RECENT ADVANCES IN STEREOCHEMICAL CONTROL: MULTIPLE ASYMMETRIC INDUCTION

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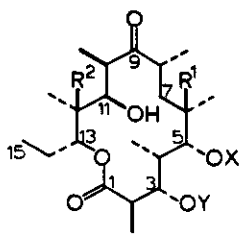
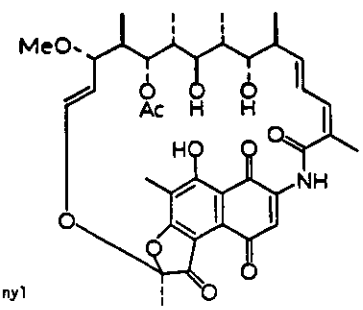
Abstract —— A new synthetic strategy based on the concept of multiple asymmetric induction is capable of constructing any new chiral center or centers on a chiral substrate as demonstrated in three major organic reactions: the aldol reaction, the Diels-Alder reaction, and epoxidation of allylic alcohols.
Several natural product syntheses serve to illustrate the degree of stereoselection that has now been achieved.

1. Introduction

For many years our major research efforts have been directed toward the synthesis of several macrolide antibiotics, a group of compounds which may be exemplified by erythromycin A (1), amphotericin B (2), and rifamycin S (3).*1 Distinct in their



$R^1 = R^2 = OH$
1 X = β-D-desosaminyl
Y = α-L-cladinosyl



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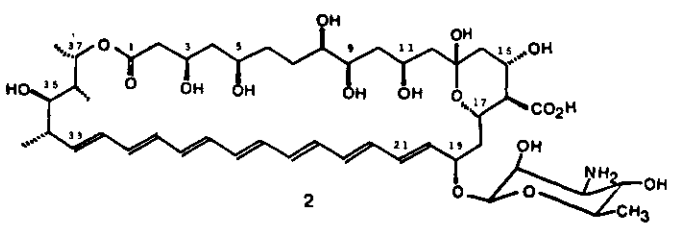

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* The word "macrolide" is used in a broad sense and includes macrolactams, for example the ansamycins such as rifamycin S.

structural features, these compounds revealed, even at the outset of this project, the existence of three major unsolved problems associated with macrolide synthesis: macro-lactonization, glycosidation, and stereochemical control.[2] This last problem concerns the proper assembly of numerous chiral centers embedded in the large lactonic and lactamic systems, and demands a conceptually new approach for its solution. In this lecture I will first discuss the stereochemical outcome of organic reactions involving a set of two reactants (substrate and reagent), each of which is either achiral or chiral. The analysis of these reaction courses will lead to a new strategy which is potentially applicable to the construction of any new chiral center or centers on a chiral substrate in a predictable manner. This process is fundamentally important and frequently encountered in natural products synthesis. It will become clear that the strategy demands the development of enantiomerically pure (homochiral) reagents that must meet a new set of criteria (see below). Such reagents have indeed been prepared to effect three major organic reactions with high stereoselection: the aldol reaction, the Diels-Alder reaction, and epoxidation.* The lecture will also include the use of these reagents in the total synthesis of several natural products of medium complexity, which serves to demonstrate the degree of stereocontrol that has now been achieved.

2. Multiple Asymmetric Induction[3]

Let us consider at first a general case where a chiral substrate (S-I) having an sp^2 carbon reacts with an achiral reagent to give products P_a and P_b (Scheme 1). Because S-I is chiral, one of the two diastereomeric transition (si-attack or re-attack)** will be lower in energy than the other. This results in one product being produced to a greater extent, and thus the P_a/P_b is not unity. This ratio P_a/P_b is referred to as the diastereofacial selectivity (D.S.) of S-I. For instance, reduction of norcamphor (4) with lithium aluminum hydride provides a mixture of endo- and exo-norborneols (5 and 6), the D.S. being 89 : 11.[4] This example, although very

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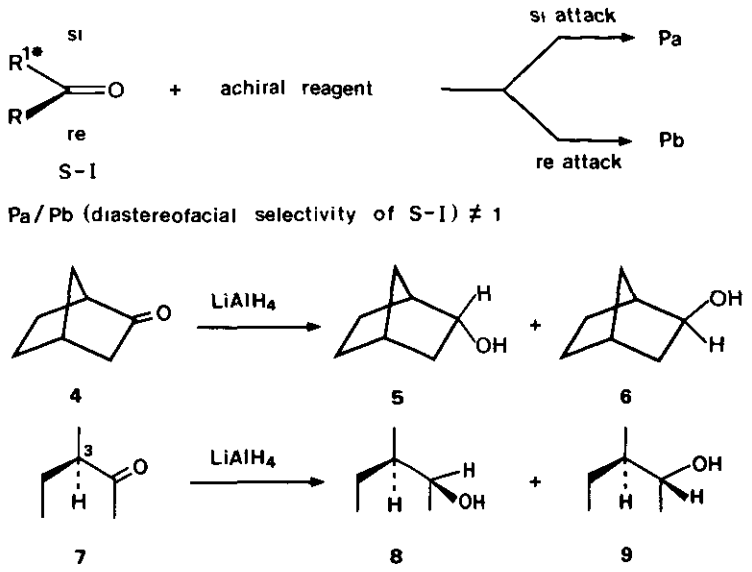
* This refers to Sharpless' epoxidation, as will be discussed in the lecture.

** Assuming that Cahn-Ingold-Prelog priority of R^1 (or R^{1*}) is higher than that of R, the si and re faces of S-I are those designated in Schemes 1-3.

Scheme 1

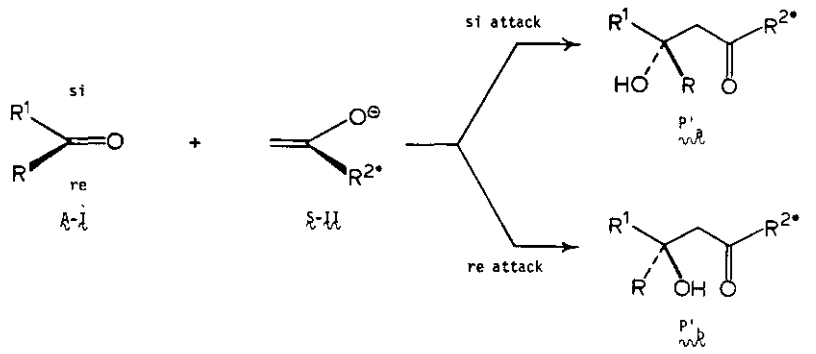


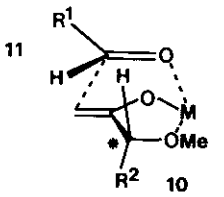
simple, illustrates a principle that has guided synthetic organic chemists in designing the structure of a substrate, starting material or intermediate, in order to incorporate proper stereochemistry in the reaction product. A variety of complex natural products with many chiral centers have almost invariably been synthesized in this way.

In contrast to the cyclic system exemplified above by 4, a high diastereofacial selectivity, significant enough to be synthetically useful, is normally difficult to attain with acyclic systems. For instance, hydride reduction of 3-methylpentan-2-one (7) will, in all likelihood, proceed non-stereoselectively, because the acyclic ketone 7 is conformationally flexible and the difference in both steric and stereoelectronic effect exerted by the methyl and ethyl groups attached to the C-3 carbon of 7 is insignificant. Two products 8 and 9 will result in nearly equal quantities. This non-stereoselectivity led us to search for a new means of stereocontrol other than structural modification of the substrate. Thus we sought methodology capable of not only producing either 8 or 9 predominantly from 7, but also of reversing the "normal" stereochemical course of reduction of 4 if so chosen.

Let us condsider another general case where an achiral substrate (A-I) reacts with a chiral reagent, e.g., a chiral enolate (S-II), to give rise to products P´a and P´b (Scheme 2). In an analogous manner to that mentioned for Scheme 1 (S-II is chiral in Scheme 2) two diastereomeric transition states that emerge from the si- and re-attack will differ in energy, resulting in the ratio P´a/P´b not being unity. This ratio is referred to as the diastereofacial selectivity of S-II. For instance, it can be easily predicted that the chiral enolate 10, if prepared, would react with aldehyde 11 preferentially from one side of 11.

Scheme 2





P'a/P'b ≠ 1

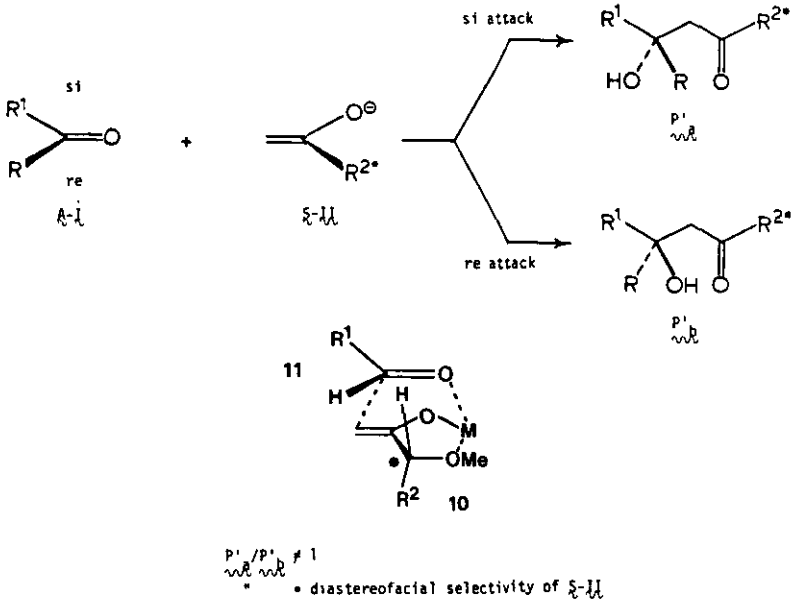
" = diastereofacial selectivity of S-II

When (reagent) S-II is homochiral, the outcome of the stereochemical consequence of the reaction between A-I and S-II constitutes the basis of (single) asymmetric synthesis as originally defined by W. Marckwald.*

* (Ber. 1904, 37, 1368): "Those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes."

Now consider the case where a chiral substrate (S-I) reacts with chiral reagent (S-II) to afford products P"$_a$ and P"$_b$ (Scheme 3), with the assumption that both S-I and S-II favor the si-attack transition state (i.e., P_a/P_b>1 and P'_a/P'_b>1, respectively). This process is characterized by multiple (double) asymmetric induction

Scheme 3



as the chirality in both S-I and S-II affects the stereochemical course of the reaction. By simple (and naive) analysis, the ratio of products, P"$_a$/P"$_b$ may be approximated to be (P_a/P_b) x (P'_a/P'_b). If this approximation holds, the P"$_a$/P"$_b$ will be larger than either P_a/P_b or P'_a/P'_b. Since their diastereofacial selectivities complement each other, S-I and S-II are called a matched pair. In contrast, when S-I reacts with R-II*, the ratio of products, P"$_a$/P"$_b$, may be approximated to be (P_a/P_b) ÷ P'_a/P'_b. Thus, P"$_a$/P"$_b$ will be inferior to the larger of P_a/P_b and

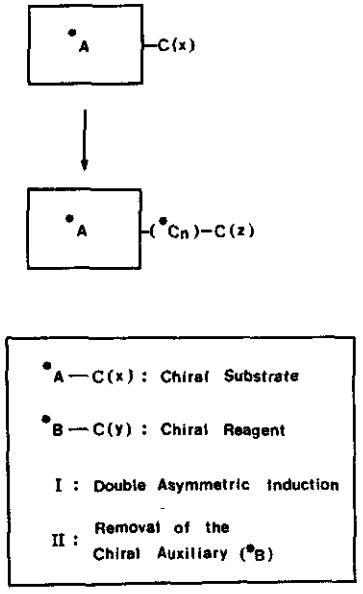
* R-II, the enantiomer of S-II, should have a diastereofacial selectivity that is equal in magnitude but opposite in selection to that of S-II (i.e., R-II favors the re-attack transition state).

P'_a/P'_b. Now that their diastereofacial selectivities oppose each other, S-I and R-II constitute *a mismatched pair*. The approximate multiplicativity of diastereofacial selectivities thus inferred unfortunately lacks rigorous theoretical justification, and therefore must be tested experimentally to be accepted. At the outset of this project we simply assumed its validity.

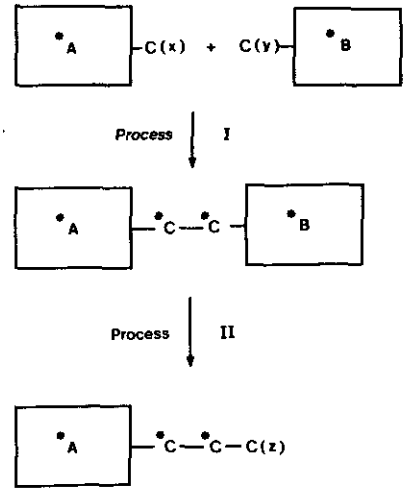
3. A New Strategy for Stereochemical Control

In natural products synthesis, we frequently encounter the need to build a new chiral center or centers on a chiral substrate. Scheme 4 formulates this transformation: *A-C(x) (equivalent to S-I in Section 2) is converted to *A ($^*C_n$)-C(z) where both C(x) and C(z) denote appropriate functional groups for the chemical operation.* In order to achieve this task a chiral reagent *B-C(y) (equivalent to S-II in Section 2) is allowed to react with *A-C(x) to provide a mixture of stereoisomers

Scheme 4



Scheme 5



BOTH *A AND *B MUST BE ENANTIOMERICALLY PURE (HOMOCHIRAL).

expressed by *A-*C-*C-*B (process I). The reagent *B-C(y) is so chosen that a high stereoselection (at *C) is achieved in this process. Having served this purpose, the chiral auxiliary *B *is removed in* such a fashion so as to leave a functional group

* *A and *C denote a chiral group and a chiral center, respectively.

C(z) for further transformation. From the analysis detailed in Section 2, it follows that (1) when the desired *A-*C-*C-*B is P''$_a$, the major product in the matched pair reaction, the resulting stereoselection should be higher than the diastereofacial selectivity of *A-C(x), being augmented by that of the reagent; (2) if the *A-$^{\bullet}$C-$^{\bullet}$C-*B happens to be P''$_b$, then the use of reagent of the opposite chirality (a mismatched pair) whose diastereofacial selectivity is substantially large enough to outweigh that of *A-C(x) is recommended. Such reagents of either chirality (at B*) can be, and have been, prepared.

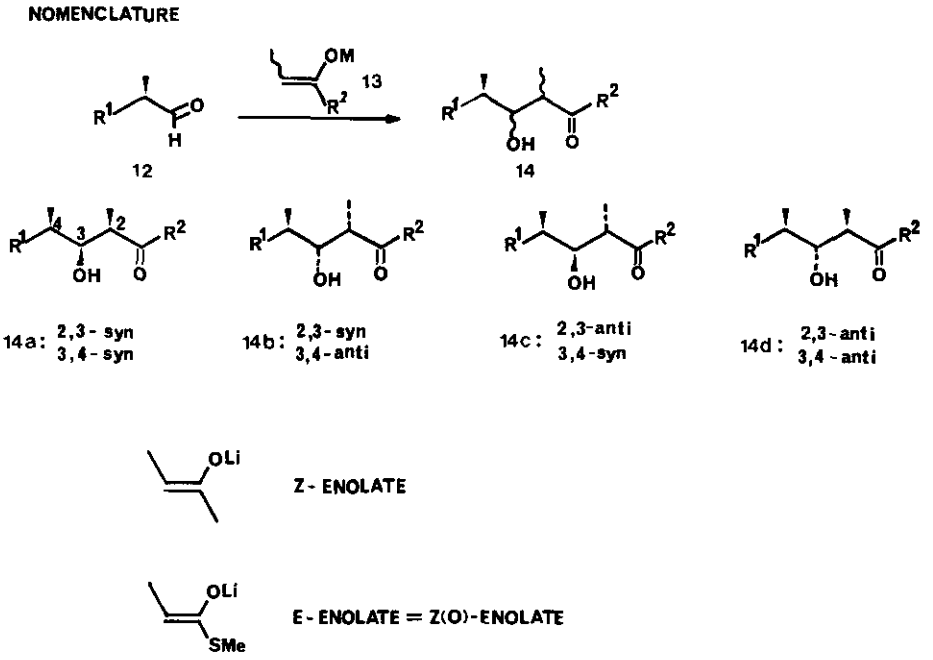
In contrast to many cyclic systems, acyclic chiral substrates normally exhibit a smaller diastereofacial selectivity ranging from 1 to 5. Therefore, reagents which have a diastereofacial selectivity of >100 can meet the above demand. In this way a >100 : 1 stereoselection is expected for a matched pair, while even a mismatched pair brings about a minimal isomeric ratio of 1 : >20, the degree of stereoselection which is of practical significance in organic synthesis. Thus, the concept of multiple asymmetric induction discloses the possibility that the stereochemistry of organic reactions may be controlled by the chirality of reagents (and substrates) rather than substrates alone as it has been in the cases to date, and that the stereoselection one order of magnitude higher than that previously attained in the latter cases may accrue through this methodology. Let us see to what extent this possibility has been realized in actual experiments.

4. Aldol Reaction [1a]

Before we discuss chiral enolate reagents newly developed for the asymmetric aldol reaction, it appears appropriate to present some salient stereochemical features of this well-known carbon-carbon bond-forming reaction. The reaction involves an aldehyde (12) and an enolate (13) and creates, in principle, two new chiral centers in the product (14) (Scheme 6). When 12 is a chiral aldehyde and 13 is an enolate derived from an ethyl ketone, four possible diastereomeric products (14a-14d) may be formed as indicated in Scheme 6.*

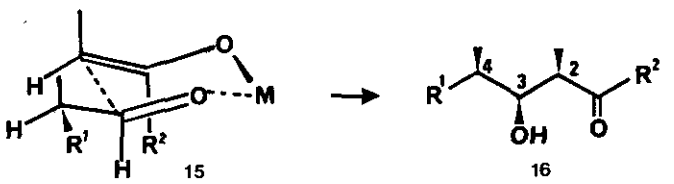
* For these stereochemical descriptions [syn, anti, Z(O), and E(O)], see ref. 5.

Scheme 6



The aldol is influenced by many reaction parameters and thus its mechanism is complex, varying from one case to another. Today's discussion is confined to the reactions of a rather general type where the chair-type cyclic intermediate 15 (Zimmerman-Traxler model) (Scheme 7) can serve to rationalize experimental results.

Scheme 7



15 : Z(O)-ENOLATE
α(RE)-ENANTIOFACE
ATTACK

Z(O), α : 2,3-SYN
3,4-SYN

Z(O), β : 2,3-SYN
3,4-ANTI

E(O) α : 2,3-ANTI
3,4-SYN

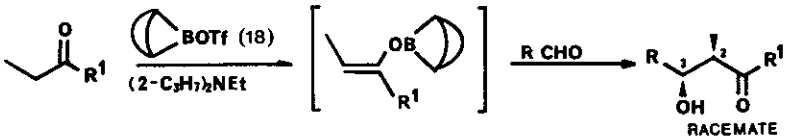
E(O) β : 2,3-ANTI
3,4-ANTI

The outcome of the reaction proceeding through 15 which delineates the case of Z(O)-enolate approaching the α (re)-face of the aldehyde is straightforward: The aldol product 16 should have the 2,3-syn, 3,4-syn stereochemistry. The other combinations for the assembly of the enolate and aldehyde are: E(O)-enolate approaching the α-face or β (si)-face of the aldehyde, and the Z(O)-enolate, the β-face. The stereochemistry of the product in each case is tabulated. It is clear that (1) the Z(O) and E(O) geometries of the enolate are translated into the 2,3-syn and 2,3-anti stereochemistry of the aldol product, respectively, and (2) the enolate's approach to the aldehyde from the α- or β-face determines the absolute configuration of the C-3 hydroxyl group created in the reaction. The α- and β-face attacks correspond to the β- and α-absolute configurations of the C-3 hydroxyl group of the product, respectively. Since the β-absolute configuration of the C-4 methyl group in 16 is "handed over" from the aldehyde, the 3,4-stereochemistry of 16 is syn in this case. Therefore, the stereochemical problem in the aldol reaction consists of two parts — the 2,3- and 3,4-stereochemical control.

One simplistic conformational analysis of the transition state has fortunately led to an expeditious solution of this problem. The relatively short O-B and C-B bond-lengths as well as the strong affinity of boron toward an oxygen lone pair would "tighten" the transition state and simultaneously a bulky ligand attached to the boron atom would exert a steric demand in the lower space of the chair ring. These factors could thus force the orientation of the aldehyde in the manner shown in 15. This prediction has indeed been realized and, in a way, validates the Zimmerman-Traxler model, particularly in the case of boron-mediated aldol reaction.

The experimental results are briefly summarized in Scheme 8. Treatment of S-phenyl propionate (17a) and ethyl cyclohexyl ketone (17b) with 9-borabicyclo[3.3.1]nonyl trifluoromethanesulfonate (9-BBN triflate) (18) effects the stereoselective formation of the corresponding Z(O)-boron enolates 17'a and 17'b, respectively, which react with a variety of aldehydes to provide the racemic 2,3-syn-3-hydroxy-2-methyl-carbonyl compounds 19a and 19b with a stereoselection of at least 30 : 1. On the other hand, dicyclopentylborinyl triflate 20 converts S-tert-butyl propionate into 17'c, which is capable of producing racemic 2,3-anti aldol products (21), again with excellent stereoselection (>20 : 1). Although a number of methods for the stereoselective synthesis of racemic 2,3-syn- and anti-3-hydroxy-2-methylcarbonyl compounds are now available, the boron-enolate aldol reaction remains the method of choice in terms of overall selectivity, yield, and operational simplicity.

Scheme 8

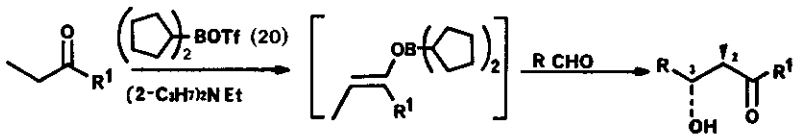


17a: R^1=SPh
17b: R^1=c-C_6H_{11}

17'a
17'b

19a: R^1=SPh
19b: R^1=c-C_6H_{11}

Stereoselectivity >30 : 1



17c : R^1=$SC(CH_3)_3$

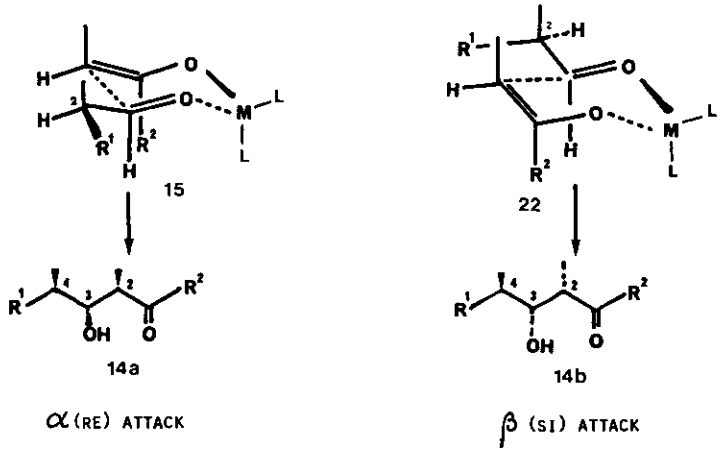
17'c

RACEMATE
21: R^1=$SC(CH_3)_3$

Stereoselectivity >20 : 1

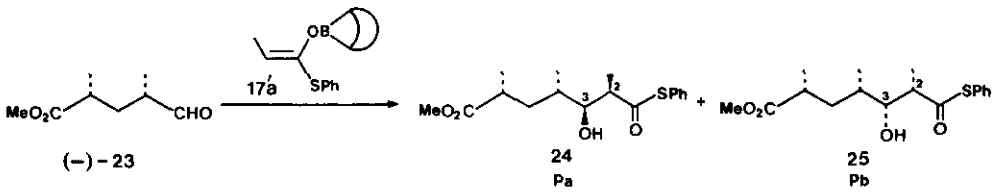
While the 2,3- problem quickly came to a successful end, the 3,4- problem consumed a great deal of our effort. One can readily recognize that the 3,4- problem concerns the relative disposition of the aldehyde and enolate, inasmuch as 15 and 22 lead to 14a and 14b, respectively (Scheme 9). From the discussion in Section 3, this 3,4-stereochemical control clearly demanded the development of chiral enolate reagents whose diastereofacial selectivity (>100 : 1) was regarded at that time as unattainably high.

Scheme 9



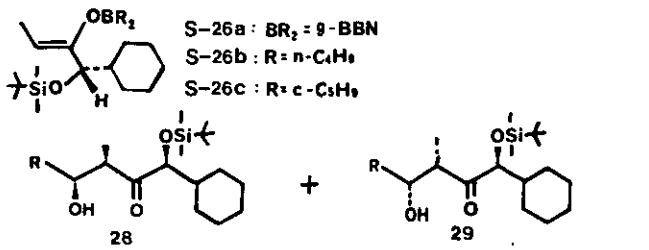
One of our very first tasks encountered in the aldol work was the construction of the 2,3-syn, 3,4-anti system (see 24) from (-)-dimethylglutaric hemialdehyde (23). The aldol reaction of 23 with an achiral Z(O)-enolate, e.g., 17'a provides an approximately 3 : 2 mixture of 24 and 25 which correspond to P_a and P_b discussed in Section 2 (Scheme 10). The 3 : 2 ratio is the diastereofacial selectivity of aldehyde 23 and represents roughly the degree of diastereoselection one can attain in the aldol reactions of 23 without recourse to double asymmetric induction.

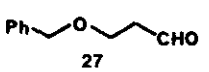
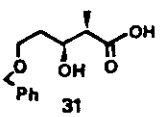
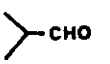
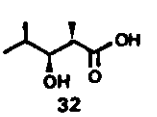
Scheme 10



Many chiral Z(O)-enolates had been prepared and examined before those (S- or R-26a,b,c,) shown below emerged as strong candidates for the solution of this 3,4-stereochemistry.[6] All of these reagents are readily prepared from commercially

Scheme 11

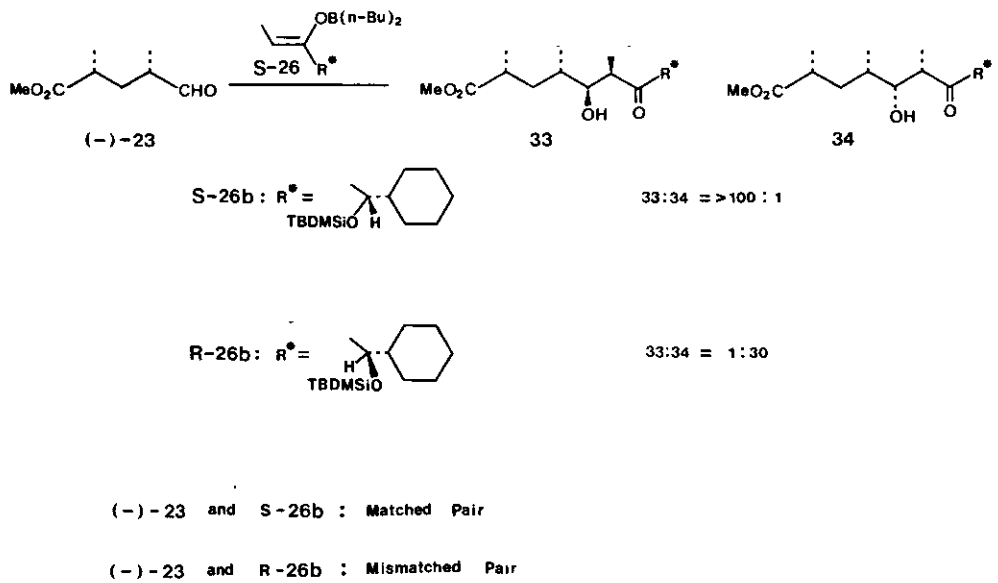


ALDEHYDE	BORON ENOLATE	RATIO OF 28 TO 29	MAJOR β-HYDROXYACID
 27	S-26a S-26b S-26c	16 : 1 23 : 1 100 : 1	 31
 30	S-26a S-26b S-26c	>100 : 1 >100 : 1 NO REACTION	 32

available, optically pure (S or R) mandelic acid via three steps and differ in the ligand attached to the boron atom. The diastereoselectivities of the reagents are impressive even by today's standards (Scheme 11). For instance, achiral aldehyde 27 undergoes aldol reaction with S-26c, the most stereoselective (but least reactive) boron enolate of the three (26a-26c) to provide a 100 : 1 mixture of diastereoisomers 28 and 29 (R=$PhCH_2O$-CH_2-CH_2-). With isobutyraldehyde (30), an α-branched aldehyde, the selectivity of the reaction is very high [>100 : 1 of 28 and 29 (R=2-Pr)] even with the least selective (but most reactive) boron enolate S-26a. Successive treatment of a mixture of 28 and 29 with hydrogen fluoride (or fluoride anion) followed by sodium metaperiodate provide the corresponding 2,3-syn-3-hydroxy-2-methylcarboxylic acids (31 and 32) with an enantiomeric excess higher than 98 %. These results meet the criteria set for the chiral reagents (Section 3).

We were then ready to tackle the first task mentioned earlier. Thus, the reaction of homochiral aldehyde (-)-23 with homochiral enolate S-26b proceeded to provide two diastereoisomers 33 and 34 in a ratio of >100 : 1 (Scheme 12). The change in the chirality of the enolate reagent brought about a reversal of the result: A combination of (-)-23 and R-26b led to the formation of 33 and 34 in a ratio of 1 : 30

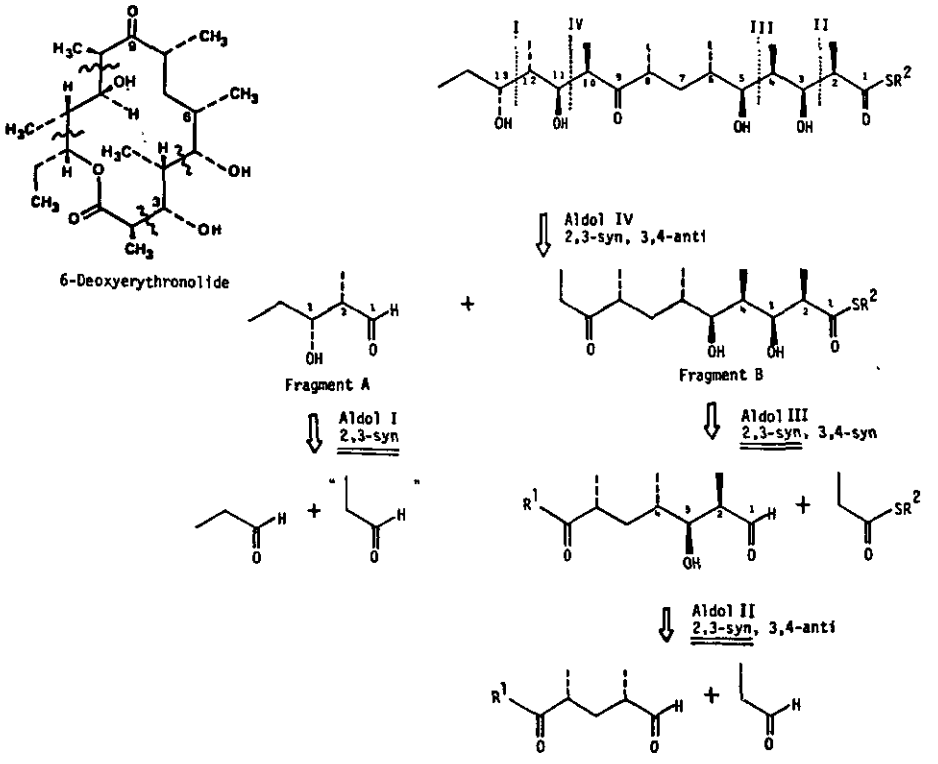
Scheme 12



favoring the latter (34).[7a] The significance of these two reactions is three fold: (1) Both ratios are far superior to the ratio 3 : 2 obtained with an achiral enolate (see above), (2) the chirality of R* in S-26b is directly correlated to the stereochemistry at the 3,4-positions of the reaction products, and thus either the 2,3-syn, 3,4-anti or 2,3-syn, 3,4-syn system can be constructed in a preselected manner, and (3) the two reactions, (-)-23 + S-26 and (-)-23 + R-26 represent matched and mismatched pairs, respectively, and the multiplicativity of the two diastereofacial selectivities (3 : 2 and 100 : 1) are roughly realized. The stereochemical course of the aldol reaction is now fully under control and the power of double asymmetric induction is clearly demonstrated.*

Let us see how the aldol reaction has been utilized in the synthesis of 6-deoxyerythronolide B (35).[7b] Once the seco-acid aldol approach is adopted,[1b,2] designing a synthetic scheme is straightforward. Splitting the seco-acid derivative (36),

Scheme 13

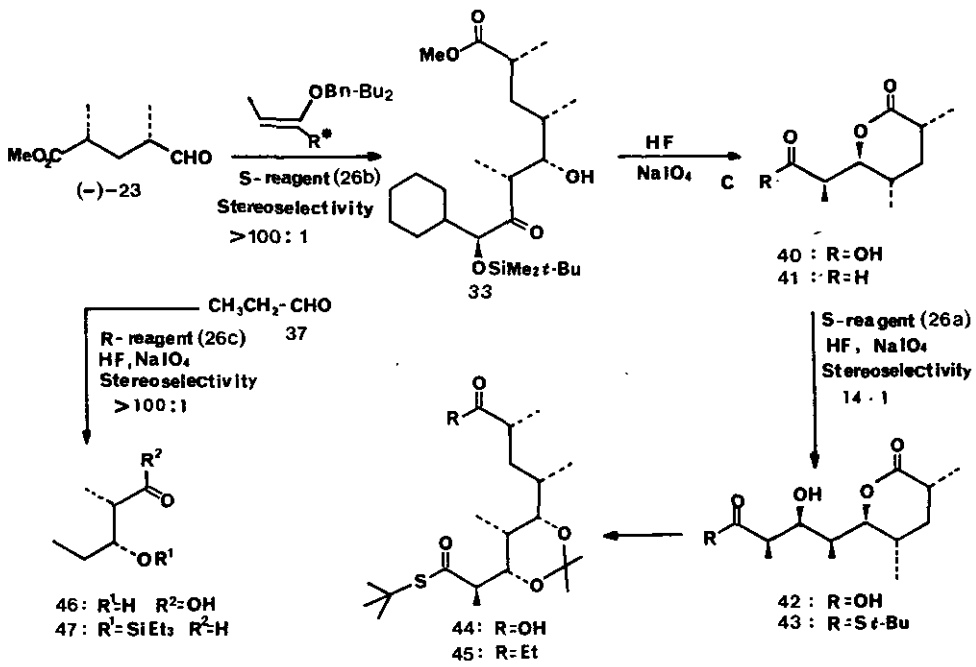


* These examples represent one of the first such demonstrations of stereochemical control by means of multiple asymmetric induction. Also see ref. 3d.

drawn in a zigzag fashion, into fragments A and B immediately suggests the order of the aldol reactions to be used in the synthesis. Aldol I (involving propanal 37 and its 3-carbon equivalent) produces fragment A, while aldol II (37 and 38) and III (39 and equivalent of 37) complete a synthesis of fragment B. Finally, both fragments are combined via aldol IV. Note that aldol I, II, and III all concern the creation of 2,3-*syn* stereochemistry, a task that can be readily achieved with 26a,b,c.

The first step of the seco-acid synthesis has already been discussed (Scheme 14). The reaction of (-)-23 with 26b provides the desired product with >100 : 1 stereoselection. The aldol product 33 which, after removal of the chiral auxiliary (HF and then $NaIO_4$), is converted to the *Prelog-Djerassi lactonic acid* 40 *in optically* pure form (>98 % e.e.). Addition of the C-1, C-2 fragment (see 36) to 41, the aldehyde

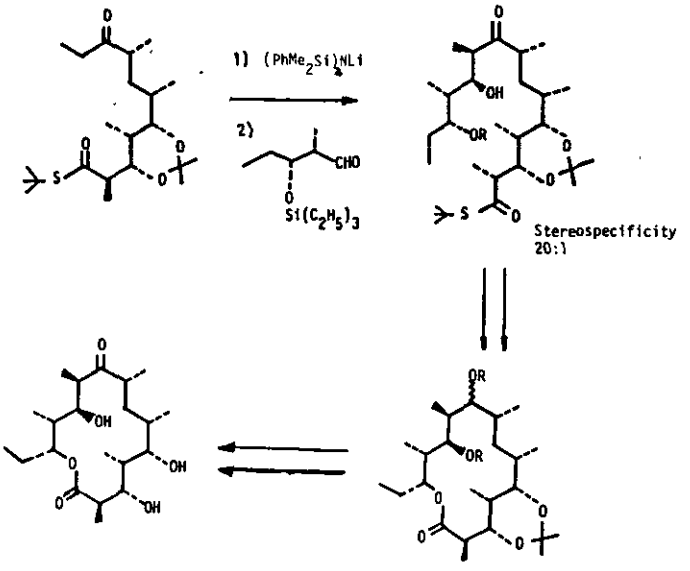
Scheme 14



corresponding to 40, uses the S-chiral reagent 26a (Aldol III). Thus, reaction of the aldehyde 41 provides (with 14 : 1 stereoselection) the major product which, upon standard treatment (see 33 to 40), is transformed to the carboxylic acid 42 and then to its thiol ester 43. After modification of the functional groups of 43 through a series of routine reactions the resulting carboxylic acid 44 is further converted to the corresponding ethyl ketone 45, which is an equivalent of fragment B. The

enantioselective synthesis (selectivity >100 : 1) of the hydroxy acid 46 corresponding to fragment A is readily achieved using propanal (37) and R-chiral reagent 26c (Aldol I). A sequence of standard operations converts 46 into aldehyde 47. Thus, eight chiral centers out of the ten embedded in the target molecule 35 have been created with remarkable efficiency and stereoselection. At this stage the overall yield is 30 % and overall stereoselectivity is approximately 90 %. The remaining tasks consist of the final aldol coupling (aldol IV in Scheme 13) of fragment A with B and the macro-lactonization of the resulting seco-acid derivative, both of which have been successfully executed, as outlined in Scheme 15.

Scheme 15



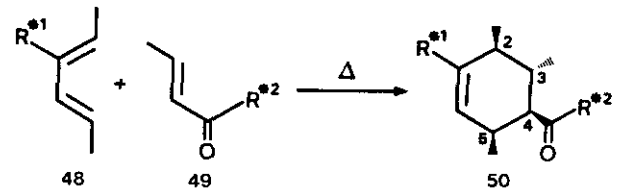
The macro-lactonization has already been adequately reviewed, and the stereochemical control in aldol IV is methodologically different from what has been discussed above.* Therefore, both transformations in the final stages of the 6-deoxyerythronolide B synthesis are omitted from this discussion.

* Aldol IV is distinguished from aldol I-III in that it (IV) involves the coupling of two structurally prefixed components.

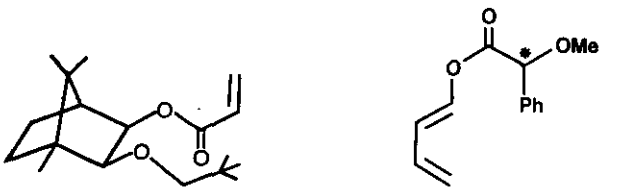
5. Diels-Alder Reaction

This reaction effects one of the most efficient organic transformations in that it (D.A. reaction) normally proceeds in excellent yield and creates, in principle, four chiral centers as exemplified in Scheme 16. The pericyclic reaction of two chiral components, diene 48 and dienophile 49 can hypothetically produce 2^4=16

Scheme 16



48 49 50



51 52

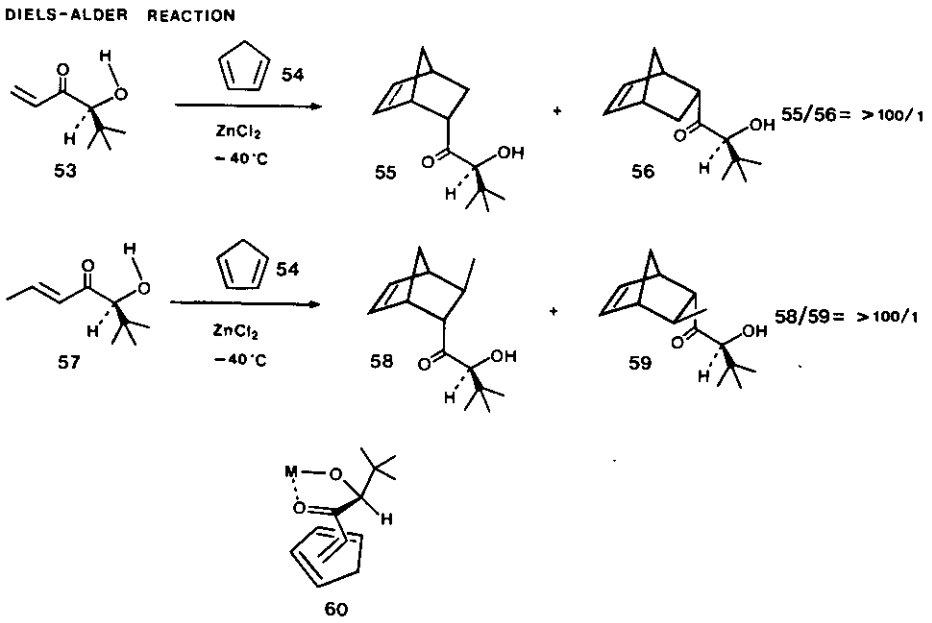
I II

stereoisomers, isomeric at the C(2), C(3), C(4), and C(5) atoms in 50. The attainment of the potential stereoselection requires the advantageous (and simultaneous) exercise of, at least, four elements which govern the stereochemical course of the reaction. These elements are indeed well known: cis-addition, endo-addition, and diastereofacial selectivities of both the chiral ene and diene.* With regard to the last factors, diastereoselectivities have indeed received renewed interest in recent years, and some excellent chiral reactants such as dienophile 51[8] and diene 52[9] are now available. After a close review of this previous development, our attention has been directed to the design of chiral dienophiles in which a chiral auxiliary (R*) is attached one atom closer to the three-carbon enone unit (Type I) than in the reagents (type II) often used earlier (see 51).

* The last factor (the selectivity of the chiral diene) is closely related with the orientation of 48 to 49 in the transition state (regio-chemistry of 48).

The type I reagent of choice was 53.[10] Coupling of 53 with cyclopentadiene (54) in the presence of $ZnCl_2$ at -40°C is completed within 1 h to provide two endo-products 55 and 56 in a ratio of >100 : 1, in addition to a small amount of the exo-isomers (Scheme 17). Likewise the reaction of 57, a homolog of 53, with 54 under the ident-

Scheme 17

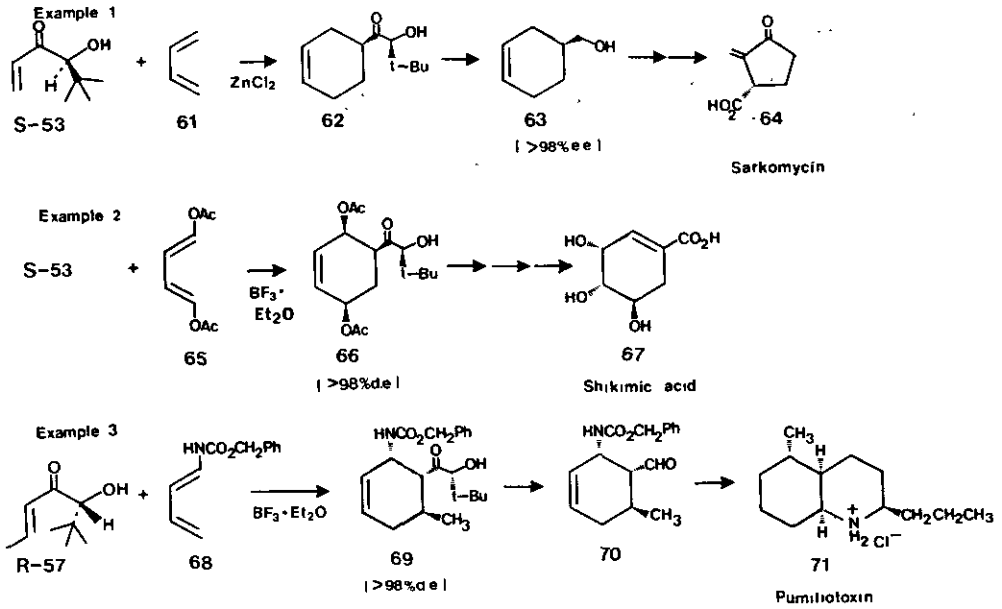


ical conditions proceeds smoothly with equally high stereoselection (58 : 59 =>100 : 1). The results of these and other related experiments disclose, at least, two important features of the D.A. reaction. First, the coordination of the Lewis acid catalyst with the α-hydroxyketone moiety of the dienophile 53 leads to the formation of a rigid five-membered chelate, thus making the two diastereotopic faces of the enone system highly distinguishable (see 60). Second, from the established absolute configurations of 53 and 55 (and also 57 and 58), one concludes that, which the chelated framework of 60, the D.A. reaction proceeds with the enone fragment in its cisoid (synplanar) conformation, at least, in these particular instances [as opposed to the transoid conformation often postulated earlier for chiral esters of type II (see above)].

A variety of dienes react with 53 and 57.[10] In the three examples shown in Scheme 18 the cycloaddition reaction provides a single adduct to the detection limits of ^1H NMR spectroscopy (270 Hz). Oxidative removal of the chiral auxiliary group from the adduct (cf. a similar transformation of the aldol products discussed in Section

4) leads to a homochiral product (at minimum 98 % e.e.), which serves as an intermediate for the synthesis of a natural product. Example 1. Reaction of S-53 with excess butadiene (61) in the presence of $ZnCl_2$ gives rise to 62 which is in turn

Scheme 18

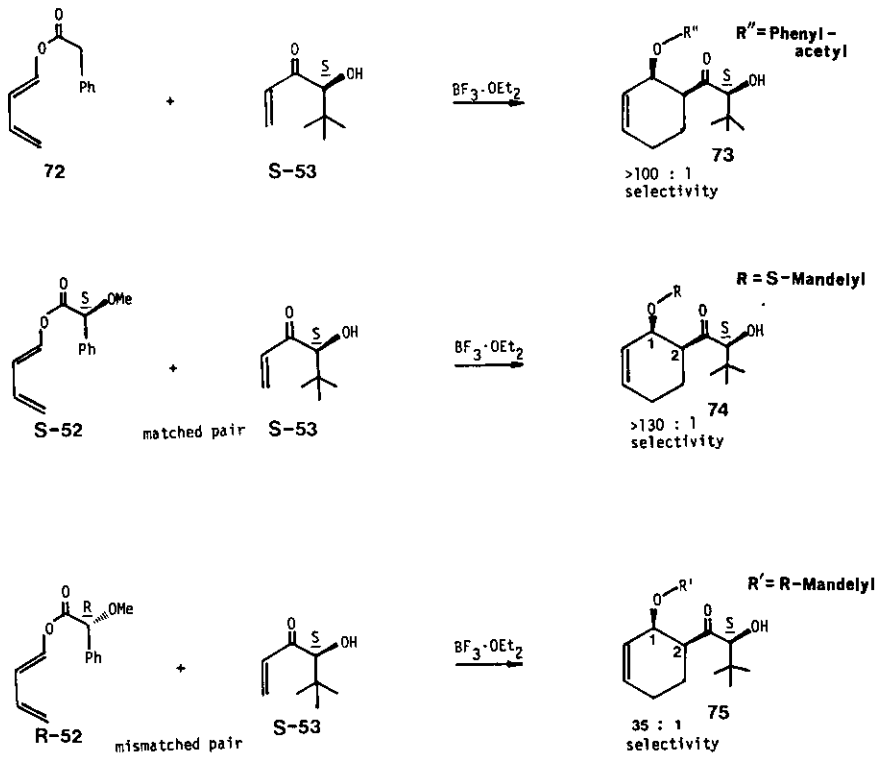


transformed via three steps to alcohol 63 (98 % e.e.). Conversion of the enantiomer of 63 to natural sarkomycin 64 has already been documented.[10] Example 2. 1,4-Diacetoxybutadiene (65) and S-53 are coupled with the aid of $BF_3 \cdot OEt_2$. Product 66, which is the exclusive stereoisomer of this cycloaddition, is then subject to a series of six transformations analogous to those used earlier to provide optically pure shikimic acid (67). Example 3. A mixture of R-57 and $BF_3 \cdot OEt_2$ is allowed to react with excess diene 68 to provide an adduct 69 with >100 : 1 diastereoselection, which is in turn converted in two steps to aldehyde 70. Conversion of 70 to the hydrochloride of (+)-pumiliotoxin 71 follows the published procedure.[12]

The above examples of single asymmetric induction clearly demonstrate that our chiral dienophilic reagents 53 and 57 are highly diastereofacially selective (>100 : 1), and satisfy the prerequisites for successful double asymmetric induction which is, of course, the issue of our prime concern. In order to examine the validity of the matching and mismatching concept as applied to the D.A. reaction, a set of experiments

has been carried out, using butadienyl phenylacetate (72), as an achiral diene and S- and R-O-methyl mandelates (S-52 and R-52) as chiral dienes. Diene 52 has a moderate diastereoselectivity (Scheme 19).

Scheme 19

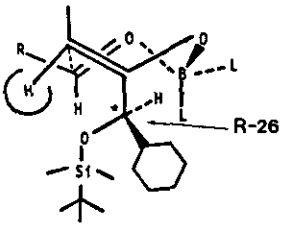


The first experiment involving S-53 and 72 reconfirm, the high diastereofacial selectivity of S-53 as applied to 72, which is close in structure to chiral diene 52. As expected, 73 is the major product of the reaction which proceeds with >100 : 1 stereoselection in the presence of the catalyst $BF_3 \cdot OEt_2$. In the next two experiments, two chiral reactants are coupled under the conditions identical to those used in the first one. The reaction of diene S-52 with dienophile S-53 provides a >130 : 1 mixture of 74 and its diastereoisomer, while the ratio of adduct 75 and its stereoisomer obtained from diene R-52 turns out to be 35 : 1.[10b] Note that in the latter two cycloadditions the absolute configurations of the two major products 74 and 75 are the same at the C-1 and C-2 centers and are directly correlated with the chirality of 53, thus the stereochemistry of these reactions is

controlled through the selection of R or S-53. In a manner similar to that demonstrated in the aldol reaction (Section 4), this outcome reflects the large diastereofacial selectivity of 53 as compared with that of 52.* The different ratios (130 : a and 35 : 1) observed in the above reactions obviously correspond to matched and mismatched pairs, respectively. Thus, both 53 and 57 have been proved to be capable of creating new chiral centers in a predictable manner.

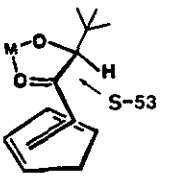
6. Some Comments on the Aldol and Diels-Alder Reaction

The two reactions discussed in the preceding sections are proposed to proceed through the transition states depicted in 76 and 60. In both cases, the two sides (or faces) of the plane defined by the sp^2 carbon atoms, and perpendicular to the π cloud, of



with the R reagent

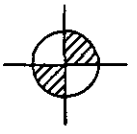
76



60

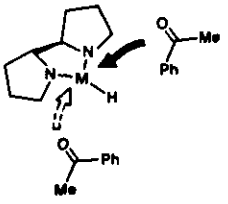
with C_1

77

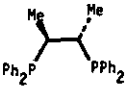


with C_2

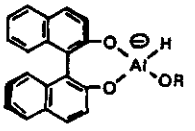
78



79



80



81

the chiral reagent R-26 (in 76) [and also of S-53 (in 60)] are distinctly diastereo-

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* The chiral center of 52 is close to the reaction site, and thus the diastereofacial selectivity of most chiral dienes normally encountered in the synthesis is smaller than that of 52. Therefore, the chirality of 53 would control the stereochemistry of most double asymmetric reactions.

topic (as shown in a more schematical manner in 77*). Thus a reacting counterpart (the aldehyde in 76 and cyclopentadiene in 60) is forced to approach the reagent almost exclusively from one "open" side. The presence of an asymmetric center in each reagent, of course, is responsible for the resulting high diastereoselectivity of the reaction, and the reagent lacks any symmetry element (C_1 symmetry).
Another design of chiral reagents is based on the concept of axial symmetry, in particular that of C_2 (see 78), the advantage of which is clearly seen in a hypothetical case of hydride reduction of acetophenone (see 79). Assuming a four-membered transition state for this reaction, one would expect that the ketone approaches the five-membered diaza-metallocycle from the two directions (see the solid and broken arrows) with the orientations indicated in 79 [the methyl on the right** and phenyl on the left side of the carbonyl in the top approach (solid arrow) and the reverse in the bottom approach (broken arrow)]. Both approaches result in the formation of S-1-methylbenzyl alcohol. Thus, with a chiral reagent of C_2-symmetry a substrate is allowed to enter one of the two stereochemically equivalent quadrants (non-shaded parts of the circle in 78). The space is now limited and thereby the stereoselection will be enhanced (cf., 78 and 77). For the aldol and Diels-Alder reactions, the reagents of C_1 symmetry have been devised because both reactions involve a multicentered (6-membered) transition state, which demands a large space and can be accommodated by a hemisphere but perhaps not by a quadrant in most cases. In contrast, some other reactions are not as space-demanding; indeed several excellent reagents of C_2 symmetry are now known as exemplified by Chiraphos (80) for homogeneous catalytic hydrogenation and also by the Binap-Al reagent 81 in ketone reduction. Sharpless' titanium reagent for epoxidation may be included in this category and is discussed in the next Section.

7. Epoxidation of Allylic Alcohols

Sharpless' reagent consists of titanium tetraisopropoxide, tert-butyl hydroperoxide, and diethyl (+)-or (-)-tartrate (Scheme 20). With (+)-tartrate the oxidant approaches the allyl alcohol from the topside of the plane shown in 82, whereas the bottom side

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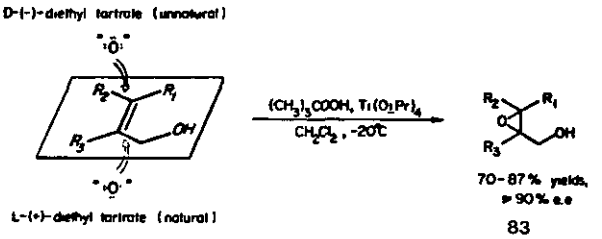
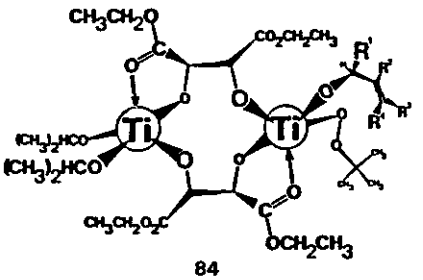
* The empty and shaded sides indicate the side open for the attack of a reactant and the blocked side, respectively.

** As it is drawn in 79.

Scheme 20



82 83



84

is open for the (-)-tartrate reagent*, giving rise to the corresponding optically active epoxy alcohols 83. This asymmetric epoxidation (hereafter abbreviated as A.E.) is proposed to proceed through the reagent-substrate complex 84, which exhibits the high face-selection (demonstrated in this reaction) which approaches 100 : 1 in many cases. Therefore, we became interested to see if this A.E. verifies the concept of multiple asymmetric induction, thus being capable of constructing two new chiral centers on a chiral substrate in a predictable manner.

One way to demonstrate its validity is to achieve, in a general and systematic manner, the stereoselective synthesis of all eight aldohexoses, each of which has four chiral hydroxymethylene groups. Our strategy is based on a reiterative two-carbon extension cycle, and its double application leads to the chiral centers embedded in the sugars.[13]

The device of the cycle is straightforward: It involves four key transformation (Scheme 21). I. Conversion of an aldehyde into its corresponding E- and Z-allylic alcohols (or their precursors) via the known Wittig olefination. II. Sharpless' A.E. III. Treatment of the epoxy alcohol with benzenethiolate anion in a basic medium. IV. The Pummerer reaction of the sulfide followed by hydrolysis.

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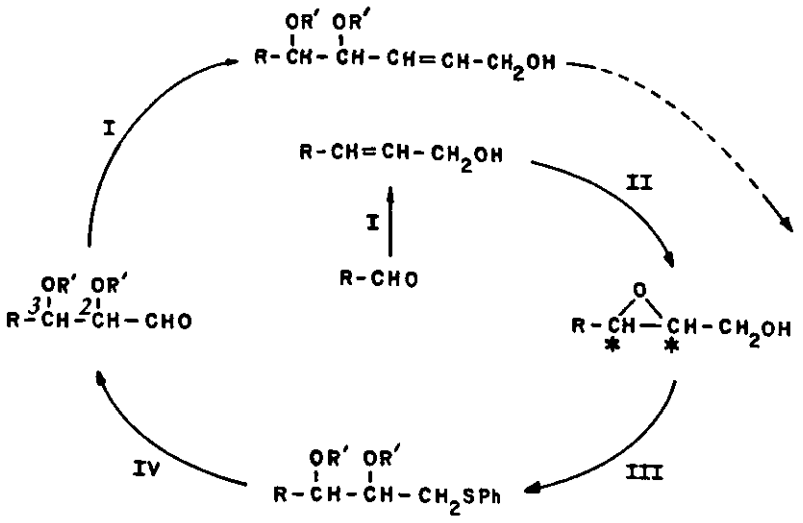
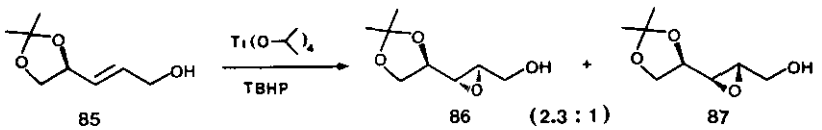
* The reagent has approximate D_2 symmetry, cf., 84.

Scheme 21

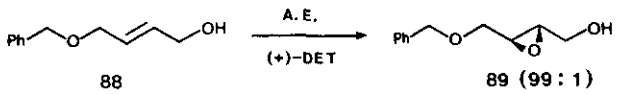


Of prime concern is the doubly asymmetric induction for which the allylic alcohol 85 derived from D-glyceraldehyde was chosen as a model (Scheme 22). Treatment of 85

Scheme 22



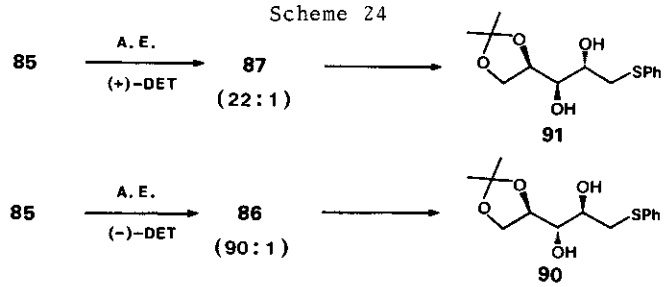
Scheme 23



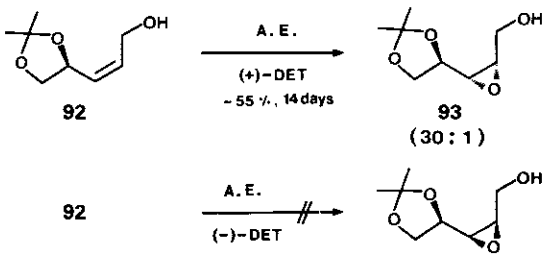
with titanium tetra-isopropoxide and tert-butyl hydroperoxide (Sharpless' reagent without diethyl (+)- or (-)-tartrate) provides a 2.3 : 1 mixture of epoxy alcohols 86 and 87. This ratio (2.3 : 1) that represents the diastereofacial selectivity of 85 is much smaller than that of the chiral epoxidizing agent, as reconfirmed with the A.E. reaction of epoxy alcohol 88, providing 89 with a 99 : 1 stereoselection (Scheme 23). All the conditions necessary for the stereochemical control of epoxidation in a double asymmetric reaction appears to have been met.

The asymmetric epoxidation of 85 with (+)- and (-)-tartrate proceeds smoothly to provide epoxy alcohols 87 and 86 in ratios of 22 : 1 and 1 : 90, respectively (Scheme 24).[13b] As predicted and also verified with these results, 85 with A.E.-(+)-DET and A.E.-(-)-DET constitutes mismatched and matched pairs, respectively. Under basic conditions both 86 and 87 are in equilibrium with the corresponding terminal epoxides (Payne rearrangement) which can be trapped with benzenethiolate anion to provide dihydroxysulfides 90 and 91 in excellent yields, respectively.

Scheme 24



Scheme 25

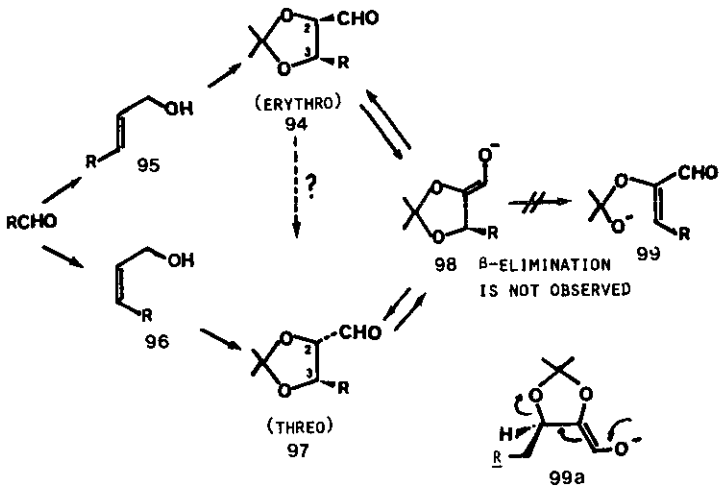


In contrast to the successful stereocontrol exhibited above for 85, the Z-allylic alcohol 92 is found to react with the A.E. reagent extremely slowly (Scheme 25): With (+)-DET the epoxidation reaches only 55 % completion in 14 days at -20°C. However, the stereoselectivity is excellent favoring the formation of 93 in a 30 : 1 ratio. With (-)-DET, the reaction is too slow to be practical.

As originally envisioned and described above, our basic cycle is intended to create

two new chiral centers using two elements of stereocontrol: the Wittig reaction (Z-and E-olefin) and A.E. Since one of them now cannot be used fully to our advantage, we must seek an alternative. Let me summarize the results we have seen thus far. The cycle (Scheme 26) leading to the 2,3-erythro products 94 via the E-isomer 95 is satisfactory, but, the A.E. of the Z-isomer 96 in the 2,3-threo series 97 often proceeds intolerably slowly. The stereocontrolling element thus lost is now replaced by another and the cycle is modified as outlined below.

Scheme 26

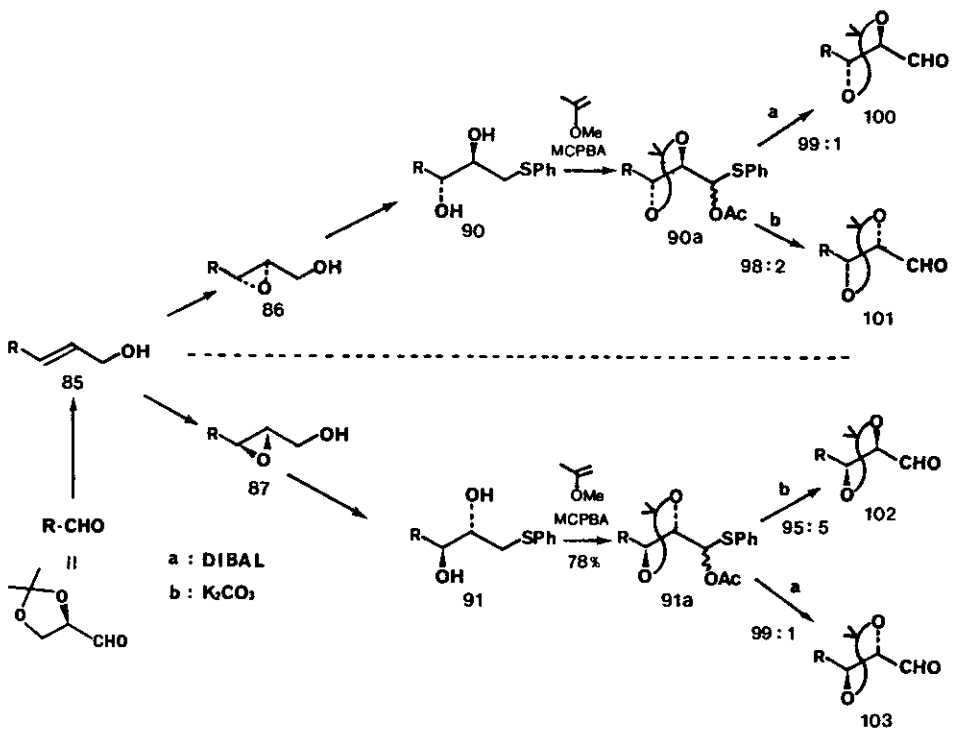


In compounds 94 and 97 the proton at C-2 is α to the aldehyde group and thus epimerizable. From the expected stability of 97 relative to 94, the latter which is readily obtainable can be equilibrated to give mainly 97, which has been up to now of limited access. The acetonide chosen as a protecting group apparently suppresses the potential complication of a β-elimination (98 to 99) inasmuch as the acetonide group helps maintain orthogonality between the enolate π system and the β-alkoxyl substituent (see 99a). Thus, treatment of several compounds represented by the general formula 94 with potassium carbonate in methanol at 25℃ indeed effects smooth isomerization (>20 : 1). Incorporation of this critical epimerization technique in our basic cycle leads to the satisfactory synthe-

sis of all possible stereoisomers (four in one cycle).

Our final version is shown in Scheme 27, using the pentoses as illustration. The epoxy alcohol 86 undergoes ring opening to provide 90 which is converted to the acetonide 90a through kinetically controlled acetonation followed by oxidation and

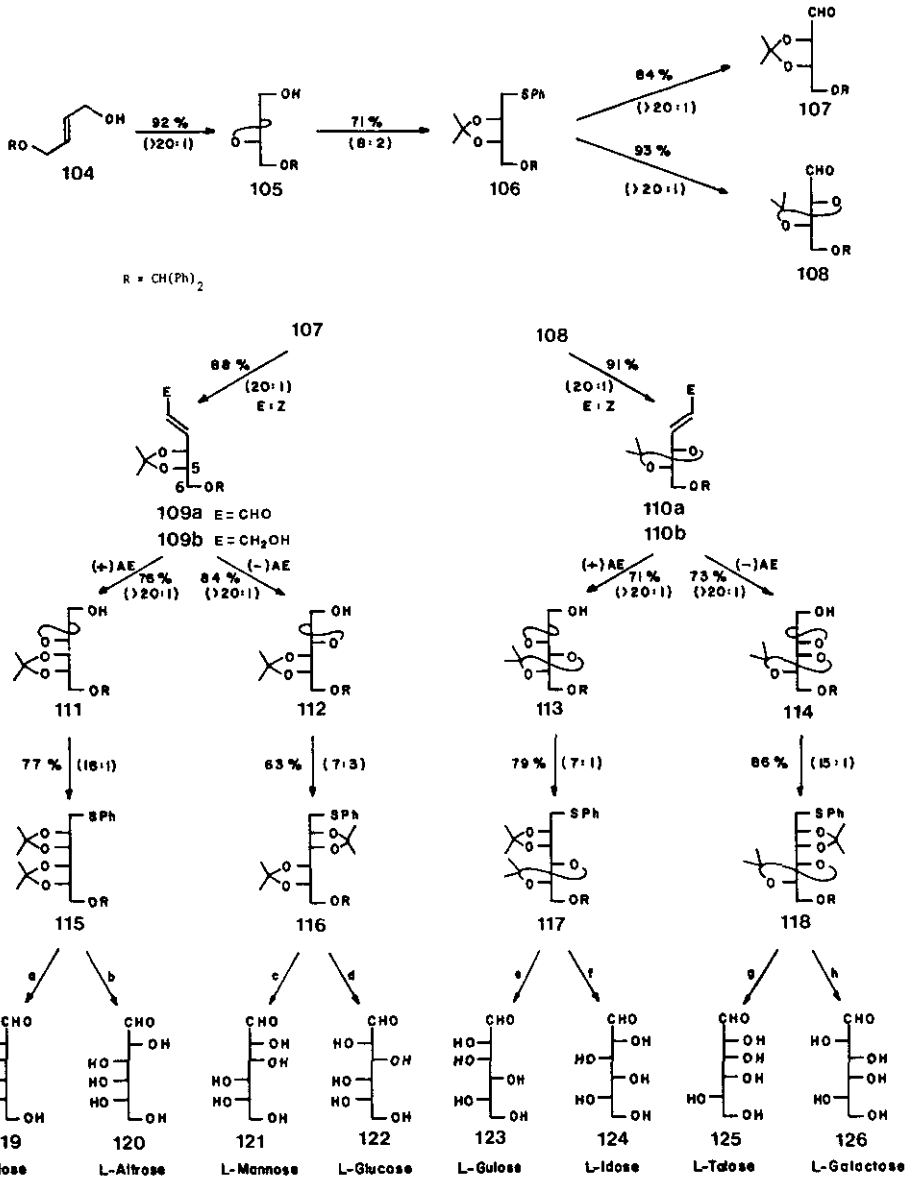
Scheme 27



acetylation. Reaction of 90a with Dibal provides, virtually without epimerization, a product (100) which proves to have the ribose configuration. Compound 90a can also be converted to the C-2 epimer of 100. Thus, treatment of 90a with potassium carbonate in methanol causes hydrolysis of the acetoxythioacetal group and epimerization at the C-2 center to give a mixture of 101 and 100 in a 98 : 2 ratio. Compound 101 has the arabinose configuration. The acetonides (102 and 103) of xylose and lyxose are prepared in exactly the same manner. The key intermediate 91a obtained from 87 via 91 provides 102 and 103 in the manner indicated in the scheme.

In this way a highly efficient route from the same intermediate 85 to either the erythro- or threo-2,3-dihydroxy aldehydes has been established. It is obvious that the success of the above scheme depends heavily upon high asymmetric induction realized by the titanium-catalyzed epoxidation with (+)- or (-)-tartrates. The diastereofacial selectivity of this reagent outweights the influence of the pre-existing chirality in the allylic alcohol. Now that efficient, practical routes from a chiral or achiral aldehyde to all the four possible bishomologated aldehydes

Scheme 28



have been established, these final products are ready for a second two-carbon extension. Indeed, the synthesis of all the possible hexoses has now been completed, as shown in Scheme 28.

The top row of the scheme represents the first cycle of the hexose synthesis, which begins with a single building block, 4-benzhydryloxy-(E)-but-2-en-1-ol (104), a compound which is readily prepared from (Z)-2-butene-1,4-diol. Step I of the extension cycle is therefore eliminated in this initial case. Conversion of 104 into 107 and 108 completes the first cycle, and the conversion of 107 and 108 into 119 to 126 constitutes the entire set of the second cycle. The yield and selectivity are described for each step. I am not going into the details of the sequences leading to all hexoses. It suffices to say that all steps in this scheme except for the steps 112 - 116 proceed with remarkable regio- and stereoselection. Since the mirror image of every compound can be prepared by simple exchange of the chiral ligand (tartrate ester) in the A.E. reaction, the formal synthesis of the D-hexoses has also been achieved. This achievement adequately proves that the concept of matching and mismatching is valid in the A.E. reaction as well.

8. Councluding Remarks

The power of the strategy based on the concept of multiple asymmetric induction has now been amply demonstrated. In the process of creating a new chiral center or centers, the reagent used in a matched pair augments the stereoselectivity intrinsic to the substrate, whereas the stereochemical course of a mismatched reaction is governed by the diastereoselectivity of the reagent. There is no reason to believe that the validity of multiplicativity of two (or more) diastereoselectivities is limited either to the cases of the above three major organic reactions or to the cases of the acyclic systems used to illustrate this concept. Therefore, the introduction of highly diastereoselective reagents into organic synthesis has brought about an era characterized by the evolution from substrate-controlled to reagent-controlled organic reactions. The multiplicativity of diastereoselectivities is only approximate, and not precise. This is so because our simple analysis completely ignores many factors which are considered to play a minor role in the face selection, e.g., such interactions that arise in the regions remote from the reaction site. All of the examples quoted in this lecture show that the stereoselectivities in both matched and mismatched pairs are somewhat lower than those calculated from the diastereoselectivity of each reactant partici-

pating in the reaction. This lowering is in all likelihood caused by these minor factors.

I conclude this presentation by pointing out some intersting features of multiple asymmetric induction. It is obvious that the two (or more) reactants involved in a reaction must be homochiral in order to gain full control of its stereochemistry in the manner described above. Needless to say, the resulting product is optically active. For example, we have succeeded in synthesizing L-glucose, but we are unable to prepare racemic glucose directly and with equal efficiency. Nature rarely synthesizes d,l-mixtures. Perhaps there is no pressing demand for racemates when the corresponding enantiomers can be made.

ACKNOWLEDGMENTS

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Drs. W. Choy, B. Imperiali, and H. Tobita have read and improved the written version of this lecture, and this assistance I gratefully acknowledge.

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