Studies toward the total synthesis of pentalenic acid
by Steven Michael Reister

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

Abstract:
The intent of the research contained herein was to synthesize the natural product pentalenic acid. Pentalenic acid is a small molecule with antibiotic properties. This molecule was chosen as a way to showcase ongoing synthetic methodologies of the Grieco research group. Unfortunately the complete synthesis of pentalenic acid was never realized, but the research proved to be both interesting and surprising. The original route proposed for a key intermediate was much more of a synthetic challenge than was anticipated. In fact it was eventually decided that the desired intermediate could not be obtained via this route and an alternative route was sought after. The alternative route proposed was successful and the desired intermediate was obtained in the same number of synthetic steps as the original. With this intermediate in hand, the key step in the synthesis was performed with rather surprising results. The major product obtained was not the desired one. In fact it was found that the reaction had proceeded in a manner which was thought to be very unlikely. Models and literature precedent predicted that the reaction would proceed the desired way, but in practice it did not. Regrettably the product obtained was not amenable to the synthesis of pentalenic acid, and synthetic efforts concluded. Although these results were unfortunate/they have proven interesting and may be of use to future scientists.

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APPROVAL

of a thesis submitted by

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This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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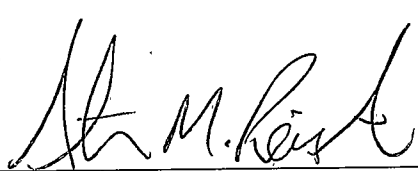
Signature 

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ABSTRACT

The intent of the research contained herein was to synthesize the natural product pentalenic acid. Pentalenic acid is a small molecule with antibiotic properties. This molecule was chosen as a way to showcase ongoing synthetic methodologies of the Grieco research group. Unfortunately the complete synthesis of pentalenic acid was never realized, but the research proved to be both interesting and surprising. The original route proposed for a key intermediate was much more of a synthetic challenge than was anticipated. In fact it was eventually decided that the desired intermediate could not be obtained via this route and an alternative route was sought after. The alternative route proposed was successful and the desired intermediate was obtained in the same number of synthetic steps as the original. With this intermediate in hand, the key step in the synthesis was performed with rather surprising results. The major product obtained was not the desired one. In fact it was found that the reaction had proceeded in a manner which was thought to be very unlikely. Models and literature precedent predicted that the reaction would proceed the desired way, but in practice it did not. Regrettably the product obtained was not amenable to the synthesis of pentalenic acid, and synthetic efforts concluded. Although these results were unfortunate, they have proven interesting and may be of use to future scientists.

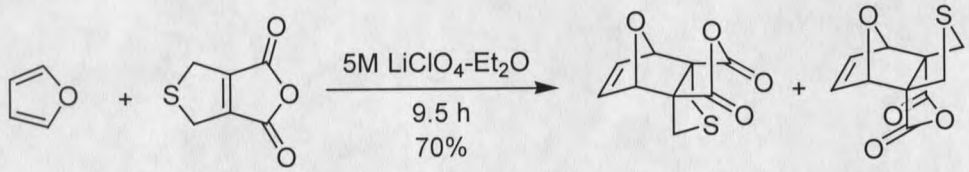
CHAPTER 1

INTRODUCTION

Diels-Alder Reaction

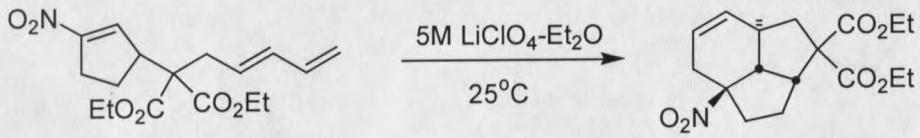
Since its discovery over 50 years ago, the Diels-Alder reaction has become one of the most useful tools in the synthetic organic chemist's arsenal. New variations and applications are continually being developed, allowing for the construction of a wide range of synthetic targets. In recent years, studies have shown that reaction medium can have a powerful influence upon these pericyclic reactions. In this study, we set out to investigate the applicability of these recent advances of the Diels-Alder reaction in the construction of spiro fused ring systems.

Grieco and coworkers have shown that the use of 5M $LiClO_4$-Et_2O as a medium greatly enhances the reaction rate and selectivity of classically difficult Diels-Alder transformations.[1] This exciting revelation showed that reactions which normally required elevated temperatures and pressures could now be performed at room temperature and ambient pressure. Dauben found that the following reaction required a 6 hour reaction time under 15 kbar of pressure in methylene chloride,[2] whereas Grieco found the same reaction proceeded in 9.5 hours at ambient temperature and pressure in 5M $LiClO_4$-Et_2O (Equation 1).



Equation 1. Grieco Diels-Alder

Guy and Serva found similar rate enhancements when moving from thermal conditions to 5M $LiClO_4$-Et_2O.[3] The following reaction proceeded in only 22% yield after 65 hours at 80°C; however, after just 24 hours at room temperature in 5M $LiClO_4$-Et_2O, a 70% yield was obtained (Equation 2). It is interesting to note that only one stereoisomer was obtained in this reaction.



Equation 2. Guy Diels-Alder

It is apparent from these examples that the Diels-Alder reaction is extremely useful in allowing access into otherwise difficult ring systems. With that, we set out to attempt to apply this methodology to the angular fused triquinane nucleus.

Terpenes

Terpenes are an exciting class of natural products due to their wide array of carbocyclic ring systems and functional groups. As a result, these compounds have generated a significant amount of synthetic interest over the years. A relatively small subtype of these compounds is the polyquinanes, which are composed entirely of fused five-membered rings.[4] These compounds represent a fairly recent discovery, in fact the structure of the first polyquinane natural product hirsutic acid-C was determined in only 1966.[4] It is not surprising that a number of synthetic strategies have been developed around this unusual framework.

A subclass of the polyquinanes is the triquinanes. These compounds are distinguished by a carbocyclic framework which consists of three fused five membered rings. These ring systems can occur in one of three arrangements: angular, linear, or axial (Figure 1).[4]

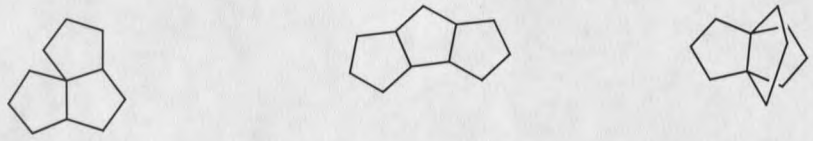


Figure 1. Possible Arrangements of Triquinane Nucleus

Each of these arrangements has been the subject of synthetic interest over the years, and as a result the synthesis of a number of representative natural products can be found in the literature.[4]

For the purpose of this study the angular fused analogues were of sole interest, and in particular the natural product pentalenic acid (Figure 2).

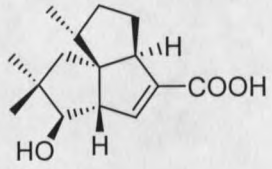


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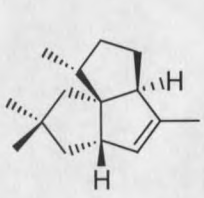
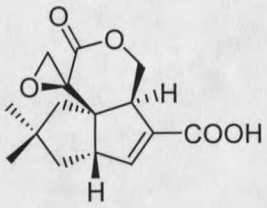
Figure 2. Pentalenic Acid

Pentalenic acid was isolated in 1978 from the fermentation broth of the fungus *Streptomyces Griseochromogenes* along with its counter parts pentalenene and pentalenolactone-H (Figure 3). It is a member of the pentalenolactone group of fungal metabolites which exhibit antibiotic activity.[4]



Pentalenene



Pentalenolactone-H

Figure 3. Analogues of Pentalenic Acid