[2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis

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Contents

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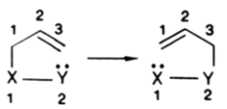
I. Introduction

As a general reaction type, [2,3]-sigmatropic rearrangements, like their [3,3]-counterparts such as the Claisen and Cope rearrangements, constitute an exceptionally versatile class of bond organization processes which have many obvious applications in organic synthesis. The [2,3]-sigmatropic reaction, generalized by eq 1, can be defined as a thermal isomerization that



(1)

proceeds through a six-electron, five-membered cyclic transition state. Over the last few decades the reactions have held the interests of chemists, both as the subjects of mechanistic investigations, and as increasingly utilized methodologies for organic synthesis.[1,2] This type of sigmatropic process encompasses a vast number of variants in terms of both the atom pair (X, Y) and the electronic state of Y (anions, nonbonding electron pairs, or ylides).[1] In this review the main emphasis will be

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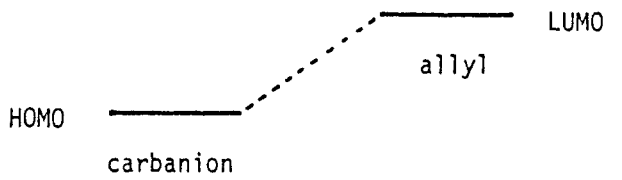
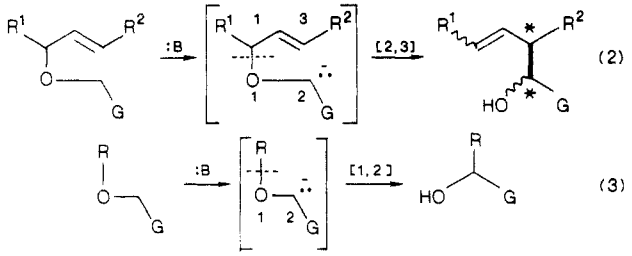


Figure 1. Frontier orbitals for the [2,3]-Wittig process.

placed *primarily* on a special class of [2,3]-variants that involves oxycarbanions (X = oxygen, Y = carbanions) as the migrating termini. This type of rearrangement, represented in eq 2, is now termed the [2,3]-Wittig



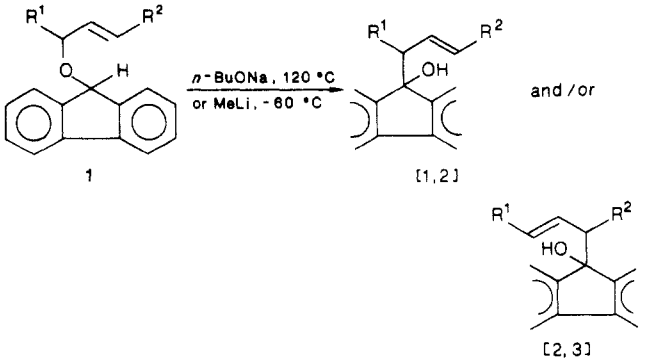
sigmatropic rearrangement since this is a formal [2,3]-sigmatropic version of the classic Wittig rearrangement, a well-known 1,2-alkyl shift of oxycarbanions (eq 3).[3]

From the synthetic standpoint, the [2,3]-Wittig rearrangement possesses several valuable features which include (a) the regiospecific carbon–carbon bond formation with the allylic transposition of oxygen function, (b) the generation of specific olefin geometries, (c) the stereoselective creation of vicinal chiral centers, and (d) the transfer of chirality. During the past several years numerous applications of the [2,3]-Wittig rearrangements have been reported particularly in the context of acyclic stereocontrol and natural product synthesis.[2c] The purpose of this review is to compile the recent studies on synthetic applications of the [2,3]-rearrangements with stereochemical emphasis. Earlier studies aimed at elucidating reaction mechanisms are only briefly described in this review.

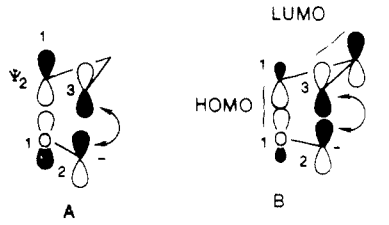
II. Mechanistic Background

A. [2,3]- vs. [1,2]-Shift

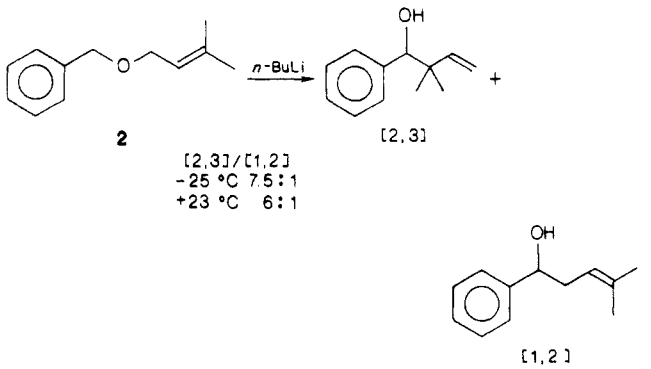
The first observation of the [2,3]-Wittig rearrangement is that of the allyl fluorenyl ethers (**1**) which was



made in the context of mechanistic studies on the Wittig rearrangement.[4] At that time the mechanism of the carbanion rearrangement was the subject of intensive investigations. It is now widely accepted that the [1,2]-Wittig rearrangement proceeds via a radical-pair dissociation–recombination mechanism,[3] whereas the [2,3]-Wittig counterpart is, in contrast, a concerted, thermally allowed sigmatropic process following the Woodward–Hoffmann rule[5] or the Fukui's frontier orbital theory.[6] Thus, the [2,3]-shift is a one-step S_Ni' reaction that proceeds in a suprafacial fashion with respect to both fragments as depicted in **A** or **B**.



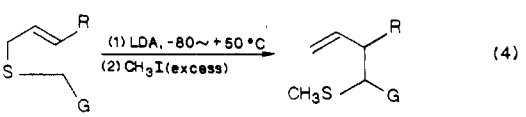
At this point it should be emphasized that the concerted [2,3]-shift does not always prevail completely over the nonconcerted [1,2]-shift. In fact, many cases have been reported where the [1,2]-shift competes with the [2,3]-shift to an appreciable extent, depending markedly on the structural environment and the reaction temperature. For instance, the rearrangement of the benzyl ether (**2**) affords a mixture of the [2,3]- and



[1,2]-product, the ratio varying with the temperature used.[7a] One should therefore keep in mind that the [2,3]-Wittig rearrangement must be conducted at as low a temperature as possible to avoid the contamination by the [1,2]-product.

B. HOMO–LUMO Interaction

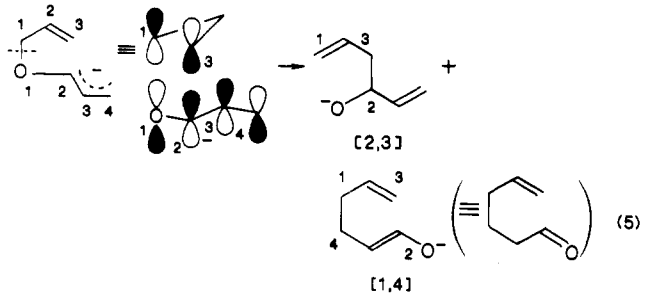
The structure–reactivity relationship for the [2,3]-Wittig process is of both mechanistic and synthetic importance. Considering the frontier orbital interaction between the HOMO of the carbanion site and the LUMO of the allylic site,[6] it seems evident from a theoretical point of view that the smaller the energy gap between $HOMO_{anion}$ and $LUMO_{allyl}$, the more readily the rearrangement occurs (Figure 1). This means roughly that the less stable the carbanion involved, the faster the rearrangement. While no quantitative evidence for this prediction has been reported, the reviewers' semiquantitative study on the thio-[2,3]-Wittig variants (eq 4)[8] has shown that the relative rate of re-



arrangement decreases in the following orders: G = Ph > CO_2Li > CN > CO_2Et > $COCH_3$; R = Ph > H > CH_3 for G = CO_2Et and CN. Thus, the presence of substituents which either lowers the $HOMO_{anion}$ level or raises the $LUMO_{allyl}$ level makes the reaction slower.

C. [2,3]- vs. [1,4]-Shift

The [2,3]-Wittig process of the bis(allylic) ether system, of which synthetic applications will be described later, produces an additional problem of mechanistic interest. In this particular case both the $[2_s,3_s]$- and $[1_s,4_s]$-shift are allowed by orbital symmetry as depicted in eq 5, along with the nonconcerted [1,2]- and [3,4]-



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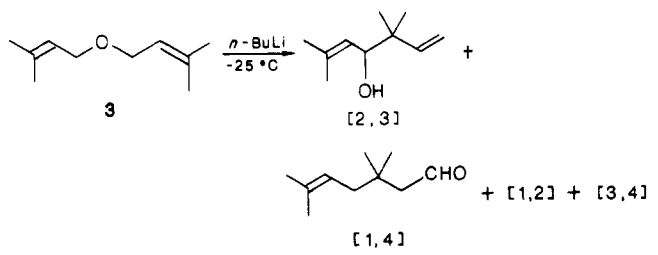
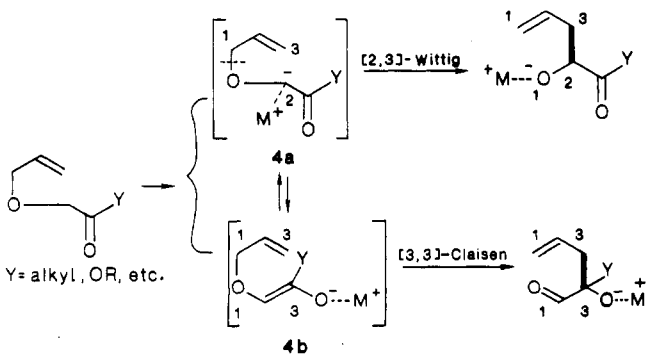
shift. In fact, the carbanion rearrangement of diprenyl ether (**3**) afforded ca. 8% of the [1,4]-product, along with the [2,3]- (67%), [1,2]- (14%), and [3,4]-product (10%).[7a] The question as to whether the [1,4]-shift



proceeds via a concerted mechanism or a cleavage–recombination pathway is still a controversial subject of current studies.[9] The periselectivity problem of the [2,3]- vs. [1,4]-shift becomes intensified with the allyl 2-cyclohexenyl ether system as will be shown later.

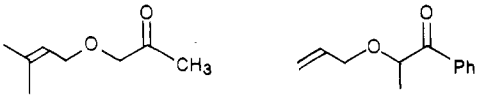
D. [2,3]-Wittig vs. [3,3]-Claisen

The enolate of the α-(allyloxy) carbonyl system presents another mechanistically intriguing case where the two competing modes of sigmatropic processes are conceivable as depicted below. Of the two plausible forms, **4a** may be envisioned as an allyloxy carbanion which can undergo the [2,3]-Wittig rearrangement,



whereas **4b** may be viewed as a 3-oxa-1,5-diene system which is capable of undergoing the novel type of [3,3]-Claisen variant. Thus, studies on a variety of enolate sigmatropic processes would provide a unique opportunity of obtaining an insight into the solution structure of enolates involved.

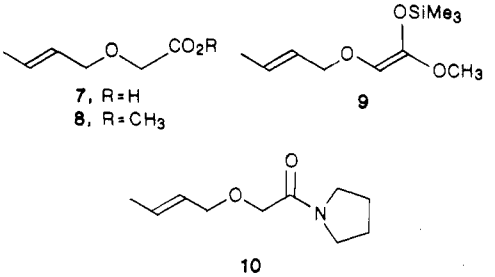
As to the rearrangement of α-allyloxy ketones, conflicting experimental results have been reported. Treatment of ketone **5** with potassium *tert*-butanolate gives the [2,3]-Wittig product as the only isolable product,[10] whereas treatment of ketone **6** with potas-



5 **6**

sium hydride (or sodium hydride) results in the exclusive formation of the [3,3]-Claisen product.[11] The reasons for this discrepancy remain unclear.

Recently the reviewers have examined the sigmatropic processes of enolates derived from acid **7**, ester **8**, its ketene silyl acetal (**9**), and amide **10**. The results



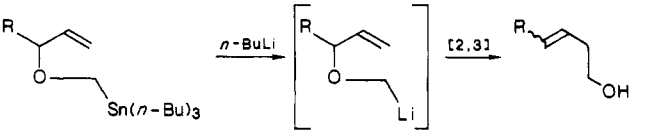
thus obtained are as follows: (a) the dilithium species of **7** (generated with LDA in THF) undergoes the [2,3]-Wittig rearrangement at −70 °C,[12] whereas the lithium enolate of **8** (LDA/THF) unexpectedly does not,[13] (b) in contrast, the lithium species of **8** generated in HMPA–THF undergoes the [2,3]-Wittig shift at −70 °C,[14] (c) heating **9** at 80 °C affords the [3,3]-Claisen product quantitatively,[13] whereas transmetalation of **9** with $SnCl_4$ or $TiCl_4$ in dichloromethane at −50 °C, by contrast, effects the [2,3]-Wittig shift,[15] and (d) the lithium enolate of **10** (LDA/THF) undergoes the [2,3]-Wittig rearrangement at −85 °C.[16]

From a synthetic standpoint, the "enolate [2,3]-Wittig rearrangement" is of particular value since its asymmetric versions involving chiral enolates should constitute an entirely new strategy for asymmetric synthesis. The subject will be discussed in section IVE.

III. Scope and Limitations

A. Structural Variations

Generally speaking, the [2,3]-Wittig rearrangement can be accomplished on any α-(allyloxy) carbanions having different substituents G (cf. eq 2), which may be generated via either direct metalation (deprotonation) or transmetalation. Still has reported an extreme case (G = H) in which the unstable oxymethyllithium is generated by the tin–lithium exchange reaction (eq 6).[17] Thus the [2,3]-Wittig strategy has

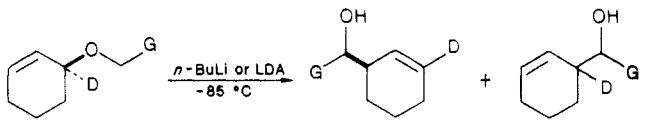


(6)

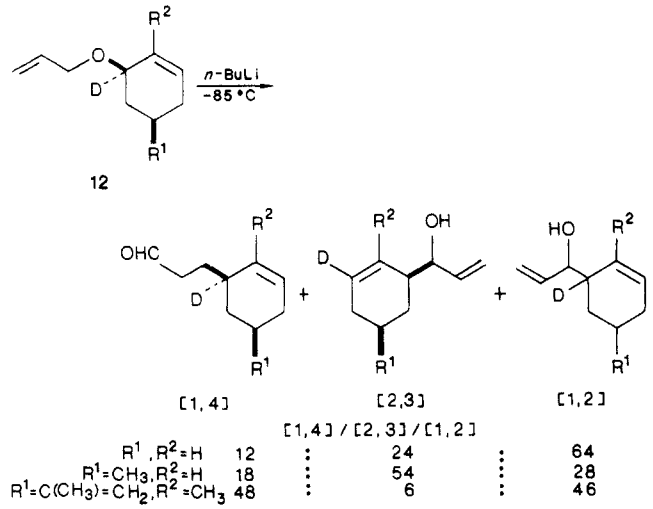
a wide scope of synthetic utility which is defined mainly by the availability of methods for generating carban-

ionic species at temperatures low enough to minimize occurrence of the [1,2]-shift. Nevertheless, the [2,3]-Wittig strategy has some limitations in the range of applicable substrates.

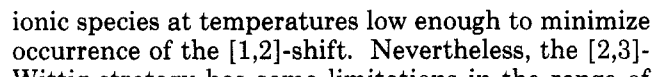
One major limitation is encountered with 2-cycloalkenyl ether systems such as **11** where the undesired

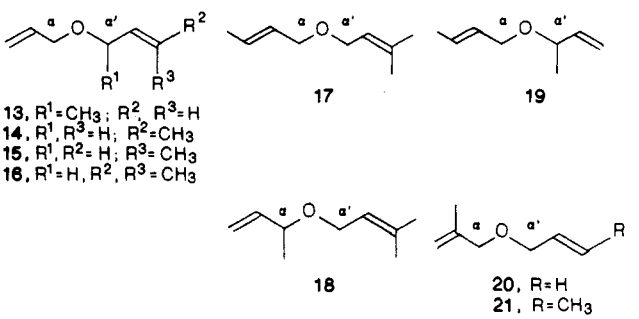


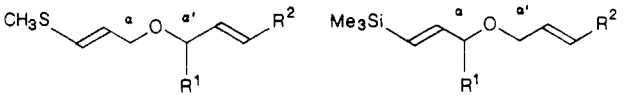
[1,2]-shifts compete considerably as shown above.[18] Of particular interest is the case of allyl cyclohexenyl ether (**12**) where the [1,4]-product is formed as an additional product, the proportion of which varies with the type of substituents as shown below;[19,20] a conformational effect has been suggested for the variation in perise-lectivity.



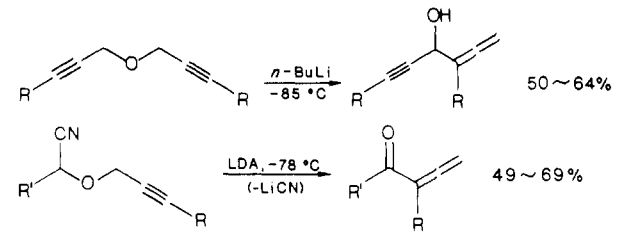
The carbanion rearrangement of the *unsymmetrical* bis(allylic) ether system produces an additional regiochemical problem in terms of the possibilities for α- vs. α'-lithiation (eq 7). The reviewers have studied rearrangements of a wide variety of bis(allylic) ethers (**13–21**) under the standard conditions (*n*-BuLi, THF, −85 °C).[21] The results thus obtained reveal the following regiochemical features. (a) All the rearrangements proceed exclusively in a [2,3]-fashion without detectable occurrence of the [1,2]- and [1,4]-shifts. (b) The crucial regiochemistry in the lithiation step is remarkably controlled by the different in the substitution pattern at the α- and γ-positions between the two allylic moieties, thereby giving the single regioisomer arising from the exclusive lithiation on the *less* substituted allylic moiety. Thus, ethers **13–18** all provide the corresponding α-[2,3]-product as the single regioisomer, whereas **19** affords a 1:2 mixture of the α- and α'-[2,3]-products. (c) The β-alkyl substitution has little effect as expected. Thus, **20** provides a 3:4 mixture of α- and α'-[2,3]-products, whereas **21** affords exclusively the α-[2,3]-product. However, no problem of regioselectivity arises when a carbanion-stabilizing group such as methylthio and trimethylsilyl is introduced at the γ-position of one allylic moiety; both **22a**[22] and **22b**[23] yield exclusively the α-[2,3]-product, independent of the substitution pattern.







Replacement of the allyl migrating group by a propargyl group constitutes another general class of [2,3]-Wittig variants which afford the allenic alcohols as exemplified below.[24,25] However, it appears that the concerted [2,3]-shift involving a triple bond is a relatively unlikely process in general.[9a]

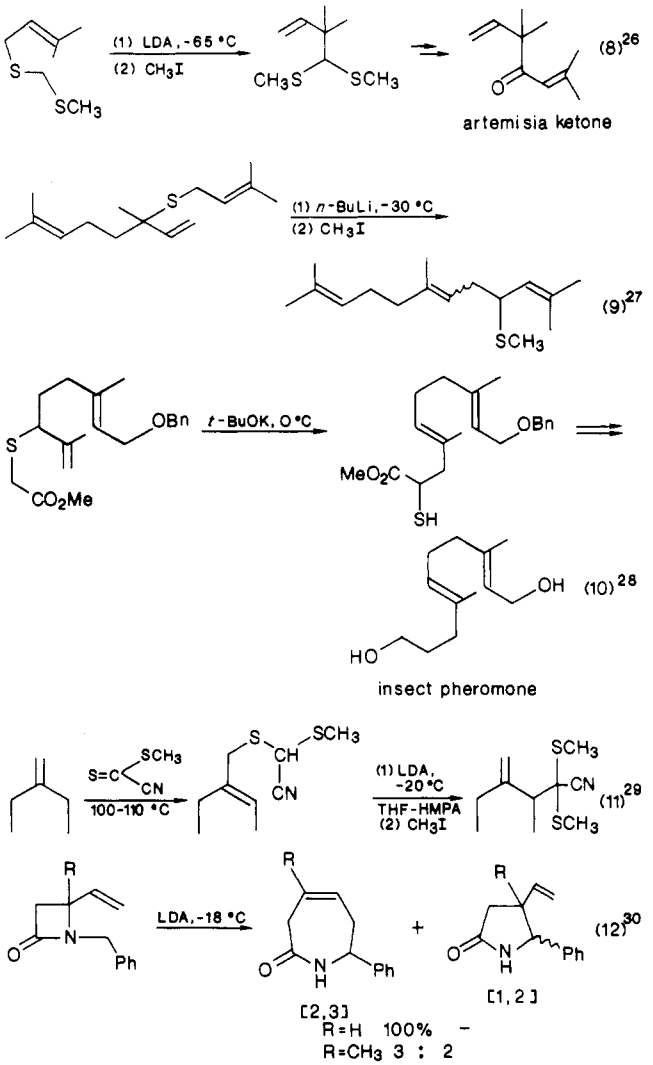


B. Hetero-[2,3]-Wittig Variants

A similar carbanionic [2,3]-rearrangement is also feasible on allylic sulfides (cf. eq 4) and amine counterparts. The synthetic utility of such a thio-[2,3]-Wittig variant is now widely recognized particularly in the terpenoid synthesis as exemplified by eq 8–11. Equation 11 shows an example of the novel ene–thio-[2,3]-Wittig sequence, the net effect of which allows an allylic functionalization of olefins without double bond migration. In contrast, little has been studied on the amino-[2,3]-Wittig variant except for the one example depicted by eq 12. Finally, it should be added that the ylide counterparts of these hetero-[2,3]-Wittig variants fall into the category of the well-known Stevens and Sommelet–Hauser rearrangements,[31,33] which is beyond the scope of this review.

IV. Stereochemical Control

The [2,3]-Wittig rearrangement usually proceeds through a highly ordered cyclic transition state to create both a new C–C double bond and a new C–C single bond (cf. eq 2). Consequently, this type of [2,3]-rear-

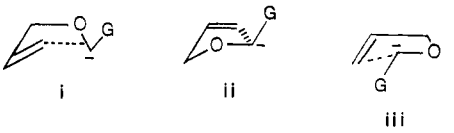


rangement can, in principle, exhibit the same types of stereocontrol as observed in the well-established [3,3]-Claisen rearrangement:[2,32] generation of double bonds of specific geometry, both internal and relative asymmetric induction, and transfer of chirality along an allylic array. Studies on the stereochemistry with respect to the newly formed double bond began simultaneously to the initial mechanistic studies. On the other hand, the issues of stereocontrol over the newly created chiral centers is the subject of relatively recent investigations mainly because the [2,3]-sigmatropic rearrangement in general has been shown to exhibit only modest levels of asymmetric induction in comparison with the [3,3]-Claisen counterparts.[2]

Over the past several years, however, considerable progress has been made in the development of stereoregulated [2,3]-Wittig variants, and hence the [2,3]-Wittig strategy has been increasingly employed to great advantage in the construction of acyclic systems. Moreover, the favorable transition-state geometry is now predictable from principles of conformational analysis. Thus, the stereochemical outcome may be predicted and controlled. This section summarizes the stereochemical principles that govern the [2,3]-Wittig process and describes some important examples.

A. Basic Transition-State Conformation

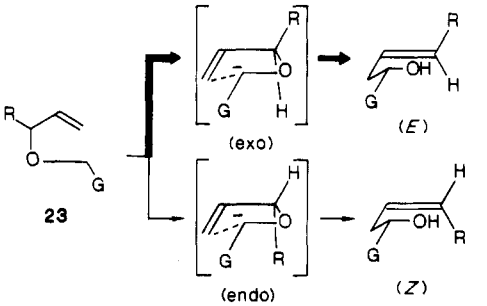
In order to explain and predict the stereochemistry of the [2,3]-Wittig rearrangement one must determine the basic conformation for the five-membered transition states. Just as the [3,3]-sigmatropic transition state resembles the chairlike conformation of the cyclohexane ring,[32] the preferred conformation of the [2,3]-sigmatropic transition state should resemble the "folded envelope" conformation of the cyclopentane ring.



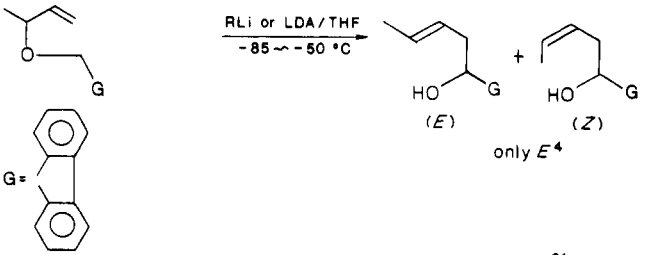
However, there are still three options for the envelope conformation as depicted above. Conformer **i** has been most frequently assumed (e.g., in ref 1, 7a, and 17), while conformer **ii** has been used for the ylide [2,3]-processes.[33] Nonetheless, the reviewers have recently proposed conformer **iii** as the basic conformation for the [2,3]-Wittig rearrangement which best accommodates the stereochemical outcomes described below.[34] The basic conformation of type **iii** is used throughout this review to analyze the transition-state geometries *only* for the sake of consistency. Thus, it should be emphasized here that the basic conformation of type **i** in particular works equally well for explaining a variety of the stereoselections discussed in the following sections.

B. Olefinic Stereoselection

The [2,3]-Wittig rearrangement of ethers (**23**) derived from secondary allylic alcohols affords the (*E*)- and (*Z*)-olefins. Examination of the envelope transition-



state conformations suggests that the R group should prefer the exo orientation, thus leading to the preferential formation of the *E* isomer.[35] The strong preference for *E* products has been amply confirmed by numerous experiments, and is clearly a general attribute of the [2,3]-Wittig family. Typical examples are shown below.



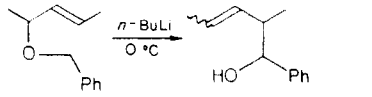
G = C(R)=CH$_2$ (R = H, CH$_3$)	98% *E*[21]
G = C≡CR (R = H, CH$_3$, SiMe$_3$)	93 ~ 98% *E*[36]
G = Ph	only *E*[7]
G = CO$_2$H	74% *E*[12]
G = CO$_2$CH$_3$ (run in 25% HMPA-THF)	78% *E*[14]

TABLE I. Diastereoselectivity in the [2,3]-Wittig Variations[a]

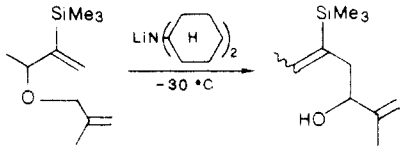
entry	substrate	E:Z[b]	threo:erythro[c]
A	**26a**, G = $CH{=}CH_2$	93:7	79:21 (84:16)
		5:95	12:88 (8:92)
B	**26b**, G = $C(CH_3){=}CH_2$	93:7	67:33 (72:28)
		17:83	16:84 (5:95)
C[d]	**26c**, G = $C(SiMe_3){=}CH_2$	95:5	70:30
D	**26d**, G = C≡CH	93:7	93:7 (99:1)
		2:98	12:88 (10:90)
E	**26e**, G = Ph	93:7	37:63 (39:61)
		5:95	7:93 (5:95)
E[e]	**26e**, G = Ph	93:7	51:49 (55:45)
		5:95	5:95 (2:98)
F	**26f**, G = p-$CH_3OC_6H_4$	93:7	56:44 (60:40)
		2:98	1:99 (0:100)
G	**26g**, G = CH=CHPh-(*E*)	93:7	71:29 (74:26)
		2:98	30:70 (28:72)
H[f]	**26h**, G = CO_2H	93:7	12:88 (8:92)
		5:95	75:25 (79:21)

[a] Unless otherwise noted, all reactions were run with *n*-BuLi in THF at −85 °C for 6–8 h. [b] Refers to the geometric ratio of the crotyl alcohols used for the substrate preparations. [c] Values in parentheses refer to the calculated values based on 100% of geometric purity. [d] Lithium dicyclohexylamide was used as the base at −30 °C. [e] The reaction was run in TMEDA/ether/hexane (1:1:1.2). [f] LDA was used as the base.

The rearrangements of ethers containing an additional substituent on the allylic moiety frequently exhibit relatively low levels of *E* selectivity as shown below; these undoubtedly reflect the smaller energy differences between the envelope transition states.

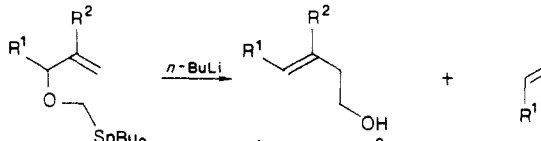


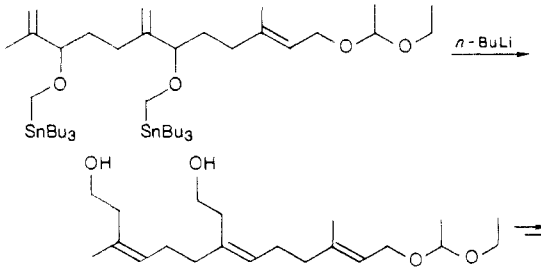
E/*Z* = 83:17[37]



E/*Z* = 41:59[38]

A notable exception to this *E* selection is the rearrangement of the tin-substituted ethers (**24**) which affords the (*Z*)-homoallyl alcohols as the major products; several explanations have been advanced for this reversal of stereoselectivity.[1,17] This unusual *Z* selectivity has found an ideal application in the synthesis of the C_{18} Cecropia juvenile hormone (eq 13).[39]



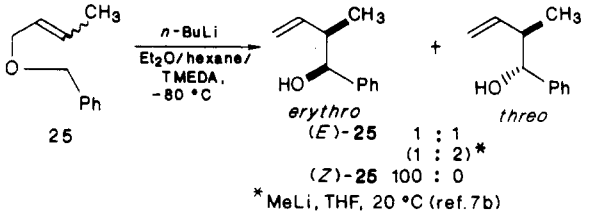


J.H (13)

C. Diastereoselection[40]

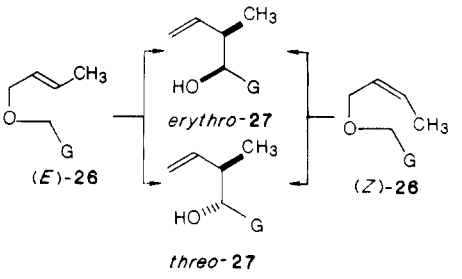
1. Transition-State Model

Among the stereoselections involved in the [2,3]-Wittig process, diastereoselection with respect to the newly created vicinal chiral centers is the most important from the standpoint of acyclic stereocontrol. From a historical standpoint, Rautenstrauch's work[7a] on the rearrangement of the geometric pair of benzyl crotyl ethers (**25**) is of considerable significance because



it was the first to address the implication of allyl geometry on the diastereoselectivity.

In 1981 the reviewers reported diastereoselections in a broad range of [2,3]-Wittig variations (eq 14).[21,34] These results are summarized in Table I.



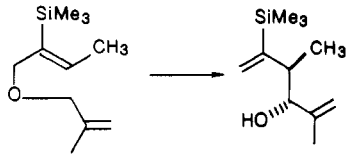
(14)

Inspection of the data in Table I reveals several general trends in terms of the sense and degree of stereoselection, which impart considerable stereochemical predictability to this methodology. (1) In general, the *Z* substrate exhibits erythro selection, whereas the *E* substrate shows threo selection. A notable exception to this generalization is entry H (G = CO_2H),[12] where the opposite sense of stereoselection is observed. Entries E–F (G = Ar) are also somewhat exceptional, in that the *Z* substrate constantly exhibits an extremely high erythro selectivity, whereas the *E* counterpart shows an extremely low level of diastereoselection. (2) The degree of stereoselection is critically dependent on the kind of substituent (G), suggesting that the carbanion structure conferred by a given G plays an important role in dictating the stereoselectivity. (3) Another notable trend is that the erythro selectivity for *Z* series is of the order G = Ph > $C(CH_3){=}CH_2$ > $CH{=}CH_2$ > C≡CH, whereas the threo selectivity for *E* series is of the opposite order G = C≡CH > $CH{=}CH_2$ > $CR{=}CH_2$ (R = CH_3, $SiMe_3$) > Ph. (4) Particularly noteworthy are the remarkably high stereoselections observed in entries D and E, which find synthetic applications as will be described later.

Extensive analysis of these stereochemical trends has led the reviewers to propose the transition-state model depicted in Scheme I, which provides logical bases for explaining and predicting the stereoselection in a wide range of [2,3]-Wittig variations as follows.[34,35] First, the general sense of diastereoselection, i.e., *E* → threo and *Z* → erythro, is readily explained in terms of the pseudo-1,3-diaxial interaction of G ⇔ H_β in T_2 and T_3;

e.g., T_3 should be sterically less favorable than T_4, thus leading to erythro selection, the degree increasing with an increase in the 1,3-repulsion. Second, the marked dependence of threo selection on the G substituent is best explained by assuming an additional G ⇔ CH_3 steric parameter (gauche interaction) in the preferred T_1; hence the threo selectivity would decrease with an increase in the gauche interaction. Third, a similar argument could be extended to rationalize the unusual stereoselection observed in entry H (Table I); i.e., the gauche interaction would prevail over the 1,3-repulsion in both the *E* and *Z* substrates, eventually leading to selection opposite in sense to the general selection rule.

This transition-state model has been further strengthened by additional examples.[34] For instance, the rearrangement of ether **28** provides a remarkably



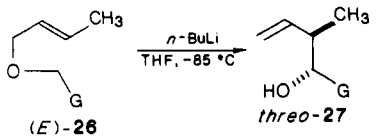
28 (92% *E*) threo/erythro = 91:9

enhanced threo selectivity compared to the nonsilylated counterpart (entry B, Table I) as a result of the increased 1,3-repulsion of G ⇔ $SiMe_3$ relative to that of G ⇔ H_β for the latter.

2. *Highly Stereoselective Variants*

In order to develope the [2,3]-Wittig rearrangement into a new basic strategy for acyclic stereocontrol, one has to develop stereoselective variants which exhibit at least 95% of either threo or erythro selectivity. Among the variants described so far, however, only two variants (G = Ph for erythro and G = C≡CH for threo) meet the requirement. Thus, the reviewers have directed considerable effort toward the development of more highly selective variants based on pertinent analyses of the transition-state model described above.

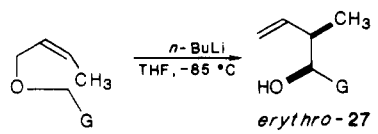
The highly threo- and erythro-selective variants thus developed are summarized by eq 15 and 16, respectively. The extremely high stereoselection in the



(15)

(*E*)-**26** *threo*-**27**

d, G = C≡CH 99% select[21]
i, G = C≡CCH3 99% select[41]



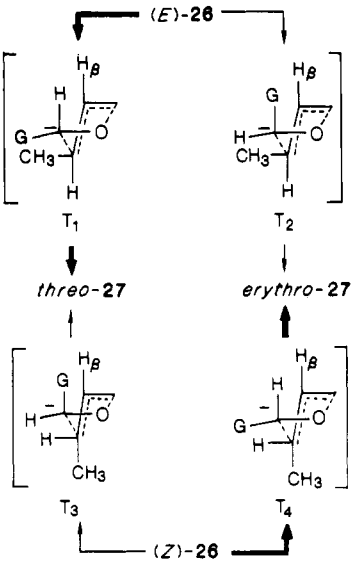
(16)

(*Z*)-**26** *erythro*-**27**

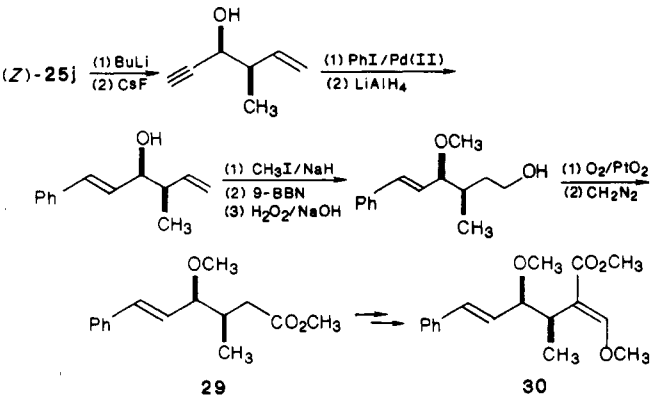
e, G = Ph 95~98% select[7a,34]
i, G = C≡CCH3 100% select[41]
j, G = C≡CSiMe3 100% select[41]

propargyl ether series can be rationalized by the transition-state model (Scheme I); the increased *E* → threo selectivity is interpreted as a result of the diminished gauche repulsion of G ⇔ CH_3 in the favored T_1, whereas the enhanced *Z* → erythro selectivity is explicable in terms of the increased 1,3-repulsion of G ⇔ H_β in the disafavored T_3.[41]

SCHEME I



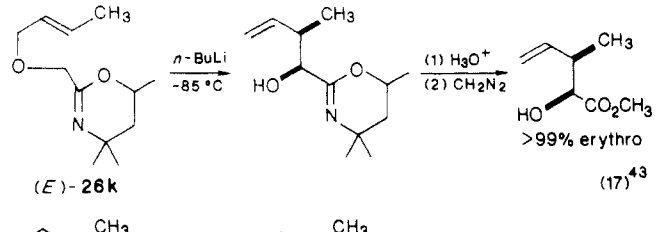
SCHEME II



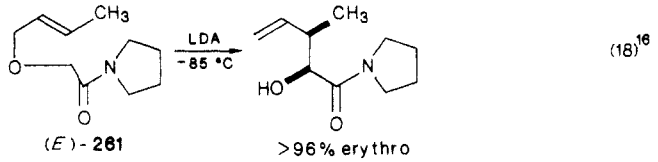
At this point it should be emphasized that the key substituent G leading to enhanced threo selectivity does not provide enhanced erythro selectivity and vice versa, except for the **26i** pair. Of special interest is the rearrangement of the **26j** pair (G = C≡CSiMe$_3$) since (*Z*)-**26j** exhibits a remarkably enhanced erythro selectivity that exceeds the geometric purity of the substrate used, whereas (*E*)-**26j** also shows erythro selection, which is opposite to the general selection rule, though the degree is moderate (73%).[41]

From the synthetic standpoint, the propargylic variants (**26d,i,j**) possess particular advantages: (a) it is possible to attain an extremely high level of either diastereoselection through the proper choice of the crotyl geometry and the ethynyl group in substrate; (b) the rearrangement product possesses unique multifunctionality which readily allows a variety of further synthetic transformations. The latter feature is highlighted in the formal total synthesis of (±)-oudemansin **30** (Scheme II).[41] Conversion of **29** to **30** has been already reported.[42]

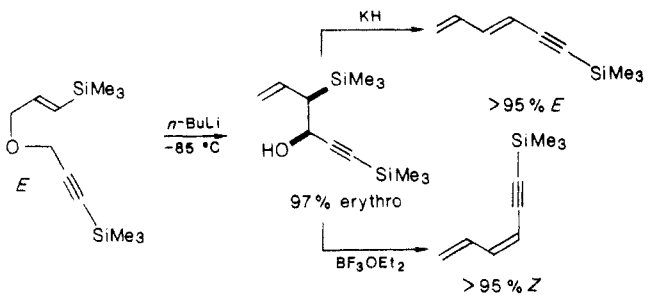
Furthermore, the reviewers have developed a novel class of erythro-selective variants depicted by eq 17–19, where the *E* substrate provides an extremely high erythro selectivity; in contrast, the *Z* counterpart of **26l** shows low threo selectivity (55%). The unusual *E* → erythro selectivities are explained by the overwhelmingly enhanced gauche repulsion of G ⇔ CH_3 in T_1 (cf. Scheme I). These variants are also of synthetic value; the first two variants permit ready access to *erythro*-



(17)[43]



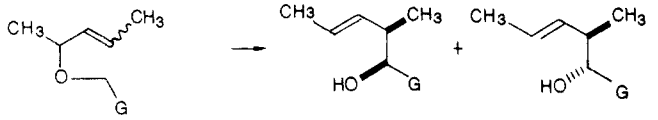
(18)[16]



(19)[44]

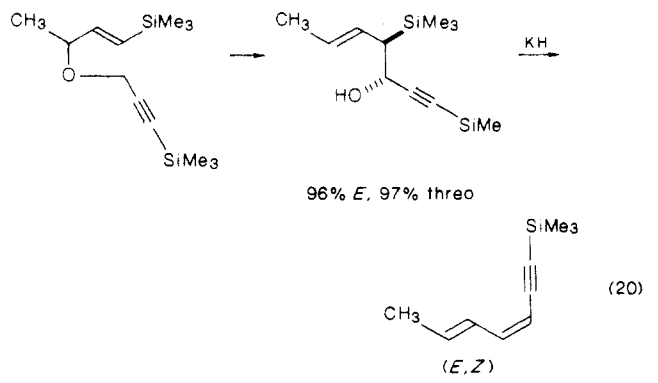
α-hydroxy-β-alkyl carboxylic acid derivatives, an important class of compounds for natural product synthesis and the last one, coupled with the Peterson elimination, provides a highly stereocontrolled entry into the conjugated dienyne systems.

The question quickly arises as to whether these high levels of diastereoselection are retained in the rearrangements of α-substituted crotyl systems (**31**) which



	(*E*)-*erythro*	(*E*)-*threo*
(*E*)-**31d**, G=C≡CH	9	91
(*Z*)-**31j**, G=C≡C−SiMe3	99	1

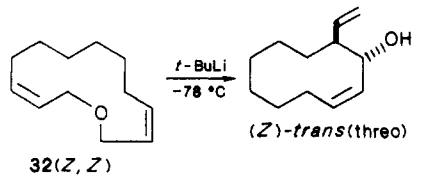
are anticipated to exhibit a high *E* selectivity as already discussed. In the cases of **31d** and **31j**, for instance, it has been shown that the high levels of diastereoselection are completely retained along with exclusive formation of (*E*)-olefin in either diastereomer.[41] However, this is not always the case. The α-methylcrotyl counterpart of the dihydrooxazine variant shown by eq 17 affords a complex mixture of the (*E*)- and (*Z*)-*threo* and (*E*)- and (*Z*)-*erythro* products,[45] whereas that of the novel variant depicted by eq 19 surprisingly exhibits a reversal in diastereoselection along with retention of the high *E* selectivity (eq 20).[44] This question is of considerable



(20)

importance in connection with chirality transfer via [2,3]-Wittig strategy and hence will be discussed again in section IVD.

More recently Takahashi and Tsuji have reported a quite novel example in which the 13-membered bis(allylic) ether (**32**) is used as a substrate to exhibit an

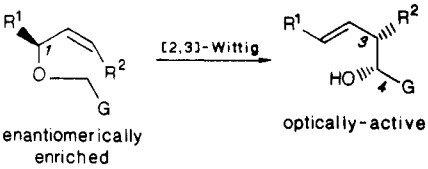


extremely high level of unusual *Z* → threo selection, while the (*E*,*E*)-counterpart shows the usual *E* → threo selectivity.[46]

D. Chirality Transfer

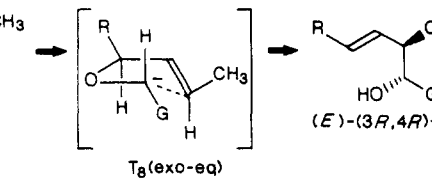
1. Guiding Principles

The most synthetically valuable feature of the [2,3]-Wittig rearrangement is its ability to specifically transfer the chirality at C-1 of the allylic moiety to the newly created chiral center(s) at C-3 and/or C-4 as depicted in eq 21.[47] This type of asymmetric rearrangement destroys the original chiral center while simultaneously creating new ones, and hence conservation of optical activity is experimentally observed, a situation that Mislow has referred to as a "self-immolative" asymmetric synthesis.[48]



(21)

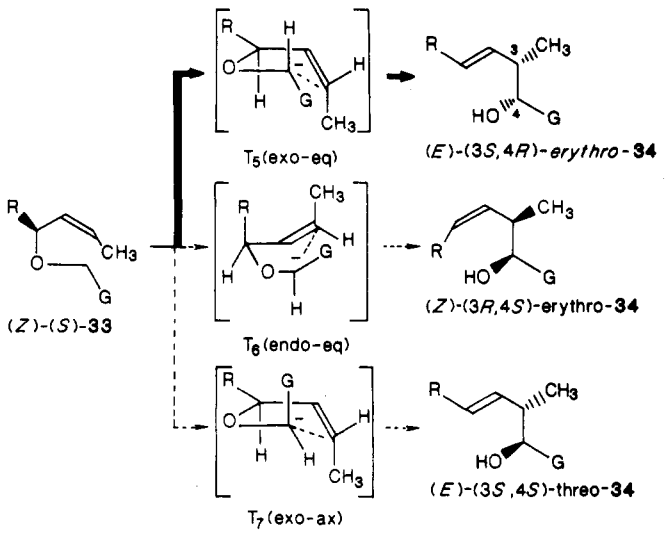
Guided by the transition-state model advanced above for olefinic stereoselection and diastereoselection, one can readily predict both the olefin geometry and the relative and absolute configuration of the product from the three variables in the substrate: the absolute configuration, the double-bond geometry, and the nature of G. In an asymmetric version of the highly (*Z* → erythro)-diastereoselective variants shown in eq 16, for instance, (*Z*)-(*S*)-**33** rearranges to (*E*)-(3*S*,4*R*)-*erythro*-**34** through the transition state T_5 with exo-R and equatorial-G in preference to other alternatives including T_6 and T_7 which would lead to (*Z*)-(3*R*,4*S*)-*erythro*- and (*E*)-(3*S*,4*R*)-*threo*-**34**, respectively (Scheme III). Similarly, an asymmetric version of the highly (*E* → threo)-selective variants depicted in eq 15 should afford (*E*)-(3*R*,4*R*)-*threo*-**34** as the major product via the transition state T_8 (eq 22). Thus, the asymmetric



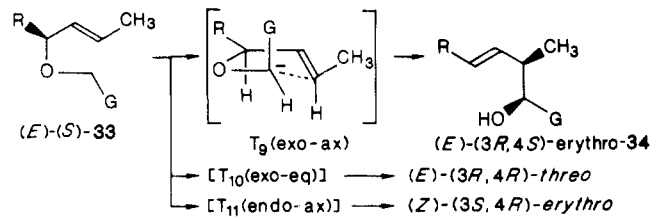
(22)

[2,3]-Wittig strategy, if properly designed, allows for the complete and specific transmission of the chirality of optically-active allylic alcohols to the new chiral centers in a predictable manner; thus making it one of the most powerful tools for asymmetric synthesis, particularly for

SCHEME III

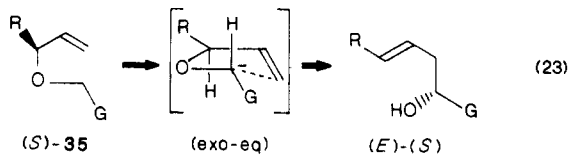


SCHEME IV



the concurrent control of diastereo- and enantioselection in acyclic systems.

Of further note is that such an asymmetric [2,3]-Wittig strategy, when applied to enantiomerically defined substrates of type **35**, allows 1,4-chirality transfer across the new C–C bond, guided by the same stereochemical principle as described above (eq 23). Some examples will be given later.

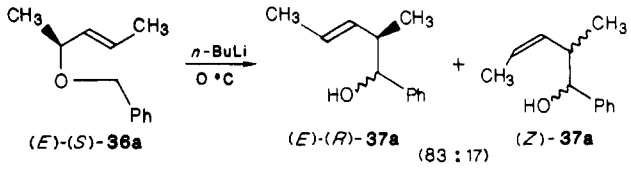


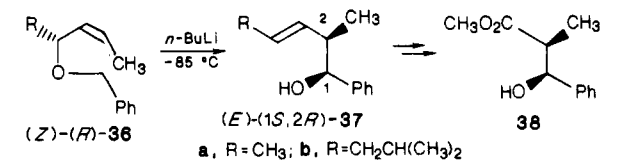
(23)

One major problem confronting this strategy is associated with the chirality transfer in an asymmetric version (Scheme IV) of the highly (E → erythro)-selective variants shown in eq 17 and 18. Examination of the transition-state geometries suggests that the normally preferred transition state T_9 is greatly destabilized by an additional steric interaction of R ⇔ G, thus leading instead to a lowered (*E*) and/or erythro selectivity as a result of considerable contributions of T_{10} and T_{11}; overall, a complicated mixture of the stereoisomers should be formed. In fact, the use of the dihydro-1,3-oxazine ring as the key G in (*E*)-(*S*)-**33** (R = CH_3) has been shown to provide a complex, inseparable stereomixture with an extremely low erythro selectivity.[45]

2. 1,3-Chirality Transfer

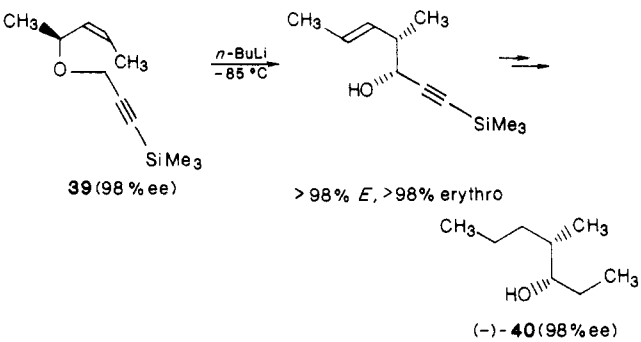
The first observation of chirality transfer in a [2,3]-Wittig process was that of Baldwin and Patrick in 1971,[37] who showed that the rearrangement of (*E*)-(*S*)-**36a** gave an 83:17 ratio of (*E*)- and (*Z*)-**37a** and the [2,3]-shift leading to (*E*)-**37a** proceeded with essentially 100% 1,3-chirality transfer,[49] while the diastereoselectivity was not determined. Later the reviewers' group has established that a similar reaction of (*Z*)-(*R*)-**36a** at −85 °C proceeds with at least 97% chirality transfer together with 100% *E* selectivity and only 80% erythro selectivity and also that the use of **36b** provides an enhanced erythro selectivity (96%) to



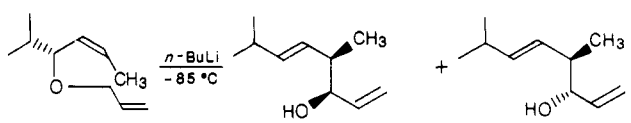


afford (*E*)-(1*S*,2*R*)-**37b** in high diastereo- and enantiomeric purity; the major product has been converted to the formal aldol product (**38**), a precursor to *l*-ephedrine (an adrenergic drug).[50]

More recently chirality transfer in synthetically more versatile variants has been examined independently in the reviewers' and Midland's laboratories. The most striking example is the rearrangement of **39**,[51] where complete transfer of chirality is achieved with practically 100% of both *E* and erythro selectivity as predicted above in Scheme III. Its synthetic potential has been illustrated in the chiral synthesis of (−)-**40**, an

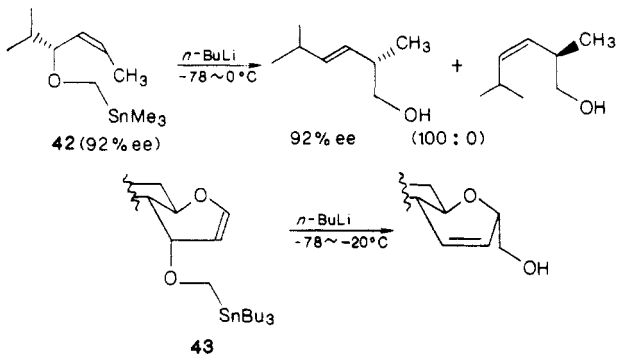


aggregation pheromone of the smaller European elm bark beetle.[51] Complete chirality transfer has also been confirmed in the rearrangement of **41** which exhibits



100% *E* selectivity along with 92% erythro selectivity, while the *E* counterpart provides only 60% threo selectivity.[52] Midland has also reported that the rearrangement of **42**, an asymmetric version of Still's variant, proceeds with virtually complete transfer of chirality with unexpectedly high *E* selectivity, while the *E* counterpart affords a 53:47 mixture of *E* and *Z* products.[53] Prior to these studies, Fraiser–Reid and his co-workers attempted to apply this technology to the carbohydrate framework **43**; unfortunately, however, the rearrangement afforded only a 25% yield of the desired product.[54]

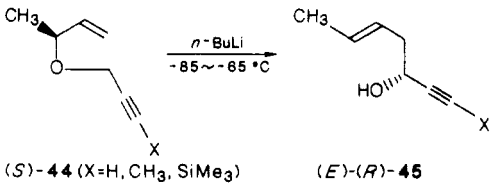
The asymmetric [2,3]-Wittig variants thus developed provide convenient and powerful tools for the concur-



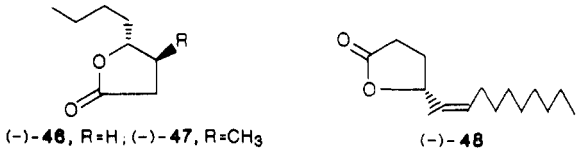
rent control of both diastereo and enantio selection in the construction of acyclic systems, with considerable stereochemical predictability guided by the reliable transition-state model. Thus, the asymmetric [2,3]-Wittig strategy should find more applications in asymmetric syntheses of a variety of natural products. Further applications in this area will be described in section V.

3. 1,4-Chirality Transfer

The 1,4-chirality transfer in [2,3]-Wittig processes, despite its great potential, has received only scant attention. The reviewers' group has confirmed that the rearrangement of (*S*)-**44** proceeds with 81–93% enan-

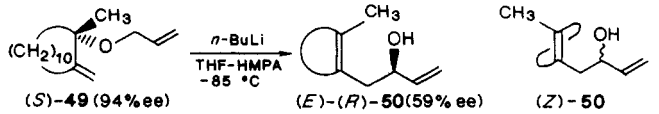


tiospecificity together with 93–98% *E* selectivity (depending on the nature of X) to afford (*E*)-(*R*)-**45** as the major product.[55] The synthetic utility of (*E*)-(*R*)-**45** (X = H) as a chiral building block has been demonstrated by its conversion to (−)-**46**, a precursor to canadensolide,



(−)-**47**, quercus lactone-a, and (−)-**48**, a sex pheromone of the Japanese beetle.[56]

Marshall and Jenson have recently reported that the rearrangement of the novel cyclic system (*S*)-**49** gives a 50:1 ratio of (*E*)- and (*Z*)-**50** and the [2,3]-shift to (*E*)-**50** proceeds with only 65% 1,4-chirality transfer;

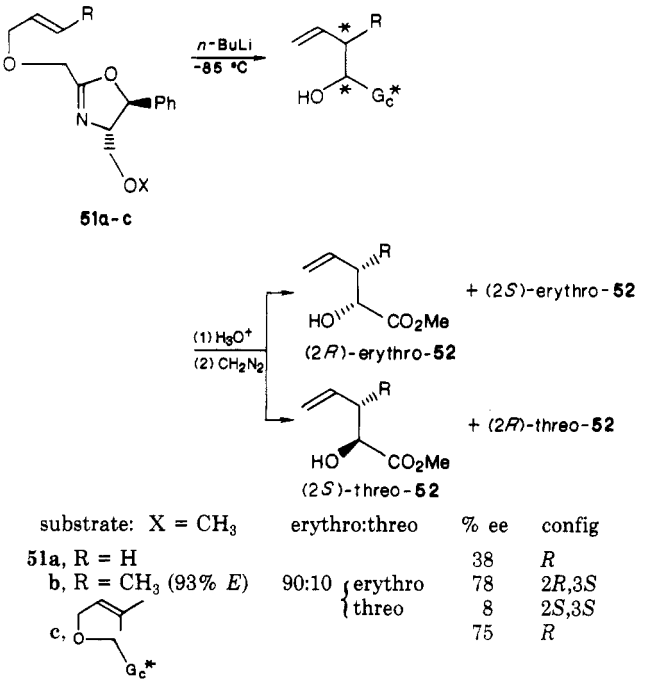


an explanation has been advanced for the relatively low enantiospecificity.[57]

E. Asymmetric Synthesis

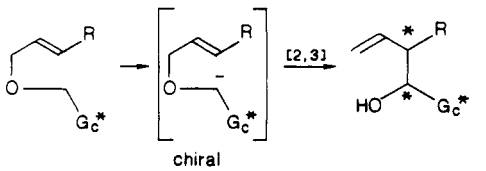
The preceding discussion has been concerned with "self-immolative" asymmetric synthesis (chirality transfer) via the [2,3]-Wittig rearrangement. Alternatively, the [2,3]-rearrangement, when applied to substrates with a chiral auxiliary (G_c*), should constitute

SCHEME V



substrate: X = CH_3	erythro:threo	% ee	config
51a, R = H		38	*R*
b, R = CH_3 (93% *E*)	90:10 erythro	78	2*R*,3*S*
	threo	8	2*S*,3*S*
c,		75	*R*

a new, general strategy for "conservative" asymmetric synthesis (eq 24).

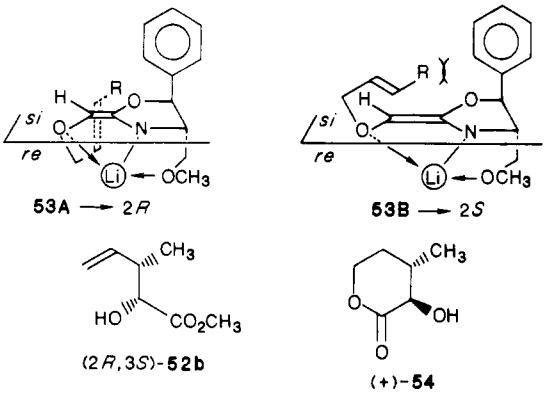


(24)

In view of the tremendous progress recently made in the development of chiral enolates and their utility in asymmetric aldol and alkylation reactions,[58] the asymmetric [2,3]-Wittig variants involving a chiral enolate as the migrating terminus seem most promising, despite the potential competition posed by the [3,3]-Claisen route as discussed in Section IID. The reviewers have reported the first example of such a rearrangement (Scheme V),[59] where Meyers' chiral 2-oxazoline ring[60] serves as the G_c* which can be nondestructively removed.

As can be seen from the data presented, the rearrangements occur preferentially from the *re* face, the degree of preference depending significantly upon the methyl-substitution pattern of the allylic moiety. Particularly notable are the rearrangements of **51b** (X = CH_3) and **51c** (X = CH_3) which provide relatively high degrees of diastereoface selection; the former also exhibits a substantially high erythro selectivity. These trends are not readily explainable owing to the great complexities of this process. Nonetheless, the observed diastereoface selection appears to implicate metal-chelated (*E*)-enolate **53A** undergoing the [2,3]-shift preferentially from the bottom-side (*re* face), the degree of preference varying markedly with the magnitude of the R ⇔ Ph steric parameter present in the top-side (*si* face) rearrangement (cf. **53B**).

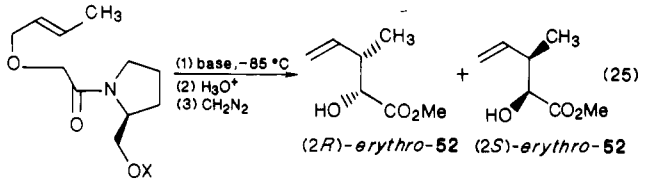
From the standpoint of synthetic utility, this asymmetric [2,3]-Wittig variant permits ready access to optically active α-hydroxy carboxylic acid derivatives. Its potential has been demonstrated[59] by the asymmetric synthesis of "unnatural" verrucarinolactone (+)-**54** from



(2*R*,3*S*)-**52b** obtained above according to the reported four-step procedure.[61]

In a continuation of these studies, the reviewers have recently found that treatment of **51** (X = H) with potassium hydride at −20 to 20 °C induces the [2,3]-shift either in the absence or presence of 18-crown-6 to give an entirely different type of diastereoface selection, while the diastereoselectivity is greatly lowered (Table II).[62] The KH-induced process in the absence of 18-crown-6 exhibits not only the opposite sense of diastereoface selection but also the opposite effect of methyl-substitution on the allylic moiety to those observed in the BuLi-induced counterpart; **51a** (R = H) provides the highest optical yield to afford (*S*)-**52a**. On the other hand, the KH-induced process in the presence of the crown ether surprisingly exhibits a further reversal in π-facial selection, along with a similar dependence on the methyl-substitution pattern; again, **51a** provides the highest selectivity to give (*R*)-**52a** in this case. The origin of this dramatic changeover in π-facial selection remains unclear mainly because information pertaining to the actual solution structure of the potassium azaenolate is not available. Nonetheless, the observed diastereoface selection implies that the KH-induced rearrangement occurs preferentially from the topside of the enolate system; i.e., from the *si* face of the (*E*)-enolate (cf. **53**) formed in the absence of the crown ether and from the *re* face of the (*Z*)-enolate formed in the presence of the crown ether.

The reviewers have also studied the rearrangement of the (*S*)-prolinol-derived amide system **55** (eq 25).[16]



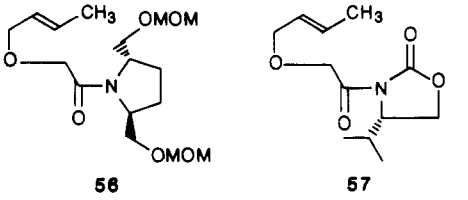
substrate	base	erythro:threo	% ee[a]	conf at C-2
a, X = H (Li)	LDA	95:5	52	*R*
	LDA/$MgBr_2$	96:4	36	*R*
b, X = MEM ($CH_2OCH_2CH_2OMe$)	LDA	97:3	20	*S*
	LDA/Cp_2ZrCl_2[b]	98:2	60	*S*

[a] Refers to that of the erythro product. [b] Di(cyclopentadienyl)-zirconium dichloride.

This variant, while providing extremely high erythro selectivity, exhibits a much lower diastereoface selectivity than one might anticipate from the *intermolecular* versions extensively studied by Evans' group.[58,63]

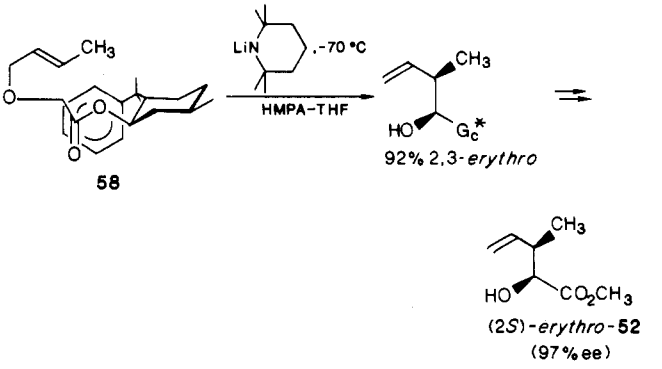
The trends thus observed are two-fold and are superficially consistent with Evans' observation: the reversal of π-facial selection upon changing the pendent oxygen substituent (X) from H (Li) to MEM and the enhancement in π-facial selection by using the zirconium enolate.

Two other points should be noted here. Recently Yamaguchi and co-worker have shown that the Zr-enolate rearrangement of a similar amide system with C_2-symmetry (**56**) exhibits essentially 100% diastereo-



face and erythro selection.[64] Unfortunately, on the other hand, the reviewers have found[65] that the lithium enolate derived from the oxazolidone imide system (**57**), another chiral auxiliary developed by Evans,[58] does not undergo the [2,3]-shift under the standard conditions.

Furthermore, the reviewers have quite recently found that the rearrangement of the (−)-8-phenylmenthol-derived ester system (**58**) in HMPA–THF exhibits an



extremely high degree of diastereoface selection along with a high erythro-selectivity to afford (2*S*)-*erythro*-**52** in high optical purity,[66,67] which is convertible to "natural" verrucarinolactone (−)-**54**.

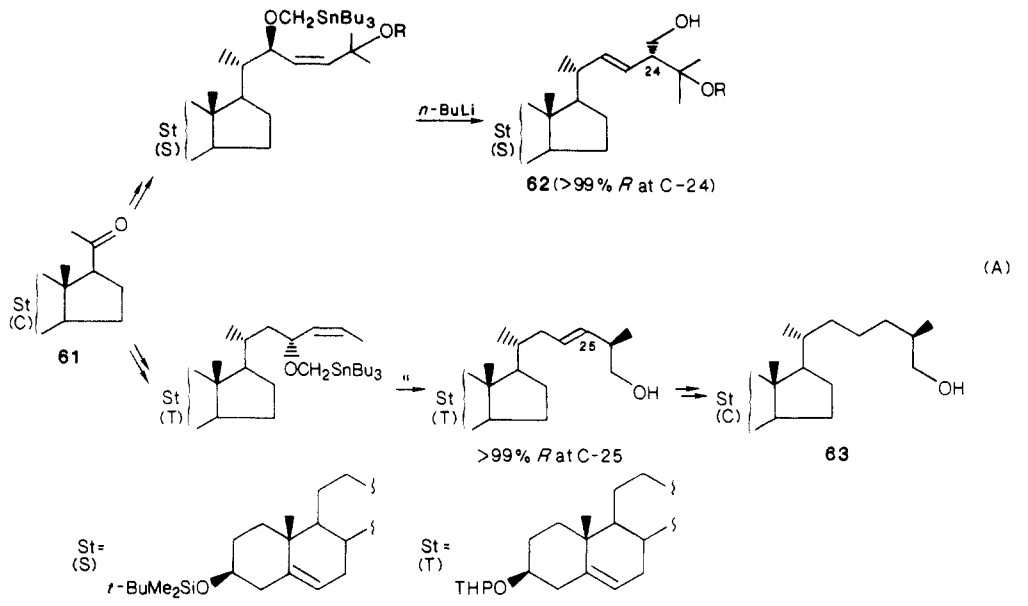
It is thus clear that the asymmetric enolate [2,3]-Wittig strategy provides a new powerful tool for asymmetric synthesis of α-hydroxy-β-alkyl carbonyl compounds, an important class of intermediates for natural product synthesis.[67] Some of the observed levels of asymmetric induction are comparable to those in the well-noted asymmetric aldol strategy which yield α-alkyl-β-hydroxy carbonyl compounds. Given the current level of interest in chiral enolate chemistry, one can predict with certainty that more impressive advances are on the horizon in this area.

V. Synthetic Applications

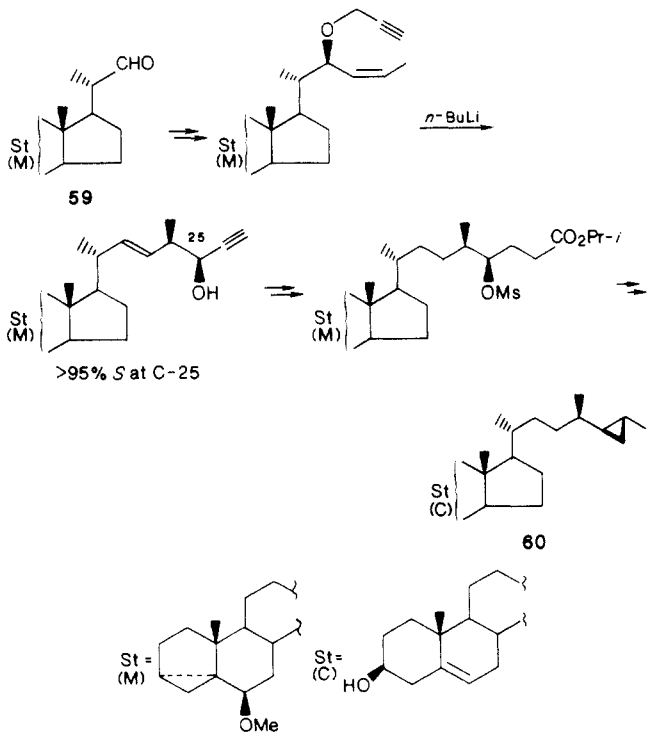
In the preceding sections the focus has been centered on the regio- and stereochemical features of the [2,3]-Wittig rearrangements themselves. This section will describe their applications in projected organic syntheses.

A. Steroid Side Chain Synthesis

In the past few years the concept of stereochemical transmission via [2,3]-Wittig rearrangement discussed



above has found highly successful applications in steroid side-chain synthesis which is the current subject of intense investigations.[68] One general and simple application is to employ the [2,3]-Wittig strategy for specifically transferring a configurationally defined chirality on the steroidal side chain to another center within the side-chain framework, analogous to simple acyclic counterparts described in section IVD. The [2,3]-Wittig variant of the propargyl ether system has been used in an elegant way by Ikekawa and his coworkers in the synthesis of petrosterol (**60**), a marine

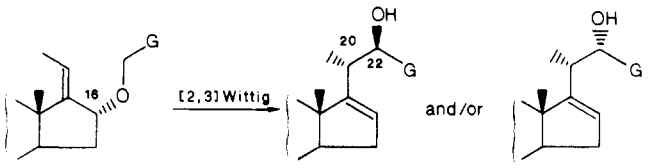


steroid, from C-22 aldehyde **59**.[69] Midland and Kwon have successfully utilized Still's variant in the synthesis of the (24*R*)-25,28-dihydroxy side chain **62** (and its 24-epimer)[70] and also of (25*R*)-26-hydroxycholesterol (**63**)[71] from 20-ketosteroid **61**: noticeable in these cases is the complete transfer of chirality coupled with surprisingly high *E* selectivity.

TABLE II. KH-Induced Rearrangements of 51 (X = H)

substrate, X = H(K)	base/ temp, °C	erythro:threo		% ee	config at C-2
51a	KH/20			84	*S*
51b		41:59	erythro	0	
			threo	74	*S*
51c				56	*S*
51a	KH/18-crown-6/-20			96	*R*
51b		46:54	erythro	86	*R*
			threo	84	*R*
51c				82	*R*

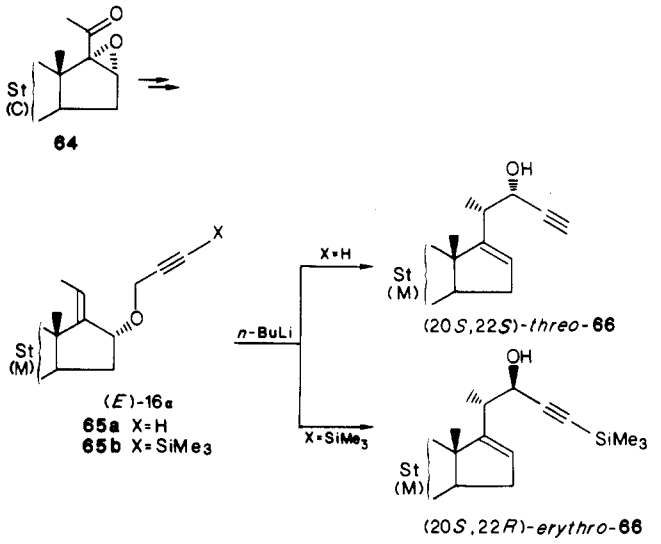
Alternatively and more importantly, the [2,3]-Wittig strategy can also be used for specifically transmitting an epimerically defined chirality at C-16 of the steroidal nucleus to the new chiral center(s) at C-20 and C-22 of the side chain as illustrated by eq 26. Its significant



(26)

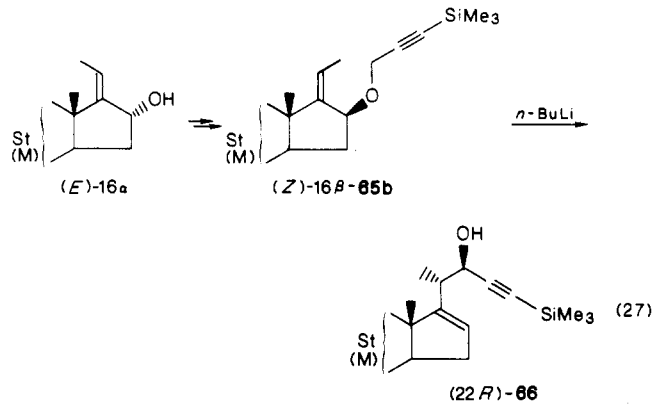
feature is that it allows the concurrent control of absolute and relative configurations at C-20 and C-22 through the proper combination of the *exo*-olefin geometry, the configuration (α or β) at C-16, and the key G group. Quite recently the reviewers have successfully demonstrated the utility of this approach in the fully stereocontrolled synthesis of either (22*S*)- or (22*R*)-hydroxy-23-acetylenic side chains from the single precursor (Scheme VI).[72] The most significant feature in this example is that the dianion rearrangement of **65a** affords the (20*S*,22*S*)-threo product as a single stereoisomer, whereas the introduction of the silyl group induced the reversal of diastereoselection to give the (20*S*,22*R*)-erythro product as a single stereoisomer; a mechanistic rationale has been offered for the unusual *E* → erythro selection of **65b**.[72] The substrate **65** is easily derived from the commercially available epoxypregnenolone **64**, and the products can undoubtedly serve as key intermediates for the synthesis of many important side-chain modified steroids;[68] e.g., (22*S*)- and (22*R*)-**66** can be converted to the insect hormone ec-

SCHEME VI

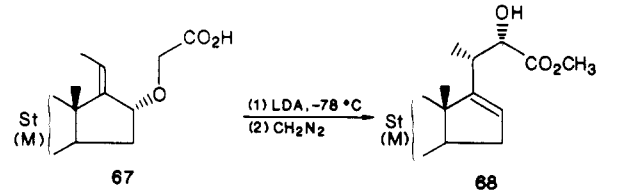


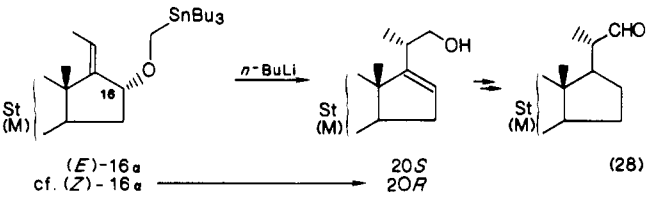
dysones[73] and the plant growth regulator brassinolides,[74] respectively.

More recently, a similar rearrangement has been shown to proceed even on the sterically congested β-face (eq 27), where the rearrangement exhibits the usual *Z* → erythro selection to afford (22*R*)-**66** as a single stereoisomer.[75]



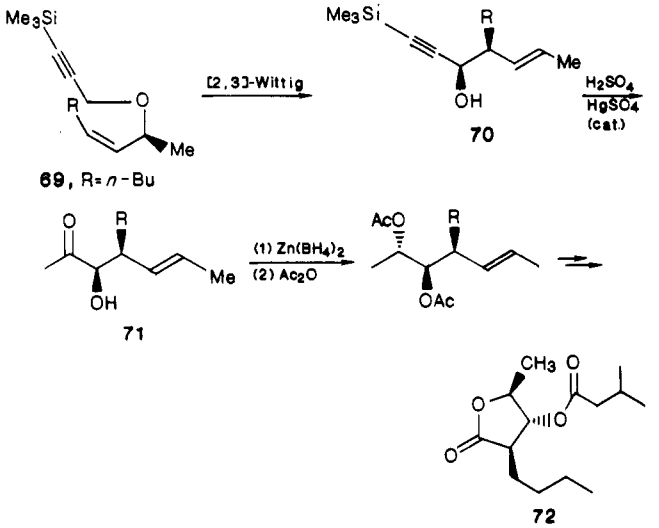
In studies not yet published, Koreeda's and reviewers' groups have independently found that the dianion rearrangement of **67** affords the (20*S*,22*S*)-threo product **68** as a single stereoisomer.[76] A Spanish group has reported a rather simple case where Still's variant is employed for transmitting the 16α-chirality to the chiral center at C-20 (eq 28).[77]





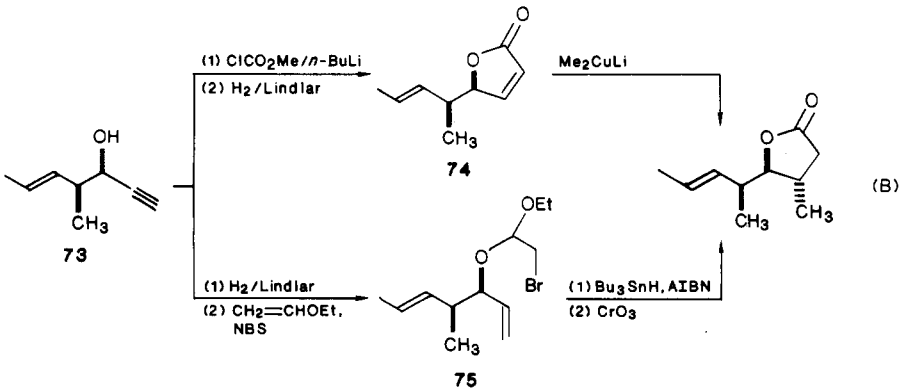
B. Stereocontrol over Three Contiguous Chiral Centers

In the preceding sections some of the [2,3]-Wittig variants have been shown to create vicinal chiral centers with an extremely high level of asymmetric induction. Since the resulting products possess a unique multifunctionality which permits further stereocontrolled manipulations, the [2,3]-Wittig process should constitute a versatile methodology for stereocontrol over three contiguous chiral centers. A typical example[78] is the asymmetric synthesis of (+)-blastmycinone (**72**), a

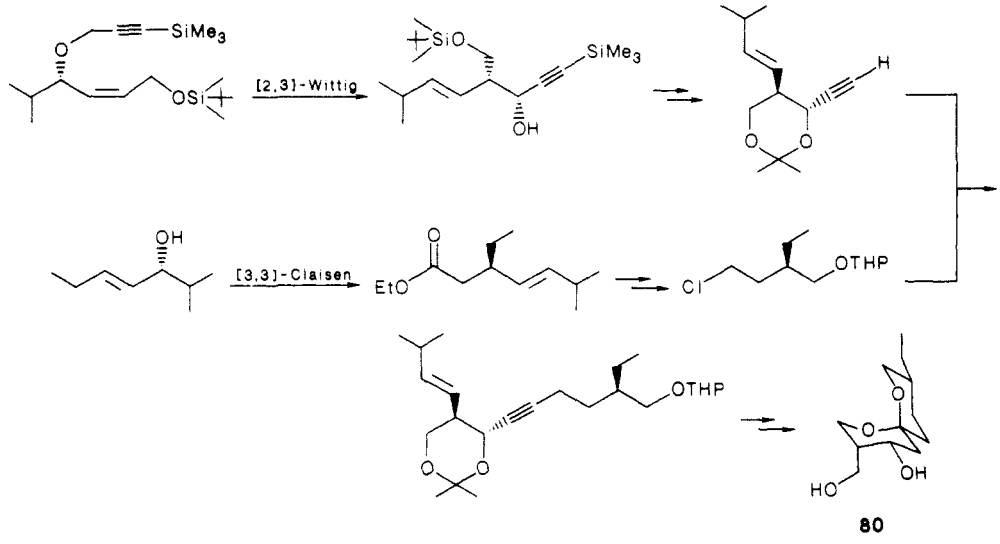


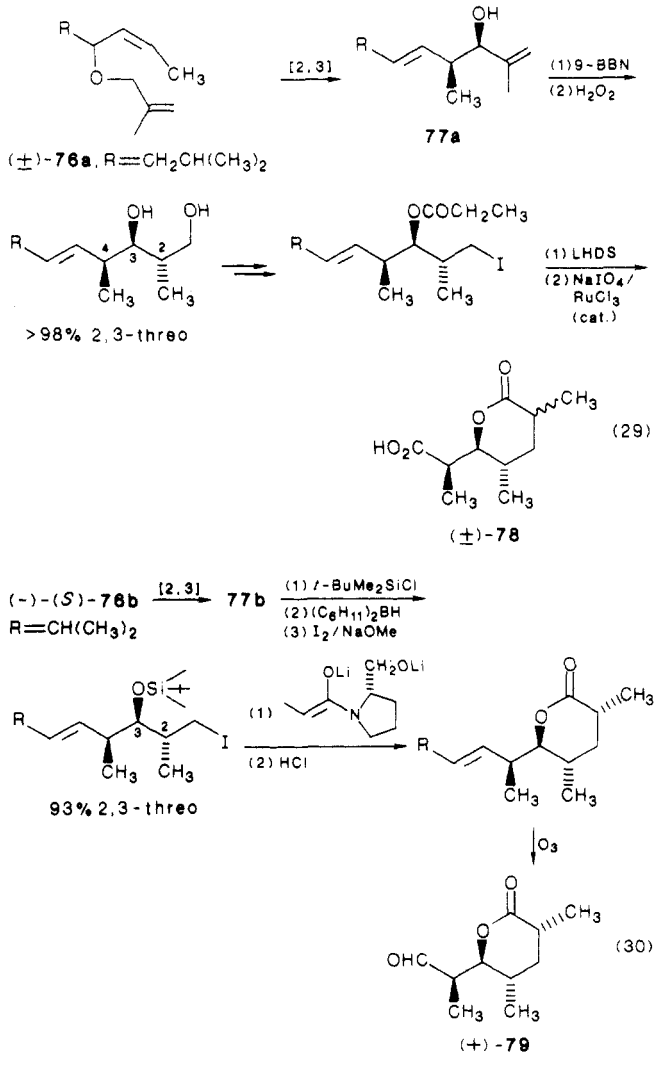
degradation product of the antibiotic antimycin A_3.[79] This synthesis features the sequential combination of the rearrangement of **69** with the zinc borohydride reduction[80] of the hydroxy ketone **71** derived from the [2,3]-Wittig product **70**.

In a continuation of these studies, the reviewers' group has also defined the utility of a similar [2,3]-

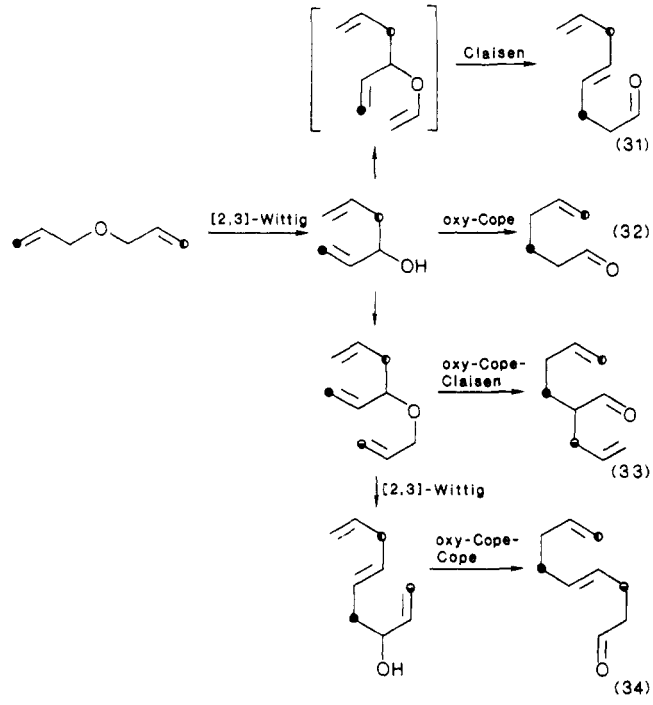


SCHEME VII





SCHEME VIII



Wittig product (**73**) by establishing a different type of three chiral centers;[81] the former route involves the Michael addition[82] to butenolide **74** as the stereo-directing process, whereas the latter employs as the key step the regio- and stereoselective radical cyclization[83] of acetal **75**.

Furthermore, the reviewers' and Midland's groups have independently demonstrated the use of the [2,3]-Wittig process of the methallyl ether system (**76**) in the synthesis of the Prelog–Djerassi lactonic acid (±)-**78** (eq 29)[81] and the aldehyde (+)-**79** (eq 30),[84] respectively. Both syntheses employ a stereoselective hydroboration[85] of the [2,3]-Wittig product (**77**) for introducing the third chiral center. Particularly noteworthy in the latter is that the relative and absolute configuration of two of the four chiral centers are controlled by the [2,3]-Wittig process and the remaining two centers are introduced by the hydroboration and an asymmetric alkylation of a prolinol-derived amide enolate.[86]

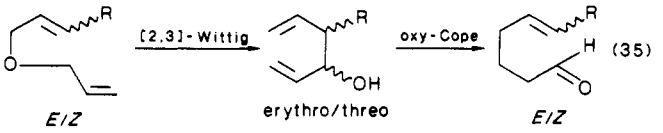
These examples convincingly demonstrate the potential utility of the [2,3]-Wittig rearrangement in the construction of complex molecules. In this connection, other Midland's work[87] is noteworthy on the synthesis of (-)-talanomycin A (**80**), a toxic metabolite[88] (Scheme VII). In this synthesis, both a [2,3]-Wittig process and a Johnson–Claisen modification are elegantly used in succession as key steps in controlling the overall stereochemistry.

C. Sigmatropic Sequences

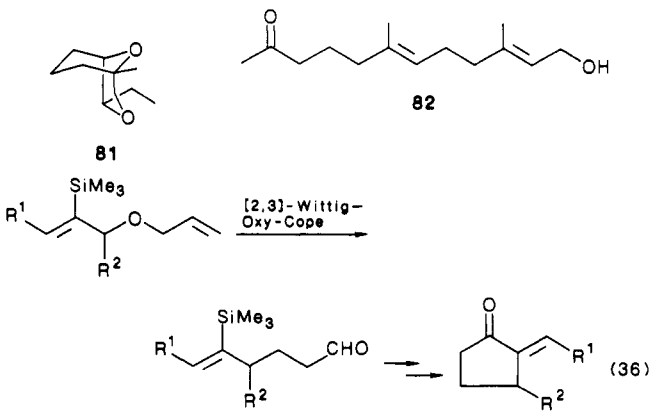
In the preceding sections the [2,3]-Wittig rearrangement of unsymmetrical bis(allylic) ethers has been shown to provide a regio- and stereoselective entry to 1,5-dien-3-ols. Since the [2,3]-Wittig products and their derivatives are well qualified as substrates for different sigmatropic rearrangements such as oxy-Cope and Claisen, the particular [2,3]-Wittig variant may trigger various types of sigmatropic sequences.[89] The reviewers have developed the four sequences illustrated in Scheme VIII, which provide unique and facile methods for the synthesis of various classes of unsaturated carbonyl compounds possessing interesting molecular frameworks.[90] Of particular significance is that the net effect of these sequences allows two or three allylic moieties initially linked by a readily formed ether bond(s) to be recombined by new C–C bond(s) in a regiospecific fashion.

1. Tandem [2,3]-Wittig–Oxy-Cope Rearrangement (cf. eq 32)

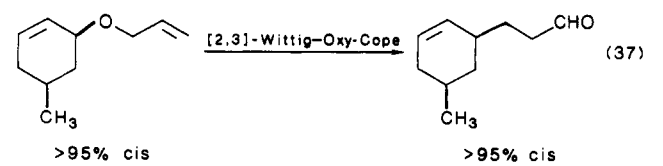
As exemplified by eq 35, this *tandem*[91] sequence provides a versatile synthetic route to δ,ε-unsaturated carbonyl compounds.[92] Of particular interest is that the *E*/*Z* stereochemistry of the oxy-Cope product is not



dependent on the erythro/threo ratio of the [2,3]-Wittig product but on the rearrangement procedures. Application of the anionic oxy-Cope[93] and siloxy-Cope[94] procedures provides a modest degree of *E* selection (67–79%), whereas thermolysis in decane (ca. 170 °C) exhibits an enhanced *E* selectivity (92–95%). Recently the utility of this sequence has been demonstrated in the synthesis of insect pheromone (±)-brevicomin (**81**) and the marine natural product oxocrinol (**82**),[95] and of functionalized vinylsilanes (eq 36).[96]



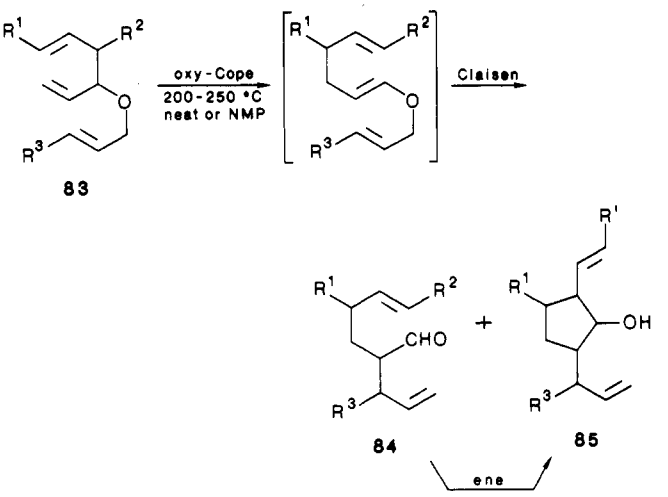
Furthermore, the [2,3]-Wittig–Oxy-Cope sequence has been shown to proceed with complete net retention of configuration (eq 37), while the [2,3]-Wittig product



is contaminated with the [1,2]-Wittig product as previously described.[19]

2. [2,3]-Wittig–Oxy-Cope–Claisen Sequence (cf. eq 33)

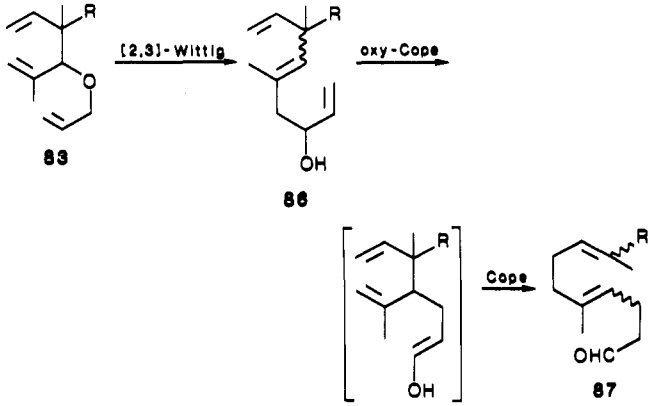
This triple sequence can be achieved by thermolysis of the allylic ether (**83**), prepared via etherification of the [2,3]-Wittig product, to afford 41–46% yields of dienal **84** as the major product.[92] In certain cases the



cyclic alcohol **85** is also formed which has been shown to arise from an intramolecular ene reaction[97] of **84**. The transformation offers the first example of a tandem sequence in which an oxy-Cope triggers a Claisen process.

3. [2,3]-Wittig–[2,3]-Wittig–Oxy-Cope–Cope Sequence (cf. eq 34)

The quadruple sequence can be achieved by another regiocontrolled [2,3]-Wittig rearrangement of the above-mentioned allyl ether **83** followed by thermolysis of the resulting trienol **86**.[92] For instance, **86a** was heated in NMP at 202 °C to give a geometric mixture (*E*/*Z* ratio of 2.0) of geranylacetaldehyde (**87a**) in 41% isolated yield. An increased yield (86%) is obtained when the silyl ether of **86a** is heated neat at 250 °C. A similar thermolysis of **86b**, derived from geraniol via the aforementioned sequence, affords a geometric mixture of farnesylacetaldehyde (**87b**) which is a promising

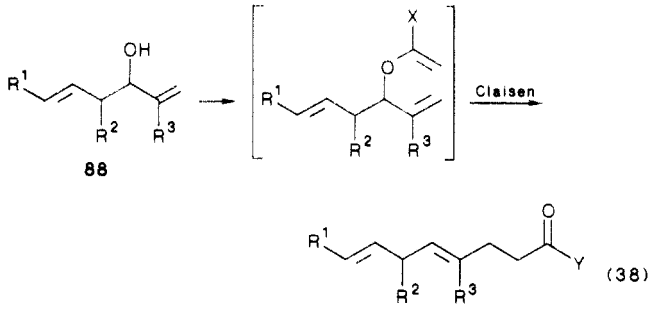


precursor of geranyl farnesylacetate (so-called gefarnate), a commercial antiulcer agent.[98] The sequence not

only includes the first example of a tandem sequence in which an oxy-Cope triggers a Cope process, but also provides a novel, versatile method for terpenoid synthesis.

4. Sequential [2,3]-Wittig–Claisen Rearrangement (cf. eq 31)

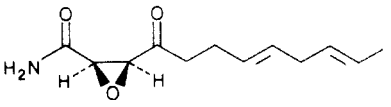
As depicted by eq 38, the [2,3]-Wittig products (88) are subjected to the Claisen modifications to provide



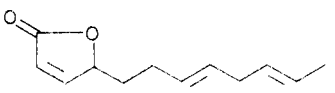
89, Y = H; 90, Y = OEt; 91, Y = OH

(a) $R^1 = CH_3$, $R^2, R^3 = H$; (b) $R^1 = n\text{-}C_5H_{11}$, $R^2, R^3 = H$

the functionalized 1,4-dienes (**89–91**) without occurrence of the oxy-Cope process.[99] For instance, the enol ether Claisen process[100] of **88a** affords the (*E,E*)-dienal **89a** and the Johnson–Claisen modification[101] of **88b** affords the (*E,E*)-dienoate **90b**, whereas the Ireland–Claisen modification[102] of the acetate of **88b** produces the (*E,E*)-dienoic acid **91b**. Thus, this sequence permits ready access to a wide variety of functionalized (*E,E*)-1,4-dienes[103] which are frequently found in natural products and synthetic intermediates thereof. Its synthetic potential has been illustrated[99] by formal total synthesis of antibiotic (±)-cerulenin (**92**)[104] in which (*E,E*)-nonadienal (**89a**) is elaborated, by four simple steps, to butenolide **93**, which is a well-known precursor of (±)-**92**.[105]



92



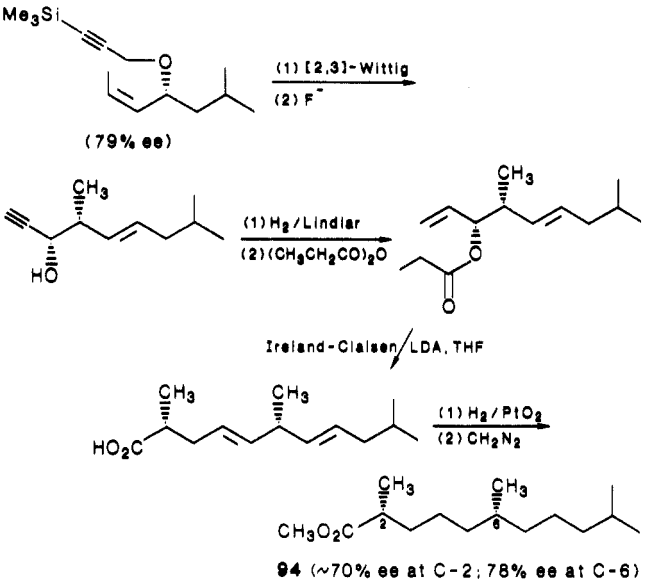
93

Finally, another important application should be noted which deals with the otherwise difficult 1,5-remote stereocontrol. Recently the reviewers have successfully applied the asymmetric [2,3]-Wittig–Claisen sequence in a chiral synthesis of the vitamin E side chain **94** (Scheme IX).[106] Its key feature is to sequentially combine the 1,3-chirality transfer via the [2,3]-Wittig process described in section IVD2 with the 1,4-chirality transfer via the Ireland–Claisen process[107] to establish the 1,5-stereo relationship in both a relative and absolute sense.

Abbreviations

AIBN	2,2′-azobis(isobutyronitrile)
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital

SCHEME IX



LDA	lithium diisopropylamide
LHDS	lithium (hexamethyldisilyl)amide
LUMO	lowest unoccupied molecular orbital
NBS	*N*-bromosuccinimide
NMP	*N*-methylpyrrolidone
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine

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