

Thermal Stereomutations and Stereochemically Elucidated [1,3]-Carbon Sigmatropic Shifts of 1-(*E*)-Propenyl-2-methylcyclobutanes Giving 3,4-Dimethylcyclohexenes

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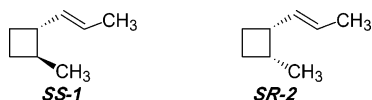
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Abstract: The thermal stereomutations and [1,3] carbon sigmatropic shifts shown by (+)-(1*S*,2*S*)-*trans*-1-(*E*)-propenyl-2-methylcyclobutane and by (-)-(1*S*,2*R*)-*cis*-1-(*E*)-propenyl-2-methylcyclobutane in the gas phase at 275 °C leading to 3,4-dimethylcyclohexenes have been followed. The reaction-time-dependent data for concentrations and enantiomeric excess values for substrates and [1,3] shift products have been deconvoluted to afford rate constants for the discrete isomerization processes. Both *trans* and *cis* substrates react through four stereochemically distinct [1,3] carbon shift paths. For one enantiomer of the *trans* reactant the relative rate constants are $k_{si} = 58\%$, $k_{ar} = 5\%$, $k_{sr} = 33\%$, and $k_{ai} = 4\%$. For a single enantiomer of the *cis* reactant, $K_{si} = 18\%$, $K_{ar} = 11\%$, $K_{sr} = 51\%$, and $K_{ai} = 20\%$. A *trans* starting material reacts through orbital symmetry allowed *suprafacial, inversion* and *antarafacial, retention* paths to give *trans*-3,4-dimethylcyclohexenes 63% of the time. A *cis* isomer reacts to give the more stable *trans*-3,4-dimethylcyclohexenes through orbital symmetry-forbidden *suprafacial, retention* and *antarafacial, inversion* paths 71% of the time. The [1,3] carbon sigmatropic shifts are not controlled by orbital symmetry constraints. They seem more plausible rationalized as proceeding through diradical intermediates having some conformational flexibility after formation and before encountering an exit channel. The distribution of stereochemical outcomes may well be conditioned by dynamic effects. The thermal stereomutations of the 1-(*E*)-propenyl-2-methylcyclobutanes take place primarily through one-center epimerizations. For the *trans* substrate, the relative importance of the three distinction rate constants are $k_2 = 48\%$, $k_1 = 34\%$, and $k_{12} = 18\%$. For the *cis* isomer, $K_2 = 44\%$, $K_1 = 32\%$, and $K_{12} = 24\%$. These patterns are reminiscent of ones determined for stereomutations in 1,2-disubstituted cyclopropanes.

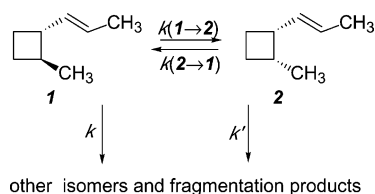
Introduction

The first study to define the full stereochemistry of a thermal vinylcyclopropane-to-cyclopentene rearrangement followed the reactions of a nonracemic sample of *trans*-1-(*E*)-propenyl-2-methylcyclopropane.¹ The same utilization of methyl substituents as stereochemical markers was employed in this our first definition of the full stereochemistry for a vinylcyclobutane-to-cyclohexene rearrangement using (+)-(1*S*,2*S*)-*trans*-1-(*E*)-propenyl-2-methylcyclobutane (**SS-1**) and (-)-(1*S*,2*R*)-*cis*-1-(*E*)-propenyl-2-methylcyclobutane (**SR-2**) as reactants.



The experimental challenges posed by this or any program seeking to define the stereochemical characteristics of [1,3] carbon shifts leading from vinylcyclobutanes to cyclohexenes are complicated by other kinetically competitive reactions. One cannot simply heat a stereochemically well-defined substituted vinylcyclobutane, isolate the mixture of cyclohexene products,

Scheme 1



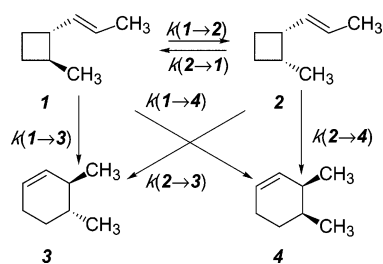
and infer the kinetically controlled stereochemistry of the reaction. Fragmentations to give olefins, pentadienes, and hexadienes as well as isomerizations to dimethylcyclohexenes and octadienes lead to complex mixtures of products. Scheme 1, in which **1** and **2** represent diastereomers without enantiomeric distinctions, introduces the kinetic situation in an abbreviated and quite simplified form.

The first-order fragmentations and isomerizations included in Scheme 1 consume vinylcyclobutane reactants. They may be accommodated experimentally and within a kinetic model, but all of them that compete with [1,3] shifts diminish the amount of dimethylcyclohexene products **3** and **4** available for stereochemical scrutiny (Scheme 2).

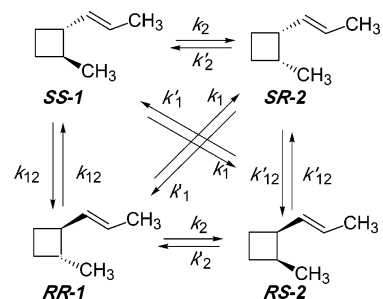
The thermal stereomutations of substituted vinylcyclobutane reactants present more of a problem (Scheme 3). Here subscripts

(1) Andrews, G. D.; Baldwin, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 6705–6706.

Scheme 2



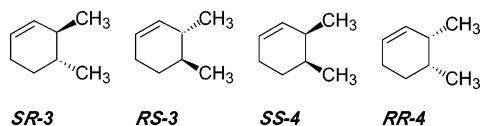
Scheme 3



label rate constants to distinguish one-center (k_1 , k_2) and simultaneous two-center (k_{12}) epimerizations shown by one trans isomer, **SS-1** or **RR-1**. The epimerizations of a cis isomer have rate constants k'_1 , k'_2 , and k'_{12} . One must follow the time-dependent evolution of all four possible stereoisomers of a stereochemically well-defined reactant and then take account of each reacting to afford all four possible 3,4-dimethylcyclohexene products. Appropriate experimental data must be secured, and the deconvolutions of rate data to afford specific rate constants must be managed carefully.

Other challenges associated with the required syntheses of substrates and assignments of absolute stereochemistry for all substituted vinylcyclobutanes and cyclohexenes involved are of a different sort and can be dealt with through well-known methods.

Parts of our extended effort to unravel the thermal reactions of the 1-(*E*)-propenyl-2-methylcyclobutanes have been reported.² This culminating report provides a full account of kinetic experiments with nonracemic *trans*- and *cis*-1-(*E*)-propenyl-2-methylcyclobutanes **SS-1** and **SR-2** as starting materials. The steps and simple equations required for rigorous deconvolutions of raw rate data to obtain the eight independent rate constants leading from 1-(*E*)-propenyl-2-methylcyclobutanes to the 3,4-dimethylcyclohexenes **SR-3**, **RS-3**, **SS-4**, and **RR-4** are detailed. The thermal stereomutation rate constants defined in Scheme 3 are also obtained and reported.



Results and Discussion

Purified Reactants and Reproducible Kinetic Behavior.

The 1-(*E*)-propenyl-2-methylcyclobutanes **SS-1** and **SR-2**, each

of better than 99% ee by capillary GC analyses of synthetic precursors, were prepared from 2-methylcyclobutanecarboxaldehydes through a Wittig-like coupling reaction employing CH_3CHI_2 and CrCl_2 .^{3,4} The olefinic products were obtained in high yield and with $\sim 14:1$ *E:Z* stereoselectivity. The *E* isomers were then purified by preparative GC on a β,β' -oxydipropionitrile (ODPN) column.

In trial runs samples of racemic **1**, the internal standard cyclooctane, and pentane to serve as a bath gas were heated for given times in a 300-mL quartz bulb encased in a well-insulated thermostated aluminum block. At the end of a thermal reaction the samples were transferred to a vacuum line, cooled and condensed, and analyzed by capillary GC.

Some trial runs gave complex product mixtures in complete accord with expectations, while others led to mixtures containing additional, unexpected products and irreproducible isomer distributions. This random oscillation between well-behaved thermal reactions and totally useless kinetic runs was eventually traced to a minor impurity. The capillary GC analyses run to measure the relative proportions at $t = 0$ of **1** and cyclooctane (retention times 8.0 and 21.8 min) showed a small peak (0.05%) at 24.1 min in some of the solutions, the ones that gave rise in thermal reactions to the irregular kinetic trends and additional products. Solutions that did not contain that slight impurity displayed well-behaved kinetic profiles and the anticipated array of isomers. The trace component at 24.1 min was determined to be CH_3CHI_2 , a treacherous contaminant to have in a gas-phase static reactor at 275 °C, for it could well decompose and initiate unwanted reactions.

1,1-Diiodoethane “bleeds” slowly from the ODPN column. A first collection of **1** after long GC column conditioning gave **1** free of any 1,1-diiodoethane, while samples of **1** collected through repeated preparative GC runs, one after the other, were often contaminated with small amounts of this impurity. Samples of **1** subjected to a second preparative GC purification using an SE-30 column to remove all traces of 1,1-diiodoethane exhibited good kinetic behavior and the anticipated products reliably. Hence, **SS-1** and **SR-2** samples for kinetic work were purified through preparative GC separations first on a ODPN column and then on an SE-30 column.

Concentration Versus Time Kinetic Profiles. Kinetic work on thermal rearrangements of hydrocarbons usually depends on capillary gas chromatographic analyses. Relative concentration versus time profiles and individual rate constants for various reactions of *trans*- and *cis*-1-(*E*)-propenyl-2-methylcyclobutanes **SS-1** and **SR-2** dependent upon capillary GC columns having achiral liquid phases have been published.^{2e} The eight rate constants defined in Schemes 1 and 2 and summarized in Table 1 were measured independently by following thermal reactions of racemic samples of **1** and **2**.^{2e} These rate constants were reproduced to within an average deviation of 2.0% (from 0.7 to 3.1%).

The kinetic situation outlined in Scheme 1 dictates the form of $\mathbf{1}(t)$ and $\mathbf{2}(t)$ equations. Each is equal to $B_1 \exp(-\lambda_1 t) + B_2 \exp(-\lambda_2 t)$; the constants B_1 and B_2 depend on the starting material, with an initial relative concentration equal to $(B_1 + B_2)$. The parameters λ_1 and λ_2 ($\lambda_1 = 1.84 \times 10^{-5} \text{ s}^{-1}$ and $\lambda_2 =$

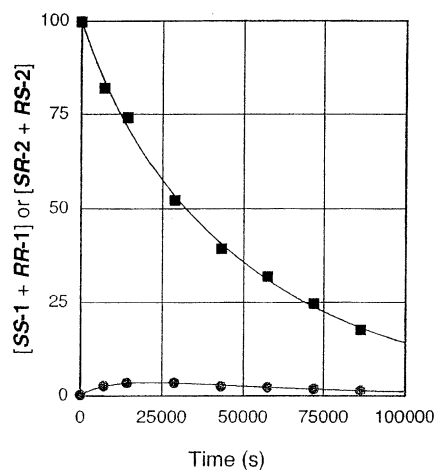
(2) (a) Alexander, J. S.; Baldwin, J. E.; Burrell, R. C.; Ruhlandt-Senge, K. *Chem. Commun.* **2000**, 2201–2202. (b) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **2000**, *65*, 7139–7144. (c) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **2000**, *65*, 7145–7150. (d) Baldwin, J. E.; Burrell, R. C. *J. Am. Chem. Soc.* **2001**, *123*, 6718–6719. (e) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **2002**, *67*, 3249–3256. (f) Baldwin, J. E.; Burrell, R. C. *J. Phys. Chem. A* **2003**, *107*, 10069–10073.

(3) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951–953.

(4) Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 4607–4621.

Table 1. Rate Constants in Schemes 1 and 2, for Reactions of **SS-1** and **SR-2** at 275 °C

rate constant	value ^{2e}
k	$1.70 \times 10^{-5} \text{ s}^{-1}$
k'	$6.81 \times 10^{-5} \text{ s}^{-1}$
$k(1 \rightarrow 2) = k_1 + k_2$	$6.55 \times 10^{-6} \text{ s}^{-1}$
$k(2 \rightarrow 1) = k'_1 + k'_2$	$2.24 \times 10^{-5} \text{ s}^{-1}$
$k(1 \rightarrow 3) = k_{si} + k_{ar}$	$2.44 \times 10^{-6} \text{ s}^{-1}$
$k(1 \rightarrow 4) = k_{sr} + k_{ai}$	$1.45 \times 10^{-6} \text{ s}^{-1}$
$k(2 \rightarrow 3) = k'_{sr} + k'_{ai}$	$5.34 \times 10^{-6} \text{ s}^{-1}$
$k(2 \rightarrow 4) = k'_{si} + k'_{ar}$	$2.19 \times 10^{-6} \text{ s}^{-1}$

**Figure 1.** Mole percent concentrations of [SS-1 + RR-1] (■) and [SR-2 + RS-2] (●) for reactions at 275 °C starting from **SS-1**, and least-squares-fit functions of the theoretically required form given in eqs 1 and 2.

$9.02 \times 10^{-5} \text{ s}^{-1}$) are the same in all four equations. For reactions starting with **SS-1** eqs 1 and 2 apply.^{2e}

$$1(t) = (\text{SS-1} + \text{RR-1})(t) = 89.2 \exp(-\lambda_1 t) + 10.6 \exp(-\lambda_2 t) \quad (1)$$

$$2(t) = (\text{SR-2} + \text{RS-2})(t) = 6.5 \exp(-\lambda_1 t) - 6.3 \exp(-\lambda_2 t) \quad (2)$$

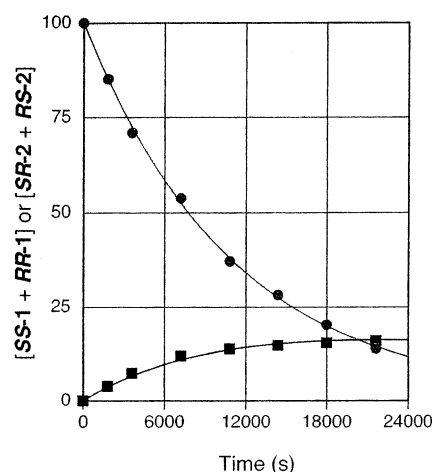
For reactions using **SR-2** as substrate, eqs 3 and 4 correlate experimental points with theory-consistent functions.^{2e} Figures 1 and 2 display GC-derived data and the functions given in eqs 1–4.

$$1(t) = (\text{SS-1} + \text{RR-1})(t) = 30.7 \exp(-\lambda_1 t) - 30.7 \exp(-\lambda_2 t) \quad (3)$$

$$2(t) = (\text{SR-2} + \text{RS-2})(t) = 0.4 \exp(-\lambda_1 t) + 99.6 \exp(-\lambda_2 t) \quad (4)$$

From functions 1–4 and the rate constants for [1,3] shifts quoted in Table 1 it is easy to calculate mole percent concentrations for **1**, **2**, **3**, and **4** at the given reaction times. These values are summarized in Tables 2 and 3.

Enantiomeric Excess Values Versus Time Profiles. The stereochemical ambitions of the present study depended on gaining information on enantiomeric excess values for **1**, **2**, **3**, and **4** at various reaction times. For the 3,4-dimethylcyclohexenes sound methods based on capillary GC analyses using columns with chiral stationary phases were worked out and validated early on.^{2c} Unfortunately, all attempts to find “chiral”

**Figure 2.** Mole percent concentrations of [SS-1 + RR-1] (■) and [SR-2 + RS-2] (●) for reactions at 275 °C starting **SR-2**, and least-squares-fit functions of the theoretically required form given in eqs 3 and 4.**Table 2.** Mole Percent Concentrations Calculated for **1**, **2**, **3**, and **4** from Thermal Reactions of **SS-1** at 275 °C

time (s)	1	2	3	4
0	99.8	0.2	0.0	0.0
7200	83.7	2.4	1.7	1.0
14400	71.3	3.3	3.1	1.8
28800	53.3	3.4	5.6	3.2
43200	40.5	2.8	7.4	4.3
57600	31.0	2.2	8.9	5.1
72000	23.7	1.7	10.0	5.7
86400	18.2	1.3	10.8	6.2

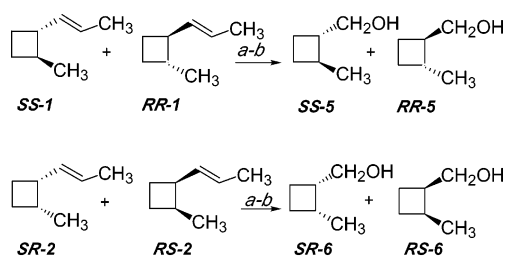
Table 3. Mole Percent Concentrations Calculated for **1**, **2**, **3**, and **4** from Thermal Reaction of **SR-2** at 275 °C

time (s)	1	2	3	4
0	0.0	100.0	0.0	0.0
1800	3.6	85.1	0.9	0.4
3600	6.6	72.4	1.7	0.7
7200	10.9	52.4	2.9	1.2
10800	13.6	37.9	3.9	1.6
14400	15.2	27.5	4.7	2.0
18000	16.0	19.9	5.2	2.2
21600	16.3	14.5	5.7	2.5

GC columns able to achieve similar resolutions of the enantiomers of **1** and of **2** proved unsuccessful.

This temporary impasse stimulated a search for some alternative approach. By combining chemical and chromatographic methods a satisfactory solution to the analytical challenge was found. Following a run the product mixture was analyzed by GC, and integrated peak intensities gave mole percent concentration data. The mixture was then separated into four fractions by preparative GC on a ODPN column. The first fraction contained both enantiomers of **1**; the second contained *trans*-1,5-octadiene, *cis*-3,6-dimethylcyclohexene, and both enantiomers of **2**; the third contained *cis*-1,5-octadiene, *trans*-1,6-octadiene, and the *trans*-3,4-dimethylcyclohexenes (**3**); the fourth contained *cis*-3,4-dimethylcyclohexenes (**4**). Analysis of fraction 3 by capillary GC using a CycloSil B column gave the enantiomeric excess of *trans*-3,4-dimethylcyclohexene (**3**). Analysis of fraction 4 by GC using a Cyclodex B column provided the enantiomeric excess value for *cis*-3,4-dimethylcyclohexene (**4**).

Scheme 4

(a) OsO₄/NaIO₄. (b) LiAlH₄.**Table 4.** Enantiomeric Excess Data for **1**, **2**, **3**, and **4** in Reaction Mixtures Derived from **SS-1** at 275 °C

time (s)	SS-1	RS-2	SR-3	SS-4
0	99.0	99.0		
7200	96.6	12.3	85.1	80.7
14400	94.1	7.3	80.2	82.5
28800	89.5	2.2	75.6	69.9
43200	85.1	4.8	72.1	70.1
57600	82.4	7.4	70.3	67.5
72000	79.0	4.3	69.5	63.4
86400	71.1	-4.2	67.6	61.7

Table 5. Enantiomeric Excess Data for **1**, **2**, **3**, and **4** in Reaction Mixtures Derived from **SR-2** at 275 °C

time (s)	SS-1	SR-2	SR-3	SS-4
0		99.0		
1800	9.6	96.4	44.0	24.4
3600	11.5	93.6	42.3	27.6
7200	14.3	89.0	41.2	22.9
10800	16.1	85.8	40.7	24.5
14400	15.5	81.6	38.4	22.9
18000	15.2	79.1	36.4	21.2
21600	13.4	71.2	36.2	18.6

The first and second fractions were combined, dissolved in aqueous dioxane, and oxidized with OsO₄/NaIO₄.⁵ Following a normal workup the crude mixture of aldehydes obtained was reduced with LiAlH₄ to give a mixture of 2-methylcyclobutanemethanol isomers (Scheme 4).

The enantiomeric excess values for *trans*-methylcyclobutanemethanols (**SS-5** and **RR-5**) were found using a capillary CycloSil B column. Analyses with the same column at a slightly higher temperature gave ee values for samples of *cis*-2-methylcyclobutanemethanols (**SR-6** and **RS-6**). Authentic racemic samples of the *trans* and *cis* alcohols and of (+)-(1*S*,2*S*)-*trans*-2-methylcyclobutanemethanol (**SS-5**) and (-)-(1*S*,2*R*)-*cis*-2-methylcyclobutanemethanol (**SR-6**) were prepared and used to assign the separated GC peaks to specific enantiomers.

Analyses of thermal reaction mixtures derived from **SS-1** and from **SR-2** gave the ee data summarized in Tables 4 and 5. From these data and the rate constants of Table 1, and eqs 1–4, the eight independent rate constants for [1,3] carbon shifts linking 1-(*E*)-propenyl-2-methylcyclobutanes with 3,4-dimethylcyclohexenes were found.

The **SS-1** material used in the kinetic runs summarized in Table 2 was 99.8% **1** and 0.2% **2**. Both components were 2*S* isomers as a result of common synthetic precursors, and both

were of better than 99% ee.^{2b} The ee data for **RS-2** in Table 4 thus reflects **2** from a composite of sources, with some formed from nonracemic **SS-1** through *k*₁ and *k*₂ paths, some associated with the original **RS-2**, and some contingent on *k*'₁₂. Fortunately, these complications turned out to have no significant bearing on the stereochemical concerns at hand.

The **SR-2** used in the kinetic runs summarized in Table 3 was free of the *trans* isomer, and the trends in ee values of Table 5 presented no seeming anomalies.

Differences in Mole Percent Concentrations of Enantiomers Versus Time. The differential equations governing time-dependent changes of mole percent concentrations of each isomer of 1-(*E*)-propenyl-2-methylcyclobutane are given in eqs 5–8.

$$-d[\text{SS-1}]/dt = (k + k_1 + k_2 + k_{12})[\text{SS-1}] - k_{12}[\text{RR-1}] - k'_2[\text{SR-2}] - k'_1[\text{RS-2}] \quad (5)$$

$$-d[\text{RR-1}]/dt = -k_{12}[\text{SS-1}] + (k + k_1 + k_2 + k_{12})[\text{RR-1}] - k'_1[\text{SR-2}] - k'_2[\text{RS-2}] \quad (6)$$

$$-d[\text{SR-2}]/dt = -k_2[\text{SS-1}] - k_1[\text{RR-1}] + (k' + k'_1 + k'_2 + k'_{12})[\text{SR-2}] - k'_{12}[\text{RS-2}] \quad (7)$$

$$-d[\text{RS-2}]/dt = -k_1[\text{SS-1}] - k_2[\text{RR-1}] - k'_{12}[\text{SR-2}] + (k' + k'_1 + k'_2 + k'_{12})[\text{RS-2}] \quad (8)$$

Subtracting expression 6 from 5 and expression 8 from 7 gives expressions 9 and 10.

$$-d[\text{SS-1} - \text{RR-1}]/dt = (k + k_1 + k_2 + 2k_{12})[\text{SS-1} - \text{RR-1}] + (k'_1 - k'_2)[\text{SR-2} - \text{RS-2}] \quad (9)$$

$$-d[\text{SR-2} - \text{RS-2}]/dt = (k_1 - k_2)[\text{SS-1} - \text{RR-1}] + (k' + k'_1 + k'_2 + 2k'_{12})[\text{SR-2} - \text{RS-2}] \quad (10)$$

This pair of differential equations will have solutions of the form shown in expressions 11 and 12.

$$[\text{SS-1} - \text{RR-1}](t) = C_1 \exp(-\lambda_3 t) + C_2 \exp(-\lambda_4 t) \quad (11)$$

$$[\text{SR-2} - \text{RS-2}](t) = D_1 \exp(-\lambda_3 t) + D_2 \exp(-\lambda_4 t) \quad (12)$$

Thus, according to theory, the two functions should depend on the same two exponential terms whatever the initial conditions, while *C*₁, *C*₂, *D*₁, and *D*₂ will depend on initial concentrations. The differences in mole percent concentrations of enantiomers at any time are readily calculated, knowing the sum of the two mole percent concentrations from eqs 1–4 and the enantiomeric excess values summarized in Tables 4 and 5. The

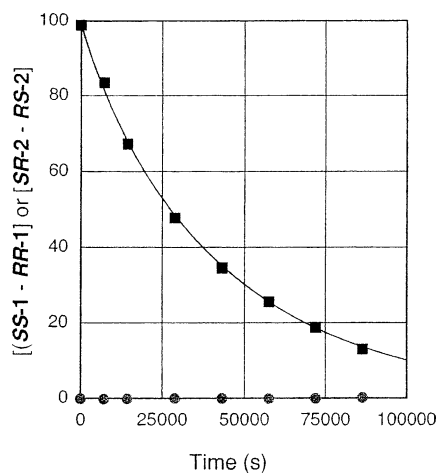
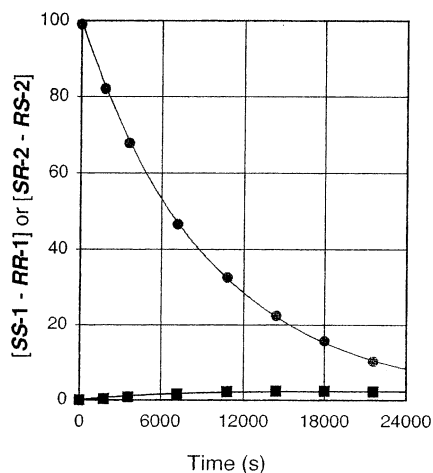
Table 6. Mole Percent Differences of Enantiomers of **1**, **2**, **3**, and **4** in Mixtures from **SS-1**

time (s)	RR-1	SR-2 - RS-2	SR-3 - RS-3	SS-4 - RR-4
0	98.8	-0.2	0.0	0.0
7200	80.9	-0.3	1.4	0.8
14400	67.1	-0.2	2.5	1.5
28800	47.7	-0.1	4.2	2.2
43200	34.5	-0.1	5.3	3.0
57600	25.5	-0.2	6.3	3.4
72000	18.7	-0.1	7.0	3.6
86400	12.9	0.1	7.3	3.8

(5) Pappo, R.; Allen, D. S. Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.

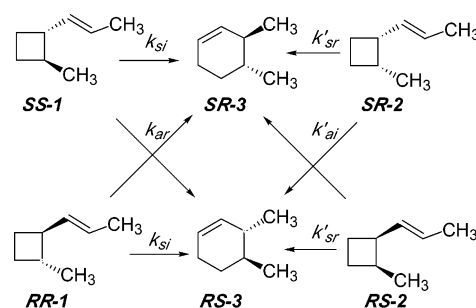
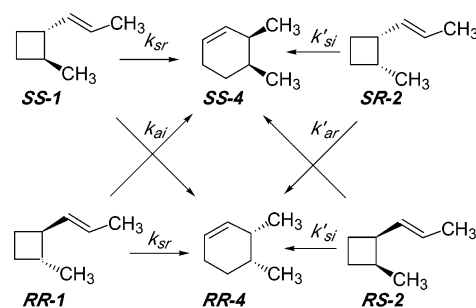
Table 7. Mole Percent Differences of Enantiomers of 1, 2, 3, and 4 from **SR-2** at 275 °C

time (s)	SS-1 – RR-1	SR-2 – RS-2	SR-3 – RS-3	SS-4 – RR-4
0	0.0	99.0	0.0	0.0
1800	0.3	82.0	0.4	0.1
3600	0.8	67.8	0.7	0.2
7200	1.6	46.6	1.2	0.3
10800	2.2	32.5	1.6	0.4
14400	2.4	22.4	1.8	0.5
18000	2.4	15.7	1.9	0.5
21600	2.2	10.3	2.1	0.5

**Figure 3.** Mole percent concentrations of [SS-1 – RR-1] (■) and [SR-2 – RS-2] (●) for reactions at 275 °C starting from **SS-1**, and least-squares-fit function of the theoretically required form shown in eq 13 for the [SS-1 – RR-1] data.**Figure 4.** Mole percent concentrations of [SS-1 – RR-1] (■) and [SR-2 – RS-2] (●) for reactions at 275 °C starting from **SR-2**, and least-squares fits of the theoretically required form shown in eqs 14 and 15.

differences in mole percent concentrations for the enantiomers of 1 and 2, starting from either **SS-1** or **SR-2** (Tables 6 and 7), follow well the functional forms required (Figures 3 and 4).

When **SS-1** is the starting material, eq 13 applies. The [SR-2 – RS-2](*t*) difference is essentially zero at all times (Table 6, Figure 3). When **SR-2** is the substrate, eqs 14 and 15 are the appropriate functions. In eqs 13–15 $\lambda_3 = 2.20 \times 10^{-5} \text{ s}^{-1}$ and $\lambda_4 = 10.6 \times 10^{-5} \text{ s}^{-1}$. The functions 13–15 are easily differentiated to provide $d[\text{SS-1} - \text{RR-1}]/dt$ and $d[\text{SR-2} - \text{RS-2}]/dt$ values at any time *t*.

Scheme 5**Scheme 6**

$d[\text{SR-2} - \text{RS-2}]/dt$ values at any time *t*.

$$[\text{SS-1} - \text{RR-1}](t) = 89.3 \exp(-\lambda_3 t) + 9.5 \exp(-\lambda_4 t) \quad (13)$$

$$[\text{SS-1} - \text{RR-1}](t) = 4.4 \exp(-\lambda_3 t) - 4.4 \exp(-\lambda_4 t) \quad (14)$$

$$[\text{SR-2} - \text{RS-2}](t) = 1.3 \exp(-\lambda_3 t) + 97.7 \exp(-\lambda_4 t) \quad (15)$$

Enantioselective Rate Constants for [1,3] Carbon Sigma-tropic Shifts. At any given time during a thermal reaction the processes leading to the two trans enantiomers of 3,4-dimethylcyclohexene, **SR-3** and **RS-3**, are as portrayed in Scheme 5. The corresponding reactions leading to cis enantiomers **SS-4** and **RR-4** are shown in Scheme 6.

The relationships of Schemes 5 and 6 may be expressed through expressions 16 and 17 or, in integrated form, 18 and 19.

$$d[\text{SR-3} - \text{RS-3}]/dt = (k_{si} - k_{ar})[\text{SS-1} - \text{RR-1}] + (k'_{sr} - k'_{ai})[\text{SR-2} - \text{RS-2}] \quad (16)$$

$$d[\text{SS-4} - \text{RR-4}]/dt = (k_{sr} - k_{ai})[\text{SS-1} - \text{RR-1}] + (k'_{si} - k'_{ar})[\text{SR-2} - \text{RS-2}] \quad (17)$$

$$[\text{SR-3} - \text{RS-3}](t) = (k_{si} - k_{ar}) \int_0^t [\text{SS-1} - \text{RR-1}] dt + (k'_{sr} - k'_{ai}) \int_0^t [\text{SR-2} - \text{RS-2}] dt \quad (18)$$

$$[\text{SS-4} - \text{RR-4}](t) = (k_{sr} - k_{ai}) \int_0^t [\text{SS-1} - \text{RR-1}] dt + (k'_{si} - k'_{ar}) \int_0^t [\text{SR-2} - \text{RS-2}] dt \quad (19)$$

When **SS-1** is the starting material, very little **2** builds up: it reacts further much faster than it is formed. The mole percent difference [SR-2 – RS-2] is essentially zero throughout the reaction (Table 6), and hence the simple linear relationships of 20 and 21 may be used to determine $(k_{sr} - k_{ai})$ and $(k_{si} - k_{ar})$. The corresponding plots are shown in Figure 5. The values found

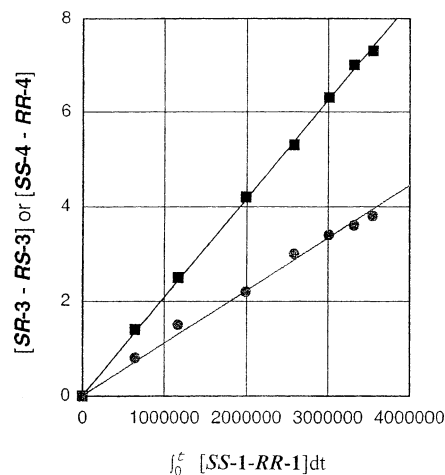


Figure 5. Mole percent concentrations of [SR-3 - RS-3] (■) and [SS-4 - RR-4] (●) as functions of \int_0^t [SS-1 - RR-1]dt as in eqs 20 and 21, for reactions at 275 °C starting from SS-1.

Table 8. Rate Constants for [1,3] Carbon Shifts from SS-1 and SR-2 in Schemes 5 and 6

constant	value	value (%) ^a
k_{si}	$2.26 \times 10^{-6} \text{ s}^{-1}$	58
k_{ar}	$0.18 \times 10^{-6} \text{ s}^{-1}$	5
k_{sr}	$1.28 \times 10^{-6} \text{ s}^{-1}$	33
k_{ai}	$0.17 \times 10^{-6} \text{ s}^{-1}$	4
k'_{si}	$1.37 \times 10^{-6} \text{ s}^{-1}$	18
k'_{ar}	$0.82 \times 10^{-6} \text{ s}^{-1}$	11
k'_{sr}	$3.85 \times 10^{-6} \text{ s}^{-1}$	51
k'_{ai}	$1.50 \times 10^{-6} \text{ s}^{-1}$	20

^a Of $(k_{si} + k_{ar} + k_{sr} + k_{ai})$ or $(k'_{si} + k'_{ar} + k'_{sr} + k'_{ai})$.

are $(k_{si} - k_{ar}) = 2.08 \times 10^{-6} \text{ s}^{-1}$ and $(k_{sr} - k_{ai}) = 1.12 \times 10^{-6} \text{ s}^{-1}$.

$$[SR-3 - RS-3](t) = (k_{si} - k_{ar}) \int_0^t [SS-1 - RR-1] dt \quad (20)$$

$$[SS-4 - RR-4](t) = (k_{sr} - k_{ai}) \int_0^t [SS-1 - RR-1] dt \quad (21)$$

When SR-2 is the starting material, some of its diastereomer **1** builds up as it decays, but the **1** formed is of relative low ee (Table 5). Nevertheless, the values of \int_0^t [SS-1 - RR-1]dt at various reaction times do make contributions to expressions 18 and 19. These equations may be rearranged to give 22 and 23, expressions expressing a simple linear relationship, for all terms on the left-hand sides of these equations are known.

$$[SR-3 - RS-3](t) - (k_{si} - k_{ar}) \int_0^t [SS-1 - RR-1] dt = (k'_{sr} - k'_{ai}) \int_0^t [SR-2 - RS-2] dt \quad (22)$$

$$[SS-4 - RR-4](t) - (k_{sr} - k_{ai}) \int_0^t [SS-1 - RR-1] dt = (k'_{si} - k'_{ar}) \int_0^t [SR-2 - RS-2] dt \quad (23)$$

The linear plots based on these equations are shown in Figure 6. The slopes of these plots provide $(k'_{sr} - k'_{ai}) = 2.35 \times 10^{-6} \text{ s}^{-1}$ and $(k'_{si} - k'_{ar}) = 0.55 \times 10^{-6} \text{ s}^{-1}$.

These four differences of rate constants and the sums of the constants from Table 1 provide all eight of the rate constants for [1,3] carbon sigmatropic shifts (Table 8).

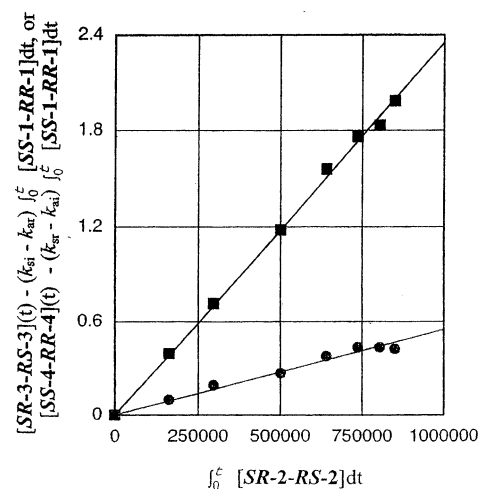


Figure 6. Known functions [SR-3 - RS-3](t) - $(k_{si} - k_{ar}) \int_0^t$ [SS-1 - RR-1]dt (■) and [SS-4 - RR-4](t) - $(k_{sr} - k_{ai}) \int_0^t$ [SS-1 - RR-1]dt (●) versus \int_0^t [SR-2 - RS-2]dt as in eqs 22 and 23, for reactions at 275 °C starting from SR-2.

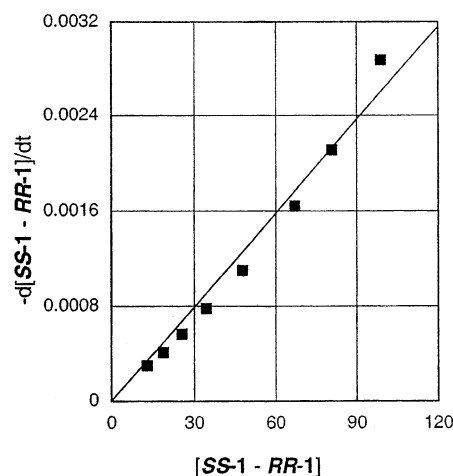


Figure 7. Function $-d[SS-1 - RR-1]/dt$ calculated from eq 13 versus [SS-1 - RR-1] as in eq 24 for reactions at 275 °C starting from SS-1.

Rate Constants for Thermal Stereomutations of SS-1 and SR-2. The derivations of rate constants for the [1,3] carbon shifts given above did not depend on explicit knowledge of stereomutation rate constants (Scheme 3), although these equilibrations played a role in determining time-dependent variations in ee values for **1** and **2**. They may be obtained with the aid of expressions 9 and 10 and 13–15. For runs starting from SS-1, $-d[SS-1 - RR-1]/dt$ is easily calculated for any time t from 13 and [SS-1 - RR-1] is known at any t (Table 6); [SR-2 - RS-2] is quite negligible (Table 6). Equation 9 simplifies to (24), and the corresponding plot gives a slope equal to $(k + k_1 + k_2 + 2k_{12})$, as shown in Figure 7. That slope is $2.63 \times 10^{-5} \text{ s}^{-1}$. Since $(k + k_1 + k_2)$ is $23.55 \times 10^{-6} \text{ s}^{-1}$ (Table 1), $k_{12} = 1.4 \times 10^{-6} \text{ s}^{-1}$.

$$-d[SS-1 - RR-1]/dt = (k + k_1 + k_2 + 2k_{12})[SS-1 - RR-1] \quad (24)$$

For runs starting from SR-2, expressions 14 and 15 may be used to calculate $-d[SS-1 - RR-1]/dt$ and $-d[SR-2 - RS-2]/dt$ at any time t . Equation 9 may be rearranged to give a simple linear relationship 25 with both terms on the lefthand side

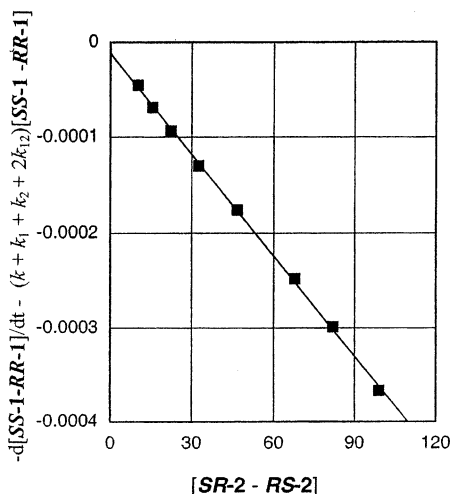


Figure 8. Known function $-d[SS-1 - RR-1]/dt - (k + k_1 + k_2 + 2k_{12})[SS-1 - RR-1]$ versus $[SR-2 - RS-2]$ as in eq 25 for reactions at 275 °C starting from **SR-2**.

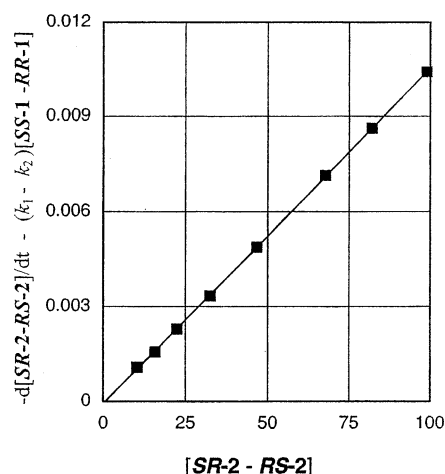


Figure 9. Known function $-d[SR-2 - RS-2]/dt - (k_1 - k_2)[SS-1 - RR-1]$ versus $[SR-2 - RS-2]$ as in eq 26 for reactions at 275 °C starting from **SR-2**.

known. The corresponding plot (Figure 8) provides $(k'_1 - k'_2) = -3.54 \times 10^{-6} \text{ s}^{-1}$.

$$-d[SS-1 - RR-1]/dt - (k + k_1 + k_2 + 2k_{12})[SS-1 - RR-1] = (k'_1 - k'_2)[SR-2 - RS-2] \quad (25)$$

Since $(k'_1 + k'_2) = 2.24 \times 10^{-5} \text{ s}^{-1}$ (Table 1), then $k'_1 = 0.94 \times 10^{-5} \text{ s}^{-1}$, $k'_2 = 1.30 \times 10^{-5} \text{ s}^{-1}$, and $k'_1/k'_2 = 0.72$. Here microscopic reversibility comes into play, for $k_1k'_2 = k'_1k_2$ (Scheme 3), or $k_1/k_2 = k'_1/k'_2$. From $(k_1 + k_2) = 6.55 \times 10^{-6} \text{ s}^{-1}$ and $k_1/k_2 = 0.72$, $k_1 = 0.27 \times 10^{-5} \text{ s}^{-1}$, and $k_2 = 0.38 \times 10^{-5} \text{ s}^{-1}$, and $(k_1 - k_2) = -1.1 \times 10^{-6} \text{ s}^{-1}$. Thus, both left-hand side terms in the rearranged form of eq 10, that is, 26, are known at any t , and the equation defines a simple linear function. Plotting this function (Figure 9) gives slope $= (k' + k'_1 + k'_2 + 2k'_{12}) = 10.48 \times 10^{-5} \text{ s}^{-1}$. With $(k' + k'_1 + k'_2) = 9.05 \times 10^{-5} \text{ s}^{-1}$ (Table 1), the two-center epimerization rate constant $k'_{12} = 0.71 \times 10^{-5} \text{ s}^{-1}$.

$$-d[SR-2 - RS-2]/dt - (k_1 - k_2)[SS-1 - RR-1] = (k' + k'_1 + k'_2 + 2k'_{12})[SR-2 - RS-2] \quad (26)$$

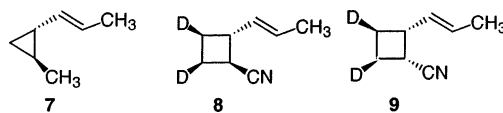
The stereomutation rate constants for **SS-1** fall in the order $k_2 = 0.38 \times 10^{-5} \text{ s}^{-1}$, $k_1 = 0.27 \times 10^{-5} \text{ s}^{-1}$, and $k_{12} = 0.14 \times 10^{-5} \text{ s}^{-1}$. In percentage terms, the ordering is 48% k_2 , 34% k_1 , and 18% k_{12} . For stereomutations of **SR-2**, the order is $k'_2 = 1.30 \times 10^{-5} \text{ s}^{-1}$, $k'_1 = 0.94 \times 10^{-5} \text{ s}^{-1}$, $k'_{12} = 0.71 \times 10^{-5} \text{ s}^{-1}$, or, in percentage terms, 44% k'_2 , 32% k'_1 , and 24% k'_{12} . The sum of one-center epimerizations shown by each diastereomer is 3 to 4 times more significant than the competitive two-center stereomutation process, a pattern totally consistent with relative rate constants found for many examples of thermal stereomutations shown by 1,2-disubstituted cyclopropanes.⁶

Summary

The complexities inherent in the multiple sorts of thermal reactions shown by vinylcyclobutanes such as **SS-1** and **SR-2** can be sorted out through careful experimental and analytical studies, as the present work focused on the stereochemistry of [1,3] carbon sigmatropic shifts amply demonstrates. The results obtained bear directly on long contested mechanistic issues and allow a very clear primary inference to be drawn: The [1,3] shifts are not controlled by the dictates of orbital symmetry theory.

Full stereochemical studies of [1,3] carbon sigmatropic shifts leading from substituted vinylcyclopropanes to isomeric cyclopentenes have been reported for a range of systems.⁷ The results obtained constitute a consistent pattern of stereochemical preferences best interpreted in terms of short-lived diradical intermediates capable of some conformational flexibility before closing to an isomeric vinylcyclopropane or one of four isomeric cyclopentenes. Orbital symmetry constraints are not in evidence. Dynamic factors appear to be instrumental determinants of stereochemical outcomes.⁸

A direct comparison between **SS-1** and the [1,3] shifts shown by the analogous cyclopropane system **7** reveals considerable similarities. The distribution of reaction paths favors the “allowed” options and formation of *trans*-dimethyl-substituted products, but some *cis* products are evident as well. The proportions are *si:ar:sr:ai* = 58:5:33:4 for **SS-1**, and 65: 8:22:5 for **7**.¹



Two other substituted vinylcyclobutanes, the deuterium-labeled racemic *trans* and *cis* isomers of 1,2-dicyanocyclobutanes (**8** and **9**), have been subjected to careful experimental studies leading to full stereochemical details for the [1,3] carbon shifts leading to substituted cyclohexenes.^{9,10} The stereochemical findings for the isomerizations shown by **8** and **9** are remarkably similar to those found here for **SS-1** and **SR-2**. The *trans* systems

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favor trans products, formed through orbital symmetry “allowed” paths: *si:ar:sr:ai* = 58:5:33:4 for **SS-1** and 47:20:27:6 for **8**.¹⁰ The cis systems also favor formation of trans cyclohexene products, which can be reached only through orbital symmetry “forbidden” paths: *si:ar:sr:ai* = 18:11:51:20 for **SR-2** and 13:5:66:16 for **9**.¹⁰

The experimental evidence leaves little room for imagining that these sigmatropic shifts may be influenced by orbital symmetry considerations. The stereochemical outcomes strongly suggest the intervention of transient diradical intermediates which may either revert to starting material or an isomeric version of starting material, giving a stereomutation product, or proceed to form one or another [1,3] carbon shift product, a substituted cyclohexene. The stereochemical outcome may depend on the conformational details of the diradical as the new C–C bond begins to form, which may in turn hinge on dynamic effects as well as on the potential energy surface.

Other vinylcyclobutane systems within bicyclic structures which rearrange through [1,3] carbon sigmatropic shifts, including some once thought to be controlled by orbital symmetry rules, now seem on closer consideration to probably involve diradical intermediates.¹¹ There are instances of high selectivity in favor of orbital symmetry allowed stereochemical outcomes, others showing strong preferences for forbidden paths, and some following allowed and forbidden paths to comparable extents. A diradical mechanistic formulation rationalizes them all in a consistent fashion.¹¹

One may anticipate that theoretical work to afford good potential energy surfaces and reaction dynamics calculations for vinylcyclobutane-to-cyclohexene isomerizations will be forthcoming, probably after experimental information on reaction stereochemistry becomes available for a system labeled so minimally that all four [1,3] carbon sigmatropic shift paths have equal enthalpic barriers.¹² Suitable deuterium-labeled versions of (*E*)-propenylcyclobutane or of vinylcyclobutane could be prepared and studied to provide full stereochemical information. In such studies, however, the stereochemical characteristics of reactants and products could not be secured as functions of reaction time through the sorts of GC analyses on which the present work relied. Analytical separations by capillary GC and by “chiral” GC methods would be of no avail!

Experimental Section

(+)-(1*S*,2*S*)-*trans*-2-Methylcyclobutanemethanol (**SS-5**). To a 25-mL flask were added an ethereal solution of (+)-(1*R*,2*S*)-*cis*-1-methoxycarbonyl-2-methylcyclobutane^{2b} (better than 99% ee by capillary GC on a G-TA γ -cyclodextrin column at 45 °C, 15 psi; $[\alpha]_D$ +58 (*c* 0.25, CHCl₃); 1.05 g, 8.2 mmol) and a 1 M solution of potassium *tert*-butoxide (16.4 mL, 16.4 mmol) in THF.¹³ The yellow solution was stirred for 10 min at room temperature under argon. At that time the mixture was quenched with water (75 mL), and the aqueous layer was extracted with ether (5 × 25 mL). The organic layers were combined and washed with water (2 × 25 mL). The aqueous solution was acidified with 2 M HCl and extracted with ether (3 × 25 mL). The organic solutions were combined, dried (Na₂SO₄), filtered, and partially

concentrated by distillation. The ethereal solution (200 mL) was cooled to 0 °C, and LiAlH₄ (0.62 g, 16.4 mmol) was added.^{14,15} A concentrated crude product was secured through a conventional workup. It was found to contain *trans*-2-methylcyclobutanemethanol (**SS-5**) and a small amount of *cis*-2-methylcyclobutanemethanol (**RS-6**) (0.68 g, 83% for the two steps, *trans/cis*, 84/16, Ultra 2 column) as an 8% solution. A small sample of **SS-5** was purified by preparative GC (1-m, 17% Carbowax, 110 °C) and had $[\alpha]_D$ +91 (*c* 0.085, CHCl₃). Analysis by GC using a CycloSil B capillary column (70 °C, 15 psi) gave one peak with a retention time of 17.1 min. A racemic sample of **5**^{2b} under these conditions gave two peaks with retention times (relative peak areas) 16.6 min (48.2%) and 17.1 min (51.8%). Samples of **5** and **SS-5** were combined and analyzed as described above to give two peaks with retention times (relative peak areas) of 16.7 min (17.4%) and 17.1 min (82.6%).

(-)-(1*S*,2*R*)-*cis*-2-Methylcyclobutanemethanol (**SR-6**). A solution of (-)-(1*S*,2*R*)-*cis*-2-methylcyclobutanecarboxylic acid^{2b} of better than 99% ee (0.88 g, 7.7 mmol) in ether (10 mL) was added dropwise to a suspension of LiAlH₄ (0.29 g, 7.7 mmol) in ether (60 mL) at 0 °C. The reaction and workup proceeded to give 0.68 g (87% yield) of (-)-(1*S*,2*R*)-*cis*-2-methylcyclobutanemethanol (**SR-6**). A small sample was purified by preparative GC (1-m, 17% Carbowax, 100 °C) and had $[\alpha]_D$ -15 (*c* 0.39, CHCl₃). Analysis by GC using a CycloSil B column (85 °C, 15 psi) gave one peak with a retention time of 13.0 min. A sample of racemic **6**^{2b} on this column under the same conditions gave two peaks with retention times (relative peak areas) of 12.7 min (48.4%) and 13.1 min (51.6%). Samples of **6** and **SR-6** were combined and analyzed as described above to give two peaks with retention times (relative peak areas) of 12.8 min (25.1%) and 13.1 min (74.9%).

Thermal Reactions of SS-1 and SR-2. A sample of **SS-1** of better than 99% ee was purified by preparative GC (2.3-m, 20% ODPN on Chromosorb P AW-DMCS, 50 °C) and again on a second column (1-m, 10% SE-30, 60 °C) to provide 123 mg of **SS-1** free of any trace of 1,1-diiodoethane. This **SS-1** material was dissolved in pentane (3.9 mL), and cyclooctane (62 mg) was added as an internal standard. Eight 500- μ L samples of this stock solution were injected into a 300-mL quartz bulb encased in an aluminum block and heated at 275.1 ± 0.1 °C for various times.^{2c} At the end of each kinetic run the thermal reaction mixture was removed from the bulb and analyzed by GC (DB-1301), then separated into four fractions by preparative GC (2.3-m, 20% ODPN on Chromosorb P AW-DMCS, 50 °C). Fraction 1 contained **1**; fraction 2 contained *trans*-1,5-octadiene, *cis*-3,6-dimethylcyclohexene (**4**), and **2**; fraction 3 contained *cis*-1,5-octadiene, *trans*-1,6-octadiene, and *trans*-3,4-dimethylcyclohexene (**3**); fraction 4 contained *cis*-3,4-dimethylcyclohexene (**4**). Analysis of fraction 3 by GC using a CycloSil B column (50 °C, 15 psi) gave the enantiomeric excess of **3**.^{2c} Analysis of fraction 4 by GC using a column with a Cyclodex B column (30 °C for 38 min, inc 10 °C/min to 100 °C, 12 psi) gave the enantiomeric excess of **4**.^{2c} Fractions 1 and 2 were combined and dissolved in 2 mL of dioxane. This mixture was placed in a round-bottomed flask along with water (0.6 mL) and OsO₄ (~10 mg, 2.5% solution in *tert*-butyl alcohol).⁵ After 5 min at room temperature, NaIO₄ (20 mg) was added. The brown solution was then stirred for 1 h at room temperature. At that time the solution was quenched with water (5 mL), and the aqueous layer was extracted with ether (4 × 5 mL). The organic layers were combined, washed with water (3 × 5 mL), dried (Na₂SO₄), and filtered. The mixture of aldehydes in ether was added to a round-bottomed flask. The solution was cooled to 0 °C, and LiAlH₄ (~50 mg) was added. The gray suspension was warmed to room temperature and stirred for 15 min. At that time the mixture was cooled to 0 °C and quenched with water (5 mL). The aqueous layer was acidified with 2 M HCl (5 mL) and extracted with ether (4 × 5 mL). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated by distillation to

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give a mixture of alcohols **5** and **6**. Analysis of the concentrate by GC using a CycloSil B column (75 °C, 15 psi) gave an ee value for **5**. Analysis of the concentrate by GC on the same column at a moderately higher temperature (85 °C, 15 psi) gave the ee of **6**. The ee measurements for **3**, **4**, **5**, and **6** were performed in duplicate, and the data were tabulated and averaged (Table 4, where data for **5** and **6** are ascribed to **1** and **2**).

Similarly, a sample of (–)-(1*S*,2*R*)-*cis*-1-(*E*)-propenyl-2-methylcyclobutane (**SR-2**) of better than 99% ee was purified by preparative GC (2.3-m, 20% ODPN on Chromosorb P AW-DMCS, 55 °C) and then using a second GC column (1-m, 10% SE-30, 60 °C) to give 122 mg of **SR-2** completely free of any trace of 1,1-diiodoethane. The sample was dissolved in pentane (3.9 mL), and cyclooctane (61 mg)

was added as an internal standard. Eight 500- μ L samples of this stock solution were injected into the bulb and heated at 275.1 ± 0.1 °C over a range of times. When the time period planned for a given kinetic run was over, the thermal reaction mixture was removed from the bulb and analyzed by GC (DB-1301). It was processed as described above, and ee values for **3**, **4**, **5**, and **6** were measured in duplicate, and the data were tabulated and averaged (Table 5, where data for **5** and **6** are ascribed to **1** and **2**).

Acknowledgment. We thank the National Science Foundation for supporting this work through Grants CHE-9902184 and CHE-0211120.

JA030516T