



Studies directed toward the synthesis of pentalenic acid
by Mark James Schulz

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in
Chemistry

Montana State University

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Abstract:

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This method was utilized in the synthesis of the tricyclic core of the natural product, pentalenic acid. Subsequent fragmentation/cyclization of the formed cyclobutane ring can be accomplished through the use of an oxovanadium reagent to establish the 5-5-5 ring system of pentalenic acid.

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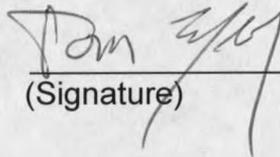
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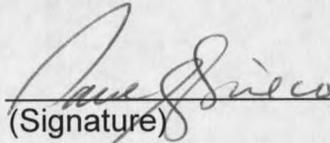
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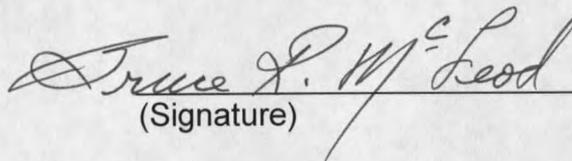
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Date

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CHAPTER 1

INTRODUCTION

Terpenoids are a diverse group of natural products with a stunning array of polycyclic frameworks. Nature has bestowed these natural products with an unusual assemblage of rings and functionalities. Within the terpene family exists an interesting subgroup known as polyquinanes, which are composed of fused five-membered rings. Polyquinane natural products have been discovered in marine, plant, and microbial sources. They have been known to contain up to four fused five-membered rings, which display four characteristic carbocyclic skeleta (Figure 1).

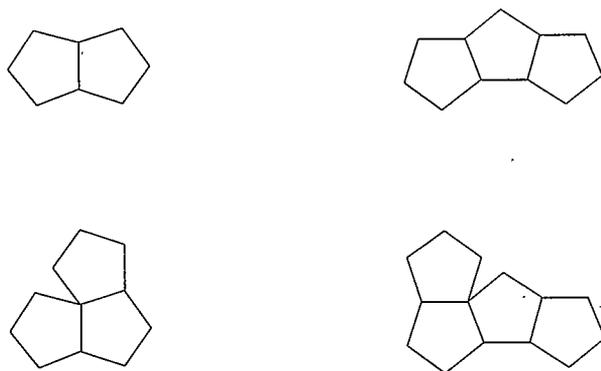


Figure 1. Characteristic Polyquinane Skeleta

Many polyquinane natural products have been shown to exhibit significant biological activities, which range from antibiotic properties to antitumor activity. As a consequence of this biological activity, polyquinanes have attracted rigorous attention from the scientific community. They have been used as prime subjects for synthetic and biosynthetic studies. In addition to the potential for drug discovery, interest in polyquinanes has resulted from their structural diversity. Which is primarily due to the structurally alluring assembly of five-membered rings, displaying a variety of functionality. As with many classes of natural products, polyquinanes hold promise as ground for developing and testing new synthetic strategies. In fact, polyquinanes have provided the impetus for the development of synthetic strategies for cyclopentannulations. The literature is rich with methods directed toward polyquinane synthesis.¹⁻⁵ Throughout the last twenty years, polyquinane synthesis has been an intriguing area of natural product synthesis and interest in them still remains.

Polyquinanes, which contain three fused five-membered rings, are known as triquinanes. The first natural product containing a triquinane nucleus, retigeranic acid was isolated twenty-nine years ago by Shibata (Figure 2).⁶ Since then, numerous triquinanes have been isolated from natural sources. Triquinanes are classified as either linear or angular (nonlinear), based on the topology of the ring fusion.

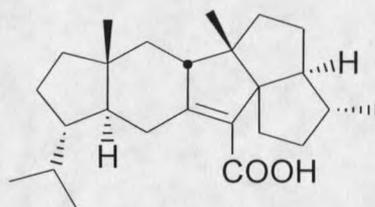
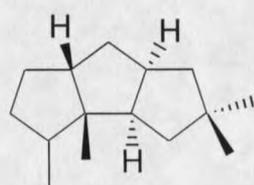
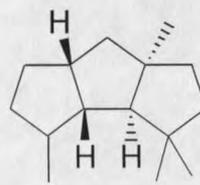


Figure 2. Retigeranic Acid

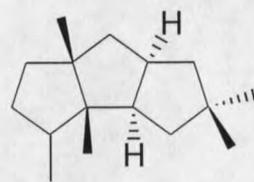
Linear triquinanes favor the *cis,anti,cis*-ring fusion, which is overwhelmingly preferred (thermodynamically). Among the linear triquinanes, only four different skeletal types exist (Figure 3). These skeletal types only differ



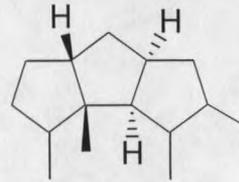
Hirsutane



Capnellane



Ceratopicane



Pleurotellane

Figure 3. Linear Triquinane Skeletal Types

in the location of the four carbon substituents and quaternary carbon centers. The difficult task in linear triquinane synthesis has been the rapid formation of five-membered rings. Numerous synthetic strategies for cyclopentannulation have been developed, which allow for the stereochemical control of the ring junction (*cis,anti,cis*-stereochemistry). The linear triquinane Hirsutic acid-C was isolated from Basidiomycete *Stereum hirsutum* (Figure 4).⁷ It was the first triquinane natural product to be isolated and characterized through spectroscopy and x-ray crystallography.⁸ Ceratopicanol is the only member of the ceratopicane skeletal type, isolated from the fungus *Ceratoystis piceae* in 1988 (Figure 4).⁹ The two quaternary bridgehead carbons and five stereocenters make ceratopicanol quite a structurally intriguing molecule.

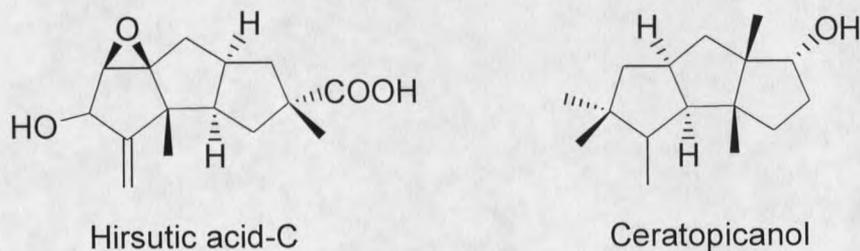


Figure 4. Linear Triquinanes

Among the natural products bearing an angular triquinane skeleton, only four different skeletal types are known (Figure 5). Classification within the

angular triquinane family is based on the arrangement of the four carbon substituents on the tricyclo[6.3.0.0]undecane core. Difficulty encountered in the synthesis of angular triquinanes is primarily due to installation of methyl groups and quaternary carbon centers as well as stereocontrol of the remote secondary methyl group.

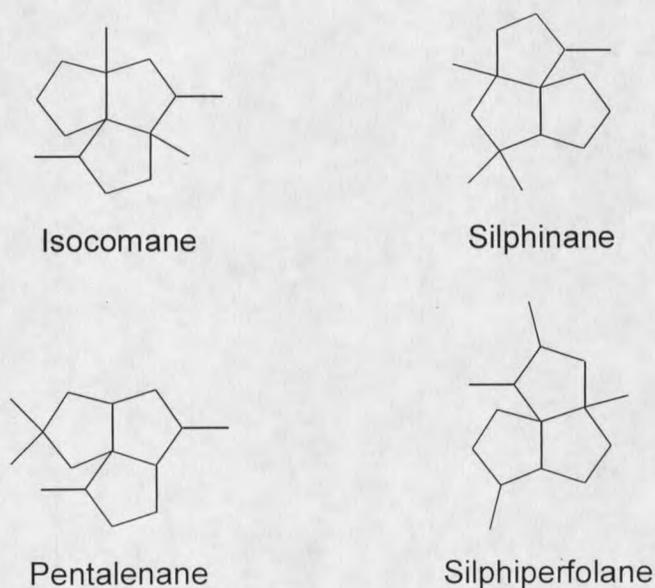


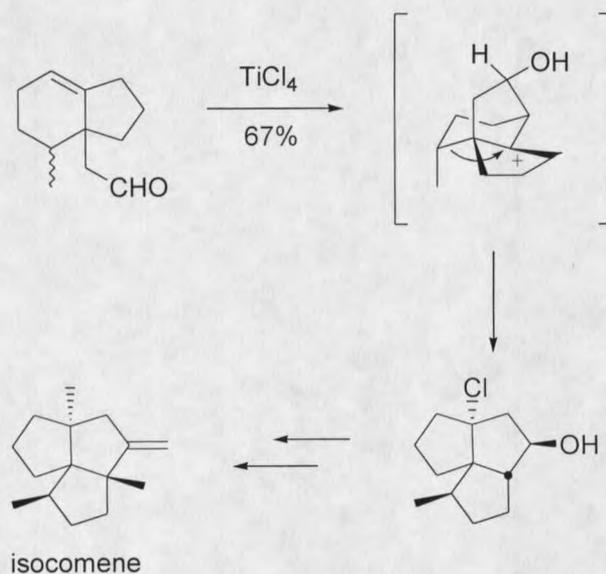
Figure 5. Angular Triquinane Skeletal Types

Isocomanes have been isolated from *Isocoma wrightii* and display three contiguous quaternary centers, which contain two angular methyl groups.

Isocomene was the first angular triquinane to be isolated and characterized.¹⁰

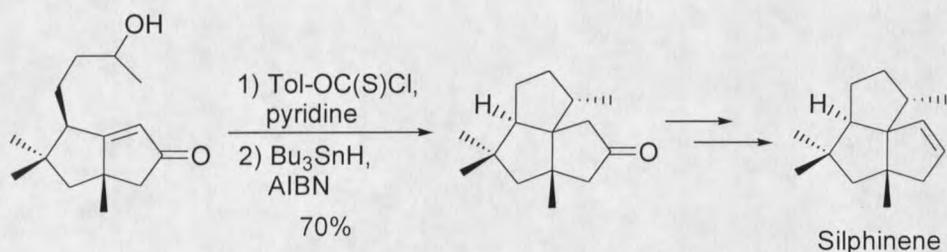
Several syntheses have followed its discovery. Kennedy and co-workers¹¹ have

employed a TiCl_4 -promoted Prins reaction and subsequent carbonium ion-mediated ring contraction for installation of the tricyclic core (Scheme 1). Further elaboration completed the synthesis of isocomene.



Scheme 1

The angular triquinane silphinene, of the silphinane family, was isolated from the plant *Silphium perfoliatum* by Bohlmamn and co-workers.¹² In the past, its synthesis has aroused significant interest. Nagarajan and Rao¹³ utilized an intramolecular radical cyclization as a key step in the synthesis of silphinene (Scheme 2).



Scheme 2

Pentalenic acid **1**, pentalenene **2**, and pentalenic acid glucuron **3** were isolated together with pentalenolactone from the fermentation broth of *Streptomyces* sp. in 1978 (Figure 6).¹⁴ The angular triquinanes **1**, **2**, and **3** are biosynthetically related to the antibiotic, pentalenolactone, which has displayed antibiotic activity against fungi and bacteria.¹⁵ Intensive efforts have been directed toward the synthesis of these compounds and several synthetic approaches have appeared in the literature.^{1,3}

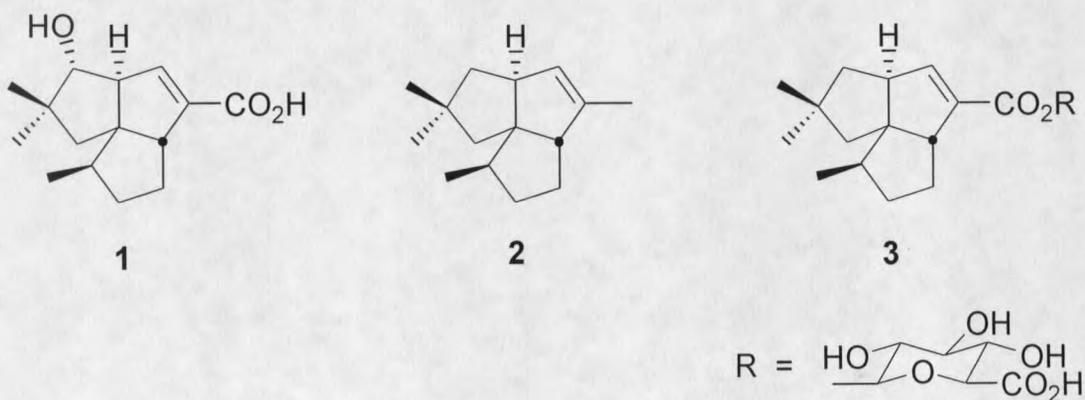


Figure 6. Pentalenane Family

