Synthetic studies toward natural products
by Timothy Ryall Schwartz

A thesis submitted in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY in Chemistry
Montana State University

Abstract:
The importance of the supra-annular effect as a controlling factor in the determination of the exo/endo product ratio of substituted 6,8-dioxabicyclo[3.2.1]octanes was studied through the use of competitive kinetics and nuclear magnetic resonance spectroscopy. It was determined that the supra-annular effect does not exist in the compounds studied and therefore cannot be used to control product stereochemistry. The carbon NMR spectra of these ' bicyclic ketals were examined and the general chemical shift regions of the ring carbons noted. The role of metal ion complexation in determining exo/endo product ratios was also studied and shown to be of minor importance.

The double oxymercuration-demercuration of selected dienes was investigated for potential use in a concurrent synthesis of brevicomin and the sex aggregating pheromone of Trypodendron lineeatum. Model compounds were synthesized and studied, and progress was made toward the proposed concurrent syntheses.

"A good teacher has been defined as one who makes himself progressively unnecessary."

Thomas J. Carruthers

"I am astonished, disappointed, pleased with myself. I am distressed, depressed, rapturous. I am all these things at once, and cannot add up the sum."

C. G. Jung

"Det henskit af Krig er ta overleve." ("The object of war is to survive it", which struck me as the object of graduate school.)

John Irving

to my wife

Sandy

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August, 1982

ACKNOWLEDGEMENT

I would like to thank several people, without whom this thesis would not have been accomplished.

I would like to thank Dr. Arnold Craig for his helpful discussions and a good sense of humor, and the fellow members of my research group for their friendship and assistance. I would also like to thank Dr. Ron Warnet for his manifold talents as chemist, editor, and friend. A very special "thank you" goes to Professor Mundy, after whom I have patterned both my teaching and research ideas, for his long suffering optimism and encouragement and for the hours of discussion on all manner of topics.

Finally, my deepest love and gratitude to my wife Sandy, whose sacrifice and patience really made this work possible.

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ABSTRACT

The importance of the supra-annular effect as a controlling factor in the determination of the exo/endo product ratio of substituted 6,8-dioxabicyclo[3.2.1]octanes was studied through the use of competitive kinetics and nuclear magnetic resonance spectroscopy. It was determined that the supra-annular effect does not exist in the compounds studied and therefore cannot be used to control product stereochemistry. The carbon NMR spectra of these bicyclic ketals were examined and the general chemical shift regions of the ring carbons noted. The role of metal ion complexation in determining exo/endo product ratios was also studied and shown to be of minor importance.

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CHAPTER ONE

Introduction

The Western pine bark beetle, Dendroctonus brevicomis, has done extensive damage to the coniferous forests of the western United States. Infested trees begin to turn brown and will eventually lose their needles and become dry, lifeless, standing snags. The large number of these dead trees resulting from bark beetle infestation poses a serious fire danger in western forests. This destruction of valuable timber resources has prompted research into methods of controlling bark beetle populations.

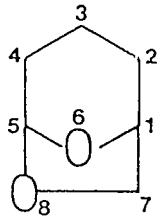
One such method of control involves the use of the beetle's own sex aggregating pheromone. The female produces a pheromone which attracts male beetles and thereby increases the likelihood of mating. Control of beetle populations in small areas is possible by using the aggregating pheromone to lure male beetles into insect traps. A small region can be protected by distributing these traps throughout the area and thus effectively removing most of the male beetles. It is not feasible, however, to protect large areas of forest by this method. Instead, it has been proposed that the pheromone be sprayed aerially over large areas. The ubiquitous presence of the pheromone would severely reduce the chance of a male beetle locating a female, and, again, no mating would occur. Large

quantities of pheromone are required for this type of operation. Seeing this need, synthetic chemists have studied the aggregating pheromone for D. brevicomis, named brevicomin, and many syntheses exist today. The synthesis of brevicomin is complicated by the fact that while brevicomin can exist in several isomeric forms, only one isomer is biologically active. A good synthesis will, therefore, allow the chemist to control the various synthetic reactions which determine the stereochemistry of the product pheromones. We have chosen to study two phenomena which might determine the extent of stereoselectivity possible in two brevicomin syntheses originating in our research group. These two phenomena are the supra-annular effect and metal ion complexation. In addition to evaluating control of stereoselectivity in existing syntheses, we have also explored a new and novel synthesis of two bark beetle pheromones. The proposed scheme will allow the concurrent synthesis of the sex aggregating pheromones for D. brevicomis and Trypodendron lineatum, the Norway spruce bark beetle. A concurrent synthesis would allow the chemist access to two different pheromones using the same reaction sequence and thereby facilitate the synthesis of the pheromones and control of the bark beetles.

CHAPTER TWO

Historical Background

The 6,8-dioxabicyclo[3.2.1]octane ring system (1), a common structural component of sugars, is found in a wide variety of compounds and metabolites.



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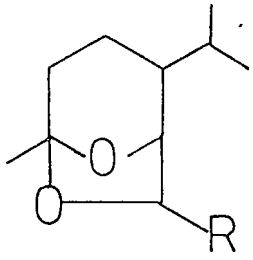
Several compounds, 2-4, containing this skeletal structure have been isolated from tobacco.[1]

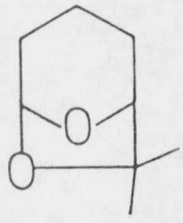


2 $-\overset{\overset{R}{|}}{\underset{\underset{O}{\|}}{C}}CH_3$

3 $-\underset{\underset{OH}{|}}{CH}CH_3$

4 $-\underset{\underset{OH}{|}}{C}(CH_3)_2$

A similar compound, (5), has been identified as a constitutent of Japanese hop oil isolated from Humuls lupulus[2], and 6 has been shown to occur during fatty acid metabolism in yeast.[3]



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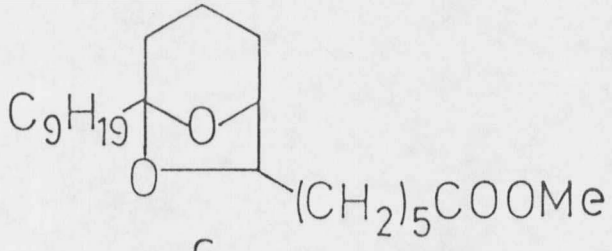

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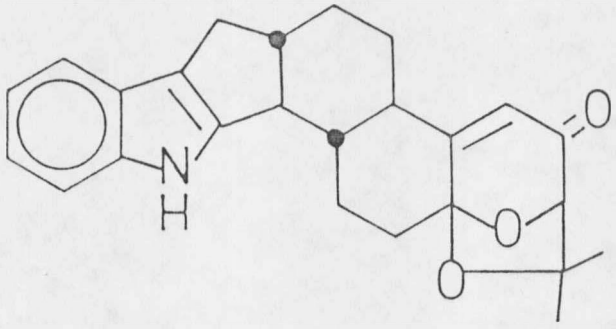
A variety of natural products containing this bicyclic ketal structure and exhibiting signifiant biological activity have been isolated as well. Compound 7, containing a modified bicyclic ketal moiety, has been isolated from Claviceps paspali[4] and is responsible for a condition in cattle known as the "paspalum staggers". Cattle which have eaten Paspalum dilatatum infected with C. paspali show symptoms of anorexia, tremors, and hyperexcitability.



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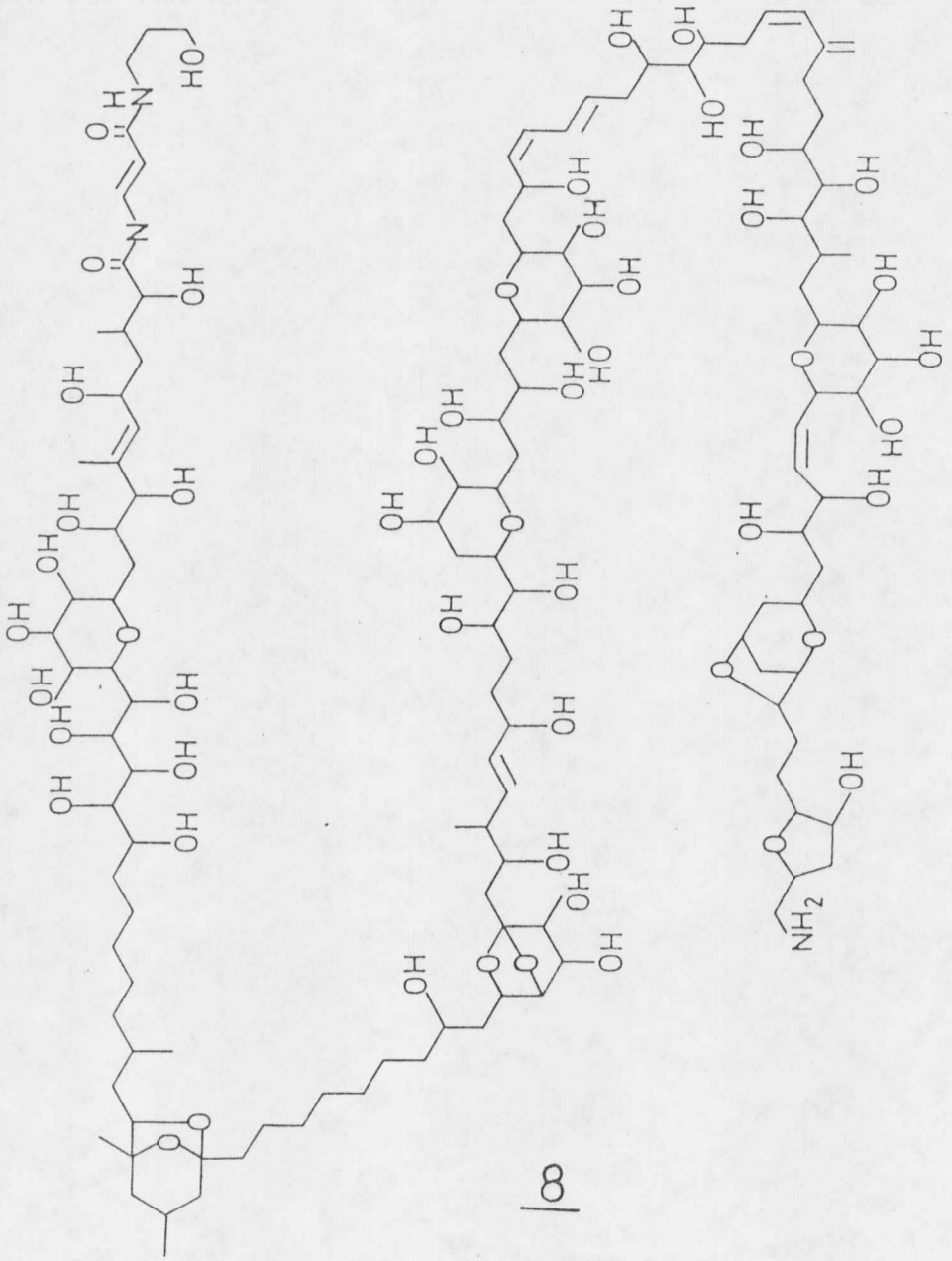
Palytoxin, (8), isolated from several Palthoa sp.[5] is one of the most potent toxins known to man and contains several bicyclic ketal structural fragments.



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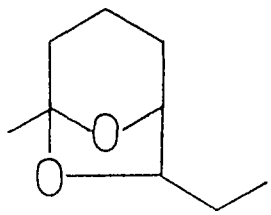
A group of insect sex attractants also contain the 6,8-dioxabicyclo[3.2.1]octane skeleton. The pheromone for the Western pine bark beetle Dendroctonus brevicomis has been isolated, assigned structure (9), and named brevicomin.[6] The aggregating pheromone for



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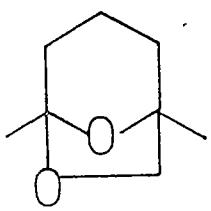
the Eastern pine bark beetle, Dendroctonus frontalis named frontalin[7] (10), and the pheromone for the European elm bark beetle, Scolytus multistriatus, named multistriatin[8] (11), have been isolated and show considerable bioactivity while working in concert with endogenous tree constituents.



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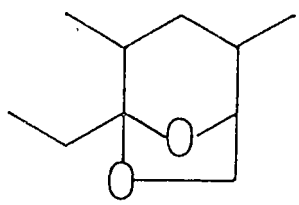

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