Kinetic Resolution of *Meso/dl* Stereoisomeric Mixtures: Theory and Practice

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Abstract: A mathematical model, based on reactions of independent functional groups, is derived to describe kinetic resolutions of bifunctional *meso/dl* stereoisomeric mixtures. The model indicates that only the slow reacting enantiomer can be obtained (as recovered starting material) with high stereoisomeric purity in these processes; the products from the fast reacting enantiomer and the *meso* diastereomer are predicted to have limited diastereoisomeric purity. Recycling strategies are presented that can serve to enhance the purity of the these products. In particular, if recycling can be performed using a reaction with selectivity opposite to that in the first cycle, it is predicted that all three components of a *meso/dl* mixture (or their derived products) can be obtained with high stereoisomeric purity, even from a process with modest enantiotopic group selectivity. These predictions were tested by Sharpless epoxidation of a 1:1 mixture of *meso* and racemic stereoisomers of 6,6-ethylenedioxy-1,10-undecadiene-3,9-diol (**1**) under conditions of high (40:1) and modest (9:1) selectivity. In both scenarios, the two C_2 enantiomers and the monoepoxide derivative of the *meso* diastereomer of **1** were obtained with high stereoisomeric purity (≥97% dp, >99% ee) from an initial L-tartarate mediated epoxidation of the mixture followed by recycling of the mono- and diepoxide fractions by deoxygenation (KSeCN) and reepoxidation using a D-tartarate derived catalyst. The results are in reasonable agreement with those calculated with the mathematical model.

Introduction

The increasing demand for enantiomerically pure compounds (EPC)[1] has provided a significant challenge to both the theory and practice of modern synthetic organic chemistry.[2] Typically, chiral compounds with multiple stereogenic elements are prepared by reaction sequences which introduce new elements of stereogenicity into substrates that already possess one or more such elements. If the reaction diastereoselectivity is substrate-controlled,[3] then racemic substrates give racemic products and enantiopure products are available (in principle) simply by using an enantiopure starting material. Thus, the methods to achieve EPC synthesis have generally involved the diastereoselective transformation of chiral nonracemic compounds[4] which either are readily available[1,5] or are obtained by exploiting one of two basic strategies: separation of enantiomers (resolution)[6] or enantioselective transformation of achiral compounds (asymmetric synthesis).[7] More sophisticated strategies have recently evolved where two or more processes are coupled *in situ* resulting in EPC syntheses with enhanced selectivity and/or efficiency.[8−11]

The potential for both high yield and high selectivity makes asymmetric synthesis (cf. resolution) a particularly attractive strategy for EPC synthesis. The enantioselective conversion of an achiral substrate into a chiral nonracemic product requires a process where enantiotopic faces or groups in the substrate are differentiated. The majority of known methods for asymmetric synthesis involve additions to π-bonds, and for almost every type of addition reaction, examples with at least 10−20:1 levels of enantiotopic face selectivity can be found; however, very few methods have the desirable properties of reliable generality and high (>20:1) selectivity.[7] By contrast, the use of enantiotopic group selective reactions to achieve asymmetric synthesis is much less common. Although various enzyme mediated processes have been employed for some time,[12] the development of nonenzymatic group selective reactions for asymmetric synthesis has only recently attracted attention.[13−15]

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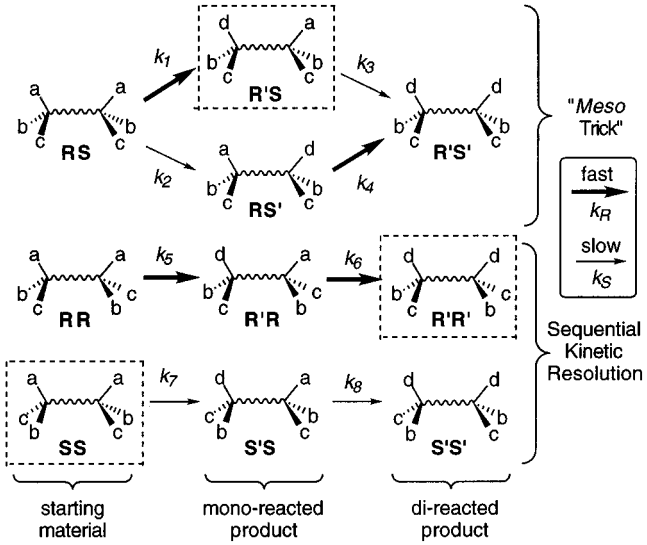

Figure 1. Kinetic resolution of a *meso/dl* mixture with a reaction where the ligand "a" is replaced by the ligand "d" and *R* groups react faster than *S* groups (i.e., $k_R > k_S$).

The desymmetrization of symmetrical bifunctional compounds by enantiotopic group selective reactions has emerged as a powerful strategy for asymmetric synthesis ("*meso* trick",[1] cf. Figure 1).[16] This approach is particularly effective when the enantiotopic groups can react sequentially, thereby coupling an asymmetric synthesis with a kinetic resolution and producing products with high stereoisomeric purity,[11] even from reactions of moderate[17] group selectivity.[18] The application of such processes in EPC synthesis depends on the ready availability of suitable C_s or C_i symmetrical bifunctional substrates; this desymmetrization strategy will be considerably less attractive when the complexity of the synthesis of the achiral substrate rivals that of the EPC product. Although achiral substrates without stereogenic centers are, in general, easily prepared, *meso* bifunctional substrates[19] require stereoselective syntheses.

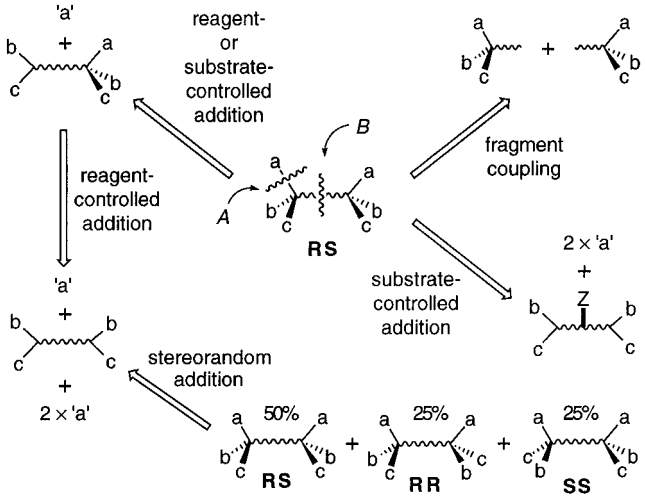

Figure 2. Retrosynthetic analysis for a *meso* bifunctional substrate.

Simultaneous two-directional chain synthesis[16] is an excellent tactic for the preparation of *meso* bifunctional substrates but is applicable only in cases where intervening groups provide substrate-controlled diastereoselectivity in the formation of new stereogenic centers. The stereoselective synthesis of *meso* bifunctional substrates where groups are too remote to influence diastereoselectivity is nontrivial. A two-directional chain synthesis is possible with reagent-controlled diastereoselectivity by stepwise application of reactions with opposite stereoselectivity.[20] However, analysis of synthetic pathways that would construct the required stereogenic centers in a stepwise fashion suggests that they are as complex and as long as pathways that would produce a "desymmetrized" *meso* derivative directly (see Figure 2).[21] For example, the synthesis of **RS** according to disconnection "*A*" requires a reagent-controlled diastereoselective addition of ligand "a" to an EPC fragment; disconnection "*B*" would require the coupling of two EPC fragments. In either case, only a slight structural modification in either fragment (e.g., a protecting group) would result in a desymmetrized *meso* derivative.[22]

An alternative to the stepwise stereoselective syntheses of *meso* compounds outlined above involves a stereorandom two-directional transformation of a C_{2v} (or C_{2h}) bifunctional substrate

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(19) Defined here as achiral (C_s or C_i symmetric) bifunctional substrates possessing two or more chirotopic stereogenic centers (or, more generally, stereogenic elements).

(20) For an example of this strategy, see: Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 2687−2689.

(21) Stepwise introduction of stereogenic centers will necessarily produce EPC intermediates. A strategy for EPC synthesis involving "symmetrization" of a chiral starting material to give a *meso* intermediate which is then desymmetrized has obvious disadvantages.

(22) For an example of this strategy, see: Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6526−6528.

to give a 1:1 mixture of C_2 and C_s symmetric products (Figure 2).[23] Separation of the diastereomers would provide a very simple route to *meso* bifunctional compounds in up to 50% yield.[24] Reasoning that a physical separation of stereoisomers could be difficult, we considered the consequences of a *meso/dl* mixture of bifunctional starting materials undergoing sequential enantiotopic group selective reaction (see Figure 1). Assuming a reaction where the *R* groups consistently react faster than the *S* groups, such a process should concentrate the **SS** substrate, the **R′S** monoreacted product, and the **R′R′** direacted product simultaneously. If this kinetic resolution were efficient, the "desymmetrized" *meso* product **R′S** could be obtained at this stage *by separation of compounds that are not stereoisomeric*, thus making a stereoselective synthesis of the *meso* bifunctional starting material unnecessary.

A few examples of enzyme mediated acylation (or hydrolysis) of *meso/dl* mixtures of diols (or diesters) have been reported.[25] Most of these enzymatic resolutions efficiently separate the C_2 symmetric enantiomers from each other but not necessarily from the *meso* isomer.[26] To evaluate the synthetic potential of this type of process, especially with nonenzymatic reactions, it was necessary to develop an appropriate theoretical framework for predicting the relationship between the group selectivity (k_R/k_S) of a reaction and the yield and stereoisomeric purity of the product(s) that might be obtained. In a preliminary account, we described a mathematical model for kinetic resolutions of *meso/dl* stereoisomeric mixtures and, using that model, derived a recycling protocol to obtain desymmetrized *meso* derivatives with excellent diastereomeric purity from such processes.[27] In this paper, we present a detailed analysis of the mathematical model considering the fate of all of the isomers in a *meso/dl* mixture undergoing kinetic resolution. This analysis reveals optimal protocols for obtaining each of the *meso/dl* isomers (individually or all them simultaneously) with high stereoisomeric purity even from a reaction with modest enantiotopic group selectivity. These protocols were tested by Sharpless epoxidation of **1** under conditions of both high and modest enantiotopic group selectivity. In both scenarios, the two C_2 enantiomers and a desymmetrized monoepoxide derivative of the *meso* diastereomer of **1** were obtained with high stereoisomeric purity (≥97% dp, >99% ee), as predicted by the model.

Results and Discussion

The group selective reaction of a mixture of *meso* and *dl* stereoisomers is equivalent to a sequential kinetic resolution[8] simultaneous with a "*meso* trick" process[1] (see Figure 1). The kinetics for this situation can be analyzed as a set of three independent parallel reactions if the reaction(s) of each substrate is independent of the other substrates (i.e., if aggregation effects are negligible). Analytical expressions to describe the conversion dependent evolution of the "mono" products concentrations in sequential kinetic resolutions (eqs 1 and 2)[8] and in "*meso* trick" processes (eqs 3 and 4)[11,17] have been previously described.[28,29] Equations 5−7 are a consequence of the stoichiometry of the process. Using eqs 1−7 with appropriate substitution of the readily derived expressions[29] for the relationships between the **RS**, **RR**, and **SS** concentrations (eqs 8 and 9) allows determination of the concentrations of all of the components for the process represented in Figure 1 as a function of the conversion of one of the substrates.

$$[\mathbf{R'R}] = \frac{k_5[\mathbf{RR}]_0}{k_5 - k_6}\left[\left(\frac{[\mathbf{RR}]}{[\mathbf{RR}]_0}\right)^{k_6/k_5} - \frac{[\mathbf{RR}]}{[\mathbf{RR}]_0}\right] \quad (1)$$

$$[\mathbf{S'S}] = \frac{k_7[\mathbf{SS}]_0}{k_7 - k_8}\left[\left(\frac{[\mathbf{SS}]}{[\mathbf{SS}]_0}\right)^{k_8/k_7} - \frac{[\mathbf{SS}]}{[\mathbf{SS}]_0}\right] \quad (2)$$

$$[\mathbf{R'S}] = \frac{k_1[\mathbf{RS}]_0}{k_1 + k_2 - k_3}\left[\left(\frac{[\mathbf{RS}]}{[\mathbf{RS}]_0}\right)^{k_3/(k_1+k_2)} - \frac{[\mathbf{RS}]}{[\mathbf{RS}]_0}\right] \quad (3)$$

$$[\mathbf{RS'}] = \frac{k_2[\mathbf{RS}]_0}{k_1 + k_2 - k_4}\left[\left(\frac{[\mathbf{RS}]}{[\mathbf{RS}]_0}\right)^{k_4/(k_1+k_2)} - \frac{[\mathbf{RS}]}{[\mathbf{RS}]_0}\right] \quad (4)$$

$$[\mathbf{R'R'}] = [\mathbf{RR}]_0 - [\mathbf{RR}] - [\mathbf{R'R}] \quad (5)$$

$$[\mathbf{S'S'}] = [\mathbf{SS}]_0 - [\mathbf{SS}] - [\mathbf{S'S}] \quad (6)$$

$$[\mathbf{R'S'}] = [\mathbf{RS}]_0 - [\mathbf{RS}] - [\mathbf{R'S}] - [\mathbf{RS'}] \quad (7)$$

$$\frac{[\mathbf{RR}]}{[\mathbf{RR}]_0} = \left(\frac{[\mathbf{RS}]}{[\mathbf{RS}]_0}\right)^{k_5/(k_1+k_2)} \quad (8)$$

$$\frac{[\mathbf{SS}]}{[\mathbf{SS}]_0} = \left(\frac{[\mathbf{RS}]}{[\mathbf{RS}]_0}\right)^{k_7/(k_1+k_2)} \quad (9)$$

To assess the behavior of this type of process (Figure 1) as a function of the reaction enantiotopic group selectivity, it is convenient to assume that the functional groups react independently.[30] Thus, all *R* groups and all *S* groups were assumed to have same reactivity (k_R and k_S, respectively) regardless of the substrate.[31] This assumption will be reasonable if the groups are sufficiently remote[30] and, in any event, small deviations should not influence general conclusions.[17b] In this way, eqs 1−9 are soluble at any conversion (e.g., $[\mathbf{RS}]/[\mathbf{RS}]_0$) given the initial conditions and the ratio k_R/k_S.[31] For example, the data obtained with $k_R/k_S = 10$ are plotted in Figure 3.[32] As expected for a kinetic resolution,[6a] the calculations indicate that both the enantiomeric purity (ee) and the diastereomeric purity (dp)[33]

(23) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312, 5313; *Tetrahedron* **1986**, *42*, 2855−2862.

(24) Any inherent substrate-controlled diastereoselectivity could bias the product mixture in favor of either the C_2 (racemic) or the C_s product.[16] Reagent-controlled diastereoselectivity would favor a C_2 (nonracemic) product.[23]

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(26) For other methods of separating *meso/dl* mixtures: (a) Caron, G.; Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1994**, *5*, 657−664. Also see refs 13d and 25e.

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(28) The analytical expressions will be valid for a process represented by Figure 1 if all reactions are first order with respect to substrate and the same order with respect to any reagent(s).

(29) See the supporting information for derivation of the equations.

(30) For a discussion and examples of reactions of independent functional groups, see: Macomber, R. S.; Constantinides, J. K.; Smith, G.; Button, A.; Lindstrom, D. O. *J. Org. Chem.* **1996**, *61*, 727−734 and cited references.

(31) Assumption: $k_1 = k_4 = k_6 = k_R$, $k_2 = k_3 = k_8 = k_S$, $k_5 = 2k_R$, and $k_7 = 2k_S$. Initial conditions: $[\mathbf{RS}]_0 = 2[\mathbf{RR}]_0 = 2[\mathbf{SS}]_0 = 0.5$ arbitrary units.

(32) Calculations were performed as described previously;[17,27] see supporting information for details.

(33) The diastereomeric purity (dp) of a mixture of diastereomers is defined here as the mole fraction of the major diastereomer.

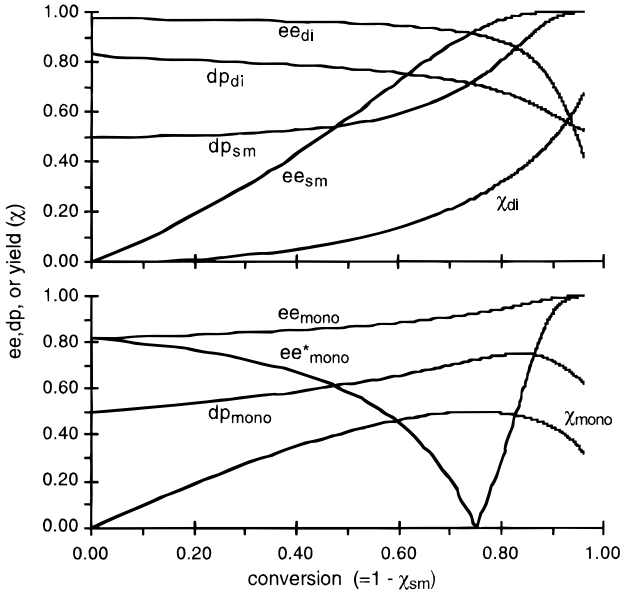


Figure 3. Calculated[31] mole fractions (χ), ee's, and dp's as a function of converstion for the components of a process as described in Figure 1 from a reaction with $k_R/k_S = 10$. $[sm]_0 = ([\mathbf{RR}]_0 + [\mathbf{SS}]_0 + [\mathbf{RS}]_0)$; $\chi_{sm} = ([\mathbf{RR}] + [\mathbf{SS}] + [\mathbf{RS}])/[sm]_0$; $\chi_{mono} = ([\mathbf{R'S}] + [\mathbf{RS'}] + [\mathbf{S'S}] + [\mathbf{R'R}])/[sm]_0$; $\chi_{di} = ([\mathbf{R'R'}] + [\mathbf{S'S'}] + [\mathbf{R'S'}])/[sm]_0$; $ee_{sm} = ([\mathbf{SS}] - [\mathbf{RR}])/([\mathbf{SS}] + [\mathbf{RR}])$; $ee_{mono} = ([\mathbf{R'S}] - [\mathbf{RS'}])/([\mathbf{R'S}] + [\mathbf{RS'}])$; $ee^*_{mono} = |([\mathbf{S'S}] - [\mathbf{R'R}])|/([\mathbf{S'S}] + [\mathbf{R'R}])$; $ee_{di} = ([\mathbf{R'R'}] - [\mathbf{S'S'}])/([\mathbf{R'R'}] + [\mathbf{S'S'}])$; $dp_{sm} = ([\mathbf{RR}] + [\mathbf{SS}])/([\mathbf{RR}] + [\mathbf{SS}] + [\mathbf{RS}])$; $dp_{mono} = ([\mathbf{R'S}] + [\mathbf{RS'}])/([\mathbf{R'S}] + [\mathbf{RS'}] + [\mathbf{S'S}] + [\mathbf{R'R}])$; $dp_{di} = ([\mathbf{R'R'}] + [\mathbf{S'S'}])/([\mathbf{R'R'}] + [\mathbf{S'S'}] + [\mathbf{R'S'}])$.

of the unreacted starting material (mostly **SS**) increases and that of the "di" product (mostly **R′R′**) decreases with increasing conversion.[34] On the other hand, while the ee's for the "mono" products (mostly **R′S**) increase with conversion, the dp rises to a maximum and then decreases with increased conversion. As indicated by the curve for ee^*_{mono}, the minor diastereomer in the "mono" product is mainly the **R′R** enantiomer at low conversion and the **S′S** enantiomer at high conversion. Qualitatively, these relationships can be understood by considering that the **SS** starting material is being concentrated by simultaneous kinetic resolution from **RR** (selectivity $= E = k_R/k_S$)[6a] and from **RS** ($E' = (1 + k_R/k_S)/2$). Because $E' \approx 0.5E$ and $[\mathbf{RS}]_0 = 2[\mathbf{SS}]_0$, the C_2 symmetric enantiomers **RR** and **SS** are separated much more efficiently from each other than from the C_s symmetric diastereomer **RS** (i.e., diastereomeric purity is significantly less than enantiomeric purity).[34] For the "mono" products, **R′S** and **R′R** are formed at the same rate (initially) but undergo efficient kinetic resolution ($E = k_R/k_S$) during formation of the "di" product; by contrast, **S′S** is produced slowly but is not resolved from **R′S** ($E = 1$).

How efficiently can a *meso/dl* mixture be separated by an enantiotopic group selective reaction? One possible measurement of the efficiency of the process is at 75% conversion where the remaining starting material (25%), the "mono" product (50%), and the "di" product (25%) will have identical ee's and identical dp's;[31] the calculated stereoisomeric purity of these components as a function of the reaction group selectivity (k_R/k_S) is shown in Figure 4.[32] The model clearly indicates that a process as in Figure 1 can simultaneously separate the *meso/dl* stereoisomers with only limited efficiency. Of course, the

(34) A consequence of the assumptions and initial conditions is that, for both the starting material and "di" product, the dp is related to the ee by the simple expression: $dp = 1/(1 + [(1 + ee)(1 - ee)]^{0.5})$. Thus, dp's of 0.80, 0.90, 0.95, and 0.99 require ee's of 0.97, 0.994, 0.9986, and 0.99995, respectively.

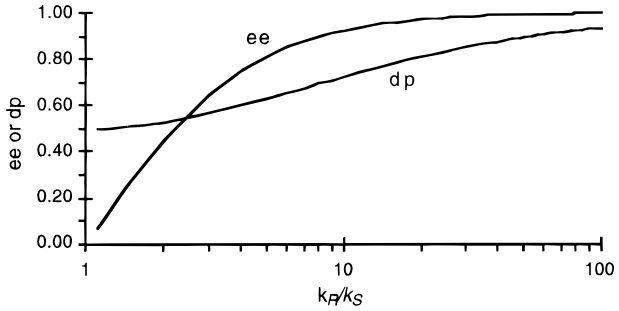


Figure 4. Calculated[31] ee and dp for the components of a process as described in Figure 1 at 75% conversion as a function of the reaction enantiotopic group selectivity (k_R/k_S). See Figure 3 for definitions.

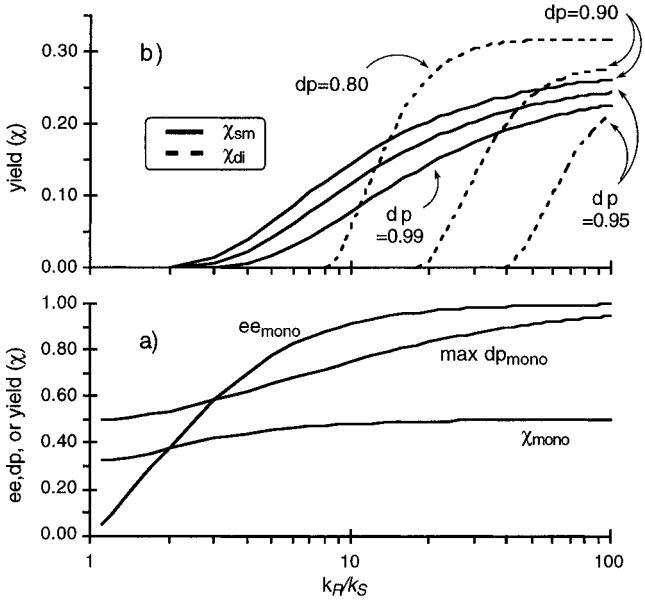


Figure 5. Calculated[31] potential yields (χ) and stereoisomeric purities for the components of a process as described in Figure 1 as a function of the reaction enantiotopic group selectivity (k_R/k_S). (a) maximum dp_{mono} (cf. Figure 3) and the associated ee_{mono} and χ_{mono}; (b) potential yields of unreacted sm and "di" product with a specific dp (ee's are related and much higher).[34] See Figure 3 for definitions.

stereoisomeric purity of one of the components can be improved (at the expense of the others) by varying the conversion (cf. Figure 3). The calculated relationships between the group selectivity (k_R/k_S) of the reaction and the potential stereoisomeric purities and yields of the individual components are shown in Figure 5.[32] Thus, the mathematical model based on independent functional groups[30] predicts that it is possible to obtain the slow reacting C_2 isomer (as unreacted starting material) with any arbitrary high degree of stereoisomeric purity (albeit by sacrificing yield) from kinetic resolution of a *meso/dl* stereoisomeric mixture. By contrast, the potential diastereomeric purities of both the "mono" and "di" products from such a process are significantly limited, even from very selective reactions.[25] For example, a reaction with enantiotopic group selectivity of 100:1 is predicted to give the "mono" product **R′S** with a maximum dp of only 94.7%.[33] Because this level of stereoisomeric purity is insufficient for many applications, the possibility of improving the dp of the "mono" and "di" products by recycling was considered.

Although rarely exploited in nonenzymatic processes,[35] recycling is an established method for improving the stereo-

(35) (a) Brown, S. M.; Davies, S. G.; de Sousa, J. A. A. *Tetrahedron: Asymmetry* **1991**, *2*, 511−514. (b) Jefford, C. W.; Timári, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1501, 1502.

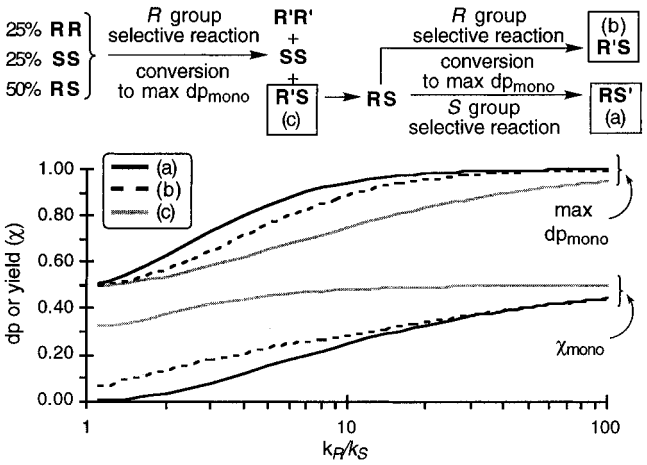


Figure 6. Calculated[31] maximum dp_{mono} and the associated χ_{mono} for the indicated process (cf. Figure 1) as a function of the reaction enantiotopic group selectivity (k_R/k_S): (a) recycling with a reaction of inverse selectivity; (b) recycling with a reaction of the same selectvity; (c) without recycling (cf. Figure 5a). See Figure 3 for definitions.

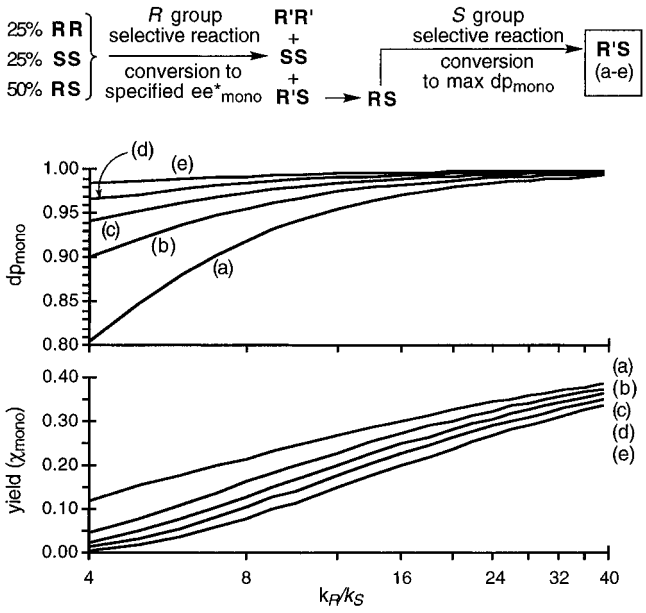


Figure 7. Calculated[31] maximum dp_{mono} and the associated χ_{mono} for the indicated process (cf. Figure 1) as a function of the reaction enantiotopic group selectivity (k_R/k_S) with recycling (with inverse selectivity) after various conversions in the first reaction. Recycling after (a) maximum dp_{mono} ($ee^*_{mono} \approx 0.5-0.6$; cf. Figure 6a); (b) $ee^*_{mono} = 0.8$; (c) $ee^*_{mono} = 0.9$; (d): $ee^*_{mono} = 0.95$; (e): $ee^*_{mono} = 0.98$. See Figure 3 for definitions.

isomeric purity of products from enzyme mediated kinetic resolutions.[36] This method has been used to improve the diastereoisomeric purity of the monoacetate fraction from enzyme mediated acetylation of *meso/dl* diols.[25a,b] To model the effects of recycling on a process as in Figure 1, it was assumed that the initial reaction was halted at the conversion where the dp_{mono} had reached its maximum value (cf. Figure 3) and the "mono" product (and "di" product, *vide infra*) could be isolated and converted back into starting material quantitatively. The isomer distribution of this hypothetical new starting material is easily computed and, using these values as the new initial conditions, the results of a second enantiotopic group selective reaction were calculated as above.[32] As shown in Figure 6, the dp for the "mono" product is significantly improved by recycling, especially if the sense of the enantiotopic group selectivity is reversed in the second reaction.[37,38]

Considering that the "mono" product from an *R* group selective process as in Figure 1 is increasingly depleted in the **R′R** isomer at higher conversions (cf. ee^*_{mono} in Figure 3), and that the maximum dp_{mono} is dependent on the amount of slow reacting C_2 enantiomer present in the starting material,[38] we reasoned that any arbitrary high dp_{mono} might be achievable by recycling (with inverse selectivity) the "mono" product obtained after a sufficiently high conversion. To model this scenario, it was assumed that an *R* group selective process was halted at conversions where the ee^*_{mono} had reached various values (0.8, 0.9, 0.95, and 0.98) and the "mono" products were converted back into starting material quantitatively. The isomer distributions of these hypothetical new starting materials were used as the new initial conditions for calculating the outcome of a second reaction with *S* group selectivity.[32] The results are shown in Figure 7 and compared to the recycling strategy above (i.e., Figure 6) where the first reaction is stopped at lower conversion.[39] As expected, recycling after higher conversion can increase the stereoisomeric purity of the "mono" product obtained (at the expense of yield), particularly for reactions with modest selectivity. Although, in principle, this recycling scheme could provide any high level of dp_{mono}, the loss in chemical yield associated with this strategy will impose a limitation.

The fast reacting C_2 enantiomer is concentrated as "di" product (i.e., **R′R′** from an *R* group selective reaction; see Figure 1). The limited dp for this product (see Figure 5) can also be enhanced by recycling; very high dp is achievable if a reaction with inverse selectivity is employed.[40] For example, Figure 8 shows the calculated results from recycling the "di" product obtained after an *R* group selective reaction stopped at the conversion where dp_{mono} has reached its maximum value.

A simple strategy to obtain all three components of a *meso/dl* mixture with high stereoisomeric purity emerges by combining the recycling schemes above. Thus, for a given desired dp, the first reaction is run to a conversion where the slow reacting C_2 enantiomer has reached the desired dp, and then the "mono" and "di" products obtained are recycled (individu-

(36) (a) Chen, C.-S.; Fujimoto, G.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299. (b) Brown, S. M.; Davies, S. G.; de Sousa, J. A. A. *Tetrahedron: Asymmetry* **1993**, *4*, 813−822 and cited references.

(37) For example, the modest 75% dp (96% ee, 48% yield) predicted for the "mono" product resulting from a reaction with a group selectivity of 10:1 is improved to 89% (91% ee, 28% overall yield) upon recycling with the same reaction and 94% (99% ee, 25% overall yield) when using a reaction with inverse selectivity. A reaction with $E > 88$ would be required to give a "mono" product with 94% dp (99.9% ee, 50% yield) without recycling.

(38) The enhancement in stereoisomeric purity resulting from a reaction with reverse selectivity can be understood by considering the kinetic resolution of the "mono" products that occurs during formation of the "di" products. For a process as in Figure 1, an *R* group selective reaction can resolve **R′S** from **R′R** but not from **S′S** (i.e., the "mono" product arising from the fast reacting C_2 enantiomer is removed more efficiently than that from the slow reacting C_2 enantiomer). Thus, the maximum dp_{mono} is limited by the amount of slow reacting C_2 enantiomer in the starting material. Conversion of the "mono" product with maximum dp obtained from an *R* group selective reaction into starting material gives material in which the minor C_2 diastereomer is enriched in the slow reacting enantiomer (i.e., [**SS**] (Figures 1 and 3). Because [**SS**] > [**RR**] in the "new" starting material, greater dp_{mono} can be obtained if an *S* group selective reaction is used for recycling.

(39) Reactions of 1:1 mixtures of *meso/dl* substrates halted at the conversion where the dp_{mono} is maximum are calculated to have $ee^*_{mono} = 0.5-0.6$, depending on the selectivity ($k_R/k_S = 2-100$).

(40) Recycling assumes that the "di" product is isolated and transformed back into starting material (mainly **RR**) quantitatively. Subjecting this new starting material to an *R* group selective reaction will provide "di" product (mainly **R′R′**) with enhanced dp; an *S* group selective reaction leaves unreacted **RR** with any arbitrary high stereoisomeric purity, depending on conversion.

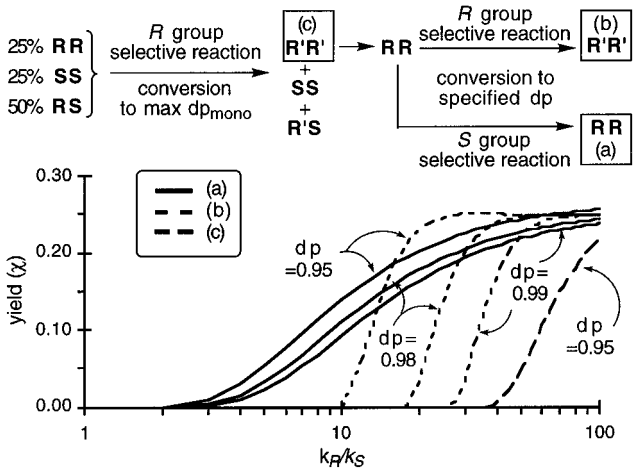


Figure 8. Calculated[31] potential yields of sm or "di" product with a specific dp for the indicated process (cf. Figure 1) as a function of the reaction enantiotopic group selectivity (k_R/k_S): (a) after recycling with a reaction of inverse selectivity (χ_{sm} and dp_{sm}); (b) recycling with a reaction of the same selectvity (χ_{di} and dp_{di}); (c) without recycling (χ_{di} and dp_{di}). In each case, the conversion for the first reaction is at the maximum dp_{mono}. See Figure 3 for definitions.

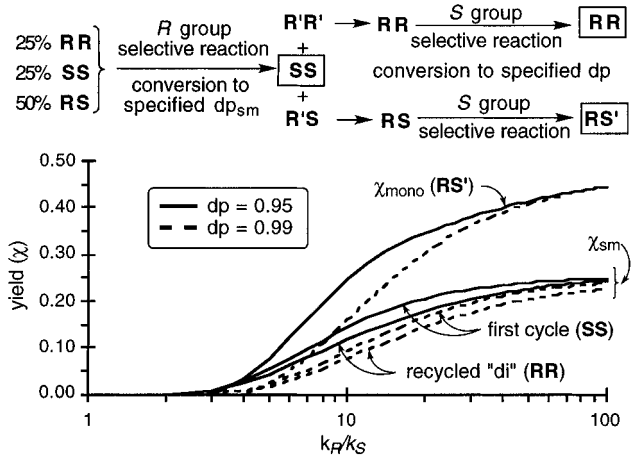


Figure 9. Calculated[31] potential yields of sm and recycled "mono" and "di" products with a specific dp for the indicated process (cf. Figure 1) as a function of the reaction enantiotopic group selectivity (k_R/k_S). See Figure 3 for definitions.

ally) using a reaction with inverse selectivity,[41] in each case, to the conversion sufficient to reach the desired dp.[42] The calculated results from such a strategy are shown in Figure 9. For example, kinetic resolution of a 1:1 *meso/dl* stereoisomeric mixture by a reaction with enantiotopic group selectivity of 10:1 ($k_R > k_S$; see Figure 1) can provide each of the three components (as **SS**, **R′S**, **R′R′**; see Figure 4) with only 72% dp (92% ee); if recycling with inverse selectivity ($k_R < k_S$) is possible, the same components (as **SS**, **RS′**, **RR**; see Figure 9) can be obtained with 99% dp (≫99% ee)[34] in 33% combined yield (50% yield for 95% dp). A reaction with an enantiotopic group selectivity of 1050:1 would be required to provide all three components (as **SS**, **R′S**, **R′R′**) with 99% dp without recycling.

To summarize, a mathematical model based on reactions of independent functional groups[30] is derived to describe kinetic resolutions of bifunctional *meso/dl* stereoisomeric mixtures. This model suggests that the enantiomers are separated from each other much more efficiently than from the *meso* diastereomer. In general, only the slow reacting enantiomer (as recovered starting material) can be obtained with high stereoisomeric purity from these processes; the predicted diastereoisomeric purities of the products derived from the fast reacting enantiomer and from the *meso* diastereomer are limited. A detailed analysis of the model reveals various recycling strategies that can serve to enhance the purity of the these products. In particular, if recycling is performed using a reaction with an enantiotopic group selectivity opposite to that in the first cycle, then it is predicted that all three components of a *meso/dl* mixture (or their derived products) can be obtained with high stereoisomeric purity, even from a process with modest enantiotopic group selectivity.

To test the above predictions, we examined the Sharpless epoxidation[43] of the diene **1** to give the monoepoxide **2** and diepoxide **3** (Scheme 1). A Sharpless epoxidation was selected because it is one of the few reactions with high and predictable enantiotopic group selectivity[43] and can be easily reversed by various[44] epoxide deoxygenation methods. The diene **1** was readily prepared from the known **4**[45] by sequential treatment with DIBAL and vinylmagnesium bromide according to Schreiber's protocol.[46] We were unable to differentiate the C_s and C_2 isomers of **1** (or the corresponding bisacetate and bis-TBDMS ether derivatives) either by NMR spectroscopy (^{1}H and ^{13}C) or by GC (with a chiral [Cyclodex B] or achiral column). Esterification[47] of **1** with (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (Mosher's acid, MTPA-OH)[48] gave the bisesters **5r** whose ^{1}H NMR spectrum indicated the presence of a 2:1:1 mixture of *RS*, *RR*, and *SS* stereoisomers.[49,50]

The diene **1**, as a 2:1:1 mixture of *RS*, *RR*, and *SS* stereoisomers, was subjected to standard Sharpless epoxidation conditions[51] using L-(+)-diisopropyl tartarate (L-DIPT) at −23 °C (Scheme 2). After 52 h (20% of **1** remaining by GC), the diene **1** (18%), monoepoxide **2** (40%), and diepoxide **3** (16%) were isolated. The recovered diene **1** ($[\alpha]^{25}_D = -3.7$; *c* 3.9, $CHCl_3$) was shown to be the *RR* isomer (<1% *RS*, <1% *SS*) by conversion into the corresponding Mosher's bisester **5**.[52] Among the eight possible stereoisomers, **2** was shown (*vide infra*)[54] to consist of a 85:9:3:2:1 mixture of *RSR*, *SRR*, *RRR*, *SSR*, and *RSS* isomers,[55] respectively. A rigorous determination of the stereoisomer distribution of **3** was not attempted;[56] however, deoxygenation[57] of **3** by treatment with KSeCN gave **1** (80%), which was a 69:27:4 mixture of *SS*, *RS*, and *RR* isomers, respectively.[54]

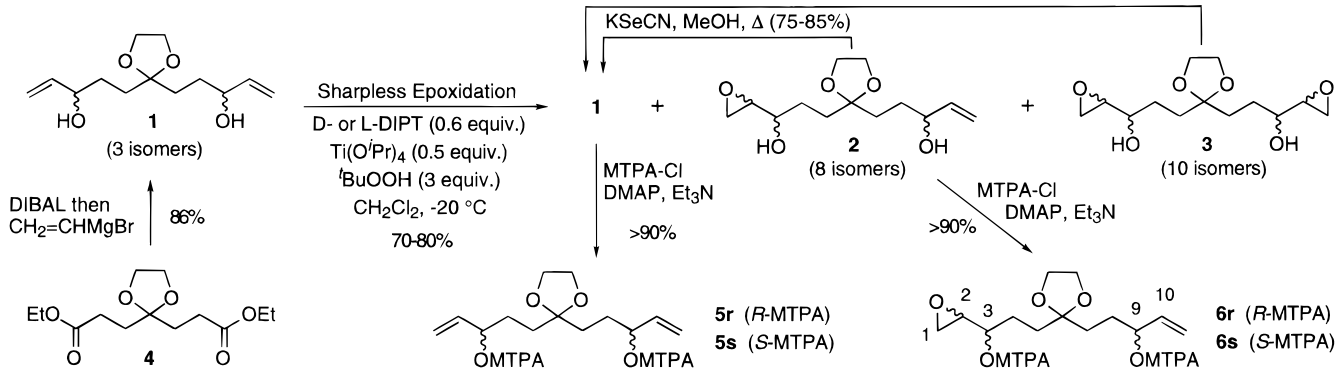
The stereoisomer composition of the monoepoxide **2** was

(41) If inverse selectivity is not possible, then the first reaction should be stopped (approximately) at the conversion where dp_{mono} is at the maximum value. The calculated results for resubjecting unreacted starting material, recycled "mono" product, and recycled "di" product to the same reaction are shown in Figures 5, 6, and 8, respectively. In this scenario, the potential dp for the "mono" and "di" products is considerably more limited.

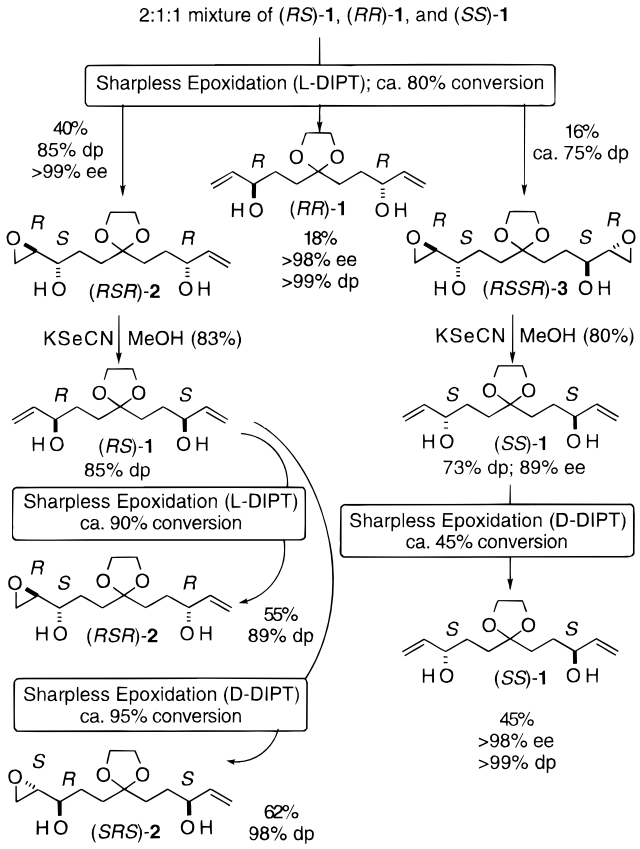
(42) In this scenario, a higher dp (with lower yield) is potentially achievable for the recycled "mono" product because the "desired" dp occurs at a conversion lower than that corresponding to the maximum dp_{mono}. Of course, any high dp (with lower yield) can be obtained for the recycled "di" product by running the reaction to higher conversion.[40]

(43) Review: Katsuki, T.; Martin, V. S. *Org. React.* **1995**, *48*, 1−300.
(44) Larock, R. H. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 140−142.
(45) Solladié, G.; Huser, N.; Fischer, J.; Decian, A. *J. Org. Chem.* **1995**, *60*, 4988−4990.
(46) Schreiber, S. L.; Kelly, S. E.; Porco, J. A., Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210−6218.
(47) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.*, **1991**, *32*, 7165, 7166.
(48) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.*, **1969**, *34*, 2543−2549. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.*, **1973**, *95*, 512−519.
(49) The vinyl methine proton appeared as four equally intense signals (each 25 ± 1%) at δ 5.80, 5.79, 5.70, 5.69 (each as a ddd with $J \approx 7$, 10, 17 Hz).
(50) For the use of Mosher's bisesters to analyze *meso/dl* diols, see refs 25a, 25i, and: Baldwin, B. W.; Morrow, C. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2871−2878.
(51) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

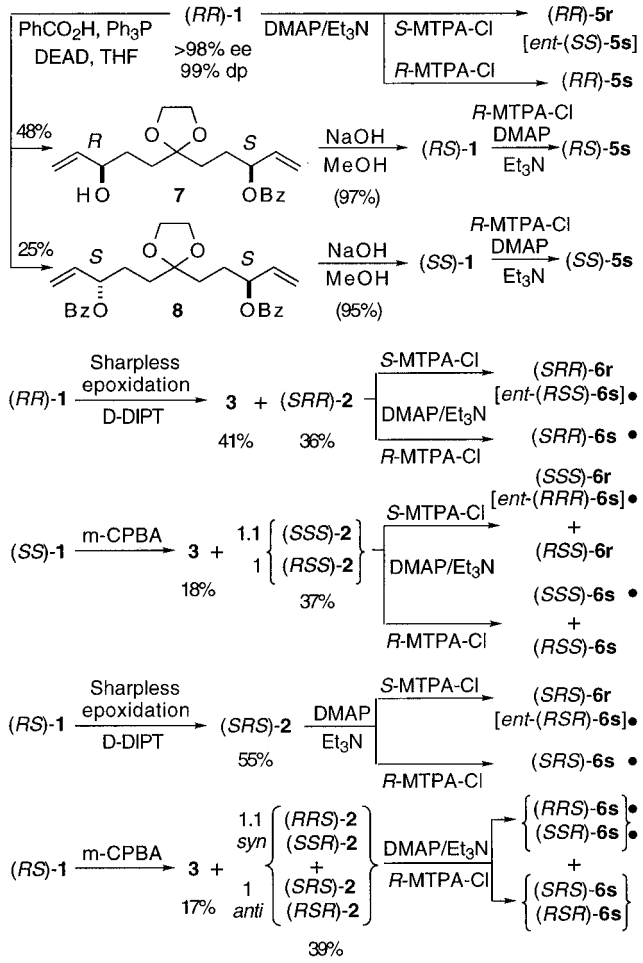
Scheme 1



Scheme 2



Scheme 3



determined by ^{1}H NMR of the corresponding Mosher's bisester derivative **6**. We had previously established the validity of this method by preparing standards for the eight possible stereoisomers (four pairs of enantiomers) of **2** by independent stereoselective synthesis. The strategy for obtaining stereochemically pure monoepoxide standards of known stereochemistry involved epoxidation of stereochemically pure isomers of **1** which were available by Mitsunobu reaction of the previously obtained (*RR*)-**1** (see Scheme 3). Epoxidation under Sharpless conditions was expected to give monoepoxide products with high and predictable *anti* diastereoselectivity.[43] On the other hand, epoxidation with *m*-CPBA gave mixtures of monoepoxide diastereomers (*syn*/*anti* ca. 1.1:1) which were separable after conversion to the Mosher's bisester derivatives **6**. Finally, preparing both (*R*)- and (*S*)-MTPA derivatives of the monoepoxide diastereomers allows the preparation of all eight

(52) The ^{1}H NMR spectrum of the bisester (*RR*)-**5s** obtained after esterification with (*S*)-MTPA-OH (via (*R*)-MTPA-Cl)[47] showed a single vinyl methine proton at δ 5.70 (2H, ddd, J = 6.5, 10.5, 17 Hz). The presence of <1% of other isomers[49] was indicated by using the ^{13}C satellite from this signal as an internal standard. The bisester (*RR*)-**5r** obtained after reaction with (*S*)-MTPA-Cl showed a single vinyl methine proton at δ 5.79 (2H, ddd, J = 7, 10.5, 17.5 Hz) [note: this is the enantiomer of the the (*S*)-Mosher's bisester from (*SS*)-**1**, i.e., (*SS*)-**5s**]. The absolute stereochemistry is assigned as (*RR*)-**1** based on the advanced Mosher's method[53] (i.e., $\Delta\delta$ for the vinyl methine proton is $\delta_{SMTPA} - \delta_{RMTPA} = -0.09$) and is consistent with the established propensity for the (L)-(+)-DIPT derived Sharpless catalyst to epoxidize (*S*)-allyic alcohol groups.[43]

(53) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(54) Stereoisomer composition determined by ^{1}H NMR of the corresponding Mosher's bisester derivative.

(55) Stereochemical labels (e.g., *RRR*) refer to the absolute configuration at the 2, 3, and 9 positions, respectively, of 1,2-epoxy-6,6-ethylenedioxy-10-undecene-3,9-diol (**2**).

(56) Ten possible stereoisomers (four chiral and two *meso* diastereomers).

(57) Behan, J. M.; Johnstone, R. A. W.; Wright, M. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1216, 1217.

Table 1. Diagnostic ^{1}H NMR Chemical Shifts for (*S*)-MTPA Esters of the Isomers of **2**

isomer	HC-1[a]	HC-1[b]	HC-2[c]	HC-2[d]	HC-10[e]
(*RRR*)-**6s**	2.59	2.79	3.06		5.71
(*SSS*)-**6s**	2.69	2.89	3.08		5.79
(*SRR*)-**6s**	2.64	2.70		2.94	5.70
(*RSS*)-**6s**	2.71	2.75		3.03	5.79
(*RRS*)-**6s**	2.57	2.77	3.03		5.80
(*SSR*)-**6s**	2.68	2.86	3.07		5.69
(*RSR*)-**6s**	2.70	2.74		3.02	5.68
(*SRS*)-**6s**	2.61	2.68		2.91	5.80

[a] dd ($J \approx 2.5$, 5 Hz). [b] dd ($J \approx 4$, 5 Hz). [c] *Syn* isomers; ddd ($J \approx 2.5$, 4, 7 Hz). [d] *Anti* isomers; ddd ($J \approx 2.5$, 4, 5 Hz). [e] ddd ($J \approx 7$, 10, 17 Hz).

standards from only four substrates.[58] As shown in Table 1, the Mosher's bisester derivative of each isomer of **2** is distinguishable by ^{1}H NMR.

The stereoisomer compositions of the products from Sharpless epoxidation of **1** were examined at several conversions (Table 2). The relative reactivities of the *SS*, *RR*, and *RS* isomers of **1** were determined as 40, 1, and 20, respectively, by calculating the rate constant ratios k_7/k_5 ($=k_S/k_R$)[31] and $(k_1 + k_2)/k_5$ ($=0.5[k_S/k_R + 1]$)[31] using eqs 8 and 9 and the stereoisomer distribution of recovered **1** at a given conversion (cf. Figure 1; note: using L-(+)-DIPT, $k_S > k_R$).[59] Thus, the enantiotopic group selectivity of the reaction under these conditions is estimated to be 40:1.[59] As shown in Table 2, the stereoisomer compositions for **2** and recovered **1** calculated from the mathematical model using $k_S/k_R = 40$ agree quite closely with the experimentally observed values.[61,62] By contrast, the observed stereoisomeric purity of **3** (determined after deoxygenation) was always less than that calculated suggesting that the group selectivity for epoxidation of **2** may be somewhat lower than for **1**. As expected, despite the high group selectivity of the Sharpless epoxidation, only unreacted diene **1** could be obtained with high purity; both the monoepoxide **2** and diepoxide **3** had poor stereoisomeric purity.

Treatment[57] of the 85:9:3:2:1 mixture of *RSR*, *SRR*, *RRR*, *SSR*, and *RSS* monoepoxide isomers **2** (obtained from **1** as described above) with KSeCN in refluxing methanol gave **1** as a 85:14:1.5 mixture of *RS*, *RR*, and *SS* isomers (Scheme 2).[54] Resubjecting this sample of **1** to Sharpless epoxidation under standard conditions (L-DIPT, 48 h; >90% conversion) gave **2** as a 89:7:2:2 mixture of *RSR*, *SRR*, *RRR*, and *SSR* isomers, respectively.[54,55,63] Alternatively, Sharpless epoxidation of **1** under identical conditions but using a D-DIPT derived catalyst (48 h; >95% conversion) gave **2** as a 98:2 mixture of *SRS* and *RRS* isomers (<1% of any other isomer),[54,55] which was identical in all respects, including optical rotation ($[\alpha]_D$ +6.9; *c* 1.5, MeOH), with the monoepoxide product obtained from Sharpless epoxidation of pure (*RS*)-**1**.[64] From the perspective of kinetic resolution of *meso/dl* stereoisomeric mixtures, the latter product can be considered as diastereomerically pure because the minor diastereomer (*RRS*-**2**) results from the imperfect *anti/syn* diastereoselectivity in the Sharpless epoxidation and not from imperfect differentiation of enantiotopic groups.[61,64]

The diepoxide product from **1** was recycled in a similar manner (Scheme 2). The 69:27:4 mixture of *SS*, *RS*, and *RR* isomers **1**, obtained by deoxygenation of **3**, was subjected to Sharpless epoxidation using a D-DIPT derived catalyst (48 h; ca. 45% conversion); the recovered diene (45% yield) was essentially pure (*SS*)-**1** (<1% *RS*, <1% *RR*).[54,65] In summary, Sharpless epoxidation (L-DIPT) of a 1:1:2 mixture of (*RR*)-**1**, (*SS*)-**1**, and (*RS*)-**1** followed by recycling of the mono- and diepoxide products by deoxygenation (KSeCN) and reepoxidation (D-DIPT) provides (*RR*)-**1** (72% yield, one step), (*SS*)-**1** (23% yield, three steps), and the desymmetrized *meso* derivative (*SRS*)-**2** (41% yield, three steps), each with a diastereoisomeric purity of ≥99%[61] and >99% ee. These results are in accord with those calculated using the above model and assuming a 40:1 enantiotopic group selectivity.

The mathematical model of kinetic resolution of *meso/dl* mixtures suggests that, by using the appropriate recycling protocol, products with high stereoisomeric purity can be obtained even from reactions with modest selectivity. To test this scenario, we examined the Sharpless epoxidation of a 1:1:2 mixture of (*RR*)-**1**, (*SS*)-**1**, and (*RS*)-**1** using a catalyst derived from L-DIPT of ca. 75% ee.[66] The stereoisomer distributions of the products obtained from Sharpless epoxidation of **1** using this catalyst system were examined at several conversions (Table 3). All products, other than the recovered **1** at high conversion, were obtained with poor dp. The enantiotopic group selectivity of the reaction under these conditions is estimated to be 9:1 from the relative reactivities of the *SS*, *RR*, and *RS* isomers of **1** (calculated[59] as 9, 1, and 5, respectively, using the results from the 4 h reactions).[67] As above (cf. Table 2), the observed results are in reasonable agreement with those calculated assuming a 9:1 selectivity.[61]

To test the recycling strategy under conditions with modest selectivity, the monoepoxide **2** obtained from epoxidation (L-

(58) For a given isomer of **2** [e.g., (*RRR*)-**2**], the (*S*)-MTPA derivative [e.g., (*RRR*)-**6s**] is enantiomeric (i.e., will have the same NMR spectrum) with the (*R*)-MTPA derivative of its enantiomer [e.g., (*SSS*)-**6r**). Thus, only one of the enantiomers of each of the four possible diastereomers of **2** is required to prepare eight standards.

(59) The data from 4 h reactions were used. The reaction was performed in triplicate with careful measurement of conversion (by GC with an internal standard). The calculation is quite sensitive to the conversion. If we assume that the measured conversion is accurate to ±1%, then $k_S/k_R = 25-100$. For comparison, the reported enantiotopic group selectivity (i.e., k_S/k_R) for Sharpless epoxidation (−20 °C) of nonen-3-ol is 29 under catalytic conditions (10 mol%)[51] and 83 with stoichiometric Ti(IV).[60]

(60) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ideda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240.

(61) Sharpless epoxidation introduces a new stereogenic center with a diastereoselectivity (ca. 25−50:1 *anti/syn* for the "matched" reaction)[43] that, in principle, is independent of the conversion.[62] Thus for comparison with the model (cf. Figure 1), the mole fractions for the *syn* and *anti* isomers of **2** (e.g., *SSR* and *RSR*, respectively) should be summed.

(62) Selective decomposition of epoxide stereoisomers under the reaction conditions can result in a conversion dependence of *anti*:*syn* epoxide ratios.[43,60] From the data presented in ref 43 (p 36), one can calculate that the relative rate constants for decomposition of the *syn* and *anti* epoxides derived from (*R*)- and (*S*)-nonen-3-ol under the Sharpless epoxidation conditions (L-DET/Ti(O^iPr)$_4$) are 8.6 (*syn R*), 3.1 (*syn S*), 1.6 (*anti S*), and 1 (*anti R*). By extrapolation, (*RRR*)-**2** should decompose with a rate constant eight times greater than that for (*SRR*)-**2** during epoxidation of **1** with L-DIPT/Ti(O^iPr)$_4$. Because the (*SRR*)-**2**/(*RRR*)-**2** ratio shows little change with conversion (ca. 2:1 at 6 h and 3:1 at 52 h; cf. Table 2), we conclude that selective decomposition of epoxide stereoisomers under the reaction conditions has no significant effect on the stereoisomer distribution of the products.

(63) For comparison with the model this corresponds to a dp of 91%.[61] The maximum dp predicted for the "mono" product from a reaction with 40:1 selectivity with recycling after reaching the maximum dp (see Figure 6b) is 98%. Similar recycling after reaching $ee^*_{mono} = 0.8$ is predicted to give the "mono" product with 95% dp at 90% conversion and 91% dp at 93% conversion.

(64) The maximum dp predicted for the "mono" product from a reaction with 40:1 selectivity with recycling after reaching the maximum dp (see Figure 7a) is 99.3%; recycling after reaching $ee^*_{mono} = 0.8$ (see Figure 7c) is predicted to give the "mono" product with 99.6% dp.

(65) The mixture of diene isomers is predicted to reach 99% dp at 43.5% conversion in a reaction with 40:1 selectivity.

(66) Prepared by mixing pure DIPT enantiomers in a ratio of 6.80:1 (by mass).

(67) The enantiotopic face selectivity of the Sharpless epoxidation shows a positive nonlinear correlation with the ee of the tartarate catalyst; presumably, the enantiotopic group selectivity is similarly effected: (a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357 (b) Guillaneux, D.; Zhao, S.-H., Samuel, O.; Rainford, D.; Kagan, H. B. *Ibid*. **1994**, *116*, 9430−9439.

Table 2. Observed[a] and Calculated[b] Stereoisomer Distributions for the Products of Sharpless Epoxidation of **1** (L-DIPT) as a Function of Conversion

		stereoisomer distribution		
time (h)	% conversion	**1** *RR:SS:RS*	**2** *RSR:SSR:RRS:SRS:RRR:SRR:RSS:SSS*	**3**[c] *RR:SS:RS*
4	35.2[d]	37.7:14.6:47.7[d]		
7	52	53:7:40	66:2:−:−:2:4:26:−	
	(52)	(51:8:41)	(68:1:3:28)[e]	
16	75	85:1.5:13.5	83:1.5:−:1:2:5:7:0.5	3:71:26
	(75)	(87:0.5:12)	(87:0.5:6:6)[e]	(0.5:87:12)
52	80	>99:−:−	85:2:−:−:3:9:1:−	4:69:27
	(80)	(99:−:1)	(89:−:10:1)[e]	(1:80:19)
	(82)	(99.7:−:0.3)	(87:−:13:−)[e]	(2:75:23)

[a] Determined by ^{1}H NMR of the corresponding Mosher's bisester derivative. [b] Calculated results (in parentheses) are from eqs. 1−9 assuming an enantiotopic group selectivity of 40:1. [c] Determined after deoxygenation to **1**. [d] The average of three experiments. [e] The ratio of *R*SR:R*RS:R*RR:R*SS* isomers (i.e., the sum of *syn* and *anti* epimers).

Table 3. Observed and Calculated[a] Stereoisomer Distributions for the Products of Sharpless Epoxidation of **1** (L-DIPT, 75% ee) as a Function of Conversion

		stereoisomer distribution[b]		
time (h)	% conversion	**1** *RR:SS:RS*	**2** *RSR:SSR:RRS:SRS:RRR:SRR:RSS:SSS*	**3**[c] *RR:SS:RS*
4	28.9[d]	32.7:18.3:49[d]		
72	78	74:3:23	65:3.5:−:−:7:19:5:−	
	(78)	(73:2:25)	(70:2:16:12)[e]	(3.5:66:30)
120	90	97:−:3	68:2:−:−:6:22:2:−	10:47:43
	(90)	(96:−:4)	(71:0.5:27:1.5)[e]	(8:52:40)
	(91)	(97:−:3)	(69.5:0.5:29:1)[e]	(9:50:41)

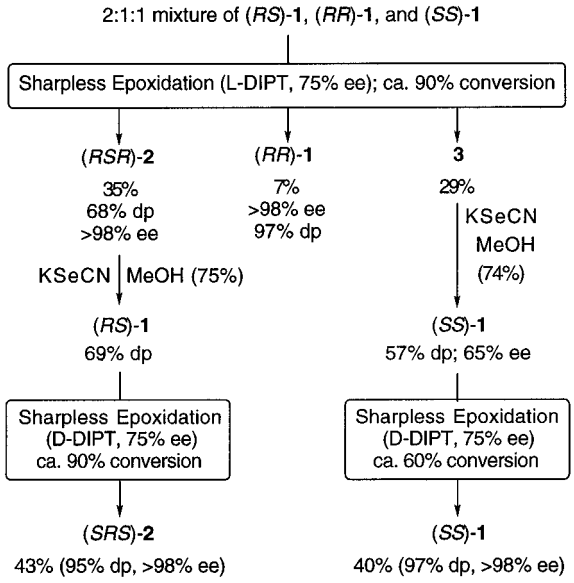
[a] Determined by ^{1}H NMR of the corresponding Mosher's bisester derivative. [b] Calculated results (in parentheses) are from eqs. 1−9 assuming an enantiotopic group selectivity of 9:1. [c] Determined after deoxygenation to **1**. [d] The average of three experiments. [e] The ratio of *R*SR:R*RS:R*RR:R*SS* isomers (i.e., the sum of *syn* and *anti* epimers).

(+)-DIPT, 75%ee)[66] of a 2:1:1 mixture of *RS*, *RR*, and *SS* stereoisomers of **1** at 78% conversion was deoxygenated to give **1** (77%) as a 71:24:5 mixture of *RS*, *RR*, and *SS* isomers.[54] Sharpless epoxidation (72 h) of this sample of **1** using a catalyst derived from D-DIPT of 75% ee[66] gave **2** (40%) as a 91:4:2:2:1 mixture of *SRS*, *RSS*, *RRS*, *SRR*, and *SSS* isomers, respectively.[54,55,68] According to the model (cf. Figure 7), the dp of the "mono" product should be improved by recycling after a higher conversion where the ee*$_{mono}$ is greater. Thus, deoxygenation of **2** obtained at 90% conversion gave **1** (75%) as a 69:29:2 mixture of *RS*, *RR*, and *SS* isomers, respectively (see Scheme 4).[54,55] Resubjecting this diene mixture to Sharpless epoxidation (D-DIPT, 75% ee;[66] 72 h) gave **2** (43%) as a 95:2:1.5:1:0.5 mixture of *SRS*, *RRS*, *SRR*, *RSS*, and *SSS* isomers, respectively.[54,55,69] As predicted,[38] recycling of the mono-epoxide obtained at 90% conversion gives a purer product (dp = 97%)[61] than that obtained by recycling after 78% conversion (dp = 93%).[61] This result is due to the smaller amount of the slow reacting *SS*-**1** (after deoxygenation of **2**) in the diene subjected to the second epoxidation from the former case (2% vs 5%).[38] To complete the recycling protocol, the diepoxide **3** obtained at 90% conversion was deoxygenated to give **1** (74%) as a 47:43:10 mixture of *SS*, *RS*, and *RR* isomers. The recovered diene **1** (40%) after Sharpless epoxidation (72 h) of this sample using a catalyst derived from D-DIPT of 75% ee[66] was a 97:3 mixture of *SS* and *RS* isomers, respectively (<1% *RR*).

In conclusion, a mathematical model of kinetic resolutions of bifunctional *meso/dl* stereoisomeric mixtures predicts that (i) only the slow reacting enantiomer can be obtained with high stereoisomeric purity in these processes; (ii) the stereoisomeric purity of the other components can be improved by recycling; (iii) recycling using a reaction with opposite selectivity is superior to recycling using the same reaction; and (iv) with recycling, all three components of a *meso/dl* mixture (or their derived products) can be obtained with high stereoisomeric purity, even from a process with modest enantiotopic group selectivity. Sharpless epoxidation of a stereorandomly generated mixture of *meso* and racemic diastereomers of the diene **1** served to test the predictions of the model; by using catalysts derived from enantiomerically pure and 75% ee DIPT, reactions with high (40:1) and modest (9:1) enantiotopic group selectivity were examined. In both cases, the two C_2 enantiomers and a desymmetrized derivative of the *meso* diastereomer of **1** were obtained with high stereoisomeric purities that are in reasonable agreement with those calculated by the model using experimentally measured values for the reaction selectivity.

The preparation of stereochemically pure C_s or C_2 bifunctional

Scheme 4



(68) The maximum dp predicted for the "mono" product from a reaction with 9:1 selectivity with recycling after reaching the maximum dp (see Figure 7a) is 93%.

(69) The maximum dp predicted for the "mono" product from a reaction with 9:1 selectivity with recycling after reaching ee*$_{mono}$ = 0.9 (see Figure 7c) is 98%.

substrates is difficult by classical methods, especially when substrate-controlled diastereoselectivity is not applicable. By contrast, *meso/dl* mixtures are readily available by stereorandom two-directional transformation of a C_{2v} (or C_{2h}) bifunctional substrate. Kinetic resolution of such mixtures can provide a simple and predictable route both to enantiomerically pure C_2 bifunctional substrates *and* to "desymmetrized" derivatives of the corresponding C_s isomers. Alternatively, such processes might be exploited to enhance the stereoisomeric purity of C_s or C_2 bifunctional substrates prepared by stereoselective methods. Numerous nonenzymatic reactions have been reported that have enantiotopic group selectivities of >10:1. Those that can be easily "reversed" are good candidates for kinetic resolution of stereoiomeric mixtures.

Experimental Section

6,6-Ethylenedioxy-1,10-undecadiene-3,9-diol (1). A solution of DIBAL (1.5 M in toluene, 11.0 mL, 16.5 mmol) was added via syringe to a solution of **4**[45] (2.00 g, 7.19 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After 30 min, a solution of vinylmagnesium bromide (1 M in THF, 22 mL, 22 mmol) was added.[46] After stirring at −78 °C for 30 min and for 1.5 h at room temperature, the cooled (0 °C) reaction mixture was quenched by careful addition of aqueous NaOH (1 M, 5 mL). The mixture was filtered through a pad of Celite and the filtrate was sequentially washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was fractionated by flash column chromatography (FCC; 50% EtOAc in hexane) yielding **1** (2:1:1 mixture of *RS*, *RR*, and *SS* isomers)[54] as a colorless oil (1.5 g, 86%): IR ν_{max} 3428, 2078, 2955, 2881, 1642, 1061 cm^{-1}; ^1H NMR δ 5.82 (2H, ddd, J = 6, 10.5, 17 Hz, H-2, 10), 5.12 (2H, dd, J = 1.5, 17 Hz, H-1, 11), 5.07 (2H, dd, J = 1.5, 10.5 Hz, H-1, 11), 4.06 (2H, ddd, J = 5.5, 5.5, 6 Hz, H-3, 9), 3.93 (4H, ap s, CH_2O), 2.00−1.80 (2H, br s, OH), 1.76−1.65 (4H, m), 1.65−1.53 (4H, m); ^{13}C NMR δ 141.0 (d, C-2, 10), 114.6 (t, C-1, 11), 111.6 (s, C-6), 72.8 (d, C-3, 9), 64.9 (t × 2, CH_2O), 32.6 (t, C-5, 7), 31.0 (t, C-4, 8); CIMS (NH_3), *m/z* (relative intensity) 225 ([(M + 1) − 18]$^+$, 1), 181 (100). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.33; H, 8.94. Spectral data obtained from pure stereoisomers of **1** were indistinguishable; for (*RR*)-**1** (>99%),[54] $[\alpha]_D$ −3.7 (*c* 3.9, $CHCl_3$); for (*SS*)-**1** (>99%),[54] $[\alpha]_D$ +3.6 (*c* 3.1, $CHCl_3$); for (*RS*)-**1** (>99%),[54] $[\alpha]_D$ 0.0 (*c* 3.5, $CHCl_3$).

General Procedure for Sharpless Epoxidation. The procedure was similar to that previously described by Sharpless *et al.*[51] To a suspension of 4Å molecular sieves (0.12 g/mmol of **1**) in CH_2Cl_2 (3 mL/mmol of **1**) at −23 °C were added a solution of (L)-(+)- or (D)-(−)-DIPT (0.6 mmol/mmol of **1**) in CH_2Cl_2 (1 mL/mmol of **1**) and $Ti(O^iPr)_4$ (0.5 mmol/mmol of **1**). After 10 min, a solution of **1** in CH_2Cl_2 (1 mL/mmol of **1**) and dodecane (ca. 0.05 mL/mmol of **1**; internal standard for GC) was added to this reaction mixture under Ar (workup of a small aliquot at this point provided a t_0 sample for GC analysis). The reaction mixture was stirred for 1 h at −23 °C and then a predried (4Å molecular sieves) solution of TBHP in isooctane (ca. 4 M, 0.75 mL/mmol of **1**) was added. After standing in the freezer (−18 to −23 °C) for the appropriate time (conversion can be monitored by workup of a small aliquot and GC analysis), the reaction was quenched by the addition of an aqueous solution of 30% NaOH (w/v) in saturated brine (1.5 mL/mmol of **1**) and Et_2O (ca. 10% v/v of the reaction mixture). The mixture was stirred for 10 min at 10 °C, and then magnesium sulfate (1 g/mmol of **1**) and Celite (0.2 g/mmol of **1**) were added. After stirring for 15 min, the resulting mixture was allowed to settle (conversion determined by GC analysis) and then was filtered through a pad of Celite and concentrated. The resulting liquid was fractionated by medium pressure chromatography (MPC; gradient elution: 3−7% ^{i}PrOH in ether) yielding **1**, **2**, and **3**. Typical material recovery was 70−80%. The stereoisomer distribution present in **1** and **2** could be determined by ^1H NMR after conversion to the corresponding Mosher's bisester derivatives **5** and **6**, respectively.

1,2-Epoxy-6,6-ethylenedioxy-10-undecene-3,9-diol (2): IR ν_{max} 3421, 3074, 2956, 2883, 1061 cm^{-1}; ^1H NMR δ 5.85 (1H, ddd, J = 6, 10.5, 17 Hz, H-10), 5.23 (1H, d, J = 17 Hz, H-11), 5.11 (1H, d, J = 10.5 Hz, H-11), 4.11 (1H, ddd, J = 6, 6, 6 Hz, H-9), 3.97 (4H, ap s, CH_2O), 3.76 (1H, ddd, J = 3.5, 3.5, 8.5 Hz, H-3),[70] 3.47 (1H, ddd, J = 4.5, 5, 6.5 Hz, H-3),[71] 3.01−2.96 (1H, m, H-2), 2.82−2.78 (1H, m, H-1), 2.76−2.71 (1H, m, H-1), 2.35−2.15 (2H, br s, OH), 1.91−1.55 (8H, m, H-4, 5, 7, 8); ^{13}C NMR δ: 141.0 (d, C-10), 114.8 (t, C-11), 111.4 (s, C-6), 72.9 (d, C-9), 71.3 (d, C-3),[71] 69.0 (d, C-3),[70] 65.0 (t ×2, CH_2O), 55.2 (d, C-2),[71] 54.4 (d, C-2),[70] 44.9 (t, C-1),[71] 43.8 (t, C-1),[70] 32.8 (t ×2, C-5 or C-7), 32.7 (t ×2, C-5 or C-7), 31.1 (t, C-8), 28.6 (t, C-4),[71] 27.7 (t, C-4);[70] CIMS (NH_3) *m/z* (relative intensity) 259 ([M + 1]$^+$, 3), 199 (14), 197 (100). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.50; H, 8.73.

1:2,10:11-Bis(epoxy)-6,6-(ethylenedioxy)undecane-3,9-diol (3): IR ν_{max} 3427, 2956, 2925, 2887, 1257, 1062 cm^{-1}; ^1H NMR δ 3.98 (4H, ap s, CH_2O), 3.76 (2H, m, H-3(9)),[70] 3.50 (2H, m, H-3(9)),[71] 2.99 (2H, m, H-2, 10), 2.81 (2H, m, H-1, 11), 2.74 (2H, m, H-1, 11), 2.20 (2H, br s, OH), 1.90−1.57 (8H, m, H-4, 5, 7, 8); ^{13}C NMR δ 111.3 (s, C-6), 71.2 (d, C-3(9)),[71] 69.0 (d, C-3(9)),[70] 65.0 (t ×2, CH_2O), 55.2 (d, C-2(10)),[71] 54.4 (d, C-2(10)),[70] 44.9 (t, C-1(11)),[71] 43.8 (t, C-1(11)),[70] 32.8 (t, C-5(7)),[71] 32.7 (t, C-5(7)),[70] 28.7 (t, C-4(8)),[71] 27.7 (t, C-4(8));[70] CIMS (NH_3), *m/z* (relative intensity) 275 ([M + 1]$^+$, 3), 259 (12), 213 (100). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.85; H, 8.29.

General Procedure for the Preparation of Mosher's Bisesters 5 and 6. To a solution of the diol (**1**, **2**, or **3**; 3−10 mg) in CH_2Cl_2 (0.5 mL) were added DMAP (ca. 1 mg), Et_3N (0.1 mL), and a solution of (*R*)- or (*S*)-MTPA-Cl [2.6 equiv; prepared[47] from the corresponding (*S*)- or (*R*)-MTPA-OH (note the change in the stereochemical descriptor)] in CH_2Cl_2 (0.2 mL). After stirring for 4 h, the reaction mixture was washed sequentially with saturated $NaHCO_{3(aq)}$ and brine, dried over Na_2SO_4, and concentrated. The crude product was analyzed by ^1H NMR to ensure complete conversion (if the presence of monoester or starting diol was detected then the residue was resubjected to the above reaction conditions). The residue was fractionated by FCC (33% EtOAc in hexane) yielding the corresponding Mosher's bisesters (> 90% yield). If desired, *syn* and *anti* isomers of **6** could be separated (the *anti* isomer is less polar) by careful preparative TLC (25% EtOAc in hexane; multiple development).

^{1}H NMR Analysis of Mosher's Esters. ^1H NMR spectra for **5** and **6** were obtained at 27 °C with a digital resolution of 0.082 Hz/pt (FID = 64 K data points) using a 90° pulse and a ca. 7 s repetition rate ($T_1 \approx$ 1.2 s) and were processed with Gaussian resolution enhancement. Sufficient scans were obtained to achieve a signal to noise ratio of at least 3:1 for the low field ^{13}C satellite of the vinylic methine proton for the major isomer. Isomer ratios were determined from the intensity of the diagnostic signals listed in Table 1. The ^{13}C satellites for the major isomer were used as internal standards (assumed to be 0.55%) for measurement of the very minor isomers. We estimate the absolute errors in the determination of isomer distribution to be ±0.5% for the very minor isomers and ±2% for the others.

General Procedure for the Deoxygenation of 2 and 3. A stirred solution of the epoxide (**2** or **3**) in MeOH (ca. 20 mL/mmol of substrate) and KSeCN (2 equiv. per epoxide) was heated under reflux for 72 h.[57] The mixture was concentrated, diluted with CH_2Cl_2, and washed with H_2O; the organic layer was dried over Na_2SO_4, concentrated, and fractionated by MPC (3% ^{i}PrOH in hexane) to give **1** (75−85% yield). The stereoisomer distribution was determined by ^1H NMR after conversion to the Mosher's bisester derivative **5**.

Kinetic Resolution of *meso/dl* 1. Sharpless epoxidation (with L-(+)-DIPT) of *meso/dl* **1** (628 mg, 2.60 mmol) for 52 h (ca. 80% conversion) gave (*RR*)-**1** (>99% dp, >99% ee; 113 mg, 18%), **2** (ca. 85% dp; 266 mg, 40%), and **3** (ca. 75% dp; 116 mg, 16%). Deoxygenation of the above monoepoxide **2** (115 mg, 0.442 mmol) gave the diene **1** as a colorless oil (ca. 85% dp, 86% ee; 94 mg, 83%). Sharpless epoxidation (with D-(−)-DIPT) of this diene **1** (49 mg, 0.20 mmol) for 52 h (95% conversion) gave **1** (2 mg, 4%), (*SRS*)-**2** (98% dp; 28 mg, 54%), and **3** (8.5 mg, 15%). Alternatively, Sharpless epoxidation (with L-(−)-DIPT) of the above diene **1** (56 mg, 0.25 mmol) for 48 h (90% conversion) gave **1** (5 mg, 9%), (*RSR*)-**2** (90% dp; 35 mg, 55%), and **3** (8 mg, 12%). Deoxygenation of the above diepoxide **3** (100 mg, 0.364 mmol) from *meso/dl* **1** gave the diene **1** (73% dp, 89% ee; 66

(70) *Anti* diastereomer.
(71) *Syn* diastereomer.

mg, 74%). Sharpless epoxidation (with D-(−)-DIPT) of this diene **1** (22 mg, 0.091 mmol) for 48 h (45% conversion) gave recovered diene (*SS*)-**1** (>99% dp, >99% ee; 10 mg, 45%).

Sharpless epoxidation (with L-(+)-DIPT, 75% ee) of *meso/dl* **1** (556 mg, 2.30 mmol) for 120 h (ca. 90% conversion) gave (*RR*)-**1** (97% dp, 99% ee; 40 mg, 7%), **2** (68% dp; 206 mg, 35%), and **3** (180 mg, 29%). Deoxygenation of the above monoepoxide **2** (92 mg, 0.36 mmol) gave the diene **1** as a colorless oil (69:29:2 mixture of *RS*:*RR*:*SS* isomers; 65 mg, 75%). Sharpless epoxidation (with D-(−)-DIPT, 75% ee) of this diene **1** (35 mg, 0.14 mmol) for 72 h (ca. 90% conversion) gave **1** (3 mg, 9%), (*SRS*)-**2** (95% dp; 16 mg, 43%), and **3** (8 mg, 20%). Deoxygenation of the above diepoxide **3** (104 mg, 0.364 mmol) from *meso/dl* **1** gave the diene **1** (57% dp, 65% ee; 68 mg, 74%). Sharpless epoxidation (with D-(−)-DIPT, 75% ee) of this diene **1** (30 mg, 0.12 mmol) for 72 h (ca. 60% conversion) gave recovered diene (*SS*)-**1** (97% dp, >98% ee; 12 mg, 40%).

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Supporting Information Available: Derivation of equations, calculation procedures, experimental procedures, and spectral data for the preparation of stereochemical standards **5** and **6** (17 pages). See any current masthead page for ordering and Internet access instructions.

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