The thesis entitled “Studies Directed Towards The Synthesis of Naturally Occurring Lactones, Amino Alcohols and Polyols” has been divided into three chapters.

Chapter I: Introduction to Sharpless asymmetric epoxidation, Jacobsen’s hydrolytic kinetic resolution, Ring Closing Metathesis and proline catalyzed reactions.

Chapter II: Synthesis of naturally occurring lactones
Section A: Studies directed towards the synthesis of Stagonolide C & Modiolide A.
Section B: Studies directed towards the synthesis of Seimatopolide B.
Section C: Studies towards the synthesis of Dodoneine.

Chapter III: Studies directed towards the synthesis of Jaspine B and analogues

This chapter gives a brief introduction to Sharpless asymmetric epoxidation, Jacobsen’s hydrolytic kinetic resolution (HKR), ring closing metathesis (RCM) and proline-catalyzed organic transformations.

The Sharpless asymmetric epoxidation is an enantioselective chemical reaction to prepare 2,3-epoxyalcohols from primary and secondary allylic alcohols. This metal catalyzed epoxidation process was discovered by K. Barry Sharpless in 1980 and allows the transformation of a prochiral substrate into an optically active (or optically pure) product using a chiral catalyst. The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative. This epoxidation is arguably one of the most important reactions discovered in the last 30 years. This has been recognized by the award of the 2001 Nobel Prize to Professor Barry Sharpless.

In this epoxidation reaction, double bond of allylic alcohols is converted into epoxides using a transition metal catalyst titanium tetra-isopropoxide and a chiral additive (di-alkyltartrate, i.e., DET or DIPT used). The oxidant for the epoxidation is
tertbutylhydroperoxide. Notably, this reaction exhibits high levels of enantioselectivity (usually $>90\%$ ee) and proceeds under mild condition with good chemical yield.

The hydrolytic kinetic resolution (HKR)$^2$ of terminal epoxide catalyzed by chiral (salen)-Co(III)-OAc complex affords both recovered epoxide and 1,2-diol product in highly enantio-enriched form. In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

Ring closing metathesis (RCM)$^3$ is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged to give cycloalkene. It utilizes no additional reagents beyond a catalytic amount of metal carbene. Various well-defined metathesis catalysts which are tolerant to many functional groups as well as reactive towards a diverse range of substrates have been developed.

In recent years, area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis, thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.$^4$ Proline has been defined as a “universal catalyst” because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Brönsted acid.

These methods have contributed to more advances in research not only in chemistry but also in material science, biology and medicine. This work gave access to new molecules needed to investigate hitherto undiscovered and unexplained phenomena in the molecular world.

Chapter 2: Section A: Studies directed towards the synthesis of Stagonolide C & Modiolide A.

Stagonolide C$^5$ was isolated by Antonio Evidente in 2008 from a fungal pathogen Stagonospora Cirsii isolated from Cirsium arvense. They were found weakly toxic to Colpoda steinii, a protozoan, when tested at 0.05 mg/mL.
Modiolide A\(^6\) was isolated from the cultured broth of a marine fungus *Paraphaeosphaeria* sp. (Strain N-119) which was separated from marine horse mussel. Modiolide A showed antibacterial activity against *Micrococcus luteus* (MIC value 16.7 µg/mL) and antifungal activity against *Neurospora crassa* (MIC value 33.3 µg/mL).

Total synthesis of stagonolide C and Modiolide A has been attempted using Ring closing metathesis and Yamaguchi esterification as key steps. The Steregenic centers were generated by Sharpless asymmetric epoxidation and hydrolytic kinetic resolution (HKR) of terminal epoxides.

Our synthesis started with the conversion of L\(+\)-malic acid 3 to the known primary alcohol 6. One pot conversion of the alcohol to the \(\alpha,\beta\)-unsaturated ester 7 was achieved by IBX oxidation followed by treating the same reaction mixture with (ethoxycarbonylmethylene)triphenylphosphorane. The ester was selectively reduced to allylic alcohol 8 by DIBAL-H (Scheme-1).

![Scheme 1](image)

**Scheme 1 : Reagents and conditions:** (a) (i) IBX, DMSO, THF, (ii) PPh\(_3\)CHCOOC\(_2\)H\(_5\), THF, reflux, 70 \%; (b) DIBAL, CH\(_2\)Cl\(_2\), -78 °C, 1 h, 75%.

Sharpless asymmetric epoxidation of the allylic alcohol 6 with (+)-DET gave the \((S,S)\) epoxide 7. The primary hydroxyl group of the epoxide 7 was transformed to its iodo derivative 8. Opening of the epoxide of the iodo compound was achieved with Zn in refluxing EtOH. The secondary allylic alcohol 9 was protected as its \(p\)-methoxybenzyl ether 10. Then the isopropylidine group was deprotected by treatment with \(p\)-TSA to give diol 11. In order to secure the alcohol fragment 13, we deoxygenated the primary hydroxyl group of diol. The diol 11 was selectively monoprotected with a tosyl group to give 12. Then, 12 was treated with excess of lithium aluminium hydride (LAH) to give the required alcohol 13 in good yield (scheme-2).
Scheme 2: Reagents and conditions: (f) (+)-DET, Ti(O\text{OPr})\text{4}, TBHP, CH\text{2}Cl\text{2}, 12 h, 80%; (g) TPP, imidazole, iodine, CH\text{2}Cl\text{2}, 75%; (h) Zn, Ethanol, reflux, 81%; (i) NaH, PMBCl, DMF, 0 °C to rt, 3 h, 81%; (j) MeOH, PTSA, 91%; (k) TsCl, Bu\text{2}SnO, CH\text{2}Cl\text{2}, 12 h, 70%; (l) LAH, THF, 1 h, 77%.

A similar retrosynthetic strategy was planned for the acid fragment 23. The D-glyceraldehyde derivative (14) when subjected to two-carbon Wittig olefination using (carbethoxymethylene)triphenylphosphorane gave α,β-unsaturated ester which on catalytic hydrogenation with Pd/C afforded saturated ester. This ester was reduced with lithium aluminium hydride (LAH) in anhydrous THF to furnish the alcohol 15. In order to secure allyl alcohol 17, the primary hydroxyl group of 15 was oxidized with IBX to afford an aldehyde which was treated with (carbethoxymethylene)triphenylphosphorane to furnish 16. Hydride reduction of 23 with DIBAL afforded the key precursor allyl alcohol 17 (scheme 3).

Generation of the second chiral centre relevant to the target was achieved by employing Sharpless asymmetric epoxidation on 17, in a catalytic process using (-)-DET as chiral ligand, to furnish (2R,3R)-epoxide 18. The next, epoxy alcohol was converted to epoxy iodide by iodination procedure to give 19. Direct reduction with commercial zinc dust gave the diastereomerically pure terminal alkenic alcohol 20. The terminal alkenic alcohol was protected as p-methoxybenzyl (PMB) ether 21. The isopropylidene group of 21 was hydrolyzed under acidic conditions, to furnish diol 22. The diol 22 was oxidatively cleaved with sodium metaperiodate to provide aldehyde which on further treatment with NaClO\text{2} in presence of NaH\text{2}PO\text{4} and 2-methyl-2-butene as a scavenger gave required coupling partner acid 23 (Scheme 4).
Scheme 4: Reagents and conditions: (i) (-)-DET, Ti(O\text{OPr})_4, TBHP, 4Å MS powder, CH_2Cl_2, -20°C, 12 h, 82%; (j) TPP, imidazole, iodine, CH_2Cl_2, 72%; (k) Zn, Ethanol, reflux, 70%; (l) NaH, PMBCl, DMF, 0°C to r.t., 3 h, 85%; (m) 80% AcOH, r.t., 2 h, 90%; (n) (i) Silica Supported NaIO_4, 30 min. r.t.; (ii) NaClO_2, NaH_2PO_4, 2-Methyl-2-butene, t-BuOH:H_2O, r.t., 2 h, 54% (two steps).

As synthesis of acid fragment was achieved in twelve steps, we were interested in the short and concise synthesis of acid fragment by applying the hydrolytic kinetic resolution.

**Synthesis of acid fragment using Hydrolytic Kinetic Resolution:** Our synthesis of acid fragment 23 started from 4-pentene-1-ol (24). Protection of 24 with TBSCl in presence of imidazole afforded 25 in 90% yield, which was subjected to m-CPBA epoxidation followed by hydrolytic kinetic resolution using S,S-salen Co(III)-OAc complex to furnish enantiopure epoxide 27 in 45% yield. The epoxide 27 was opened by dimethylsulfonium methyldie to give allylic alcohol 28 which was then protected as its PMB ether to give compound 29. This PMB ether was then treated with TBAF to give desilylated alcohol 30. This alcohol 30 was then oxidized to aldehyde using IBX and then to acid by using NaClO_2 in presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger gave required coupling partner acid 23 (Scheme 5).

Scheme 5: Reagents and conditions: (a) TBSCI, imidazole, CH_2Cl_2, 0°C- r.t., overnight, 90%; (b) m-CPBA, CH_2Cl_2, 0°C to r.t., 5 h, 70%; (c) (S,S) Salen-Co(III)-(OAc), H_2O, 16 h, 45%; (d) Trimethylsulphonium iodide, n-BuLi, THF, -23°C, 8 h, 78%; (e) NaH, DMF, PMBCl, 0°C-r.t., 6 h, 72%; (f) TBAF, THF, 0°C, 90%; (g) (i) IBX, EtOAc, reflux (ii) NaClO_2, NaH_2PO_4, 2-Methyl-2-butene, t-BuOH:H_2O, rt, 2 h, 64% (two steps).
**Coupling of alcohol and acid fragments:** Alcohol 13 was coupled with acid 23 by using EDCI and catalytic amount of DMAP to give the diene ester 31. The structure of 31 was proved by $^1$H NMR and $^{13}$C NMR spectra. The compound 31 was subjected for ring closing metathesis in CH$_2$Cl$_2$ with Grubbs’ II generation catalyst under reflux conditions; we observed no reaction as we recovered the starting material even after 36 h (scheme 6).

![Scheme 6: Reagents and conditions: (a) EDCI, DMAP, 12 h, 70%; (b) Grubbs II Gen. CH$_2$Cl$_2$.](image)

**Synthesis of Modiolide A:**

**Synthesis of alcohol fragment using Hydrolytic Kinetic Resolution:** Our synthesis of 41 requires iterative Jacobsen’s hydrolytic kinetic resolution to install the stereogenic centers (Scheme 7). Thus racemic propylene oxide (±)-33 was resolved by HKR method to give the enantiopure epoxide (R)-33 and diol (S)-34. The epoxide (R)-33 was opened with vinylmagnesium bromide followed by TBS protection and epoxidation to give the epoxide 37 as a mixture of syn and anti compounds. In order to get the diastereomically pure epoxide, the epoxide 37 was resolved using (S,S)-salen Co(III)-OAc and water in THF to give the diastereomically pure epoxide 38 as well as diol 39. With substantial amount of epoxide 38 in hand we further proceeded for the synthesis of 41 by opening of epoxide with trimethylsulfonium iodide to get the allylic alcohol followed by protection as its MEM ether and deprotection of TBS ether using TBAF.

![Scheme 7: Reagents and conditions: (a) (R,R)-Salen-Co$^{III}$-(OAc) (0.5 mol%), dist. H$_2$O, (0.55 equiv), 0 oC, 14 h, (45% for 33 and 43% for 34); (b) vinylmagnesium bromide, Cul, THF, -20 oC, 12 h, 85%; (c) TBSCl, imidazole, CH$_2$Cl$_2$, 0 oC – r.t., 6 h, 80%; (d) m-CPBA, CH$_2$Cl$_2$, 0 oC- r.t., 72%; (e) (S,S)-Salen-](image)
Having synthesized alcohol fragment 41 and acid fragment 42 which is synthesized by another colleague, we proceeded for the coupling of compound 41 and 42 to achieve the diene ester. Further synthesis of Modiolide A is in progress (Scheme 8).

**Scheme 8**: Coupling acid and alcohol fragment for synthesis of modiolide A.

Chapter 2: Section B: Studies directed towards the synthesis of Dodoneine

Dodoneine (44) was isolated from the methanolic extract of a hemiplant parasite, *Tapinanthus dodoneifolius*. *T. dodoneifolius* is known to be used as a remedy to treat cardiovascular and respiratory diseases, and also for cholera, diarrhoea, stomach ache and wounds. Dodoneine was found to exhibit relaxation effects on preconstricted rat aortic rings with an IC₅₀ value of 81.4 ± 0.9 μM. Hence we planned to synthesize dodoneine and till date eight syntheses are reported in the literature.

**Synthesis of Dodoneine by hydrolytic Kinetic resolution:** Synthesis of Dodoneine was started with reaction of p-methoxybenzyl magnesium chloride with epichlorohydrin 45 to give the chlorohydrin, which on potassium hydroxide treatment gave the epoxide 46. The hydrolytic kinetic resolution of epoxide 46 using S,S-salen-Co catalyst gave the enantiopure epoxide 47 which was then opened with vinylmagnesium bromide in presence of copper iodide to give homoallylic alcohol 48. This homoallylic alcohol 48 on epoxidation followed by TBS protection of alcohol group gave compound 50. TBS protected epoxide 50 was then subjected for hydrolytic kinetic resolution using S,S-salen-Co-catalyst which gave the chiral epoxide 51. This chiral epoxide 51 was then opened with vinylmagnesium bromide to give the homoallylic alcohol 52 which was then converted into its acrylate 53. This acrylate 53 on ring closing metathesis with Grubbs 1ˢᵗ Gen. catalyst gave the desired RCM product 54 in 85% yield. Further conversion of RCM product 54 to the natural product Dodoneine 44 is in progress (Scheme 9).
Scheme 9: Reagents and Conditions: (a) (i) PMB-MgCl, THF, Cul, -20 °C, 5 h; (ii) KOH, CH₂Cl₂, 73% (for two steps); (b) (S,S) Salen-Co⁺³-(OAc), H₂O, 16h, 45%; (c) vinlymagensium bromide, Cul, THF, -23 °C, 5h, 85%; (d) m-CPBA, CH₂Cl₂, 0 °C, 4 h, 72%; (e) TBSCI, imidazole, CH₂Cl₂, 0 °C- r.t., 24 h, 90%; (f) (S,S) Salen-Co⁺³-(OAc), H₂O, THF, 16 h, 45%; (g) Vinlymagnesium bromide, Cul, THF, -23 °C, 12 h, 80%; (h) Acryloyl chloride, NEt₃, 0 °C, 1 h, 90%; (i) Grubbs 1st, CH₂Cl₂, 85%

Organocatalytic approach towards the synthesis of Dodoneine:

Organocatalytic route for the synthesis of Dodoneine started with 2-(4-methoxyphenyl) ethanol 55 which on oxidation-Wittig-reduction sequence gave aldehyde 56.

Scheme 10: (a) (i) IBX, EtOAc, reflux, 7 h; (ii) PPh₃CHCOOC₂H₅, Toluene, reflux; (iii) NiCl₂.6H₂O, NaBH₄, MeOH, -30°C; (iv) DIBAL-H, CH₂Cl₂, -78 °C, 60% (over four steps); (b) (i) D-proline, DMSO, Nitrosobenzene; HWE salt, DBU, LiCl, CH₃CN; (ii) H₂-Pd/C, EtOAc, 8 h, 65% (over two steps); (c) TBSCI, imidazole, DMF, Overnight, 87%; (d) DIBAL-H, CH₂Cl₂, 78%; (e) (i) D-Proline, Nitrosobenzene, DMSO (ii) NaBH₄, MeOH, 70%

Aldehyde 56 on D-proline catalysed α-amination gave α-anilinoxaldehyde which on in-situ HWE-olefination, and hydrogenation gave γ-hydroxy ester 63 which was then silylated with TBSCI. This O-silylated ester 58 was then reduced to aldehyde with DIBAL-H at -78°C. This aldehyde was then aminoxylated using D-
proline to α-anilinoxy aldehyde which was in situ reduced to alcohol by using sodium borohydride in methanol. Further conversion of diol 60 into synthesized epoxide 51 is in progress (Scheme 10).

Chapter 2: Section C: Studies directed towards the synthesis of Seimatopolide B

Seimatopolides A (61) and B (62), two polyhydroxylated 10-membered macrolides, were recently isolated by Jang and Lee et al.8 from an ethyl acetate extract of *Seimatosporium discosioide* culture. Seimatopolides exhibited significant activity in a reporter gene assay for activation of peroxisome proliferator activated receptor c (PPAR-c) with EC₅₀ values of 11.05 µM, which shows therapeutic potential in the treatment of type 2 diabetes, inflammatory disease and certain cancers.

As depicted below (scheme 11), synthesis of acid fragment 69 commenced from commercially available 3-butene-1-ol which was protected as its TBS ether and then the double bond was epoxidised with m-CPBA to give epoxide. This epoxide was then resolved using (R,R)-salen-Co-complex to give enantiopure epoxide 65. This chiral epoxide on ring opening with dimethylsulfoxonium methyldie afforded one-carbon homologated allylic alcohol 66 which was protected as the MEM ether using MEMCl and DIPEA followed by removal of the TBS group to furnish alcohol 68. TEMPO-catalysed oxidation of the alcohol with NaOCl resulted in the formation of acid 69 in excellent yield.

**Scheme 11:** Reagents and conditions: (a) TBDMSCl, imidazole, CH₂Cl₂, 0 °C to r.t., 4 h, 88%; (b) m-CPBA, CH₂Cl₂, 0 °C to r.t., 1 h, 90%; (c) (R,R)-salen-Co-(OAc) (0.5 mol %), dist. H₂O (0.55 equiv), isopropyl alcohol, 0 °C, 24 h, (46% for diol, 45% for 65); (d) (CH₃)₃Si, n-BuLi, THF, 4 h, 86%; (e) MEMCl, DIPEA, CH₂Cl₂, 16 h, 87%; (f) TBAF, THF, 1 h, 88%; (g) TEMPO, Na₂HPO₄, NaOCl, NaClO₂, CH₃CN, overnight, 95%.

With substantial amounts of acid 69 and alcohol fragment 70 which was synthesized by another colleague, the coupling of acid and alcohol was achieved by using
intermolecular DCC coupling to afford the diene ester 71 in 91% yield. This diene ester was then subjected to ring closing metathesis conditions using Grubbs’ 2nd generation catalyst in CH₂Cl₂ under reflux conditions which led to the formation of cyclised product 72, in only 50% yield. Subsequent deprotection of MEM ethers using TFA in CH₂Cl₂ afforded the natural product, seimotopolide B.

![Scheme 12](image)

Scheme 12: (a) DCC, DMAP, CH₂Cl₂, 6 h, rt, 91%; (b) Grubbs II Gen. Catalyst, CH₂Cl₂, reflux, 16 h, 50%; (c) TFA, CH₂Cl₂, rt, 16 h, 70%.

**Conclusion:** We prepared the acid and alcohol fragments for the both Stagonolide C and modiolide A via different via different routes. Thus, the formal synthesis of Stagonolide C, synthesis of precursor for Dodoneine and total synthesis of seimotopolide B achieved.

**Chapter III: Studies directed towards the synthesis of Jaspine B and analogues**

Pachastrissamine (73) is an anhydrophytosphingosine derivative, which was initially isolated from a marine sponge *Pachastrissa sp.* in 2002 by Higa and co-workers. Soon after, the same compound was isolated from a different marine sponge *Jaspis sp.* and named Jaspine B by Debitus and co-workers. This marine natural product exhibits a high cytotoxic activity against various tumor cell lines in vitro.

Our synthesis began with the oxazolidine aldehyde known as Garner’s Aldehyde (74). The addition of lithium 1-pentadecyne to the Garner’s aldehyde gave an 8:1 mixture of propargylic alcohols 75a and 75b. The erythro-propargyl alcohol 75a was converted to trans-allyl alcohol 76 using sodium bis(2-methoxyethoxy)aluminium hydride. The alcohol 76 was then treated with p-TSA and methanol to hydrolyse isopropylidene group to give the N-Boc protected amino alcohol 77. Oxymercuration-demercuration sequence of the amino alcohol 77 afforded a mixture of Boc protected Jaspine B and 2-epi-jaspine B (scheme 13).
Scheme 13: Reagents and conditions: (a) Lithium-1-pentadecyne, -23 °C, 3 h, 63%; (b) Red-Al, ether, 0 °C-r.t., 60%; (c) p-TSA, Methanol, 4 h, 90%; (d) (i) Hg(OCOCF<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 2 h; (ii) alk. NaBBH<sub>4</sub>, 0 °C, 15%.

To improve the yield of the jaspine B we revised our strategy. Garner’s aldehyde 74 (scheme 14), on reaction with vinylmagnesium bromide gave 6:1 mixture of 79 and 80. The allyl alcohol 79 was then treated with p-TSA and methanol to hydrolyse the isopropylidene group to give the diol 81. The oxymercuration of 81 with Hg(OAc)<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> gave the desired product 82 in 67% yield. The stereochemistry of which was determined by 2D NMR study. Oxidative demercuration<sup>12</sup> using six equivalents of TEMPO gave the mercury displaced product 83 in 80% yield. Reductive cleavage of the N-O bond using Pd(OH)<sub>2</sub>/C and H<sub>2</sub>, at 70 psi gave the desired product 84 in 80% yield. The compound 84 was converted into its tosylate 85.

The study is under progress to functionalise 85 into Jaspine B and its analogues.

Scheme 14: Reagents and conditions: (a) vinyl magnesium bromide, THF, 0°C-rt, 10h, 70% (b) p-TSA, Methanol, 6h, 90% (c) Hg(OAc)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 3h, 67% (d) DMF, O<sub>2</sub>, NaBH<sub>4</sub>, then 59, TEMPO (6 equiv.), 30 min, 80% (e) H<sub>2</sub>/Pd(OH)<sub>2</sub>/C, 70 psi 3d, 80%;(f) TsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 90%.

To improve the yield of the compound 84, we modified our strategy. The allylic alcohol 81 was epoxidised with m-CPBA at 0 °C which gave a mixture of products.
This mixture was treated with tosyl chloride to get the monotosylated product \textbf{85} only in 40\% yield.

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle] (A) at (0,0) {90};
\node[draw,rectangle] (B) at (1,0) {\text{m-CPBA, DCM,} \at (0.5,0) \text{0}^\circ\text{C - rt}};
\node[draw,rectangle] (C) at (2,0) {93};
\draw[->] (A) -- (B);
\draw[->] (B) -- (C);
\end{tikzpicture}
\end{center}

In summary, we have synthesized \textit{2-epi} Jaspine B via oxymercuration method. Also we have synthesized the key intermediate for the synthesis of Jaspine B. Further functionalisation into various analogues of Jaspine B is in progress.
References:


2. For various application of HKR in synthesis of bioactive compounds, see review, (a) Kumar, P.; Naidu, S. V.; Gupta, P. Tetrahedron 2007, 63, 2745 (b) Kumar, P.; Gupta, P. Synlett 2009, 1367


