SYNOPSIS

The thesis entitled “Application of desymmetrization towards the synthesis of natural products: Saliniketals, Venturicidin-X and Emericellamide B” is divided into three chapters.

CHAPTER I: Formal total synthesis of (–)-saliniketals A and B:

Section A: This section deals with application of desymmetrization technique in asymmetric synthesis and description of earlier synthetic approaches of (–)-Saliniketals A and B.

Section B: This section describes the formal total synthesis of (–)-saliniketals A and B.

CHAPTER II: Synthesis of C15-C27 fragment of Venturicidin X:

Section A: This section brings flavor of some biologically active antibiotic molecules and earlier synthetic approaches towards the synthesis of C15-C27 fragment of Venturicidin X.

Section B: This section projects the synthesis of C15-C27 fragment of Venturicidin X.

CHAPTER III: Formal total synthesis of Emericellamide B:

Section A: This section deals with the introduction and earlier synthetic approach for the synthesis of Emericellamide B.

Section B: This section describes the formal total synthesis of Emericellamide B.
CHAPTER-I

Section A: Desymmetrization technique in asymmetric synthesis and description of earlier synthetic approaches of (–)-Saliniketals A and B.

The journey of development of life saving organic compound (drug) started in the twentieth century. Modern drug discovery has consisted of a series of thematic development that began with isolation and identifying the active ingredients from traditional medicines or by serendipitous discovery. Very often natural abundance of active natural products is very low. For their further studies and clinical trial, its laboratory synthesis is essential from an easily available chief starting intermediate. The chemical syntheses of natural molecules without the aid of enzymes often present formidable challenges to human ingenuity and skill. The structure of natural products in an almost infinite range of complexity and stability therefore often present distinct synthetic problems, which require strategies and tactics for their solutions. It is the almost unlimited variation in structure and the constant discovery of new molecular constructs that keep the field of natural products syntheses so attractive and vibrant. The dazzling biological properties exhibited by many natural products and the attendant opportunities these molecules offer for probing biological questions also serve as major attractions in this field of investigation.

Section B: Formal Total Synthesis of (–)-Saliniketals A and B:

Saliniketals A (1) and B (2) are bicyclic polyketides isolated in 2007 by Fanical and co-workers from marine actinomycete *Salinispora arenicola*. They inhibit ornithine decarboxylase (ODC) induction. Such ODC inhibitors may be used as valuable chemotherapeutic agents for cancer. Saliniketals A and B possesses a 2,8-dioxabicyclo[3.2.1]octane ring featuring a elaborate side chain at C11 that terminates in an unsaturated primary amide. The interesting molecular frame work combined with promising biological activity makes them an attractive target for total synthesis (Figure 1).

![Figure 1](image_url)
The details of our approach towards the synthesis of Saliniketals A and B are described in scheme 1, which illustrates that they both could be accessed from a common intermediate 3, which in turn could be obtained from 4 and 5 via Pirrung-Heathcock anti-aldol reaction condition. Intermediate 4 could be obtained by an intramolecular Wacker type cyclization of the olifine 6. The compound 6 could be obtained from a known bicyclic intermediate 7, which in turn could be obtained from furan and 2,4-dibromo-3-pentanone following seven steps reaction sequence.

**Retrosynthetic Analysis of (−)-Saliniketals A and B.**

![Scheme 1](image)

**Scheme 1**

We commenced our synthesis from intermediate 7, which could be obtained by the following sequence, Zn-Cu couple mediated [4+3] cycloaddition between 2,4-dibromo-3-pentanone and furan to form 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene-3-one, DIBAL-$H$ reduction, benzyl protection, chiral hydroboration, PCC mediated oxidation, Bayer-Villeger oxidation, followed by diastereoselective methylation afforded 7 (Scheme 3).
Acid catalysed methanolysis of bicyclic lactone 7 proceeded smoothly to furnish ester 14. LAH mediated reduction of ester followed by IBX oxidation in DMSO afforded aldehyde 15. Substrate controlled Grignard reaction with protected bromo ketone 16 in THF afforded Felkin-Anh alcohol 17 with good selectivity (86:14 by HPLC). Compound 17 upon treatment with BF₃·Et₂O in CH₂Cl₂ afforded a new compound 18 instead of 4 (Scheme 4). To avoid the protecting group manipulation, we chose Grignard reaction of 15 with 1-butenylmagnesium bromide in THF afforded 19. This time we got even better yield and better selectivity (96:4 by HPLC).
The absolute stereochemistry of the newly introduced chiral centre was determined at a later stage of synthesis. The hydroxyl group was protected as its acetate derivative and upon treatment with aqueous acetic acid furnished hemiacetal 20. Lithium borohydride mediated reduction followed by selective protection with TBDPSCl and Imidazole afforded 6 (Scheme 5).

Scheme 4

Scheme 5
Intramolecular Wacker type cyclization of 6 with catalytic amount of PdCl₂ and CuCl₂ under oxygen atmosphere proceeded smoothly to produce bicyclic acetal 21 with good yield. The silyl protecting group was removed with 1(M) solution of TBAF in THF and the resulting alcohol was oxidized to corresponding aldehyde 4 using IBX. The aldehyde 4 on ant-aldol reaction with ester 5 following Pirrung-Heathcock protocol afforded 22 in good yield and with good anti selectivity (96:4 by HPLC).

X-Ray Crystal Structure of 23.
Catalytic hydrogenation of compound 22 followed by acetonide protection afforded compound 23 whose NOE correlation and $^{13}$C value at 100.6 ppm supports the anti geometry between C7 and C9 hydroxy group. The single crystal X-ray crystallographic analysis unambiguously confirmed its relative and absolute stereochemistry (Figure 2). Reduction of compound 23 using LAH in THF afforded an advanced common intermediate 3 (Scheme 6). The spectral analytical data of 3 $\{[\alpha]_D^{25} +6.1$ (c 1.24 CHCl$_3$); lit. $[\alpha]_D^{25} +6.2$ (c 0.81 CHCl$_3$)$\}$ were in good agreement with the reported values by Paterson et al.

CHAPTER-II

Section A: This Section Deals With The Importance of Some Biologically Active Antibiotic Molecules and Earlier Synthetic Approaches Towards The Synthesis of C15-C27 Fragment of Venturicidin X.

Discovery of antibiotics is the greatest achievement of 20$^{th}$ century. They are the drug molecules derived wholly or partially from certain microorganisms and are used to treat bacterial or fungal infections. They are ineffective against virus. They kill either microorganism or stop them from reproducing, allowing the body’s natural defense to eliminate them. The effectiveness of the treatment depends on how well the drug is absorbed into the bloodstream, how much of the drug reaches the sites of infection in the body, and how quickly the body eliminates the drug.

Several hundreds of compounds with antibiotic activity have been isolated from microorganisms or synthesized in laboratory over few decades, but only a few of them like Erythromycin, Azithromycin, Telithromycin, Tetracyclines etc. are clinically useful, and others are not, because most of them are toxic to human body.

Mutation of bacteria, like other living organism over time in response to environmental challenges is a common phenomenon and hence resistance of bacteria to antibiotics is an unavoidable side effect of their use. Thus introduction of a new antibiotic molecule by isolation or modifications of natural or synthetic antibiotics have become a challenging task to synthetic organic chemist.
Section B: Synthesis of C15-C27 Fragment of Venturicidins:

Venturicidin A, B and its aglycon Venturicidin X are 20-membered macrolide antibiotics were isolated from several *streptomyces*. Their structure and absolute configuration were elucidated by chemical degradation, spectroscopic correlation and X-ray crystallographic analysis. They show strong activity against a number of plant pathogenic fungi and mitochondrial H⁺ATPase. Among all nine stereocentres within Venturicidin-X (Figure 3), alternate 1,3,5-anti-methyl substitutions is quite challenging and we have interested to apply our desymmetrization protocol for the synthesis of C15-C27 fragment of venturicidin X.

![Venturicidin X (24)](image)

Our primary synthetic strategy divided the macrolide Venturicidin X into two major segments, acid C1-C14 (25) and alcohol C15-C27 (26), which could be coupled by esterification followed by intramolecular Wittig-Hornor condensation (Scheme 7).

**Retrosynthetic analysis of venturicidin X.**

![Scheme 7](image)
The C15-C27 fragment could be obtained from intermediate 27 via Sharples asymmetric epoxidation followed by TBDMSOTf mediated rearrangement. Intermediate 27 could be obtained from highly substituted alcohol 28 via standard reaction procedure. 28 could be obtained from substrate controlled Grignard reaction with highly substituted aldehyde 29 and ethylmagnesium bromide. The synthesis of lactone 29 already been depicted in previous chapter.

**Synthetic strategy for the C15-C27 unit of venturicidin X.**

The synthesis of C15-C27 fragment (26) of venturicidin X was envisaged from a highly substituted known aldehyde 29, widely used by our group for the synthesis of various biologically active natural products (Scheme 8).

The synthesis was commenced from aldehyde 29 whose synthesis has already been disclosed in the previous chapter. The highly substituted aldehyde 29 under Grignard reaction condition with ethyl magnesium bromide yielded Felkin-Anh alcohol 28. The newly generated alcohol was converted to its acetate derivative 30 and the anomeric methyl group was removed with 60% acetic acid followed by TEMPO mediated oxidation yielded lactone 31. The axial α-methyl centre was isomerized to equatorial isomer 32 with DBU as non nucleofilic base (Scheme 9).
LAH mediated reduction of lactone 32 yielded mono protected triol which on acetonide protection furnished 33. Hydrogenation of compound 33 followed by selective primary protection with TBDMSocl and imidazole yielded compound 34. The secondary hydroxyl group was converted to its xanthete ester followed by treatment with Bu3SnH and catalytic amount AIBN furnished 35. Desilylation of compound 35 using TBAF in THF yielded compound 36 (Scheme 10).
The primary hydroxyl group was oxidised to aldehyde which on Wittig olefination yielded 27. The α,β- unsaturated ester was reduced with DIBAL-H in CH₂Cl₂ at –78 °C and the resulting allylic alcohol on Sharpless epoxidation condition yielded 37. This epoxy alcohol on treatment with TBDMSOTf and DIPEA at –78 °C yielded rearranged aldehyde 38. The aldehyde on Wittig homologation with Ph₃P=CHCO₂Et in refluxing benzene afforded olefin which on hydrogenation yielded 39 (Scheme 11).

The ester was converted to lactone 40 upon treatment with catalytic PPTS in CH₂Cl₂:MeOH (10:1). Diastereoselective methylation of 40 with LDA and MeI in THF at –78 °C yielded 41 in good yield. The lactone was reduced to diol using LAH in THF and the primary hydroxyl group was selectively protected with TBDMSCl and Imidazole in CH₂Cl₂ yielded the desired product 26 in good yield (Scheme 12).
Scheme 12

The spectral analytical data of 26 \([\alpha]_D^{25} +35.0 (c 1.2 \text{ CHCl}_3); \text{lit. } [\alpha]_D^{24} +33.6 (c 2.09 \text{ CHCl}_3)\} were in good agreement with the reported literature. Thus we have completed the C15-C27 segment of venturicidin X following twenty three steps liner sequence starting from a known intermediate 29 and efforts to complete the synthesis of C1-C14 fragment with minor manipulations are in progress in our group.

CHAPTER-III

Section A: Introduction and Earlier Synthetic Approach for Emericellamide B.

Emericellamide A (42) and B (43) (Figure 4) are the two cyclic depsipeptide were isolated in 2007 from marine fungus Emericella sp. The planar structure of these two depsipeptides were assigned by the application of Merfy’s method, \(J\)-based coupling constant analysis and

![Emericellamide A (42)](image)

![Emericellamide B (43)](image)

Figure 4
modified Mosher method. They both show antibacterial activities against methicillin-resistant *Staphylococcus aureus* with MIC value 3.8 and 6.0 µM respectively. The interesting chemical structure and impressive biological activity has made them attractive target for total synthesis. To date only one total synthesis of Emericellamide B (43) has been reported by Tao Ye et. al.

**Section B: Formal Total Synthesis of Emericellamide B:**

The detail of our approach towards the synthesis of Emericellamide B is depicted in Scheme 13. Disconnection of the emericellamide B (43) at the two alanine residues would give an advanced intermediate 44 which on further fragmentations would provide tetrapeptide 45 and a polyketides 46. The tetrapeptide 45 could be obtained following standard peptide coupling protocol starting from commercially available protected L-amino acids and the polyketide fragment 46 could be envisaged following desymmetrization protocol to afford four chiral centers starting from a known bicyclic lactone 48 which in turn could be obtained from 10 via desymmetrization with chiral hydroborane.
Tetrapeptide 45 was synthesized from commercially available protected L-amino acids. The coupling of Cbz-leu-OH (49) with H-ala-O′Bu ester using EDCI and HOBT afforded the dipeptide 50. Deprotection of the Cbz-group with Pd-C (10%) in ethyl acetate under hydrogen atmosphere followed by coupling with Cbz-val-OH afforded the tripeptide 51. Following the same sequence of reactions, 45 was obtained in good yield (Scheme 14).

The synthesis of 46 was initiated from a known bicyclic intermediate 48, which in turn could be prepared from 10 following desymmetrization with chiral (+)-Ipc2BH, PCC mediated oxidation, Bayer-Villiger reaction, and diastereoselective methylation (Scheme 15).
Reduction of the bicyclic lactone 48 with LAH in THF furnished mono-protected triol and the 1,3-diol moiety was protected with acetonide to afford 55. The primary hydroxyl group was converted to its TBS-ether using TBDMSCl and imidazole in CH$_2$Cl$_2$ followed by deprotection of the benzyl-ether with Pd/C (10%) under hydrogen atmosphere gave 56. The secondary hydroxyl group was converted to its xanthate derivative and subsequent treatment with Bu$_3$SnH in presence of catalytic amount of AIBN afforded 57. Desilylation of 57 with TBAF in THF provided alcohol and the primary hydroxyl group was oxidized with IBX in DMSO and THF furnished aldehyde 47. Wittig homologation yielded olefin which on treatment with catalytic amount of Pd-C (10%) under hydrogen atmosphere afforded 58 (Scheme 16).

Scheme 16

The acetonide was deprotected using 6N HCl in ethyl acetate provided diol and the primary hydroxyl was selectively silylated with TBDMSCl and imidazole to obtain the TBS-ether 59. Esterification of the Boc-ala-OH with 59 using EDCI and DMAP followed by desilylation with CSA afforded 60. The primary hydroxyl group was converted to acid following TEMPO mediated oxidation to furnish 46. The acid 46 was activated with EDCI in presence of HOBT and the amine 45 was coupled to obtain our desired product 44 (Scheme 17).
In conclusion, we have achieved the formal total synthesis of Emericellamide B from a bicyclic precursor in fifteen longest linear steps in a convergent fashion which reconfirmed the absolute stereochemistry of Emericellamide B.