



New synthetic methodologies for natural products
by William Gerard Bornmann

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:

The orbital symmetry allowed [3.3] sigmatropic rearrangement of enamines derived from 2-acetyl-6-methyl-3,4-dihydro-2H-pyran has allowed for facile entry into highly functionalized cyclohexanone derivatives. This new synthetic methodology offers promise for entry into sesquiterpene natural products. A by-product of this research has led to a simple synthesis of brevicomin, the aggregating sex pheromone of the pine bark beetle, *Dendroctonus brevicomis*.

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Signature William G. Bannann

Date December 28, 1978

To my wife,

Daria

NEW SYNTHETIC METHODOLOGIES

FOR NATURAL PRODUCTS

by

WILLIAM GERARD BORNMANN

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of

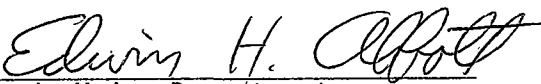
MASTER OF SCIENCE

in

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Approved:


Chairperson, Graduate Committee


Head, Major Department


Graduate Dean

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ABSTRACT

The orbital symmetry allowed [3.3] sigmatropic rearrangement of enamines derived from 2-acetyl-6-methyl-3,4-dihydro-2H-pyran has allowed for facile entry into highly functionalized cyclohexanone derivatives. This new synthetic methodology offers promise for entry into sesquiterpene natural products. A by-product of this research has led to a simple synthesis of brevicomin, the aggregating sex pheromone of the pine bark beetle, *Dendroctonus brevicomis*.

Experimental ideas are often born by chance, with the help of some casual observation. Nothing is more common; and this is really the simplest way of beginning a piece of scientific work. We take a walk, so to speak, in the realm of science, and we pursue what happens to present itself to our eyes.

"Serendipity"
Claude Bernard
1865

Part I:

A NEW SYNTHETIC APPROACH TO SESQUITERPENE INTERMEDIATES

CHAPTER I

HISTORICAL

In recent years, two concepts have emerged in synthetic methodology; that of latent functionality and the use of heterocyclic compounds in organic synthesis. D. Lednicer¹ in 1972 quite aptly verbalized the concept of latent functionality as: "One carries some necessary function through one or more steps of a synthesis in a precursor form; and at the proper stage the precursor is converted to the needed group." One could say that this concept is a more sophisticated use of protecting groups. The second and the most important concept was discussed by A. I. Meyers,² and involves the use of heterocyclic compounds in organic synthesis. By directly applying the principle of latent functionality in a heterocyclic synthesis, one could, in effect, design a heterocycle which could allow for the introduction of a variety of functional groups or carbon skeletons. Thus in short, Meyers' concept was that of using a heterocycle as a precursor or vehicle for the synthesis of a more complex molecule.

These concepts were reflected in the synthetic approach to substituted cyclohexenes taken by Buchi^{3,4} which was based on the previous work by J. D. Roberts⁵ and Lutz that deuterium-labeled 2-formyl-2,5-dimethyl-2,3-dihydro-4H-pyran [1] could thermally isomerize by means of a [3,3] sigmatropic rearrangement. A series of well-planned NMR studies conclusively demonstrated that the aldehydic deuterium CDO label ex-

changed with H-6. It was also noted that the optical activity due to the asymmetric center (*) was not lost.

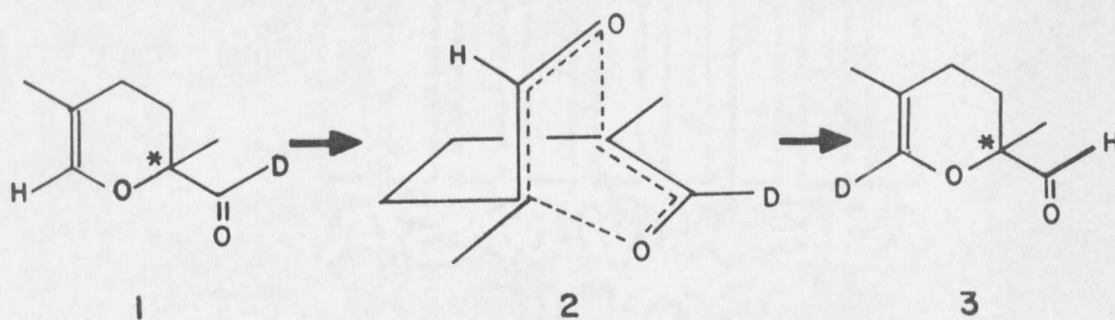


Figure 1. [3,3] Sigmatropic Rearrangement of 2-formyl-2,5-dihydro-4H-Pyran

By dimerizing α,β -unsaturated compounds [4], Büchi was able to obtain acyl dihydropyrans [5] which, when followed by a Wittig condensation, gave 3,4-dihydro-2H-pyranethylenes [5]. These compounds were, in essence, allyl vinyl ethers whose thermal oxy-Cope rearrangement had been previously well documented in the literature. Just as had been expected, these substituted 3,4-dihydro-2H-pyran ethylenes underwent oxy-Cope rearrangements to yield substituted cyclohexene [7] compounds. Such substituted acyl cyclohexenes are not readily obtainable from mixed Diels-Alder reactions and, in fact, are only minor products from these reactions.

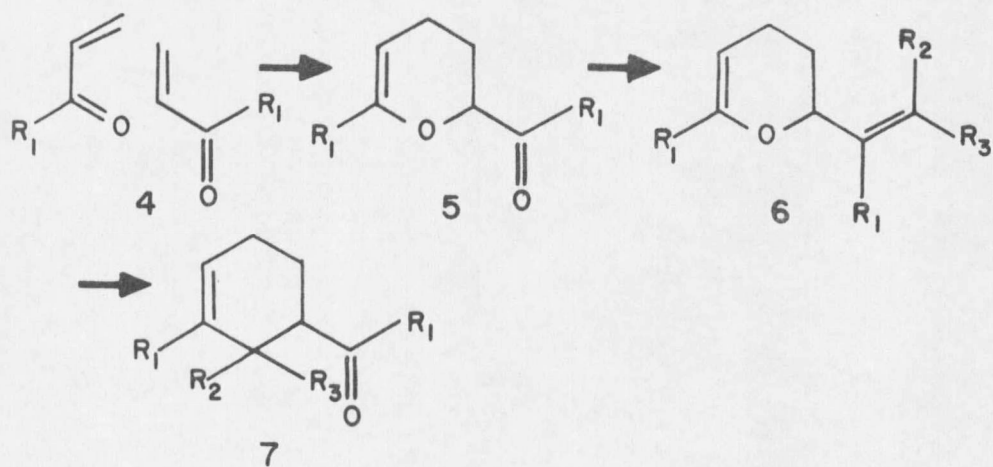


Figure 2. Büchi Synthesis of Substituted 4-Acetylcyclohexenes

Now, in a continuing effort in this laboratory to realize the full implications of this work, it was conceived to substitute different heteroatoms for the carbonyl oxygen and rearrange them into the ring. Thus K. Lipkowitz^{7,8} first made the thiocarbonyl by refluxing 2-acetyl-6-methyl-3,4-dihydro-2H-pyran in pyridine and phosphorous pentasulfide. Sealed tube pyrolysis of the thioacetyl pyran [9] yielded the thiapyranyl system [10].

