Diastereoselectivity of Additions to Chiral Carbonyl Oxides

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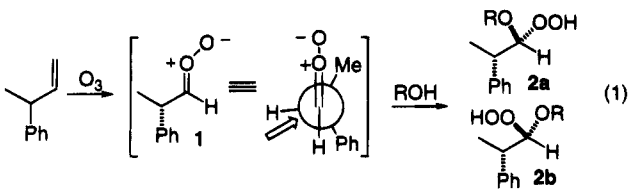
Received July 24, 1995[⊗]

The influence of a resident stereocenter on the formation of hydroperoxy acetals from carbonyl oxides is investigated. Addition of either methanol or 2-propanol to 2-phenylpropanal *O*-oxide proceeds with modest stereoselectivity; addition of a tertiary alcohol proceeds with higher selectivity. Product stereochemistry, which is confirmed by conversion of a functionalized hydroperoxy acetal to a 1,2-dioxane, is found to derive from nucleophilic attack through a Felkin–Anh type transition state. Trapping of a carbonyl oxide containing a neighboring hydrogen bond donor proceeds with modest selectivity for both *syn*- and *anti*-carbonyl oxide isomers. Ozonolysis of a 3-(trialkylstannyl)-1-enol ether proceeds with loss of the stannyl-bearing carbon through the possible intermediacy of a vinyl peroxide.

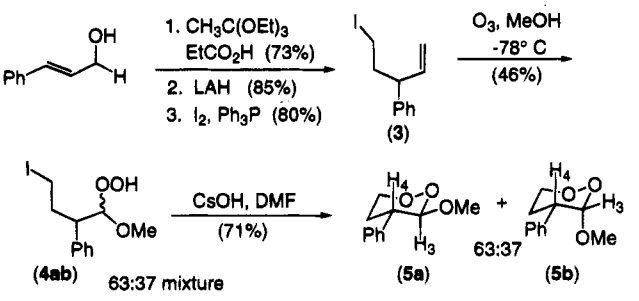
As part of research into new methodology for peroxide synthesis, we became interested in the diastereoselective formation of hydroperoxy acetals through addition of alcohols to acyclic carbonyl oxides (eq 1). Whereas the Felkin–Anh and related models provide a clear basis on which to predict the stereochemical influence of an adjacent chiral center on additions to an aldehyde or ketone,[1] no similar guidelines exist for carbonyl oxides. Our results indicate that additions to chiral carbonyl oxides proceed with a qualitatively similar sense of diastereoselection as that observed for additions to the corresponding carbonyl group.



(1)

Several groups have investigated the effect of resident stereocenters on the formation of *exo* or *endo* bicyclic ozonides from cyclic alkenes,[2,3] and the bicyclization of alcohols or silyl ethers onto cyclic carbonyl oxides was shown to proceed with good stereoselectivity.[4,5] However, only limited stereochemical data has been reported regarding additions to acyclic carbonyl oxides. Ozonolysis of the isopropenyl side chain of carvone in the presence of methanol produced a random mixture of hydroperoxy acetals.[6] Although ozonolysis of 1-methyl-2-propenylpulegol produced a single 3-alkoxy-1,2-dioxane after acid-catalyzed cyclization,[7] the observed stereoselection is most likely due to acid-catalyzed equilibration of the product.[8,9]

Scheme 1



Carbonyl oxide **1**, a substrate whose addition reactions could be easily compared against literature reports for the corresponding aldehyde, was selected as an initial target (eq 1). Ozonolysis of 3-phenyl-1-butene in MeOH afforded diastereomeric hydroperoxy acetals **2a** and **2b** as a 64:36 mixture.[10] The observed diastereoselection almost certainly reflects kinetic selection; equilibration of related peroxyacetals is known to require much more acidic conditions than are present during ozonolysis.[8,9,11]

Assignment of relative stereochemistry was achieved through use of a modified substrate (**3**) bearing an iodoethyl side chain (Scheme 1). The iodide was prepared from 3-phenyl-4-pentenol, available through reduction of the ester derived from Claisen rearrangement of cinnamyl alcohol.[12] Ozonolysis of **3** in MeOH produced a 63:37 ratio of hydroperoxy acetals **4a** and **4b**. The nearly identical levels of diastereoselection in formation of the hydroperoxy acetals validates the use of **4a**/**4b** for assignment of the stereochemistry of **2a**/**2b**. Cyclization of the mixture of **4a** and **4b** with CsOH in DMF afforded a 63:37 mixture of *trans*- and *cis*-3-methoxy-4-phenyl-1,2-dioxanes **5a** and **5b**. The stereochemical assignments are based on the 7.2 Hz (**5a**) and 3.3 Hz (**5b**) coupling constants observed between H_3 and H_4. The stereochemistry of the major product supports a Felkin–Anh type transition state in which the "medium" alkyl group is

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1995.

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(10) The ratio of diastereomeric hydroperoxy acetals was determined by comparison of either the methoxyl (typically 3.6 and 3.4 ppm) or isopropoxyl (typically 4.0 and 3.8 ppm) signals in the crude ^1H NMR spectrum. Hydroperoxy acetals **13ab** were characterized both by NMR as well as by analytical HPLC.
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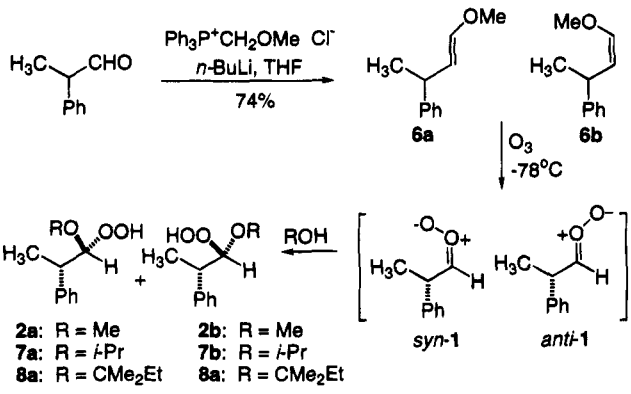
Table 1. Trapping of 2-Phenylpropanal *O*-Oxide

substrate	ratio of hydroperoxy acetals 2a:2b	7a:7b	8a:8b
3-phenyl-1-butene	64:36	66:34	82:18
6a	60:40	65:35	–
6b	66:33	70:30	–
6a + **6b** (68:32)	63:37	68:32	81:19

Scheme 2



nearly eclipsed with the carbonyl oxide, and alcohol addition occurs opposite to the "large" phenyl group (eq 1).

We were curious as to whether the syn and anti isomers of **1** would undergo trapping with similar diastereoselectivity. Enol ethers are known to be efficient carbonyl oxide precursors, and (*E*) and (*Z*) enol ethers undergo ozonolysis to preferentially afford *syn* and *anti* carbonyl oxides, respectively.[13] A recent study has demonstrated that interconversion of *syn* and *anti* carbonyl oxides is slow relative to intramolecular trapping.[14] Methoxymethylenation of 2-phenyl propanal furnished a 62:38 mixture of *E* and Z-enol ethers **6a** and **6b** (Scheme 2). The *E*-enol ether **6a**, which would be expected to react via *syn*-**1**, the *Z*-enol ether **6b**, which would react via *anti* **1**, and the 62:38 mixture of enol ethers all underwent ozonolysis to furnish a similar ration of **2a**:**2b** favoring the Felkin–Anh product (Table 1). The geometry of the enol ether clearly has little bearing on the diastereoselection.

The relationship between diastereoselection and steric bulk of the nucleophile was probed through variation of the alcohol trapping agent. As illustrated in Table 1, the ratio of hydroperoxy acetals derived from trapping with methanol (**2a**/**2b**) and 2-propanol (**7a**/**7b**) were nearly identical. Although attempts to trap the carbonyl oxide with *tert*-butyl alcohol were frustrated by low solubility, ozonolysis in the presence of *tert*-amyl alcohol proceeded in moderate yield to provide hydroperoxy acetals **8a** and **8b** with markedly improved diastereoselectivity.

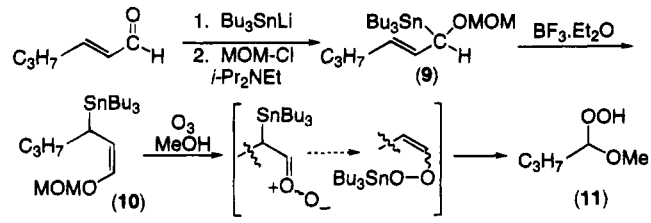
Given the decreased electron density of a carbonyl oxide relative to a carbonyl group, we reasoned that hyperconjugation with an adjacent stannyl-substituted stereocenter might lead to a dramatic increase in diastereoselection. A γ-alkoxyallyl stannane (**10**) was prepared as shown in Scheme 3.[15] Surprisingly, ozonolysis of **10** cleanly provided a hydroperoxy acetal (**11**) resulting from oxidation of the stannyl-bearing carbon. A possible

Table 2. Ozonolysis of *N*-BOC-Substituted Enol Ethers

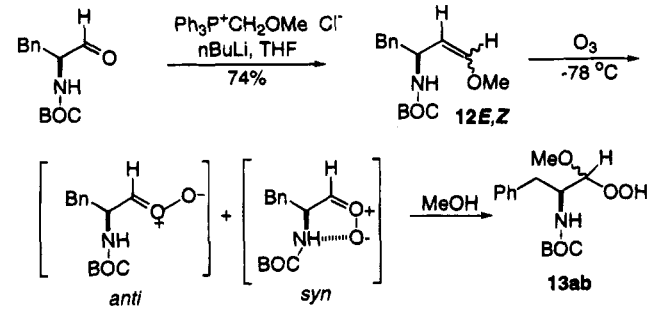
enol ether	carbonyl oxide	enol ether:MeOH	13a:13b
12*E*, 12*Z*	*syn* + *anti*	1:2500	50:50[a,b]
12*E*	*syn*	1:2500	50:50[a]
12*E*	*syn*	1:100	65:35[a,b]
12*E*	*syn*	1:50	65:35[a,b]
12*E*	*syn*	1:20	65:35[a,b]
12*E*	*syn*	1:5	80:20[a,b]
12*Z*	*anti*	1:2500	50:50[a]
12*Z*	*anti*	1:50	65:35[a]
12*Z*	*anti*	1:20	65:35[a]
12*Z*	*anti*	1:5	nd

[a] Diastereomer ratios determined by ^{1}H NMR and HPLC. [b] Diastereomer ratios determined by HPLC.

Scheme 3



Scheme 4



mechanism accounting for this result involves initial cleavage to form a 2-stannyl carbonyl oxide. Isomerization to a stannyl vinyl peroxide would be followed by further ozonolytic cleavage to a new, chain-shortened, carbonyl oxide. This mechanism is interesting in light of recent theoretical calculations supporting the stability of vinyl hydroperoxide.[16]

Chelation-controlled additions to carbonyl groups are often highly stereoselective and we next investigated the ability of a neighboring hydrogen bond donor to induce a cyclic transition state in additions to a carbonyl oxide. An enol ether substrate (**12*E*,*Z***) was synthesized from *N*-(*tert*-butoxycarbonyl)-L-phenylalaninal (Scheme 4).[17] Ozonolysis of a 1:1 mixture of (*E*)-**12** and (*Z*)-**12** provided two diastereomers **13ab** in a 1:1 ratio. Although the hydroperoxy acetal diastereomers were separable, we were unable to make stereochemical assignments.

As only the syn isomer of the carbonyl oxide was expected to be capable of internal hydrogen bonding, we next investigated the reactions of pure (*E*)-**12**. Ozonolysis in the presence of a large excess of methanol produced a 1:1 mixture of diastereomers (Table 2), a result attributed to the competition of inter- and intramolecular hydrogen bonding. Stereoselection increased as the ratio of methanol/enol ether was decreased, reaching a maximum of 4:1. Surprisingly, ozonolysis of (*Z*)-**12**, which would be expected to proceed via the *anti*-carbonyl oxide, proceeded

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with the same sense of stereochemistry and the same trend toward improved diastereoselection at reduced concentrations of methanol. In both cases, reactions conducted with near-stoichometric amounts of methanol were accompanied by substantial amounts of tetroxanes formed through carbonyl oxide dimerization; attempts to perform oxidations in the presence of stoichometric methanol afforded only tetroxanes.

In conclusion, we have found that carbonyl oxides bearing a neighboring stereocenter undergo addition of nucleophiles with the same sense of stereoselection as is observed for additions to the corresponding aldehyde. Attempts to control diastereoselectivity through selective intramolecular hydrogen-bonding were unsuccessful. Ozonolysis of chiral allylstannanes proceeds with oxidation of the stannyl-bearing carbon, a result which may imply the transient formation of a vinyl peroxide.

Caution: As in any work involving peroxides, standard precautions (use of safety shields, avoidance of heat, light, or metal salts, performance of reactions on minimal scale) should be faithfully observed.[18-20]

Experimental Section[21]

3-Phenyl-1-butene.[22] To a 0 °C solution of methyltriphenylphosphonium bromide (3.83 g, 10.7 mmol) in dry THF (50 mL) was added *n*-BuLi (4.3 mL, 10.7 mmol, 2.5 M in hexane). After 4 h, a solution of 2-phenylpropanaldehyde (1.30 g, 9.75 mmol) in THF (10 mL) was added dropwise via cannula, and the reaction was refluxed for 44 h. The reaction was quenched with water (10 mL) and cooled to room temperature. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography in 2% ethyl acetate in hexanes (EA/hex) yielded 463 mg (36%) of alkene along with recovered starting material: R_f = 0.77 (10% EA/hex); ^{1}H NMR (300 MHz) δ 7.25 (m, 5H), 6.02 (ddd, 1H, J = 6.4, 10.2, 16.9), 5.06 (dt, 1H, J = 1.6, 17.1), 5.04 (dt, 1H, J = 1.4, 10.2), 3.48 (app pentet, 1H, J = 6.6), 1.38 (d, 3H, J = 7.1); ^{13}C NMR (75 MHz) δ 145.5, 143.2, 128.3, 127.2, 126.1, 113.0, 43.2, 20.7; IR (neat) 3075, 3052, 3018, 2952, 2923, 1635, 1600, 1490, 1448, 1369, 1070, 995, 908. Anal. Calcd. C, 90.86; H, 9.14. Found: C, 90.69; H, 9.31.

1-Methoxy-2-phenylpropane 1-Hydroperoxide (2ab). Into a −78 °C solution of 3-phenyl-1-butene (25 mg, 0.19 mmol) in methanol (15 mL) was passed a gaseous stream of O_3/O_2 until a blue color persisted. The reaction was then flushed with O_2 to dissipate the blue color and concentrated behind a shield. The residue was purified by flash chromatography with 10% EA/hex to yield 22 mg (65%) of a 64:36 mixture of hydroperoxy acetals: R_f = 0.11 (10% EA/hex); ^{1}H NMR (300 MHz) δ 9.74 (bs, 0.6H), 9.59 (bs, 0.4H), 7.35 (m, 5H), 4.88 (d, 0.4H, J = 6.4), 4.83 (d, 0.6H, J = 7.1), 3.57 (s, 1.1H), 3.4 (s, 1.9H), 3.2 (pentet, 0.6H, J = 7.1), 3.19 (pentet, 0.4H, J = 6.9), 1.38 (d, 1.9H, J = 7.1), 1.37 (d, 1.1H, J = 7.1); ^{13}C NMR (75 MHz) δ 142.1, 142.0, 128.2, 128.2, 127.8, 127.8, 126.5, 126.4, 111.8, 111.7, 57.4, 57.3, 42.1, 41.8, 16.8, 16.5; IR (neat) 3315 cm^{-1}. Anal. Calcd C, 65.92; H, 7.74. Found: C, 66.00; H, 7.60.

Ethyl 3-phenyl-4-pentenoate was prepared in 73% through Claisen rearrangement of cinnamyl alcohol and triethyl orthoacetate:[23] R_f = 0.8 (10% EA/hex); ^{1}H NMR (300 MHz) δ 7.31(m, 2H), 7.2 (m, 3H), 5.99 (ddd, 1H, J = 7.1, 10.0, 17.4), 5.08 (dt, 1H, J = 1.1, 10.2), 5.08 (dt, 1H, J = 1.1, 17.4), 4.08 (q, 2H, J = 7.1), 3.87 (q, 1H, J = 7.3), 2.77 (dd, 1H, J = 8.1, 15.2), 2.69 (dd, 1H, J = 7.3, 14.7), 1.18 (t, 3H, J = 7.1); ^{13}C NMR (75 MHz) δ 171.8, 142.4, 140.2, 128.5, 127.5, 126.6, 114.7, 60.3, 45.6, 40.2, 14.1; IR (neat) : 1735 cm^{-1}. Anal. Calcd C, 76.44; H, 7.89. Found: C, 76.16 ; H, 8.02.

3-Phenyl-4-penten-1-ol.[24] To a 0 °C solution of ethyl 3-phenyl-4-pentenoate (100 mg, 0.49 mmol) in THF (25 mL) was added $LiAlH_4$ (18.6 mg, 0.49 mmol). After 4 h, the reaction was quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were dried over Na_2SO_4. After concentration, flash chromatography (20% EA/hex) afforded 67 mg (85%) of alcohol: R_f = 0.1 (15% EA/hex); ^{1}H NMR (300 MHz) δ 7.35 (m, 2H), 7.25 (m, 3H), 6.00 (ddd, 1H, J = 7.6, 10.2, 17.1), 5.11 (dt, 1H, J = 1.4, 17.1), 5.09 (dt, 1H, J = 1.4, 10.2), 3.61 (dt, 2H, J = 4.2, 6.6), 3.49 (q, 1H, J = 7.6), 2.24 (bs, 1H).

(4-Iodo-1-penten-3-yl)benzene (3). To a 0 °C solution of 3-phenyl-4-penten-1-ol (310 mg, 1.92 mmol) in CH_2Cl_2 (30 mL) was added imidazole (183.3 mg, 2.69 mmol), Ph_3P (757 mg, 2.88 mmol), and iodine (342 mg in 5 mL CH_2Cl_2). After 30 min, the reaction was allowed to warm to room temperature and stirred for an additional 2 h. The solution was washed with 10% Na_2SO_3 (1 × 20 mL) and dried over Na_2SO_4. Concentration, followed by flash chromatography (1% EA/hex), provided 429 mg (82%) of iodide: R_f = 0.86 (10% EA/hex); ^{1}H NMR (300 MHz) δ 7.37 (m, 2H), 7.25 (m, 3H), 5.95 (ddd, 1H, J = 7.6, 10.2, 17.1), 5.15 (dt, 1H, J = 1.1, 17.1), 5.13 (td, 1H, J = 1.1, 10.2), 3.48 (q, 1H, J = 7.3), 3.16 (dt, 1H, J = 6.9, 9.5), 3.1 (dt, 1H, J = 6.9, 9.7), 2.24 (dt, 2H, J = 2.3, 7.1); ^{13}C NMR (75 MHz) δ 142.4, 140.3, 128.6, 127.6, 126.6, 115.1, 49.9, 38.6, 4.7.

1-Methoxy-1-hydroperoxy-2-phenyl-4-iodobutane (4ab). By a similar procedure as employed for 3-buten-2-ylbenzene, ozonolysis of 1-iodo-3-phenyl-4-pentene (118 mg, 0.43 mmol) afforded 65 mg (46%) of hydroperoxy acetal: R_f = 0.12 (10% EA/hex); ^{1}H NMR (500 MHz) 8.5 (bs, 0.5H), 8.28 (bs, 0.5H), 7.3 (m, 5H), 4.86 (apparent triplet, 1H, J = 6.8), 3.56 (s, 1.1H), 3.40 (s, 1.9H), 3.18 (ddd, 1H, J = 4.8, 8.0, 10.4), 3.11 (ddd, 1H, J = 4.8, 8.0, 9.4), 2.83 (app pentet, 1H, J = 8.0), 2.44 (m, 1H), 2.15 (m, 1H); ^{13}C NMR (125 MHz) δ 138.6, 138.5, 128.7, 128.6, 128.5, 127.2, 127.1, 110.6, 110.6, 57.4, 57.4, 48.7, 48.5, 34.8, 34.6, 4.3, 4.2.

3-Methoxy-4-phenyl-1,2-dioxane (5ab). To a 0 °C solution of 1-methoxy-1-hydroperoxy-2-phenyl-4-iodobutane (1.37g, 4.25 mmol) in dry DMF (15 mL) was added CsOH (0.786 g, 4.68 mmol). After 15 min, the reaction was quenched with water (150 mL) and extracted with 10% ethyl acetate in hexanes (3 × 50 mL). The dried organic layer was concentrated and subjected to flash chromatography (2% ethyl acetate in hexanes) to yield 585 mg (71%) of a 63:37 mixture of isomers. Small amounts of pure diastereomers could be obtained through gravity chromatography with 2% EA/hex.

Major: **5a** R_f = 0.42 (10% EA/hex); ^{1}H NMR (500 MHz) δ 7.34 (m, 5H), 5.0 (d, 1H, J = 7.2), 4.31 (ddd, 1H, J = 3.6, 5.2, 12.0), 4.24 (ddd, 1H, J = 4.4, 9.6, 13.7), 3.45 (s, 3H), 2.95 (dt, 1H, J = 6.8, 9.3), 2.14 (m, 2H); ^{13}C NMR (125 MHz) δ 140.1, 128.4, 127.7, 126.7, 107.8, 71.1, 57.0, 44.2, 30.5. Anal. (mix. of isomers) Calcd C, 68.03; H, 7.26. Found: C, 67.93; H, 7.34.

Minor: **5b** R_f = 0.42 (10% EA/hex); ^{1}H NMR (300 MHz) δ 7.3 (m, 5H), 4.88 (t, 1H, J = 3.3), 4.49 (dt, 1H, J = 2.1, 12.4), 4.31 (m, 1H), 3.2 (dt, 1H, J = 3.8, 12.8), 2.6 (dq, 1H, J = 4.7, 13.1), 1.72 (d, 1H, J = 13.1); ^{13}C NMR (75 MHz) 139.8, 128.5, 128.2, 126.9, 104.8, 72.7, 55.4, 43.5, 25.1.

(1*E*,1*Z*)-1-Methoxy-3-phenyl-1-butene (6*E*,6*Z*). To a −78 °C solution of (methoxymethyl)triphenylphosphonium chloride (10.6 g, 30.9 mmol) in THF (75 mL) was added *n*-BuLi (12.4 mL, 2.5 M solution in hexane). The reaction was warmed to 0 °C and stirred for 30 min, turning dark during that time. To this was added dropwise a solution of 2-phenylpropanal

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(3.77 g, 28.2 mmol) in THF (10 mL) via cannula. The reaction was allowed to warm to room temperature and stirred for 12 h prior to quenching with water (10 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4. The concentrated solution was purified by flash chromatography (1% EA/hex) to yield 3.377 g (74%) of the (*E*) and (*Z*) enol ethers as a 63:37 mixture:

R_f = 0.85 (10% EA/hex); ^{1}H NMR (500 MHz) δ 7.3 (m, 5H), 6.4 (d, 0.6H, 12.4), 5.93 (d, 0.4H, *J* = 6.0), 5.00 (dd, 0.6H, *J* = 7.6, 12.4), 4.6 (dd, 0.4H, *J* = 6.0, 9.2), 4.02 (app pentet, 0.4H, 6.8), 3.64 (s, 1.1H), 3.56 (s, 1.9H), 3.47 (app pentet, 0.7H, *J* = 6.4), 1.42 (d, 1.9H, *J* = 7.2), 1.38 (d, 1.1H, *J* = 7.2); ^{13}C NMR (125 MHz) δ 46.8, 145.0, 133.8, 133.6, 128.3, 128.2, 126.9, 126.7, 125.9, 125.6, 112.3, 108.7, 59.5, 55.8, 38.3, 34.3, 22.6, 22.2. Anal. Calcd C, 81.44; H, 8.69. Found: C, 81.44; H, 8.57.

The two isomers could be incompletely separated through gravity chromatography with 1% ethyl acetate in hexanes.

1-Methoxy-2-phenylpropane 1-hydroperoxide (2ab) was isolated in 95% yield upon ozonolysis of **6*E*** or **6*Z*** under similar conditions as employed for butenyl benzene.

1-[(1-Methylethyl)oxy]-2-phenylpropane 1-Hydroperoxide (7ab). By a similar procedure, ozonolysis of 3-phenyl-1-butene (25 mg, 0.19 mmol) in isopropyl alcohol (15 mL) afforded 23 mg (59%) of a 66:34 mixture of hydroperoxy acetals: R_f = 0.26 (10% EA/hex); ^{1}H NMR (300 MHz) δ 8.96 (broad s, 1H), 7.45 (m, 5H), 4.96 (d, 0.3H, *J* = 6.6 Hz), 4.86 (d, 0.7H, *J* = 7.1 Hz), 4.00 (heptet, 0.3H, *J* = 6.2 Hz), 3.80 (heptet, 0.7H, 6.2 Hz), 3.16 (m, 1H), 1.36 (d, 1.9H, *J* = 6.8), 1.34 (d, 1.1H, *J* = 6.8), 1.30 (d, 1.1H, *J* = 6.4), 1.19 (d, 1.9H, *J* = 6.0), 1.13 (d, 1.1H, *J* = 6.0), 0.8 (d, 1.9H, *J* = 6.4); ^{13}C NMR (125 MHz) δ 142.4, 142.3, 128.2, 128.1, 128.0, 127.9, 126.5, 126.4, 109.4, 109.1,72.1, 71.9, 42.6, 42.1, 23.1, 22.9, 22.0, 21.6, 16.6, 16.5; IR (neat) 3353 cm^{-1}. Anal. Calcd C, 68.89; H, 8.18. Found: C, 68.89; H, 8.17.

1-[(1-Methylethyl)oxy]-2-phenylpropane 1-hydroperoxide (7ab) was obtained in 95% yield from ozonolysis of a 63:37 mixture of (*E*)- and (*Z*)-methoxyphenylbutene in 2-propanol under similar conditions as employed above.

1-[(1,1-Dimethylpropyl)oxy]-2-phenylpropane 1-hydroperoxide (8ab) was obtained in 42% yield as an 82:18 ratio of diastereomers from ozonolysis of 3-phenyl-1-butene (55 mg, 0.41 mmol) in CH_2Cl_2 (35 mL) containing *t*-amyl alcohol (0.45 mL, 4.1 mmol). The ratio of diastereomers, which were incompletely resolved by chromatography, is based upon the ratio of signals for the acetal hydrogens at 4.87 ppm (major) and 5.03 ppm (minor) in the crude ^{1}H NMR spectrum:

Major: R_f = 0.30 (10% EA/hex); ^{1}H NMR (300 MHz) δ 7.68 (s, 1H), 7.25 (5H), 4.87 (d, 1H, *J* = 7.6 Hz), 3.27 (pentet, 1H, *J* = 7.3 Hz), 1.37 (d, 2H, *J* = 6.4), 1.38 (m, 1H), 1.33 (m, 1H), 1.04 (s, 3H), 0.81 (s, 3H), 0.66 (t, 3H, *J* = 7.3); ^{13}C NMR (125 MHz) δ 143.1, 128.4, 128.0, 128.1, 126.4, 104.8, 42.9, 34.8, 29.7, 26.0, 24.5, 16.3, 8.2. IR (neat) 3500−3300 cm^{-1}.

Minor: R_f = 0.30 (10% EA/hex); ^{1}H NMR (300 MHz) δ 7.46 (bs, 1H), 7.3−7.2 (5H), 5.03 (d, 1H, *J* = 7.4 Hz), 3.34 (pentet, 1H, J = 7.3), 1.6 (m, 1H), 1.31 (d, 3H, *J* = 7.1), 1.3 (m, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 0.95 (t, 3H, *J* = 7.5).

The same hydroperoxide was also obtained in 61% yield as an 81:19 ratio of diastereomers from ozonolysis of a 63:37 mixture of **6*Z*** and **6*E*** (320 mg, 1.97 mmol) in CH_2Cl_2 (170 mL) containing *t*-amyl alcohol (2.2 mL, 19.7 mmol).

(*E*)-1-[(Methoxymethyl)oxy]-1-(tri-*n*-butylstannyl)-2-hexene (9) was prepared from 2-hexenal in 83% yield according to a reported method:[15] R*f* 0.71 in 10% ethyl acetate/hexanes; ^{1}H NMR (500 MHz) δ 5.53 (dd, 1H, *J* = 7.3, 15.3), 5.37 (dtd, 1H, *J* = 1.2, 6.8, 15.3), 4.65 (d, 1H, *J* = 6.4), 4.55 (d, 1H, *J* = 7.25), 4.47 (d, 1H, *J* = 6.45), 3.32 (s, 3H), 1.98 (apparent quartet, *J* = 7.25), 1.48 (m, 6H), 1.35 (q, 2H, *J* = 7.25), 1.29 (sextet, 6H, *J* = 7.25), 0.9 (m, 9H), 0.87 (t, 9H, *J* = 7.25); ^{13}C NMR (75 MHz) δ 131.4, 125.5, 95.0, 72.4, 55.2, 34.5, 29.0, 27.3, 22.9, 13.6, 9.1. Anal. Calcd C, 55.44; H, 9.76. Found: C, 55.46; H, 9.58.

(*Z*)-1-[(Methoxymethyl)oxy]-3-(tri-*n*-butylstannyl)-1-hexene (10) was prepared from **9** under reported conditions.[15] To a −78 °C solution of (*E*)-1-[(methoxymethyl)oxy]-1-(tri-*n*-butylstannyl)-2-hexene (300 mg, 0.693 mmol) in CH_2Cl_2 (1.4 mL) was added BF_3·Et_2O (0.1 mL, 0.8 mmol). The solution was stirred for 1 h and then quenched at −78 °C with saturated aqueous $NaHCO_3$ (4 mL). The separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was subjected to flash chromatography (2% EA/hex) to afford 226 mg (76%) of alkoxy stannane: R_f = 0.71 (10% EA/hex); ^{1}H NMR (300 MHz) δ 5.94 (d, 1H, *J* = 6.0), 4.74 (ABq, 2H, *J* = 6.4, 10.7), 4.46 (dd, 1H, *J* = 6.2, 11.2), 3.36 (s, 3H), 2.5 (dt, 1H, *J* = 11.2, 7.6), 1.46 (m, 10H), 1.28 (sextet, 6H, *J* = 7.6), 0.87 (t, 9H, *J* = 7.1), 0.85 (t, 3H, *J* = 7.3), 0.79 (m, 6H); ^{13}C NMR (75 MHz) δ 137.8 (d), 113.7 (d), 96.1 (t), 55.5 (q), 35.5 (t), 29.3 (t), 27.5 (t), 23.5 (t), 23.1 (d), 13.7 (q), 13.6 (q), 8.9 (t). Anal. Calcd C, 55.44; H, 9.76. Found: C, 55.28; H, 9.50.

1-Methoxybutane 1-Hydroperoxide (11). Ozonolysis of allylstannane **9** (90 mg, 0.20 mmol) in methanol under conditions similar to those employed earlier produced 10 mg (40%) of the hydroperoxy acetal and 14% of recovered starting material: R_f = 0.11 (10% EA/hex); ^{1}H NMR (500 MHz) δ 7.94 (s, 1H), 4.73 (t, 1H, *J* = 6.0), 3.47 (s, 3H), 1.65 (m, 2H), 1.41 (sextet, 2H, *J* = 7.2), 0.92 (t, 3H *J*= 7.2); ^{13}C NMR (75 MHz) δ 108.6, 55.7, 33.3, 17.9, 13.8; IR (neat) 3380 cm^{-1}.

***N*-(*tert*-Butoxycarbonyl)-L-phenylalaninal** was synthesized through Swern oxidation of *N*-(*t*-butoxycarbonyl)-L-phenylalaninol.[25,26]

(3*EZ*)-*N*-(*tert*-Butoxycarbonyl)-2-amino-4-methoxy-3-butene (12*E*, 12*Z*). To a −78 °C suspension of (methoxymethyl)triphenylphosphonium chloride (3.529 g, 10.29 mmol) in THF (100 mL) was added *n*-BuLi (4.3 mL, 2.5 M solution in hexane). The reaction was allowed to warm to 0 °C and then maintained at that temperature for 30 min, whereupon a red color developed. Into this suspension was added a solution of N-(*tert*-butoxycarbonyl)-L-phenylalaninal (2.34 g, 9.36 mmol) in THF (10 mL) via cannula. After 3 h, the reaction was quenched by addition of water (10 mL) and brought to rt. The separated aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4. The concentrated material was purified by flash chromatography (20% EA/hex) to give 1.63 g (63%) of enol ether as a mixture of *E* and *Z*-isomers: R_f = 0.54 (50% EA/hex); ^{1}H NMR (500 MHz) δ 7.25 (m, 5H), 6.39 (d, 0.5H, *J* = 12.5), 5.86 (d, 0.5H, *J* = 6.4), 4.8 (bs, 0.5H), 4.65 (dd, 1H, *J* = 8.0, 12.4), 4.43 (bs, 0.5H), 4.32 (app triplet, 1H, *J* = 6.4), 3.35 (s, 1.5H), 3.47 (s, 1.5H), 2.85 (m, 2H), 1.42 (s, 4.5H), 1.41 (s, 4.5H); ^{13}C NMR (125 MHz) δ 149.3, 147.3, 138.3, 137.7, 129.7, 129.6, 128.2, 128.0, 126.3, 126.1, 106.5, 103.3, 59.8, 56.1, 42.7, 41.7, 28.43, 28.4; IR (neat) cm^{-1} 3354, 1710, 1658 cm^{-1}.

Separation of the geometric isomers could be achieved by gravity chromatography (18% EA/hex) on silica containing 5% (w/w) $AgNO_3$:

(*E*)-12: R_f = 0.67 (50% EA/hex on 5% $AgNO_3$/silica); ^{1}H NMR (500 MHz) δ 7.25 (m, 5H), 6.4 (d, 1H, *J* = 12.5), 4.65 (dd, 1H, *J* = 8.0, 12.8), 4.44 (broad s, 1H), 4.43 (broad s, 1H), 3.47 (s, 3H), 2.87 (dd, 1H, *J* = 6.4, 13.7), 2.80 (dd, 1H, *J* = 6.8, 13.2), 1.41 (s, 9H).

(*Z*)-12: R_f = 0.45 (50% EA/hex on 5% $AgNO_3$/silica); ^{1}H NMR (500 MHz) δ 7.25 (m, 5H), 5.87 (d, 1H, *J* = 6.45), 4.79 (broad s, 1H), 4.62 (broad s, 1H), 4.32 (dd, 1H, *J* = 6.4, 7.6),3.54 (s, 3H), 2.90 (dd, 1H, *J* = 6.0, 13.3), 2.82 (dd, 1H, *J* = 7.2, 13.2), 1.42 (s, 9H).

***N*-(*tert*-Butoxycarbonyl)-2-amino-3-hydroperoxy-3-methoxypropane (13ab).** Ozonolysis of a −78 °C solution of a 1:1 mixture of the (*E*) and (*Z*) enol ethers (56 mg, 0.2 mmol) in methanol (15 mL) furnished, after flash chromatography (20% ethyl acetate in hexanes), 46 mg (77%) of a 1:1 mixture of diastereomeric hydroperoxy acetals. The diastereomers could be quantified both by ^{1}H NMR as well as by analytical HPLC on a 0.5 × 25 cm Si column with RI detection (25% EA/hex, eluting at 7.1, 9.3 min).

First eluting: R_f = 0.11 (50% EA/hex); ^{1}H NMR (500 MHz δ 10.6 (s, 1H), 7.6 (m, 5H), 4.55 (d, 1H, *J* = 9.2), 4.18 (m, 2H),

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3.56 (s, 3H), 3.04 (dd, 1H, J = 4.4, 14.5), 2.92 (dd, 1H, J = 7.2, 14.1), 1.42 (s, 9H); ^{13}C NMR (125 MHz) δ 136.3, 129.3, 128.8, 126.9, 107.3, 55.2, 50.0, 35.6, 28.2; IR (neat) 3332, 1724, 1604 cm^{-1}. HRMS (EI) of **13a** was obtained after formation of the corresponding methoxypropyl peroxy ketal;[9,21] calcd for $C_{19}H_{30}O_6N$ 264.1583, found 264.1601.

Second eluting: R_f = 0.11 (50% EA/hex); ^{1}H NMR (500 MHz) δ 10.01 (s, 1H), 7.27 (m, 5H), 4.72 (d, 1H, J = 7.6), 4.59 (s, 1H), 4.29 (app. quartet, 1H, J = 8.4), 3.54 (s, 3H), 2.8 (d, 2H, J = 7.6), 1.43 (s, 9H); ^{13}C NMR (125 MHz) δ 129.0, 128.6, 126.6, 106.9, 58.0, 51.6, 36.0, 28.2; IR (neat) 3463, 1729, 1606 cm^{-1}.

Acknowledgment. This work was supported by funding from the American Cancer Society (CN-34).

JO951348T