General Synthesis of Polyunsaturated Fatty Acid Hydroperoxides Involving a Novel Vinylcyclopropyl Bromide Ring Opening

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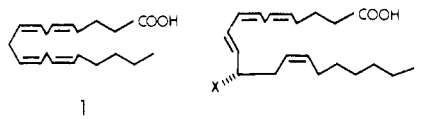
A variety of 18- and 20-carbon polyunsaturated fatty acid hydroperoxides were synthesized via an orbital symmetry controlled ring opening of vinylcyclopropyl bromides. Six 20-carbon vinylcyclopropyl bromides (**20–25**) were synthesized by a route starting from 2-ethoxy-$\Delta^{3,5}$-dihydropyran (**3**) and an 18-carbon vinylcyclopropyl bromide by a route starting from propargyl alcohol. All six vinylcyclopropyl bromides underwent facile Ag^+-assisted ring opening in the presence of excess H_2O_2 to form the target fatty acid hydroperoxide isomers in good yields. In most cases the products were produced with stereochemical control. The product hydroperoxides formed in this ring-opening reaction are consistent with a mechanism involving the formation of a pentadienyl cation intemediate. A minor product found in the reaction of vinylcyclopropyl bromide **26** provides evidence that homoallylic participation by alkenyl substituents can change the course of the electrocyclic ring opening.

Polyunsaturated fatty acid hydroperoxides are a ubiquitous group of intermediates found in nature. These hydroperoxides (and their metabolites) play important roles in a variety of biochemical events. The formation of various isomeric hydroperoxyeicosatetraenoic acids (HPETEs) and hydroxyeicosatetraenoic acids (HETEs) from arachidonic acid (**1**) is catalyzed by lipoxygenase



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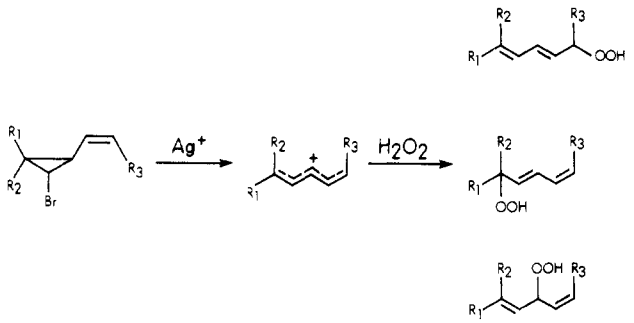
2a, X = OOH, 12-HPETE
2b, X = OH, 12-HETE

enzymes. Important structural features of these HPETE and HETE isomers such as **2a** and **2b** are the trans,cis-conjugated diene system, the absolute configuration at the chiral center, and the position of oxygen substitution. The complete biological and pharmacological function of these compounds remains to be elucidated. Nevertheless, intensive investigation has implicated HPETE and HETE products of platelet and leukocyte lipoxygenases as mediators of blood platelet aggregations,[1,2] inflammation, and the allergic response.[3,4] Furthermore, these lipoxygenase products have been shown to modulate enzymes that control prostaglandin metabolism.[5–7] The compounds **2a** and **2b** exhibit chemotactic and chemokinetic activity on human neutrophils.[8]

Various syntheses of fatty acid hydroperoxides (FAHPs) and alcohols have appeared in the literature over the past 10 years. The oldest and perhaps easiest preparation of a particular isomer is an enzymatic oxidation of arachidonic acid (**1**). For example, soybean lipoxygenase converts **1** to 15(*S*)-HPETE[9] while human platelet lipoxygenase

Scheme I



forms specifically **2a**.[10] Other methods involve either a random singlet oxygen[11] or a free-radical oxidation of **1**.[12] These procedures, while convenient, provide relatively low conversion from fatty acid to isolated HPETE products. We[13] and others[14–19] have reported synthetic methods for preparation of HPETE and HETE isomers. In this paper we expand our original work by presenting in full detail the synthesis of a wide range of HPETE and HETE products.

An overview of our synthetic approach to FAHPs is presented in Scheme I. Thus, the synthesis is general and relies on an orbital symmetry controlled vinylcyclopropyl bromide (VCPB) ring-opening reaction as the key step. Central to this approach is the desire to control the product conjugated diene stereochemistry. In the presence of H_2O_2, three possible regioisomers could be formed from the expected pentadienyl cation intermediate. Additionally, a judicious choice of R and R′ in the synthesis of the VCPB precursors would allow ready variation in FAHP product structure.

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(9) Funk, M. O.; Isaac, R.; Porter, N. A. *Lipids* **1976**, *11*, 113.
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(11) Porter, N. A.; Logan, J.; Kontoyiannidou, V. *J. Org. Chem.* **1979**, *44*, 3177.
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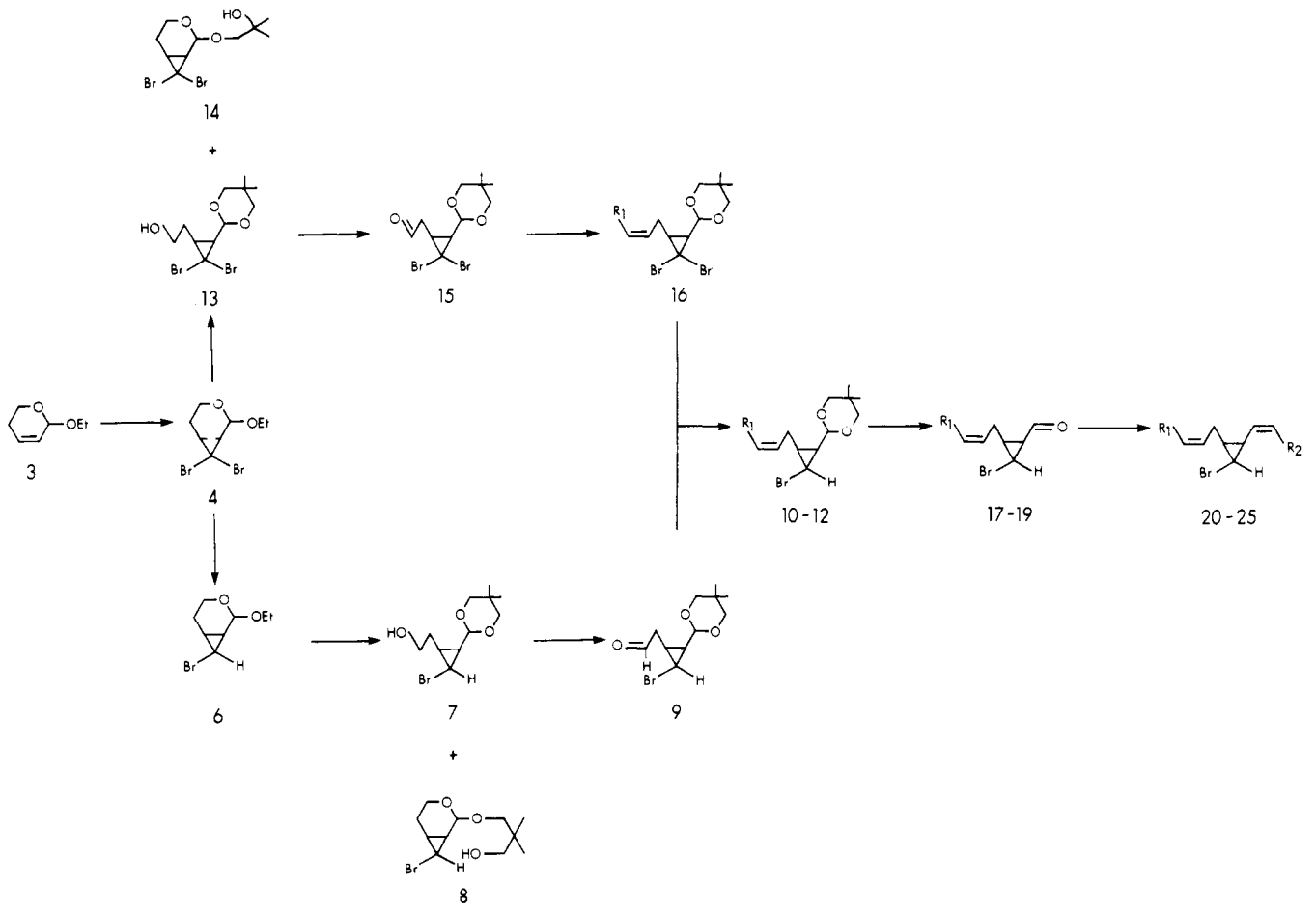
Scheme II

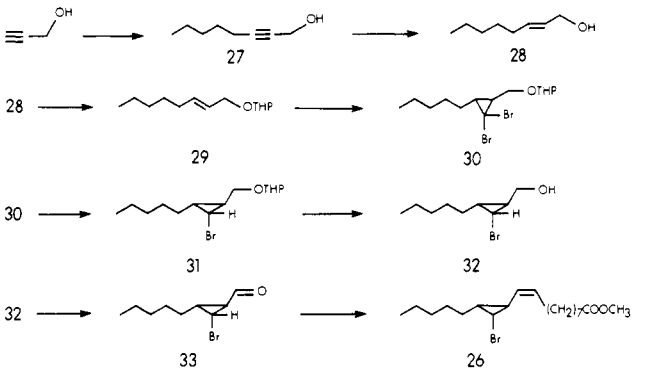


Silver ion assisted displacement of halides in the synthesis of prostaglandins and allylic hydroperoxides has been documented.[20-21] Similarly, the silver ion assisted ring opening of alkylcyclopropyl halides is a well-established reaction.[22-26] These reactions obey the orbital symmetry conservation rules of Woodward and Hoffmann. We anticipated that hydrogen peroxide attack on the intermediate cation would occur before isomerization and loss of stereochemistry. Model electrocyclic ring-opening reactions[13] involving novel vinylcyclopropyl bromides established the validity of this overall synthetic approach generalized in Scheme I.

Results

Vinylcyclopropyl Bromide Synthesis. The initial focus of this synthetic approach centered on the construction of appropriate 18- and 20-carbon vinylcyclopropyl bromide (VCPB) precursors. One goal was to design a general synthesis of these compounds that would allow ready structure variation. Thus, Scheme II presents a general synthesis of allyl-substituted VCPBs,[27] and in Scheme III is shown the synthesis of the 18-carbon VCPB **26**. The discussion that follows deals with the synthesis of these VCPBs.

Scheme III



The initial reaction shown in Scheme II is the dibromocarbene addition to 2-ethoxy-$\Delta^{3,5}$-dihydropyran (**3**). The product dibromide **4** was obtained in 46% yield and was the only diastereomer formed according to ^1H and ^{13}C NMR. This result is also supported by epoxidation studies of similar compounds.[28] The monobromide **6** was obtained via selective low-temperature metalation with CH_3Li that was followed by a water quench.[29] A separable mixture of alcohols **7** and **8** (6:1) was formed in the transacetalation of **6** with 2,2-dimethylpropanediol in the presence of an acid catalyst. Oxidation of **7** with pyridinium chlorochromate produced the aldehyde **9** in 75% yield. This

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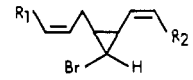
(26) Baird, M. S.; Reese, C. B. *Tetrahedron Lett.* **1967**, 1379.
(27) For Scheme II, R and R′ are as follows: R′ = $CH_2CH{=}CH(CH_2)_4CH_3$ for **10**, **17**, **24**, and **25**; R′ = $CH_2CH{=}CH(CH_2)_3COOCH_3$ for **11**, **18**, and **23**; R′ = $(CH_2)_4CH_3$ for **12**, and **19–22**; R = $CH_2CH{=}CH(CH_2)_3COOCH_3$ for **20**; R = $CH_2CH{=}CH(CH_2)_3COOH$ for **22**; R = $(CH_2)_4CH_3$ for **23**; R = $(CH_2)_3COOH$ for **24**; R = $(CH_2)_3COOCH_3$ for **25**.
(28) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1968**, *46*, 707.
(29) Taylor, K. G.; Chaney, J. *J. Am. Chem. Soc.* **1976**, *98*, 4158.

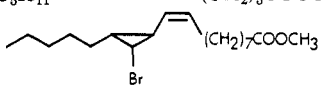
Table I. Structures of Vinylcyclopropyl Bromides



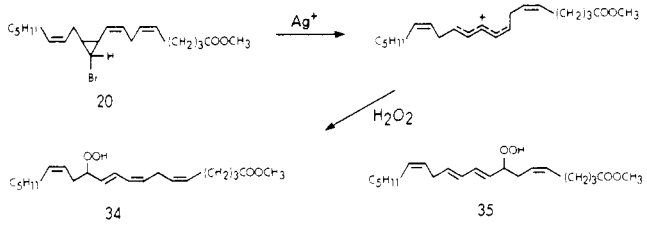
20-25

	R^1	R^2
20	C_5H_{11}	$CH_2CH{=}CH(CH_2)_3COOCH_3$
21	C_5H_{11}	$(CH_2)_6COOCH_3$
22	C_5H_{11}	$CH_2CH{=}CH(CH_2)_3COOH$
23	$CH_2CH{=}CH(CH_2)_3COOCH_3$	C_5H_{11}
24	$CH_2CH{=}CHC_5H_{11}$	$(CH_2)_3COOH$
25	$CH_2CH{=}CHC_5H_{11}$	$(CH_2)_3COOCH_3$

2



Scheme IV



thermally labile aldehyde readily reacted with Wittig ylides. Thus, monobromides **10** and **11** (Scheme II) were prepared via this pathway. A parallel pathway, utilizing intermediates **13–16**, was also pursued (with no substantial advantage) to obtain the monobromide **12** (Scheme II). The remaining two steps of this general VCPB synthesis involved a low-temperature hydrolysis of the monobromides **10–12**. These product aldehydes **17–19** were then each transformed via a final Wittig reaction to yield to VCPBs **20–25**. The synthesis of VCPB **26** is shown in Scheme III. This synthesis starts from propargyl alcohol and generally follows the same strategy used for the preparation of VCPBs **20–25**. Yields of reactions leading to VCPB **26** were good to excellent with the exception of the cyclopropanation (30%) and the Wittig condensation of **33** with the phosphonium salt of methyl 9-bromononanoate[30] (53%). Each of the VCPB products (Table I) was thermally labile but the compounds could be stored indefinitely at −80 °C.

Ring-Opening Reactions of VCPBs. An ether solution of the vinylcyclopropyl bromide was treated with a mixture containing a large excess of silver trifluoroacetate and hydrogen peroxide at 20 °C. The ensuing reaction required less than 10 min to complete. Following an aqueous workup, the crude lipid hydroperoxide product mixture was purified, first by cold-column silica gel chromatography and then by preparative HPLC. Each isolated component was characterized either as the hydroperoxide or as the more stable alcohol (by triphenylphosphine reduction of the hydroperoxide).[11] Ultimately, all the FAHPs were catalytically reduced (H_2, PtO_2) and then subjected to GC/MS analysis as their trimethylsilyl derivatives.

The reaction of VCPB **20** is illustrative. On reaction with Ag^+/H_2O_2, **20** ring opened, presumably via the pentadienyl cation shown in Scheme IV, to form the isomers **34** and **35** (2:1) in 78% total yield. Several other minor products were formed in the ring opening, but these compounds were not characterized in this system. In a subsequent study of VCPB **26**, all minor components were characterized. The structural proof of the two products **34** and **35** was made by IR,[31] UV,[32] GC/MS,[33] comparison of HPLC retention with authentic samples,[34] and ^1H NMR.

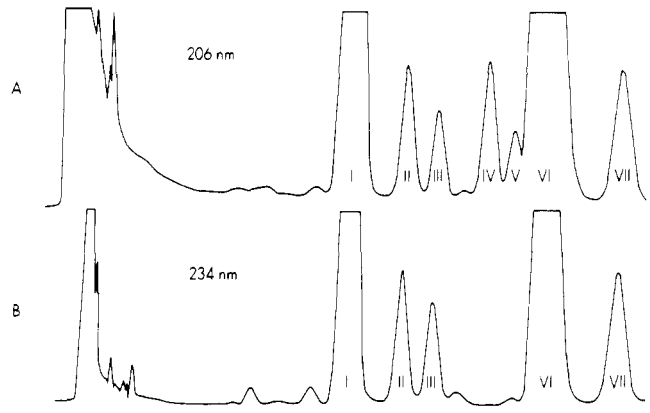
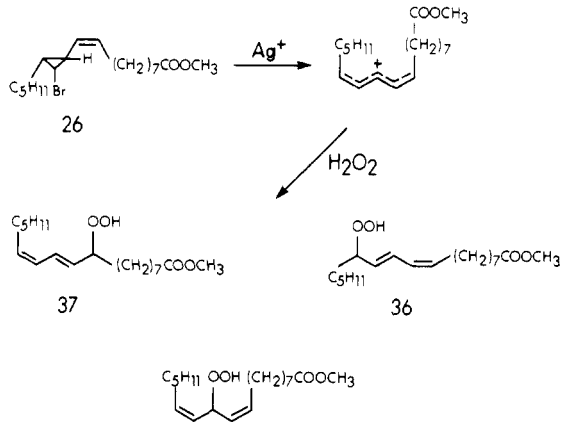


Figure 1. HPLC chromatogram for reaction of **26** with Ag^+/H_2O_2. Analysis of product mixture: (A) at 206 nm; (B) at 234 nm.

Scheme V



The VCPB **26** reacted with Ag^+/H_2O_2 to give a mixture of products analogous to those obtained from **20**. In Figure 1 is shown the HPLC chromatogram for the product mixture from **26** (after reduction of hydroperoxide to alcohol with Ph_3P). Scheme V shows the expected reaction pathway for VCPB **26** based on the results of experiments with **20**. The major products anticipated were the 13-trans,cis and 9-trans,cis compounds. This was indeed the experimental result. The two dominant HPLC fractions I and VI were identified as being the 13-trans,cis compound **36** (41%) and the 9-trans,cis compound **37** (44%), respectively. Fractions IV, **38** (3.5%), and V, **39** (1.3%), were detected by HPLC at 206 nm but were transparent to detection at 234 nm (Figure 1, parts A and B). This observation implied that **38** and **39** had a nonconjugated diene and GC/MS confirmed both to be "11"-substituted. Both **38** and **39** were unstable, and as a consequence no spectral data could be obtained for **39**. For **38**, however, it was determined through decoupling and spectral simu-

(30) Seoane, E.; Arno, M. *An. Quim.* **1977**, *73*, 1336.

(31) IR absorption were seen at 950 and 989 cm^{-1} for the alcohol derivatives of **34**, indicative of trans, cis conjugation, whereas the alcohol derivatives of **35** showed a single absorption in this region (990 cm^{-1}, trans,trans). Chan, H.-S.; Levett, G. *Lipids* **1977**, *12*, 837.

(32) Ultraviolet absorption spectroscopy also was useful in elucidating product stereochemistry of the PPh_3-reduced alcohol products. Maximum values of 235 and 232 nm were measured for **34** and **35**, respectively.

(33) GC/MS principal fragmentation for the 8- and 12-HPETE derivatives all gave identical fragmentation patterns agreeing with known literature values.[11]

(34) This was possible only if a natural cis,trans isomer was formed. For example, the synthesized 12-HPETE methyl ester **34** coeluted with the naturally occurring isomer.[11]

Table II. Products from Silver Ion Catalyzed Ring Opening of Vinylcyclopropyl Bromides 20–26

products	product ratio	total yield, %
20		
12-OOH,8-cis,10-trans	2	78
8-OOH,9-trans,11-trans	1	
21		
12-OOH,8-cis,10-trans	2	71
8-OOH,9-trans,11-trans	1	
22		
12-OOH,8-cis,10-trans	2	
8-OOH,9-trans,11-trans	1	
23		
15-OOH,11-trans,13-trans	6	
11-OOH,12-trans,14-cis	3	66
13-OOH	1	
24		
9-OOH,7-trans,5-cis	1	
5-OOH, 6-trans,8-trans	2	
5-lactone,6-trans,8-trans	1	
25		
9-OOH,7-trans,5-cis	3	
9-OOH,7-trans,5-trans	3	
5-OOH,6-trans,8-trans	3	
7-OOH,5,6-diene	1	
7-OOH,5,6-diene	1	
26		
9-OOH,10-trans,12-cis	44	
9-OOH,10-trans,12-trans	4	
11-OOH,trans,cis	1	
11-OOH	3	
13-OOH,11-trans,9-trans	3	
13-OOH,11-trans,9-cis	41	
13-OOH,11-cis,9-cis	1	

lation that both a trans double bond and a cis double bond were present in the molecule. Unfortunately, the assignment of stereochemistry to a particular chain location (Δ^9 or Δ^{12}) could not be made. On the basis of subsequent arguments however, it seems likely that **38** had 9-cis,12-trans stereochemistry.

Fractions II (3.3%) and VII (4.6%) were identified as the known 13-trans,trans (**40**) and 9-trans,trans (**41**) isomers and are probably formed as secondary products by isomerization (acid or free radical) of the primary products.

The remaining fraction, III (2.1%), eluted on HPLC, where no, as yet, known hydroxy linoleate had been seen. We were surprised to determine that this compound was the 13-cis,cis isomer **42**. This assignment was confirmed by GC/MS and ^{1}H NMR decoupling studies. In the NMR, two of the four vinyl protons overlapped in the ^{1}H NMR, but the other two vinyl protons stood alone and were fortuitously located on different double bonds. Successive decoupling of the methine protons at δ 4.6 and the allylic methylene protons at δ 2.1 revealed vinyl vicinal coupling constants of 7.7 and 9.2 Hz for the double bonds. Both values are indicative of cis stereochemistry.

In Table II is presented the product distribution obtained for the silver ion catalyzed ring opening of several VCPBs we prepared. The method of ring opening utilized was similar for all VCPBs, and the products were analogous for VCPBs **20–22** and **26**. Compound **24** gave products resulting from carboxylate participation in the ring opening. Thus, the lactone **44** was the major product of this reaction, with some of the expected FAHPs being isolated. The product mixture from ring opening of methyl ester **25** is extremely complex, with significant amounts of nonconjugated products being formed.

Discussion

The approach to lipid hydroperoxides via vinylcyclopropyl bromides proves to be a useful method for the preparation of these biologically important compounds. Of particular interest in the synthetic scheme is the ring-opening reaction. Theory suggests that ring opening should occur in a disrotatory mode with groups trans to the leaving bromide rotating outward. For the cis dialkyl VCPB **20**, the cation predicted by this mode of opening is shown in Scheme IV. Attack by hydrogen peroxide nucleophiles on this cationic intermediate provides FAHPs with stereochemistry derived from the cation precursor. Thus, **20** ring opens to give **34** (8-cis,10-trans,12-OOH) and **35** (9-trans,11-trans-8-OOH) as the major products. Nonconjugated products are also sometimes isolated from the product mixture, but these compounds are unstable and difficult to isolate and purify. The regiochemical preference for product from the cationic intermediates is curious. For **20–22**, the trans,cis-conjugated diene hydroperoxide is favored by 2:1 over the trans,trans compounds, while this is not the case for **23**, where the trans,trans product is dominant. We have no compelling arguments to offer in explanation of this observed regiochemical selection.

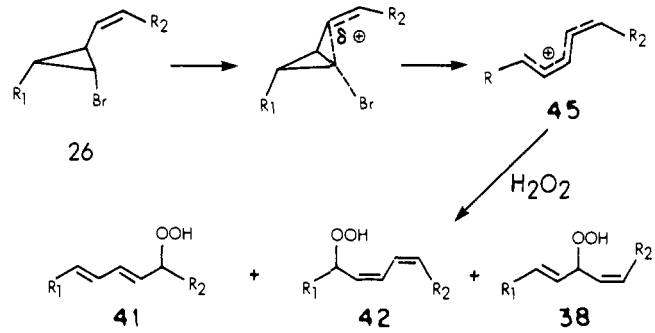


Figure 2. Alternate mode of ring-opening of **26**.

Compound **26** differs from the other VCPBs of this study in that the alkyl groups are substituted trans on the cyclopropane ring for this compound while all the other VCPB have cis-oriented alkyl substituents. The major products obtained from ring opening of VCPB **26** are interpreted on the basis of the anticipated cation. This cation, shown in Scheme V, gives both the 13- and 9-substituted trans,cis-conjugated dienes as major products (**36** and **37**). The minor products from ring opening of **26** are of particular interest. The trans,trans products (**40** and **41**) are probably the result of isomerization of other primary products but isomerization pathways do not account for formation of the nonconjugated products or the 9-cis,11-cis,13-OOH product (**42**). We suggest that, via homoallylic participation, the cyclopropyl ring has opened in the disrotatory mode opposite to that put forth by Woodward and Hoffmann and by DePuy. This "alternative" disrotatory mode (allowed by symmetry considerations) involves "inward" rotation of groups trans to the leaving group, leading to cation **45** (Figure 2). Intermediate **45** would lead to the 9-trans,trans,13-cis,cis, and nonconjugated 9-cis,12-trans,11-OOH (**38**) compound.

Homoallylic participation is known to induce considerable enhancements in solvolytic reactions when the geometry of the molecule is favorable. Molecular models of VCPB **26** indicate that the necessary overlap for homoallylic participation is a reasonable proposition.

Normally in the disrotatory opening of cyclopropyl halides the reaction occurs such that the orbitals of the cleaving cyclopropyl σ bond rotate up and behind the departing halide. Qualitatively, this places electron density backside to the leaving group and thus assists its departure. Disrotatory opening in the so-called "alternative" manner does not enjoy this stabilizing feature and therefore is in most instances a pathway of prohibitively high energy.

Considering VCPB **26**, however, an alkenyl substituent is now situated trans to the bromine. During "alternative" opening the π-bond of the alkenyl substituent can situate backside to the departing bromine and supply stabilization to the incipient carbocation.

The "alternative" ring opening put forth here is novel, but we belive meritorious in light of the unique structural features of VCPB **26**. First, **26** possesses the crucial alkenyl substituent disposed trans to the halide. Second, the two alkyl substituents are thermselves trans to one another. This is important in that were the alkyl substituents positioned cis to each other, then "alternative" ring opening would require the groups to rotate toward each other as shown in Figure 2. The steric congestion found in the pentadienyl intermediate so-formed has been estimated to retard the reaction rate relative to the corresponding trans compound by a significant factor. Thus, it can be concluded that it is only in cyclopropyl systems substituted analogously to VCPB **26** that one might expect to see the novel disrotatory ring opening proposed here.

Experimental Section

^{1}H NMR spectra were determined on a Varian EM-360 at 60 MHz or a JEOL JNM-100 at 100 MHz or a Bruker WM-250 FT spectrometer at 250 MHz.

A JEOL JNM-FX 60 fourier transform spectrometer was used in obtaining ^{13}C NMR spectra at 22.6 MHz.

Elemental analyses were performed by MHW Laboratories, Phoenix, AZ, Galbraigh Laboratories, Knoxville, TN, or Integral Microanalytical Labs, Inc., Raleigh, NC.

2-Ethoxy-$\Delta^{3,5}$-dihydropyran (3). This compound was prepared according to Sanders.[35]

Preparation of Dibromide 4. A mixture containing 27.9 g (0.22 mol) of olefin **3** and 145 g (0.6 mol) of $CHBr_3$ was diluted with 60 mL of CH_2Cl_2. To this solution were added 100 mL of 50% aqueous NaOH and 4.46 gm (0.021 mol) of $PhCH_2N(C_2H_5)_3^+Cl^-$. The resulting reaction mixture was stirred rapidly at 40 °C for 2 h. At this point the reaction was ~50% complete. Another 70 g (0.3 mol) of $CHBr_3$ and 100 mL of NaOH solution was added. The reaction mixture was stirred at 40 °C for another 12 h after which time another 2.23 g (0.01 mol) of catalyst was added followed by a final 4-h of reaction time. Thus, the total reaction time was 40 h.

On workup, the contents of the reaction were cooled to room temperature and then filtered over Celite. The entire filtrate was extracted in a liquid–liquid extractor for 24 h (pentane solvent), the extracted solution was passed through a column of Florisil (400 g) and eluted with C_6H_{14}, thus separating the polar side products. The combined eluents were reduced in volume on the rotovap. At this point the product mixture contained $CHBr_3$ and dibromide **4**. The $CHBr_3$ was removed by vacuum distillation [50 °C (0.1 mm Hg)]. Care should be taken not to exceed 50–60 °C in this distillation. The product weighed 30 g (46%) and required no further purification: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H, CH_3), 2.0 (m, 4 H, 2 cyclopropyl CH_2), 3.64 (m, 4 H, 2 CH_2O), 4.84 (s, 1 H, CHOEt); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 2.5 (cyclopropyl), 26.1, 27.8, 32.7 (CBr_2), 54.3 (OCH_2CH_3), 63.1 (CH_2O), 93.8 (OCHO).

Anal. Calcd for $C_8H_{12}Br_2O_2$: C, 32.02; H, 4.00. Found: C, 31.87; H, 4.05.

Synthesis of Monobromide 6. This synthesis was similar to that reported by Taylor.[29] Dibromide **4** (13 g, 43.3 mmol) yielded 5.2 g (54%) of monobromide after purification on Florisil cold-column (–25 °C) chromatography (1% Et_2O/99% C_6H_{14} eluent): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H, CH_3), 1.42 (dd, 1 H, CH_2CH_2O), 1.67 (m, 1 H, cyclopropyl), 1.88 (m, 2 H, CH_2C_2O, cyclopropyl), 2.7 (t, 1 H, CHBr), 3.23 (1 H, CH_2O), 3.5 (m, 1 H, CH_2O), 3.72 (m, 2 H, CH_3CH_2O), 5.0 (s, 1 H, OCHO); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 19.3 (cyclopropyl), 21.8 (CH_2), 22.7 (cyclopropyl), 23.6 (CHBr), 53.8 (OCH_2C_3), 63.1 (CH_2CH_2O), 94.0 (OCHO).

Anal. Calcd for $C_8H_{13}BrO_2$: C, 43.46; H, 5.92. Found: C, 43.16; H, 5.72.

Synthesis of Acetal 7. In a round-bottomed flask under a N_2 atmosphere, 1.62 g (7.2 mmol) of monobromide **6** and 7.5 g (72 mmol) of 2,2-dimethylpropanediol were dissolved in 30 mL of benzene. A catalytic amount of toluenesulfonic acid (0.53 g) was added, and the resulting solution was stirred at 40–50 °C for 21 h. The reaction progress was monitored by TLC.

On workup, the reaction was cooled to room temperature followed by dilution with 50 mL of Et_2O. It was washed ten times with 25-mL aliquots of H_2O and finally with saturated $NaHCO_3$ solution. The organic solution was dried ($MgSO_4$). TLC analysis of the crude reaction mixture revealed some starting monobromide, two minor side products, and one major product increasing in polarity, respectively. Purification of the major and minor products via cold-column Florisil chromatography (–20 °C) gave the following yield based on 0.126 g (8%) of recovered starting material: least polar product, **8**, 0.126 g (8%); most polar major product, **7**, 0.910 g (49%) (45% Et_2O/55% C_6H_{14} eluent).

The least polar side product (**8**) gave the following spectral data: ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 6 H, CH_3), 1.4 (dd, 1 H, cyclopropyl), 1.61 (m, 1 H, cyclopropyl), 1.85 (m, 2 H, CH_2), 2.27 (br s, 1 H, OH), 2.67 (t, 1 H, CHBr), 3.24–3.6 (m, 6 H, CH_2O), 4.92 (s, 1 H, OCHO); ^{13}C NMR ($CDCl_3$) δ 19.5 (cyclopropyl), 21.8 (c-$(CH)_2$), 22.5 (cyclopropyl), 23.6 (C_2), 36.2 (CHBr), 54.1 (ring CH_2O), 70.8 (CH_2OH), 75.9 (acyclic CH_2O), 94.9 (OCHO).

The most polar major product (**7**) gave the following spectral data: ^{1}H NMR ($CDCl_3$) δ 0.7 (s, 3 H, CH_3), 1.2 (s, 5 H, CH_3 plus impurity), 1.45 (m, 1 H, cyclopropyl), 1.7 (m, 2 H, CH_2CH_2OH), 1.96 (m, 1 H, cyclopropyl), 2.53 (br t, 1 H, OH), 2.8 (t, 1 H, CHBr), 3.58 (m, 8 H, CH_2O, impurity), 4.36 (d, 1 H, OCHO); ^{13}C NMR ($CDCl_3$) δ 20.7 ($C(CH_3)_2$), 21.8, 23.0 (2 CH_3), 24.9 (CH_2), 30.0, 30.1 (cyclopropyl), 30.6 (CHBr), 62.2 (CH_2OH), 77.4 (CH_2OC), 100.3 (OCHO). This product was stored at 0 °C.

Synthesis of Aldehyde 9. A modified procedure of Corey[36] was used. A 20-mL CH_2Cl_2 solution containing 0.782 g (2.8 mmol) of alcohol **7** with 0.82 g (10 mmol) of solid NaOAc was stirred under a N_2 atmosphere at room temperature. In one portion, 2.1 g (9.8 mmol) of pyridinium chlorochromate was added to this solution. The resulting mixture was allowed to stir for 1 h.

On workup, the reaction mixture was diluted with Et_2O and decanted from the gummy residue. This residue was triturated several times with ether aliquots until it became granular in texture. The combined ether triturates were passed through a short column of Florisil at room temperature. Removal of the solvent left a colorless oil, 0.502 g (64%), that was pure by TLC. The product was stored in a –20 °C freezer: ^{1}H NMR ($CDCl_3$) δ 0.72 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.22 (2 s, impurity), 1.6 (s, H_2O), 1.74 (m, 2 H, cyclopropyl), 2.6 (m, impurity), 2.7 (m, 2 H, CH_2CHO), 2.94 (t, 1 H, CHBr), 3.5 (m, 4 H, 2 C_2O), 4.2–4.54 (m, impurity), 4.58 (d, 1 H, OCHO), 9.8 (t, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 20.0 ($C(CH_3)_2$), 20.8 (cyclopropyl), 21.8, 23.1 (2 CH_3), 29.4 (CHBr), 30.1 (cyclopropyl), 41.9 (CH_2CHO), 77.4 (2 CH_2O), 99.5 (OCHO), 200.6 (CHO).

Synthesis of Wittig Product 11. The synthesis of **11**, **18**, and **23** is outlined here as illustrative. Details for preparation of **10**, **12–17**, **19–22**, **24**, and **25** follow similar procedures. ((3*Z*)-8-Methoxy-8-oxo-3-octenyl)triphenylphosphonium iodide (1.6 g, 3 mmol) previously dried in vacuo was suspended in 8 mL of dry THF solution at 0 °C under a N_2 atmosphere. A THF solution containing 2.4 mmol (4.6 mL of 0.52 M solution) of $KOC(CH_3)_3$ was added dropwise. Thus, the orange ylide solution was stirred 10 min before the dropwise addition of 86 mg (0.31 mmol) of aldehyde **9** in 2.5 mL of THF. The Wittig mixture was allowed to stir for 3.75 h at 0 °C.

On workup, 0.5 mL of H_2O was added dropwise prior to ether dilution of the reaction mixture. The quenched Et_2O/THF mixture was washed three times with brine solution followed by drying the organic phase with $MgSO_4$. Crude product TLC analysis indicated that all the aldehyde had reacted and showed the presence of three nonpolar products. On purification via cold-column chromatography the least polar of the three products was Ph_3P (C_6H_{14} eluent).

(35) Woods, G. F.; Sanders, H. *J. Am. Chem. Soc.* **1946**, *68*, 2483.

(36) Corey, E. J.; Suggs, W. *Tetrahedron Lett.* **1975**, 2647.

(37) Morton, D. R.; Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880.

The second most polar product was the conjugated diene methyl 5,7-octadienoate (E2 elimination of Ph_3P), 147 mg (33% based on phosphonium salt; 2% Et_2O/98% C_6H_{14} eluent): ^1H NMR ($CDCl_3$) δ 1.63 (p, 2 H, $CH_2CH_2CO_2CH_3$), 2.19 (q, 2 H, allylic), 2.3 (t, 2 H, $CH_2CO_2CH_3$), 3.65 (s, 3 H, OCH), 5.1 (dd, 2 H, H_8), 5.25 (q, 1 H, H_7), 6.0 (t, 1 H, H_6), 6.57 (m, 1 H, H_5, $J_{5,6}$ = 11 Hz, cis 5,6); ^{13}C NMR ($CDCl_3$) δ 24.8 ($CH_2CH_2CO_2C_3$), 27.0 (allylic), 33.4 (CH_2CO), 51.3 (OCH_3), 117.3 (C-8), 130.3, 131.1, 132.0 (C-5,6,7).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 70.12; H, 9.12.

The most polar and major product was 11, 67 mg (52%; 8% Et_2O/92% C_6H_{14} eluent): ^1H NMR ($CDCl_3$) δ 0.7 (s, 3 H, CH_3), 1.2 (s, 3 H, CH_3), 1.4 (m, 1 H, 2 H, C_4 allylic), 2.3 (dt, 4 H, $CH_2CO_2CH_3$, C-10 allylic), 2.76 (br t, 2 H, bis allylic), 2.85 (t, 1 H, CHBr), 3.5 (m, 4 H, CH_2O), 3.7 (s, 3 H, OCH_3), 4.4 (d, 1 H, OCHO), 5.4 (m, 4 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 21.1 ($C(CH_3)_2$), 21.8, 23.0 (2 CH_3), 24.8 ($CH_2CH_2CO_2CH_3$), 25.5, 25.7, 26.6, 27.2 (cyclopropyl allylic), 20.1 (cyclopropyl), 30.3 (bis allylic), 33.5 ($CH_2CO_2CH_3$), 51.4 (OCH_3), 77.4 (2 CH_2O), 100.2 (OCHO), 127.8 (vinyl), 128.8 (2 vinyl), 129.0 (vinyl), 173.9 (CO_2CH_3).

Anal. Calcd for $C_{20}H_{31}BrO_4$: C, 57.83; H, 7.52. Found: C, 57.54; H, 7.37.

Hydrolysis of Acetal 11. This experiment was a modification of that reported by Morton. Acetal 11 (220 mg, 0.53 mmol) was stirred with 13 mL of HCO_2H (88%) and 3 mL of THF at 0 °C under a N_2 atmosphere for 20 h. The reaction progress was monitored by TLC. The product was only slightly more polar than the starting acetal.

On workup, the reaction mixture was diluted with ether and then washed four times with cold H_2O, followed by two washings with cold saturated $NaHCO_3$ solution. After the organic portion was dried with $MgSO_4$, the mixture was filtered and the ether removed, leaving an oil that was partially purified via cold-column chromatography on Florisil (-20 °C). The product was contaminated with the diformate ester of 2,2-dimethylpropanediol, which coeluted with the product 18: ^1H NMR ($CDCl_3$) δ 1.0 (s, 2 CH_3 of impurity), 1.57 (s, H_2O), 1.7 (p, 2 H, $CH_2C_2CO_2CH_3$), 2.1 (m, 3 H, allylic, cyclopropyl), 2.34 (s, 2 H, $CH_2CO_2CH_3$), 2.48 (m, 3 H, allylic, cyclopropyl), 2.72 (br t, 2 H, bis allylic), 3.44 (dd, 1 H, CHBr), 3.66 (s, 3 H, OCH_3), 4.0 (s, CH_2O of impurity), 5.38 (m, 4 H, vinyl), 8.08 (s, HCO of impurity), 8.72 (d, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.7 ($C(CH_3)_2$ of impurity), 24.0 (cyclopropyl), 24.8 ($CH_2CH_2CO_2CH_3$), 25.8, 26.6 (allylic), 33.5 ($CH_2C-O_2C_3$), 36.3 (CHBr), 36.7 (CHCHO), 51.5 (OCH_3), 68.4 (2 CH_2O of impurity), 126.4, 128.4, 129.4, 130.2 (4 vinyl), 160.7 (HCOO of impurity), 137.9 (CO_2CH_3), 197.7 (CHO). The aldehyde was thermally unstable and stored at -20 °C.

Synthesis of Wittig Product 23. In a round-bottomed flask, 1.15 g (2.7 mmol) of *n*-hexyltriphenylphosphonium bromide was suspended in 6 mL of dry THF under a N_2 atmosphere. To the suspension was added 2.4 mmol of $KOC(CH_3)_3$ (5 mL of a 0.45 M solution) in THF. The ylide solution was stirred at room temperature for 10–15 min, and then the temperature was lowered to 0 °C. To this solution was added the inseparable mixture of aldehyde and diformate ester of 2,2-dimethylpropanediol from the previous experiment dissolved in 1 mL of THF solution. The resulting mixture was stirred at 0 °C for 2 h, followed by the addition of 0.5 mL of H_2O to quench the reaction. Aproximately 50 mL of ether was added to this solution followed by three washings with brine. After drying ($MgSO_4$), filtration, and removal of the solvent, the crude product (a single spot by TLC analysis) was purified via Florisil cold-column chromatography (-20 °C, 8% Et_2O92% C_6H_{14}). The yield of the purified Wittig product, 183 mg (87%), was based on the amount of acetal 11 used in the hydrolysis experiment. The Wittig product **23** was unstable at room temperature and stored at -20 °C: ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, C_3), 1.35 (m, 6 H, $(CH_2)_3C_3$), 1.5 (m, 1 H, cyclopropyl), 1.57 (s, H_2O), 1.7 (p, 2 H, $CH_2CH_2CO_2CH_3$), 2.12 (m, 7 H, allylic, cyclopropyl), 3.33 (t, 2 H, $CH_2CO_2CH_3$), 2.65 (t, 1 H, CHBr), 1.75 (br t, 2 H, bis allylic), 3.67 (s, 3 H, C_2CH_3), 5.0 (dd, 1 H, H_{14}, $J_{14,15}$ = 10.7 Hz), 5.4 (m, 4 H, vinyl), 2.58 (m, 1 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 22.6 (cyclopropyl), 24.8 ($CH_2CH_2CO_2CH_3$), 25.8 ($(CH_2)_3CH_3$), 26.6, 26.8, 27.9, 29.2 (cyclopropyl and three allylic), 29.4 (CHBr), 31.5 (bis allylic), 33.5 ($CH_2CO_2C_3$), 51.5 (OCH_3), 124.6, 127.5, 128.8, 129.0 (2 C), 134.3 (6 vinyl), 173.9 (CO).

Anal. Calcd for $C_{21}H_{33}BrO_2$: C, 63.47; H, 8.12. Found: C, 63.66; H, 8.18.

2-Octyn-1-ol (27). The procedure of Brandsma was used.[38] Approximately 0.75 L of anhydrous liquid ammonia was distilled into a dry 2-L three-neck flask. Lithium metal (3.7 g, 2.1 equiv) were prepared in small chunks. One chunk was added (resulting in a deep blue solution) followed by approximately 100 mg of ferric nitrate. The remaining lithium metal was added chunkwise with stirring over 15 min. After 1.25 h, the solution was a milky white. Propargyl alcohol (14.0 g) was added to the solution over 15 min followed by 38.7 g of neat pentyl bromide over 60 min. The reaction was stirred for 1 h and then allowed to warm to room temperature. An amorphous solid remained.

Water (500 mL) was added and the flask swirled to dissolve as much solid as possible. The mixture was extracted five times with 100 mL portions of ether. The combined organic layers were dried ($MgSO_4$), filtered, and stripped. The resulting oil was distilled to give 22.4 g (70%) of pure octynol: bp 46–47 °C (0.1 mmHg); 90/-MHz ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.3 (m, 6 H), 2.2 (m, 2 H), 3.2 (s, 1 H), 4.2 (t, 2 H, J = 2.1 Hz).

2-Octen-1-ol (28). Reduction of the octynol to the *trans*-olefin via sodium in liquid ammonia was incomplete in one trial. Lithium aluminum hydride reduction, however, gave a very good yield and proved more convenient. $LiAlH_4$ reduction was done according to the procedure of Chanley.[39]

A 500-mL three-neck flask was charged with 4.35 g of $LiAlH_4$ and 90 mL of anhydrous ether under nitrogen. The solution was cooled to 0 °C and 5.3 g of **27** in 50 mL of ether was added dropwise. The solution was heated to reflux for 10 h, cooled, diluted with ether, and quenched with water. Cold 2 N HCl was added to facilitate layer separation. The layers were separated, and the aqueous layer was extracted once with ether. The combined organic layers were dried ($MgSO_4$), filtered, and stripped to give 4.99 g (93%) of the crude octenol. The product was purified by Kugelrohr disillation: 100-MHz ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.3 (m, 6 H), 2.1 (m, 2 H), 3.3 (br s, 1 H), 4.1 (m, 2 H), 5.7 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.01, 22.54, 28.87, 31.43, 32.20, 63.76, 128.97, 133.43.

2-Octen-1-yl Tetrahydropyranyl Ether (29). To a 25-mL flask flushed with nitrogen at 0 °C were added 540 mg of octenol, 5 mL of dihydropyran, and a catalytic amount of *p*-toluenesulfonic acid. After the mixture was stirred for 30 min, thin-layer chromatography showed no starting material remaining. The reaction was diluted with ether, washed once with saturated sodium bicarbonate and once with water, dried ($MgSO_4$), filtered, and stripped. Quick column chromatography (alumina, 20% ether-/hexane) gave 770 mg (86%) of the pure THP ether: 80-MHz ^1H NMR ($CDCl_3$) δ 0.9 (m, 3 H), 1.4 (m, 12 H), 2.0 (m, 2 H), 3.3–3.7 (m, 1 H), 3.7–4.3 (m, 3 H), 4.6 (m, 1 H), 5.6 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.05, 19.65, 22.54, 25.58, 28.83, 30.78, 31.47, 32.32, 62.29, 67.94, 97.83, 126.13, 134.82.

Dibromocarbene Adduct 32. A number of methods were attempted here. "Standard" dibromocarbene methods (potassium *tert*-butoxide and $CHBr_3$ in pentane) failed to give any detectable reaction as did potassium *tert*-butoxide and bromoform in *tert*-butyl alcohol at 60 °C.

Success was found in using a phase-transfer method. Combined in a 250-mL three-neck flask were 7.4 g of olefin **29**, 30 mL of $CHBr_3$ (9 equiv), and 1.5 g of benzyltriethylammonium chloride (20 mol %). NaOH (16 mL, 50% solution) was added dropwise with overhead stirring. The solution was heated to 60 °C for 24 h after which time the reaction was cooled and diluted with ether and water. The layers were separated. The aqueous layer was extracted once with pentane. The organic layers were combined, dried ($MgSO_4$), filtered, and stripped. The remaining bromoform was removed in vacuo by using a warm water bath. Column chromatography of the resulting crude (silica gel, 1% EtOAc/hexane) gave a 4.89-g mixture of product and starting olefin in an 85:15 ratio (30% yield). Kugelrohr distillation [55 °C (0.2 mmHg)] successfully removed the remaining olefin to yield the pure diastereomeric dibromide: 80-MHz ^1H NMR ($CDCl_3$) δ 0.9

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(39) Chanley, J. D.; Sobotka, H. *J. Chem. Soc.* **1949**, *71*, 4140.

(m, 3 H), 1.0–1.9 (m, 16 H), 3.4–4.1 (m, 4 H), 4.7 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.01, 19.2, 19.45, 22.58, 25.50, 27.90, 30.62, 30.74, 31.43, 32.20, 35.15, 35.82, 36.14, 62.09, 62.25, 69.12, 93.6, 98.56, 98.84.

Exact mass calcd for $C_{14}H_{24}Br_2O_2$: 382.0143. Found: 382.0148.

Monobromide 31. A procedure from Taylor was adapted. In a 15-mL flask flushed with nitrogen were combined 80 mg of dibromide **30** and 3 mL of anhydrous ether, the solution was cooled to −78 °C, and 480 μL (1.3 M) of MeLi–LiBr complex in ether (3 equiv) was added over 2 min. The reaction was stirred for 3 h and then quenched by dropwise addition of water to the −78 °C solution. The solution was then diluted with ether and water, and the layers were separated. The organic layer was dried ($MgSO_4$), filtered, and stripped to yield 46 mg (70%) of the crude monobromide: 80-MHz ^1H NMR ($CDCl_3$) δ 0.9 (m, 3 H), 1.1–1.8 (m, 16 H), 3.0 (dd, 1 H), 3.3–4.1 (m, 4 H), 4.6 (m, 1 H).

Cyclopropylcarbinol 32. In a 50-mL flask were combined 1.7 g of THP ether, 50 mL of methanol, and a catalytic amount of *p*-toluenesulfonic acid. The solution was stirred for 24 h at 0 °C at which time TLC showed consumption of starting material. The reaction was diluted with saturated bicarbonate solution and ether. The layers were separated, and the aqueous layer was extracted once with ether. The combined organic layers were washed once with brine, dried ($MgSO_4$), filtered, and stripped to give 1.21 g (98%) crude alcohol. Purification was performed on a Whatman Magnum 10 Column (10% EtOAc/hexane): 80-MHz ^1H NMR ($CDCl_3$) δ 0.9 (m, 3 H), 1.1–1.7 (m, 10 H), 3.0 (dd, 1 H), 3.6 (br dd, 2 H).

Anal. Calcd for $C_9H_{17}Br_3$: C, 48.88; H, 7.75. Found: C, 48.97; H, 7.74.

Cyclopropanecarboxaldehyde 33. In a 25-mL flask under nitrogen were combined 40 mg of pyridinium chlorochromate (2 equiv), 0.7 mg of sodium acetate (10 mol %), and 1 mL of methylene chloride. Alcohol **32** (20 mg) in 2 mL of methylene chloride was added in one portion. After the mixture was stirred for 2.5 h, TLC showed only a trace starting material. This trace still remained even after 10 h. The reaction was diluted with ether and passed through a Florisil column (100% ether). The solvent was stripped to give 18.8 mg (95%) of essentially pure aldehyde: 80-MHz ^1H NMR ($CDCl_3$) δ 0.9 (m, 3 H), 1.2–1.8 (m, 9 H), 2.0 (m, 1 H), 3.6 (m, 1 H), 9.6 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.97, 22.55, 28.26, 28.5, 29.69 (2 C), 31.45, 38.59, 198.56.

Methyl 9-Bromononanoate. Into a 200-mL three-neck flask were placed 10 g of 9-bromononanoic acid, 100 mL of methanol, and approximately 1.5 mL of sulfuric acid. The solution was refluxed under N_2 for 10 h, cooled, and then diluted with ether and water. The aqueous layer was extracted once with ethyl acetate. The combined organic layers were washed once with sodium bicarbonate solution, dried ($MgSO_4$), filtered, and stripped. Column chromatography (neutral alumina, 50% ether/hexane) gave the desired product in fair yield: 80-MHz ^1H NMR ($CDCl_3$) δ 1.2–2.1 (m, 12 H), 2.3 (t, 2 H), 3.4 (t, 2 H), 3.7 (s, 3 H).

Phosphonium Salt of Methyl 9-Bromononanoate. Approximately 6 g of methyl 9-bromononanoate were dissolved in 100 mL of benzene. Triphenylphosphine (1.1 equival) was added and the solution refluxed for 2 days under nitrogen. Upon cooling, an oil separated. The oil was washed five times with benzene and dried over P_2O_5. The product failed to crystallize as had been previously reported.[18] Instead, the salt was the consistency of a thick syrup. For routine use, a stock solution of the phosphonium salt in THF was used: ^{31}P NMR ($CDCl_3$) δ 24.027.

Vinylcyclopropyl Bromide 26. Phosphonium salt (844 g, 3 equiv) in 5.8 mL of THF was placed in a 25-mL three-neck flask under nitrogen at 0 °C. Potassium *tert*-butoxide in THF (5.46 mL, 0.266 M) was added over 20 s. The resultant milky organic solution was stirred an addition 2 min.

To the above ylide solution was added 110 mg of aldehyde **33** in 2 mL of THF over 40 s; the milky orange color persisted. After approximately 7 min, the reaction was allowed to warm to room temperature. TLC at this time showed consumption of starting material. The reaction was quenched by the addition of wet ether. A small amount of water was added, and the layers were separated. The aqueous layer was extracted once with ethyl acetate. The combined organic layers were washed once with brine, dried ($MgSO_4$), filtered, and stripped. The crude mixture was treated with a small amount of hexane and filtered to remove unreacted phosphonium salt and other less soluble contaminants. The hexane was then stripped and the crude material passed through a column (Florisil, 2% ether/hexane, 0 °C) to give 100.2 mg (53%) of pure product. Only the cis-olefin was found: 250-MHz ^1H NMR ($CDCl_3$) δ 0.9 (m, 3 H), 1.3–1.7 (m, H), 2.1 (m, 2 H), 2.3 (t, 2 H, J = 7.3 Hz), 3.0 (dd, 1 H, J = 3.7 and 7.3 Hz), 3.7 (s, 3 H), 4.8 (ddt, 1 H, J = 10.8, 9.16, and 1.5 Hz), 5.4 (dtd, 1 H, J = 10.8, 7.3, and 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.61, 24.95, 26.25, 27.74, 28.59, 2..11 (4 or more C), 29.56, 30.73, 31.58, 34.11, 51.39, 129.62, 131.31, 174.26.

Ring Opening of 26. The silver ion ring-opening reaction of **26** is illustrative.

In a 10-mL flask were combined 30 mg of **26**, 665 μL of HOOH (350 equiv), and 1 mL of anhydrous ether at room temperature. $AgOCOCF_3$ (900 mg, 50 equiv) was added and the solution stirred 15 min. Another 50 equiv of silver salt was added, and after 20 min the reaction was diluted with ether and sodium bicarbonate solution. The layers were separated, and the organic layer washed once with brine. The organic layer was cooled to 0 °C and treated with an excess of triphenylphosphine. The solution was swirled as it was allowed to warm to room temperature over 30 min. The solution was then dried ($MgSO_4$), filtered, and stripped. The product was taken up in 0.27% isopropyl alcohol/hexane for HPLC separation.

HPLC of Hydroxymethyl Linoleates. Separations were carried out on a Waters 10-μm Porasil 30-cm column protected by a 5-cm guard column. The eluting solvent was 0.27% isopropyl alcohol in hexane. Omnisolvents were filtered and used without further purification. Triphenylphosphine oxide was periodically washed from the column with a 10% isopropyl alcohol/hexane solution.

For preparative work, the fractions were simply collected into cold flasks, stripped, and then vaccuum pumped.

Hydrogenation of Hydroxymethyl Linoleates. A small amount of hydroxymethyl linoleate (0.25 g to 2 mg) was dissolved in approximately 25 mL of methanol. This was placed in a Parr shaker with a catalytic amount of palladium on carbon and charged with 30 lb of hydrogen gas. After shaking for 30 min, the solution was filtered and stripped to yield the hydroxymethyl stearates as a white solid.

Silylation of Hydroxymethyl Stearates. To the hydroxymethyl stearates in a 25-mL flask were added 50 μL of high-purity pyridine, 50 μL of hexamethylsilazane, and 1 drop of trimethylsilyl chloride. The solution was swirled for a minute of two and was then ready for mass spectral analysis.

GC/MS Analysis. The trimethylsiloxy ethers were analyzed under the following conditions: injection port, 240 °C; column temperature, 220 °C isothermal; He flow rate, 20 mL/min. Injections of 1 μL were used. Fragmentation patterns found are as follows: 9-substitution, m/e 259.4, 229.5; 11-substitution, m/e 287.5, 201.4; 13-substitution, m/e 315.5, 173.3.

Supplementary Material Available: Additional analytical data including combustion analyses of **10**, **12**, and **19** and NMR data of fatty acid hydroperoxides and alcohols (8 pages). Ordering information is given on any current masthead page.