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Acyclic Stereocontrol Through the Aldol Condensation

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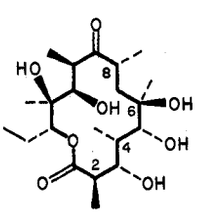
Summary. For the scientist who wishes to synthesize complex organic compounds, the most difficult problem is often establishing the correct configuration at the various chiral centers as the synthesis is being carried out. In the past decade, there has been an increasing effort to find direct solutions to this problem, which is particularly acute in the synthesis of acyclic and other conformationally flexible molecules. One of the oldest organic reactions, the aldol condensation, is emerging as a powerful tool for use in achieving such stereocontrol.

One of the most vexing problems in the synthesis of complex organic compounds is control of relative stereochemistry. The problem arises from the fact that each tetracoordinate carbon may represent a center of chirality (*1*). Thus, any carbon that is bonded to four different substituents may exist in either "right-handed" or "left-handed" forms, and there are two stereoisomeric forms of a molecule that contains such a chiral element. In general, a molecule containing n chiral elements may exist in as many as 2^n stereoisomeric forms. For example, erythronolide A (**1**), the aglycone of the important antibiotic erythromycin A, has ten chiral centers and may exist in 1024 stereoisomeric forms (*2*). Compound **2**, the aglycone of the polyether antibiotic septamycin, has 21 chiral centers and may exist in more than 2 million stereoisomeric forms.



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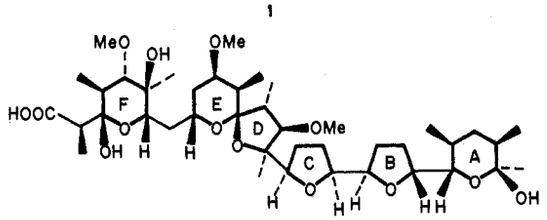
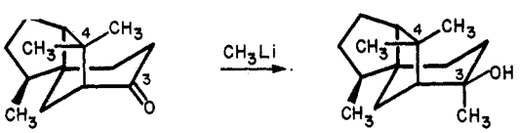


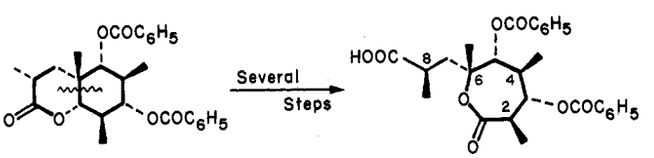
2

To be able to carry out efficient syntheses of complex molecules such as **1** and **2**, chemists must be able to control the sense of chirality at each chiral center as it is introduced in the course of a synthesis. Traditionally, this has been accomplished by making use of the rather rigid structures of small-ring compounds. For example, in a synthesis of the tricyclic sesquiterpene alcohol cedrol (**4**) the correct relative stereochemistry at C-3 results from addition of methyllithium to ketone **3** because one face of the carbonyl group is shielded by one of the methyl groups at C-4 (*3*).



3 **4**

When the molecule to be synthesized does not have such a rigid structure, control of stereochemistry is much more difficult. A classic way in which chemists have approached this problem is to establish the sense of chirality of new asymmetric carbons by using small-ring intermediates, and then break open the ring to obtain an acyclic building block containing the desired asymmetric carbons. For example, in one synthesis of erythronolide A (**1**) the correct relative chirality at the five asymmetric centers in the C-2 to C-8 portion of the molecule was established by using intermediate



5 **6**

5, which contains two six-membered rings (*4*). This material is manipulated by a series of steps including cleavage of the indicated carbon-carbon bond to obtain lactonic acid (**6**), a further intermediate in the preparation of **1**.

Such indirect methods of achieving stereocontrol, although conceptually elegant, limit the options available to the synthetic chemist and often cause syntheses to be long and cumbersome. Consequently, many research groups have been

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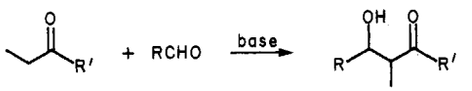
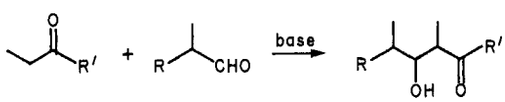
investigating methods in which effective stereocontrol might be realized without resorting to such indirect methods (*5*). For the past 5 years, my research group at Berkeley and several other groups in the United States, Japan, and Germany have been reexamining one of the oldest organic reactions—the aldol condensation (Eq. 1). This venerable process (*6*) has



(1)

several desirable features which highly recommend it as a synthetic method. First, a new carbon-carbon bond is formed. Reactions in which carbon-carbon bonds are formed are especially important, relative to those involving simply the conversion of one functional group into another, since they allow us to build up larger molecules from small building blocks. Second, the aldol condensation provides a product having two useful functional groups, which can serve as reaction sites for further synthetic transformations. Finally, in a case such as that depicted in Eq. 1, two new chiral centers are created. If one of the reactants is chiral, the aldol product contains three chiral elements and there are $2^3 = 8$ possible stereoisomers (Eq. 2). Thus, the aldol condensation is poten-

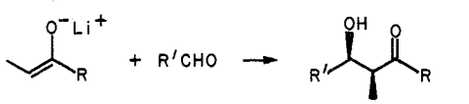


(2)

tially a powerful method for synthesizing polyfunctional compounds with many chiral centers, such as compounds **1** and **2**, provided we can learn to control its stereochemical outcome.

The first significant breakthrough was the development of reagents that enable the chemist to control the relative chirality of the two new asymmetric carbons formed in an aldol condensation such as Eq. 1. Dubois and co-workers showed that in the reaction of a preformed lithium enolate with an aldehyde, there is a natural predisposition for *cis* enolates to give *erythro* aldols (Eq. 3) while *trans* enolates tend to give *threo* aldols (Eq. 4) (*7, 8*).

We capitalized on this important observation by finding that, when the substituent R in Eqs. 3 and 4 is large, the



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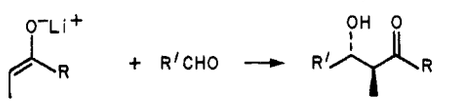
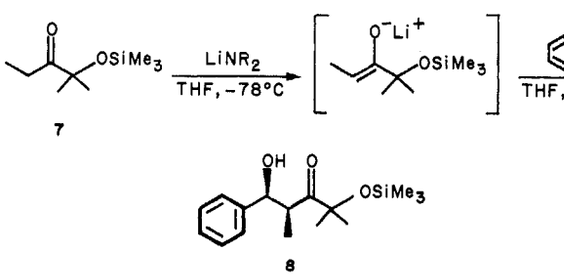


(4)

stereoselectivity observed is quite high (*9*). Thus, the preformed lithium enolate of the ethyl ketone **7** (a *cis* enolate) reacts with benzaldehyde in tetrahydrofuran (THF) to give virtually exclusively the *erythro* aldol **8**. Similar high stereoselectivity is seen in the reaction of ketone **7** with a variety of other aldehydes. On the other hand, the preformed *trans*



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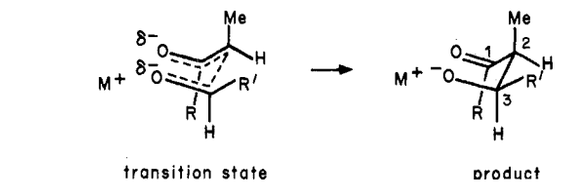
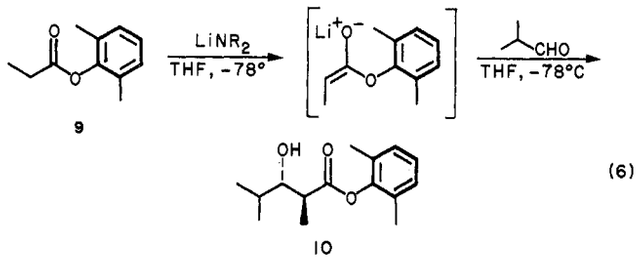


Fig. 1. Zimmerman transition state for the aldol condensation: *cis* enolate giving *erythro* aldol.

enolate from 2,6-dimethylphenyl propionate (**9**) condenses with isobutyraldehyde to afford solely the *threo* β-hydroxy ester **10** (*10*).

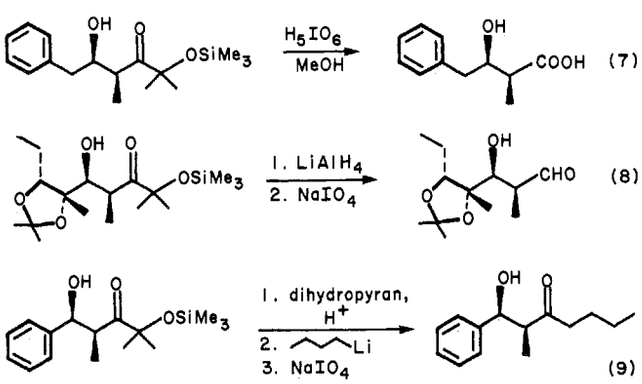
The high stereoselectivity of aldol condensations such as those depicted in Eqs. 5 and 6 has usually been interpreted in



(6)

terms of a transition state proposed by Zimmerman and Traxler (*11*) for a related reaction in 1957. The basic assumption of their proposal is that the new carbon-carbon bond is partially formed in the transition state for the reaction. Thus, there is partial negative charge on each of the two oxygens and it is reasonable that the assembly would be ordered so that these partial negative charges are both oriented in the general direction of the cation. This electrostatic ordering of the transition state results in a *cis* enolate giving an *erythro* aldol if the distance between R and R′ is maximized (Fig. 1). The alternative arrangement is shown in Fig. 2 (*12*). In this arrangement R and R′ are closer together. This arrangement is disfavored for simple steric reasons, particularly for enolates having large R groups (*13*).

Reagents such as **7** and **9** are useful because they allow the formation of either the *erythro* or the *threo* β-hydroxy carbonyl system and because the products may be converted into a variety of other useful intermediates. For example, the aldols formed from reagent **7** may easily be transformed into *erythro* β-hydroxy acids (Eq. 7) (*9*), *erythro* β-hydroxy aldehydes (Eq. 8) (*14*) or other *erythro* β-hydroxy ketones (Eq. 9) (*15*). In a similar manner, the *threo* aldols prepared from reagents such as **9** can be transformed into a variety of useful *threo* β-hydroxy carbonyl compounds.



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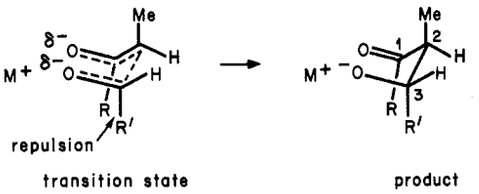
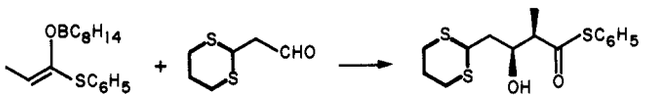


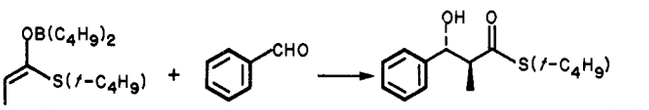
Fig. 2. Zimmerman transition state for the aldol condensation: *cis* enolate giving *threo* aldol.

At Berkeley, we have concentrated on using preformed lithium enolates to accomplish kinetic stereoselection. Other research groups have investigated stereocontrol with enolates of other metals and also with thermodynamic selection (*16*). Masamune at Massachusetts Institute of Technology and Evans at Caltech and their respective co-workers find that highly stereoselective aldol condensations may be realized with boron enolates. For example, *S*-phenyl propanethioate may be converted in the *cis* enolate **10**, which gives *erythro* aldols of high stereochemical purity (Eq. 10) (*17*). On the other



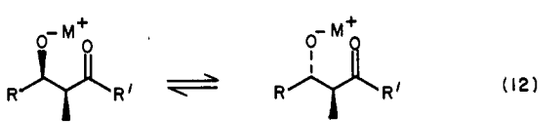
10 (10)

hand, *S-tert*-butyl propanethioate affords a *trans* enolate (**11**) which gives rise to *threo* aldols (Eq. 11) (*18*).



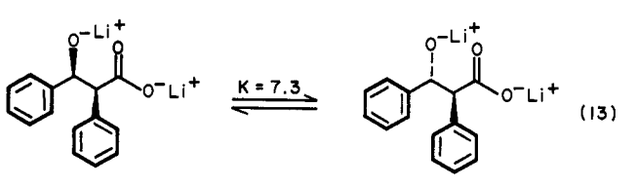
11 (11)

Progress has also been made in achieving thermodynamic stereoselection (*16*). The aldol condensation is easily reversible, and *erythro-threo* equilibration is often observed when an ethereal solution of the aldolate (the salt of the aldol) is allowed to stand for a period of time (Eq. 12) (*9*). The rate of



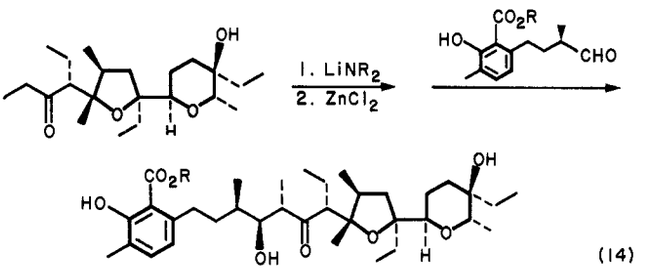
(12)

this equilibration depends on a number of factors, including the nature of the cation, M. In general, cations that are strongly chelated by the two oxygens of the aldolate (B, Al, and to some extent Li) stabilize it and retard retroaldolization. Aldolates are more prone to undergo retroaldolization when the cation is one that is largely dissociated (K, Na, and R_4N). Thus, *erythro-threo* equilibration is a process that can often be promoted by a judicious choice of reaction conditions. It turns out that the *threo* isomers of many aldolates are substantially more stable than their *erythro* counterparts (for instance, Eq. 13) (*19*). Thus, equilibration can sometimes be



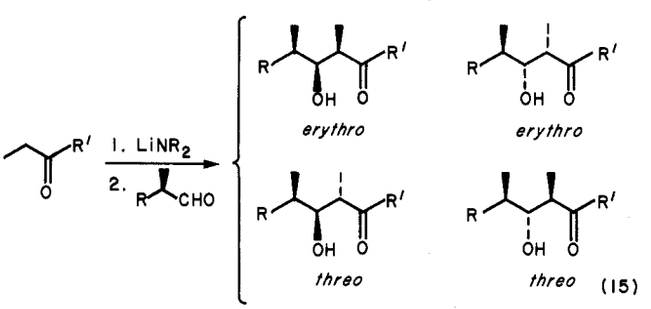
(13)

used to achieve *threo* stereoselection. In addition, House *et al.* (*20*) at Georgia Tech discovered that certain cations, notably Zn^{2+} and Mg^{2+}, actually enhance the thermodynamic *threo* selectivity in many cases. The House procedure has become one of the standard methods for achieving modest *threo* stereoselectivity. For example, it was used by Kishi and co-workers in a crucial aldol coupling of two intermediates in a synthesis of the polyether antibiotic lasalocid (Eq. 14) (*21*). Lasalocid, which has the *threo* configuration at the pertinent chiral centers, is obtained as the major isomer of a 40:10:7:3 mixture of stereoisomers.



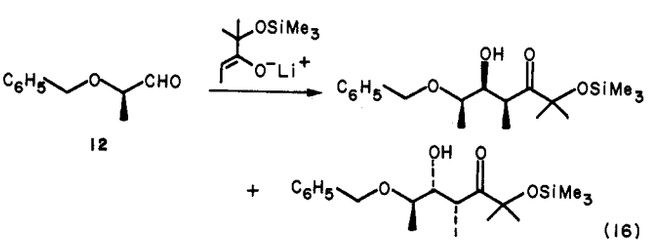
(14)

The ability to rather confidently control the relative configuration of the two chiral centers produced in an aldol condensation is only half a victory. A much more difficult problem presents itself when the aldehyde is chiral. As pointed out earlier, the product from such an aldol condensation (Eq. 2) has three chiral centers, and hence there are eight possible stereoisomers. Four of these stereoisomers are depicted in Eq. 15; the other four are the enantiomers (mirror-image stereoisomers) of the ones shown. Two of the isomeric products are *erythro* and two are *threo*, because in a chiral aldehyde the two faces of the carbonyl group are diastereotopic rather than enantiotopic (*22*). Of course, by using an *erythro*-selective or *threo*-selective reagent, we can select two of the four stereoisomers. For example, addition of the



(15)

enolate of ketone **7** with chiral aldehyde **12** provides a 2:1 mixture of two *erythro* aldols (Eq. 16) (*14*). The 2:1 ratio



(16)

reflects the inherent difference in reaction rate when the enolate of ketone **7** attacks the two diastereotopic faces of the aldehyde; it is called the diastereoface preference of the aldehyde.

At present, the only effective way to influence the diastereoface preference in additions to such chiral aldehydes is a strategy called double stereodifferentiation (*23*). To understand how this method works, one must first realize that either reactant in an aldol condensation can be chiral and can show diastereoface selectivity. For example, as shown in Eqs. 17

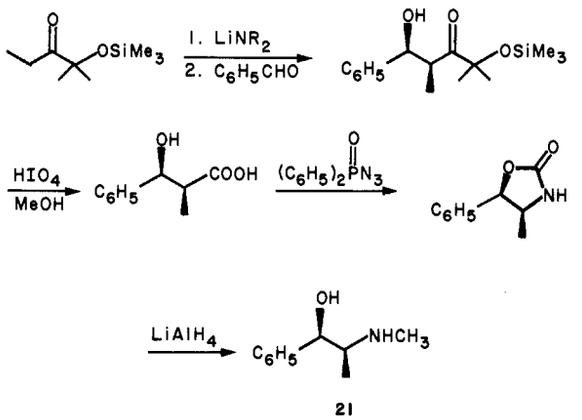


Fig. 3 (left). Synthesis of (±)-ephedrine.

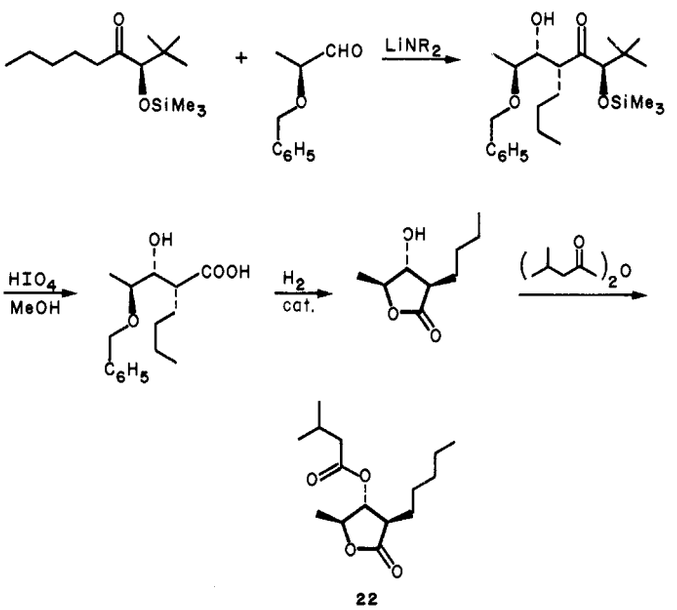
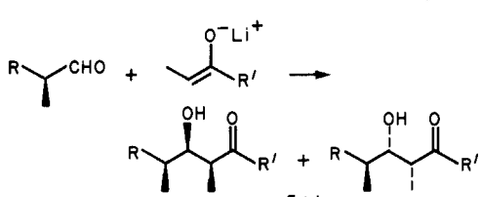


Fig. 4 (right). Synthesis of (±)-blastmycinone.

and 18, assume that one has a chiral aldehyde that shows diastereoface preference of 5:1 in the indicated sense and a chiral enolate that also shows diastereoface preference of 5:1 as indicated. Now consider what happens when one allows the indicated enantiomer of the chiral aldehyde to react with the



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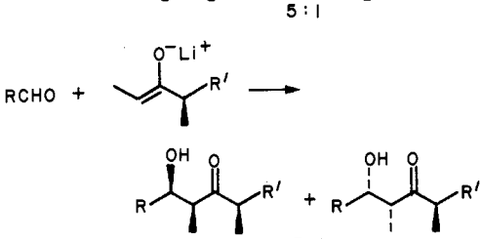
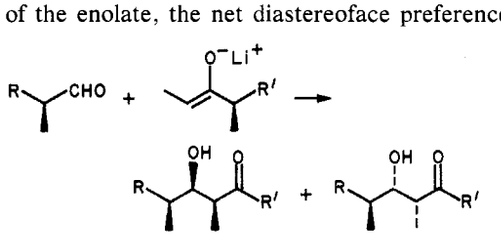


(18)

indicated enantiomer of the chiral enolate. As shown in Eq. 19, one of the *erythro* aldols will be formed in much greater quantity than the other, since both chiral reactants are promoting the same sense of chirality at the newly created centers; to a first approximation, the two *erythro* aldols will be formed in a ratio of 25:1. Of course, if one allows the same enantiomer of the aldehyde to react with the other enantiomer of the enolate, the net diastereoface preference of the aldehyde should be even worse than in its reaction with a typical achiral enolate, since the two chiral reactants are now working at cross-purposes in inducing the sense of chirality at the two new centers (Eq. 20).



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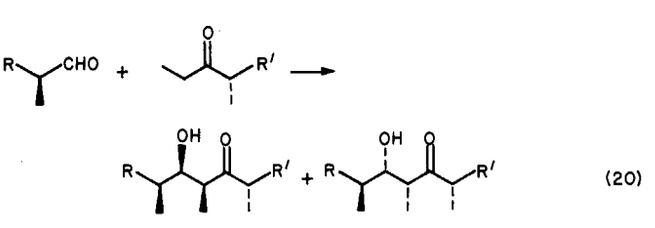
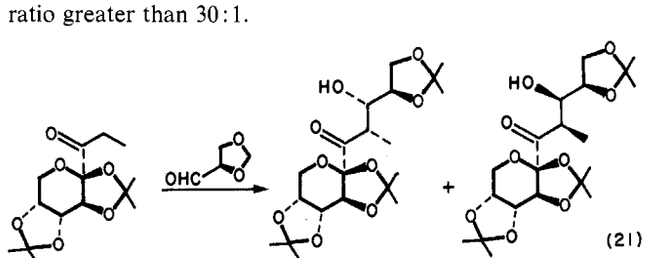


(20)

An example of double stereodifferentiation in an aldol condensation is shown in Eqs. 21 and 22. The condensation depicted in Eq. 21 represents an unproductive combination of ketone and aldehyde; the two *erythro* aldols are produced in a ratio of only 2:1. However, when the other enantiomer of the aldehyde is used, both reactants promote the same sense of chirality at the new centers. Productive double stereodifferentiation results and the two *erythro* aldols are produced in a ratio greater than 30:1.



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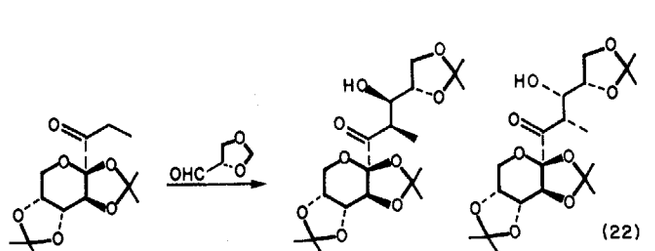
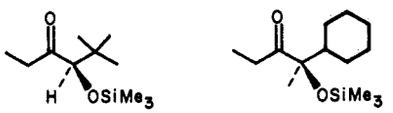


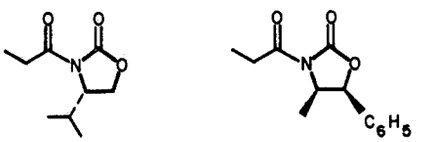
(22)

In order to capitalize on this strategy, chiral reagents **13** and **14** have been developed by my research group at Berkeley and by Masamune's group (*23*). A related class of highly selective reagents has recently been introduced by Evans and co-



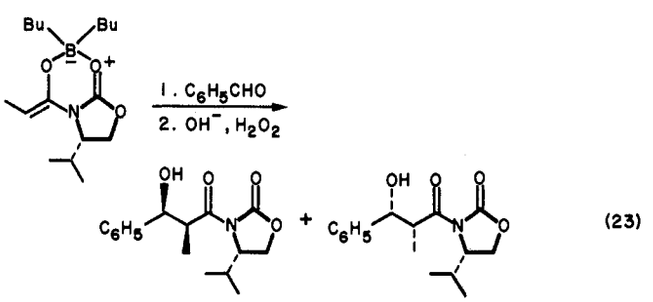
13 **14**

workers (*24*). The Evans reagents are propionyl imides **15** and **16**, which are derived from the readily available amino alcohols valinol and norephedrine. The value of the Evans re-



15 **16**

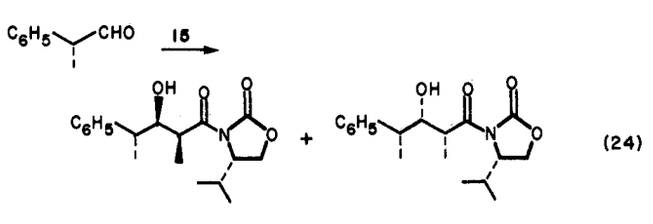
agents is that the derived enolates show exceptional inherent diastereoface selectivity in aldol condensations. For example, the dibutylboron enolate derived from **15** reacts with benzaldehyde to give aldols **17** and **18** in a ratio of 332:1 (Eq. 23).



(23)

17 **18**

These reagents are so demanding in promoting a given sense of chirality at the newly created chiral centers that they should totally overwhelm the modest inherent diastereoface preferences of most chiral aldehydes. Thus, compound **15** should react with the indicated enantiomer of 2-phenylpropanal to give almost completely aldol **19**, even though the innate diastereoface preference of this aldehyde is for formation of **20** (Eq. 24).



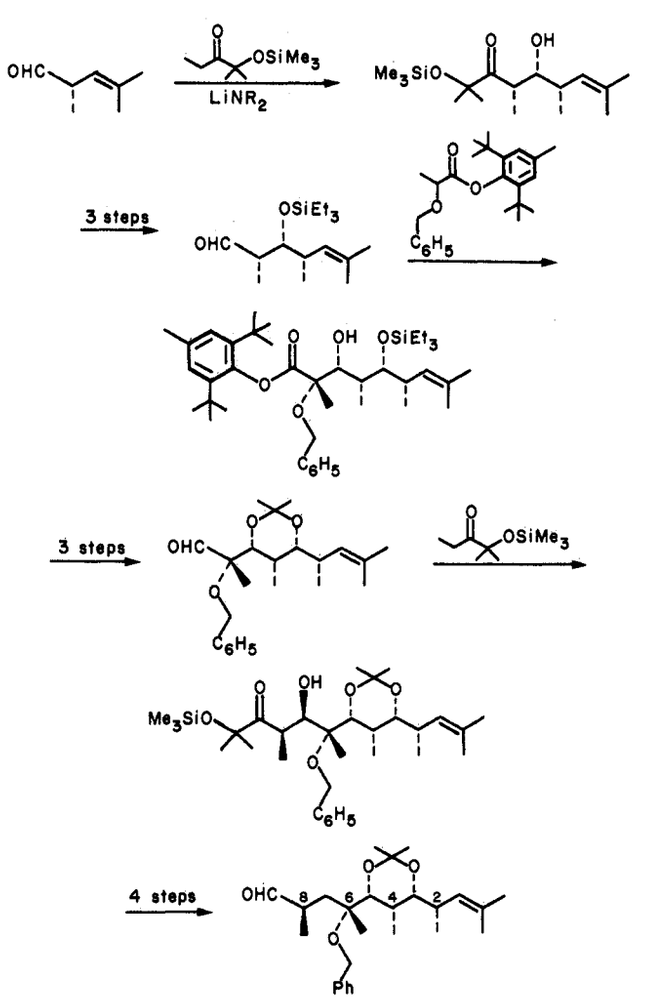
(24)

19 **20**

Up to the present, most of the research on aldol stereoselection has been aimed at understanding the factors responsible for stereoselectivity and developing reagents for controlling the *erythro-threo* and diastereoface preference problems. Application of the technique in the synthesis of complex structures has barely begun. However, some progress in this direction has been made. A simple example in which a stereoselective aldol condensation provides stereochemical control is the synthesis of the alkaloid ephedrine (**21**), outlined in Fig. 3 (*9*). This synthesis, which has a 71 percent overall yield, illustrates the power of the aldol condensation as a synthetic method for a variety of structural types, since ephedrine does not even contain the 1,3-keto alcohol functionality typical of an aldol. However, by using well-established functional group chemistry, it is easy to transform the COOH group into $NHCH_3$.

A second example is the synthesis of blastmycinone (**22**), a degradation product of the antibiotic antimycin A_3 (Fig. 4) (*25*).

For about 18 months, several of my co-workers have been developing a synthesis of erythronolide A (**1**) (*26*). Our goal is to use a series of stereoselective aldol condensations to form all of the necessary carbon-carbon bonds. Although the synthesis is not yet complete, we have successfully negotiated three of the five necessary aldol condensations and have prepared an intermediate that has six of the ten chiral centers of erythronolide A (Fig. 5). The three aldol condensations in Fig. 5 proceed with stereoselectivities of 15:1, 5.7:1, and 5.3:1, respectively. Thus, the overall stereochemical yield for the preparation of aldehyde **23** is 69 percent. Since **23** has six chiral centers, there are 64 possible stereoisomers. A stereorandom synthesis would give **23** (and its enantiomer) in a stereochemical yield of only 3 percent. It is interesting to note that intermediate **23** has the same six chiral centers as compound **6**, an intermediate in one of the previous successful syntheses of compound **1**.



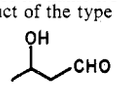
23

Fig. 5. Stereoselective aldol approach to (±)-erythronolide A.

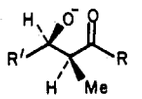
In this brief article, I think I have given a taste of the exciting progress that has been made in bending the aldol condensation to our will over the past 5 years. Much has been accomplished and much remains to be done. At the same time, other research groups are actively investigating many other organic reactions from the standpoint of achieving good stereocontrol in the synthesis of conformationally flexible systems. It is clear that this field will continue to be an active area of research for some time to come.

References and Notes

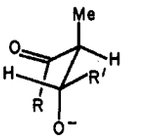
1. The terms chiral and chirality were first introduced by Lord Kelvin when he wrote: "I call any geometrical figure, or any group of points chiral, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself" [*Lord Kelvin: Baltimore Lectures* (Clay, London, 1904)]. The terms have gained widespread use in chemistry since 1966 due to the landmark article "Specification of molecular chirality" [R. S. Cahn, C. K. Ingold, V. Prelog, *Angew. Chem. Int. Ed. Engl.* **5**, 385 (1966)]. Cahn *et al.* define chiral and chirality in the following manner: "A model which has no element of symmetry except at most axes of rotation may be called chiral. Thus, chirality expresses the necessary and sufficient condition for the existence of enantiomers. Chirality means handedness, and, in our context, topological handedness." Because of the nature of three-dimensional space, there are three kinds of chiral element: centers, axes, and planes. The most common one is the center of chirality—the familiar asymmetric carbon.
2. In this article, the following conventions are used in depicting structures. The main skeleton of the molecule is written as a geometric figure so that each vertex and the end of each line represents an atom, which is carbon unless otherwise indicated. Hydrogens bonded to tetracoordinate carbons are usually omitted unless the omission would lead to confusion. Lines of normal density represent bonds that lie more or less in the plane of the page. Bold lines indicate bonds that project toward the viewer, and dashed lines represent bonds that project away from the viewer. Thus, each vertex bearing bold or dashed bonds corresponds to a chiral center.
3. G. Stork and F. H. Clarke, *J. Am. Chem. Soc.* **77**, 1072 (1955); *ibid.* **83**, 3114 (1961).
4. E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar, J. R. Falck, *ibid.* **101**, 7131 (1979).
5. For an excellent review of the field see P. A. Bartlett, *Tetrahedron* **36**, 2 (1980).
6. R. Kane, *Ann. Phys. Chem.* **44**, 475 (1838); *J. Prakt. Chem.* **15**, 129 (1838). The aldol condensation takes its name from the trival name for 3-hydroxybutanal, the simplest product of the type (*al*dehyde, alco*hol*).



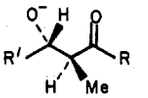
7. J. E. Dubois and M. Dubois, *Chem. Commun.* (1968), p. 1567; J. E. Dubois and P. Fellman, *C. R. Acad. Sci. Ser. C* **274**, 1307 (1972); *Tetrahedron Lett.* (1975), p. 1225.
8. In describing enolates, *cis* and *trans* refer to the relationship of the enolate oxygen and the alkyl group attached to the adjacent carbon of the double bond. The convention used to describe the relative configuration of aldols is as follows: when the aldol is written in an extended (zigzag) manner, if the β-hydroxy group and the alkyl group at the α position both extend either toward the viewer or away from the viewer, this is an *erythro* stereoisomer. If one of these substituents projects away from the viewer and one toward the viewer, this is a *threo* stereoisomer. In reactions involving only achiral reactants, such as Eqs. 3 and 4, the indicated products are accompanied by an equal amount of the mirror-image stereoisomer (enantiomer) in each case. Normally, only one member of each pair of enantiomers is depicted, since we are usually concerned with the relative chirality of the two newly created chiral centers.
9. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, J. Lampe, *J. Org. Chem.* **45**, 1066 (1980).
10. M. C. Pirrung and C. H. Heathcock, *ibid.*, p. 1727.
11. H. Zimmerman and M. Traxler, *J. Am. Chem. Soc.* **79**, 1920 (1957).
12. Deconvolution of perspective drawings such as those labeled "product" in Figs. 1 and 2 is often difficult, even for experienced chemists. These drawings are related to the planar, zigzag depictions used elsewhere in this article in the following way. For the product in Fig. 1, note that the chain of atoms C_1-C_2-C_3-R′ lies in a plane. If we view this plane from the top we see



For the product in Fig. 2, we must first rotate about the C_2-C_3 bond so that the chain of atoms C_1-C_2-C_3-R′ again lies in a plane:



Viewing this plane from the top we see



13. Other mechanistic interpretations have also been advanced. For instance, see J. Mulzer, M. Zippel, C. Brüntrup, J. Segner, J. Finke, *Justus Liebigs Ann. Chem.* (1980), p. 1108.
14. C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, D. Van Derveer, *J. Org. Chem.* **45**, 3846 (1980).
15. C. T. White and C. H. Heathcock, *ibid.* **46**, 191 (1981).
16. Stereoselectivity in a reaction can result from either the kinetics or the thermodynamics of the process. Kinetic stereoselection means that the desired stereoisomer is formed faster than other stereoisomers that might be formed. Thermodynamic stereoselection operates when the desired stereoisomer is more stable than other stereoisomers with which it is in equilibrium.
17. D. E. Van Horn and S. Masamune, *Tetrahedron Lett.* (1979), p. 2229.
18. D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **103**, 3099 (1981).
19. J. Mulzer, J. Segner, G. Brüntrup, *Tetrahedron Lett.* (1977), p. 4651.
20. H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmsted, *J. Am. Chem. Soc.* **95**, 3310 (1973); see also (*9*).
21. T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, Y. Kishi, *J. Am. Chem. Soc.* **100**, 2933 (1978); see also R. E. Ireland, G. J. McGarvey, R. C. Anderson, R. Badouch, B. Fitzsimmons, S. Thaisrivongs, *ibid.* **102**, 6180 (1980).
22. Addition of a nucleophile to an achiral aldehyde gives a pair of enantiomers; hence, the two faces of the aldehyde carbonyl are said to have an enantiotopic relationship. However, addition of a nucleophile to the two faces of a chiral aldehyde produces two diastereomers (nonmirror-image stereoisomers). Thus, the faces of a chiral aldehyde are said to have a diastereotopic relationship.
23. C. H. Heathcock and C. T. White, *J. Am. Chem. Soc.* **101**, 7076 (1979); ———, J. J. Morrison, D. Van Derveer, *J. Org. Chem.* **46**, 1296 (1981); S. Masamune, S. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem. Int. Ed. Engl.* **19**, 557 (1980).
24. D. A. Evans, personal communication.
25. C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, S. D. Young, *J. Org. Chem.* **46**, 2290 (1981).
26. The co-workers are S. Young, J. Hagen, and U. Badertscher.

27. I owe a great deal to a talented group of students and postdoctoral associates who have done much of the experimental work on which this account is based. I also acknowledge my colleagues at other universities for valuable exchanges of information, particularly D. Evans of Caltech. Finally, I thank the U.S. Public Health Service for financial support for our aldol project under grant AI-15027.