Acid Catalysis of a Linoleic Acid Hydroperoxide: Formation of Epoxides by an Intramolecular Cyclization of the Hydroperoxide Group†

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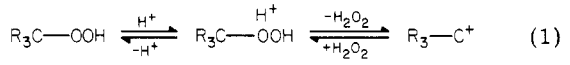
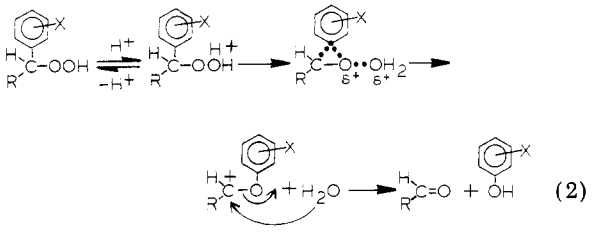
Acid catalysis (0.1 M H_2SO_4) of (13*S*)-(9*Z*,11*E*)-13-hydroperoxy-9,11-octadecadienoic acid (**1**) in methanol–water (9:1) did not afford appreciable yields of anticipated products, hexanal and (*Z*)-12-oxo-9-dodecenoic acid, via the known Hock rearrangement of hydroperoxides. Instead, intramolecular rearrangement of the 13-hydroperoxide into 12,13-epoxides, accompanied by solvent substitution, was the primary course of reaction (all products were isolated after conversion to methyl esters). Three isomeric methyl (*Z*)-12,13-epoxy-11-methoxy-9-octadecenoates were isolated in 20.2 mol % yield; methyl (11*R*,12*R*,13*S*)-(*Z*)-12,13-epoxy-11-methoxy-9-octadecenoate (**2a**) comprised 81% of the three. The stereoselectivity observed in the formation of **2a** implied anchimeric assistance by the epoxide group in substitution by methanol. Kinetic evidence, as well as a 20.4 mol % yield of stereoisomers of methyl (*E*)-13-hydroxy-9,12-dimethoxy-10-octadecenoates, was indicative of intermediate (*E*)-12,13-epoxy-9-methoxy-10-octadecenoic acids. These allylic epoxides could not be isolated, presumably because they solvolyzed rapidly in the presence of acid. On the other hand, the nonallylic epoxides **2a–c** solvolyzed more slowly. The following reaction mechanism is proposed: (a) a conjugate acid forms by addition of a proton to a hydroperoxy group; (b) electrophilic attack on C-12 by a partially positive-charged α-oxygen of the hydroperoxy group affords a 12,13-epoxy-9,11-allylic cation; (c) C-9 or C-11 undergoes substitution from methanol; (d) the products of substitution, isomeric epoxymethoxyoctadecenoic acids, are solvolyzed further to hydroxydimethoxyoctadecenoic acids. The possibility that heterolysis of **1**, as well as of other hydroperoxides of polyunsaturated fatty acids, may have significance in biological transformations is discussed.

Acid treatment of organic hydroperoxides readily initiates heterolytic cleavage of the hydroperoxide moiety. Formation of a conjugate acid with the hydroperoxide at the oxygen either α or β to carbon has been theorized to cause heterolysis. With certain hydroperoxides, H_2O_2 and product(s) originating from reaction of a carbonium ion with a nucleophile indicated the occurrence of protic attack at the α-oxygen[1] (eq 1). When the R substituents were



(1)

substantially electron-releasing, this type of conversion became important. However, for most organic hydroperoxides the reactions originating from a conjugate acid of the β-oxygen predominated, and these led to an irreversible O–O heterolysis and carbon to oxygen rearrangement[1,2] as shown by the migration of an aryl group in eq 2. The



(2)

migratory aptitude of this kind of rearrangement was greater for vinyl and aryl groups, particularly aryl groups with substituents able to sustain a positive charge, than for H and alkyl moieties.[1,3] Rearrangement occurred without prior O–O bond cleavage, and this evidence has been cited to support the concerted oxy bridge mechanism.[4] Thus, an electron-deficient or incipiently positive α-oxygen, initiated by the conjugate acid, promoted the carbon to oxygen transfer.

Application of the latter rearrangement to acid heterolysis of (13*S*)-(9*Z*,11*E*)-13-hydroperoxy-9,11-octadecadienoic acid (**1**) predicted a preferential migration of the unsaturation rather than the alkyl chain, affording hexanal and (*Z*)-12-oxo-9-dodecenoic acid. Acid treatment of fatty hydroperoxides,[5,6] including **1**,[6] has provided evidence for this type of rearrangement with cleavage. In this study we also report evidence for the expected rearrangement by treatment of **1** with acid in CH_3OH–H_2O solvent; however, this reaction was relatively unimportant. Instead, a carbon to oxygen rearrangement occurred without carbon–carbon cleavage. The oxy bridge, long proposed as a transition state, was trapped as an epoxide group, affording isomeric epoxymethoxyoctadecenoic acids by further substitution from methanol solvent.

Experimental Section

General Methods. Samples of **1** were prepared by oxidation of linoleic acid (Nu-Chek Prep) with soybean lipoxygenase (Sigma) followed by column chromatography of the product.[7] Similarly, 1-^{14}C-labeled **1** was obtained on a smaller scale from purified [1-^{14}C]linoleic acid (Radiochemical Centre, Amersham, England). The [1-^{14}C]linoleic acid (57 μCi/μmol) was purified by column chromatography (0.9 × 12.5 cm) with SilicAR CC4 (Mallinkckrodt) by stepwise elution utilizing 10%, 15%, 20%, and 25% ether in hexane. The specific activity of purified [1-^{14}C]linoleic acid was adjusted to 1.17 μCi/μmol prior to preparation of **1** by the procedure above.

In a kinetic experiment, [1-^{14}C]labeled **1** (3.2 mM) was reacted with 0.100 M H_2SO_4 in CH_3OH/H_2O (9:1 v/v) at 25 °C. Aliquots of the reaction mixture were transferred at various times to a

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‡ The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

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volume of H_2O and $CHCl_3$ sufficient to achieve a $CHCl_3/CH_3OH/H_2O$ (2:1:1) mixture. The $CHCl_3$ layer was recovered and washed twice with a half volume of H_2O. The compounds recovered from $CHCl_3$ were esterified with diazomethane and then applied to thin-layer chromatography (TLC) plates (ca. 0.075 μCi/application) for separation. Radioactivity of the separated components was recorded with a Berthold LB 2760 TLC scanner.

The reaction rate of **1** (0.2 mM) in CH_3OH/H_2O (76.03:23.97, w/w) was determined at various HCl concentrations of known Hammett acidity (H_0).[8] Rate constants (k) were determined from the rate of loss of conjugated diene absorption at 233 nm[9] by utilizing a Beckman DB spectrophotometer and a 1-mm cell maintained at 25 °C with a water-jacketed cell compartment.

For product isolation and characterization, 0.36 g of **1** (3.2 mM) was treated with 0.10 M H_2SO_4 in CH_3OH/H_2O (9:1 v/v) at room temperature for 1 h. Products were extracted by $CHCl_3/H_2O$ by using the procedure described above, and then esterified with diazomethane. After esterification the components were isolated by sequential column chromatography and high-performance liquid chromatography (HPLC).

Chromatography. Products were fractionated by column chromatography with a 2.5-cm-i.d. column containing 50 g of SilicAR CC4. Elution was stepwise with 0.25 L each of 10% and 20% ether, 0.3 L each of 25% and 30% ether, 0.25 L each of 40% and 50% ether in hexane, and 0.2 L of ether. The elution volumes (in liters) of the components were as follows: **1** and **2a,b**, 0.51–0.65; **2c** and **10**, 0.65–0.8; **4**, 0.99–1.14; **3** and **5a–d**, 0.99–1.43; **6a–c** and **7–9**, 1.43–1.8.

HPLC was performed on a 9.4 × 250 mm column packed with 10-μm silicic acid (Whatman, Inc.) and eluted with hexane/acetone. Elution times (in minutes) with hexane/acetone (94:6) at a 3.0 mL/min delivery rate were as follows: **2b**, 12; **2a**, 14; **2c**, 18; **10**, 20; **1**, 27; **4**, 32.5; **5a**, 34.3; **5b**, 39.5; **5c**, 41; **5d**, 45; **3**, 66; **6a**, 87; **6b**, 104; **6c**, 110; **7**, 141; **8** and **9**, 153. Most products required two or three preparative separations to achieve purity, with the solvent being adjusted between 3% and 6% acetone for maximum separation.

TLC was performed on 0.25 mm × 5 × 20 cm E. Merck precoated silica plates (60 F-254) by utilizing hexane/ether/acetone (33:4:3) as the developing solvent. Three general classes of compounds were readily separated: **2a–c** (R_f 0.47–0.69), **1** (methyl ester, R_f 0.40), **3–9** (R_f 0–0.27). Preparative TLC of **11** and **12** was performed with 0.5 mm × 20 × 20 cm silica gel G plates with hexane/acetone/ether (5:3:2) as the solvent.

Spectral Methods. Optical rotations were measured in a 10-cm microcell (CH_3OH solution at the designated concentration in g/100 mL) with a Perkin-Elmer Model 241 polarimeter. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 621 spectrophotometer, and absorptions were described in terms of frequency (reciprocal centimeters), intensity, and assignment in that order with the following abbreviations: w, weak; m, medium; s, strong; br, broad. ^{1}H NMR spectra were recorded ($CDCl_3$ solution) with either a Varian XL-100 or a Bruker WM-300. The signals are described in terms of parts per million (δ) from tetramethylsilane (δ 0.00), multiplicity, relative intensity, coupling constants (hertz), and location of proton by carbon number in that order with the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; app, apparent multiplicity partially obscured. Mass spectra were obtained with a gas–liquid chromatograph operating in tandem with a Kratos MS-30 mass spectrometer utilizing an ionizing voltage of 70 eV. Gas–liquid chromatography employed a 4 mm × 0.9 m column packed with 3% OV-1 on Gas-Chrom Q with temperature programming from 160 to 250 °C at 2 °C/min. The chemical ionization (CI) mass spectrum of **10** was obtained at ca. 150 eV with a NH_3 source pressure of about 0.5 torr. For mass spectrometry trimethylsilyloxy derivatives were prepared with hexamethyldisilazane/trimethylchlorosilane/pyridine (2:1:1).

Methyl (11*R*,12*R*,13*S*)-(*Z*)-12,13-epoxy-11-methoxy-9-octadecenoate (2a): $[\alpha]^{25}_D$ −56.8°, $[\alpha]^{25}_{578}$ −59.2°, $[\alpha]^{25}_{546}$ −67.2°, $[\alpha]^{25}_{436}$ −113.6°, $[\alpha]^{25}_{365}$ −178.0° (*c* 0.50); IR (CS_2) 2815 (m, OCH_3), 1095 (s, ether), 890 (m) and 900 (m) (*trans*-epoxide), 758 (w, *Z* olefin) cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 5.69 (dt, 1, J = 11, 7 Hz, H9), 5.32 (dd, 1, J = 11, 9 Hz, H10), 3.76 (dd, 1, J = 5.5, 9 Hz, H11), 3.36 (s, 3, C-11 OCH_3), 2.77 (dd, 1, J = 5.5, 2 Hz, H12), 2.74 (m, 1, H13), 2.08 (m, 2, H8); mass spectrum, *m/z* (relative intensity) 309 (1, $M^+ - OCH_3$), 240 (7, $M^+ - CH_3(CH_2)_4CHO$), 227 (62, $^+CHOCH_3CH{=}CH(CH_2)_7COOCH_3$), 209 (3, 240 − OCH_3), 195 (4, 227 − CH_3OH), 163 (15, 227 − 2 CH_3OH), 97 (85, $CH_3(CH_2)_4CH{=}CH^+$), 84 (22, $CH_3(CH_2)_4CH^+$), 71 (100, $CH_3(CH_2)_4^+$).

Methyl (11*S*,12*R*,13*S*)-(*Z*)-12,13-epoxy-11-methoxy-9-octadecenoate (2b): $[\alpha]^{25}_D$ +20.8°, $[\alpha]^{25}_{578}$ +22.3°, $[\alpha]^{25}_{546}$ +25.3°, $[\alpha]^{25}_{436}$ + 46.4°, $[\alpha]^{25}_{365}$ +80.4° (*c* 0.26); IR (CS_2) 2815 (m), 1090s, 890 (m) and 900 (w), 740 (w) cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 5.74 (dt, 1, J = 11, 7 Hz, H9), 5.28 (dd, 1, J = 11, 9 Hz, H10), 4.03 (dd, 1, J = 4, 9 Hz, H11), 3.32 (s, 3, C-11 OCH_3), 2.92 (dt, 1, J = 2, 6 Hz, H13), 2.74 (dd, 1, J = 2, 4 Hz, H12), 2.08 (m, 2, H8); mass spectrum, within experimental error the same as **2a**.

Methyl (12*S*,13*S*)-(*Z*)-12,13-epoxy-11-methoxy-9-octadecenoate (2c): $[\alpha]^{25}_D$ +9.9°, $[\alpha]^{25}_{578}$ +10.3°, $[\alpha]^{25}_{546}$ +11.6°, $[\alpha]^{25}_{436}$ +20.9°, $[\alpha]^{25}_{365}$ +34.7° (*c* 0.23); IR (CS_2) 2805 (m), 1085 (s), 842 (m) and 852 (m) (*cis*-epoxide), 745 (w) cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 5.72 (dt, 1, J = 11, 7 Hz, H9), 5.32 (dd, 1, J = 11, 8.5 Hz, H10), 3.80 (dd, 1, J = 10, 8.5 Hz, H11), 3.38 (s, 3, C-11 OCH_3), 2.98 (dd, 1, J = 4, 10 Hz, H12), ca. 2.92 (app, m, H13), 2.08 (m, 2, H8); mass spectrum, within experimental error the same as **2a**.

Methyl (11*R*,12*R*,13*S*)-(*Z*)-12,13-Epoxy-11-hydroxy-9-octadecenoate (3). The spectral data were the same as those reported previously.[10] Although the specific rotation vs. wavelength plotted a similar plain, negative curve as reported,[10a] the magnitude of the specific rotations were somewhat larger, indicating improved chiral purity in this study: $[\alpha]^{25}_D$ −49.5°, $[\alpha]^{25}_{578}$ −51.4°, $[\alpha]^{25}_{546}$ −57.9°, $[\alpha]^{25}_{436}$ −97.7°, $[\alpha]^{25}_{365}$ −151.1° (*c* 0.16).

Methyl (11*R*,12*R*,13*R*)-(*Z*)-12-hydroxy-11,13-dimethoxy-9-octadecenoate (4): $[\alpha]^{25}_D$ −10.7°, $[\alpha]^{25}_{578}$ −11.3°, $[\alpha]^{25}_{546}$ −13.2°, $[\alpha]^{25}_{436}$ −24.5°, $[\alpha]^{25}_{365}$ −42.6° (*c* 0.63); IR (CS_2) 3555 (m, free OH), 3460 (br w, H-bonded OH), 2810 (m), 1100 (s), 756 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dtd, 1, J = 11.2, 7.4, 0.7 Hz, H9), 5.27 (ddt, 1, J = 11.2, 9.7, 1.6 Hz, H10), 3.98 (ddd, 1, J = 6.0, 9.7, 0.7 Hz, H11), 3.56 (m, 1, H12; ^{1}H decoupled by irradiation of OH, dd, J = 6.0, 5.2 Hz), 3.36 (s, 3, C-11 OCH_3), 3.28 (s, 3, C-13 OCH_3), 3.13 (m, 1, H13), 2.48 (br s, 1, C-12 OH), 2.10 (m, 2, H8); mass spectrum (12-trimethylsilyloxy derivative), *m/z* (relative intensity) 329 (0.6, $M^+ - CHOCH_3(CH_2)_4CH_3$), 309 (5, $M^+ - CH_3(CH_2)_4 - 2CH_3OH$), 300 [17, 227 + $Si(CH_3)_3$],[11] 227 (6, $^+CHOCH_3CH{=}CH(CH_2)_7COOCH_3$), 217 (100, M^+ − 227), 185 (7, M^+ − 227 − CH_3OH), 115 (32, $^+CHOCH_3(CH_2)_4CH_3$), 73 [87, $^+Si(CH_3)_3$], 71 [63, $CH_3(CH_2)_4^+$].

Methyl (12*S*,13*S*)-(*E*)-13-hydroxy-9,12-dimethoxy-10-octadecenoate (5a): $[\alpha]^{25}_D$ −12.3°, $[\alpha]^{25}_{578}$ −13.4°, $[\alpha]^{25}_{546}$ −15.6°, $[\alpha]^{25}_{436}$ −25.7°, $[\alpha]^{25}_{365}$ −40.2° (*c* 0.090); IR (CS_2) 3570 (m), 3460 (br w), 2815 (m), 1095 (s), 975 (m) (*E* olefin) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (dd, 1, J = 15.7, 7.3 Hz, H10), 5.41 (dd, 1, J = 15.7, 7.7 Hz, H11), 3.55 (dt, 1, J = 7.3, 6.5 Hz, H9), 3.47 (m, 1, H13), 3.36 (app, dd, 1, J = 7.7, 7.7 Hz, H12), 3.29 (s, 3, C-12 OCH_3), 3.26 (s, 3, C-9 OCH_3), 2.66 (br s, 1, C-13 OH); mass spectrum (13-trimethylsilyloxy derivative), *m/z* (relative intensity) 240 (11, $M^+ - 173 - CH_3O$), 201 [1, $^+CHOCH_3(CH_2)_7COOCH_3$], 173 [100, $^+CHOSi(CH_3)_3(CH_2)_4CH_3$], 73 (59).

Methyl (12*S*,13*S*)-(*E*)-13-hydroxy-9,12-dimethoxy-10-octadecenoate (5b) is epimeric with **5a** at C-9: $[\alpha]^{25}_D$ +10.1°, $[\alpha]^{25}_{578}$ +11.2°, $[\alpha]^{25}_{546}$ +14.2, $[\alpha]^{25}_{436}$ +24.4°, $[\alpha]^{25}_{365}$ +38.1° (*c* 0.20); IR (CS_2) indistinguishable from IR of **5a**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dd, 1, J = 15.7, 7.5 Hz, H10), 5.40 (dd, 1, J = 15.7, 7.9 Hz, H11), 3.54 (dt, 1, J = 7.5, 6.5 Hz, H9), 3.46 (m, 1, H13), 3.35 (app, dd, 1, J = 7.9, 7.9 Hz, H12), 3.31 (s, 3, C-12 OCH_3), 3.27 (s, 3, C-9

(8) H_0 values for various concentrations of HCl in CH_3OH/H_2O (76.03:23.97, wt/wt) were determined by: Salomaa, P. *Acta Chem. Scand.* **1957**, *11*, 125.

(9) From our determinations of the molar absorptivity of **1**, many literature values are too high. The cited value, ϵ 24 500, most closely approximated ours: Johnston, A. E.; Zilch, K. T.; Selke, E.; Dutton, H. J. *J. Am. Oil Chem. Soc.* **1961**, *38*, 367.

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(11) For a discussion of fragment ion plus $Si(CH_3)_3$, see: Kleiman, R.; Spencer, G. F. *J. Am. Oil Chem. Soc.* **1973**, *50*, 31.

OCH_3), 2.67 (br s, 1, C-13 OH); mass spectrum (13-trimethylsilyloxy derivative), the same as 5a within experimental error.

Methyl (12*R*,13*S*)-(*E*)-13-hydroxy-9,12-dimethoxy-10-octadecenoate (5c): $[\alpha]^{25}_D$ −3.8°, $[\alpha]^{25}_{578}$ −4.6°, $[\alpha]^{25}_{546}$ −5.8°, $[\alpha]^{25}_{436}$ −13.1°, $[\alpha]^{25}_{365}$ −22.7° (*c* 0.26); IR (CS_2) 3575 (m), 3460 (br m), 2815 (m), 1095 (s), 975 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (dd, 1, *J* = 15.7, 7.5 Hz, H11), 5.50 (dd, 1, *J* = 15.7, 7.1 Hz, H10), 3.71 (app, dt, 1, *J* = 3.6, ca. 6 Hz, H13), 3.55 (app, dt, 1, *J* = 7.1, 6.4 Hz, H9), 3.52 (app, dd, 1, *J* = 7.5, 3.6 Hz, H12), 3.28 (s, 3, C-12 OCH_3), 3.25 (s, 3, C-9 OCH_3), 2.13 (br s, 1, C-13 OH); mass spectrum (13-trimethylsilyloxy derivative), the same as **5a** within experimental error.

Methyl (12*R*,13*S*)-(*E*)-13-hydroxy-9,12-dimethoxy-10-octadecenoate (5d) is epimeric with **5c** at C-9: $[\alpha]^{25}_D$ −37.7°, $[\alpha]^{25}_{578}$ −38.8°, $[\alpha]^{25}_{546}$ −44.1°, $[\alpha]^{25}_{436}$ −74.3°, $[\alpha]^{25}_{365}$ −114.5° (*c* 0.36); IR (CS_2) indistinguishable from IR of **5c**, but different in fine structure from IR of **5a** and **5b**; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (dd, 1, *J* = 15.7, 7.4 Hz, H11), 5.49 (dd, 1, *J* = 15.7, 6.9 Hz, H10), 3.70 (dt, 1, *J* = 3.6, 6.3 Hz, H13), 3.54 (app, dt, 1, *J* = 6.9, 6.4 Hz, H9), 3.50 (dd, 1, *J* = 7.6, 3.6 Hz, H12), 3.30 (s, 3, C-12 OCH_3), 3.26 (s, 3, C-9 OCH_3), 2.14 (br s, 1, C-13 OH); mass spectrum (13-trimethylsilyloxy derivative), the same as **5a** within experimental error.

Methyl (13*S*)-(*E*)-13-hydroxy-9,10-dimethoxy-11-octadecenoate (6a) was one of three diastereomers (**6a–c**) characterized: $[\alpha]^{25}_D$ +28.1°, $[\alpha]^{25}_{578}$ +29.6°, $[\alpha]^{25}_{546}$ +33.8°, $[\alpha]^{25}_{436}$ +58.2°, $[\alpha]^{25}_{365}$ +91.6° (*c* 0.26); IR (CS_2) 3600 (w), 3440 (br m), 2815 (m), 1105 and 1088 (s), 973 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (dd, 1, *J* = 15.7, 6.3 Hz, H12), 5.58 (dd, 1, *J* = 15.7, 7.3 Hz, H11), 4.15 (app, dt, 1, *J* = 6.3, 6.4 Hz, H13), 3.58 (dd, 1, *J* = 7.3, 3.7 Hz, H10), 3.40 (s, 3, C-10 OCH_3), 3.27 (s, 3, C-9 OCH_3), 3.19 (app, dt, 1, *J* = 7.9, 3.7 Hz, H9); mass spectrum (13-trimethylsilyloxy derivative), *m/z* (relative intensity) 243 (21, M^+ − 201), 240 (7, M^+ − 173 − CH_3O), 201 [100, $^+CHOCH_3(CH_2)_7COOCH_3$], 173 [28, $^+CHOSi(CH_3)_3(CH_2)_4CH_3$], 169 (29, 201 − CH_3OH), 154 (17), 137 (37, 201 − $2CH_3OH$), 73 (87).

Methyl (13*S*)-(*E*)-13-hydroxy-9,10-dimethoxy-11-octadecenoate (6b): $[\alpha]^{25}_D$ −2.8°, $[\alpha]^{25}_{578}$ −4.2°, $[\alpha]^{25}_{546}$ −5.6°, $[\alpha]^{25}_{436}$ −7.0°, $[\alpha]^{25}_{365}$ −9.9° (c 0.071); IR (CS_2) 3600 (w), 3440 (br m), 2815 (m), 1093 (s), 970 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (dd, 1, *J* = 15.7, 6.4 Hz, H12), 5.55 (ddd, 1, *J* = 15.7, 7.4, 0.8 Hz, H11), 4.15 (app, dt, 1, *J* = 6.4, 6.4 Hz, H13), 3.62 (dd, 1, *J* = 7.4, 5.3 Hz, H10), 3.41 (s, 3, C-10 OCH_3), 3.29 (s, 3, C-9 OCH_3), 3.15 (app, dt, 1, *J* ≃ 5, 6.2 Hz, H9); mass spectrum (13-trimethylsilyloxy derivative), the same as **6a** within experimental error.

Methyl (13*S*)-(*E*)-13-hydroxy-9,10-dimethoxy-11-octadecenoate (6c): $[\alpha]^{25}_D$ −18.0°, $[\alpha]^{25}_{578}$ −19.2°, $[\alpha]^{25}_{546}$ −20.4°, $[\alpha]^{25}_{436}$ −34.1°, $[\alpha]^{25}_{365}$ −51.5° (*c* 0.17); IR (CS_2) indistinguishable from IR of **6a**; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (dd, 1, *J* = 15.7, 6.3 Hz, H12), 5.58 (ddd, 1, *J* = 15.7, 7.4, 0.9 Hz, H11), 4.15 (app, dt, 1, *J* = 6.3, ca. 6.4 Hz, H13), 3.57 (dd, 1, *J* = 7.4, 3.7 Hz, H10), 3.40 (s, 3, C-10 OCH_3), 3.29 (s, 3, C-9 OCH_3), 3.18 (app, dt, 1, *J* ≃ 8, 3.7 Hz, H9); mass spectrum (13-trimethylsilyloxy derivative), the same as **6a** within experimental error.

Methyl (*Z*)-12,13-dihydroxy-11-methoxy-9-octadecenoate (7): IR (CS_2) 3555 (m), 3490 (m), 2815 (m), 1090 (s), 750 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (dt, 1, *J* = 11.2, ca. 7.5 Hz, H9), 5.37 (dd, 1, *J* = 11.2, 9.6 Hz, H10), 4.11 (dd, 1, *J* = 5.2, 9.6 Hz, H11), 3.62 (m, 1, H12), 3.45 (app, dt, 1, H13), 3.27 (s, 3, C-11 OCH_3), 2.39 and 2.70 (br s, 1 each, C-12 and C-13 OH), 2.10 (m, 2, H8); mass spectrum [12,13-bis(trimethylsiloxy) derivative], *m/z* (relative intensity) 300 [7, 227 + $Si(CH_3)_3$], 275 (45, M^+ − 227), 227 (2, $^+CHOCH_3CH{=}CH(CH_2)_7COOCH_3$), 185 [17, 275 − $(CH_3)_3SiOH$], 173 [26, $^+CHOSi(CH_3)_3(CH_2)_4CH_3$], 147 (9), 73 (100).

Methyl 11,13-dihydroxy-12-methoxy-9-octadecenoate (8): mass spectrum [11,13-bis(trimethylsiloxy) derivative], *m/z* (relative intensity) 285 [47, $^+CHOSi(CH_3)_3CH{=}CH(CH_2)_7COOCH_3$], 217 (24, M^+ − 285), 173 [21, $^+CHOSi(CH_3)_3(CH_2)_4CH_3$], 73 (100).

Methyl 12,13-dihydroxy-9-methoxy-10-octadecenoate (9): mass spectrum [12,13-bis(trimethylsiloxy) derivative], *m/z* (relative intensity) 329 (0.5, M^+ − 173), 298 (14, M^+ − 173 − CH_3O), 239 (2, M^+ − 173 − SiOH), 173 [100, $^+CHOSi(CH_3)_3(CH_2)_4CH_3$], 73 (97).

Methyl (*E*)-12-oxo-10-dodecenoate (10): IR (CS_2) 2720 (w, CHO), 1695 (s, CHO), 1640 (m, CH=CHCHO), 973 (m, *E* olefin) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 9.5 (d, 1, *J* = 7.5 Hz, H12), 6.85 (dt, 1, *J* = 16, 7 Hz, H10), 6.11 (dd, 1, *J* = 16, 7.5 Hz, H11), 2.31 (app, t, 4 H, H2, H9); mass spectrum (NH_3 CI), *m/z* (relative intensity) 244 (18, $M^+ + NH_4$), 241 (6), 227 (100, $M^+ + H$), 224 (16), 212 (29, $M^+ - CH_3OH + NH_4$), 209 (8), 195 (8, $M^+ - CH_3OH$), 166 (3, 195 − CHO), 149 (3), 98 (5), 81 (7).

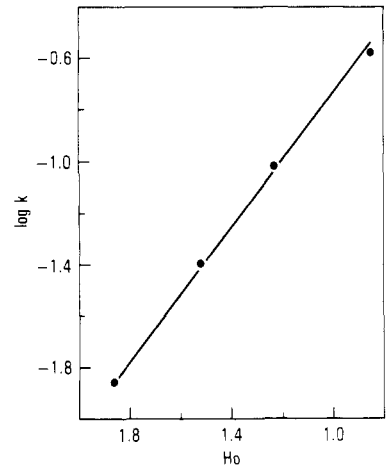


Figure 1. Correlation between H_0 and rate constants for acid catalysis of 1. Catalyzing acid was HCl in CH_3OH/H_2O (76.03:23.97, w/w), and the reaction mixture was held at 25 °C.

Methyl (9*S*,12*R*,13*S*)-(*E*)-9,13-Dihydroxy-12-methoxy-10-octadecenoate (11). Methyl (9*S*,12*S*,13*S*)-(*E*)-12,13-epoxy-9-hydroxy-10-octadecenoate (**13**) obtained by the procedure of van Os et al.[12] was solvolyzed with 7% BF_3 in methanol for 10 min at room temperature. Preparative TLC of the solvolysis products afforded separation into 76% **11** and 24% of the corresponding (9*S*,12*S*,13*S*) threo isomer (data not shown). ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (dd, 1, *J* = 15.7, 6.3 Hz, H10), 5.59 (dd, 1, *J* = 15.7, 8.0 Hz, H11), 4.16 (m, 1, H9), 3.69 (m, 1, H13), 3.51 (dd, 1, *J* = 8.0, 3.6 Hz, H12), 3.30 (s, 3, C-12 OCH_3), 2.10 (br d, 2, C-9 and C-13 OH).

Methyl (9*R*,12*R*,13*S*)-(*E*)-9,13-Dihydroxy-12-methoxy-10-octadecenoate (12). Methyl (9*R*,12*S*,13*S*)-(*E*)-12,13-epoxy-9-hydroxy-10-octadecenoate (**14**) was solvolyzed by the method described for formation of compound **11**, affording 79% **12** and 21% of the corresponding (9*R*,12*S*,13*S*) threo isomer (data not shown): ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (dd, 1, *J* = 15.7, 6.0 Hz, H10), 5.59 (dd, 1, *J* = 15.7, 8.0 Hz, H11), 4.16 (app, dd, 1, *J* = 6.0, 11.8 Hz, H9), 3.68 (m, 1, H13), 3.51 (dd, 1, *J* = 7.9, 3.7 Hz, H12), 3.28 (s, 3, C-12 OCH_3), 2.10 (br s, 2, C-9 and C-13 OH).

Results

Acid Catalysis. As measured by ultraviolet absorption at 233 nm, acid treatment of **1** in CH_3OH/H_2O (9:1) solution resulted in loss of conjugated diene. The reaction was apparent first order with respect to **1**. At a 0.1 M concentration, strong mineral acids such as HCl, H_2SO_4, and $HClO_4$ required less than 1 h at 25 °C for appreciable conversion to products, whereas several days were necessary with the weak organic acids citric and acetic. TLC separation of the esterified products revealed several components that were qualitatively similar regardless of the acid utilized for catalysis.

Since the results with various acids indicated general-acid catalysis, this assumption was tested. Accordingly, the rate of diene loss was measured as a function of H_0 (Figure 1). Although the HCl concentrations used were not large enough for the distinctive character of H_0 to become important, the plot of H_0 vs. log *k* was linear; whereas log C_{acid} vs. log *k* deviated from linearity.

Product Isolation. Acid-catalyzed reaction of **1** with 0.1 M H_2SO_4 in CH_3OH/H_2O (9:1 v/v) for 1 h at room

(12) van Os, C. P. A.; Vliegenthart, J. F. G.; Crawford, C. G.; Gardner, H. W. *Biochim. Biophys. Acta* **1982**, *713*, 173.

temperature consumed 94% of 1 and afforded at least 16 products. The products were converted to methyl esters prior to chromatographic isolation. The isolates were primarily three isomeric methyl (*Z*)-12,13-epoxy-11-methoxy-9-octadecenoates (20.2 mol %) and eight isomeric methyl hydroxydimethoxyoctadecenoates (28.8 mol %). Relatively minor isolates (less than 0.3 wt %) were not analyzed, but several additional products (totaling 6.1 mol %) were quantitatively significant enough to characterize. The total recovery after chromatography was 74 wt %; thus, the yields obtained may have been reduced owing to inadvertent losses. The loss of material was attributed to use of samples for analytical separations, column adsorption, and other losses normally encountered with sample manipulation. Additionally, some of the most polar products were not eluted by column chromatography, but they were comparatively minor as assessed by TLC of the total compared to TLC of the fractions isolated from column chromatography. Some of these very polar compounds were surmised to be certain isomers of methyl dihydroxymethoxyoctadecenoates and methyl trihydroxyoctadecenoates.

Epoxide Fatty Esters. Yields of epoxides (in mol %) were as follows: **2a**, 16.3; **2b**, 1.9; **2c**, 2.0; **3**, 2.3. Other than assignments of chirality, the structural features of these compounds readily were interpreted from spectral data.

A 13*S* stereoconfiguration was assigned to these 12,13-epoxides based on the configuration of the reactant, 1.[13] The chiralities of the substituents on C-11 and C-12 follow from structural analyses. Spectral data (^{1}H NMR and IR) showed that **2a,b** and **3** were *trans*-epoxides (12*R*,13*S*) and that **2c** was a *cis*-epoxide (12*S*,13*S*). The stereoconfiguration of the substituent at C-11 was determined from its erythro/threo isomerism relative to the C-12 epoxide. Since the spectral data for **3** in this study were essentially the same as those reported previously for the same compound,[10] this product is threo and, therefore, was assigned as 11*R*,12*R*,13*S*. The threo and erythro assignments of **2a** and **2b**, respectively, were based on a spectral comparison with their 11-hydroxy analogues, **3** and methyl (11*S*,12*R*,13*S*)-(*Z*)-12,13-epoxy-11-hydroxy-9-octadecenoate (**15**), respectively. The differences in H-11 chemical shift (**2a**, δ 3.76; **2b**, δ 4.03) and $J_{11,12}$ (**2a**, 5.5 Hz; **2b**, 4 Hz) were approximately the same in magnitude and direction as those reported for the corresponding 11-hydroxy analogues [**3**, δ 4.26, $J_{11,12}$ = 5 Hz; **15**, δ 4.63, $J_{11,12}$ = 3 Hz]. Additionally, the directions of the optical rotations of (−)-**2a** and (+)-**2b** corresponded to those observed for the 11-hydroxy analogues.[10a] An appropriate model was not available for **2c**, and thus the stereoconfiguration of its 11-methoxy derivative was not assigned.

Hydroxydimethoxy Fatty Esters. Compound **4** was isolated in 5.3 mol % yield. Other than its chirality assignment, the determination of structural features was without complication. Since **4** was also obtained directly from **2a** by overnight methanolysis, utilizing the same conditions as the acid-catalyzed reaction of **1**, the stereoconfiguration of **4** can be deduced. Acid solvolysis of epoxides inverts the carbon being substituted by the protic solvent;[14] therefore, the configuration 11*R*,12*R*,13*R* was implied.

Stereoisomers **5a–d** were isolated in 3.0, 2.7, 8.2, and 6.5 mol % yields in that order. These compounds are diastereomers and are all optically active; presumably each retains the original *S* configuration at C-13. However, configurations of the methoxyl groups at C-9 and C-12 differ; products with all four of the possible configurational combinations were formed. The ^{1}H NMR spectra of **5a–d** were characterized as two pairs with features similar to each other but different from the other pair. Accordingly, the ^{1}H NMR $J_{12,13}$ coupling constants (**5a**, 7.7 Hz; **5b**, 7.9 Hz; **5c,d**, 3.6 Hz) indicated that **5a,b** were threo (12*S*,13*S*) and **5c,d** were erythro (12*R*,13*S*).[15] These assignments were confirmed by methanolysis of previously characterized epoxides,[12] **13** and **14**, affording **11** and **12** in 76–79 mol % yield. The erythro configuration was expected from methanolysis of these *trans*-epoxides,[14,16] and thus $J_{12,13}$ values (**11**, 3.6 Hz; **12**, 3.7 Hz) confirmed that **5c,d** were erythro. Inasmuch as **11** and **12** differ only by their chirality at C-9, it follows that their ^{1}H NMR spectra were nearly identical. This result confirmed our contention that **5a,b** and **5c,d** were 9*R*/9*S* pairs, not necessarily in that order.

Only three stereoisomers of **6** (**6a–c**) were isolated in 1.6, 0.4, and 1.0 mol % yields, in that order. Because of the relatively small yield of the **6** isomers, it is conceivable that one of the four possible was either lost or not analyzed because of its low yield. HPLC analyses of the total product mixture revealed a fourth component migrating with the three isomers of **6**, indicating the presence of the missing isomer. A 13*S* chirality was assigned to the hydroxyl group of **6a–c** on the basis of the parent compound, **1**. One isomeric pair, **6a** and **6c**, afforded ^{1}H NMR spectra that were comparable in features, while the spectrum of **6b** was dissimilar from the other two. As observed with isomers of **5**, the ^{1}H NMR spectral differences between **6a**/**6c** vs. **6b** were surmised to be owing to erythro/threo isomerism of the 9,10-dimethoxyls. Although the differences in $J_{9,10}$ values (**6a** and **6c**, 3.7 Hz; **6b**, 5.3 Hz) were similar to those observed for $J_{12,13}$ of **5a–d**, the erythro/threo assignments may actually be the reverse of those assigned to **5** isomers.[17] In any case, the stereoconfiguration of the 9,10-dimethoxyls cannot be assigned with any confidence without the benefit of a known model compound(s).

Other Products. Products **7** and **10** were isolated in 1.6 and 1.9 mol % yields, respectively. These isolates were identified from spectral data without difficulty. No attempt was made to assess the chirality of **7**.

Compounds **8** and **9**, together amounting to 0.3 mol % yield, were tentatively identified by their mass spectra.

Reaction Kinetics. 1-^{14}C-Labeled **1** was utilized to follow the kinetics of both **1** disappearance and product formation by TLC–radiography (Figure 2). Plotted with time are (a) loss of **1**, (b) formation and subsequent loss of **2a–c**, and (c) formation of epoxide solvolysis products **4–9**. Because epoxide **3** could not be separated by TLC

(13) Hamberg, M. *Anal. Biochem.* **1971**, *43*, 515.

(14) Erythro and threo isomers are afforded from solvolysis of *trans*- and *cis*-epoxides, respectively: Swern, D. "Fatty Acids", 2nd ed.; Markley, K. S., Ed.; Interscience: New York, 1961; Part 2, p 1371.

(15) Because of H bonding between the 12-methoxyl and 13-hydroxyl, the erythro isomers, compared to threo, usually have a preponderance of rotamers with the methine protons in the gauche configuration. This results in smaller $J_{12,13}$ values for erythro than threo isomers. H bonding was affirmed by ^{1}H NMR of **5d** in an H-bonding solvent, deuterioacetone, which increased $J_{12,13}$ to 4.1 Hz compared to 3.6 Hz in $CDCl_3$. See: Kingsbury, C. A. *J. Org. Chem.* **1970**, *35*, 1319.

(16) In methanolysis of **13** and **14** to **11** and **12**, smaller yields (21–24 mol %) of the corresponding threo isomers were also isolated, indicating that substitution occurred to some extent by an S_N1 mechanism, a behavior not unexpected for solvolysis of an allylic epoxide.

(17) For non-hydrogen-bonding systems, such as the 9,10-dimethoxyls of **6a–c**, the preferred rotamers usually are determined by steric and electric dipole repulsion. With erythro isomers there usually is a preference for a trans alignment of the methine protons, causing their coupling constants to be larger than the corresponding values for threo isomers. See: Kingsbury, C. A.; Thornton, W. B. *J. Org. Chem.* **1966**, *31*, 1000 and references therein.

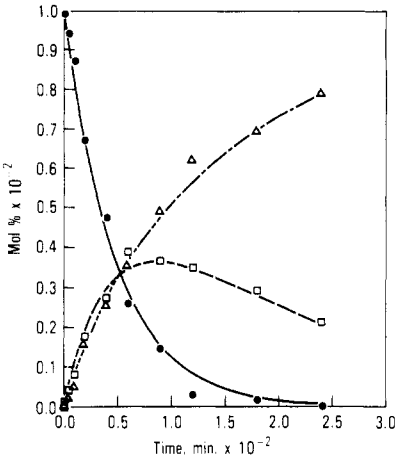
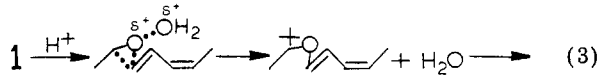


Figure 2. Kinetics of acid-catalyzed reaction of 1: disappearance of 1, ●; formation of epoxides **2a–c**, □; formation of epoxide solvolysis products, △. Radiolabeled 1 was used as a tracer to obtain the mole percent yield of TLC-separated products and 1.

from the cluster of solvolysis products, **3** was included in the solvolysis products category in Figure 2. From product analysis (above), it can be surmised that **3** contributed little (ca. 2–3 mol % after 1 h) to the total solvolysis product analyses.

Discussion

Ordinarily, treatment of organic hydroperoxides with acid results in carbon–carbon bond cleavage via a carbon to oxygen rearrangement.[1,2] There are many known examples of this type; e.g., acid treatment of cumene hydroperoxide afforded phenol and acetone.[18] The expected products from 1 are hexanal, which has been demonstrated,[6] and (*Z*)-12-oxo-9-dodecenoic acid (eq 3). No



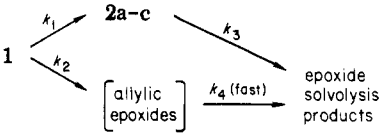
(3)

Hexanal
(Z)-12-Oxo-9-dodecenoic acid

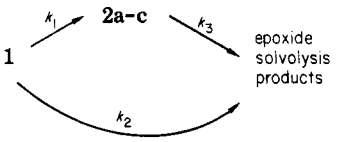
attempt was made to isolate hexanal in this study; but after esterification, **10** was isolated in small yield. It is a reasonable assumption that the expected (*Z*)-12-oxo-9-dodecenoic acid was isomerized readily by acid to **10** (free fatty acid). In contrast to the present study, the formation of hexanal and **10** was favored substantially by treatment of 1 (methyl ester) with a Lewis acid in aprotic solvent.[19]

The major products from acid catalysis of 1 in CH_3OH–H_2O were isomeric epoxymethoxyoctadecenoic and hydroxydimethoxyoctadecenoic acids. The kinetics shown in Figure 2 for epoxides **2a–c** are indicative of their sequential formation and decline. After the reaction mixture had been allowed to stand overnight, no epoxides could be detected, but instead, the products consisted almost wholly of compounds that can be described as epoxide solvolysis products, mainly hydroxydimethoxyoctadecenoic acids. However, the early appearance and rapid rate of formation of the putative epoxide solvolysis products did not appear to conform with the kinetics expected of a series or sequential reaction (Figure 2). Additionally, the structures of the major solvolysis compounds, **5a–d** and **6a–c**, were not in accord with those expected from methanolysis of **2a–c**. These data can be explained by invoking intermediate epoxide(s) that were easily solvolyzed by the conditions employed. The allylic epoxide, (13*S*)-(*E*)-12,13-epoxy-9-methoxy-10-octadecenoic acid (four stereoisomers possible), would be an attractive possibility. Such epoxides would be particularly labile to acid, and methanolysis would lead to isomers of **5** by a straightforward route. An attempt to isolate the postulated intermediate epoxides early in the reaction (10 min) was unsuccessful. The 10-min reaction products, extracted by the usual $CHCl_3$–H_2O method, were subjected directly to HPLC separation. Previous work with the allylic epoxides **13** and **14**[10a] have shown that they are very susceptible to acid solvolysis, including chromatography with SilicAR CC4 (pH 4 silicic acid); however, these allylic epoxides were sufficiently stable to separate by the HPLC system used here.[12] The instability in 0.1 M H_2SO_4 of the allylic epoxides postulated here as intermediates is not unexpected. On the other hand, the nonallylic epoxides **2a–c** were comparatively more stable under the conditions employed.

In accordance with the postulated intermediacy of both allylic and nonallylic epoxides, the following kinetics are suggested:



Since k_4 was relatively large, the kinetics simplify to



By use of this kinetic scheme, the experimental data points were used to computer generate the curves shown in Figure 2. The best-fit rate constants (min^{-1}) were computed as follows: k_1, 0.0122; k_2, 0.008 38; k_3, 0.005 61.

Figure 1 afforded further insight into the reaction mechanism. A plot of log k vs. H_0 may be indicative of the mechanism for acid solvolysis. According to Rochester,[20] a slope of the plot >0.8 can be suggestive of an A-1 mechanism (actual slope = 1.3) (eq 4–6). Consistent with

$$S + H^+ \rightleftharpoons SH^+ \text{ (fast, preequilibrium)} \quad (4)$$

$$SH^+ \rightarrow A^+ \text{ (slow)} \quad (5)$$

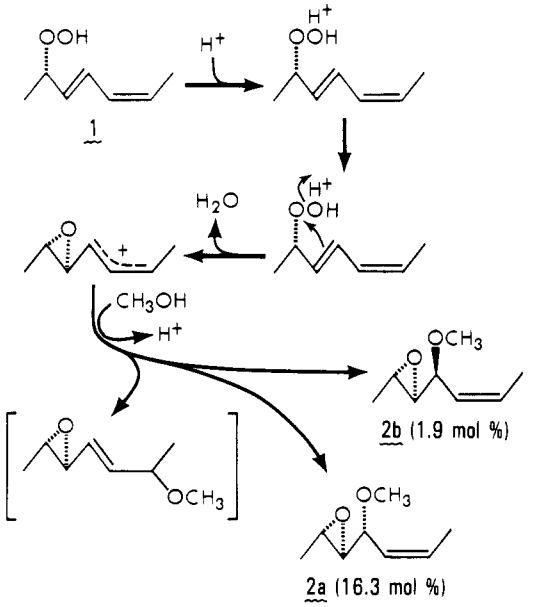
$$A^+ + CH_3OH \rightarrow \text{products (fast)} \quad (6)$$

this mechanism, the products, and the kinetics of Figure 2, a pathway is proposed for the formation of *trans*-epoxides **2a,b** as well as the postulated allylic epoxide (Scheme I). The proposed scheme displays many features reminiscent of the ordinary carbon to oxygen rearrangement, with attendant carbon–carbon cleavage, that is observed with acid catalysis of most organic hydroperoxides. However, in the rearrangement outlined by Scheme I the charged intermediate is stabilized by a 9,11-allylic cation, and, apparently, this feature directs the course of reaction.

Epoxide solvolysis is the cause of the major portion of the products isolated. Methanolysis of **2a** led to **4** (Scheme II), and this was demonstrated directly. The low yields of **2b** and **2c** prevented the detection of their methanolysis products. Similarly, methanolysis of the postulated allylic epoxide (*R* or *S* at carbon-9) would afford **5a–d** and **6a–c** as shown by Scheme II. The preponderance of **5c,d** (erythro isomers) found by us, compared to **5a,b** (threo iso-

(18) (a) Hock, H.; Lang, S. *Ber.* **1944**, *77B*, 257. (b) Seubold, F. H., Jr.; Vaughan, W. E. *J. Am. Chem. Soc.* **1953**, *75*, 3790.
(19) Gardner, H. W.; Plattner, R. D., unpublished results.
(20) Rochester, C. H. "Organic Chemistry: A Series of Monographs. Acidity Functions"; Academic Press: London, 1970; p 195.

Scheme I. Mechanism Proposed for the Formation of *trans*-Epoxides by Acid Catalysis of 1 [a]



[a] Structures are abbreviated; brackets indicate postulated intermediate.

mers), implies that its precursor was predominantly a *trans*-epoxide. Compounds **5a,b** could originate from allylic *cis*-epoxides by S_N2 solvolysis; however, it should be noted that methanolysis of known allylic *trans*-epoxides **13** and **14** afforded not only **11** and **12** (erythro isomers) but also 21–24% of the corresponding threo isomers. The percentage of threo isomers **5a,b** of the total amount of **5** was about the same (28%). The reason for the isomeric distribution of **5** can be explained by accepting methanolysis not only via S_N2 but partially by an S_N1 mechanism as indicated by the solvolysis of **13** and **14** (Experimental Section). Additionally, the isolation of **6** isomers argues persuasively for some S_N1 character in the methanolysis of the proposed intermediate allylic epoxides (Scheme II).

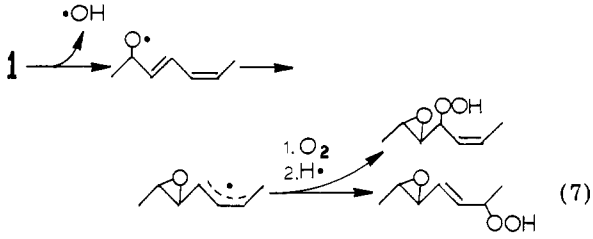
It was obvious that *trans*-epoxides and their corresponding solvolysis products were far more abundant than *cis*-epoxides and their derivatives. Apparently, the least hindered rotamer of the carbon-12,13 bond was trans with respect to the carbon chains. The tendency toward formation of *trans*-epoxides from **1** also has been observed for cyclization of a hydroperoxide-generated oxy radical to the α unsaturation.[10a] Both the homolytic mechanism and the one reported here should be influenced by rotamer populations.

It follows then that the genesis of *cis*-epoxides is less favored by reason of decreased rotamer population (Scheme III). In agreement with this hypothesis, **2c** was found in only 2.0 mol % yield, and there was little evidence for substantial quantities of allylic *cis*-epoxides as discussed above.

A stereoselectivity for production of **2a** was noted. Isomers **2a** and **2b** differ only by the *R* vs. *S* configuration of the 11-methoxyl, but **2a** was favored in yield over **2b** by nearly 9:1. With **2a**, cyclization of the epoxide and substitution by solvent must occur from the same side of the molecule. Preference for this arrangement suggests anchimeric assistance by the epoxide during substitution (Scheme IV). After heating **1** in ethanol–H_2O solution, Hamberg and Gotthammar[21] noted a similar preference for the formation of *threo*-12,13-epoxy-11-hydroxy-9-octadecenoic acid (probably **3**), and they demonstrated that the 11-hydroxyl originated from H_2O in the solvent. A concerted, heterolytic mechanism was proposed, but they suggested that solvent, without the benefit of acid, was the direct cause of the reaction. The condition of heat (100 °C) used by them may have accelerated the action of incipient protons in solution; but, of course, the predominance of acid catalysis would be dependent upon other possible competing reactions.

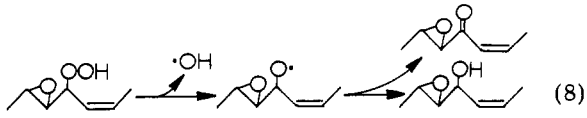
Undoubtedly, the small quantities of **3** and **7–9** isolated from the product mixture was due to the participation of 10% H_2O (by volume) in the reaction solution. These compounds were each related to major products of methanolysis; thus, **3**, **7/8**, and **9** were analogous to **2a**, **4**, and **5** (isomer unspecified), respectively. As expected, acid catalysis of **1** in tetrahydrofuran–H_2O demonstrated clearly that H_2O could substitute in lieu of CH_3OH (data not shown).

The literature is replete with reports of the decomposition of fatty hydroperoxides into epoxyhydroxy and trihydroxy fatty acids analogous to the methoxyl-substituted compounds reported above,[22] and thus the question is raised about the possible general prevalence in those studies of acid catalysis in H_2O. Since there is a free-radical pathway to the same compounds, distinguishing between the two processes may be difficult in the absence of decisive experiments. The free radical pathway affords epoxyhydroperoxy fatty acids[23] (eq 7). The epoxy-



(7)

hydroperoxy fatty acids are also subject to homolysis, and this reaction results in epoxyoxo and epoxyhydroxy fatty acids,[10a] e.g., eq 8. Whereas epoxyhydroperoxy and ep-



(8)

oxyoxo fatty acids may serve as indicators of a free-radical route, their absence may not be a reliable measure of the involvement of heterolysis. Epoxyhydroperoxy fatty acids are relatively unstable, and the selective formation of epoxyhydroxy fatty acids may be favored by availability of an easily abstractable hydrogen.

Since there is the possibility for either a heterolytic or homolytic route to epoxyhydroxy and trihydroxy fatty acids, as well as related fatty acids, the mechanistic origin of these compounds should be reevaluated in the light of the results reported here. As discussed above, Hamberg and Gotthammar[21] undoubtedly observed the thermal heterolysis of **1** into **3**. The enzyme linoleic acid hydroperoxide isomerase has been postulated to catalyze a heterolytic transformation of linoleic acid hydroperoxides into α- and γ-ketol fatty acids.[24] In that report the enzyme-catalyzed intermediate was proposed to be an epoxyallylic cation identical with the one indicated by this

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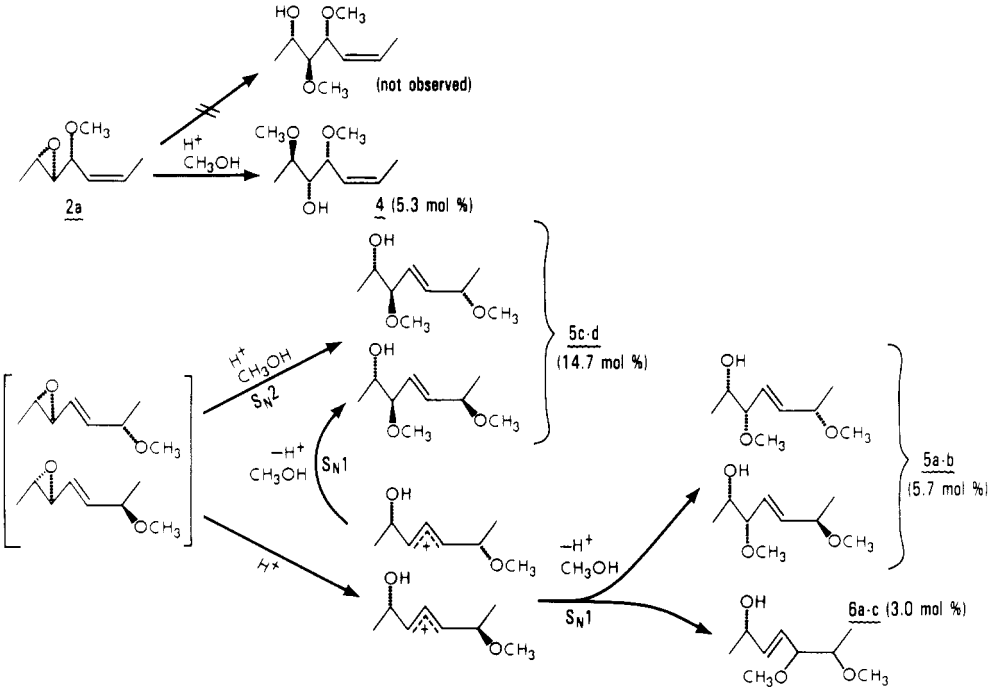
(22) Gardner, H. W. "Autoxidation in Food and Biological Systems"; Simic, M. G., Karel, M., Eds.; Plenum: New York, 1980. See also ref 10a and citations therein.

(23) Gardner, H. W.; Weisleder, D.; Kleiman, R. *Lipids* **1978**, *13*, 246.

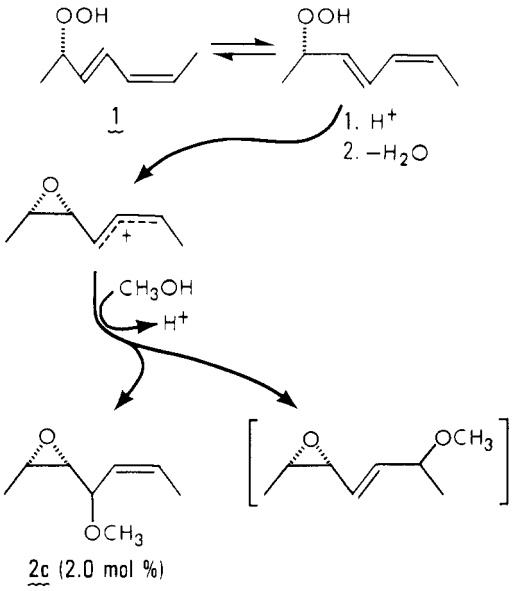
(24) Gardner, H. W. *Lipids* **1979**, *14*, 208.

Scheme II. Acid-Catalyzed Methanolysis of 2a and the Hypothetical Allylic Epoxides[a]



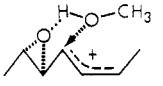
[a] Structures are abbreviated; brackets indicate postulated intermediate.

Scheme III. Proposed Mechanism for Formation of *cis*-Epoxides by Acid Catalysis of 1[a]



[a] Structures are abbreviated; brackets indicate postulated intermediate.

Scheme IV. Anchimeric Assistance Proposed for the Observed Stereoselectivity of Substitution in the Formation of 2a from 1[a]



[a] Fatty acid structure is abbreviated.

study. Similarly, the epoxyallylic cation intermediate had been invoked for the enzymic formation of a cyclic fatty acid, phytodienoic acid, from linolenic acid hydroperoxide.[25] There are many other reports for which the mechanism of conversion is less definitive. For example, the transformation of 1 into 3 by soybean lipoxygenase resulted in retention of both oxygens from the $^{18}O_2$-labeled hydroperoxy group.[10c] This could be interpreted on the basis of a "cage effect" exerted by lipoxygenase which could transfer either ^{18}·OH (homolytic) or $H_2{}^{18}O$ (heterolytic) from the hydroperoxide to C-11 of 3. A similar transfer of $^{18}O_2$ label has been observed for the 12-hydroperoxide of arachidonic acid by a rat lung preparation.[26] Epoxyhydroxy and trihydroxy fatty acids have been reported as secondary products from autoxidation of monolayers of linoleic acid on silica gel.[27] Although these workers claimed an "intramolecular rearrangement" of hydroperoxide attributable to a model membrane effect of the monolayer, the actual cause of conversion may have been due to the Lewis acid character of silica. For many reaction systems there are insufficient data at this time to speculate on the heterolytic vs. homolytic aspect of hydroperoxide conversion into epoxyhydroxy and trihydroxy fatty acids such as with autoxidation of liposomes[28] or enzymic oxidation of arachidonic acid by blood platelets.[29] Because definition of the mechanism may have biological relevance, future work could be directed toward this end.

Acknowledgment. We thank L. W. Tjarks for providing the 100-MHz ^{1}H NMR spectra and R. E. England for the mass spectral data. We also thank Dr. C. G. Crawford for assistance with the radiochemical equipment and R. O. Butterfield for the computer program to analyze rate constants.

Registry No. 1, 33964-75-9; **2a**, 88335-39-1; **2b**, 88303-77-9; **2c**, 88335-40-4; **3**, 88335-44-8; **4**, 88303-78-0; **4** (Me_3Si derivative), 88303-85-9; **5** (isomer 1), 88303-79-1; **5** (isomer 1, Me_3Si derivative),

(25) Vick, B. A.; Feng, P.; Zimmerman, D. C. *Lipids* **1980**, *15*, 468.

(26) Pace-Asciak, C. R.; Mizuno, K.; Yamamoto, S.; Granström, E.; Samuelsson, B. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1983**, *11*, 133.

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(28) Wu, G.-S.; Stein, R. A.; Mead, J. F. *Lipids* **1982**, *17*, 403.

(29) Walker, I. C.; Jones, R. L.; Wilson, N. H. *Prostaglandins* **1979**, *18*, 173.

88303-86-0; **5** (isomer 2), 88335-41-5; **5** (isomer 2, Me_3Si derivative), 88335-50-6; **5** (isomer 3), 88335-42-6; **5** (isomer 3, Me_3Si derivative), 88335-49-3; **5** (isomer 4), 88335-43-7; **5** (isomer 4, Me_3Si derivative), 88335-51-7; **6**, 88303-80-4; **6** (Me_3Si derivative), 88303-87-1; **7**, 88303-81-5; **7** (Me_3Si derivative), 88303-88-2; **8**, 88303-82-6; **8** (bis Me_3Si derivative), 88303-89-3; **9**, 88303-83-7; **9** (bis Me_3Si derivative), 88303-90-6; **10**, 63024-87-3; **11**, 88303-84-8; (9*S*,12*S*,13*S*)-*threo*-**11**, 88335-45-9; **12**, 88335-46-0; (9*R*,12*S*,13*S*)-*threo*-**12**, 88335-47-1; **13**, 84107-41-5; **14**, 84107-40-4; **15**, 88335-48-2; linoleic acid, 60-33-3; [1-^{14}C]linoleic acid, 3131-66-6.

Oxidative Decarboxylation of Propiolic Acids

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The combination of iodine and iodine pentoxide in methanol was used to convert phenylpropiolic acid and 2-hexynoic acid to the corresponding ketal esters of one less carbon. In both cases, iodoacetylenic compounds were shown to be intermediates. In the case of the phenylpropiolic acid, a diiodoalkene was isolated and shown to be a second intermediate.

The oxidations of diphenylacetylene by I^{7+} and I^{5+} compounds in methanol have been reported to afford ketals of benzil.[1] It was shown that the active species in these oxidations were not any of the several oxides of iodine. Rather, these oxides in combination with molecular iodine lead to iodonium-like species, which could attack the triple bond to form a vinyl cation, captured subsequently by the solvent. Another such attack on the resulting olefins could lead to iodo ketals, the precursors of the observed ketals or diones. Gebeyehu, in a preliminary effort, extended such oxidations to propiolic acids, such as phenylpropiolic acid, and noted the formation of esters rather than keto acids or ketal acids.[2] The subjects of this report resulted from further investigations of these initial observations. The principal findings were that two representative alkynoic acids were converted to decarboxylated products and that iodine-containing intermediates were isolated.

Results and Discussion

The oxidations of phenylpropiolic acid (**1**) were carried out initially by I_2O_5 in refluxing methanol.[2] This system was replaced with iodine and I_2O_5 in methanol at room temperature. The methanol was dried with and distilled over $CaSO_4$ under nitrogen and stored over molecular sieves to minimize water content. Previous studies with diphenylacetylene had demonstrated that more ketones than ketals are formed in untreated methanol.[1] Several products could be isolated depending upon the reactant ratios. If the oxidants were in excess, the principal product was the methyl ketal of methyl phenylglyoxylate (**2**). For example, phenylpropiolic acid (10 mmol) was converted to the ketal ester (**2**) in 82% yield after reaction with iodine pentoxide (5 mmol) and iodine (60 mmol). When the alkynoic acid was the excess reagent, the principal products were 2-iodo-1-phenylethyne (**3**) and (2,2-diiodo-1-methoxyethenyl)benzene (**4**). Thus, a ratio of acid to iodine to oxide of 10:1:5 afforded a yield of the iodoalkyne (**3**) of 73% and the diiodoalkene (**4**) of 27% on a 30% conversion of acid. The latter two compounds are the major intermediates on an oxidation pathway from the acid **1** to ketal ester **2**, as shown in Scheme I. The triiodo precursor **5** was not isolated.

Scheme I

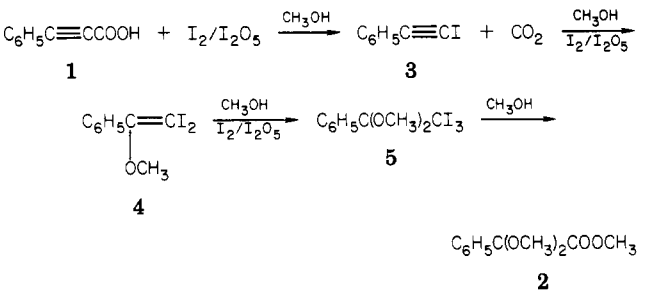

Table I. Oxidation of Phenylpropiolic Acid with I_2 and I_2O_5[a]

I_2, mmol	I_2O_5, mmol	conversion, %	% yield of products 3	4	2
1	5	30	73	27	
5	5	56	52	37	11
10	5	84	7	59	34
20	5	100		19	57
60	5	88			82
10	0.5	65	64	32	4
10	50	100			71

[a] Conditions: 10 mmol of acid **1** in dry methanol (100–150 mL) at room temperature under N_2 for 24 h.

The product **2** was identified by comparison with the known compound prepared from acidic methanol with the methyl ester of phenylglyoxylic acid.[3] The methyl phenylglyoxylate was prepared from the acid and diazomethane. The route via the acid chloride and methanol was not used because decarbonylation of phenylglyoxylyl chloride took place to yield methyl benzoate. The known iodoalkyne **3** was prepared by the treatment of phenylethyne with a Grignard reagent and iodine. The diiodoalkene **4** was identified by ^{1}H NMR, MS, and elemental analysis. Its NMR absorptions at 3.35 (s, 3 H) and 7.31 (s, 5 H) ppm were similar to that reported for the corresponding dichloro compound (3.45 and 7.46 ppm).[4]

(1) Gebeyehu, G.; McNelis, E. *J. Org. Chem.* **1980**, *45*, 4280.
(2) Gebeyehu, G. Thesis, New York University, 1980.
(3) Posner, T.; Aschermann, G. *Chem. Ber.* **1920**, *53B*, 1925.

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