

## Supporting Information

Synthesis of six epoxyketoctadecenoic acid (EKODE) isomers, their generation from non-enzymatic oxidation of linoleic acid, and their reactivity with imidazole nucleophiles

De Lin, Jianye Zhang, and Lawrence M. Sayre\*

Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106

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**General experimental procedures.** Unless otherwise stated, the solvents and reagents were of commercially available analytical grade quality. All preparative reactions were carried out at ambient temperature (24-26 °C) unless stated otherwise. All buffer solutions were made with distilled water with subsequent purification by deionization. For <sup>1</sup>H (200, 400, or 600 MHz) and <sup>13</sup>C (50, 100, or 150 MHz) NMR spectra, tetramethylsilane or the solvent peak served as an internal standard for reporting chemical shifts, expressed on the  $\delta$  scale. Attached proton test (APT) designations for <sup>13</sup>C NMR spectra are given in parentheses. High-resolution mass spectra (HRMS) were obtained at 20 eV.

**Analytical HPLC.** For reverse phase HPLC (diode array UV detection), a gradient eluent system was used with an Agilent Zorbax SB-C18 (250 × 4.6 mm, 5  $\mu$ m) column: Eluent A was a mixture of 95% H<sub>2</sub>O, 5% acetonitrile with 0.02% TFA and eluent B was a mixture of 5% H<sub>2</sub>O, 95% acetonitrile with 0.02% TFA. The flow rate was 1.0 min/ml and the gradient program was 80% A to 10% A over 20 min; 10% A for 5 min; 10% A to 80% A over 5 min; 80% A for 5 min. The injection volume was 20  $\mu$ L.

**Preparative HPLC.** For reverse phase preparative HPLC, a gradient eluent system was used with an Agilent Zorbax SB-C18 (250 x 9.4 mm, 5 $\mu$ m) column: Eluent A was a mixture of 95% H<sub>2</sub>O, 5% acetonitrile with 0.02% TFA and eluent B was a mixture of 5% H<sub>2</sub>O, 95% acetonitrile with 0.02% TFA. The flow rate was 3.0 mL/min and the gradient program was 60% A for 3 min; 60% A to 10% A over 17 min; 10% A for 5 min; 10% A to 60% A over 5 min; 60% A for 2 min. The injection volume was 100  $\mu$ L.

**HPLC-ESI-MS/MS.** Reverse phase HPLC with electrospray (ESI) mass spectrometry of the samples was performed using an Agilent Zorbax SB-C18 column (250 x 4.6 mm, 5  $\mu$ m). Eluent A is a mixture of 95% HPLC grade H<sub>2</sub>O, 5% HPLC grade methanol and 0.1% formic acid; and eluent B is a mixture of 5% H<sub>2</sub>O, 95% methanol and 0.1% formic acid. The flow rate was 400  $\mu$ L/min and the gradient was 60% A to 90% B over 40 min; 90% B for 5 min; 90% B to 60% A over 10 min; 60% A for 5 min. Injection volume was 5  $\mu$ L. The eluent profile was monitored as the total ion chromatogram (TIC) on a ThermoFinnigan LCQ Advantage electrospray ion trap mass spectrometer in the positive mode using nitrogen as sheath and auxiliary gas. The heated capillary temperature was 300 °C, the source voltage was 4.5 keV, and the capillary voltage was set to 35 V. A scan event of 0-700 m/z full scan MS was used. All data were processed using the manufacturer's browser Xcalibur program.

**Methyl 9-hydroxynonanoate (2).**<sup>11</sup> A solution of ethyl chloroformate (2.81 g, 26.0 mmol) in THF (70 mL) was added to a solution of azelaic acid monomethyl ester **1** (5.00 g, 24.7 mmol) and NEt<sub>3</sub> (2.63 g, 26.0 mmol) at -5 °C, and the mixture was allowed to stir for 1 h at -5 °C. NEt<sub>3</sub>HCl was removed by filtration and the filtrate was treated with NaBH<sub>4</sub> (1.92 g, 52.0 mmol) in H<sub>2</sub>O (20 mL) at 0 °C. The mixture was acidified with 3N HCl to pH 3-4 and extracted with ether. The combined organic extracts were washed twice with 0.5 N NaOH and then once each with H<sub>2</sub>O and brine. After the mixture was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated, the crude product was purified by silica gel chromatography (eluent hexanes-ether 1:2), affording **2** as a colorless oil (3.20 g, 81%): <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.22-1.36 (8H), 1.48-1.70 (4H), 2.30 (t, 2H,  $J$  = 7.2 Hz), 3.63 (t, 2H,  $J$  = 6.6 Hz), 3.66 (s, 3H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  25.0 (+), 25.7 (+), 29.1 (+), 29.2 (2, +), 32.8 (+), 34.1 (+), 51.5 (-), 63.0 (+), 174.4 (+).

**Methyl 9-oxononanoate (3).**<sup>11</sup> According to a modification of the published procedure,<sup>11</sup> a solution of methyl 9-hydroxynonanoate (**2**) (2.00 g, 10.6 mmol) in 5 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added to a suspension of pyridinium chlorochromate (3.44 g, 15.9 mmol) and Celite (3.44 g) in 25 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub>. After stirring at room temperature for 2 h, the mixture was diluted with 50 mL of ether and filtered through a pad of Florosil. The filter cake was washed with ether (2  $\times$  50 mL). The organic solvent was removed and the crude product was purified by silica gel chromatography (eluent hexanes-ether 2:1), affording **3** as a colorless oil (1.59 g, 80%): <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.22-1.36 (6H), 1.54-1.72 (4H), 2.30 (t, 2H,  $J$  = 7.2 Hz), 2.42 (td,

2H,  $J = 7.2$  Hz and  $1.8$  Hz),  $3.67$  (s, 3H),  $9.76$  (t, 1H,  $J = 1.8$  Hz);  $^{13}\text{C}$  NMR (50MHz,  $\text{CDCl}_3$ )  $\delta$  22.0 (+), 24.9 (+), 28.95 (+), 29.00 (+), 29.04 (+), 34.1 (+), 43.9 (+), 51.5 (-), 174.3 (+), 202.9 (-); HRMS (FAB) calcd for  $\text{C}_{10}\text{H}_{19}\text{O}_3$  ( $\text{MH}^+$ ) 187.1334, found 187.1329.

**Methyl 11-oxoundec-9(*E*)-enoate (4).**<sup>12</sup> A solution of methyl 9-oxononanoate (**3**) (1.00 g, 5.38 mmol) and (triphenylphosphoranylidene)acetaldehyde (1.96 g, 6.45 mmol) in dry chloroform (10 mL) was heated at reflux at  $70^\circ\text{C}$  for 48 h. The solvent was removed and the crude product was purified by silica gel chromatography (eluent hexanes-ether 2:1), affording **4** as a yellow oil (672 mg, 59%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.22-1.36 (6H), 1.40-1.66 (4H), 2.28 (t, 2H,  $J = 7.6$  Hz), 2.22-2.38 (2H), 3.63 (s, 3H), 6.08 (ddt, 1H,  $J = 15.6$  Hz, 8.0 Hz and 1.5 Hz), 6.82 (dt, 1H,  $J = 15.6$  Hz, and 7.8 Hz), 9.47 (d, 1H,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  24.9 (+), 27.8 (+), 28.95 (+), 28.99 (2, +), 32.7 (+), 34.0 (+), 51.5 (-), 133.0 (-), 158.9 (-), 174.2 (+), 194.2 (-).

**Methyl 8-(chlorocarbonyl)octanoate (9).**<sup>15</sup> To azelaic acid monomethyl ester (**1**) (4.0 g, 20 mmol) was added oxalyl chloride (30 mmol) under argon at room temperature. Once evolution of gas had ceased (ca. 30 min), the mixture was heated to reflux for 2 h and then cooled to room temperature. The excess oxalyl chloride was distilled off at atmospheric pressure and the remaining material was distilled under high vacuum producing a colorless liquid (3.4 g, 91%): bp  $125^\circ\text{C}/5$  Torr (lit.<sup>15</sup> bp  $84^\circ\text{C}/0.1$  torr);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.29-1.34 (6H), 1.59-1.71 (4H), 2.30 (t, 2H,  $J = 7.4$  Hz), 2.87 (t, 2H,  $J = 7.2$  Hz), 3.66 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  25.0, 25.2, 28.4, 28.9, 29.0, 34.2, 47.2, 51.7, 174.0, 174.4.

***trans*(*cis*)-2,3-Epoxyoctanal (12).**<sup>16</sup> A 30% aqueous  $\text{H}_2\text{O}_2$  solution (3.0 mL, 29 mmol) was added to a solution of *trans*-2-octenal (**11**) (1.26 g, 10 mmol) in MeOH (12 mL), vigorously stirred and cooled to  $1-3^\circ\text{C}$ , and then  $\text{NaHCO}_3$  (1.0 g, 12 mmol) was added. After 1.5 h reaction at room temperature, brine (20 mL) was added, and the resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL). The combined extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated, and the crude product was purified by silica gel chromatography (eluent hexanes-EtOAc 9:1), affording **12** as a yellow oil (1.05 g, 65%) as a mixture of major *trans* and trace *cis* isomers in the ratio 9:1, which was used for the next step directly:  $^1\text{H}$  NMR (major isomer, 200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.90 (t, 3H,  $J = 7.0$  Hz), 1.22-1.75 (8H), 3.14 (dd, 1H,  $J = 6.4$  Hz and 2.0 Hz), 3.23 (td, 1H,  $J = 5.3$  Hz and 2.0 Hz), 9.02 (d, 1H,  $J = 6.4$  Hz);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  14.0 (-), 22.5 (+), 25.5 (+), 31.2 (+),

31.4 (+), 56.9 (-), 59.2 (-), 198.6 (+).

**Methyl 9-oxo-*trans*(*cis*)-12,13-epoxy-10(*E*)-octadecenoate (13).** *n*-Butyllithium (4.8 mL, 2.5 M in hexane, 3.8 mmol) was added to a cooled (-70 °C) solution of methyltriphenylphosphonium bromide (2.3 g, 10 mmol) in THF (20 mL), causing a red color to develop. The mixture was stirred for 1 h, whereupon methyl 8-(chlorocarbonyl)octanoate (**9**) (1.1 g, 5.0 mmol) was added dropwise, and the final mixture was then allowed to stir at room temperature for 1 h. After evaporation of THF, the resulting oil was dissolved in EtOAc (50 mL). The organic layer was washed with aqueous NaOH (2 N, 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to afford crude methyl 9-oxo-10-(triphenylphosphoranylidene)decanoate (**10**) as a viscous oil in essentially quantitative yield (2.3 g). A solution of crude **10** (460 mg, 0.10 mmol) in 6 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added to a solution of *trans*(*cis*)-2,3-epoxyoctanal (**12**) (71 mg, 0.5 mmol) in 2 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. After stirring for 4 h, the mixture was washed with water (10 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the resulting crude product was purified by silica gel chromatography (eluent hexanes-EtOAc 9:1), affording **13** as a yellow oil (105 mg, 65%): <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 0.88 (t, 3H, *J* = 6.6 Hz), 1.22-1.70 (18H), 2.27 (t, 2H, *J* = 7.4 Hz), 2.51 (t, 2H, *J* = 7.3 Hz), 2.88 (td, 1H, *J* = 5.3 Hz and 2.0 Hz), 3.19 (dd, 1H, *J* = 6.5 Hz and 2.0 Hz), 3.64 (s, 3H), 6.36 (d, 1H, *J* = 15.9 Hz), 6.49 (dd, 1H, *J* = 15.9 Hz and 6.5 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 14.0 (-), 22.6 (+), 23.9 (+), 24.9 (+), 25.5 (+), 29.0 (+), 29.1 (2, +), 31.6 (+), 31.9 (+), 34.1 (+), 40.6 (+), 51.5 (-), 56.7 (-), 61.7 (-), 131.3 (-), 142.6 (-), 174.3 (+), 199.6 (+). NMR resonances for the minor *cis* isomer could not be readily ascertained. HRMS (FAB) calcd for C<sub>19</sub>H<sub>33</sub>O<sub>4</sub> (MH<sup>+</sup>) 325.2379, found 325.2380.

**Methyl 11-oxododec-9(*E*)-enoate (18).** A solution of methyl 9-oxononanoate (**3**) (1.0 g, 5.4 mmol) and, 1-(triphenylphosphoranylidene)-2-propanone **6** (1.9 g, 6.0 mmol) in dry dichloromethane (10 mL) was heated at reflux for 18 h. The solvent was removed, and the crude product was purified by silica gel chromatography (eluent hexanes-ether 2:1), affording **18** as a yellow oil (915 mg, 75%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.22-1.36 (6H), 1.38-1.48 (2H), 1.52-1.62 (2H), 2.19 (dtd, 2H, *J* = 7.2 Hz, 7.2 Hz, and 1.6 Hz), 2.21 (s, 3H), 2.27 (t, 2H, *J* = 7.6 Hz), 3.63 (s, 3H), 6.03 (dt, 1H, *J* = 16.0 Hz and 1.6 Hz), 6.76 (dt, 1H, *J* = 16.0 Hz and 7.2 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 25.1, 27.1, 28.2, 29.16, 29.18, 29.20, 32.6, 34.2, 51.7, 131.5,

148.7, 174.4, 199.0; HRMS (FAB) calcd for C<sub>13</sub>H<sub>23</sub>O<sub>3</sub> (MH<sup>+</sup>) 227.1647, found 227.1650.

**Methyl 13-hydroxy-11-oxooctadec-9(*E*)-enoate (19).** To a precooled (-78 °C) solution of methyl 11-oxododec-9(*E*)-enoate (**18**) (246 mg, 1.0 mmol) and hexanal (100 mg, 1.0 mmol) in anhydrous THF (2 mL) was added lithium diisopropylamide (0.5 mL, 2 M in THF/*n*-heptane, 4.0 mmol) slowly. The resulting solution was stirred at -78 °C for 15 min, quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (1 mL), and then allowed to warm to room temperature. The mixture was partitioned between EtOAc and water, and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The crude product was purified by silica gel chromatography (hexanes-ether 1:1), affording **19** as a slightly yellow oil (55 mg, 17%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.86 (t, 3H, *J* = 6.8 Hz), 1.20-1.62 (18H), 2.19 (dtd, 2H, *J* = 6.8 Hz, 6.8 Hz and 1.6 Hz), 2.27 (t, 2H, *J* = 7.6 Hz), 2.59 (dd, 1H, *J* = 17.6 Hz and 9.2 Hz), 2.72 (dd, 1H, *J* = 17.6 Hz and 2.8 Hz), 3.22 (d, 1H, *J* = 3.2 Hz), 3.64 (s, 3H), 4.00-4.05 (1H), 6.06 (dt, 1H, *J* = 16.0 Hz and 1.6 Hz), 6.83 (dt, 1H, *J* = 16.0 Hz and 6.8 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.3, 22.8, 25.1, 25.4, 28.1, 29.16 (2), 29.19, 32.0, 32.7, 34.2, 36.7, 46.2, 51.7, 68.0, 130.9, 149.0, 174.5, 201.5; HRMS (FAB) calcd for C<sub>19</sub>H<sub>35</sub>O<sub>4</sub> (MH<sup>+</sup>) 327.2535, found 327.2534.

**Methyl *trans*-9,10-epoxy-11-oxo-13-hydroxyoctadecanoate (20).** An aqueous solution of H<sub>2</sub>O<sub>2</sub> (30%, 0.15 mL, 1.4 mmol) was added slowly to a stirred solution of methyl 13-hydroxy-11-oxooctadec-9(*E*)-enoate (**19**) (81 mg, 0.25 mmol) in methanol (1 mL) at 5 °C. Aqueous NaOH (1N, 0.25 mL) was added over 30 min, and the mixture was stirred at room temperature for 4 h. Saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (0.25 mL) was added to destroy any remaining peroxide while maintaining the temperature below 40 °C. The mixture was then diluted with water (5 mL) and extracted with ether (3 × 5 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The crude product was purified by silica gel chromatography (eluent hexanes-ether 1:1), affording **20** as a colorless oil as mixture of two isomers (ratio: 1.14/1) (74 mg, 87 %): <sup>1</sup>H NMR (major isomer, 400 MHz, CDCl<sub>3</sub>) δ 0.85 (t, 3H, *J* = 7.2 Hz), 1.20-1.62 (20H), 2.27 (t, 2H, *J* = 7.6 Hz), 2.35 (dd, 1H, *J* = 17.6 Hz and 9.2 Hz), 2.52 (dd, 1H, *J* = 17.6 Hz and 7.2 Hz),

2.82-2.86 (1H), 3.02 (ddd, 1H,  $J = 6.0$  Hz, 4.8 Hz and 2.0 Hz), 3.19 (d, 1H,  $J = 2.0$  Hz), 3.64 (s, 3H), 3.97-4.04 (1H);  $^1\text{H}$  NMR (minor isomer, 400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.85 (t, 3H,  $J = 7.2$  Hz), 1.20-1.62 (20H), 2.27 (t, 2H,  $J = 7.6$  Hz), 2.44 (dd, 1H,  $J = 17.6$  Hz and 3.2 Hz), 2.53 (dd, 1H,  $J = 17.6$  Hz and 5.6 Hz), 2.74-2.78 (1H), 3.08 (ddd, 1H,  $J = 6.0$  Hz, 4.8 Hz and 2.0 Hz), 3.17 (d, 1H,  $J = 2.0$  Hz), 3.64 (s, 3H), 3.97-4.04 (1H);  $^{13}\text{C}$  NMR (isomeric mixture, 100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.8, 25.0, 25.3, 25.9, 29.13, 29.18, 29.20, 29.24, 31.91, 31.93, 34.2, 36.8, 43.7, 44.1, 51.7, 58.4, 58.7, 59.9, 60.2, 67.4, 67.7, 174.5, 208.9, 209.0; HRMS (FAB) calcd for  $\text{C}_{19}\text{H}_{35}\text{O}_5$  ( $\text{MH}^+$ ) 343.2484, found 343.2487.

**Methyl *trans*-9,10-epoxy-11-oxo-12(*E*)-octadecenoate (21).** Methanesulfonyl chloride (42  $\mu\text{L}$ , 0.55 mmol) was added portionwise by syringe to a stirred solution of methyl *trans*-9,10-epoxy-11-oxo-13-hydroxyoctadecanoate (**20**) (85 mg, 0.25 mmol) and triethylamine (105  $\mu\text{L}$ , 0.75 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) at 0  $^\circ\text{C}$ . Upon complete addition, the reaction mixture was stirred for 30 min at 0  $^\circ\text{C}$ , allowed to warm to room temperature with stirring for 1 h, diluted with  $\text{CH}_2\text{Cl}_2$  (5 mL), and washed with water (5 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5$  mL), and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The crude product was purified by silica gel chromatography (eluent hexanes-EtOAc 6:1), affording **21** as a colorless oil (55 mg, 69 %):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t, 3H,  $J = 7.2$  Hz), 1.22-1.70 (18H), 2.20 (dtd, 2H,  $J = 6.8$  Hz, 6.8 Hz and 1.6 Hz), 2.28 (t, 2H,  $J = 7.6$  Hz), 3.02 (ddd, 1H,  $J = 6.4$  Hz, 5.2 Hz and 2.0 Hz), 3.32 (d, 1H,  $J = 2.0$  Hz), 3.65 (s, 3H), 6.22 (dt, 1H,  $J = 16.0$  Hz and 1.6 Hz), 7.06 (dt, 1H,  $J = 16.0$  Hz and 6.8 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 22.6, 25.1, 26.0, 27.8, 29.17, 29.27, 29.29, 31.6, 32.0, 32.9, 34.2, 51.7, 58.5, 59.2, 124.1, 150.8, 174.4, 195.9; HRMS (FAB) calcd for  $\text{C}_{19}\text{H}_{33}\text{O}_4$  ( $\text{MH}^+$ ) 325.2379, found 325.2368.

***trans*-5,6-Epoxy-3(*E*)-octen-2-one (23).** A 30% aqueous  $\text{H}_2\text{O}_2$  solution (3.0 mL, 30 mmol) was added to a solution of *trans*-2-pentenal (0.84 g, 10 mmol) in MeOH (12 mL), vigorously stirred and cooled to 1-3  $^\circ\text{C}$ , and then  $\text{NaHCO}_3$  (1.0 g, 12 mmol) was added. After 1.5 h reaction at room temperature, brine (20 mL) was added to the reaction mixture, and the resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ),



and the solvent was removed by distillation through a Vigreux column. The liquid remaining corresponds to crude *trans*-2,3-epoxypentanal (**22**). To a solution of the latter (400 mg, 4.0 mmol) in 4 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> at 0 °C was added a solution of 1-(triphenylphosphoranylidene)-2-propanone (2.2 g, 7.0 mmol) in 10 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub>. After stirring for 4 h, the mixture was washed with water (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated, and the crude product was purified by silica gel chromatography (eluent hexanes-EtOAc 6:1), affording **23** as a yellow oil (286 mg, 49%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.01 (t, 3H, *J* = 7.4 Hz), 1.55-1.70 (2H), 2.25 (s, 3H), 2.89 (td, 1H, *J* = 5.5 Hz and 2.0 Hz), 3.23 (dd, 1H, *J* = 6.5 Hz and 2.0 Hz), 6.36 (d, 1H, *J* = 16.0 Hz), 6.49 (dd, 1H, *J* = 16.0 Hz and 6.5 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 9.72 (-), 25.03 (+), 27.31 (-), 56.24 (-), 62.58 (-), 132.29 (-), 143.76 (-), 197.49 (+); HRMS (FAB) calcd for C<sub>8</sub>H<sub>13</sub>O<sub>2</sub> (MH<sup>+</sup>) 141.0916, found 141.0912.

**Purities and extinction coefficients of EKODE isomers.** The final EKODE isomers contained no organic contaminants evident by NMR, but because they were obtained from preparative TLC, the samples contained a variable amount of binder. Thus, in order to obtain accurate extinction coefficients for weighed samples, the purities of EKODE samples were determined by a double-internal standard NMR method. First, a solution of CHCl<sub>3</sub> in CD<sub>3</sub>OD was prepared and the concentration of CHCl<sub>3</sub> based on the singlet at 7.9 ppm was determined by <sup>1</sup>H NMR using maleic acid (6.3 ppm) as an internal standard. Then, aliquots of EKODE samples were dissolved in a known volume of the above CHCl<sub>3</sub>/CD<sub>3</sub>OD solution and the <sup>1</sup>H NMR spectrum was taken. The purity of the EKODE sample was thus calculated by comparing the total integral of the olefinic proton signals of EKODE (6.2-6.8 ppm) with the CHCl<sub>3</sub> singlet. After evaporation of measured aliquots of the EKODE solutions, the residues were dissolved in ethanol to prepare 0.05 mM EKODE solutions, and the absorbance was measured at 232 nm. All weighings and measurements were repeated three times, and the average value was used. According to this method, the weighed samples of EKODE isomers were shown to have a purity of 77-85% by weight.

**Oxidation of linoleic acid in the presence of Fe(II)/ascorbic acid.** A solution of Fe(NH<sub>4</sub>)<sub>2</sub>(SO<sub>4</sub>)<sub>2</sub> (0.625 mM) and ascorbic acid (1.25 mM) in 50 mM HEPES buffer at pH 7.4

(800  $\mu$ L) was incubated with linoleic acid in ethanol (25 mM, 200  $\mu$ L) at 37  $^{\circ}$ C, and aliquots were taken and mixed with an equal volume of ethanol for HPLC analysis at different time points (0, 2, 8, 18 h).

**Spiking of authentic EKODE isomers into the linoleic acid autoxidation product mixture.** Each of the six isomers of EKODE was dissolved in 100  $\mu$ L of ethanol and mixed with an equal volume of the reaction mixture from above after incubation for 18 h. For comparison, an aliquot of the reaction mixture was diluted with an equal volume of ethanol.

**Kinetics of reaction of imidazole nucleophiles with EKODE isomers.** Kinetics were performed with  $[\text{nucleophile}] > 10 \times [\text{EKODE}]$  so that the calculated  $k_{\text{obs}}$  values represent pseudo-first order rate constants. We used 5.0 mM nucleophile (imidazole or  $N^{\omega}$ -Ac-histamine) to react with 0.2 mM EKODE. The reactions were executed in 50 mM pH 7.4 sodium phosphate buffer containing 20% ethanol at 30  $^{\circ}$ C and monitored by repetitive spectral scanning from 225-280 nm. The reaction rates were monitored by observing the decrease over time in absorbance at 237 nm due to the  $\alpha,\beta$ -unsaturation of EKODEs. The pseudo first-order plots of the reactions were linear to at least 3 half-lives, and the first order rate constants  $k_{\text{obs}}$  were determined from the linear regression of  $\ln((A_{\infty}-A_0)/(A_{\infty}-A_t))$  versus time, where  $A_{\infty}$  was determined by estimation of the plot of  $A$  vs. time. In the cases of the slower reactions, we also calculated rate constants by choosing values of  $A_{\infty}$  that gave optimal linearity of the first-order plot (rate constants obtained this way were within 5% of those obtained by estimation of  $A_{\infty}$ ). First-order  $k_{\text{obs}}$  values were converted to second-order rate constants by dividing by the concentration of nucleophile used, and the values listed in Table 1 represent the average of at least two rate determinations.

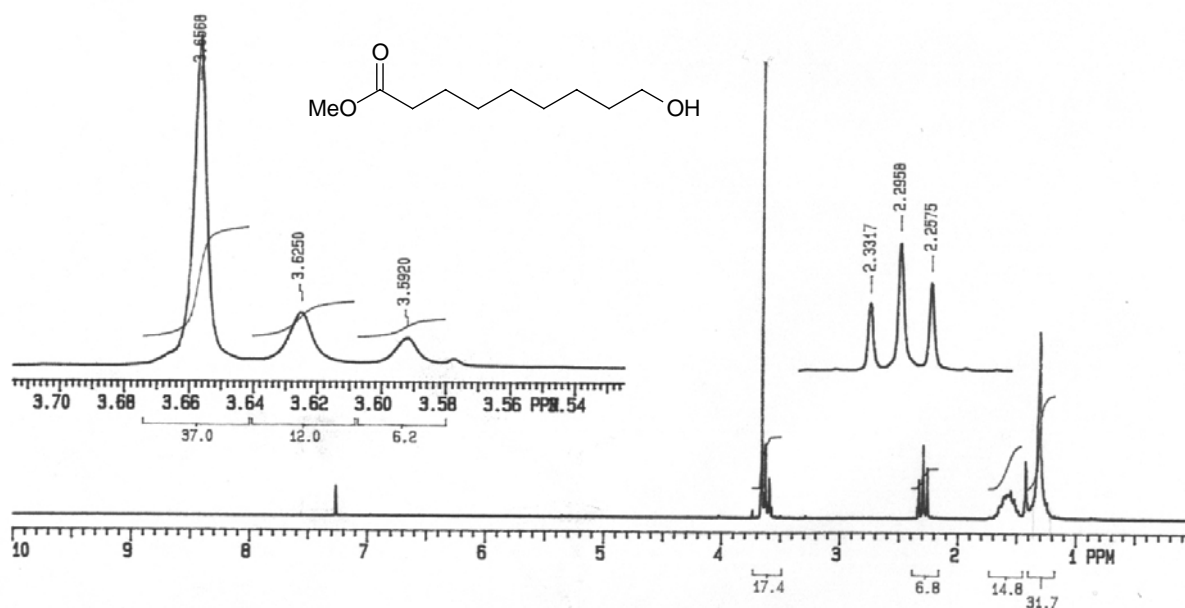
**Incubation of  $N^{\alpha}$ -benzoyl-L-histidine (BzHis) with linoleic acid in the presence of Fe(II) or EKODE isomers.** A solution of BzHis (2.5 mM),  $\text{Fe}(\text{NH}_4)_2(\text{SO}_4)_2$  (0.5 mM), and ascorbic acid (1.0 mM) in 50 mM, pH 7.4 HEPES buffer (800  $\mu$ L) was incubated with 200  $\mu$ L of linoleic acid (25 mM) in ethanol. Also, solutions of BzHis (2.5 mM) in 50 mM, pH 7.4 HEPES buffer (80  $\mu$ L) was incubated with 20  $\mu$ L of each EKODE isomer (1 mM) in ethanol. After 18 h incubation at 37  $^{\circ}$ C, the reaction mixtures were diluted 20 times and analyzed by LC-MS as described above.

**NMR tube scale reaction of 23 with imidazole in CDCl<sub>3</sub>.** To a solution of *trans*-5,6-epoxy-3(*E*)-octen-2-one (**23**) (6.8 mg, 0.049 mmol) in CDCl<sub>3</sub> (700 μL) in an NMR tube was added imidazole (10 mg, 0.146 mmol). The reaction was kept at room temperature and monitored periodically by <sup>1</sup>H NMR spectroscopy. After 36 h, the spectrum indicated 100% conversion to a mixture of two Michael adduct isomers.

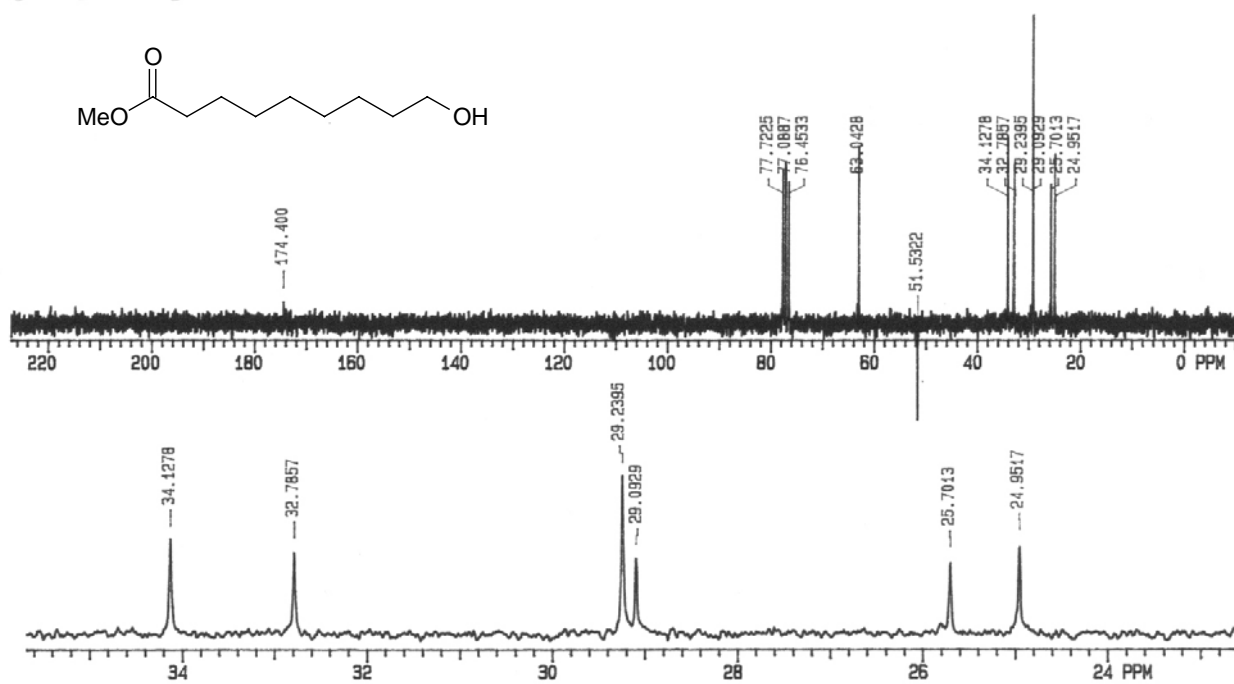
**Isomer I** (81% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.92 (t, 3H, *J* = 7.6 Hz), 2.16 (s, 3H), 1.48-1.58 (2H), 2.41 (td, 1H, *J* = 5.6 Hz and 2.4 Hz), 3.01 (d, 1H, *J* = 6.8 Hz), 3.01 (dd, 1H, *J* = 4.0 Hz and 2.4 Hz), 3.06 (d, 1H, *J* = 6.8 Hz), 4.81 (dd, 1H, *J* = 6.8 Hz and 4.0 Hz), 6.93 (t, 1H, *J* = 1.2 Hz), 7.03 (t, 1H, *J* = 1.2 Hz), 7.51 (t, 1H, *J* = 1.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 9.85 (-), 24.52 (+), 30.64 (-), 45.70 (+), 52.70 (-), 57.98 (-), 58.97 (-), 118.23 (-), 129.52 (-), 136.78 (-), 204.07 (+).

**Isomer II** (19% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.91 (t, 3H, *J* = 7.6 Hz), 2.12 (s, 3H), 1.48-1.58 (2H), 2.70 (td, 1H, *J* = 5.6 Hz and 2.0 Hz), 2.96 (d, 1H, *J* = 6.4 Hz), 2.99 (dd, 1H, *J* = 4.8 Hz and 2.0 Hz), 3.10 (d, 1H, *J* = 6.4 Hz), 4.72 (dd, 1H, *J* = 6.4 Hz and 4.8 Hz), 7.00 (t, 1H, *J* = 1.2 Hz), 7.06 (t, 1H, *J* = 1.2 Hz), 7.58 (t, 1H, *J* = 1.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 9.85 (-), 24.66 (+), 30.64 (-), 44.70 (+), 53.57 (-), 57.98 (-), 59.01 (-), 117.80 (-), 129.83 (-), 136.88 (-), 204.07 (+).

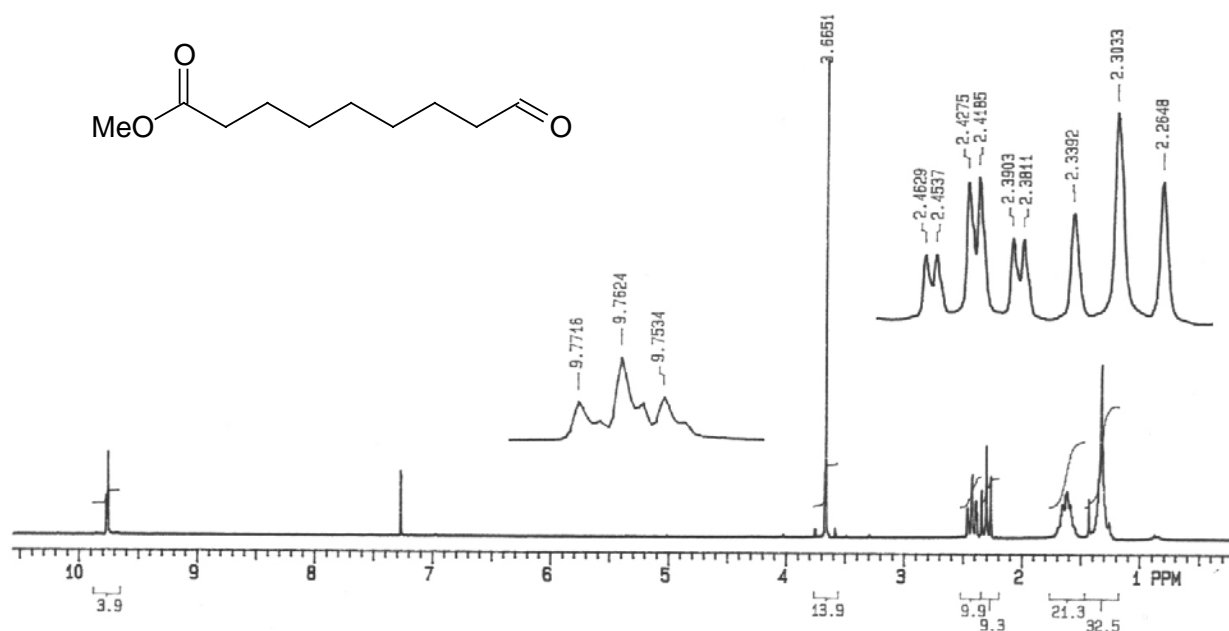
**NMR tube scale reaction of 23 with imidazole in deuterated sodium phosphate buffered D<sub>2</sub>O/CD<sub>3</sub>CN.** To a solution of **23** (3.4 mg, 0.025 mmol) in CD<sub>3</sub>CN (560 μL) in an NMR tube was added imidazole (5 mg, 0.073 mmol) in 100 mM, pD 7.4 deuterated sodium phosphate buffer. The reaction in the tube was monitored at different time over 6 days at 25 °C.



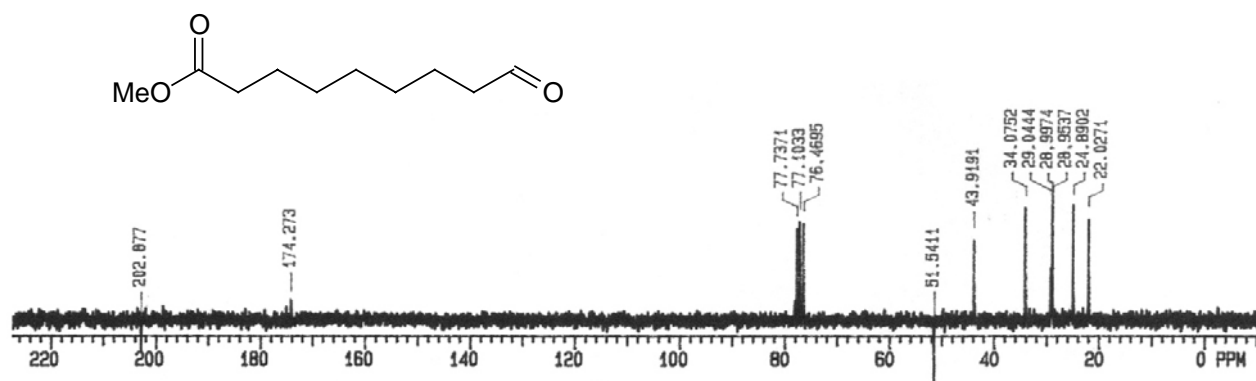
**Figure S1.** The 200 MHz  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) spectrum of methyl 9-hydroxynonanoate (**2**).



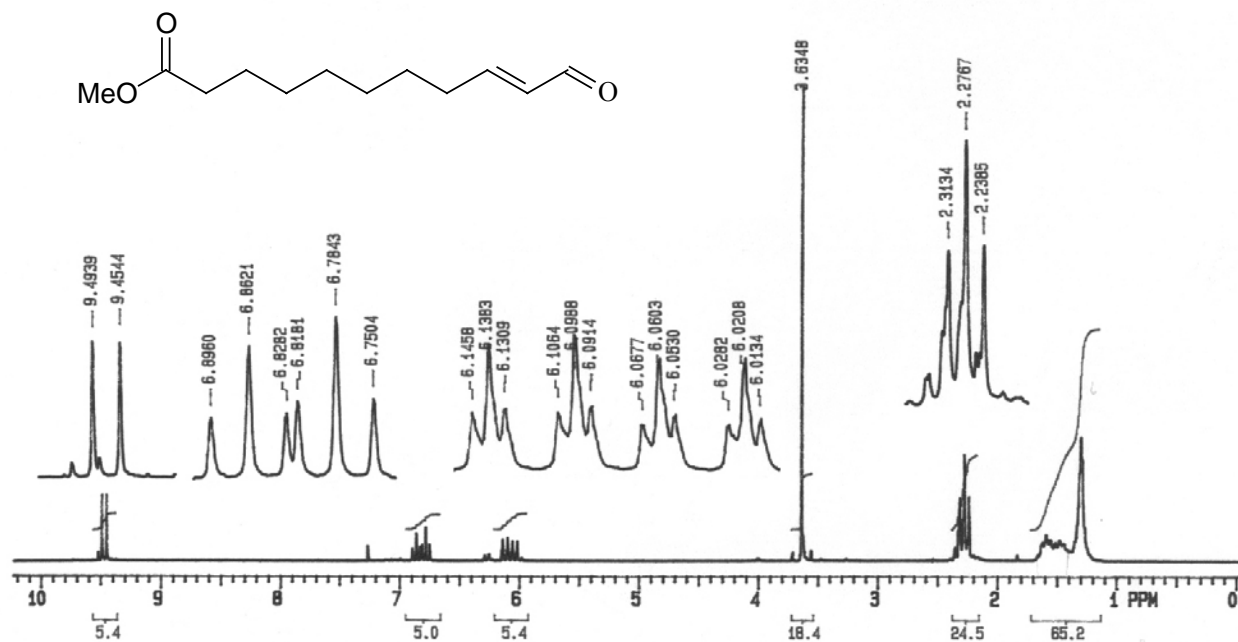
**Figure S2.** The 50 MHz  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ) spectrum of methyl 9-hydroxynonanoate (**2**).



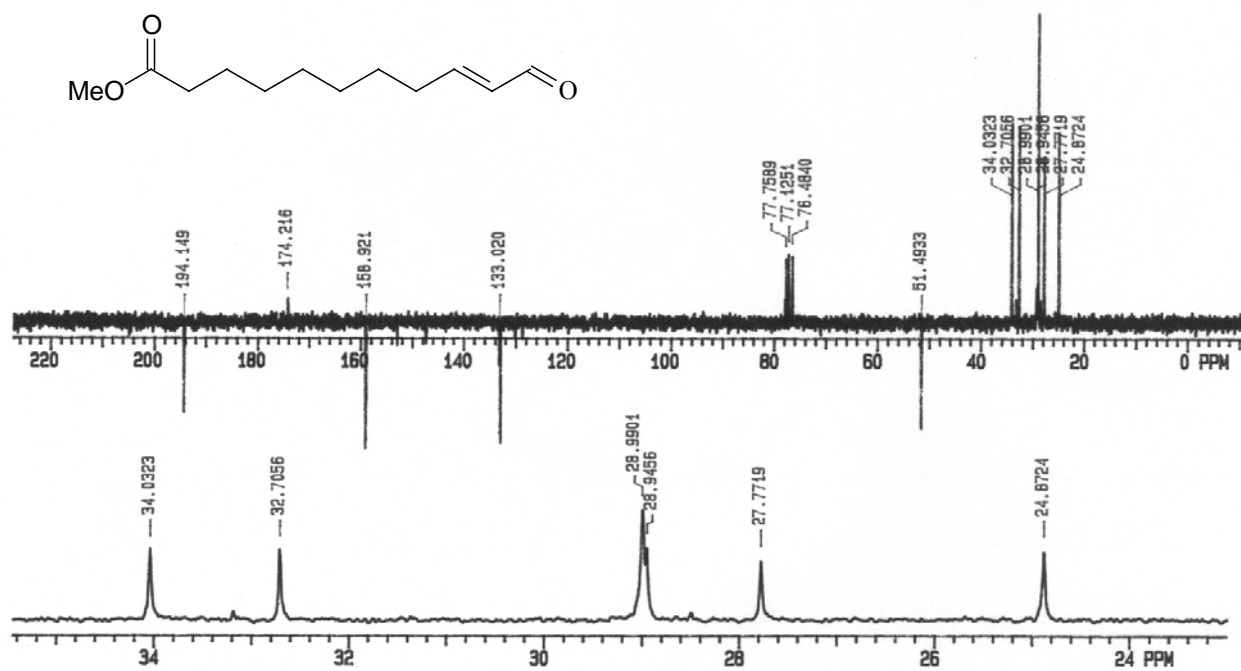
**Figure S3.** The 200 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 9-oxononanoate (3).



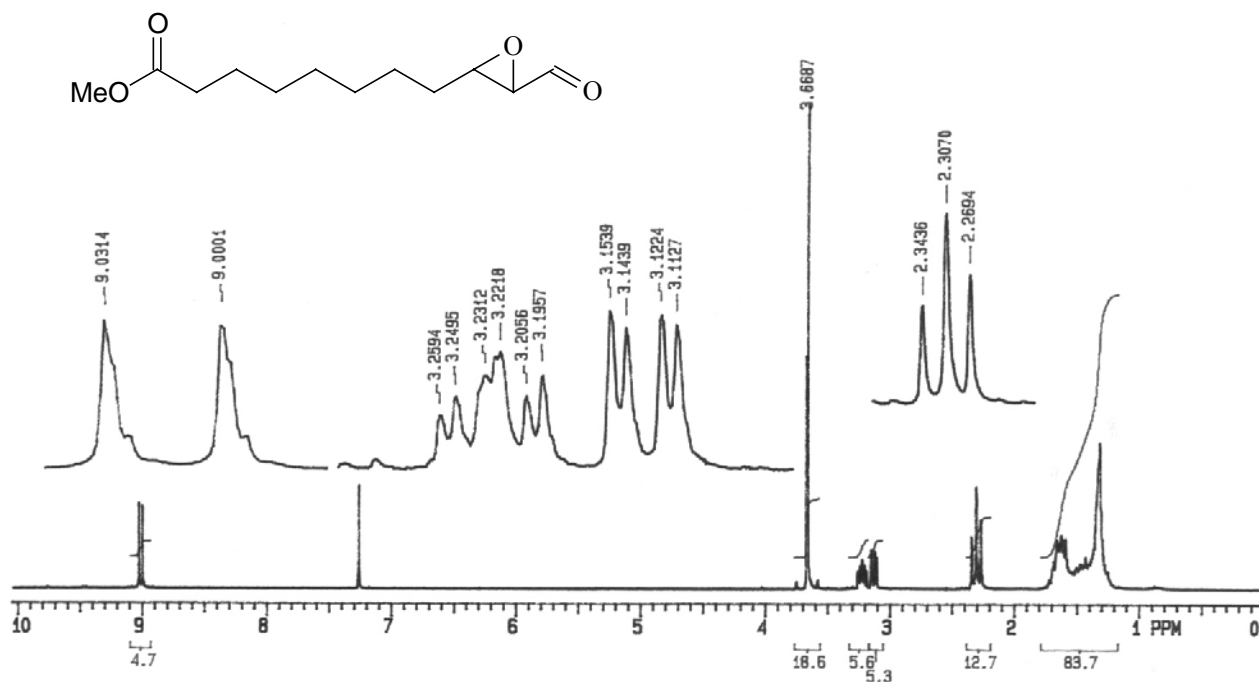
**Figure S4.** The 50 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 9-oxononanoate (3).



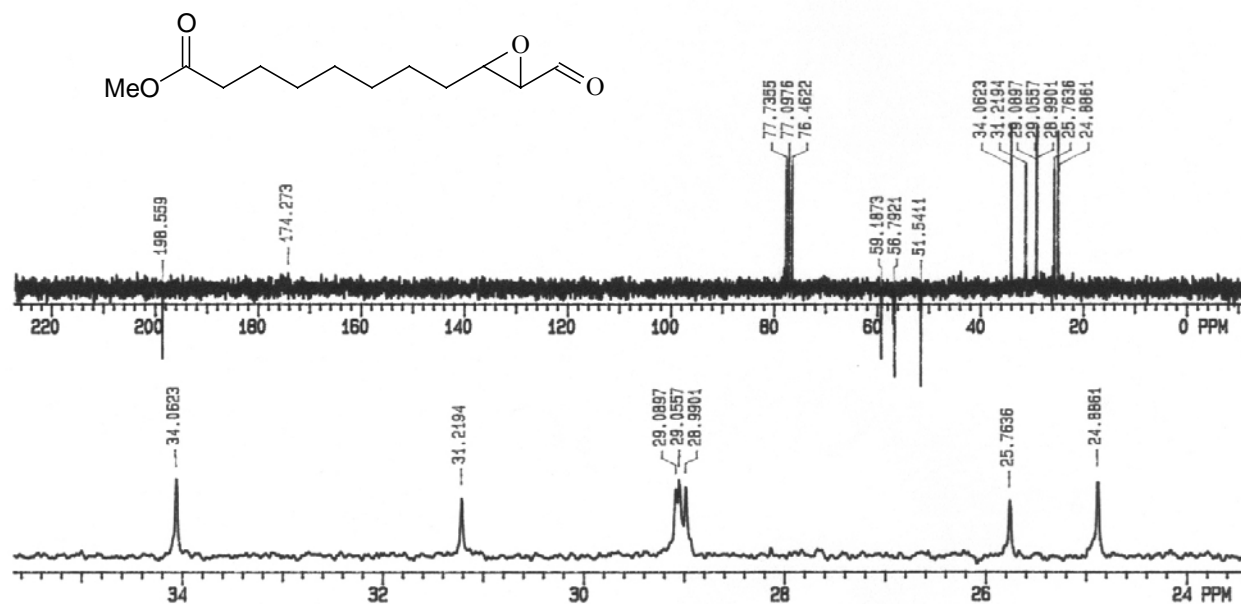
**Figure S5.** The 200 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 11-oxoundec-9(*E*)-enoate (4).



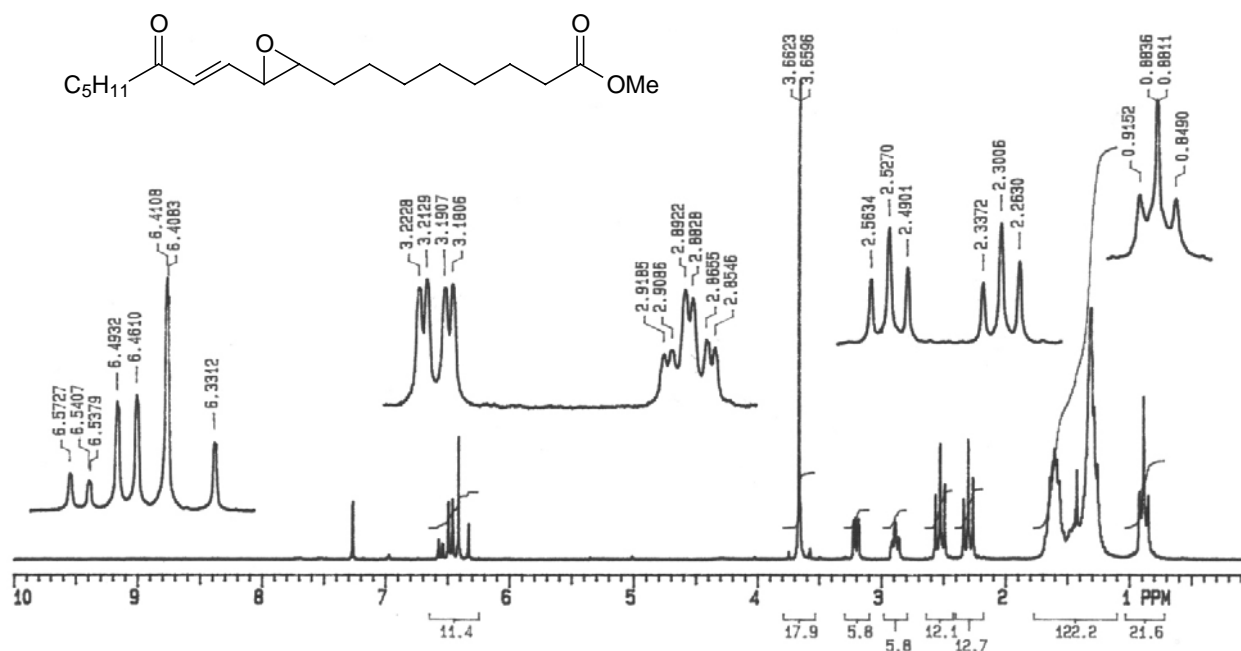
**Figure S6.** The 50 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 11-oxoundec-9(*E*)-enoate (4).



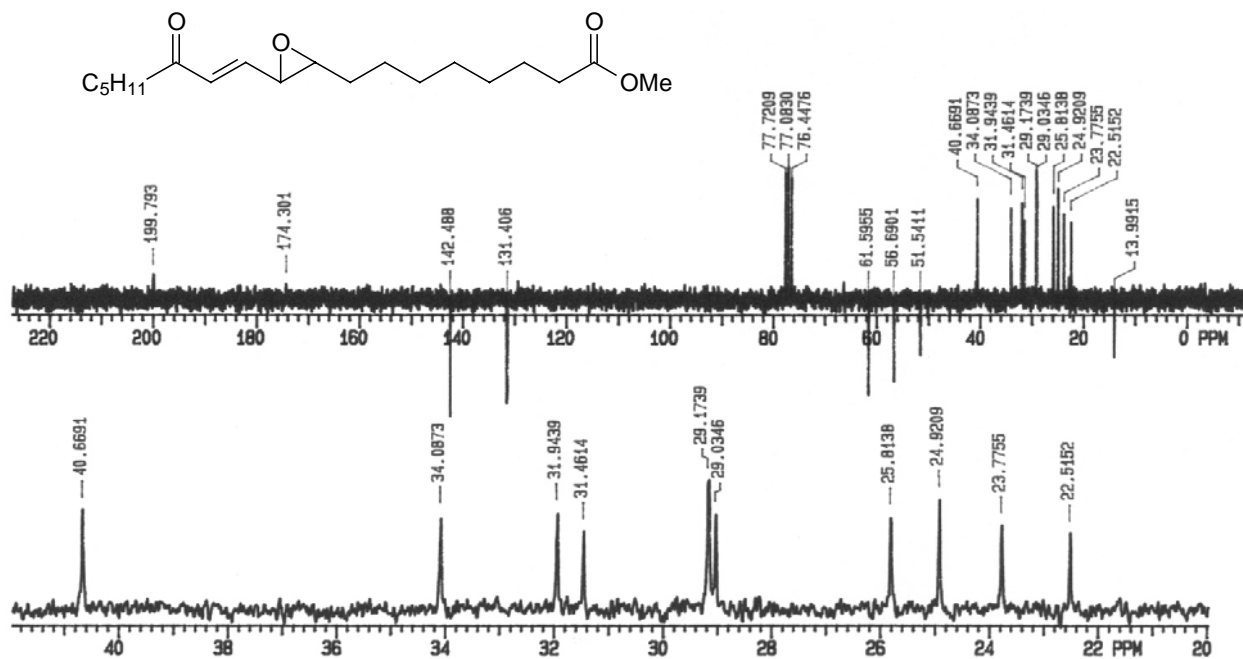
**Figure S7.** The 200 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 9,10-epoxy-11-oxoundecanoate (5).



**Figure S8.** The 50 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 9,10-epoxy-11-oxoundecanoate (5).

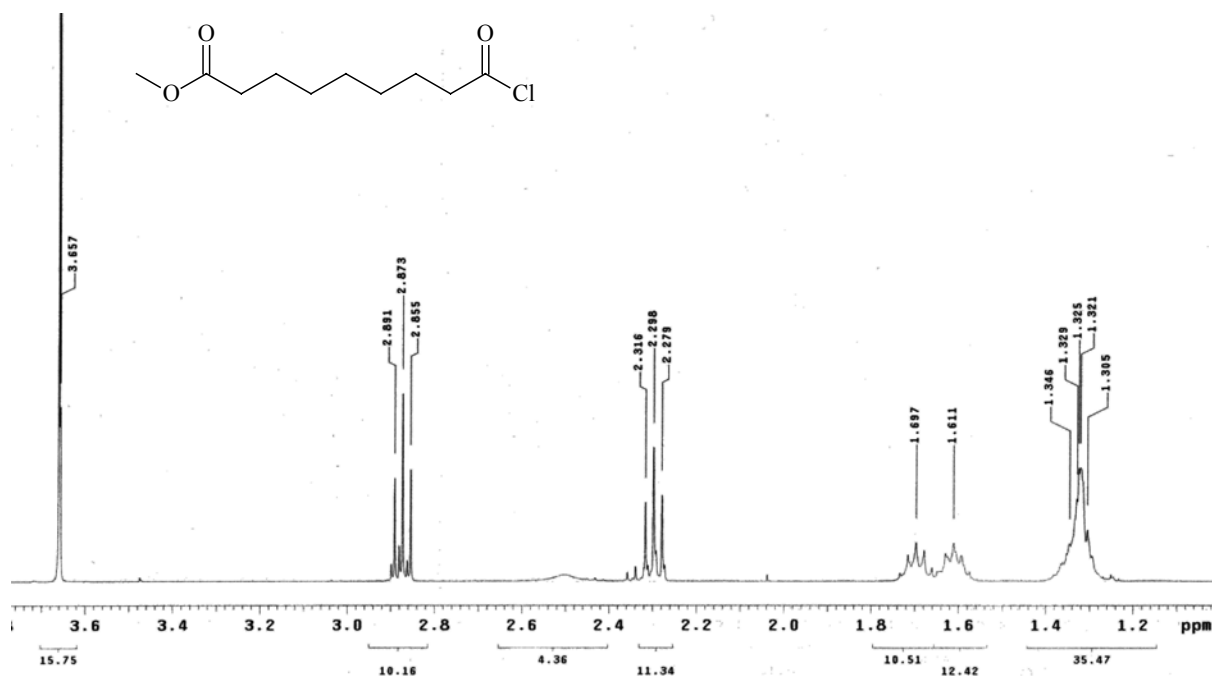


**Figure S9.** The 200 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 13-oxo-*trans*-9,10-epoxy-11(*E*)-octadecenoate (8).

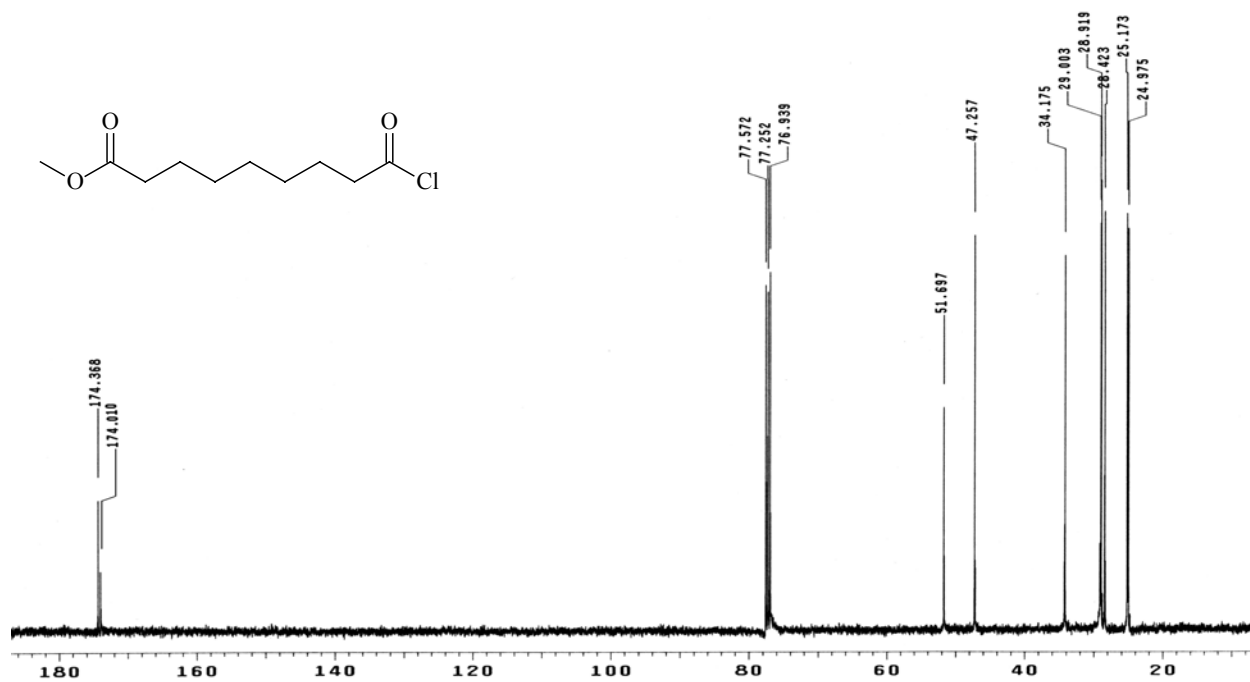


**Figure S10.** The 50 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 13-oxo-*trans*-9,10- epoxy-11(*E*)-octadecenoate (8).

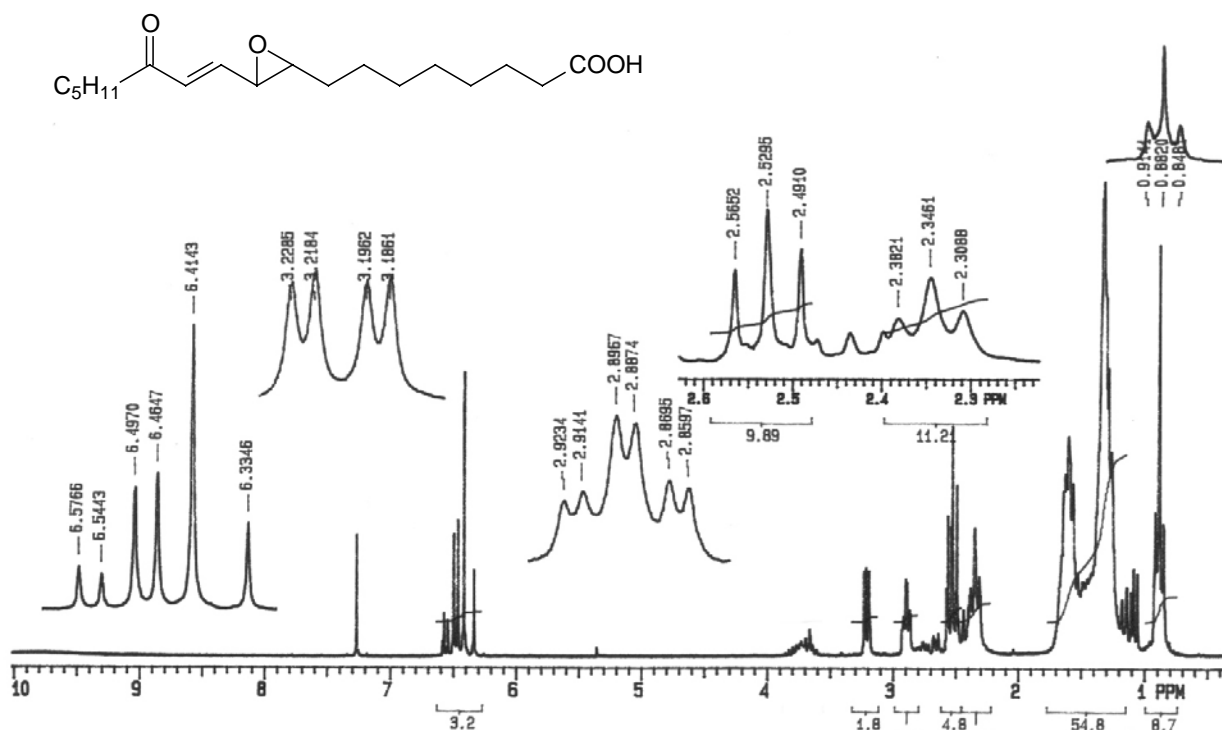




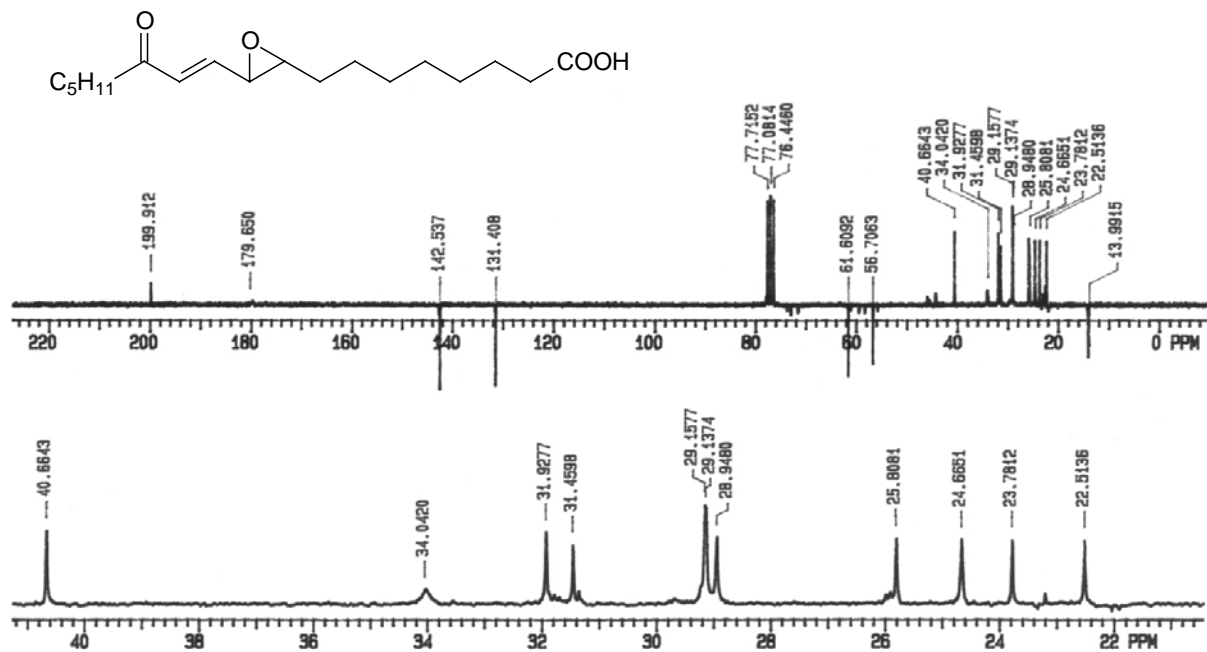
**Figure S11.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 8-(chlorocarbonyl)octanoate (9).



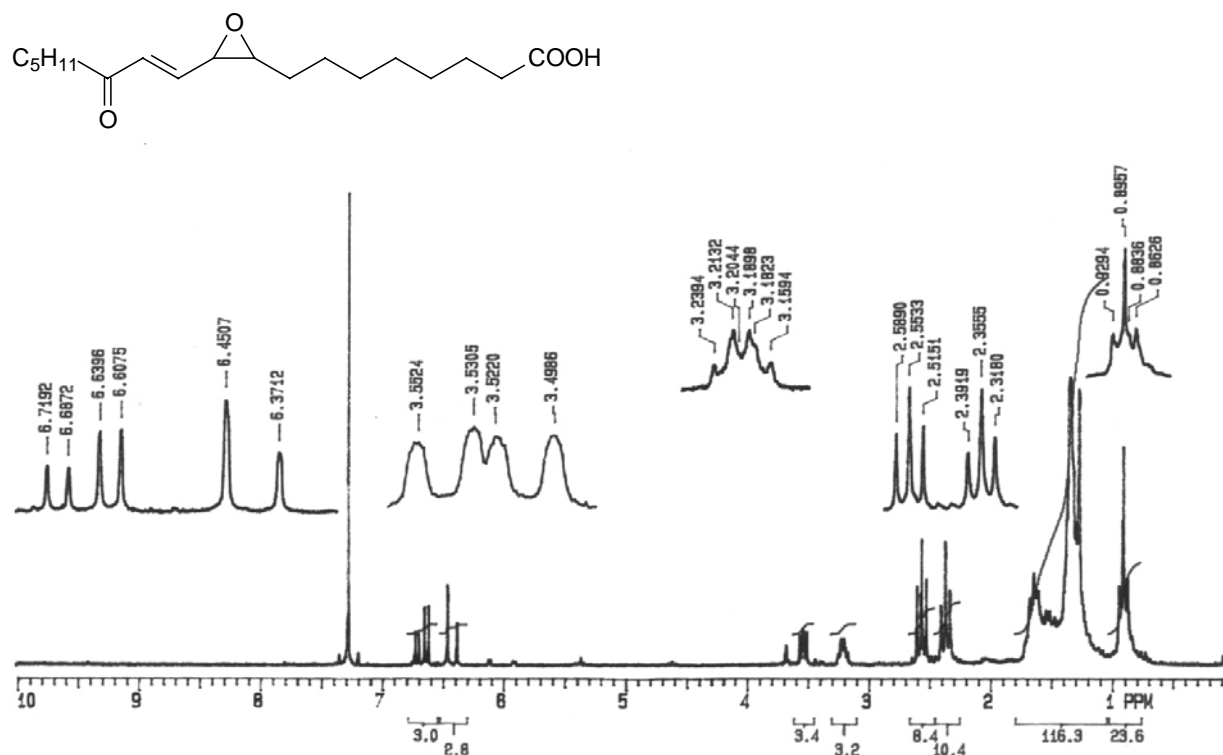
**Figure S12.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 8-(chlorocarbonyl)octanoate (9).



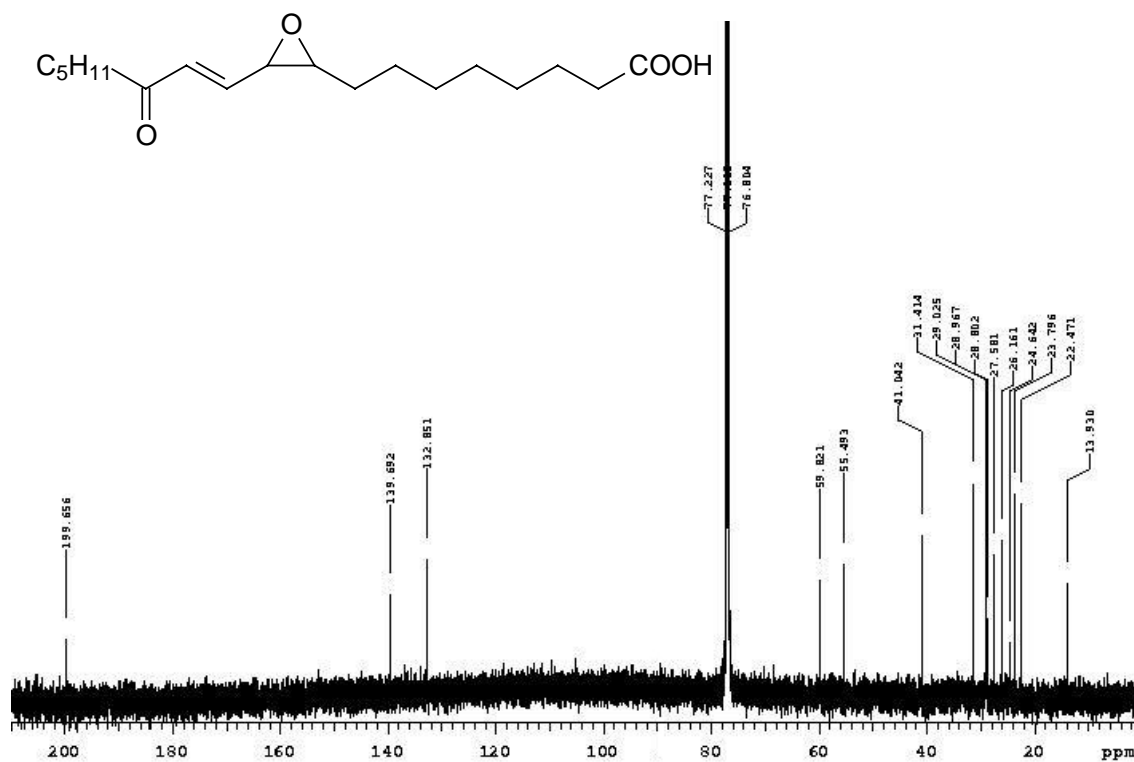
**Figure S13.** The 200 MHz  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) spectrum of 13-oxo-*trans*-9,10-epoxy-11(*E*)-octadecenoic acid (*trans*-EKODE-Ia).



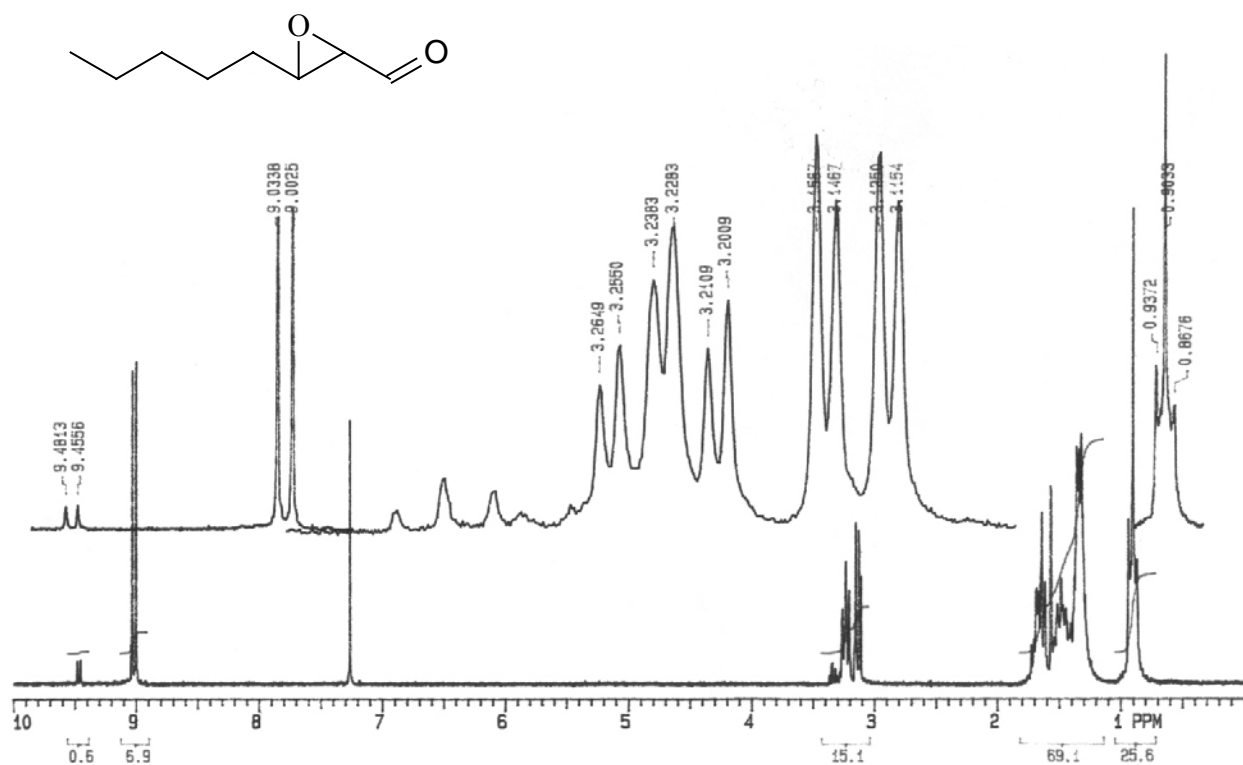
**Figure S14.** The 50 MHz  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ) spectrum of 13-oxo-*trans*-9,10-epoxy-11(*E*)-octadecenoic acid (*trans*-EKODE-Ia).



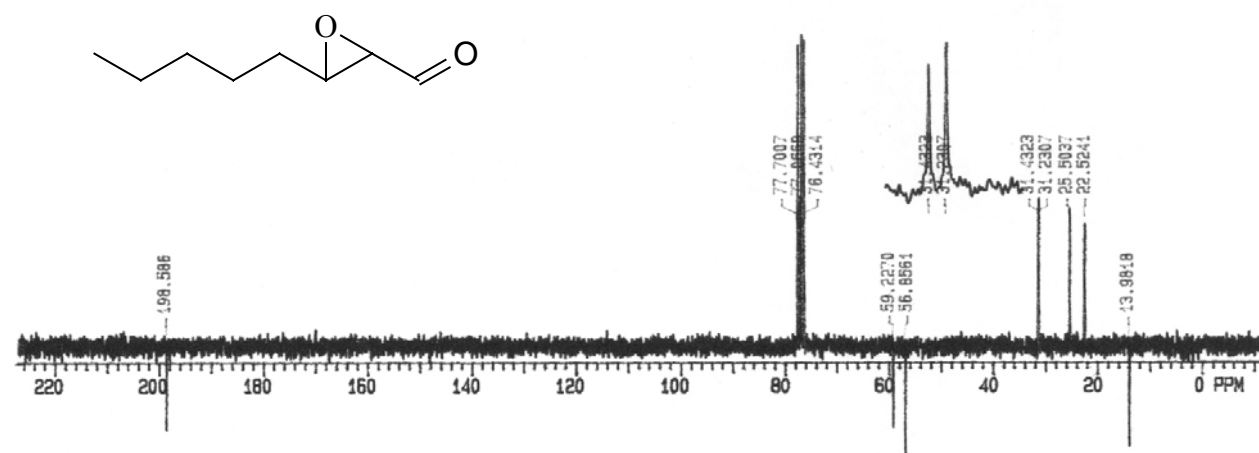
**Figure S15.** The 200 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of 13-oxo-*cis*-9,10-epoxy-11(*E*)-octadecenoic acid (*cis*-EKODE-Ia)



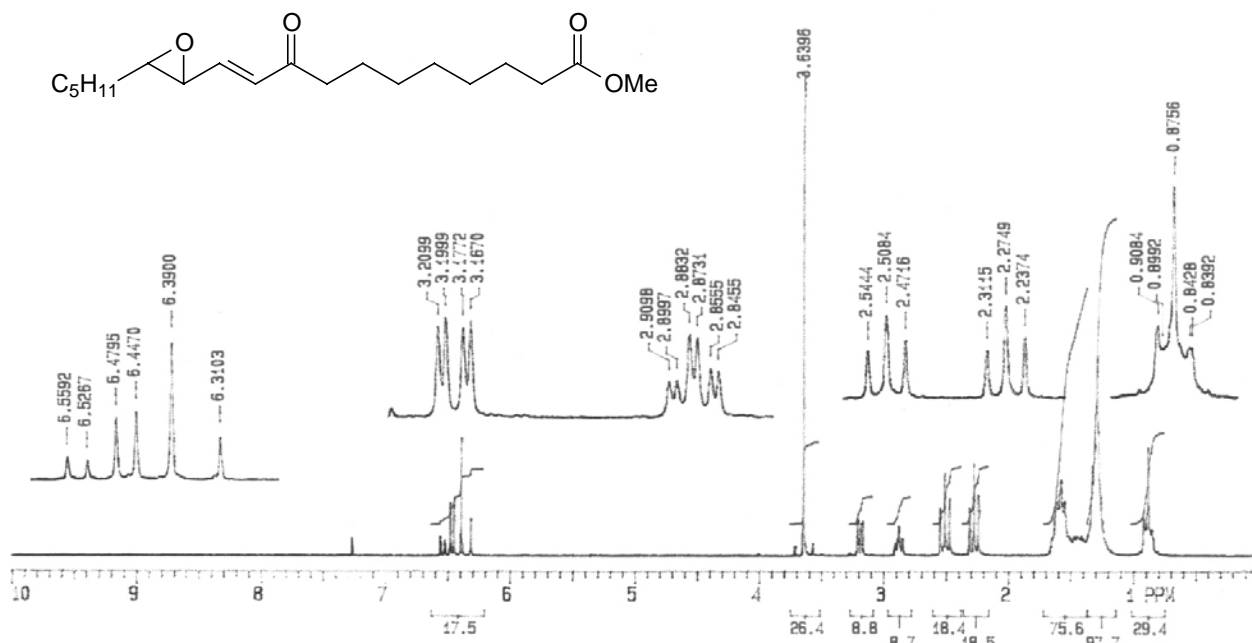
**Figure S16.** The 150 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of 13-Oxo-*cis*-9,10-epoxy-11(*E*)-octadecenoic acid (*cis*-EKODE-Ia)



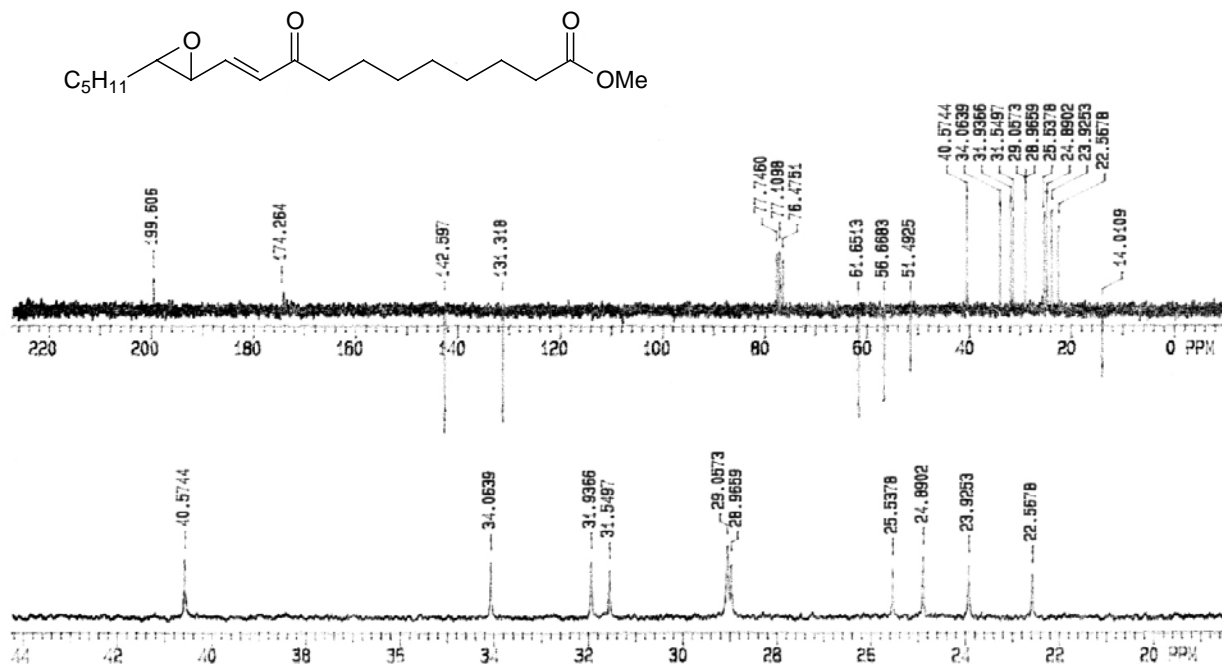
**Figure S17.** The 200 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of *trans*-2,3-epoxyoctanal (**12**).



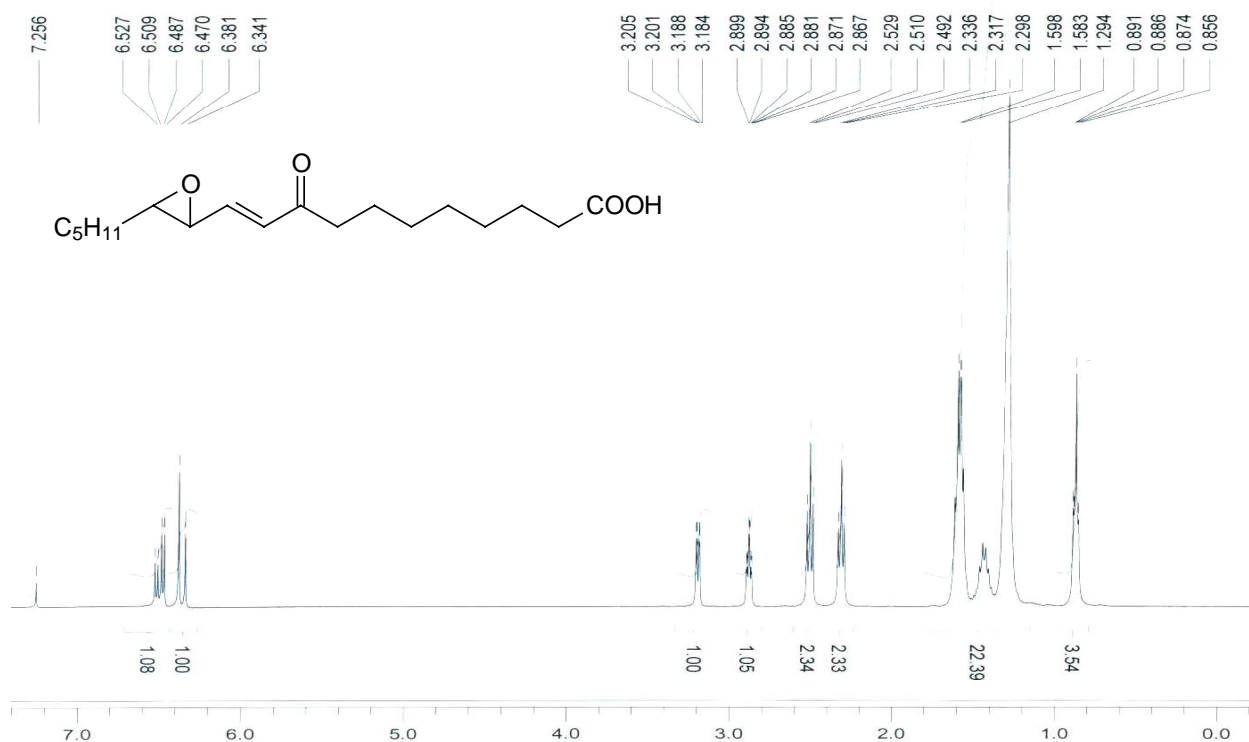
**Figure S18.** The 50 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of *trans*-2,3-epoxyoctanal (**12**).



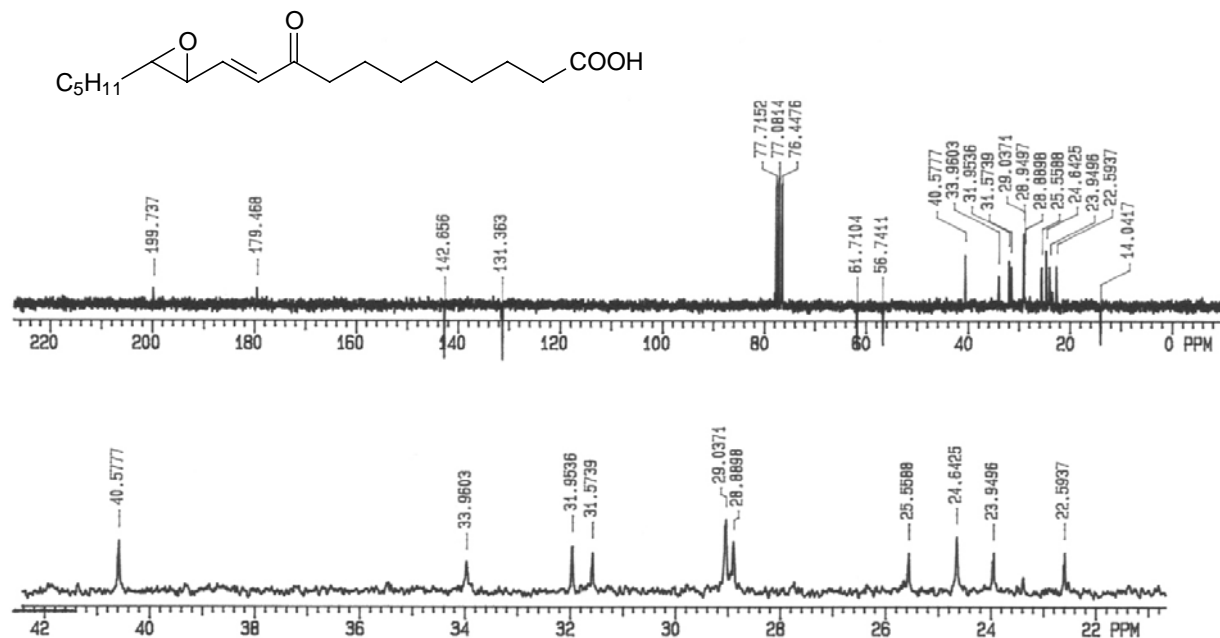
**Figure S19.** The 200 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 9-oxo-*trans*-12,13-epoxy-10(*E*)-octadecenoate (**13**).



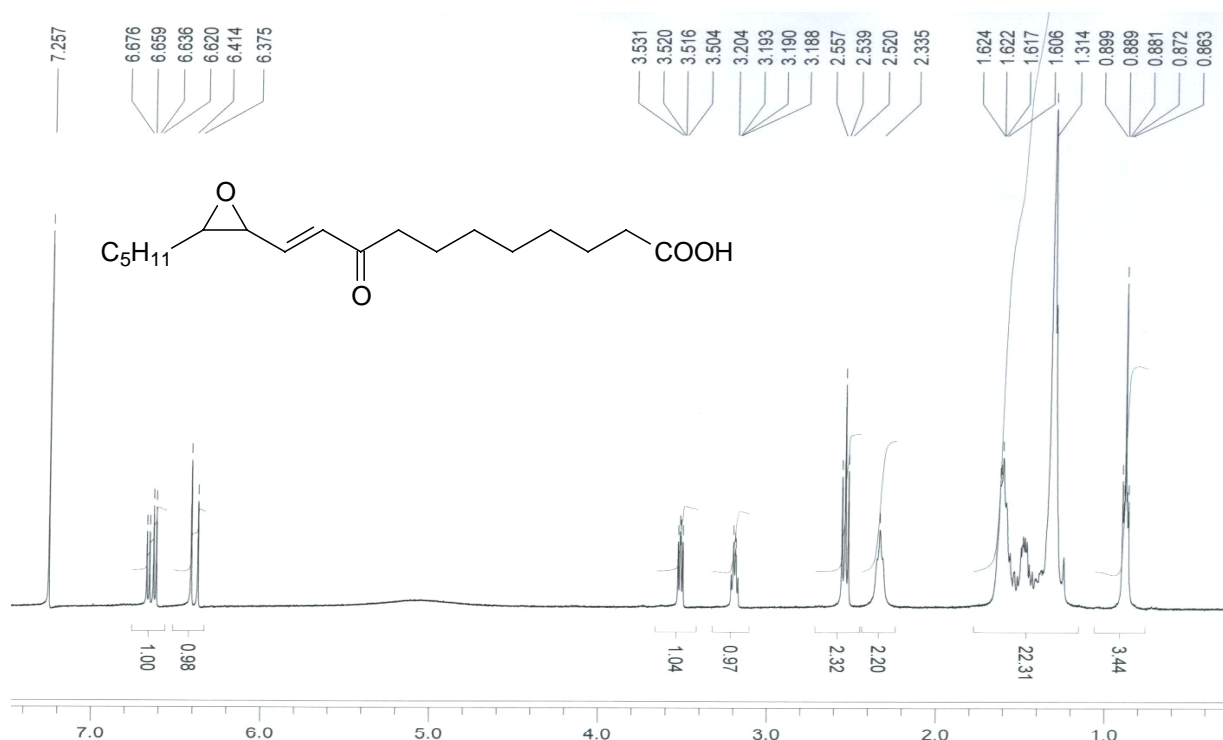
**Figure S20.** The 50 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 9-oxo-*trans*-12,13-epoxy-10(*E*)-octadecenoate (**13**).



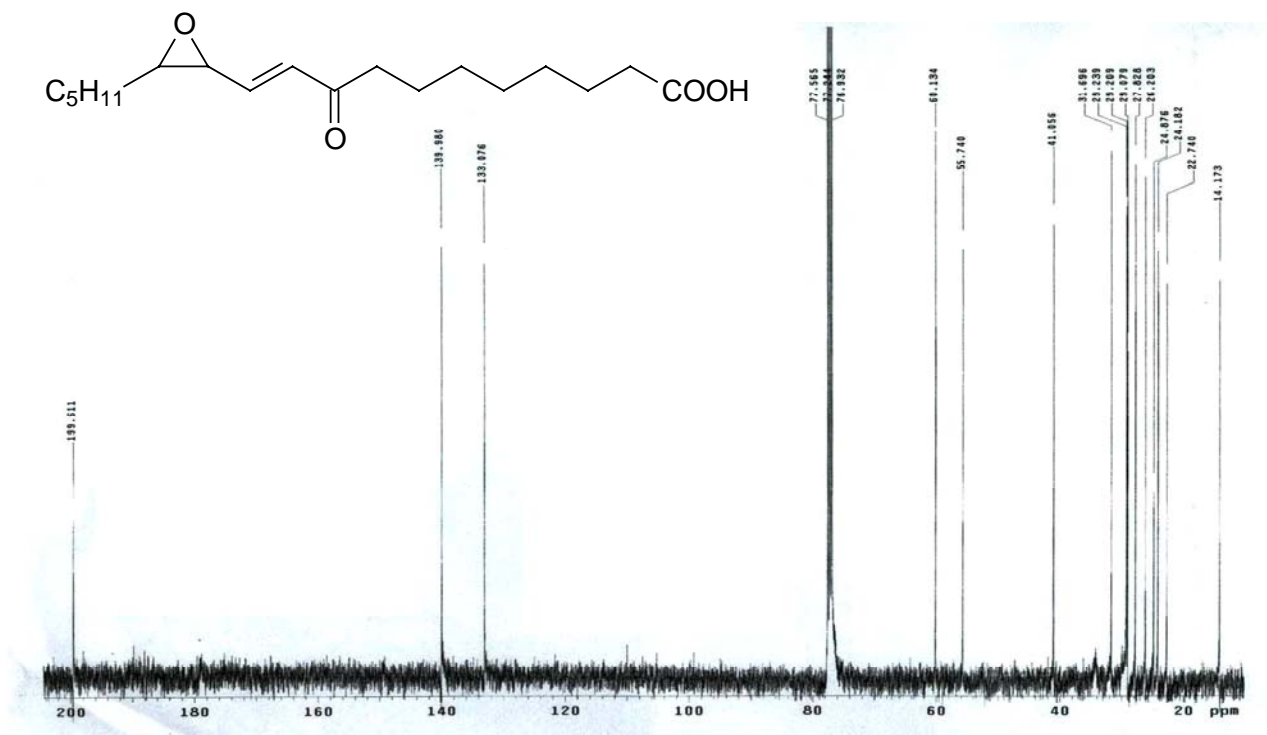
**Figure S21.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of 9-Oxo-*trans*-12,13-epoxy-10(*E*)-octadecenoic acid (*trans*-EKODE-Ib).



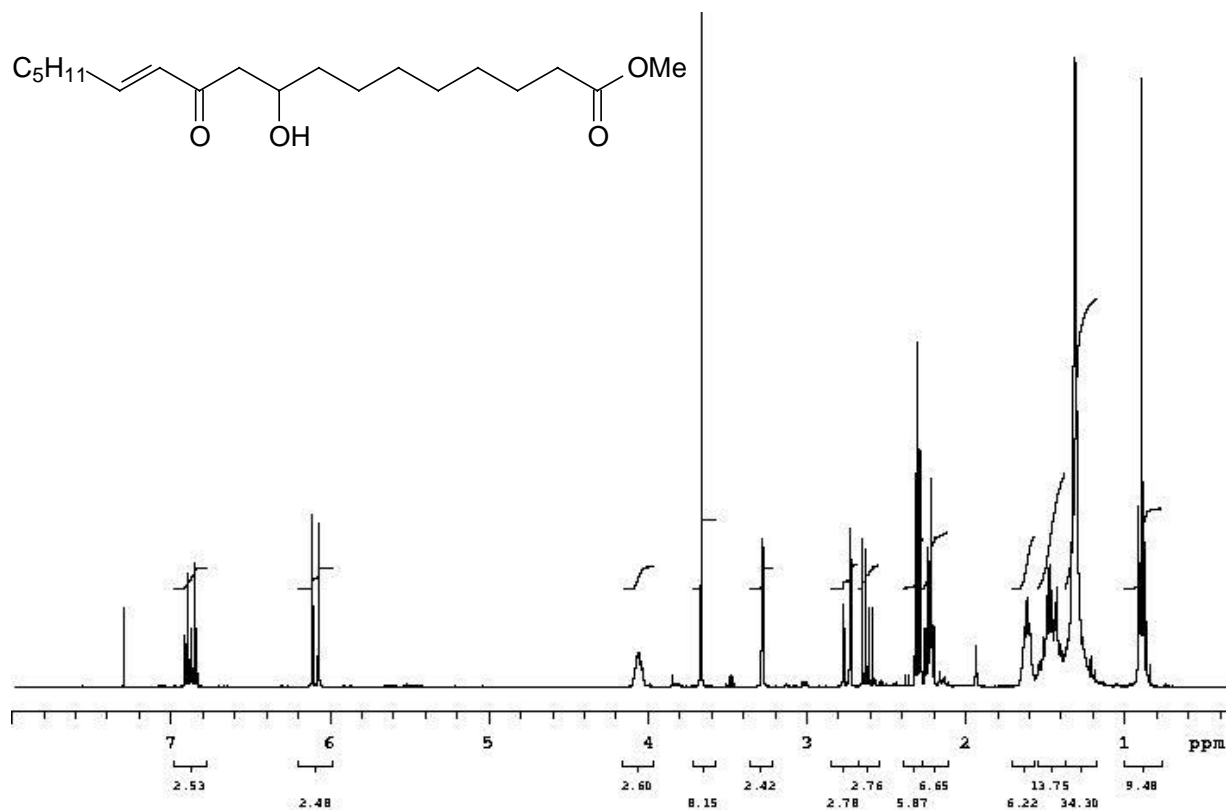
**Figure S22.** The 50 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of 9-oxo-*trans*-12,13-epoxy-10(*E*)-octadecenoic acid (*trans*-EKODE-Ib).



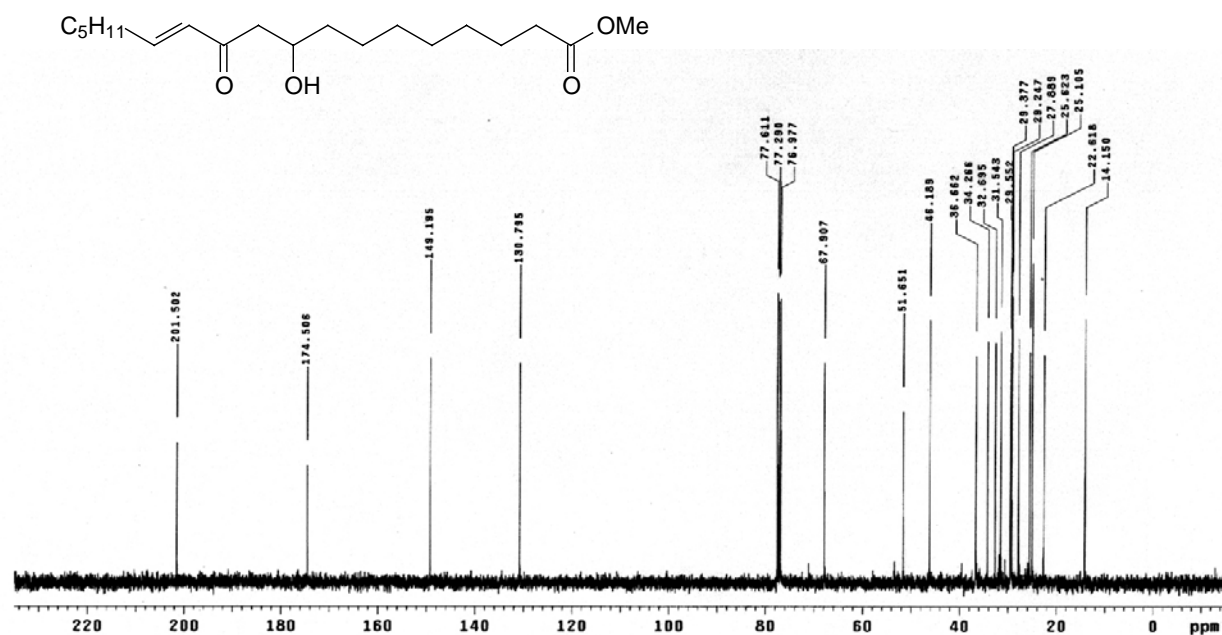
**Figure S23.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of 9-oxo-*cis*-12,13-epoxy-10(*E*)-octadecenoic acid (*cis*-EKODE-Ib).



**Figure S24.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of 9-oxo-*cis*-12,13-epoxy-10(*E*)-octadecenoic acid (*cis*-EKODE-Ib).

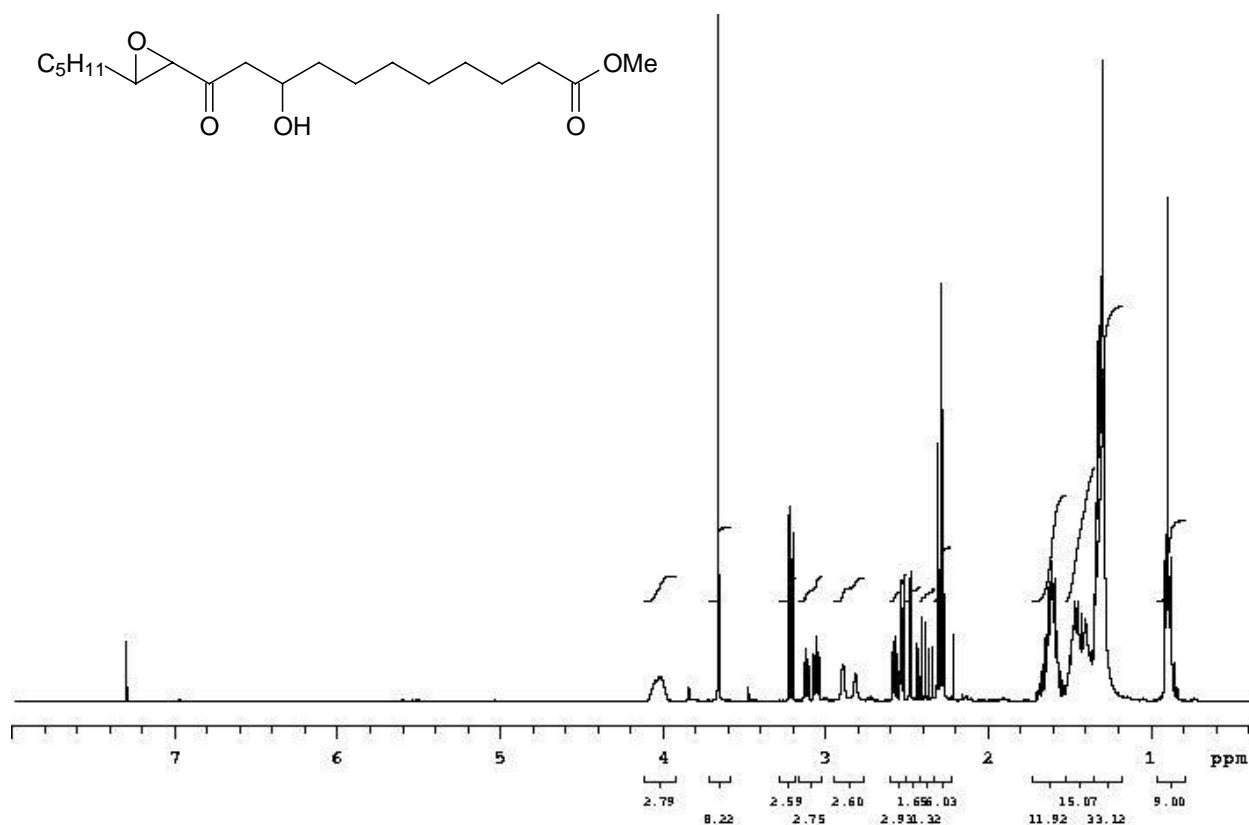


**Figure S25.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 9-hydroxy-11-oxooctadec-12(*E*)-enoate (**15**).

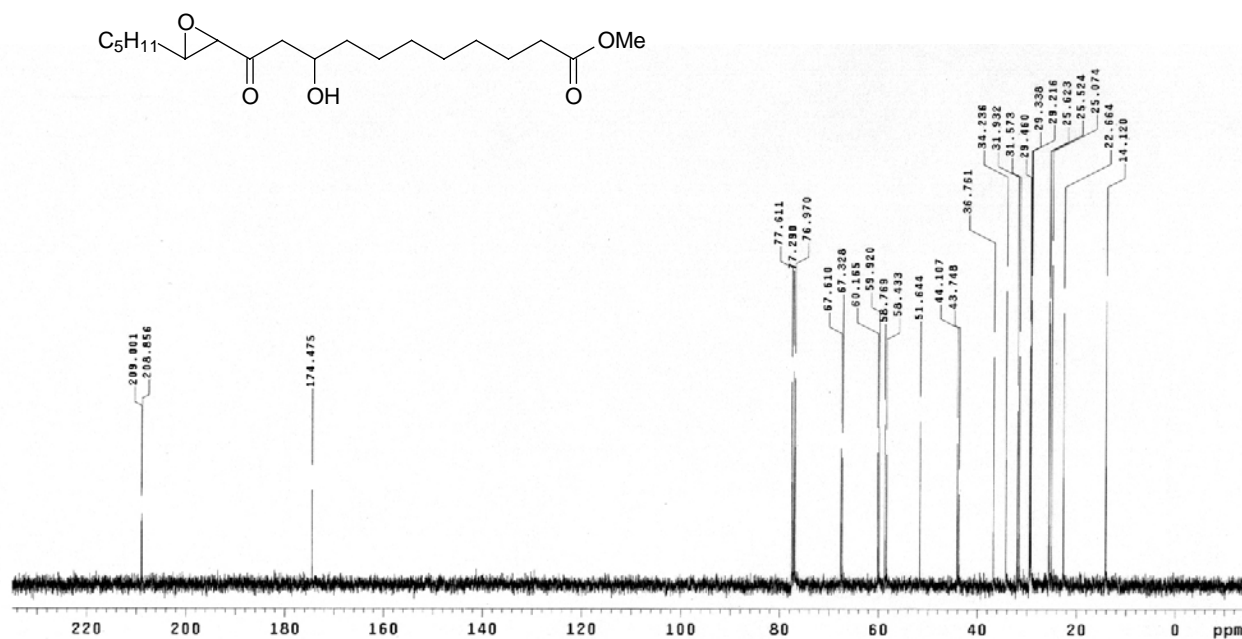


**Figure S26.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 9-hydroxy-11-oxooctadec-12(*E*)-enoate (**15**).

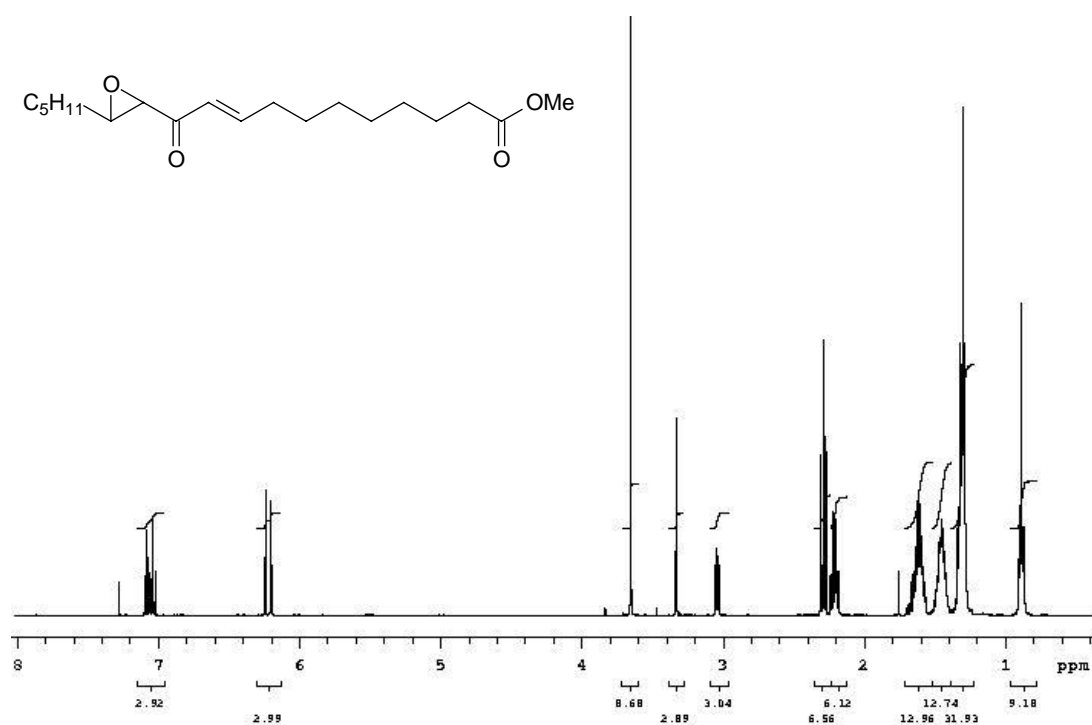




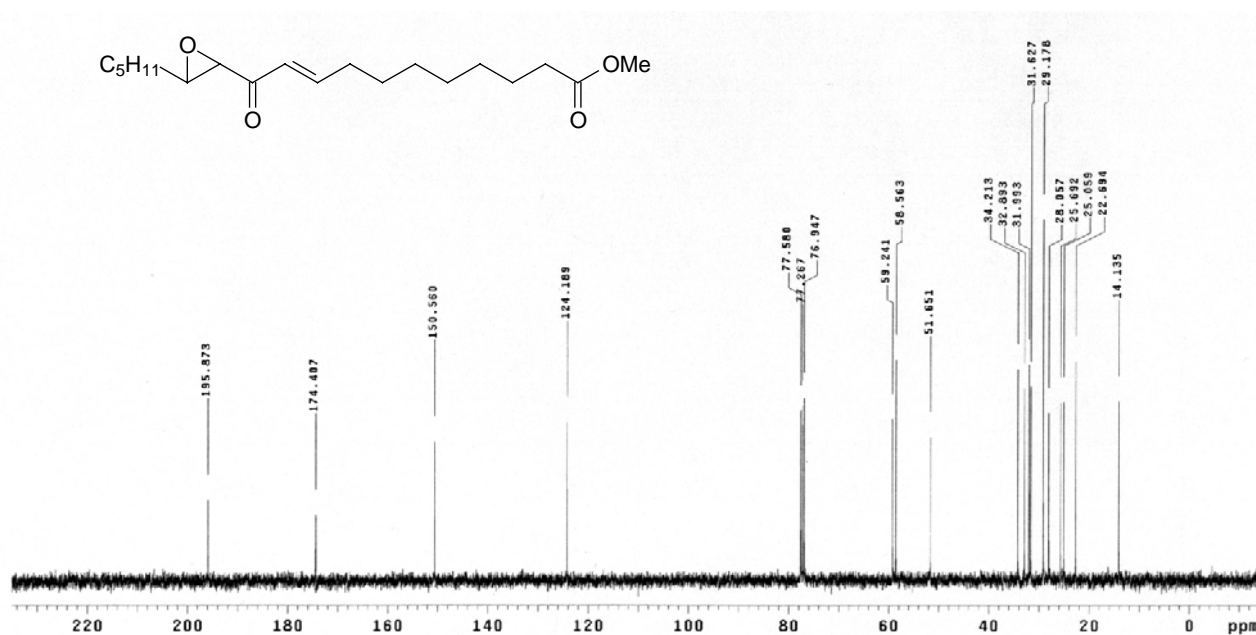
**Figure S27.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl *trans*-12,13-epoxy-11-oxo-9-hydroxyoctadecanoate (**16**).



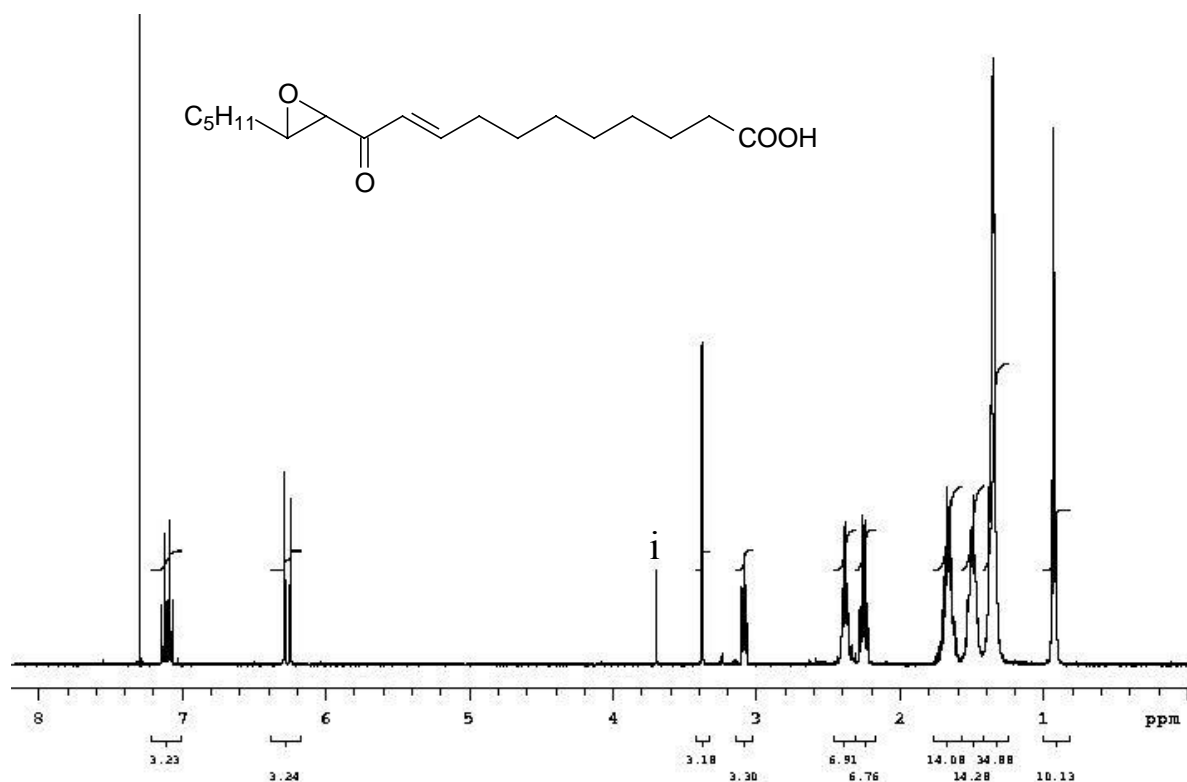
**Figure S28.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl *trans*-12,13-epoxy-11-oxo-9-hydroxyoctadecanoate (**16**).



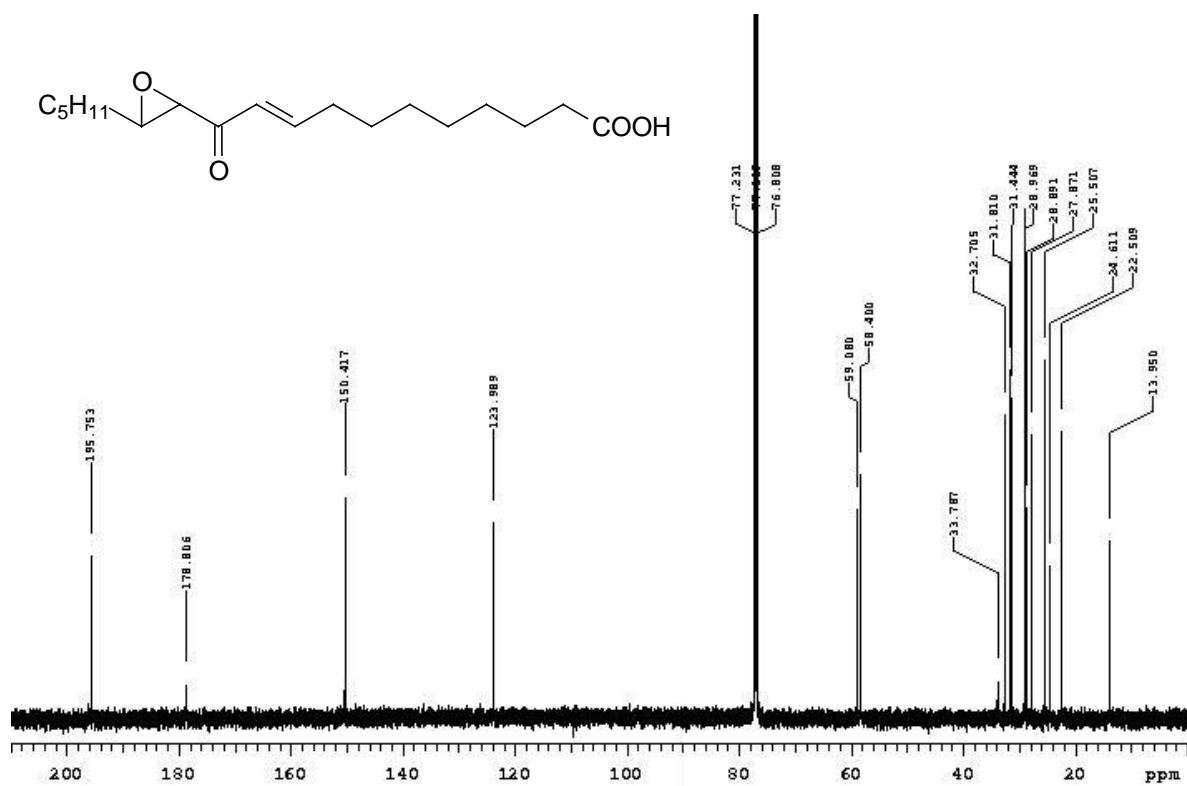
**Figure S29.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl *trans*-12,13-epoxy-11-oxo-9(*E*)-octadecenoate (**17**).



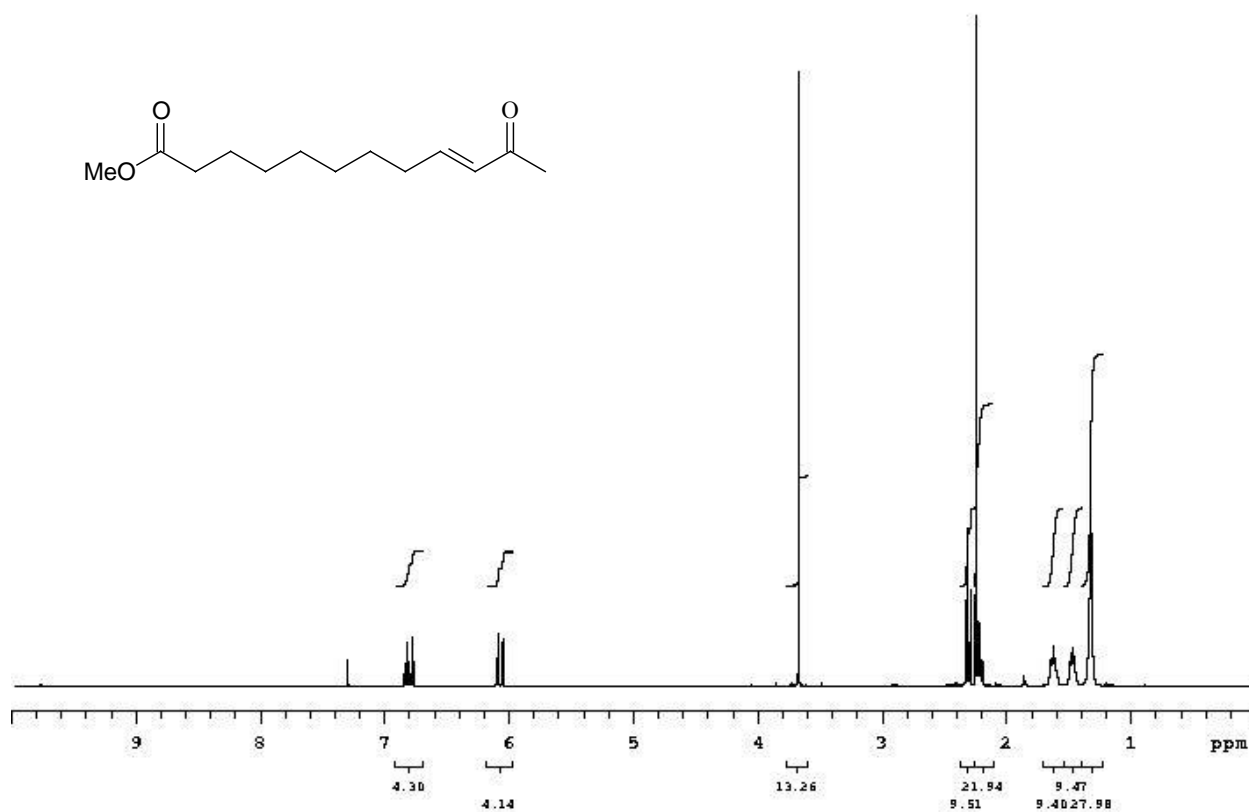
**Figure S30.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl *trans*-12,13-epoxy-11-oxo-9(*E*)-octadecenoate (**17**).



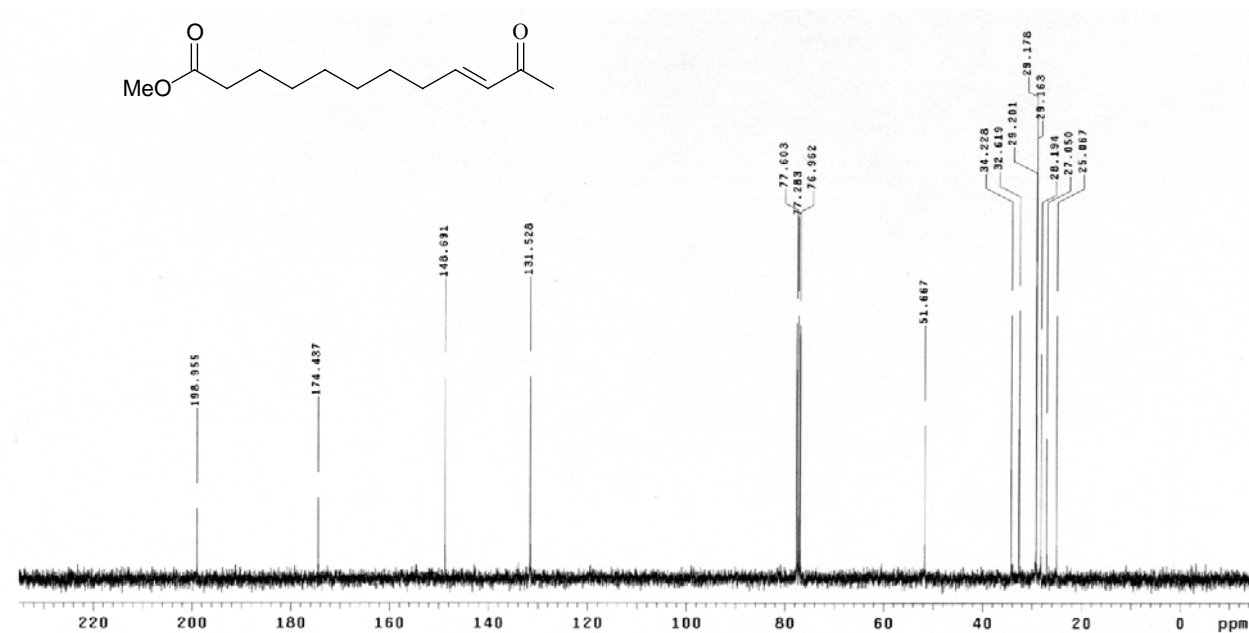
**Figure S31.** The 400 MHz  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) spectrum of *trans*-12,13-epoxy-11-oxo-9(*E*)-octadecenoic acid (*trans*-**EKODE-IIb**).



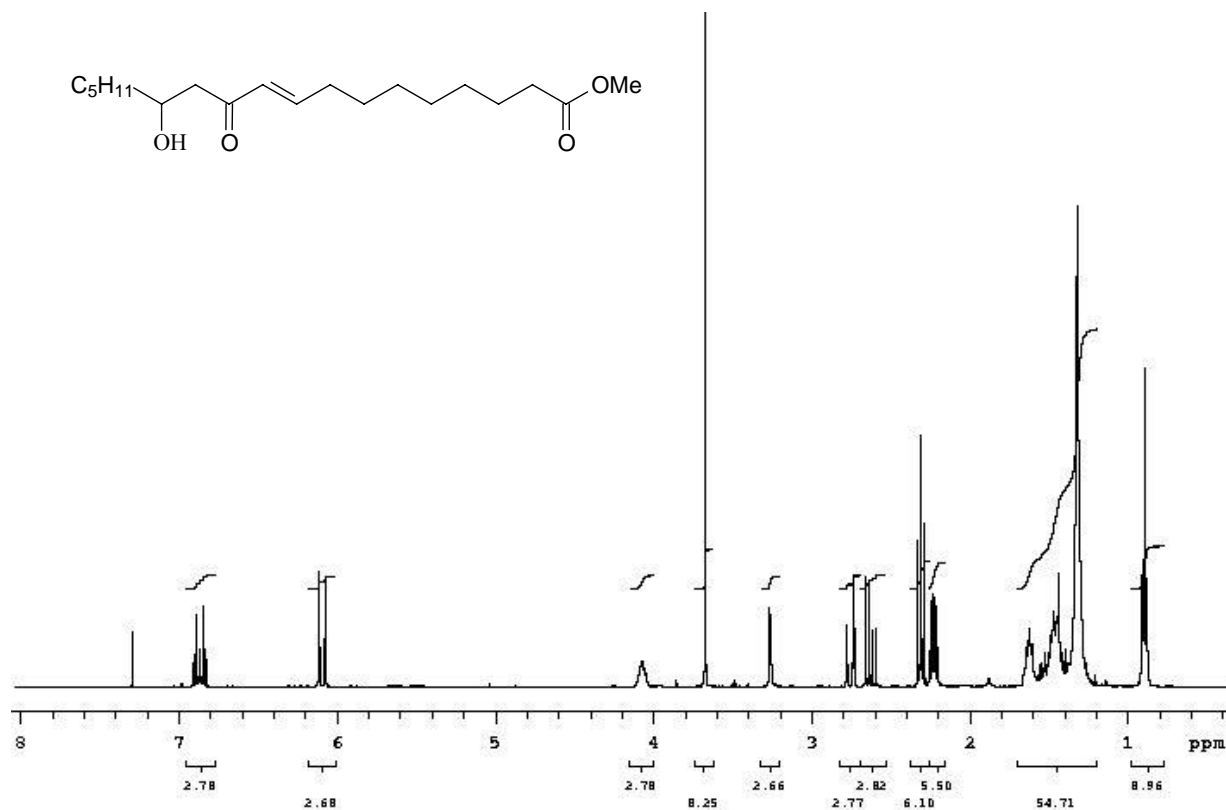
**Figure S32.** The 150 MHz  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ) spectrum of *trans*-12,13-epoxy-11-oxo-9(*E*)-octadecenoic acid (*trans*-**EKODE-IIb**).



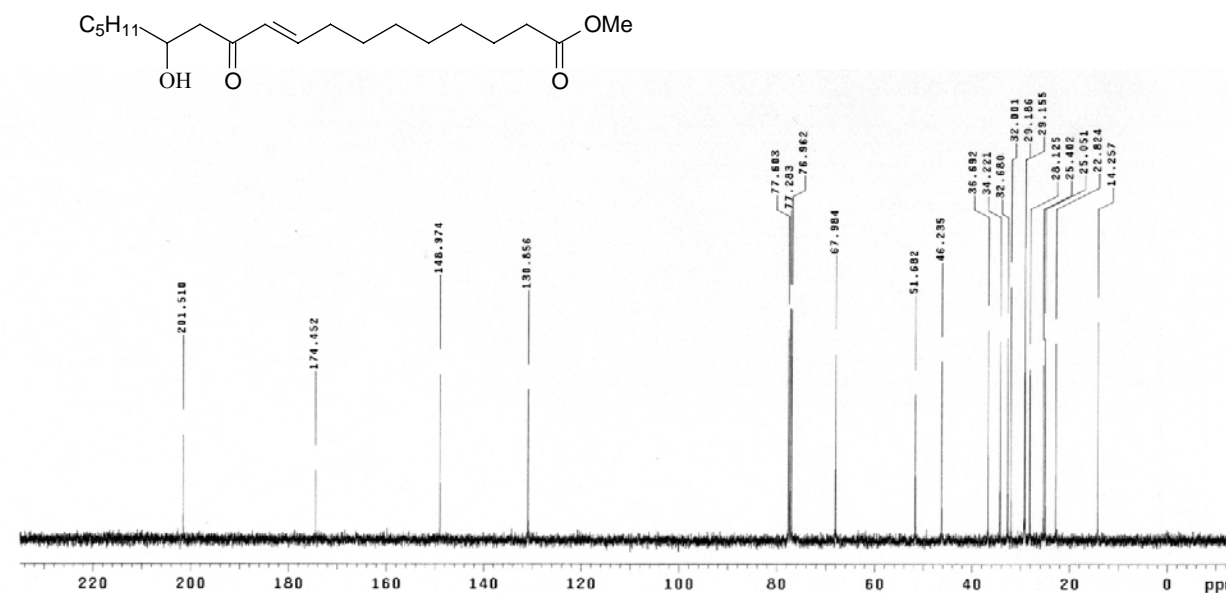
**Figure S33.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 11-oxododec-9(*E*)-enoate (**18**).



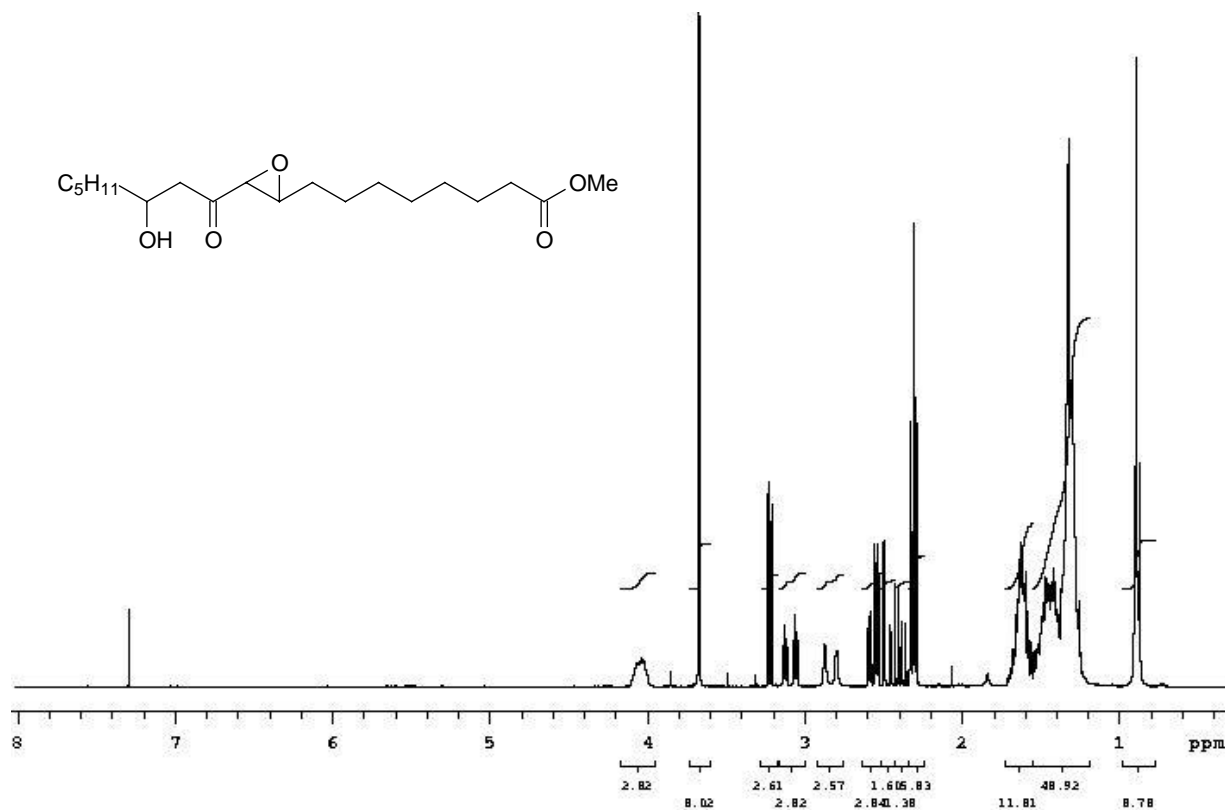
**Figure S34.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 11-oxododec-9(*E*)-enoate (**18**).



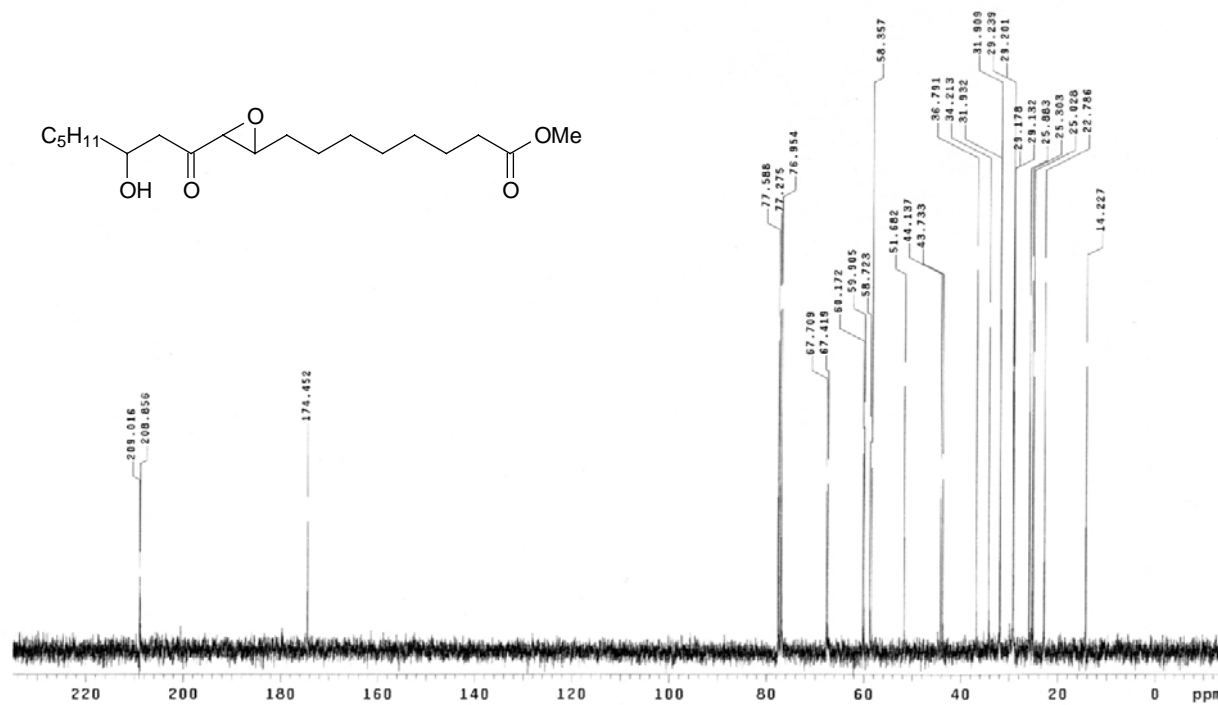
**Figure S35.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl 13-hydroxy-11-oxooctadec-9(*E*)-enoate (**19**).



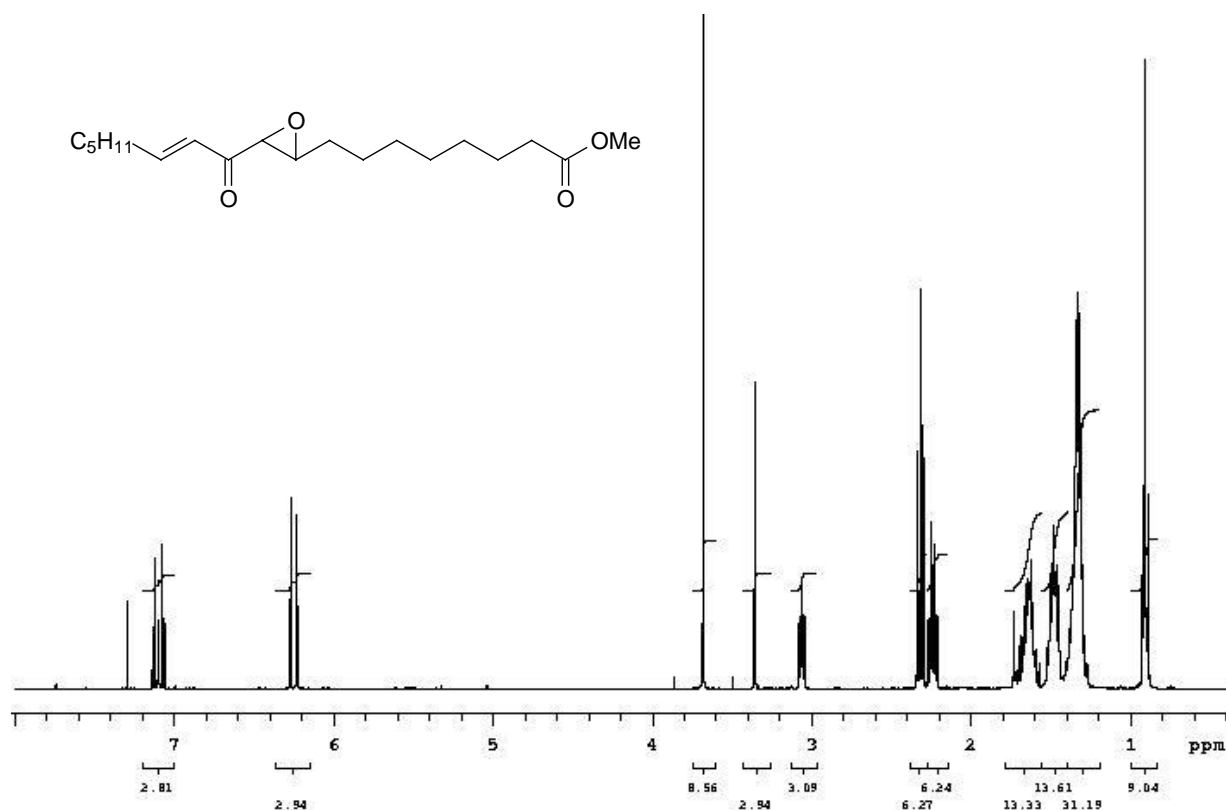
**Figure S36.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl 13-hydroxy-11-oxooctadec-9(*E*)-enoate (**19**).



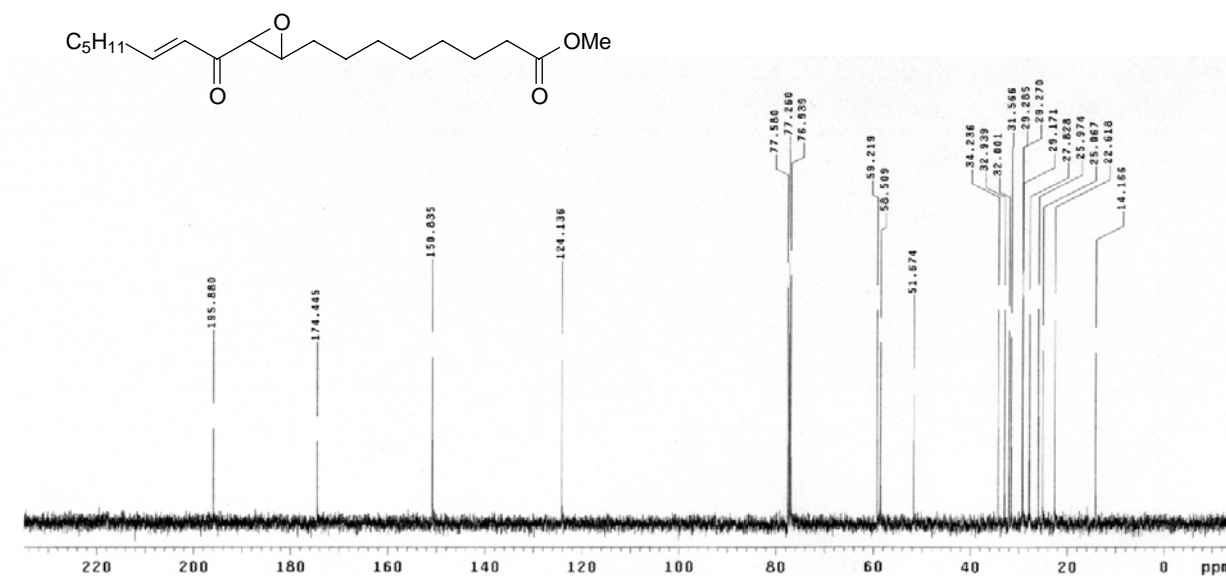
**Figure S37.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl *trans*-9,10-epoxy-11-oxo-13-hydroxyoctadecanoate (**20**).



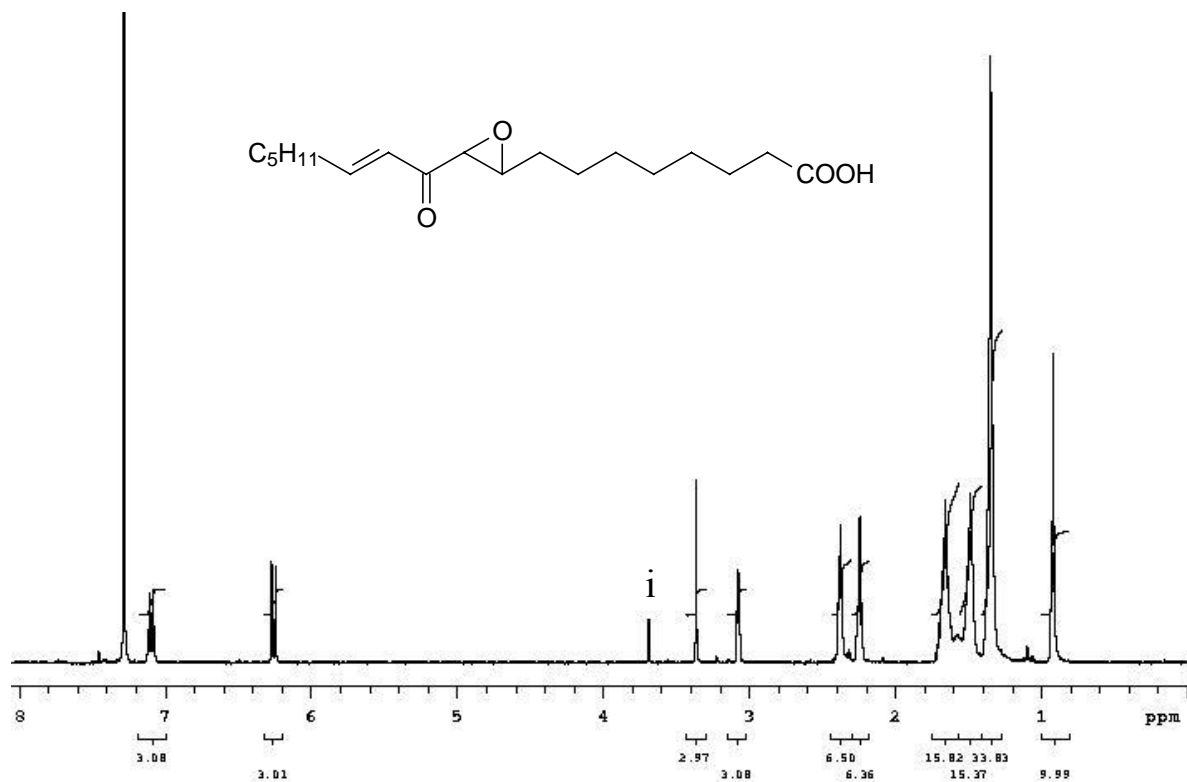
**Figure S38.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl *trans*-9,10-epoxy-11-oxo-13-hydroxyoctadecanoate (**20**).



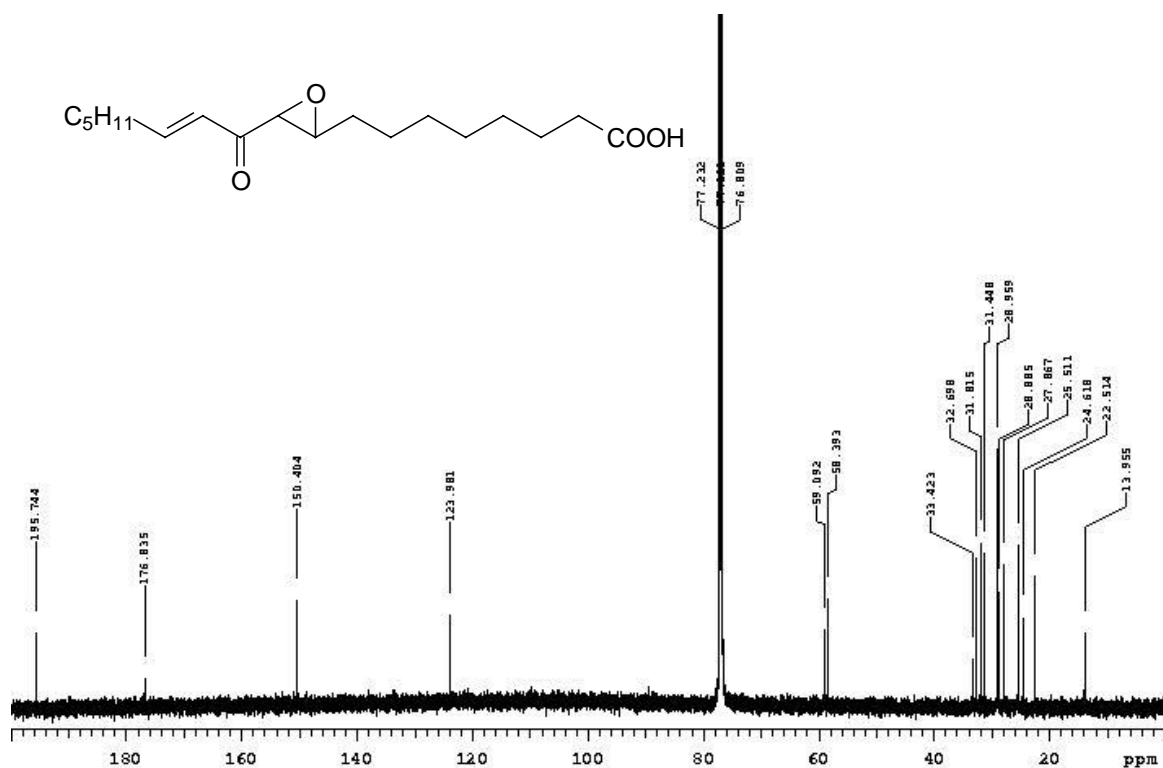
**Figure S39.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of methyl *trans*-9,10-epoxy-11-oxo-12(*E*)-octadecenoate (21).



**Figure S40.** The 100 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of methyl *trans*-9,10-epoxy-11-oxo-12(*E*)-octadecenoate (21).

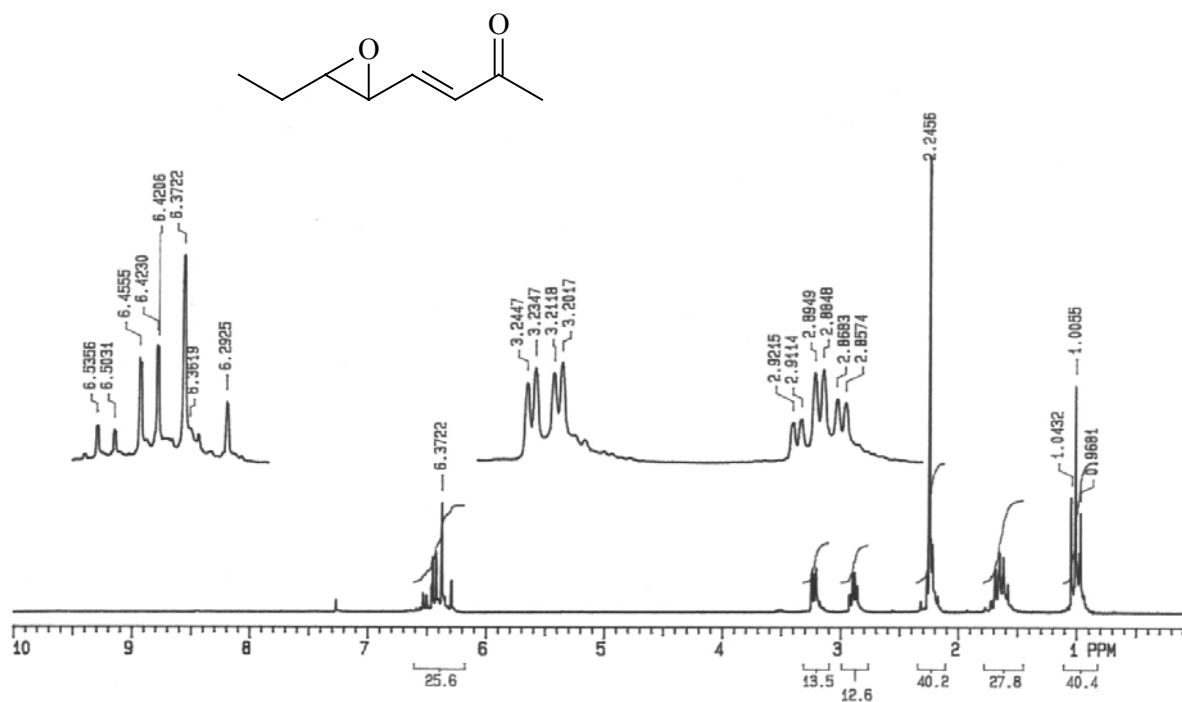


**Figure S41.** The 400 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of *trans*-9,10-epoxy-11-oxo-12(*E*)-octadecenoic acid (*trans*-EKODE-IIa).

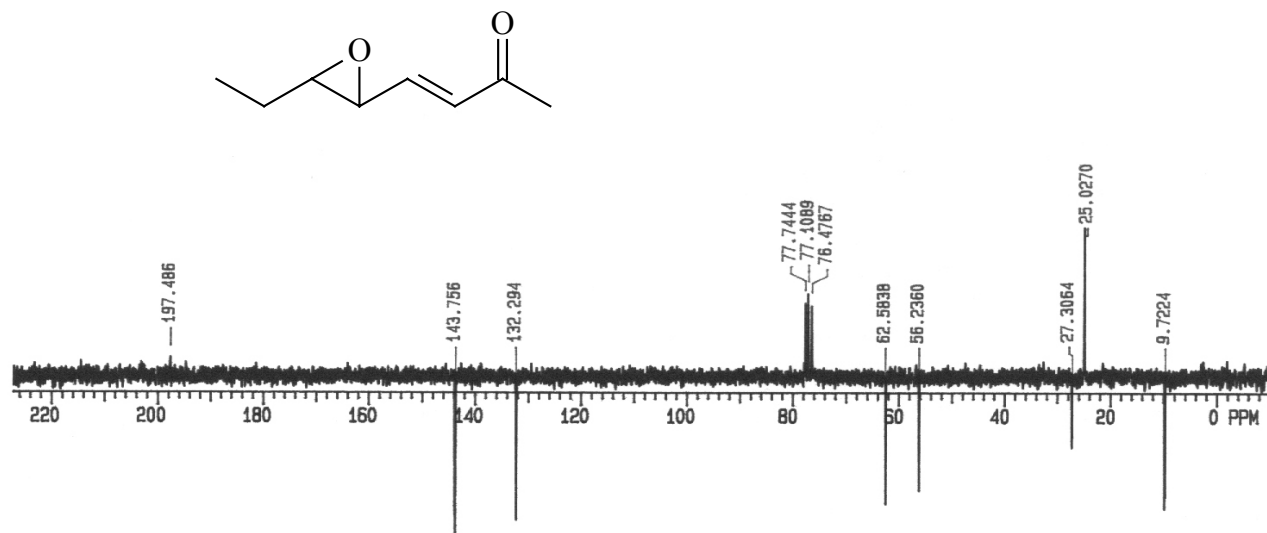


**Figure S42.** The 150 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of *trans*-9,10-epoxy-11-oxo-12(*E*)-octadecenoic acid (*trans*-EKODE-IIa).



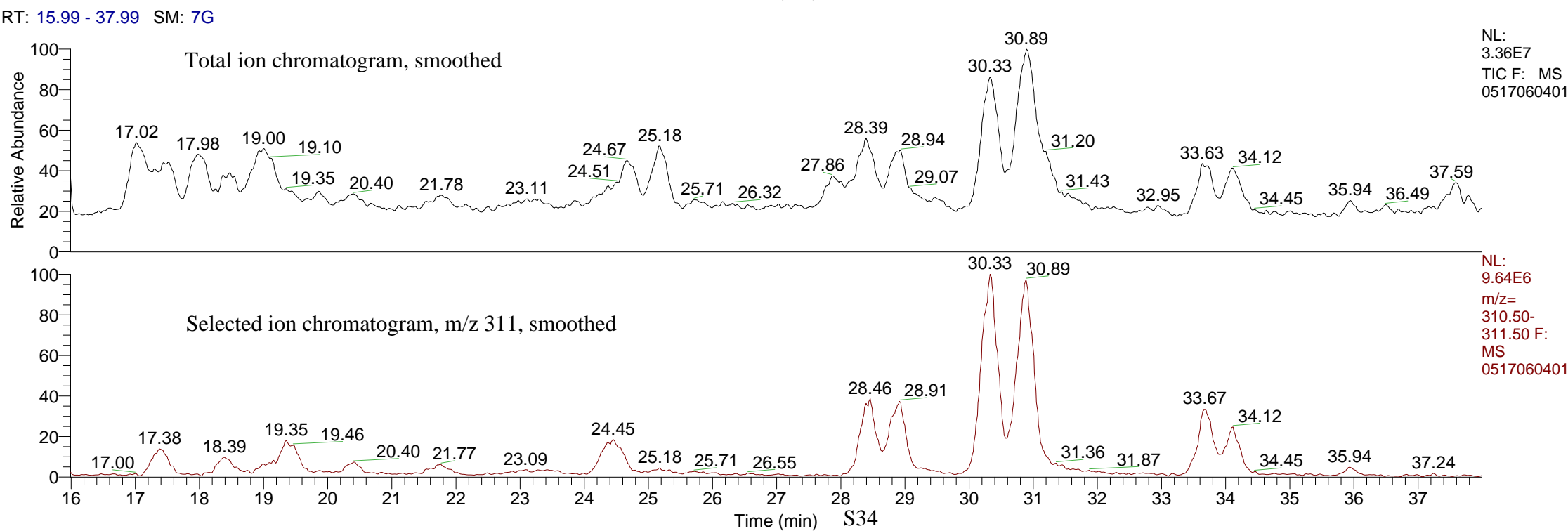
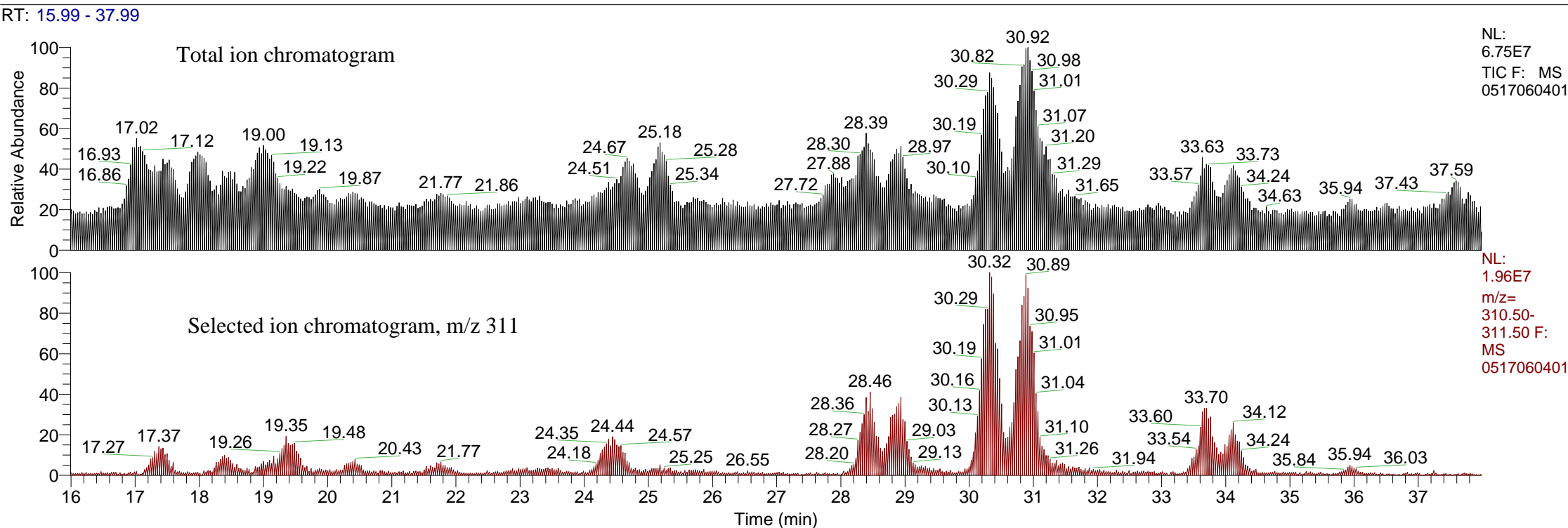


**Figure S43.** The 200 MHz <sup>1</sup>H-NMR (CDCl<sub>3</sub>) spectrum of *trans*-5,6-epoxy-3(*E*)-octen-2-one (23).

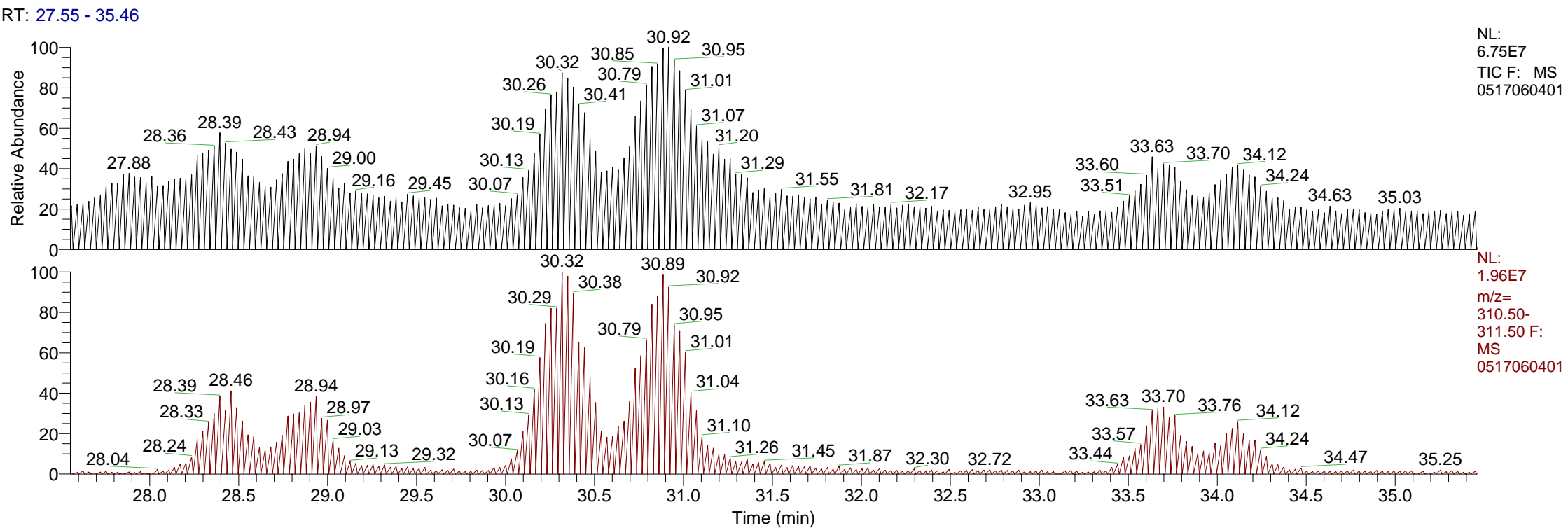


**Figure S44.** The 50 MHz <sup>13</sup>C-NMR (CDCl<sub>3</sub>) spectrum of *trans*-5,6-epoxy-3(*E*)-octen-2-one (23).

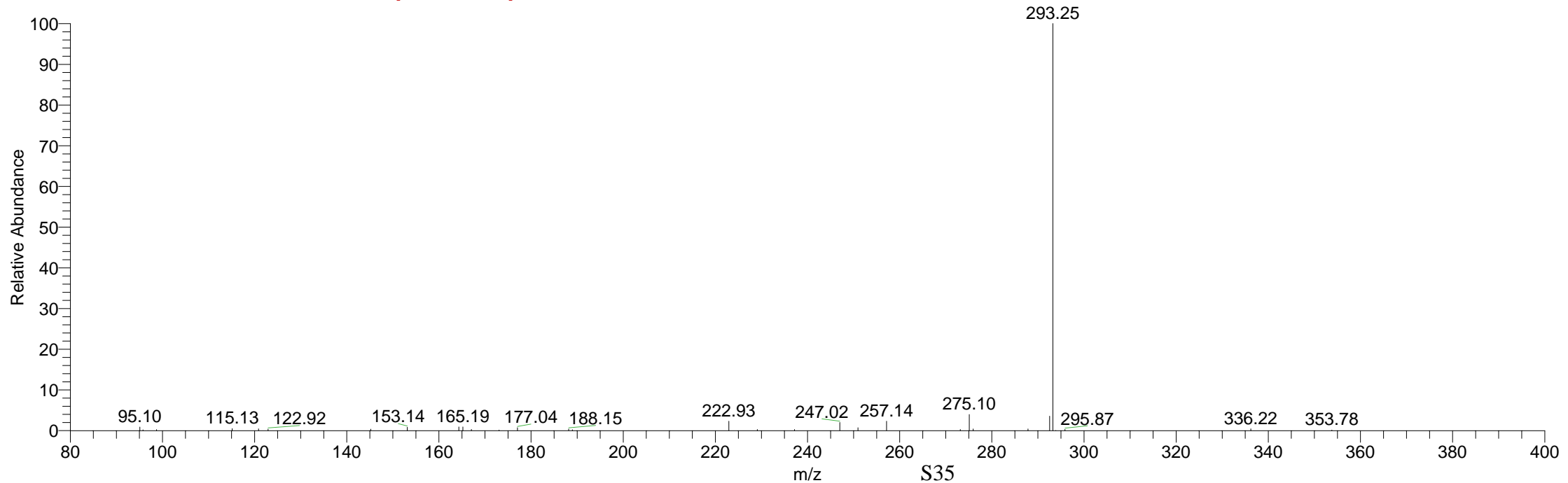
**Figure S45.** LC-MS TIC and SIC (m/z 311) for autoxidized linoleic acid

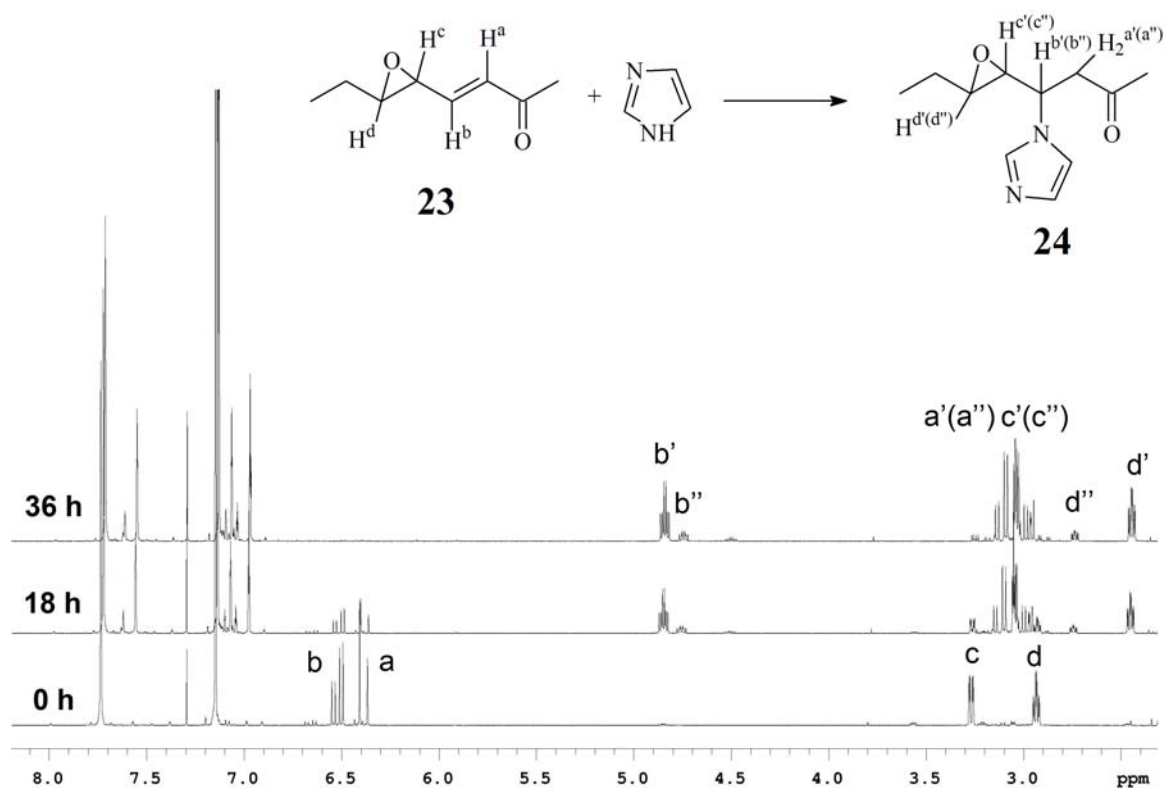


**Figure S46.** LC-MS TIC, SIC (m/z 311), and MS3 for cis-EKODE-(E)-Ia peak



0517060401 #2461-2477 RT: 28.31-28.56 AV: 9 NL: 5.86E4  
F: + c ESI Full ms3 311.10@35.00 293.00@35.00 [ 80.00-400.00]





**Figure S47.** Conversion of **23** to imidazole Michael adduct **24** ( $^1\text{H}$  NMR spectra in  $\text{CDCl}_3$  recorded at different times).