Chapter 2: Synthetic studies toward \textit{trans-}(2R,3R)-3-hydroxypipeolic acid and (−)-swainsonine

Section 1: Introduction of \textit{trans-}(2R,3R)-3-hydroxypipeolic acid
2.1.1 Introduction

Functionalized piperidines especially polyhydroxylated ones represent one of the most ubiquitous skeleton found in varied natural and non-natural compounds and have demonstrated activity against a wide range of biochemical targets in diverse therapeutic.¹

An important subclass of polyhydroxypiperidines is composed of natural products containing a 3-hydroxy piperidine scaffold. The 3-hydroxypiperidine is one of the most privileged scaffolds, which is present in a variety of natural products. The representative example is 3-hydroxypipecolic acid ¹ which is a non-proteinogenic cyclic α-amino acid. It is used in the preparation of conformationally restricted peptides and ligand binding studies.² The cis-isomer of ¹ is a structural unit of the antitumor antibiotic tetrazomine ³. The carboxyl group reduced analogues of ¹, namely 3-hydroxy-2-hydroxymethylpiperidine ², are known as fagomine congeners which are promising glycosyltransferases and glycosidase inhibitors.⁴ It is also an important scaffold present in many natural as well as synthetic biologically active molecules having

![Figure 1](image-url)
potent biological activities like (−)-prosopinene 4 and (−)-prosophylline 5 which act as antibiotic and anaesthetic, 5 (+)-febrifugine 6 and (+)-isofebrifugine 7 which show antimalarial activities. 6 (−)-Swainsonine 8 which also contains this very significant 3-hydroxy piperidine skeleton was found to be an effective inhibitor of both lysosomal α-mannosidase, and mannosidase II along with antimestastic, antitumor-proliferative, anticancer, immunoregulating activity and attracted the attention of medicinal chemists due to its pharmacological properties and reached phase I clinical trials as an anticancer drug (Figure 1). 7

2.1.2 Literature review

The wide applicability and occurrence of this scaffold 1 attracted attention of many organic chemists towards its synthesis. The reported routes for the synthesis of 1 and 2 are broadly divided into two groups, (a) Synthesis using chiral pool approach and (b) synthesis using chiral induction. Some of the important syntheses in each class have been described here.

(a) Syntheses using chiral pool approach:

Casiraghi’s approach

Casiraghi et al. (Scheme 1) developed a novel diastereoselective addition of silyloxy furan TBSOF and imines derived from L and D glyceraldehydes with excellent diaste-reomeric excess and exploited it for the synthesis of both the enantiomers of 3-hydroxypipeolic acid 1. 8

![Scheme 1](image-url)
Thus, the 2-silyloxyfuran 9 and imine 10 were coupled to provide butenolide amine 11 and 12 in the ratio 9:1. Butenolide amine 11 was subjected to hydrogenation followed by treatment with DBU to provide amide 13. Amide 13 was reduced using LAH, AlCl₃ to provide aminol acetate 14 which on subsequent transformations was converted to 3-hydroxyxipipeolic acid 1. The enantiomer of 1 was also prepared starting from D-glyceraldehyde.

**Zhu’s approach**

Zhu *et al.* synthesized enantiomer of 3-hydroxyxipipeolic acid 1 starting from amino alcohol 15 derived from serine (Scheme 2). Amino alcohol 14 was oxidized to aldehyde and subjected to reaction with Grignard reagent 16 to obtain anti amino alcohol 17 as a major product which was exploited for the synthesis of (2R,3R)-2. Protected amino alcohol 17 was subjected to hydrogenation and subsequently for Boc protection to provide diol 18. The primary alcohol in diol 18 was protected with TBDPS group selectively and then secondary alcohol with MOM, then the TBDPS group was deprotected, and the resulting alcohol was subjected to oxidation and subsequently MOM group was deprotected to provide (2R,3R)- 3-hydroxyxipiperolic acid 1.⁹

**Datta’s approach**

Datta *et al.* synthesized *ent-*1 starting from D-serine 20 (Scheme 3), using diastereoselective reduction of ketone and reductive cyclization as the key steps. They prepared Weinreb amide 21 from 20 by known procedure.¹⁰ Weinreb amide 21 on reaction with 22 forms ketone which was reduced using zinc borohydride along with cerium chloride to provide alcohol 23. The acetonide deprotection of 23 and subsequent protection of diol with TBS provided aminol 24. Aminol 24 was subjected to dihydroxyla-
tion followed by cleavage of diol using NaIO$_4$ followed by reduction and deprotection to furnish 25. Piperidine derivative 25 upon oxidation and deprotection resulted in to the formation of hydrochloride salt of 3-hydroxypipeolic acid ent-1.

Chiou’s approach

Chiou et al. synthesized cis and trans 3-hydroxypipeolic acid starting from Garner’s aldehyde employing diastereoselective Grignard reaction and Rh catalyzed cyclohydrocarbonylation (Scheme 4). Nucleophilic addition of vinyl magnesium bromide on aldehyde 26 furnished diastereomeric mixture of alcohol, which was protected with benzyl bromide to give benzyl ether 27. Compound 27 was subjected to acetonide de-protection to provide mixture of alcohols 28 and 29, which were separated. Alcohol 28 was subjected to cyclohydrocarbonylation followed by reduction to provide piperidine alcohol 30, which was further explored to (2R,3R)-3-hydroxypipeolic acid. Similarly the alcohol 29 was explored for the synthesis of cis 3-hydroxypipeolic acid.$^{11}$
Vankar’s approach

Vankar et al. (Scheme 5) completed formal synthesis of pipecolic acid along with deoxoprosophylline starting from D-glycal by taking advantage of Perlin hydrolysis, chemoselective saturation of olefins and reductive amination as the key steps. D-Glycols 32 and 33 were subjected to Perlin hydrolysis to provide unsaturated aldehydes 34 and 35 respectively, which were subjected to reduction followed by hydrogenation to furnish diols 36 and 37. Diols 36 and 37 on mesylation and subsequent treatment with benzyl amine provided piperidines 38 and 39, which on hydrogenation and Boc protection gave diols 40 and 41 respectively.
(b) Synthesis using chiral induction:

**Takahata’s approach**

Takahata *et al.* reported synthesis of 1 using RCM and enzymatic resolution as the key steps (Scheme 6). Ester 42 was treated with LiHMDS and then with acrolein to provide di-allyl compound 43, which was subsequently subjected to RCM reaction to furnish a mixture of piperidines 44 and 45. The major piperidine derivative 44 on enzymatic resolution gave acetate 46 and alcohol 47 with excellent ee. The acetate ester 46 on hydrogenation followed by acidic hydrolysis provided 3-hydroxypipeolic acid 1.13

![Scheme 6](image)

**Couty’s approach**

Couty *et al.* used diastereoselective reduction of ketone and stereoselective addition of cyanide as key steps in their route for the synthesis of 1 (Scheme 7).14 Synthesis was carried out according to the sequence of steps shown in Scheme 9. The hemiaminal acid 50 was prepared from 48 in there steps. Acid 50 was converted to Wienreb amide 51 and subsequently treated with lithium acetalide to provide ketone and the resulting ketone was reduced to furnish alcohol 52. Alcohol 52 was protected as benzyl ether, the triple bond was reduced using LAH followed by TBS deprotection, mesylation and cyclization to give bicyclic compound 54. Nucleophilic addition on 54 with cyanide anion followed by hydrolysis and hydrogenation resulted in to formation of 3-hydroxypipeolic acid.
Williams’s approach

Williams et al. utilized commercially available lactone 56 for the synthesis of 1 using diastereoselective aldol condensation between 56 and aldehyde 57 to provide alcohol 58. Ozonolysis of the olefin 58 furnished aldehyde 59, which on mild catalytic hydrogenation afforded bicyclic compound 60. Finally 60 on hydrogenation on carbon black furnished (2R,3R)-3-hydroxypipecolic acid. Similarly (2S,3S)-3-hydroxypipecolic acid was synthesized using enantiomer of 56 as the starting material (Scheme 8).15

Corey’s approach

Corey et al. developed a novel method for the preparation β-hydroxy-α-amino acids by aldol condensation between various aldehydes and imine 62 catalyzed by cinchona derived chiral catalyst. Thus, the aldol condensation between aldehyde 61 and silyl-
nol ether 62 gave a mixture of amino alcohols 63 and 64 in the ratio 1:1. The method was exploited for the synthesis of cis as well as trans 3-hydroxypipeolic acid (Scheme 9).

The mixture of amino alcohols 63 and 64 was treated with sodium bicarbonate to provide a mixture of piperidine derivatives and separation on column chromatography gave pure diastereomeric piperidine alcohols 66 and 67. The piperidine derivatives 66 and 67 were treated with TFA to provide (2S,3R)-3-hydroxypipeolic acid 68 and (2S,3S)-3-hydroxy piperolic acid 1 respectively.

**Genêt’s approach**

Genêt et al. reported synthesis of 3-hydroxypipeolic acid starting from keto ester 69, employing chiral reduction of ketone and chiral amination as the key steps (Scheme 10). Keto ester 69 on reduction using Ru-BINAP catalyst furnished hydroxy ester 70, which was subjected to α-amination to provide aminol 71. The aminol 71 was protected with TBS and subsequently subjected to ozonolysis followed by mesylation of resulting alcohol to give 72. The mesylate 72 on acidification, treatment with Raney Ni and triethylamine provided piperidine derivative 73 which was subjected to TBS deprotection and ester hydrolysis to give (2R, 3R)-3-hydroxy piperolic acid 1.
Pradeep Kumar's approach

Pradeep Kumar et al. used Sharpless chiral dihydroxylation as a key step in the synthesis of 3-hydroxy pipecolic acid ent-1 starting from butane diol 74 (Scheme 11).18

Diol 74 was protected selectively, oxidized and subsequently subjected to Wittig reaction to give unsaturated ester 75. Unsaturated ester 75 was subjected to Sharpless dihydroxylation and resulting diol was protected as a sulfate 76. Sulfate 76 was opened with sodium azide, which on reduction followed by Boc protection provided amino-
diol 77. The diol 77 on selective mesylation gave piperidine 78, which on acid hydrolysis followed by Boc deprotection furnished 3-hydroxypicolic acid ent-1.

**Pradeep Kumar’s 2nd approach**

Pradeep Kumar et al. (Scheme 12) achieved formal synthesis of 1 starting from same starting material as in Scheme 11. The mono-PMB protection of 74, followed by oxidation of resulting alcohol and Wittig reaction gave unsaturated ester 75. The ester functionality in 75 was reduced using DIBAL-H, followed by asymmetric dihydroxylation employing Sharpless dihydroxylation to furnish triol 79. The 1,3-acetal protection was carried out to provide 80 followed by mesylation and subsequent reaction with sodium azide to provide azide 81.

![Scheme 12](image)

The compound 81 was subjected to p-methoxybenzyl ether deprotection and the resulting hydroxy compound was mesylated and subsequently subjected to hydrogenation to provide piperidine diol ent-40.

The authors prepared 82 by an alternate route which involved reduction of ester 75 with DIBAL-H followed by Sharpless epoxidation of the resulting allyl alcohol to
provide epoxy alcohol $82$. The alcohol moiety in $82$ was protected as its TBS derivative followed by PMB ether deprotection and mesylation to give mesylate $83$. The mesyl group in $83$ was replaced with azide followed by reduction of azide to furnish the diol $\textit{ent-40}$.$^{19}$

**Jung’s approach**

Jung et al. reported synthesis of $\textit{ent-1}$ starting from known diol $84$ (Scheme 13). Diol $84$ was protected as dibenzyl ether $85$ and further reacted with chlorosulfonyl isocyanate (CSI) followed by treatment with base to provide amino alcohol $86$. Amine in $86$ was allylated followed by RCM reaction to furnish piperidine derivative $87$. Olefin in $87$ was reduced using PtO$_2$ as the catalyst followed by oxidation of aryl ring by Ru catalyst and acidification to furnish (2$S$,3$S$)-3-hydroxypipeolic acid $\textit{ent-1}$.$^{20,21}$

**Riera’s approach**

Riera et al. started synthesis of (2$R$,3$R$)-3-hydroxypipeolic acid from epoxide $88$ which in turn was prepared by Sharpless epoxidation (Scheme 14). Epoxide $88$ was intramolecularly opened at C-2 by nitrogen using benzyl isocyanate to provide cyclic carbamate $89$. Cyclic carbamate $89$ was deprotected under basic condition and the resulting diol was protected as its TBS derivative. The olefin $90$ was subjected to hydroboration using 9-BBN followed by oxidation to furnish alcohol $91$. The N-benzyl in $91$ was deprotected under hydrogenation conditions followed by protection with Boc. Subsequently alcohol was mesylated followed by treatment with base to furnish piperidine derivative $92$. Selective primary OTBS ether deprotection was carried out using PTSA followed by oxidation using Ru catalyst and acidification to give hydrochloride salt of (2$R$,3$R$)-3-hydroxypipeolic acid $1$.$^{22}$
Wang’s approach

Wang et al. (Scheme 15) developed a Pinacol type reductive coupling between aldehyde 93 and sulfinyl imine 94 with excellent ee and exploited it for the synthesis of ent-1. The removal of the sulfinyl auxiliary followed by selective N-protection with Boc₂O afforded carbamate 95. The pivalyl group in 95 was deprotected and the resulting alcohol was converted into its mesyl derivative followed by treatment with base to furnish piperidine derivative 97. The benzyl group in 97 was deprotected under hydrogenation conditions followed by oxidation of alcohol and acidification to give final product 3-hydroxypipeolic acid ent-1.
Charette’s approach

Charette et al. reported the formal synthesis of 3-hydroxypicolinic acid *ent*-1 using a diastereoselective addition of phenyl magnesium bromide on *N*-pyridinium salt 99 (Scheme 16). The dihydropyridine derivative 100 was subjected to (4+2) cycloaddition with oxygen followed by treatment with aluminum hydride to furnish piperidine derivative 102. The protection of amine as well as alcohol gave 103 which on hydrogenation led to known intermediate 104.24

![Scheme 16]

Chavan’s approach

This group has recently reported the enantioselective synthesis of 3-hydroxypicolinic acid *ent*-1 by Sharpless dihydroxylation as a key step starting from commercially available starting material *cis*-2-butene-1, 4-diol 105 (Scheme 17). The *cis*-2-butene-1, 4-diol 105 was converted into *γ*,*δ*-unsaturated ester 106 by known method reported by this group. The ester 106 was subjected to Sharpless asymmetric dihydroxylation to provide lactone 107. The hydroxy group in lactone 107 was mesylated followed by replacement with azide to give azido lactone 108 which on hydrogenation gave lactam 109. Lactam 109 was reduced to give amine followed by protection with Boc₂O to furnish hydroxy piperidine 110. Protection of hydroxy group in 110 as its TBS derivative followed by benzyl deprotection gave piperidine alcohol 111. Alcohol in 111 was
oxidized to acid using Ru catalyst followed by acidification to furnish hydrochloride salt of ent-1.25

Chavan’s 2nd approach

Yet another synthetic strategy for (2S,3S)-3-hydroxypicolic acid ent-1 as shown in Scheme 18 was reported by the same group using Mitsunobu reaction and kinetically controlled butenolide formation as the key steps. The C-2 and C-3 chiral centers in ent-1 were fixed using the natural chirality in L-(+)-tartaric acid. The Z-alkene 114 was readily obtained from L-(+)-tartaric acid by simple functional group transformations via aldehyde 113. Taking the advantage of kinetic control of formation of five membered lactone ring over six and seven membered lactone, butyrolactone 115 was constructed by deprotection of acetonide as well as TBS group in Z-alkene 114. The azido alcohol 116 was obtained by protection of primary alcohol followed by conversion of secondary alcohol to azide using Mitsunobu reaction on 115. The six membered piperidine core 117 was accessed from protected azido alcohol 116 by reduction followed by cyclisation which can be easily converted to ent-1.26
2.1.3 References


Chapter 2: Synthetic studies toward trans-(2R,3R)-3-hydroxypipecolic acid and (−)-swainsonine

Section 2: Total synthesis of trans-(2R,3R)-3-hydroxypipecolic acid
2.2.1 Present work

2.2.1.1 Objective

The literature survey revealed that (2R,3R)-3-hydroxypipeolic acid and its enantiomer have attracted the attention of many organic chemists due to their presence in number of natural as well as synthetic biologically active compounds. The literature reports also revealed that there are a few routes for the synthesis of 3-hydroxypipeolic acid 1 starting from chiral natural starting materials. The reported chiral pool approaches are associated with low yields and lengthy routes or involve usage of potentially hazardous chemicals such as azides. In this context, there is a need of convenient and efficient route for its enantiopure synthesis. This group over several years is engaged in the syntheses of biologically active compounds, including piperidine alkaloids. Recently this group accomplished the synthesis of (2S,3S)-3-hydroxypipeolic acid (ent-1) employing Sharpless asymmetric dihydroxylation1 as well as chiron approach utilizing L-(+)-tartaric acid.2 In the present section an alternative approach based on chiral pool strategy is described. The current novel route for its synthesis involved the use of chiral aziridine-2-carboxylate derived from D-mannitol diacetonide which is cheap and commericaly available starting material.

2.2.1.2 Retrosynthetic analysis

Owing to their ring strain, aziridines are very prone to nucleophilic ring opening reactions with various nucleophiles with predictable chemo and regio selectivity to give either α or β-amino compounds. Taking account of this, as shown in Scheme 1, it was thought that trans-3-hydroxy skeleton of the acid 1 can be obtained from γ-hydroxy-δ-amino-α,β-conjugated ester 3 via amide 2. Compound 3 can be easily obtained from α,β-unsaturated aziridine ester 4 by regioselective nucleophilic ring opening reaction using water as the nucleophile under acidic conditions which in turn can be easily accessed from aziridine-2-carboxylate 5. Aziridine-2-carboxylate 5 can be synthesized from commercially available and cheap starting material like D-mannitol diacetone 6.
2.2.1.3 Results and discussion

The present section describes the total synthesis of trans (2R,3R)-3-hydroxypipeolic acid 1 (Scheme 2). The α,β-unsaturated aziridine ester 4 was synthesized from D-mannitol diacetonide 6 over six steps and in 38% overall yield as described previously (chapter 1, section 2, Schemes 14 and 23). After achieving the site selective functionalization at the acetonide group of aziridine-2-carboxylate 5, it was thought of regioselective ring opening of aziridine ring in compound 4. Literature review revealed that ring opening reaction of aziridines flanked between ester and α,β-unsaturated ester generally occurs regioselectively from α,β-unsaturated ester side with a preference over simple ester. Thus, in the next step, compound 4 was treated with TFA (2 equiv.) in CH₃CN–H₂O (9:1) to undergo regioselective nucleophilic ring opening reaction using water as nucleophile to afford γ-hydroxy-δ-amino-α,β-conjugated ester 3 as the only isomer in 76% yield (Scheme 2). ¹H NMR spectrum showed characteristic doublet at δ 3.53 (J = 5 Hz, 1H) indicating α-amino ester functionality (α-hydroxy ester proton would have given a doublet at much downfield δ value). Peak at δ 4.52-4.56 (m, 1H) was assigned to γ-hydroxy,α,β-unsaturated ester proton. Peaks at δ 3.68 (d, J = 13.0 Hz, 1H) and 3.94 (d, J = 13.0 Hz, 1H) indicated the presence of N-benzylic protons. Peaks at δ 1.29 (m, 6H) and 4.13-4.28 (m, 4H) were assigned to ethyl ester while peaks at 6.08 (dd,
\( J = 2.0 \) & \( 15.5 \) Hz, 1H) and 6.75 (dd, \( J = 2.0 \) & \( 15.5 \) Hz, 1H) confirmed the presence of \( \alpha,\beta \)-unsaturated ester. Its \( ^{13}C \) and DEPT spectra showed peaks at \( \delta 70.1 \) and \( 64.12 \) corresponding for two -CH groups clearly indicating opening of aziridine ring. Molecular ion peak at \( m/z \) 344.18 (M+Na)\(^+\) further confirmed its molecular formula. In next step selective protection of hydroxyl group of amino-alcohol 3 was achieved using TBSCl, imidazole and cat. DMAP in refluxing dichloromethane to furnish TBS ether 8 in 85% yield.

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{EtO}_2\text{C} & \quad \text{C} \\
\text{N} & \quad \text{H} \\
\text{Br} & \quad \text{N} \\
\text{EtO}_2\text{C} & \quad \text{C} \\
\text{OH} & \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

**Total synthesis of (2R,3R)-3-hydroxypipeolic acid**

**Scheme 2. Reagents and conditions:** (a) 1) NaIO\(_4\), aq. NaHCO\(_3\), CH\(_2\)Cl\(_2\); 2) Ph\(_3\)PCBrCO\(_2\)Et, CH\(_2\)Cl\(_2\), 84\% over two steps; 3) BnNH\(_2\), Et\(_2\)N, toluene, 0°C to rt, 68\%; 4) TMSOTf, CH\(_2\)Cl\(_2\), 0°C, 90\%; 5) NaIO\(_4\), (CH\(_3\))\(_2\)CO:H\(_2\)O (2:1); 6) NaH, (EtO\(_2\))\(_2\)POCH\(_2\)CO\(_2\)Et, THF, 0°C, 70\% over two steps; (b) TFA, CH\(_3\)CN:H\(_2\)O (9:1), 0 °C to rt, 76\%; (c) TBSCl, Im, cat. DMAP, CH\(_2\)Cl\(_2\), reflux., 85\%; (d) H\(_2\), 10\% Pd(OH)\(_2\)/C, NaOAc, EtOH, 85\%; (e) BH\(_3\)-DMS, THF, 78\%; (f) HCl 6N, 91\%.

The crucial step viz reductive cyclization of 8 was carried out under hydrogenation conditions using hydrogen and palladium hydroxide over carbon in ethanol to provide amide 2 in 85\% yield (Scheme 2). Absence of peaks at 1620 cm\(^{-1}\) in its IR spectrum strongly supported the reduction of double bond and appearance of peaks at 1643 and 1732 cm\(^{-1}\) clearly showed the presence of amide and ester functionalities respectively.
Disappearance of characteristic peaks of protons of double bond (δ 6.08 & 6.75) and aromatic region (δ 7.21-7.28) in its 1H-NMR spectrum indicated the double bond reduction and N-benzyl deprotection. The broad singlet at δ 5.96 was assigned to the proton on amide nitrogen. The quartet at δ 4.23 and triplet at δ 1.30 integrating for two and three protons respectively were assigned to ethyl ester protons. Its 13C-NMR spectrum showed peaks at δ 171 and 170 corresponding to ester and amide carbonyl carbons. Peak at δ 65 was assigned to methylene carbon in ethyl ester and peaks at δ 62 and 61 were assigned to two tertiary carbons. Its DEPT spectrum showed presence of three CH₂ carbons and six -CH and -CH₃ carbons which is in accordance with structure of amide 2. Further, the formation of amide 2 was confirmed by its mass spectrum which showed a molecular ion peak at m/z 302 (M+H)⁺. In order to check the chiral purity at C2 and C3, the amide 2 was subjected to reduction using lithium aluminum hydride in anhydrous THF. Gratifyingly the ester, amide reduction as well as TBS deprotection was observed in a single step. The LAH reduction of 2 followed by N-Boc protection provided N-Boc amine 11. The chiral HPLC analysis of the 11 revealed that the chiral purity was ~97% ee (Scheme 3).

\[
\text{Scheme 3. Reagents and conditions: (a) LAH, THF, 0 °C to reflux; (b) (Boc)$_2$O, NaHCO$_3$, THF:HO (2:1), 75% over two steps.}
\]

In next step amido ester 2 was subjected to selective reduction of amide functionality using borane dimethyl sulfide complex in anhydrous THF to furnish the amino ester 10 in 78% yield. The presence of strong band at 1731 cm⁻¹ and disappearance of band at 1643 cm⁻¹ in its IR spectrum strongly supported the reduction of amide. In its 1H-NMR spectrum, the -CH₂ protons of ethyl ester were split into two multiplets, appearing at δ 4.31-4.39 and 4.10-4.18 and the triplet appearing at δ 1.36 was assigned to the methyl
protons of ester. Multiplet at δ 3.98 and doublet of triplet at δ 3.78 were attributed to the two -CH protons. The characteristic peaks of TBS group appeared at δ 0.86, 0.06 and 0.00. Peak at δ 170 in its $^{13}$C-NMR spectrum corresponded to ester carbonyl and the two tertiary carbons appeared at δ 70.5 and 70.2. Further, the -CH$_3$ carbons appeared at δ 25.5, 13.9, -4.5, -5.3 and CH$_2$ carbons appeared at δ 61.8, 52.2, 32.2 and 23.1. Further, peaks at $m/z$ 288 (M+H)$^+$ and 310 (M+Na)$^+$ in its mass spectrum confirmed the formation of 10.

Finally the ester hydrolysis as well as TBS group deprotection of 9 was carried out in a single step using 6N HCl to provide 3-hydroxypipeolic acid 1 in 91% yield. Its $^1$H-NMR spectrum showed multiplet at δ 4.13-4.17 and doublet at δ 3.83 corresponding to -CH protons. Other peaks included multiplets at δ 3.36-3.40, 3.07-3.12 and 1.64-1.80 and singlet at δ 2.22. Peak at δ 170.1 in its $^{13}$C-NMR spectrum was attributed to the acid carbonyl carbon and the peaks at δ 65.5 and 61.0 were due to the tertiary carbons. The three carbons appearing at δ 42.5, 28.8 and 18.6 all corresponded to the -CH$_2$ carbons. Its DEPT spectrum showed two carbons corresponding to CH carbons and three carbons due to the -CH$_2$ carbons. Molecular ion peak at $m/z$ 146 (M+H)$^+$ in its mass spectrum confirmed the formation of 1. The spectral data and optical rotation values were in good agreement with the reported one.$^5$

2.2.2 Conclusion

In conclusion, a total synthesis of trans (2R,3R)-3-hydroxypipeolic acid 1 was achieved starting from cheap and abundant starting material D-mannitol diacetonide in 11 steps and in 14% overall yield. The main steps used are the regioselective aziridine ring opening reaction, reductive cyclization and selective amide reduction. The intermediate 3 could be further explored for the synthesis of other imino sugars.
2.2.3 Experimental

\((4R,5R,E)\)-Diethyl 5-(benzylamino)-4-hydroxyhex-2-enedioate (3)

To a stirred solution of ester 4 (0.9 g, 2.97 mmol) in CH\(_3\)CN:water (9:1, 20 mL) was added TFA (0.45 mL, 5.94 mmol) dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 5-6 h). Reaction was quenched by excess NaHCO\(_3\), water (10 mL) was added and organic mass was extracted with ethyl acetate (3 × 15 mL). Combined organic layers were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure followed by column chromatographic purification using ethyl acetate:pet ether (15:85) to yield 1.18 g of amino-alcohol 3 as thick liquid.

\(R_f\): 0.5 (Pet ether-ethyl acetate, 3:7).
Yield: 76% over two steps.
MF: C\(_{17}\)H\(_{23}\)NO\(_5\), MW: 321.36.
\([\alpha]^{25}_{D}\) +20 (c 0.5, CHCl\(_3\))

IR (CHCl\(_3\), cm\(^{-1}\)): \(v_{\text{max}}\) 3554, 3359, 2980, 1720, 1620.

\(^1\)H NMR (200 MHz, CDCl\(_3\)+CCl\(_4\)): 1.26-1.34 (m, 6H), 3.53 (d, \(J = 5\)Hz, 1H), 3.68 (d, \(J = 13\) Hz, 1H), 3.94 (d, \(J = 13\) Hz, 1H), 4.13-4.28 (m, 4H), 4.52-4.56 (m, 1H), 6.08 (dd, \(J = 2 \& 15.5\) Hz, 1H), 6.75 (dd, \(J = 4.0 \& 15.5\) Hz, 1H), 7.27-7.30 (m, 5H).

\(^{13}\)C NMR (50 MHz, CDCl\(_3\)+CCl\(_4\)): 14.2, 52.6, 60.3, 61.3, 64.1, 70.1, 122.7, 127.5, 128.2, 128.4, 138.9, 145.2, 165.7, 171.6.

MS (ESI): \(m/z\): 344.18 (M+Na)+.

Elemental Analysis: Calculated:C-63.54, H-7.21, N-4.36%; found: C-63.22, H-7.31, N-4.60%.

\((4R,5R,E)\)-Diethyl 5-(benzylamino)-4-((tert-butyldimethylsilyl)oxy)hex-2-enedioate (8)

To a stirred solution of hydroxyl amino ester 3 (0.7 g, 2.18 mmol), imidazole (0.3 g, 4.36 mmol) and DMAP (0.027 g, 0.22 mmol) in CH\(_2\)Cl\(_2\) (20 mL) was added TBSCI (0.6 g,
4.36 mmol) dissolved in CH$_2$Cl$_2$ (5 mL) slowly at 0 ºC after which reaction was heated to reflux for 6 h until completion of reaction. Reaction mass was concentrated under reduced pressure followed by column chromatography using ethyl acetate-pet ether (5:95) to yield 0.8 g of TBS ether 8 as thick colorless liquid.

$R_f$: 0.5 (Pet ether-ethyl acetate, 2:8).

**Yield:** 85% over two steps.

**MF:** C$_{23}$H$_{37}$NO$_5$Si, **MW:** 435.62.

$[\alpha]_{D}^{25}$ $-7.69$ (c 1, CHCl$_3$)

**IR (CHCl$_3$, cm$^{-1}$):** v$_{max}$ 2980, 1720, 1620.

$^1$H NMR (500 MHz, CDCl$_3$+CCl$_4$): $0.01$ (s, 3H), $0.03$ (s, 3H), 0.87 (s, 9H), 1.29-1.31 (m, 6H), 2.17 (br s, 1H), 3.28 (d, $J = 5.5$ Hz, 1H), 3.65 (d, $J = 13$ Hz, 1H), 3.84 (d, $J = 13.0$ Hz, 1H), 4.12-4.20 (m, 5H), 4.47-4.48 (m, 1H), 5.95 (dd, $J = 1.5$ & $15.5$ Hz, 1H), 6.95 (dd, $J = 5.2$ & $15.5$ Hz, 1H), 7.21-7.28 (m, 5H).

$^{13}$C NMR (125 MHz, CDCl$_3$+CCl$_4$): $−49$, $−4.1$, $14.3$, $18.1$, $25.7$, $52.2$, $60.3$, $60.7$, $65.7$, $73.7$, $121.7$, $127.1$, $128.2$, $128.3$, $139.4$, $147.5$, $166.0$, $172.0$.

**MS (ESI):** m/z: 436.68 (M$+H$)$^+$. 

**Elemental Analysis:** Calculated C-63.41, H-8.56, N-3.22%; found C-63.45, H-8.36, N-3.35%.

(2R,3R)-Methyl 3-((tert-butyldimethylsilyl)oxy)-6-oxopiperidine-2-carboxylate (2)

The amino ester 8 (0.8 g, 2.2 mmol) was dissolved in ethanol (10 mL) and to that was added catalytic amount of palladium hydroxide over carbon (10%, 20 mg). The resulting reaction mixture was stirred under hydrogen atmosphere using balloon for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using silica gel (pet ether-ethyl acetate, 7:3) to provide amide 2 (0.52 g) as a colorless thick oil.

$R_f$: 0.4 (Pet ether-ethyl acetate, 8:2).

**Yield:** 85%.

**MF:** C$_{14}$H$_{27}$NO$_4$Si, **MW:** 301.

$[\alpha]_{D}^{25}$ $-26$ (c 1.5, CHCl$_3$).
Chapter 2

**IR (CHCl₃, cm⁻¹):** \( \nu_{\text{max}} \) 3399, 2955, 2857, 1732, 1643, 1215.

**1H NMR (200 MHz, CDCl₃):** \( \delta \) 0.12 (s, 6H), 0.90 (s, 9H), 1.30 (t, \( J = 7.2 \) Hz, 3H), 1.68 (br s, 1H), 1.79-1.88 (m, 2H), 2.26-2.40 (m, 1H), 2.54-2.72 (m, 1H), 3.99-4.02 (m, 1H), 4.23 (q, \( J = 7.2 \) Hz, 2H), 4.35-4.39 (m, 1H), 5.96 (br s, 1H).

**13C-NMR (50 MHz, CDCl₃):** \( \delta \) –5.1, –4.9, 14.1, 17.9, 25.6, 26.4, 26.5, 61.8, 62.3, 65.4, 170.1, 171.4.

**MS (ESI):** \( m/z \): 302.2 (M+H)⁺.

**Elemental analysis:** Calculated: C-55.78, H-9.03, N-4.65%; found: C-55.69, H-9.11, N-4.78%.

**(2R,3R)-Ethyl 3-((tert-butyldimethylsilyl)oxy)piperidine-2-carboxylate (9)**

To the amide 2 (0.2 g, 0.7 mmol) in anhydrous THF (5 mL) was added BH₃-DMS (0.2 mL, 2 mmol) dropwise at 0 °C. The resulting reaction mixture was further stirred at 5 °C for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using dichloromethane (3 × 10 mL). The collected organics were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified using flash chromatography over silica gel (70:30, EtOAc: pet ether) to furnish amine 9 (0.147 g, 78%) as a colorless dense liquid.

**Yield:** 78%.

**MF:** C₁₄H₂₉NO₃Si; **MW:** 287.47.

**\([\alpha]_{D}^{25} \)** –27 (c 1.0, CHCl₃)

**IR (CHCl₃, cm⁻¹):** \( \nu_{\text{max}} \) 3436, 3020, 2931, 2400, 1731, 1215 cm⁻¹.

**1H NMR (200 MHz, CDCl₃+CCl₄):** \( \delta \) 0.00 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.36 (t, \( J = 7.3 \) Hz, 3H), 1.41-1.51 (m, 2H), 1.58-1.68 (m, 2H), 1.84-1.87 (m, 1H), 2.01-2.05 (m, 1H), 2.53-2.64 (m, 1H), 3.11 (dd, \( J = 1.1 \) & 10.1 Hz, 1H), 3.32 (d, \( J = 13.5 \) Hz, 1H), 3.78 (dt, \( J = 5.4 \) & 10.5 Hz, 1H), 3.98 (m, 1H), 4.10-4.18 (m, 1H), 4.31-4.39 (m, 1H).

**13C-NMR (100 MHz, CDCl₃+CCl₄):** \( \delta \) –5.3, –4.2, 13.9, 17.8, 23.1, 25.5, 32.2, 52.2, 61.8, 70.2, 70.5, 170.8.
**Chapter 2**

**MS (ESI):** m/z: 288.23 (M+H)⁺, 310.14 (M+Na)⁺.

**Elemental analysis:** Calculated: C-58.49, H-10.17, N-4.87%; found: C-58.52, H-10.26, N-4.95%.

(2R,3R)-3-Hydroxypiperidine-2-carboxylic acid (1)

A mixture of amine 9 (100 mg, 0.35 mmol) and 6 N HCl (10 mL) was kept at 120 °C for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in H₂O (50 mL). The mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H₂O and then with aq. NH₃ solution. The eluate of aq. NH₃ was concentrated to dryness under reduced pressure to give 1 (46 mg, 91%) as a crystalline solid.

**Yield:** 91%.

**MF:** C₆H₁₁NO₃; **MW:** 145.15.

**MP:** 238–243 °C (dec.), lit.⁶ 230-238 °C.

[α]²⁵ D -13.8 (c 1.0, aq. HCl 10%), {lit.⁵ [α]²⁰ D -14 (c 0.5, aq. HC1 10%)}

**IR (CHCl₃, cm⁻¹):** νₓ 3287, 2920, 1625, 1405 cm⁻¹.

**¹H NMR (400 MHz, D₂O):** δ 1.64-1.80 (m, 2H), 2.02-2.08 (m, 2H), 2.22 (s, 1H), 3.07-3.12 (m, 1H), 3.40-3.36 (m, 1H), 3.83 (d, J = 7.8 Hz, 1H), 4.17-4.13 (m, 1H).

**¹³C-NMR (100 MHz, D₂O):** δ 28.8, 42.5, 61.0, 65.5, 118.6, 170.0.

**MS (ESI):** m/z: 146 (M+H)⁺.

**Elemental analysis:** Calculated: C-49.65, H-7.64, N-9.65%; found: C-49.73, H-7.45, N-9.74%.

(2S,3R)-tert-Butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (10)

To stirred suspension of LAH (0.152 g, 4 mmol) in anhydrous THF (3 mL) was added the lactam 2 (240 mg, 0.8 mmol) dissolved in anhydrous THF (3 mL) and the reaction mixture was stirred for 8 h at room temperature. Water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue thus obtained was
purified by flash chromatography (pet ether–ethyl acetate 10:90) to afford diol 2 (138 mg) as a white crystalline solid.

\[ R_f : 0.5 \text{ (Pet ether-ethyl acetate, 2:8).} \]

**Yield:** 75%.

**MF:** C\(_{11}\)H\(_{21}\)NO\(_4\), **MW:** 231.28

**MP:** 126-128 °C, lit.\(^7\) 124-126 °C.

\[ [\alpha]^{25}_D +27 \text{ (c 1.0, MeOH), \{lit.}^7 [\alpha]^{25}_D +29.8 \text{ (c 0.99, MeOH)}} \].

**IR (CHCl\(_3\), cm\(^{-1}\)):** \( \nu \text{ max 3448, 3025, 2945, 1674, 1215, 1120, 838 cm}^{-1}. \)

**\(^1\)H NMR (200 MHz, CDCl\(_3\)+CCl\(_4\)+DMSO-d\(_6\)):** \( \delta 1.15-1.29 \text{ (m, 1H), 1.39 (s, 9H), 1.61-1.82 \text{ (m, 3H), 2.69-2.82 \text{ (m, 1H), 3.45-3.61 \text{ (m, 2H), 3.89-3.92 \text{ (m, 2H), 4.08-4.16 \text{ (m, 1H).)}}} \}

**\(^13\)C (125 MHz, CDCl\(_3\)+CCl\(_4\)+DMSO-d\(_6\)):** \( \delta 18.8, 26.3, 28.0, 39.6, 59.1, 59.8, 63.8, 79.1, 155.9. \)

**MS (ESI):** \( m/z \): 232 (M+H)\(^+\), 254 (M+Na)\(^+\).

**HRMS (CI+):** Calcd for C\(_{11}\)H\(_{21}\)NO\(_4\): 231.1484; found: 231.1470.
2.2.4 Analytical Data

\(^1\)H-NMR spectrum of compound 3 (CDCl\(_3\)+CCl\(_4\), 200 MHz)

\(^13\)C-NMR spectrum of compound 3 (CDCl\(_3\)+CCl\(_4\), 50 MHz)
DEPT spectrum of compound 3 (CDCl₃+CCl₄, 50 MHz)

1H-NMR spectrum of compound 8 (CDCl₃+CCl₄, 200 MHz)
$^{13}$C-NMR spectrum of compound 8 (CDCl$_3$+CCl$_4$, 50 MHz)

DEPT spectrum of compound 8 (CDCl$_3$+CCl$_4$, 50 MHz)
Chapter 2

$^1$H-NMR spectrum of compound 2 (CDCl$_3$+CCl$_4$, 200 MHz)

$^{13}$C-NMR spectrum of compound 2 (CDCl$_3$, 50 MHz)
DEPT spectrum of compound 2 (CDCl₃, 50 MHz)

\[ \text{OTBS} \]
\[ \text{CO₂Et} \]

\[ \text{H-NMR spectrum of compound 9 (CDCl₃+CCl₄, 400 MHz)} \]

\[ \text{OTBS} \]
\[ \text{CO₂Et} \]
\( ^{13} \text{C-NMR spectrum of compound 9 (CDCl}_3+\text{CCl}_4, 100 \text{ MHz)} \)

\( \text{DEPT spectrum of compound 9 (CDCl}_3+\text{CCl}_4, 100 \text{ MHz)} \)
Chapter 2

$^1$H-NMR spectrum of compound 1 (D$_2$O, 400 MHz)

$^{13}$C-NMR spectrum of compound 1 (D$_2$O, 100 MHz)
Chapter 2

DEPT spectrum of compound 1 (D_2O, 100 MHz)

1H-NMR spectrum of compound 10 (CDCl_3+CCl_4+DMSO-d_6, 400 MHz)
$^{13}$C-NMR spectrum of compound 10 (CDCl$_3$+CCl$_4$+DMSO-d$_6$, 100 MHz)

DEPT-NMR spectrum of compound 10 (CDCl$_3$+DMSO-d$_6$, 100 MHz)
Chapter 2

Chiral HPLC analysis of compound 10 (Racemic)

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Project Leader: Dr. S P Chavan
Column: Chiralcel OJ-H (250x4.6 mm)
Mobile Phase: Pet Ether:IPA (95:05)
Wavelength: 210 nm
Flow Rate: 0.5ml/min (23Kgf)
concent.: 1mg/1.0mL
Inj vol.: 10 ul

Chiral HPLC analysis of compound 10 (2S,3R)

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Project Leader: Dr. S P Chavan
Column: Chiralcel OJ-H (250x4.6 mm)
Mobile Phase: Pet Ether:IPA (95:05)
Wavelength: 210 nm
Flow Rate: 0.5ml/min (23Kgf)
concent.: 1mg/1.0mL
Inj vol.: 10 ul
2.2.5 References


Chapter 2: Synthetic studies toward trans-(2R,3R)-3-hydroxypipeolic acid and (−)-swainsonine

Section 3: Introduction of (−)-swainsonine
2.3.1 Introduction to (−)-swainsonine

Iminosugars are small organic compounds that mimic carbohydrates or their hydrolysis transition states but contain a nitrogen atom instead of oxygen in the ring system templates. Ring size, poly-functionality, and multiple chirality are the factors that offer structural diversity among iminosugars that modulates the kind and the potency of the activity of each one of them.\textsuperscript{1}

\textbf{Figure 1.} Structures of (−)-swainsonine 1, deoxynojirimycin 2, castanospermine 3, and 1,2-di-\textit{epi}-swainsonine 4.

The first-generation iminosugars have been founded on three natural products: swainsonine 1, deoxynojirimycin (DNJ, 2), castanospermine 3 (Figure 1) and have been the starting point for the development of this class of compound as therapeutic agents. Iminosugars, although initially seen as anti-cancer or anti-HIV agents, they have subsequently demonstrated activity against a range of biochemical targets in diverse therapeutic areas.\textsuperscript{2}

(−)-Swainsonine 1 (Figure 1) is a naturally occurring trihydroxylated indolizidine alkaloid first isolated from the fungus \textit{Rhizoctonia leguminicola}.\textsuperscript{3a} Since then, it has also been extracted from diverse fungi such as \textit{Embellisia}\textsuperscript{3b} and \textit{Metharhizium anisopliae F-36222}\textsuperscript{3c} and from other plants of the \textit{Swainsona}\textsuperscript{3d} (flowering plants of western Australia), \textit{Astragalus}, and \textit{Oxytropis} species\textsuperscript{3e} (herbs and small shrubs of southwestern USA). These plants are collectively known as locoweeds because of their chronic intoxication effect with a variety of neurological disorders in livestock. Interest in this indolizidine stems principals from its role as a better inhibitor of Golgi \(\alpha\)-mannosidase II (GMII)\textsuperscript{4} \textit{vs} lysosomal \(\alpha\)-mannosidase (LM).\textsuperscript{5} Furthermore, this molecule exhibits interesting activity against some mammalian tumor cell lines\textsuperscript{6} and possesses immunomodulatory\textsuperscript{7} and antiviral activities.\textsuperscript{8} (−)-Swainsonine 1 also has potential uses as adjuvant for anticancer
drugs and other therapies in use. It was the first glycoprotein processing inhibitor to be selected for clinical testing as an anticancer drug.

The high potential for using this alkaloid in a wide range of biological applications makes it an attractive target for synthesis. In particular, the preparation of unnatural epimers and other structural analogues of (−)-swainsonine has created much interest since the biological activity of these compounds varies substantially with the number, position and stereochemistry of the hydroxy groups in the indolizidine skeleton. A number of syntheses of stereoisomers of (−)-swainsonine and other analogues have been developed nevertheless most of these target (−)-swainsonine itself, thus reflecting the importance placed upon this molecule and remained as an attractive synthetic target for organic chemists.

2.3.2 Review of literature

Due to their ‘sugar-like’ structure it is not surprising that many syntheses of 1,2,8-trihydroxyindolizidines utilize carbohydrate starting materials. Hexoses and their derivatives are often used with four chiral centers required in the product. There is also a strategy based on the utilisation of pentoses. Many syntheses of 1,2,8-trihydroxyindolizidines also employ non-carbohydrate starting materials. Extensive work towards syntheses of swainsonine and its analogues has been done and reviewed. A few interesting syntheses of swainsonine are described below.

**Richardson’s approach**

The first total synthesis of (−)-swainsonine by Richardson’s group established its absolute stereochemistry as (1S,2R,8R,8aR)-1,2,8-trihydroxyindolizidine (Scheme 1). Compound 6 was obtained from the amino hydrochloride 5 over five steps in 31% overall yield. Reaction of 6 with ethanethiol afforded the dithioacetal 7. Acetylation of 7 was followed by HgCl2/CdCO3 oxidation and subsequent treatment with Ph3PCHCO2Et to give 8 as a non-separable 1:1 mixture of E and Z isomers. Hydrogenation of the E/Z mixture 8 gave a 1:1 mixture of the lactam 10 and the product 9 and, after chromatographic separation, the lactam 10 was converted in two steps to (−)-swainsonine 1.
Scheme 1. Reagents and conditions: (a) 1) NaHCO₃, 1:1 EtOH-H₂O, CbzCl, rt, 2 h; 2) TsCl, py, rt, 36 h, 82% over 2 steps; 3) H₂, 10% Pd/C, EtOH, then NaOAc, reflux, 8 h; 4) NaHCO₃, CbzCl, 2 h, 73% over 2 steps; 5) HCl, 95-100 °C, 16 h, 52%; (b) EtSH, conc. HCl, 74%; (c) 1) acetylation, 73%; 2) HgCl₂, CdCO₃, acetone, reflux, 96%; 3) Ph₃PCHCO₂Et, CH₃CN, reflux, 86%; (d) H₂, 10% Pd/C, 2 h, 9 (25%) and 10 (25%); (e) 1) BH₃·DMS, THF, under N₂, 71-94%;2) NaOCH₃, CH₃OH, 3 h, 100%.

Fleets’ approach

Another synthesis of (–)-swainsonine 1 was accomplished by Fleet’s group utilizing D-mannose as the starting material (Scheme 2). D-Mannose was transformed into the manno-azide 11 in eight steps, including double inversion at C-4, in 46% overall yield. Oxidation of the free hydroxyl group in 11 with PCC followed by treatment with Ph₃PCHCHO gave 12 in 60-65% yield and the dienal 14 in 12% yield, which were separated by chromatography. Prolonged hydrogenation of 12 and 13 followed by removal of the isopropylidene protecting group in 16 afforded (–)-swainsonine 1.
**Scheme 2. Reagents and conditions:** (a) 1) BnOH-HCl, 83%, 2) TBDPSCI, imidazole, DMF, rt, 6 h, 89-97%; 3) DMP, CSA, acetone, 100%; 4) PCC, CH₂Cl₂, rt, 2 h; 5) NaBH₄, EtOH, 81% over 2 steps; 6) Tf₂O, py, CH₂Cl₂, −50−20°C; 7) NaN₃, DMF, rt, 68% over 2 steps; 8) Bu₄NF, THF, rt, 4 h; (b) 1) PCC, 3 Å M.S., CH₂Cl₂, 45 min; 2) Ph₃PCHCHO, 45 min, 68%, over 2 steps; (c) H₂, 10% Pd/C, CH₃OH, 6 h; (d) H₂, Pd-black, CH₃OH, 48 h; (e) H₂, Pd-black, AcOH, rt, 3 days, 60-87% for c, d and e; (f) TFA, H₂O, rt, 50 h, 74%.

**Pearson’s approach**

Pearson reported an efficient synthesis of (−)-swainsonine 1 which started with inexpensive D-ribose, which was converted to the known acetonide 17 in 99% yield (Scheme 3). Treatment of 17 with vinylmagnesium bromide gave the crude triol 18 in 80% yield without the need for purification. Oxidative cleavage of the 1,2-diol moiety of 18 using sodium periodate on silica gel gave the lactol 19 in 96% yield without purification. Reductive amination of 19 with dibenzylamine gave the amino-alcohol 20, which underwent a Johnson-Claisen ortho ester rearrangement to give the unsaturated ester 21. Purification of this material by column chromatography provided 21 in 43% overall yield from D-ribose. Osmium catalysed syn-dihydroxylation of 21 using AD-mix-β gave the hydroxylactone 22 in 60% yield after purification by column chromatography. The hydroxyl group in 22 was converted to its mesylate 23 (60% yield), which upon transfer hydrogenolysis of the N-benzyl groups gave the bicyclic lactam 24 in 80% yield after crystallization. This compound was converted to (−)-swainsonine 1 in 96% overall yield. (−)-Swainsonine was prepared in 10 steps in 12% overall yield in a synthetic route that requires only 2 purifications by column chromatography and 1 crystallization.
Scheme 3. Reagents and conditions: (a) Acetone, conc. HCl; (b) vinylmagnesium bromide, 5 equiv, THF; (c) NaIO₄ on SiO₂, CH₂Cl₂; (d) Bn₂NH, AcOH, NaBH₃CN, MeOH; (e) MeC(OMe)₃, (cat.) EtCO₂H, toluene, reflux; (f) K₃Fe(CN)₆, K₂OsO₄·2H₂O, K₂CO₃, MeSO₂NH₂, (DHQD)₂PHAL, H₂O, t-BuOH, 58%; (g) MsCl, Et₃N, CH₂Cl₂, reflux, 80%; (h) Pd(OH)₂, HCO₂NH₄, AcOH, MeOH, reflux, 80%; (i) BH₃·DMS, THF; (j) aq. HCl 96%.

Cha’s approach
A short enantioselective synthesis of (−)-swainsonine 1 has been reported in seven steps from 2,3-O-isopropylidene D-erythrose 25 in an overall yield of 35% (Scheme 4). The olefinic ester 26, prepared from 25 in two steps, underwent tosyl displacement with NaN₃ and subsequently 1,3-dipolar cycloaddition to afford the imino ester 28 in 81% overall yield. Mild hydrolysis of 28, followed by cyclisation in refluxing toluene via the lactone 29, gave the desired lactam 30. This was then treated with borane and hydrogen peroxide to produce the swainsonine acetonide 16 as a single diastereomer and concomitant acid hydrolysis gave (−)-swainsonine 1.
Scheme 4. Reagents and conditions: (a) BrPh₃P(CH₂)₃CO₂Et, KN(TMS)₂, THF, -78 °C; (b) TsCl, Et₃N, CH₂Cl₂; (c) NaN₃, DMF; (d) NaOH, H₂O, CH₂Cl₂; (e) Toluene; (f) BH₃·DMS, THF, H₂O₂, H₂O, NaOH; (g) HCl, Dowex, OH⁻ resin.

Ham’s approach

Ham et al. reported a new asymmetric method for the synthesis of (−)-swainsonine 1 using a diastereoselective chiral oxazoline formation by Pd(0) catalyst, diastereoselective dihydroxylation and the stereocontrolled allylation with TiCl₄₁⁶. The synthesis of (−)-swainsonine started with trans-oxazoline 33 which was treated with benzyl chloroformate in the presence of aqueous sodium bicarbonate, to afford the carbamate 34 in 96% yields. The dihydroxylation of 34 followed by acetonide protection of resulting diol 35 gave the compound 36. Oxidation of alcohol 36 with Dess-Martin periodinane gave the corresponding aldehyde which was subsequently reacted with allyltrimethylsilane in the presence of TiCl₄ to give the adduct of amino alcohol 37 with high anti-selectivity (15:1) (Scheme 5). The protection of the alcohol 37 by TBSOTf and subsequent oxidation of the alkene with borane-methyl sulphide gave the corresponding alcohol 38 in 70% yield.
Scheme 5. Reagents and conditions: (a) CbzCl, NaHCO₃, CH₂Cl₂, H₂O, 0 °C-rt, 3 h, 96%; (b) OsO₄, NMO, acetone:H₂O, then Na₂SO₃, 0 °C, 10 h, 99% (dr = 9 :1); (c) 1) DMP, PPTS, acetone, 40 °C, 8 h; 2) HF, py, THF, 0 °C-rt, 3 h, 78% (2 step); (d) 1) Dess-Martin periodinane; 2) Allyltrimethylsilane, TiCl₄, CH₂Cl₂, -78°C, (e) 1) TBSOTf, 2,6-lutidine, CH₂Cl₂; 2) BH₃.DMS, THF, 0 °C - rt, 70% over 2 steps; (f) 1) MsCl, TEA, CH₂Cl₂; 2) NaH, THF, then 2N NaOH, 76% over 2 steps; (g) 1) MsCl, Et₃N, CH₂Cl₂; 2) Pd(OH)₂/C, H₂, MeOH, 84% over 2 steps; (h) 6N HCl, Dowex-50WX8-100, 82%.

Mesylation of compound 38 and then exposure of the corresponding mesylate to NaH and then to 2N NaOH led to intramolecular cyclization and then benzoate hydrolysis provided 39 in 76% yield. Again mesylation of compound 39 followed by hydrogenolysis of mesylate afforded the protected (−)-swainsonine 16. Finally, acidic hydrolysis of the acetonide group gave (−)-swainsonine 1 in 82% yield (Scheme 5).

Hirama’s approach

(+)—Swainsonine ent-1 and (−)-8,8a-di-epi-swainsonine ent-4 were synthesized stereoselectively using L-glutamic acid via highly diastereoselective intramolecular conjugate addition of amide. Another key step is stereoselective osmium catalysed dihydroxylation of indolizidine double bond.¹⁷
Butyrolactone 41 prepared from L-glutamic acid was converted to amide 42 over three steps. Amide 42 was protected as Boc derivative followed by PMB deprotection, oxidation, two carbon Wittig elongation and highly diastereoselective intramolecular conjugate addition of amide to give lactam 43. Lactam 43 was converted to indolizidine framework 48 over eight steps (Scheme 6). Dihydroxylation of 48 under Upjohn conditions occurred predominantly from opposite face of OTBS group to give β-diacetate 49 while under reagent controlled conditions (catalyst 51) gave α-diacetate 50 as major product which were converted to (+)-swainsonine ent-1 and (−)-8,8a-di-epi-swainsonine ent-4 respectively (Scheme 7).
Scheme 7. Reagents and conditions: (a) 1) OsO₄, NMO, acetone, H₂O, rt, 82%; 2) TFA, THF:H₂O; then Ac₂O, pyridine, CH₂Cl₂, 84%, α/β 1:6.9; (b) 51, CH₂Cl₂, −78°C; then Na₂S₂O₅, aq THF, reflux; then Ac₂O, pyr, DMAP, 81%; (c) BH₃·THF, reflux; K₂CO₃, CH₃OH; then 2M HCl, reflux, 85%.

Pohmakotr’s approach

A concise asymmetric synthesis of (+)-swainsonine ent-1 in 11.8% overall yield in 10 steps is described by Pohmakotr’s group starting from 40, which was readily prepared from commercially available L-glutamic acid. The method features installation of the indolizidine ring via an intramolecular cyclisation of α-sulfinyl carbanion as a key step to get intermediate 48. Dihydroxylation of 48 under Upjohn conditions followed by amide reduction and TBS deprotection afforded (+)-swainsonine ent-1 as a single diastereomer (Scheme 8).¹⁸

Cyclisation of compound 54 to 55 and 56 required treatment of 54 with 2.2 equiv of LHMDS in THF at -78 °C followed by slowly warming up to room temperature for 16 hours via competitive proton abstraction that occurred preferentially at the α-imide proton rather than the α-proton adjacent to the phenylsulfinyl moiety of sulfinylimide 54. Proton abstraction of the initially formed enolate by a second equivalent of LHMDS gave α-sulfinyl carbanion which readily underwent cyclisation to yield hydroxy indolizidine amide which on treatment with p-TsOH in refluxing CH₂Cl₂ furnished 55 and 56 in 15%
and 65% yields, respectively. Intermediate 56 was converted to (+)-1 via known intermediate 48.

Scheme 8. **Reagents and conditions:** (a) 1) (COCl)$_2$, CH$_2$Cl$_2$; 2) NH$_2$(CH$_2$)$_3$SPh, CH$_2$Cl$_2$, Et$_3$N, 16 h; (b) tBuOK, THF, 67%; (c) 1) TBSCI, Im, CH$_2$Cl$_2$, 87%; 2) NaIO$_4$, MeOH-H$_2$O, 90%; (d) LHMDS, THF, –78–0°C, LHMDS then pTsOH, 15% for 55 and 65% for 56; (e) NaBH$_3$CN, AcOH-TFA, 0°C then 50°C; (f) CaCO$_3$, toluene, reflux, 85%; (g) 1) NMO, acetone, H$_2$O, rt; 2) LiAlH$_4$, THF, reflux; 3) Dowex 50W-X8 (H$^+$), 84% over 3 steps.

**Kang’s approach**

Kang’s approach involves highly enantioselective iodoetherification of γ-hydroxy-cis-alkenes 58 using iodine in the presence of salen–Co(II) complex 66 and N-chloro succinimide (NCS) and chemoselective oxidation as key steps to synthesize indizolide 65, an important intermediate for (−)-swainsonine. The synthesis commenced with the iodo-cyclization of the azidoalkenol 58 to afford the azido tetrahydrofuran 59 with 90% ee in 86% yield (Scheme 9). The azido group of 59 was reduced with stannous chloride and the resulting amino iodide was cyclized under basic conditions. The crude bicyclic tetrahy-
drofuranyl pyrrolidine 60 was protected to furnish carbamate 61 in 80% overall yield from 59.

Scheme 9. Reagents and conditions: (a) 66, NCS, I2, K2CO3, PhMe, −78°C, 86% (90% ee); (b) 1) SnCl2, PhSH, Et3N, MeCN, rt; 2) NaOAc, EtOH, reflux; (c) (Boc)2O, NaHCO3, H2O, MeOH, rt, 80% (for steps b–d); (d) RuCl3·3H2O, NaIO4, CCl4, H2O, MeCN, rt, 65%; (e) 1) TMSI, BF3·OEt2, CH2Cl2, 0°C; 2) TBSOTf, 2,6-lutidine, CH2Cl2, 0°C; 3) NaH, THF, 0°C, 88%; f) LDA (3 equiv), PhSeBr (1 equiv), THF, −78°C, then 2,6-di-tertbutyl-4-methylphenol, −78°C, 74%; (g) 1) LiAlH4, AlCl3, THF, −78°C, 97%; 2) NaIO4, NaHCO3, H2O, MeOH, 0°C, 91%.

When 61 was subjected to the oxidation conditions using RuCl3·3H2O/NaIO4, it gave 65% of the pyrrolidinone 62. For the synthesis of swainsonine, compound 62 was treated with TMSI in the presence of BF3–etherate to open the tetrahydrofuranyl ring. The resultant hydroxyl iodide was silylated, the carbamate group of which was concomitantly deprotected, and then cyclized to render the requisite indolizidinone 63 in 88% overall yield. Then compound 63 was phenylselenylated using LDA/PhSeBr to provide compound 64 (3:1 mixture of α and β) in 74% combined yield. After separation, α-64 was reduced to indolizidine with alane generated in situ from LiAlH4 and AlCl3, and oxidatively eliminated to produce the known indoline 65 in 88% overall yield, which was readily converted to (−)-swainsonine 1 via stereoselective dihydroxylation.
Lee’s approach

A formal synthesis of enantiomerically pure (−)-swainsonine 1 was successfully achieved using Intramolecular cyclization of the amino alcohol 71 which was derived from a readily available 1-(R)-α-methylbenzylaziridine-2-carboxylic acid (−)-menthol ester 67 (Scheme 10). Compound 68 is readily available by application of general synthetic methods from the (2S)-aziridine carboxylic acid (−)-menthol ester 67, via the Weinreb amide. The chelation-controlled reduction of the 2-acylaziridine 68 by NaBH₄ in the presence of ZnCl₂ was followed by protection of the secondary alcohol moiety to provide

![Scheme 10. Reagents and conditions:](image)

69 in 99% yield. The regioselective ring-opening reaction of the resulting protected diol 69 with AcOH in CH₂Cl₂ at room temperature provided the ring-opening product 70 in 88% yield. Then, deprotection of the primary silyl ether in 70 was selectively achieved by reaction with AcOH/H₂O/THF (3:1:1) at room temperature, to give 71. The primary alcohol of 71 was activated, after which the mesylate was transformed into the substituted-piperidine 72 in 61% yield via intramolecular cyclization under the hydrogenation reac-
tion conditions in the presence of 30% Pd(OH)$_2$/C followed by reaction of the resulting disubstituted piperidine with (Boc)$_2$O in methanol. Then the acetyl group was quantitatively hydrolyzed by KOH in methanol at room temperature to provide 2-hydroxymethyl-N-Boc-piperidine 73. The Swern oxidation of the primary alcohol 73 provided the piperidine-2-carbaldehyde which, by Wittig olefination with methylenetriphenylphosphorane at 0 °C, provided the desired vinylpiperidine 74 in 46% overall yield from 73 which constitutes the formal synthesis of (−)-swainsonine 1.

**Cossy’s approach**

Formal synthesis of (−)-swainsonine 1 has been developed from L-proline by using a diastereoselective addition of vinyl Grignard reagent on N-trityl-prolinal, an enantioselective ring expansion of a substituted prolinol into a 3-hydroxypiperidine via an aziridinium ion, and a ring closing metathesis as the key steps by Cossy’s group. $^{21}$ The synthesis of (−)-swainsonine 1 started with the preparation of prolinol 77, obtained in four steps from L-proline. After esterification and N-alkylation by using trityl chloride, amino-ester 76 was obtained in 90% yield. A reduction by LiAlH$_4$ in THF gave prolinol 77 which on Swern oxidation, followed by the addition of vinylmagnesium chloride gave allylic alcohol 78 with a diastereomeric excess superior to 98:2 (88% yield). The trityl group in prolinol 78 was removed and replaced by an allyl group to produce the substituted prolinol 79 in 50% yield. Treatment of prolinol 79 under the ring enlargement conditions provided, after saponification, 3-hydroxy-piperidine 81 in 95% yield with a diastereomeric excess superior to 95%. The free hydroxy group at C3 was protected as a TBS ether group and piperidine 82 was isolated in 70% yield (Scheme 11). For ring closing metathesis, piperidine 82 was transformed to the ammonium salt by treatment with camphorsulfonic acid followed by the ring closing metathesis using first generation Grubbs’ catalyst to give the unsaturated indolizidine 65 in 82% yield. This approach constitutes a formal synthesis of (−)-swainsonine 1 in 14 steps from L-proline with an overall yield of 14%.
Scheme 11. *Reagents and conditions:* (a) 1) SOCl$_2$, MeOH; 2) Ph$_3$CCl, Et$_3$N, CHCl$_3$, 90%; (b) LiAlH$_4$, THF; (c) 1) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, $-78^\circ$C; 2) Vinylimagnesium bromide, Et$_2$O, $-78^\circ$C, 88%; (d) 1) HCl, Et$_2$O; 2) Allyl bromide, K$_2$CO$_3$, n-Bu$_4$NBr, toluene, 50%; (e) 1) TFAA, Et$_3$N, THF, reflux, 95%; 2) NaOH; f) TBSCl, DMAP, CH$_2$Cl$_2$, 0 °C to rt, 70%; (g) Grubbs’ 1st gen. cat., CSA, CH$_2$Cl$_2$, reflux, 2) K$_2$CO$_3$, 82%.

Wardrop’s approach

The total synthesis of (−)-swainsonine 1 from 2,3-O-isopropylidene-D-erythrose in 12 steps and an overall yield of 28% is reported by Wardrop’s group. The pivotal transformation in this route to indolizidine alkaloid 1 is the formation of the pyrrolidine ring and C-8a/8 stereodiad through the diastereoselective, bis-cyclofunctionalization of an $\gamma,\delta$-unsaturated O-alkyl hydroxamate 86.$^{22}$ Synthetic route to (−)-swainsonine 1 began from 2,3-O-isopropylidene-D-erythronolactone 83. Reduction of 83 with DIBAL-H yielded the corresponding D-erythrose derivative, which through stereoselective addition of vinylmagnesium bromide and selective O-silylation of the primary alcohol was converted to allylic alcohol 84 in excellent overall yield. Upon heating with trimethylorthoacetate in the presence of propionic acid, compound 84 underwent Johnson-Claisen rearrangement to provide $\beta,\gamma$-unsaturated ester 85 as the E-isomer. Compound 85 was then converted to
O-alkyl hydroxamate 86. Cyclization of substrate 86 was accomplished by treatment with PhI(OCOCF₃)₂ and TFA to provide a bis-cyclization product 88.

Scheme 12. Reagents and conditions: (a) 1) DIBAL-H, CH₂Cl₂, −78°C; 2) Vinylimagnesium bromide, THF; 3) TBSCI, DMAP, CH₂Cl₂, 0 °C to rt, 71%; (b) CH₃C(OCH₃)₃, EtCO₂H, 110 °C, 99%; (c) 1) TBAF, THF; 2) DMP, CH₂Cl₂; 3) NaClO₂, NaH₂PO₄; 4) iBuOCCl, Et₃N, MeONH₂·HCl; d) PhI(OCOCF₃)₂, TFA, CH₂Cl₂, 0 °C, 60%; (e) LiAlH₄, 1,4-dioxane, reflux, 85%; (f) CBr₄, PPh₃, Et₃N, CH₂Cl₂, 88%; (g) aq. HCl, THF, rt, 96%.

This transformation is believed to proceed via the intramolecular capture of an N-acyl-N-alkoxyaziridinium ion 87 generated by the diastereoselective addition of a singlet acylnitrinium ion to the pendant alkene. Reaction of 88 with LiAlH₄ leads to the reduction of all three functional groups and formation of 1-amino-2,5-diol 89 in excellent yield. Formation of the indolizidine ring system was accomplished through use of an Appel reaction to generate 16. Finally, removal of the acetonide group, using 6M HCl provided (−)-swainsonine 1.
Tsai's approach

The synthesis of (+)-swainsonine (ent-1) was achieved using intramolecular free radical cyclization as key step by Tsai’s group. As shown in Scheme 13, Mitsunobu coupling of alcohol 90 with phthalimide afforded imide 91 in 95% yield. Imide 91 was deprotected by hydrazine to produce the crude amine and then reacted with (S)-5-oxotetrahydrofuran-2-carbonyl chloride to provide lactone 92 (65%). Rearrangement of lactone 92 to glutarimide 93 was achieved via potassium tert-butoxide treatment at low temperature in 91% yield. Sodium borohydride reduction of glutarimide 93 selectively reduced the more reactive carbonyl group, and then reaction of the crude carbinol with thiophenol under acidic condition followed by protection of the hydroxyl group as a benzoate gave compound 94.

Scheme 13. Reagents and conditions: (a) PPh3, DIAD, phthalimide, 95%; (b) Hydrazine, Et3N, 65%; (c) (S)-5-oxotetrahydrofuran-2-carbonyl chloride, t-BuOK, 91%; (d) 1) NaBH4; 2) p-TsOH, PhSH; 3) BzCl, DMAP, 70%; (e) PhI(OOCOCF3)2, 80%; (f) 1) Bu3SnH, ACCN; 2) TBAF, 86%; (g) Martin sulfurane, 73%; (h) 1) OsO4, NMO; 2) Ac2O, DMAP, 55%.

Hydrolysis of the dithiane moiety of 94 using PhI(OOCOCF3)2 gave acylsilane 95. Radical cyclization reaction of 95 proceeded with TBTH and catalytic amount of 1,10-
azobis(cyclohexanecarbonitrile) (ACCN) in refluxing toluene to produce diastereomeric mixture of crude silyl ethers that was desilylated to afford corresponding mixture of alcohols 96. Dehydration of the alcohol mixture 96 by Martin sulfurane gave a 73% yield of olefin 97. Dihydroxylation of 97 was accomplished by catalytic amount of osmium tetroxide in the presence of NMO and the resulting crude diol was acetylated to give ester 98. Borane reduction of 98 followed by removal of the ester groups of 98 by sodium hydroxide treatment in methanol afforded (+)-swainsonine ent-1.

2.3.3 References


Chapter 2: Synthetic studies toward $\text{trans}-(2R,3R)-3$-hydroxypipecolic acid and $(-)$-swainsonine

Section 4: Formal synthesis of $(-)$-swainsonine
2.4.1 Present work

2.4.1.1 Objective
Since its isolation, (–)-swainsonine 1 has proven a highly popular target of both total and formal syntheses.\(^1\) Furthermore, the search for more potent glycosidase inhibitors, which display improved GMII vs LM selectivity, has spurred the preparation of a large number of analogues. Swainsonine has recently been the subject of a process research study which further underscores the continued relevance of this natural product as a synthetic target.\(^2\) As part of this group’s effort toward an efficient syntheses of pharmaceutically important molecules,\(^3\) this group was attracted towards the efficient synthesis of (–)-swainsonine 1 from commercially available and cheap starting material. A modern synthetic design demands better yielding sequences coupled with mild reaction conditions, high stereoselectivity as well as versatile template that could be used as platform to launch other analogues simultaneously from readily available starting materials. Keeping these features in mind, an efficient route to 1 and its analogue 2 has been chosen from D-mannitol diacetonide as a starting material for the synthetic endeavor because of its ready availability in enantiopure form.

2.4.1.2 Retrosynthetic analysis
From a retrosynthetic perspective, it was envisioned that the indolizidine skeleton of 1 and 2 could be generated from stereoselective/stereocontrolled dihydroxylation of the unsaturated bicyclic lactam 3\(^4\) which can be accessed by ring closing metathesis reaction\(^5\) of compound 4 (Scheme 1). This di-alkene 4 can be easily prepared through N-allylation, selective deprotection of acetonide group, diol cleavage and Wittig reaction of lactam 5. On the basis of our previous studies it was anticipated that this lactam 5 can be obtained from \(\gamma\)-hydroxy-\(\delta\)-amino-\(\alpha,\beta\)-conjugated ester 6 via \(\alpha,\beta\)-unsaturated aziridine ester 7 by nucleophilic ring opening reaction using water as the nucleophile under acidic conditions which in turn can be accessed from aziridine-2-carboxylate 8. Finally, aziridine-2-carboxylate 8 can be synthesized from commercially available and cheap starting material like D-mannitol diacetonide 9.
Scheme 1: Retrosynthetic analysis of (-)-swainsonine 1 and (+)-1,2-di-epi-swainsonine 2.

2.4.1.3 Results and discussion

This section describes the formal synthesis of (-)-swainsonine 1. As shown in Scheme 2, its synthesis started from D-mannitol diacetonide 9 as described previously via aziridine-2-carboxylate 8 whose acetonide moiety was kept intact as a masked aldehyde while ester group was propagated to give trans-aziridine-α,β-unsaturated ester 7 in five steps and 43% overall yield (Chapter 1, Section 2, Scheme 14 and 21). Following the aziridine ring opening reaction under acidic conditions, compound 7 gave aziridine ring opened product 6. Its IR spectrum showed peak at 3453 cm⁻¹ indicating hydroxy functionality. Its ¹H NMR spectrum showed disappearance of peak at δ 2.12 (dd, 1H), 2.72 (dd, 1H) and appearance of characteristic peaks at δ 2.74 (dd, 1H) and 4.55 (dd, 1H) indicating γ-hydroxy,δ-amino,α,β-unsaturated ester functionality. Other peaks appeared at expected positions. The DEPT-NMR spectrum also showed disappearance of peaks at δ 40.1, 49.6 and
appearance of new peaks at δ 61.3 and 67.3 corresponding to –CH group clearly suggesting the ring opening of aziridine 7. Finally HRMS analysis affirmed the molecular formula (calculated for C_{19}H_{28}O_{5}N-350.1962, found-350.1967) of compound 6.

Scheme 2. Reagents and conditions: (a) 1) NaIO₄, aq. NaHCO₃, CH₂Cl₂; 2) Ph₃PCBrCO₂Et, CH₂Cl₂, 84% over two steps; 3) BnNH₂, Et₃N, toluene, 0°C to rt, 68%; 4) DIBAL-H (1M in toluene), CH₂Cl₂, -78°C, 1h; 5) (EtO)₂POCH₂CO₂Et, NaH, THF, 0 °C, 2h, 75% over 2 steps; (b) TFA, CH₃CN:H₂O (9:1), 0 °C to rt., 80%; (c) TBSCl, Im, cat. DMAP, CH₂Cl₂, reflux, 90%; (d) H₂, 10% Pd(OH)₂/C, MeOH, 92%; (e) NaH, allyl bromide, cat. TBAI, DMF, 85%; (f) Aq. 80% AcOH, 80 °C, 75%; (g) 1) NaIO₄, acetone:water; 2) Ph₃PCHCO₂Et, CH₂Cl₂, 75% over 2 steps; (h) Grubbs’ 2nd gen. catalyst, CH₂Cl₂, reflux, 80%.

Hydroxyl functionality of this amino-alcohol 6 was protected selectively using TBSCl, imidazole and cat. DMAP in refluxing dichloromethene to give TBS ether 10 in 90% yield. The ¹H NMR spectrum of compound 10 showed peaks at δ 0.04 (s,3H), 0.09 (s,3H) and 0.91 (s, 9H) corresponding to -OTBS group.
In next step, compound 10 was subjected to hydrogenation/hydrogenolysis condition using 10% Pd(OH)$_2$/C in MeOH to afford lactam 5 in 92% yield via one-pot concomitant double bond reduction, debenzylation and cyclisation. A characteristic strong band at 1670 cm$^{-1}$ in its IR spectrum clearly indicated the formation of amide carbonyl. Its $^1$H-NMR spectrum showed broad singlet at $\delta$ 6.02 corresponding to a characteristic peak of lactam proton. Its $^{13}$C-NMR spectrum showed a peak at $\delta$ 170.6 indicating the presence of lactam carbonyl. Finally, HRMS analysis of lactam 5 provided further substantiation for its molecular formula (calculated for C$_{16}$H$_{32}$O$_4$NSi-330.2095, found-330.2095).

Allylation of lactam 5 was carried out in next step using allyl bromide and NaH in DMF as solvent to give N-allylated compound 11 in 85% yield. IR spectrum of compound 11 showed strong absorption peak at 1633 cm$^{-1}$ indicating the presence of lactam carbonyl. In its $^1$H NMR spectrum, disappearance of lactam proton at $\delta$ 6.02 and appearance of additional peaks at 4.02 (m, 2H), 4.90 (m, 1H), 5.16 (m, 2H) and 5.61-5.81 (m, 1H) corresponding to N-allyl moiety were observed. In $^{13}$C NMR spectrum, appearance of additional peaks at $\delta$ 48.4 (N-CH$_2$), 117.1 (-CH) and 133.41 (-CH$_2$) further ascertained the presence of N-allyl group. Its mass spectrum showed molecular ion peaks at $m/z$ 356.41 [M+H]$^+$ confirming the formation of 11. In next step, the lactam 11 was exposed to 80% aqueous acetic acid at 80 °C to furnish diol 12 by selective deprotection of terminal acetonide functionality in presence of secondary –OTBS group in 75% yield. Disappearance of peaks at $\delta$1.35 and 1.43 and presence of peaks at $\delta$ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H) corresponding to TBS group in its$^1$H NMR spectrum clearly indicated the selective deprotection of acetonide functionality over -OTBS group. In $^{13}$C NMR spectrum, disappearance of peaks at $\delta$ 25.5, 26.6 and 109.6 corresponding to acetonide group supported the formation of diol 12. Its mass spectrum showed molecular ion peak at $m/z$ 352.41 [M+Na]$^+$ thus validating the formation of 12.

Diol 12 was cleaved using NaIO$_4$ in acetone:water to furnish crude aldehyde which was subjected without purification to 2-carbon Wittig homologation in dichloromethane to yield $\alpha,\beta$-unsaturated ester 4 in 75% yield over two steps. IR spectrum of compound 4 showed strong absorption band at 1723 cm$^{-1}$ indicating ester carbonyl functionality. Its $^1$H NMR spectrum showed peaks at $\delta$ 1.30 (t, 3H), 4.19 (q, 2H), 5.88 (dd, $J$ = 1 and 16 Hz, 1H), 6.73 (dd, $J$ = 6 and 16 Hz, 1H) pointing towards the formation of $\alpha,\beta$-
unsaturated ethyl ester. The magnitude of \( J \) values indicated the exclusive formation of \( E \)-isomer. Appearance of peaks at \( \delta \) 14.2 (-CH\(_3\)), 60.7 (-CH\(_2\)), 123.9, 144.5 (-CH) and 165.40 (-CO-) in its \( ^{13}\)C NMR and DEPT spectra ascertained the presence of \( \alpha,\beta \)-unsaturated ethyl ester. Lastly MS(ESI) analysis revealed a peak at \( m/z \) 390.12 [M+Na]\(^+\) and HRMS analysis peak at 368.2247 (calculated for \( \text{C}_{19}\text{H}_{34}\text{O}_{4}\text{NSi}\)-368.2252) validated the formation of diene 4.

Finally performing the ring closing metathesis reaction on compound 4 using Grubbs’ 2\(^{nd}\) generation catalyst in refluxing anhydrous dichloromethane gave access to key intermediate \( \text{viz.} \) bicyclic lactam 3. IR spectrum of lactam 3 showed strong absorption bands at 1640 and 1620 cm\(^{-1}\) indicating the presence of amide and double bond functionality. \( ^1\)H NMR spectrum showed disappearance of peaks corresponding to \( \alpha,\beta \)-unsaturated ethyl ester and appearance of peak at \( \delta \) 5.93 (m, 2H) indicating formation of alkene group. \( ^{13}\)C and DEPT spectra of compound 3 showed peaks at \( \delta \) 126.8 and 128.5 for two alkene –CH groups along with peaks at \( \delta \) -4.6, -4.1, 18.0 and 25.7 (for TBS group), 29.7 (-CH\(_2\)), 30.28 (-CH\(_2\)), 53.33 (-N-CH\(_2\)), 69.16 (-CH-N), 71.15 (-CH-O) and 168.29 (-CO-) confirming the formation of desired unsaturated indolizidine skeleton of compound 3. MS(ESI) analysis revealed a peak at \( m/z \) 268.02 [M+H]\(^+\) and HRMS analysis peak at 268.1741 (calculated for \( \text{C}_{14}\text{H}_{26}\text{NO}_{2}\text{Si}\)-268.1733) firmly substantiated the formation of unsaturated indolizidine 3.

Enantiomer of 3 and its conversion to \( \text{ent-1}^4 \) and \( \text{ent-2}^{4b} \) is well documented in the literature. The spectral data of 3 were in good agreement with the reported one except for the sign of optical rotation \( \{[\alpha]^{25}_D +53 \text{ (c 1, CHCl}_3)\}; \text{lit}^{4b} \text{ for ent-3-}[\alpha]^{25}_D -53.73 \text{ (c 1.10, CHCl}_3)\} \).

### 2.4.2 Conclusion

In conclusion, the present work constitutes an efficient formal synthesis of \((–)\)-swainsonine 1 and \((+)-1,2,\text{di-epi-swainsonine} 2\) employing aziridines ring opening and ring closing metathesis reactions as the key steps from commercially available and cheap starting material D-mannitol diacetonide. Synthesis of \((–)\)-swainsonine 1 was achieved in 11 purification steps with 9\% overall yield.
2.4.3 Experimental

**(4R,5R,E)-Ethyl 5-(benzylamino)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxypent-2-enoate (6)**

To a stirred solution of ester 7 (1.4 g, 4.2 mmol) in CH$_3$CN: water (9:1, 25 mL) was added TFA (0.64 mL, 8.4 mmol) dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 5-6 h). Reaction was quenched by addition of excess NaHCO$_3$, water (10 mL) was added and organic mass was extracted with ethyl acetate (3 × 20 mL). Combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure followed by column chromatographic purification using ethyl acetate-pet ether (15:85) to yield 1.11 g of amino-alcohol 6 as thick liquid.

$R_f$: 0.5 (Pet ether-ethyl acetate, 1:1).

**Yield**: 80%.

**MF**: C$_{19}$H$_{27}$NO$_5$, **MW**: 349.40.

**IR (CHCl$_3$, cm$^{-1}$)**: $\nu_{\text{max}}$ 3453, 2985, 1717, 1656, 1455, 1370, 1263, 1175.

$[\alpha]_{\text{D}}^{25}$ $-$50 (c 1.8, CHCl$_3$).

**$^1$H NMR (200 MHz, CDCl$_3$+CCl$_4$)**: $\delta$ 1.29 (t, $J = 7.0$ Hz, 3H), 1.32 (s, 3H), 1.39 (s,3H), 2.74 (dd, $J = 3.6$ & 5.4 Hz, 1H), 3.77-4.03 (m, 4H), 4.1-4.26 (m, 3H), 4.55 (dd, $J = 3.6$ & 5.4Hz, 1H), 6.2 (dd, $J = 2$ & 15.6 Hz, 1H), 6.9 ( dd, $J = 3.7$ & 15.6 Hz, 1H), 7.26-7.34 (m, 5H).

**$^{13}$C NMR (50 MHz, CDCl$_3$)**: $\delta$ 14.1, 25.1, 26.3, 51.0, 60.3, 61.3, 67.3, 69.0, 74.9, 109.0, 121.3, 127.1, 128.1, 128.4, 139.5, 147.0, 166.1.

**MS (ESI):** $m/z$: 372.14 [M+Na]$^+$.  

**HRMS**: Calculated for C$_{19}$H$_{28}$O$_5$N-350.1962, found 350.1967.

**(4R,5S,E)-Ethyl 5-(benzylamino)-4-((tert-butyldimethylsilyl)oxy)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-enoate (10)**

To a stirred solution of hydroxyl amino ester 6 (1 g, 4.22 mmol), imidazole (0.4 g, 6 mmol) and DMAP (0.024 g, 0.2 mmol) in CH$_2$Cl$_2$ (20 mL) was added TBSCl (1.27 g, 8.44 mmol) dissolved in CH$_2$Cl$_2$ (5 mL) slowly at 0°C after which reaction was heated to
reflux for 6 h until completion of reaction. Reaction mass was concentrated under reduced pressure followed by column chromatography using ethyl acetate: pet ether (5:95) to yield 0.84 g of -OTBS protected amino-alcohol 10 as thick colourless liquid.

$R_f$: 0.5 (Pet ether-ethyl acetate, 1:9).

Yield: 90 %.

MF: $C_{25}H_{41}NO_5Si$, MW: 463.68.

IR (CHCl$_3$, cm$^{-1}$): v max 2984, 2931, 1721, 1657, 1472, 1369, 1260, 1160, 1059.

$\left[\alpha\right]_{D}^{25}$ +11.11 (c 2.7, CHCl$_3$).

$^1$HNMR (200 MHz, CDCl$_3$+CCl$_4$): $\delta$ 0.04 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.31 (t, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 2.72 (br s, 1H), 3.70 (t, $J = 7.7$ Hz, 1H), 3.84-4.04 (m, 1H), 4.22 (q, 2H), 4.29-4.46 (m, 2H), 6.08 (dd, $J = 1.4 & 15.6$ Hz, 1H), 7.1 (dd, $J = 5.2 & 15.6$ Hz, 1H), 7.25-7.36 (m, 5H).

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ −4.9, −4.5, 14.1, 18.1, 25.2, 25.8, 26.8, 53.1, 60.3, 63.7, 66.9, 73.3, 75.5, 108.8, 121.4, 126.9, 128.2, 149.0, 166.2.

MS (ESI): $m/z$: 486.27 [M+Na]$^+$. 

HRMS: Calculated for $C_{25}H_{42}O_5NSi-464.2827$, found-464.2847.

(5RS,6S)-5-((tert-Butyldimethylsilyl)oxy)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (5)

A suspension of 10 (0.9 g, 1.94 mmol) and 10% Pd(OH)$_2$/C (60 mg) in MeOH (20 mL) was stirred under a H$_2$ atmosphere at room temperature for 2.5 h, filtered through Celite and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/Pet ether = 1:3) to afford 5(0.59 g) as a colorless thick liquid.

$R_f$: 0.4 (Pet ether-ethyl acetate, 1:1).

Yield: 92 %.

MF: $C_{16}H_{31}NO_4Si$, MW: 329.51

IR (CHCl$_3$, cm$^{-1}$): v max 3408, 2927, 1670, 1457, 1380, 1216.
\[ \alpha \]_D^{25} -22.9 (c 1.15, CHCl₃).

\(^1\)HNMR (400 MHz, CDCl₃+CCl₄): δ 0.1 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.34 (s, 3H), 1.41 (s, 3H), 1.78-1.87 (m, 1H), 1.94-2.01 (m, 1H), 2.29-2.38 (m, 1H), 2.47-2.85 (m, 1H), 3.20 (t, J = 7 Hz, 1H), 3.72-3.77 (m, 1H), 3.84 (dd, J = 5 & 8 Hz, 1H), 4.00-4.1 (m, 2H), 6.02 (br s, 1H).

\(^1\)C NMR (100 MHz, CDCl₃+CCl₄): δ –4.5, –4.1, 17.9, 25.2, 25.8, 26.6, 28.5, 29.1, 61.7, 67.2, 68.1, 76.3, 109.3, 170.6.


HRMS: Calculated for C₁₆H₃₂O₄NSi-330.2095, found-330.2095.

(5R,6S)-1-allyl-5-((tert-butyldimethylsilyl)oxy)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (11)

To the NaH (0.044 g, 1.8 mmol, prewashed with dry n-hexane) in DMF (2 mL) was added amide 5 (0.4 gm, 1.21 mmol) in DMF (2 mL) dropwise at 0 ºC and stirred for 1 h at room temperature. Allyl bromide (0.154 mL, 1.8 mmol) was added dropwise at 0 ºC. The resulting reaction mixture stirred for 3-4 h at room temperature. Reaction mixture was then quenched using water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organics washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was column purified on flash chromatography (pet ether-ethyl acetate, 7:3) to afford the allylated product 11 as colorless liquid.

R_f: 0.4 (Pet ether-ethyl acetate, 1:2).

Yield: 0.357 g, 85%.

MF: C₁₉H₃₇NO₃Si, MW: 355.59.

IR (CHCl₃, cm⁻¹): vmax 2986, 1630, 1420, 1107.

\[ \alpha \]_D^{25} -83.4 (c 1, CHCl₃).

\(^1\)HNMR (200 MHz, CDCl₃+CCl₄): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.35 (s, 3H), 1.43 (s, 3H), 1.88-1.92 (m, 4H), 2.33-2.44 (m, 1H), 2.53-2.67 (m, 1H), 3.33-3.37 (m, 1H), 3.54-3.75 (m, 3H), 4.03-4.05 (m, 2H), 4.9 (m, 1H), 5.11-5.24 (m, 2H), 5.61-5.81 (m, 1H).
$^{13}$C NMR (50 MHz, CDCl$_3$+CCl$_4$): $\delta$ –4.9, 17.8, 25.4, 25.5, 25.6, 26.3, 26.5, 48.4, 64.4, 65.4, 66.7, 78.5, 109.6, 117.1, 133.4, 168.8.

MS (ESI): $m/z$: 356.41 [M+H]$^+$. 

Elemental analysis: Calcd.: C-61.75; H-9.55; N-3.79; found: C-61.57; H-9.51; N-3.56.

$((5R,6S)$-1-Allyl-5-((tert-butyldimethylsilyl)oxy)-6-(($S$)-1,2-dihydroxyethyl)piperidin-2-one (12)

Protected lactam 11 (0.2 g, 0.56 mmol) was treated with 80% aqueous acetic acid (2 mL), and the resulting mixture was allowed to react at 80 °C. The reaction was monitored by TLC and was judged to be complete after 3 h. The solution was then diluted with H$_2$O (8 mL) and extracted with EtOAc (3 × 10 mL). The extracts were treated with saturated NaHCO$_3$ solution, and the combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated to give a crude residue that was purified by flash chromatography (pet ether-ethyl acetate, 1:9). Pure terminal diol 12 (0.14 g) was obtained as a thick gummy liquid. 

$R_f$: 0.4 (Ethyl acetate).

Yield: 75 %.

MF: C$_{16}$H$_{31}$NO$_4$Si, MW: 329.50

IR (CHCl$_3$, cm$^{-1}$): v$\max$ 3554, 3340, 2986, 1627, 1423, 1107.

$[\alpha]^{25}_D$ $-$34.9 (c 1, CHCl$_3$).

$^1$HNMR (200 MHz, CDCl$_3$+CCl$_4$): $\delta$ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.99-2.11 (m, 2H), 2.14-2.33 (m, 1H), 2.53-2.63 (m, 1H), 3.35-3.37 (m, 1H), 3.54-3.69 (m, 4H), 3.94 (s, 1H), 4.71-4.77 (m, 2H), 5.26-5.58 (m, 2H), 5.72-5.88 (m, 1H).

$^{13}$C NMR(100 MHz, CDCl$_3$+CCl$_4$): –4.8, –4.7, 18.0, 25.3, 25.8, 26.9, 50.3, 64.1, 64.7, 66.1, 73.6, 117.5, 132.8, 171.0.


$((E)$-Ethyl 3-((2S,3R)-1-allyl-3-((tert-butyldimethylsilyl)oxy)-6-oxopiperidin-2-yl)acrylate (4)

Diol 12 (0.2 g, 0.607 mmol) was dissolved in acetone–water (3 mL, 2:1) at 0 °C, treated with sodium metaperiodate (0.2 g, 0.9 mmol) and stirred at 15 °C for 15 min. The
reaction was quenched using ethylene glycol (0.01 mL), extracted with CH₂Cl₂ (3 × 10 mL), washed with brine, dried over anhydrous Na₂SO₄ and filtered. The combined organics were concentrated under reduced pressure to afford crude aldehyde which was used as such for next reaction.

To a solution of aldehyde from above reaction in CH₂Cl₂ (15 mL) was added (carboethoxymethylene) triphenylphosphorane (0.4 g, 1.2 mmol) and the reaction mixture was stirred for 6 h. Solvent was evaporated and the reaction mixture was adsorbed on silica. Purification by column chromatography (pet ether–ethyl acetate, 8:2) gave 4 as a thick liquid (0.167 g).

Rf: 0.5 (Pet ether–ethyl acetate, 1:1).
Yield: 75% over two steps.
MF: C₁₉H₃₃NO₄Si, MW: 367.55.
IR (CHCl₃, cm⁻¹): v max 2986, 1723, 1656, 1630, 1107.

[α]D²⁵ –45 (c 1, CHCl₃)

¹HNMR (200 MHz, CDCl₃+CCl₄): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.30 (t, J = 7 Hz, 3H), 1.73-1.75 (m, 1H), 1.86-1.93 (m, 1H), 2.35 (m, 1H), 2.59-2.68 (m, 1H), 2.99 (dd, J = 7 & 16 Hz, 1H), 3.99 (m, 1H), 4.19 (q, J = 7 Hz, 2H), 5.84 (dt, J = 2 & 16 Hz, 1H), 5.11-5.18 (m, 1H), 5.62-5.72 (m, 1H), 5.88 (dd, J = 1 & 16 Hz, 1H), 6.73 (dd, J = 6 & 16 Hz, 1H).

¹³C NMR (50 MHz, CDCl₃+CCl₄): δ -4.8, 14.2, 24.8, 25.6, 26.7, 47.3, 60.7, 64.3, 67.0, 117.3, 123.9, 132.3, 144.5, 165.4, 169.1.


HRMS: Calculated for C₁₉H₃₄O₄NSi-368.2252, found-368.2247.

(8R,8aS)-8-((tert-Butyldimethylsilyloxy)-6,7,8,8a-tetrahydroindolizin-5(3H)-one (3)

The olefinic compound 4 (0.075 g, 0.2 mmol) and Grubbs’ 2nd generation catalyst (5 mg, 2 mol %) in anhydrous CH₂Cl₂ (50 mL) was refluxed for 5 h. The reaction mixture was filtered through Celite and concentrated in vacuo to provide crude 3. The
crude product was purified using column chromatography (pet ether-ethyl acetate, 1:1) to provide the ring closed product 29 (0.044 g, 80%) as a colorless sticky liquid.

$R_f$: 0.4 (Pet ether-ethyl acetate, 1:1).

Yield: 80 %.

MF: C$_{14}$H$_{25}$NO$_2$Si, MW: 267.43

IR (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 1640, 1620.

[$\alpha$]$^\text{D}_{25}$ +53 (c 1, CHCl$_3$); lit$^{ab}$ {for ent-[$\alpha$]$^\text{D}_{25}$ −53.73 (c 1.10, CHCl$_3$)}.

$^1$HNMR (400 MHz, CDCl$_3$+CCl$_4$): $\delta$ 0.08 (s, 6H), 0.90 (s, 9H), 1.79-1.81 (m, 1H), 2.02-2.03 (m, 1H), 2.39-2.46 (m, 1H), 2.60-2.62 (m, 1H), 3.53-3.55 (m, 1H), 4.02-4.06 (m, 1H), 4.15-4.16 (m, 1H), 4.45-4.50 (m, 1H), 5.92-5.94 (m, 2H).

$^{13}$C NMR(100 MHz, CDCl$_3$+CCl$_4$): $\delta$ −4.6, −4.1, 18.0, 25.7, 29.7,30.2, 53.3, 69.1, 71.1, 126.8, 128.5, 168.2.

MS (ESI): m/z: 268.02 [M+H]$^+$.  

HRMS: Calculated for C$_{14}$H$_{26}$NO$_2$Si-268.1733; found-268.1741.
2.4.4 Analytical Data

$^1$H-NMR spectrum of compound 6 (CDCl$_3$+CCl$_4$, 200 MHz)

$^{13}$C-NMR spectrum of compound 6 (CDCl$_3$, 50 MHz)
DEPT spectrum of compound 6 (CDCl₃, 50 MHz)

1H-NMR spectrum of compound 10 (CDCl₃+CCl₄, 200 MHz)

Chloroform-d
$^{13}$C-NMR spectrum of compound 10 (CDCl$_3$, 50 MHz)

DEPT spectrum of compound 10 (CDCl$_3$, 50 MHz)
**Nuclear Magnetic Resonance Spectra of Compound 5**

**1H-NMR Spectrum of Compound 5 (CDCl₃+CCl₄, 400 MHz)**

**13C-NMR Spectrum of Compound 5 (CDCl₃+CCl₄, 100 MHz)**

**NMR Data**

- **1H-NMR**: 7.27, 6.88, 6.69, 6.42, 6.23, 5.94, 5.65, 5.36, 5.07, 4.78, 4.52, 4.24, 4.05, 3.86, 3.67, 3.48, 3.29, 3.10, 2.91, 2.72, 2.53, 2.34, 2.15, 1.96, 1.77, 1.58, 1.39, 1.20, 1.01, 0.82, 0.63, 0.44, 0.25, 0.06

- **13C-NMR**: 170.69, 109.39, 77.00, 76.34, 68.14, 67.21, 61.77, 29.16, 28.53, 26.67, 25.82, 25.20, 17.99, -4.15, -4.52, 10.11, 6.363.352.10, 1.11, 1.09, 1.07, 1.00, 0.90

**Chemical Shifts**

- Chloroform-d (7.27, 6.88, 6.69, 6.42, 6.23, 5.94, 5.65, 5.36, 5.07, 4.78, 4.52, 4.24, 4.05, 3.86, 3.67, 3.48, 3.29, 3.10, 2.91, 2.72, 2.53, 2.34, 2.15, 1.96, 1.77, 1.58, 1.39, 1.20, 1.01, 0.82, 0.63, 0.44, 0.25, 0.06)

- CCl₄ (170.69, 109.39, 77.00, 76.34, 68.14, 67.21, 61.77, 29.16, 28.53, 26.67, 25.82, 25.20, 17.99, -4.15, -4.52, 10.11, 6.363.352.10, 1.11, 1.09, 1.07, 1.00, 0.90)
DEPT spectrum of compound 5 (CDCl₃+CCl₄, 100 MHz)

1H-NMR spectrum of compound 11 (CDCl₃+CCl₄, 200 MHz)

Chloroform-d
Chapter 2

$^{13}$C-NMR spectrum of compound 11 (CDCl$_3$+CCl$_4$, 50 MHz)

![C-NMR spectrum of compound 11](image1)

DEPT spectrum of compound 11 (CDCl$_3$+CCl$_4$, 50 MHz)

![DEPT spectrum of compound 11](image2)
Chapter 2

$^1$H-NMR spectrum of compound 12 (CDCl$_3$+CCl$_4$, 200 MHz)

$^{13}$C-NMR spectrum of compound 12 (CDCl$_3$+CCl$_4$, 100 MHz)
DEPT spectrum of compound 12 (CDCl₃+CCl₄, 100 MHz)

1H-NMR spectrum of compound 4 (CDCl₃+CCl₄, 200 MHz)
$^1$H-NMR spectrum of compound 4 (CDCl$_3$+CCl$_4$, 50 MHz)

$^1$C-NMR spectrum of compound 4 (CDCl$_3$+CCl$_4$, 50 MHz)

DEPT spectrum of compound 4 (CDCl$_3$+CCl$_4$, 50 MHz)
$^1$H-NMR spectrum of compound 3 (CDCl$_3$+CCl$_4$, 400 MHz)

$^{13}$C-NMR spectrum of compound 3 (CDCl$_3$+CCl$_4$, 100 MHz)
2.4.5 References


