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Proof-of-Principle Direct Double Cyclisation of a Linear C_{15}-Precursor to a Dibrominated Bicyclic Medium-Ring Ether Relevant to *Laurencia* Species†

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General Experimental

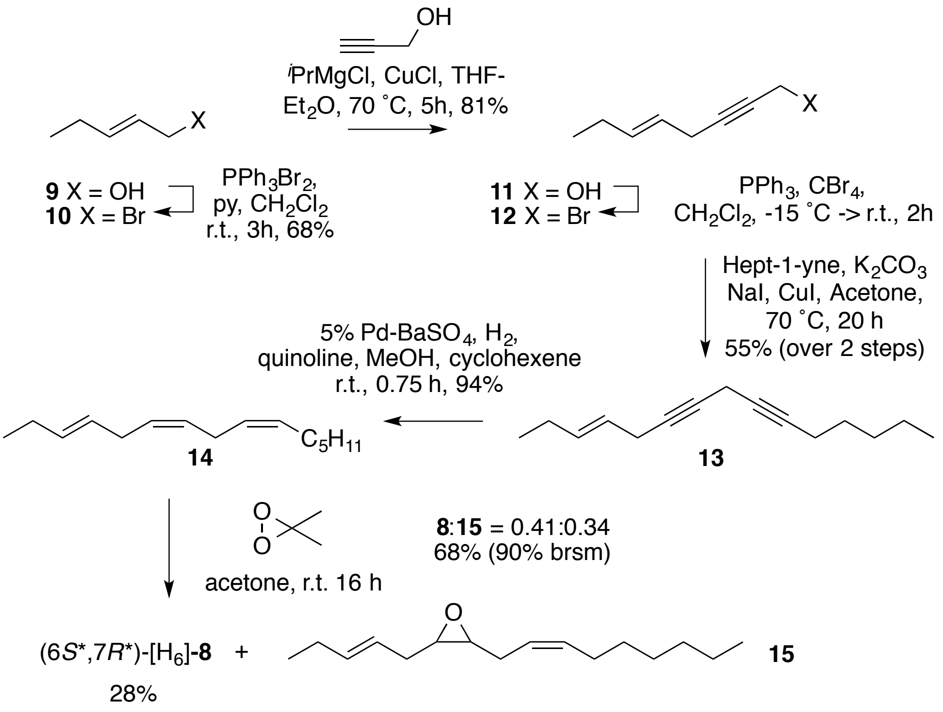
Reagents: DMDO solutions were prepared following the procedure of Murray.[1] A flask was charged with oxone (6.0 g, 19.5 mmol), acetone (10 mL, 131 mmol) and finally $NaHCO_3$ (2.9 g, 34.5 mmol). The resulting DMDO was distilled under reduced pressure and collected in a receiver flask at -100 °C as adapted from the reported procedure. The concentration was determined by iodometric titration and the solution was used immediately. Pyridine was distilled from CaH_2 and used immediately. ^{i}PrMgCl in THF was titrated against L-menthol prior to use. NBS was purified by recrystallisation from water and stored at 4 ^{o}C in the dark. All other reagents were obtained from commercial sources and used as received.

Solvents: Anhydrous tetrahydrofuran, diethyl ether, and dichloromethane were obtained from a purification column composed of activated alumina. Solvents employed in work-up procedures and chromatography were used as purchased. Petroleum ether corresponds to BDH AnalarR petroleum spirit (40-60 ^{o}C b.p.).

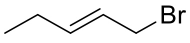
Experimental techniques: Reactions were carried out in oven-dried glassware under a positive pressure of nitrogen, unless otherwise stated. Air and/or moisture sensitive reagents were transferred by syringe. Reaction temperatures other than room temperature were recorded either as aluminium dry-syn or bath temperature. The phrases removed/concentrated under reduced pressure or, *in vacuo*, refer to rotary evaporation. Column chromatography was performed on Geduran® silica gel, particle size 40-63 μm. Analytical Thin Layer Chromatography was performed on Kieselgel 60 F254 pre-coated aluminium backed plates which were visualized by chemical staining with potassium permanganate or vanillin.

Characterisation: FT-IR spectra were recorded using an AT-IR machine. ^{1}H NMR spectra were recorded at 400 or 500 MHz. ^{13}C NMR spectra were recorded at 101 or 125 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak (7.26 ppm for $CDCl_3$). Coupling constants (J) are quoted in Hertz (Hz). All spectra were acquired at room temperature. The following abbreviations correspond to the multiplicity of NMR signals: s - singlet, br - broad, d – doublet, t – triplet, q – quartet, qu – quintet, m – multiplet. Low resolution MS, GCMS or LCMS and high resolution MS were recorded by the Imperial College Department of Chemistry Mass Spectrometry Service.

Experimental details and characterising data for compounds leading to model epoxide (6*S**,7*R**)-[H_6]-8



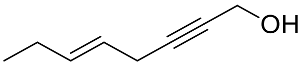
(*E*)-1-Bromopent-2-ene[2] (10)



According to a modified procedure of Bonney,[2] a solution of bromine (8.64 g, 54.1 mmol, 1.1 equiv) in dichloromethane (17 mL) was added dropwise to a solution of triphenylphosphine (14.2 g, 54.1 mmol, 1.1 equiv) in dichloromethane (60 mL) at 0 °C. The orange-yellow triphenylphosphine dibromide suspension was stirred at 0 °C for 30 min then pyridine (4.26 g, 54.1 mmol, 1.1 equiv) was added, followed by a solution of (*E*)-2-penten-1-ol (4.23 g, mmol, 1.0 equiv) in dichloromethane (25 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was washed with 1M hydrochloric acid solution (2 × 50 mL), washed with saturated aqueous sodium hydrogen carbonate solution (2 × 50 mL), the layers were separated and the aqueous was extracted with dichloromethane (2 × 50 mL). The combined organics were dried over sodium sulphate and carefully concentrated *in vacuo* until precipitation of the triphenylphosphine oxide occurred. To the resulting slurry, *n*-pentane (20 mL) was added and the resulting mixture was filtered through a small plug of silica eluting with pentane. The resulting mixture was carefully concentrated *in vacuo* to afford an azeotropic liquid containing a 1 : 1.3 molar ratio of the title compound and dichloromethane plus a small amount (< 10%) triphenylphosphine oxide. The residue was purified by column chromatography eluting with neat pentane to give bromide **10** (4.9 g, 68%) as a colourless oil:

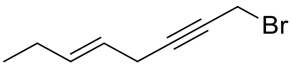
R_f 0.46 (neat pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (dt, *J* = 15.1, 6.2, 1H, $CH_3CH_2C\underline{H}$=), 5.71 (dtt, *J* = 15.1, 7.6, 1.4, 1H, =$C\underline{H}CH_2Br$), 3.98 (d, *J* = 8.0, 2H, $C\underline{H_2}Br$), 2.12 (app qu, *J* = 6.9, 2H, $C\underline{H_2}CH_3$), 1.03 (t, *J* = 7.4, 3H, $C\underline{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1 ($\underline{C}$H=), 125.4 ($\underline{C}$H=), 33.7 ($\underline{C}H_2$-Br), 25.1 ($CH_3\underline{C}H_2$), 13.1 ($\underline{C}H_3$).

(*E*)-Oct-5-en-2-yn-1-ol (11)



Using a modified procedure of Bonney,[2] a solution of isopropylmagnesium chloride in THF (45.6 mL, 1.8 M, 82.5 mmol, 2.5 equiv), was added dropwise to a stirred solution of propargyl alcohol (2.4 g, 43.0 mmol, 1.3 equiv) in THF (20 mL) at 0 °C. The reaction mixture was heated at 70 °C for 1.5 h, re-cooled to 0 °C, copper(I) chloride (0.65g, 6.6 mmol, 0.2 equiv) was added, followed by dropwise addition of bromide **10** (5.0 g, 33.5 mmol, 1 equiv) in diethyl ether (32 mL). The mixture was heated at 70 °C for 3 h, then allowed to cool to room temperature. Saturated aqueous ammonium chloride solution (50 mL) was added, the layers separated and the organics washed with saturated aqueous ammonium chloride solution (2 × 50 mL). The combined aqueous layers were extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL) and dried over sodium sulphate. After concentration *in vacuo*, the residue was purified by flash column chromatography (petroleum spirit : ethyl acetate 4 : 1) to give the known title compound **11** (3.31 g, 81%) as a pale yellow oil: R_f 0.20 (petroleum spirit : ethyl acetate 4 : 1); ^{1}H NMR (400 MHz, $CHCl_3$) *δ* 5.74 (dtt, *J* = 14.4, 6.3, 1.6, 1H $CH_3CH_2C\underline{H}$=), 5.42 (dtt, *J* = 14.9, 5.7, 1.5, 1H, $C\underline{H}$=$CHCH_2CH_3$), 4.31 (br s, $C\underline{H_2}OH$), 2.97 (br s, 2H, $C\underline{H_2}C{\equiv}CCH_2OH$), 2.07 (qu, *J* = 6.8, 2H, $C\underline{H_2}CH_3$), 1.01 (t, *J* = 7.5, 3H, $C\underline{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 134.1 ($\underline{C}$H=), 122.6 ($\underline{C}$H=), 84.1 ($\underline{C}$≡), 79.9 ($\underline{C}$≡), 51.4 ($\underline{C}H_2OH$), 25.3 ($\underline{C}H_2$), 22.0 ($\underline{C}H_2$), 13.5 ($\underline{C}H_3$).

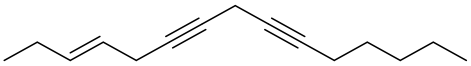
(*E*)-1-Bromooct-5-en-2-yne (12)



According to the method of Bonney,[2] a solution of alcohol **11** (1.0 g, 8.1 mmol) in dichloromethane (30 mL), was cooled to -15 °C. Carbon tetrabromide (3.2 g, 9.66 mmol, 1.2 equiv) was added followed by the dropwise addition of a solution of triphenylphosphine (2.74 g, 10.5 mmol, 1.3 equiv) in dichloromethane (11 mL). The mixture was allowed to warm to room temperature and stirred for 2 h after which it was concentrated *in vacuo* to approximately 5 mL. Petroleum spirit (25 mL) was added and the resulting mixture was cooled to -78 °C, filtered through a small plug of silica to remove triphenylphosphine oxide and bromoform, and the solid was washed with petroleum spirit (2 × 10 mL). The solvent was removed under reduced pressure to give known bromide **12** contaminated with approximately 10% bromoform: R_f 0.22 (100% petroleum spirit); ^{1}H NMR (400 MHz, $CHCl_3$) *δ* 5.74

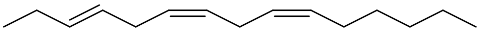
(dtt, *J* = 14.4, 6.3, 1.6, 1H, $CH_3CH_2C\underline{H}=$), 5.41 (dtt, *J* = 15.1, 5.6, 1.5, 1H, $CH_3CH_2CH=C\underline{H}$), 3.98 (t, *J* = 2.2, $C\underline{H_2}OH$), 3.00 (br s, 2H, $C\underline{H_2}C\equiv CCH_2OH$), 2.10-2.03 (m, 2H, $C\underline{H_2}CH_3$), 1.01 (t, *J* = 7.5, 3H, $C\underline{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.3 ($\underline{C}H=$), 122.2 ($\underline{C}H=$), 85.7 ($\underline{C}\equiv$), 76.8 ($\underline{C}\equiv$), 25.3 ($\underline{C}H_2Br$), 22.1 ($\underline{C}H_2$), 15.6 ($\underline{C}H_2$), 13.5 ($\underline{C}H_3$). The crude product was used in the next step without further purification.

(3*E*)-Pentadec-3-en-6,9-diyne (13)



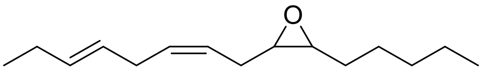
A solution of bromide **12** (8.1 mmol, 1.0 equiv) in acetone (5 mL) was cooled to 0 °C and a solution of 1-pentyne (0.78 g, 8.1 mmol, 1 equiv) in acetone (30 mL) was added. Potassium carbonate (2.23 g, 16.1 mmol, 2.0 equiv), sodium iodide (2.41 g, 16.1 mmol, 2 equiv) and copper(I) iodide (1.53 g, 8.1 mmol, 1 equiv) were added and the cloudy yellow mixture was heated to 70 °C for 18h. The reaction mixture was concentrated *in vacuo* to approximately 5 mL and ethyl acetate (25 mL) was added. The mixture was washed with saturated aqueous ammonium chloride solution (2 × 20 mL) and water (2 × 20 mL). The aqueous washings were combined and extracted with ethyl acetate (3 × 50 mL) and the combined organics were dried over sodium sulphate, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography eluting with neat petroleum spirit to give the title compound **13** (0.89 g, 55% over 2 steps) as yellow oil: R_f 0.38 (neat petroleum spirit); ATIR 2961, 2932, 2860, 1460, 1419, 1313, 966 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 5.73 (dtt, *J* = 15.0, 6.3, 1.6 Hz, 1H, $CH_3CH_2C\underline{H}=$), 5.41 (dtt, *J* = 15.0, 5.6, 1.5, 1H, $CH_3CH_2CH=C\underline{H}$), 3.18 (br s, 2H, $C\equiv CC\underline{H_2}C\equiv C$), 2.97 (br s, 2H, $=CHC\underline{H_2}C\equiv$), 2.19 (tt, *J* = 7.0 and 2.4, 2H, $C\equiv CC\underline{H_2}CH_2$), 2.10-2.02 (m, 2H, $CH_3C\underline{H_2}CH=$), 1.55-1.48 (m, 2H, $C\equiv CCH_2C\underline{H_2}$), 1.42-1.30 (m, 4H, $C\underline{H_2}C\underline{H_2}$), 1.01 (t, *J* = 7.5, 3H, $C\underline{H_3}$), 0.90 (br t, *J* = 7.0, 3H, $CH_2CH_2C\underline{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7 ($CH_3CH_2C\underline{H}=$), 123.1 ($CH_3CH_2CH=C\underline{H}$), 80.7 ($\equiv\underline{C}CH_2CH_2$), 78.0 ($\underline{C}\equiv CH_2CH_2$), 76.2 ($\equiv\underline{C}CH_2C\equiv CCH_2CH_2$), 74.2 ($\equiv\underline{C}CH_2CH=CH$), 31.1 ($\equiv C\underline{C}H_2C\equiv$), 28.5 ($=C\underline{C}H_2C\equiv$), 25.3 ($=CH\underline{C}H_2CH_3$), 22.2 ($C\equiv C\underline{C}H_2CH_2$), 22.0 ($C\equiv CCH_2\underline{C}H_2$), 18.7 ($CH_3\underline{C}H_2CH_2$), 14.0 ($\underline{C}H_3CH_2CH=$), 13.6 ($CH_3\underline{C}H_2CH_2$), 9.8 ($\underline{C}H_3CH_2CH_2$); HRMS ($EI^+$) *m/z* calcd for $C_{15}H_{22}$ ($M^{+\bullet}$) 202.1722, found 202.1716.

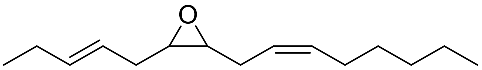
(3*E*,6*Z*,9*Z*)-Pentadeca-3,6,9-triene (14)



To a degassed solution of diyne **13** (0.40 g, 2.0 mmol) in methanol / cyclohexene (1 / 1, 60 mL) was added quinoline (0.35 mL). The reaction mixture was flushed with nitrogen, 5% Pd-$BaSO_4$ (0.16 g) was added followed by hydrogen gas *via* a balloon. The reaction mixture was stirred vigorously and monitored by TLC. After approximately 2.0h, TLC indicated consumption of starting material, the reaction was filtered through a short plug of silica and concentrated *in vacuo*. The residue was filtered through a short plug of silica eluting with neat petroleum ether to give the title compound **14** (0.38 g, 94%) as a colourless oil: R$_f$ 0.68 (neat petroleum spirit); ATIR 3012, 2960, 2925, 2856, 1460, 1440, 965, 721 cm^{-1}; ^{1}H NMR (400 MHz, CHCl$_3$) δ 5.55-5.31 (m, 6H, 6 × $\mathrm{C\underline{H}=}$), 2.85-2.76 (m, 4H, 2 × $\mathrm{=CHC\underline{H}_2CH=}$), 2.11-1.98 (m, 4H, 2 × $\mathrm{C\underline{H}_2CH=}$), 1.43-1.38 (m, 6H, $\mathrm{C\underline{H}_2C\underline{H}_2C\underline{H}_2}$), 1.00 (t, J = 7.5, 3H, $\mathrm{C\underline{H}_3}$), 0.91 (br t, J = 7.0, 3H, $\mathrm{C\underline{H}_3CH_2CH_2}$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 132.5, 130.4, 128.6, 128.0, 127.7, 127.1 (6 × $\mathrm{\underline{C}H=}$), 31.5, 30.4 (2 × $\mathrm{=CH\underline{C}H_2CH=}$), 29.4, 27.2 ($\mathrm{CH_3\underline{C}H_2CH=}$, $\mathrm{CH_2\underline{C}H_2CH=}$), 25.6, 25.5, 22.6 (3 × $\mathrm{\underline{C}H_2CH_2}$), 14.1, 13.9 (2 × $\mathrm{\underline{C}H_3}$); MS (EI$^+$) m/z 206 (M$^{+\bullet}$); HRMS (EI$^+$) m/z calcd for C$_{15}H_{26}$ (M$^{+\bullet}$) 206.2035, found 206.3041.

2-((2*Z*,5*E*)-Octa-2,5-dien-1-yl)-3-pentyloxirane (8) and 2-((*Z*)-oct-2-en-1-yl)-3-((*E*)-pent-2-en-1-yl) oxirane (15)





Using a modified method of Murray,[1] to a solution of triene **14** (240 mg, 1.2 mmol, 1 equiv) in acetone (2 mL), a solution of dimethydioxirane in acetone (12.9 mL, 0.1M, 1.05 equiv) was added. The reaction vessel was sealed and left to stir overnight at room temperature. The acetone was removed *in vacuo*, the residue was dissolved in dichloromethane, dried over sodium sulphate, filtered, and concentrated *in vacuo* to afford a colourless oil. The residue was subjected to flash column chromatography three times eluting with toluene : petroleum spirit 6 : 4, giving first oxirane **15** (59 mg, 23%) as a colourless oil and second oxirane **8** (71 mg, 28%) as a colourless oil.

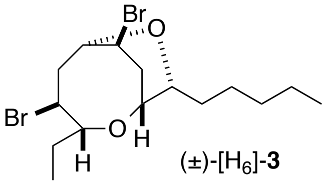
2-((*Z*)-Oct-2-en-1-yl)-3-((*E*)-pent-2-en-1-yl)oxirane (**15**) (59 mg, 23%), colourless oil: R$_f$ 0.36 (toluene : petroleum spirit, 6 : 4); ^{1}H NMR (400 MHz, CHCl$_3$) δ 5.71-5.39 (m, 4H, 4 × $\mathrm{C\underline{H}=}$), 3.03-2.95 (m, 2H, $\mathrm{C\underline{H}OC\underline{H}}$), 2.51-2.32 (m, 2H, $\mathrm{=CHC\underline{H}_2CHO}$), 2.28-2.17 (m, 2H, $\mathrm{CHOC\underline{H}_2CH=}$), 2.12-2.00 (m, 4H, 2 × $\mathrm{C\underline{H}_2CH=}$), 1.44-1.25 (m, 6H, $\mathrm{C\underline{H}_2C\underline{H}_2C\underline{H}_2}$), 1.00 (t, J = 7.5, 3H, $\mathrm{C\underline{H}_3}$), 0.91 (br t, J = 7.0, 3H, $\mathrm{C\underline{H}_3CH_2CH_2}$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 135.1, 132.8, 123.7, 123.6, (4 × $\mathrm{C\underline{H}=}$), 56.6, 56.5 ($\mathrm{\underline{C}O}$), 31.5, 31.2, 29.3, 27.4, 26.2, 25.7, 22.6, 14.1, 13.7. MS (CI$^+$) m/z 223 (M + H)$^+$; HRMS (CI$^+$) m/z calcd for C$_{15}$H$_{27}$O (M + H)$^+$ 223.2062, found 223.2048.

Epoxide ($6S^*$,$7R^*$)-[H$_6$] (**8**): R$_f$ 0.34 (toluene : petroleum spirit, 6 : 4); ^{1}H NMR (400 MHz, CHCl$_3$) δ 5.62-5.34 (m, 4H, 4 × $\mathrm{C\underline{H}=}$), 3.01-2.91 (m, 2H, $\mathrm{C\underline{H}OC\underline{H}}$), 2.84-2.72 (m, 2H, $\mathrm{=CHC\underline{H}_2CH=}$), 2.46-2.36 (m, 1H, $\mathrm{=CHC\underline{H}_2CHO}$), 2.28-2.19 (m, 1H, $\mathrm{=CHC\underline{H}_2CHO}$), 2.10-1.99 (m, 2H, $\mathrm{CH_3C\underline{H}_2CH=}$), 1.59-1.40 (m, 6H, $\mathrm{C\underline{H}_2C\underline{H}_2C\underline{H}_2}$), 1.00 (t, J = 7.5, 3H, $\mathrm{C\underline{H}_3}$), 0.91 (br t, J = 7.0, 3H, $\mathrm{C\underline{H}_3CH_2CH_2}$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 132.8, 130.5, 126.7, 124.5, (4 × $\mathrm{\underline{C}H=}$), 57.2, 56.5 (2 × $\mathrm{\underline{C}O}$), 31.8, 30.6, 27.8, 26.3, 26.2, 25.6, 22.6, 14.0, 13.8. MS (CI$^+$) m/z 223 (M + H)$^+$; HRMS (CI$^+$) m/z calcd for C$_{15}$H$_{27}$O (M + H)$^+$ 223.2062, found 223.2070.

Procedure for cyclisation of model epoxide (6*S**,7*R**)-[H_6]-8

Epoxide (6S*,7R*)-[H_6] (**8**) (2 × 92.5 mg batches, 0.84 mmol, 1 equiv) was vigorously stirred in degassed water (2 × 420 mL) for 30 minutes. To each batch NBS (148 mg, 0.84 mmol, 2 equiv) was added in one portion. The reaction mixtures were left to stir for 18 h at room temperature and products were extracted with ethyl acetate (3 × 200 mL). The organics were combined and washed with 10% w / w sodium sulphite solution (2 × 150 mL) and brine (100 mL). The organics were dried over sodium sulphate, and the solvent was removed *in vacuo* to give a colourless oil. The reactions were observed to be essentially the same by TLC analysis and the crudes were combined. The resulting material was subjected to two stage column chromatography first eluting with petroleum spirit : diethyl ether, 8 : 2 to collect non-polar components then with dichloromethane : methanol, 9 : 1 to collect polar components. Polar components were concentrated *in vacuo* to give 159 mg of a yellow oil which was not further analysed. The non-polar components were concentrated in vacuo to give 53 mg of a colourless oil. The material was subjected to column chromatography (petroleum spirit : diethyl ether 99 : 1 to 70 : 30).

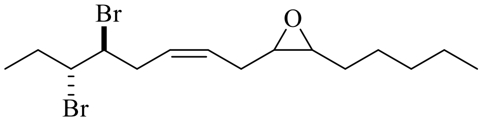
Hexahydrolaureoxanyne (±)-[H_6]-(3)



(±)-[H_6]-**3**

Colourless oil (containing 5% of an unidentified compound) (8 mg 2.5%): R_f 0.16 (petroleum spirit : diethyl ether, 9 : 1) ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (dt, *J* = 11.0, 3.4, 1H), 4.13 (ddd, *J* = 9.0, 6.5, 4.0, 1H), 4.03 (td, *J* = 8.3, 3.8, 1H), 3.88 (ddd, *J* = 9.8, 8.4, 7.3, 1H), 3.22 (dt, *J* = 8.4, 4.2, 1H), 3.02 (dt, *J* = 4.8, 6.3, 1H), 2.68 (dt, *J* = 13.3, 6.8, 1H), 2.35 (ddd, *J* = 13.0, 9.8, 9.0 1H), 2.23 (ddd, *J* = 15.6, 9.2, 5.2, 1H, H_8), 1.99 (ddd, *J* = 14.9, 7.3, 3.2, 1H, H_8), 1.81 (ddq, *J* = 14.0, 3.9, 7.5, 1H), 1.60-1.48 (m, 6H), 1.37-1.30 (m, 3H) 1.01 (t, *J* = 7.5, 3H), 0.90 (br t, *J* = 7.5, 3H); ^{13}C NMR (101 MHz, $CDCl_3$), δ 87.3, 79.6, 57.7, 55.5, 55.2, 46.6, 40.4, 33.3, 31.7, 28.2, 26.2, 25.2, 22.6, 14.0, 9.8; HRMS (TOF-ES$^+$) *m/z* calcd for $C_{15}H_{27}{}^{79}BrO_2$ $(M + H)^+$ 397.0378, found 397.0395.

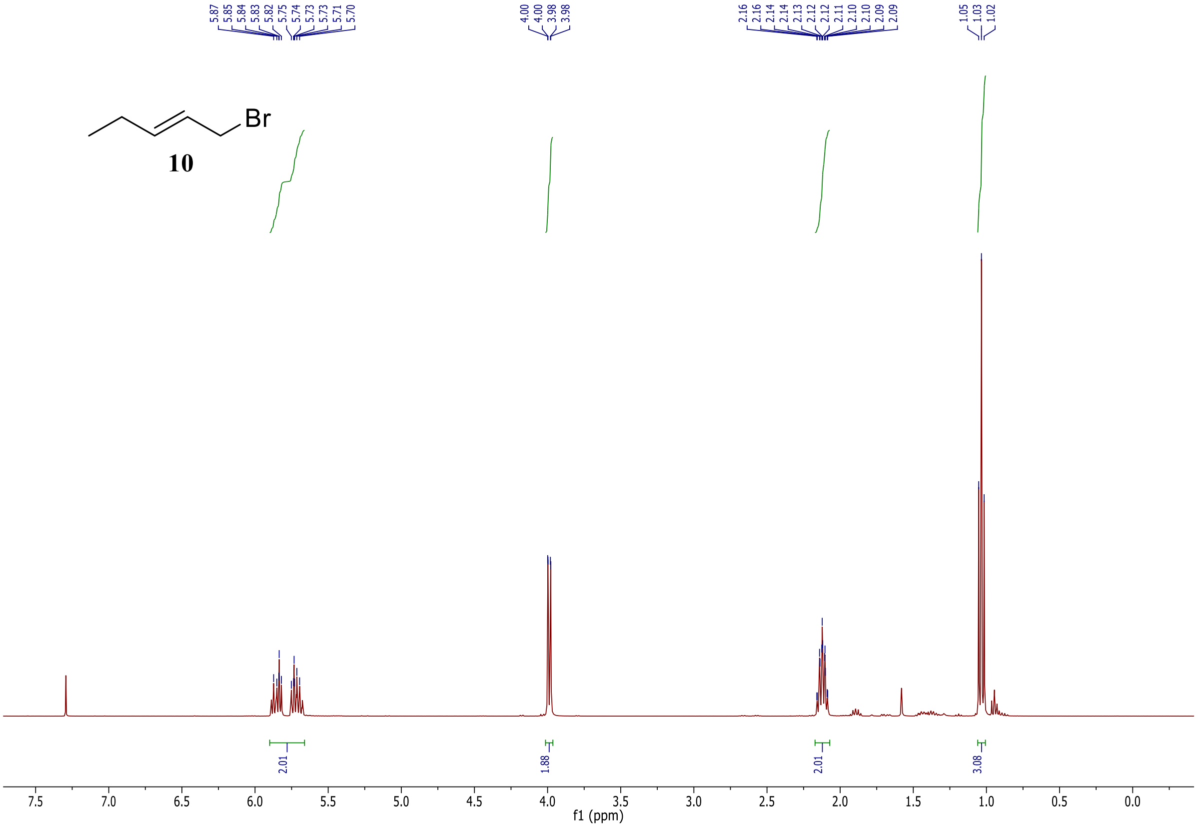
2-[(2*Z*)-5,6-Dibromooct-2-en-1-yl]-3-pentyloxirane (16)



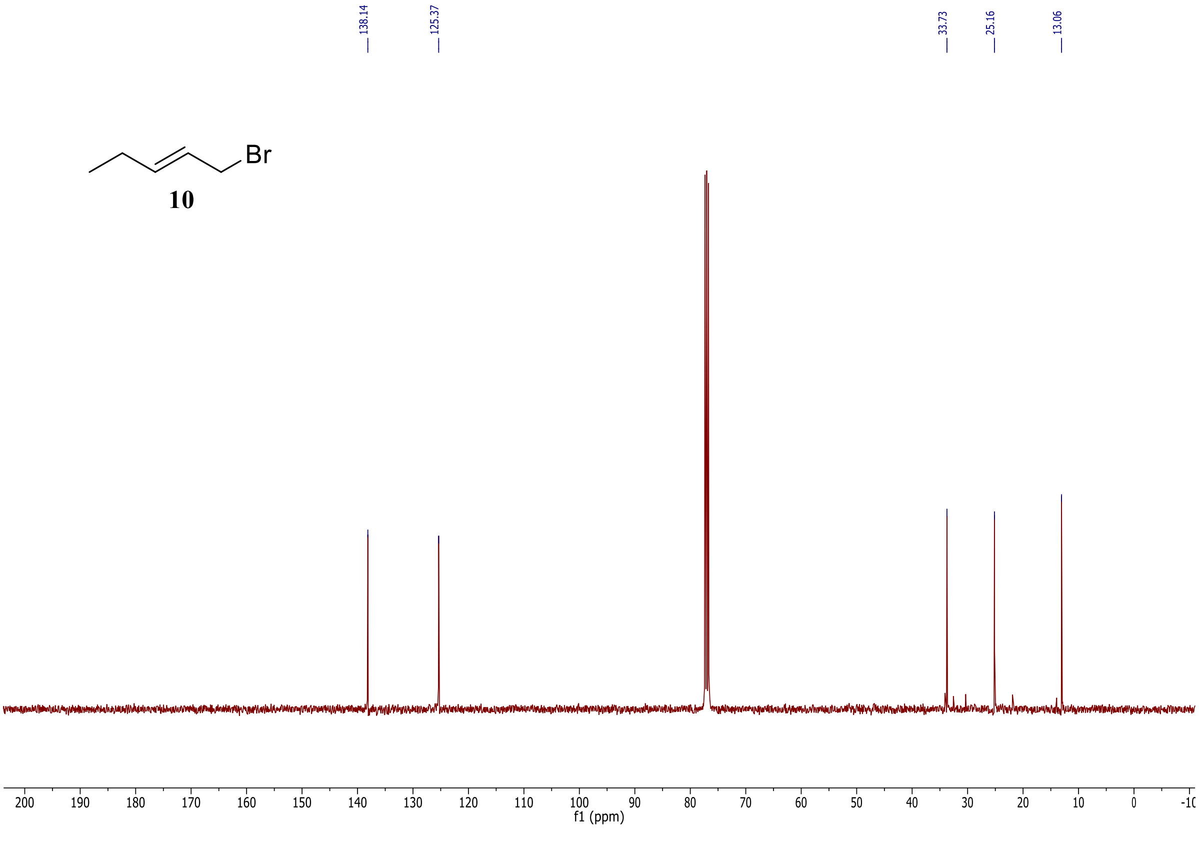
(2 diastereomers)

Isolated at a 50 : 50 mixture of two diastereomers, 5 mg in total, R_f 0.56 (petroleum spirit : diethyl ether, 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 – 4.08 (m, 4H), 2.82-2.95 (m, 4H), 2.85 (m, 2H), 2.57 – 2.17 (m, 8H), 1.95-2.06 (m, 2H), 1.66 – 1.50 (m, 8H), 1.42 – 1.31 (m, 12H), 1.11 (t, J = 7.2, 6H), 0.99 – 0.86 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.1, 128.0, 127.1, 127.0, 77.3, 77.2, 77.00, 76.9, 76.7, 76.6, 60.6, 60.4, 57.6, 57.4, 57.3, 57.2, 57.2, 56.3, 56.2, 35.2, 35.1, 31.7, 30.3, 27.8, 27.7, 27.7, 26.7, 26.3, 22.6, 14.0, 11.1, 11.1; MS (CI$^+$) *m/z* 379, 381, 483 $(M + H)^+$; HRMS (ES-TOF) *m/z* calcd for $C_{15}H_{30}{}^{79}Br_2$ $(M + H)^+$ 383.0330, found 303.0463.

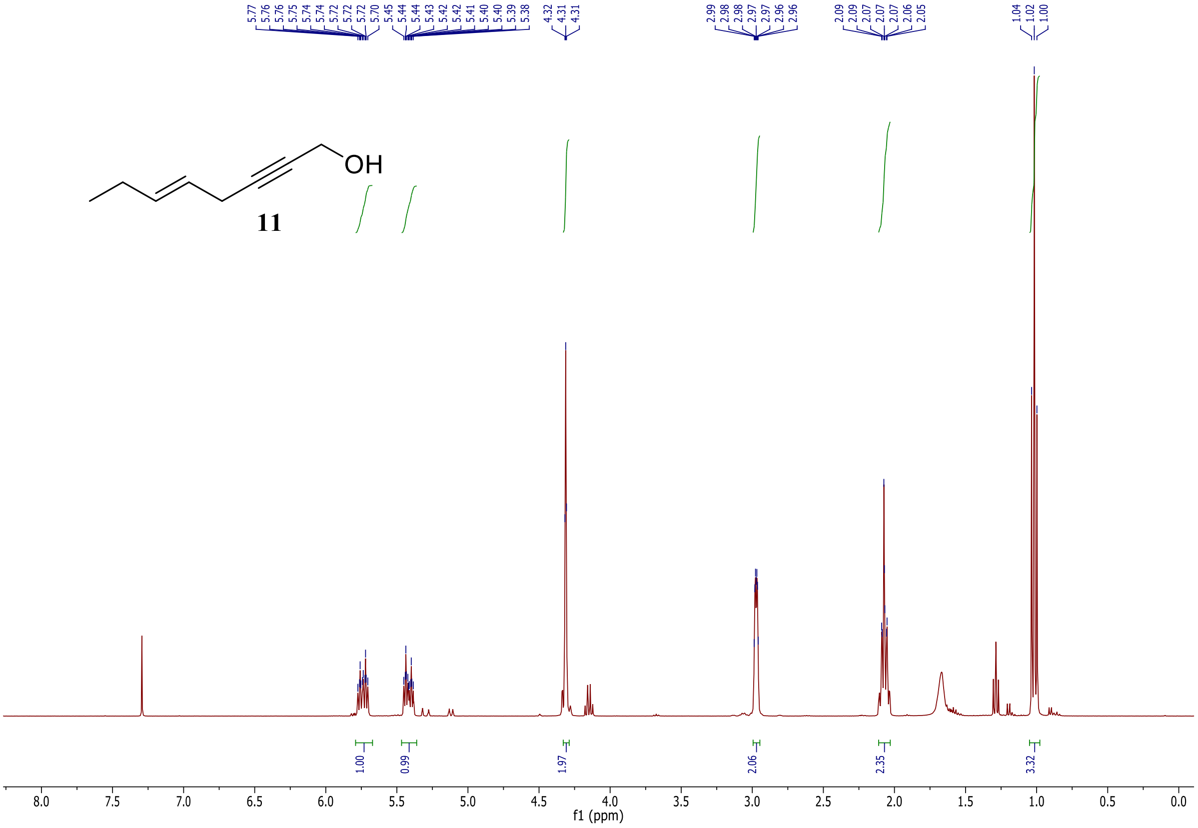
^{1}H NMR spectrum of (*E*)-1-bromopent-2-ene (**10**) (400 MHz, $CDCl_3$)



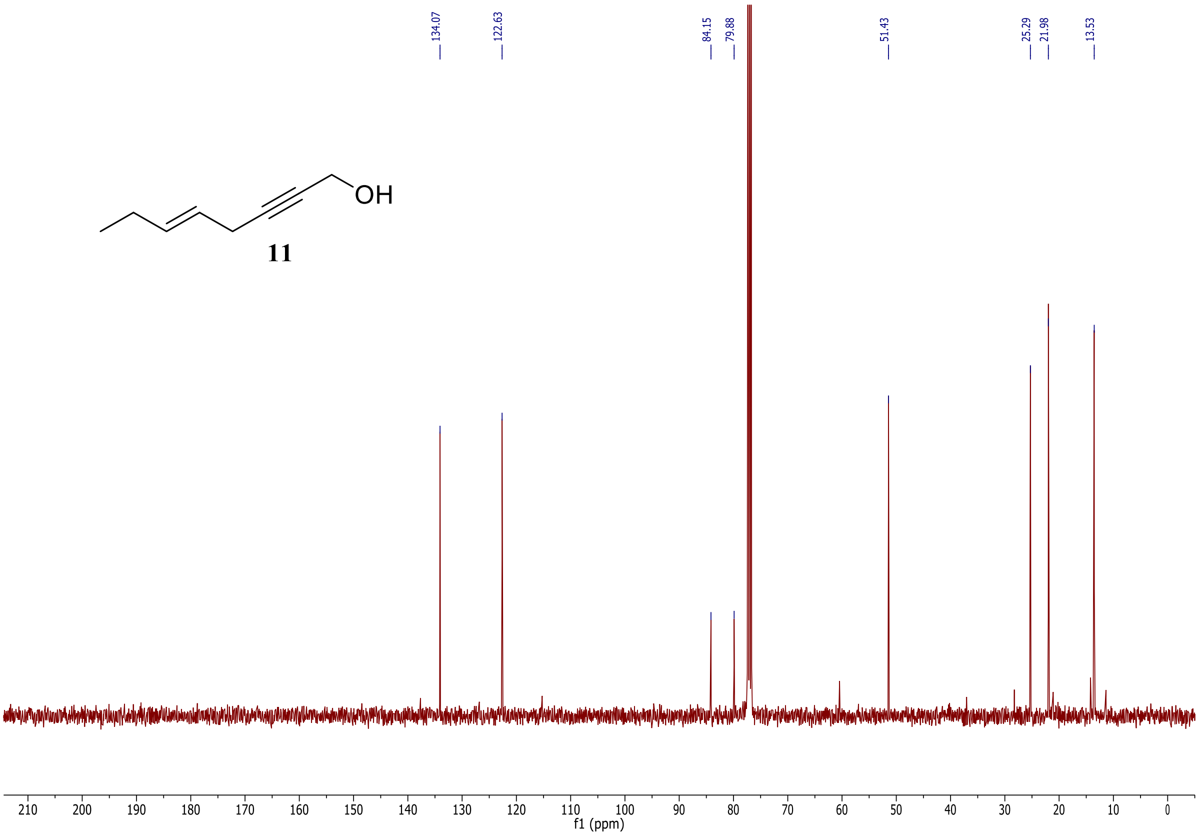
^{13}C NMR spectrum of (*E*)-1-bromopent-2-ene (**10**) (101 MHz, $CDCl_3$)



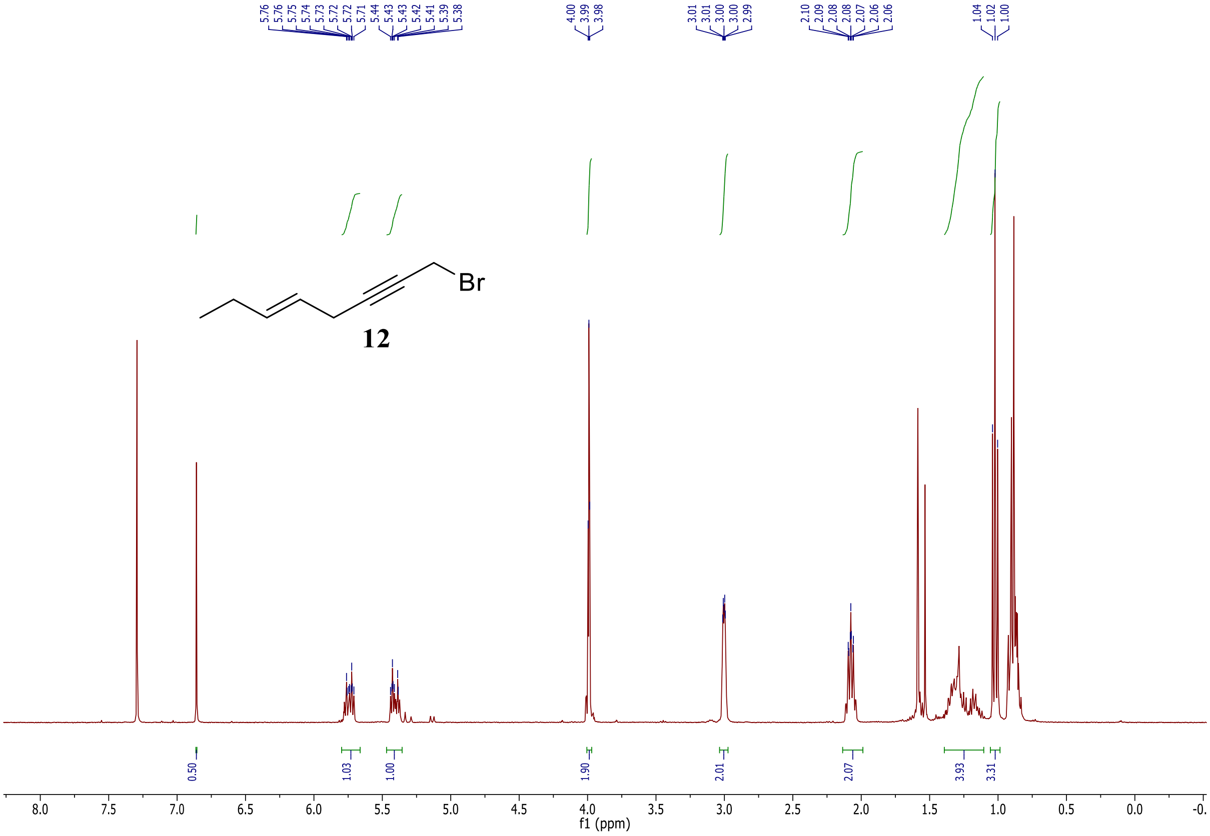
^{1}H NMR spectrum of (*E*)-oct-5-en-2-yn-1-ol (**11**) (400 MHz, $CDCl_3$)



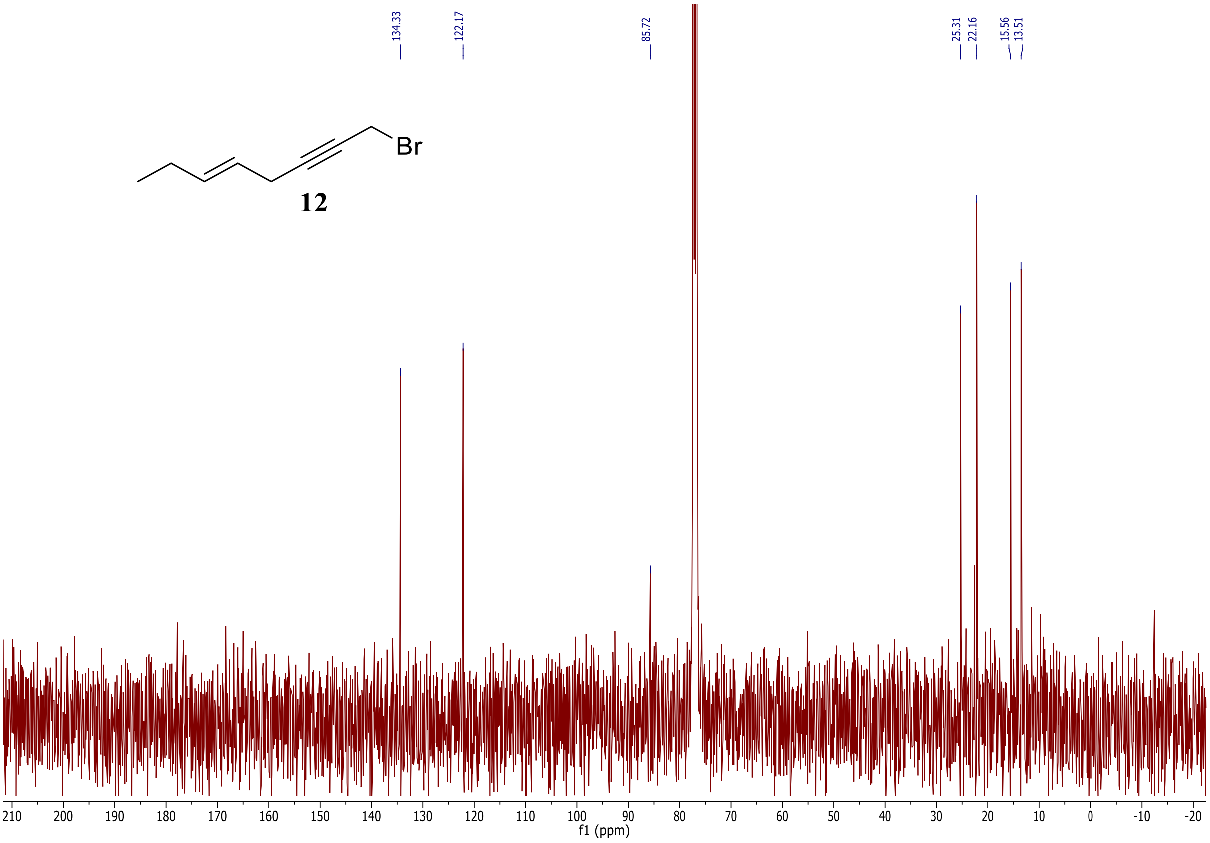
^{13}C NMR spectrum of (*E*)-oct-5-en-2-yn-1-ol (**11**) (101 MHz, $CDCl_3$)



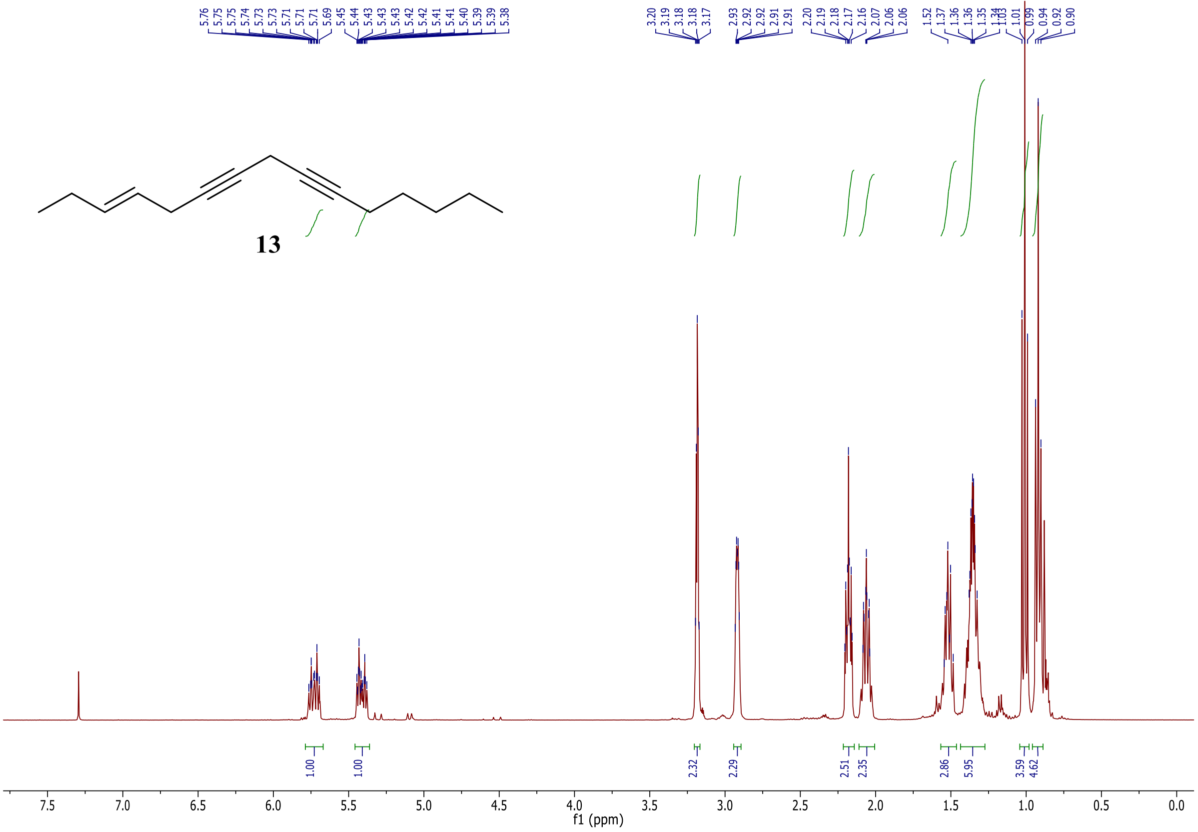
^{1}H NMR spectrum of crude (*E*)-1-bromooct-5-en-2-yne (**12**) (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of crude (*E*)-1-bromooct-5-en-2-yne (**12**) (101 MHz, $CDCl_3$)

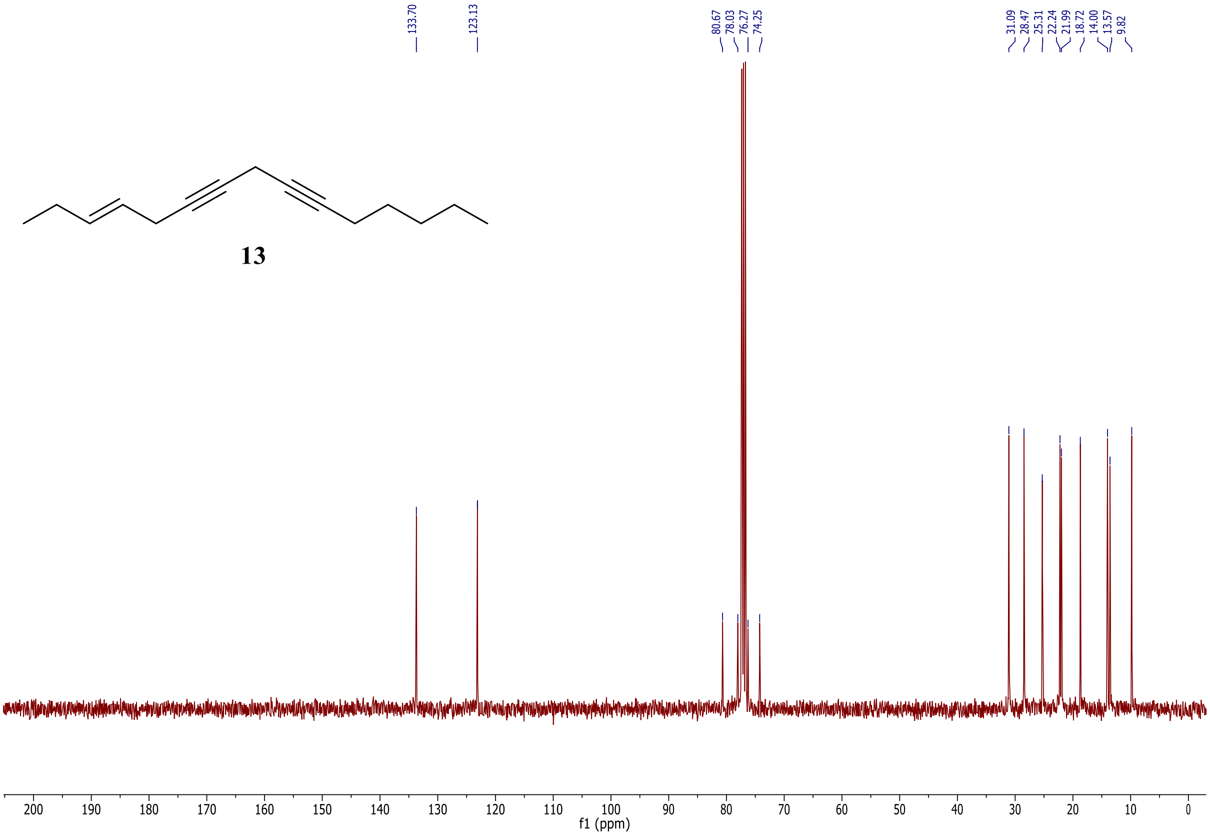


^{1}H NMR spectrum of (3*E*)-pentadec-3-en-6,9-diyne (**13**) (400 MHz, $CDCl_3$)



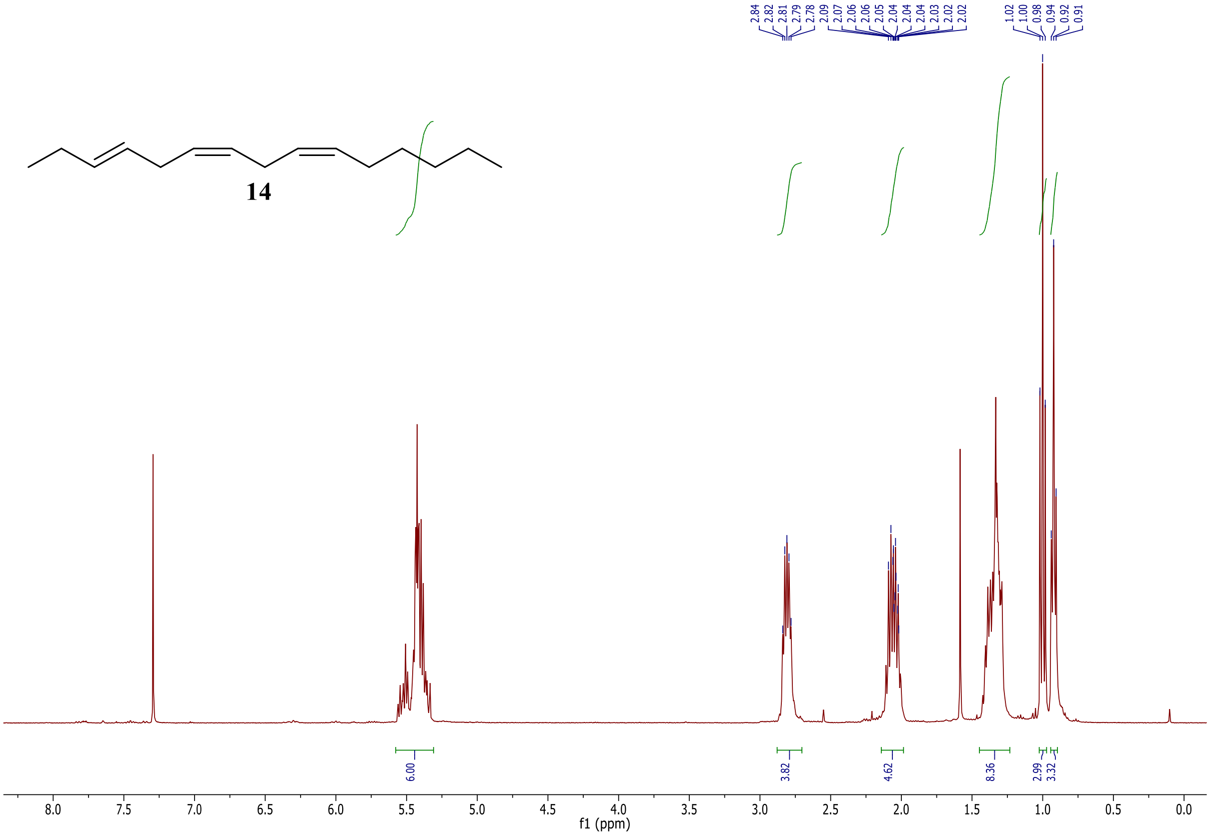
13

^{13}C NMR spectrum of (3*E*)-pentadec-3-en-6,9-diyne (**13**) (101 MHz, $CDCl_3$)

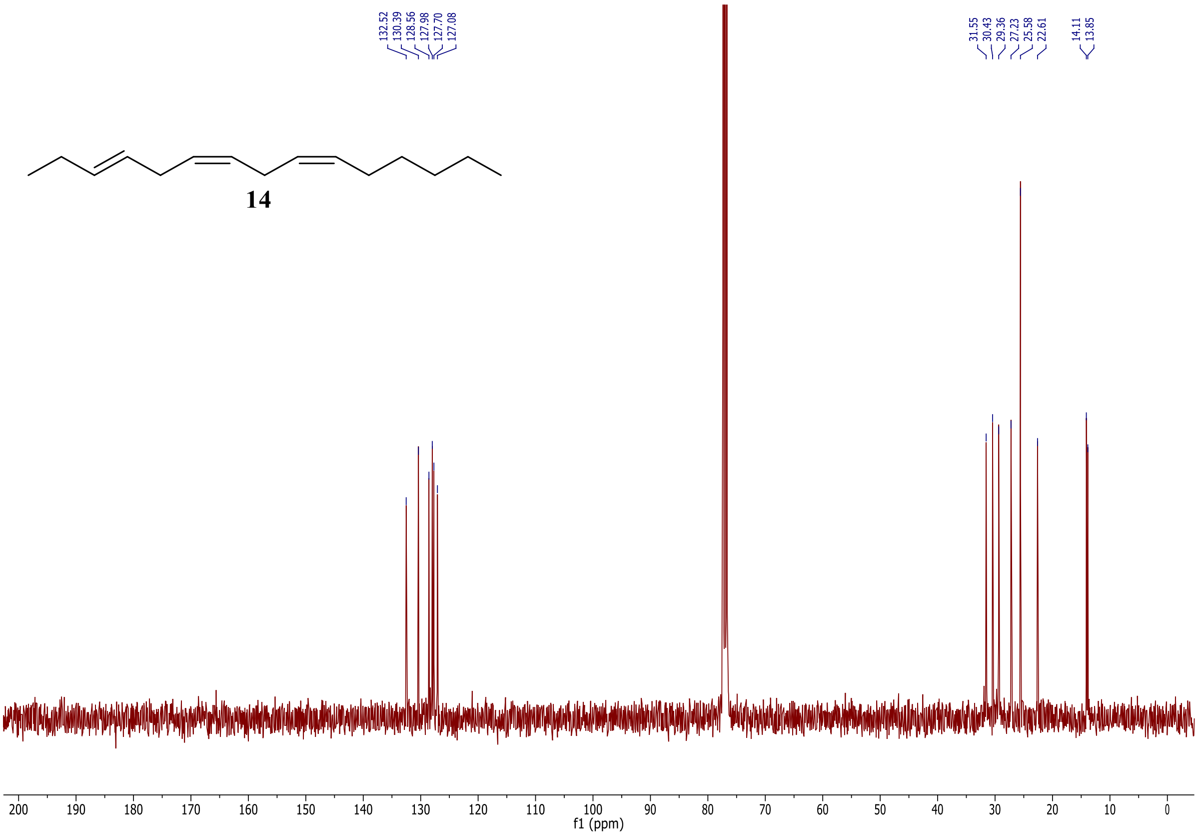


13

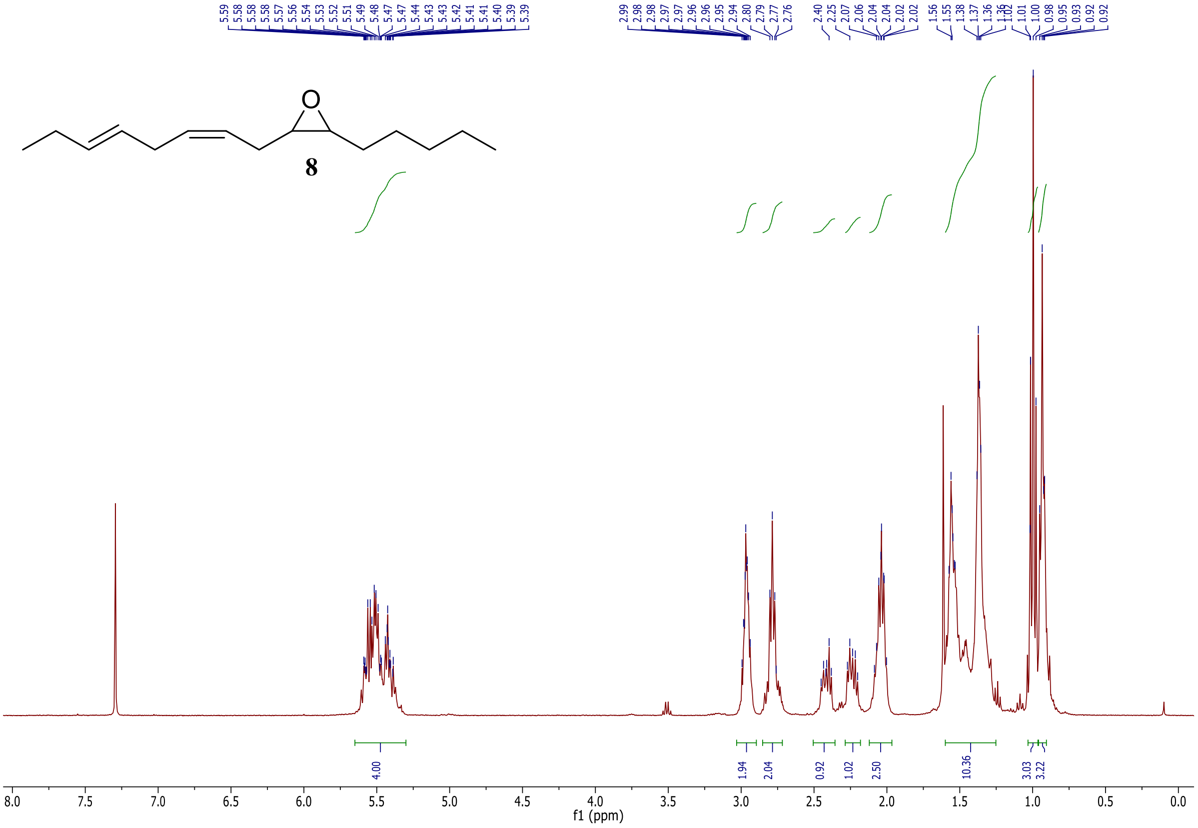
^{1}H NMR spectrum of (3*E*,6*Z*,9*Z*)-pentadeca-3,6,9-triene (**14**) (400 MHz, $CDCl_3$)



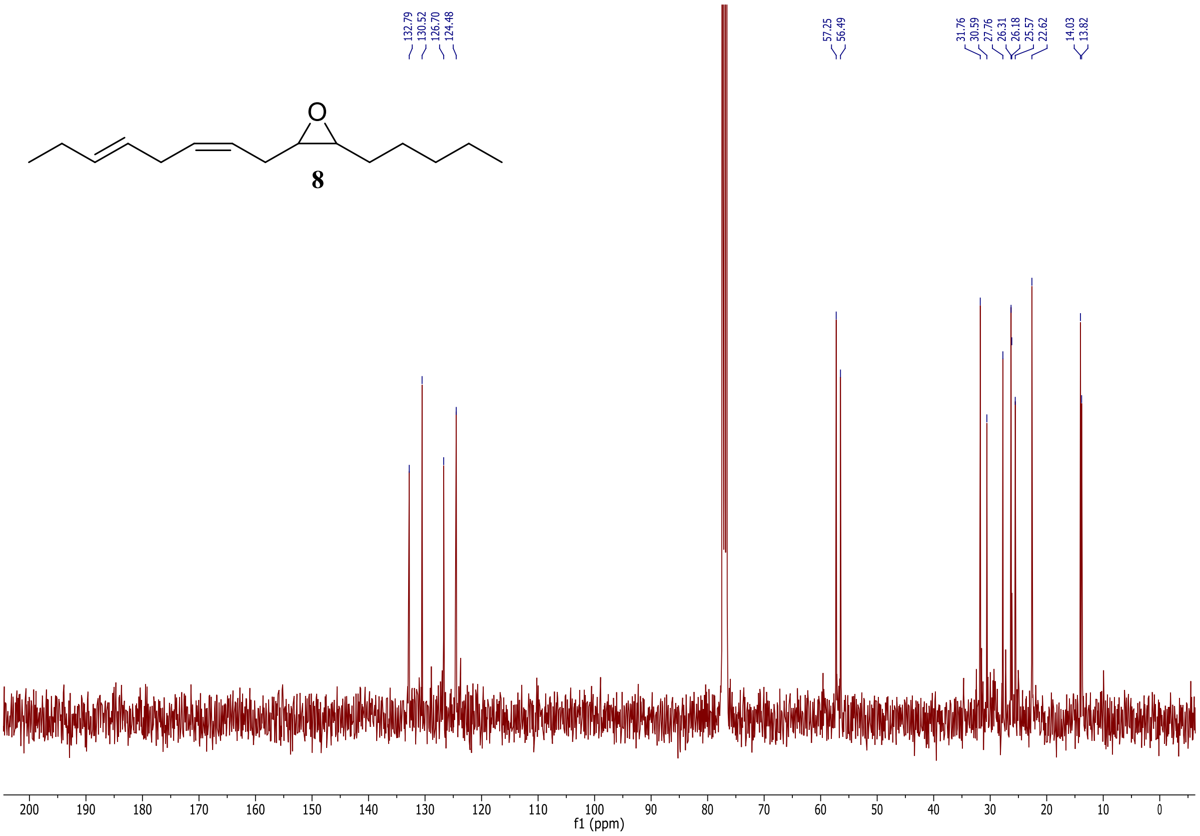
^{13}C NMR spectrum of (3*E*,6*Z*,9*Z*)-pentadeca-3,6,9-triene (**14**) (101 MHz, $CDCl_3$)



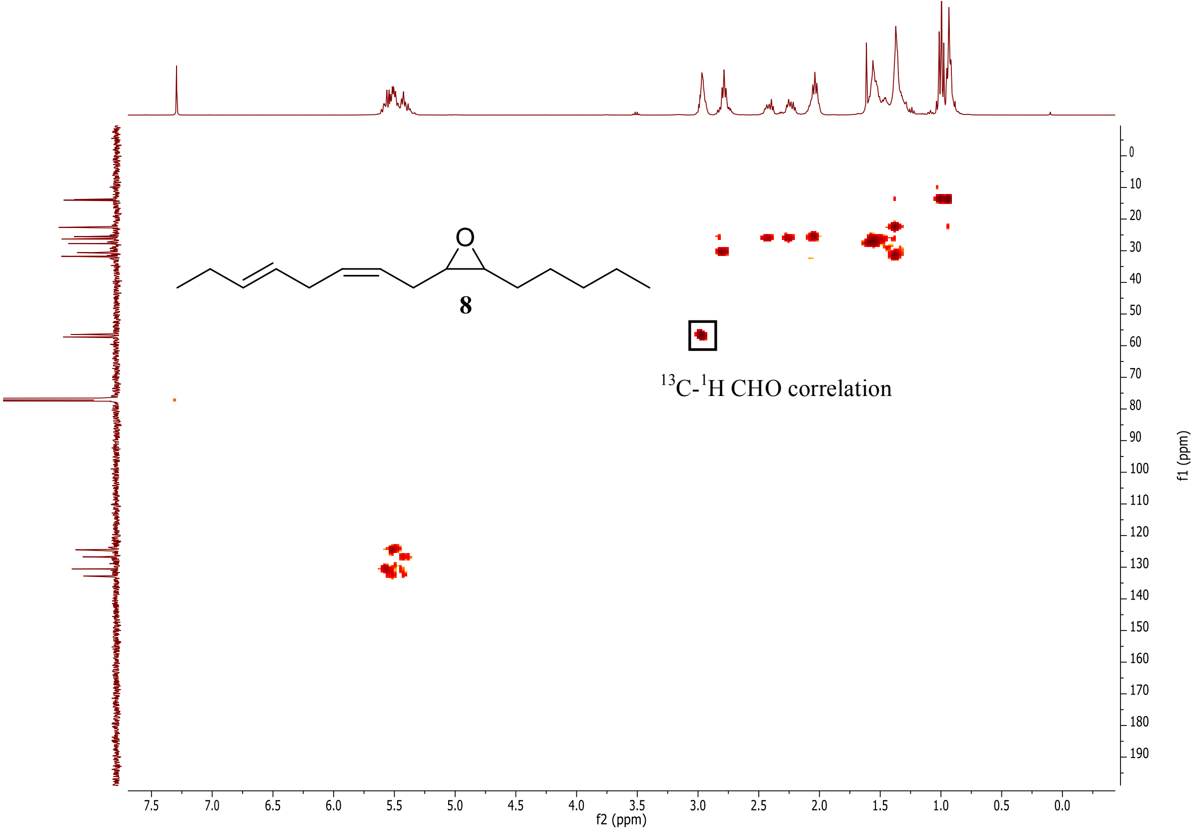
^{1}H NMR spectrum of model epoxide (6*S**,7*R**)-[H_6]-**8** (400 MHz, $CDCl_3$)



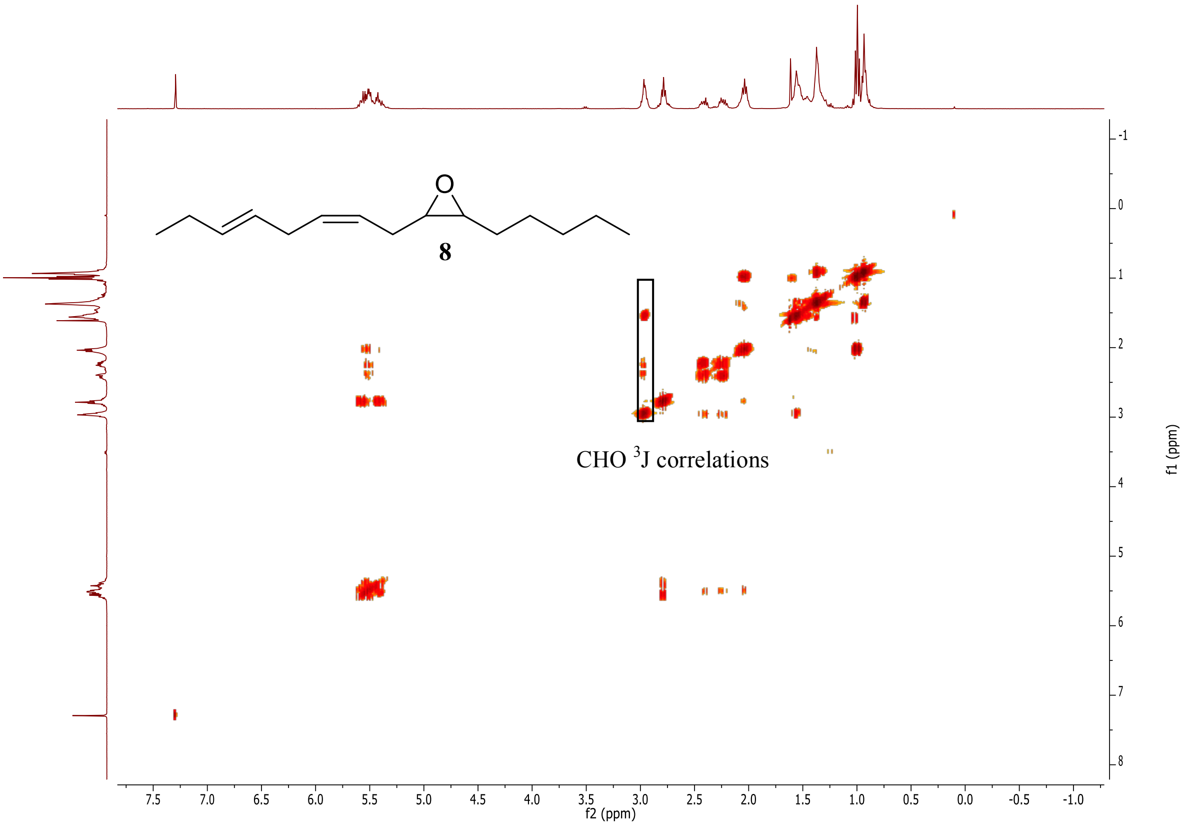
^{13}C NMR spectrum of model epoxide (6*S**,7*R**)-[H_6]-**8** (101 MHz, $CDCl_3$)



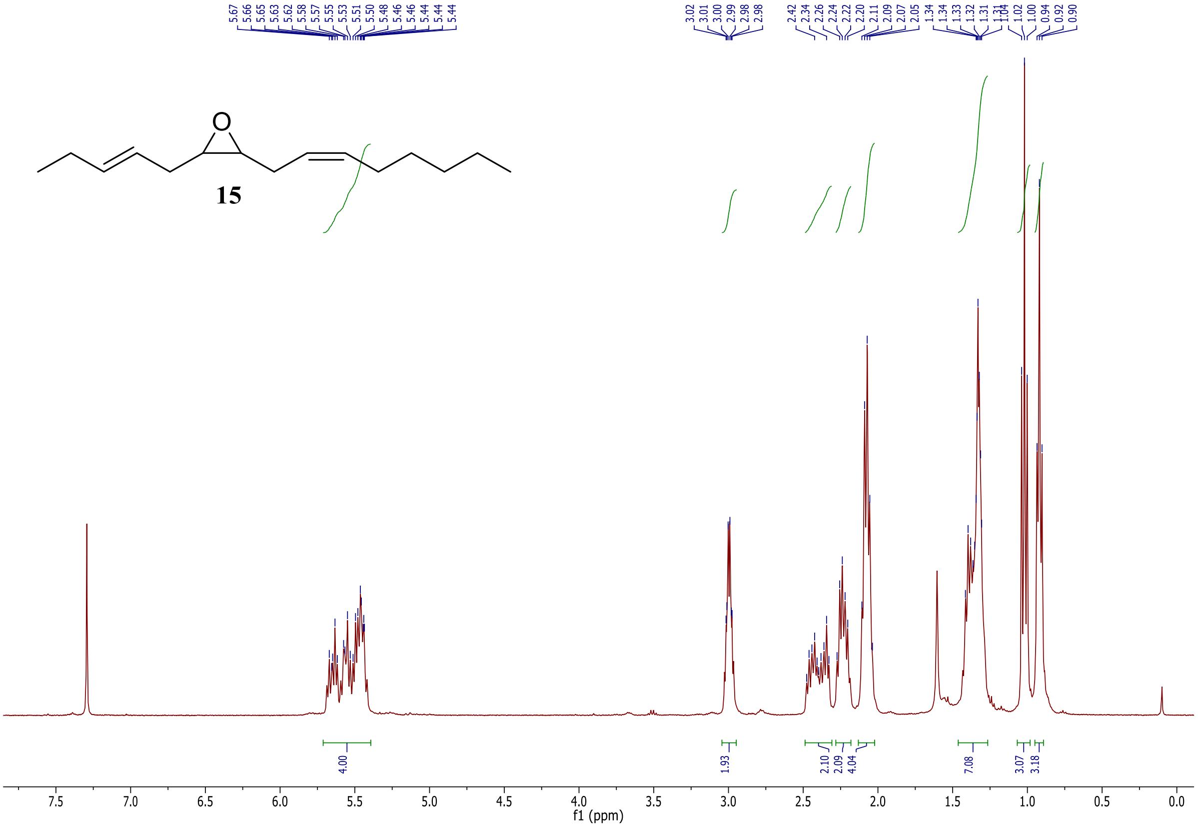
HSQC spectrum of model epoxide (6*S**,7*R**)-[H_6]-**8**



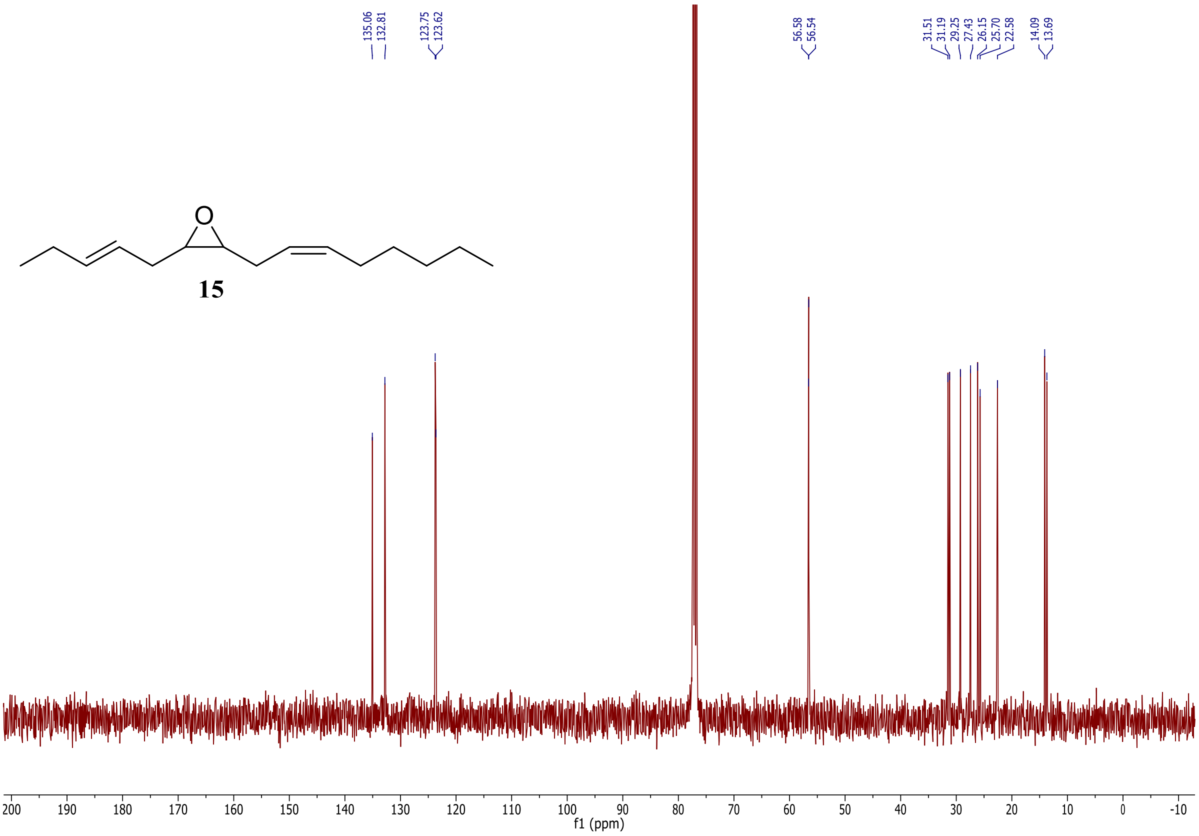
2D COSY spectrum of model epoxide (6*S**,7*R**)-[H_6]-**8**



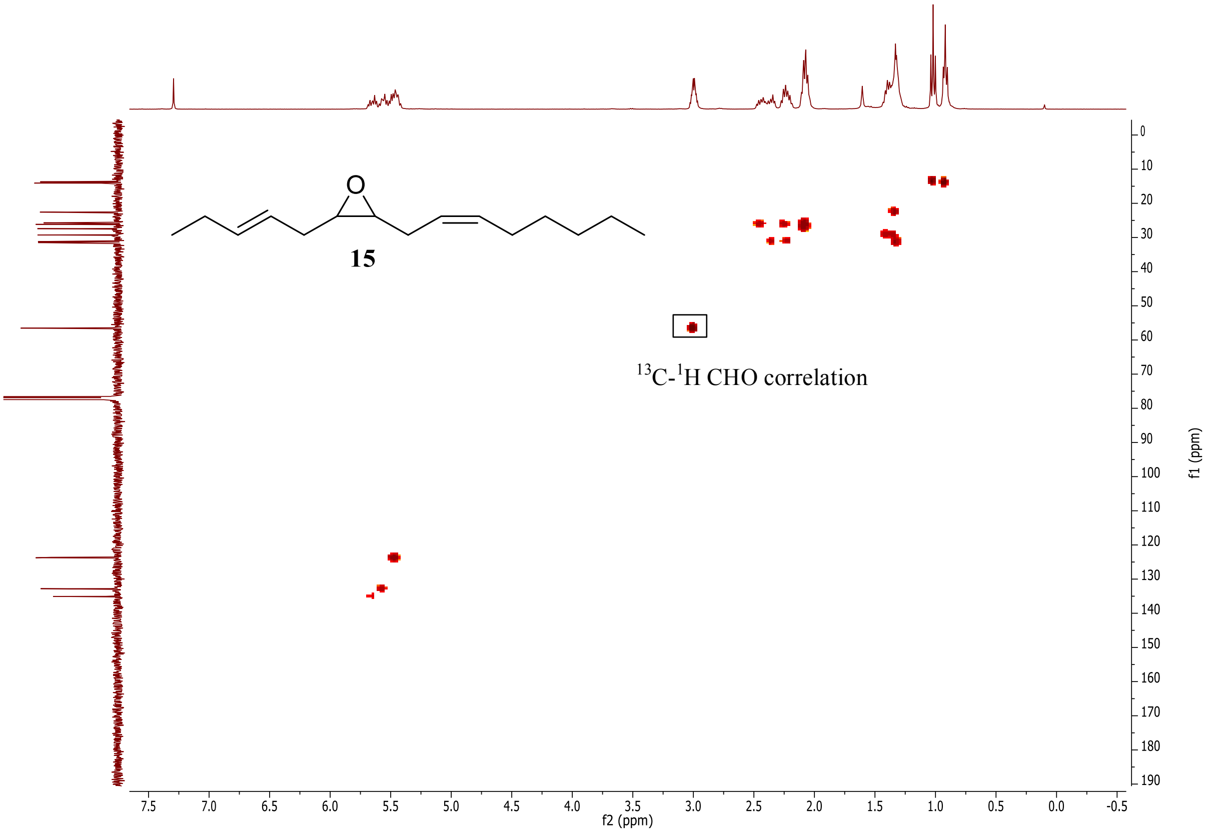
^{1}H NMR spectrum of 2-((*Z*)-oct-2-en-1-yl)-3-((*E*)-pent-2-en-1-yl) oxirane (**15**) (400 MHz, $CDCl_3$)



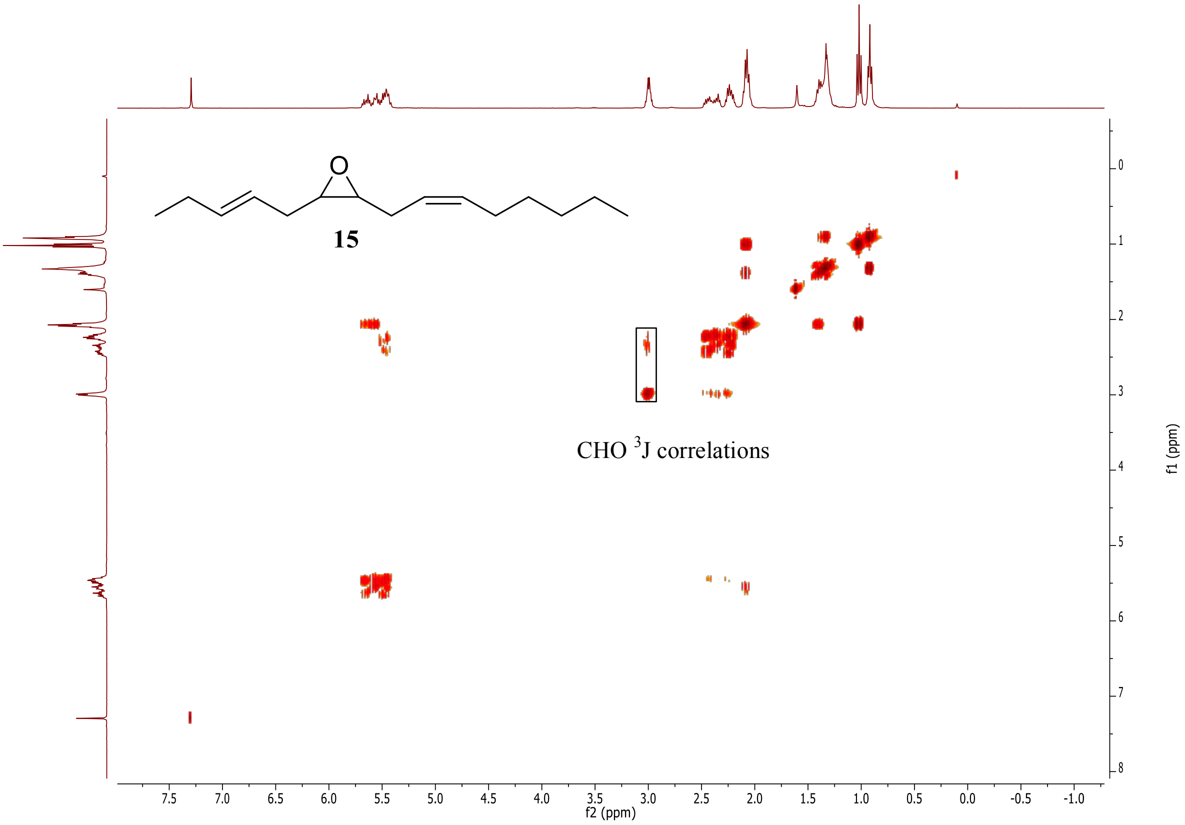
^{13}C NMR spectrum of 2-((*Z*)-oct-2-en-1-yl)-3-((*E*)-pent-2-en-1-yl) oxirane (**15**) (101 MHz, $CDCl_3$)



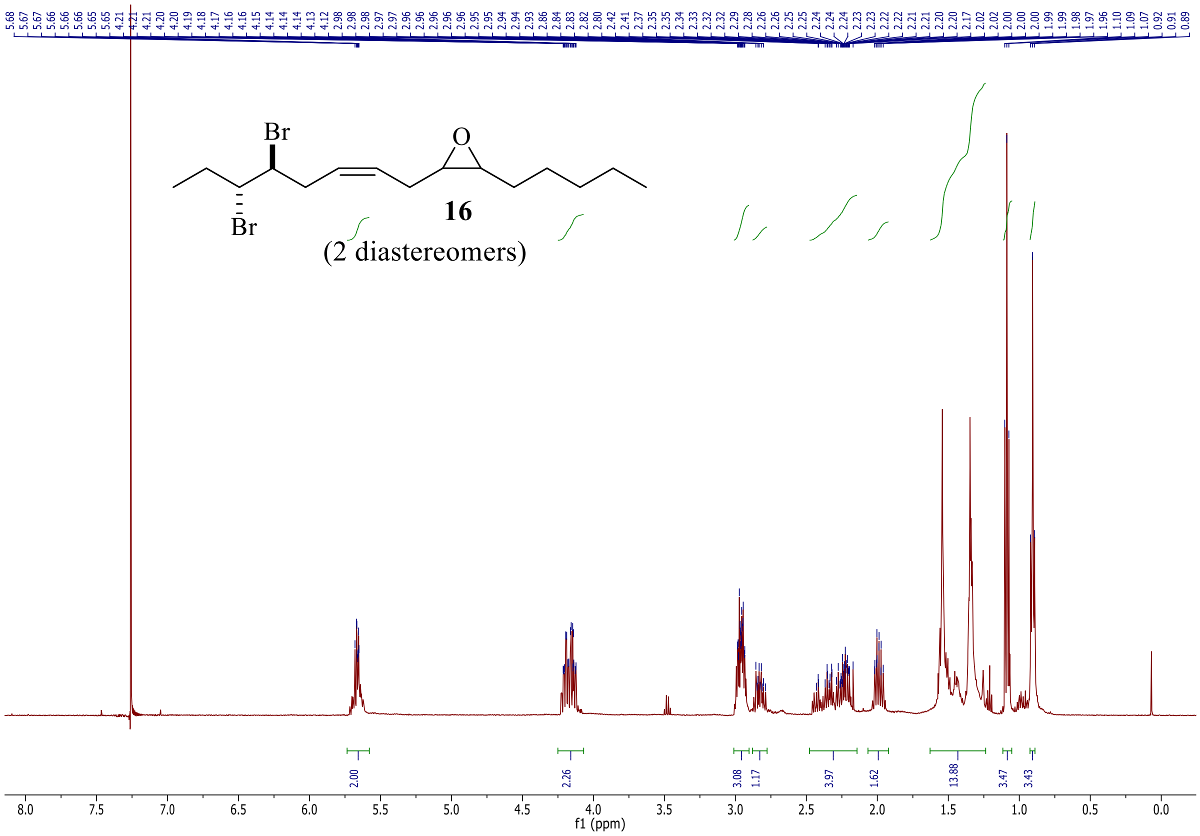
HSQC spectrum of 2-((*Z*)-oct-2-en-1-yl)-3-((*E*)-pent-2-en-1-yl) oxirane (**15**)



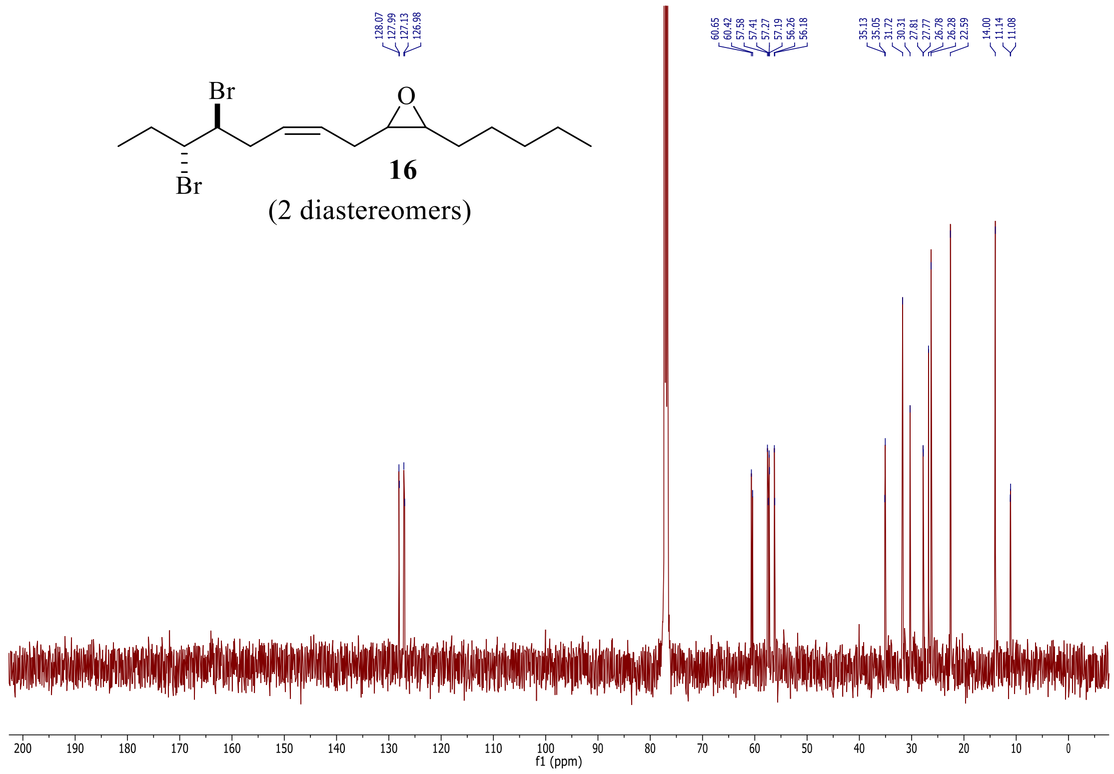
2D COSY spectrum of 2-((*Z*)-oct-2-en-1-yl)-3-((*E*)-pent-2-en-1-yl) oxirane (**15**)



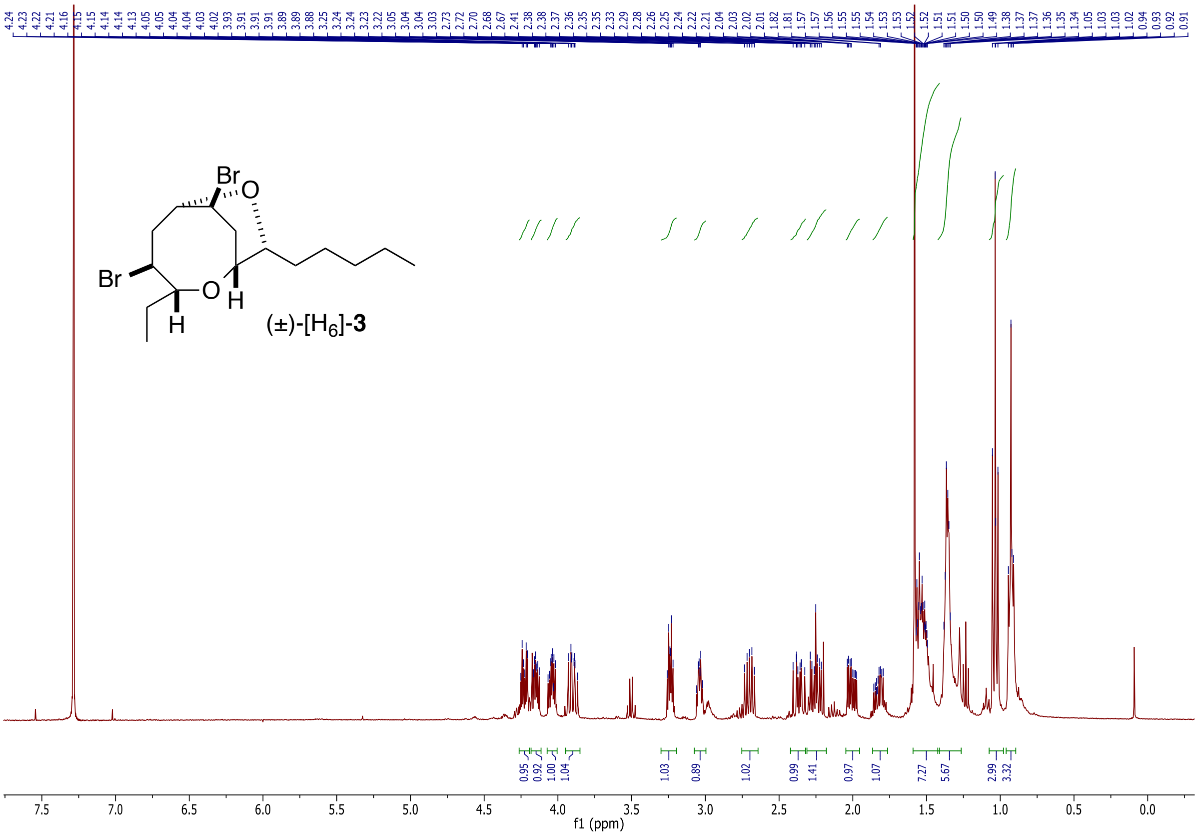
^{1}H NMR spectrum of 2-[(2Z)-5,6-Dibromooct-2-en-1-yl]-3-pentyloxirane (**16**) (400 MHz, CDCl$_3$)



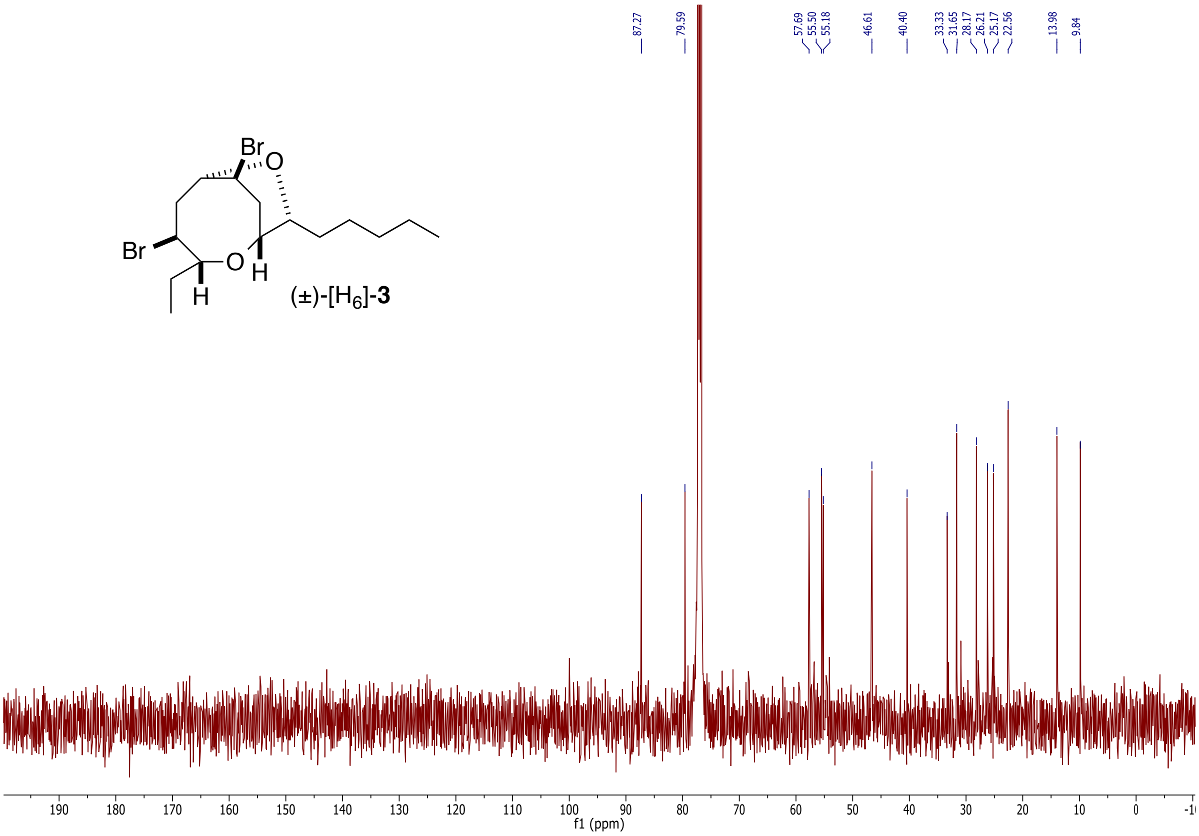
^{13}C NMR spectrum of 2-[(2Z)-5,6-Dibromooct-2-en-1-yl]-3-pentyloxirane (**16**) (101 MHz, CDCl$_3$)



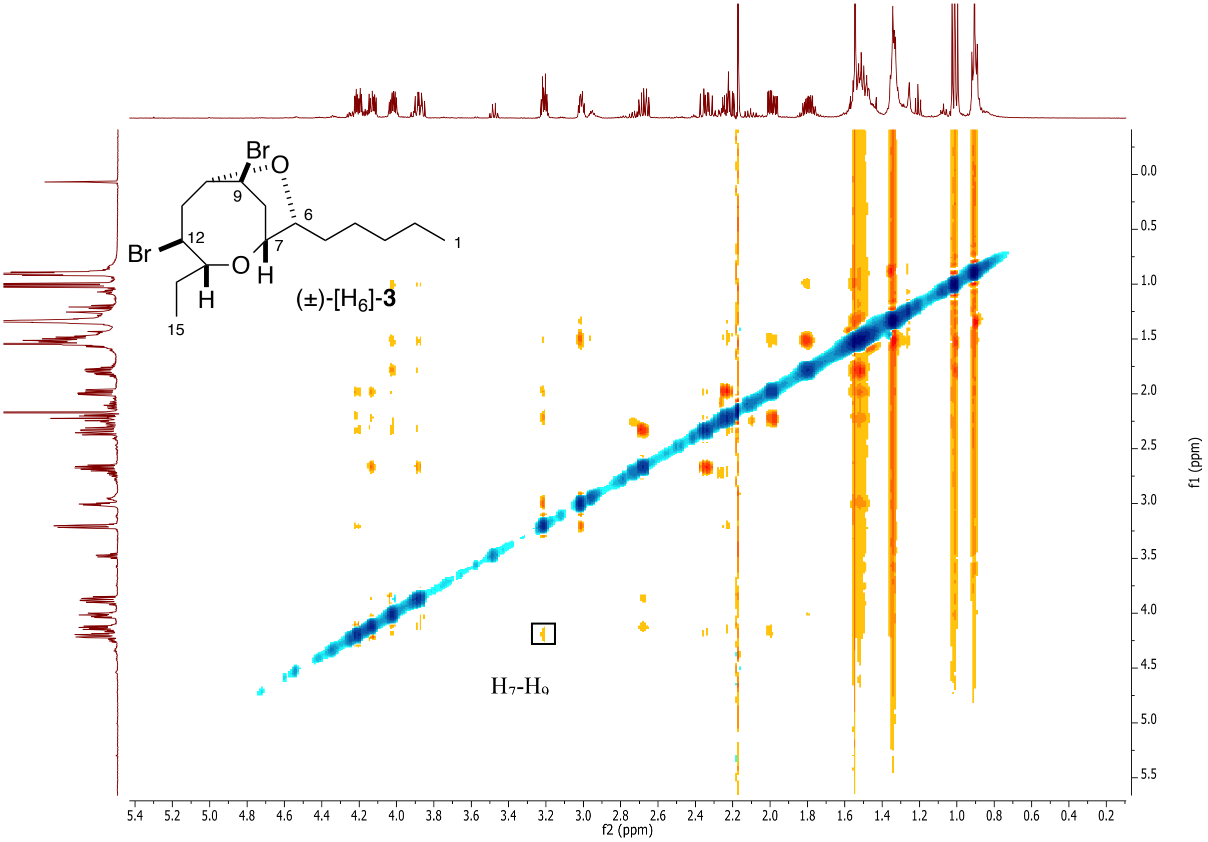
^{1}H NMR spectrum of hexahydrolaureoxanyne (±)-[H$_6$]-**3** (400 MHz, CDCl$_3$)



^{13}C NMR spectrum of hexahydrolaureoxanyne (±)-[H$_6$]-**3** (101 MHz, CDCl$_3$)



2D-NOESY spectrum of hexahydrolaureoxanyne (±)-[H_6]-**3**



HRMS (TOF-ES$^+$) of hexahydrolaureoxanyne (±)-[H_6]-**3**

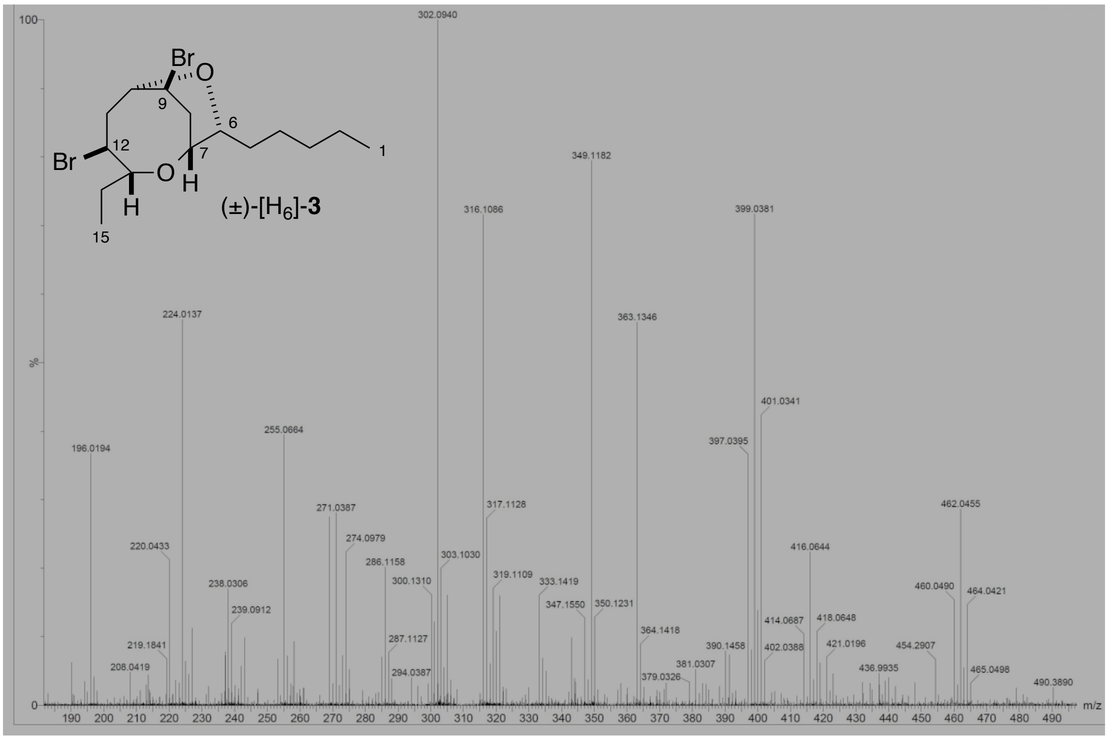


Table 1 – Comparison of (±)-[H_6]-**3** ^{1}H NMR chemical shifts with literature values[3,a]

δ/ppm, (±)-[H_6]-**3** (400 MHz, $CDCl_3$)	δ/ppm, Hexahydrolaureoxanyne (400 MHz,[b] $CDCl_3$)[3]	Δδ/ppm
4.21 (1H)	4.20 (1H)	0.01
4.13 (1H)	4.13 (1H)	0.00
4.03 (1H)	4.02 (1H)	0.01
3.88 (1H)	3.87 (1H)	0.01
3.22 (1H)	3.21 (1H)	0.01
3.02 (1H)	3.01 (1H)	0.01
2.68 (1H)	2.67 (1H)	0.01
2.35 (1H)	2.34 (1H)	0.01
2.23 (1H)	2.23 (1H)	0.00
1.99 (1H)	2.03 (1H)	0.04
1.81 (1H)	1.79 (1H)	0.02
1.62-1.38 (6H)	1.57 (6H)	-[c]
1.36-1.25 (3H)	1.32 (3H)	-[c]
1.01 (3H)	1.01 (3H)	0.00
0.90 (3H)	0.90 (3H)	0.00

[a] ^{1}H NMR chemical shifts are available, but ^{13}C NMR values for this compound were not reported; [b] Spectrometer operating frequency was not explicitly reported for this compound in reference 3, but the ^{1}H NMR data for laureoxanyne itself was reported at 400 MHz; [c] Protons reported as multiplets and are not directly comparable.

Root-mean-square difference: 0.014 ppm

For comparison the same analysis for hexahydrolaureatin (ref. 12b in the main text) and hexahydroisolaureatin (ref 12c in the main text) gave rms difference values of 0.536 and 0.462 ppm respectively. For hexahydroisoprelaurefucin (ref. 12d in the main text and literature cited therein), only the two resonances for the two methyl groups are reported and the rms analysis is meaningless.

Table 2 – Comparison of (±)-[H_6]-**3** multiplicities with literature values[3,a]

Multiplicities, (±)-[H_6]-**3** (400 MHz, $CDCl_3$)	Multiplicities, hexahydrolaureoxanyne (400 MHz,[b] $CDCl_3$)[3]	Matching multiplicity? (TRUE or FALSE)
4.21 (dt)	4.20 (dt)	TRUE
4.13 (ddd)	4.13 (ddd)	TRUE
4.03 (td)	4.02 (dt)	TRUE[c]
3.88 (ddd)	3.87 (dt)	TRUE[d]
3.22 (dt)	3.21 (dt)	TRUE
3.02 (dt)	3.01 (dt)	TRUE
2.68 (dt)	2.67 (dt)	TRUE
2.35 (ddd)	2.34 (dt)	TRUE[d]
2.23 (ddd)	2.23 (ddd)	TRUE
1.99 (ddd)	2.03 (ddd,)	TRUE
1.81 (ddq)	1.79 (ddq)	TRUE
1.62-1.38 (m)	1.57 (m)	TRUE
1.36-1.25 (m)	1.32 (m)	TRUE
1.01 (t)	1.01 (t)	TRUE
0.90 (br t)	0.90 (br t)	TRUE

[a] ^1H NMR chemical shifts are available, but ^{13}C NMR values for this compound were not reported; [b] Spectrometer operating frequency was not explicitly reported for this compound in reference 3, but the ^1H NMR data for laureoxanyne itself was reported at 400 MHz; [c] Assuming a triplet of doublets is equivalent to a doublet of triplets where the order of reporting of *J* values is not defined (see also Table 3); [d] Assuming that a ddd is equivalent to a dt when two of the coupling constants are of similar magnitude (see also Table 3).

Table 3 – Comparison of (±)-[H_6]-**3** *J* values with literature values[3,a]

(±)-[H_6]-**3** (400 MHz, $CDCl_3$)		Hexahydrolaureoxanyne (400 MHz,[b] $CDCl_3$)[3]		
δ/ppm	*J*/Hz	δ/ppm	*J*/Hz	Δ*J*/Hz
4.21 (dt)	11.0	4.20 (dt)	10.7	–0.3
	3.4		3.4	0.0
4.13 (ddd)	9.0	4.13 (ddd)	9.8	0.8
	6.5		8.3	1.8
	4.0		3.4	–0.6
4.03 (td)	8.3	4.02 (dt)	8.3[c]	0.0
	3.8		3.9[c]	0.1
3.88 (ddd)	9.8	3.87 (dt)	9.8	0.0
	8.4		8.3	0.1
	7.3		8.3[d]	1.0
3.22 (dt)	8.4	3.21 (dt)	6.8	–1.6
	4.2		4.4	0.2
3.02 (dt)	4.8	3.01 (dt)	4.4	–0.4
	6.3		6.3	0.0
2.68 (dt)	13.3	2.67 (dt)	13.2	–0.1
	6.8		8.3	1.5
2.35 (ddd)	13.0	2.34 (dt)	13.0	0.0
	9.8		9.8	0.0
	9.0		9.8[d]	0.8
2.23 (ddd)	15.6	2.23 (ddd)	15.1	–0.5
	9.2		6.7	–2.5
	5.2		4.8	–0.4
1.99 (ddd)	14.9	2.03 (ddd,)	15.1	0.2
	7.3		6.8	–0.5
	3.2		3.4	0.2
1.81 (ddq)	14.0	1.79 (ddq)	14.0	0.0
	3.9		3.9	0.0
	7.5		7.5	0.0
1.62-1.38 (m)	-	1.57 (m)	-	–
1.36-1.25 (m)	-	1.32 (m)	-	–
1.01 (t)	7.5	1.01 (t)	7.5	0.0
0.90 (br t)	7.5	0.90 (br t)	7.5	0.0

[a] ^1H NMR chemical shifts are available, but ^{13}C NMR values for this compound were not reported; [b] Spectrometer operating frequency was not explicitly reported for this compound in reference 3, but the ^1H NMR data for laureoxanyne itself was reported at 400 MHz; [c] Assuming a triplet of doublets is equivalent to a doublet of triplets where the order of reporting of *J* values is not defined; [d] Assuming that a ddd is equivalent to a dt when two of the coupling constants are of similar magnitude.

Root-mean-square difference (*J*): 0.8 Hz

References

1. Murray, R. W.; Ramasubbu, J. *J. Org. Chem.* **1985**, *50*, 2847-2853.
2. Bonney, K. J.; Braddock, D. C. *J. Org. Chem.* **2012**, *77*, 9574-9584.
3. Fukuzawa, A.; Nakamura, M.; Tanura, M.; Murai, A. *Tetrahedron Lett.* **1990**, *31*, 4895-4898.