



Synthetic routes to perhydroazulenes; studies with oxygenated models
by Amo Richard DeBernardis

A thesis submitted to the Graduate Faculty in partial fulfillment of the requirements for the degree of
MASTER OF SCIENCE in Chemistry
Montana State University
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Abstract:

The research program was initiated to learn whether diazomethane ring expansion might prove a reasonable method of arriving at perhydroazulenes that are related to some sesquiterpenes. In the course of the investigation, which involved 4-methyl-cis 3a,4,7,7a-tetrahydrophthalan as a model, it was concluded that a methyl group can have powerful directive effects; possibly more electronic in nature than steric. Also, the choice of an oxygen heterocyclic system as a model for the carbocyclic systems resulted in an analysis of the long range directive effects of oxygen. Additional studies using a sulfur hetero-atom confirmed the long range hetero-interactions. As part of the study using oxygenated systems, the sex attractant of the bark beetle, *Dendroctonus brevicomis*, was prepared by an unambiguous synthesis. The initial question of the program, that of investigating the use of diazomethane ring expansion, was answered and evidence shows that the desired product is that obtained in greater quantity. Overall yields, however, appear to be prohibitive in using this as a synthetic route. The poor ring expansion may result from electronic and/or steric effects.

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Date August 6, 1971

SYNTHETIC ROUTES TO PERHYDROAZULENES

STUDIES WITH OXYGENATED MODELS

by

A.^{MD} Richard DeBernardis

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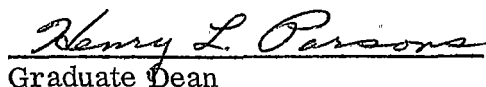
in

Chemistry

Approved:


Head, Major Department


Chairman, Examining Committee


Graduate Dean

MONTANA STATE UNIVERSITY

Bozeman, Montana

August, 1971

to

Beau

who has suffered many lonely hours

ACKNOWLEDGMENT

Several people have had a major role in making this research study possible and I would like to take this opportunity to thank them.

I would especially like to thank my parents without whose help the completion of this thesis would not have been possible. I would like to acknowledge the Chemistry Department of Montana State University for its support in the way of teaching assistantships; and for making it possible for me to participate in the Northwest regional meeting of the American Chemical Society (Utah, summer 1969) and to attend the National Organic Symposium (Utah, 1969). For its generosity in the way of partial summer support in the summer of 1968 and complete support during the summer of 1970, I would like to thank Dr. Roy Huffman, vice president of research, and the Endowment and Research Foundation of Montana State University. I would like to thank Dr. A. P. Krapcho, University of Vermont, for his helpful information. I also thank my fellow researcher, Mr. R. D. Otzenberger, for his time involved in discussions and in helping to build laboratory apparatus.

My special thanks is extended to Dr. Bradford P. Mundy for his guidance in this research and his special patience with my many tangents.

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ABSTRACT

The research program was initiated to learn whether diazomethane ring expansion might prove a reasonable method of arriving at perhydroazulenes that are related to some sesquiterpenes. In the course of the investigation, which involved 4-methyl-cis 3a,4,7,7a-tetrahydrophthalan as a model, it was concluded that a methyl group can have powerful directive effects; possibly more electronic in nature than steric. Also, the choice of an oxygen heterocyclic system as a model for the carbocyclic systems resulted in an analysis of the long range directive effects of oxygen. Additional studies using a sulfur heteroatom confirmed the long range hetero-interactions. As part of the study using oxygenated systems, the sex attractant of the bark beetle, Dendroctonus brevicomis, was prepared by an unambiguous synthesis. The initial question of the program, that of investigating the use of diazomethane ring expansion, was answered and evidence shows that the desired product is that obtained in greater quantity. Overall yields, however, appear to be prohibitive in using this as a synthetic route. The poor ring expansion may result from electronic and/or steric effects.

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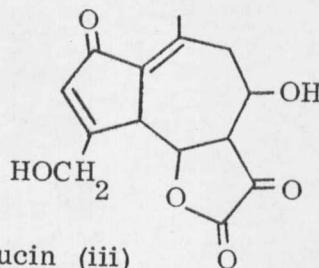
PART I

INTRODUCTION

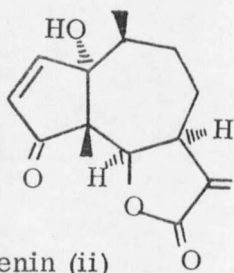
Although terpenes have, in general, occupied a position of interest to organic chemists based almost entirely on interesting skeletal features, and ability to undergo complex skeletal reorganization, in the past their pharmacological use has been of little concern. The synthesis of perhydroazulenes has recently become of considerable interest, due to their pharmacological activity. Members of this unique class of sesquiterpenes bear in common the characteristic ring system composed of mutually fused five and seven ring (figure 1). The positioning of additional moieties are, as a rule, predictable on simple biogenetic reasoning. However, non-isoprenoid structures are known, and are particularly common in the perhydroazulene terpenes.



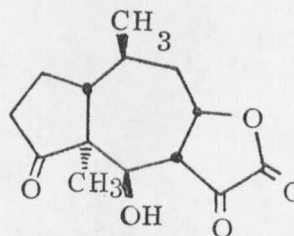
(i)



Lactucin (iii)



Parthenin (ii)



Helenalin (iv)

Figure 1: Examples of perhydroazulene compounds.

Examples of several perhydroazulene sesquiterpenes are shown in figure 1. The extent of pharmacological and other physiological activities are well represented in the sesquiterpene parthenin (ii)¹ in which both effects have been exhibited. Lactucin (iii)² and helenalin (iv)³ have also been shown to be active pharmacologically.

The potential of these interesting compounds has not been reflected in abundant synthesis. Research in this synthetic area is exemplified by the notable synthesis of Aromadendrene by Buchi⁴ (figure 3), and β -vetivone by A. P. Krapcho and B. P. Mundy⁵ (figure 4) and also the independent synthesis of β -vetivone by J. A. Marshall⁶ (figure 5) with these examples, the complexities of the synthesis can be noted. In the case of the Aromadendrene synthesis the assigned structure (vii) was shown not to agree with the synthetic product (vi). The two independent syntheses of β -vetivone gave products which were not consistent with the isolated natural product and led to eventual structure reassignment. The correct structure, as was finally determined by Marshall⁷, is shown in figure 2. Thus, in both cases it was only because of the attempted syntheses that the assigned structures were found to be incorrect.

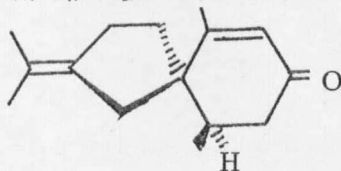


Figure 2 : The correct structure for β - vetivone.

