Stereochemistry of an Ene Reaction of Dimethyl Azodicarboxylate

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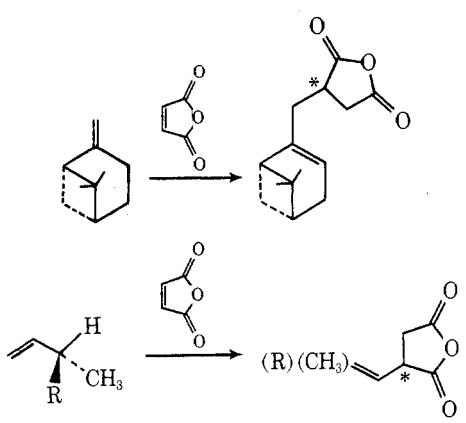
Dimethyl azodicarboxylate reacts smoothly with (*S*)-*cis*-1-deuterio-1-phenyl-4-methyl-2-pentene in a typical ene reaction. The abstraction from the chiral benzylic center occurs with an isotope effect of 2.5–3.5. Since this ratio matches the ratio of enantiomers produced in the formation of the new carbon–nitrogen bond, the reaction meets all expectations for a concerted process.

The ene reaction[1] is a complex transformation in which an unsaturated "enophile" bonds to an olefin (the ene), abstracts an allylic hydrogen from the ene, and effects a shift of the ene double bond. Systematic investigations of the ene reaction began with the studies[2] of Alder and his students in 1943. Early mechanistic proposals for the reactions of enes with various enophiles involved radical or ionic intermediates.[3] However, as the ubiquity of the allylic shift became established, proposals involving concerted mechanisms gained favor.[4] Further stimulus for proposing concerted mechanisms was afforded by the Woodward–Hoffmann orbital symmetry rules[5a,b] of the 1960's. This analysis described the concerted ene reaction as symmetry allowed, and made predictions about the stereochemical consequences of a concerted reaction.

The first detailed stereochemical investigation of an ene reaction was described[6] by Arnold and Showell in 1957. When the enophile maleic anhydride was treated with the ene β-pinene, a 3:1 preference for one configuration in the resulting substituted succinic anhydride was observed. Hill and Rabinowitz reported a similar induction of chirality using an acyclic ene.[7] (See Scheme I.)

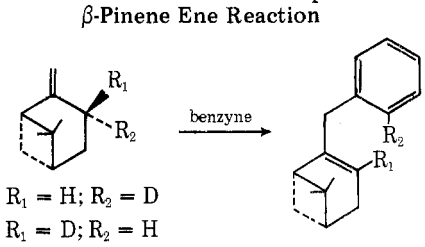
Scheme I. Transfer of Chirality in the Ene Reaction



Stereospecificity in the hydrogen abstraction has also been demonstrated by Arnold and co-workers in the β-pinene system.[8] The enophile benzyne abstracts the allylic atom opposite to the dimethyl-substituted bridge (Scheme II), even when such abstraction involves choosing deuterium over hydrogen. Similar results with the deuteriopinene and the enophile maleic anhydride have been reported by Hill and coworkers.[9]

The experiments depicted in Schemes I and II are obviously consistent with concerted mechanisms. They cannot, however, be taken to require a concerted mechanism since a *stepwise* mechanism in which the carbon–carbon bond is formed first is also compatible with each result. Berson, Wall, and Perlmutter[5b] made this point with particular clarity in their description of endoid preference in several ene reactions.

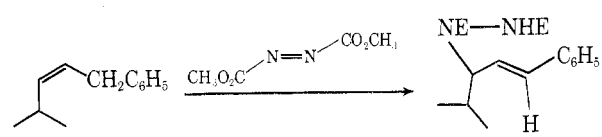
Scheme II. Steric Effects vs. Isotope Effects in a β-Pinene Ene Reaction



a, R_1 = H; R_2 = D
b, R_1 = D; R_2 = H

We wish to report here the synthesis and ene reaction of an olefin chiral by virtue of deuterium substitution. This substrate possesses sufficient structural complexity to allow a definitive demonstration that this ene reaction is only consistent with a concerted description.

General Approach. The olefin employed in this study, (*S*)-*cis*-1-deuterio-1-phenyl-4-methyl-2-pentene, has three distinctive characteristics: asymmetry at the reactive allylic carbon by virtue of monodeuteriation, distinguishable groups (*i*-C_3H_7 and H) at the other olefin terminus such that the ene adducts will contain a new center of asymmetry, and an acyclic structure with no unusual steric constraints. This olefin and its perprotiated analogue, react with dimethyl azodicarboxylate to produce the trans adduct **2**. We will subsequently use

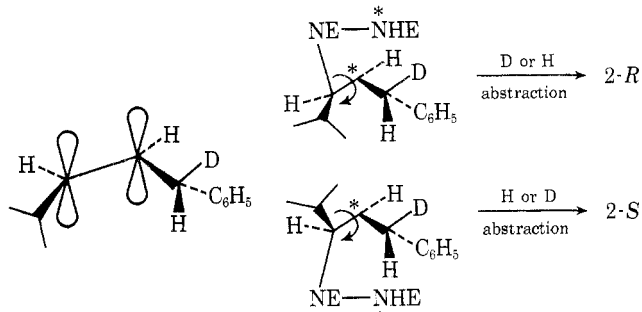


1 2

the symbols **2**-(*R*-H), **2**-(*R*-D), **2**-(*S*-H), and **2**-(*S*-D) to identify *R* or *S* stereoisomers with H or D remaining in the product.

Consider first the consequences of a stepwise mechanism Scheme III) with initial carbon–nitrogen bond formation.

Scheme III. General Stepwise Mechanism[a]



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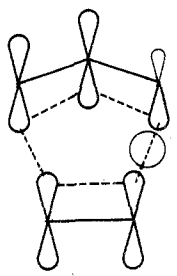
For a stepwise ionic or radical mechanism (Scheme III), intermediates are expected to be formed *equally* by attack on the olefin from above or below the π system. Here, in contrast to previous studies, Cram–Prelog-like asymmetric induction by the chiral center (in this case –CHD–) should be immeasurably small. This means that neither *R* nor *S* products will be preferentially formed, and the product will be essentially racemic.

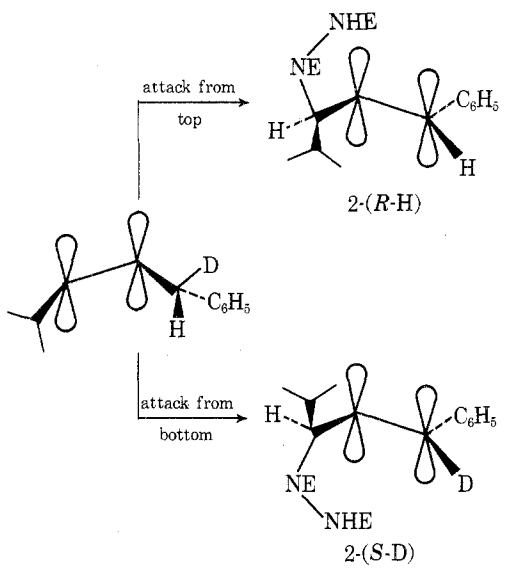
We note that carbon–carbon bond rotation which precedes H/D abstraction in the intermediates would lead to products which would further serve to implicate a stepwise mechanism. Thus, if rotation were to compete with abstraction, a product deuterium isotope effect could arise in the abstraction steps, and tend to favor the formation of **2**-(*S*-D) and **2**-(*R*-D) over **2**-(*S*-H) and **2**-(*R*-H). As we shall see, such a decoupling of the enantiomeric purity from the isotopic content of the product is not possible in the concerted reaction. It should be emphasized, however, that the key finding in support of the stepwise mechanism would be racemic product.

For the concerted reaction, if one presumes that orbital symmetry considerations are dominant, two pathways must be considered. The first of these, involving a doubly suprafacial transition state, is shown below.



Application of this model to the reaction in question reveals that only two products are possible. See Scheme IV.

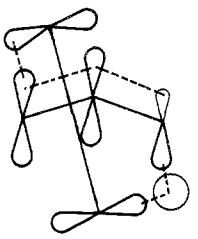
Scheme IV. Possible Products from a Concerted Reaction Which is Suprafacial



Attack of the enophile from above the plane of the ene gives *R* stereoisomer with H in the key vinylic position; attack from below gives *S* product with D at the vinyl carbon. We label these two products **2**-(*R*-H) and **2**-(*S*-D).

In addition to restrictions in possible products, a concerted mechanism should display a measurable isotope effect, leading to the preferential formation of one product, **2**-(*S*-D), over the other. The product mixture will thus retain more deuterium than hydrogen in the vinylic position, and will be chiral. Furthermore, the ratio of vinylic deuterium to hydrogen will be quantitatively correlated with the *S*/*R* ratio of the sample.

The doubly antarafacial route, also orbital symmetry allowed, is pictured below. This mechanism again restricts the



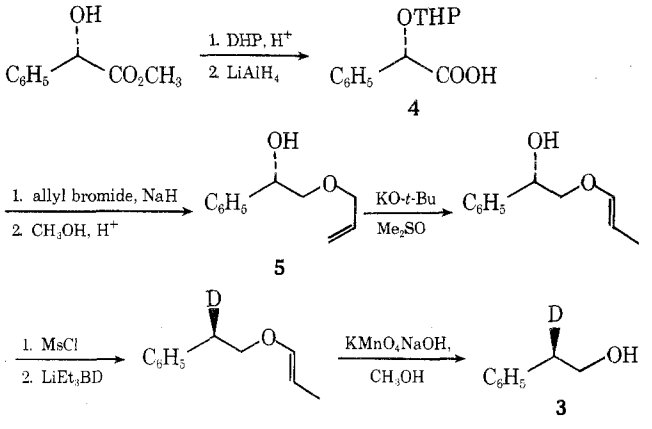
reaction to two products, in this case **2**-(*R*-D) and **2**-(*S*-H). Again, the anticipated isotope effect would favor the deuterium containing product.

Other (forbidden) concerted reactions would also lead to similar results. Thus it is apparent that *any* concerted reaction will lead to optically active products. This result will not obtain only in those special cases where the reaction displays no isotope effect, or where a *mixture* of mechanisms leads to a fortuitous cancelling of enantiomer excesses.

Results and Discussion

The optically active, deuterated olefin employed for the ene reaction was prepared from the methyl ester of (+)-mandelic acid. The route to the key intermediate, 2-deuterio-2-phenylethanol (**3**), is shown in Scheme V. The hydroxyl of methyl mandelte was protected as the tetrahydropyranyl (THP) ether. The resulting ester was reduced with lithium aluminum hydride to the alcohol, giving **4**. The free hydroxy group was then protected as the allyl ether by treatment with sodium hydride and allyl bromide in dimethylformamide. The allyl ether of the resulting doubly protected glycol is stable to *p*-toluenesulfonic acid in methanol, conditions which quantitatively remove the THP ether, freeing the benzylic alcohol (**5**). The first step in the removal of the allyl protecting group, the isomerization from the allyl ether to the 1-propenyl ether, was then accomplished by treatment with potassium *tert*-butoxide in hot Me_2SO. The previously freed benzylic hydroxyl was then converted to the mesylate, and displacement of methanesulfonate was accomplished with lithium triethylborodeuteride. The final step in the removal of the allyl protecting group was now accomplished by oxidizing the propenyl ether with potassium permanganate in methanolic sodium hydroxide. The overall yield of alcohol **3** from methyl mandelate was 28%.

Scheme V. Preparation of (*R*)-2-Deuterio-2-phenylethanol



The stereospecificity of this reaction sequence was determined by a ^1H NMR study of **3**. The ^1H NMR spectrum of

racemic **3** in the presence of the chiral shift reagent $Eu(dcm)_3$ shows an absorption for each of the two benzylic protons if they are decoupled from the adjacent methylene protons. The spectrum of chiral **3**, resulting from methyl mandelate, shows that only one of the diastereomeric complexes is present. Allowing for spectrum noise, **3** was determined to be >95% enantiomerically pure.

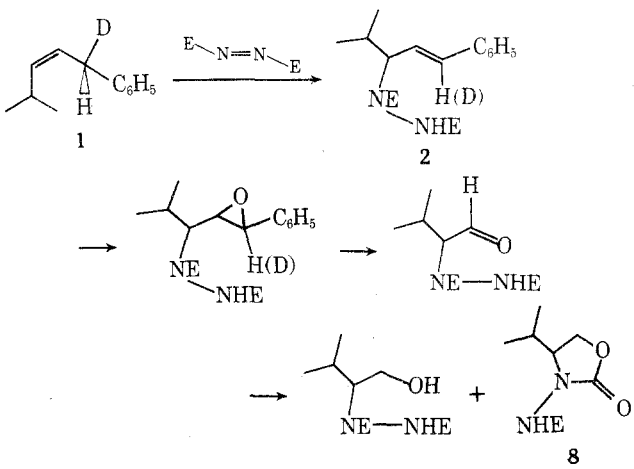
The substrate for the ene reaction, deuterated olefin **1**, was prepared in 38% yield from the alcohol **3** by a Wittig procedure. The mesylate of **3** was prepared in near-quantitative yield, and was converted to the phosphonium salt by heating for 3 days with triphenylphosphine in the absence of solvent. The salt was not isolated, but was directly dissolved in dry Me_2SO. Methyllithium solution was added to form the ylide which reacted with isobutyraldehyde to give olefin. Authentic samples of undeuterated *E* and *Z* olefins were prepared from the corresponding acetylene by dissolving metal reduction and poisoned catalytic hydrogenation, respectively. The *Z* isomer was identical with the Wittig product by NMR, ir, and VPC retention time comparisons. The deuterium position and deuterium content were established by ^1H NMR as 1.0 ± 0.1 d_1 benzylic. The optical purity of this olefin was not established independently but may be inferred from the optical purity (ee >95%) of the precursor alcohol **3**.

The reaction of the olefin **1** with dimethyl azodicarboxylate produced adduct **2** which contained vinylic deuterium and was optically active.

Analysis of the ^{13}C NMR spectra gave reliably reproducible results for the vinyl deuterium content. In run 1, using small amounts of adduct, a vinyl proton content of 0.28 ± 0.06 was obtained ($k_H/k_D = 2.6 \pm 0.8$). In the more reliable run 2 a value of 0.23 ± 0.03 was found ($k_H/k_D = 3.3 \pm 0.7$). The results compare favorably with a previous determination of an isotope effect in an ene reaction by Huisgen and Pohl[10] of 2.8–4.1.

The optical rotations of the ene adducts from runs 1 and 2 were comparable; $[\alpha]^{20}D$ −14.2° ($CHCl_3$, 11.3), −17.3° ($CHCl_3$, 11.0), respectively. The absolute configuration and optical purities were unknown, however, and the preparation of simple diasteromeric derivatives in order to accomplish this analysis was unsuccessful. The configuration and purity were thus established by converting the adduct to a compound whose chiroptical properties could be established unambiguously. The route shown in Schemes VI and VII was em-

Scheme VI. Degradation of Ene Adduct to 8



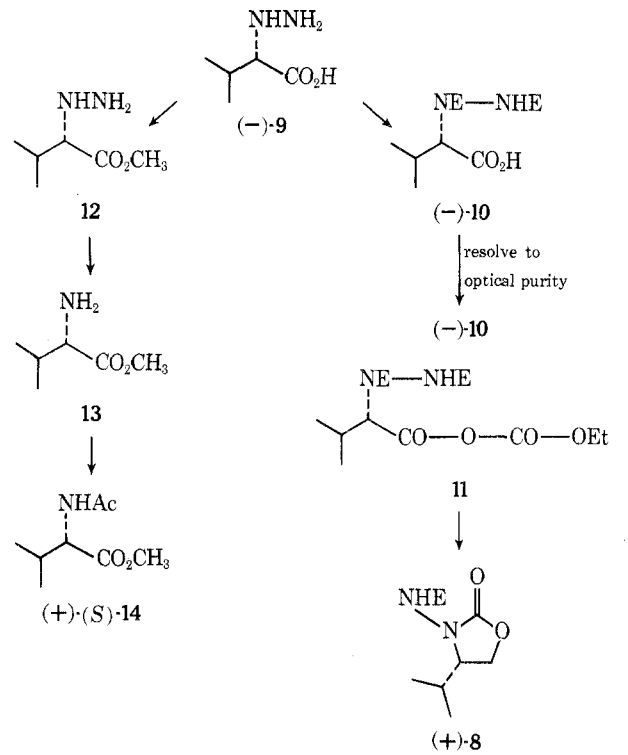
ployed. The adduct was degraded by epoxidation, followed by cleavage with periodic acid to the aldehyde, **6**. The aldehyde was immediately reduced with sodium borohydride to a mixture of alcohol **7** and the oxozolidone **8**. These compounds were separable by silica gel TLC. The optical rotations of **8** derived in this way are given in Table I.

Table I

	Run 1	Run 2
Vinyl proton content	0.28 ± 0.06	0.23 ± 0.03
k_H/k_D = D/H at vinyl position	2.6 ± 0.8	3.3 ± 0.7
$[\alpha]D$ of ene adduct **2**	−14.2°	−17.3°
$[\alpha]D$ of compound **8**	+6.7 ± 0.8°	+13.9 ± 0.8°
Optical purity	37 ± 4%	51 ± 3%
S/*R* ratio	2.2 ± 0.2	3.1 ± 0.3

Compound **8** of known optical purity was prepared as shown in Scheme VII. The hydrazino acid **9**, when treated with

Scheme VII. Scheme for Assignment of Configuration and Maximum Rotation to 8



methyl chloroformate in aqueous base, gave the acid **10** in good yield. This material could be resolved to the (+) antipode with *l*-ephedrine, or to the (−) antipode with *l*-α-methylbenzylamine. The resolved acids had equal but opposite rotations. The resolved levorotatory acid **10** was converted to dextrorotatory **8** through $NaBH_4$ reduction of the mixed anhydride **11**. Thus, rotation for optically pure **8** was determined as $[\alpha]^{20}D$ 23.7° ($CHCl_3$, 4.0), and this was used to calculate the optical purity of the samples of **8** given in Table I.

Finally, the absolute configuration of **8** was determined by relating the levorotatory acid **10** to material of known configuration. This material was obtained by methyl chloroformate treatment of the (−)-hydrazino acid **9** which was prepared partially active by the reaction of optically pure (*S*)-2-bromoisovaleric acid with hydrazine. The displacement was shown to have proceeded with partial retention by conversion to the methyl ester **12**, followed by hydrogenolysis of the N–N bond to give **13** which was characterized as the dextrorotatory acetyl derivative **14**. This compound is known to be of the *S* configuration.[28] Thus, dextrorotatory **8** is also *S*.

These correlations allow the computations of the *S*/*R* ratios of 2.2 and 3.1. Again the value from run 2 (3.1) should be taken as more reliable since it involves substantially larger amounts of material.

The high *S*/*R* ratio found for adduct **2** is a result fully in

accord with a concerted mechanism for this reaction. Indeed, induction of considerable asymmetry at the allylic position of the adduct **2** by the chiral methylene unit in **1** is unreasonable unless the hydrogen–deuterium abstraction occurs concomitantly with carbon–nitrogen bond formation. We thus discard any stepwise mechanism for the azodicarboxylate ene reaction, and conclude that it is concerted.

The detailed agreement of the *S/R* and D/H ratios in compound **2** clearly identify the role of the ene component of this concerted reaction as *suprafacial*. Thus the lone remaining point of controversy with respect to *this* reaction is whether it is properly described as doubly suprafacial or whether the reaction might be suprafacial at the ene and antarafacial at the azo linkage. While this decision cannot be made here, other studies have shown that the reaction is predominantly suprafacial with both acetylenic[29] and olefinic[30] enophiles.

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

Nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 spectrometer or a Varian XL-100 spectrometer. All spectra were taken in deuteriochloroform, except where noted.

Optical rotations were determined on a Perkin-Elmer 141 polarimeter.

Vapor phase chromatographic (VPC) analyses were performed on a 6 ft × 0.125 in., 10% UC W98 column in an F & M Scientific 700 gas chromatograph from Hewlett-Packard, at the specified oven temperature.

(*S*)-(+)-Methyl Mandelate. Fischer esterification of 90 g of (*S*)-(+)-mandelic acid (Norse Chemical Co.) gave 71.7 g of methyl mandelate (73%), mp 53.5–56 °C, $[\alpha]_D$ 143° (CH_3OH, *c* 1.67) (lit. mp 50°, $[\alpha]_D$ 143°).

Tetrahydropyranyl (THP) Ether of (*S*)-Methyl Mandelate. Active methyl mandelate (71.8 g, 430 mmol), 250 ml of absolute ether dihydropyran (58.8 g, 700 mmol), and 50 mg of *p*-toluenesulfonic acid (TsOH) were mixed at ice bath temperature and allowed to warm to room temperature overnight. The reaction mixture was then washed with saturated Na_2CO_3, dried with $MgSO_4$, and flash evaporated to a clear syrup, in crude quantitative yield: ^1H NMR δ 7.4 (broad singlet, C_6H_5), 5.3 (d, diastereotopic benzylic), 4.9, 4.6 (m, OCHO), 4.2–3.0 (OCH_3, CH_2O), 2.2–1.2 (aliphatic THP).

(*S*)-2-Tetrahydropyranyloxy-2-phenylethanol (4). A solution of 114.6 g (457 mmol) of the above ester in 275 ml of absolute ether was added dropwise to a stirred, ice-cooled suspension of 11.0 g (289 mmol, 1160 mequiv) of lithium aluminum hydride in 275 ml of absolute ether. The mixture was allowed to stir and warm to room temperature overnight. After standard base workup, the desired alcohol was obtained, 97 g (96%): ^1H NMR δ 7.4 (C_6H_5), 5.2–4.4 (m, benzylic and acetal), 4.2–3.0 (m, CH_2O), 2.5 (broad, OH), 2.2–1.3 (broad, aliphatic THP).

For *R* material prepared in the above manner and purified by column chromatography (silica gel, 5% ether in CH_2Cl_2), $[\alpha]^{20.5}_D$ −84.8° (MeOH, *c* 2.7).

(*S*)-2-Allyloxy-1-tetrahydropyranyloxyphenylethane. To 96.6 g (435 mmol) of the alcohol above and 47.0 ml (65.3 g, 542 mmol) of allyl bromide stirring in 300 ml of ice-cooled reagent-grade dimethylformamide (DMF) was added in small portions 20.2 g of NaH dispersion (11.5 g of NaH, 481 mmol) which had been washed twice with pentane. The reaction mixture was allowed to stir and warm to room temperature overnight. It was then poured into 400 ml of water and extracted five times with petroleum ether totaling 575 ml. The petroleum ether was washed with saturated NaCl, $MgSO_4$ dried, and flash evaporated to give 103.6 g of the allyl ether, 91%: ^1H NMR δ 7.4 (s, C_6H_5), 6.4–5.5 (m, internal vinyl), 5.5–4.4 (benzyl, acetal, and terminal vinyl), 4.4–3.2 (m, CH_2O), 2.3–1.3 (broad, aliphatic THP).

(*S*)-2-Allyloxy-1-phenylethanol (5). The diether (103.6 g, 394 mmol), 550 ml of absolute methanol, and 130 mg of *p*-toluenesulfonic acid were left at room temperature overnight. The removal of the THP protecting group could be monitored with TLC (silica gel, 5% ether in CH_2Cl_2, starting ether, R_f 0.5; product alcohol, R_f 0.4). When complete, the reaction was worked up by swirling with solid $NaCO_3$ and concentrating the filtered solution by flash evaporation; the residue was poured into 5% HCl and extracted four times with CH_2Cl_2 totaling 325 ml. The organic layers were washed with saturated NaCl, dried with $MgSO_4$, and concentrated by flash evaporation, with occasional addition of CCl_4, to give a crude quantitative yield. This material was analyzed by VPC (140 °C) and shown to be 95% pure with 5% of a longer retention time component (product, t_R 9.1, 95%; unknown, t_R 11.3, 5%).

^1H NMR δ 7.4 (s, C_6H_5), 6.3–5.5 (m, internal vinyl), 5.5–5.0 (m, terminal vinyl), 5.0–4.7, (dd, benzylic), 4.0 (d, allylic CH_2), 3.8–3.2 (m, CH_2O), 3.1–2.6 (broad, OH), 1.7–0.5 (1 H impurity); $[\alpha]_D$ +51.4° ($CHCl_3$, *c* 4.9).

(*S*)-2-Propenyloxy-1-phenylethanol. The isomerization procedure of Gigg and Gigg[11] was used in a modified form. About 120 ml of dimethyl sulfoxide (Me_2SO), dried by distillation from CaH_2 and stored over activated molecular sieves, was stirred in an 80 °C bath. When the temperature of the mixture reached 75 °C, 13.4 g of the allyl ether **5** (75.3 mmol) was added, followed by 12.7 g (113 mmol) of crushed potassium *tert*-butoxide (*t*-BuOK). A few drops of the reaction mixture could be partitioned between ligroin and water in a test tube, and the ligroin fraction subjected to VPC (140 °C) analysis (product, t_R 6.4; starting material, t_R 8.8). The speed and cleanness of the reaction varied from run to run; the reaction was usually stopped after about 60% of the mixture was product. The reaction mixture was then poured into sufficient ice and water to make 350 ml of solution. This was extracted six times with CH_2Cl_2 totaling 350 ml. The CH_2Cl_2 was concentrated to about 80 ml by flash evaporation, poured into 200 ml of ligroin, and washed with water and saturated NaCl to remove Me_2SO. The aqueous layers were extracted with ligroin and the combined organic layers concentrated by flash evaporation to 23.03 g, 86% crude recovery. This material was distilled at 2.6 Torr, the fraction distilling at 104–112 °C representing a 64% recovery (55% yield) of material shown to be 85% product by the above VPC assay: ^1H NMR δ 7.4 (s, C_6H_5), 6.0 (m, OCH=), 4.9 (dd, benzylic), 4.4 (m, =CHC), 3.8 (d, CH_2O), 2.7 (s, OH), 1.6 (dd, CH_3 $J_{CH_3\text{-vinyl}}$ = 7 Hz); $[\alpha]_D$ +50.2° ($CHCl_3$, *c* 3.2).

(*S*)-1-Mesyloxy-1-phenyl-2-propenyloxyethane (Standard Mesylation Procedure).[12] To 4.00 g (22.4 mmol) of the above alcohol in 110 ml of ice-cooled, stirred absolute ether was added triethylamine (4.4 ml, 3.2 g, 31 mmol, 1.4 relative equiv), followed by methanesulfonyl chloride (1.88 ml, 2.85 g, 24.8 mmol, 1.1 relative equiv). Immediate precipitate formation was observed. After 2 h, the solution was diluted with ether and washed with iced 5% HCl (this washing should be done quickly since the propenyl protecting group is acid sensitive), iced 5% $NaHCO_3$ until the washings were basic, and saturated NaCl. The solution was dried with $MgSO_4$ and concentrated by flash evaporation to give a crude quantitative yield: ^1H NMR δ 7.4 (C_6H_5), 6.1 (m, –OCH=), 5.8 (dd, benzylic), 4.5 (m, =$CHCH_3$), 4.1 (m, CH_2), 3.0 (s, OSO_2CH_3), 1.6 (dd, CH_3).

(*R*)-2-Propenyloxy-1-phenyl-1-deuterioethane. The crude mesylate (5.9 g, 22.4 mmol) was dissolved in 20 ml of absolute ether and stirred at 0 °C. A 1 M solution of lithium triethylborodeuteride in THF (Aldrich Chemical Co. "Super-deuteride") was added until the evolution of gas ceased, thus signifying the reaction of all residual water in the solvent; this required 14 ml. An additional 29 ml (29 mmol) of the reagent was then added and the reaction mixture stirred for 30 h. The progress of the reaction could be followed by VPC (140 °C) (product, t_R 4.1). After 1 h, 37% of the mixture was product; after 6 h, 59%; after 19 h, 88%. The reaction mixture was worked up by the addition of 150 ml of water. The resulting two phases were extracted with three portions of ligroin totaling 200 ml. The combined organic layers were washed twice with saturated NaCl, dried with $MgSO_4$, and concentrated by flash evaporation to 3.86 g of the deuterated product, 106% crude yield. VPC assay showed the sample to be 93% pure.

(*R*)-(−)-2-Phenylethanol-*2-d* (3). The general method of Cunningham, Gigg, and Warren[13] was followed. The crude enol ether (3.86 g) was dissolved in 90 ml of 0.5 N methanolic NaOH. While stirring at 0 °C, 88 ml (22 mmol) of 0.25 N aqueous $KMnO_4$ was added dropwise. The reaction can be followed by VPC (140 °C) (starting material, t_R 4.2; product, t_R 2.5). After 50 min of reaction time, VPC indicated 78% conversion. Therefore, another 22 ml of $KMnO_4$ was added. After another 30 min, 97% conversion was observed. The mixture was then filtered through Celite to remove MnO_2 and the filtrate extracted five times with ether totaling 250 ml. The organic layers were washed three times with saturated NaCl to remove the by-product acetol, dried with $MgSO_4$, and concentrated by flash evaporation to give 2.12 g of crude alcohol, 73% yield. VPC as described above indicated the product was 95% pure.

Several samples of alcohol prepared in the above manner but generally of lower quality were distilled at 3.0 Torr. The fraction at 81.5–85.5 °C represented a 47% recovery and was 82% pure by VPC. The fraction at 86–96 °C represented 17% recovery and was 94% pure by VPC, $[\alpha]^{20}_D$ −1.86° (neat), −2.56° ($CHCl_3$, *c* 41); adjusted for

chemical purity, −1.98° (neat); −2.72° ($CHCl_3$) [lit.[14] for enantiomer, +1.74° (neat)]. Impurities in the sample have low t_R values and are not likely to be optically active, with the exception of about 1% of material with t_R of about 6.5. This could be an incompletely deprotected alcohol, although these alcohols, being dextrorotatory, could not enhance the rotation for **3**.

Chiral shift studies were done on the XL-100 spectrometer, using the shift reagent tris(*d,d*-dicamphoylmethanato)europium(III).[15] A sample of racemic deuteriophenylethanol, prepared as in the above sequence but from racemic mandelic acid, when treated with the shift reagent gave two peaks for the benzyl proton (decoupled from the α methylene group). The optically active sample gave only one peak under the same conditions. Based on the noise in the spectrum, the enantiomeric purity of the alcohol was estimated to be 95–100%.

(*R*)-1-Deuterio-2-mesyloxyphenylethane. This material was prepared from the alcohol **3** by the standard mesylation procedure, giving a 98% crude yield: ^{1}H NMR δ 7.2 (s, C_6H_5), 4.4 (d, CH_2O), 3.0 (m, –CHO–), 2.8 (s, $-OSO_2CH_3$).

(*R*)-1-Deuterio-1-phenylethyltriphenylphosphonium Mesylate. The mesylate (1.56 g, 7.77 mmol) and triphenylphosphine (1.97 g, 7.5 mmol) were stirred neat in a three-necked, 50-ml, round-bottom flask at 85 °C, protected from moisture by a $CaSO_4$ drying tube. After 3 days the mixture was allowed to cool to a glass. The salt was used without isolation in the next reaction.

(*S*)-*cis*-1-Deuterio-1-phenyl-4-methyl-2-pentene (1) (Wittig Reaction). The salt prepared above was swept with nitrogen, and 15 ml of dried Me_2SO was injected. The mixture was stirred until the glassy salt dissolved. A 1.88 M solution of methyllithium (7.15 mmol) was added dropwise from an addition funnel. After 30 min, the mixture was stirred briefly in an ice bath while isobutyraldehyde (1.34 ml, 1.66 g, 15 mmol) was injected. Pentane (4 ml) was added, and the mixture stirred at room temperature overnight. The Me_2SO was then extracted six times with pentane. The pentane was washed two times with saturated NaCl, dried with $MgSO_4$, and removed to give the crude product.

This material was purified by column chromatography (silica gel, elution with ligroin). The fractions were monitored by TLC and VPC (140 °C, product t_R 3.7). The yield of purified olefin was 483 mg, 38% from the mesylate. VPC analyses indicated a purity of 85%, with five minor impurity peaks: $[\alpha]_D$ −1.11°; ^{1}H NMR δ 7.2 (s, impurity, 1 H), 2.0–0.5 (broad hydrocarbon from ligroin eluent, 4 H integration), 7.1 (s, C_6H_5), 5.5–5.0 (m, vinyl), 3.3 (m, –CHD–), 3.0–2.3 (m, –CH–), 0.9 (d, CH_3).

The designation of the product as *Z* (cis) is based on comparisons of authentic samples of *E* and *Z* olefin (described below) with perprotio Wittig olefin prepared in the above manner. The perprotio Wittig olefin had the following characteristics: NMR, same as the deuterated sample with the following exception, δ 3.3, d, 2 H; ir (neat film) 2950, 1604 m, 1500 m, 1470 m, 1370 w, 1260 w, 1190 w, 1155 m, 1100–925 broad m, 740 s, 690 s.

1-Phenyl-4-methyl-2-pentyne. The acetylene required for the synthesis of authentic *E* and *Z* olefins was prepared from 3-methylbutyne through conversion to 4-methylpentyne by addition of formaldehyde, protection of the acetylene as the dibromide, conversion of hydroxy to chloride, Friedel–Crafts alkylation of benzene, and finally deprotection to the acetylene. The procedures are described by Bradsma[16] and Gelin and Pigasse:[17] ^{1}H NMR δ 7.2 (s, C_6H_5), 3.5 (d, $-CH_2$), 2.9–2.2 (m, CH), 1.2 (d, CH_3).

(*E*)- and (*Z*)-1-Phenyl-4-methyl-2-pentene. The *E* isomer was prepared from the above acetylene by Na reduction in liquid ammonia–*tert*-butyl alcohol as described by Campbell and Eby.[18] The *Z* isomer was prepared by catalytic reduction over $Pd/BaSO_4$/quinoline as described by Cram and Allinger.[19] The Wittig derived olefin cochromatographed with the *Z* isomer, prepared above, VPC (50 °C, Carbowax 400 3%, $AgBF_4$ 2% on AW-DMCS Chromosorb P, 6 ft × 0.125 in.) (*E*, t_R 19.5; 2, t_R = 27.2), and had identical NMR and ir spectral properties.

3-(1,2-Dicarbomethoxyhydrazino)-1-deuterio-1-phenyl-4-methyl-1-pentene (2) (Ene Reaction Adduct). The ene substrate olefin 1 (200 mg, 1.24 mmol) was dissolved in about 5 ml of benzene. Dimethyl azodicarboxylate[20] (100 mg, 0.685 mmol) was added and the solution stirred at 70–75 °C. Four more portions of azodicarboxylate (50 mg, 0.342 mmol) were added at daily intervals. The reaction was followed with TLC (silica gel, 5% ether in CH_2Cl_2; olefin, R_f 0.8; azodicarboxylate, R_f 0.7; adduct, R_f 0.3; azodicarboxylate polymer, R_f 0.05). After 5 days of reaction, the solution was flash evaporated to 532 mg of orange syrup, 140% crude yield. This material was purified by column chromatography. Fractions containing adduct were identified by TLC and collected as a thick syrup, 118 mg, 30% yield: ^{1}H NMR δ 7.5–6.9 (C_6H_5 and NH), 6.9–5.9 (m, vinyl, 1.20 protons), 4.3 (t, allyl), 3.9 (s, $-OCH_3$ from azodicarboxylate polymer), 3.5–3.9 (m, OCH_3 adduct), 2.3–1.5 (m, CH), 1.0 (dd, CH_3); ^{13}C NMR δ 156.8, 156.3 (C=O); 136.3 (C_1 phenyl); 133.0 (α-styrene); 128.0, 127.2, 126.0 (*o*-, *m*-, *p*-phenyl); 125.8 (β-styrene); 67.3 (C–N); 53.1, 52.5 (OCH_3); 29.6, 19.8, 19.5 [$CH(CH_3)_2$]; $[\alpha]^{20}_D$ −14.2° ($CHCl_3$, *c* 11.3) (run 1); −17.3° ($CHCl_3$, *c* 11.0) (run 2).

Perprotio adduct 1 was prepared in a similar manner. The deuterium content was determined by comparing the relative intensity of the pertinent carbon signal in the partially deuterated sample to the relative intensity of the corresponding signal in perprotiated adduct.

3-Carbomethoxyamino-4-methylethyl-2-oxazolidone (8) (from the Ene Adduct). The approach of Stephenson, Cavigli, and Parlett[21] to the cleavage of the double bond was employed. A solution of the deuterated ene adduct (151 mg, 0.493 mmol) in 4 ml of $CHCl_3$ was added dropwise to a solution of *m*-chloroperbenzoic acid (85%, 87 mg, 0.5 mmol) in 2 ml of $CHCl_3$. After stirring for 7 h, the solution was washed with 5% $NaHCO_3$, dried with Na_2SO_4, and concentrated by flash evaporation: ^{1}H NMR δ 8.0–7.1 (m, C_6H_5 and NH), 4.2–3.4 (m, OCH_3, NCH, and benzylic), 3.2 (d, CHOC nonbenzylic), 2.5–1.6 (broad, *i*-PrCH), 1.1 (dd, CH_3).

The epoxide, without purification, was dissolved in 2 ml of dry ether. A saturated solution of periodic acid in ether[22] (7.1 ml, 0.5 mmol) was added, giving rapid precipitation. After stirring for 3 h, the solution was filtered, rinsed with ether, washed with saturated NaCl, and concentrated by flash evaporation. The characteristic odor of benzaldehyde was noted. This mixture was immediately taken into 2 ml of THF and added dropwise with stirring to 47 mg (1.23 mmol) of sodium borohydride in 2 ml of water, cooled by an ice bath. After 11 h, the mixture was poured into 5% HCl and extracted three times with CH_2Cl_2. The CH_2Cl_2 layer was dried with Na_2SO_4 and removed by flash evaporation, leaving 109 mg of crude products. These were purified by preparative TLC on Uniplate 20 × 20 cm, 1000-μ thick HF-254 silica gel plates (Analtech) using 1/1 benzene/ether. Run 1 gave 8–10 mg of oxazolidone with TLC and ir identical with those of authentic material described below (*c* 10.4 ± 0.5, $CHCl_3$).

λ	589	579	546	436	365
α	0.097	0.0676	0.0805	0.1195	0.1415
[α]	6.7	6.5	7.7	11.5	13.6
Calcd ee	24.5	23.0	24.4	24.1	21.2

Run 2 gave 15 mg of oxazolidone with rotations given below (*c* 15.0 ± 0.5 mg, $CHCl_3$).

λ	589	578	546	436	365
α	0.208	0.213	0.245	0.367	0.466
[α]	13.9	14.2	16.3	24.5	31.1
ee	51	50	52	51	48

(*S*)-(−)-2-Bromo-3-methylbutanoic Acid. The procedure of Fischer and Scheibler[23] was used. L-(*S*)-(+)-valine (10.0 g, 85.5 mmol), 27 ml (236 mmol) of 48% hydrobromic acid, and 24 ml of water were stirred in an ice bath as nitric oxide was bubbled through the solution. Bromine (4.03 ml, 12.6 g, 78.6 mmol) was added dropwise; after 2 h, another 1.55 ml (4.8 g, 30 mmol) was added. After another 2 h, air was bubbled through the reaction mixture in place of nitric oxide; sodium thiosulfate was then added to decompose the remaining bromine. The aqueous mixture was extracted six times with CH_2Cl_2, which was washed with saturated NaCl, dried with $MgSO_4$, and concentrated by flash evaporation to 13.6 g (88%) of the crude bromo acid. The material was crystallized from 5.5 ml of petroleum ether to give 7.69 g of crystals, 56% yield, mp 37.3–42.5 °C (lit.[23] mp 44 °C), $[\alpha]^{20}_D$ −23.8° (benzene, *c* 37.2) (lit.[24] +22.1° for the enantiomer).

2-Hydrazinoisovaleric Acid (9). Racemic α-bromoisovaleric acid[25] (7.82 g, 43.2 mmol) was dissolved in 40 ml of absolute ethanol. Hydrazine hydrate (10.4 ml, 10.8 g, 218 mmol) was added slowly with stirring. The solution was heated at 80 °C for 45 min while the product and hydrazinium bromide precipitated. Hot water (150 ml) was added to dissolve the precipitate, followed by 210 ml of hot 95% ethanol. After cooling at 5 °C overnight, 1.82 g (32%, lit.[26] 45%) of fluffy white crystals were collected, mp 240–242 °C dec (lit. mp 230–235 °C). The optically active material was prepared in the same manner from the optically pure bromoisovaleric acid described above in 19% yield, mp 227.5–232 °C dec, $[\alpha]_D$ −2.2° (10% HCl, *c* 0.98).

(*S*)-Valine Methyl Ester Hydrochloride (13). The partially optically active methyl ester **12** was prepared by Fischer esterification of 100 mg (0.76 mmol) of the partially active hydrazino acid **9**. It was isolated from the reaction mixture as the hydrochloride salt by removal of the methanol by flash evaporation, trituration with CCl_4 to transform the resulting gum to a solid, and removal of the CCl_4 by

flash evaporation, giving 146 mg, 106% crude yield. This material was hydrogenated in acetic acid with 15 mg of PtO_2.[27] After the mixture absorbed 15 ml of H_2 (~17 ml theoretical), the mixture was filtered and the acetic acid removed by flash evaporating the acetic acid–heptane azeotrope. The resulting material was triturated with ether until it changed from a paste to a solid. Further removal of solvent gave 71 mg of crude product, 56% yield, with an extremely wide melting range. The material was used without purification in the next step.

(*S*)-(+)-*N*-Acetylvaline Methyl Ester (14). The crude amine hydrochloride **13** was reacted as described by Reihlen and Knöpfle[28] with 71 mg of sodium acetate, 0.5 ml of acetic anhydride, and 1 drop of pyridine. After stirring overnight, water was added, along with solid Na_2CO_3 until the solution was basic. The solution was extracted three times with CH_2Cl_2, and the organic layers were dried with $MgSO_4$ and concentrated by flash evaporation to 54 mg (74% yield). The crude material was purified by column chromatography. The NMR spectrum was superimposable on a spectrum of material prepared from commercial valine methyl ester hydrochloride. The $[\alpha]^{20}D$ was +4.1° (lit.[28] $[\alpha]^{20}D$ +30.6°); the sample was thus 13% optically pure. Dextrorotatory material is of the *S* configurational series.[28]

2-(1,2-Dicarbomethoxyhydrazino)isovaleric Acid (10). To an ice-cooled solution of 396 mg (3 mmol) of the hydrazino acid **9** in 15 ml of water and 3.0 ml of 1 N NaOH was added 230 μl (284 mg, 3.0 mmol) of methyl chloroformate dropwise. Then 275 μl (340 mg, 3.6 mmol) of methyl chloroformate was added simultaneously with 6.6 ml (6.6 mmol) of 1 N NaOH and the mixture stirred overnight. The solution was made more basic with a few drops of 15% NaOH and washed with CH_2Cl_2. The solution was then made acidic with concentrated HCl, saturated with NaCl, and extracted 20 times with CH_2Cl_2. The CH_2Cl_2 extracts were dried with Na_2SO_4 and flash evaporated to give 486 mg of a sticky gum, 61% crude yield.

(*S*)-(−)-2-(1,2-Dicarbomethoxyhydrazino)isovaleric Acid (10-*S*). The same procedure used to prepare the racemic sample of the previous compound was employed to prepare a partially active sample from the (−) hydrazino acid described below in 61% yield: ^1H NMR δ 9.5 (s, CO_2H), 7.8 (s, NH), 4.6 (broad, CHN), 3.9 (s, OCH_3), 2.8–2.0 (m, *i*-PrCH), 1.2 (d, *i*-$PrCH_3$); $[\alpha]^{20}D$ −1.8° ($CHCl_3$, *c* 1.9). Thus (−)-hydrazinovaleric acid is of the same configurational series as this compound.

Resolutions of 10. The acid **10** was resolved with *l*-ephedrine two times, in 2 and 20% yield, to the following constant properties, after several crystallizations from methanol/ethyl acetate/petroleum ether: mp 155–156.5 °C; specific rotation of the salt, $[\alpha]^{546}$ +1.5° (H_2O, *c* 2.4); and specific rotation of the free acid, $[\alpha]D$ +10.5 ± 0.2° ($CHCl_3$, *c* 7.9). The levorotatory enantiomer was isolated by resolving the residue from the ephedrine resolutions with (−)-phenethylamine. After several crystallizations from the same solvents, the following constant properties were obtained: mp 164–165.5 °C; specific rotation of the salt, $[\alpha]D$ −21.9° (H_2O, *c* 13.8); and specific rotation of the free acid, $[\alpha]D$ −10.5° ($CHCl_3$, *c* 13.8).

(*S*)-(+)-*O*-Carboethoxyl-2-(1,2-dicarbomethoxyhydrazino)-3-methylbutyrate (11). A sample of (*S*)-(−) resolved acid **10** (128 mg, 0.48 mmol) was stirred at 5 °C in 5 ml of absolute ether. Triethylamine (93 μl, 68 mg, 0.67 mmol) was added, followed by ethyl chloroformate (50.5 μl, 57 mg, 0.53 mmol). After stirring overnight, the reaction mixture was diluted with ether and washed with 5% HCl, 5% $NaHCO_3$, and saturated NaCl. The resulting solution was dried with Na_2SO_4 and concentrated by flash evaporation to give 114 mg of the mixed anhydride (70% yield): ^1H NMR δ 6.8 (s, NH), 4.8–4.0 (d + q, NCH and OCH_2), 3.8 (d, OCH_3), 2.7–2.0 (m, *i*-PrCH), 1.7–0.9 (t + d, CH_3).

(*S*)-(+)-3-Carbomethoxyamino-4-methylethyl-2-oxazolidone (8) (from Resolved Acid). The above sample of mixed anhydride in 1 ml of THF was added dropwise with vigorous gas evolution to a suspension of 32 mg (0.84 mmol) of sodium borohydride in 1 ml of water, at 0 °C. After 11 h, the mixture was acidified with 5% HCl and extracted six times with CH_2Cl_2. The organic layers were dried with Na_2SO_4 and concentrated by flash evaporation to 75 mg (109% crude yield). Column chromatography (2/1 benzene/ether, 53:1) was used to purify the material, giving 40 mg, 58% yield: ^1H NMR δ 7.6 (s, NH), 4.5–3.9 (m, NCH and OCH_2), 3.8 (s, OCH_3), 2.5–1.8 (broad, *i*-PrCH), 1.0 (d, CH_3); $[\alpha]D$ +27.3 ± 0.3° ($CHCl_3$, *c* 4.0).

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Registry No.—**1,** 60168-60-7; **2,** 60168-61-8; **2** epoxide derivative, 60168-62-9; **3,** 60208-56-2; **4,** 60168-63-0; **5,** 60168-64-1; **8,** 60168-65-2; (±)-**9,** 19866-38-7; (−)-**9,** 60208-57-3; (±)-**10,** 60168-66-3; (*R*)-**10,** 60208-58-4; (*R*)-**10** *l*-ephedrine salt, 60208-59-5; (*S*)-**10,** 60208-60-8; (*S*)-**10** (−)-1-phenylethylamine salt, 60208-61-9; **11,** 60168-67-4; **12,** 60168-68-5; **13,** 6306-52-1; **14,** 1492-15-5; (*S*)-(+)-methyl mandelate, 21210-43-5; (*S*)-(+)-mandelic acid, 17199-29-0; (*S*)-methyl mandelate THP ether, 33973-12-5; dihydropyran, 25512-65-6; (*S*)-2-allyloxy-1-tetrahydropyranyloxyphenylethane, 60168-69-6; allyl bromide, 106-95-6; (*S*)-2-propenyloxy-1-phenylethanol, 60168-70-9; (*S*)-1-mesyloxy-1-phenyl-2-propenyloxyethane, 60168-71-0; methanesulfonyl chloride, 124-63-0; (*R*)-2-propenyloxy-1-phenyl-1-deuterioethane, 60168-72-1; (*R*)-1-deuterio-2-mesyloxyphenylethane, 60168-73-2; (*R*)-1-deuterio-1-phenylethyltriphenylphosphonium mesylate, 60168-75-4; triphenylphosphine, 603-35-0; isobutyraldehyde, 78-84-2; 1-phenyl-4-methyl-2-pentyne, 60168-76-5; (*E*)-1-phenyl-4-methyl-2-pentene, 51795-76-7; (*Z*)-1-phenyl-4-methyl-2-pentene, 60168-77-6; dimethyl azodicarboxylate, 2446-84-6; (*S*)-(−)-2-bromo-3-methylbutanoic acid, 26782-75-2; (+)-α-bromoisovaleric acid, 10323-40-7; *l*-ephedrine, 299-42-3; *l*-α-methylbenzylamine, 2627-86-3; ethyl chloroformate, 541-41-3.

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