Communications to the Editor

Preparation of Desymmetrized Meso Derivatives by Kinetic Resolution of *meso*/DL Stereoisomeric Mixtures

Dale E. Ward,* Yadong Liu, and David How

Department of Chemistry, University of Saskatchewan Saskatoon, Saskatchewan S7N 5C9, Canada

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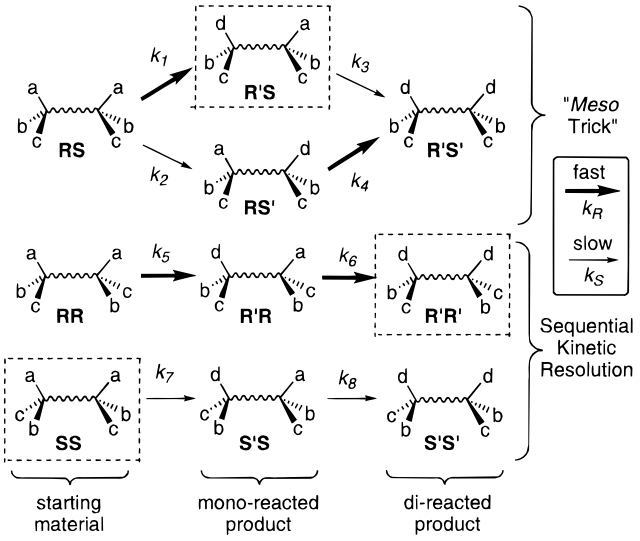
The desymmetrization of symmetrical bifunctional compounds by enantiotopic group-selective reactions has been established as a powerful strategy for asymmetric synthesis ("*meso* trick",[1] see Scheme 1).[2] This approach is particularly effective when the enantiotopic groups can react sequentially, thereby coupling an asymmetric synthesis with a kinetic resolution and producing products with high stereoisomeric purity,[3] even from reactions of moderate group selectivity.[4] A significant limitation to the application of such processes in organic synthesis is the availability of stereochemically pure *meso* bifunctional substrates.[5] In this paper, we present a mathematical model that describes kinetic resolutions of *meso*/DL mixtures and shows the effective use of such processes to obtain "desymmetrized" *meso* derivatives with high stereochemical purity from stereorandom substrate mixtures.

Two-directional chain synthesis[6] is an excellent tactic for the preparation of *meso* compounds but is applicable only in cases where intervening groups provide substrate-controlled diastereoselectivity. The stereoselective synthesis of *meso* substrates when groups are too remote to influence diastereoselectivity is nontrivial. 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.[7] Alternatively, a two-directional stereorandom transformation of a C_{2v} (or C_{2h}) bifunctional substrate gives a 1:1 mixture of C_2 and C_s products.[8] Separation of the diastereomers would provide a simple route to *meso* compounds.

As an alternative to physical separation of stereoisomers, we considered the consequences of a *meso*/DL mixture of bifunctional starting materials undergoing sequential enantiotopic group selective reaction (see Scheme 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 byseparation of compounds that are not stereoisomeric, thus making the stereoselective synthesis of a *meso* bifunctional starting material unnecessary.

Scheme 1. Group-Selective Reaction ('a' → 'd') with $k_R > k_S$



A few examples of enzyme-mediated acylation (or hydrolysis) of *meso*/DL mixtures of diols (or diesters) have been reported.[9] Most of these enzymatic resolutions efficiently separate the C_2-symmetric enantiomers from each other but not necessarily from the *meso* isomer. 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.

The group-selective reaction of a mixture of *meso* and DL stereoisomers 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., aggregation effects are negligible; see Scheme 1). Analytical expressions have been derived to describe sequential kinetic resolutions[10] and "*meso* trick" [3,4] processes. Substitution of the readily derived expressions for the relationships between the **RS**, **RR**, and **SS** concentrations allows determination of the concentrations of all of the components for a process represented in Scheme 1 as a function of the conversion of one of the substrates.[11] As expected, the calculations indicate that the stereoisomeric purity (both ee and dp)[12] of the remaining starting material (mostly **SS**) increases and that of the "di" product (mostly **R′R′**) decreases with increasing conversion. On the other hand, while the ee for the "mono" product increases with conversion, the dp[12] rises to a maximum and then decreases with increased

(1) Seebach, D.; Hungerbüler, E. *Mod. Synth. Methods* **1980**, *2*, 91−173.

(2) Reviews: (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1−19. (b) Maier, M. *Nachr. Chem. Tech. Lab.* **1993**, *41*, 314−330.

(3) (a) Wang, Y.-F.; Chen, C.-S.; Girdaukaus, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695−3696. (b) Dokuzokic, Z.; Roberts, N. K.; Sawyer, J. F.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034−2039. (c) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525−1529.

(4) (a) Ward, D. E.; Liu, Y.; Rhee, C. K. *Synlett* **1993**, 561−563. (b) Ward, D. E.; Liu, Y.; Rhee, C. K. *Can. J. Chem.* **1994**, *72*, 1429−1446.

(5) These might be defined as achiral (C_s or C_i symmetric) bifunctional substrates possessing two or more chirotopic stereogenic centers (or, more generally, stereogenic elements).

(6) Reviews: (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563−566. (b) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17. (c) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213.

(7) For examples of stereoselective syntheses of **R′S**-type compounds (Scheme 1) that do not involve desymmetrization of a *meso* compound, see: (a) Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6526−6528. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873−3888.

(8) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312−5313.

(9) (a) Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. *J. Org. Chem.* **1992**, *57*, 5231−5239. (b) Takemura, T.; Saito, K.; Nakazawa, S.; Mori, N. *Tetrahedron Lett.* **1992**, *33*, 6335−6338. (c) Kim, M.-J.; Lee, I. S.; Jeong, N.; Choi, Y. K. *J. Org. Chem.* **1993**, *58*, 6483−6485. (d) Mattson, A.; Öhrner, N.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1993**, *4*, 925−930. (e) Bisht, K. S.; Parmar, V. S.; Crout, D. H. G. *Tetrahedron: Asymmetry* **1993**, *4*, 957−958. (f) Adjé, N.; Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1993**, *34*, 4631−4634. (g) Nagai, H.; Morimoto, T.; Achiwa, K. *Synlett* **1994**, 289−290. (h) Levayer, F.; Rabiller, C.; Tellier, C. *Tetrahedron: Asymmetry* **1995**, *6*, 1675−1682.

(10) (a) Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63−125. (b) Kazlauskas, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953−4959. (c) Guo, Z.-H.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942−4945.

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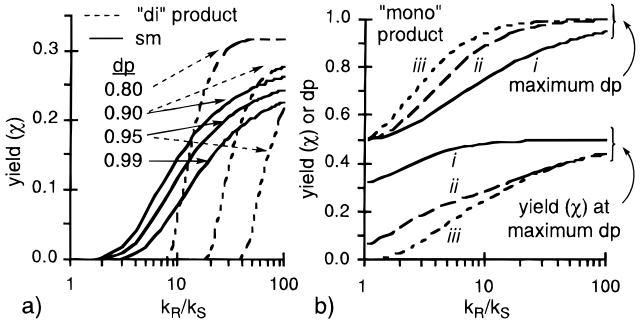
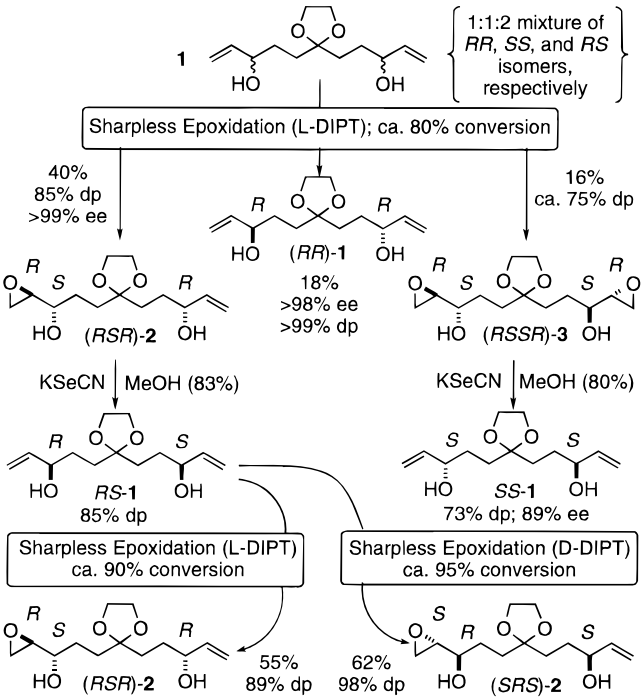


Figure 1. Calculated[11] obtainable diastereomeric purities (dp) and the corresponding yields (as mole fractions, χ) of starting material (sm), direacted product, and monoreacted product as a function of the reaction enantioptopic group selectivity for a process as described in Scheme 1. $[sm]_0 = [\mathbf{RR}]_0 + [\mathbf{SS}]_0 + [\mathbf{RS}]_0$. (a) $\chi_{sm} = ([\mathbf{RR}] + [\mathbf{SS}] + [\mathbf{RS}])/[sm]_0$; $\chi_{di} = ([\mathbf{R'R'}] + [\mathbf{S'S'}] + [\mathbf{R'S'}])/[sm]_0$; $dp_{sm} = ([\mathbf{RR}] + [\mathbf{SS}])/([\mathbf{RR}] + [\mathbf{SS}] + [\mathbf{RS}])$; $dp_{di} = ([\mathbf{R'R'}] + [\mathbf{S'S'}])/([\mathbf{R'R'}] + [\mathbf{S'S'}] + [\mathbf{R'S'}])$. (b) $\chi_{mono} = ([\mathbf{R'S}] + [\mathbf{RS'}] + [\mathbf{S'S}] + [\mathbf{R'R}])/[sm]_0$; $dp_{mono} = ([\mathbf{R'S}] + [\mathbf{RS'}])/([\mathbf{R'S}] + [\mathbf{RS'}] + [\mathbf{S'S}] + [\mathbf{R'R}])$; (i) without recycling; (ii) recycling with the same selectivity; (iii) recycling with inverse selectivity.

Scheme 2



conversion. The calculated relationships between the group selectivity (k_R/k_S) of the reaction and the potential stereoisomeric purities and yields of the components are shown in Figure 1. Thus, although it is possible to obtain starting material with any arbitrary high degree of stereoisomeric purity (albeit by sacrificing yield), the potential diastereomeric purity of both the mono and di products is significantly limited, even from very selective reactions.

Although rarely exploited in nonenzymatic processes,[13] recycling is an established method for improving the stereoisomeric purity of products from enzyme-mediated kinetic resolutions.[14] Conversion of the mono product with maximum diastereomeric purity obtained from an *R* group-selective reaction into starting material should give material enriched in the **RS** substrate and depleted in **RR** substrate. Resubjecting this material to an *S* group-selective reaction (i.e. the inverse selectivity from the initial reaction) was calculated to give mono products with significantly improved dp[12] (see Figure 1).[15,16]

To test the above predictions, the diene **1**, as a 2:1:1 mixture of *RS*:*RR*:*SS* stereoisomers,[17] was subjected to standard Sharpless epoxidation conditions[18] using L-(+)-diisopropyl tartarate (L-DIPT) at −23 °C (Scheme 2). After 52 h, (20% **1** by GC), the diene **1**, monoepoxide **2**, and diepoxide **3** were isolated. The diene **1** was shown to be the *RR* isomer (<1% *RS*, <1% *SS*).[17] Among the eight possible stereoisomers, **2** was shown to consist of a 85:9:3:2:1 mixture of *RSR*, *SRR*, *RRR*, *SSR*, and *RSS* isomers, respectively.[17,19] A rigorous determination of the stereoisomer distribution of **3** was not possible; however, deoxygenation[20] of **3** gave **1**, which was a 69:27:4 mixture of *SS*, *RS*, and *RR* isomers, respectively.[17] Similar treatment of **2** gave **1** as a 85:14:1.5 mixture of *RS*, *RR*, and *SS* isomers, respectively.[17] As expected, despite the high group selectivity of the Sharpless epoxidation, **2** and **3** were obtained with only modest dp.[12,19] Resubjecting **1** (obtained from **2**) to Sharpless epoxidation with L-DIPT gave **2** as a 89:7:2:2 mixture of *RSR*, *SRR*, *RRR*, and *SSR* isomers, respectively.[17] Alternatively, Sharpless epoxidation with D-DIPT gave **2** as 98:2 mixture of *SRS* and *RRS* isomers (<1% of any other isomer), which was identical with the monoepoxide product obtained from Sharpless epoxidation of pure (*RS*)-**1**.[19]

In summary, a mathematical model for kinetic resolution of C_s/C_2 stereoisomeric mixtures predicts that only the slow-reacting C_2 enantiomer can be obtained with high purity. By recycling, especially using a reaction with inverse selectivity, it is possible to obtain the other isomers (or their products) with very high purity. These predictions have been verified by the preparation of the desymmetrized *meso* derivative (*SRS*)-**2** from a randomly generated mixture of stereoisomers of **1**.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Supporting Information Available: Calculation procedures, experimental procedures and spectral data for **1**−**3**, and scheme for the preparation of stereochemical standards (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(11) Calculations were simplified by assuming that all *R* groups and all *S* groups had the same reactivity regardless of the substrate. Initial conditions: $[\mathbf{RS}]_0 = 2[\mathbf{RR}]_0 = 2[\mathbf{SS}]_0 = 0.5$ arbitrary units. See the supporting information.

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

(13) (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.

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(15) Qualitatively, **R′S** and **R′R** are formed at the same rate but are efficiently resolved ($E = k_R/k_S$), while **S′S** is produced slowly but not resolved from **R′S** ($E = 1$). Thus, the first reaction effectively removes *R′R* (but not **S′S**) from **R′S**, and recycling (with inverse selectivity) removes **S′S** from **RS′**.

(16) Similar conversion of the di product gives starting material enriched in **RR** substrate from which stereoisomerically pure **RR** substrate is obtained after an *S* group-selective reaction.

(17) Stereoisomer distribution was determined by ^{1}H NMR of the Mosher's bis-esters derivatives. The stereochemistry of these derivatives was assigned by comparison with authentic samples prepared by independent stereoselective synthesis (see supporting information).

(18) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(19) Sharpless epoxidation introduces a new stereogenic center with a diastereoselectivity (~50:1 for the "matched" reaction)[18] that should be independent of the conversion. Thus, for comparison with Figure 1, the mole fractions for the *syn* and *anti* isomers of **2** (e.g., *SSR* and *RSR*, respectively) should be summed. In the present case, the group selectivity (i.e., k_R/k_S) for epoxidation of **1** is estimated to be 30:1 (cf. 1-undecene-3-ol),[18] and the calculated maximum dp_{mono} is 0.87 (0.99 after recycling).

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