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Introduction 3

I. REACTIONS AND STRATEGIES
A. Additions to carbon–carbon double bonds
1. With internal asymmetric induction 4
2. With relative asymmetric induction 8
B. Additions to carbonyl compounds
1. With relative asymmetric induction 15
2. With internal symmetric induction 22
C. Sigmatropic rearrangements
1. Claisen and Cope rearrangements 28
2. [2,3]-Sigmatropic rearrangements 39

II. SYNTHETIC TARGETS
A. Controlling C-15 in the prostaglandins 41
B. Ionophore antibiotics
1. Nonactic acid 46
2. Lasalocid A 49
3. Monensin 51
C. Macrocyclic natural products
1. The Prelog–Djerassi lactonic acid 54
2. Macrolide antibiotics 57
3. Maytansine 59
D. Extracyclic chiral centers in terpene synthesis 61
E. Alkaloids
1. Quinine 63
2. Emetine 66
3. Phthalideisoquinoline alkaloids 66
F. Multistriatin 67

References 68

STEREOCONTROL IN THE SYNTHESIS OF ACYCLIC SYSTEMS: APPLICATIONS TO NATURAL PRODUCT SYNTHESIS

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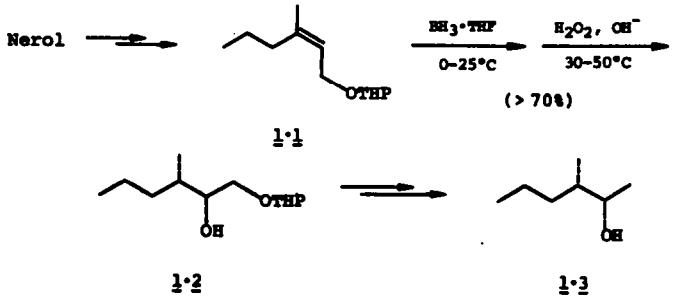
INTRODUCTION

Although organic chemists have been fascinated by the three-dimensionality of their science for more than a century, it has been during recent decades that the challenge of stereochemical control has come to the forefront of synthesis. In some areas, the state of this art has become spectacularly sophisticated, notably in the construction of rigid or conformationally well understood systems. Far less evolved is methodology for the stereocontrolled elaboration of acyclic molecules; that is, for the introduction of chiral centers which are not contained within the same ring system. This area is becoming increasingly important, however, as organic chemists focus their attention on the synthesis of macrolide and ionophore antibiotics.

This report examines the methods currently available for controlling the stereochemistry of acyclic systems, with an emphasis on their applications in natural product synthesis.[1,2] The first part of the report presents a number of reactions and strategies for effecting acyclic stereocontrol; the second part outlines syntheses of targets of major interest in which such control has been required. In the first part, strategies which rely upon the coupling of optically active fragments or upon the arrangement of chiral centres on a cyclic framework prior to ring cleavage are not specifically covered, since in conception they rely on prior art. In the second part, such strategies are discussed in connection with specific synthetic targets.

At the outset, we can identify two fundamentally different types of stereochemical relationships which may be established during the course of a reaction. The chiral centers generated in a reaction can bear a specific relationship to preexisting chiral centers in the molecule, and/or they can bear a specific relationship only among themselves. Stereocontrol in the former sense is referred to as relative asymmetric induction, and we propose that stereocontrol in the latter sense be referred to as internal asymmetric induction. While Schlosser[3] has defined α,β-diastereogenic reaction types and their α,α'-diastereogenic counterparts for the same purpose, we feel that the terminology we suggest is more general and less cumbersome. In each case we are referring to the establishment of *intra*molecular relationships; the establishment of intermolecular relationships falls under the aegis of absolute asymmetric induction.

The anti-Markovnikov hydration of a double bond by hydroboration-oxidation, as in Mori's synthesis of one of the components (**1** · **3**) of the aggregation pheromone of *S. multistriatus*[4] (Scheme 1), is an example of a reaction which proceeds with internal asymmetric induction. The *Z*-geometry of the olefin, the

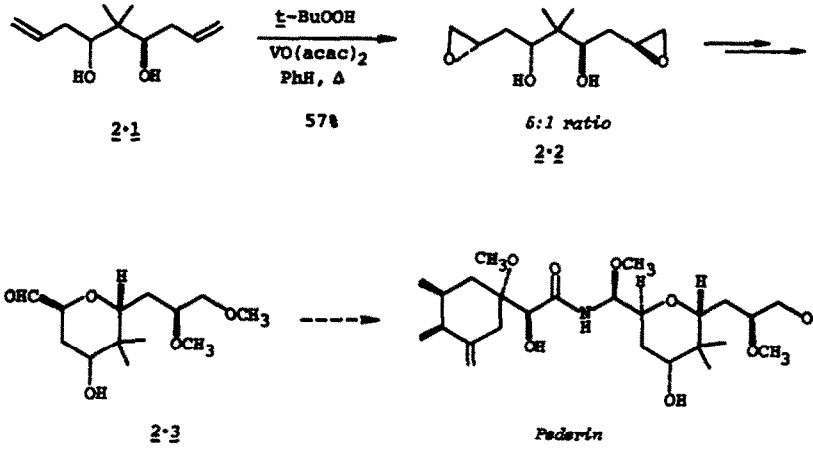


1·**1** **1**·**2** **1**·**3**

Scheme 1.

syn-addition specificity of the hydroboration process, and the retention of configuration in the oxidation step combine to produce the racemic, *threo* alcohol **1 · 2** stereospecifically.

The hydroxyl-directed epoxidation of the diol **2 · 1** proceeds with relative asymmetric induction, on the other hand, as depicted in an approach to the beetle defensive substance pederin[5] (Scheme 2). In this instance, the association of each OH group with the epoxidizing species allows the chirality of the carbinol carbon to determine which face of the homoallylic double bond will be attacked, resulting in selective establishment of the *erythro* relationship at each end.



Scheme 2.

Clearly, for the synthesis of stereochemically complex substances, reactions of this latter class are obligatory, unless one plans to couple optically active fragments. Most of the effort in acylic stereocontrol, therefore, has been directed toward effecting relative asymmetric induction.

PART I. REACTIONS AND STRATEGIES

The most easily established relationships are those between adjacent carbon atoms; i.e. 1,2-relationships. Not only are these readily produced by stereospecific addition to a carbon–carbon double bond (as in the example of Scheme 1), but relative asymmetric induction is more likely to be exerted the closer the chiral centers are to each other. Reactions which establish 1,3- (as in the example of Scheme 2), 1,4-, and even 1,5-relationships are rarer and correspondingly more valuable.

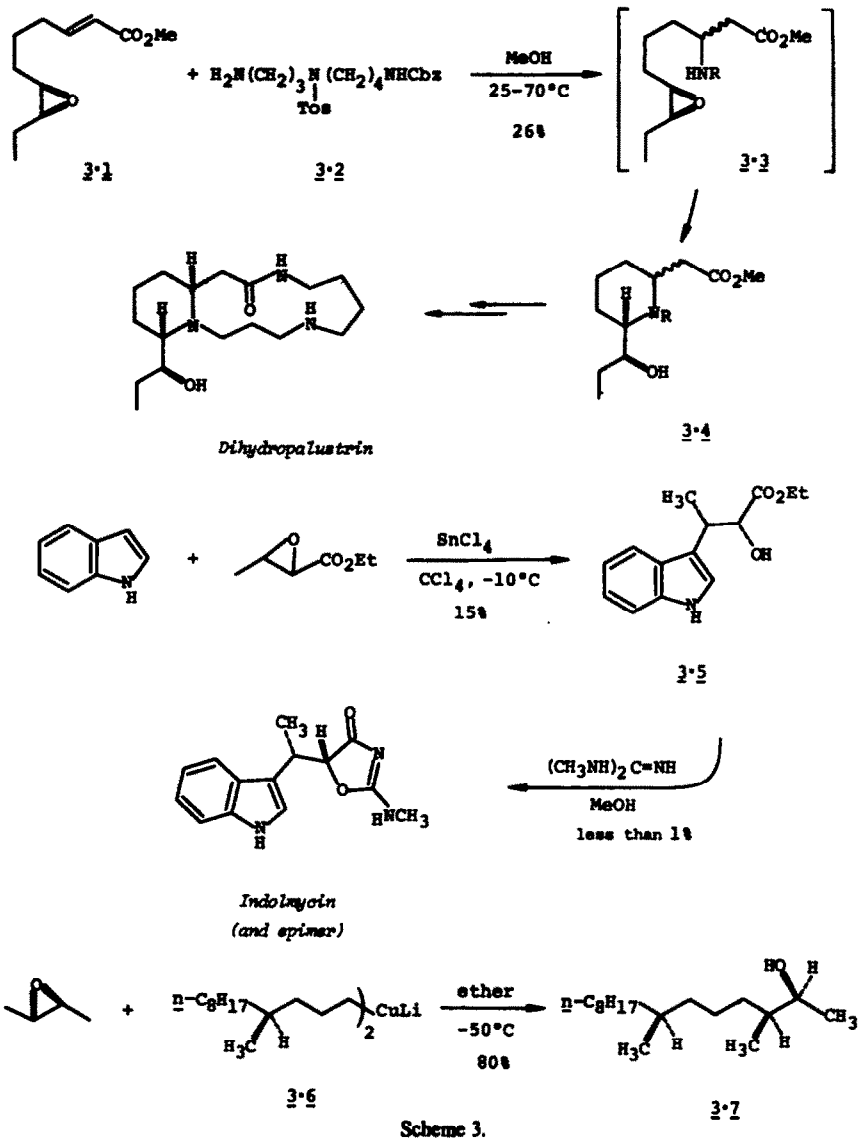
(A) *Additions to carbon–carbon double bonds*

1. *With internal asymmetric induction.* Any sequence in which a double bond undergoes stereospecific addition can be used to generate chiral centers with a defined 1,2-relationship. Moreover, this strategy is versatile in the sense that either diastereomeric product is potentially available, depending on the geometry of the starting olefin. For instance, the *erythro* diastereomer of **1 · 3** was also prepared stereospecifically, using geraniol as the starting material.[4]

The epoxidation of an olefin and subsequent ring opening, as illustrated by the examples of Scheme 3, constitute another specific application of this strategy. In the synthesis of dihydropalustrin,[6] the *threo* relationship of the adjacent chiral centers results from displacement on a *cis*-epoxide. Because this opening occurs intramolecularly, via the adduct **3 · 3**, it is regiospecific. However, not unexpectedly there is no relative asymmetric induction in the Michael addition, and intermediate **3 · 4** is formed as a mixture of epimers. A similar epoxide opening reaction has found use in the synthesis of *Cinchona* alkaloids, as will be discussed in Part II.

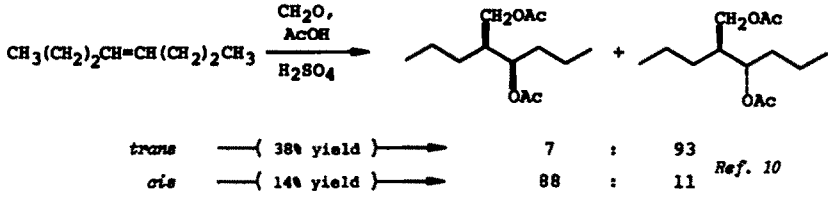
The fact that epoxides undergo stereospecific opening with carbon as well as with heteroatom nucleophiles is particularly useful. In the synthesis of indolmycin,[7] the desired stereochemistry of indolmycinic ester **3 · 5** is introduced specifically in this manner. Unfortunately, indolmycin is epimerized (to a 1:1 mixture) under the conditions of its formation from **3 · 5**.

Mori has prepared all four 2R*3R* isomers (e.g. **3 · 7**) of the Sawfly pheromone by coupling the enantiomers of *trans*-2,3-epoxybutane and lithium di(4-methyldodecyl)cuprate.[8] Other examples of



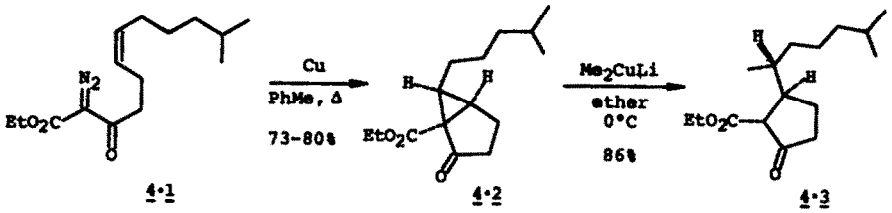
Scheme 3.

cuprate openings of epoxides are discussed in Part II, in connection with synthetic approaches to maytansine and multistriatin.



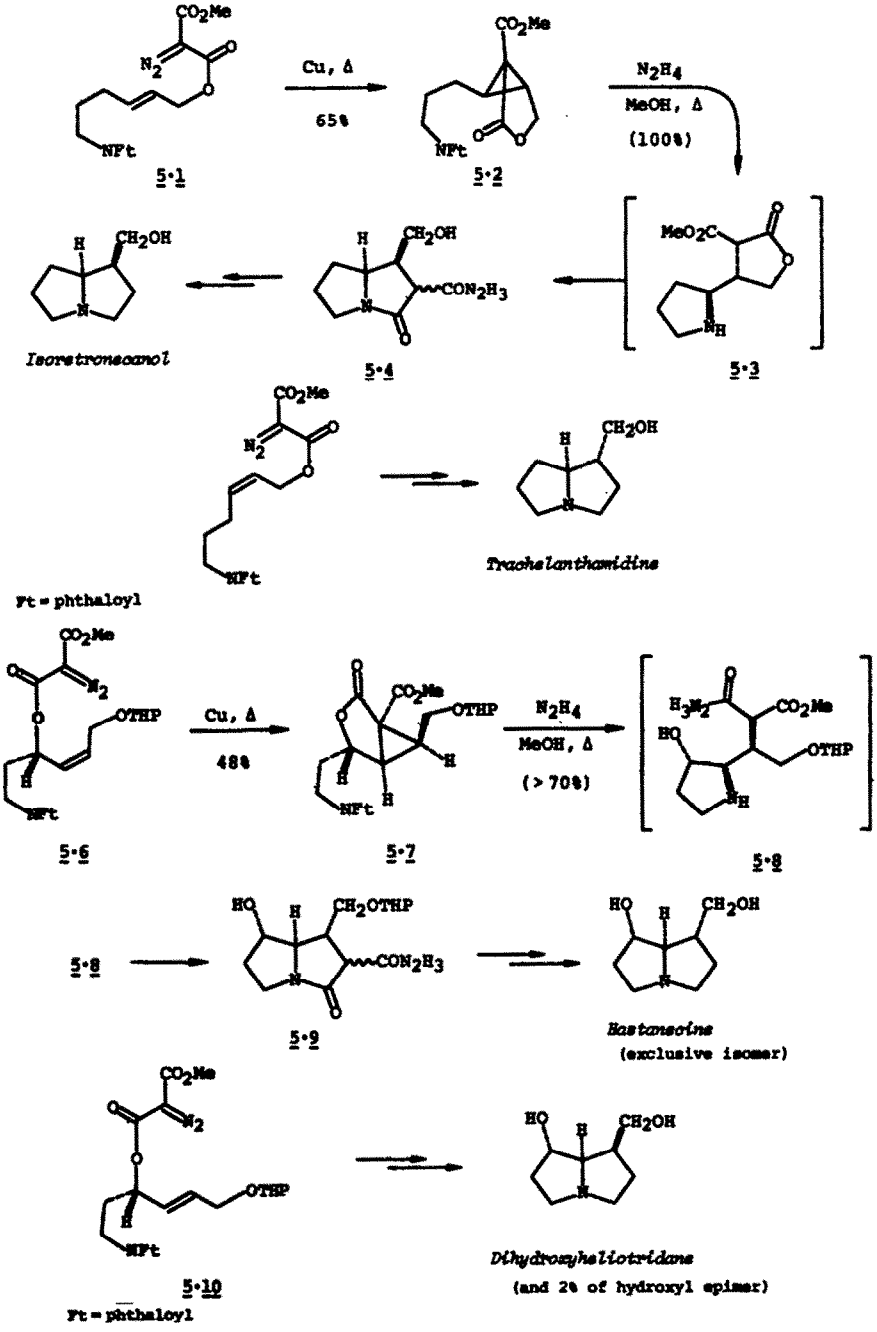
The overall *anti* addition of a C atom and an OH group to a double bond can also be accomplished by the Prins reaction,[9,10] although the generally poor yields and harsh conditions required have restricted its use in natural product synthesis.[11]

A more efficient process for the *anti* addition of a C atom and a heteroatom to a double bond has found application in a number of natural product syntheses. This sequence involves the cyclopropanation of an olefin with a diazomalonate or α-diazo-β-ketoester, and subsequent ring opening by nucleophilic displacement.[12] Examples are found in Trost's model system for the steroid side chain (Scheme 4),[13] in Danishefsky's syntheses of the pyrrolizidine bases (Scheme 5),[14,15] and in the prostaglandin area, as discussed in Part II.

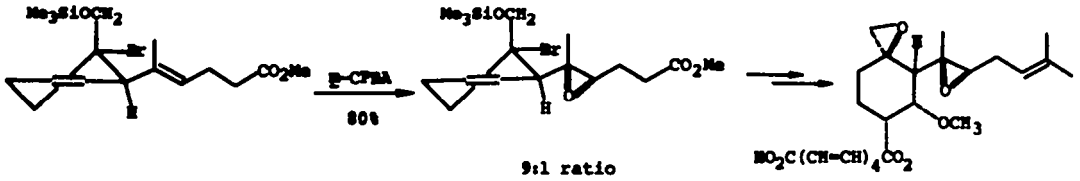


Scheme 4.

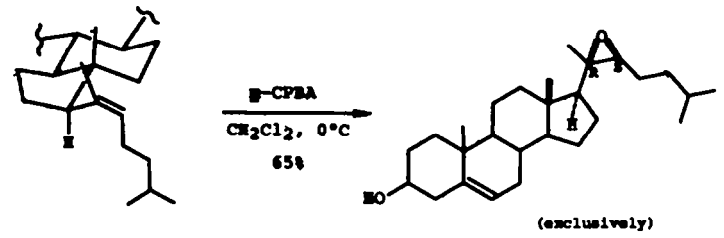
The dimethylcuprate reaction of compound 4 · 2 proceeds regiospecifically, because only the cyclopropane bond which is exocyclic to the 5-membered ring can overlap with both of the CO groups. Similar regio- and stereospecificity are observed in the prostaglandin examples of Part II and in the syntheses of isoretronecanol and trachelanthamidine[14] (Scheme 5).



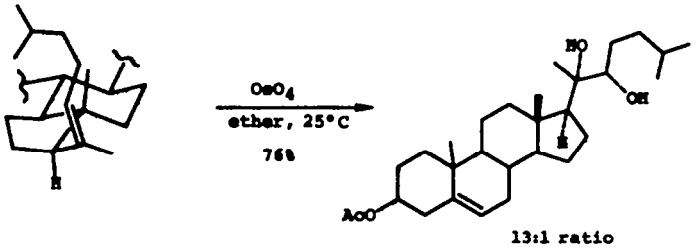
Scheme 5.



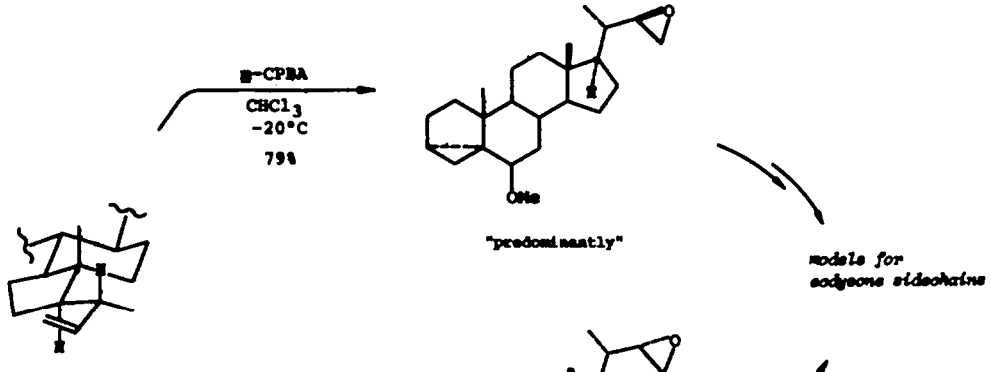
Pumaglillin *Ref. 19*



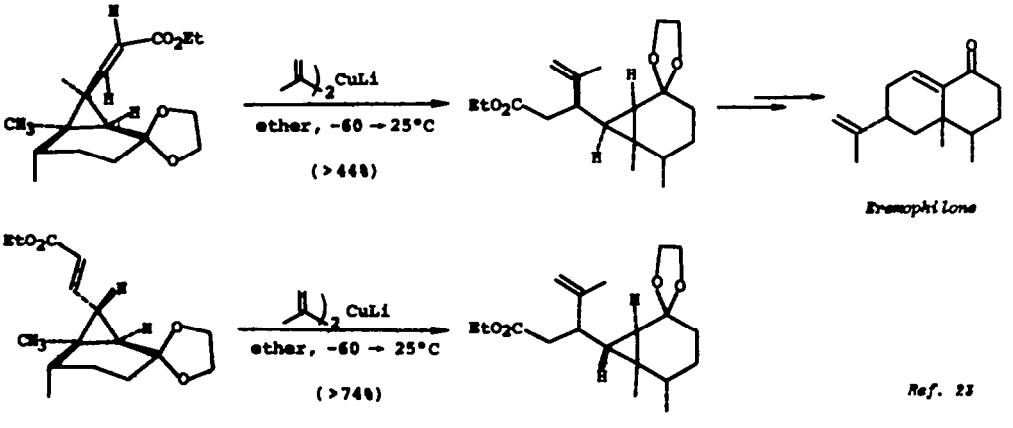
Ref. 20



Ref. 20



Ref. 21, 22



Ref. 23

Ref. 23

Scheme 6.

The syntheses of hastanecine and dihydroxyheliotridane are noteworthy in two respects.[15] The intramolecular nature of the carbene additions provides for very efficient relative asymmetric induction from the allylic chiral centers of **5 · 6** and **5 · 10**. Additionally, the regiospecificity in the cyclopropane opening reaction is opposite that observed in the other cases above. The constraint of intramolecular "spiro-mode" attack necessitates cleavage of the bond common to both rings. This cannot occur in the bicyclic system, as pointed out above, and the reaction of **5 · 7** and its stereoisomer proceeds with hydrazinolysis of the lactone prior to the intramolecular displacement reaction.

2. *With relative asymmetric induction.* As pointed out in the Introduction and suggested by the last examples of Scheme 5, stereospecific addition to a double bond is most useful when it can be accomplished with relative asymmetric induction from preexisting chiral centers. In many instances, the conformational and steric constraints on an olefinic substrate are sufficiently strong that one diastereotopic face of the double bond is significantly more accessible than the other one. Several examples of this phenomenon are depicted in Scheme 6. In most instances such as these, the double bond is directly attached to a ring system which provides a strongly asymmetric steric environment. An extended conformation about the ring-olefin bond and approach of the reagent from the least congested direction appear to explain the observed stereospecificity adequately in most cases.

Noteworthy for their absence from Scheme 6 are catalytic hydrogenation reactions, ordinarily known for their stereoselective *cis* hydrogen delivery and sensitivity to steric influences. Examples of hydrogenations of substrates similar to those of Scheme 6 are found mainly in the steroid area,[16] in the reduction of 20(22)-unsaturated derivatives, and the reported results are inconsistent.[17,18] Moreover, some of the earlier claims of stereospecificity appear to be incorrect.

Recently, Kishi has described some remarkable instances of asymmetric induction in the hydroboration of acyclic olefins, as will be discussed in Part II in connection with the synthesis of monensin.

In purely acyclic systems, examples and studies of relative asymmetric induction in olefin additions usually involve cases in which some kind of intramolecular assistance is provided. (This is in contrast to nucleophilic addition reactions of carbonyl compounds, which will be addressed below.) When the reagent is associated either covalently or non-covalently with functional groups on the acyclic chain, nearby chiral centers can exert a high degree of stereocontrol in the functionalization of acyclic double bonds.

As was recognized a number of years ago, hydrogen bonding of the hydroxyl group with an epoxidizing species greatly assists in the epoxidation of allylic alcohols.[24,25] The stereochemistry of the reaction of acyclic allylic alcohols[26] was first studied in a thorough manner by Pierre and Chautemps,[27] using *p*-nitroperoxybenzoic acid, and later by Sharpless and Nozaki[28] using peracids and the more selective transition metal catalyzed *t*-butylhydroperoxide systems. Their results, reproduced in Table 1, indicate that in a number of instances very high 1,2-asymmetric induction can be obtained.

By analysis of the structural dependence of the stereoselectivity, Chautemps and Pierre[27b] concluded that conformations such as those illustrated below are responsible for the observed specificity. Based on their results,[27] and those of Whitham,[25] with the epoxidation of 2-methylenecyclohexanol and 2-cyclohexenol derivatives, Chautemps and Pierre[27b] deduced that epoxidation takes place preferentially via conformations II and III. The less encumbered direction of approach is that depicted in II, implying that the R*R* isomers should be favored in the absence of other steric influences. In fact, the R*R*

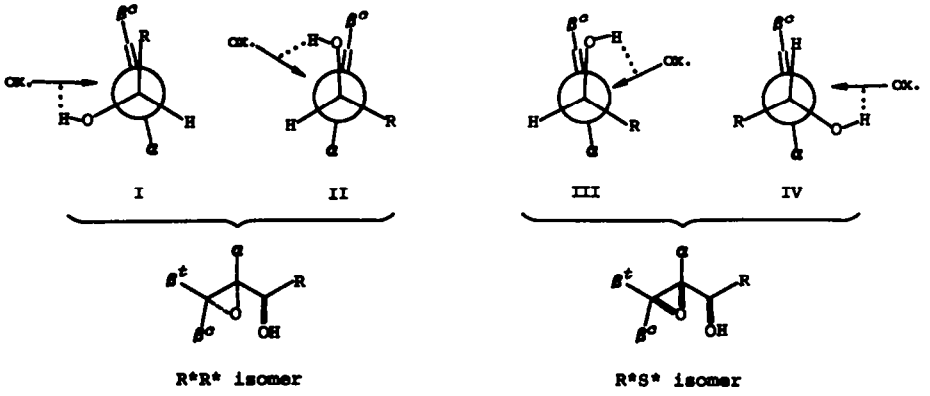
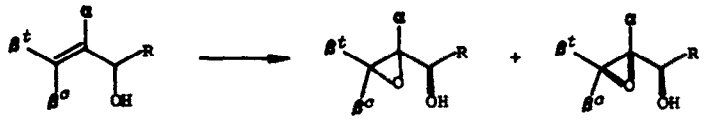


Table 1. Epoxidation of allylic alcohols[a]



R*R* (*erythro*) R*S* (*threo*)

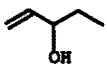
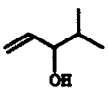
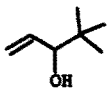
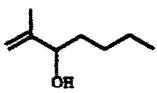
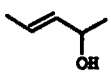
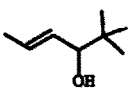
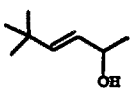
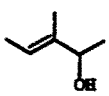
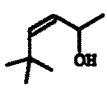
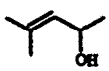
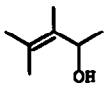
Entry	Substrate	Ratio R*R*/R*S*			
		m-CPBA CH_2Cl_2, 0°C	p-NO_2C$_6$H$_4$CO$_3$H, ether, 0°C	t-BuOOH, VO(acac)$_2$, CH_2Cl_2, 0°C	t-BuOOH, Mo^{+6} CH_2Cl_2, 25°C
1		40:60	36:64[b] 37:63[c]	80:20	56:44
2		39:61		80:20	58:42
3		42:58		85:15	65:35
4			54:46[c]		
5		55:45	68:32[b] 62:38[c]	95:5	84:16
6		59:41		98:2	84:16
7		36:64 31:69[f] (25°C)	10:90[c,d,e]	71:29 60:40[f] (PhMe, 25°C)	38:62 39:61[f] (PhH, 60°C)
8		40:60[f]	> 98:2[c,e]	81:19[f] (PhMe, 0°C)	45:55[f] (PhH, 60°C)
9			40:60[c]		
10			55:45[c]		
11		5:95	2:98[c]	29:71	16:84
12			5:95[c]		
13		5:95	4:96[b] 4:96[c]	14:86	5:95

Table 1. (*Contd*)

Entry	Substrate	Ratio R*R*/R*S* m-CPBA CH_2Cl_2, 0°C	p-NO_2PhCO$_3$H, ether, 0°C	t-BuOOH, VO(acac)$_2$, CH_2Cl_2, 0°C	t-BuOOH, Mo^{+6} CH_2Cl_2, 25°C
14			10:90[c]		

[a] Ref. 28b, unless otherwise indicated [b] Ref. 28a [c] Ref. 27

[d] The stereochemical assignment originally reported by Pierre, Chautemps, and Arnaud[27a] and used by Sharpless, et al.[28a] was later corrected.[27b] Note also recent corrections[28b,c] in much of this work.

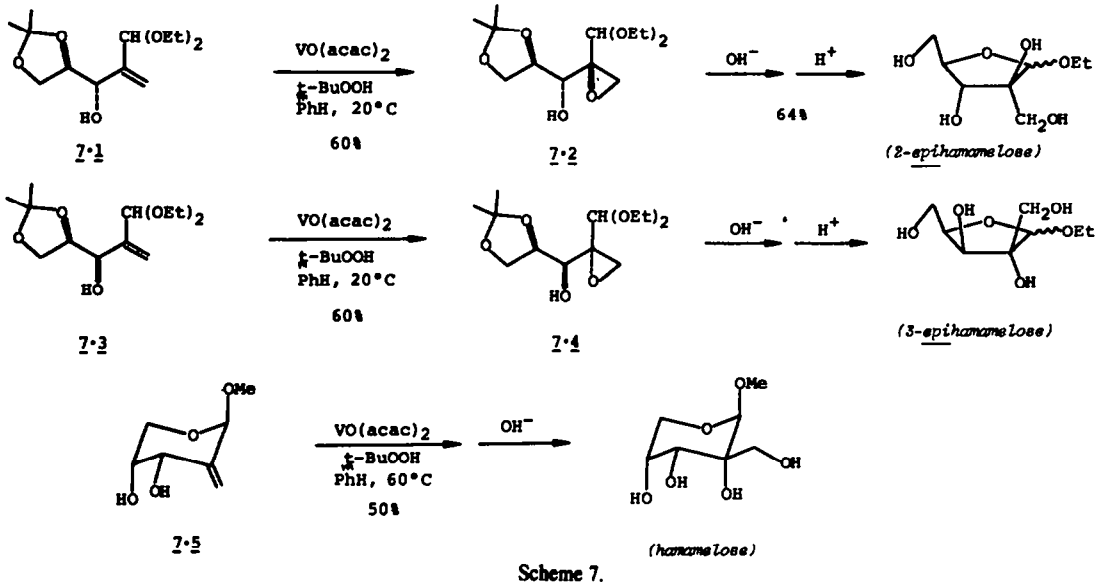
[e] Recent corrections by Sharpless[28b] and Mihelich[28c] call this result into question.

[f] Ref. 28c

By analysis of the structural dependence of the stereoselectivity, Chautemps and Pierre[27b] concluded that conformations such as those illustrated below are responsible for the observed specificity. Based on their results,[27] and those of Whitham,[25] with the epoxidation of 2-methylenecyclohexanol and 2-cyclohexenol derivatives, Chautemps and Pierre[27b] deduced that epoxidation takes place preferentially via conformations II and III. The less encumbered direction of approach is that depicted in II, implying that the R*R* isomers

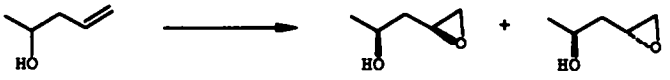
isomers are the major products only when there is a substituent in the α-position, with the exception of Entry 4. The majority of the observed results can be explained, however, by considering conformation IV, which is favored when there is no α-substituent and strongly favored in the presence of a *cis* β-substituent.[27a] In connection with a recent correction[28b] of their earlier published results,[28a] Sharpless has reached substantially the same conclusion, favoring C=C–C–O dihedral angles of ~50° for the vanadium-catalyzed epoxidation and ~120° for the peracid epoxidations. For a series of cyclic allylic alcohols, S. Teranishi *et al.* suggest that these angles are ~90° and ~150° respectively.[28d]

The stereocontrolled epoxidation of acyclic allylic alcohols has been employed in an approach to maytansine (Part II), and has also been applied to the synthesis of isomers of the branched chain sugar hamamelose,[29,30] as illustrated in Scheme 7. In the latter work, each diastereomer of the intermediate allylic alcohol afforded a single epoxy alcohol with *t*-BuOOH/VO(acac)$_2$. Unfortunately, neither of these isomers led to the natural stereoisomer, which was finally obtained by epoxidation of the pyranoside **7 · 5**, followed by alkaline hydrolysis.[31]



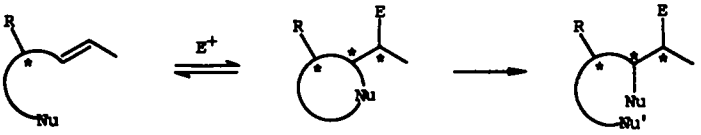
Scheme 7.

Analogous, systematic studies of the epoxidation of homoallylic alcohols have not been reported, although some specific cases, such as that depicted in Scheme 2,[5] and one employed in Kishi's monensin synthesis (Part II), are quite selective. In contrast, the simplest homoallylic alcohol, 4-penten-2-ol, exhibits little 1,3-asymmetric induction with a variety of reagents, as indicated below.[32]

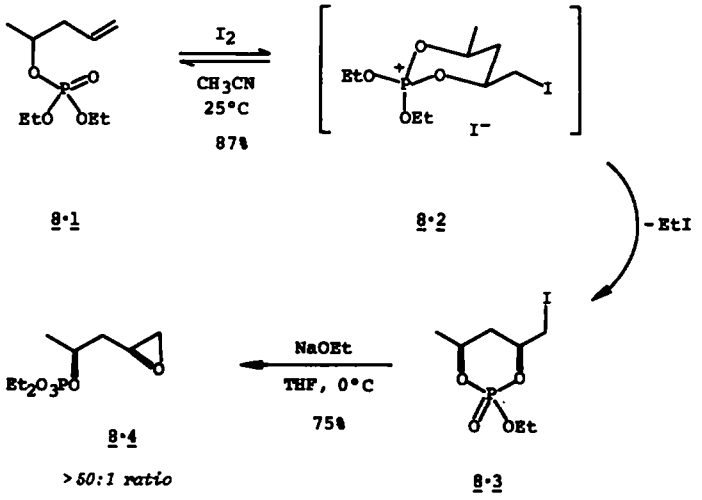


m-CPBA, $CHCl_3$, 25°C	55	:	45
t-BuOOH, $VO(acac)_2$, benzene, 25°C	66	:	33
t-BuOOH, $Mo(CO)_6$, benzene, Δ	45	:	55

We reasoned that if the carbinol moiety could be made to participate in the functionalization of the double bond in a more direct manner, improved 1,3-asymmetric induction might be realized in a predictable fashion. In approaching this problem, we sought to take advantage of the high stereochemical preferences of 5- and 6-membered rings, as well as the tendency for electrophilic attack on an olefin to lead to cyclization by appropriately positioned nucleophiles.[33] As illustrated schematically below, this "oxidative-cyclization" process we envisaged would be used to control the relative stereochemistry of the chiral centers, either kinetically or thermodynamically. Subsequent elaboration would then restore the acyclic system, in a sequence which, overall, would accomplish the asymmetric functionalization of the double bond.



To apply this strategy to homoallylic alcohols, we required a functional group which was symmetric (so as to avoid difficulties arising from diastereomeric starting materials), which extended the reach of the nucleophilic OH group (so that it could participate in a cyclization reaction), and which allowed the stereochemical information to be transmitted effectively to the olefinic center.[34] We chose the phosphate moiety for this purpose, and were delighted to find that diethyl 4-penten-2-yl phosphate undergoes an intramolecular Arbuzov-type reaction in the presence of iodine, giving the cyclic phosphate **8 · 3** in 87% yield[32] (Scheme 8). Ring opening of the phosphate and ring closure to the epoxide **8 · 4** occur upon treatment with sodium ethoxide, and provide material which is more than 98% pure stereochemically. This extremely high 1,3-asymmetric induction results from intermediacy of cyclic tetraalkoxyphosphonium ion, **8 · 2**, and avoidance of the 1,3-diaxial interactions which would necessarily be present in its diastereomer, and reflects thermodynamic control over the cyclization process.



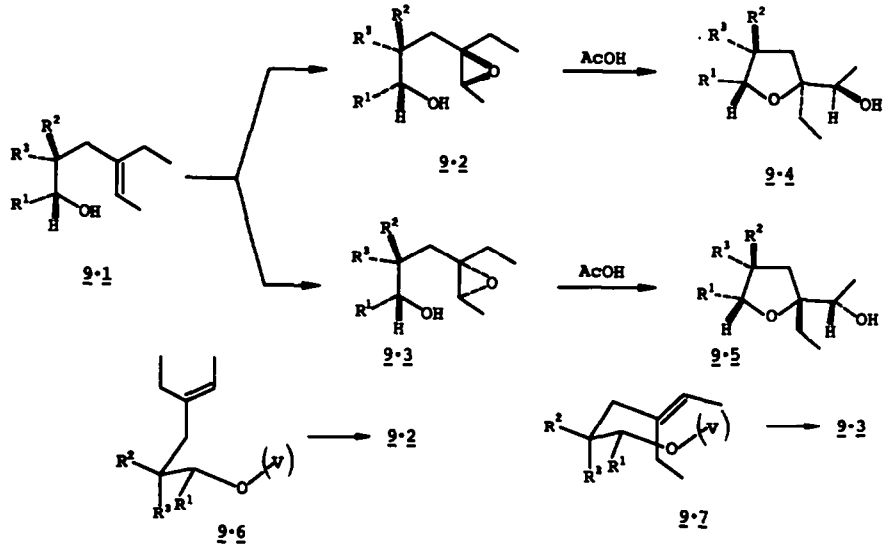
Scheme 8.

As Table 2 indicates, this strategy for epoxidation of homoallylic alcohols is general for a variety of derivatives.[32] Furthermore, it is specific for 1,3- as opposed to 1,2-asymmetric induction, as illustrated by the results observed for the *erythro* and *threo* diastereomers of diethyl 3-methyl-4-penten-2-yl phosphate (Entries 2 and 3, respectively). In addition, the cyclic iodophosphates and the epoxyphosphates may be reduced directly to the *erythro* diols with lithium aluminum hydride.[35] The application of this phosphate-directed functionalization procedure in a synthesis of nonactic acid is outlined in Part II.

1,4-Asymmetric induction in the epoxidation of bishomoallylic alcohols has been observed by Kishi,[36] using the highly selective *t*-BuOOH/VO(acac)$_2$ reagent (Scheme 9 and Table 3). The stereoselectivity of the epoxidation process was ascertained after acid-catalyzed cyclization of the epoxy alcohols to the tetrahydrofuran derivatives **9 · 4** and **9 · 5**. Surprisingly high selectivity is obtained, and again, it is the carbinol center (1,4-) rather than the closer tertiary carbon (1,3-) which controls the stereochemistry (compare Entries 3 and 4). The preference for **9 · 2** over **9 · 3** is explained by reference to diastereomeric transition state conformations **9 · 6** and **9 · 7**,[36] with the suggestion that the steric interaction of R^3 and the Et group destabilizes the latter. It is difficult to see, however, why there isn't a similar

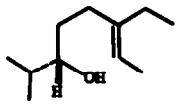
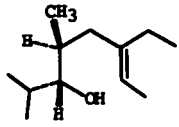
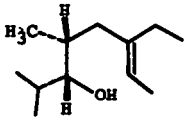
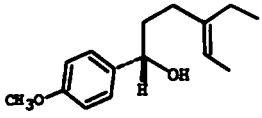
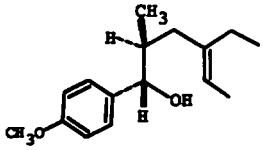
Table 2. Epoxidation of homoallylic alcohols via iodolactonization

Entry	Substrate	Products	Overall Yield (%)
1	R = Me, n-Pr	>98 : 2	64-65
2		95 : 5	58
3		80 : 20	62
4		95 : 5	23



Scheme 9.

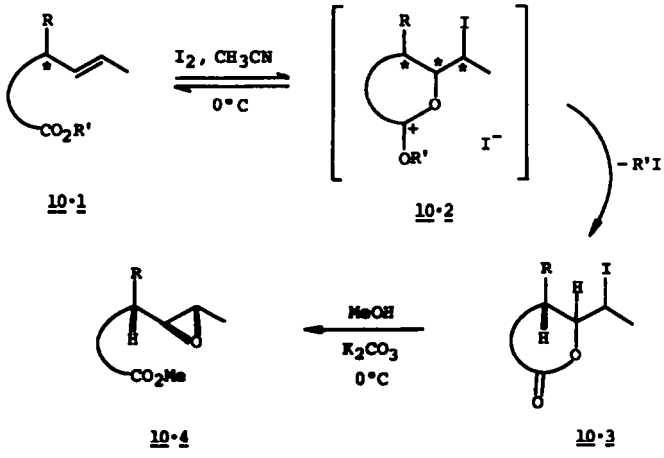
Table 3. Epoxidation-cyclization of bishomoallylic alcohols

Entry	Substrate	Ratio, 2·4/2·5[a]
1		1:1[b]
2		9:1
3		6:1
4		> 20:1
5		8:1
6		8:1

[a]Conditions: (1) *t*-BuOOH,VO(acac)$_2$, benzene, 25°C; (2) AcOH; unless otherwise indicated.
[b]*m*-CPBA, $CHCl_3$, 25°C.

interaction with R^2 in conformation **9 · 6**, or why 1,4- and not 1,3-asymmetric induction is observed for Entries 3 and 4. While a definitive evaluation of possible transition state conformations must await a more comprehensive study, the high 1,4-asymmetric inductions observed are impressive, as are the syntheses of the ionophore antibiotics which incorporate this reaction (see Part II).

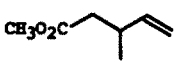
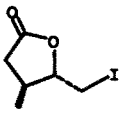
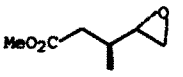
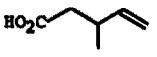
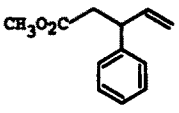
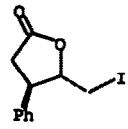
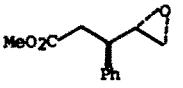
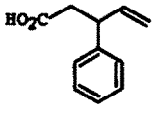
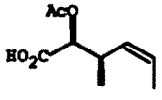
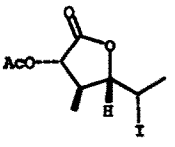
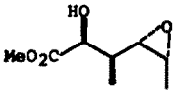
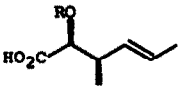
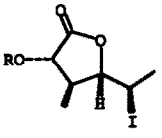
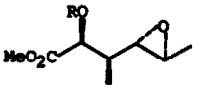
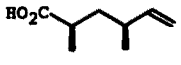
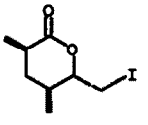
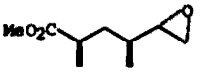
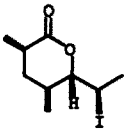
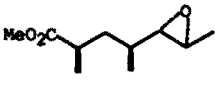
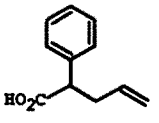
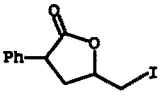
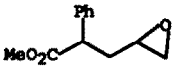
A carboxyl group can also be used to direct the epoxidation of an olefin by an "oxidative cyclization" process[37] (Scheme 10). With the proper choice of conditions (iodine in acetonitrile with either the carboxylic acid or the ester), the cyclization step is reversible (via **10 · 2**), and the thermodynamically



Scheme 10.

favored iodolactone can be obtained very selectively. Alkaline methanolysis opens the ring, providing the epoxy ester **10** · **4** in an overall sequence which proceeds with very high asymmetric induction (1,2- in these cases), as illustrated in Table 4.[37]

Table 4. Epoxidation of olefinic acids

Entry	Substrate	Iodolactone	Ratio, *trans/cis*	Yield (%)[a]	Epoxyester
1			10:1	80[b]	
2		"	10:1	84	"
3			10:1	97[b]	
4		"	20:1	98	"
5			20:1	75	
6			20:1 20:1	77 (R = OAc) 71 (R = Me)	
7			20:1	89	
8			10:1	52	
9			(3:2)[c]	98	

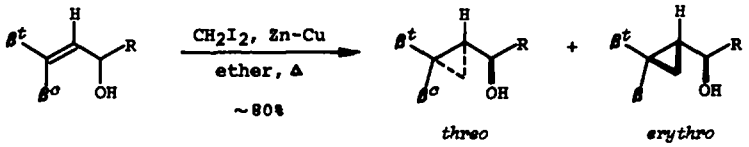
[a] Conditions: 3 equiv. of I_2, CH_3CN, 0°C, 2–12 hr unless otherwise indicated.
[b] Reaction run at 25°C for 1–2 days.
[c] Stereochemistry unknown.

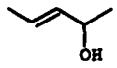
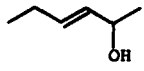
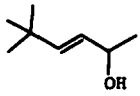
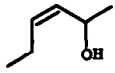
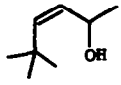
Conversion of the epoxy ester in Entry 7 to α-multistriatin is discussed in Part II. The epoxides from Entries 5 and 6 are of interest as potential intermediates in the synthesis of the rifamycins,[5,6a] streptovaricins,[38] and the related tirandamycin[39] and streptolydigin.[39]

The Simmons–Smith cyclopropanation of olefins is also very strongly directed by OH groups,[40] and recently the stereospecificity of this reaction has been studied with acyclic allylic alcohols.[41] A comparison of these results (Table 5) with those of the analogous epoxidations (Table 1)[27,28] reveals a very close similarity, and the directing effects have been explained in the same manner.[41]

A number of other reactions of olefins are known to be directed by OH coordination, but their application to acyclic systems remains largely unexplored. Among these are catalytic hydrogenation[42] and the addition of complex hydrides[43] and organometallic species.[44] A preliminary study suggests that dichlorocarbene addition to acyclic allylic alcohols is not directed by the OH group.[45]

Table 5. Cyclopropanation of allylic alcohols



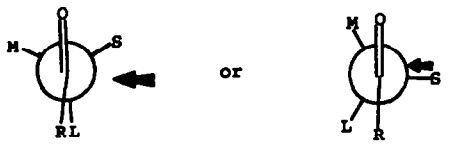
Entry	Substrate	Ratio (*threo/erythro*)
1		43:57
2		36:64
3		33:67
4		< 1:99
5		< 1:99
6		< 1:99

(B) *Additions to carbonyl compounds*

1. *With relative asymmetric induction.* The greatest effort in the area of acyclic stereochemistry has been devoted to understanding relative asymmetric induction in nucleophilic additions to chiral carbonyl compounds.[1,2] The study originated with Fischer's work on hydrogen cyanide addition to aldoses,[46] led to the efforts by Cram,[47,48] Cornforth,[49] Karabatsos,[50] and Felkin[51] to provide consistent and useful models for predicting relative asymmetric induction, and continues to the present with theoretical treatments of the phenomenon.[52,53]

The specific conformations of the carbonyl substrates which were originally considered in order to explain α-asymmetric induction are illustrated below. Cram proposed an "open-chain model"[47] for simple alkyl-substituted carbonyl compounds, expecting the carbonyl oxygen and the largest α-substituent to adopt an *anti* relationship for the addition. Cornforth's "dipolar" model[49] suggests that for α-halo derivatives, the carbon-halogen and carbonyl dipoles prefer an *anti* conformation. For com-

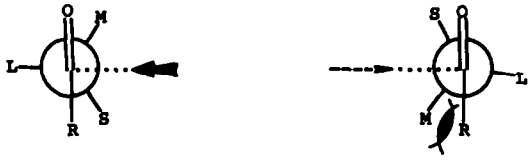
pounds which contain an α-substituent capable of coordinating the cationic part of the reagent, the "cyclic" model[47,48] predicts that this substituent will be eclipsed with the carbonyl by formation of a chelate in the favoured conformation. In each case, nucleophilic addition is understood to occur from the least encumbered side of the π-bond, that which faces the smallest substituent, as indicated below.



open-chain model[47]

dipolar model[49] *cyclic model*[47,48]

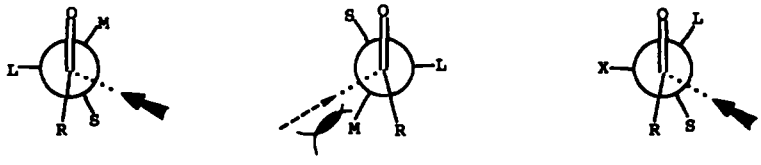
While these models adequately guide synthetic chemists in their predictions of the major isomeric products, the quantitative discrepancies between predicted and observed results as the substituents are systematically varied has led to alternative suggestions.[50,51] A major portion of this work has been reviewed by Morrison and Mosher[1] and will not be expanded upon here. One of the more successful alternative models is that of Felkin,[51] who proposes that the appropriate conformations to consider for the open-chain model are those in which the bond to the largest α-substituent is perpendicular to the CO group. The carbonyl oxygen is considered to be less sterically demanding than the CO substituent, therefore favoring conformation A below.



A B

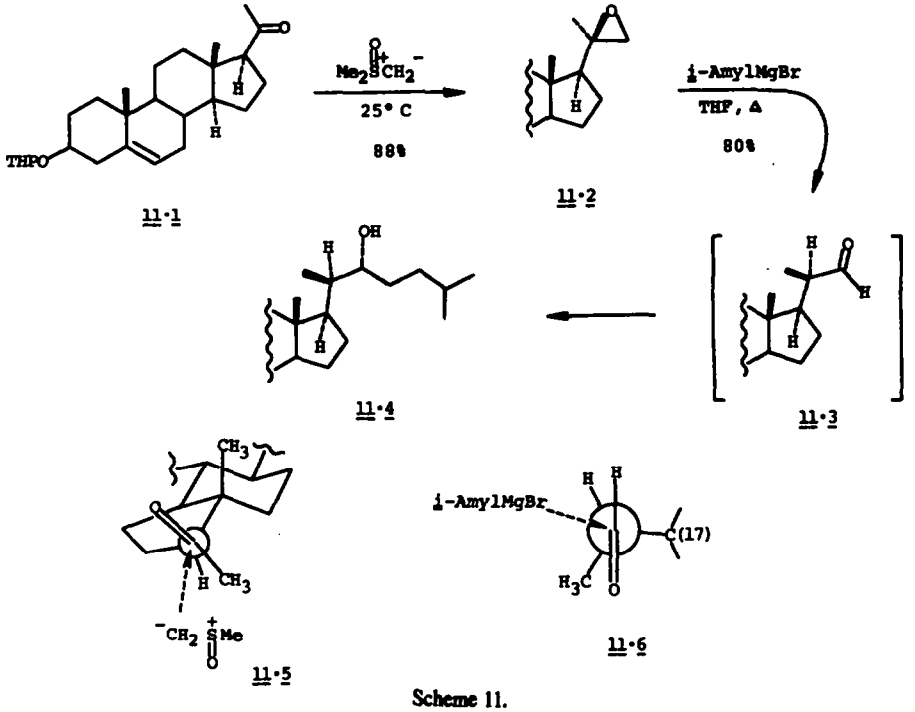
Recently, Anh and Eisenstein[53] have reported the results of their *ab initio* calculations of appropriate transition states for both the open-chain and dipolar models. They conclude that the conformation chosen by Felkin[51] for the open-chain system lies closest to the minimum energy for the transition state, primarily because of σ–π mixing of the α-substituent and CO orbitals. They further propose that attack as in A is favored over B, but for a different reason than that suggested by Felkin. The direction of nucleophile approach to the carbonyl carbon is not perpendicular to the C–O bond, but is instead from a direction tilted away from it.[54] This trajectory brings the nucleophile closer to the medium-sized substituent in B' below, destabilizing this transition state relative to A'. The prediction by Anh and Eisenstein[53] of the favored conformation for the dipolar model meshes smoothly with this picture as well, with the halogen occupying the position perpendicular to the carbonyl, as in C below.

In the chemistry of natural products, the most extensive studies of relative asymmetric induction in carbonyl addition reactions are encountered in the steroid field, in connection with the construction of the acyclic side chain. As this specific topic has been reviewed very recently,[21] only a few illustrative examples will be given.



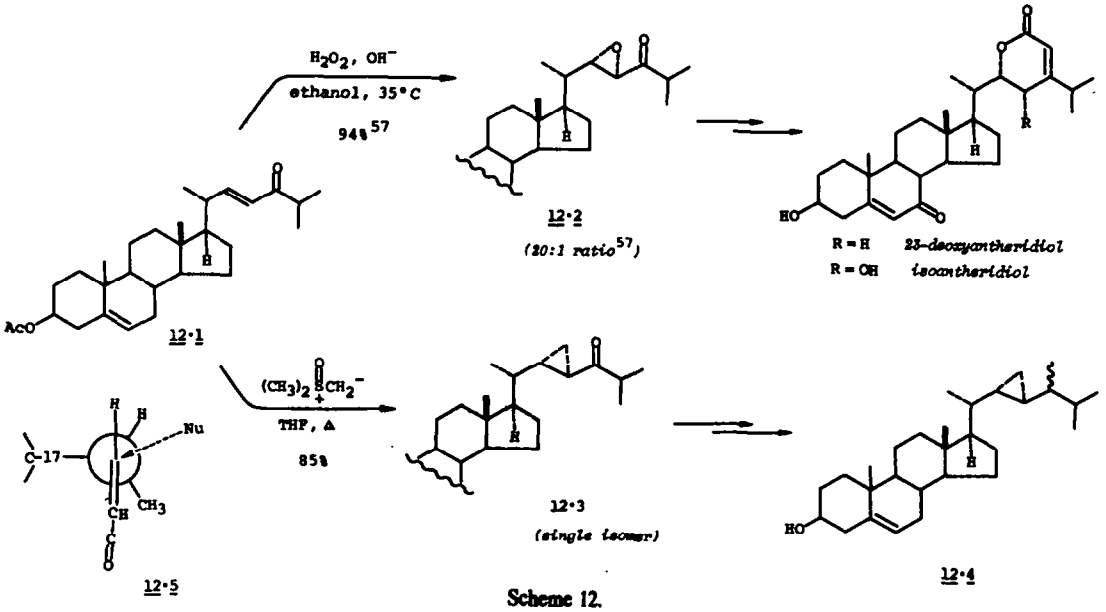
A' B' C

Nucleophilic addition to the 20-keto steroids is highly selective for the *si* face.[21,55] This is consistent with the open-chain model, which predicts that the transition state should resemble **11 · 5**. In the sequence depicted in Scheme 11,[23] this leads to the 20*R* epoxide **11 · 2**. In the presence of isoamylmagnesium bromide, this compound undergoes rearrangement to the 20*R* aldehyde **11 · 3**, which in turn undergoes another highly selective addition reaction, again in the predicted sense (**11 · 6**), to give the 22*R* alcohol **11 · 4**. As would be expected, 22*S* alcohols are the major products from addition to aldehydes of the epimeric 20*S* series.[21] While the addition of organometallic reagents to 22-aldehydes proceeds in the expected manner, in some instances the hydride reduction of 20-ketones occurs in the "anti-Cram" sense.[21]



Scheme 11.

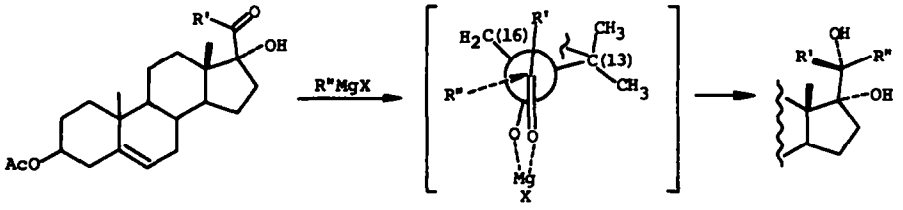
Although the substrates are quite different, the stereochemical outcome of nucleophilic addition to the double bond of *E*-22-ene-24-one steroid derivatives can be interpreted in a manner similar to the reactions of 22-aldehydes. For instance, the alkaline epoxidation of **12 · 1** affords very selectively (95:5) the 22*S*,23*R* epoxide **12 · 2**,[56-58] as depicted in Scheme 12. A reasonable proposal for the transition state



Scheme 12.

structure is **12 · 5**, which is analogous to that for carbonyl addition and predicts the observed specificity for **12 · 2**. Similarly, enone **12 · 1** reacts with dimethylsulfoxonium methylide to give exclusively the 22*S*,23*S* cyclopropyl ketone **12 · 3**,[59] also as predicted by **12 · 5**. The epoxy ketone **12 · 2** has been employed in syntheses of the fungal hormones 23-deoxyantheridiol[57] and isoantheridiol,[58] and the cyclopropyl ketone **12 · 3** has been converted to isomers (**12 · 4**) of the marine sterol demethylgorgosterol.[59]

Grignard additions to 17α-hydroxy-20-keto steroids follow the predictions of the cyclic model quite well, as revealed in the examples below.[55] On the other hand, the 16α,17α-epoxides react relatively nonselectively,[55,60] and without consistent adherence to either the cyclic or dipolar models.



R', R" = alkyl

A number of natural product syntheses employing additions to chiral carbonyl compounds having α- or β-oxygen substituents are outlined in Scheme 13. In Johnson's synthesis of the antibiotic cycloheximide,[61] the correct side chain configuration is introduced stereospecifically in the course of hydrogenation of the racemic enol ketone **13 · 1**. The hydroxy ketone **13 · 2** was shown to be an intermediate in this reduction, and it was suggested that an intramolecular H-bond fixes the conformation of this molecule such that further hydrogenation occurs from the direction indicated in **13 · 4**. Surprisingly, the course of the hydrogenation is different when applied to optically active **13 · 1**, affording both **13 · 3** (30% yield) and the diastereomer **13 · 5** (20% yield) with the same relative diol stereochemistry.

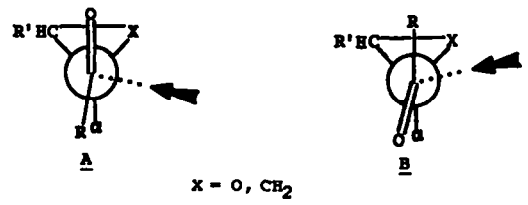
As an example of titanium tetrachloride-catalyzed aldol condensations, Mukaiyama treated 2-benzyloxyhexanal with diketene, obtaining an 85:15 mixture of diastereomeric esters (**13 · 6**) after methanolysis of the acid chloride intermediate.[62] The major product, which is that predicted by the cyclic model **13 · 7**, affords the fungal product pestalotin upon further manipulation.

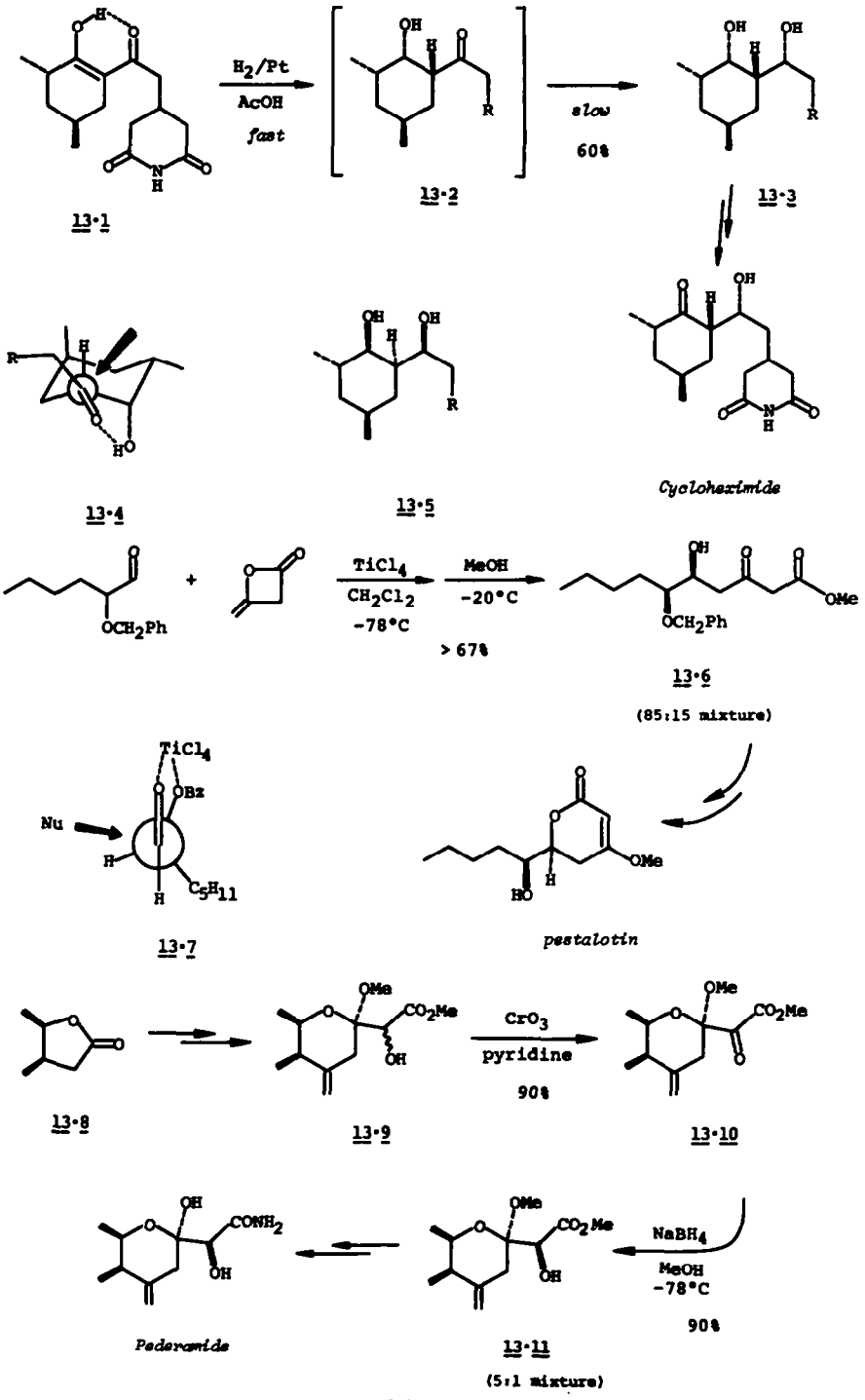
In a recently reported synthesis of pederamide,[63] the amide fragment of the molecule pederin, a ketone reduction is employed to introduce the extracyclic chiral center stereoselectively. However, the basis for the observed selectivity is not immediately clear in the absence of appropriate models having two α-oxygen substituents.

Although the 16α,17α-epoxy-20-keto steroids exhibit little selectivity in their reactions,[55,60] in a series of acyclic α,β-epoxy-ketones, high selectivities can be observed on sodium borohydride reduction[27b,64] (Table 6). Epoxy ketones lacking an α-substituent afford the R*R* isomers specifically. The presence of an α-Me diminishes or abolishes the selectivity entirely. This asymmetric induction has been rationalized on the basis of the cyclic model,[27b] although it is unlikely that sodium ion is chelated by these compounds in alcohol solvents to any great extent. Moreover, in hydride reductions of ketones in which this type of chelation would be much more likely,[65] only limited stereocontrol is observed.

Regardless of the interpretation of the basis for the observed selectivity, this route is quite valuable for the synthesis of epoxy alcohols of opposite relative stereochemistry to those produced by OH-directed epoxidation of allylic alcohols[27,28] (compare Tables 1 and 6). In an analogous (albeit more limited) study[41] (Table 7), the reduction of chiral cyclopropyl ketones also proceeds selectively, to give the carbinols complementary to those obtained by the Simmons–Smith cyclopropanation of allylic alcohols[41] (compare Tables 5 and 7).

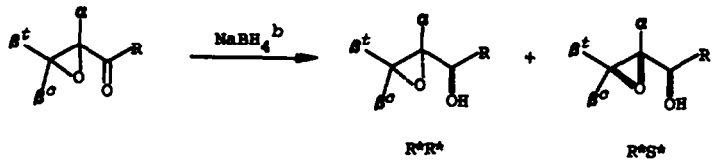
It seems likely that the same factors are responsible for the stereoselectivity of both epoxyketone and cyclopropyl ketone reductions,[41] and we suggest that the transition states for each resemble conformation A below when the α-substituent is hydrogen. This conformation allows the CO π-orbital to mix with the Walsh orbital of the 3-membered ring, and minimizes the steric interactions of the ring with the CO substituent R and the incoming complex hydride. Moreover, the favored conformer for methyl cyclopropyl ketone itself resembles A.[66] When a Me group occupies the α-position, conformation A is destabilized, and increasing reaction via conformation B diminishes the stereoselectivity of the reduction.

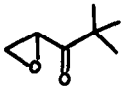
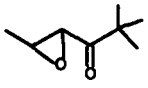
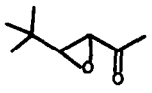
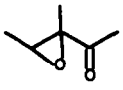
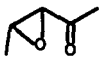
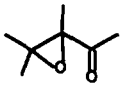

R'HC
X
R
O
A
B
X = O, CH2


H2/Pt
AcOH
fast
slow
60%
13·1
13·2
13·3
13·4
13·5
Cycloheximide
TiCl4
CH2Cl2
-78°C
MeOH
-20°C
> 67%
OCH2Ph
OMe
13·6
(85:15 mixture)
Nu
OBz
C5H11
13·7
pestalotin
CrO3
pyridine
90%
13·8
13·9
13·10
CONH2
CO2Me
NaBH4
MeOH
-78°C
90%
Pederamide
13·11
(5:1 mixture)

Scheme 13.

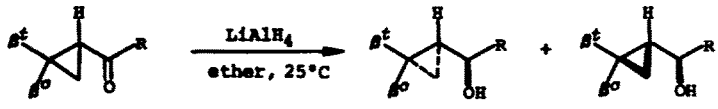
Table 6. Borohydride reduction of α,β-epoxyketones[a]



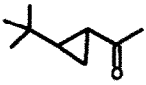
Entry	Substrate	Ratio, R*R*/R*S*
1		100:0
2		> 95:5
3		55:45
4		> 95:5
5		> 95:5
6		85:15
7		65:35
8		90:10
9		100:0
10		86:14
11		46:54

[a] Each compound is racemic; the products are depicted in this fashion to facilitate comparison with Table 1.
[b] No reaction solvent or conditions were reported.[27b,44]

Table 7. Reduction of cyclopropyl ketones[a]



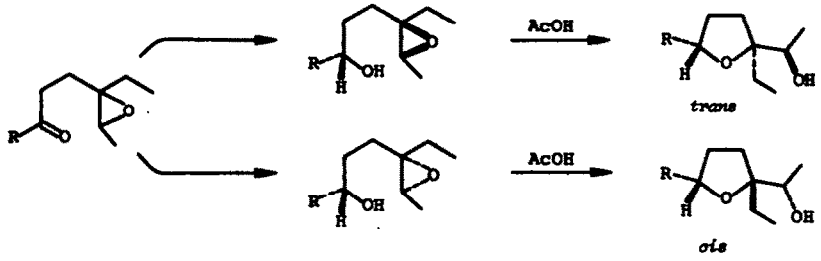
threo *erythro*

Entry	Substrate	Ratio (*threo/erythro*)
1		52:48
2		52:48
3		62:38
4		88:12
5		84:16
6		87:13

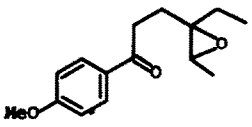
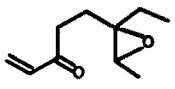
[a]Each compound is racemic; the products are depicted in this fashion to facilitate comparison with Table V.

Kishi has developed conditions for the stereoselective reduction of some γ,δ-epoxy ketones,[36] as shown in Table 8, and has employed this reaction in his ionophore syntheses (Part II). Although only a few substrates were investigated, the reductions again proceed with a specificity complementary to the epoxidation process (see Table 3).

Table 8. Reduction-cyclization of γ,δ-epoxy ketones[a]



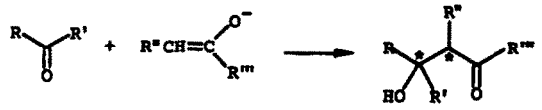
trans *cis*

Entry	Substrate	Reagent	Ratio (*trans/cis*)
1		$NaBH_4$, MeOH, 25°C or L-Selectride, ether, 25°C	1:1
2	"	$LiAlH_4$, ether, 0°C	1:3
3	"	$LiAlH(O\underline{t}\text{-Bu})_3$, ether, 0°C	1:4
4	"	$LiAlH_4$·Diamine[b], ether, -78°C	1:11
5		$LiAlH_4$·Diamine[b], ether, -78°C	1:10

[a]All compounds are racemic; they are depicted in this manner to facilitate comparison with Table III.
[b]Diamine = di-2-(*o*-toluidinomethyl)pyrrolidine.

2. *With internal asymmetric induction.* Addition reactions of carbonyl compounds are not only capable of establishing vicinal chiral centers in the sense of eqn (1) below (with relative asymmetric induction), but, in the case of enolate addition, in the sense of eqn (2) (with internal asymmetric induction) as well. Many variations of the aldol condensation and the Reformatsky reaction have been pursued in an attempt to achieve stereoselectivity in the latter sense, and for the aldol condensation some notable success has been realized.

eq. 1

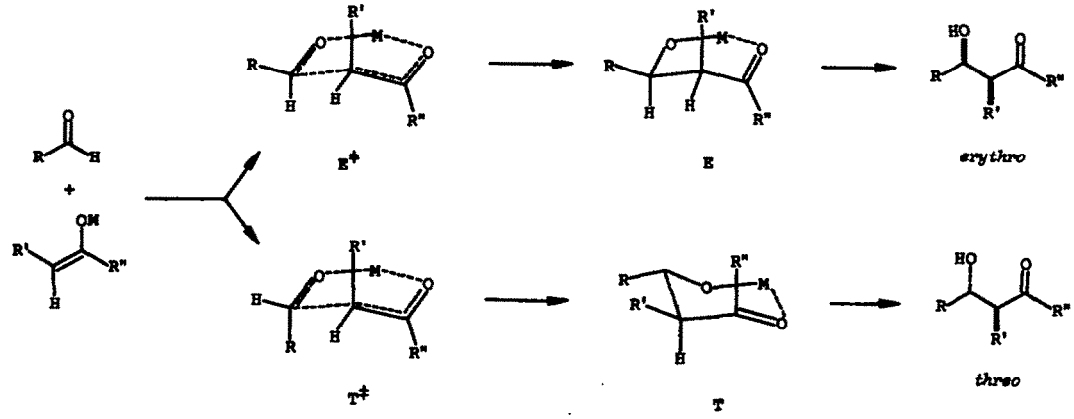


eq. 2

The work of Heathcock,[67,68] Dubois,[69] and House[70] (among others),[70a] has led to an understanding of the factors responsible for stereocontrol in the aldol condensation. Scheme 14 depicts the condensation of an aldehyde with a ketone enolate of the *Z*-geometry. The reaction proceeds via the chelated transition states, E‡ and T‡, and the intermediates E and T, when the reaction is carried out in aprotic solvents in the presence of a coordinating counterion. Similar structures can be envisaged for enolates of the *E*-geometry.

For kinetically controlled reactions (discrimination between E‡ and T‡; see Table 9), the *erythro* isomer is the favored product from *Z*-enolates, while the *threo* product predominates from *E*-enolates (with some exceptions). The bulk of R" is important: with decreasing size, steric interference with the "axially" disposed R group in T‡ (Scheme 1) diminishes and stereoselectivity decreases. Moreover, as R' becomes bulky, its *gauche* interaction with R destabilizes E‡ (Scheme 14) and favors the *threo* product with *Z* enolates.

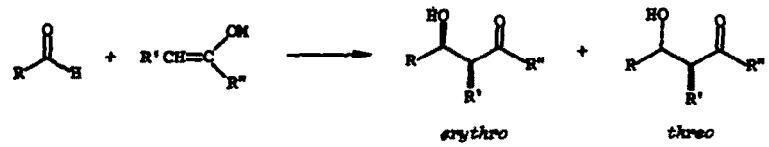
Under conditions of thermodynamic control (discrimination between E and T in Scheme 14), the *threo* product is favored, regardless of the geometry of the starting enolate.[70-72] For instance, the *Z*-bromomagnesium enolate of ethyl *t*-butyl ketone condenses with benzaldehyde to give the *erythro* product kinetically (entry 1), but if the reaction mixture is allowed to stand (period of time unspecified), the *threo* isomer is nearly the exclusive product.[72] In a report evaluating the influence of different counterions on the aldol condensation, House found that either stereoisomeric enolate of phenylacetone condenses rapidly (less than 5 min) with butyraldehyde in dimethoxyethane/ether at 7–10° in the presence of zinc chloride to give predominantly the *threo* product.[70] This stereochemical result and the invariance of product composition with longer reaction times are consistent with thermodynamic control over formation of the alkoxide chelates E and T. A number of highly coordinating metals have been studied as counterions in the aldol condensation, including boron,[73] aluminum,[71,74] and titanium[75] in addition to those mentioned above, with varying degrees of stereoselectivity observed.



Scheme 14.

In the absence of a coordinating cation, for instance with a quaternary ammonium enolate, reverse aldol equilibration is very rapid.[76] In some instances (e.g. entry 15 in Table 9)[67] these non-chelated condensations are quite stereoselective, with a *Z*-enolate affording the *threo* product.[67,77] In protic media, where control via chelated intermediates is also unavailable, very low stereoselection is usually observed.[69,78]

Table 9. Aldol condensation with kinetic control



erythro *threo*

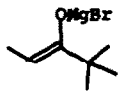
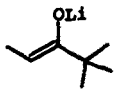
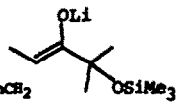
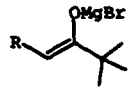
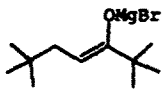
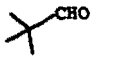
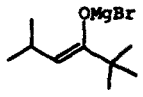
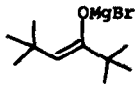
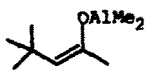
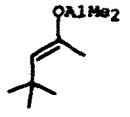
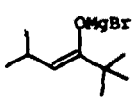
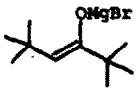
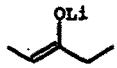
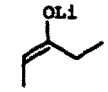
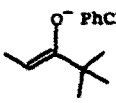
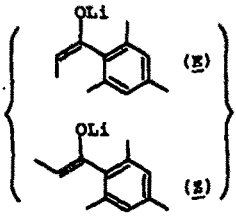
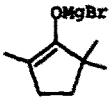
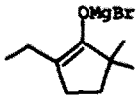
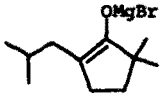
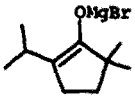
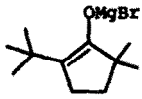
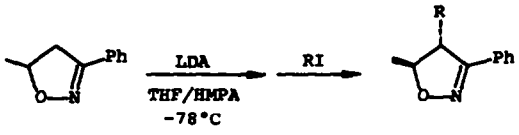
Entry[a]	Substrates	Conditions	Ratio, *erythro/threo* (Yield, %)
1	RCHO R = Me[b], Et, i-Pr, t-Bu, Ph[c] 	20°C, ether	*erythro* only (56-76)
2[d]	PhCHO 	-72°C, THF	*erythro* only (78)
3	 "	-10°C, ether	*erythro* only
4[e]	RCHO R = Ph, i-Pr, $PhCH_2$ 	-72°C, ether	*erythro* only (86-90)
5	  R = Et, n-Pr, i-Bu	20°C, ether	> 97:3 (52-72)
6	" 	20°C, ether	82:18 (58)
7	 	20°C, ether	29:71 (46)
8	" 	20°C, ether	*threo* only (74)
9[f]	CH_3CHO 	-20° → 25°C, PhMe	*threo* only (66)
10[f]	" 	-20° → 25°C, pentane	93:7 (69)
11	" 	0°C, ether	48:52

Table 9. (*Contd*)

12	"		0°C, ether	20:80
13			-10°C, ether	88:12
14	"		-10°C, ether	48:52
15[d]	PhCHO		-72°C, THF	*threo* only (52) (thermodynamic control)[g]
16[d]	PhCHO	 E/Z = 92:8	-72°C, THF	8:92 (52)
17	RCHO R = Me, Et, i-Bu, neopentyl		0°C, ether	6:94 (48-69)
18		"	0°C, ether	3:97 (62)
19		"	0°C, ether	<1:99 (50)
20		"	0°C, ether	27:73
21	"		0°C, ether	12:88 (52)
22	"		0°C, ether	20:80
23			0°C, ether	54:46 (59)
24	CH_3CHO		0°C, ether	71:29

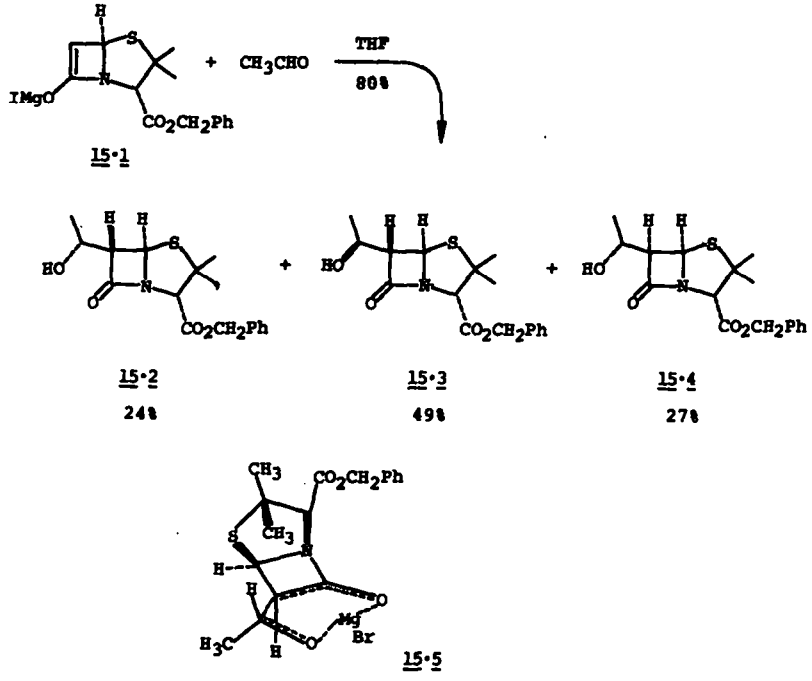
[a] Ref. 69, unless otherwise noted.
[b] Reaction run at 0°C.
[c] Ref. 72.
[d] Ref. 67.
[e] Ref. 68.
[f] Ref. 71.
[g] Ref. 76.

Another potential method for obtaining *threo* α-alkyl-β-hydroxy-ketones is suggested by Jäger's report[79] that isoxazoline "enolates" can be alkylated stereoselectively to give the *trans* isomers, as shown below. While they do not report attempts to cleave these or similar products to hydroxy ketones, they were able to reduce them stereoselectively to 1,3-amino alcohols.



R	*trans/cis*	Yield	
CH_3	93:7	73%	(Ref. 79)
C_2H_5	92:8	88%	(Ref. 79)

The unusual hydroxyethyl side chain of the antibiotic thienamycin has generated interest in aldol-type condensations of β-lactam derivatives. In this connection, the stereochemistry of the reaction of benzyl penicillinate enolates with acetaldehyde has been elucidated (Scheme 15).[80] Addition from the exo (α) face of the enolate **15 · 1** affords a comparable mixture of *erythro* and *threo* isomers **15 · 2** and **15 · 3**, whereas addition from the more sterically encumbered endo (β) face provides only the *threo* isomer **15 · 4**. The chelated transition state (**15 · 5**) proposed by the Merck chemists rationalizes this result quite well.



15·1

15·2 24%

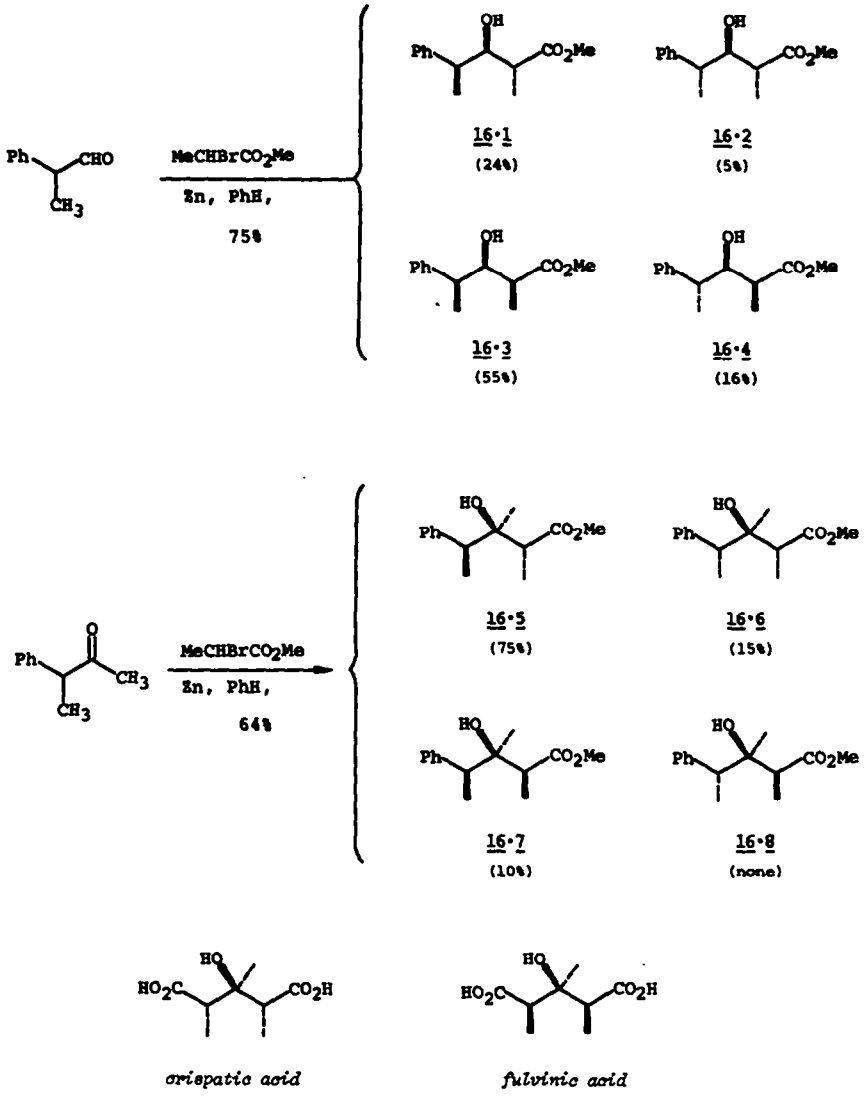
15·3 49%

15·4 27%

15·5

Scheme 15.

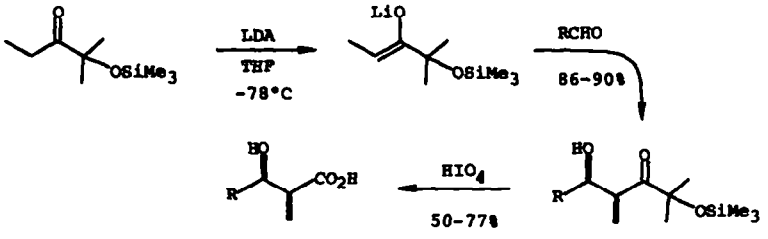
As one might anticipate from the importance of a bulky R" substituent and a stereochemically pure enolate in the model of Scheme 14, the classical Reformatsky reaction[81,82] and its modern counterparts using lithium enolates[83] usually exhibit only moderate stereoselectivity.[70a] In this regard, the Reformatsky condensation of methyl bromopropionate with 2-phenylpropanal[84] (Scheme 16) is representative: a *threo/erythro* selectivity (internal asymmetric induction) of 29:71 (**16 · 1 + 16 · 2/16 · 3 + 16 · 4**) and a relative asymmetric induction of 79:21 (**16 · 1 + 16 · 3/16 · 2 + 16 · 4**) are observed. The reaction of 3-phenyl-2-butanone,[85] on the other hand, is particularly interesting because the *threo/erythro* selectivity (90:10 for **16 · 5 + 16 · 6/16 · 7 + 16 · 8**) is *reversed*, and both it and the relative asymmetric induction (85:15 for **16 · 5 + 16 · 7/16 · 6 + 16 · 8**) are even higher. Unfortunately, it was the minor isomers **16 · 6** and **16 · 7** which were desired for conversion to the naturally-occurring necic acids (crispatic and fulvinic, respectively) by ozonolysis and hydrolysis.[85]



Scheme 16.

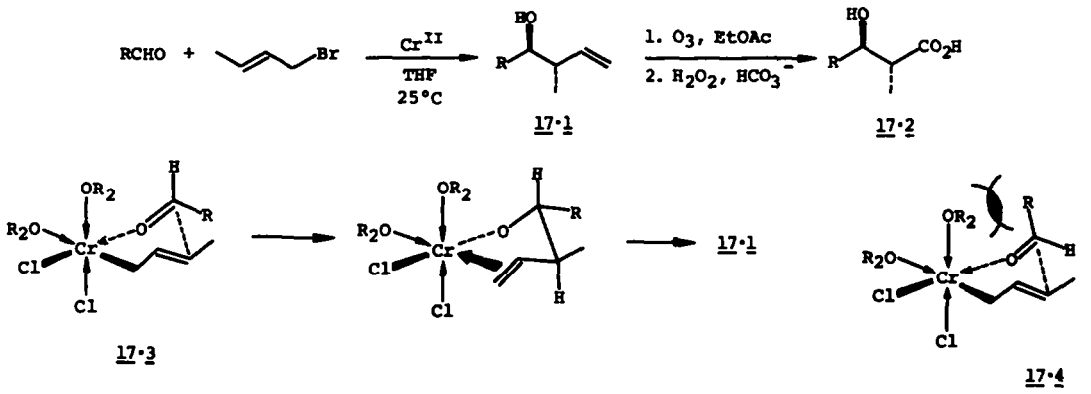
The particular experiments illustrated in Scheme 16 raise an interesting question of *kinetics*, because the *internal* asymmetric induction for the reaction of the ketone is presumably established by a thermodynamically controlled process,[81a] while the *relative* asymmetric induction is presumably established by a kinetically controlled process.[47,81a]

In order to circumvent the generally low stereoselectivity of ester enolate condensations, Heathcock used 2-methyl-2-trimethylsilyloxy-3-pentanone as the enolate precursor in the aldol condensation.[68] After generation of the *Z*-enolate and kinetically controlled formation of the *erythro* aldol product (see Entry 4, Table 9), periodic acid removes the silyl group and unmasks the carboxylic acid by cleavage of the β-hydroxy ketone. *Erythro* β-hydroxy-α-methyl acids are thus available as outlined below.



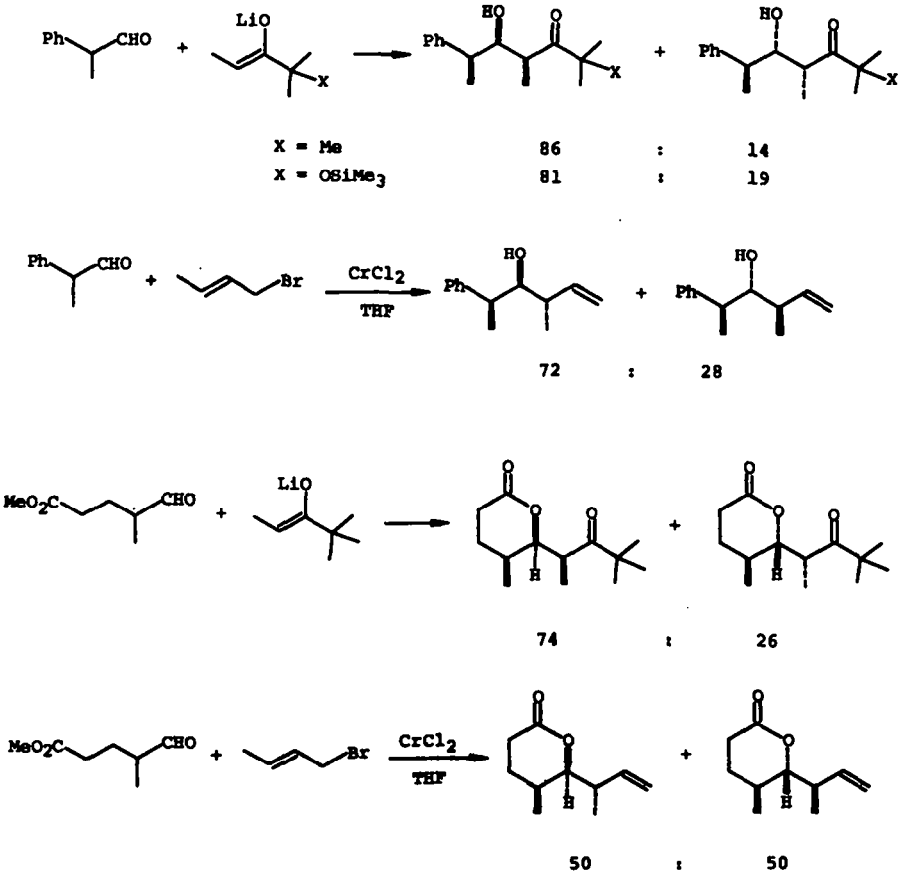
The difficulty of obtaining the analogous *E*-enolates renders the diastereomeric *threo* β-hydroxy-α-methyl acids inaccessible by this route. However, Heathcock[86] has demonstrated that Hiyama's

method[87] for the addition of crotyl bromide to aldehydes with chromous ion provides the *threo* products very selectively (Scheme 17). The *threo* acids are then available by cleavage of the double bond. The stereospecificity of this transformation is explained[86] by reference to the chair-like cyclic transition states 17 · 3 and 17 · 4, in which the axially oriented ligands of the octahederally coordinated metal play a major role in destabilizing the conformation (17 · 4) which would lead to the *erythro* product. This suggestion is particularly interesting since a variety of similar reactions employing other metals are believed not to proceed via cyclic transition states.[88]



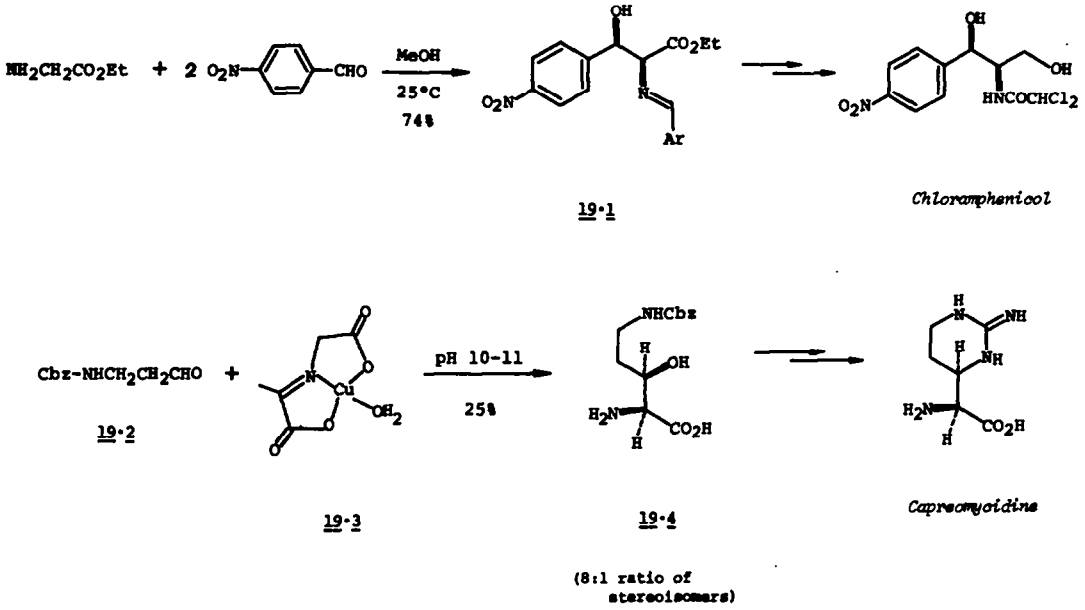
Scheme 17.

The relative asymmetric induction attainable in the aldol condensation[68] and the reaction of Scheme 17[86] has also been studied by Heathcock (Scheme 18). Both reactions exhibit the specificity predicted by the models discussed above, although the selectivity is only moderate in the case of the crotylchromium addition.



Scheme 18.

A few less common reactions involving ester enolate condensations have been used successfully for acyclic stereocontrol in natural product synthesis (Scheme 19). Among these are the self-catalyzed condensation of ethyl glycinate with two molecules of *p*-nitrobenzaldehyde to give the *threo* adduct **19 · 1**.[89] Since this isomer crystallizes from the solution, the stereocontrol observed may result from an equilibration process. Further elaboration of **19 · 1** affords the antibiotic chloramphenicol.[90]



Scheme 19.

Condensation of the protected 3-aminopropanal derivative (**19 · 2**) with the activated glycine reagent (**19 · 3**)[91] proceeds in a similar stereochemical sense, providing the *threo* hydroxyamino acid **19 · 4** with its diastereomer in a ratio of 8:1.[92] Replacement of the OH group with ammonia in a double inversion sequence and condensation with cyanogen bromide lead to capreomycidine, a constituent of the antibiotic capreomycin. Similar *threo* selectivity was noted for the condensation of **19 · 3** with aldehyde sugars.[91]

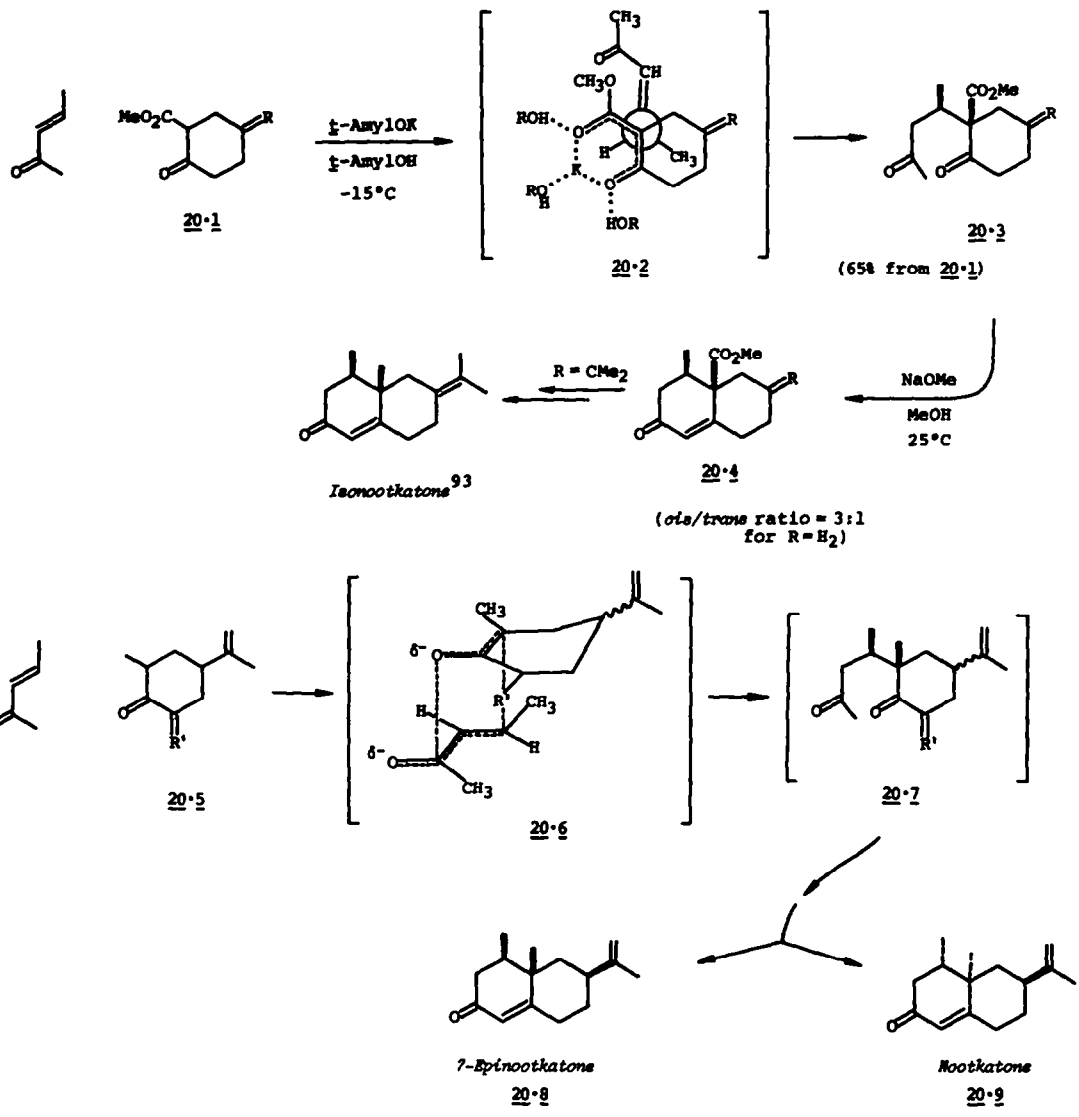
A number of Michael reactions proceed with high internal asymmetric induction.[93-99] In particular, the addition of cyclohexanone enolates to 3-penten-2-one has been thoroughly studied as a means of establishing the *cis* dimethyl relationship in the eremophilane sesquiterpenes[93-98] (Scheme 20). Marshall's original application of this strategy employed 2-carbomethoxy-4-isopropylidenecyclohexanone (**20 · 1**, R = CMe_2) as the nucleophile.[93] In this reaction, carefully controlled conditions were required to optimize the stereoselectivity (about 3:1 in favor of the *cis* product **20 · 4**). The transition state structure **20 · 2** was proposed to account for this selectivity and its dependence on solvent and counterion.[93]

Under poorly dissociating conditions and with the more basic enolates derived from α-methylcyclohexanones **20 · 5**, the Michael addition is kinetically controlled and stereospecific,[94-98] proceeding via a transition state such as **20 · 6** which minimizes steric interactions and charge separations. While the acyclic stereocontrol depicted in Scheme 20 was employed only for the construction of intermediates, the potential application of this strategy for specifically acyclic targets is obvious.

(C) *Sigmatropic rearrangements*

The transition states ofthe [3,3]- and the [2,3]-sigmatropic rearrangements are usually highly ordered, with the result that specific stereochemical relationships in a starting material are faithfully transformed to specific relationships in the product. These reactions are capable of both relative and internal asymmetric induction, and have therefore been employed to great advantage in the construction of acyclic systems.[100]

1. *Claisen and Cope rearrangements.* In general, the [3,3]-sigmatropic rearrangements of acyclic molecules show a preference for a chair-like conformation of the transition state (C), as depicted in

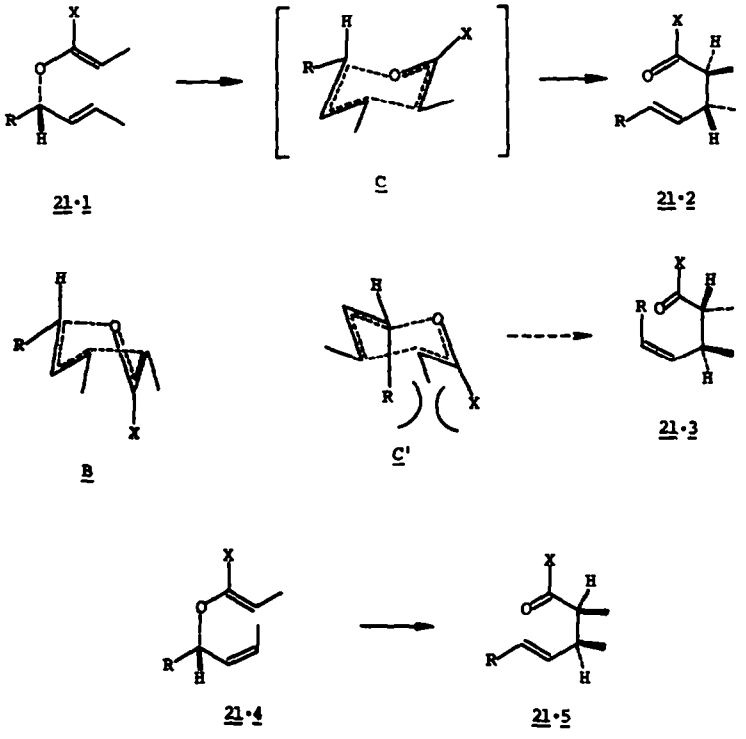


Reference	R'	Conditions (Yield)	Product Ratio, 20·8/20·9
94	H_2	1. $NaNH_2$, DME, -5°C; 2. KOH, MeOH, (29%)	20·8 only
95	H_2	NaH, ether, 0°C (< 4%)	9:1
96	$CHSCH_2Ph$	t-AmOK, t-AmOH, 100°C (30%)	1:1

Scheme 20.

Scheme 21 for the Claisen rearrangement.[101-104] For the crotyl propenyl ethers (stereoisomers of **21 · 1**; R = X = H), rearrangement through an alternative boat-like conformation (**B**) is disfavored by 2.5–2.7 kcal/mole.[101] When applied to secondary allylic alcohols, a high propensity for formation of the *E*-olefin is observed, particularly when X ≠ H, because of the "pseudo-diaxial" interaction in the chair-like transition state (**C'**) leading to the *Z*-isomer **21 · 3**.[104]

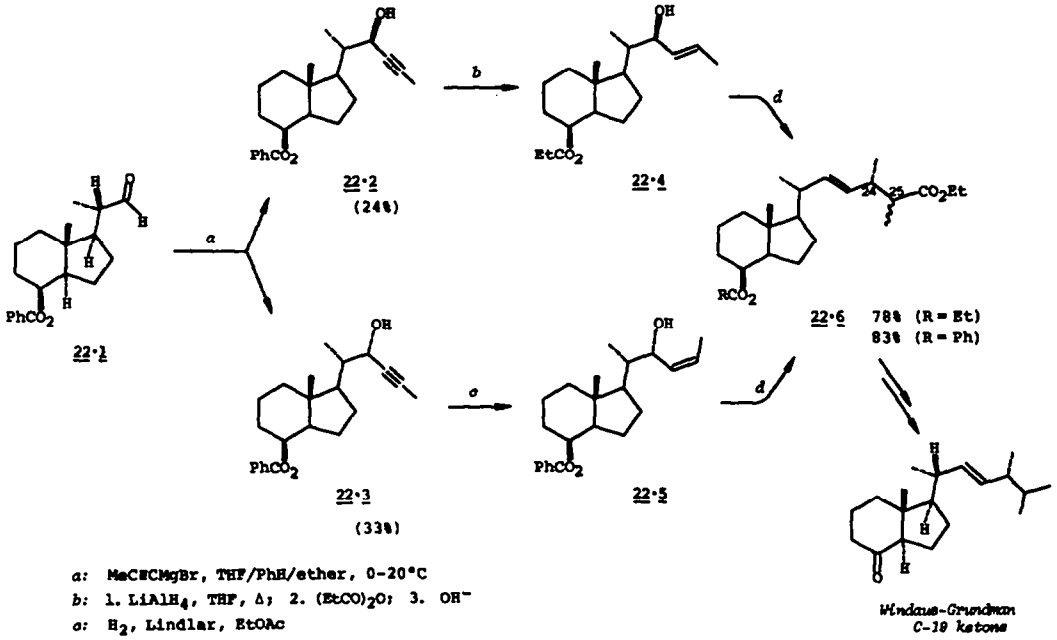
There can be up to three chiral centers directly involved in the Claisen rearrangement: that of the starting material **21 · 1** and those of the product **21 · 2** (the Cope rearrangement can involve up to four chiral centers if the oxygen is replaced by a chiral carbon). Hill has shown that these rearrangements proceed suprafacially with regard to the allylic moiety,[105] so that the configuration of the allylic chiral center of the product is specifically related to that of the starting material. Moreover, either configuration of the new chiral center may be obtained by changing the geometry of the allylic double bond (compare



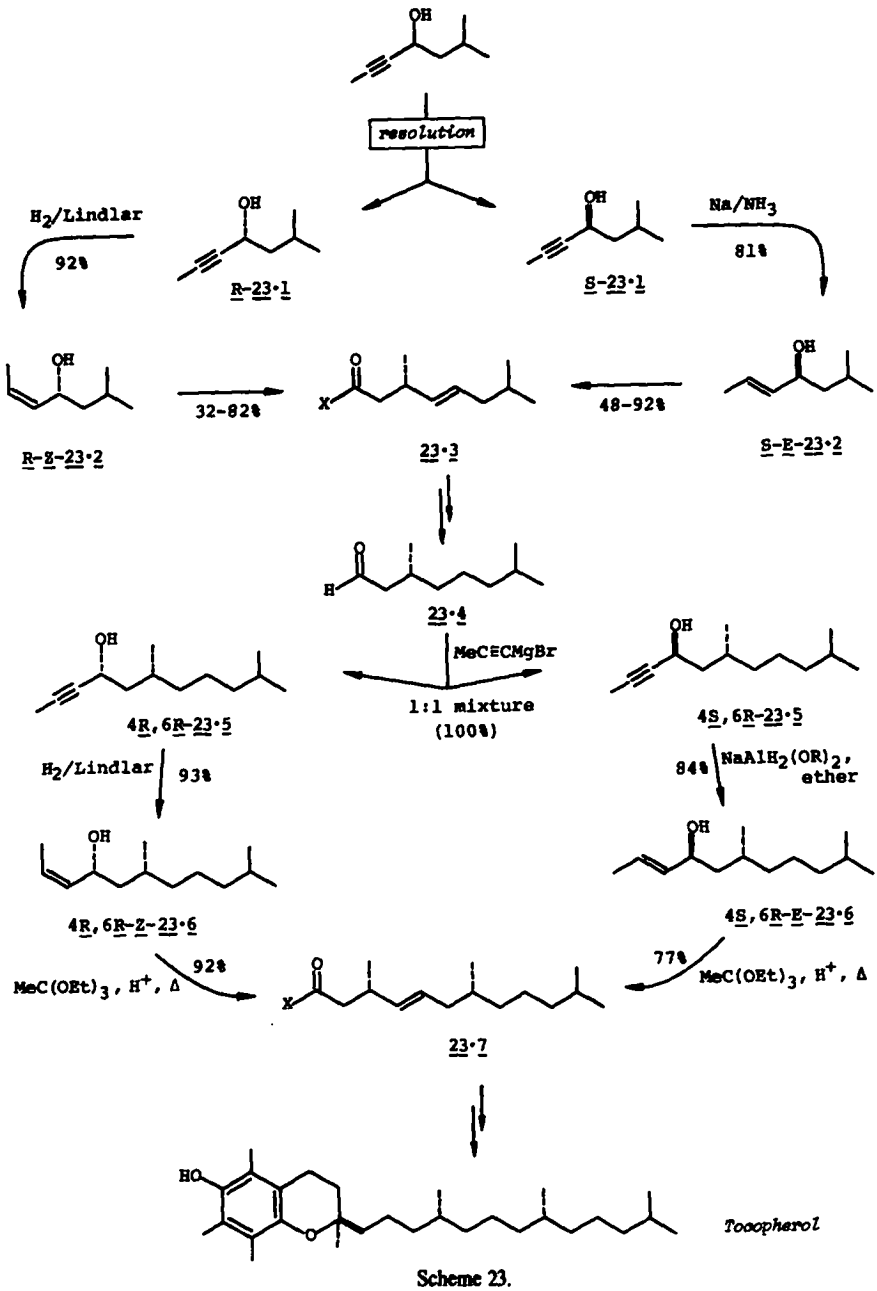
Scheme 21.

21 · 1→21 · 2 with 21 · 4→21 · 5). Although a chiral center is destroyed in the rearrangement, it reappears in the allylic position. One of the useful features of the reaction, therefore, is the ability to transmit chirality along a carbon chain (relative asymmetric induction), as illustrated in Schemes 22–24 for the construction of the steroid[106] and tocopherol[107–109] sidechains.[110a]

In Lythgoe's route to the Windaus–Grundman C-19 ketone (Scheme 22), a key intermediate for the synthesis of Vitamin D_2, propynyl Grignard addition to the 22-aldehyde 22 · 1, gives a mixture of isomers



Scheme 22.

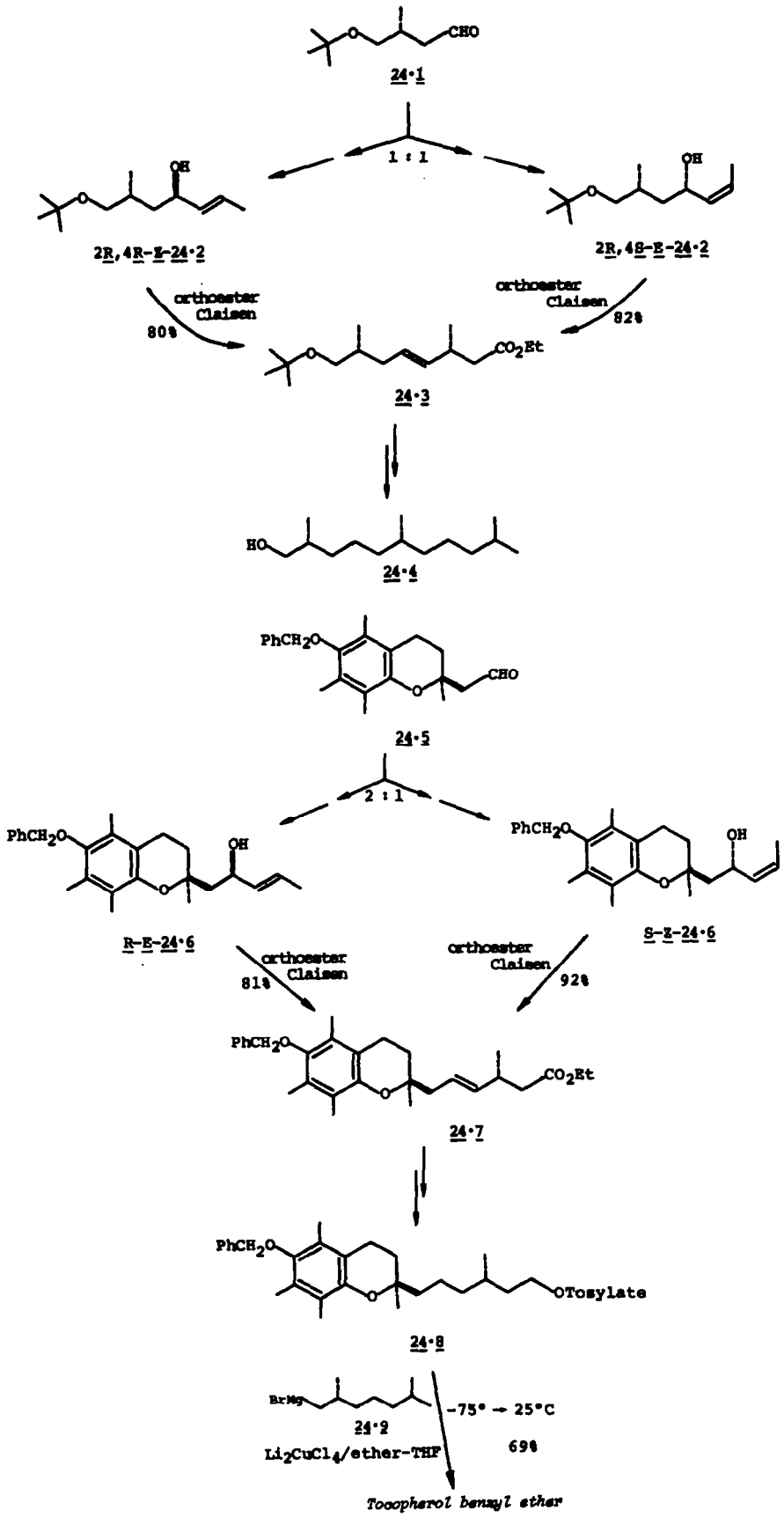


Scheme 23.

22 · 2 and 22 · 3 (contrast with Scheme 11). However, by separation of these isomers and reduction to the *22R,23E* (22 · 4) and *22S,23Z* (22 · 5) allylic alcohols, respectively, each can be converted to the desired product (22 · 6) by the orthoester Claisen procedure.[104] In this route, the chiral center at C-25 in 22 · 6 is not introduced stereospecifically because it is removed in subsequent steps. An earlier elaboration of ethylated sidechains in an analogous manner by Sucrow[56,100] is discussed below.

A similar strategy is employed in the Roche syntheses of the phytyl side chain of tocopherol[107] (Scheme 23). Either enantiomer of the propargylic alcohol 23 · 1 can be converted to the *S–E* products 23 · 3 via the *R–Z* and *S–E* allylic alcohols (23 · 2). In a thorough investigation of this sequence, the Roche group studied four variants of the Claisen rearrangement: the vinyl ether (R = H), orthoester (R = OEt), amide acetal ($R = NMe_2$), and ester enolate $R = OSiMe_2t$-Bu) procedures. Each reaction is nearly stereospecific (97–99 ± 1% chiral transmission).

The aldehyde 23 · 4 is homologated in the same manner. 1-Propynylmagnesium bromide addition occurs without relative asymmetric induction to provide a 1:1 mixture of diastereomers 23 · 5. Each in

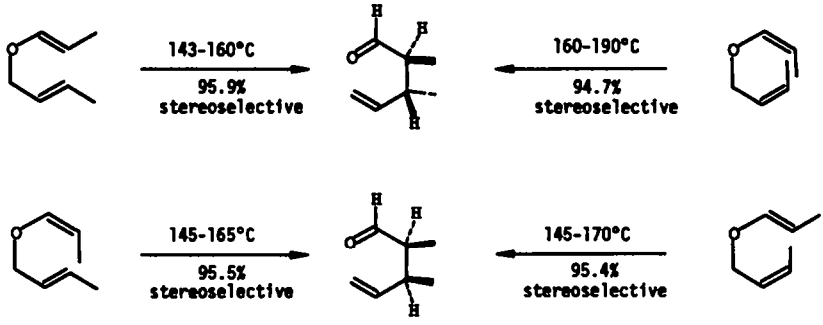

CHO
24·1
1 : 1
OH
2R,4R-E-24·2
2R,4S-E-24·2
orthoester Claisen
80%
orthoester Claisen
82%
CO2Et
24·3
HO
24·4
PhCH2O
CHO
24·5
2 : 1
R-E-24·6
S-Z-24·6
orthoester Claisen
81%
orthoester Claisen
92%
24·7
OTosylate
24·8
BrMg
24·9
Li2CuCl4/ether-THF
-75° → 25°C
69%
Tocopherol benzyl ether

Scheme 24.

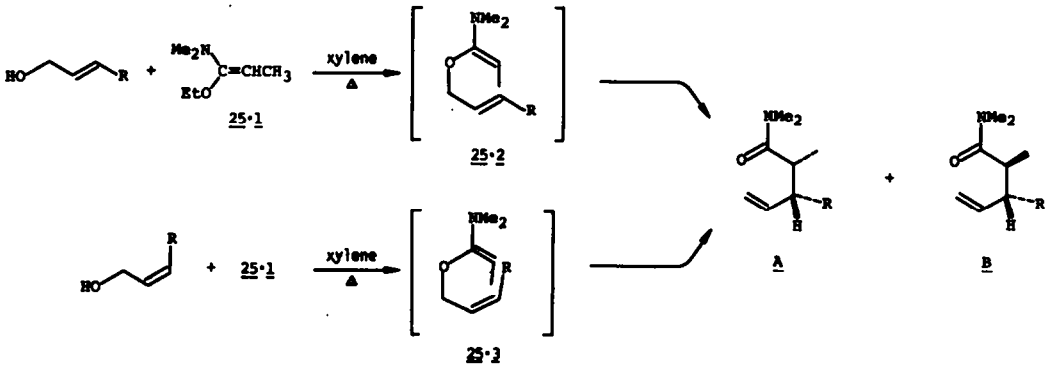
turn is converted by Claisen rearrangement to the 3*S*,7*R* product **23 · 7**, which can be coupled with an optically active chroman unit to give tocopherol.[107]

Other similar routes to this vitamin developed by the Roche group (Scheme 24) entail transmission of the chirality in the other direction, with the conversion of microbiologically-derived *S*-aldehyde **24 · 1** to the rearranged ester **24 · 3**,[108] and the *S*-chromane aldehyde **24 · 5** to ester **24 · 7**.[109] While the latter material could conceivably be homologated again, the remaining chiral center of tocopherol was introduced by coupling the tosylate **24 · 8** with the *R*-Grignard reagent **24 · 9**.

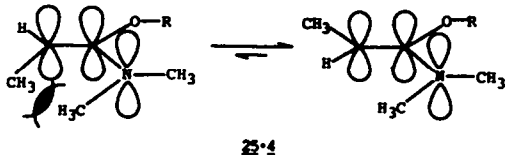
As suggested by Scheme 21, the Claisen rearrangement can introduce two chiral centers in the product with internal asymmetric induction as well. Their relationship is established by the chair-like transition state and depends on the geometry of the double bonds of the starting material, as illustrated below for the isomeric 2-butenyl-1-propenyl ethers.[101] This feature of the reaction, combined with the suprafacial nature of the rearrangement, allows both of the chiral centers of the product to be related to that of the starting material, and to be introduced with either configuration by controlling the geometry of the double bonds.



Control of the geometry of the enol ether double bond is the most difficult to achieve, although a variety of methods for doing so are now available.[111-113] Sucrow demonstrated that the allylic ketene-N,O-acetals produced by exchange with the ethoxy derivative **25 · 1** are generated and rearranged with high selectivity, affording *erythro* products from *trans*-allylic alcohols, and *threo* products from *cis*-allylic alcohols[111] (Scheme 25). These results imply a *Z*-geometry for the ketene-N,O-acetal inter-



Starting Alcohol: R		Ratio, A/B	Yield (%)
trans	CH_3	95:5	76
trans	Ph	92:8	85
cis	CH_3	3:97	65
cis	Ph	7:93	79

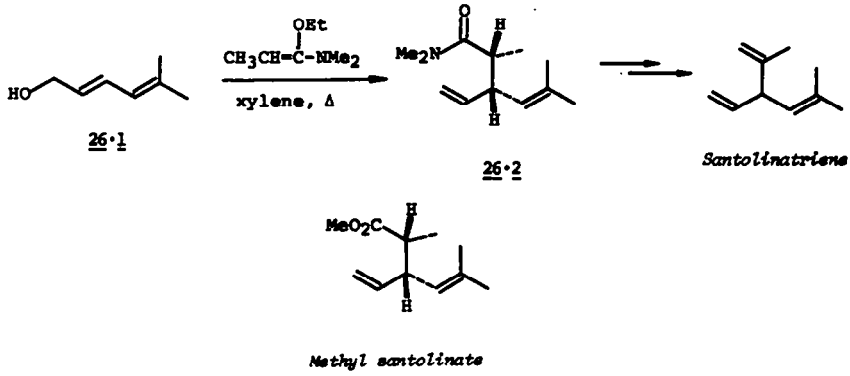


25·4

Scheme 25.

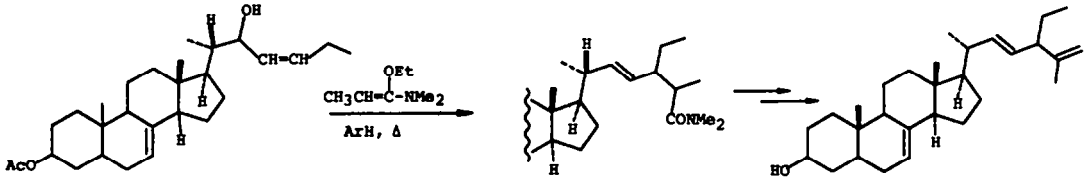
mediates **25 · 2** and **25 · 3**. The large bulk of the dimethylamino substituent (especially when the nitrogen lone pair is conjugated with the π-system; see **25 · 4**) accounts for this preference.

In a synthesis of santolinatriene[114] (Scheme 26), Sucrow first prepared the amide **26 · 2** using this procedure. The corresponding methyl ester (methyl santolinate) was later recognized as a natural product.[115]



Scheme 26.

Sucrow has also employed this reaction for both relative and internal asymmetric induction in the stereoselective construction of all of the diastereomers of **27 · 2**, precursors to steroids which contain the 25-ethylated side chain (Scheme 27).[56,110]

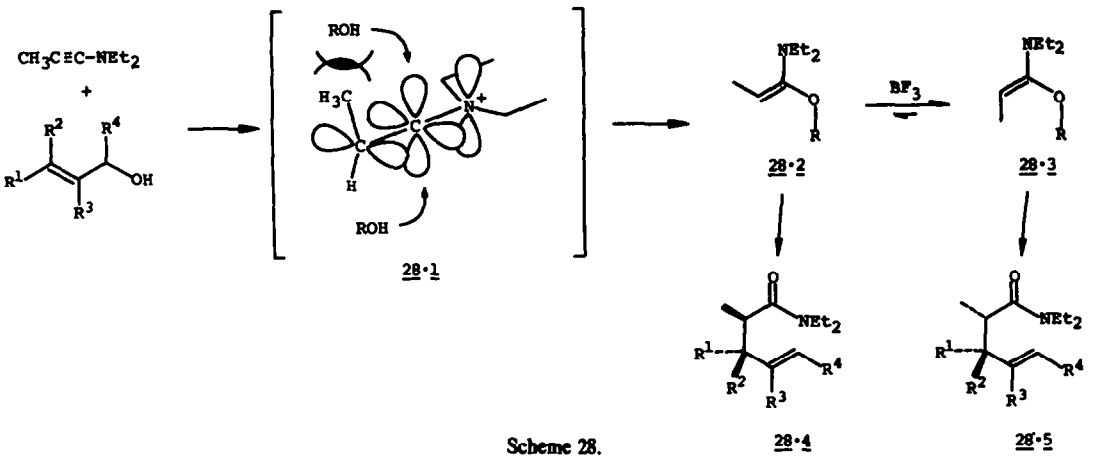


	Major Isomer	Ratio with C-25 Epimer	Yield (%)
22R,23-Z	24S,25R	94:6	82
22S,23-Z	24R,25S	89:11	--
22R,23-E	24R,25R	97:3	79
22S,23-E	24S,25S	97:3	70

Scheme 27.

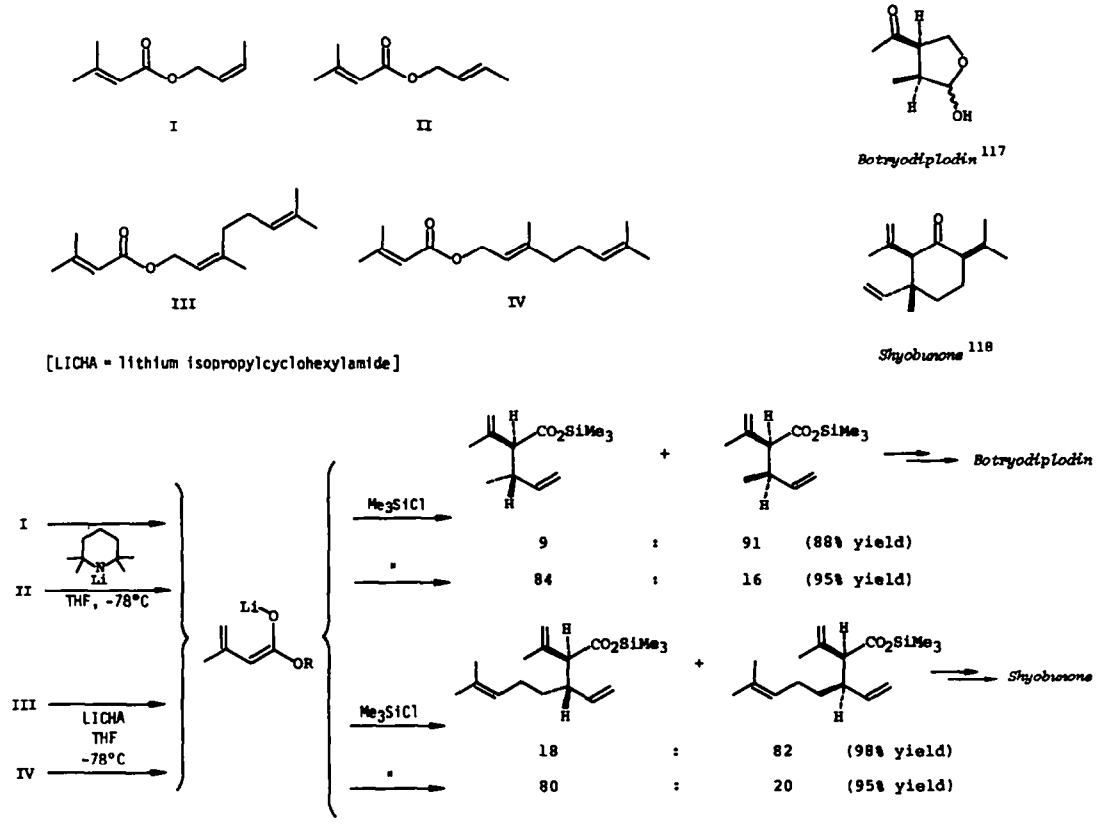
Although the ynamine-Claisen rearrangement, which involves an alternative means of generating an allylic ketene-N,O-acetal (such as **25 · 2**), was described by Ficini and Barbara[116] a number of years ago, the stereoselectivity of this process was not reported. We have found that this reaction (Scheme 28) can be controlled to give either of the diastereomeric products selectively, depending on the choice of conditions.[113] If the reaction is carried out at room temperature with BF_3 catalysis, equilibration of the ketene-N,O-acetals occurs and rearrangement takes place via the thermodynamically favored *Z*-isomer **28 · 3**. If the reaction is carried out under conditions of kinetic control (by adding the alcohol slowly to a refluxing solution of the ynamine in xylene), rearrangement via the *E*-ketene-N,O-acetal **28 · 2** is observed. Kinetic selectivity for the *E*-isomer arises from attack of the alcohol on the keteniminium intermediate (**28 · 1**) from the least congested direction.

R^1	R^2	R^3	R^4	Ratio of 28·4/28·5 (Yield) Catalyzed by $BF_3 \cdot Et_2O$, 25°C	Slow addition of alcohol, 140°C
CH_3	H	H	H	1:20 (44%)	2:1 (62%)
H	CH_3	H	H	1:5 (37%)	2.5:1 (74%)
CH_3	H	CH_3	H	1:10 (50%)	10:1 (56%)
CH_3	H	H	CH_3	1:3 (19%)	4:1 (38%)
Ph	H	H	H	1:10 (60%)	2:1 (61%)

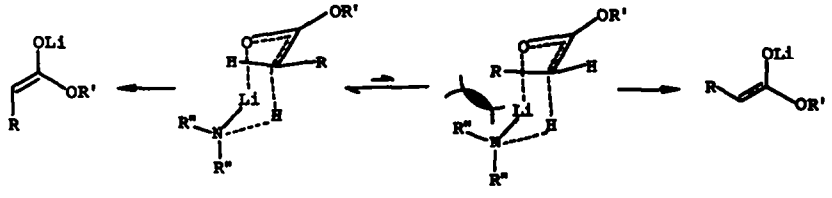


Scheme 28.

Enolization of allylic esters may also be stereocontrolled, with appropriate choice of substrate and deprotonation conditions.[112] Wilson and Fräter have taken advantage of the *E*-enolate selectivity exhibited by senecioc esters on deprotonation with hindered lithium amides for syntheses of botryodiplodin[117] and shyobunone[118] (as shown below).

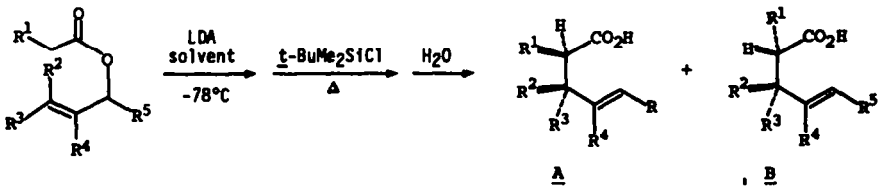


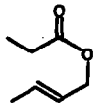
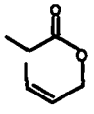
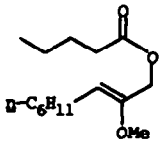
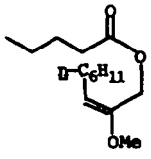
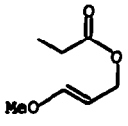
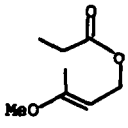
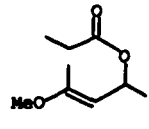
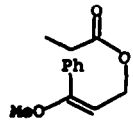
The most versatile method for controlling the stereochemistry of the ester enolate Claisen rearrangement originated with Ireland,[112,119] who showed that either enolate isomer of a propionate ester can be generated selectively, depending on the choice of reaction solvent. In THF alone at −78°C,



association of a bulkyl lithium dialkylamide with the ester substrate in the transition state, suggested to resemble the structures above,[112] leads to formation of the *Z*-enolate predominantly. In 23% HMPA/THF, intramolecular coordination is less important, the ester oxygen becomes the more sterically demanding one, and the *E*-enolate is favored. After silylation and rearrangement, the diastereomeric products are obtained with very good selectivity, as Table 10 reveals.

Table 10. Ester enolate Claisen rearrangement



Entry	Substrate	Solvent	Ratio, A/B	Yield (%)
1[a]		THF	87:13	79
		23% HMPA/THF	19:81	73
2[a]		THF	11:89	75
		23% HMPA/THF	86:14	75
3[a]		THF	88:12	68
		23% HMPA/THF	20:80	57
4[a]		THF	21:79	59
		23% HMPA/THF	85:15	69
5[b]		THF	18:82	80
		23% HMPA/THF	80:20	75
6[b]		THF	17:83	76
		23% HMPA/THF	77:23	80
7[b]		THF	30:70	60
		23% HMPA/THF	78:22	59
8[b]		THF	53:47	67
		23% HMPA/THF	52:48	72

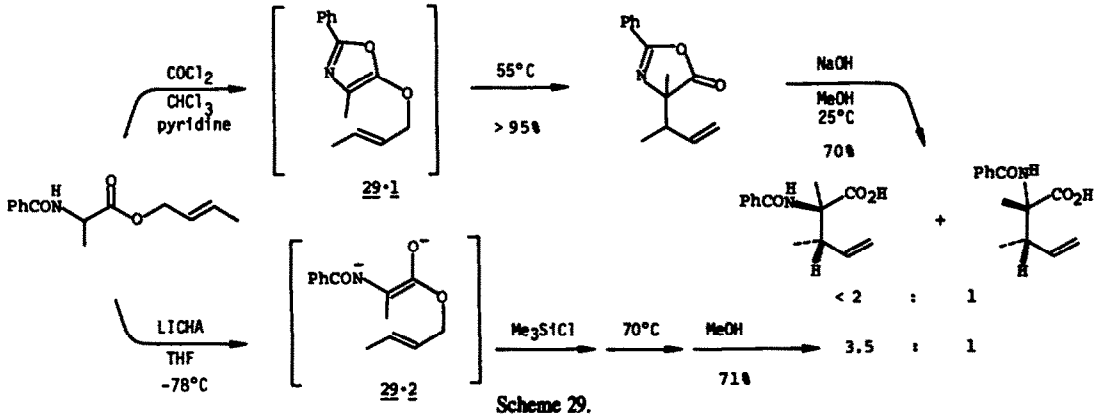
[a]Ref. 112.

[b]Ref. 119.

Entries 5–8 are particularly interesting because they demonstrate an alternative route to compounds having the α-alkyl-β-hydroxy (aldol) substitution pattern.[119] This route has the advantages of affording either isomer selectively, even when there is a β-alkyl substituent. The cinnamyl-type esters (Entry 8), however, rearrange essentially non-selectively, reflecting appreciable reaction via a boat-like transition state.[119]

Methyl santolinate (Scheme 26) has also been synthesized stereoselectively (8:1 ratio, 53% yield) from *E*-5-methyl-2,4-hexadienyl propanoate by the ester enolate Claisen procedure.[120]

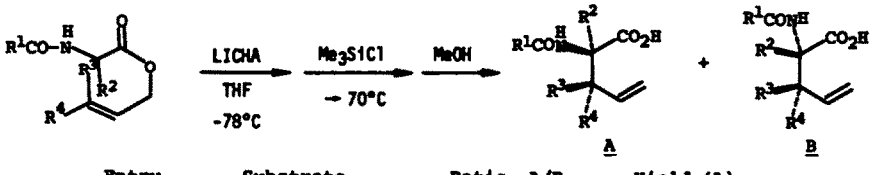
A number of Claisen rearrangements of esters which are α-substituted with heteroatom groups have been reported,[121,122] but only the phosgene-induced rearrangements of benzoylalanine[122] allylic esters have been suggested to occur stereoselectively. Since this latter reaction proceeds via an oxazole (e.g. **29** · **1**), the double bond geometry is obviously fixed; however, the rearrangement of the crotyl ester affords at best a 2:1 mixture of diastereomers[123] (Scheme 29), indicating that part of the reaction involves a boatlike transition state conformation. This rearrangement has been reported to be stereospecific for the geranyl esters[122] on the basis of ^{1}H NMR analysis of the product.



Scheme 29.

We have studied the rearrangement of these derivatives by the ester enolate procedure, via the dianions **29** · **2**, and find that this process is more stereoselective (as illustrated in Scheme 29 and Table 11).[123] The stereoselectivity of the reaction can be improved by carrying out the deprotonation in the

Table 11. α-Amidoester Claisen rearrangements

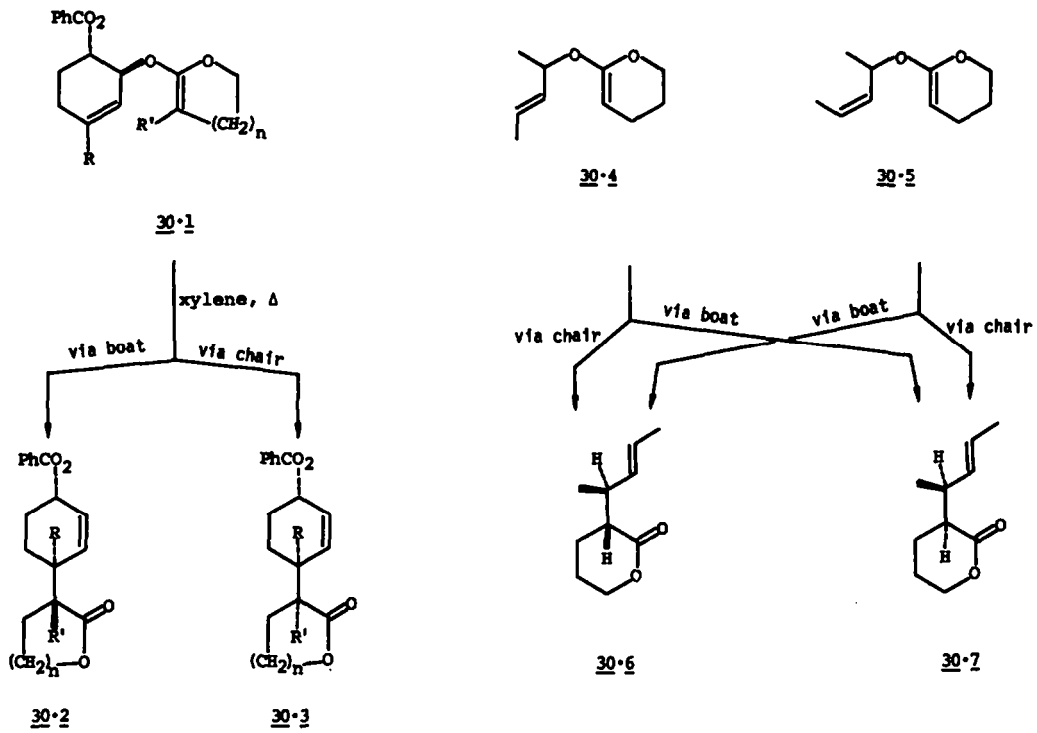


Entry	Substrate	Ratio, A/B	Yield (%)
1	t-BocN	3:1 5:1[a]	76 95[a]
2	t-BocN	3:1	60
3	PhCON	3.5:1	71
4	t-BocN	--	79

[a]Deprotonation carried out in the presence of $MgCl_2$

presence of chelating cations (Entry 2), but it appears to be relatively insensitive to solvent composition. The *E* stereochemistry of the enolates was inferred by converting the products from rearrangement of *cis*- and *trans*-crotyl *t*-Boc-gylcinate to *t*-Boc-isoleucine and *-allo*-isoleucine, respectively, by hydrogenation.

In spite of the high selectivity for chair-like transition states in the Claisen rearrangement of acyclic molecules (except see Entry 8, Table 10), in the face of geometric or steric constraints the reaction can proceed partly or exclusively through a boat-like transition state geometry.[102,124,125] These constraints are usually encountered in substrates in which one or the other double bond is part of a ring, as in the oxazole example illustrated in Scheme 29. Lythgoe has reported a number of cases with cyclohexenol derivatives, involving cyclic enol ethers of fixed geometry, in which the rearrangement proceeds exclusively via the boat (Scheme 30; Table 12).[125]



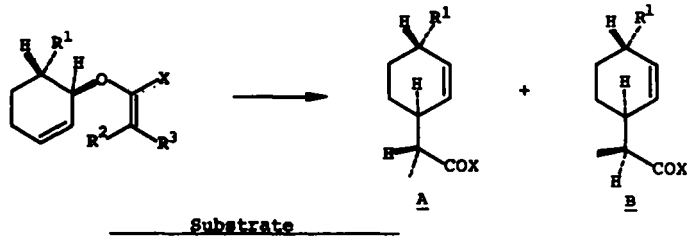
Scheme 30.

Table 12. Chair/boat selectivity

Entry	Substrate	Chair/Boat	Yield (%)
1	30·1 (R = Me, R' = H, n = 1)	0:100	64
2	30·1 (R = R' = H, n = 2)	0:100	80
3	30·1 (R = Me, R' = H, n = 2)	0:100	84
4	30·1 (R = H, R' = Me, n = 2)	63:37	75
5	30·1 (R = R' = Me, n = 2)	65:35	77
6	30·4	88:12	48
7	30·5	70:30	--

We have studied the ester enolate, amide acetal, and ynamine Claisen rearrangement of 2-cyclohexenol itself, and find that the preference for chair- or boat-like transition state conformations depends on the geometry of the enol derivative and the heteroatom substituent[126] (Table 13). Intermediates which

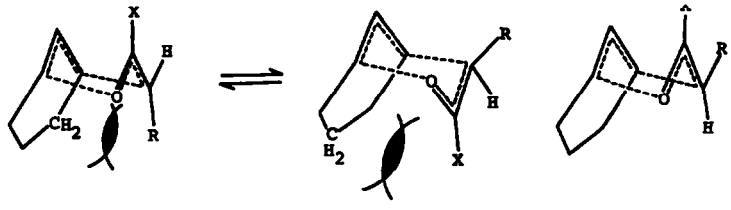
Table 13. Claisen rearrangement of 2-cyclohexanol derivatives



	Substrate					
Entry	X	R^1	R^2	R^3	Ratio, A/B	Yield (%)
1[a]	NEt_2	H	H	CH_3	90:10	62
2[b]	NEt_2	H	CH_3	H	50:50	36
3[c]	$OSiMe_2$t-Bu	H	H	CH_3	75:25	36
4[d]	$OSiMe_2$t-Bu	H	CH_3	H	85:15	47
5[a]	NEt_2	CH_3	H	CH_3	85:15	36
6[c]	$OSiMe_2$t-Bu	CH_3	H	CH_3	57:43	30
7[d]	$OSiMe_2$t-Bu	CH_3	CH_3	H	80:20	41

[a] Cyclohexenol + ynamine, xylene, Δ.
[b] Cyclohexanol + 1-ethoxy-1-diethylaminopropene, xylene, Δ.
[c] 1. Ester + LDA, 23% HMPA/THF, −78°C; 2. Me_3SiCl; 3. Δ.
[d] 1. Ester + LDA, THF, −78°C; 2. Me_3SiCl; 3. Δ.

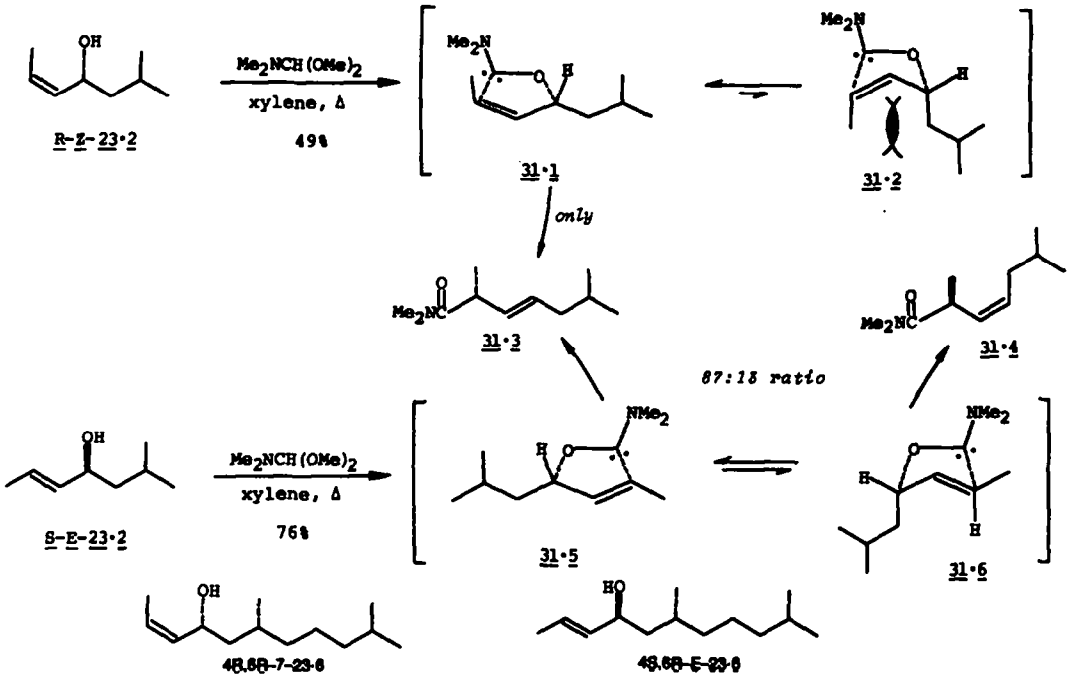
have a vinyl hydrogen *cis* to the ether oxygen (R^2 = H) rearrange predominantly via the boat; those having a Me in that position (R^2 = Me) rearrange predominantly via the chair. These results are fully consistent with those of Lythgoe[125] (Table 12, Entries 1–3 and 4,5 respectively), and suggest that both the heteroatom substituent X and vinyl substituent R prefer to be *exo* in the bicyclic transition states depicted below. For substrates in which one is forced into the endo position (Entries 4 and 5, Table 12; Entries 2, 4 and 7, Table 13) the competition favors the chair (R *exo*).



A study by Evans[127] of the oxy-Cope rearrangements of cyclohexenyl derivatives has also unearthed examples in which boat-like transition states contribute to the reaction pathway.[127a]

2. [2,3]-*Sigmatropic rearrangements.* The [2,3]-sigmatropic rearrangements are capable of the same types of stereocontrol as their [3,3]-counterparts: generation of double bonds of specific geometry,[128–135] migration of chirality along a carbon chain,[128,131–133] and (to a lesser extent) internal asymmetric induction.[134,136–138] A high preference for the formation of *trans* olefins has been noted for the rearrangements of allylic amine oxides,[131] sulfoxides,[128,129] sulfonium ylids,[131] and allyloxy carbenes[132] and carbanions,[133,134] although Still has noted[135] some specific exceptions for the latter reaction. The concerted rearrangements proceed suprafacially with respect to the allyl moiety,[128,131–133] and the chirality of the allylic chiral center can be transmitted predictably as in the Claisen rearrangement. Applications of this strategy are found in prostaglandin syntheses (to be discussed in Part II) and in yet another approach to tocopherol[139] (Scheme 31).

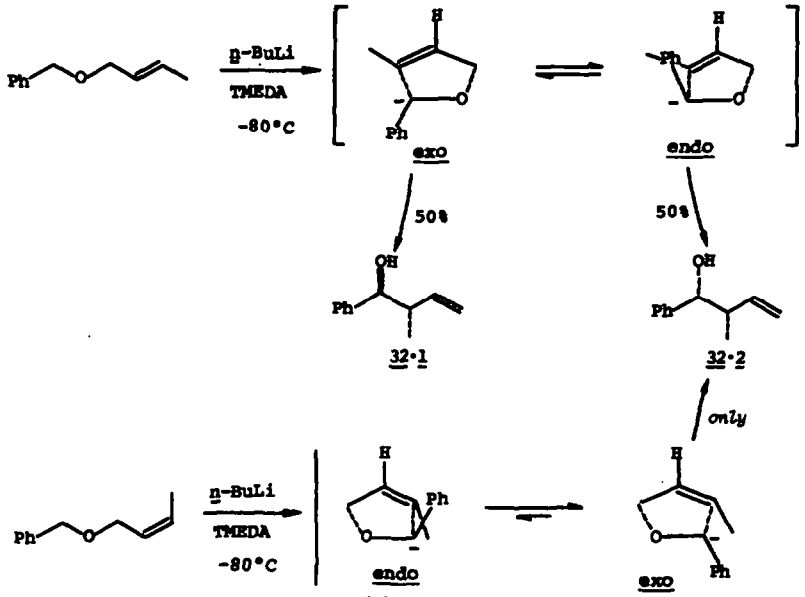
Using the same allylic alcohols discussed in connection with Scheme 23,[107] Chan *et al.* studied the stereochemistry of the [2,3]-sigmatropic rearrangements of the dimethylformamide acetal-derived car-



Scheme 31.

benes. The rearrangement of the *cis*-allylic alcohol *R-Z*-23 · 2 proceeds stereospecifically to give the desired product (31 · 3). The *trans*-allylic alcohol, however, rearranges to an 87:13 mixture of 31 · 3 and 31 · 4. Although the geometry of the double bond in the product is unimportant, the fact that transition state conformation 31 · 5 is only slightly favored over 31 · 6 means that control over the Me configuration is not complete. The higher selectivity of the rearrangement of the *cis*-alcohol is clearly the result of more severe alkyl–alkyl interactions in the disfavored transition state conformation 31 · 2.[139] Similar stereochemical results are seen on rearrangement of the homologs 23 · 6.

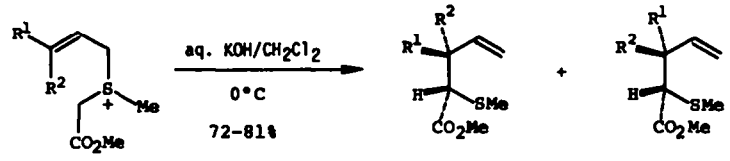
The [2,3]-sigmatropic rearrangements suffer in comparison with their Claisen and Cope counterparts since they in general do not create vicinal chiral centers with internal asymmetric induction. For sulfonium[136] and ammonium[137] ylid and Wittig rearrangements,[133,134] no great selectivity for either the *exo* or the *endo* transition states has been reported except for one case: the Wittig rearrangement of *cis*-crotyl benzyl ether[134] (Scheme 32). This material affords exclusively the *threo* homoallylic alcohol



Scheme 32.

via the *exo* transition state. On the other hand, in the case of a stabilized sulfonium ylid rearrangement, we have observed that the geometry of the olefin has no influence on the selectivity[138] (Scheme 33).

The [2,3]-rearrangements do, however, offer the opportunity for another center of chirality in the substrate to control the new asymmetric centers. This phenomenon, which has been labeled "self-immolative asymmetric synthesis",[140] has been observed in the rearrangements of optically active sulfoxides,[141] amine oxides,[140] and sulfonium ylids.[142] In some instances the asymmetric induction is nearly quantitative. This strategy has not yet been employed in natural product synthesis, however.

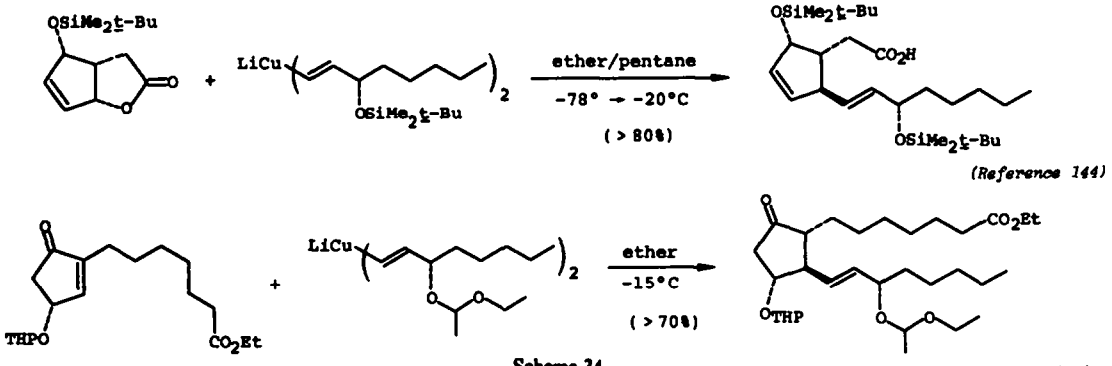


Scheme 33.

PART II. SYNTHETIC TARGETS

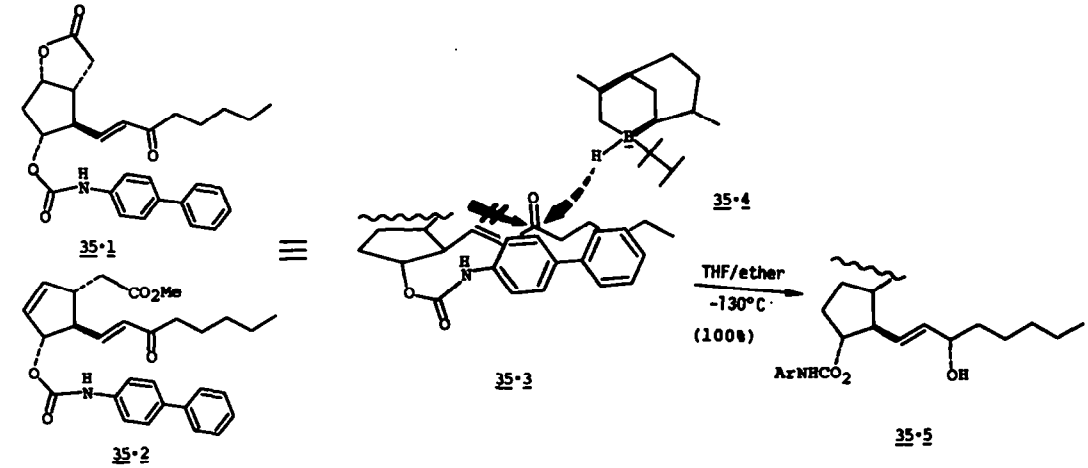
(A) *Controlling* C-15 *in the prostaglandins*

The tremendous interest in prostaglandin synthesis[143] and the challenge of the remote chiral center at C-15 have inspired many elegant examples of acyclic stereocontrol. While early syntheses relied on the coupling of optically active fragments to control the configuration at C-15, as illustrated in Scheme 34 by examples from Corey's[144] and Sih's[145] laboratories, a number of routes have been developed which involve relative asymmetric induction.



Scheme 34.

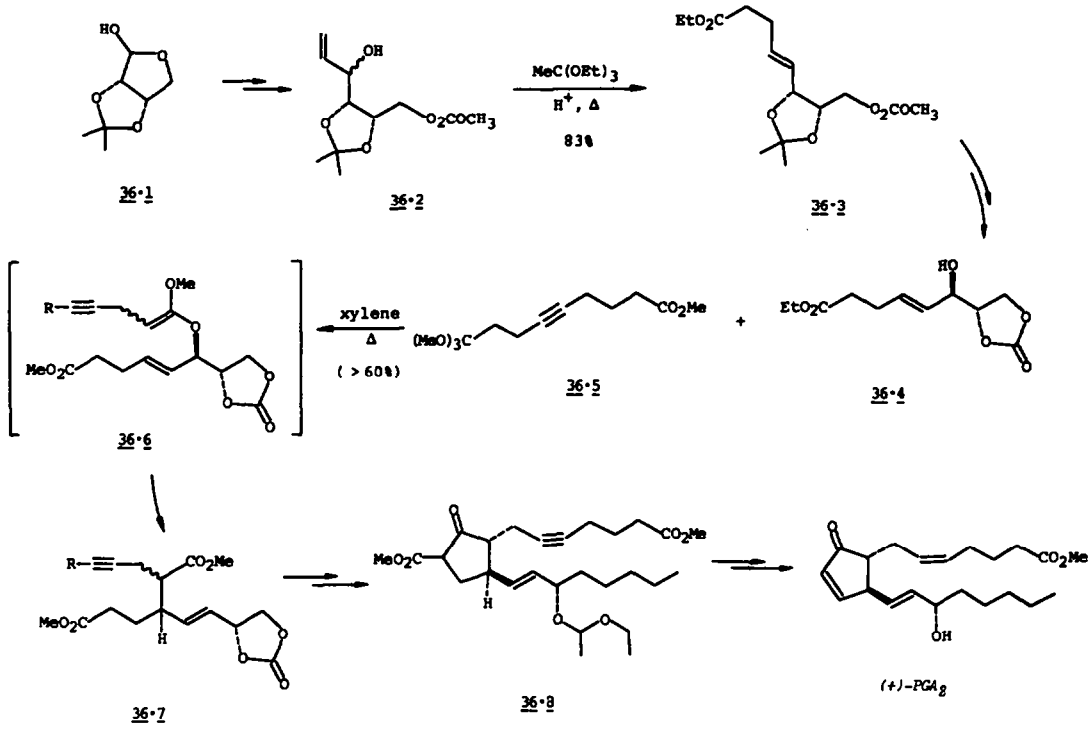
In an extensive and inspired investigation,[146] Corey devised a method for the stereoselective reduction of a C-15 ketone derivative which relies on the use of the 4-phenylphenyl carbamate moiety as a protecting group on the C-11 OH (Scheme 35). The van der Waals attraction between this rigid



Scheme 35.

substituent and the enone sidechain favors a conformation (35 · 3) of these two groups which protects the α-face of the ketone from the approach of a bulky reducing reagent.[146] By operating at $-130°$, the desired 15α alcohols 35 · 5 are obtained with greater than 90% selectivity, using the limonene-derived borohydride 35 · 4.

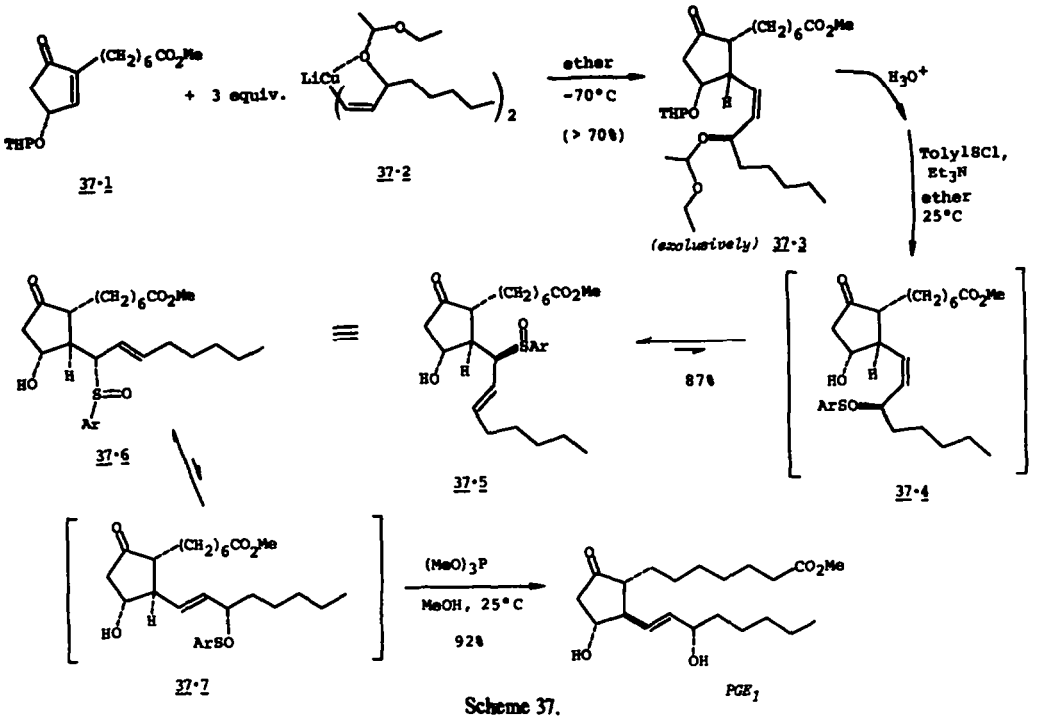
Among the many routes to prostaglandins which Stork has reported are two which entail the stereospecific relation of the C-12 and C-15 chiral centers via sigmatropic rearrangements (Scheme 36[147] and Scheme 37[148]). Starting with L-erythrose acetonide (36 · 1), the *trans*-allylic alcohol 36 · 4 is constructed by vinyl Grignard addition, orthoester Claisen rearrangement, and suitable protection and deprotection steps. The vicinal stereochemical relationship of 36 · 4, which is provided by the starting material, is then converted into a 1,4-relationship by another orthoester Claisen rearrangement. The chiral center α to the carboxyl group of 36 · 7 is not controlled in the orthoester procedure, but is epimerized during subsequent steps to give the thermodynamically favored configuration at C-8.



Scheme 36.

Using a substantially different approach[148] (Scheme 37), Stork was able to capitalize on an observation initially reported by chemists at Syntex;[149] namely, that the coupling of the *Z*-vinyl cuprate 37 · 2 with hydroxycyclopentenone 37 · 1 is highly selective for combination of *R**-enone with *R**-cuprate instead of *R** with *S**. This kinetic selection is exclusive when *R*-enone 37 · 1 is treated with an excess of *racemic* cuprate 37 · 2, effecting in essence resolution of the latter component.[148] Addition of the *trans*-cuprate is neither as efficient nor as selective.[149]

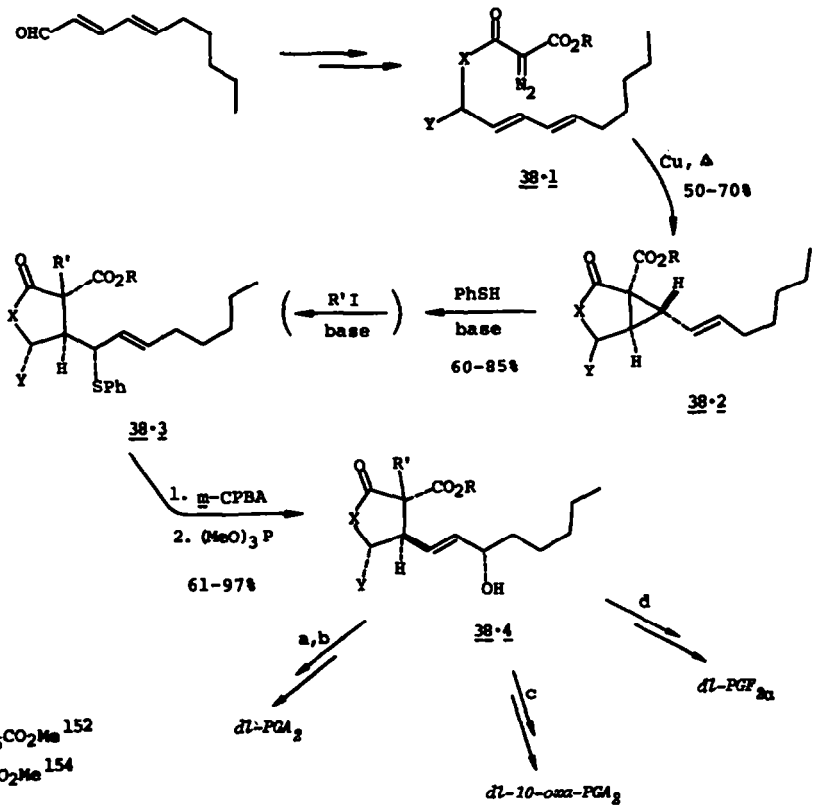
In an earlier collaboration with the Syntex chemists, Stork had devised an elegant method for correcting the stereochemistry of both the double bond and the C-15 center of 37 · 3,[150] taking advantage of both the suprafacial nature of the sulfoxide-sulfenate [2,3]-sigmatropic rearrangement[128] and its specificity for formation of *trans*-double bonds.[129] The 13-*Z*,15*R* sulfenate ester 37 · 4 is a transiently formed intermediate when the corresponding alcohol is treated with tolylsulfenyl chloride and triethylamine, and it rearranges specifically to the 13*S*,15-*E* sulfoxide 37 · 5. This isomer, in turn, is in equilibrium with a small amount of the 13-*E*,15*S* sulfenate 37 · 7, which can be trapped with trimethyl phosphite more rapidly than it reverts to the allylic sulfoxide. The suprafacial specificity of the rearrangement thus couples the configurations of the two stereochemical elements of the allylic system. This isomerization is more specific than simple *cis*⇄*trans* equilibration of a 1,2-disubstituted alkene, because the selectivity is determined by the free energy difference between two rate-determining transition states of the sigmatropic rearrangement (C–S→O ⟶ S–O–C).[128]



37·1 37·2 37·3 37·6 37·5 37·4 37·7 PGE_1

Scheme 37.

Taber[151] and Kondo *et al.*[152-155] have independently reported an alternative method for the stereospecific introduction of 13α sulfoxides in prostanoid systems (Scheme 38). A β-ketoester[151-153] or malonate[154] moiety and a phenylthio group are added in an *anti* manner across a double bond via the cyclopropanes **38 · 2**. The doubly-activated cyclopropanes are cleaved regio- and stereospecifically with

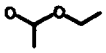


38·1 38·2 38·3 38·4

(a): X = CH_2, Y = H, R' = H[151]

(b): X = CH_2, Y = H, R' = $(CH_2)_6CO_2Me$[152]

(c): X = O, Y = H, R' = $(CH_2)_6CO_2Me$[154]

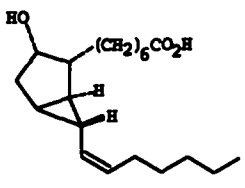
(d): X = CH_2, Y =  , R' = H[153]

dl-PGA_2 dl-10-oxa-PGA_2 dl-$PGF_{2\alpha}$

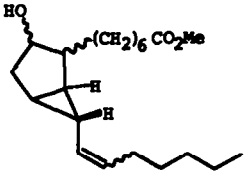
Scheme 38.

benzenethiolate to provide the desired 13α sulfides **38** · **3**. Either before [151,153] or after[152,154] introduction of the remaining sidechains, the sulfur is oxidized and the sulfoxide-sulfenate rearrangement is employed to introduce the 15α-OH specifically. Although the intramolecular carbene addition of **38** · **1**(d) proceeds with only modest relative asymmetric induction (*exo*(α)/*endo*(β) = 2:1), conditions were discovered under which only the desired isomer reacts with benzenthiol (triethylamine, 0°C) to form the adduct **38** · **3**(d).[153]

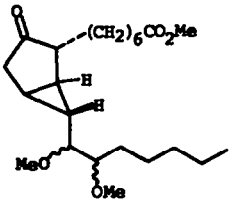
Cyclopropane opening has been used in another approach to prostaglandins involving bicyclo[3.1.0]hexane derivatives[155-157] (Scheme 39). The known preference for solvolysis and ring opening of cyclopropyl carbinyl systems to give *trans*-double bonds[158] could be utilized to relate the configurations of the cyclopropyl carbinyl and homoallylic centers of the starting material and product, respectively, if cleavage of the leaving group were concerted with rearrangement. Following Just's controversial claim[155] of the formation of $PGF_{1\alpha}$ on treatment of the vinyl cyclopropane **39** · **1** with H_2O_2/HCO_2H, he and Upjohn chemists thoroughly explored the solvolysis of stereoisomeric mixtures of the epoxides of **39** · **2**[156] and of each, separate stereoisomer of the dimesylates **39** · **3**.[157] In each case, a 4–10% yield of the desired 15α products (**39** · **4**) are obtained, accompanied by comparable amounts of the 15β-isomers (**39** · **5**). The major products are solvolyzed but unrearranged glycol derivatives, reflecting a non-concerted solvolysis-rearrangement mechanism.



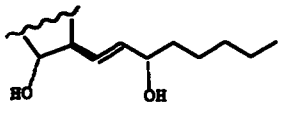
39·**1**



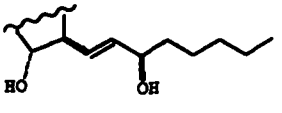
39·**2**



39·**3**



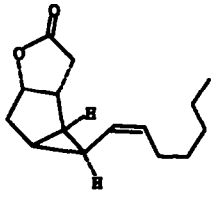
39·**4**



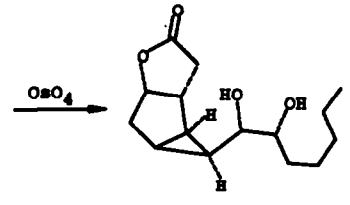
39·**5**

Scheme 39.

On the other hand, using the same approach on a somewhat different system[159] (Scheme 40), Kelly and van Rheenen demonstrated that the orthoester derivative (**40** · **4**) of the glycol obtained from the *cis,cis* vinyl cyclopropane **40** · **1** rearranges to provide a single isomer, with the desired configuration at C-15. This example demonstrates that the cyclopropyl carbinyl→homoallyl isomerization can be utilized

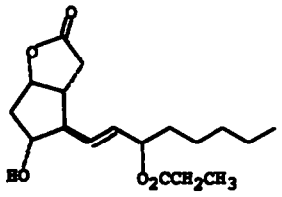


40·**1**

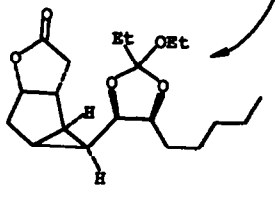


40·**2**

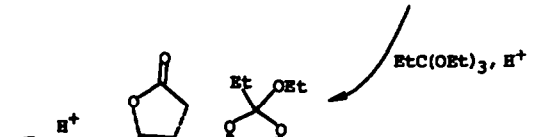
40·**3**



40·**5**



40·**4**

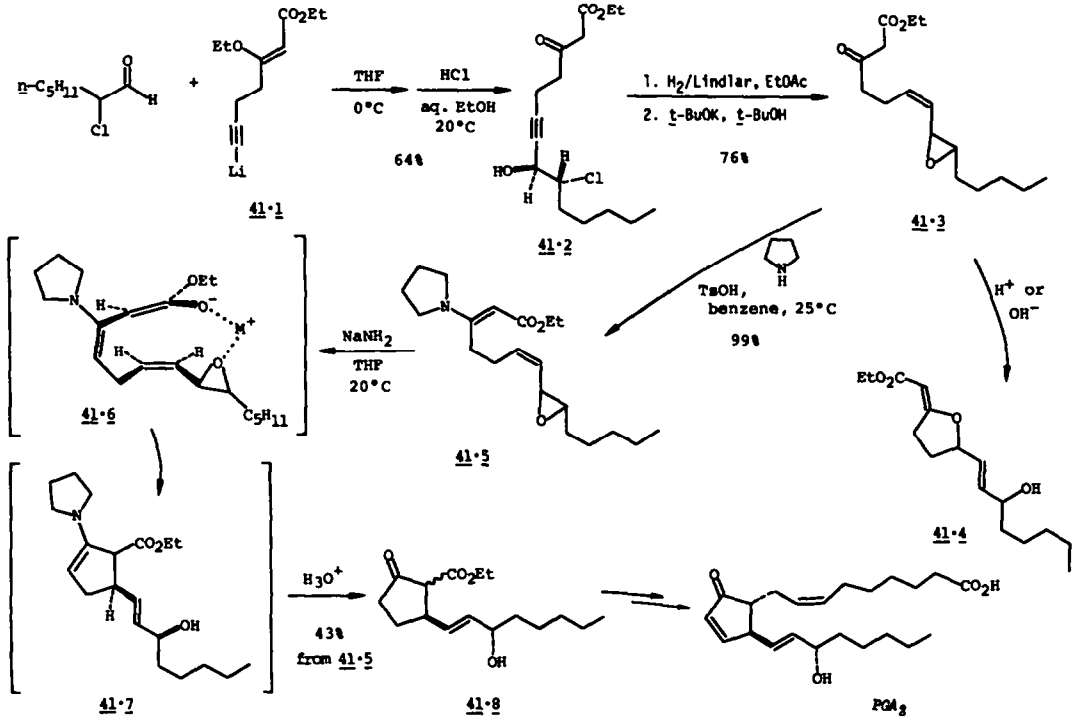


Scheme 40.

under appropriate conditions to convert a 1,2-relationship to a 1,5-relationship, although in the system under scrutiny the glycol configurations are not introduced with relative asymmetric induction.

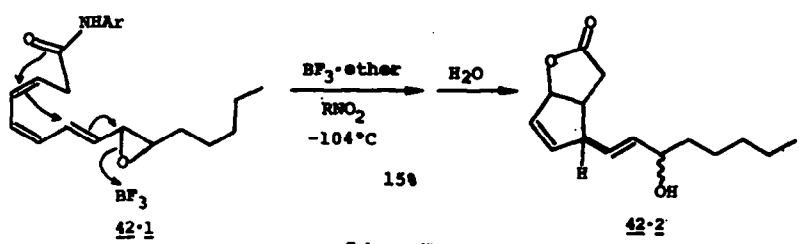
Formation of the 5-membered ring of the prostaglandins with concomitant generation of the correct relationship between C-12 and C-15 has been accomplished by chemists at Roussel–Uclaf,[160] as outlined in Scheme 41. The *Z*-olefin *trans*-epoxide **41 · 3** is prepared stereospecifically by a route which involves addition of lithioacetylide **41 · 1** to 2-chloroheptanal to give the *erythro* chlorohydrin **41 · 2**, in agreement with the models discussed in Part I.[49,53] Either acid- or base-catalyzed cyclization of the β-ketoester **41 · 3** affords predominantly the tetrahydrofuran **41 · 4**, as consideration of the geometric constraints of the orbitals involved would suggest.[161,162] The pyrrolidine enamine **41 · 4** is unreactive; however, treatment of this material with strong base effects the desired cyclization in 43% yield.[160] While the introduction of another sp^2-hybridized carbon in the enolate intermediate would appear to further constrain it, the fact that the enolate must rotate out of conjungation with the enamine during cyclization (**41 · 6**) actually introduces a degree of freedom which allows this step to proceed. In effect, the ring closure becomes an allowed 5-*exo*-trigonal instead of a disallowed 5-*endo*-trigonal process.[161]

The S_N2' opening of the vinyl epoxide proceeds stereospecifically from the *syn* direction, generating the *E*-olefin and the 15α alcohol. Although the factors responsible for *syn* or *anti* selectivity in S_N2' displacements are still the subject of investigation,[163] it is clear from examination of models of **41 · 6** that the cation can simultaneously coordinate the oxygens of the enolate and the epoxide in the transition state for *syn* addition.



Scheme 41.

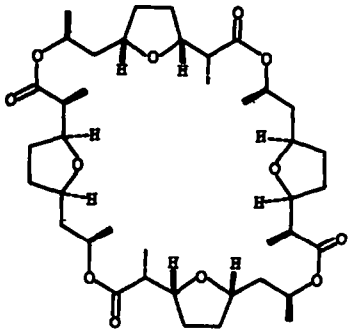
A somewhat similar, cationic cyclization inspired by a biogenetic postulate[164] (Scheme 42) affords equal amounts of the C-15 epimers of **42 · 2**. With the *trans,trans* stereochemistry of the vinyl epoxide moiety in **42 · 1**, stereospecific *syn* S_N2' displacement would have led to the 15β alcohol.



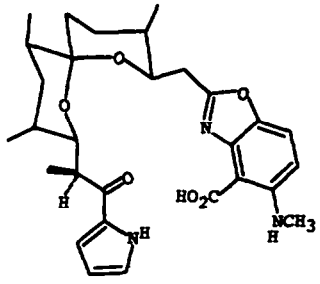
Scheme 42.

(B) *Ionophore antibiotics*

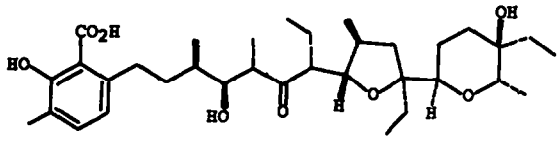
Among the more formidable challenges to be tackled by the synthetic chemist are the ionophore antibiotics, such as the nonactins, antibiotic A-23187,[164a] lasalocid A, and monensin. The multitude of chiral centers and their distribution over an acyclic or tetrahydropyran or -furan framework call for stereocontrol of greater sophistication than in any other class of synthetic targets.



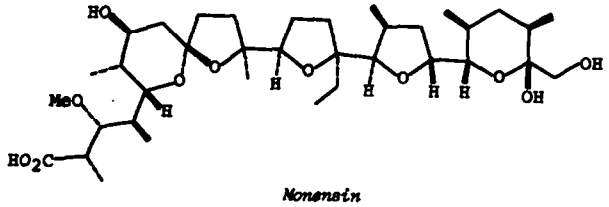
Nonactin



A-23187



Lasalocid A

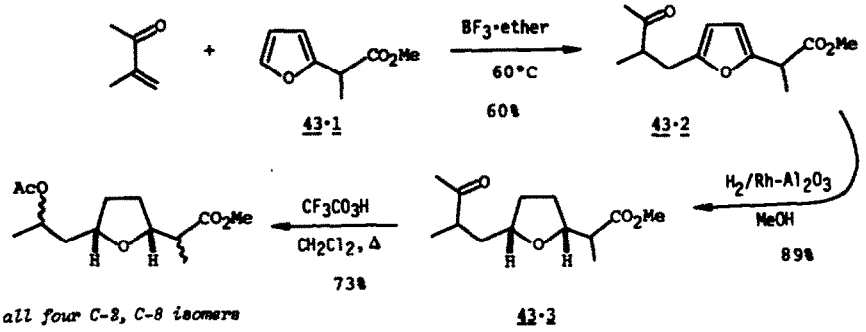


Monensin

1. *Nonactic acid.* The macrotetralide nonactin is a *meso* compound, constructed from alternating enantiomers of nonactic acid. The synthetic precursor to nonactin, the linear tetramer of subunits, has been assembled both with[165,166] and without[167] control of the alternating chirality required. A number of syntheses of the nonactic acid subunit have been reported (Scheme 43), although none is stereospecific.

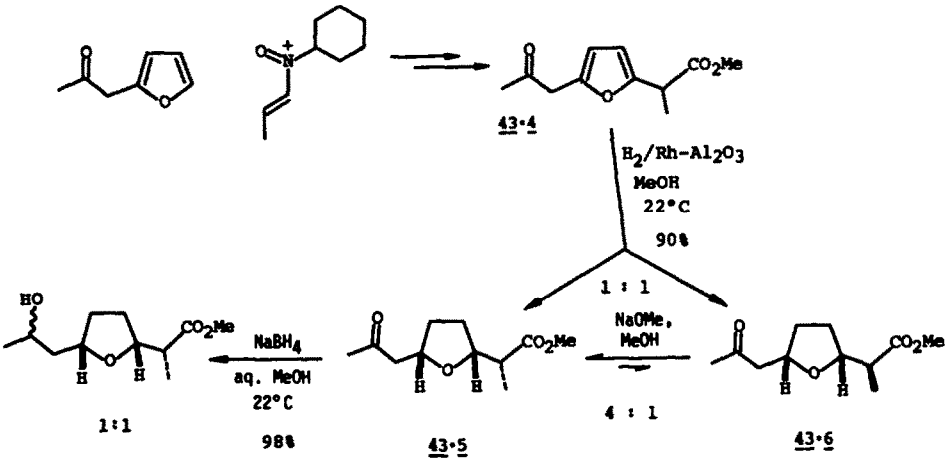
With two exceptions (Route V[168] and Route VI[169]), these syntheses rely on hydrogenation of a 2,5-disubstituted furan to establish the *cis* stereochemistry of the ring. Controlling the configurations of the extracyclic chiral centers (C-2 and C-8) has been a much greater challenge. In the first synthesis of nonactic acid to be reported[170] (Route I), no control over these centers was attempted. Several of the other routes intersect, at various intermediates, and take more or less advantage of two observations for controlling the C-2 and C-8 centers. First, with a *cis* tetrahydrofuran ring, base-catalyzed epimerization favors the natural *threo* relationship between the C-2 and C-3 positions. This equilibration apparently can proceed without ring opening, since the *cis* stereochemistry of the tetrahydrofuran ring is preserved. Although Gerlach reports, without experimental detail, that the equilibration of the 8-keto-derivatives **43 · 5** and **43 · 6** favors the *threo* isomer by a ratio of 80:20,[168] Schmidt *et al.*[165,171] and White[169] were able to enrich methyl nonacetate and the ketoester **43 · 5** over their C-2 epimers by only 60:40. Interestingly,

Route I (Beck and Hensaleit, 1971)[170]

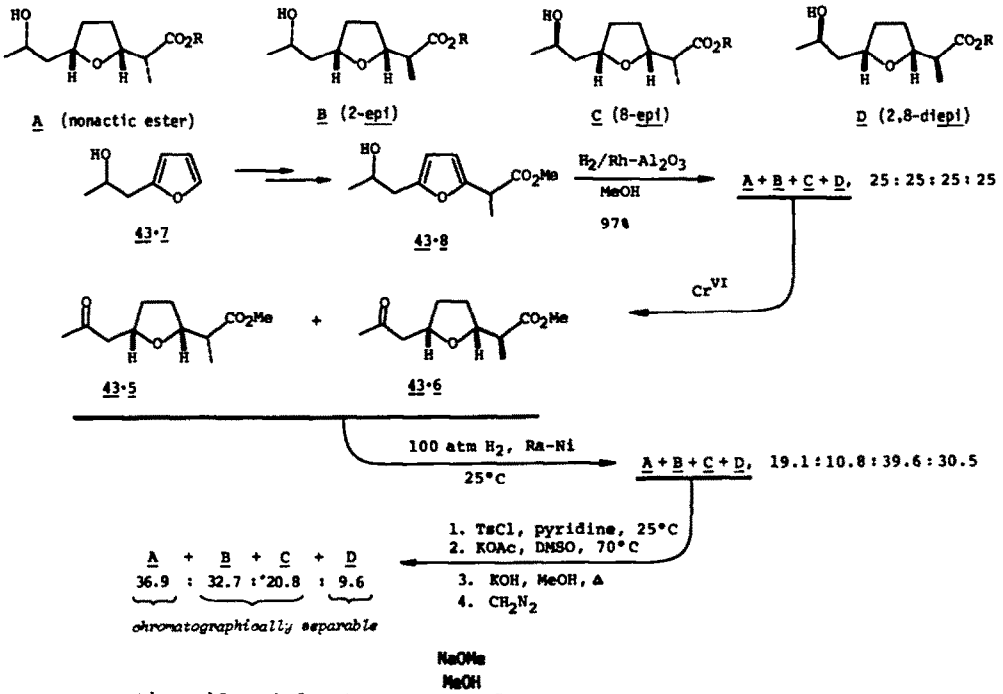


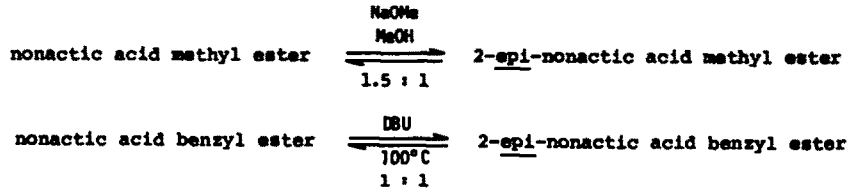
all four C-2, C-8 isomers

Route II (Gerlach and Wetter, 1974)[168]



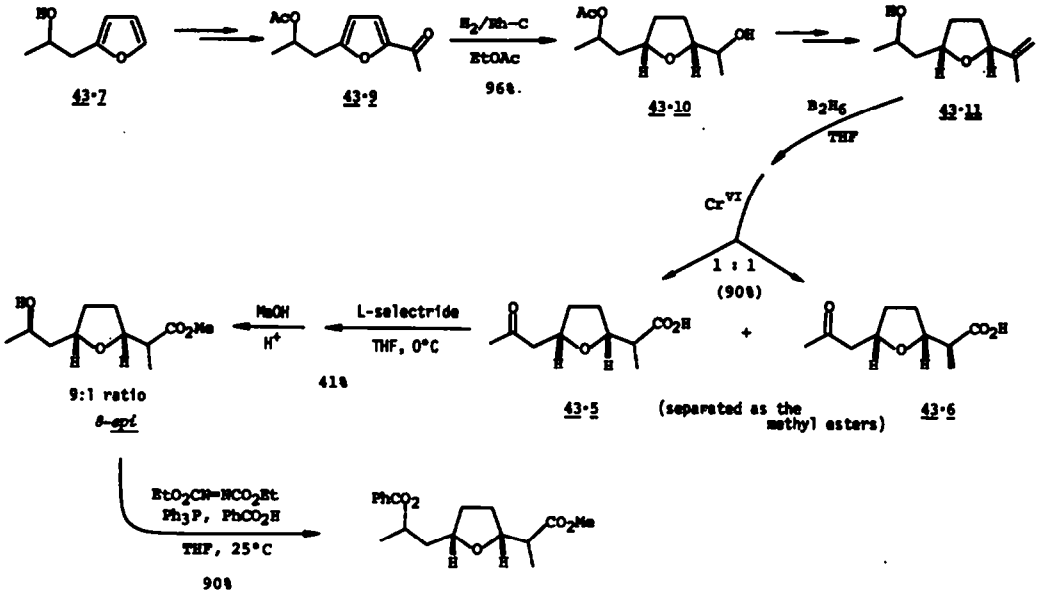
Route III (Schmidt et al., 1975)[165,171,172]



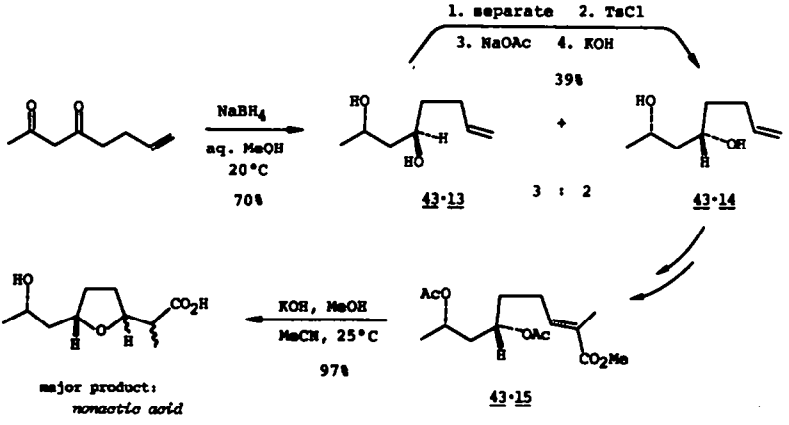


Scheme 43.

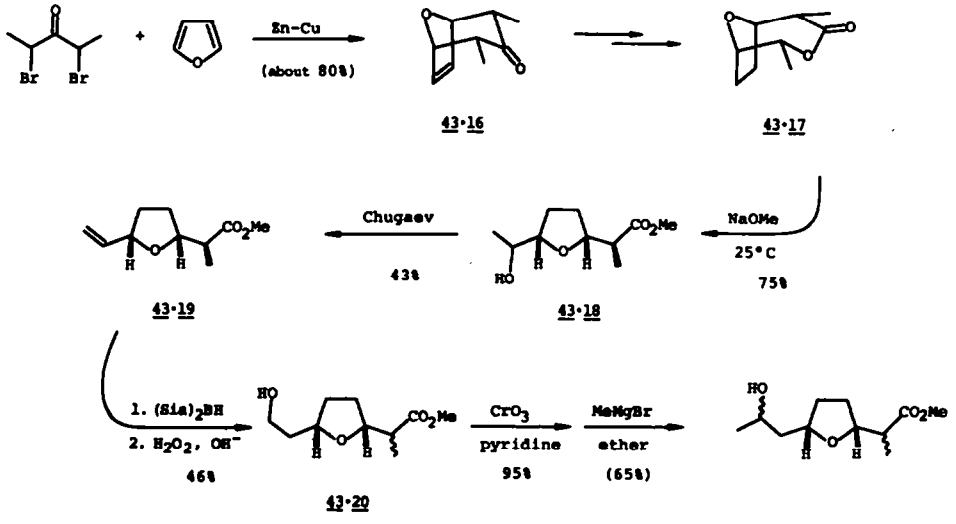
Route IV (Arco, Trammel, and White, 1976)[169]



Route V (Gerlach and Wetter, 1974)[168]



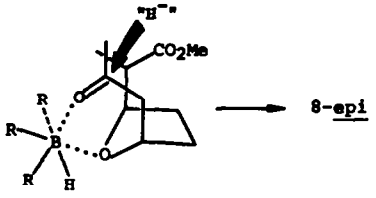
Route VI (Arco, Trammell, and White, 1976)[169]



Scheme 43. (*Contd*)

Gerlach also reports that methanol/potassium hydroxide in acetonitrile equilibrates *both* the C-2 and C-3 centers of methyl nonactate.[168]

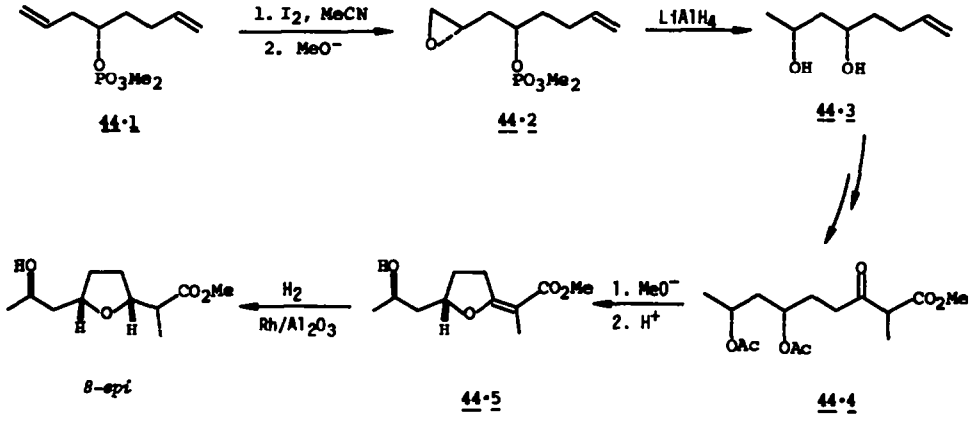
Second, catalytic hydrogenation[165,171] or lithium tri(sec-butyl)-borohydride reduction[168,169] of the 8-keto derivative **43 · 5** affords 8-*epi*-nonactic acid selectively. The natural isomer can then be obtained by inversion of configuration either before[169,171] or during[165] condensation and cyclization to nonactin. White[169] suggests that the 1,3-asymmetric induction observed in the complex borohydride reduction may result from coordination of a borohydride species with both the ketone carbonyl and ether oxygens, as depicted below.



By combining both the selectivity of the ketone hydrogenation and the ability to epimerize the C-2 center, Schmidt *et al.*[165,171,172] developed a scheme for enriching in nonactic acid a mixture of equal amounts of all C-2 and C-8 diastereomers (Route III). This strategy is not applicable to the optically active series (starting with *S*-**43 · 7**) however, methyl nonactate and its 2,8-"diepimer" can be obtained in pure form by chromatography.[165]

An alternative procedure for relating the C-6 and C-8 chiral centers[168] (Route V) involves reduction of the dione **43 · 12** to a 1:1 mixture of diols **43 · 13** and **43 · 14**. The *threo* isomer **43 · 14** is incorporated in a synthesis which generates all four C-2 and C-3 epimers by an intramolecular Michael addition.

We have recently completed a synthesis of nonactic acid[172a] (Scheme 44) in which the "phosphate extension" strategy[32] discussed in Part I is utilized to establish the relative stereochemistry of C-6 and C-8. The phosphate moiety directs the epoxidation of the diene **44 · 1** both stereo- and regiospecifically, providing the *erythro* diol **44 · 3** after reduction. After elaboration of the β-ketoester moiety (**44 · 4**), methanolysis and



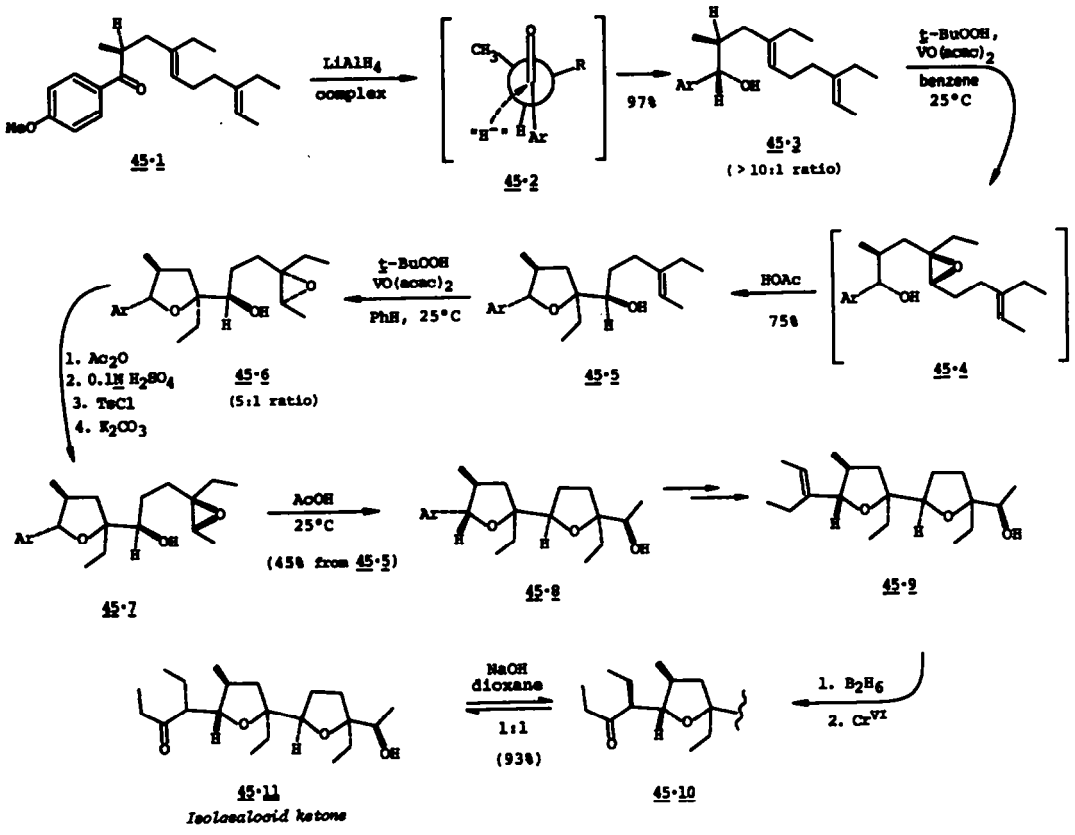
44 · 1 **44 · 2** **44 · 3**

44 · 5 **44 · 4**

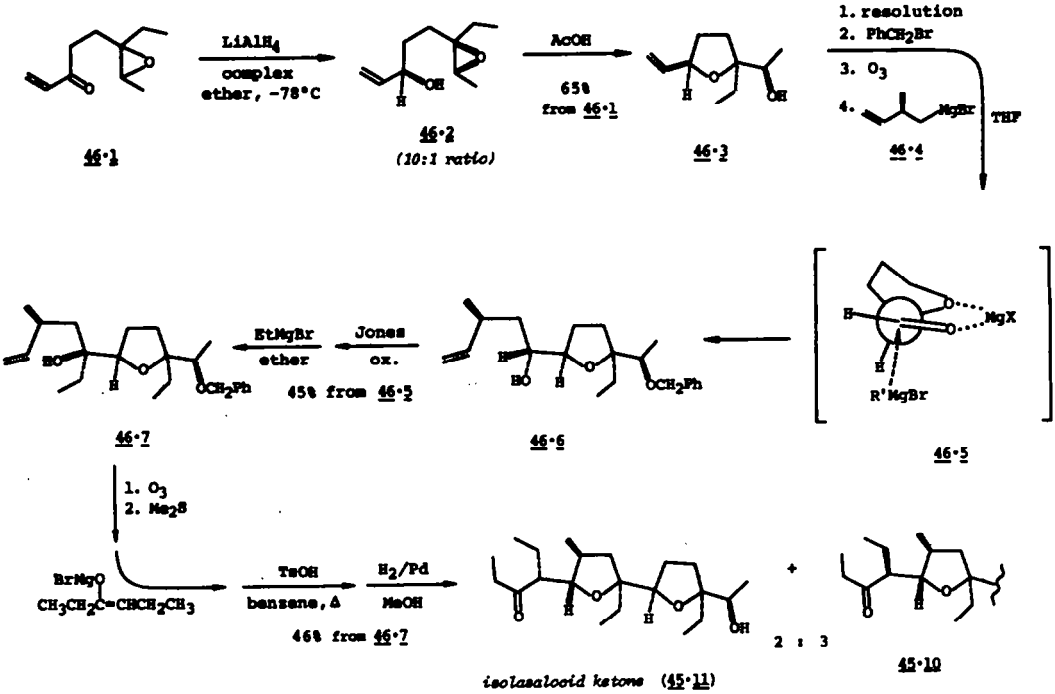
Scheme 44.

acid-catalyzed dehydration lead to the dehydro compound **44 · 5** having the desired *E* geometry.[173] Hydrogenation of this material proceeds from the less hindered direction, *cis* to the hydrogen at C-6, to introduce the remaining chiral centers correctly. The undesired *erythro* relationship between C-6 and C-8 is corrected by the reported inversion procedure.[169]

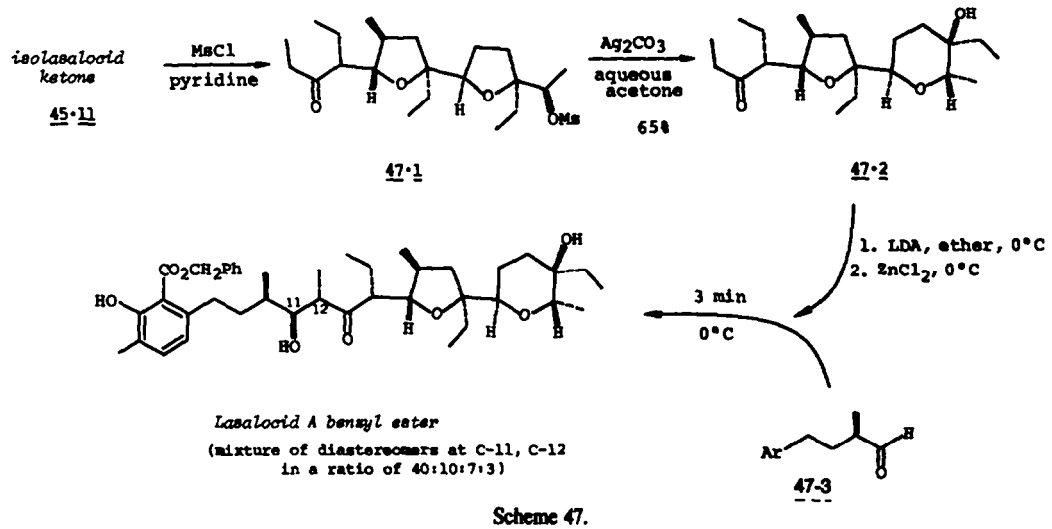
2. *Lasalocid A.* Kishi has developed two routes to isolasalocid ketone (Scheme 45[174] and Scheme 46[175]), and has carried this material on to the ionophore lasalocid A[174] (Scheme 47). The first synthesis of the ketone intermediate employs lithium aluminum hydride · *dl*-2-(*o*-toluidinomethyl)pyrrolidine complex for the highly selective (better than 10:1 ratio) reduction of aryl ketone **45 · 1**, in the sense expected from conformation **45 · 2**. The double bonds are functionalized by epoxidation using *t*-butyl hydroperoxide/$VO(acac)_2$ in benzene at room temperature, relying on the bis-homoallylic OH groups of **45 · 3** and **45 · 5** to control the stereochemistry, as described for model compounds in Part I.[36] Epoxidation of compound **45 · 5** actually affords the wrong diastereomer for conversion to **45 · 8**, and the epoxide must be inverted prior to this cyclization.



Scheme 45.



Scheme 46.



Scheme 47.

The aryl moiety is degraded to the olefin **45 · 9**, which undergoes a stereospecific hydroboration reaction, affording only ketone **45 · 10** after Jones oxidation. Although the relative asymmetric induction in this hydrocarbon step is remarkable, it unfortunately provides the undesired stereoisomer, and isolasalocid ketone (**45 · 11**) itself is obtained only after alkaline epimerization.

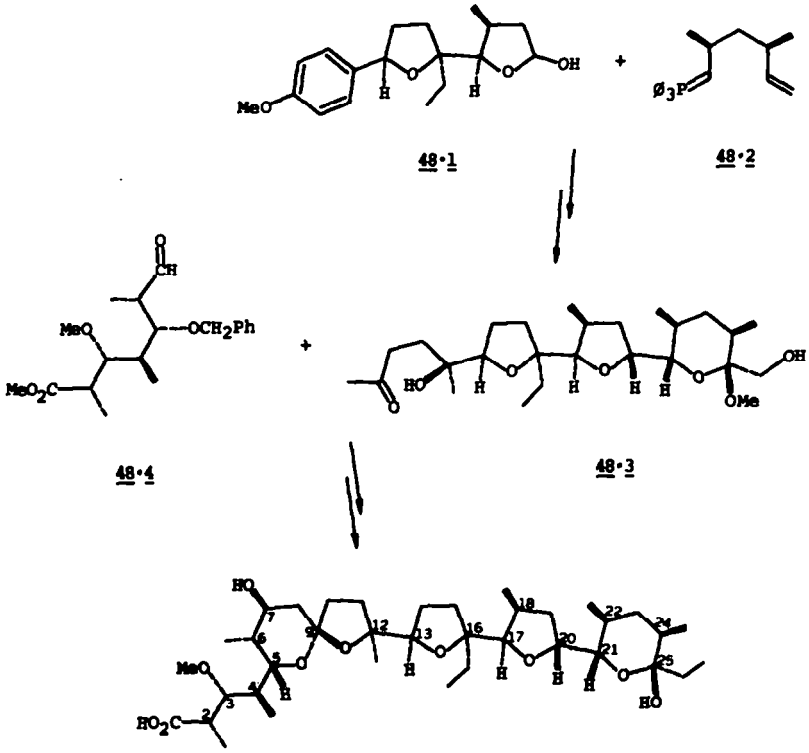
A considerably shorter synthesis of isolasalocid ketone[175] (Scheme 46) employs the alternative strategy of generating epoxy alcohols by selective ketone reduction.[36] As discussed in Part I, this process is stereochemically complementary to the epoxidation reaction, and provides **46 · 2** with 10:1 selectivity without resorting to the epoxide inversion sequence which was required earlier to obtain **45 · 7**. After resolution, protection, and ozonolysis, the addition of resolved Grignard reagent **46 · 4** gives carbinol **46 · 6** specifically. Grignard addition to the 2-acyltetrahydrofuran is highly stereoselective, affording the product predicted by the cyclic model (e.g. **46 · 5**).[175] The carbinol center in **46 · 6** is destroyed by oxidation, but it is reintroduced specifically in **46 · 7** by ethyl Grignard addition to the corresponding ketone. While Grignard reactions of this type are highly stereoselective, the outwardly similar organolithium additions to 4-acyldioxalanes are much less so. For instance, treatment of glyceraldehyde acetonide with 3,3-diethoxy-2-lithiopropane affords **7 · 1** and **7 · 3** in a ratio of only 7:3,[29] a preference contrary to that predicted by the cyclic model.

The remaining carbon atoms and chiral centers of isolasalocid ketone are introduced by an aldol condensation followed by acid-catalyzed cyclization. This dehydration, most likely occurring via Michael addition to the enone, generates the thermodynamically favored *trans* relationship between the two adjacent substituents on the tetrahydrofuran ring. However, both ethyl epimers are obtained and an epimerization-separation procedure (as in the first route) is necessary.

The conversion of isolasalocid ketone to lasalocid A necessitates two transformations[174] (Scheme 47). Solvolytic rearrangement of mesylate **47 · 1** provides the dihydropyran **47 · 2**, along with a small amount of **45 · 11**. Finally, addition of the zinc enolate of **47 · 2** (generated with lithium diisopropylamide and zinc chloride) to optically active aldehyde **47 · 3** furnishes lasalocid A as the major component of a mixture of four compounds (96% yield, with 67% conversion of starting materials). The configurations of the chiral centers introduced by this condensation are as predicted for α-asymmetric induction and for zinc-chelated aldol condensations[70] (Part I). The former is a kinetic selectivity and the latter reputedly a thermodynamic one, raising the same question pointed out in connection with the Reformatsky reactions[85] of Scheme 16. Improved stereoselectivity but poorer conversion were noted on using dimethoxyethane as solvent.

3. *Monensin.* One of the most spectacular achievements in the area of acyclic stereocontrol has been the synthesis of monensin by Kishi *et al.*[176–178] This compound, which contains seventeen chiral centers, was assembled from three subunits as depicted in Scheme 48.

Scheme 49[176] outlines the preparation of the ester component **48 · 4**, which contains carbons 1–7 of the monensin backbone. All of the relative stereochemistry of this compound is established very selectively in the course of two hydroboration reactions. While hydroboration is often employed to hydrate olefins with internal asymmetric induction, few examples of relative asymmetric induction have

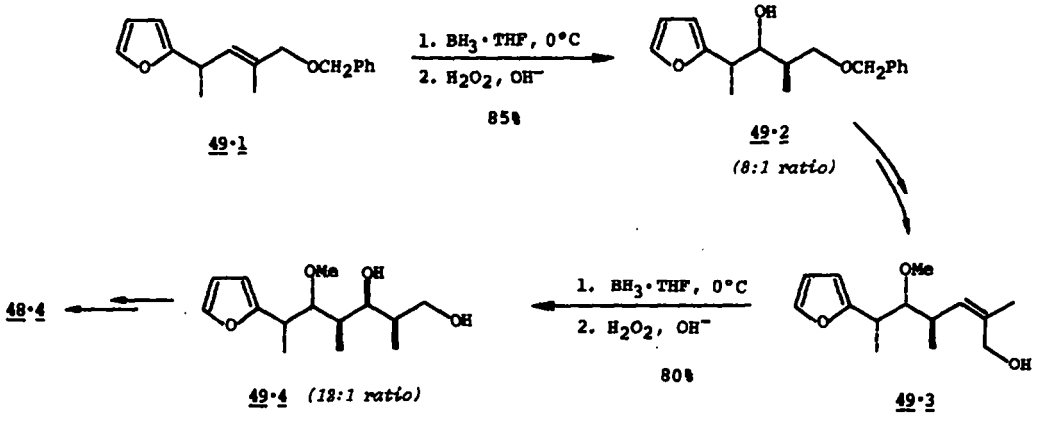


48·1 48·2

48·4 48·3

Monensin

Scheme 48.

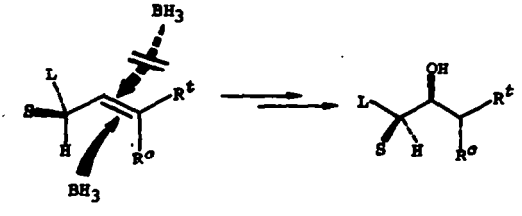


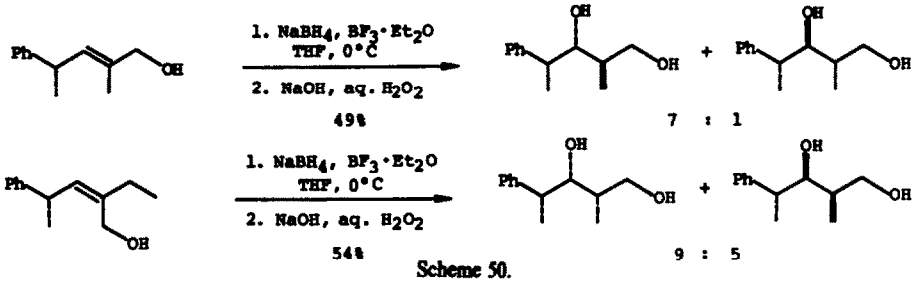
49·1 49·2 (8:1 ratio)

48·4 49·4 (18:1 ratio) 49·3

Scheme 49.

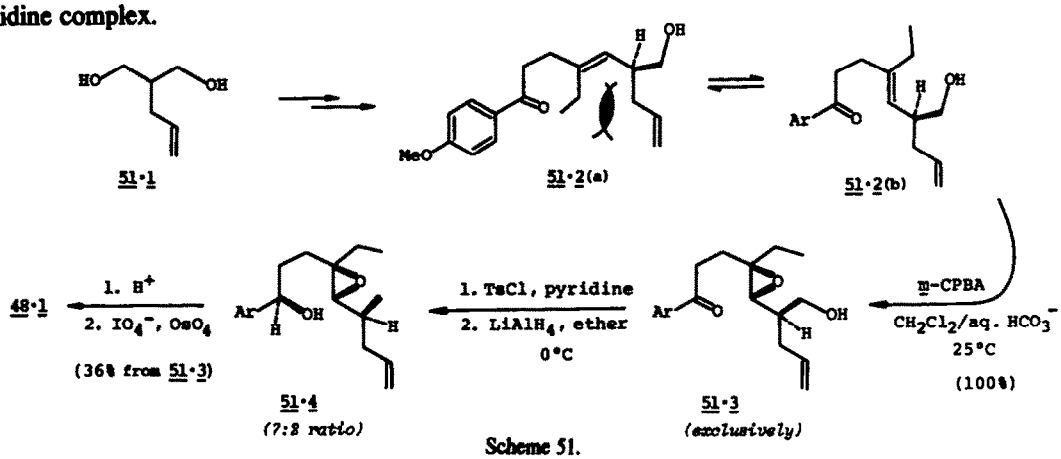
been reported for this reaction in acyclic systems. The stereospecificity is adequately rationalized[176] by the model below, which depicts borane approaching the face of the double bond that is least hindered in the most likely conformation of the starting material. The key element in these systems would appear to be the presence of a *cis* substituent on the double bond (R^c below), in order to favor as strongly as possible the indicated conformation. The scope of this asymmetric induction needs to be explored, however, since some similar substrates exhibit less selectivity[84] (see Scheme 50), while other quite different ones react stereospecifically (e.g. **45** · **9**).[174]





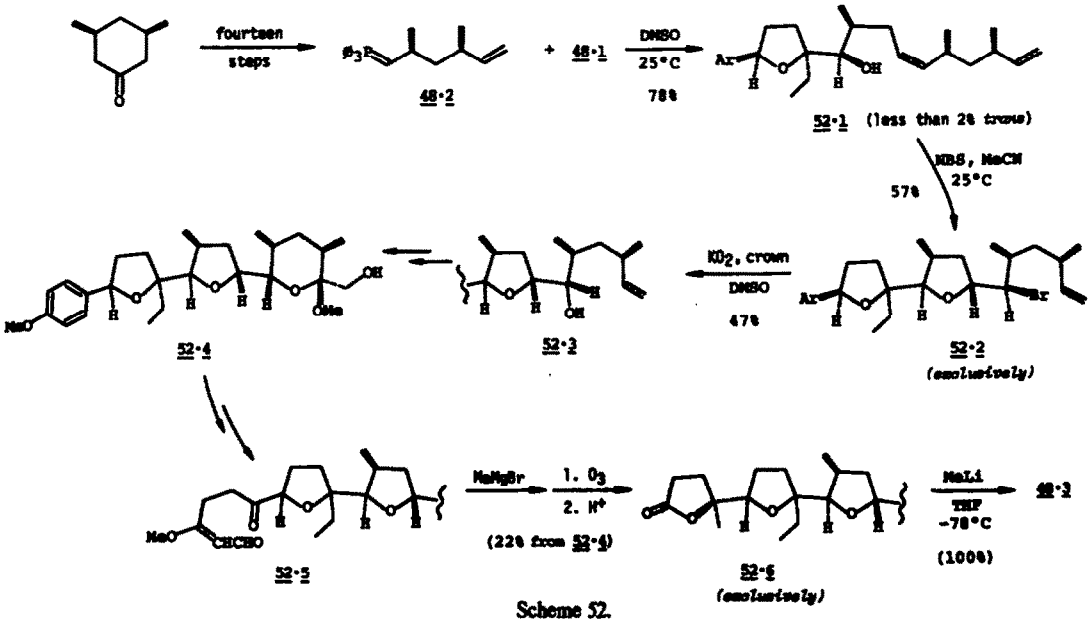
Scheme 50.

In the construction of segment **48 · 1**[177] (Scheme 51), peracid epoxidation of **51 · 2** proceeds with 1,2-asymmetric induction and affords isomer **51 · 3** exclusively. Only one face of the double bond can be accessible to OH-directed epoxidation if steric interference of the allyl and Et substituents is to be avoided (compare **51 · 2**(a) with **51 · 2**(b)).[177] The OH group is removed (via the tosylate) and the ketone is reduced with lithium aluminum hydride, to give a 7:2 ratio of alcohol diastereomers (**51 · 4**). This reduction exhibits the same specificity but lower selectivity than the model reactions described in Part I[36] and in Scheme 46,[175] which employ the lithium aluminum hydride · *dl*-2-(*o*-toluidinomethyl)-pyrrolidine complex.



Scheme 51.

Two more chiral centers are introduced by coupling the optically active lactol **48 · 1** with optically active ylid **48 · 2**[177] (Scheme 52). The relative stereochemistry of **48 · 2** can be traced to the *cis*-3,5-dimethylcyclohexanone starting material. The *cis*-disubstituted double bond of the Wittig product is



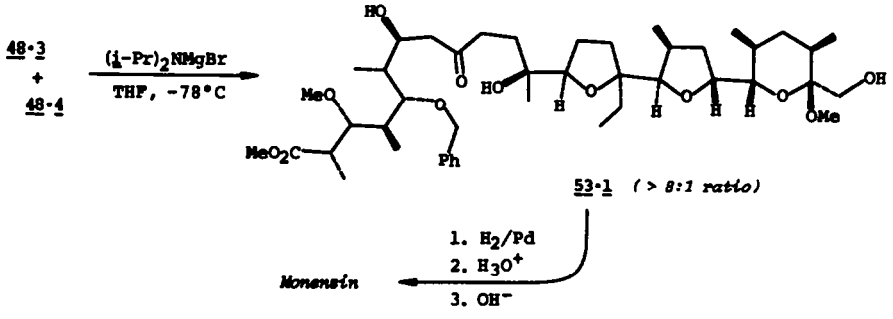
Scheme 52.

stereoselectively functionalized by an oxidative cyclization process, using N-bromosuccinimide in acetonitrile. The stereochemistry of this kinetically controlled process reflects the participation of the OH group in the rate-determining step, since it proceeds so as to avoid the steric interactions which would arise during formation of the alternative isomer (compare **52 · 7** and **52 · 8**).

The hemiketal moiety of monensin exists in its thermodynamically favored configuration.[177] Hence, it presents no stereochemical problem and merely requires appropriate protection (as the methyl ketal) in the course of constructing intermediate **48 · 3**. The remaining chiral center of this intermediate, the tertiary carbinol, arises from a stereospecific Grignard reaction of ketone **52 · 5**. The specificity of this reaction was discussed in connection with the synthesis of isolasalocid ketone[175] (Scheme 46).

52·7 **52·8**

As far as stereochemistry is concerned, only maximization of relative asymmetric induction in the aldol condensation of the two optically active fragments **48 · 3** and **48 · 4** was necessary for completion of the synthesis[178] (Scheme 53), because the spiroketal configuration of monensin is the one which is thermodynamically favored.[179] Even under optimized conditions, employing bromomagnesium diisopropylamide as base, this aldol condensation requires a trade-off between conversion and stereoselectivity, suggesting that retro-aldol equilibration of the bromomagnesium alkoxide product is competitive with the rate of addition, even at low temperature. By conducting the reaction at −78° and carrying it to 23% conversion, a 92% yield (based on unrecovered ketone **48 · 3**) of a better than 8:1 ratio of isomers **53 · 1** can be obtained. Deprotection and dehydration provide the spiroketal of correct configuration,[179] and finally, monensin.

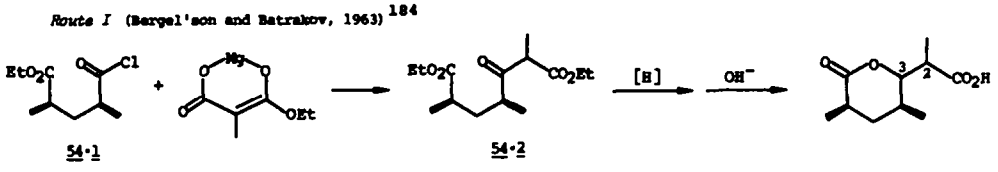


Scheme 53.

(C) *Macrocyclic natural products*

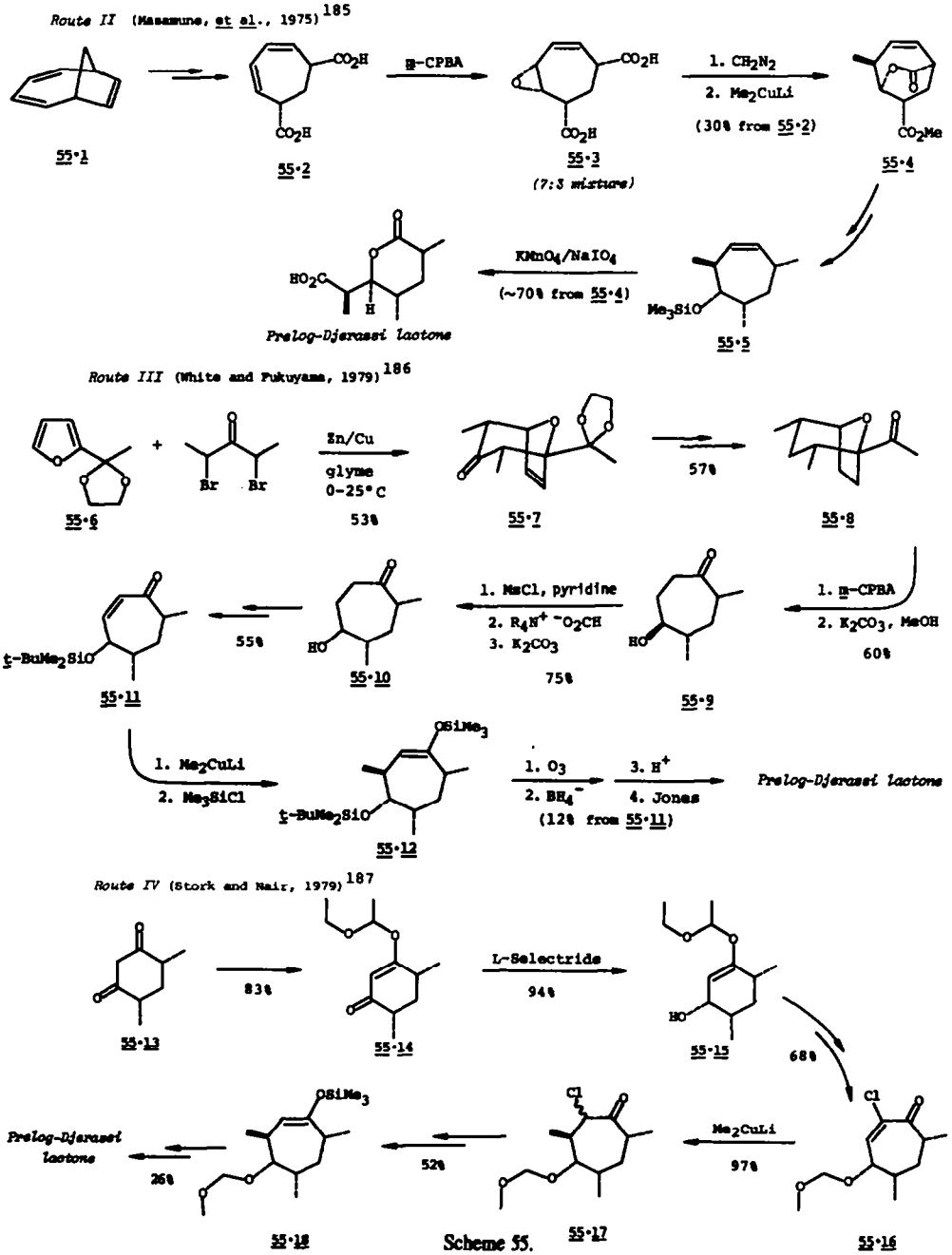
Although the chiral centers of the macrocyclic natural products are contained within a ring system, the majority of approaches to the synthesis of these compounds entail the establishment of the chiral centers on acyclic precursors,[180] hence their relevance to this report. Much of the work in this area is quite recent, and many of the examples presented will concern pertinent model studies or synthetic approaches.

1. *The Prelog–Djerassi lactonic acid.* A degradation product which figured prominently in the structure elucidation of the macrolide antibiotics, the Prelog–Djerassi lactone[181–183] was first synthesized by Bergel'son and Batrakov[184] before the complete three-dimensional structure was known.[183] Their route (outlined in Scheme 54) involved the reduction of β-ketoester **54 · 2**, affording different diastereomeric products depending on the choice of reducing agent. They claimed that reduction with lithium aluminum hydride in ether at −65°, with subsequent hydrolysis and chromatographic purification, affords a 28% yield of racemic Prelog–Djerassi lactone having m.p. 125–126°. The isomer isolated from this reaction was apparently incorrectly identified as the Prelog–Djerassi lactone by IR comparison with an authentic sample (see footnote, Ref. 183*a*). Although all the C-2, C-3 stereoisomers were prepared (by using other reducing agents), it is not possible to evaluate the stereoselectivity of these reductions from the published information.[184]



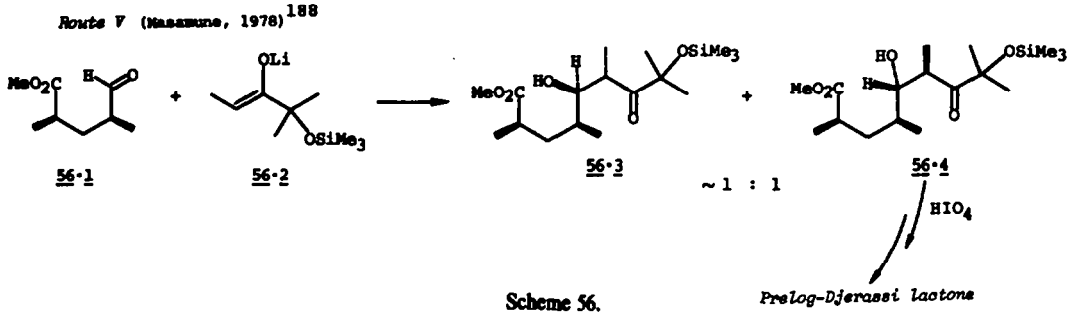
Scheme 54.

In Scheme 55 are depicted three syntheses of the Prelog–Djerassi lactone in which the chiral centers are established on bicyclic and cycloheptane frameworks prior to cleavage and lactonization. In connection with his synthesis of methymycin,[185] Masamune prepared the lactone in a twelve-step sequence (Route II) starting with bicyclo[4.2.1]nona-2,4,7-triene, obtaining racemic material (mp 119–120°). More recently, White[186] and Stork[187] have completed fully stereocontrolled syntheses which also entail the construction and cleavage of cycloheptene intermediates.[187a] They report melting points for racemic material of 110–113° and 114–115°, respectively.



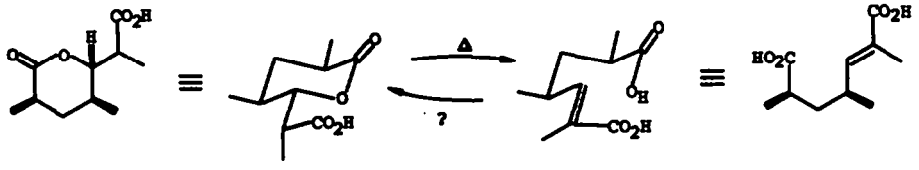
Scheme 55.

Masamune has referred to a different approach[188] to this compound which relies on an aldol condensation of the type developed by Heathcock[68] for the synthesis of *erythro*-β-hydroxy-α-methylcarboxylic acids (Scheme 56). The aldehyde component (**56** · 1) is prepared from *meso*-2,4-dimethylglutaric anhydride.[189] Interestingly, and quite fortunately from the synthetic standpoint, the relative asymmetric induction observed on condensation of this material with the enolate **56** · 2 is minimal, with the result that nearly equal amounts of the diastereomeric *erythro* products are obtained. The models for α-asymmetric induction, as well as similar condensations observed by Heathcock's group[68] (Scheme 18), suggest that the undesired isomer should predominate.

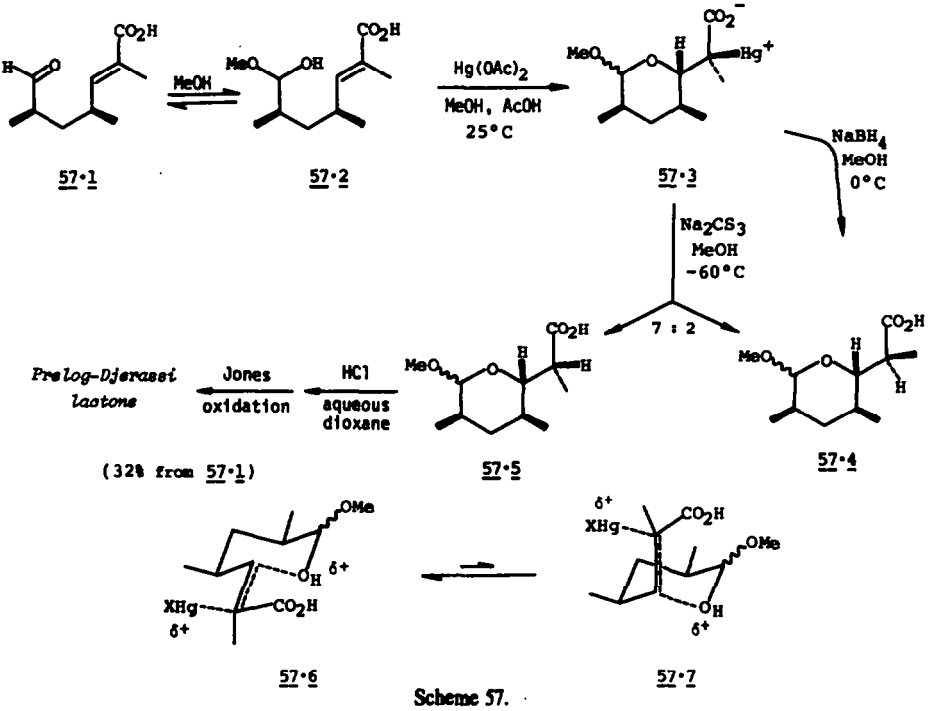


Scheme 56.

We have approached the problem of controlling the stereochemistry of the Prelog–Djerassi lactone from a different point of view,[190] desiring to reverse (in essence) the elimination reaction[182] which leads to an olefinic diacid depicted below. This diacid is readily obtained from the aldehyde ester **56** · 1 by a Wittig reaction, but it exhibits no tendency to cyclize under a variety of conditions.



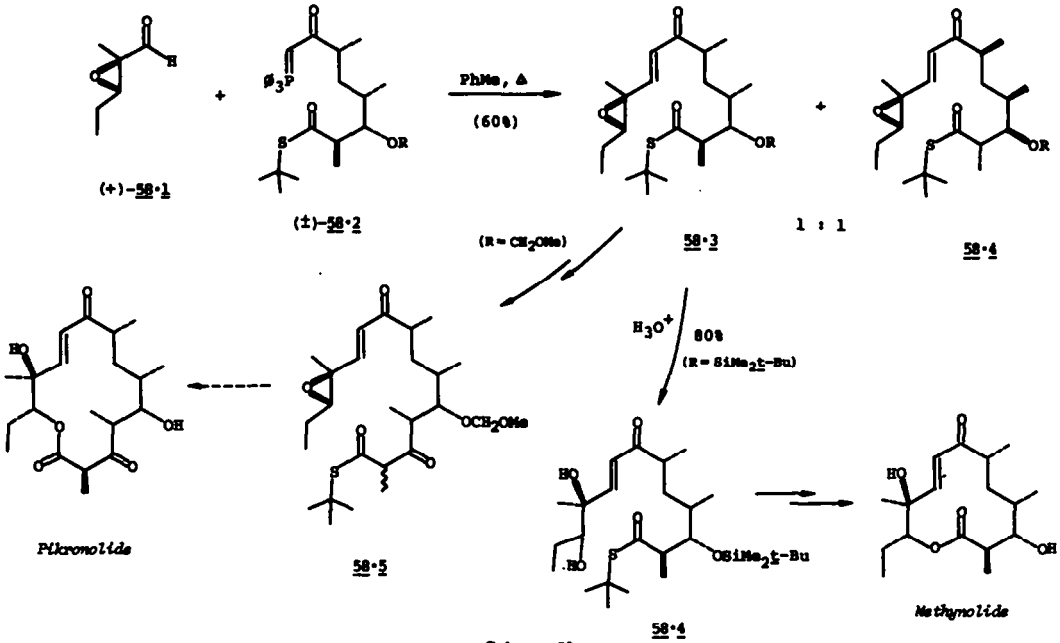
On the other hand, the aldehyde acid **57** · 1 cyclizes as its methyl hemiacetal in the presence of mercuric ion, permitting stereocontrol at the C-2 and C-3 carbons by an oxidative cyclization process (Scheme 57). Cyclization by attack on the other face of the double bond is strongly disfavored since it would lead to severe steric interactions in the transition state (cf **57** · 6 with **57** · 7).[33]



Scheme 57.

Demercuration using sodium borohydride in alkaline methanol produces almost exclusively the inverted isomer **57 · 4**, which on hydrolysis and oxidation is converted to 2-*epi*-Prelog–Djerassi lactone. On the other hand, the desired isomer (**57 · 5**) can be obtained as the predominant product on cleavage with sodium trithiocarbonate in methanol at $-60°$. After hydrolysis and oxidation, the Prelog–Djerassi lactone (m.p. 116–117°) and its C-2 epimer are obtained in a ratio of up to 7:2. Since the aldehyde acid **57 · 1** is available from *meso*-2,4-dimethylglutaric anhydride in 55% yield, this synthesis is quite efficient.

2. *Macrolide antibiotics.* In the first synthesis of a member of the propionate-derived macrolide antibiotics[185] (Scheme 58), Masamune coupled the (+)-aldehyde **58 · 1** with racemic Wittig reagent **58 · 2** (R = $SiMe_2t$-Bu) derived from the Prelog–Djerassi lactone and obtained a diastereomeric mixture of epoxy enones. After hydration of the correct diastereomer (**38 · 3**, R = $SiMe_2t$-Bu), the glycol was lactonized and deprotected to afford the aglycone methynolide.[187a] Complete stereocontrol could of course be accomplished by coupling resolved fragments. The epoxy enone **58 · 3** (R = CH_2OCH_3) is also being used in a synthesis of pikronolide,[188] the homologous 14-membered aglycone.

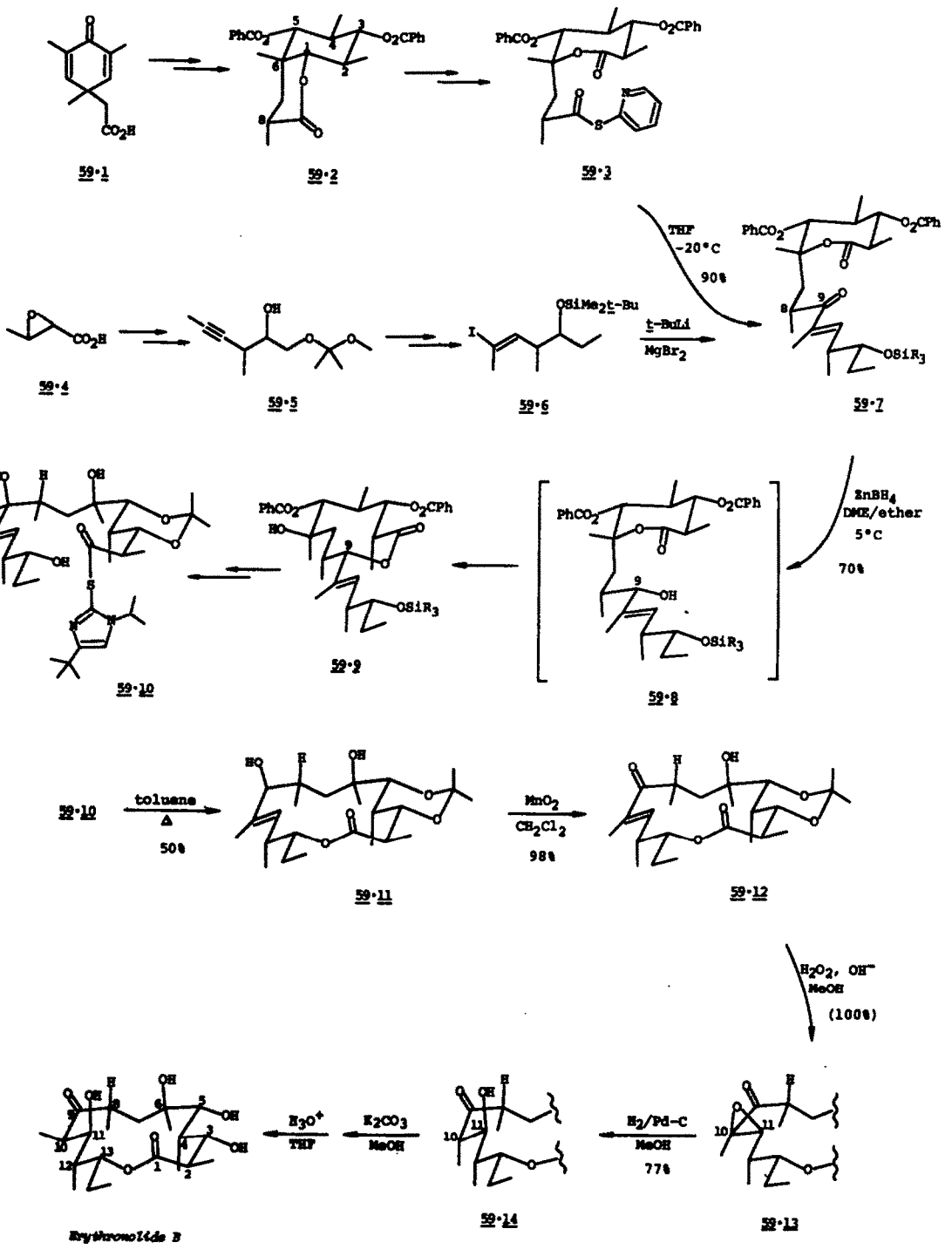


Scheme 58.

The first total synthesis of the 14-membered macrolide erythronolide B was recently reported by Corey and his team at Harvard[191,192] (Scheme 59). The stereocontrol in this synthesis is exercized primarily on cyclic intermediates, prior to cleavage to the acyclic lactonization substrate. The stereocenters at C-2 through C-8 are established by the construction of bicyclic lactone **59 · 2** from the dienone **59 · 1**.[191] After hydrolysis of the lactone and Jones and Baeyer–Villiger oxidations, the 2-pyridylthiol ester **59 · 3** is condensed with a vinyl Grignard reagent, affording the enone **59 · 7**.[192] Both of the components of this condensation are available in optically pure form, although the preliminary work was carried out with racemic thiol ester. The relative stereochemistry of the Grignard reagent is established by a regioselective epoxide opening.

1,2-Reduction of the enone system of **59 · 7** with zinc borohydride in glyme/ether (2:1) at 5° occurs stereospecifically and with concomitant translactonization to give the 10-membered lactone **59 · 9**. Although the new chiral center at C-9 is ultimately destroyed by reoxidation, it is interesting to note that it is generated with the opposite configuration than would be predicted by the open-chain models. Perhaps coordination of the zinc counterion with the lactone and ketone oxygens plays a role in determining this specificity.

After suitable deprotection/protection steps,[192] the thiol ester **59 · 10** is cyclized in 50% yield to the 14-membered lactone. The remaining chiral centers (C-10 and C-11) are then introduced stereospecifically, employing a previously developed route[193] which takes advantage of the conformational rigidity of the ketal-bridged ring system.[194] With one face of the enone double bond shielded by the ring, alkaline hydrogen peroxide provides the β-epoxy ketone **59 · 13**. Hydrogenolysis of this epoxide, epimerization at C-10, and deketalization afford totally synthetic erythronolide B.

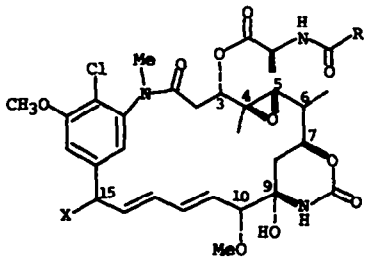


(The conformations depicted for 59·3 - 59·10 were chosen only for clarity of presentation)

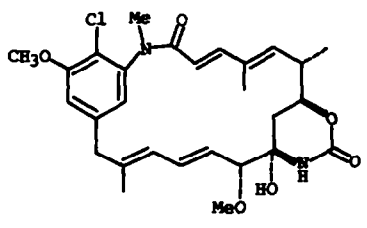
Scheme 59.

Several alternative approaches to the problem of stereocontrol in macrolide synthesis should be mentioned. Among them are the aldol condensation studies of Heathcock[67,68,86] and the Claisen rearrangement work of Ireland,[119] which were discussed in Part I. Vedejs has demonstrated that both the macrocyclic ring system and the relative stereochemistry of methymycin can be generated by a series of sulfonium ylid ring expansion reactions.[195] In a completely different approach, Hanessian has derived from D-glucose two fragments of correct absolute and relative stereochemistry corresponding to carbons 1 through 7 and 9 through 15 of erythronolide A.[196]

3. *Maytansine.* The promising antileukemic activity and limited availability have made the Maytenus macrocyclic lactams[197,198] a prime target for the synthetic chemist. Corey has recently reported the first total synthesis of a maytansinoid, N-methylmaysenine,[199] a derivative lacking the oxygen substituents at C-3, C-4 and C-5.[199a] Of the chiral centers present in maytansine, the carbinolamide at C-9 can be epimerized to give the desired isomer,[199] and the possibility exists that, for some intermediates,[199,200] the center at C-10 can be epimerized also. For the most part, attempts at the stereocontrolled synthesis of acyclic precursors have focussed on centers C-3 through C-7,[201-205] and particularly on C-6 and C-7.

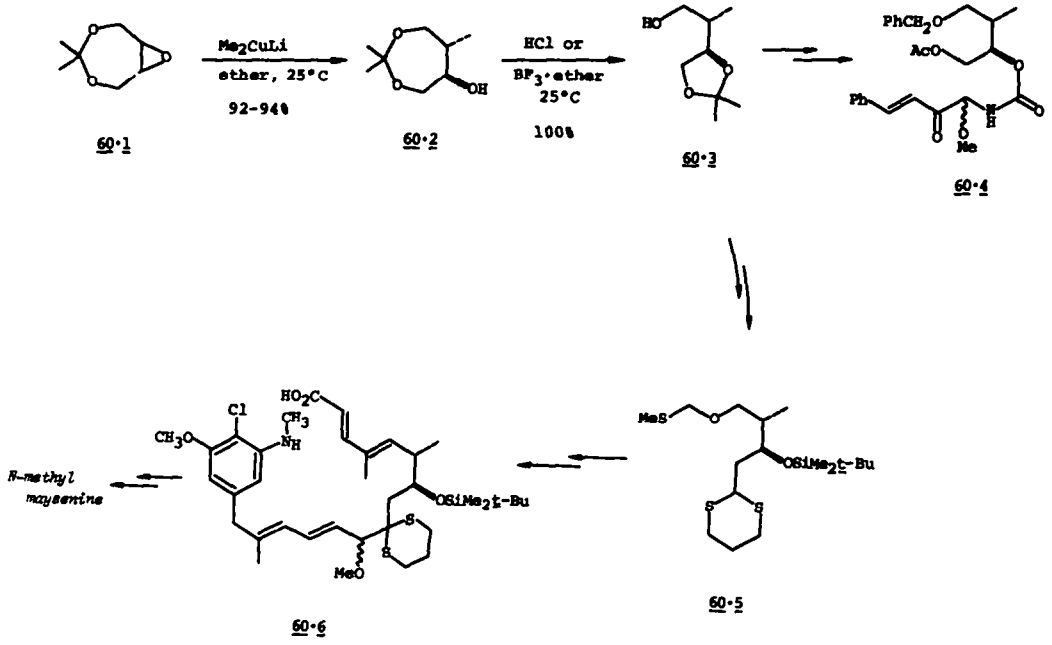


R = Me, X = H *Maytansine*
R = i-Pr, X = OH *Colubrinol*



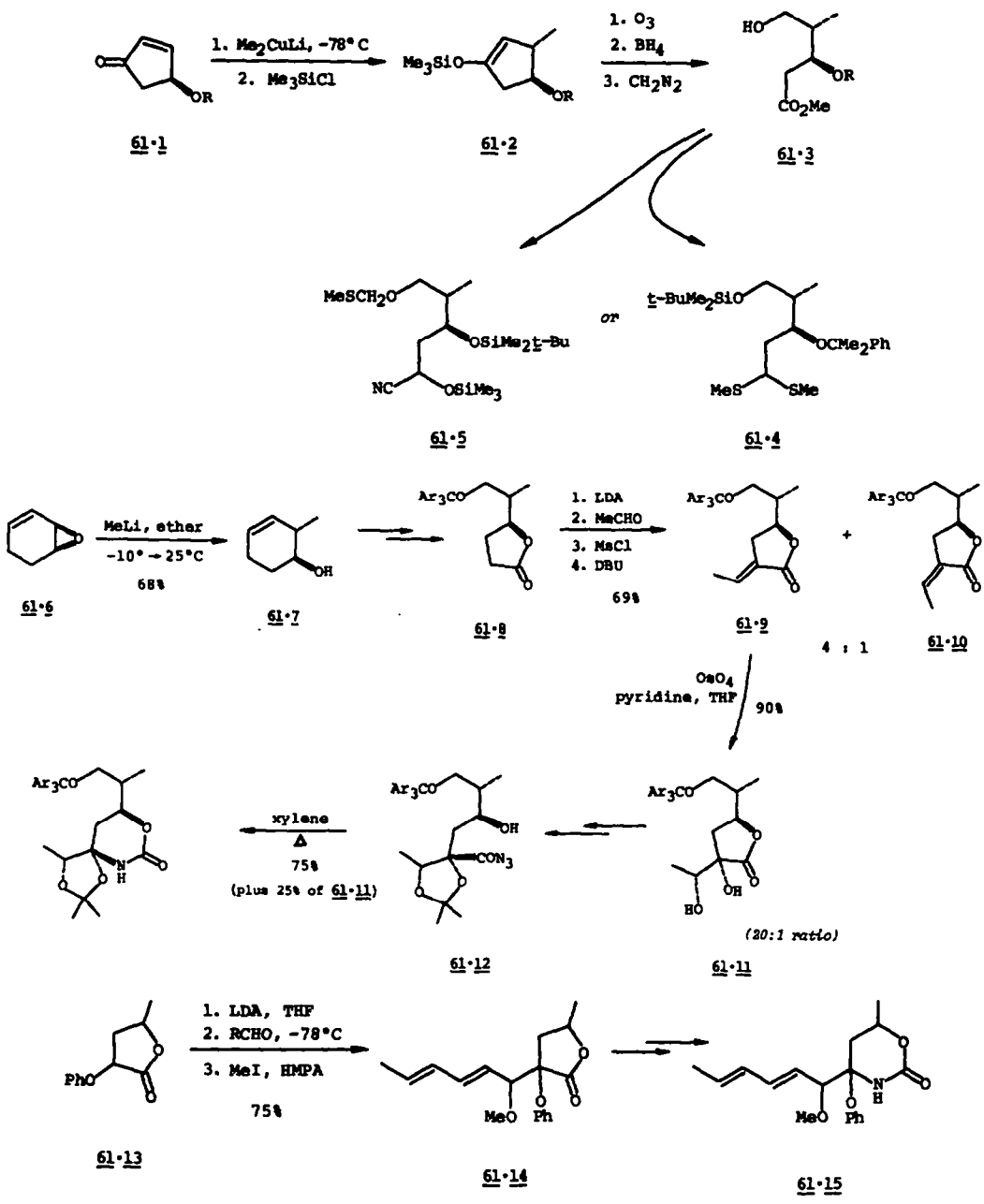
N-Methylmaysenine

Corey[201] and Fried[202] independently selected dimethylcuprate opening of the ketal epoxide **60 · 1** to generate the C-6,C-7 relationship and to facilitate selective protection of the triol derivative **60 · 3**. In model studies,[202] Fried elaborated **60 · 3** into the carbamate **60 · 4**; Corey converted it to the dithiane **60 · 5**[201] and employed it in his synthesis of N-methylmaysenine.[199]



Scheme 60.

Two other model studies which lead to fragments containing the C-6 and C-7 chiral centers involve ring cleavage of carbocyclic precursors as reported by Samson *et al.*,[203] and by Edwards and Ho (Scheme 61).[204] The sequence devised by Samson *et al.*, based on prostanoid chemistry, leads to acyl anion equivalents **61 · 4** and **61 · 5**. The other sequence is particularly interesting since it provides for the stereoselective generation of the C-10 chiral center. It relies on selective formation of the *E*-ethylidene lactone **61 · 9** and osmium tetroxide hydroxylation from the less hindered side of the double bond. After protection of the diol, the cyclic carbamate model system is formed on pyrolysis of the acyl azide **61 · 12**. Ganem has employed a similar Curtius rearrangement in an as yet non-stereocontrolled synthesis of the model compound **61 · 15**.[206]

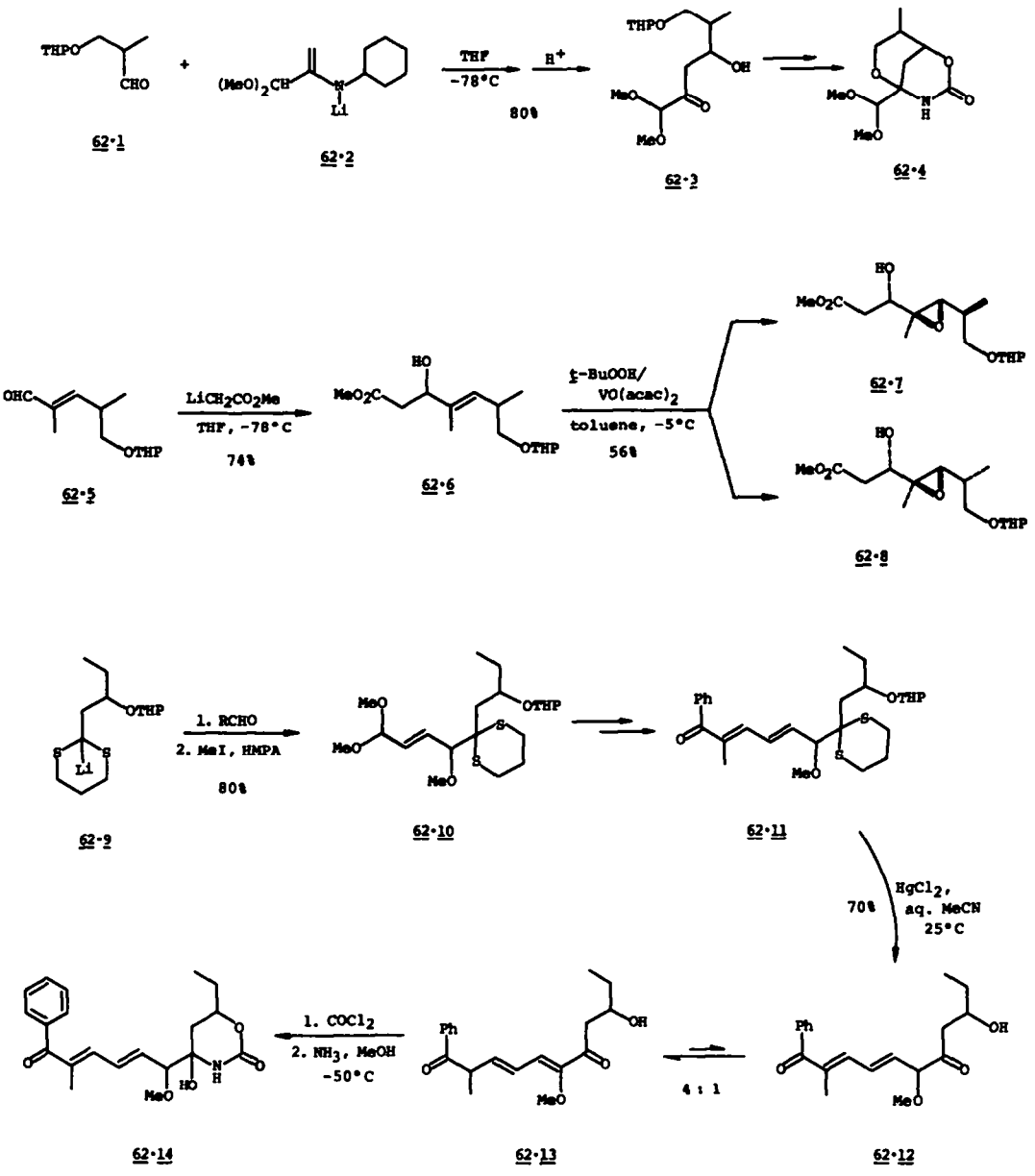


Scheme 61.

A number of model studies for various quadrants of the maytansenoid ring system have been reported by Meyers[200,205,207] (Scheme 62). One which establishes the two chiral centers at C-6 and C-7 by a Wittig directed aldol condensation proceeds without any apparent stereocontrol to give **62 · 3**.[207] After further elaboration of this β-hydroxy ketone to the bicyclic carbamate **62 · 4**, two stereoisomers in approximately equal amounts are observed.

Another approach,[205] which produces a fragment corresponding to carbons 1–7, entails the addition of the enolate of methyl acetate to **62 · 5**, a reaction with little potential for 1,4-asymmetric induction. The *t*-butylhydroperoxide/vanadyl acetylacetonate epoxidation of allylic alcohols such as **62 · 6** is known to be highly selective for formation of the *erythro* isomers, as discussed in Part I.[28] Column chromatography of a derivative gives the desired stereoisomer (**62 · 8**) as 42% of the mixture.

Meyers has also assembled carbons 7 through the aromatic ring via intermediates which may ultimately lead to colubrinol, as well as provide a mechanism for epimerizing the configuration at C-10 (via **62 ·** $\rightleftharpoons$ **62 · 13**).[200,199a]

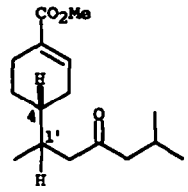


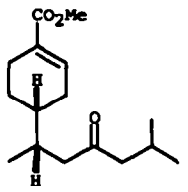
Scheme 62.

(D) *Extracyclic chiral centers in terpene synthesis*

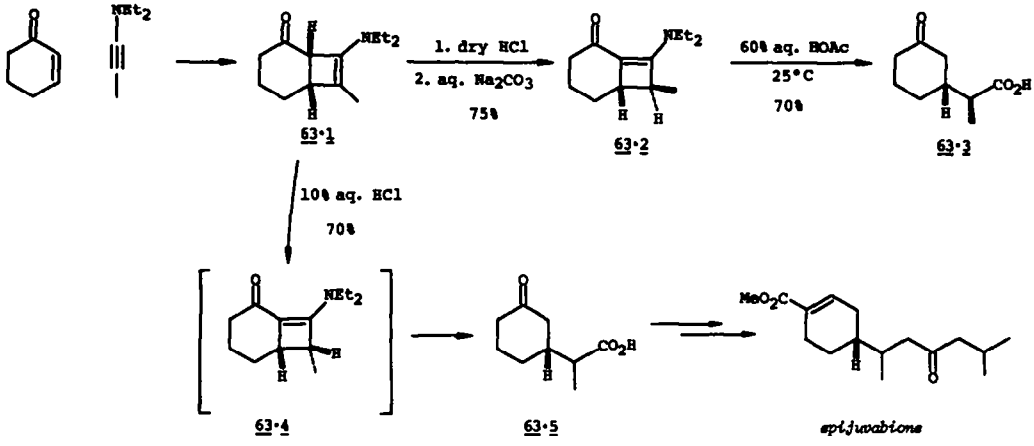
Most efforts directed toward acyclic stereocontrol in the area of terpene synthesis have focussed on the steroid side chains. Because many examples were mentioned in Part I, and since (as pointed out above) this subject has recently been reviewed,[21] further comment on this specific topic will not be made here. However, a number of additional terpene targets contain extracyclic chiral centers, usually at a position adjacent to a ring, although relatively few synthetic approaches have satisfactorily addressed this problem.

The stereochemical challenge to be met in the synthesis of juvabione is representative of that alluded to above. Although the stereochemical assignments of the juvabione diastereomers have followed a somewhat checkered history,[208-210] it now appears[210] that the substance originally isolated from Canadian balsam[208] in fact has the 4*R*,1′*R* stereochemistry as initially assigned. Nonetheless, epijuvabione can be isolated from other sources.[211] Because of its juvenile hormone-like activity in insects, juvabione has been the goal of many synthetic studies,[212-216] although a number of these were misdirected stereochemically due to confusion over the correct configuration at the extracyclic center.


(+)-juvabione

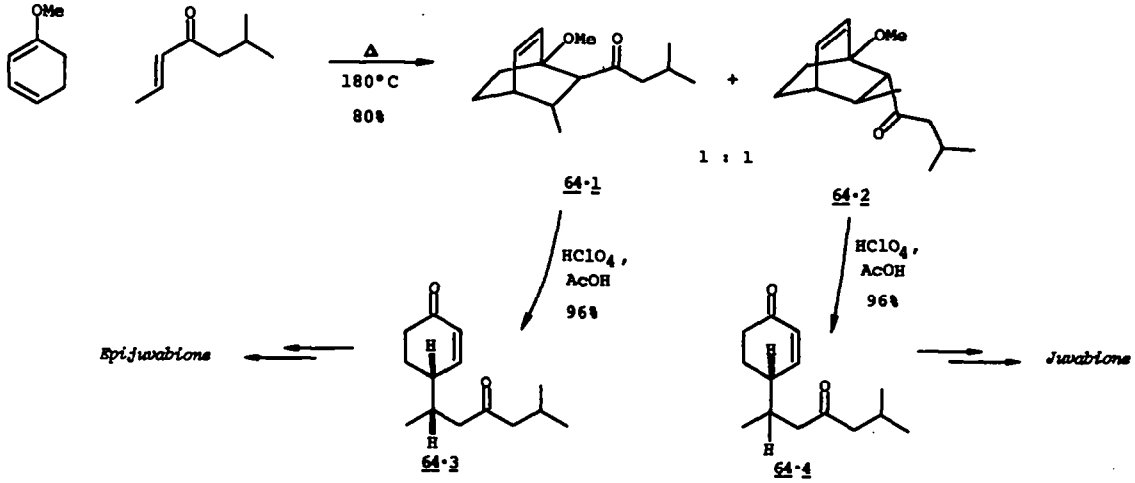

(+)-epijuvabione

To date, the only stereocontrolled synthesis of one of these isomers has been that of Ficini[216] (Scheme 63).[127a] Her approach relies on the ability to control the hydrolysis of cycloalkenone-ynamine adducts, such as **63 · 1**, to furnish either diastereomeric product specifically.[217] Anhydrous HCl isomerizes **63 · 1** to the thermodynamically favored *exo* isomer **63 · 2** and subsequently provides the R*S* isomer **63 · 3** on hydrolysis; direct aqueous acid-catalyzed hydrolysis of **63 · 1** proceeds with kinetically controlled protonation of the enamine and affords the R*R* product **63 · 5**. Since the stereochemistry of juvabione was believed at this point to be 4*R*,1'*S*,[209] the R*R* isomer **63 · 5** was carried on to the final product. Juvabione and epijuvabione are essentially indistinguishable except by optical rotatory dispersion,[215] which was inappropriate for comparison of the racemic product obtained by Ficini with authentic material. Nonetheless, the versatility of the hydrolysis reaction in providing either diastereomer clearly makes it possible to achieve a stereospecific synthesis of juvabione itself by this route.[217a]



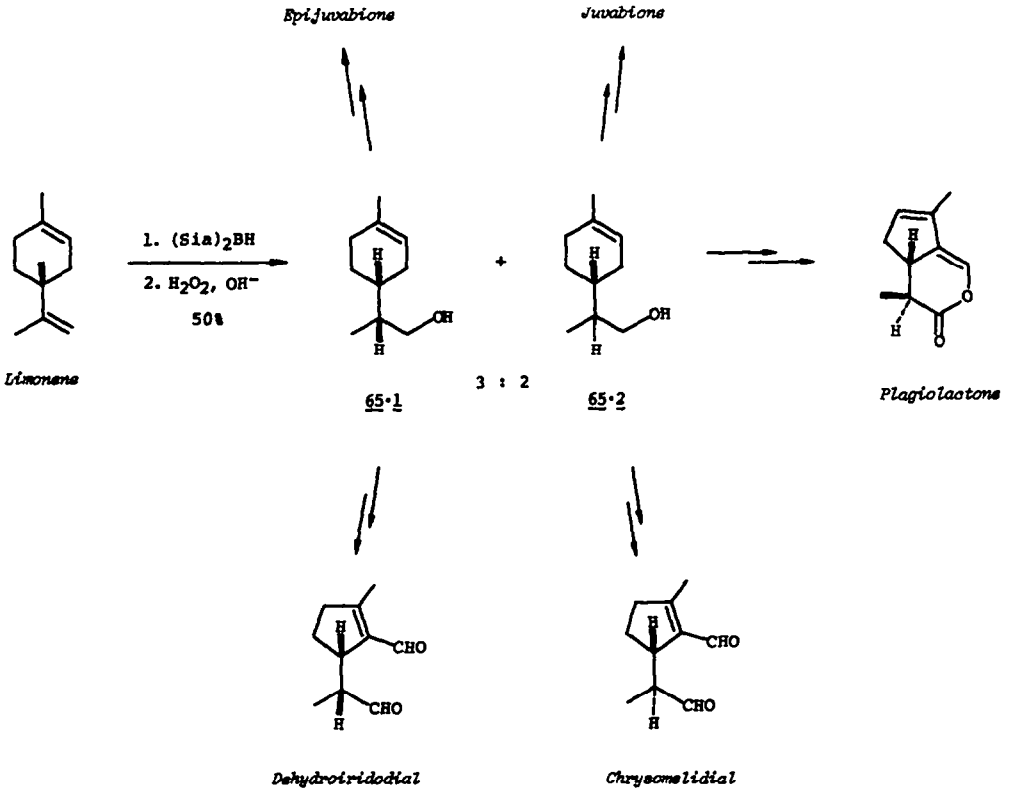
Scheme 63.

Among the alternative, non-stereoselective syntheses of juvabione is that reported by Birch[214] (Scheme 64). The relative stereochemistry is established by a Diels–Alder reaction which unfortunately affords a 1:1 mixture of *endo* and *exo* isomers **64 : 1** and **64 : 2**. These are separated by distillation and carried on to the juvabione isomers as illustrated.



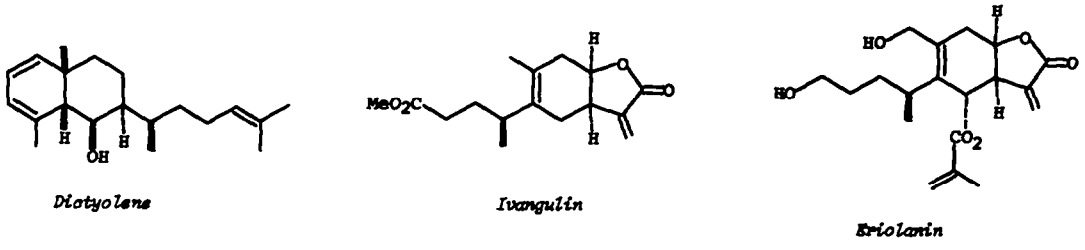
Scheme 64.

Pawson's synthesis[215] of the juvabione isomers utilized as starting materials the isomeric alcohols **65 · 1** and **65 · 2**, obtained as a 3:2 mixture by hydroboration/oxidation of limonene (Scheme 65).[217b] The same alcohols have also served in the syntheses of the beetle defense substances chrysomelidial,[208] plagiolactone,[218] and dehydroiridodial.[219] Other syntheses of juvabione also have employed hydroboration as a means of functionalizing the isopropenyl group of a terpene precursor.[213]



Scheme 65.

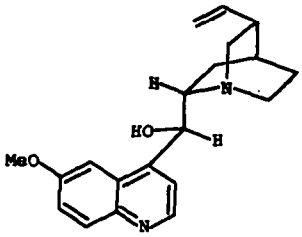
In other areas of terpene synthesis, chiral centers of this nature have been introduced stereoselectively on a cyclic framework, with eventual cleavage of the ring. Examples of this approach are found in Marshall's synthesis of dictyolene[220] and Grieco's syntheses of ivangulin[221] and eriolanin.[222]



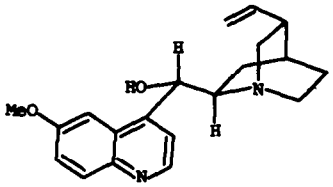
(E) *Alkaloids: quinine, emetine, and the phthalideisoquinolines*

Alkaloids are renowned primarily for their polycyclic complexity; however, a number of them contain chiral centers which are not included within the same ring system. Systematic approaches to this stereochemical aspect of alkaloid synthesis have been rare, although a number of intriguing reactions have been uncovered.[217a]

1. *Quinine.* In spite of continued interest in quinine since the first total synthesis of this substance by Woodward and Doering in 1945,[223] no stereospecific route has ever been reported. The stereochemistry of the carbinol center relative to the quinuclidine ring can be established in a variety of ways, but the known synthetic routes all produce comparable amounts of the quinidine stereoisomer at some stage of the synthesis.



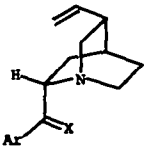
Quinine

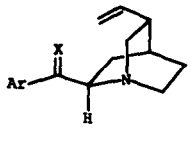


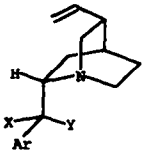
Quinidine

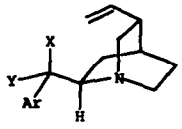
Several methods have been developed for generating the *erythro* relationship between the amino and hydroxyl centers in a selective manner (Scheme 66). Base-catalyzed oxygenation [224-227] of desoxyquinine and desoxyquinidine affords the natural *erthyro* isomers in predominance over the 9-*epi* (*threo*) products. A recent paper by Gutzwiller and Uskoković[227] indicates that this oxygenation is stereospecific, although earlier communications from their laboratory,[224] as well as others,[225,226] report a ratio of *erythro* to *threo* products of approximately 5:1. Repulsion between the nitrogen lone pair electrons and the oxygen radical anion intermediate (as depicted in **66 · 8**, following page) is suggested to account for the observed specificity.[227]

With appropriate choice of reducing agent,[228,229] quininone and quinidinone can be reduced selectively to either the *erythro* or the *threo* amino alcohols. Borohydride in ethanol provides a mixture of the 9-*epi* compounds, while disobutylaluminum hydride gives the natural configuration. The specificity of the latter reaction is explained by reference to the amino-alane complex **66 · 9** (following page), from which hydride transfer occurs intramolecularly.[228] The dipolar models discussed in Part I[49,53] adequately explain

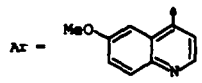


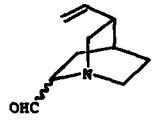




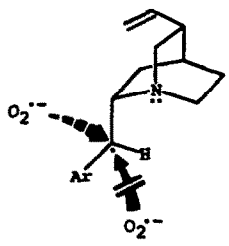


66·1a (desoxyquinine): X=H_2 66·2a (desoxyquinidine): X=H_2 66·3 (quinine): X=OH, Y=H 66·5 (9-epiquinidine): X=OH, Y=H
66·1b (quininone): X=O 66·2b (quinidinone): X=O 66·4 (9-epiquinine): X=H, Y=OH 66·6 (quinidine): X=H, Y=OH

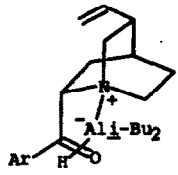
Ar = 

		66·3	66·4	66·5	66·6	Ref.
66·1a	t-BuOK, O_2 / t-BuOH, DMSO	69%	--	--	--	226
66·1a + 66·2a	"	32%	15% of mixture		41%	224 (225, 226)
66·1b + 66·2b	$NaBH_4$, EtOH, 0°C	4%	45%	39%	7%	228
66·1b + 66·2b	i-Bu_2AlH, benzene, 20°C	33%	--	--	39%	228
	ArLi, ether/THF, -70°C	20%	12% of mixture		23%	229

Scheme 66.



66·8

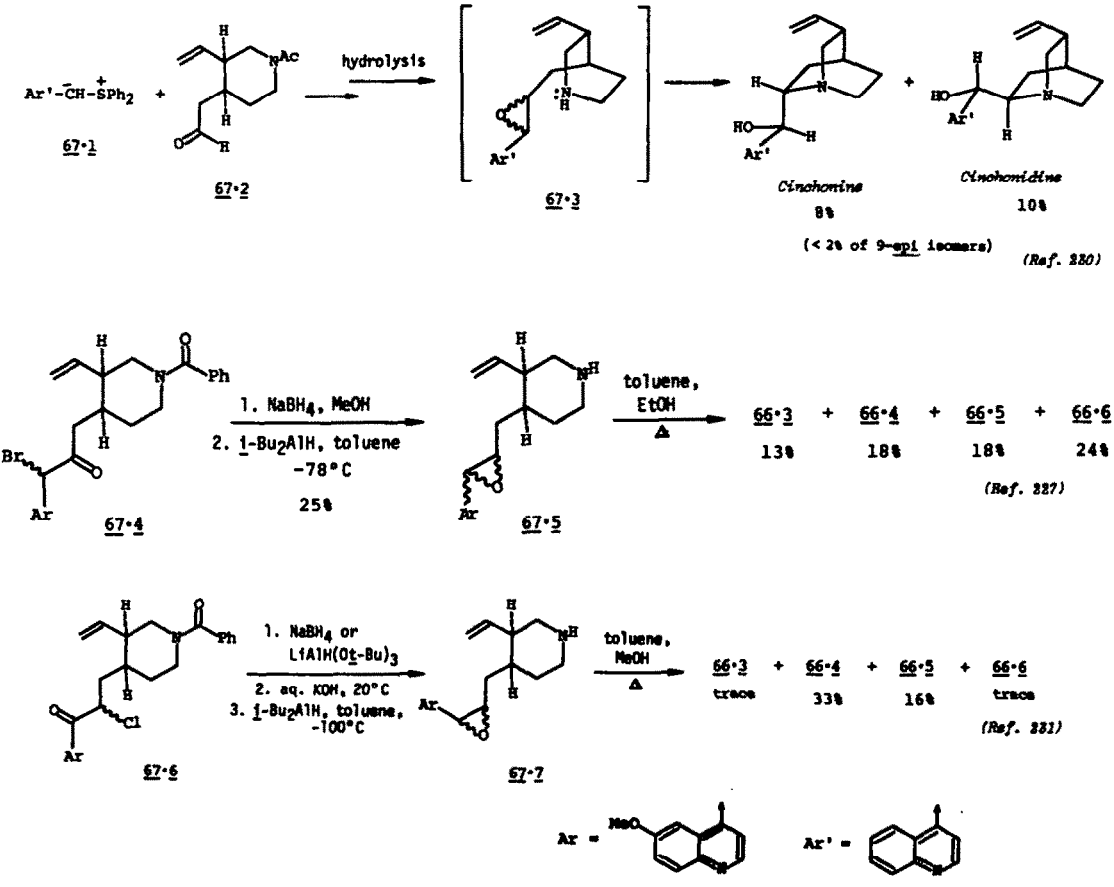


66·9

the borohydride specificity. Aryllithium addition to the quinuclidine aldehydes **66 · 7** also proceeds selectively,[229] apparently controlled in the same manner as the borohydride reduction, to furnish predominantly *erythro* products.

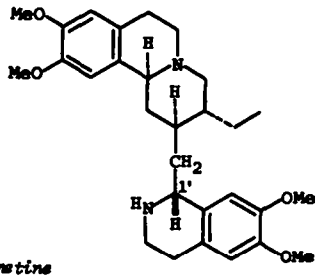
Concomitant formation of the quinuclidine ring system and establishment of the amino alcohol stereochemistry can be accomplished by cyclization of the amino epoxides depicted in Scheme 67. Selective formation of the *trans*-epoxides has been carried out for the cinchonine/cinchonidine series (Ar = 4-quinolyl) by sulfonium ylide addition to the aldehyde **67 · 2**.[230] The methoxy derivatives (Ar = 6-methoxy-4-quinolyl) have been obtained by other methods only as a mixture with the *cis*-isomers (**67 · 5**),[227] which therefore result in *threo/erythro* product mixtures. On the other hand, the *cis*-isomers **67 · 7**, and thus the 9-*epi* products, can be obtained selectively by reduction of the chloroquinotoxine diastereomers **67 · 6** and subsequent ring closure of the chlorohydrins.[228,231]

The routes to quinone via the epoxide emphasize the problem to be overcome in devising a stereospecific synthesis: relating the epoxide (and thereby the amino alcohol) chirality to that of the piperidine ring (and thereby the quinuclidine moiety).



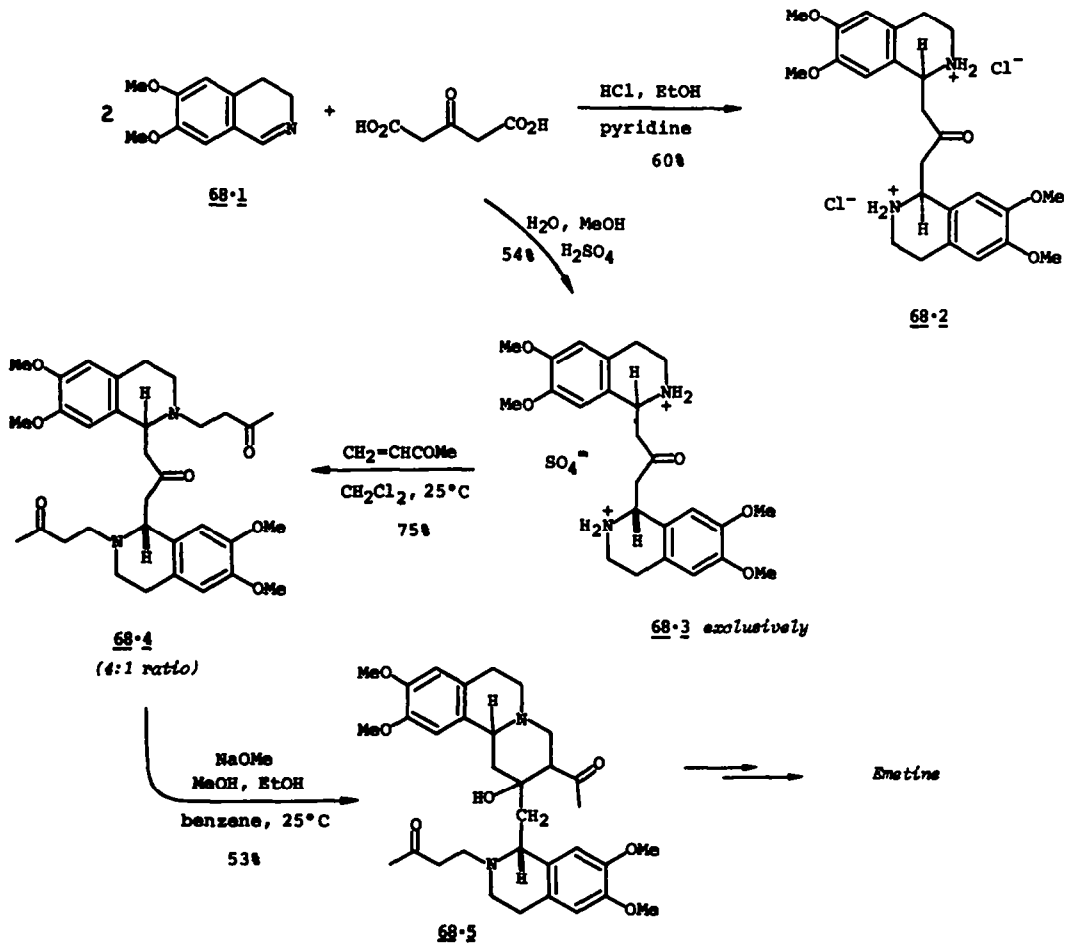
Scheme 67.

2. *Emitine.* Of the many syntheses of emitine and related alkaloids,[232] only one provides for stereoselective introduction of the C-1′ chiral center[233] (Scheme 68). Condensation of acetonedicarboxylic acid with imine **68 · 1** and equilibration of the product diastereomers can be controlled to furnish



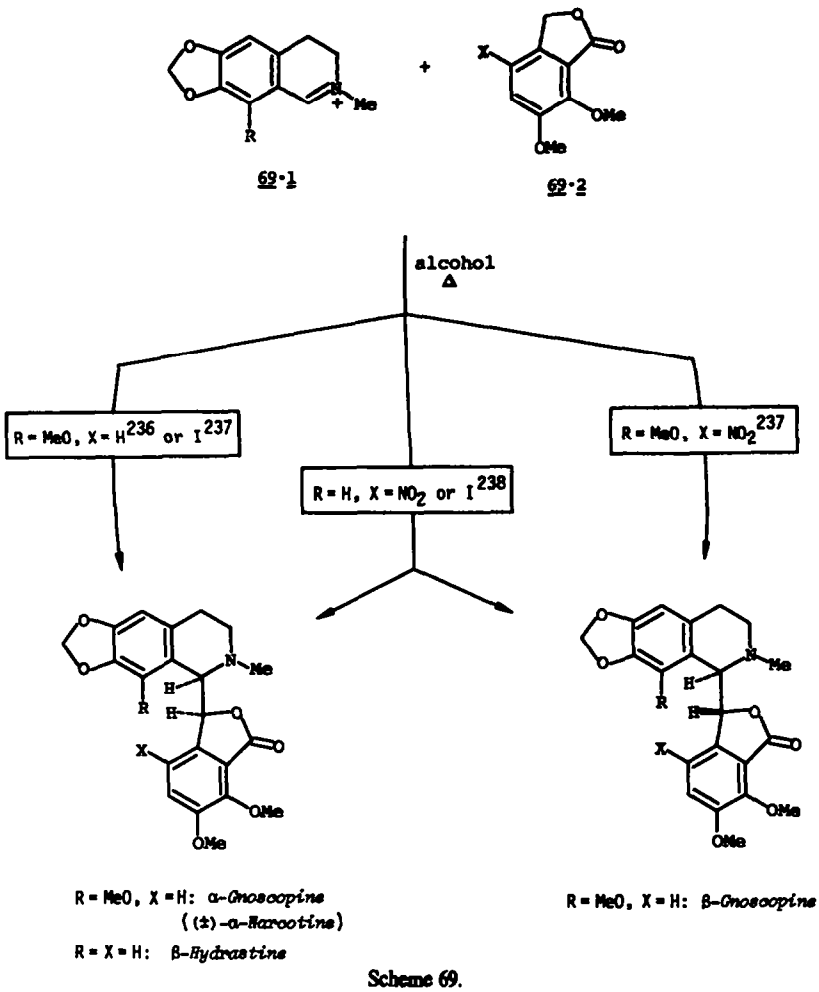
Emetine

either the *dl* or *meso* product specifically, by appropriate manipulation of the solvent and acid counterion so that a single diastereomer crystallizes from the mixture.[233a] These isomers are easily interconverted, however, and some epimerization is observed on conversion of the *meso* compound **68 · 3** to the Michael adduct **68 · 4**.[233b] The two ends of this symmetrical molecule are differentiated by aldol cyclization during the course of its conversion to emetine.



Scheme 68.

3. *Phthalideisoquinoline alkaloids.* The synthetic approaches developed for these alkaloids have involved with few exceptions[234] the addition of a phthalide derivative to an immonium ion[235–238] (Scheme 69). For some combinations of reactants, this process affords a single diastereomeric product.[236,237] However, because the products were isolated by crystallization, this apparent stereoselectivity is not proof of the absence of isomeric material.

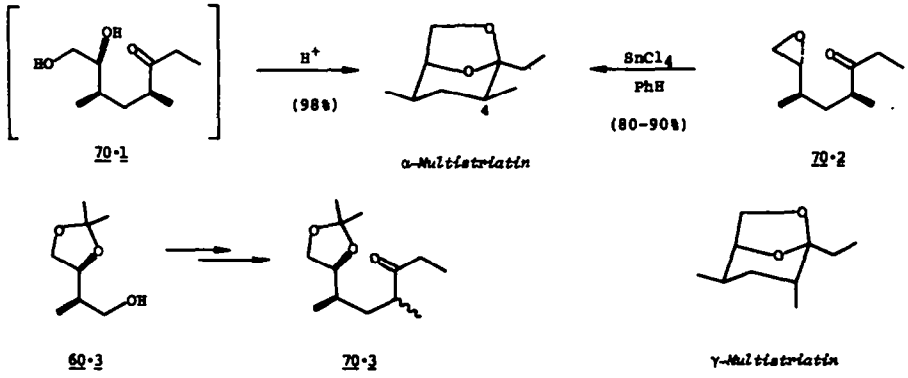


Scheme 69.

(F) *Multistriatin*

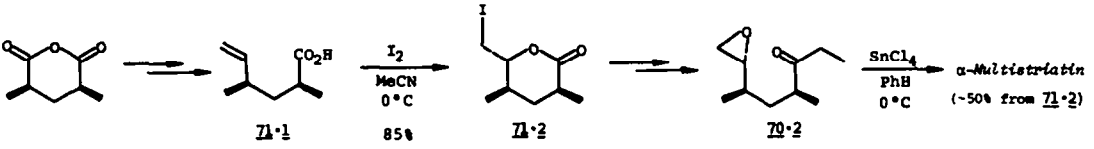
The bicyclic ketal, α-multistriatin, is one of the components of the aggregation pheromone of the lesser European elm bark beetle. It has been synthesized non-stereospecifically a number of times via the acyclic ketodiol **70 · 1**[239,240] and epoxy ketone **70 · 2**[241,242] (Scheme 70). The stereochemical challenge presented in these approaches is therefore one of acyclic control in the construction of these precursors, although the chiral center at C-4 can be epimerized in the final product.[239-241,242a]

Elliott and Fried[239] utilized the ketal **60 · 3**, which they had prepared in conjunction with their maytansine model work[202] (Scheme 60), to establish the non-epimerizable relationship of ketodiol **70 · 1**. After elaboration of the rest of the chain (to give **70 · 3**), an 85:15 mixture of α-multistriatin and γ-multistriatin is obtained after cyclization and epimerization.



Scheme 70.

We have recently completed a highly stereoselective synthesis of (±)-α-multistriatin[243] (Scheme 71), starting from *meso*-2,4-dimethylglutaric anhydride and utilizing an iodolactonization reaction[37] to introduce the third chiral center. The olefinic acid **71 · 1** cyclizes with iodine in acetonitrile to provide the all-equatorial lactone **71 · 2**, with better than 95% selectivity. After conversion to the epoxyketone **70 · 2**,



Scheme 71.

Lewis acid-catalyzed cyclization proceeds with inversion at the epoxide center to furnish α-multistriatin. This material is obtained with better than 95% purity, although chromatography (VPC or absorption) is not necessary at any stage of the synthesis.

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