Table VII. Calculated Heats of Formation of Adduct Intermediates[a]

n	$H_3CC(H)C_{n-1}N^+$	$C_nN(H)CH_3^+$
4	285	373
5	312	380
6	320	415
7	347	424
8	359	460

[a] For the singlet electronic state in kcal/mol.

this observation can be found in the energetics (see Figure 3). The rearrangement from intermediate **1** has a higher barrier for odd *n* reactant ions, leading to a preference for the direct mechanism. Though nitrene attack (Schemes IV and VI) is energetically allowed, it does not appear to play a role in these reactions. The MNDO calculations suggest that the reactant ions in fact have little nitrene character. Electronic state effects are important for the odd *n* reactant ions. These ions have closely spaced triplet and singlet states. The even *n* reactant ions have singlet ground states with no nearby triplet states. Hydrogen abstraction to form radical products occurs on a triplet surface and is an important product channel in the reactions of the odd *n* ions.

Acknowledgment. The author thanks Brett Dunlap for his assistance with the MNDO calculations and useful discussions, Steve McElvany and Vicki Wysocki for helpful suggestions, and the reviewer for suggesting the possibility of electronic state effects.

Appendix

The heats of formation obtained from the MNDO calculations described in the Theory section are tabulated in Table V (hydrocarbon compounds), Table VI (cyano compounds), and Table VII (intermediates).

Stereochemistry of the Thermal Acetylenic Cope Rearrangement. Experimental Test for a 1,4-Cyclohexenediyl as a Mechanistic Intermediate
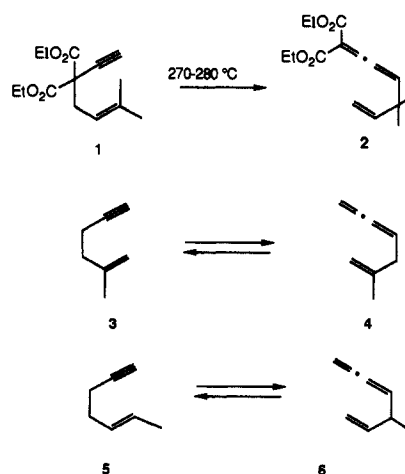
Karen Ann Owens and Jerome A. Berson*

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. Received May 8, 1989. Revised Manuscript Received March 28, 1990

Abstract: The reversible [3,3]-sigmatropic rearrangement that interconverts optically active 4-methyl-5-hepten-1-yne and 4-methyl-1,2,5-heptatriene (an acetylenic Cope rearrangement) occurs with a stereochemistry corresponding to an orbital symmetry allowed suprafacial pathway with essentially complete preservation of enantiomeric purity. Computational simulation of the time-composition profile shows that 1% or less of the rearrangement goes by the stereochemical equivalent of a forbidden antarafacial pathway. Combined with a recent experimental determination of the rate constant for ring conformational inversion of the model 4-cyclohexenyl radical, the results suggest that for the biradical 3,5-dimethyl-1-cyclohexene-1,4-diyl to occur on the energy surface of the rearrangement its rate of decomposition would have to be in the range $1.6–3.8 \times 10^{13}$ s^{-1}. This rate exceeds the upper limit imposed by transition-state theory for the decomposition of an intermediate, which is the rate of decomposition of the transition state itself, about 1×10^{13} s^{-1} at the reaction temperature of 471 K. The results strongly suggest that the stepwise mechanism involving the biradical intermediate does not occur to a significant extent in this rearrangement. An allowed concerted mechanism best accounts for the experimental observations.

The acetylenic Cope rearrangement,[1–4] of which the first examples were provided by Black and Landor[1] (**1** → **2**) and by Huntsman, DeBoer, and Woosley (**3** → **4**,[2a] **5** → **6**[2b]), has attracted our attention as the basis of a mechanistic test for a true intermediate on the energy surface of a thermal [3,3]-sigmatropic process. Reasons for the choice of this reaction rather than the more familiar Cope rearrangement of 1,5-hexadienes emerge from a detailed analysis of the interpretive limitations inherent in the latter systems.

Although Cope's proposal[5] of a concerted pathway has provided the framework of most mechanistic discussions of thermal

[3,3]-sigmatropic processes,[1–8] the possibility that a cyclohexane-1,4-diyl might intervene in the ordinary dienic Cope rearrangement was first considered by Grob, Link, and Schiess in 1963.[9] For the parent case (1,1-dideuteriohexa-1,3-diene, **7** →
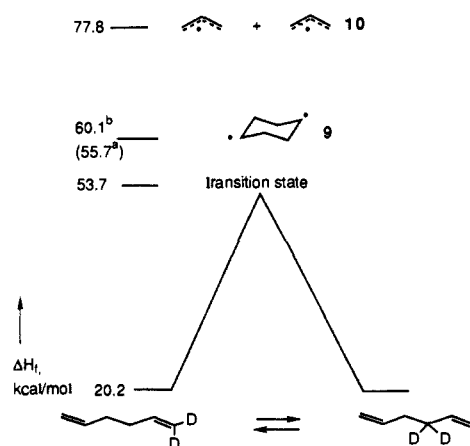
(1) Black, D. K.; Landor, S. R. *J. Chem. Soc.* **1965**, 6784.
(2) Huntsman, W. D.; De Boer, J. A.; Woosley, M. H. *J. Am. Chem. Soc.* **1966**, *88*, 5846. (b) De Boer, J. A. Ph.D. Thesis, Ohio University, Athens, OH, 1967; as cited in ref 3. (c) Huntsman, W. D.; Dykstra, K. A. Unpublished work. Dykstra, K. A. Ph.D. Dissertation, Ohio University, Athens, OH, 1972; as cited in ref 3.
(3) Review: Huntsman, W. D. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley-Interscience: New York, 1980; Part 2, p 605.
(4) Review: Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron* **1981**, *37*, 3765.
(5) Foster, E. G.; Cope, A. C.; Daniels, F. *J. Am. Chem. Soc.* **1947**, *69*, 1893.

Figure 1. Enthalpies of formation of hexa-1,3-diene, its transition state (calculated from the observed[10] Arrhenius activation energy), cyclohexane-1,4-diyl (9), and two allyl radicals (10).[10,14] See footnotes *a* and *b* in the figure: [a]The value in parentheses is calculated by using the dissociation energy of the secondary C–H bond in propane given in refs 11–13 as a model. [b]Calculated by using the dissociation energy of the secondary C–H bond in propane given in ref 14 as a model.

3,3-dideuteriohexa-1,3-diene, 8[10]), the intermediate would be 9, which hypothetically could be generated in a cyclization–cleavage mechanism by formation of the C_1–C_6 bond before any bond breaking occurs at C_3–C_4.
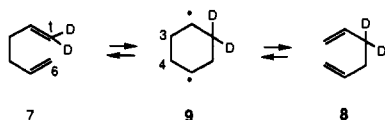
The possibility of a role for such intermediates has been examined from the thermochemical-kinetic[11–13] point of view by Doering, Toscano, and Beasley,[10] who have considered the energetic relationships of the various points on the energy surface from the relevant heats of formation (ΔH_f, see Figure 1). The values for biradical 9, 55.7 and 60.1 kcal/mol, are respectively based upon earlier[11–13] and later[14] estimates of the secondary C–H bond dissociation energy. Although either value for ΔH_f, if taken literally, would place the energy of 9 too high for this species to lie on the reaction coordinate, a more realistic appreciation of the uncertainties in the use of bond-additivity schemes for biradicals would suggest that these species should not be too quickly dismissed on this basis. In particular, the insight from quantum theoretical calculations[15] that through-bond coupling may stabilize such biradicals substantially points to an influence on the heat of formation that is not encompassed in the thermochemical estimates.

Experimental Design

The experiment[16] is constructed to distinguish between a transition state and a true intermediate by a measurement of the
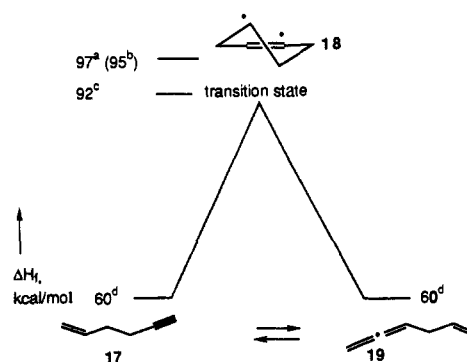

Figure 2. Enthalpies of formation in kcal/mol for species relevant to the acetylenic Cope rearrangement. See footnotes *a–d* in the figure: [a]The value in parentheses is calculated by using the dissociation energy of the secondary C–H bond in propane given in refs 11–13 as a model. [b]Calculated by using the dissociation energy of the secondary C–H bond in propane given in ref 14 as a model. [c]The energy of the transition state is calculated from the Arrhenius activation energy for the reaction 17 → 19 as reported in refs 2c and 3. [d]Calculated from the data in refs 11–13.

rate of conversion of the putative species to product. According to transition-state theory,[17] the rate of decomposition of a transition state is $\kappa RT/Nh$, which is about 1×10^{13} s^{-1} at 200 °C, when the value of the transmission coefficient κ is taken as unity. This is roughly the rate of a molecular vibration. On the other hand, a true intermediate, by definition, is represented by a well in a multidimensional energy surface, which must be deep enough so that a finite barrier opposes passage onward to product. Therefore, the decomposition of an intermediate must be appreciably slower than that of a transition state.

We propose to use the rate of a ring conformational inversion of the hypothetical biradical of a [3,3]-sigmatropic rearrangement as an internal clock with which to measure the competing rate of cleavage of the C_3–C_4 bond. Conformational inversion would be signaled in the products by loss of stereochemical information built into the reactant, but if bond cleavage in the biradical were much faster than stereomutation, the products would be formed with complete preservation of stereochemistry. If the actual rate of ring conformational inversion were known or could be estimated, the absolute value (or at least a lower limit) of the rate of bond cleavage in the biradical then could be determined, and if this rate should be equal to or greater than 10^{13} s^{-1}, a true intermediate could not be involved.

Although the literature does not contain any examples of the intentional application of this strategy to the dienic Cope rearrangement itself, an important experiment carried out for another purpose by Hill and Gilman[18] is relevant to this issue. Thus, the thermal rearrangement of (*R,E*)-3-phenyl-3-methylhepta-1,5-diene gives only (*R,Z*)- and (*S,E*)-2-phenyl-5-methylhepta-2,6-diene, the products expected from concerted reactions by way of the energetically preferred[19] chair transition states.[20,21] An analysis given elsewhere[22] shows that had these rearrangements occurred by way of a cyclohexanediyl intermediate whose conformational isomerization rate was competitive with bond cleavage, the crossover (*S,Z*) and (*R,E*) products should have been observed. Unfortunately, this still leaves open two interpretations: Either the mechanism is concerted and completely bypasses such intermediates, or the intermediates are formed but their conformational isomerization rates are too slow to compete with bond

(6) (a) Review: Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; p 165. (b) Review: Berson, J. A. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980. (c) Reference 6a, p 141.

(7) Review: Rhoads, S. J.; Rawlins, R. N. *Org. Reactions* 1975, 22, 1.

(8) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim/Bergstrasse, Germany, and Academic Press: New York, 1970.

(9) Grob, C. A.; Link, H.; Schiess, P. W. *Helv. Chim. Acta* 1963, 46, 483.

(10) Doering, W. von E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* 1971, 27, 5299.

(11) Benson, S. W. *Thermochemical Kinetics*, Wiley: New York, 1976.

(12) O'Neal, H. E.; Benson, S. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; pp 275–360.

(13) Golden, D. M.; Benson, S. W. *Chem. Rev.* 1969, 69, 125.

(14) Doering, W. von E. *Proc. Natl. Acad. Sci. U.S.A.* 1981, 78, 5279.

(15) Review: Borden, W. T., III; Houk, K. N.; Loncharich, R. J. *Ann. Rev. Phys. Chem.* 1988, 39, 213.

(16) Preliminary communication: Owens, K. A.; Berson, J. A. *J. Am. Chem. Soc.* 1988, 110, 627.

(17) Review: Moore, J. W.; Pearson, R. G. *Kinetics and Mechanism*, 3rd ed.; Wiley-Interscience: New York, 1981; p 159ff.

(18) Hill, R. K.; Gilman, N. W. *J. Chem. Soc., Chem. Commun.* 1967, 619.

(19) Doering, W. von E.; Roth, W. R. *Tetrahedron* 1962, 18, 67.

(20) For discussions of the significance of these results to the question of possible "twist" transition states in the Cope rearrangement, see refs 6a and 21.

(21) Gajewski, J. J.; Benner, C. W.; Hawkins, C. M. *J. Org. Chem.* 1987, 52, 5198.

(22) Owens, K. A. Ph.D. Thesis, Yale University, New Haven, CT, 1988; and also the Supplementary Material to the present paper.

cleavage. In the terminology of our experimental design, the latter situation would correspond to the use of too slow a clock for the measurement of the lifetime of the intermediate. That this is probably the case is documented by arguments[22] modeling the ring inversion and bond cleavage rates.

Ring Conformational Inversion vs Bond Cleavage in Cyclohexene-1,4-diyls. A biradical intermediate in a two-step mechanism might have a better chance to make its presence known if the conformational clock could be made to run faster. For this purpose, the hypothetical cyclohexene-1,4-diyl intermediate (18) in a two-step acetylenic Cope rearrangement (17 → 18 → 19) represents an attractive alternative.
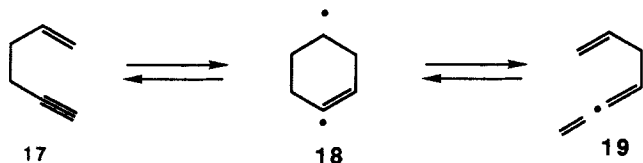
Thermochemically (Figure 2), the energy gap between biradical 18 and the transition state for the acetylenic Cope rearrangement is even smaller than the one between 9 and the transition state for the dienic Cope rearrangement (Figure 1). If energetic proximity was a good reason to consider a biradical pathway in the dienic Cope rearrangement, it is a better one in the acetylenic case.

The conformational barrier (5.2 kcal/mol[23a,b]) for cyclohexene is substantially lower than that for cyclohexane (10.2 kcal/mol[23b]), and it would be reasonable to assume that the barriers in the corresponding biradicals should be in the same order. The C_1 radical center of 18 is a σ vinyl radical and is not expected to perturb the geometry or the conformational barrier of the biradical significantly relative to that of cyclohexene.[22,23d-f] It is likely that the major contributions to such changes will be due to the π radical at C_4. Therefore, we expect that the diyl's conformational barrier can be effectively modeled by those of compounds with 1, 2, and 4-sp^2 hybridized centers,[22] such as 4-methylenecyclohexene (4.2 kcal/mol by IR), 3-cyclohexenone (1.3 kcal/mol by IR), and, probably best of all, 4-cyclohexenyl radical, 20, whose barrier has been measured expressly for this purpose and found to be 2.4 kcal/mol by dynamic EPR spectroscopy.[24]
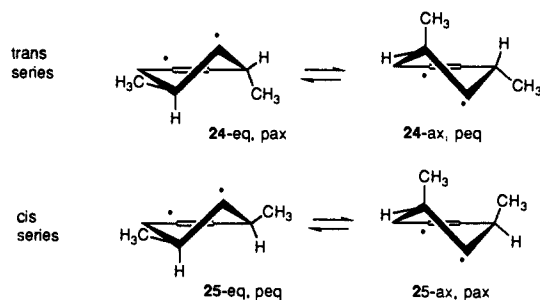
The hyperfine coupling constants extracted from line shape analysis of the EPR spectra of 20 indicate that the radical, like cyclohexene itself, exists as an interconverting pair of half-chair conformations, 20a,b, in which the conformational isomerization interchanges the magnetic identity of protons H_1 with H_2 and H_3 with H_4. At 200 °C, a typical reaction temperature for the acetylenic and dienic Cope rearrangements, the observed Arrhenius parameters log A = 12.6 (A in s^{-1}), E_a = 2.4 kcal/mol, correspond to a rate constant of 3 × 10^{11} s^{-1}. If the rate of inversion of
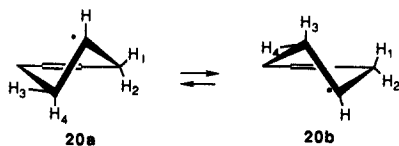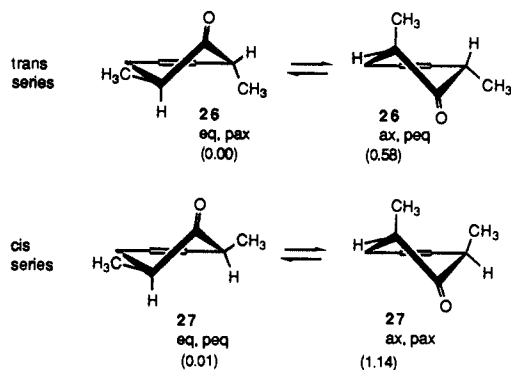

cyclohexene-1,4-diyl 18 is the same as that of the model monoradical 20, then the hypothetical biradical intermediate in the acetylenic Cope process undergoes conformational inversion about five times as fast as that in the dienic Cope rearrangement.[22]

Moreover, because of less favorable orbital overlap, the cleavage rate of the acetylenic Cope rearrangement biradical 18 is likely

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(23) (a) Jensen, F. R.; Bushweller, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 5774. (b) Anet, F. A. L.; Haq, M. Z. *J. Am. Chem. Soc.* **1965**, *87*, 3147. (c) Squillacote, M.; Sheridan, R. S.; Chapman, O. L.; Anet, F. A. L. *J. Am. Chem. Soc.* **1975**, *97*, 3244 and references cited therein. (d) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147. (e) Cochran, E. L.; Adrian, F. J.; Bowers, V. A. *J. Chem. Phys.* **1964**, *40*, 213. (f) Fessenden, R. W. as quoted in footnote 21 in the following: Kampmeier, J. A.; Chen, G. *J. Am. Chem. Soc.* **1965**, *87*, 2608.

(24) Berson, J. A.; Griller, D.; Owens, K.; Wayner, D. D. M. *J. Org. Chem.* **1987**, *52*, 3316.

Scheme I

Scheme II. Relative MM2 Energies in kcal/mol Are Shown in Parentheses


to be slower than that of its counterpart 9 in the dienic system. The greater distortion needed to achieve reaction from 18 as compared to 9 is evident in the representations shown, in which the bond that must be broken is marked. The anticipated increased inversion rate and decreased cleavage rate in the putative biradical intermediate 18 cooperate to make the acetylenic case a more sensitive test than the dienic one.

Conformational Inversion in 3,5-Dimethylcyclohexene-1,4-diyls. We propose to use methyl groups as stereochemical markers in the acetylenic Cope rearrangement, as shown in 21–23. It is crucial to know whether the 3,5-dimethyl substitution in the hypothetical intermediate 22 materially affects the rate constant of 3 × 10^{11} s^{-1} deduced above for the conformational isomerization of the unsubstituted cyclohexene-1,4-diyl.
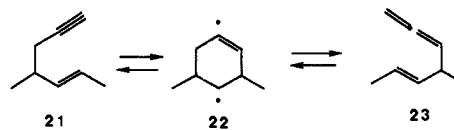
The *trans-* and *cis*-3,5-dimethylcyclohexene-1,4-diyls 24 and 25 (Scheme I) can adopt either of a pair of interconvertible half-chair conformations. In the trans series, one conformation has equatorial (eq) and pseudoaxial (pax) groups, and the other has axial (ax) and pseudoequatorial (peq) groups, whereas in the cis series, the conformations are eq, peq and ax, pax.
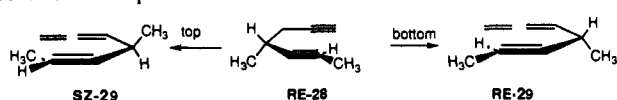
In either pair, if one member is much higher in energy than the other, then a substantial barrier to conformational isomerization will be added to that of the unsubstituted cyclohexene-1,4-diyl, and the ring inversion will be retarded. Qualitatively, the steric effects of substituents on cyclohexene rings are expected to be smaller than those on cyclohexane rings, because no direct analogue of the chair cyclohexane-1,3-diaxial repulsion exists in half-chair cyclohexene.

More quantitative estimates of such effects can be modeled after those in the 3,5-dimethyl-3-cyclohexenones, 26 and 27 (see Scheme II). MM2 calculations[25] show that each has two half-chair
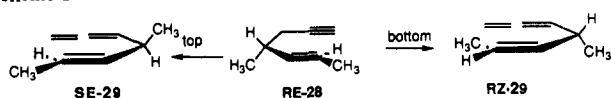
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Scheme III. Suprafacial Allowed

SZ-29   RE-28   RE-29

Scheme IV. Antarafacial Forbidden

SE-29   RE-28   RZ-29

conformations corresponding to energy minima. The relative MM2 energies are shown in Scheme II. As expected, the energy differences indeed are small, amounting to 0.58 kcal/mol favoring the eq, pax conformer over the ax, peq one in the trans series and to 1.13 kcal/mol favoring the eq, peq over the ax, pax one in the cis series. At 471 K, the temperature of most of the experiments described below, these energy differences correspond to conformational equilibrium constants of 3.3 in the cis series and 1.9 in the trans, assuming negligible entropy differences. Therefore, no reason to expect a large thermodynamic conformational barrier is apparent.

Moreover, a body of experimental evidence[22] shows that cyclohexenes with a substituent in an equatorial position have a barrier to ring inversion to the axial conformation that is only about 1 kcal/mol higher than that in cyclohexene itself. These data suggest that only slight modifications of the conformational isomerization rate constant of 3×10^{11} s^{-1} for cyclohexene-1,4-diyl will be needed to produce reasonable models of the rate constants for the interconversions of the 3,5-dimethyl derivatives 24 and 25. For the purposes of the present study, we have done this by adopting for the conformational isomers of the diyls the equilibrium constants calculated for the model compounds in Scheme II and calculating forward and reverse rate constants compatible with these by multiplication of 3×10^{11} s^{-1} by the appropriate factor. We assumed, for example, that an ax, pax conformation would invert slightly faster than the unsubstituted diyl because strain is relieved and that an eq, peq one would invert slightly slower because strain is increased. Details are given in the Results section.

Stereochemical Characteristics of the Acetylenic Cope Rearrangement. Schemes III and IV, respectively, show the suprafacial allowed and antarafacial forbidden pathways hypothetically available to the interconverting 4-methyl-5-hepten-1-yne (28) and 4-methyl-1,2,5-heptatriene (29) pair, the test system of the present experiment. Another set of pathways not shown in Schemes III and IV involves bond formation on the "back" face of the propargyl system, remote from the allyl moiety. Very probably, the latter reactions represent only formal possibilities, since they must overcome severe steric difficulties in order to compete with the sterically favorable "front" face reactions. Strong presumptive evidence that the "back" face pathways may be neglected in the present discussion comes from experimental observations[26] on the propargylic Claisen rearrangement, where such reactions have been ruled out explicitly.

The allowed pericyclic pathway (odd number of suprafacial (s) two-electron elements) is suprafacial overall and enjoys a large apparent advantage over the antarafacial forbidden one because, in addition to the benefit of the usual electronic factors[27,28] as-
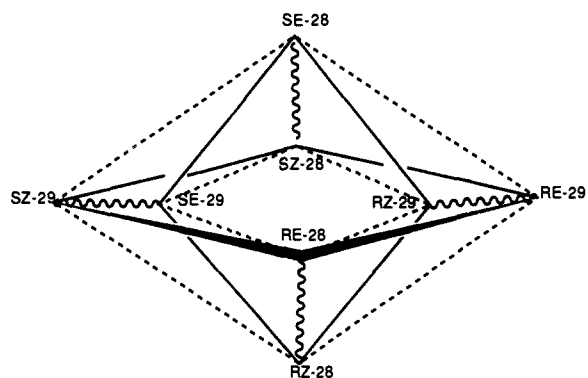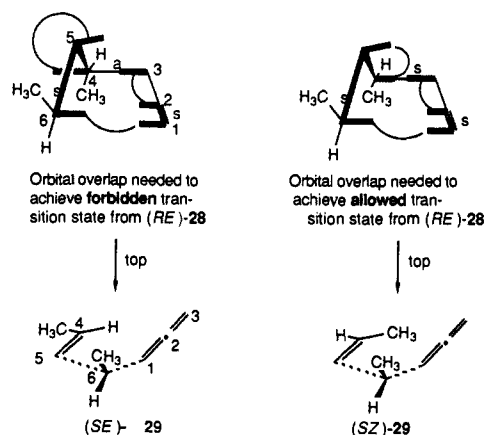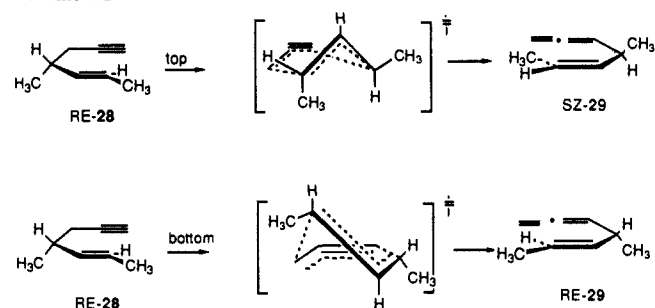

Figure 3. Interconversion paths among acetylenes 28 and allenes 29. The stereochemical descriptors are indicated before the numerals. Solid and dashed lines, respectively, represent suprafacial allowed and antarafacial forbidden sigmatropic rearrangements; wiggly lines represent stereomutation resulting from the equivalent of torsion about the olefinic bond by the mechanism of Scheme VII. Crossover between adjacent suprafacial and antarafacial pathways also can occur by way of hypothetical interconverting biradicals, which are shown in Scheme VII.

Scheme V

Orbital overlap needed to achieve **forbidden** transition state from (*RE*)-28

Orbital overlap needed to achieve **allowed** transition state from (*RE*)-28

(*SE*)-29   (*SZ*)-29

Scheme VI

RE-28   SZ-29

RE-28   RE-29

sociated with an aromatic transition state, the reactant's geometry requires much less distortion to achieve orbital overlap in the allowed transition state (Scheme V). A comparison of the two allowed reactions shows that if the transition-state geometry is assumed to resemble a half-chair, there is no difference in overlap between the top and bottom pathways (Scheme VI). In fact, if the substituents are ideal, that is, serve merely as stereochemical markers, the top and bottom transition states are equienergetic. In the actual case, small biases might be expected in favor of the pathways leading to (*E*)-alkenes, which usually are more stable than their *Z* counterparts.
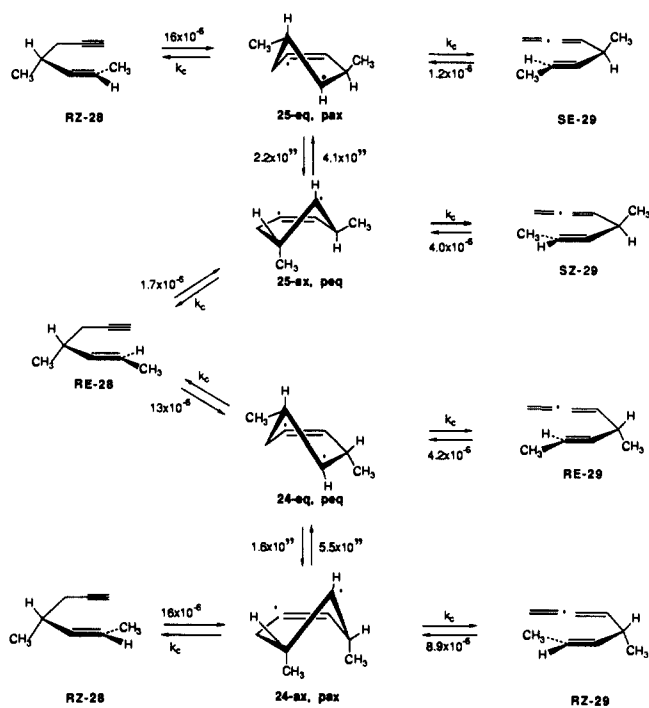
With reference to Schemes III and IV, we expect the stereochemical descriptors to remain locked together if the rearrangement occurs solely by suprafacial allowed or solely by antarafacial forbidden pathways. Thus, the acetylene (*R,E*)-28 should give

(25) (a) Wilson, S. *Chemistry by Computer*; Plenum Press: New York, 1986; pp 85-111. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, D.C., 1982; ACS Monograph Series No. 177. (c) We thank Professor Martin Saunders for making available his graphics input routine for the MM2 calculations.

(26) (a) Evans, R. J. D.; Landor, S. R.; Regan, J. P. *Chem. Commun.* 1965, 397. (b) Evans, R. J. D.; Landor, S. R.; Regan, J. P. *J. Chem. Soc., Perkin Trans.* 1974, *1*, 552. (c) Landor, S. R.; Miller, B. J.; Regan, J. P.; Tatchell, A. R. *Chem. Commun.* 1966, 585. (d) Landor, S. R.; Miller, B. J.; Regan, J. P.; Tatchell, A. R. *J. Chem. Soc., Perkin Trans.* 1974, *1*, 557.

(27) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim/Bergstrasse, Germany, and Academic Press: New York, 1970; p 148ff.

(28) Fukui, K. *Acc. Chem. Res.* 1971, *4*, 57. (b) Fukui, K. *Theory of Orientation and Stereoselection*; Springer-Verlag: Berlin, 1975; p 62.

Thermal Acetylenic Cope Rearrangement Stereochemistry

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Scheme VII[a]

[a] Rate constants in s[-1].

two allenes, (S,Z)- and (R,E)-29, if the reaction is allowed, and two different allenes, (S,E)- and (R,Z)-29, if it is forbidden. In this sense, the outcome recalls the result of the Hill–Gilman experiment mentioned above. However, the substitution pattern in the present work ensures that the rearrangements all will be reversible, and each allene formed in the first rearrangement will be capable of rearranging back to its precursor acetylene directly. Moreover, a competing rearrangement will convert the allene to a diastereomeric acetylene which in turn can rearrange to a new allene and so on. This constitutes an indirect pathway for eventual return to the starting material by a continuation of the forward rearrangements in a total of four steps. If the reaction is mechanistically homogeneous (all suprafacial allowed or all antarafacial forbidden), the original acetylene will be recovered uncontaminated by its enantiomer. These pathways may be represented by the nested lozenges shown in Figure 3, which depicts strict adherence to the suprafacial allowed (full line) or antarafacial forbidden (dashed line) pathway as unerring forward or reverse motion along such a line. If, however, *both* pathways can be populated, racemization can occur, most simply (but not only) by two successive steps, suprafacial and antarafacial, or vice versa. A favorable feature of this experimental design is the sensitivity to small incursions of a minor pathway. Since racemization is irreversible, a small amount of the racemic mixture formed in each pass through the scheme gradually will build up, and the enantiomeric purity of the system gradually will be degraded, so that at infinite time, all of the sigmatropically related components will be racemic.

In principle, such racemizations might occur by concurrent suprafacial and antarafacial pathways without intermediates or, more pertinently to the present test, by crossover between the suprafacial and antarafacial pathways through a true intermediate that lives long enough to undergo conformational isomerization (see Scheme VII). (The source of the rate constant values shown in this scheme is described below.) For example, if biradical 25-ax, peq, formed by closure of (R,E)-28 on the top face of the double bond, were simply to proceed to allenic product (S,Z)-29, the reaction would be indistinguishable from a suprafacial concerted rearrangement. However, conformational isomerization 25-ax, peq → 25-eq, pax followed by cleavage of one of the bonds β to the radical centers of 25-eq, pax could occur to give either $(S,-E)$-29, an orbital symmetry forbidden allenic product, or (R,Z)-28, an acetylene that differs from the starting one only in the con-

Scheme VIII
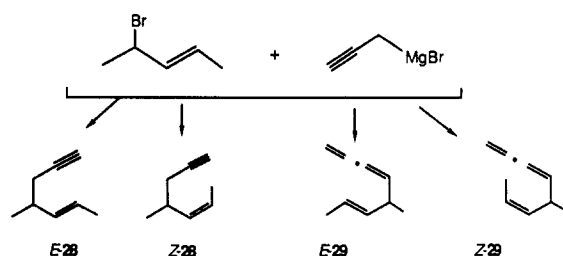
figuration of the double bond. Similarly, in the bottom-face pathway, the interconversion of biradicals 24-eq, peq → 24-ax, pax would permit the formation of forbidden allenic product (R,Z)-29 as well as stereoisomerized acetylene (R,Z)-28. The double bond torsion pathways are shown as wiggly lines in Figure 3.

Notice that the individual biradical isomerizations themselves (e.g., 25-ax, peq → 25-eq, pax) are not racemizing events because the conformations are not enantiomeric. Nevertheless, they have the ultimate effect of producing racemization by connecting the suprafacial and antarafacial pathways (Figure 3 and Scheme VII). For example, (R,E)-28 could be converted to its enantiomer (S,E)-28 by a sequence of steps such as top ring closure to biradical 25-ax, peq, conformational isomerization 25-ax, peq → 25-eq, pax, bottom ring opening to allene (S,E)-29, top ring closure of $(S,-E)$-29 to a biradical, and ring cleavage of the latter to (S,E)-28.

Results

Pyrolyses of the 4-Methyl-5-hepten-1-ynes and the 4-Methyl-1,2,5-heptatrienes 28 and 29. The racemic E and Z isomers of 28 and 29 were obtained as a mixture from the reaction of 4-bromo-2-pentene with propargylmagnesium bromide (Scheme VIII). In each case, the E isomer was formed in preference to its Z counterpart by a ratio of about 8:1. The acetylenes 28 were separated from the allenes 29 by preparative gas chromatography (GC) on a column with a Carbowax 20M stationary phase. Separation of the E and Z isomers of acetylene 28 and allene 29 then were achieved with γ-methyl-γ-nitropimelonitrile and silver tetrafluoroborate/Carbowax 600 columns, respectively.

The four components (E)-28, (Z)-28, (E)-29, and (Z)-29, interconvert through Cope rearrangements at temperatures near 200 °C. In addition, the allenic materials 29 undergo other slow irreversible side reactions. In order to determine the rate constants for all the reactions over the widest possible range of composition, a mixture of acetylenes (E)- and (Z)-28 was used as the starting material. The pyrolyses were conducted on gaseous samples at approximately 0.9 atm in silanized glass tubes.

Because of the symmetrical allylic moiety, the labeling pattern used here does not explicitly exclude the formal possibility that the rearrangement 28 → 29 could be a 1,3-shift of the 3-pentenyl-2-yl group across the propargyl system, instead of a [3,3]-rearrangement. However, this mechanism would predict that the double bond stereochemistry would be preserved, which conflicts with the observed formation of *both* double bond isomers of allene 29 from either double bond configuration of acetylene 28. Moreover, it would require that the present system employ a different mechanism from that of its immediate lower homolog 30, whose unsymmetrical allylic system permits the distinction to be made on simple structural grounds. Compound 30 gives only the [3,3]-rearrangement product 31, instead of the [1,3]-product 32.[2b,3]
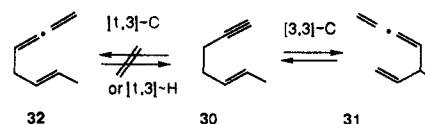
This experiment also excludes a [1,3]-*hydrogen* shift in 30, which would have given the absent product 32. Also, by isotopic labeling, we now have provided direct evidence against a [1,3]-hydrogen shift in 28-7-*d*. Pyrolysis of this material gave

Scheme IX[*a*]

Scheme X
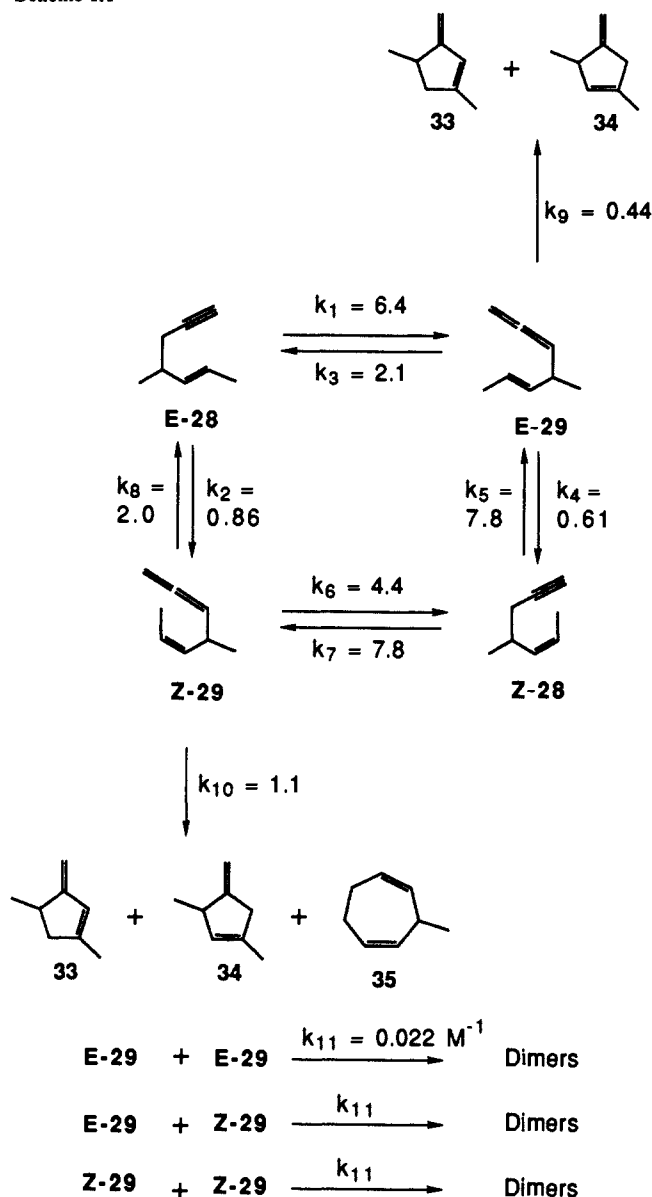
[*a*] Rate constants k in units of 10^6 s^{-1} at 471 K.

(*E*)-29 with >98% of the deuterium label located at C_3, as required for carbon [3,3]-sigmatropy.
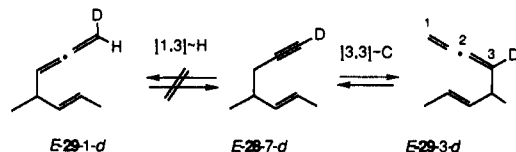
Pyrolysis of the 8:1 (*E,Z*)-28 mixture gave (*E*)- and (*Z*)-29 as major products along with three minor components, formed initially in a total yield of ~3%. We believe these to be the cyclization products 33–35 (Scheme IX), formally derived by well-precedented[2] intramolecular ene reactions. Reaction times up to almost 2 half-lives gave nearly quantitative material balances of the rearrangement and cyclization products, but at longer times the formation of new secondary products with long GC retention times became apparent. We assume these are allene dimers.[6c] The rate of dimer formation should increase as the concentration of allene isomers increases. The dimerization, being bimolecular, occurs at a rate that is a function of the pressure of the starting material. Since this pressure varied in the range of 0.7–1.1 atm, the composition vs time data at high conversions contain some inherent scatter. The irreversible diversion of the Cope isomers 28 and 29 to cyclization and dimerization products fortunately
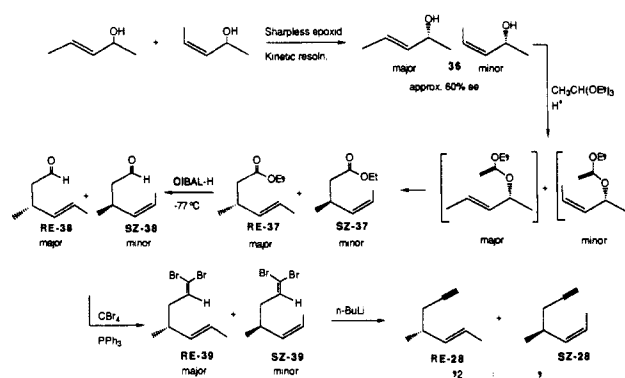
was slow enough to permit recovery of 28 and 29, even after 6 half-lives of the rearrangement of 28.

One can derive approximate equilibrium ratios (*E*)-28/(*E*)-29/(*Z*)-28/(*Z*)-29 of 1.0:2.7:0.2:0.3 from the product ratios at long reaction times. These are in reasonable agreement with the composition predicted from group additivities:[11-13] 1.00:2.35:0.34:0.81.

Simulation of Concentration vs Time Profiles and Extraction of Individual Rate Constants in the Racemic Series. Scheme IX shows the rate constants for the reversible circuit of acetylenic Cope rearrangements and the irreversible exits to cyclic ene products and dimers. The numbered rate constants for the rearrangements are phenomenological, that is they include all mechanistic contributions. For convenience, the conversions to ene cyclization products were assigned a composite rate constant from each of the allenes. The allene dimerizations were assumed to be governed by a single rate constant.

The kinetic characterization can be achieved by matching the observed composition vs time data with values calculated from Scheme IX, by using the phenomenological rate coefficients as adjustable parameters. Initial estimates were made from early kinetic points and the equilibrium constants, which were evaluated from group additivity constants as just described. The composition profile was then calculated by two separate procedures: a Runge–Kutta numerical integration[29a-d] of the set of kinetic differential equations and a stochastic simulation.[29e] Both methods gave essentially identical results. The rate coefficients were then adjusted, and the calculation was repeated to optimize the fit. Throughout this procedure, the constraints of microscopic reversibility ($k_1 \times k_4 \times k_7 \times k_8 = k_2 \times k_6 \times k_5 \times k_3$) were imposed upon the sets of rate coefficients for the cyclic interconversions of Scheme IX. The equilibrium constants between the pairs of interconverting isomers of Scheme IX calculated from the ratios of the corresponding pairs of simulated rate coefficients differ from the values originally approximated experimentally by an average of about 15%.

Synthesis of Optically Active (–)-(*R*)-*trans*-4-Methyl-5-hepten-1-yne ((*R,E*)-28) and (+)-(*S*)-*cis*-4-Methyl-5-hepten-1-yne ((*S,Z*)-28) (Scheme X). The enantiomerically enriched pyrolysis substrates were prepared from the optically active esters (*R,E*)-37 and (*S,Z*)-37, which in turn were available by orthoester Claisen rearrangement from the trans and cis isomers of (*R*)-3-penten-2-ol (36) following a procedure of Hill, Soman, and Sawada.[30a-c] We obtained the latter alcohols as a mixture consisting mostly of the

(29) (a) The program originally was written by Professor M. Saunders and subsequently modified by P. M. Lahti, D. M. Birney, and S. J. Getty. (b) For a more detailed description of the application of the program, see: Holder, R. W. Ph.D. Thesis, Yale University, 1972; pp 197–206. (c) For a description of numerical integration procedures, see: Milne, W. E. *Numerical Solution of Differential Equations*; Wiley: New York, 1953. (d) The numerical integration program is most accurate for small time intervals. A value of 0.01 h was typically used. The quality of the fit was judged by the total absolute difference between the experimental and simulated values at several representative times. (e) Bunker, D. L.; Houle, R. A. MSIM4 Discrete Mechanism Simulator, Program No. 293, Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN.

Thermal Acetylenic Cope Rearrangement Stereochemistry

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Table I. Specific Rotations ($[a]^{21}_{365}$, deg) of Starting Materials and Products after Pyrolysis at 198 °C (471 K) for 75 h

compound	before pyrolysis	after pyrolysis
RE-28	-7.7 ± 1	-10 ± 2
SZ-28	$+74 \pm 10$	$+62 \pm 10$
E-29		-219 ± 20
Z-29		$+323 \pm 20$

Scheme XI

(+)-(*R*)-trans isomer from racemic 3-penten-2-ol (97% trans, 3% cis) in about 60% enantiomeric excess (ee) by a kinetic resolution by using Sharpless[30d,e] epoxidation conditions. As is discussed elsewhere,[31] the ee of (*R*,*E*)-**37** and of (*S*,*Z*)-**37** may differ slightly from each other, but the subsequent findings in the pyrolyses of the hydrocarbons derived from them showed that the difference, if present, is negligibly small.

Reduction of the isomeric esters **37** with diisobutylaluminum hydride (DIBAL-H) at −78 °C gave the aldehydes (*R*,*E*)-**38** and (*S*,*Z*)-**38**. Conversion of the formyl group to ethynyl by a modification[32a] of a two-step procedure in the literature[32b] involved dibromomethylenation of the aldehydes to the 1,1-dibromoalkenes (*R*,*E*)-**39** and (*S*,*Z*)-**39**, which upon treatment with 2 equiv of *n*-butyllithium followed by a water quench gave a mixture of terminal alkynes. Final purification of the alkynes (*R*,*E*)-**28** and (*S*,*Z*)-**28** was accomplished by preparative GC.

Pyrolysis of Optically Active Acetylenes (*R*,*E*)-28 and (*S*,-Z)-28. Analysis by Polarimetry. In the first series of experiments, the optical rotations of the starting alkynes (*R*,*E*)-**28** and (*S*,*Z*)-**28** were compared to those of (*R*,*E*)-**28** and (*S*,*Z*)-**28** recovered after gas-phase pyrolysis at 198 °C of a 12:1 mixture of (*R*,*E*)- and (*S*,*Z*)-**28** for 75 h (approximately 2.5 half-lives). The pyrolysis products, allenes (*E*)- and (*Z*)-**29**, also were recovered. The results are presented in Table I. Because the amounts of material were limited, and because the rotations had to be determined on mixtures by the solution of two simultaneous equations for two unknowns (see the Experimental Section), the data have a substantial uncertainty. It is clear that although little if any racemization of the starting alkynes **28** occurs under these conditions, small but significant amounts of it might well have escaped detection by the crude method used. The allenic products also were optically active (Table I), but the rotation values could not be interpreted, since stereochemical correlations of these substances with the starting alkynes were lacking. Thus, not only was the degree of preservation of enantiomeric purity in the products not determinable but also the configurations of the dominant enantiomers of the allenic products were not known. It is the latter piece of information that would permit a decision on whether the major rearrangement pathway belongs to the suprafacial allowed or antarafacial forbidden designation.
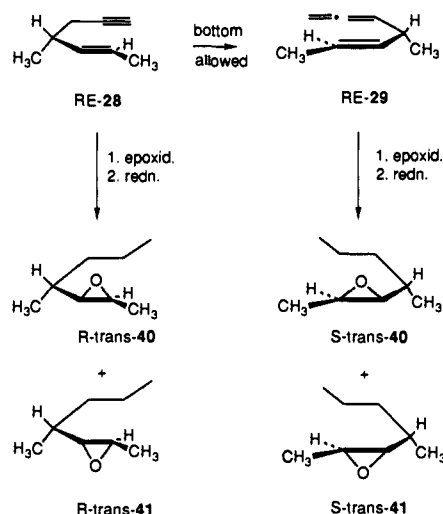
Analysis by Enantioselective Gas Chromatography ("Complexation GC"). The separation of enantiomers by complexation GC on capillary columns wall-coated with stationary phases consisting of enantiomerically pure metal complexes[33,34] provides a more accurate method of analysis for enantiomeric purity. Although the columns used in the present work were ineffective in separating the enantiomers of either the starting alkynes (*E*)- and (*Z*)-**28** or the products allenes (*E*)- and (*Z*)-**29**, suitable substrates for this purpose were found in the oxirane derivatives of the hydrocarbons prepared by epoxidation of the double bond and reduction of the acetylenic or allenic function (Scheme XI).[35] Moreover, this particular derivative permitted the direct correlation of the configuration of the *trans*-allene to that of the *trans*-acetylene (which had been established by synthesis), because the saturated epoxide from either source has the same structure. This formed the basis for an assignment of the pathway to the formally allowed or the formally forbidden category. For example, Scheme III and Figure 3 show the product of a suprafacial allowed rearrangement of acetylene (*R*,*E*)-**28** to be allene (*R*,*E*)-**29**. Scheme XI shows that epoxidation and reduction of (*R*,*E*)-**28** would give two diastereomeric epoxides, (*R*)-*trans*-**40** and (*R*)-*trans*-**41**, whereas the same treatment of (*R*,*E*)-**29** would give (*S*)-*trans*-**40** and (*S*)-*trans*-**41**. (Note that by the nomenclatural sequence rule, the priorities are allenyl > propenyl > propargyl.) The suprafacial allowed rearrangement therefore gives an (*E*)-allene whose reduced epoxides each are *enantiomeric* with those derived from the starting acetylene. Similarly, the allowed allenic products in the cis series, (*Z*)-**29**, would give reduced epoxides enantiomeric with those from the corresponding acetylene, (*Z*)-**28**. If the rearrangement occurs stereospecifically by the suprafacial allowed pathway, and if the complexation column is enantiomerically discriminatory, the value of the enantiomeric ratio determined from the peak areas of the chromatogram of the reduced epoxide of the *acetylenic* reactant (*E*)- or (*Z*)-**28** recovered from pyrolysis should be the same as that derived from the starting acetylene. The value of the enantiomeric ratio in the reduced epoxide from the *allenic* product, (*Z*)- or (*E*)-**29**, should be the *inverse*. Any mechanistic departure from this pathway would be signalled not only by a decrease in the ratio in recovered acetylene but also by a less than exact adherence to the inverse relationship in the allene product.

(30) (a) Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem.* **1972**, *37*, 3737. (b) See, also: Chan, K.-K.; Cohen, N.; DeNoble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (c) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505, 3512. (d) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6239. (e) The reaction workup was based on a procedure described by Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (f) For absolute configurational correlation, see: refs 30d, 30g, and 30h. (g) Levene, P. A.; Haller, H. J. *J. Biol. Chem.* **1929**, *81*, 703. (h) Hills, H. W. J.; Kenyon, J.; Phillips, H. J. *J. Chem. Soc.* **1936**, 576.
(31) (a) Owens, K. A. Ph.D. Thesis, Yale University, New Haven, CT, 1988; pp 144–146. (b) For further discussion, see Supplementary Material.
(32) (a) Modified by Stark, E. J. Unpublished work at Yale University. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(33) (a) Gil-Av, E.; Feibush, B.; Charles-Sigler, R. *Tetrahedron Lett.* **1966**, 1009. (b) Schurig, V. *Kontakte* (Darmstadt) **1986**, *1*, 3.
(34) (a) Schurig, V.; Weber, R. *J. Chromatogr.* **1981**, *217*, 51–70. (b) We thank Professor S. L. Schreiber for calling this work to our attention.
(35) Prof. Dr. Frank-Volker Schurig kindly provided us with much helpful advice. His group initially recommended the Ni-R-Cam column and found conditions that allowed *trans*-**40**, *trans*-**41**, *cis*-**40**, and *cis*-**41** each to be analytically resolved into their enantiomeric components. In the preliminary analyses performed by the Schurig group, both cis diastereomers were detected and cleanly resolved into their enantiomers.

Scheme XII

RE-28   SZ-28

1 eq. m-CPBA

R-trans-42   R-trans-43
major   major

S-cis-42   S-cis-43
minor   minor

Pt/C, H₂
———
THF

R-trans-40   R-trans-41
major   major

S-cis-40   S-cis-41
minor   minor

Scheme XIII

E-29   Z-29
major   minor

m-CPBA

2 diastereomers   2 diastereomers
trans-44 and   cis-44 and
trans-45   cis-45
major   minor

N₂H₄
———
H₂O₂

2 diastereomers   2 diastereomers
trans-40 and   cis-40 and
trans-41   cis-41
major   minor
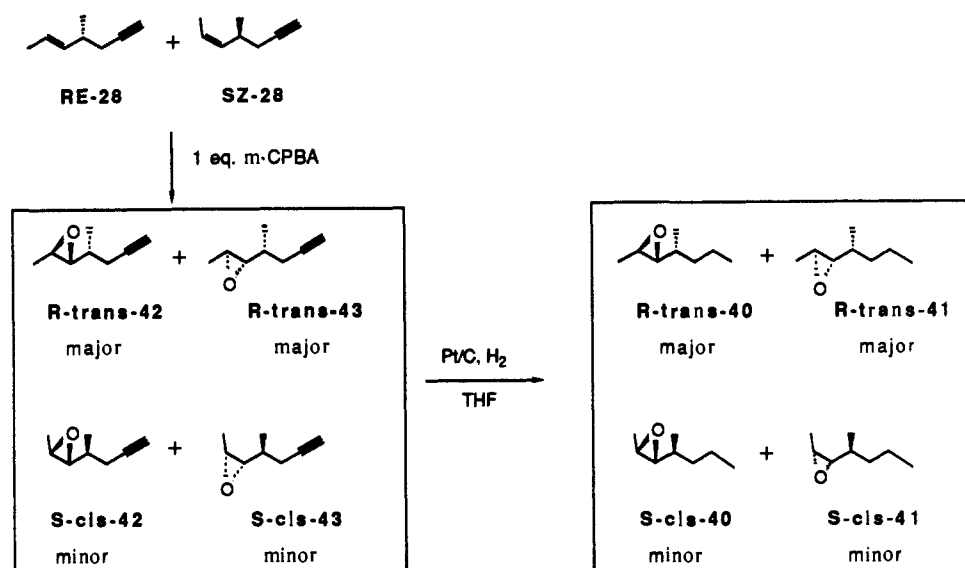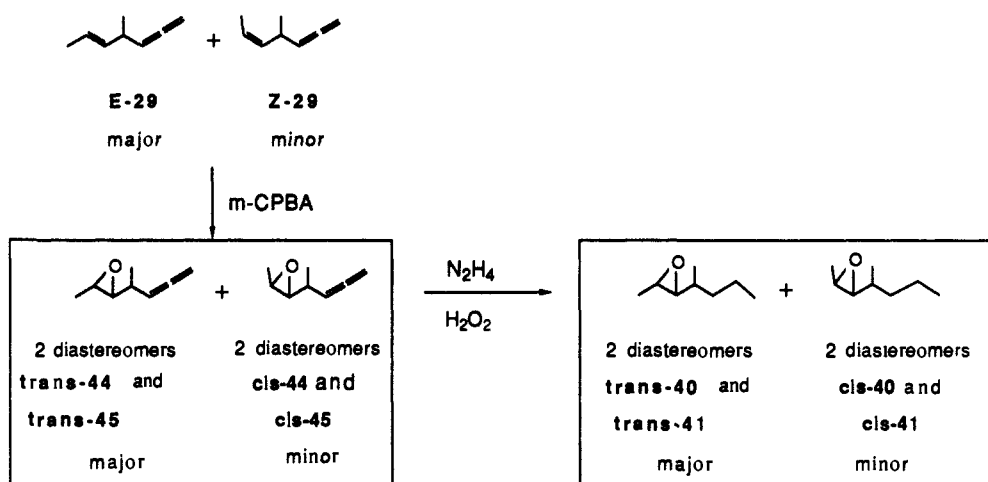
The two-step sequence exemplified in Scheme XI was applied to the starting mixture (12:1) of acetylenes, (R,E)-28 and (S,Z)-28 (Scheme XII). One equivalent of m-chloroperbenzoic acid epoxidized these substances selectively at the double bond, presumably by syn addition[36a] to both faces, to give a mixture of four diastereomeric acetylenic epoxides. From the product ratio of 12:11:1.2:1.0 determined by achiral stationary phase capillary GC, it is apparent that the epoxidation is facially nonstereoselective. The two major components were assigned as the two trans diastereomers (2R,3R,4R)-3-methyl-2-(1-methyl-3-butynyl)oxirane, (R)-trans-42, and (2S,3S,4R)-3-methyl-2-(1-methyl-3-butynyl)oxirane, (R)-trans-43. Which chromatographic peak corresponds to which diastereomer is not known. Similarly, the two minor components were assigned as the two cis diastereomers, (2R,3S,4S)- and (2S,3R,4S)-3-methyl-2-(1-methyl-3-butynyl)-oxirane, (S)-cis-42 and (S)-cis-43. Again, specific peak assignments cannot be made on the basis of the available information. The mixture of four diastereomeric acetylenic epoxides was catalytically hydrogenated to a mixture of four diastereomeric 3-methyl-2-(1-methylbutyl)oxiranes, two ((R)-trans-40 and (R)-trans-41) with trans and two ((S)-cis-40 and (S)-cis-41) with cis configurations at the carbon centers of the oxirane ring (Scheme XII).

Similarly, epoxidation of the mixture of allenic rearrangement products (E)- and (Z)-29 (Scheme XIII) gave four diastereomeric

allenic epoxides, consisting of two major isomers trans-44 and trans-45 (diastereomers of trans-3-methyl-2-(1-methyl-2,3-butadienyl)oxirane) and two minor isomers cis-44 and cis-45 (diastereomers of cis-3-methyl-2-(1-methyl-2,3-butadienyl)oxirane). Again, the epoxidation was facially nonstereoselective, the trans and cis pairs of isomers being formed in ratios of 1.0:1.0 and 1.0:1.8, respectively. In the optically active series, we found that catalytic hydrogenation of these allenic epoxides to the four diastereomers trans- and cis-40 and -41 resulted in some loss of enantiomeric purity, presumably because of the vulnerability of the allylically activated stereogenic center at C₄.[36b] Accordingly, we resorted to diimide reduction, which proceeded without this difficulty (Scheme XIII).

To determine the enantiomeric composition of the individual diastereomeric components of the reduced epoxides, we used a tandem column capillary GC system consisting of a 50-m achiral methyl silicone column followed by a 23-m column wall-coated with a stationary phase of enantiomerically pure nickel(II) bis-(3-heptafluorobutyryl-1-R-camphorate) (Ni-R-Cam) in methyl silicone.[34,35] The optimum analytical conditions[22] for the present case were established by analysis of a mixture of the racemic forms of the four diastereomers trans- and cis-40 and -41.

The starting 12:1 mixture of optically active acetylenes (R,E)-28 and (S,Z)-28 obtained from the synthesis of Scheme X had approximately 60% ee as determined by NMR analysis of the spectrum of a mixture of the acetate of the (R)-3-penten-2-ol used there with a sample of optically active lanthanide shift reagent. A more accurate value was obtained by analysis of the reduced epoxides (see Scheme XII) (R)-trans-40 and (R)-trans-41 derived

(36) (a) Carruthers, W. *Some Modern Methods of Organic Synthesis*; Cambridge University Press: Cambridge, 1978; p 364. (b) Carruthers, W. *Ibid.* pp 424-426.

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Table II. Percent Optical Yield[a] of Products After Pyrolysis at 198 °C Determined by "Complexation GC" of the Derived Epoxides[b]

pyrolysis time (h)	pyrolysis product	
	RE-28	RE-29
48	96% ± 3%	90% ± 2%
144	94% ± 4%	90% ± 4%

[a] Defined as the percent of enantiomeric purity of (*R,E*)-**28** before pyrolysis retained in the pyrolysis products. [b] Errors are given as twice the standard deviation of the mean $(2s_m)$ of at least five repeated measurements.

from (*R,E*)-**28** with the tandem GC system which showed areas of the peaks of the enantiomers of the resolvable trans diastereoisomer in a ratio corresponding to 62.2 ± 0.8% ee in good agreement with the value of 60% expected from the synthesis.

Two pyrolyses of the 12:1 mixture of optically active acetylenes under the standard conditions at 198 °C were carried out, one for 48 h and one for 144 h. These times correspond to about 1.6 and 4.8 half-lives, respectively, of the major rearrangement reaction (*E*)-**28** → (*E*)-**29** by the direct pathway of Scheme IX (k_1 = 6.4 × 10⁻⁶ s⁻¹).

A mixture of acetylenes (*R,E*)-**28** and (*S,Z*)-**28** was isolated from the 48-h pyrolysate by preparative GC and converted to the epoxides **42** and **43**, which were hydrogenated to the mixture of four diastereomers (*R*)-*trans*-**40**, (*R*)-*trans*-**41**, (*S*)-*cis*-**40**, and (*S*)-*cis*-**41** (see Scheme XII). As before, the tandem capillary column resolved only one of the hydrogenated trans diastereomers into enantiomers. These were present in a ratio of 79.75:20.25, or 59.5 ± 1.6% ee, which corresponds to 96 ± 3% preservation of the enantiomeric purity of the starting material. Note that the predominant enantiomer in this diastereomeric epoxide is the same as that derived from the starting acetylene (*R,E*)-**28**, as would be expected. The 144-h pyrolysate after the same procedure furnished resolvable reduced epoxide with 94 ± 4% preservation of enantiomeric purity. These results are summarized in Table II.

Similarly, a mixture of the allenes (*E*)- and (*Z*)-**29** formed in the pyrolyses were isolated by preparative GC, epoxidized, and reduced (Scheme XIII) to a mixture of the same four diastereomers as had been obtained from the acetylenes. Analysis with the tandem capillary GC column showed that the ratio of enantiomers in the resolvable diastereomer from the (*E*)-allene rearrangement product **29** was the *inverse* of that from the (*E*)-acetylene reactant **28**, as would be expected if the reaction had taken predominantly the suprafacial allowed path. The enantiomeric purity delivered in the allene was determined by GC to be 90 ± 2% and 90 ± 4% of that of the starting material for the 48-h and 144-h runs, respectively (see Table II).[37]

Table II shows an apparent loss of enantiomeric purity in both the rearrangement product and the recovered starting material after pyrolysis. Some doubt is cast on the reality of these small losses, however. Because of the reversibility of the rearrangements, the amount of racemization would be expected to increase with continued pyrolysis, but the experimental values do not change appreciably between 1.6 and 4.8 half-lives. Thus, if all of the apparent racemization of the starting (*R,E*)-**28** and product **29** after 1.6 half-lives were associated with the rearrangement, the optical yields after 4.8 half-lives should have been (on the assumption of first-order racemization kinetics) 88% and 73%, respectively, which are significantly below the values observed (Table II).

The apparently greater racemization of the allenic product as compared to the recovered acetylene (Table II) is attributable at least in part to a systematic error in the capillary GC analysis. The source of this difficulty appears in the chromatogram[31] of the resolvable diastereoisomeric reduced epoxide from the allenic product, where a small impurity peak encroaches on the tail of the peak of the (*S*)-enantiomer. This made integration of the entire area of the major enantiomer peak difficult and had the
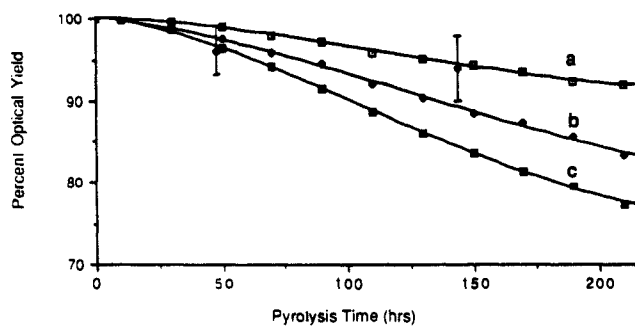

Figure 4. Simulated optical yield of (*R,E*)-**28** versus time in the pyrolysis of (*R,E*)-**28** assuming competitive allowed and forbidden pathways. The curves marked a, b, and c represent forbidden contributions (*m*) of 1%, 2%, and 3%, respectively. Experimental points with error bars are shown.
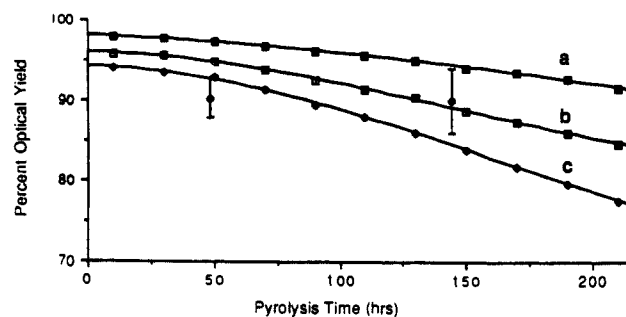

Figure 5. Simulated optical yield of (*R,E*)-**29** versus time in the pyrolysis of (*R,E*)-**28**. The labels on the curves have the same significance as in Figure 4.

effect of decreasing the apparent ee.

Kinetic Simulations of the Rearrangement Mechanism. A better estimate of the fidelity with which these rearrangements follow the allowed suprafacial pathway in the mechanism of Figure 3 is given by a computational simulation of the optical yield vs time profile for varying assumed small contributions of the antarafacial forbidden pathway, by using the stochastic program[29e] (MSIM4 discrete mechanism simulator). (Not shown explicitly in Figure 3 but included in the simulations are the secondary cyclization and dimerization reactions of the allenic products (*E*)- and (*Z*)-**29**.) The details are given in the Supplementary Material and elsewhere.[22]

Figures 4 and 5 show the optical yields (relative percent ee) of (*R,E*)-**28** and (*R,E*)-**29** versus time calculated for 1%, 2%, and 3% hypothetical contributions from the antarafacial forbidden pathways. Although the losses of ee initially would be small, they steadily would increase with time as the molecules experienced consecutive rearrangements. The graphs indicate that the antarafacial pathway cannot account for more than about 2% of the total rearrangement.

What now remains to be deduced is the ratio of rate constants for bond cleavage and ring conformational inversion of the hypothetical 3,5-dimethylcyclohexene-1,4-diyl intermediates permitted by the experimental data. The first step in the extraction of this ratio is the assignment of rate constants for conformational inversion by multiplying the experimentally determined rate of inversion of unsubstituted cyclohexene-1,4-diyl, 3 × 10¹¹ s⁻¹, by factors that take into account the presence of the methyl substituents. These factors were obtained from the MM2 calculations summarized in Scheme II. The energy differences in the 2,6-dimethyl-3-cyclohexenone model compounds show a preference of 0.58 kcal/mol for the eq, pax over the ax, peq conformation in the trans series **26** and a preference of 1.13 kcal/mol for the eq, peq over the ax, pax conformation in the cis series **27**. At the reaction temperature of 471 K, these correspond to ratios of rate constants (equilibrium constants) for ring conformational inversion of 1.9 in the trans series and 3.3 in the cis series, as previously discussed. We assume that these model ratios apply to the hypothetical biradicals **24** and **25** in the present acetylenic Cope rearrangements, and we further assume that the absolute values
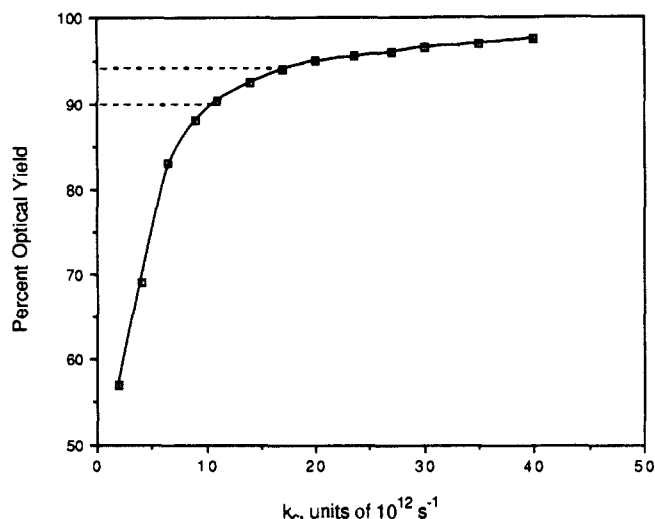
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Figure 6. Simulated optical yield of (R,E)-28 after pyrolysis for 144 h at 198 °C versus rate constant (k_c) of cleavage of the hypothetical biradical. Upper and lower dashed lines represent optical yield observed and the lower limit allowed by experimental error, respectively.
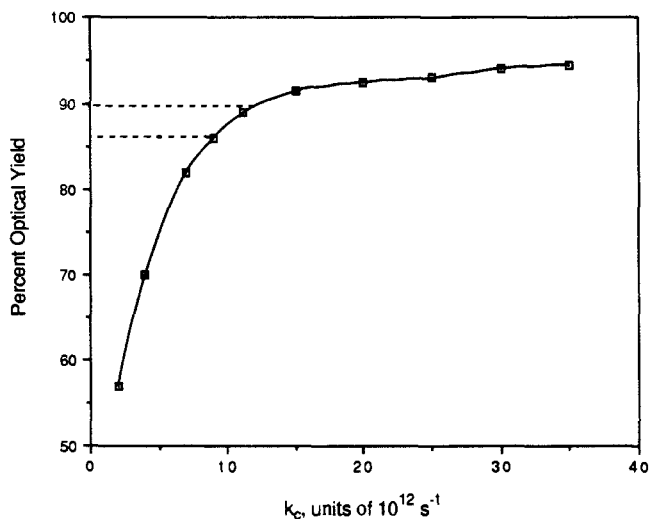

Figure 7. Simulated optical yield of (R,E)-29 from the 144 h pyrolysis at 198 °C versus rate constant (k_c) of cleavage of the hypothetical biradical. Upper and lower dashed lines represent optical yield observed and the lower limit allowed by experimental error, respectively.

of the isomerization rate constants in the substituted cases may be treated as perturbations on the experimentally measured rate, 3×10^{11} s^{-1}, for the unsubstituted cyclohexene-1,4-diyl. Thus, the isomerization rate constants ($\times 10^{-11}$ s) in the trans series from (R,E)-28 reactant are 4.1 ($3 \times \sqrt{1.9}$) and 2.2 ($3 \times 1/\sqrt{1.9}$) for ax, peq → eq, pax and eq, pax → ax, peq, respectively (see Scheme VII). In the cis series, the corresponding values are 1.6 ($3 \times 1/\sqrt{3.3}$) and 5.5 ($3 \times \sqrt{3.3}$) for eq, peq → ax, pax and ax, pax → eq, peq, respectively. By symmetry, these values apply also in the series of transformations initiated from (S,E)-28 reactant.

We assume that all of the rate constants (k_c of Scheme VII) for cleavage of the biradicals are equal. The conclusions we shall draw do not depend sensitively on whether the cleavage rates differ slightly.

Next, we assign rate constants to the various ring-closure steps in which biradicals are formed, taking into account that so little racemization was observed experimentally that the biradicals must be assumed to cleave predominantly from their natal conformation. For example, when (R,E)-28 cyclizes by "bottom" closure, it forms biradical 24-eq, peq, which cleaves efficiently to (R,E)-29 (Scheme VII). The rate constant for "bottom" closure of (R,E)-28 is twice the overall rate constant for the conversion of (E)-28 to (E)-29, because the biradical eq, peq undergoes cleavage to (R,E)-28 and (R,E)-29 at equal rates. Since the (E)-28 → (E)-29 rate constant was found above experimentally to be 6.4×10^{-6} s^{-1} at the reaction temperature of 198 °C (Scheme IX), the closure rate constant for (R,E)-28 → eq, peq is 13×10^{-6} s^{-1}.

Since the rate constants for all of the steps except cleavage now have been assigned values, the simulation problem is reduced to finding the value of the cleavage rate constant that optimizes the fit of the simulated optical yield (ee) vs time profile to the experimental data. The simulation was carried out with the MSIM4 program under the constraints that microscopic reversibility be obeyed and that the relative product distribution of (E)-28, (E)-29, (Z)-28, and (Z)-29, as well as that of the cyclization and dimerization products, fit the experimental values over the range of cleavage rates tested. The mechanism simulated involved the full set of interconversions of Figure 3 occurring by the biradical intermediates of Scheme VII (and the corresponding enantiomeric scheme not shown here), in addition to irreversible exits to dimerization and cyclization products shown in Scheme IX.

The simulation results are shown in Figures 6 and 7, which show the percent optical yield of acetylenic ((R,E)-28) and allenic ((R,E)-29) products vs the tested cleavage rate constant after 144 h (4.8 half-lives) of pyrolysis of (R,E)-28 at 198 °C. Figure 6 shows that achievement of the observed 94% optical yield (90% lower limit) in recovered (R,E)-28 requires a cleavage rate constant of 19×10^{12} s^{-1} (11×10^{12} s^{-1} lower limit). Similarly, Figure

7 shows that for the pyrolysis to furnish (R,E)-29 with the observed optical yield of 90% (86% lower limit) requires a cleavage rate constant of 12×10^{12} s^{-1} (8.3×10^{12} s^{-1} lower limit). The optical yield values fall precipitately when the cleavage rate constant is chosen to be less than 10×10^{12} s^{-1} and drop below 50% for a k_c value of 10^{12} s^{-1}. The total rate constant for decomposition of the biradical intermediate is twice the value of k_c, which leads to assignments of values of 10^{13} s^{-1} $\times$ 3.8 (2.2) and 10^{13} s^{-1} $\times$ 2.4 (1.7). Since the upper limit from transition-state theory for the decomposition of the biradical at this temperature is 1×10^{13} s^{-1}, it may be deduced that at most a small contribution of the stepwise pathway through a biradical intermediate is permitted.

To demonstrate that these results require that all of the cleavage rates be fast and are not an artifact of the assumption of equal cleavage rates for all the hypothetical biradical intermediates, we repeated the simulation with the cleavage leading from the biradical to the acetylenic products set at a fast rate constant, 10 $\times 10^{12}$ s^{-1}, and the cleavage leading from the biradical to allenic products set at a slower value, 0.2×10^{12} s^{-1}. (To achieve the correct product distributions, the rates of formation of the biradicals had to be adjusted, so that the closure rate constants from the acetylenes and from the allenes were set at three times and 0.6 times the values shown in Scheme VII.) This simulation computed the optical yields for (R,E)-28 and (R,E)-29 after 144 h of pyrolysis to be 64% and 70%, respectively. Clearly these results are incompatible with the experimental data and demonstrate that no slow cleavage rate constant can be hiding in the mechanism.

Conclusions. The present work shows that the acetylenic Cope rearrangement is highly specific for the stereochemistry corresponding to a suprafacial orbital symmetry allowed pathway. The flow of material through the reaction channel corresponding to the stereochemical equivalent of an antarafacial orbital symmetry forbidden pathway cannot exceed 1–2% of the total reactant converted. This result is itself presumptive (even if not decisive) evidence of a concerted mechanism, but its implication is strengthened by the estimate of the absolute value of the conformational lifetime of any hypothetical cyclohexene-1,4-diyl intermediate on the reaction pathway. If the model chosen for this estimate is correct, then in order to preserve stereochemical integrity in the products and in the recovered reactant, the rate of bond cleavage in the biradical must exceed 10^{13} s^{-1}. This rate is characteristic of a transition state, not of a true intermediate.

We consider the present results sufficient to exclude a cyclohexene-1,4-diyl as a true intermediate[38] in the present example of the thermal acetylenic Cope rearrangement. The possibility remains that a reactant with a structure designed to generate a much more stable potential intermediate might permit the de-

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tection of the long sought 1,4-diyl.[39] Work along these lines is in progress.

Experimental Section

Standard procedures and details of analytical methods are given in the Supplementary Material.

Racemic *trans*- and *cis*-4-Methyl-5-hepten-1-yne, (*E*)-28 and (*Z*)-28, and Racemic *trans*- and *cis*-4-Methyl-1,2,5-heptatriene, (*E*)-29 and (*Z*)-29 (Scheme VIII). These four isomeric compounds were produced by Grignard couplings in a single reaction.[40] Into a 500-mL, three-necked, round-bottom flask, equipped with a magnetic stirrer, addition funnel, and condenser fitted with a nitrogen inlet, was placed 4.8 g (0.41 mol) of magnesium turnings, 100 mL of THF (freshly distilled from Na/K), and a small spatula tipful of mercury(II) chloride. This mixture was heated with stirring to 50–60 °C at which time 9 mL (0.16 mol) of propargyl bromide (Aldrich, 80 wt % solution in toluene) in 30 mL of dry THF was added dropwise over the period of an hour.

With a wide-bore cannula the Grignard solution was then transferred away from the excess magnesium to another dry 300-mL, three-necked flask equipped as the previous flask. To the stirring Grignard solution was added 6 mL (67 mmol) of (±)-*trans*- and *cis*-4-bromo-2-pentene (Wiley Organics) in 20 mL of dry THF. The reaction mixture was then heated at 60 °C for 2 h, cooled to room temperature, and quenched by carefully adding 50 mL of saturated ammonium chloride solution dropwise.

The mixture was then poured, with filtering to remove any magnesium salts, into a separatory funnel; 100 mL of pentane was added, and the layers were separated. The organic layer was washed once with saturated ammonium chloride solution, twice with saturated sodium bicarbonate solution, six times with water, and once with brine solution. The organic layer was then dried over magnesium sulfate and filtered.

The pentane was then carefully removed by distillation through a 13-cm Vigreux column. The remaining solution was distilled at reduced pressure, and the fraction boiling at 70–90 °C/100 mmHg was collected to yield 5 mL of a clear liquid. Analytical capillary GC (column temperature 38 °C) showed the composition of the liquid to be 34% toluene, 4% (*Z*)-28, 28% (*E*)-28, 2% (*Z*)-29, and 32% (*E*)-29 (retention times 23.3, 27.5, 28.2, 33.5, and 34.6 m, respectively. This composition varied somewhat between different reactions.

This mixture could be separated into three components by preparative GC (column: 10 ft × 1/4 in., Carbowax 20M 25% on Chromosorb A 45/60; column temperature = 100 °C; retention times: 29 = 3.5 min, 28 = 4.5 min, toluene = 5.5 min).

The trans and cis components of 28 could subsequently be separated by preparative gas chromatography (column: 8 ft × 1/4 in., γ-methyl-γ-nitropimelonitrile (γ,γ) 25% on Chromosorb A 60/80; column temperature = 35 °C, injector temperature = 160 °C, detector temperature = 160 °C; retention times: (*E*)-28 = 55 min, (*Z*)-28 = 62.5 min).

(*E*)-28: ^{1}H NMR (500 MHz) δ 5.48 (left portion of ABX$_3$Y pattern, *J* = 15.8, 5.7, 0.9 Hz, 1 H, C$_6$ vinyl proton), 5.41 (right portion of ABX$_3$Y pattern, *J* = 15.2, 6.6, 1.2 Hz, 1 H, C$_5$ vinyl proton), 2.33 (apparent septet, *J* = 6.5 Hz, 1 H, methine proton), 2.22 (left portion of ABXY pattern, *J* = 16.6, 6.1, 2.64 Hz, 1 H, propargylic proton), 2.19 (right portion of ABXY pattern, *J* = 16.6, 7.1, 2.64 Hz, 1 H, propargylic proton), 1.97 (apparent triplet, *J* = 2.7 Hz, 1 H, acetylenic proton), 1.66 (doublet of doublets, *J* = 5.9, 1.1 Hz, 3 H, allylic methyl group protons), 1.07 (doublet, *J* = 6.8, 3 H, methyl group protons).

(*Z*)-28: ^{1}H NMR (250 MHz) δ 5.47 (left portion of ABX$_3$Y pattern, *J* = 10.6, 6.85, 0.9 Hz, 1 H, C$_6$ vinylic proton), 5.28 (right portion of ABX$_3$ pattern, *J* = 10.8, 9.8, 1.7 Hz, 1 H, C$_5$ vinylic proton), 2.78–2.69 (multiplet, 1 H, methine proton), 2.19–2.14 (multiplet, 2 H, propargylic protons), 1.97 (apparent triplet, *J* = 2.7 Hz, 1 H, acetylenic proton), 1.65 (doublet of doublets, *J* = 6.7, 1.7 Hz, 3 H, allylic methyl group protons), 1.07 (doublet, *J* = 6.6 Hz, 3 H, methyl group protons).

The following physical characteristics are of a 7:1 mixture of (*E*)-28 and (*Z*)-28: ^{13}C NMR (62.5 MHz) δ 135.4 (CH, vinylic carbon), 124.1 (CH, vinylic carbon), 83.3 (quaternary C, C$_2$ acetylenic carbon), 69.2 (CH, C$_1$ acetylenic carbon), 35.8 (CH, C$_4$ methine carbon), 26.4 (CH$_2$, C$_3$ methylene carbon), 19.8 (CH$_3$), 18.0 (CH$_3$); IR ν (cm^{-1}) 3306, 3029, 2963, 2872, 2114; GC-MS (70 eV) *m/z* 107 (–H, 3%), 93 (–CH$_3$, 88%), 91 (33%), 69 (100%); HRMS (CI, isobutane) *m/z* 109.1021 (+H, calcd 109.1018).

The trans and cis components of 29 were separated by preparative gas chromatography (column: 1 m × 1/4 in., 43% AgBF$_4$ in CW 600, 6% on Chromosorb P AW DMCS 60/80; column temperature = 40 °C injector temperature = 160 °C, detector temperature = 170 °C; retention times: (*E*)-29 = 5.5 min, (*Z*)-29 = 10.5 min). We thank Dr. F.-G. Klärner, Universität Bochum, for the recipe for this column: To 10 g of Chromosorb P AW DMCS 60/80, suspended in CH$_2$Cl$_2$, was added a filtered solution of AgBF$_4$ in 10 mL of acetone (care was taken to keep this solution out of the light) and a solution of 1 g of Carbowax 600 in 20 mL of CH$_2$Cl$_2$. After 5 min of vigorous mixing, the solvents were removed in vacuo at room temperature. All manipulations were carefully performed to exclude light. The packing was dried on the high vacuum line overnight and then used to pack a 1-m column. This column has a temperature limit of 60 °C. These columns lose their ability to resolve cis and trans isomers after a couple of months. It is suggested that they be stored in a drybox to extend their life.

(*E*)-29: ^{1}H NMR (500 MHz), δ 5.49 (left portion of ABX$_3$Y pattern, *J* = 15.4, 6.0, 0.9 Hz, 1 H, C$_6$ vinylic proton), 5.39 (right portion of ABX$_3$Y pattern, *J* = 15.2, 6.6, 1.3 Hz, 1 H, C$_5$ vinylic proton), 5.11 (apparent quartet, *J* = 6.6 Hz, 1 H, C$_3$ allenic proton), 4.73–4.71 (multiplet, 2 H, C$_1$ allenic protons), 2.77–2.85 (multiplet, 1 H, methine proton), 1.66 (doublet, *J* = 6.0 Hz, 3 H, allylic methyl group protons), 1.09 (doublet, *J* = 6.9 Hz, 3 H, methyl group protons).

(*Z*)-29: ^{1}H NMR (500 MHz) d 5.41 (left portion of ABX$_3$Y pattern, *J* = 10.7, 6.8, 0.9 Hz, 1 H, C$_6$ vinylic proton), 5.25 (right portion of ABX$_3$Y pattern, *J* = 10.6, 9.0, 1.2 Hz, 1 H, C$_5$ vinylic proton), 5.10 (apparent quartet, *J* = 6.2 Hz, 1 H, C$_3$ allenic proton), 4.68–4.74 (multiplet, 2 H, C$_1$ allenic protons), 3.28–3.10 (multiplet, 1 H, methine proton), 1.65 (doublet of doublets, *J* = 5.3, 1.2 Hz, 3 H, allylic methyl group protons), 1.09 (doublet, *J* = 6.8 Hz, 3 H, methyl group protons).

The following physical characteristics are of a 16:1 mixture of (*E*)-29 and (*Z*)-29, predominantly (*E*)-29: ^{13}C NMR (62.5 MHz) δ 207.8 (quaternary C, C$_2$ allenic carbon), 135.6 (CH, vinylic carbon), 123.8 (CH, vinylic carbon), 95.4 (CH, C$_3$ allenic carbon), 76.0 (CH$_2$, C$_1$ allenic carbon), 35.8 (CH, C$_4$ methine carbon), 20.3 (CH$_3$), 17.8 (CH$_3$); IR ν (cm^{-1}) 3024, 2968, 2868, 1953; GC-MS (20 eV) *m/z* 107 (–H, 4%), 93 (–CH$_3$, 100%), 69 (40%); HRMS (CI, isobutane) *m/z* 109.1014 (+H, calcd 109.1018).

Kinetic Resolution of (±)-3-Penten-2-ol 36 (Predominantly Trans). A kinetic resolution of (±)-3-penten-2-ol (36) (97% trans, 3% cis) was carried out according to the enantioselective epoxidation method of Sharpless et al.[30d,e] The absolute configuration of (*S*)-(–)-*trans*-3-penten-2-ol had been previously determined both by ozonolysis[30f] to the levorotatory zinc salt of (*S*)-(+)-lactic acid and by hydrogenation[30f] to (*S*)-(+)-2-pentanol. The sign of the specific rotation, [α]^{23}$_D$ = +11.02° (*c* 1.18 × 10^{-2} g/mL, CDCl$_3$), confirms the assignment of the trans alcohol as an (*R*) configuration. The cis isomer had previously been shown to have an (*R*) configuration after this resolution, as is typical for the procedure.[30d,e]

The enantiomeric excess (ee) of the partially resolved allylic alcohol was estimated by a ^{1}H NMR study on the corresponding acetate, predominantly trans, in the presence of tris[3-[(heptafluoropropyl)-hydroxymethylene]-(+)-camphorato]europium(III) (Eu(hfpc)$_3$) to be approximately 60%.

(*R*)-Ethyl *trans*-3-Methyl-4-hexenoate and (*S*)-Ethyl *cis*-3-Methyl-4-hexenoate ((*R,E*)-37 and (*S,Z*)-37) (Scheme X). Optically active (*R*)-*trans*- and *cis*-3-penten-2-ol (predominantly trans) was allowed to react with triethyl orthoacetate in a Claisen reaction to yield (*R,E*)-37 and (*S,Z*)-37, according to the method of Hill et al.[30a] The workup of the product was modified slightly: the remaining triethyl orthoacetate was decomposed to ethyl acetate and ethanol by treatment with 300 mL of 4% HCl, 100 g of ice, and 250 mL of Et$_2$O.

(*R*)-*trans* and (*S*)-*cis*-3-Methyl-4-hexenal ((*R,E*)-38 and (*S,Z*)-38). A 1-L, round-bottomed flask was fitted with a 100-mL addition funnel (all glassware oven-dried), nitrogen inlet, and magnetic stirrer. The flask was then charged with 15 mL of hexane (freshly distilled from CaH$_2$) and 9.94 g (63.6 mmol) of ester 37 (a mixture of (*R,E*)-37 and (*S,Z*)-37, predominantly (*R,E*)-37. This solution was then cooled to –77 °C, and a 70-mL portion of a 1 M solution of diisobutylaluminum hydride (DI-BAL-H) in hexanes was added over a period of an hour. The reaction mixture was allowed to stir for another 1 h at –77 °C whereupon 15 mL of absolute MeOH was dripped in. The stirring was continued an ad-

(37) This result strongly suggests that the absolute configuration of (*Z*)-29 is *S* since any of the mechanisms considered that produce predominantly (*R,E*)-29, (*R,E*)-28, and (*S,Z*)-28 would also produce predominantly (*S,Z*)-29. Thus, the configuration of (*Z*)-29 will be assumed to be *S* throughout the remainder of this work.

(38) Of course, the results are noncommittal with respect to the structure of the *transition state*, which may have appreciable biradical character.

(39) (a) For an example of this strategy in a [1,3]-sigmatropic rearrangement, see: Pikulin, S.; Berson, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 8274; **1988**, *110*, 8500. (b) See, also: Berson, J. A. *Chemtracts—Organic Chem.* **1989**, *2*, 213.

(40) For descriptions of similar reactions, see: (a) Dykstra, K. A. Ph.D. Dissertation, Ohio University, Athens, OH, 1972. (b) Groizeleau-Miginiac, L. *Compt. Rend.* **1959**, *248*, 1190. (c) Huntsman, W. D.; De Boer, J. A.; Woosley, M. H. *J. Am. Chem. Soc.* **1966**, *88*, 5846.

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ditional hour at -77 °C, after which the mixture was allowed to warm to room temperature. A white gelatinous precipitate formed, which was substantially decomposed when the mixture was stirred overnight with 200 mL of a saturated aqueous solution of sodium potassium tartrate. The reaction mixture was extracted three times with 100-mL portions of Et_2O. The combined organic layers were washed with 2 × 200 mL of H_2O and ! × 200 mL of saturated brine solution, dried with $MgSO_4$, and filtered.

The solvents were removed by careful distillation (under a nitrogen atmosphere) through a 13-cm Vigreux column to yield 5.3 g of a slightly yellow liquid which ^1H NMR showed to be mainly the desired aldehyde **38** (a mixture of (R,E)-**38** and (S,Z)-**38**, predominantly (R,E)-**38**, yield approximately 60%). This material was typically carried on without further purification. It could, however, be purified by distillation at reduced pressure (bp = 85 °C/30 mmHg). An analytically pure sample (a mixture of (R,E)-**38** and (S,Z)-**38**, predominantly (R,E)-**38**) could be obtained by preparative gas chromatography (column: 5 ft × 1/4 in., OV-101 2% on Anakrom AS 110/120; column temperature = 50 °C, retention time = 5 min): ^1H NMR (250 MHz) δ 9.72 (triplet, J = 2.3 Hz, 1 H, aldehyde proton), 5.47 (left portion of ABX_3Y pattern, J = 15.3, 5.8 Hz, 1 H, C_5 vinylic proton), 5.36 (right portion of ABX_3Y pattern, J = 15.8, 6.4 Hz, 1 H, C_4 vinylic proton), 2.72 (apparent septet, J = 6.8 Hz, 1 H, methine proton), 2.42 (left portion of ABXY pattern, J = 16.0, 7.0, 2.3 Hz, 1 H, methylene proton), 2.33 (right portion of ABXY pattern, J = 16.1, 6.9, 2.2 Hz, 1 H, methylene proton), 1.65 (doublet, J = 5.5 Hz, allylic methyl group protons), 1.05 (doublet, J = 6.8 Hz, methyl group protons). ^{13}C NMR (62.5 MHz) δ 202.8 (CH, aldehyde carbon), 135.3 (CH, vinylic carbon), 124.4 (CH, vinylic carbon), 50.6 (CH_2, C_2), 31.6 (CH, methine carbon), 20.6 (CH_3, allylic methyl carbon), 17.7 (CH_3, methyl group carbon); ν (cm^{-1}) 3030, 2965, 2727, 1722; GC-MS (70 eV) m/z 112 (M^+, 25%), 111 (-H, 10%), 97 ($-CH_3$, 90%), 83 (-HCO, 30%), 69 (80%), 55 (60%), 41 (100%); HRMS m/z 112.0891 (calcd 112.0889). Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.79. Found: C, 74.85; H, 10.79.

(R)-trans and (S)-cis-1,1-Dibromo-4-methyl-1,5-heptadiene ((R,-E)-39 and (S,Z)-39). The dibromoolefin **39** (a mixture of (R,E)-**39** and (S,Z)-**39**, predominantly (R,E)-**39**) was synthesized from the aldehyde **38** (a mixture of (R,E)-**38** and (S,Z)-**38**, predominantly (R,E)-**38**) by using a method adapted from that of Corey and Fuchs.[32] In a dry 2-L, round-bottom flask was placed 5.30 g (81.1 mmol) of finely powdered zinc dust, 1 L of CH_2Cl_2 (freshly distilled from CaH_2), and 41.0 g (0.156 mol, recrystallized) of triphenylphosphine, these operations being carried out in a glovebox. The mixture was placed under nitrogen and stirred for 5 min at the end of which time 25.9 g (78.1 mmol) of carbon tetrabromide was added. This mixture was stirred until the color of the mixture, when the zinc dust settled, was a golden orange (usually between 5 and 10 min). At this time, 3.43 g (30.6 mmol, predominantly trans) of the aldehyde **38** was added dropwise, by syringe. After 5 min, TLC (silica gel, pentane) showed the disappearance of aldehyde and the appearance of a spot with an R_f of 0.56 corresponding to the 1,1-dibromoolefin **39**.

The reaction mixture was then washed three times with H_2O, dried with $MgSO_4$, and concentrated in vacuo to a total volume of approximately 300 mL. Pentane was then added to precipitate triphenylphosphine oxide and triphenylphosphine, which was then filtered off. The filtrate was then concentrated in vacuo to 20 mL. This material was chromatographed (silica gel, pentane) to yield 4.73 g (17.6 mmol, 58%) of the 1,1-dibromoolefin **39**. This compound is light-sensitive.

An analytically pure sample (mixture of (R,E)-**39** and (S,Z)-**39**) could be obtained by preparative gas chromatography (column: 5 ft × 1/4 in., OV-101 2% on Anakrom AS 110/120; column temperature = 100 °C). Physical properties of **39** (a mixture of (R,E)-**39** and (S,Z)-**39**, predominantly (R,E)-**39**): ^1H NMR (250 MHz) δ 6.38 (apparent triplet, J = 7.0 Hz, 1 H, C_2 vinylic proton), 5.45 (left portion of ABXY pattern, J = 15.4, 5.7 Hz, 1 H, C_6 vinylic proton), 5.31 (right portion of ABXY pattern, J = 15.4, 5.6 Hz, 1 H, C_5 vinylic proton), 2.26 apparent septet, J = 6.8 Hz, 1 H, methine proton), 2.11–2.04 (four lines of an ABXY pattern, 2 H, C_3 protons), 1.67 (doublet of doublets, J = 5.0, 0.8 Hz, allylic methyl group protons), 1.02 (doublet, J = 6.7 Hz, methyl group protons); ^{13}C NMR (62.5 MHz) δ 137.6 (CH, vinylic carbon), 135.8 (CH, vinylic carbon), 124.4 (CH, C_2 vinylic carbon), 89.0 (C, C_1 vinylic carbon), 40.3 (CH_2, C_3 carbon), 35.8 (CH, methine carbon), 20.2 (CH_3, methyl group carbon), 16.2 (CH_3, methyl group carbon); IR ν (cm^{-1}) 3026, 2964, 2870, 1735, 1619, 1450, 1436, 1376, 969; GC-MS (70 eV) m/z 119, 117, 69; (Cl, isobutane) m/z 267 (-H, 1.3%), 189 (-Br, 11%), 187 (-Br, 12%), 149 (20%), 107 (35%), 69 (100%); HRMS m/z 266.9207 (-H, calcd 266.9207). Anal. Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51; Br, 59.63. Found: C, 35.86; H, 4.45; Br, 58.48.

(R)-trans- and (S)-cis-4-Methyl-5-hepten-1-yne, (R,E)-28 and (S,Z)-28. By using a procedure modeled on that of Corey and Fuchs,[32]

a dry 250-mL, round-bottom flask was charged with 4.20 g (15.7 mmol) of 1,1-dibromoolefin **39** (a mixture of (R,E)-**39** and (S,Z)-**39**, predominantly (R,E)-**39**) and 75 mL of THF (freshly distilled from Na/K). The flask was sealed with a septum, placed under nitrogen, stirred magnetically, and cooled to -78 °C. To the solution was added dropwise by syringe 14.5 mL of 2.4 M (34.8 mmol) of n-butyllithium in hexanes. The solution turned yellow. After stirring for 1.5 h, the solution was warmed to room temperature, poured into a separatory funnel containing 50 mL of pentane and 150 mL of H_2O, washed six times with H_2O, and dried with $MgSO_4$.

The organic layer was then concentrated by distilling off the pentane through a 13-cm Vigreux column until approximately 6 mL remained. This liquid was distilled at reduced pressure through a short-path distillation apparatus, and the fraction distilling at 90–130 °C/100 mmHg was collected to yield 2.92 g of a clear liquid which capillary gas chromatography analysis showed to be approximately half the desired product **28** (a mixture of (R,E)-**28** and (S,Z)-**28**, predominantly (R,E)-**28**) and half n-octane (presumably an impurity in the n-butyllithium). The yield corrected for this impurity was 86%.

The product was purified further for pyrolyses by preparative GC, as described in the racemic synthesis. Analytical capillary gas chromatography of this material showed it to consist of 7.5% of the (S,Z)-**28** isomer and 92.5% of the (R,E)-**28** isomer.

A sample of pure (R,E)-**28** and a sample of 65% (R,E)-**28** and 35% (S,Z)-**28** were obtained by preparative gas chromatography. Spectropolarimetric measurements on these two samples allowed the assignment of the following specific rotations (additivity of the rotations was assumed, concentrations in g/mL): (R,E)-**28** $[\alpha]_{365}$ = -7.74° (c 2.20 × 10^{-3}, pentane) ($[\alpha]_D$ = -1.37°); (S,Z)-**28**) $[\alpha]_{365}$ = +73.6° (c 7.45 × 10^{-4}, pentane) ($[\alpha]_D$ = +16.7°).

All other physical characteristics were identical with those of the racemic compounds.

Racemic trans- and cis-4-Methyl-5-hepten-1-yne-7-d, (E)-28-7-d and (Z)-28-7-d. Into a dry 25-mL, round-bottom flask was placed 143 mg (1.32 mmol) of **28** (a mixture of (E)-**28** and (Z)-**28**, predominantly (E)-**28**) and 5 mL of pentane. The flask was fitted with a magnetic stirrer, sealed with a septum, placed under nitrogen, and placed in a room temperature water bath. To the stirred solution was added dropwise by syringe 1 mL of 2.5 M n-butyllithium (2.5 mmol) in hexanes. A deep red solution formed. After the mixture had been stirred for half an hour, a mL of D_2O was added, and the solution was stirred for an additional hour, after which time all color had disappeared.

The layers were separated; the organic layer was dried over $MgSO_4$, filtered, and concentrated by distilling away the pentane through a 13-cm Vigreux column until about 1/2 mL remained. The product, **28-7-d** (a mixture of (E)-**28-7-d** and (Z)-**28-7-d**, predominantly (E)-**28-7-d**), was isolated by preparative gas chromatography. The ^1H NMR spectrum of **28-7-d** was similar to that of racemic **28** except that the acetylenic proton peak at 1.97 ppm had disappeared.

(2R,3R,4R)-trans- and (2S,3S,4R)-trans-3-Methyl-2-(1-methyl-3-butynyl)oxirane ((R)-trans-42 and (R)-trans-43) and (2R,3S,4S)-cis- and (2S,3R,4S)-cis-3-Methyl-2-(1-methyl-3-butynyl)oxirane ((S)-cis-42 and (S)-cis-43) (Scheme XII). Into a 10-mL, pear-shaped flask were placed 25.8 mg (0.24 mmol) of a mixture of (R,E)-**28** and (S,Z)-**28** (predominantly (R,E)-**28**) and 1 mL of CH_2Cl_2 (freshly distilled from CaH_2). Into a second 10-mL, pear-shaped flask were placed 41 mg (0.24 mmol) of 3-chloroperoxybenzoic acid (m-CPBA) and 1 mL of CH_2Cl_2. Both flasks were cooled to 0 °C in an ice bath; the **28** solution was then transferred to the m-CPBA solution by pipette, and the resulting solution was then sealed and placed in the freezer. The progress of the reaction could be followed by working up a small aliquot of the reaction mixture and analyzing it by capillary GC.

The reaction proceeded cleanly to completion. After 2 days, 4 mL of Et_2O and 5 mL of a saturated solution of $NaHCO_3$ were added to the reaction mixture, and the resulting two layers were mixed vigorously. The aqueous layer was removed, and the organic layer was washed three more times with the $NaHCO_3$ solution, dried over $MgSO_4$, and filtered.

The products were typically carried on to the subsequent reduction step without further purification. Analytical capillary GC showed that the trans diastereomers eluted first followed by the two cis diastereomers. These products were present in the ratio of 12.2:10.6:1:1.2.

An analytically pure sample (of the four diastereomers) could be obtained by gravity column chromatography (silica gel, CH_2Cl_2/pentane 1:1) or by preparative gas chromatography (column: 8 ft × 1/4 in., CW 20 M 25% on Chromosorb A; column temperature = 130 °C, retention time = 5 min). Physical characteristics (mixture of the four diastereomers, but predominantly the two trans diastereomers in an approximately 1:1 ratio): ^1H NMR (250 MHz) δ 2.91 (doublet of quartets, J = 5.2, 2.2 Hz, 1 H, C_3 epoxide ring proton), 2.86 (doublet of quartets, J = 5.2, 2.2 Hz, 1 H, C_3 epoxide ring proton), 2.60 (doublet of doublets, J = 7.4

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and 2.1 Hz, 1 H, C_2 epoxide ring proton), 2.55 (doublet of doublets, J = 7.2 and 2.2 Hz, 1 H, C_2 epoxide ring proton), 2.44–2.22 (multiplet, 4 H, propargylic methylene protons), 2.01 (triplet, J = 2.6 Hz, 1 H, acetylenic proton), 2.00 (triplet, J = 2.6 Hz, 1 H, acetylenic proton), 1.66–1.52 (multiplet, 2 H, methine protons), 1.32 (doublet, J = 5.2 Hz, 6 H, epoxide ring methyl group protons), 1.10 (doublet, J = 6.8 Hz, 3 H, methyl group protons), 1.08 (doublet, J = 6.9 Hz, 3 H, methyl group protons); ^{13}C NMR (62.5 MHz) δ 82.3 (quaternary C, internal acetylenic carbon), 82.1 (quaternary C, internal acetylenic carbon), 69.7 (CH, terminal acetylenic carbon), 69.6 (CH, terminal acetylenic carbon), 63.3 (CH, epoxide ring carbon), 62.8 (CH, epoxide ring carbon), 54.3 (CH, epoxide ring carbon), 53.7 (CH, epoxide ring carbon), 35.3 (CH, methine carbon), 35.0 (CH, methine carbon), 22.9 (CH_2, propargylic carbon), 22.8 (CH_2, propargylic carbon), 17.6 (CH_3), 16.4 (CH_3), 15.3 (CH_3); IR ν (cm^{-1}) 3306, 2967, 2929, 2873, 2118, 1254; GC-MS (70 eV) m/z 123 (–H, 2%), 109 (–CH_3, 35%), 95 (18%), 85 (35%), 81 (31%), 79 (100%), 77 (38%), 69 (47%), 67 (31%), 65 (23%); HRMS (Cl) m/z 125.0978 (+H, calcd 125.0967).

(2*R*,3*R*,4*S*)-*trans*- and (2*S*,3*S*,4*S*)-*trans*-3-Methyl-2-(1-methyl-2,3-butadienyl)oxirane (*S*-*trans*-44 and *S*-*trans*-45) and (2*R*,3*S*,4*R*)-*cis*- and (2*S*,3*R*,4*R*)-*cis*-3-Methyl-2-(1-methyl-2,3-butadienyl)oxirane ((*R*)-*cis*-44 and (*R*)-*cis*-45) (Scheme XIII). These compounds were synthesized by a procedure similar to that described in the previous experiment, by using 195 mg (1.81 mmol) of a mixture of allenes (*R*,-*E*)-29 and (*S*,*Z*)-29 (predominantly (*R*,*E*)-29) 312 mg (1.81 mmol) of *m*-CPBA, and a total of 20 mL of CH_2Cl_2. The course of the reaction, which proceeded cleanly, could be followed by capillary GC. After 2 days the reaction was complete; it was worked up and chromatographed (silica gel, CH_2Cl_2/pentane 1:1, UV visualization, R_f 0.25–0.21) to yield 98 mg (0.79 mmol, 44% yield) of a mixture of (*S*)-*trans*-46, (*S*)-*trans*-47, (*R*)-*cis*-46, and (*R*)-*cis*-47. Analytical capillary GC showed that the two trans diastereomers eluted first followed by the two cis diastereomers. These products were present in the ratio 20.6:20.1:1.8:1.

The amount of (*R*,*E*)-29 and (*S*,*Z*)-29 being epoxidized was typically in the range of 10 mg. These smaller reactions were worked up and carried on to the subsequent reduction step without purification.

An analytically pure sample of (*S*)-*trans*-46, (*S*)-*trans*-47, (*R*)-*cis*-46, and (*R*)-*cis*-47 could be obtained by preparative gas chromatography (column: 8 ft × 1/4 in., CW 20 M 25% on Chromosorb A; column temperature = 130 °C, retention times = 5 and 7 min). Under these conditions, the two major diastereomers were nearly separated. Physical characteristics (mixture of the four diastereomers, but predominantly the two trans diastereomers in an approximately 1:1 ratio): ^{1}H NMR (250 MHz) δ 5.19 (apparent quartet, J = 6.7 Hz, 1 H, internal allenic proton), 5.12 (apparent quartet, J = 5.9 Hz, 1 H, internal allenic proton), 4.79–4.74 (multiplet, 4 H, terminal allene protons), 2.89–2.81 (multiplet, 2 H, C_3 epoxide ring protons), 2.60 (doublet of doublets, J = 6.5, 2.2 Hz, 1 H, C_2 epoxide ring proton), 2.54 (doublet of doublets, J = 7.1, 2.2 Hz, 1 H, C_2 epoxide ring proton), 2.20–2.02 (multiplet, 2 H, methine protons), 1.31 (doublet, 3 H, J = 5.2, epoxide ring methyl group protons), 1.31 (doublet, 3 H, J = 5.2, epoxide ring methyl group protons), 1.14 (doublet, 3 H, J = 6.9, methyl group protons), 1.07 (doublet, 3 H, J = 6.9, methyl group protons); ^{13}C (62.5 MHz) δ 208.4 (quaternary C, center allenic carbon), 208.2 (quaternary C, center allenic carbon), 92.0 (CH, internal allenic carbon), 91.5 (CH, internal allenic carbon), 76.1 (CH_2, terminal allenic carbon), 76.1 (CH_2, terminal allenic carbon), 63.5 (CH, epoxide ring carbon), 63.4 (CH, epoxide ring carbon), 53.8 (CH, epoxide ring carbon), 53.2 (CH, epoxide ring carbon), 35.1 (CH, methine carbon), 35.0 (CH, methine carbon), 17.5 (CH_3), 16.6 (CH_3), 15.9 (CH_3); IR ν (cm^{-1}) 2970, 2928, 2872, 1953, 1449, 1433, 1377, 1263, 997, 969; GC-MS (70 eV) m/z 123 (–H, 2%), 109 (–CH_3, 26%), 95 (27%), 82 (15%), 81 (24%), 80 (29%), 79 (100%), 77 (42%), 69 (18%), 67 (55%), 65 (37%), 53 (11%); HRMS m/z 124.0890 (calcd 124.0889).

(2*R*,3*R*,4*R*)-*trans*- and (2*S*,3*S*,4*R*)-*trans*-3-Methyl-2-(1-methylbutyl)oxirane ((*R*)-*trans*-40 and (*R*)-*trans*-41) and (2*R*,3*S*,4*S*)-*cis*- and (2*S*,3*R*,4*S*)-*cis*-3-Methyl-2-(1-methylbutyl)oxirane ((*S*)-*cis*-40 and (*S*)-*cis*-41) from the Acetylenic Epoxide Mixture of (*R*)-*trans*-42, (*R*)-*trans*-43, (*S*)-*cis*-42, and (*S*)-*cis*-43 (Scheme XII). Into a 10-mL, round-bottom flask was placed 12 mg (0.10 mmol, estimated) of a mixture of (*R*)-*trans*-42, (*R*)-*trans*-43, (*S*)-*cis*-42, and (*S*)-*cis*-43 (predominantly the two trans diastereomers in an approximately 1:1 ratio, used without purification from the epoxidation reaction), 2 mL of THF, a small spatula tip of 5% platinum on powdered charcoal, and a small "flea" stirrer. The sample was degassed, placed under hydrogen at ambient pressure, and stirred vigorously overnight. The reaction was worked up by adding 4 mL of Et_2O, filtering through a short pad of $MgSO_4$ to remove the catalyst, washing twice with H_2O and twice with saturated

NaHCO$_3$ solution, drying with $MgSO_4$, and filtering. The product mixture of (*R*)-*trans*-40, (*R*)-*trans*-41, (*S*)-*cis*-40, and (*S*)-*cis*-41 could be analyzed by capillary GC, which showed that the two trans diastereomers eluted first followed by the two cis diastereomers. The products were present in the ratio 6.2:7.2:1.2:1, respectively.

When the reaction was performed on a larger scale (100 μL), an analytically pure sample (of the four diastereomers) could be obtained by chromatography (silica gel, pentane/ether 20:1, PMA stain) or by preparative gas chromatography (column: 8 ft × 1/4 in., CW 20 M 25% on Chromosorb A; column temperature = 110 °C, retention time = 4 min).

Physical characteristics (mixture of the four diastereomers, but predominantly the two trans diastereomers in an approximately 1:1 ratio): ^{1}H NMR (250 MHz) δ 2.84–2.75 (multiplet, 2 H, C_3 epoxide ring protons), 2.45 (doublet of doublets, J = 7.0, 2.2, 1 H, C_2 epoxide ring proton), 2.38 (doublet of doublets, J = 7.0, 2.2, 1 H, C_2 epoxide ring proton), 1.2–1.7 (multiplet, 16 H, methine, methylene, and methyl group protons), 0.9–1.1 (multiplet, 12 H, methyl groups); ^{13}C (62.5 MHz) δ 64.8 (CH, epoxide ring carbon), 64.7 (CH, epoxide ring carbon), 54.6 (CH, epoxide ring carbon), 52.6 (CH, epoxide ring carbon), 36.8, 36.2, 35.9, 35.6, 20.5, 20.1, 17.8, 17.3, 14.4, 15.9; IR ν (cm^{-1}) 2960, 2927, 2872, 1466, 1456, 1433, 1379, 1251, 1124, 972; GC-MS (70 eV) m/z 113 (–CH_3, 5%), 99 (11%), 86 (20%), 85 (13%), 84 (48%), 71 (13%), 69 (37%), 56 (100%); (Cl, isobutane) m/z 129 (+H, 37%), 111 (90%), 85 (100%), 71 (12%), 69 (70%); HRMS (Cl, isobutane) m/z 129.1275 (+H, calcd 129.1280).

(2*R*,3*R*,4*S*)-*trans*- and (2*S*,3*S*,4*S*)-*trans*-3-Methyl-2-(1-methylbutyl)oxirane ((*S*)-*trans*-40 and (*S*)-*trans*-41) and (2*R*,3*S*,4*R*)-*cis*- and (2*S*,3*R*,4*R*)-*cis*-3-Methyl-2-(1-methylbutyl)oxirane ((*R*)-*cis*-40 and (*R*)-*cis*-41) from the Allenic Epoxide Mixture of (*S*)-*trans*-46, (*S*)-*trans*-47, (*R*)-*cis*-46, and (*R*)-*cis*-47 (Scheme XIII). Into a 100-mL, round-bottom flask with a magnetic stirrer was placed 12 mg (0.1 mmol) of a mixture of (*S*)-*trans*-46, (*S*)-*trans*-47, (*R*)-*cis*-46, and (*R*)-*cis*-47 (predominantly (*S*)-*trans*-46 and (*S*)-*trans*-47 in an approximately 1:1 ratio), 4 mL of absolute ethanol, 1 mL of THF, and 3 g of hydrazine hydrate, 85% (50 mmol). The solution was placed in a water bath and stirred vigorously, while 10 g of hydrogen peroxide, 30 wt %, (89 mmol) was added dropwise slowly over the period of half an hour. An aliquot was removed, worked up, and analyzed by capillary GC which showed that the reduction was incomplete. An additional 2 mL of THF, 3 g of 85% hydrazine hydrate, and 10 g of 30 wt % hydrogen peroxide were added.

The reaction mixture was then extracted with 20 mL of hexane. The organic layer was then washed: 1 × 30 mL dilute solution HCl, 2 × 30 mL H$_2$O, and 1 × 30 mL saturated solution of NaHCO$_3$. The organic layer was then dried over MgSO$_4$ and then handled as described for the previous experiment.

Analytical capillary GC showed that the two trans diastereomers eluted first followed by the two cis diastereomers. The products were present in the ratio 9.8:10.8:1:1.7, respectively.

Physical characteristics of the epoxide products were as described in the previous experiment.

Computational simulations were carried out on the Yale chemistry department's VAX system and are described in detail elsewhere.[22] The average difference between the computed and observed absolute % concentrations of the major species (*E*)-28 and (*E*)·29 was ±2.2% and ±3.9%, respectively. Because of the experimental scatter in the data for (*E*)-29 already mentioned, 4 of the 16 experimental points differed from the calculated by 6.5–7.4%. The average difference of the remaining (*E*)-29 points was 2.9%. The simulation matched the observed concentrations of the minor components (*Z*)-28, (*Z*)-29, and 33–35 (Scheme IX) to better than 1%. The supplementary material gives the experimental data, the simulated values, and a plot of the concentration-time profiles.

Supplementary Material Available: Data and discussion of modeling of conformational inversion barriers, details of kinetic simulation, and experimental data (22 pages). Ordering information is given on any current masthead page.