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

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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November 1987

APPROVAL

of a thesis submitted by

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.

Nov. 12, 1987
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Signature Richard R Copp Jr.

Date 11-12-87

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

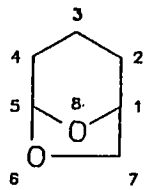
Bicyclic ketals of the 6,8-dioxabicyclo[3.2.1]octane[1] series, 1, have been the focus of attention for numerous natural products research efforts in recent years. The fundamental importance of this heterocyclic system originated in carbohydrate chemistry and has since expanded through its recognition 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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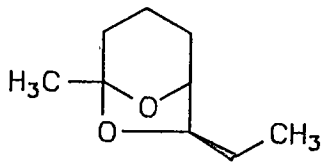

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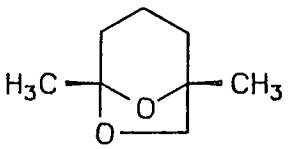

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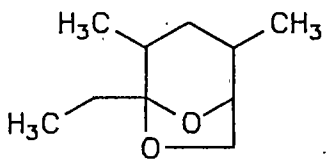

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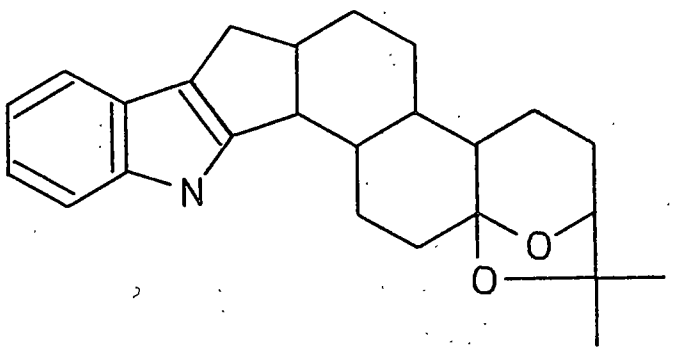
Structurally related systems include 6, a constituent of Japanese hop, "Shinshu-wase",[6] 7, a product of fatty acid metabolism in yeast,[7] and 8, the aggression pheromone of the mouse Mus musculus.[8]



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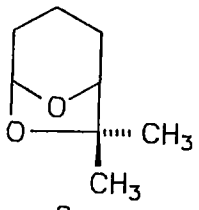

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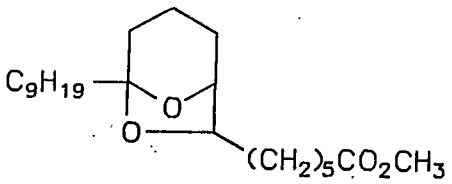

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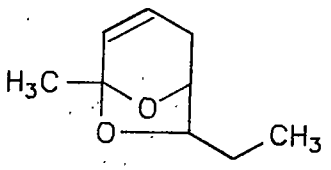

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The diversity in substitution and stereochemistry of these ketals, as well as their biological and economical importance, has sparked considerable interest in organic synthesis. As a result, numerous methodologies have been developed which provide 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]

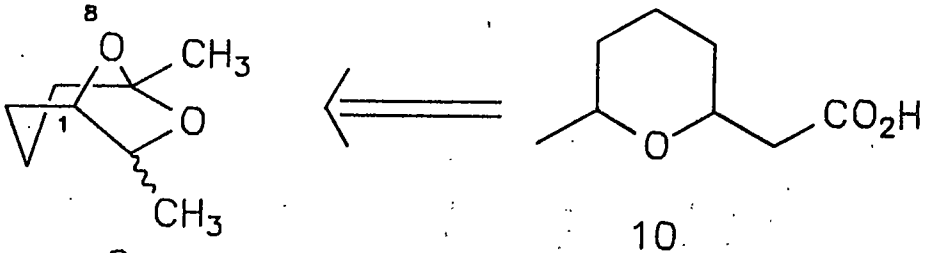

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Figure 1. Kims' Synthesis of a Civet Cat Component.

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).

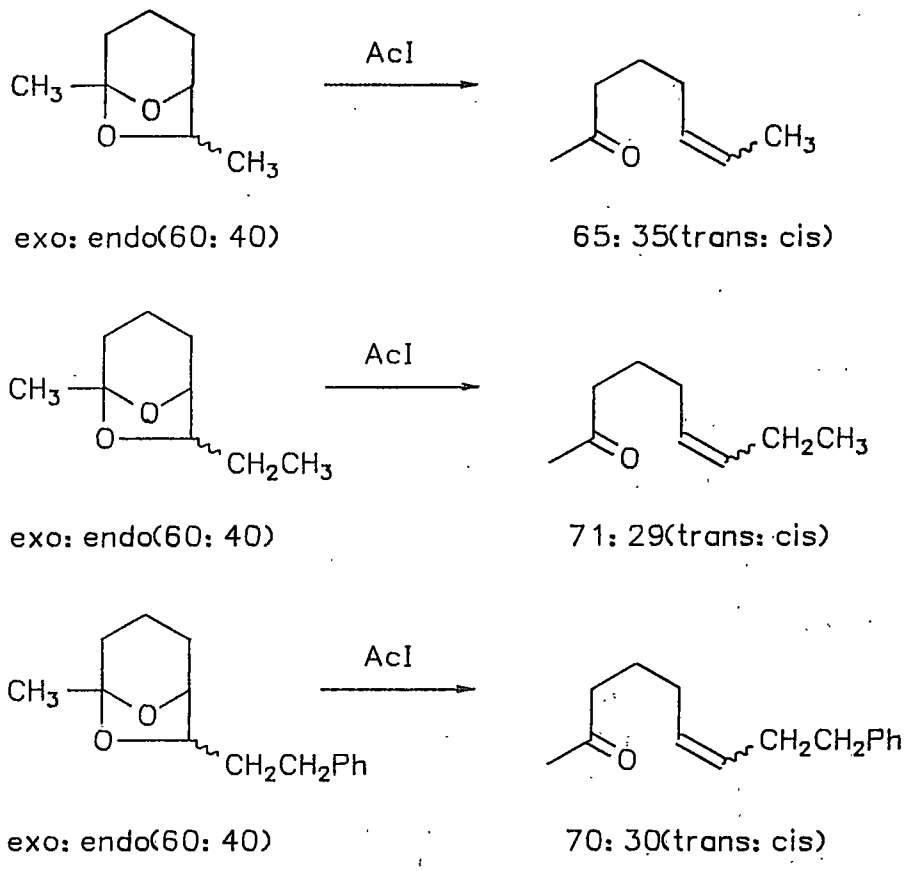

Figure 2. Fragmentations of Bicyclic Ketals with Acetyl Iodide.

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]

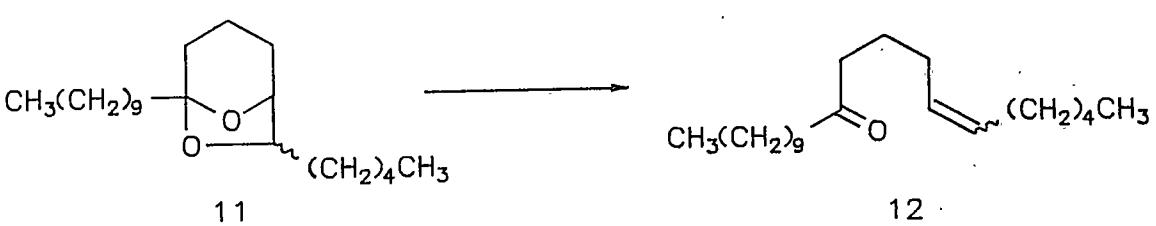

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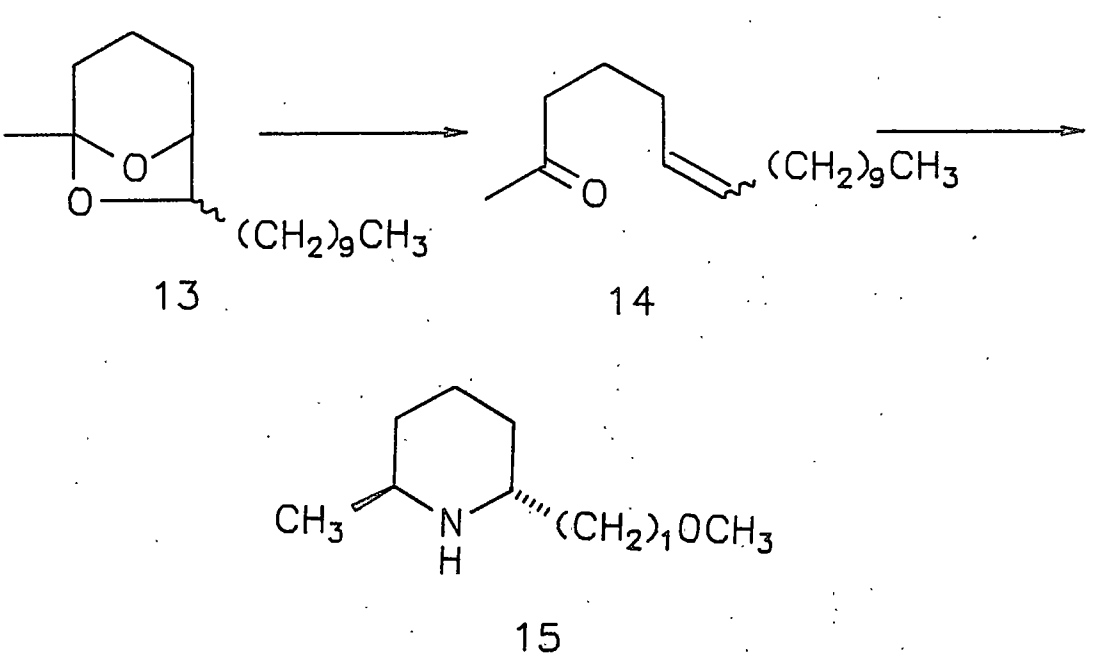
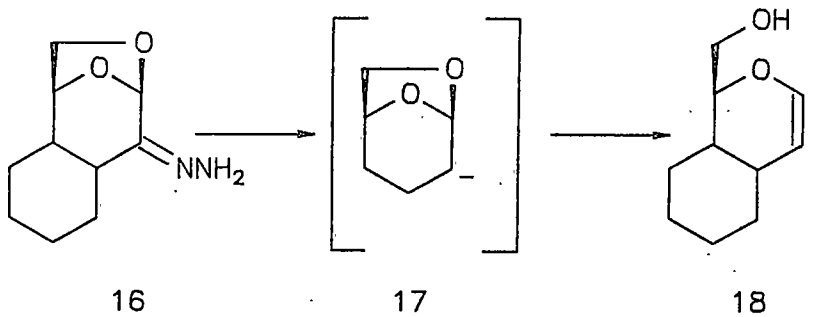
Figure 3. Mundy Synthesis of [12].



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).

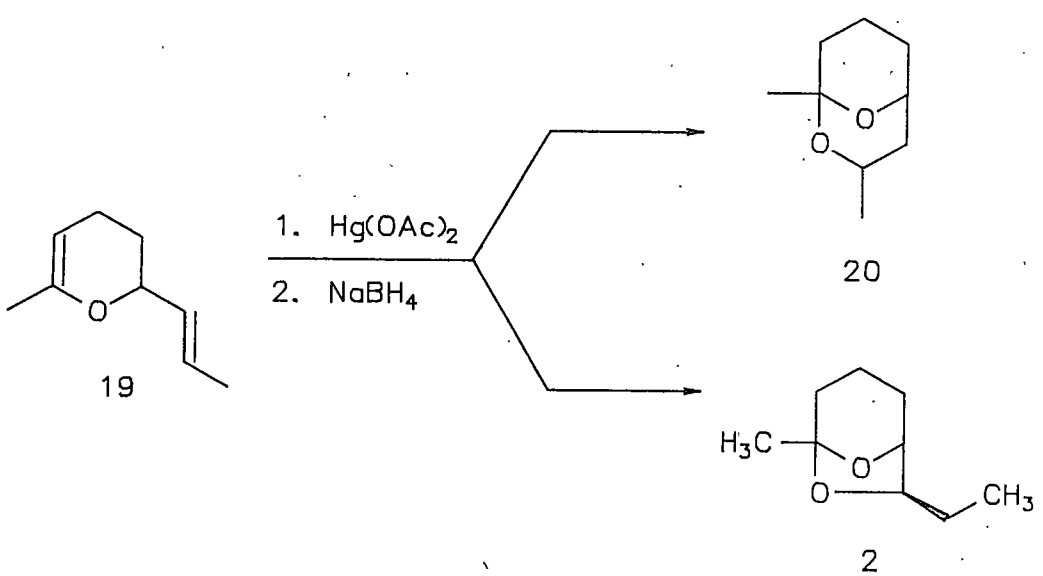


Figure 6. Concurrent Pheromone Syntheses.

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

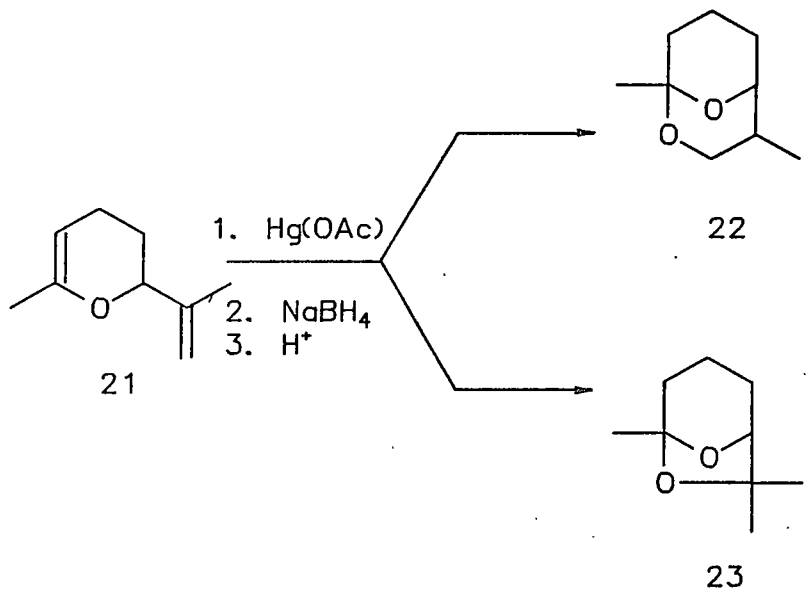


Figure 7. Model Tandem Oxymercuration-Demercuration Procedure.

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).

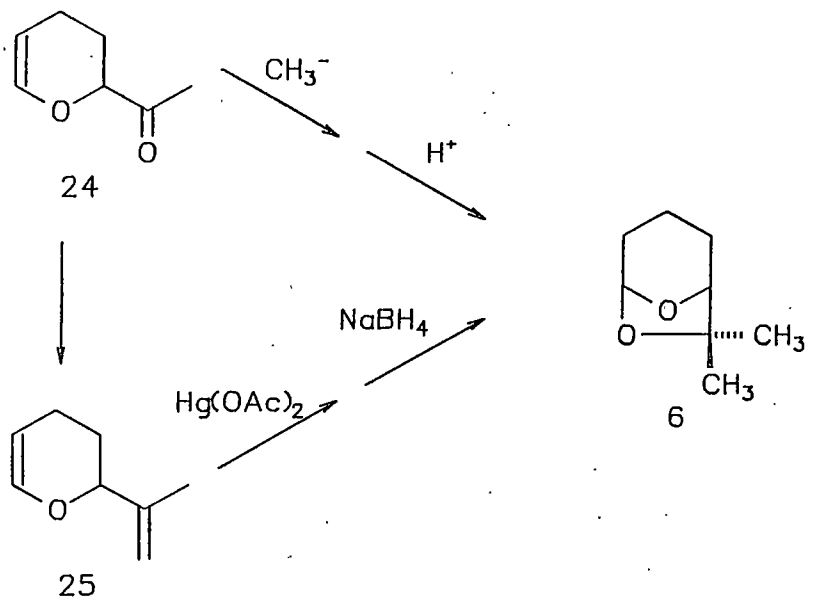


Figure 8. Separate Conversions of [24] to [6].

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.

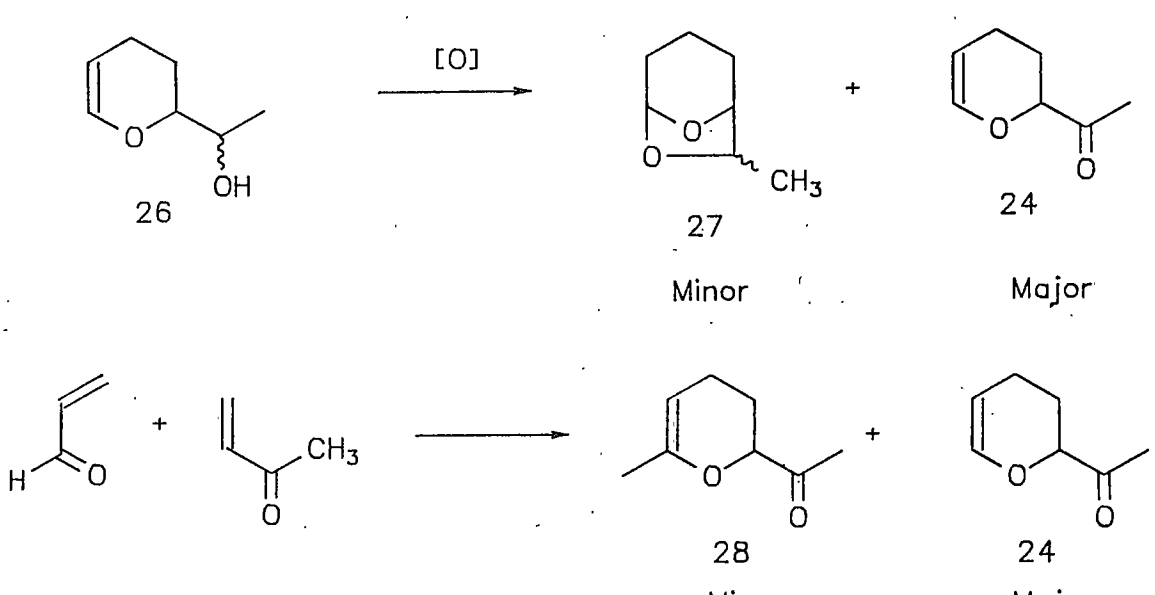


Figure 9. Preparations of 21.

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]

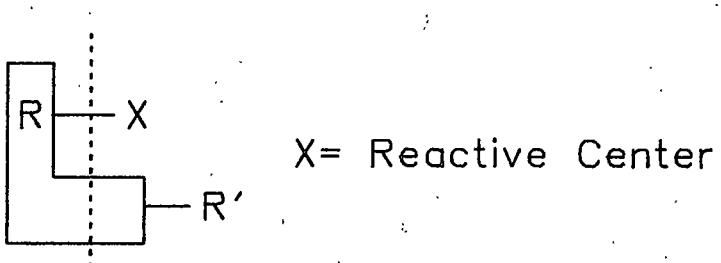


Figure 10. Facial Selectivity Offered By a Concave Site.

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.

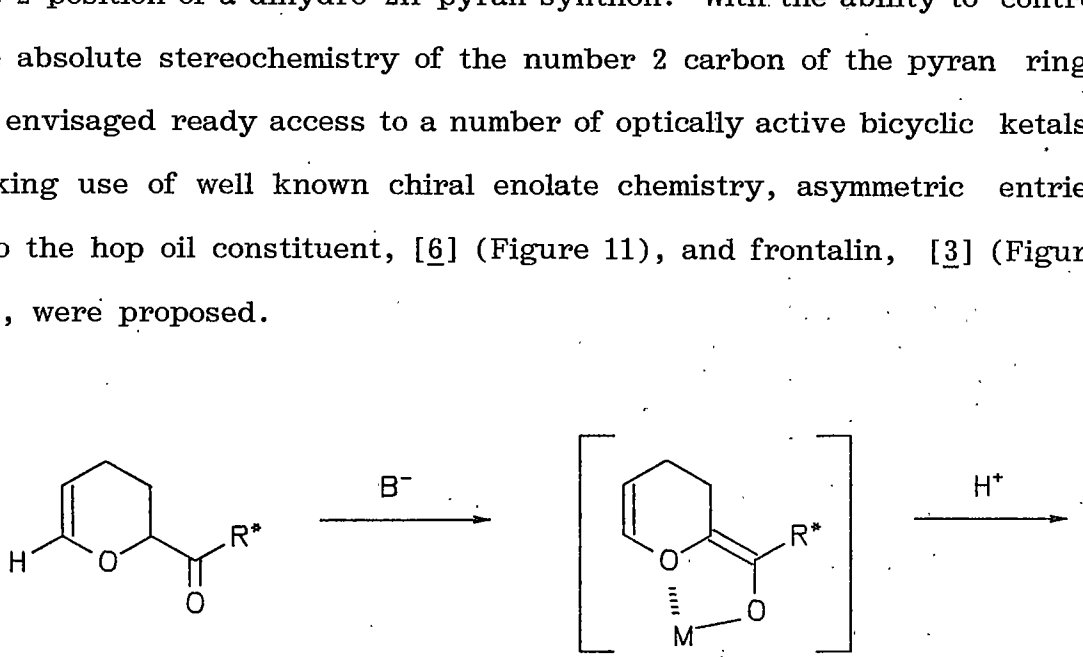


Figure 11. Proposed Asymmetric Synthesis of the Hop Oil Constituent [6].

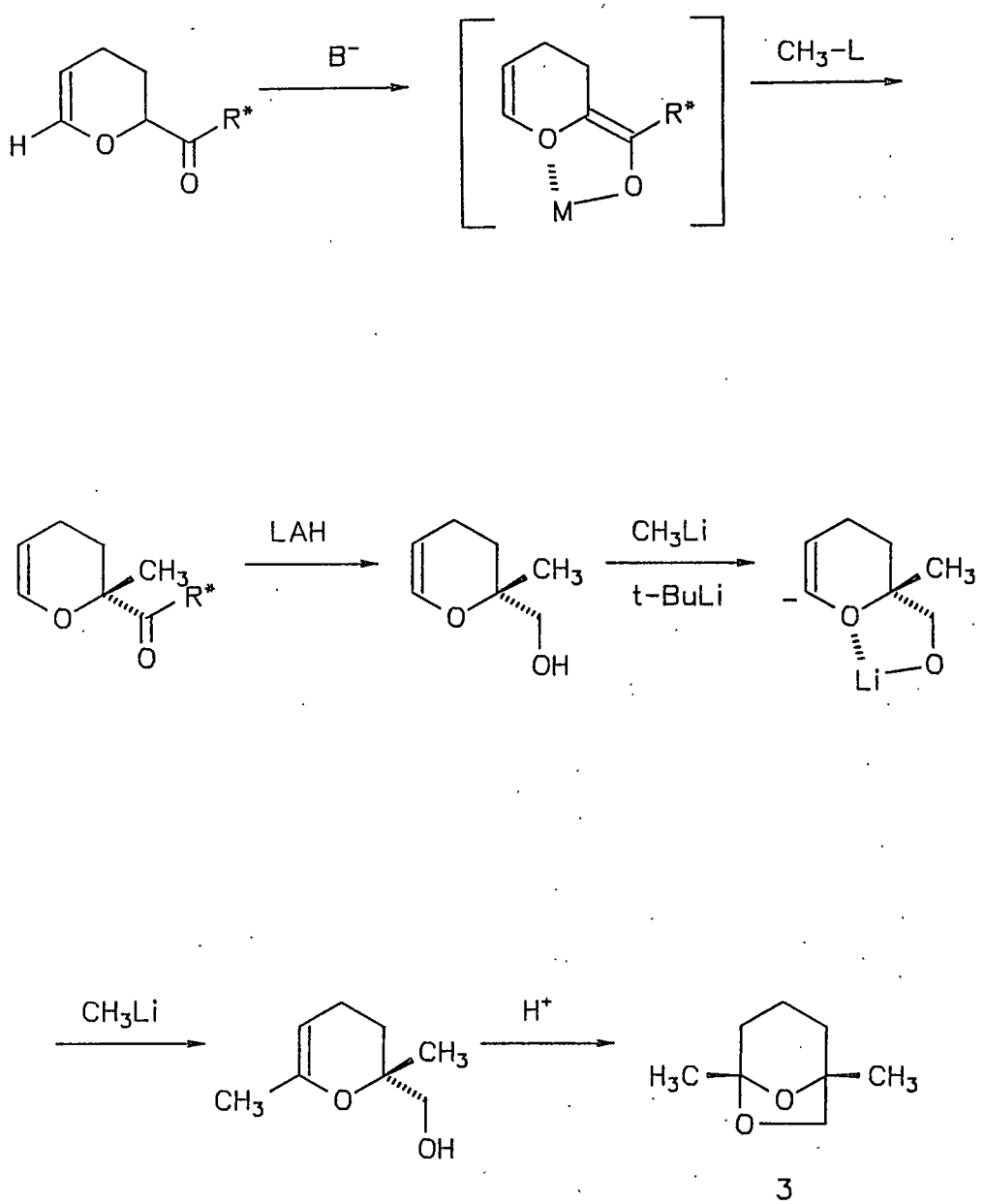
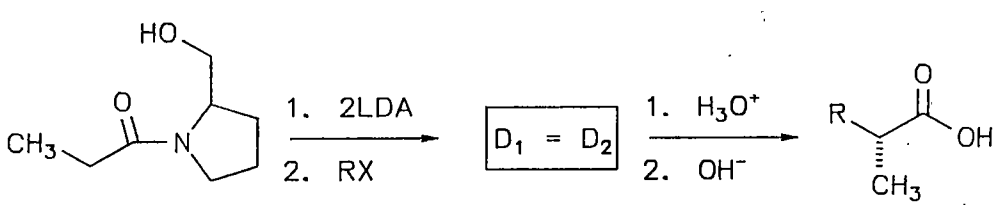


Figure 12. Proposed Asymmetric Synthesis of Frontalin, [3].

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).



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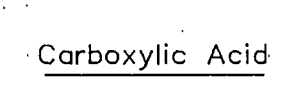
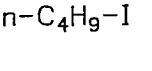
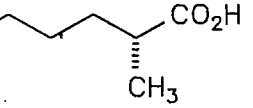
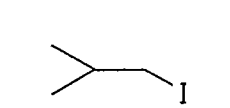
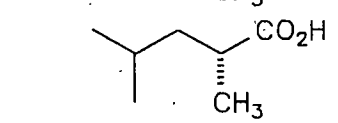
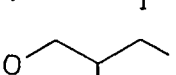
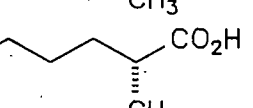
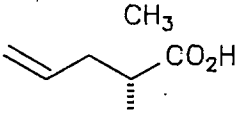
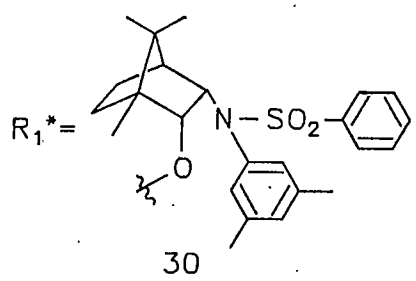
Electrophile	$D_1 : D_2$	Carboxylic Acid	
$n\text{-}C_4H_9\text{-}I$	94 : 6		82%
	97 : 3		85%
	97 : 3		54%
	96 : 4		81%
$PhCH_2Br$	88 : 12		69%

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).



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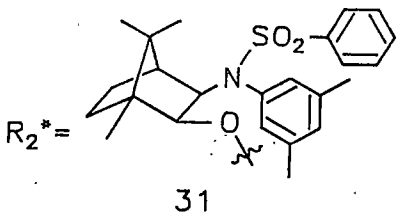

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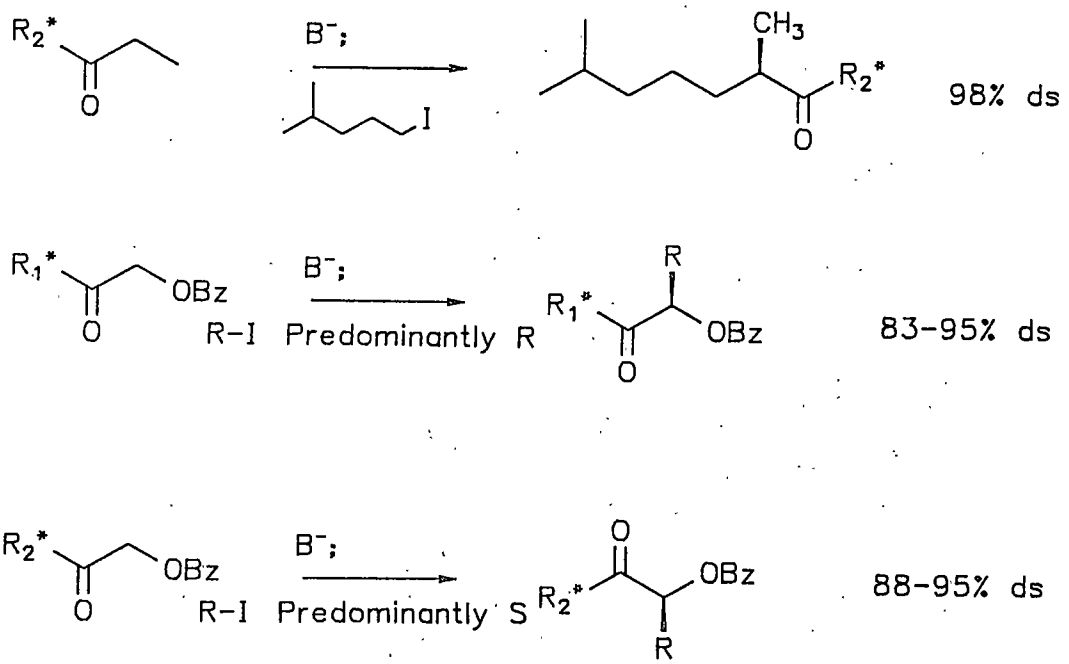


Figure 14. Helmchen Camphor-Derived Chiral Auxiliary.

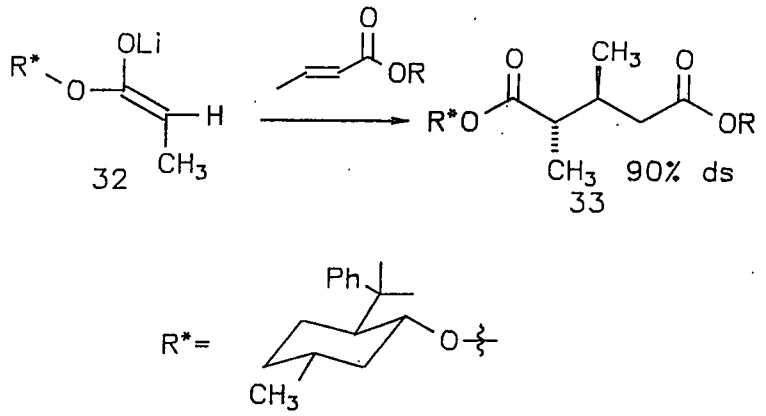


Figure 15. Corey Application of 8-Phenylmenthol

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).

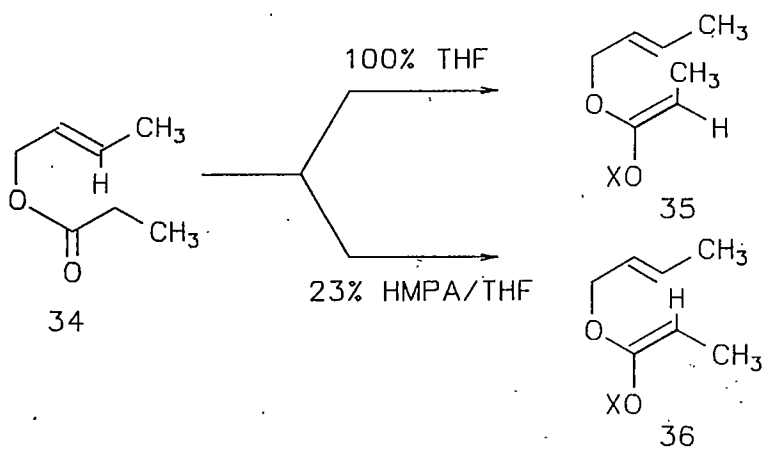
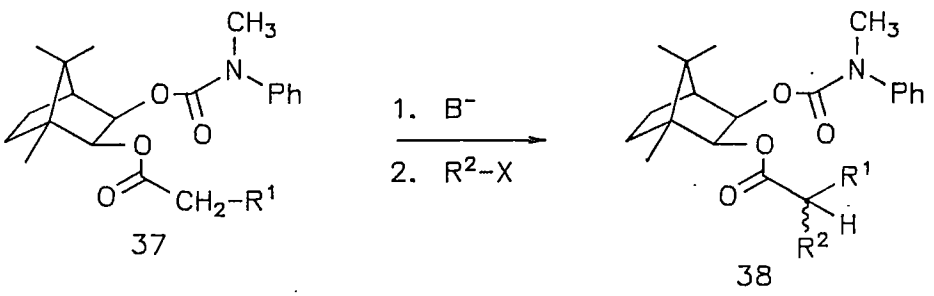


Figure 16. Stereoselective Generation of Ester Enolates.

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.

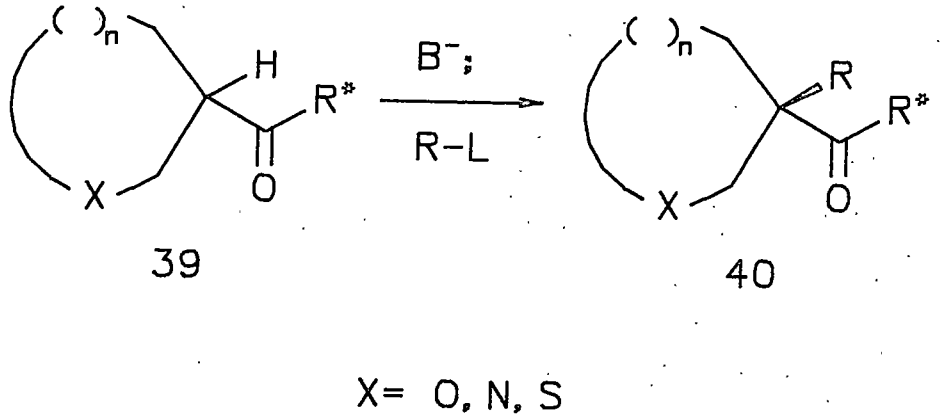


Figure 18. Chiral Enolate Alkylation at a Ring Carbon.

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

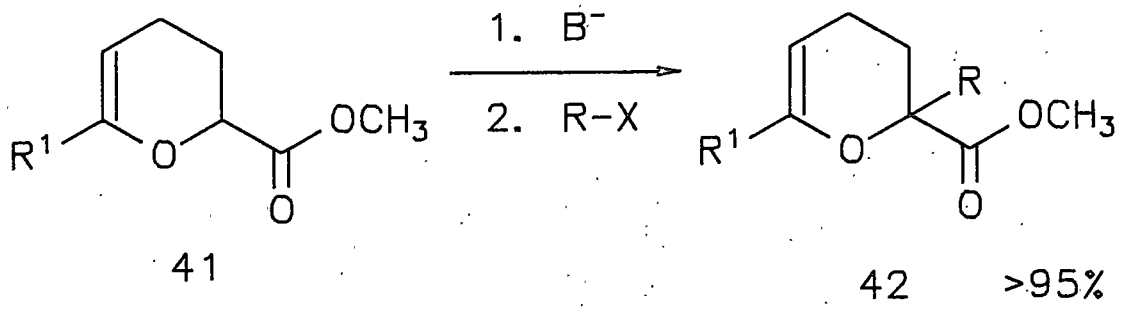


Figure 19. Alkylation of 2-Carboxyl-Dihydro-2H-Pyrans.

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.

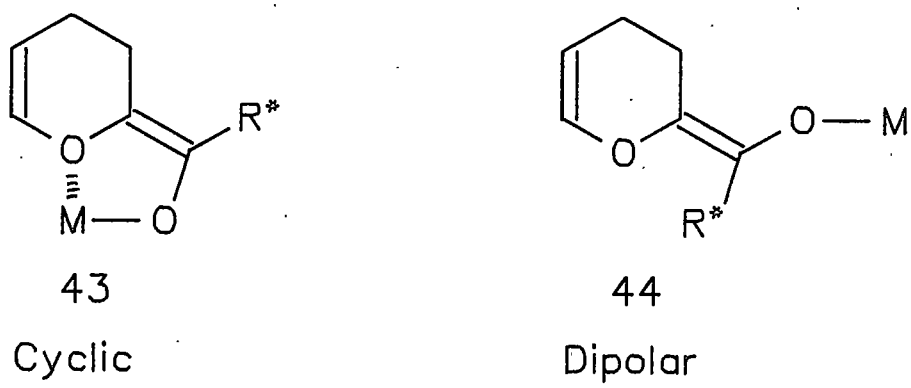


Figure 20. Control of Enolate Stereochemistry

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.

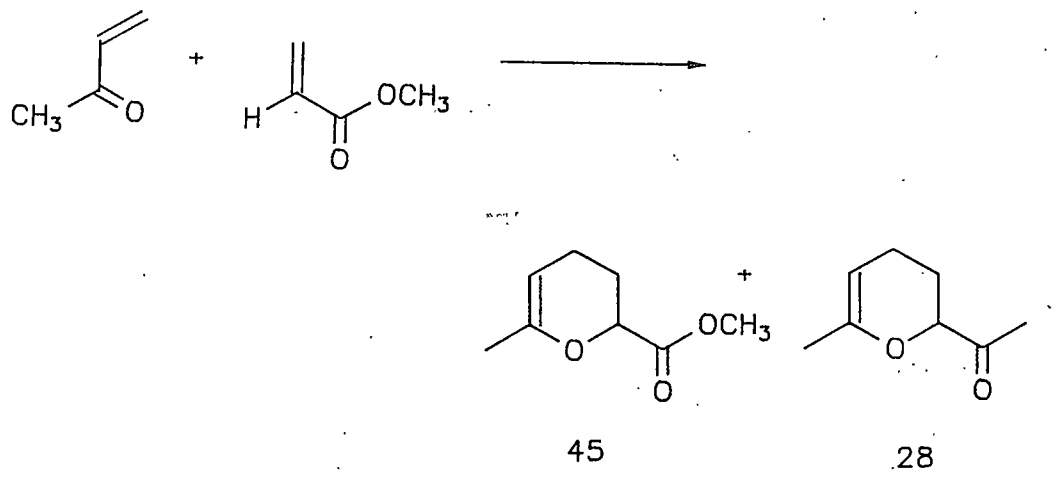
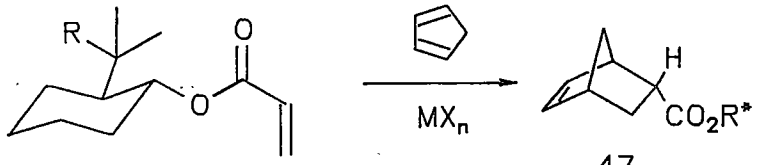


Figure 21. Diels-Alder Reaction with MVK and Methyl Acrylate.

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).

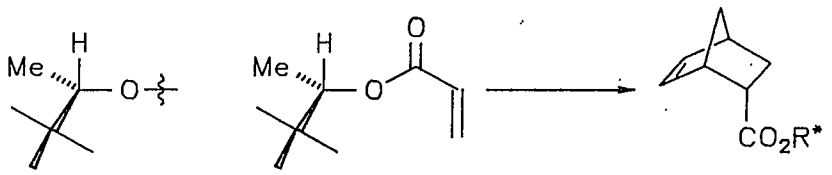


46 47

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]

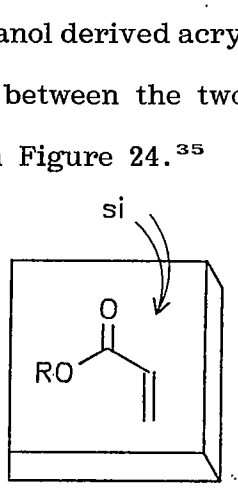
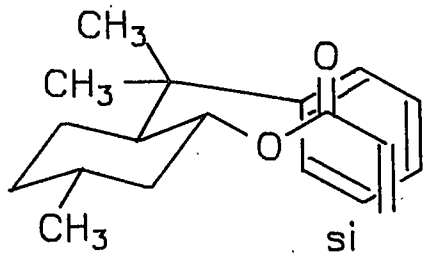


Figure 24. Facial Differentiation in Acrylates.

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.

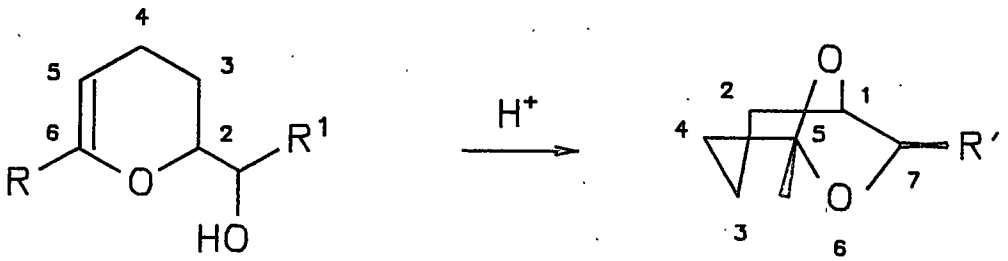


50

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].

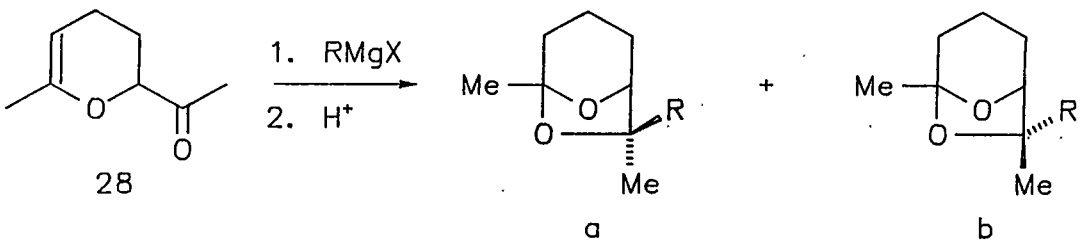


51 52

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).

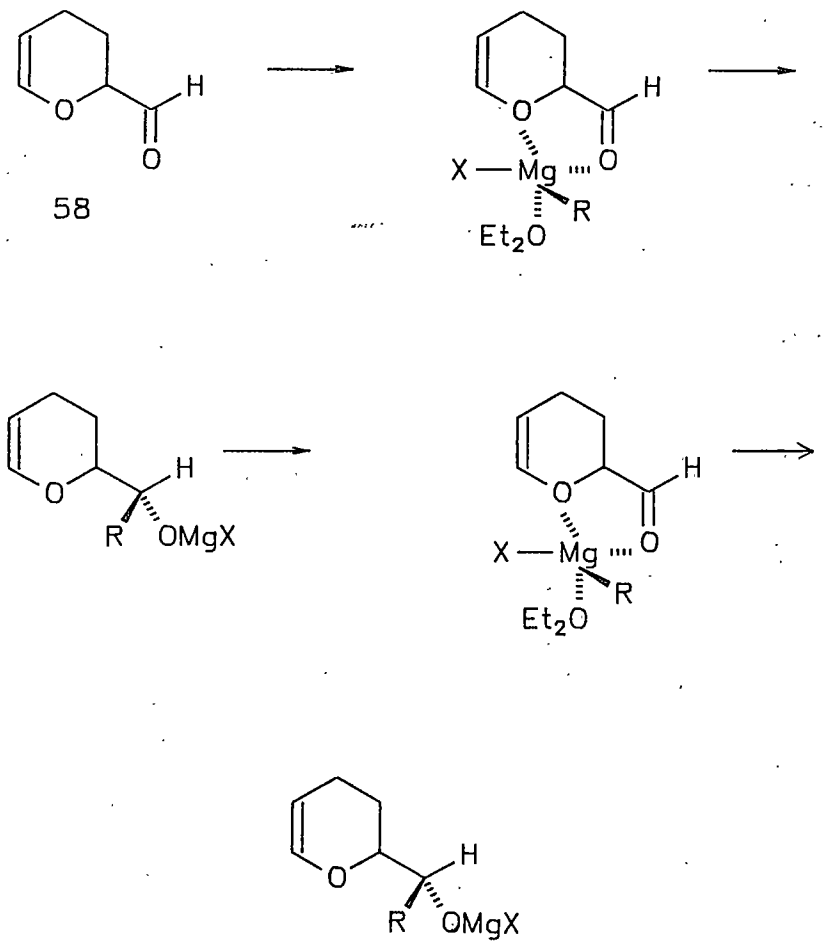
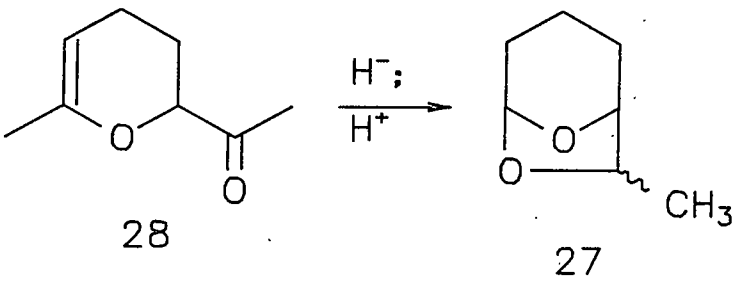


Figure 28. Reaction of Grignard Reagents with 58.

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).

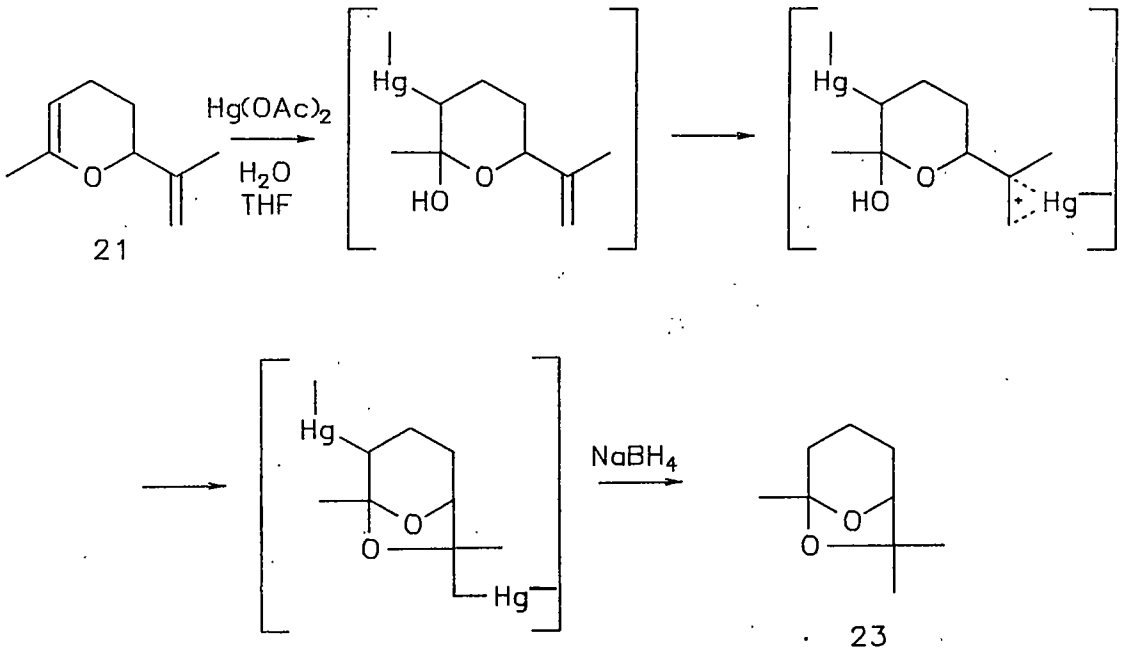
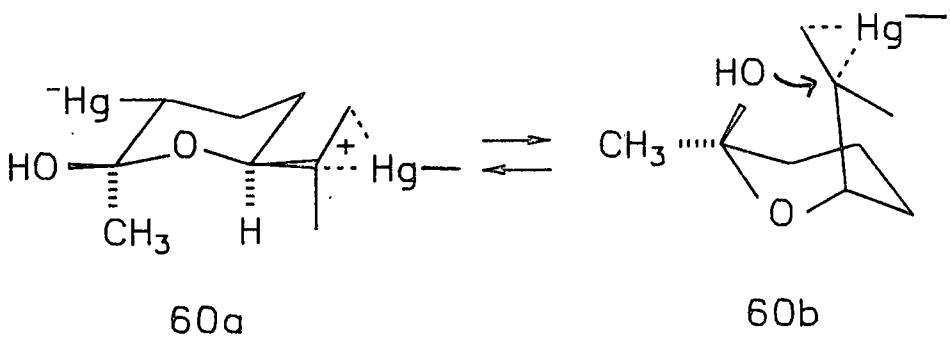


Figure 30. Original Tandem Oxymercuration-Demercuration-Bicyclic Ketal Preparation.

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].

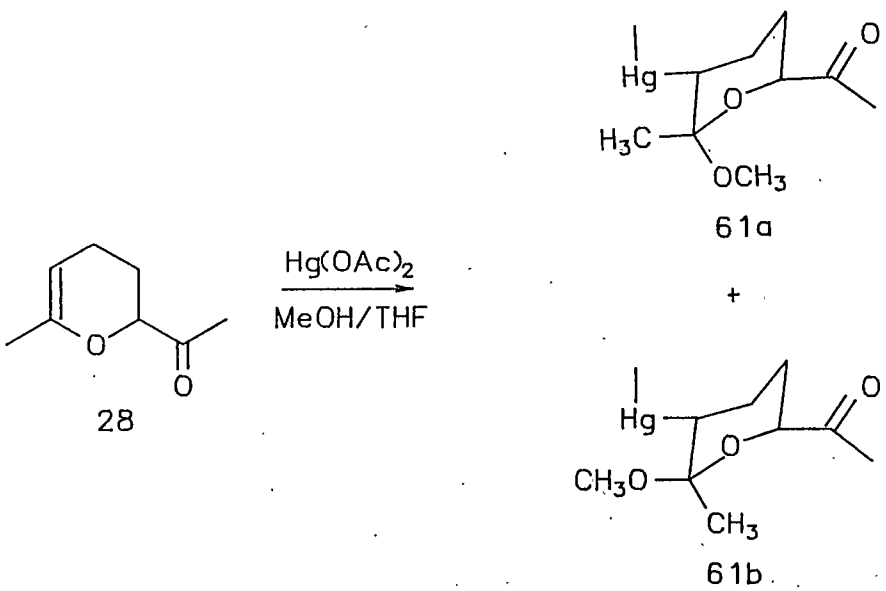


Figure 32. Solvomercuration of ketone [28].

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).

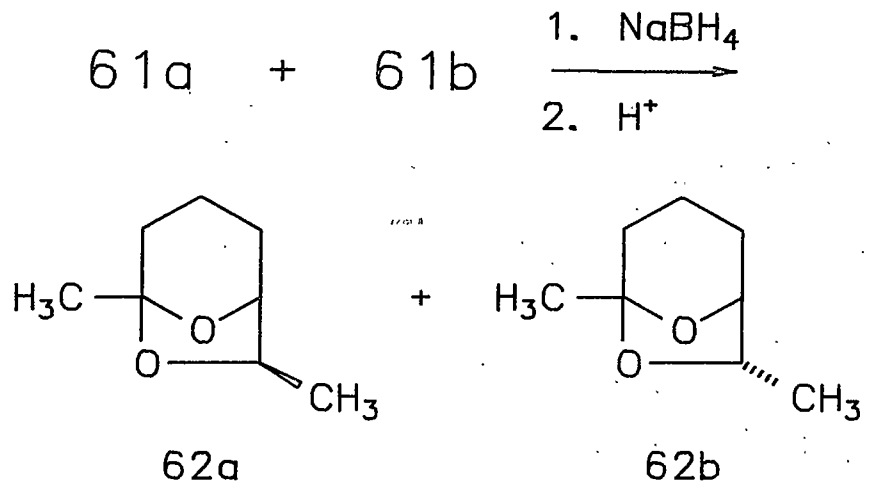


Figure 33. Demercuration/Cyclization of ketals 61a and 61b.

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).

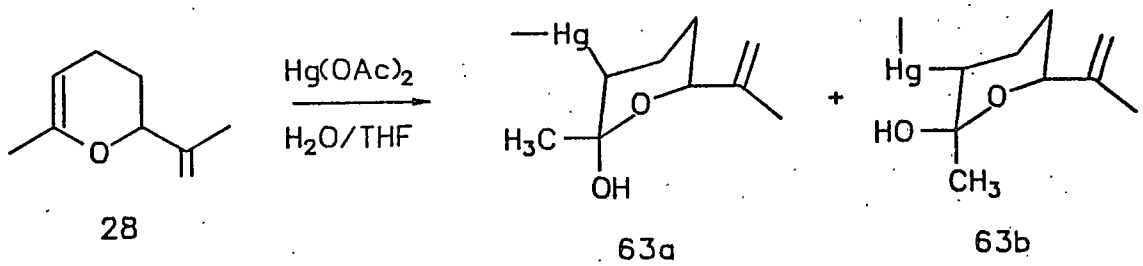
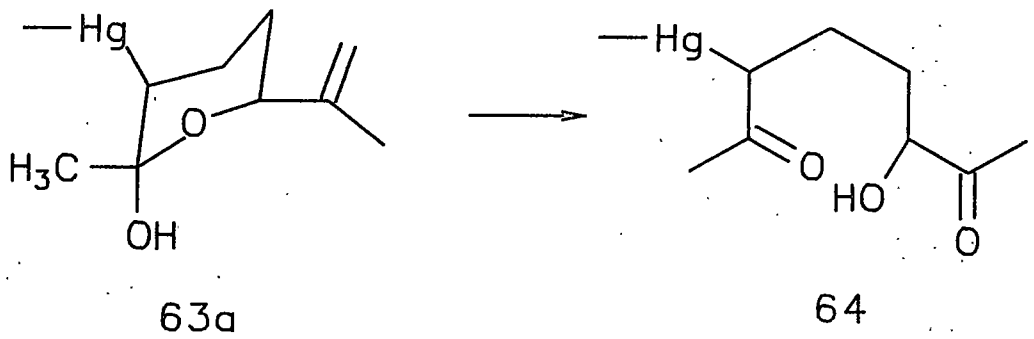


Figure 34. Proposed Non-stereoselective oxymercuration of Diene [21].

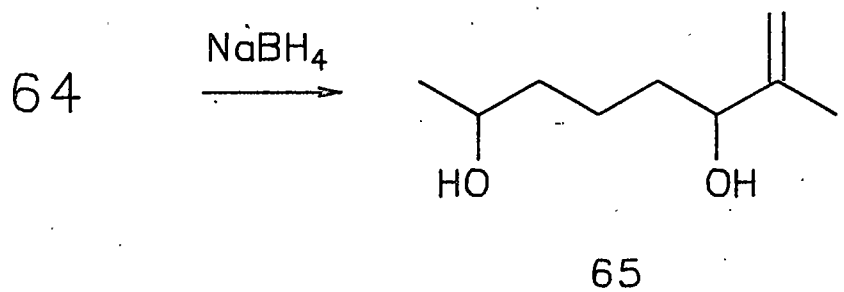
Having nearly equal amounts of cis and trans OH-substitution, with respect to the isopropenyl group, one would expect that only the cis-isomer would be capable of cyclizing. The trans isomer, 63a, might then be susceptible to ring opening as shown in Figure 35.



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.

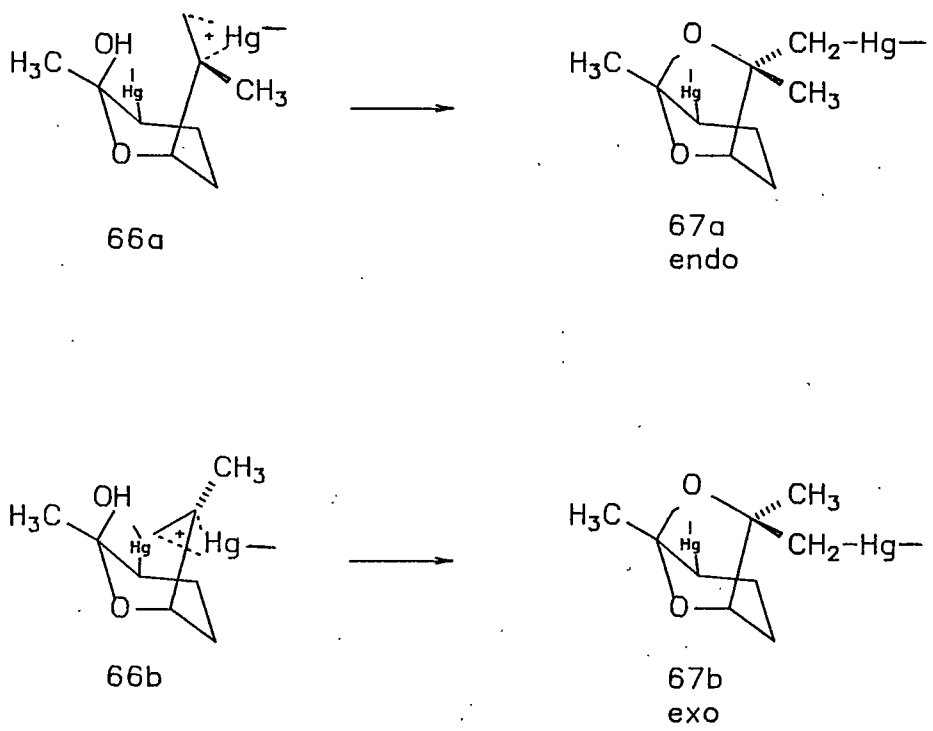


Figure 37. Proposed Stereochemical Control in Mercurinium Ion Cyclization.

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.

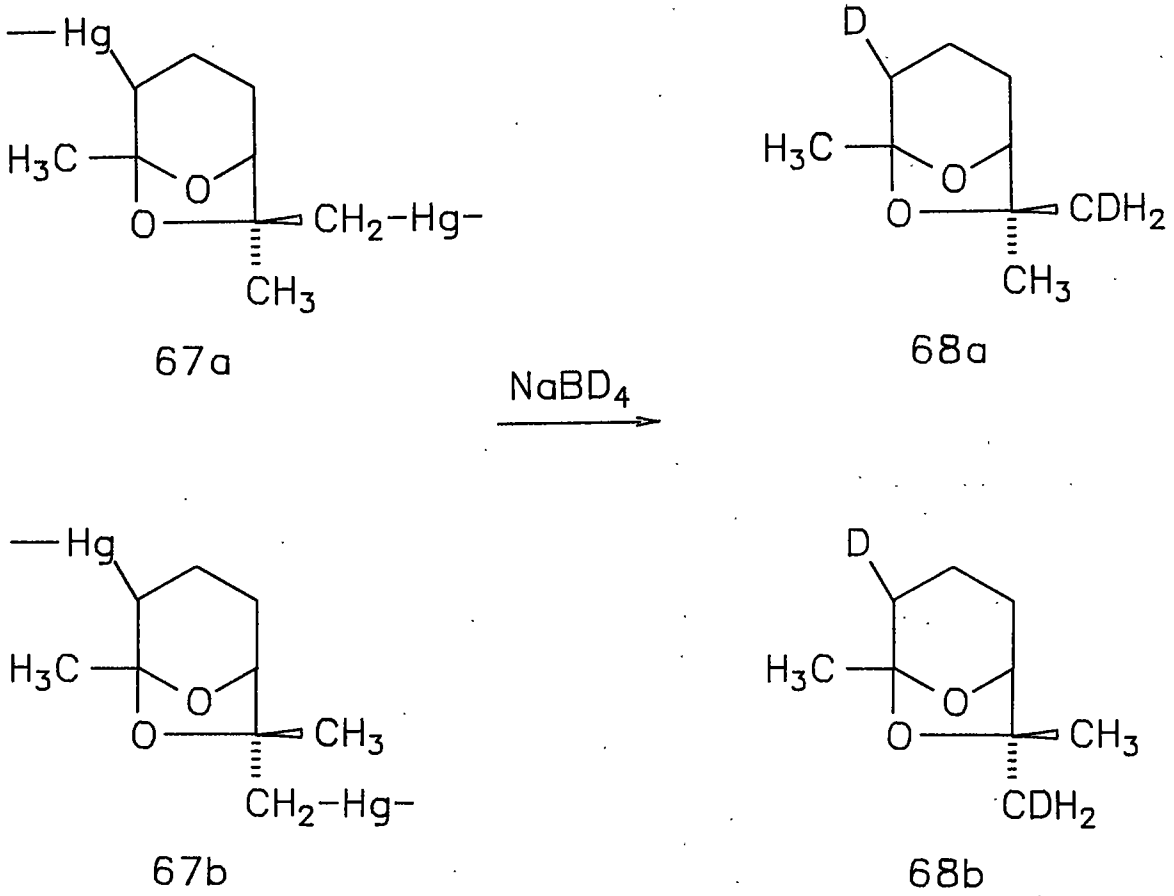


Figure 38. Demercuration with Sodium Borodeuteride.