



A novel bicyclic ketal fragmentation reaction
by Michael Gerard Bjorkland

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:

A new methodology for the cleavage of the 6,8-dioxabicyclo[3.2.1] octane skeletal system is examined. The use of acetyl iodide as a reagent to cleave the bicyclic ketals to the corresponding δ,ϵ -unsaturated ketones is observed. In each cleavage carried out in this study, the trans/cis ratio found in the products correlates directly to the exo/endo ratio of the starting materials and a mechanism for the cleavage reaction based on these findings is proposed. The utility of the methodology is demonstrated in two synthetic pathways; one leading to the sex attractant of the Douglas-fir tussock moth, *Orgyia pseudotsugata*, and the other to a major constituent of the venom of the Fire Ant, *Solenopsis savissima*.

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Date

July 24, 1984

To my grandfather, Delbert Bjorklund

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ABSTRACT

A new methodology for the cleavage of the 6,8-dioxabicyclo-[3.2.1]octane skeletal system is examined. The use of acetyl iodide as a reagent to cleave the bicyclic ketals to the corresponding δ,ϵ -unsaturated ketones is observed. In each cleavage carried out in this study, the trans/cis ratio found in the products correlates directly to the exo/endo ratio of the starting materials and a mechanism for the cleavage reaction based on these findings is proposed. The utility of the methodology is demonstrated in two synthetic pathways; one leading to the sex attractant of the Douglas-fir tussock moth, Orgyia pseudotsugata, and the other to a major constituent of the venom of the Fire Ant, Solenopsis savissima.

INTRODUCTION

Bicyclic ketals containing the 6,8-dioxabicyclo[3.2.1]octane skeletal system, (**1**), (Figure 1), several examples of which are illustrated in Figure 2, comprise a group of natural products that has received a substantial amount of attention by chemists in recent years.

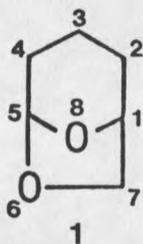


Figure 1. The 6,8-Dioxabicyclo[3.2.1]octane Skeletal System

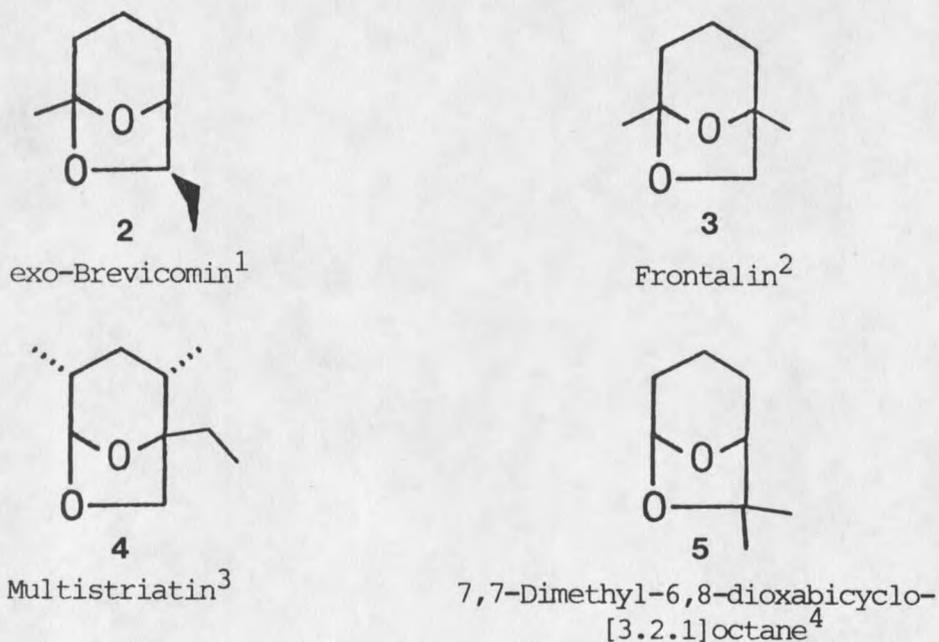
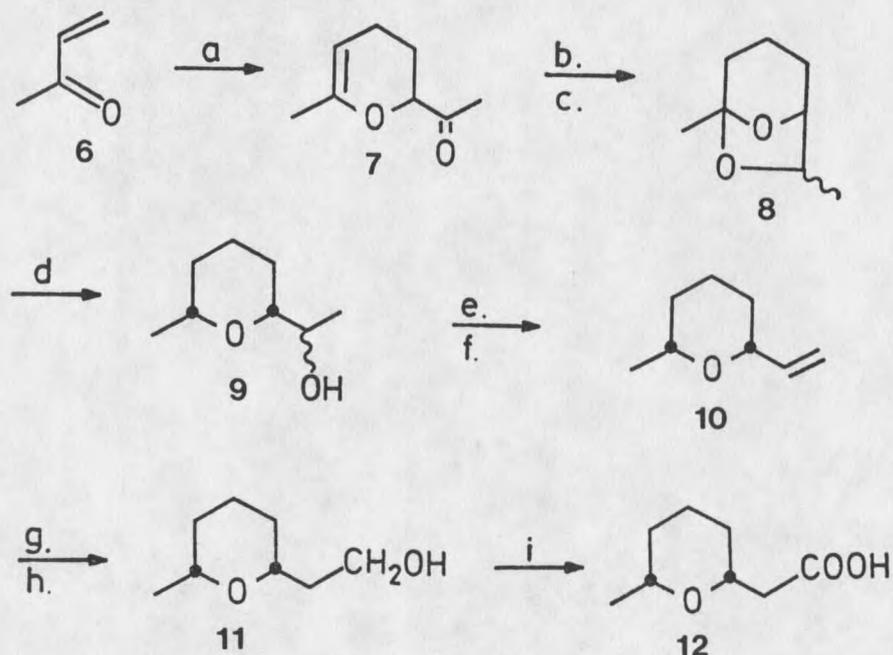


Figure 2. Natural Products Containing the 6,8-Dioxabicyclo[3.2.1]octane Skeletal System

As a result of the myriad of different methodologies for synthesizing specifically substituted bicyclic acetals and ketals, the usefulness of such systems as intermediates in the preparation of other natural products became apparent to this group.

In 1982, Kim utilized the hydrogenolysis of **8** with aluminum hydride as the key step in the synthesis of **12**, a minor constituent of the glandular secretion from the civet cat (*Viverra civetta*)⁵ (Figure 3).



- (a) 185°C, 2h; (b) NaBH₄/i-PrOH; (c) TSOH/C₆H₆; (d) AlH₃;
 (e) AcCl/Pyd; (f) 450°C, N₂; (g) B₂H₆; (h) H₂O₂/OH⁻;
 (i) CrO₃/H₂SO₄ or PDC

Figure 3. Kim's Synthesis of (cis-6-Methyl tetrahydropyran-2-yl)-acetic Acid

The observed ring opening of 8 to 9 is readily explained by coordination of the Lewis acid with O-6, followed by cleavage of the C-5 - O-6 bond, and is in agreement with similar work done by Brown,⁶ Baker⁷ and Mundy.⁸ It has, in fact, been established that the preferred site of lanthanide interaction during lanthanide - induced shift studies is O-6.⁹ CNDO/2 calculations indicate that the electron density around O-6 and O-8 are very similar and suggest that the specificity does not seem to arise from electronic factors.

Having observed the specific cleavage of the C-5 - O-6 bond, a question that came to mind was, could a reagent be found that would specifically cleave the C-5 - O-8 bond? Such a cleavage would result in a novel entry into oxepane derivatives and allow for a potential synthesis of zoapatanol, (13) (Figure 4), a potent contragestational diterpenoid isolated from the leaves of zoapatle (*Montanoa tomentosa*) by Levine and co-workers in 1979.¹⁰

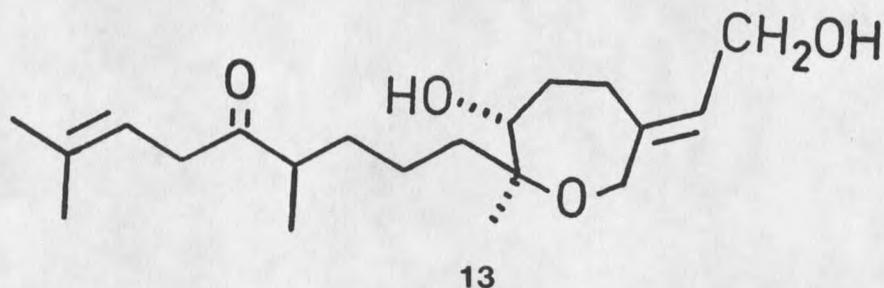


Figure 4. Structure of Zoapatanol

In an attempt to find such a reagent, 8 was reacted with acetyl iodide generated in situ.¹¹ Surprisingly, the elimination of both bridging oxygens was obtained, resulting in the ketone, (14), as shown in Figure 5.

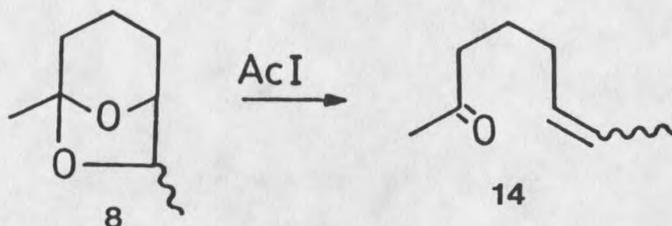


Figure 5. The Reaction of 5,7-Dimethyl-6,8-dioxabicyclo-[3.2.1]octane With Acetyl Iodide

The fact that the robust bicyclic system, generally resistant to hydrolysis, is fragmented to give a ketone is interesting in itself; however, the presence of the δ, ϵ - unsaturation in the product made this result even more intriguing. The similarity of the ketone, **(14)**, to several insect pheromones was striking.

Unsaturated ketones have been found to be both major and minor constituents in the sex pheromones of various insects. Several examples are illustrated in Figure 6. (Z)-7-nonadecen-11-one, **(15)**, and (Z)-7-eicosen-11-one, **(16)**, were found by Tamaki et al.¹² to be components of the sex attractant of the peach fruit moth (*Carposina niponensis*). (Z)-9-tricosen-14-one, **(17)**, a stimulant from the female housefly (*Musca domestica* L.) was identified by Uebel et al.¹³ in 1978.

(Z)-6-Heneicosen-11-one, **(18)**, and (Z)-1,6-heneicosadien-11-one, **(19)**, are the principle and minor sex pheromone components of the Douglas-fir tussock moth (*Orgyia pseudotsugata*), as reported by Smith and co-workers.^{14,15} The Douglas-fir tussock moth (DFTM) is a severe defoliator of fir forests of western North America.

