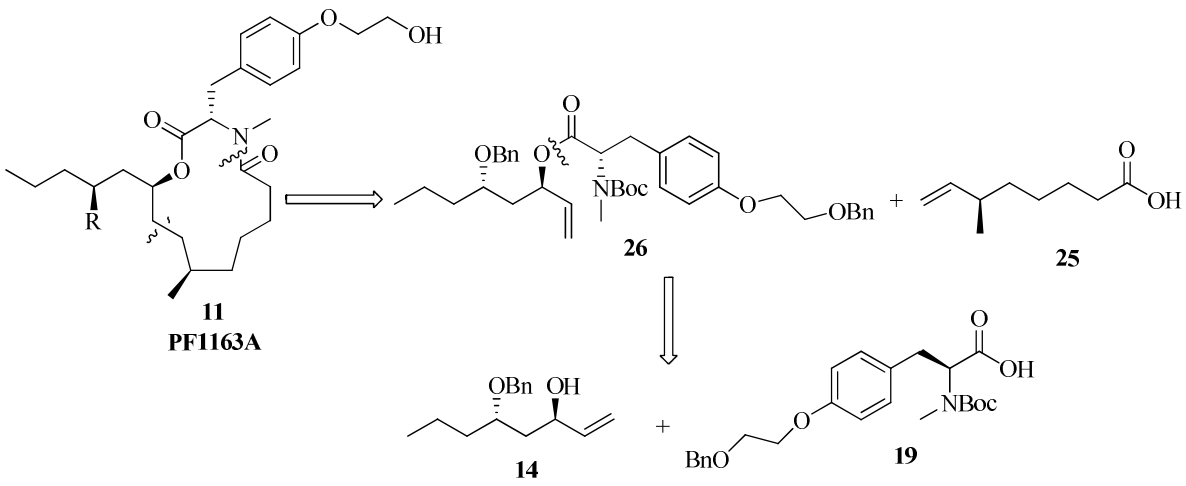
inhibit the biosynthetic pathway from lanosterol to ergosterol in *Candida albicans*, but inhibiting activity of **11** being equal to fluconazol and four folds higher than **12** (Figure 2). Sasaki *et al*[18b] elucidated structures of **11** and **12** by extensive chemical and spectroscopic analysis. The absolute structure of **11** was confirmed by its total synthesis.[19a] Unique structural features of **11** includes a 13-membered macrolide consisting of an ester and amide functional groups; 2-hydroxy ethyl derivative of *N*-methyl L-tyrosine, isolated methyl stereocentre on the macrocyclic core and an aliphatic side chain possessing one hydroxyl group. The structures of **11** and **12** are similar except for the presence of an additional hydroxyl group in the side chain of **11**, this change may be responsible for four folds higher biological activity than **12**. Attractive biological activity and our interest in the synthesis[20] of biologically active macrolide natural products inspired us to take up the synthesis of **11**. So far two syntheses[19a,b] have been reported for **11**. While in the first synthesis,[19a] asymmetric allyltitanation and esterification were the key steps and the second synthesis[19b] was accomplished by Prins cyclization and RCM protocol. Herein this chapter, total synthesis of **11** was accomplished using Keck asymmetric allylation, Sharpless kinetic resolution, regioselective epoxide-ring opening and ring-closing metathesis as the key reactions, details will be dicussed.



R = OH, PF1163A 11

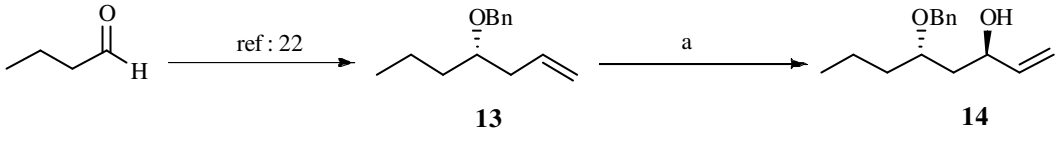
R = H, PF1163B 12

Figure 2



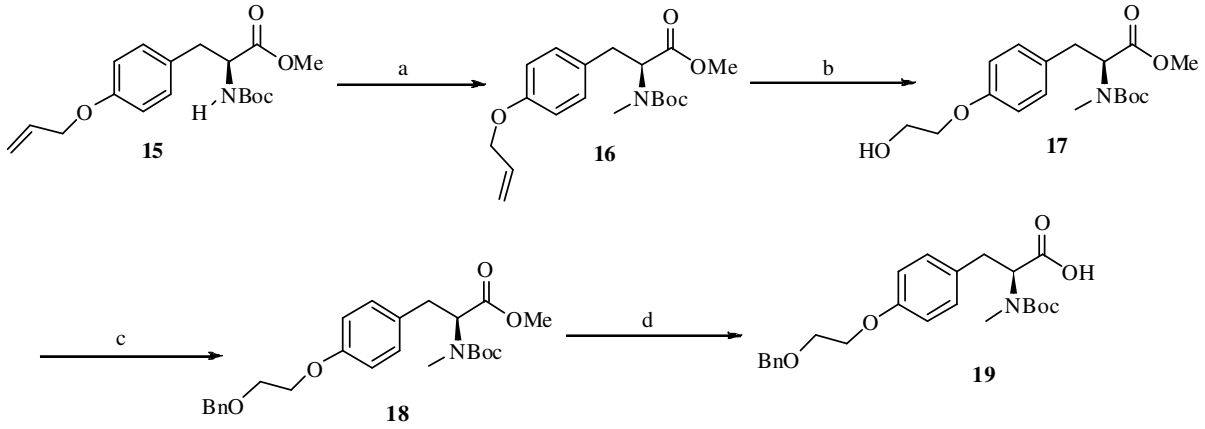
Scheme 3. Retrosynthetic analysis

From retrosynthetic analysis (Scheme 3) it could be deduced that **14**, **19** and **25** are the key building blocks. Initially, a cross-metathesis based approach between ester **26** and **25** was attempted resulting in the corresponding product. However, this approach was discontinued due to scale up problems. Alternatively, a ring-closing metathesis (RCM) approach was envisioned. Accordingly, fragment **14** identified as one of the building blocks, in turn could be visualized from compound **13** (*vide infra* Scheme 4) through a series of reactions such as oxidative cleavage of the olefin, vinylation and Sharpless kinetic resolution. Compound **13** in turn could be obtained from commercially available *n*-butyraldehyde by Keck asymmetric allylation[21] followed by further transformations as reported in the literature.[22] Synthesis of L-tyrosine derivative **19** commenced from known compound **15**.[23] To conceive the lone methyl stereocentre of **25**, the known allylic alcohol **20**[24] was chosen which upon Sharpless asymmetric epoxidation and regioselective ring-opening of 2,3-epoxy alcohol with trimethyl aluminium in an S_N2 fashion as the reaction-set and further transformations of the ensuing product would eventually lead to olefin **23**. Deprotection of TBDPS protecting group in **23** would give primary alcohol **24** which on oxidation under TEMPO and BIAB conditions furnishes the requisite carboxylic acid **25**.



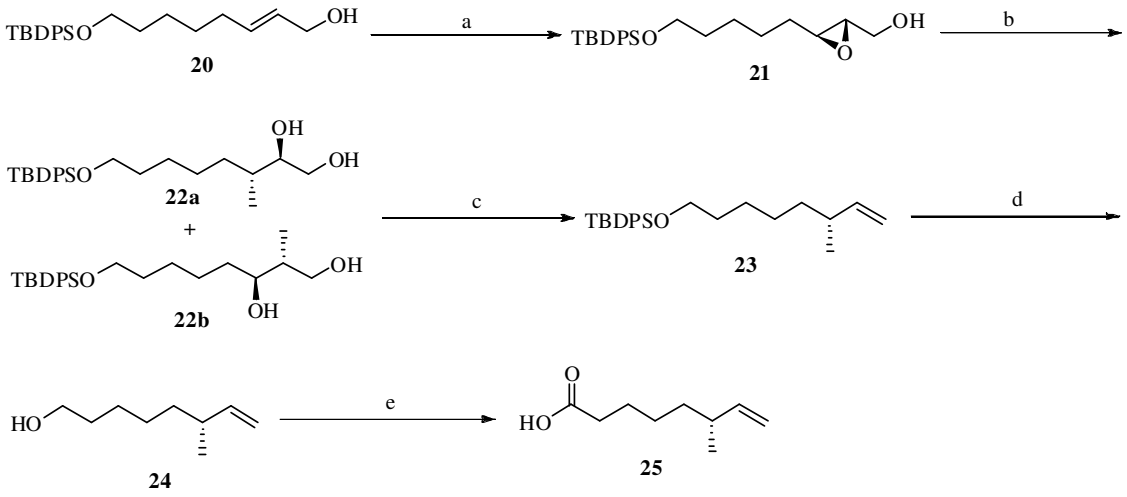
Scheme: 4. *Reagents and conditions*. (a) (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane:H_2O (3:1), rt, 4.5h; (ii) vinyl magnesium bromide, dry THF, -20 ^oC, 1h, 75%; (iii) (+)-DIPT, $Ti(O^iPr)_4$, CHP, 4Å MS, dry CH_2Cl_2, -20 ^oC, 12h, 45%.

Thus, initial focus was on the synthesis of fragment **14** (Scheme 4), from commercially available *n*-butyraldehyde. Transformation of *n*-butyraldehyde into benzyl protected homoallyl alcohol **13**[22] (it was thoroughly characterized earlier. Its ee was found to be 95%) was earlier demonstrated in our group during the synthesis of piperidine alkaloids. Taking cue, oxidative cleavage[25] {$NaIO_4/OsO_4$/2,6-lutidine/1,4-dioxane:H_2O (3:1)/rt/4.5h} of the terminal double bond in **13** afforded aldehyde, which on vinylation (vinyl magnesium bromide/dry THF/-20 ^oC/1h) gave a 1:1 diastereomeric mixture of allylic alcohol **14** (75% combined yield). Alternatively, diastereomerically pure compound **14** was obtained by Sharpless kinetic resolution[26] {(+)-DIPT/Ti(O^iPr)$_4$/CHP/4Å MS/dry CH_2Cl_2/-20 ^oC/12h/45%}.



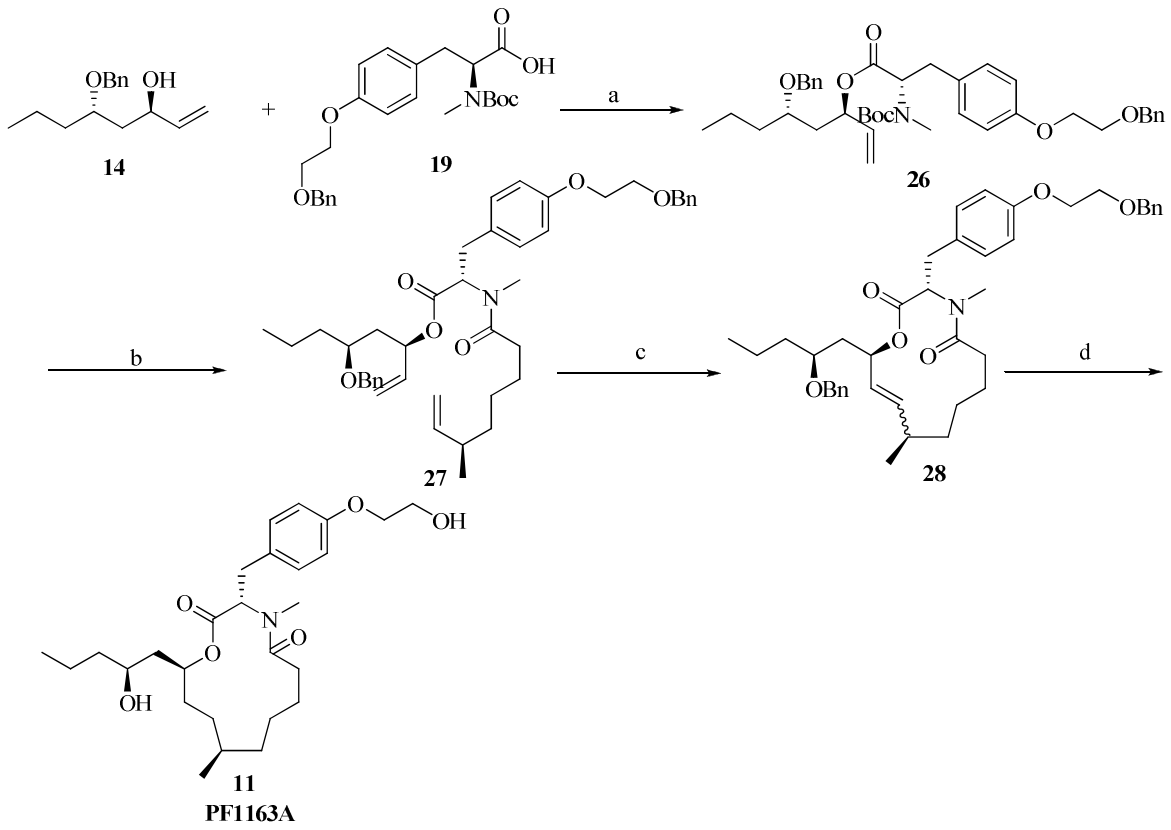
Scheme: 5. *Reagents and conditions.* (a) MeI, Ag_2O, DMF, rt, 9h, 85%; (b) (i) $NaIO_4$, OsO_4, 2,6-lutidine, 1,4-dioxane:H_2O (3:1), rt, 4h; (ii) $NaBH_4$, MeOH, 0 ^oC-rt, 1h, 80% (over two steps); (c) Benzyl bromide, Ag_2O, DMF, rt, 12h, 83%; (d) LiOH, THF:MeOH:H_2O (3:1:1), 0 ^oC-rt, 6h, 84%.

The synthesis of amino acid fragment **19** (Scheme 5) commenced from known compound *O*-allyl *N*-Boc-L-tyrosine **15**.[23] *N*-Methylation (CH_3I/Ag_2O/DMF/rt/9h) of compound **15** afforded **16** (85%). Oxidative cleavage[25] {$NaIO_4/OsO_4$/2,6-lutidine/1,4-dioxane:H_2O (3:1)/rt/4h} of olefin in compound **16** afforded aldehyde which without further purification was subjected to reduction ($NaBH_4$/MeOH/0 ^oC-rt/1h) to afford **17** (80%, over two steps). The thus obtained primary alcohol **17** was protected as its benzyl ether (BnBr/Ag_2O/DMF/rt/12h) to furnish **18** (83%). Finally, saponification of the compound **18** {LiOH/THF:MeOH:H_2O (3:1:1)/0 ^oC-rt/6h} gave **19** (84%). The spectroscopic data of **18** and **19** matched with the reported values.[27]



Scheme: 6. *Reagents and conditions.* (a) (+)-DIPT, $Ti(O^iPr)_4$, CHP, 4Å MS, dry CH_2Cl_2, -20 ^oC, 6h, 90%; (b) Me_3Al, hexane, 0 ^oC, 1h, 86%; (c) I_2, TPP, imidazole, dry CH_2Cl_2, 0 ^oC-rt, 2h, 70%; (d) TBAF, dry THF, 0 ^oC-rt, 1h, 90%; (e) TEMPO, BIAB, CH_2Cl_2:H_2O (3:1), 0 ^oC-rt, 12h, 82%.

Synthesis of fragment **25** (Scheme 6) commenced from the known allylic alcohol **20**.[24] Accordingly, Sharpless epoxidation[28] {(+)-DIPT/$Ti(O^iPr)_4$/CHP/4Å MS/dry CH_2Cl_2/-20 ^oC/6h/90%} of **20** afforded **21** and its ee was evaluated by HPLC as 88.76%. The 2,3-epoxyalcohol **21** on regioselectively[29] ring-opening reaction by the methyl nucleophile generated *in situ* from Me_3Al (Me_3Al/hexane/0 ^oC/1h) in S_N2 fashion gave a mixture of 1,2-diol (**22a**) and 1,3-diol (**22b**) (C3:C2, in a 8:2 ratio, 86% combined yield), the mixture as such was subjected to iodination (I_2/TPP/imidazole/dry CH_2Cl_2/0 ^oC-rt/2h), wherein only 1,2-diol **22a** was consumed to afford terminal olefin **23** (70%). The isomeric diols were thus purified. Olefin **23** was characterised from its spectral data. Next, desilylation (TBAF/dry THF/0 ^oC-rt/1h) of **23** furnished the corresponding primary alcohol **24** (90%). Thus obtained primary alcohol **24** was subjected to oxidation {TEMPO/BIAB/CH_2Cl_2:H_20 (3:1)/0 ^oC-rt/12h} to afford carboxylic acid **25** (82%) whose formation was substantiated by the appearance of α-methylene protons in the ^1H NMR spectrum resonating at δ 2.35 ppm (J = 7.5 Hz) as a triplet and the carbonyl signal in ^{13}C NMR appearing at δ 180.1 ppm apart from other spectral evidence.



Scheme: 7. *Reagents and conditions.* (a) DCC, DMAP, dry CH_2Cl_2, 0 ^oC-rt, 12h, 85%; (b) (i) TFA, dry CH_2Cl_2, 0 ^oC-rt, 2h; (ii) **25**, EDCI, HOBT, DIPEA, dry CH_2Cl_2, 0 ^oC-rt, 12h, 78% (over two steps); (c) 10 mol% G-II, dry CH_2Cl_2, 12h, reflux, 83%; (d) H_2, Pd-C, EtOAc, rt, 12h, 80%.

Next, esterification of **19** with alcohol **14** under DCC conditions (DCC/DMAP/dry CH_2Cl_2/0 ^oC-rt/12h) afforded ester **26** (85%). The deprotection (TFA/dry CH_2Cl_2/0 ^oC-rt/2h) of Boc group in ester **26** resulted in the corresponding *sec*-amine which without further purification was acylated with carboxylic acid **25** (EDCI/HOBT/DIPEA/dry CH_2Cl_2/0 ^oC-rt/12h) to provide diene **27** (78% over two steps). Ring-closing metathesis[30a,b] of diene **27** (10 mol% G-II/dry CH_2Cl_2/12h/reflux) afforded **28** (83%) as '*E*' and '*Z*' diastereomers (2:1). No attempts were made to separate the *E* and *Z* isomers since the isomeric status was irrelevant because of the ensuing olefinic reduction step. Accordingly, the saturation of the double bond and hydrogenolysis of the benzyl groups (H_2/Pd-C/EtOAc/rt/12h) occurred in a single step providing the target compound **11** (80%) as a colorless oil with $[\alpha]_D^{25}$ = -89.3 (*c* 0.5, MeOH) {lit.[19a] $[\alpha]_D^{25}$ = -91.0 (*c* 0.73, MeOH), lit.[19b] $[\alpha]_D^{25}$ = -88.5 (*c* 1.0, MeOH)}. The spectroscopic data of **11** was identical to the reported values.[19a,b]

Thus in conclusion, total synthesis of a novel antifungal antibiotic PF1163A **11** was accomplished and described in detail in this chapter wherein Keck asymmetric allylation,

Sharpless kinetic resolution, regioselective epoxide-ring opening, esterification and ring-closing metathesis were the key reactions.

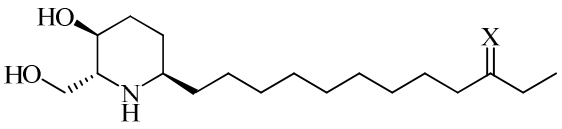
Chapter III: Diastereoselective allylation of iminium ion an easy access to 2,6-disubstituted 3-piperidinol alkaloids

This chapter is divided into two parts.

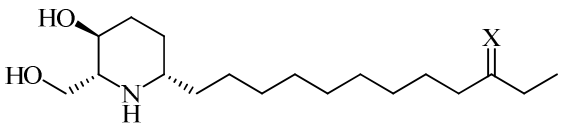
Piperidine alkaloids are very common chemical entities found in the nature abundantly and exhibit various biological activities.[31] Particularly, 2,6-disubstituted piperidines have drawn much attention in both academics and the pharmaceutical industry because they are one of the most common piperidine skeletons and are found in many pharmaceutically interesting compounds. As a consequence, numerous synthetic methods have been developed for the stereoselective synthesis of 2,6-disubstituted piperidines. In this chapter, the diastereoselective allylation of iminium ion protocol, which is an easy access to (+)-deoxoprosopinine and (+)-deoxoprosophylline, will be discussed in detail.

Section A: *This section deals with short and efficient total synthesis of (+)-deoxoprosopinine*

Prosopis alkaloids are one class among the various naturally occuring biologically active piperidine alkaloids. Some of the prosopis alkaloids are: (+)-prosopinine **30**, (+)-prosophylline **32** and their reduced analogs (+)-deoxoprosopinine **29**, and (+)-deoxoprosophylline **31** (Figure 3). These alkaloids were isolated from *Prosopis Africana*[32] and exhibit antibiotic and anaesthetic properties. Structurally, these alkaloids contain a 2,6-disubstituted 3-piperidinol skeleton bearing an aliphatic alkyl side chain. Earlier, Radha Krishna *et al* reported synthesis of some piperidine-based alkaloids.[33]



29. X = H, H, (+)-deoxoprosopinine
30. X = O, (+)-prosopinine

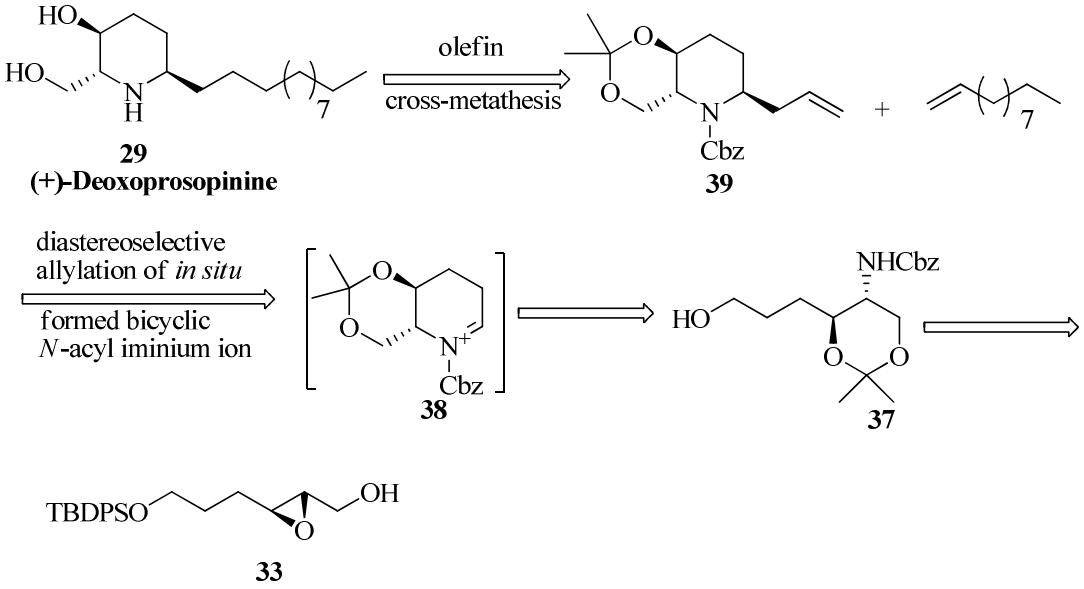


31. X = H, H, (+)-deoxoprosophylline
32. X = O, (+)-prosophylline

Figure 3. Prosopis alkaloids

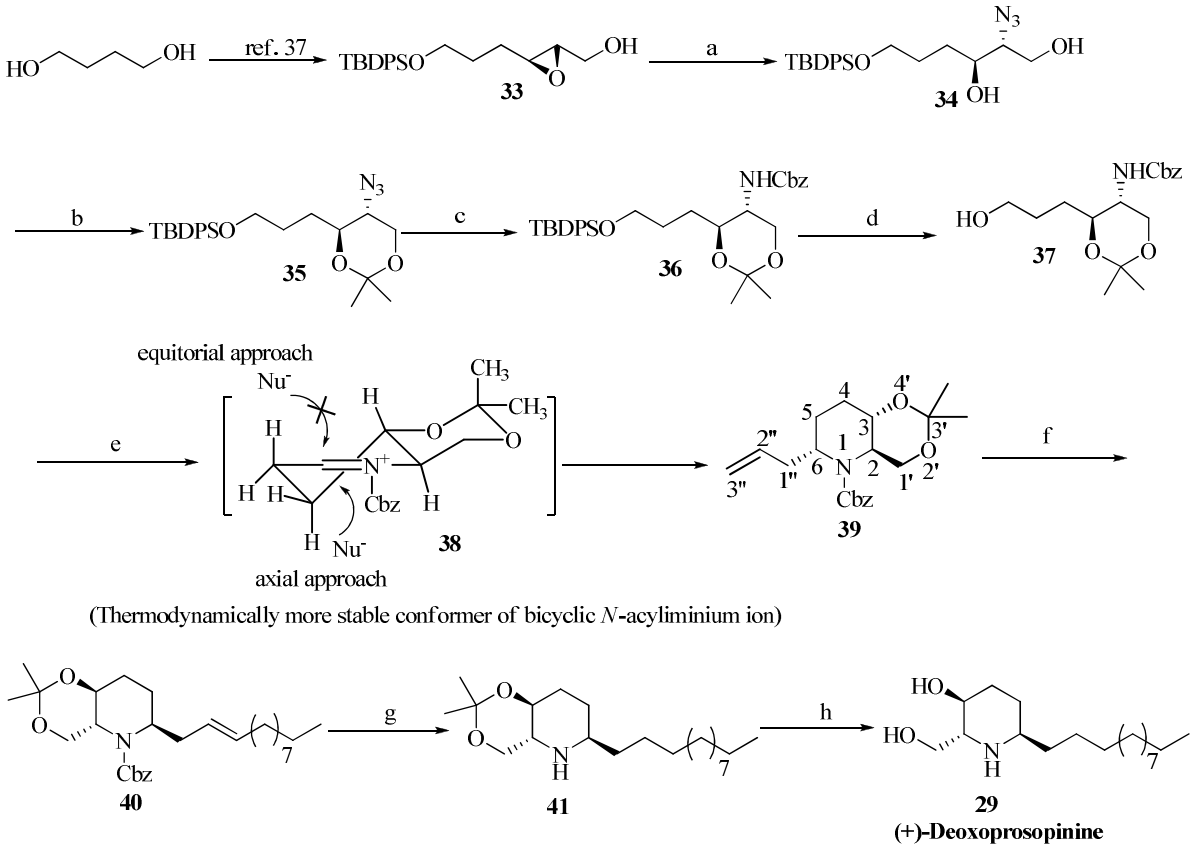
In continuation of our interest in the synthesis of piperidine alkaloids, the synthesis of (+)-deoxoprosopinine **29** was taken up and the results are described in this chapter. Though several syntheses[34] have been reported for **29**, a strategically different route was

envisioned. The synthetic strategy involves Miyashita endoselective epoxide-ring opening, more importantly exploitation of diastereoselective allylation of *in situ* formed bicyclic *N*-acyl iminium ion to construct 6-allyl piperidine derivative **39** and its subsequent transformation into the target molecule **29**.



Scheme 8. Retrosynthetic analysis

There were several reports concerning diastereoselective allylation of *N*-acyl iminium ion.[35] Some of them account for the formation of *cis*-2,6-disubstituted piperidines[35a,b] and few evidence the formation of *trans*-2,6-disubstituted piperidines.[35d-f] In this section total synthesis of **29** (Scheme 8) by utilizing a one pot oxidation of **37** and diastereoselective allylation of the *in situ* formed bicyclic *N*-acyl iminium ion[35c-e] **38** to furnish the allyl piperidine ring system **39** followed by its olefin-cross metathesis[36] with 1-undecene the other olefinic partner, as the key steps en route to afford the target molecule will be discussed. Amino alcohol **37** in turn could be derived from epoxy alcohol **33** by the Miyashita's endoselective epoxide ring-opening reaction with azide nucleophile and its subsequent conversions. Thus, it is evident that *trans*-2,6-disubstituted piperidine derivative **39** is the key building block in the synthesis of (+)-deoxoprosopinine **29**.



Scheme 9. *Reagents and conditions*: a) (i) NaN_3, $B(OMe)_3$, DMF, 60 °C, 3h, 78%; (ii) $NaIO_4$, aq. sat. $NaHCO_3$, THF:H_2O (4:1), 1h; b) 2,2 DMP, PTSA, dry CH_2Cl_2, 0 °C-rt, 2h, 92%; c) (i) H_2, Pd/C, EtOAc, 6h, (ii) Cbz-Cl, $NaHCO_3$, EtOAc:H_2O (1:1), rt, 2h, 83%; d) TBAF, dry THF, 0 °C-rt, 1h, 90%; e) (i) Dess-Martin periodinane, dry CH_2Cl_2, rt, 1h (ii) TFA, -40 °C, 20 mins. (iii) allyltrimethylsilane, -40 °C, 1.5h, 70%; f) G-II, 1-undecene, dry CH_2Cl_2, reflux, 12h, 90%; g) H_2, Pd/C, EtOAc, 7h, 90%; h) cat. PTSA, MeOH, 0.5h, 89%.

Accordingly, a short and efficient total synthesis of **29** was described in eight steps from known chiral epoxy alcohol **33**[37] in a 27% overall yield (Scheme 9). The chiral epoxy alcohol **33** upon highly regioselective ring-opening reaction from C-2 position by the azide nucleophile afforded **34** (78%) as major isomer (C2:C3, 9:1), minor 1,2-diol formed due to C3 opening was removed by the $NaIO_4$ mediated oxidative cleavage. The ring-opening reaction was carried out by utilizing Miyashita[38] endoselective epoxide-opening protocol (NaN_3/$B(OMe)_3$/DMF/60 °C/3h). The thus obtained diol **34** was protected as its acetonide derivative **35** (92%) using 2,2-dimethoxy propane and cat. PTSA in anhydrous CH_2Cl_2. Subsequently, the azide functionality in compound **35** was converted to its benzyl carbamate by catalytic hydrogenation (H_2/Pd-C/EtOAC/rt/6h), followed by the treatment of resulting amine with benzyl chloroformate and sodium bicarbonate in EtOAc:H_2O (1:1 ratio) solvent system gave the corresponding carbamate **36** (83% over 2-steps). Later, the TBDPS group was deprotected (TBAF/dry THF/0 °C-rt/1h) to afford the primary alcohol **37** (90%) and it was oxidized under Dess-Martin conditions to afford an aldehyde which

without further purification on exposure to TFA at -40 ^{o}C for 20 min. was converted to the bicyclic *N*-acyl iminium ion[35c-e] *in situ*. The thus formed iminium ion **38** was diastereoselectively trapped by π-type nucleophile *viz*. allyltrimethylsilane to afford the allyl piperidine **39** (70%) as an exclusive *trans* adduct.

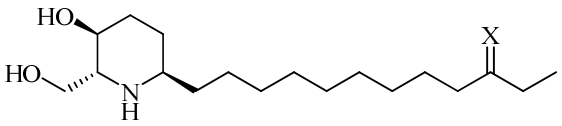
The structure and stereochemistry of allyl piperidine **39** were thoroughly characterized by extensive NMR experiments including 2-D double quantum filtered correlation spectroscopy (DQF-COSY), nuclear Overhauser effect spectroscopy (NOESY) and HSQC. The strong NOE cross peaks observed between H2/H1", H3/H1', H3/CH_3 (acetonide methyl) and H6/H2" protons are indicative of their relative spatial orientation; their relationship with one another and their respective planar arrangement. Thus the relative and absolute stereochemistry of C2 and C6 was unequivocally proved. Additionally, the coupling constant between H2 and H3 $J_{H2\text{-}H3}$=10.2 Hz confirms that these protons are trans to each other. Further, the exclusive formation of the *trans*-isomer may be rationalized due to stereoeletronically controlled addition of π-type nucleophile (from allyltrimethylsilane) axially on thermodynamically stable conformation of bicyclic *N*-acyliminium ion[35d,e] led to **39**. The equitorial approach of nucleophile is ruled out based on fact that nucleophile experience more steric repulsion from Cbz group due to $A^{(1,2)}$ strain. The characteristic H2 appeared at δ 3.21 ppm as a doublet of a triplet (J = 6.1, 10.2 Hz) and H6 proton appeared at 4.52-4.40 as a multiplet and HRMS (*m/z*) $[M+Na]^+$ calcd. 368.1837, found 368.1834 for $C_{20}H_{27}NO_4Na$. The presence of terminal olefinic protons substantiated the structure assigned. Ally piperidine **39** constitutes the key building block in the synthesis of **29**. Later, the terminal olefin in **39** was utilized in olefin cross-metathesis, as means of C-C bond formation, with 1-undecene under standard conditions {G-II catalyst (10 mol%)/dry CH_2Cl_2/reflux/12h} to afford compound **40**. During this reaction though no homodimerisation of **39** was observed, 1-undecene however underwent dimerization. Consequently, in order to effect the complete conversion of **39** and obtain an optimum yield of the desired cross-product **40** (90%), it was found necessary to use 3.0 equivalents of 1-undecene. The ^{1}H NMR spectrum of **40** revealed the olefinic protons at δ 5.58-5.42 and at δ 5.32-5.21 ppm as multiplets, apart from other characteristic peaks pertaining to the aliphatic carbon chain. Having obtained compound **40,** next its extrapolation to the target molecule **29** was all that remaining. Accordingly, deprotection of Cbz-group and saturation of double bond took place in one-pot *via* the catalytic hydrogenation (H_2/Pd-C/EtOAc/rt/7h) of **40** to furnish the acetonide protected (+)-deoxoprosopinine **41** which was purified by column

chromatography and characterized. Later the same was treated with cat. PTSA in methanol to afford (+)-**29** (89%). The physical and spectroscopic data of synthetic **29** is consistent with the reported values.[34] The HRMS spectrum displayed the $[M+H]^+$ 300.2911, calculated 300.2902 for the molecular formula $C_{18}H_{38}NO_2$.

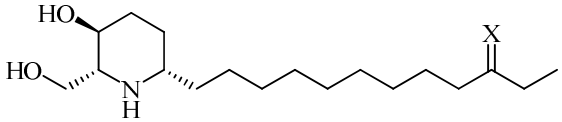
In summary, herein a short and efficient total synthesis of (+)-deoxoprosopinine **29** was accomplished *via* the Miyashita endoselective epoxide ring-opening reaction, diastereoselective allylation of the *in situ* formed bicyclic *N*-acyl iminium ion, Grubbs olefin cross-metathesis reaction as key reactions. This strategy could be adopted for the synthesis of related natural products.

Section B: *This section deals with studies towards total synthesis of (+)-deoxoprosophylline*

(+)-Deoxoprosophylline **31** is one of the prosopis alkaloids, isolated from *Prosopis Africana*[32] along with other prosopris alkaloids such as (+)-deoxoprosopinine **29,** (+)-prosopinine **30** and (+)-prosophylline **32** (Figure 4). This alkaloid exhibits antibiotic and anaesthetic properties. Though several syntheses[39] have been reported for **31**, a strategically different route was envisioned which mainly involves diastereoselective allylation of *in situ* formed *N*-acyl iminium ion[35a,b,c] to construct 6-allyl piperidine derivative **46**, followed by its olefin-cross metathesis[36] with 1-undecene the other olefinic partner, as the key steps.

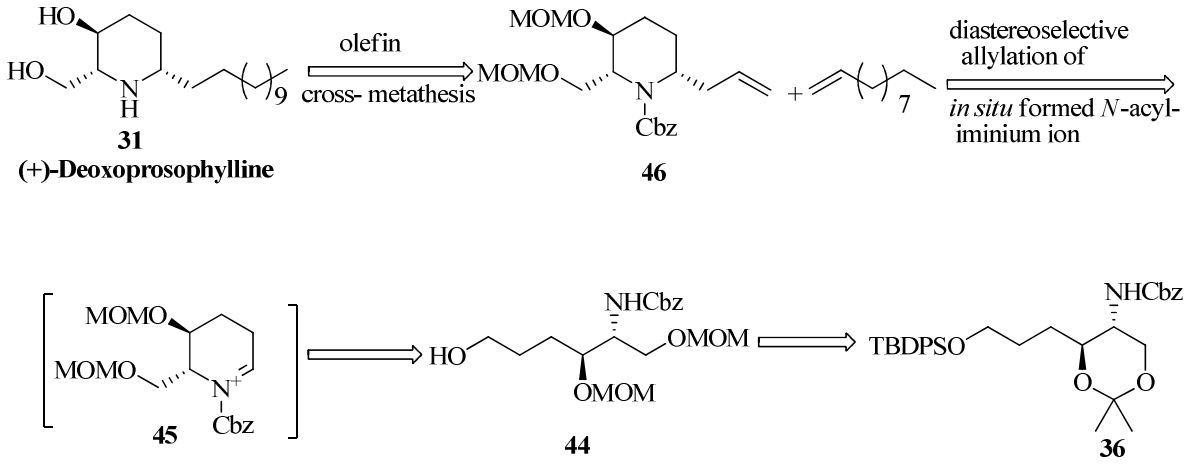


29. X = H, H, (+)-deoxoprosopinine
30. X = O, (+)-prosopinine



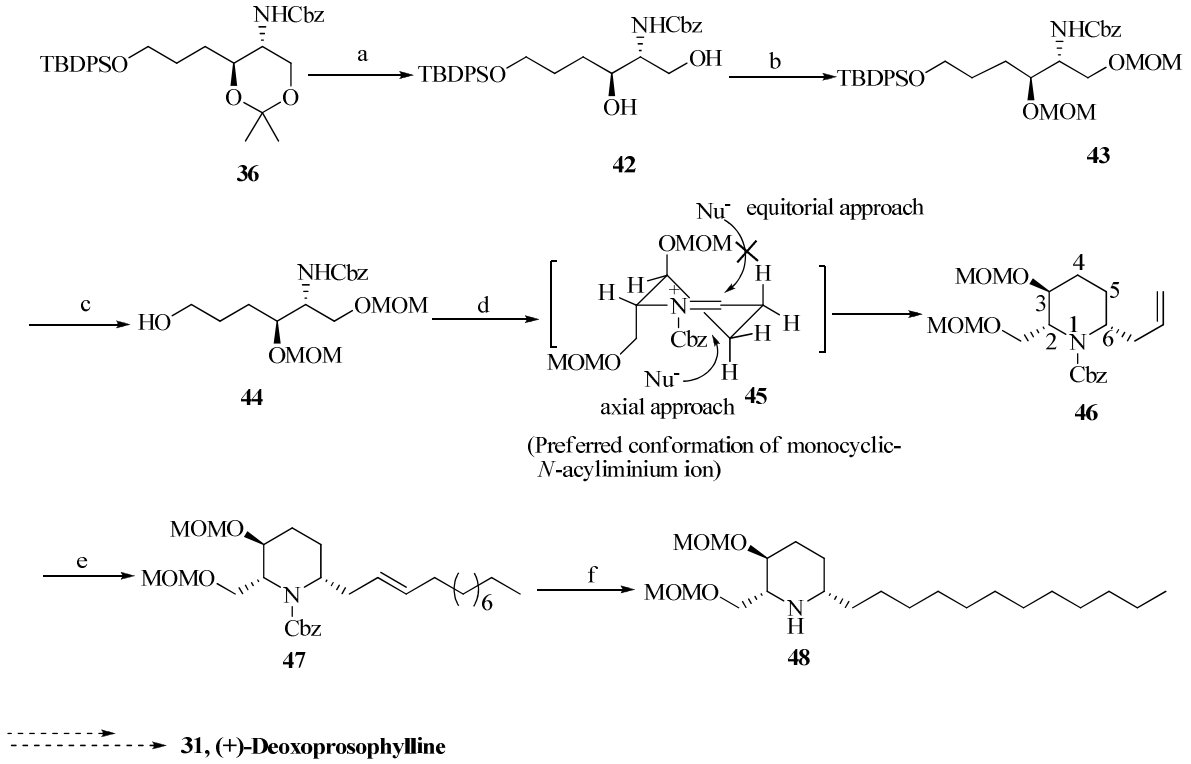
31. X = H, H, (+)-deoxoprosophylline
32. X = O, (+)-prosophylline

Figure 4. Prosopis alkaloids



Scheme 10. Retrosynthetic analysis

The studies towards total synthesis of **31** was described (Scheme 10) by utilizing a one pot oxidation of **44** and diastereoselective allylation of the *in situ* formed *N*-acyl iminium ion **45** to furnish the allyl piperidine ring system **46** followed by its olefin-cross metathesis with 1-undecene the other olefinic partner, as the key steps en route to afford the target molecule. Amino alcohol **44** in turn could be derived from compound **36**. Thus, it is evident that *cis*-2,6-disubstituted piperidine derivative **46** is the key building block in the synthesis of (+)-deoxoprosophylline **31** (Scheme 10).



Scheme 11. a) $CuCl_2$,CH_3CN, 0 ºC-rt, 0.5h, 89%; b) MOM-Cl, DIPEA, dry CH_2Cl_2, 0 ºC-rt, 6h, 88%; (c) TBAF, THF, 0 ºC-rt, 1h, 92%; (d) (i) Dess-Martin periodinane, dry CH_2Cl_2, rt, 1h, (ii) TFA, -40 ºC, 20 mins., (iii) allyltrimethylsilane, -40 ºC, 1.5h, 76%; (e) G-II, 1-undecene, dry CH_2Cl_2, reflux, 12h, 83%; (f) H_2, Pd-C, EtOAc, rt, 8h, 87%.

Accordingly synthesis began from the compound **36**[40] (Scheme 11). The acetonide protecting group in **36** was selectively deprotected in presence of other acid sensitive protecting group such as TBDPS. When the compound **36** was treated with $CuCl_2$ in acetonitrile (CH_3CN) at 0 ^oC for 0.5h led to the formation of compound **42** (89%). The selection of appropriate protecting group is important as it must be tolerant to reagents in subsequent steps, hence MOM protection was chosen to protect hydroxyl groups in compound **42**. To achieve that, compound **42** was treated with MOM-Cl (methoxy methylene chloride) under basic conditions using DIPEA (*N*,*N*-diisopropylethylamine) in dry CH_2Cl_2 at 0 ^oC-rt for 6h afforded compound **43** (88%). Desilylation of compound **43** (TBAF/dry THF/0 ^oC-rt/1h) afforded compound **44** (92%). It is precursor for the the synthesis of key building block allyl piperidine derivative **46.** The transformation from compound **44** to allyl piperidine derivative **46** is key step and multiple steps took place in one pot. Initially, primary alcohol **44** was subjected to oxidation using Dess-Martin periodinane in dry CH_2Cl_2 solvent at room temperature, when tlc showed that alcohol was completely transformed into aldehyde, triflouroacetic acid (TFA) was added to the reaction mixture at -40 ^oC, to initiate the formation of iminium ion *in situ*. The iminium ion formed in this case is monocyclic in nature, hence it's preference over confirmation is dictated by $A^{(1,2)}$ strain (allylic strain), the preferred confirmation of *N*-acyliminium ion **45** was shown in Scheme 11. The thus formed iminium ion was diastereoselectively trapped by π-type nucleophile *viz* allyltrimethylsilane to afford the allyl piperidine **46** (76%) as an exclusive *cis* adduct (Scheme 11). The formation of the *cis*-isomer may be rationalized due to stereoeletronically controlled addition of π-type nucleophile (from allyltrimethylsilane) axially on conformation **45** of monocyclic *N*-acyliminium ion[35a,b,c] led to **46**. The equitorial approach of nucleophile is ruled out based on fact that nucleophile experience more steric repulsion from Cbz group due to $A^{(1,2)}$ strain. The structure of compound **46** was thoroughly analysed by spectroscopic analysis but relative stereochemistry at newly generated stereogenic centre (C_6) was not assigned due to broad signals in ^1H NMR, hence this study was performed on subsequent fragment.

The terminal olefin in **46** was utilized in olefin cross-metathesis,[36] as means of C-C bond formation, with 1-undecene under standard conditions {G-II catalyst (10 mol%)/dry CH_2Cl_2/reflux/12h} to afford compound **47** (Scheme 11). During this reaction though no homodimerisation of **46** was observed, 1-undecene however underwent dimerization. Consequently, in order to effect the complete conversion of **46** and obtain an optimum yield

of the desired cross-product **47** (83%), it was found necessary to use 3.0 equivalents of 1-undecene.

Deprotection of Cbz-group and saturation of double bond took place in one-pot *via* the catalytic hydrogenation (H_2/Pd-C/EtOAc/rt/8h) of **47** to furnish compound **48**(87%) (Scheme 11). The ^{1}H NMR spectrum of **48** revealed that disappearance of protons pertaining to benzyl and olefinic protons, is significant evidence to show that reaction proceeded successfully. The compound was thoroughly characterized by extensive NMR experiments including 2-D double quantum filtered correlation spectroscopy (DQF-COSY) and nuclear Overhauser effect spectroscopy (NOESY). The strong NOE cross peaks observed between H2/H6 protons are indicative of their relative spatial orientation. Thus the relative and absolute stereochemistry of C2 and C6 was unequivocally proved. Additionally, the coupling constant between H2 and H3 $J_{H2\text{-}H3}$ = 9.4 Hz confirms that these protons are *trans* to each other. The characteristic H2 appeared at δ 2.77-2.72 ppm as a multiplet and H6 proton appeared at δ 2.52-2.46 as a multiplet. The compound **48** was also confirmed by mass spectral analysis, HRMS (*m/z*) $[M+Na]^+$ calcd. 388.3421. Found 388.3433for $C_{22}H_{46}NO_4$.

In conclusion, herein studies towards the total synthesis of (+)-deoxoprosophylline **31** was described *via* diastereoselective allylation of the *in situ* formed *N*-acyl iminium and Grubbs olefin cross-metathesis reaction.

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