Supplementary information:

General Information

Procedures using oxygen- and/or moisture-sensitive materials were performed with anhydrous solvents (vide infra) under an atmosphere of anhydrous argon in flame-dried flasks, using standard Schlenk techniques. Analytical thin-layer chromatography was performed on precoated glass-backed plates (Silica Gel 60 F254; Merck), and visualised using a combination of UV light (254 nm) and aqueous ceric ammonium molybdate (CAM), aqueous basic potassium permanganate stains or vanillin solution. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, VWR (40-63 μm) silica gel and Sigma Aldrich silica gel. Pressure was applied at the column head via hand bellows or a flow of nitrogen with the solvent system used in parentheses.

Reactions at 0°C were performed using an ice-water bath, covered with cotton and foil if overnight stirring is needed. Other temperatures were obtained using a Julabo FT902 immersion cooler or the heating plate of the stirrer. Unless stated otherwise, solution NMR spectra were recorded at room temperature; ^{1}H and ^{13}C NMR experiments were carried out using Bruker DPX-200 (200/50 MHz), AVN-400 (400/100 MHz), DQX-400 (400/100 MHz) or AVC-500 (500/125 MHz) spectrometers. Chemical shifts are reported in ppm from the residual solvent peak. Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Labels H and H' refer to diastereotopic protons attached to the same carbon and impart no stereochemical information. Assignments were made with the assistance of gCOSY, DEPT-135, gHSQC and gHMBC or gHMQC NMR spectra.

The distillation of certain products was performed at the stated temperature using Buchi Glass Oven B-585 Kugelrohr (100V-230 V, 50/60 Hz). Solvents used were of HPLC grade (Fisher Scientific, Sigma Alrich or Rathburn); all eluent systems were isocratic.

Chiral GC measurements were conducted on a HP6890 (H_2 as vector gas) or HP6850

(H_2 as vector gas) GC with the stated column in the characterization. Temperature programs are described as follows: initial temperature (°C) - initial time (min) - temperature gradient (°C/min) –[certain temperature – holding time - temperature gradient (°C/min)]- final temperature (°C) – holding time. Retention times (R_T) are given in min. Low-resolution mass spectra was recorded using a Walters LCT premier XE. High-resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford.

Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 600-4000 cm^{-1}. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 25°C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} $deg.cm^2$ g^{-1} (concentration c given as g/100 mL).

Chemicals General chemicals:

Dry THF, CH_2Cl_2, Et_2O, hexane, pentane and acetonitrile were collected fresh from an mBraun SPS-800 solvent purification system having been passed through anhydrous alumina columns. All other dry solvents used were dried over 3 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Alrich, Rathburn or Fisher Scientific.

Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Apollo Scientific, Acros Organics, Strem Chemicals, Alfa Aesar or TCI UK and were used without purification. Petroleum ether refers to light petroleum boiling in the range 30-40 °C. Deuterated solvents were purchased from Sigma-Aldrich (CD_2Cl_2, $CDCl_3$).

Schwartz reagent was prepared according to the literature procedure[1] from Cp_2ZrCl_2 purchased from Alfa Aesar or Strem Chemicals. The phosphoramidite ligand **C** was synthesized according to the literature procedure [2].

General Methods：

Procedure used in the synthesis of racemic products:

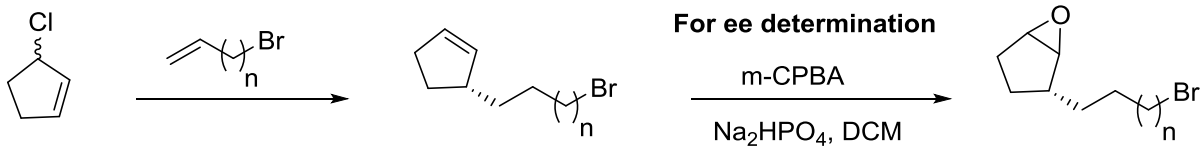
Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (2.0 mL) under an argon atmosphere. After stirring for 20 to 40 min, CuBr Me_2S (82 mg, 0.40 mmol, 1.0 eq), was added to the resulting clear yellow solution and the resulting black mixture was allowed to stir for an additional 10 min before a cyclic allylchloride (0.40 mmol, 1.0 eq) was added via microsyringe over about 1 min. Stirring at room temperature was continued arbitrarily overnight before the reaction was diluted and quenched by addition of petrol (ca 3 mL) and then NH_4Cl (1M aq., ca 1.5 mL). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo* to give the crude product. Flash column chromatography of the residue (pentane 100 %; SiO_2) gave the desired cyclic allylic product.

Procedure used in the synthesis of asymmetric products:

CuI (7.7 mg, 0.04 mmol, 0.1 eq) and phosphoramidite ligand C (21.2 mg, 0.04 mmol, 0.1 eq) were dissolved in $CHCl_3$ (0.8 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.3 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of corresponding alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 20 to 40 min, the resulting clear yellow solution was transferred *via* syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before the cyclic allylchloride (0.40 mmol, 1.0 eq) was added dropwise via microsyringe and stirring was arbitrarily continued overnight. The reaction mixture was diluted by addition of petrol (ca 3 mL) and then quenched by addition of NH_4Cl (1 M aq., ca 1.5 mL). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was

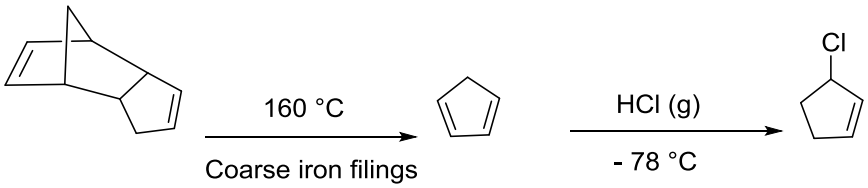
washed with $NaHCO_3$ (aq. sat. ca 10 mL), dried (MgSO4), filtered and concentrated in vacuo to give the crude product. Flash column chromatography of the residue (pentane 100%; SiO_2) gave the desired cyclic allylic product.

Derivatization of products to epoxides[3]:



m-CPBA (2 eq) and Na_2HPO_4 (3 eq) were added at room temperature to a stirred solution of the isolated product (1 eq) in CH_2Cl_2 (6 mL, for a 0.4 mmol scale reaction) under an argon atmosphere. The reaction mixture was stirred arbitrarily for 2 h before being diluted and quenched by addition of Et_2O (10 ml) and an aqueous solution of saturated $Na_2S_2O_3$ (10 ml). The organic phase was washed with NaOH (1 M aq., 3× 5 ml), dried over Mg2SO4, filtered and concentrated under vacuum. The resulting crude mixture of diastereomeric epoxides was directly analyzed by GC chromatography using a chiral non-racemic stationary phase.

3-chlorocyclopent-1-ene[4]: (a)



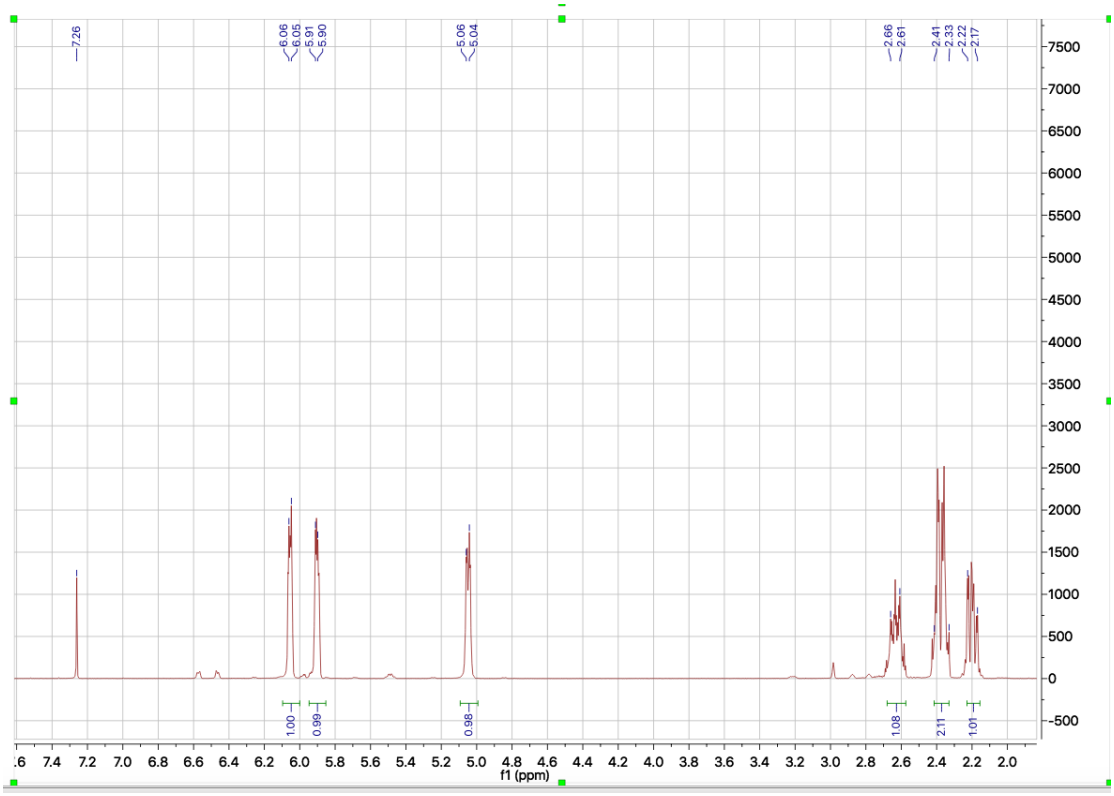
a) In a flame-dried distillation system (Scheme a), dicyclopentadiene (200 mL, 195 g) and coarse iron filings (2 g) were added to a 500mL flask. The outlet of the Friedrichs condenser is connected to a simple distilling head fitted with a thermometer and attached to an efficient water-cooled condenser. The collection flasks was immersed into an acetone/dry ice bath and a $CaCl_2$ tube was connected to the top. The flask containing dicyclopentadiene was heated to 160 °C. Cyclopentadiene distils off at 42.5 °C and dicyclopentadiene refluxes from the cold-

finger (Friedrichs) condenser. After two-thirds of the dicyclopentadiene had been pyrolyzed, the residue was discarded according to the literature procedure.

b) The flask containing cyclopentadiene was weighed and connected to the right hand side of the HCl gas-producing facility (b) and cooled to -78 °C. Using a slow addition funnel, concentrated HCl was added dropwise to a flask filled about halfway with dry solid $CaCl_2$. During this operation the cyclopentadiene-containing flask was swirled to ensure good mixing, and weighed quickly roughly every 2 min in order to determine the amount of hydrogen chloride that has been added. The addition is stopped when the weight of the flask indicated that the reaction reached 86% theoretical yield based on weight. The crude was purified by Kugelrohr distillation (22 mmbar, 22 °C, about 15 min); further kugelrohr distillation (5 mmbar, 22 °C, for about 30 min) provided pure product as a colourless oil (8.7 g). The pure product should be stored in a -78 °C freezer.

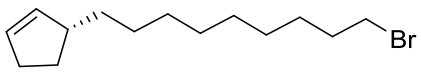
c) 1 H NMR (400 MHz, $CDCl_3$): δH /ppm 6.05-6.06 (m, 1H), 5.90-5.91 (m, 1H), 5.04-5.06 (m, 1H), 2.61-2.66 (m, 1H), 2.33-2.41 (m, 2H), 2.17-2.22 (m, 1H).

d) 13 C NMR (100 MHz, $CDCl_3$): δC /ppm 31.0, 34.6, 65.6, 132.1, 136.1



Natural products: synthesis of Alepric Acid (5)

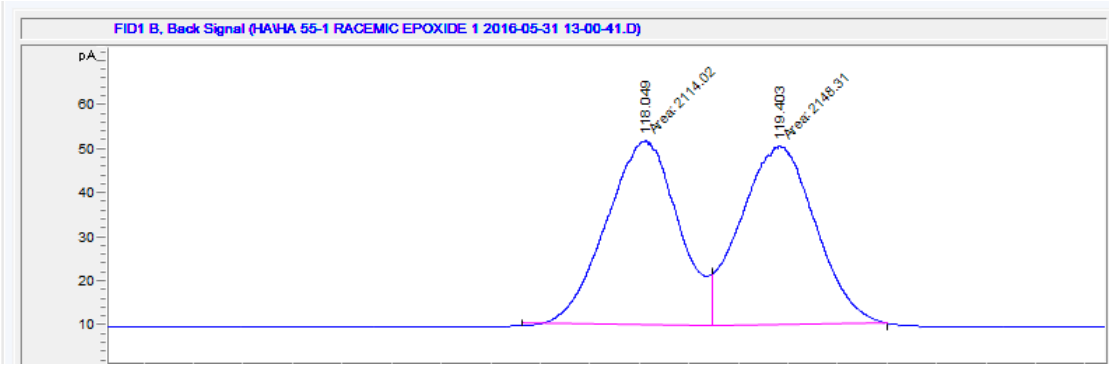
(*R*)-3-(9-bromononyl)cyclopent-1-ene: (d_3)

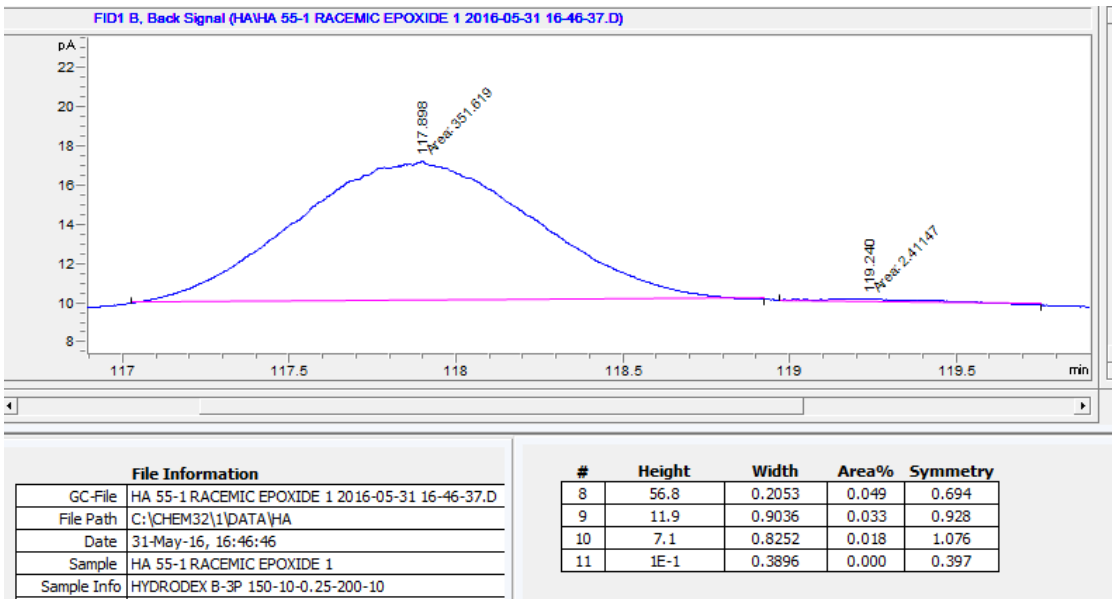


CuI 98% (76 mg, 0.4 mmol, 0.10 eq) and (*R*,*R*,*R*)-Ligand **C** (65.0 mg, 0.4 mmol, 0.10 eq) were stirred in $CHCl_3$ (6 ml) at room temperature for 1 h, In another flask Cp_2ZrHCl (2070 mg, 8 mmol, 2 eq) was added to a solution of 9-bromohept-1-ene (1.86 ml, 10 mmol, 2.5 eq) in CH_2Cl_2(3 ml) at room temperature and stirred until a clear yellow solution was obtained in 15 min. The freshly prepared organozirconium reagent was then transferred to the copper-ligand solution dropwise, using a 5 mL syringe, over 3 min. The resulting orange solution was stirred for 10 minutes before 3-chlorocyclopent-1-ene (0.4 mL, 4 mmol, 1.00 eq) was added and stirring was arbitrarily continued for an additional 12 h before the reaction was quenched by the addition of Et_2O (15 mL) and NH_4Cl (1 M, 10 mL). The aqueous phase was extracted with Et_2O (2x6 mL) and the combined organic materials were washed with $NaHCO_3$ (sat. sol. ~10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed

under reduced pressure. Purification by flash column chromatography using 100% pentane yielded the desired product in 89% yield (0.973 g, 3.56 mmol).

GC analysis of the crude mixture of epoxides derived from (**d_3**) indicated an enantiomeric excess of 99% (Hydrodex B-3P 150-10-0.25-200-10) in the following conditions: held for 150 ˚C for 10 min and 0.25 ˚C/min to 200 ˚C and held 10 min, major enantiomer t_R = 117.898 min, minor enantiomer t_R = 119.240 min.





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Sample	HA 55-1 RACEMIC EPOXIDE 1
Sample Info	HYDRODEX B-3P 150-10-0.25-200-10

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9	11.9	0.9036	0.033	0.928
10	7.1	0.8252	0.018	1.076
11	1E-1	0.3896	0.000	0.397

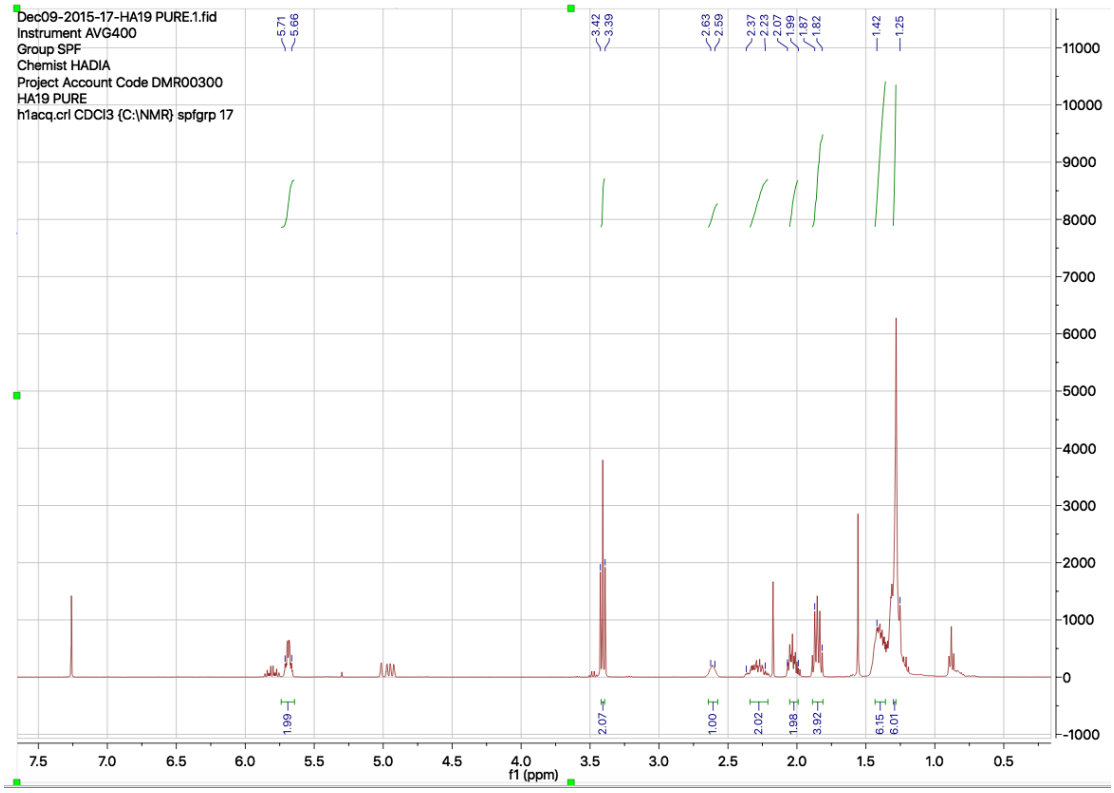
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.20 - 1.31 (m, 6 H), 1.42-1.51 (m, 6 H), 1.82-1.87 (quin, *J*=7.2 Hz, 4 H), 1.99-2.07 (quin, *J*=7.2 Hz, 2 H), 2.23-2.37 (quin, *J*=7.2 Hz, 2 H), 2.59-2.63 (m, 1 H), 3.42-3.39 (t, *J*=6.8 Hz, 2 H), 5.65 - 5.71 (m, 2 H)

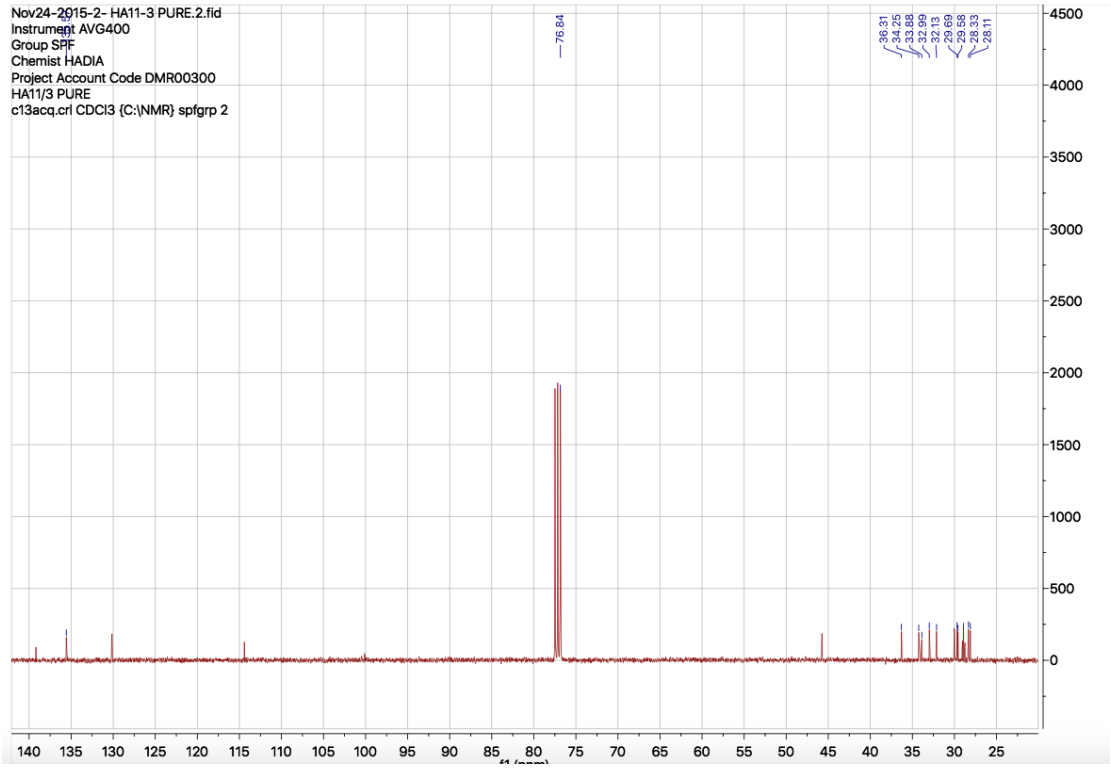
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 28.1, 28.3, 29.5, 29.6, 32.1, 32.9, 33.3, 33.8, 34.1, 34.2, 36.3, 45.7, 130.1, 135.5.

HRMS (ESI) *m/z* calcd for $C_{14}H_{25}Br$ $[M]^+$: 272.1140, found: 272.1170.

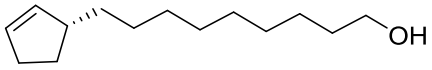
IR (ATR)ν(cm^{-1}): 2923, 2852, 1458.

$[\alpha]^{20}_{589}$ = +66.12 (*c* 1.00, $CHCl_3$) for 99% ee.





(*R*)-9-(cyclopent-2-en-1-yl)nonan-1-ol: (e_3)



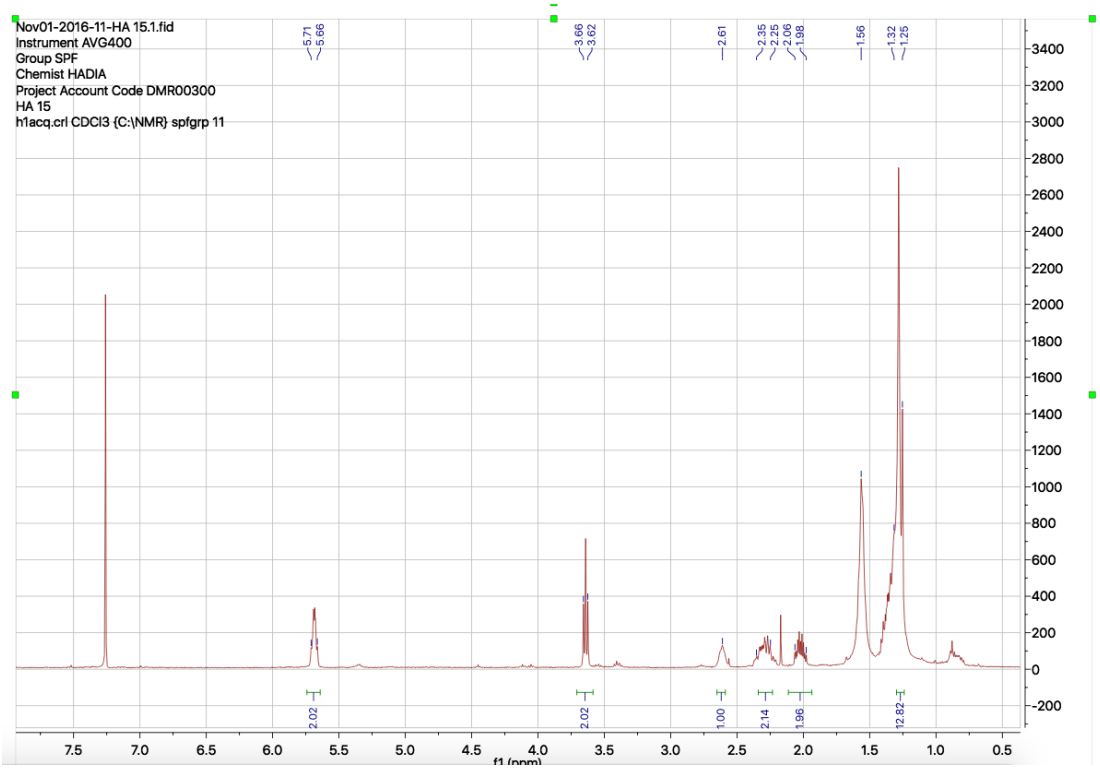
$NaHCO_3$ (160 mg, 1.9 mmol, 3.11 eq) was added to a stirred solution of bromide **(d_3)**(165 mg, 0.61 mmol, 1.00 eq) in a mixture of DMSO (3.05 mL) and water (0.79 mL). The resulting suspension was stirred 22 h at 95 °C before being quenched by addition of water (2 mL). The aqueous phase was extracted with Et_2O (3 x 4 mL) and the combined organic extracts were washed with water, brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude product that was used in the next step without further purification.

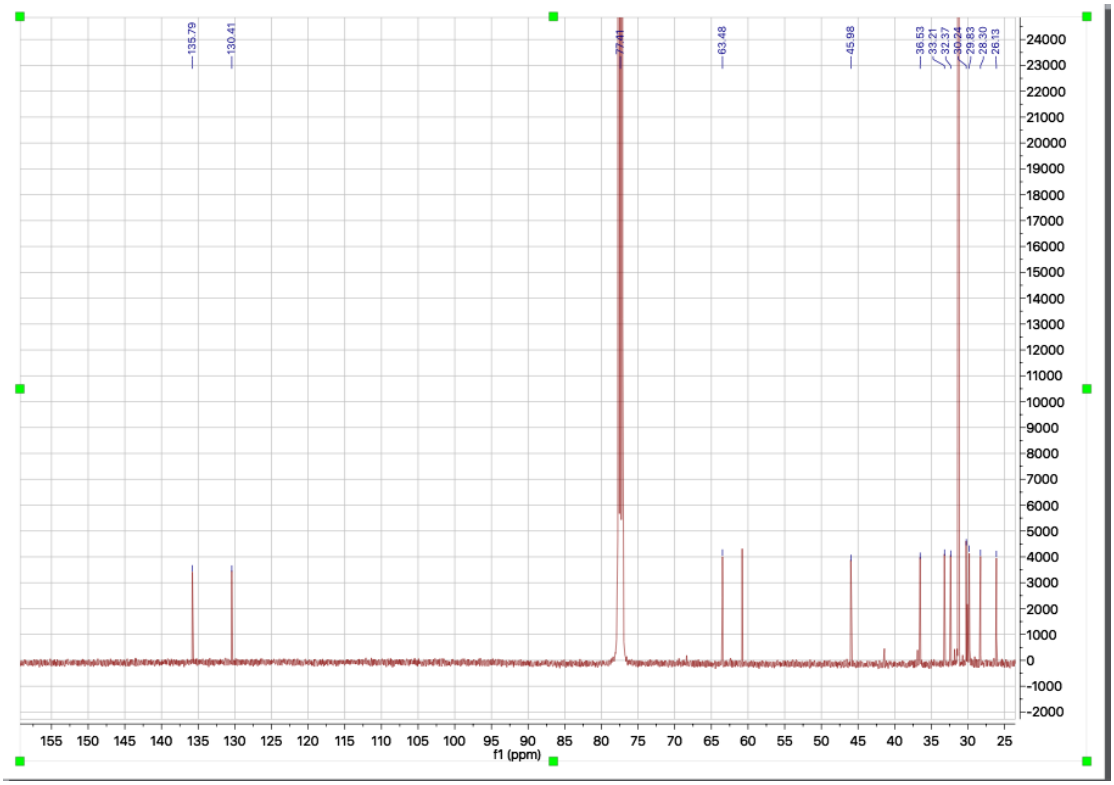
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.25 - 1.32 (m, 6 H), 1.42-1.51 (m, 6 H), 1.55-1.58 (quin, *J*=7.2 Hz, 4 H), 1.98-2.06 (quin, *J*=7.2 Hz, 2 H), 2.25-2.35 (quin, *J*=7.2 Hz, 2 H), 2.61 (m, 1 H), 3.62-3.66 (t, *J*=6.8 Hz, 2 H), 5.66 - 5.71 (m, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 26.1, 28.3, 29.8 (2C), 30.2, 32.3 (2C), 33.2 (2C), 36.5, 45.9, 63.8, 130.4, 135.7

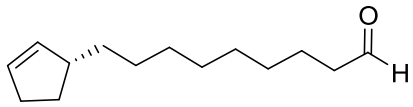
HRMS (ESI) *m/z* calcd for $C_{14}H_{26}O$ $[M]^+$: 210.1984, found: 210.1965.

IR (ATR) ν (cm^{-1}): 2922.6, 2852.7, 1538.9.



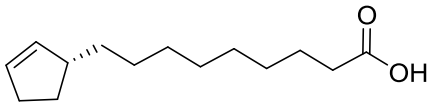


(*R*)-9-(cyclopent-2-en-1-yl) nonanal: (f_3)



Dess-Martin periodinane (433 mg, 1.02 mmol, 2.00 eq) was added to a stirred solution of the crude alcohol (0.51 mmol) in CH_2Cl_2 (20 mL). The suspension was stirred for 1h at room temperature before 20 mL of mixture of $NaHCO_3$: $Na_2S_2O_3$ (1:5, both sat. aq.) was added in one portion. 20 mL of CH_2Cl_2 was added, the phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3x8 mL). The crude aldehyde was used in the next step without further purification.

(*R*)-9-(cyclopent-2-en-1-yl)nonanoic acid (Alepric acid): (5)



A freshly prepared solution of $NaClO_2$ (290 mg, 3.2 mmol, 10.00 eq) in 20% aqueous NaH_2PO_4 (1.77 mL) was added to a vigorously stirred solution of the crude aldehyde (0.32 mmol, 1.00 eq) in *t*BuOH (5.27 mL). After vigorous stirring at room temperature 1 h the reaction mixture was then poured into EtOAc (10 mL) and the phases separated. The aqueous phase was extracted with EtOAc (4 x 5 mL) and a rotary evaporator was used to remove the volatiles. The crude oil was purified by flash column chromatography (SiO_2) eluting with hexane:EtOAc (8:2) to give the desired product in 56% yield (44.9 mg, 0.18 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 1.22 - 1.39 (m, 12 H), 1.60 - 1.65 (m, 2 H), 1.99-2.05 (m, 2 H), 2.23 - 2.28 (m, 2 H), 2.35-2.38 (t, *J*=7.7 Hz, 2 H), 2.61-2.66 (m, 1 H), 5.66 - 5.71 (m, 2 H).

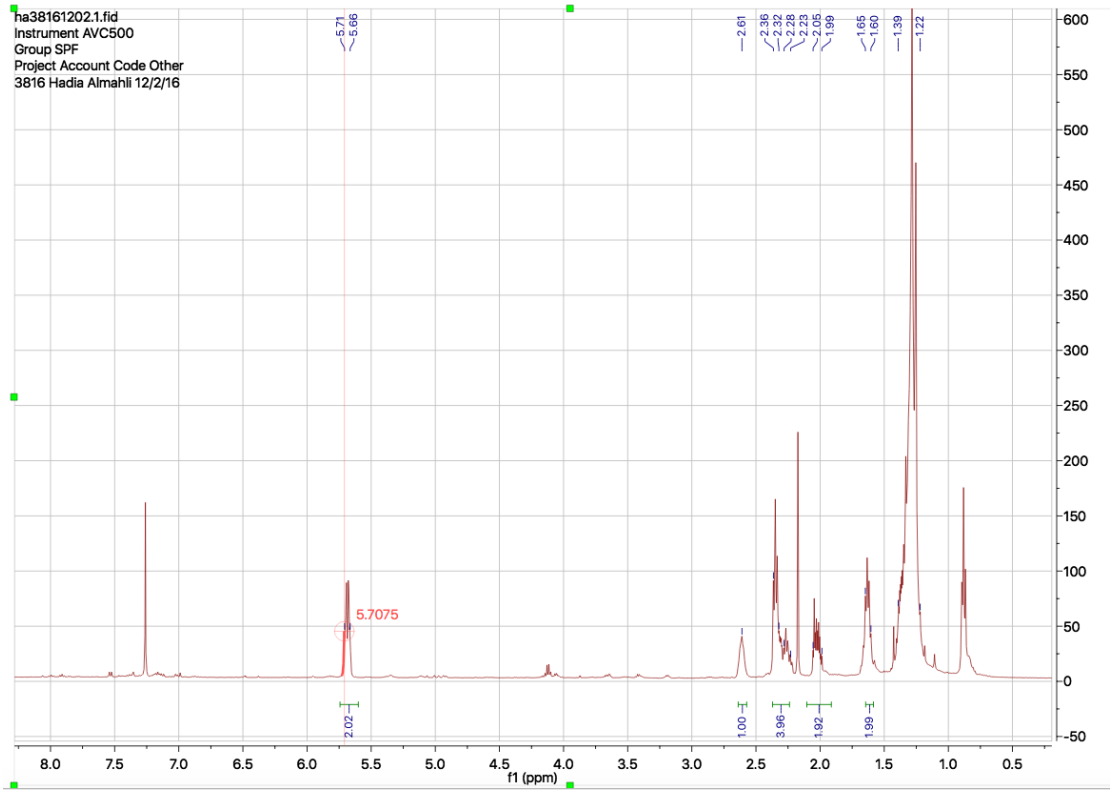
^{13}C NMR (125 MHz, $CDCl_3$): δ_C /ppm 22.7, 23.1, 25.0, 28.3, 29.6, 30.2 (2C), 32.3, 34.3, 36.5, 45.9, 130.4, 135.8, 179.6.

HRMS (ESI) *m/z* calcd for $C_{14}H_{24}O_2$ $[M]^+$: 224.17371, found: 224.02782

, **HRMS** (ESI) *m/z* calcd for $C_{14}H_{23}O_2$ $[M]^-$: 223.17035 , found: 223.17017

IR (ATR) ν (cm^{-1}): 3015.2, 2980.63, 2360.35, 1716.51

$[\alpha]^{20}_{589}$ = +68.29 (*c* 1.05, $CHCl_3$); [lit. +77.12, *c* 10.00][5].



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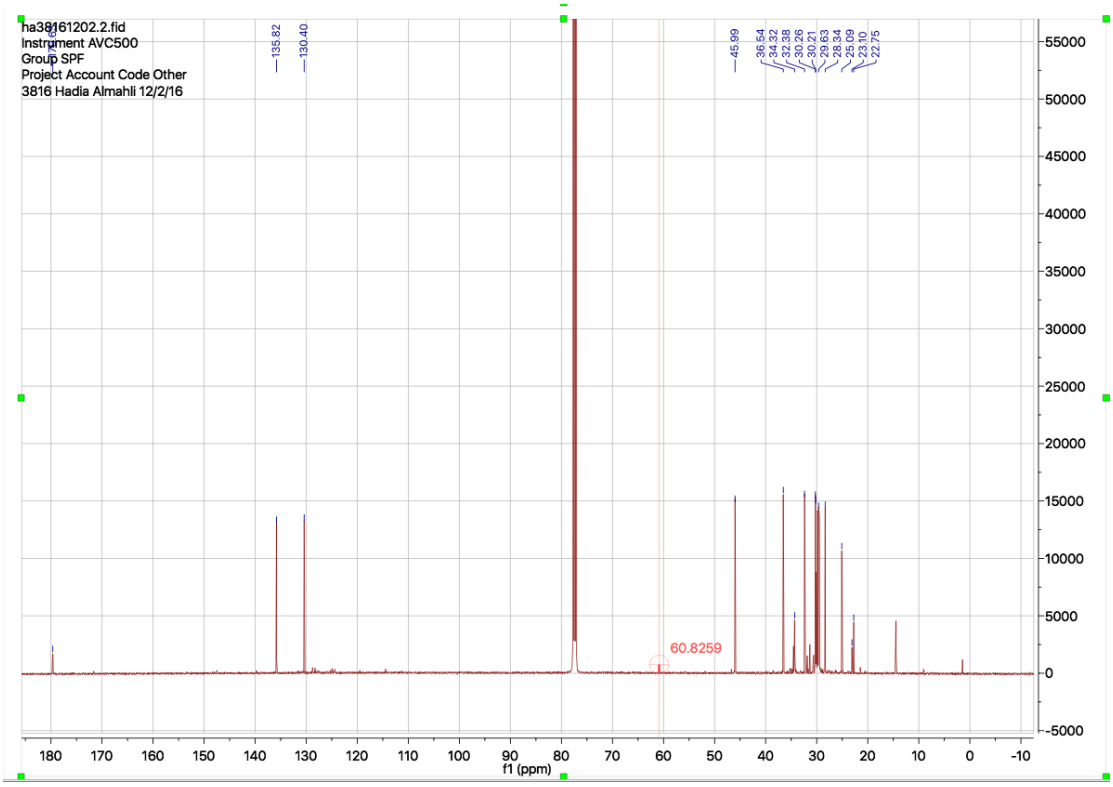
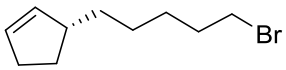


Natural products: synthesis of Aleprestic Acid (4)

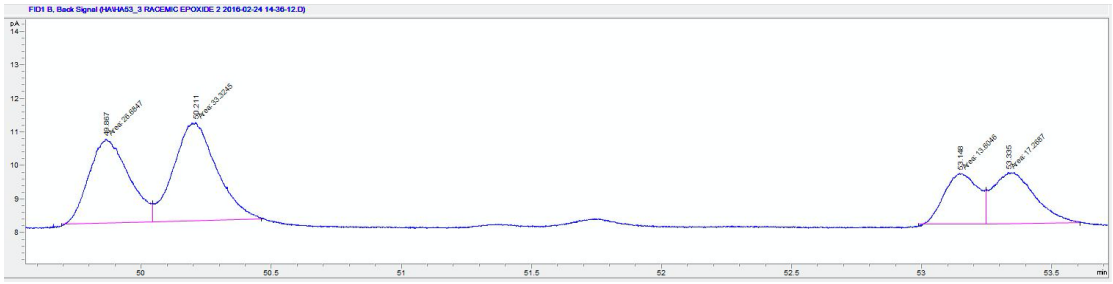
(*R*)-3-(5-bromopentyl)cyclopent-1-ene: (d_1)

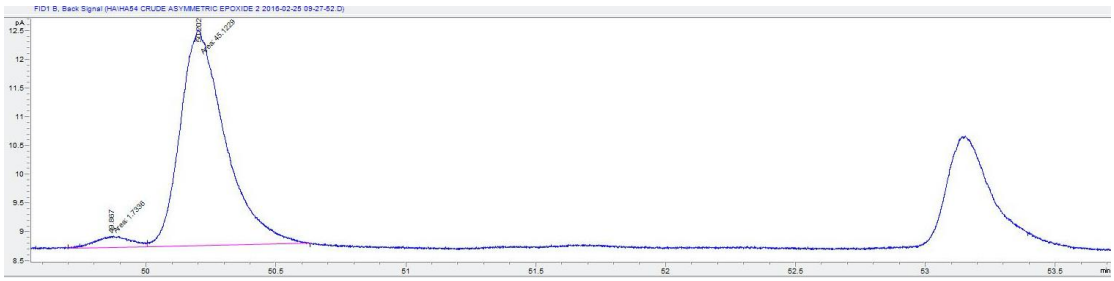


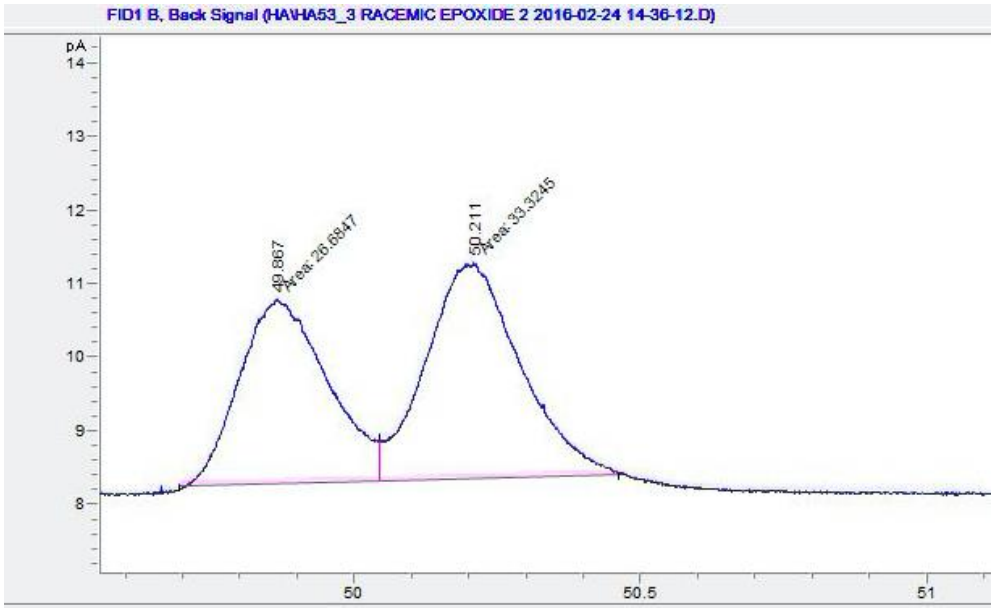
CuI 98% (0.052 g, 0.272 mmol, 0.10 eq) and (*R*,*R*,*R*)-Ligand **C** (0.148 g, 0.272 mmol, 0.10 eq) were stirred in $CHCl_3$ (5.24 ml) at room temperature for 1 h, In another flask Cp_2ZrHCl (1.4 g, 5.44 mmol, 2.5 eq) was added to a solution of 9-bromohept-1-ene (0.82 ml, 6.8 mmol, eq) in CH_2Cl_2(2.64 ml) at room temperature and stirred until a clear yellow solution was obtained (15-20 min). The freshly prepared organozirconium reagent was then transferred to the copper-ligand solution dropwise, using a 5 mL syringe, over 3 min. The resulting orange solution was stirred for 10 minutes before 3-chlorocyclopent-1-ene (0.26 mL, 2.72 mmol, 1.00 eq) was added and stirring was arbitrarily continued for an additional 12 h before the reaction was quenched by the addition of Et_2O (15 mL) and NH_4Cl (1 M, 10 mL). The aqueous phase was extracted with Et_2O (2x6 mL) and the combined organic materials were washed with $NaHCO_3$ (sat. sol. ~10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and the

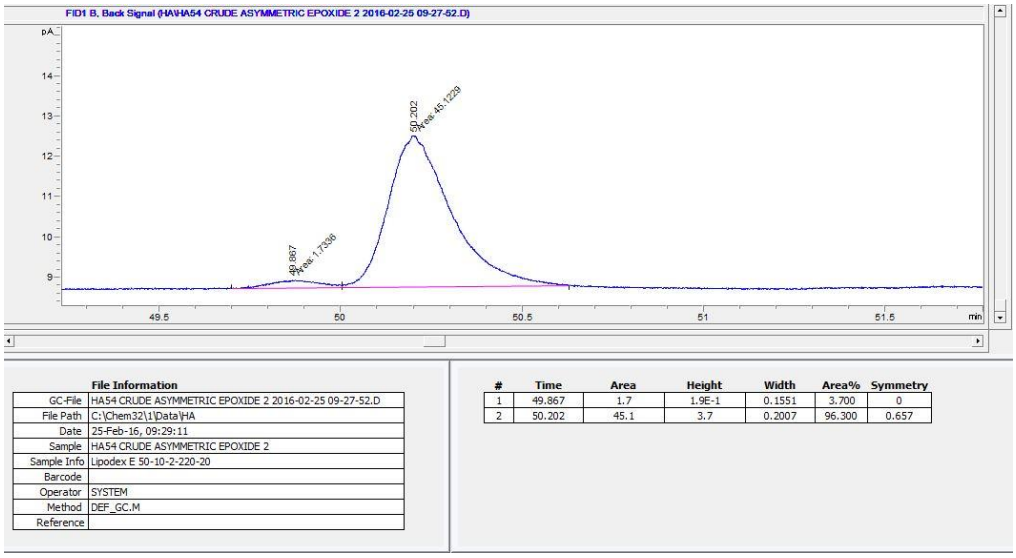
solvent removed under reduced pressure. Purification by flash column chromatography using 100% hexane yielded the desired product in 92% yield (0.54 g, 2.49 mmol).

GC analysis of the crude mixture of epoxides derived from **(d_1)** indicated an enantiomeric excess of 93% (Lipodex E 50-10-2-220-20) in the following conditions: held for 50 ˚C for 10 min and 2 ˚C/min to 220 ˚C and held 20 min , major enantiomer t_R = 50.202 min, minor enantiomer t_R = 49.867 min.









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Barcode	
Operator	SYSTEM
Method	DEF_GC.M
Reference	

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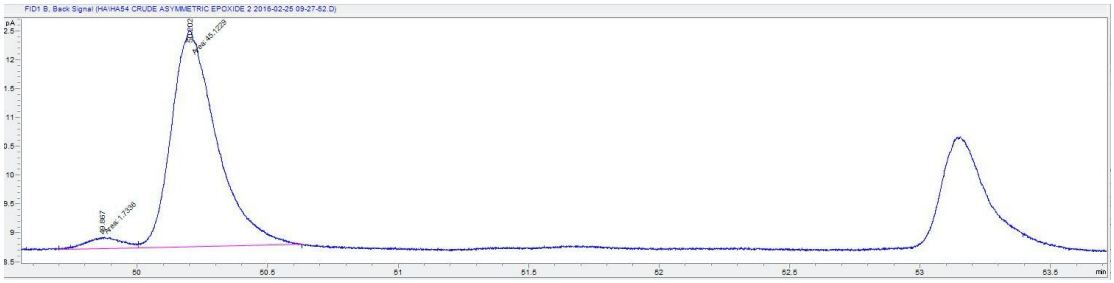
2	50.202	45.1	3.7	0.2007	96.300	0.657



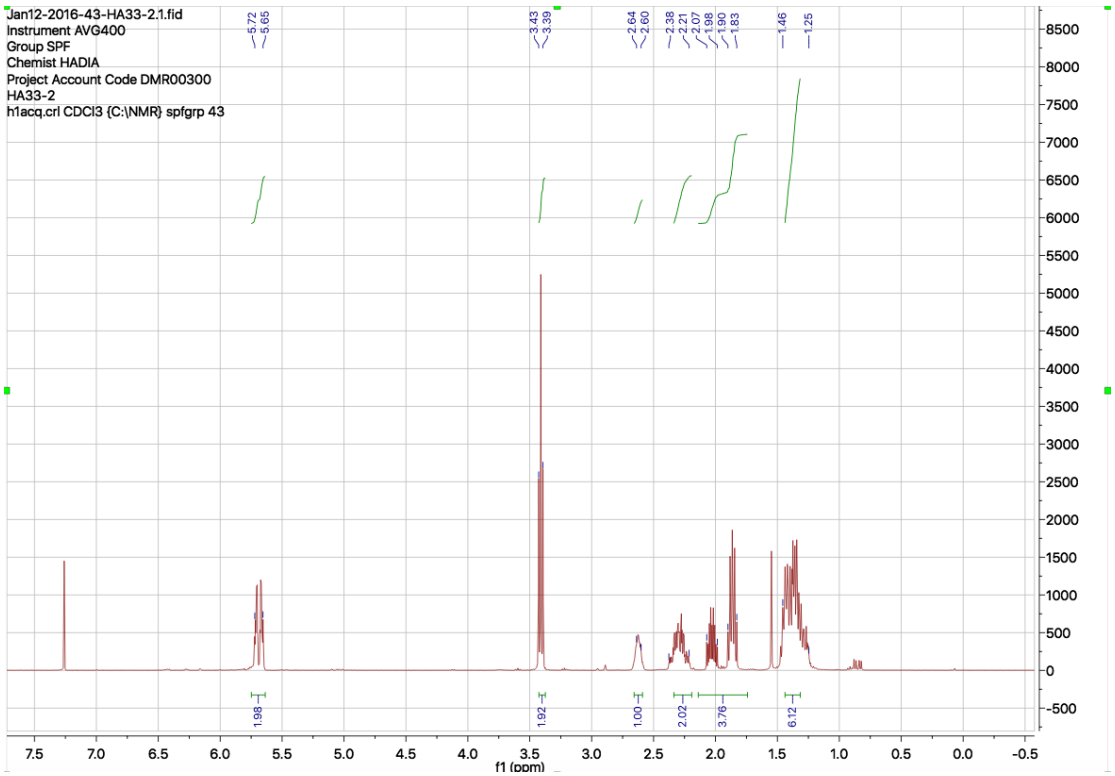
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.25 - 1.46 (m, 6 H), 1.83-1.90 (quin, *J*=7.2 Hz, 2 H), 1.98-2.07 (quin, *J*=7.2 Hz, 2 H), 2.21-2.38 (quin, *J*=7.2 Hz, 2 H), 2.60-2.64 (m, 1 H), 3.39-3.43 (t, *J*=6.8 Hz, 2 H), 5.65 - 5.72 (m, 2 H)

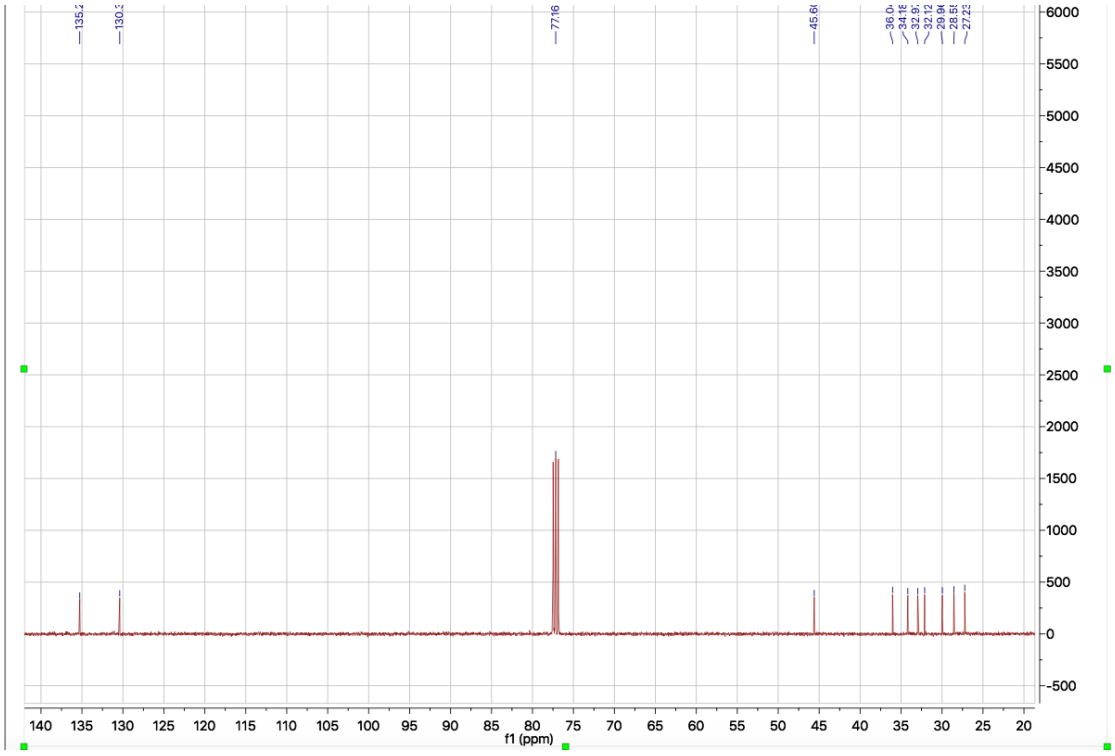
^{13}C NMR (100 MHz, $CDCl_3$): δ_C /ppm 27.2, 28.5, 29.9, 32.1, 32.9, 34.1, 36.0, 45.6, 130.3, 135.2.

HRMS (ESI) *m*/*z* calcd for $C_{10}H_{17}Br$ $[M]^+$: 216.0514, found: 216.0545.

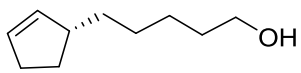
IR (ATR) ν (cm^{-1}): 2980.13, 2924.25, 1473.12.

$[\alpha]^{20}_{589}$ = +64.73 (*c* 1.00, $CHCl_3$) for 93% ee.





(*R*)-5-(cyclopent-2-en-1-yl) pentan-1-ol: (e_1)

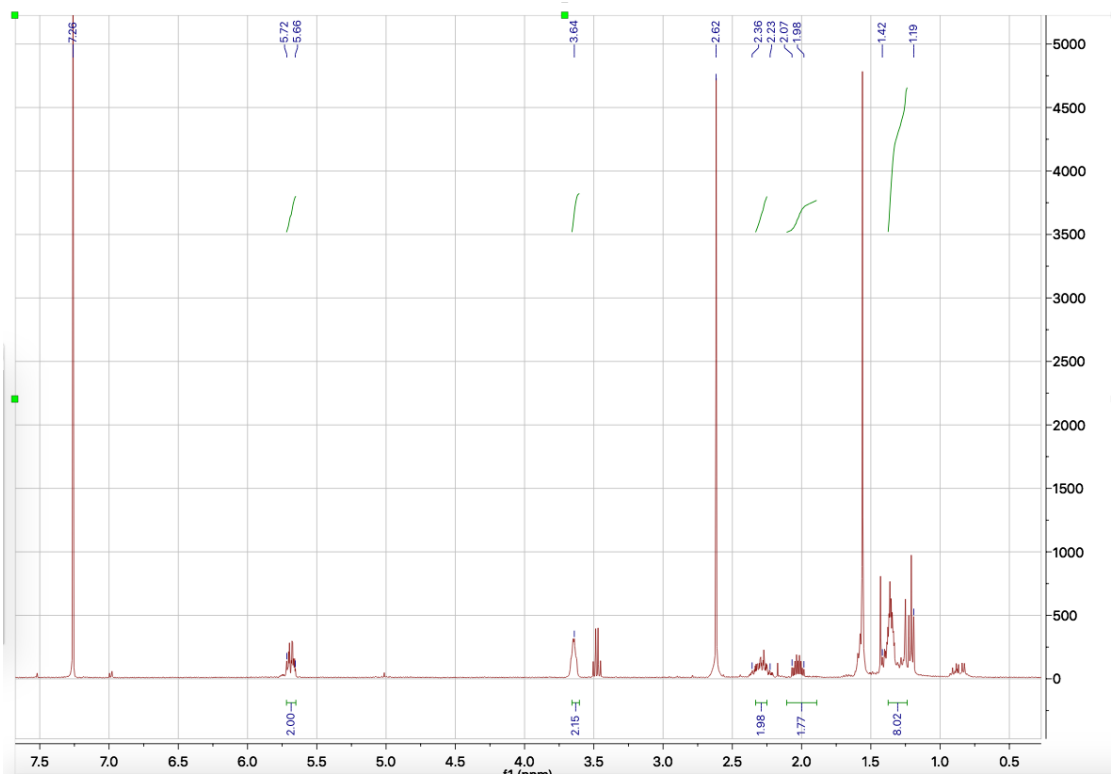


$NaHCO_3$ (380 mg, 4.45 mmol, 3.11 eq) was added to a stirred solution of bromide **(d_1)** (310 g, 1.43 mmol, 1.00 eq) in a mixture of DMSO (7.15 mL) and water (1.86 mL). The resulting suspension was stirred 22 h at 95 °C before being quenched by addition of water (8 mL). The aqueous phase was extracted with Et_2O (3 x 4 mL) and the combined organic extracts were washed with water, brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude product that was used in the next step without further purification.

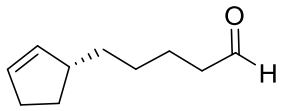
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.19 - 1.42 (m, 6 H), 1.56-1.59 (quin, *J*=7.2 Hz, 2 H), 1.98-2.07 (quin, *J*=7.2 Hz, 2 H), 2.23-2.36 (quin, *J*=7.2 Hz, 2 H), 2.60-2.64 (m, 1 H), 3.64 (t, *J*=6.8 Hz, 2 H), 5.66 - 5.72 (m, 2 H)

HRMS (ESI) *m/z* calcd for $C_{10}H_{18}O$ $[M]^+$: 154.1358, found: 154.1349.

IR (ATR) v (cm^{-1}): 3557.3, 2888.54, 2851.9, 1558.4.

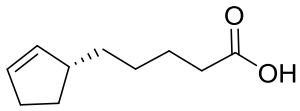


(*R*)-5-(cyclopent-2-en-1-yl) pentanal: (f_1)



Dess-Martin periodinane (220 mg, 0.52 mmol, 2.00 eq) was added to a stirred solution of the crude alcohol (0.26 mmol, 1 eq) in CH_2Cl_2 (10 mL). The suspension was stirred for 1h at room temperature before 10 mL of mixture of $NaHCO_3$: $Na_2S_2O_3$ (1:5, both sat. aq.) was added in one portion. 10 mL of CH_2Cl_2 was added, the phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3x4 mL). The crude aldehyde was used in the next step without further purification.

(*R*)-5-(cyclopent-2-en-1-yl)pentanoic acid (Aleprestic acid): (4)



A freshly prepared solution of $NaClO_2$ (0.69 g, 7.6 mmol, 10.00 eq) in 20% aqueous NaH_2PO_4 (4.2 mL) was added to a vigorously stirred solution of the crude aldehyde (0.115 g, 0.76 mmol, 1.00 eq) in *t*BuOH (8 mL). After vigorous stirring at room temperature 2 h the reaction mixture was then poured into EtOAc (15 mL) and the phases separated. The aqueous phase was extracted with EtOAc (4 x 8 mL) and a rotary evaporator was used to remove the volatiles. The crude oil was purified by flash column chromatography (SiO_2) eluting with hexane:EtOAc (8:2) to give the desired product in 54% yield (0.069 g, 0.41 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 1.35- 1.43 (m, 4 H), 1.64 - 1.67 (m, 2 H), 2.00-2.06 (m, 2 H), 2.24 - 2.32 (m, 2 H), 2.35-2.38 (t, *J*=7.7 Hz, 2 H), 2.60-2.66 (m, 1 H), 5.65 - 5.72 (m, 2 H).

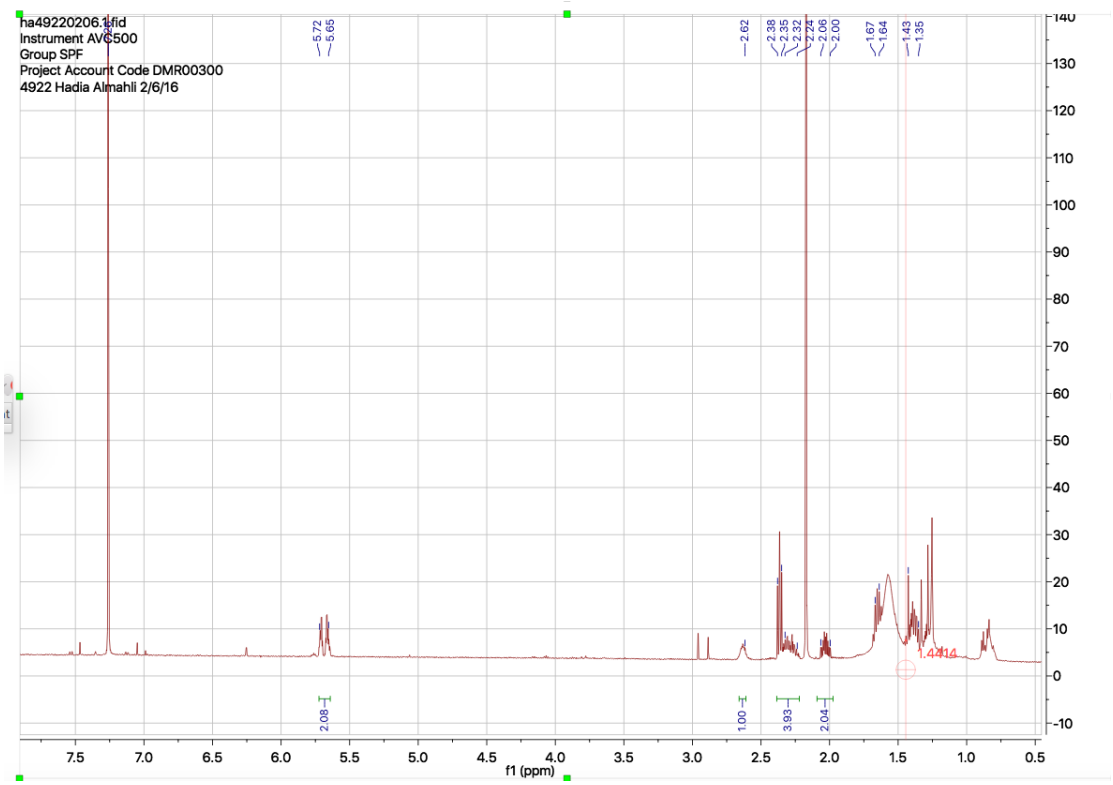
^{13}C NMR (125 MHz, $CDCl_3$): δ_C /ppm 27.5, 29.9, 31.0, 32.1, 33.5, 35.8, 45.5, 130.4, 135.1, 176.5.

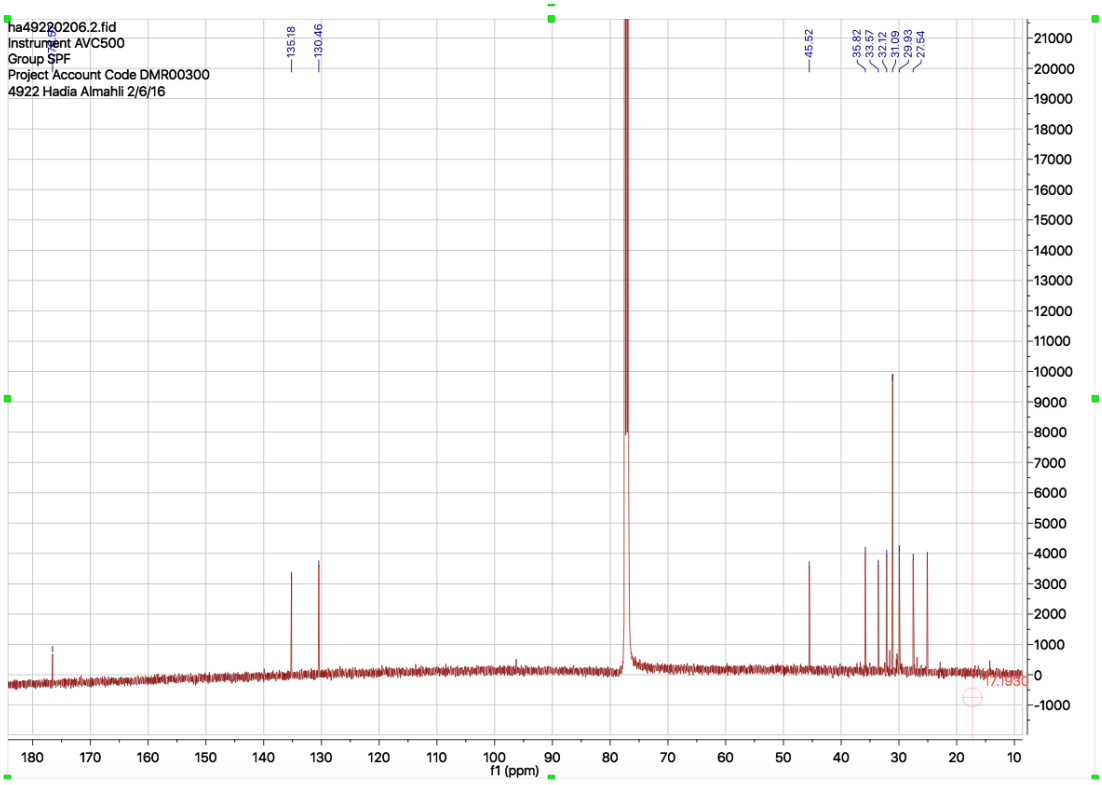
HRMS (ESI) *m/z* calcd for $C_{10}H_{16}O_2$ $[M]^+$: 168.1111, found: 168.11097.

(ESI) *m/z* calcd for $C_{10}H_{15}O_2$ $[M]^-$: 167.10775, found: 167.10792

IR (ATR) ν (cm^{-1}): 3007, 2923, 1733.

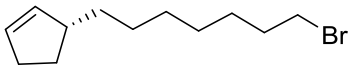
$[\alpha]^{20}_{589}$ = +78.51 (*c* 1.07, $CHCl_3$); [lit. +100.5, *c* 10.00][5].





Natural products: synthesis of Gorlic Acid (6)

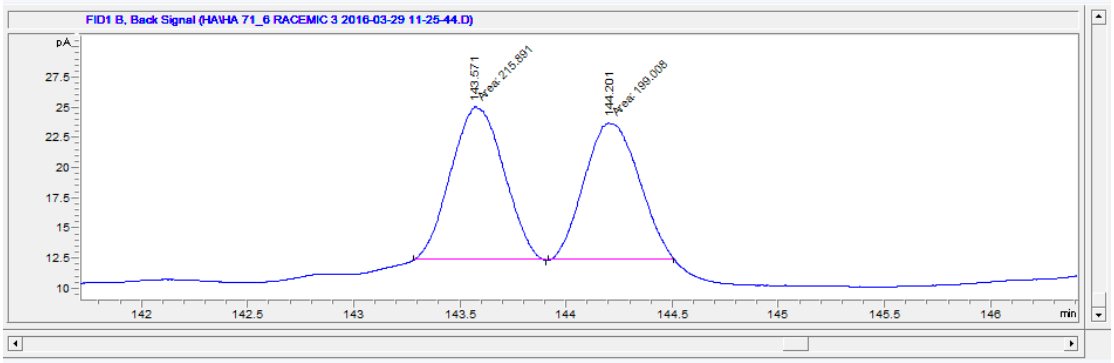
(*R*)-3-(7-bromoheptyl)cyclopent-1-ene : (d_2)



CuI 98% (78 mg, 0.4 mmol, 0.10 eq) and (*R*,*R*,*R*)-Ligand **C** (219 mg, 0.4 mmol, 0.10 eq) were stirred in $CHCl_3$ (9 ml) at room temperature for 1 h, In another flask Cp_2ZrHCl (5.78 g, 22.4 mmol, 5.6 eq) was added to a solution of 7-bromohept-1-ene (3.1 ml, 20 mmol, 5 eq) in CH_2Cl_2(4 ml) at room temperature and stirred until a clear yellow solution was obtained (15-20 min). The freshly prepared organozirconium reagent was then transferred to the copper-ligand solution dropwise, using a 5 mL syringe, over 3 min. The resulting orange solution was stirred for 10 minutes before 3-chlorocyclopent-1-ene (0.39 mL, 4 mmol, 1.00 eq) was added and stirring was arbitrarily continued for an additional 12 h before the reaction was quenched by the addition of Et_2O (15 mL) and NH_4Cl (1 M, 10 mL). The aqueous phase was extracted with Et_2O (2x6 mL) and the combined organic materials were washed with $NaHCO_3$ (sat. sol. ~10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and the

solvent removed under reduced pressure. Purification by flash column chromatography using 100% pentane yielded the desired product in 87% yield (0.853 g, 3.48 mmol).

GC analysis of the crude mixture of epoxides derived from **(d_2)** indicated an enantiomeric excess of 93% (Hydrodex B-3P 50- 10- 1- 180- 40- 10- 220- 10) in the following conditions: held for 50 ˚C for 10 min, 1˚C/min to 180 ˚C and held 40 min then 10˚C/min for 220˚C held 10 min, major enantiomer t_R = 143.513 min, minor enantiomer t_R = 144.178 min.



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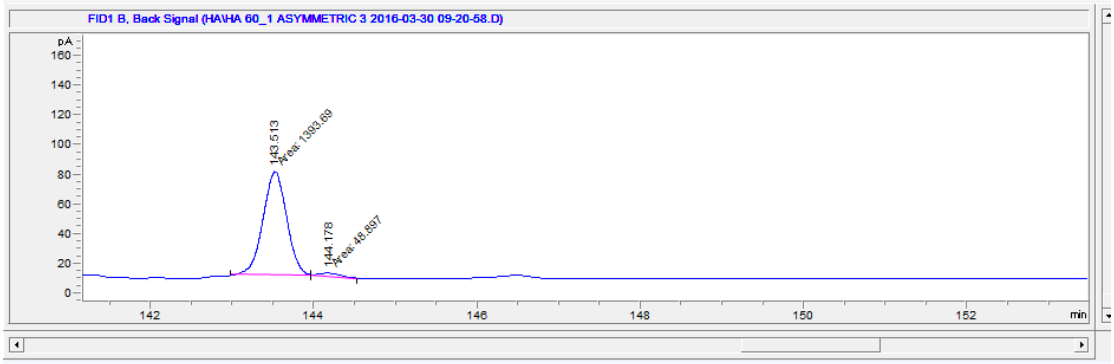
File Path	C:\CHEM32\1\DATA\HA
Date	29-Mar-16, 11:25:52
Sample	HA 71/6 RACEMIC 3

#	Time	Area	Height	Width	Area%	Symmetry
9	143.571	215.9	12.6	0.2858	0.004	0.834
10	144.201	199	11.3	0.2937	0.004	0.794



File Information	
GC-File	HA 60_1 ASYMMETRIC 3 2016-03-30 09-20-58.D
File Path	C:\CHEM32\1\DATA\HA
Date	30-Mar-16, 09:21:07
Sample	HA 60/1 ASYMMETRIC 3
Sample Info	HYDRODEX B-3P 50-10-1-180-40-10-220-10

#	Time	Area	Height	Width	Area%	Symmetry
18	143.513	1393.7	69.8	0.3329	0.029	0.908
19	144.178	48.9	2.4	0.3331	0.001	0.439

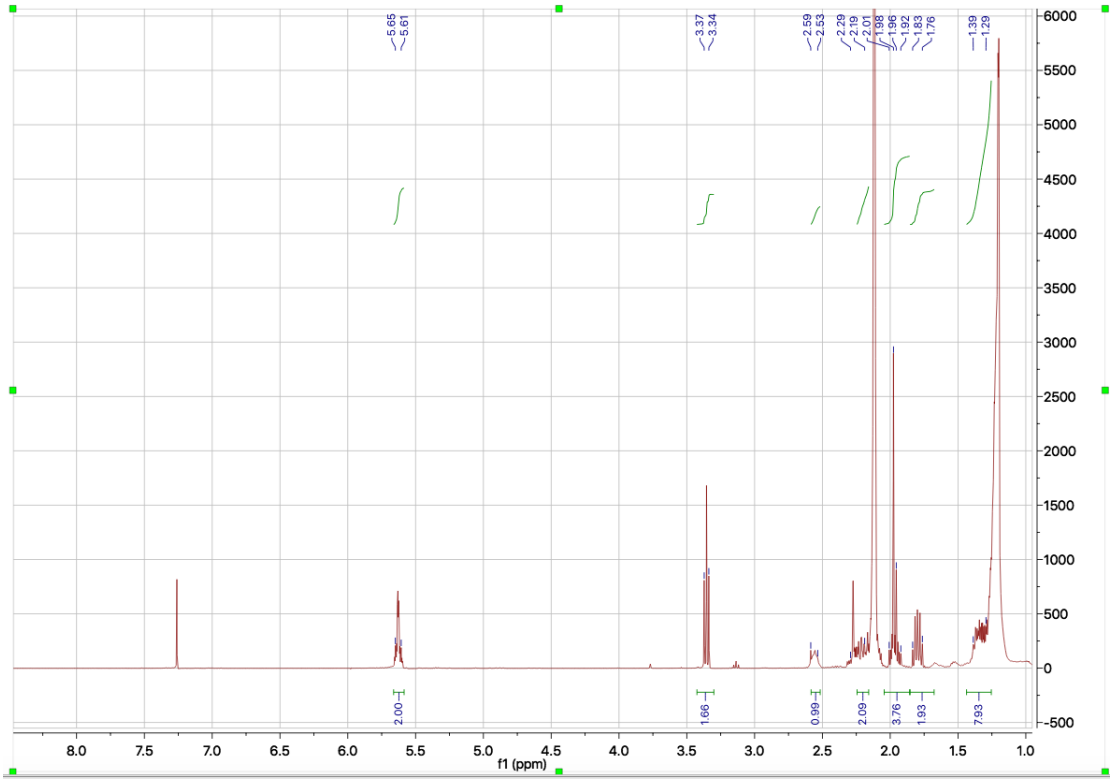
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.29 - 1.39 (m, 8 H), 1.76-1.83 (quin, *J*=7.2 Hz, 2 H), 1.92-1.96 (quin, *J*=7.2 Hz, 4 H), 2.19-2.29 (m, 2 H), 2.53- 2.59 (m, 1 H), 3.34-3.37 (t, *J*=6.8 Hz, 2 H), 5.65 - 5.71 (m, 2 H)

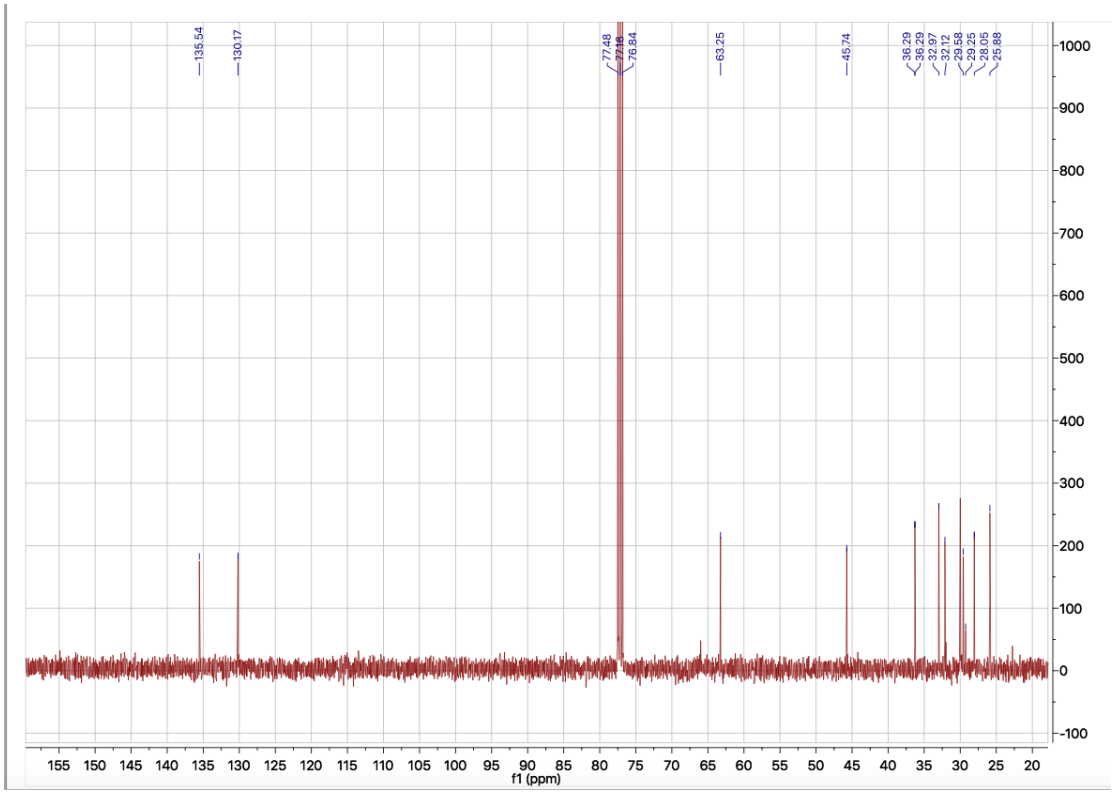
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 25.8, 28.0, 29.2, 29.5, 32.1 (2C), 32.9, 36.2 (2C), 45.7, 130.1, 135.5.

HRMS (ESI) *m/z* calcd for $C_{12}H_{21}Br$ $[M]^+$: 244.0827, found: 244.0887.

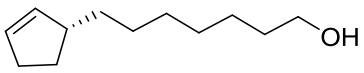
IR (ATR) ν (cm^{-1}): 2980.60, 2360.42, 1458.41.

$[\alpha]_{589}^{20}$ = +44.33 (*c* 1.00, $CHCl_3$) for 93% ee.





(*R*)-7-(cyclopent-2-en-1-yl) heptan-1-ol: (e_2)



$NaHCO_3$ (2.3 g, 27.4 mmol, 3.11 eq) was added to a stirred solution of bromide **(d_2)** (2.16 g, 8.81 mmol, 1.00 eq) in a mixture of DMSO (14.6 mL) and water (3.8 mL). The resulting suspension was stirred 22 h at 95 oC before being quenched by addition of water (10 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL) and the combined organic extracts were washed with water, brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude product that was used in the next step without further purification.

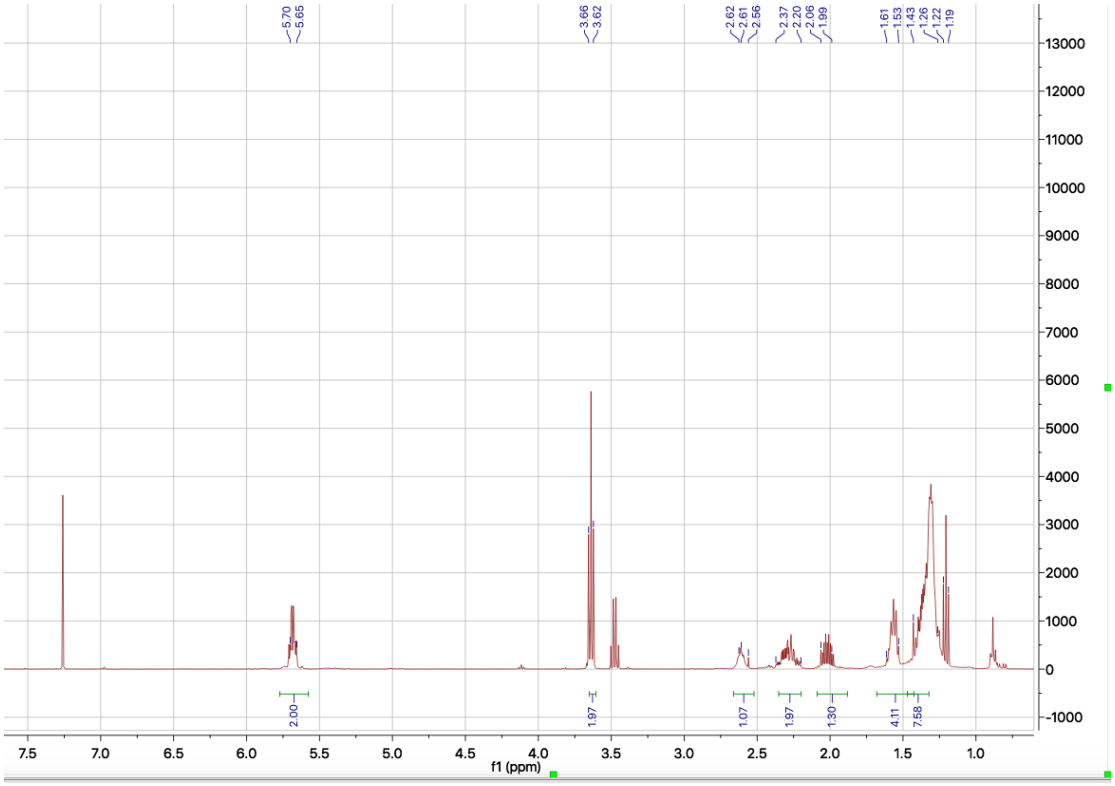
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.19 - 1.43 (m, 8 H), 1.53-1.61 (quin, *J*=7.2 Hz, 4 H), 1.99-2.06 (quin, *J*=7.2 Hz, 2 H), 2.20-2.37 (quin, *J*=7.2 Hz, 2 H), 2.56-2.62 (m, 1 H), 3.62-3.66 (t, *J*=6.8 Hz, 2 H), 5.65 - 5.70 (m, 2 H)

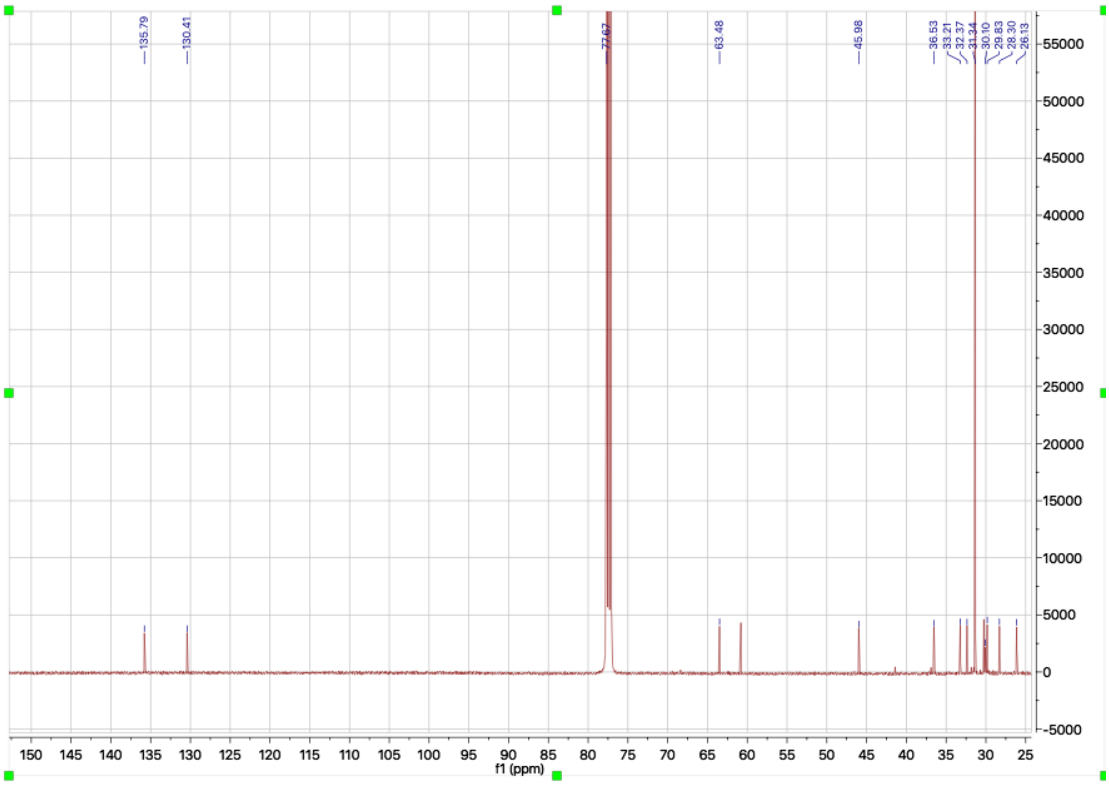
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 26.1, 28.3, 29.8, 30.1, 31.3, 32.3, 33.2, 36.5, 45.9,

63.4, 130.4, 135.7.

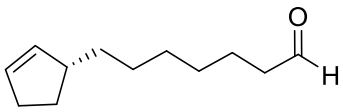
HRMS (ESI) *m/z* calcd for $C_{12}H_{22}O$ $[M]^+$: 182.1671, found: 182.1665.

IR (ATR) v (cm^{-1}): 3209.0, 2980.6, 2888.8, 1558.4.





(*R*)-7-(cyclopent-2-en-1-yl)heptanal: (f_2)



Dess-Martin periodinane (730 mg, 1.72 mmol, 2.00 eq) was added to a stirred solution of the crude alcohol (133 mg, 0.86 mmol) in CH_2Cl_2 (8.6 mL). The suspension was stirred for 30 min at room temperature before 5 mL of mixture of $NaHCO_3$: $Na_2S_2O_3$ (1:5, both sat. aq.) was added in one portion. 5 mL of CH_2Cl_2 was added, the phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3x2 mL). The crude aldehyde was used in the next step without further purification.

Prepared by Swern oxidation[6]:

In a flamed dry 2 necks flask 50 ml, the oxalyl chloride (0.87 ml, 10.32 mmol, 2 eq) was added to CH_2Cl_2 (6 mL) at -78 °C, DMSO (1.46 ml, 20.64 mmol, 4 eq) under N_2 was added dropwise to this solution and was stirring under N_2. After 20 min a solution of the alcohol (0.94 g, 5.16 mmol, 1 eq) in CH_2Cl_2 (4 mL) was slowly added dropwise at -78 °C. After 30 min, Et_3N (3.6 ml, 25.8 mmol, 5 eq) was added dropwise at -78 °C. The

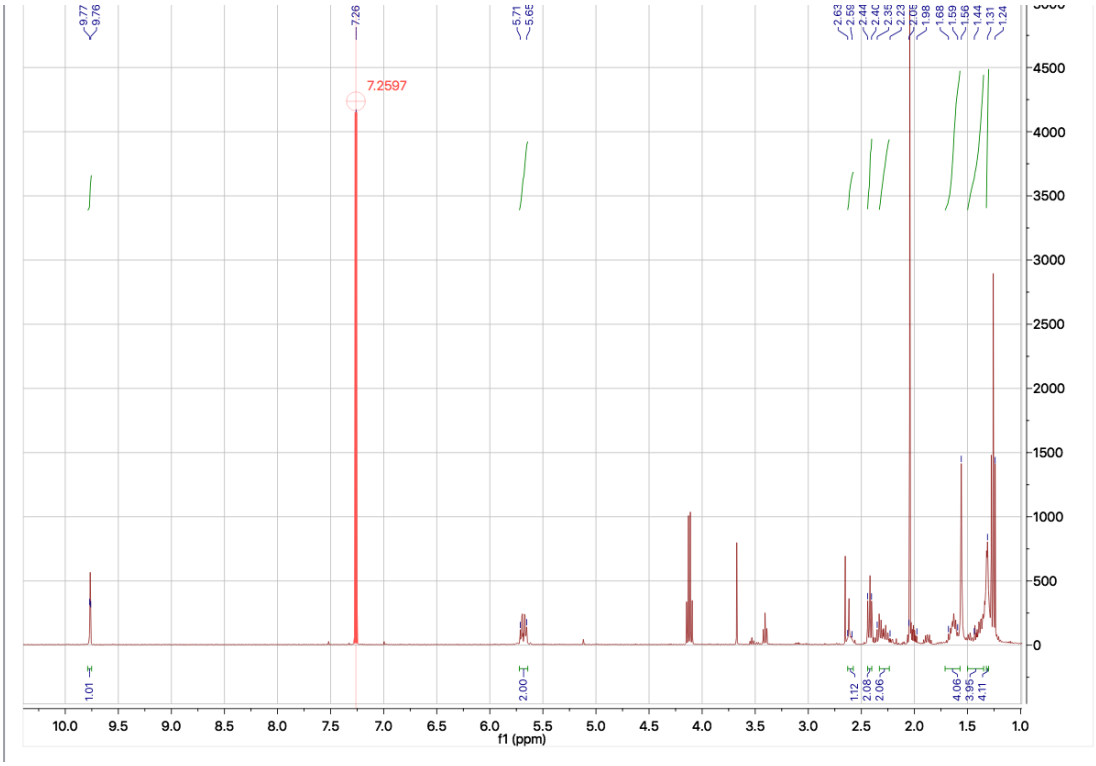
reaction was stirred 30 min at -78 °C then slowly allowed to warm to room temperature for 4 h, the reaction mixture was then quenched by water (10 ml) and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL) and washed by water, and brine, dried over $MgSO_4$ and a rotary evaporator was used to remove the solvent. The crude aldehyde was used in the next step without further purification.

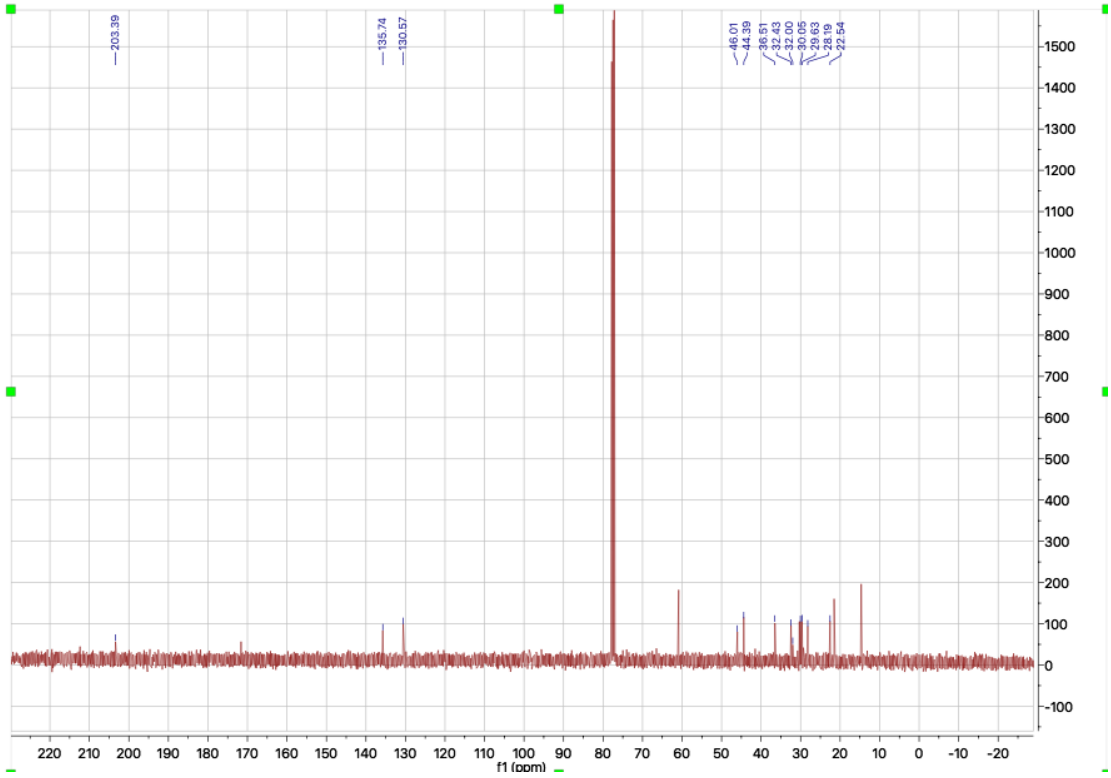
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.24 - 1.31 (m, 4 H), 1.44-1.56 (m, 4 H), 1.59-1.68 (quin, *J*=7.2 Hz, 4 H), 2.23-2.35 (quin, *J*=7.2 Hz, 2 H), 2.40-2.44 (m, 2 H), 2.59-2.63 (m, 1 H), 5.65 - 5.71 (m, 2 H), 9.76-9.77 (t, *J*=6.8 Hz, 1H),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 22.5, 28.1, 29.6, 30.0, 32.0, 32.4, 36.5, 44.3, 46.0, 130.5, 135.7, 203.3.

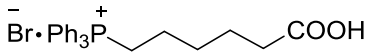
HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found: 180.1508.

IR (ATR) ν (cm^{-1}): 3057.9, 2980.6, 1716.7.





5-Carboxypentyltriphenylphosphinium bromide: (h)



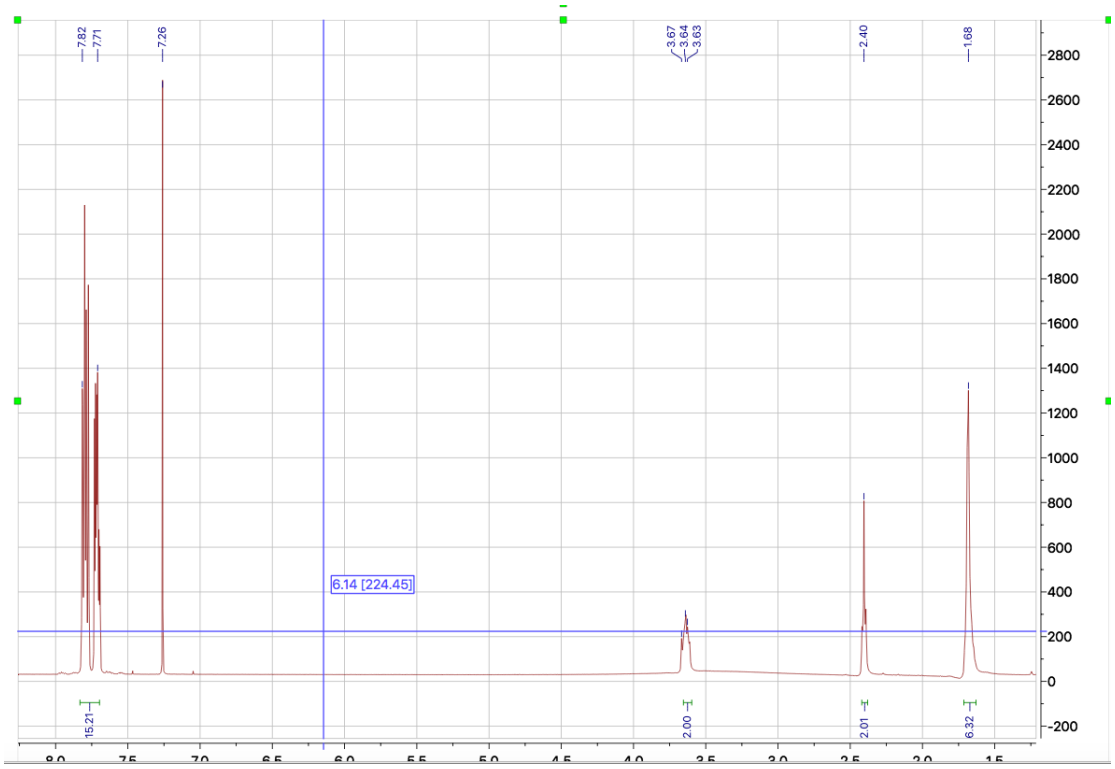
A mixture of 6-bromohexanoic acid (3 g, 15.4 mmol, 1 eq) and Ph_3P (4.12, 15.71 mmol, 1.02 eq) in CH_3CN (20 ml) was refluxed for 45 h. Most of the solvent was removed in *vacuo* and the residue titurated with solvent ether. The precipitated pale yellow solid was filtered, washed thoroughly with ether and dried in vacuo over P_2O_5 to get the desired salt with excellent yields (6.9 g, 98 %).

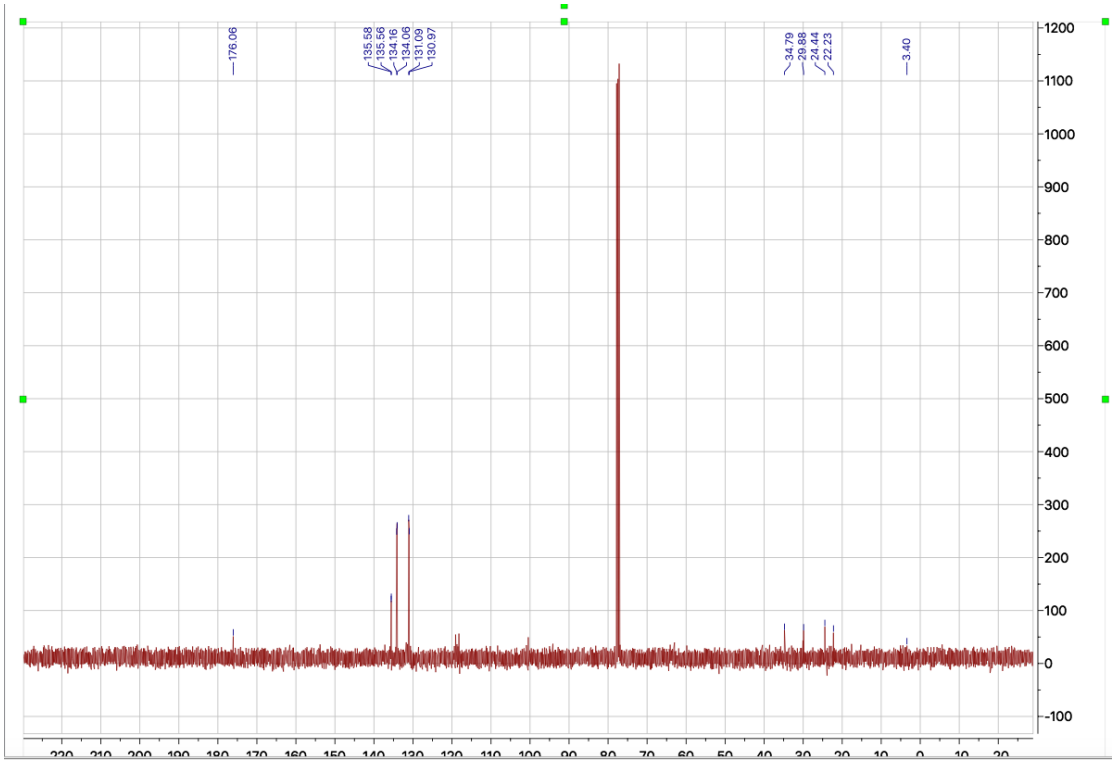
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.66-1.69 (m, 6 H), 2.4-2.44 (m, 2 H), 3.63-3.67 (t, *J*=6.8 Hz, 2H), 7.71-7.88 (m, 15H $_{aromatic}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 22.2, 24.4, 29.8, 29.5, 34.7, 130.9, 131.0, 134.0, 134.1, 135.5 (2C), 135.6, 176.0.

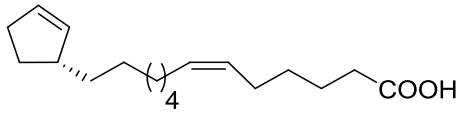
Yield: 6.9 g, 98 %, mp: 204 °C, (lit.200-205 C)[7,8].

IR (ATR) v (cm^{-1}): 2980.5, 2888.5, 1382.5, 1716.9.





(*R*,*Z*)-13-(cyclopent-2-en-1-yl)tridec-6-enoic acid (Gorlic acid): 6



1-By NaHMDS:

A flask charged with phosphonium salt **(h)** (1.46 g, 3.2 mmol, 2eq) was purged with argon. THF (6 mL) was added and the solution was cooled to 0°C. A solution of 1.0 M NaHMDS in THF (1.94 mL, 9.6 mmol, 6 eq) was added, and the reaction was stirred for 30 min and then cooled to –78 °C. The aldehyde (**f_2**) (290 mg, 1.6 mmol, 1 eq) in 6 mL of THF was added dropwise and the reaction was stirred at -78 °C for 3 h, and then slowly warmed to room temperature overnight. H_2O (6 mL) was added and the solution was extracted with ether (4 x 15 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The residual oil was purified by flash chromatography (hexane/ EtOAc: 8/2) to give the desired acid in 69 % yield (310 mg, 1.1 mmol)

2- By NaH:

A flask charged with phosphonium salt **(h)** (0.915 mg, 2 mmol, 2eq) was purged with argon. THF (6 mL) was added and the solution was cooled to 0 C. NaH (0.096 g, 4 mmol, 4 eq) was added, and the reaction was stirred for 30 min and then cooled to –78 °C. The aldehyde f_2 (180 mg, 1 mmol, 1 eq) in 6 mL of THF was added dropwise and the reaction was stirred at -78 °C for 3 h, and then slowly warmed to room temperature overnight. NH_4Cl (sat. aq. 6 mL) was added and the solution was extracted with ethyl acetate (4 x 15 mL). The combined organic layers were washed with brine then dried with $MgSO_4$, filtered and concentrated. The residual oil was purified by flash chromatography (hexane/ EtOAc: 8/2) to give the desired acid in 13 % yields (36 mg, 0.13 mmol)

^{1}H NMR (400 MHz, C_6D_6): δH/ppm 1.35-1.42 (m, 12H), 1.63–1.67 (m, 2H), 2.00-2.06 (m, 6H), 2.14-2.17 (m, 2H), 2.19-2.27 (m, 2H), 2.59 (m, 1H), 5.29–5.40 (m, 2H), 5.68–

5.73 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): δ_C /ppm 24.7, 27.2, 27.6, 28.4, 29.5, 29.7, 30.1, 30.2, 30.3, 32.4, 34.4 , 36.6, 46.0, 129.4, 130.4, 130.9, 135.8, 180.6.

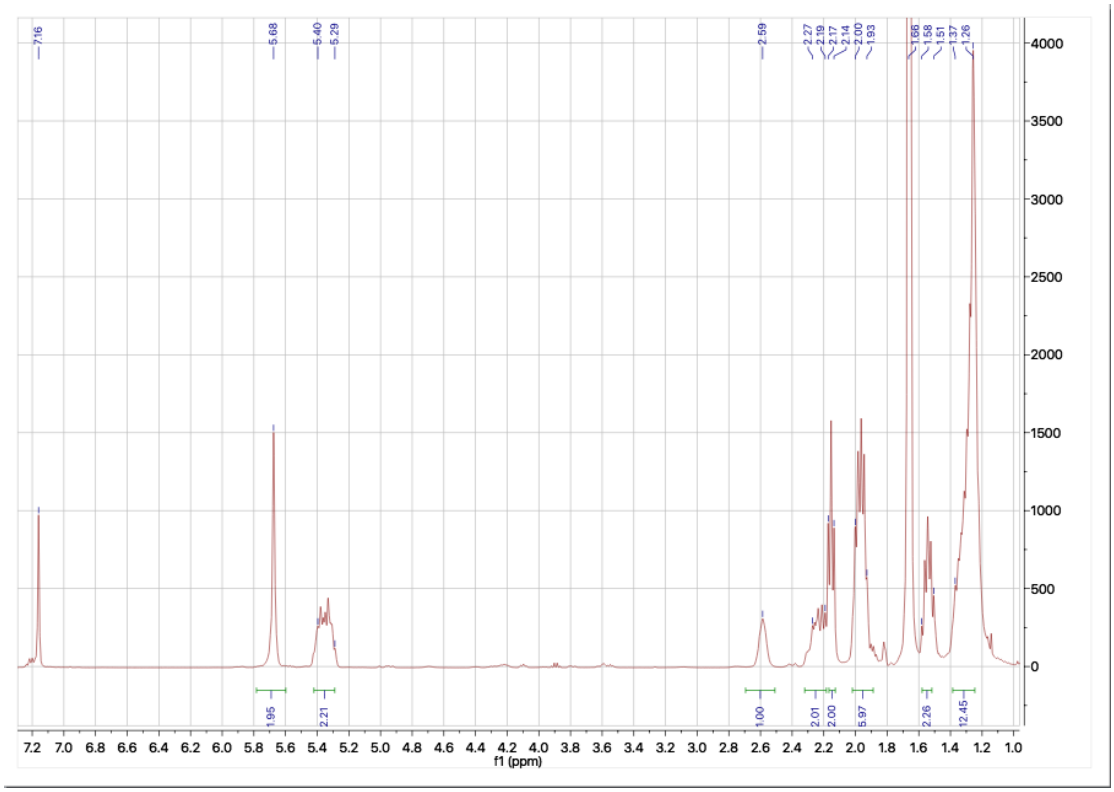
HRMS (ESI) *m*/*z* calcd for $C_{18}H_{30}O_2$ $[M]^+$: 278.22066, found: 278.22036.

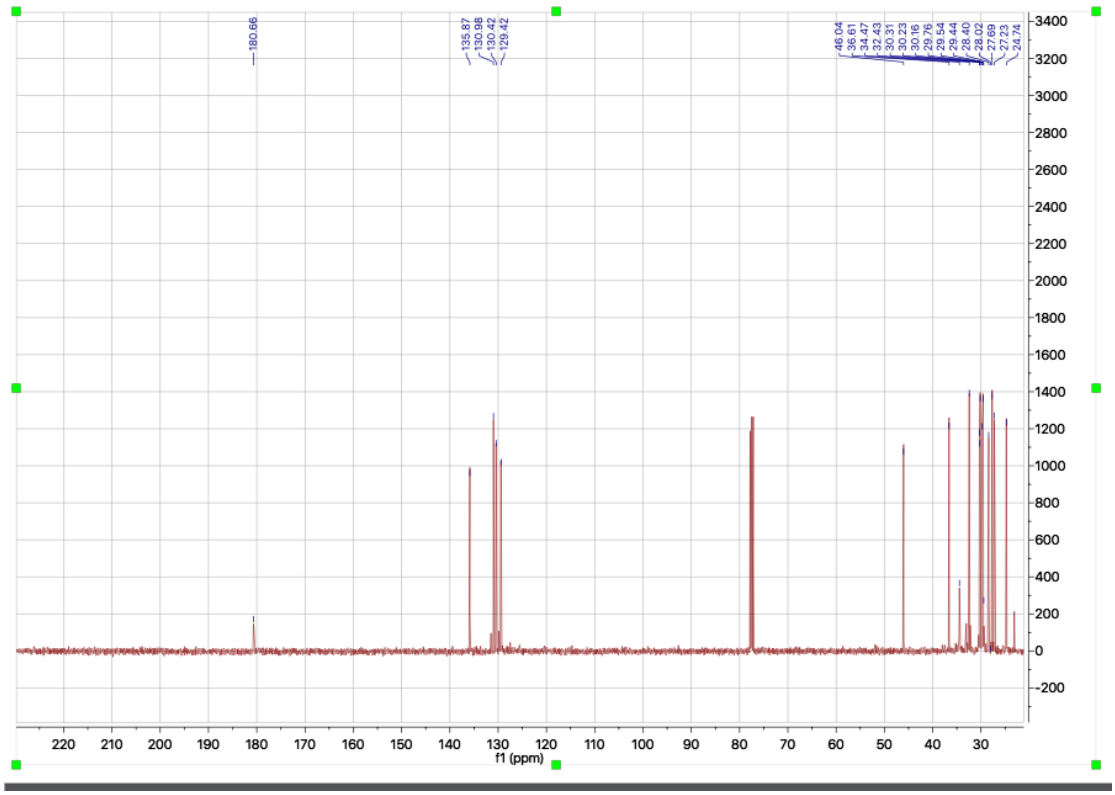
(ESI) *m*/*z* calcd for $C_{18}H_{29}O_2$ $[M]^-$: 277.21730, found: 277.21744

IR (ATR) ν (cm^{-1}): 3557.4, 2980.5, 3030, 1699.4.

$[\alpha]_{589}^{20}$ = +49.71 (c 1.15, $CHCl_3$), [lit. +60.7, *c* 10.00][5,9]

In C_6D_6:


7.16
5.68
5.40
5.29
2.59
2.27
2.19
2.17
2.14
2.00
1.93
1.66
1.58
1.51
1.37
1.26
1.95
2.21
1.00
2.01
2.00
5.97
2.26
12.45
f1 (ppm)


180.66
135.87
130.98
130.47
129.42
46.04
36.61
34.47
32.43
30.31
30.23
30.16
29.76
29.54
29.44
29.40
28.02
27.69
27.23
24.74
f1 (ppm)

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