

Stereoselective synthetic methodologies : mechanistic studies toward natural products
by Richard Ronald Copp

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
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Abstract:
A mechanistic approach toward stereochemical control in bicyclic ketal synthesis is presented. An investigation of the stereochemical consequences of the tandem solvomercuration-demercuration sequence, as applied to 2-alkenyl-3,4-dihydro pyrans, is explored. It is found that methanol addition to the enol ether moiety is highly stereoselective whereas methoxymercuration is non-selective. The absence of π-facial differentiation in the 2-alkenyl moiety is revealed through isotopic labeling. Circumvention of by-product contamination in the synthesis of 2-carboxylate esters of 3,4-dihydro pyrans is achieved. The scope and limitations of chiral enolate alkylation of C-2 of such systems is probed through enolate trapping. It is found that nonselective enolization precludes efficient asymmetric induction. A systematic and critical investigation of factors influencing nucleophilic addition to 2-acetyl pyran derivatives provides a highly efficient chelation - controlled hydride reduction method.

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by

Richard Ronald Copp

A thesis submitted in partial fulfillment
of the requirements for the degree

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in

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APPROVAL

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Richard Ronald Copp

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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I think and think for months and years. Ninety-nine times, the conclusion is false. The hundredth time I am right.

-- Albert Einstein

Eppur si muove.

(But it does move.)

-- Attributed to Galileo Galilei after his recantation in 1632.

Fools are not born, they are educated.

-- Elbert Hubbard

VITA

Richard Ronald Copp, Jr., the first son of Richard and Sharlene Copp, was born October 1, 1959 in Aurora, Illinois. In December of 1981 he received a Bachelor of Science degree in chemistry from Illinois State University and in January of 1982 he enrolled in graduate school at Montana State University. Upon receiving his Doctor of Philosophy degree, under the directorship of Professor Bradford Mundy, he received an NIH postdoctoral fellowship at the National Cancer Institute, as an Intramural Research Training Awardee.

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ABSTRACT

A mechanistic approach toward stereochemical control in bicyclic ketal synthesis is presented. An investigation of the stereochemical consequences of the tandem solvomercuration-demercuration sequence, as applied to 2-alkenyl-3,4-dihydro pyrans, is explored. It is found that methanol addition to the enol ether moiety is highly stereoselective whereas methoxymercuration is non-selective. The absence of π-facial differentiation in the 2-alkenyl moiety is revealed through isotopic labeling. Circumvention of by-product contamination in the synthesis of 2-carboxylate esters of 3,4-dihydro pyrans is achieved. The scope and limitations of chiral enolate alkylation of C-2 of such systems is probed through enolate trapping. It is found that nonselective enolization precludes efficient asymmetric induction. A systematic and critical investigation of factors influencing nucleophilic addition to 2-acetyl pyran derivatives provides a highly efficient chelation-controlled hydride reduction method.

CHAPTER 1

INTRODUCTION AND BACKGROUND

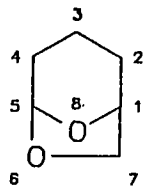
Bicyclic ketals of the 6,8-dioxabicyclo[3.2.1]octane[1] series, 1, have been the focus of attention for numerous natural products research efforts in recent years. The fundamental importance of this heterocyclic system originated in carbohydrate chemistry and has since expanded through its recognition as a common structural component in metabolites from insects, plants and microbes. Of particular interest, from a synthetic methodology viewpoint, is the rich array of functional group substitution patterns about the bicyclic skeletal framework. The regio and stereochemical features of ketal substitution have provided numerous synthetic challenges.

A number of pernicious, and as yet uncontrolled, bark beetles produce and/or respond to sex attractants which exhibit varying substitution about the 6,8-dioxabicyclo[3.2.1]octane ring system. Brevicomin, [2], has been isolated from the female Western pine bark beetle, Dendroctonus brevicomis.[2] The aggregation pheromone, [3], of females of the southern pine bark beetle, Dendroctonis frontalis, has been named frontalin.[3] The tri-substituted bicyclic ketal, multistriatin, [4],[4] is the pheromone for the European elm bark beetle Scolytus multistriatis.

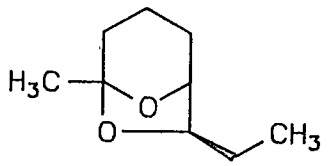
Extensive destruction of forest land caused by these insects has provided the major impetus for research towards efficient preparations of

their pheromones. It is foreseeable that large scale preparations of these compounds, in their natural stereochemical forms, may result in successful methods of control of the insects by trapping.

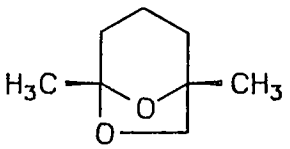
Of significant concern in the cattle industry is the highly substituted ketal, [5], which causes a condition known as "paspalum staggers" when cattle ingest Paspalum dilatatum infected with Claviceps paspali.[5]



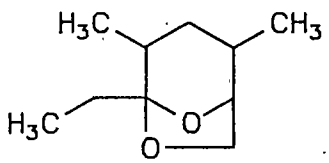
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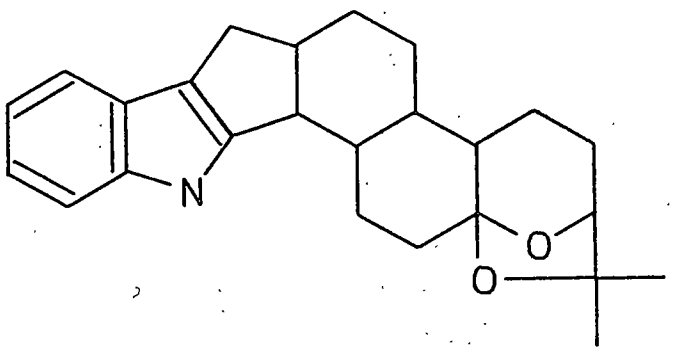


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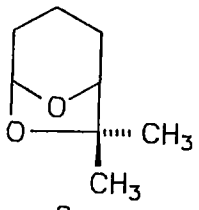


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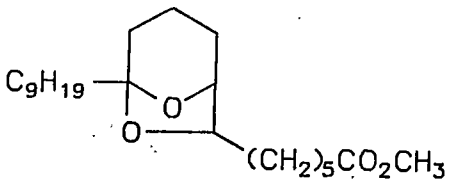
Structurally related systems include 6, a constituent of Japanese hop, "Shinshu-wase",[6] 7, a product of fatty acid metabolism in yeast,[7] and 8, the aggression pheromone of the mouse Mus musculus.[8]



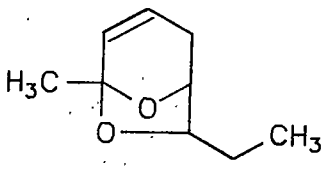
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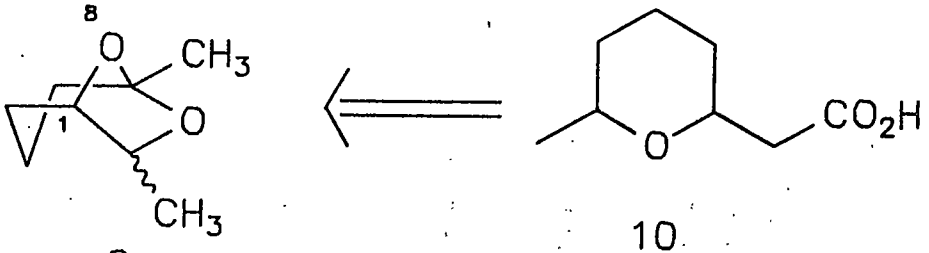
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The diversity in substitution and stereochemistry of these ketals, as well as their biological and economical importance, has sparked considerable interest in organic synthesis. As a result, numerous methodologies have been developed which provide access to many of the desired substitution patterns. As a consequence of continuing interests in the chemistry of bicyclic ketals, recent endeavors have unveiled useful fragmentation methodologies which convert readily accessible bicyclic ketals into other interesting synthetic intermediates.

Mundy has demonstrated the utility of cleaving the 0-8-C-1 bond in the preparation of pyran rings (Figure 1). This particular chemical modification resulted in the synthesis of a component of the glandular secretion of the Civet cat, [10].[9]



9 10

Figure 1. Kims' Synthesis of a Civet Cat Component.

Our group has shown that bicyclic ketals are readily fragmented with acetyl iodide[10], resulting in the cleavage of both C-1 bridging oxygen bonds.

This general fragmentation sequence affords δ,ε-unsaturated enones in which the stereochemistry of the C-7 substituent (endo vs. exo) is reflected in the geometry of the newly formed olefin moiety (Figure 2).

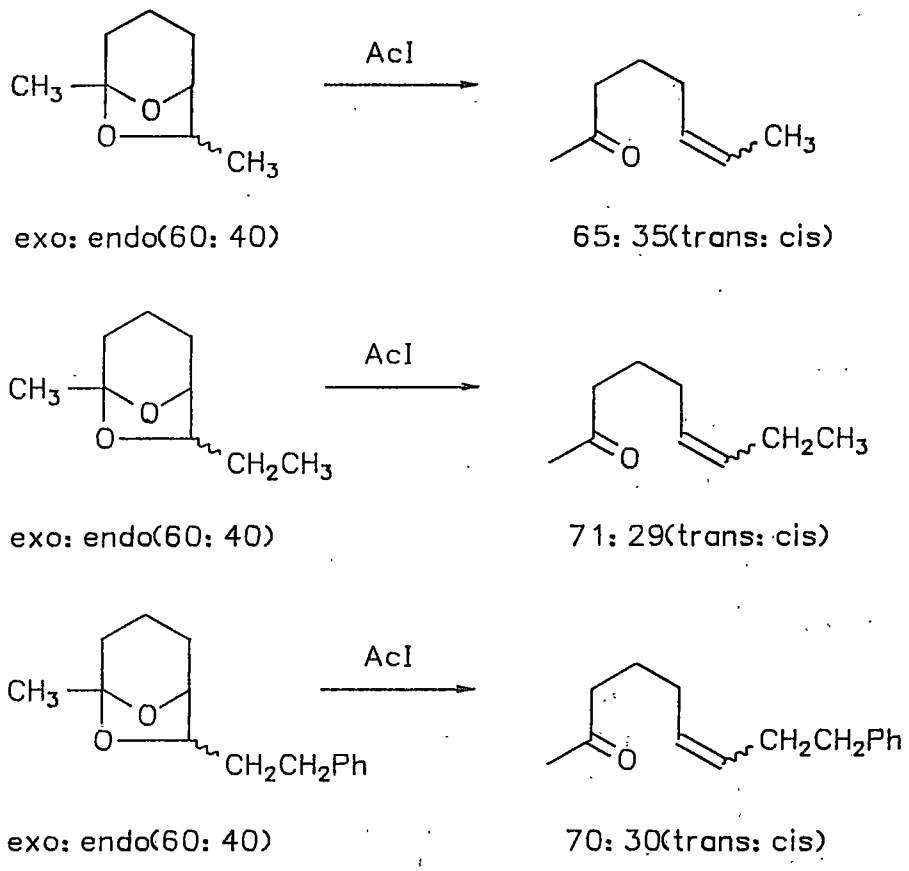
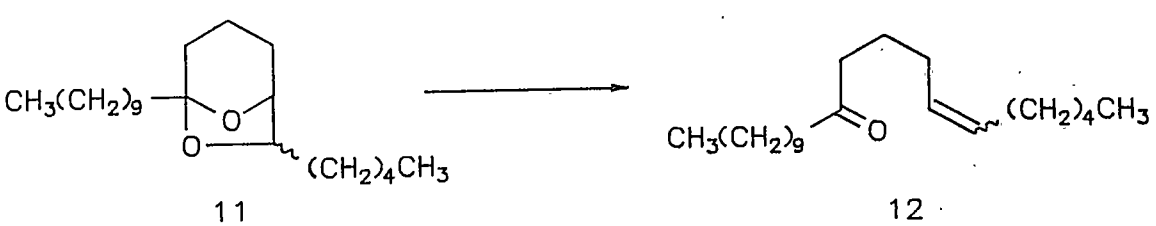


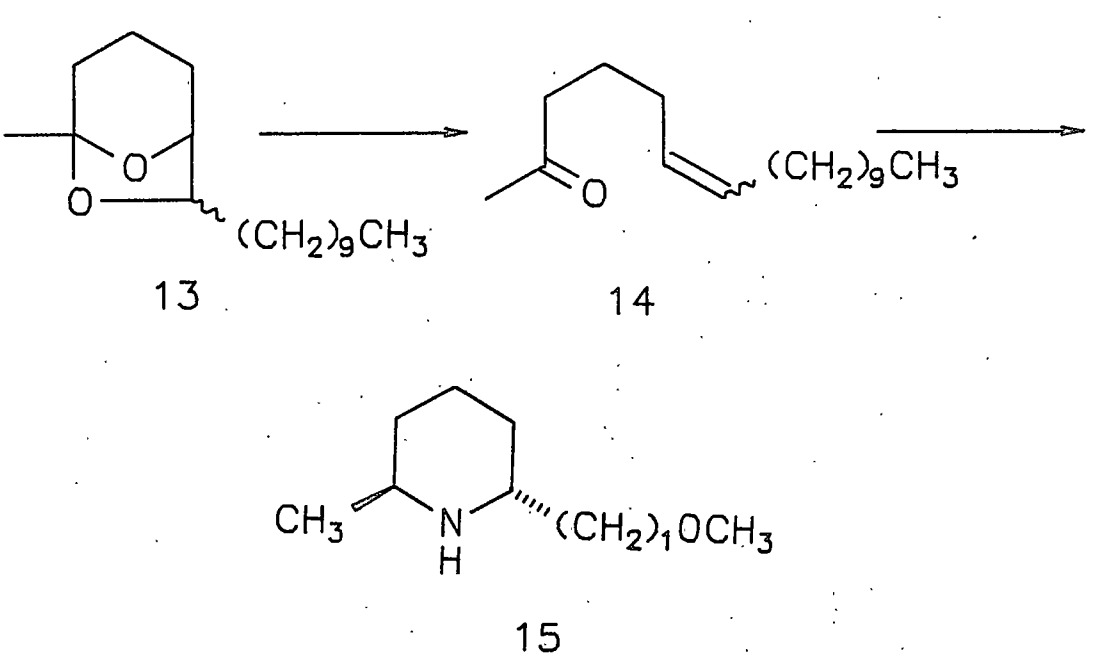
Figure 2. Fragmentations of Bicyclic Ketals with Acetyl Iodide.

The synthetic utility of the acetyl iodide-mediated fragmentation procedure was demonstrated in the syntheses of the sex attractant of the Douglas - fir tussock moth [12] (Figure 3) and Solenopsin A, [15], a major constituent of the venom of the fire ant, Solenopsis savissima (Figure 4).[11]



11 12

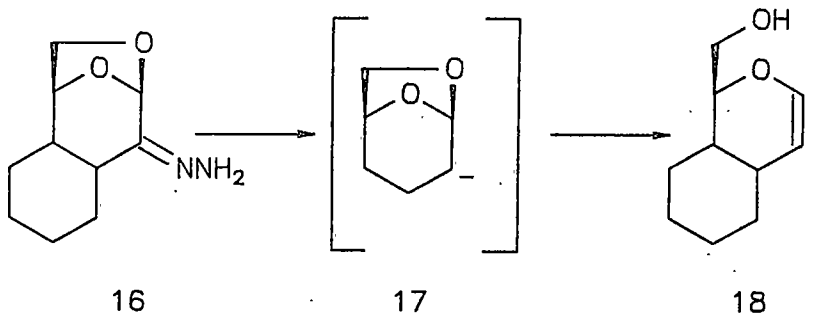
Figure 3. Mundy Synthesis of [12].



13 14 15

Figure 4. Mundy Synthesis of Solenopsin A.

In an elegant synthesis of (-)-Allo-yohimbane,[12] Isobe utilized a common elimination procedure to fragment the bicyclic ketal [16], resulting in a high yield of alcohol [18] (Figure 5).



16 17 18

Figure 5. Isobe Bicyclic Ketal Fragmentation.

The chemistry discussed thus far, albeit only a cursory examination, clearly indicates the value of stereocontrol in bicyclic ketal preparations. Continuing with previous investigations in our group, we chose to "fine tune" existing methodologies, as well as embark on novel, undeveloped procedures, which utilize inexpensive and readily available 2-carbonyl-substituted dihydro-2H-pyrans. With emphasis on chemoselectivity, regioselectivity, enantioselectivity and stereoselectivity, the general focus of this work will be directed toward modifications of substituents at the 2-position of dihydro-2H-pyrans. In addition, consequent functionalization of the cyclic enol ether moiety will be addressed. Through previous investigations employing oxymercuration-demercuration methodology, developed by Brown,[13] Mundy has demonstrated the utility of mercuric salts for promoting cyclizations in bicyclic ketal preparations. To explore the regioselectivity of a tandem

oxymercuration-demercuration sequence, Mundy[14] recognized the possible synthesis of brevicomin, [2], and 20, the aggregating pheromone of the Norway spruce beetle, Trypodendron lineatum, from the common intermediate, [19] (Figure 6).

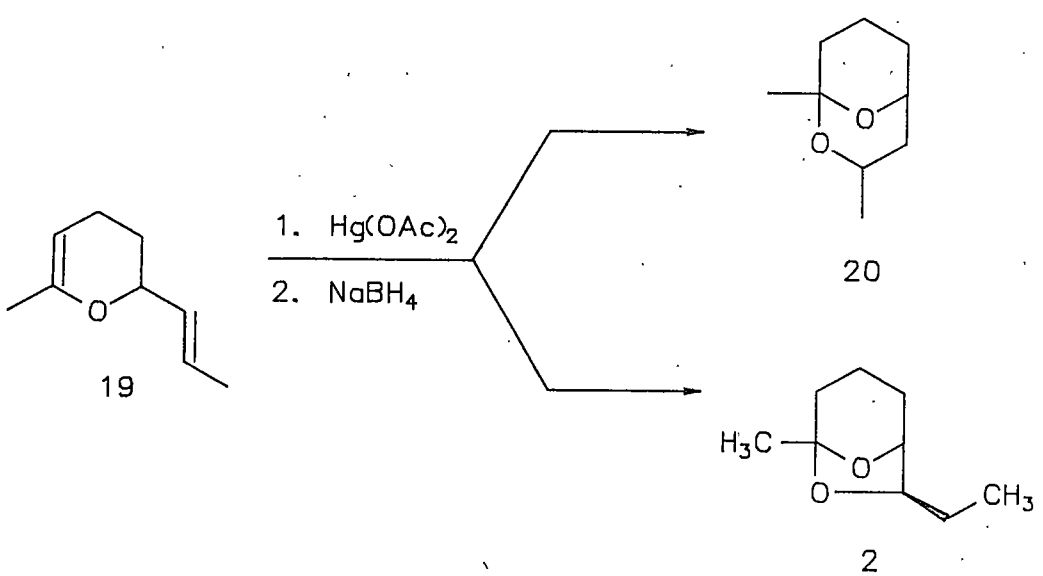


Figure 6. Concurrent Pheromone Syntheses.

The model reaction which gave credibility to the tandem oxymercuration-demercuration ketal preparation was the conversion of [21] to [23] (Figure 7).

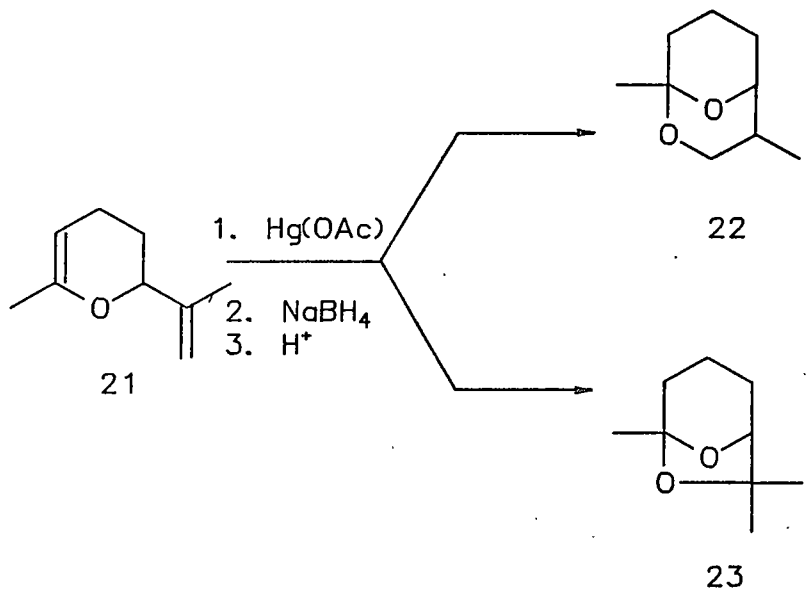


Figure 7. Model Tandem Oxymercuration-Demercuration Procedure.

Obtaining 23 as the major product, with no detectable formation of 22, raised two important questions. First of all, was the regioselective formation of the five-membered ring a consequence of bond angle preference or carbonium ion stability? Secondly, was there rotational preference for the isopropenyl moiety prior to ring closure; i.e. which geminal methyl group, endo or exo, contained mercury prior to demercuration?

Insight concerning both questions was obtained when 1[9] was subjected to the oxymercuration-demercuration sequence.

Brevicomin, **[2]**, was obtained, with no detectable presence of [20]. Because the substitution pattern of the olefin side chain precludes substantial carbonium ion differential, it was reasoned that enthalpy and entropy effects were the combined driving force behind five-membered ring formation.[15]

The question regarding rotational preference of the reacting olefin side chain was answered, in part, by the observation that brevicomin was obtained as a 45:55 mixture of the exo:endo ethyl isomers. This indicated a lack of substantial facial differentiation of the double bond, at least in the case of compound 19, prior to ring closure. However, it was not known whether the lack of facial selectivity originated in unimpeded free rotation of the unreacted olefin moiety or unimpeded rotation of the mercurinium ion, or both.

Additional studies relevant to these questions seemed greatly warranted.

Our group had also applied the tandem oxymercuration-demercuration sequence to the synthesis of the hop oil constituent, [6].[16] Because the original synthesis by the Japanese workers[17] suffered significantly from contamination of by-products, the goal was to overcome the loss of selectivity in the preparation of the pyran starting materials. The synthetic strategy employed utilized the intermediate ketone, 24, which could be directly converted to 6 by way of addition of methyllithium, or by a Wittig reaction, followed by the solvomercuration procedure. (Figure 8).

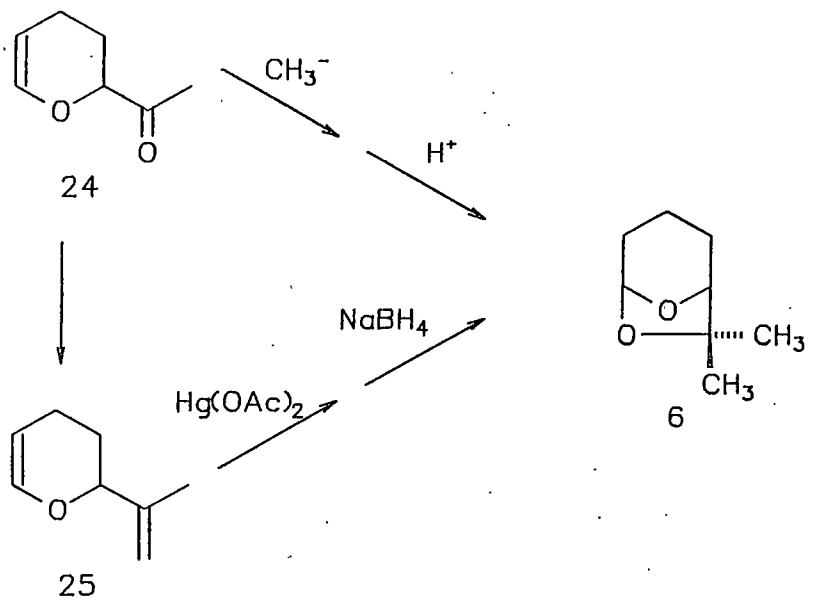


Figure 8. Separate Conversions of [24] to [6].

Although compound [24] proved to be a versatile starting material for novel preparations of [6], it was not obtainable in pure form. Figure 9 illustrates the contaminants which could not be separated from 24.

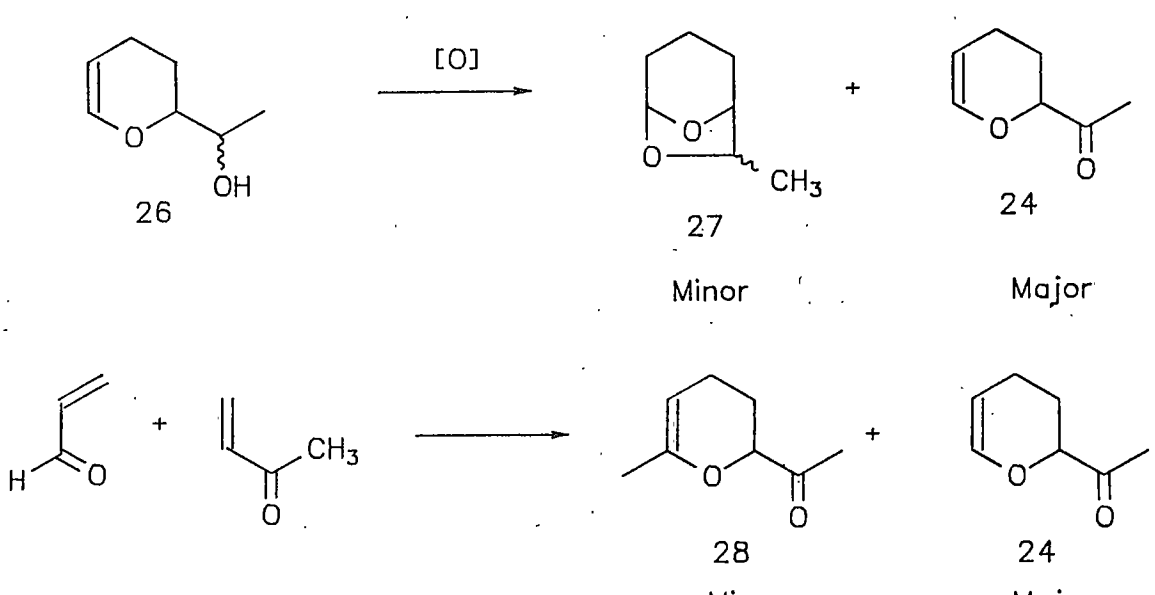


Figure 9. Preparations of 21.

The acquisition of 24 in pure form, as well as the development of additional novel preparations of 6, appeared to be necessary and challenging.

Because the bulk of these research efforts center around racemic starting materials, the product bicyclic ketals are obtained as racemates. We recognized that the enantioselective manipulation of 2-substituted dihydro-2H-pyrans could result in the synthesis of enantiomerically pure bicyclic ketals. Such efforts would result in the preparations of optically pure natural products, as well as chiral synthons for further asymmetric synthesis endeavors.

The use of chiral auxiliaries in asymmetric synthesis has become well recognized as an efficient and general method for preparing optically active compounds. Several auxiliaries are now available which not only are effective at directing the stereochemical outcome of bond-formation, but, also are recyclable.[18] The degree to which a chiral auxiliary can direct the stereochemistry of a reaction has been termed diastereoselectivity.[19] A general explanation of this phenomenon is illustrated in Figure 10. The facial differentiation of the reactive center is due to the spacial arrangement of that center within a concave site.[20]

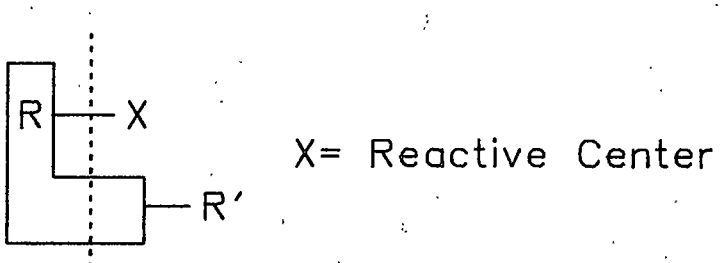


Figure 10. Facial Selectivity Offered By a Concave Site.

Given the scope and efficiency of methodologies previously developed in our group, we recognized the potential synthetic utility of having a suitable chiral directing group attached to a carbonyl group at the 2-position of a dihydro-2H-pyran synthon. With the ability to control the absolute stereochemistry of the number 2 carbon of the pyran ring, we envisaged ready access to a number of optically active bicyclic ketals. Making use of well known chiral enolate chemistry, asymmetric entries into the hop oil constituent, [6] (Figure 11), and frontalin, [3] (Figure 12), were proposed.

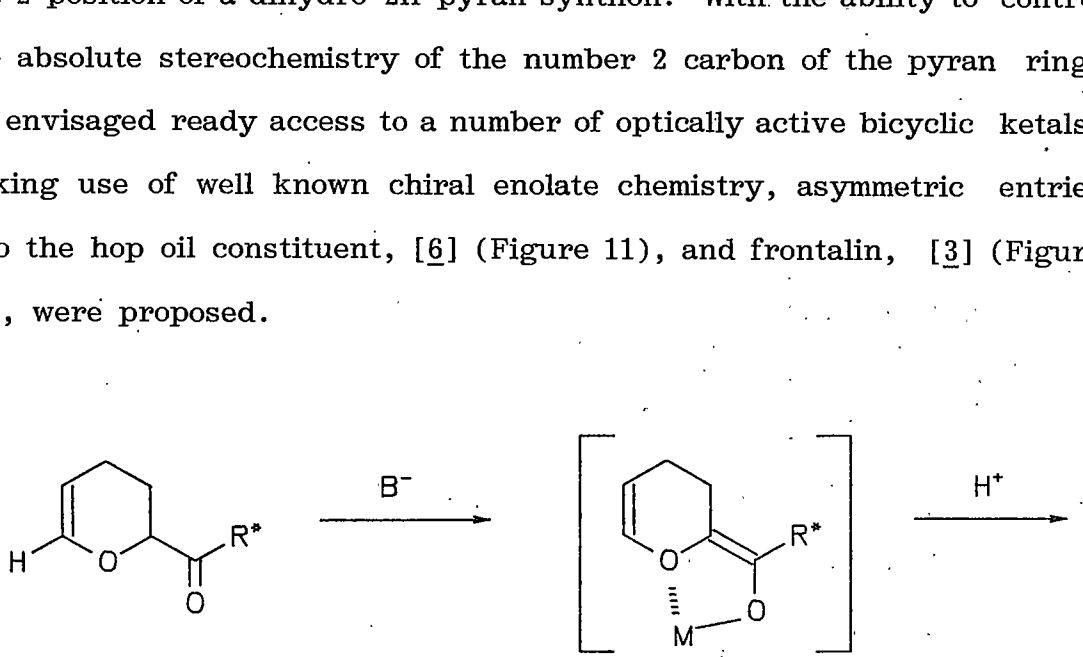


Figure 11. Proposed Asymmetric Synthesis of the Hop Oil Constituent [6].

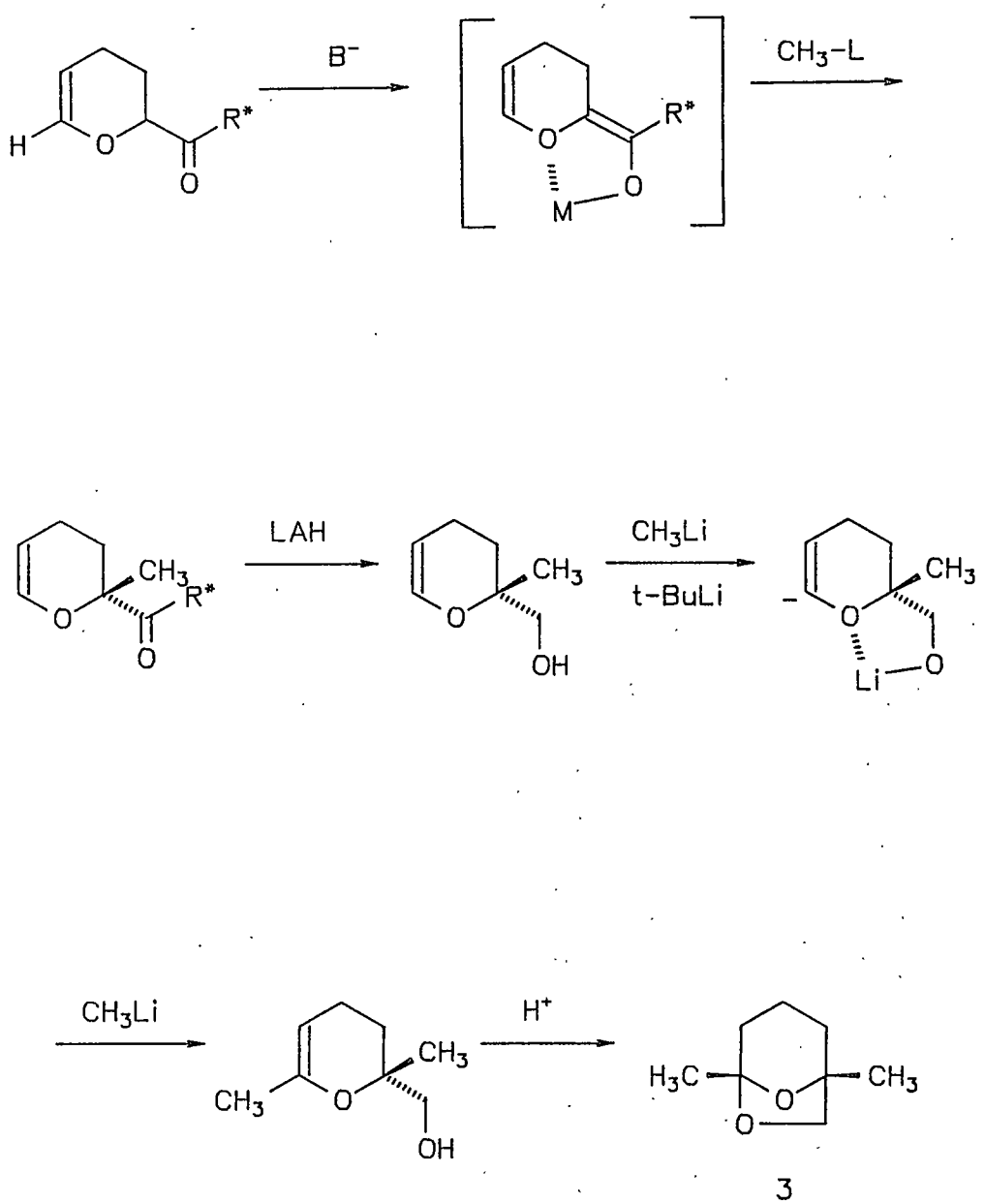
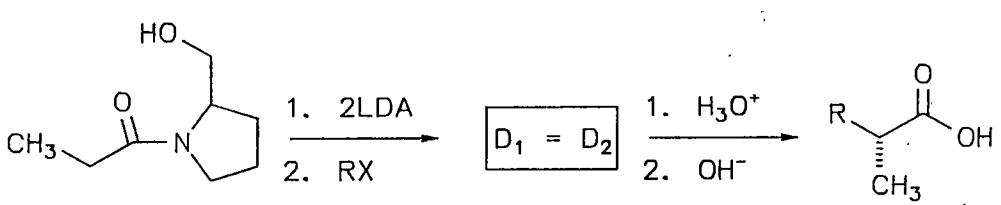


Figure 12. Proposed Asymmetric Synthesis of Frontalin, [3].

Reactions of chiral enolates with various electrophiles are widespread in the current literature.[21] Evans[22] has demonstrated the efficiency of enolate alkylations employing derivatives of S-prolinol [29] as the chiral auxiliaries (Figure 13).



29

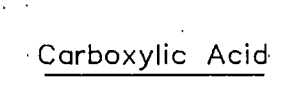
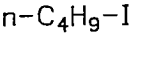
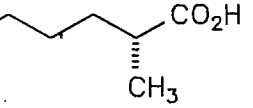
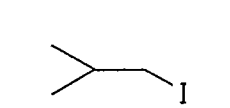
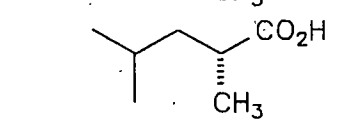
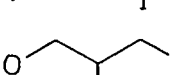
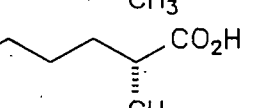
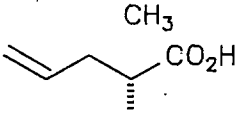
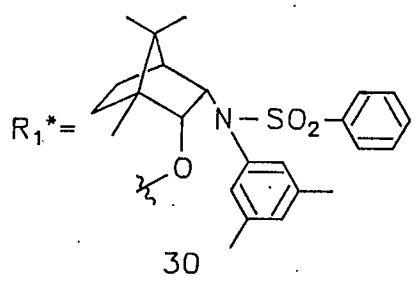
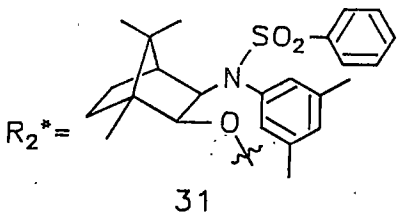
Electrophile	$D_1 : D_2$	Carboxylic Acid	
$n\text{-}C_4H_9\text{-}I$	94 : 6		82%
	97 : 3		85%
	97 : 3		54%
	96 : 4		81%
$PhCH_2Br$	88 : 12		69%

Figure 13. Evans' Use of S-Prolinol in Enolate Alkylations

Helmchen and co-workers[23] have reported on the versatility of camphor-derived chiral auxiliaries (30 and 31) for enolate alkylations (Figure 14). Corey[24] has shown that 8-phenylmenthol enolates [32] undergo "Michael Addition" with high diastereoselectivity (Figure 15).



30



31

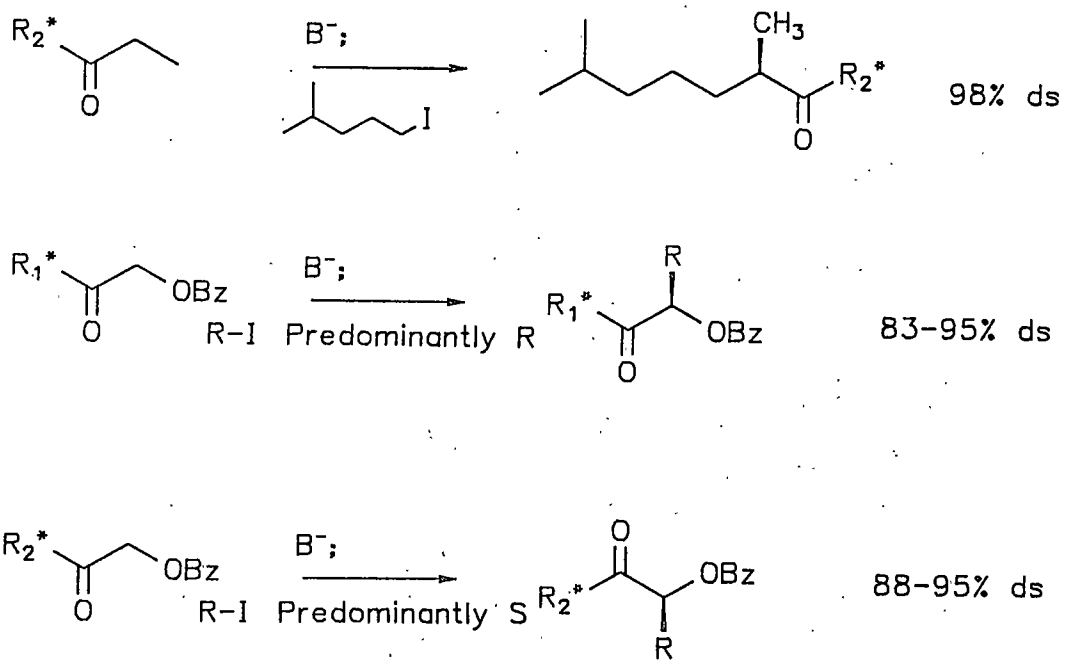


Figure 14. Helmchen Camphor-Derived Chiral Auxiliary.

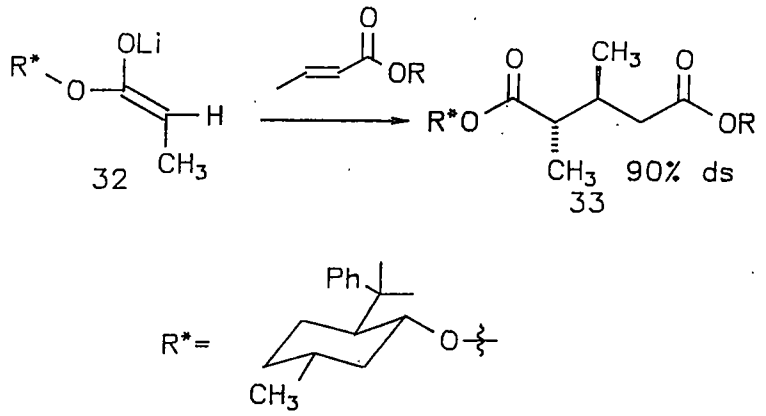


Figure 15. Corey Application of 8-Phenylmenthol

The stereochemical outcome of enolate alkylations has been attributed to enolate geometry. In 1975 Ireland[25] reported on the stereoselective generation of ester enolates as a function of solvent. It was found that in 100% THF the Z-enolate, [35], is favored whereas, in 23% hexamethyl-phosphoramide (HMPA) in THF, the E-enolate, [36], predominates (figure 16).

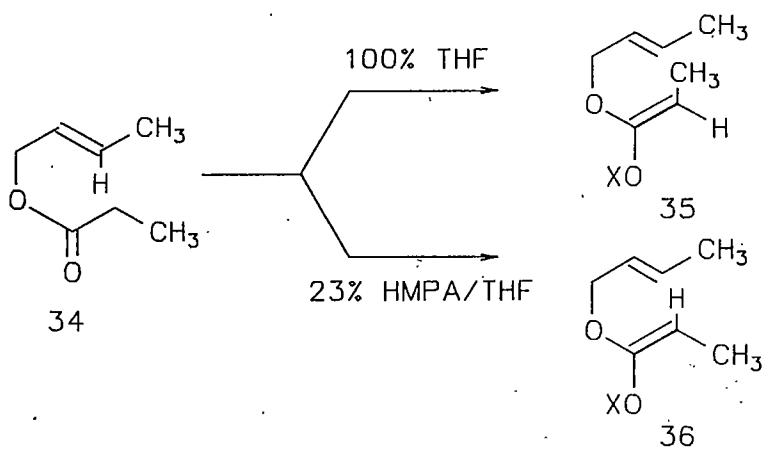
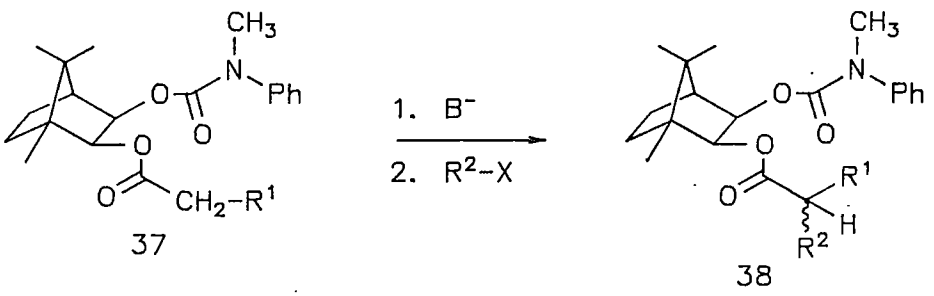


Figure 16. Stereoselective Generation of Ester Enolates.

The character of the solvent proved essential in controlling the diastereoselectivity of enolate alkylation with Helmchens bornanol-derived auxiliary.[26] Figure 17 illustrates the complete reversal in diastereoselectivity, with the same auxiliary, by changing the solvent from 100% THF to THF-HMPT (4:1).



37 38

Educt R^1	R^2-X	Solvent	ds	Configuration
CH_3	$PhCH_2Br$	THF	94: 6	S
CH_3	$PhCH_2Br$	THF/HMPA(4: 1)	70: 30	R
CH_2Ph	$n-C_4H_9I$	THF	90: 10	R
CH_2Ph	$n-C_4H_9I$	THF/HMPA(4: 1)	85: 15	S

Figure 17. Solvent-Dependent Diastereoselectivity

In view of the many impressive examples of chiral enolate alkylations available in the literature we became intrigued by the paucity of applications involving alkylations at ring carbons (Figure 18) of unsymmetrical heterocycles.

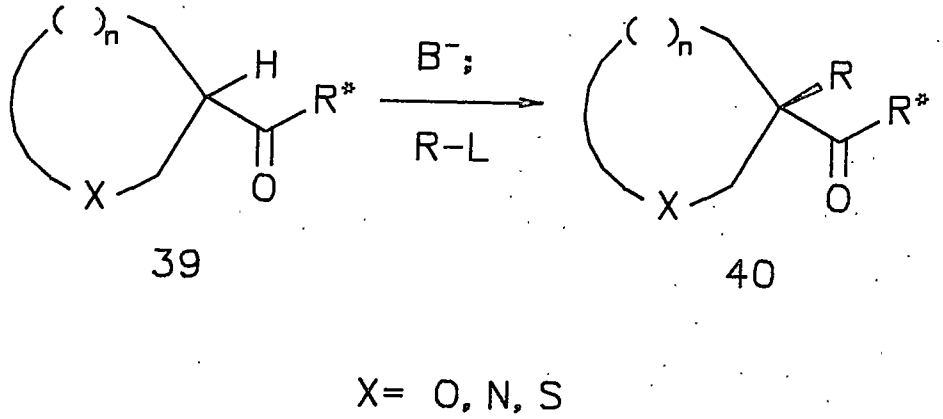


Figure 18. Chiral Enolate Alkylation at a Ring Carbon.

Previous work in our group has revealed the ease with which 2-carboxyl-substituted dihydro-2H-pyrans may be alkylated (Figure 19).

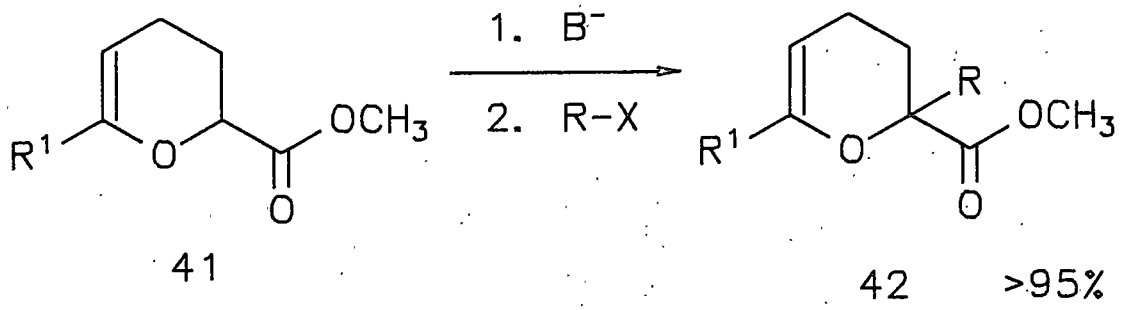


Figure 19. Alkylation of 2-Carboxyl-Dihydro-2H-Pyrans.

The key question which arose was; could a suitable chiral ester or amide moiety afford significant diastereofacial differentiation in the derived enolate? Considering the geometry of such an enolate, we recognized the potential for control by way of chelation between the metal counter ion and the ring oxygen (Figure 20). Should either transition state, cyclic, [43], or dipolar, [44], be significantly favored, perhaps asymmetric alkylation would proceed efficiently. A study into the effects of solvent polarity and auxiliary type seemed highly warranted.

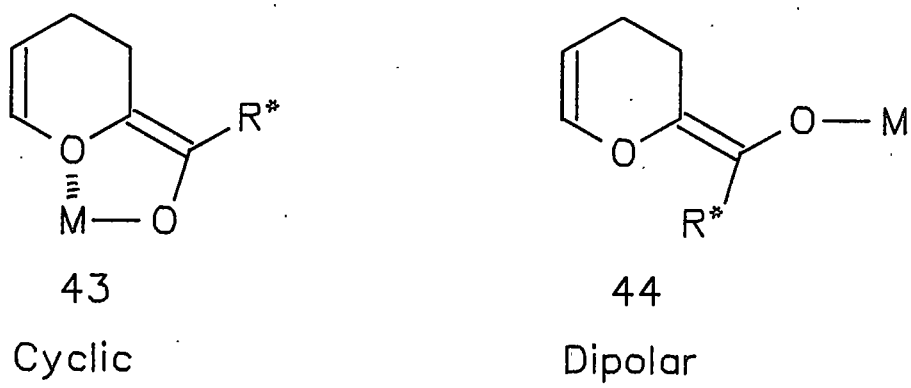


Figure 20. Control of Enolate Stereochemistry

An alternative approach to achieving chirality at C-2 was envisaged in an asymmetric Diels-Alder cycloaddition. Figure 21[27] illustrates the reaction scheme which prompted us to consider cycloadditions with chiral auxiliaries.

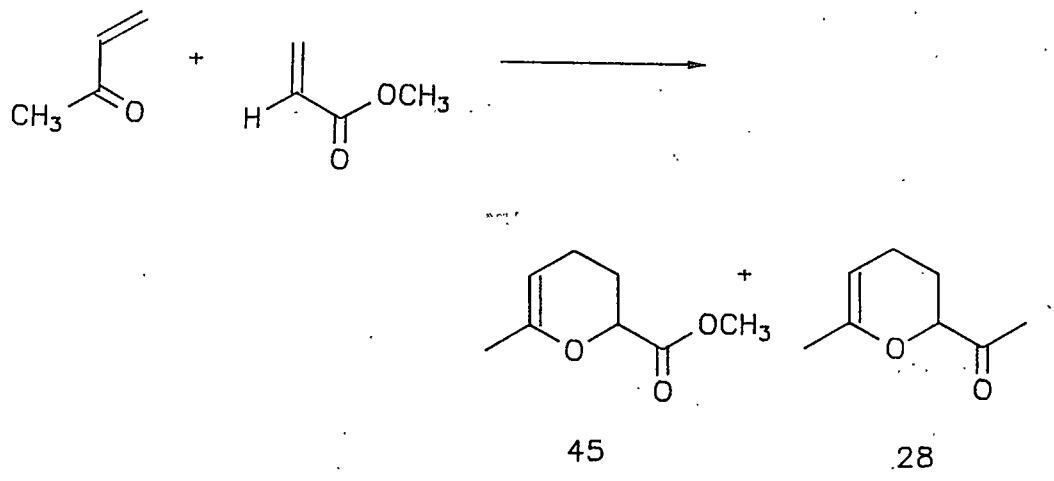
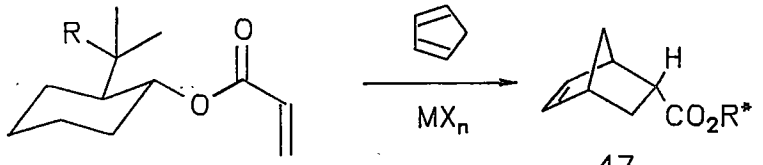


Figure 21. Diels-Alder Reaction with MVK and Methyl Acrylate.

It was thought that replacement of the methoxy group of methyl acrylate with a suitable chiral directing group might result in significant diastereofacial differentiation of the dienophile. Optimal conditions might then be found to effect the asymmetric Diels-Alder reaction.

Numerous examples of chiral Diels-Alder reactions of acrylate derivatives have appeared in the literature.[28] Early studies by Farmer[29] and Sauer[30] showed that (-)-menthol provided moderate diastereoselectivity in Diels-Alder reactions with cyclopentadiene (Figure 22). Corey[31] found that the diastereotopic face differentiation exerted by 8-phenylmenthol was significantly higher (Figure 22). Oppolzer[32] has shown that selection depends on the nature of the Lewis acid (Figure 22).

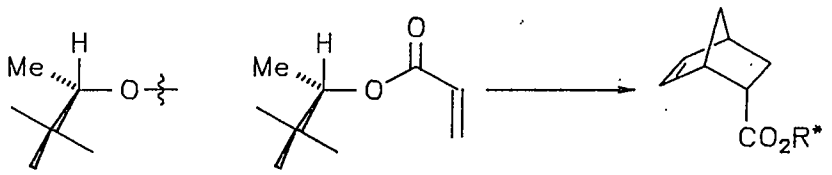


46 47

Reference	Entry	R	$: MX_n	MX_n	Yields(%)	endo(%)	de(%)
29	1	H	1: 1.0	$SnCl_4$	76	89	41
30	2	H	1: 0.43	$BF_3 \cdot Et_2O$	74-81	95	74
32	3	H	1: 1.5	$TiCl_4$	65	92	62
31	4	Ph	1: 1.5	$SnCl_4$	-	-	(99)
32	5	Ph	1: 1.5	$SnCl_4$	95	84	89
32	6	Ph	1: 1.5	$TiCl_4$	83	89	90
32	7	Ph	1: 0.7	$AlCl_3$	89	91	65

Figure 22. Diels-Alder Reactions Employing (-)-Menthol Derivatives.

A comparatively efficient auxiliary, (S)-(+)-3,3-dimethyl-2-butanol [48], has been employed by Sauer[33] and the reaction yield has since been improved by Greene[34] (Figure 23).



48 49

Entry	Reference	Yield(%)	endo(%)	de(%)
1	44	>95	88	33
2	75	97	80-85	34

Figure 23. Diels-Alder Reaction with (S)-(+)-3,3-Dimethyl-2-Butanol Auxiliary

The difference in π-facial selectivity offered by the (-)-menthol and (S)-(+)-3,3-dimethyl-2-butanol derived acrylates is particularly noteworthy. The geometrical difference between the two faces of the double bond of an acrylate is illustrated in Figure 24.[35]

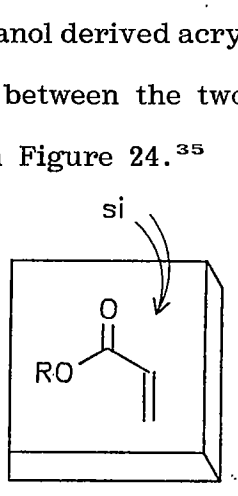
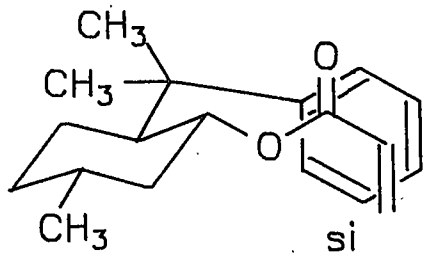


Figure 24. Facial Differentiation in Acrylates.

Topological biasing of the π-faces of arylates is inherent in the structure of the secondary alcohol chiral auxiliary. As depicted in Figure 23, the si-shielding offered by the t-butyl moeity affords re-selective diene addition.

Figure 25 illustrates re-shielding of the 8-phenylmenthol auxiliary which rationalizes the high si-selective diene addition.

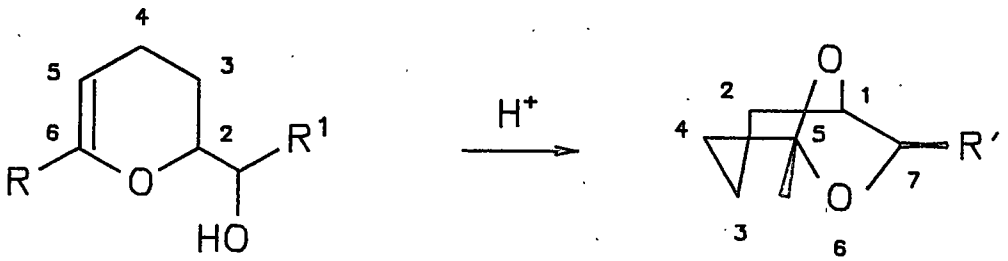


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Figure 25. Facial Biasing with 8-Phenylmenthol Auxiliary

A wide variety of camphor-derived auxiliaries have since been developed[36] which strategically, and quite selectively, shield the respective π-faces of acrylates. However, the application of chiral acrylates to pyran synthesis has not, as yet, received significant attention in the literature. We were thus prompted to embark on a study involving the Diels-Alder heterocycloaddition of methylvinyl ketone to various acrylates.

Control of the stereochemistry about C-2 in dihydro-2H-pyrans, by way of asymmetric induction, invariably translates into control of the stereochemistry about C-5 in the product bicyclic ketals. As shown in Figure 26, the 6-substituent of pyran [51], bound to a pro-chiral center, always adopts equatorial substitution, with respect to the pyran ring, in the cyclized product ketal [52].

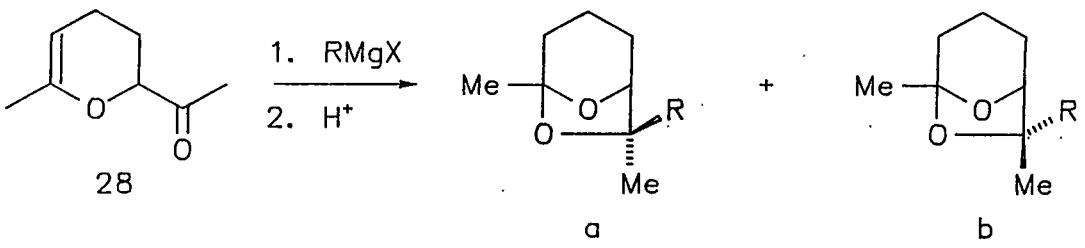


51 52

Figure 26. Fixed Stereochemistry of Ring Closure in Bicyclic Ketal Formation.

However, considering the importance of C-7 substitution in bicyclic ketals, any sequence non-stereoselective for C-7 would cut in half the efficacy of asymmetric control at C-2 in the precursor 51.

A study into the stereoselective manipulation of the carbonyl of 2-acyl-dihydro-2H-pyrans was compulsory. Previous work by our group[37] demonstrated the potential for stereocontrol in the addition of nucleophiles to methylvinyl ketone dimer, [28]. The various nucleophiles studied were alkyl Grignard reagents. The selectivity in the addition of ethylmagnesium halide could not be determined by GLC as the isomers were inseparable (Figure 27).



28 a b

	R	exo	endo
53	CD_3*	60	40
54	Et	-	-
55	i-Pr	89	11
56	t-Bu	84	16
57	Ph	75	25

*Reference 39.

Figure 27. Stereoselective Grignard Addition to 28.

The stereoselectivity of Grignard addition to 28, with the relatively bulky nucleophiles, was confirmed by an x-ray crystallography study[38] on the exo-phenyl isomer [57a]. To assess the stereoselectivity of Grignard addition of a relatively "small" nucleophile, Jun[39] found that addition of deuteriomethyl Grignard resulted in an exo:endo deuteriomethyl ratio of 60:40.

The inherent source of stereodifferentiation was proposed to be chelation between the incoming Grignard reagent and both oxygens of 28. Early work by Cologne[40] in which acrolein dimer, [58], was treated with a variety of Grignard reagents, showed the same trend toward exo-substitution of the nucleophile (Figure 28).

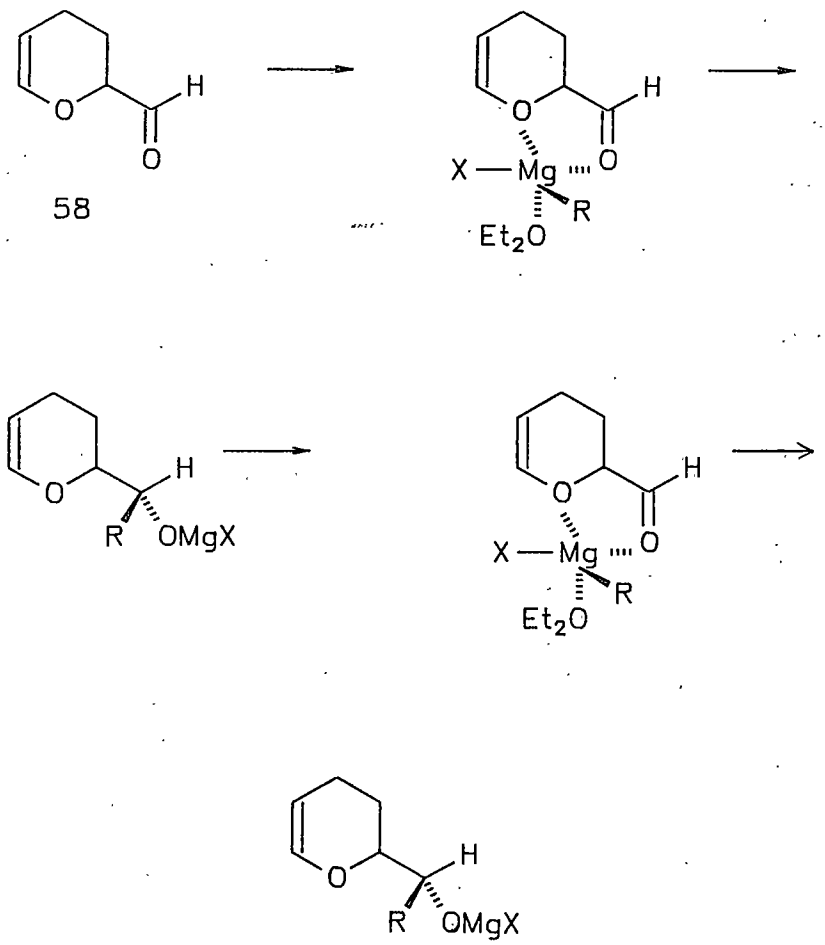
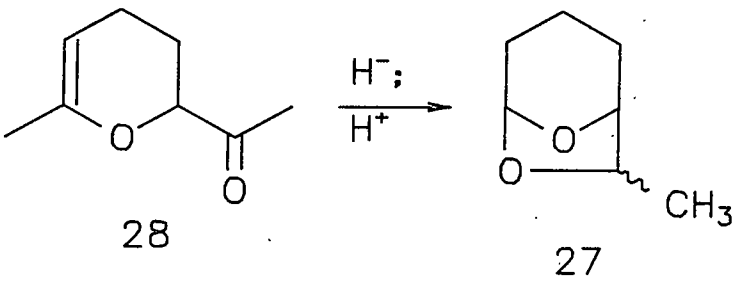


Figure 28. Reaction of Grignard Reagents with 58.

Our group had also found limited selectivity in the reduction of 28 with various metal hydride reagents. The degree and direction of selectivity varied widely (Figure 29) which precluded the formation of any formal conclusions regarding the reaction mechanism.



28 27

exo: endo 0.96 to 4.0

Figure 29. Hydride Reductions of 28.

To extend our knowledge of stereoselective nucleophilic addition to 28, we embarked on a program to study alkyl-nucleophiles other than Grignard reagents and the possible effects of adding a Lewis acid to enhance chelation control. We also decided to pursue several other metal hydride reducing reagents and reaction conditions in order to gain a fundamental understanding of stereocontrol in hydride reductions of 28.

No mechanistic studies (spectroscopic or otherwise) concerning carbonyl manipulations of dihydro-2H-pyrans have been previously reported. Thus, we chose to study the phenomenon of chelation control by way of proton NMR spectroscopy. The interactivity of methylvinyl ketone dimer with an appropriate Lewis acid, at various temperatures, seemed to be a phenomenon worthy of study.

Intrigued by these observations, we embarked on three comprehensive studies, the results of which are presented in the upcoming text. The questions we addressed in the solvomercuration-demercuration procedure were could we control the stereochemistry of solvent addition to the cyclic enol ether moiety and to what degree does free rotation of the alkene side chain affect stereofacial differentiation?

With respect to asymmetric induction, we asked could a suitable and efficient method for the attachment of chiral auxiliaries be developed? If so, could we control the stereochemistry of enolization as well as provide a strong bias for diastereoface selection?

Focusing on stereoselective nucleophilic addition to 2-acyl pyrans, we questioned the role of Lewis acid complexation and searched for spectroscopic evidence of such with methylvinyl ketone dimer. It then became necessary to investigate the effects of solvent and reagent type on the intermediacy of chelated vs. dipolar mechanisms.

CHAPTER 2

RESULTS AND DISCUSSION

The one-pot multistep tandem oxymercuration-demercuration bicyclic ketal preparation sequence provides a rather interesting entry into the 6,8-dioxabicylo[3.2.1]octane system. The complexity and plausible chronology of the series of functional group transformations involved have recently been the focus of active interest in our research group. A number of provocative questions may be asked when one views a logical delineation of the original process carried out by Mundy (Figure 30).

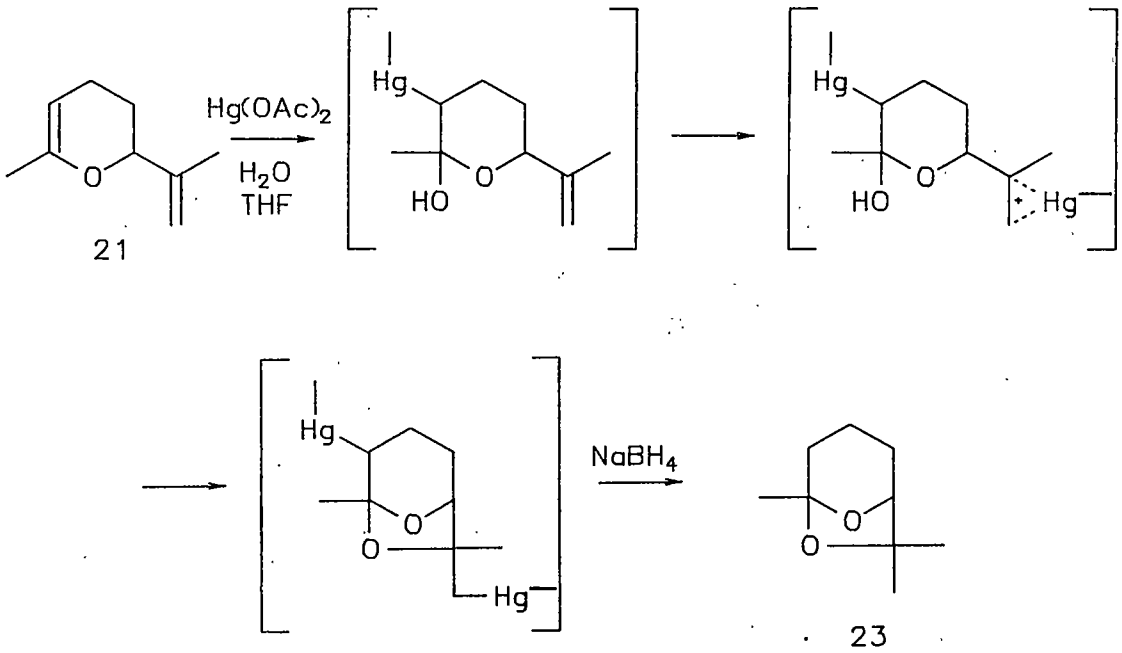
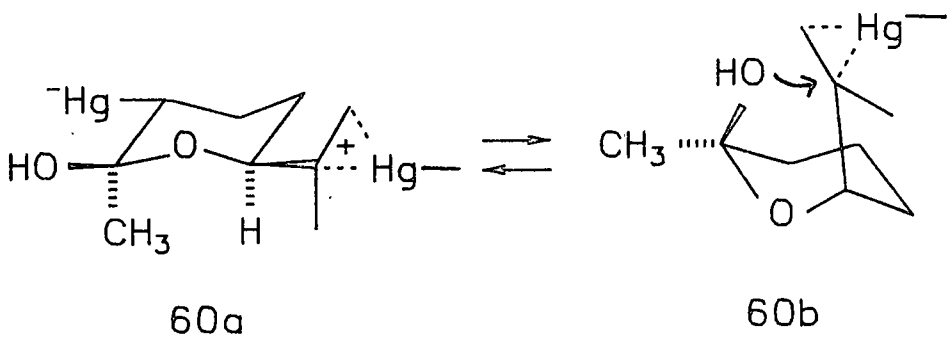


Figure 30. Original Tandem Oxymercuration-Demercuration-Bicyclic Ketal Preparation.

The questions we chose to address were: (1) what are the stereochemical implications of mercurinium ion formation at each of the double bonds, and, (2) what role does carbonium ion stability play in influencing the stereochemistry of ring closure?

To approach the intricacies involved in the oxymercuration steps, we first had to look ahead at the stereochemical requirements of pyran ring substitution prior to cyclization. As shown in Figure 31, a syn-relationship between the hydroxyl and isopropenyl groups is required for ring closure.



60a 60b

Figure 31. Required cis-Substitution Between the Hydroxyl and Isopropenyl Functions Prior to Ring Formation.

Thus we became interested in determining the stereochemical outcome of solvomercuration of the enol ether moiety. The model we chose to investigate was methylvinyl ketone dimer, [28]. It seemed likely that 28 would exhibit the same comformational biasing, with respect to the pyran ring, as diene [21]. In addition, the absence of the 2-isopropenyl group in ketone [28] would preclude unfavorable olefin competition for mercury which might complicate the reaction mixture.

It should also be noted that owing to the relative instability of hemiketals,[41] we chose to substitute methanol for water, and analyze the product ketal.

Treatment of ketone [28] with one equivalent of mercuric acetate and three equivalents of methanol, in THF, followed by evaporation of solvent, resulted in a semi-solid. Integration of the carbonyl and ketal carbon resonances by ^{13}C NMR revealed the presence of two conformational isomers in the approximate ratio of 56:44. It was presumed that the isomers obtained were 61a and 61b (Figure 32), assuming that the acetyl group occupied pseudo equatorial positioning in [28].

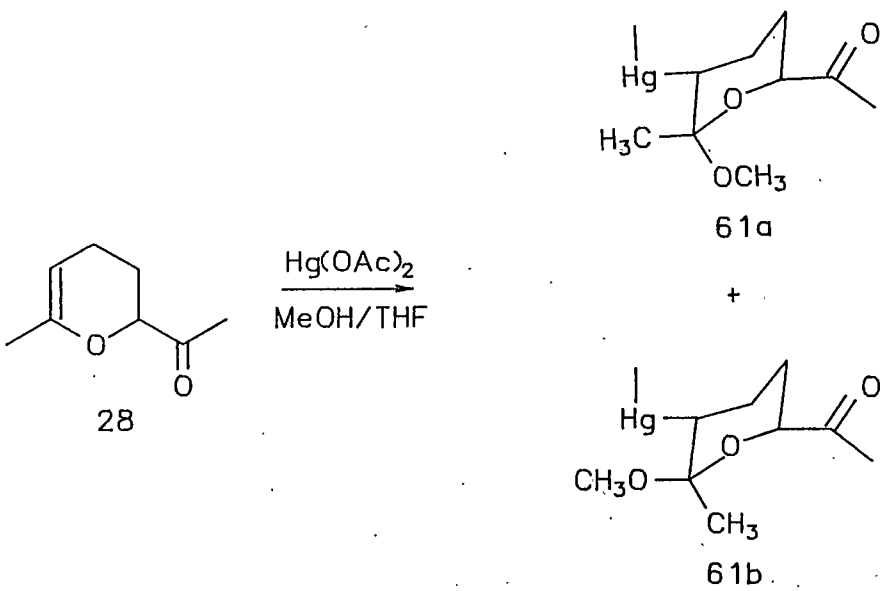


Figure 32. Solvomercuration of ketone [28].

The isomers 61a and 61b were quantitatively converted to the bicyclic ketals 62a and 62b, upon treatment with sodium borohydride, followed by acid catalyzed cyclization (Figure 33).

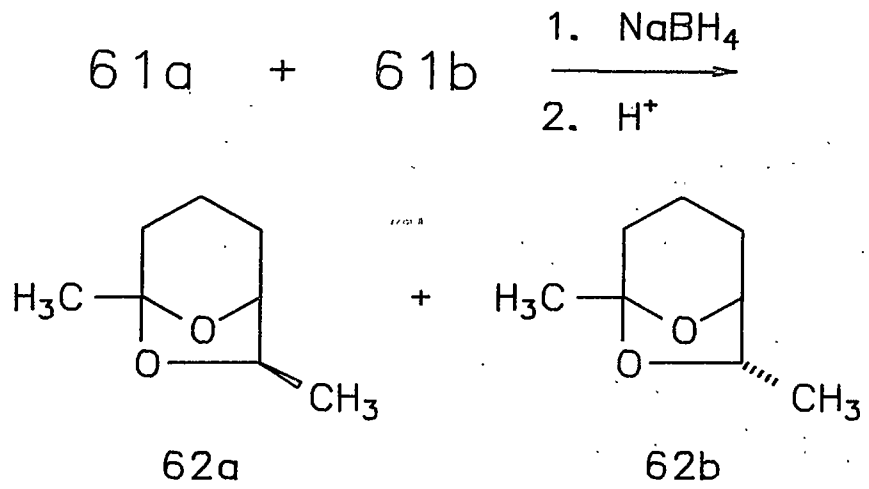


Figure 33. Demercuration/Cyclization of ketals 61a and 61b.

The ratio of 62a to 62b was determined, by capillary GLC, to be approximately 60:40.

With strong evidence indicating non-stereoselective solvomercuration of the enol ether moiety, we rationalized that from a reasonably assumed conformation with the (2-isopropenyl) group equatorial, one would not, apriori expect other than about a 1:1 mixture of axial and equatorial hydroxyl substitution (Figure 34).

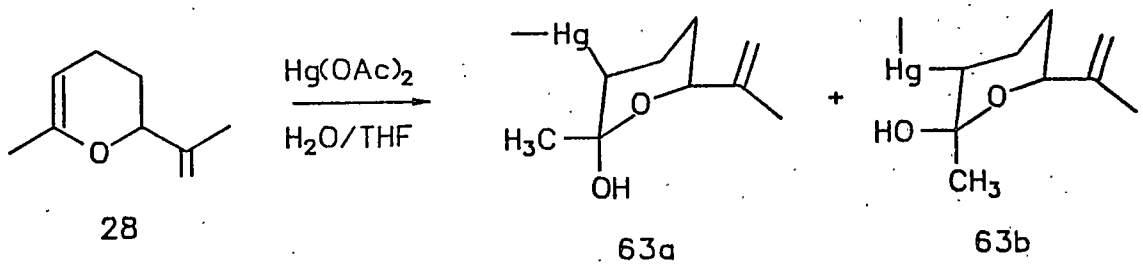
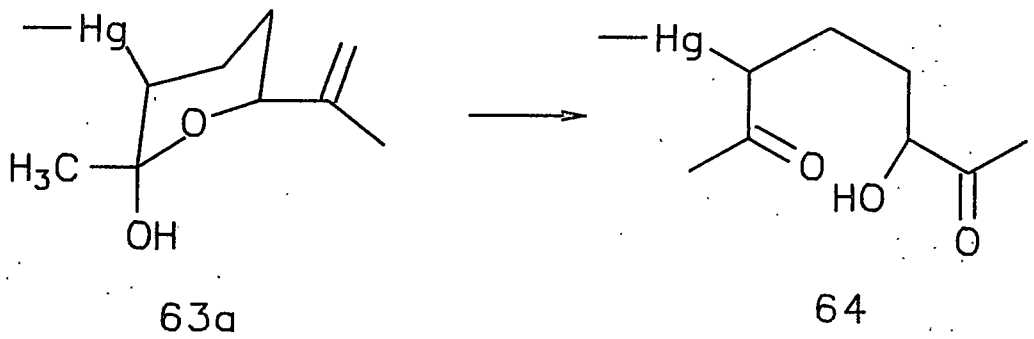


Figure 34. Proposed Non-stereoselective oxymercuration of Diene [21].

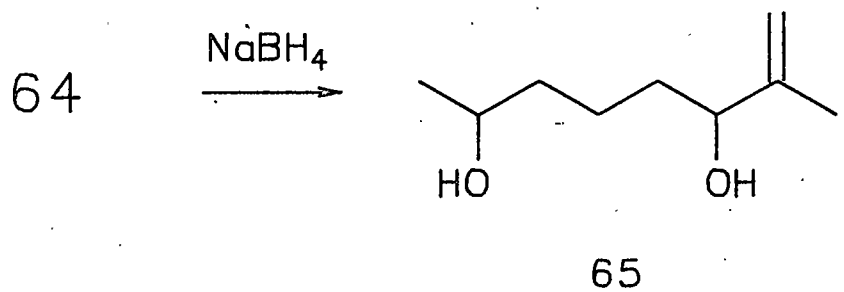
Having nearly equal amounts of cis and trans OH-substitution, with respect to the isopropenyl group, one would expect that only the cis-isomer would be capable of cyclizing. The trans isomer, 63a, might then be susceptible to ring opening as shown in Figure 35.



63a 64

Figure 35. Ring Opening of 63a.

Reflecting on previous work from our group, Schwartz had found that applying the tandem solvomercuration/demercuration procedure to diene [21] afforded, as the major product, diol [65]. It was presumed that diol [65] was formed by ring opening followed by borohydride reduction (Figure 36).



65

Figure 36. Proposed Mechanism for Diol Formation.

This finding offers rationale for the moderate yields often obtained for the target bicyclic ketals. We then decided to pursue the stereochemical requirements of ring closure for the cis isomer [63b]. Focusing on the rotational preferences of the isopropenyl group, it was recognized that π-facial differentiation of the double bond could translate into diastereofacial selectivity in mercurinium ion formation/ ring closure. Such an event would result in preferential positioning of mercury in either the exo or the endo C-7 methyl group (Figure 37) in the product bicyclic ketal.

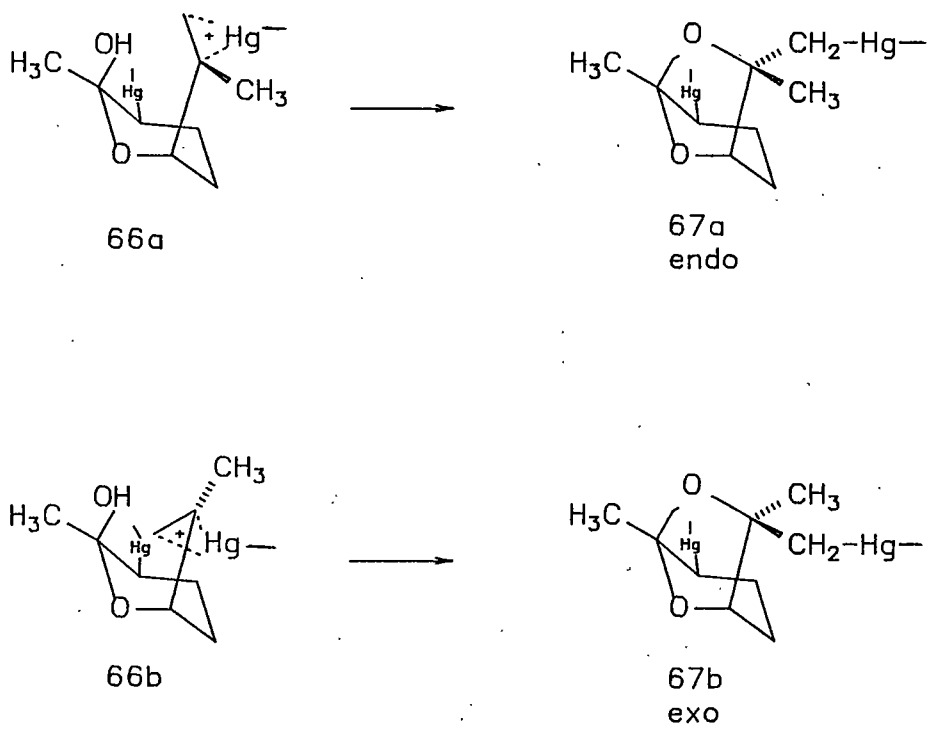


Figure 37. Proposed Stereochemical Control in Mercurinium Ion Cyclization.

Because demercuration with borohydride results in geminal dimethyl substitution of C-7, the identity of the methylene containing mercury,

prior to demercuration, was masked. Therefore the tandem solvomercuration procedure was repeated with diene, [21], followed by demercuration with sodium borodeuteride (Figure 38). The identity of the methylene carbons bearing mercury prior to ring closure could then be determined by proton NMR integration of the geminal methyl signals containing deuterium.

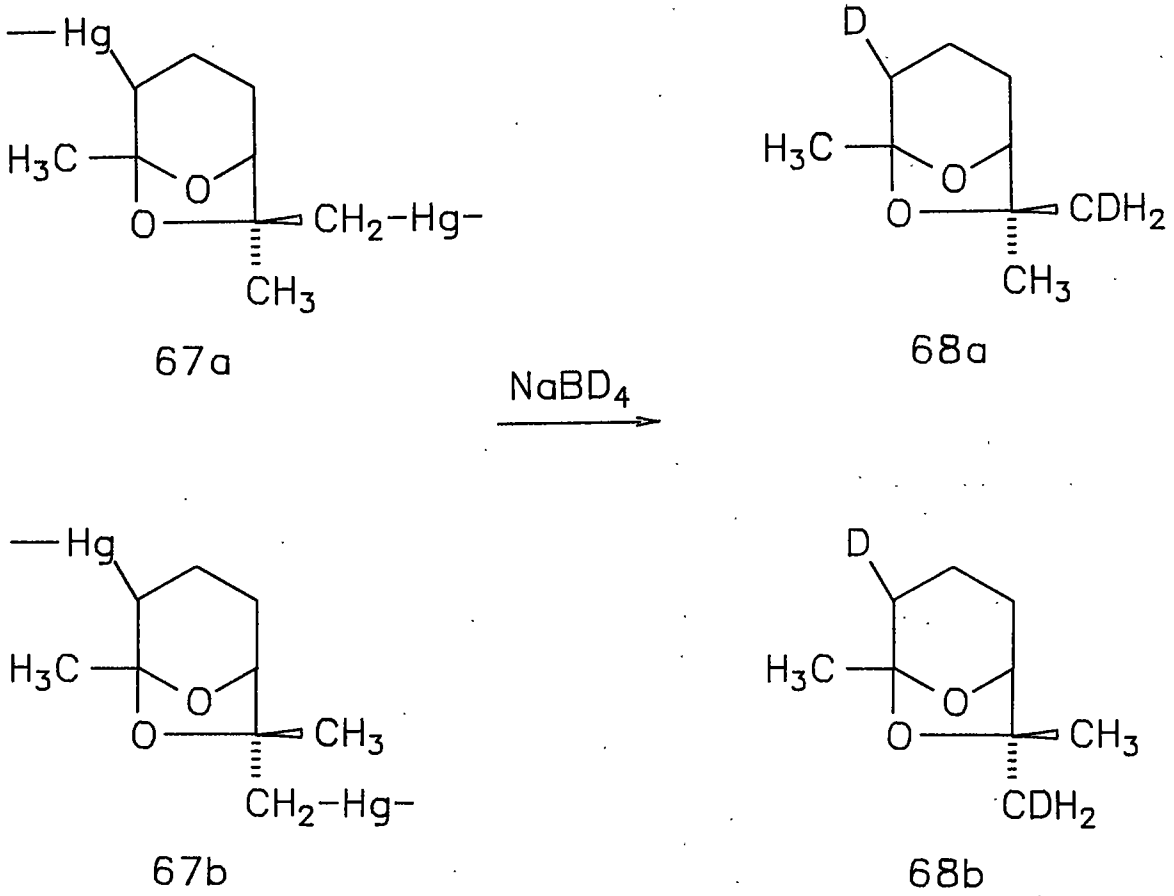


Figure 38. Demercuration with Sodium Borodeuteride.

It has been established that in the ^1H NMR spectrum of ketal [23] the exo methyl group resonates at about 1.26 ppm and the endo group resonates at about 1.36 ppm, relative to TMS. As illustrated in Figure 39, ^1H NMR integration of the C-7 methyl region of 68a and 68b revealed a ratio of approximately 55:45 (endo:exo) deuterium substitution.

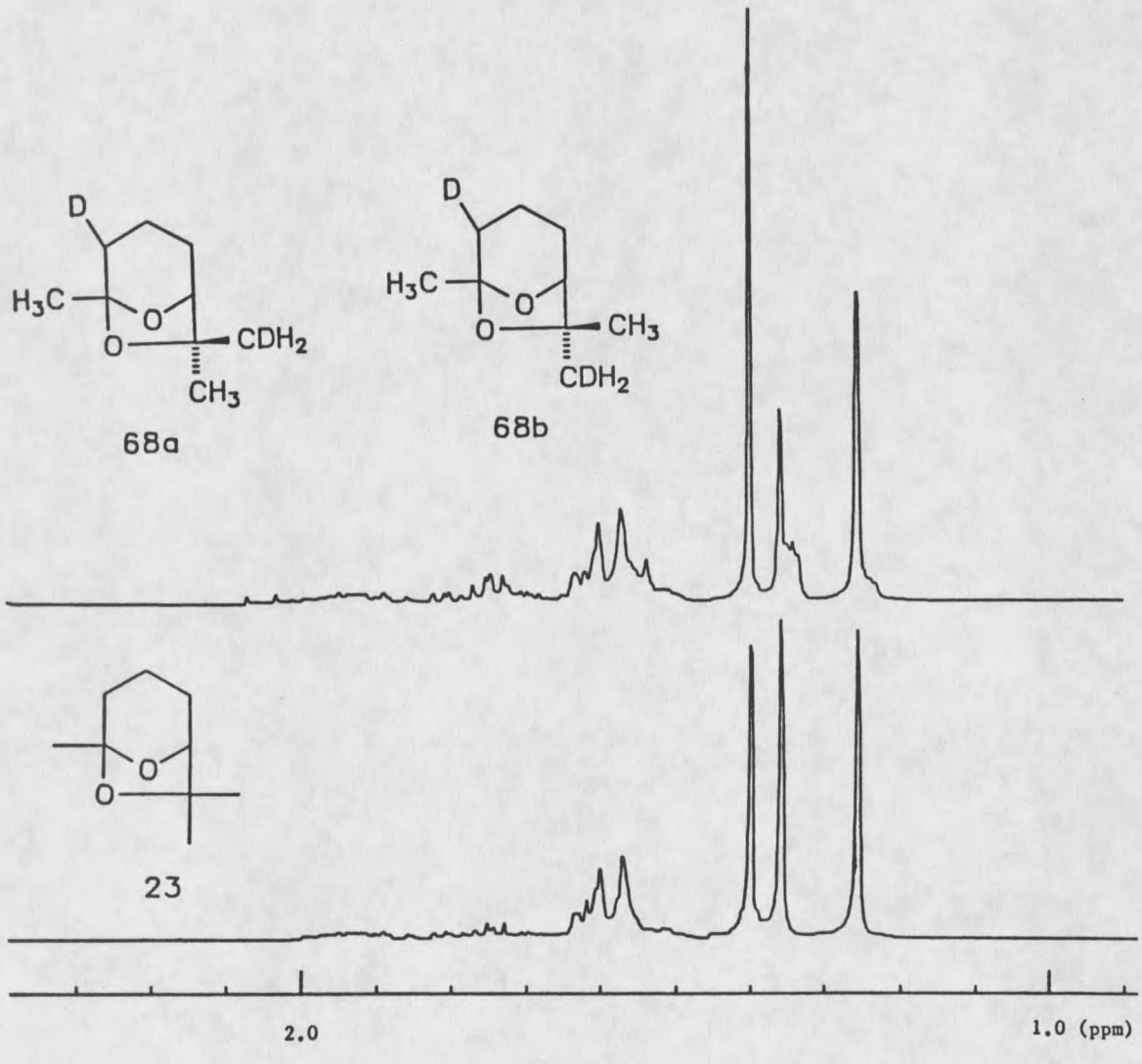


Figure 39. ^1H NMR Spectra for 23, 68a and 68b.

This ratio suggests that solvomercuration of the isopropenyl group is largely non-stereoselective. These data correlate well with Mundy's previous observation that solvomercuration/demercuration of diene [19] resulted in a 55:45 ratio of the endo and exo brevicomins (Figure 40).

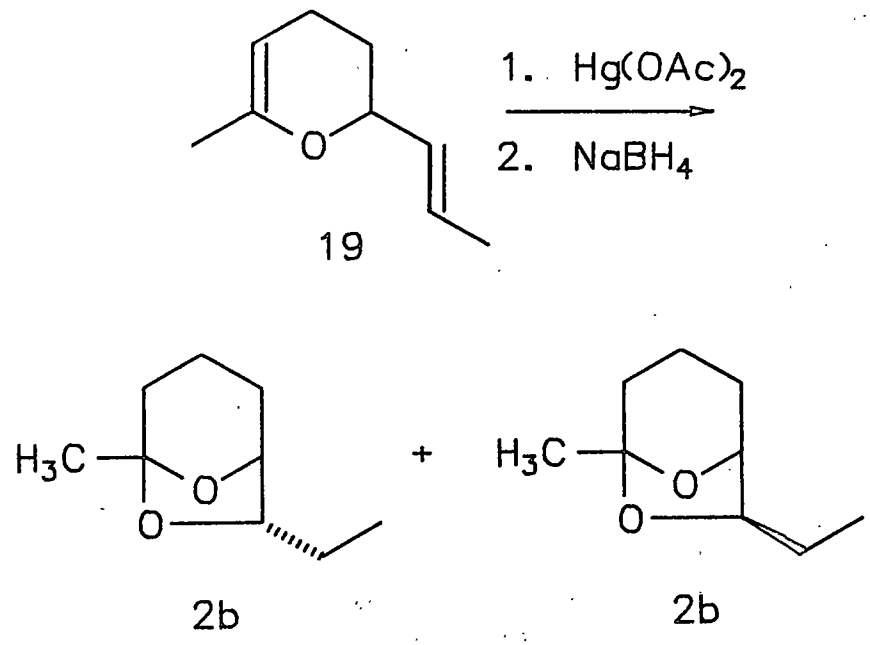


Figure 40. Relative Non-Stereoselectivity in the Tandem Solvomercuration-Preparation of Brevicomin.

The characteristic lack of π-facial differentiation of the olefin side chain of and 19 may be attributed to unimpeded rotation. Figure 41 illustrates the loss of selectivity, in the addition of mercury, which would result if all three rotamers of contribute to the reaction outcome.

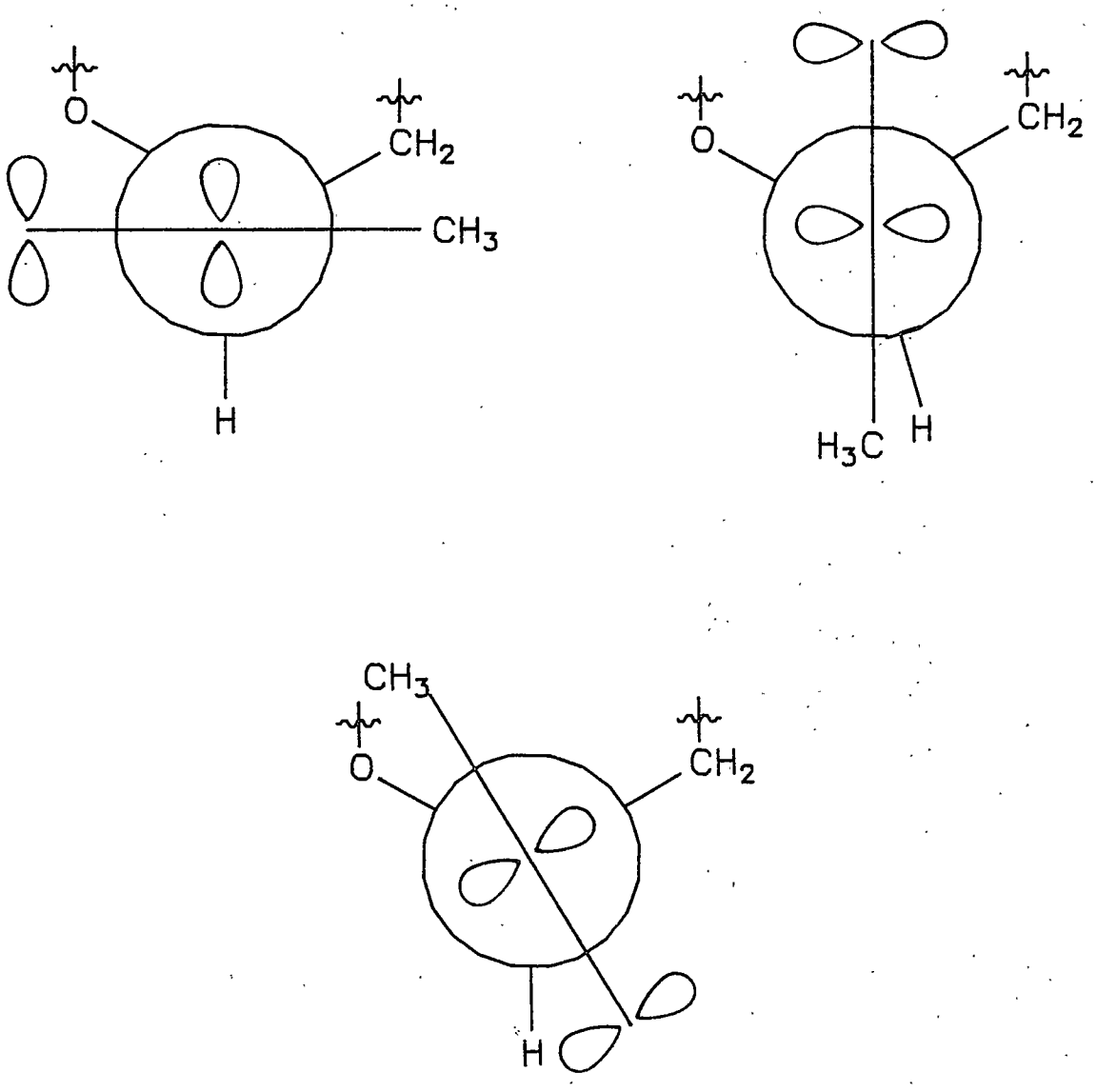


Figure 41. Proposed Source of Non-Stereoselection Due to Rotational Freedom.

As a consequence of obtaining significant insight into the scope and limitations of the tandem solvomercuration procedure, we were motivated to pursue some related objectives. We sought to further explore various modifications of the enol ether moiety and 2-carbonyl substituents of dihydro-2H-pyrans in order to expand our arsenal of methodologies for entry into bicyclic ketals. Reflecting on the previous application of the solvomercuration procedure to a synthesis of 6 (Figure 8), we chose to focus on the difficulties encountered in obtaining ketone [24] in pure form (Figure 42).

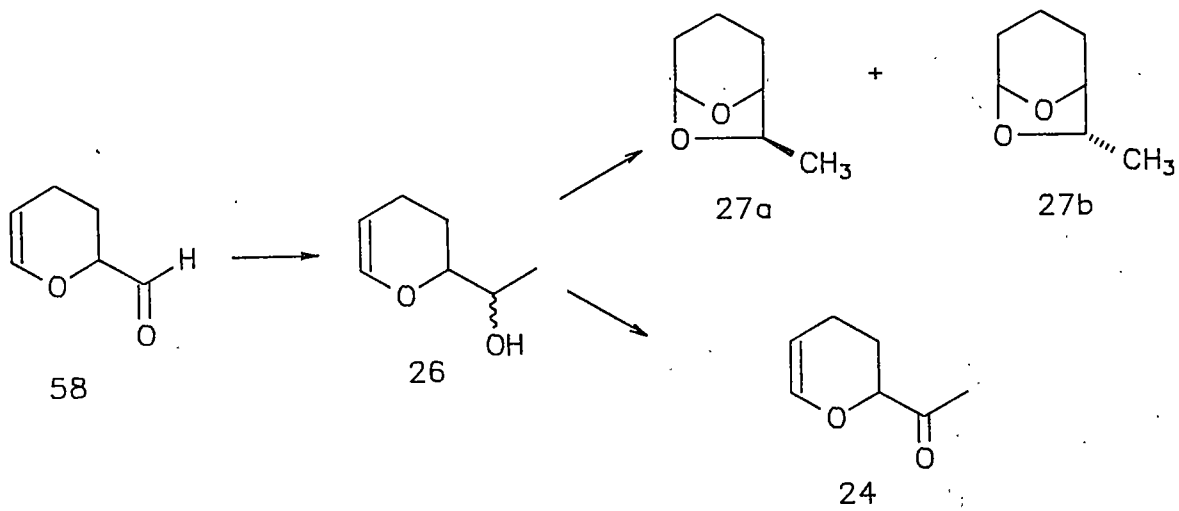


Figure 42. Preparation of Ketone [24].

The isolation and subsequent oxidation of alcohol [26] proved troublesome as the product mixture was contaminated with 10-25% of the ketals 27a and 27b. To further assess the limitations of chemically modifying alcohols like 26, an improved procedure for the synthesis of ketone [24] was needed. Because contact by neutral or acidic protic media promotes cyclization of [26], care was taken to ensure that the isolation and oxidation steps (58-26-24) remained basic.

The successful conversion of 58 to 24 was achieved through the following procedure: treatment of acrolein dimer,[58] with excess methyllithium (or methylmagnesium bromide) followed by quenching with excess 10% potassium hydroxide and extraction with diethyl ether quantitatively afforded alcohol [26], as a colorless oil. The crude product was immediately taken on to the oxidation step without purification. Alcohol, [26], was dissolved in freshly distilled methylene chloride (P_2O_5) and added slowly to a stirred solution of excess pyridinium dichromate (3-4 equivalents) in freshly distilled methylene chloride containing sodium acetate and molecular sieves[42] at 0°C. After stirring 8-12 hours, the resulting dark suspension was suction filtered and the filtrate was passed through a short pad of silica gel, affording pure ketone [24] in approximately 40% isolated yield (2 steps).

Although the overall yield was moderate, this procedure circumvented the problem of contamination by inseparable by-products. Noteworthy is the fact that repeated attempts to scale up this procedure six to seven grams results in significant amounts of unoxided alcohol [26].

Having ketone [24] pure, the sequences previously carried out (Figure 8) were repeated, resulting in improved yields of the hop oil constituent, [6]; i.e. 6 was obtained free of the undesired by-products (27a) and (27b).

We then decided to explore the scope and limitations of modifying 2-carboxyl derivatives of dihydro-2H-pyrans by making use of the commercially available (Aldrich) 3,4-dihydro-2H-pyran-2-carboxylic acid, sodium salt, [71].

We recognized that 71 might serve as a versatile intermediate in the

preparation of esters which have previously been difficult to isolate. For example, the synthesis of ester 69 (a precursor to frontalin) by way of a Diels-Alder heterocycloaddition (Figure 43) resulted in the formation of the inseparable by-product methylvinyl ketone dimer, [28].

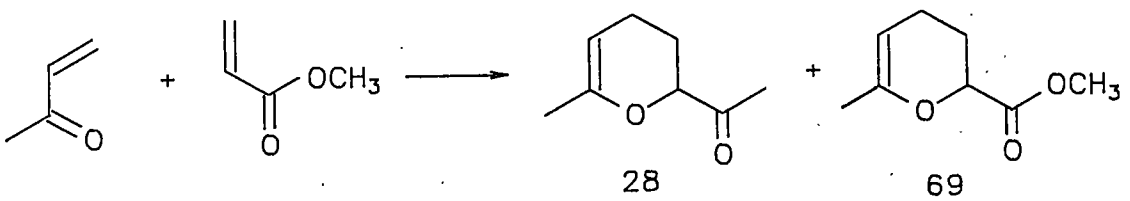


Figure 43. Diels-Alder Preparation of Ester [69].

It was thought that a Diels-Alder reaction employing acrolein and methylacrylate would proceed in a similar fashion, resulting in both ester [70] and dimer [58] (Figure 44).

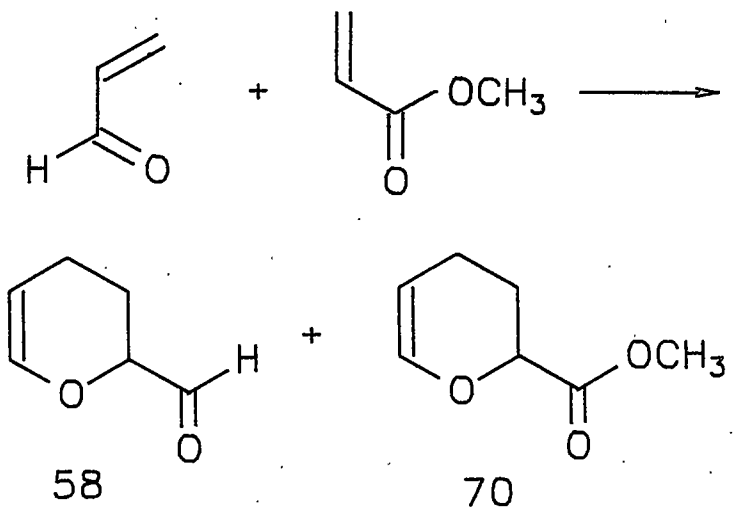


Figure 44. Proposed Outcome of a Diels-Alder Reaction Employing Acrolein and Methylacrylate.

Based on this premise, the preparation of 70 by Diels-Alder cycloaddition was not attempted and an alternative procedure was pursued. The pyran salt [71] was refluxed in tetrahydrofuran (THF) with two equivalents of HMPA. Aqueous extraction with water and diethyl ether, followed by silica gel chromatography (8:2 hexane:ethylacetate) afforded pure ester [70] in approximately 62% isolated yield.

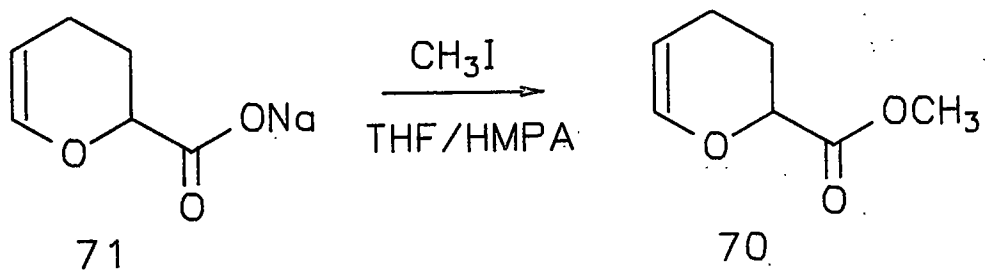


Figure 45. Alternative preparation of Ester [70].

Repeated attempts to effect the conversion of 71 to 70 in the absence of HMPA met with failure, as no reaction was observed.

The successful preparation of 70 represents a suitable circumvention of the formation of inseparable by-products obtained by Diels-Alder cycloaddition. With 70 in hand, we chose to pursue an alternative synthesis of the hop oil constituent [6]. Thus, ester [70] was treated with 2.5 equivalents of methyllithium in THF at -78°C. The reaction was carefully quenched with two equivalents of water, followed by acid-catalyzed cyclization with 15% HCl, affording 6 in nearly quantitative yield (Figure 46).

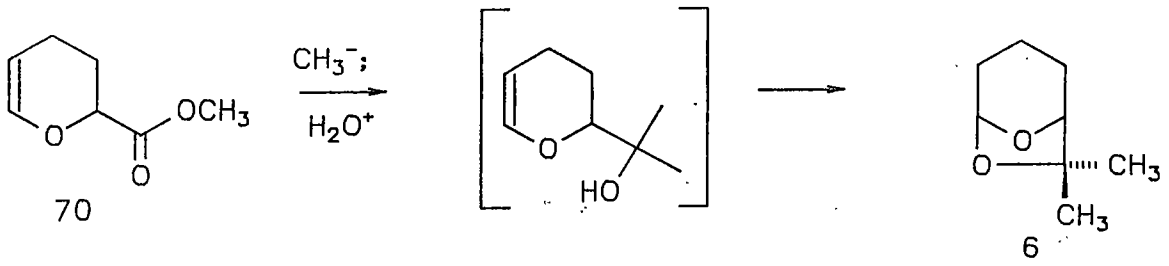
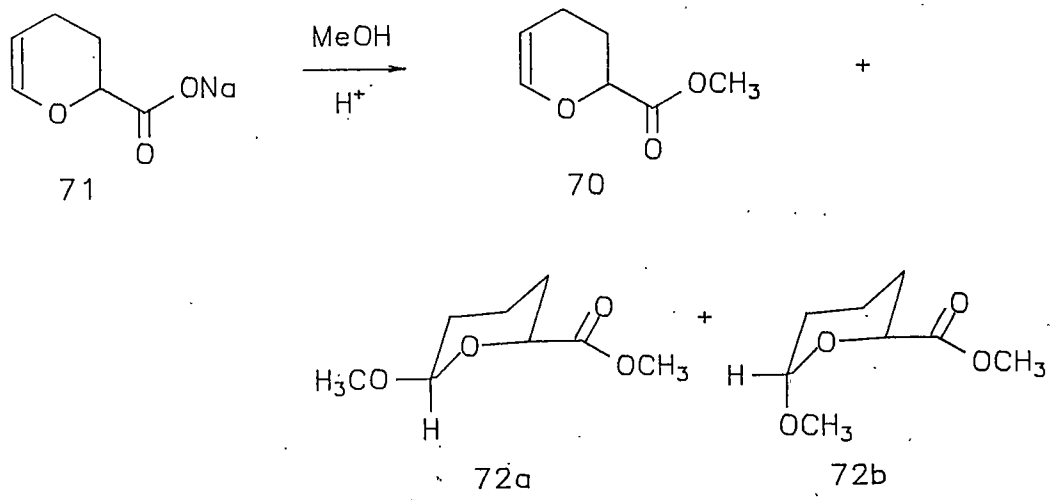


Figure 46. Alternative Preparation of the Hop Oil Constituent [6].

We then decided to explore the reactivity of 71 in acid-catalyzed esterifications. Treatment of 71 with 3-5 equivalents of H_2SO_4, using methanol as the solvent, yielded ester [70] and the isomeric acetals [72a] and [72b] (Figure 47) in a temperature-dependent ratio.



Temperature	Ratio of Reaction Products		
	57	58a	58b
35°C	0	1	9
Reflux	1	1	5

Figure 47. Acid-Catalyzed Esterification of 71.

The stereochemistry of the acetals 72a and 72b was easily elucidated with ^1H NMR spectroscopy, by using the Karplus equation[43]. Analysis of Dreiding models revealed the relative environments of the acetal protons with respect to the protons of the adjacent ring methylene. Measurement of the dihedral angles (Figure 48) between the acetal proton and the respective axial and equatorial protons of the adjacent methylene allows for an approximation of the expected vicinal ^1H-^1H coupling patterns for each of the isomers 72a and 72b.

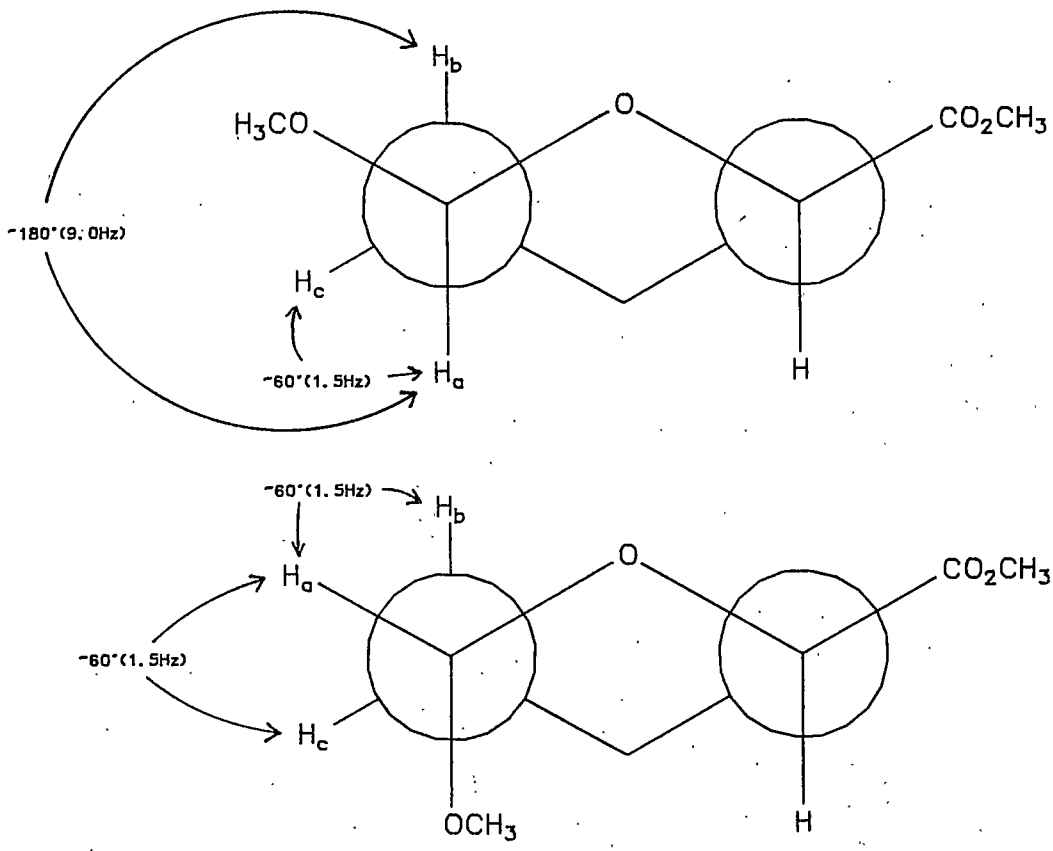


Figure 48. Approximation of Dihedral Angles H_a - H_b and H_a - H_c and predicted ^3J values.

Based upon the dihedral angle dependence for vicinal proton coupling constants(^3J), the equatorial methoxy isomer [72a] was expected to exhibit $3J(H_a\text{-}H_b)$ of about 9Hz ($\theta = 175°$) and ^3J (H_aH_c) of about 1.5 Hz ($\theta = 60°$) resulting in a doublet of doublets pattern. The observed pattern was a broadened doublet with ^3J= 8.46 Hz. The axial methoxy isomer [72b] was expected to exhibit ^3J= 1.5 Hz for $H_a\text{-}H_b$ and $H_a\text{-}H_c$ ($\theta = 60°$) which would result in a broadened singlet signal. Such was the observed pattern.

The preferential formation of the more sterically hindered axial methoxy isomer was attributed to the "Anomeric Effect."[44] A well accepted explanation for this phenomenon suggests that the stereo-electronic effects of overlap between the non-bonding-orbital of the pyran ring oxygen with the antibonding orbital of the methoxy oxygen atom, override the steric influences of the methoxy substituent.

Noteworthy is the apparently equal ability of each isomer, 73a and 73b, to cyclize (Figure 49). After the acid-catalyzed cyclization step was initiated, samples were taken at 5 minutes (approximately 2% of completion) and 1.5 hours (approximately 60% of completion) for GC analysis. Integration of relative peak areas indicated nearly equal ratios of 73a to 73b for each sample. These data suggest the intermediacy of a solvolytic (S_N1) pathway as opposed to (S_N2) displacement. A highly controlled kinetic experiment seemed unnecessary and was not pursued.

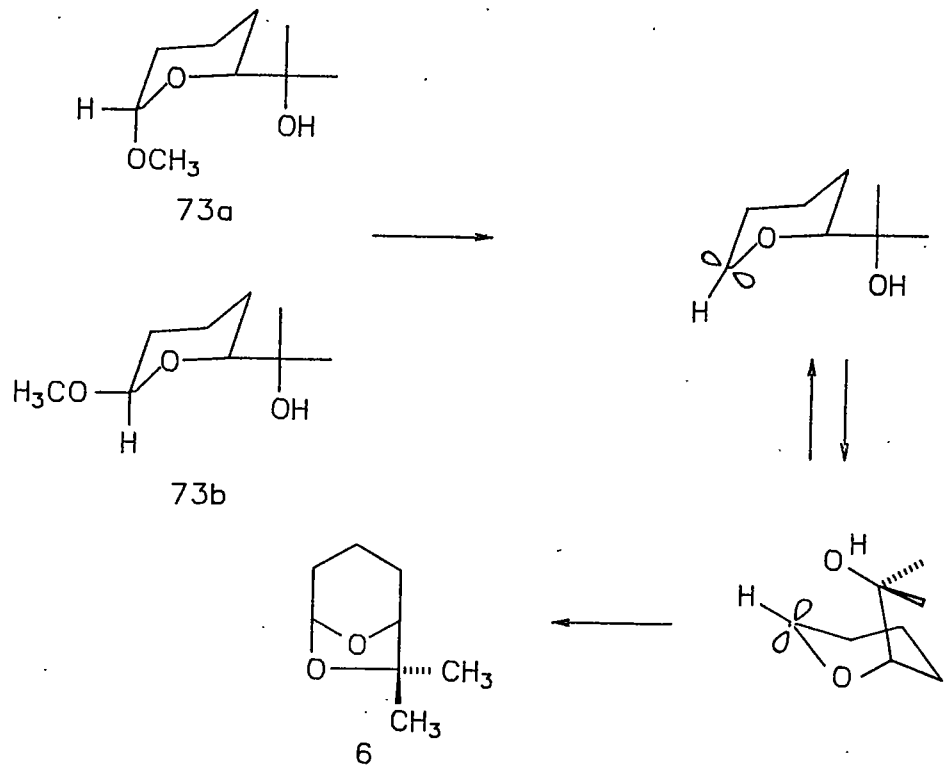


Figure 49. Proposed Solvolytic Pathway for Methoxy Displacement.

Having demonstrated the utility of the pyran salt [71] in the preparation of methoxy esters, we chose to investigate the preparation of acid halides, with an emphasis on maintaining the integrity of the acid-sensitive enol ether moiety (Figure 50). We felt that an acid chloride such as 74 might be readily converted into a variety of useful intermediates bearing alkyl, alkoxyl or amine functionalities, including chiral auxiliaries.

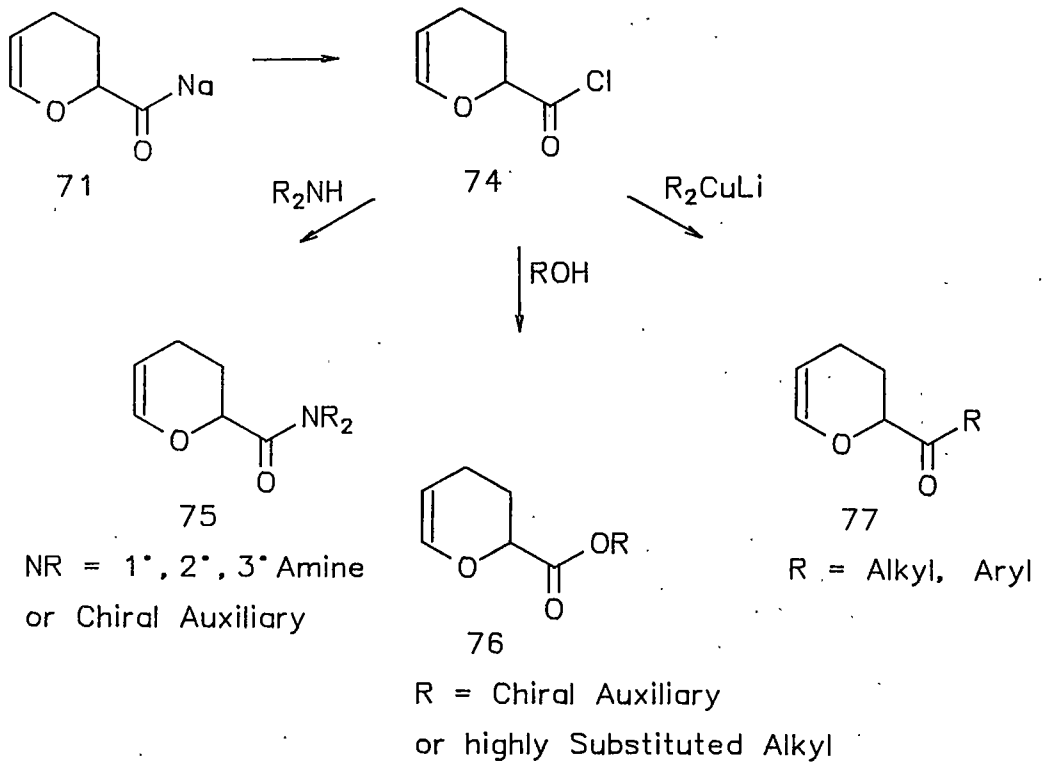


Figure 50. Proposed Synthetic Utility of Acid Chloride 74.

Although historically it has been more common to prepare acid chlorides from carboxylic acids [45] we recognized two particular advantages to employing the carboxylate salt [71] rather than the carboxylic acid [78]. First, it was thought that attempts to isolate 78 might result in significant formation of the lactone [79] by way of acid catalyzed lactonization (Figure 51).

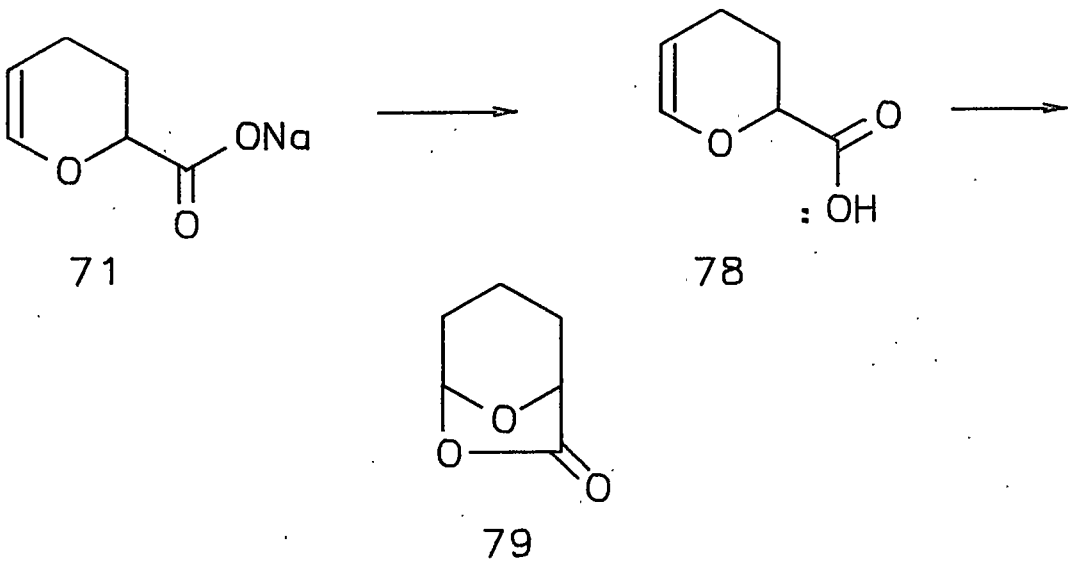


Figure 51. Proposed Lactonization of Carboxylic Acid [78].

Second, we recognized the sensitivity of the enol ether moiety to HCl, which is a characteristic by-product of acid chloride preparations from carboxylic acids (Figure 50). Thus, the conversion of 71 to 74 would result in the formation of sodium chloride as by-product, which would be inert toward the substrate.

Pyran [71] was suspended in dichloromethane, with rapid stirring, and treated with excess thionyl chloride ($SOCl_2$). Refluxing for 2-6 hours, followed by filtration of salts and distillation at diminished pressure, afforded a mixture of 74 and the HCl addition product [80], in varying ratios (Figure 52) and in 20-30% yield.

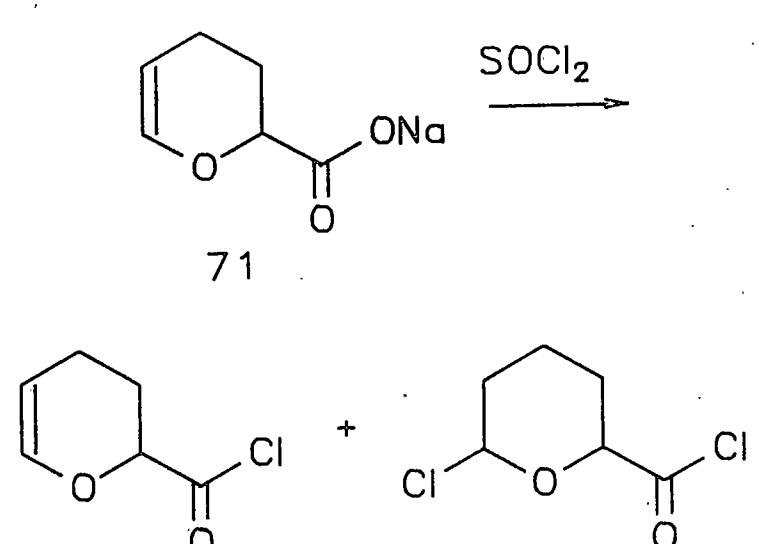


Figure 52. Reaction of 71 with Thionyl Chloride.

The formation of 80 was proposed to have resulted from contamination of water in the pyran salt [71]. Thionyl chloride was ruled out as the source of H^+ as it had been freshly distilled from triphenylphosphine.[46] The reaction was repeated several times, with and without the addition of pyridine as an HCl trap, affording the same results.

Although redistillation of the product mixture (50-60°C asp.) afforded pure 74, the yields were consistently low (10-30% isolated). We were then compelled to pursue an alternative procedure involving oxalyl chloride. The conversion of carboxylate salts to acid chlorides with oxalyl chloride and catalytic dimethylformamide (DMF) has been previously documented. [46]

The carboxylate salt [52] was then treated with oxalyl chloride at 0°C under argon, in the absence of solvent (Figure 53). A catalytic amount of DMF was added, followed by refluxing for 2-6 hours. The usual workup was employed, affording pure 74 in 54% yield. Repeated attempts to dry the pyran salt by prolonged warming under vacuum, prior to treatment with oxalyl chloride, failed to improve the yield. Although the yield of acid chloride [74] was moderate (54%), the oxalyl chloride/DMF procedure was an improvement over the previous 30% yield with $SOCl_2$.

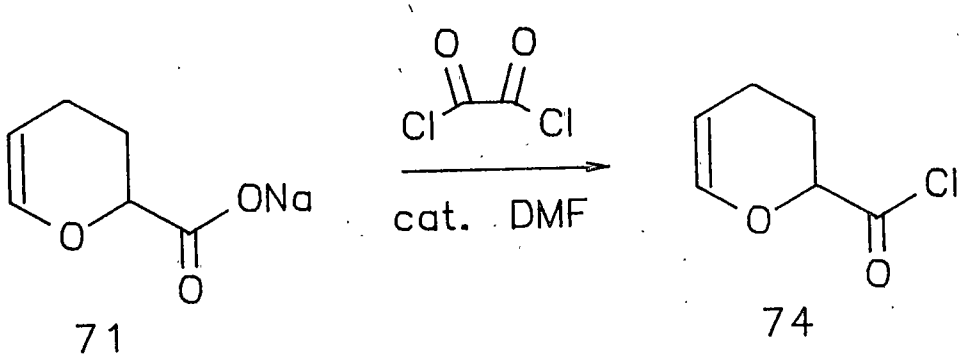


Figure 53. Preparation of 74 with Oxalyl Chloride.

CHAPTER 3

ASYMMETRIC SYNTHESIS

Our investigations of chemical modifications of 2-carbonyl substituents of dihydro-2H-pyrans provided us with a wealth of background information concerning the attachment of removable functionalities. With access to the versatile acid chloride [74] we directed our attention toward the preparation of pyrans bearing chiral control groups. It was recognized that having a suitable chiral auxiliary covalently bound to the 2-carbonyl substituent might provide a means by which asymmetry could be induced in a carbon-carbon bond forming reaction involving the pyran ring. Controlling the absolute configuration of C-2 substitution of dihydro-2H-pyrans might bode well for the preparation of enantiomerically pure bicyclic ketals.

A number of highly enantioselective syntheses of insect pheromones have recently been published which do not utilize dihydro-2H-pyran intermediates. The synthetic strategies employed in each of the reported asymmetric preparations involve Type "a" methodologies[48] (Figure 54). Chirality in the precursor keto-diols results from two contrasting strategies: (1) asymmetric induction employing chiral reagents and (2) chiral building blocks derived from carbohydrates.

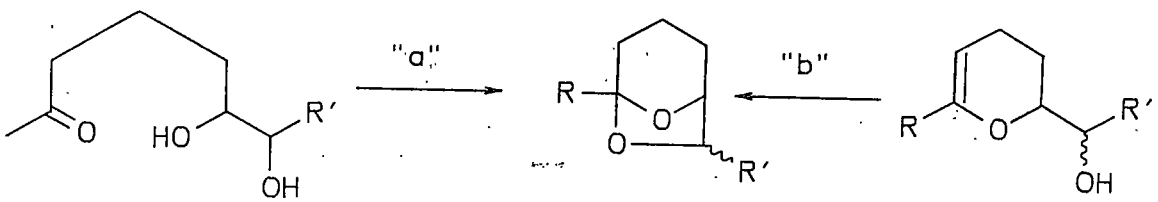


Figure 54. Synthetic Strategies for Bicyclic Ketal Synthesis.

Whitesell[49] has employed 8-phenylmenthol in two novel conversions of glycolate esters to (+)- and (-)- frontalin (Figure 55). Eliel[50] has demonstrated the synthetic utility of a chiral 1,3-oxathiane precursor in the preparation of each enantiomer of frontalin (Figure 56).

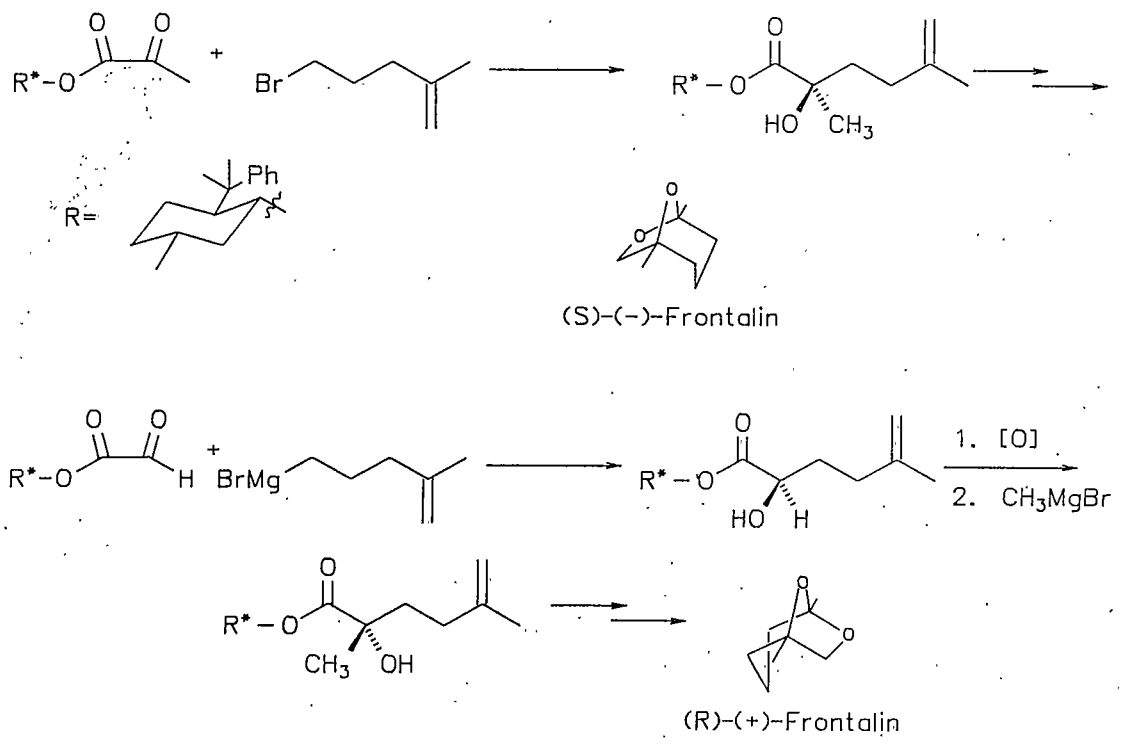


Figure 55. Whitesell Syntheses of (+)- and (-)- Frontalin.

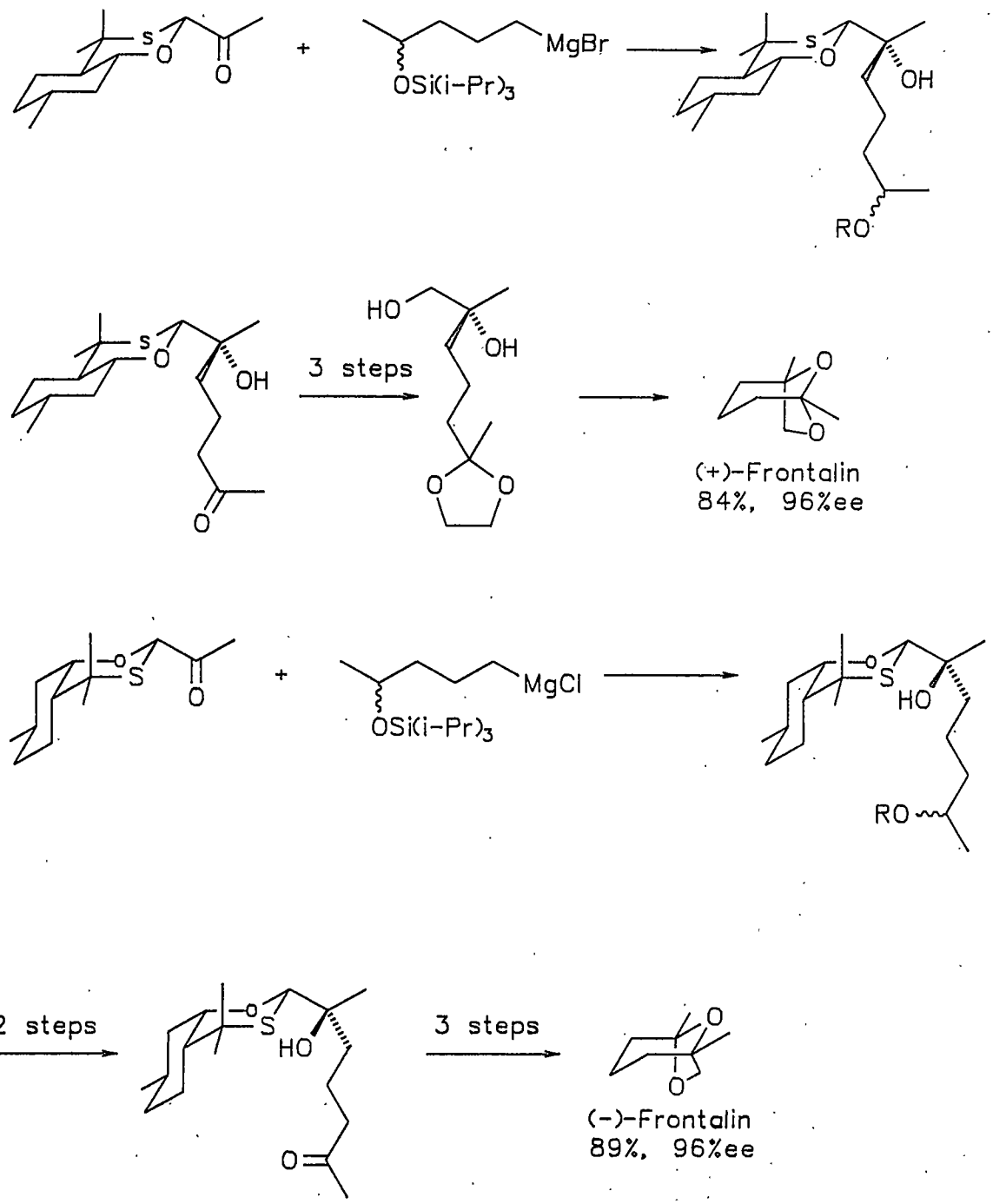


Figure 56. Eliel Syntheses of (+)- and (-)- Frontalin.

The well known "Sharpless Epoxidation"[51] procedure was employed by Oehlschlager[52] in the syntheses of both (+)- and (-)-endo-brevicomin (Figure 57). A unique chiral boronic ester mediated synthesis of (+)-exo-brevicomin was recently reported by Matteson[53] (Figure 58).

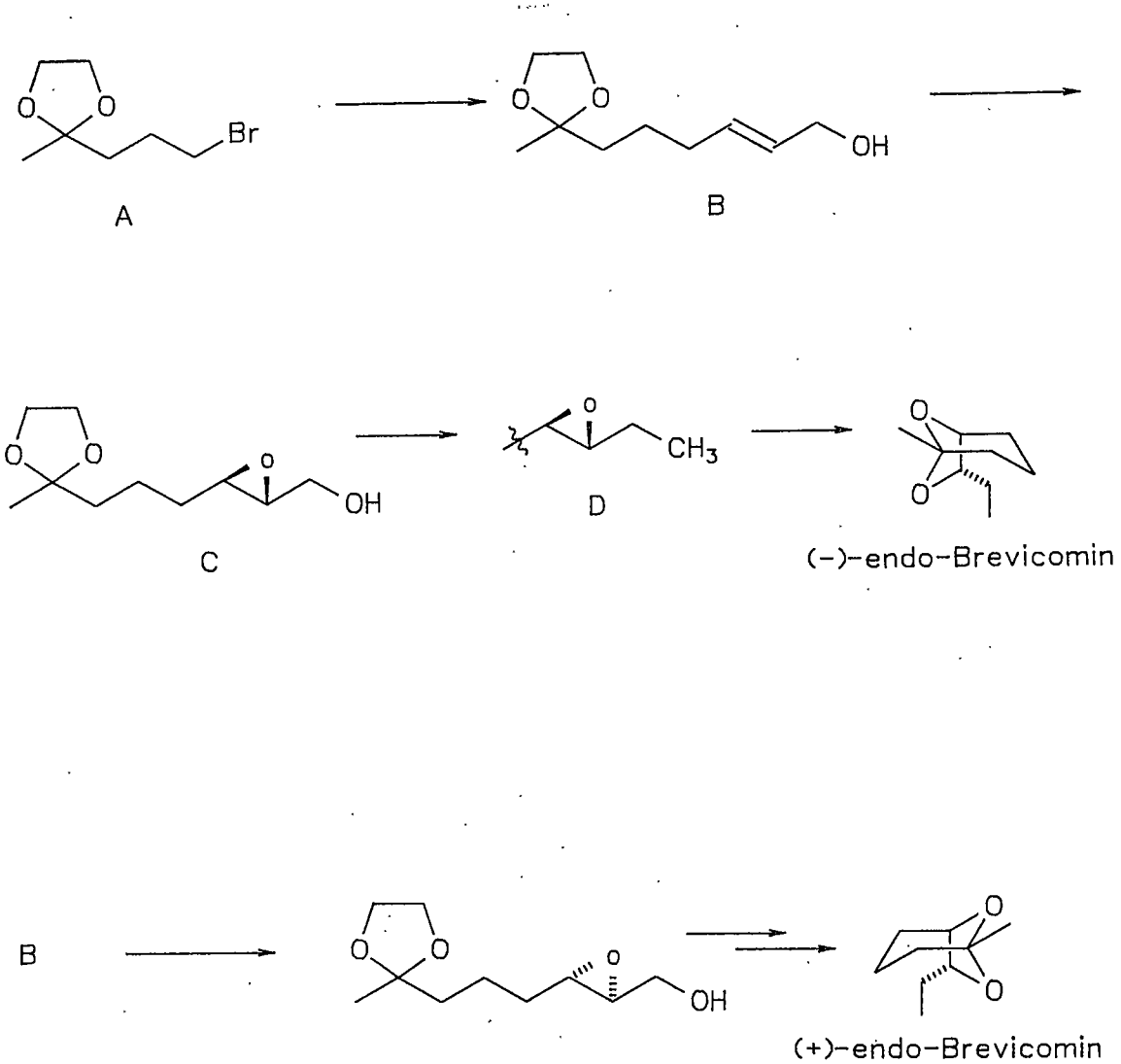


Figure 57. Oehlschlager Syntheses of (+)- and (-)- endo-Brevicomin.

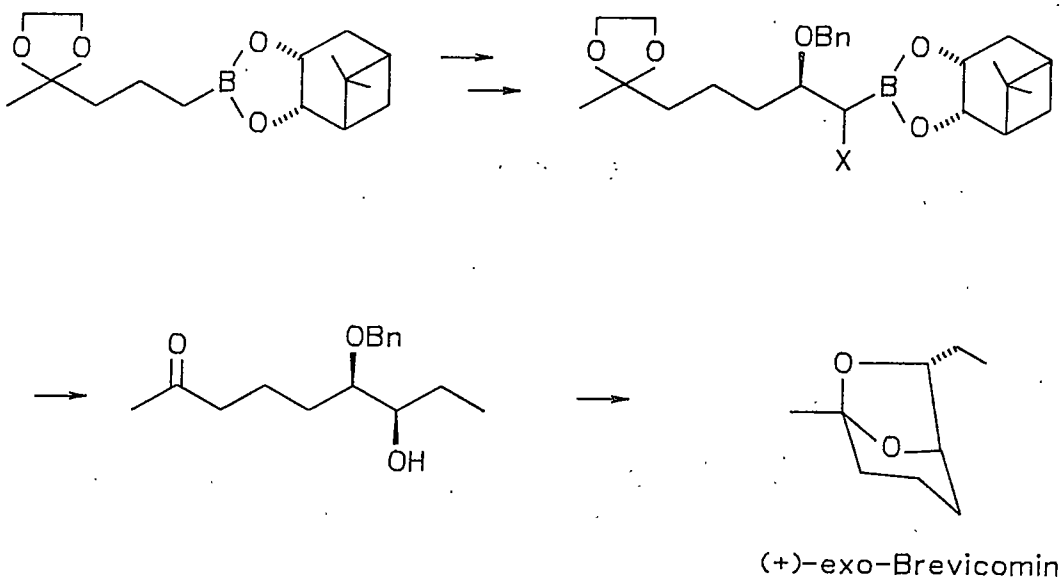


Figure 58. Matteson Synthesis of (+)- exo-Brevicomin.

In 1982 Fraser-Reid[54] reported a novel preparation of (+)-exo-brevicomin from a chiral building unit derived from ribose (Figure 59).

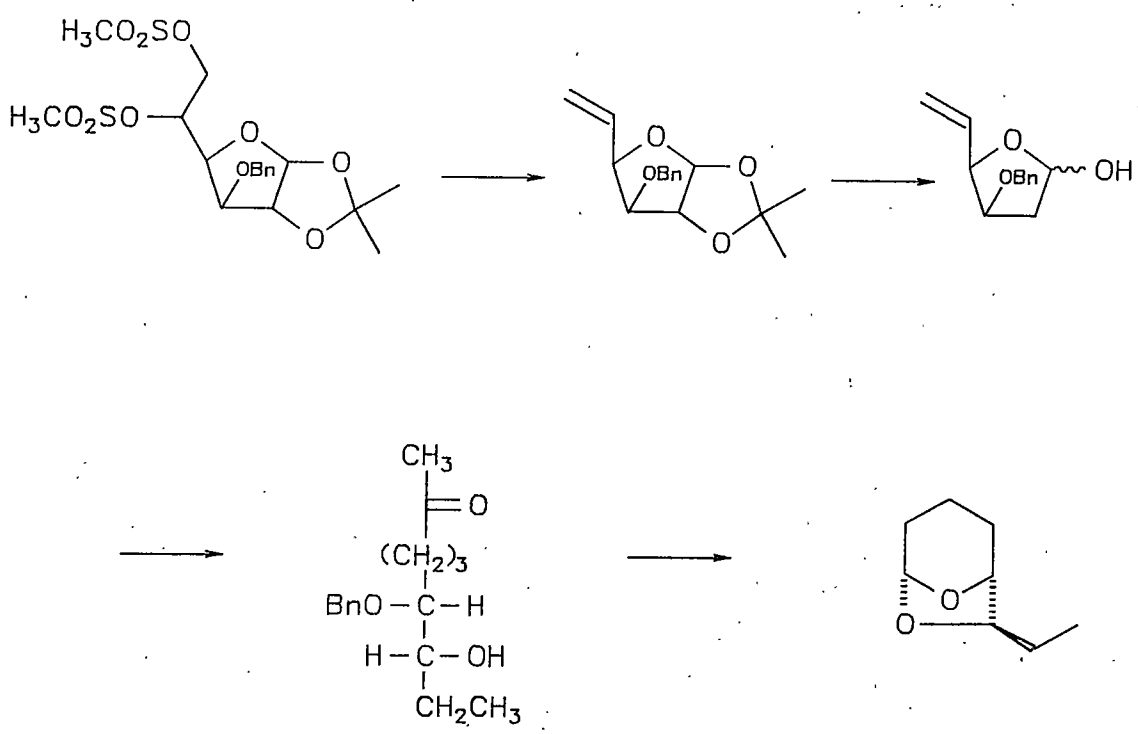


Figure 59. Fraser-Reid Synthesis of Brevicomin.

Redlich[55] has recently reported two alternative syntheses of both enantiomers of endo-brevicomin starting from D-ribose (Figure 60).

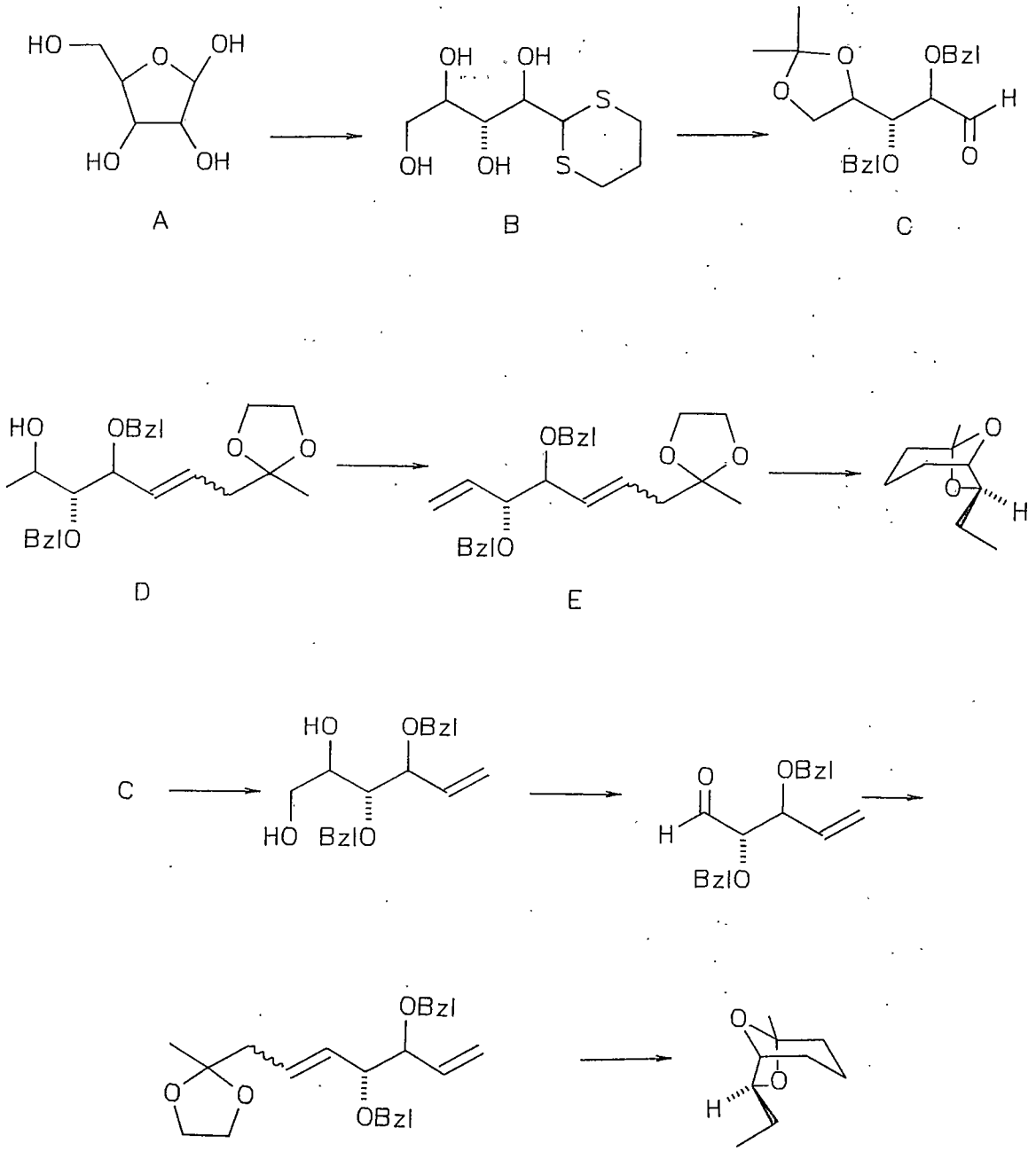


Figure 60. Redlich Syntheses of endo-Brevicomin.

The type "a" asymmetric syntheses of insect pheromones, albeit, highly enantioselective, represent multistep sequences, many of which require tedious chromatographic separations of diastereomers. Considering the low cost and ready availability of dihydro-2H-pyran precursors, we envisaged highly efficient entries into chiral bicyclic ketals via type "b" strategy, which plausibly would require only one diastereomer separation step.

Conscious of the paucity of published examples of chirality transfer to ring carbons via enolate alkylation (Figure 19), we began our studies with a model system employing (-)-menthol as the recyclable chiral directing group. Although menthol had not previously been reported as a highly efficient chiral auxiliary its low cost and robust resistance to chemical degradation offered significant appeal.

Treatment of acid chloride [74] with (-)-menthol [81] (Figure 61) and pyridine afforded the desired diastereomeric esters [82] in a ratio of approximately 1:1 (^{13}C NMR).

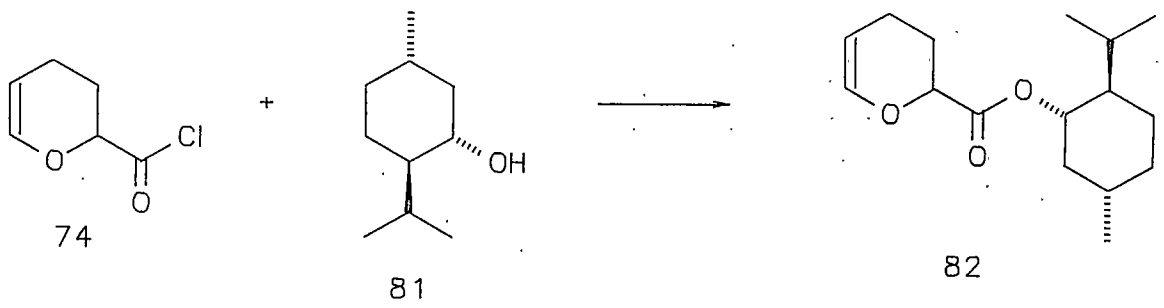
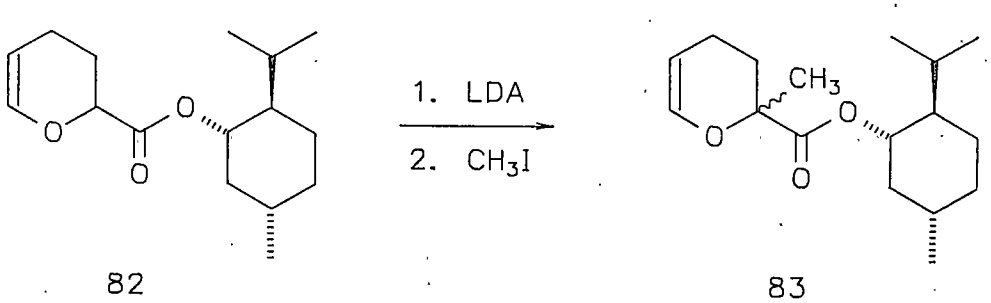


Figure 61. Ester Formation with (-)-Menthol.

Ester [82] was easily purified via silica gel chromatography (8:2 hexane: ethyl acetate) affording the desired product in good yield.

An alternative procedure, which afforded identical results, involved the addition of 74 to a cold (0°C) solution of lithium mentholate (menthol + n-BuLi) in THF. We then sought to methylate 82 in an attempt to prepare a proposed precursor to frontalin (Figure 12). Thus, 82 was exposed to 1.1 equivalents of lithium diisopropylamide (LDA) at -78°C, followed by excess methyliodide, affording 83 in quantitative yield (Figure 62).



82 83

Figure 62. Methylation of Menthol-Derived Ester

Analysis of 83 by integratable ^{13}C NMR spectroscopy revealed a diastereomeric ratio of approximately 55:45. Repeated attempts to increase stereoselectivity by varying the temperature failed to improve the ratio beyond 57:43.

We then directed our attention to the steric size of the electrophile. It was thought that increasing the size of the leaving group, L (Figure 63) might result in enhanced steric interaction at the more encumbered face of the chiral enolate.

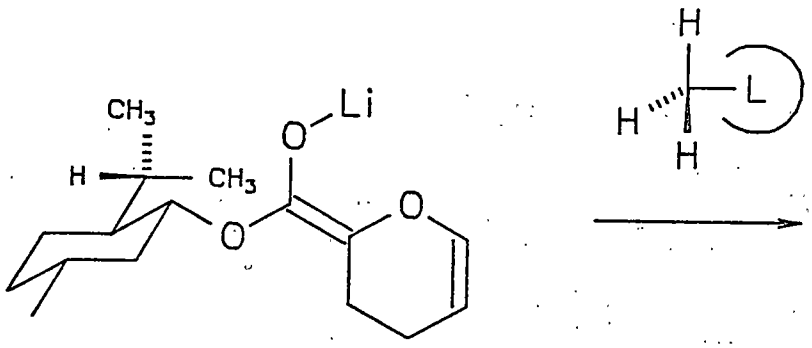


Figure 63. Proposed Selectivity Enhancement by Increasing Steric Demand of Electrophile.

The alkylation procedure was then repeated employing methyl p-toluene-sulfinate as the alkylating reagent. The reaction proceeded in quantitative yield (GLC) however, the stereoselectivity enhancement was modest as 83 was obtained as a 63:37 mixture of diastereomers (^{13}C NMR).

We then decided to study the effects of solvent character on the stereochemistry of the derived enolate. Reflecting on the previous studies by Ireland [25] (Figure 16) and Helmchen [26] (Figure 17) we elected to employ HMPA as the co-solvent in an attempt to alter the enolate geometry. Indeed, we did not rule out the possibility that in THF, both enolate geometries might exist, thus, defeating the inductive capability of the chiral auxiliary.

The alkylation procedure was repeated using THF, containing 23% HMPA, and methyl p-toluenesulfinate as the alkylating reagent. Much to our disappointment, the observed diastereoselectivity was a modest 57:43.

Careful examination of Dreiding models indicated that with either enolate (E or Z) derived from 82, the π-facial shielding offered by the isopropyl moiety of menthol, is somewhat offset by puckering of the pyran ring (Figure 64).

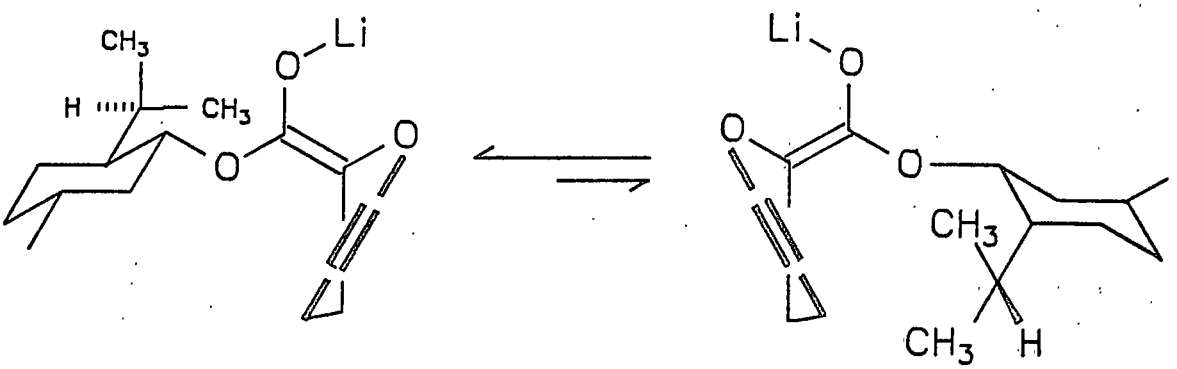


Figure 64. Pyran Ring Conformational Flopping.

We rationalized that with a chiral auxiliary bearing a significantly larger π-facial shielding moiety the encumbrance due to pyran ring folding might be favorably offset. We envisaged employing a camphor-derived (Helmchen) auxiliary bearing aryl π-facial shielding groups. Figure 65 illustrates the desired π-stacking we sought to achieve between the chiral auxiliary and the extended π-system of the pyran.

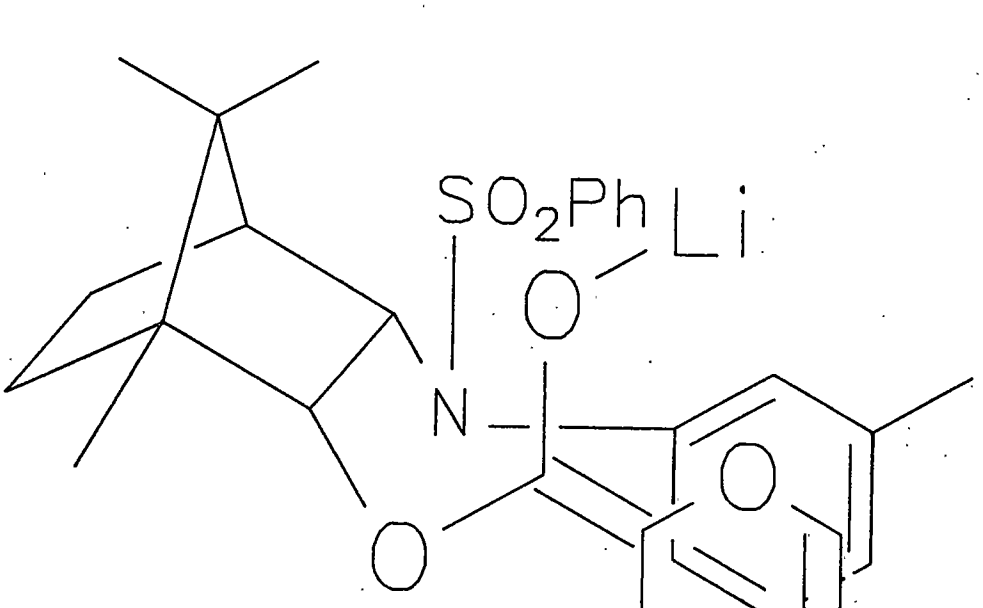


Figure 65. Proposed π-Stacking with Camphor-Derivative.

We then focused our attention on the preparation of ester [86] from 74 (Figure 66).

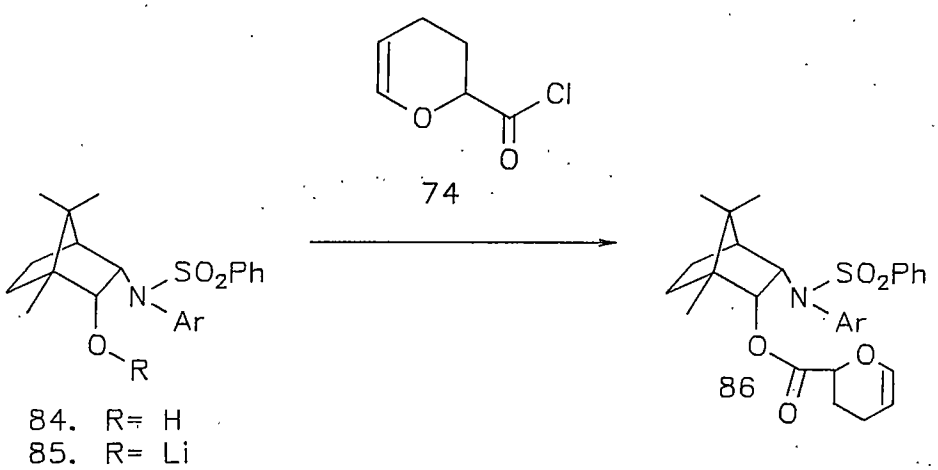


Figure 66. Proposed Preparation of 86.

The bornanol derivative [84], in dichloromethane, was treated with three equivalents of triethylamine and one equivalent of 74 at 20°C for twelve hours. Rapid extraction with diethyl ether and water afforded unreacted 84 along with trace amounts of several indistinguishable polymeric by-products (^{13}C NMR and GC/MS).

The reaction was then repeated, at reflux, followed by evaporation of solvent under reduced pressure. Analysis of the crude product by thin layer chromatography (TLC) with 20:1 pentane:ethyl acetate revealed two products (R_f = 0.45 and 0.29) in trace amounts, and unreacted 84 (R_f = 0.16) as the major component. At this point we recognized the potential instability of the desired ester and omitted aqueous extraction. Likewise, GLC analysis was avoided, for fear that the hot (>240°C) injection port may cause decomposition of 86.

Therefore, the crude product was rapidly taken up in anhydrous deuteriochloroform and quickly analyzed by ^{13}C NMR and Direct Insertion Probe (DIP) mass spectrometry. However, our delicate efforts went unrewarded as no evidence for the target ester [86] was detected.

Repeated attempts to prepare 86 from its corresponding lithium alkoxide [85] also failed, as did an attempt employing calcium hydride[56] in place of pyridine, as the HCl scavenger. We then rationalized that steric interactions between 74 and the auxiliary [84] highly prevent proper orientation of the reacting centers. Information in support of this hypothesis was obtained through perusal of the literature. For esterification reactions of 84, we found no reported examples employing 2,2-disubstituted acid halides, nor did we encounter discussions of such.

Because 74 represents a 2,2-disubstituted acid halide, we abandoned attempts to prepare 86 and elected to pursue an alternative procedure, employing S-prolinol-derived amides. As previously cited,[22] alkylations of enolates derived from S-prolinol (Figure 13) proceed with high diastereoselectivity, yet the auxiliary is far less functionalized than its camphor-derived counterparts.

S-prolinol [88] and (s)-(+)-2-methoxymethylpyrrolidine [91] were prepared by the method of Enders[57] and co-workers (Figure 67).

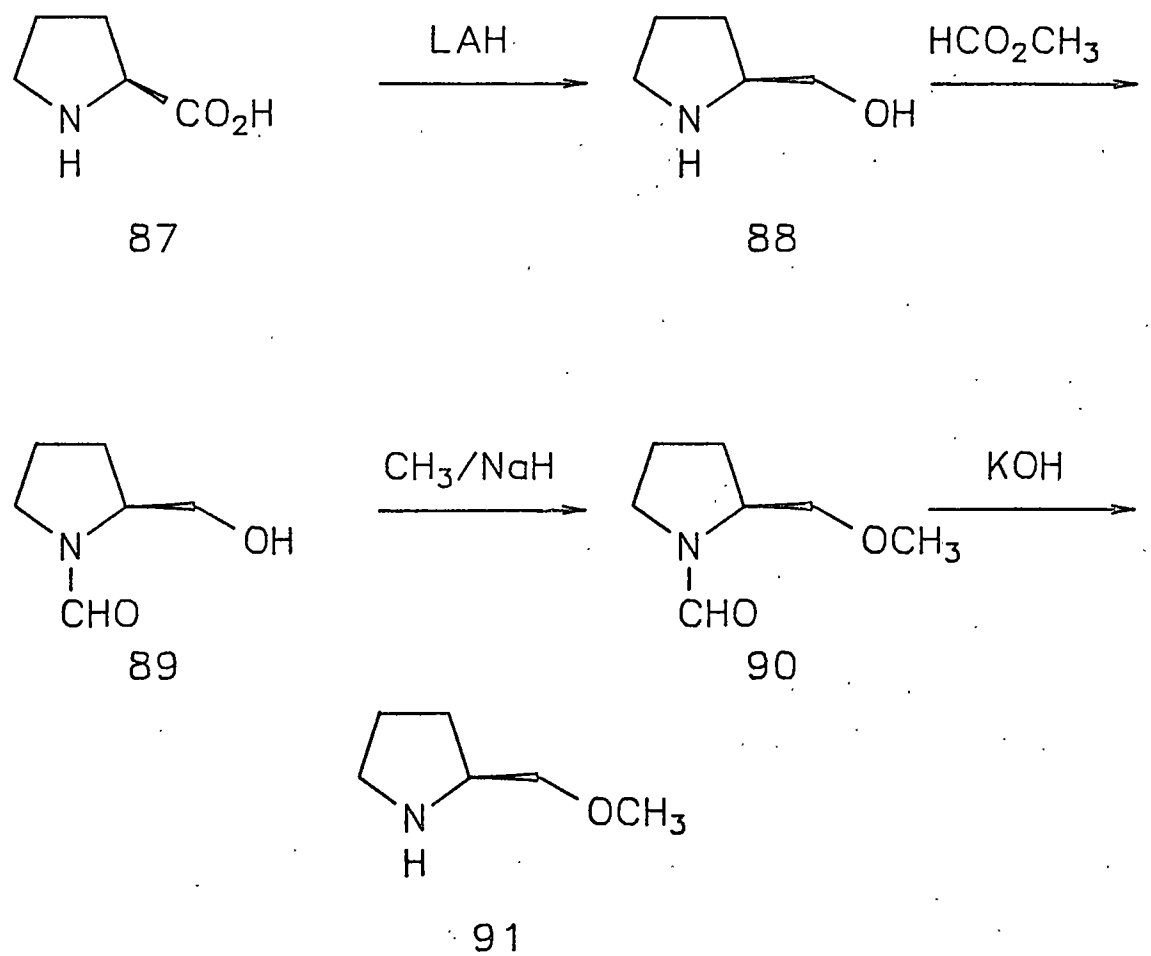


Figure 67. Preparation of S-Prolinol and (S)-(+)-2-methoxymethylpyrrolidine.

We then focused our attention on the preparation of 92 (Figure 68). Treatment of s-prolinol with pyridine and 74, followed by extraction with dilute HCl (to remove pyridine) afforded crude product which accounted for only half of the material balance.

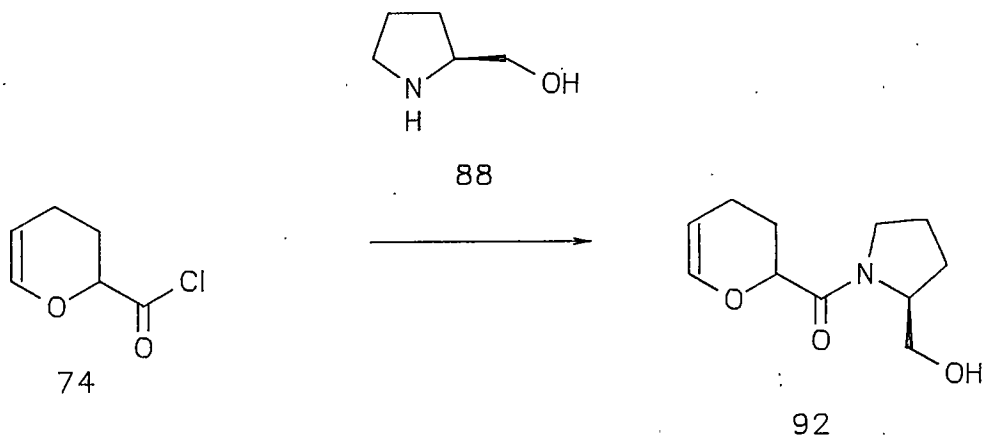


Figure 68. Preparation of 92.

Pure 92 was obtained by silica gel chromatography (CH_2Cl_2) in low yield (ca. 20%). Unsatisfied with this procedure, we reviewed a report by Evans[58] which revealed the ease with which amides derived from s-prolinol are hydrolyzed in the presence of aqueous acid (Figure 69).

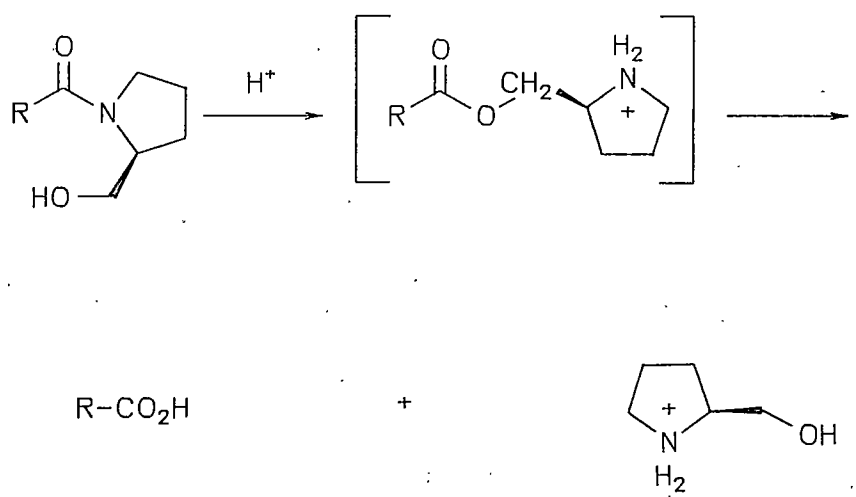


Figure 69. Acid-Catalyzed Hydrolysis of S-Prolinol Derived Amides.

It was then rationalized that the acidic conditions of the extraction step resulted in partial hydrolysis of the desired product [92] which would account for the low yield obtained.

An alternative preparation of 92 was found in the treatment of 70 with s-prolinol, in the absence of solvent (Figure 70). Removal of methanol by evaporation, under diminished pressure, afforded 92, as a pale orange oil, in quantitative yield.

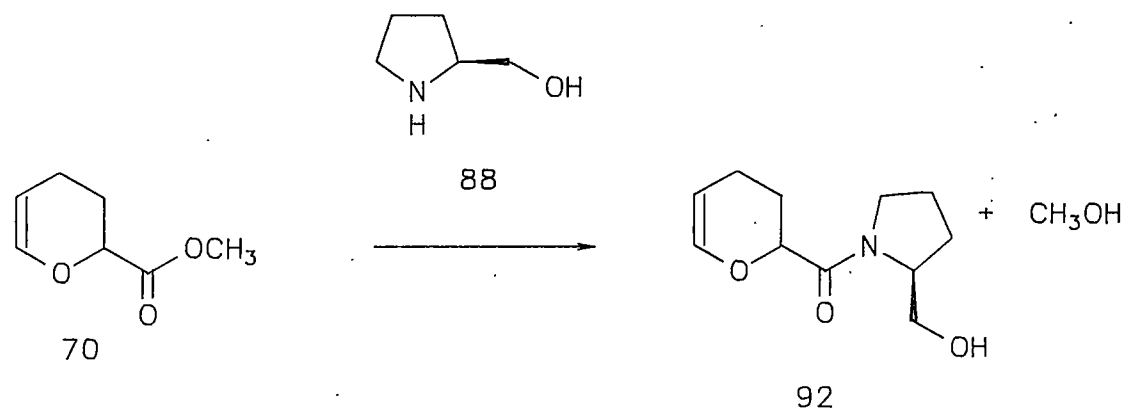


Figure 70. Alternative Preparation of 92.

Analysis by ^{13}C NMR and capillary GC/MS revealed essentially pure 92 as a 1:1 mixture of diastereomers. The crude product was then taken to the next step without further purification.

To test the diastereoselectivity of enolate alkylation, 92 was treated with two equivalents of LDA, followed by 1.3 equivalents of methyliodide (Figure 71). Analysis of the crude product by integratable ^{13}C NMR indicated the presence of polymeric material. Analysis by capillary GC/MS revealed several by-products and two baseline separated peaks, consistent for 93(M^+), in a ratio of approximately 68:32. Based upon the poor diastereoselectivity observed, and presence of inseparable by-products, this method was abandoned.

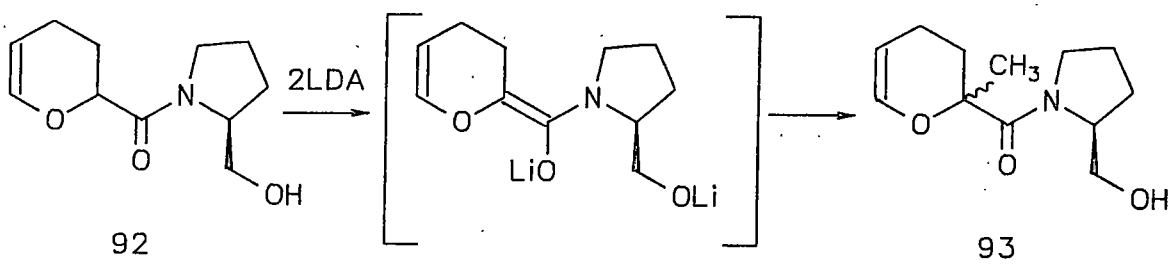


Figure 71. Alkylation of 92.

We then prepared the analog 94 (Figure 72) using a procedure similar to that for 92. Alkylation of 94 was smoothly effected using LDA and methyliodide, (Figure 73) affording 93 in quantitative yield.

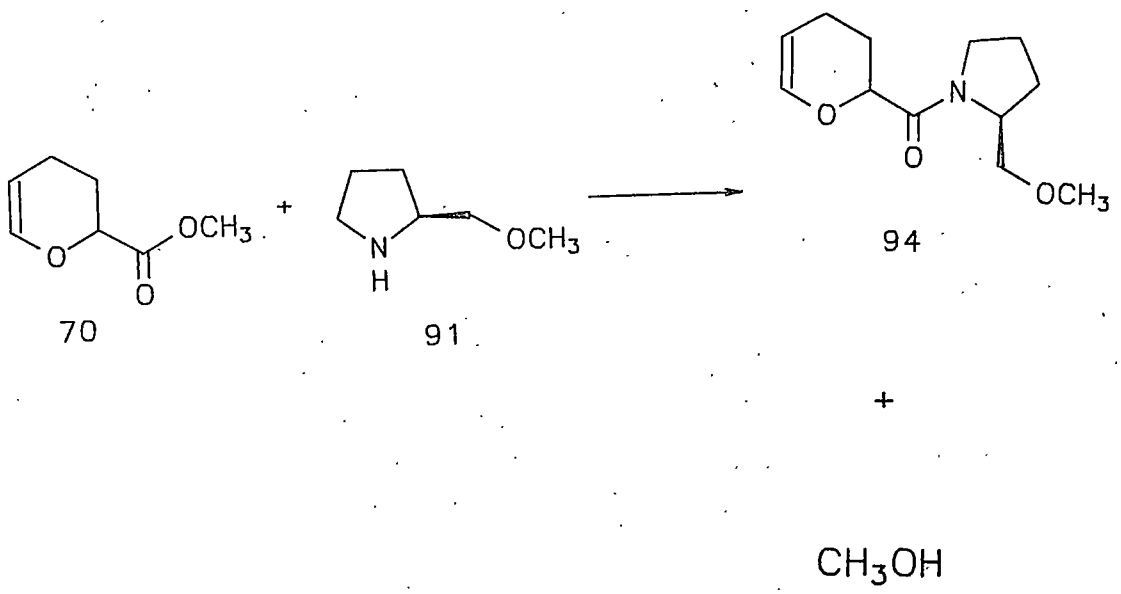
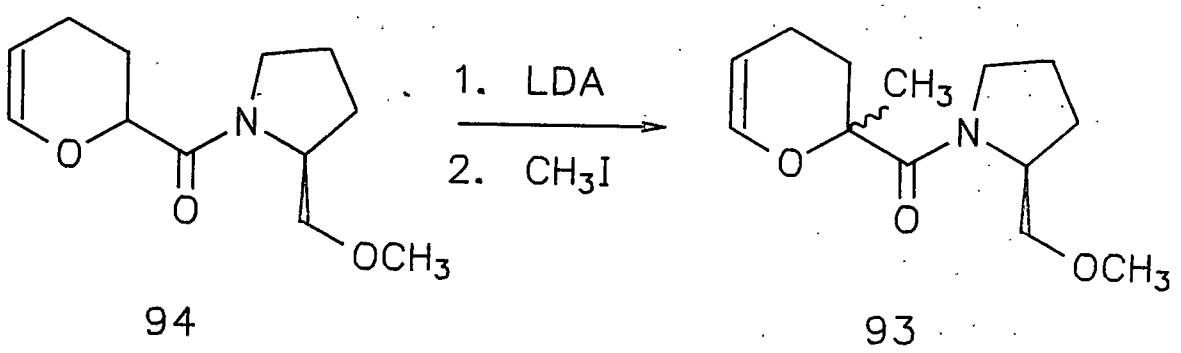


Figure 72. Preparation of 94.



94 93

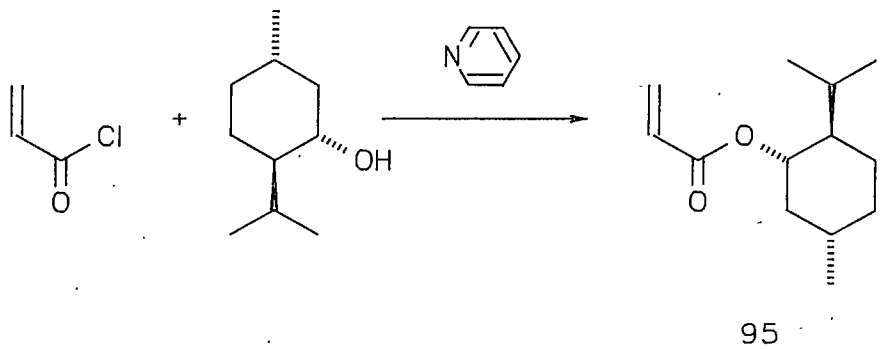
Figure 73. Alkylation of 94.

Once again, the resulting diastereomer ratio was approximately 55:45 (GC/MS and ^{13}C NMR). In view of the almost total lack of diastereoselectivity with [88] and [91] as the chiral auxiliaries, studies employing additional analogues of S-prolinol seemed unwarranted.

We concluded that enolate π-facial shielding offered by the chiral auxiliaries studied, is offset by unfavorable folding of the pyran ring toward the π-face opposite the chiral directing group.

We then turned our attention toward Diels-Alder heterocycloadditions as a method for preparing chiral dihydro-2H-pyrans. We began with the model chiral dienophile [96] in an attempt to effect a Diels-Alder reaction with a heteroatom-containing diene.

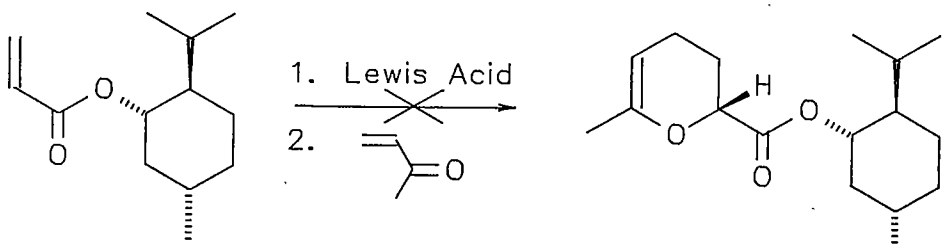
Acryloyl chloride was treated with excess pyridine and (-)-menthol affording [95] in 43% yield (Figure 74).



95

Figure 74. Preparation of Menthyl Acrylate.

Menthyl acrylate was then treated with a variety of Lewis acids ($AlCl_3$, $TiCl_4$, $SnCl_4$, $EtAlCl_2$) in dichloromethane, in the presence of methylvinyl ketone (Figure 75).



96

Figure 75. Attempted Preparation of 96 by Lewis Acid Catalysis.

Much to our disappointment, all attempts to prepare [96] by way of Lewis acid catalysis failed to provide any product. Various reaction conditions were studied, however, each attempt afforded only unreacted menthyl acrylate.

As a final effort, we attempted to effect a Diels-Alder reaction between methyl methacrylate and methylvinyl ketone via catalysis with $Eu(tfc)_3$, (Figure 76), a chiral Lewis acid previously employed by Danishefsky.[59] $Eu(tfc)_3$, however, failed to provide any product.

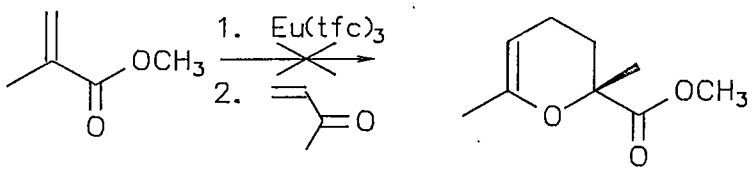
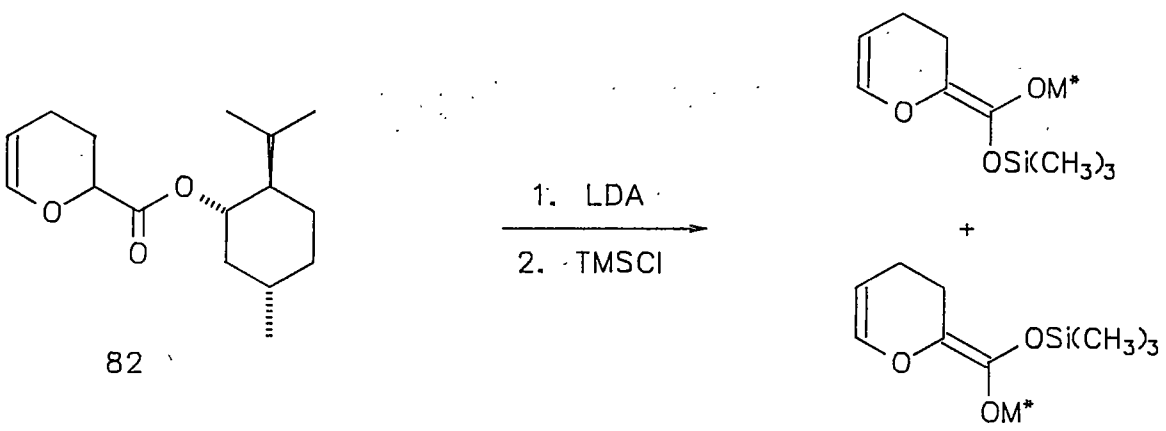


Figure 76. Attempted Cycloaddition Catalyzed by $Eu(tfc)_3$.

Disappointed with the outcome of this study we were strongly compelled to reevaluate the enolate alkylation work. Although both ester and amide-derived chiral enolates were investigated, we had no evidence in support of stereoselective enolate formation. To further probe (and perhaps settle) this matter we elected to repeat the enolization procedure which offered the highest degree of diastereoselection (albeit 63:37), and trap the enolate as a trimethylsilyl ether.

Thus [82] was deprotonated with LDA at -78°C and treated with chlorotrimethylsilane. Upon rotoryevaporation of the solvent, the crude product mixture was passed through a short column of silica gel with hexane-ethyl acetate (10:1).

The resulting product was quickly taken up in deuterochloroform and analyzed by ^{13}C NMR, revealing approximately 15% unreacted [82] and a complex set of signals in the olefinic region (145-100ppm). GC/MS analysis revealed three major products (4:1:1) consistent with [82] and two isomeric silyl ketene acetals derived from [82] (Figure 77).



82

Figure 77. Apparent Non-Stereoselective Enolization of 82.

The data strongly suggest that enolate formation is non-stereo selective which would account for the low diastereoselection observed in the alkylation procedures.

It should be noted that the apparent discrepancy (^{13}C vs. GC/MS) regarding the product ratios is attributed to partial hydrolysis of the sensitive silyl ethers in insufficiently dried solvent prior to mass spectral analysis.

We temporarily abandoned these efforts and turned our attention toward chelation-controlled nucleophilic addition to 2-acetyl pyrans.

CHAPTER 4

STEREOSELECTIVE NUCLEOPHILIC ADDITIONS

Recognizing the need for diastereofacial differentiation of the carbonyl of [28], we began our studies by analyzing previous work by Colonge et.al.[10] in which acrolein dimer, [58], was treated with a number of Grignard reagents, affording varying mixtures of erythro vs. threo alcohols (Figure 78). Subsequent treatment with acid afforded the bicyclic acetals [98a] and [98b] respectively.

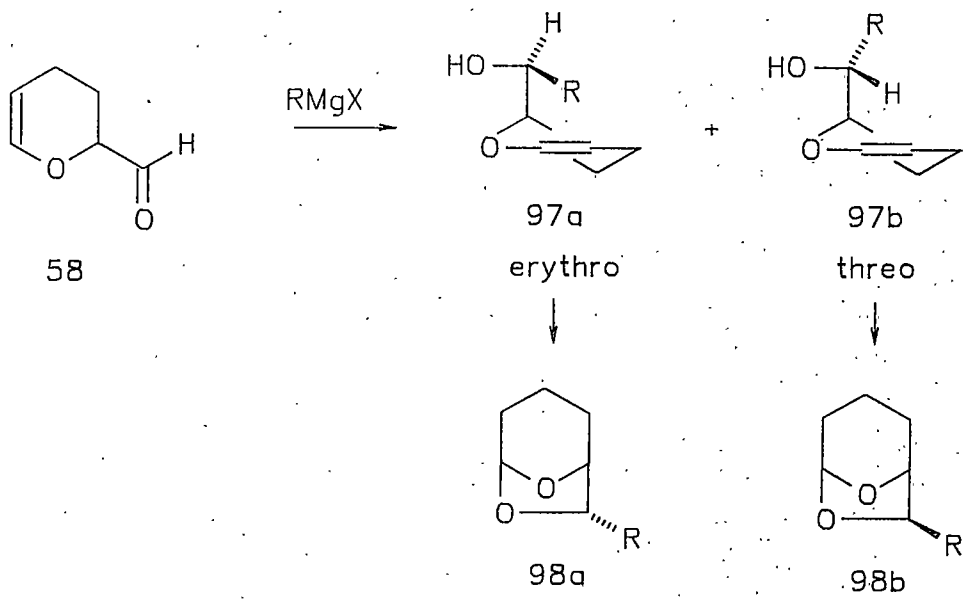


Figure 78. Reaction of Acrolein Dimer with Grignard Reagents

In an investigation exploring a potential stereoselective synthesis of brevicomin[14], Mundy observed a similar trend in the addition of Grignard reagents to [28] (Figure 79).

To rationalize the observed stereoselectivity, Colonge postulated a mechanism by which magnesium complexation with both oxygen atoms of [58] facilitates facial biasing of the carbonyl, resulting in the stereoselective delivery of the nucleophile. Figure 80 illustrates Colonge's proposed intermediate [100].

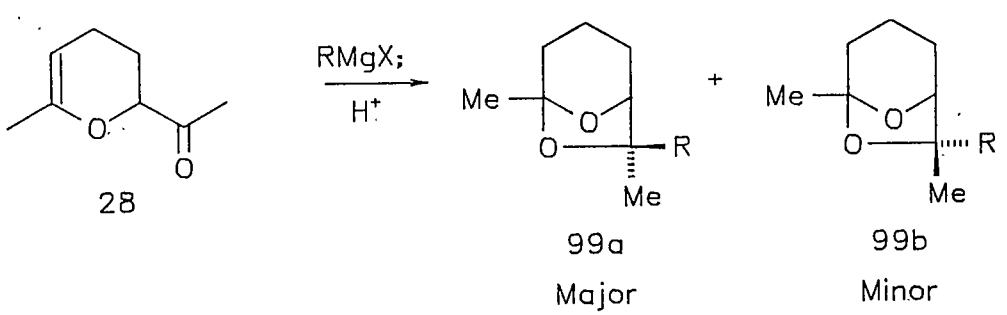


Figure 79. Reaction of Methylvinyl Ketone Dimer with Grignard Reagents.

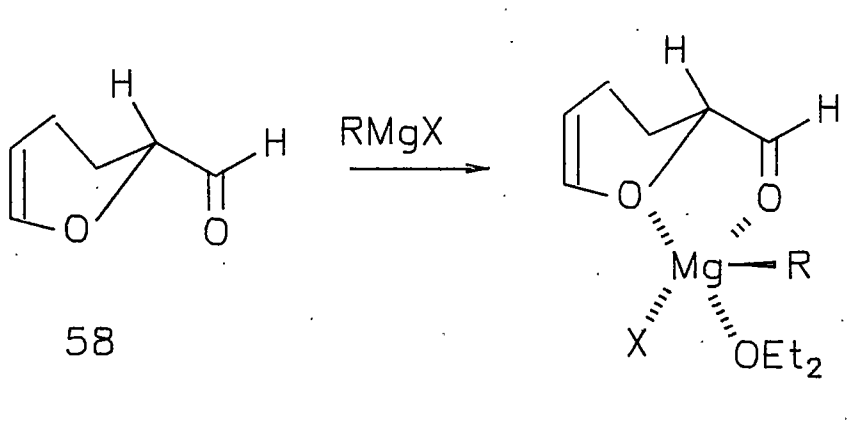
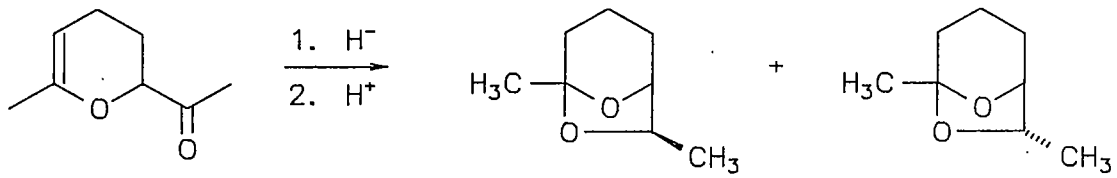


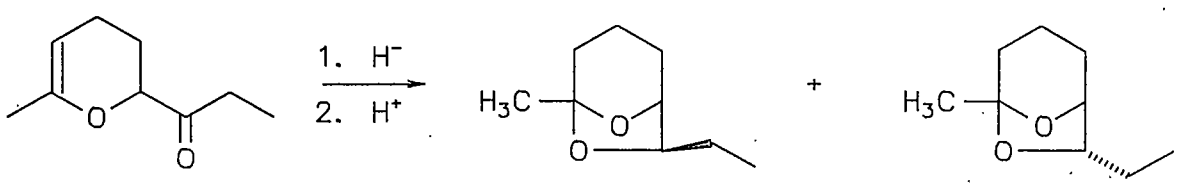
Figure 80. Magnesium Complexation with Acrolein Dimer.

In an attempt to apply the chelation theory to hydride reductions, Mundy treated the pyran intermediates [28] and [101] with a variety of metal hydride reducing agents. The degree of stereoselectivity varied greatly with reagent type (Figure 81).



28 62a 62b

Reagent	exo	endo
L-Selectride	80	20
$LiBH_4$	60	40
$NaBH_4$	57	43
KBH_4	49	51
$LiAlH_4$	51	49



101 102a 102b

$LiBH_4$	65	35
$NaBH_4$	55	45
KBH_4	65	35
$LiAlH_4$	51	49

Figure 81. Reduction of 2-Acetyl and 2-Propionyl-6-Methyl-Dihydro-2H-Pyran with Various Reducing Reagents.

In view of these results, we decided to reassess the origin of diastereoselectivity with respect to the various reagents capacities for chelation with substrate. A review of the literature revealed work by Katzenellenbogen and Bowlus[60] in which they studied the reductions of a number of α-ketols with various aluminum hydride reagents. They concluded that reagents monomeric in solution, namely triisobutyl-aluminum, [61] provided the greatest degree of selectivity, presumably via a cyclic transition state. Katzenellenbogen, as well as others,[62] ascribe variations in diastereoselectivity to reagent agglomeration; increased steric bulk associated with the aggregated metal hydride-carbonyl complex results in competition between cyclic and dipolar transition states (Figure 82).

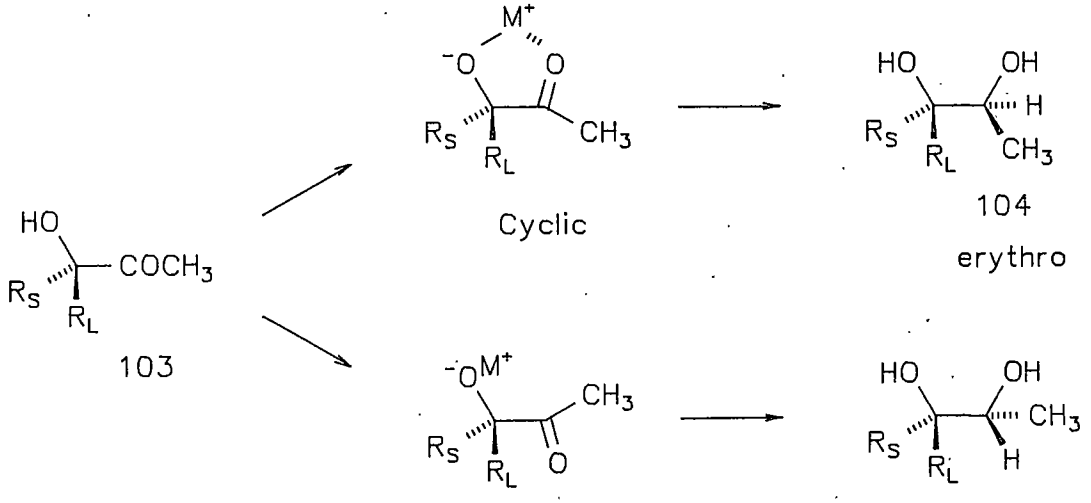


Figure 82. Cyclic and Dipolar Transition States in α-Ketol Reductions.

In light of these observations, we elected to employ triisobutyl aluminum (TIBA) and diisobutylaluminum hydride (DIBAH), a reportedly bulkier trimer.[63] Katzenellenbogen employed a three fold molar excess of TIBA and DIBAH in the α-ketol reductions, presumably due to the reactivity of the α-hydroxyl functionality. In the absence of hydroxyl interactions with aluminum, we treated methylvinyl ketone dimer, [28], with 1.1 equivalents of TIBA (in toluene) and 1.2 equivalents of DIBAH (in CH_2Cl_2) at -78°C respectively. The reaction temperature, in each case, was maintained at -78°C for 1.5 hours, after which time the solutions were allowed to slowly warm to 20°C overnight. Acid catalyzed cyclization afforded the desired ketals, in good yield, in exo:endo ratios consistently higher than those obtained by the agglomerating reagents Table 1. It should be noted that reduction with lithium tri-secbutylborohydride[64] (L-Selectride) also proceeded with significant stereoselectivity providing the desired ketals in an exo:endo ratio of 80:20. Considering facial biasing due to pyran ring puckering, these data appear consistent with a dipolar mechanism (Figure 83).

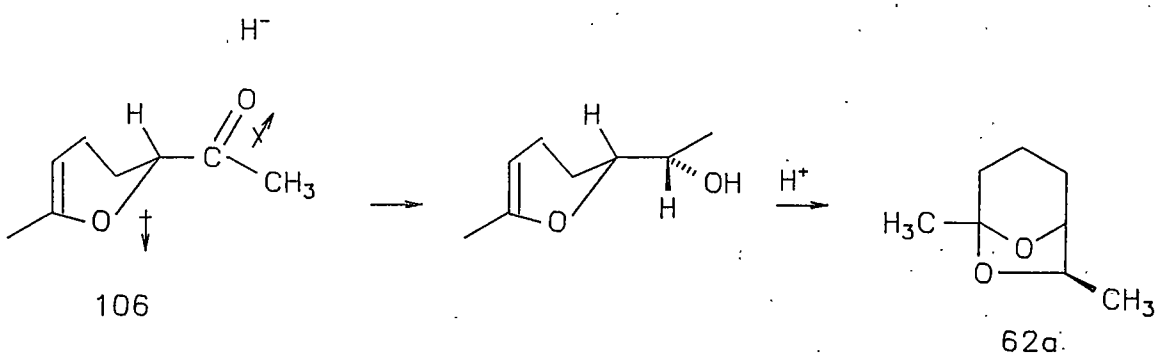
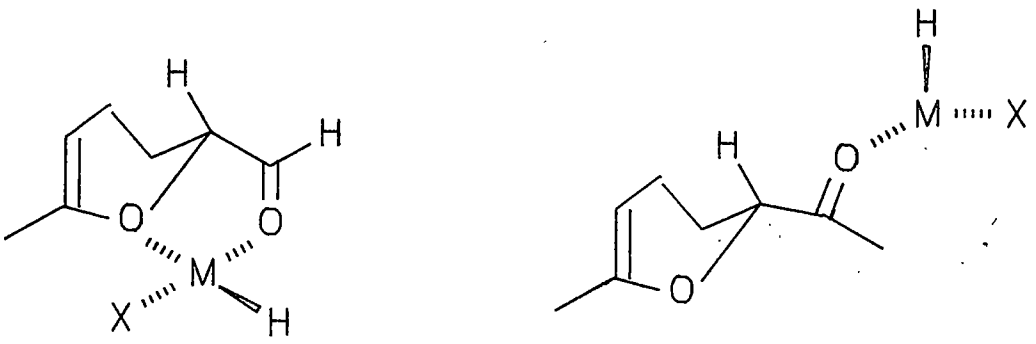


Figure 83. Hydride Reduction via Dipolar Mechanism.

Having obtained extensive insight into the nature of reagent agglomeration vs. diastereoselectivity with the 2-acyl-substituted dihydro-2H-pyran system, we felt that our data were in accord with the conclusions drawn by the Katzenellenbogen group. However, the absence of hydroxyl functionality in [28] precluded the intermediacy of alkoxide formation (Figure 82) prior to delivery of hydride.

We were then compelled to reevaluate the role of electronic inter actions in the reductions of [28]. Two models were developed, (Figure 84) focusing on the rotational preference of the acetyl moiety.



107
Cyclic

108
Dipolar

Figure 84. Plausible Models for the Reduction of 28.

The chelation model [107], analogous to Colonge's proposed intermediate, illustrates the preferential delivery of hydride to the less encumbered "top" face of the carbonyl. Subsequent acid catalyzed cyclization would result in the formation of the endo-substituted ketal 62b. On the other hand, reduction via the dipolar model [108], followed by cyclization would result in the formation of the exo-isomer, 62a. Analysis of Dreiding models of 2-acetyl-6-methyl-dihydro-2H-pyran, [28], revealed the "bottom" facial encumbrance of the carbonyl, in each model, due to puckering of the pyran ring.

To assist our evaluation of this matter we elected to obtain information regarding the rotational preference of the 2-acetyl group of 28. We rationalized that dipole-dipole interaction involving the carbonyl and the ring oxygen would be dependent upon the extent to which the lone pair electrons of the ring oxygen are delocalized.

We then employed the semiempirical molecular orbital program MNDO (Modified Neglect of Diatomic Overlap) developed by Dewar.[65] The data indicate that the preferred ground state rotational isomer is that which directs the carbonyl dipole farthest from the ring oxygen, (Figure 85). This suggested that the intermediacy of the cyclic transition state [107] is dependent upon the chelating ability of the reducing reagent.

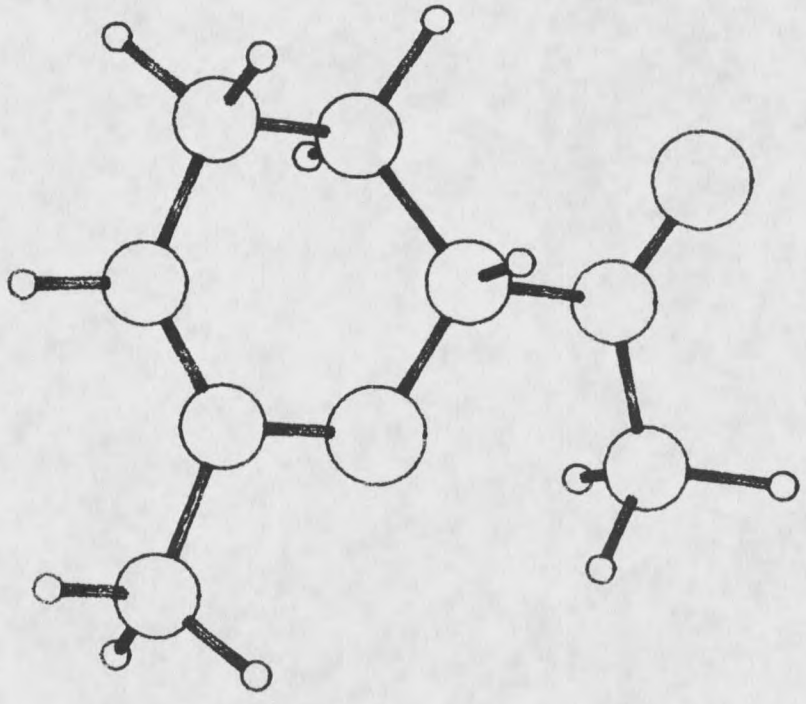


Figure 85. Computer-Drawing of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran.

Although experimental results (Figure 81) favor the dipolar Model, an absolute conclusion as such seemed greatly unwarranted. Chelation control, a well documented phenomenon, [66] has historically been purely speculative, owing to a paucity of direct spectroscopic evidence probing the structures of putative intermediates in solution. Of additional concern to our efforts was the realization that successful chelation-controlled processes traditionally have been confined to acyclic systems.

A recent report by Keck and Castellino[22] offered the first available spectroscopic evidence supporting the structural source of diastereoselection in nucleophilic addition to ß-alkoxy aldehydes. Although their study concerned acyclic stereochemical control (Figure 86) application of the technique to pyran [28] showed considerable promise.

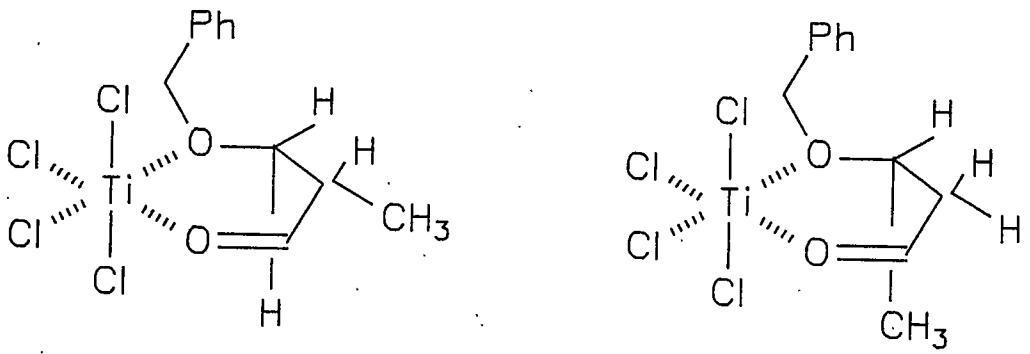


Figure 86. Titanium IV Chloride Complexes with ß-Alkoxy Aldehydes.

Reflecting on our results with Grignard additions to [28] and Colonge's postulated intermediate (Figure 80), we chose $MgBr_2$ as a relevant Lewis acid for complexation with [28]. Two plausible complexes were envisioned (Figure 85) in which the carbonyl of [28] might chelate with $MgBr_2$.

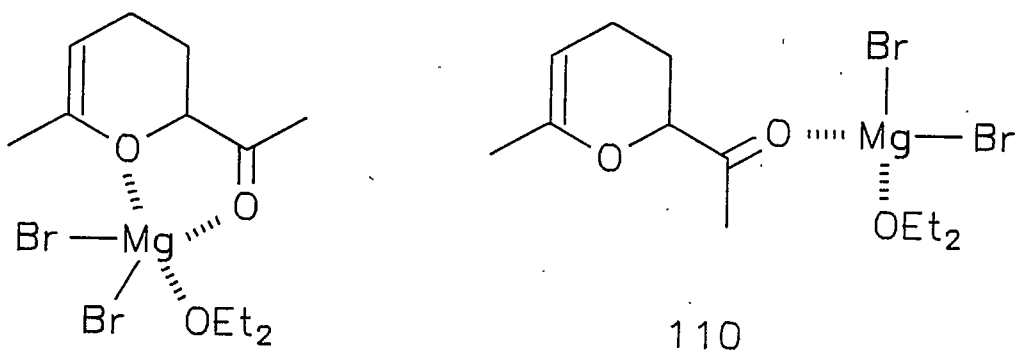


Figure 87. $MgBr_2$ Complexes with 28.

Methylvinyl Ketone dimer, [28], was treated with $MgBr_2 \cdot Et_2O$ at 0°C in $CDCl_3$ and a sample of the resulting solution was immediately introduced into the NMR spectrometer. Variable temperature ^1H NMR spectra were recorded at +10°, -10°, -30° and -50°C respectively (Figure 88).

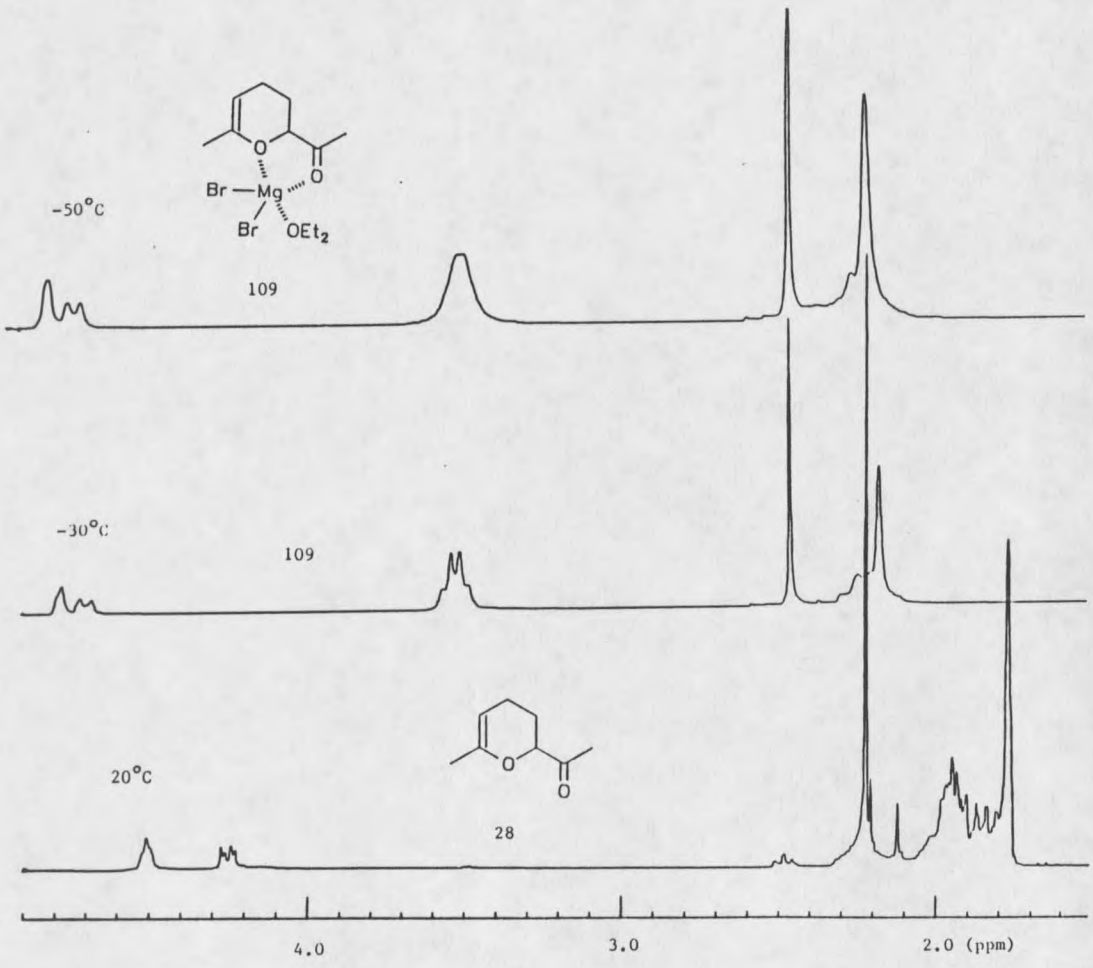
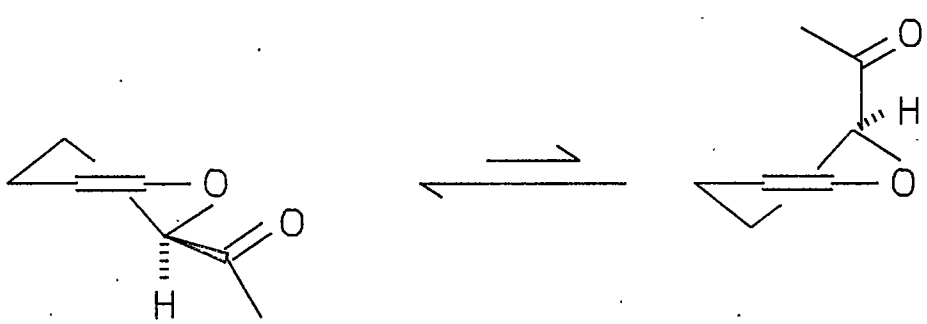


Figure 88. ^{1}H NMR Spectra for 28·$MgBr_2$

The data clearly indicate the formation of a complex as evidenced by the significant change in chemical shift of every signal representing substrate. Noteworthy are the signals at ca. 3.6 ppm and 0.8 ppm which are due to ether and may represent averaging between free and complexed species.[68]

The significant downfield shifting of the entire spectrum for the complex, with respect to uncomplexed 28, argues in favor the cyclic intermediate chelate, [109]. Of particular significance is the change in the coupling patterns of the ring protons (the broad multiplet between the two methyl signals) throughout the temperatures studied. It appears that with cooling, conformational flipping of the pyran ring (Figure 89) is inhibited. It should be noted that a control study with uncomplexed 28, conducted over the same temperature range, revealed essentially no changes in chemical shifts or coupling patterns.



111 112

Figure 89. Conformational Flipping of Pyran [28].

It seems reasonable to assume that analogous to uncomplexed 28, the formation of the dipolar complex, [110], would result in uninhibited conformational flipping and a temperature-independent ^1H NMR spectrum. A Dreiding model of 28 indicated a preference for pseudo-equatorial positioning of the 2-acetyl substituent. Arguing once again in favor of the cyclic complex, [108], a Lewis acid complexed or tethered between the two oxygens would inhibit the ring oxygen from passing through the plane of the ring via a conformational flop, resulting in a semi-rigid complex exhibiting a temperature-dependent ^1H spectrum.

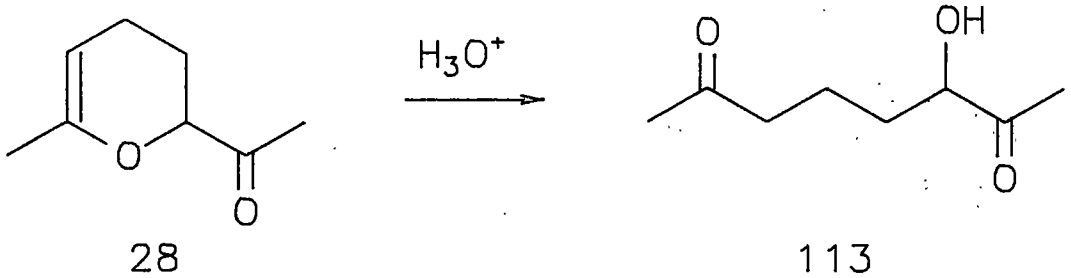
With spectral evidence strongly supporting a semi-rigid cyclic complex, we elected to treat the intermediate chelate with a variety of Grignard and metal hydride reducing reagents. Methylvinyl ketone dimer was exposed to $MgBr_2 \cdot Et_2O$ at -78°C for twenty to thirty minutes, in various solvent systems, prior to exposure to nucleophiles and subsequent acid catalyzed cyclization. The results of this study, comparing nucleophilic addition to 28 in the presence and absence of $MgBr_2$, are summarized in Table 1. One anomaly was observed in the reductions employing DIBAH. The nearly complete reversal in stereo-selectivity is an enigma for which we offer no rationale.

Table 1. Observed Stereoselectivities in Reductions of 28 and 28·$MgBr_2$.

		28 → (1. Reduction; 2, Cyclization)			28·$MgBr_2$ → (1. Reduction; 2. Cyclization)	
Reagent	Solvent	62a	62b	Solvent	62a	62b
KBH_4	THF	49	51	THF	61	39
$NaBH_4$	THF	57	43	---	--	--
$LiBH_4$	THF	60	40	Toluene/THF(3:1)	61	39
$LiAlH_4$	THF	51	49	---	--	--
DIBAH	CH_2Cl_2	68	32	CH_2Cl_2	37	63
TIBA	Toluene	83	17	Toluene	79.6	20.4
L-Selectride	Toluene	80	20	Toluene	79	21
LTBA	Toluene/THF(4:3)	57	43	THF	3	97
i-PrMgCl	Toluene	89	11	Toluene	94	6
PhMgBr	Toluene	75	25	Toluene	93	7

Diastereoselectivity enhancement, due to complexation with $MgBr_2$, was generally modest. Two notable exceptions were observed. With phenylmagnesium bromide the exo:endo ratio of 75:25 was improved to 93:7. Even more dramatic was the enhancement observed with lithium tri-tert-butoxyaluminohydride. In this case the exo:endo ratio of 57:43 was changed to 3:97. The extreme reversal in selectivity was indeed intriguing. Considering the trend toward exo-substitution with the various reducing reagents studied, we concluded that agglomeration of all the reducing reagents (other than LTBAH) results in competition between the cyclic and dipolar mechanisms.

Reflecting on Katzenellenbogen's α-ketol reductions we were compelled to make use of the ring-opening product, 113, which results from treatment of 28 with aqueous acid (Figure 90).



28 113

Figure 90. Acid Catalyzed Ring Opening of 28.

Successful application of 113 to the preparation of the bicyclic ketals [62a] and [62b] relied on the regioselective reduction of the 2-carbonyl carbon (Figure 91). In the event of preferential reduction of the 7-carbonyl, the resulting alkoxide, [114], would preclude bicyclic ketal formation.

The diketone [113] was treated with a number of reducing reagents, in the absence and presence of $MgBr_2$, followed by acid catalyzed cyclization (Figure 92). In each reduction, the fortuitous detection of ketals [62a] and [62b] was promising as no by-products resulting from reduction of the number 7 carbonyl were observed. The reductions were generally high in yield with unreacted starting dione [113] resulting in some cases.

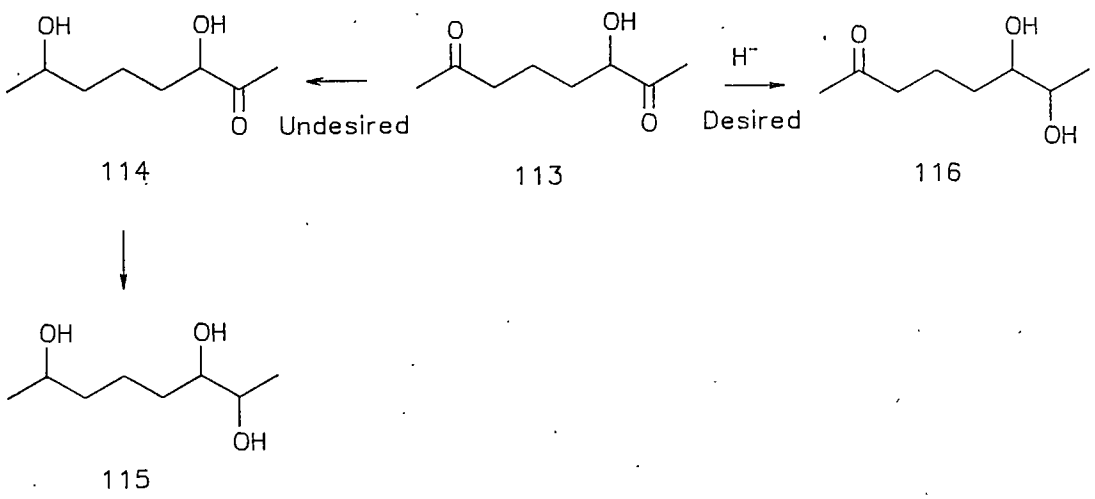


Figure 91. Required Regioselection in Hydride Reductions of 113.

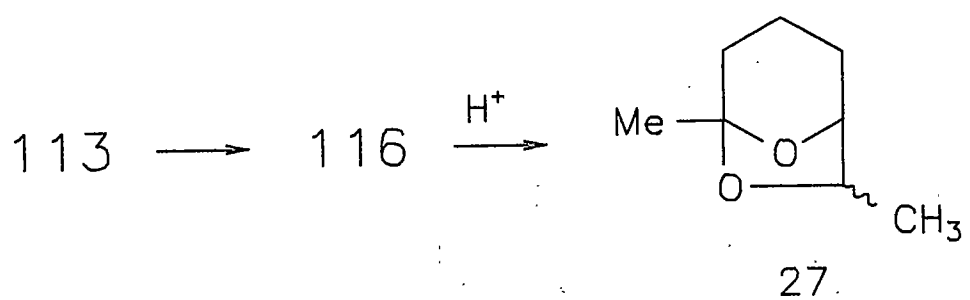
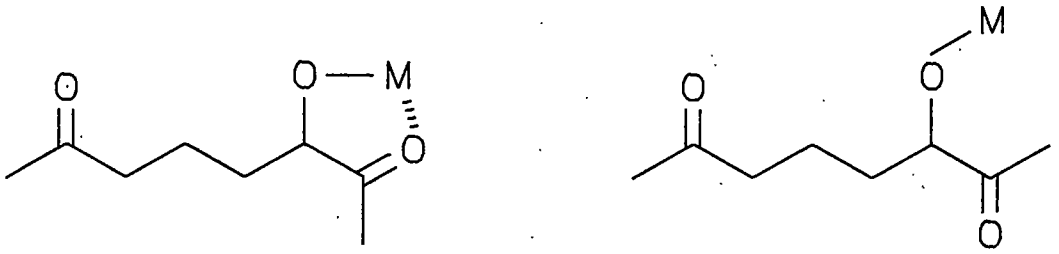


Figure 92. Ketal Preparation from Dione [113].

In the absence of by-products resulting from undesired regioselection, namely 2,7-diol or 2,3,7-triol, the reaction appears to proceed predominantly via the cyclic model originally proposed by Cram.[69]

Two significant factors supporting this mechanism (Figure 93) warrant discussion. If the initial step of the reaction involves alkoxide formation, it seems likely that the cyclic transition state would, through chelation, activate the carbonyl at the 2-position, rendering it more susceptible to hydride attack, with respect to the uncomplexed carbonyl at position-7. Conversely, intermediacy of the dipolar transition state would result in both carbonyls unactivated and equally susceptible to attack by hydride.



117 Cyclic

118 Dipolar

Figure 93. Cyclic and Dipolar Transition States for Hydride Reduction of Dione 113.

Although the reductions of dione [113] afforded the desired ketals [62a] and [62b], the degree of stereoselectivity was again moderate (Table 2).

Table 2. Observed Stereoselectivities in Hydride Reductions of 113.

113	Reagent	Solvent	Temperature(°C)	Time	62a : 62b		%Yield (Crude)
	TIBA	Toluene	-78°	1.5h	55	45	66
	DIBAH	Toluene	-78°	2h	54	46	42
	LTBA	THF	-78°	2h	17	83	41
	$NaBH(OAc)_3$	THF	20°	10h	40	60	51[a]
	$NaBH(OAc)_3$	THF/HOAc(5:1)	20°	10h	40	60	32[b]
	$NaBH(OAc)_3$	CH_3CN	-40°	1h	43	57	48
113 $MgBr_2$	TIBA	Toluene	-78°	1.5h	79	21	60
	TIBA	THF	-78°	2h	30	70	84[c]
	DIBAH	THF	-78°	2h	44	56	53
	TBA	THF	-78°	2h	33.5	66.5	60

a) Represents 75% of product mixture which contained 25% unreacted (113).
b) Represents isolated yield.
c) Solvent evaporation carried out at 0°C.

Turning once again to the literature, we found work by Evans and co-workers [70] in which they employed ammonium triacetoxy-borohydride in the reductions of ß-hydroxy ketones affording 1,3-diols in high diastereoselective yields. The authors suggest that the ß-hydroxyl function directs the reducing reagent to the syn-face of the carbonyl, resulting in the formation of a trans 1,3-diol.

In an effort to apply this technique to our α-hydroxyl system, dione [113] was treated with sodium triacetoxyborohydride in various molar ratios and solvent systems. Unfortunately, the reagent failed to provide significant stereoselectivity (Table 2).

Having explored the stereoselectivity of nucleophilic additions to the 2-acyl-dihydro-2H-pyrans and 3-hydroxy-2,6-octanedione, we elected to test one additional system. From a previous study involving the synthesis of 7,7-dimethyl-6,8-dioxobicyclo[3.2.1]octane, [6], we realized that the acetals [72a] and [72b] could be cleanly converted to product via the addition of methyllithium followed by subsequent acid catalyzed cyclization. Conversion of the acetals to the bicyclic system suggested that an analogous ketal system would work as well (Figure 94).

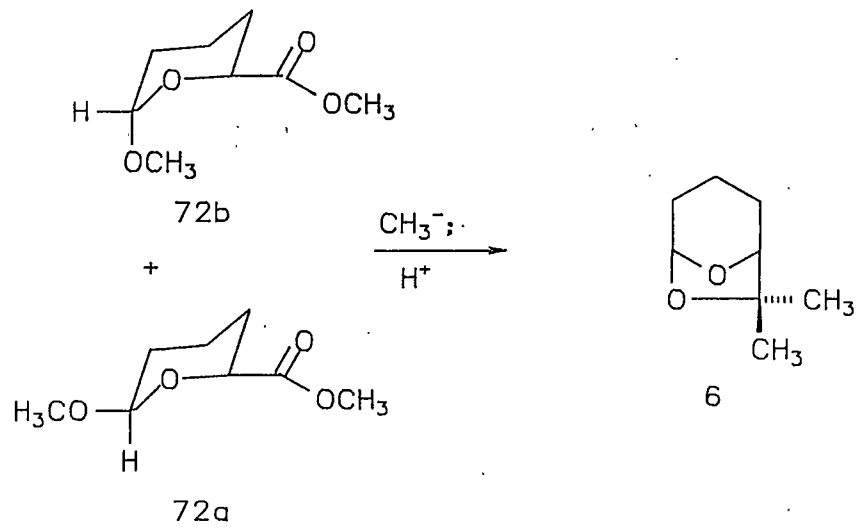


Figure 94. Conversion of Isomeric Ester Acetals to 7,7-Dimethyl-6,8-Dioxabicyclo [3.2.1] octane.

We then envisioned the preparation of ketals [119a] and [119b] by reacting methylvinyl ketone dimer with methanol (Figure 95) and testing their potential stereoselective conversion to bicyclic ketals.

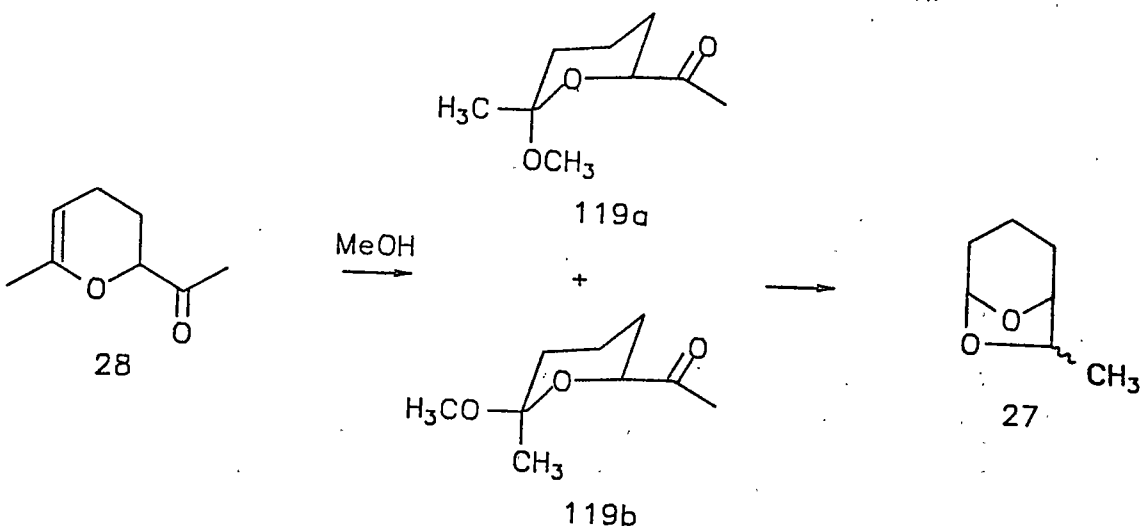


Figure 95. Preparation of Bicyclic Ketals from Monocyclic Ketals Derived from Methylvinyl Ketone Dimer.

Treatment of 28 with excess methanol in the presence of Dowex 50W-X8 cation exchange resin followed by distillation of the crude product, afforded only one isomer. This was presumed to be the anomeric product [119a].

Rationale for this structure was based on the reasonably-assumed equatorial positioning of the 2-acetyl and 6-methyl substituents, and, due to the anomeric effect, preferential axial positioning of the 6-alkoxyl substituent.

Spectroscopic evidence in support of the assigned structure for 119a was obtained via ^1H NMR analysis. NOE experiments (Table 3) revealed a significant enhancement in the signal for H_a (4.0ppm) upon irradiation of the methoxyl signal (3.20ppm), indicating a relatively close through-space relationship between the two groups (Figure 96). Irradiation of the ketal methyl signal had no apparent affect on the signal for H_a.

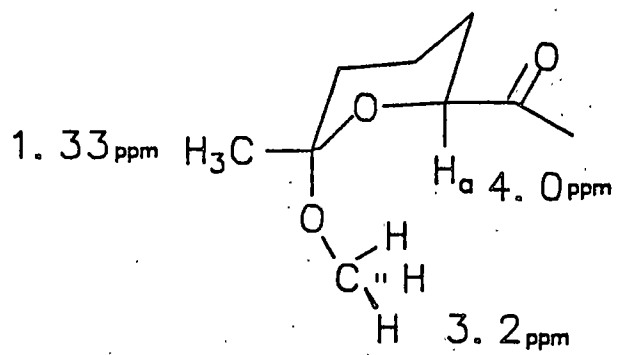
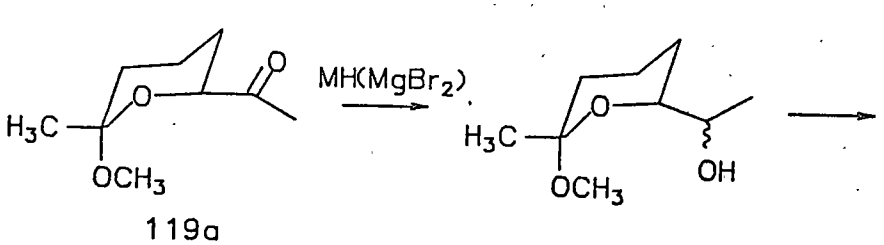


Figure 96. ^1H NMR Resonances for 119a.

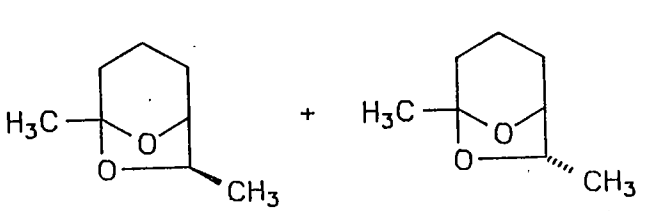
Table 3. Observed NOE Induced Enhancement of H_a Irradiated

Signal (ppm)	%Enhancement of H_a.
3.20	5.2
1.33	0

We then studied the stereoselectivity of hydride reduction of 119a with various metal hydride reagents. Ketal [119a] was subjected to the previous reaction conditions in the presence and absence of $MgBr_2$, followed by acid catalyzed cyclization to the corresponding bicyclic ketals (Figure 97). Table 4 shows the exo:endo ratios observed via GLC integration of peak areas.



119a



62a 62b

Figure 97. Bicyclic Ketal Preparation from 119a.

The data indicate a trend toward endo-methyl substitution in the product ketals [62a] and [62b]. One unexplained anomaly was observed with DIBAH. Of particular interest was the repeated "higher" selectivity with LTBA as was observed in the reductions of 28 and 113.

Table 4. Observed Stereoselectivities in Hydride Reductions of 28a.

28a	Reagent	Solvent	Temperature(°C)	Time	62a : 62b	%Yield (Crude)
	TIBA	Toluene	-78°	4h	34.7 65.3	26
	TIBA	CH_2Cl_2	-78°	2h	32.7 67.3	60
	DIBAH	Toluene	-78°	4h	61.4 38.6	80
	DIBAH	THF	-78°	2h	10 90	21
	LTBA	THF	-78°	2h	11.4 88.6	44
	$NaBH(OAc)_3$	CH_3N/HOAc(6:1)	0°	3h	No Rxn	
28a·$MgBr_2$	TIBA	THF	-78°	3h	28.3 71.7	66
	LTBA	THF	-78°	3h	50 50	42

To rationalize the observed stereoselection, we focused on two important factors; carbonyl facial biasing offered by the conformational features of the pyran ring, and the rotational preference of the 2-acetyl group.

Analysis of Dreiding models of 119a indicate significant steric hindrance of the carbonyl π-face opposite H_a in both cyclic [120] and dipolar [121] models (Figure 98).

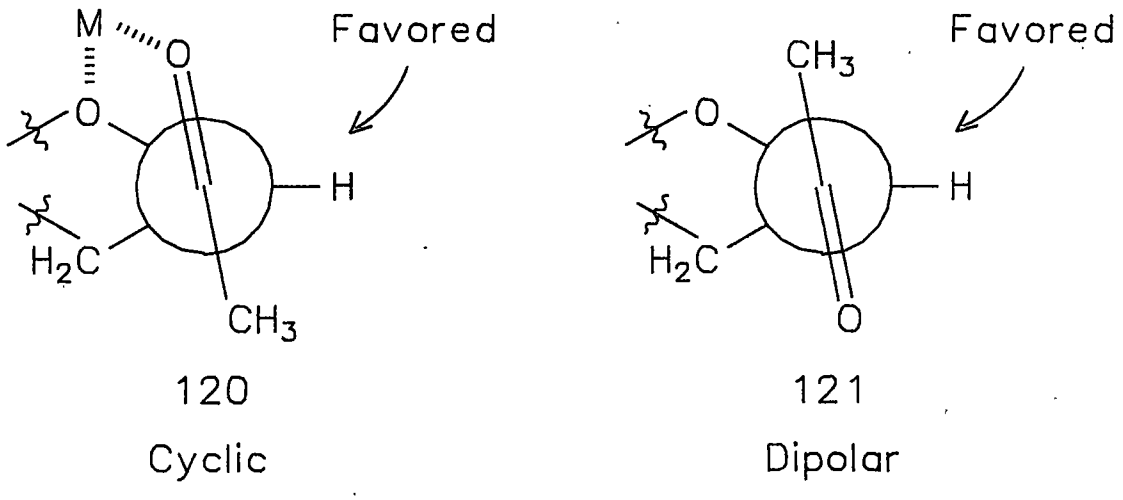


Figure 98. Steric Hindrance Offered by Pyran Ring.

Analogous to reductions of 28, carbonyl reductions of 119a appear to follow a related pattern of stereoselective bicyclic ketal formation. For each substrate, attack by hydride to the less encumbered π-face of the carbonyl via the cyclic transition state, [122] will result in cyclization to the endo-methyl isomer [62b]. Conversely, the intermediacy of the dipolar model [123] favors formation of the exo-methyl isomer [62a] (Figure 99).

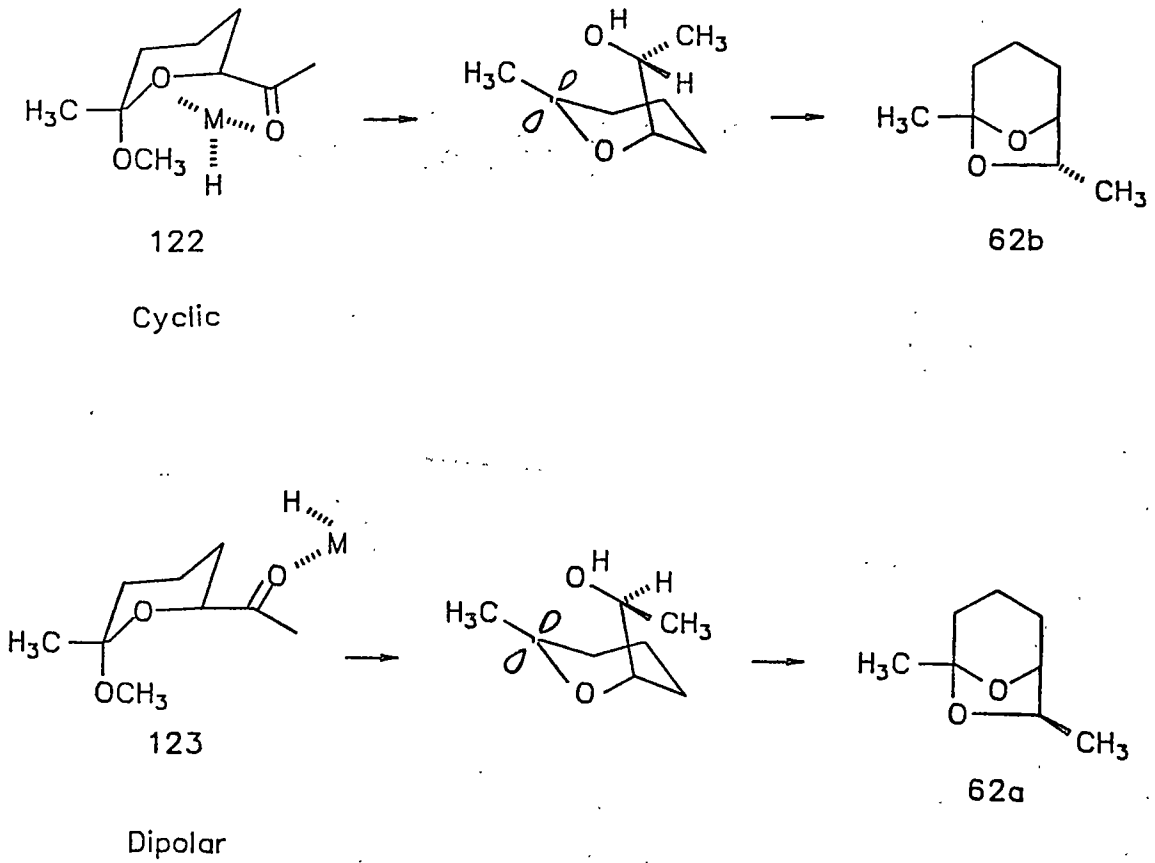


Figure 99. Cyclic and Dipolar Transition State Rationale for Stereoselective Bicyclic Ketal Formation.

On the basis of steric arguments, one would predict high stereoselectivity, should hydride reduction proceed solely by way of one of the two possible models (Figure 99). The observed variations might then be rationalized by competition between the cyclic and dipolar transition states.

To further probe this matter, we sought to quantitatively assess the rotational preference of the 2-acetyl group of 119a. We again employed the semiemperical molecular orbital program MNDO.

As we had anticipated, the preferred ground-state rotational isomer proved to be that which directs the carbonyl dipole farthest from the pyran oxygen atom (Figure 100).

In light of these studies it seems reasonable to assume that competition between cyclic and dipolar models exists and is quite dependent upon reaction conditions and reagent agglomeration.

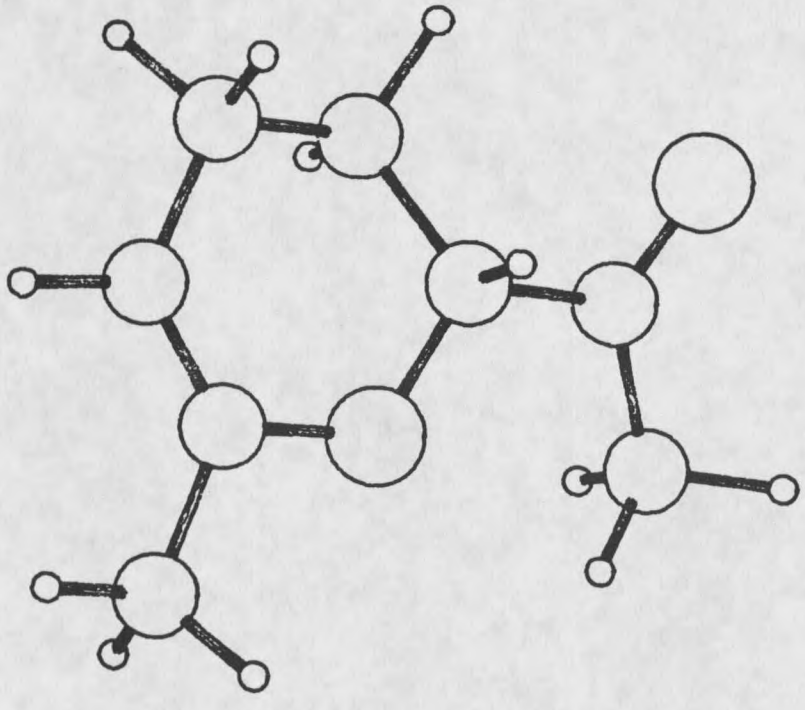


Figure 100. Computer Drawing of 5-Methyl-5-Methoxy-2-Acetyl-Tetrahydropyran.

CHAPTER 5

SUMMARY

This work has provided a wealth of information regarding the scope and limitations of stereoselectively modifying 2-carbonyl-substituted dihydro pyran derivatives. Through isotopic labeling studies, the tandem solvomercuration-demercuration protocol has been shown to be non-stereoselective with respect to C-7 substitution in the product bicyclic ketals.

Several previous difficulties with by-product contamination in the preparation of 2-acyl and 2-carboalkoxy pyrans have been circumvented. The successful synthesis of 3,4-dihydro-2H-pyran-2-carboxylic acid chloride provides a versatile intermediate suitable for a wide variety of chemical modifications.

The limitations of asymmetric alkylation of chiral lithium enolates derived from 2-carboxyl-3,4-dihydro-2H-pyrans has been established employing ester and amide functionalized chiral auxiliaries. Non-stereoselective enolization, studied by enolate trapping, was shown to be the major factor which defeats asymmetric induction.

Significant progress was made toward gaining a fundamental understanding of the mechanistic intricacies of chelation-controlled nucleophilic addition to 2-acyl-dihydro pyran derivatives. MNDO calculations were employed to show that in the absence of Lewis acids, 2-acetyl-substituted

pyrans strongly favor dipolar reduction mechanisms. A variable temperature ^{1}H NMR study was used to observe the formation of a 1:1 chelate between methylvinyl ketone dimer and magnesium bromide etherate.

This experiment offered valuable insight concerning the electron donating ability of the ring oxygen as well as the temperature dependent rigidity of the complex.

Magnesium bromide complexation was applied to Grignard and metal hydride reductions of methylvinyl ketone dimer, resulting, in some cases, in 80-94% diastereoselection.

The chelation theory was also applied to an unsymmetrical hydroxy-diketone, resulting in essentially 100% regioselection in hydride reductions.

CHAPTER SIX

EXPERIMENTAL

Carbon and variable-temperature proton NMR spectra were recorded on a Bruker 250 MHz spectrometer equipped with a liquid nitrogen VT unit and an Aspect 2000 data processing system. Spectra were obtained using deuterochloroform as solvent and chemical shifts are reported in ppm with reference to TMS. Mass spectral analyses were conducted on a VG MMI6 spectrometer interfaced with a Varian 3700 gas chromatograph equipped with a 30m DB-1 capillary column. Accurate mass measurements were made on a VG 7070 mass spectrometer. Anhydrous THF, benzene, toluene, diethyl ether and hexane were obtained by distillation from benzophenone ketyl. TMSCl, diisopropylamine, triethylamine, pyridine, and HMPA were distilled from calcium hydride. Dichloromethane was distilled from P_2O_5 and thionylchloride was distilled from triphenyl phosphine. Unless otherwise noted, all reactions were conducted in an atmosphere of argon.

Preparation of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran [28].

Methylvinyl ketone (105mL, 88.2g) was heated to 175°C in an autoclave, for two hours. Evaporation of unreacted starting material, followed by distillation of the crude product (65-70°C, asp) afforded 50.6g (57.4%) of pure product (GLC).

1H NMR:	4.53	t	1H
	4.27	dd	1H
	2.25	s	3H
	1.97	m	4H
	1.79	s	3H

^{13}C NMR: 209.6(ppm), 149.6, 92.6, 8001, 25.9, 23.3, 19.9, 18.9

IR: 3060(cm^{-1}), 2960, 1724, 1675, 1440, 1390, 1365, 1280, 1240, 1170, 1108, 1075, 920

MS: 140(M^+), 97, 69, 55, 43, 41

Preparation of 2-Isopropenyl-6-Methyl-3,4-Dihydro-2H-Pyran [21].

To 9.8g of methyltriphenylphosphonium bromide (27.4mmol) in 120mL of anhydrous THF at 0°C was added 11.0mL of a 2.5M solution (hexane) of n-butyllithium. After 30 minutes, methylvinyl ketone dimer (3.61g, 25.7mmol) was added at 20°C. The reaction was stirred for 12 hours, after which time the precipitate was filtered (suction) and washed with 50mL of Et_2O. The filtrate was concentrated under reduced pressure (asp) and the crude product distilled (35-45°C, 0.3torr) affording 1.66g (46.6%) of a colorless liquid. Analysis by GC/MS showed one product.

[21] (cont'd)

1H NMR:	4.83(ppm)	s	1H
	4.72	s	1H
	4.31	brS	1H
	4.06	dd	1H
	1.96	m	2H
	1.71	S	3H
	1.69	S	3H
	1.67	m	2H

^{13}C NMR: 150.6(ppm), 144.9, 11.3, 95.0, 78.4, 26.3, 20.4, 20.0, 18.6

IR: 3070(cm^{-1}), 2920, 1680, 1440, 1390, 1245, 1170, 1075, 1055, 900

MS: 138(M^+), 134, 119, 95, 91, 79, 77, 68, 67, 53, 43, 41

Solvomercuration/Demercuration of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran [28].

To 1.14g mercuric acetate (3.58mmol) in 20mL THF at 0°C was added 0.3mL methanol, followed by a solution of 0.50g dimer,[28], in 2.0mL THF. Stirring was continued for 30 minutes, after which time an additional 15mL of methanol was added to assist the dissolution of mercuric acetate. After 30 minutes the solvents were removed by rotoryevaporation affording a pale-yellow semisolid.

Analysis of the crude product by ^{13}C NMR indicated the presence of two isomeric ketones, (ca.1:1) along with approximately 10-15% starting material, [28].

The crude semisolid was washed with 1:1 Et_2O:Hexane, to remove unreacted methylvinyl ketone dimer, and the solvents decanted. Drying of the crude product by rotoryevaporation afforded approximately 615mg crude product which was taken directly to the next step.

Borohydride Reductions of 6-Methyl-6Methoxy-5-(Acetoxy-mercurial)-2-Acetyl-tetrahydropyran with $NaBH_4$ and $LiBH_4$.

To 307mg of the crude organomercurial in 10mL of THF/H_2O (9:1) was added 40.5mg $NaBH_4$ with stirring. The reaction mixture darkened immediately and was stirred an additional 30 minutes, followed by careful quenching with 5.0mL 15% HCl. Et_2O (15mL) was added and the mixture was allowed to stand overnight. The combined phases were passed through a pad of Hyflo Super Cel and separated. The aqueous layer was extracted with Et_2O and the combined organics were washed with bicarbonate, brine and dried over Na_2SO_4 . Analysis by GC/MS showed two products identified as 62a and 62b (60:40).

The reduction procedure was repeated with $LiBH_4$ affording identical results.

[62a] ^{1}H NMR:	4.16(ppm)	q	1H
	4.03	bs	1H
	1.96-1.43	m	6H
	1.42	S	3H
	1.1	d(J=6.15)	3H

MS: 142(M^+), 114, 100, 98, 72, 71, 67, 55, 43, 41

[62b]^{1}H NMR:	4.25-4.15	m	2H
	2.10-1.55	m	6H
	1.46	S	3H
	1.35	d(J=6.15)	3H

MS: 142(M^+), 114, 100, 98, 83, 72, 71, 55, 49, 43, 41

Preparation of 4-Deuterio-5-Deuterio-7-Methyl Dioxabicyclo[3.2.1]octane [68a and 68b].

Mercuric acetate (914mg, 2.87mmol) was stirred in 2.0mL water, followed by 4.0mL THF. To the resulting yellow solution was added diene [21] (180mg, 1.30mmol) in 1.0mL THF, at 23°C. The reaction was stirred at 23°C for 30 minutes, after which time a solution containing 55mg $NaBD_4$ in 1.0mL 5% NaOH was added. After 30 minutes, the usual workup was carried out (filtration/extraction) and crude product (123mg) was taken up in 5.0mL hexane and stirred overnight with 0.5g 4Å molecular sieves and 20mg p-toluenesulfonic acid. The mixture was then filtered, condensed and chromatographed over SiO_2 (10:1 hexane:CH_2Cl_2) affording 96.3 mg of a colorless liquid. Analysis by GC/MS showed one product.

^{1}H NMR:	3.85(ppm)	d(J=3.3Hz)	1H
	2.0-1.5	m	5H
	1.41	S	3H
	1.35	m	2.2H (endo-CDH_2)
	1.25	bs	2.8H (exo-CDH_2)

^{13}C NMR: 107.3(ppm), 81.1, 80.9, 34.2, 29.2, 25.9, 24.3,

^{13}C NMR: 107.3(ppm), 81.1, 80.9, 34.2, 29.2, 25.9, 24.3, 20.9, 17.2

MS: 158(M^+), 157, 142, 115, 98, 97, 87, 69, 58, 49, 43

Preparation of 2-Formyl-3,4-Dihydro-2H-Pyran [58].

Acrolein (110mL, 92.3g) was heated to 160°C in an autoclave for two hours. Distillation (50-55°C, asp) afforded 41g of a colorless liquid (44.4%). Spectral data for this compound proved identical with literature values.

Preparation of 2-(1-Hydroxyethyl)-3,4-Dihydro-2H-Pyran (26).

Acrolein dimer, [58], (3.44g, 30.7mmol) was stirred in 50mL of anhydrous THF at -50°C under a blanket of argon. Methylmagnesium bromide (15.4mL of 3.0M solution in THF, 1.5eq) was added over 10 minutes and the reaction allowed to slowly warm to 0°C over one hour. The reaction was carefully quenched with 10mL of 5% KOH and extracted with Et_2O (4 x 20mL). The combined organics were washed with brine, dried over K_2CO_3 and condensed, affording a colorless liquid (3.20g). Analysis by GC/MS showed only the isomeric alcohols, [26], in a threo:erythro ratio of 55:45. The product was quickly taken to the next step without purification.

Preparation of 2-Acetyl-3,4-Dihydro-2H-Pyran [24].

To 75mL of freshly distilled dichloromethane (P_2O_5) was added 4.05g (10.7mmol) of PDC, 4.0g NaOAC and 4.0g 4Å molecular sieves. The mixture was cooled to 0°C and treated with a solution of 1.81g

of crude alcohol, [26], in 5mL dichloromethane. After vigorous stirring for 5.5 hours (20°C) the thick suspension was gravity filtered, the solid washed with 30mL dichloromethane, and the filtrate condensed. The crude product was passed through a 5" x 1" pad of silica gel with hexane:ethyl acetate (7:3). Removal of solvent by rotaryevaporation (5°C bath) afforded 700mg of a colorless liquid. Analysis by GC/MS showed one product determined as ketone,[24].

It should be noted that this procedure was repeated several times affording 24 in an isolated yield of 40% from acrolein dimer.

1H NMR:	4.75(ppm)	bs	1H
	4.25	d	1H
	2.25	s	3H
	2.1-1.75	m	5H

1^3C NMR: 208.7(ppm), 142.5, 101.2, 79.5, 25.7, 23.7, 18.4

MS: 126(M^+), 98, 97, 83, 55, 43, 41

IR: 3050(cm^{-1}), 2950, 1720, 1650, 1425, 1360, 1235, 1072, 930, 905

HRMS: Calculated for $C_7H_{10}O_2$, 126.0681
Observed, 126.0681

Preparation of [6] from Ketone [24].

The ketone [24] (700mg, 5.56mmol), in 10mL dry THF at 0°C, was treated with methylmagnesium bromide (3.8mL of a 3.1M solution in THF) and allowed to stir overnight. The reaction was quenched with 0.5mL H_2O and 10mL 15% HCl and extracted with Et_2O (4x25mL). The organics were dried ($MgSO_4$), filtered, and treated for 6 hours with one drop of concentrated H_2SO_4. The solution was washed with bicarbonate, dried, condensed, and the crude product passed through a

pad of SiO_2 with Hexane-ethyl acetate (7:3) affording 330mg of a colorless liquid. GC/MS analysis revealed 6 contaminated with approximately 30% of three uncharacterized by-products.

1H NMR:	5.52(ppm)	bs	1H
	3.85	bs	1H
	2.1-1.5	m	6H
	1.45	s	3H
	1.28	s	3H

^{13}C NMR: 101.8(ppm)(d), 80.2(s), 79.3(d), 30.1(t), 28.9(q), 24.9(t), 20.5(q), 15.5(t)

MS: 142(M^+), 124, 109, 96, 84, 81, 71, 68, 57, 55, 53, 43, 41

HRMS: Calculated for $C_8H_{14}O_2$, 142.0993798
Observed, 142.0992279

Preparation of 2-(2-Isopropenyl)-3,4-Dihydro-2H-Pyran [25].

To a solution of methyltirphenylphosphonium bromide (15.1g, 1.3eq) in 125mL dry Et_2O and THF (4:1), was added 17.0mL of n-Butyllithium (2.5M solution in Et_2O). After 30 minutes the resulting red solution was treated for 1.5 hours with 4.1g (32.5mmol) of ketone [24] in 7.0mL THF, after which time an additional 10mL Et_2O was added. After 14 hours the mixture was treated with wet Et_2O and suction filtered. The solid was washed with 30mL Et_2O and combined filtrate condensed by rotoryevaporation. Distillation of the crude product (40-50°C, asp) afforded 1.09g of a colorless liquid.

GLC analysis indicated target [25] contaminated with approximately 7% of unreacted [24]. Chromatography over silica gel with pentane-ethyl acetate (9:1) afforded 850mg (21%) of pure [25] (GLC).

^{1}H NMR:	6.42(ppm)	d	1H
	5.01	s	1H
	4.90	s	1H
	4.70	bs	1H
	4.20	d	1H
	2.2-1.65	m	
	1.77	s	3H

^{13}C NMR: 144.7(ppm), 143.8, 111.4, 100.2, 78.2, 26.8, 19.9, 18.2

MS: 124(M^+), 109, 95, 93, 81, 68, 67, 55, 53, 41

IR: 3080(cm^{-1}), 2920, 1650, 1430, 1240, 1070, 1041, 902

HRMS: Calculated for $C_8H_{12}O$, 124.0888
Observed, 124.0891

Solvomercuration-Demercuration of [25].

To a solution of $Hg(OAc)_2$ (1.7g, 2.1eq) in 10mL THF and 3.0mL H_2O was added a solution of 314.5mg, [25] (2.54mmol) in 1.0mL THF. After 45 minutes, the reaction was treated, for 30 minutes, with a solution containing 105mg $NaBH_4$ (1.1eq) in 4.0mL of 5% NaOH. The mixture was passed through a pad of Hyflo Super Cell, extracted with Et_2O (4x15mL), the organics dried over Na_2SO_4 and condensed. The crude product was stirred for 12 hours in 15mL benzene containing 20mg tosic acid. Extraction with bicarbonate, followed by drying (Na_2SO_4) and rotoryevaporation afforded 95mg of a colorless liquid. GLC and ^{13}C NMR analysis indicated target [6] contaminated with approximately 10% of an uncharacterized by-product.

Synthesis of 2-(Carboxymethyl)-3,4-Dihydro-2H-Pyran [70].

The salt, [71] , (4.2 g, 27.9 mmol) was suspended in 20mL dry THF and 1.5 mL of freshly distilled HMPA (CaH_2) and an argon atmosphere was established. Iodomethane (2.6mL, 1.5eq) was injected and the reaction mixture refluxed for 14 hours. The mixture was cooled to 20° C and poured into a separatory funnel containing 50mL of hexane : Et_2O (1:1) and 5mL H_2O. Extraction with dilute acid (2 x 10mL 15%HCl), brine and bicarbonate, followed by drying of the organic phase (Na_2SO_4) and rotaryevaporation, afforded a pale-yellow liquid.

Distillation (55-61°C, asp.) of the crude product afforded 2.46g (62%) of a colorless liquid. Analylsis by GC/MS showed one product determined as target ester, [70].

^{1}H NMR:	6.42(ppm)	d	1H
	4.77	bS	1H
	4.50	dd	1H
	3.80	S	3H
	2.24-1.80	m	4H

^{13}C NMR: 171.3(ppm)(s), 142.6(d), 100.9(d), 73.0(d), 52.2(q), 24.7(t), 18.4(t)

MS: 142(M^+), 124, 114, 113, 110, 83, 82, 74, 68, 55, 53, 43, 41

Preparation of 7,7-Dimethyl-6,8-Dioxabicyclo[3.2.1]Octane [6] From [70].

To 1.07g (7.53mmol) of ester, [70], in 20mL dry THF at -78°C

under a blanket of argon, was added methyllithium (13.5mL of a 1.4M solution in Et_2O, 2.5eq) in one portion. The reaction was allowed to warm to 20°C over one hour and stirring continued for an additional 1.5 hours. The reaction was quenched with H_2O and extracted with Et_2O(3 x 20mL). The combined organics were treated with 3 drops H_2SO_4 for five hours and extracted with dilute bicarbonate, dried over Na_2SO_4 and condensed. The crude brown liquid (620mg) was distilled affording 170 mg of a colorless liquid (35-45°C, 0.3torr). Analysis by GC/MS showed target, [6], contaminated with approximately 3% of ketone, [24].

Esterification of 3,4-Dihydro-2H-Pyran-2-Carboxylic Acid, Sodium Salt [71] with Methanol.

To 6.28g (41.8mmol) of 71 was added 5 mL H_2O and 5mL of 15% HCl. Extraction with Et_2O (5 x 20mL) followed by evaporation of solvent afforded 5.25g of colorless liquid. Methanol (55mL) and one drop of H_2SO_4 were added and the reaction refluxed for 14 hours. Methanol was removed by rotary evaporation and the crude product distilled (55-70°C, 0.3torr) affording 3.32g of a mixture of 70, 72a and 72b in a ratio of 2.15:1:4.8 (GLC).

syn-2-(Carbomethoxy)-6-Methoxy-Tetrahydropyran [72a]

1H NMR:	4.39(ppm)	dd	1H
	4.10	dd	1H
	3.78	S	3H
	3.51	S	3H
	2.04-1.40	m	6H

^{13}C NMR: 170.8, 102.7, 73.9, 72.5, 55.8, 30.1, 27.5, 21.2

MS: 173(M^+), 153, 147, 142, 115, 114, 83, 82, 71, 58, 55, 53, 43, 41

anti-2-(Carbomethoxy)-6-Methoxy-Tetrahydorpyran [72b]

^{1}H NMR:	4.85(ppm)	bs	1H
	4.39	dd	1H
	3.76	S	3H
	3.40	S	3H
	2.01-1.50	m	6H

^{13}C NMR: 171.9(ppm), 98.3, 67.8, 54.6, 51.7, 28.7, 27.9, 17.3

MS: 174(M^+), 173, 159, 147, 142, 115, 114, 83, 82, 71, 58, 55, 53, 43, 41

The procedure was repeated using 5.0g of 71 and the esterificaiton step was carried out at 35°C. Distillation afforded 3.55g of ketals 72a and 72b (1:5) with no apparent detection of 70.

Alternative Preparation of 7,7-Dimethyl-6,8-Dioxabicyclo[3.2.1]Octane [6].

To a solution containing 2.15 g of a mixture of 72b, 72a and 70 (41:9:1) in 100mL THF at 0°C, was added 35mL of a 1.4M solution (Et_2O) of methyllithium (4eq). The reaction was allowed to slowly warm to 20°C over a period of 2.5 hours after which time 10mL of H_2O was added. The mixture was extracted with Et_2O (4 x 30 mL) and the combined organics dried over Na_2SO_4 and condensed. The crude product was refluxed 12 hours in 50mL benzene containing

50mg tosic acid. The product was again extracted (dichloromethane/dilute bicarbonate) affording 960mg of a pale brown liquid. Purification over silica gel with pentane : ethylacetate (7:3) afforded 600 mg of a colorless liquid. Analysis by GC/MS revealed approximately 90% target [6] and approximately 10% of uncharacterized by-products.

Preparation of 3,4-Dihydro-2H-Pyran Carboxylic Acid Chloride [74].

To 1.52 g of salt [71] in 3.0mL dry dichloromethane at 0°C under a blanket of argon, was added 2.6mL of freshly distilled thionyl chloride, ($P(OPh)_3$). The reaction was warmed to 50°C for 15 hours and distilled (70-90°C,asp) providing 350mg of a colorless liquid. Analysis by ^{13}C NMR revealed two products (1:1) presumed to be target [74] and HCl adduct [80].

Upon scale-up of the reaction, it was found that redistillation of the product mixture through a 13cm vigreaux column (50-55°C, 0.3torr) afforded pure 74.

The identity of the HCl adduct is speculative and based upon ^{13}C NMR comparison to pure 74 and the presence of three upfield triplet resonances ($-CH_2-$).

Attempts to dry the sodium salt, [71], by warming under vacuum, prior to treatment with thionyl chloride, failed to alter the reaction outcome.

3,4-Dihydro-2H-Pyran-2-Carboxylic acid chloride [74]

^{13}C NMR: 172.6(s), 141.8(d), 101.3(d), 79.3(d), 23.7(t), 17.1(t)

6-Chloro-Tetrahydropyran-2-Carboxylic Acid Chloride [80].

^{13}C NMR: 171.9(S), 92.7(d), 76.6(d), 32.7(t), 27.2(t), 16.8(t)

Improved Synthesis of 3,4-Dihydro-2H-Pyran-Carboxylic Acid Chloride [74].

To the sodium salt, [71], was added 1.0mL of freshly distilled oxalyl chloride at 0°C (exothermic!). Upon complete addition, exothermicity subsided and the reaction was refluxed 1.5 hours. Evaporation of unreacted oxalyl chloride, followed by the addition of 1.0mL dry toluene (benzophenone + sodium) and repeated evaporation, afforded a pale-brown thick suspension. Distillation (52-60°C, asp) provided 840mg (53.6%) of pure acid chloride, [74] (^{13}C NMR).

Synthesis of 3,4-Dihydro-2H-Pyran-2-Carboxylic Menthol Ester [82].

To 371mg (2.53mmol) of acid chloride, [74], in 15mL anhydrous toluene at 0°C was added 396mg (1eq) (-)-menthol followed by 1.5mL dry pyridine. The reaction was stirred overnight at 20°C under a blanket of argon.

Extraction with H_2O/Et_2O, followed by chromatography over silica gel with hexane-ethyl acetate (9:1) afforded 317mg (47%) of pure (GLC) diastereomeric menthol ester, [82].
The procedure was repeated many times, affording [82] in yields as high as 70%.

Diastereomeric [82]:

^{1}H NMR:	6.42(ppm)	d	1H
	4.75	m	2H
	4.45	m	1H
	2.20-1.35	m	11H
	1.26-0.70	m	11H

^{13}C NMR: 170.6(ppm), 170.5, 142.86, 142.83, 100.8, 100.7, 75.1, 75.0, 73.2, 73.1, 46.9, 34.1, 31.3, 26.1, 24.9, 24.8, 23.2, 23.1, 22.0, 20.8, 20.7, 18.5, 18.3, 16.1

HRMS: Calculated for $C_{16}H_{26}O_3$, 266.1882
Observed 266.1848

Alternative Preparation of 3,4-Dihydro-2H-Pyran-2-Carboxylic-(-)-Menthol Ester [82].

n-Butyllithium (1.7mL of a 2.5M solution in hexanes) was added dropwise to a 0°C solution of (-)-menthol (670mg) in 8mL of an anhydrous mixture Toluene:Hexane. After 30 minutes, the acid chloride (in 0.5 ml Toluene) was added and the reaction stirred overnight (0-20°C). The reaction was quenched with 4 mL H_2O followed by 5 mL Et_2O. The layers were separated, the organic phase dried over Na_2SO_4 and condensed under reduced pressure.

The crude product was purified over SiO_2 with Pentane to yield 840 mg (79%) of a pale yellow oil. GC/MS and ^{13}C NMR indicated an approximately 99% pure mixture of diastereomeric esters.

Preparation of 2-Methyl-3,4-Dihydro-2H-Pyran-2-Carboxylic (-)-Menthol Ester [83].

LDA was generated by adding 1.4mL of a 2.5M solution of n-Buli (1.1eq) to 20mL of anhydrous THF containing 0.48mL diisopropyl amine at 70°C under argon. After 20 minutes, ester, [82], (830 mg, 3.12 mmol), in 2.0 mL THF, was added dropwise at -78°C. The reaction was stirred one hour from -78 to -10°C then cooled to -60°C and treated with CH_3I (0.25 mL, 1.3 eq) in one portion. After one hour the ice bath was removed and stirring continued for 2.5 hours. The usual workup (extraction) followed by drying over Na_2SO_4 and evaporation afforded 760 mg (87%) of crude yellow oil. Integration of the diastereomeric carbonyls by ^{13}C NMR indicated a 55:45 mixture. Identical results were obtained when the reaction was repeated maintaining the alkylation temperature at -78°C for 3 hrs.

^{13}C NMR: 172.8(ppm), 172.7, 142.6, 142.5, 99.8, 99.7, 76.9, 74.7, 46.6, 40.2, 34.0, 31.1, 30.1, 25.8, 25.6, 24.8, 24.6, 22.9, 22.8, 21.8, 20.5, 17.5, 15.7, 15.5

MS: 280(M^+), 218, 180, 141, 139, 123, 97, 95, 83, 81, 69, 57, 55, 43, 41

HRMS: Calculated for $C_{17}H_{28}O_3$, 280.2039
Observed 280.2042

Alternative Methylation of [82] with Methyl-p-Toluenesulfinate.

LDA was generated by combining 0.25mL diisopropylamine (1.78mmol) with 0.75mL of a 2.5M solution (Et_2O) of n-butyllithium in 20mL of anhydrous THF at 0°C for 20 minutes.

Ester, [82], (390mg, 1.47mmol) in 2mL THF, was added dropwise at 0°C. After 1.75 hours the solution was cooled to -70°C, followed

by treatment with 330mg (1.77mmol) of methyl-p-toluenesulfinate. The reaction temperature was maintained at -70°C for 1.5 hours, followed by slow warming to 20°C. After 12 hours, the usual extraction procedure (Et_2O) was carried out, affording 360mg (87.5%) of crude product. Analysis by ^{13}C NMR indicated quantitative conversion to a 61:39 mixture of diastereomeric, [83].

Alternative Methylation of [82] Employing HMPA Co-Solvent.

n-Butyllithium (1.05 ml, 1.2 eq) was added to diisopropylamine (0.37 ml, 1.2 eq) in 25 ml anhydrous THF at -70°C under an atmosphere of Argon. After 20 minutes, HMPA (0.5mL) and ester, [82], in 5 ml THF, was added and stirring continued from -70 to -40°C over 1 hr. The reaction was cooled to -78°C and CH_3I (0.2 ml, 1.5 eq) was added. Stirring was continued from -70 to 20°C over 3 hrs. Et_2O and dilute HCl were added and the phases transfered to a separatory funnel. The layers were separated and the aqueous phase extracted 4 X 25 ml Et_2O. The combined organic layers were washed with dilute bicarbonate followed by brine, dried over Na_2SO_4 and concentrated. Purification over Si_2 with 1:1 Hexane:ethylacetate afforded 440 mg of 83 as a pale yellow oil. Integration by ^{13}C NMR indicated a 56:44 mixture of diastereomers.

Attempted Esterifications of [74] with (1R, 2R, 3S)-(-)-[N-Benzenesulphonyl-N-(3,5-Dimethylphenyl)Amino]-2-Bornanol [84].

To 400mg (0.97mmol) of chiral auxiliary, [84], in 10mL dry chloroform under a blanket of argon was added 190mg (1.3mmol) of acid chloride, [74] followed by 0.1mL of freshly distilled

triethylamine.

The reaction was stirred for 12 hours at 20°C at which time analysis by TLC showed only starting material. The reaction was then brought to reflux for an additional 12 hours. The solvent was removed by rotoryevaporation and the crude product analyzed by TLC with pentaneethylacetate (20:1). Two very faint spots (R_f=0.45 and 0.29) appeared, upon development with acid (CrO_3/H_2SO_4) spraying, along with one very dark spot (R_f=0.16) representing unreacted [84].

The crude product was taken up in $CDCl_3$ and analyzed by ^{13}C NMR and DIP-GC/MS, revealing unreacted [84] and uncharacterized decomposition products polymeric in nature. No evidence for a newly-formed ester was detected in the ^{13}C NMR spectrum.

Several alternative procedures for the preparation of ester, [86], were examined, with minimal success, and are presented as follows:

To 509mg (1.23mmol) of chiral auxiliary, [86], in 15mL dry THF at 0°C under an atmosphere of argon, was added 0.5mL of a 2.5M solution (Et_2O) of n-butyllithium. After one hour, the resulting alkoxide was treated with a solution of 190mg (1.30mmol) of [74] in 8.0mL of freshly distilled hexane and 5.0mL dry THF. The reaction was refluxed for one hour and forty minutes and the solvents removed by rotaryevaporation, providing a brown oil. The crude product was extracted with dichloromethane and dilute bicarbonate followed by drying over Na_2SO_4 and rotaryevaporation of solvent, affording 780mg of a pale-brown oil. Analysis by ^{13}C NMR failed to show any evidence for a newly formed ester.

The original procedure, employing triethylamine, was repeated as

were two similar procedures employing pyridine and calcium hydride respectively as HCl scavengers. None of these methods proved useful as evidence for target ester [86] was not detected (^{13}C NMR and GC/MS).

It should be noted that unreacted chiral auxilary, in each procedure, could be recovered by chromatography over silica gel with hexane-ethyl acetate (10 to 15:1). Recrystallization from ethanol-water (95-5) generally afforded 70-80% recovery of pure [84] which could be reused in following reactions.

Preparation of (S)-(+)-2-Pyrrolidinemethanol(S-Prolinol)[88].

Following the procedure of Enders [62], s-proline (12.0g, 0.10 4 mole) was slowly added (in 15 parts!) to a suspension of 6.1g LAH in 250mL dry THF. The flask was chilled with an ice bath to prevent excessive reflux. The addition of s-proline (exothermic) required 30 minutes and was followed by refluxing for 1.5 hours. The reaction was quenched by slow addition of 30 mL of 15% NaOH. The liquid was decanted and salts washed with Et_2O (2 x 80mL). Rotoryevaporation followed by distillation of the crude product (71-75°C , 0.5torr) afforded 7.9g (75%) of a colorless liquid. Analysis by GC/MS and ^{13}C NMR revealed one product.

^{13}C NMR: 64.2(ppm), 59.6, 45.8, 27.1, 25.2

MS: 101(M^+), 100, 70, 68, 55, 54, 43, 41

Preparation of (S)-(+)-2-Methoxymethylpyrrolidine [91].

Continuing with the procedure of Enders[62], freshly distilled s-prolinol (4.0g, 39.5mmol) was treated with 2.9mL (1.2eq) of methyl formate at 0°C under a blanket of argon. The reaction was stirred for one hour and condensed by rotaryevaporation. The crude product was taken up in 4.0mL dry THF and added to a -50°C suspension of 1.14g (47.5mmol) NaH, 3.2mL iodomethane (1.3eq) and 25mL dry THF.

The reaction was warmed to 20°C over 40 minutes then refluxed for 20 minutes and cooled to 20°C. Dilute HCl (0.5mL of 15% aqueous solution) was added, followed by 35mL of 17% KOH. After 12 hours the solution was extracted with Et_2O (5 x 25mL) and the product distilled affording 2.1 g of a colorless liquid. Analysis by GC/MS indicated 90% target [91] contaminated with 10% of an by-product presumed on the basis of mass spectral data (M^+=129) to be (S)-(+)-N-methyl-2-methoxymethyl-pyrrolidine.

MS: 115(M^+), 84, 82, 71, 70, 68, 56, 55, 45, 43, 41

Preparation of 3,4-Dihydro-2H-Pyran-2-Carboxylic-(S)-(+)-2-Hydroxymethyl-Pyrrolidine Amide [92].

A -78°C solution containing s-prolinol (540mg, 5.0 mmol) and pyridine (1.2 g) in 25mL of dry THF, was treated with 730 mg of acid chloride, [74], in 4.0mL THF. The mixture was warmed to 30°C to dissolve the salts. After 30 minutes, hexane (15mL) was added and the reaction stirred for 14 hours. The mixture was extracted with Et_2O and 10% HCl, dried ($NaSO_4$) and condensed affording 590 mg of a colorless oil which exhibited the odor of pyridine. Chromatography

over SiO_2 with CH_2Cl_2 Et_2O (1:1) provided 210 mg (ca.20%) of a colorless oil. Analysis by GC/MS showed only the diastereomeric amides, [92].

HRMS: Calculated for $C_{11}H_{17}NO_3$, 211.1202850 (Scan 617)
Observed, 211.1210937 (Scan 649)

Alternative Preparation of [92] .

s-prolinol (264mg, 2.61mmol) and ester [70] (370mg, leq.) were combined and warmed to 50°C for 3 hours under an atmosphere of argon. Removal of methanol by rotoryevaporation afforded 545 mg (99%) of a pale-orange oil. Analysis by GC/MS and ^{13}C NMR revealed only the diastereomeric amides, [92].

It should be noted that attempts to purify crude [92] by Kugelrhor distillation affords product as a pale-yellow oil in approximately 50% yield. Crude product was found to be suitable for alkylation steps.

Methylation of Amide [92].

LDA (2.9mmol) was prepared from 0.41 mL diisopropylamine and 1.2mL of 2.5M n-butyllithium (in Et_2O) in 20mL dry THF. The solution was cooled to -78°C and treated with amide [92] (250mg, 1.18mmol) in 1.0mL THF. After one hour, iodomethane (0.1mL, 1.3eq) was added and the temperature maintained at -78°C for 1.5 hours. The reaction was extracted (Et_2O/H_2O) affording 180mg of a pale-yellow oil. Analysis by GC/MS and ^{13}C NMR revealed much polymer formation as well as several minor uncharacterized

by-products. The reaction mixture proved inseparable by preparative GLC and silica gel chromatography thus precluding accurate ^{1}H and ^{13}C NMR analysis. Although a complete structure elucidation was not possible, we do offer the mass spectral data for the two compounds eluting the capillary GC at 17.28 and 17.68 minutes respectively (peak ratios approximately 68:32).

Peak 1037 (Area 559359): 225($^{+}$), 223, 197, 194, 157, 140, 128, 126, 97, 70, 57, 43, 42

Peak 1061 (Area 261796): 225($^{+}$), 197, 194, 157, 154, 141, 112, 97, 84, 70, 69, 57, 55, 43, 42

HRMS: Calculated for $C_{12}H_{19}NO_3$, 225.136436
Observed, 225.1346130 (Scan 817)
225.1368103 (Scan 838)

Preparation of 3,4-Dihydro-2H-Pyran-2-Carboxylic-[(S)-(+)-2-(Methoxymethyl)pyrrolidine] Amide [94].

Pyran ester, [70], (525mg, 3.7mmol) was treated with a 500mg mixture of (S)-(+)-2-methoxymethylpyrrolidine (90%) and (S)-(+)-N-methyl-2-methoxymethylpyrrolidine (10%). After warming to 50°C for 12 hours the crude product was chromatographed over silica gel with hexane- ethyl acetate (15:1 followed by 10:1) affording 160mg of the diastereomeric mixture [94] (GLC).

^{1}H NMR:	6.4(ppm)	d	1H
	4.8-4.2	m	3H
	3.7-3.35	m	4H
	3.32	s	3H
	2.2-1.7	m	8H

MS: (Scan 724) 225(M^+), 197, 181, 180, 157, 152, 124, 97, 83, 70, 55, 45, 41

(Scan 735) 225(M^+), 197, 180, 157, 152, 142, 124, 112, 98, 83, 70, 55, 45, 41

IR: 3020(cm^{-1}), 2850, 1660, 1452, 1405, 1260, 1103, 1055, 920, 720

HRMS: Calculated for $C_{12}H_{19}NO_3$, 225.1364936
Observed, 225.1368561 (Scan 505)
225.1372681 (Scan 527)

Methylation of Amide [94].

To 0.15 mL diisopropylamine (1.07mmol) in 4.0mL dry THF was added 0.42mL of a 2.5M solution of n-butyllithium in Et_2O at 0°C. After 20 minutes amide [94] (195mg), in 1.5 mL THF, was added dropwise at -78°C. After 1.5 hours, iodomethane (0.07mL, 1.3eq) was added and the reaction stirred at -78°C for 2 hours, followed by the usual extraction procedure. Evaporation of solvent afforded 180mg of a pale-yellow oil. GC/MS analysis revealed only the diastereomeric amides, [95] in a ratio of approximately 39:61.

MS: (Scan 838) 239(M^+), 211, 194, 171, 142, 126, 97, 82, 70, 69, 55, 44, 42

(Scan 850) 239(M^+), 194, 171, 138, 126, 97, 82, 70, 69, 57, 46, 44, 42

IR: 3025(cm^{-1}), 2875, 1640, 1440, 1260, 1045, 860, 725

Preparation of (-)-Menthyl Acrylate [96].

A mixture of acryloyl chloride (1.34g, 14,7mmol), (-)-menthol (2.1g, 13.4mmol) and 2.0mL pyridine, in 50.0mL dry dichloromethane, was warmed to 50°C for 10 hours, followed by extraction with

dichloromethane and 10% HCl. The organic phase was dried over Na_2SO_4 and condensed affording 1.66g of a brown liquid. Purification over silica gel with hexane-ethyl acetate (7:3) provided 1.22g of a colorless liquid.

^{13}C NMR: 165.6(ppm)(s), 130.1(t), 128.9(d), 74.1(d), 46.9(d), 40.7(t), 34.1(t), 31.2(d), 26.2(d), 23.4(t), 21.9(q), 20.6(q), 16.3(q)

Attempted Diels-Alder Heterocycloadditions with (-)-Menthyl Acrylate.

Four Lewis acid-catalyzed Diels-Alder reactions were attempted using (-)-menthyl acrylate and methylvinyl ketone. The catalysts used were $AlCl_3$ $SnCl_4$, $TiCl_4$, and $EtAlCl_2$ in 1.0 to 1.4:1 molar ratios with acrylate. In each case, no reaction was detected. A representative procedure is as follows:

To 310mg (1.4mmol) of (-)-menthyl acrylate in 6.0mL freshly distilled dichloromethane (P_2O_5) at 0°C, was added 1.0mL of a 25% solution of ethylaluminum dichloride, under a blanket of nitrogen. Methylvinyl ketone (0.2mL, 2eq) was added dropwise over 10-12 minutes and the reaction stirred for 12-14 hours. Analysis by GC/MS showed only starting material.

Procedure for Menthol-Derived Ester Enolate Trapping with Chlorotrimethylsilane.

LDA (1.55mmol) was generated by combining diisopropylamine (0.22mL) and n-butyllithium (0.70mL of a 2.5M solution in Et_2O) in 15 mL dry THF at 0°C for 15 minutes. Ester (82) (317mg, 1.19mmol), in 1.0mL THF, was added slowly at -78°C. After one hour,

chlorotrimethylsilane (0.22 mL, 1.73mmol) was added and the reaction temperature maintained at -78°C for one hour. The solution was condensed by rotory evaporation (35°C) and the crude product chromatographed over silica gel with hexane-ethyl acetate (10:1). Removal of solvent afforded 435mg of a colorless liquid. Analysis by ^{13}C NMR indicated approximately 15% unreacted [82] along with several newly generated olefinic signals. Capillary GC/MS revealed a complex mixture containing [82] and two peaks (M^+=338) as the major products in a ratio of approximately (4:1:1).

MS:

Retention Time (Minutes)	
21:53 :	338(M^+), 201, 200, 184, 129, 110, 83, 82, 75, 73, 69, 55, 43, 41
22:32 :	338(M^+), 323, 201, 200, 184, 129, 115, 110, 97, 83, 82, 75, 73, 69, 57, 55, 43, 41

Reduction of Methylvinyl Ketone Dimer with Various Reducing Reagents.

The results of the borohydride and lithium aluminum hydride reductions of [28] were taken from the doctoral thesis of Schwartz.[14]

The procedures employing diisobutylaluminum hydride (DIBAH), triisobutylaluminum hydride (TIBA) and L-Selectride were identical. A representative procedure using TIBA is described.

It should be noted that throughout this study, isolated yields of 62a and 62b were generally moderate owing to two critical factors; loss due to partial water solubility during extraction, and loss due to

high volatility during rotoryevaporation. No attempts were made to optimize yields as emphasis was placed on stereoselectivity.

Procedure for the Determination of Bicyclic Ketal Loss Due to Rotoryevaporation.

This procedure represents a general reproduction of the common solvent removal technique used throughout this study. A 440mg sample containing 60% [62a] and 40% [62b] was dissolved in 75.0 mL of Et_2. The solvent was then removed by rotoryevaporation for 12.0 minutes with the bath temperature maintained at 33-34°C. The weight of the resulting sample was 280mg, revealing a loss of 160mg (36.4%).

Reduction of [28] with triisobutlyaluminum hydride (TIBA) (Cyclization Reflux).

Methylvinyl ketone, [28], (400mg, 2.86mmol) was treated, for 1.5 hours at -78°C, with TIBA (1.05mL of a 3.0M solution in toluene, 1.1eq) after which time the reaction was warmed to 20°C for 14 hours. Treatment with 10mL of 15% HCl at 65°C for 4 hours, followed by extraction with Et_2O, drying ($NaSO_4$) and evaporation of solvent, afforded 160mg of a pale- yellow liquid. Analysis by capillary GLC integration of peak areas showed only 62a and 62b in a ratio of approximately 83:17.

Reduction of [28] with Lithium tri-tert-Butoxyaluminohydride (LTBA) (Cyclization at 20°C).

To methylvinyl ketone dimer, [28],+ (300mg, 2.14mmol), in 20mL dry toluene at -78°C under a blanket of argon, was added LTBA (945mg, 3.72mmol). The resulting suspension was treated with 15mL

THF, to effect dissolution of LTBA. After 2 hours, the reaction was warmed to 20°C for 30 minutes and treated with 1.0mL H_2O followed by 5.0mL 15% HCl and extraction with Et_2O (3 x 10mL). Upon standing for 24 hours (20°C) the drying agent (Na_2SO_4) was filtered and the solvent evaporated affording 210mg of crude colorless liquid. Capillary GC/MS analysis showed only [62a] and [62b] in a ratio of 57:43.

Reduction of Methylvinyl Ketone Dimer [28] with $MgBr_2$ and Various Metal Hydride and Grignard Reagents.

The procedures for the reduction of 28·$MgBr_2$ are similar, involving the addition of one equivalent of $MgBr_2 \cdot Et_2O$ to 28, followed by cooling to -78°C and treatment with excess metal hydride or Grignard reagent. Acid-catalyzed cyclization was effected by refluxing for 30 minutes or by allowing to stand at 20°C for several hours. Example procedures for LTBA and PhMgBr are shown below.

Reduction of [28]·$MgBr_2$ with LTBA.

To [28] (300mg, 2.14mmol) in 25mL dry THF at 0°C under argon, was added 553mg $MgBr_2$ Et_2O (1.0eq) followed by rapid cooling to -78°C. After 20 minutes, the mixture was treated with LTBA (1.36g, 5.3mmol) and the temperature held at -78°C for 2 hours. The reaction was then treated with 5.0mL of 15% HCl and allowed to stand for 14 hours. The product was extracted with Et_2O the organics dried (Na_2SO_4) and evaporated, affording 79mg of crude product. GC/MS analysis revealed [62a] and [62b] (3:97) contaminated with approximately 10% uncharacterized by-products.

Reaction of 28·$MgBr_2$ with PhMgBr.

A mixture of [28] (500mg, 3.57mmol) and $MgBr_2$ Et_2O (920mg, 1eq.) in 20mL dry toluene at -78°C under argon, was treated with 0.5 equivalents PhMgBr (0.6mL of a 3.0M solution in Et_2O).

After 30 minutes a second aliquot of PhMgBr was added and the temperature was slowly brought to 0°C over a period of 40 minutes. The usual extraction/cyclization sequence was carried out, followed by purification of the crude product by silica gel chromatography with hexane-ethyl acetate (7:3) affording 510mg of a pale-yellow oil. Analysis by GC/MS showed only 57a and 57b (93:7).

Preparation of 3-Hydroxy-2,7-Octanedione [113].

A solution containing 10mL acetone, 10mL H_2O 10mL THF and 6 drops of concentrated H_2SO_4 was treated for 10 minutes with dimer, [28], (2.0g, 14.3mmol). The solution was extracted with Et_2O (5 x 25mL) and the combined organics washed with bicarbonate, dried over Na_2CO_3 and condensed affording 1.74 g of crude colorless liquid. Analysis by ^{13}C NMR showed one product, identified as [113].

It should be noted that distillation and preparative GLC analysis results in partial conversion to dimer, [28].

^{1}H NMR: 4.2(ppm) m 1H
3.55 d 1H
2.48 t 2H
2.21 s 3H
2.12 s 3H
1.92-1.50 m 4H

^{13}C NMR: 209.9(ppm), 208.6(s), 76.4(d), 42.6(t), 32.3(t), 29.7(q), 25.0(q), 18.7(t)

MS: 158(M^+), 140, 115, 113, 97, 85, 71, 59, 57, 55, 45, 43, 41

HRMS: Calculated for $C_8H_{14}O_3$, 158.0942944
Observed, 158.0944672

General Procedure for the Reduction of 3-Hydroxy-2, 7-octanedione [113] with Various Reducing Reagents.

All reductions of 113 utilized the same procedure involving the addition of excess reducing reagent to a cold solution of 113 or 113·$MgBr_2$ followed by acid catalyzed (10-15% HCL) cyclization. Reaction conditions and yields are summarized in Table 11.

Preparation of anti-2-Acetyl-6-Methoxy-6Methyl-Tetrahydropyran [28a].

Treatment of methylvinyl ketone dimer (2.5g, 17.9mmol) with 20mL of methanol and 100 mg of Dowex 50W-X8 for 14 hours, followed by filtration and distillation afforded 2.36g (76.7%) of a colorless liquid (b.p. 57°C, 0.4torr). Analysis by ^{13}C NMR showed one product identified as [28a].

1H NMR:	4.0(ppm)	dd	1H
	3.20	s	3H
	2.19	s	3H
	1.9-1.2	m	6H
	1.33	s	3H

^{13}C NMR: 209.1(ppm)(s), 101.9(s), 75.8(d), 47.7(q), 34.8(t), 26.4(t), 25.5(q), 23.5(q), 18.4(t)

Reduction of anti-2-Acetyl-7-Methoxy-7-Methyl-Tetrahydropyran [28a] with Various Reducing Reagents.

The procedures for hydride reductions of 28a and 28a $MgBr_2$ are identical to the procedures used for methylvinyl ketone dimer [28].

REFERENCES CITED

1. B. Mundy, A. DeBernardis and R. Otzenburger, J. Org. Chem., (1971), 36, 3830.

2. R. Silverstein, R. Brownlee, T. Bellas, D. Wood and L. Browne, Science,(1968), 159, 889.

3. G. Kinzer, A. Fentiman, T. Page, and R. Foltz, Nature (1970), 221 477.

4. G. Pearce, W. Gore, R. Silverstein, J. Peacock, R. Cuthbert, G. Lanier and J. Simone, J. Chem. Ecol., (1975), 1, 115.

5. R. Cole, J. Dorner, J. Lansden, R. Cox, C. Pape, B. Cunfer, S. Nicholsen and D. Bedell, J. Agric. Food Chem., (1977), 25, 1197.

6. Y. Naya and M. Kotake, Tetrahedron Lett., (1976), 26, 2459.

7. R. Light and J. Hunter, Biochemistry, (1970), 9, 4289.

8. D. Weislwer, F. Schwende, M. Carmack and M. Novotny, J. Org. Chem., (1984), 49, 882.

9. Y. Kim and B. Mundy, J. Org. Chem., (1982), 47 3556.

10. M. Bjorklund, J. Jun, and B. Mundy, Tetrahedron Lett., (1985), 33, 3895.

11. M. Bjorklund and B. Mundy, Tetrahedron Lett., (1985), 33, 3899.

12. M. Isobe, N. Fukami and T. Goto, Chem. Lett., (1985), 1, 71.

13. H. Brown and P. Geoghegan, J. Org. Chem., (1970), 35, 1844; H. Brown, P. Geoghegan, J. Kurek and G. Lynch, Organometal. Chem. Syn., (1970), 1, 7; H. Brown, P. Geoghegan, G. Lynch and J. Kurek, J. Org. Chem., (1972), 37, 1941; H. Brown and J. Kawakami, J. Am. Chem. Soc., (1973), 95, 8665; H. Brown and W. Hammar, Tetrahedron, (1978), 34, 3405.

14. D. Bruss, Ph.D. Thesis, Montana State University, (1985).

15. B. Mundy, Concepts of Organic Synthesis: Carbocyclic Chemistry, Marcel Dekker, Inc., New York, 1979, p 51.

16. T. Schwartz, Ph.D. Thesis, Montana State University, (1982).

17. Non-Specificity in Diels-Alder heterocycloaddition, see reference 6, calculational parameter studied by Mundy.

18. J. Apsimon and R. Sequin, Tetrahedron, (1979), 35, 2797. A. Meyers, J. Pure Appl. Chem., (1979), 51, 1255.

19. D. Seeback and R. Naef, Helv. Chim. Acta., (1981), 64, 2704.

20. V. Prelog, Nachr. Chem. Tech., (1975), 23, 461; G. Helmchen and R. Schmierer, Angew. Chem. Int. Ed. Engl., (1981), 2, 205.

21. A. Meyers, G. Knaus, K. Kamata and M. Ford, J. Am. Chem. Soc., (1976) 98, 567; A. Meyers, E. Snyder and J. Ackerman, Ibid., (1978), 100, 8186; M. Hoobler, D. Bergbreiter and M. Newcomb, Ibid., (1978), 100 8182; M. Larcheveque, E. Ignatova and T. Cuvigny, J. Organomet. Chem. (1979), 177, 5; E. Ade, G. Helmchen and G. Heiligenmann, Tetrahedron Lett., (1980), 28, 1137; D. Evans, J. Takacs, L. McGee, M. Ennis, D. Mathre and J. Bartroli, J. Pure Appl. Chem., (1981), 53, 1109.

22. D. Evans, Aldrich. Acta, (1982), 15, 23.

23. G. Helmchen, A. Selim, D. Dorsch and I. Taufer, Tetrahedron Lett. (1983), 24, 3213; G. Helmchen and R. Wierzchowski, Angew. Chem. Int. Ed. Engl., (1984), 1, 23.

24. E. Corey and R. Peterson, Tetrahedron Lett. (1985), 26, 5025.

25. R. Ireland and A. Willard, Tetrahedron Lett., (1975), 16, 3975.

26. R. Schmierer, G. Grotemeier, G. Helmchen and A. Selim, Angew. Chem. Int. Ed. Engl. (1981), 20, 207.

27. K. Lipkowitz, Ph.D. Thesis, Montana State University, (1975); see also reference 16.

28. W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt and R. Moffatt, Helv. Chim. Acta., (1981), 64, 2802; G. Stork and K. Atwal, Tetrahedron Lett., (1983), 24, 3819; W. Oppolzer, C. Chapuis, G. Dao, D. Reichlin and T. Godel, Tetrahedron Lett., (1982), 23, 4781; W. Oppolzer, C. Chapuis and G. Dao, Tetrahedron Lett., (1984), 25, 5383; W. Oppolzer, C. Chapuis and M. Kelley, Helv. Chem. Acta., (1983), 66 2358; T. Poll, G. Helmchen and B. Bauer, Tetrahedron Lett., (1984), 25, 2191.

29. R. Farmer and J. Hamer, J. Org. Chem.,(1966), 31, 2418.

30. J. Sauer and J. Kredel, Tetrahedron Lett., (1966), 6359.

31. E. Corey and J. Ensley, J. Am. Chem. Soc., (1975), 97, 6908.

32. W. Oppolzer, M. Kurth, D. Reichlin and F. Moffat, Tetrahedron Lett., (1981), 22 2545.

33. J. Sauer and J. Kredel, J. Org. Chem., (1966), 6359.

34. C. LeDrain and A. Greene, J. Am. Chem. Soc.,(1982), 104, 5473.

35. W. Oppolzer, Angew. Chem. Int. Ed. Engl., (1984), 23, 876.

36. W. Oppolzer, Tetrahedron, (1987), 43, 1969.

37. T. Lowry and K. Richardson, Mechanism and Theory In Organic Chemistry, Harper and Row, New York, (1987), pp 132.

38. B. Mundy, G. Dirks, R. Larsen and C. Caughlan, J. Org. Chem., (1978), 43, 2347.

39. J. Jun, Ph.D. Thesis, Montana State University, (1985).

40. J. Colonge, J. Buendia and H. Guignard, Bull. Soc. Chim. Fr., (1969), 956.

41. J. March, Advanced Organic Chemistry, John Wiley and Sons, New York, (1985), pp 789.

42. S. Czernecki, Tetrahedron Lett., (1985), 26, 1699.

43. D. Williams and I. Flemming, Spectroscopic Methods in Organic Chemistry, McGraw-Hill, (1980), pp 100.

44. P. Deslongchamps, Stereoelectronic Effects in Organic Chemistry, Pergamon Press, (1983), pp 5.

45. M. Ansell, The Chemistry of Acid Halides, Interscience, London, (1972), pp 35-68.

46. L. Fieser and M. Fieser, Reagents for Organic Synthesis, John Wiley and Sons, New York, (1967), pp 1158.

47. A. Wissner and C. Grudzinskas, J. Org. Chem., (1978), 43, 3972.

48. B. Mundy, K. Lipkowitz and G. Dirks, Heterocycles, (1977), 6, 51.

49. J. Whitesell and C. Buchanan, J. Org. Chem., (1986), 51, 5443.

50. M. OHWA and E. Eliel, Chem. Lett., (1987), 41.

51. K. Sharpless, B. Rossiterr and T. Katsuki, J. Am. Chem. Soc. (1981), 103, 464.

52. A. Oehlschlager and B. Johnston, J. Org. Chem., (1987), 52, 940.

53. D. Matteson, J. Am. Chem. Soc., (1986), 108, 810.

54. A. Sherk and B. Fraser-Reid, J. Org. Chem., (1982), 47, 932.

55. H. Redlich, W. Bruns, W. Francke, V. Schurig, T. Payne and J. Vite, Tetrahedron, (1987), 43, 2029.

56. G. Helmchen and G. Wegner, Tetrahedron Lett., (1985), 26, 6051.

57. D. Enders, P. Fey and H. Kipphardt, Org. Syn., (1987), 65, 173.

58. D. Evans and J. Takacs, Tetrahedron Lett., (1980), 21, 4233.

59. M. Bednarski and S. Danishefsky, J. Am. Chem. Soc., (1983), 105, 3716.

60. J. Katzenellenbogen and S. Bowlus, J. Org. Chem., (1973), 38, 627.

61. E. Hoffman, Justus Liebigs Ann. Chem., (1960), 629, 104; K. Ziegler, W. Kroll, W. Larbigand and O. Steudle, Ibid., (1960), 629, 53.

62. E. Ashby, J. Sevenair and F. Dobbs, J. Org. Chem. (1971), 36, 197.

63. H. Schroetter and E. Hoffman, Ber. Bunsenges. Phys. Chem., (1964), 68, 627; also see reference 66.

64. D. Cram and K. Kopecky, J. Am. Chem. Soc., (1959), 31, 2748; M. Reetz, Angew. Chem. Int. Ed. Engl., (1984), 23, 556.

65. G. Keck and S. Castellino, J. Am. Chem. Soc., (1986), 108, 3847.

66. Ibid.; and Professor G.E. Keck, University of Utah, personal communication April, 1987, ACS Nation Meeting, Denver, CO.

67. D. Cram and D. Wilson, J. Am. Chem. Soc., (1963), 85, 1245.

68. D. Evans and K. Chapman, Tetrahedron Lett., (1986), 27, 5939.

69. L. Jelinski, Chem. Eng. News, (1984), November 5, p. 26.

70. M. Dewar and W. Thiel, J. Am. Chem. Soc., (1979), 99, 4900.

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