SYNOPSIS

The thesis entitled “Total synthesis of palmerolide A, dihydroconduritols and lentiginosine” is divided into two chapters.

First chapter of the thesis describes the formal total synthesis of bioactive marine macrolide palmerolide A. Palmerolide A was isolated by Baker and co-workers from an Antarctic tunicate Synoicum adareanum. Palmerolide A is a 20-membered macrolactone containing five chiral centers and seven unsaturations. Palmerolide A was found to be potent and selectively cytotoxic against human melanoma cancer cell lines and was also shown to inhibit vacuolar V-ATPase.

In section A, enantioselective formal total synthesis of palmerolide A is described. Key steps in the synthesis involve Jung non-aldol aldol reaction to construct the C16-C23 fragment 1 and oxidation of a chiral furyl carbinol to assemble the C1-C15 fragment 2.

Scheme 1: Synthesis of C16-C23 fragment of palmerolide A.
Scheme 2: Formal total synthesis of palmerolide A.

In section B, enantiospecific formal total synthesis of palmerolide A is presented from chiral pool tartaric acid. This approach is based on coupling of the three fragments viz. C1-C8 enoic acid fragment 3, C9-C15 vinyl stannane fragment 4 and the C16-C23 vinyl iodide fragment 1. The C1-C8 enoic acid fragment 3 is synthesized from L-threotol obtained from L-tartaric acid, while synthesis of the C9-C15 fragment 4 involved the elaboration of a γ-hydroxy amide derived from the bis-Weinreb amide of tartaric acid. Stille coupling of the vinyl iodide 1 obtained by Jung non-aldol aldol process with the vinyl stannane 4 delivered the C9-C23 unit. Esterification of this unit with the enoic acid 3 followed by zinc mediated Boord olefination and RCM furnished the macrolactone which is further elaborated to palmerolide A.

Scheme 3: Synthesis of C1-C8 fragment of palmerolide A.
Scheme 4: Enantiospecific formal total synthesis of palmerolide A.

Section A of the second chapter deals with the enantiospecific synthesis of dihydroconduritols E and F from tartaric acid. Conduritols are 1,2,3,4-cyclohex-5-ene tetrols and are shown to be inhibitors of glycosidase. A number of derivatives of conduritols were found to possess various biological activities. Enantiospecific synthesis of dihydroconduritol E and F is accomplished from tartaric acid employing the Boord type fragmentation and ring closing metathesis as the key steps.

Scheme 5: Enantiospecific synthesis of dihydroconduritols E and F.
Section B of the second chapter describes the enantiospecific total synthesis of (+)-lentiginosine. Lentiginosine is a dihydroxylated indolizidine alkaloid isolated from leaves of the plant *Astragalus lentiginosus*. Lentiginosine is the most powerful and competitive inhibitor (IC$_{50}$ 5µg/mL) of amyloglucosidase known so far. Key transformation in the synthesis include the *in situ* reduction and cyclization of a dihydroxyazide derived from the γ-hydroxy amide prepared from tartaric acid amide.

![Scheme 6: Enantiospecific total synthesis of (+)-lentiginosine.](image-url)