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

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

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

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Bozeman, Montana

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APPROVAL

of a thesis submitted by

Karen Elizabeth Bartelt

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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To Bob, Erik, and Jill

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

Garrison Keillor

Lake Wobegon Days

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ABSTRACT

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

CHAPTER 1

INTRODUCTION

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

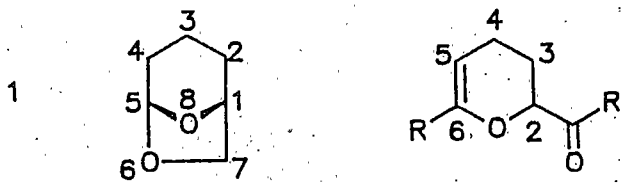
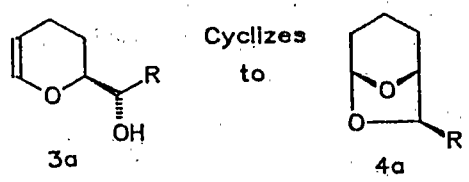


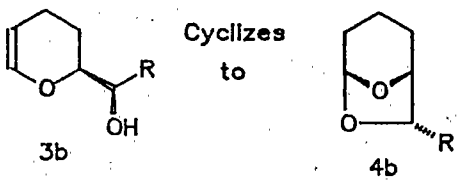
Figure 1. The 3,4-dihydro-2H-pyran [1] and 6,8-dioxabicyclo [3.2.1]octane [2] skeletons and numbering systems

Stereoselective Reductions

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



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



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

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

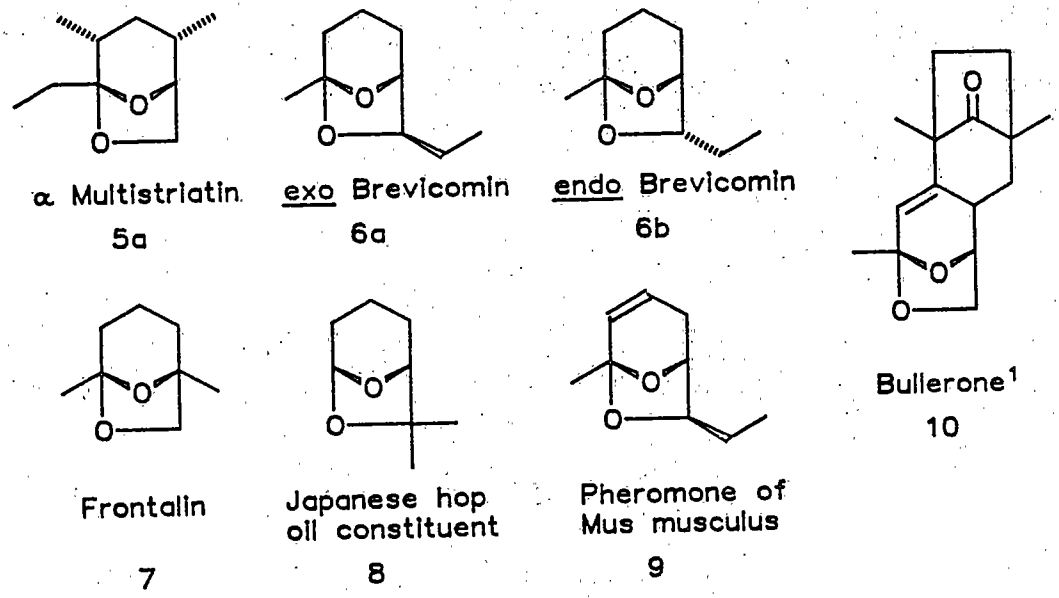


Figure 3. Natural products possessing the 6,8-dioxabicyclo [3.2.1]octane skeleton

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

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

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

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

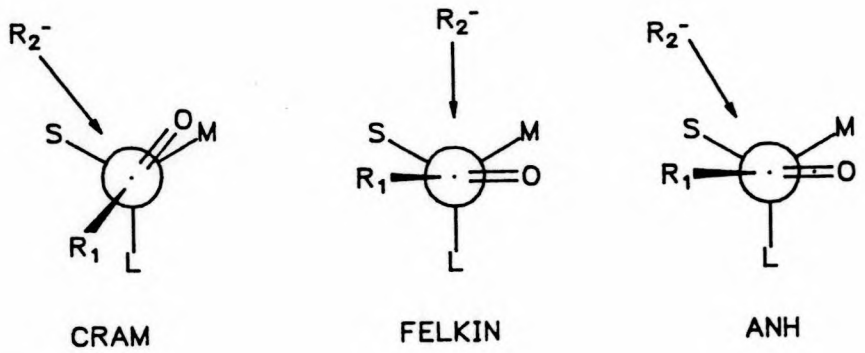


Figure 4. A comparison of Cram, Felkin, and Anh models of carbonyl reduction

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

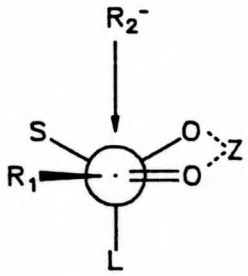
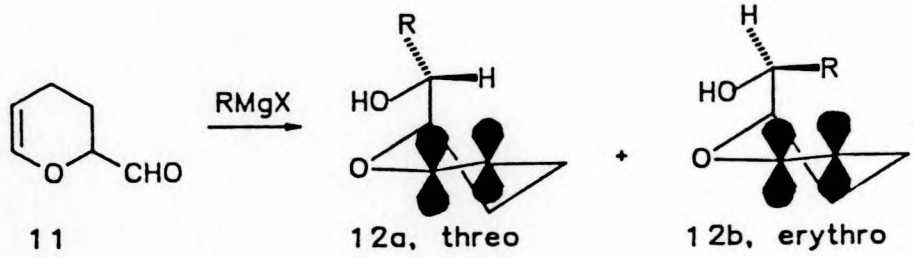


Figure 5. Cyclic model, chelation control

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



11 12a, threo + 12b, erythro

Figure 6. Steric course of Grignard addition

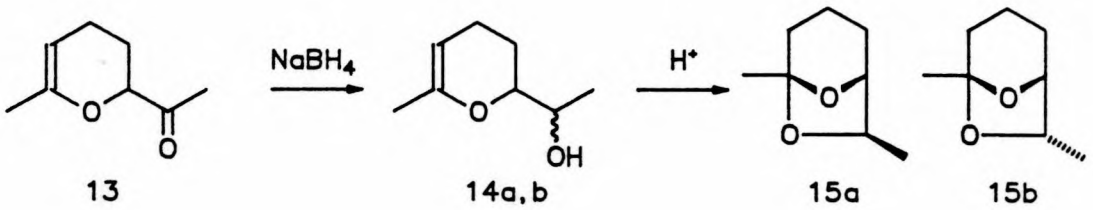


Figure 7. Reduction by $NaBH_4$

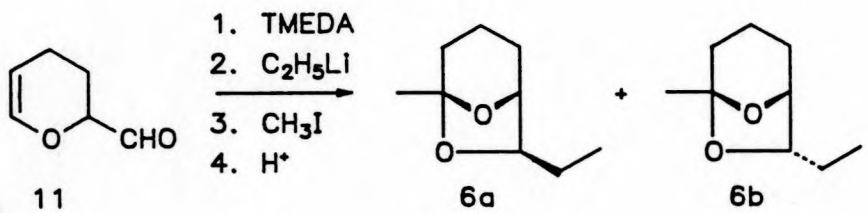


Figure 8. Stereoselective synthesis of endo brevicomin [6b]

Stereochemical control of carbonyl reductions is an important topic currently pursued by many research groups. Howe[8] has alkylated alpha, beta-epoxyaldehydes using methyllithium, methyl Grignards, and allylstannanes to give non-chelation control products with moderate to high stereoselectivity (Figure 9). Keck[9] investigated the addition of allyl-tri-n-butylstannane to alpha-hydroxyaldehydes, and found that the proper choice of a Lewis acid and protecting group can result in excellent stereoselectivity for either the erythro or threo alcohol (Figure 10). Reetz[10] reported on 1,2- and 1,4- asymmetric inductions on beta-hydroxyaldehydes (Figure 11). The stereoselectivity shown in Figure 11 could be reversed if the weaker Lewis acid, $H_3Ti(O\text{-}Ipr)_3$, was substituted for H_3TiCl_3. Koreeda and Tanaka[11] reduced aldehydes with gamma-alkoxy-allylstannanes under chelation control conditions to

give a preponderance of threo vicinal diols (Figure 12). Danishefsky and Dininno[12] were able to control the allylation of ribo- and galacto-aldosulose derivatives by varying the Lewis acid catalyst (Figure 13). In their synthesis of 6-acetoxy-5-hexadecanolide [27], Jefford[13] could select for either isomer by varying the carbanion and suppressing or enhancing chelation (Figure 14).

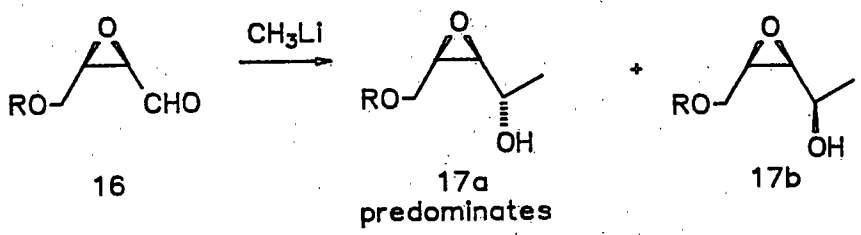


Figure 9. Howe's alkylation of alpha, beta-epoxyaldehydes

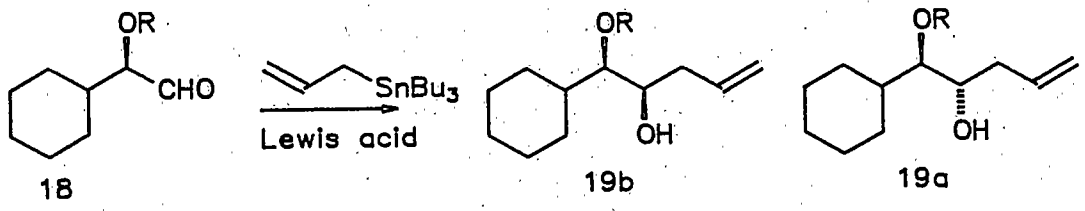


Figure 10. Keck's erythro and threo stereoselection

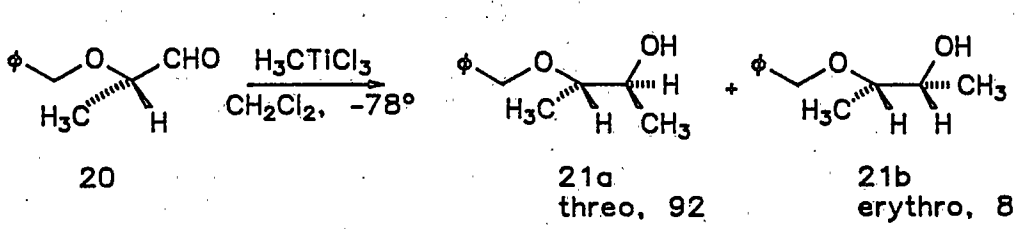


Figure 11. Reetz's asymmetric inductions

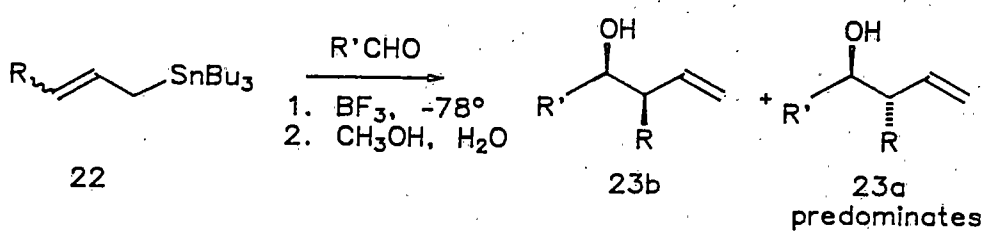


Figure 12. Alkylations by Koreeda and Tanaka

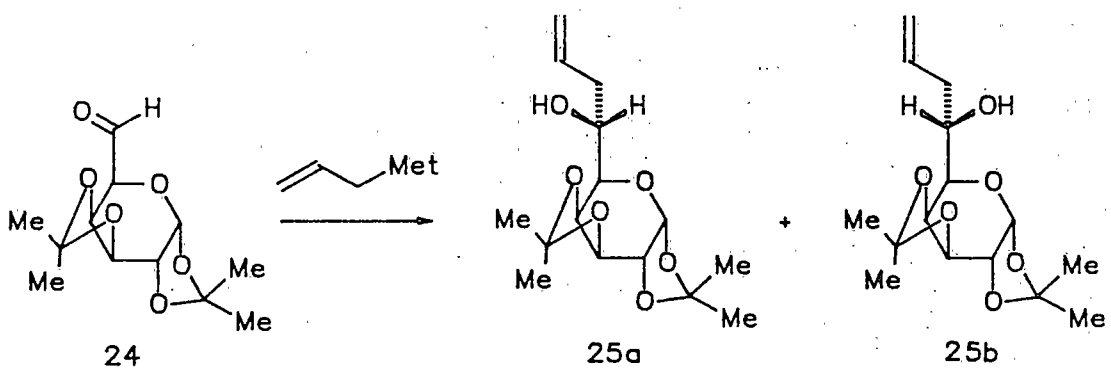


Figure 13. Stereocontrol of allylation of aldosulose derivatives

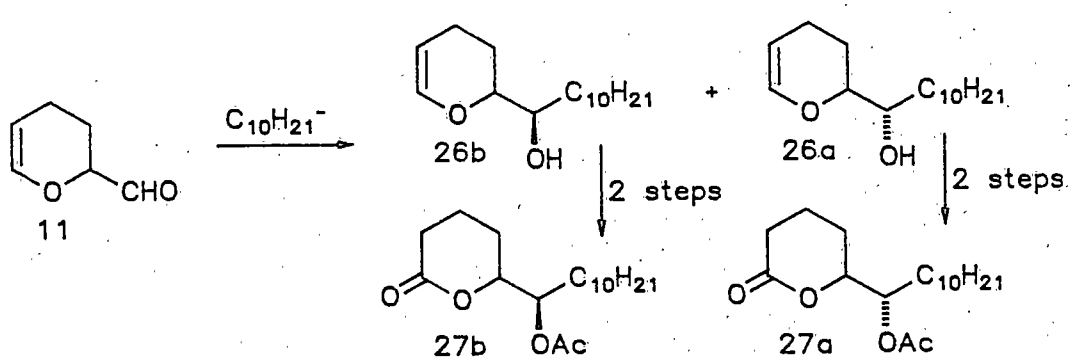
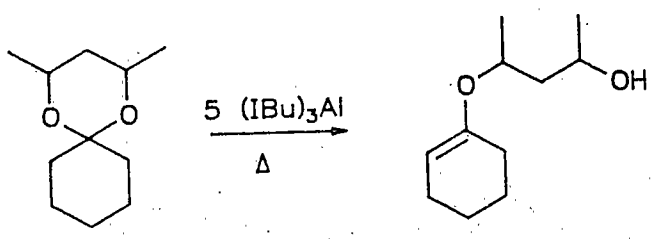


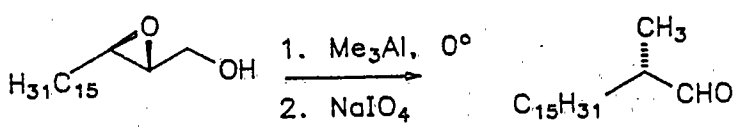
Figure 14. Synthesis of erythro/threo-6-acetoxy-5-hexadecanolide

Trialkylaluminums, specifically, have not been studied recently as reagents for carbonyl reductions. Their use as acetal cleavage reagents is well documented[14] (Figure 15), as is their use in regioselective additions to 2,3-epoxyalcohols[15] (Figure 16) and reductive rearrangement of alkoxyenol ethers[16] (Figure 17). The use of trialkylaluminums in stereoselective reduction and alkylation of alicyclic ketones has been discussed by Ashby and Laemmle[17], who found that a two-fold excess of trimethylalumium will attack the carbonyl group 90% from the more hindered side (Figure 18).



28 29

Figure 15. Acetal cleavage by triisobutylaluminum



30 31

Figure 16. Regioselective addition by trimethylaluminum

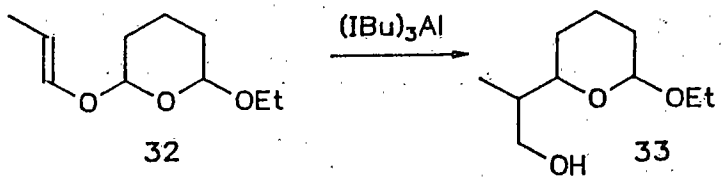


Figure 17. Rearrangement induced by R_3Al

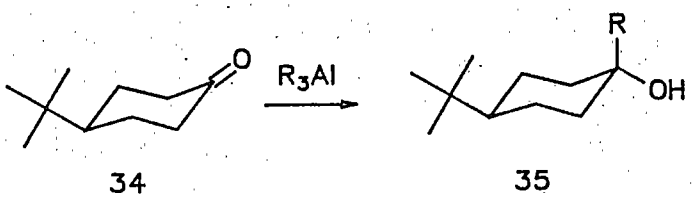
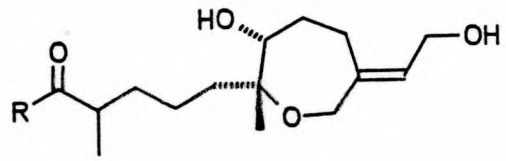


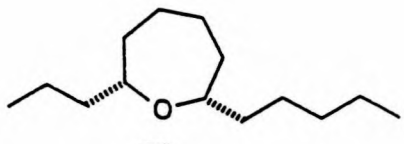
Figure 18. Reaction of alicyclic ketones with R_3Al

Diethylzinc, while widely used in the Simmons-Smith reaction, has not been used extensively in the reduction of carbonyls. Dimethylzinc has been utilized to some extent by Reetz[10].

Cleavage Reactions

It became a second goal of this research to find methods to effect regioselective cleavage of the O-8 bond and provide a means of entry into oxepanes. Several examples of representative natural products are shown in Figure 19. If cleavage of the O-8 bond were not realized, the stereochemistry of the cleavage that did occur was to be determined. When the number of stereocenters in natural products, for example those shown in Figure 19 is noted, the stereochemical outcome of the cleavage can be of significance even if the regioselective outcome of cleavage is not realized.





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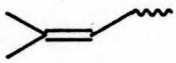
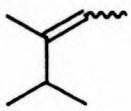
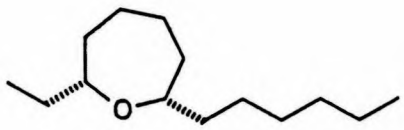
Laurenan

Zoopatanol, R =  36

Montanol, R =  37

Tomentanol, R =  38



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Lauthisan

Figure 19. Montanol[18], zoopatenol[18], tomentanol[19], laurenan[20], lauthisan[20]

The ease of synthesis of the 6,8-dioxabicyclo[3.2.1]octane skeleton from 3,4-dihydro-2H-pyranyl alcohols makes these ketals attractive synthetic intermediates. Cleavage of bicyclic ketals by various reagents has been an on-going study in this research group. Schwarz[21] effected the cleavage of the 5,7-dimethyl system using Pd(C) to get the cis-pyran alcohols (Figure 20). Kim[22] employed AlH_3 as a ketal cleavage reagent in his synthesis of civet cat glandular component (Figure 21). When Kim[23] used AlH_2Cl on the 5,7-dimethyl system, he noted the product ratio of cis- and trans-pyran-alcohols

shown in Figure 22. In his Ph.D thesis[24], Jun demonstrated the ability to cleave the O-6 bond with triethylsilylhydride, and open both rings with $MgBr_2$ (Figure 23).

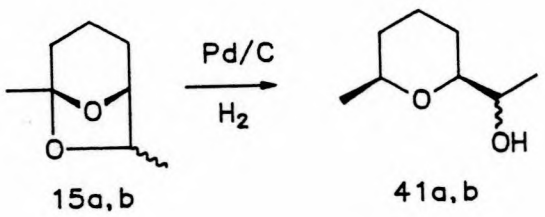


Figure 20. Cleavage with Pd(C)

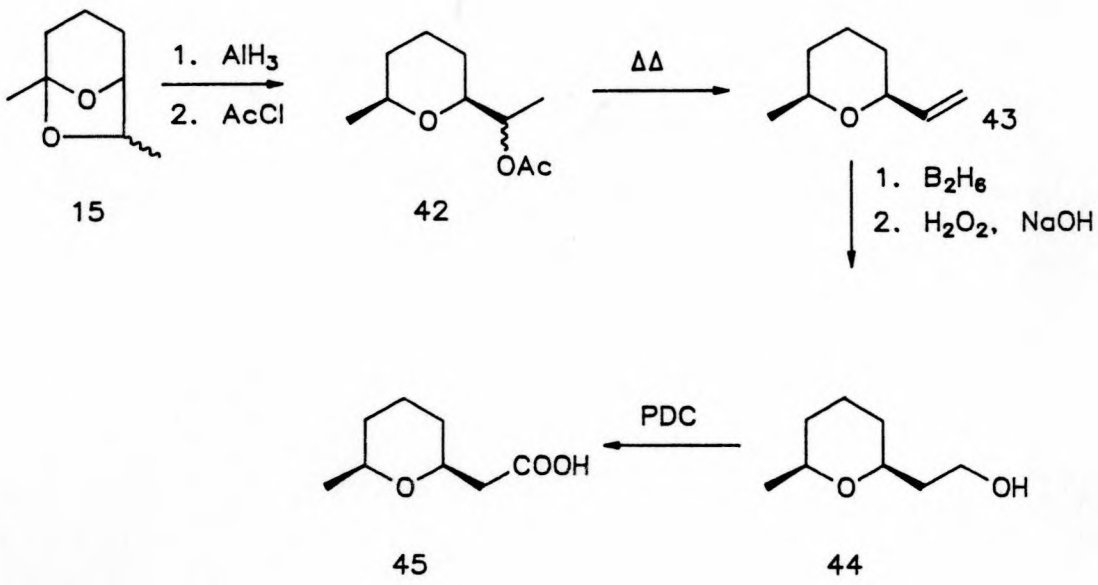


Figure 21. Synthesis of civet cat glandular component

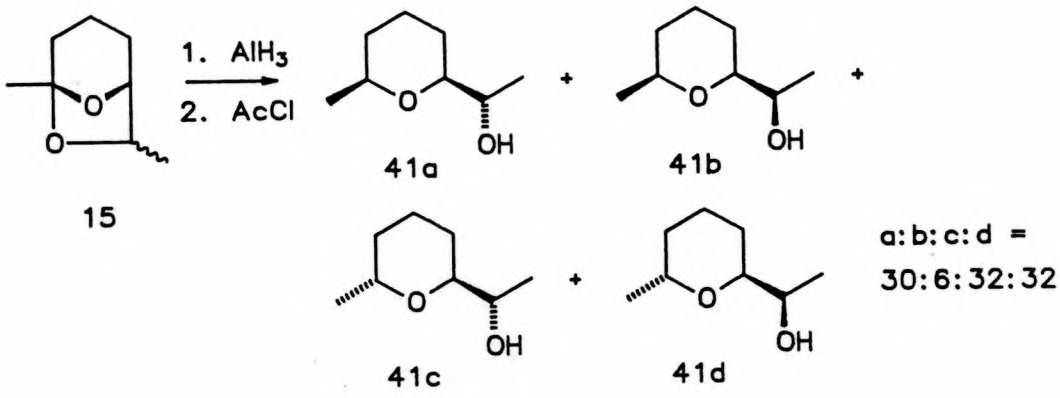


Figure 22: AlH_2Cl cleavages

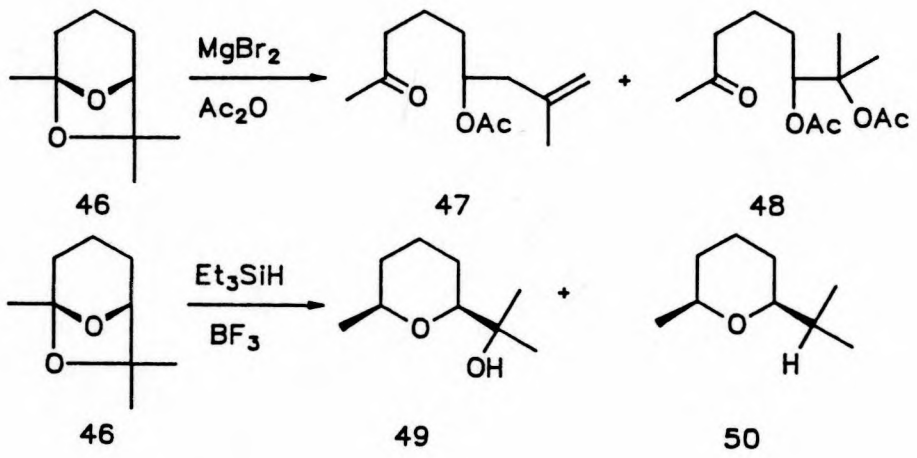
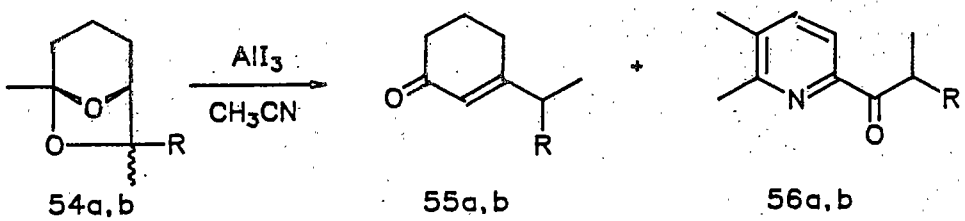


Figure 23: Et_3SiH and $MgBr_2$ cleavages

Certain cleavage reagents have resulted in more spectacular rearrangements. Two novel products resulted when Jun[24] used AlI_3 on certain bicyclic ketal systems (Figure 24). Acetyl iodide, employed by Bjorklund and Jun[25], converted ketals to delta, epsilon-unsaturated ketones by elimination of <u>both</u> bridging oxygens. This procedure was

used in the synthesis of the Douglas fir Tussock moth pheromone (Figure 25).

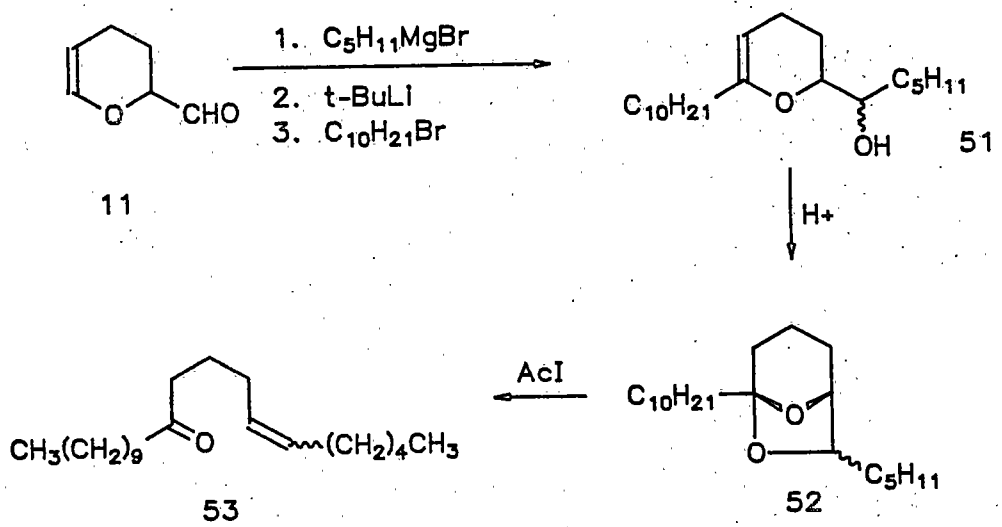


54a,b 55a,b 56a,b

a, R = Ipr

b, R = n-Bu

Figure 24. Pyridine and enone produced by AlI_3 cleavages



11 51 53 52

Figure 25. Acetyl iodide cleavages of 6,8-dioxabicyclo [3.2.1]octanes

Other research groups have employed bicyclic ketals as synthetic intermediates. Utaka's group[26] converted frontalin lactone to alpha cinenic acid and other products, including an oxepane in low yield

(Figure 26). Recently a spirocyclopropyl bicyclic ketal was used as an intermediate in the synthesis of pederol[27] (Figure 27).

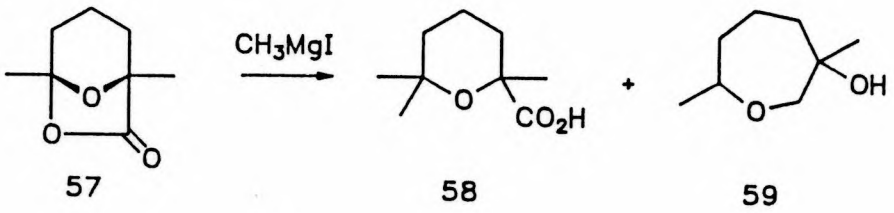


Figure 26. Conversion of frontalin lactone to alpha cinenic acid and an oxepane

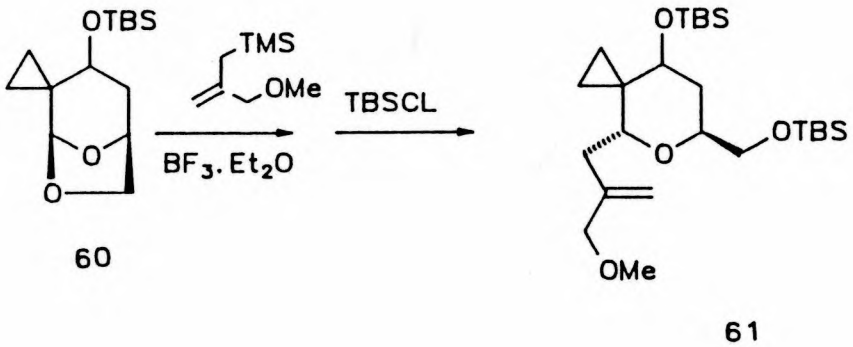
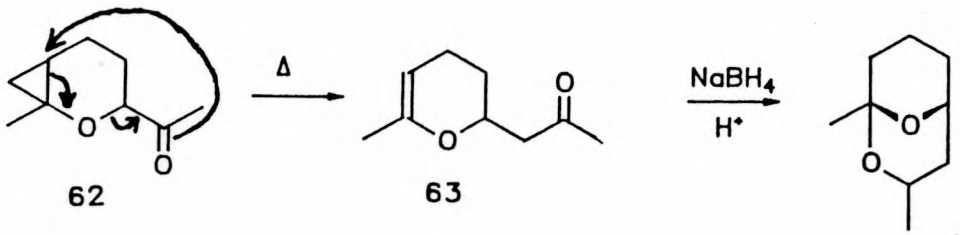


Figure 27. Bicyclic ketal in the synthesis of pederol

Cyclopropanations and Ring Openings

The third goal of this research was to cyclopropanate protected 3,4-dihydro-2H-pyrans or pyranyl alcohols. An unexplored alternative route into oxepane natural products might be found via the cyclopropanation of 3,4-dihydro-2H-pyran derivatives, followed by ring opening. The 6,9-dioxabicyclo[3.3.1]nonane skeleton, exemplified by 64, is potentially available via thermal rearrangement (Figure 28).

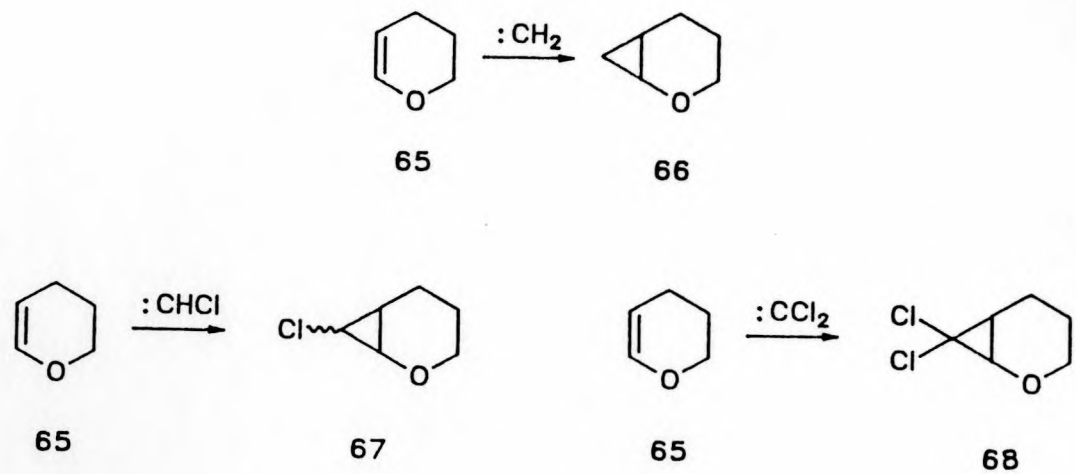


62 63

Striped ambrosia beetle pheromone
64

Figure 28. Conversion of 3,4-dihydro-2H-pyrans to oxepanes and 6,9-dioxabicyclo[3.3.1]nonanes

Cyclopropanations of 3,4-dihydro-2H-pyran are known in the literature, and include Simmons-Smith reactions[29], use of dichlorocarbenes[30], and monochlorocarbene[31] (Figure 29). Duggan Hall[32] reported the dichlorocarbenation of the 2-methoxy derivative. (Figure 31).



65 66

65 67 65 68

Figure 29. Cyclopropanations of 3,4-dihydro-2H-pyran compounds

Cyclopropanation of 3,4-dihydro-2H-pyran carbonyl derivatives is not well documented in the literature. This is because generation of a carbenoid in the the presence of diethylzinc would result in reduction of the aldehyde or ketone functionalities; esters, however, would be inert. Generation of monochlorocarbene requires n-butyllithium, which reacts with carbonyls, while dichlorocarbene is generated in sodium methoxide (or potassium-t-butoxide), which may result in enolate formation.

The third goal of this research would be fully realized only if the cyclopropane ring could be opened to an oxepin or oxepane system. Ring opening in cyclopropane systems well known. Opening of medium sized dihalo non-oxygenated rings has been accomplished by silver ion and found to proceed in a disrotatory manner via an allylic intermediate[33] (Figure 30). Diboranes have been found to cleave alkyl-cyclopropanes at 100^{o} [34]. A spirocyclopropane was opened with Adam's catalyst[27]. Ring opening of one isomer of the monochlorocarbene derivative of 3,4-dihydro-2H-pyran has been accomplished using both silver ion and quinoline[30] (Figure 31). A 2-methoxy-3,4-dihydro-2H-pyran has been opened by silver ion to give chloromethoxyhexenes and chloromethoxyhepten-2-ones[32] (Figure 31). It was hoped that one of these reagents would successfully open the dihydropyran-derived cyclopropanes.

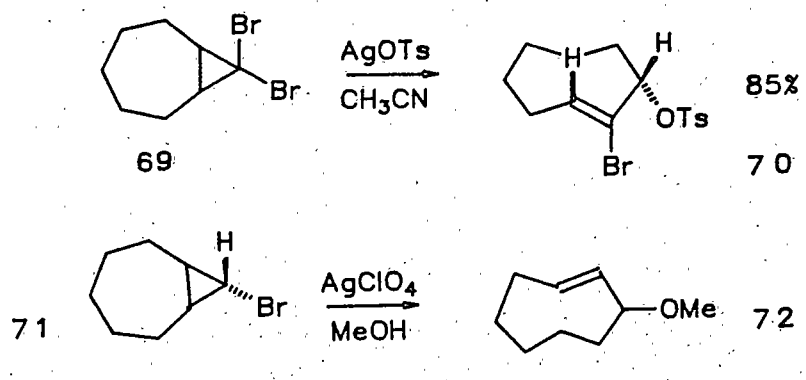


Figure 30. Ring-opening of alkyl cyclopropanes

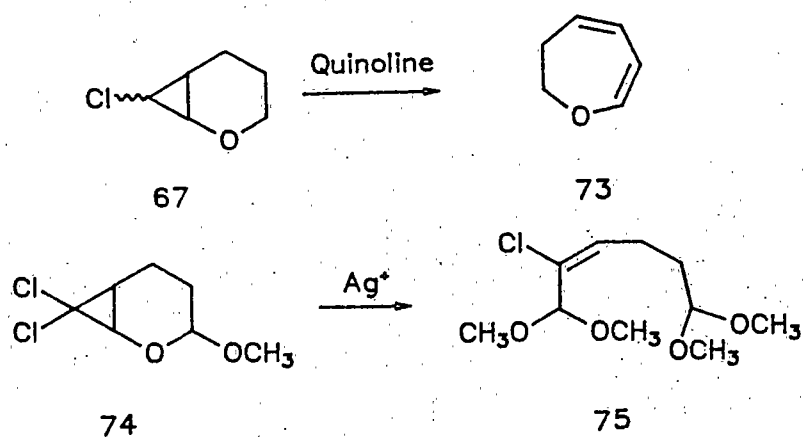


Figure 31. Ring-opening of 3,4-dihydro-2H-pyran-derived cyclopropanes

As the group effort continues to develop new synthetic methods that will allow for the preparation of natural products, the following questions became the focus of this research. Can 3,4-dihydro-2H-pyrans be reduced in a stereoselective manner using trialkylaluminums or diethylzinc? Can new methods of ketal fragmentations be found, especially those which afford stereoselection? Can cyclopropane

intermediates be prepared and utilized as precursors to oxepin or oxepane ring systems? In the sections that follow, the work required to answer these questions will be presented.

CHAPTER 2

RESULTS AND DISCUSSION

Reductions

Trialkylaluminums

The work of Ashby and Laemmle[17] in the late 1970's demonstrated the stereoselectivity of reaction in the reduction of alicyclic ketones with trialkylaluminums. The postulated mechanism, shown in Figure 32, involved a six-center intermediate. If the trialkylaluminum possessed a beta hydrogen, reduction could occur as well as delivery of an "R" group. Reduction was favored with small amounts (ca 1.2 eq) of trialkylaluminum; alkylation dominated in these systems with larger amounts (ca 2.0 eq) of trialkylaluminum.

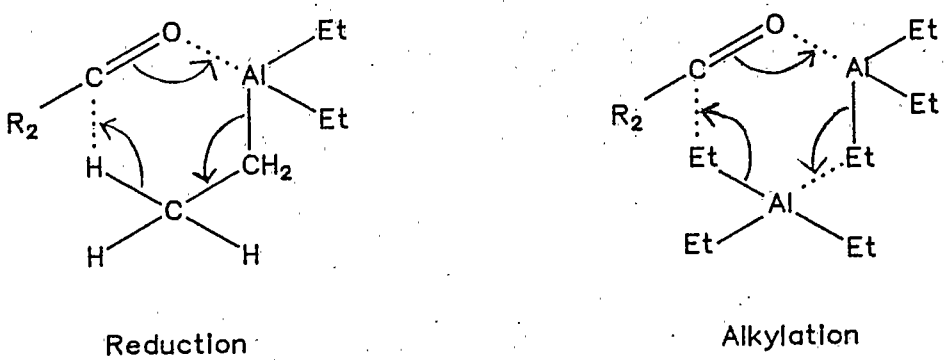
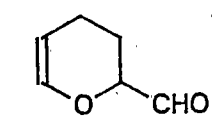
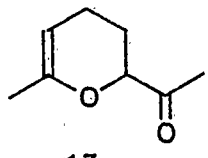


Figure 32. Mechanism of reduction and alkylation by trialkylaluminums[17]

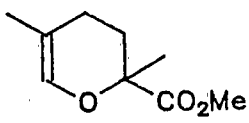
Several 3,4-dihydro-2H-pyran carbonyl derivatives were subjected to reduction conditions, using three different trialkylaluminum reagents (Figure 33). A companion analysis with diethylzinc was also carried out. Structure determination relied heavily on ^{1}H-NMR data and comparison to known bicyclic ketals. Exo/endo isomer ratios were determined by a specific protocol. When there was baseline separation by GLC, isomer ratios were taken by determining the area of the GLC peaks for each isomer. If GLC separation was poor, a ^{1}H-NMR spectrum of the isomer mixture was interpreted. Resonances corresponding to exo or endo positions at C-4 and C-7 are well documented[25, 35] (Figure 34). Isomer ratios were then determined from integration of analogous ^{1}H-NMR peaks. If no other separation was possible, integration of GCMS peaks were used. Since these are proportional to the energy of the molecule rather than the amount present, they offered the poorest exo/endo comparison, and were avoided unless there was no alternative.



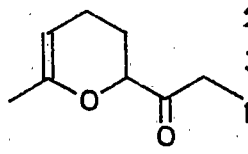
11 2-formyl-3,4-dihydro-2H-pyran



13 2-acetyl-6-methyl 3,4-dihydro-2H-pyran



82 2-carbomethoxy-2,5-dimethyl 3,4-dihydro-2H pyran



94 2-propanoyl-6-methyl 3,4-dihydro-2H-pyran

Figure 33. Substrates reduced by trialkylaluminums

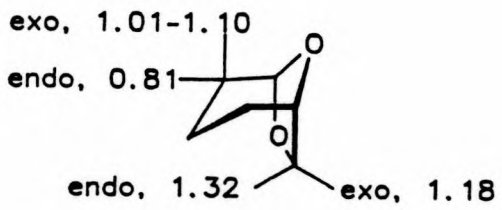


Figure 34. Known ^{1}H-NMR resonances of exo and endo bicyclic ketals

When 2-formyl-3,4-dihydro-2H-pyran [11] was allowed to react with 1.2 equivalents of trimethylaluminum, GCMS revealed a small amount of starting material and two products with M+ = 128, apparently due to methylations. Analysis of the ^{1}H-NMR spectrum was difficult in $CDCl_3$, but possible in benzene d-6. Integration of the methyl doublets of alcohols [12a,b] determined the ratio of threo/erythro to be 25:75 (Figure 35). The alcohols were further characterized by cyclizing them to their easily identified bicyclic ketals [76a,b] by stirring them with a catalytic amount of toluenesulfonic acid in benzene. The ketals were the exo/endo-7-methyl-6,8-dioxabicyclo[3.2.1]octanes [76a,b] and matched previous ^{1}H-NMR data from our group [19]. The ratio of methyl doublets in 76a,b was 27:73. Since the endo ketal arises from the erythro alcohol, it can be said that there is a stereofacial selectivity of 3 for the erythro alcohol.

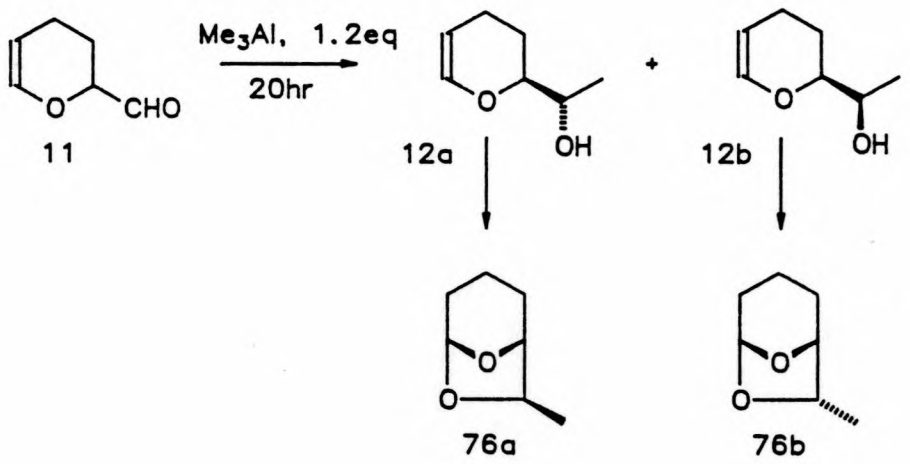


Figure 35. Alkylation of 11 with trimethylaluminum

Reaction of 11 with 1.2 equivalents of triethylaluminum produced a mixture which was assigned the composition shown in Figure 36 on the basis of GLC areas. The structure of the erythro isomer 77b was determined by comparison of its ^{1}H-NMR spectrum to that of 12b which was determined previously. Further confirmation was made by cyclizing all products to bicyclic ketals. Ketal [1] is known; identification of 78b as being endo was made by comparison to ^{1}H-NMR shifts of the methyl triplets of brevicomin [6] isomers[36]. A peak present in the GLC trace but never identified was in the correct elution spot for the exo ketal, [78a]. Since the threo alcohol was identified in the mass spectrum, it is suggested that this was, indeed, the exo ketal. Ratio of GLC exo/endo peaks was 1:10, thereby suggesting a selection for the endo ketal [78b] of 91:9. Thus under these conditions, 35% simple reduction occurred; ethylation accounted for 60% of the products, with selection for endo ketal [78b] of 91:9.

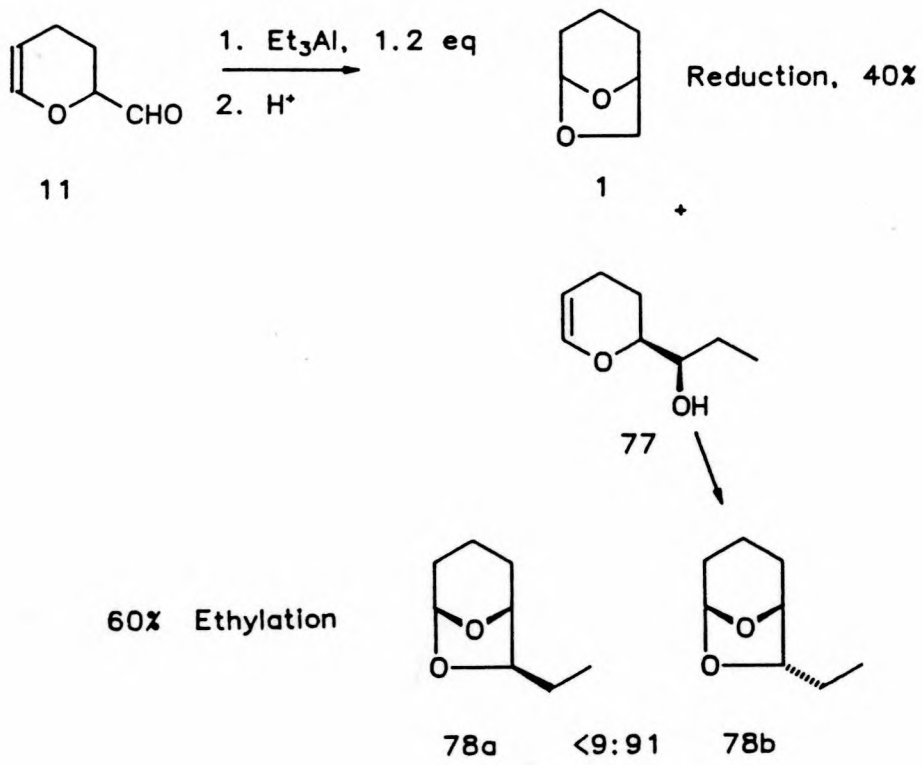


Figure 36. Reaction of 11 with triethylaluminum and product composition

Previously, Ashby and Laemmle[17] noted that an increase in the amount of R_3Al increased the amount of alkyl delivery. The experiment was repeated, this time with 2.0 equivalents of triethylaluminum (Figure 37). In excess of 90% of recovered material were the alcohols [77a,b]. Analysis of the methyl triplets in the ^{1}H-NMR spectrum of the alcohol mixture in benzene d-6 showed that there was an 89:11 ratio of erythro 77b to threo 77a. Subsequent attempts to use this mixture in a stereoselective synthesis of endo brevicomin [6b] were unsuccessful. Although the alkylation procedure was used by

Bjorklund[25b] successfully, a variety of attempts to alkylate 77 in this manner failed. One example is shown in Figure 38.

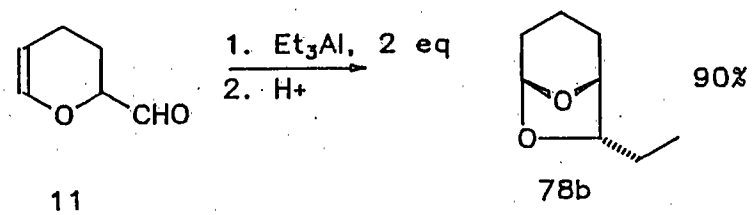


Figure 37. Reaction of 11 with 2.0 eq triethylaluminum

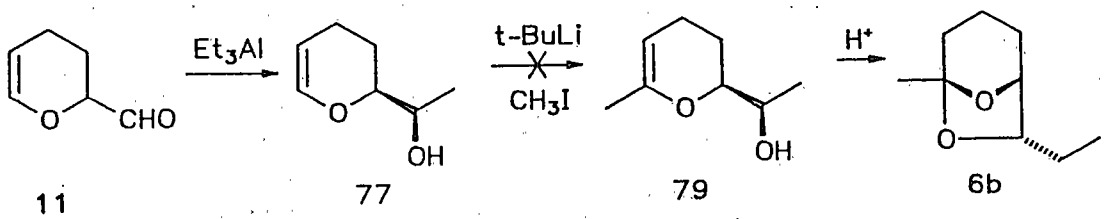
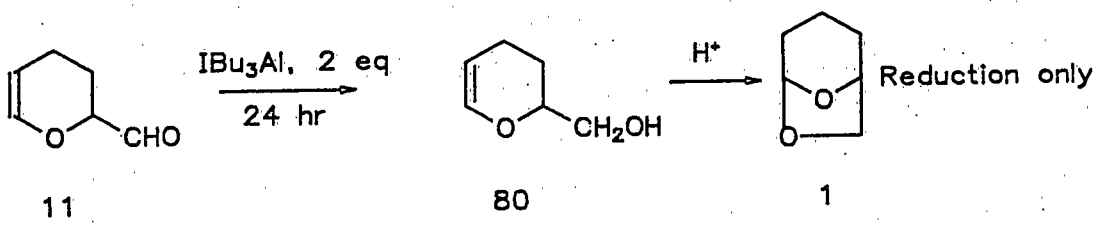


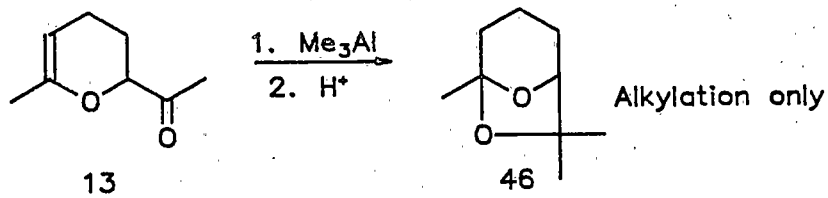
Figure 38. Attempted synthesis of endo brevicomin [6b]

Reaction of 11 with 2.0 equivalents of triisobutylaluminum afforded largely the simple reduction product [80], which was cyclized to ketal [1] and identified (Figure 39). When 2-acetyl-5-methyl-3,4-dihydro-2H-pyran [13] was allowed to react with 1.2 equivalents of trimethylaluminum and cyclized, the only product obtained was 5,7,7-trimethyl-6,8-dioxabicyclo[3.2.1]octane [46] (Figure 40).



11 80 1

Figure 39. Reaction of 11 with triisobutylaluminum



13 46

Figure 40. Reaction of 13 with trimethylaluminum

In a reaction of 13 with 2.0 equivalents of triethylaluminum, GCMS of the reaction mixture indicated that a substantial amount of the simple reduction product alcohols as well as the ethylated alcohols were formed (Figure 41). The products were cyclized and analyzed as bicyclic ketals. Although 2.0 equivalents of triethylaluminum substantially ethylated 11, simple reduction prevailed (57%) in this case. Exo/endo-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octanes [15a,b] were formed in the ratio 65:35, a slight enrichment of the exo isomer over the typical 60:40 $NaBH_4$ reduction. Reductive ethylation accounted for 37% of the products. Exo/endo-7-ethyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octanes [81a,b] nearly co-eluted on GLC (OV-17). However, analysis was possible due

to good separation of methyl triplets and singlets in the ^{1}H-NMR spectrum. Exo 81a had a methyl triplet at 0.87 ppm and a singlet at 1.29 ppm; endo 81b had a methyl triplet at 0.95 ppm and a singlet at 1.23 ppm. The methyl triplet of exo brevicomin [6a] is centered at 0.88 ppm; while for endo 6b,this signal is centered at 0.97 ppm. The C-7 methyl groups of 15 also are characteristic of the isomer, as the exo isomer has a signal at 1.16 ppm while the endo resonates at 1.31 ppm (see Figure 34). The methyl singlet of 81a occurs at lower field than that of 81b, consistent with the positions assigned. The isomer ratio exo/endo 81 was determined to be 57:43. Both of these ratios can be rationalized as resulting from Cram products. As shown in Figure 42, preferred attack is from the same side.

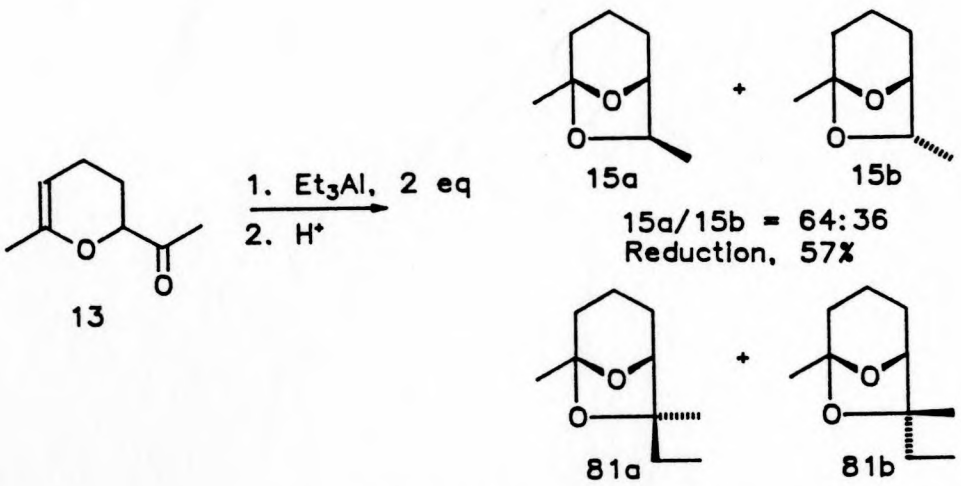


Figure 41. Reaction of 13 with triethylaluminum

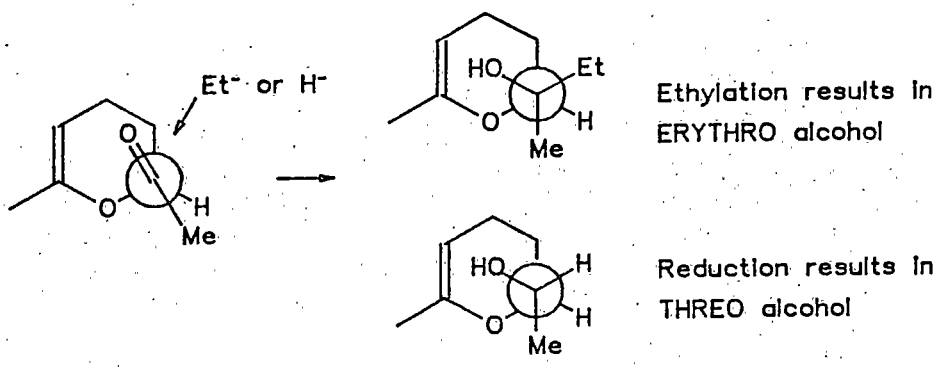


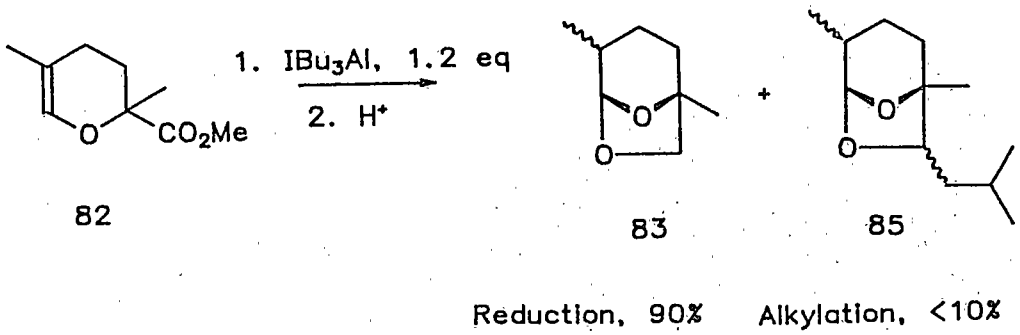
Figure 42. Preferred attack by triethylaluminum showing Cram products

Emphasis of the research then shifted to the stereoselective reduction of the ester, 2-carbomethoxy-2,5-dimethyl-3,4-dihydro-2H-pyran [82] by trimethyl-, triethyl-, and triisobutylaluminum. The cyclized products thus formed generated some interesting stereochemical questions at the C-4 center of the resultant bicyclic ketals, in addition to contributing to knowledge of reduction at C-7.

When ester [82] was reacted with 1.2 equivalents of triisobutylaluminum, GCMS of the reaction mixture revealed a pair of isomers, M+= 142, and another pair of isomers, M+= 198 (Figure 43). The lower molecular weight pair, which accounted for 90% of the product mix, were identified as exo/endo-1,4-dimethyl-6,8-dioxabicyclo[3.2.1]octanes [83a,b]. The later-eluting ketal, exo [83] in this case, was the more abundant by a factor of 2/1. Assignment of stereochemistry at the C-4 center was made by comparison to multistriatin [5] C-4 shifts assigned by Gore[35]. Exo (axial) C-4 methyl groups in these ketals always resonate at lower field than endo (equatorial) methyls. Table 1 compares the C-4 methyl resonances in

83a,b, all four multistriatin [27] isomers, and another ketal, [84], synthesized in a 50/50 mixture by Gore[37].

The M^+ = 198 isomers accounted for less than 10% of the products and could not be totally characterized. The mass spectrum was used for isomer ratio, with the later-eluting isomer in a 60:40 ratio over the earlier-eluting isomer. The 0.8-1.1 ppm region of the ^{1}H-NMR spectrum of the isomer pair was exceedingly complex -- not an unusual prospect if the exo/endo-isobutylated ketals were formed. The molecular ion and ^{1}H-NMR features point toward the isobutylated ketals [85a,b] (Figure 43). Since there are two independent stereocenters in this molecule, yet only two isomers present by GCMS, one of the stereocenters is presumed to have the same configuration. Since only one heteroatom proton signal was seen in the ^{1}H-NMR spectrum, it was assumed that the C-7 positions have the same stereochemistry. The fact that the heteroatom signal present was a triplet of doublets indicates that it should be in the exo position so as to undergo "W" coupling with the axial proton at C-2. Both 83 and 85 are formed with a preponderance of the exo (axial) C-4 methyl group.

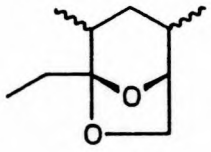
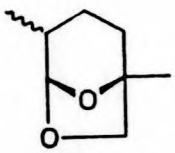
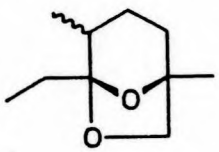


82 83 85

Reduction, 90% Alkylation, <10%

Figure 43. Reaction of 82 with IBu_3Al

Table 1. Comparison of C-4 methyl groups of 83, 84, and 5

	C-4 Axial Methyl	C-4 Equatorial Methyl
 5	1.01 ppm	0.81 ppm
 83	0.98 ppm	0.83 ppm
 84	0.99 ppm	0.83 ppm

Ester [82] was then reacted with 2.1 equivalents of triethylaluminum. GCMS analysis of the crude material showed only three components: ketals [83a,b] from reduction of the aldehyde impurity (,1%), ester [82] (64%), and one peak present as 35% of the products, M^+ = 170, presumably one ethylated alcohol (Figure 44). ^{1}H-NMR of a collected fraction indicated primarily the erythro isomer [86b].

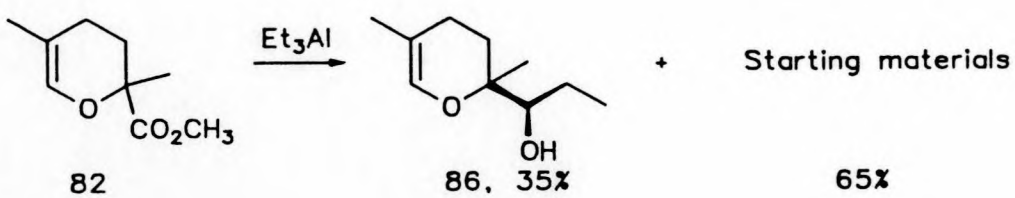
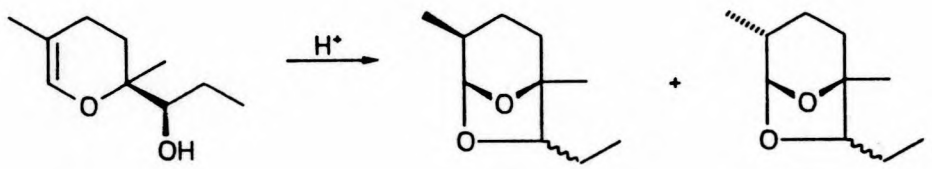


Figure 44. Reaction of ester 82 with triethylaluminum

Obviously, triethylaluminum is an unsuitable reducing agent for this system at room temperature. However, since only one apparent product resulted, the reaction mixture was recombined with toluenesulfonic acid in benzene and allowed to cyclize. It was thought that the ester would be unaffected, and that two ketals, epimeric at C-4 [87, 88] would be the only other products (Figure 45).



86 87 88

Figure 45. Expected products of cyclization of 86b

In retrospect, a better approach would have been separation followed by cyclization of alcohol [86b], or to attempt total reduction of the ester (this was done later). Analysis of the cyclized mixture indicated that while the alcohol [86b] cyclized to give the expected products, ester [82] was not inert to cyclization and indeed generated some interesting products itself. No less than five derivatives were present in the proportions shown in Figure 46. Poor separation on OV-17 precluded assigning percentages to each fraction.

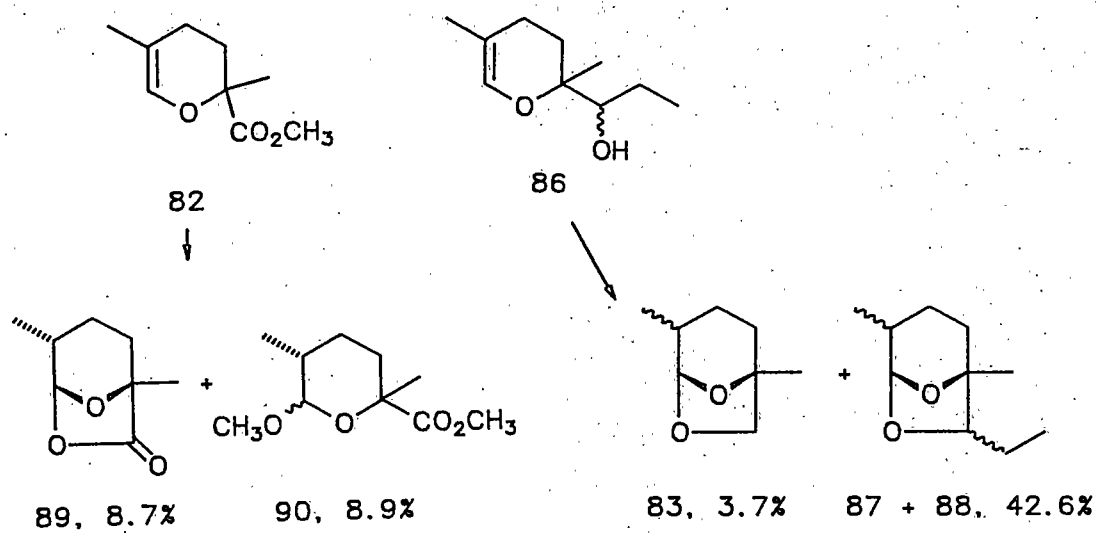


Figure 46. Products of alcohol/ester cyclization

To prove that some products did arise from ester [82] only, the ester was stirred in tosic acid/benzene as above. A comparison of the GLC traces is shown in Figure 47. Products arising solely from the ester will be discussed at the end of this section.

To summarize the data from the reduction and cyclization, simple reduction products constituted a minor (3.7%) amount of the reaction mixture. As in previous reductions, the exo isomer [83a] was formed in an 82:18 ratio over the endo isomer [83b]. The major ethylation product (32%) was a pair of isomers [87] epimeric at C-7 and with an axial methyl group at C-4. There was no stereoselectivity at C-7; nearly equal amounts of the exo and endo isomers were evident by analysis of ^{1}H-NMR data. The minor ethylation product (10%) was a pair of isomers [88] having an equatorial methyl group at C-4. In this case there was reasonable stereoselection for the Cram product via reduction at C-7; exo/endo = 25:75 (Figure 48).

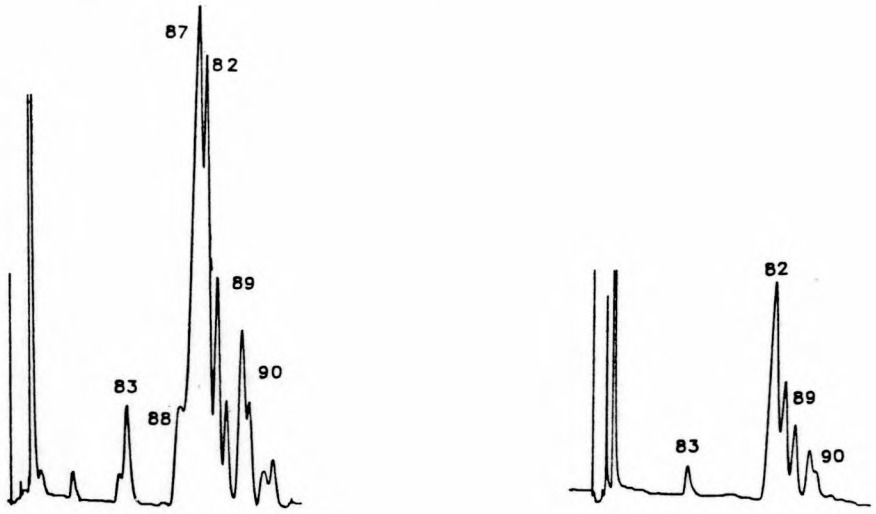


Figure 47. GLC traces of cyclization products of ester [82]/alcohol [86b], and ester [82] alone

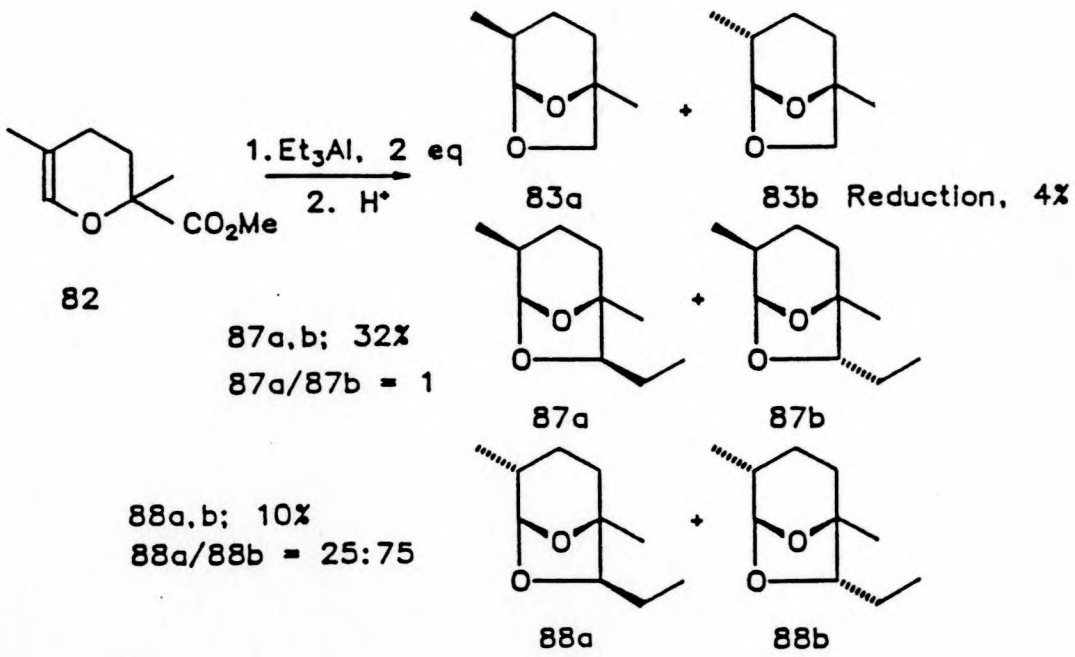


Figure 48. Stereoselection in reduction/alkylation of ester [82]

Ester [82] was then submitted to 3.0 equivalents of trimethylaluminum under reflux conditions. GCMS analysis of the crude mixture indicated a nearly complete conversion (95%) to the dimethylated alcohol [91]. This was confirmed by analysis of IR and ^{13}C-NMR spectra. In addition, GLC fractions were collected and identified by their ^{1}H-NMR spectra. The main component (95%) was the result of 91 cyclizing in the gas chromatograph to bicyclic ketals [92a,b]. Again the axial C-4 methyl group predominated, this time by 82:18. Minor components were ca 2% of ester [82] and 2% of the monomethylated ketals [93a,b]. In the latter, there was slight selectivity for the axial C-4 methyl group (60:40). This pair of ketals was judged to have an endo methyl group at C-7 on the basis of the ^{1}H-NMR shifts of the methyl doublets (1.27 and 1.24 ppm) (Figure 49).

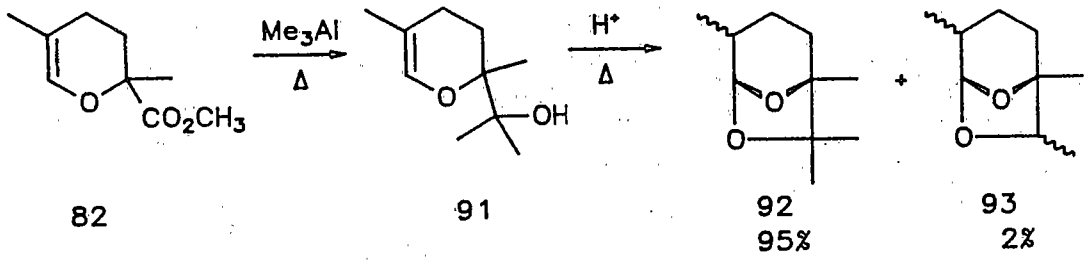


Figure 49. Products of alkylation of ester [82] by trimethylaluminum and subsequent cyclization

Brevicomin Synthesis

It was thought that this new knowledge of the stereoselectivity of trialkylaluminums could be applied to a synthesis of exo-brevicomin

[6a]. The ketone chosen for attack was 2-propanyl-6-methyl-3,4-dihydro-2H-pyran, [94]. This was prepared by alkylating the enamine of 13. Because in previous attempts triisobutylaluminum tended to give the most reduction and least alkyl delivery, it was used to insure delivery of hydride only. Ketone 94 was converted to brevicomin in 98% yield; stereoselection for the exo form 6a was 84:16 (Figure 50).

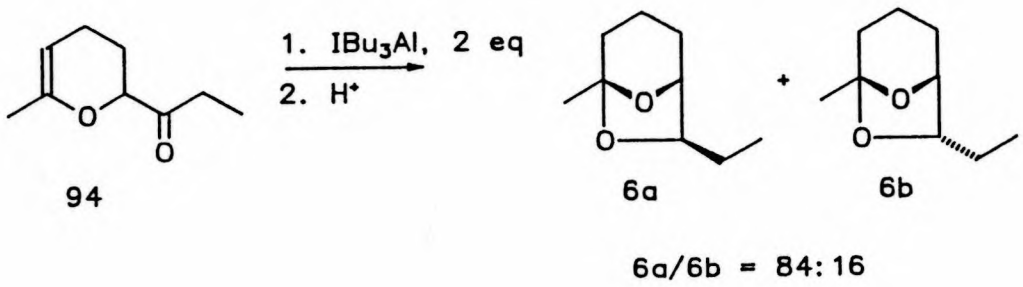


Figure 50. Stereoselective synthesis of exo-brevicomin

Diethylzinc Reductions

Ester [82] proved to be inert to attack by diethylzinc, so use of the agent was confined to 2-acetyl-6-methyl-3,4-dihydro-2H-pyran, [13]. When 2.0 equivalents of diethylzinc were allowed to attack 13, the product mix was comprised of 20% ketals [15a,b] in the ratio 56:44. The other 80% consisted of only 81b, the endo ketal. No 81a was detected by ^{1}H-NMR or GCMS. This constitutes the best selectivity for a Cram product yet seen (Figure 51).

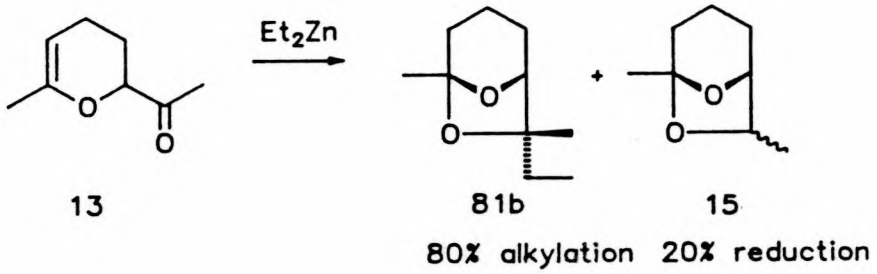


Figure 51. Reaction of 13 with diethylzinc

Stereochemical Anomalies and Molecular Mechanics

Reduction of ester [82] with trialkylaluminums resulted in products with apparent anomalies in the orientation of the methyl group at C-4. In all cyclizations, an axial, or exo, C-4 methyl group was formed preferentially. The pheromone multistriatin [5] has been extensively studied and its stereochemistry is well known.[35] Natural multistriatin is endo, that is, the C-2 and C-4 methyl groups are equatorial. A non stereospecific synthesis of multistriatin resulted in all four isomers; however, endo C-4 isomers predominated by 92:8. Acid catalyzed hydrolysis of α or γ multistriatin will epimerize the C-4 center to give an 20:80 mixture of exo/endo. Similar equilibration of β or δ multistriatin results in a 5:95 exo/endo mixture. A recent synthesis of (-)-α-multistriatin [5] proceeded by formation of ester intermediate 95a,b in a 50:50 ratio.[38] Heating this mixture in aqueous acid for four hours converted this to 25:75 exo/endo mixture (Figure 52). In all systems discussed so far in this work, the trend is just the reverse: the axial (exo) C-4 methyl group is formed preferentially.

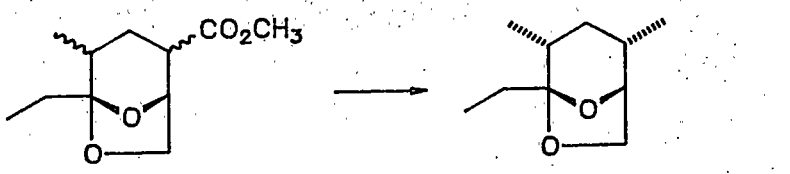


Figure 52. Intermediate in the synthesis of (-)-α-multistriatin

To further investigate the stereochemistry of the C-4 center during cyclization, ester [82] was reduced to the expected alcohol [96] by lithium aluminum hydride, then cyclized. In two separate reductions, different ratios of exo/endo resulted. In one case, 83a/83b = 60:40; in the other, the ratio was 82:18 (Figure 53). To determine whether the C-4 center could be isomerized to increase the proportion of endo isomer, as had been done with multistriatin, ketals [83a,b] with an initial exo/endo of 60:40 were placed in toluenesulfonic acid/benzene for a period of two weeks. Ratios of three analogous ^{1}H-NMR peaks are shown after zero, one, and two weeks on Table 2. As is evident, trends are difficult to quantify on the basis of a single ^{1}H-NMR peak ratio. What can be said is that after two weeks, the 60:40 ketal mix can be converted to a roughly 50:50 mix. In no way is there a facile conversion to the equatorial isomer.

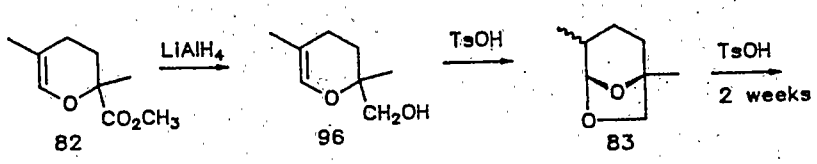
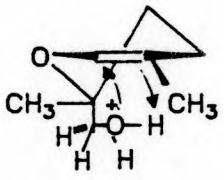


Figure 53. Conversion of 82 to the alcohol; cyclization to ketals

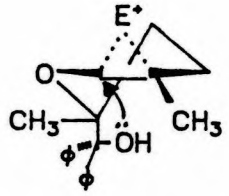
Table 2. ^{1}H-NMR peak ratios during attempted epimerization

	Methyl doublets (0.98, 0.83)	Heteromethine doublets (3.88,3.82)	Olefinic methines (5.22, 5.17)
0 weeks	1.17	1.50	1.67
1 week	1.24	1.68	1.74
2 weeks	0.61	1.09	1.04

A molecular mechanical treatment of model ketal systems sheds some light upon the apparent anomaly at the C-4 methyl group (Table 3). In any axial/equatorial pair, the axial methyl compound is higher in energy than the equatorial isomer. The presence of a methyl group at C-7 raises the energy of the system; an endo group raises the energy more than an exo methyl. Two methyl groups raise the energy more. The products resulting from reduction of ester [82] are, then, the thermodynamically unstable ketals. The axial C-4 methyl group must arise from kinetic phenomena. Suggested mechanisms for both axial and equatorial methyl groups are depicted in Figure 54.



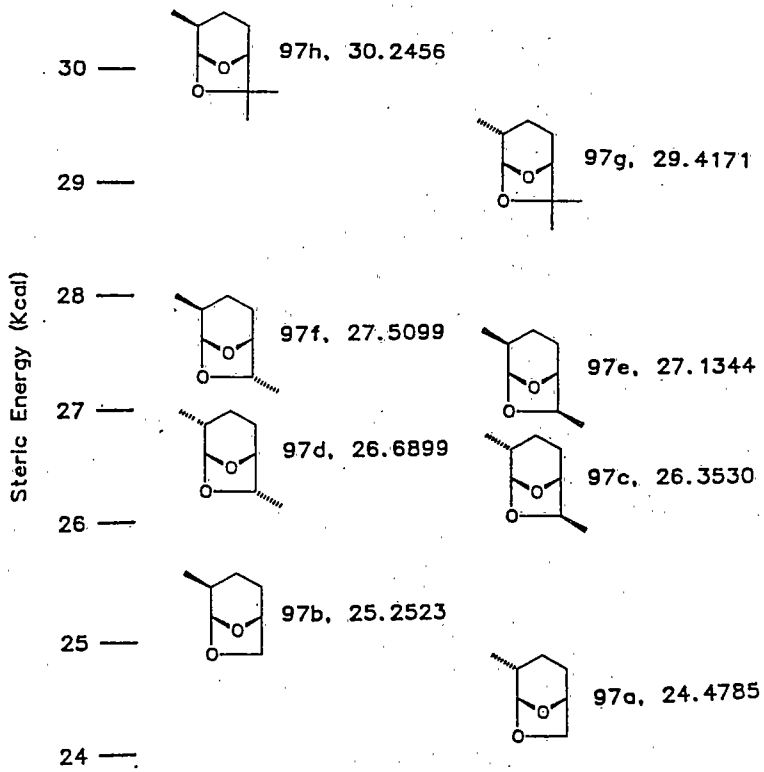
Alkyl or H at C-7
Delivery of H to equatorial position



Bulky groups at C-7
Bridged intermediate, methyl assumes equatorial position

Figure 54. Mechanism of formation of axial C-4 methyl group

Table 3. Molecular mechanics summary



Other Cyclization Products

Cyclization of ester [82] resulted in a pair of ketal lactones [89] which offer further insight into stereochemical questions at the C-4 center. Structure elucidation included ^{1}H-NMR, ^{13}C-NMR, IR, and GCMS data. In the mass spectrum, no ion larger than 128 could be analyzed, although occasionally a small 156 peak appeared. HRMS of the 128 peak gave $C_8H_{16}O$; HRMS of the 127 peak gave $C_7H_{11}O_2$, indicating the presence of at least two oxygens. Facile loss of CO_2 would be expected in this system; $(M+ - CO_2) = 112$ is the third largest peak. A comparison of ^{13}C-NMR spectra to a known system[26] is shown in Figure 55. Two signals are not seen with 89. One could easily be obscured by solvent ($CDCl_3$). Both peaks not seen are

quaternary carbons, and their absence can be attributed to the small size of the sample in addition to the relatively short (15 sec) receiver delay which would have caused saturation. The infared spectrum gave compelling evidence for the proposed structure -- a large resonance at 1801 cm^{-1}, consistent with a 5-membered lactone carbonyl.[39] The ^{1}H-NMR spectrum was in all ways consistent with the proposed structure, and was similar in many respects to ketal-lactone [57], synthesized for comparison purposes.

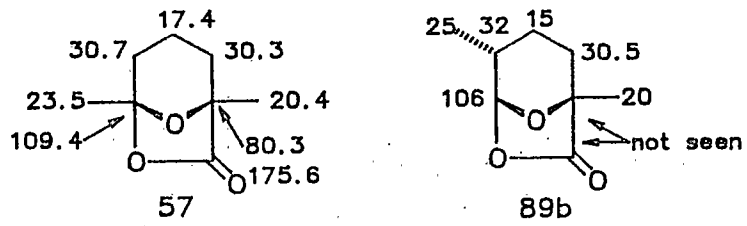


Figure 55. Comparison of ^{13}C-NMR data of known system [57] to proposed lactone [89]

Confirmation of structure 89 was further supported by hydrolizing ester [82] in KOH, acidifying, isolating acid [98], and stirring this acid in tosic acid/benzene (Figure 56). Mass spectral and ^{1}H-NMR data of the product matched the ester cyclization product exactly. Both C-4 isomers were characterized fully, and the presence of a carbonyl was further substantiated by observing large aromatic solvent induced shifts by recording the ^{1}H-NMR spectra in benzene d-6. The ketal methines and C-4 methyl groups were shifted upfield 0.45-0.51 ppm, implying the structural features shown in Figure 57. It is also

interesting to note that the equatorial (endo) C-4 methyl group predominates in this isomer pair by a ratio 68:32.

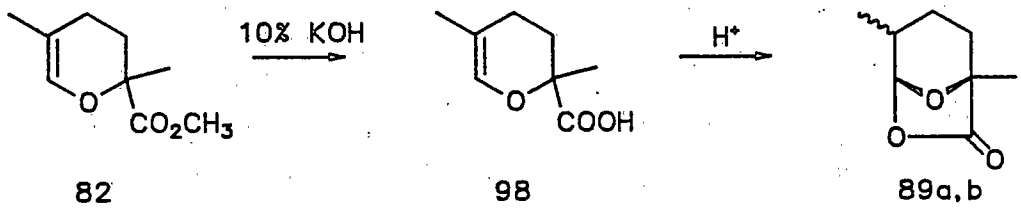
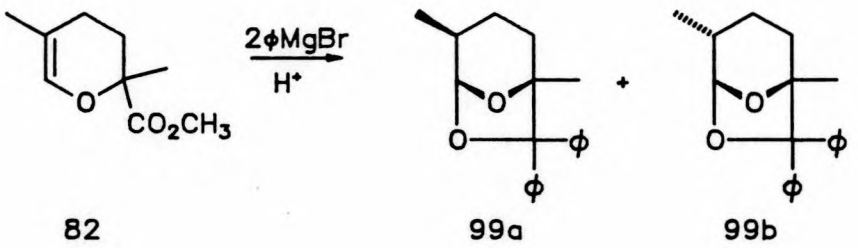


Figure 56. Hydrolysis of 82 and cyclization

Figure 57. ASIS shifts of 89, structural features

It was hypothesized that presence of bulky groups at C-7 may affect the stereochemistry at C-4, since the favored stereoisomer at C-4 in ketal lactone [89] had the equatorial group. Exo/endo-1,5-dimethyl-7,7-diphenyl-6,8-dioxabicyclo[3.2.1]octanes [99a,b] were synthesized from ester [82] and 2.0 equivalents of phenylmagnesium bromide (Figure 58). The pure ketals were isolated by distillation, and two stereoisomers were present in a 67:33 ratio. This time the major isomer had the higher field methyl doublet at 0.92 ppm, indicating the preponderance of the endo (equatorial) ketal. Perhaps

due to the presence of benzene rings, an equatorial methyl at C-4 is favored.



82 99a 99b

Figure 58. Synthesis of bulky ketals [99]

A second product of the tosic acid/benzene cyclization of ester [82] worth discussing is the pair of isomers [90a,b]. A working hypothesis to account for this interesting transformation might include loss of methanol form the ester hydrolysis; followed by a subsequent attack of this released molecule to another protonated 82 (Figure 59). Stereochemistry was determined as follows. In a separated fraction of 90a, four methyl groups were in evidence: a methoxy group at 3.74 ppm characteristic of an ester, a methoxy group at 3.52 ppm characteristic of an ether, a singlet at 1.23 ppm, and a doublet at 0.86 ppm. Other signals included a doublet at 4.12 ppm (J = 8.6), an apparent doublet of triplets at 2.18 ppm (J = 16.7, 3.1), an apparent quartet at 1.68 ppm, and protons at 1.4 and 1.06 ppm. When the methyl doublet at 0.86 ppm was irradiated, the signal at 1.06 sharpened and 1.68 resonance was changed to a broad doublet of doublets. Irradiation of the signal at 1.06 collapsed 1.68 to broad singlet, and changed the signal at 2.18 to a doublet, J = 11.

Irradiation of the resonance at 1.43 collapsed the signal at 4.12 to a singlet, changed the signal at 1.68 to a broad doublet, J = 11, sharpened the signals at 1.06 and 2.18, and collapsed the 0.86 methyl doublet to a singlet. When the signal at 1.68 was irradiated, the signal at 1.06 was sharpened and 2.18 resonance changed to a doublet of doublets, J = 13, 2. Irradiation of 2.18 affected the area around 1.43 (which was partially obscured by a large methyl signal), changed the signal at 1.68 to a triplet, and collapsed the 1.06 resonance to a triplet, J = 13. Figure 59 shows the structure consistent with this data. The magnitude of the coupling at 4.12 (8.6Hz) indicates diaxial hydrogen interaction, as does the relatively shielded region of the resonance ($H_{ax}<H_{eq}$). The methyl group at C-5 is relatively shielded; this indicates an equatorial methyl[40]. The methoxy group is equatorial -- deshielded relative to 90b (3.52 vs 3.37). In cyclohexanes, equatorial methoxy groups resonate at lower field than do axial methoxy groups [41].

The other isomer 90b is epimeric at C-6. In the ^{1}H-NMR spectrum, a broad singlet at 4.43 ppm replaces the doublet at 4.12. This is consistent with an equatorial hydrogen at C-6 coupled to an axial hydrogen at C-5; $J_{ax/eq}$ is much smaller that $J_{ax/ax}$. The methyl doublet at C-5 resonates at 0.83 ppm, indicating the same stereochemistry at that center. The methoxy group is relatively shielded, and therefore axial. The ester methoxy group resonates at 3.70 ppm. All other resonances were not resolved, as this isomer could not be collected separately and was analyzed as a mixture of 90a and 90b.

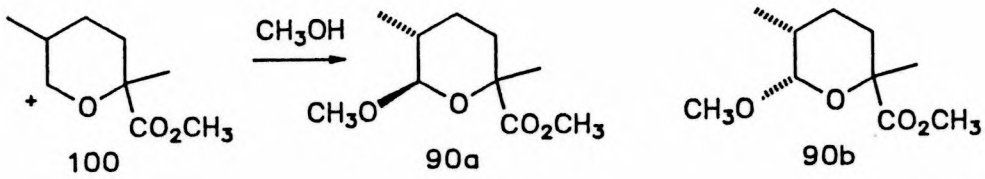


Figure 59. Attack upon 100 to give 90a,b

Cleavages

Trialkylaluminum Cleavages

A second emphasis of this research was to demonstrate the utility of trialkylaluminums, diethylzinc, and selected other reagents for the cleavage of bicyclic ketals. It is known that acetals are good low temperature protecting groups when using DIBAH, but are cleaved to ethers at 70° [42]. A report by Mori and Yamamoto [43] investigated the removal of a (2R,4R)-2,4-pentanediol protecting group with high stereoselectivity using 5 equivalents of triisobutylaluminum (Figure 60). We imagined extending the idea for the possible use of trialkylaluminum reagents in cleaving bicyclic ketals with stereoselection.

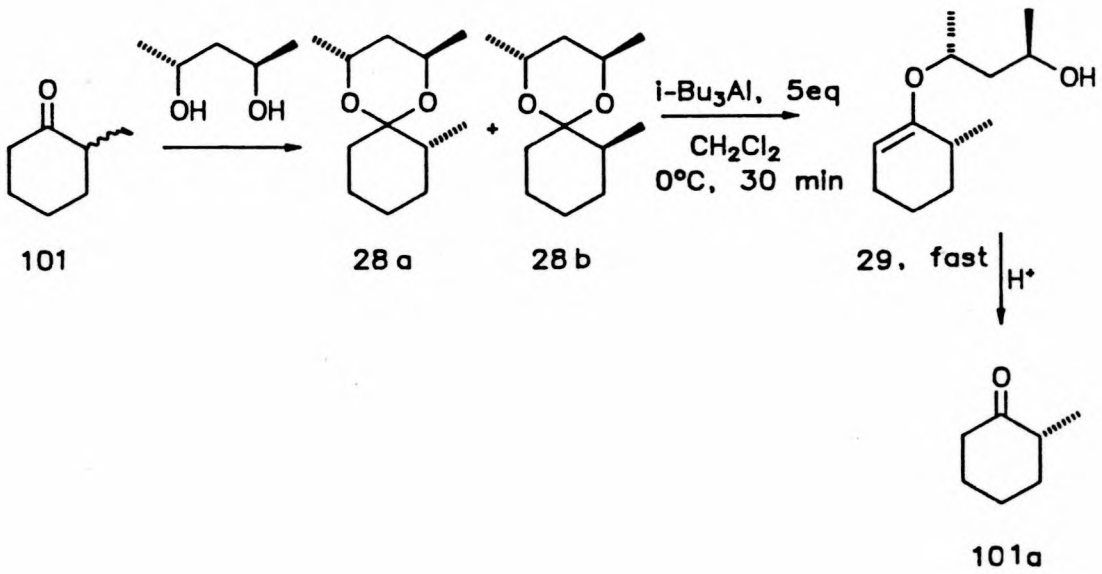


Figure 60. Cleavage of ketal by triisobutylaluminum

Preliminary data made it apparent that the only possible products of this reaction resulted from cleavage of either the O-6 or O-8 bond, with alkyl group addition (Figure 61). Unfortunately, alkyl-substituted pyran alcohols and tertiary oxepane alcohols have many spectral features in common. A look at two cleavage products from a different reaction[26] brings to light the similarity of spectral data (Table 4).

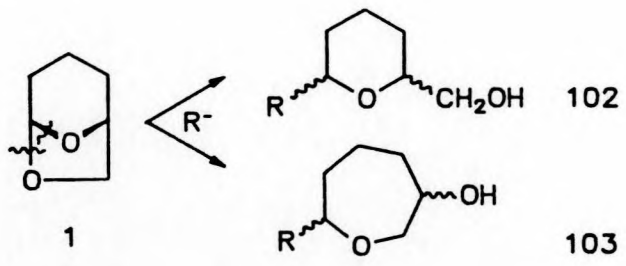
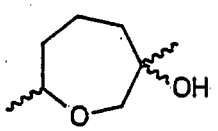


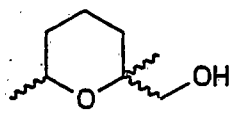
Figure 61. Potential cleavage points on bicyclic ketals

Table 4. ^{1}H-NMR and ^{13}C-NMR data from oxepane and pyran alcohols



59

^{1}H: 3.94 1H d, 3.60 1H m, 3.20 1H d, 2.30 1H s, 1.50 6H m, 1.18 3H s, 1.13 3H, d.
^{13}C: 18.2 q, 19.4 t, 22.5 q, 29.9 t, 33.4 t, 66.6 d, 71.5 t, 73.9 s.



104

^{1}H: 3.60 1H m, 3.34 2H s, 2.55 1H s, 1.50 6H m, 1.17 3H s, 1.14 3H d.
^{13}C: 19.7 t, 22.6 q, 26.7 q, 31.9 t, 32.7 t, 62.6 t, 66.7 d, 73.6 s.

The most obvious difference in the proton data involves the ring (3.20, 3.94 ppm) versus non-ring (3.34 ppm) proton signals. In the case of compound [104], equivalence of the protons is fortuitous -- they are, in fact, non-equivalent by virtue of being vicinal to an asymmetric center. In other words, presence of a singlet as opposed to two signals is not definitive of a pyran. In compounds [59] and [104] there are differences in the ^{13}C-NMR spectrum -- 18.2 vs 26.7 ppm and 71.5 vs 62.6 ppm. When experiments were carried out on other systems, the quantity of cleavage product necessary for a good off-resonance spectrum was never obtained.

The literature has other examples of ^{1}H-NMR data of oxepane rings[44]. In Figure 62, two oxepanes of different stereochemistry are compared. Here three slight differences between oxepanes and pyrans become apparent. The shift of H-2 is ca 3.66 ppm -- a little

deshielded for an axial pyran hydrogen. The J values for the H-7 ax-ax and ax-eq interactions are atypical for pyrans; $J_{ax/ax}$ is rather small (9 vs 11 Hz), while $J_{ax/eq}$ is large (4 vs 2 Hz). Lastly, the axial methyl groups at 1.26 and especially 1.37 ppm are deshielded relative to pyran axial methyl groups. These subtle differences can be diagnostic.

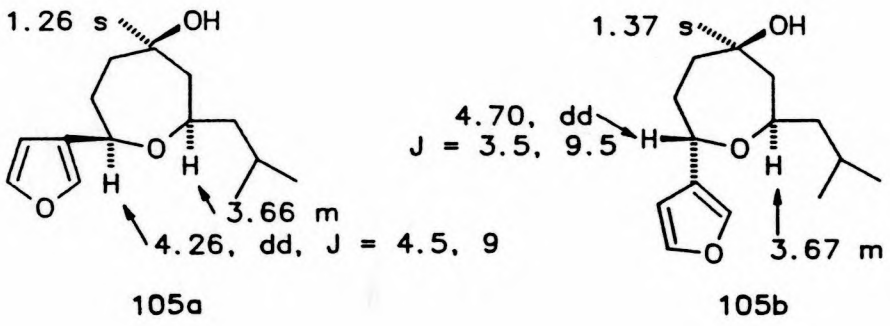


Figure 62. Oxepane system, diagnostic ^{1}H-NMR data

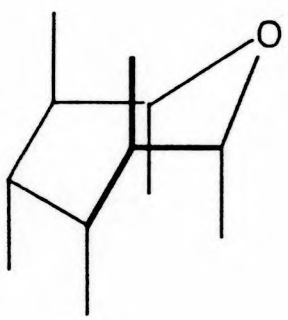


Figure 63. Axial positions in the oxepane ring

Cleavage of 7-methyl-6,8-dioxabicyclo[3.2.1]octane [76a,b] by five equivalents of trimethylaluminum was allowed to proceed for 18 hours. Starting materials had an exo/endo = 28:72. Recovered