New Perspectives in Asymmetric Induction

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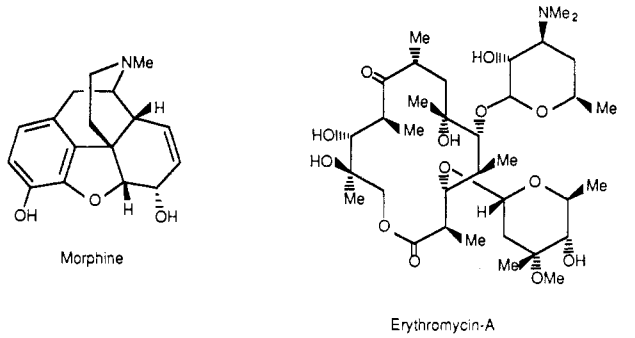
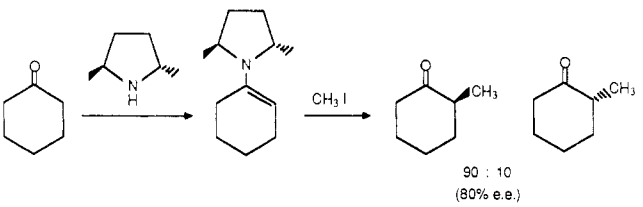
The need to control stereochemistry, both in a relative and absolute sense, within the framework of the synthesis of complex molecules represents a forefront of research in this area. While there exists a great wealth of information concerning methods which can be used to control new stereochemical centers from preexisting ones, relatively few techniques are available for achieving absolute stereochemical control. Indeed, as of 1970, the only preparatively viable methods for the control of absolute stereochemistry by asymmetric induction were those that produced α-amino acids.[1]

It became apparent that as synthetic organic chemistry evolved, so did the nature of the target molecules. Thus, while the foundations of modern synthetic chemistry were laid with the syntheses of such molecules as morphine, more recently attention has been focussed on targets such as the macrocyclic antibiotics for which erythromycin-A is representative (Scheme I). The techniques that had been developed to address the stereochemical challenges presented by polycyclic molecules such as morphine were not well suited to the construction of conformationally less well-defined targets. On the other hand, the introduction of remote stereochemical centers, especially in acyclic systems, by the control of absolute stereochemistry seemed an ideal solution. Such an approach has the intrinsic advantage that by the very nature of the independent construction of stereochemical centers, the control of their ultimate relative relationships are automatically fixed. Woodward was the first to put these ideas in print, although surely many of his contemporaries and predecessors had thought along similar lines. "Each of these building blocks must be prepared in optically-active form, and of properly specified absolute configuration. Then, when such building blocks are combined, the relative configurations at the various centers of chirality must necessarily be the desired ones. This principle of absolute asymmetric synthesis, simple though it may be, has been relatively little utilized—except in certain conspicuous instances—for example, in the synthesis of oligopeptides and oligonucleotides, where its use, though of crucial importance, has tended to be rather inherent than explicitly recognized."[2]

Scheme I



Scheme II



Strategy for Controlling Absolute Stereochemistry

The application of absolute stereochemical control to the synthesis of stereochemically complex natural products or other targets requires that each of the subunits containing stereochemical information must be prepared not only with the correct relative stereochemical relationships within the unit, but also with correct absolute stereochemistry before they are brought together. While the concept of such a synthesis is straightforward, its application as a general tool to a variety of synthetic targets demands that a correspondingly diverse group of synthetic transformations be developed wherein not only relative but also absolute stereochemistry is controlled. The most efficient application of the concept of absolute stereochemical control would demand that the reactions for the control of absolute stereochemistry be an inevitable part of the synthesis as only in this way would their use not complicate the synthesis. Since syntheses generally involve the gradual elaboration of a carbon skeleton, it would appear that special attention should be paid to asymmetric induction in the formation of carbon–carbon bonds.

Alkylations of Enamines and Imine Anions

The process of enamine alkylation developed by Stork[3] has found widespread application in natural product synthesis. Since the overall sequence involves the reaction of a nitrogen moiety with a ketone to form a reactive intermediate, modification of the process through the use of chiral amines seemed ideal for asymmetric induction.

Previous attempts to obtain stereochemical control were by and large unsuccessful because proper attention had not been directed to the involvement of two re-

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(1) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; American Chemical Society: Washington, D.C., 1976.
(2) Woodward, R. B. In "Pointers and Pathways in Research"; CIBA of India Limited: Bombay, 1963.
(3) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.

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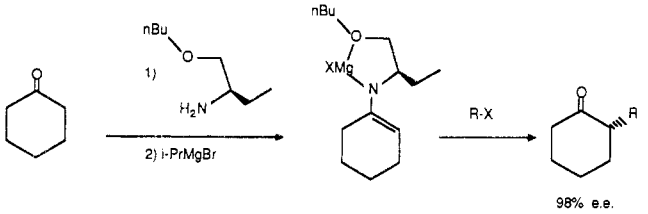
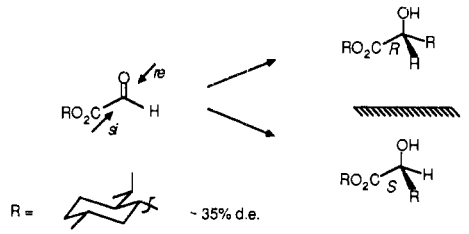
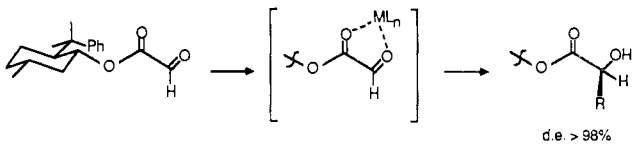
Scheme III



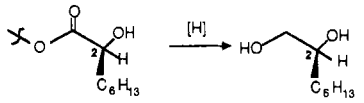
Scheme IV



Scheme V



Scheme VI



Scheme VII

active conformations, interconvertible by rotation about the CN bond.[4] Indeed, it would be anticipated that the more reactive of these two would be that which was least well disposed to direct the stereochemical outcome. A simple solution to this problem involved the use of a chiral amine so constituted that a local C_2 symmetry element would be present about the nitrogen-containing portion of the enamine and indeed, the *trans*-2,5-dimethylpyrrolidine enamine of cyclohexanone underwent alkylation with quite satisfactory levels of asymmetric induction,[5] Scheme II.

In a similar vein, we[6] and others[7] have examined the alkylation of the analogous imine anions, where bulky ligands about the metal in the chelated species shown in Scheme III might well make the arrangement shown the most reactive conformation. While the mechanistic details of the alkylation of imine anions (as well as hydrazone anions) have not yet been resolved, these pathways clearly provide very high levels of stereochemical control.

While these methods for alkylation do indeed form chiral centers with respectable levels of asymmetric induction, they are nonetheless not ideally suited for use in complicated synthetic sequences. These approaches are limited to ketones which are symmetrically substituted (relative to the 2-α-carbons) since, in the majority of cases, unsymmetrical ketones already possess at least one chiral center. This restriction placed on the starting ketone would appear to be inherent to the processes, and thus these reactions will find application only to rather special cases.

In the alkylation reactions described above, incorporation and removal of the chiral auxiliaries represented trivial operations because of the kinetic lability of the carbon–nitrogen linkages involved. It became apparent that a firmer connection between the auxiliary and the reacting substrate would provide distinct advantages. For example, the addition of nucleophiles to glyoxylate esters in which the ester moiety contains a chiral directing influence (Scheme IV) results in products that are diastereomeric and therefore separable, both on an analytical as well as a preparative scale. This approach had been examined by many different groups over a period of over 80 years prior to our own activities in this area.[8] Nonetheless, none of this research had provided levels of stereochemical control which might be considered synthetically useful as the highest level observed had been 35% diastereomeric excess when the alcohol moiety of the ester was menthol. We were not dissuaded by these results since we felt far too much attention had been paid in the past to the use of naturally occurring, chiral alcohols and that an appropriate auxiliary could be designed and synthesized that would be more suitable for this process.

Our first experiments in this area involved the use of 8-phenylmenthol, a chiral auxiliary which is readily prepared from pulegone and which had already been demonstrated to have quite powerful stereochemical directing influences in other reactions[9] (Scheme V). This alcohol provided extraordinary high levels of diastereomeric control in the addition of Grignard reagents to the corresponding glyoxylate ester.[10] The sense of stereochemical control in this process was demonstrated by reduction of the adduct formed from hexylmagnesium bromide and the glyoxylate to form 1,2-dihydroxyoctane where the absolute stereochemistry had been previously determined, Scheme VI.

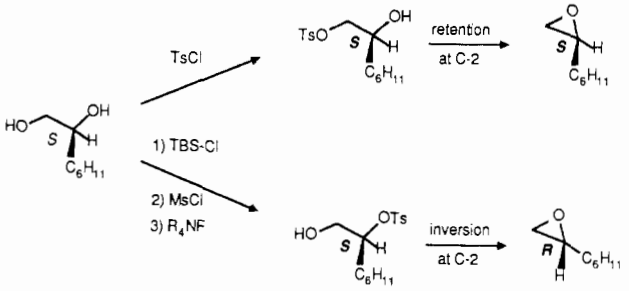
The dominant formation of the *S* stereochemistry raised interesting questions as to its origin. The vast collection of prior experiments with chiral glyoxylates had been empirically rationalized by Prelog[11] to be the result of addition via a conformation wherein the carbonyl groups were disposed anti to each other and with the largest of the substituents of the chiral alcohol unit anti to the ester carbonyl (Scheme VII). In this model the direction of the stereochemical outcome is then predicted to be the result of a favored approach past the small rather than the medium-sized group.

Our results, especially as they compared with those using menthol itself, could not be readily rationalized

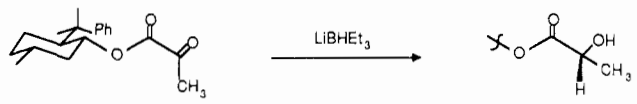
(4) Yamada, S.; Hiroi, K.; Achiwa, K. *Tetrahedron Lett.* **1969**, 4233.
(5) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755.
(6) Whitesell, J. K.; Whitesell, M. A. *J. Org. Chem.* **1977**, *42*, 377.
(7) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329.

(8) The first experiments were reported by Kipping, Cohen, and Whiteley in 1900. This subject is reviewed in ref 1, Chapter 2.
(9) Oppolzer, W.; Robbiani, C.; Battig, K. *Helv. Chem. Acta* **1980**, *63*, 2015. Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Ibid.* **1981**, *64*, 2802. Oppolzer, W.; Loher, H. J. *Ibid.* **1981**, *64*, 2808. Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffatt, F. *Tetrahedron Lett.* **1981**, *22*, 2545.
(10) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988.
(11) Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308; *Bull. Soc. Chim. Fr.* **1956**, 987.

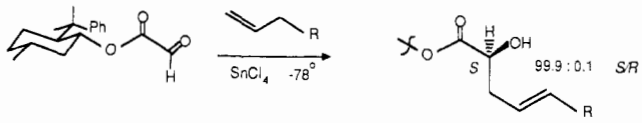
Scheme VIII



Scheme IX



Scheme X



by this model. The preference for the large group being anti to the ester carbonyl in the Prelog model is based on its size. With menthol, that group is already sufficiently large such that the conformation with this group anti to the carbonyl would be vastly superior to that with the medium group so disposed. Thus, increasing the size of the large group would not be anticipated to have a significant effect on the level of stereochemical control based on the Prelog model where the direction of approach is determined by the difference in size between the small and the medium groups.

The conformation proposed for the transition state in the Prelog model is also inconsistent with what has been shown by a large number of X-ray crystal structures to be the ground-state conformation of esters.[12] Invariably, when the ester unit is substituted with two carbons and a hydrogen, the hydrogen lies nearly coplanar and syn to the ester carbonyl (with two hydrogens and one carbon, the single carbon is found anti to the ester carbonyl). While in general, ground-state interactions need not translate directly into similar biases in transition-state conformation, such would appear to be the case here. A model for the transition state with this conformational arrangement about the ester unit would explain why proceeding from menthol to 8-phenylmenthol should lead to an increase in diastereomeric preference in approach past either the medium or the large group. However, for this latter model to correctly predict the sense of asymmetric induction, the two carbonyl groups must be held in a syn, coplanar arrangement in the transition state. While an anti arrangement of would be favored on the basis of dipole interactions alone, bridging by a metal species involved in the reaction could be responsible for a syn disposition in the transition state. This model can also be used to explain why the addition of methyllithium led to essentially no stereochemical preference if it is assumed that carbon–carbon bond formation would be so rapid as to overwhelm kinetically the formation of a chelate.

These results were exciting not only in that they provided adducts with high levels of asymmetric induction but also that the functionality provided was amenable to further manipulations such as conversion to amino acids by nucleophilic displacement.[13] Alternatively, the α-hydroxy esters produced can be reduced to 1,2-glycols which can be further transformed to epoxides by pathways (Scheme VIII) that involve either retention or inversion of configuration at carbon 2. Thus, either the *S* or the *R* epoxide can be obtained with facility using a single enantiomer of the chiral auxiliary. A wide range of reactions that involve nucleophilic opening of epoxides by attack at the less substituted carbon has been well established as useful synthetic processes.[14] These reactions then provide entry into a wide range of acyclic species that can be prepared with control for either absolute stereochemistry.

An alternate entry into the series with the *R* configuration involves the addition of a hydride to a glyoxylate already substituted with the appropriate carbon substituent (Scheme IX). Thus, reduction of the pyruvate ester provided the alcohol with the *R* configuration, although not with as high levels of asymmetric induction as observed in the Grignard reaction.[15] The decrease in the level of asymmetric induction can be attributed to the counterion, and unfortunately there are not readily available reducing agents that involve magnesium as the counterion.

The same concept of reversing the order of addition of substituents can also be used in the formation of either the *R* or the *S* stereoisomer of tertiary alcohols. Addition of ethylmagnesium bromide to the phenyl-substituted glyoxylate provided the *R* configuration while addition of phenylmagnesium bromide to the methyl substituted glyoxylate (pyruvate) provided the *S* product. In both cases, the level of asymmetric induction was quite good, although somewhat lower than observed with the parent glyoxylate.

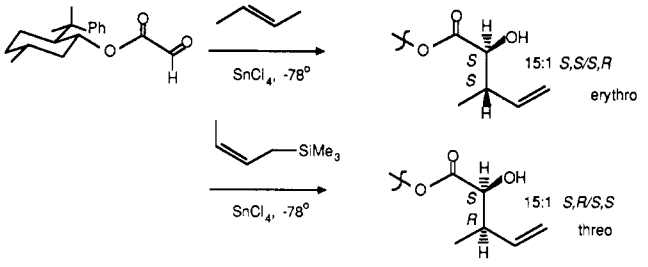
Ene Reactions

The addition of Grignard reagents to the chiral glyoxylate as described above provided a powerful means for the construction of carbon–carbon bonds with asymmetric induction. However, the nature of functionality which can be introduced with Grignard reagents is severely limited by their reactivity. The ene reaction of glyoxylates with alkenes has the potential to form carbon–carbon bonds and create not only the functionality present in the Grignard adducts but also a homoallylic alcohol. The tin tetrachloride catalyzed reaction of the glyoxylate with alkenes at −78 °C in methylene chloride afforded adducts with both high chemical yield and exceptional levels of asymmetric induction. For example, the propene adduct was obtained in a 99% crude yield, virtually pure by ^{13}C analysis. Chromatographic analysis carried out after removal of the double bond by reduction revealed that the minor diastereomer, if present at all, represented less than 1/10 of 1% of the major stereoisomer, Scheme X.

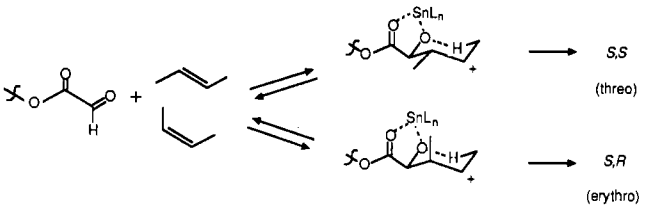
With longer, terminal alkenes, approximately 10% of the cis geometric isomer was formed as a contami-

(12) Mathieson, A. McL., *Tetrahedron Lett.* **1965**, 4137.
(13) Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 65.
(14) Sharpless, K. B. *Pure Appl. Chem.* **1983**, *55*, 589.
(15) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802.

Scheme XI



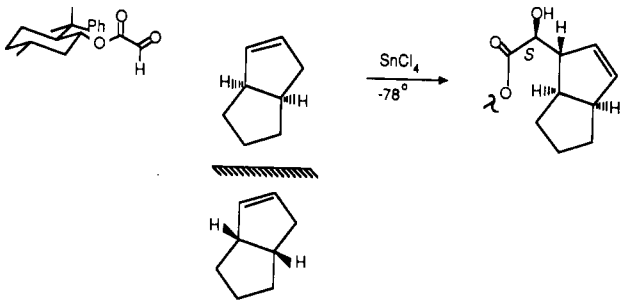
Scheme XII



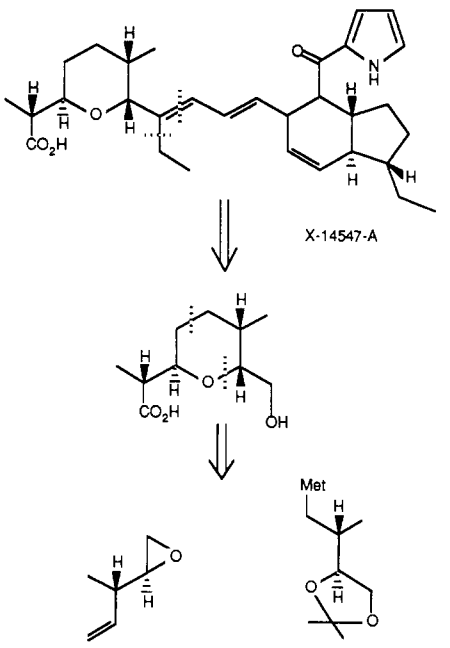
nant of the major, *trans* product. With disubstituted, nonterminal alkenes, two new stereochemical centers are formed in the ene reaction (Scheme XI). Reaction of the glyoxylate with *trans*-butene provided a 15:1 ratio of the *S,S* to *S,R* diastereomer, corresponding to a preference for what would be referred to as the threo relative configurational relationship between the two centers.[16] With *cis*-1-(trimethylsilyl)butene, the opposite or erythro relative relationship was favored (that is *S,R*) also in a ratio of 15:1.

There are several features of these reactions which make them mechanistically quite interesting. Our results contrast to those normally observed in similar ene reactions. For instance with methyl glyoxylate, where the yields are considerably lower, the products are usually contaminated by halogen adducts, and the level of diastereomeric control (threo/erythro) is poorer.[17] In addition, we observed that the stereochemical outcome was the same whether we used *trans*- or *cis*-butene. Analysis of the alkene in either case after completion of the reaction revealed extensive double bond isomerization. This interconversion of the *trans*- and *cis*-butenes required the presence of the glyoxylate, for tin tetrachloride (as well as the catalyst plus isopropyl alcohol) was not effective in inducing this isomerization. The stereochemical outcome is unaffected by the reaction time, and thus the overall process would appear to be irreversible. Consistent with these observations is a reaction mechanism which proceeds reversibly to an intermediate carbocation and where progression from this cation to product is slower than reversal to starting materials. Thus, the isomerization of the butenes occurs along the ene reaction pathway. However, this scenario would require that the stereochemistry, at least in the erythro/threo sense, be determined by the second step where a proton is lost to form the alkene. Bimolecular deprotonation of the intermediate carbocation would not be expected to proceed with the levels of diastereomeric control that we have observed. We postulate that an intramolecular proton transfer to the oxygen within a six-membered transition state is involved, as illustrated in Scheme XII. The dominant formation of the threo isomer would then be explained

Scheme XIII



Scheme XIV



by a preference for an equatorial rather than an axial methyl group on this a chair-like transition state. Nonetheless, we would point out that the same stereochemical outcome could be rationalized by a concerted reaction process with a transition state closely resembling the one for proton transfer. The only evidence for a discretely two-step process is the observation of alkene isomerization.

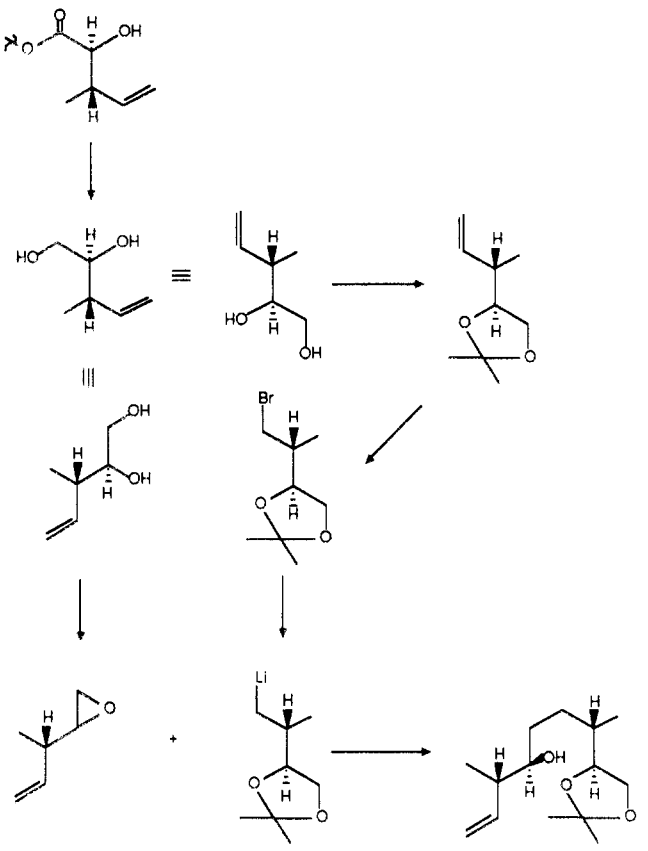
Kinetic Resolution

The face selectivity inherent in the glyoxylate of 8-phenylmenthol represents an exceptionally powerful tool for the formation of new carbon–carbon bonds with control of the absolute and relative stereochemistry of newly formed asymmetric centers, as in the reactions described above. An added advantage is inherent when this selectivity is combined with the face selectivity present in a chiral alkene such as that in Scheme XIII since only one of the two enantiomers of the alkene can react with the chiral glyoxylate through a transition state where the face selectivity of both partners is observed. Thus, not only are new centers of asymmetry formed in the reaction, but those initially present in the alkene are selected by a kinetic resolution. This combination represents a powerful tool for the elaboration of stereochemically complex arrays.[18]

(16) Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296.
(17) Snider, B. B.; van Straten, J. W. *J. Org. Chem.* **1979**, *44*, 3567.

(18) Sharpless was the first to describe a practical, non-enzymatic kinetic resolution. See: Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

Scheme XV



Application to Total Synthesis

The implementation of the ene reaction process within the framework of absolute asymmetric synthesis is well illustrated by the synthesis of the left half of the antibiotic X-14547-A.[19] Each of the subunits that are illustrated in Scheme XIV had previously been prepared in racemic form.[20] As a consequence, their combination resulted in a mixture of four stereoisomers (as two mirror-image pairs) where only approximately one fourth of the product mixture is constituted with both the correct relative as well as absolute stereochemistry. Application of asymmetric induction to the synthesis of each of these fragments results in essentially a single stereoisomer, and thus only one stereoisomer can be formed upon their combination. It is important to note that the ability to select for either the threo or the erythro diastereomer in the ene reaction and the fact that epoxides can be formed from glycols with either retention or inversion of stereochemistry combine to provide access with essentially equal facility to any one of the 16 possible stereoisomers of the pyran ring with its four stereochemical centers. Thus, the question of both relative as well as absolute stereochemical control has thus been lifted from the confines of a specific target and has been solved in a quite general way.

It should be clear that significant progress has occurred in the past decade in the design and application of asymmetric induction to synthetic endeavors, and indeed the results described here represent only a portion the growing arsenal of methods for carbon–carbon bond formation with antisymmetric induction. However, much remains to be accomplished and the area of stereochemical control will reach maturity only when a full cornucopia of techniques are available.

It has been my pleasure during the course of many years to have been associated with a loyal, dedicated, and perseverant group of researchers to whom belongs the credit for the successful chemistry described above. Funding has been provided by the Research Corp., the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Robert A. Welch Foundation (F-626), and the National Institutes of Health (GM-31750).

(19) Westley, J. W.; Evans, R. H.; Sello, L. H.; Troupe, N.; Liu, C. H.; Blount, J. F. *J. Antibiot.* **1979**, *32*, 100.

(20) Ho, P.-T. *Can. J. Chem.* **1982**, *60*, 90.

Oxoalkylation of Carbonyl Compounds with Conjugated Nitro Olefins

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Carbon–carbon bond-forming processes involving nitro aliphatics are of increasing importance because of the remarkable versatility of nitro groups in their conversion into a variety of organic functional groups. For example, nitro olefins have been well documented as versatile and prominent acceptors in conjugated addition reactions.[1] The addition of a nucleophile (NuH) to a nitro olefin **1** results in the formation of a saturated nitro compound **2**, which is readily convertible

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(1) For general reviews on the synthesis and chemistry of conjugated nitro olefins, see H. H. Bauer and L. Urbas, "The Chemistry of the Nitro and Nitroso Groups", part 2, H. Feuer, Ed., Interscience, New York, 1970, pp 75–200. (b) O. Schickh, G. Apel, H. G. Padeken, H. H. Schwarz, and A. Segnitz, "Methoden der Organischen Chemie (Houben-Weyl)", E. Müller, Ed.; Georg Thieme Verlag, Stuttgart, 1971, Vol. 10/1, pp 9–462. (c) J. Kochany. *Wiad. Chem.*, **32**, 723 (1978). (d) D. Seebach, E. W. Colvin, F. Lehr, and T. Weller, *Chimia*, **33**, 1 (1979).

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