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The Thermal, Aliphatic Claisen Rearrangement

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I. Introduction

This past year the diamond anniversary of the publication of Ludwig Claisen's paper "Über Umlagerung von Phenol-allyl-äthern in C-allyl-phenole" describing his now eponymous rearrangement[1] was observed. And what a gem it has proved to be! Ironically, the majority of the text of the paper and all the experimental details dealt with the substance of the title while the first paragraph mentioned, in almost parenthetical fashion, the rearrangement of the O-allylation product of acetoacetic ester **1** to its C-allylated isomer **2** upon distillation in the presence of ammonium chloride. Arguably, the aliphatic rearrangement has stimulated more interest in both its mechanistic and synthetic aspects than its aromatic counterpart. Today, the aliphatic Claisen rearrangement is but one member of the class of [3,3] sigmatropic rearrangements. The prototype for the rearrangement is the transformation of allyl vinyl ether **3** into 4-pentenal (**4**).

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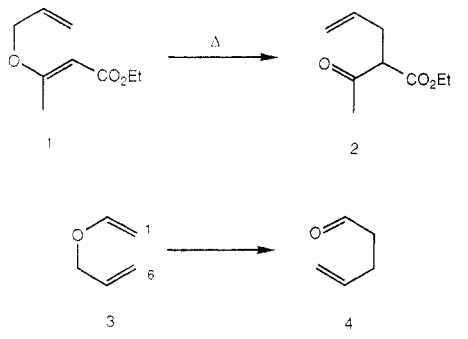
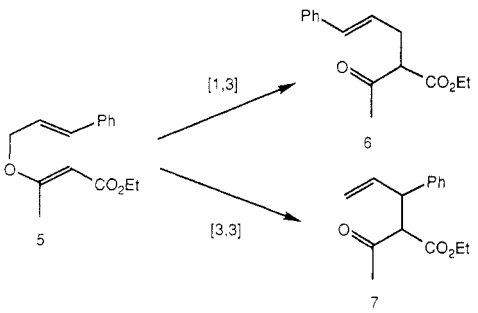


This review will deal with the history, mechanism, stereochemistry, and applications of the thermal, aliphatic rearrangement[2] over the past 75 years, as recent publications have provided excellent summaries of the effect of catalysts on the rearrangement.[3] While the contributions to this area are legion, an effort will be made to deal with both historical contributions and those reports that exemplify the scope of the reaction. Although heteroatom Claisen rearrangements will not be covered, examples will be provided as they apply to the discussions at hand.

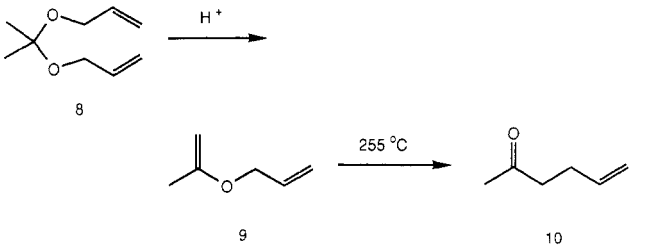
II. Historical Overview

Bergmann and Corte (1935)[4] and Lauer and Kilburn (1937)[5] investigated the rearrangement of ethyl β-cinnamyloxycrotonate (**5**) in the presence of ammonium chloride to determine if "transposition" of the allyl unit occurs, as had been established in the aromatic series.[6] The former collaborators reported the formation of the "nontransposed" product **6** and "transposed" **7** while the latter investigators observed only the product of "transposition". The formation of β-keto ester **7** provided access to a product formally derived from the S_N2' C-alkylation of cinnamyl halides with acetoacetic ester anion.

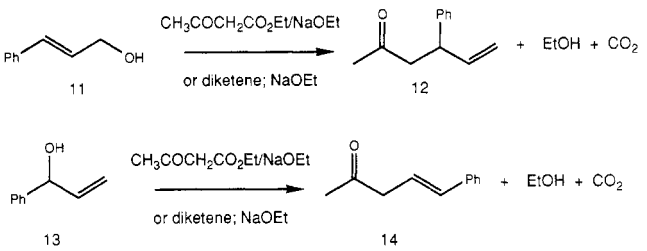


Bergmann and Corte employed Claisen's method[7] of ammonium chloride catalyzed exchange of cinnamyl alcohol with ethyl 3-ethoxy-2-crotonate for the formation of **5** while Lauer and Kilburn used sodium cinnamylate and ethyl β-chlorocrotonate. The use of ammonium chloride in the rearrangement step soon disappeared, although it had been shown to have "a small, but significant, increase in rate" as a heterogeneous catalyst.[8]

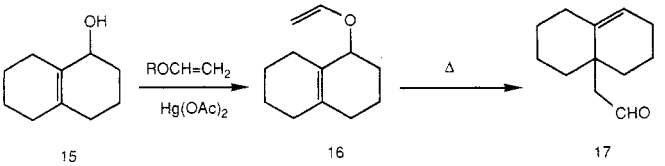
While the β-keto esters provided access to γ,δ-unsaturated acids by Haller–Bauer cleavage (i.e., retro-Claisen condensation) and γ,δ-unsaturated ketones by acid hydrolysis, formation of γ,δ-unsaturated aldehydes had not been realized. In 1938, Hurd and Pollack[9a] subjected β-bromoethyl allyl ether to base-promoted dehydrohalogenation to form the archetypical allyl vinyl ether (**3**), which underwent successful rearrangement to aldehyde **4** at 255 °C. In addition, allyl isopropenyl ether (**9**) was prepared by acid-catalyzed elimination and was subjected to rearrangement to afford ketone **10**.



In the early 1940s, Carroll[10] investigated the base-catalyzed reaction of acetoacetic ester with allylic alcohols to produce olefinic ketones.[11] In particular, the stereospecificity of the reaction was demonstrated in the case of the structural isomers cinnamyl alcohol (**11**) and phenylvinylcarbinol (**13**), each giving a transposed product. Aware of the results of Bergmann and Lauer, Carroll proposed a mechanism that invoked S_N2' displacement of hydroxide by acetoacetate anion. Kimel and Cope[12] (1943) clarified the mechanism by demonstrating that acetoacetic acid esters derived from allylic alcohols undergo the rearrangement. Moreover, the use of diketene provided a reactive equivalent of acetoacetate that made the formation of substrates routine. Thus, this variation of the reaction provided nonacidic conditions, compared to those of Hurd, for the generation of γ,δ-butenyl methyl ketones.



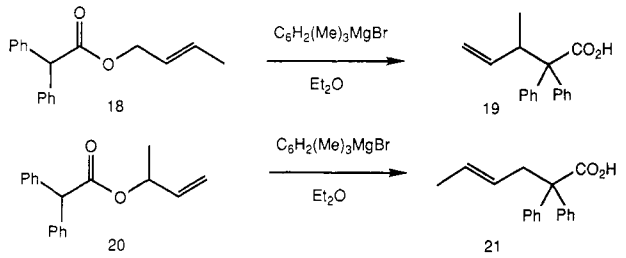
The generation of vinyl ethers by the dehydrohalogenation procedure of Hurd did not provide a general route for the derivatization of allylic alcohols. A solution to this problem was provided by Burgstahler and Nordin[13] who adapted the mercuric acetate catalyzed exchange of alcohols with alkyl vinyl ethers[14] to the formation of allyl vinyl ethers (**15** → **16**).[15] These investigators were able to demonstrate that the rearrangement was successful in systems wherein at least one of the double bonds is contained in a ring (**16** → **17**).



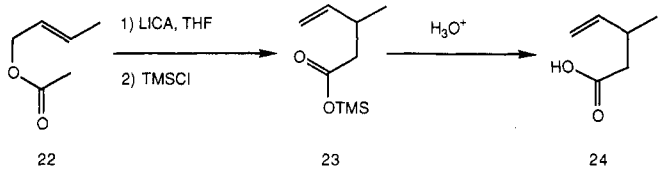
In 1967, Marbet and Saucy reported[16] the acid-catalyzed exchange and rearrangement of seemingly labile tertiary allylic alcohols with 2,2-dimethoxypropane or 2-methoxypropene that resulted in the formation of methyl ketones.[17] The conversion of linalool to gera-

nylacetone laid the groundwork for a commercial synthesis of vitamin A alcohol.

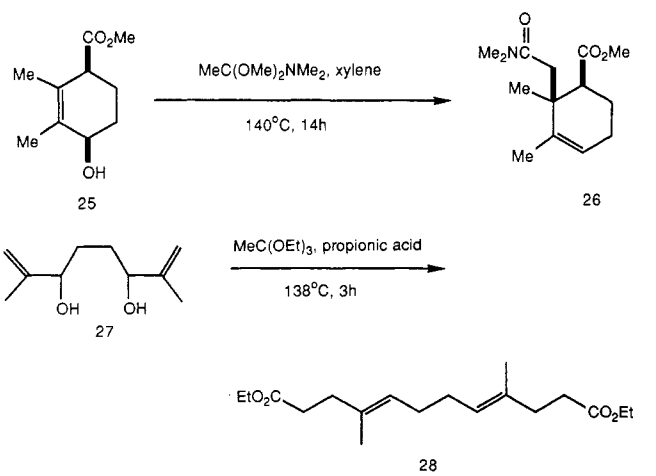
The first practical example of the preparation of γ,δ-unsaturated carboxylic acids via the aliphatic Claisen rearrangement was demonstrated by Arnold and co-workers[18] in 1949.[19] The allylic esters **18** and **20** of diphenylacetic acid underwent stereospecific rearrangement upon treatment with mesitylmagnesium bromide at ambient temperature.



Other variations employed sodium hydride as the base in refluxing toluene;[18a,20] however, a significant breakthrough was reported by Ireland[21] who, following Rathke's report[22] of the use of lithium dialkylamide bases for the generation of ester enolates, demonstrated that the method served as a means to achieve the Claisen rearrangement of acylated allylic alcohols at ambient temperature (**22** → **23**) and, as will be seen later, provided a method for the control of enolate geometry. Both the enolates and their *O*-silyl ketene acetals underwent facile rearrangement.[23]



Although Ireland's contribution improved the formation of γ,δ-unsaturated acids, it was preceded by two independent contributions that realized amides and esters via the Claisen rearrangement. In 1964 Eschenmoser[24a,b] adapted Meerwein's observations[24c] on the exchange of amide acetals with allylic alcohols, thereby facilitating the formation of γ,δ-unsaturated amides upon rearrangement (**25** → **26**). In a similar fashion, 1970 witnessed Johnson's report[25] of the acid-catalyzed exchange of ethyl orthoacetate with allylic alcohols and the subsequent formation of γ,δ-unsaturated esters upon rearrangement (**27** → **28**).



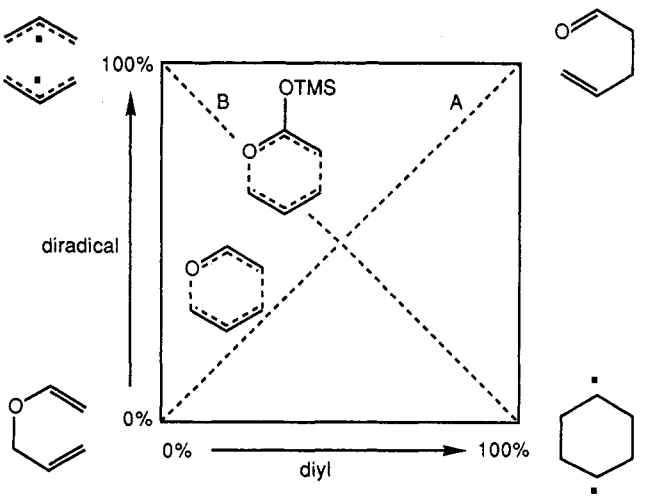


Figure 1. Transition-state profile of the aliphatic Claisen rearrangement.

III. Mechanistic Aspects

A. Kinetics

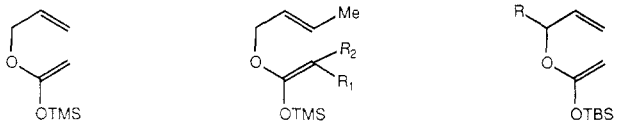
The ability of the Claisen rearrangement to give transposed structures led Hurd and Pollack[9b] to suggest a cyclic mechanism. The rearrangement of allyl vinyl ethers displays a negative entropy[26] and volume[27] of activation, both of which support a constrained transition state relative to ground-state geometries. First-order kinetics[8,26] and the lack of crossover products[8] argue for the intramolecularity of the reaction.

The overall exothermicity[26] of the rearrangement of allyl vinyl ethers indicates an early transition state.[28,29] Using secondary deuterium isotope effects as a mechanistic probe, Gajewski[29] has concluded that bond-breaking is more advanced than bond-making in the rearrangement of allyl vinyl ether itself. Thus, the transition state (TS) has been suggested to resemble more closely the diradical than the 1,4-diyl. Figure 1 (More O'Ferrall-Jencks diagram) locates the transition state for allyl vinyl ether above diagonal A (diradical > diyl) and below diagonal B (early, not late, TS). Dewar, using MINDO/3 calculations, has supported an early transition state for allyl vinyl ether with bond-making being more advanced than bond-breaking, thereby requiring diyl character in the transition state.[30]

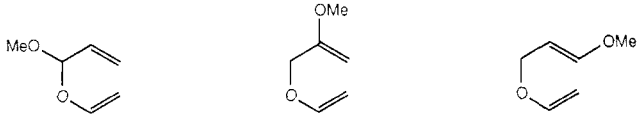
Substituents play an important role in affecting the rate of the Claisen rearrangement. Burrows and Carpenter,[31] using phenyl anion as a transition-state model, have predicted that π-donor substituents at C_1, C_2, and C_4 of allyl vinyl ether should increase the rate of the rearrangement, while substitution at C_5 and C_6 should cause deceleration. However, Dewar[30] has argued that a C_5-methoxy substituent should have a greater accelerating effect than a C_2-methoxy group.

The presence of electron-donating groups, e.g., EtO–, R_3SiO–, and Me_2N–, at C_2 of the allyl vinyl ether causes a dramatic rate acceleration. Thus, the 2-(trimethylsilyl)oxy (**29**; $t_{1/2}$ = 210 ± 30 min at 32 °C)[21] and the 2-(*tert*-butyldimethylsilyl)oxy (**31a**; $t_{1/2}$ = 107 min at 35 °C)[32] derivatives rearrange with facility under near ambient conditions, while allyl vinyl ether ($t_{1/2}$ = 1.7 × 10^4 min at 80 °C)[33] requires higher temperatures for rapid rearrangement. While both **29** and its 6-methyl congener **30a** ($t_{1/2}$ = 150 ± 30 min at 32 °C)[21] rearrange

at nearly the same rate, the C_4-alkyl-substituted isomer **31b** rearranges an order of magnitude more rapidly than either.[34] This difference suggests a kinetic stabilization of the bond-breaking process by the alkyl group in **31b**.



29 30a, R_1=R_2=H; b, R_1=Me, R_2=H; c, R_1=R_2=Me 31a, R=H; b, R=C_5H_{11}

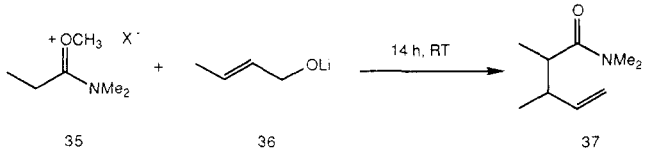


32 33 34

Coates and Curran[33] have measured the rates of rearrangement of the C_4-, C_5-, and C_6-methoxy-substituted allyl vinyl ethers at 80 °C in benzene. The 4-methoxy derivative **32** rearranges 100 times faster than the parent while the 6-methoxy isomer **34** is 10 times faster, thereby demonstrating a strong kinetic stabilization in the former case and a vinylogous, kinetic anomeric effect in the latter.[35] The observation of this effect is contrary to the Burrows–Carpenter model. In addition, the 5-methoxy isomer **33** is found to rearrange 40 times slower than the parent, in disagreement with the Dewar prediction. Coates and Curran have suggested a transition state for these systems with dipolar character (enolate–oxonium ion pair). When the solvent is changed from benzene to methanol, **32** and **34** show a 20- and 70-fold rate increase, respectively. In general, solvents have little effect on the rate of the rearrangement.

Gajewski[36] has attributed the rate enhancement and the greater degree of bond-breaking in the transition state of the Ireland–Claisen rearrangement to the greater stability of the 2-[(trimethylsilyl)oxy]-1-oxaallyl moiety over its oxaallyl counterpart (Figure 1). This conclusion derives from an examination of the heats of formation of the oxaallyl radicals and supports[21b] the finding that the relative rates of rearrangement of silyl ketene acetals **30** are **30c > 30b > 30a**.[37] The effect of the (trimethylsilyl)oxy group is not general to all [3,3] sigmatropic rearrangements as 2-[(trimethylsilyl)-oxy]-3-methyl-1,5-hexadiene undergoes a Cope rearrangement with a half-life of 2 h at 210 °C.

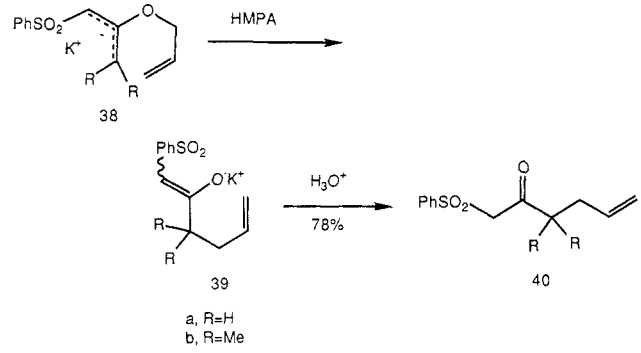
Although the Johnson and the Eschenmoser variants are conducted at elevated temperature, these conditions are required for the alcohol exchange reaction, not necessarily for the rearrangement. This point is amply demonstrated in the latter instance when ketene *O,N*-acetals are generated by an alternative route (**35** + **36** → **37**).[38]



35 36 37

In an independent study, Carpenter and Burrows[39] have synthesized the five isomeric cyano-substituted derivatives of allyl vinyl ether and have measured their kinetic parameters. Rate accelerations are observed for the C_2-CN (k_{rel} = 111), C_3-CN (k_{rel} = 270), and C_4-CN (k_{rel} = 15.6) compounds while decelerations occur for the C_1-CN (k_{rel} = 0.90) and C_5-CN (k_{rel} = 0.11) isomers relative to allyl vinyl ether.

The formation of anionic species increases the rate of the rearrangement. The enolates of allyl esters should be considered as the prototypes of strong C_2 π-donors as they rearrange at ambient temperatures.[21] Denmark has reported[40] the first example of a carbanion-accelerated Claisen rearrangement.[41] The use of hexamethylphosphoramide (HMPA), as opposed to 18-crown-6/THF, accomplishes the conversion of **38a** → **39a** at a lower temperature (50 °C) and in a higher yield (78%). This solvent-induced rate enhancement has been interpreted as ion-pair dissociation. Disubstitution at C_1 (**38b** → **39b**) causes a greater rate enhancement (20 °C, 15 min),[42] similar to the silyl ketene acetal case.

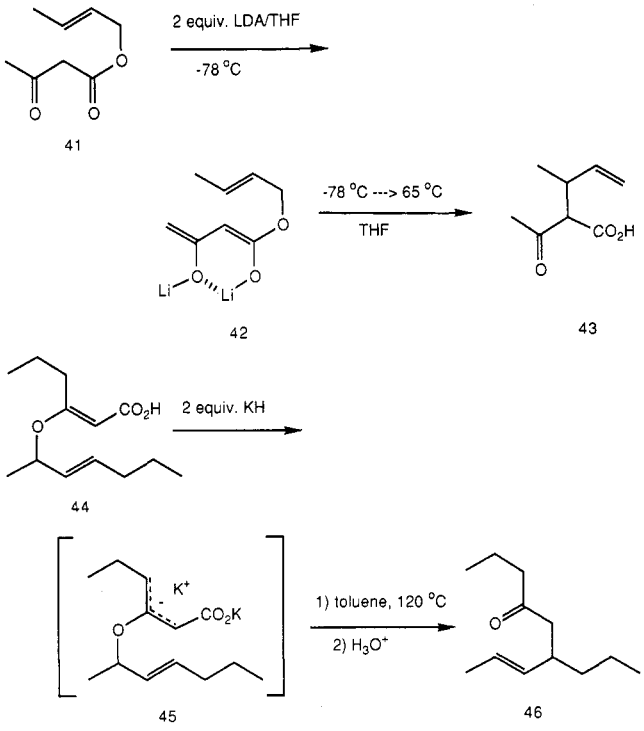


38 39 a, R=H; b, R=Me 40

The Carroll rearrangement is accelerated by carbanion formation. Wilson[43] has demonstrated that β-keto ester **41**, formed by 4-(dimethylamino)pyridine (DMAP) catalyzed addition of (*E*)-2-buten-1-ol to diketene,[44] provides the β-keto acid **43** when treated with 2 equiv of lithium diisopropylamide (LDA) at −78 °C in THF followed by heating to reflux. Decarboxylation is readily accomplished in refluxing carbon tetrachloride to give the ketone in 95% yield. When 1 equiv of base is used, no reaction is observed. The thermal reaction in the absence of base requires heating at 200 °C, and the ketone is isolated in only 37% yield.

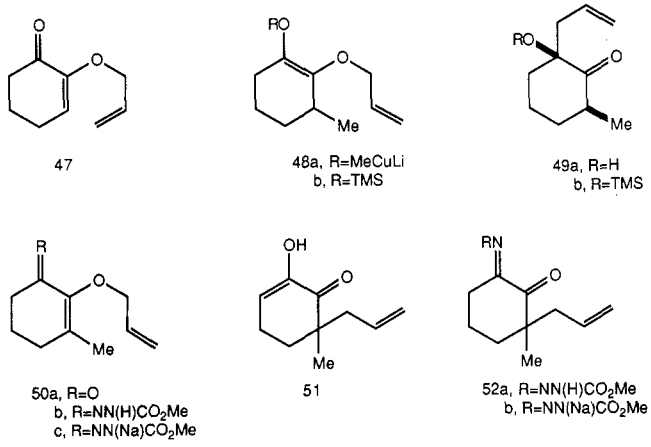
In a similar fashion, Büchi[45] has observed acceleration in the rearrangement of 3-(allyloxy)-2-butenoic acid **44** prepared by alkoxide addition to the 3-chloro-2-butenoate. When the acid is treated with 1 equiv of KH in refluxing toluene for 2–6 h, the potassium carboxylate is stable. However, the use of 2 equiv of KH effects rearrangement via dianion **45** under the same conditions, affording ketone **46** in 68% yield upon acidification and decarboxylation. The rate enhancement occurs for substrates derived from secondary allylic alcohols, but not for primary allylic alcohols. Silyl ketene acetals prepared from secondary alcohols have been observed to rearrange faster than those derived from primary allylic alcohols.[21b]

α-Allyloxy ketones have displayed remarkable rate accelerations. For example, Koreeda and Luengo[46a] have generated the enolate **48a** by conjugate addition of Me_2CuLi to 2-(allyloxy)-2-cyclohexenone (**47**); rearrangement to acyloin **49a** is complete in 15 min at 0 °C.[46b] The rate enhancement has been attributed to an allyl radical/oxyoxaallyl radical anion (semi-dione) pair. For comparison, the silyl enol ether **48b** is slower



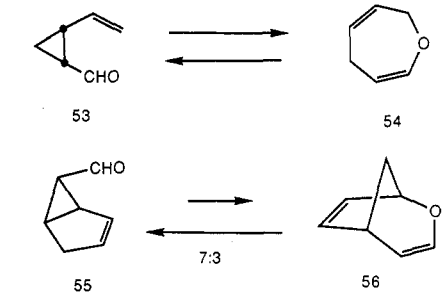
to rearrange, having $t_{1/2}$ = 1.6 h at 62.5 °C.

In a related study, Ponaras[47] has compared the relative rates of rearrangement of 2-(allyloxy)-3-methyl-2-cyclohexenone and its derivatives. In refluxing THF (65 °C), the parent ketone **50a** has $t_{1/2}$ = 340 h, affording the diosphenol **51**, while the rearrangement of carbomethoxyhydrazone **50b** to **52a** is appreciably faster ($t_{1/2}$ = 22 h). The sodium salt of the hydrazone (**50c**) is the fastest of the three, rearranging to give **52b** with $t_{1/2}$ = 1.5 h. This method has proved amenable to forming vicinal quaternary centers, and in the case of the carbomethoxyhydrazones **52**, a subsequent Wolff–Kishner reduction can be conducted to remove the accelerating functionality.[48]

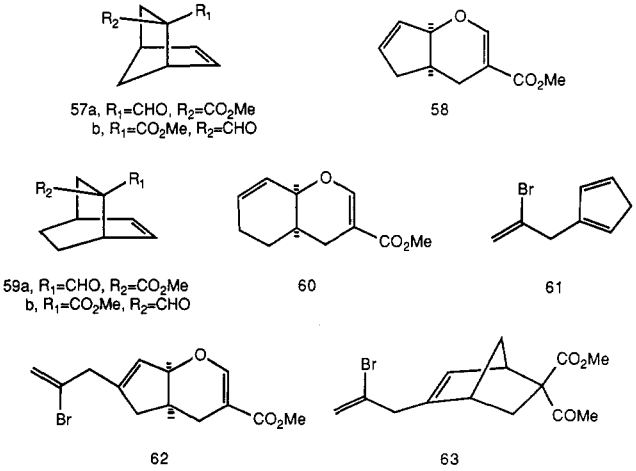


B. Retro-Claisen Rearrangement

The Claisen rearrangement, unlike its all carbon analogue the Cope rearrangement, is an irreversible reaction, except for several specially designed substrates. Vinylcyclopropanecarboxaldehyde (**53**) has been shown to be in rapid equilibrium with dihydrooxepine (**54**). Similarly, unsaturated aldehyde **55** forms a 7:3 equilibrium mixture with vinyl ether **56**. The equilibrium is shifted to the right by trapping the vinyl ether as its tetracyanoethylene derivative and to the left by formation of the bisulfite adduct of the aldehyde. Decomposition of the bisulfite adduct reestablishes the equilibrium. These equilibria are presumably driven by the strain of the cyclopropane ring.[49,50]



Oppolzer[51] has observed that silica gel chromatography of aldehyde ester **57a** provides recovered substrate (68%) in addition to unsaturated ester **58**. During the same period, Boeckman[52] observed that the rearrangement of **57a** to **58** occurs quantitatively at room temperature in 24 h. However, the less strained homologue **59a**, upon heating in refluxing toluene in the presence of a catalytic amount of HOAc, provides an equilibrium mixture of **59a** and **60** (89:11). Support for a sigmatropic rearrangement rather than a pathway invoking stepwise formation of carbocation intermediates follows from the observation that the stereoisomer **59b** does not undergo rearrangement under conditions that are successful with **59a**. However, BF_3·Et_2O at room temperature is able to convert stereoisomer **57b** into **58**, ostensibly through a carbocation intermediate that may only be required for the isomerization (**57b** → **57a**) and not necessarily for the rearrangement. These investigators have also observed acceleration in the BF_3.Et_2O-catalyzed rearrangement at −78 °C in alkyl-substituted congeners of **59a**. These observations have led Boeckman to suggest that the minor product, unsaturated ester **62**, formed in the BF_3·Et_2O-catalyzed Diels–Alder reaction (−78 °C) between cyclopentadiene **61** and methyl 2-acetylacrylate, may well arise from the major product of the reaction, norbornene **63**, by way of the catalyzed retro-Claisen rearrangement.[53]

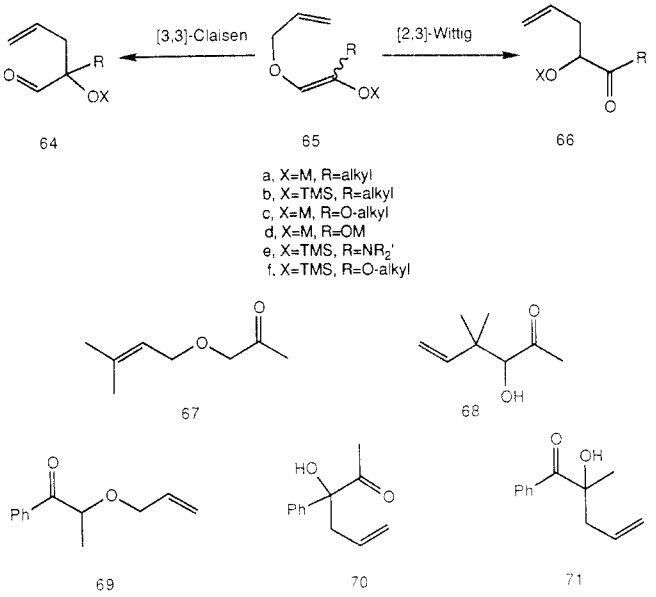


C. Competitive Rearrangements

1. [3,3] Claisen vs [2,3] Wittig Rearrangement

Conceptually, α-allyloxy enolates of the type **65a** can undergo either [3,3] sigmatropic rearrangement (anionic

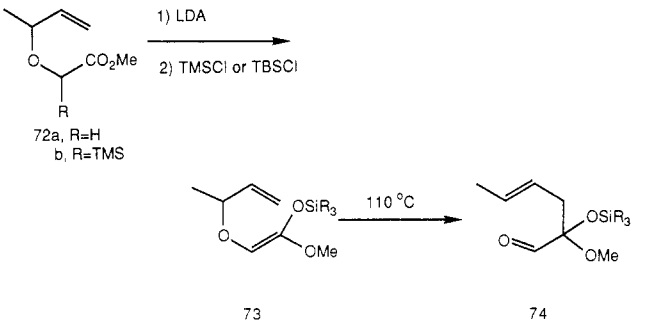
oxy-Claisen rearrangement)[46] or [2,3] Wittig rearrangement.[54] Thomas[55] has observed that ketone **67**, upon exposure to *t*-BuOK/*t*-BuOH, undergoes a [2,3] Wittig rearrangement to "mainly" ketol **68**. In contrast, Koreeda[46a] has reported that the enolate of phenyl ketone **69** (from MH and MeOH) in toluene not only shows rate enhancement (M = K, −23 °C, $t_{1/2}$ = 3.3 h; M = Na, 0 °C, $t_{1/2}$ = 2.6 h; M = Li, 96.5 °C, $t_{1/2}$ = 1.1 h) but also gives a ratio of Claisen to Wittig product (**70**:**71**) of >98:<2 (M = K, Na) and a ratio of ~80:20 when M = Li. To ensure exclusive formation of the Claisen product, enolates need only be O-silylated (**65a** → **65b**) and rearranged to aldehydes (**64b**). Accordingly, the *O*-trimethylsilyl enol ether of ketone **69** affords the *O*-trimethylsilyl derivative of ketone **70** upon heating (71 °C, $t_{1/2}$ = 0.5 h). Earlier, Salomon[56] had demonstrated the utility of the transformation **65b** → **64b** by preparing the *O*-trimethylsilyl enol ethers with (TMS)Cl/Et_3N. The α-silyloxy aldehydes could be cleaved readily with methanolic periodic acid to afford β,γ-unsaturated ketones.



Surprisingly, the ester enolates of generic structure **65c** do not undergo a [2,3] Wittig rearrangement[57] while their carboxylate-derived dianions (**65d**) and dialkylamide anions (**65e**) do rearrange by this pathway.[58] Exclusive Claisen rearrangement of these substances can be accomplished via the trimethylsilyl ketene acetals (**65f** → **64f**). This procedure has been described independently by Nakai[57] and Raucher[59] in the transformation of ester **72a** to its (*Z*)-*O*-silyl ketene acetal **73** followed by Claisen rearrangement to the masked α-keto aldehyde **74**. Significantly, when the C-silylated ester **72b** is treated with tetra-*n*-butylammonium fluoride, formation of the [2,3] Wittig product occurs. On the other hand, the *O*-silyl derivative **73** gives the starting ester **72a**. This observation has led Nakai to suggest that a common "naked" anion is not involved in the two pathways but that separate C- and O-hypervalent silicon species are responsible for the dual reaction pathways.

2. Divinylcarbinol Derivatives

The competitive rearrangement of 4-vinylallyl vinyl ethers has provided information on the relative rates

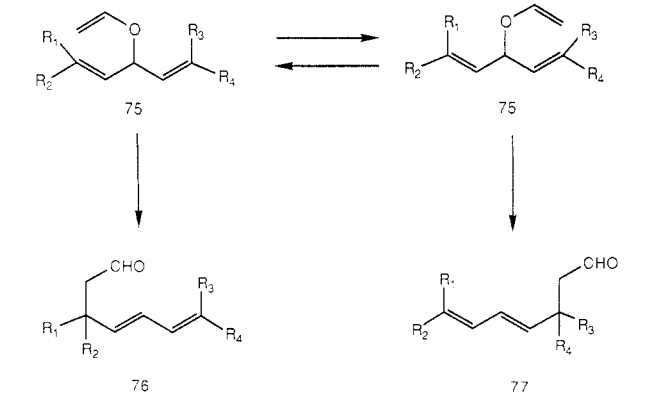


of substituted allyl residues. Scheme I illustrates such a study[60] wherein the β-substitution pattern of the allylic residue of allyl vinyl ether **75** is systematically altered. The vinyl residue reacts twice as fast as the (*E*)-β-vinyl group (**76a**:**77a**) and 19 times faster than the (*Z*)-β-vinyl (**76b**:**77b**). At first hand, these data suggest that, in a competition between the (*E*)- and (*Z*)-β-vinyl groups, the E isomer should react 9.5 times faster (**76b**:**77b** to **76a**:**77a**); the observed result is ~3:1 (**76c**:**77c**). As has been suggested,[61] each nonreacting group is a substitution for its reacting partner and need not offer additive substituent effects in each rearrangement. The presence of a 6-methyl substitution (*E* configuration) has a limited effect on the rate of rearrangement of vinyl ethers or silyl ketene acetals (cf., **29** vs **30a**). Terminal 6,6-substitution with two methyl substituents completely favors formation of **76d** over **77d**.

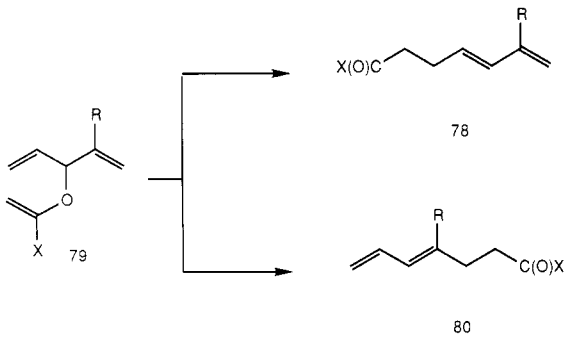
Parker and Farmar[62] have uncovered a subtle selectivity in the rearrangement of the series of divinylcarbinol derivatives **79**. The methyl substituent in **79a** and **79b** provides a small steric deceleration[63] while the less sterically demanding methoxyl group manifests itself as a decelerating C_5-donor group in both **79c** and **79d**. These observations lend additional support to the Burrows–Carpenter model for C_5-donors.[31]

For divinylcarbinols wherein one of the vinyl substituents is contained in a ring, rearrangement with the acyclic vinyl group is preferred when the acyclic unit is unsubstitued. Thus, vinyl ethers **82a** and **82b** give **81a** and **81b**, respectively, with high selectivity. The presence of an (*E*)-β-methylvinyl group retards acyclic rearrangement, but it still remains the major pathway for the rearrangement of **82d**.[64,65]

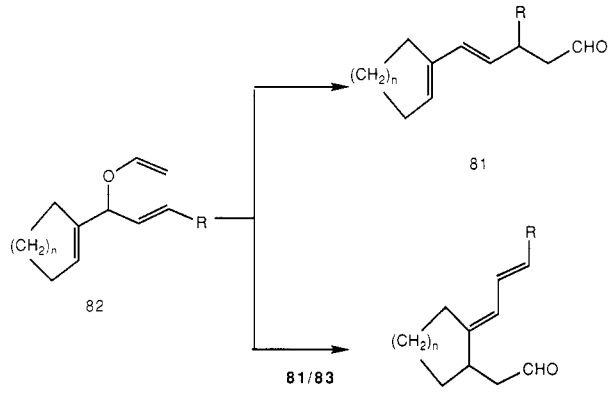
SCHEME I



	76/77
a, R_1=R_2=R_3=H; R_4=Me	2/1
b, R_1=R_2=R_4=H; R_3=Me	95/5
c, R_1=R_4=H; R_2=R_3=Me	78/22
d, R_1=R_2=H; R_3=R_4=Me	100/0



78/80	
a, R=Me, X=OEt	65/35
b, R=Me, X=NMe_2	74/26
c, R=OMe, X=OEt	95/5
d, R=OMe, X=NMe_2	97/3

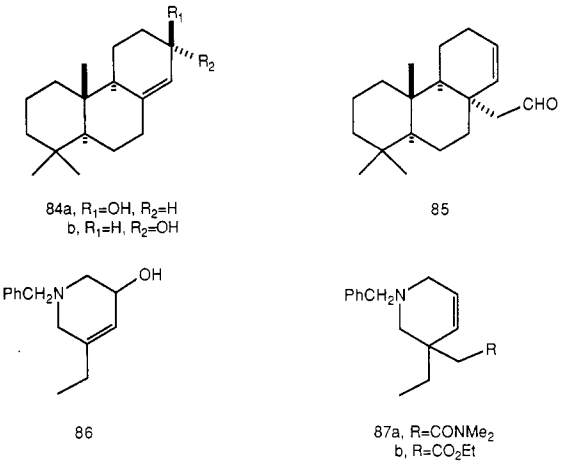


81/83	
a, R=H, n=1	89/11
b, R=H, n=2	88/12
c, R=Me, n=1	50/50
d, R=Me, n=2	65/35

3. Elimination

Alternative sigmatropic rearrangements are not the only irreversible processes that can compete with the Claisen rearrangement; elimination reactions are troublesome. This undesirable, competitive process is particularly acute when at least one olefin is contained in a ring. Cyclohex-2-en-1-ols have been particularly notorious in this regard. Ireland and co-workers[66] have prepared the isomeric allylic alcohols **84a** and **84b** by reduction of the corresponding enone. The minor axial alcohol **84a**, when subjected to mercuric ion catalyzed exchange with ethyl vinyl ether, undergoes elimination to dienic products. On the other hand, the major, equatorial allylic alcohol rearranges to aldehyde **85** without incident. An unfavorable transition state for the Claisen rearrangement in the former case may be the result of steric interactions between the angular methyl group and the forming C–C bond.

When confronted with the problem of elimination, the use of an alternative strategy is often beneficial. Thus, allylic alcohol **86**, when subjected to the Eschenmoser ketene *O,N*-acetal variant, provides only a 45% yield of the desired amide **87a** along with the products of disproportionation of the dihydropyridine, the immediate product of elimination. However, the Johnson orthoester route gives the ester **87b** in 74% yield.[67,68]



D. Stereochemistry

1. Transition State

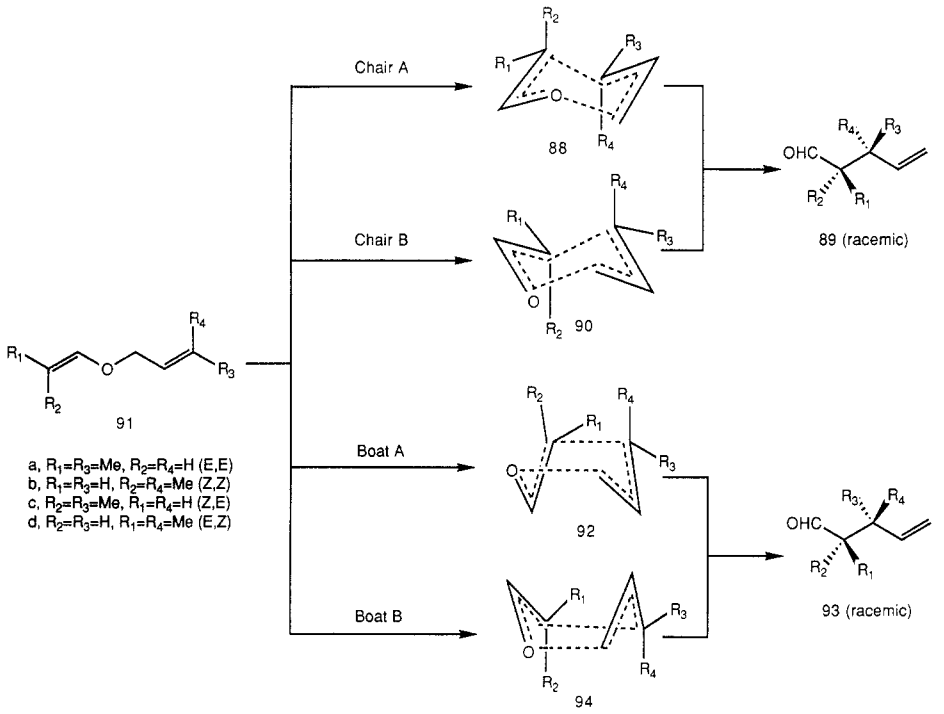
The Claisen rearrangement is a suprafacial, concerted, nonsynchronous pericyclic process that may be considered phenomenologically as an intramolecular S_N2' alkylation. When the sp^2-hybridized C_1- and C_6-positions of allyl vinyl ether are substituted to provide enantiotopic faces at both termini, the rearrangement can proceed through two pairs of stochastically achiral transition states to provide two racemic diastereomers bearing newly created centers of asymmetry at C_2 and C_3 of the products (Scheme II). Thus, achiral allyl vinyl ether **91** can provide two enantiomeric chairlike transition states **88** and **90**, both of which lead to the racemic diastereomer **89**. Similarly, the enantiomeric boatlike transition states **92** and **94** provide racemic, diastereomeric aldehyde **93**. The two transition states are inherently unequal in energy and the ratio **89**:**93** reflects the transition-state geometry.

In a detailed study modeled after the Doering and Roth experiments that revealed the preferred chairlike transition state for the Cope rearrangement,[69] Schmid[26b,c] and his collaborators have examined the rate and stereochemistry of rearrangement of the four crotyl propenyl ethers **91a–d** in the gas phase at 160 °C. All isomers show the expected negative entropy of activation ($\Delta S^{\ddagger}$ = −10 to −15 eu) with enthalpies of activation ranging from 25 to 27 kcal/mol. Each isomer shows a clear preference for the chairlike transition state (**91a**, 95.9:4.1; **91b**, 94.7:5.3; **91c**, 95.5:4.5; **91d**, 95.4:4.6). The *E* isomer **91a** is found to rearrange an order of magnitude faster than the *Z,Z* isomer **91b**, with the other two geometric isomers intermediate in rate. The *E,E* and *Z,Z* isomers rearrange through a chairlike transition state to give the threo isomer **89a** (**89b**) as the major product; likewise, the *Z,E* and *E,Z* isomers give the erythro isomer **89c** (**89d**) as the predominant stereoisomer. Since the four isomers **91** all proceed through the chairlike transition state, a change in the geometry of a single double bond exchanges the enantiotopicity of the faces of the double bond and leads to the opposite stereoisomer. Indeed, any pairwise change in olefin geometry for a given transition state, or single change of olefin geometry and change in transition state, results in the formation of the same diastereomer.[70]

2. Vinyl Double-Bond Geometry

Before proceeding to other substituent effects and how they control the transition state of the Claisen rearrangement, it is appropriate to consider the methods that are available to control the geometry of the vinyl double bond. Unfortunately, no convenient

SCHEME II

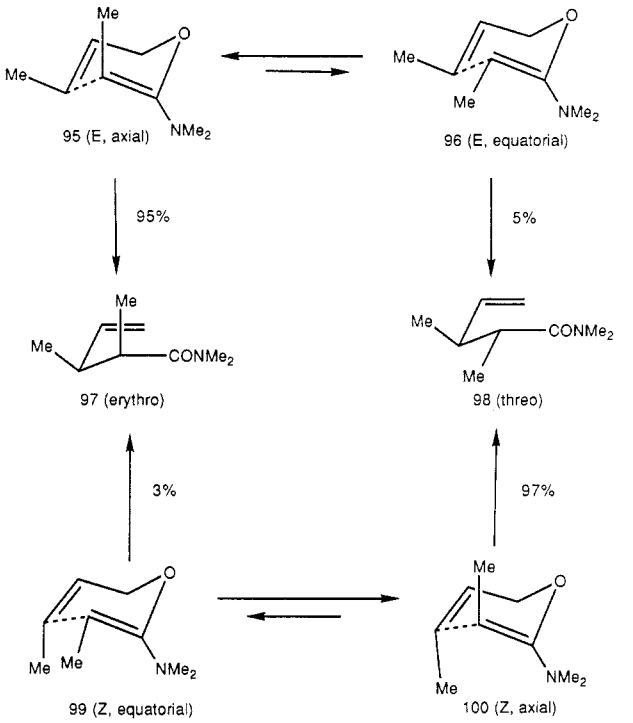


methods are available for the selective preparation of propenyl ethers. The same difficulty exists with the Johnson orthoester method. The use of orthoesters derived from propionic acid derivatives and their higher analogues fail to give stereochemically defined ketene acetals.[71] However, the ketene *O,N*-acetal rearrangement does provide for selectivity. Sucrow and Richter[72] have examined the Claisen rearrangement of the dimethyl acetal of *N,N*-dimethylpropionamide with (*E*)- and (*Z*)-crotyl alcohol (Scheme III). Although the intermediate ketene *O,N*-acetals are generated in situ and are not isolated, the assumption that a chairlike transition state is operable, coupled with a preferred axial orientation of the C_1-methyl group of the (*E*)-ketene *O,N*-acetal (**95**, **100**), correctly accounts for the stereochemistry of the products. The latter supposition is tenable as the dimethylamino group assists in delocalizing charge in the transition state and interacts with the C_1 substituent when it is equatorially disposed.[73]

An alternative approach to the use of the ketene *O,N*-acetals has been offered by the work of Ficini[74] who has employed 1-(*N,N*-diethylamino)-1-propyne (**101**) as the propionate source; however, no stereochemical study was conducted. Recognizing that the (*Z*)-ketene *O,N*-acetals of Scheme III are the products of thermodynamic control, Bartlett and Hahne[75] have prepared the less stable, kinetic (*E*)-ketene *O,N*-acetal by the stepwise, cis addition of the crotyl alcohols across the triple bond of the Ficini ynamine (Scheme IV). The slow addition of the crotyl alcohol to the ynamine at 140 °C serves to make rearrangement, a trap for the kinetic addition product, competitive with isomerization. Protonation of the ynamine provides the ketene immonium cation **102**, which adds alkoxide preferentially syn to the hydrogen atom via path A. In the case of the (*Z*)-alcohol, a 2.5:1 ratio of **108** to **107** is obtained; the (*E*)-alcohol also preferentially follows path A through **105** leading to a 2:1 ratio of **107** to **108**.

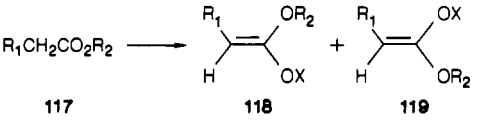
The Ireland variant[21] of the Claisen rearrangement has proved the most adaptable for the control of vinyl

SCHEME III



olefin geometry. The deprotonation of esters by lithium dialkylamide bases developed by Rathke[22,76] has proved amenable to the generation of specific enolates. Thus, treatment of butenyl propionates **110** and **114** (Scheme V) with lithium diisopropylamide (LDA) in THF under these kinetic conditions forms principally the (*Z*)-lithium enolates, which upon silylation (*tert*-butyldimethylsilyl (TBS) gives the (*E*)-*O*-silyl ketene acetal.[77,78] Rearrangement of silyl ketene acetal **109** provides an 87:13 mixture of acids **111** and **115** after desilylation while **116** gives an 89:11 ratio of **115** and **111**. These two products can also be obtained by using 23% HMPA–THF (HMPA = hexamethylphosphoramide)

TABLE I. Geometry of Enolate Formation

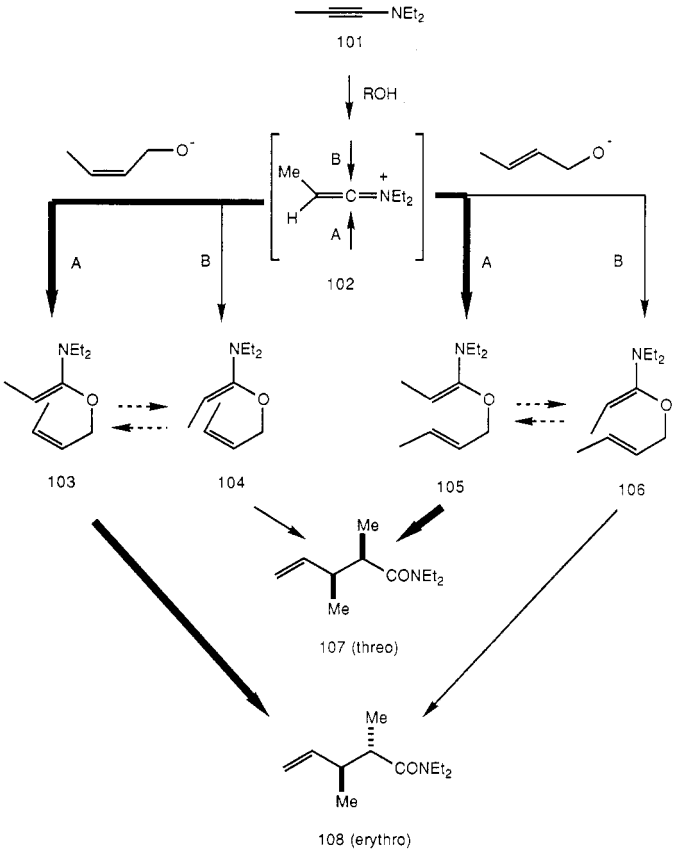


117 118 119

entry	ester	R_1	R_2	X[a]	solvent[b]	118/119
1	**117a**	C_2H_5	CH_3	TBS	THF	91/9[21b]
2	**117b**	$(CH_3)_3C$	CH_3	TBS	THF	97/3[21b]
3	**117c**	CH_3	C_2H_5	TMS	THF	85/15[80]
4	**117d**	C_2H_5	$(CH_3)_3C$	TBS	THF	95/5[21b]
5	**117e**	CH_3	CH_3	TES	23% HMPA-THF	9/91[81]
6	**117a**	C_2H_5	CH_3	TBS	23% HMPA-THF	16/84[21b]
7	**117b**	$(CH_3)_3C$	CH_3	TBS	23% HMPA-THF	9/91[21b]
8	**117c**	CH_3	C_2H_5	TMS	23% HMPA-THF	0/100[80]
9	**117c**	CH_3	C_2H_5	TES	23% HMPA-THF	13/87[81]
10	**117f**	CH_3	$(CH_3)_2CH$	TES	23% HMPA-THF	17/83[81]
11	**117d**	C_2H_5	$(CH_3)_3C$	TBS	23% HMPA-THF	23/77[21b]

[a] TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; TES = triethylsilyl. [b] Enolates were generated with LDA, −70 to −78 °C.

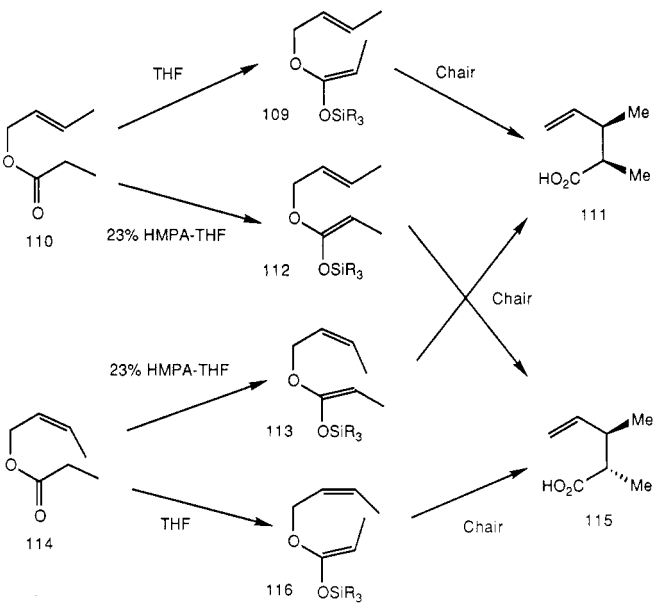
SCHEME IV



as an optimal solvent system for the generation of the thermodynamic[79] (*E*)-lithium enolates ((*Z*)-*O*-silyl ketene acetals **112** and **113**). *Z*-(*O*)-Silyl ketene acetal **112** provides an 81:19 mixture of **115** and **111** while **113** affords an 86:14 mixture of **111** and **115**. The major diastereomer in each rearrangement arises through the chairlike transition state, and once again, a single exchange of olefin geometry results in the other diastereomer becoming the major product. The erosion of diastereoselectivity can be attributed to two factors: the geometric integrity of the silyl ketene acetals and the selectivity of the chairlike vs boatlike transition state.

Table I provides examples for the selectivity of enolate formation by the LDA/silylation procedure.[82] The entries are listed in ascending bulk of the alcohol portion of the ester group for a given solvent. In general, enolate formation by the kinetic deprotonation procedure is somewhat more selective than the thermodynamic conditions. Because the silyl ketene acetal ratios are approximately equal to, or better than, the ratio of diastereomers **111** to **115**, the chairlike transition state is virtually the exclusive pathway for rearrangement.

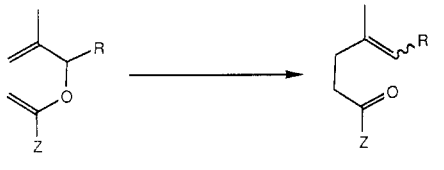
SCHEME V



3. Secondary Allylic Alcohols

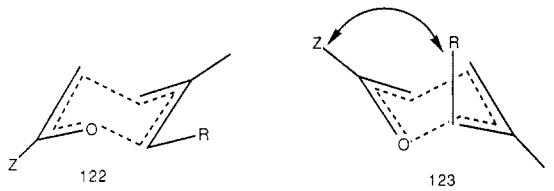
Although the aliphatic Claisen rearrangement of secondary allylic alcohols had been recognized to provide *E* double bonds,[83] Faulkner and Petersen[84] have examined the selectivity of olefin formation as a function of C_2 substituents. The vinyl ether rearrangement of vinyl ether **120a** provides a 90:10 ratio of (*E*)- to (*Z*)-unsaturated aldehydes **121a**. The congener **120b** bearing an isopropyl rather than an ethyl substituent is more selective affording a 93:7 ratio of (*E*)- to (*Z*)-olefinic aldehydes **121b**. An increase in the steric bulk of the C_2 substituent produces higher stereoselectivity. Thus, ketene *O*,*N*-acetal rearrangement of **120c** gives an *E*:*Z* ratio of 99.4:0.6 while the product from the 2-methoxypropene derivative of 2-methylpent-1-en-3-ol (**120d**) provides less than 1% of the (*Z*)-olefin. Simi-

larly, Katzenellenbogen[85] has reported less than 1% of (*Z*)-olefin in the silyl ketene acetal rearrangement of **120e** and Johnson[86] has observed >98% *E* selectivity in the orthoester rearrangement of **120f**. This dramatic increase in selectivity observed in the C_2,C_4-substituted examples has been rationalized as the result of a pseudo-1,3-diaxial interaction in chairlike transition state **123** that leads to the (*Z*)-olefin as opposed to the less congested chairlike transition state **122** that gives the (*E*)-olefin.[84,87,88]



120 121

a, R=Et, Z=H
b, R=i-Pr, Z=H
c, R=Et, Z=NMe_2
d, R=Et, Z=Me
e, R=n-C_6H_{13}, Z=OTBS
f, R=$CH_2CH_2CH(Me)=CH_2$



122 123

When the secondary allylic alcohol has a substituent at the terminus of the double bond (i.e., C_6), a center of asymmetry is destroyed during the rearrangement as a new one is created. This process has been often called "self-immolative"[89] and involves the "transfer of chirality".[2f] In the sense that racemic substances bearing centers of asymmetry are chiral, and recognizing the concerted, suprafacial nature of the rearrangement, the transformation of Scheme VI is, by necessity, chiral throughout. In more modern terms, that which is transferred is stereogenicity[90] (i.e., stereochemical information), and when practiced with enantiomerically pure allyl vinyl ethers (**124**), the rearrangement affords enantiomerically pure products (**126**).

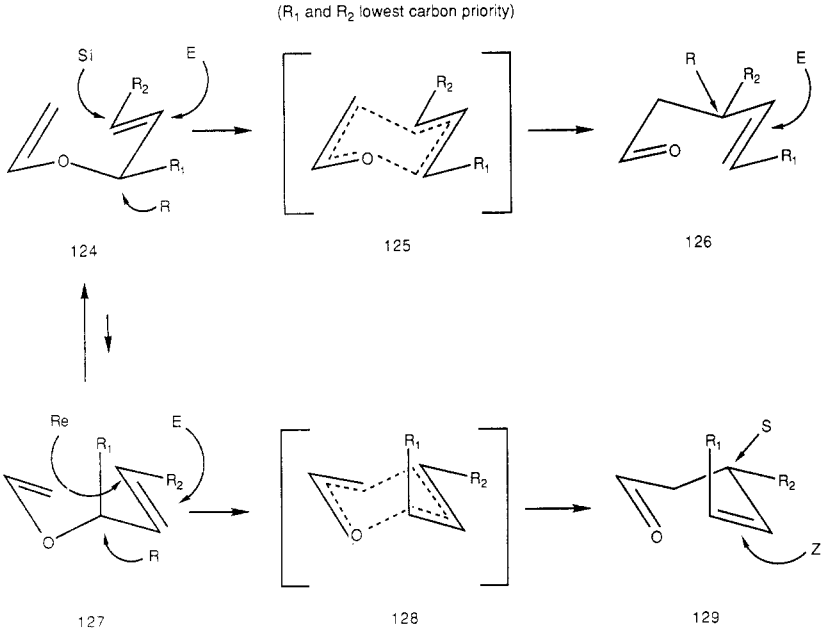
In the example of Scheme VI, the *R*,*E* enantiomer **124** bearing an equatorial R_1 substituent undergoes bond formation on the *si* face of the allylic double bond to produce the *R*,*E* enantiomer **126**. Conformational inversion of **124** leads to (*R*,*E*)-**127**. This conformation can undergo *re* bond formation through transition state **128** having the R_1 substituent axial, resulting in the formation of *S*,*Z* enantiomer **120**. Thus, the transition-state integrity may be monitored with enantiomerically pure reactants by measuring the enantiomeric excess of the dihydro aldehydes from reduction of **126** and **129**. In the racemic series, the value $(E - Z)/(E + Z)$ equals the enantiomeric excess that would be obtained using enantiomerically pure allylic alcohols. The chairlike vs boatlike transition state is not detectable in this case because there is no C_1 substituent.

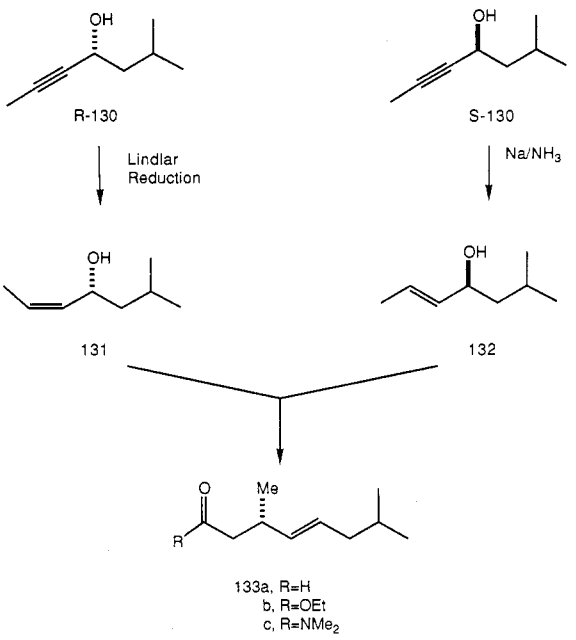
Hill has observed the "transfer of chirality" in the vinyl ether rearrangement of enantiomerically pure cyclopent-2-en-1-ol.[91a] The Eschenmoser and Johnson variants with enantiomerically pure (*E*)-pent-3-en-2-ol give products with 90% retention of enantiomeric purity as determined by optical rotation.[91b,c,92]

An ingenious, enantioconvergent variation on this theme has been executed by Chan.[93a] The enantiomers of propargyl alcohol **130** are prepared by resolution. The *R* enantiomer is reduced to the (*R*,*Z*)-allylic alcohol **131** while the *S* enantiomer is converted to the (*S*,*E*)-allylic alcohol **132**. Rearrangement to form the aldehyde, ester, or amide **133** occurs with "chirality transmission" of 94–99%. Thus, the (*R*,*Z*)-olefin exposes the *re* face while the (*S*,*E*)-olefin invokes the same *re* face, affording a single enantiomer, the (*S*,*E*)-olefin **133**. Clearly, the other enantiomer, (*R*,*E*)-**133**, is accessible by exchanging the reduction procedure for each enantiomer of **130**.[94]

The advent of the Sharpless kinetic resolution procedure[95] and the Midland asymmetric reduction of α,β-acetylenic ketones[96] has made a variety of secondary allylic alcohols readily available in both enantiomeric forms, thereby obviating the use of classical resolution.

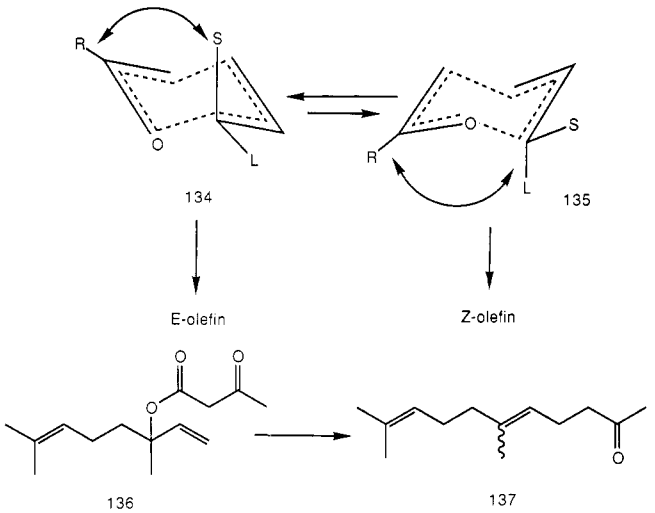
SCHEME VI





4. Tertiary Allylic Alcohols

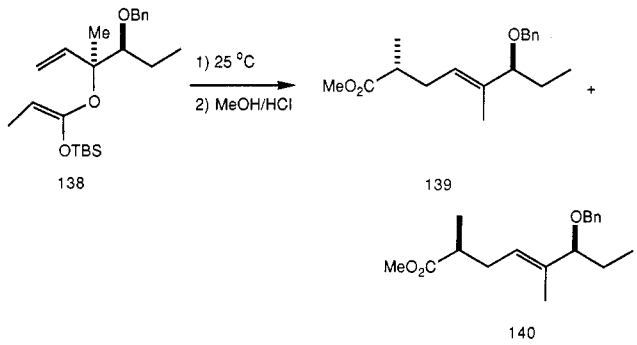
Tertiary allylic alcohols fail to give trisubstituted olefins with high selectivity. The transition states **134** and **135** are nearly isoenergetic when the substituents S (small) and L (large) are not branched. The lack of selectivity is present even when C_2 is substituted.



As an example, linalool acetoacetate (**136**), when subjected to the Carroll rearrangement, gives a 54:46 *E*:*Z* ratio of olefinic ketones **137**.[97] A similar ratio is realized with linalool using the Marbet–Saucy conditions (2-methoxypropene).[15a,16] Rearrangement of (*Z*)-silyl ketene acetal **138**, which is derived from a tertiary allylic alcohol bearing an α-branched "large" group and a methyl, provides a 7:1 ratio of esters **139** and **140**, respectively.[98] The olefin geometry is exclusively of the *E* geometry which requires the branched group to occupy an equatorial position in the transition state. The ratio of diastereomers is in accord with the enolization stereoselectivity.[99]

5. Ring-Bearing Substrates

Thus far the stereochemical discussions have focused upon rearrangements wherein neither olefin is contained in a ring, i.e., acyclic substrates. In ring-bearing allyl vinyl ethers, the boatlike transition state can be the major, if not exclusive, pathway for rearrangement.

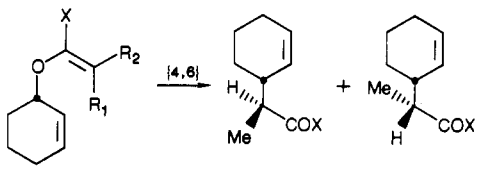


Before proceeding, it is worthwhile to consider a mnemonic device to describe various ring systems. The carbons (see structure **3**) to which the tether bridging the pericyclic array is attached are expressed in the form {*m*,*n*;*o*,*p*;...}. Thus, acyclic system **138** → **139** would be designated as a {0,0}, **86** → **87** a {4,6}, and **54** → **53** a {1,6}-rearrangement.

Bartlett and Pizzo[68d] have investigated the {4,6}-rearrangement illustrated in Table II with several propionate equivalents. Entries 1–4 involve routes that control C_1 stereochemistry; entry 5 does not. Entries 1 and 2 permutate two control elements, vinyl group geometry, and transition state, thereby providing the same major isomer. Entry 3, wherein the vinyl group has predictable *Z* geometry,[72] partitions equally between the chairlike and boatlike transition states. The ynamine experiment suggests high *E* selectivity in the formation of the vinyl group and a strong preference for the boatlike transition state as any (*Z*)-olefin would cause erosion of stereoselectivity.

Ireland and his collaborators have examined the stereochemical course of the {4,6}-rearrangement of a number of carbohydrate-derived pyranoid and furanoid glycals as a prelude to the synthesis of complex natural products. (*Z*)-*O*-Silyl ketene acetal **144a**, derived by deprotonation of the propionate ester with lithium hexamethyldisilazide (LiHMDS, a reagent equivalent to 23% HMPA–THF for the generation of *Z* OLi enolates),[100] rearranges to provide ultimately a 90:10 mixture of esters **145** and **146**, respectively, wherein the boatlike transition state dominates. However, (*E*)-*O*-silyl ketene acetal **144b** gives a 65:35 ratio of the two diastereomers, with ester **145** still predominating, re-

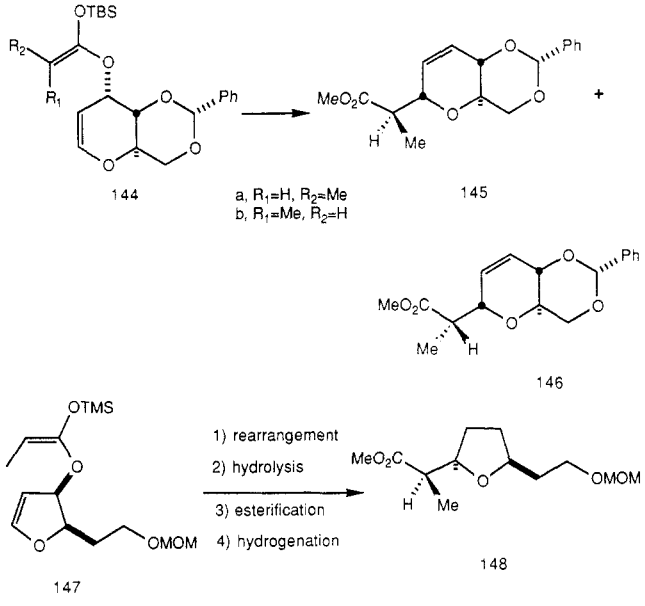
TABLE II. Chair vs Boat Transition States in Cyclohexenol Derivatives



141 142 143

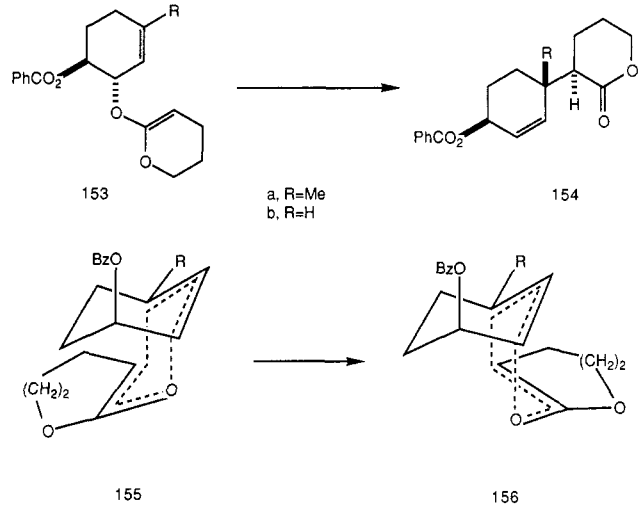
entry	method	X	R_1	R_2	142/143	favored TS
1	LDA/THF	OTBS	Me	H	85/15	chair
2	LDA/THF, 23% HMPA	OTBS	H	Me	75/25	boat
3	orthoamide	NEt_2	Me	H	50/50	neither
4	ynamine	NEt_2	H	Me	>90/10	boat
5	orthoester	OEt	(Me, H)		70/30	???

quiring the chairlike transition state to be slightly favored. In a related example, the (*E*)-*O*-silyl ketene acetal of the furanoid glycal **147** (from LDA deprotonation) gives principally (86–89% selectivity) stereoisomer **148** via a boatlike transition state.[101]

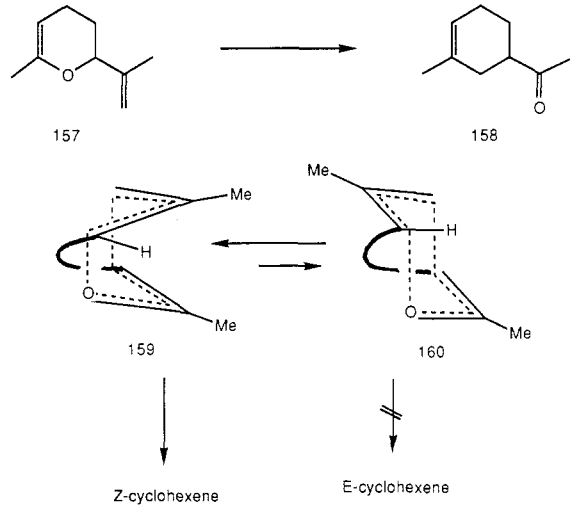


The Bartlett[68d] and Ireland[100,101] studies have been rationalized for the 6-membered ring case as is illustrated in Scheme VII. Chairlike transition state **149** is disfavored relative to the boat **150** as the methyl and X groups interact with ring substituents. The chairlike transition state **151** is slightly favored over the boat **152** as the steric interactions of the methyl group with the ring in **152** are seemingly greater than the interactions experienced by the X substituent in **151**. Once again, the change of two stereocontrol factors produces the same diastereomer.

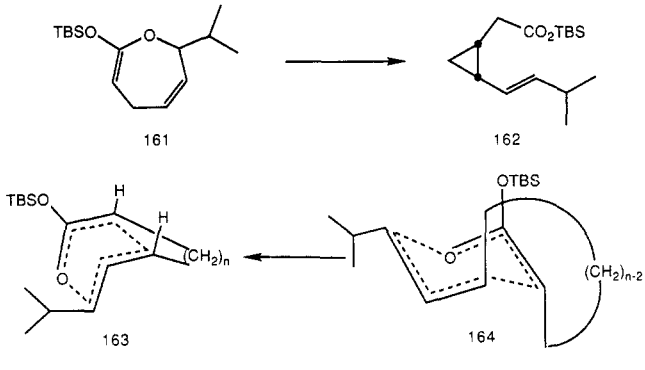
Perhaps the most dramatic example of the intercedence of the boatlike transition state comes from Lythgoe's elegant application of the Claisen rearrangement to syntheses in the vitamin D field.[102] Ketene acetals **153a,b** of the {1,2;4,6}-type, whose vinyl olefins are perforce of the *E* geometry owing to the presence of the ring, rearrange exclusively through the boatlike transition state. The substituents of conformation **149**, having been transformed into the ring of **155**, exacerbate the steric interactions and allow only the boatlike transition state **156** to prevail.



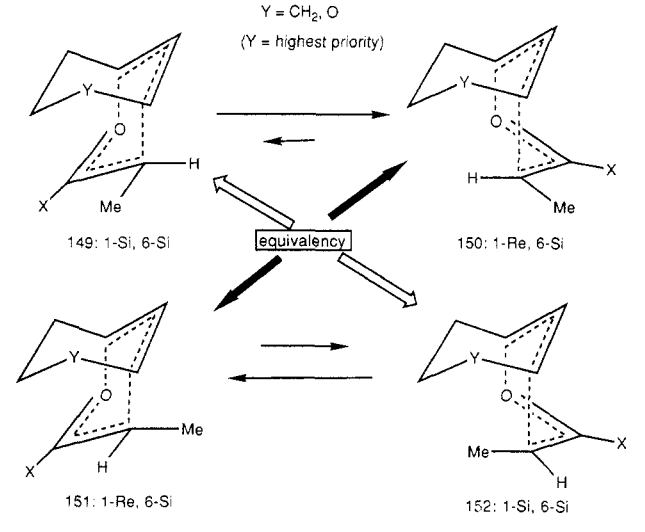
Conformational restraints on the transition state can be observed in both the {1,4}- and {1,6}-rearrangements. The former case, the operational equivalent of a "meta-Diels–Alder reaction" (**157** → **158**) when the tether is two carbons in length,[103] is constrained to proceed through boatlike transition state **159**, as the chairlike transition state **160** would lead to a strained (*E*)-cyclohexene.



The {1,6}-rearrangement, when constrained by a short tethered chain (**54** → **53**, **56** → **55**, or **161** → **162**), can proceed with greater facility through the boatlike transition state **163** rather than the more strained chairlike transition state **164**.[104]



SCHEME VII

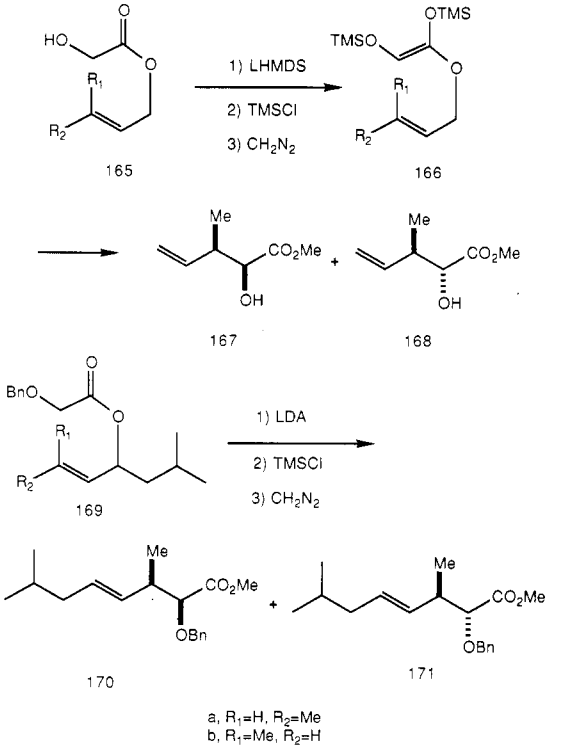


IV. Heteroatom Substituents

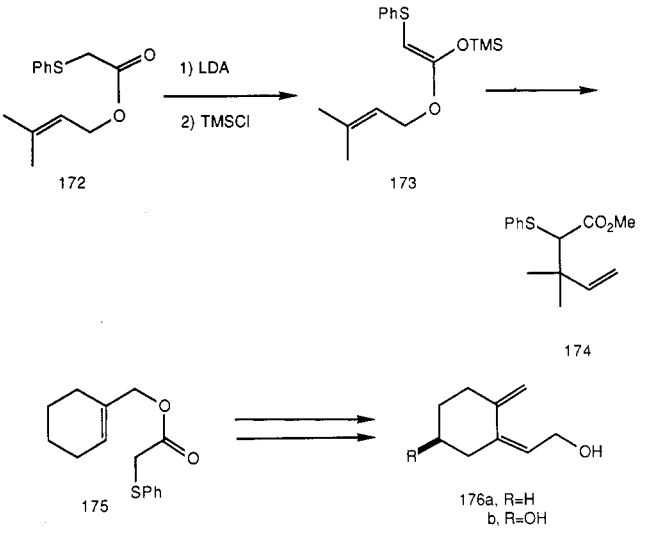
A. The Vinyl Group

1. C_1 Hetero Substituents

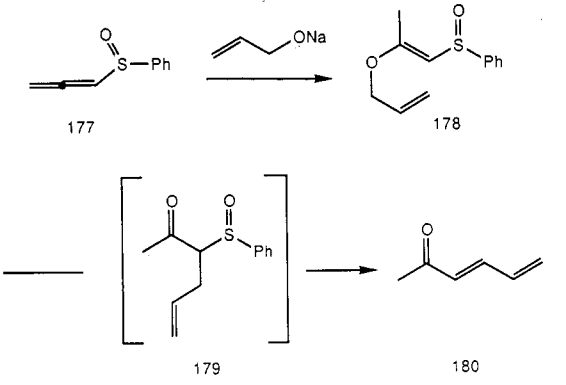
The presence of a C_1-hydroxyl or -alkoxy group has been utilized to control enolate geometry. While early investigations exploited the reaction from the synthetic viewpoint,[105] a detailed analysis of the stereochemistry of the reaction awaited the studies of Bartlett[106a] on lactate and mandelate esters and, contemporaneously, Burke,[106b] Fujisawa,[106c,e,f] and Kallmerten[94a,106d] on glycolate esters. The hydroxyl or alkoxy group serves to form a chelated enolate. In the case of the α-hydroxy ester dianion, rearrangement does not proceed smoothly;[106c] but, it may be expedited by bis-O-silylation prior to rearrangement. The α-alkoxy ester enolates are also converted to their *O*-silyl ketene acetals prior to rearrangement. The (*E*)-butenyl glycolate ester **165a** affords a 98:2 ratio of esters **167** and **168**, respectively, after rearrangement, hydrolysis, and esterification. The reaction is stereospecific as the (*Z*)-butenoate gives a 2:98 ratio (**167** and **168**) of the two α-hydroxy esters.[106c] Similarly, allylic esters **169a** and **169b** rearrange with 100:1 diastereoselectivity; (*E*)-allylic ester gives principally α-benzyloxy ester **170** while **169b** provides mainly ester **171**.[94a] Worthy of note is the observation that an α-[(*tert*-butyldimethylsilyl)oxy]-acetate ester forms the nonchelated *Z* lithium enolate.[94b,107]



While the role of α-amino functionality has been explored, the reaction has been applied principally to the synthesis of unique amino acids.[108] On the other hand, α-thio substituents have proved useful as agents for the manipulation of functionality. The rearrangement of allyl α-(phenylthio)acetates, which can lead to a variety of sulfur-free products, has been reported by Lythgoe.[109] The α-phenylthio ester **174** can be oxidatively degraded to 2,2-dimethyl-3-butenal. The rearrangement of α-phenylthio ester **175** leads after several operations to (*Z*)-dienol **176a**, a model transformation for the preparation of diol **176b**, a degradation product of vitamin D_2.[106g]

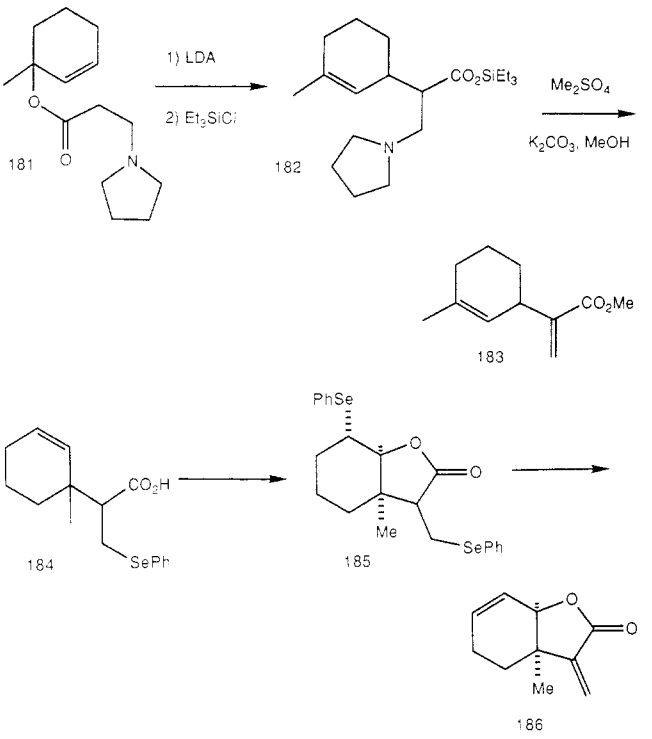


Cookson[110a] has examined the addition of allylic alkoxides to allenic sulfoxide **177**. When the isolated adduct **178** is subjected to rearrangement, subsequent sulfoxide elimination occurs, leading to dienone **180**. Similar processes have been initiated by the addition of allylic alcohols to (phenylthio)acetylene to form dienals[110b] and to phenylthio ynamines to produce α,β;β,γ-unsaturated amides.[110c]

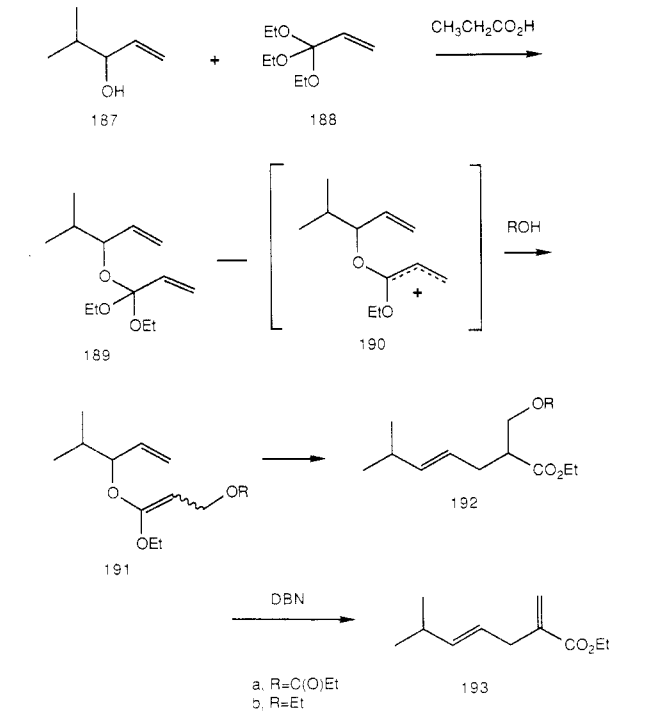


2. C_1 Carbon Hetero Substituents

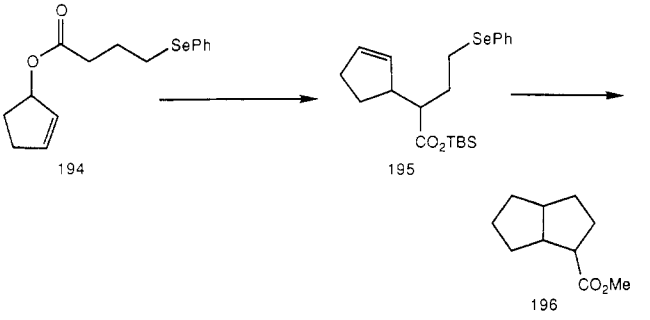
An increase in the oxidation level at the β-position of propionate residues permits the formation of α-methylene esters and α-methylene γ-butyrolactones, the latter functionality arising through halo- and selenolactonization techniques. Still[111] has demonstrated that allyl 3-pyrrolidinopropionate **181** can be deprotonated without elimination and the resultant triethylsilyl ketene acetal rearranges to ester **182**. The silyl ester is transformed into the methyl acrylate in a single operation. Similarly, Raucher[112] has used 3-methylcyclohex-2-en-1-ol in conjunction with trimethyl 3-(phenylseleno)orthopropionate to produce acid **184**. Selenolactonization and subsequent double selenoxide elimination leads to the α-methylene γ-butyrolactones **186**. Owing to the thermal instability of the selenium-based reagent, trimethyl β-methoxyorthopropionate is a suitable substitute. The resultant β-methoxy esters undergo facile elimination to the acrylates with potassium *tert*-butoxide.[113]



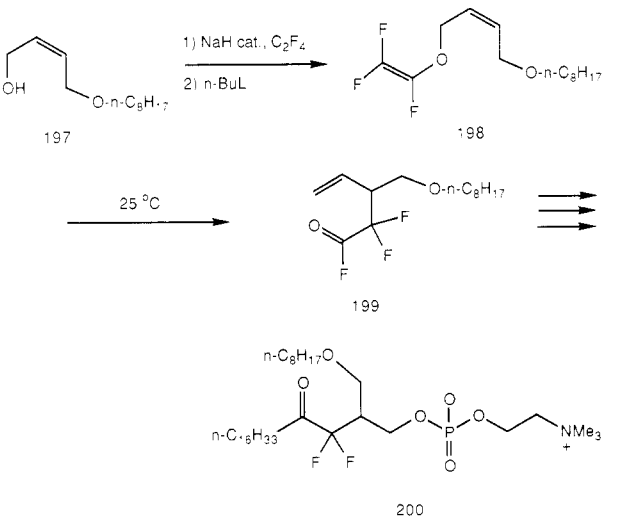
An intriguing variation on the preceding themes employs triethyl orthoacrylate (**188**).[114] The presence of the acrylate double bond in exchange product **189** prohibits elimination to a ketene acetal until a nucleophile (ethanol or propionic acid) adds to the highly stabilized carbocation **190**. The use of catalytic acid is deleterious as the cation consumes the acid (**191a**).[115] Use of excess acid (1.5 equiv) provides **192a** and **192b** in 66 and 16% yields, respectively. While the major product undergoes elimination with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN), the use of potassium *tert*-butoxide, as described by Raucher,[113] should also afford acrylate **193**.



The 4-(phenylseleno)butyrate ester **194** serves as a source for radical-initiated carbocyclization. Rearrangement of the silyl ketene acetal of **194** provides the cyclopentene **195**, which is subject to reductive cyclization with triphenylstannane followed by transesterification to methyl ester **196**.[116]



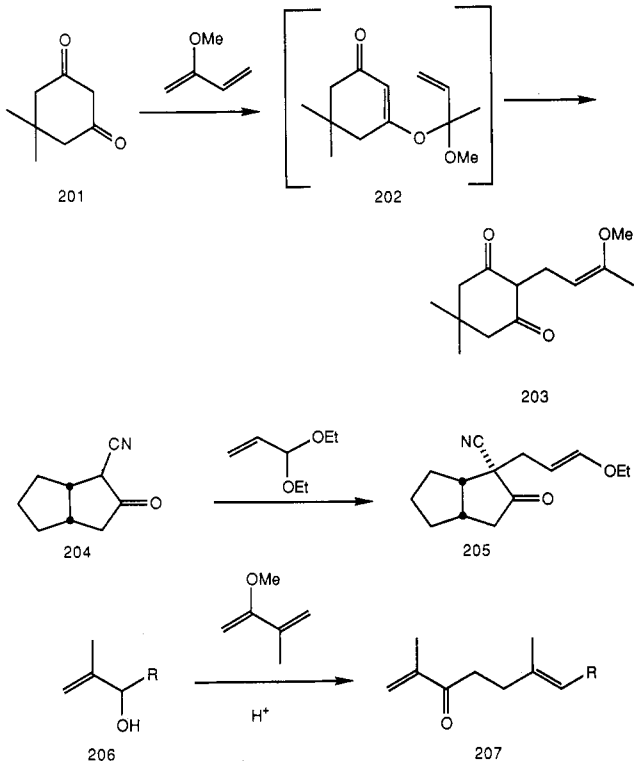
The fluorine-containing phospholipid **200**, designed as an inhibitor of cobra venom phospholipase A_2, has been prepared via rearrangement of trifluorovinyl ether **198**.[117] Not only is the vinyl ether prepared by a unique method not available in the protio series, but the rearrangement is markedly accelerated by the presence of the fluorine atoms.[48]



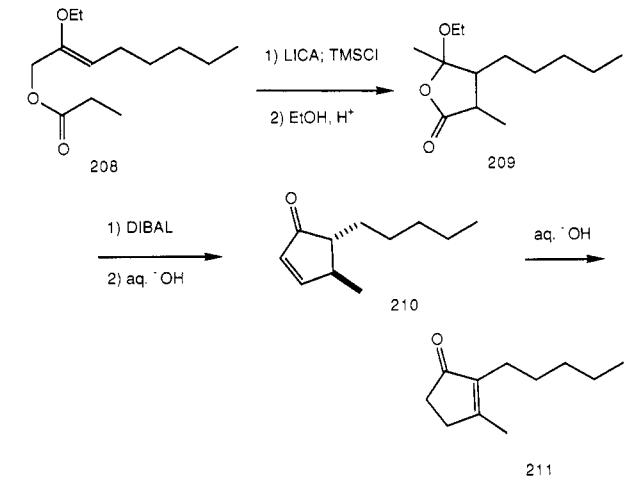
B. The Allylic Group

1. Oxygen Substituents

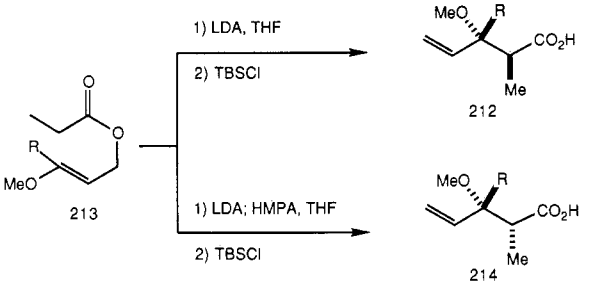
Dimedone (**201**) is in facile equilibrium with its enol, which can effect autocatalytic exchange with 2-methoxy-1,3-butadiene to generate the 4-methoxy allyl vinyl ether **202**. Rearrangement affords enol ether **203**, whose hydrolysis product is the equivalent of having effected a Michael addition of dimedone to methyl vinyl ketone.[118] Similarly, β-keto nitrile **204** reacts with the diethyl acetal of acrolein in refluxing benzene to provide enol ether **205**, with bond formation occurring on the convex face of the bicyclooctanone ring system.[119] In the transformation **201** → **203**, the 3,4 double bond of 2-methoxy-1,3-butadiene functions as an allyl component. The 1,2 double bond of the diene may also serve as a vinyl component in reactions with allylic alcohols (**206** → **207**).[25] These processes are also accomplished with ketals of α,β-unsaturated ketones.[120]



The use of C_5-oxygen-substituted allyl vinyl ethers can serve as 1,4-dicarbonyl compounds that lead to cyclopentenones via an intramolecular aldol condensation. This process had been implemented by Ireland and Mueller[21a] in their early studies on the ester enolate rearrangement. Rearrangement of vinyl ether **208**, having C_5 at a ketone oxidation level, results in the isomeric vinyl ether that undergoes facile lactonization to **209**. Generation of an intermediate hemiacetal by reduction with DIBAL and subsequent mild base treatment realizes cyclopentenone **210**; more vigorous base treatment isomerizes enone **210** to the more stable dihydrojasmone (**211**).[121]

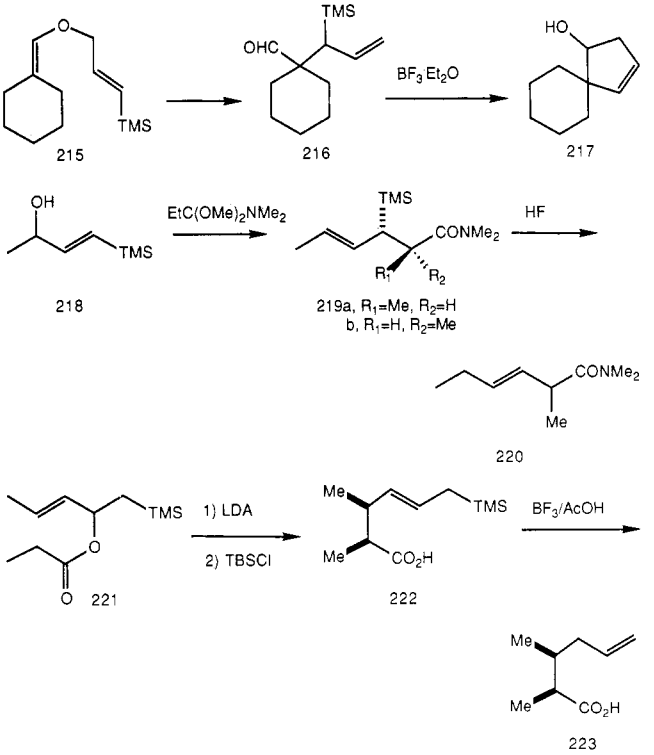


The rearrangement of systems bearing C_6-oxygen substituents has been explored by Ireland as a prelude to the synthesis of ionophores.[105c,122] The preparation of β-alkoxy alcohols and their acyl derivatives is troublesome because they are susceptible to polymerization and isomerization. The Claisen rearrangement of ester **213** (R = H, Me) is ~70–80% diastereoselective, presumably the result of a lack of control over enolate geometry. Secondary allylic alcohols in this series are extremely unstable, requiring in situ generation of the acylation products, enolization, and rearrangement. Operationally, the preparation of acids **212** and **214** is equivalent to a diastereoselective aldol condensation.



2. Silicon Substituents

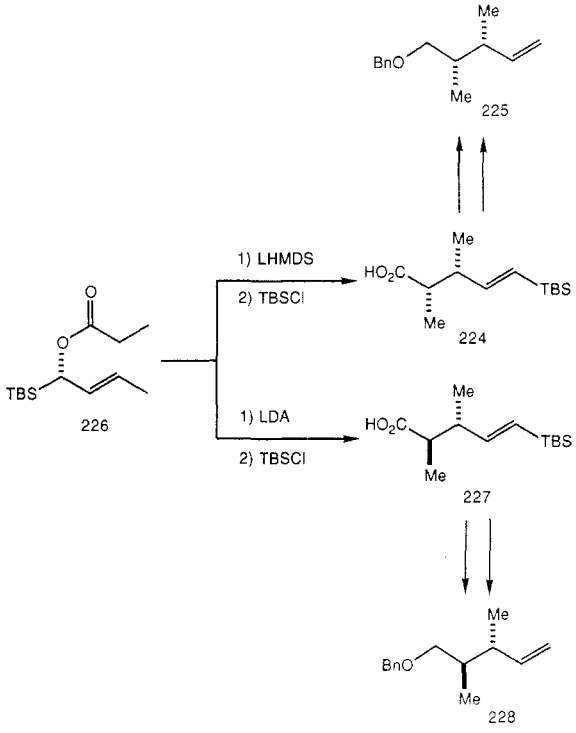
The ability of silicon to direct and facilitate the reactions of olefins has led to the introduction of silicon substituents into the framework of allyl vinyl ethers. Kuwajima[123] has formed C_6-substituted allyl vinyl ether **215** in situ by the exchange of α-ethoxymethylenecyclohexane and (*E*)-β-(trimethylsilyl)allyl alcohol in the presence of acid. Rearrangement gives allylsilane **216**, which provides the spiro-β,γ-unsaturated alcohol **217** upon Lewis acid catalysis. In a related experiment,[124] the propionamide acetal rearrangement of allylic alcohol **218** affords amides **219a** and **219b** in a 3:1 ratio, respectively. Protodesilylation of either isomer gives the β,γ-unsaturated amide **220**. The formation of alcohol **217** and amide **220** involves the migration of the γ,δ-double bond from the initial Claisen products toward the carbonyl carbon.



The olefin migration may be practiced in the opposite sense. Rearrangement of the (*E*)-*O*-silyl ketene acetal of ester **221** occurs with 90% stereoselectivity, providing acid **222** as the major diastereomer. Acid-catalyzed migration of the olefin away from the carbonyl realizes the δ,ϵ-acid **223**.[125,126] A severe erosion of stereochem-

istry has been observed when the rearrangement of the allylic alcohol component of **221** is conducted as its Eschenmoser variant,[127] similar to the selectivity in the formation of **219a** and **219b**.

A silicon substituent at C_4 serves to introduce asymmetry into achiral allylic alcohols. Propionate ester **226** is prepared from the resolved alcohol and subjected to stereospecific rearrangement. Reduction, alkylation, and protodesilylation of acids **224** and **227** give enantiomerically pure ethers **225** and **228**, respectively.[128]



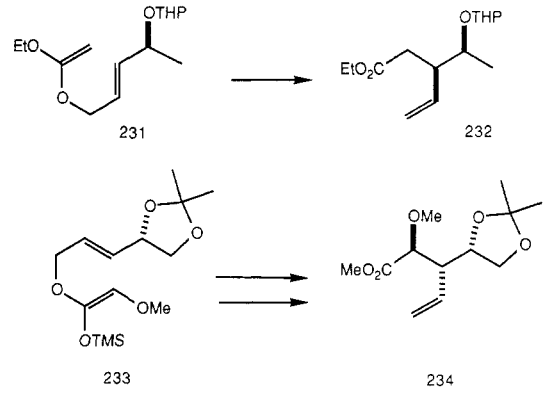
V. Remote Asymmetry

A. Acyclic Substrates

The only asymmetric effects discussed thus far have been related strictly to the C_4 carbon, an integral part of the Claisen rearrangement framework. But what of remote asymmetry and its ability to induce diastereoselective reactions?

The rearrangement of allyl vinyl ether **229**, wherein the remote asymmetry at the quaternary center (C_6 β-substituent) renders the faces of the olefin diastereotopic, shows no sign of diastereoselection; both isomers **230** are produced in equal amounts.[129] When the

center of asymmetry is located vicinal to the developing center of asymmetry, modest selectivity is observed. Thus, ketene acetal **231**, derived from (*S*)-ethyl L-lactate,[130] rearranges with 3:1 diastereoselectivity (**232**, major diastereomer), while D-glyceraldehyde acetonide derived silyl ketene acetal **233** affords principally **234** (75% ds).[131,132] In each instance, the predominant stereoisomer has the same relative stereochemistry at the β- and γ-positions and has been suggested to be in accord with Felkin[133] and Houk[134] transition-state models.[135]

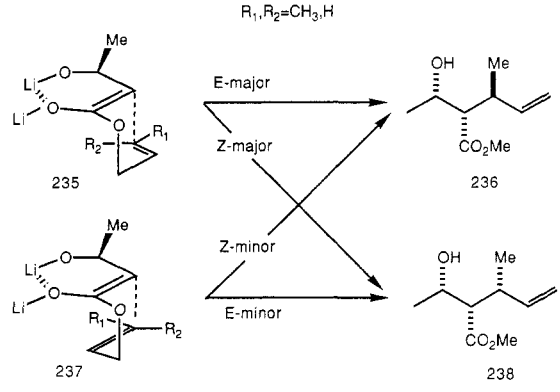


Kurth has examined the rearrangement of the dianion of the (*E*)- and (*Z*)-butenyl esters of β-hydroxybutyric acid in THF (Scheme VIII) and has applied the reaction to the synthesis of the mycotoxin botryodiplodin.[136,137] In principle, the reaction can provide four diastereomers; only two are detected. Bond formation cis to the methyl group of the ring formed by chelation is inoperative on steric grounds while bond formation trans to the methyl occurs via the chairlike and the boatlike transition states. The *E* isomer provides an 81:19 mixture and the *Z* isomer gives a 15:85 ratio of β-hydroxy esters **236** and **238**, respectively. In both instances the chairlike transition states predominate.[138] The availability of enantiospecific enzymatic reductions of β-keto esters[139] makes this rearrangement amenable to the preparation of enantiomerically pure products. Indeed, the hydroxyethyl unit functions as a "chiral auxiliary"[140] as it can be oxidized to a ketone and the resultant β-keto ester can undergo Haller–Bauer deacylation or decarboxylation.[138,141]

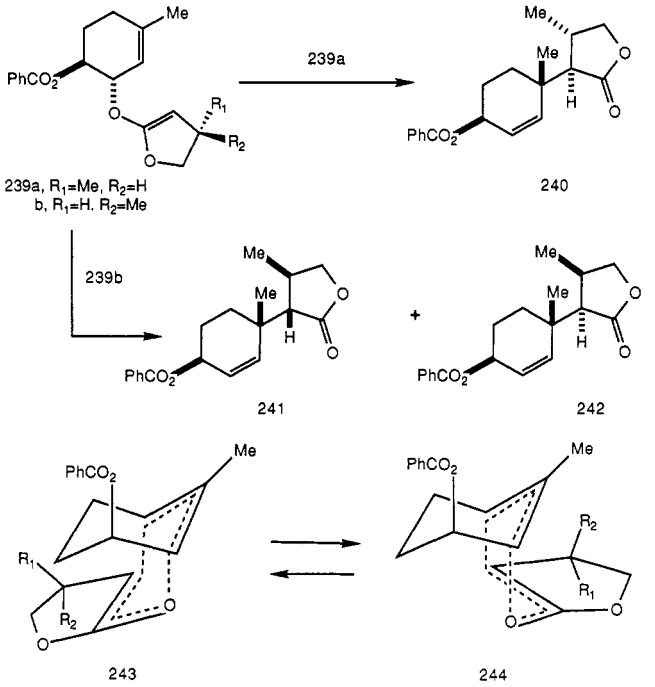
B. Ring-Bearing Substrates

The effect of the chelated ring discussed in the previous section leads logically to the influence of remote ring substituents on stereochemistry. A more elaborate version of the Lythgoe experiments[102b] (**153** → **154**) involves the union of an enantiomerically pure reactant, 6(*S*)-(benzoyloxy)-3-methylcyclohex-2-en-1(*S*)-ol, with the *R* or *S* enantiomers of 2,2-diethoxy-3-methyltetrahydrofuran. Ketene acetal **239a**, derived from the

SCHEME VIII



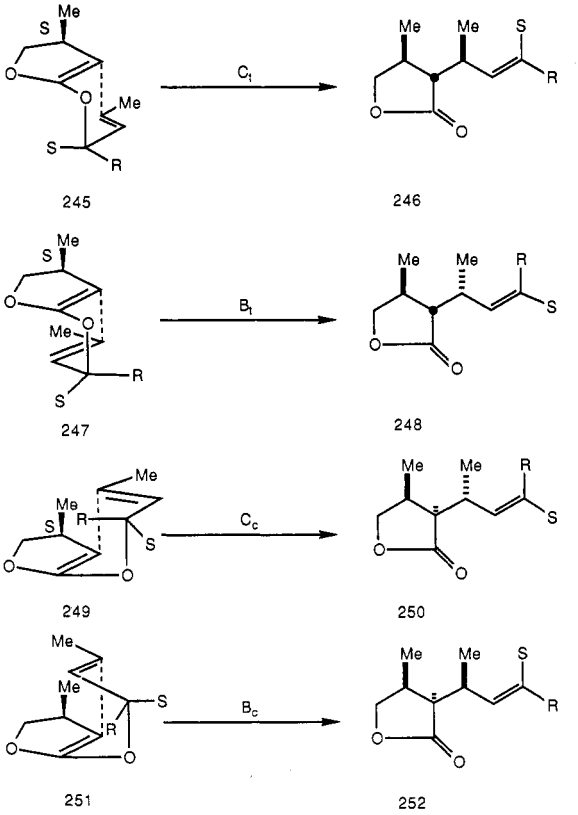
(*S*)-ortholactone, rearranges to give exclusively diastereomer **240** through the boatlike transition state. However, the diastereomeric reaction with the (*R*)-ortholactone via **239b** affords a 70:30 mixture of diastereomers **241** and **242**, respectively, with the chairlike transition state leading to the major isomer. The transition state for the rearrangement of these systems normally favors the boat **156** (no substituents on the heterocyclic ring). The presence of the substituent in **239a** (R_1 = Me) serves only to destabilize further the chairlike transition state **243** relative to the boatlike transition state **244**. On the other hand, **239b** possesses the methyl substituent in a sterically demanding position in the boatlike transition state **244** that is mitigated in the chairlike transition state **243**. The preference for the chairlike transition state in the latter example requires the substituent effect to be more influential than the chair–boat factor.



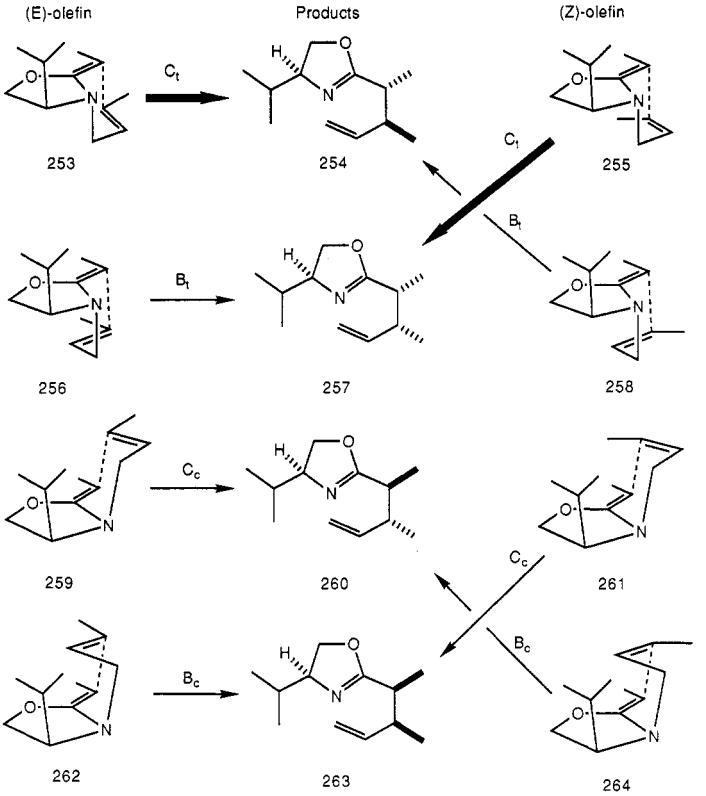
In this laboratory, the reaction of the enantiomers of the ortholactones of 3-methyl-γ-butyrolactone with enantiomerically pure secondary (*E*)-allylic alcohols has been studied.[142,143] Scheme IX provides details on the stereochemistry of these reactions. The transition states **245**, **247**, **249**, and **251** represent the four possible permutations of olefin facial selectivity. The four control elements are chair (C) vs boat (B) and trans (t) (to the methyl group) vs cis (c). The four products are derived from the (*S*)-ortholactone with the R and S substituents representing the absolute configuration of the allylic alcohol residue when an isopropyl group occupies the R or S position. When the (*R*)-alcohol is employed, only the lactone **246** is obtained. Transition states **247** and **249** are precluded as they lead to products **248** and **250**, respectively, bearing (*Z*)-olefins. While boatlike transition state **251** would lead to an (*E*)-olefin, steric interactions make this pathway less favorable than **245** → **246**. Indeed, when R = S = H, (i.e., (*E*)-2-buten-1-ol), no product having the stereochemistry of **252** is formed.

Alternatively, the (*S*)-alcohol excludes transition states **245** and **251**; transition states **247** and **249** provide

SCHEME IX



SCHEME X



lactones **248** and **250**, respectively, in a 55:45 ratio. In spite of this mixture, either diastereomer is able to be prepared from the other by chemical means.

The aza Claisen rearrangement,[144] in conjunction with an amino acid derived type I chiral auxiliary, has been employed by Kurth[145] to provide 2′- and 3′-alkyl, and 2′,3′-dialkyl 2-substituted oxazolines.[146] The starting

N-allyl-*N*,*O*-acetals are prepared by N-alkylation of the 2-ethyloxazoline with the requisite allylic tosylate followed by stereoselective *n*-butyllithium deprotonation of the oxazolinium salt. The removal of the oxazoline moiety liberates an enantiomerically pure carboxylic acid. Scheme X illustrates this principle for the formation of the four possible diastereomeric 2′,3′-dimethyl-2(*S*)-oxazolines. When an (*E*)-butenyl residue is employed, the four operative transition states **253**, **256**, **259**, and **262** lead to products **254**, **257**, **260**, and **263**, respectively, in a ratio of 81:15:2:2. Thus, the isopropyl group is an effective control element for the facial selectivity of bond formation at the oxazoline double bond (96%, facial excess (fe) = 92%),[147] while the chair vs boat selectivity is not as effective (fe = ~67%). When the (*Z*)-butenyl group is employed, the products **254**, **257**, **260**, and **263** are formed in a ratio of 14:82:2:2, respectively. While the energetics of the transition states remain the same as for the (*E*)-olefin, the major product **257**, arising through the C_t transition state, provides a product with the opposite configuration at the β-position of the chain from that which was obtained in the (*E*)-butenyl series.

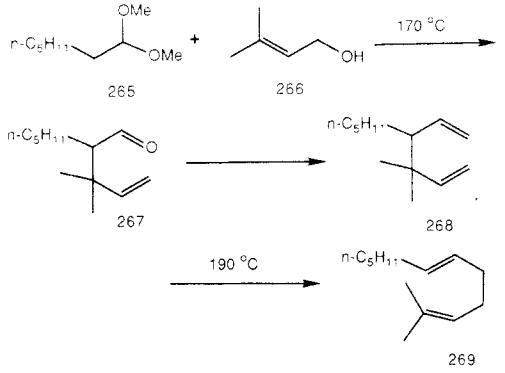
The synthetic success of type I chiral auxiliaries is dependent on the facility with which diastereomers **254** and **260** can be separated from **257** and **263** and the ease with which the members of each pair (or their hydrolysis products prepared without epimerization) can be separated from one another.

VI. Consecutive Rearrangements

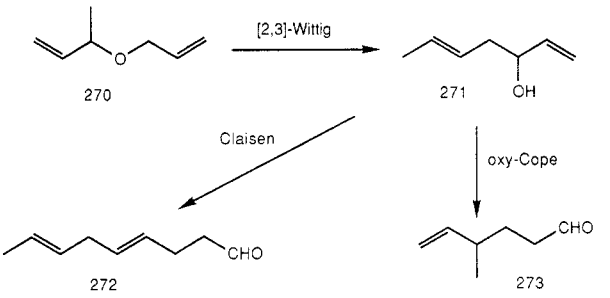
The Claisen rearrangement and its associated sigmatropic processes create the opportunity for the design and execution of consecutive rearrangements. These processes may be divided into three categories: sequential, tandem, and iterative. A sequential rearrangement requires derivatization of a rearrangement product prior to a subsequent rearrangement. A tandem rearrangement has all the atoms for consecutive rearrangements installed in the starting substrate prior to the first rearrangement. An iterative rearrangement requires a number of transformations to be conducted on a rearrangement product prior to a subsequent "identical" rearrangement.[148]

A. Sequential Rearrangements

Cookson and Hughes[149] have performed a sequential Claisen and Cope rearrangement in preparing the diene **269**. When the acetal **265** is heated with β,β-dimethylallyl alcohol (**266**) in mesitylene with *o*-nitrobenzoic acid as a catalyst, rearrangement of the intermediate allyl vinyl ether produces the aldehyde **267**. Isolation of the aldehyde and subsequent Wittig methylenation provide the 1,5-diene, which undergoes a Cope rearrangement to the more substituted, thermodynamically more stable diene **269**.

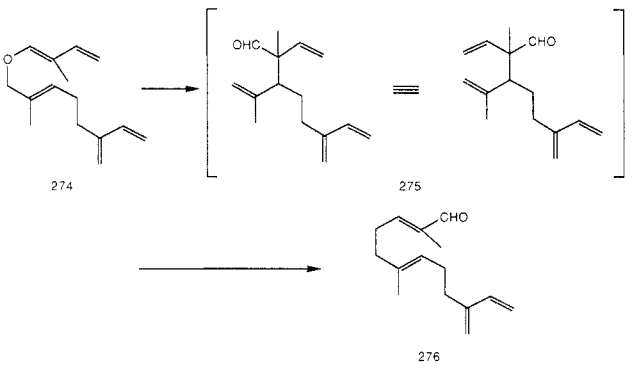


As an outgrowth of their extensive studies on the [2,3] Wittig rearrangement of diallyl ethers,[54] Nakai and his collaborators[150] have executed a sequential [2,3] Wittig–Claisen rearrangement. Selective metalation of diallyl ether **270** at the allyl residue followed by rearrangement produces dienol **271**. Subsequent Claisen rearrangement provides the 4,7-dienal **272**. The sequence is also successful when the Johnson and Ireland variants are employed. Dienol **271** provides the opportunity for an oxy-Cope rearrangement to unsaturated aldehyde **273**. The oxy-Cope process provides an unsaturated aldehyde bearing one more carbon between the functional groups than is obtained in the Claisen rearrangement.



B. Tandem Rearrangements

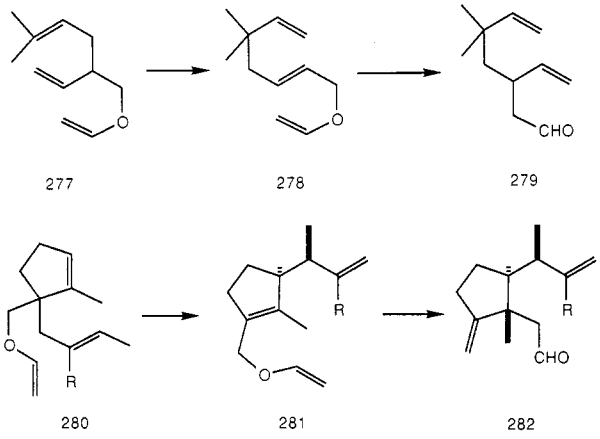
The seminal studies on aliphatic,[151] tandem rearrangements—namely, the Claisen–Cope rearrangement, have come from the laboratories of Thomas[152] and Cookson.[153-155] These investigations are best exemplified by the synthesis of β-sinesal (**276**), an essential oil of the Chinese orange.[152a] The dienyl ether function of **274** is generated from (*E*)-1-ethoxy-2-methyl-1,3-butadiene with mercuric ion catalysis. The intermediate aldehyde(s) **275** from Claisen rearrangement undergo Cope rearrangement to form the (2*E*,6*E*)-β-sinesal (**276**). The presence of the 6(*E*)-olefin requires the chain bearing the 1,3-diene of **275** to be equatorial in the transition state for the Cope rearrangement. The 2(*E*) configuration may arise either by direct means from the rearrangement or by isomerization of any 2(*Z*)-olefin produced. The success of the tandem [3,3] sigmatropic process requires a substituent (in this instance a methyl group) at C_1 of allyl vinyl ether **274** to avoid conjugation of the β,γ double bond of **275**, which



would short-circuit the Cope rearrangement.[153b,155b] For the purpose of synthetic planning, the reaction should be recognized as a formal γ-allylic alkylation of an (*E*)-2-butenal.

The tandem Claisen–Cope rearrangement has two other important characteristics. First, the Claisen rearrangement, which generally has the lower activation energy, precedes the Cope rearrangement, thereby creating the opportunity for the isolation of intermediates. Second, the success of the reversible Cope rearrangement depends upon the judicious choice of target substrate because the more stable product is the 1,5-diene having the more substituted double bonds.

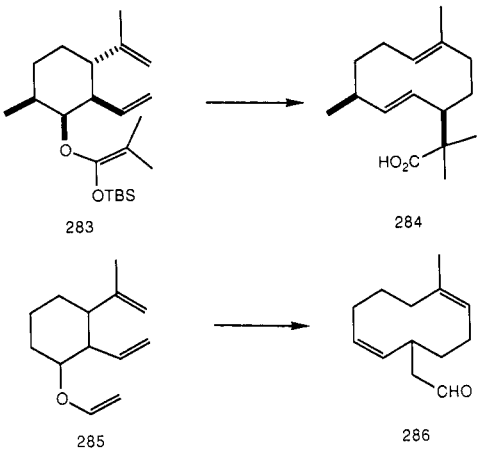
In the context of several synthetic projects, the reverse order of these sigmatropic processes—namely, the Cope–Claisen rearrangement has been explored in this and other laboratories. An unfavorable equilibrium in the Cope step would be inconsequential as the irreversible Claisen rearrangement would drive the reaction; no intermediates would be anticipated. The Cope rearrangement of triene **277** to **278** is a thermodynamically unfavorable process that is driven to aldehyde **279** by the Claisen rearrangement. Similarly, the Cope rearrangement of trienes **280** (R = H, Me) gives rise to **281**, the stereochemistry of which is created through a chairlike transition state. The olefin facial selectivity of the Claisen rearrangement (**281** → **282**) occurs principally trans to the substituent at the newly created center of asymmetric of the ring to afford aldehyde **282**. The process permits the generation of three contiguous, stereodefined centers of asymmetry.[156,157]



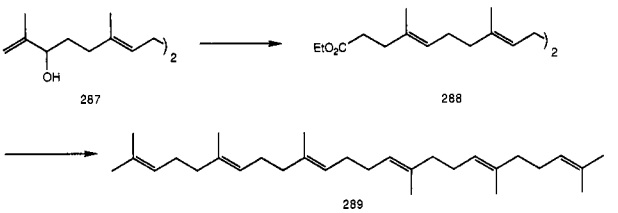
An excellent test for the tandem Cope–Claisen rearrangement is the formation of (*E,E*)-1,6-cyclodecadienes from the more stable 1,2-divinylcyclohexanes. Rauscher[158] has successfully converted the isobutyrate-derived silyl ketene acetal **283** to the decadiene **284**. The use of the disubstituted silyl ketene acetal is critical in obtaining the desired product. Since the starting material is prepared from (*S*)-(+)-carvone, the product is obtained in enantiomerically pure form. This method has been utilized in the preparation of the sesquiterpene, (+)-dihydrocostunolide.[159] In an earlier study, three of the four diastereomers of triene **285** gave aldehyde **286** as the only 10-membered ring product.[156a,160]

C. Iterative Rearrangements

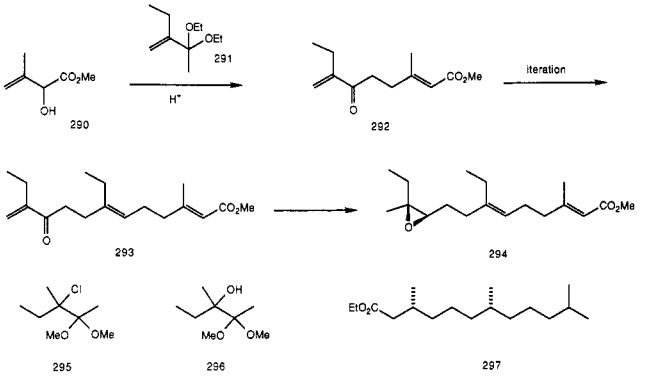
The use of 3-methoxyisoprene[84] and related ketals permits the repetitive formation of olefinic residues.



Bis(allylic alcohol) **287** (cf., **206** → **207**), prepared by the reduction of the enone, is subject to chain extension using the Johnson variant. Conversion of the terminal esters of **288** to propylidene groups provides an "inside–outside" synthesis of the symmetrical triterpene squalene (**289**), with each of the four central double bonds having their stereochemistry controlled by the Claisen rearrangement.[25]

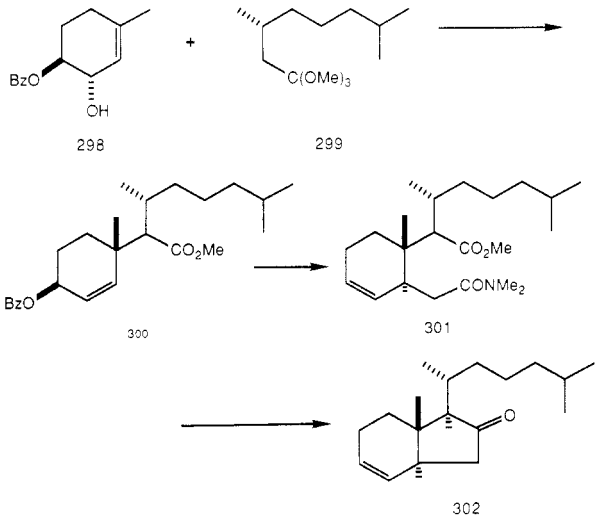


The C_{18}-*Cecropia* juvenile hormone (JH) (**294**) has lent itself to iterative synthesis. Olefinic ketal **291** serves as the agent for two chain extensions (**290** → **292** → **293**). The enone functionality of **293** is readily converted into JH (**294**). The iteration of **292** has also been accomplished with both enantiomers of the chiral ketals, **295**[161] and **296**,[162] which has led to the synthesis of both diastereomers and the enantiomers of the hormone. An iterative process has converted ester **133b** to ester **297**, a unit utilized in the synthesis of the vitamin E side chain.[93a,94a]



Lythgoe and co-workers[71a,102a] have employed an iterative Claisen sequence to construct the enantiomerically pure ketone **302**, an intermediate in the synthesis of tachysterol and precalciferol. The relative stereochemistry of the two oxygen functionalities of **298** sets the stereochemistry of the acetic acid residues of **301** and thereby assures the trans-fused ring system of **302**. The lack of stereocontrol adjacent to the ester group

in ester **300** is inconsequential as equilibration during the Dieckmann ring closure (**301** → **302**) achieves the required stereochemistry.[163,164]

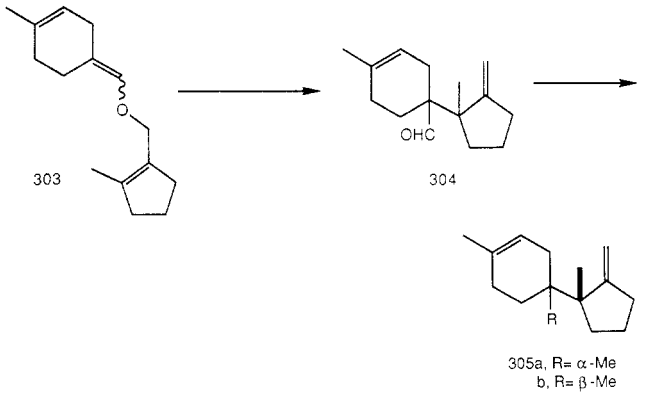


VII. Synthetic Applications

Although numerous synthetic applications of the aliphatic Claisen rearrangement have been discussed in previous sections to illustrate various aspects of the reaction, this section considers additional applications from the perspective of the tethered rings attending the rearrangement nucleus.

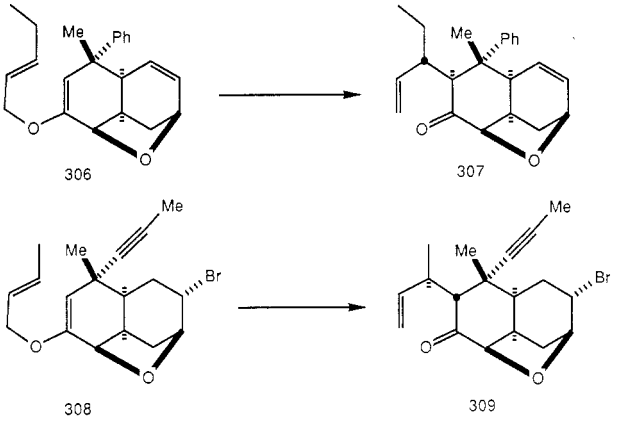
A. {1,1}-Rearrangements

This system is typified by efforts to synthesize trichodiene (**305a**), the biogenetic progenitor of the trichothecenes, via a {1,1;5,6} Claisen rearrangement. Allyl vinyl ether **303**, as an undetermined mixture of geometrical isomers, gives rise to a 1:1 mixture of aldehydes **304** and, ultimately, to the same mixture of trichodiene and bazzanene (**305b**).[165] The chairlike transition state is recognized as the dominant pathway,[166a] but the inability to control vinyl ether or ester enolate geometry[166b-d] has made this route nonselective.[167]

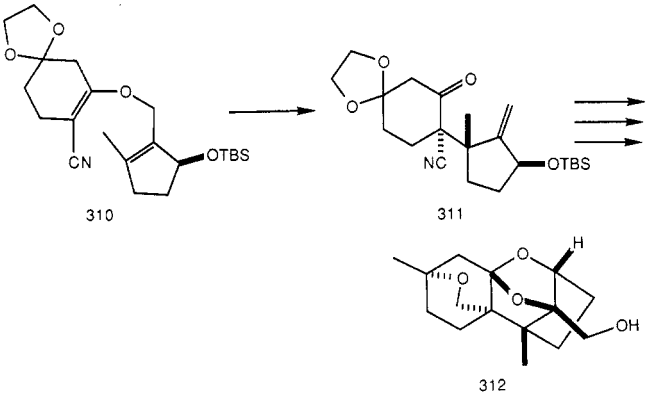


B. {1,2}-Rearrangements

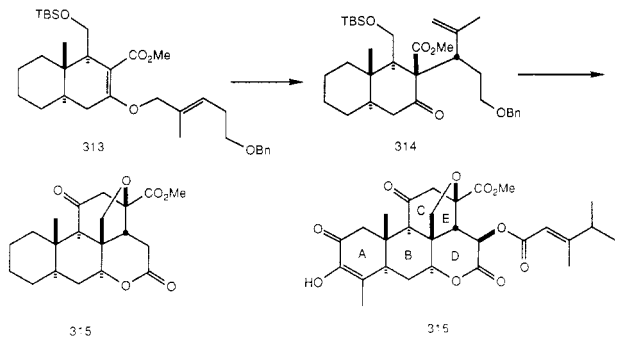
The rearrangement of the allyl enol ether of cyclohexanone to 2-allylcyclohexanone is the prototype of this group.[168] In a study related to the synthesis of the fungal phytotoxins betaenone B and stemphyloxin I, Hopkins[169] has investigated the rearrangement of allyl vinyl ethers **306** and **308**. While both rearrangements occur through the chairlike transition state, the steric bulk of the phenyl substituent in **306** directs bond formation to the concave face of the tricyclic nucleus. The less sterically demanding acetylenic residue of **308** allows bond formation to occur on the inherently more accessible convex face.



The lack of stereochemical control in the {1,1;5,6}-rearrangement of **303** → **304** has been overcome by employing a different construction of the vinyl ether residue. The {1,2;5,6}-rearrangement of nitrile **310** provides ketone **311** having vicinal quaternary centers with the desired stereochemistry of the trichodiene-derived trichothecenes. The rearrangement occurs exclusively on the face of the cyclopentene ring remote from the oxygen substituent with 16:1 chair/boat selectivity. Ketone **311** serves as an intermediate in the synthesis of neosporol (**312**).[170]

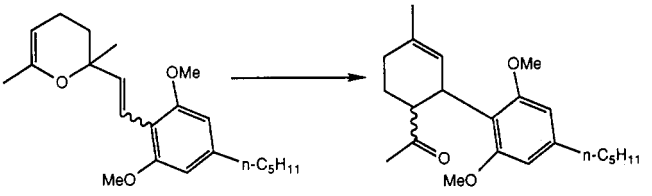


In a model study directed toward the synthesis of the quassinoid bruceantin (**316**), the {1,2}-rearrangement of unsaturated ester **313** results in bond formation on the α-face of ring B, remote from the angular methyl group through a chairlike transition state. With the stereochemistry set in the side chain, the sequential construction of rings C, E, and D is accomplished to provide pentacyclic lactone **315**.[171,172]

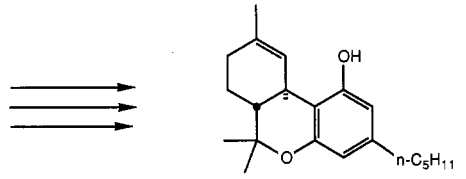


C. {1,4}-Rearrangements

The {1,4} group was discussed earlier (III.D.5) in the context of a "meta-Diels–Alder reaction",[103] a method that creates carbocycles from heterocycles. Pinnick[173] has employed the {1,4}-rearrangement in the synthesis of the cannabinoid, *trans*-Δ^1-THC (**319**). A 1:1 mixture of styrenes **317** gives the same mixture of ketones **318**. Remarkably, the reaction proceeds at ambient temperature as opposed to the elevated temperatures (200–400 °C) often required for this class of rearrangement. *O*-Methoxystyrene **317** appears to be ideally suited for dissociation at the allylic ether bond, suggesting the possibility of extensive bond breaking in the transition state, or even the intercedence of an ionic process.



317 318

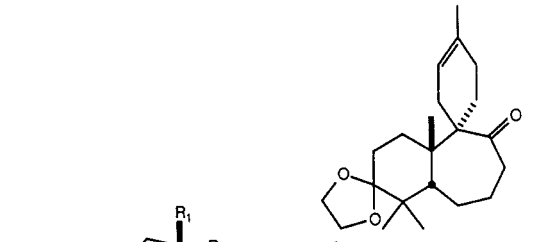


319

In an investigation directed toward the total synthesis of aphidicolin (**322**), Ireland and Aristoff[174] have realized the stereospecific {1,2;1,4}-rearrangement of allyl vinyl ethers **321**. While olefin **320** provides the correct substitution pattern to solve the synthetic problem, isomer **323** is suitable as an intermediate in the synthesis for the closely related stemodane skeleton. This good fortune is not always withstanding, and the success of such a venture is predicted upon the stereoselective introduction of the substituents R_1 and R_2 in allyl vinyl ethers such as **321**. In this instance, a hetero Diels–Alder reaction between methyl methacrylate and the appropriate *exo*-methylene α,β-unsaturated ketone is regioselective, but not stereoselective.

Danishefsky and his collaborators have extended the {1,4}-rearrangement to silyl ketene acetals. Thus, the lactone **324** rearranges as its silyl ketene acetal through the obligatory boatlike transition state[175a] to give rise to acid **325**. Subsequent oxidative decarboxylation provides the sesquiterpene widdrol (**326**).[175b,176]

The ionophore antibiotic indanomycin (X-14547A, **327**) provides two opportunities for the application of the {1,4}-rearrangement. The obvious application is the construction of the perhydroindane ring system. Burke[177] has utilized the Danishefsky approach to this end, but not without a surprise. Rearrangement of silyl ketene acetal **328** at 135 °C affords a mixture of four diastereomers (31:9:5:1) of **329**, the major component of which is the product allegedly arising from the {1,4}-rearrangement (**329**, α-H, α-Et). However, at 95–100 °C, the triene **330** is isolated, thermolysis of which at 135 °C produces the same mixture of diastereomers. A similar result is obtained with the diastereomer of **328** that is epimeric at the vinyl center, although a single ester **329** (β-H, α-Et) is realized. An additional caveat is warranted. Since the source of the lactones for these reactions is invariably derived from the 1,2-addition of a vinyl organometallic to an aldehyde

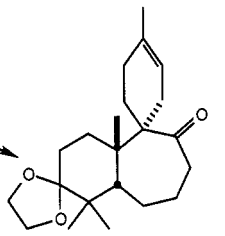


321a, R_1 = CH=CH$_2$, R_2 = Me
b, R_1 = Me, R_2 = CH=CH$_2$

320

321a

321b



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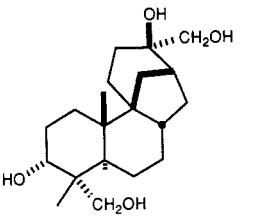

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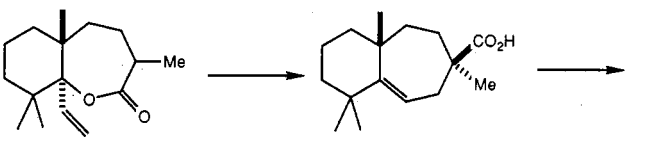

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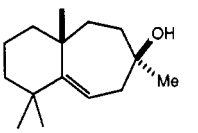

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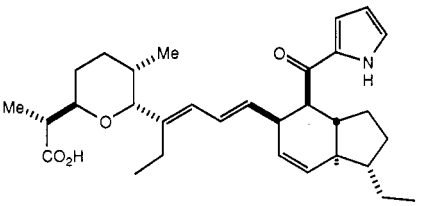

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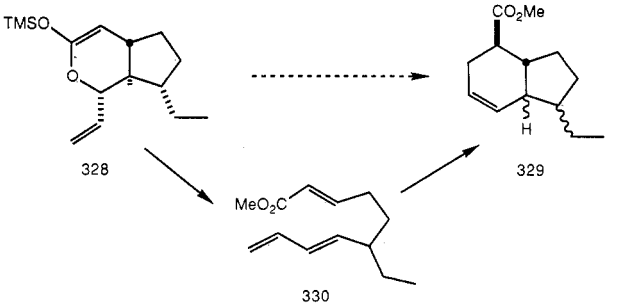

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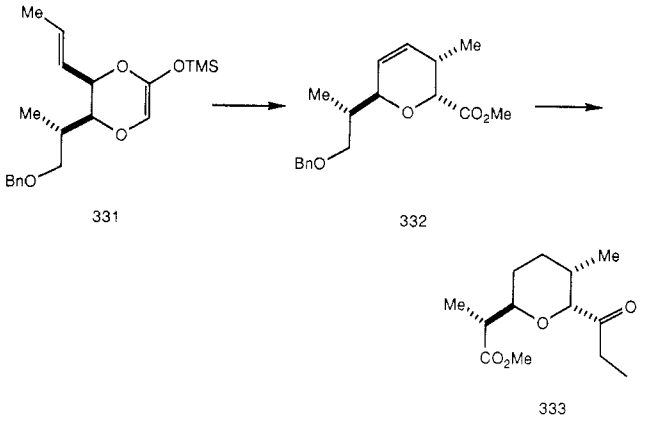
followed by lactonization, it is important to control the stereoselectivity of the addition, whether or not the Diels–Alder pathway is operative.[175c]

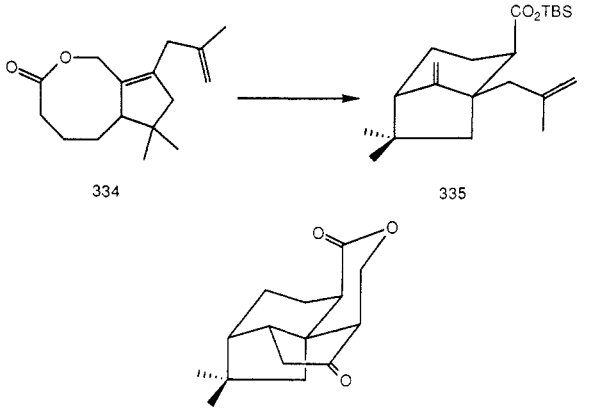


331 332 333

Although the propionic acid residue in the "left-wing" of indanomycin seemingly dictates the Ireland strategy (**144** → **145** + **146**), an alternative analysis reveals that the ester **332** is accessible via the {1,4} route.[178] Its conversion to ketone **333** creates a viable synthon for further elaboration. The caveat offered above is also applicable to the formation of the lactone precursor to **331**.[178c]

D. {1,5}-Rearrangements

The {1,5}-rearrangement results in a two-atom ring contraction. In an approach to the synthesis of quadrone (**336**), Funk[179] has demonstrated that fused lactone **334**, by way of its silyl ketene acetal, gives rise to the bridged, ring-contracted ester **335**. Mechanistic restraints require the ester group to be axial to the newly formed ring, thereby setting the stage for further transformations directed toward quadrone.

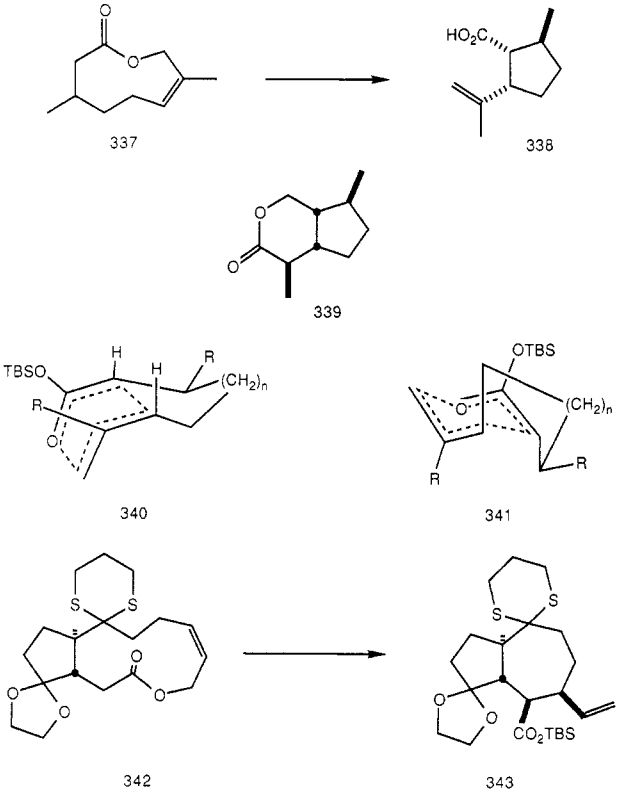


334 335 336

E. {1,6}-Rearrangements

The {1,6}-rearrangement permits ring contraction by four atoms wherein the newly formed ring bears vicinally substituted vinyl and carbonyl substituents. Thus far, the examples studied have been medium to macrocyclic lactones for which there are ample methods for their synthesis. Funk[180] and Knight[181] have provided the seminal contributions to this class of Claisen rearrangement.

In a synthesis of the iridoid iridomyrmecin (**339**), Funk[104] has demonstrated that the key intermediate **338** is formed upon rearrangement of the (*E*)-*O*-silyl ketene acetal of lactone **337**. The boatlike transition state **340** (n = 1), bearing the tethered chain in a cis relationship, accounts for the observed stereochemistry. For (*E*)-*O*-silyl ketene acetals, the cis-fused ring system is observed for n = 1–4. Transition state **341** is found to be operable, in part, when n = 7. Similarly, Knight[181b] has accomplished the stereoselective ring contraction of lactone **342** to afford ester **343**, an intermediate in a proposed route to guaianolide and pseudo-guaianolide sesquiterpenes.

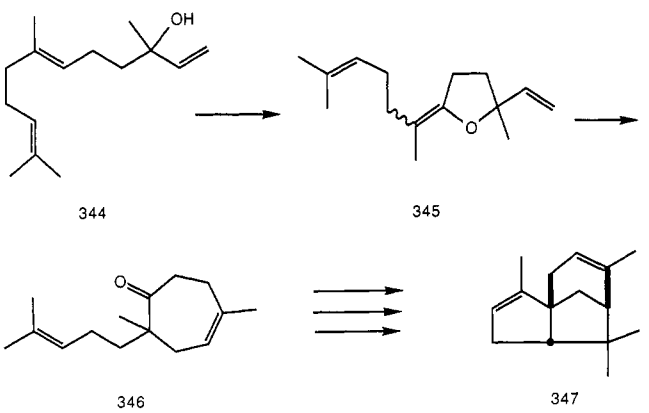


337 338 339 340 341 342 343

F. {2,4}-Rearrangements

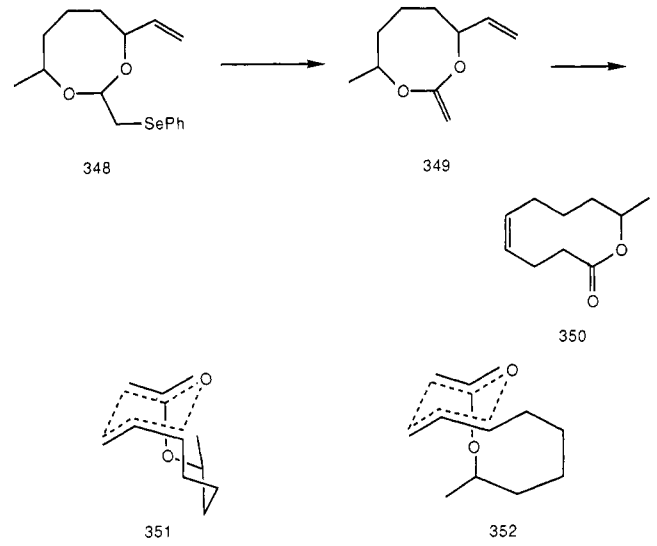
This class of Claisen rearrangements permits ring expansion by two carbons and is the exocyclic vinyl ether analogue of the {1,4}-rearrangement. The vinyl ether functionality can be generated by intramolecular bromoetherification followed by base-catalyzed elimination of HBr,[182] alkoxide-promoted addition to an acetylene,[183] dehydration,[184] or radical cyclization.[185] For example, nerolidol (**344**) affords allyl vinyl ether **345** upon implementation of the bromoetherification procedure and elimination. Subsequent thermolysis of **345** gives the cycloheptenone **346**. Several operations convert the cycloheptenone into 2,5-cedradiene (**347**).[182b]

A variation on the bromoetherification theme has been developed by Petrzilka—namely, selenoxide elimination to generate ketene acetals.[186a,b] This technique is exemplified by the synthesis of the decenolide **350**, phoracantholide J. The eight-membered acetal is prepared under high-dilution conditions by intramolecular phenylselenenyl etherification of an acyclic chain bearing allylic alcohol and vinyl ether termini. Oxidation of selenide **348** to the selenoxide, subsequent elimination to ketene acetal **349**, and rearrangement afford the target substance. The formation of the (*Z*)-olefin is derived from transition state **351** (assuming



a chairlike transition state) rather than the seemingly more strained transition state **352** that would lead to the (*E*)-olefin.[186c,187]

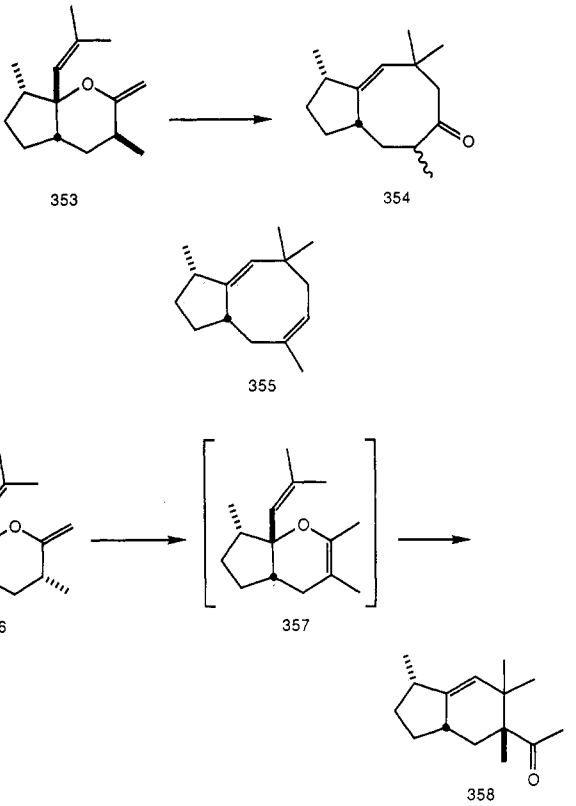
One of the difficulties associated with this class of rearrangement is the problem of vinyl ether isomerization that can partition products between the {1,4}- and {2,4}-manifolds.[184] An intriguing case of this process is seen in the Paquette synthesis of the sesquiterpene precapnelladiene (**355**).[188] Epimeric allyl vinyl ethers **353** and **356**, both prepared from their respective lac-



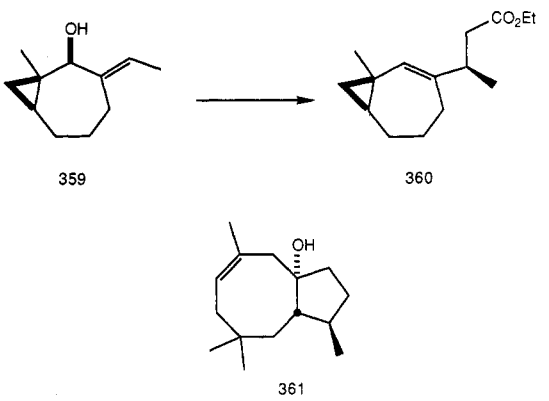
tones with Tebbe's reagent ($Cp_2TiCH_2ClAlMe_2$),[17] undergo rearrangement via different pathways. Isomer **353**, bearing the β-methyl group, rearranges to give the desired cyclooctenone **354**. On the other hand, the α-isomer **356** is susceptible to prototropic isomerization of the vinyl ether double bond. Rearrangement via the {1,4} pathway gives the cyclohexene **358**. The prototropic shift appears less favorable in isomer **353** as the allylic proton is less accessible on the concave face than it is on the convex face of **356**.

G. {4,5}-Rearrangements

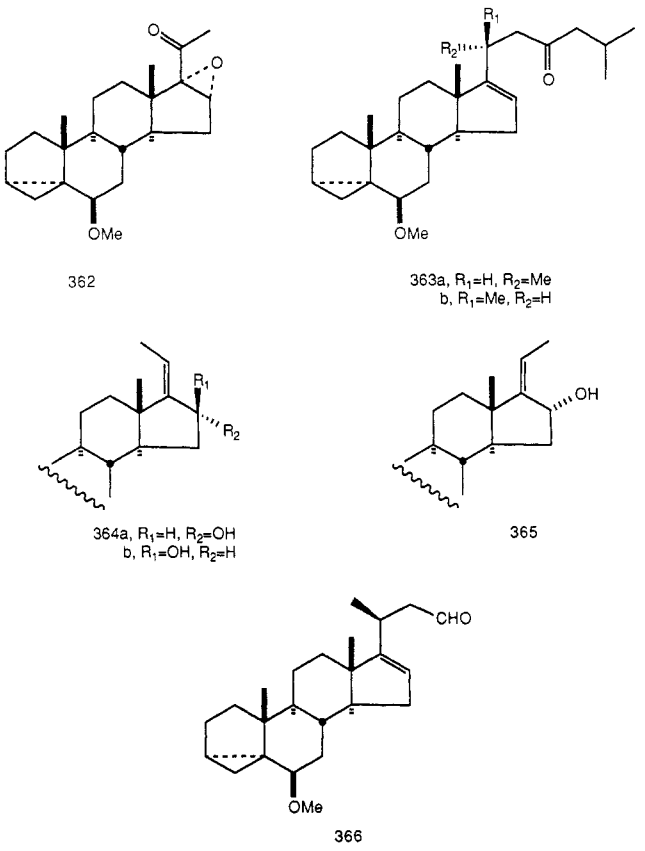
This type of rearrangement has been utilized by Paquette[189] in the synthesis of the sesquiterpene dactylol (**361**). The reaction permits the control of allylic side chain stereochemistry (**360**) if the geometry of the exocyclic double bond and the stereochemistry of the hydroxyl group can be controlled. In the case at hand, allylic alcohol **359**, the former requirement is readily met by introduction of the ethylidene group via condensation between a 1-methyl[5.1.0]bicyclooctan-2-one



and acetaldehyde followed by dehydration. The latter condition is achieved by selective Luche reduction ($CeCl_3/NaBH_4$) of the enone.



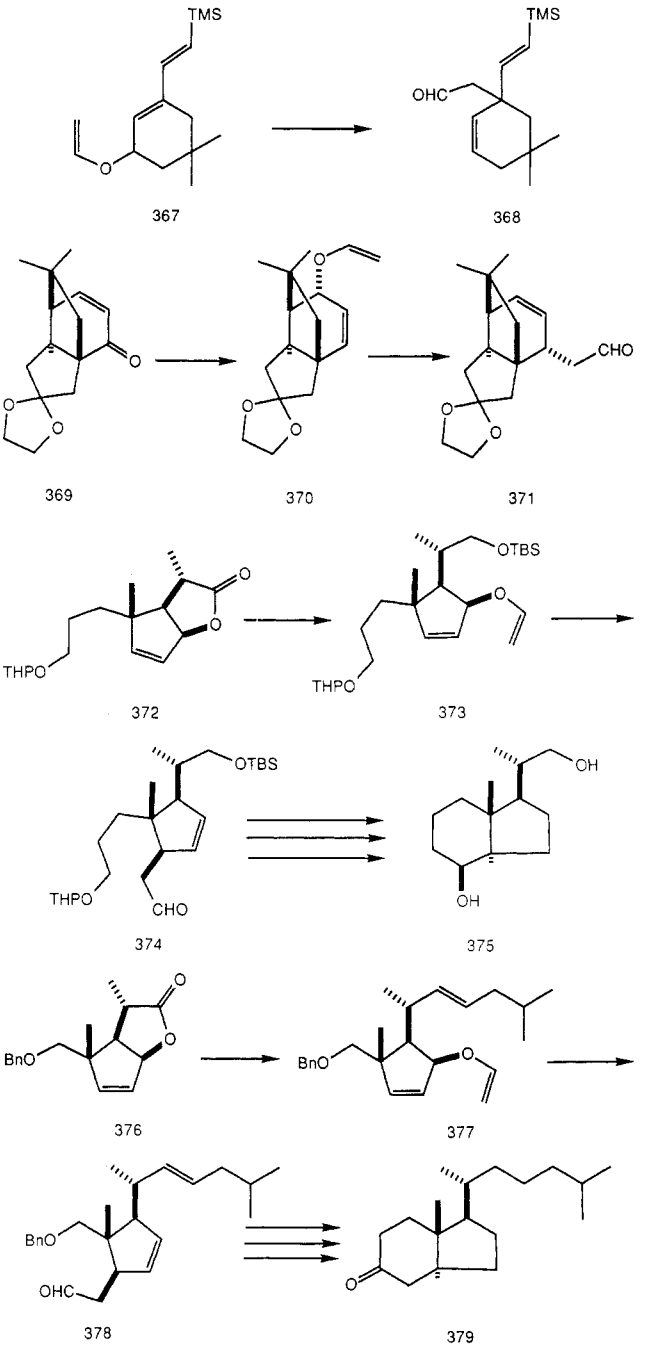
The {4,5}-rearrangement has served admirably in the steroid field to provide a route for the stereospecific introduction of the C_{20} side-chain stereochemistry and clearly indicates how product stereochemistry may be controlled if double-bond geometry and alcohol stereochemistry can be appropriately manipulated. Pregnane (**362**), readily available by α-face epoxidation of the D-ring enone, is reduced under Wharton conditions[190] to a mixture of allylic alcohols **364a** (63%) and **365** (27%). Carroll rearrangement of (*E*)-alcohol **364a** affords the C_{20} α-stereochemistry of **363a** while (*Z*)-olefin **365** provides the C_{20} β-stereochemistry (**363b**).[191] Side-chain stereoisomers **363a** and **363b** are converted to cholesterol and C_{20}-isocholesterol, respectively.[192] Alcohol **364b**, formed by oxidation and α-face reduction of the intermediate enone, gives rise to aldehyde **366**. Thus, *Z* α-allylic alcohol **365** and *E* β-allylic alcohol **364b** are operationally equivalent as they both yield the same relative stereochemistry at C_{20}.[193]



H. {4,6}-Rearrangements

The perceptive reader will have recognized many examples of this common version of the Claisen rearrangement in earlier discussions. The {4,6}-rearrangement is typified by the formal S_N2' addition of an acetic acid residue to an endocyclic cycloalkenol and provides a convenient route to quaternary allylic carbon atoms.[194] In a synthesis of quadrone (**336**), Burke[195] has employed two {4,6}-rearrangements. The first, **367** → **368**, creates a quaternary allylic center that serves to form subsequently a spirocyclopentenone. Whereas the allylic alcohol precursor of vinyl ether **367** arises via 1,2-reduction of the parent enone, the α-allylic alcohol progenitor of vinyl ether **370** would not, owing to the steric effect of the *gem*-dimethyl group, be accessible by the same pathway. Accordingly, the accessible α-face of the six-membered ring is exploited by employing the isomeric enone **369** in conjunction with the Wharton rearrangement.[190] The stereochemistry of the carbon–oxygen bond in the sequence is established during the α-face epoxidation of enone **369**. The combination of the Wharton and Claisen rearrangements results in the net substitution of the carbonyl of **369** by the acetaldehyde moiety of **371** with retention of the site of the double bond.

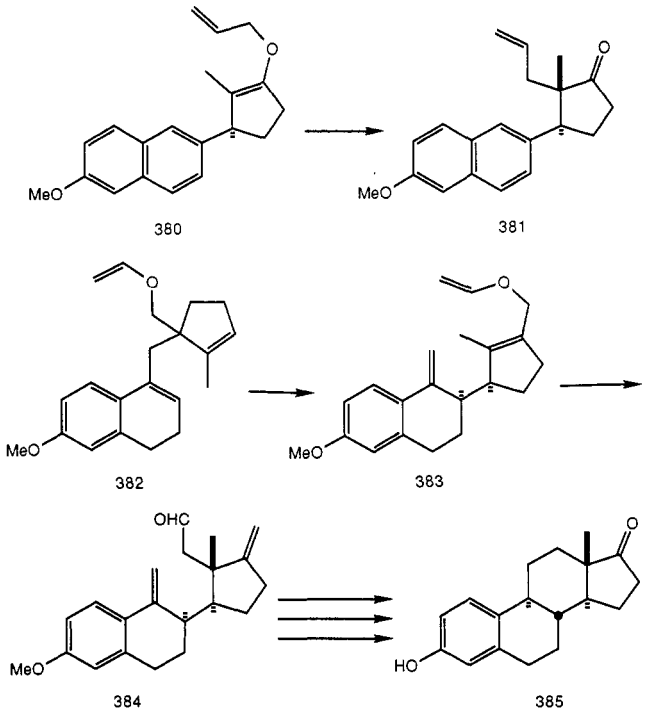
Another method for the all-important control of allylic alcohol stereochemistry, albeit target-dictated, is illustrated in the preparation of the Inhoffen–Lythgoe diol **375**,[196] a critical intermediate in vitamin D syntheses, and the steroid C/D ring synthon **379**.[197] Both approaches utilize cis-fused [3.3.0] bicyclic lactones (**372** and **376**, respectively) to generate the correct allylic alcohol stereochemistry. In each instance, a Baeyer–Villiger oxidation of a bicyclo[2.2.1]heptenone serves as the source of the lactones.



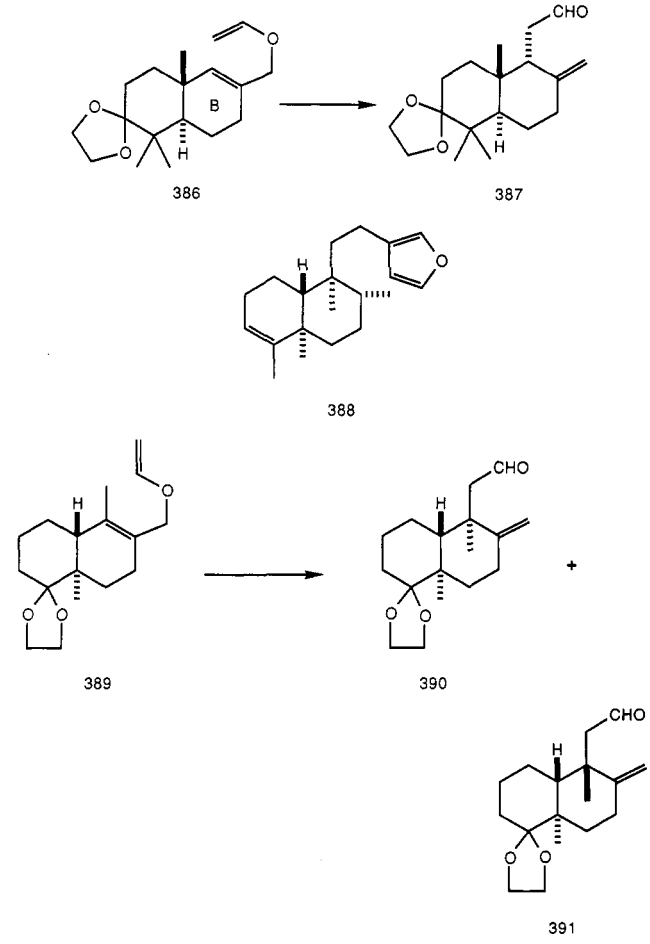
I. {5,6}-Rearrangements

The {5,6}-rearrangement is closely related to the {1,2}-rearrangement as the two processes serve to interchange carbonyl and olefin functionality. Horeau[198] has observed the stereoselective {1,2}-rearrangement of allyl vinyl ether **380** to allyl ketone **381**, an intermediate in a synthesis of equilenin. Application of the {5,6} variant as the second step of the tandem rearrangement **382** → **383** → **384** results in aldehyde **384** that is transformed into estrone **385** in several operations.[156b] Both seco derivatives **381** and **384** are the major stereoisomers from their respective rearrangements as the bulky naphthalene and dihydronaphthalene groups direct the bond formation.

The propensity for this class of rearrangement to give axial bond formation in cyclohexenyl systems with the attendant ring in a chair conformation has been demonstrated by Ireland.[199] This tendency is often observed

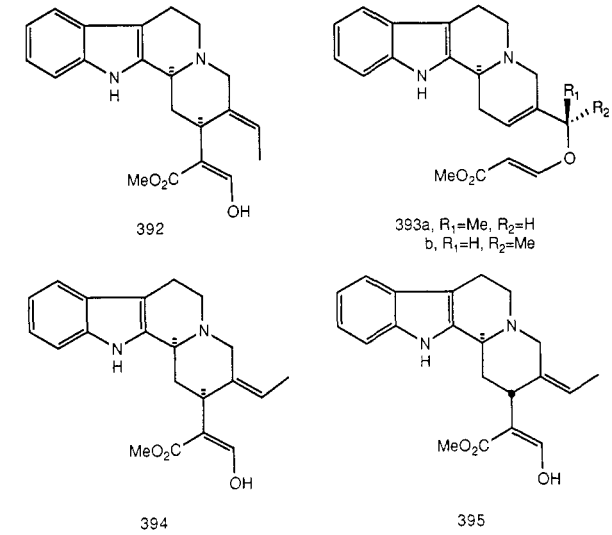


in rigid systems as typified by the conversion **386** → **387**.[200a] Bond formation occurs axially from the α-face of **386** with ring B in a chairlike conformation. However, steric factors can play an important role in altering the course of events. In a synthetic route to the clerodane diterpene annonene (**388**). Kakisawa[201] has observed an 85:15 ratio of aldehydes **390** and **391**, respectively, upon rearrangement of allyl vinyl ether **389**.

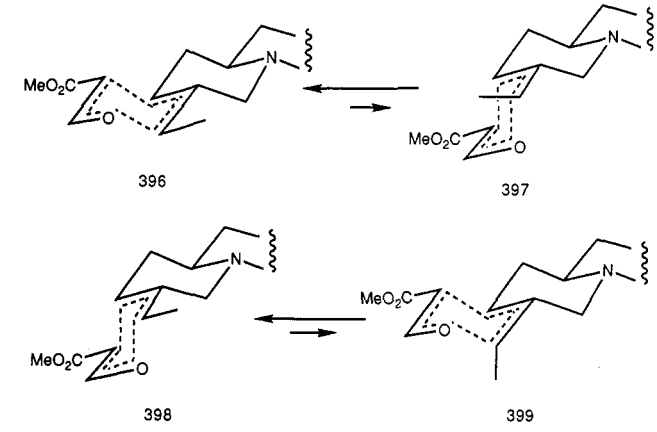


The major isomer arises from equatorial, β-face attack on ring B (chair conformation), avoiding the 1,3-diaxial interaction with the axial methyl group of the α-face.

The use of secondary allylic alcohols in the {5,6}-rearrangement generally follows the tendency of secondary allylic alcohols in {0,0}-rearrangements to give "trans" double bonds. An unsuccessful approach to the synthesis of the alkaloid geissoschizine (**392**) utilizes the rearrangement of a 1:1 mixture of the stereoisomers **393**[202,203] that provides stereoisomeric (*Z*)-olefins **394** and **395**. Allyl vinyl ether **393a** rearranges through

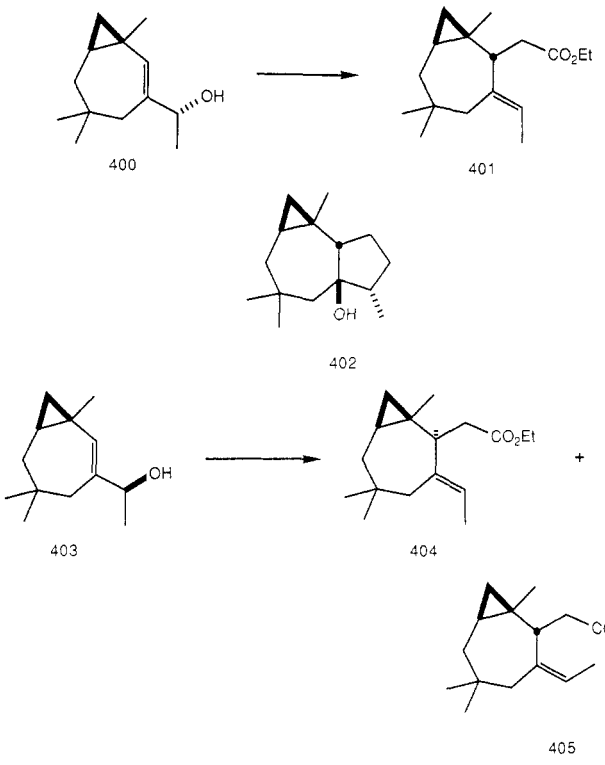


chairlike transition state **396** as opposed to its alternative chair conformation **397** which can encounter 1,3-diaxial interactions. Similarly, isomer **393b** rearranges through transition state **398** rather than **399**. In addition, transition state **399**, if late enough, can suffer from $A^{1,3}$ interactions (cf. the ground-state equivalent, **392**).



Unfortunately, high stereospecificity in this rearrangement is not always the case. In a synthesis of africanol (**402**), Paquette[189] has observed the expected ester product **401** from orthoester rearrangement of alcohol **400**. However, the rearrangement of epimeric alcohol **403** gave a 1:1 mixture of isomers **404** ((*E*)-olefin) and **405** ((*Z*)-olefin). Ester **404**, the anticipated product, encounters steric interactions with the *gem*-dimethyl group in the transition state for its formation, thereby allowing bond formation to occur trans to the cyclopropane ring in spite of the axial methyl group in

the transition state for the formation of **405**.[204]



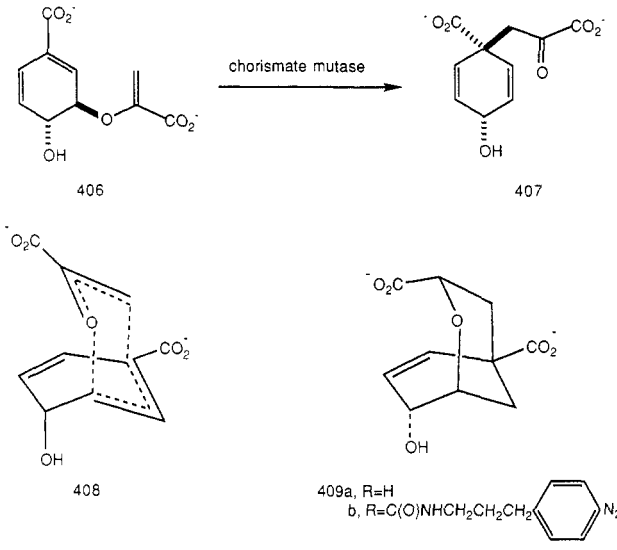
VIII. Biochemical Aspects

All the rearrangements that have been discussed thus far are inventions developed over the course of 76 years. The elucidation of the structure and absolute stereochemistry of chorismate (**406**)[205] and the discovery of its [3,3] sigmatropic rearrangement to prephenate (**407**),[206] the precursor to aromatic amino acids via the shikimic acid pathway, demonstrates that Nature has been regularly executing the "Claisen" rearrangement for some time. The synthesis of racemic chorismic acid[207a,b] and labeled[207c] chorismate was followed by the studies of Knowles, who has shown that chorismate rearranges through a chairlike transition state both in vivo and in vitro.[208] The process is catalyzed in vivo by the enzyme chorismate mutase by a factor of 10^6.[209] The accrued evidence suggests that rearrangement under either set of conditions proceeds through dipolar transition state **408** with both the hydroxyl and enol pyruvate units diaxial.[210] Bartlett has recently prepared transition-state analogue **409a** and has found it to be a potent inhibitor of chorismate mutase-prephenate dehydrogenase from *Escherichia coli*.[211,212]

Monoclonal antibodies have recently been employed to catalyze the chorismate to prephenate rearrangement. The transition-state model **409a** is bound to the carrier protein using the diazonium salt **409b**, and monoclonal antibodies are isolated that catalyze the conversion of chorismate to prephenate with a rate enhancement of 10 000.[213]

IX. Concluding Remarks

From what began as a casual introduction to a paper 76 years ago has blossomed a reaction of considerable significance. The Claisen rearrangement has stimulated the interest of several generations of chemists. Physical organic chemists have been provided with a mechanistic



challenge, the synthetic organic community has had the opportunity to expand the scope of the reaction and apply it to complex syntheses, and bioorganic chemists have solved a formidable challenge in the chemistry of enzymes. Perhaps a new and imaginative generation will see new opportunities for this reaction and expand upon the chemistry discussed in this review.

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