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RECENT APPLICATIONS OF ANIONIC OXY-COPE REARRANGEMENTS

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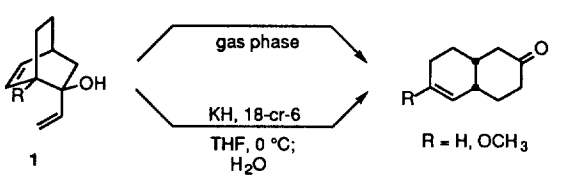
1. Introduction

Oxy-Cope rearrangements, most significantly their anionic variants, have emerged in recent years as highly useful sigmatropic-type reactions for organic synthesis. 1,5-Dien-3-ols of widely varied type readily undergo this electronic reorganization, and the relative ease of preparation of these precursors contributes to the broad appeal of this chemistry. An anionic oxy-Cope rearrangement is often performed at or near room temperature and exhibits a considerable tolerance toward functional groups present in the original reactant. The stereochemical outcome of these reactions is directly linked to the geometric alignment of the double bonds in the lowest energy transition state. Since adoption of a chair or boat arrangement can often be forecasted on the basis of structure, the installation of stereogenic centers is often accomplished with a high level of predictability. Much of the development of the title reaction has been fueled by its capacity for quickly elaborating complex polycyclic structures in a very small number of laboratory operations. This impressive scaffolding power can be further enhanced by merging the oxy-Cope rearrangement in tandem with a second chemical transformation.

This report summarizes many of the newer applications of oxy-Cope sigmatropy to synthetic organic chemistry. The discussion shall focus predominantly on developments disclosed during the past decade, since detailed reviews covering the earlier work are available.[1-5] Particular emphasis is placed, where possible, on transformations that are novel and synthetically useful.

2. Background

The term "oxy-Cope" rearrangement, first coined in 1964, was advanced to emphasize the fact that placement of a hydroxyl subsitutent at C-3 of a 1,5-diene as in **1** did not inhibit the classical thermal Cope process. A further significant advance came along in 1975 when enormous rate accelerations (up to 10^{15}!) were



1

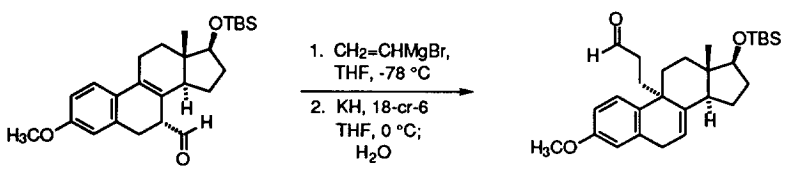
observed following conversion of the alcohols to the corresponding potassium alkoxides.[7] The considerable temperature lowering made possible by these impressive rate accelerations has proven central to the adoption of

this methodology for natural product synthesis. Some of the early landmark events include the preparation of acoragermacrone[8] and (-)-periplanone B.[9]

The alkoxide substituent actually plays a role other than dramatically lowering the bond dissociation energy. The fact that a resonance-stabilized enolate anion is now the first-formed product of the sigmatropic event causes the rearrangement to become irreversible in most contexts. Also enormously attractive is the enhanced structural embellishment that often develops in the unsaturated ketone product, whose two new functional groups can be independently manipulated for synthetic purposes.

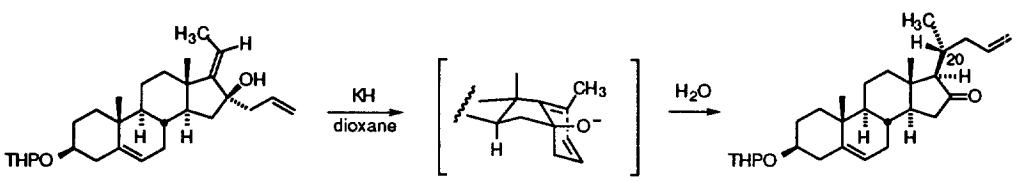
3. Preparation of 1,5-Dien-3-ols

The two most commonly utilized means for gaining access to oxy-Cope substrates involve the addition of vinyl organometallics to β,γ-unsaturated aldehydes or ketones and the condensation of allyl anions with conjugated carbonyl compounds. Both of these processes can bring into focus specific considerations of π-facial selectivity and diastereoselectivity. Neither of these factors comes into play during the conversion of the estratetraene aldehyde **2** into its sigmatropically reorganized counterpart **3**.[10] In this example, the aldehyde functionality is initially anchored on the α-face, such that rearrangement is necessarily restricted to that surface. The formation of a diastereomeric mixture of alcohols after vinylmagnesium bromide addition is of little consequence since both compounds subsequently converge to **3**.



2 **3**

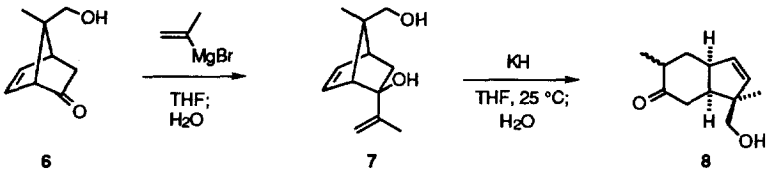
When the ketone carbonyl resides in a ring, control of the direction of nucleophilic capture becomes important. For **4**, the combination of allyl entry from the α-surface and neighboring double bond geometry is required for setting C-20 of the desmosterol side chain correctly as in **5**.[11]



4 **5**

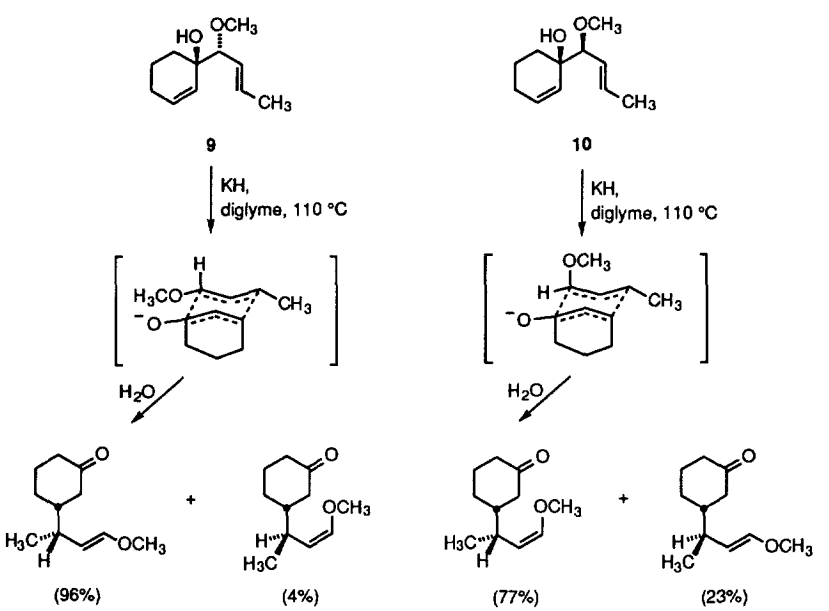
Steric control elements have often been utilized for guiding entry of the alkenyl anion, particularly in bicyclic ketones. In addition to the usual alkyl and aryl groups, steric shielding by hydroxy-substituted side chains as in **6** can be nicely accommodated.[12] In this example, the 2-propenyl Grignard reagent undergoes 1,2-

addition exclusively from the endo surface to deliver **7**. Only in this isomer are the π-bonds in sufficient proximity to participate in the [3,3] sigmatropic process, which takes place readily and efficiently (94%) at room temperature in tetrahydrofuran containing potassium hydride.

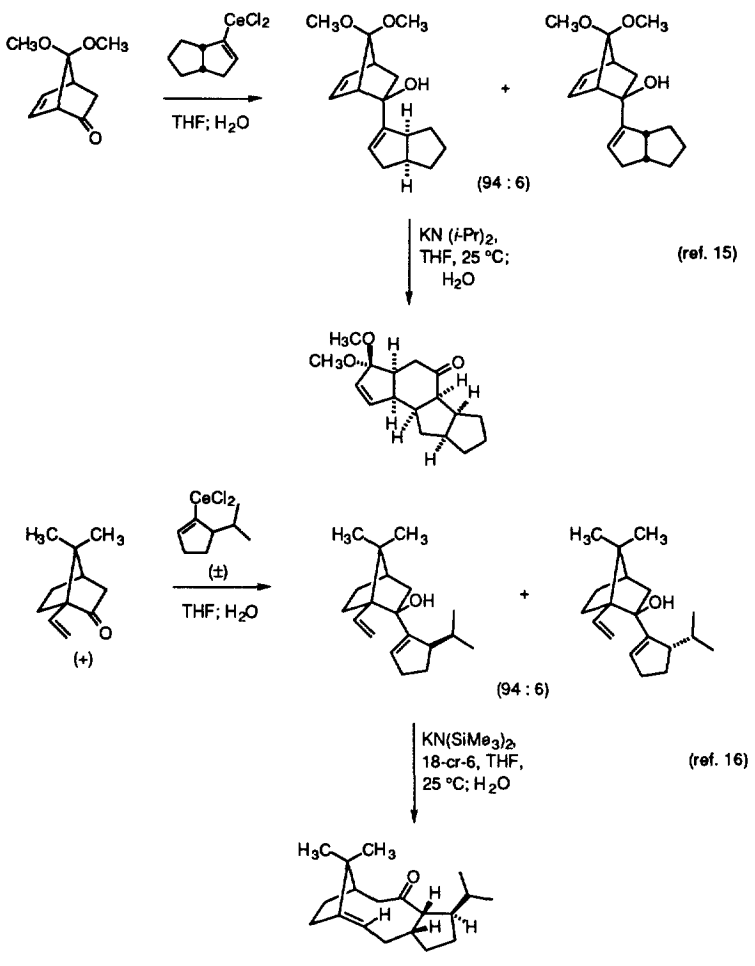


6 **7** **8**

Considerably less attention has been paid to the diastereoselective addition of substituted allylic or propargylic anions to ketones. In all of the reported examples, mixtures of carbinols result. These diastereomers must be separated in advance of the oxy-Cope step because of high-level chirality transfer during the rearrangement. Informative examples include **9** and **10**, both of which isomerize in concerted fashion predominately via chair-like transition states.[13] Both carbinols were heated with potassium hydride in diglyme to 110 °C for 24 h in order to complete the conversion to products. These rather elevated temperatures may be responsible for the 4% loss of stereocontrol observed for **9**. When the methoxy group is oriented β as in **10**, the associated chair-like transition state has this substituent necessarily projected in a pseudoaxial orientation, thereby destabilizing this arrangement and allowing 23% of the sigmatropic isomerization to proceed competitively by way of the boat-like option.

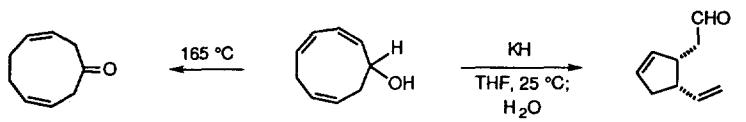


When nucleophilic capture of a chiral alkenyl anion by a chiral ketone is relegated exclusively to one prochiral face by suitable steric control, and a high level of diastereoselectivity operates, it becomes theoretically possible to produce predominantly a racemic carbinol of well defined stereochemistry. Further, the use of either reactant in optically pure form under these conditions can easily be adapted to kinetic resolution with formation of a single product.[14] As a direct consequence of recent studies, our understanding of the extent and direction of diastereoselection attainable in such processes has been considerably expanded.[15-24] The examples given below show that suitably selective recognition patterns can be developed between diverse reactants provided that one attack trajectory is strictly enforced. These two-step sequences enable one to elaborate relatively intricate carbocyclic networks with control over a significant number of stereogenic centers. Although the product ratios are not always heavily imbalanced, the technology remains highly utilitarian since chromatographic separation of the diastereomeric carbinols allows for independent rearrangement to stereoisomerically pure ketones.



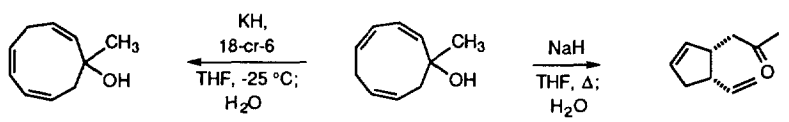
4. Rearrangement Conditions

Synthetic application of the oxy-Cope rearrangement can be implemented under purely thermal conditions or with anionic assistance. Although recourse is most often made to potassium alkoxide generation in the presence of 18-crown-6 in order to take advantage of the greatly reduced operational temperature, other reasons exist for proceeding in this direction. An understanding of several important kinetic interrelationships is helpful in making the proper decision from the outset. For example, thermal activation of **11** results in the exclusive operation of a [1,5] hydrogen migration to deliver **12**.[25] This facile reaction is completely overridden following generation of the potassium salt. Under the latter conditions, the [3,3] sigmatropic pathway is highly accelerated to the point where hydrogen shifting is not at all observed. The aldehyde **13** that now results has served as an important precursor to all of the primary prostaglandins[26,27] as well as to the algal sperm attractant multifidene.[28]



12 **11** **13**

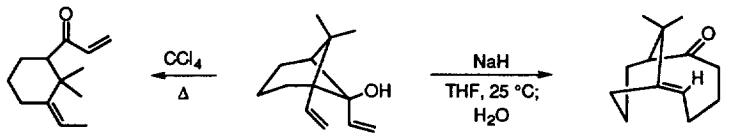
The methyl homolog **14** provides additional insight from a somewhat different perspective. With an excess of potassium hydride in dry tetrahydrofuran containing 18-crown-6, **14** is cleanly isomerized to **15** at -25 °C. On the other hand, heating **14** with sodium hydride in tetrahydrofuran results instead in conversion predominately into **16** (90%).[29,30] Evidently, the high basicity of the "naked" potassium alkoxide fosters facile intramolecular proton abstraction with double bond reorganization. The sodium salt is less basic, but still sufficiently anionic to promote the sigmatropic process.



15 **14** **16**

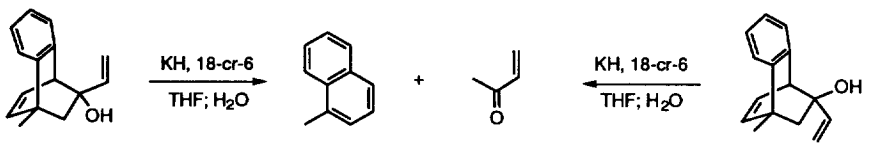
Another revealing example is the cyclobutanol **17**.[31] When simply heated in carbon tetrachloride at the reflux temperature, **17** undergoes quantitative conversion to **18** via a retro-ene reaction. This fragmentation is completely curtailed by alternative treatment with sodium hydride in tetrahydrofuran at room temperature. These anionic conditions deliver **19** in high yield.

Obviously, benzene rings are reluctant to enter into sigmatropic transformations because of the transient loss of aromatic character that must necessarily be incurred in the rate-determining step. As a consequence, it comes as no surprise that the bicyclo[2.2.2]octenol **20** prefers to undergo oxyanionically-promoted retro Diels-Alder fragmentation.[32] The finding that this conversion to 1-methylnaphthalene is independent of oxyanion



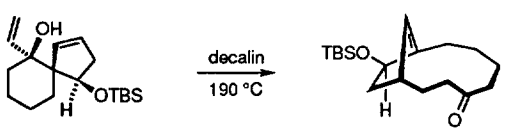
18 17 19

stereochemistry (see **21**) was unexpected. The less than ideal distance and angular relationship resident in **21** probably act in unison to slow the rate of the [3,3] sigmatropic change.



20 21

Cases have been reported in which anionic conditions need to be avoided because of extreme sensitivity of the enolate anion product. For **22**, submission to standard anion-accelerated conditions eventuates in rapid tar formation.[33] On the other hand, heating a solution of **22** in decalin at 190 °C for 9 hours results in efficient conversion to **23** (92%). For reactions which proceed sluggishly under neutral conditions, it is possible to achieve some kinetic acceleration by carrying out the process in a polar aprotic solvent. To date, N-methylpyrrolidinone[34] and dimethylformamide[35,36] have proven to be particularly serviceable in this capacity.



22 23

A variety of potassium bases have been utilized to promote the anionic oxy-Cope rearrangement, often in conjunction with 18-crown-6 to effect greater charge separation and maximization of the kinetic acceleration. Cation chelation is not necessary when alignment of the π bonds is very good and/or strain release accompanies the structural stage. When the latter condition applies, sodium hydride is adequate to the task. On occasion, it is advisable to remove impurities present in commercial potassium hydride. Pretreatment with iodine has been recommended.[37]

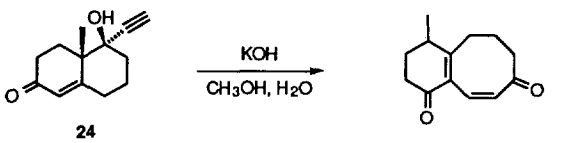
5. Thermodynamic Driving Force

The oxyanionic rate acceleration phenomenon, which has been observed in the gas phase[38] as well as in solution, stems primarily from a charge-induced weakening of the C(3)-C(4) bond.[39-42] Since the donor properties of an oxygen substituent increases substantially in the order OH → O^-M^+ → $O^-///M^+$, the

electrostatic effects of the metal ion and the degree of its separation from the alkoxide will impact directly on the extent of orbital destabilization in the reactant. Thermodynamic estimates of the maximum alkoxide substituent influence on the associated bond homolysis range from 13 to 17 kcal/mol. No change in mechanism appears to be involved. However, the available theoretical studies deemphasize the relevance of a transition state effect potentially arising from the incipient greater delocalization of negative charge in the enolate anion product relative to the alkoxide center in the starting material.

6. Alkyne, Allene, and Diene Participation

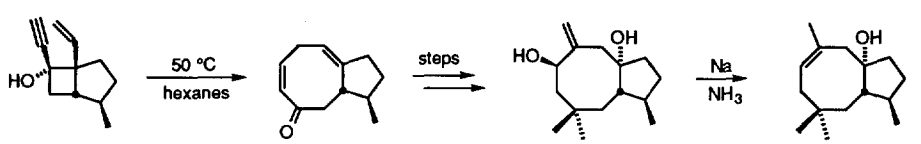
Although kinetic data is lacking, alkynyl and allenic groups appear to enter into oxy-Cope rearrangement as readily as their alkenyl counterparts. Alcohols **24** and **25** represent the earliest known examples of each type.[43,44] The possibility exists that **24** isomerizes by an alternative retro-Michael/Michael pathway.



24

25

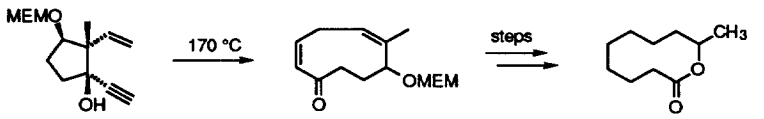
Where alkynols are involved, the [3,3] sigmatropic process is responsive to ring strain effects as reflected in the ease of thermal isomerization of **26**.[45] The net ring expansion associated with the conversion to **27** provided a convenient starting point for the rapid elaboration of poitediol (**28**) and dactylol (**29**).



26 **27** **28** **29**

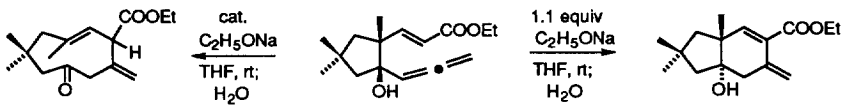
The less strained carbinol **30** requires a higher temperature for entering into the oxy-Cope rearrangement, but does so very efficiently at 170 °C in the absence of solvent.[46] The resulting *Z,Z*-dienone **31** can be transformed in a concise number of steps into (+)-phoracantholide I (**32**), the defensive substance of the Australian coleoptera.

If the rearrangement of allenic alcohol **33** is induced with 0.25 equivalent of sodium ethoxide in tetrahydrofuran at room temperature, it is possible to arrest rearrangement at the stage of the ring-expanded



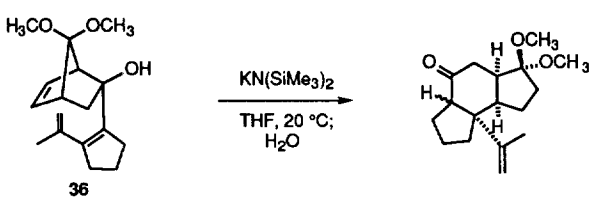
30 31 32

ketone **34**.[47] An increase in the amount of base to slightly more than the equimolar level results in transannular cyclization of the initially formed **34** to give **35**. The effect of the ring size in **33** on both steps has been investigated. While the anionic oxy-Cope step proceeds with equal readiness when the ring is six- or seven-membered, isomerization to give the transannular product is not seen in the latter instance.



34 33 35

Although the extension of one or both alkenyl chains into conjugated dienyl units opens up the possibility for alternative structural rearrangement, the anionic oxy-Cope option is adhered to in highly reliable fashion. For the singly extended examples **36** and **37**, oxyanion formation resulted in operation of the [3,3] sigmatropic reaction manifold.[48] In like fashion, the macroexpansion of **38** and related compounds[44-52] proceeds in a stepwise manner via enolates **39a** and **39b**. Since **39a** does not accumulate as the reaction proceeds, the second purely Cope rearrangement must be accelerated relative to the first. Trienone **40** has served as a precursor to (±)-muscone and (-)-(3Z)-cembrene A.



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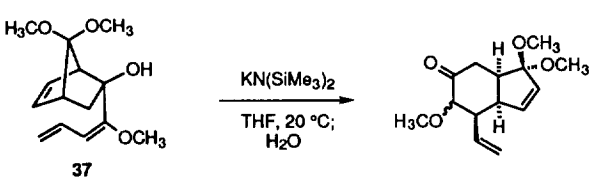

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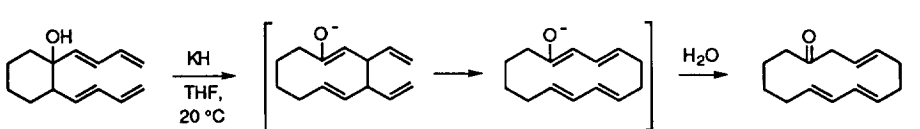
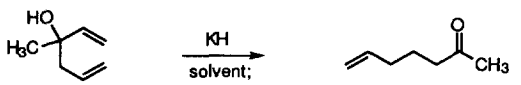


38 39a 39b 40

7. Transition State Considerations

3-Methyl-1,5-hexadien-3-ol (**41**) has been subjected to detailed study and shown to adhere to first-order kinetics while undergoing anionic oxy-Cope rearrangement under several sets of reaction conditions.[53] Its potassium salt in dimethyl sulfoxide rearranges 1000 times faster than when dissolved in tetrahydrofuran. The acceleration is comparable to that observed when at least one equivalent of 18-crown-6 is present in the tetrahydrofuran. Secondary deuterium isotope effects, determined at the bond-breaking and bond-making sites in these different media, give evidence of a highly dissociative transition state with substantial bond breaking at C(3)-C(4) and little bond making at C(1) and C(6), the allylic termini.



41

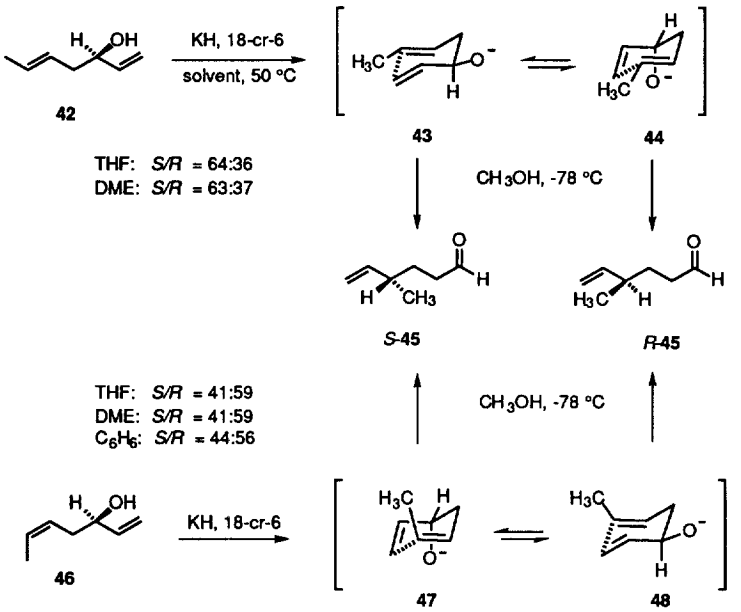
As a direct consequence of the involvement of highly ordered cyclic transition states, near- quantitative transmission of asymmetry is often realized. For the usual energetic reasons,[54] chair-like conformations are most commonly adopted unless the steric, electronic, and/or structural features of the reactant dictate otherwise. Indeed, boat-like alternatives are energetically accessible and their involvement does not arrest kinetically enhanced structural reorganization. For this reason, the reaction trajectory needs to be clearly appreciated, particularly in the more subtle examples, since product stereochemistry derives directly from transition state geometry.

A. Acyclic Substrates

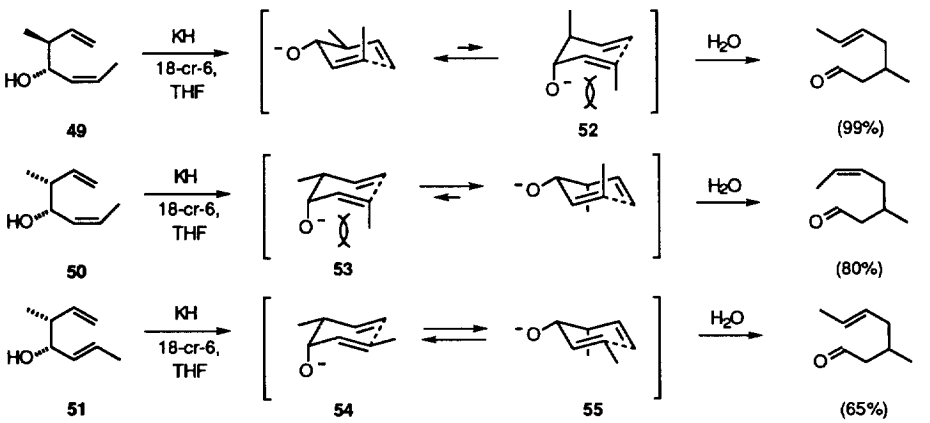
The stereochemistry associated with the anionic oxy-Cope rearrangement of genuinely acyclic systems has come under intense scrutiny in recent years.[55-61] In the least substituted examples typified by **42** and **46**, the efficiency of chirality transfer depends exclusively on the orientational preference of the alkoxide substituent. Thus, heating the geometrically and optically pure alkoxides of **42** and **46** at 50 °C in tetrahydrofuran, 1,2-dimethoxyethane, or benzene followed by quenching with methanol at -78 °C gave rise to the indicated proportions of (*S*)- and (*R*)-**45**.[57,58] The data show clearly that this *E*/*Z* pair of alcohols prefers to undergo the [3,3] sigmatropic process through that chair transition state having the oxyanion oriented pseudoequatorially as in **43** and **48**. However, the extent of this preference is rather slight, signaling that the pseudoaxial alternatives are virtually as accessible.

Improved diastereoselection can be realized by placing an alkyl substituent on the tetrahedral carbon adjacent to that carrying the hydroxyl group.[54,55] Alcohols **49-51** are particularly informative examples. In the first two instances, axial positioning of the oxido functionality induces 1,3-diaxial interactions that discourage operation of the pathways involving **52** and **53**. Where dienol **51** is concerned, the alkoxide and methyl groups are forced to vie for equatorial orientation. The 65:36 distribution of *E* and *Z* aldehydes requires that rearrangement proceed more readily through transition state **54**. The possibility exists that electronic factors

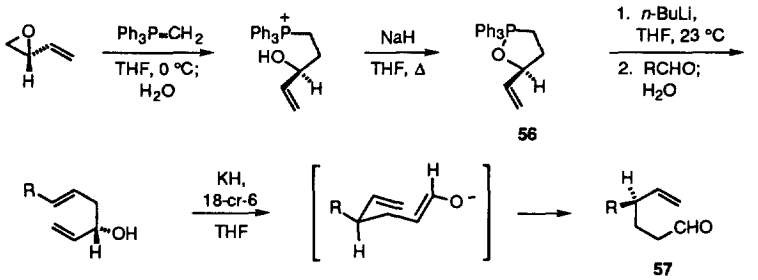
may contribute to the stabilization of axial oxyanion orientation.[59] If so, this effect is not especially significant and can be easily overridden.



The synthetic potential associated with the use of erythro dienols related to **49** has been demonstrated by the efficient preparation of precursors to (+)-furanal and (-)-antirhine.[60] In a different context, 1,2λ^5-oxaphospholanes, which are directly available by the reaction of methylenetriphenylphospholanes with epoxides, undergo Wittig olefination with good control of olefin geometry in the homoallyl alcohol product. The high *E* selectivity, rarely observed in related processes, nicely sets the stage for stereocontrolled oxy-Cope



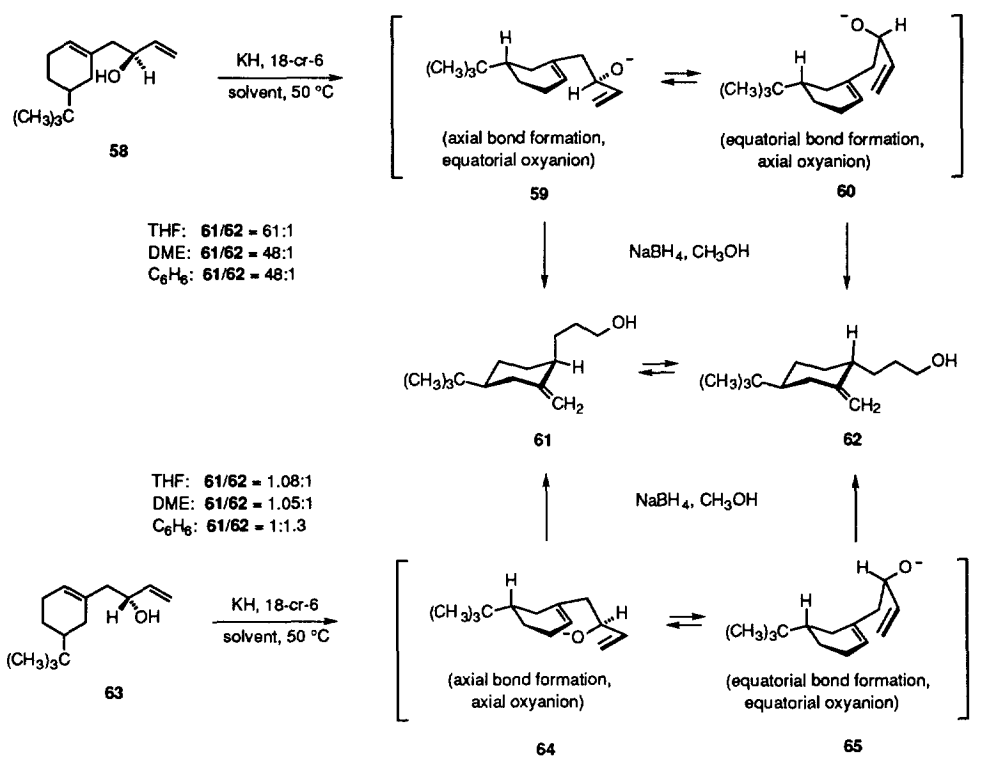
rearrangement.[62] The conversion of **56** to **57** constitutes a convenient method for replacing an aldehyde carbonyl with a difunctionalized carbon substituted with a vinyl group and a terminally oxygenated three-carbon chain.



Applications of the siloxy-Cope rearrangement to remote asymmetric induction have been reported.[61,63]

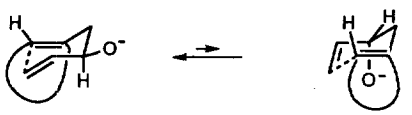
B. Cyclic Reactants

On the strength of Claisen rearrangement studies, the stereoelectronic preference for cyclohexenes to engage in axial bond formation during [3,3] sigmatropy is recognized to be in excess of 85%.[64] For the



stereoisomeric carbinols **58** and **63**, anionic oxy-Cope rearrangement with subsequent sodium borohydride reduction has shown that a change in the relative configuration of the alkoxide-substituted reaction center can have a significant impact on product distribution.[57,58] While **58** gives rise almost exclusively to **61**, the product partitioning observed for **63** is near unity. These findings reveal that the transition state geometry peculiar to **59**, which involves axial bond formation and equatorial disposition of the oxido anion, is substantially more conducive than **60** to operation of the sigmatropic reorganization. The involvement of **60** would necessitate axial projection of the oxyanion with bond formation from the equatorial surface. For **63**, the energetic costs of rearranging either by way of **64** (axial bonding, axial oxyanion) or **65** (equatorial bonding, equatorial oxyanion) are remarkably equitable irrespective of solvent.

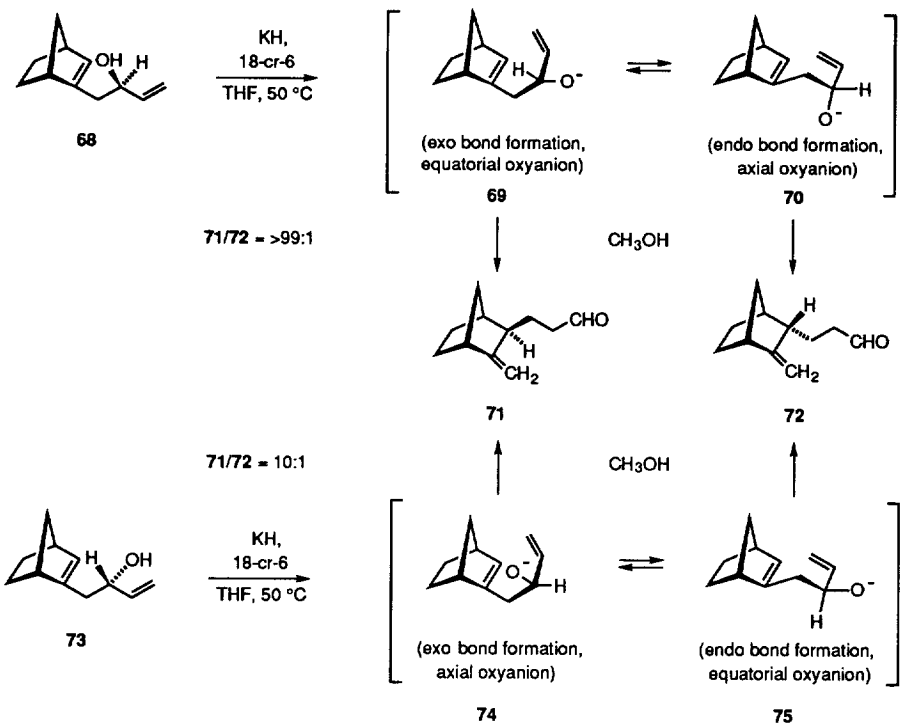
This contrasting stereoselectivity appears to have its origins in the trisubstituted nature of the homoallylic double bond. The general examples of **66** and **67** show that under these circumstances axial projection of the oxyanion introduces an important 1,3-steric interaction not present in acyclic systems. This added compression can be expected to impact on reaction stereoselectivity irrespective of the precise nature of the ring. The approximately equal partitioning between **64** and **65** likely signifies that the 1,3-diaxial interaction perpetrated in **64** is closely mirrored by the energetic disadvantages associated with equatorial C-C bonding to the cyclohexene ring.



66 **67**

The entire situation is compounded in its complexity when attachment to the π-bond internal to the ring is limited by stereoelectronic or steric factors. The response of norbornenyl derivatives **68** and **73** is illustrative of these newly incorporated factors.[57,58] The major aldehyde in both examples is **71**. As before, the product distributions are modulated by the steric demands of the oxido functionality. Of the four possible chair-like transition state structures, **69** certainly represents the most favorable energetic situation. In this instance, the equatorial orientation of the oxyanion works in cooperation with sterically favored exo bond formation. For comparison, exo linkage of the π termini in **74** requires axial projection of the oxyanion. As a consequence, the involvement of **74** is rendered sufficiently energy demanding to allow **75** to compete to the 5-10% level. Evidently the driving force for exo bond formation is sufficiently strong that the orientation of the oxyanion cannot easily override its importance.

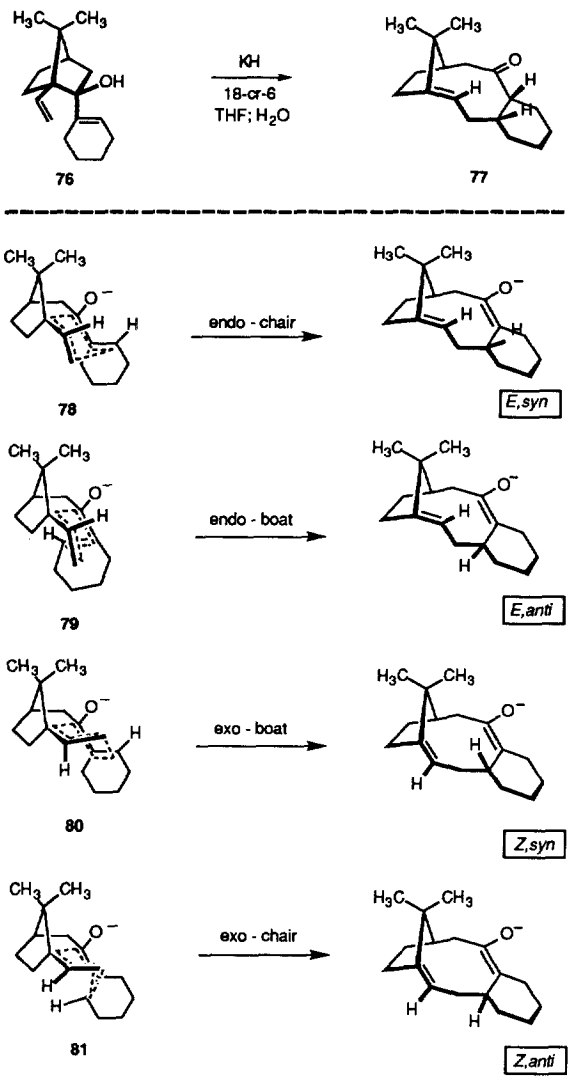
Systematic investigation has been made of the degree to which norbornane frameworks are capable of exerting control over the outcome of oxy-Cope rearrangements in other structural arrangements. The alcohol **76**, for example, has the option of orienting its bridgehead vinyl substituent either in an endo or exo direction.[65] The cyclohexenyl ring in turn can accommodate either arrangement in a chair or boat fashion. An endo vinyl orientation would lead to an *E* bridgehead olefin geometry while the exo option correlates with a *Z* configuration as shown in **78-81**. The conformation adopted by the cyclohexene is necessarily transferred to the homoallylic ring juncture site. In actuality, the anionic oxy-Cope rearrangement of **76** occurs rapidly at room temperature



exclusively via the endo-chair transition state **78** to give **77** in high yield. As will be seen below, this process is entirely general. Higher levels of substitution of the carbinol do not bring on any evidence of mechanistic crossover.

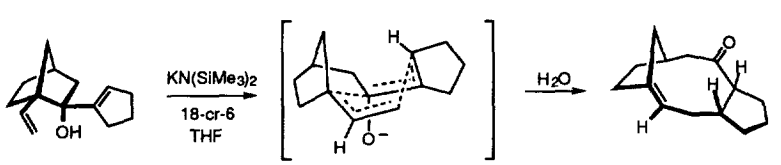
Structurally related *endo*-2-norbornanols likewise hold the option of undergoing the oxy-Cope rearrangement via four geometrically distinctive transition states.[66] In examples such as **82**, the exo-boat alternative of type **83** is selected by the large majority of substrates. Only when the electronic redistribution is slowed is a tendency to involve an exo-chair arrangement seen.

Other constructs are possible where the boat/chair topography issue has no direct stereochemical consequence. Two revealing examples are found in **85** and **87**.[35,36] When the double bonds involved are arranged trans as in **85**, only in the chair-boat-chair arrangement are they sufficiently proximate for bonding. On this basis, the expectation is that **85** will evolve into the *Z*-enol **86** and subsequently ketone **87**. This is indeed the case. When the vinyl substituent is α-oriented as in **88**, the sigmatropic event is likely to proceed via both **88A** and **88B**. Tautomerism in the pair of resulting enols **89** and **90** now leads to **91**! The important



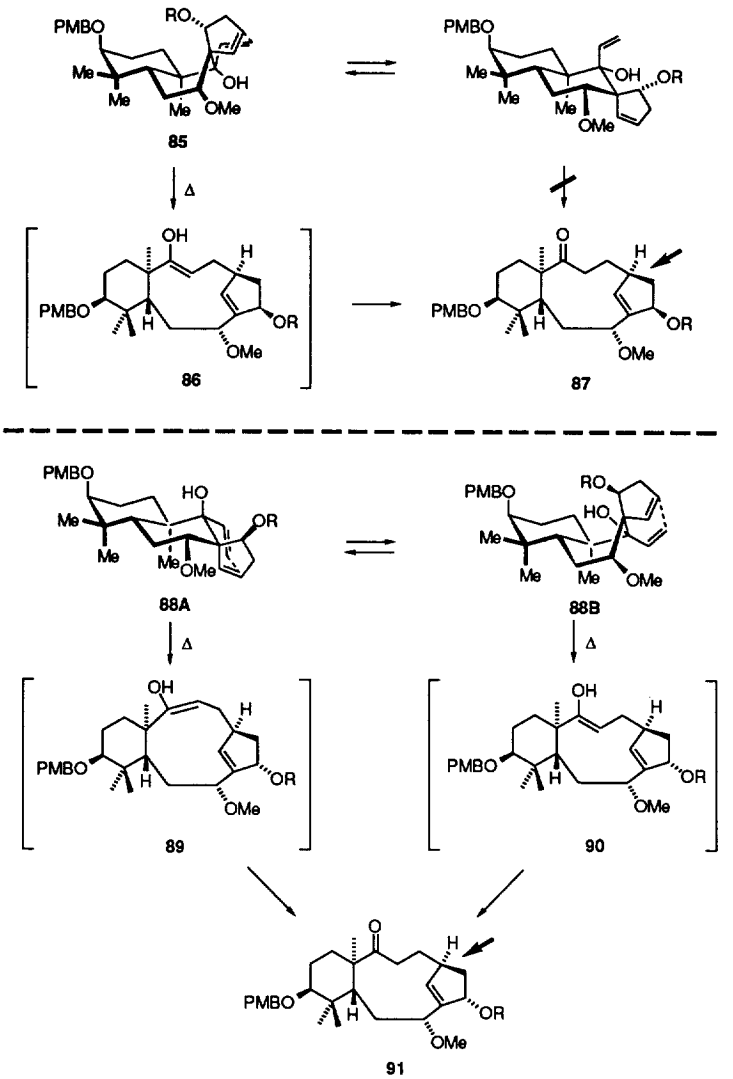
76 77 78 79 80 81

issue here is that the configuration of the newly formed bridgehead carbon in **87** and **91** is uniquely dependent on the configuration of the spirocyclic carbon in **85** and **88**.

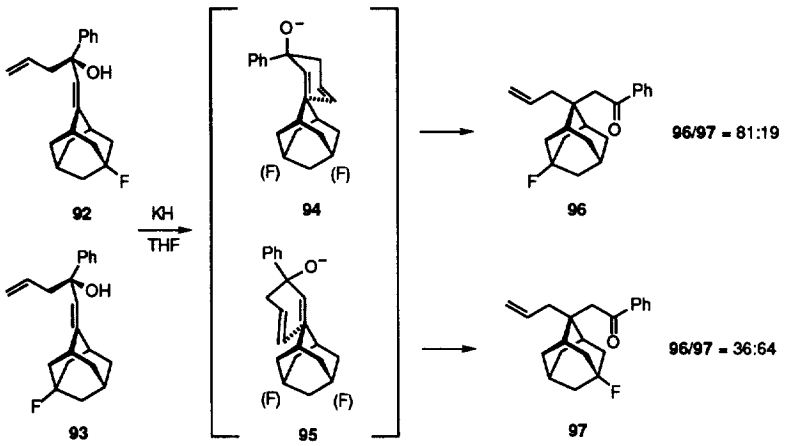


82 83 84

In order to probe the question of face selection at one π terminus during the oxy-Cope step, the fluoroadamantane alcohols **92** and **93** have been individually subjected to the action of potassium hydride in tetrahydrofuran.[67] At issue here is whether the electronic contributions of the halogen atom exert stereocontrol. The chair-like transition states available in either case are **94**, where the phenyl group is axial, and **95**, where it is equatorial. Consequently, steric factors would favor rearrangement via **94**, while the hyperconjugative effect



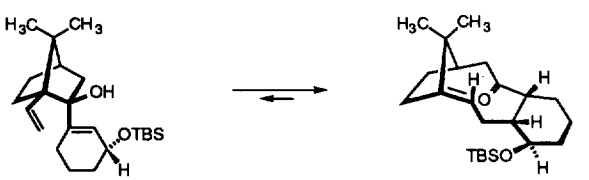
of the fluorine would prefer to induce bonding syn to itself. The resultant product distributions **96/97** of 81:19 and 36:64, respectively, indicate that syn approach is favored by a factor of 1.4. This finding has been construed to be compatible with Cieplak's hyperconjugation model.[68]



C. Reversibility

An important characteristic of the oxy-Cope rearrangement is its strong thermodynamic driving force to proceed to product. Although the principle of microscopic reversibility requires that the process be reversible, this is only very rarely observed. This is because the conversion to enol and then ketone or to an enolate ion is accompanied by a reduction in energy content. Consequently, an observable equilibrium will be established only when the relative energies of the reaction components are brought more closely into balance.

In the only known example reported to date, the alcohol **98** and ketone **99** experience equilibration in refluxing toluene.[69] At this temperature, **99** is favored to the extent of 66%. No reversibility is encountered under anionic conditions.

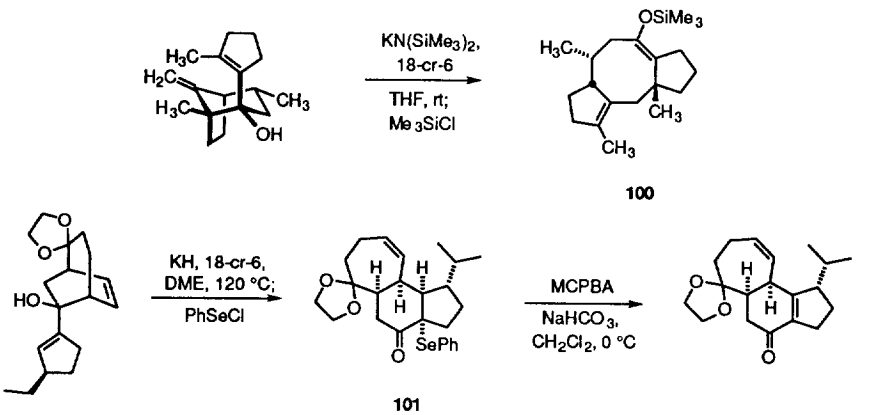


8. Tandem Processes

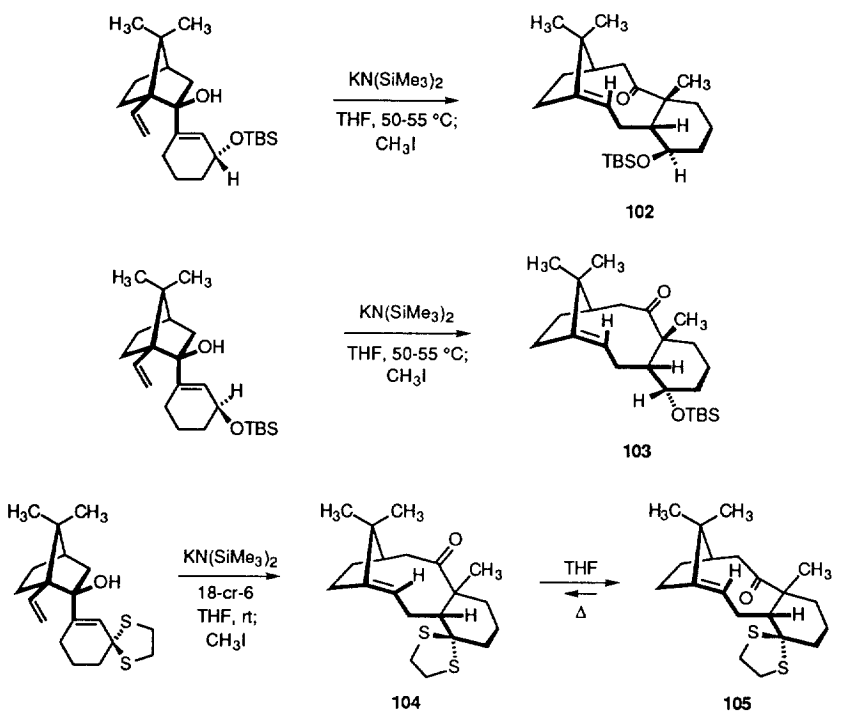
Direct linking of the oxy-Cope rearrangement to a second chemical event has greatly expanded its capacity for stereoselective molecular construction. Examples in which the [3,3] sigmatropic process is made to operate first have been known for a decade and have taken on considerable synthetic significance. Tandem reaction sequences having the oxy-Cope process in second position are of more recent vintage. More examples are certain to follow. Both reaction combinations are briefly discussed below.

A. Post-Sigmatropic Functionalization

For the most part, the anionic oxy-Cope arrangement delivers an enolate anion regiospecifically. When



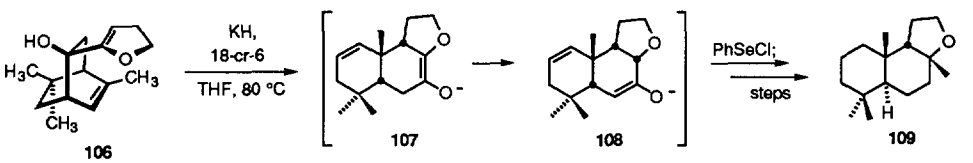
18-crown-6 is added for the purpose of accelerating the [3,3] shift, the enolate anion possesses high latent reactivity because the potassium ion continues to be strongly chelated. As a result, the initially generated intermediate can be readily captured at oxygen as in **100**[70] or at carbon as in **101**.[23] Phenylselenylation allows for convenient introduction of α,β-unsaturation.



Some of the possibilities opened up by *in situ* alkylation are reflected in the methylated ketones **102-104**. In the first two examples, the configuration of the *tert*-butyldimethylsilyloxy carbon is seen to control the specific conformation of the ketonic product.[71,72] β-Orientation of the OTBS group contributes thermodynamically to preferred adoption of the "carbonyl down" conformation. The "carbonyl up" geometry is more stable when the same substituent is derived from the *S*-carbinol. In cases where sulfur atoms are also present, enolate reactivity is sufficiently high to be dominant. This kinetic ordering allows, for example, the formation of **104** without concomitant *S*-methylation.[65] When heated in THF, atropisomerism to **105** is observed. Several atropselective oxy-Cope rearrangements are now known.

B. Enolate Equilibration

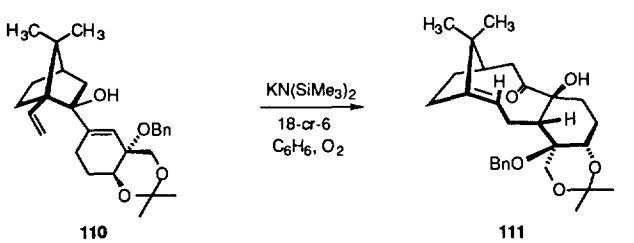
Should the initially formed enolate anion be electronically or sterically destabilized,[17] the emergence of enolate equilibration is sometimes observed. When these circumstances arise, it becomes possible to take advantage of the new locus of negative charge. An expedient means for synthesizing (-)-9-epi-ambrox (**109**) was based precisely on this principle.[73] The anionic oxy-Cope rearrangement of **106**, which necessarily must proceed via a boat-like transition state geometry, leads to **107**, which in turn experiences rapid conversion to **108**.



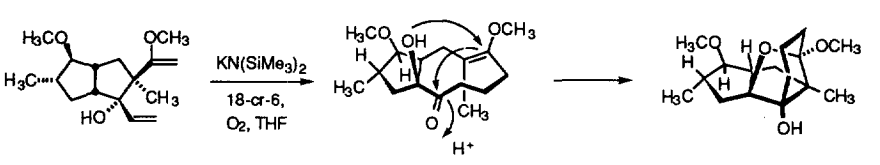
106 107 108 109

C. Enolate Oxygenation

The elevated reactivity of enolate anions generated by means of [3,3] sigmatropy allows for facile conversion to α-hydroxy ketones.[74] A recent application of this chemistry is exemplified by the formation of **111** from **110**.[22] As before, the locus of the newly introduced hydroxyl group depends on the regiochemistry



110 111

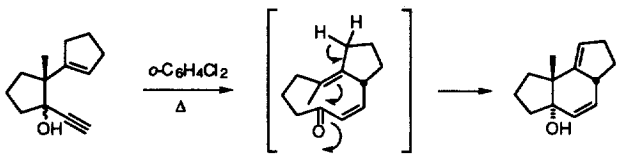


112 113

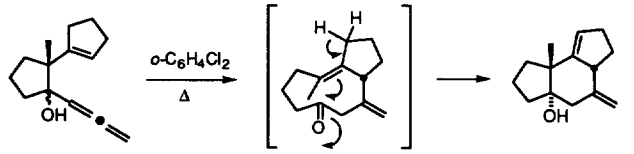
of enolate formation. The acid-catalyzed cyclization of **112** to give **113** illustrates one specific application of these oxidative transformations.

D. Ultimate Transannular Ring Closure

As a direct consequence of the tolerance of the oxy-Cope process to various functional groups, it has become commonplace to incorporate within the starting alcohols features that lend themselves to ensuing transannular reaction. Studies have been reported in which the ring closure occurs spontaneously under purely thermal conditions,[74,75] following the addition of base,[76-81] and by triggering the release of a reactive functional group in a separate chemical event.[82-85]

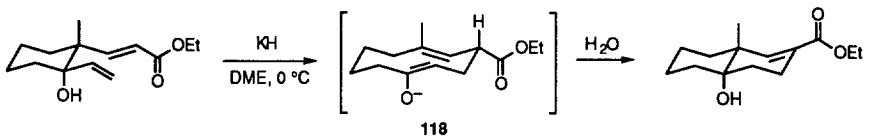


114 **115** **116**



117

Examples in the first category include refluxing **114** in *o*-dichlorobenzene under nitrogen, conditions which result in ring expansion to give **115** in advance of an ene-type prototropic migration and formation of **116**.[75] An entirely similar process occurs when both rings are six-membered[74] and when homologous allenes such as **117** are involved.



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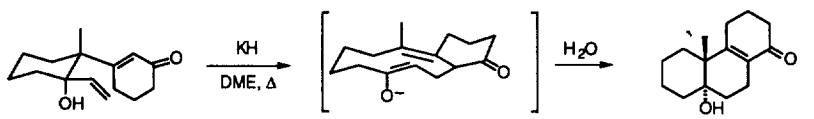

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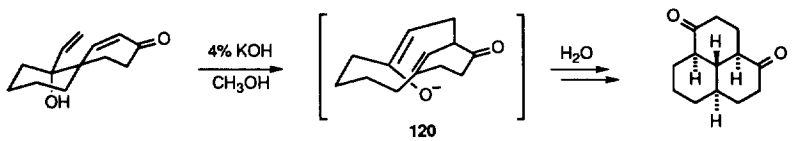
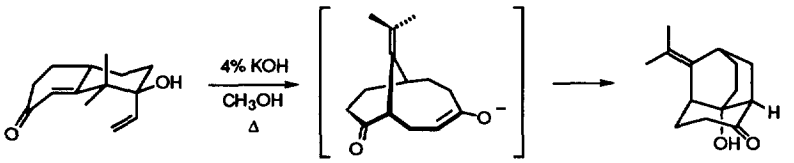


120

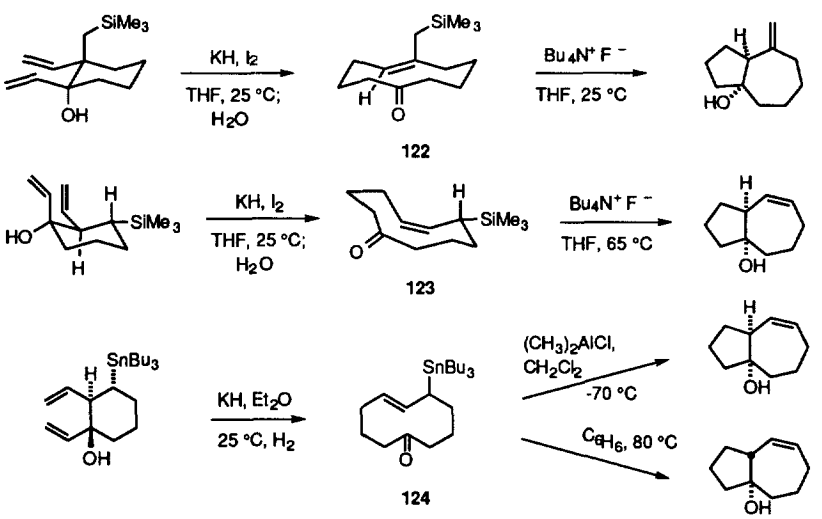
The proper positioning of acidifying carbonyl functionality and a crossover to anionic conditions are conducive to facilitating transannular ring closures. The carboethoxy group in **118** and the ketone carbonyl resident in both **119** and **120** illustrate some ingenious ways in which a variety of bi- and tricyclic ring systems can be rapidly assembled. In the various intermediates, proton transfer generates a new enolate or enone that is suitably stereoaligned for intramolecular nucleophilic capture of the nonconjugated carbonyl.

Orbital overlap control is also operational in **121**. In this instance, however, the end result is an aldol reaction.[81]



121

The strategic placement of a trimethylsilyl or tributylstannyl moiety in the starting carbinol allows for isolation of allylsilane or allylstannane intermediates such as **122-124** in good yield following anionic oxy-Cope rearrangement. These products can be independently engaged in intramolecular cyclization. The silanes require exposure to a fluoride ion source, and the more reactive stannanes are responsive to a variety of promoters. Remarkably, the stereochemistry of the ring closure of **124** can be controlled so as to deliver either the cis- or trans-fused ketones.[83]



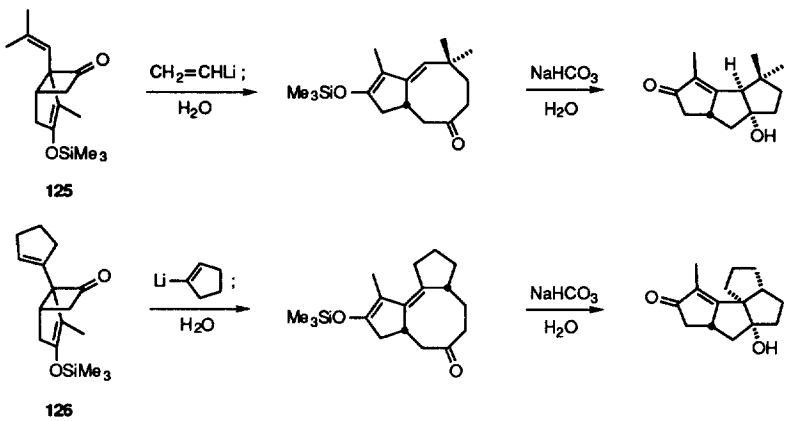
122

123

124

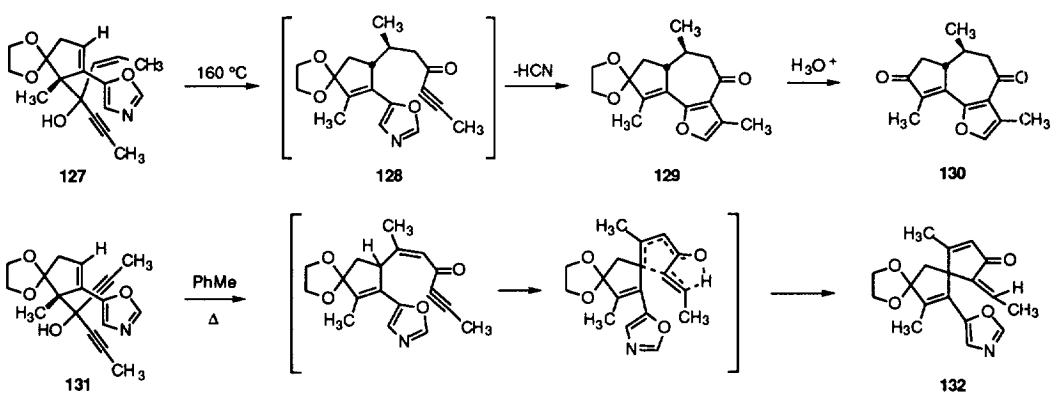
Bicycloheptenones **125**, **126** and their congeners add alkenyl and allenic anions from the exo surface to give cyclobutanoxides, which respond readily to oxy-Cope rearrangement because of the accompanying substantive strain release. The net ring expansion leads to silyl enol ethers amenable to hydrolysis in aqueous

sodium bicarbonate solution. Unleashing of the enolate anion in this manner results in transannular cyclization with the formation of polyquinane end-products.[84]



E. Cycloaddition and Electrocyclization Involving the Ketonic Product

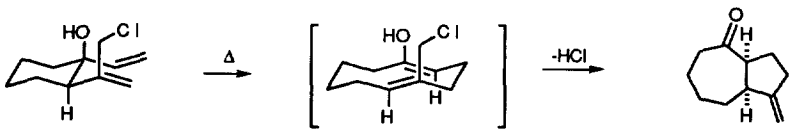
The regiochemical control assured by the geometrical constraints of the oxy-Cope rearrangement have been utilized to set the scenario for second-stage intramolecular cycloaddition or electrocyclization. An elegant example of ensuing Diels-Alder chemistry is given by **127**, which when heated to 160 °C proceeds via **128** to ketal **129**. Mild acidic hydrolysis of this product afforded gnididione (**130**).[85] Thermal activation of bis-acetylenic alcohol **131** in toluene afforded an *E* and *Z* enynone mixture, the enolization of which opens the door for ring closure with the formation of **132**.[86]



F. Second-Stage S_N' Rearrangement

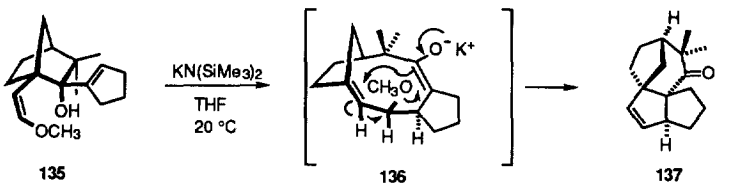
In this section, medium-ring enolate anions generated by the oxy-Cope process are shown to be capable of S_N' displacement of remote alkoxy groups when the proper stereoelectronic alignment is attainable. These fascinating reactions were perhaps foreshadowed by the thermal response of the chloro alcohol **133**. In this

example, arrival at the dienol is followed by an irreversible intramolecular alkylation with the liberation of HCl to give bicyclic ketone **134**.[87]

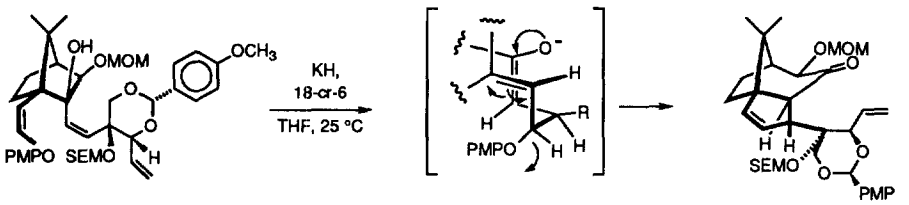


133 **134**

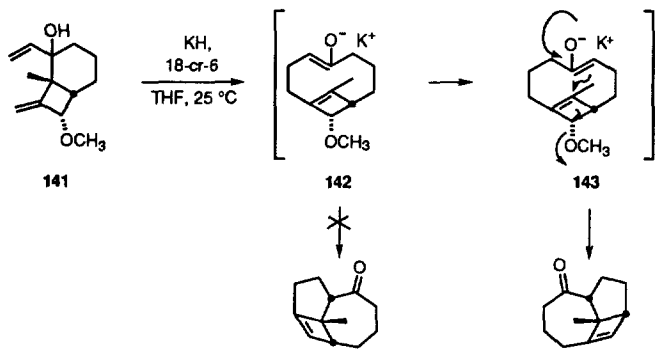
When anionic conditions are being utilized and a medium-ring enolate anion is generated, reaction can continue if the system finds it possible to eject an allylic alkoxy substituent via an intramolecular S_N pathway. As seen in the case of **135** and **138**, structural complexity is greatly enhanced during this maneuver. In these illustrated examples, **136** and **139** are smoothly transformed under mild conditions into **137** and **140**, respectively.[88,89] This methodology has been applied to the stereocontrolled elaboration of hydroazulenones.[90]



135 **136** **137**



138 **139** **140**

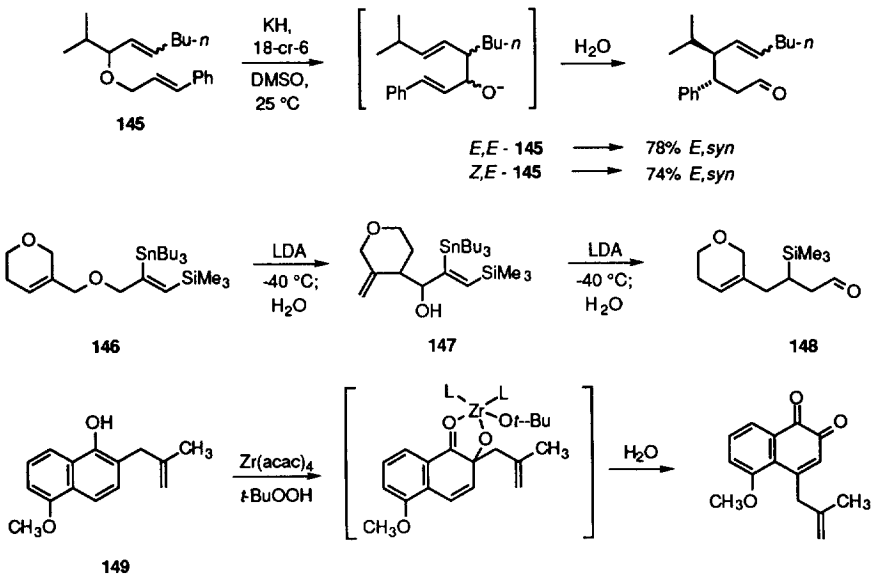


141 **142** **143** **144**

In yet another example, alcohol **141** is rapidly converted initially into **142**. This enolate anion does not find it possible to undergo displacement of methoxide ion because of the enormous buildup of strain that would be required.[88] When heated in tetrahydrofuran, however, enolate equilibration sets in, thereby allowing for the conversion of **143** to **144**.

G. The Oxy-Cope Process in Second Position

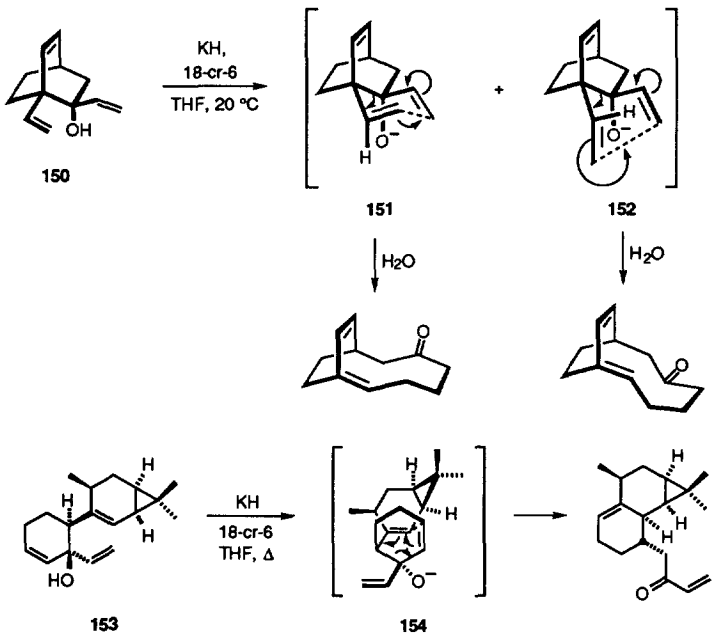
Although tandem Claisen-Cope rearrangements have been known for some time,[91] no example of a two-step reaction sequence involving oxy-Cope sigmatropy in the final stage appears to have been reported prior to 1993. At that time, the synthetic potential of interfacing [2,3]-Wittig and anionic oxy-Cope rearrangements for acyclic stereocontrol and transmission of asymmetry made its appearance.[60,92] A necessary requirement for success is the use of a base that is capable of effecting both transformations. Lithium and sodium bases appear not to be useful. Where **145** is concerned, recourse to potassium hydride and 18-crown-6 in dimethyl sulfoxide was required. Under these conditions, reaction proved rapid at room temperature and gave predominantly the *E,syn* product irrespective of the double bond geometry in **145**.[92] The silylstannyl-substituted diallyl ether **146** is more reactive, and under carefully controlled conditions proceeds via **147** to **148**.[93] 2-Allyl-1-naphthols exemplified by **149** have been observed to be susceptible to tandem zirconium-catalyzed oxidation and oxy-Cope rearrangement.[94a] The capacity for carrying out sequential vinylcyclopropylcarbene and anionic oxy-Cope rearrangements has also been reported.[94b]



H. Intramolecularly Competitive Processes

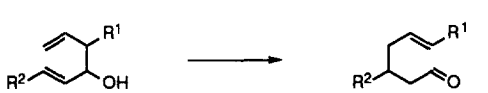
The degree to which anionically accelerated oxy-Cope rearrangements can operate competitively within the same molecule has scarcely received attention. Only two structural motifs have been evaluated to date.[95,96]

The *endo*-trienol **150** strongly prefers to engage its less substituted vinyl group in the sigmatropic process, with a modest preference for chair option **151** over the boat-like alternative **152**. In contrast, **153** skirts this option completely, very likely because the π-termini cannot overlap sufficiently well during approach to the less sterically hindered surface of the norcarene segment. Rather, transition state **154** is adopted because of minimal nonbonded interactions in this structural arrangement (compare the rearrangements of **168** and **169**).



9. Generation of Functionalized Alicyclic Compounds

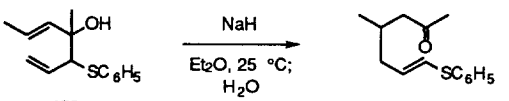
The stereochemical aspects of the anionic oxy-Cope rearrangement in open-chain systems have been discussed above. Another important factor is the effect of substituents at the several available sites on the overall ease of reaction. A particularly revealing series of compounds is comprised of the simple substrates **155a-d**.[97] In contrast to the alkyl derivatives **155a** and **155b**, which do not undergo [3,3] sigmatropy at a reasonable rate until their potassium salts are heated to 85 °C in 1,2-dimethoxyethane, the phenylthio substituted example **155c**



155a, $R^1 = CH_3$, $R^2 = H$
b, $R^1 = C_2H_5$, $R^2 = H$
c, $R^1 = SC_6H_5$, $R^2 = H$
d, $R^1 = CH_2{=}CH_2$, $R^2 = CH_3$

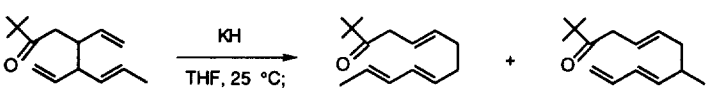
isomerizes smoothly at 20 °C in tetrahydrofuran as a consequence of the anion-stabilizing contribution of the sulfur atom. A methoxyl substituent exerts a rate-retarding effect.[2] When the R group is vinyl as in **155d**, bond breaking is likewise promoted in the transition state and reaction is accelerated. Its zinc salt is reported to be capable of isomerization in tetrahydrofuran.[98]

If cleavage side reactions (see below) gain importance, they can often be suppressed by decreasing the ionic character of the metal-alkoxide bond.[13a] For example, although the potassium salt of **156** undergoes fragmentation in tetrahydrofuran, rearrangement proceeds normally when catalysis is effected with sodium hydride in diethyl ether.



156

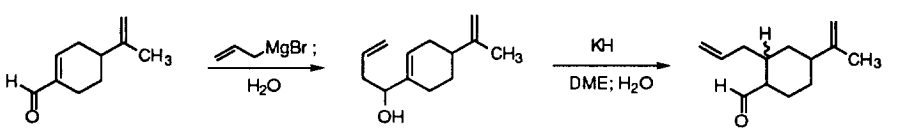
In another interesting example, the potassium enolate of ketone **157** has been shown to undergo anionically accelerated [3,3] sigmatropy along two competing pathways to provide near equal amounts of the isomeric trienones **158** and **159**.[52]



157 **158** (40%) **159** (33%)

10. Transfer Reactions on Cyclic Frameworks

Procedures have been developed that utilize the anionic oxy-Cope rearrangement for the migration of groups around the periphery of rings of different sizes and type. Previously cited applications of this strategy include **2**, **4**, **9**, **10**, **58**, **63**, **68**, and **73**. Two additional examples that reflect the relative ease of migrating alkenyl chains are given by **160**[99] and **161**.[100]



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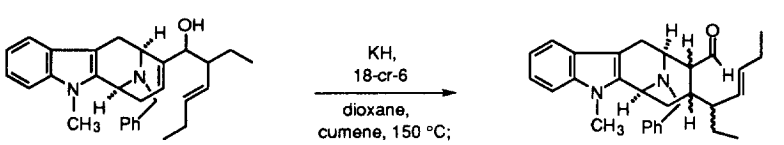
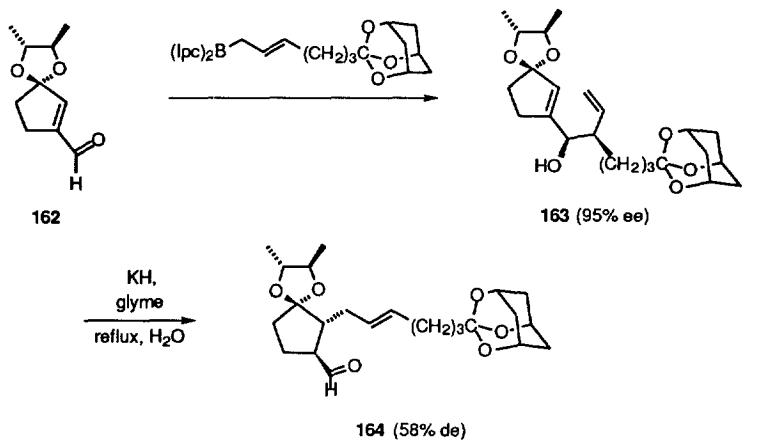


161

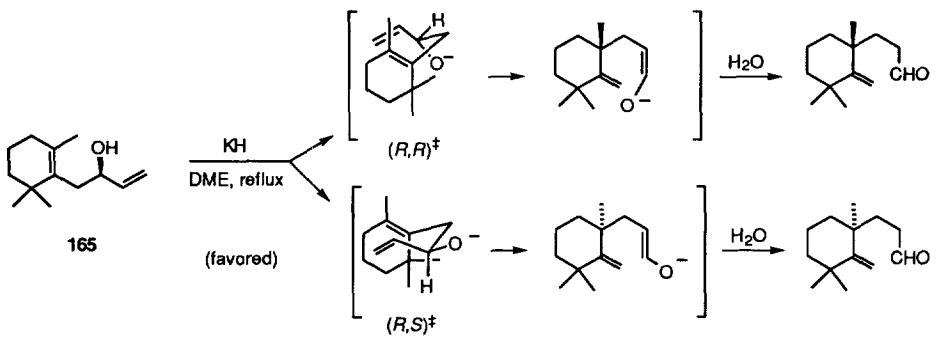
As a consequence of the preferred adoption of chair-like transition states, it is possible to achieve good levels of chirality transfer in such transformations. Adducts derived from the highly diastereoselective reaction of optically active allylboranes with α,β-unsaturated aldehydes, e.g., **163**, offer considerable promise.[101] Despite the fact that the anionic oxy-Cope rearrangement in this instance required refluxing in glyme for 40 hours, significant stereocontrol was observed as the side chain was introduced.



162 **163** (95% ee)

164 (58% de)

The subtle question of whether the oxyanionic bond prefers to be axial or equatorial in these situations has been addressed in the case of **165**.[102] Careful analysis of the product distribution has convincingly established the heavily predominant (>95:5) adoption by the potassium alkoxide of the (*R*,*S*) transition state **166**. Consequently, chirality transfer is highly efficient due to the strong preference for according equatorial status to the oxido substituent.

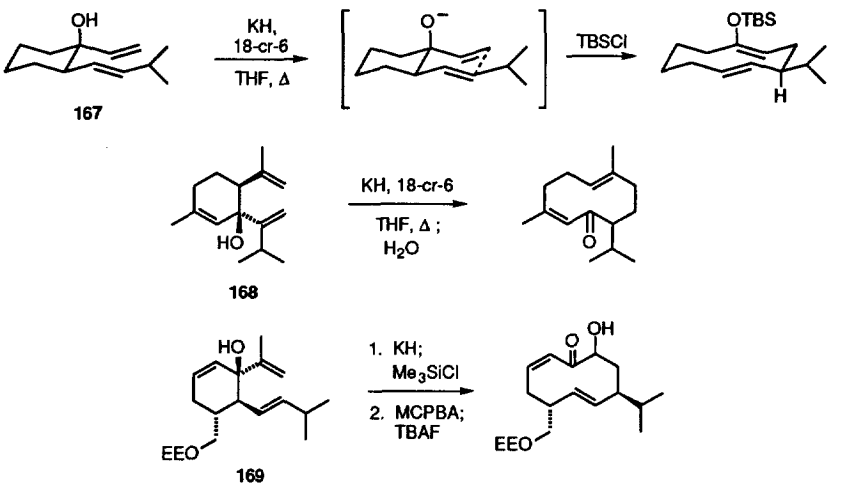


165 **166**

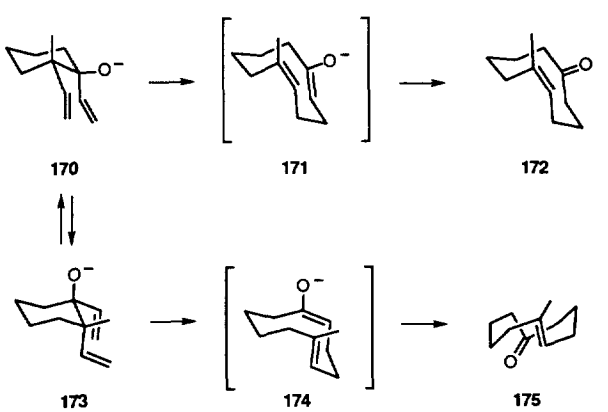
11. Elaboration of Mono- and Bicyclic Ketones

A. Ring Expansions Leading to Non-Annulated Medium-Sized Rings

1,2-Divinylcyclohexanol systems have been utilized in many syntheses of cyclodecenones. When the alkenyl substituents are initially arranged in a trans relationship as they are in **167-169**,[8,9,103,104] the chair-like transition state for the oxy-Cope process requires axial oxyanionic bond arrangement. The result is that a new *E* double bond is invariably generated. The synthesis of (-)-periplanone B has been achieved via this ring expansion by three research groups.[9,105,106] The successful crafting of a 3-oxygenated 13-norheliangolide from (-)-carvone has been similarly accomplished.[107]



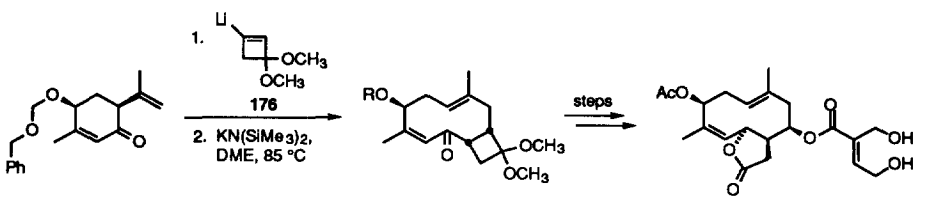
When the alkenyl groups are in a cis relationship, a situation not dissimilar from that detailed above for **165** comes into play. In effect, product stereochemistry is again conformation dependent. If the oxyanion adopts an equatorial orientation relative to the six-membered ring undergoing the sigmatropic transfer (but axial



to the established cyclohexane ring) as in **173**, an (*E*)-cyclodecene double bond will again be formed. On the other hand, if the oxyanion is projected axially as depicted in **170**, the resultant double bond geometry will be *Z*. Experimentally, only 3% of **172** is produced via **171**.[108] Clearly the alkoxide finds it kinetically preferable to undergo bond relocation when the oxido substituent is equatorial. This phenomenon should be viewed as axiomatic at this point.

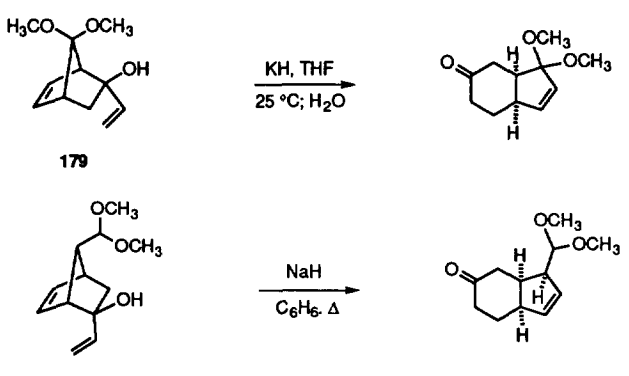
B. Construction of Bicyclic Frameworks

If a cycloalkenyl anion is utilized in examples related to **167-169**, the stage is set for direct conversion to annulated medium-ring ketones. An imaginative application of this chemistry is illustrated for the lithiocyclobutene **176**.[109] The resulting trans divinyl alcohol adopts the usual chair-like transition state geometry and rearranges to give **177**, which has served as a suitable precursor to eucannabinolide (**178**).

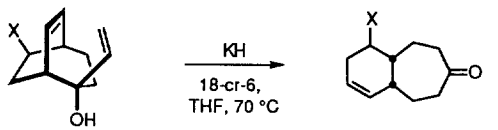


177 178

A wide variety of fused bicyclic ring systems are readily available by proper adaptation of the anionic oxy-Cope rearrangement. Among the more popular classes of starting materials are *endo*-vinylnorbornenols already exemplified herein by **7**, **36**, **37**, **76**, and **98**. In this setting, the ring strain inherent to the bicyclo[2.2.1]heptane moiety is released upon arrival at the transition state, a consequence of which is rapid reaction at low temperature. As reflected in **179**[110] and the other representative cases (e.g., **180**[111]), the tolerance of the rearrangement to several types of substituents allows for the preparation of highly functionalized products.

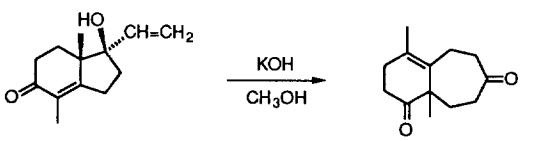


Enlargement of the bicyclic alcohol to the [2.2.2]octenyl level as in **1** and **150** does not have a qualitatively significant effect on the rate of the [3,3] sigmatropic process, whereas further increases in bridge size do incur appreciable kinetic retardation as reflected in the production of **101**. In other examples, alcohols **181a** and **181b** are recognized to possess the ability to undergo the oxyanion Cope transposition, but do so at a convenient rate only at 70 °C.[112]



181a, X = *n*-BuO
b, X = *n*-BuS

A widely studied variant is that founded on the utilization of a bicyclic enone scaffold having the second double bond external to an adjoining ring. Examples include **182**[113] and **183**.[114] Although the possibility exists that these isomerizations may proceed by an alternative fragmentation-recombination pathway,[115] recent studies involving optically active substrates suggest that the concerted sigmatropic process is adopted under specific conditions.[116]



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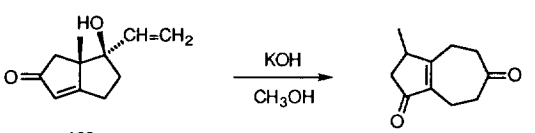
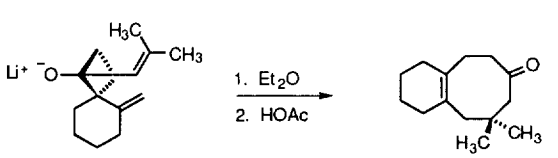


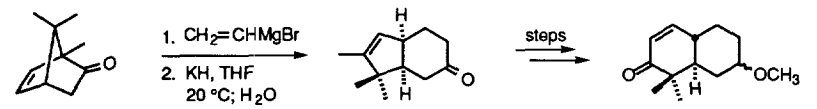
183

When spirocyclic cyclobutanoxides are involved and the β,γ-double bond is exocyclic to the adjoining ring as in **184**, the oxy-Cope rearrangement operates with such facility that isolation of the intermediate alcohols is often not possible.[117] This reduction in activation energy has been attributed to the rigid *s-cis* boat-like orientation of the double bonds.

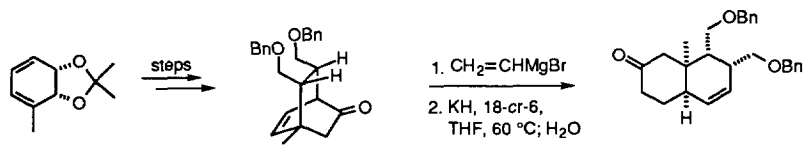


184

While the earlier investigations focused primarily on the structural limitations and stereochemistry of these reactions, more recent reports have stressed applications to natural products synthesis. Examples include the conversion of 5,6-dehydrocamphor (**185**) to the terpenoid intermediate **186**,[118] the preparation of enantiopure *cis*-decalins such as **187** from microbially-derived *cis*-1,2-dihydrocatechols,[119] enantioselective construction of the 5,11-fused framework of dolabellane diterpenes as represented by **188**,[120] arrival at functionalized bicyclo[5.3.1]undecanes (e.g., **189**) related to taxol and vinigrol,[121] and stereoselective syntheses of the alleged *cis*-clerodane acid **190**[122] and the decahydroquinoline alkaloid **191**.[123]



185 186



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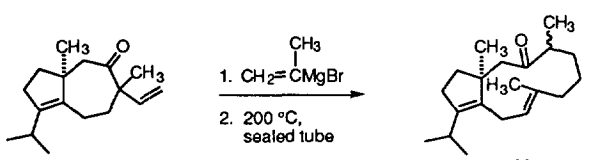

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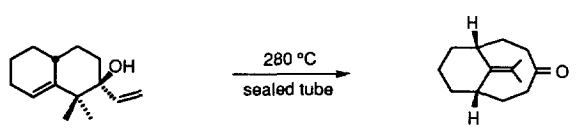

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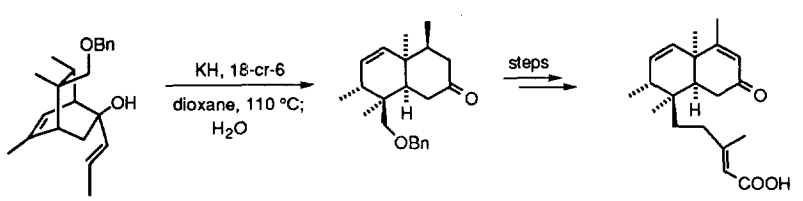

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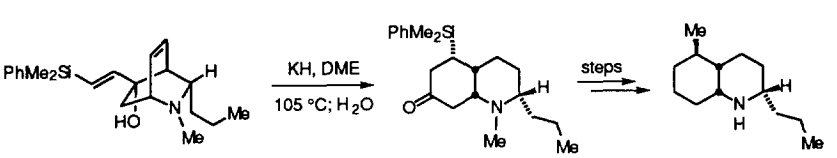


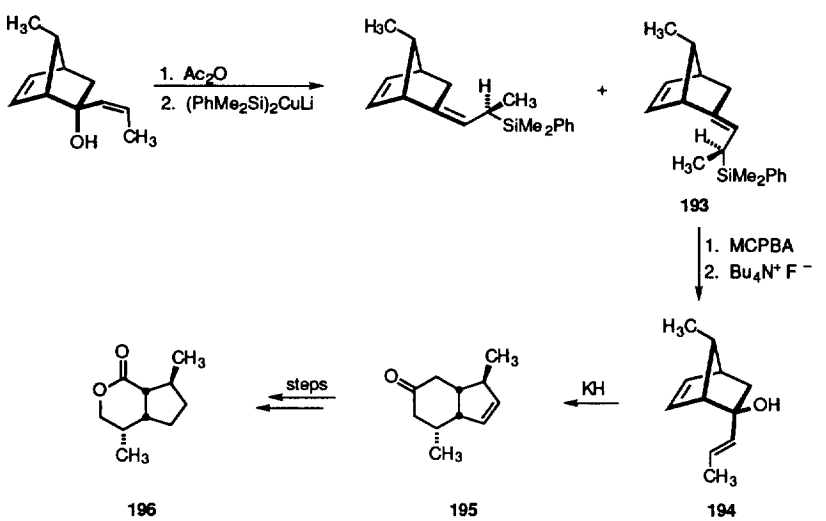
191

C. Altering Substrate Stereochemistry

The 1,2-addition of alkenyl anions to β,γ-unsaturated ketones operates under kinetic control. The face selectivity of the attack is most often dictated by steric factors. For 2-norbornenones that lack syn C-7 substitution, exo bonding is the norm. When this occurs as in **192**, the double bonds are not proximal and anionic sigmatropy is not possible. Two protocols have been developed to remedy this state of affairs. The first utilizes a [2,3] sulfenate-sulfoxide rearrangement cycle.[124] Once the unsaturated sulfoxide is produced, reversal of the process now orients the hydroxyl group exo with concomitant repositioning of the vinyl substituent nearby to the internal olefinic center.

192

The second alternative is based on a highly stereocontrolled allylsilane epoxidation.[125] The smooth production of **194** from **193** allows for the subsequent formation of bicyclic ketone **195** from which dihydronepetalactone (**196**) was synthesized.

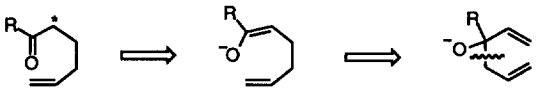


196 **195** **194**

12. Access to Bridgehead Olefinic Systems

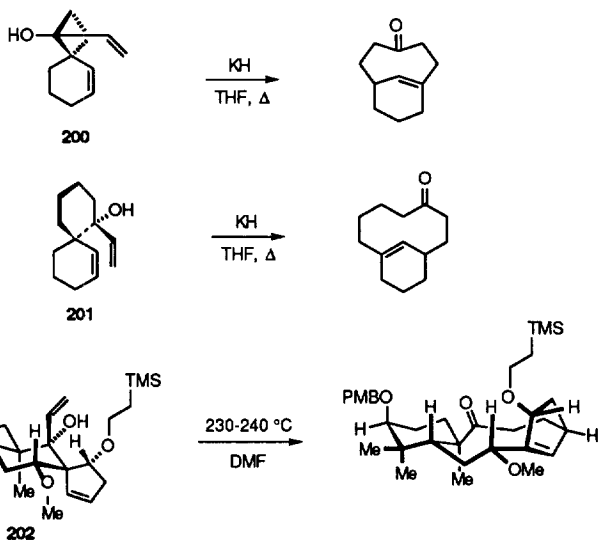
Retrosynthetic analysis based on the anionic oxy-Cope transform necessarily involves a direct link between enolate anion **198** and alkoxide **199**. Since the protonation of **198** leads ultimately to enone **197**, the

requisite conceptual perception for proper synthetic adaptation of this protocol is to work backward from **197** with enolization at the asterisked carbon as the key focal point.

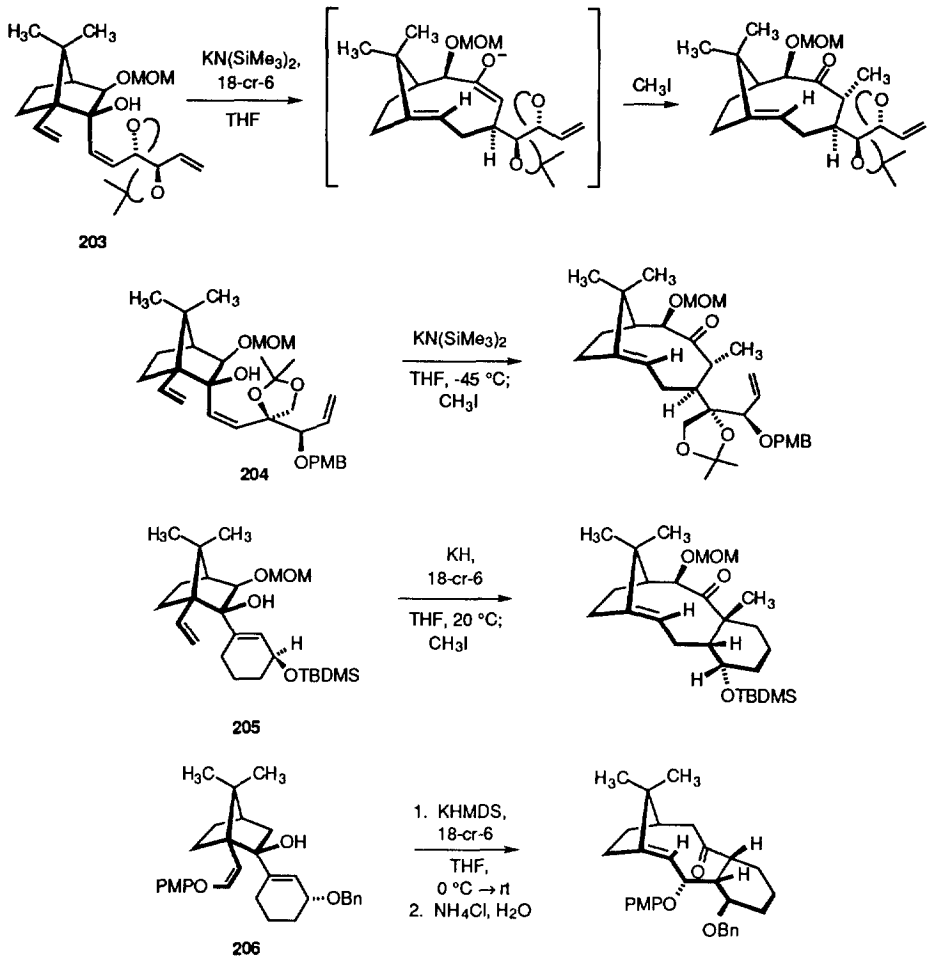


197 **198** **199**

The capacity of this transposition for positioning the **197** double bond at a bridgehead site is unrivaled. The structural requirement conducive to this end result is simply the exocyclic - endocyclic positioning of the olefinic centers resident in **199** into two spiro-conjoined rings within proper bonding distance. Examples **200** and **201** demonstrate the feasibility of incorporating the carbonyl group in the larger bridge and the double bond in the molecular interior.[117,126,127] The spirocyclic motif has been extended to larger (e.g., **22**) and more complex alcohols such as **202** with equal success.[35,36]

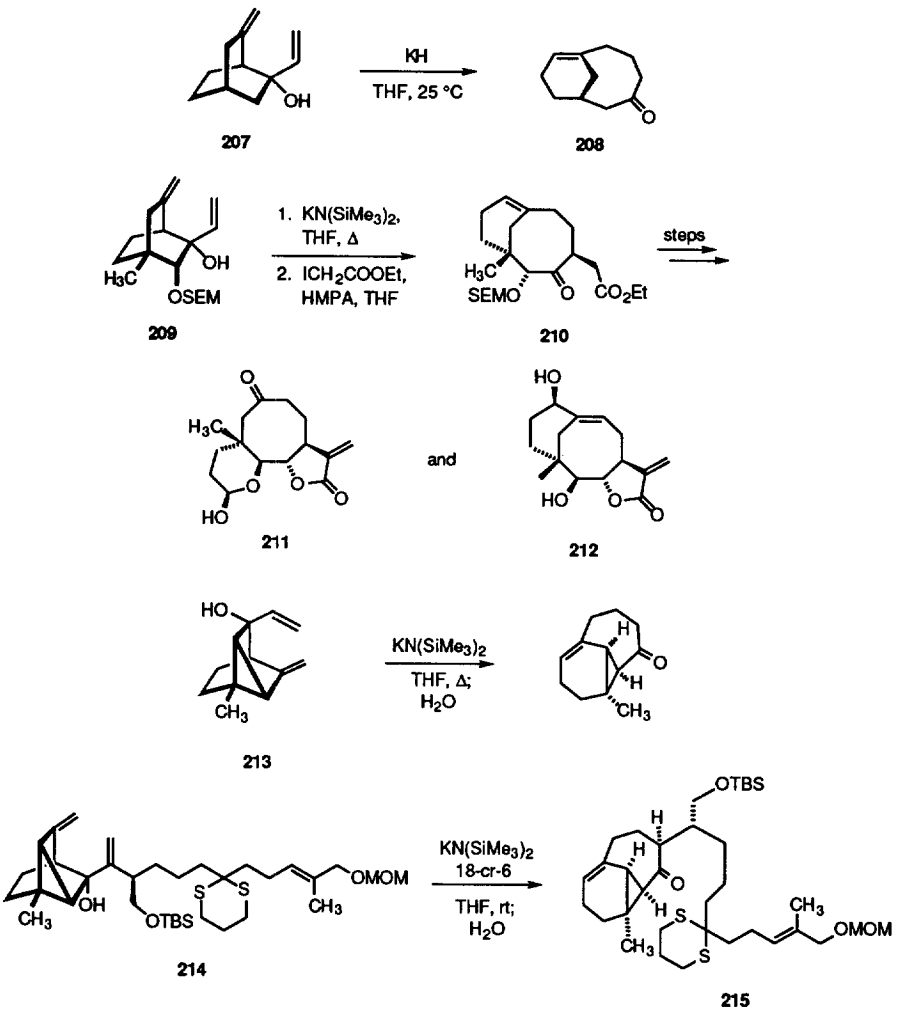


More highly substituted analogs of **76** and **82** have been intensively explored as possible precursors to taxol and taxusin.[128] In neither the exo nor the endo series does the presence of additional functional groups alter the transition state alignment adopted by the parent alcohols. As a consequence, increased transmission of stereochemical information is reliably made possible as in **203-206**.[129-133] Since conformational mobility within the initially formed enolate anions is somewhat restricted, it becomes possible to bring about stereocontrolled α-alkylation after the sigmatropic reorganization. As a result, the entire backside of taxol's B-ring can be assembled in a single step. In vinyl ethers represented by **206**, the *E* or *Z* geometry of the oxygenated double bond is intimately linked to the configuration of the benzyloxy-substituted carbon atom in the product.



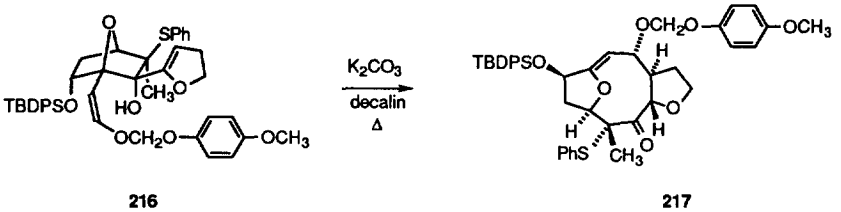
The conversion of **207** to **208** represents another variant that has found considerable utility.[134] Example **209** has been developed for obtaining **210** en route to the stereocontrolled construction of vulgarolide (**211**) and deoxocrispolide (**212**).[135,136]

Owing to the increased conformational rigidity present in tricyclo[3.2.1.$0^{2,7}$]octan-6-ols such as **213**, compounds of this type are quite amenable to [3,3] sigmatropic rearrangement.[137] The high reactivity of the more extensively functionalized counterpart **214** serves as an indicator that ponderal effects play no significant adverse role in these processes.[20,21] Products such as **215** have been evaluated as possible precursors to cerorubenic acid-III.

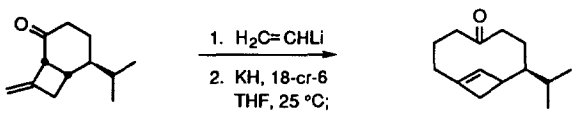


The carbinol **216** represents a reactant that is highly constrained by steric factors. Nonetheless, thermal oxy-Cope rearrangement proceeds rather well to deliver **217** in 61% yield.[138]

Methylenecyclobutanes have proven to be serviceable components in related oxyanionic processes. Since ketones such as **218** are conveniently prepared by the [2+2] photoaddition of allene to 2-cycloalkenones, strained bridgehead olefins represented by **219** can be obtained with minimal effort.[138-141] Thermolysis of **219** and its congeners proceeds with conrotatory ring opening and formation of medium-ring dienes. These conjugated systems have served as synthetic precursors to germacrene D and periplanone B.

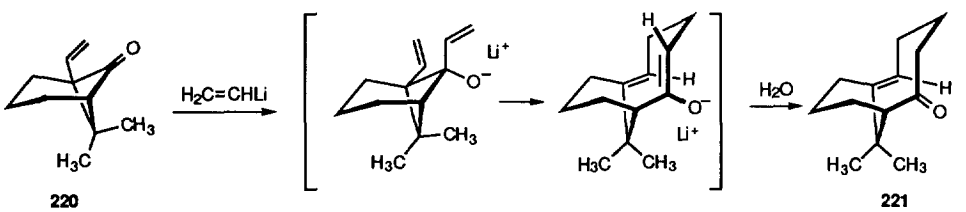


216 217

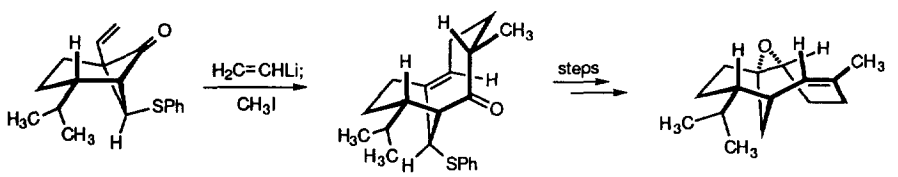


218 219

The 1-vinylbicyclo[3.1.1]heptan-6-one **220** and close relatives thereof such as **222** add alkenyl anions exclusively from the less hindered carbonyl π-face to give divinyl alkoxides that undergo oxy-Cope rearrangement spontaneously through a chair-like transition state.[31,142-145] The geometry of the isolated double bond is thereby fixed. The regiospecifically generated enolate can be protonated or alkylated. While **221** features the AB ring system of taxol, **223** has served as a key intermediate in a synthesis of (-)-salsolene oxide (**224**).[144]



220 221

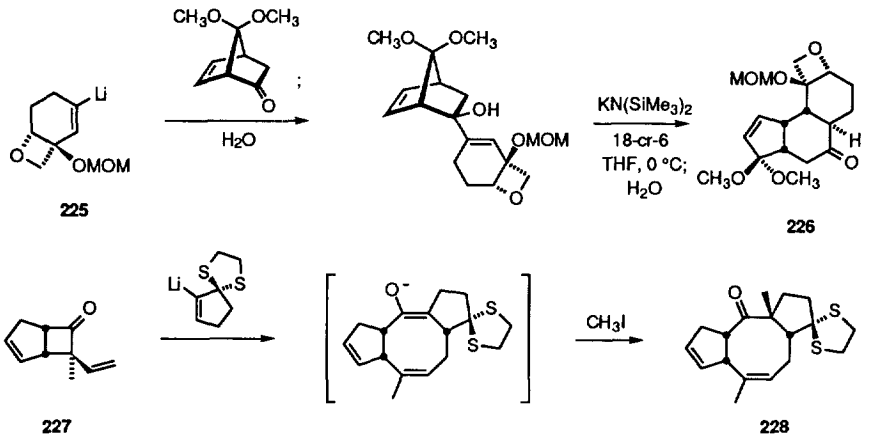


222 223 224

13. Stereocontrolled Construction of Polycyclic Networks

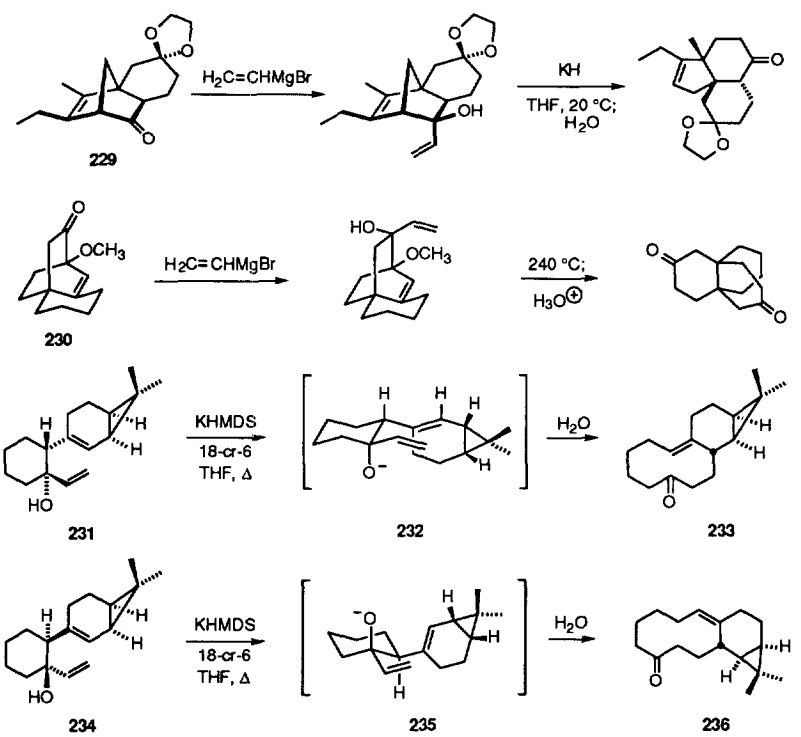
In most cases, the replacement of alkenyl anions by cycloalkenyl anions in the convergent coupling step utilized for preparing most oxy-Cope substrates lends itself reliably to substantial enhancements in the structural

complexity of the rearrangement products. The use of **225** to form **226**, and of **227** to generate **228** are instructive examples.[22,145]



225 **226** **227** **228**

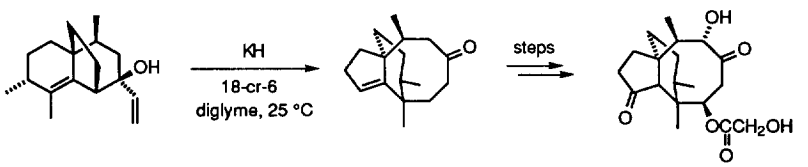
In other settings such as **229**[146] and **230**,[147] the structural features of the starting ketones contribute maximally to product complexity. One must always be cognizant of the transition state geometries being adopted



229 **230** **231** **232** **233** **234** **235** **236**

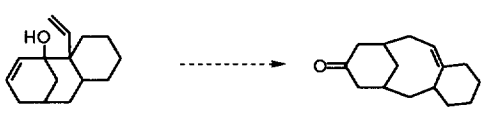
when more than one alternative is potentially available. Such concerns are nicely illustrated by **231**, which is converted to **233** via the chair-like transition state **232**, and **234**, the rearrangement trajectory for which is boat-like as in **235** and consequently leads to **236**.[90,148] The specific orientation present in **235** is forced on the system because of the requirement to approach the vinylcyclopropane from the less hindered direction.

The primary challenge underlying an efficient construction of pleuromutilin (**239**) has been met by the stereocontrolled intermediate generation of **238** via the sterically demanding oxy-anionic rearrangement of **237**.[149] Despite β,β-disubstitution in the homoallylic double bond, a chair-like transition state geometry is smoothly adopted by **237** to afford **238** in 99% yield.



237 **238** **239**

Computer-based calculations built around the oxy-Cope functionality transform, *viz.* **199** → **197**, have offered a number of yet untested options for possible access to diterpenoids of the taxane family.[150] Three of the more intriguing suggestions are **240-242**.



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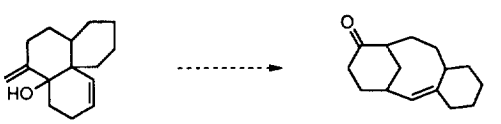

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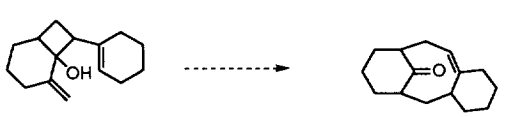
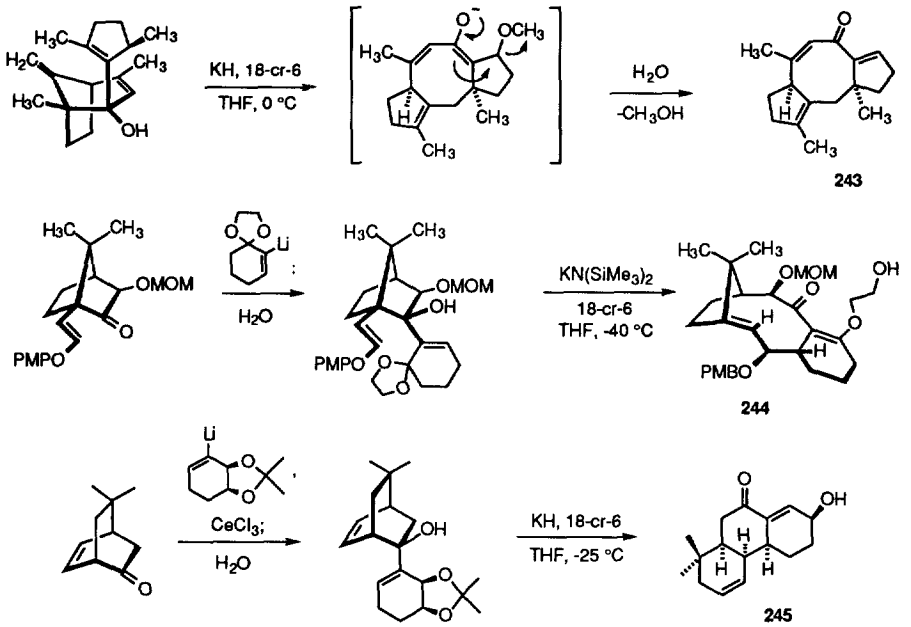


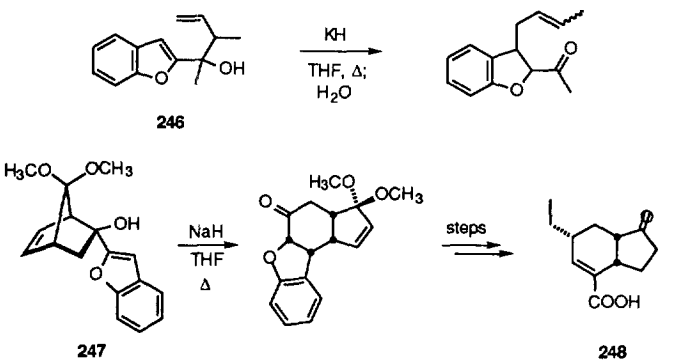
242

The preincorporation of a leaving group in the cycloalkenyl anion at that position which will emerge β to the enolate anion after the [3,3] sigmatropic shift has found use in the regiocontrolled formation of α,β-unsaturated ketones.[70b,133,151] The relevance of this innovation is reflected in the direct isolation of **243-245**. The first of these entries was developed for the stereoselective construction of the structural core of the ceroplastin sesterterpenes. The acetal cleavage events in the other two examples were designed for the specific purpose of generating an enol ether and an allylic alcohol, respectively.

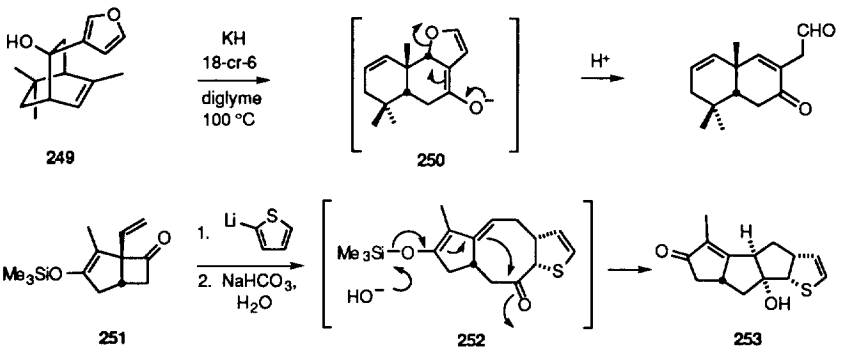


14. Participation of Aromatic Rings

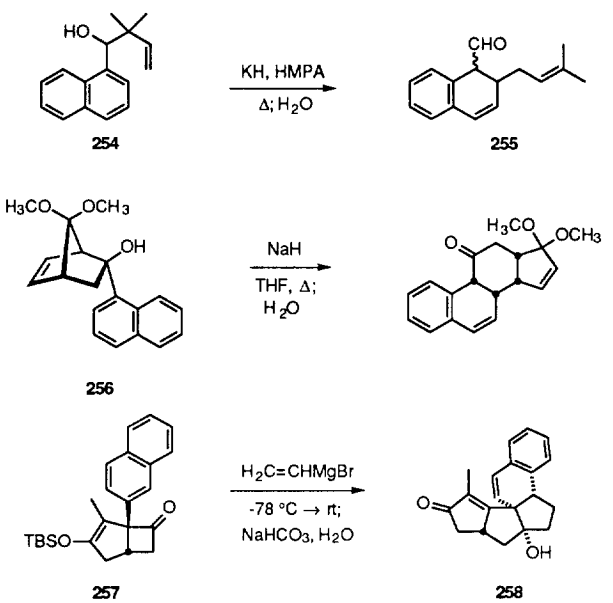
In many instances, aromatic groups are reluctant to participate in anionic oxy-Cope rearrangements because of the need to disrupt π-electron delocalization at the transition state. Two examples involving 2-substituted benzofurans have been defined.[110,152] The norbornenol **247** proved to be the starting material for an ingenious synthesis of coronafacic acid (**248**). The simpler furan analog of **246** gave no [3,3] sigmatropic product even at elevated temperature.



The rather forcing conditions required to drive the anionic oxy-Cope process in the 3-furanylcarbinol **249** are responsible for inducing subsequent ring cleavage in **250**.[73] When a significant level of ring strain is available for release during the sigmatropic rearrangement, the associated exothermicity allows for participation of an aromatic component in a preparatively useful way.[153] The transformation of **251** into **252** represents a relevant case study. The *in situ* hydrolytic desilylation of **252** triggers transannular ring closure to **253** in 60% overall yield.

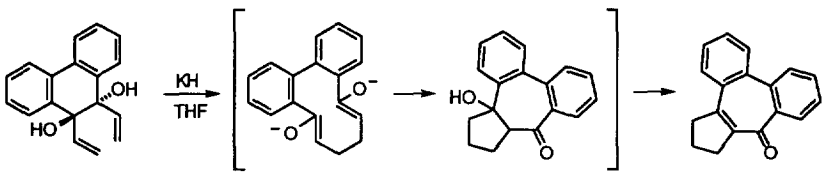


Although the naphthalenic carbinol **254** reluctantly undergoes oxyanionic sigmatropy under forcing conditions (10% of **255**),[154] the balance of energetic forces is sufficiently improved in **256** to represent a useful method for the rapid elaboration of steroidal hormone analogs.[110] More facile yet is the conversion of **257** into **258** for the reasons stated above.[153]

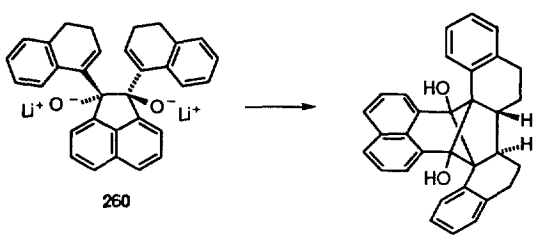


15. Behavior of Doubly Charged Systems

Although the responsiveness of divinyl glycols to thermal [3,3] sigmatropy has long been recognized,[155] dianionic variants of this process are of much more recent vintage. In possibly the earliest report of this transformation involving **259**, the likelihood of post-rearrangement aldolization was also made apparent.[156] A peculiar result is the discovery that dilithio alkoxide **260** undergoes spontaneous dianionic oxy-Cope rearrangement followed by "criss-cross" [2+2] cycloaddition of the two enolate anions formed in this step.[157] A precise mechanism for the final stage of this sequence remains elusive.



259



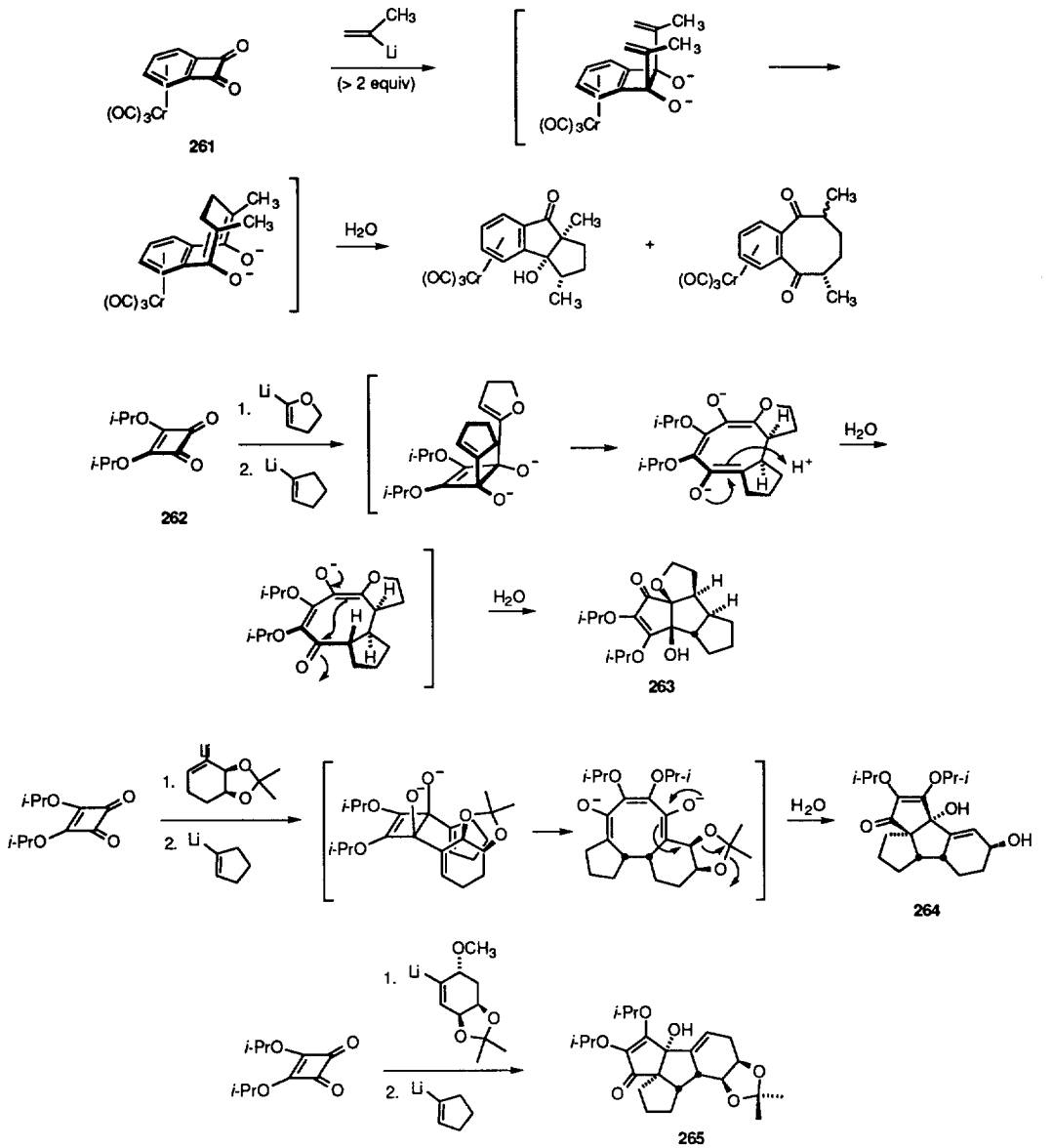
260

Cyclobutene-1,2-diones and squarate esters are more responsive still to dianionic oxy-Cope rearrangement because of pending strain release. However, the second-stage alkenyl anion addition must occur cis to the first for proximity reasons. One way to guarantee this is to involve chromium carbonyl complexes such as **261**.[158-160] If facial selectivity is not biased in this way, trans addition will predominate and direct reaction into an electrocyclic manifold.[161-168] The modest level of cis addition observed in those examples involving cycloalkenyllithiums[169-172] can be significantly enhanced by chelation control tactics.[173,174] The advantages offered by the presence of one or more ethereal oxygens in the first anion to be introduced are quite apparent as one progresses from dihydrofuranyllithium (26% cis addition leading ultimately to **263**) to an acetal (35% of **264**), and ultimately to a trioxygenated nucleophile (58% of **265**).

Notwithstanding the attractiveness of this correlation, the available data clearly show that these are not straightforwardly matched and mismatched structural arrangements for the syn delivery of the second alkenyllithium.

16. Concluding Remarks

From what began as an investigation of substituent effects on the [3,3] sigmatropic process several decades ago has blossomed a synthetic transformation of considerable importance. The anionic oxy-Cope rear-



rangement possesses the intrinsic capability for achieving efficient internal chirality transfer in complex structural settings. Hopefully, this review will spur on more sophisticated applications of this chemistry in diverse and highly varied contexts, with a view to gaining overall synthetic efficiency when setting multiple stereogenic centers in one step. Other exciting and challenging adaptations lie ahead. These include suitable development of the knowledge base that would allow for kinetic resolution during the alkenyl anion-β,γ-unsaturated ketone

coupling step, and inclusion of the two-step sequence into combinational schemes. The fine tuning to be demanded by these new thrusts can be expected to heighten further the versatility of the method.

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17. References and Notes

1. Hill, R. K. in *Comprehensive Organic Synthesis, Vol. 5*, Trost, B. M. and Fleming, I., Eds., Pergamon Press, Oxford, 1991, Chapter 7.1
2. Wilson, S. R. *Org. Reactions* **1993**, *43*, 93.
3. Paquette, L.A. *Synlett* **1990**, 67.
4. Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.
5. Paquette, L. A. *Chem. Soc. Rev.* **1995**, 9.
6. Berson, J. A.; Jones, M., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5017, 5019.
7. Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.
8. Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186.
9. Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493.
10. Bojack, G.; Künzer, H.; Rölfing, K.; Thiel, M. *Tetrahedron Lett.* **1996**, *37*, 6103.
11. Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172.
12. Hsieh, S.-L.; Chiu, C.-T.; Chang, N.-C. *J. Org. Chem.* **1989**, *54*, 3820.
13. (a) Evans, D. A.; Baillargeon, D. J.; Nelson, G. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242. (b) Evans, D. A.; Nelson, G. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.
14. Paquette, L. A. in *Organic Synthesis: Modern Trends*, Chizov, O., Ed.; Blackwell Scientific Publications, 1988, pp. 1-12.
15. Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879.
16. Paquette, L. A.; DeRussy, D. T.; Vandenheste, T.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 5562.
17. Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107.
18. Paquette, L. A.; DeRussy, D. T.; Gallucci, J. C. *J. Org. Chem.* **1989**, *54*, 2278.
19. Paquette, L. A.; He, W.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, 2291.
20. Paquette, L. A.; Lassalle, G. Y.; Lovely, C. J. *J. Org. Chem.* **1993**, *58*, 4254.
21. Paquette, L. A.; Deaton, D. N.; Endo, Y.; Poupart, M.-A. *J. Org. Chem.* **1993**, *58*, 4262.
22. Paquette, L. A.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 4952.

23. Dahnke, K. R.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 887.
24. Doyon, J.; He, W.; Paquette, L. A. *J. Org. Chem.* **1994**, *69*, 2033.
25. Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 4411.
26. Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 3972.
27. Paquette, L. A.; Crouse, G. D. *Tetrahedron* **1981**, *37*, 281.
28. Paquette, L. A.; Coghlan, M. J.; Hayes, P. C. *J. Org. Chem.* **1984**, *49*, 4516.
29. Crouse, G. D.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 3167.
30. Paquette, L. A.; Crouse, G. D. *J. Am. Chem. Soc.* **1981**, *103*, 6235.
31. Zucker, P. A.; Lupia, J. A. *Synlett* **1990**, 729.
32. Banwell, M. G.; Dupuche, J. R.; Gable, R. W. *Aust. J. Chem.* **1996**, *49*, 639.
33. (a) Paquette, L. A.; Ladouceur, G. *J. Org. Chem.* **1989**, *54*, 4278. (b) Ladouceur, G.; Paquette, L. A. *Synthesis* **1992**, 185.
34. Utagawa, A.; Hirota, H.; Ohno, S.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1207.
35. Paquette, L. A.; Backhaus, D.; Braun, R. *J. Am. Chem. Soc.* **1996**, *118*, 11990.
36. Backhaus, D.; Paquette, L. A. *Tetrahedron Lett.* **1997**, *38*, 29.
37. Macdonald, T. L.; Natalie, K. J., Jr.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1981**, *103*, 6235.
38. Rozeboom, M. D.; Kiplinger, J. P.; Bartmess, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1025.
39. Evans, D. J.; Baillargeon, D. J. *Tetrahedron Lett.* **1978**, 3319.
40. Ahlgren, G. *Tetrahedron Lett.* **1979**, 915.
41. Steigerwald, M. L.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994.
42. Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877.
43. Rao, C. S. S.; Kumar, G.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron* **1982**, *38*, 2195 and references cited therein.
44. (a) Doutheau, A.; Balme, G.; Malacria, M.; Goré, J. *Tetrahedron Lett.* **1978**, 1803. (b) See also Cookson, R. C.; Singh, P. *J. Chem. Soc. C* **1971**, 1477.
45. Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3869; *J. Am. Chem. Soc.* **1986**, *108*, 6343.
46. Ohnuma, T.; Hata, N.; Miyachi, N.; Wakamatsu, T.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 219.
47. Balakumar, A.; Janardhanam, S.; Rajagopalan, K. *J. Org. Chem.* **1993**, *58*, 5482.
48. Paquette, L. A.; DeRussy, D. T.; Rogers, R. D. *Tetrahedron* **1988**, *44*, 3139.
49. Wender, P. A.; Holt, D. A.; Sieburth, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 3348.
50. Wender, P. A., Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7771.
51. Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1985**, *37*, 3967.
52. Wender, P. A.; Ternansky, R. J.; Sieburth, S. M. *Tetrahedron Lett.* **1985**, *26*, 4319.
53. Gajewski, J. J.; Gee, K. R. *J. Am. Chem. Soc.* **1991**, *113*, 967.
54. Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.
55. Tomooka, K.; Wei, S.-Y.; Nakai, T. *Chem. Lett.* **1991**, 43.
56. Wei, S.-Y.; Tomooka, K.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 5973.
57. Paquette, L. A.; Maynard, G. D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1368.

58. Paquette, L. A.; Maynard, G. D. *J. Am. Chem. Soc.* **1992**, *114*, 5018.
59. Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59*, 1444.
60. Wei, S.-Y.; Tomooka, K.; Nakai, T. *Tetrahedron* **1993**, *49*, 1025.
61. Tomooka, K.; Nagasawa, A.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 8899.
62. Enholm, E. J.; Satici, H.; Prasad, G. *J. Org. Chem.* **1990**, *55*, 324.
63. Black, W. C.; Giroux, A., Greidanus, G. *Tetrahedron Lett.* **1996**, *37*, 4471.
64. Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1983**, *48*, 1829.
65. Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.
66. Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 265.
67. (a) Lin, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 997. (b) Lin, M.-h.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1990**, *55*, 3597.
68. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
69. Elmore, S. W.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 319.
70. (a) Paquette, L. A.; Liang, S.; Galatsis, P. *Synlett* **1990**, 663. (b) Paquette, L A.; Liang, S.; Wang, H.-L. *J. Org. Chem.* **1996**, *61*, 3268.
71. Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Rogers, R. D. *J. Am. Chem. Soc.* **1991**, *113*, 1335.
72. Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755.
73. (a) Paquette, L. A.; Maleczka, R. E., Jr. *J. Org. Chem.* **1991**, *56*, 912. (b) Maleczka, R. E., Jr., Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 6538.
74. Janardhanam, S.; Devan, B.; Rajagopalan, K. *Tetrahedron Lett.* **2993**, *34*, 6761.
75. Shanmugam, P.; Rajagopalan, K. *Tetrahedron* **1996**, *52*, 7737.
76. Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. *Synth. Commun.* **1993**, *23*, 311.
77. Shanmugam, P.; Rajagopalan, K. *Synth. Commun.* **1996**, *26*, 2119.
78. Rao, C. S. S.; Kumar, G.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron* **1982**, *38*, 2195.
79. Thangaraj, K.; Srinivasan, P. C.; Swaminathan, S. *Tetrahedron Lett.* **1982**, *23*, 4983.
80. Sathyamoorthi, G.; Thangaraj, K.; Srinivasan, P. C.; Swaminathan, S. *Tetrahedron Lett.* **1989**, *30*, 4427.
81. Raju, N.; Rajagopalan, K.; Swaminathan, S.; Schoolery, J. N. *Tetrahedron Lett.* **1980**, *21*, 1577.
82. Jisheng, L.; Gallardo, T.; White, J. B. *J. Org. Chem.* **1990**, *55*, 5426.
83. Fan, W.; White, J. B. *Tetrahedron Lett.* **1993**, *34*, 957.
84. Santora, V. J.; Moore, H. W. *J. Am. Chem. Soc.* **1995**, *117*, 8486.
85. Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041.
86. Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6825.
87. Sworin, M.; Lin, K.-C. *J. Org. Chem.* **1987**, *52*, 5640; *J. Am. Chem. Soc.* **1989**, *111*, 1815.

88. Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331.
89. Johnson, J. N. unpublished.
90. Paquette, L A.; Shi, Y.-J. *J. Org. Chem.* **1989**, *54*, 5205; *J. Am. Chem. Soc.* **1990**, *112*, 8478.
91. Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.
92. Greeves, N.; Vines, K. J. *Tetrahedron Lett.* **1994**, *35*, 7077; *J. Chem. Soc., Chem. Commun.* **1994**, 1469.
93. Mitchell, T. N.; Geisselmann, F. *Synlett* **1995**, 333.
94. (a) Krohn, K.; Bernhard, S. *Synthesis* **1996**, 699. (b) Herndon, J. W.; McMullen, L. A.; Daitch, C. E. *Tetrahedron Lett.* **1990**, *31*, 4547.
95. Paquette, L.A.; Guevel, R.; Sauer, D. R. *Tetrahedron Lett.* **1992**, *33*, 923.
96. Guevel, R.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 1776.
97. Mikami, K.; Taya, S.; Nakai, T.; Fujita, Y. *J. Org. Chem.* **1981**, *46*, 5447.
98. Gerard, F.; Miginiac, P. *C. R. Hebd. Seances Acad. Sci.* **1971**, *273*, 674.
99. Hauser, F. M.; Baghdanov, V. M. *Tetrahedron* **1984**, *40*, 4719.
100. Fu, X.; Cook, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 6910.
101. Truesdale, L. K.; Swanson, D.; Sun, R. C. *Tetrahedron Lett.* **1985**, *26*, 5009.
102. Lee, E.; Shin, I.-J.; Kim, T.-S. *J. Am. Chem. Soc.* **1990**, *112*, 260.
103. Marvell, E. N.; Whalley, W. *Tetrahedron Lett.* **1970**, 509.
104. Macdonald, T. L.; Natalie, K. J., Jr.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1986**, *51*, 1124.
105. Kuwahara, S.; Mori, K. *Heterocycles* **1989**, *28*, 167.
106. (a) Hauptmann, H.; Mühlbauer, G.; Walker, N. P. C. *Tetrahedron Lett.* **1986**, *27*, 1315. (b) For more recent work, consult Kuwahara, S.; Mori, K. *Tetrahedron* **1990**, *46*, 8075, 8083.
107. (a) Kuroda, C.; Hirota, H.; Takahashi, T. *Chem. Lett.* **1982**, 249. (b) Kuroda, C.; Nakamura, T.; Hirota, H.; Enomoto, E.; Takahashi, T. *Bull Chem. Soc., Jpn.* **1985**, *58*, 146.
108. Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632.
109. Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625.
110. Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4309.
111. Chang, N.-C.; Day, H.-M.; Lu, W.-F. *J. Org. Chem.* **1989**, *54*, 4083.
112. Rigby, J. H.; Sage, J.-M.; Raggon, J. *J. Org. Chem.* **1982**, *47*, 4815.
113. Ramani, P. V.; John, J. P.; Narayanan, K. V.; Swaminathan, S. *J. Chem. Soc. Perkin Trans. 1* **1972**, 1516.
114. Raju, N.; Geetha, A.; Rajagopalan, K.; Swaminathan, S. *Indian J. Chem. Sect. B* **1981**, *20*, 238.
115. (a) John, J. P.; Ramachandran, S.; Swaminathan, S. *Tetrahedron Lett.* **1962**, 720. (b) John, J. P.; Srinivasan, K. G.; Venkataramani, P. S.; Swaminathan, S. *Tetrahedron* **1969**, *25*, 2661. (c) Swaminathan, S.; Srinivasan, K. G.; Venkataramani, P. S. *Tetrahedron* **1970**, *26*, 1453.
116. (a) Uma, R.; Swaminathan, S.; Rajagopalan, K. *Tetrahedron Lett.* **1984**, *25*, 5825. (b) Uma, R.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron* **1986**, *42*, 2757.
117. Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268.

118. Hutchinson, J. H.; Kuo, D. L.; Money, T.; Yokoyama, B. *J. Chem. Soc., Chem. Commun.* **1988**, 1281.
119. Banwell, M. G.; Dupuche, J. R. *Chem. Commun.* **1996**, 869.
120. Mehta, G.; Karra, S. R.; Krishnamurthy, N. *Tetrahedron Lett.* **1994**, *35*, 2761.
121. Mehta, G.; Subba Reddy, K. *Synlett* **1996**, 625.
122. Lee, T.-H.; Liao, C.-C. *Tetrahedron Lett.* **1996**, *37*, 6869.
123. Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57*, 4103.
124. Brown, W. L.; Fallis, A. G. *Tetrahedron Lett.* **1985**, *26*, 607; *Can. J. Chem.* **1987**, *65*, 1828.
125. Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1984**, *25*, 5103.
126. Kahn, M. *Tetrahedron Lett.* **1980**, *21*, 4547.
127. Levine, S. G.; McDaniel, R. L., Jr. *J. Org. Chem.* **1981**, *46*, 2199.
128. Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772.
129. Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849.
130. Paquette, L. A.; Montgomery, F. J.; Wang, T.-Z. *J. Org. Chem.* **1995**, *60*, 7857.
131. Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 889.
132. Paquette, L. A.; Huber, S. K.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 6874.
133. Paquette, L. A.; Su, Z.; Bailey, S.; Montgomery, F. J. *J. Org. Chem.* **1995**, *60*, 897.
134. Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190.
135. Paquette, L. A.; Koh, D.; Wang, X.; Prodger, J. C. *Tetrahedron Lett.* **1995**, *36*, 673.
136. Paquette, L. A.; Sturino, C. F.; Wang, X.; Prodger, J. C.; Koh, D. *J. Am. Chem. Soc.* **1996**, *118*, 5620.
137. (a) Paquette, L. A.; Poupart, M.-A. *Tetrahedron Lett.* **1988**, *29*, 273. (b) Paquette, L. A.; Poupart, M.-A. *J. Org. Chem.* **1993**, *58*, 4245.
138. Brown, D. S.; Paquette, L. A. *J. Org. Chem.* **1992**, *57*, 4512.
139. Schreiber, S. L.; Santini, C. *Tetrahedron Lett.* **1981**, *22*, 4651.
140. Schreiber, S. L.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971.
141. Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038.
142. Snider, B. B.; Allentoff, A. J.; Walner, M. B. *Tetrahedron* **1990**, *46*, 8031.
143. Snider, B. B.; Allentoff, A. J. *J. Org. Chem.* **1991**, *56*, 321.
144. Paquette, L. A.; Sun, L.-Q.; Watson, T. J. N.; Friedrich, D.; Freeman, B. T. *J. Am. Chem. Soc.* **1997**, *119*, 2767.
145. Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1985**, *50*, 201.
146. Bérubé, G.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 4045.
147. Pramod, K.; Subba Rao, G. S. R. *Ind. J. Chem. Section B* **1982**, 984.
148. Paquette, L. A.; Sauer, D. R.; Edmondson, S. D.; Friedrich, D. *Tetrahedron* **1994**, *50*, 4071.
149. Boeckman, R. K., Jr.; Springer, D. M.; Alessi, T. R. *J. Am. Chem. Soc.* **1989**, *111*, 8284.
150. Mehta, G.; Barone, R.; Azario, P.; Barberis, F.; Arbelot, M.; Chanon, M. *Tetrahedron* **1992**, *48*, 8953.
151. Paquette, L. A.; Tsui, H.-C. *Synlett* **1996**, 129.

152. Martin, D.; Wurster, J. A.; Boylan, M. J.; Borzilleri, R. M.; Engel, G. T.; Walsh, E. J. *Tetrahedron Lett.* **1993**, *34*, 8395.
153. Santora, V. J.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 7976.
154. Marvell, E. N.; Almond, S. W. *Tetrahedron Lett.* **1979**, 2779.
155. Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 63.
156. Geetha, P.; Hug, C. A. M. A.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron Lett.* **1982**, *23*, 569.
157. Alder, R. W.; Colclough, D.; Grams, F.; Orpen, A. G. *Tetrahedron* **1990**, *46*, 7933.
158. Brands, M.; Goddard, R.; Wey, H. G.; Butenschön, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 267.
159. Brands, M.; Bruckmann, J.; Krüger, C.; Butenschön, H. *J. Chem. Soc., Chem. Commun.* **1994**, 999.
160. Brands, M.; Wey, H. G.; Bruckmann, J.; Krüger, C.; Butenschön, H. *Chem. Eur. J.* **1996**, *2*, 182.
161. Morwick, T.; Doyon, J.; Paquette, L. A. *Tetrahedron Lett.* **1995**, *36*, 2369.
162. Paquette, L. A.; Morwick, T. *J. Am. Chem. Soc.* **1995**, *117*, 1451.
163. Paquette, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799.
164. Paquette, L. A.; Doyon, J.; Kuo, L. H. *Tetrahedron Lett.* **1996**, *37*, 3299.
165. Morwick, T. M.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 627.
166. Paquette, L. A.; Hamme, A. T., II; Kuo, L. H.; Doyon, J.; Kreuzholz, R. *J. Am. Chem. Soc.* **1997**, *119*, 1242
167. Paquette, L. A.; Doyon, J. *J. Org. Chem.* **1997**, *62*, 1723.
168. Paquette, L. A.; Kuo, L. H.; Hamme, A. T., II; Kreuzholz, R.; Doyon, J. *J. Org. Chem.* **1997**, *62*, 1730.
169. Negri, J. T.; Morwick, T.; Doyon, J.; Wilson, P. D.; Hickey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 12189.
170. Wilson, P. D.; Friedrich, D.; Paquette, L. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1351.
171. Paquette, L. A.; Morwick, T. M.; Negri, J. T.; Rogers, R. D. *Tetrahedron* **1996**, *52*, 3075.
172. Paquette, L. A.; Morwick, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 1230.
173. Paquette, L. A.; Kuo, L.-H.; Doyon, J. *J. Am. Chem. Soc.* **1997**, *119*, 3038.

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Biographical Sketch

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Leo Paquette received his B.S. degree in chemistry *magna cum laude* from Holy Cross College in 1956 and his Ph.D. from M.I.T. in 1959. After serving as a medicinal chemist at The Upjohn Company from 1959 to 1963, he joined the faculty at The Ohio State University and was promoted to Professor in 1969. Subsequently, he held the Kimberly Professorship in Chemistry (1981-1987) and now is a Distinguished University Professor there (1987-present).

Leo was named an Alfred P. Sloan Foundation Fellow in 1965, a Guggenheim Fellow in 1976-77, a Senior Humboldt Fellow in 1989, and an Awardee of the Japanese Society for the Promotion of Science in 1992. On several occasions he has been honored by the American Chemical Society: Morley Medalist of the Cleveland Section in 1971 and recipient of the Columbus Section Award in 1979, the national Award for Creative Work in Synthetic Organic Chemistry in 1984, the Arthur C. Cope Scholar Award in 1987, and the Ernest Guenther Award in 1992. He was elected to the National Academy of Sciences and presented an honorary degree from his Alma Mater the same year (1984). The Ohio State University presented him with a Senior Research Award in 1980 and its highest honor, the Sullivant Medal, in 1990. He has also been the recipient of many international awards including, most recently, the Centenary Lectureship of the Royal Society of Chemistry and the first France/Belgium Award for Research Excellence.

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