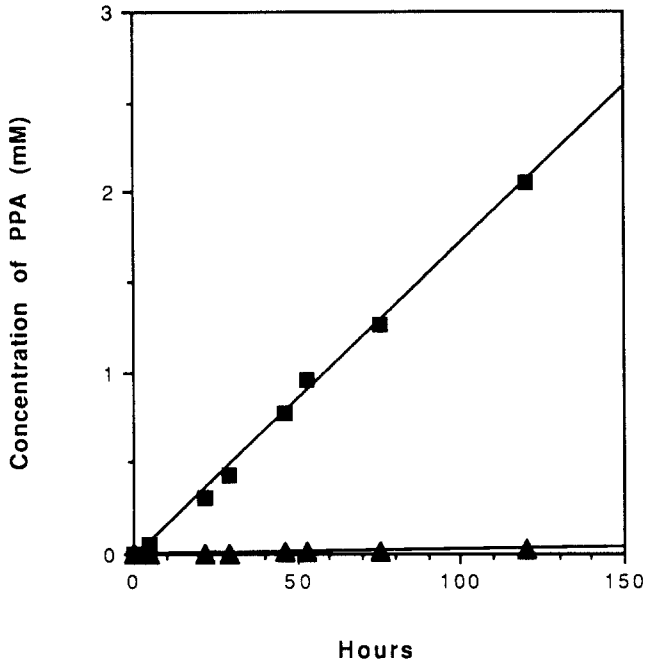

Figure 2. Enzyme-facilitated transport of 2-phenoxypropionic acid (PPA) across an organic liquid membrane: (■), enzyme-facilitated; (▲), control, no enzyme. Aqueous phase I initially consisted of 50 mM NaCl, pH 6.3,[10] 10 mM PPA, and 30 mg/mL CCL, while aqueous phase II initially consisted of 50 mM NaCl, pH 6.3, and 20 mg/mL PPL. The rate of PPA transport across the liquid membrane was dependent on the concentration of both enzymes and reached a maximum at the enzyme concentrations given above. PPA was quantitatively measured by using reverse phase HPLC and detection at 280 nm. This experiment represented the average of five independent runs with a standard error of ±5%.

was used as the esterification catalyst in aqueous phase I, while lipase from porcine pancreas (PPL) was used as the hydrolysis catalyst in aqueous phase II. The organic liquid membrane phase consisted of isooctane[8] supplemented with 1 M *n*-butyl alcohol. A control was performed by omitting the enzymes. The addition of enzymes resulted in a 70-fold increase in the amount of organic acid transported through the liquid membrane. Specifically, after 120 h, 2.05 (±0.10) mM PPA was measured in aqueous phase II in the enzyme-assisted case, while less than 0.03 mM PPA was transported in the control. Furthermore, the ester, butyl 2-phenoxypropionate, was observed in the isooctane phase only in the presence of the enzymes, while no PPA was observed in the organic phase, indicating that the species transporting through the liquid membrane is the butyl ester of the 2-phenoxypropionic acid. An increase in the PPA concentration to 25 and 100 mM resulted in 40 and 32% transport, respectively, after 10 days of operation.

In addition to PPA, we have studied the transport of other organic acids (Table I). Phenylacetic acid and 2-(4-chlorophenoxy)propionic acid were transported across the liquid membrane with efficiencies similar to those obtained for PPA. Furthermore, *n*-octyl alcohol was capable of replacing *n*-butyl alcohol and lipase from *Penicillium* sp. (lipase G) could replace CCL, although in the latter substitution, the rate of transport was significantly reduced. No transport was observed with PPL employed as the esterification catalyst.

The enzyme-assisted liquid membrane was also shown to be selective. Mandelic acid could not be transported across the liquid membrane. This selectivity was induced by the great selectivity afforded by CCL.[9] To demonstrate selective separation, a solution

(8) Isooctane was selected as the liquid membrane phase because it is immiscible with and less dense than water, provides for a favorable partitioning of the resulting ester, and has a low vapor pressure that limits evaporation during the separation.

(9) In independent experiments, it was found that CCL could not catalyze the esterification of mandelic acid with butanol in either toluene or hexane under conditions analogous to organic acid esterifications in nearly anhydrous media.[5a]

Table I. Enzyme-Facilitated Transport Rates of Organic Acids through an Organic Liquid Membrane[a]

enzyme[b] (30 mg/mL)	organic acid (10 mM)	alcohol (1 M)	initial rate of transport (μmol/L-h)
CCl	PPA	*n*-butyl alcohol	60
CCl	PPA	*n*-octyl alcohol	28
CCl	4-Cl-PPA[c]	*n*-butyl alcohol	67
CCl	phenylacetic	*n*-butyl alcohol	123
CCl	mandelic	*n*-butyl alcohol	0
PPL	PPA	*n*-butyl alcohol	0
lipase G	PPA	*n*-butyl alcohol	5

[a] For experimental conditions, see text. [b] Enzymes were obtained from commmercial suppliers and were used witout prior pretreatment. Lipase G is from a *Penicillium* sp. [c] 2-(4-Chlorophenoxy)propionic acid.

of 10 mM 2-phenoxypropionic acid and 10 mM mandelic acid was prepared in aqueous phase I (all other conditions as described above). After 170 h, 3.3 (±0.17) mM PPA was transported across the liquid membrane with the total exclusion of mandelic acid (<0.01 mM detected in aqueous phase II). Hence, ca. 100% selectivity was achieved, and this selectivity was imparted by the enzyme.

Our findings demonstrate that coupling enzymes with liquid membranes provides a simple, single-step method to selectively separate and purify organic acids through a facilitative transport mechanism. We are presently expanding this methodology to include optical resolutions and purifications as well as alternate membrane geometries. It can ben envisioned that by varying the enzyme used, it may be possible to control membrane selectivity for specific separations.

Acknowledgment. Financial support was provided by the Whitaker Foundation and the National Institutes of Health through a Biomedical Research Support Grant.

(10) It may be expected that the CCL-catalyzed esterification of organic acids occurs through the acid form of the substrate. Hence, it is desirable to operate at the lowest pH possible without significant loss of enzyme activity. In this case, pH 6.3 fulfilled both requirements.

Stereochemistry of the Thermal Homodienyl Hydrogen Shift Reverse Ene Reaction. Stereoelectronic Control of Stereogenicity Transfer through the Anisotropic Influence of a Cyclopropane Ring

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Powerful stereoelectronic effects control the rate[1,2] and stereochemistry[2] when a C–C bond of a cyclopropane or cyclobutane ring breaks in concert with other participating bonds in homo-Diels–Alder cycloreversions. If similar influences operate generally, the stereochemical outcome of homodienyl 1,5-hydrogen shifts should be predictable from the necessity for good overlap of the reacting C–H σ- and C–C π-bond orbitals with the breaking ring bond (C_2–C_3).[3,4] From the tendency of orbital phase

(1) (a) Allred, E. L.; Hinshaw, J. C.; Johnson, A. L. *J. Am. Chem. Soc.* **1969**, *91*, 3383. (b) Allred, E. L.; Voorhees, K. J. *Ibid.* **1973**, *95*, 620 and references cited therein.

(2) (a) Berson, J. A.; Olin, S. S. *J. Am. Chem. Soc.* **1969**, *91*, 777. (b) Berson, J. A.; Olin, S. S.; Petrillo, E. W., Jr.; Bickart, P. *Tetrahedron* **1974**, *30*, 1639 and references cited therein.

(3) (a) An earlier formulation[4] stated that "models indicate that this conformation (i.e., **1**) is the most favorable for overlap of the developing p-orbitals derived from the cyclopropane ring bond with the olefinic group and also the developing p-orbital derived from the C–H bond".

(4) Glass, D. S.; Boikess, R.; Winstein, S. *Tetrahedron Lett.* **1966**, 999.

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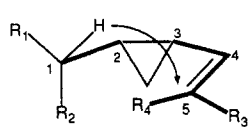
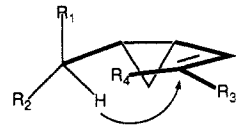
properties to persist along the reaction coordinate,[5] we deduce that pathway **1** should be preferred over pathway **2**, even though both

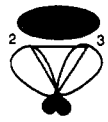


1

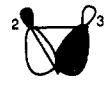


2

are formally suprafacial and allowed by orbital symmetry. In terms of the canonical orbitals, only that component of the degenerate $3E'$ cyclopropane HOMOs[6] (schematically **3** rather than **4**) which is bonding at the site of ring-cleavage (C_2–C_3) can correlate[5,7] with a bonding π-orbital of the product. The favored orbital alignment then would be produced by the geometry shown in **1**. Similar arguments apply in the case of the cyclobutane analogues.



3



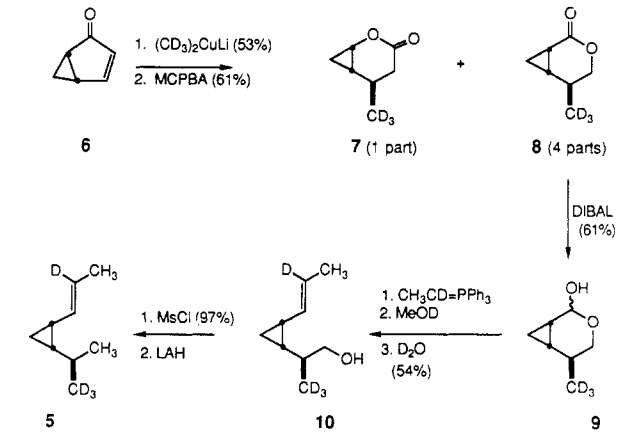
4

Although a preference for reaction from the endo conformation of the olefinic bond has been observed repeatedly[8-11] and its magnitude has been both measured experimentally[11] and calculated by ab initio theory,[12] the stereochemistry of the hydrogen migration itself heretofore has not been determined. The present paper and an accompanying one[13] experimentally solve the stereochemistry of the homodienyl hydrogen shifts for the cyclopropane and cyclobutane cases, respectively.

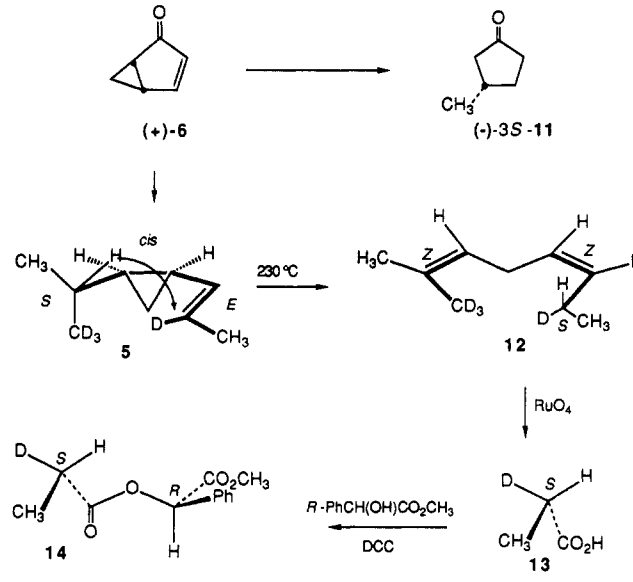
The cyclopropane test system is *cis*-2*S*-(2*S*-propyl-1-d_3)-1*S*-(1*E*-propenyl-2-*d*)cyclopropane (**5**), whose racemic isotopically unlabeled counterpart rearranges in a clean first-order gas-phase reaction to 2-methyl-2*Z*,5*Z*-octadiene at temperatures near 230 °C with activation parameters E_a = 35.5 ± 0.6 kcal/mol and log A = 12.05 ± 0.5 (A in s^{-1}).

Starting from the bicyclic enone **6**, available[14a] in five steps from dicyclopentadiene, we synthesized **5** by the route shown in Scheme I in seven additional steps, the first of which was an optical resolution with Johnson's sulfoximine reagent.[14b] Chemical correlation (actually carried out in the enantiometric series) of the synthetic intermediate (+)-**6** to (−)-3*S*-**11** of known[15] configuration and enantiomeric excess (ee) established the configurations of the ring carbons of **5** as shown and the ee as 87.0 ± 2% (Scheme II). The ee of ketone **6** was confirmed by reduction to a mixture of the corresponding allylic alcohols, which were converted to methyl ethers and analyzed with a capillary gas chromatographic (GC) column wall-coated with Ni-*R*-Cam[16] enantiomerically homogeneous stationary phase. The synthesis

Scheme I



Scheme II



introduced the chiral isopropyl group with >99.5 ± 0.5% diastereomeric specificity, and the deuterium incorporation in the 2*E*-configuration of the propenyl group double bond was 97.0 ± 0.5%.

Pyrolysis of **5**, chemical purity 99.1 ± 0.1%, at 230.0 ± 0.5 °C gave diene **12** (Scheme II), in which the configuration at C_2 was *Z* to the extent of 99.2 ± 0.4% (^{1}H and ^{2}H NMR analysis). None of the 5*E*-alkene isomer of **12** (<0.1% by capillary GC) was detected. The type-1 stereochemistry thus is highly preferred, both at the origin of migration and at the developing double bond adjacent to the receptor stereogenic center.

Diene **12** was oxidized to *S*-propanoic acid-2-*d* (**13**). Reaction of the latter with enantiomerically pure methyl *R*-mandelate and *N*,*N*′-dicyclohexylcarbodiimide[17] gave the propionate ester **14**. Using the known[17] diastereotopic shift difference of the *pro-R* and *pro-S* hydrogens of the unlabeled ester, we determined by NMR analysis the configuration and diastereomeric excess (de) at C_2 of the propionyl group of **14** obtained from the diene pyrolysis product. Corrected for the incomplete deuteration at the vinyl position of the reactant **5**, the de expected by ^{1}H analysis for 100% stereospecificity in the product is 82.0 ± 2%, whereas the value expected by ^{2}H analysis is 87.0 ± 2%. The observed ^{1}H and ^{2}H values were shown to be 81.5 ± 3% *S* and 86.1 ± 4% *S*, which correspond to 99 ± 4% and 99 ± 5% of those maximally available from the reactant hydrocarbon **5**. The outcome of the rear-

(5) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970; p 10. (b) Longuet-Higgins, H. C.; Abrahamson, E. W. *J. Am. Chem. Soc.* **1965**, *87*, 2045.

(6) See: (a) Jorgensen, W. L.; Salem, L. *The Organic Chemist's Book of Orbitals*; Academic Press: New York, 1973; p 154. (b) Honegger, E.; Heilbronner, E.; Schmelzer, A. *Nouv. J. Chim.* **1982**, *6*, 519.

(7) (a) This is perhaps most easily seen by the application of Zimmerman's "MO-following" procedure.[7b] Actually, in this model, the cyclopropane ring σ-bond and the olefinic π-bond both correlate with product π-bonds, and the reactant C–H bond correlates with the newly formed product C–H bond. (b) Zimmerman, H. E. *Acc. Chem. Res.* **1972**, *5*, 393.

(8) (a) Ellis, R. J.; Frey, H. M. *J. Chem. Soc.* **1964**, 5578. (b) Proc. *Chem. Soc.* **1964**, 221.

(9) Frey, H. M.; Solly, R. K. *Int. J. Chem. Kinet.* **1969**, *1*, 473.

(10) Roth, H. R.; König, J. *Justus Liebigs Ann.* **1965**, *688*, 28.

(11) Daub, J. P.; Berson, J. A. *Tetrahedron Lett.* **1984**, *25*, 4463.

(12) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 2089.

(13) Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.*, following paper in this issue.

(14) (a) Cox, O.; Rivera, L. *Synth. Commun.* **1978**, *8*, 261. (b) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021.

(15) Eisenbraun, E. J.; McElvain, S. M. *J. Am. Chem. Soc.* **1955**, *77*, 3383.

(16) (a) Gil-Av, E.; Feibush, B.; Charles-Sigler, R. *Tetrahedron Lett.* **1966**, 1009. (b) Schurig, V.; Weber, R. *J. Chromatogr.* **1981**, *217*, 51. (c) Owens, K. A.; Berson, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 627.

(17) Parker, D. *J. Chem. Soc., Perkin Trans. II* **1983**, 83.

rangement at the terminus of migration thus is also highly stereospecific in the sense required by type-1 geometry in the transition state.

The results form an instructive contrast with the stereochemistry of the regular dienyl 1,5-hydrogen shift. In the case of (*S*)-(2*E*,4*Z*)-6-methyl-2,4-octadiene-2-*d*,[18] for example, the electron distribution above and below the plane of the C_4–C_5 double bond (C_2–C_3 of the 1,5-system) of the diene is essentially isotropic, and suprafacial allowed reaction occurs on *both* faces of the receptor site at roughly equal rates. However, in the homodienyl case, where a cyclopropane unit replaces the C_2–C_3 double bond, the anisotropic electron distribution in the C_s-symmetric 3*E*′ ring orbital guides the flight of the hydrogen to only one stereochemical destination.

Acknowledgment. We thank the National Institute of General Medical Sciences for a grant in support of this work. E. J. Stark collaborated on the synthetic approach to lactol **9**.

Supplementary Material Available: Analytical, spectroscopic, and compositional charaterization of **5**, **12**, and the intermediates of Scheme I (18 pages). Ordering information is given on any current masthead page.

(18) Roth, W. R.; König, J.; Stein, K. *Chem. Ber.* **1970**, *103*, 426.

Persistence of Stereospecificity of Thermal Homodienyl Hydrogen Shift Reverse Ene Reactions in Cyclobutane Systems

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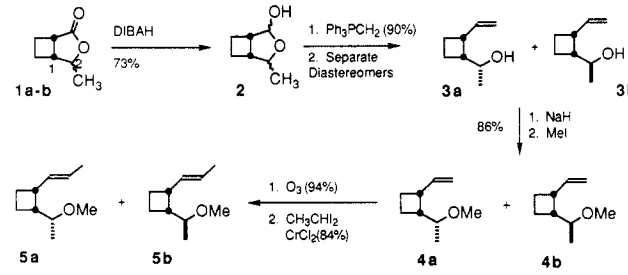
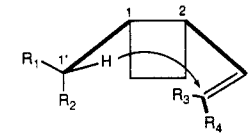
Stereospecificity survives in the thermal homo-Diels–Alder cycloreversions of 4,5-cyclobuta-3,4,5,6-tetrahydropyridazines despite the sharp diminution of the cycloreversion rate relative to the corresponding cyclopropanes.[1a,b] With the recent demonstration that a cyclopropane ring can control the stereochemistry of the 1,5-homodienyl hydrogen shift,[2] a comparison study is needed to test whether a cyclobutane can exert a similar influence in this sigmatropic rearrangement.[3]

In contrast to the *cis*-1-alkenyl-2-alkylcyclopropane case,[2] in which the only reaction was homodienyl hydrogen shift, the present *cis*-1-alkenyl-2-alkylcyclobutane experiment is complicated by the formation of several products, among which those resulting from homodienyl hydrogen shift constitute only about a fifth or less of the total. Moreover, the 1,5-diene structure of the product of the homodienyl hydrogen shift opens the possibility of further transformation by a Cope rearrangement. This problem can be suppressed by the choice of a methoxy group as a stereochemical marker, as in **4a,b** and **5a,b**, whose syntheses from the known[4] lactone **1** are described in Scheme I. Homodienyl hydrogen shift then leads to an enol ether whose subsequent Cope rearrangement is insignificant under these conditions.

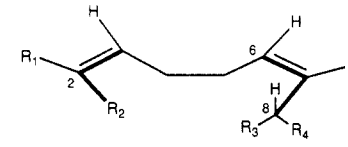
Scheme I



Upon being heated in the gas phase in basic lead glass ampoules[5] at 250 °C, compound **4b** disappeared at a first-order rate about



4a: $R_1 = CH_3$, $R_2 = OMe$, R_3, $R_4 = H$
4b: $R_1 = OMe$, $R_2 = CH_3$, R_3, $R_4 = H$
5a: $R_1 = CH_3$, $R_2 = OMe$, $R_3 = D$, $R_4 = CH_3$
5b: $R_1 = OMe$, $R_2 = CH_3$, $R_3 = D$, $R_4 = CH_3$



6: $R_1 = CH_3$, $R_2 = OMe$, R_3, $R_4 = H$
7: $R_1 = OMe$, $R_2 = CH_3$, R_3, $R_4 = H$
8: $R_1 = OMe$, $R_2 = CH_3$, $R_3 = D$, $R_4 = CH_3$
9: $R_1 = CH_3$, $R_2 = OMe$, C_8 config. not determined
10: $R_1 = OMe$, $R_2 = CH_3$, C_6 config. *E*, C_8 config. not determined

4×10^{-3} that of *cis*-2-isopropyl-1 *E*-propenylcyclopropane.[2] The respective Arrhenius parameters for **4a** and **4b** determined from measurements at 243.8, 255.9, and 267.5 °C were $E_a = 47.8 \pm 2$ and 48.6 ± 2 kcal/mol and $A = 10^{14.8\pm0.9}$ and $10^{15.2\pm0.9}$ s^{-1}. The major products were formed by four pathways: (1) fragmentation to 1,3-butadiene and 2-methoxy-3-butene (35%); (2) epimerization at one or both of the ring stereogenic centers (35%); (3) [1,3]-sigmatropic rearrangement to 4-(1-methoxyethyl)cyclohexenes (10%); and (4) homodienyl hydrogen shift (retro-ene reaction) to 2-methoxy-2,6-octadienes (20%).

The retro-ene reactions strongly prefer the endo vinyl orientation, the sum of dienes **6** and **7** with the 6*Z*-configuration being 90% and 94%, respectively, of the total retro-ene product. Small amounts of 6*E*-dienes resulting from the stereochemical equivalent of reaction in the exo vinyl orientation are also formed, in contrast with the absence of such products in the cyclopropane series.[6] Within the endo manifold, the stereochemical course at the enol ether double bond also is highly stereospecific. The ratio **6**:**7** is about 26:1 from **4a**, and the inverse ratio **7**:**6** is about 56:1 from **4b**. These ratios are minimum estimates of the actual specificity of the hydrogen shifts in the endo manifold, since the competing double epimerization interconverts the two diastereomeric cyclobutane reactants. In fact, a computer-assisted simulation of the kinetic scheme shows that within experimental error, all of the minor 6*Z*-diene product in the endo manifold is accounted for by this side reaction. With respect to the rotational orientations of the receptor double bond and the alkyl hydrogen donor, the rearrangements of both diastereomers in the vinylcyclobutane series thus mimic the preference of the cyclopropane rearrangements[2] fo the overlap-favored geometry symbolized in **4a,b**/**5a,b**, despite the much slower rates in the cyclobutane systems. Since all of the stereospecificities in these and the previous[2] experiments are essentially off-scale, a quantitative comparison of the degree of stereochemical control by the cyclopropane and cyclobutane rings is not available.

The transition-state geometry deduced from these results

(1) (a) Berson, J. A.; Petrillo, E. W., Jr.; Bickart, P. *J. Am. Chem. Soc.* **1974**, *96*, 636. (b) Berson, J. A.; Olin, S. S.; Petrillo, E. W., Jr.; Bickart, P. *Tetrahedron* **1974**, *30*, 1639.

(2) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) A preliminary approach was made by Jordan and Berson (Jordan, L. M.; Berson, J. A. Unpublished work). (b) Jordan, L. M. Ph.D. Thesis, Yale University, New Haven, CT, 1973. (c) Reviewed by Gajewski, J. J. In *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; p 178.

(4) Kosugi, H.; Sekiguchi, S.; Sekita, R.; Uda, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 520.

(5) Doering, W. von E.; Beasley, G. H. *Tetrahedron* **1973**, *29*, 2231.

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