ethylating agent: mp 147–148 °C (presoftening at 136 °C); ^{1}H NMR (CF_3COOH) δ 1.73 (t, 3, CH_3CH_2), 3.11 (s, 3, CH_3), 4.91 (q, 2, CH_3CH_2), 8.25 (t, 1, C-7), 8.88 (d, 1, C-8), 9.15 (d, 1, C-6), 9.33 (s, 1, C-4), 10.09 (s, 1, C-1).

Anal. Calcd for $C_{12}H_{13}BF_4N_2O_3$: C, 45.00; H, 4.06; N, 8.75. Found: C, 44.93; H, 4.05; N, 8.81.

General Procedure for Cycloaddition Reactions. The appropriate quantity of the isoquinolinium salt (3 or 4) and the olefinic compound was dissolved in acetonitrile and (except as noted) the solution allowed to stand at room temperature until the ^{1}H NMR signal due to the H-1 proton of the isoquinolinium cation disappeared or until UV absorption at 236 nm disappeared. The solution was concentrated and anhydrous ether added to precipitate the adduct. The adduct was washed with ether to remove excess alkene and polymer and then recrystallized from methanol–acetonitrile.

Registry No. 3 (X = BF_4), 6220-89-9; **4** (X = BF_4), 71837-95-1; **4** (X = PF_6), 71837-96-2; (±)-**5**, 71837-98-4; (±)-**6**, 71838-00-1; (±)-**7**, 71838-02-3; (±)-**9**, 71886-79-8; (±)-**10**, 71838-04-5; (±)-**11**, 71886-81-2; (±)-**12a**, 71838-06-7; (±)-**12b**, 71883-68-6; (±)-**13a**, 71838-08-9; (±)-*syn*-**13**, 71927-79-2; (±)-*syn*-**13**, 71838-10-3; 3-methylisoquinoline *N*-oxide, 14548-00-6; nitrosylsulfuric acid, 7782-78-7; 3-methyl-5-nitroisoquinoline, 18222-17-8; *p*-methoxystyrene, 637-69-4; styrene, 100-42-5; indene, 95-13-6; 2-norbornene, 498-66-8; 2-phenyl-2-norbornene, 4237-08-5; cyclopentadiene, 542-92-7.

Mechanism of Allylic Hydroxylation by Selenium Dioxide

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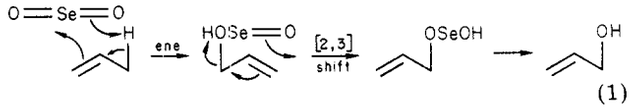
Both regiochemical and stereochemical aspects of the allylic hydroxylation reactions of selenium dioxide have been investigated. The principal findings are as follows. (1) In *tert*-butyl alcohol the mechanism is more complex than would be predicted by using the ene–[2,3]sigmatropic shift scheme proposed by Sharpless. (2) The stereochemical complexities appear to derive from ionic intermediates and can be suppressed in more basic media, e.g., *tert*-butyl alcohol/pyridine. (3) The strong preference for trans allylic alcohol products in the reaction is due to steric preferences in the [2,3]sigmatropic migration. The ene step is nonselective.

Allylic oxidation by selenium dioxide is one of a limited number of chemical reactions which introduce oxygen into a hydrocarbon molecule selectively and without structural rearrangement. Since its development by Guillemonat in the 1930's,[1] several mechanisms have been proposed for this transformation. Each of the early proposals had difficulty explaining the remarkable site selectivity of the reaction. A recent proposal by Sharpless and co-workers[2] has been able to overcome most of these difficulties. Their mechanism consists of a three-step sequence commencing with an ene reaction followed by a [2,3]sigmatropic rearrangement which generates an easily solvolyzed Se^{II} ester (reaction 1). In this mechanism the ene step can explain



(1)

the site selectivity of the reaction while the [2,3] shift explains the preference for *E* allylic alcohol products. Both key steps of this sequence can be formulated as a thermally allowed six-electron pericyclic process under the Woodward–Hoffmann formalism. This transformation could then be expected to proceed with clearly defined stereochemical constraints. We wish to report here the results of a study of the detailed stereochemistry of this reaction. These results are not entirely consistent with the rigid stereochemical pattern predicted by the ene–[2,3]-shift mechanism. The data are better accommodated by a mixture of mechanisms involving a stereospecific path such as that proposed and a stereochemically random path involving a stepwise ene reaction equivalent.

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Results and Discussion

This reaction has two important stereochemical aspects: (1) the relationship of the site attacked in the ene step to the final olefin geometry of the allylic alcohol and (2) the overall stereochemistry of the C–H → C–O transformation. Since the question of olefin geometry is crucial to the interpretation of the allylic stereochemistry, we will address this aspect of the problem first.

Olefin Geometry. Synthetic applications of the SeO_2 allylic oxidation have revealed that the reaction proceeds to give predominantly *E* olefin products.[3] These results parallel the geometric preference shown by [3,3] sigmatropic rearrangements of the Cope and Claisen variety.[4] The preference in the [3,3] cases apparently arises from the most favorable transition state geometry, generally a pseudochair cyclohexane with the largest groups in equatorial positions.[5] Similar geometric selectivity is evident in the selenium dioxide rearrangement studied by Sharpless and Lauer[2,6] (eq 2), indicating that an analogous steric effect might be operating in the pseudocyclopentane transition state.

Only one systematic study of this aspect of the SeO_2 reaction exists. Bahlerao and Rapoport[7] have examined a series of (*E*)- and (*Z*)-2-alkyl-2-heptenes. While this

(1) A. Guillemonat, *Ann. Chem. (Warsaw)*, 11, 143 (1939).
(2) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **94**, 7154 (1972).
(3) J. J. Plattner, U. T. Bahlerao, and H. Rapoport, *J. Am. Chem. Soc.*, **91**, 4933 (1969).
(4) (a) W. S. Johnson et al., *J. Am. Chem. Soc.*, **98**, 1038 (1976); (b) *ibid.*, **92**, 741 (1970).
(5) (a) D. J. Faulkner and M. R. Peterson, *Tetrahedron Lett.*, 3243 (1969); (b) C. L. Perrin and D. Faulkner, *ibid.*, 2783 (1969).
(6) K. B. Sharpless, H. P. Jensen, D. Arigoni, and A. Vasella, *J. Am. Chem. Soc.*, **95**, 7917 (1973).
(7) U. T. Bahlerao and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 4835 (1971).

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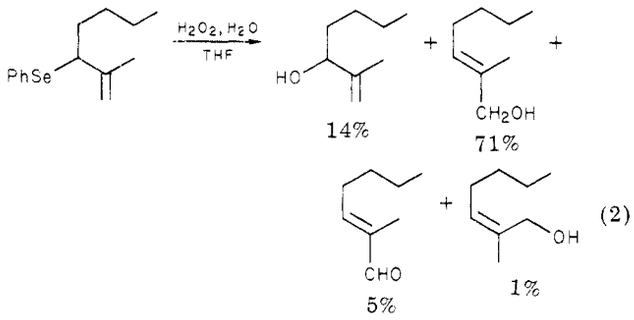
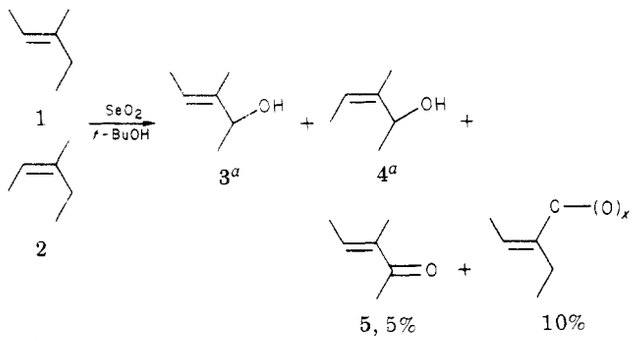


(2)

study clearly demonstrated the preference for *E* products, the origin of this preference was not determined. Further, for *gem*-dimethyl olefins it is not known if the *E* product results from preferred attack at the *E* methyl or from some other mechanistic factor. When larger alkyl groups were employed, isomerization of the olefin prior to reaction was not ruled out.

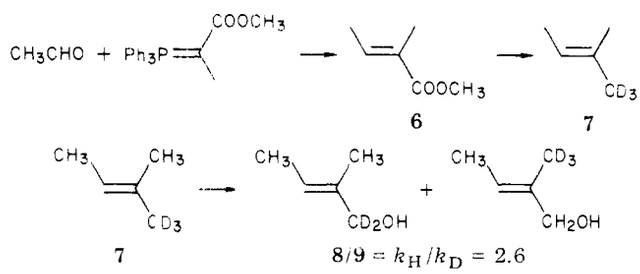
To examine the origin of this geometric preference, our initial work focussed on 3-methyl-2-pentene (**1** and **2**). In



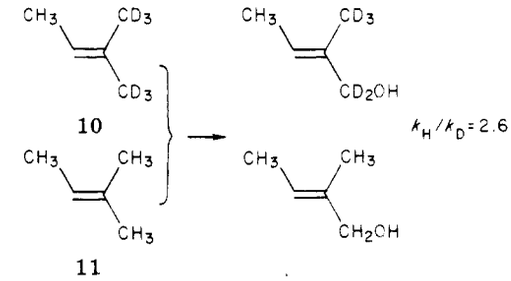
[a] 3 and 4 (in a 97:3 ratio) make up 85% of the total yield.

this case both the allylic alcohols and the starting olefins were configurationally stable under the reaction conditions. Interestingly, the product distribution was the same from both olefin isomers. Since neither starting material nor product isomerization was observed, this equilibration must occur in an intermediate along the reaction sequence.

While this result clarifies the effect of the reaction on the olefin geometry, it is uninformative about any preferences in the site of initial attack. In the pentene case the two most favored sites of attack, CH_2 and CH_3, differ substantially in reactivity (CH_2/CH_3 ~8–9). To factor this aspect of the reactivity out of this problem and to confirm that the *E* product preference is the result of equilibration of a reactive intermediate, we studied the oxidation of (*E*)-1,1,1-trideuterio-2-methyl-2-butene (**7**).[8] Analysis of



the deuterium content of the olefin (by the Eu(fod)$_3$-shifted proton NMR of the corresponding epoxide) showed it to be more than 95% trideuterated at this position shown. Comparison of the intramolecular isotope effect measured here with an intermolecular value obtained by competition between 2-methyl-d_6-2-butene (**10**) and 2-



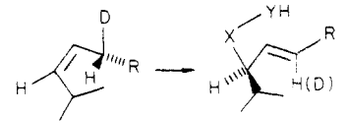
methyl-2-butene (**11**) should reveal the extent to which any geometric factor determines the initial site of attack.

The equivalence of the inter- and intramolecular isotope effects in these oxidations (k_H/k_D = 2.6 ± 0.3) strongly suggests that there is no strong geometric factor involved in the preferred site of hydrogen abstraction.

Several features of this reaction are defined by these results. First, isomerization of the olefin geometry occurs in an intermediate along the oxidation pathway and leads to a strong preference for *E* products. Second, structurally similar geminal groups on an olefin are likely to be equally reactive in hydrogen removal step. Finally, the equivalence of the inter- and intramolecular isotope effects indicates that breaking of the allylic C–H bond is an important component of the rate-determining step of the transformation. These points are consistent with the ene–[2,3]-shift mechanism but might also be consistent with other mechanisms as well.

Allylic Stereochemistry. Recent studies of the ene reactions of dimethyl azodicarboxylate[9] and single oxygen[10] have shown the value of careful examination of reaction stereochemistry in testing mechanistic hypotheses. Since an ene-type reaction is apparently a crucial step in the SeO_2 oxidation, a similar study seemed warranted.

The key experiment in both prior studies of ene chemistry involved the use of a chiral deuteriated olefin. Substrates such as this permit simultaneous monitoring of isotope effects and reaction stereochemistry (reaction 3). The degree of coupling between the kinetic isotope



(3)

effect (measured as the isotopic content of the product) and the reaction stereoselectivity (found by comparing reactant and product stereochemistry) indicates the amount of coordination that exists between C–H bond cleavage and C–X bond formation. Complete coupling (k_H/k_D equal to the product enantiomeric ratio) indicates a stereospecific, probably concerted reaction. An isotope effect of zero (k_H/k_D = 1.0) or an uncoupling of the isotope effect and the product stereochemistry indicates the possibility of a stepwise pathway in which bond breaking and bond making occur in two separate steps.

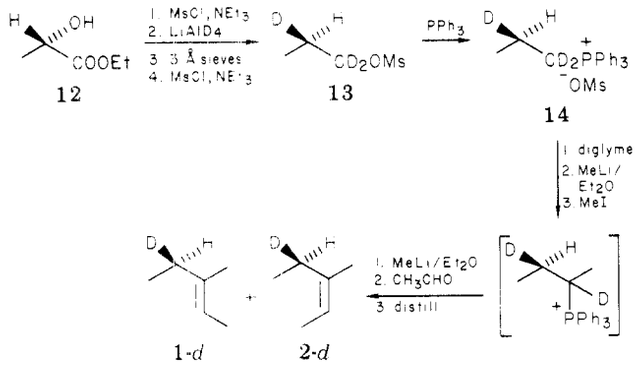
Both steps of the ene–[2,3]-shift mechanism involve a cyclic system of six electrons and may thus be considered thermally allowed pericyclic reactions under the Woodward–Hoffmann scheme. This formalism predicts that both reactions should occur suprafacially. Since the equivalence of the intra- and intermolecular isotope effects shows that the ene reaction is rate-determining step in the

(8) H. O. House and G. H. Rasmussen, *J. Org. Chem.*, **26**, 4278 (1961).

(9) L. M. Stephenson and D. L. Mattern, *J. Org. Chem.*, **41**, 3614 (1976).

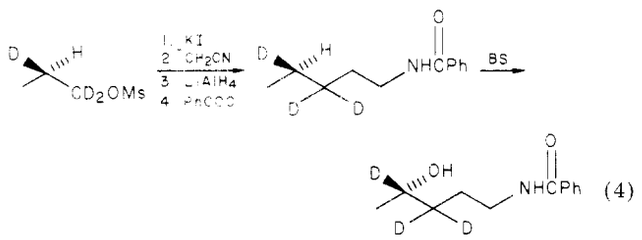
(10) L. M. Stephenson, D. E. McClure, and P. K. Sysak, *J. Am. Chem. Soc.*, **95**, 7888 (1973).

Scheme I



transformation, the proposed mechanism predicts a direct coupling between the isotope effect and the product stereochemistry.

Both (*E*)- and (*Z*)-(*R*)-4-deuterio-3-methyl-2-pentene (**1-*d*** and **2-*d***) were employed as the chiral substrates for the reaction. This olefin was chosen because oxidation occurs 85% at the CHD position, because little secondary oxidation to ketone occurs, and because these deuterioalkenes were readily available from L-ethyl lactate by the reduction and Wittig reaction sequence shown in Scheme I. The isomers were separated by spinning-band distillation [(*Z*)-**2-*d***, bp 67 °C; (*E*)-**1-*d***, bp 70 °C].[11] The optical purity of the olefin was not determined. An estimate of the purity of the 1,1,2-trideuteriopropyl mesylate is available, however. In a parallel study this substrate was converted to *n*-pentylbenzamide (eq 4) and incubated with



(4)

actively growing fungus, *Beuvaria sulfurescens* (BS). The hydroxylated amide produced was of >90% ee (enantiomeric excess) and retained *all* of the deuterium present in the starting material.[13] The precursor propanol must therefore be at least 90% ee. Later evidence (given below) supports this contention.

The suprafacial reaction path that is prediced by the ene–[2,3]-shift mechanism requires that the kinetic isotope effect and the product stereochemistry be directly related. The details of this relationship are shown in Figure 1. This figure shows attack of SeO_2 on both faces of the double bond with suprafacial removal of either H or D. Through the proposed mechanism, only two *E* products, (*R*)-3-methyl-3-penten-2-ol, *R*(H), and (*S*)-2-deuterio-3-methyl-3-penten-2-ol, *S*(D), can be formed. The stereochemistry of the product is thus tied directly to the isotopic content, and the enantiomeric ratio S/R should mirror the kinetic isotope effect.

The results for two synthetically distinct samples of trans deuterio olefin are shown.

	k_H/k_D	S/R	$R(H)/S(H)$
E-I	3.7 ± 0.25	2.0 ± 0.1	3.0
E-II	3.3 ± 0.25	2.1 ± 0.1	2.6

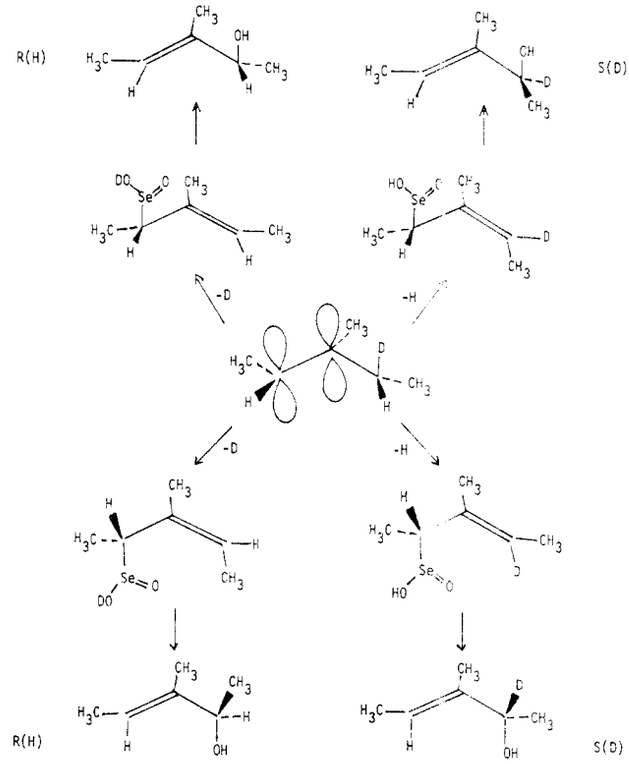


Figure 1. Stereochemical–isotopic correlation of the products derived from the oxidation of (*E*)-(*R*)-4-deuterio-3-methyl-2-pentene.

Table I. Percent Composition for E-I and E-II

	E-I			E-II		
	R	*S*	k_H/k_D	*R*	*S*	k_H/k_D
H	16	5	21	17	6	23
D	18	61	79	15	62	77
R/*S*	34	66		32	68	

This analysis was performed entirely by NMR as follows. After recovery of the product from the reaction mixture, the isotopic composition was determined by comparison of the NMR signals for the vinyl and carbinol protons. Product stereochemistry was determined by converting the alcohol to its (+)-methoxy(trifluoromethyl)phenylacetic acid ester [(+)-MTPA] by using (+)-MPTA-Cl according to the technique of Mosher et al.[12] Fluorine-19 NMR can then be used to determine the S/R ratio from the signals for the diastereomeric CF_3 groups. Carbon-13 NMR can also be used to determine the enantiomeric ratio. Deuterium splits a carbon signal into a triplet and shifts the peak ~0.3 ppm upfield. Since deuterium substitution also gives no ^{13}C signal enhancement, only those carbons bearing hydrogen are clearly visible. Thus the ratio of *R*(H) to *S*(H) is available from the ^{13}C signals of the diastereomeric ester carbinol carbons at ~76 ppm.

Both sets of results show a moderate isotope effect consistent with other observations.[9,14] The stereochemistry of the process, as reflected by the S/R ratio, is not as clean as the mechanism predicts. This fact can be made even more apparent if the values above are put into percentage composition tables (see Table I). It can be seen here that 21–23% of the product is either *R*(D) or *S*(H), products not accessible by the ene–[2,3]-shift mechanism.

Several experimental sources of these crossover products can be eliminated quickly. Contamination of *E* olefin with

(11) K. W. Greenlee and V. G. Wiley, *J. Org. Chem.*, **27**, 2304 (1962).
(12) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
(13) L. M. Stephenson, J. Halpern, and B. Stephenson, unpublished work.
(14) J. P. Schaefer, B. Horvath, and H. P. Klein, *J. Org. Chem.*, **33**, 2647 (1968).

Table II. Percent Composition for the Oxidation of the Cis Olefin Isomer

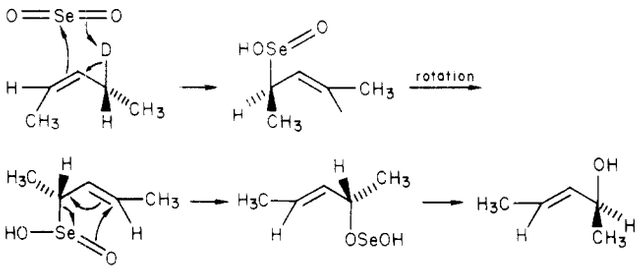
	R	S	k_H/k_D
H	4.5	17.5	22
D	63.5	14.5	78
R/S	68	32	

$k_H/k_D = 3.6 \pm 0.25$; $R/S = 2.1 \pm 0.02$; $S(H)/R(H) = 3.7$.

Z isomer can be eliminated by VPC analyses. All samples used in this study were more than 97% pure E olefin. Similarly, incomplete deuteriation cannot explain the result (particularly the excess R(D) product), and in any event, mass spectral and NMR analyses show the olefin to be ≥98% monodeuterated.

Enantiomeric impurity in the olefin is the most obvious systematic source of crossover in this experiment. In all three experiments the requirement for fractional enantiomeric impurity (R/S) would be reasonably constant: for E-I (D removal) 5/21, (H removal) 18/79; for E-II (D removal) 6/23, (H removal) 15/77; for the Z isomer (see below) (D removal) 4.5/22, (H removal) 14.5/78. These reduce to the percentages 24, 23, 26, 19, 20, and 19%, an average of 22%. Such a source of systematic error would require that our synthesis give material of only 56% enantiomeric excess [(78 − 22)/100]. Two points argue against this source of error. First, we have already presented evidence which demonstrates that the key synthetic intermediate, 1-propanol-2-*d*, is >90% enantiomerically pure. We see no obvious possibility for racemization in the reaction sequence proceeding from propanol to olefin. Second, variation in solvent basicity (see Discussion) removes a large fraction of the crossover products. We are thus left with the conclusion that the crossover is mechanistically significant and not an artifact or experimental error.

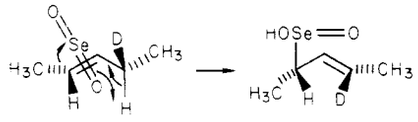
As a check on the results, oxidation of the cis olefin isomer was examined. In this case R(D) and S(H) products are expected. The inversion is a result of the conversion of Z olefin to E alcohol. This requires a net 180° rotation about the double bond such that the ene reaction and the [2,3] shift occur on opposite faces of the allyl unit, leading to inversion at the allylic carbon (reaction 5). In spite of



(5)

this greater mechanistic complexity, the results are completely analogous. Substantial crossover to, in this case, R(H) and S(D) occurs. Again, experimental error cannot explain these results (see Table II).

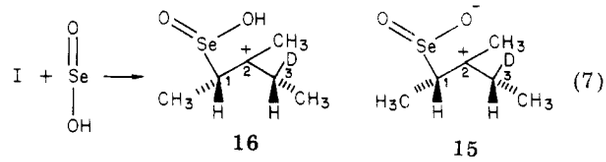
Crossover occurs when the C–Se bond is formed on one face of the allyl unit, while the hydrogen isotope is removed from the opposite face (eq 6). There are several obvious



(6)

routes by which this could occur. Most simply there is the antarafacial component of the ene reaction. Just as the suprafacial reaction is Woodward–Hoffmann allowed, so is the reaction that is antarafacial on both components. We do not favor this explanation, however, since the antarafacial ene reaction would be subject to severe steric congestion, and the orbital overlap would undoubtedly be less good than for the suprafacial scheme. Since there is no precedent for an antarafacial six-electron process such as this, we feel it is an unlikely possibility.

It is also possible to uncouple isotopic composition and stereochemistry by employing stepwise equivalents of the ene reaction. One such class of intermediates might be zwitterionic, or protonated analogues (eq 7). Rotation



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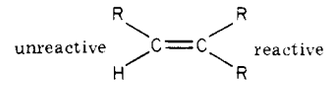
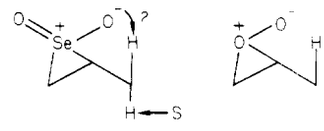
about either the C_1–C_2 or C_2–C_3 bonds in these intermediates during the period between C–Se bond formation and C–H (or C–D) bond cleavage would lead to a loss of stereoselectivity. Two restrictions must be placed on such species if they are to be viable intermediates for this reaction. First, they must be formed irreversibly since olefin isomerization is not observed. Second, they cannot have a lifetime sufficient for Wagner–Meerwein rearrangements to occur since these have not been observed under oxidation conditions. While these restrictions appear limiting, recent work by Rogic and Masilamani on the SO_2-catalyzed ene isomerization of olefins has shown that such intermediates may indeed exist without the intrusion of Wagner–Meerwein rearrangements or cis–trans isomerizations.[15] We note parenthetically that intermediates of this type would provide a clear explanation for the regioselectivity in this reaction which is invariably directed to the more substituted end of the olefin.



The second potential "ene" intermediate is an episelenone analogous to the perepoxide that has been proposed as the intermediate in the singlet-oxygen ene reaction. Crossover in this case can occur if the solvent becomes involved in breaking the allylic C–H bond. Since one face of the allyl unit would be sterically congested by the episelenone, this solvent interaction would probably occur best on the opposite face, leading to "crossover".



In order to test this postulate the SeO_2 oxidation was conducted in *tert*-butyl alcohol containing 20% pyridine. If the solvent can be an integral part of the reaction, this more basic mixture should lead to an increase in crossover products, i.e., a decrease in stereoselectivity. For the E deuterio olefin the results in this system are $k_H/k_D = 3.4 \pm 0.2$, $S/R = 2.9 \pm 0.2$, and $R(H)/S(H) = 4.7$. These reduce to the percentages shown below.

	R	S	k_H/k_D
H	19	4	23
D	7	70	77
R/S	26	74	

(15) M. M. Rogic and D. Masilamani, *J. Am. Chem. Soc.*, **99**, 5219 (1977).

Contrary to expectation, adding pyridine increases the stereoselectivity of the reaction. Here only 11% "crossover" has occured in contrast to some 21% in *t*-BuOH alone.

The apparent stereoselectivity of this reaction cannot be further improved by addition of larger fractions of pyridine. Neat pyridine shows $k_H/k_D = 3.7 \pm 0.2$ (79/21) and $S/R = 2.8 \pm 0.2$ (74/26), probably not interpretably different from the results in 20% pyridine. It is entirely possible that this residual ~10% crossover may represent the sensitivity limit of this particular system. By VPC analysis we know that olefin and product alcohol contain isomeric impurities of 2–3% each. If this is coupled to an expectation of incomplete deuteration, enantiomeric impurities in the range of 5% total would lead to an expectation of about 10% apparent crossover even under rigid stereochemical control. There remains, however, the result that this reaction is measurably less stereospecific in *t*-BuOH than in *t*-BuOH with added pyridine.

Although the nature of the selenium species active in this reaction is unknown, many solvent-sensitive equilibria could be involved. We propose that a particularly simple and important one could be

$$SeO_2 + \text{solvent}—H \rightarrow O{=}Se^+—OH + \text{solvent}^-$$

Our results could then be satisfactorily rationalized by a mixture of a stereospecific component involving SeO_2 and a stereorandom pathway involving attack by protonated SeO_2 to produce an ionic intermediate. The addition of pyridine would shift the equilibrium above to favor the SeO_2 species and the stereospecific path, as observed.

Conclusion

Our results concerning the stereochemistry of the SeO_2 allylic oxidation are more complex than the ene–[2,3]-shift mechanism would predict. In basic solution the reaction does appear to be operationally concerted, consistent with the proposed mechanism of Sharpless et al. In alcoholic solvents, however, the reaction is more complex. Our results favor a solvent-sensitive mixture of mechanisms involving both a stereospecific (major) and a stereorandom (minor) path. We propose that this stereorandom path is a stepwise ene reaction equivalent which proceeds under conditions favoring carbonium ion formation.

Experimental Section

General Methods. Proton NMR spectra were obtained by using dilute carbon tetrachloride or deuteriochloroform solutions with a Varian A60A spectrometer. Chemical shifts are reported in ppm from internal tetramethylsilane (δ). Fluorine-19 NMR spectra were taken by using either a Varian A56-60 spectrometer (operating at 56 MHz) or a Varian XL-100 instrument (at 94.5 MHz). Proton-decoupled carbon-13 NMR spectra were obtained by using dilute deuteriochloroform or benzene-d_6 solutions on a Varian XL-100 spectrometer (operating at 25.1 MHz) in the gyrocode mode with an internal deuterium lock.

Optical rotations were determined with a Perkin-Elmer Model 141 automatic polarimeter which allows rotations to be taken at the following wavelengths (nm): Na 589; Hg 578, 546, 432, 365. The jacketed cell employed had a path length of 10 cm and a total volume of less than 1.0 mL. A Thomas-Hoover capillary melting point apparatus was used to determine all melting points. They are uncorrected.

Chemicals. Diethyl ether was distilled under nitrogen from sodium/benzophenone just prior to use. Diglyme was purified by the following procedure. Crude solvent was distilled and the fraction boiling below 140 °C was discarded. The distillate was stored over KOH overnight and distilled from KOH under vacuum; bp 60 °C (20 mmHg). This second distillate was then heated under nitrogen at 100 °C over sodium/benzophenone until the characteristic blue ketyl color was observed. The solvent was distilled under vacuum just prior to use. Pyridine and dimethyl sulfoxide were distilled from barium oxide under nitrogen. Triethylamine was stored over KOH pellets. All other solvents were used as received.

Table III

compd	bp, °C	% comp
2-ethyl-1-butene	65	10
(*Z*)-3-methyl-2-pentene	67	35
(*E*)-3-methyl-2-pentene	70	55

Selenium dioxide (Kawecki Berylco technical grade) was moistened with concentrated nitric acid and sublimed (by using a flame). Ethyl lactate (Fluka, $[\alpha]^{20}_D = -12$ (neat)] and lithium aluminum deuteride-d_4 (Stohler Isotope Chemical, 99% D) were used as received. Triphenyl phosphine was recrystallized from 95% ethanol and dried under vacuum. All other reagents were used as received or distilled prior to use as indicated.

(*E*)- and (*Z*)-3-Methyl-2-pentene (1 and 2). In a typical preparation 7.2 g (300 mmol) of magnesium turning suspended in ether was treated with 47.5 g (310 mmol) of ethyl iodide. After formation of the Grignard reagent was complete, 21.6 g (300 mmol) of 2-butanone was added. Following an aqueous ammonium chloride workup, the ether solution was dried with $MgSO_4$ and the alcohol recovered by distillation; bp 121–123 °C (25.4 g, 83% yield).

About 100 g of ground potassium bisulfate ($KHSO_4$) was placed in a flask equipped with an addition funnel and a short-path distillation head. The flask was heated to 200 °C in a sand bath to fuse the salt. The alcohol was then dropped onto the molten salt slowly so that the temperature at the head of the column never exceeded 80 °C. Following separation of the layers, the organic layer was dried with $MgSO_4$ and distilled; bp 67–72 °C. The olefin mixture was subjected to careful spinning-band distillation with a Perkin-Elmer Model 151 Auto Annular still (1-m column, Teflon band). The isomeric olefins could be separated cleanly in this fashion, as confirmed by VPC (Table III).

The stereochemistry of the olefins was assigned according to Greenlee and Wiley.[16] The total recovery of olefins was 60–70% when benzene was used as a chaser in the distillation: ^{1}H NMR (*Z* isomer) δ 1.0 (t, 3 H), 1.55 (d, 3 H), 1.60 (s, 3 H) (singlet overlaps the downfield peak of the doublet), 2.0 (q, 2 H), 5.25 (m, 1 H); ^{1}H NMR (*E* isomer) δ 0.95 (t, 3 H), 1.6 (d, 3 H), 1.65 (s, 3 H) (singlet overlaps as above), 2.1 (q, 2 H), 5.2 (q, 1 H).

Oxidation of 1 and 2 by SeO_2. In a 10-mL flask, 183 mg (1.66 mmol) of sublimed SeO_2 was dissolved in 5 mL of *tert*-butyl alcohol. About 1 h was required for complete solution. To this solution was added 500 μL (350 mg, 4.14 mmol) of 3-methyl-2-pentene. This corresponds to 0.4 mol of SeO_2/mol of olefin. The solution yellowed rapidly and was left overnight. After 18 h the yield, as assayed by VPC using an internal standard, was approximately 30%. The orange reaction mixture was poured into 50 mL of water and extracted with ether. After being dried with $MgSO_4$, the ether was removed through a 10-cm Vigreux column distillation. Carbon tetrachloride was then added to "chase" the remainder of the ether and to azeotrope away the residual water and *tert*-butyl alcohol. When the total solution volume was reduced to 2–3 mL (after the head temperature reached 76 °C) the mixture was bulb-to-bulb distilled to remove organoselenium compounds and remaining selenium metal (red solid). The distilled mixture was then concentrated at 80 mmHg to about 0.5 mL total volume. VPC analysis (5% FFAP, 10 ft × $^1/_8$ in.) revealed the product distribution: 85% allylic alcohol (97/3 *E*-3/*Z*-4); 5% α,β-unsaturated ketone (*E* only, 5); 10% other products (probably derived from oxidation at CH_3).

^{1}H NMR of *E* allylic alcohol 3: δ 1.2 (d, 3 H), 1.6 (m, 6 H), 2.1 (s, 1 H), 4.2 (q, 1 H), 5.4 (q, 1 H).

To ensure correct structural assignments, we synthesized the major oxidation products by the following independent routes. The *E* ketone (5) was prepared by the method of Hunkel et al.[17] and the *E* allylic alcohol (3) by $LiAlH_4$ reduction of this substance.

(16) K. W. Greenlee and V. G. Wiley, *J. Org. Chem.*, **27**, 2304 (1962).
(17) L. E. Hunkel et al., *J. Chem. Soc.*, 814 (1931).

The *Z* allylic alcohol (**4**) was prepared via the method of House and Ro.[18]

(*E*)-1,1,1-Trideuterio-2-methyl-2-butene (7). Synthesis and Oxidation. A 30-mL ethereal suspension of 1.62 g (77 mmol) of $LiAlD_4$ in a flame-dried 100-mL flask was cooled to 0 °C under nitrogen. To this was added 8.0 g (70 mmol) of methyl tiglate, **6** (prepared by the method of House and Rasmussen[19]), in about 10 mL of dry ether. After 30 min the reduction was worked up by using 20% NaOH solution. Following 2 h over a 4 Å sieves (to remove methanol) the ether was removed and the product, (*E*)-1,1-dideuterio-2-methyl-2-buten-1-ol, was recovered by distillation, bp 135–137 °C, in 85% yield (5.2 g): ^1H NMR δ 1.65 (d, 3 H), 1.70 (s, 3 H) (singlet overlaps doublet), 3.7 (s, 1 H), 5.5 (m, 1 H).

In a 250-mL flask, 3.9 g (45 mmol) of this dideuterated allylic alcohol was mixed with 6.8 g (9.4 mL, 67.5 mmol) of triethyl amine in 50 mL of dry ether. This solution was cooled to −50 °C under an N_2 atmosphere, and a solution of 5.7 g (50 mmol) of methane sulfonyl chloride was added slowly. After 1 h at −30 °C, the solution was allowed to warm to 0 °C and was transferred to a chilled separatory funnel. The organic layer was then washed twice with cold saturated 5% HCl, once with saturated Na_2CO_3, and once with brine. After being dried with $MgSO_4$, the solvent was removed, giving the mesylate in 90–100% yield: ^1H NMR δ 1.70 (d, 3 H), 1.75 (s, 3 H) (singlet overlaps doublet), 3.0 (s, 3 H), 5.7 (m, 1 H).

The unstable mesylate, 6.6 g (40 mmol), was dissolved immediately in 10 mL of dry diglyme and added to a suspension of 450 mg (10.5 mmol) of $LiAlD_4$ in 30 mL of diglyme contained in a flame-dried 100-mL flask under nitrogen. After 2 h at room temperature the product was recovered by distillation directly from the reaction mixture through a 10-cm Vigreux column. The product, bp 35 °C, was collected in an efficient, ice-cooled, spiral trap in 80% yield (2.3 g): ^1H NMR δ 1.6 (m, 6 H), 5.2 (m, 1 H); ^{13}C NMR δ 136, 122.5, 21, 17 (peak at 30 ppm in the protio olefin is missing).

Oxidation, isolation, and product analysis were performed with only minor variations in the procedure described above for olefins **1** and **2**. In this case a 0.15 molar ratio of SeO_2/olefin was employed to minimize oxidation of allylic alcohol to aldehyde. Conversion to product was 10–15%, of which 85% was allylic alcohol. Proton NMR analysis of the allylic alcohol fractions showed it to be *E*, with a ratio of CD_2OH material **8** to CH_2OH material **9** of 1:2.6.

Determination of Intermolecular Isotope Effect. The hexadeuterio olefin **10** was prepared by Wittig reaction of hexadeuterioacetone with ethylidenetriphenylphosphorane. Oxidation of an equimolar quantity of this material and the perprotio compound with SeO_2, again under conditions which led to only a small quantity of aldehyde, gave a ratio of pentadeuterated allylic alcohol to undeuterated allylic alcohol of 1:2.55, as determined by proton NMR.

Mesylate of (*S*)-(+)-Ethyl Lactate (12). (*S*)-(+)-Ethyl lactate (47.6 g) was treated with 70 mL of triethylamine and 50.4 g of methanesulfonylchloride (MsCl) under the standard conditions of Crossland and Servis.[20] The mesylate was obtained in 91% yield: $[\alpha]_D$ −64.98; bp 115 °C (0.2 mmHg); ^1H NMR δ 1.3 (t, 3 H), 1.6 (d, 3 H), 3.1 (s, 3 H), 4.2 (g, 2 H), 5.1 (q, 1 H).

(*R*)-(+)-1-(Mesyloxy)-1,1,2-trideuteriopropane (13). In a flame-dried 1000-mL flask 5.0 g (199 mmol) of $LiAlD_4$ was suspended in 200 mL of dry ether under dry nitrogen. The flask was equipped with an addition funnel, a reflux condenser, and a mechanical stirrer. To this was added 23.5 g (119 mmol) of the mesylate of ethyl lactate **12**. The addition was done at 0 °C, after which the reaction was warmed to room temperature and left overnight. The reaction was then refluxed for an additional 6 h. The standard base workup was then used, except that the alumina produced was refluxed twice with ether to extract the last traces of alcohol. To the combined ether solution of ethanol and propanol-*1,1,2-d*$_3$ was added 40 g of 3 Å sieves (about 1.0–1.25 g of sieves/0.1 g EtOH) to remove the ethanol. (**Caution**: Batches of sieves should be checked before use. According to the literature,[21] 3 Å sieves should not absorb ethanol. The appropriate sieve should be 4 Å. In our hands, however, the 4 Å sieves absorbed both ethanol and propanol.) After 12–18 h (monitored by VPC) less than 10% of the ethanol remained, while more than 90% of the propanol was still present.

The sieves were removed by filtration and washed twice with ether. The ether was diluted to a total volume of 500 mL, and 10 mL (7.5 g, 75 mmol) of triethylamine was added. After the flask was fitted with an addition funnel, a nitrogen atmosphere was introduced. The solution was then cooled to −15 °C, and 9.0 g (78 mmol) of freshly distilled mesyl chloride was added. After 4 h at −10 °C the reaction mixture was transferred to a separatory funnel and washed twice with cold 5% HCl, once with saturated Na_2CO_3, and once with brine. The solvent was removed after being dried with $MgSO_4$, and the product was distilled, bp 90 °C (0.250 mmHg), and recovered in 70% overall yield from ethyl lactate. [α] −0.595; ^1H NMR δ 1.05 (d, 3 H), 1.05 (d, 3 H), 1.2–1.9 (m, 1 H), 2.9 (s, 3 H).

Triphenylphosphonium Salt of Propanol-*1,1,2-d*$_3$ (14). The salt was prepared by heating 18.0 g (127.5 mmol) of propyl mesylate-*d*$_3$ (**13**) and 33.4 g (127.5 mmol) of triphenylphosphine in a flask under nitrogen at 130–140 °C for 12 h. Solid began to form almost immediately upon heating. Following removal of the salt from the flask, it was triturated three times each with benzene and ether and dried under vacuum. The salt, mp 252–257 °C, was isolated in 80–90% yield: ^1H NMR δ 1.2 (br d, 3 H), 1.65 (q, 1 H), 2.7 (s, 3 H), 7.9 (m, 15 H).

Wittig Synthesis of (*R*)-4-Deuterio-3-methyl-2-pentene (1-*d* and 2-*d*). A 250-mL flask fitted with an addition funnel, a serum cap, and a stopcock-controlled gas inlet tube was flame-dried under vacuum and cooled under nitrogen. After the flask was cooled, 12.0 g (30 mmol) of phosphonium salt **14** was added and suspended in 60 mL of *dry* diglyme which was added via cannula. The suspension was cooled to 0 °C, and 18 mL (35 mmol) of 1.95 M ethereal methyllithium (titrated by the procedure of Watson and Eastham[22]) was added at a moderate rate via syringe. During the addition the solution became orange, and gas was evolved. After stirring for 1 h at room temperature, only traces of solid remained. When the solution was cooled to 0 °C, however, a copious precipitate formed. To this cooled suspension was then added 8.5 g (3.7 mL, 60 mmol) of methyl iodide (freshly distilled from P_2O_5) in 20 mL of diglyme, slowly via syringe. The new phosphonium salt formed precipitated rapidly as the color of the solution disappeared (rapid addition of the iodide should be avoided since this causes rapid precipitation which traps unreacted ylide). Following an additional hour at room temperature, vacuum was applied to the flask to remove the ether and excess methyl iodide. Pumping was continued until the pressure remained at less than 2 mmHg for more than 10 min. The secondary phosphonium salt was not isolated. Instead, the suspension was cooled to 0 °C, and another 18 mL (35 mmol) of ethereal methyllithium was added. Gas was again evolved and a deep cherry red ylide solution was formed. After 1 h, vacuum was again applied until the pressure was less than 2 mmHg for a period of 15 min. Nitrogen was then readmitted, and the reaction mixture was cooled to −50 °C. A solution of 4.0 g (90 mmol) of freshly distilled acetaldehyde in 20 mL of diglyme was then slowly added to the reaction through the addition funnel. It was necessary to manually agitate the mixture since the low temperature and high concentration of salts made the reaction mixture too viscous to be stirred. As the addition proceeded, the color of the ylide gradually disappeared. Following the addition, the reaction was kept at −50 °C for 2 h and then allowed to warm to room temperature. The product was recovered by direct distillation of the reaction mixture through a 10-cm Vigreux column into an efficient spiral collector. Material boiling at less than 100 °C was collected as product. The yield of olefin was 60–70% by GC.

The crude olefin mixture was purified by careful spinning-band distillation which permitted the isolation of gram-scale quantities of the isomerically pure *E* and *Z* olefins, as before (bp 67 °C for *Z*, 70 °C for *E*): ^1H NMR (E isomer) δ 1.0 (d, 3 H), 1.5 (d, 3 H),

(18) H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 2427 (1958).
(19) H. O. House and G. H. Rasmussen, *J. Org. Chem.*, **26**, 4278 (1961).
(20) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).
(21) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p 703.
(22) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).

1.55 (s, 3 H) (singlet overlaps doublet), 1.7–2.1 (m, 1 H), 5.2 (m, 1 H); ^{13}C NMR δ 142 (s), 121 (s), 36 (t), 20 (s), 18 (s), 17 (s).

Oxidation of (*E*)-(*R*)-4-Deuterio-3-methyl-2-pentene. In a 10-mL flask, 185 mL (1.67 mmol) of SeO_2 was dissolved in 5 mL of *tert*-butyl alcohol. When all of the solid had dissolved, 500 μL (350 mg, 4.17 mmol) of *E* deuterio olefin [98/2 *E*/*Z*; $[\alpha]_D$ −0.91 (*c* 35, *tert*-butyl alcohol)]. The reaction was monitored by VPC. After 24 h the yield as estimated by VPC was 30%, of which 87% was the desired secondary alcohol and less than 2% was the corresponding ketone. The remaining 11% of the product was unidentified, but it is probably the result of oxidation at CH_3. Further VPC analysis revealed that the allylic alcohol was 97% *E* and 3% *Z*.

At this point the reaction mixture was poured into water and extracted with ether. The water was then saturated with salt and extracted again. The ether extracts were dried with K_2CO_3, and the ether was removed by distillation and worked up as previously indicated, $[\alpha]_D$ −0.33. (The product was not purified by preparative VPC since dehydration was noted under preparative conditions.)

Analysis of the Allylic Alcohol. Proton NMR was used to determine the deuterium content of the product. This was done by comparison of the integrals for the singlet quartet signals due to the vinyl and methine protons. The methine quartet was overlapped by a singlet, probably due to the primary alcohol derived from oxidation at methyl. Addition of approximately 5–10 mol % of $Pr(fod)_3$ shift reagent cleanly separated the two peaks.

Integration of the shifted spectrum led to a measure for the isotope effect of 4.0 ± 0.25. Bulb-to-bulb distillation separated the product from the shift reagent.

MTPA Ester of the Allylic Alcohol. The alcohol was dissolved in 2.0 mL of carbon tetrachloride and 2.0 mL of dry pyridine. To this was added 350 μL of (+)-methoxy(trifluoromethyl)phenylacetyl chloride, $[\alpha]_D^{20}$ +132.9 [*c* 7.5, CCl_4 (obtained from H. S. Mosher and co-workers)]. A precipitate formed immediately upon addition of the acid chloride. After stirring at room temperature overnight, 180 μL of (dimethylamino)propylamine was added to remove excess acid chloride and any anhydride formed during the reaction. This mixture was stirred for 90 min and then diluted with ether. The ether solution was washed twice with cold 5% HCl, once with saturated Na_2CO_3, and once with brine. The ether was then dried with $MgSO_4$. Following removal of the ether on the rotary evaporator, CCl_4 was added and the solution reconcentrated. When proton NMR revealed the presence of MTPA anhydride (extra methoxy peak upfield from the ester methoxy peak), the product was redissolved in 5 mL of CCl_4 and treated with 50 μL of (dimethylamino)propylamine for 1 h, followed by a repetition of the workup above. NMR δ 1.5–1.8 (m, 9 H), 3.55 (br s, 3 H), 5.5 (q, 1.3 H), 7.5 (m, 5 H).

Analysis of the MTPA Esters. Three separate NMR analyses of the diastereomeric MTPA esters were undertaken. Carbon-13 spectra were taken at 25.1 MHz by using a 30–45° pulse with a 0.8-s acquisition time and a 1.2-s pulse delay. While several peaks showed broadening due to the presence of diastereomers, only the carbinol carbon (at about 76 ppm downfield from Me_4Si) clearly showed a doublet due to the existence of diastereomers. Examination of the spectrum allowed an estimate of 3.0 to be made for the *R*(H)/*S*(H) ratio. Only carbons bearing hydrogen are observed in this spectrum because the deuterium-bearing carbon signals are reduced in intensity (no NOE) and split into triplets.

Analysis of the fluorine-19 spectrum taken at 56 MHz showed an overlapping doublet. Addition of $Eu(fod)_3$ shifted both peaks upfield and split them farther apart so that they were base-line separated after about 20 mol % of shift reagent had been added. Integration of the shifted spectrum led to a value of 2.0 ± 0.1 for the *S*/*R* ratio.

Addition of more $Eu(fod)_3$ up to about 40–50 mol % also separated the diastereomeric methoxy group signals in the proton NMR spectrum. Data from this integrated spectrum supported the fluorine-19 results.

Oxidation of (*Z*)-4-Deuterio-3-methyl-2-pentene. In a 10-mL flask, 183 mg (1.67 mmol) of SeO_2 was dissolved in 5 mL of *tert*-butyl alcohol as before. To this was added 485 μL (348 mg, 4.14 mmol) of *Z* olefin that VPC analysis showed was 5% low boiling point impurity, 94% *Z* olefin, 1% *E* olefin, $[\alpha]_D$ +0.66. After 48 h, the yield of the oxidation as assayed by VPC was 27%, of which 78% was secondary alcohol, 2% was ketone, and 17% was due to oxidation at methyl. The alcohol was shown to be 95% *E* and less than 4% *Z*. The product was worked up as before. Integration of the $Pr(fod)_3$-shifted proton spectrum gave an isotope effect of 3.8 ± 0.4. The alcohol was recovered by bulb-to-bulb distillation and converted to the (+)-MTPA ester as before. Shift studies using $Eu(fod)_3$ gave an *R*/*S* ratio of 2.1 ± 0.2 and an estimate of the *S*(H)/*R*(H) ratio of 3.7.

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Registry No. 1, 616-12-6; 1-*d*, 71927-52-1; 2, 922-62-3; 2-*d*, 71927-53-2; 3, 24652-51-5; 4, 64683-06-3; 5, 1567-73-3; 6, 6622-76-0; 7, 69432-94-6; 8, 71831-22-6; 8 mesylate, 71831-23-7; 9, 71831-24-8; 10, 1787-45-7; 11, 513-35-9; 12, 687-47-8; 12 mesylate, 63696-99-1; 13, 71831-25-9; 14, 71831-27-1; 2-ethyl-1-butene, 760-21-4; (*E*)-1,1-dideuterio-2-(trideuteriomethyl)-2-buten-1-ol, 71831-28-2; (*E*)-2-methyl-2-buten-1-ol, 497-02-9; ethyl iodide, 75-03-6; 2-butanone, 78-93-3.

Protonic and Conformational Equilibria of 1,3-Dithiaalkanes and Their Congeners in Highly Acidic Media

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Disulfides of the structure $CH_3S(CH_2)_nSCH_3$ are fully diprotonated in FSO_3H when $n = 2$ or 3 but are only monoprotonated when $n = 1$. These compounds were examined as models for cyclic disulfides. The ^{13}C resonances of 1,3-dithiane in FSO_3H have been assigned by comparison with isotopic modifications containing deuterium in the 2, 5, or 4/6 positions. The same deuterated modifications permit a more complete assignment of the ^1H spectra. In FSO_3H, there are approximately equal amounts of a monoprotonated form of 1,3-dithiane and of a second form that is probably the ring-opened sulfonium ion or a decomposition product therefrom. Similar phenomena are observed in 1,3-diselenane, 1,3,5-trithiane, 1,3-dithiolane, and other saturated group 6 heterocycles.

Protonation of dithiaalkanes in which the sulfur atoms are separated by one or more carbon atoms (eq 1) leads to a number of kinetic and conformational consequences. First, protonation can occur on one or both sulfur atoms,

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