Stereoselective transformations of oxygen-bearing ring compounds
by Karen Elizabeth Bartelt

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University

Abstract:
New methodologies or reagents which can find application in the stereocontrolled synthesis of natural products are always in demand. A series of stereoselective transformations of the 6,8-dioxahicyclo[3.2.1]octane and the 2-(1-carbonyl)-3,4-dihydro-2H-pyran skeletons is investigated. Reduction of 2-(1-carbonyl)-3,4-dihydro-2H-pyrans by either trialkylaluminums or diethylzinc is stereoselective for the Cram product; in the case of diethylzinc only the Cram product is seen. Triethylaluminum is used in a synthesis of brevicomin in which the exo isomer predominates by better than five to one. The structures of interesting by-products are determined, and a molecular mechanical treatment of C-4 substituted bicyclic ketals is given. Reductive cleavage of 6,8-dioxabicyclo[3.2.1]octane systems is performed with both trialkylaluminums and diethylzinc. In all cases, the 0-6 bond is cleaved and the alkyl group delivered trans to the original one atom bridge. As precursors for cleavage by aluminum iodide, two solid 7-anisoyl-6,8-dioxabicyclo[3.2.1]octanes are synthesized. X-ray data determine the anisoyl groups to be exo. Cleavage by AlI3, does not give expected products. Attempted cleavage of these same systems by bromine results in dibromination at the C-4 position instead. Cyclopropanation of 3,4-dihydro-2H-pyran derivatives is accomplished using both carbenoid and chlorocarbene reagents. Cyclopropanation is more facile when a protecting group is applied to hydroxyl groups present or when the substituent at the C-2 position is a methoxy group. Ring-opening of the cyclopropanes formed is attempted using silver ion, HBr, H2/Pd, and B2H6 but no useful ring openings occur.

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APPROVAL

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Karen Elizabeth Bartelt

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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Date March 30, 1988

To Bob, Erik, and Jill

"Some luck lies in not getting what you thought you wanted but getting what you have, which once you have it you may be smart enough to see is what you would have wanted had you known."

Garrison Keillor

Lake Wobegon Days

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ABSTRACT

New methodologies or reagents which can find application in the stereocontrolled synthesis of natural products are always in demand. A series of stereoselective transformations of the 6,8-dioxabicyclo[3.2.1]octane and the 2-(1-carbonyl)-3,4-dihydro-2H-pyran skeletons is investigated. Reduction of 2-(1-carbonyl)-3,4-dihydro-2H-pyrans by either trialkylaluminums or diethylzinc is stereoselective for the Cram product; in the case of diethylzinc only the Cram product is seen. Triethylaluminum is used in a synthesis of brevicomin in which the exo isomer predominates by better than five to one. The structures of interesting by-products are determined, and a molecular mechanical treatment of C-4 substituted bicyclic ketals is given. Reductive cleavage of 6,8-dioxabicyclo[3.2.1]octane systems is performed with both trialkylaluminums and diethylzinc. In all cases, the O-6 bond is cleaved and the alkyl group delivered trans to the original one atom bridge. As precursors for cleavage by aluminum iodide, two solid 7-anisoyl-6,8-dioxabicyclo[3.2.1]octanes are synthesized. X-ray data determine the anisoyl groups to be exo. Cleavage by AlI_3 does not give expected products. Attempted cleavage of these same systems by bromine results in dibromination at the C-4 position instead. Cyclopropanation of 3,4-dihydro-2H-pyran derivatives is accomplished using both carbenoid and chlorocarbene reagents. Cyclopropanation is more facile when a protecting group is applied to hydroxyl groups present or when the substituent at the C-2 position is a methoxy group. Ring-opening of the cyclopropanes formed is attempted using silver ion, HBr, H_2/Pd, and B_2H_6, but no useful ring openings occur.

CHAPTER 1

INTRODUCTION

The synthesis of natural products is an exciting area of organic chemistry today. The 6,8-dioxabicyclo[3.2.1]octane [1] and 2-(1-carbonyl)-3,4-dihydro-2H-pyran [2] systems (Figure 1) represent useful intermediates in the synthesis of small cyclic oxygen-containing natural products. Since these natural products often contain a number of stereocenters, there is a constant search for new methodologies or reagents which will facilitate stereoselective transformations. Three types of reactions were considered to be useful in stereoselective natural product syntheses; reagents not used on these systems previously were investigated. Carbonyl reductions were performed on 3,4-dihydro-2H-pyran compounds by trialkylaluminums and diethylzinc; cleavages of the 6,8-dioxabicyclo[3.2.1]octane systems were attempted with trialkylaluminums, diethylzinc, aluminum iodide, and bromine; and cyclopropanation of 3,4-dihydro-2H-pyran systems were attempted with both carbenoid and chlorocarbene reagents. A variety of ring opening agents, including HBr, silver ion, and H_2/Pd were used to open the cyclopropanes formed.

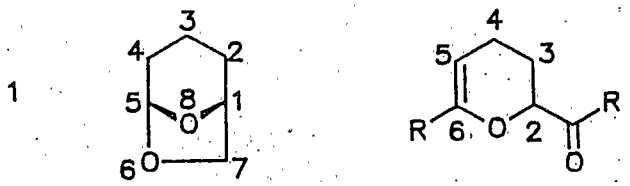
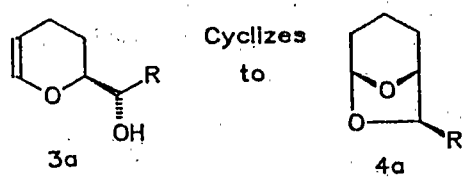


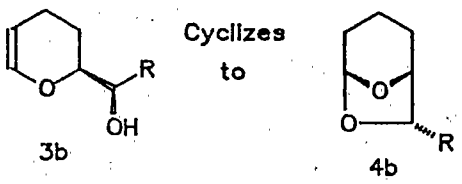
Figure 1. The 3,4-dihydro-2H-pyran [1] and 6,8-dioxabicyclo [3.2.1]octane [2] skeletons and numbering systems

Stereoselective Reductions

It was a goal of this research to investigate the stereochemical consequences of converting 3,4-dihydro-2H-pyran carbonyl compounds to substituted 3,4-dihydro-2H-pyran alcohols with trialkylaluminums and diethylzinc. The alcohols formed could be cyclized to bicyclic ketal natural and unnatural products (Figure 2), and serve as synthetic intermediates for other natural product skeletons (Figure 3).



Threo alcohol results in EXO ketal.
Group of higher priority will be CIS to one-membered bridge



Erythro alcohols give ENDO ketals.
Group of greater priority is TRANS to one-member bridge.

Figure 2. Cyclization of 3,4-dihydro-2H-pyran alcohols to 6,8-dioxabicyclo[3.2.1]octanes

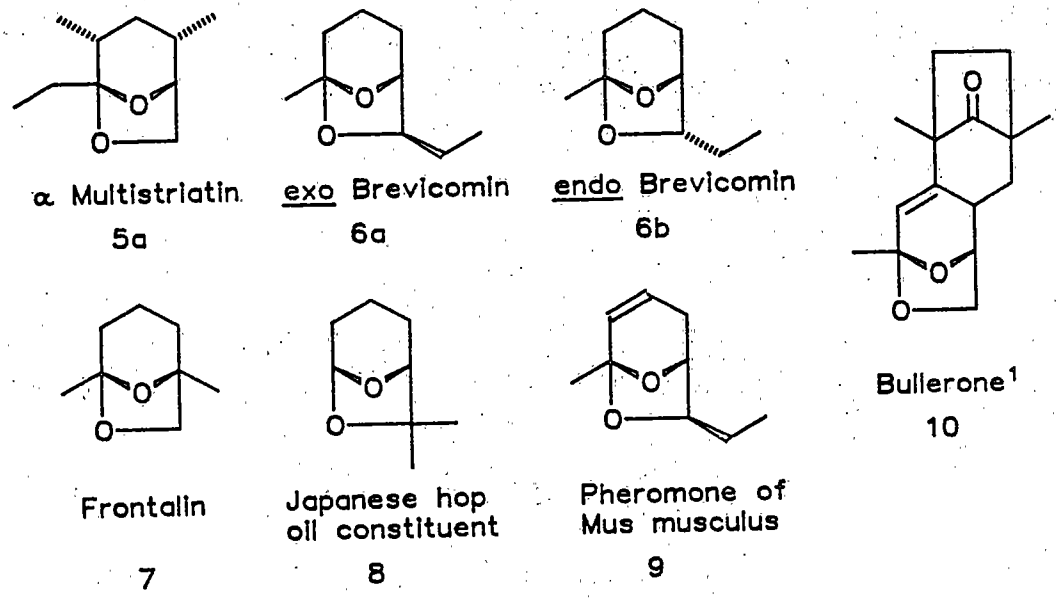


Figure 3. Natural products possessing the 6,8-dioxabicyclo [3.2.1]octane skeleton

It is evident by the number of stereocenters in the natural products in Figure 3 that control of the stereochemistry is essential in any natural product synthesis. The stereochemical course of a reaction can be explained using the model first put forth by Cram[2], and modified by Felkin[3] and Anh[4]. To quote from the original Cram paper,

"in non-catalytic (kinetically controlled) reactions ... that diastereomer will predominate which would be formed by the approach of the entering group from the less hindered side of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least hindered bulky groups attached to the asymmetric center."

Modification of the Cram model by Felkin involved a different rotational conformation in which perpendicular attack is still assumed[3]. Anh considered non-perpendicular attack to be crucial[4], and

steric interaction of the entering group with the small versus the medium ligand predicts the dominant product. However, as Figure 4 shows, any of the models predict the same "Cram" product ought to predominate in the absence of chelation.

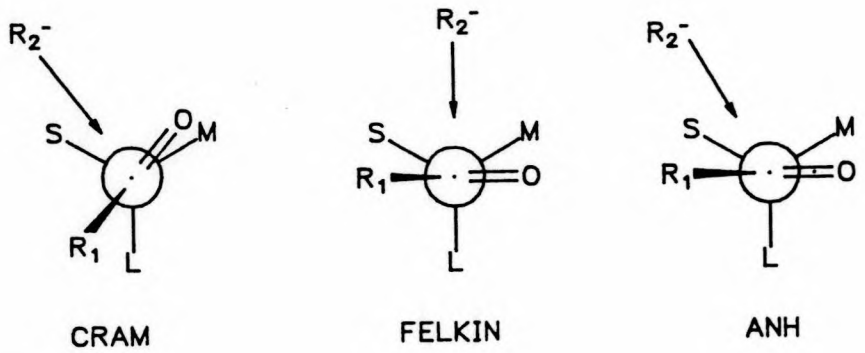


Figure 4. A comparison of Cram, Felkin, and Anh models of carbonyl reduction

A cyclic model can be applied to systems that contain a heteroatom, where the heteroatom and carbonyl oxygen may complex with the reagents, as shown in Figure 5. However, application of this model must be done with care, since it is known that reductions are sensitive to such conditions as solvent, reagent, and substituents on the heteroatom[5]. Indeed, neither model can predict the outcome of this type of reaction; the stereochemical outcome implies the model which best applies to reaction conditions.

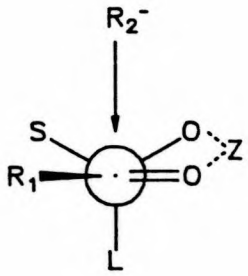
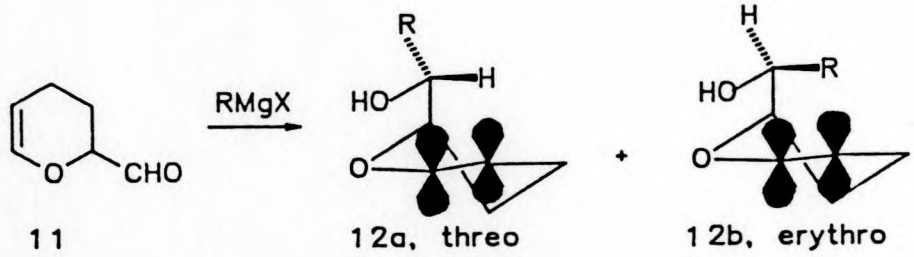


Figure 5. Cyclic model, chelation control

Reactions of 3,4-dihydro-2H-pyran carbonyl compounds by a wide variety of carbanions have been studied extensively and have resulted in a number of natural product syntheses. Prior work has included studies on the steric course of Grignard addition to 2-formyl-3,4-dihydro-2H-pyran [11]. It was concluded that the steric bulk of the incoming "R" group affected the erythro/threo alcohol mix (Figure 6).[6] Reduction of 2-acetyl-6-methyl-3,4-dihydro-2H-pyran by $NaBH_4$ has been found to proceed with slight stereoselection for the threo alcohol (60:40) (Figure 7).[6] Brevicomin[7] [6b] has been synthesized with 4:1 stereoselection for the endo isomer (Figure 8).



11 12a, threo + 12b, erythro

Figure 6. Steric course of Grignard addition