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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Matthew Scott Rees

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MONTANA STATE UNIVERSITY
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APPROVAL

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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Date 6-18-93

To

My wife Heidi for her absolute support and understanding.

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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. Winstein[1] 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.

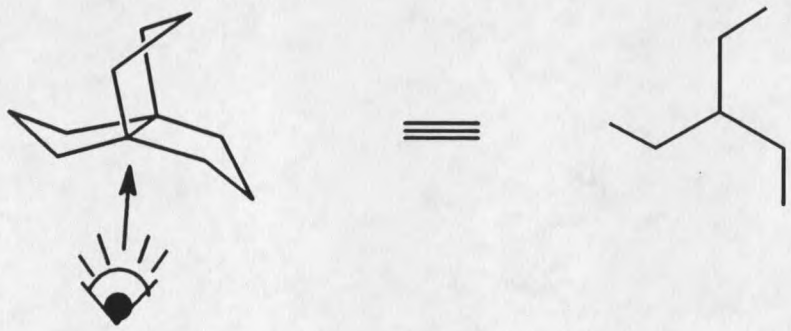
Propellanes are an interesting class of compounds that have appealed to chemists for almost three decades. There are numerous reasons why propellanes continue to be the focus of scientific research. The previously mentioned use of propellanes as tools for the investigation of substituent effects is only 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



View along bridgehead axis Viewed superimposed on itself

Figure 1. Propeller like appearence in "Propellanes".

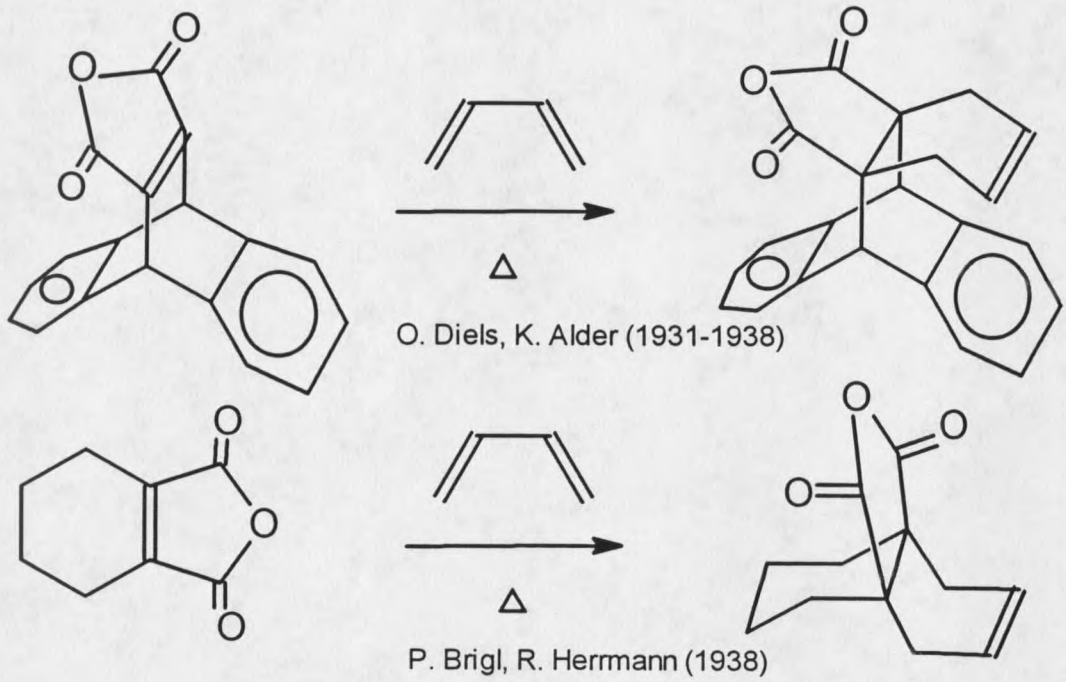


Figure 2. Examples of Diels-Alder reactions to make propellanes in the 1930's.

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 became victorious) provides a 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 Ginsburg[13] 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 / Br_2 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 acycloin 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

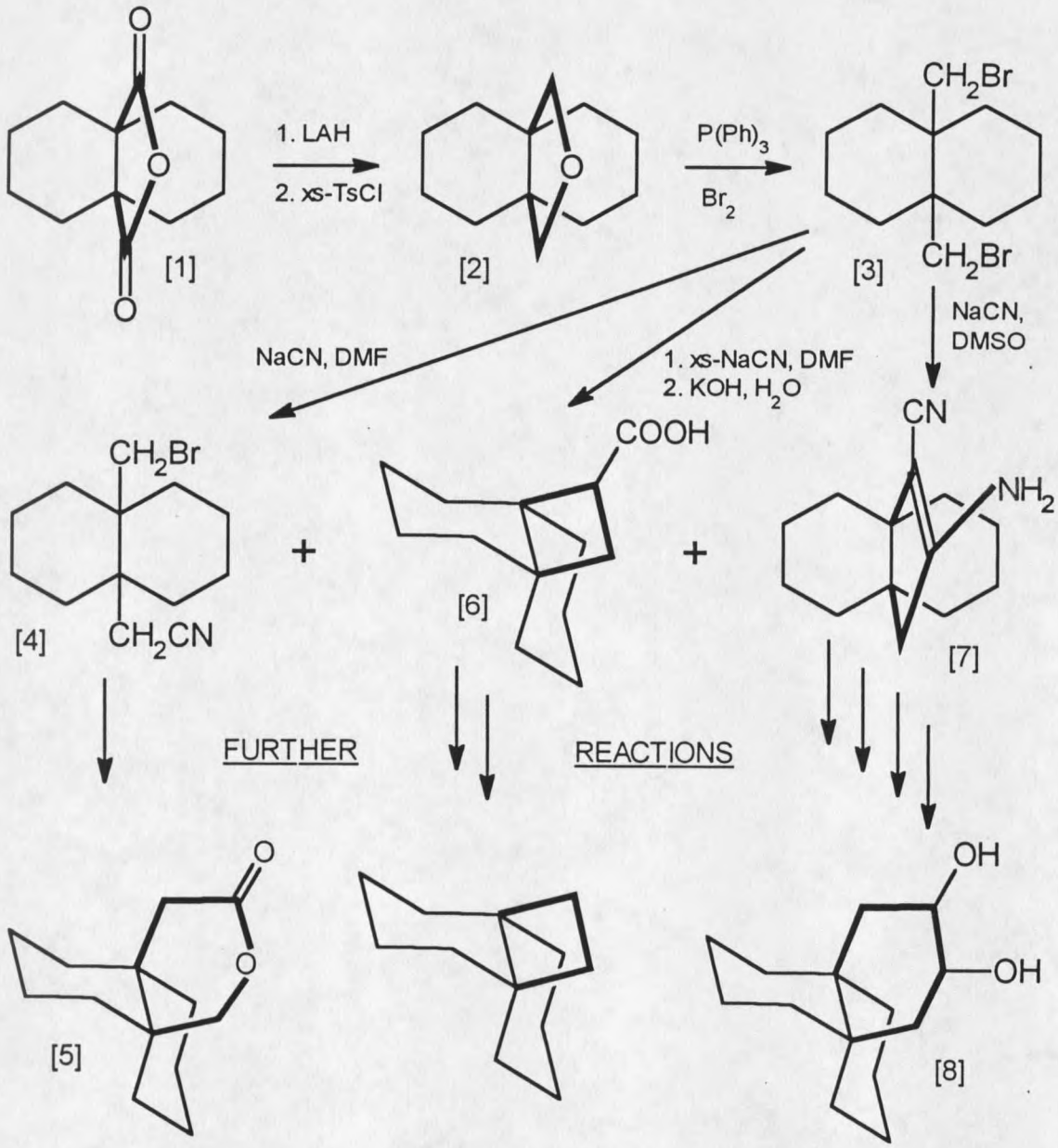


Figure 3. Some representative early propellane synthesis.

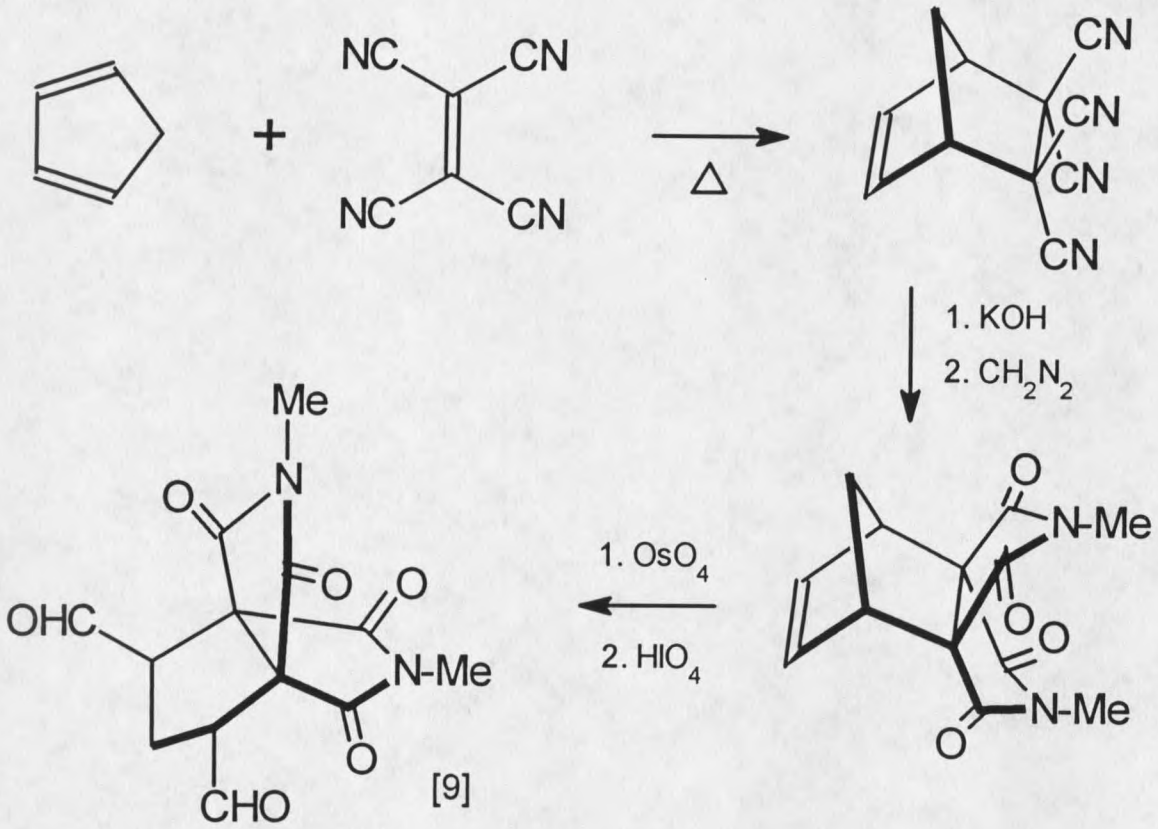


Figure 4. Synthesis of an analgesic.

future. The middle to late 1960's was the golden age for exploring the boundaries of what was actually possible in the construction of propellanes. The only limit was the imagination of the chemist and the shortcomings of the available synthetic technology.

These early syntheses proved the conceptual validity of designing propellanes. The ideas for new target molecules quickly went beyond academic intellectual pursuits and entered the pharmaceutical arena. In 1966, Ginsburg published the synthesis of an analgesic propellane, [9],

from readily available materials.[14] The synthesis of this compound is shown in Figure 4.

Nature has always taken a perverse delight in frustrating synthetic organic chemists. The past few decades have seen extraordinary advancement in synthetic methodology and approaches. Many of the synthetic obstacles that limited organic chemistry have been defeated or replaced with new barriers. However, there are always new and interesting compounds that provide a synthetic challenge. The propellane class of compounds has also contributed to this synthetic intrigue. Some examples of natural products containing the propellane structure are shown in Figure 5. There are also many examples of propellane intermediates invoked in the synthesis of various natural products.[15] A recent series of papers on cationic rearrangements provide examples of propellane participation in a synthetic scheme. In general, propellanes are predisposed to a variety of cationic rearrangements due to their molecular shape and variation in size. The quaternary bridgehead structure and possible relief of ring strain influence the ability of propellanes to undergo cationic rearrangements. The [3.3.3] propellane system exhibits unique thermodynamic stability but may be induced to undergo rearrangements by including a carbonyl moiety in one of the rings. This acid catalyzed carbocation rearrangement produces the tricyclo[4.3.2]undecane (quadrane), [10], and

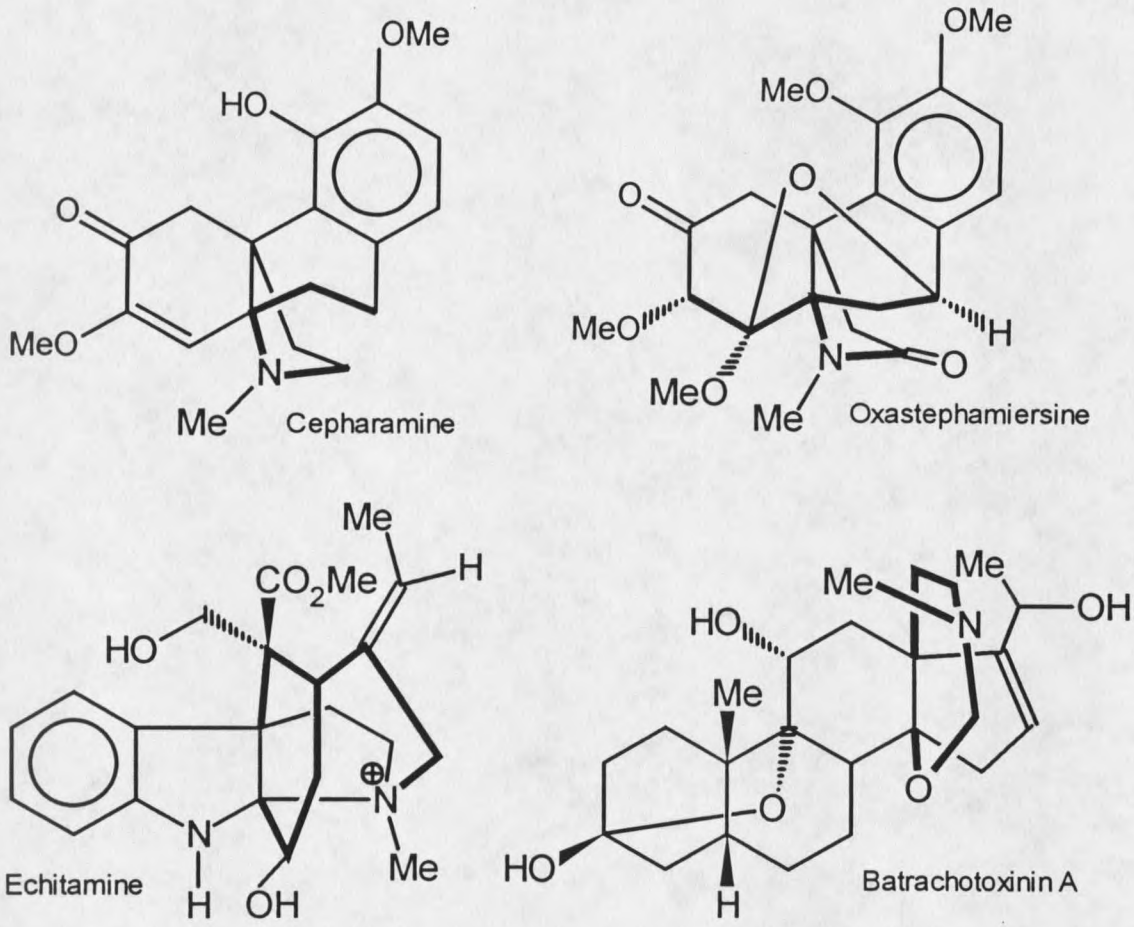


Figure 5. Some representative propellane natural products.

the tricyclo[6.3.0]undecane (angular triquinane), [11], ring systems.[16] These skeletal arrangements are common in several anti-tumor sesquiterpenes, [12-14], as shown in Figure 6.

Propellanes are involved in areas of industrial activity other than pharmaceutical interests. It seems logical that after working with propellanes, one is unable to ignore their symmetrical beauty. This may account for

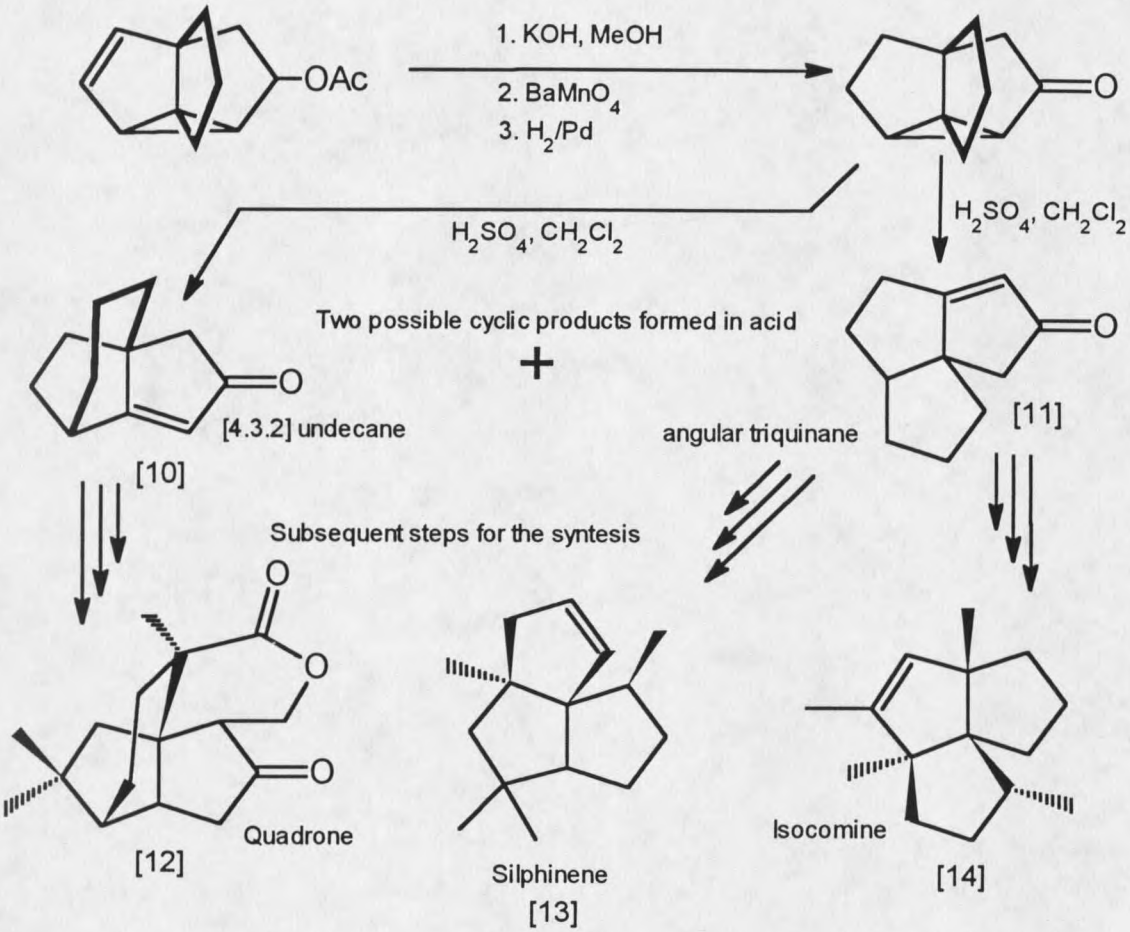


Figure 6. Synthetic applications of propellane cationic rearrangements.

the interest by the cosmetic and fragrance industry in a Swiss patent (filed in 1990).[17] A reasonable explanation may be that if the propellanes look good they also may provide engaging olfactory stimulation. From my personal experience, propellane odors are extremely pungent and would not be a hot seller in the competitive fragrance industry (for humans anyway).

It seems that physical organic chemistry has generally expended much more effort to understand and predict relative

stabilities of conformations. Propellanes helped to change the emphasis to evaluation of the chemical and physical properties of these conformations. Therefore, research activity and advancements in propellane chemistry were paralleled in many ways with that of neighboring group participation. One point that became clear, was that there are different forms of neighboring group participation. The various classifications of substituent interactions recognized are the electrons from sigma, pi, and nonbonding sources. In heterocycles, the interactions that originate primarily from the heteroatomic lone pairs play a dominant role in any neighboring group participation. The amount of influence that each heteroatom contributes to reactivity has generally been related to the ability to stabilize cations (either partially or fully formed). This explanation was first described in regard to solvolytic conditions and reactions.[18]

When this type of explanation is applied to oxygen, complications enter the picture and begin to limit the experimental support. Oxygen, with its high electronegativity, does not share electrons readily; the exception being to stabilize positive charges at adjacent carbons. The results of many studies have painted a contradictory picture, therefore the total effect is not completely understood at this time.

An historical example of oxygen neighboring group participation[19] in a norbornyl system is shown by the displacement of brosylate by the acetate group in a buffered acetic acid solution (Figure 7). The exo substrate rate of reaction is over 10^7 times faster than the endo counterpart. This anchimeric assistance supports the rationale that the oxygen donates some of its nonbonding electronic density, when possible, into the back-side lobe of the substituent. The ratio of the products also is indicative of oxygen participation. The endo isomer formed a complete cation which the acetate attacked from the exo side to produce a exo / endo product ratio of 85% / 2%. The exo isomer was assisted by the oxygen to produce a exo / endo product ratio of 99% / 1%.

This type of behavior was also observed by Otzenberger[20] for an oxygen bicyclic compound, [15]. The oxymercuration of a bicyclic propellane precursor, tetrahydrophthalan, afforded a mixture of products in a ratio of syn [16] : anti [17] of 3:1. He proposed that the bicyclic cyclopentane ring was folded over and that there was a heteroatom effect that determined the products. The developing charge on the mercurinium ion received stabilization from the nonbonding electrons on the oxygen (Figure 8). There is however, a slight difference in the facial selectivity in the double bond due to the boat conformation of the cyclohexene ring and the cis bridgehead

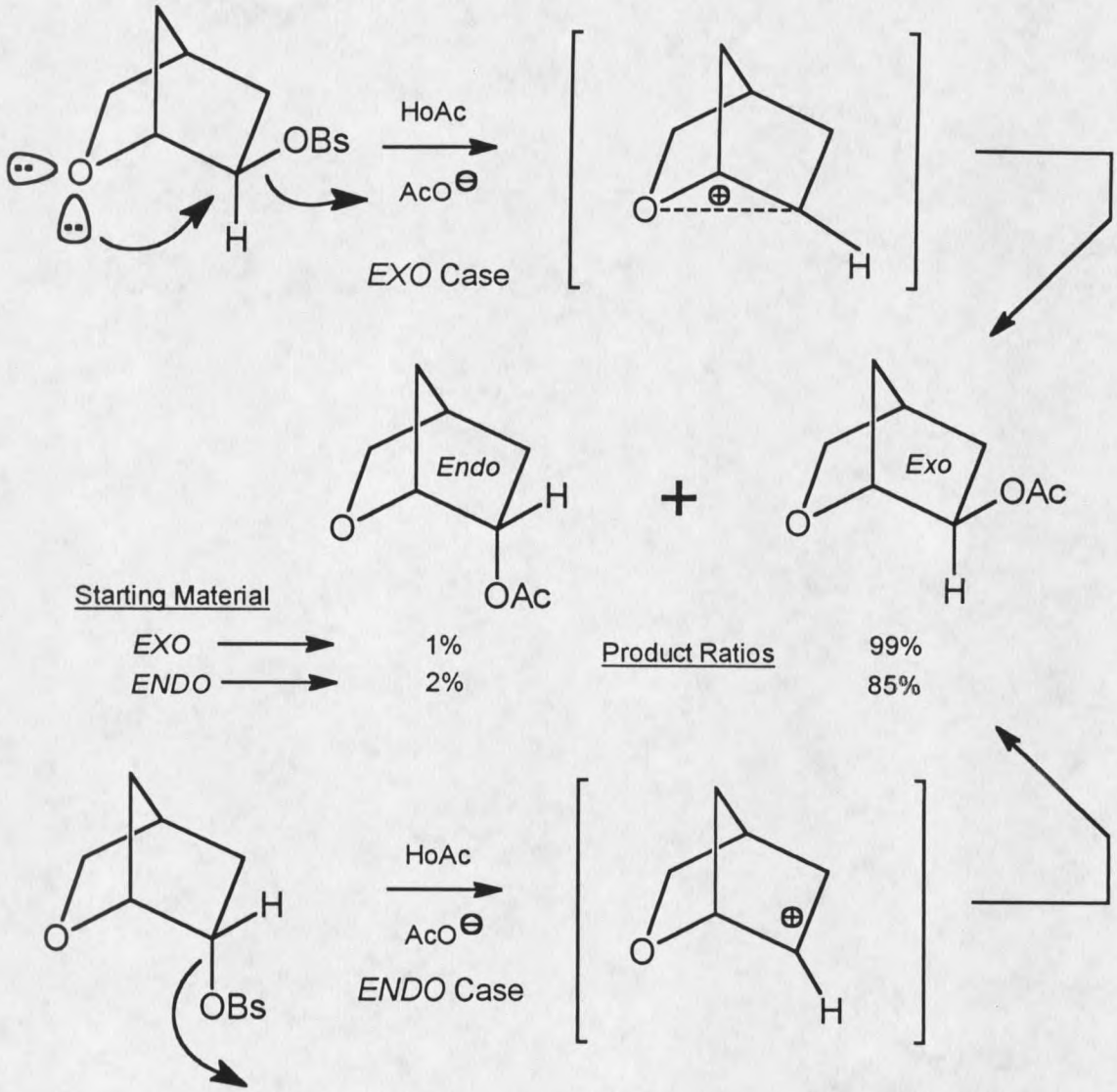


Figure 7. Oxygen heteroatom neighboring group participation.

alignment. These steric variances proved to be impossible to quantitate and were only partially addressed.

Other heteroatoms have a more pronounced influence than that of oxygen. This is related to the lower electronegativities and a more diffuse lone pair orbital.

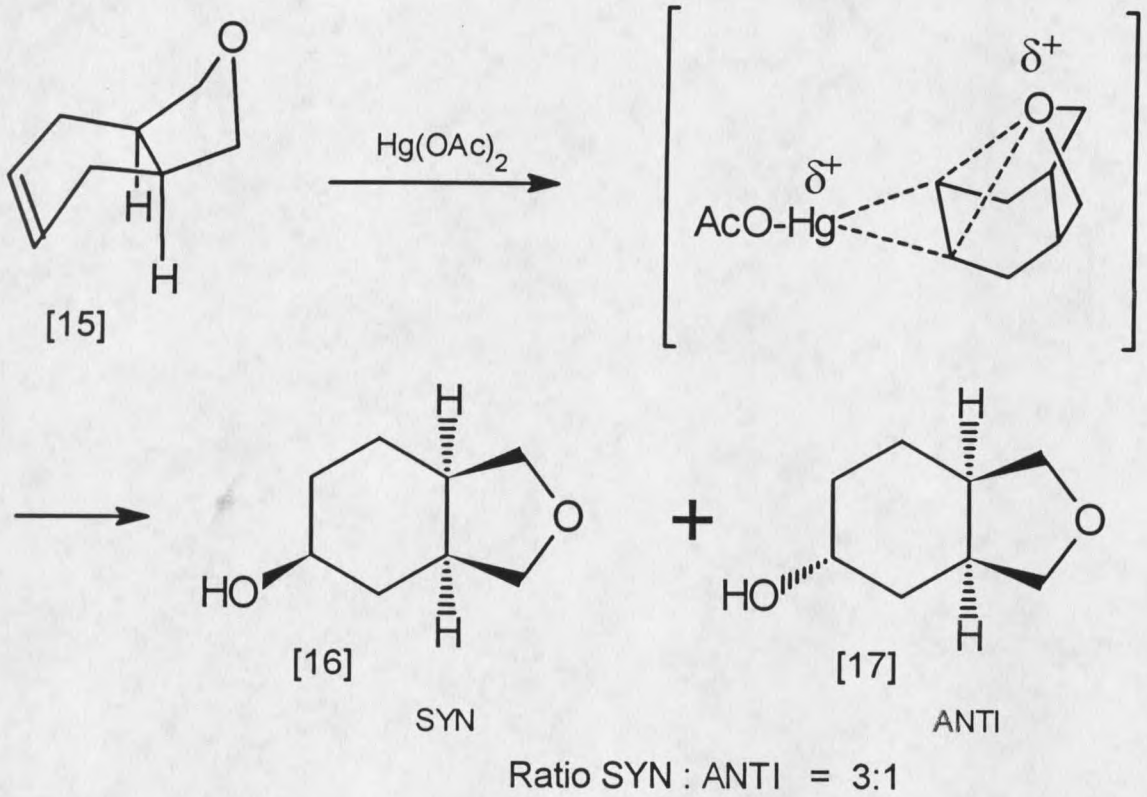


Figure 8. Otzenberger's experimental results for tetrahydrophthalan

Sulfur is slightly different due to the availability of d orbitals to participate in bonding which further complicates the issues involved.

An earlier example of nitrogen neighboring group participation in norbornyl systems was examined by Paquette.[21] He showed that heteroatom participation was involved in the observed stereoselectivity at the double bond (Figure 9). Lipkowitz investigated[22] the nitrogen analog to Otzenburger's bicyclic compound shown above. In this system, the reverse relation of oxygen to the alkene

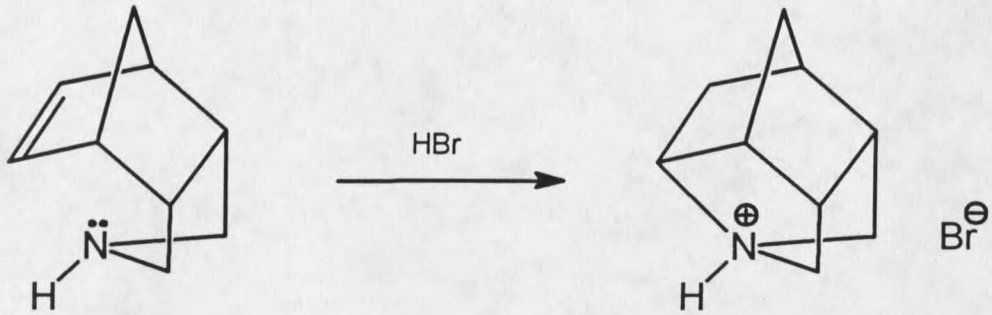
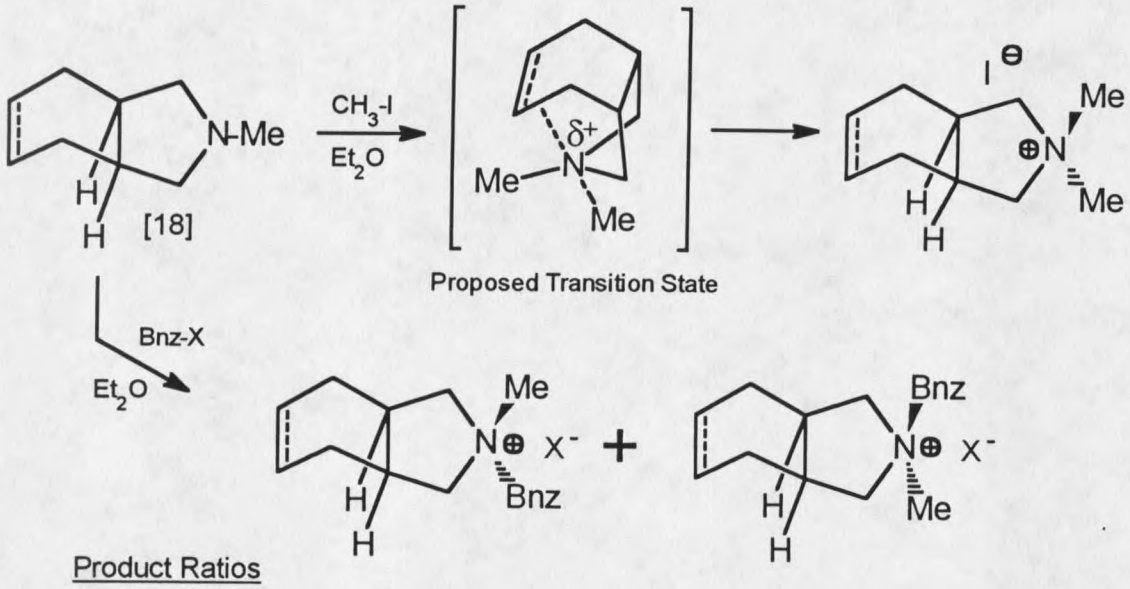


Figure 9. Participation of heteroatom in a Aza-norbornyl system.

was investigated. Theoretically, if the heteroatom can influence the reaction at the alkene, the converse effect should hold. The magnitude of the effect should contrast with the differences in electron density between the two species. The N-methyl amine of the 8-azabicyclo[4.3.0]non-3-ene series, [18], was subjected to alkyl halide electrophiles to quaternize the nitrogen and produce the ammonium cation. The stereochemistry of the nitrogen quaternization products were investigated by NMR. The product ratios of the different approach isomers should be indicative of the alkene pi electron donation into the nitrogen in the transition state. Methyl iodide and benzyl iodide were used as the electrophilic substrates for salt formation. The reactions are shown in Figure 10 with the respective product ratios. It is interesting to note, benzyl chloride was also evaluated. The product ratio was essentially equivalent to the iodo species which demonstrated a very small dependence of anionic species in



Product Ratios		
X=I (Bnz-I)	86%	14%
X=Cl (Bnz-Cl)	84%	16%
X=I (CD_3I)	8%	92%

Figure 10. Menschutkin quaterization reaction results by Lipkowitz.

the outcome of the reaction. This is somewhat surprising because of the vastly different character of the halogen as leaving groups. Lipkowitz also showed that there were substantial steric effects that were expressed in the quaternizations. The study of the inverse reaction of taking the tertiary benzyl amine and reacting it with methyl iodide switched the product ratio outcome.

Jones[23] had explored the quaternization of tropane with $^{13}CH_3I$ and discovered a preference for axial attack (relative to the 5-membered ring). This result

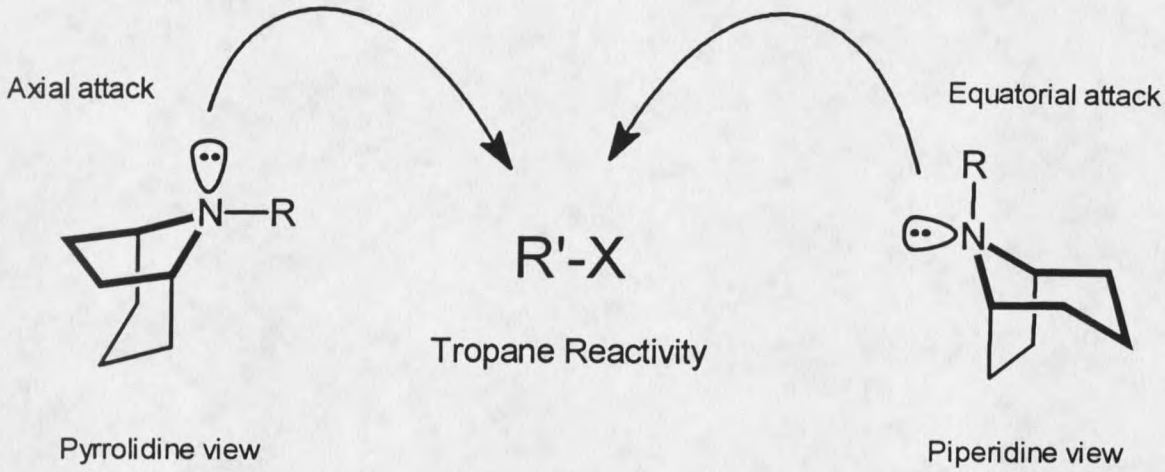


Figure 11. Novel approach to explain tropane reactivity with piperdine.

contrasts with piperidine and morpholine which prefer equatorial alkylation. Lipkowitz also related the bicyclic results obtained above to the tropane system.[24] He suggested that tropanes are less sterically hindered on the pyrrolidine ring side than the piperidine ring side (Figure 11). This forces a predominance of pyrrolidine ring side or axial attack. Once again, the struggle between steric and electronic effects allowed the expression of the sum but not of the parts.

The results of Otzenberger and Lipkowitz showed that there were subtle electronic effects in the bicyclic ring system. The steric differences in approach between a pair of hydrogens and the other ring were obvious but attempts to isolate the influences proved futile. The steric differences often depended on the energy of conformational ring inversion and flexation of the five membered ring

containing the heteroatom. One possible solution to the problem was to replace the hydrogen pair with another ring and move fully into the realm of propellanes.

This next logical step into the propellanes was investigated by Wilkening.[25] He synthesized 8-Oxatricyclo-[4.3.3.0]-undec-3-ene, [19], and tested the reactivity in different types of reactions as shown in Figure 12. In this series of reactions, the alkene was treated with mercury acetate and also with MCPBA. The results of the reactions showed no selectivity and therefore no neighboring group assistance. It was reasoned that the early selectivity of the bicyclic systems must have been due to steric effects. However, there were differences in the rate of the

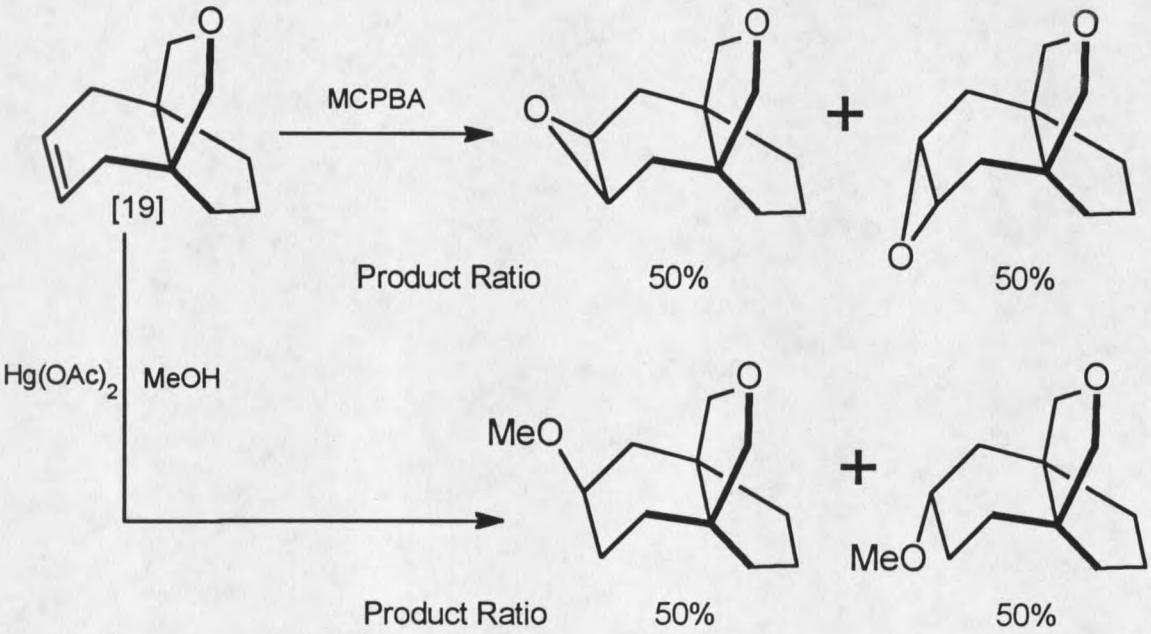


Figure 12. Wilkening's results for reactions on 8-oxatricyclo-[4.3.3.0]-undec-3-ene.

reactions. The oxymercuration of the propellane was much more difficult than the bicyclic system. Much harsher conditions were needed to get any conversion at all. One could imagine that the more vigorous conditions may have effected the outcome. It was somewhat discouraging that for this substrate, no neighboring group participation could be detected in the product ratios. Johnson[26] also showed an absence of stereoselectivity for 8-oxatricyclo-[4.3.3.0]-undec-3-ene. Calculations indicated that the π-faces of the double bond are sterically equivalent because the two anticipated boat conformations are energetically equal. His attempt to look for possible anchimeric assistance showed a small amount of rate enhancement (1.53 : 1 favoring anti product to oxygen) for solvolysis of tosylates. There was also a 3 fold (favoring anti product to oxygen) enhancement for catalytic hydrogenation. However, there was some indication of oxygen / catalyst interaction at the metal surface as previously suggested by Otzenberger and Wilkening. The question of hydroboration of the selected propellane was studied recently by Lee.[27] He concluded that the product ratio depended mostly on steric factors. The results of both solvolysis and calculation studies also suggested that steric interaction was the dominating force in the selectivity.

With the generally higher recognized potential of nitrogen to participate in selectivity, it was hoped that

nitrogen would possibly provide the sterics a "better fight" in a formal propellane system. The proposed project was to explore the analogous nitrogen system and compare with the oxygen propellanes described previously. We would hopefully look for some neighboring group participation by π-electrons of the alkene. It was also thought that by changing the ring size, we might obtain a more complete understanding of the steric contribution to product ratios in quaternization reactions.

Nitrogen Quaternization

The discussion of the results of a propellane study would be premature without first understanding some relevant aspects of this quaternization reaction. The quaternization of a tertiary amine is also called the Menschutkin (also spelled Menshutkin) reaction. There has been an historic interest in the stereochemical aspects of nitrogen quaternization for several reasons. The major reason for the focus of attention on the Menschutkin reaction was linked to the basic understanding of organic chemistry in exploring the mechanistic limits of classic bimolecular substitution (Sn2 reaction).

One of the questions that always concerns researchers is what type of transition state does the reaction have. There was a considerable amount of interest in this area in the late 1960's and early 1970's (*e.g.* McKenna[28]). In 1972, Swain[29] asserted that steric crowding increases greatly during the early part of the reaction as the N-C distance shortens in reactions of triethylamine and methyl chloride. The angular change for the methyl hydrogens is very slight. Swain also proposed that during passage into the transition state, the overall steric strain decreased. This crowding is relieved by the interactions of the non-bonded hydrogens on the amine and the methyl.

A furor of sorts was caused in 1980 by Arnett and Reich.[30,31] They proposed that in the absence of severe steric hindrance or strong hydrogen bonded solvents, quaternizations may be represented by a transition state structure with about one third positive charge on the nitrogen (Figure 13). An almost complete negative charge would develop at the point of solvent reorganization on the leaving group. This picture of extensive bond breaking in the transition state (also called a "late" transition state) differs from the accepted classical Sn2 mechanism. Abraham[32] disagreed with this charge separation ("late"

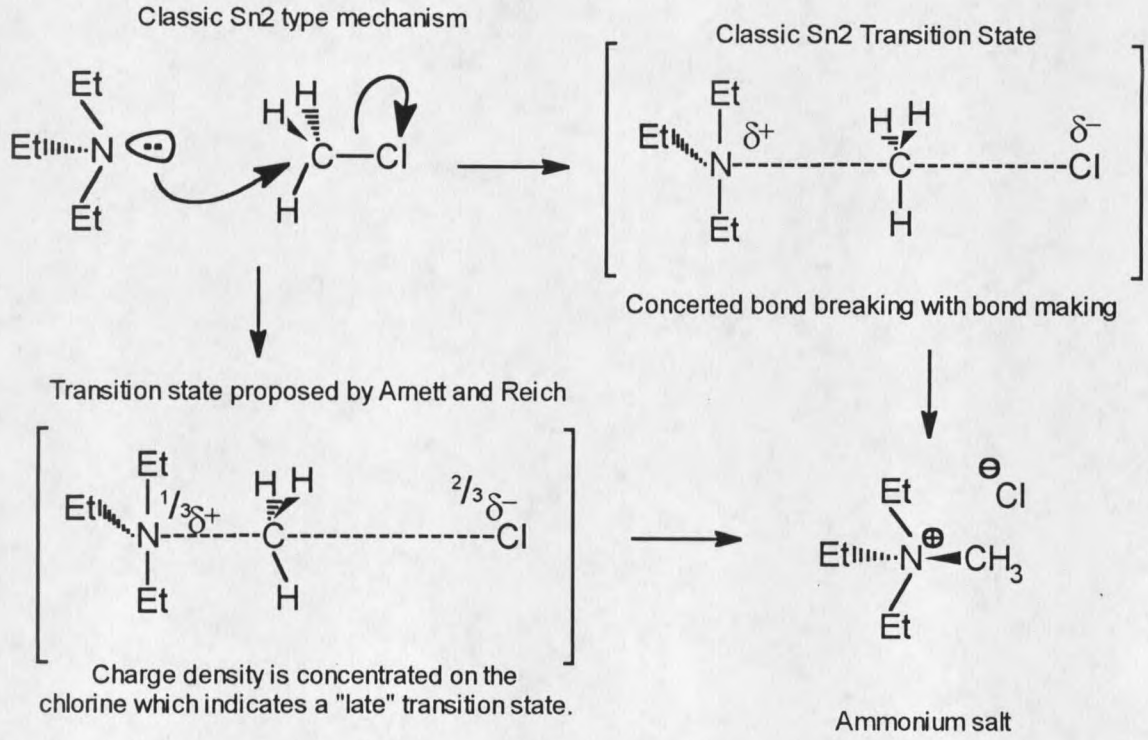


Figure 13. Menschutin transiton state controversy.

transition state) argument. He suggested that the transition state more resembles the uncharged reactants than the product pair of dissociated ions and favored the classical Sn2 treatment of the transition state with approximately synchronous bond making and breaking. Abraham noted that the actual charge separation would be affected by variances in the reactants and solvent but would generally be balanced on either side. More recently, there have been attempts to link the appearance of the transition state with nucleophilic character.[33] Kondo believed that as the nucleophile improves, the transition state shifts toward the product side. This results in more charge development at the transition state. This is shown by greater progression of N-C bond making with accompanying C-X bond breaking at the transition state. This idea of a balanced or possibly "early" transition state is generally accepted, however, the final outcome remains the focus of ongoing research.

CHAPTER 2

SYNTHETIC DISCUSSION

The focus of this investigation was to synthesize a series of N-alkyl-8-azatricyclo[3.4.n]propellanes by varying the ring size of the third (nth) ring from four to seven carbons. The six membered ring would have double bond unsaturation opposite from the bridgehead to provide possible donation of π-electron density towards the nitrogen. The five membered N-alkylpyrrolidine ring would remain constant throughout the examination to allow the steric environment at α-carbons of the nitrogen in the ring to stay as constant as possible (Figure 14). We hoped that there would be a larger neighboring group effect than was previously seen in reactions of the analogous oxygen propellane systems.

In our proposed study, nitrogen would undergo quaternization with an electrophile to provide a product ratio of the two possible quaternization salts. The actual product ratio of these salts should be easily discernible by NMR spectroscopy techniques. We could not avoid some steric involvement of the propellane system, therefore, the corresponding saturated systems would also be examined. These saturated systems, with no possible π-electron

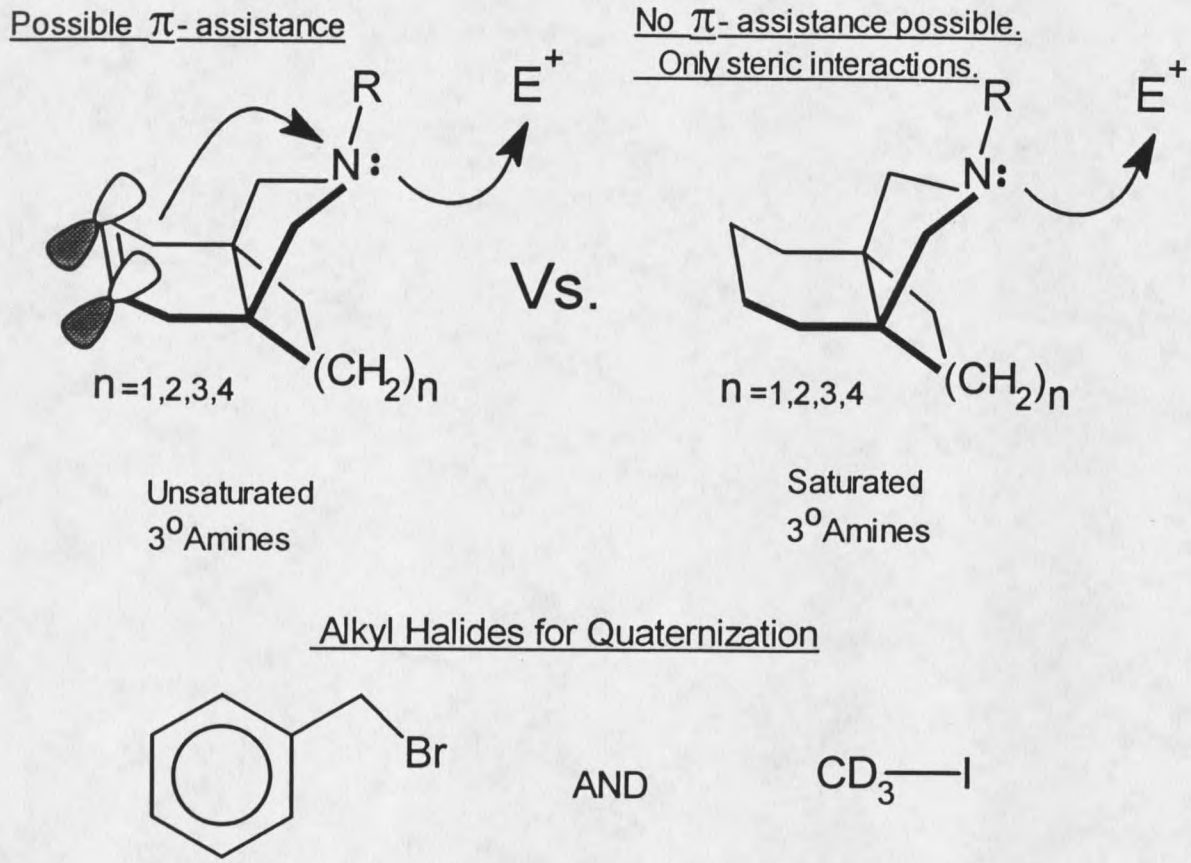


Figure 14. Proposed N-methyl propellanes to synthesize for Menschutkin reaction analysis.

donation, would quantify the steric contributions of the different propellane ring sizes in quaternization reactions. To further examine the approach sterics of the electrophiles, we chose different alkyl halides in trideuteromethyl iodide and benzyl bromide. These sterically divergent alkyl halide electrophiles are both very reactive, but have much different steric interactions with the propellane framework.

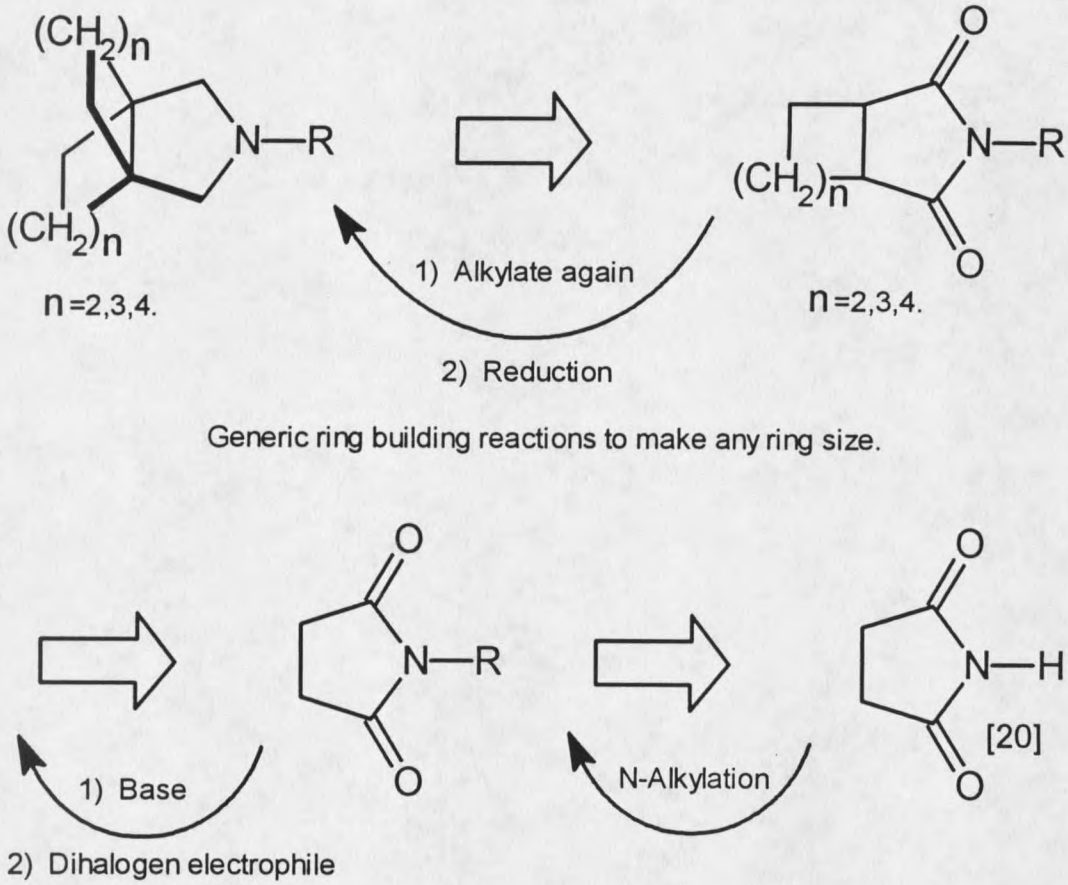


Figure 15. Retrosynthesis of more flexible approach at propellane synthesis.

We thought of several different synthetic approaches into the desired propellane system. The first idea would provide the greater amount of synthetic versatility at the cost of increased length and difficulty. This generalized approach of using a static pyrrolidine ring with an N-benzyl or N-methyl group would provide the starting material. We envisioned building two other different ring sizes onto this pyrrolidine ring. As described before, one major ring target would be a six membered ring. The third ring of the

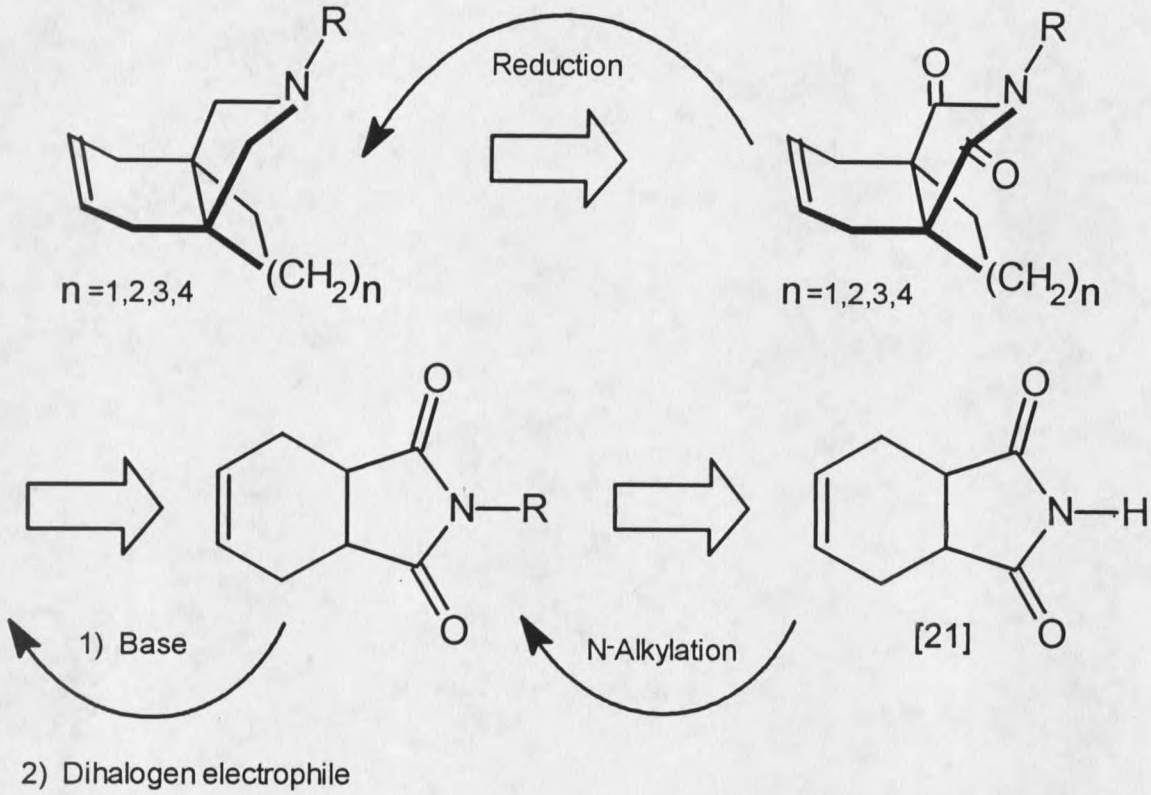


Figure 16. Retrosynthetic analysis of direct approach to propellanes.

propellane would vary from four to seven in size. The versatility of this synthesis would allow the option of building other ring sizes in addition to the six membered ring. This would allow, in theory, synthesis of any tricyclo[3.n.m] possible propellane system (Figure 15). The pivotal reaction would be the dianion ring closure. The amine would conceivably originate from the N-alkyl imide via a lithium aluminum hydride reduction. In this approach, succinimide, [20], is indicated as the most likely candidate for a commonly available starting material. The problem to

this flexible approach was the inherent difficulty of a tandem dianion cycloaddition to make two rings.

The more direct approach to the propellane synthesis was to use a bicyclic starting material (*cis*-1,2,3,6-tetrahydrophthalimide, [21]) where the cyclohexene ring is already present. After the nitrogen methylation, the synthesis continues with ring closure on the third ring which provides entry into the propellane system (Figure 16). The size of the appended ring would change as described above.

Both of these overall synthetic methods employ, to different degree, a key ring closure reaction of a dianionic nucleophile attacking a dielectrophile to effect ring closure. While they differ in overall flexibility and difficulty, they both should be synthetically feasible in the laboratory.

The work in the lab started with the necessary alkylation of succinimide. Following the procedure of Jun,[34] succinimide, [20], was benzylated with benzyl chloride and potassium carbonate in THF. The extremely poor isolated yields, while similar to the reference (~45%), prompted us to look for better methods of alkylation. The problem was the poor solubility of the succinimide in organic solvents. Changing the solvent failed to improve the yield. We attempted to improve the succinimide solubility by employing phase transfer reaction conditions.

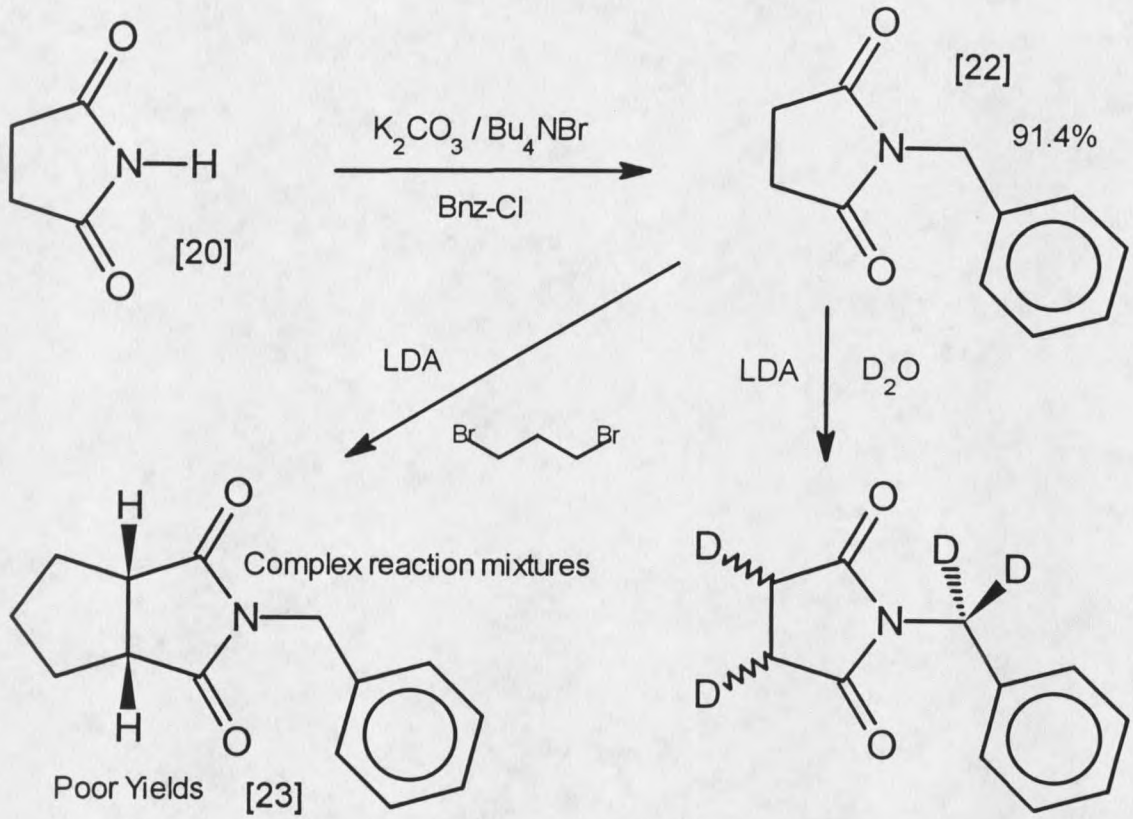


Figure 17. One failed approach at propellane synthesis.

Using tetrabutylammonium bromide in a 1:1 water / benzyl chloride solution with potassium carbonate as the base eventually afforded the N-benzylsuccinimide, [22], in 92% isolated yield. This product was subsequently treated with LDA to make the dienolate of the succinimide followed by slow addition of 1,3-dibromopropane to make the bicyclic 5-membered ring compound, [23]. The reaction unfortunately yielded mostly recovered starting material. The product was formed only in small amounts (Figure 17). In an effort to determine the cause of the reaction difficulties, the

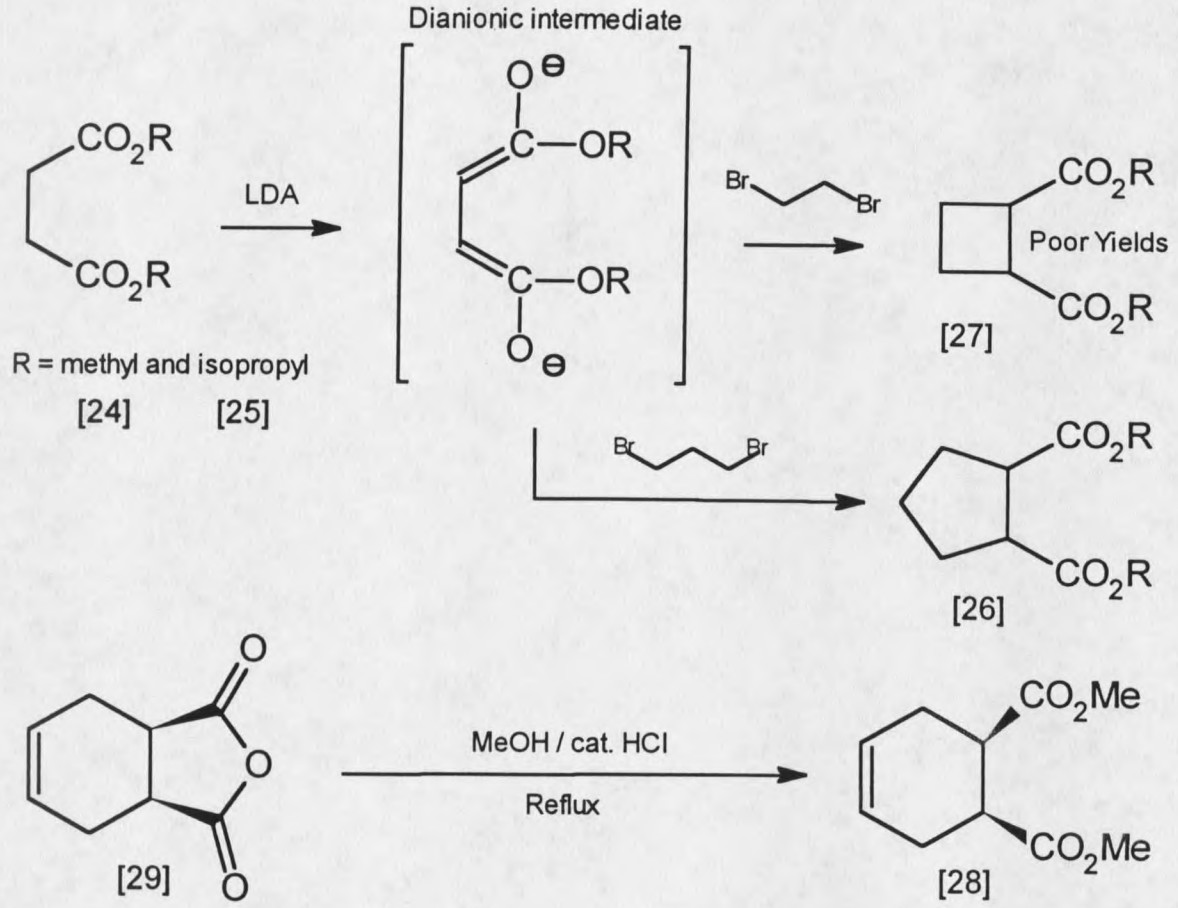


Figure 18. Synthesis of monocyclic starting materials.

dienolate was quenched with D_2O. The NMR spectrum showed that both the benzylic and the enolizable protons had undergone exchange with deuterium. The reaction conditions were changed (solvent, base concentration, temperature) in numerous attempts to optimize the yield. These attempts ultimately proved unsuccessful. With the problems of acidity of the benzylic protons, it was clear that another method would be needed.

The next step was to find another procedure in the spirit of the former synthetic route. This new method was based on using a dianion of dimethyl succinate, [24], with dielectrophiles to make the monocyclic structures. This approach also proved problematic during the alkylation processes. The method (Figure 18) worked reasonably well for formation of the cyclopentane adduct, but presented problems with the formation of the cyclobutane. The formation of four membered rings is generally considered an uphill battle. These problems are usually associated with the ring closure. We were however surprised, with the difficulties found in solubility of the cyclobutane product during workup. This problem was magnified by the persistent problem of dienolate solubility in systems with a small number of carbons. As the succinate was added to the LDA solution, a gelatin like suspension formed that was only slightly soluble in THF. Yamamato[35] also noted this, and favored the isopropyl, [25], over the methyl, [24], ester to achieve increased low temperature solubility. This change of ester functionality for these succinate reactions increased our yields, but the overall reaction outcome proved disappointing. Another aspect of the succinate approach was the difficulty of obtaining quality NMR interpretive data. This was due to the conformation of the undesired trans isomer from the enolate reaction. The difficult separation of the isomers, while theoretically

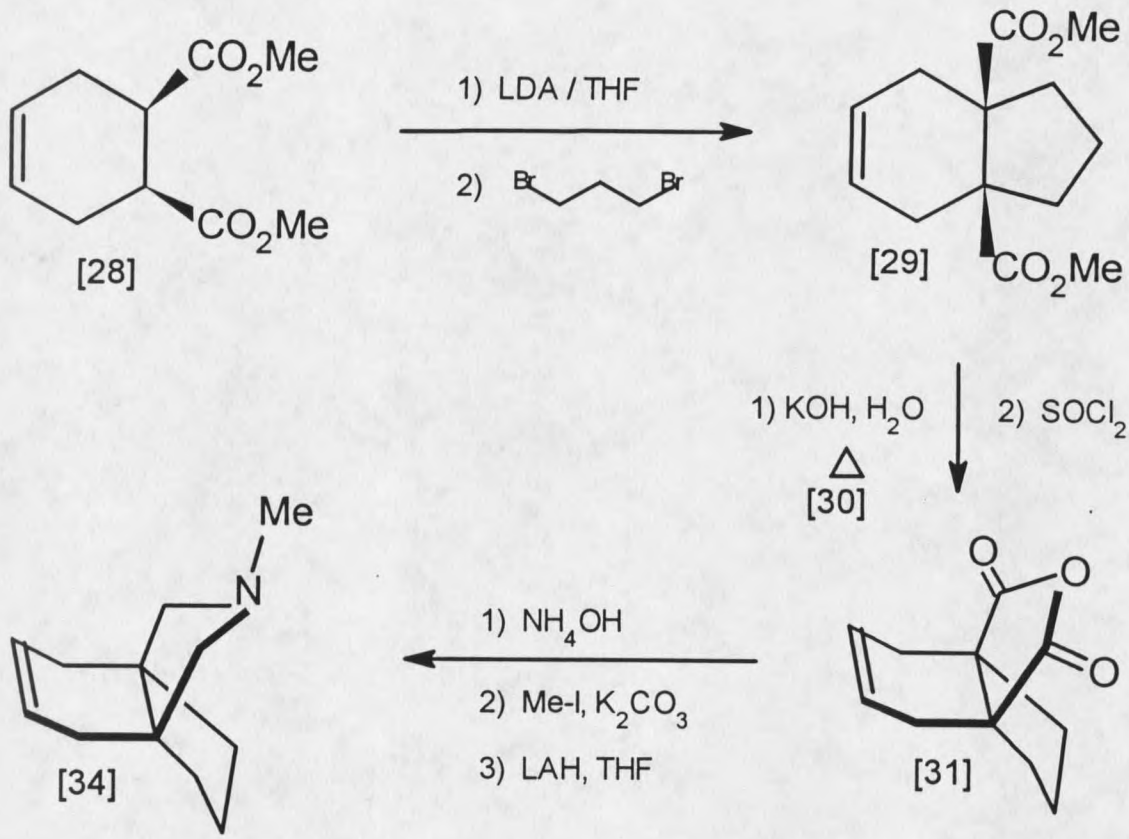


Figure 19. Proposed synthetic transformations to make propellane.

feasible, was unnecessary because of dianion formation in subsequent steps would eliminate the isomer problem.

The formation of the cyclohexyl compound, *cis*-3,4-dicarbomethoxycyclohexene, [28], was easily produced without an succinate alkylation reaction. It was created from an acid catalyzed solvolysis to open the ring of *cis*-1,2,3,6-tetrahydrophthalic anhydride, [29]. This compound avoided the purification steps employed in the alkylation reactions and could easily be produced in large quantities.

At this point, we have an entry point into the synthesis of the target propellanes with the monocyclic rings of six, five, and (somewhat) the four membered rings. We thought that we would focus on one of the monocycles and test the complete synthetic protocol in reaching the final N-alkyl amine propellane product (Figure 19). The cyclohexene ring system was chosen as the starting material for the model synthesis because it was the easiest to produce in larger amounts.

An amount of *cis*-1,2-Dicarbomethoxycyclohex-4-ene, [28], was converted to the dianion by treatment with LDA following the Wilkening method[36] as shown in Figure 20. This dienolate solution was treated with 1,3-dibromopropane in a slow addition. This new bicyclic product, *cis*-1,6-dicarbomethoxybicyclo[4.3.0]non-3-ene, [29], was produced in relatively good yield (~50%). The diester was hydrolyzed by refluxing in excess aqueous KOH to produce the diacid, [30].

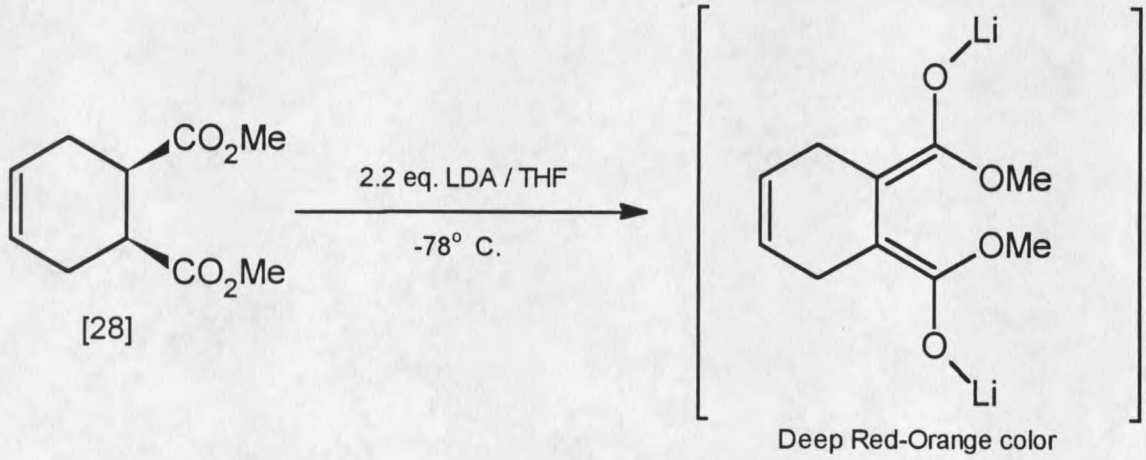


Figure 20. Dienolate dianion of *cis*-1,2-dicarbomethoxycyclohex-4-ene

The diacid was dehydrated by $SOCl_2$ to afford ring closure to form the anhydride propellane, [31]. Nitrogen insertion was accomplished by stirring the anhydride with excess ammonium hydroxide. This reaction is somewhat exothermic, and needed to be iced in the beginning stages. The secondary imide, *cis*-7,9-dioxo-8-azatricyclo[4.3.3]dodec-3-ene, [32], was treated with potassium carbonate and methyl iodide in THF to accomplish the nitrogen alkylation. The N-methyl imide, [33], was reduced to the tertiary amine, [34], by refluxing with lithium aluminum hydride in THF.

At this point we had one of the target compounds in hand, and needed to evaluate the previous synthetic protocol that was used to get there. We felt that although the target molecule was reached, the excessive number of reactions that were required presented other problems. The availability of monocyclic starting materials caused some concern because the cyclohexenyl ring was the easiest to obtain. Other monocyclic compounds were formed in much lower overall yields. While the overall synthetic approach was proven, the conclusion we reached was the synthetic flexibility desired was unbalanced by the amount of time and expense expended. It was felt that a more efficient approach should be used to obtain the desired target molecules. Therefore, other ideas were investigated.

The bicyclic starting material approach began with the readily available *cis*-1,2,3,6-tetrahydrophthalimide, [21],

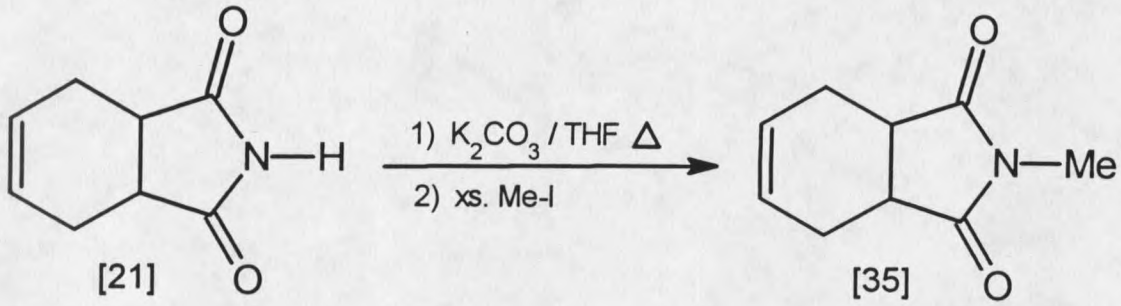


Figure 21. Methylation reaction conditions

as the starting material. This compound was alkylated with potassium carbonate and methyl iodide to make the N-methyl imide, [35], as shown in Figure 21. We choose the N-methyl instead of the N-benzyl to avoid the base problems with the vulnerable benzylic protons in further alkylation steps. The N-methyl imide was alkylated using the previously described dianion approach. An unusual difficulty arose during the alkylation steps. The problem was that the dianion became extremely viscous. This viscosity caused a reduction in the overall yields in the reaction. Magnetic stirbars were shown to be useless in mixing the fully formed dianion. Higher dilution of substrate in solvent failed to correct the problem, which was ultimately solved through use of a mechanical stirrer. These alkylations were carried out for each of the four separate propellane frameworks. The propellane structures differed by the size of the third alkane ring from four to seven carbons. The yields of the alkylations were not generally representative of standard

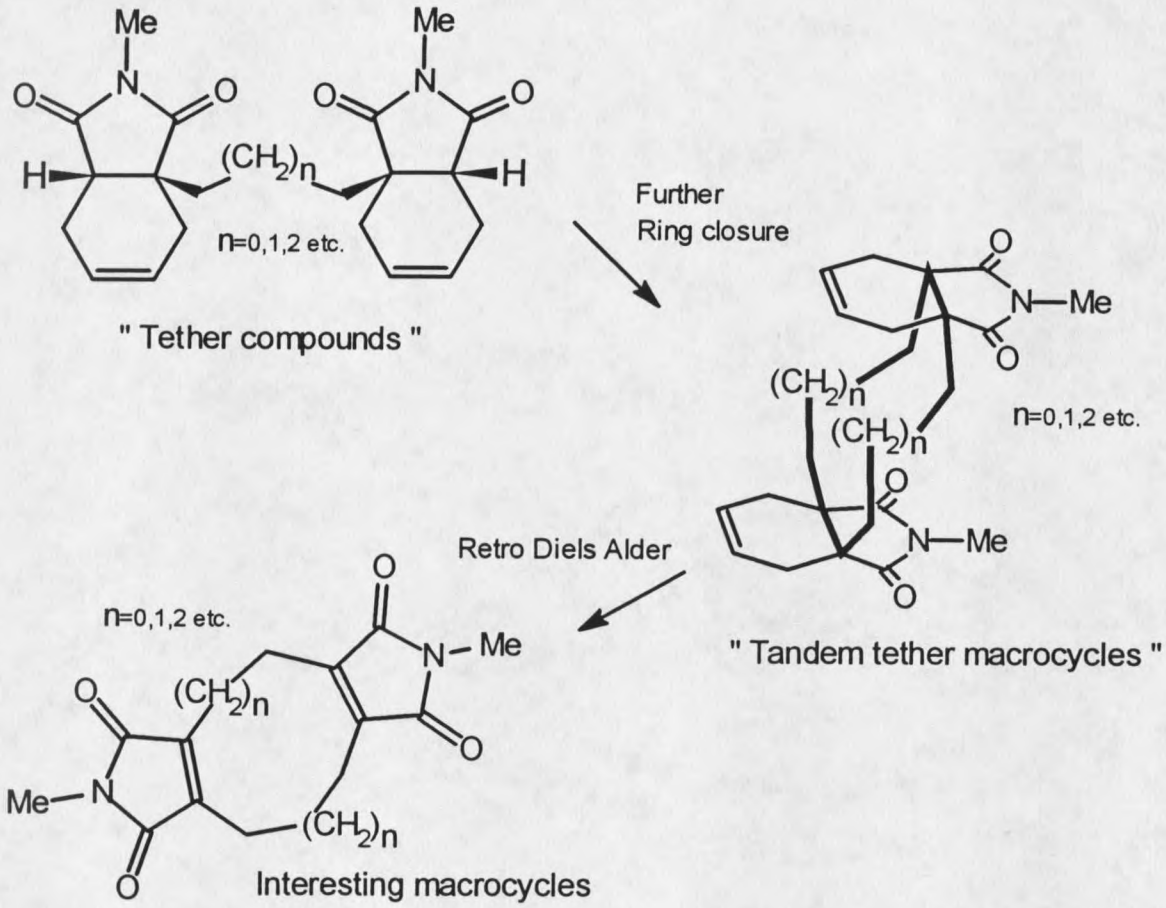


Figure 22. " Tethered " compounds and possible synthetic uses.

ring closure reactions. The yields for the five and four membered rings were the highest, followed by the six and seven membered rings. The reason for the disparity was an interesting byproduct that was significant in the alkylations to make six and seven membered rings. This byproduct was formed by tethering of two molecules of starting material between one molecule of the dielectrophile. The ring closure to make the propellane must be faster for the four and five membered rings. When

the rings get larger, tethering can compete (Figure 22) as a side reaction. It was surprising that at the high dilution conditions of the alkylation that an intermolecular tethering would effectively compete with the intramolecular ring closure. These compounds show an interesting version of the Robinson dictum[37] that where multiple products are possible from a reaction, one frequently gets the less desirable product in greater yields than one would like. We attempted to facilitate ring closure of the other positions of these tether compounds. We were unsuccessful in achieving closure in even low dilution conditions. Based on entropy alone, the ring closure of the tether compound should be easier than formation of the original tether. Regrettably, this area was not the immediate focus of our research efforts, but deserves further study in the future. One could envision entry into macrocyclic rings based on the tandem tethered compounds also shown in Figure 22.

The next stage of the synthesis was the reduction of each imide to the respective amine. In order to insure complete reduction to the amine, excess reducing agent in refluxing THF was used. Figure 23 shows the previously discussed alkylation and the hydride reduction to the amines. It was our experience in the previous monocyclic synthesis that reduction with LAH presented some unforeseen problems. The difficulty occurred during the analysis of the Menschutkin quaternization product ratios by proton NMR.

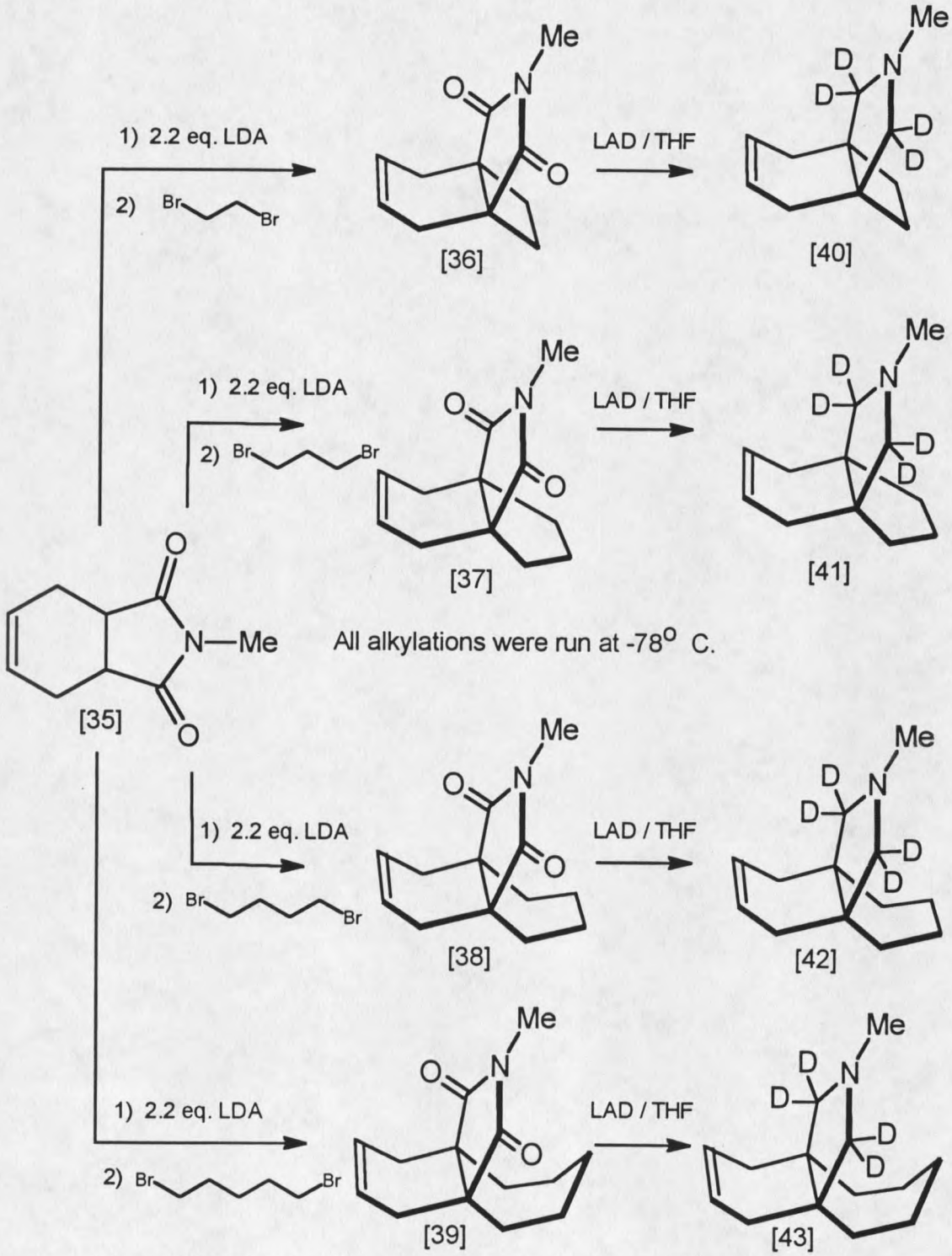


Figure 23. Bicyclic alkylations and reductions to make propellanes.

The α-pyrrolidine ring protons peaks would sometimes overlap and interfere with the integration of the N-methyl singlets. This problem of occasional overlap of signals arose at even higher field (500 Mhz) instruments. We decided to use LAD for the imide reduction to deuterate the alpha-methylene positions to remove the offending peaks from the NMR spectrum (Figure 24). This selective deuteration resulted in more accurate N-methyl group integration and more reliable isomer quantitation.

Originally, the synthetic plan was to produce the saturated propellane analogs by catalytic hydrogenation of the target unsaturated amines. A problem arose in attempting this reduction using H_2 over a platinum catalyst. The normal workup of the reaction generally returned the starting material. Higher pressure and longer reaction times with higher catalyst concentrations didn't seem to help. We retreated to the imide compound and found that the reduction proceeded normally (Figure 25). A probable explanation of the sluggish reaction is that the electron density of the amine caused a strong nitrogen-metal bond. This bonding caused the metal to be bound up and thus poisoned the catalytic activity of the metal. This type of activity in not new and is used to advantage in quinoline (Lindlar) reductions of alkynes. The imide, with greater charge delocalization, was unaffected by the metal and the reduction occurred in a normal matter.

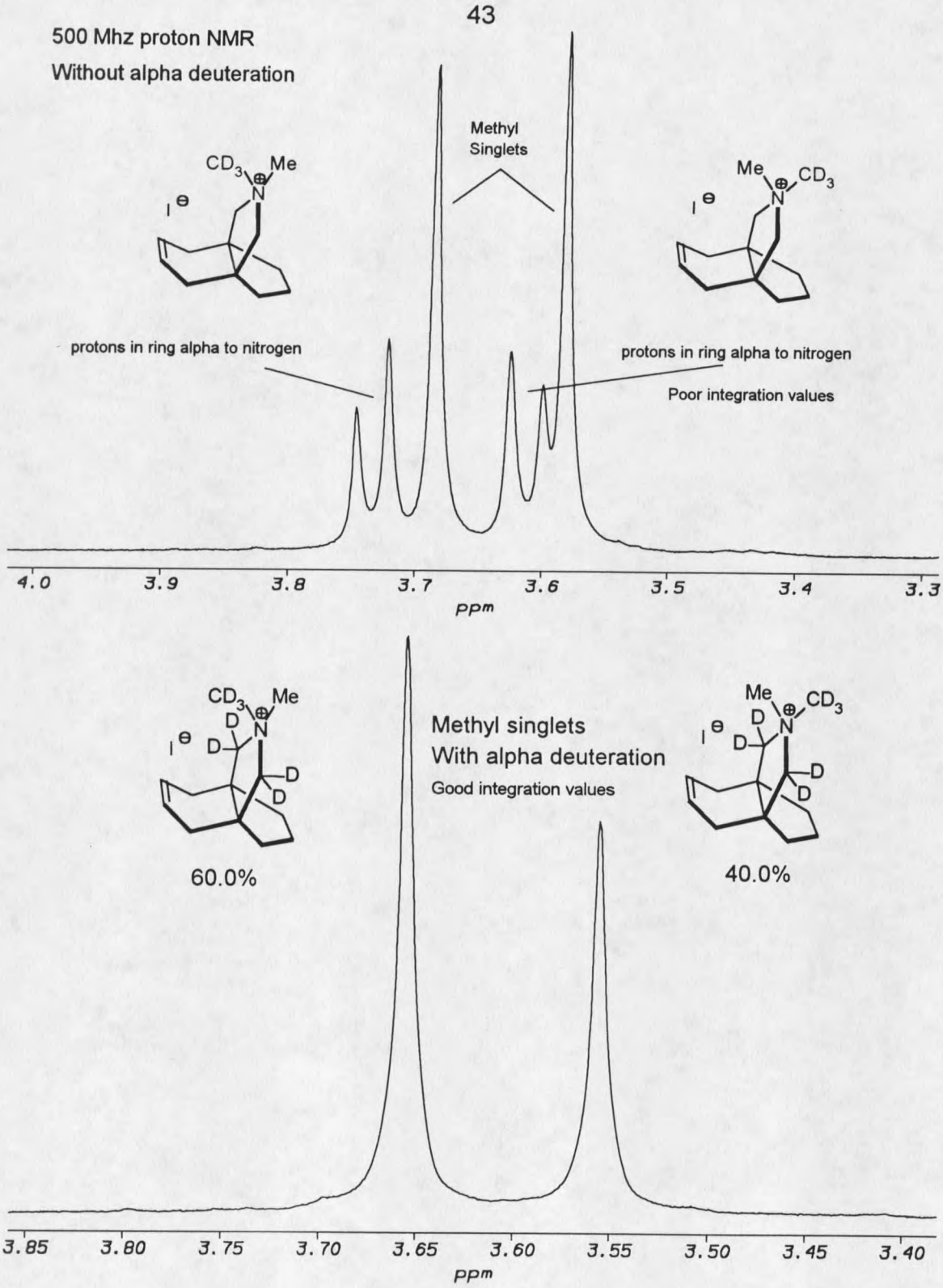


Figure 24. NMR spectra of propellane N-methyl regions.

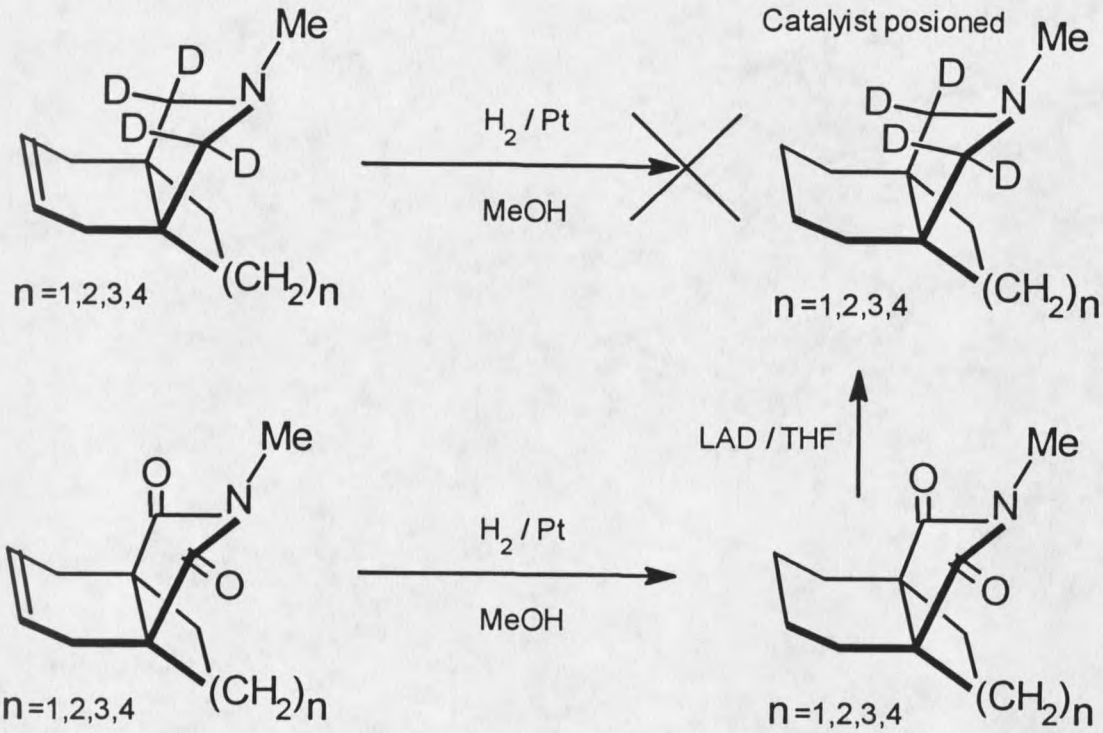


Figure 25. Reduction of the unsaturated amine and imine .

With the desired tertiary amine propellanes in hand, we undertook the quaternization reactions to produce a mixure of isomeric salts. Each propellane framework produces eight different compounds during the various quaternization reactions (Figure 26). The reaction conditions were relatively simple. The amine was mixed with an excess of the selected alkyl halide in diethyl ether solution. The salts precipitated from the ether solution while the reaction stirred overnight. The salts were washed with hexane to remove the excess alkyl halide and then dried.

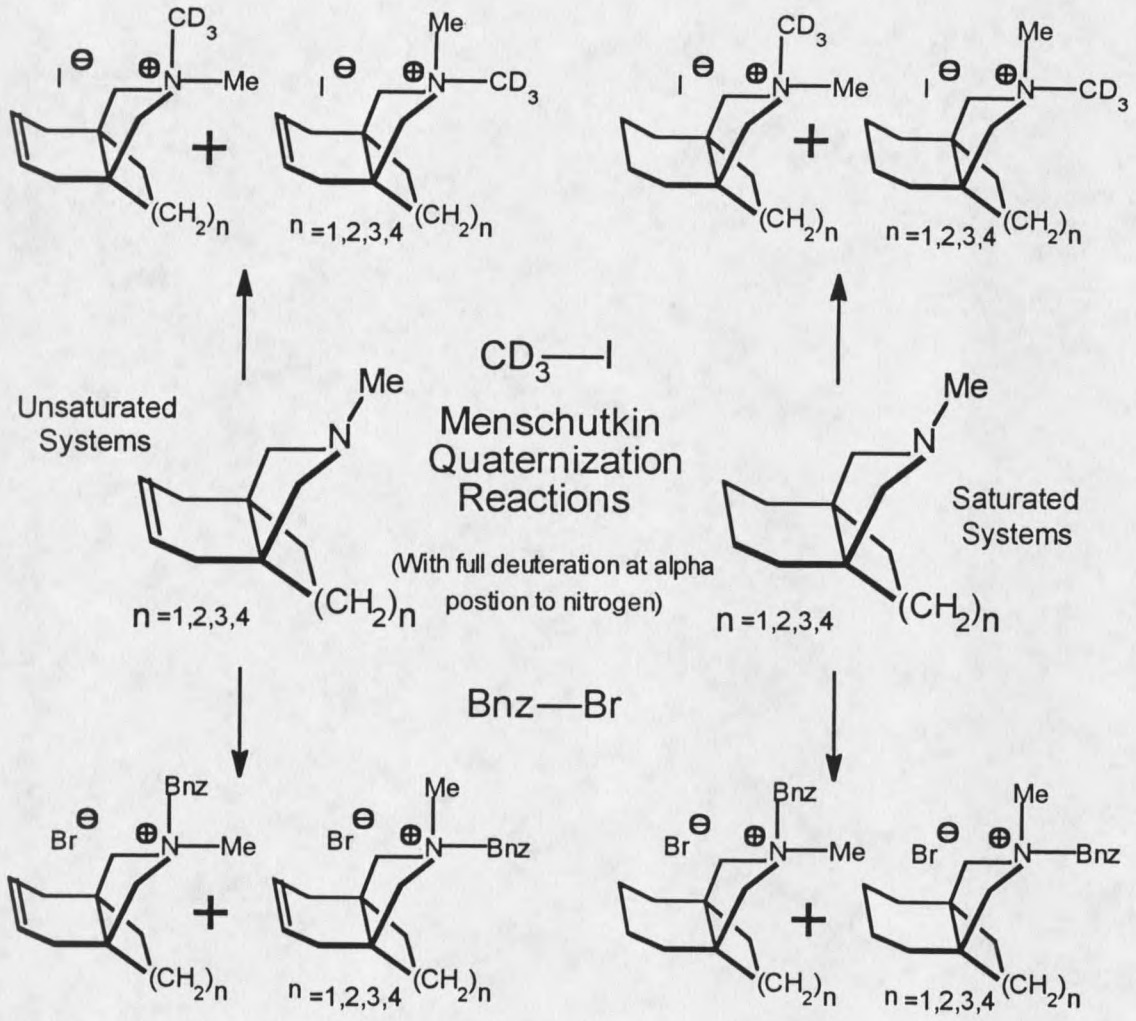


Figure 26. Scope of Menschutkin reactions.

The salts were then dissolved in $CDCl_3$ for the NMR determination of product ratio.

The NMR product ratio was fairly easy to determine; however, the actual identity of the two product isomers presented an interesting problem. Lipkowitz[38] used a chemical shift argument for identification. With the more modern NMR techniques and higher field instrumentation we

thought that identification could be easily accomplished by using the Nuclear Overhauser Effect (NOE). This technique does not rely on normal through bond coupling and instead uses a through space coupling. The first attempt at routine one dimensional NOE failed to produce any correlations. Next we tried a general 2-D technique of NOESY followed by a phase sensitive NOESY. These too proved inconclusive and failed to show any real correlation's. It was concluded that the tumbling rate of the propellane salt was very similar to the Lamor frequency, therfore no NOE was able to be consistantly determined. This resulted in the failure of the normal NOE experiments in our system. It was suggested that we try a rotating frame NOE experiment referred to as a ROESY experiment. This experiment differs from a common NOE experiment because it is independent of the T1 decay of the protons. This experiment gave beautiful results in our case and quickly determined the through space couplings between the N-methyl and the lower two rings. An representative example of a ROESY spectrum is shown in Figure 27.

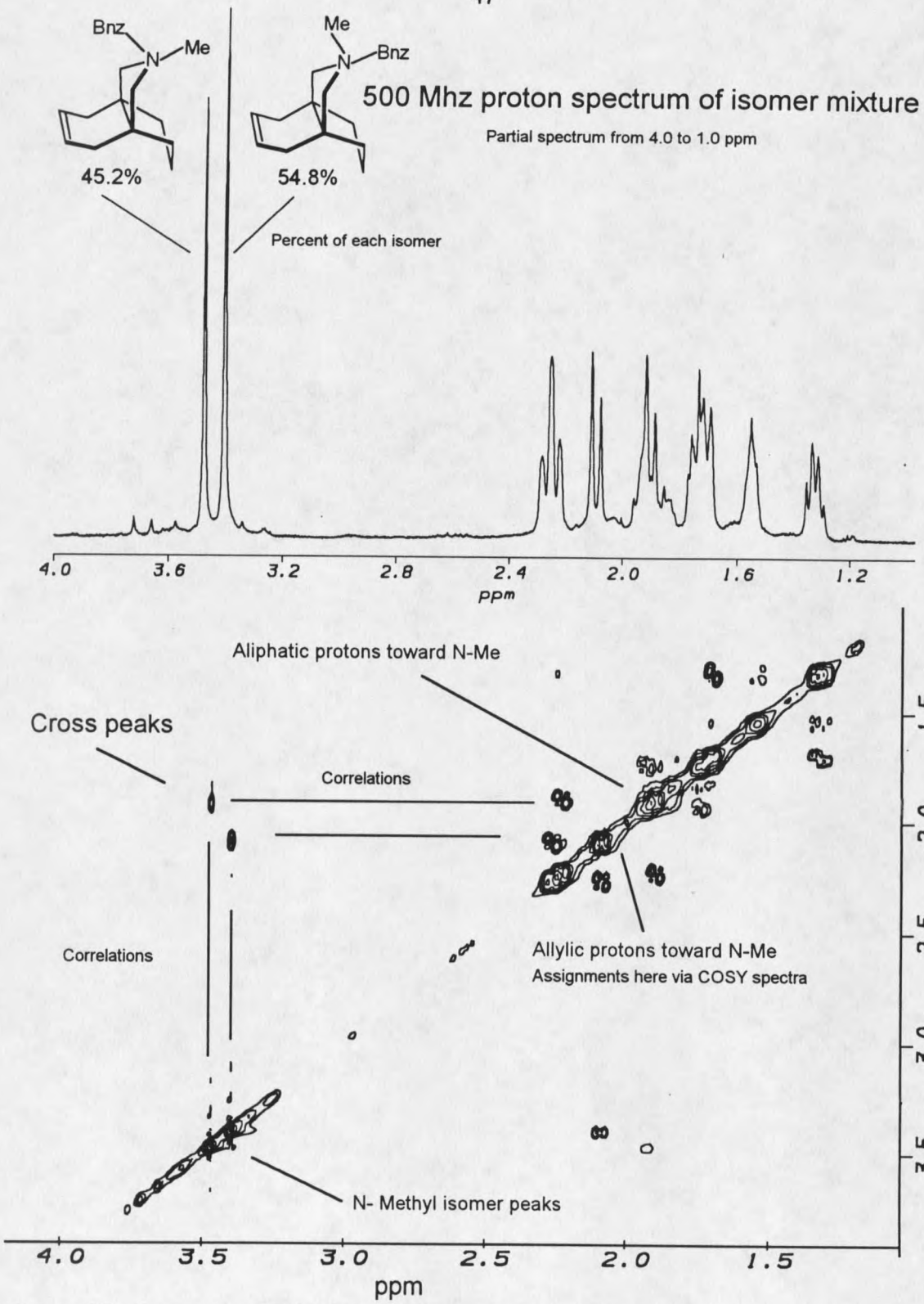


Figure 27. Example of ROESY spectrum of a propellane salt.

CHAPTER 3

RESULTS AND DISCUSSION

Before discussing the results of the Menschutkin quaternization reaction it would be helpful to describe our shorthand nomenclature for the salts. We developed this system to give us a quick way of describing the results of quaternization reactions. The abbreviated name starts with the leftmost ring size (the number six for our system), followed by the letter s or u referring to the saturated or unsaturated nature of the cyclohexene ring. Then there is a comma or a space that separates the other size ring. The N-methylpyrrolidine ring does not change and is ignored in our system. The last three letters (either CD_3 or Bnz = Benzyl) reveal what type of alkyl halide was used to make the salt. Therefore 6s,7 CD_3 is the salt shown as an example in Figure 28. The isomeric salt mixtures were all checked by NMR to determine the ratio of each product isomer. Each ratio number was determined on both a Bruker AC-300 Mhz and AM-500 Mhz spectrometers. The total number of integral values that were averaged together ranged from a minimum of two to a maximum of eight. The ratio of the methyl and other peaks were easily integrated to give a ratio of isomers for all the salts except for the saturated six-seven-CD_3 (6s,7-CD_3)

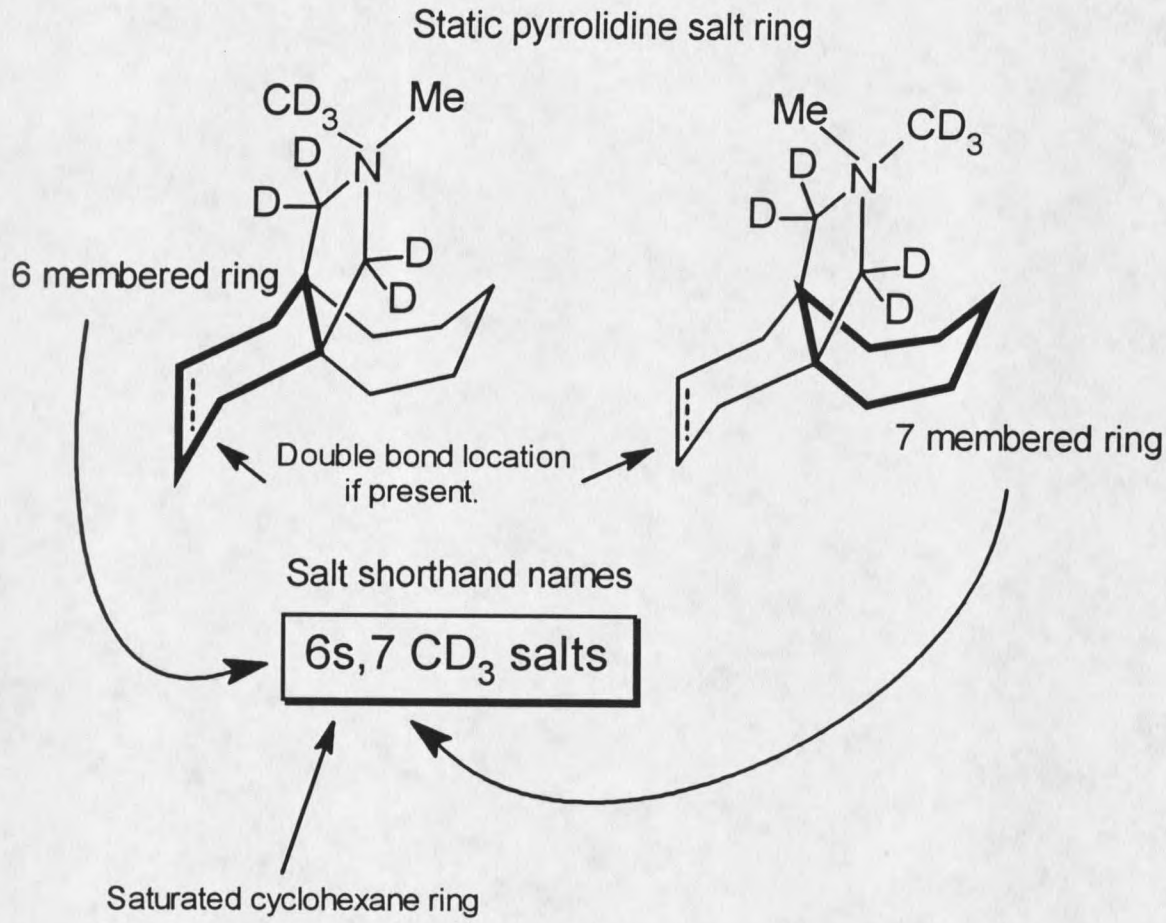


Figure 28. Nomenclature shorthand system.

salt mixture (Figure 29). It was unresolved at 500Mhz but by using resolution enhancement techniques, we were able to show that there were different isomers. These resolution enhancement methods do increase the resolution of the sample. However, they alter the area under each isomer peak and therefore no integration values were obtained. The saturated 6s,6 salt system for both electrophiles contain a plane of symmetry. This symmetry precludes formation of isomers which produces a singlet in the NMR spectra. These

difficulties do not impact greatly on the analysis of the benzyl series. There is only loss of one data point in the 6s,6 saturated case. In the saturated CD_3 series, the loss of two successive data points makes any comparisons more difficult with the saturated CD_3 system.

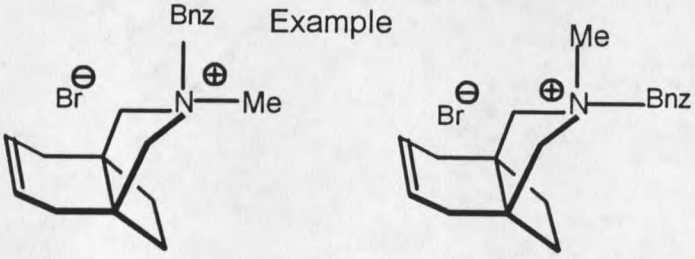
We investigated most aspects of the data for the ring systems. In addition to determining the ratio percent, we noted the NMR chemical shift values which were plotted to note any subtle data trends. The raw data is shown in the following tables. Table 1 contains the benzyl ratio data which shows each ratio average, the standard deviation of the averaged series and the total number of data points used for the average. Table 2 includes all the NMR data for the benzyl isomer series. This includes the proton and carbon chemical shift values for the methyl, benzyl, and vinyl signals where appropriate. Table 3 has the CD_3 averaged isomer ratio data. The relevant statistical data for the series is also shown in Table 4.

When looking at the tables dealing with the percent ratio data, a few things become immediately clear. The first of these is that the ratio data charts generally show only small deviations (5-10%) from the 1:1 ratio. The highest ratio in the benzyl system is represented by the unsaturated four membered ring (Me6,6u-4), [52], at 58.8%. The highest ratio for the CD_3 system is also found in the

Table 1. Benzyl System Ratio Data

Size of the Ring System	% Ratio	Standard Dev.	Number of Data Points
Me6,6u-4 bnz [52]	58.8	0.438	8
Me4,6u-4 bnz [53]	41.2	0.438	8
Me6,6s-4 bnz [60]	44.8	2.28	6
Me4,6s-4 bnz [61]	55.2	2.28	6
Me6,6u-5 bnz [54]	54.8	0.781	4
Me5,6u-5 bnz [55]	45.2	0.781	4
Me6,6s-5 bnz [62]	52.25	1.5	4
Me5,6s-5 bnz [63]	47.75	1.5	4
Me6u,6u-6 bnz [56]	53.7	0.594	5
Me6s,6u-6 bnz [57]	46.3	0.594	5
Me6s,6s-6 bnz [64]	50	0	0
Me6,6u-7 bnz [58]	50.4	1.24	4
Me7,6u-7,bnz [59]	49.6	1.24	4
Me6,6s-7 bnz [66]	55.6	2.25	3
Me7,6s-7 bnz [67]	44.4	2.25	3

Example



41.2% Averaged Ratio 58.8%

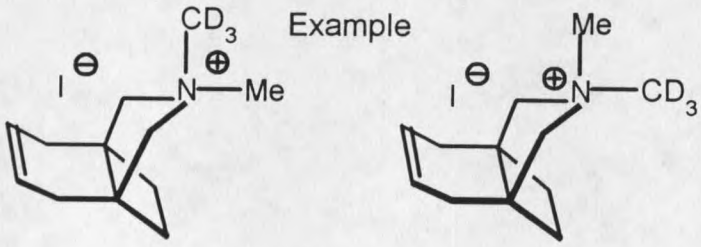
Me6 = Methyl group is toward cyclohexyl ring

Table 2. Benzyl System NMR Data

Size of the ring system	Methyl 1H ppm	Methyl 13C ppm	Benzyl 1H ppm	Benzyl 13C ppm	Vinyl 1H ppm	Vinyl 13C ppm
Me6,6u-4 bnz salt [52]	3.11	49.5	5.39	66.8	5.9	126.4
Me4,6u-4 bnz salt [53]	3.55	50.1	5.29	69.4	5.95	127.4
Me6,6s-4 bnz salt [60]	3.38	51.3	5.37	69.6		
Me4,6s-4 bnz salt [61]	3.62	52.6	5.22	68.8		
Me6,6u-5 bnz salt [54]	3.4	50.5	5.31	68.7	5.84	129.1
Me5,6u-5 bnz salt [55]	3.47	51.4	4.99	68.3	5.84	129.1
Me6,6s-5 bnz salt [62]	3.57	55.4	5.24	71.6		
Me5,6s-5 bnz salt [63]	3.6	54.5	5.22	71.4		
Me6u,6u-6 bnz [56]	3.58	56.3	5.31	72.7	5.62	129.2
Me6s,6u-6 bnz [57]	3.65	56.3	5.22	72.4	5.68	129.2
Me6s,6s-6 bnz [64]	3.67	56.8	5.31	73		
Me6,6u-7 bnz salt [58]	3.29	50.8	5.27	69.7	5.9	129.9
Me7,6u-7,bnz salt [59]	3.59	52.1	4.96	67.8	6.03	129.9
Me6,6s-7 bnz salt [66]	3.59	56	5.23	72.3		
Me7,6s-7 bnz salt [67]	3.62	56.2	5.23	71.8		

Table 3. CD_3 System Ratio Data

Size of the Ring System	% ratio	Standard Dev.	Number of Data Points
Me6,6u-4 [68]	76.3	0.762	4
Me4,6u-4 [69]	23.7	0.762	4
Me6,6s-4 [76]	42.8	1.42	4
Me4,6s-4 [77]	57.2	1.42	4
Me6,6u-5 [70]	39	1.57	3
Me5,6u-5 {71]	61	1.57	3
Me6,6s-5 [78]	47.8	1.13	2
Me5,6s-5 [79]	52.2	1.13	2
Me6u,6u-6 [72]	52.6	0.919	2
Me6s,6u-6 [73]	47.4	0.919	2
Me6s,6s-6 [80]	50	0	0
Me6,6u-7 [74]	69.8	0.557	3
Me7,6u-7 [75]	30.2	0.557	3
Me6,6s-7 [82]	Not		
Me7,6s-7 [83]	Resolved		



Example

23.7% Averaged Ratio 76.3%

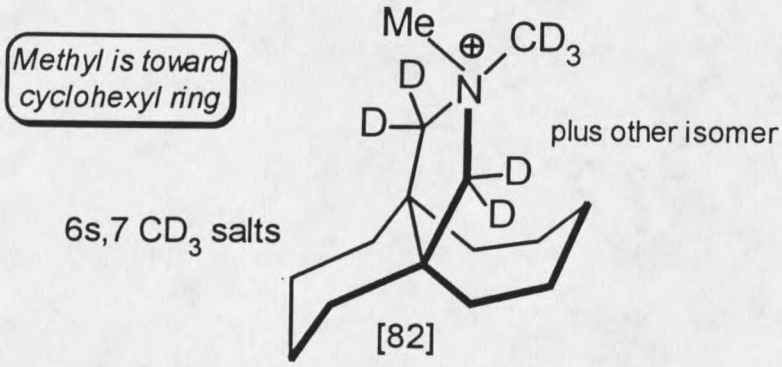
Me4 = Methyl toward cyclobutyl ring

Table 4. CD_3 System NMR Data

Size of the CD3 ring system		Methyl 1H ppm	Methyl 13C ppm	Vinyl 1H ppm	Vinyl 13C ppm
Me6,6u-4 [68]		3.52	55.5	5.99	127
Me4,6u-4 [69]		3.74	54	5.99	127
Me6,6s-4 [76]		3.56	57.4		
Me4,6s-4 [77]		3.75	56.9		
Me6,6u-5 [70]		3.57	55.2	5.92	128.4
Me5,6u-5 [71]		3.67	55.8	5.92	128.4
Me6,6s-5 [78]		3.72	59.5		
Me5,6s-5 [79]		3.74	60.2		
Me6u,6u-6 [72]		3.73	60.8	5.62	122.9
Me6s,6u-6 [73]		3.81	60.8	5.62	122.9
Me6s,6s-6 [80]		3.81	61.2		
Me6,6u-7 [74]		3.44	55.6	6.04	129.5
Me7,6u-7 [75]		3.71	57	6.04	129.5
Me6,6s-7 [82]	Res.	3.729			
Me7,6s-7 [83]	Enhanced	3.732			

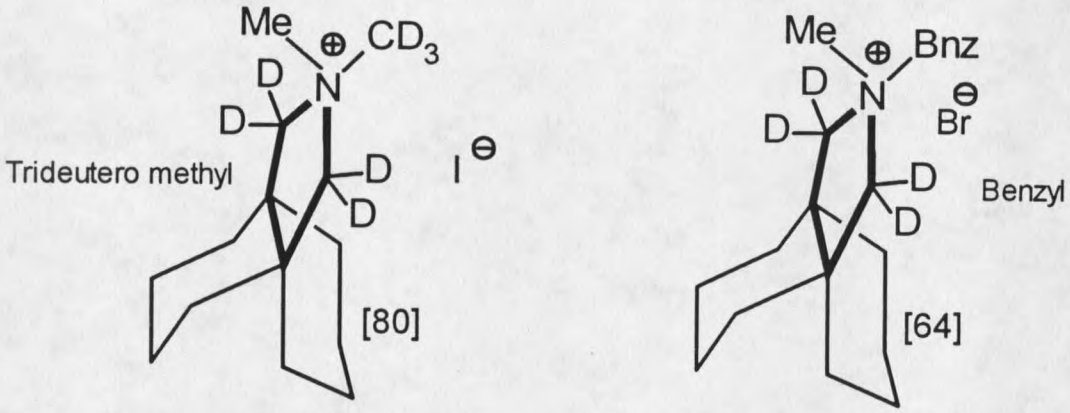
four membered unsaturated system (Me6,6u-4), [68], at 76.3%. Integral data for both electrophilic systems are completely consistent, with the largest standard deviation in a set of ratio data calculated to be 2.28 (most are much smaller). The data is much tighter for the CD_3 case because there were generally fewer peaks to integrate. Using this variance in integration values as a guide, the total error in the integration averages are thought to be less than ±1.5 percent.

In the benzyl series, the largest ratio isomer is generally the one with the approach of the electrophile over the saturated rings as they vary from four to seven in size (alternatively described as the original methyl group mostly on the side of the saturated or unsaturated cyclohexyl ring). This is shown graphically by an example at the bottom of the benzyl ratio data Table 1. The only exception to this trend is the saturated 6s-4 isomer pair, which is reversed (the original methyl is on the side of the four membered ring). The CD_3 system had somewhat more variance in the facial selectivity of the larger isomer. There are only six different isomer pairs in this system (due to the aforementioned resolution and symmetry problems). Three of the isomers favor approach of the electrophile from the four to seven membered ring side. These are the 6u-4, 6u-6, and 6u-7 rings systems respectively. The other three ring



These system produced isomers but they were unresolvable at 500 Mhz without resolution enhancement.

Note: While all these structures did not provide data points they do show the arbitrarily chosen isomer (Methyl toward the cyclohexyl ring) that was used for all data comparisons between different ring systems.



These ring systems have a high degree of symmetry and produce only one compound.

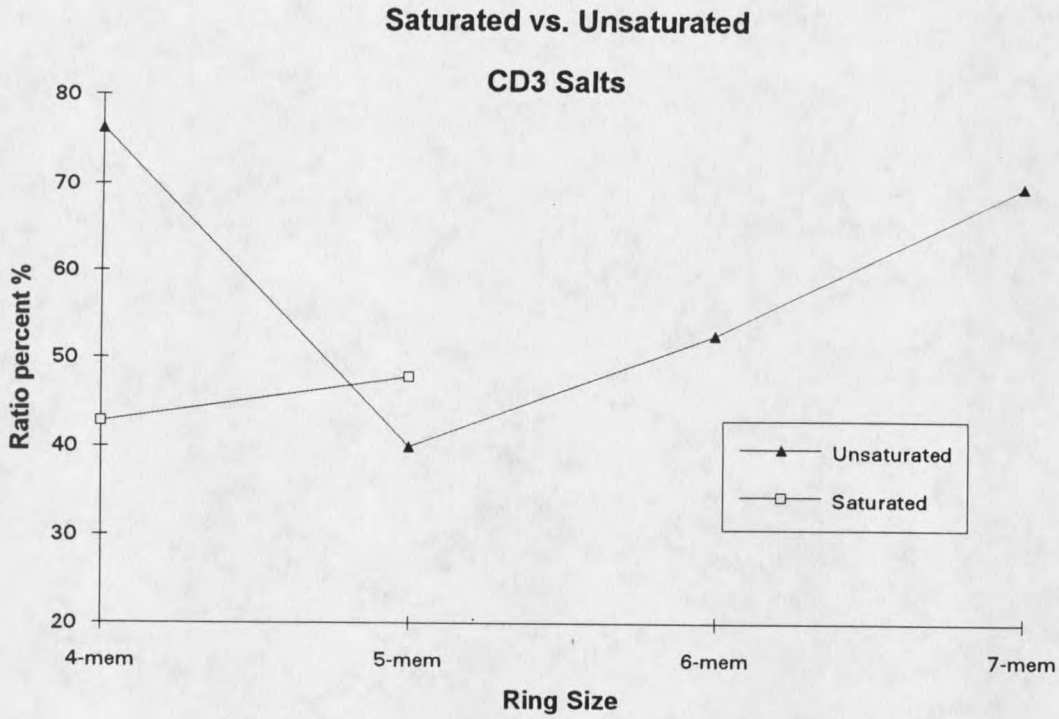
Figure 29. The ring systems that didn't provide data points.

systems (6s-4, 6u-5, and 6s-5) prefer approach of the electrophile from the side of the static cyclohexyl ring.

In keeping with our original focus of looking for possible neighboring group participation by the alkene, we looked at graphical comparisons of the saturated and

unsaturated salts for the two different electrophiles. We chose to compare only one representative isomer of the pair. This is possible because each isomer is intrinsically related to the other. The two data points (ratio percent values) add up to unity (or 100%) and therefore one of the values can be neglected for the comparative analysis. This is only valid if the same isomer is used for comparison for all other ring systems. In our analysis, we used the isomer salt with the original N-methyl group on the side of the pyrrolidine ring toward the unsaturated or saturated cyclohexyl ring. This is shown graphically for the isomers in Figure 29. The graphical representation of these ratio comparisons are shown in Figure 30 for both the CD_3 isomers and the benzyl isomers.

The CD_3 comparison is difficult with the missing data points for the saturated isomers. There is little that can be inferred about the line drawn between the four and five membered rings. The unsaturated curve shows an inflection point between the four and five membered rings. Recall that the 6u-4 ring system had the largest ratio, which seems misplaced in comparison with the other ring sizes. There is a trend of increasing ratio from the five to seven membered rings. These points appear somewhat linear but the slope is different from the saturated case. The data suggest a complex interaction and an indefinite relationship between



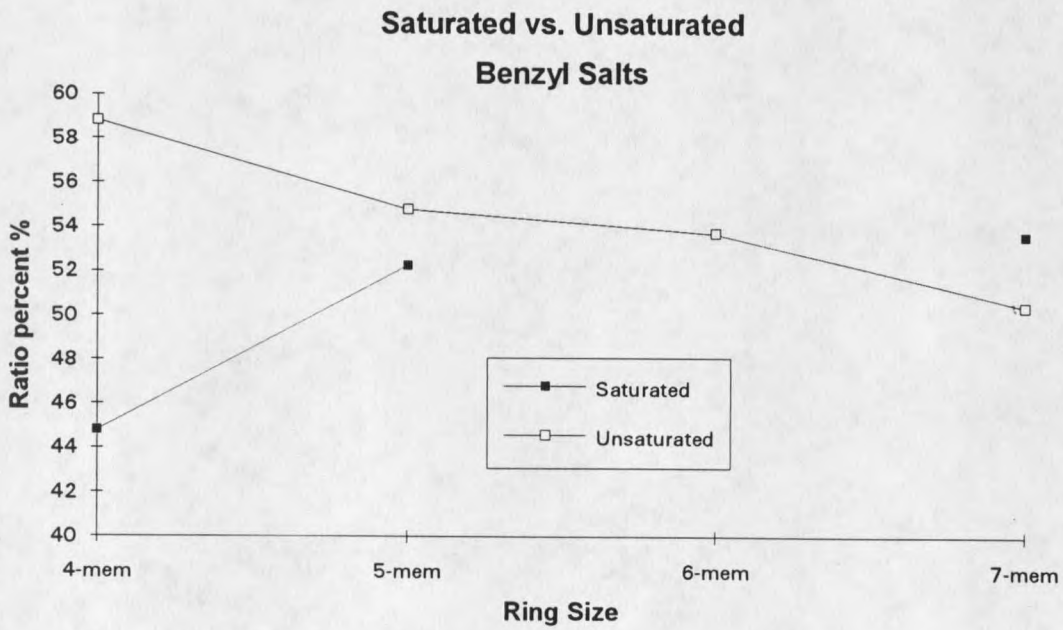


Figure 30. CD_3 and Benzyl ratio percent comparison.

the saturated and unsaturated ring series for the CD_3 system.

The benzyl system shows an inflection point between the graphs somewhere between the five and six membered rings. On the left side of this point, the unsaturated system gives a higher ratio than for the saturated system. The four membered ring system has a difference of approximately fourteen percent from the unsaturated to the saturated. This difference is reduced to three percent for the five membered ring. The significance is that the slope of both lines are similar which seems to continue as the ring size increases for both saturated and the unsaturated systems.

What was responsible for the consistent change of slope in the benzyl system and why was it not seen in the CD_3? The evident answer to this question is that electronics or sterics (or possibly some unforeseen other factor) dictates the outcome of the reaction. With the inherent limitations of studying a reaction from the product point of view, we tried to find an answer to this question. We made the assumption that the outcome of the reaction was due to steric approach control of the faces of the pyrrolidine from the other rings or an electronic interaction from the alkene (or possibly both acting together). We assumed that if we could prove that the sterics controlled the reaction we could rule out the electronic contribution to the reaction.

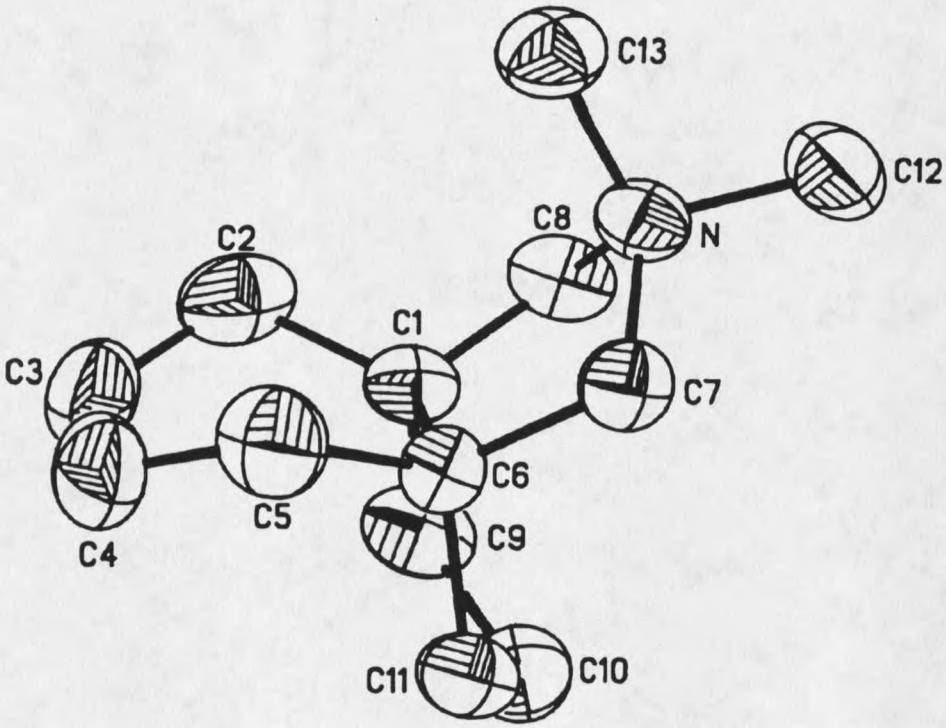


Figure 31. ORTEP drawing of 6u,5 CH_3 salt [81].

The first step in this was to obtain some crystals to submit for x-ray crystallography and hopefully obtain information about the structure of a saturated and a unsaturated salt product. A representative unsaturated product was crystallized (6u,5 CH_3 salt [81] with only one isomer) and is shown in Figure 31. This salt shows a considerable amount of symmetry. The general propellane is almost completely superimposable on itself when viewed from the bridgehead. The saturated system proved to be more elusive. After considerable effort, a crystal was formed and a data set was taken for the crystal. We could not

however, find a solution to the data set. All successive attempts to crystallize a saturated salt have failed to date.

The small experimental percent ratio differences when changing the carbon ring system from four to seven prompted investigation of the effect of a nonbonding electron source

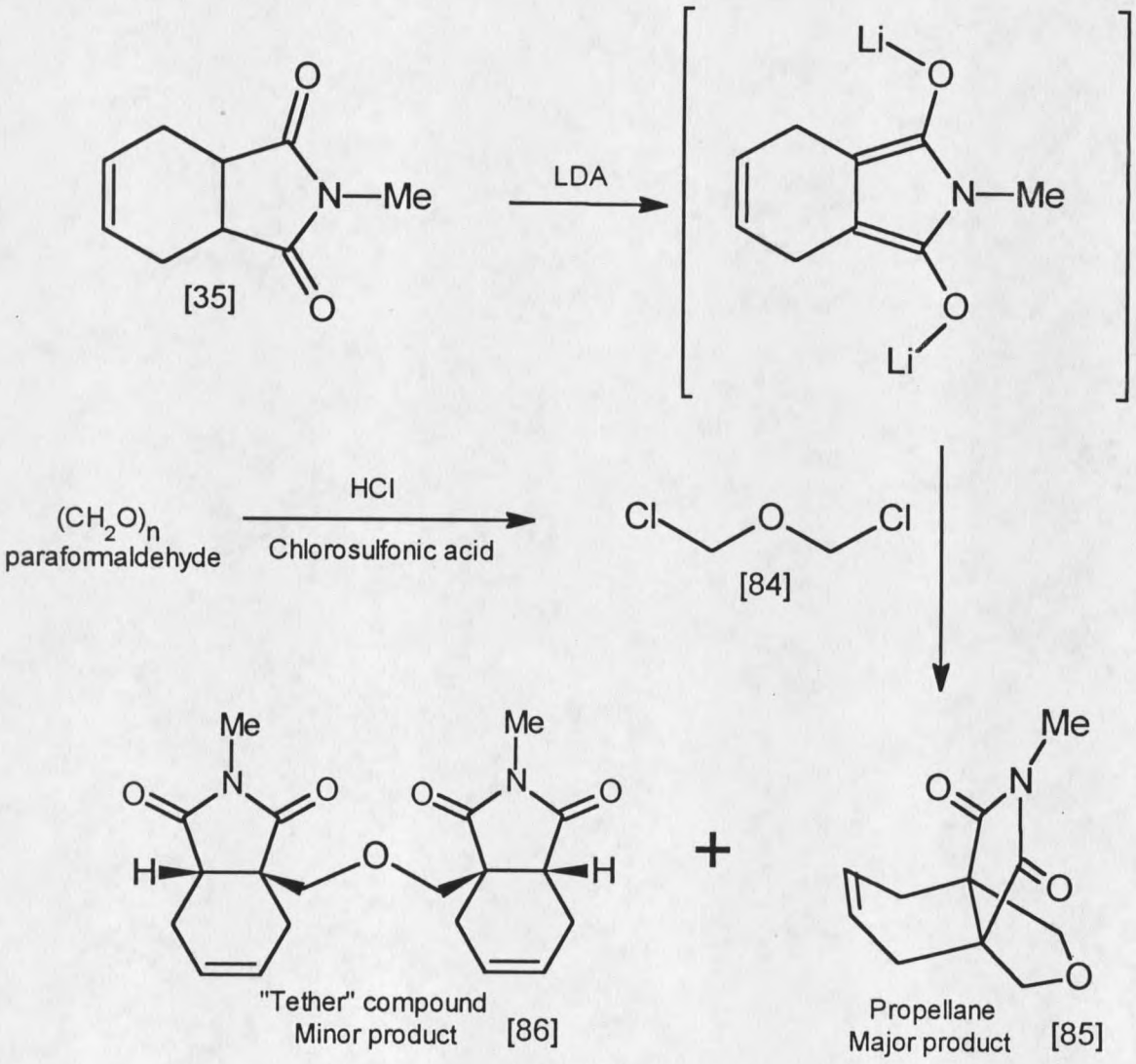


Figure 32. Synthesis of tetrahydrofuran ring propellanes.

in similar Menschutkin reactions. The ideal system would be to incorporate a tetrahydrofuran ring and replace the cyclopentane ring. We felt that the most efficient method to close off these types of rings was the use of the dianion method. The synthesis of tetrahydrofuran ring systems in this fashion required a special trifunctional electrophile. The obvious choice for this transformation is bis-dichloromethyl ether, [84]. These types of ethers are

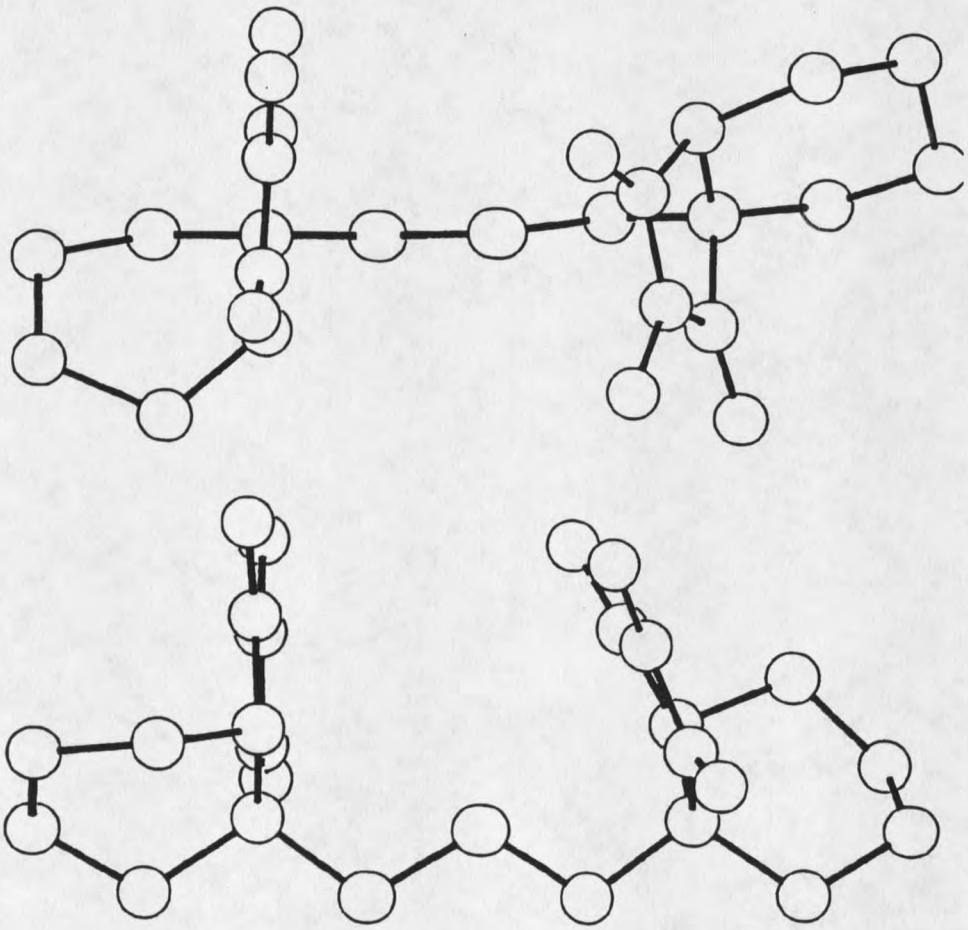


Figure 33. Saturated oxygen "tether" [87], x-ray structures.

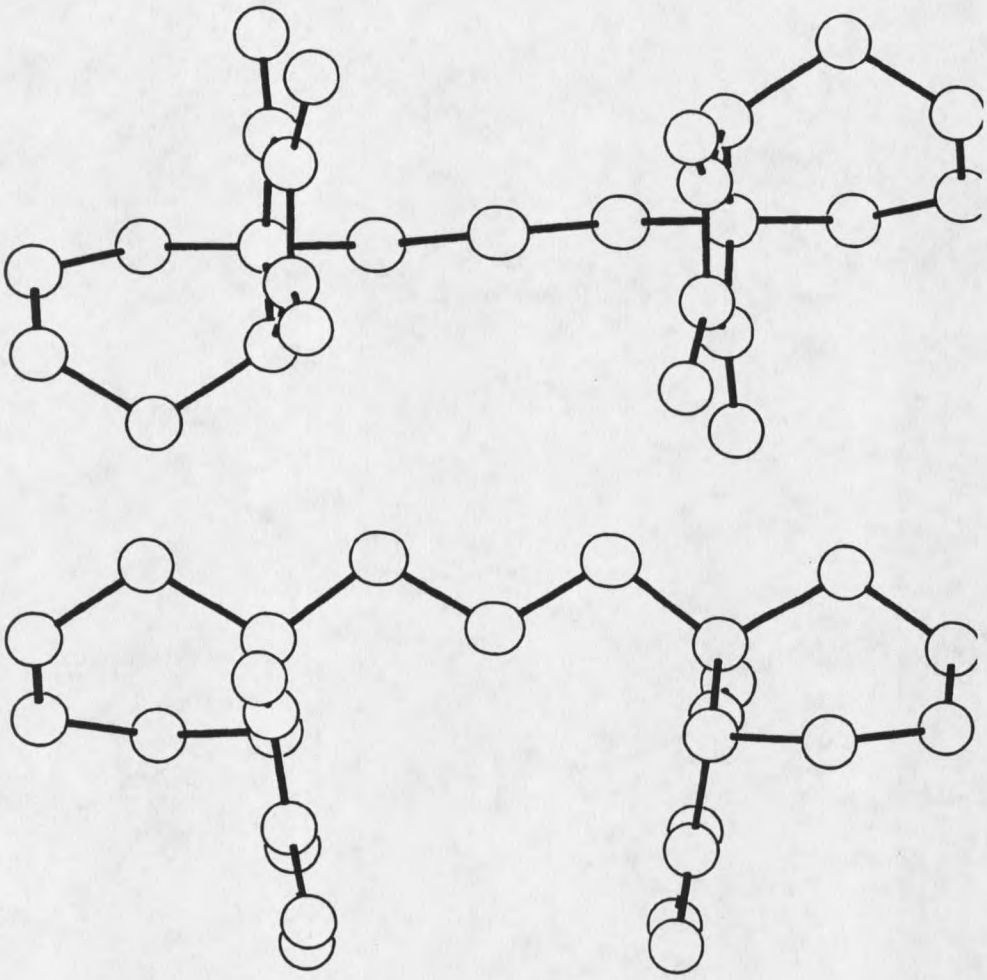


Figure 34. Unsaturated oxygen "tether" [86], x-ray structures

regarded as potent carcinogens and are not readily available in the current chemical marketplace. However, we found a procedure in Organic Synthesis[39] that easily produced bis-dichloromethyl ether, [84], in high yields. With this electrophile in hand, we performed the dianion alkylation of [35] to produce the N-methyl-8-aza(7,9-keto)imide-11-oxotricyclo[4.3.3]dec-3-ene, [85], shown in Figure 32. As in the carbon alkylations to make larger (6 and 7 membered)

rings, appreciable amounts of the tether compounds [86,87], were formed in the reaction.

It is interesting to note that there was some confusion in the identification of these oxygenated compounds. However, the tether compounds crystallized and we were able to obtain x-ray structures of both the saturated and unsaturated compounds. The ORTEP drawings of these compounds are shown in Figure 33 (saturated) and Figure 34 (unsaturated). The unsaturated tether compound, [86], was very symmetrical as evidenced by the simplicity of the NMR spectrum. This unsaturated compound, as expected, was found in the boat conformation in both cyclohexene rings. This matches the structures found in other unsaturated salts. The saturated tether compound, [87], gave a complex and interesting NMR spectrum which was somewhat unexplained until the x-ray data became available. When the unsaturated compound was reduced using standard catalytic hydrogenation conditions, one of the cyclohexane rings flipped into the chair conformer while the other remained in the boat conformation. This interesting but unexplained behavior does not allow symmetry to simplify the NMR and results in the more complex spectra.

The tetrahydrofuran imide propellanes gave new additional insight into the Menschutkin reaction studies. This new system would allow the non bonded electrons to compete against the π-bond electrons in the cyclohexene

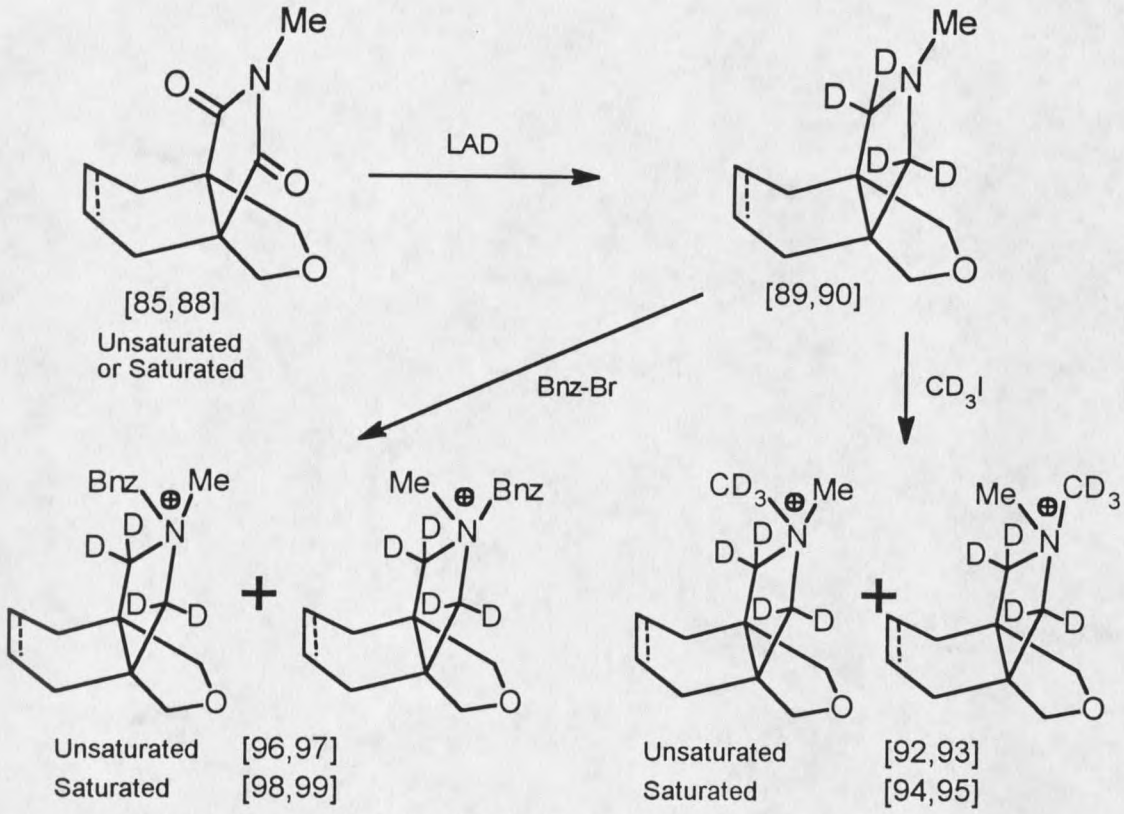


Figure 35. Tetrahydrofuran ring propellane ammonium salts.

ring. Both the saturated, [88], and the unsaturated, [85], imide were reduced to the amine with LAD and converted to the ammonium salt isomer mixture with trideuteromethyl iodide and benzyl bromide as before (Figure 35). The benzyl quaternary salts presented a problem during the isolation of the product. The salt precipitated as an ultra fine solid that was trapped within the glass frit during filtration. There were insufficient quantities of the salt material to scrape from the frit surface. The problem was averted by washing the salts with excess pentane to remove any impurities and starting materials, the salts were then

washed from the frit by washing with a polar solvent. The NMR spectroscopy of some of the salts once again showed overlapping signals that prevented accurate integration. This peak interference difficulty of the α-methylene to the oxygen with the N-methyl singlets was somewhat overcome by changing the solvent from $CDCl_3$ to d^6-acetone.

In comparison of the oxygen propellane system with the analogous carbon system, the oxygen shifted the ratio of the products toward lower selectivitys viewing the methyl toward the six-membered ring. The same isomer dominated in all four examples (Sat-CD3 [94], Unsat-CD3 [92], Sat-Bnz [98], Unsat-Bnz [96]) as shown in Figure 36. This data is also shown in graphical format in Figure 37. This graph shows that with all other things remaining equal, the oxygen forces much greater selectivity toward the other isomer. These differences are very consistent between the electrophiles with a calculated average between the benzyl and CD_3 being 14.5% and 4.8% respectively. The question once again is what is the cause of the difference in reactivity. Is it because of any steric differences, or is it electronic in nature?

One possible method to get steric information without x-ray data was to perform a series of computer calculations on the salt structures. These allow a better understanding of the steric differences on each face of the pyrrolidine ring. Crude salt structures were developed and the

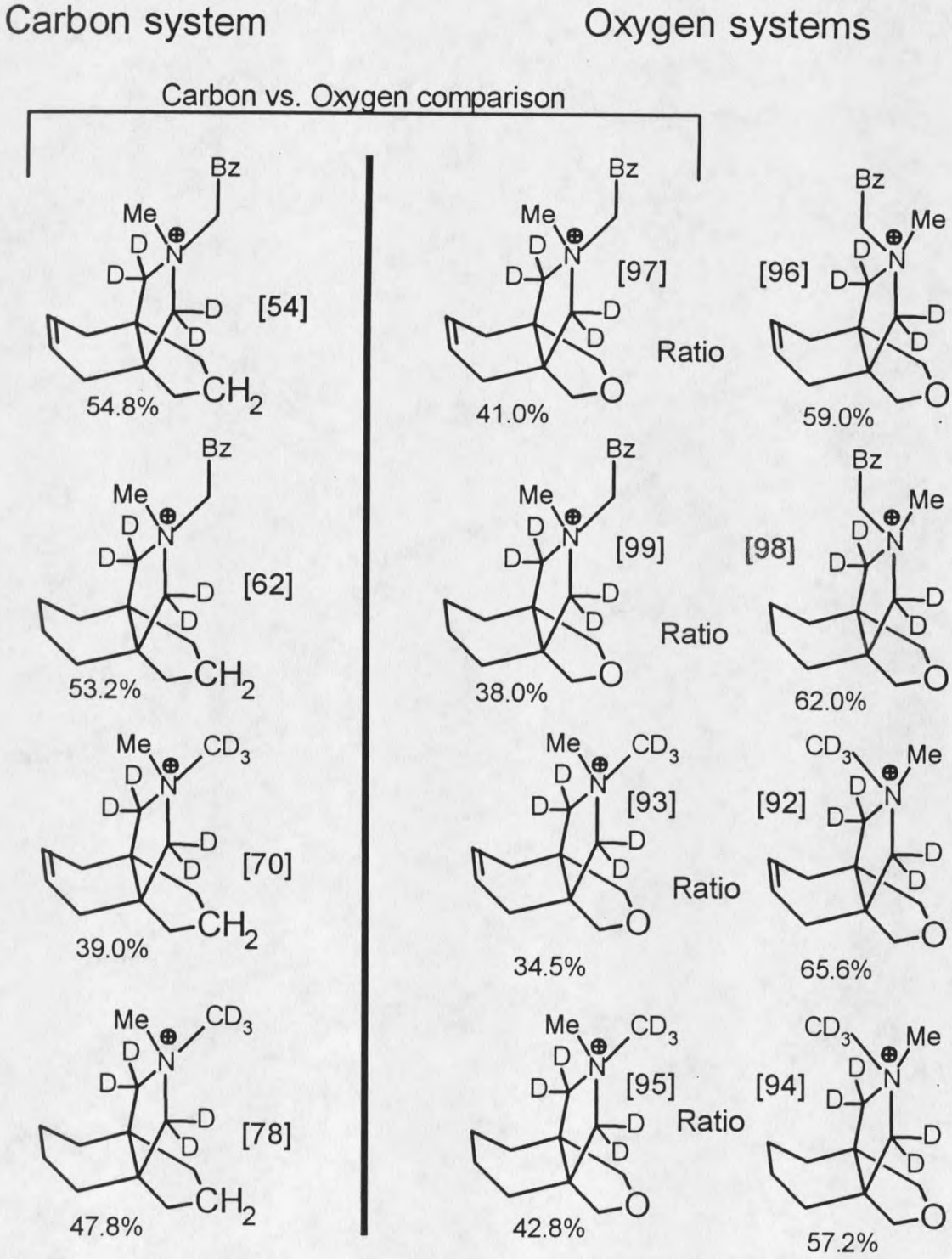


Figure 36. Comparison of Oxygen and Carbon propellanes.

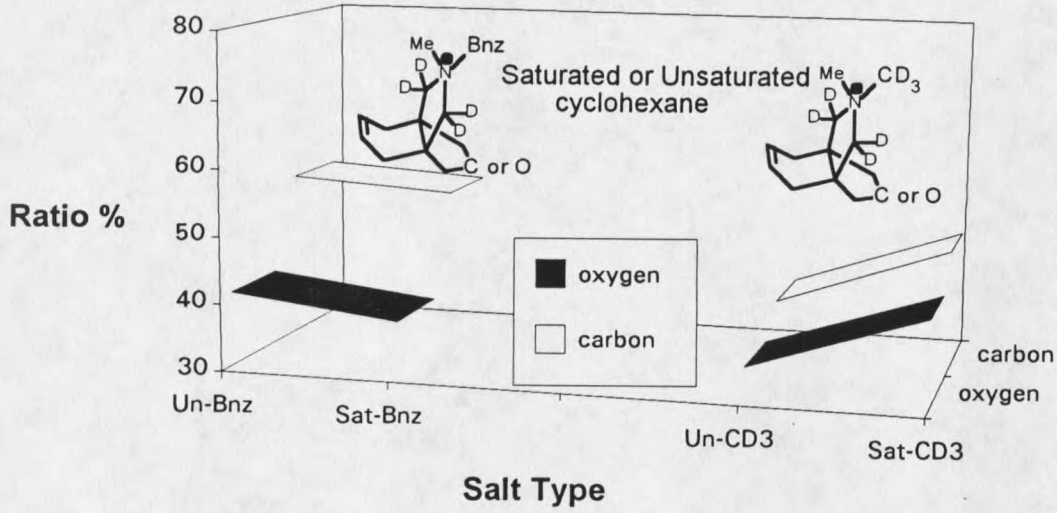


Figure 37. Graphical view of similar Oxygen and Carbon propellanes.

geometrys optimized with the SIMS program[40] before using the semi-empirical AMPAC calculation. This program was part of the TRIBL calculation package. The AMPAC program was run using the AM1 hamiltonian option with the keyword precise to obtain 100 times increased minimization criteria. The minimized energy (Heat of formation; Hf) of each salt is shown in Table 5.

A quick review of the calculational output in Table 5 shows that in general, there are very small Hf differences between most isomer pairs. The range of this isomer difference is from a low of 0.002 Kcal in the 6s5 CD_3 carbon system to a high of 1.456 in the 6u5 CD_3 carbon system. That larger number is much higher than the next highest value of 0.666 in the 6u5 benzyl system. The energy gap

Table 5. AMPAC Calculation with AM1

Propellane	CD3 salts	BNZ salts	Benzyl : CD3
	Am1 Hf Kcals	Am1 Hf Kcals	Energy Diff.
Me6,6u4	179.994	204.611	24.617
Me4,6u4	179.398	204.815	25.417
Energy Diff.	0.596	0.204	
Me6,6s4	152.14	177.502	25.362
Me4,6s4	152.181	177.244	25.063
Energy Diff.	0.041	0.258	
Me6,6u5 Carbon	156.435	181.195	24.76
Me5,6u5 Carbon	154.979	181.861	26.882
Energy Diff.	1.456	0.666	
Me6,6s5 Carbon	126.677	152.12	25.443
Me5,6s5 Carbon	126.679	152.318	25.639
Energy Diff.	0.002	0.198	
Me6,6u5 Oxygen	128.067	152.642	24.575
Me5,6u5 Oxygen	128.083	152.852	24.769
Energy Diff.	0.016	0.21	
Me6,6s5 Oxygen	99.508	124.119	24.611
Me5,6s5 Oxygen	99.534	124.34	24.806
Energy Diff.	0.026	0.221	
Me6u,6u6	150.43	176.074	25.644
Me6s,6u6	150.625	175.888	25.263
Energy Diff.	0.195	0.186	
Me6s,6s6	120.559	145.717	25.158
Me6,6u7	151.955	178.341	26.386
Me7,6u7	151.959	178.131	26.172
Energy Diff.	0.004	0.21	
Me6,6s7	121.928	146.968	25.04
Me7,6s7	121.932	147.043	25.111
Energy Diff.	0.004	0.075	
		Average	25.301

Table 6. Stability of Saturated Cyclohexane Rings

Six Membered Ring Type	Four-Membered	Five-Membered Carbon	Five-Membered Oxygen	Six-Membered	Seven-Membered
CHAIR	CD3	CD3		CD3 and Benzyl	CD3 and Benzyl
TWIST BOAT	Benzyl	Benzyl			
FULL BOAT			CD3 and Benzyl		

between the CD_3 and the benzyl is very consistent with the average ΔE is 25.3 Kcal (standard deviation 0.63). The unsaturated salts are an average of 29.2 Kcal (standard deviation 0.63) higher in energy than the saturated salts. The resulting unsaturated minimized structures are very similar to the x-ray data with the cyclohexene in a boat conformation. We assumed that the saturated structure would revert to the chair conformation after the hydrogenation. However, if we were to rationalize the reactivity differences that were observed between the unsaturated and the saturated ring systems (remember the saturated tether compound boat and chair difference), it was important to determine the actual conformation of the saturated ring. It

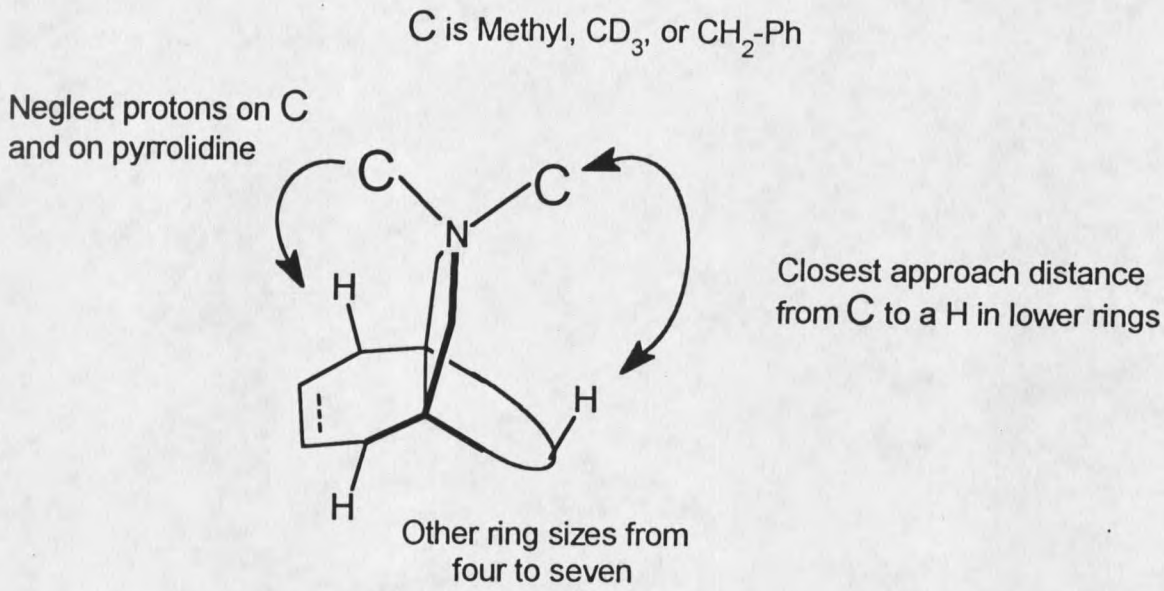


Figure 38. Method of determining steric approach distances.

was surprise that the saturated THF structures minimized in a true boat conformation that was energetically lower than the chair (approximately 1.7 Kcal lower for the CD_3 and 3.5 Kcal lower for the benzyl system). The results of the calculations are shown in Table 6. These calculations showed a disparity in the minimized structures for the benzyl and CD_3 systems for the smaller four and five membered rings. The benzyl ring must exert some effect on the overall minimization because the smaller rings prefer a twist boat over the chair conformation. The AMPAC calculation output also allows determination of any distances between groups within a molecule. We needed a method for relating these distances to overall steric

Table 7. CD_3 Calculated Steric Approach.

Ring Size	CD3 toward 6-Mem Angstroms	CH3 toward other Angstroms	steric difference	Ratio/ Steric Diff.	Ratio/ CD3 side	Ratio/ CH3 side	Ratio Percent
4-Mem Sat [77]	4.23	3.04	1.19	47.90	13.48	18.75	57
4-Mem Unsat [69]	4.41	2.78	1.63	14.72	5.44	8.63	24
5-Mem Carbon Sat [79]	2.96	3.02	0.06	866.67	17.57	17.22	52
5-Mem Carbon Unsat [71]	4.02	3.15	0.68	89.71	15.17	19.37	61
5-Mem Oxygen Sat [94]	4.2	3.27	0.93	69.89	15.48	19.88	65
5-Mem Oxygen Unsat [92]	4.27	3.27	1	57.00	13.35	17.43	57
6-Mem Sat [80]	2.81	2.81	0		17.79	17.79	50
6-Mem Unsat [73]	3	3.53	0.53	88.68	15.67	13.31	47
7-Mem Sat [83]	2.92	2.86	0.06				Not resolved
7-Mem Unsat [75]	3.69	2.72	0.97	30.93	8.13	11.03	30

approach between faces of the pyrrolidine ring. A model that we chose to use was based on the distances at the conclusion of the reaction as shown inFigure 38. At this stage, the nitrogen is fully sp^3 hybridized, forcing the carbons to the closest approach geometry with respect to the lower rings on the reaction coordinate. Using the conformational structure with the minimum energy for comparison purposes, we determined the shortest steric distance of approach for a selected set of salts (with the

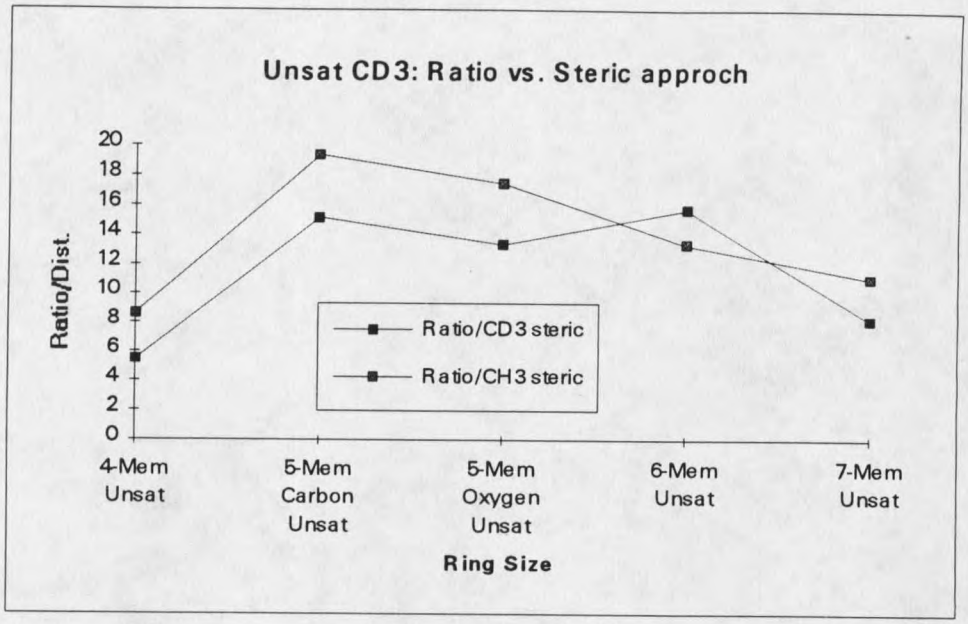


Figure 39. Unsaturated CD_3 steric approach comparison.

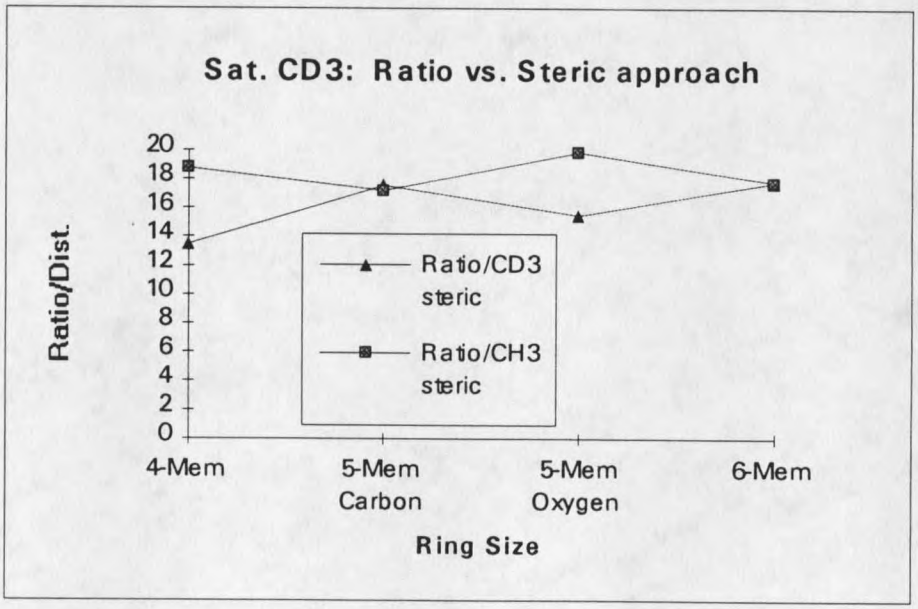


Figure 40 . Saturated CD_3 steric approach comparison.

Table 8. Benzyl Steric Approach Distances.

Ring Size	Bnz toward 6-Mem Angstroms	CH3 toward Other Angstroms	Steric Diff.	Ratio/ Steric Diff.	Ratio/ Bnz side	Ratio/ CD3 side	Ratio Percent
4-Mem Sat [61]	3.29	3.92	0.63	87.30	16.72	14.03	55
4-Mem Unsat [53]	4.24	3.14	1.1	37.27	9.67	13.06	41
5-Mem Carbon Sat [63]	3.78	3.1	0.68	70.59	12.70	15.48	48
5-Mem Carbon Unsat [55]	4.26	3.14	1.12	40.18	10.56	14.33	45
5-Mem Oxygen Sat [98]	4.22	3.27	0.95	65.26	14.69	18.96	62
5-Mem Oxygen Unsat [96]	4.3	3.24	1.06	55.66	13.72	18.21	59
6-Mem Sat [64]	3	3.53	0.53	94.34	16.67	14.16	50
6-Mem Unsat [57]	2.99	3.94	0.95	48.42	15.38	11.68	46
7-Mem Sat [67]	2.94	2.85	0.09	488.89	14.97	15.44	44
7-Mem Unsat [59]	2.93	2.82	0.11	454.55	17.06	17.73	50

electrophile approaching from the cyclohexane or cyclohexene face of the pyrrolidine ring). The assumption was made that there would be very small steric differences between each isomer pair. As a test of this assumption, the steric distances were determined for each isomer set of the 6u5 and the 6s5 system. The steric distances proved to be very similar for each isomer pair. During the remaining data

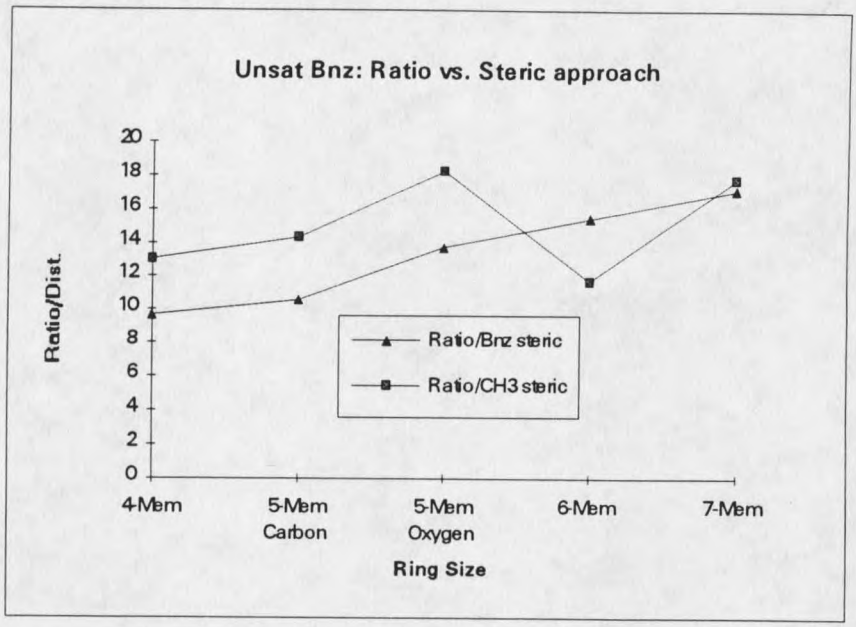


Figure 41. Unsaturated Benzyl steric approach comparison.

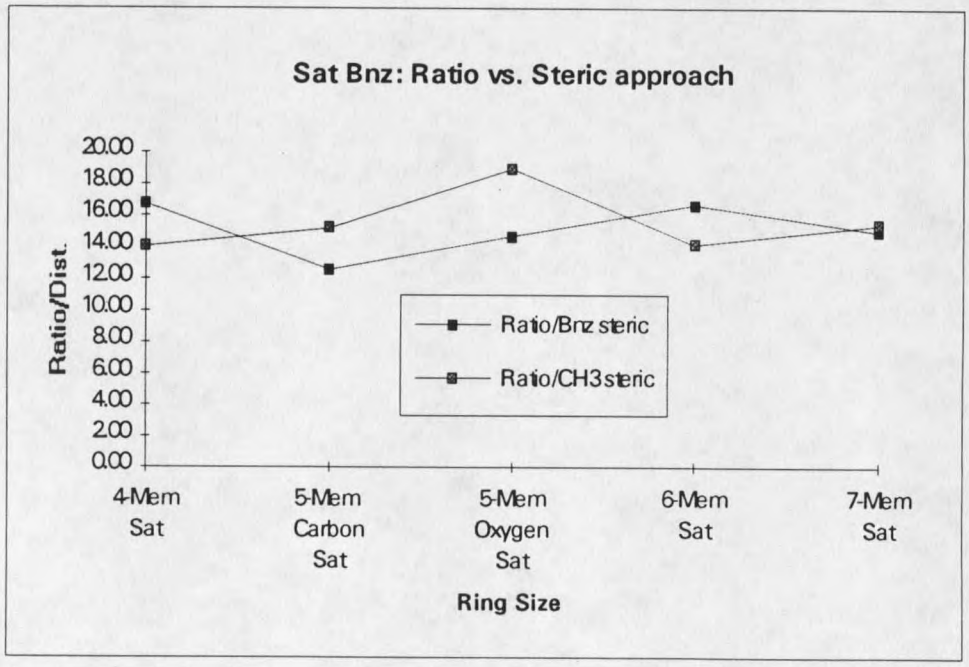


Figure 42. Saturated Benzyl steric approach comparison.

analysis, this relationship was also proven several times in other ring systems. The results of this steric approach study is shown in Table 7 for CD_3 salts. The distances were observed to look for a correlation between the steric approach and the experimental ratio for that isomer. To this end, we calculated the steric difference between both faces (in the third column of the table). This value was divided into the experimental ratio to give another column of numbers. However, these numbers don't seem to follow any observable trend. In another attempt at data analysis we took the raw distance values and divided them into the percent ratio. These calculated numbers were plotted against the ring size to check for any trends. These plots are shown in Figures 39 and 40 for the unsaturated and saturated cases.

The steric approach distance analysis was repeated for the benzyl system in the same method described above. The raw numbers are shown in Table 8. The calculated results are shown in the plots in Figure 41 for the unsaturated benzyl and Figure 42 for the saturated benzyl.

The plots of steric approach versus ring size were disappointing because they showed very little correlation. There was a partial linear relationship on one side of the benzyl system. However, the meaning of the partial trend and the seemingly random scattering of the CD_3 system is not

Table 9. CD_3 Steric Control.

Ring Size	CD3 toward 6-Mem Angstroms	CH3 toward Other Angstroms	6-Mem Face More Open	Steric Control Influences Rxn.
4-Mem Sat [77]	4.23	3.04	yes	yes
4-Mem Unsat [69]	4.41	2.78	yes	no
5-Mem Carbon Sat [79]	2.96	3.02	no	no
5-Mem Carbon Unsat [92]	3.78	3.1	yes	yes
5-Mem Oxygen Sat [94]	4.2	3.27	yes	yes
5-Mem Oxygen Unsat [92]	4.27	3.27	yes	yes
6-Mem Sat [80]	2.81	2.81	Same	*
6-Mem Unsat [73]	2.81	2.8	yes	no
7-Mem Sat [83]	2.92	2.86	yes	*
7-Mem Unsat [75]	3.69	2.72	yes	no

Table 10. Benzyl Steric Control.

Ring Size	Bnz toward 6-Mem Angstroms	CH3 toward Other Angstroms	6-Mem Face More Open	Steric Control Influences Rxn.
4-Mem Sat [61]	3.29	3.92	no	no
4-Mem Unsat [53]	4.24	3.14	yes	no
5-Mem Carbon Sat [63]	3.78	3.1	yes	no
5-Mem Carbon Unsat [55]	4.26	3.14	yes	no
5-Mem Oxygen Sat [98]	4.22	3.27	yes	yes
5-Mem Oxygen Unsat [96]	4.3	3.24	yes	yes
6-Mem Sat [64]	2.82	2.79	yes	*
6-Mem Unsat [57]	2.99	3.94	no	yes
7-Mem Sat [67]	2.94	2.85	yes	no
7-Mem Unsat [59]	2.93	2.82	yes	no

completely clear and another method of linking the sterics with the experimental ratio percent data was necessary.

The next attempt to check for relationships started with the realization that except for the oxygen propellane series, the steric bulk on the side opposite to the static cyclohexyl ring generally decreased as the ring size increased from four to seven. This could be explained in the increasing degrees of freedom in the structure as the ring size changes from four to seven. As the ring size increases, it is better able to conform to a less sterically hindered position.

We also noted that the cyclohexyl face was the least sterically hindered in the majority of the isomers. In the CD_3 system, eight out of nine of the isomers were in the less sterically hindered cyclohexyl side. The exception was the 6s5 system, but the difference in the approach face distance was a minuscule 0.06 angstroms. For the benzyl system, the number was eight out of ten for approach on the less sterically hindered cyclohexyl side. The exceptions here were the 6s4 [61] and the 6u6 [57] systems. The deviation in these two were much more significant (0.37 and 0.95Å respectively). When this information was compared with the experimental ratio percent data, some trends began to appear. In the CD_3 system, the higher experimental ratio percentage was toward the cyclohexyl side (less steric hindrance) in four out of eight isomers. The exception here

were the 6u4 [69], 6s5 [79], 6u6 [73], and the 6u7 [75] salts.

We next looked at the benzyl system to establish a steric control trend. The benzyl system generally ignored a steric trend in that only three of the isomers seemed to be under steric control. The above data is shown graphically in Table 9 for the CD_3 system and Table 10 for the benzyl system. The 6s7 [67] and 6u7 [59] benzyl salts that are not under steric control have very similar steric requirements on each face (only 0.09Å difference). This is probably close to the experimental error for the calculation. The other four nonsterically controlled benzyl isomers (6u4 [53], 6s4 [61], 6u5 [55], 6s5 [63]) form a interesting trend. Recall that in Figure 30, the unsaturated benzyl system shows higher ratio percent isomer than the analogous saturated system. The lines in the saturated and unsaturated systems cross somewhere between the five and six membered rings. The interesting relationship between the lack of steric control and the selectivity toward higher isomer ratio would seem to be related in some fashion. It is plausible that these reactivity differences may result from the electronic differences between the rings adjacent to the pyrrolidine ring for the unsaturated salts. This does not explain the results for the saturated salts. They are close to 1:1 ratio (55.2% for 6s4 [61] and 52.3% for 6s5

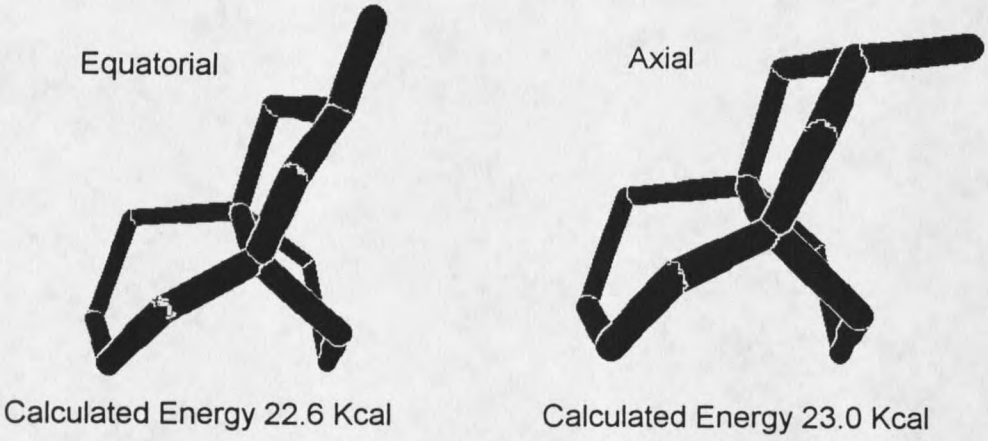


Figure 43. Tertiary amine propellane differences.

[63]) but these numbers are above the perceived experimental error and remained unexplained at this time.

The calculations showed another interesting clue as to why the steric interactions of the rings were influencing the reaction. In viewing pictures of the calculated minimized salts and some of the precursor amines it is clear that relative to most cyclopentyl rings with pseudo axial and pseudo equatorial protons in the ring there is a glaring difference in our system. In our propellane system, the pyrrolidine methyl group exists in a true axial and equatorial conformers. The envelope of the ring was always (x-ray data and calculations) folded away from the static cyclohexyl ring. This effectively opened the face toward the cyclohexyl more than the opposite face (which is also shown by the calculated steric distances). An example of this in the tertiary amine propellane minimized in a force field calculation (Alchemy III program provided by R. and A.

Craig) showed a 0.4 Kcal difference between isomers as shown in Figure 43. The reassuring result is that the equatorial isomer has the lower energy. This validates the idea that on a time-averaged basis the methyl group would be in the equatorial position more of the time than the axial. With the methyl group in the equatorial position, the lone pair of electrons is poised to react on the face opposite to the static cyclohexyl ring. This information agrees with the steric and somewhat the experimental results. The energy difference between isomers is very small so as to only partially shift the population from the 1:1 equilibrium. The differences in amines are also similar to the energy differences between the salt products.

In summation, steric interactions seem to partially influence the outcome of the reaction in the CD_3 ring systems. However, here is very little influence by sterics in the benzyl system. The benzyl system has the greatest possibility for electronic interactions with the smaller ring benzyl salts. These differences between the benzyl and CD_3 electrophiles may suggest that there is more than one reaction pathway available for the reaction. Therefore, search for these electronic effects is always difficult when one considers the magnitude of other, mostly more dominant effects. Placing nonbonding electrons into the ring system had substantial effects on the experimental ratio. Subsequent investigations need to pursue these larger, more

easily identifiable effects. The best situation would be to limit the other offending interactions to get a more complete picture of any electronic activity.

The transition state will always remain an elusive species when one can gain understanding only by viewing from either side of the abyss between reactants and products. The propellane system has inherent flaws but future work with the kinetics of the this propellane system (anchimeric effects) may help provide a clearer picture of what is really happening.

CHAPTER 4

NEWER PROPELLANE SYSTEMS

The difficulties with steric interactions masking electronic contributions in the larger ring propellanes prompted us to look to other ring systems. One possible arrangement contained three five membered rings (tricyclic[3.3.3]undecane). The cyclopentane envelope flap is relatively immune to the conformational ring perturbations that are possible for rings six carbons and larger. The triple five propellane system would also avoid the high energetics and synthetic difficulties of the small four and three membered rings. When even-numbered rings are present, π-electron donation is the favored approach for studying N.G.P. because it preserves the symmetry of the

Arrows show possible routes for nonbonding electron participation

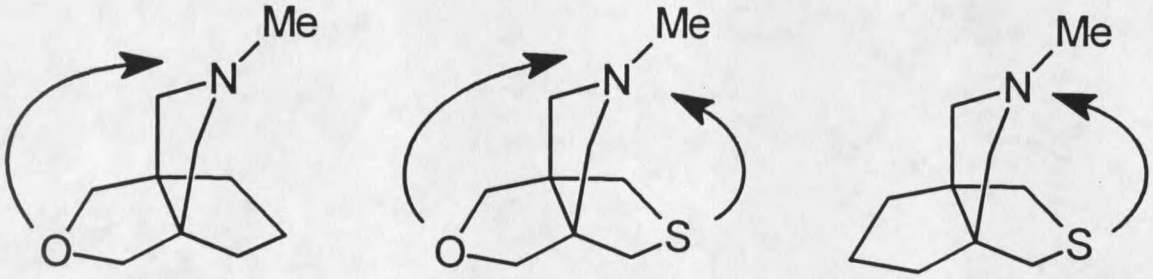


Figure 44. Tricyclo[3.3.3]undecane ring systems

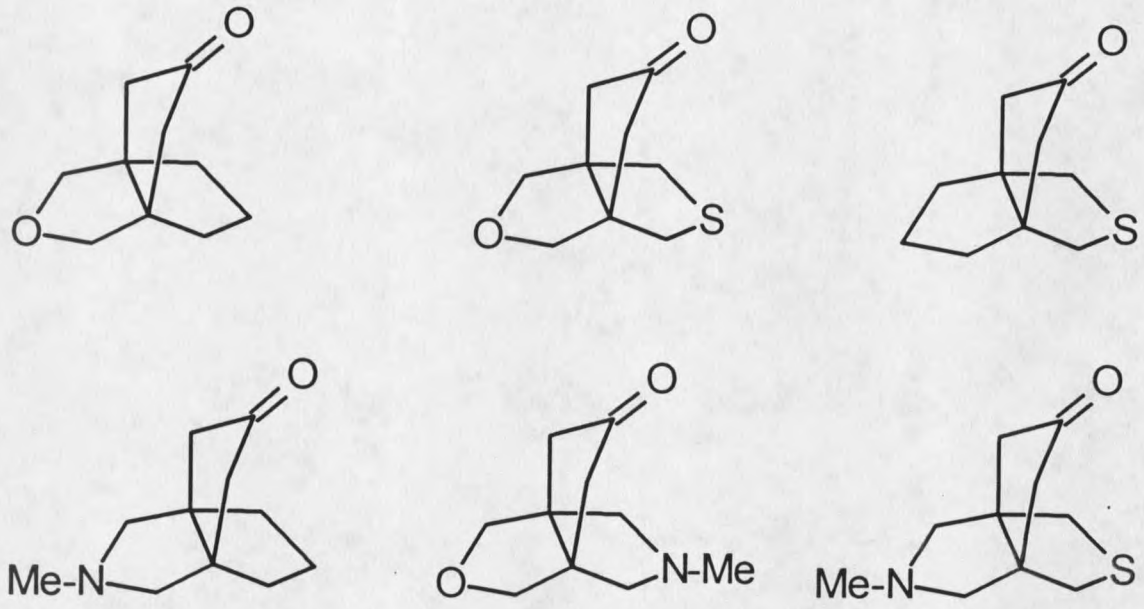


Figure 45. Keto-tricyclo[3.3.3]undecane ring systems

system. The propellane skeleton dictates even numbered ring systems to be unsymmetrical with a heteroatom at only one point on the ring. The odd number ring size of cyclopentyl ring, coupled with previous results in the nitrogen Menschutkin studies favor nonbonded heteroatom electron involvement for future studies in neighboring group participation. Originally we hoped that we could continue studying the quaternization reaction as a gauge for measurement of the overall effect. The desired compounds are shown in Figure 44. The retro synthesis of these new Menschutkin compounds enabled the possibility of a new class of versatile compounds. These other intermediate compounds for study are shown in Figure 45. The ketone intermediates

can be reduced to the original tertiary amine propellanes in one step. These ketone systems have the advantage that nitrogen is able to participate in the study and not just be used for a measurement tool. We wanted to use the experience of our previous propellane systems to guide the synthesis of the proposed tricycles.

Our retro synthetic analysis of these new propellane

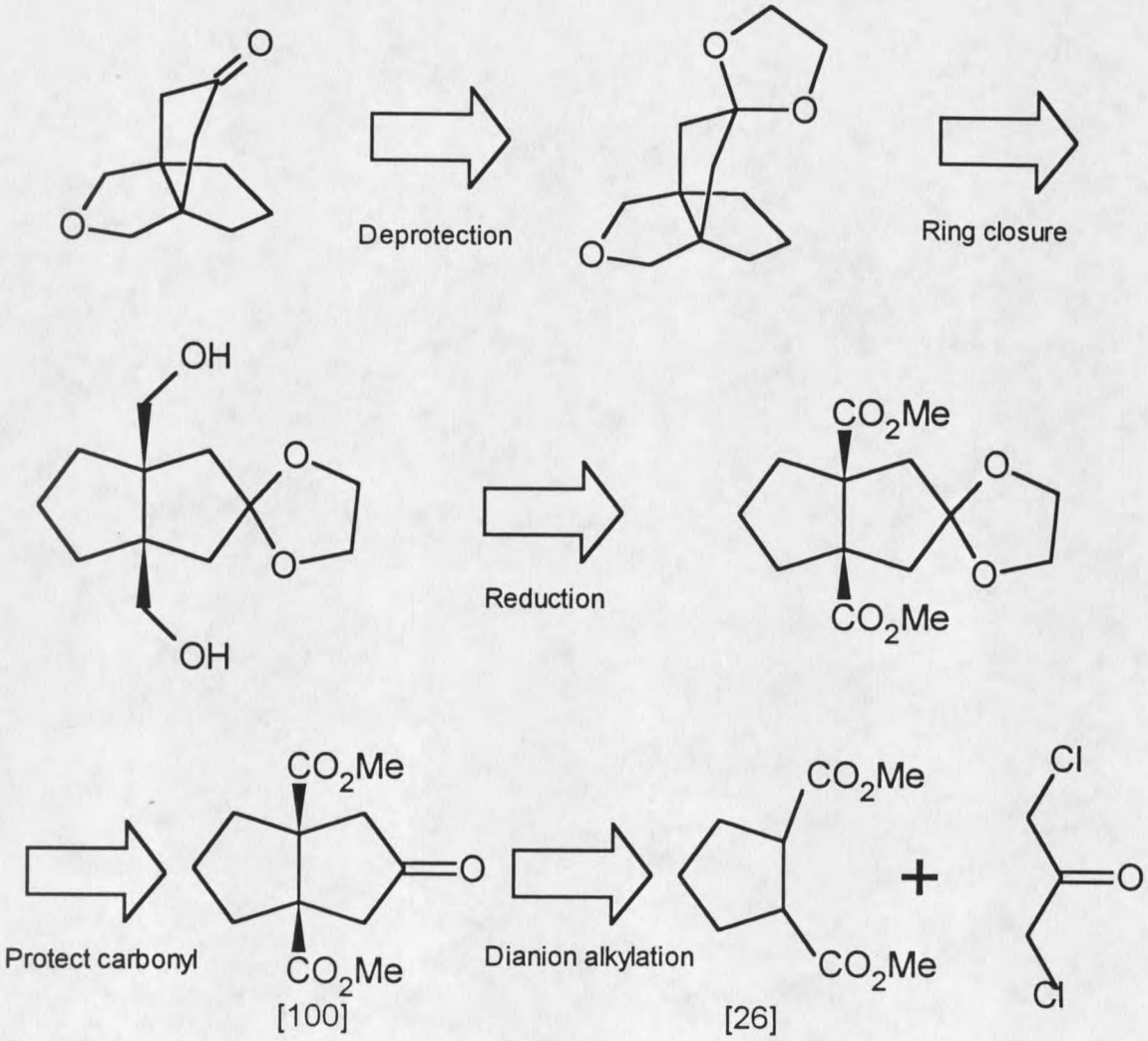


Figure 46. Retro synthetic plan for tricyclic ketone propellanes.

systems hinged on our proven dianion approach of ring addition. To prove the validity of the ideas we chose to make the oxygen/carbon system to check the viability of our synthetic plan. The retro synthetic scheme is shown in Figure 46.

The synthesis began with the previously produced 3,4-dicarbomethoxycyclohexene, [26], (which originated from the alkylation of dialkylsuccinate with 1,3-dibromopropane). The dienolate was formed easily with LDA which was treated with 1,3-dichloroacetone to effect the ring closure. The low yields for this reaction presented a problem. During a series of reactions, the conditions were changed (ultra low temp (-100° C), reaction times, solvent, etc..) that gave a maximum yield of only 34% of the bicyclic ketone, [100]. We discovered that the reaction with the dichloroacetone was very rapid at -78° C (alkylation was mostly complete after 5-10 minutes). Longer reaction times only increased enolate attack on the ketone carbonyl of the product. We thought that protecting the ketone as the cyclic ketal with ethylene glycol would eliminate some of the side products and also save a later synthetic step. However, when the dienolate was alkylated with the 1,3-dichloroacetone cyclic ketal, [101], we could only isolate starting material. The change from the ketone to the ketal completely nullified the reactivity of the electrophile. It was clear that the steric interaction of the ketal approach must inhibit the

enolate from finding the dichloro electrophile. We tried to increase the reactivity of the electrophile by exchanging iodine atoms for chlorine by a standard Finkelstein reaction. We were however, unable to achieve any exchange under normal reaction conditions. Both gas chromatography and NMR showed that only the chloro starting material was present after refluxing with NaI in acetone. We stepped back again and performed the Finkelstein reaction on 1,3-dichloroacetone in high yield. We then attempted protecting the 1,3-diiodoacetone as the cyclic ketal. This reaction also proved disappointing with only a small amount of the desired diiodo ketal formed after rather harsh conditions. These reactions are shown in Figure 47.

At this stage, while we were successful in adding the ketone ring, the poor yields and separation difficulties forced us to reconsider the overall approach to the synthesis. A review of the common synthetic methods of producing the cyclopentanone moiety in a ring closure reaction proved somewhat disappointing. There are many proven ways to effect ring closure and insert carbonyl groups at the alpha position to the bridgehead. There are not many methods to place a carbonyl at the beta position from the bridgehead in a symmetrical manner. The most common approach was using a Dieckmann condensation to produce the ketone in a cyclopentyl ring. With this in

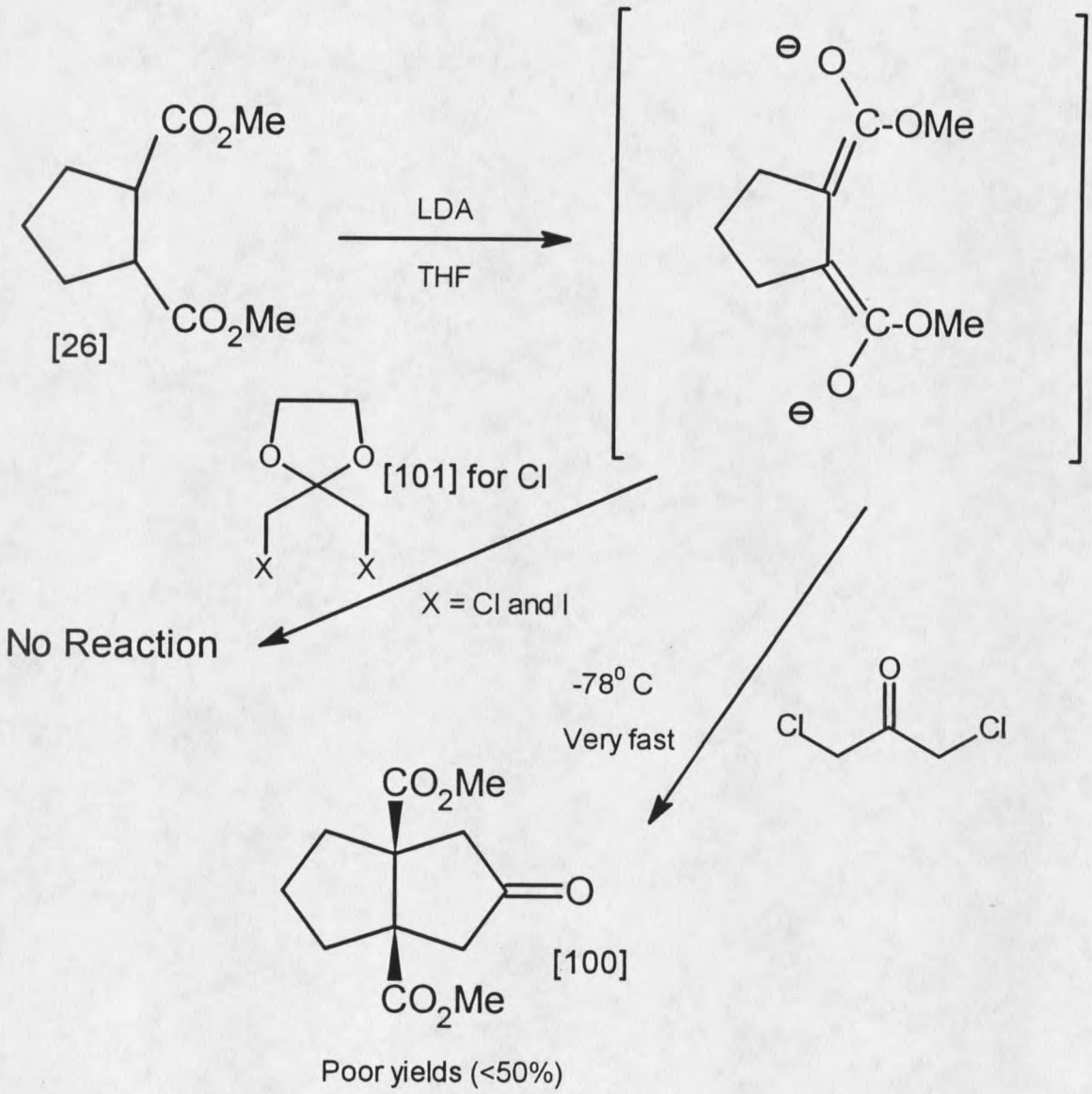


Figure 47. Attempts at using 1,3-dichloroacetone as an electrophile.

mind, we tried another synthetic procedure to gain entry into our desired propellane systems.

This new approach had many benefits over the previous design. A major advantage was that it used intermediates that were produced previously in another investigation. The

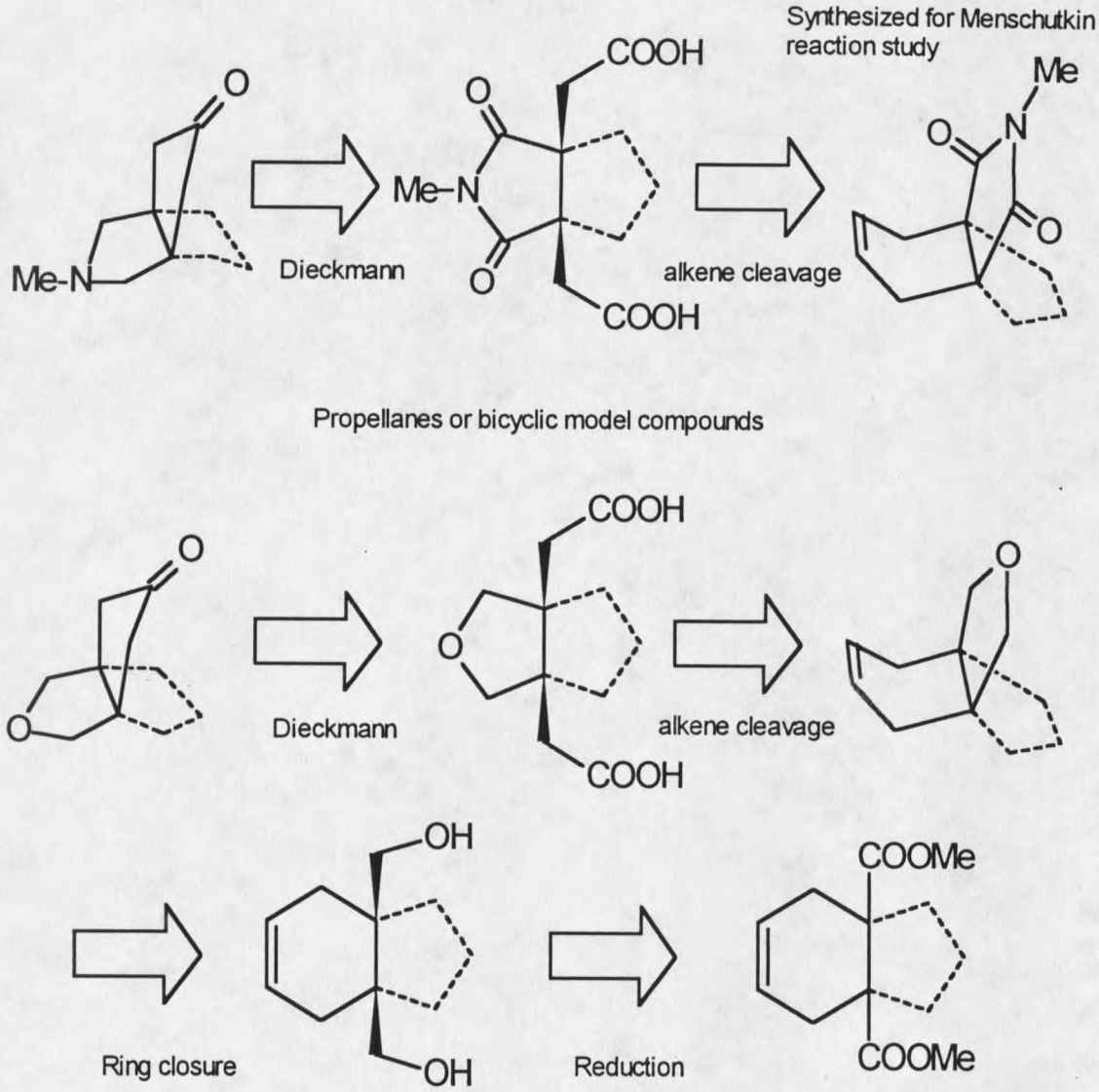


Figure 48. Retro synthetic analysis of tricyclo[3.3.3]undec-3-ones.

starting material for the nitrogen system was an intermediate in the previous Menschutkin studies. The protocol for producing the oxygen starting material was used previously in the Mundy laboratories by Johnson and Lee.[41]

Another major improvement over the earlier unsuccessful synthesis was the brevity of the newer method. The only step that could cause potential problems would be the Dieckmann condensation to effect the cyclopentane ring closure. There were examples in the literature of this type of closure for larger similar bicyclic ring systems but not for our bicyclo[3.3.0] system. The retrosynthetic analysis of this new idea is shown in Figure 48. This new approach also allowed the use of bicyclic model compounds to test the synthetic protocol where appropriate.

For the oxygenated systems, the only difference between the bicyclic and the propellane synthetic routes is the initial alkylation of the diesters in the propellane system. The diester, [29], was then reduced to the respective diol, [103], using LAH. The diol, [103], was treated with one equivalent of MsCl in pyridine to close the tetrahydrofuran ring. This oxygenated propellane, 8-oxotricyclo[4.3.3]undec-3-ene, [104], or its bicyclic counterpart, [102], was then subjected to ozonolysis followed by oxidative workup. We originally tried to use the Lemieux-Johnson reaction ($NaIO_4$, $KMnO_4$ excess water) but were unable to achieve reproducible results on all of the compounds. Part of the problem was in the solubility of the diacids product in the water layer. Continuous liquid extraction increased the overall recovery but low yields and expense forced our attention toward ozonolysis. The

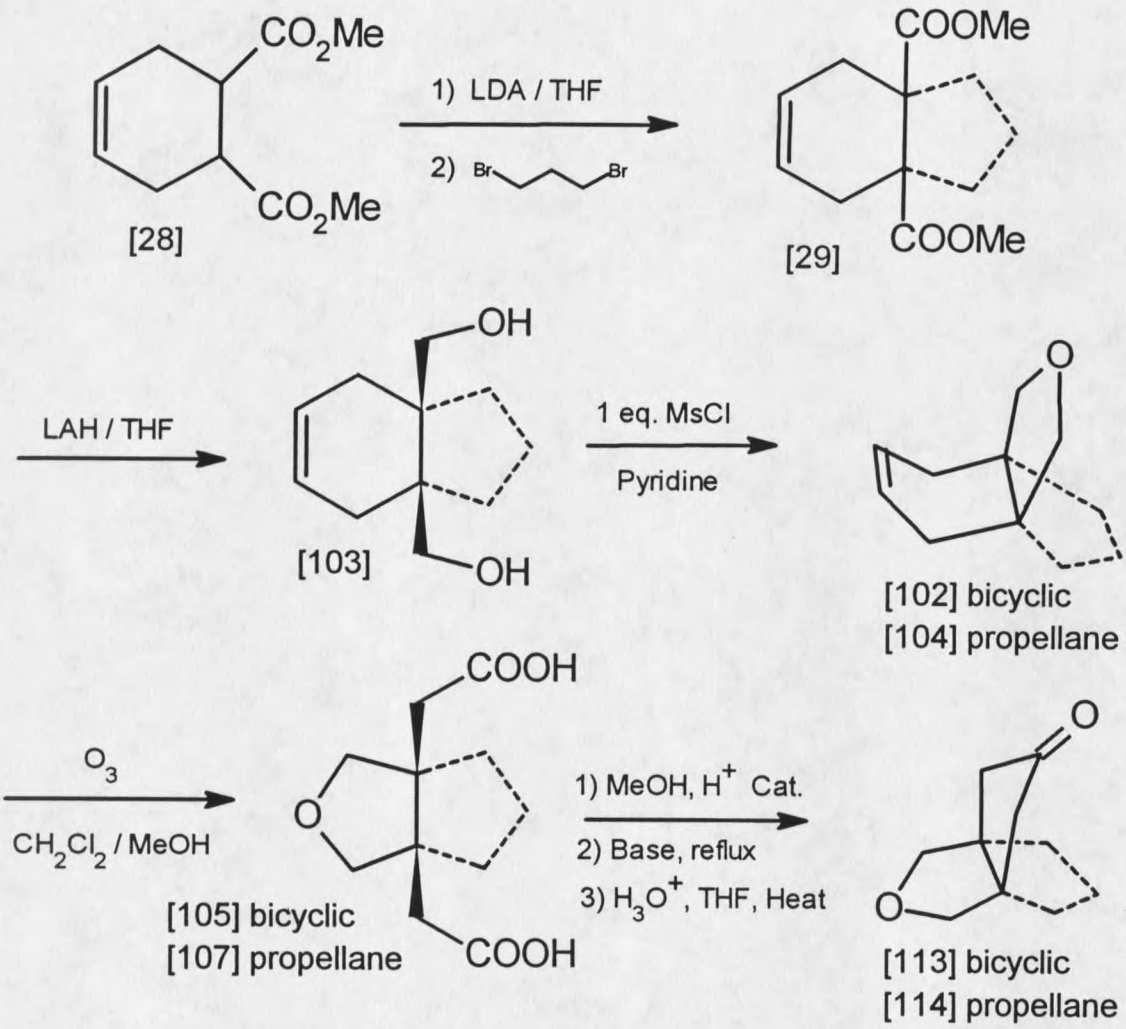


Figure 49. Synthesis of 5,5,5 oxygen keto propellanes.

resulting *cis*-diacids, [105]&[107], were esterified using the procedure of Fisher (excess dry methanol with acid catalyst). At this stage of the synthesis, the only remaining step was the Dieckmann condensation to close the tetrahydrofuran ring followed by acid hydrolysis with concurrent decarboxylation to afford the target molecule. These reactions on the oxygen system are shown in Figure 49.

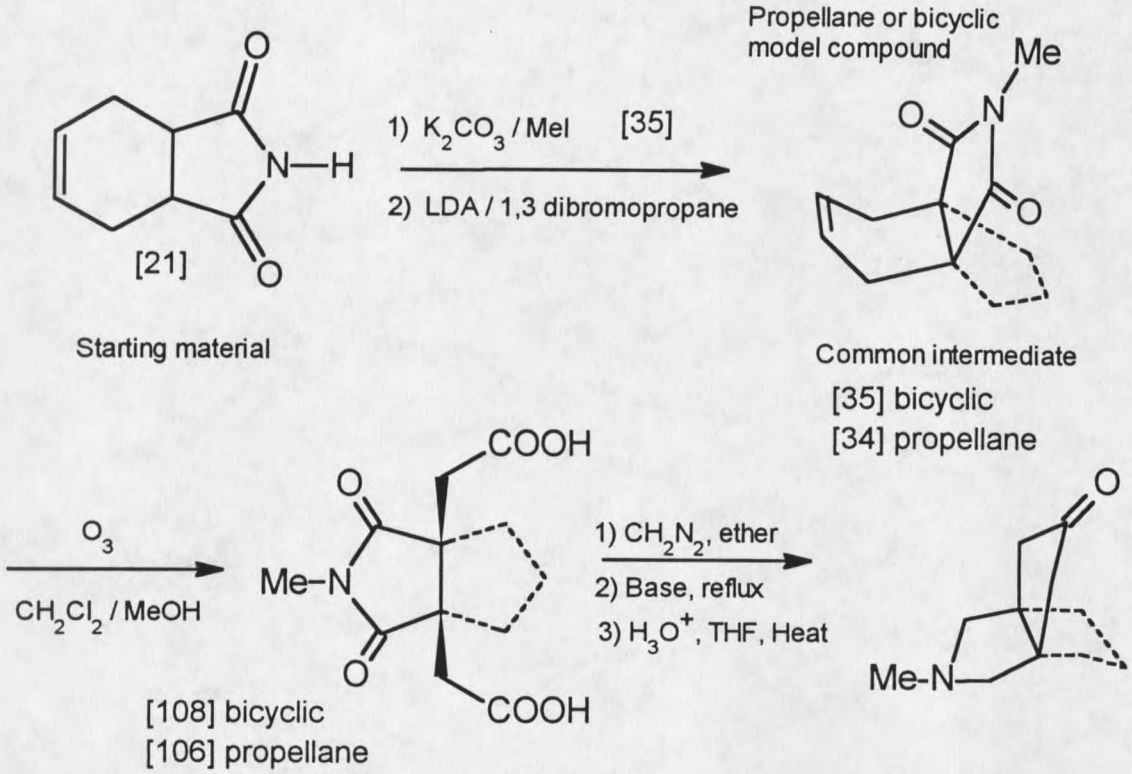


Figure 50. Synthesis of 5,5,5 nitrogen keto propellanes.

The nitrogen system was synthesized from an intermediate that was common with the previous propellane quaternization study. To review, the previous synthesis began with methylation of *cis*-1,2,3,6-tetrahydrophthalimide, [21], followed by alkylation with LDA and 1,3-dibromopropane to add the cyclopentane ring. This common intermediate, N-methyl-7,9-dioxo-8-azatricyclo[4.3.3.]dodec-3-ene, [34], (or its bicyclic counterpart, [35]) was then subjected to oxidative alkene cleavage with ozone to produce the diacid compound. The acids were smoothly converted to their respective diesters, [111]&[112], by treatment with

diazomethane in ether. The last remaining step in this synthesis was also the ring closure using the Dieckmann procedure. The idea was to treat the esters with base to effect the ring closure, followed by refluxing with mild acid to hydrolyze the α-carbomethoxy ketone and cause decarboxylation. All these synthetic steps are shown in Figure 50.

Unfortunately, the ring closure stages proved somewhat problematic for both the oxygen and nitrogen propellane systems. The Dieckmann cyclization reactions returned mainly starting material for the propellane systems. We used a multitude of different bases (Na, NaOMe, t-BuOK, NaH, KH, $KN(TMS)_2$) and solvents (benzene, toluene, xylene) without success. We did however, fare slightly better in the bicyclic systems. The bicyclic oxygen system was closed off successfully using methods that failed for the propellanes.

We looked for alternative methods to possibly effect the ring closure for the propellane systems. One method that could be easily integrated into our synthesis is the Ruzicka condensation. This older procedure from the draconian era of chemistry uses a "flame-thrower approach" to induce ring closure using the diacid compound, $Ba(OH)_2$ and some iron filings. The compounds are mixed together with a mortar and pestle and are heated quickly with an open flame. The ketone distills away (hopefully before

polymerizing to a dark black tar) from the mixture with the water from the barium hydroxide. We tried this method on the bicyclic nitrogen compound, [35], based on a pyrotechnic phobia of flame heating compounds that are the end products of a multi step synthesis. This bicyclic compound could be easily reproduced (only one step from starting material), and could be comfortably risked to the dynamics of a thermal reaction. The reaction worked on a small scale; however, the yields seemed to vary a great deal from one reaction to another. It seemed that the heating method and type of glassware contributed to variance in yield. The yield was the greatest when heat was applied quickly and the glassware was designed so that the product was quickly removed before decomposition via short path distillation. It was disappointing that when the reaction was scaled up, the yield dropped to almost nonexistent levels.

At this point we had a multitude of acids and esters and no obvious method to close off the third propellane ring. We felt that the overall synthesis was efficient; but the elusive final ring closure has delayed the progress to reach the propellane target molecules. It is ironic that the desired rigid features of the ring system eventually halted the synthetic progress at the ring closure stage. It is hoped that future research will focus on this area of propellane synthesis. These class of compounds are clearly the next logical step in the investigation of neighboring

group participation and deserve further research activity that is beyond the scope of this current study.

CHAPTER 5

ALDEHYDE PEROXIDATION

Introduction

There is increasing evidence that reactive oxygen species may be responsible for many types of diseases in higher mammals. A correlation between disease and oxidative tissue degradation is implicated in the aging process, heart disease, growth inhibition, genotoxicity, arthritis, cataract and retinal degeneration.[42] Reactive oxygen species cause oxidative degeneration when they attack polyunsaturated fatty acids (PUFAS) that are present in the tissues as glycerylesters and triglycerides in phospholipids. This oxidation of PUFA is called lipid peroxidation and is believed to increase cell membrane permeability and restrict membrane ion transport.[43] This cell barrier restriction is thought to result in edema, electrolyte imbalance, and an increase of calcium concentrations within the cell environment. All of these factors contribute to cell dysfunction and distress.[44]

The eye has a greater likelihood to sustain this type of damage than other types of tissue because of the high concentration of oxygen and PUFAS in the retina.

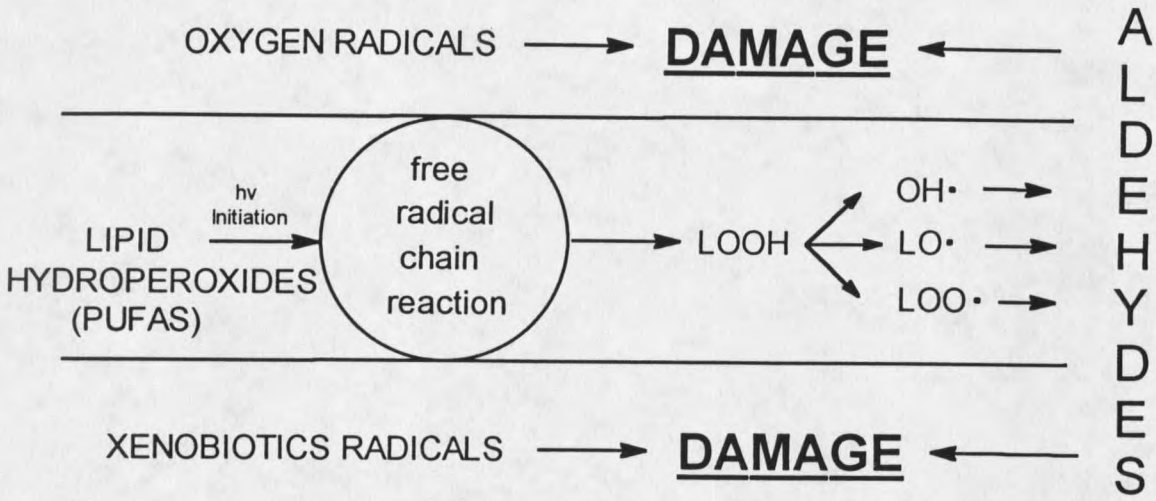
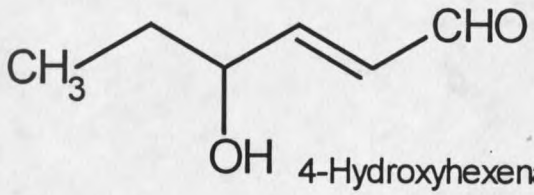


FIGURE 51. Possible free radical damage scheme.

Peroxidation of these fatty acids results from a free radical chain reaction with the subsequent initiation, propagation and termination steps. The PUFAS are prone to oxidation due to the easy abstraction of allylic hydrogens by initiating radicals. After initiation, the intermediates formed include hydroperoxides (ROOH), which may decompose to give peroxy radicals (ROO•), hydroxy radicals (HO•), and oxy radicals (RO•). The probable mechanism of this breakdown process requires a beta-cleavage of lipid hydroperoxides to produce aldehydes. However, the mechanism of this process is complex and not fully understood .

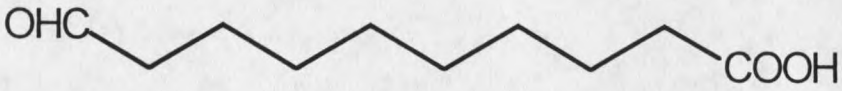
There is also increasing evidence that these aldehydes generate pathophysiological effects in cells and tissues (Figure 51).[45] However, there are distinct differences between the damage potential between free radical peroxides and their resulting aldehydes. The free radicals have very

limited lifetimes and therefore may be restricted in the amount of damage they can cause. The aldehydes have much longer lifetimes and can diffuse from the origination site and could generate cell damage in distant locations. With the potential to produce greater cell destruction, they have been called the "second toxic messengers".[46] These aldehydes also provide researchers a way to quantitate the peroxidation process in tissues. Of all the possible aldehydes produced in this process, there are only a few

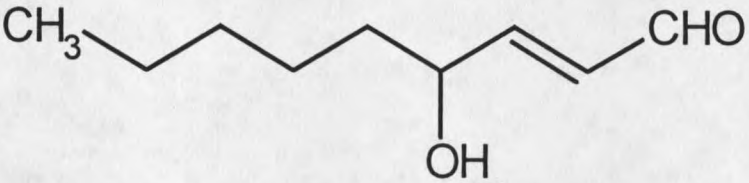


4-Hydroxyhexenal (HHE)

Malonaldehyde (MDA)



9-Oxononanoic acid



4-Hydroxynonenal (HNE)

FIGURE 52. Aldehydes formed from free radical PUFA oxidation.

that have been used as markers of cell damage (Figure 52). These compounds that are used for identification are malonaldehyde (MDA), 4-hydroxyalkenals, specifically 4-hydroxynonenal (HNE) and 4-hydroxyhexenal (HHE). There are many other possible markers, such as 9-oxononanoic acid, which have seen limited use due to problems in isolation and recovery.

One major class of these aldehydes, the 4-hydroxyalkenals, were discovered in the early 1960's by Esterbauer.[47] This was later independently confirmed by several research groups. During the 1970's, most of the research focused on the carcinogenic activity of these aldehydes. In 1982, Nakamura isolated HNE, along with other aldehydes, in autoxidized linseed oil.[48] Later, in 1987, Kaneko, published a study where HNE was identified as one of the most toxic aldehydes to cultured fibroblasts.[49] These and other articles generated an explosion of interest in the further study of HNE. Nearly 90% of the literature in the field appeared after 1980 when HNE was identified as a cytotoxic product of peroxidation of liver microsomal lipids.[50]

There were problems in obtaining large amounts of pure HNE for research via the tedious and difficult autoxidation of lipids procedure. A chemical synthesis was employed to overcome this problem.[51] This original synthetic method by Esterbauer employs an attack by a Grignard, [116], on

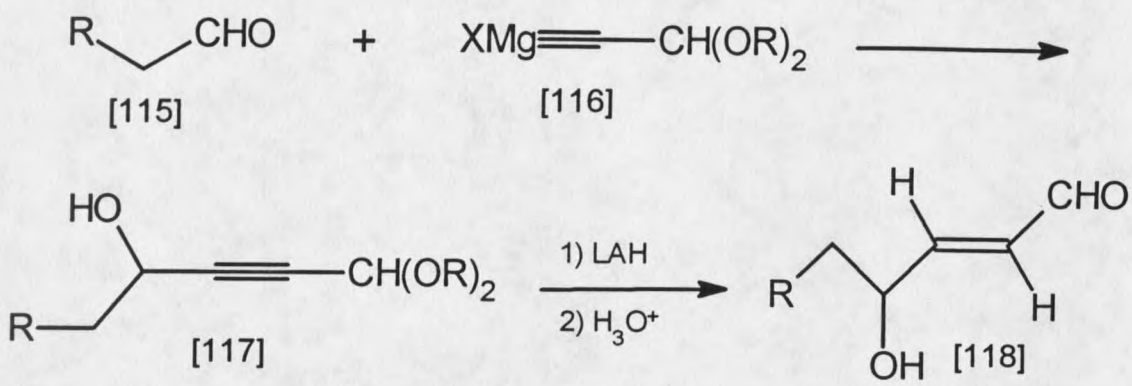


FIGURE 53. Original Esterbauer synthesis.

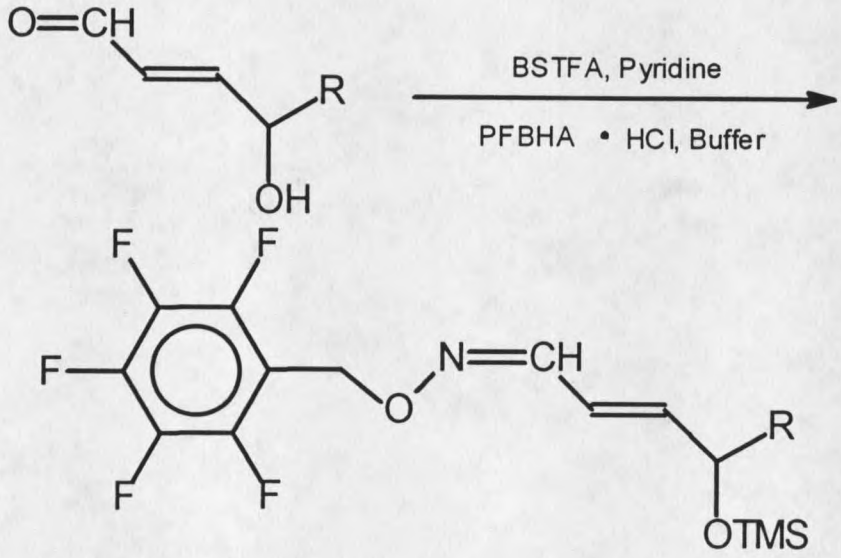
valeraldehyde, [115]. The α-hydroxy alkyne acetal product, [117], was then reduced with LAH to give the *trans* alkene, [118]. The final part of the synthesis was the hydrolysis of the acetal to give the desired 4-hydroxyalkenal. This synthetic method is shown in Figure 53. Other methods of syntheses were subsequently published.[52] In the first of these, 1,3-bis(methylthio)allyl-lithium is reacted with an aldehyde. This thio intermediate was then hydrolyzed in the presence of $HgCl_2$ to give 4-hydroxyalkenal. The other published syntheses are similar, with the exception of an optically active preparation in which an iron tricarbonyl complex of sorbic acid is used to resolve a racemic mixture of 4-HNE.[53]

Quantification of Aldehydes

There are many published methods[54] for determination and quantification of aldehydic products of lipid peroxidation. Calculation of the actual amounts of HNE present in biological samples can be troublesome. This results from a possibility of HNE being formed during the extraction and derivatization process. This problem may be avoided by addition of antioxidants (ETDA, BHT) to the samples. During the original work that exposed HNE as a major product of microsomal lipid peroxidation, the samples were derivatized with 2,4-dinitrophenylhydrazine. The resulting hydrazones were then analyzed using HPLC. This method is considered the best approach when analysis of the complete spectrum of all possible aldehydes is desired. Another method for measurement of HNE in plasma or liver employs HPLC analysis after derivatization with 1,3-cyclohexanedione to give fluorescent dihydroacridine derivatives. The HPLC method using UV detection of quantification and derivatization is somewhat restricted due to the nanogram limit of detection.

A more specific and sensitive method allows determination of hydroxyalkenals with picogram sensitivity.[55] The general extraction scheme generally provides a large amount of incidental aldehyde fragments.

The ion selective GC-MS technique permits one to ignore the background and focus on a specific mass. The chromatography characteristics of alcohols and acids are a limiting factor in using GLC to separate the isomers. To eliminate the chromatographic incompatibilities a derivatization procedure for the alkenals and acids must be performed. This technique converts the aldehydes under mild conditions to their perfluorobenzyl (PFB) oxime derivatives. This is followed by treatment with trimethylsilyl (TMS) chloride to eventually provide the perfluorobenzyl oxime TMS ether (Figure 54). The derivative is then analyzed (e.g. a m/e of



BSTFA = Bis(trimethylsilyl)trifluoroacetamide + 1% TMSCl
PFBHA.HCl = Perfluorobenzyl hydroxylamine hydrochloride

FIGURE 54. Aldehyde derivatization procedure for neg-ion GC-MS.

152 to show the total HNE content) via negative ion GC-MS. Conversely, the 9-oxononanoic acid is converted to the PFB benzyl ester and is analyzed in a similar fashion. The main disadvantage of this method is the requirement of appropriate isotope labeled internal standards to quantitate the absolute amount of any of these aldehydes in the tissues. This requirement for a synthetic adventure, not routinely carried out by biochemists, was the impetus for the syntheses that follows.

Synthesis of labeled 4-hydroxyalkenals

Initially 2,3-dideutero-4-hydroxyalkenals were synthesized by reduction of a triple bond precursor with $LiAlD_4$[56,57] in a method analogous to the original Esterbauer procedure. This standard provided some important information, but became limited in use because of an observed deuterium exchange of up to 15% during sample preparation (D.W. Thomas, R.J. Stephens, and F.J.G.M. van Kuijk, unpublished results). This exchange is proposed to occur during the keto-enol tautomerization of the α-β unsaturated aldehyde-alcohol and is shown in Figure 55. It was clear a new approach was needed and a different internal standard was designed to eliminate this problem.

Placing the isotope label at the terminal end of the alkyl chain would completely eliminate the exchange process. The earlier approaches to the non-labeled synthesis of HNE provide a template for the design of the labeled synthesis. All of these approaches differ in practicality when isotope labeling is brought into consideration, since the isotope should be introduced into the synthetic scheme as late as possible to avoid losses of labels in subsequent steps. This synthesis provides the flexibility of a common intermediate that allows late introduction of any

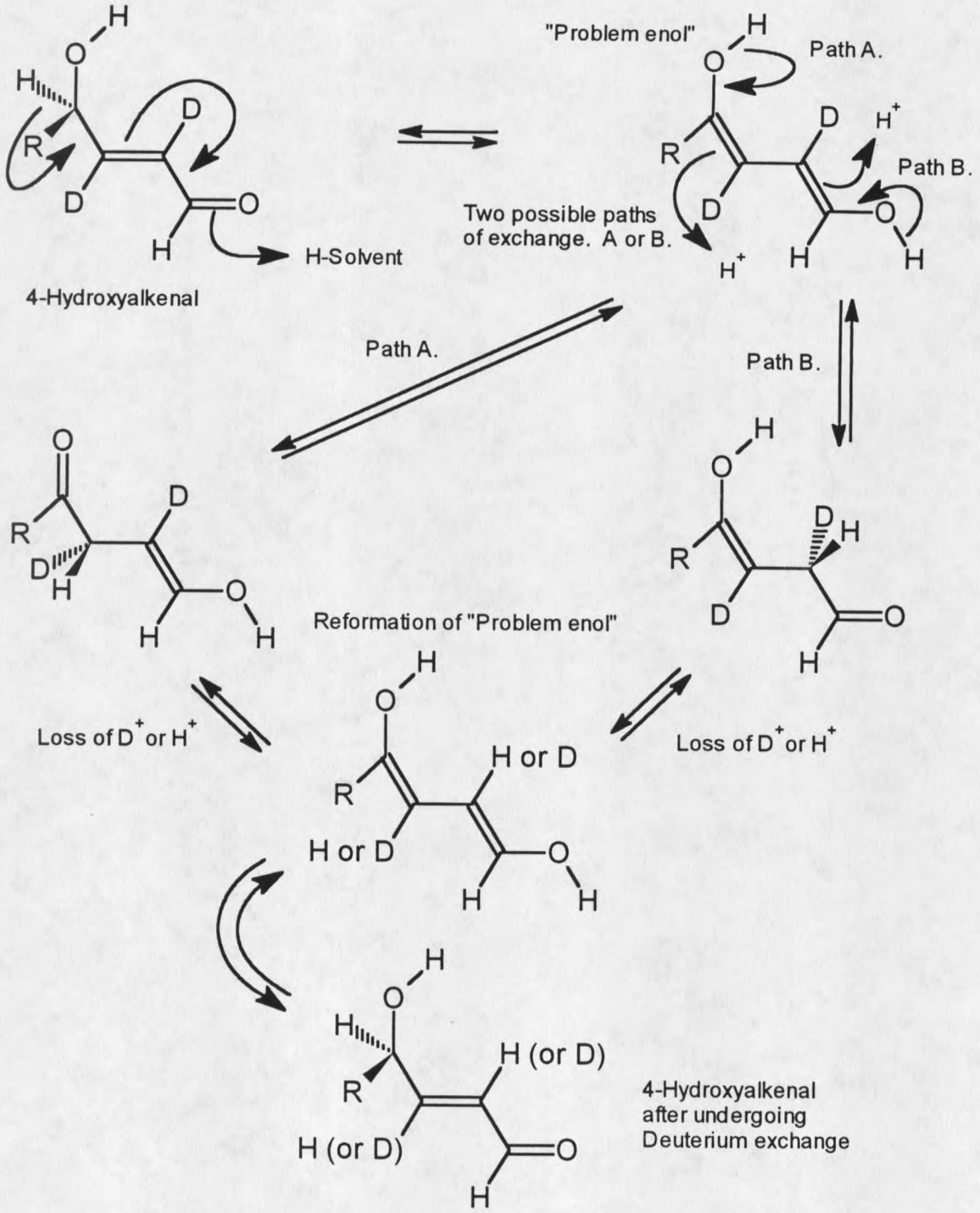


Figure 55. Proposed mechanism for deuterium exchange in α–β Dideutero 4-hydroxyalkenal.

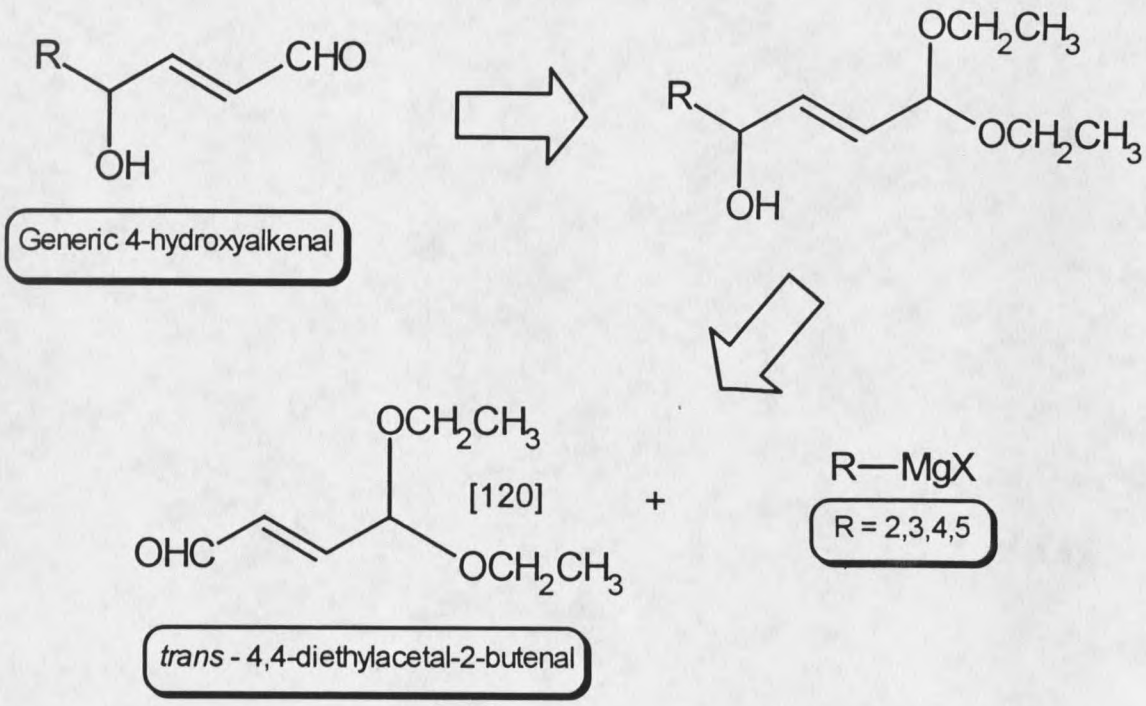


FIGURE 56. Retro-synthetic analysis of 4-hydroxyalkenals.

nucleophile with or without isotopic labels (D, ^{13}C, ^{14}C, or T).

The original idea for the synthesis of the 4-hydroxy alkenals started with the production of a basic intermediate, *trans*-4,4-diethylacetal-2-butenal, [120].

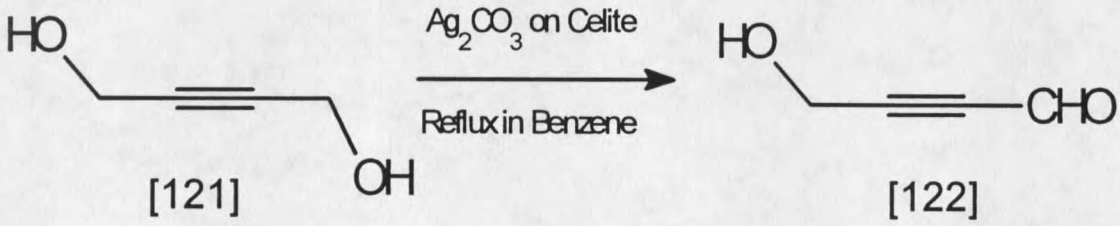


FIGURE 57. Silver carbonate oxidation of diol.

This intermediate would be attacked by a nucleophile (a Grignard was chosen) to produce the alcohol. The acetal protecting group would then be removed via hydrolysis as shown by the retro-synthetic analysis (Figure 56). This intermediate *trans*-4,4-diethylacetal-2-butenal, [120], could

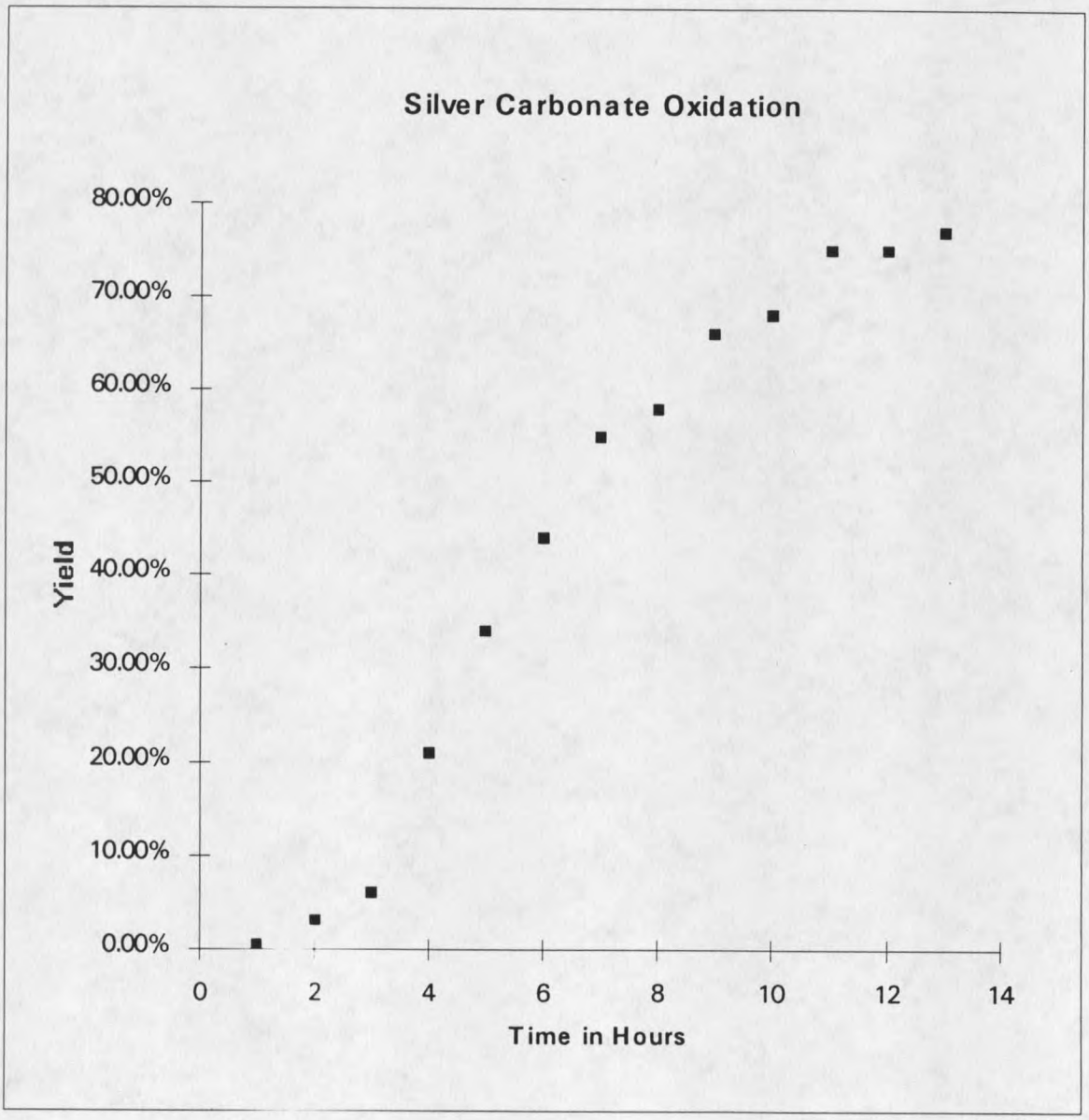


FIGURE 58. Plot of silver carbonate oxidation vs. time.

be envisioned a number of ways. We proposed a couple of approaches to produce the intermediate. The first is a selective oxidation of 1,4-dihydroxy-2-butyne, [121], with Ag_2CO_3 supported on Celite in refluxing benzene (Figure 57).[58] This method showed some promise on small scale and was fully optimized. The results of the aliquots taken at timed intervals are shown in the plot of yield versus time in Figure 58. The higher yields shown here came from a large excess (10 fold) of the silver carbonate. It was decided that the reaction was somewhat impractical on a larger scale due to the expense of the silver carbonate.

Another good approach is a selective alkylation of propargyl alcohol. The difference in the acidity of the alcohol and the acetyleneic proton can be used to advantage. Ideally, the goal would be to avoid protecting groups at this stage of the synthesis. Therefore, the strategy was to force carbon alkylation in favor of oxygen alkylation without using protecting groups. This is accomplished by addition of two equivalents of base to form the dianion. This is followed by addition of the electrophile. A retro-synthetic analysis of this is shown in Figure 59. The literature shows many alkyne-ol alkylation examples but demonstrates clearly that base selection is critical for success. The nature of the anion-metal bond directly affects the amount of carbon or oxygen alkylation that occurs. The more commonly used cations of Li^+, Na^+, and K^+

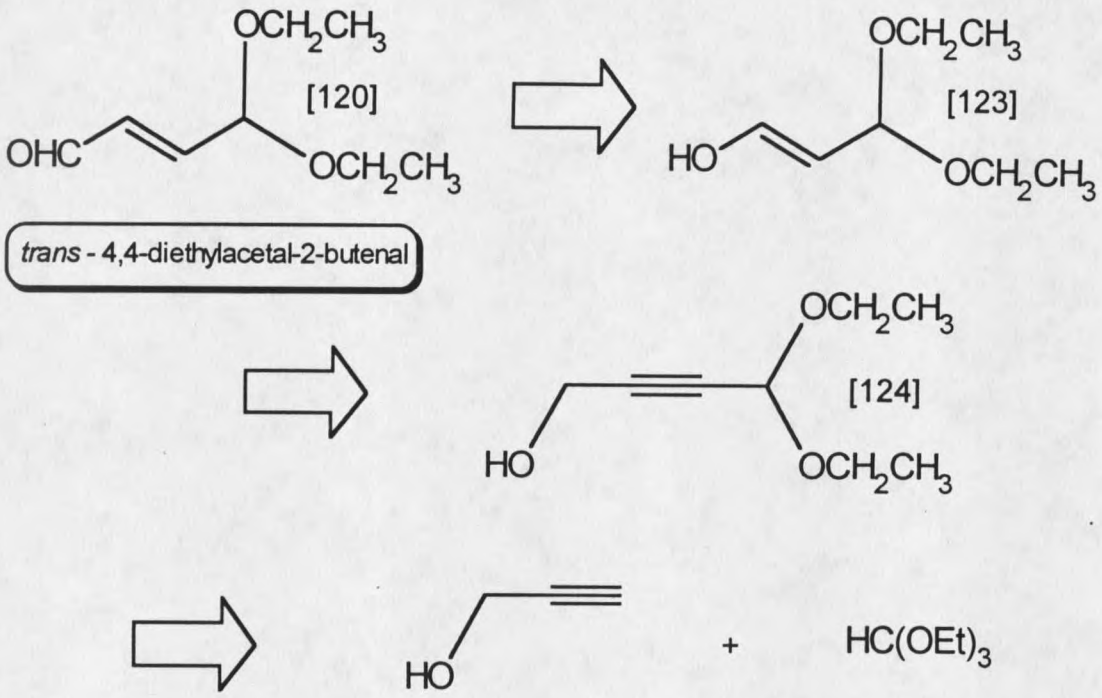


FIGURE 59. Retro-synthetic analysis of intermediate trans-4,4-diethylacetal-2-butenal.

elicit more oxygen alkylation based on the stronger bond with carbon. The choice of Mg^{2+} seems to favor a larger amount of carbon alkylation based on the stronger oxygen metal bond.[59] The alkylation is followed by a selective cold temperature reduction of the substituted propargylic alcohol with LAH to form the *trans* alkene.[60] The alcohol is then oxidized selectively using the Swern reaction to form the intermediate, *trans*-4,4-diethylacetal-2-butenal, [120].

The difficulty in isotope incorporation into the nucleophilic part of 4-hydroxy alkenals was not foreseen in the synthesis. We wanted to make a convergent synthesis with similar reactions to produce labeled HNE and HHE. This

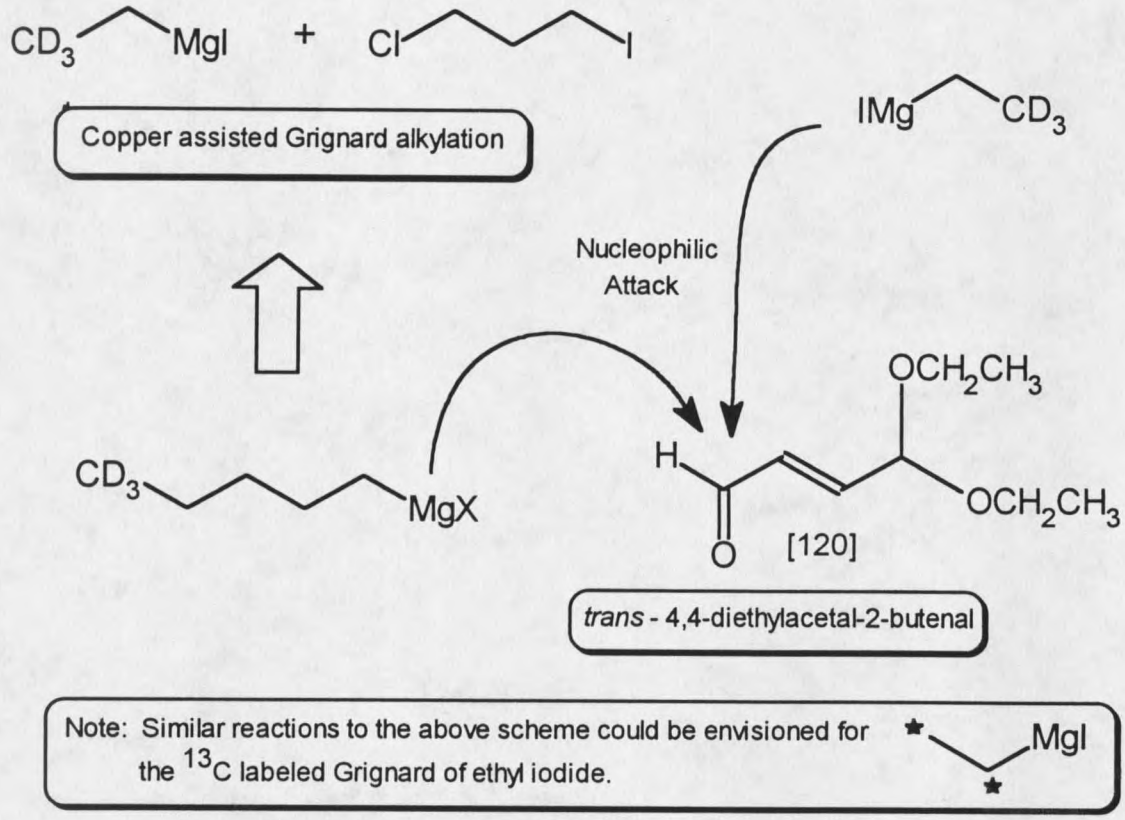


FIGURE 60. Retro-synthetic analysis of labeled alkyl nucleophiles.

required a two carbon nucleophile for HHE and a five carbon nucleophile for HNE. The proposed retro-synthetic path to the labeled alkyl halides (Figure 60), was envisioned from simple, commercially available starting materials while attempting to keep the isotope expense as low as possible. This approach would also work well for ^{13}C labeling due to the availability of 1,2 labeled iodoethane. A copper(I) assisted Grignard reaction was selected to couple the two carbon nucleophile with 1,3 chloroiodopropane to give the five carbon alkyl halide. Use of the general reaction

conditions gave unsatisfactory yields for isotope labeling. Attempted optimization of the reaction conditions was only partly successful but proved difficult and time consuming. Solvent selection was a major difficulty. On a small scale, we were unable to get satisfactory Grignard formation in freshly distilled THF which is needed for the alkylation. The problem was solved with formation of the Grignard in diethyl ether, followed by addition of freshly distilled THF to facilitate the coupling reaction. After addition of the THF, the solution turned from the Grignard gray color to a milky white solution. This was alarming because of the perception of water contamination and therefore a failed reaction. This unexplained complexation did not however influence the results. The white solution changed immediately to the characteristic blue color after addition of the solid copper salt. Yields were also affected by the choice of copper species. Copper(I) bromide and iodide gave satisfactory results but were difficult to handle and add to the reaction. We found that a solution of Li_2CuCl_4 in THF afforded the highest yield (87% by GLC) and offered greater ease in measurement and use.[61] The major problem of the method was in the purification and isolation of the labeled pentyl chloride, [125], which has a 110° C boiling point. The pentyl chloride produced in the reaction had 1,3-chloroiodopropane as a byproduct which would compete with the final Grignard formation. The trace amounts of water

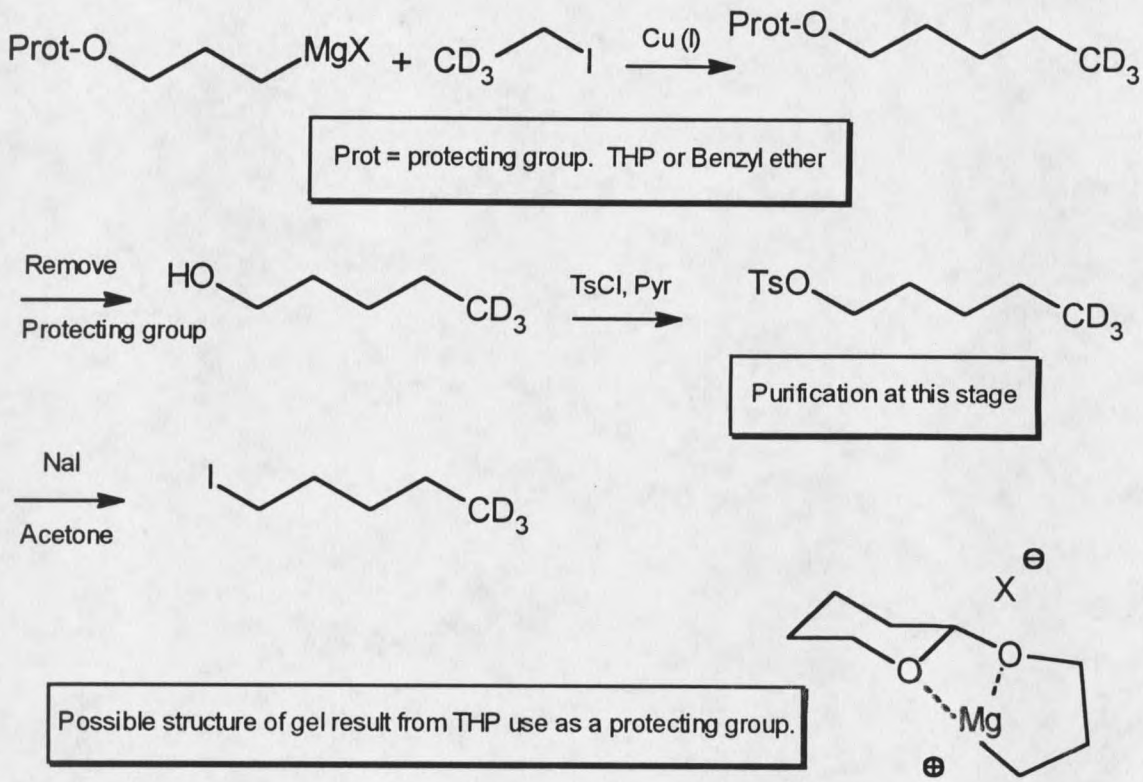


FIGURE 61. A new approach to labeled alkyl halides.

remaining after workup of the first Grignard reaction also had to be removed. The ideal answer would be to distill the volatile pentyl chloride, [125], over drying agent. However, the small scale of the reaction would not tolerate this and forced a preparative gas chromatography approach. The process was marginally successful, but slow and tedious. We were able to synthesize a small amount of labeled HNE, however, other methods were investigated after the product was lost when a stirbar broke out the bottom of the flask during hydrolysis of the acetal.

In an effort to resolve the volatility issue and allow the use of column chromatography for purification, another process was tried. In this new approach, shown in Figure 61 the problem of volatile intermediates was addressed. It was thought that an alcohol would provide a better handle to cope with the problem of volatile intermediates. This alcohol would have to be protected during the alkylation step of the synthesis. A tetrahydropyran (THP) protecting group was the first choice to protect 1-hydroxy-3-iodopropane. In theory, one could prepare Grignard adducts of both labeled ethyl iodide (as shown in previous attempts) or of the protected alcohol. The practice of late introduction of isotopes suggested that Grignard production using the protected alcohol was a better choice than using the labeled ethyl iodide. Both methods were successful; however, an unforeseen problem arose during Grignard formation of the protected alcohol. When the THP protected iodo compound, [126], was added to an ether solution of magnesium, a vigorous reaction ensued at first. As the solution became more saturated, the viscosity of the solution rose to the point of a thick gel. This gel became a complete solid and the reaction would not stir or even pour out of the flask. We hypothesized that a complex was formed between the magnesium and the two oxygens forming the THP group (Figure 61) Changing solvents to THF allowed more of the complex to go into solution but the outcome was

similar. Attempts were made to crystallize the product without success.

This low volatility approach was repeated with a benzyl protected alcohol which solved the complexation problems but presented some new difficulties in synthesis. Initial attempts to make the alkoxide of 3-iodopropanol followed by addition of benzyl bromide proved unsuccessful. The intramolecular ring closure reaction was much faster than addition of the benzyl group. Next we tried making the alkoxide of benzyl alcohol with subsequent attack on 1,3-dibromopropane. The major product of this attempt was elimination of the terminal bromo group to make benzyl allyl ether. Bromination of the alkene gave a mix of isomers that proved difficult to separate. Success was at last achieved by using a chlorine instead of an iodine to slow the internal ring closure. Changing the leaving group slowed the intramolecular ring closure and allowed 3-chloropropane alkoxide to attack benzyl bromide to give benzyl 3-chloropropyl ether, [127], in reasonable yield. A Finkelstein reaction exchanged the chlorine for an iodine to give benzyl 3-iodopropyl ether, [128], when Grignard formation proved sluggish or nonexistent with the chloro group. These steps are outlined in Figure 62. The resulting Grignard was produced and titrated to get exact concentration. This Grignard was then coupled with 2,2,2-trideuteroethyl iodide similarly to the previous alkylation

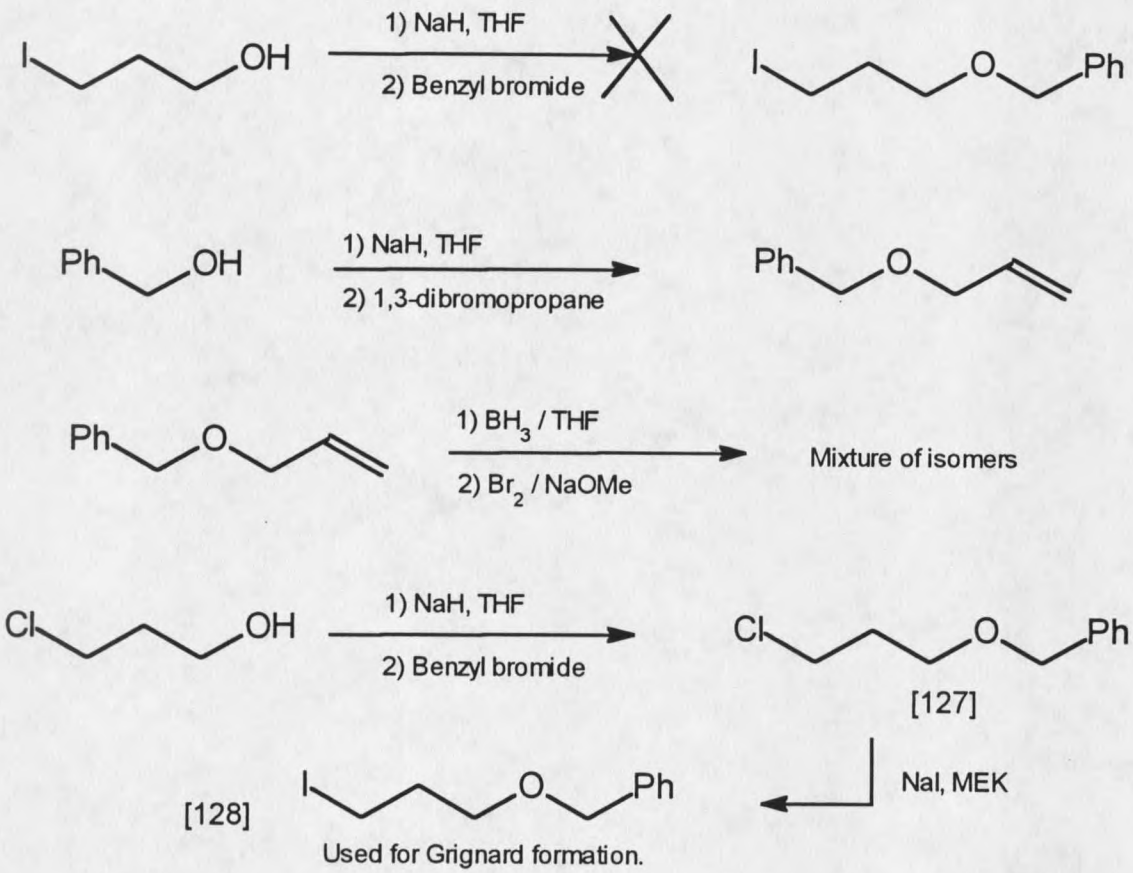


FIGURE 62. Attempts at making benzyl protected 3-halopropanol.

but using CuI as the copper(I) species. The protecting benzyl group proved somewhat difficult to remove by catalytic hydrogenolysis with 5% Pt/C in methanol. Acidification helped the yields somewhat but eventually, the catalyst was changed to 5% Pd/C. The choice of Pd is known to cause deuterium scrambling, however that effect was not seen as a factor in this reaction. The remaining alcohol was carefully removed from the methanol solvent. There were some inevitable losses at this step due to the azeotropic behavior of the methanol and the product. The remaining

alcohol was converted to the tosylate, [131], with TsCl in pyridine. The tosylate was much easier to handle and purify via column chromatography than the earlier alkyl halides. This was because of the higher boiling point and the UV activity of the tosylate. A Finkelstein reaction displaced the tosylate with NaI to produce the desired labeled alkyl iodide, [132]. This product was once again purified and dried, and Grignard formation was attempted. Regrettably, there was only limited formation of the Grignard. The problems in this step were eventually attributed to trace amounts of remaining acetone from the Finkelstein halogen exchange reaction in the previous step. Attempts to remove these impurities eventually consumed the alkyl iodides prepared up to this point.

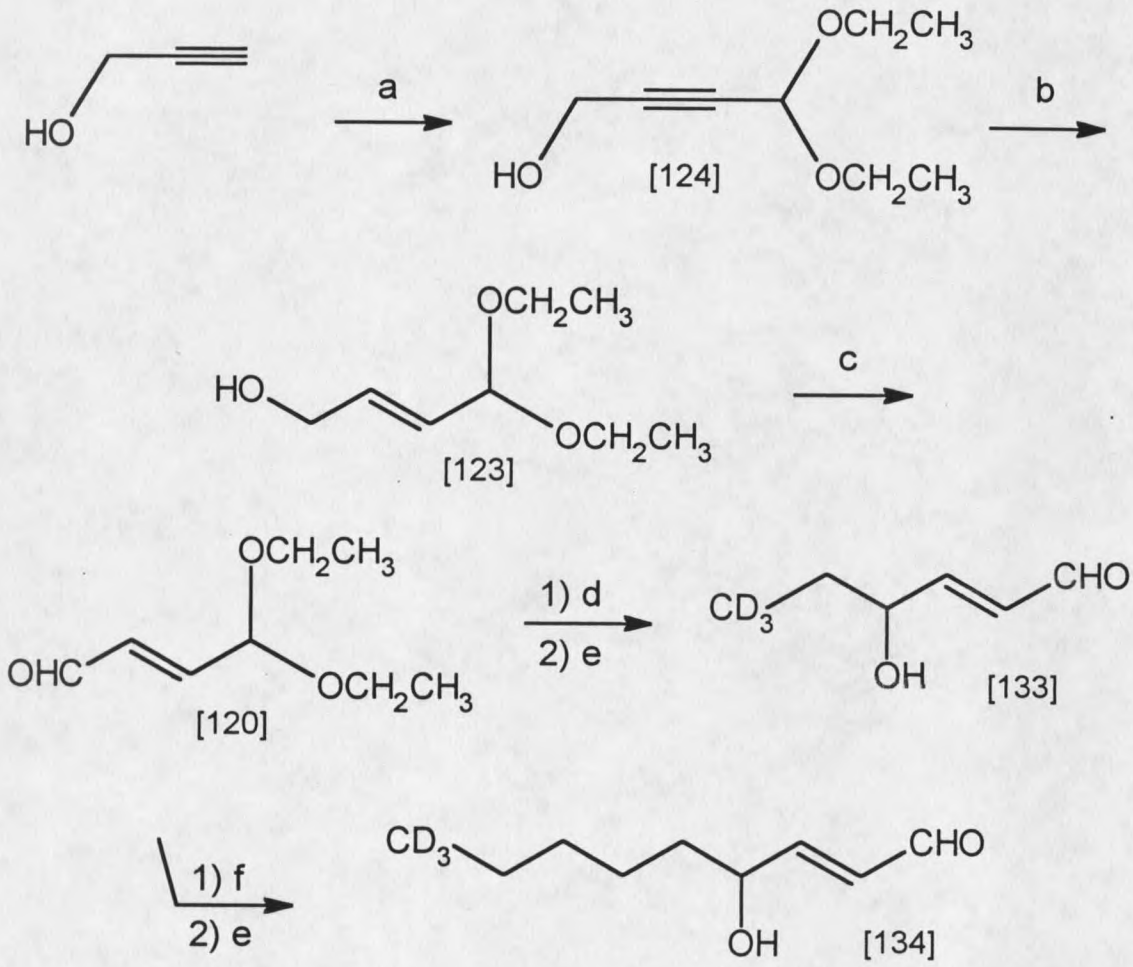
We currently possessed two proven approaches to make the labeled pentyl Grignards in small amounts. The crux of the recurring difficulties was in the small scale purification of these volatile compounds. A new issue forced us to adopt the fastest approach to get the compounds. This urgency was related to the eventual testing profile in rats. There were colonies of rats on special diets that were reaching the end of their life span. These standards were needed to prove a relationship between diet and disease in the geriatric rodents. The eventual solution was to purchase the labeled pentyl bromide directly from a newly available commercial source (MSD isotopes). The

labeled ethyl iodide remained from the earlier attempts to produce the pentyl Grignard. These Grignards would be coupled with the synthesized intermediate *trans*-4,4-diethylacetal-2-butenal, [120].

The issues involved with volatility and purity were major contributing factors that led to the problems in the synthesis of a labeled pentyl halide. In retrospect, the time and expense of trying to make the desired labeled pentyl halides was much greater than the cost to purchase the desired pentyl halide. The difficulties discussed here are very instructive on the unique aspects of synthetic isotope labeling that need to be addressed. While the proposed synthesis was theoretically sound, other factors unique to an isotope project eventually halted the momentum of the project.

The synthesis was easily completed with the required isotope labeled compounds at hand. The full synthesis follows the outline presented above and is shown in Figure 63. It began with a carbon alkylation of propargyl alcohol with triethylorthoformate to produce 1,1-diethoxy-2-butyn-4-ol.[62] The use of an orthoformate served the purpose of adding to the carbon skeleton an aldehyde pre-protected as the diethyl acetal. The yield of this alkylation is marginal because of the lower electrophilicity of the orthoformate and the competition between oxygen and carbon nucleophiles. The low yield is only tolerable because it is

used in the initial stages of the synthesis and it eliminates protection and deprotection sequence of the alcohol. The alkyne was then reduced stereospecifically to the *trans* alkene with $LiAlH_4$ in THF providing *trans*-1,1-diethoxy-2-butene-4-al, in high yield.[63] The alcohol was oxidized to the aldehyde, following the procedure of Swern.[64] This key intermediate, trans-4,4-diethylacetal-2-butenal, was treated with Grignard reagents produced from 2,2,2-trideuteroethyl iodide and 5,5,5-trideuteropentyl bromide, respectively. The resulting allylic alcohols were subjected to mild acid hydrolysis, without isolation of the acetals, to give the corresponding alkenals, *trans*-4-hydroxy-6,6,6-trideutero-2-hexenal, and *trans*-4-hydroxy-9,9,9-trideutero-2-nonenal, respectively.



a) EtMgBr, $HC(OEt)_3$ b) $LiAlH_4$ C) Swern Oxidation

d) CD_3CH_2MgI e) H_3O^+ f) $CD_3CH_2CH_2CH_2CH_2MgBr$

FIGURE 63. Synthesis of deuterated 4-hydroxyalkenals.

Synthesis of labeled 9-oxononanoate

The extended chain length of this target molecule provides numerous places to make disconnections in a retro-synthetic analysis. One of the first thoughts was to use an alkyne to provide the disconnection point and then use it for reductive insertion of labels. This would give the standard four deuterium labels positioned so they were unavailable for exchange. This required that the alkyne disconnection needed to be away from the functionalized terminal ends of the target molecule. There were therefore six possible sites for disconnection that were available as shown in Figure 64. We chose the middle point of

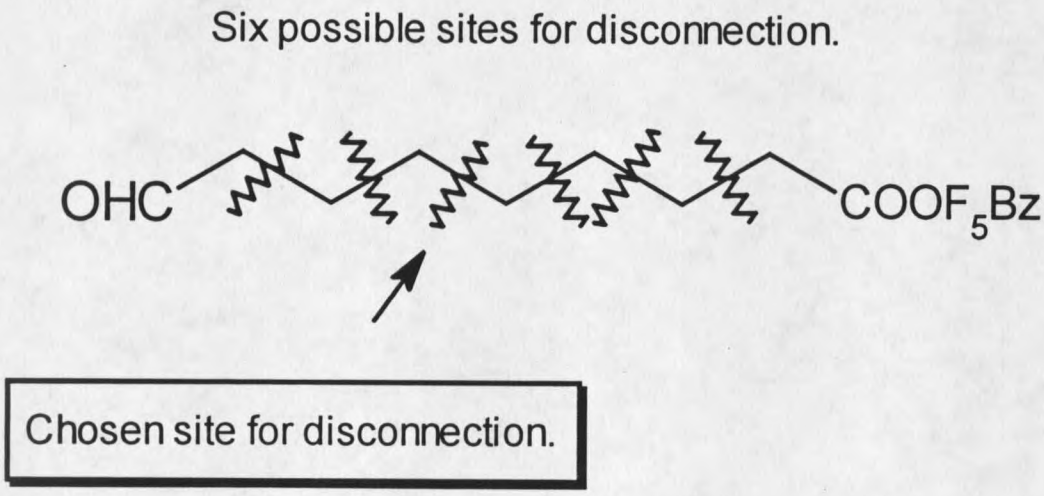


FIGURE 64. Possible disconnection sites.

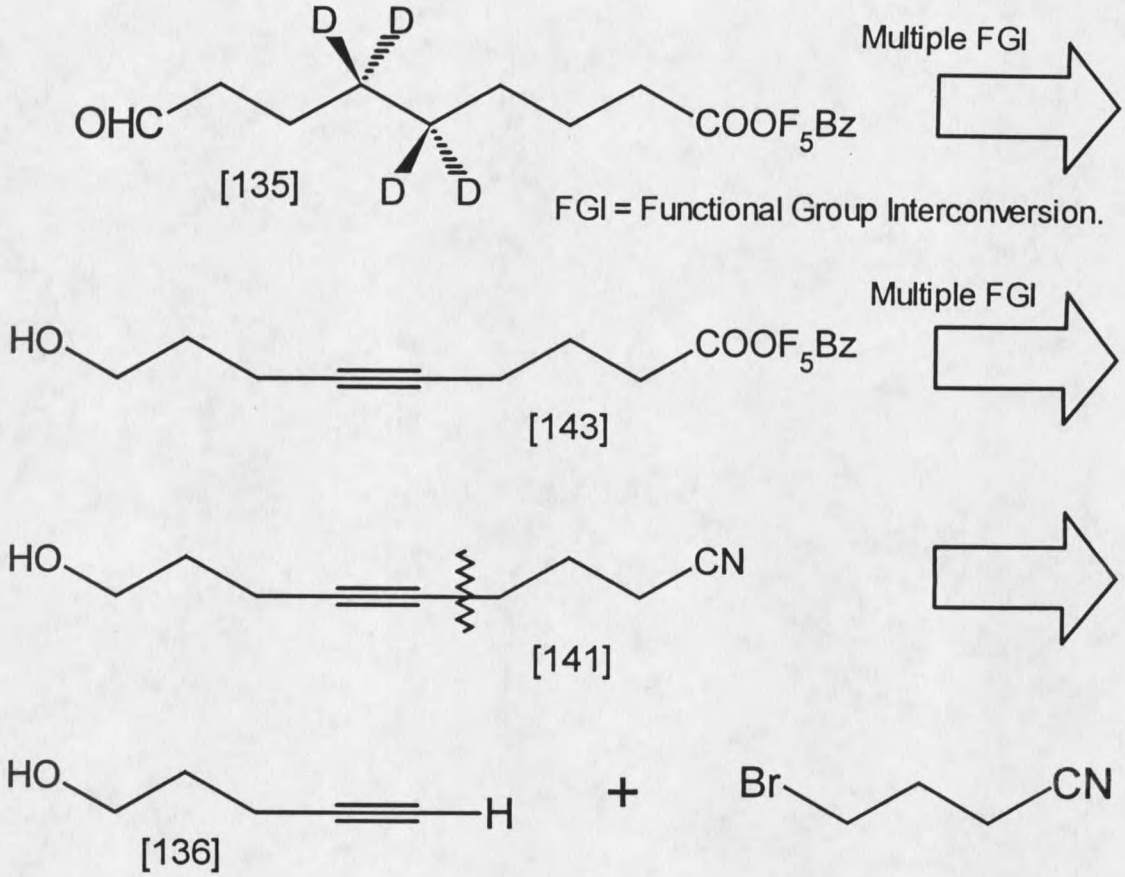


FIGURE 65. Retro-synthetic analysis of 9-oxononanoate.

disconnection because that would allow for two relatively large equal size pieces to work with. Therefore the standard of choice is perfluorobenzyl-5,5,6,6-tetradeutero-9-oxononanoate. Based on this decision, a retro-synthetic scheme was devised as shown in Figure 65. This scheme includes a few functional group conversions that would allow a degree of flexibility to solve any synthetic problems that might arise. The synthetic route required a carbon alkylation of 5-hydroxy-1-pentyne to provide one half of the

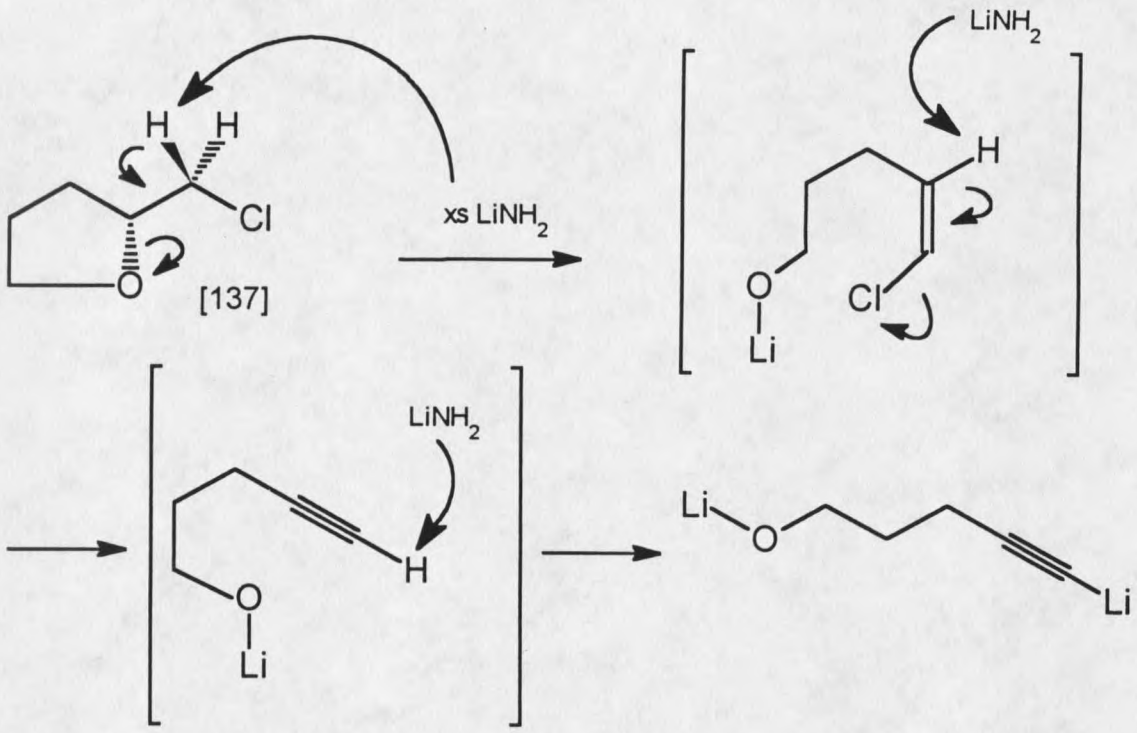


FIGURE 66. Unique approach to dianion of 5-hydroxy-1-pentyne.

basic skeletal framework. While the entry into this system could be accomplished in many ways, we investigated three of them. The first method uses a competitive alkylation of a 5-hydroxy-1-pentyne, [136], using a Grignard as the base. This is similar to the alkylation issues found in the synthesis of the 4-hydroxyalkenals.[65] In the second route, the alcohol is protected (a tetrahydropyranyl (THP) ether was chosen) and the carbon alkylation is performed in the normal fashion. The last approach is a generation of the dianion of the pentynol in-situ by a base mediated ring opening of tetrahydrofurfuryl chloride, [137].[66] This

unique method is shown in Figure 66. It worked relatively well, but is only applicable to production of 5-hydroxy-1-pentyne. All three methods proved effective; however, we chose the second option to protect the alcohol with a THP protecting group based on higher overall yield and the ease of conversion to other chain lengths.

Synthesis began with the protection of 5-hydroxy-1-pentyne as the THP ether, [138]. This protected alkyne was alkylated with *n*-Bu-Li in THF followed by addition of the electrophile, 3-bromopropionitrile. This reaction produced a host of unexpected products. We were unable to obtain the required nitrile as the major product even after experimenting with the conditions. On further inspection, it was concluded that these types of halo-nitriles are extremely poor electrophiles (Figure 67). The halide competes with the nitrile for the attention of the nucleophile. This produces the possibility of many different products. To solve this problem, another type of an electrophile was needed. An obvious choice was the 1,3-chloroiodopropane we had used in the 4-hydroxyalkenal synthesis previously described. The reaction was successfully repeated using 1,3-chloroiodopropane as the electrophile to give mostly 1-chloro-8-tetrahydropyranyloct-4-yne, [139], (although some of the iodo product was detected).[67] The halide products were not isolated, and were immediately subjected to mild acid hydrolysis to remove

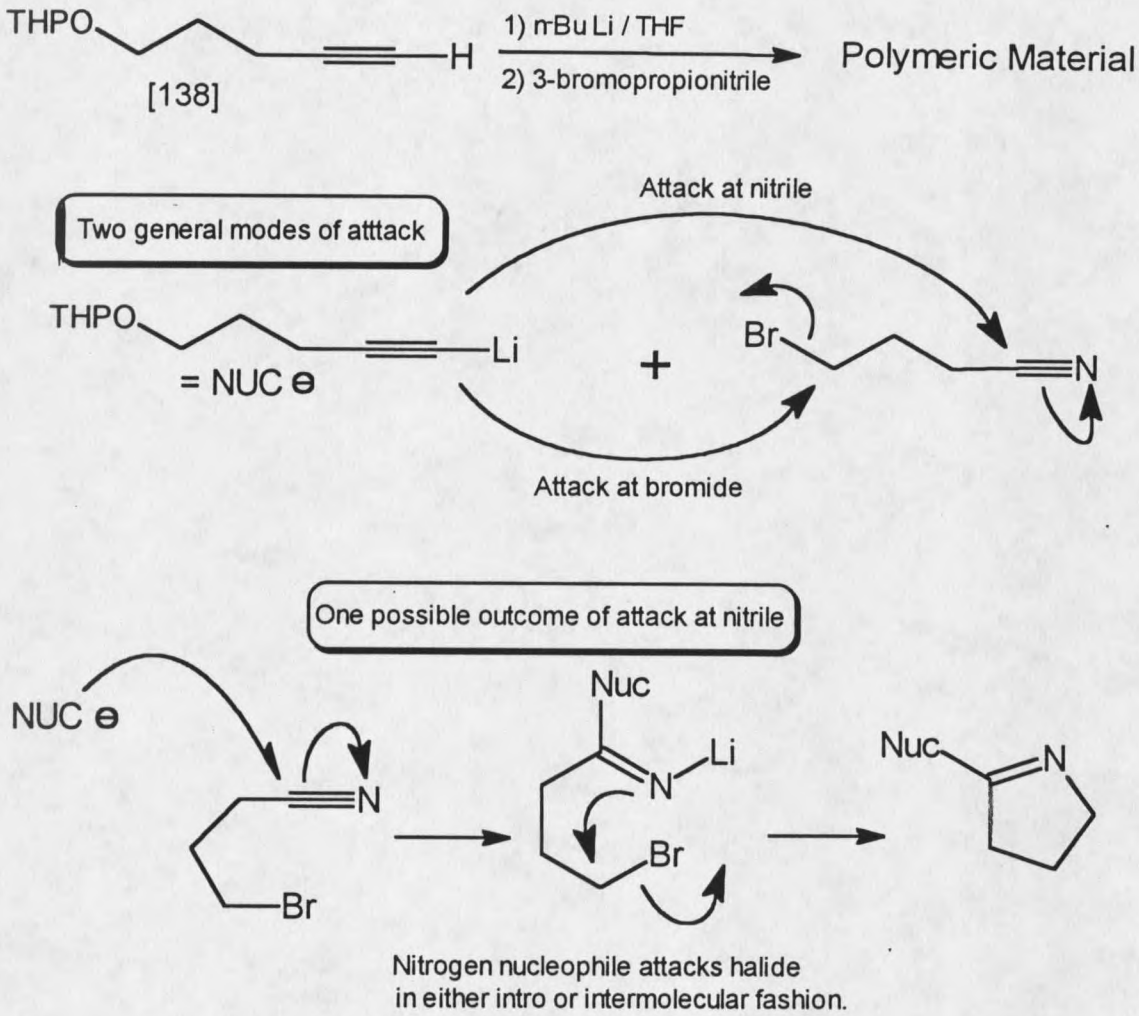
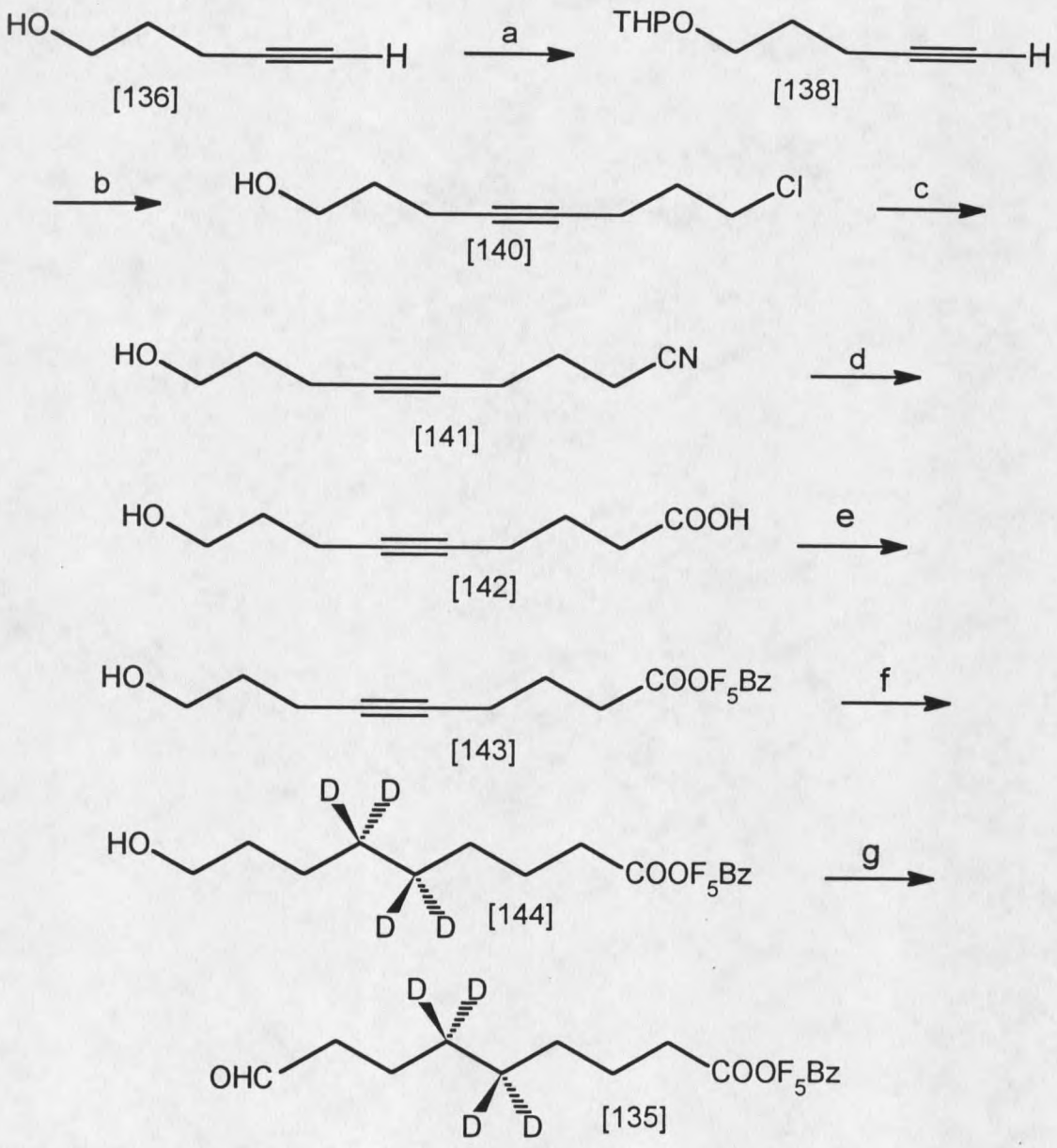


FIGURE 67. 3-bromopropionitrile as a electrophile.

the THP protecting group to give the alcohol, {140]. The carbon chain still needed one additional carbon unit to achieve the requisite nine carbons. We chose to convert the halide mixture to the nitrile using NaCN in DMSO[68] which smoothly give 8-hydroxynon-4-ynenitrile, [141]. An unexpected bonus of the nitration conditions was that any side products or impurities were removed by the harsh

conditions. The reaction gave essentially pure 8-hydroxynon-4-ynenitrile, [141], without any need for cleanup. An exhaustive basic hydrolysis provided 9-hydroxynon-4-yne carboxylic acid, [142], in reasonable yield. The acid was converted into a perfluorobenzyl ester in the presence of the alcohol to facilitate isolation and characterization by negative ion GC-MS. This step required the proper base selection to remove the proton from the acid without affecting the alcohol. Many bases were tried but sodium bicarbonate proved to be the most general choice. After refluxing the acid in THF with the bicarbonate, an excess of perfluorobenzyl bromide effected the esterification to make [143]. The perfluorobenzyl ester was selected as a synthetic target in this case, however the benzyl ester can be produced similarly and is used in actual tissue analysis. This stage of the synthesis offers the easiest route to introduction of the deuterium labels. The easiest method is to reduce the alkyne. While there are many methods to do this reduction, catalytic deuteration was chosen due to the high yields and ease of workup. The choice of the catalyst is critical to eliminate or reduce deuterium scrambling throughout the molecule. It is widely known that palladium is prone to deuterium scrambling, therefore the triple bond was selectively reduced using D_2 over platinum on carbon. This reduction was easily accomplished in the presence of the ester by using reduced

pressure (<2 ATM) and shorter reaction times. It is important that a highly deuterated alcohol is used as the solvent. Complete flushing of the Parr flask with nitrogen, then with deuterium gas is also needed. This step is critical to achieve a high rate of incorporation of the deuterium labels. The resulting alcohol, benzyl 9-hydroxy-5,5,6,6-tetradeuterononanoate, [144], is oxidized to the aldehyde with PCC. The final product, benzyl-5,5,6,6-tetradeutero-9-oxononanoate, [135], passes all available spectral tests and indicates greater than 90% isotope incorporation. All of the above synthetic procedures are shown in Figure 68.



a) DHP, H^+ b) n BuLi, HMPA/THF, $ICH_2CH_2CH_2Cl$; H_3O^+, THF c) NaCN, DMSO d) KOH, H_2O

e) $NaHCO_3$, F_5 Bz-Br f) D_2, 5% Pt/C g) PCC, CH_2Cl_2

FIGURE 68. Synthetic scheme for 9-oxononanoate.

Section Summary

The synthesis of the two terminally deuterated 4-hydroxyalkenals and 9-oxononanoate lipid peroxidation fragments was accomplished. The original plan for the synthesis was used as a framework and modified as needed in order to complete the synthesis. The major difficulties were encountered in handling and purification of labeled intermediates. Once these problems were solved, the synthesis was quickly completed. The target compounds have already been utilized in preliminary experiments in several projects as of this date. They turned out to work very well as internal standards for quantitative GC-MS analysis. In addition, we have received a number of requests for samples of the compounds to assist other research groups in their lipid peroxidation studies. It appears that these standards will help provide new insights into this fast growing and important research area.

CHAPTER 6

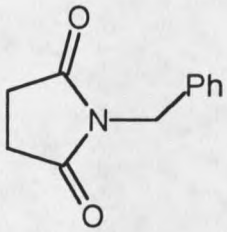
EXPERIMENTAL

Unless otherwise noted, reagents were obtained from commercial suppliers and were used without further purification. Diethyl ether and THF were distilled from sodium/benzophenone ketyl immediately before use. HMPA was distilled from CaH and stored over molecular sieves prior to use. All reactions using organometallic reagents were conducted under a dry Argon atmosphere with oven dried glassware. Gas chromatography was performed on a Perkin-Elmer 3920B equipped with a FID detector. A 15m Megabore DB-5 column from Suppelco was used with He carrier gas. Flash chromatography was performed with silica gel (grade 60) 230-400 mesh average particle size provided by Aldrich. The TLC plates used were aluminum backed, UV_{254}, 250 micron layer supplied by Whatman. NMR spectra were obtained on a Bruker AC-300 or Bruker AM-500 spectrometers with 5mm C/H dual probeheads. All ^{13}C spectra are reported as proton decoupled except where noted. High resolution (HR), electron impact (EI) and chemical ionization (CI) mass spectra were obtained on a VG 7070E-HF mass spectrometer. Calculations were performed using the TRIBL package on a Microvax and Vax mainframe cluster; also on the InsightII

Discover package on a Silicon Graphic Personal Iris workstation.

Propellane experimental

N-Benzylsuccinimide [22]:



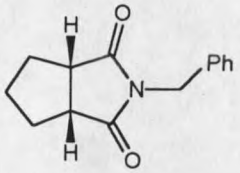
A mixture of succinimide, [20], (25.0 g), potassium carbonate (35.7 g), and phase transfer catalyst (Bu_4NBr 6.90 g) was placed in 100 mL of water. The stirred solution was heated until no solids remained. Benzyl chloride (100 mL) was added dropwise and the solution was heated at reflux temperature for 18 hours. Approximately 75.0 mL of the benzyl chloride layer was removed and replaced with fresh benzyl chloride. The reflux was continued for another 48 hours. The mixture was extracted with 75.0 mL of chloroform three times and combined with the 75 mL removed earlier. The combined organic material was washed with saturated brine and dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the excess benzyl chloride was distilled away on a Kugelrohr still. The crude solid was recrystallized from benzene to yield 42.1 g (91.7%) of the product.

m.p. 102-104° C (uncorrected). (Literature 101-103° C)[34]

^{1}H NMR: ($CDCl_3$) 2.68(4H,s); 4.64(2H,s); 7.27-7.29(3H,m); 7.36-7.39(2H,m).

^{13}C NMR: ($CDCl_3$) 28.17(t); 42.37(t); 128.0(d); 128.6(d); 128.9(d); 135.8(s); 176.8(s).

<u>*cis*-N-Benzyl-2,4-dioxo-3-azabicyclo[3.3.0]octane [23]:</u>



In a 100 mL three-neck round bottom flask with septa and stirbar under an argon atmosphere was placed 1.7 mL of diisopropyl amine and 40 mL of THF. The flask was chilled to 0° C and n-butyl lithium (4.9 mmoles) was added to make the LDA. The reaction was stirred in at 0° C for 30 minutes. After this time, the flask was chilled to -78° C, and the imide was added dropwise. The solution changed from the yellow LDA color to orange and eventually turned green. After the addition, the reaction was stirred for 15 minutes at the dry ice temperature. The electrophile, 1,3-dibromopropane (0.75 mL) was added slowly and the reaction was allowed to reach RT and stir overnight. The reaction was quenched by addition of 20 mL of 5% HCl followed by extraction three times with ether. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude mixture showed complex mixure by GLC. The product was isolated in only very low yield (<20%). Column chromatography on silica gel in 1:1 ether/

pet ether was used to purify the reaction product to obtain a sample for spectral characterization (yellow liquid).

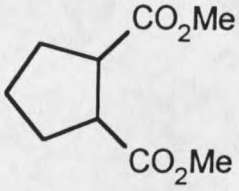
^{1}H NMR: ($CDCl_3$) 1.16-1.24(2H,m); 1.68-1.88(2H,m); 2.02-2.14(2H,m); 3.09-3.15(2H,m); 4.60(2H,s); 7.21-7.34(5H,m).

^{13}C NMR: ($CDCl_3$) 24.71(t); 30.42(t); 42.38(t); 45.14(d); 127.8(d); 128.4(d); 128.6(d); 136.0(s); 180.0(s).

General procedure for attempted dianion alkylation of dimethyl succinate:

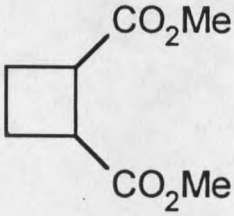
In a three neck flask with septa under an argon atmosphere was placed 2.0 mL of diisopropyl amine in 40 mL of THF. The flask was chilled in an ice bath to 0° C and n-butyl lithium (2.1 equivalents or 0.14 moles) was added. The solution was stirred for 30 minutes followed by a change in temperature to -78° C. The dimethyl succinate, [24], (1.0 g in 20 mL of THF) was added dropwise. The reaction was stirred for 15 minutes and 1.1 equivalents of 1,3-dibromopropane (0.76 mL for 5-membered ring formation) (or 1,2-dibromoethane for 4-membered rings) was added slowly. The reaction was allowed to slowly return to RT over a period of hours and stir overnight. The reaction was quenched with an addition of 5% HCl followed by three ether extractions. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The reaction was purified by washing through a dry column of silica gel with 1:1 EtOAc / hexane.

1,2-Dicarbomethoxycyclopentane[26]:



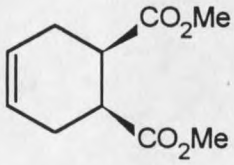
The above reaction yielded 0.50 g of a *cis* & *trans* product mixture (67% yield). Note: Complex isomeric mixtures preclude useful interpretation or integration values therefore no NMR will be reported.

1,2-Dicarbomethoxycyclobutane [27]:



Based on larger scale (10 g of succinate) the reaction is relative to example shown above. There were significant solubility problems of the product in organic solvents. The overall yield was 0.33 g of a *cis* & *trans* mixture (9.3%). Note: Complex isomeric mixtures preclude useful interpretation or integration values therefore no NMR will be reported.

3,4-dicarbomethoxycyclohexene [28]:



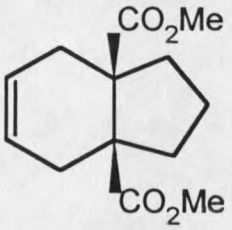
A five equivalent excess of anhydrous methanol with a few drops of concentrated HCl was refluxed with one equivalent of *cis*-1,2,3,6-tetrahydrophthalic anhydride for 24 plus hours. The reaction mixture was cooled to below the boiling point of methanol and molecular sieves (3 angstrom pore size) were added to absorb excess water. The reaction was heated to approximately 50° C (< than reflux

temperature) for a period of eight hours. The sieves were filtered away and the excess solvent was removed on a rotary evaporator to provide the monocyclic adduct in quantitative yield.

^{1}H NMR: ($CDCl_3$) 2.28-2.35(2H,m); 2.48-2.56(2H,m); 2.99-3.03(2H,m); 3.65(6H,s); 5.64(2H,s).

^{13}C NMR: ($CDCl_3$) 25.73(t); 39.73(t); 51.73(q); 125.1(d); 173.7(s).

<u>*cis*-1,6-Dicarbomethoxybicyclo[4.3.0]non-3-ene [29]:</u>



In a 1000 mL three-neck flask equipped with a stirbar, dropping funnel and septa under an argon atmosphere was placed approximately 700 mL of THF and 25.9 mL of diisopropyl amine. The flask was chilled in an ice bath to 0° C and 25.9 mL of 7.1M n-butyl lithium was added. The reaction was stirred for 30 minutes. At this time, the reaction was cooled to -78° C and 20.0 g of 3,4-dicarbomethoxycyclohexene, [28], dissolved in 50 mL of THF was added dropwise to the reaction. A red dianion color quickly developed. After the addition was complete, the reaction was stirred for 15 minutes. The temperature was changed to -10° C and stirred for 15 minutes. The viscosity of the reaction thickened after a few minutes. The electrophile, 1,3-dibromopropane (9.4 mL, 1.1 eq) in THF was added dropwise and the reaction was stirred 2.5 hours and

allowed to return to RT. The reaction was quenched with 5% HCl, extracted three times with diethyl ether and the ether extracts were combined and dried over $MgSO_4$. The solvent was removed via rotary evaporation. Distillation of the crude product (95-110 @0.8mmHg) yielded 18.4 g of product (76.6%).

^1H NMR: ($CDCl_3$,) 1.6-1.75(4H,m); 2.11-2.41(6H,m); 3.62(6H,s); 5.60 (2H,t, J=1.5Hz).

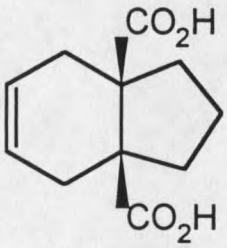
^{13}C NMR: ($CDCl_3$) 18.73(t); 31.74(t); 34.63(t); 51.70(q); 52.22(s); 123.32(d); 176.45(s).

MS: (EI) m/e 206; 178; 119(base); 91; 77; 59; 41.

MS: (CI,CH_4) m/e (% abundance): 239 ($M+H^+$,2); 207(100); 179(28); 119(35).

HRMS: (CI) m/e calculated for $C_{13}H_{19}O_4$ = 239.1283; found =239.1280

<u>*cis*-1,6-Dicarboxybicyclo[4.3.0]non-3-ene [30]:</u>



A sample of 12.0 g of crude *cis*-1,6-dicarbomethoxybicyclo[4.3.0]non-3-ene, [29], was placed in a round bottom flask with approximately 100 mL of a 10% aqueous KOH solution. The mixture was refluxed for 36 hours. The basic solution was extracted once with ether to remove any organic impurities. The remaining aqueous fraction was placed in an ice bath and acidified with

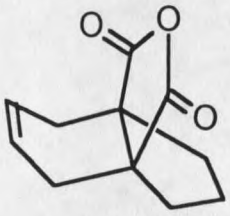
concentrated HCl to a pH of 2 by Hydrian paper. At this point, some of the acid product precipitated from the solution and was removed by filtration. The remaining aqueous layer was placed in a continuous liquid-liquid extractor with diethyl ether for 24 hours. The ether layer was separated and dried over $MgSO_4$. The solvent was removed by rotary evaporation to yield a total of 10.1 g of the bicyclic diacid (95.3%).

m.p. 161-164° C (uncorrected).

^1H NMR: (d6-DMSO) 1.51-1.69(4H,m); 2.05-2.50(6H,m); 5.56(2H,s); 11.99(2H,br s).

^{13}C NMR: (d6-DMSO) 18.24(t); 31.64(t); 34.64(t); 50.90(s); 123.3(d); 177.0(s).

<u>*cis*-1,6-Dicarboxytricyclo[4.3.3]dodec-3-ene anhydride [31]:</u>



An amount of *cis*-1,6-dicarboxybicyclo[4.3.0]non-3-ene, [30], (10.1 g) was placed in a two necked round bottom flask equipped with a stirbar and condenser. A small amount of THF (15 mL) was added to increase solubility. This solution was chilled to 0° C and excess $SOCl_2$ (approximately 100 mL) was added dropwise to keep the reaction from getting too warm. After the $SOCl_2$ addition was complete, the ice bath was replaced by a heating mantle and the reaction was refluxed overnight. The

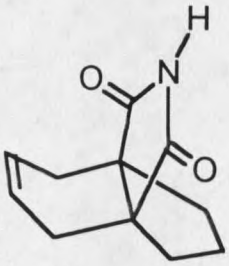
crude reaction mixture was placed on a rotary evaporator to remove any excess $SOCl_2$ or THF. The remaining yellow oil was placed on a high vacuum pump to remove any excess $SOCl_2$ to yield 9.17 g of anhydride (99.3%).

m.p. 118-121° C (uncorrected).

^1H NMR: ($CDCl_3$): 1.71-1.85(4H,m); 2.04-2.09(2H,dd); 2.35-2.43(2H,m); 2.72-2.79(2H,m); 5.97-5.99(2H,dt).

^{13}C NMR: ($CDCl_3$): 24.75(t); 31.05(t); 39.17(t); 57.17(s); 128.5(d); 177.3(s).

7,9-Dioxo-8-azatricyclo[4.3.3]dodec-3-ene [32]:



The anhydride, [31], (9.2) was placed in a small amount of CH_2Cl_2 (35 mL) in a 2 neck round bottom flask with a stirbar and a condenser. The contents of the flask were chilled to 0° C, and excess ammonium hydroxide (100 mL) was added slowly to keep the temperature less than 5° C. After the addition was complete, the ice bath was removed and the reaction was refluxed overnight. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$. The solvent was removed on a rotary evaporator to yield 7.7g of the imide (84%).

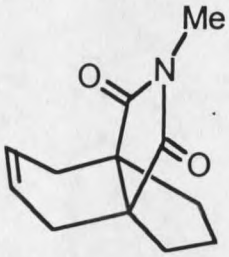
m.p. 162-163° C (uncorrected).

^1H NMR: ($CDCl_3$): 1.33-2.68(10H,m); 5.90-5.92(2H,m); 8.85(1H, br).

^{13}C NMR: ($CDCl_3$): 24.46(t); 30.96(t); 38.05(t); 57.19(s); 128.44(d); 182.90(s).

MS (EI,70Ev) m/e (% abundance): 191 (M^+,100), 148(42), 120(47),91(61), 65(9), 41(5)

HRMS (EI) m/e calculated for $C_{11}H_{13}O_2N$ = 191.0946; found = 191.0938



N-Methyl-7,9-dioxo-8-azatricyclo[4.3.3]dodec-3-ene [33]:

Potassium carbonate (8.7 g) was added to approximately 250 mL of THF. The mixture was brought to reflux and allowed to stir for 1 hour. The imide, [32], (7.7 g) was added, and the reaction was refluxed for 6-8 hours. After cooling to RT, 1.2 equivalents of methyl iodide (2.4 mL) were added slowly and the solution was again refluxed for 24 hours. Water was added to the milky yellow solution and the mixture was extracted three times with ether. The organic extracts were combined and dried over $MgSO_4$, the solvents were removed on a rotary evaporator to yield 6.2g (75%) of the N-methyl product.

m.p. 67-69° C (uncorrected).

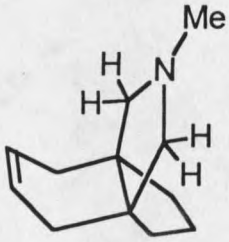
^1H NMR: ($CDCl_3$, 500Mhz) 1.23-1.27(1H,m); 1.57-1.64(2H,m); 1.67-1.70(1H,m); 1.99-2.02(2H,dd); 2.20-2.24(2H,m); 2.62-2.66(2H,dd); 2.92(3H,s); 5.85-5.87(2H,dd).

^{13}C NMR: ($CDCl_3$) 24.31(t); 25.08(q); 31.12(t); 37.94(t); 55.98(s); 128.5(d); 182.6(s).

MS: (EI 70Ev) m/e 205 base; 176; 162; 148; 120; 105; 91.

N-Methyl-8-azatricyclo[4.3.3]dodec-3-ene [34]:

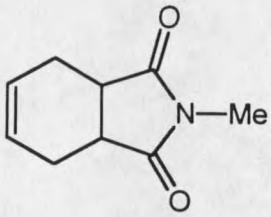
Lithium aluminumhydride (or deuteride) (1.9 g, 2.5 equivalents) was placed in dry THF in a round bottom flask equipped with a stirbar and condenser at 0° C under an argon atmosphere. The imide, [33], (4.2 g) was dissolved in THF and added dropwise to keep the reaction under control. After the addition, the reaction was removed from the ice bath and refluxed overnight. The reaction was chilled again to 0° C and a mixture of water and ether was added cautiously. The aluminum salts were filtered in a Büchner funnel and the remaining aqueous layer was extracted three times with diethyl ether. The organic extracts were combined and dried over $MgSO_4$, and the solvents were removed on a rotary evaporator to yield 3.4g (82%) of the N-methyl product.



^{1}H NMR: ($CDCl_3$) 1.39-1.59(6H,m); 1.91-1.95(2H,dd); 2.20(3H,s); 2.28-2.37(4H,dd); 5.80-5.82(2H,dd).

^{13}C NMR: ($CDCl_3$); 23.83(t); 34.15(t); 40.97(t); 42.21(t); 54.55(s); 70.97(t); 129.2(d).

N-Methyl-*cis*-1,2,3,6-tetrahydrophthalimide [35]:



Potassium carbonate (0.91 g) was added to approximately 50 mL of THF. The mixture was brought to reflux and allowed to stir for 1 hour. The imide, [21], (0.59 g) was added, and the reaction was refluxed 6-8 hours. After cooling to RT, 1.2 equivalents of methyl iodide (0.25 mL) was added slowly and the solution was again refluxed for 24 hours. Water was added to the milky yellow solution and the mixture was extracted three times with ether. The organic extracts were combined and dried over $MgSO_4$, the solvents were removed on a rotary evaporator to yield 0.54g (83%) of the crude product. Further purification (if needed) was accomplished by recrystallization in EtOAc / hexane.

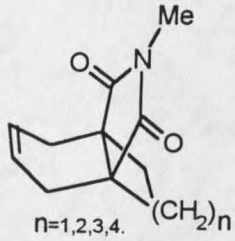
m.p. 68-71° C uncorrected.

^1H NMR: ($CDCl_3$) 2.17-2.23 (2H,m); 2.54-2.60 (2H,m); 2.92 (3H,s); 3.04-3.06 (2H,dd); 5.84-5.86 (2H,dd).

^{13}C NMR: ($CDCl_3$) 23.45(t); 24.92(q); 39.12(d); 127.73(d); 180.14(s).

MS: (EI 70Ev) m/e (abundance) 165(m+,100); 136(2); 80(9); 77(4).

General alkylation procedure to produce N-methyl-7,9-dioxo-8-azatricyclo[4.3.n.]alk-3-enes (where n=2-5).



In a round bottom flask equipped with a stirbar, dropping funnel and septa under an argon atmosphere was placed approximately 400 mL of THF and 9.2 mL of diisopropyl amine. The flask was chilled in an ice bath to 0° C and 9.3 mL of 7.2M (0.07 moles, 2.2 eq) n-butyl lithium was added. The reaction was stirred for 30 minutes. At this time, the reaction was cooled to -78° C and 5.0 g (1.0 eq) of N-methyl-*cis*-1,2,3,6-tetrahydrophthalimide dissolved in 50 mL of THF was added dropwise to the reaction. After the addition was complete, the reaction was stirred for 15 minutes. The temperature was changed to -10° C and stirred for 10 minutes. The viscosity of the reaction became much greater and the color changed to yellow brown after a few minutes. Sometimes a mechanical stirrer was used to stir the dianion during electrophile addition on large scale reactions. The electrophile, (1,3-dibromopropane in this case 3.4 mL or 1.1 eq) in THF was added dropwise and the reaction was stirred 2.5 hours while allowing the reaction to reach RT. The reaction was quenched with excess 5% HCl, extracted three times with diethyl ether and the ether extracts were combined and dried over $MgSO_4$. The solvent was removed via rotary evaporation. Smaller scale reactions (less than about 3.0 g) were purified via column chromatography (silica

gel 8:2 hexane\ EtOAc). Larger scale reactions were purified by vacuum distillation.

N-Methyl-7,9-dioxo-8-azatricyclo[4.3.2]undec-3-ene [36]:

Yield 53%.

m.p. = 55-57° C (uncorrected).

^{1}H NMR: ($CDCl_3$) 1.99-2.29(8H,m); 2.99(3H,s); 5.91-5.92(2H,dd).

^{13}C NMR: ($CDCl_3$) 25.03(q); 24.41(t); 27.81(t); 44.67(s); 126.3(d); 181.9(s).

MS: (EI 70Ev) m/e 191; 162(base); 134; 105; 91; 78.

N-Methyl-7,9-dioxo-8-azatricyclo[4.3.3]dodec-3-ene [37]:

Yield 60%.

m.p. = 67-69° C (uncorrected).

^{1}H NMR: ($CDCl_3$, 500Mhz) 1.23-1.27(1H,m); 1.57-1.64(2H,m); 1.67-1.70(1H,m); 1.99-2.02(2H,dd); 2.20-2.24(2H,m); 2.62-2.66(2H,dd); 2.92(3H,s); 5.85-5.87(2H,dd).

^{13}C NMR: ($CDCl_3$) 24.31(t); 25.08(q); 31.12(t); 37.94(t); 55.98(s); 128.5(d); 182.6(s).

MS: (EI 70Ev) m/e 205 base; 176; 162; 148; 120; 105; 91.

N-Methyl-7,9-dioxo-8-azatricyclo[4.3.4]tridec-3-ene [38]:

Yield 32%.

m.p. = 79-81° C (uncorrected).

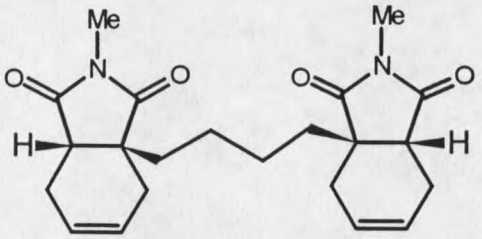
^1H NMR: ($CDCl_3$) 1.27-1.53(6H,m); 1.76-1.95(4H,m); 2.43-2.49(2H,m); 2.91(3H,s); 5.72(2H,dd).

^{13}C NMR: ($CDCl_3$) 19.16(t); 24.80(q); 30.22(t); 31.49(t); 47.33(s); 126.3(d); 182.6(s).

MS: (EI 70Ev) m/e 219(m+,base); 190; 176; 162; 134; 119; 105; 91; 77.

4 Carbon tether byproduct of above alkylation.

m.p. = 154-158° C (uncorrected).



^1H NMR: 1.10-1.12(2H,m); 1.30-1.34(2H,m); 1.52-1.75(4H,m); 1.84-1.90(2H,dd); 2.09-2.17(2H,m); 2.46-2.53(2H,m); 2.56-2.72(4H,m); 2.90(6H,m); 5.81-5.84(4H,dd).

^{13}C NMR: 24.08(t); 24.40(q); 24.86(t); 31.15(t); 37.40(t); 44.55(d); 48.38(s); 127.7(d); 127.9(d); 179.4(d); 182.2(d).

MS: (EI 70Ev) m/e 384; 298; 220; 178; 165(base); 91; 71.

N-Methyl-7,9-dioxo-8-azatricyclo[4.3.5]tetradec-3-ene [39]:

Yield 25%.

m.p. = 126-129° C (uncorrected).

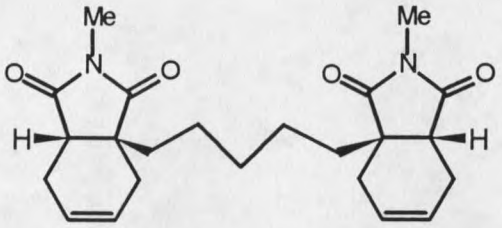
^1H NMR: ($CDCl_3$) 0.85-1.33(4H,m); 1.53-1.87(4H,m); 1.92-2.14(2H,m); 2.32-2.56(2H,m); 2.91(3H,s); 5.79(2H,m).

^{13}C NMR: ($CDCl_3$) 24.67(q); 26.25(t); 30.42(t); 34.77(t); 35.97(t); 53.21(s); 128.6(d); 182.7(s).

MS: (EI 70Ev) m/e 233(m+,base); 204; 178; 165; 162; 148; 133; 122; 105; 91; 79.

5 Carbon tether byproduct of above alkylation.

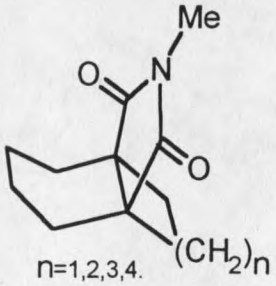
M.P. = 161-163° C



^{1}H NMR: 1.07-1.36(8H,m); 1.48-1.60(3H,m); 2.83-2.92(2H,d); 2.07-2.18(2H,m); 2.44-2.73(5H,m); 2.89(6H,s); 5.81-5.83(4H,dd).

^{13}C NMR: 24.05(t); 24.13(t); 24.87(q); 30.14(t); 31.09(t); 37.59(t); 44.58(d); 48.44(s); 127.7(d); 128.0(d); 179.5(s); 182.4(s);

General procedure for catalytic reduction of alkene for the propellane imide series.



An amount of anhydrous methanol was placed in a Parr® hydrogenation flask and a spatula tip (approximately 10 mg) of 5% Pt/C was added carefully. The imide (0.61 g of N-methyl-7,9-dioxo-8-azatricyclo[4.3.3]dodec-3-ene) was added and the flask was purged of air and put under 50 psi of H_2 pressure. The flask was shaken for 8 hours at RT. Vacuum filtration of the solid through a

Celite® pad on a medium fritted filter yielded 59 mg of pure alkane product (97%).

N-Methyl-7,9-dioxo-8-azatricyclo[4.3.2]undecane [44]:

Yield 94%.

Dark yellow liquid.

^{1}H NMR: ($CDCl_3$) 1.17-1.27(2H,m); 1.44-1.53(2H,m); 1.62-1.71(2H,m); 1.83-1.93(2H,m); 2.05-2.15(4H,dd); 2.97(3H,s).

^{13}C NMR: ($CDCl_3$) 23.83(t); 27.63(q); 29.98(t); 30.29(t); 47.44(s); 184.8(s).

MS: (EI 70Ev) m/e 193; 165; 152; 108(base); 93; 79.

N-Methyl-7,9-dioxo-8-azatricyclo[4.3.3]dodecane [45]:

Yield 97%.

Dark yellow liquid.

^{1}H NMR: ($CDCl_3$,) 1.22-1.28(4H,m); 1.43-1.73(6H,m); 1.96-2.02(2H,m); 2.10-2.17(2H,m).

^{13}C NMR: ($CDCl_3$) 18.15(t); 23.70(t); 24.93(q); 28.20(t); 37.36(t); 54.05(s).

MS: (EI 70Ev) m/e 207; 179; 166; 150; 122(base); 107; 93; 79.

N-Methyl-7,9-dioxo-8-azatricyclo[4.3.4]tridecane [46]:

Yield quantitative.

Dark yellow liquid.

^{1}H NMR: ($CDCl_3$) 1.33-1.66(16H,m); 2.92(3H,s).

^{13}C NMR: ($CDCl_3$) 22.02(t); 24.66(q); 31.12(t); 47.17(s); 182.5(s).

MS: (EI 70Ev) m/e 221(m+,base); 192; 179; 167; 136; 121; 107; 94; 79.

N-methyl-7,9-dioxo-8-azatricyclo[4.3.5.]tetradecane [47]:

Yield quantitative.

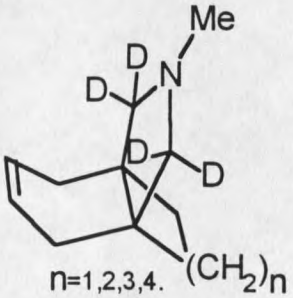
m.p. 83-85° C. (uncorrected).

^{1}H NMR: ($CDCl_3$) 0.98-1.12(6H,m); 1.42-1.67(10H,m); 1.89-1.94(2H,m); 2.93(3H,s);

^{13}C NMR: ($CDCl_3$) 16.63(t); 24.33(q); 25.80(t); 30.20(t); 30.92(t); 36.47(t); 51.73(s); 183.2(s).

MS: (EI 70Ev) m/e 235(m+); 192; 180; 167(base); 135; 139; 121; 107; 91; 79.

General procedure for imide reduction to amines for propellane series using lithium aluminum deuteride.



Lithium aluminum deuteride (2.5 equivalents) was placed in dry THF in a round bottom flask equipped with a stirbar and condenser at 0° C under an argon atmosphere. The imide (1 equivalent) was dissolved in THF and added dropwise to keep the reaction under control. After the addition, the reaction was removed from the ice bath and refluxed

overnight. The reaction was chilled again to 0° C and a mixture of water and ether was added cautiously. The aluminum salts were filtered and the remaining aqueous layer was extracted three times with diethyl ether. The organic extracts were combined and dried over $MgSO_4$, the solvents were removed on a rotary evaporator to give the N-methyl amine product.

N-Methyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.2]undec-3-ene [40]:

Yield 96%.

^1H NMR: ($CDCl_3$) 1.56-1.60(2H,m); 1.78-1.84(4H,m); 2.01-2.08(2H,m); 2.34(3H,s); 5.91-5.93(2H,m).

^{13}C NMR: ($CDCl_3$) 28.92(t); 32.62(t); 42.54(q); 46.28(s); 128.0(d).

MS: (EI 70Ev) m/e 167; 139; 125; 109; 97; 93; 85; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{11}H_{13}D_4N$ = 167.1612 ; found = 167.1601

N-Methyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.3]dodec-3-ene [41]:

Yield 86%.

^1H NMR: ($CDCl_3$,) 1.35-1.58(6H,m); 1.89-1.92(2H,dd); 1.99-2.02(2H,dd); 2.18(3H,s); 5.79(2H,dd).

^{13}C NMR: ($CDCl_3$) 23.81(t); 34.05(t); 40.86(t); 42.10(q); 54.31(s); 129.2(d).

MS: (EI 70Ev) m/e 181; 151; 140; 125; 109; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{12}H_{15}D_4N$ = 181.1769 ; found = 181.1768

N-Methyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.4]tridec-3-ene [42]:

Yield 78%.

^1H NMR: ($CDCl_3$) 1.16-1.51(8H,m); 1.81-1.93(4H,m); 2.47(3H,s); 5.52(2H,s).

^{13}C NMR: ($CDCl_3$) 22.24(t); 32.25(t); 32.86(t); 41.26(q); 44.84(s); 64.86(t,Br); 124.0(d).

MS: (EI 70Ev) m/e 195; 180; 150; 139; 120; 189; 97; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{13}H_{17}D_4N$ = 195.1925 ; found = 195.1918

N-Methyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.5]tetradec-3-ene [43]:

Yield quantitative.

^1H NMR: ($CDCl_3$) 1.43-1.51(8H,m); 1.64-1.81(6H,m); 1.90-1.95(2H,m); 2.13(3H,s); 5.87-5.89(2H,m).

^{13}C NMR: ($CDCl_3$) 25.08(t); 29.70(t); 35.64(t); 41.41(t); 42.35(q); 49.50(s); 129.6(s).

MS: (EI 70Ev) m/e 209; 180; 166; 153; 140; 122; 97; 85; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{14}H_{19}D_4N$ = 209.2082 ; found = 209.2081

N-Methyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.2]undecane [48]:

Yield 64%.

^1H NMR: ($CDCl_3$) 1.37-1.55(8H,m); 1.76-1.83(4H,m); 2.36(3H,m).

^{13}C NMR: ($CDCl_3$) 19.86(t); 28.40(t); 31.69(t); 42.44(q); 44.23(s).

MS: (EI 70Ev) m/e 169; 139; 97; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{11}H_{15}D_4N$ = 169.1769 ; found = 169.1770

N-Methyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.3]dodecane [49]:

Yield 78%.

^1H NMR: ($CDCl_3$,) 1.18-1.64(14H,m); 2.23(3H,s).

^{13}C NMR: ($CDCl_3$) 18.30(t); 22.78(t); 30.53(t); 38.09(t); 42.82(q); 50.39(s).

MS: (EI 70Ev) m/e 183; 97; 93; 84; 67; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{12}H_{17}D_4N$ = 183.1925 ; found = 183.1915

N-Methyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.4]tridecane [50]:

Yield 96%.

^{1}H NMR: ($CDCl_3$) 1.38(16H,m); 2.76(3H,s).

^{13}C NMR: ($CDCl_3$) 21.10(t); 30.62(t); 42.47(q); 44.39(s); 62.98(t,Br).

MS: (EI 70Ev) m/e 197; 182; 166; 139; 111; 97; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{13}H_{19}D_4N$ = 197.2082 ; found = 197.2075

N-Methyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.5]tetradecane [51]:

Yield 90%.

^{1}H NMR: ($CDCl_3$) 1.22-1.58(18H,m); 2.30(3H,s).

^{13}C NMR: ($CDCl_3$) 18.96(t); 23.56(t); 30.02(t); 33.06(t); 38.90(t); 43.44(q); 45.98(s).

MS: (EI 70Ev) m/e 211; 196; 182; 167; 153; 139; 123; 97; 81; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{14}H_{21}D_4N$ = 211.2238 ; found = 211.2232

General procedure for quaternization (Menschutkin reaction) of propellane amines.

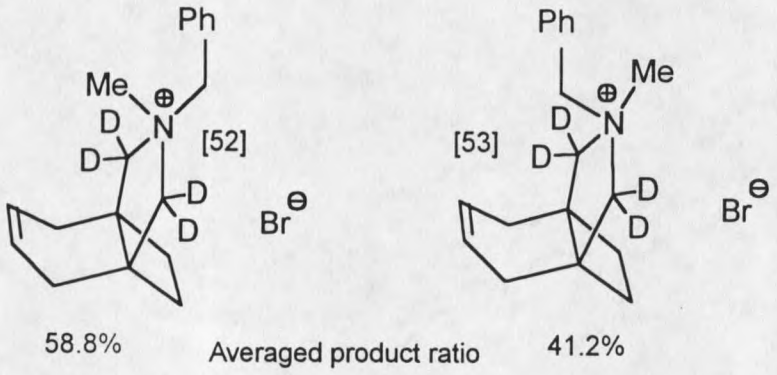
The α-tetradeutero propellane amine (0.10 mg) was dissolved with stirring in 2 mL of dry diethyl ether. To this

solution was added an excess amount (approximately 3 eq. or 0.21 mL) of trideuteromethyl iodide (or 0.39 mL of benzyl bromide). The reaction was stirred overnight at RT. Pentane was added to fully precipitate all of the salt produced during the reaction. The salt was filtered by a medium fritted filter, washed with pentane, and dried in the air.

Note: The following data is from a isomer mixture of salts. The integration values rounded off to nearest whole integer. The data is reported without modification or adjustments regarding the total number of carbon and proton peaks, etc.

N-Methyl-N-benzyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.2]undec-3-ene ammonium salt isomer mixture

Yield 70%.



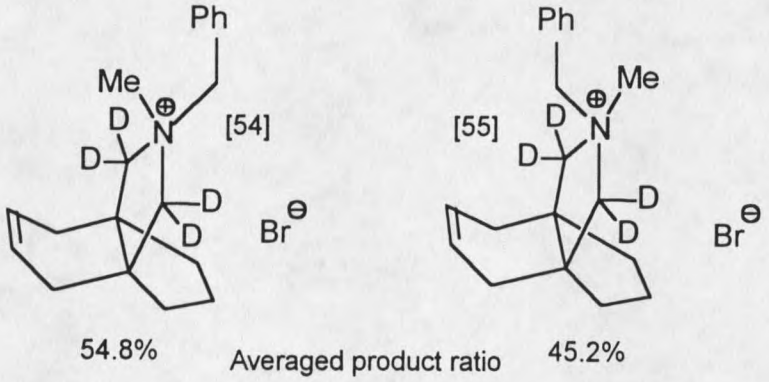
^{1}H NMR: ($CDCl_3$) 1.68-1.72(2H,m); 1.97-2.07(3H,m); 2.20-2.32(2H,m); 3.11(2H,s); 3.55(1H,s); 5.29(2H,m); 5.39(1H,m); 5.39(1H,m); 5.89-5.90(1H,m); 5.95-5.96(1H,m); 7.33-7.38(3H,m); 7.70-7.75(2H,m).

^{13}C NMR: ($CDCl_3$) 27.76,29.46(t); 32.85,34.28(t); 44.29,47.06(s); 49.50,50.13(q); 66.81,69.40(t); 126.4,127.4(d); 128.6(s); 130.3(d); 128.7,138.9(d).

MS: (Electrospray) m/e 258 for cationic species (less Br^-).

N-Methyl-N-benzyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.3]dodec-3-ene ammonium salt isomer mixture

Yield 79%.



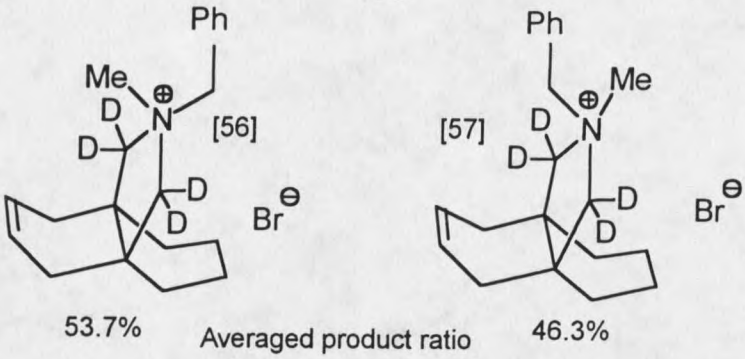
^1H NMR: ($CDCl_3$,) 1.68-2.25(20H,m); 3.40(3H,s); 3.48(3H,s); 4.99(2H,s); 5.30(2H,s); 5.83(4H,m); 7.35-7.39(5H,m); 7.58-7.75(4H,dd).

^{13}C NMR: ($CDCl_3$) 22.36,24.68(t); 33.94,34.88(t); 42.08,42.24(t); 50.50,51.37(q); 52.43,54.79(s); 68.28,68.74(t); 128.0,128.3(d); 129.0,129.1(d); 130.4,130.6(s); 133.0,133.1(d).

MS: (Electrospray) m/e 272 for cationic species (less Br^-).

N-Methyl-N-benzyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.4]tridec-3-ene ammonium salt isomer mixture

Yield 76%.



^{1}H NMR: ($CDCl_3$) 1.51-1.53(8H,m); 1.65-1.70(4H,m); 2.14(4H,s); 2.19(4H,s); 3.58(3H,s); 3.65(3H,s); 5.22(2H,s); 5.31(2H,s); 5.62(2H,s); 5.68(2H,s); 7.41-7.46(6H,m); 7.60-7.66(4H,dd).

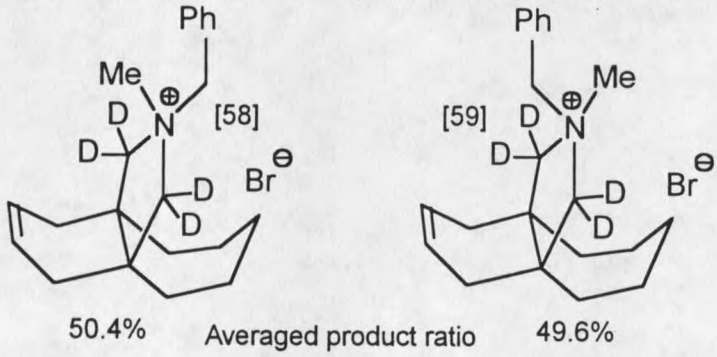
^{13}C NMR: ($CDCl_3$) 21.46,21.63(t); 32.16,32.38(t); 32.69,33.00(t); 41.69,41.76(t); 56.26(q); 72.41-72.71(t); 123.1(d); 128.4,128.5(s); 129.2(d); 130.7(d); 133.0,133.1(d).

MS: (Electrospray) m/e 286 for cationic species (less Br^-).

<u>N-Methyl-N-benzyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.5]tetradec-3-ene ammonium salt isomer mixture</u>

Yield 54%.

^{1}H NMR: ($CDCl_3$) 1.48-2.30(14H,m); 3.29(3H,s); 3.59(3H,m);



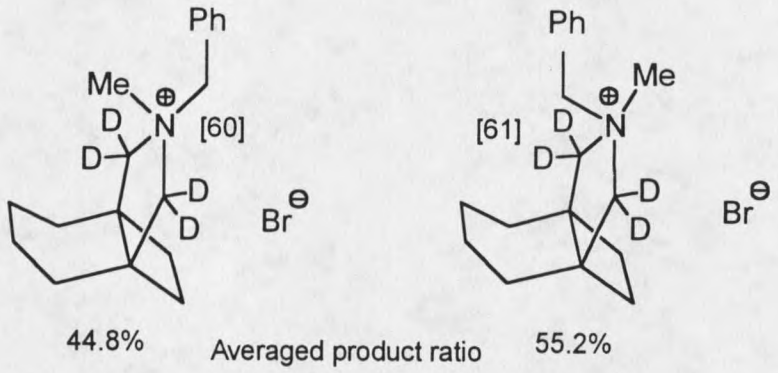
4.96(2H,s); 5.27(2H,s); 5.89-5.90(2H,dd); 6.02-6.03(2H,dd); 7.38-7.43(2H,m); 7.59-7.71(2H,m).

^{13}C NMR: ($CDCl_3$) 24.51,25.30(t); 30.92,31.47(t); 33.34,34.35(t); 41.36,42.00(t); 50.09,50.37(t); 51.76,52.14(q; 67.78,69.75(t); 127.9,128.3(s); 129.1,129.3(d); 129.9(d); 13.6,130.7(d); 133.0,133.2(d).

MS: (Electrospray) m/e 300 for cationic species (less Br^-).

N-Methyl-N-benzyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.2]undecane ammonium salt isomer mixture

Yield 48%.



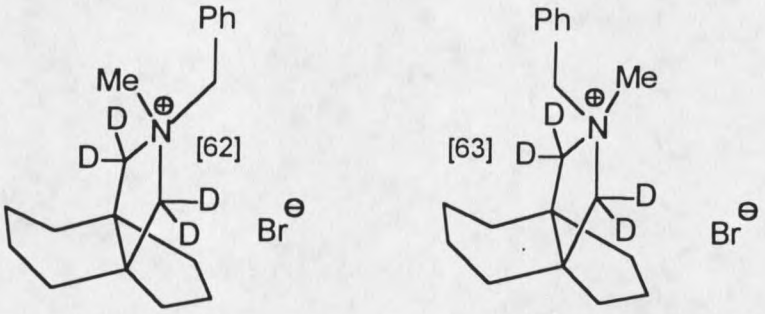
^1H NMR: ($CDCl_3$) 1.41-1.67(12H,m); 1.87-2.08(12H,m); 3.39(3H,s); 3.62(3H,s); 5.21(2H,s); 5.36(2H,s); 7.37-7.42(6H,m); 7.67-7.79(4H,m).

^{13}C NMR: ($CDCl_3$) 18.10,20.08(t); 26.80,27.80(t); 30.29,31.94(t); 44.84,45.40(s); 52.64,53.14(q); 68.78,69.61(t); 128.6,128.8(s); 129.1,133.2(d); 130.5,130.6(d).

MS: (Electrospray) m/e 260 for cationic species (less Br^-).

N-Methyl-N-benzyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.3]dodecane ammonium salt isomer mixture

Yield 55%.



52.2% Averaged product ratio 47.8%

^{1}H NMR: ($CDCl_3$,) 1.48-1.85(28H,m); 3.57(3H,s); 3.60(3H,s); 5.22(2H,s); 5.24(2H,s); 7.42-7.46(4H,s); 7.66-7.70(6H,s).

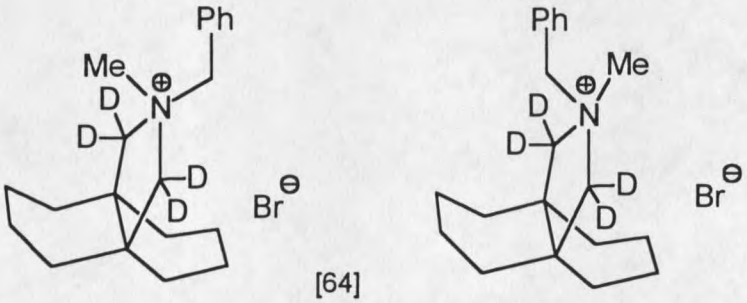
^{13}C NMR: ($CDCl_3$) 18.41,20.10(t); 21.33,21.68(t); 31.12(t); 36.77,37.35(t); 51.10,51.51(q); 54.40,55.50(s); 71.36,71.61(t); 128.5(d); 129.3(d); 130.8(s); 133.2(d).

MS: (Electrospray) m/e 274 for cationic species (less Br^-).

N-Methyl-N-benzyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.4]tridecane ammonium salt isomer mixture

Yield

60%.



[64]

Only one peak NO RATIO

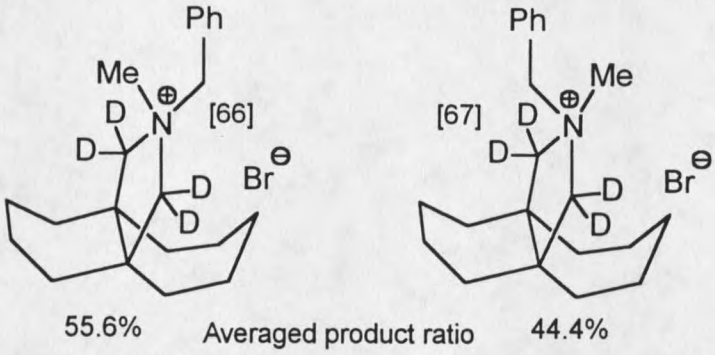
^{1}H NMR: ($CDCl_3$) 1.51-1.64(16H,m); 3.66(3H,s); 5.31(2H,s); 7.42-7.45(3H,m); 7.64-7.67(2H,m).

^{13}C NMR: ($CDCl_3$) 21.36(t); 31.57(t); 43.08(t); 56.82(q); 61.26(s); 72.98(t); 128.7(s); 129.3(d); 130.8(d); 133.2(d).

MS: (Electrospray) m/e 288 for cationic species (less Br^-).

N-Methyl-N-benzyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.5]tetradecane ammonium salt isomer mixture

Yield 76%.

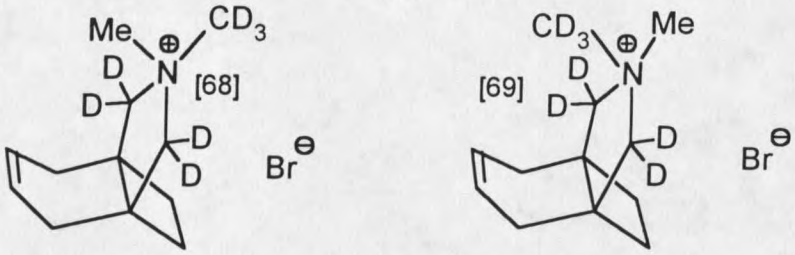


^{1}H NMR: ($CDCl_3$) 1.39-1.85(18H,m); 3.60(3H,s); 3.63(3H,s); 5.23(2H,s); 7.40-7.42(3H,m); 7.62-7.67(3H,m).

^{13}C NMR: ($CDCl_3$) 19.83,20.79(t); 21.11,21.68(t); 26.60,27.49(t); 31.20,32.00(t); 36.09,37.34(t); 46.69,46.86(s); 55.96,56.21(q); 71.84,72.27(t); 128.5(s); 129.2(d); 130.7(d); 133.2(d).

MS: (Electrospray) m/e 302 for cationic species (less Br^-).

N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.2]undec-3-ene ammonium salt isomer mixture



76.3% Averaged product ratio 23.7%

Yield 75%.

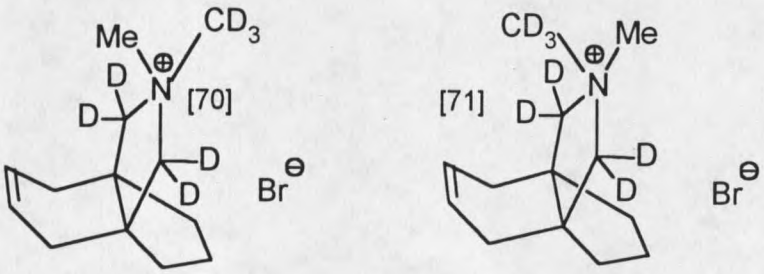
^{1}H NMR: ($CDCl_3$) 1.76-1.82(2H,dd); 2015-2.22(6H,m); 3.53(2H,s); 3.76(1H,s); 5.99-6.0(2H,dd).

^{13}C NMR: ($CDCl_3$) 28.46(t); 33.39(t); 46.79(s); 54.00(q); 55.54(q); 127.0(d).

MS: (Electrospray) m/e 185 for cationic species (less I^-).

<u>N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.3]dodec-3-ene ammonium salt isomer mixture</u>

Yield 76%.



39.1% Averaged product ratio 60.9%

^{1}H NMR: ($CDCl_3$,) 1.55-1.60(4H,m); 1.68-1.78(4H,m); 1.87-1.91(4H,m); 2.16-2.25(8H,m); 3.57(3H,s); 3.67(3H,s); 5.92-5.93(4H,m).

^{13}C NMR: ($CDCl_3$) 23.53(t); 34.25(t); 41.78(t); 54.26(s); 55.24(q); 55.76(q); 128.4(d).

MS: (Electrospray) m/e 199 for cationic species (less I^-).

X-ray Structure Determinations: (CH_3 salt [81])

$[C_{13}H_{22}N]I$ crystal data: FW = 319.2, monoclinic, space group $P2_1/c$, a = 14.847(2) Å, b = 7.287(1) Å, c = 13.486(2) Å, _ = _ = 90 °, ß = 109.74(1) °, V = 1373.3(3) $Å^3$, Z = 4, D_{calc} = 1.54 g/cm^3, T = 25 °C, radiation MoK_ (_ = 0.71069 Å), μ = 22.8 cm^{-1}, R = 0.061, R_W = 0.069, S = 1.20, 137 parameters. Intensity data were taken as omega scans on a Nicolet R3mE four-circle diffractometer for 3989 unique reflections in the range 3° < 2_ < 60 °, of which 1973 with I > 3_(I) were used for structure solution and refinement. The data were corrected for Lorentz and polarization effects and for absorption by Gaussian integration (transmission factor range 0.291 to 0.656). The structure was solved from a Patterson synthesis for the iodine position. Non-hydrogen atoms were refined by block-cascade least-squares with anisotropic thermal parameters, using statistical weighting[1]. Calculated hydrogen positions were used with a common refined thermal parameter. Methyl group orientations were determined from a difference map. Five reflections showing significant extinction were eliminated from the data set for the final cycles of refinement.

(1) Crystallographic calculations were done with the **SHELXTL** program package by G. M. Sheldrick; Siemens Analytical X-Ray Instruments, Inc.: Madison, WI.

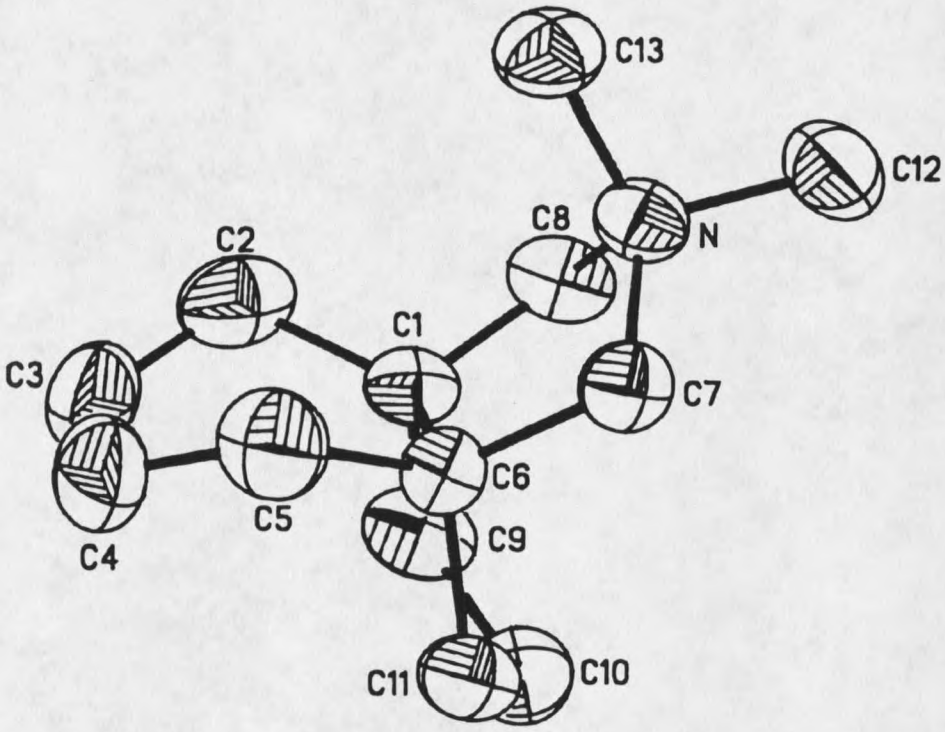


Table 11. $[C_{13}H_{22}N]I$ Positional Coordinates and Isotropic Thermal Parameters (Å^2) with Standard Deviations in Parentheses

	x/a	y/b	z/c	U
I	0.88484(4)	0.25068(6)	0.26019(4)	0.0635(2)
C(1)	0.6773(5)	0.698(1)	0.3883(5)	0.046(2)
C(2)	0.6144(5)	0.855(1)	0.4070(7)	0.073(3)
C(3)	0.5583(7)	0.794(1)	0.472(1)	0.088(5)
C(4)	0.5971(7)	0.690(1)	0.556(1)	0.078(4)
C(5)	0.6991(5)	0.643(1)	0.5857(5)	0.063(3)

C(6)	0.7245(4)	0.5762(7)	0.4898(4)	0.039(2)
C(7)	0.8319(4)	0.583(1)	0.5061(5)	0.047(2)
N	0.8488(4)	0.7501(6)	0.4500(4)	0.047(2)
C(8)	0.7602(5)	0.755(8)	0.3547(5)	0.055(2)
C(9)	0.6121(5)	0.560(1)	0.3082(5)	0.065(3)
C(10)	0.6544(5)	0.371(1)	0.3425(6)	0.068(3)
C(11)	0.6849(4)	0.381(1)	0.4600(5)	0.054(2)
C(12)	0.9362(6)	0.732(1)	0.418(1)	0.069(3)
C(13)	0.8619(5)	0.920(1)	0.5167(5)	0.057(3)

Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

Table 12. $[C_{13}H_{22}N]I$ Bond Lengths (Å)

C(1)-C(2)	1.55(1)	C(1)-C(6)	1.58(1)	C(1)-C(8)	1.51(1)
C(1)-C(9)	1.56(1)	C(2)-C(3)	1.47(2)	C(3)-C(4)	1.32(2)
C(4)-C(5)	1.47(1)	C(5)-C(6)	1.54(1)	C(6)-C(7)	1.54(1)
C(6)-C(11)	1.54(1)	N-C(7)	1.50(1)	N-C(8)	1.50(1)
N-C(12)	1.50(1)	N-C(13)	1.50(1)	C(9)-C(10)	1.52(1)
C(10)-C(11)	1.50(1)				

Table 13. $[C_{13}H_{22}N]I$ Bond Angles (°)

C(2)-C(1)-C(6)	112.9(6)	C(2)-C(1)-C(8)	116.3(6)
C(6)-C(1)-C(8)	104.3(5)	C(2)-C(1)-C(9)	108.9(5)
C(6)-C(1)-C(9)	103.1(5)	C(8)-C(1)-C(9)	110.5(6)

C(1)-C(2)-C(3)	111.6(7)	C(2)-C(3)-C(4)	121(1)
C(3)-C(4)-C(5)	119(1)	C(4)-C(5)-C(6)	111.3(6)
C(1)-C(6)-C(5)	112.7(5)	C(1)-C(6)-C(7)	104.0(5)
C(5)-C(6)-C(7)	114.0(5)	C(1)-C(6)-C(11)	106.0(4)
C(5)-C(6)-C(11)	109.2(6)	C(7)-C(6)-C(11)	110.5(5)
C(6)-C(7)-N	107.2(4)	C(7)-N-C(8)	101.8(4)
C(7)-N-C(12)	112.2(5)	C(8)-N-C(12)	110.6(6)
C(7)-N-C(13)	107.1(5)	C(1)-C(8)-N	107.8(6)
C(1)-C(9)-C(10)	106.3(5)	C(9)-C(10)-C(11)	103.1(6)
C(6)-C(11)-C(10)	105.8(5)		

Table 14. $[C_{13}H_{22}N]I$ Anisotropic Thermal Parameters ($Å^2$)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I	0.0736(4)	0.0664(3)	0.0497(3)	-.0133(2)	0.0197(2)	-.0050(2)
C(1)	0.042(3)	0.046(3)	0.039(3)	0.001(2)	0.000(2)	-.006(2)
C(2)	0.059(4)	0.054(4)	0.087(6)	0.007(4)	-.002(4)	0.006(3)
C(3)	0.062(5)	0.076(6)	0.13(1)	-.026(6)	0.041(6)	0.007(4)
C(4)	0.077(6)	0.084(5)	0.088(7)	-.029(5)	0.048(5)	-.009(5)
C(5)	0.075(5)	0.073(5)	0.045(4)	-.005(3)	0.028(4)	-.006(4)
C(6)	0.042(3)	0.043(3)	0.031(3)	0.003(2)	0.009(2)	0.004(2)
C(7)	0.045(3)	0.045(3)	0.045(3)	0.005(3)	0.009(3)	0.003(3)
N	0.047(3)	0.049(3)	0.042(3)	-.002(2)	0.012(2)	-.008(2)
C(8)	0.062(4)	0.060(4)	0.036(3)	0.008(3)	0.007(3)	-.012(3)
C(9)	0.059(4)	0.078(5)	0.043(4)	0.001(3)	-.003(3)	-.020(4)
C(10)	0.064(4)	0.069(5)	0.069(5)	-.028(4)	0.018(4)	-.016(4)
C(11)	0.050(4)	0.050(3)	0.059(4)	0.006(3)	0.014(3)	-.006(3)

C(12)	0.061(4)	0.076(5)	0.079(5)	-.019(4)	0.035(4)	-.018(4)
C(13)	0.054(4)	0.053(4)	0.054(4)	-.012(3)	0.005(3)	-.008(3)

The anisotropic temperature factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

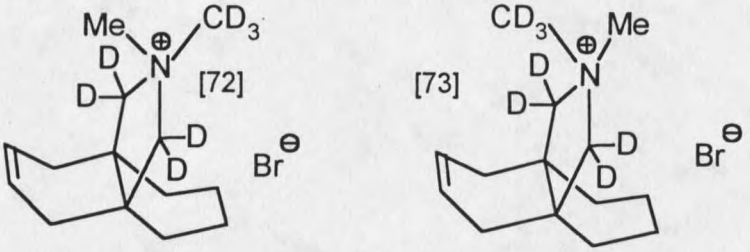
Table 15. $[C_{13}H_{22}N]I$ Calculated Hydrogen Positional Coordinates

	x/a	y/b	z/c
H(2a)	0.5660	0.9015	0.3318
H(2b)	0.6601	0.9674	0.4463
H(3)	0.4843	0.8354	0.4517
H(4)	0.5548	0.6406	0.6013
H(5a)	0.7415	0.7623	0.6187
H(5b)	0.7151	0.5346	0.6439
H(7a)	0.8526	0.4609	0.4734
H(7b)	0.8727	0.5912	0.5891
H(8a)	0.7486	0.8925	0.3227
H(8b)	0.7673	0.6615	0.2957
H(9a)	0.6118	0.5894	0.2296
H(9b)	0.5399	0.5662	0.3096
H(10a)	0.7149	0.3456	0.3170
H(10b)	0.6015	0.2646	0.3120
H(11a)	0.6246	0.3567	0.4860
H(11b)	0.7398	0.2799	0.4953
H(12a)	0.9301	0.6100	0.3710

H(12b)	0.9990	0.7217	0.4881
H(12c)	0.9423	0.8508	0.3733
H(13a)	0.8001	0.9386	0.5406
H(13b)	0.8700	1.0372	0.4717
H(13c)	0.9250	0.9049	0.5856

N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.4]tridec-3-ene ammonium salt isomer mixture

Yield 71%.



52.8% Averaged product ratio 47.2%

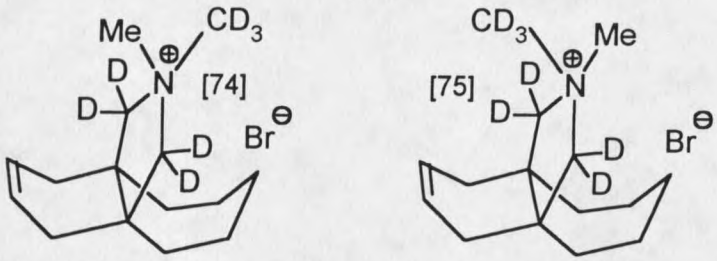
^{1}H NMR: ($CDCl_3$) 1.44-1.68(8H,m); 2.14(4H,s); 3.73(3H,s); 3.81(3H,s); 5.62(2H,s).

^{13}C NMR: ($CDCl_3$) 21.51(t); 31.86(t); 32.31(t); 42.32(s); 60.80(q); 122.9(d).

MS: (Electrospray) m/e 213 for cationic species (less I^-).

N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.5]tetradec-3-ene ammonium salt isomer mixture

Yield 72%.



69.8% Averaged product ratio 30.2%

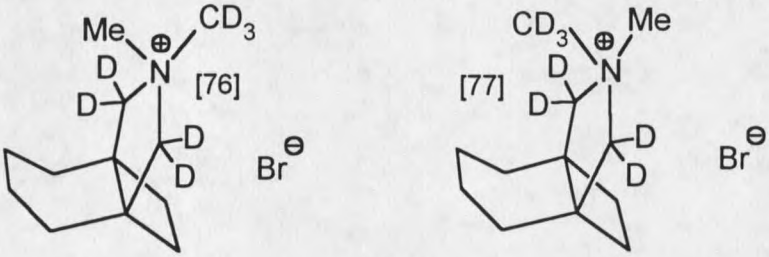
^{1}H NMR: ($CDCl_3$) 1.48-2.26(14H,m); 3.44(3H,s); 3.71(3H,s); 6.04-6.05(2H,dd).

^{13}C NMR: ($CDCl_3$) 24.81(t); 30.96(t); 33.24(t); 41.20(t); 50.81(s); 56.96,55.8(q); 129.5(d).

MS: (Electrospray) m/e 227 for cationic species (less I^-).

<u>N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.2]undecane ammonium salt isomer mixture</u>

Yield 45%.



42.7% Averaged product ratio 57.3%

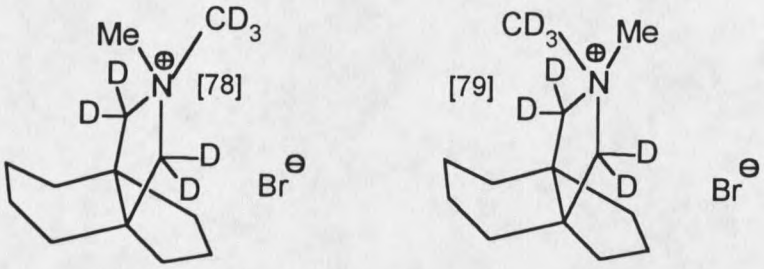
^{1}H NMR: ($CDCl_3$) 1.47-1.49(2H,m); 1.56-1.58(2H,m); 1.66-1.70(4H,m); 2.04-2.08(4H,m); 3.57-3.58(1H,d); 3.75-3.77(1H,d).

^{13}C NMR: ($CDCl_3$) 19.49(t); 27.37(t); 31.26(t); 46.24(s); 56.94(q); 57.36(q).

MS: (Electrospray) m/e 187 for cationic species (less I^-).

N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.3]dodecane ammonium salt isomer mixture

Yield 60%.



47.8% Averaged product ratio 52.2%

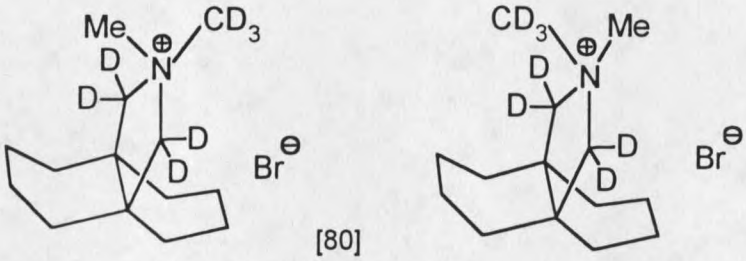
^{1}H NMR: ($CDCl_3$,) 1.49-1.60(16H,m); 1.81-1.93(12H,m); 3.72(3H,s); 3.74(3H,s).

^{13}C NMR: ($CDCl_3$) 20.88(t); 21.11(t); 30.81(t); 36.29(t); 52.30(s); 59.50(q); 60.20(q).

MS: (Electrospray) m/e 201 for cationic species (less I^-).

N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.4]tridecane ammonium salt isomer mixture

Yield 69%.



[80]

Only one peak NO RATIO

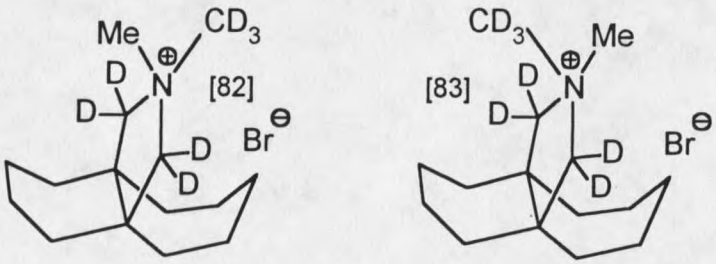
^{1}H NMR: ($CDCl_3$) 1.42-1.69(16H,m); 3.81(3H,s).

^{13}C NMR: ($CDCl_3$) 21.20(t); 31.16(t); 43.80(s); 61.24(q).

MS: (Electrospray) m/e 215 for cationic species (less I^-).

N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-azatricyclo[4.3.5]tetradecane ammonium salt isomer mixture

Yield 79%.



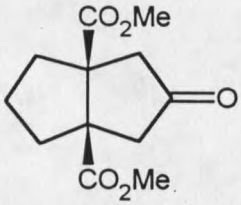
Ratio not resolved at 500 Mhz

^{1}H NMR: ($CDCl_3$) 1.42-1.87((18H,s); 3.73(3H,s).

^{13}C NMR: ($CDCl_3$) 20.84(t); 21.01(t); 26.54(t); 31.42(t); 35.72(t); 47.47(s); 60.61(q).

MS: (Electrospray) m/e 229 for cationic species (less I^-).

1,5-Dicarbomethoxybicyclo[3.3.0]octan-3-one [100]:



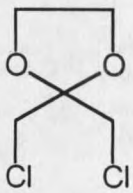
In a multi neck flask with septa under an argon atmosphere was placed 0.79 mL of diisopropyl amine in 40 mL of THF. The flask was chilled in an ice bath to 0° C and n-butyl lithium (2.1 equivalents or 3.1 mL of a 1.8M solution) was added. The solution was stirred for 30 minutes followed by a change in temperature to -78° C. The substrate, 1,2-dicarbomethoxycyclopentane (0.50 g in 20 mL of THF) was added dropwise. The reaction was stirred for 5 minutes and 1.1 equivalents of 1,3-dichloroacetone (0.37 g in THF

solution) was added slowly. The reaction was allowed to stir at -78° C for 1.5 hrs then quenched with 5% HCl while still cold followed by three ether extractions. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The reaction was purified by washing through a dry column of silica gel with 3:7 EtOAc / hexane to yield 0.22 g of product (34%) by GLC.

^1H NMR: ($CDCl_3$) 1.17-1.22(2H,m); 1.75-1.81(4H,m); 2.43-2.46(2H,d); 2.93-2.99(2H,d); 3.63(6H,s).

^{13}C NMR: ($CDCl_3$) 23.14(t); 36.36(t); 48.22(t); 52.23(q); 59.92(s); 174.79(s); 213.64(s).

2,2-Dichloromethyl-1,3-dioxolane [101]:



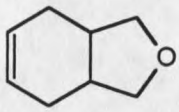
To a solution of 1,3-dichloracetone (2.0 g) in CH_2Cl_2 was added with stirring 1.2 eq. of anhydrous ethylene glycol (1.1 g) with a drop of HCl as a catalyst. The solution was refluxed overnight, cooled to RT, and the solution was allowed to stand over molecular sieves to remove excess water. The product was filtered through a silica gel bed with 1:1 hexane / EtOAc to give an 88% yield of the ketal.

^1H NMR: ($CDCl_3$) 3.65(4H,s); 4.08(4H,s).

^{13}C NMR: ($CDCl_3$) 44.86(t); 66.40(t); 107.61(s).

cis-8-Oxabicyclo{4.3.0]non-3-ene [102]:

A solution of excess LAH (6.4 g) in dry THF is chilled to 0° C with stirring. To this solution was added slowly 15 g of 3,4-dicarbomethoxycyclohexene. The ice bath was removed and the reaction was heated to reflux temperature overnight. The reaction was once again chilled to 0° C and a 1:1 water ether solution was added cautiously until evolution of hydrogen ceased. The reaction was filtered to remove excess aluminum salts. The salts were washed with water and diethyl ether and the liquids were placed in a separatory funnel. The water layer was extracted three times with diethyl ether. The organic layer was combined and dried over $MgSO_4$ and the solvent was removed by rotary evaporation to give (10.5 g) of a yellowish oil (98% yield). The diol was not characterized and was immediately condensed with loss of water to make the ether moiety *cis*-8-oxabicyclo[4.3.0]non-3-ene.



To a stirred solution of 10 g of diol in 40 mL of dry pyridine at 0° C in a two neck round bottom flask under argon atmosphere was added 5.5 mL of MsCl. The reaction mixture was stirred at room temperature overnight. The reaction was poured over iced aqueous HCl. The pH was adjusted until acidic by Hydrian paper. Extract the water layer three times with CH_2Cl_2. The organic extracts were combined and dried over $MgSO_4$ and the solvent removed by rotary evaporation. The crude

product was filtered through a bed of silica gel with 1:1 hexane\EtOAc to yield 8.5 g product as a colorless oil (96%)

^{1}H NMR: ($CDCl_3$) 1.81-1.93(2H,m); 2.09-2.27(2H,m); 3.41-3.46(4H,dd); 3.76-3.80(2H,dd); 5.57-5.58(2H,dd).

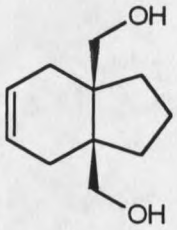
^{13}C NMR: ($CDCl_3$) 23.93(d); 35.11(t); 72.94(t); 124.72(d).

MS: 124; 106; 93; 79(base); 69; 54; 39; 27.

HRMS: (EI) Calculated for $C_8H_{12}O$ = 124.184; Found = 124.189

<u>*cis*-1,6-Dihydroxymethylbicyclo[4.3.0]non-3-ene [103]:</u>

A solution of *cis*-1,6-dicarbomethoxybicyclo[4.3.0]non-3-ene, [29], (16.5 g) in 50.0 mL of dry THF was added dropwise at 0°C to a stirring solution LAH (3.00 g) in 350 mL of dry THF. The reaction mixture was refluxed overnight. The reaction was once again chilled to 0° C and a 1:1 water/ether solution was added cautiously until the excess LAH reacted. The reaction was vacuum filtered to remove excess aluminum salts. The salts were washed with water and diethyl ether and the liquids were placed in a separatory funnel. The water layer was extracted three times with diethyl ether. The organic layer was combined and dried over $MgSO_4$ and the solvent was removed by rotary evaporation to give (10.7 g) of a product (84% yield).



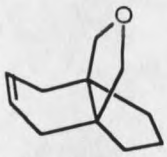
^1H NMR: ($CDCl_3$) 1.47-1.67(6H,m); 1.86-1.92(2H,d); 2.08-2.14(2H,d); 3.38-3.44(2H,dd); 3.57-3.62(2H,dd); 3.83-3.87(2H,m); 5.58(2H,s).

^{13}C NMR ($CDCl_3$): 18.45(t); 31.37(t); 33.44(t); 46.39(s); 67.10(t); 124.50(d).

MS (EI) m/e: 164; 133; 117; 106; 91(base); 77; 65; 41.

HRMS calculated for $C_{11}H_{19}O_2$ = 183.1385; found = 183.1385.

8-Oxatricyclo[4,3,3,0]dodec-3-ene [104]:



The diol (4.3 g) was chilled at 0° C in 25 mL of dry pyridine in a two neck round bottom flask under argon atmosphere. To this solution was added dropwise with stirring 1.8 mL of MsCl. The reaction mixture was stirred at room temperature overnight. The reaction was poured over iced aqueous HCl. The pH was adjusted until acidic by Hydrian paper. Extract the water layer three times with CH_2Cl_2. The organic extracts were combined and dried over $MgSO_4$ and the solvent removed by rotary evaporation. The crude product was filtered through a bed of silica gel with 1:1 hexane\EtOAc to yield 3.6 g product as a pungent colorless oil (91%)

^1H NMR: ($CDCl_3$) 1.46-1.67(6H,m); 2.00(2H,d); 1.99(2H,d,); 3.54(4H,d); 5.82(2H,t).

^{13}C NMR: ($CDCl_3$) 23.96(t); 32.68(t); 40.19(t); 55.30(s); 81.38(t); 128.63(d).

LRMS (EI) m/e (% abundance): 164 (M^+,18); 146(11); 133(31); 119(32); 109(26); 104(14); 95(31); 91(100); 79(39); 67(25); 53(16); 41(33).

HRMS (EI) m/e calculated for $C_{11}H_{16}O$ = 164.1202; found = 164.1205

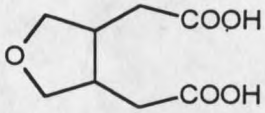
General procedure for oxidative ozonolysis of alkenes:

NOTE: Ozonolysis is a potentially explosive procedure and all reactions were carried out in a hood using an approved blast shield.

The unsaturated imide compound, N-methyl-*cis*-1,2,3,6-tetrahydrophthalimide (2.5 g) was placed with stirring in a 250 mL flask in a solution of 80 mL of CH_2Cl_2 and 40 mL of methanol (2:1 mixture). The solution was chilled in a dry ice bath (-78° C). A bubbler was submerged in the solution to increase the amount of surface contact with the ozone gas that was added at a flow rate of approximately 0.1 SCFM. The ozone was produced by passing oxygen from a tank through a water cooled Wesbach ozonolysis machine (arc volts 90, 10 psi of O_2 inlet pressure). The flow was continued until a pale blue color persisted. The excess ozone was removed by bubbling argon through the solution for a few minutes noting the disappearance of the blue color. The excess solvent was removed using a rotary evaporator. The remaining dry solid material was dissolved in 13 mL of anhydrous formic acid. To this solution was added slowly 2.3 mL of a 30% peroxide

solution. This mixture was warmed to approximately 30-40° C and stirred overnight. A air condenser was used above a bump trap to retain the reaction in the flask. The solution was cooled and the excess solvent was removed by rotary evaporation. The remaining solid was recrystallized in diethyl ether to yield 4.9 g of the diacid (78%).

cis-3,4-Di(carboxymethyl)tetrahydrofuran [105]:



Yield 69%.

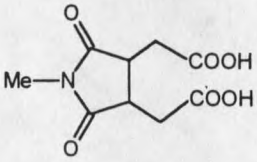
M.P. = 134-137° C

^{1}H NMR: (CD_3OD) 2.26-2.30(2H,dd); 2.40-2.47(2H,dd); 2.70-2.74(2H,m); 3.51-3.56(2H,dd); 3.95-4.00(2H,dd).

^{13}C NMR: (CD_3OD) 33.26(t); 38.84(d); 73.19(d); 175.66(s).

MS: (CI, NH_3, DIP) m/e(% of base): 189(m+1,base,100); 171(28); 153(22); 145(37); 129(87); 111(33).

cis N-Methyl-3,4-di(carboxymethyl)pyrrolidine [106]:



Yield 78%.

M.P. = 137-139° C

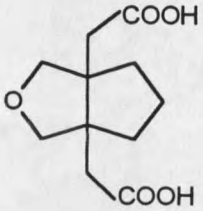
^{1}H NMR: (CD_3OD) 3.57-3.60(4H,m); 3.79(3H,s); 4.23-4.25(2H,m).

^{13}C NMR: (CD_3OD) 25.13(q); 31.59(t); 40.21(d); 175.08(s); 180.91(s).

MS: (EI,70Ev, DIP) m/e(% of base): 229(16); 211(18); 183(56); 165(24); 126(45); 108(base, 100); 98(31); 55(79).

cis-1,2-Di(carboxymethyl)-4-oxobicyclo[3.3.0]heptane [107]:

Yield 74%.



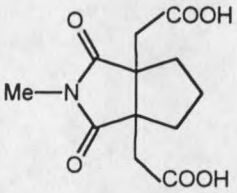
M.P. = 236-240° C

^{1}H NMR: (CD_3OD) 1.62-1.73(4H,m); 1.87-1.90(2H,m); 2.33-2.46(4H,dd); 3.70-3.89(4H,dd).

^{13}C NMR: (CD_3OD) 24.94(t); 40.12(t); 40.85(t); 54.60(t); 81.44(t); 175.77(s).

MS: (CI, NH_3, DIP) m/e(% of base): 228(m+1,49); 211(29); 193(40); 185(27); 168(27); 153(13); 136(27); 122(44); 109(base,100).

cis-N-Methyl-1,2-di(carboxymethyl)-4-azabicyclo[3.3.0]heptane [108]:



Yield 63%.

Viscous yellow oil.

^{1}H NMR: (CD_3OD) 1.72-2.18(6H,m); 2.48-2.70(4H,m); 3.77(3H,s).

^{13}C NMR: (CD_3OD) 23.17(t); 25.49(q); 36.91(t); 38.34(t); 55.29(s); 174.56(s); 183.36(s).

MS: (EI,70Ev, DIP) m/e(% of base): 269(21); 223(31); 166(55); 138(base, 100); 93(74); 79(55).

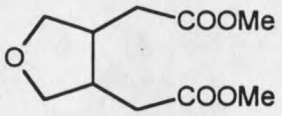
General approaches to esterification of diacids:

Oxygenated systems.

A solution of 2.5 g of *cis*-3,4-di(carboxymethyl)tetrahydrofuran in anhydrous methanol was refluxed overnight with a drop of HCl as a catalyst. Molecular (3 angstrom) sieves were added to remove the water and push the equilibrium to the right. The solution was heated gently (kept below boiling point) for 8 hours. The reaction was cooled and gravity filtered to remove the sieves. The excess methanol was removed by rotary evaporation to yield 2.3 g of the diester (81%).

cis-3,4-Di(carboxymethyl)tetrahydrofuran [109]:

Yield 88%.

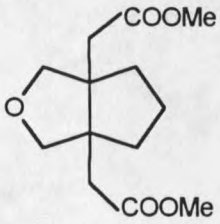


^{1}H NMR: ($CDCl_3$) 2.22-2.40(4H,m); 2.68-2.72(2H,m); 3.45-3.50(2H,dd); 3.61(3H,s); 3.90-3.96(2H,dd).

^{13}C NMR: ($CDCl_3$) 32.53(t); 37.73(d); 51.68(q); 72.29(t); 172.58(s).

cis-1,2-Di(carboxymethyl)-4-oxobicyclo[3.3.0]heptane [110]:

Yield 81%.



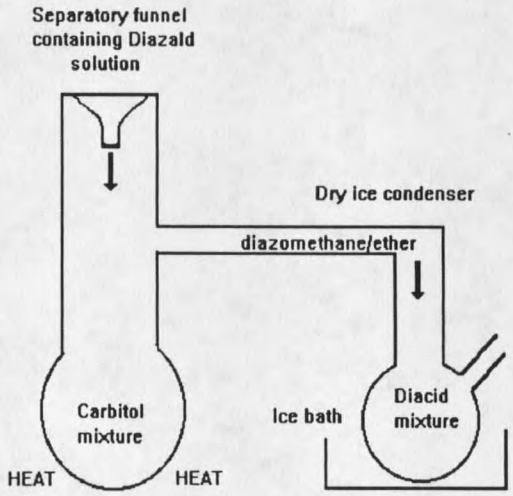
^{1}H NMR: ($CDCl_3$) 1.55-1.73(4H,m); 1.82-1.95(2H,m); 2.31-2.33(4H,d); 3.63(6H,s); 3.69-3.94(4H,m).

^{13}C NMR: ($CDCl_3$) 12.81(t); 38.57(t); 39.94(t); 51.57(q); 53.63(s); 79.99(t); 172.43(s).

Nitrogen systems.

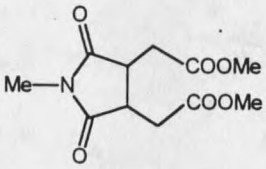
NOTE: Diazomethane is a potentially explosive process, so all reactions were carried out in a hood using an approved blast shield.

A mixture of carbitol (20 mL), potassium hydroxide (0.2 g), a few mL of water and 5 mL of diethyl ether was placed in the diazomethane generator (Aldrich small scale, graciously borrowed from Dr. Jennings). This solution was heated to approximately 35° C. A separatory funnel containing 0.2 g Diazald® dissolved in ether was connected directly above the carbitol mixure. A flask chilled in a ice bath that was connected to the above system was placed 0.1 g of *cis*-N-methyl-1,2-di(carboxymethyl)-azabicyclo[3.3.0]heptane in a ether solution. The Diazald® solution was dripped slowly into the basic carbitol mixture. The ether was codistilled with the diazomethane which was condensed into the flask containing the diacid. The distillation continued until the diacid flask turned



slightly yellow indicating a saturated diazomethane solution. The reaction was allowed to stand until the color dissipated. The excess ether was removed by rotary evaporation to give a quantitative yield of the corresponding diester.

cis N-Methyl-3,4-di(carboxymethyl)pyrrolidine [111]:



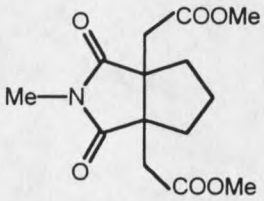
Yield quantitative.

M.P. = 85-87° C

^{1}H NMR: ($CDCl_3$) 2.53-2.62(2H,dd); 2.70-2.77(2H,dd); 2.91(3H,s); 3.28-3.30(2H,dd); 3.61(6H,s).

^{13}C NMR: ($CDCl_3$) 24.88(q); 30.61(t); 38.81(q); 52.09(d); 178.77(s); 178.01(s).

cis-N-Methyl-1,2-di(carboxymethyl)-4-azabicyclo[3.3.0]heptane [112]:



Yield quantitative.

Viscous yellow oil.

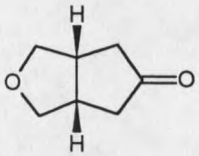
^{1}H NMR: ($CDCl_3$) 1.52-1.88(6H,m); 2.41-2.62(4H,dd); 3.28(3H,s); 3.73(6H,s).

^{13}C NMR: ($CDCl_3$) 22.31(t); 25.02(q); 35.93(t); 37.70(t); 51.69(q); 54.10(s); 171.88(s); 181.17.

Representative Dieckmann ring closure reaction:

The diester, *cis*-3,4-di(carboxymethyl)tetrahydrofuran (0.83 g) was placed in a two neck flask in anhydrous xylene (20 mL) equipped with a stirbar and condenser under an argon atmosphere. Sodium metal (~ 70 mg) was added and the reaction was brought to reflux with stirring overnight. The reaction was quenched with saturated ammonium chloride and extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed on a rotary evaporator. The crude reaction mixture (0.62 g) had a ketone functionality in the carbon NMR spectrum and was formed in 36% overall yield. The intermediate was not isolated and was immediately decarboxylated.

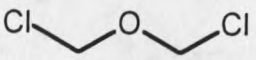
The keto intermediate from above (0.1 g) was placed in a 2:1 water / THF solution with a drop of HCl catalyst. This reaction mixture was refluxed overnight. The reaction was extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed on a rotary evaporator to yield 0.8 g of crude bicyclic ketone, [113], (93%).



^1H NMR: ($CDCl_3$) 2.06-2.14(2H,dd); 2.43-2.52(2H,dd); 2.91(2H,m); 3.52-3.56(2H,dd); 3.87-3.92(2H,dd).

^{13}C NMR: ($CDCl_3$) 39.58(d); 42.66(t); 74.39(t); 217.73(s).

bis-dichloromethyl ether [84]:

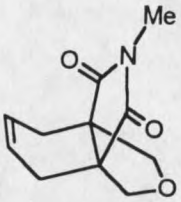


A 500 mL two neck flask equipped with a stirbar, thermometer, and dropping funnel was charged with paraformaldehyde (120 g) and 84.0 mL of concentrated HCl. The temperature of the reaction was cooled to 0° C. The dropping funnel was filled with 226 mL of chlorosulfonic acid which was added at such a rate not to allow the temperature to rise above 10° C. This addition took over eight hours to complete. The reaction was stirred overnight and allowed to slowly reach RT. The layers were separated and the upper organic layer was washed twice with ice water. The organic component was poured over ice and 40% NaOH (approximately 125 mL) was added cautiously until the aqueous layer was basic to litmus paper. The reaction was poured into a separatory funnel and extracted with ether three times. The organic fractions were combined and dried over Na_2SO_4 and the solvent was removed by rotary evaporation. Distillation of the crude product 96-99° C (Organic Synthesis IV p.101 B.P. 101-104) gave 156 g of pure dry product (68% yield).

^1H NMR: ($CDCl_3$) 5.54(4H,s).

^{13}C NMR: ($CDCl_3$) 76.42(t).

N-Methyl-8-aza-7,9-diketo-11-oxotricyclo[4.3.3]undec-3-ene [85]:



In a round bottom flask equipped with a stirbar, dropping funnel and septa under an argon atmosphere was placed approximately 700 mL of THF and 24.7 mL of diisopropyl amine. The flask was chilled in an ice bath to 0° C and 21.5 mL of 8.2M (0.18 moles, 2.2 eq) n-butyl lithium was added. The reaction was stirred for 30 minutes. At this time, the reaction was cooled to -78° C and 13.2 g (1.0 eq) of N-methyl-*cis*-1,2,3,6-tetrahydrophthalimide dissolved in 100 mL of THF was added dropwise to the reaction. After the addition was complete, the reaction was stirred for 15 minutes. The temperature was changed to -10° C and stirred for 10 minutes. Bis-dichloromethyl ether (7.60 mL, 1.1 eq) in THF was added dropwise and the reaction was stirred 2.5 hours while allowing the reaction to reach RT. The reaction was quenched with excess 5% HCl, extracted three times with diethyl ether and the ether extracts were combined and dried over $MgSO_4$. The solvent was removed via rotary evaporation to yield 20.4 g crude yield. Recrystallization from hexane / chloroform gave 11.6 g of the crystalline product (74%).

M.P. = 109-111° C

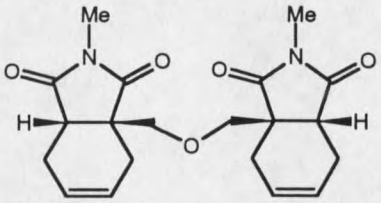
^1H NMR: ($CDCl_3$) 2.17-2.23(2H,dd); 2.45-2.51(2H,dd); 2.95(3H,s); 3.47-3.50(2H,d); 4.30-4.33(2H,d); 5.88-5.90(2H,dd).

^{13}C NMR: ($CDCl_3$) 25.39(q); 26.53(t); 56.30(s); 77.26(t); 127.39(d); 180.72(s).

MS: EI 70Ev m/e (% of base): 207(base,100); 176(33); 162(54); 148(22); 120(25); 91(83); 77(24).

Tether byproduct of above alkylation [86]:

M.P. = 175-178° C



^{1}H NMR: ($CDCl_3$) 1.74-1.79(2H,m); 2.11-2.16(2H,m); 2.39-2.44(2H,m); 2.53-2.58(2H,m); 2.78-2.80(2H,m); 2.86(6H,s); 3.39-3.40(2H,d); 3.66-3.68(2H,d); 5.75-5.86(4H,m).

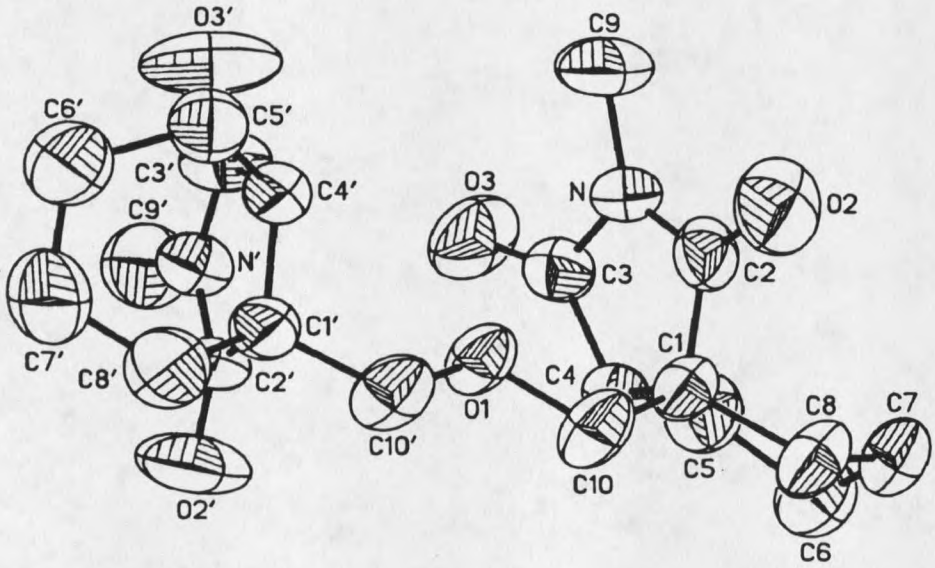
^{13}C NMR: ($CDCl_3$) 23.57(t); 24.93(q); 26.57(t); 42.64(t); 49.83(s); 74.41(t); 126.50(d); 128.24(d); 179.26(s); 180.88(s).

MS: EI, 70Ev, DIP (% of base): 372(65); 209(11); 196(33); 177(45); 164(base,100); 120(30); 92(72); 77(40).

X-ray structure determinations:

$C_{20}H_{24}N_2O_5$ crystal data: FW = 372.4, monoclinic, space group C2/c, a = 21.163(3) Å, b = 7.684(1) Å, c = 12.282(2) Å, _ = _ = 90 °, ß = 107.51(1) °, V = 1904.8(5) Å^3, Z = 4, D_{calc} = 1.30 g/cm^3, T = 25 °C, radiation MoK_ (_ = 0.71069 Å), μ = 0.9 cm^{-1}, R = 0.045, R_w = 0.049, S = 1.39, 124 parameters. Intensity data were taken as omega scans on a Nicolet R3mE four-circle diffractometer for 2779 unique reflections in

the range 3° < 2_ < 60 °, of which 945 with I > 3_(I) were used for structure solution and refinement. The data were corrected for Lorentz and polarization effects. No corrections for absorption or extinction were needed. The structure was solved by direct methods. Non-hydrogen atoms were refined by block-cascade least-squares with anisotropic thermal parameters, using statistical weighting[1]. Calculated hydrogen positions were used for structure refinement with a common refined thermal parameter. The orientation of the methyl group was taken from a difference map, which showed peaks in reasonable positions for all of the hydrogen atoms.



(1) Crystallographic calculations were done with the **SHELXTL** program package by G. M. Sheldrick; Siemens Analytical X-Ray Instruments, Inc.: Madison, WI.

Table 16. $C_{10}H_{24}N_2O_5$ Positional Coordinates and Isotropic Thermal Parameters (Å^2) with Standard Deviations in Parentheses

	x/a	y/b	z/c	U
C(1)	0.3841(1)	0.4871(3)	0.1600(2)	0.042(1)
C(2)	0.4004(1)	0.3787(4)	0.0688(2)	0.047(1)
N	0.4070(1)	0.2082(3)	0.1026(2)	0.047(1)
C(3)	0.3935(2)	0.1816(4)	0.2037(3)	0.054(1)
C(4)	0.3756(1)	0.3523(4)	0.2463(2)	0.046(1)
C(5)	0.3054(2)	0.3436(4)	0.2587(3)	0.063(1)
C(6)	0.2533(2)	0.3661(5)	0.1464(3)	0.068(2)
C(7)	0.2605(2)	0.4837(4)	0.0743(3)	0.065(1)
C(8)	0.3207(2)	0.5952(4)	0.1042(3)	0.060(1)
C(9)	0.4289(2)	0.0712(4)	0.0402(3)	0.075(2)
C(10)	0.4419(1)	0.6094(4)	0.2094(3)	0.057(1)
O(1)	0.5000(1)	0.5062(3)	0.2500(3)	0.051(1)
O(2)	0.4069(1)	0.4290(3)	-.0199(2)	0.078(1)
O(3)	0.3955(1)	0.0410(3)	0.2482(2)	0.096(1)

Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

Table 17. $C_{10}H_{24}N_2O_5$ Bond Lengths (Å)

C(1)-C(2)	1.516(4)	C(1)-C(4)	1.531(4)	C(1)-C(8)	1.551(4)
C(1)-C10)	1.518(4)	C(2)-O(2)	1.202(4)	N-C(2)	1.369(4)
N-C(3)	1.371(4)	N-C(9)	1.457(5)	C(3)-C(4)	1.502(4)
C(3)-O(3)	1.206(4)	C(4)-C(5)	1.540(5)	C(5)-C(6)	1.493(4)
C(6)-C(7)	1.306(5)	C(7)-C(8)	1.486(4)	C(10)-O(1)	1.421(3)

Table 18. $C_{10}H_{24}N_2O_5$ Bond Angles (°)

C(2)-C(1)-C(4)	103.9(2)	C(2)-C(1)-C(8)	109.0(2)
C(4)-C(1)-C(8)	113.7(3)	C(2)-C(1)-C(10)	107.5(3)
C(4)-C(1)-C(10)	113.0(2)	C(8)-C(1)-C(10)	109.3(2)
C(1)-C(2)-N	109.1(3)	C(1)-C(2)-O(2)	127.3(3)
N-C(2)-O(2)	123.6(3)	C(2)-N-C(3)	112.8(3)
C(2)-N-C(9)	123.5(3)	C(3)-N-C(9)	123.7(3)
N-C(3)-C(4)	109.2(3)	N-C(3)-O(3)	123.8(3)
C(4)-C(3)-O(3)	127.0(3)	C(1)-C(4)-C(3)	104.8(3)
C(1)-C(4)-C(5)	114.6(2)	C(3)-C(4)-C(5)	110.4(2)
C(4)-C(5)-C(6)	111.7(3)	C(5)-C(6)-C(7)	120.1(3)
C(6)-C(7)-C(8)	119.9(3)	C(1)-C(8)-C(7)	111.3(2)
C(1)-C(10)-O(1)	107.6(2)	C(10)-O(1)-C(10')	112.1(3)

Table 19. $C_{10}H_{24}N_2O_5$ Anisotropic Thermal Parameters (Å^2)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0.043(2)	0.037(1)	0.046(2)	0.001(1)	0.012(1)	0.005(1)
C(2)	0.047(2)	0.056(2)	0.038(2)	0.006(2)	0.012(1)	0.006(2)
N	0.059(2)	0.043(1)	0.041(1)	-.001(1)	0.019(1)	0.012(1)
C(3)	0.068(2)	0.045(2)	0.047(2)	0.007(2)	0.017(2)	0.006(2)
C(4)	0.057(2)	0.047(2)	0.037(2)	-.001(1)	0.018(1)	0.001(1)
C(5)	0.065(2)	0.074(2)	0.060(2)	-.009(2)	0.033(2)	-.005(2)
C(6)	0.050(2)	0.078(3)	0.074(2)	-.019(2)	0.018(2)	-.003(2)
C(7)	0.047(2)	0.074(2)	0.068(2)	-.008(2)	0.007(2)	0.013(2)
C(8)	0.057(2)	0.051(2)	0.069(2)	0.006(2)	0.015(2)	0.015(2)
C(9)	0.083(3)	0.071(2)	0.072(2)	-.016(2)	0.025(2)	0.021(2)
C(10)	0.054(2)	0.039(2)	0.074(2)	0.003(2)	0.015(2)	0.007(2)
O(1)	0.045(2)	0.035(1)	0.068(2)	0	0.010(1)	0
O(2)	0.105(2)	0.089(2)	0.053(1)	0.023(1)	0.041(1)	0.016(1)
O(3)	0.158(3)	0.052(2)	0.095(2)	0.026(1)	0.061(2)	0.021(2)

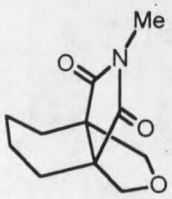
The anisotropic temperature factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

Table 20. $C_{10}H_{24}N_2O_5$ Calculated Hydrogen Positional Coordinates

	x/a	y/b	z/c
H(4)	0.4066	0.3867	0.3307
H(5a)	0.3001	0.4456	0.3158
H(5b)	0.2987	0.2186	0.2939
H(6)	0.2096	0.2849	0.1248
H(7)	0.2228	0.5000	-.0068
H(8a)	0.3251	0.6557	0.0274
H(8b)	0.3159	0.6946	0.1633
H(9a)	0.4740	0.0140	0.0943
H(9b)	0.4378	0.1258	-.0349
H(9c)	0.3910	-.0277	0.0150
H(10a)	0.4339	0.6831	0.2789
H(10b)	0.4471	0.6976	0.1441

N-methyl-8-aza-7,9-diketo-11-oxotricyclo[4.3.3]undecane [88]:



Reduction of alkene moiety via catalytic hydrogenation conditions previously described.

^1H NMR: ($CDCl_3$) 1.18-1.27(2H,m); 1.52-1.58(4H,m); 1.96-2.01(2H,m); 2.93(3H,s); 3.41-3.44(2H,d); 4.20-4.24(2H,d).

^{13}C NMR: ($CDCl_3$) 17.74(t); 24.66(t); 25.13(q); 54.18(s); 76.76(t); 180.89(s).

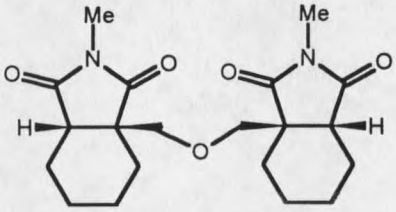
MS: EI, 70Ev, DIP (% of base): 209(27); 180(base,100); 166(33); 138(27); 122(25); 95(31); 79(27).

Tether byproduct of above reduction [87]:

M.P. = 128-130° C

^{1}H NMR: ($CDCl_3$) 1.27-1.61(14H,m); 1.83-1.92(2H,m); 2.64-2.67(2H,m); 2.90(6H,s); 3.38-3.41(2H,d); 3.61-3.64(2H,d).

^{13}C NMR: ($CDCl_3$) 19.87(t); 20.51(t); 21.63(t); 24.64(q); 26.99(t); 41.70(d); 47.97(s); 73.42(t); 178.99(s); 180.82(s).

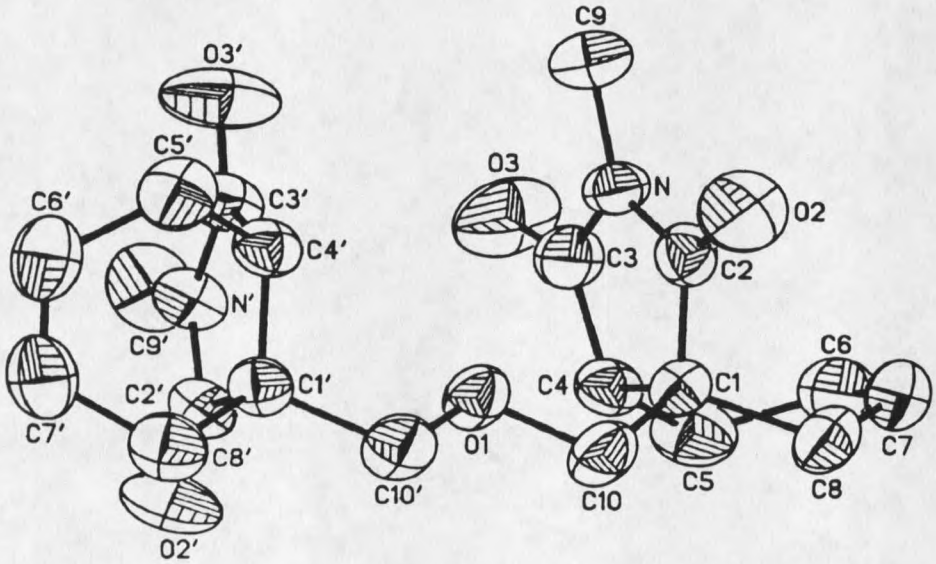


MS: EI, 70Ev, DIP (% of base): 376(12); 210(50); 181(56); 166(base,100); 139(30); 123(25); 95(83); 79(18).

X-ray structure determinations:

$C_{20}H_{28}N_2O_5$ crystal data: FW = 376.5, monoclinic, space group $P2_1/c$, a = 12.262(2) Å, b = 7.746(1) Å, c = 21.621(4) Å, _ = _ = 90 °, ß = 104.03(1) °, V = 1992.5(6) $Å^3$, Z = 4, D_{calc} = 1.26 g/cm^3, T = 25 °C, radiation MoK_ (_ = 0.71069 Å), μ = 0.8 cm^{-1}, R = 0.064, R_W = 0.069, S = 1.99, 245 parameters. Intensity data were taken as omega scans on a Nicolet R3mE four-circle diffractometer for 5801 unique reflections in the range 3° < 2_ < 60 °, of which 1960 with I > 3_(I) were

used for structure solution and refinement. The data were corrected for Lorentz and polarization effects. No corrections for absorption or extinction were needed. The structure was solved by direct methods. Non-hydrogen atoms were refined by block-cascade least-squares with anisotropic thermal parameters, using statistical weighting[1]. Calculated hydrogen positions were used for structure refinement with a common refined thermal parameter. A difference map, which showed peaks in reasonable positions for all of the hydrogen atoms, indicated that one of the methyl groups, C(9), is disordered with approximately equal occupancy in each of two sets of hydrogen positions. Calculated hydrogen positions for both orientations at fifty percent occupancy were included in the refinement model,



along with the single orientation for the C(9') methyl group taken from the difference map.

(1) Crystallographic calculations were done with the **SHELXTL** program package by G. M. Sheldrick; Siemens Analytical X-Ray Instruments, Inc.: Madison, WI.

Table 21. $C_{10}H_{28}N_2O_5$ Positional Coordinates and Isotropic Thermal Parameters (Å^2) with Standard Deviations in Parentheses

	x/a	y/b	z/c	U
C(1)	0.7292(3)	0.4795(4)	0.4042(2)	0.054(1)
C(2)	0.8386(3)	0.5817(6)	0.4120(2)	0.067(2)
N	0.8192(2)	0.7491(4)	0.4265(1)	0.063(1)
C(3)	0.7087(3)	0.7780(5)	0.4263(2)	0.059(1)
C(4)	0.6419(2)	0.6246(4)	0.3969(2)	0.051(1)
C(5)	0.5851(3)	0.6742(5)	0.3277(2)	0.075(2)
C(6)	0.5617(3)	0.5257(6)	0.2822(2)	0.090(2)
C(7)	0.6678(4)	0.4236(6)	0.2845(2)	0.084(2)
C(8)	0.7120(3)	0.3474(5)	0.3497(2)	0.078(2)
C(9)	0.9080(4)	0.8758(7)	0.4478(2)	0.103(2)
C(10)	0.7377(3)	0.3823(5)	0.4661(2)	0.071(2)
O(1)	0.7592(2)	0.5024(3)	0.5174(1)	0.060(1)
O(2)	0.9287(2)	0.5256(5)	0.4085(2)	0.114(2)
O(3)	0.6748(2)	0.9119(4)	0.4438(2)	0.093(1)

C(1')	0.7738(3)	0.5587(4)	0.6270(2)	0.057(1)
C(2')	0.6688(3)	0.6656(5)	0.6086(2)	0.065(2)
N'	0.6957(2)	0.8359(4)	0.6047(1)	0.061(1)
C(3')	0.8098(3)	0.8608(5)	0.6188(2)	0.071(2)
C(4')	0.8675(3)	0.6907(4)	0.6307(2)	0.057(1)
C(5')	0.9575(3)	0.6870(6)	0.6930(2)	0.076(2)
C(6')	0.9098(3)	0.6945(6)	0.7509(2)	0.092(2)
C(7')	0.8079(4)	0.5821(7)	0.7459(2)	0.102(2)
C(8')	0.7808(4)	0.4673(6)	0.6914(2)	0.093(2)
C(9')	0.6148(3)	0.9739(5)	0.5886(2)	0.092(2)
C(10')	0.7685(3)	0.4217(4)	0.5770(2)	0.072(2)
O(2')	0.5730(2)	0.6150(4)	0.5986(2)	0.113(2)
O(3')	0.8530(2)	1.0020(4)	0.6210(2)	0.124(2)

Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

Table 22. $C_{10}H_{28}N_2O_5$ Bond Lengths (Å)

C(1)-C(2)	1.531(5)	C(1')-C(2')	1.501(5)
C(1)-C(4)	1.533(4)	C(1')-C(4')	1.525(5)
C(1)-C(8)	1.535(5)	C(1')-C(8')	1.547(5)
C(1)-C10)	1.518(5)	C(1')-C(10')	1.505(5)
C(2)-O(2)	1.206(5)	C(2')-O(2')	1.207(4)
N-C(2)	1.369(5)	N'-C(2')	1.367(5)
N-C(3)	1.371(5)	N'-C(3')	1.371(5)
N-C(9)	1.455(5)	N'-C(9')	1.443(5)

C(3)-C(4)	1.495(5)	C(3')-C(4')	1.486(5)
C(3)-O(3)	1.212(5)	C(3')-O(3')	1.212(5)
C(4)-C(5)	1.539(4)	C(4')-C(5')	1.522(4)
C(5)-C(6)	1.495(6)	C(5')-C(6')	1.505(6)
C(6)-C(7)	1.513(6)	C(6')-C(7')	1.505(7)
C(7)-C(8)	1.504(5)	C(7')-C(8')	1.450(6)
C(10)-O(1)	1.422(4)	C(10')-O(1)	1.412(4)

Table 23. $C_{10}H_{28}N_2O_5$ Bond Angles (°)

C(2)-C(1)-C(4)	101.8(3)	C(2')-C(1')-C(4')	103.3(3)
C(2)-C(1)-C(8)	112.5(3)	C(2')-C(1')-C(8')	110.3(3)
C(4)-C(1)-C(8)	116.6(3)	C(4')-C(1')-C(8')	112.5(3)
C(2)-C(1)-C(10)	106.7(3)	C(2')-C(1')-C(10')	108.3(3)
C(4)-C(1)-C(10)	110.5(3)	C(4')-C(1')-C(10')	114.3(3)
C(8)-C(1)-C(10)	108.3(3)	C(8')-C(1')-C(10')	107.9(3)
C(1)-C(2)-N	108.6(3)	C(1')-C(2')-N'	110.1(3)
C(1)-C(2)-O(2)	126.8(4)	C(1')-C(2')-O(2')	127.1(4)
N-C(2)-O(2)	124.6(4)	N'-C(2')-O(2')	122.7(3)
C(2)-N-C(3)	112.4(3)	C(2')-N'-C(3')	111.7(3)
C(2)-N-C(9)	123.6(3)	C(2')-N'-C(9')	124.6(3)
C(3)-N-C(9)	123.6(3)	C(3')-N'-C(9')	123.7(3)
N-C(3)-C(4)	108.1(3)	N'-C(3')-C(4')	109.4(3)
N-C(3)-O(3)	123.5(3)	N'-C(3')-O(3')	123.2(3)
C(4)-C(3)-O(3)	128.2(3)	C(4')-C(3')-O(3')	127.5(3)

C(1)-C(4)-C(3)	104.0(2)	C(1')-C(4')-C(3')	105.3(3)
C(1)-C(4)-C(5)	115.0(3)	C(1')-C(4')-C(5')	114.1(3)
C(3)-C(4)-C(5)	106.7(3)	C(3')-C(4')-C(5')	112.5(3)
C(4)-C(5)-C(6)	114.7(3)	C(4')-C(5')-C(6')	113.0(3)
C(5)-C(6)-C(7)	110.8(3)	C(5')-C(6')-C(7')	113.7(3)
C(6)-C(7)-C(8)	110.4(3)	C(6')-C(7')-C(8')	115.8(4)
C(1)-C(8)-C(7)	114.1(3)	C(1')-C(8')-C(7')	113.8(4)
C(1)-C(10)-O(1)	108.9(3)	C(1')-C(10')-O(1')	108.8(3)
C(10)-O(1)-C(10')	112.4(3)		

Table 24. $C_{10}H_{28}N_2O_5$ Calculated Hydrogen Positional Coordinates

	x/a	y/b	z/c		x/a	y/b	z/c
H(4)	0.5752	0.5831	0.4182	H(4')	0.9144	0.6617	0.5957
H(5a)	0.6393	0.7638	0.3112	H(5'a)	1.0124	0.7965	0.6941
H(5b)	0.5062	0.7366	0.3274	H(5'b)	1.0052	0.5692	0.6949
H(6a)	0.5000	0.4422	0.2949	H(6'a)	0.8865	0.8265	0.7576
H(6b)	0.5293	0.5744	0.2345	H(6'b)	0.9740	0.6534	0.7918
H(7a)	0.7306	0.5081	0.2735	H(7'a)	0.7365	0.6656	0.7437
H(7b)	0.6494	0.3209	0.2498	H(7'b)	0.8218	0.5040	0.7885
H(8a)	0.6531	0.2511	0.3575	H(8'a)	0.8449	0.3688	0.6977
H(8b)	0.7920	0.2870	0.3510	H(8'b)	0.7005	0.4078	0.6898
H(9a)	0.9794	0.8424	0.4291	H(9'a)	0.6139	1.0221	0.5416
H(9b)	0.9330	0.8768	0.4992	H(9'b)	0.6377	1.0770	0.6229

H(9c)	0.8776	1.0021	0.4307	H(9'c)	0.5324	0.9260	0.5892
H(9d)	0.8966	0.9391	0.4903				
H(9e)	0.9047	0.9705	0.4107				
H(9f)	0.9887	0.8118	0.4581				
H(10a)	0.8056	0.2899	0.4730	H(10'a)	0.6962	0.3401	0.5748
H(10b)	0.6597	0.3155	0.4644	H(10'b)	0.8440	0.3444	0.5888

Table 25. $C_{10}H_{28}N_2O_5$ Anisotropic Thermal Parameters ($Å^2$)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0.054(2)	0.052(2)	0.054(2)	-.012(2)	0.008(2)	0.002(2)
C(2)	0.045(2)	0.098(3)	0.061(2)	-.019(2)	0.016(2)	0.005(2)
N	0.054(2)	0.070(2)	0.068(2)	-.017(2)	0.018(1)	-.022(2)
C(3)	0.063(2)	0.055(2)	0.064(2)	-.001(2)	0.021(2)	-.005(2)
C(4)	0.045(2)	0.052(2)	0.055(2)	-.005(2)	0.014(2)	-.006(2)
C(5)	0.071(2)	0.095(3)	0.055(2)	0.000(2)	0.005(2)	0.006(2)
C(6)	0.085(3)	0.118(4)	0.059(3)	-.014(3)	0.004(2)	-.013(3)
C(7)	0.091(3)	0.099(3)	0.061(3)	-.029(2)	0.015(2)	-.014(3)
C(8)	0.092(3)	0.068(3)	0.072(3)	-.028(2)	0.015(2)	-.002(2)
C(9)	0.083(3)	0.121(4)	0.104(3)	-.017(3)	0.019(2)	-.054(3)
C(10)	0.098(3)	0.045(2)	0.065(3)	-.010(2)	0.009(2)	0.005(2)
O(1)	0.086(2)	0.041(1)	0.049(1)	-.002(1)	0.010(1)	-.001(1)
O(2)	0.054(2)	0.168(3)	0.121(3)	-.046(2)	0.024(2)	0.020(2)
O(3)	0.106(2)	0.057(2)	0.115(2)	-.023(2)	0.027(2)	0.007(2)
C(1')	0.066(2)	0.055(2)	0.051(2)	0.003(2)	0.016(2)	-.009(2)

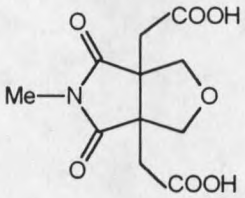
C(2')	0.069(2)	0.065(2)	0.069(3)	-.010(2)	0.033(2)	-.031(2)
N'	0.054(2)	0.061(2)	0.069(2)	0.003(2)	0.018(1)	-.002(2)
C(3')	0.068(3)	0.061(2)	0.078(3)	0.009(2)	0.007(2)	-.017(2)
C(4')	0.059(2)	0.062(2)	0.053(2)	-.003(2)	0.018(2)	-.010(2)
C(5')	0.060(2)	0.094(3)	0.072(3)	-.008(2)	0.013(2)	-.001(2)
C(6')	0.089(3)	0.112(4)	0.069(3)	-.002(3)	0.007(2)	-.006(3)
C(7')	0.124(4)	0.124(4)	0.063(3)	0.012(3)	0.030(3)	-.004(3)
C(8')	0.130(4)	0.087(3)	0.068(3)	0.011(3)	0.032(3)	-.024(3)
C(9')	0.089(3)	0.088(3)	0.100(3)	-.002(3)	0.026(3)	0.007(3)
C(10')	0.104(3)	0.045(2)	0.061(2)	0.006(2)	0.008(2)	-.004(2)
O(2')	0.068(2)	0.098(2)	0.182(3)	-.007(2)	0.046(2)	-.031(2)
O(3')	0.095(2)	0.068(2)	0.187(3)	0.030(2)	-.005(2)	-.032(2)

The anisotropic temperature factor exponent takes the form:

$-2_^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

<u>*cis*-N-Methyl-1,2-di(carboxymethyl)-4-aza-7-oxobicyclo[3.3.0]heptane [91]:</u>

Produced via general oxidative ozonolysis conditions previously described.



Yield 72%.

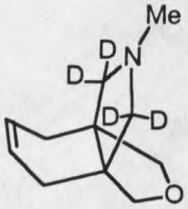
M.P. = 219-222° C

^{1}H NMR: (CD_3OD) 2.89(4H,s); 2.96(2H,s); 3.82-3.86(2H,d); 4.20-4.23(2H,d).

^{13}C NMR: (CD_3OD) 25.61(q); 33.73(t); 56.12(s); 77.55(t); 174.10(s); 181.85(s).

MS: (EI, 70Ev, DIP) m/e(% of base): 271(26); 212(65); 184(88); 165(86); 138(100, base); 126(77); 95(68); 81(65).

N-Methyl-8-aza-7,7,9,9-tetradeutero-11-oxatricyclo[4.3.3]undec-3-ene [89]:



Produced via general deuteride (LAD) reduction conditions previously described.

Yield 87%.

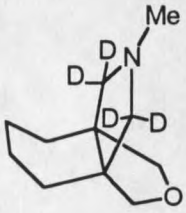
^{1}H NMR: ($CDCl_3$) 2.10-2.18(4H,dd); 2.32(3H,s); 3.57-3.60(2H,d); 3.74-3.77(2H,d); 5.91-5.93(2H,m).

^{13}C NMR: ($CDCl_3$) 30.99(t); 41.52(q); 56.06(s); 68.22(br, Deuterium muliplet); 79.85(t); 128.57(d).

MS: (EI, 70Ev) m/e: 183; 154; 152; 140; 111; 97; 79; 62; 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{11}H_{13}D_4NO$ = 183.1561; found = 183.1561

N-Methyl-8-aza-7,7,9,9-tetradeutero-11-oxatricyclo[4.3.3]undecane [90]:



Produced via general deuteride (LAD) reduction conditions previously described.

Yield 86%.

^{1}H NMR: ($CDCl_3$) 1.44(8H,s,br); 2.25(3H,s); 3.62(4H,s).

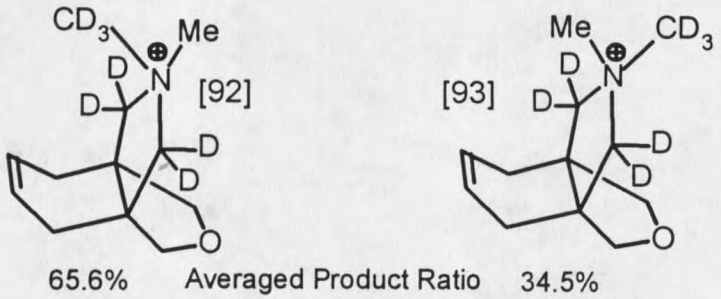
^{13}C NMR: ($CDCl_3$) 17.98(t); 28.40(t); 42.16(q); 51.37(s); 65.65(br, Deuterium muliplet); 79.25(t).

MS: (EI, 70Ev) m/e(% of base): 185((17); 142(45); 61(base).

HRMS: (EI 70Ev) m/e calculated for $C_{11}H_{15}D_4NO$ = 185.1718; found = 185.1719

N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-aza-11-oxatricyclo[4.3.3.]dodec-3-ene ammonium salt isomer mixture

Yield 64%.



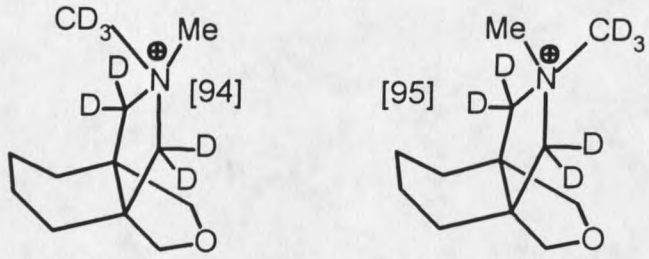
^1H NMR: ($CDCl_3$) 2.24-2.48(4H,m); 3.42-3.47(2H,d); 3.64(3H,s); 3.71(3H,s); 4.02-4.05(2H,d); 5.99(2H,m).

^{13}C NMR: ($CDCl_3$) 30.54(t); 54.24(q); 55.16(s); 55.57(q); 80.12(t); 128.02(d).

MS: (Electrospray) m/e 201 for cationic species (less I^-).

N-Methyl-N-trideuteromethyl-7,7,9,9-tetradeutero-8-aza-11-oxatricyclo[4.3.3.]dodecane ammonium salt isomer mixture

Yield 72%.



57.2% Averaged Product Ratio 42.8%

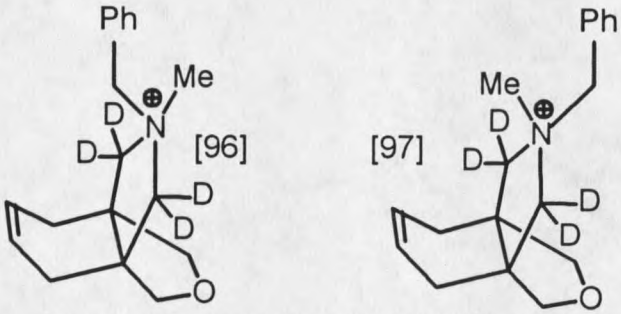
^{1}H NMR: (d6-acetone) 1.60-1.89(8H,m); 3.59(3H,s); 3.61(3H,s); 3.68-3.70(2H,d); 4.09-4.11(2H,d).

^{13}C NMR: (d6-acetone) 17.79(t); 27.92(t); 53.04(s); 55.51(q); 57.47(q); 78.41(t).

MS: (Electrospray) m/e 203 for cationic species (less I^-).

<u>N-Methyl-N-Benzyl-7,7,9,9-tetradeutero-8-aza-11-oxatricyclo[4.3.3.]dodec-3-ene ammonium salt isomer mixture</u>

Yield 46%.



59.0% Averaged Product Ratio 41.0%

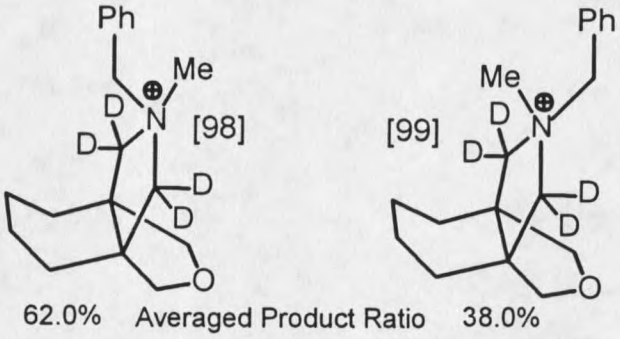
^{1}H NMR: ($CDCl_3$) 2.22-2.43(4H,m); 3.38-3.55(5H,m); 3.91-4.06(2H,dd); 5.07(2H,s); 5.31(2H,s); 5.86-5.98(2H,m); 7.26-7.84(5H,m).

^{13}C NMR: ($CDCl_3$) 30.64(t); 53.03(s); 53.82(q); 55.68(q); 67.39(t); 68.94(t); 80.01(t); 80.40(t); 123.64(d); 124.24(d); 128.15(d); 128.34(d); 128.75(d); 129.30(d); 130.47(d); 130.75(d); 132.92(d); 133.23(d).

MS: (Electrospray) m/e 274 for cationic species (less Br^-).

N-Methyl-N-Benzyl-7,7,9,9-tetradeutero-8-aza-11-oxatricyclo[4.3.3.]dodecane ammonium salt isomer mixture

Yield 53%.



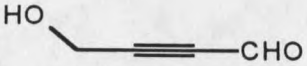
^1H NMR: ($CDCl_3$) 1.42-1.94(8H,m); 3.52(3H,s); 3.58(3H,s); 3.60-3.65(2H,dd); 3.92-3.97(2H,dd); 5.14(2H,s); 5.38(2H,d); 7.38-7.77(5H,m).

^{13}C NMR: ($CDCl_3$) 15.24(t); 17.14(t); 22.29(t); 26.90(t); 50.50(q); 51.46(s); 53.22(q); 65.82(t); 69.45(t); 77.74(t); 78.22(t); 128.06(d); 128.66(d); 129.16(d); 129.37(d); 13.62(d); 130.84(d); 133.21(d); 133.24(d).

MS: (Electrospray) m/e 276 for cationic species (less Br^-).

Aldehyde Experimental

4-Hydroxy-2-butynal [122]:



In a 100 mL two neck round bottom was placed with stirring 0.09g (1.0 mM) of 1,4-dihydroxy-2-butyne in 60 mL of freshly distilled benzene under an inert atmosphere. To this solution was added 5.7g (10 mM) of the Ag_2CO_3/Celite® oxidizing agent (1.0×10^{-3} moles of Ag_2CO_3 on 0.57 moles of Celite®). The slurry was heated to reflux temperature and approximately 20 mL of benzene was distilled from the reaction. The reflux was continued for 8 hours or until an aliquot showed a lack of starting material. The reaction was then filtered to remove the solids and dried over $MgSO_4$ to give 4-hydroxy-2-butynal in 85.7% yield by GLC. Due to instability, the aldehyde was not isolated and was immediately converted to the ethyl acetal by refluxing the crude product in ethanol (50 mL) with a catalytic amount of HCl.

1,1-Diethoxy-2-butyn-4-ol.

^1H NMR: ($CDCl_3$) 1.15-1.20 (6H,t); 3.50-3.56 (2H,dq); 3.66-3.72(2H,dq); 4.25-4.26 (2H,d); 5.25(1H,s).

^{13}C NMR: ($CDCl_3$) 14.90 (q); 50.62 (t); 60.95(t); 80.76(s); 83.78(s); 91.22(d).

General Procedure for Copper assisted Grignard alkylation: 5,5,5,-Trideuteropentyl chloride or Pentyl chloride [125]:

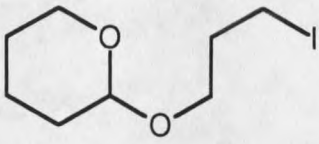
Magnesium (0.03 g) was placed under argon atmosphere in a flame dried 10 mL 2 neck flask with a stirbar and condenser at RT. To this was added 4.0 mL of freshly distilled diethyl ether. A few drops of 2.5 M methyl lithium were added to remove any excess water on the surface of the magnesium and the reaction was heated gently with a heat gun. While the solution was still warm, 0.08 mL of ethyl iodide (or 2,2,2-trideuteroethyl iodide) was added dropwise to the flask followed by heat from a heat gun. After allowing the reaction to stir for 0.5 hour, 1.0 mL of dry THF was added to the reaction. To the remaining cloudy white solution was added 8 drops of a Li_2CuCl_4 solution (0.67 g anhydrous $CuCl_2$, 0.42 g anhydrous LiCl in 50 mL of 1:1 diethyl ether / THF). The reaction immediately turned into a deep blue color and 1,3-chloroiodopropane (0.09 mL) was added dropwise followed by a 24 hour reflux. The reaction was quenched by addition of water, followed by three diethyl ether extractions. The combined organic extracts were dried over $MgSO_4$ to give the desired pentyl chloride in 87% yield by GLC. Note: some of the iodo product was seen also.

^{1}H NMR: ($CDCl_3$) 0.87-91 (3H,t) (absent in the ^{2}H labeled version); 1.28-1.42(4H,m); 1.71-1.81 (2H,m); 3.49-3.54 (2H,t).

^{13}C NMR: ($CDCl_3$) 13.86 (q) (small and broad in the ^{2}H labeled version); 21.99 (t); 29.07 (t); 32.39 (t); 45.08 (t).

MS: (EI) m/e (% abundance) (5,5,5-trideuteropentyl iodide): 201(m^+, 31); 155(4); 127(29); 74(100); 58(13); 46(45).

<u>3-Iodo-1-tetrahydropyranylpropane via 3-Chloro-1-tetrahydropyranylpropane {126]:</u>



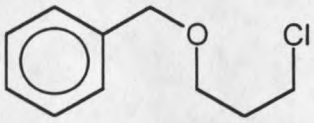
A solution of 3-chloropropanol (20 g) in 150 mL of methylene chloride was cooled with stirring to 0° under an argon atmosphere. Dropwise addition of 23.3 mL of dihydropyran was followed by 2 drops of concentrated HCl. The reaction was stirred and allowed to reach RT slowly. The stirring was discontinued and a moderate amount (~3 g) of molecular sieves were added to absorb the remaining water. After standing overnight, the molecular sieves were filtered away, the solvent was removed via rotary evaporation to give a quantitative yield of the THP protected alkyl chloride. The chlorine was exchanged with I^- and thus converted to the iodo compound as described in the following paragraph.

NaI (39 g) was added to 0.27 L of MEK in a round bottom flask equipped with a stirbar and a condenser. The mixture was brought to reflux for one hour followed by addition of 38 g of 3-chloro-1-tetrahydropyranylpropane. The reaction was refluxed for 24 hours. The mixture was cooled to RT and the salts were filtered away. Solvent was removed by rotary evaporation and hexane was added to further precipitate the salts. After filtration of the remaining salts, the solvent was again removed and the product was distilled at 75-78° @ 0.45 mm Hg to yield 32 g of 3-iodotetrahydropyranylpropane.

^{1}H NMR: ($CDCl_3$) 1.44-1.79 (6H,m)THP; 2.00-2.08 (2H,m); 3.23-3.27 (2H,t)THP; 3.36-3.50 (2H,m); 3.72-3.85 (2H,m); 4.54-4.57 (1H,t)THP.

^{13}C NMR: ($CDCl_3$) 3.20 (t); 19.43 (t)THP; 25.39 (t)THP; 30.56 (t)THP; 33.58 (t); 62.20 (t)THP; 66.79 (t); 98.83(d).

Benzyl 3-chloropropyl ether [127]:



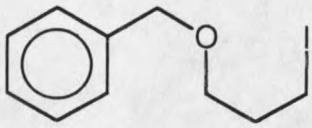
NaH (2.0 g of 50% dispersion in mineral oil) was placed in a 2 neck round bottom equipped with a stirbar and condenser. THF (75 mL) was added slowly to the NaH and the mixture was cooled in a ice bath. To this basic solution was added slowly, 3-chloropropanol (1.8 mL). The temperature of the solution was changed to RT after completing the addition. The reaction was stirred at RT for approximately one hour.

After cooling the reaction again to 0°, benzyl bromide (2.1 mL) was added to the reaction which was allowed to stir overnight and return to RT. The crude reaction product was filtered through a Florisil® pad and the solvent was removed via rotary evaporation. Distillation of the crude product 68-71° @ 0.25 mm Hg gave 3.2 g of the product (96%).

^{1}H NMR: ($CDCl_3$) 2.04-2.08 (2H,m); 3.60-3.69 (4H,m); 4.52 (2H,s); 7.30-7.35 (5H,s).

^{13}C NMR: ($CDCl_3$) 32.80(t); 41.91(t); 66.72(t); 73.09(t); 127.57(2C,d); 128.36(2C,d); 138.28(s).

Benzyl 3-iodopropyl ether [128]:

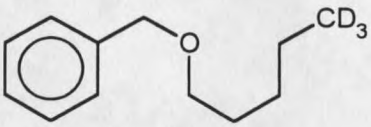


Methyl ethyl ketone (150 mL) and NaI (21.8 g) were placed in a round bottom flask equipped with a stirbar and a condenser under an inert argon atmosphere. The contents of the flask were refluxed for approximately one hour. Benzyl 3-chloropropyl ether (17.9 g) was added dropwise and the reaction was refluxed for 24 hours. The mixture was cooled to RT and the salts were filtered away. Solvent was removed by rotary evaporation. Hexane was added to further precipitate the salts. After filtration of the remaining salts, the solvent was again removed and the product was distilled at 85-90° @ 0.3 mm Hg to give the iodo product in 90% yield.

^{13}C NMR: ($CDCl_3$) 2.07 (2H,m); 3.29-3.33 (2H,t); 3.52-3.56 (2H,t); 4.52 (2H,s); 7.31-7.36 (,5H,s).

^{1}H NMR: ($CDCl_3$) 3.26(t); 33.51(t); 69.58(t); 73.08(t); 127.60(2C,d); 128.36(2C,d); 138.23(s).

General procedure for Copper assisted Grignard alkylation II: Benzyl 5,5,5-trideuteropentyl ether or Benzyl pentyl ether [129]:



Benzyl 3-iodopropyl ether (1.8 mL or 2.8g) was added to a stirred solution of dry excess magnesium (0.7 g) in freshly distilled diethyl ether in a flame dried argon atmosphere. The vigorous reaction that ensues was allowed to slow. Heat was applied from a heat gun for a couple of minutes and the reaction was allowed to stir for 30 min. This Grignard solution was titrated with 1,10-phenanthroline and 1M *sec*-butanol in THF. The results of three titrations were averaged to give a concentration of 0.7 M of Grignard. In a 10 mL flame dried 2 neck round bottom under argon atmosphere was placed with stirring 0.46 g of oven dried CuI with 6 mL of dry THF. The flask was chilled to -78° in a dry ice / acetone bath. To this solution was added 3.2 mL (2.5 mM of the 0.7 M Grignard solution) of the above freshly prepared Grignard. The reaction was stirred and allowed to slowly return to 0°. The temperature was allowed to stay at 0° for one minute or until a blue color persisted. The blue

solution was chilled to -25° and ethyl iodide or 2,2,2-trideuteroethyl iodide (2.5 mM or 0.2 mL) was added. The reaction was allowed to stir overnight and slowly return to RT. The reaction workup consisted of adding saturated NH_4Cl followed by three successive hexane extractions. The organic layers were combined and dried over $MgSO_4$. The solvent was removed via rotary evaporation to give 72% yield of benzyl pentyl ether after purification and 62% of benzyl 5,5,5-trideuteropentyl ether by GLC.

Benzyl pentyl ether

^1H NMR: ($CDCl_3$) 0.91-0.98 (3H,m); 1.35-1.40 (4H,m); 1.63-1.67 (2H,m); 3.47-3.51 (2H,t); 4.53 (2H,s); 7.29-7.37 (5H,m).

^{13}C NMR: ($CDCl_3$) 13.92(t); 22.47(t); 28.33(t); 29.42(t); 70.47(t); 72.79(t); 127.50(2C,d); 128.24(2C,d); 138.73(s).

Benzyl 5,5,5-trideuteropentyl ether

^1H NMR: ($CDCl_3$) 1.32-1.37 (4H,m); 1.58-1.65(2H,m); 3.44-3.49 (2H,t); 4.50 (2H,s); 7.27-7.35 (5H,m).

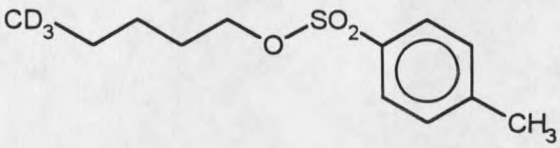
^{13}C NMR: ($CDCl_3$) 22.26(t); 28.29(t); 29.48(t); 70.53(t); 72.84(t); 127.58(2C,d); 128.31(2C,d); 138.77(s).

Pentyl alcohol or 5,5,5-trideuteropentyl alcohol [130:

The benzyl 5,5,5-trideuteropentyl ether (180 mg) was placed in a Parr flask with approximately 30 mL of dry methanol. To this solution

was added a small spatula tip of the metal catalyst (5% Pd / C). The reaction was shaken under 45 psi of H_2 for 4 hours. The reaction was filtered through a pad of (top to bottom) Celite® and silica gel on a fritted filter. The solvent was removed slowly on a rotary evaporator with the flask in an ice bath to yield 69% of the alcohol by GLC. No further purification was needed. This alcohol was not isolated and was converted to the tosylate.

General procedure for making a tosylate: 5,5,5-trideuteropentyl-1-tosylate or pentyl-1-tosylate [131]:



The pentyl alcohol (60.0 mg) was dissolved in pyridine (0.6 mL) under an inert atmosphere with stirring at 0°. TsCl (0.15 g) was added and the reaction was allowed to slowly reach RT and stir overnight. The excess pyridine was removed on a rotary evaporator. Approximately 10 mL of 10% aq. HCl was added and allowed to stir for 10 minutes. The mixture was extracted three times with hexane and the organic layers were combined and dried over $MgSO_4$. Purification of the tosylate on reverse phase C18 column using 9:1 MeOH / H_2O gave the product in 65% yield.

5,5,5-Trideuteropentyl-1-tosylate

^{1}H NMR: ($CDCl_3$) 1.22-1.28 (4H,m); 1.59-1.64 (2H,m); 2.43 (3H,s); 3.97-4.02 (2H,t); 7.31-7.34 (2H,d); 7.76-7.78 (2H,d).

^{13}C NMR: ($CDCl_3$) 21.60(q); 21.75(t); 27.36(t); 28.54(t); 29.69(t); 70.68(t); 127.87(d); 129.77(d); 133.34(s); 144.58(s).

MS: (CI^+,NH_3) m/e (% abundance): 263 (m-18+1,100); 108 (5); 91(4).

Pentyl-1-tosylate.

^{1}H NMR: ($CDCl_3$) 0.80-85 (3H,t); 1.20-1.27 (4H,m); 1.56-1.69 (2H,m); 2.43 (3H,s); 3.97-4.02 (2H,t); 7.31-7.33 (2H,d); 7.75-7.81(2H,d).

^{13}C NMR: ($CDCl_3$) 13.76(q); 21.59(q); 22.01(t); 27.45(t); 28.54(t); 70.66(t); 127.87(d); 128.77(d); 133.44(s); 144.53(s).

<u>General procedure for Iodine exchange of a halogen on a small scale: The Finkelstein reaction to make pentyl iodide or 5,5,5-trideuteropentyl iodide [132]:</u>

NaI (83.7 mg) and dry acetone (2.5 mL) were placed in a 10 mL flame dried two neck flask under an argon atmosphere. The solution was brought to reflux for a period of one hour or until the NaI fully dissolved. The labeled or unlabeled tosyl pentane (55.1 mg) was added and immediately a yellow precipitate was visible. The reaction was refluxed for 3 hours after which

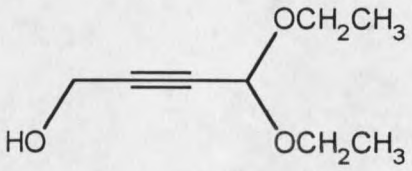
the heat was removed and the reaction was allowed to stir overnight. Pentane (~2 mL) was added and the mixture was filtered through a filter pipette filled with Florisil® and anhydrous $MgSO_4$. The pipette was washed with small portions of pentane. The solvent was removed on a rotary evaporator with the flask cooled in an ice bath. The yield was determined to be 40.0 mg of the iodo product (89%) by GLC. The product was not isolated and was immediately exposed to Grignard conditions below.

Representative attempt at Grignard formation with freshly prepared pentyl iodide:

Excess dry Mg (~50 mg) was placed in an diethyl ether solution (2.0 mL) in a flame dried 2 neck 10 mL flask under a argon atmosphere. A few drops of EtI were added to get the Mg activated and remove any water that was present. The reaction was heated to facilitate the reaction. After a few minutes, another drop of EtI was added to give a visual check of Grignard formation. A vigorous reaction was observed with activity on the Mg surface. The pentyl iodide (40.0 mg) was then slowly added, with a careful attention to note a continued reaction at the Mg surface. The reaction became slightly cloudy in appearance but some activity was noted at the Mg. The solution was heated gently with a heat gun and allowed to stir for 15 minutes. Approximately three fold excess of *trans*-4,4-diethylacetal-2-butenal (40 μL) was

added to the reaction causing a cloudy white precipitate to develop. The reaction was stirred for an additional 10 minutes and then was quenched with sat. NH_4Cl followed by extraction three times with diethyl ether. The organic extracts were combined and the solvent was removed on a rotary evaporator. GLC analysis showed only a trace of the desired product (less than 5%).

1,1-Diethoxy-2-butyn-4-ol [124]:



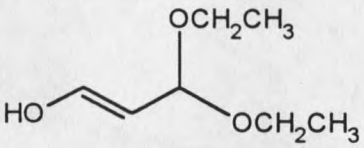
Mg (52.1 g) was placed in 570 mL of THF in a 1.00 L round bottom flask equipped with a condenser and stirbar. To this solution was slowly added 160 mL of EtBr in small portions allowing a gentle reflux of the THF. The reaction was allowed to stir for approximately one hour at RT following the addition. The flask was chilled to 0° followed by slow addition of 56.0 g of propargyl alcohol dissolved in 75.0 mL of THF. The mixture was gently refluxed for 3 hours. Triethyl orthoformate 167 mL was added in one portion and the reaction was allowed to reflux overnight. The workup of the reaction was accomplished by removal of approximately 300 mL of the THF solvent. The remaining reaction mixure was allowed to return to RT and was poured into an ice cooled solution of NH_4OAc (287 g in 1 L of water). The reaction

was extracted three times with ether. The organic extracts were combined and washed with a brine solution then dried over anhydrous $MgSO_4$. The emulsion was broken up by filtration over a Celite® pad using vacuum filtration. The remaining oil was distilled at 104°C at 1.25 mm Hg to yield 68.7g of product (43.5%).

^1H NMR: ($CDCl_3$) 1.15-1.20 (6H,t); 3.50-3.56 (2H,dq); 3.66-3.72(2H,dq); 4.25-4.26 (2H,d); 5.25 (1H,s).

^{13}C NMR: ($CDCl_3$) 14.90(q); 50.62(t); 60.95(t); 80.76(s); 83.78(s); 91.22(d).

<u>*trans*-1,1-Diethoxy-2-butene-4-ol [123]:</u>

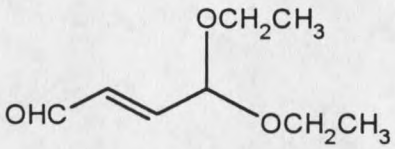


To a solution of 0.17g $LiAlH_4$ (1.0 eq.) in 5.0 mL dry ether at -25° C over argon atmosphere was added slowly with stirring 0.50g of [124] (0.60 eq.). Stirring was continued for 6 hr while maintaining the temperature at -25° C. The reaction was quenched with saturated aqueous NH_4OH. During the quench, the temperature was kept at or below -5° C. After filtration of the slurry, the remaining precipitate was washed with water, followed by ether. The aqueous layer was extracted three times with ether. The combined extracts were dried over anhydrous $MgSO_4$, the drying agent removed by filtration, and the remaining ether solution concentrated via rotary evaporation. Flash chromatography (1:1 hexane / ethyl acetate) yielded 0.41g yellow oil (87%).

^1H NMR: ($CDCl_3$) 1.15-1.20 (6H,t); 3.50-3.56 (2H,dq); 3.66-3.72(2H,dq); 4.25-4.26 (2H,d); 5.25(1H,s).

^{13}C NMR: ($CDCl_3$) 14.90 (q); 50.62 (t); 60.95(t); 80.76(s); 83.78(s); 91.22(d).

<u>*trans*-1,1-Diethoxy-2-butene-4-al [120]:</u>



Oxalyl chloride (7.6g) was placed in 110 mL of CH_2Cl_2 at -78° C. Dry DMSO (9.3 mL in 25 mL CH_2Cl_2) was added slowly over a period of 50 min. After the addition was complete, the reaction was stirred for 20 additional minutes. The alcohol, *trans*-1,1-diethoxy-2-butene-4-ol (7.0g, 0.044 moles), was added dropwise over a period of 1 hr and the mixture was stirred for another hour at a dry ice bath temperature (-78°C). Triethylamine (27g) was added dropwise and the resulting mixture stirred for 1 hr. The cold bath was then removed and reaction mixture poured into 50 mL of water and 150 mL ether. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined and washed with water and saturated brine, then dried over $MgSO_4$. Drying agent was removed by filtration and the resulting organic solution was concentrated via rotary evaporation to give 69% yield by GLC. Distillation (48-52° @ 0.70 mm Hg) yielded 2.6g product (37% isolated yield).

^{1}H NMR: ($CDCl_3$) 1.20-1.22 (6H,t); 3.50-3.67 (4H,m); 5.11-5.13 (1H,d); 6.29-6.37 (1H,dd); 6.61-6.68 (1H, dd); 9.58-9.60 (1H,d)

^{13}C NMR: ($CDCl_3$) 15.15(q); 61.71(t); 99.17(d); 133.62(d); 151.25(d); 193.12(s)

MS: (CI+) m/e (% abundance): 159(m+,11); 131(3); 129(10); 114(11); 113(100); 103(8); 101(5); 97(2).

HRMS: Calculated for $C_8H_{14}O_3$ 158.0943; Found 158.0968.

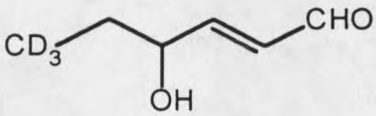
General procedure for Grignard reactions:

Powdered Mg (30 mg) was placed in 2.0 mL of dry ether under argon atmosphere at RT. To this was added 0.13 mL of 3,3,3-trideuteroethyl iodide at a rate to allow the ether to reflux. When the addition of alkyl halide was completed, another 3.0 mL of dry ether was added to increase the reaction volume. The reaction mixture was stirred for 15 min. and then the aldehyde 3 (0.23 mL in approximately one mL of dry ether) was added to the reaction. After stirring for 30 minutes, the reaction was quenched with saturated NH_4Cl. After extractions (three times with CH_2Cl_2), the organic phase was dried over anhydrous $MgSO_4$. The solvent was removed via rotary evaporator. The crude product was taken directly to the next step.

General procedure for acetal hydrolysis:

The crude acetal (0.5 g approximately) was stirred in 50 mL of a 1:1 water/THF solution containing one drop of HCl at RT overnight. The THF was removed via rotary evaporation and the remaining aqueous layer was extracted three times with ether. The combined ether extracts were dried over $MgSO_4$, filtered from the drying agent, and the solvent removed on a rotary evaporator. The crude yield was 70-85%.

trans-4-Hydroxy-6,6,6-Trideutero-2-hexenal [133]:



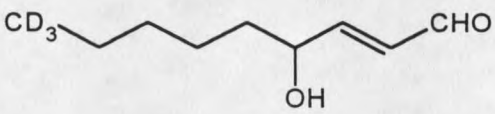
^1H NMR: ($CDCl_3$) 1.55-1.67 (2H,m); 2.10 (1H,s br); 4.31-4.35 (1H,m); 6.23-6.32 (1H,dd); 6.76-6.83 (1H,dd); 9.53-9.56 (1H,d).

^{13}C NMR: ($CDCl_3$) 9.23(3D br); 29.28(t); 72.22(d); 130.94(d); 158.41(d); 193.34(d).

MS: (CI+) m/e (% abundance): 118(m+,100); 117(4); 116(11); 115(1); 102(3); 101(6); 100(71); 99(11); 98(3).

HRMS: (CI+) Calculated for m+ $C_6H_8O_2D_3$ 118.0944.; Found 118.0940.

trans-4-Hydroxy-9,9,9-Trideutero-2-nonenal [134]:



^1H NMR: ($CDCl_3$) 1.12-1.45 (6H,m); 1.52-1.60 (2H,m); 2.81 (1H, s, br); 4.33-4.38 (1H, dd); 6.19-6.28 (1H,dd); 6.75-6.82 (1H,dd); 9.48-9.50 (1H,d)

^{13}C NMR: ($CDCl_3$) 15.02(3D, br); 22.13(t); 24.80(t); 31.42(t); 36.33(t); 70.88(d); 130.42(d); 159.58(d); 193.74(d).

MS: (CI+) m/e (% abundance): 160(m+,100); 158(6); 142(17); 130(5); 124(6); 115(6); 112(10); 102(19); 100(7); 98(9).

HRMS: (CI+) Calculated for m+ $C_9H_{14}O_2D_3$ 160.1414; Found 160.1427.

5-(Tetrahydropyranyl)-1-pentyne [138]:

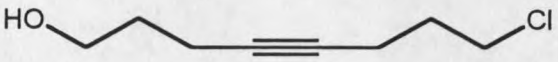
To a stirred solution of 4.5g 5-hydroxypentynol, [136], in CH_2Cl_2 (0.10 L) at 0^0 C. under an argon atmosphere was added dihydropyran (4.9 mL). A few drops of concentrated HCl were added to catalyze the reaction. The reaction was allowed to slowly return to RT and stir overnight. Water was added and the organic layer was separated from the aqueous fraction. The aqueous fraction was extracted three times with CH_2Cl_2. The combined organic material was washed with saturated brine then dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation to give the product in quantitative yield.

^1H-NMR: ($CDCl_3$) 1.40-1.65 (6H,m); 1.68-1.78 (2H,t); 1.87 (1H,s); 2.20-2.28 (2H,p); 3.35-3.48 (2H,m); 3.72-3.85 (2H,m); 4.52-4.58 (1H,t).

^{13}C-NMR: ($CDCl_3$) 15.23 (t); 19.39 (t); 25.40 (t); 28.65 (t); 30.57 (t); 62.00 (t); 65.66 (t); 68.31(d); 83.81(s); 98.66(d).

1-Chloro-8-hydroxy-oct-4-yne [140]:

First method; using tetrahydrofurfuryl chloride as the nucleophile.



Pure ammonia was distilled from a flask and condensed by a cold finger until approximately 100 mL was collected in a 250 mL round bottom flask. To this stirred solution, was added a small spatula tip of ferric nitrate followed by addition of lithium (0.05 g) in small portions. The reaction is stirred until the blue color dissipated. At this time, tetrahydrofurfuryl chloride (2.0 g) was added to the prepared lithium amide solution. The reaction was stirred for approximately 2 hours or until all of the tetrahydrofurfuryl chloride had reacted. To this solution was added 1,3-chloroiodopropane (1.8 mL) in 10 mL of THF. The reaction was stirred and cooled at -33° C. for an additional 30 minutes when the ammonia was allowed to evaporate to dryness and return to RT. Saturated ammonium chloride was added to the remaining gray solids and the aqueous solution was extracted three times with ether. The combined organic extracts were dried over $MgSO_4$ and the

solvent was removed by rotary evaporation to yield the product in 63% by GLC. (Note: this was a mixure of both iodo and chloro products.)

Second method; using 5-tetrahydropyranyl-1-pentyne as the nucleophile.

At 0° C. under an argon atmosphere was added 7.9g (47 mmoles) of 5-tetrahydropyranyl-1-pentyne, [138], in 80 mL THF. To this solution 47 mmoles of n-BuLi were added dropwise. The mixture was stirred for five minutes followed by addition of 7.8 mL HMPA. The temperature was allowed to slowly warm to RT and stirring was continued for 30min. The reaction was chilled to -78° C. and 1,3-chloroiodopropane (5.5 mL) was added. The reaction was allowed to slowly reach RT and to stir for 24 hours. Water was used to quench the reaction, followed by extraction of the aqueous layer three times with hexane. The combined organic extracts were washed with saturated brine then saturated sodium bicarbonate. The organics were dried over $MgSO_4$ and the solvent was removed via rotary evaporation to give a mostly 1-chloro-8-tetrahydropyranyloct-4-yne, [139], (some of the iodo product was present) in 79% yield by GLC (sum of both products). The product was not isolated, and was subsequently hydrolyzed to remove the THP group. The crude product was placed in 25 mL of a 1:1 THF / 5% aq. HCl

solution and heated to reflux for 8 hours. After the reaction returned to RT, the THF was removed by rotary evaporation, and the water solution was extracted three times with diethyl ether. The extracts were dried over $MgSO_4$, and the solvent was removed via rotary evaporation. Yield was quantitative for the removal of the protecting group.

^{1}H-NMR: ($CDCl_3$) 1.42-1.51 (1H,t); 1.70-1.76 (2H,dt); 1.86-1.93 (2H,dt); 2.23,2.35 (4H,m); 3.60-3.64 (2H,t); 3.70-3.76 (2H,t).

^{13}C-NMR: ($CDCl_3$) 15.36 (t); 16.24 (t); 31.67 (t); 31.79(t); 43.69 (t); 61.97 (t); 78.86 (s); 80.50 (s).

8-Hydroxynon-4-ynenitrile [141]:

A mixure of 3.9 g of halides from the above

alkylation was placed with stirring in a 100 mL round bottom flask equipped with condenser under argon atmosphere with 1.6 g NaCN in 50 mL DMSO. The mixture was heated to reflux and after approximately 1 hour the reaction mixture turned to a deep black color. The reaction was refluxed 12 additional hours. After the reaction had cooled to RT, water was added and the water layer was extracted three times with hexane. The extracts were washed with saturated brine, and dried over $MgSO_4$. The solvent was removed by

rotary evaporation to yield 3.7g of the pure product in 93% yield. No further purification was necessary.

^{1}H-NMR: ($CDCl_3$) 1.53-1.60 (2H,dt); 1.62-1.72 (2H,dt); 2.07-2.20 (4H,m); 2.33-2.47 (2H,t); 2.98 (1H,s br); 3.49-3.55 (2H,t).

^{13}C-NMR: ($CDCl_3$) 14.53 (t); 15.36 (t); 17.23 (t); 24.20 (t); 30.99 (t); 60.53 (t); 77.00 (s); 81.03 (s); 118.75 (s).

<u>9-Hydroxynon-4-yne carboxylic acid [142]:</u>

8-Hydroxynon-4-ynenitrile, [141],

(3.7g) was refluxed with 40mL of a 25% KOH solution. A few milliliters of THF was added to help the solubility of the nitrile. The reaction was refluxed until NH_3 was no longer detected at the top of the condenser. The reaction was worked up by allowing the mixture to cool to RT followed by careful addition of chilled 10% HCl until the pH was less than 4. Extraction of the organic layers three times with diethyl ether was followed by drying the organic layer over $MgSO_4$. The excess solvent was removed with rotary evaporation to yield 2.6g (83% by GLC or 65% isolated yield).

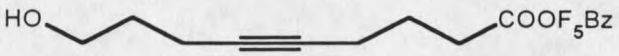
^{1}H-NMR: (CD_3OD) 1.34-155 (4H,m); 1.88-2.05 (4H,m); 2.05-2.20 (2H,t); 3.32-3.42 (2H,t); note: hydroxyl and

carboxylic protons exchanged with protic solvent and are not visible in ^1H NMR.

^{13}C-NMR: (CD_3OD) 15.82 (t); 18.85 (t); 25.50 (t); 32.98 (t); 33.75 (t); 61.71 (t); 80.07 (s); 81.18 (s); 177.01 (s).

Perfluorobenzyl 9-hydroxynon-4-ynoate [143]:

-Hydroxynon-4-yne



carboxylic acid, [142], (0.25g) was combined with 0.38 g $NaHCO_3$ in 25 mL dry DME under argon atmosphere. The reaction was heated at reflux for 2 hours. After allowing the reaction to cool to RT, 0.18 mL of perfluorobenzyl bromide was added dropwise. After the addition was complete, the reaction was returned to reflux temperature for 36 hours. The reaction was worked up by filtration through a fritted filter over a pad of silica gel followed by solvent removal via rotary evaporation to give 48% yield by GLC of the perfluorobenzyl ester.

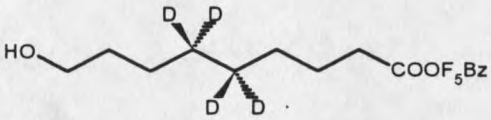
^1H-NMR: ($CDCl_3$) 1.69-1.83 (4H,m); 2.16-2.29 (4H,m); 2.41-2.48 (2H,t); 3.66-3.79 (2H,t); 5.17 (1H,s).

^{13}C-NMR: ($CDCl_3$) 15.33 (t); 18.15 (t); 24.06 (t); 31.64 (t); 32.75 (t); 53.25 (t); 61.91 (t); 79.27 (s); 80.55 (s); 109.56 (s,br); 135.89,139.17 (2C, Fluorine-doublet); 140.23,143.50 (Fluorine-doublet); 144.09,147.38 (2C,Fluorine-doublet); 172.5(s).

MS: (EI) TMS derivatized (% abundance) 422 (m^+,2); 207 (9); 181 (100); 169 (38); 155 (33); 151 (38); 109 (91); 91 (64); 77 (83); 55 (60).

Perfluorobenzyl 9-hydroxy-5,5,6,6-tetradeuterononanoate [144]:

A small amount (70mg) of [143] was placed into a solution of 15mL MeOD with approximately 5mg of 5% Pt supported on carbon. This solution was shaken in a hydrogenation apparatus at RT for five hours at 13 psi of deuterium gas. The catalyst was removed by filtration through a filter aid pad on a medium fritted filter. The solvent was removed on a rotary evaporator to yield 91% of the deuterated product by GLC.



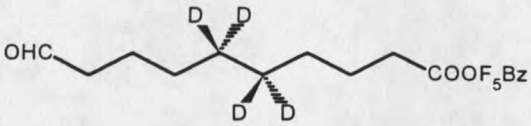
^{1}H-NMR: ($CDCl_3$) 1.32-148 (4H,dt); 1.50-1.63 (4H,m); 2.27-2.32 (2H,t); 3.58-3.63 (2H,t); 5.16 (1H,s).

^{13}C-NMR: ($CDCl_3$) 24.72 (t); 28.24 (2C, br D label); 25.39 (t); 28.69 (t); 32.71 (t); 33.89 (t); 53.12 (t); 63.00 (s); 109.67 (s,br); 136.53,138.54 (2C, Fluorine-doublet); 140.73,142.76 (Fluorine-doublet); 144.69,146.69 (2C, Fluorine-doublet); 173.01 (s).

MS: (CI^-,NH_3) m\e TMS derivatized. (% abundance) 430(M^+,1); 265(10); 249(100); 196(54); 178(38); 161(59).

HRMS: (CI^+,NH_3) (M^+-181, loss of F_5Bz group) Calculated for $C_{12}H_{21}D_4O_3Si$ 249.1824; Found 249.1823.

Perfluorobenzyl 9-oxo-5,5,6,6-tetradeuterononanoate [135]:



Perfluorobenzyl 9-hydroxy-5,5,6,6-tetradeuterononanoate, 50 mg [144], was placed in 5.0 mL of CH_2Cl_2 with 51 mg of PCC under argon atmosphere. The reaction was stirred for 8 hr at RT. A small amount of carbon black was added and the mixture was filtered through a Pasteur pipette filled with Florisil and filter aid. The pipette was washed with 20 mL of CH_2Cl_2 . The combined CH_2Cl_2 was removed on a rotary evaporator to yield 43mg of product (86%).

^{1}H-NMR: ($CDCl_3$) 1.25-1.28 (2H,t); 1.56-1.61 (4H,m); 2.28-2.31 (2H,t); 2.37-2.40 (2H,t); 5.16 (2H,s); 9.73-9.74 (1H,s).

^{13}C-NMR: ($CDCl_3$) 21.88 (t); 24.65 (t); 28.54 (t); 33.84(t); 43.78 (t); 53.15 (t) 109.85 (Fluorine-singlet); 136.78,138.81 (2C, Fluorine-doublet); 141.28,143.29 (Fluorine-doublet); 145.13,147.15 (2C, Fluorine-doublet); 173.11 (s); 202.80 (s).

MS: (EI) m\e (% abundance) 356 (M^+,1); 181(100); 176(12); 156(9); 126(9); 102(16); 85(12); 58(15); 57(15); 56(11).

HRMS: (CI^+,NH_3) Calculated for $C_{16}H_{13}D_4O_3F_5$ 356.1349; Found 356.1324.

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