Chapter 1

An Introduction to Ent-Kauranoids and Diterpenoid Alkaloids

1.1 INTRODUCTION

Terpenoid natural products are one of the largest classes of biologically active small molecules, and hold importance in areas of flavors, fragrances, poisons, and medicines.[1] The *Isodon* diterpenes, which encompass the *ent*-kauranoids, possess important biological properties such as antibacterial and anticancer activity. Further investigations of these natural products and analogues as medical treatments have been hampered by the lack of efficient synthetic routes. The biosynthetically related diterpenoid alkaloids also remain relatively understudied with respect to their syntheses, even though a significant number of the natural products possess biological activity involving modulation of voltage-gated ion channels. In this chapter, the rich history of *ent*-kauranoid and diterpenoid alkaloids is discussed in terms of biosynthesis,

distribution, structure, and biological activity with the aim of understanding motivations behind the surge of synthetic studies in recent years.

1.2 TERPENE BIOSYNTHESIS

In nature, linear hydrocarbons undergo cyclizations, rearrangements, and oxidations to create terpenoids. The building blocks of these linear hydrocarbons are C5 isoprenyl monomers (**3** and **4**) derived from acetyl coenzyme A (acetyl-CoA, **1**) or deoxyxylulose (**2**), and are produced by the biosynthetic mevalonate or deoxyxylulose pathways (Figure 1.1).[2] The monomers (**3** and **4**) are stitched together to form linear, pyrophosphorylated polyenes of varying lengths, such as geranyl pyrophosphate (**5**), farnesyl pyrophosphate (**6**), squalene (**8**) and so on, and in turn afford terpenes belonging to general classes such as monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), and triterpenes (C30, *e.g.* steroids). Cyclizations and rearrangements can form varieties of carbocyclic skeletons, and subsequent oxidations result in an even larger degree of diversity.

The biosynthesis of monoterpenes from geranyl pyrophosphate (**5**) is used as an example to demonstrate the complexity and diversity exhibited by the natural products. **5**, which contains only two prenyl units, can undergo cyclization and/or rearrangement to afford seven unique carbocyclic skeletons (Figure 1.2). Polyenes containing more prenyl units would provide an even greater number of unique carbocyclic skeletons. Oxidation of the carbocycles generates another degree of complexity, as exemplified by the many *menthane type* monoterpene natural products. Additionally, with larger terpenes such as sesquiterpenes and diterpenes, there are more possible sites for oxidation. Thus, the

complexity and diversity of terpenoid natural products increase exponentially with each additional prenyl unit.

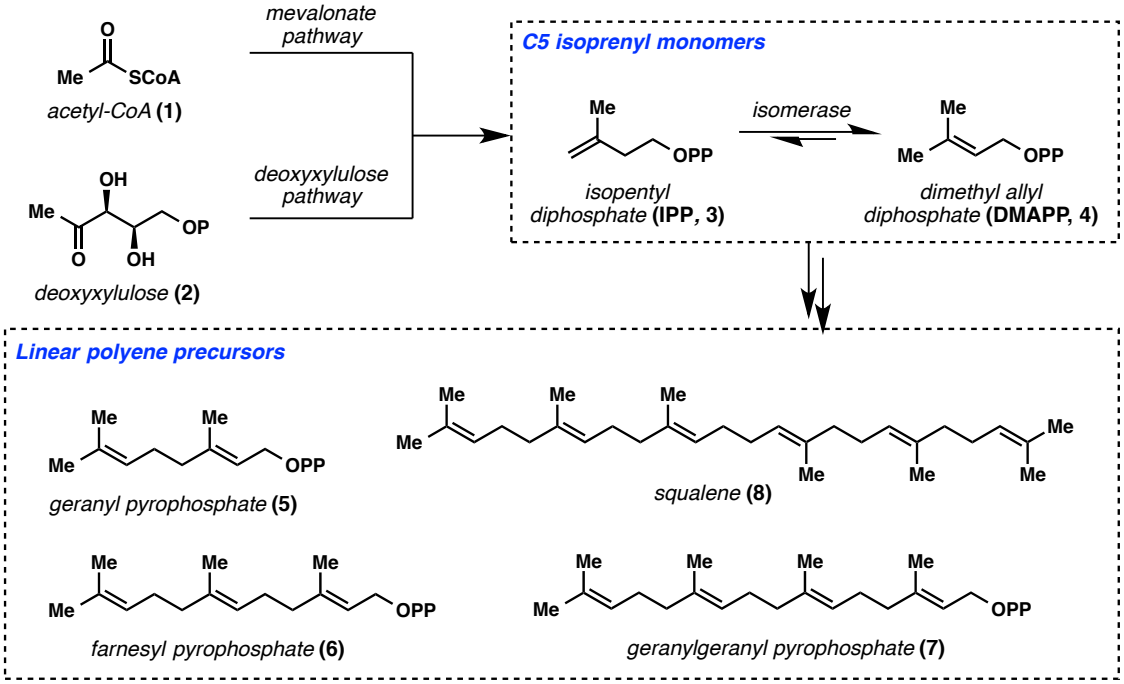

Figure 1.1. Biosynthesis of terpene precursors.

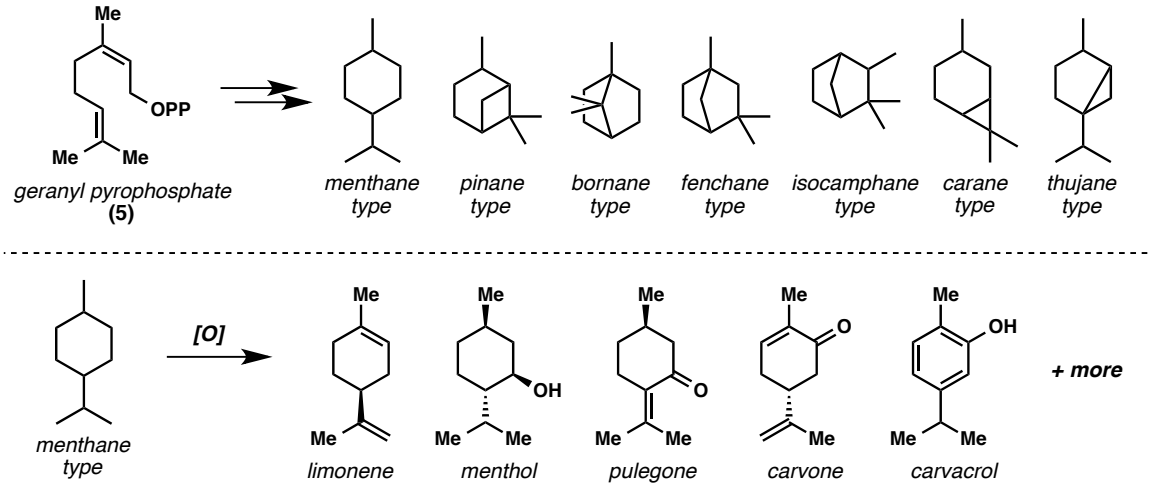

Figure 1.2. Biosynthesis of monoterpenes.

1.3 OVERVIEW OF *ENT*-KAURANOIDS

The *Isodon* diterpenoids are a large family of natural products that are principally based on the structure of the diterpene *ent*-kaurene. The first study of *Isodon* extracts dates back to 1910,[3] and the first isolation of an *Isodon* diterpenoid was achieved in 1958.[4e–g] Since then, more than 600 *Isodon* diterpenoids have been isolated, with the family exhibiting structural diversity in the form of oxygenation patterns and rearranged frameworks.[5] The structural homology between many *ent*-kauranoids suggests the benefit of a unified synthetic strategy to access this biologically active family of natural products. Plants from the genus *Isodon* have long been used for medical purposes in East Asian countries, and the isolated diterpenoids have exhibited antibacterial and antitumor properties.

1.3.1 *Structure and Biological Activity*

The vast majority of *Isodon* diterpenoids share the same carbocyclic skeleton as *ent*-kaurene (**9**, Figure 1.3). Oxidation of the skeleton returns oxygenated natural products such as adenanthin (**10**), and others with bridging oxygen heterocycles, as in 7,20-epoxy type longikaurin E (**11**). The 6,7-*seco*-*ent*-kauranoids represent the largest group of products deviating from the *ent*-kaurene carbocyclic skeleton, and are derived from oxidative scission of the C6–C7 bond of their 7,20-epoxy- precursors. Representative members of this type include trichorabdals A and B (**12** and **13**), sculponeatin N (**14**), and enmein (**15**), which has undergone translactonization at C1/C7. More exotically rearranged products have also been discovered, as exemplified by maoecrystals V and Z (**16** and **17**).

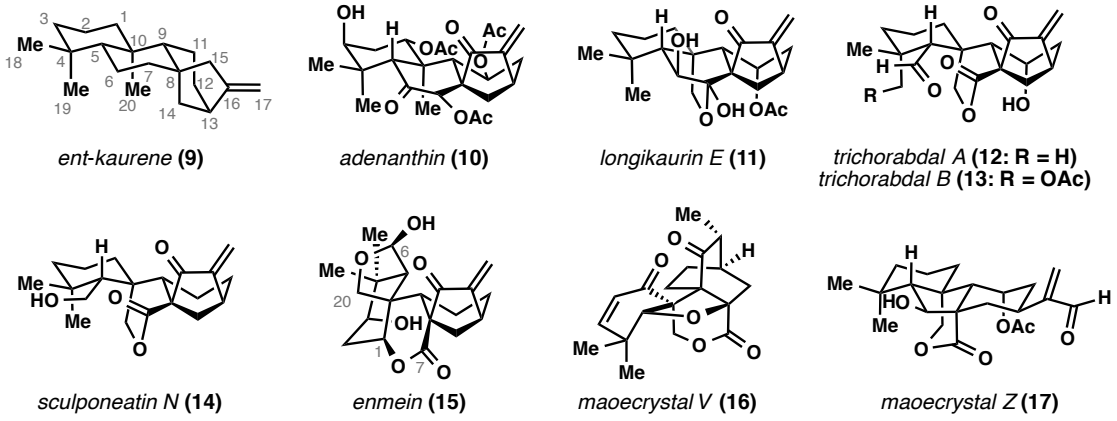

Figure 1.3. *Ent*-kaurene (**9**) and representative *ent*-kauranoids.

Most of the biologically active *ent*-kauranoids share a common α,β-unsaturated carbonyl as part of a bridging cyclopentane D-ring. This structural motif is a pharmacaphore that is crucial for biological activity of the natural products, and possibly acts through electrophilicity of the Michael acceptor for covalent modification.[6] In early studies on structure-activity relationships (SAR), Fujita and coworkers reported that hydrogenation of the enone moiety significantly weakened antitumor and antibacterial activity of *ent*-kauranoids and derivatives.[4bc,7] Furthermore, adenanthin (**10**) has been shown to selectively inhibit peroxiredoxin enzymes by covalent modification of a key cysteine residue, while its saturated analog was found to be biologically inactive.[8]

1.3.2 *Ent-Kauranoid Biosynthesis*

The diterpene *ent*-kaurene (**9**) is known to arise from enzyme-mediated cyclizations and rearrangements of geranylgeranyl diphosphate (**7**, Figure 1.4).[9] An initial cyclization mediated by copalyl diphosphate synthase affords the bicyclic product **18**, and a second cyclization mediated by kaurene synthase B results in rearrangements to

eventually provide *ent*-kaurene (**9**). Hong and Tantillo have also proposed concerted biosynthetic pathways that avoid secondary carbocations.[10]

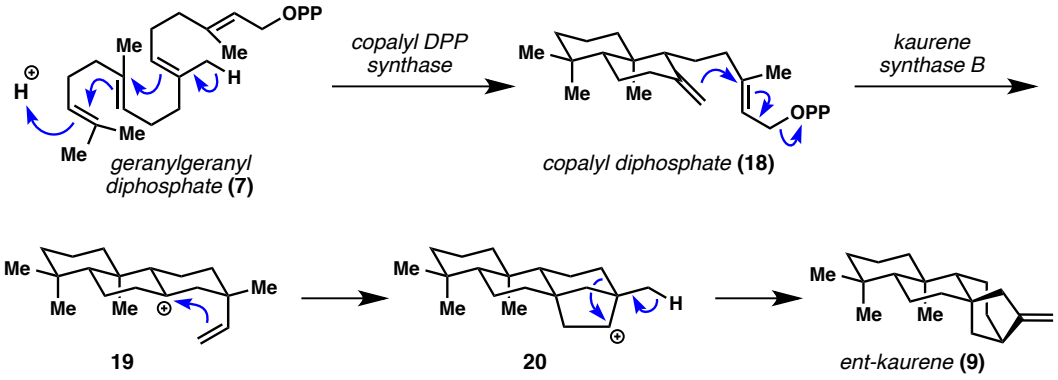

Figure 1.4. Biosynthesis of *ent*-kaurene (**9**).

Enzymatic oxidations of *ent*-kaurene (**99**) return natural products that are classified based on oxidation at C20. Notably, 7,20-epoxy-*ent*-kauranoids of the general structure **21** are prone to undergo oxidative cleavage of the C6–C7 bond to afford 6,7-*seco*-*ent*-kauranoids (**22**, Figure 1.5). The rearranged natural product, maoecrystal Z (**17**, see Figure 1.3), likely arises from a retro-aldol reaction from the 6,7-*seco* type (**22** and intramolecular aldol cyclization of the resulting enolate (**23**) to tetracycle **24**. This hypothesis is further supported by studies from Fujita and coworkers, who demonstrated that trichorabdal B (**13**) rearranged to tetracycle **25** under basic conditions (Figure 1.5b).[4c] From the *ent*-kaurene framework, sequences of oxidation, C6–C7 bond cleavage, and skeletal rearrangements ultimately produce the over 600 known structurally distinct *ent*-kauranoids.

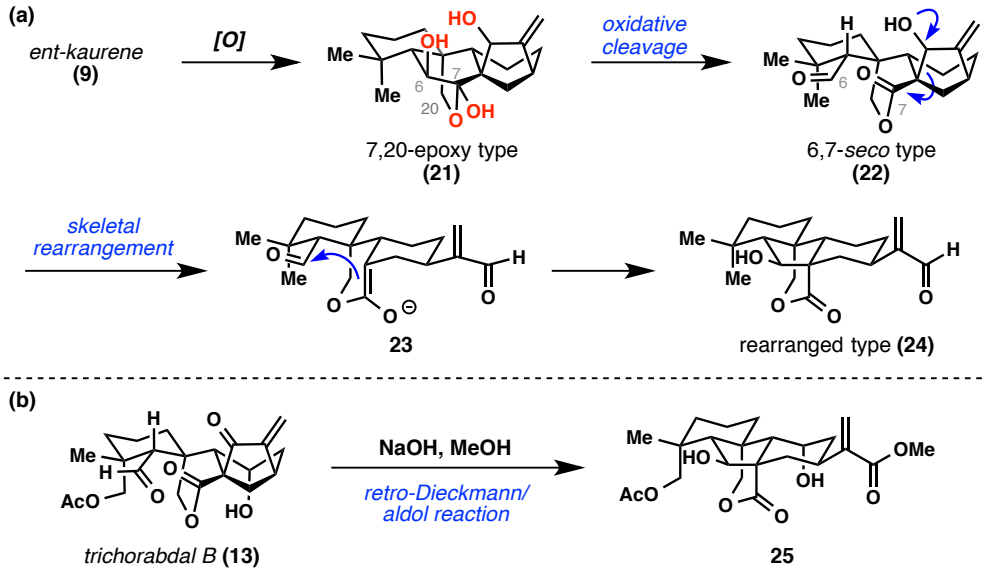

Figure 1.5. (a) Biosynthesis and rearrangement of *ent*-kauranoids. (b) Methoxide-mediated rearrangement of trichorabdal B (**13**).

1.4 OVERVIEW OF DITERPENOID ALKALOIDS

The *ent*-atisane and *ent*-kaurene diterpenes are widely considered as the biogenetic precursors to all diterpenoid alkaloids. This family alkaloids share structural features similar to those of diterpenoids, but differ from "true alkaloids" in that the carbocyclic cores are derived from terpene biosynthesis, rather than α-amino acid precursors. The diterpenoid alkaloids are divided into three general categories based on the number of carbons in the molecular framework: C_{20}-, C_{19}-, and C_{18}-diterpenoid alkaloids; and these are further divided into subclasses based on the connectivity of their skeletons (*e.g.* hetidines, hetisines, atisanes, etc…).[11] As of July 2008, about 400 C_{20}-, 700 C_{19}-, and 80 C_{18}-diterpenoids have been isolated.

In past literature, the diterpenoid alkaloids are often referred to as the *Aconitum* alkaloids, as they were primarily isolated from the *Aconitum* genus of plants.[12] However,

these widespread alkaloids have now been isolated from *Delphinium*, *Consolida*, and *Spiraea* genera of plants as well. These plants have long been used in traditional Chinese and Japanese medicine for their antiarrhythmic, antipyretic, and analgesic properties. Indeed, diterpenoid alkaloids possess a wide range of biological activities, namely anti-inflammatory, anticancer, antiepileptiform, antihypertensive, and antiarrhythmic properties. With many of the natural products possessing important pharmacological activity, strong interest in the synthesis of their complex structures has sustained over the decades since their first structural elucidation.

1.4.1 *Isolation, Structure, and Biological Activity*

The diterpenoid alkaloids are primarily isolated from the *Aconitum* and *Delphinium* genera of plants. Isolates from these plants have been known for centuries, and extracts containing aconitine ("aconite") have been used throughout history as local anesthetic, but more commonly as a poison for hunting or warfare purposes. It has therefore acquired colloquial names such as "queen of all poisons," and "wolf's bane," while its appearance has evoked nicknames such as "monkshood" or "devil's helmet". Despite the history of practical use, the chemical structures of diterpenoid alkaloids remained unknown until Wiesner's seminal report in 1954. [13] Before the advent of NMR, structural elucidation heavily relied on oxidation and dehydrogenation experiments, leading to the proposed structures of C_{20}-diterpenoid alkaloids veatchine (**25**) and garryine (**26**, Figure 1.6). The pharmacological and medicinal properties aconitine (**33**), one the most well known alkaloids, has been known since 1833.[14] However, the structure

was not fully elucidated until 1971, after decades of extensive chemical and X-ray crystallographic studies.[15]

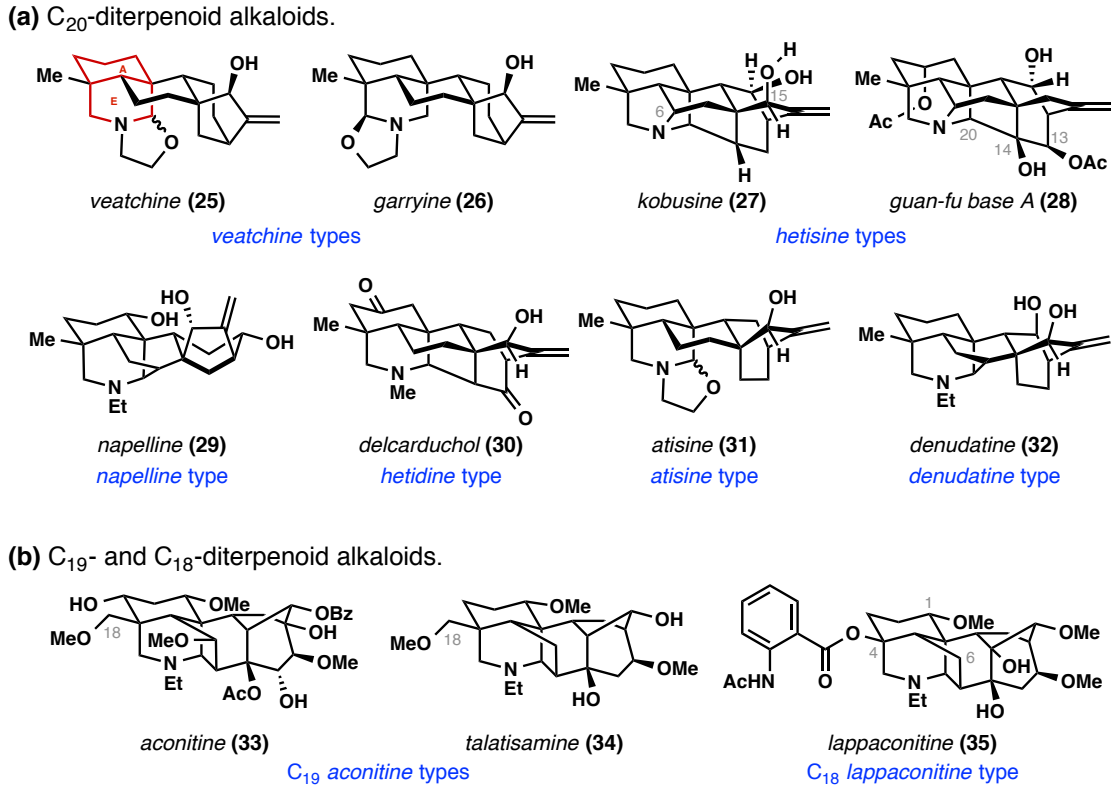

Figure 1.6. Representative Diterpenoid Alkaloids.

Many of the C_{20}-diterpenoid alkaloids structurally resemble to *ent*-atisane and *ent*-kaurene diterpenes, as one might predict based on their biosynthetic pathways. For example, the hetisine, hetidine, atisine, and denudatine types (*i.e.* **27**, **28**, **31–32,** Figure 1.6) all bear a bicyclo[2.2.2]octane, while the veatchine and napelline types (*i.e.* **25**, **26**, **29**) bear a bicyclo[3.2.1]octane. The C_{19}-diterpenoid alkaloids, which are biogenetically derived from their C_{20} counterparts, typically possess a rearranged hexacyclic framework that lacks resemblance to any diterpene equivalent. Lastly, the C_{18}-diterpenoid alkaloids share the same hexacyclic core as their C_{19} precursors, but lack the exocyclic C18 moiety.

A basic tertiary amine is common to all classes of diterpenoid alkaloids, although the nitrogen is also found in the form of lactams, hemiaminals, and cyclic imines. Among all classes, the 3-azabicyclo[3.3.1]nonane that constitutes the AE-ring system is another highly conserved structural feature.

The pharmacological properties of the diterpenoid alkaloids span a wide range, which most notably include anti-inflammatory, analgesic, and antiarrhythmic effects. Although they are notorious for their poisonous properties, several diterpenoid alkaloids have been used in East Asian medicines. The C_{20}-diterpenoid alkaloid, guan-fu base A (**28**), and its derivatives have been used for its anti-inflammatory and antiarrhythmic effects, and the C20–C14–C13 aminoalcohol subunit was determined to be a pharmacaphore.[16] Derivatives of kobusine (**27**) were also tested for antifibrillatory activity, and it was concluded that free hydroxyl groups, especially the C6 alcohol, and aromatic esters at C15 were important for biological activity.[17]

A number of C_{19}- and C_{18}-diterpenoid alkaloids have been studied for their anti-inflammatory, analgesic, and antiarrhythmic effects. 3-Acetylaconitine, lappaconitine (**35**), and crassicauline A have all been clinically used in China as non-narcotic analgesic drugs, and lappaconitine (**35**) has been used in Russia as an antiarrhythmic drug.[18] Broad SAR studies revealed that aromatic ester functionalities at C1, C4, C6, and C14 are crucial for biological activity, in addition to the basicity of the tertiary amine.[19] Ameri categorized the alkaloids in to three subgroups based on structure and biological activity,[20] and summarized the following: (1) diesters such as aconitine (**33**) suppress inactivation of voltage-gated Na^+ channels by binding to the α-subunit of the protein channel, and are the most toxic, (2) monoester alkaloids such as lappaconitine (**35**) block

voltage-gated Na^+ channels, are competitive antagonists, and are considerably less toxic, (3) natural products lacking ester groups are the least toxic, but are reported to still have antiarrhythmic action, suggesting affinities to various subtypes of the α-subunit of the sodium channel. Talatisamine (**34**) was found to block voltage-gated K^+ channels, and demonstrated an *in vitro* neuroprotective effect against β-amyloid oligomers induced cytotoxicity in cortical neurons.[21]

1.4.2 *Biosynthesis of Diterpenoid Alkaloids*

Although relatively few studies on biosynthesis have been performed,[22] it is generally accepted that the diterpenoid alkaloids are biogenetically derived from the diterpenes *ent*-kaurene and *ent*-atisane.[23] As depicted in Figure 1.7, oxidation of both parent diterpenes and incorporation of serine in the form of β-aminoethanol[24] directly provides the C_{20} veatchine and atisine type alkaloids, respectively. The exact order of oxidation and the point of amination still remain unknown. From the veatchine type alkaloid, a Mannich reaction can form the C7–C20 bond of the napelline type, or interconversion via Wagner–Meerwein rearrangement can produce the atisine type as well. From the atisine type alkaloids, a Mannich reaction can form the C7–C20 bond of the denudatine type alkaloids, with a final Wagner–Meerwein rearrangement providing the napelline type alkaloids.

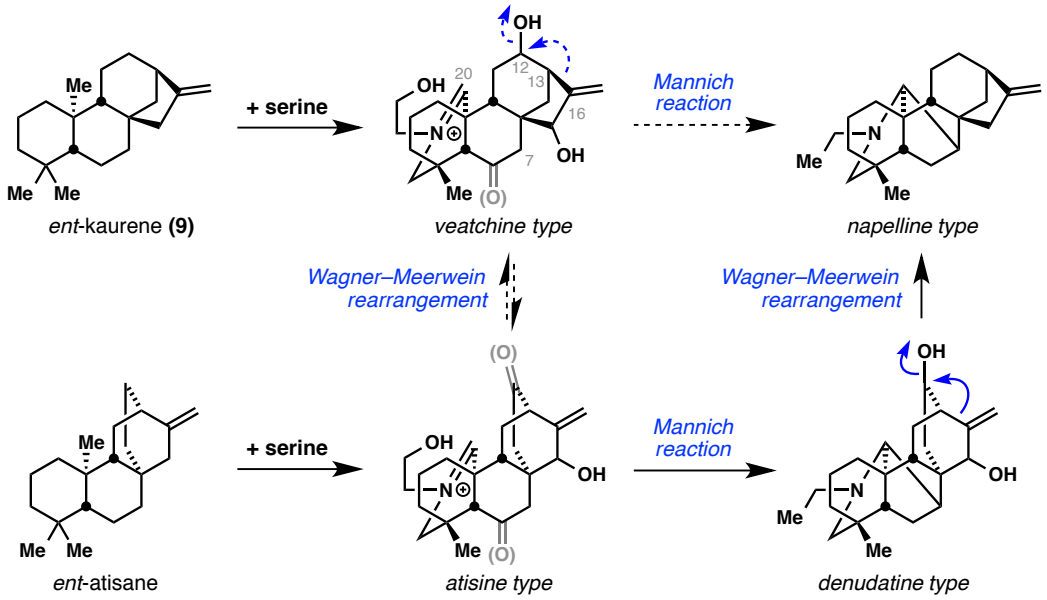

Figure 1.7. Postulated Biosynthesis of several C_{20}-Diterpenoid Alkaloids.

From the C_{20} atisine, denudatine, and napelline type alkaloids, three pathways are postulated to provide the C_{19}-, and in turn the C_{18}-diterpenoid alkaloids.[12b] In the atisine pathway, Wagner–Meerwein rearrangement affords rearranged framework A, after which oxidative scission of the exocyclic olefin provides the C_{19} proaconine (7,17-*seco*) type alkaloids. An aza-Prins reaction then forges the C7–C17 bond of the C_{19} aconitine type alkaloids. Alternatively, the denudatine pathway involves a Wagner–Meerwein rearrangement to provide rearranged type B, which provides the C_{19} aconitine type alkaloids after oxidative scission of the exocyclic olefin. Currently, there is one known alkaloid of the rearranged type B, actaline, which lends credence to this biosynthetic pathway.[25] In 1975, Kodama *et al.* proposed the napelline pathway to the C_{19}-diterpenoid alkaloids that involves two sequential Wagner–Meerwein rearrangements of the C_{20} napelline type alkaloids.[26] Based on the broad distribution of denudatine and napelline type alkaloids in plants of the *Aconitum* genus, the denudatine and napelline pathways are

considered to be the major pathways to C_{19}-diterpenoid alkaloids.[27] Functionalizations including hydroxylation, methylation, and esterification of the skeletal frameworks contribute largely to the high number and complexity of the C_{19} diterpenoid alkaloids. As the C_{18}-diterpenoid alkaloids often occur naturally with their C_{19} counterparts, it is also logical to conclude they are produced by removal of the C18 methylene unit of the aconitine type alkaloids.

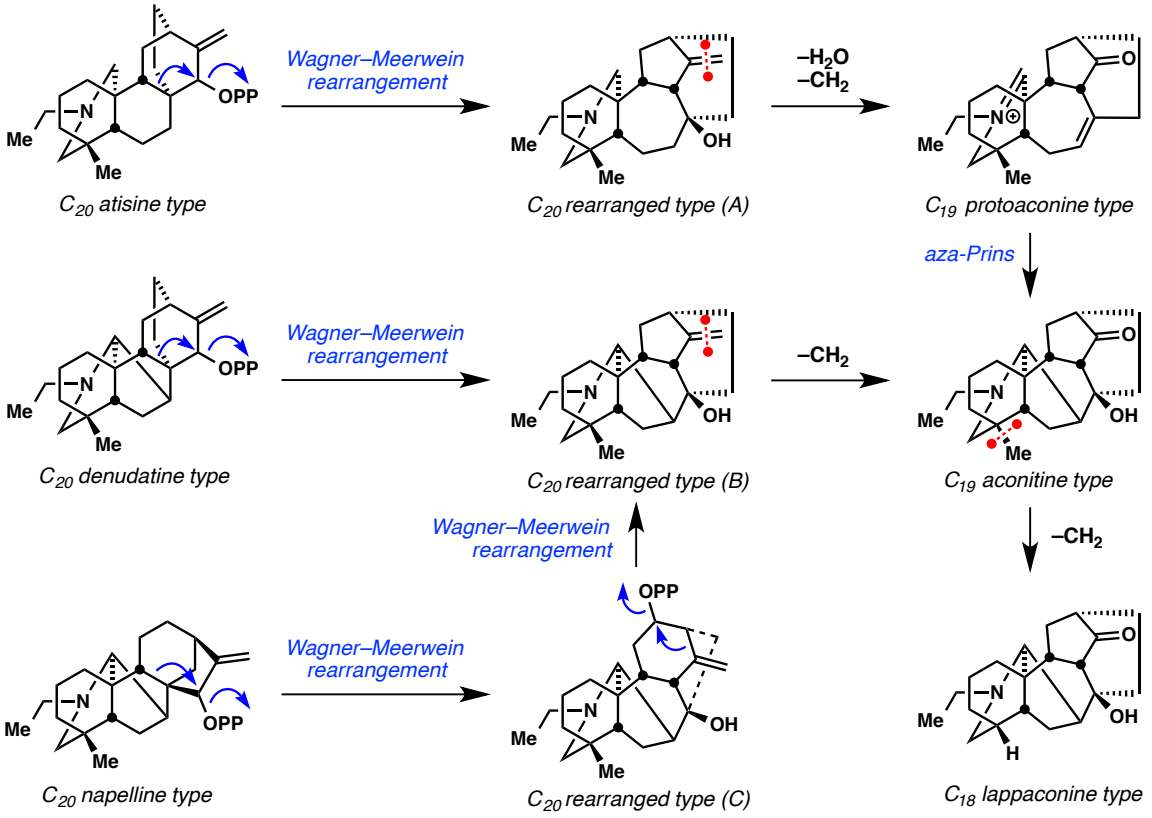

Figure 1.8. Postulated Biosynthesis of C_{19}-Diterpenoid Alkaloids.

1.5 CONCLUDING REMARKS

The *Isodon* diterpenes comprise over 600 structurally diverse natural products possessing numerous frameworks and oxidation patterns. Many of the biologically active

members share the α,β-unsaturated carbonyl moiety that is hypothesized to covalently modify target proteins. Though historically there have been strikingly few reports of synthetic studies towards *ent*-kauranoids, renewed interest in their antibacterial and anticancer properties have resulted in numerous total syntheses accomplished in the last decade. These synthetic studies will be discussed, alongside our own syntheses, in the following chapter.

The diterpenoid alkaloids possess incredibly complex structures that represent significant challenges to synthetic chemists. As these natural products are found in traditional East Asian medicines, it comes as no surprise that they possess significant and compelling biological activity, and has provided commercialized antiarrhythmic drugs. The identification of talatisamine as a novel voltage-gated K^+ channel blocker represents a novel discovery that suggests there is still unknown biological activity within this class of natural products. Efficient access to these natural products remains an elusive goal in the field of total synthesis.

1.6 NOTES AND REFERENCES

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