Stereochemistry and Mechanism of the Reverse Ene Reaction of *cis*-2-Alkyl-1-alkenylcyclobutanes. Stereoelectronic Control in a System Showing Marginal Energetic Benefit of Concert

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Abstract: In the temperature range 243.8–267.5 °C, the racemic cyclobutanes (1*RS*,2*RS*,1′*SR*)-1-(1-methoxyethyl)-2-vinylcyclobutane (**16b**) and (1*SR*,2*SR*,1′*SR*)-1-(1-methoxyethyl)-2-vinylcyclobutane (**17b**) each undergo a sigmatropic hydrogen shift (reverse ene reaction) amounting to about 18% of the total pyrolysis product, in addition to four other unimolecular processes. The other four reactions are [2 + 2]-cycloreversion, epimerization, double epimerization, and sigmatropic carbon 1,3-rearrangement. Overall disappearance of reactant occurs with first-order kinetics. The activation parameters determined for **16b** are E_a = 47.8 ± 2.1 kcal/mol and log A = 14.8 ± 0.9, and for **17b** they are E_a = 48.6 ± 2.2 kcal/mol and log A = 15.2 ± 0.9 (A, s^{-1}). In the reverse ene reactions, vinyl derivatives **16b** and **17b** yield (2*E*,6*Z*)-2-methoxyocta-2,6-diene ((*E*,*Z*)-**18**) and (2*Z*,6*Z*)-2-methoxyocta-2,6-diene ((*Z*,*Z*)-**18**), respectively, with stereospecificities of 95 and 91%. These are minimum values because of the competing interconversion of the reactant cyclobutanes **16b** and **17b**. Correction for this gives a stereospecificity of about 220:1 for the 6*Z* reverse ene product formed directly from **16b** and about 35:1 for that from **17b**. This demonstrates high stereospecificity at the double bond of the product derived from the migration origin. Secondary β-deuterium kinetic isotope effects ($\Delta\Delta G^{\ddagger}$), measured at 517 K) for [2 + 2]-cycloreversion, epimerization, and sigmatropic carbon 1,3-rearrangement of 10–20 (±120) and 80–180 (±240) cal/mol were measured for **16b** and **17b**. Primary isotope effects for reverse ene hydrogen shift were 980 ± 125 and 1760 ± 290 cal/mol, respectively. The stereochemistry at the terminus of migration can be determined in the corresponding cyclobutanes bearing a propenyl instead of a vinyl group. The enantiomerically enriched isotopically labeled cyclobutane (1*R*,2*R*,1′*S*)-(−)-1-(1-methoxyethyl)-2-(2-deuterio-1(*E*)-propenyl)cyclobutane ((−)-**37**) having 93.2% ee was prepared in nine steps from (*S*)-(−)-3-butyn-2-ol. The reverse ene reaction accounts for roughly 5% of the total product in the pyrolysis of the propenyl derivative (−)-**37**-*d* at 239.3 °C. The principal reverse ene product is (2*E*,6*Z*)-8(*S*)-deuterio-2-methoxynona-2,6-diene (**45**), formed with roughly 13:1 stereospecificity compared to the next most prevalent double bond isomer. The product 8(*S*)-**45** was chemically degraded to (*S*)-2-deuteriopropanoic acid, which was subsequently converted to the corresponding propanoate ester **49**/**50** with (*R*)-(+)-methyl mandelate. Analysis of the diastereomeric excess of this ester by ^{1}H and ^{2}H NMR indicates that 8(*S*)-**45** is formed from (1*R*,2*R*,1′*S*)-(−)-**37**-*d* with 68.9 ± 4.9% (^{1}H NMR) or 80.5 ± 3.3% (^{2}H NMR) transfer of stereogenicity. Taking into account potential stereochemical contaminants, the actual stereogenicity transfer may be as high as 100% but not lower than 64%. This suffices to show that a suprafacial hydrogen transfer dominates the retro ene reaction in the propenyl case and probably also in the vinyl cases. The results from **16b**, **17b**, and **37** are interpreted in terms of a dominant concerted mechanism for the reverse ene reactions of these compounds. They are consistent with a transition-state structure in which the alkenyl moiety is endo with respect to the ring and the breaking C–H bond orbital is aligned with the breaking C–C ring bond. This is the sole geometry consistent with predictions based on the conservation of orbital symmetry and orbital overlap control.

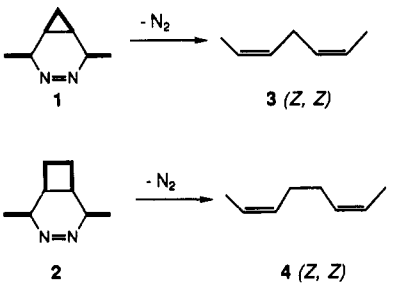
Discussion

Replacement of the cyclopropane ring of a 3,4-diazabicyclo-[4.1.0]hept-3-ene (e.g., **1**) by a cyclobutane ring, as in a 3,4-diazabicyclo[4.2.0]oct-3-ene (**2**), results in a retardation of the rate of cycloreversion by many orders of magnitude.[1,2] The energetic benefit of concert in the cyclobutane case **2** thus is marginal. Nevertheless, the characteristic stereochemistry persists: the syn, cis [4.2.0] diazene **2** forms only the *Z*,*Z* product **4**, in exact analogy to the syn, cis [4.1.0] diazene **1**, which gives only the *Z*,*Z* product **3** (Scheme I).[1] Both cyclopropane and cyclobutane rings thus seem to be able to exert stereoelectronic control over cycloreversions.

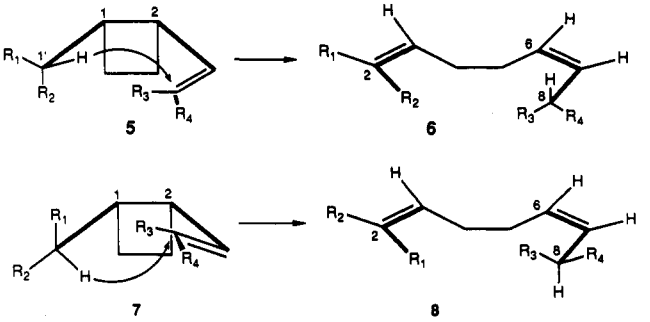
That a similar stereoelectronic effect of a cyclopropane ring can control stereochemistry in sigmatropic rearrangements has been shown in a recent study[3] of the homodienyl hydrogen shift reverse ene reaction of *cis*-2-alkyl-1-alkenylcyclopropanes. The present research[4] is intended to test whether a cyclobutane ring also can function in this way.

Experimental Design. Since the specification of each of the three stereochemical elements of the diene product (C_2=C_3 and C_6=C_7 double bond configurations and C_8 stereogenic carbon center; see Scheme II) requires a binary choice, there are hypothetically 2^3 = 8 stereochemically distinct reverse ene pathways

Scheme I



Scheme II



(1) (a) Berson, J. A.; Olin, S. S. *J. Am. Chem. Soc.* **1969**, *91*, 777. (b) Petrillo, E. W., Jr. Ph.D. Thesis, Yale University, New Haven, CT, 1973. (c) Berson, J. A.; Petrillo, E. W., Jr.; Bickart, P. *J. Am. Chem. Soc.* **1974**, *96*, 636. (d) Berson, J. A.; Olin, S. S.; Petrillo, E. W., Jr.; Bickart, P. *Tetrahedron* **1974**, *30*, 1639.

(2) (a) Allred, E. L.; Hinshaw, J. C. *J. Chem. Soc., Chem. Comm.* **1969**, 1021. (b) Allred, E. L.; Hinshaw, J. C. *Tetrahedron Lett.* **1972**, 387.

(3) (a) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1650. (b) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, companion paper in this issue.

(4) Preliminary communication: Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1652.

0002-7863/91/1513-4607$02.50/0

leading to eight possible products from a sufficiently labeled cyclobutane with *cis*-1-alkenyl-2-alkyl substitution. However, hypothetical concerted pathways for four of these processes would have to pass over eight-atom cyclic transition states severely destabilized by the strain energy of a developing trans $C_6{=}C_7$ double bond. It is true that each of these transition states presumably would be somewhat less strained than the corresponding seven-membered transition state from the *cis*-1-alkenyl-2-alkylcyclopropane, which is destabilized by >12 kcal/mol (experiment[10]) or 17 kcal/mol (ab initio calculation[11]). Nevertheless, concerted reactions leading to *E* configurations of the $C_6{=}C_7$ double bond in the diene product from a *cis*-1-alkenyl-2-alkylcyclobutane probably would be unfavorable relative to concerted pathways leading to the 6*Z* product. The formation of the 6*E* product by a biradical mechanism might compete with the concerted pathway of the 6*Z* product if the latter were slow.

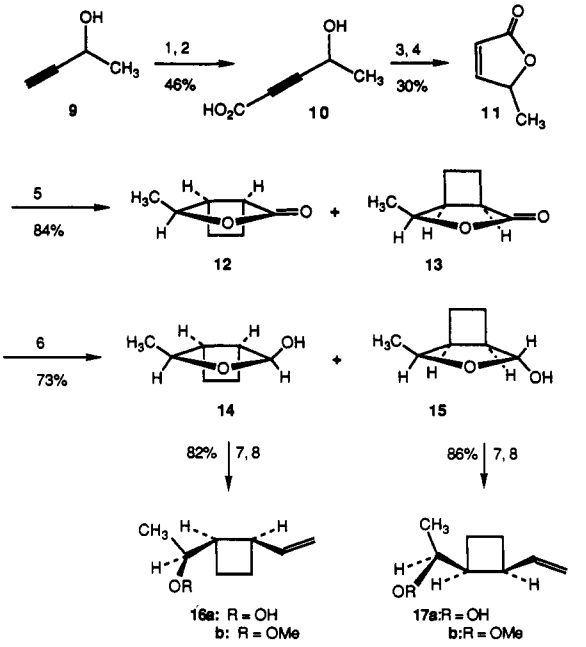
Of the four pathways leading to the 6*Z* product, two involve overall antarafacial hydrogen migration in a six-electron system and therefore are orbital-symmetry-forbidden. The remaining two pathways **5** → **6** and **7** → **8** (Scheme II) are suprafacial and allowed, but only **5** → **6** takes advantage of the favorable phase properties of the degenerate highest occupied molecular orbitals (HOMOs) of cyclobutane. Like the HOMOs of cyclopropane, the cyclobutane HOMOs have one component symmetric and one antisymmetric with respect to a plane C_s between C_1 and C_2.[5-8] Formally, therefore, the correlation diagrams[3] for the reverse ene reactions of the cyclopropane and cyclobutane systems will be similar. Only if the symmetric HOMO is taken as one of the reacting orbitals can correlation of the reactant and product bonding orbitals be achieved, and the C_s symmetric HOMO therefore may be said to control the stereochemistry of the reaction. Analogy to the cyclopropane case[3] then would predict that, for the concerted rearrangement of *cis*-2-alkyl-1-alkenylcyclobutanes, the stereoelectronically preferred transition-state geometry should be that generated from conformation **5** rather than conformation **7** and the predominant reverse ene product should be diene **6** rather than **8** (Scheme II).

Although the realization of this test was the primary motivation for the present[4] research, the findings unavoidably also bear upon issues of concertedness in thermal rearrangements, because the stereoelectronic argument just given is derived for a concerted process. It will be necessary, of course, to consider carefully whether the predicted result also could be rationalized by some other hypothesis.

Several obstacles make the execution of this plan more difficult than in the cyclopropane system. First, the reverse ene reactions of *cis*-1-alkenyl-2-alkylcyclobutanes are much slower than those of their cyclopropane counterparts.[9] As a result, fragmentation, epimerization, and carbon sigmatropic rearrangement, reactions not seen in the cyclopropane system, now all compete with the reverse ene reaction in the cyclobutane case, leaving only minor products as the depository of the desired stereochemical information.

Second, since the primary product of the reverse ene reaction is a 1,5-diene, one might expect secondary Cope rearrangement to consume it or, if the rearrangement is reversible, to alter it stereochemically. In fact, prior studies[9a,b] already had found such a stereochemical disturbance in a related case. In order to suppress this here, we proposed to make one of the substituents R_1 or R_2

Scheme III[a]



[a] Methods: 1, 2 BuLi; 2, CO_2; 3, H_2, Lindlar; 4, H_3O^+; 5, C_2H_2, *hν*; 6, DIBAL; 7, $Ph_3P{=}CH_2$; 8, NaH, CH_3I.

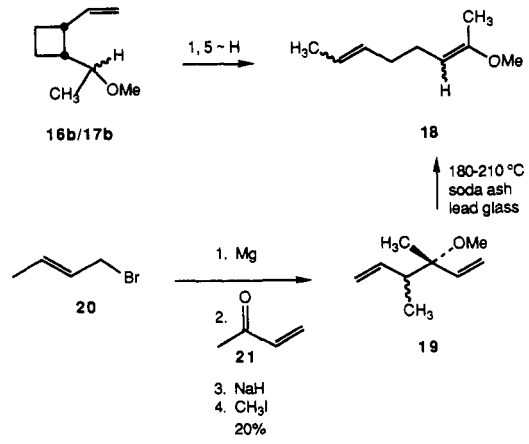
(Scheme II) a methoxy group in the anticipation that it should retard the Cope rearrangement both kinetically[12a] and thermodynamically.[12b-d] The structural and stereochemical integrity of **6** thus should be secure.

An ideal cyclobutane test molecule would bear substituents (Scheme II, R_1 and R_2) at $C_{1'}$ of equal steric requirements. The conformational steric free energies of CH_3 (A = 1.70 kcal/mol) and OCH_3 (A = 0.60 kcal/mol)[13] are not widely disparate so that this pair of $C_{1'}$ substituents might be suitable. However, it was not completely certain whether the methoxy group might exert some electronic influence that could bias the stereochemical course of the hydrogen shift. To test both the known steric and potential electronic factors of methoxy substitution, we studied both diastereomers of the reactant derivable by interchange of the nature of R_1 and R_2 (Scheme II), on the reasoning that if both were found to react by the same stereochemical pathway, the arguments for an inadvertent special effect of methoxy could be dismissed.

Although the full definition of the stereochemistry of the reverse ene reaction requires a reactant with specified configuration at three carbon atom stereocenters and one double bond (Scheme II), a less complete labeling pattern in which the reactant's double bond terminates in the stereochemically uninformative CH_2 group (Scheme II, R_3, R_4 = H) also can yield valuable partial solutions with significant savings in synthetic and analytical effort. Accordingly, we have conducted experiments in two series of reactants, one a racemic, partially labeled case (R_1 = CH_3, R_2 = OCH_3 and, vice versa, R_3, R_4 = H) and the other an enantiomerically enriched, fully labled case (R_1 = OCH_3, R_2 = CH_3, R_3 = D, R_4 = CH_3). We describe (1) the syntheses and assignments of diastereomeric configurations to the reactant molecules in the

(5) Hoffmann, R.; Davidson, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 5699.
(6) Salem, L.; Wright, J. S. *Ibid.* **1969**, *91*, 5947.
(7) Jorgensen, W. L.; Salem, L. *The Organic Chemist's Book of Orbitals*; Academic Press: New York, 1973; pp 26-27, 222-224.
(8) The orbital shapes and degeneracies are unaffected by allowing cyclobutane to relax to its puckered (D_{2d}) equilibrium geometry.
(9) (a) An earlier approach from this laboratory is described elsewhere: Jordan, L. M.; Ph.D. Dissertation, Yale University, New Haven, CT, 1974. (b) Reviewed by Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; p 178. (c) Chickos, J. S.; Frey, H. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 365. (d) Glass, T. E.; Leber, P. A. *Tetrahedron Lett.* **1990**, *31*, 1085.
(10) Daub, J. P.; Berson, J. A. *Tetrahedron Lett.* **1984**, *25*, 4463.
(11) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 2089.
(12) (a) Carpenter, B. K. *Tetrahedron* **1978**, 34, 1877. (b) Rhoads, S. J.; Waali, E. E. *J. Org. Chem.* **1970**, *35*, 3358. (c) The equilibrium constant between 1- and 3-methoxy-1,5-hexadiene cannot be calculated from the Benson group equivalents, since the tables[12d] lack entropy of formation values for some of the part structures. However, the enthalpic preference for the 1-methoxy isomer at 25 °C is calculated from the tables to be only 2.6 kcal/mol. One expects[12b] a 6.8 kcal/mol free energy preference for the enol ether 1-methoxy-1,5-hexadiene, so perhaps the lower value of the enthalpy preference is augmented by a much higher entropy of formation for the 1-methoxy- than for the 3-methoxy-1,5-hexadiene ($\Delta\Delta S_f$ = 14 gibbs/mol). It is not obvious why the entropies should differ by so much, and an alternative possibility is that the enthalpy group equivalents do not take into account an enthalpic stabilizing effect of the enol ether moiety. (d) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279.
(13) Hirsch, J. A. *Top. Stereochem.* **1967**, 1, 199.

Scheme IV



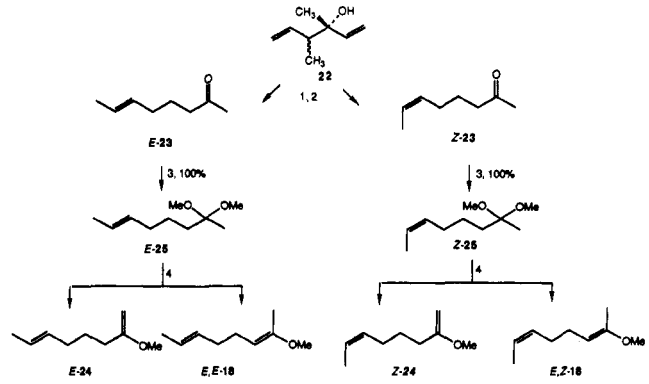
partially labeled series, (2) a detailed study of the kinetics and products of pyrolysis of these compounds, (3) the synthesis of the enantiomerically enriched, fully labeled cases, and (4) the complete analysis of the stereochemistry of the reverse ene product from one of the latter reactants.

Synthesis and Stereochemistry of the Partially Labeled Racemic Series (Scheme III). The most efficient synthesis of the racemic substrates would be one that eventually could be adapted also to the synthesis of the enantiomerically enriched series (see below). Thus, 3-butyn-2-ol (**9**), whose optical resolution by straightforward methods has been reported,[14] was an attractive starting material. Metalation and carboxylation of **9** gave 4-hydroxy-2-butynoic acid (**10**), which upon hydrogenation over a Lindlar catalyst gave the butenolide **11**. Cycloaddition of ethylene and **11** by a variation of the method of Kosugi and co-workers[15] gave a 1.7:1 mixture of bicyclic lactones **12** and **13**. They had used the ^{1}H NMR coupling constants between the C_5 bridgehead and C*H*CH$_3$ protons (J = 0.9 and 5.2 Hz) to assign the diastereomeric configurations **12** and **13**, respectively. We observed essentially the same coupling constants, and we confirmed the assignments by nuclear Overhauser studies described in the Experimental Section. These show that, in the isomers with J = 0.9 and 5.2 Hz, the methyl groups indeed are, respectively, cis and trans to the C_5 bridgehead hydrogen.

Reduction of the lactones **12** and **13** to lactols **14** and **15**, Wittig olefination to alcohols **16a** and **17a**, and methylation of the latter completed the syntheses of Scheme III. The Wittig reactions **14** → **16a** and **15** → **17a** leading to the *cis*-1-(1-methoxyethyl)-2-vinylcyclobutanes are potentially hazardous to the stereochemistry of the cyclobutane ring substituents. Should epimerization at the stereogenic center adjacent to the aldehyde form of the lactol **14** or **15** occur, it would be expected to generate a diastereomer of the final methyl ether, one that had a trans ring substituent configuration, rather than the desired cis isomer **16b** or **17b**. However, we were able to allay this fear by the independent synthesis of the trans epimer. Ozonolysis of the terminal double bond of **16b**, epimerization of the derived aldehyde with pyrrolidine, and Wittig methylenation gave *trans*-1-(1-methoxyethyl)-2-vinylcyclobutane, whose spectroscopic properties and GC retention time were diagnostically different from those of **16b**. Significantly, this trans epimer was not present in the product of the methylenation–methylation sequence **14** → **16b**. A single stereoisomer also is produced in the comparable sequence **15** → **17b**. Therefore, to assign a trans configuration of the ring substituents in the product from **15**, it would be necessary to postulate that the two Wittig sequences occur with opposite stereochemical outcomes, complete retention, as demonstrated from **14**, and complete epimerization from **15**. This is highly unlikely, and we are confident in the assignment of the cis ring substituent configuration **17b** to the product from **15** also.

(14) Weidmann, R.; Schoofs, A.; Horeau, A. *Bull. Soc. Chim. Fr.* **1976**, 645.
(15) Kosugi, H.; Sekiguchi, S.; Sekita, R.-i.; Uda, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 520.

Scheme V[a]



[a] Methods: 1, 203.8 °C, 64%; 2, GC separation; 3, HC(OMe)$_3$, TsOH, 100%; 4, Me$_3$SiI, HMDS.

Independent Synthesis and Characterization of Stereoisomeric Reverse Ene Pyrolysis Products (Experimental Details in Supplementary Material). Scheme IV shows the synthesis of the four stereoisomeric 2-methoxyocta-2,6-diene pyrolysis products **18** and the potential Cope rearrangement products **19** of them. The latter dienes were formed by methylation of the alcohol mixture **22**, (see Scheme V) obtained from the reaction of the Grignard reagent of crotyl bromide (**20**) with methyl vinyl ketone (**21**). Pyrolysis of **19** in Pyrex ampules gave not only the desired 2-methoxyocta-2,6-dienes **18** but also products of apparent surface-catalyzed reactions: the oct-6-en-2-ones **23**, derived from hydrolysis of the

enol ether functions, and the 2-methoxyocta-1,6-dienes **24**, derived from positional isomerization of the enol ether double bond. This difficulty was overcome by conducting the pyrolyses in soda ash lead glass ampules (Corning number 0010, no longer available), under which conditions the formation of **23** and **24** was almost completely suppressed.[16]

Configurational assignments in this series were aided by stereospecific syntheses (Scheme V) of the 2-methoxyocta-2,6-dienes from the gas chromatographically separated stereoisomers (*E*)-**23** and (*Z*)-**23** of oct-6-en-2-one, which in turn were obtained by the oxy-Cope rearrangement of **22** and identified by ^{1}H NMR spectroscopic examination of the olefinic coupling constants: (*E*)-**23**, J = 15.0 Hz; and (*Z*)-**23**, J = 11.1 Hz. Conversion of each of the ketones to dimethyl ketals (*E*)-**25** and (*Z*)-**25** and treatment of the ketals with iodotrimethylsilane and hexamethyldisilazane via a precedented procedure[17] gave only two products in each case. These were the (*E*)- and (*Z*)-2-methoxyocta-1,6-dienes ((*E*)-**24** from (*E*)-**25** and (*Z*)-**24** from (*Z*)-**25**) and the (2*E*,6*E*)- and (2*E*,6*Z*)-2-methoxyocta-2,6-dienes ((*E*,*E*)-**18** from (*E*)-**25** and (*E*,*Z*)-**18** from (*Z*)-**25**). The configurations of the enol ether double bonds of the 2,6-dienes were established by nuclear Overhauser experiments (NOE).

The remaining isomers of the 2-methoxyocta-2,6-diene (**18**) series (2*E*,6*Z* and 2*Z*,6*Z*) were prepared and identified by the Cope rearrangement of each of the GC-separated diastereomers of **19**. The usual preference for a chairlike transition state for the Cope rearrangement[18] would predict that one isomer (erythro) of **19** would give predominantly the 2*E*,6*E* and 2*Z*,6*Z* isomers of **18** and the other diastereomer of **19** (threo) would give predominantly the 2*Z*,6*E* and 2*E*,6*Z* isomers of **18**. Indeed, we found that one of the isomers of **19** gave upon pyrolysis at 189.1 °C the previously obtained (*E*,*E*)-**18** (80.1% of the 2,6-diene fraction) and 2.6% of the previously obtained 2*E*,6*Z* isomer, together with

(16) Doering, W. v. E.; Beasley, G. H. *Tetrahedron* **1973**, *29*, 2231 have observed that certain surface-catalyzed olefin position isomerizations can be minimized in vessels of potash lead glass (Corning 0120).
(17) Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1982**, *23*, 323.
(18) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.

Scheme VI

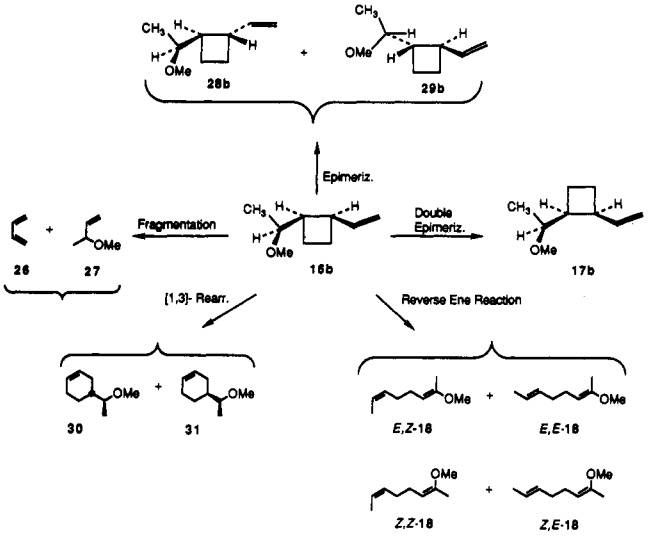


Table I. Distribution of Pyrolysis Products in the Rearrangement of Cyclobutane **16b**

process	product(s)	percent of total product (mean values) T = 243.8 °C	T = 255.9 °C	T = 267.5 °C
fragmentation	**26 + 27**	34.3 ± 1.6	36.5 ± 1.5	38.5 ± 1.6
epimerization	**28 + 29**	24.9 ± 0.9	25.3 ± 0.8	25.5 ± 0.8
double epimerization	**17**	6.9 ± 1.8	6.9 ± 1.6	6.8 ± 1.7
1,3-rearrangement	**30 + 31**	9.5 ± 0.6	9.5 ± 0.4	9.6 ± 0.4
reverse ene	(*E*,*Z*)-**18**	22.4 ± 0.9	19.7 ± 0.6	17.8 ± 0.6
reverse ene	(*E*,*E*)-**18**	1.2 ± 0.3	1.2 ± 0.2	1.0 ± 0.2
reverse ene	(*Z*,*Z*)-**18**	0.3 ± 0.3	0.4 ± 0.2	0.2 ± 0.2
reverse ene	(*Z*,*E*)-**18**	0.1 ± 0.3	0.1 ± 0.2	0.1 ± 0.2

13.5 and 3.8% of two new 2,6-dienes. We assign the major new product the 2*Z*,6*Z* configuration and the minor one the 2*Z*,6*E* configuration on the above assumption. The **19** diastereomer from which these products are derived must be erythro.

Similarly, pyrolysis of the other diastereomer (threo) of **19** gives 53.0% of the known (2*Z*,6*E*)-**18** isomer, 12.9% of the known (2*E*,6*E*)-**18**, 1.6% of the (now) known (2*Z*,6*Z*)-**18**, and 32.5% of a diene, which must be (2*E*,6*Z*)-**18** and is the same as the one formed in 3.8% contribution in the above pyrolysis of *erythro*-**19**. This completes the assignments of configuration to the four isomers of **18**.

Kinetics and Products of Gas-Phase Pyrolyses of the Diastereomeric *cis*-1-(1-Methoxyethyl)-2-vinylcyclobutanes 16b and 17b (Experimental Details in Supplementary Material). Both **16b** and **17b** disappeared in cleanly first-order processes when heated in soda ash lead glass ampules at 243.8, 255.9, and 267.5 °C. The variation of the rate constants for overall reaction over this (admittedly narrow) range permitted the extraction of the Arrhenius activation parameters: For **16b** and **17b**, respectively, E_a = 47.8 ± 2.1 and 48.6 ± 2.2 kcal/mol and log A = 14.8 ± 0.9 and 15.2 ± 0.9 (A, s^{-1}). The Eyring activation entropies $\Delta S^{\ddagger}$ are 6.2 ± 3.9 and 8.0 ± 4.1 gibbs/mol at 255.9 °C. The rate constants for disappearance of **17b** are about 10–15% larger than those for **16b**, but the activation parameters are experimentally indistinguishable.

In both cases, the reaction mixtures were complex, as had been expected from the earlier studies.[9a] The products (Scheme VI) included those derived by five pathways: fragmentation of the cyclobutane ring (1,3-butadiene (**26**) and 3-methoxy-1-butene (**27**)); single epimerization (the *trans*-1-(1-methoxyethyl)-2-vinylcyclobutanes **28** and **29**); double epimerization (diastereomer interchange, which gives **17b** from **16b** and vice versa); sigmatropic carbon 1,3-rearrangement (the 4-(1-methoxyethyl)cyclohexenes **30** and **31**); and reverse ene reaction (the four stereoisomers of 2-methoxyocta-2,6-diene ((*E*,*E*)-, (*E*,*Z*)-, (*Z*,*E*)-, and (*Z*,*Z*-**18**)). Identification of these products is described in the supplementary material.

From (1*RS*,2*RS*,1′*SR*)-*cis*-1-(1-Methoxyethyl)-2-vinylcyclobutane (16b), the distribution of the eleven products was, within experimental error, independent of the extent of conversion (Table I). This finding suggests that the processes are irreversible primary reactions and that the products are not rapidly consumed by side reactions, at least under these conditions. If this deduction is correct, the first-order rate constants for formation of the various products from the starting material, e.g., **16b**, are simply the products of the appropriate constant for overall disappearance of **16b** and the appropriate product fraction in Table I. Table II lists the rate constants derived in this way. Control experiments described in the supplementary material show that the proportions of the products of the reverse ene reactions do not change over time during the pyrolyses.

Table II. Rate Constants for Product Formation in the Pyrolysis of **16b**

process	product(s)	k (×10⁷ s) T = 243.8 °C	T = 255.9 °C	T = 267.5 °C
fragmentation	**26 + 27**	14.3 ± 1.0	43.6 ± 2.6	124 ± 7
epimerization	**28 + 29**	10.4 ± 0.6	30.2 ± 1.6	82.3 ± 4.4
double epimerization	**17**	2.88 ± 0.77	8.3 ± 2.0	22.1 ± 5.7
1,3-rearrangement	**30 + 31**	3.97 ± 0.31	11.3 ± 0.7	31.1 ± 1.8
reverse ene	(*E*,*Z*)-**18**	9.38 ± 0.58	23.6 ± 1.3	57.4 ± 3.1
reverse ene	(*E*,*E*)-**18**	0.50 ± 0.14	1.38 ± 0.28	3.17 ± 0.76
reverse ene	(*Z*,*Z*)-**18**	0.12 ± 0.13	0.44 ± 0.27	0.78 ± 0.76
reverse ene	(*Z*,*E*)-**18**	0.04 ± 0.13	0.07 ± 0.27	0.31 ± 0.74

Table III. Activation Parameters for Major Rearrangement Pathways of **16b**

process	product(s)	E_a (kcal/mol)	log A (A, s^{-1})	$\Delta S^{\ddagger}$ (gibbs/mol)
fragmentation	**26 ± 27**	50.6 ± 2.6	15.5 ± 1.1	9.4 ± 4.9
epimerization	**28 + 29**	48.4 ± 2.4	14.5 ± 1.0	4.6 ± 4.5
1,3-rearrangement	**30 ± 31**	48.2 ± 2.7	14.0 ± 1.1	2.3 ± 5.1
reverse ene	(*E*,*Z*)-**18**	42.4 ± 2.3	11.9 ± 1.0	−7.2 ± 4.3

The range of experimental error determines the degree of applicability of these data to mechanistic assignments. The error limits given in Table II reflect in large part the deviation in the mean product fractions (Table I) as the pyrolysis proceeds from low conversion (ca. 3%) to higher conversion (ca. 50%) of the substrate **16b**. For this reason, the smaller the relative error limit associated with the rate constant, the more likely that the corresponding reaction is genuinely first-order and the less likely that secondary reactions are consuming the product. The processes listed in Table II can be divided into two groups. The first group consists of the four principal reactions: fragmentation, epimerization, 1,3-rearrangement, and the major reverse ene reaction (giving (*E*,*Z*)-**18**). For these four reactions, the propagated error limit is relatively small, roughly 10% or less of the calculated value of k. Approximate Arrhenius activation parameters and Eyring activation entropies, calculated from the rate data of Table II, are presented in Table III.

The Arrhenius parameters must be regarded as approximate, because they are derived from measurements over only a small range (4.5%) of absolute temperature and because the propagated uncertainty limits are relatively large. Even so, they do suggest an energetic distinction between the reverse ene reaction on one hand and the other three reactions (fragmentation, epimerization, and carbon 1,3-rearrangement) on the other. The value of E_a for the reverse ene reaction is roughly 6–8 kcal/mol lower than the values calculated for the other three reactions. Also, only the reverse ene reaction to (*E*,*Z*)-**18** shows a negative entropy of activation beyond the propagated uncertainty limits. Despite the relative imprecision of the data, the pattern of results is consistent with a largely concerted reverse ene reaction in competition[19] with

(19) For some of the extensive literature on the subject of competition between concerted and biradical pathways, see inter alia: (a) Berson, J. A.; *Acc. Chem. Res.* **1972**, *5*, 406 and references cited therein. (b) Berson, J. A. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, p 311. (c) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981. (d) Gajewski, J. J.; Squicciarini, M. P. *J. Am. Chem. Soc.* **1989**, *111*, 6717.

Scheme VII. Hydrogen Shifts by endo and exo Alkenyl Pathways

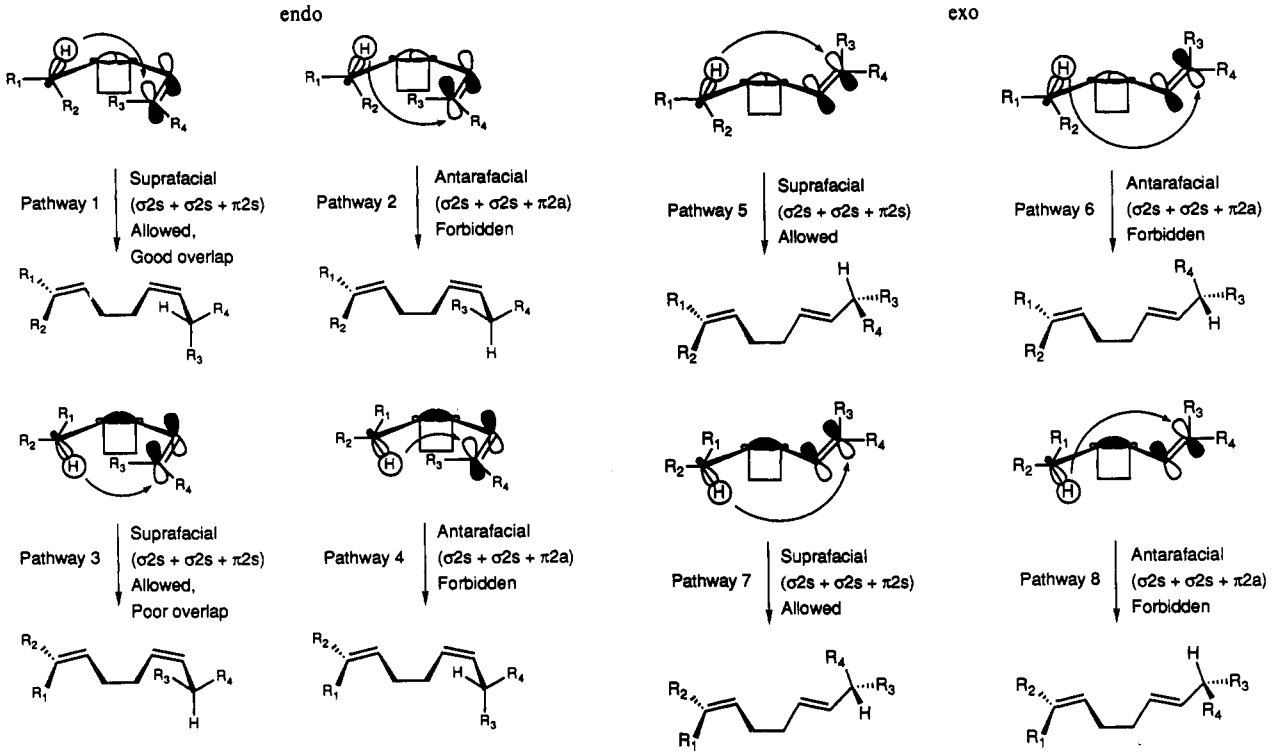


Table IV. Distribution of Pyrolysis Products in the Rearrangement of Cyclobutane **17b**

		percent of total product (mean values)		
process	product(s)	T = 243.8 °C	T = 255.9 °C	T = 267.5 °C
fragmentation	**26 + 27**	31.0 ± 4.0	34.8 ± 2.4	37.5 ± 2.5
epimerization	**28 + 29**	22.3 ± 2.4	23.4 ± 1.5	24.3 ± 1.2
double epimerization	**17**	16.7 ± 10.2	11.4 ± 5.5	10.0 ± 5.9
1,3-rearrangement	**30 + 31**	8.6 ± 1.1	9.6 ± 0.5	9.6 ± 0.9
reverse ene	(*Z*,*Z*)-**18**	17.4 ± 2.3	17.2 ± 1.5	15.4 ± 0.7
reverse ene	(*Z*,*E*)-**18**	1.6 ± 0.3	1.7 ± 0.3	1.6 ± 0.2
reverse ene	(*E*,*Z*)-**18**	1.1 ± 0.8	0.6 ± 0.4	0.5 ± 0.5
reverse ene	(*E*,*E*)-**18**	0.3 ± 0.4	0.3 ± 0.3	0.3 ± 0.3

largely nonconcerted fragmentation, epimerization, and sigmatropic side reactions. Other studies[9c,d] of *cis*-2-alkyl-1-alkenylcyclobutane reverse ene reactions also have led to proposals of concerted mechanisms. The stereochemistry of the reverse ene reactions (see below) also supports this formulation.

The second group of processes in Table I consists of the pathways leading to the four minor products: the doubly epimerized cyclobutane **17b** and the three minor reverse products (*E*,*E*)-**18**, (*Z*,*Z*)-**18**, and (*Z*,*E*)-**18**. The rate constants for these reactions have large relative error limits, often between 25 and 100% of the observed values. In the case of the double epimerization reaction, the decrease in the fraction of the total product **17b** as the conversion of the reactant **16b** increases causes a large uncertainty in the rate constant. Thus, although 9–10% of the total product is **17b** after 3% conversion, only 4–5% of **17b** is present after 50% conversion, probably because of the secondary rearrangement of **17b**, which occurs (see below) with rate constants comparable to those of **16b**. The minor reverse ene products (*E*,*E*)-**18**, (*Z*,*Z*)-**18**, and (*Z*,*E*)-**18** are formed in very low concentrations, which approach the limits of detectability under our analytical conditions. Consequently, whether these are true primary products from **16b** cannot be determined from the product data.

Reaction from (1*SR*,2*SR*,1′*SR*)-*cis*-1-(1-Methoxyethyl)-2-vinylcyclobutane (17b). Tables IV–VI give the results on product distributions, rate constants for individual competing pathways, and activation parameters for the major pathways from **17** in the

Table V. Rate Constants for Product Formation in the Pyrolysis of **17b**

		k (×10^7 s)		
process	product(s)	T = 243.8 °C	T = 255.9 °C	T = 267.5 °C
fragmentation	**26 + 27**	14.3 ± 2.0	47.4 ± 4.0	138 ± 12
epimerization	**28 + 29**	10.3 ± 1.2	31.7 ± 2.6	89.3 ± 6.3
double epimerization	**17**	7.4 ± 4.7	15.4 ± 7.6	37 ± 22
1,3-rearrangement	**30 + 31**	3.98 ± 0.53	12.9 ± 0.9	35.2 ± 3.7
reverse ene	(*Z*,*Z*)-**18**	8.0 ± 1.1	23.3 ± 2.3	56.8 ± 3.9
reverse ene	(*Z*,*E*)-**18**	0.75 ± 0.77	2.26 ± 0.39	5.92 ± 0.94
reverse ene	(*E*,*Z*)-**18**	0.49 ± 0.38	0.83 ± 0.60	1.9 ± 1.7
reverse ene	(*E*,*E*)-**18**	0.14 ± 0.19	0.45 ± 0.41	0.93 ± 0.98

Table VI. Activation Parameters for Major Rearrangement Pathways of **17b**

process	product(s)	E_a (kcal/mol)	log A (A, s^{-1})	$\Delta S^{\ddagger}$ (gibbs/mol)
fragmentation	**26 + 27**	53.1 ± 4.0	16.6 ± 1.7	14.3 ± 7.7
epimerization	**28 + 29**	50.6 ± 3.6	15.4 ± 1.5	8.9 ± 6.7
1,3-rearrangement	**30 + 31**	51.1 ± 4.3	15.2 ± 1.8	7.9 ± 8.0
reverse ene	(*Z*,*Z*)-**18**	45.9 ± 4.0	13.3 ± 1.6	−0.8 ± 7.5

Table VII. Configuration of Product **18** Predicted from Three Reactants

		product[a]		
pathway		from **16b** (racemic)	from **17b** (racemic)	from **37** (1*R*,2*R*,1′*S*)
endo	1	2*E*,6*Z*	2*Z*,6*Z*	8*S*,2*E*,6*Z*
endo	2	2*E*,6*Z*	2*Z*,6*Z*	8*R*,2*E*,6*Z*
endo	3	2*Z*,6*Z*	2*E*,6*Z*	8*R*,2*Z*,6*Z*
endo	4	2*Z*,6*Z*	2*E*,6*Z*	8*S*,2*Z*,6*Z*
exo	5	2*E*,6*E*	2*Z*,6*E*	8*R*,2*E*,6*E*
exo	6	2*E*,6*E*	2*Z*,6*E*	8*S*,2*E*,6*E*
exo	7	2*Z*,6*E*	2*E*,6*E*	8*S*,2*Z*,6*E*
exo	8	2*Z*,6*E*	2*E*,6*E*	8*R*,2*Z*,6*E*

[a] Key: **16b**, R_1 = OMe, R_2 = CH_3, R_3 = H, R_4 = H; **17b**, R_1 = CH_3, R_2 = OMe, R_3 = H, R_4 = H; **37**, R_1 = OMe, R_2 = CH_3, R_3 = D, R_4 = CH_3.

same format as those given above in Table I–III for **16b**.

Stereochemistry of the Reverse Ene Reactions of 16b and 17b. Scheme VII shows the eight formally possible stereochemical pathways of bishomodienyl hydrogen shift in a *cis*-1-alkenyl-2-alkylcyclobutane. Sufficient labeling to define the result fully is to be imagined as potentially incorporable into the reactant structure. Table VII collects the predicted outcomes for the partially labeled racemic series **16b** and **17b** and also for the fully labeled optically active case **37** to be discussed later in this paper.

Scheme VII shows that there exist four pathways in which the conformation of the receptor alkenyl group is endo and four in which it is exo. In each series (endo and exo), two of the reactions are suprafacial and orbital-symmetry-allowed and two are antarafacial and orbital-symmetry-forbidden. Of course, the pathways differ markedly in their steric requirements. One suspects, for example, that geometrical difficulties may well be too great for the antarafacial or exo alkenyl pathways to occur concertedly.

In the reactions of a partially labeled substrate, e.g., **16b**, as Table VII shows, pathways 1 and 2 would give the same product, since the labeling necessary to distinguish them has not been incorporated. Were this product ((2*E*,6*Z*)-**18**) observed to be the dominant one, a surmise that it arose by pathway 1 rather than by pathway 2 would be justifiable on the above geometrical grounds; moreover, a test free of this assumption would be available from reactant **37**, which when enantiomercially enriched (say, 1*R*,2*R*,1′*S*) would be fully labeled and would give distinguishable products for pathways 1 and 2 (Table VII, 8*S*,2*E*,6*Z* and 8*R*,2*E*,6*Z*).

A comparison of the observed products (Tables I and IV) with those predicted for the eight reverse ene possibilities in each case (Table VII) suggests that **16b** and **17b** both undergo this reaction predominantly by the stereoelectronically preferred suprafacial pathway 1. Thus, (2*E*,6*Z*)-**18** constitutes 93.3% of the retro ene product from **16b**, and (2*Z*,6*Z*)-**18** accounts for 85.3% of that from **17b**. As we shall show, these are minimum values for the actual kinetic preferences, since the apparent shortfall from complete stereospecificity is largely the result of a side reaction (see below).

Formally, the major products also are compatible with the antarafacial pathway 2, as already stated, but this channel is not expected to contribute heavily. Direct experimental evidence against a dominant contribution from pathway 2 comes from the study (see below) of the fully labeled case.

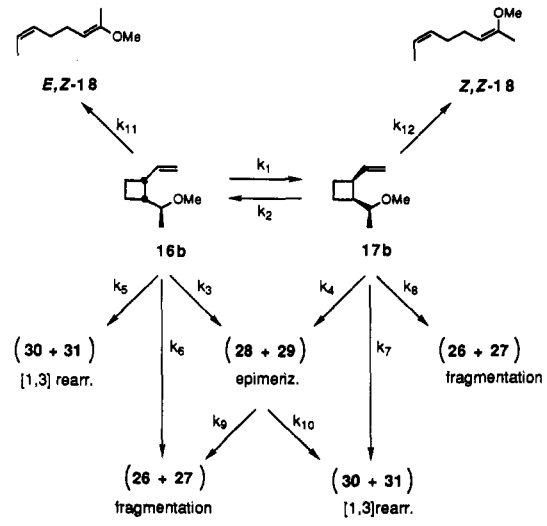
From both **16b** and **17b**, the second most prevalent of the reverse ene products is derived from one or both of the pathways 5 and 6, which have both the vinyl group and the breaking C–H bond formally exo (Scheme VII and Table VII). These are (2*E*,6*E*)-**18** from **16b** and (2*Z*,6*E*)-**18** from **17b**, which amount to about 5 and 8%, respectively, of the totals.

The next products in order of preference from both **16b** and **17b** are derived from pathways 3 and/or 4. Isomers (2*Z*,6*Z*)-**18** from **16b** and (2*E*,6*Z*)-**18** from **17b** amount to about 1 and 5%, respectively, of the total reverse ene product. Pathway 3 (Scheme VII) is the suprafacial allowed process with the endo vinyl geometry but inappropriate orbital overlap for stereoelectronic control. On the reasonable assumption of suprafacial pathways (1 rather than 2, and 3 rather than 4), the minimum preference for reverse ene product from the stereoelectronically favorable geometry to that from the unfavorable geometry in the endo vinyl manifold is ≥90:1 from **16b** and ≥85:5 from **17b**. The least favored products, formed in minute amounts, are those resulting from pathways 7 and/or 8. These are (2*Z*,6*E*)-**18** from **16b** and (2*E*,6*E*)-**18** from **17b**.

The correspondence between the diastereomeric reactants **16b** and **17b** in reactive distribution among the various pathways is remarkable and offers persuasive confirmation that the substituents act as stereochemical markers essentially free of differential steric or electronic perturbation.

If the endo/exo preference is taken as an (crude) indicator of the ratio of concerted to nonconcerted reaction,[10] a cyclopropane ring provides a much larger benefit of concert in the reverse ene reaction than does a cyclobutane. Expressed as differences in free energy of activation $\Delta\Delta G^{\ddagger}$, the kinetic preference for endo is about

Scheme VIII



3 kcal/mol from **16b** and about 2.5 kcal/mol from **17b**. These values are far less than the $\Delta\Delta G^{\ddagger} \geq 12$ kcal/mol for the cyclopropanes. This result is consistent with the higher activation energies of the cyclobutane reverse ene reactions (**16b**, $E_a = 42.4 \pm 2.3$ kcal/mol, Table III; and **17b**, $E_a = 45.9 \pm 4.0$ kcal/mol, Table VI), as compared to the cyclopropane analogues (e.g., *cis*-1,1-dimethyl-2-vinylcyclopropane,[10] $E_a = 33.5$ kcal/mol; and *cis*-2-(2-propyl)-1(*E*)-propenylcyclopropane,[3] $E_a = 35.5$ kcal/mol). This rate effect strikingly resembles the cyclopropane–cyclobutane comparison in the thermal cycloreversions of the diazenes **1** and **2**.[1]

Simulation of the Kinetics of the Pyrolysis of 16b and 17b. As Scheme VI shows, the double epimerization at the ring stereogenic centers causes diastereomeric interconversion of reactants **16b** and **17b**. Since the rates of reverse ene reaction in the pyrolyses of the two diastereomers are comparable, it must be the case that some of the product in the pyrolysis of **16b** actually arises from **17b** and vice versa. Therefore, the actual product distributions in the reverse ene reactions of mechanistic interest here will be affected by the concurrent double epimerization. The problem can compromise the mechanistic analysis seriously, because as Table VII shows the major product, which is derived by pathway 1 from one diastereomer, is identical with the product derived by pathway 3 from the other diastereoisomer. The ratio of rates of pathways 1 and 3 gives the kinetic preference for the stereoelectronically favored one of the pair of suprafacial orbital-symmetry-allowed reverse ene reactions. If a significant portion of the "pathway 3" product actually arises by the indirect mechanism of double epimerization to diastereomeric reactant followed by pathway 1 reverse ene, the observed uncorrected product ratio would give too low a measure of the true value of the stereospecificity of interest. We need to know the relative rates of formation of the reverse ene products from the individual diastereomeric reactants.

One way to obtain this information would be to inspect the product mixture at very low conversion. If the double epimerization is slow enough, the ratios then will be good approximations to the true reverse ene kinetic competition ratios. However, this procedure is impractical in the present cases, because the reverse ene product only amounts to about 20–25% of the total and the problem of instrumental dynamic range then leads to substantial analytical uncertainty in the determination of the minor components.

A better approach is to simulate the entire time–concentration profile of each reactant, with use of estimated rate constants for the individual steps. Scheme VIII shows the mechanism upon which the simulation is based. The rate constants listed in Table VIII reproduce the concentration–time profile of the five major products from each reactant **16b** and **17b** to within 2.6–4.1% relative deviation, which is about the accuracy of the experimental

Table VIII. Simulational and Experimental Rate Constants for the Rearrangements of **16b** and **17b** at 243.8 °C

rate constant	reaction	k ($\times 10^7$ s) simulational	experimental
k_1	**16** → **17**	2.95	2.88
k_2	**17** → **16**	6.38	7.4
k_3	**16** → **28** + **29**	10.8	10.4
k_4	**17** → **28** + **29**	10.9	10.3
$k_5 + k_6$	**16** → **26** + **27** + **30** + **31**	18.8	18.3
$k_7 + k_8$	**17** → **26** + **27** + **30** + **31**	20.9	18.3
$k_9 + k_{10}$	**28** + **29** → **26** + **27** + **30** + **31**	2.80	
k_{11}	**16** → (2*E*,6*Z*)-**18**	9.38	9.38
k_{12}	**17** → (2*Z*,6*Z*)-**18**	8.03	8.0

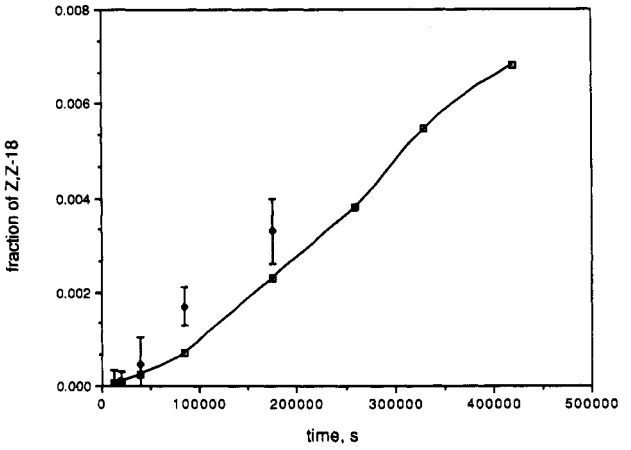


Figure 1. Fraction of stereoelectronically unfavorable reverse ene product (*Z*,*Z*)-**18** in the pyrolysis of **16b** at 243.8 °C. The curve connects values calculated from simulation based on the rate constants listed in Table VIII. The experimental points are shown with error bars.

GC data themselves. Note that the values of the derived rate constants are, in most cases, close to those obtained experimentally in Tables II and V, as necessarily must be the case if the earlier conclusion of irreversible reactions leading to stable products is justified. The only exceptions to this generalization are the derived rate constants k_9 and k_{10}, which characterize the fragmentation and sigmatropic 1,3-rearrangement of the singly epimerized cyclobutanes **28** and **29**. We had to assign a small but nonzero value for (the sum of) these in order to fit the product data.

The mechanism of the double epimerization merits a brief comment. Scheme VIII shows this as a direct pathway, presumably via a transition state or biradical intermediate in which the cyclobutane ring bond between the substituents is largely or completely broken. A readily conceivable alternative mechanism would be two sequential single epimerizations (**16b** → **28** (or **29**) → **17b**). If a biradical is imagined on this pathway, it must be one that cyclizes faster than it suffers internal rotations and hence can furnish the double epimerization product only by way of the stable singly epimerized trans 1,2-disubstituted cyclobutane.[20] The mechanism of Scheme VIII is converted into this alternative by deleting the steps associated with k_1 and k_2 and by making the steps associated with k_3 and k_4 reversible. We were unable to find a set of rate constants to fit the experimental product data to this alternative mechanism.

That most of the stereoelectronically unfavorable minor reverse ene product (2*Z*,6*Z*)-**18** in the pyrolysis of **16b** comes by the sequential mechanism is shown by a comparison of the observed values with those calculated from Scheme VIII (Figure 1). The excess of (2*Z*,6*Z*)-**18** over that calculated is barely outside experimental error. Within the endo manifold, therefore, the actual stereospecificity of rearrangement is considerably higher than that implied by the raw product comparison. Correcting for the amount of (2*Z*,6*Z*)-**18** formed by the sequential pathway, the ratio of (2*E*,6*Z*)-**18** to (2*Z*,6*Z*)-**18** formed *directly from* ***16b*** is about

(20) For an example of this mechanism in a cyclopropane derivative, see: Berson, J. A.; Balquist, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 7343.

Scheme IX

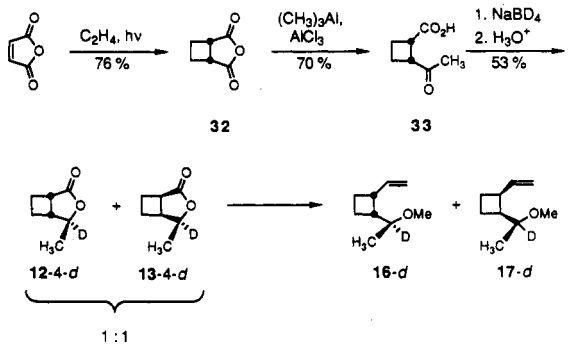


Table IX. Isotope Effects on the Pyrolyses of **16b**-*d* and **17b**-*d* at 243.8 °C

process	**16b**-*d* k_H/k_D	**16b**-*d* $\Delta\Delta G^{\ddagger}$ [a]	**17b**-*d* k_H/k_D	**17b**-*d* $\Delta\Delta G^{\ddagger}$ [a]
overall	1.14 ± 0.07	135 ± 64	1.19 ± 0.07	180 ± 60
fragmentation	1.02 ± 0.13	20 ± 120	1.08 ± 0.28	80 ± 240
epimerization	1.01 ± 0.14	10 ± 120	1.08 ± 0.28	80 ± 240
1,3-rearrangement	1.02 ± 0.14	20 ± 125	1.14 ± 0.33	180 ± 120
reverse ene reaction	2.58 ± 0.31	980 ± 125	5.5 ± 1.5	1762 ± 290

[a] $\Delta G_D^{\ddagger} - \Delta G_H^{\ddagger}$ (cal/mol). The deviations are not symmetrically located about the given value of $\Delta\Delta G^{\ddagger}$. The deviation given here is the average of the two.

220:1. Similarly, in the other diastereomeric series, at least half of the minor product (2*E*,6*Z*)-**18** from **17b** comes from the indirect mechanism, recognition of which leads to a corrected ratio of (2*Z*,6*Z*)-**18** to (2*E*,6*Z*)-**18** formed *directly from* ***17*** of about 35:1.

To summarize the complex behavior of the partially labeled reactants **16b** and **17b**, we note that the dominant processes in their pyrolysis are fragmentation, single and double epimerization, sigmatropic carbon 1,3-rearrangement, and reverse ene reaction. The principal reverse ene reaction in both cases, whether or not it is concerted, enjoys little energetic benefit relative to competing reactions that are plausibly regarded as stepwise. When compared to the reverse ene reactions by the exo vinyl route, whose products have the 6*E* configuration ((2*E*,6*E*)- and (2*Z*,6*E*)-**18**, Table VII), the major component of the reverse ene reaction (**16b** → (2*E*,6*Z*)-**18**, **17b** → (2*Z*,6*Z*)-**18**) is favored only by $\Delta\Delta G^{\ddagger} \approx$ 2.5–3.0 kcal/mol.

Despite the small energetic benefit, the reverse ene reaction in both diasteromeric cyclobutanes **16b** and **17b** is highly stereospecific. Within the endo manifold leading to reverse ene products of 6*Z* configuration, the reaction is stereospecific to the extent of 95.8% from one diastereomer (**17b**) and 98.5% from the other (**16b**), these values being the averages for the three temperatures of observation.

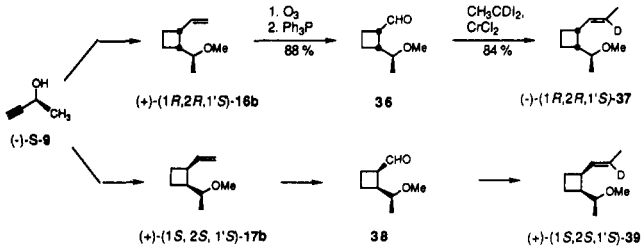
Kinetic Isotope Effects. In their study of the dienyl hydrogen shift of (*Z*)-1,3-pentadiene and its *1,1-d*$_2$ and *5,5,5-d*$_3$ isotopomers, Roth and König[21] found a primary kinetic isotope effect k_H/k_D = 4.96 at 473 K, corresponding to $\Delta\Delta G^{\ddagger}$ = 1514 cal/mol and to a value $k_H/k_D \approx 13$ at 298 K. These values are at the high edge or even beyond the suggested limits for a semiclassical isotope effect,[22] and although they concluded merely that this indicated a highly symmetrical transition state the observations set off a lively discussion of the actual geometry of the transition state and of the possible contribution of quantum mechanical tunneling to the mechanism.[23-33] To determine whether a large primary isotope

(21) (a) Roth, W. R.; König, J. *Justus Liebigs Ann. Chem.* **1966**, *699*, 24. (b) They report $k_H = 2.8 \times 10^{11}$ exp(−36.3 kcal/mol/*RT*) s^{-1}, but a plot of ln k vs T^{-1} with their data gives $k_H = 2.2 \times 10^{11}$ exp(−37.7 kcal/mol/*RT*). The latter value now may be used with their value for $k_D = 2.4 \times 10^{11}$ exp(−37.7 kcal/mol/*RT*) to give $k_H/k_D = 0.94$ exp (1.6 kcal/mol/*RT*), from which $k_H/k_D = 4.96$ at 473 K and $\Delta\Delta G^{\ddagger} = 3484$ cal/mol may be calculated.

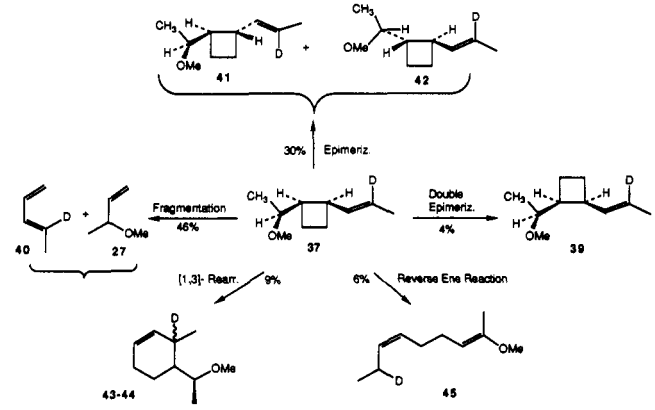
(22) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951.

(23) (a) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall: London, 1980; Chapter 4. (b) For a review, see: Getty, S. J. Ph.D. Dissertation, Yale University, New Haven, CT, 1990, p 19 ff.

Scheme X



Scheme XI



effect also prevails in a homodienyl hydrogen shift, we have studied the pyrolyses of the deuterium-labeled substrates (1*RS*,2*RS*,1'*SR*)-1-(1-methoxyethyl-*1-d*)-2-vinylcyclobutane (**16b**-*d*) and (1*SR*,2*SR*,1'*SR*)-1-(1-methoxyethyl-*1-d*)-2-vinylcyclobutane (**17b**-*d*). Scheme IX shows the synthesis of the diastereomeric substrates via the deuteriated bicyclic lactones **12**-*4-d* and **13**-*4-d*, which were converted to **16b**-*d* and **17b**-*d* by procedures already described in Scheme III.

The values of k_H/k_D for overall disappearance of the two substrates at 243.8 °C (516.8 K) and for the individual processes—fragmentation, epimerization, sigmatropic 1,3-rearrangement, and reverse ene reaction—are listed in Table IX. Because of the additional experimental errors associated with analysis for product components, the individual k_H/k_D values are less accurate than the overall k_H/k_D.

The k_H/k_D values for fragmentation, epimerization, and sigmatropic 1,3-rearrangement are near unity, as would be expected for secondary β-deuterium kinetic isotope effects on thermal bond-breaking reactions.[34-37] Expressed as $\Delta\Delta G^{\ddagger}$ values so as to minimize temperature influences, the present secondary isotope effects and those from the literature cluster around an average value of 60 ± 40 (cal/mol)/D atom.

For the reverse ene reactions (Table IX), where C–H(D) bond breaking is involved, the k_H/k_D values measure primary isotope effects and, as expected, are much larger. The $\Delta\Delta G^{\ddagger}$ values 980 and 1762 cal/mol, respectively, for **16b**-*d* and **17b**-*d* bracket the 1514 cal/mol value observed for the dienyl hydrogen shift by Roth and König.[21] Pending theoretical agreement on the interpretation of the isotope effect in the dienyl shift itself,[23-33] we offer only the comment that, within the rather loose limits of our experimental data, the primary isotope effects are similar in the homodienyl and dienyl shifts and consistent with mechanistic similarity of the two processes.

Synthesis of the Enantiomerically Enriched Fully Labeled (−)-(1*R*,2*R*,1'*S*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)-cyclobutane Reactant 37 and Its Racemate (Scheme X). Originally, we had planned to extend the synthesis of Scheme III to *E* alkene **37** of the fully labeled series by carrying out the appropriate Schlosser–Wittig reactions on the lactols **14** and **15**. We anticipated that a *Z* propenyl group would be of little value in our studies of the reverse ene reaction, so that the finding that the Schlosser–Wittig reactions gave only about a 3:1 *E*:*Z* selectivity was discouraging, as were the merely moderate chemical yields.

A more effective alternative procedure is outlined in Scheme X in which the key starting material is the vinyl compound **16b**, which already has served as a reactant in our studies of the reverse ene reaction in the partially labeled series. Since 3-butyn-2-ol, the starting material for **16b** (Scheme III), is readily available in enantiomerically enriched form,[14] the only remaining task was the conversion of the vinyl group of **16b** to the deuteriated propenyl group of **37**. This was achieved by synthesis of **16b** from both racemic **9** and from enantiomerically enriched (−)-**9**, by ozonolysis of **16b** to the aldehyde **36** followed by application of the highly *E* configurationally specific olefination of Okazoe, Takai, and Utimoto.[22] The desired *E* alkene **37** was obtained in high yield in a 19.5:1 ratio to its *Z* isomer. A small amount (1.7%) of epimerized trans *E* isomer also was observed. Similarly, the diastereomeric vinyl compound **17b** was converted to *E* alkene **39**, albeit with a somewhat lower selectivity (5.3:1).

Configuration and Enantiomeric Purity of the Propenyl Compounds 37 and 39. The absolute configuration of the derived alkenes **37** and **39** in the optically active series follows from that of the synthetic starting material (−)-(*S*)-3-butyn-2-ol (**9**), whose configuration had been correlated[37,38] with those of several reference compounds. The ee values of **37** and **39** are implied by the syntheses but also can be determined directly for **39**. The maximum reported rotation for 3-butyn-2-ol (**9**) is $[\alpha]_D$ −51.8° (*c* (dioxane)).[40] If this represents 100% ee, our starting sample of **9** ($[\alpha]_D$ −48.2 ± 0.4° (*c* 7.475 (dioxane))) and presumably the alkenes **16b** and **37** derived as in Scheme X have 93.1 ± 0.8% ee. This value for the starting **9** sample was confirmed via the Mosher's esters[41] (prepared from **9** and enantiomerically pure (+)-(*R*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid) by ^{1}H NMR integration of the diastereotopic acetylenic protons and also by capillary GC analysis on an achiral column. Moreover, direct analysis of the samples of (+)-**17b** and (+)-**39** by enantiospecific capillary GC with a bis(3-(heptafluorobutyryl)-1(*R*)-camphorato)nickel column[42] showed them to have 92.9 ± 1.7 and 93.4 ± 0.5% ee, respectively. The enantiospecific column failed to resolve **16b** or **37**, but since the results with the diastereomeric counterparts **17b** and **39** clearly establish the complete preservation of ee in the sequence **9** → **17b** → **39** we assume the same applies

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(37) Although secondary β-deuterium isotope effects on solvolysis reactions have not been included in this survey because of the potential complications of solvation, in fact the average and spread of their values do not differ greatly from those of the thermal reactions.
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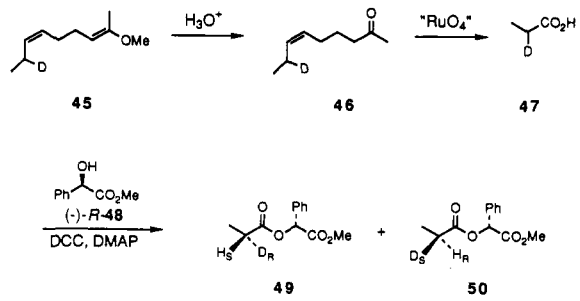
Scheme XII



to the sequence **9** → **16b** → **37**. For later calculations, we assign the weighted mean of the ee values of **17b** and **39** (93.2 ± 1.1%) to alkenes **16b** and **37**. The analytical data on the sample of (−)-(1*R*,2*R*,1′*S*)-**37** used in the subsequent pyrolysis study are isomeric purity, 99.4 ± 0.2%; deuterium incorporation, 96.6 ± 0.6%; and ee, 93.2 ± 1.1%.

Pyrolysis of Racemic Propenyl Substrate 37-*d*. This material disappeared with a rate constant of 2.9×10^{-6} s^{-1} when heated in the gas phase (soda ash lead glass ampules) at 239 °C. As in the cases of the two vinyl analogues **16b** and **17b**, the pyrolysis leads to a mixture of products (Scheme XI). Details of the isolation and identification of these products are given in the Experimental Section and in the supplementary material.

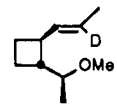
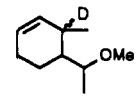
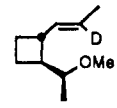
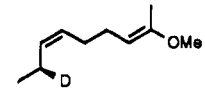
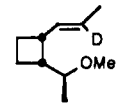
Qualitatively, the pathways for disposal of racemic **37** resemble those of the vinyl analogues **16b** and **17b**. However, it is immediately apparent from Scheme XI that the crucial experiment on the stereochemistry of the reverse ene reaction will be more difficult in the case of the propenyl substrate **37**, since this compound gives only 6% of reverse ene product, in contrast to the ~20% obtained from **16b** and **17b**. Evidently, the propenyl methyl group of **37** selectively retards the reverse ene process relative to the competing reactions. Nevertheless, of this 6% of reverse ene product, the principal component was (2*E*,6*Z*)-2-methoxynona-2,6-diene (**45**), the isomer expected from the overlap-favored pathway 1 (Scheme VII (endo)) already shown to predominate in the pyrolysis of the vinyl analogue **16b**. Preparative GC was not applicable, because the sensitive enol ether decomposed during the procedure. The reverse ene product was isolated by column chromatography on basic alumina. Its olefinic bond configurations were established by NOE experiments described in the Experimental Section.

Analytical Scheme for Determining the Enantiomeric Configuration of the Deuterium-Labeled Carbon of Product Diene 45 (Scheme XII). The objective is to convert the enol ether product **45** to a form in which the two enantiotopic hydrogens at the C_8 stereogenic center become diastereotopic and hence distinguishable by NMR spectroscopy. After hydrolysis of **45** to ketone **46**, a procedure similar to that used in the companion paper[3] was applied. Ruthenium tetroxide oxidation of **46** gave propionic acid-2-*d* (**47**), which was esterified with enantiomerically homogeneous (−)-(*R*)-methyl mandelate (**48**) to give a mixture of diastereomeric esters **49** and **50**. Control experiments in the racemic series show that the formation of the mandelate ester occurs without stereoisomeric fractionation.

Pyrolysis of Enantiomerically Enriched (−)-(1*R*,2*R*,1′*S*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-2-*d*)cyclobutane ((−)-(1*R*,2*R*,1′*S*)-37). This reaction was carried out at 512.5 K for 138 h, approximately 1.9 half-lives, exactly as in the case of the racemic compound already described. The pyrolysate was chromatographed on basic alumina, as before, to effect concentration of the enol ether products in a fraction whose composition was determined by analytical capillary GC prior to hydrolysis and is reported in Table X.

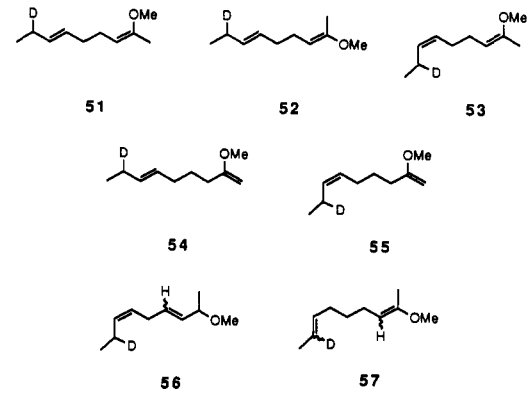
The ^1H NMR spectrum of the enol ether component of this fraction was identical with that obtained for the corresponding product in the pyrolysis of the racemic substrate **37**. The material labeled "other" in Table X consisted of five minor products having concentrations 2.2, 1.0, 1.9, 1.4, and 1.8% of the fraction. Since the amount of enol ether formed in the pyrolysis is only 6% of the total product, these "other" components were tiny fractions (0.06–0.12%) of the total and could not be isolated or characterized. Their GC retention times plausibly permit them to be isomeric with the principal reverse ene product **45**. Some of the possible structures are shown as **51**–**57** (Scheme XIII).

Table X. Composition of Enol Ether Fraction of Pyrolysate from Optically Active **37**, After Column Chromatography

component	relative concentration (%)	component	relative concentration (%)
 **41**	39.2	 **43/44**	20.0
 **42**	2.2	 **(8*S*)-45**	28.9
 (1*R*,2*R*,1′*S*)-**37**	0.7	other	8.9[a]

[a] This fraction consisted of five minor products whose percentages of the enol ether fraction were 2.2, 1.0, 1.9, 1.4, and 1.8%.

Scheme XIII

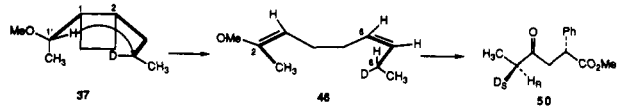


The identity of these contaminants is of concern, since any of the enol ether isomers sharing the 6*Z* configuration with **45** will be hydrolyzed to the same ketone **46**. Consequently, any 6*Z* stereoisomer will be carried along in the subsequent degradation and esterification reactions of Scheme XII, and its stereogenicity will influence the measured stereogenicity transfer for the principal reverse ene reaction. The isomers (2*Z*,6*Z*)-2-methoxynona-2,6-diene (**53**) and (6*Z*)-2-methoxynona-1,6-diene-8-*d* (**55**) would be especially significant in this connection. We estimated the minimum isomeric purity of the (2*E*,6*Z*)-**45** isolated from the pyrolysate by assuming that the two most concentrated contaminants in the "other" category (Table X) are the 6*Z* enol ethers **53** and **55**. The minimum isomeric purity of enol ether **45** with respect to a mixture of **45**, **53**, and **55** is given by 100 × 28.9/(28.9 + 2.2 + 1.9) = 87.6%.

Regardless of the exact identity of the minor isomers, the stereospecificity demonstrated in the reverse ene reactions of the partially labeled substrates **16b** and **17b** with a vinyl receptor group persists in the case of the fully labeled system **37** with a propenyl group. From the latter, the principal reverse ene product is preferred over the next most favorable stereoisomer by at least 28.9:2.2, or ≥13.1, corresponding to stereospecifity of ≥93%.

We then applied the degradative sequence of Scheme XII to the fraction containing the enol ether **45**. Hydrolysis gave the methyl ketone **46**, which was purified to ≥99.3% isomeric purity. Completion of the scheme gave the diastereomeric mixture of

Scheme XIV



esters **49** and **50**, which were analyzed by integration of the H_S (δ 2.19) and H_R (δ 2.07) regions of both the ^1H and ^2H NMR spectra. These values, corrected for the level of deuteration of the starting substrate **37** (see supplementary material), indicated the H_R, D_S configuration **50** of the propionyl methyl mandelate to be the dominant one (Scheme XIV). The transfer of stereogenicity measured by the ^1H and ^2H NMR analyses was ≥69 ± 5 and ≥81 ± 3%, respectively.

Superficially, these results appear to indicate a lower degree of stereospecificity at the terminus of migration than at the donor-derived double bond. However, there are strong reasons to believe that the true stereospecificity at the migration terminus actually is higher than that given by the analytical results.

One factor tending to diminish the observed specificities below the true values is the presence in the enol ether product fraction of the minor contaminants mentioned above. A small portion of the reverse ene process may occur by the equivalent of the stereoelectronically unfavorable pathway 3 of Scheme VII (endo), perhaps by a biradical mechanism. The product of such a reaction would be enol ether (8*R*,2*Z*,6*Z*)-2-methoxy-2,6-nonadiene ((8*R*)-**53**), and the apparent ee of the major enol ether product (8*S*)-**45** would be diminished by twice the amount of the contamination by (8*R*)-**53**. For this and other reasons described in the supplementary material, such contamination might lower true specificity values of 93 or 100%, as measured by ^1H and ^2H NMR, respectively, to those lower values observed. It is also possible to rationalize observed specificities higher than the true values, but these true values (65 and 77%) would not differ greatly from the observed ones.

Moreover, a strong presumptive contributor to artificially low observed specificities is the double epimerization **37** → **39** (Scheme XI). Although the amount of reverse ene product in the propenyl system **37** is too small to permit a reliable kinetic simulation, such a procedure is feasible in the case of the unlabeled vinyl substrate **16b** and provides direct evidence of double epimerization. As has been described, the double epimerization mechanism accounts for most or all of the 2*Z*,6*Z* minor pyrolysis product formed there. Therefore, in the fully labeled propenyl series **37**, formation of enol ether product from the doubly epimeric cyclobutane **39** also seems highly likely. Pathway 1 reverse ene reaction of **39** again would lead to 2*Z*,6*Z* enol ether product **53** with the 8*R* configuration.

The stereogenicity transfer to the migration terminus in the fully labeled propenyl experiments, although only semiquantitatively specifiable for these reasons, does show that the hydrogen shift is predominantly suprafacial. In combination with the stereochemistry of the donor-derived double bond, which can be specified with much higher accuracy (as >13:1), it leaves no doubt that the overlap-favored transition state is preferred by a substantial margin.

Conclusions

All of the studies reported here suggest a concerted mechanism for the major pathway in thermal reverse ene reactions of cyclobutane derivatives. This interpretation agrees with that favored by other researchers[9c,d] who applied different experimental criteria to related substrates.

The partially labeled cyclobutanes we have studied undergo the reverse ene reaction with high stereospecificity in the partially labeled series. Cyclobutane **16b** gives (2*E*,6*Z*)-**18** with an average (of measurements at three temperatures) 18:1 stereospecificity (95%) relative to the next most prevalent stereoisomer (2*E*,6*E*)-**18**. Similarly, cyclobutane **17b** gives (2*Z*,6*Z*)-**18** with an average 10:1 stereospecificity (91%) over (2*Z*,6*E*)-**18**. If, as seems likely, the minor products with the 6*E* configuration arise from a nonconcerted process, then the stereospecificity of the potentially concerted portion, leading to products of the 6*Z* configuration, is even higher: 68:1 (99%) (*E*,*Z*)-**18**:(*Z*,*Z*)-**18** (Table II) from **16b** and 25:1 (96%) (*Z*,*Z*)-**18**:(*E*,*Z*)-**18** (Table IV) from **17b**. Also, since the amount of minor 6*Z* isomer in each case can be accounted for largely by the indirect mechanism of double epimerization followed by reverse ene reaction of the derived diastereomeric cyclobutane, these higher values in turn are minimum measures of the true stereospecificities.

In the rearrangement of the fully labeled, enantiomerically enriched compound **37**, the stereospecificity with respect to olefinic configuration of the reverse ene product persists. The principal reverse ene product (2*E*,6*Z*)-**45** prevails over the next most prominent one by >13:1, a stereospecificity of >93%. Moreover, this specificity of olefinic configuration is linked with stereospecific creation of the carbon stereogenic center. The stereoelectronically favored pathway 1 (Scheme VII) for the hydrogen shift dominates.

Of course, none of this definitively *proves* that the pathway 1 reverse ene reactions of our cyclobutanes are not stepwise processes with discrete biradical intermediates. However, several ad hoc postulates about the behavior of biradicals then would be required to explain the stereochemical results, and unless independent reasons for them can be brought forward the concerted pathway must be favored on grounds of mechanistic economy.

Certainly, the energetic benefit of concert in the reverse ene reaction of these cyclobutanes must be small relative to competing probably nonconcerted processes. For example, pathway 1 reverse ene reaction in **16b** and **17b** is favored by only $\Delta\Delta G^{\ddagger}$ = 4–6 kcal/mol relative to epimerization of the cyclobutane ring substituents and by 2.4–3.1 kcal/mol relative to exo vinyl pathways leading to 6*E* product stereochemistry. Nevertheless, the stereospecificity of the reverse ene process remains high, like that of the cyclopropane system,[3] where the energetic benefit of concert is far more evident.

Stereochemical predictions based on orbital symmetry and orbital overlap considerations take on special significance in cases where energetic probes of mechanism are not readily applicable. When there is little energetic discrimination between concerted and stepwise reactions, stereospecificity may provide the most satisfactory test.

Experimental Section

Some common general procedures are described in ref 3b. Details of GC analyses and kinetic procedures are given in the supplementary material to the present paper and full details of all procedures and characterizations are given in ref 43.

Synthesis of 16b and 17b (Schemes III and X). Resolution of 3-Butyn-2-ol (9) was achieved by the method of Horeau and co-workers.[14] $[\alpha]_D$ −48.2 ± 0.4° (*c* 7.475 (1,4-dioxane)) (lit.[38a,39] $[\alpha]_D$ −51.8° (*c* 3.8 (dioxane)). The optical purity of this material was determined by methods described in the supplementary material.

4-Hydroxypent-2-ynoic Acid (10). This compound was prepared via the procedure of Vigneron and Bloy.[38a] The ^1H NMR and IR of **10** correspond to those reported by Schlessinger.[44]

The above procedure was repeated, with use of (−)-(*S*)-3-butyn-2-ol (**9**) as the substrate. In this manner, 5.8 g (82 mmol) of *S*-(−)-**9** was metalated and the resulting lithium acetylide was quenched with carbon dioxide to give upon workup approximately 3.5 g (30 mmol, 37%) of the optically active hydroxy acid *S*-**10**.

5-Methyl-2(5*H*)-furanone (11). The crude hydroxy acid **10** was hydrogenated under Lindlar conditions via the procedure of Schlessinger and co-workers,[44] although in our hands the reaction proved capricious. The ^1H NMR and GC/MS of the product **11** agreed with those obtained by Schlessinger.[44]

(+)-(*S*)-5-Methyl-2(5*H*)-furanone (11). The Lindlar hydrogenation described above was repeated with use of (−)-(*S*)-**10** as the substrate. Thus, hydrogenation of 5.5 g (49 mmol) of crude (*S*)-**10** led to the isolation of 1.44 g (14.7 mmol, 30%) of (+)-(*S*)-**11**, $[\alpha]_D$ + 109.4 ± 1.1° (*c* 1.440 ($CHCl_3$)) (lit.[45] $[\alpha]_D$ −107° for enantiomer (*c* 1.61 ($CHCl_3$))).

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(45) Chen, S.-Y.; Joullié, M. M. *J. Org. Chem.* **1984**, *49*, 2168.

The bicyclic lactones 12 and 13 were prepared by two procedures: Method A was a variation of that reported by Kosugi and co-workers.[15] Method B started with the photoadduct of maleic anhydride and ethylene,[46] which was treated with $AlCl_3$ and $(CH_3)_3Al$ to give *cis*-2-acetylcyclobutanecarboxylic acid. The latter gave **12** and **13** upon reduction with $NaBH_4$.

Method A. *exo*-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-one (12) and *endo*-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-one (13). This procedure is a variation on that described by Kosugi and co-workers.[15] The use of Vycor-filtered light, rather than irradiation through quartz alone, led to considerably higher yields than those reported by these researchers.

Capillary GC analysis (column A) indicated a 1.71:1 ratio of exo methyl to endo methyl diastereomers. For practical reasons, this mixture was generally used without further purification in the subsequent reaction. However, the mixture of diastereomers could be separated by preparative GC to give *exo*-4-methyl-3-oxabicyclo[3.2.0]heptan-2-one (**12**) and *endo*-4-methyl-3-oxabicyclo[3.2.0]heptan-2-one (**13**). The ^1H NMR spectra of the separated diastereomers agreed with those reported by Kosugi.[15]

Method B. 3-Oxabicyclo[3.2.0]heptan-2,4-dione [4462-96-8]. The procedure for the photocycloaddition of ethylene to maleic anhydride was a modification of the method used by Owsley and Bloomfield,[45] both in the required time for photolysis and in the yield. The principle changes are the use of Vycor-filtered rather than Pyrex-filtered light and the omission of acetophenone as an additional photosensitizer. The crude photolysate was recrystallized once from anhydrous ether to give 4.16 g (33.0 mmol, 76.5%) of the desired anhydride. ^1H NMR (250 MHz, $CDCl_3$): δ 3.60–3.44 (m, 2 H, C_1, C_2), 2.88–2.61 (m, 2 H, C_3, C_4), 2.53–2.29 (m, 2 H, C_3, C_4). GC/MS (20 eV): *m/e* 82 (19, $-CO_2$), 54 (100, $-C_2O_3$).

Method B (Continued). *cis*-2-Actylcyclobutanecarboxylic Acid. A 250-mL three-necked round-bottomed flask was equipped with a mechanical stirrer and a reflux condenser. The above bicyclic anhydride (4.16 g, 33.0 mmol) was transferred into the flask and taken up in 45 mL of dichloromethane. The solvent was refluxed for a few minutes to dissolve all of the solid and then allowed to cool to room temperature. Aluminum chloride (4.61 g, 34.6 mmol) was added, and the resulting suspension was cooled to 0 °C on an ice bath. A solution of trimethylaluminum (2.0 M, 8.3 mL, 16.6 mmol) in toluene was added dropwise over 30 min and the resulting mixture stirred at 0 °C for 4 h. The reaction was quenched by the slow, dropwise addition of 10 mL of H_2O. The resulting gelatinous mass was diluted with H_2O (200 mL), acidified to pH 1 (concentrated HCl), and extracted continuously with ether for 16 h. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give approximately 3.3 g (23 mmol, 70%) of the crude keto acid. ^1H NMR (250 MHz, $CDCl_3$): δ 3.57–3.31 (m, 2 H, C_1, C_2), 2.44–2.01 (m, 4 H, C_3, C_4), 2.11 (s, 3 H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 208.3 (s, ketone C=O), 189.5 (s, acid C=O), 47.7 (d, C_2), 40.6 (d, C_1), 27.8 (q, CH_3), 21.5 (t, C_3 or C_4), 21.2 (t, C_4 or C_3). GC/MS (70 eV): *m/e* 142 (16, M^+), 127 (26, $-CH_3$), 124 (28, $-H_2O$), 99 (77, $-C_2H_3O$), 86 (24, $-C_3H_4O$), 84 (38, $-C_3H_6O$), 82 (46, $-C_2H_4O_2$), 81 (33, $-C_2H_5O_2$), 71 (23, $-C_3H_3O_2$), 55 (35, $-C_4H_7O_2$), 54 (54, $-C_4H_8O_2$), 53 (24, $-C_4H_9O_2$), 43 (100, $-C_5H_7O_2$).

Method B (Continued). A solution of crude *cis*-2-acetylcyclobutanecarboxylic acid (3.97 g, 27.9 mmol) in anhydrous methanol (55 mL) was transferred to a 250-mL round-bottom flask equipped with a magnetic stirbar. The solution was cooled to 0 °C, and solid sodium borohydride (4.24 g, 112 mmol) was added slowly over 20 min. The resulting solution was warmed to room temperature and allowed to stir for 8 h. The methanolic solution was then diluted with 200 mL of water, acidified to pH 3 (concentrated HCl), and extracted with ether (8 × 50 mL). The ether extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed on silica gel as described above, to give 1.88 g (14.9 mmol, 53.4%) of an approximately 1:1 mixture of the diastereomeric exo and *endo* methyllactones.

Data for *exo*-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-one (12). ^1H NMR (250 MHz, $CDCl_3$): δ 4.51 (qd, 1 H, J = 6.4, 0.9 Hz, C_4), 3.14 (m, 1 H, C_1), 2.76 (m, 1 H, C_5), 2.59–2.25 (m, 2 H, C_6 and/or C_7), 2.19–2.04 (m, 2 H, C_7 and/or C_6), 1.24 (d, 3 H, J = 6.5 Hz, CH_3). NOE experiments: δ 4.51 saturated, 2.76 enhanced (1.8), 1.24 enhanced (1.6); 2.76 saturated, 4.51 enhanced (−0.2), 1.24 enhanced (0.9); 1.24 saturated, 4.51 enhanced (2.5), 2.76 enhanced (1.8). GC/MS (20 eV): *m/e* 126 (8, M), 111 (22, $-CH_3$), 83 (15, $-C_2H_3O$), 82 (6, $-CO_2$), 81 (9, $-CHO_2$), 67 (100, $-C_2H_3O_2$), 54 (30, $-C_3H_4O_2$).

Data for *endo*-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-one (13). ^1H NMR (250 MHz, $CDCl_3$): δ 4.60 (qd, 1 H, J = 6.4, 5.2 Hz, C_4), 3.17–3.02 (m, 2 H, C_1, C_5), 2.54–2.20 (m, 2 H, C_6 and/or C_7), 2.08–1.93 (m, 2 H, C_7 and/or C_6), 1.32 (d, 3 H, J = 6.4 Hz, CH_3). GC/MS (20 eV): *m/e* 126 (6), 111 (3), 83 (7), 82 (10), 81 (9), 67 (100), 54 (41). NOE experiments: δ 4.60 saturated, 3.17–3.02 enhanced (5.3),[46] 1.32 enhanced (1.4); 3.17–3.02 saturated, 4.60 enhanced (2.9), 1.32 enhanced (0.3); 1.32 saturated, 4.60 enhanced (1.3).

***exo*-(+)-(1*S*,4*S*,5*R*)-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-one (12) and *endo*-(−)-(1*R*,4*S*,5*S*)-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-one (13).** The optically active diastereomeric lactones were prepared via method A as described in the above procedure. Thus, 1.63 g (16.6 mmol) of (+)-(*S*)-5-methyl-2(5*H*)-furanone (**11**) was photolyzed with ethylene in acetone at −60 °C to give approximately 1.02 g (8.05 mmol, 48.5%) of (1*S*,4*S*,5*R*)-**12** and 656 mg (5.20 mmol, 31.3%) of (1*R*,4*S*,5*S*)-**13**. For (1*S*,4*S*,5*R*)-**12**, $[\alpha]_D$ +75.7 ± 0.7° (*c* 1.762 ($CHCl_3$)). For (1*R*,4*S*,5*S*)-**13**, $[\alpha]_D$ −65.3 ± 1.0° (*c* 0.7855 ($CHCl_3$)).

(1*SR*,4*SR*,5*RS*)-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-ol (14) and (1*RS*,4*SR*,5*SR*)-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-ol (15). A solution containing a mixture of diastereomeric lactones **12** and **13** (4.51 g, 35.8 mmol) in dry toluene (45 mL) was prepared in a 250-mL three-necked round-bottomed flask equipped with a mechanical stirrer and a pressure-equalized addition funnel. The solution was cooled to −78 °C, and diisobutylaluminum hydride (1.0 M, 39 mL, 39 mmol) in toluene was added dropwise via the addition funnel over 30 min. The resulting solution was stirred at −78 °C for 3 h and then warmed to room temperature. The reaction was quenched by the slow addition of 300 mL of 30% aqueous sodium potassium tartrate. A bulky, gelatinous precipitate formed immediately upon quenching, but this was gradually digested to give a white, granular precipitate after stirring for a few hours. The aqueous layer of the resulting two-phase mixture was submitted to continuous extraction with ether for 24 h. Th eorganic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed on silica gel eluted with hexanes/ether (gradient from 90:10 to 0:100). The diastereomeric lactols exo methyl **14** and endo methyl **15** (R_f = 0.25 and 0.18, respectively, in 50:50 hexanes/ether) were isolated together to give 3.37 g (26.3 mmol, 73.4%), as a viscous, pale yellow oil.

Data for (1*SR*,4*SR*,5*RS*)-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-ol (14). ^1H NMR (250 MHz, $CDCl_3$): δ 5.34 (d, 1 H, J = 2.4 Hz, C_2), 4.23 (q, 1 H, J = 6.6 Hz, C_4), 3.03–2.91 (m, 1 H, C_1), 2.77–2.66 (m, 1 H, C_5), 2.52 (d, 1 H, J = 2.4 Hz, OH), 2.25–2.03 (m, 2 H, C_6 and/or C_7), 1.89–1.65 (m, 2 H, C_7 and/or C_6), 1.26 (d, 3 H, J = 6.7 Hz, CH_3). ^{13}C NMR (62.9 MHz, C_6D_6): δ 105.2 (d, C_2), 84.6 (d, C_4), 46.7 (d, C_1 or C_5), 44.5 (d, C_5 or C_1), 24.6 (t, C_6 or C_7), 24.1 (q, CH_3), 21.4 (t, C_7 or C_6). GC/MS (20 eV): *m/e* 127 (0.1, −H), 126 (0.2, $-H_2$), 113 (10, $-CH_3$), 111 (3, −OH), 110 (1, $-H_2O$), 84 (17, $-CO_2$), 83 (17, $-CHO_2$), 82 (12, $-CH_2O_2$), 81 (10, $-CH_3O_2$), 67 (100, $-C_2H_3O_2$), 55 (26, $-C_3H_5O_2$). GC/MS (Cl): *m/e* 129 (46, M + H), 111 (100, −OH).

Data for (1*RS*,4*SR*,5*SR*)-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-ol (15). ^1H NMR (250 MHz, $CDCl_3$): δ 5.27 (d, 1 H, J = 2.2 Hz, C_2), 4.35 (qd, 1 H, J = 6.3, 4.7 Hz, C_4), 2.91–2.77 (m, 2 H, C_1, C_5), 2.20 (d, 1 H, J = 2.2 Hz, OH), 2.19–2.01 (m, 1 H, C_6 or C_7), 1.98–1.72 (m, 2 H, C_6 and/or C_7), 1.67–1.53 (m, 1 H, C_7 or C_6), 1.22 (d, 3 H, J = 6.3 Hz, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): (endo methyl **24**) δ 102.9 (d, C_2), 75.3 (d, C_4), 45.8 (d, C_1 or C_5), 40.4 (d, C_5 or C_1), 20.5 (t, C_6 or C_7), 16.4 (t, C_7 or C_6), 14.2 (q, CH_3). GC/MS (20 eV): *m/e* 127 (0.4), 126 (0.3), 113 (0.7), 111 (3), 110 (1), 84 (33), 83 (37), 82 (20), 81 (12), 67 (100), 55 (30).

(1*S*,4*S*,5*R*)-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-ol (14) and (1*R*,4*S*,5*S*)-4-Methyl-3-oxabicyclo[3.2.0]heptan-2-ol (15). A 1.7:1 mixture of the diasteromeric lactones (1*S*,4*S*,5*R*)-**12** and (1*R*,4*S*,5*S*)-**13** (930 mg, 7.4 mmol) was reduced with diisobutylaluminum hydride, as described above in the preparation of **14** and **15**, to give 620 mg (4.8 mmol, 65%) of the optically active lactols (1*S*,4*S*,5*R*)-**14** and (1*R*,4*S*,5*S*)-**15**.

(1*SR*,1′*RS*,2′*RS*)-1-(2-Vinylcyclobutyl)ethanol (16a) and (1*SR*,1′*SR*,2′*SR*)-1-(2-Vinylcyclobutyl)ethanol (17a). Methylidenetriphenylphosphorane[48] (0.34 M, 35 mL, 12 mmol) in THF was transferred to a 100-mL three-necked round-bottomed flask equipped with a magnetic stirbar, pressure-equalized addition funnel, and a reflux condenser. A solution containing an approximately 1:1 mixture of the diastereomeric lactols **14** and **15** (1.06 g, 8.23 mmol) in THF (7 mL) was transferred to the addition funnel and added dropwise to the ylide solution over 30 min. The resulting yellow-orange solution was stirred at room temperature for 4.5 h. The reaction mixture was poured into 125 mL

(46) Owsley, D. C.; Bloomfield, J. J. *J. Org. Chem.* **1971**, *36*, 3768.

(47) This number represents the total NOE enhancement. The actual distribution of the NOE between the protons attached to C_1 and C_5 is unknown.

(48) Schmidbaur, H.; Stühler, H.; Vornberger, W. *Chem. Ber.* **1972**, *105*, 1084.

of H_2O, and the resulting layers were separated. The aqueous layer was extracted with ether (4 × 25 mL). The organic extracts were combined, washed with H_2O (2 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed on silica gel eluted with hexanes/ether (gradient from 90:10 to 20:80). The diastereomeric alcohols **16a** and **17a** (R_f = 0.37 and 0.30, respectively, in 50:50 hexanes/ether) were isolated together to give 938 mg (7.43 mmol, 90.2%). Alcohols **16a** and **17a** were separated from each other by preparative GC to give the 1*SR*,1′*RS*,2′*RS* isomer **16a** as a clear, colorless oil in 37.1% isolated yield (386 mg, 3.06 mmol) and the 1*SR*,1′*SR*,2′*SR* isomer **17a** as a clear, colorless oil in 33.6% isolated yield (349 mg, 2.77 mmol). Total isolated yield: 735 mg, 5.82 mmol, 70.7%.

Data for (1*SR*,1′*RS*,2′*RS*)-1-(2-Vinylcyclobutyl)ethanol (16a). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.21 (ddd, 1 H, J = 16.9, 10.4, 8.9 Hz, vinyl CH), 5.19–5.10 (m, 2 H, vinyl CH_2), 3.86 (dqd, 1 H, J = 9.6, 6.4, 3.2 Hz, C_1), 3.13–2.90 (m, 1 H, $C_{2'}$), 2.37 (m, 1 H, $C_{1'}$), 2.20–1.90 (m, 2 H, $C_{3'}$ and/or $C_{4'}$), 1.76 (d, 1 H, J = 3.4 Hz, OH), 1.84–1.59 (m, 2 H, $C_{4'}$ and/or $C_{3'}$), 1.04 (d, 3 H, J = 6.2 Hz, C_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 139.8 (d, vinyl CH), 115.3 (t, vinyl CH_2), 68.7 (d, C_1), 46.7 (d, $C_{2'}$), 40.4 (d, $C_{1'}$), 23.0 (t, $C_{3'}$ or $C_{4'}$), 21.7 (t, $C_{4'}$ or $C_{3'}$), 19.8 (q, C_2). IR ($CDCl_3$): 3690 (m), 3606 (w), 2976 (m), 2936 (w), 2868 (w), 1602 (m), 1476 (m), 1472 (s), 1383 (s), 1260 (w), 1097 (w), 1003 (w) cm^{-1}. GC/MS (20 eV): *m/e* 111 (7, $-CH_3$), 98 (4, $-C_2H_4$), 97 (13, $-CHO$), 93 (33, $-CH_3O$), 79 (42, $-C_2H_7O$), 71 (81, $-C_4H_7$), 67 (44, $-C_3H_7O$), 54 (100, $-C_4H_8O$), 43 (62, $-C_6H_{11}$). GC/MS (CI): *m/e* 127 (0.6, M + H), 109 (100, $-OH$).

Data for (1*SR*,1′*SR*,2′*SR*)-1-(2-Vinylcyclobutyl)ethanol (17a). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.09 (ddd, 1 H, J = 16.6, 10.8, 8.1 Hz, vinyl CH), 5.07–4.99 (m, 2 H, vinyl CH_2), 3.83 (dqd, 1 H, J = 7.4, 6.2, 3.5 Hz, C_1), 3.00 (m, 1 H, $C_{2'}$), 2.36 (m, 1 H, $C_{1'}$), 2.17–1.77 (m, 4 H, $C_{3'}$, $C_{4'}$), 1.41 (d, 1 H, J = 3.5 Hz, OH), 1.06 (d, 3 H, J = 6.2 Hz, C_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 139.3 (d, vinyl CH), 114.7 (t, vinyl CH_2), 68.5 (d, C_1), 45.8 (d, $C_{2'}$), 40.7 (d, $C_{1'}$), 23.6 (t, $C_{3'}$ or $C_{4'}$), 21.2 (t, $C_{4'}$ or $C_{3'}$), 20.9 (q, C_2). GC/MS (20 eV): *m/e* 98 (3), 97 (11), 93 (14), 79 (21), 71 (41), 67 (25), 54 (100), 43 (48).

(−)-(1*S*,1′*R*,2′*R*)-1-(2-Vinylcyclobutyl)ethanol (16a) and (+)-(1*S*,1′*S*,2′*S*)-1-(2-Vinylcyclobutyl)ethanol (17a). A mixture (1:1) of the diastereomeric, optically active lactols (1*S*,4*S*,5*R*)-**23** and (1*R*,4*S*,5*S*)-**23** (971 mg, 7.57 mmol) was treated with methylidenetriphenylphosphorane in THF as described above in the preparation of these alcohols. In this case, the isolated yield was 367 mg (2.90 mmol, 38.3%) of the 1*S*,1′*R*,2′*R* alcohol and 275 mg (2.18 mmol, 28.8%) of the 1*S*,1′*S*,2′*S* alcohol, or 67.1% total isolated yield. For 1*S*,1′*R*,2′*R* alcohol **16a**, $[\alpha]_D$ −7.04 ± 0.43° (*c* 0.8665 ($CHCl_3$)). For 1*S*,1′*S*,2′*S* alcohol **17a**, $[\alpha]_D$ +22.4 ± 0.40° (*c* 0.7665 ($CHCl_3$)).

(1*RS*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (16b). A 25-mL three-necked round-bottomed flask was equipped with a reflux condenser and a stirbar. Sodium hydride was introduced into the flask as a 60% dispersion in mineral oil (373 mg, approximately 9.3 mmol). The sodium hydride was washed with three portions of THF (3 mL) and suspended in 5 mL of THF. Iodomethane (375 μL, 855 mg, 6.02 mmol) was added dropwise via syringe, followed by a solution of (1*SR*,1′*RS*,2′*RS*)-1-(2-vinylcyclobutyl)ethanol (**16a**) (386 mg, 3.06 mmol) in 2 mL of THF. The resulting suspension was allowed to stir at room temperature for 2.5 h. The reaction was quenched by the dropwise addition of 400 μL of methanol and poured into 50 mL of H_2O. The layers were separated, and the aqueous layer was extracted with ether (5 × 15 mL). The organic extracts were combined, washed with H_2O (2 × 15 mL), and dried ($MgSO_4$). Ether was removed by distillation at atmospheric pressure, and the residue was purified by preparative GC to give 353 mg (2.52 mmol, 82.3%) of the methyl ether **16b** as a clear colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.10 (ddd, 1 H, J = 16.9, 10.7, 7.1 Hz, vinyl CH), 5.06–4.98 (m, 2 H, vinyl CH_2), 3.27 (dq, 1 H, J = 10.0, 6.1 Hz, $C_{1'}$), 3.23 (s, 3 H, OCH_3), 3.04 (m, 1 H, C_2), 2.41 (m, 1 H, C_1), 2.06 (m, 1 H, C_3 or C_4), 1.92 (m, 1 H, C_3 or C_4), 1.78 (m, 1 H, C_3 or C_4), 1.64 (m, 1 H, C_3 or C_4), 0.96 (d, 3 H, J = 6.1 Hz, $C_{2'}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 139.5 (d, vinyl CH), 113.2 (t, vinyl CH_2), 77.1 (d, $C_{1'}$), 55.5 (q, OCH_3), 44.8 (d, C_2), 40.5 (d, C_1), 22.5 (t, C_3 or C_4), 22.1 (t, C_4 or C_3), 15.4 (q, $C_{2'}$). GC/MS (20 eV): *m/e* 139 (0.2, −H), 125 (8, $-CH_3$), 112 (8, $-C_2H_4$), 111 (10, $-C_2H_5$), 108 (4, $-CH_4O$), 98 (35, $-C_4H_6$), 97 (31, $-C_3H_7$), 93 (27, $-C_2H_7O$), 85 (100, $-C_4H_7$), 79 (26, $-C_3H_9O$), 72 (19, $-C_5H_8$), 71 (44, $-C_5H_9$), 67 (19, $-C_4H_9O$), 59 (23, $-C_6H_9$). GC/MS (CI): *m/e* 141 (12, M + H), 109 (100, $-CH_3O$). Exact mass calcd for $C_8H_{13}O$ (M − CH_3) 125.0966, found 125.0969.

(+)-(1*R*,2*R*,1′*S*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (16b). Starting with the (−)-1*S*,1′*R*,2′*R* alcohol **16a**, the (+)-1*R*,2*R*,1′*S* methyl ether **16b** was prepared via the same procedure described above for the racemic methyl ether **16b**. Thus, methylation of (−) alcohol **16a** (442 mg, 3.50 mmol) led to isolation of (+)-**16b** (397 mg, 2.83 mmol, 80.9%), $[\alpha]_D$ +15.3 ± 0.6° (*c* 0.4675 ($CHCl_3$)).

(1*RS*,2*RS*,1′*RS*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (17b). Beginning with the racemic 1*RS*,1′*RS*,2′*RS* alcohol **17a**, the 1*RS*,2*RS*,1′*RS* methyl ether **17b** was prepared, again via the procedure described above in the preparation of the diastereomeric ether **16b**. In this manner, 349 mg (2.77 mmol) of alcohol was methylated to give **17b** as a clear, colorless oil. Isolated yield: 333 mg (2.37 mmol, 85.8%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.04 (m, 1 H, vinyl CH), 5.01–4.95 (m, 2 H, vinyl CH_2), 3.28 (s, 3 H, OCH_3), 3.24 (dq, 1 H, J = 8.8, 6.1 Hz, $C_{1'}$), 2.93 (m, 1 H, C_2), 2.37 (m, 1 H, C_1), 2.18–1.88 (m, 3 H, C_3, C_4), 1.75 (m, 1 H, C_3 or C_4), 0.99 (d, 3 H, J = 6.1 Hz, $C_{2'}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 139.4 (d, vinyl *CH*), 114.4 (t, vinyl CH_2), 77.6 (d, $C_{1'}$), 56.1 (q, OCH_3), 44.8 (d, C_2), 41.4 (d, C_1), 24.3 (t, C_3 or C_4), 22.8 (t, C_4 or C_3), 16.6 (q, $C_{2'}$). IR ($CDCl_3$): 3077 (w), 2977 (m), 2934 (m), 2871 (w), 2824 (w), 1635 (w), 1175 (w), 1093 (s) cm^{-1}. GC/MS (20 eV): *m/e* 139 (0.2), 125 (3), 112 (3), 111 (13), 108 (10), 98 (16), 97 (18), 93 (33), 85 (100), 79 (36), 72 (21), 71 (85), 67 (18), 59 (50). Exact mass calcd for $C_8H_{13}O$ (M − CH_3) 125.0966, found 125.0977.

(+)-(1*S*,2*S*,1′*S*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (17b). Methylation of (+)-1*S*,1′*S*,2′*S* alcohol **17a** (279 mg, 2.21 mmol) by the same method described above in the procedure for racemic **17b** led to the isolation of the (+)-1*S*,2*S*,1′*S* methyl ether (1*S*,2*S*,1′*S*)-**17b**. Isolated yield: 115 mg (0.821 mmol, 37.2%). $[\alpha]_D$ +42.4 ± 1.5° (*c* 0.3420, $CHCl_3$).

(1*SR*,2*RS*,1′*SR*)-2-(1-Methoxyethyl)cyclobutanecarboxaldehyde (36; Scheme X). A solution of 353 mg (2.52 mmol) of the racemic vinylcyclobutane **16b** in dichloromethane (13 mL) was transferred to a 35-mL pear-shaped flask equipped with a stirbar. The flask was cooled to −78 °C, and ozone mixed with oxygen was bubbled through the solution until the first persistence of a blue color. Dimethyl sulfide (400 μL, 338 mg, 5.45 mmol) was added via syringe, and the resulting colorless solution was allowed to warm to room temperature. Hexanes (15 mL) were added, and the dimethyl sulfide and dichloromethane were removed by distillation at ambient pressure.

Analysis by TLC of the reaction at this point indicated a three-component mixture. One of these products (R_f = 0.44 in 50:50 hexanes/ether) is the desired aldehyde and comprises roughly 30% of the mixture. The other two components (R_f = 0.60 and 0.55, respectively, in 50:50 hexanes/ether) are apparently diastereomeric ozonides. The later eluting of these ozonides was identified by its ^{1}H NMR spectrum (250 MHz, $CDCl_3$): δ 5.42 (d, 1 H, J = 4.0 Hz), 5.16 (s, 1 H), 5.04 (s, 1 H), 4.52–4.40 (dq, 1 H), 3.28 (s, 3 H), 2.86–2.74 (m, 1 H), 2.56–2.40 (m, 1 H), 2.04–1.88 (m, 3 H), 1.77–1.55 (m, 1 H), 0.99 (d, 3 H, J = 5.9 Hz).

The ozonides were decomposed with triphenylphosphine with use of the method of Carles and Fliszár.[49] Nitrogen was bubbled through the solution of crude ozonolysate in hexanes for 30 min. Triphenylphosphine (972 mg, 3.78 mmol) was added, and the resulting solution was refluxed for 1 h. The reaction mixture was filtered to remove precipitated triphenylphosphine oxide, and the filtrate was concentrated in vacuo. The residue was flash chromatographed on silica gel eluted with hexanes/ether (gradient from 95:5 to 60:40). The aldehyde **36** was isolated as a pale yellow oil to give 315 mg (2.22 mmol, 88.1%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.84 (d, 1 H, J = 1.7 Hz, CHO), 3.30 (m, 1 H, C_1), 3.26 (dq, 1 H, J = 10.1, 6.0 Hz, $C_{1'}$), 3.19 (s, 3 H, OCH_3), 2.73 (m, 1 H, C_2), 2.41 (m, 1 H, C_3 or C_4), 2.06 (m, 1 H, C_3 or C_4), 1.83 (m, 1 H, C_3 or C_4), 1.56 (m, 1 H, C_3 or C_4), 1.01 (d, 3 H, J = 6.0 Hz, $C_{2'}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 202.7 (d, CHO), 76.7 (d, $C_{1'}$), 55.3 (q, OCH_3), 47.1 (d, C_1 or C_2), 46.1 (d, C_2 or C_1), 21.6 (t, C_3 or C_4), 17.1 (t, C_4 or C_3), 15.1 (q, $C_{2'}$). IR ($CDCl_3$): 2975 (w), 2937 (w), 1708 (m), 1602 (w), 1375 (w), 1192 (w), 1141 (w), 1105 (w), 1091 (m), 1061 (w) cm^{-1}. GC/MS (20 eV): 127 (0.5, $-CH_3$), 114 (1, $-CO$), 85 (46, $-C_3H_5O$), 82 (23, $-C_3H_8O$), 67 (100, $-C_3H_7O_2$), 59 (68, $-C_5H_7O$), 55 (56, $-C_5H_{11}O$).

(1*S*,2*R*,1′*S*)-2-(1-Methoxyethyl)cyclobutanecarboxaldehyde (36). The optically active vinylcyclobutane (1*R*,2*R*,1′*S*)-**16b** (397 mg, 2.83 mmol) was converted via ozonolysis to the corresponding aldehyde (1*S*,2*R*,1′*S*)-**36** with use of the procedure described above. Isolated yield: 380 mg (2.67 mmol, 94.2%).

(1*RS*,2*SR*,1′*SR*)-2-(1-Methoxyethyl)cyclobutanecarboxaldehyde (38). The racemic vinylcyclobutane **17b** was ozonolyzed, and the intermediate ozonide was decomposed exactly as described in the preparation of racemic aldehyde **38** above. Via this method, 333 mg (2.37 mmol) of vinylcyclobutane **17b** was converted into 272 mg (1.91 mmol, 80.4%) of the corresponding aldehyde **38**. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.80 (d, 1 H, J = 2.5 Hz, CHO), 3.38 (qd, 1 H, J = 6.1, 4.0 Hz, $C_{1'}$), 3.20 (s, 3 H, OCH_3), 3.01 (m, 1 H, C_1), 2.75 (m, 1 H, C_2), 2.34–1.96 (m, 4 H, C_3, C_4), 0.98 (d, 3 H, J = 6.2 Hz, $C_{2'}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 204.4 (d, CHO), 74.9 (d, $C_{1'}$), 55.5 (q, OCH_3), 47.2 (d, C_1

(49) (a) Carles, J.; Fliszár, S. *Can. J. Chem.* **1969**, *47*, 1113. (b) Carles, J.; Fliszár, S. *Ibid.* **1970**, *48*, 1309.

or C_2), 45.4 (d, C_2 or C_1), 20.0 (t, C_3 or C_4), 18.6 (t, C_4 or C_3), 14.9 (q, $C_{2'}$). IR ($CDCl_3$): 3692 (w), 2976 (m), 2936 (m), 2871 (w), 2827 (w), 1705 (s), 1472 (vs), 1381 (vs), 1097 (s) cm^{-1}. GC/MS (20 eV): *m/e* 127 (0.7), 114 (1), 85 (87), 82 (20), 67 (67), 59 (100), 55 (62).

(1*R*,2*S*,1′*S*)-2-(1-Methoxyethyl)cyclobutanecarboxaldehyde (38). The optically active vinylcyclobutane (1*S*,2*S*,1′*S*)-**18** (115 mg, 0.821 mmol) was likewise converted via ozonolysis to the corresponding aldehyde (1*R*,2*S*,1′*S*)-**38**. The yield in this case was not determined.

1,1-Diiodoethane-*1-d*. The two-step procedure of Friederich and co-workers[50] for converting acetaldehyde into 1,1-diiodoethane was employed. In our hands, however, the yield was always considerably lower than the 34% reported. Thus, 5 g (111 mmol) of acetaldehyde-*1-d* (Aldrich, 98+ atom % *D*) was converted to the corresponding hydrazone with 57.3 g (1.14 mmol) of hydrazine monohydrate at −10 °C. The crude hydrazone was treated with solid iodine (16.8 g, 65.9 mmol) in the presence of triethylamine to give, after workup and distillation, 5.21 g (18.4 mmol, 16.6%) of diiodide as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ 2.89 (s, 3 H). Integration of the residual signal at δ 5.20 indicates 95.5% deuterium incorporation. GC/MS (20 eV): *m/e* 283 (24, M), 156 (100, −I), 127 (11, $-C_2H_3DI$). Comparison of the GC/MS of deuteriated diiodoethane with that of undeuteriated material indicated 94.9–96.4% deuterium incorporation.

(1*RS*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)cyclobutane (37), (1*RS*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)cyclobutane (41), and (1*RS*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-(1-(*Z*)-propenyl-*2-d*)cyclobutane. The racemic aldehyde **36** was olefinated with a technique reported by Takai and co-workers.[22] A 50-mL round-bottomed flask was equipped with a magnetic stirrer. Anhydrous $CrCl_2$ (1.03 g, 8.40 mmol) was weighed into the flask under N_2, and the solid was suspended in THF (20 mL). A solution of the racemic cyclobutanecarboxaldehyde **13** (195 mg, 1.37 mmol) in THF (2 mL) was added to the flask via syringe, followed by 280 μL (795 mg, 2.81 mmol) of neat 1,1-diiodoethane-*1-d*. The flask was fitted with a reflux condenser, and the reaction was stirred in the dark at room temperature for 20 h. The reaction was then poured into H_2O (100 mL), and the aqueous layer of the resulting mixture was extracted with ether (5 × 25 mL). The organic layers were combined, washed with H_2O (2 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed on silica gel eluted with hexanes/ether (gradient from 100:0 to 90:10), and the desired olefin **37** (R_f = 0.68 in 50:50 hexanes/ether) was isolated in 84.3% yield (180 mg, 1.16 mmol). The principal contaminants present in this product are the trans-substituted cyclobutane and the (*Z*)-propenylcyclobutane. Analysis by capillary GC indicates that the ratio of **37** to trans to *Z* in the isolated product is 93.5:1.7:4.8. The isolated product was further purified by two successive GC separations on columns M and S to give separately the three isomeric cyclobutanes.

Data for (1*RS*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)cyclobutane (37). ^1H NMR (250 MHz, $CDCl_3$): δ 5.69 (br dt, 1 H, *J* = 5.7, 1.8, olefinic CH), 3.27 (dq, 1 H, *J* = 9.7, 6.1 $C_{1'}$), 3.22 (s, 3 H, OCH_3), 2.96 (m, 1 H, C_2), 2.35 (m, 1 H, C_1), 2.03 (m, 1 H, C_3 or C_4), 1.89 (m, 1 H, C_4 or C_3), 1.75–1.52 (m, 2 H, C_3 and/or C_4), 1.69 (br s, 3 H, allylic CH_3), 0.96 (d, 3 H, *J* = 6.1 $C_{2'}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 132.2 (d, olefinic CH), 123.7 (t, olefinic CD), 77.2 (d, $C_{1'}$), 55.6 (q, OCH_3), 45.0 (d, C_2), 39.6 (d, C_1), 23.4 (t, C_3 or C_4), 22.2 (t, C_4 or C_3), 17.9 (q, allylic CH_3 or $C_{2'}$), 15.5 (q, $C_{2'}$ or allylic CH_3). GC/MS (20 eV): *m/e* 155 (0.1, M), 140 (1, $-CH_3$), 123 (3, $-CH_4O$), 112 (6, $-C_3H_7$), 108 (3, $-C_2H_7O$), 94 (6, $-C_3H_9O$), 86 (10, $-C_5H_7D$), 85 (17, $-C_5H_8D$), 69 (100, $-C_5H_{10}O$), 68 (35, $-C_5H_{11}O$), 59 (22, $-C_7H_{10}D$), 55 (10, $-C_6H_{10}DO$). IR ($CDCl_3$): 2973 (m), 2932 (m), 1601 (vw), 1451 (vw), 1371 (vw), 1261 (vw), 1096 (m) cm^{-1}. Exact mass calcd for $C_{10}H_{17}DO$ 155.1419, found 155.1429.

Data for (1*RS*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)-cyclobutane (trans Isomer 41). ^1H NMR (250 MHz, $CDCl_3$): δ 5.52 (m, 1 H), 3.30 (s, 3 H), 3.20 (dq, 1 H, *J* = 6.9, 6.2), 2.65 (m, 1 H), 2.08 (m, 1 H), 1.90 (m, 1 H), 1.77–1.50 (m, 3 H), 1.62 (br s, 3 H), 1.01 (d, 3 H, *J* = 6.2).

Data for (1*RS*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*Z*)-propenyl-*2-d*)cyclobutane (*Z* Isomer). ^1H NMR (250 MHz, $CDCl_3$): δ 5.68 (br d, 1 H, *J* = 10.1), 3.32–3.18 (m, 2 H), 3.20 (s, 3 H), 2.42 (m, 1 H), 2.15 (m, 1 H), 1.97–1.44 (m, 3 H), 1.56 (br s, 3 H), 0.96 (d, 3 H, *J* = 6.1).

(−)-(1*R*,2*R*,1′*S*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)cyclobutane (37). With use of the procedure described above, 364 mg (2.56 mmol) of the optically active cyclobutanecarboxaldehyde (1*S*,2*R*,1′*S*)-**36** was treated with anhydrous $CrCl_2$ and 1,1-diiodoethane-*1-d* in THF to give 308 mg (1.98 mmol, 77.5%) of the desired optically active olefin (1*R*,2*R*,1′*S*)-**37**. ^1H NMR: same as that for racemic **37** above. Integration of the residual proton signal at δ 5.44 indicated 96.6% deuterium incorporation. GC/MS (CI): *m/e* 156 (5.4%, M + H), 125 (10.5, $-CH_2O$), 124 (100.0, $-CH_3O$), 123 (8.0, $-CH_4O$), 122 (3.5, $-CH_5O$). Comparison of the fragmentation pattern with that for the corresponding racemic, undeuteriated compound (see below), particularly with respect to the relative intensities of the M − CH_4O peaks, indicates the extent of deuterium incorporation to be 96.6%. $[\alpha]_D$ −0.68 ± 0.39° (*c* 0.2945 ($CHCl_3$)).

(1*RS*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl)cyclobutane (Racemic 37). The racemic cyclobutanecarboxaldehyde **36** (102 mg, 0.720 mmol) was treated with $CrCl_2$ and 1,1-diiodoethane in THF to give the undeuteriated olefin **37** (27.0 mg, 0.175 mmol, 24.3%). The procedure was the same as that reported above in the preparation of racemic, deuteriated olefin **37**. ^1H NMR (250 MHz, $CDCl_3$): δ 5.71 (ddq, 1 H, *J* = 15.3, 7.5, 1.5, propenyl C_1), 5.44 (dqd, 1 H, *J* = 15.3, 6.4, 1.1, propenyl C_2), 3.27 (dq, 1 H, *J* = 10.1, 6.1), 3.22 (s, 3 H), 2.98 (m, 1 H), 2.36 (m, 1 H), 2.06 (m, 1 H), 1.91 (m, 1 H), 1.76–1.59 (m, 2 H), 1.70 (dd, 3 H, *J* = 6.3, 1.1, allylic CH_3), 0.96 (d, 3 H, *J* = 6.1). GC/MS (20 eV): *m/e* 154 (0.1, M), 139 (1, $-CH_3$), 122 (4, $-CH_4O$), 111 (6, $-C_3H_7O$), 107 (3, $-C_2H_7O$), 93 (9, $-C_3H_9O$), 85 (26, $-C_5H_9$), 68 (100, $-C_5H_{10}O$), 67 (25, $-C_5H_{11}O$), 59 (17, $-C_7H_{11}$), 55 (10, $-C_6H_{11}O$). GC/MS (CI): 155 (5.8, M + H), 124 (11.8, $-CH_2O$), 123 (100.0, $-CH_3O$), 122 (4.5, $-CH_4O$), 121 (4.0, $-CH_5O$).

(1*SR*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl)cyclobutane (39) and Its *Z* Propenyl Isomer. The racemic cyclobutanecarboxaldehyde **38** was olefinated via the standard procedure described above. Treatment of 41.4 mg (0.291 mmol) of **38** with $CrCl_2$ and 1,1-diiodoethane in THF gave a mixture of the desired *E* olefin **39** and the corresponding *Z* olefin. Analysis of the crude olefination product by capillary GC indicated the *E* to *Z* ratio to be 6.22:1.00. Purification by preparative GC with use of column M (see Table III) gave the separated olefins. The yields were not determined.

Data for (1*SR*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl)-cyclobutane (39). ^1H NMR (250 MHz, $CDCl_3$): δ 5.65 (ddq, 1 H, *J* = 15.1, 9.1, 1.5, propenyl C_1), 5.38 (dqd, 1 H, *J* = 15.0, 6.3, 0.6, propenyl C_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 132.2 (d, propenyl C_1), 125.0 (d, propenyl C_2), 77.8 (d, $C_{1'}$), 56.0 (q, OCH_3), 45.2 (d, C_2), 40.3 (d, C_1), 25.0 (t, C_3 or C_4), 22.8 (t, C_4 or C_3), 17.8 (q, allylic CH_3 or $C_{2'}$), 16.7 (q, $C_{2'}$ or allylic CH_3). GC/MS (20 eV): *m/e* 154 (0.2), 139 (3), 122 (11), 111 (21), 1027 (12), 93 (16), 85 (26), 68 (100), 67 (33), 59 (16), 55 (8). GC/MS (CI): *m/e* 155 (2, M + H), 123 (100, $-CH_3O$).

Data for (1*SR*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*Z*)-propenyl)-cyclobutane (*Z* Isomer). ^1H NMR (250 MHz, $CDCl_3$): δ 5.66 (tq, 1 H, *J* = 10.4, 1.2, propenyl C_1), 5.43 (dq, *J* = 10.9, 6.8, propenyl C_2). GC/MS (20 eV): *m/e* 139 (2), 122 (5), 111 (12), 107 (7), 93 (11), 85 (19), 68 (100), 67 (32), 59 (25), 55 (14).

Data for (1*SR*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)cyclobutane (39-*d*) and Its *Z* Propenyl Isomer. The racemic cyclobutanecarboxaldehyde **38** (152 mg, 1.07 mmol) was treated with $CrCl_2$ and 1,1-diiodoethane-*1-d* in THF as described above to give, after GC purification, 78.3 mg (0.504 mmol, 47.3%) of the *E* olefin **39-*d*** and 14.9 mg (0.096 mmol, 9.0%) of the *Z* olefin.

Data for (1*SR*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)cyclobutane (39-*d*). ^1H NMR (250 MHz, $CDCl_3$): δ 5.63 (br dt, 1 H, *J* = 9.3, 1.7, olefinic CH), 3.28 (s, 3 H, OCH_3), 3.23 (dq, 1 H, *J* = 6.0, $C_{1'}$), 2.88 (m, 1 H, C_2), 2.32 (m, 1 H, C_1), 2.16–1.86 (m, 3 H, C_3, C_4), 1.75–1.62 (m, 1 H, C_3 or C_4), 1.66 (br s, 3 H, allylic CH_3), 0.98 (d, 3 H, *J* = 6.0, $C_{2'}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 132.1 (d, propenyl C_1), 124.6 (t, 1:1:1, propenyl C_2), 77.7 (d, $C_{1'}$), 55.9 (q, OCH_3), 45.1 (d, C_2), 40.2 (d, C_1), 25.0 (t, C_3 or C_4), 22.7 (t, C_4 or C_3), 17.7 (q, allylic CH_3), 16.7 (q, $C_{2'}$). IR ($CDCl_3$): 2975 (w), 2931 (w), 1602 (w), 1449 (vw), 1373 (vw), 1095 (w) cm^{-1}. GC/MS (20 eV): *m/e* 155 (0.1), 140 (1), 123 (5), 112 (9), 108 (5), 94 (6), 86 (7), 85 (14), 69 (100), 68 (32), 59 (18), 55 (10).

Data for (1*SR*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-(1(*Z*)-propenyl-*2-d*)cyclobutane. ^1H NMR (250 MHz, $CDCl_3$): δ 5.66 (br dt, 1 H, *J* = 10.6, 1.4, olefinic CH), 3.34–3.18 (m, 2 H, $C_{1'}$, C_2), 3.28 (s, 3 H, OCH_3), 2.38 (m, 1 H, C_1), 2.24–1.93 (m, 3 H, C_3, C_4), 1.68–1.49 (m, 1 H, C_3 or C_4), 1.54 (br s, 3 H, allylic CH_3), 0.94 (d, 3 H, *J* = 6.0, $C_{2'}$). IR ($CDCl_3$): 2974 (w), 1602 (w) cm^{-1}. GC/MS (20 eV): *m/e* 140 (1), 123 (6), 112 (9), 108 (7), 94 (7), 86 (8), 85 (17), 69 (100), 68 (35), 59 (20), 55 (10).

(+)-(1*S*,2*S*,1′*S*)-1-(1-Methoxyethyl)-2-(1(*E*)-propenyl-*2-d*)cyclobutane (39). The optically active aldehyde (1*R*,2*S*,1′*S*)-**38** (110 mg, 0.77 mmol) was converted to the corresponding olefins (1*S*,2*S*,1′*S*)-**39** and the 1*S*,2*S*,1′*S* *Z* isomer as described above. Prior to GC purification, the combined yield of these two isomers was 56 mg (0.36 mmol, 47%). For (1*S*,2*S*,1′*S*)-**39**, $[\alpha]_D$ +48.3° (*c* 1.594 ($CHCl_3$)). ^1H NMR (250 MHz, $CDCl_3$): δ 5.53 (ddq, 1 H, *J* = 15.3, 6.6, 1.3, propenyl C_1), 5.37 (dqd,

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1 H, J = 15.4, 6.1, 0.8, propenyl C_2), 3.30 (s, 3 H, OCH_3), 3.19 (m, 1 H, $C_{1'}$), 2.65 (m, 1 H, C_2), 2.09 (m, 1 H, C_1), 1.91 (m, 1 H, C_3 or C_4), 1.76–1.52 (m, 3 H, C_3, C_4), 1.62 (br dd, 3 H, J = 6.2, 1.2, allylic CH_3), 1.01 (d, 3 H, J = 6.2). GC/MS (20 eV): m/e 154 (0.1), 139 (2), 122 (6), 111 (22), 107 (10), 93 (13), 85 (24), 68 (100), 67 (32), 59 (24), 55 (10).

Preparative Pyrolysis of 16b (Scheme VI). Characterization of (2*E*,6*Z*)-2-Methoxyocta-2,6-diene, (*E*,*Z*)-18. A. Capillary GC/MS Analysis of Pyrolysate from 16b. A single lead glass ampule containing a stock solution of the 1*RS*,2*RS*,1′*SR* cyclobutane **16b** and cyclooctane was pyrolyzed at 267.4 °C for 41 530 s. The ampule was opened, and the pyrolysate was taken up in ether and analyzed by capillary GC with use of column A. The mass balance was determined to be 96.5%. The composition of the pyrolysate, in terms of N_i, is given in Table I.

Several of the principal components of the pyrolysate (**16b**, **26**, **28b** + **29b**, **17b**, **30** + **31**, and (*E*,*Z*)-**18**) could be separated and analyzed by capillary GC/MS (with the Kratos MS80 RFA spectrometer).

Data for (1*RS*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (16b). GC/MS (20 eV): m/e 125 (3), 112 (3), 111 (4), 108 (4), 98 (12), 97 (10), 93 (12), 85 (100), 79 (21), 72 (21), 71 (44), 67 (16), 59 (50).

Data for 1,3-Butadiene (26). GC/MS (20 eV): m/e 55 (5, M + 1), 54 (100, M^+), 53 (67, –H), 52 (12, $-H_2$), 51 (26, $-H_3$), 50 (25, $-H_4$).

Data for Singly Epimerized Cyclobutanes (1*RS*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (28b) and (1*SR*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (29b). GC/MS (20 eV): m/e 139 (0.4), 125 (3), 112 (4), 111 (9), 108 (19), 98 (14), 97 (15), 93 (23), 85 (100), 79 (31), 72 (22), 71 (59), 67 (20), 59 (84).

Data for (1*SR*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (17b). GC/MS (20 eV): m/e 139 (1), 125 (3), 112 (3), 111 (6), 108 (13), 98 (8), 97 (6), 93 (12), 85 (48), 79 (21), 72 (14), 71 (48), 67 (13), 59 (50).

Data for 4-(1-Methoxyethyl)cyclohexenes 30 and 31. GC/MS (20 eV): m/e 125 (1), 109 (5), 108 (39), 93 (15), 80 (9), 79 (42), 78 (10), 59 (100).

Data for (2*E*,6*Z*)-2-Methoxyocta-2,6-diene (*E*,*Z*)-18. GC/MS (20 eV): m/e 140 (5), 86 (6), 85 (100), 72 (9), 55 (46). Exact mass calcd for $C_9H_{16}O$ 140.1201, found 140.1214.

B. Isolation of (*E*,*Z*)-18. The pyrolysates used in the kinetic studies of the rearrangements of (1*RS*,2*RS*,1′*SR*)-**16b** (18 ampules total) were combined and concentrated in vacuo. The residue was flash chromatographed on basic alumina (activity II) eluted with pentane/ether (gradient from 100:0 to 90:10). The principal retro ene product (*E*,*Z*)-**18** was isolated from the early eluting fractions. ^{1}H NMR (250 MHz, C_6D_6): δ 5.60–5.45 (m, 2 H), 4.32 (distorted br t, 1 H, J = 6.8), 3.23 (s, 3 H), 2.18–1.98 (m, 4 H), 1.77 (d, 3 H, J = 0.5) 1.60–1.53 (m, 3 H). (Identical with spectrum of (*E*,*Z*)-**18** obtained by independent synthesis (see supplementary material). NOE experiments: δ 4.32 saturated, 3.23 observed (2.9); 2.18–1.98 (5.6), 1.77 (0.0). 3.23 saturated, 4.32 observed (4.6), 2.18–1.98 (0.0), 1.77 (0.0); 1.77 saturated, 4.32 observed (1.2), 3.23 (–0.2), 2.18–1.98 (1.3).

Preparative Pyrolysis of (1*SR*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (17b). Isolation of Epimerized and 1,3-Rearranged Products. Two silanized lead glass ampules were prepared according to the general procedure, and into each were syringed aliquots (ca. 5 mg) of vinylcyclobutane **17b** (capillary GC analysis indicated that the diastereomeric ratio **17b**:**16b** in the unpyrolyzed material was 97.3:2.7). Each ampule was degassed and sealed in vacuo according to the general procedure and then pyrolyzed at 282.1 °C for 72 500 s. The pyrolysates were taken up in ether, combined, and purified by preparative GC to give three fractions. The first fraction was identified as 4-vinylcyclohexene, a dimer of butadiene. The second fraction was a mixture of (1*RS*,2*SR*,1′*SR*)-**28b** and (1*SR*,2*RS*,1′*SR*)-**29b** (approximately 1:1, based on the ^{1}H NMR). The third fraction was 4-(1-methoxyethyl)-cyclohexene, a mixture of two diastereomers (**30** + **31**) (roughly 1:1, again based on the ^{1}H NMR).

Data for 4-Vinylcyclohexene. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.82 (ddd, 1 H, J = 17.2, 10.4, 6.7, vinyl CH), 5.74–5.60 (m, 2 H, C_1, C_2), 5.07–4.88 (m, 2 H, vinyl CH_2), 2.34–1.96 (m, 4 H, C_3, C_6), 1.96–1.69 (m, 2 H, C_5), 1.47–1.28 (m, 1 H, C_4). GC/MS (20 eV): m/e 108 (2, M^+), 93 (8, $-CH_3$), 80 (21, $-C_2H_4$), 79 (29, $-C_2H_5$), 67 (15, $-C_3H_5$), 66 (24, $-C_3H_6$), 54 (100, $-C_4H_6$).

Data for (1*RS*,2*SR*,1′*SR*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (28b) and (1*SR*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-vinylcyclobutane (29b). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.93 (ddd, 1 H, J = 17.2, 10.4, 6.7, vinyl CH (**28b**)), 5.85 (ddd, 1 H, J = 17.3, 10.2, 7.1, vinyl CH (**29b**), 5.04–4.84 (m, 4 H, vinyl CH_2 (**28b** + **29b**)), 3.31 (s, 3 H, OCH_3 (**29b**)), 3.30 (s, 3 H, OCH_3 (**28b**)), 3.28–3.15 (m, 2 H, $C_{1'}$ (**28b** + **29b**), 2.81–2.65 (m, 1 H, C_2 (**28b**), 2.71–2.56 (m, 1 H, C_2 (**29b**)), 2.22–1.60 (m, 1′ H, C_1, C_3, C_4 (**28b** + **29b**)), 1.02 (d, 3 H, J = 6.2, $C_{2'}$ (**29b**)), 1.01 (d, 3 H, J = 6.1, $C_{2'}$ (**28b**)). GC/MS (20 eV): m/e 125 (1), 112 (2), 111 (4), 108 (5), 98 (8), 97 (10), 93 (17), 85 (66), 79 (23), 72 (20), 71 (59), 67 (17), 59 (100), 55 (38), 54 (56).

Data for 4-(1-Methoxyethyl)cyclohexenes 30 and 31. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.73–5.59 (m, 4 H, C_1, C_2), 3.32 (s, 3 H, OCH_3), 3.31 (s, 3 H, OCH_3), 3.23–3.03 (m, 2 H, $C_{1'}$), 2.17–1.53 (m, 6 H, C_3), 1.41–1.06 (m, 2 H, C_4), 1.10 (d, 3 H, J = 6.3, $C_{2'}$), 1.08 (d, 3 H, J = 6.2, $C_{2'}$). GC/MS (20 eV): m/e 125 (0.4, $-CH_3$), 109 (2, $-CH_3O$), 108 (22, $-CH_4O$), 93 (10, $-C_2H_7O$), 80 (7, $-C_3H_8O$), 79 (35, $-C_3H_9O$), 78 (8, $C_3H_{10}O$), 59 (100, $-C_6H_9$).

Preparative Pyrolysis of (1*RS*,2*RS*,1′*SR*)-1-(1-Methoxyethyl)-2-(1-(*E*)-propenyl-2-*d*)cyclobutane (37) (Scheme XI). Approximately 100 mg (0.644 mmol) of the fully labeled, racemic cyclobutane **37** was syringed in 5-mL aliquots into each of 24 silanized lead glass ampules (no internal standard was included). Each ampule was degassed and sealed in vacuo as described in the supplementary material. The ampules were each pyrolyzed at 239.3 ± 0.5 °C for about 138 h (mean pyrolysis time for the 24 ampules: t_{mean} = 496 850 ± 250 s). After pyrolysis, the ampules were opened and the pyrolysates taken up in pentane and combined.

The resulting solution was analyzed by capillary GC, with use of column B. The data are shown in Scheme XI. For the purpose of this analysis, relative GC/FID response factors for all products isomeric with the reactant $C_{10}H_{17}DO$ were assumed to be R_{37}(i) = 1.000. Relative response factors for the fragmentation products 3-methoxy-2-butene (**27**) and 1,3-pentadiene-4-*d* (**40**) were not determined analytically but were assumed to be approximately half those of the reactant (R_{37}).

The doubly epimerized cyclobutane **39** coelutes with unreacted starting material **37** under the conditions of the GC analysis. Consequently, the amount of **39** present in the pyrolysis was determined by a ^{1}H NMR analysis of recovered starting material. Integration of the signals due to the methoxy methyl groups of **37** and **39** gives an approximate ratio of **37**:**39** = 7.05 in the pyrolysate.

On the basis of these results, the approximate first-order rate constant for the disappearance of the reactant **37** at T = 239.3 °C is determined to be 2.9 × 10^{-6} s^{-1}. This corresponds to a half-life of 66.9 h at this temperature.

Isolation and Characterization of Pyrolysis Products. The pentane solution of the combined pyrolysates was concentrated to a volume of ca. 500 μL in vacuo and flash chromatographed on basic alumina (activity II) (freshly prepared from activity I). The column was eluted with pentane/ether (gradient from 100:0 to 90:10) and monitored by TLC and capillary GC. The eluent was partitioned into three fractions, designated A, B, and C. Capillary GC analysis showed that fraction A contained principally (2*E*,6*Z*)-2-methoxynona-2,6-diene-8-*d* (**45**) (89.5%), together with the *Z*,*Z* isomer (3.9%) and 4.6% of a mixture of *E*,*E* and *Z*,*Z* isomers. Fraction C contained the bulk of the pyrolysate (starting material, epimerized starting material, 1,3-rearranged products, etc.), and fraction B was a mixture of intermediate composition.

Fraction A was concentrated in vacuo, taken up in benzene-d_6 (ca. 400 μL), and analyzed spectroscopically.

Data for (2*E*,6*Z*)-2-Methoxynona-2,6-diene-8-*d* (45). ^{1}H NMR (250 MHz, C_6D_6): δ 5.51–5.38 (m, 2 H, C_6, C_7), 4.33 (br t, 1 H, J = 6.7 C_3), 3.24 (s, 3 H, OCH_3), 2.18–1.94 (m, 5 H, C_4, C_5, C_8), 1.78 (s, 3 H, C_1), 0.92 (dt, 3 H, J = 7.4, 1.1, C_9). NOE experiments: δ 4.33 saturated, 3.24 enhanced (1.1), 2.18–1.95 enhanced (2.7), 1.78 enhanced (–0.2); 3.24 saturated, 4.33 enhanced (4.9), 2.18–1.95 enhanced (–0.3), 1.78 enhanced (0.06); 1.78 saturated, 4.33 enhanced (–0.2), 3.24 enhanced (–0.1), 2.18–1.95 enhanced (2.5). ^{13}C NMR (62.9 MHz, C_6H_6): δ 154.0 (s, C_2), 132.0 (d, C_6 or C_7), 129.1 (d, C_7 or C_6), 95.9 (d, C_3), 53.6 (q, OCH_3), 28.8 (t, C_4 or C_5), 27.6 (t, C_5 or C_4), 16.4 (q, C_1), 14.4 (q, C_9). No signal for C_8 was detected with a 2-s relaxation delay. Exact mass calcd for $C_{10}H_{17}DO$ 155.1419, found 155.1410. The contents of fraction C are described in the supplementary material.

Degradation and Stereochemical Correlation of (2*E*,6*Z*)-2-Methoxynona-2,6-diene-8-*d* (45). Non-6(*Z*)-ene-2-one-8-*d* (46). Fractions A and B from the chromatography of the racemic pyrolysates were combined and concentrated in vacuo to a volume of about 3 mL. The solution was then transferred to a 10-mL pear-shaped flask equipped with a magnetic stirrer. Dilute HCl (1 N, 1.0 mL) was added to the flask, and the resulting mixture was stirred at ambient temperature for 18 h. Water (5 mL) and ether (5 mL) were added, and the layers were separated. The aqueous layer was extracted with ether (3 × 2 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to a volume of 3 mL. The residue was purified by preparative GC on column G to give 2.11 mg (14.9 mmol) of the desired methyl ketone **46**. Approximate yield (calculated from the reactant cyclobutane **37**): 2.2%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.43–5.20 (m, 2 H, C_6, C_7), 2.41 (t, 2 H, J = 7.4, C_3), 2.11 (s, 3 H, C_1), 2.09–1.92 (m, 3 H, C_5, C_8), 1.61 (m, 2 H, C_4), 0.92 (dt, 3 H, J = 7.4, 1.0, C_9). Decoupling the allylic

signals (δ 2.09–1.92) caused the olefinic region to partially collapse: δ 5.38 (br d, 1 H, J = 11.1), 5.26 (br d, 1 H, J = 10.7). GC/MS (20 eV): m/e 142 (2, M + 1), 141 (14, M^+), 126 (8, $-CH_3$), 112 (8, –CHO), 111 (8, $-CH_2O$), 98 (6, $-C_2H_3O$), 97 (7, $-C_2H_4O$), 83 (89, $-C_3H_6O$), 71 (11, $-C_4H_6O$), 68 (100, $-C_4H_9O$), 67 (28, $-C_4H_8DO$), 58 (12, $-C_6H_9D$), 43 (17, $-C_7H_{12}D$). Exact mass calcd for $C_9H_{15}DO$ 141.1263, found 141.1269.

Preparative Pyrolysis of (−)-(1*R*,2*R*,1′*S*)-1-(1-Methoxyethyl)-2-(1-(*E*)-propenyl-2-*d*)cyclobutane (37). Approximately 180 mg (1.16 mmol) of the fully labeled, optically active cyclobutane (−)-(1*R*,2*R*,1′*S*)-**37** was syringed in 5-mL aliquots into each of 42 silanized lead glass ampules (no internal standard was included). Each ampule was degassed and sealed in vacuo as described in the supplementary material The ampules were each pyrolyzed at 239.4 ± 0.5 °C for about 138 h. Three ampules developed cracks and filled with salt during pyrolysis, so they were discarded prior to workup. Mean pyrolysis time for the 42 ampules was t_{mean} = 496 880 ± 100 s. After pyrolysis, the ampules were opened and the pyrolysates taken up in pentane and combined. Analysis of the combined pyrolysates by capillary GC indicates essentially the same distribution of products already reported for the case of the racemic reactant (+)-(1*RS*,2*RS*,1′*SR*)-**37** (see Scheme XI).

Partial Isolation of (8*S*)-(2*E*,6*Z*)-2-Methoxynona-2,6-diene-8-*d* ((8*S*)-45). The pentane solution of the combined pyrolysates was concentrated and chromatographed on basic alumina as described above in the sequence beginning with the racemic cyclobutane **37**. All fractions of the column eluent containing (8*S*)-**45** were combined and analyzed by capillary GC. The composition of the product determined in this manner is given in Table X. The isolated enol ether (8*S*)-**45** gave a proton NMR spectrum identical with that reported above for (8*RS*)-**45** obtained in the racemic series.

Degradation and Stereochemical Correlation of (8*S*)-(2*E*,6*Z*)-2-Methoxynona-2,6-diene-8-*d* (45). (8*S*)-Non-(6*Z*)-ene-2-one-8-*d* (46). The partially isolated enol ether (8*S*)-**45** was hydrolyzed as described above for the corresponding racemic enol ether **45**. After preparative GC purification, the ketone (8*S*)-**46** (5.40 mg, 38.2 μmol) was isolated in 3.3% yield (calculated from the reactant cyclobutane (−)-(1*R*,2*R*,1′*S*)-**37**). The ^{1}H NMR of (8*S*)-**46** was identical with that reported for the racemic ketone **46**.

The methyl ketone **46** was oxidized with ruthenium tetroxide according to the procedure of Sharpless and co-workers.[53] Sodium periodate (31.9 mg, 0.149 mmol) was transferred to a 10-mL vial, which had been equipped with a stirbar. The solid was dissolved in a two-phase mixture of water (375 μL) and 1:1 CH_3CN/CCl_4 (150 μL). Ruthenium dioxide hydrate (4 mg, 24 mmol) was added, and the mixture was stirred for 30 min. A solution of ketone **46** (2.11 mg, 14.9 μmol) in 1:1 CH_3CN/CCl_4 (350 μL) was added to the vial, and the resulting two-phase mixture was stirred vigorously at ambient temperature for 3 h. The mixture was then diluted with water (10 mL), acidified to pH 1 with concentrated HCl (3 drops), and extracted continuously with dichloromethane (40 mL) for 7 h. The organic layer was dried (Na_2SO_4) and concentrated to a volume of ca. 5 mL by distilling off most of the CH_2Cl_2 at ambient pressure. The remainder was purified by distillation bulb to bulb in vacuo (0.05 Torr). Analysis of the bulb to bulb distillate by capillary GC indicated the presence of a small amount of the desired propanoic acid (on the basis of a comparison of the retention time with that of an authentic sample of propanoic acid).

(2*R*,2′*S*)-2-(1-Oxopropoxy-2-*d*)-2-phenylacetic Acid, Methyl Ester and (2*R*,2′*R*)-2-(1-Oxopropoxy-2-*d*)-2-phenylacetic Acid, Methyl Ester. The racemic propanoic acid-2-*d* was converted into the diastereomeric mandelate esters via a standard technique.[51,54] The solution of propanoic acid-2-*d* in dichloromethane isolated in the above procedure was transferred to a 10-mL pear-shaped flask, which had been equipped with a stirbar. Approximately 2 mg (16 mmol) of *N,N*-dimethyl-4-aminopyridine (DMAP) was added followed by (−)-(*R*)-methyl mandelate (8.66 mg, 52.1 μmol) and 11.2 mg (54.2 μmol) of dicyclohexylcarbodiimide (DCC). The resulting solution was allowed to stir at ambient temperature for 12 h. The reaction was concentrated in vacuo and flash chromatographed on silica gel eluted with pentane/ether (gradient from 95:5 to 0:100). The column fractions were monitored by capillary GC, and the mixture of esters **49** and **50** was isolated in unknown yield. Analysis of the product by capillary GC indicated that the sample of **49** + **50** was 97.6% pure, with three detectable impurities, all unidentified. The proton NMR spectrum of **49** + **50** was identical with that obtained previously by Parker.[54] ^{1}H NMR (250 MHz, C_6D_6): δ 7.44 (br d, 2 H, J = 7.8, 1.7, ortho H's), 7.13–6.96 (m, 3 H, meta and para H's), 6.08 (s, 1 H, C_1), 3.17 (s, 3 H, OCH_3), 2.19 (m, 0.5 H, H_S), 2.07 (m, 0.5 H, H_R), 0.94 (br d, 3 H, J = 7.6, $C_{3'}$).

In the 250-MHz spectrum, the signals for H_S and H_R are insufficiently resolved to permit their precise, separate integration. Decoupling the $C_{3'}$ methyl signal (δ 0.94) causes the H_S and H_R signals to partially collapse: δ 2.19 (br t, 0.529 H, J = 2.5 H_S), 2.07 (br t, 0.471 H, J = 2.4, H_R). The proton NMR spectrum of **49** + **50** at 500 MHz was identical with that obtained at 250 MHz, with the exception that the diastereotopic $C_{2'}$ signals were baseline resolved. ^{1}H NMR (500 MHz, C_6D_6): δ 2.18 (qt, 0.509 H, J = 7.5, 2.5, H_S), 2.06 (qt, 0.491 H, J = 7.5, 2.5, H_R). ^{2}H NMR (76.8 MHz, C_6H_6): δ 2.16 (s, 0.5 D, D_S), 2.04 (s, 0.5 D, D_R). GC/MS (20 eV): m/e 223 (2, M^+), 192 (4, $-CH_3O$), 191 (22, $-CH_4O$), 190 (2, $-CH_3DO$), 167 (19, $-C_3H_4O$), 166 (25, $-C_3H_3DO$), 165 (10, $-C_3H_4DO$), 164 (47, $-C_2H_3O_2$), 105 (25, $-C_4H_4DO_4$), 58 (100, $-C_9H_9O_3$).

(2*S*)-Propanoic Acid-2-*d* (46). The optically active ketone (8*S*)-**46** was oxidized with ruthenium tetroxide, as described previously. The product was extracted with CH_2Cl_2 and purifed by bulb to bulb distillation. The optically active (2*S*) 2-*d* acid was not isolated but was immediately esterified in the subsequent step.

(2*R*,2′*S*)-2-(1-Oxopropoxy-2-*d*)-2-phenylacetic Acid, Methyl Esters 49/50. The optically active acid (2*S*)-**47** was treated with (−)-(*R*)-methyl mandelate in the presence of DCC and DMAP, as described previously in the preparation of the mixed esters from racemic **47**. The product was flash chromatographed and isolated as before in unknown yield. Analysis of the product by capillary GC indicated 95.7% purity (three detectable, unknown contaminants). The ^{1}H NMR spectrum of **49/50** was identical with that obtained for the racemic mixture, with the exception that the integrals of the diastereotopic $C_{2'}$ signals (H_S and H_R) were no longer in a 50:50 ratio. ^{1}H NMR (500 MHz, C_6D_6): δ 2.18 (m, 0.201 H, H_S), 2.06 (qt, 0.799 H, J = 7.5, 2.5, H_R). ^{2}H NMR (76.8 MHz, C_6H_6): δ 2.16 (s, 0.875 D, D_S), 2.04 (s, 0.125 D, D_R). The supplementary material describes the details of the interpretation of these data in terms of stereogenicity transfer.

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Supplementary Material Available: Details of independent syntheses and characterizations of pyrolysis products (Schemes IV and V), descriptions of GC analyses, control experiments, and kinetics, determinations of enantiomeric purities, and treatment of stereogenicity transfer data (31 pages). Ordering information is given on any current masthead page.

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(55) We thank Dr. D. Parker for a personal communication in which he reports that the chemical shifts in ref 54 for the H_S and H_R signals arising respectively from the $C_{2'}$ protons of **49** and **50** are erroneous. In fact, his spectra are identical with ours.