



Isotope labeling investigations in propellanes and aldehydes
by Matthew Scott Rees

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

Montana State University

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Abstract:

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A smaller ring series of propellanes based on the 3,3,3-tricycloundecane is examined. The synthetic protocol is analyzed and intermediates toward the final target molecules are produced.

Isotope labeling provides the framework for the synthesis of three biological intermediates formed from free radical breakdown of selected fatty acids. These intermediates are required for the quantification process using negative ion selective gas chromatography mass spectroscopy.

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Matthew Scott Rees

Advisor: Bradford Philip Mundy

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of a thesis submitted by

Matthew Scott Rees

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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To

*My wife Heidi for her absolute support and
understanding.*

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ABSTRACT

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CHAPTER 1

PROPELLANE INTRODUCTION

In the last fifty years, there have been important changes in the comprehension of the nature of chemical bonding as it relates to organic chemistry. However, there remain many areas with unanswered questions. One constant area of interest concerns how substituents influence the structure and reactivity of various reactions at remote sites.

These nonelectrostatic through-space substituent interactions are called neighboring group participation when the substituent stabilizes the transition state for the reaction. When a rate enhancement is the result, these interactions are referred to as anchimeric assistance. The term neighboring group participation (N.G.P.) was first applied by S. Winstein¹ to describe these classic interactions that are found throughout the literature.

The question in exploring these substituent influences is what type of chemical skeletal system to employ in your analysis. The synthesis of the chemical framework should be facile and the products need to be stable and easily characterized. Classically, a favorite choice of a skeletal framework for physical organic chemists was norbornane and

related compounds. The advantages of norbornane were its overall stability, plus synthetic entry into the system was well established. The cyclic arrangement of atoms allowed many approaches to investigate heteroatom effects, and provided an enhanced understanding of these substituent interactions. The inherent problem that frequently arose was the difficulty in separating the steric contributions of the norbornane framework from the electronic influences of the substituent. The rigidity of the norbornane skeletal system also reduced conformational flexibility and possibly diminished the amount of neighboring group participation. These frustrations led many researchers to look for new and different structural arrangements. This exploration eventually led to the propellane framework. Propellanes allow, in theory, an improvement over the norbornane structure for tailoring experiments to elicit greater understanding of substituent effects.

Propellanes are an interesting class of compounds that have appealed to chemists for almost three decades. There are numerous reasons why propellanes continue to be the focus of scientific research. The previously mentioned use of propellanes as tools for the investigation of substituent effects is only one of many areas of interest. Another important area of research for propellanes is using them as building blocks for natural product synthesis. Other reasons for interest concern the synthesis and physical

organic interactions of highly strained molecules. Historically, our research group's curiosity with propellanes lies somewhere in-between the study of N.G.P. and the synthesis of selected natural products.^{2,3,4,5,6,7}

Propellanes and Neighboring Group Participation

One of the first impressions of propellanes is the amount of symmetry that they may possess. Examples of this symmetry are easily viewed in the structure of many types of 5 or 6 membered propellane rings (Figure 1). These compounds clearly exhibit a propeller appearance when viewed from the side.

The discovery of a new class of compounds is often linked to the development of a new reaction that provides a convenient method of synthesis. This was not really the case for propellanes. The early syntheses of what we now call propellanes were based on the Diels-Alder reaction, which was recognized over thirty years previously. This synthetic method development to make the first propellane systems occurred simultaneously in a handful of research

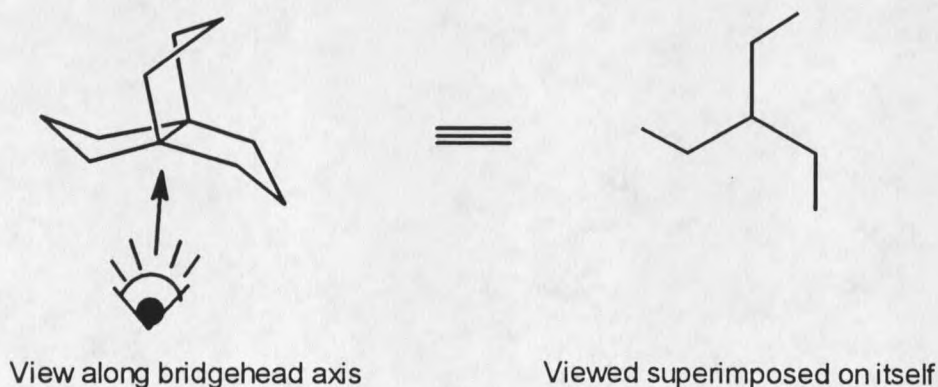


Figure 1. Propeller like appearance in "Propellanes".

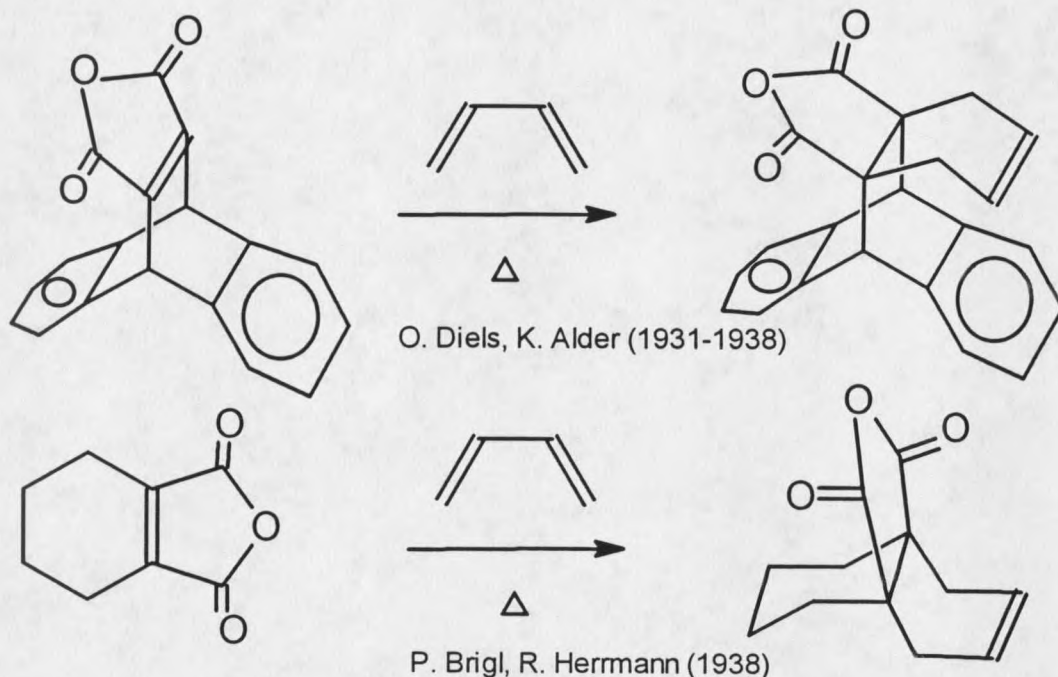


Figure 2. Examples of Diels-Alder reactions to make propellanes in the 1930's.

groups (O. Diels, K. Alder and L. F. Fieser, J.T. Dunn)⁸ during the 1930's. Some representative examples of this early work are shown in Figure 2. There was however, no common name attributed to the work until the middle to late 1960's. During this period, the literature struggled with just what to call these types of molecules. In this early tangle with nomenclature, it is very likely that there are undiscovered examples of propellanes due to the fact that Chemical Abstracts was confused as to how such compounds should be indexed. Research in this area blossomed in the middle 1960's, presenting a quandary in the nomenclature. A unofficial contest of sorts evolved between different

research groups to provide this new class of compounds a common name. The first attempt at nomenclature was made by Bloomfield.⁹ He suggested the name "propellerane" to describe the tricyclic combination of atoms he produced. A reference in Bloomfield's article asserted that Ginsburg favored the name propellane. However, Gassman managed to get the name "propellerane" into the title of a paper.¹⁰ David Ginsburg (who outlasted and outmaneuvered the competition to eventually become victorious) provides an interesting explanation surrounding the struggle for an accepted common name with this quote from his book.¹¹

"No one went to the lengths we did to get the trivial name propellane into the literature..... The editor, alas, did not permit the name propellane to appear in the title. Editors, indeed, appear to dislike trivial names for compounds and apparently stand watch so that these do not creep into the literature. Infiltration is clearly possible, however, as many such names: cubane, basketane, barrelene, etc, etc. have attained both printed form and fame in the literature. The scheming which involved the acceptance of the name propellanes (clearly a much better name than it's longer relative propelleranes according to our "objective" opinion) involved obtaining the agreement from one editor on our mode of nomenclature. After obtaining his blessing, we exploited the invitation to submit a paper honoring Sir Robert Robinson on his 80th birthday, an unrefereed paper, no less!..... We knew ahead of time that we would succeed in getting our name past the editor thus avoiding the possibility of a horrified referee expressing vehement disapproval of the term."

After propellanes became firmly established and recognized in the literature, they have enjoyed almost continuous research interest that even today remains active. Much of this research activity centered in Haifa, Israel in the laboratories of David Ginsburg and his colleagues. By his death in 1989, he had published almost 100 papers in the area and was generally recognized as the father of propellane chemistry.

The true impetus for the "discovery" of propellanes to organic chemists is linked to the progressive understanding of the nature and conformations of cyclic compounds. As the middle part of this century passed, the chemical community was absorbed in gaining knowledge of the structure and conformational analysis of bicyclic decalin or hydrindan type compounds.¹² This is also true for the study of substituent interactions. The emphasis on classical bicyclic systems preceded the next logical step of investigating the tricyclic systems joined by a single carbon-carbon bonded bridgehead. This barrier succumbed to research pressures in the middle 1960's, which began a decade of increased research activity into propellanes.

A great amount of the early work emphasis of directed propellane synthetic studies focused on the [4.4.x] ring systems. The availability of starting materials via Diels-Alder methodology allowed easy entry into the tricyclic ring systems through relatively simple modifications. A

representative example of this facile entry is shown by Ginsburg¹³ in Figure 3 (early 1966).

The reduction of the anhydride, [1], to the diol with LAH followed by the ring closure with tosyl chloride provided the saturated tricyclic [4.4.3] ether, [2]. The ether was cleaved open and brominated in triphenylphosphine / Br₂ to give cis-dibromomethyldecalin, [3]. Nitrile substitution of this key intermediate with NaCN gave entirely different products depending on the choice of conditions and solvent. One equivalent of NaCN in DMF gave the mono-nitrile product, [4], which was hydrolyzed in base to eventually give the tricyclic [4.4.4] lactone, [5]. Another possibility was to use excess NaCN also in DMF. This reaction afforded the mononitrile followed by NaCN acting as a base to remove the proton alpha to the newly added nitrile. This anion displaced the bromine to close the ring. The system then underwent basic KOH hydrolysis to afford the tricyclo [4.4.2] acid, [6]. The last approach was to use NaCN in DMSO to force a Ziegler cyclization to give a five membered imino-nitrile, [7]. This product was hydrolyzed in acid to give the cyano-ketone followed by conversion to the diacid in base. The diacid was esterified and underwent an acyloin condensation to eventually provide the diol, [8]. Although the overall yields of these transformations proved rather low, the concept of propellanes was shown to have tremendous promise for the

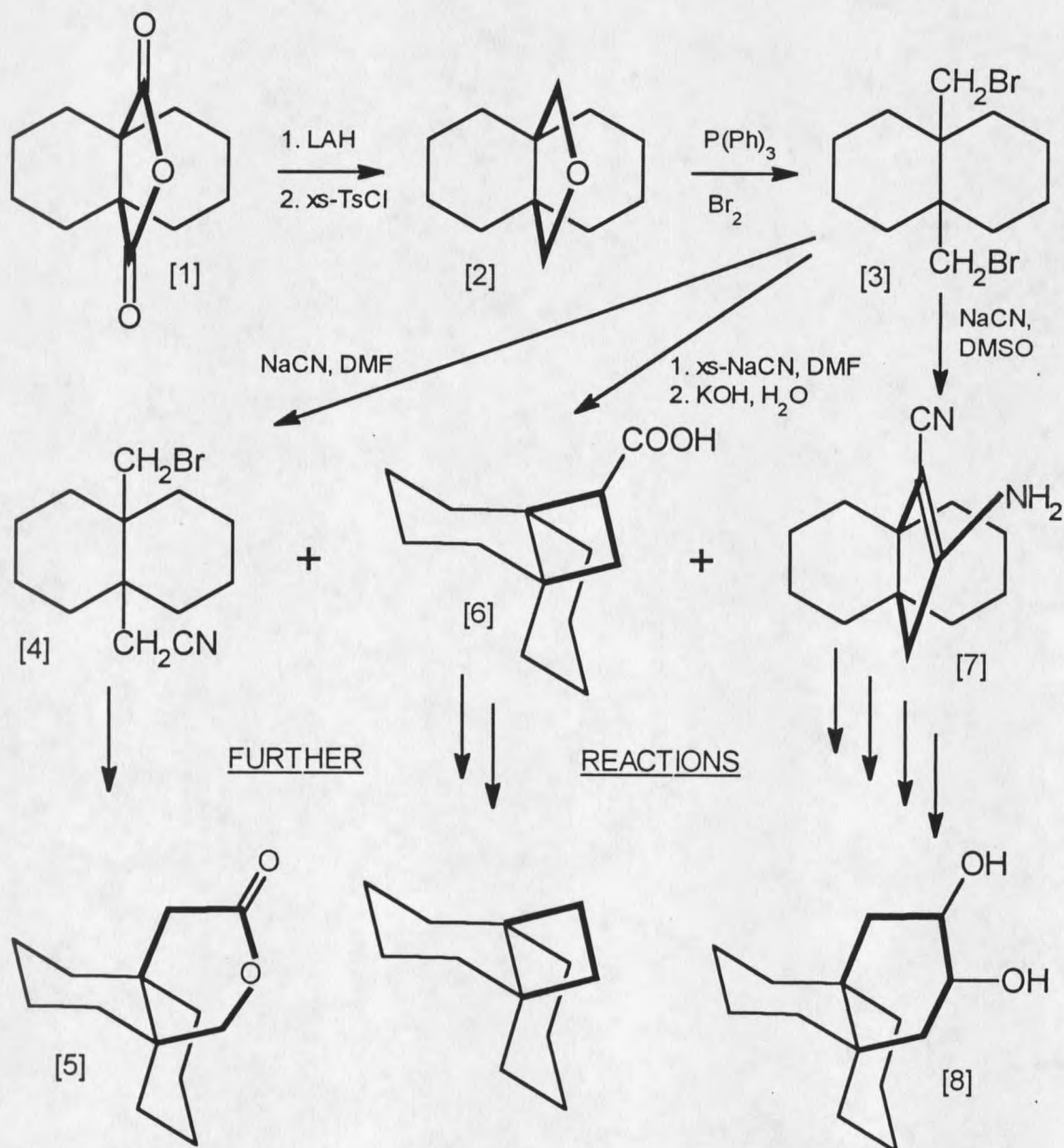


Figure 3. Some representative early propellane synthesis.

