ABSTRACT
ABSTRACT

The thesis entitled “Total synthesis of (+)-antimycin A$_{3b}$, (+)-blastmycinone, cruentaren B and synthetic studies of penifulvin D” consists of three chapters.

CHAPTER-I: Describes the total synthesis of (+)-antimycin A$_{3b}$ and (+)-blastmycinone.

CHAPTER-II: Describes the total synthesis of cruentaren B.

CHAPTER-III: Describes the synthetic studies of penifulvin D.

CHAPTER-I

Total synthesis of (+)-antimycin A$_{3b}$ and (+)-blastmycinone

Antimycins belongs to a family of antifungal antibiotics, sharing a common nine-membered dilactone ring-structure, isolated as secondary metabolites during the last 5-6 decades from various strains of *Streptomyces*. The pronounced biological activities of the antimycins ranging from antifungal to antitumor properties make them attractive targets to synthetic organic chemists. Total syntheses of (+)-antimycin A$_{3b}$ (1) and (+)-blastmycinone (2) were achieved using, as a key step, a methods developed by us for the synthesis of 2-methyl-1,3-diols via Ti(III) mediated diastereo and regioselective opening of trisubstituted 2,3-epoxy alcohols, to carry out the stereoselective construction of the hydroxyl acid segment.

![Image of (+)-Antimycin A$_{3b}$ (1) and (+)-Blastmycinone (2)]

We envisaged that the completion of 1 relied on the coupling of de-Boc dilactone amine 5 and acid 3 that was expected to be derived from 3-aminosalicylic acid 4 via EDCI-HOBt coupling. The dilactone 5 would be prepared from polyketide unit 7, which in turn could be obtained via Cp$_2$TiCl mediated opening of 2,3-epoxy alcohol 8. The epoxy alcohol 8 could be prepared from commercially available starting chiron (-)-ethyl lactate 9. (+)-Blastmycinone, a degradable product of antimycin, could be derived from polyketide unit 7 (Scheme 1).
We commenced our synthesis from commercially available starting material (S)-ethyl lactate 9. PMB protection of 9 followed by DIBAL-H reduction gave 11. Horner-Wadsworth-Emmons olefination of 11 with (EtO)₂P(O)CH(n-Bu)CO₂Et using Z selective
reagent furnished a mixture of Z and E alkenes 12. Reduction of the mixture of α,β-unsaturated ester with DIBAL-H followed by mCPBA epoxidation gave 8. In this stage both the isomers were separated by silica gel column chromatography. The trisubstituted epoxy alcohol was then treated with Cp2TiCl to carry out crucial radical mediated epoxide opening reaction to give 13. Reductive opening of 13 using Na(CN)BH3-TMSCl, followed by silyl protection using TBSCl gave 14.

Compound 14 was next subjected to stereocentre inversion following a two-step oxidation-reduction protocol to furnish the requisite isomer, which on acylation with isovaleryl chloride afforded 7. PMB deprotection of 7 using DDQ followed by coupling with Boc-Thr(Bn)-OH using DCC-DMAP gave 16. TBS deprotection followed by two-

The aromatic acid was prepared from 3-aminosalicylic acid 4 in four steps following reported procedure. N-formylation of 4, followed by esterification with MeI gave 18. Benzylation of the phenolic hydroxyl of 18 with BnBr followed by methyl ester hydrolysis using LiOH-H2O afforded aromatic acid 3.

Boc-deprotection of 5 with TFA gave amine salt, which on coupling with 3 using EDCI-HOBt gave 19. Compound 19 on debenzylation with Pd-C/ H2 furnished antimycin A3b. The 1H and 13C NMR spectra and optical rotation, [α]D 25 = +75.6 (c = 0.25, CHCl3), of our synthetic product 1 matched with those reported for antimycin A3b by other groups.

The synthesis of (+)-blastmycinone, a degradation product of antimycin, was
achieved in six consecutive steps from 7. Desilylation of 7 using (±) CSA followed by two-step oxidation using DMP and NaClO₂, and finally treatment with CH₂N₂ gave ester 10. PMB deprotection of 10 using DDQ followed by cyclisation using (±) CSA afforded (+)-blastmycinone.

The \( ^1 \)H NMR and \( ^{13} \)C NMR spectra and optical rotation \([\alpha]_D^{27} = +9.1\) (c = 0.17, CHCl₃), of our synthetic product 10 matched with those reported for the natural product (+)-blastmycinone (literature \([\alpha]_D^{27} = +11.2\) (c = 0.85, CHCl₃).

**CHAPTER-II**

**Total synthesis of cruentaren B**

In search of new biologically active natural products, myxobacteria have been proven to be a rich repertoire of innumerable secondary metabolites with novel structures and wide-ranging properties. The benzolactones, cruentaren A (1) and its ring-contracted congener cruentaren B (2) (Figure 1), are two such molecules isolated from myxobacterium *Byssvorax cruenta*. While cruentaren A strongly inhibited the growth of yeasts and filamentous fungi and showed high cytotoxicity against L929 mouse fibroblast cells, cruentaren B showed only marginal cytotoxicity and no antifungal activity. However, thorough evaluation of the cytotoxic and other biological properties of cruentaren B has not been possible due to the limited natural abundance of this compound. Chemical synthesis, not only, remains as the only option to get larger quantities of the molecule.
necessary for further biological studies, but can also help to design and build more potent synthetic analogs. Because of their novel structures and wide-ranging biological activities, cruentarens have attracted the attention of synthetic chemists worldwide.
A retrosynthetic analysis of cruentaren B (2) is shown in Scheme 1. We envisioned constructing the target molecule from the fragments 5-7 via an acetylide-triflate cross-coupling reaction (6 + 7), followed by selective hydrogenation to the Z-olefin and a Wittig olefination with 5. The resulting product after global deprotection of the protecting groups and a base-catalyzed cyclization was expected to furnish the target natural product 2. While compound 6 could be built from 2,4,6-trihydroxybenzoic acid 11, the acetylenic intermediate 7 could be derived from commercially available methyl (R)-3-hydroxyl-2-methylpropionate 14. An enantioselective aldol reaction on butyraldehyde 9 could furnish the ylide component 5.

Our synthesis commenced with the construction of the benzolactone moiety 6 (Scheme 2). Acetonide protection of 11 followed by selective O-methylation, under Mitsunobu conditions, gave 15. Next, the alcohol 15 was treated with Tf₂O in pyridine to give the triflate compound which upon Pd-catalyzed Stille coupling with allylstannane gave the desired product 10. Dihydroxylation of 10 with N-methylmorpholine (NMO) and OsO₄ followed by oxidative cleavage with NaIO₄ gave an aldehyde, which on asymmetric crotylboration following Brown’s protocol and using (–)-Ipc₂B(crotyl), resulted in the formation of an anti-adduct, the homoallylic alcohol. Silyl protection of the secondary hydroxyl group with TBSOTf gave 16. Compound 16 was converted to the primary alcohol 6 in three steps – dihydroxylation followed by oxidative cleavage and a NaBH₄ reduction.

Synthesis of 7 is depicted in Scheme 3. Aldehyde 18, prepared from commercially
available methyl (R)-3-hydroxyl-2-methylpropionate 14 in three steps by TBDPS protection, reduction and oxidation, was subjected to the modified Evans aldol reaction using propanoyl oxazolidinone 19 as a chiral auxiliary to afford aldol product 20 in good yield and diastereoselectivity after chromatographic purification. Silyl protection of the secondary hydroxyl group as TBS ether with TBSOTf followed by reductive removal of the chiral auxiliary gave the alcohol 13. Swern oxidation of the alcohol 13 followed by Mukaiyama aldol with TBS enol ether of t-butyl acetate gave the required diastereomer, which on silyl protection using TBSOTf gave 12. DIBAL-H reduction of 12 gave the alcohol 21. Dess-Martin periodinane (DMP) oxidation of 21 gave an aldehyde, which was converted to the alkyne compound 22 using Corey’s protocol. Global deprotection of the silyl protecting groups followed by selective mono tosylatio n of the primary hydroxyl group and cyanation with NaCN in the presence of a catalytic amount of NaI gave the
Abstract

cyano compound 23. Acetonide protection followed by DIBAL-H reduction, hydrolysis and finally NaBH₄ reduction gave the alcohol 24. Next, deprotection of the acetonide with CSA and global protection of the resulting triol with TBSOTf afforded 7.

Scheme 4

The synthetic route for the right hand segment 5 is depicted in Scheme 4. Non-Evans syn-aldol reaction between 25 and butanal 9 using Crimmins’ protocol gave secondary alcohol 26. Protection of the hydroxyl group as TBS ether, followed by oxidative removal of the chiral auxiliary with H₂O₂ and LiOH gave 8. Compound 8 was coupled with 2-aminoethanol using common amide bond forming protocol with EDCI and HOBT to afford 27. Wittig salt 5 was generated in two steps with conversion of the hydroxyl group to an iodo, followed by the reaction of the iodide with Ph₃P.

Scheme 5
With all the three segments 5-7 in hand, we undertook studies to stitch them together to build the entire framework of the cruentaren B (Scheme 5). The triflate, generated from 6 using Tf₂O, was treated with lithiated alkyne moiety of 7 to afford the desired coupling product 28. After successful 1st coupling, we deprotected the primary TBS selectively with HF-py complex to give an intermediate alcohol, which was reduced by hydrogenation using Pd-BaSO₄/quinoline to give the Z-olefin 4. Next, Dess-Martin periodinane (DMP) oxidation followed by a selective Z-olefination furnished the entire carbon framework 29 of the target molecule. Reaction between the ylide, generated from 5, and aldehyde at –80 °C in THF-HMPA gave the required Z-olefin. The Product 29 was subjected to global deprotection of the TBS groups to afford the desilylated product, which on treatment with LiOH.H₂O in THF afforded the target molecule, cruentaren B (2) (Scheme 5). The spectral data and optical rotation data were virtually identical to those of the natural product.

CHAPTER III

Synthetic studies of penifulvin D

\[ \text{Penifulvin D (1)} \]

*P. griseofulvum*, world wide in its distribution, shows significant insecticidal activity in assays against the fall armyworm. An organic extract from cultures of *P. griseofulvum* NRRL35584 showed potent antifungal and antiinsectan activity in preliminary assay. Studies of this extract have lead to the discovery of novel antiinsectan sesquiterpenoid penifulvin D (1). The overall structure of penifulvin D assigned by analysis of NMR data, having dioxa[5.5.5.6]fenestrance ring system in which four rings share a central quaternary carbon. Additionally there are two more quaternary carbons, a γ- and δ- lactone sharing the acylal center and a total of five streogenic centre congested on a 15 carbon.
Retro synthetic analysis of penifulvin D (1) is illustrated in Scheme 1. We envisaged that completion of 1 relied on oxidation of 2 which was expected to be derived from 3 via cyanohydrin formation, followed by functional groups interconversions. Alcohol 4 could be prepared from 5 via Cp₂TiCl mediated radical cyclisation. Ester 5 could be obtained from 6 by two carbon olefination and functional groups interconversions. The keto alcohol 6 could be derived from commercially available cyclopentanone 7 by using Michael addition followed by, one carbon olefination, allylic oxidation and functional group interconversion.

We commenced our synthesis from commercially available starting material cyclopentanone 7. According to our retro synthetic strategy, first step involved crucial Michael addition reaction. To carry out the Michael addition reaction, cyclopentanone 7 was converted to the corresponding TMS enol ether derivative 8. Compound 8, without further purification and characterization, was taken forward for the Michael addition
reaction with mesityl oxide to give 9.

\[
\begin{align*}
\text{Scheme 2} \\
\text{Selective protection of one of the carbonyl groups of 9 with 1,3-propanedithiobis(trimethylsilane) afforded 10. Compound 10 on one carbon olefination followed by allylic oxidation with SeO}_2 \text{ gave 11. Treatment of 11 with AgNO}_3, \text{ followed by reaction with lithiated ethyl ethynyl ether and finally Mayer-Schuster rearrangement furnished the } \alpha,\beta-\text{unsaturated ester 12. } m\text{CPBA epoxidation followed by radical cyclisation using } \text{Cp}_2\text{TiCl afforded 13. The relative stereochemistry of the newly generated centre was confirmed by NOESY experiment. Although we have not get the desired stercocentre, we still proceed to construct the frame work of penifulvin D. Silyl protection of 13 using } \text{TBSCl, followed by oxidation with DMP gave 14 (Scheme 2). The treatment of 14 with } \text{TMSCN and ZnI}_2 \text{ in CH}_2\text{Cl}_2 \text{ gave an unidentified compound. Many other methods for the formation of cyanohydrin were unsuccessful, leaving the total synthesis of the molecule still elusive.}
\end{align*}
\]