Electronic Supplementary Material (ESI) for ChemComm.

Supporting information

Asymmetric Conjugate Addition of Alkylzirconium Reagents to α, β-Unsaturated Thioesters: Access to fragrances and acyclic stereochemical arrays

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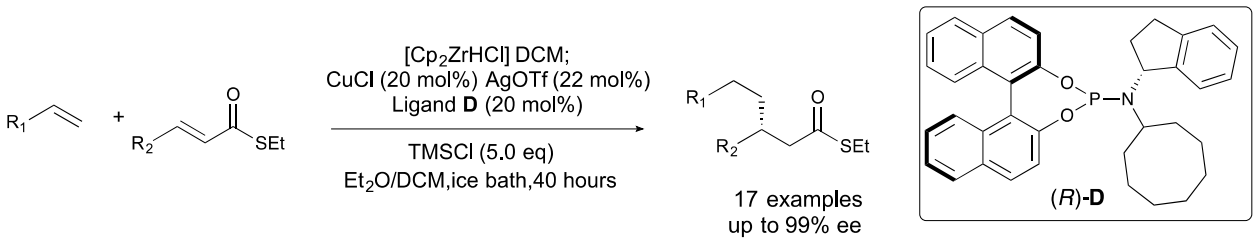

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General information

Procedures were all carried out in flame-dried flasks with anhydrous solvents under argon protection. Analytical thin-layer chromatography was conducted on precoated glass-backed plates (Silica Gel 60 F_{254}, Merck). Visualization was performed by UV light (254nm), aqueous ceric ammonium molybdate (CAM), p-Anisaldehyde Stain, aqueous basic potassium permanganate stains ($KMnO_4$) and vanillin solution. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), VWR (40-63 μm) silica gel, Sigma Aldrich silica gel.

Reaction temperatures below 0 °C were obtained using a Julabo FT902 immersion cooler. 0 °C was achieved using an ice-water bath. Light sensitive reactions were processed under Aluminium foil protection.

All NMR spectra were recorded at room temperature; ^{1}H and ^{13}C nuclear magnetic resonance experiments were carried out using Bruker DPX-200 (200/50 MHz), AVG-400 (400/100 MHz) , AVH-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). Assignments were made with the assistance of COSY, DEPT-135, HSQC and NOESY NMR spectra.

Chiral HPLC separations were achieved using an Agilent 1230 Infinity series normal phase HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Alrich or Rathburn); all eluent systems were isocratic.

Low-resolution mass spectra were recorded using a Walters LCT premier XE. High-resolution mass spectra (EI and ESI) were recorded using a Bruker Micro TOF spectrometer by the internal service at the University of Oxford.

Infrared measurements (ATR) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 cm^{-1}.

Optical rotations were recorded using a Perkin-Elmer 241 Polarimeter;

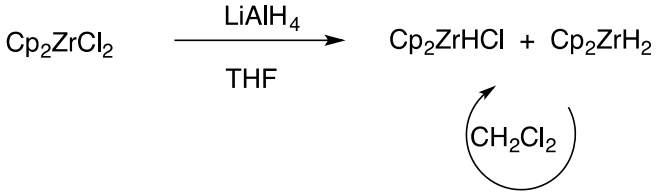
In those cases where silver salts were used the resulting solutions were filtered using syringe filters PTFE (0.2 μm, 13 mm diameter) from Camlab.

Chemicals

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 petroleum boiling in the range 40-60°C. Deuterated solvents were purchased from Sigma-Aldrich ($CDCl_3$). Schwartz reagent was prepared according to the literature procedure from Cp_2ZrCl_2 provided by Alfa Aesar. CuCl which purity is 98% is purchased from Strem Chemicals, the 99.99% purity CuCl is from Sigma-Aldrich, and all of them were directly used without any further purification. All the Trimethylsilyl chloride (TMSCl) were distilled fresh and stored in Schlenk flaskes under an argon atmosphere. All phosphoramidite ligands were synthesized by the Fletcher group.

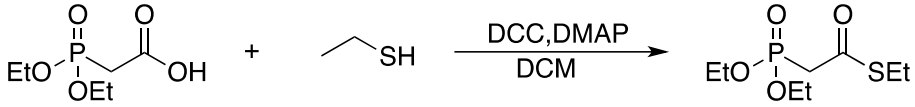
General Methods

1. Preparation of Schwartz reagent[1]



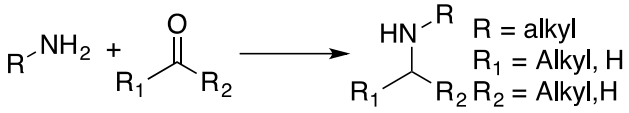
Zirconocene dichloride (30.0 g, 0.103 mol) was added to a flame-dry 250 mL Schlenk flask wrapped with aluminium foil under argon. Dry THF (120 mL) was added and the suspension was stirred at 35 °C for 30 minutes. $LiAlH_4$ in Et_2O (1 M, 28.2 mmol) was added dropwise to the mixture over about 30 minutes. The resulting suspension was stirred at room temperature for 2 hours. The mixture was then Schlenk-filtered under argon and washed with tetrahydrofuran (200 mL), methylene chloride (200 mL), and diethyl ether (200 mL). The precipitate was dried under high vacuum for two hours to give a white powder (20.3 g, 75%), which is stored under argon in a small flame-dried schlenk flask while being protected from light.

2. Preparation of *S*-ethyl 2-(diethoxyphosphoryl)ethanethioate[2] ($(EtO)_2POCHCOSEt$)



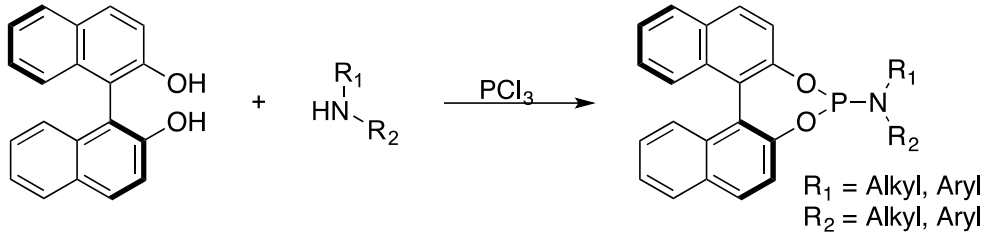
A solution of diethylphosphonoacetic acid (1.0 eq.), ethanethiol (1.0 eq.), and DMAP (0.1 eq.) in DCM was cooled to 0°C. DCC (1.0 eq.) was added in portions. The reaction mixture was left to stir overnight under argon at room temperature. The mixture was filtered through a Celite pad, and DCM was used to rinse the pad. The organic layer was washed with aqueous $NaHCO_3$, water and brine. The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The product was further purified by flash chromatography (ether: pentane) to a colourless oil.

3. Preparation of amines[3]



According to a modified procedure from Davies and co-workers[3]. Ketone (2.0 eq.) was added to a stirring solution of amine in THF at room temperature. After 5 minutes, $Na(OAc)_3H$ (2.0 eq.) was tipped into the mixture. The reaction was kept under room temperature for 48 hours, and the resulting suspension was added to a 1:1 mixture of Et_2O and $NaHCO_3$ (aq. sat.) and stirred for another half an hour. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O three times. The combined organic phase was concentrated in vacuo. Then HCl (aq.2 M) was added dropwise (pH = 1). The mixture was partitioned between the aqueous and organic phases, and the organic phase was extracted with HCl (aq. 2.0 M). Then DCM was added to the combined aqueous phases and NaOH (4 M) was added till the mixture became basic (pH>14). The mixture was partitioned between aqueous and organic phases. DCM was used to extract residual product from the aqueous layer (three extracts). The combined organic layers were concentrated, dried ($MgSO_4$), filtered and concentrated to give the, desired product.

4. Preparation of phosphoramidite ligands[4]

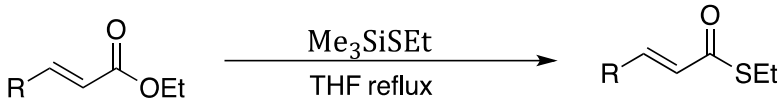


Triethylamine (5.0 eq.) was added dropwise to a stirred, ice-cooled solution of PCl_3 (1.0 eq.) in DCM. The ice bath was removed and the solution left to warm to room temperature before

(*S*)-N-cyclohexyl-2, 3-dihydro-1H-inden-1-amine (1.0 eq.) was added to the stirred solution in one portion. After 5 hours, (*S*)-binaphthol (1.0 eq.) was tipped into the suspension and the reaction mixture was left to stir for another 15 hours. The mixture was then filtered over an ~ 2cm pad of celite and silica gel, and DCM was used to rinse the pad. The filtrate was concentrated to give a yellow residue and after flash column chromatography (petroleum ether: DCM: Et_3N, 80:20:1; SiO_2) the ligand was obtained as a white crystalline solid.

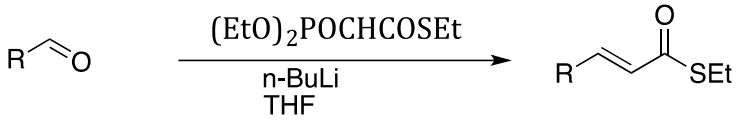
5. Preparation of unsaturated thioester

General procedure a (from unsaturated ester)[5]



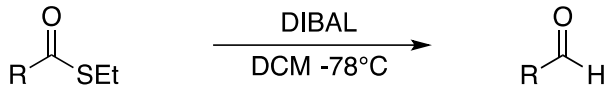
Me_3SiSEt (2.0 eq.) and $AlCl_3$ (1.2 eq.) were added to a solution of α, β-unsaturated ester (1.0 eq) in THF. The resulting mixture was stirred at reflux for 3 hours and the quenched at rt by addition of aqueous phosphate buffer solution (pH 7). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried over $MgSO_4$, filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; SiO_2) to afford the desired α,β-unsaturated thioester.

General procedure b HWE olefination (from aldehyde)[6]



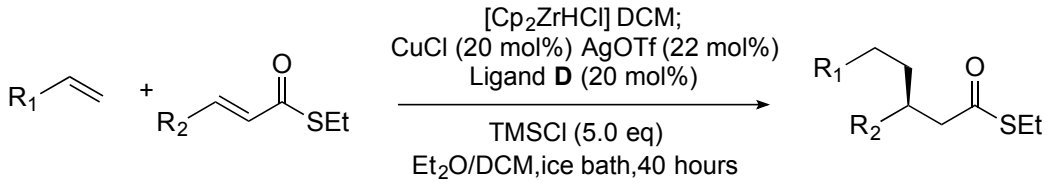
n-BuLi (1.5 eq. solution in hexane) was added to a stirring solution of $(EtO)_2POCHCOSEt$ (1.5 eq.) in THF at 0°C under argon. The mixture was stirred for another 20 min. A solution of aldehyde (1.0 eq.) in THF was added dropwise. The mixture was slowly warmed to room temperature and was continued overnight. The mixture was quenched with aqueous NH_4Cl (sat.). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried ($MgSO_4$), filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired α, β-unsaturated thioester.

6. Pd-catalyzed reduction of thioesters to aldehydes



DIBAL (1.0 eq.) was added to a stirring mixture of thioester(1.0 eq) in DCM at -78°C under argon. The mixture was kept stirring until the reduction was completed (30-60min). After that sat. Rochelle salt solution was added and Et_2O extracted the mixture three times. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product.

7. Copper catalysed conjugate addition of alkylzirconium nucleophiles



a. Racemic product

CuCl (0.2 eq.), and the racemic phosphoramidite ligand (0.2 eq.) were added to a flame dried round bottom flask containing DCM/ Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (0.22 eq.) was added and the mixture was stirred for an additional 15 min.

To a second, flame dried, round bottom flask, containing a stirred solution of alkene (2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone and TMSCl were sequentially added dropwise over about 1 min for each. Stirring at room temperature was continued for 15 additional hours, before the reaction was quenched by the addition of NH_4Cl (sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product.

1b. Asymmetric product (gaseous alkenes)

CuCl (0.2 eq.), and the phosphoramidite ligand (0.2 eq.) were added to a flame dried round bottom flask containing x ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, Cp_2ZrHCl (2.0 eq.) was added. A balloon filled with ethylene was used to purge the flask with ethylene for 5 min, and then DCM (xx mL) was added. After stirring for 15 min under an ethylene atmosphere (balloon), a clear yellow solution was obtained. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before the enone (1.0 eq.) and then TMSCl (5.0 eq.) were each added dropwise. Stirring was continued for 40 h at 0 °C, before the reaction was quenched by the addition of NH_4Cl and then Et_2O. The mixture was partitioned between the aqueous and organic phases, and the aqueous layer was extracted with Et_2O. The combined organic materials were dried with Na_2SO_4, filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product.

2b. Asymmetric product (liquid alkenes)

CuCl (0.2 eq.), and the phosphoramidite ligand (0.2 eq.) were added to a flame dried round bottom flask containing x ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (0.22 eq.) was added and the mixture was stirred for an additional 15 min.

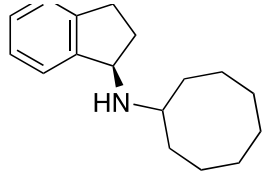
To a second, flame dried, round bottom flask, containing a stirred solution of alkene (2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone and TMSCl were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the

resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product.

Characterization of compounds

(+)-(*R*)-N-cyclooctyl-2,3-dihydro-1H-infden-1-amine



According to a modified procedure from Davies and co-workers, cyclooctanone (1.47 g, 1.5 eq. 11.6 mmol) was added to a stirring solution of (*R*)-(+)-1-Aminoindane (1.00 mL, 1.0 eq. 7.76 mmol.) in THF at room temperature. After 5 minutes, Na $(OAc)_3H$ (2.50 g, 1.5 eq., 11.6 mmol)was tipped into the mixture. The reaction was kept under room temperature for 48 hours, and the resulting suspension was added to a 1:1 mixture of Et_2O and $NaHCO_3$ (aq. sat.) and stirred for another half an hour. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O three times. The combined organic phase was concentrated in vacuo. Then HCl (aq.2 M) was added dropwise (25 ml. pH = 1). The mixture was partitioned between the aqueous and organic phases, and the organic phase was extracted with HCl (aq. 2.0 M). Then DCM was added to the combined aqueous phases and NaOH (4 M) was added till the mixture became basic (pH>14). The mixture was partitioned between aqueous and organic phases. DCM was used to extract residual product from the aqueous layer (three extracts). The combined organic layers were concentrated, dried ($MgSO_4$), filtered and concentrated to give the, desired product, (1.692 g, 90%) as dark oil

H NMR (200 MHz, CDCl3) δ_H/ppm 7.39 – 7.29 (m, 1H, Ar-*H*), 7.25 – 7.10 (m, 3H, Ar-*H*), 4.28 (t, *J* = 6.8 Hz, 1H, PhC*H*NH), 2.98 (m, *J* = 15.8 Hz, 8.5 Hz, 4.5 Hz, 2H, PhCH_2), 2.80 (q, *J* = 7.9 Hz, 1H, NHC*H*), 2.42 (dddd, *J* = 12.5 Hz, 7.9 Hz, 6.9 Hz, 4.5 Hz, 1H, $PhCH_2CH_2$), 1.81 – 1.71 (m, 1H, $PhCH_2CH_2$), 1.71 – 1.26 (m, 14H, CH_2).

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.4 – 7.3 (m, 1H, Ar-*H*), 7.2 (m, 3H, Ar-*H*), 4.3 (t, *J* = 6.8 Hz, 1H, PhC*H*NH), 3.1 – 2.9 (m, 2H, PhCH_2), 2.8 (dt, *J* = 15.8 Hz, 7.9 Hz, 1H, NHC*H*), 2.4

(dddd, *J* = 12.5 Hz, 8.1 Hz, 6.9 Hz, 4.3 Hz, 1H, $PhCH_2CH_2$), 2.0 – 1.8 (m, 1H, $PhCH_2CH_2$), 1.8 – 1.7 (m, 5H, CH_2), 1.7 – 1.4 (m, 7H, CH_2), 1.3-1.0 (m, 2H, CH_2).

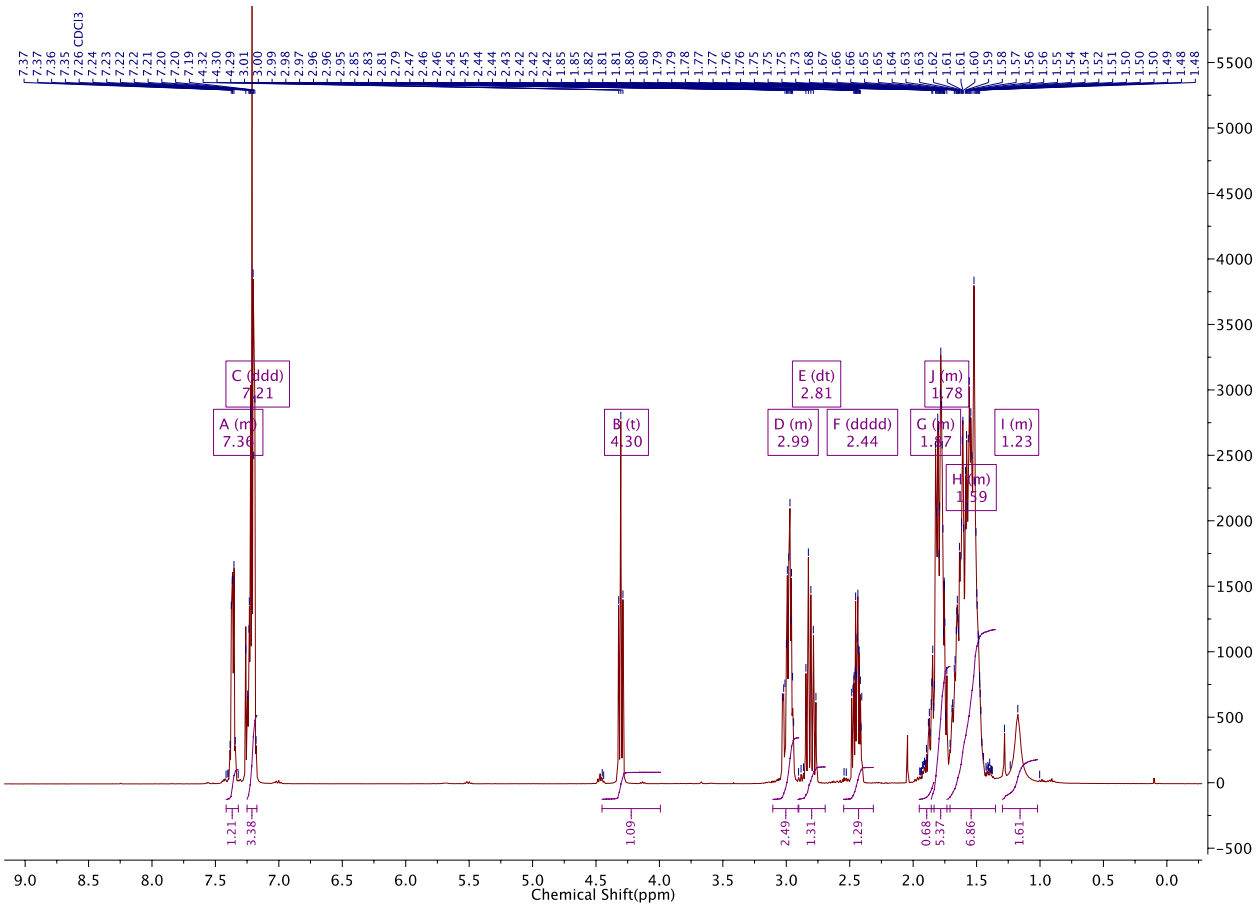
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 146.4, 143.4, 127.2, 126.3, 124.7, 123.9, 60.5, 55.7, 34.8, 33.9, 32.2, 30.3, 27.5, 27.4, 25.8, 24.2, 24.1.

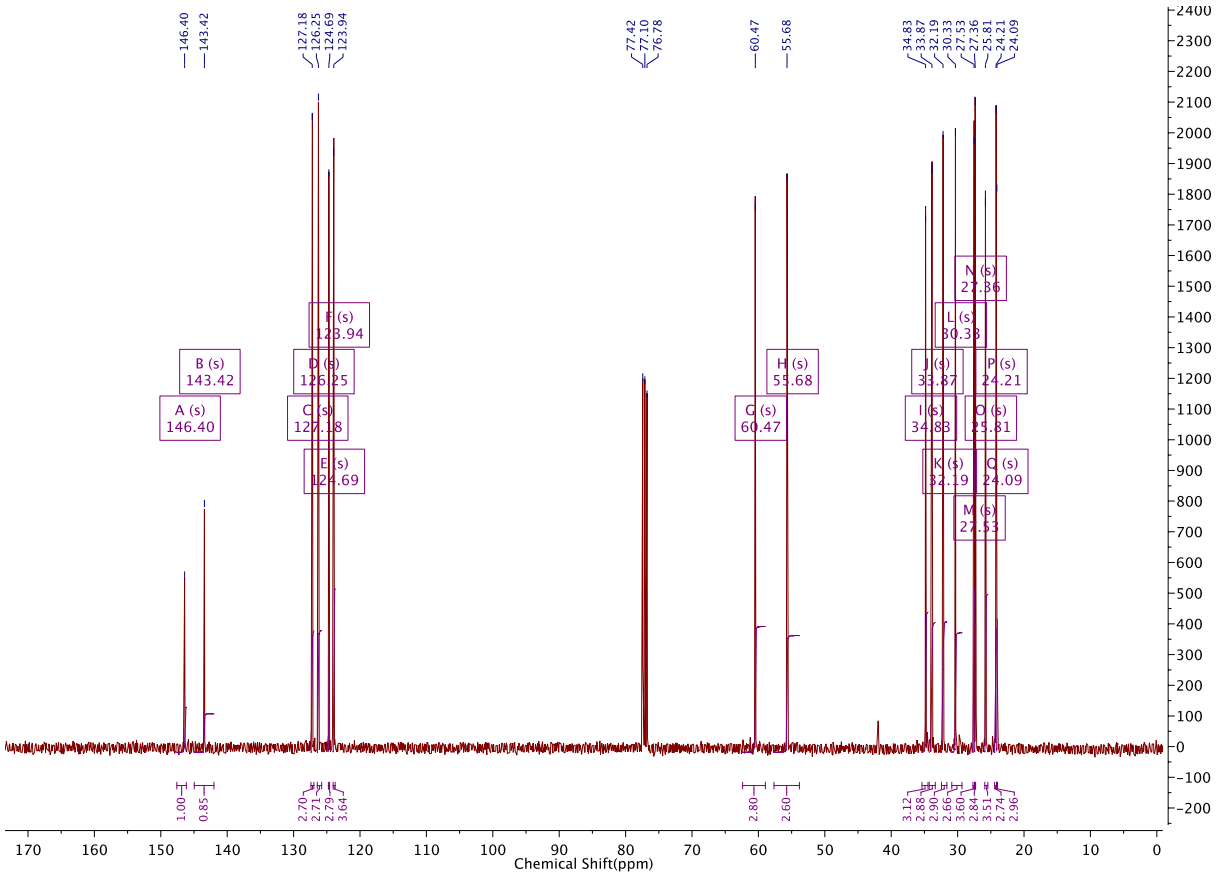
IR (ν_{max}/cm_{-1}, $CHCl_3$) 3021, 2919, 2849, 1474, 1258

MS (ESI) m/z calc. for $C_{17}H_{26}N$ $[M+H]^+$: 244.2060, found: 244.2058.

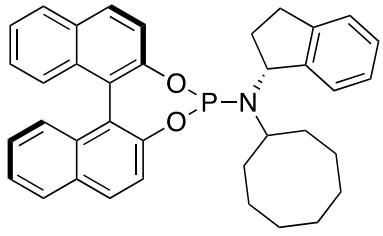
$[\alpha]^{20}_{589}$ = -37.5 ° (c 2.0, $CHCl_3$)

This data was concordant with literature values[7].





(–)*N*-cyclooctyl-*N*-((*R*)-2,3-dihydro-1*H*-inden-1-yl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (*R*)-D



Triethylamine (2.92 mL, 5.0 eq., 20.5 mmol), was added dropwise to a stirred, ice-cooled solution of PCl_3 (0.38 mL, 1.0 eq., 4.1mmol) in DCM. The ice bath was removed and the solution left to warm to room temperature before (*R*)-N-cyclohexyl-2, 3-dihydro-1H-inden-1-amine (0.94 ml, 1.0 eq. 4.1mmol) was added to the stirred solution in one portion. After 5 hours, (*R*)-binaphthol (1.12 g, 1.0 eq. 4.1 mmol) was tipped into the suspension and the reaction mixture was left to stir for another 15 hours. The mixture was then filtered over an ~ 2cm pad of celite and silica gel, and DCM (~100 mL) was used to rinse the pad. The filtrate

was concentrated to give a yellow residue and after flash column chromatography (petroleum ether: DCM: Et_3N, 80:20:1; SiO_2) the ligand was obtained as a white crystalline solid (1.17 g, 51%).

^{1}H NMR (500 MHz, Chloroform-d) δ_H/ppm 7.97 (d, J = 8.8 Hz, 1H, Ar-*H*), 7.92 (dd, J = 8.3 Hz, 1.2 Hz, 1H, Ar-*H*), 7.90 – 7.83 (m, 2H, Ar-*H*), 7.64 (d, J =7.6 Hz, 1H, Ar-*H*), 7.61 (s, 1H, Ar-*H*), 7.52 (d, J = 8.7 Hz, 1H, Ar-*H*), 7.44 – 7.37 (m, 3H, Ar-*H*), 7.37 – 7.29 (m, 2H, Ar-*H*), 7.30 – 7.18 (m, 4H, Ar-*H*), 4.76 (dt, J = 13.4 Hz, 8.1 Hz, 1H, PhC*H*NH), 3.11 (d, J = 10.6 Hz, 1H, PhCH_2CH$_2$), 3.02 – 2.90 (m, 1H, PhCH_2CH$_2$), 2.70 (p, J = 8.3 Hz, 1H, NHC*H*), 2.44 (d, J = 11.4 Hz, 1H, PhCH$_2$CH_2), 2.16 (p, J = 9.9 Hz, 1H, PhCH$_2$CH_2), 2.09 – 1.79 (m, 3H, CH_2), 1.72 – 1.57 (m, 2H, CH_2), 1.43 – 1.05 (m, 8H, CH_2), 0.99 – 0.75 (m, 1H, CH_2).

^{13}C NMR (126 MHz, Chloroform-d) δ_C/ppm 150.2 (d, J = 8.0 Hz), 150.1, 144.6, 143.14, 132.8 (d, J = 2.2 Hz), 132.8, 131.3, 130.6, 130.2, 129.7, 128.3, 128.1, 127.3, 127.1, 127.1, 126.4, 125.9, 125.9, 124.7 (d, J = 5.1 Hz), 124.6, 124.3, 124.0 (d, J = 5.3 Hz), 122.4, 122.4, 122.3, 121.7 (d, J = 2.4 Hz), 60.7 (d, J = 16.3 Hz), 54.8 (d, J = 7.7 Hz), 36.5 (d, J=131.2), 31.6, 30.2, 26.3, 25.8, 25.6, 24.5, 22.7, 14.2.

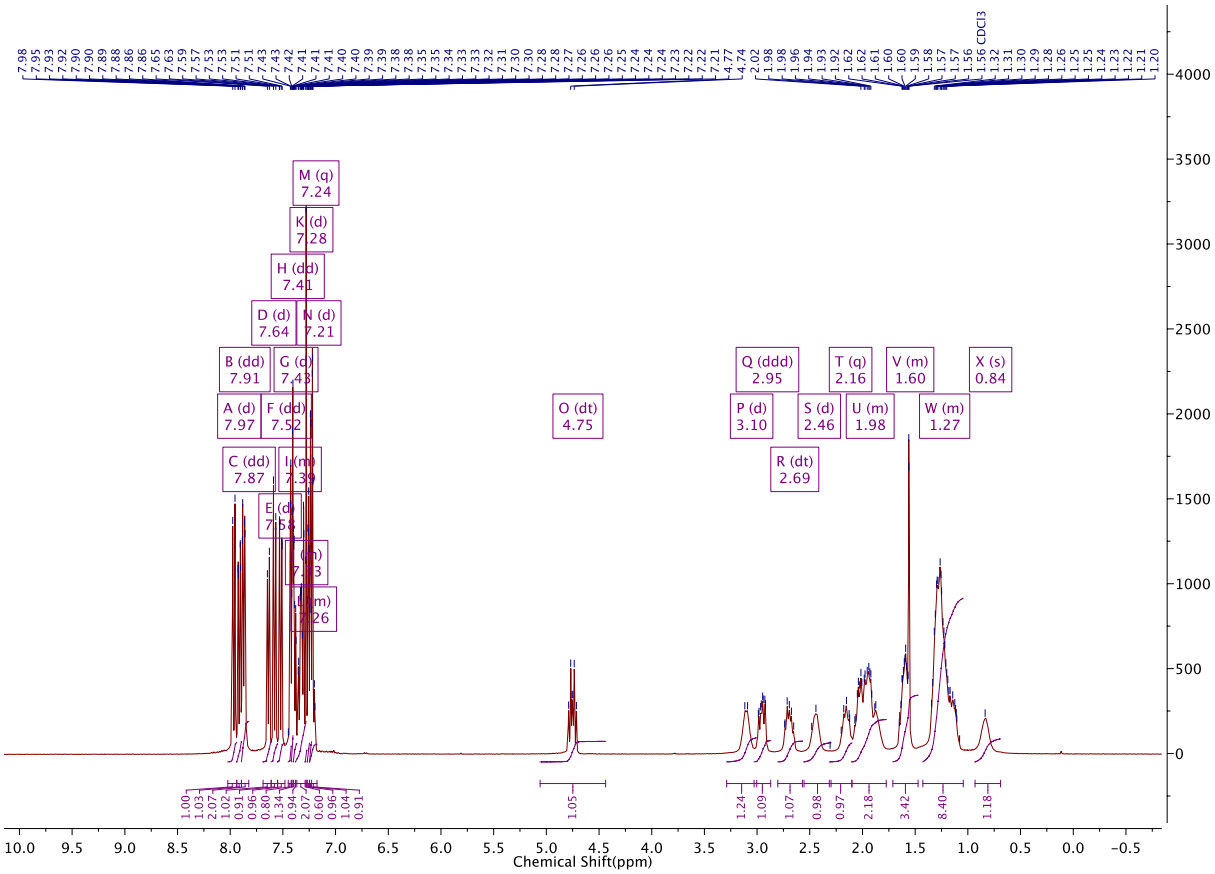
^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm 151.7.

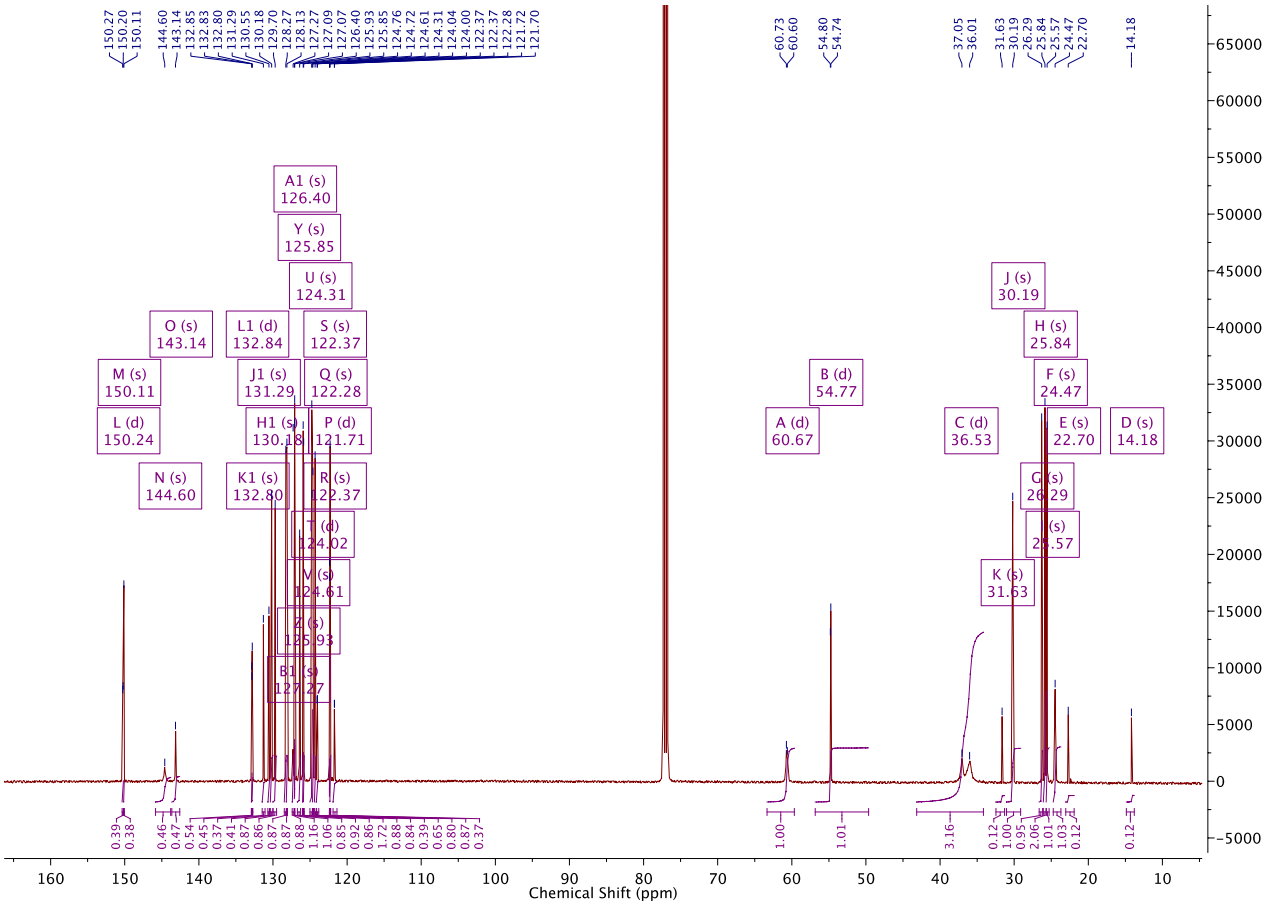
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2929, 2854, 2361, 1590, 1462

MS (GCMS Ammonica Cl Spectrum) m/z calc. for $C_{37}H_{36}O_2NP$ $[M+H]^+$: 557.2484, found: 558.2558

$[\alpha]^{20}_{589}$ = -117.1 ° (c 1.0, $CHCl_3$)

This data was concordant with literature values[7].


M (q) 7.24
K (d) 7.28
H (dd) 7.41
D (d) 7.64
N (d) 7.21
B (dd) 7.91
G (d) 7.43
A (d) 7.97
F (dd) 7.52
C (dd) 7.87
I (m) 7.39
E (d) 7.55
O (dt) 4.75
Q (ddd) 2.95
T (q) 2.16
V (m) 1.60
X (s) 0.84
P (d) 3.10
S (d) 2.46
U (m) 1.98
W (m) 1.27
R (dt) 2.69
Chemical Shift(ppm)


A1 (s) 126.40
Y (s) 125.85
U (s) 124.31
O (s) 143.14
L1 (d) 132.84
S (s) 122.37
M (s) 150.11
J1 (s) 131.29
Q (s) 122.28
L (d) 150.24
H1 (s) 130.18
P (d) 121.71
N (s) 144.60
K1 (s) 132.80
R (s) 122.37
T (d) 124.02
V (s) 124.61
X (s) 125.93
B1 (s) 127.27
B (d) 54.77
A (d) 60.67
J (s) 30.19
H (s) 25.84
F (s) 24.47
C (d) 36.53
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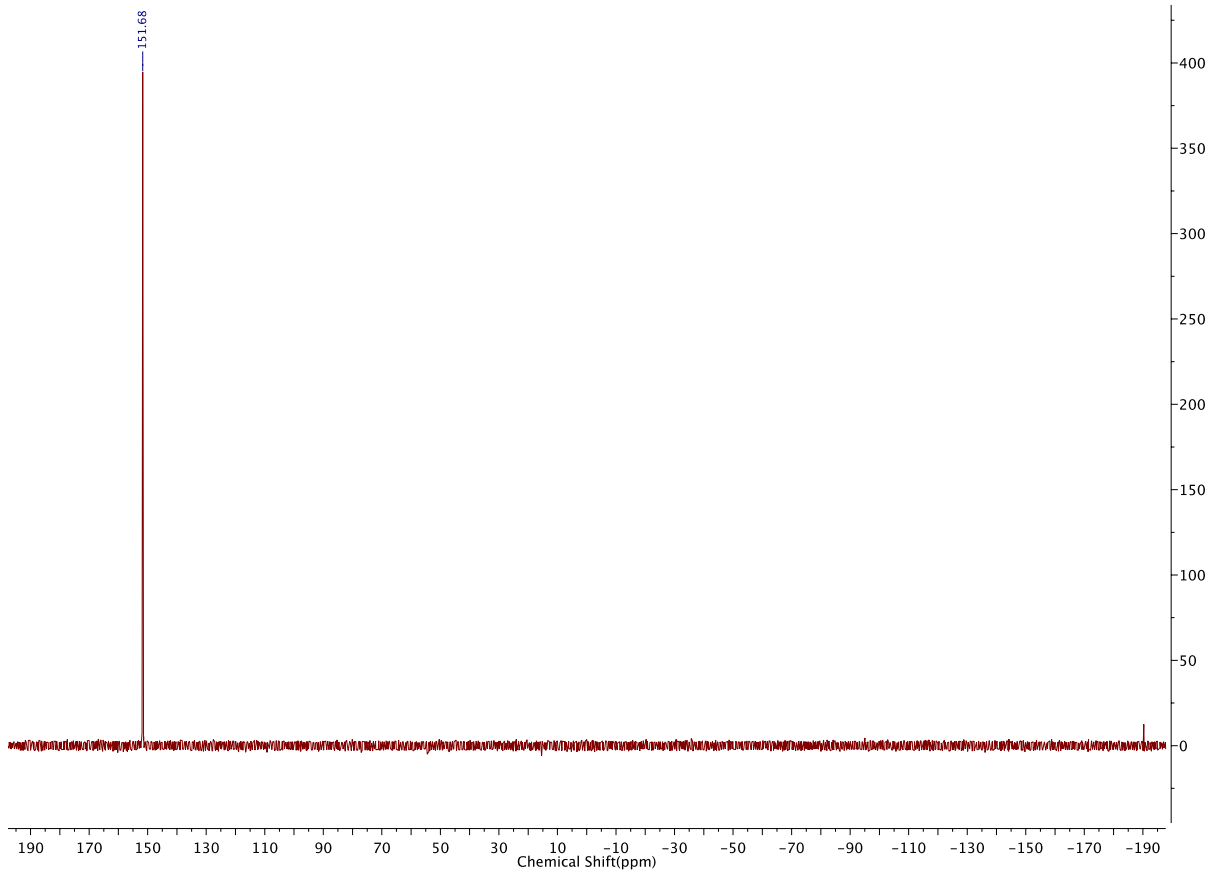
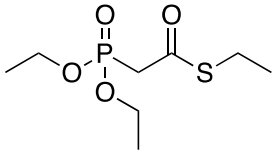
D (s) 14.18
G (s) 26.29
(s) 24.57
K (s) 31.63
Chemical Shift (ppm)



S-ethyl 2-(diethoxyphosphoryl)ethanethioate



A solution of diethylphosphonoacetic acid (10.0 ml, 60.8 mmol, 1.0 eq.), ethanethiol (5.60ml, 60.8 mmol, 1.0 eq.), and DMAP (742mg, 6.08mmol, 0.1 eq.) in DCM was cooled to 0°C. DCC (12.6g, 60.8mg, 1.0 eq.) was added in portions. The reaction mixture was left to stir overnight under argon at room temperature. The mixture was filtered through a Celite pad, and DCM was used to rinse the pad. The organic layer was washed with aqueous $NaHCO_3$, water and brine. The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The product was further purified by flash chromatography (ether: pentane; 30:70) to a colourless oil (10.5 g, 44mmol, 72% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 4.12 (dqd, *J* = 8.0 Hz, 7.0 Hz, 1.1 Hz, 4H, OC*H*$_2$CH$_3$), 3.16 (d, *J* = 21.3 Hz, 2H, C*H*$_2$COSEt), 2.88 (qd, *J* = 7.4 Hz, 0.6 Hz, 2H, COSC*H*$_2$CH$_3$), 1.29 (td, *J* = 7.1Hz, 0.6 Hz, 6H, OCH$_2$C*H*$_3$), 1.22 (t, *J* = 7.4 Hz, 3H, COSCH$_2$C*H*$_3$).

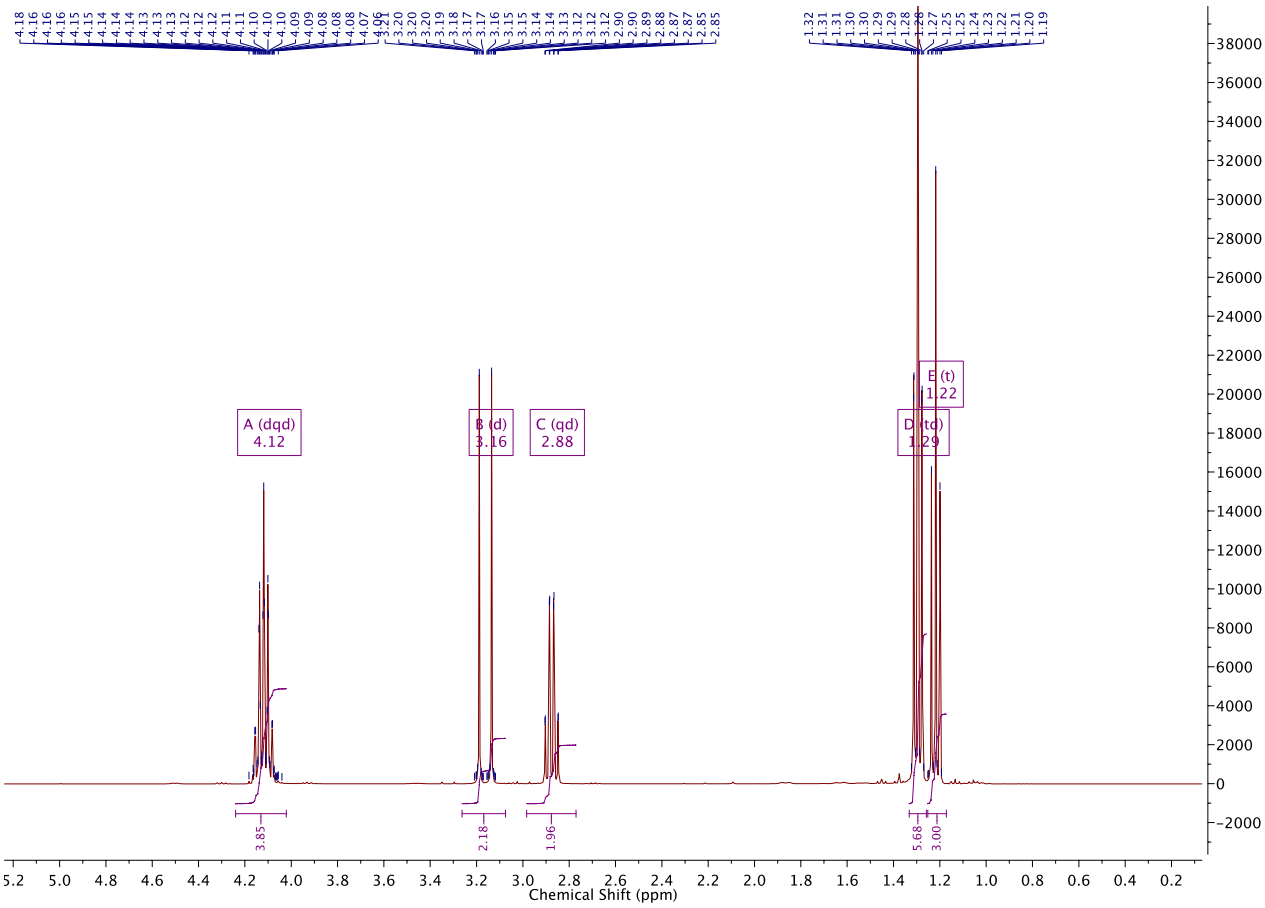
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 190.2 (d, *J* = 6.9 Hz), 62.8, 62.7, 42.8(d, J = 131.1 Hz), 24.2, 16.3, 16.2, 14.4.

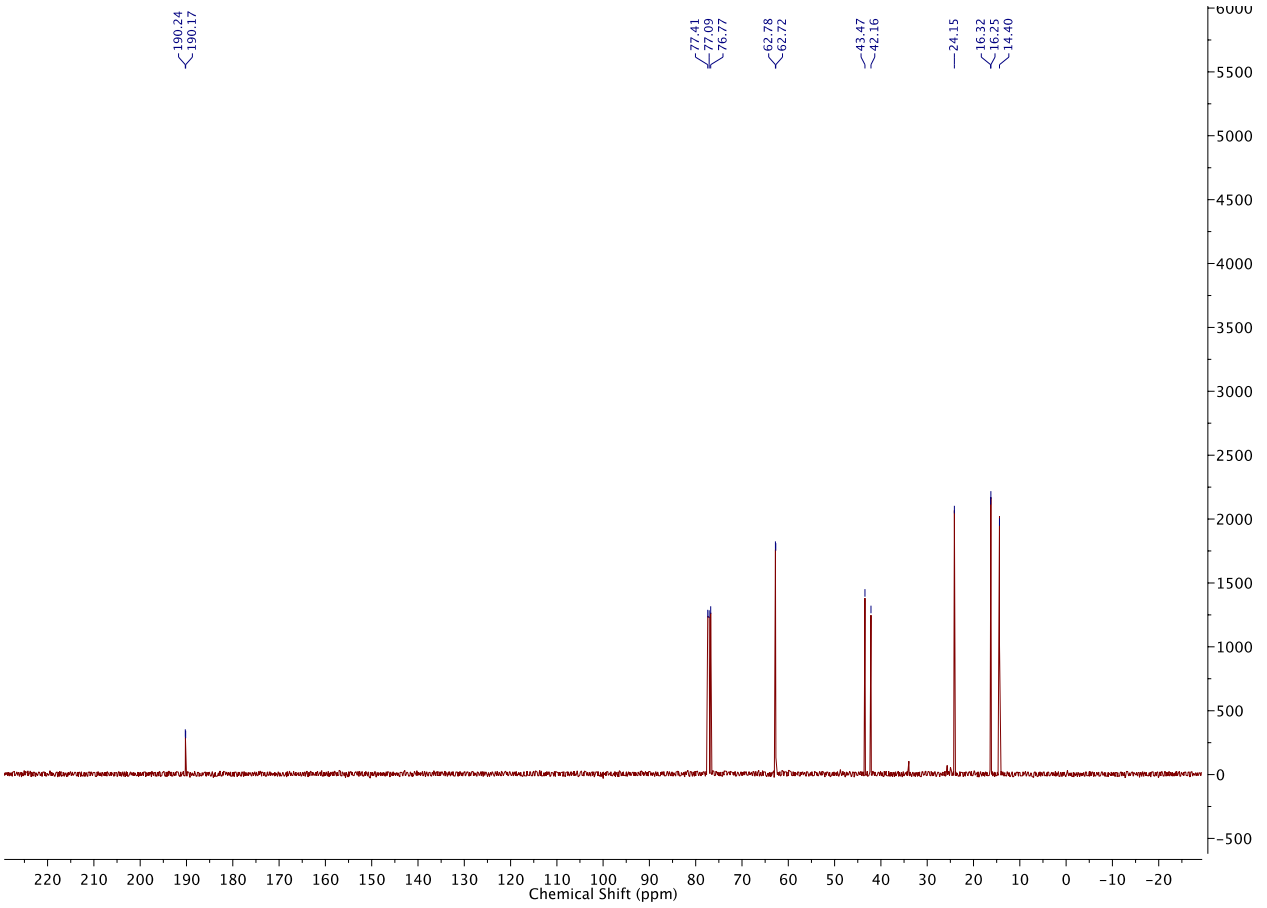
^{31}P NMR (162 MHz, Chloroform-*d*) δ_P/ppm 18.2.

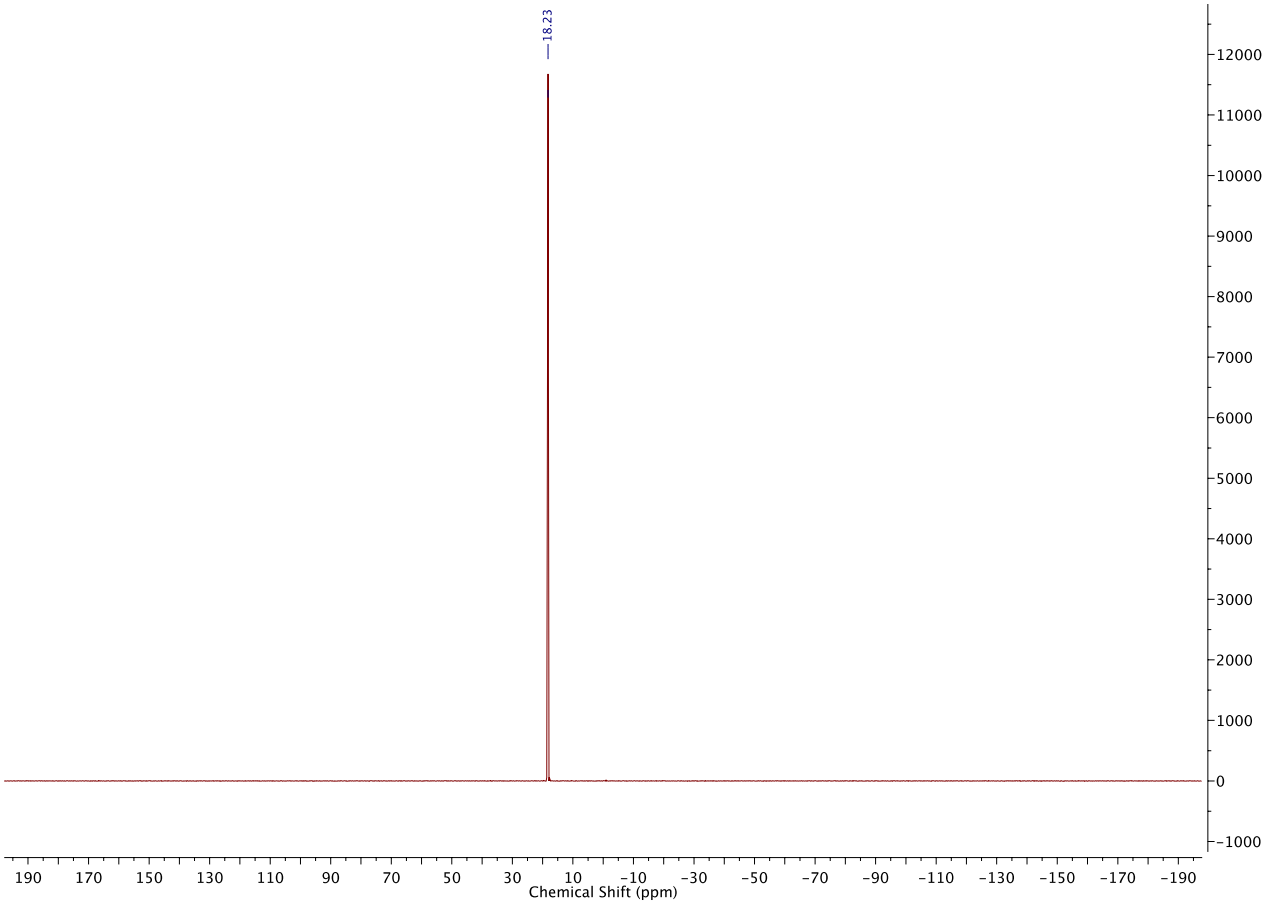
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 2360,1738,1680,1380,1257,1019,966

HRMS (ESI) m/z calc. for $C_8H_{18}O_4P^{32}S$, $[M+H]^+$: 241.0658, found: 241.0657

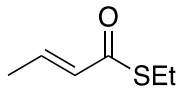
This data was concordant with literature values[2].




190.24
190.17
77.41
77.09
76.77
62.78
62.72
43.47
42.16
24.15
16.32
16.25
14.40
Chemical Shift (ppm)


18.23
Chemical Shift (ppm)

S-ethyl (*E*)-but-2-enethioate (2a)



Me_3SiSEt (9.72ml, 60mmol, 2.0 eq.) and $AlCl_3$ (4.80g, 36mmol, 1.2 eq.) were added to a solution of methyl (*E*)-but-2-enoate (3.18ml, 30mmol, 1.0 eq) in 100 ml THF. The resulting mixture was stirred at reflux for 3 hours and the quenched at rt by addition of aqueous phosphate buffer solution (pH 7). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried over $MgSO_4$, filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired α, β-unsaturated thioester (3.40g, 26mmol, 87% yield).

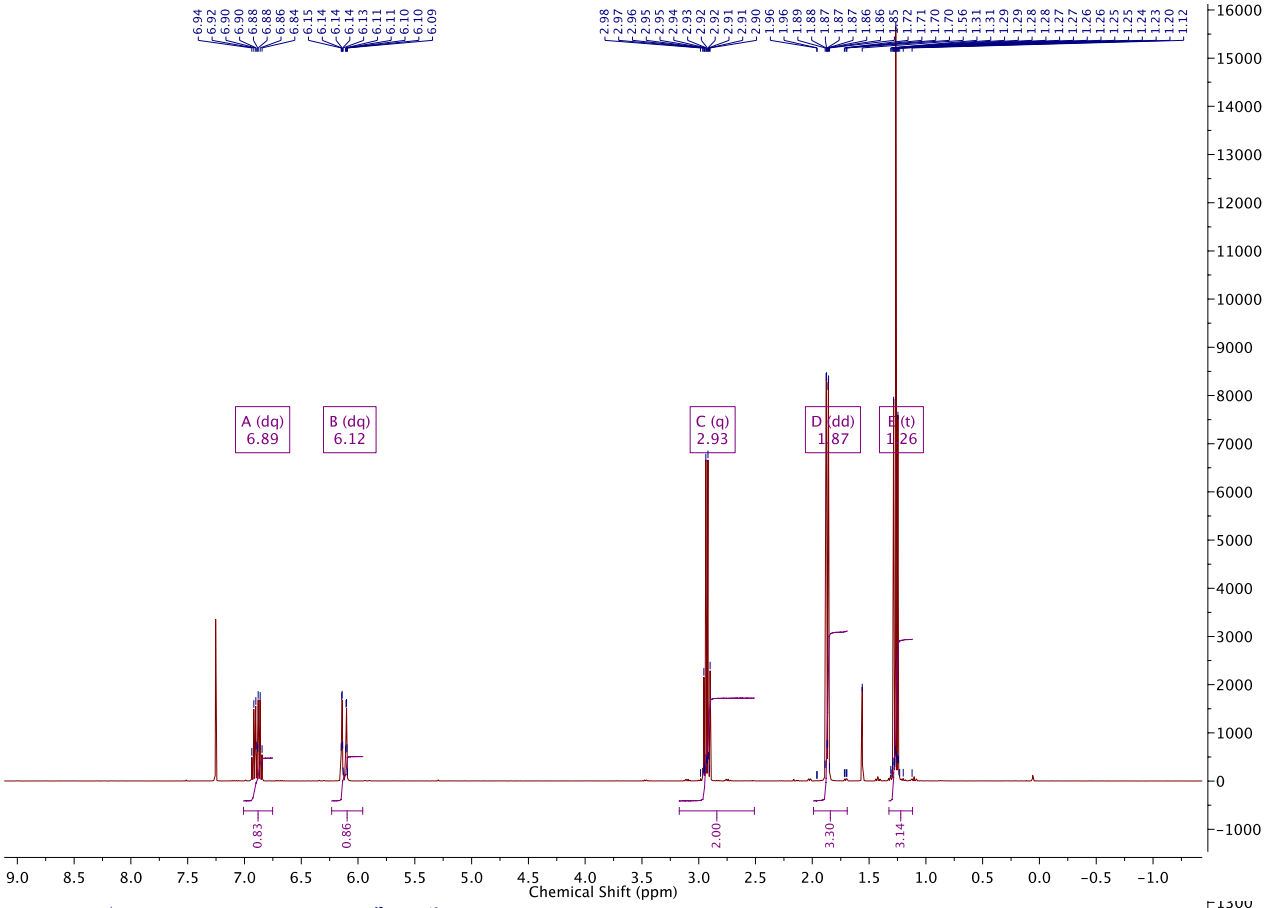
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 6.89 (dq, *J* = 15.5 Hz, 6.9, 1H, C*H*COSEt), 6.12 (dq, *J* = 15.4 Hz, 1.7 Hz, 1H, C*H*CH_3), 2.93 (q, *J* = 7.4 Hz, 2H, SC*H*$_2CH_3$), 1.87 (dd, *J* = 6.9 Hz, 1.7 Hz, 3H, CHC*H*$_3$), 1.26 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3).

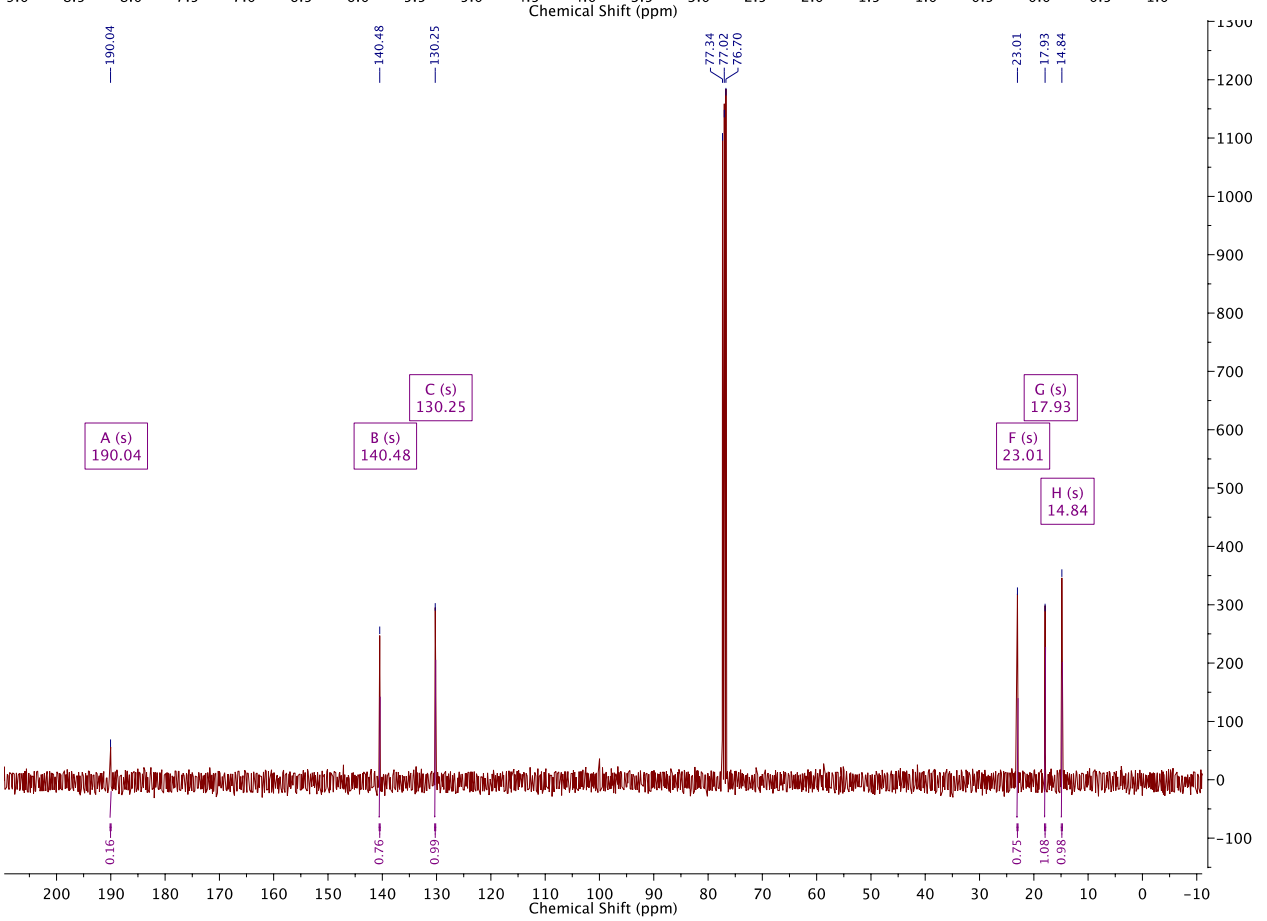
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 190.0, 140.5, 130.3, 23.0, 17.9, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658,2980, 1677,1637,1384,1252,1151,1072,99

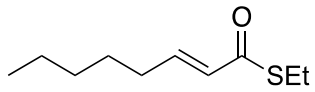
HRMS (ESI) m/z calc. for $C_6H_{11}O^{32}S$ $[M+H]^+$: 131.0525, found: 131.0526.

This data was concordant with literature values[8].


A (dq)
6.89
B (dq)
6.12
C (q)
2.93
D (dd)
1.87
E (t)
1.26
0.83
0.86
2.00
3.30
3.14
Chemical Shift (ppm)


190.04
140.48
130.25
77.34
77.02
76.70
23.01
17.93
14.84
A (s)
190.04
B (s)
140.48
C (s)
130.25
F (s)
23.01
G (s)
17.93
H (s)
14.84
0.16
0.76
0.99
0.75
1.08
0.98
Chemical Shift (ppm)

_S_-ethyl (_E_)-oct-2-enethioate (2b)



Me_3SiSEt (3.30 ml, 20mmol, 2.0 eq.) and $AlCl_3$ (1.60g, 12 mmol, 1.2 eq.) were added to a solution of ethyl (*E*)-oct-2-enoate (1.70 g, 10mmol, 1.0 eq) in 30 ml THF. The resulting mixture was stirred at reflux for 3.5 hours and the quenched at rt. by addition of aqueous phosphate buffer solution (pH 7). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried over $MgSO_4$, filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired α, β-unsaturated thioester (1.46g, 7.8mmol, 78% yield).

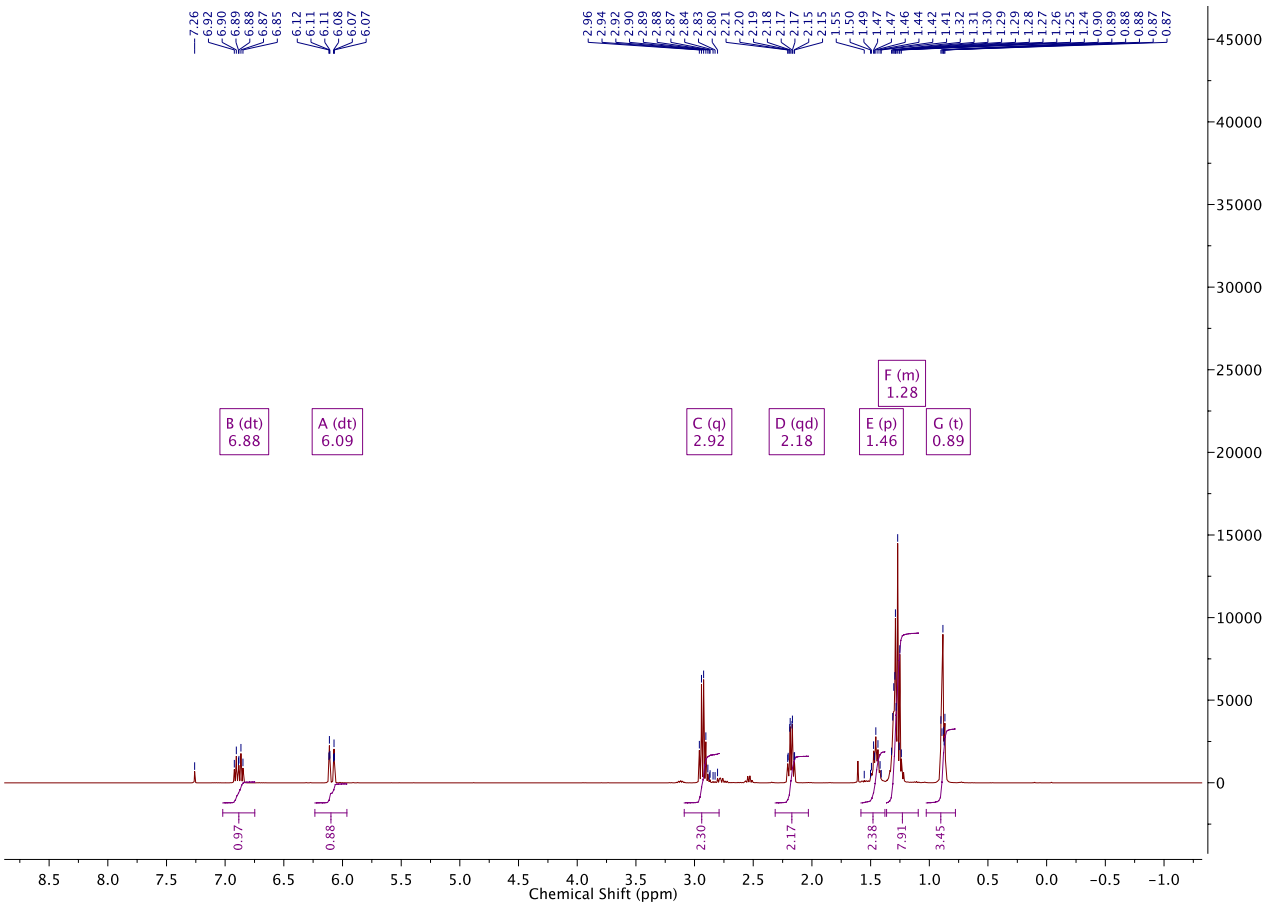
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 6.88 (dt, *J* = 15.5 Hz, 6.9Hz, 1H, C*H*COSEt), 6.09 (dt, *J* = 15.5 Hz, 1.5 Hz, 1H, C*H*=CH), 2.92 (q, *J* = 7.4 Hz, 2H, SCH_2CH$_3$), 2.18 (qd, *J* = 7.2 Hz, 1.5 Hz, 2H, CH_2CH=CH), 1.46 (p, *J* =7.3 Hz, 2H,CH_2), 1.31 – 1.09 (m, 7H, CH_2, CH$_2$CH_3), 0.89 (t, 3H, SCH$_2$CH_3).

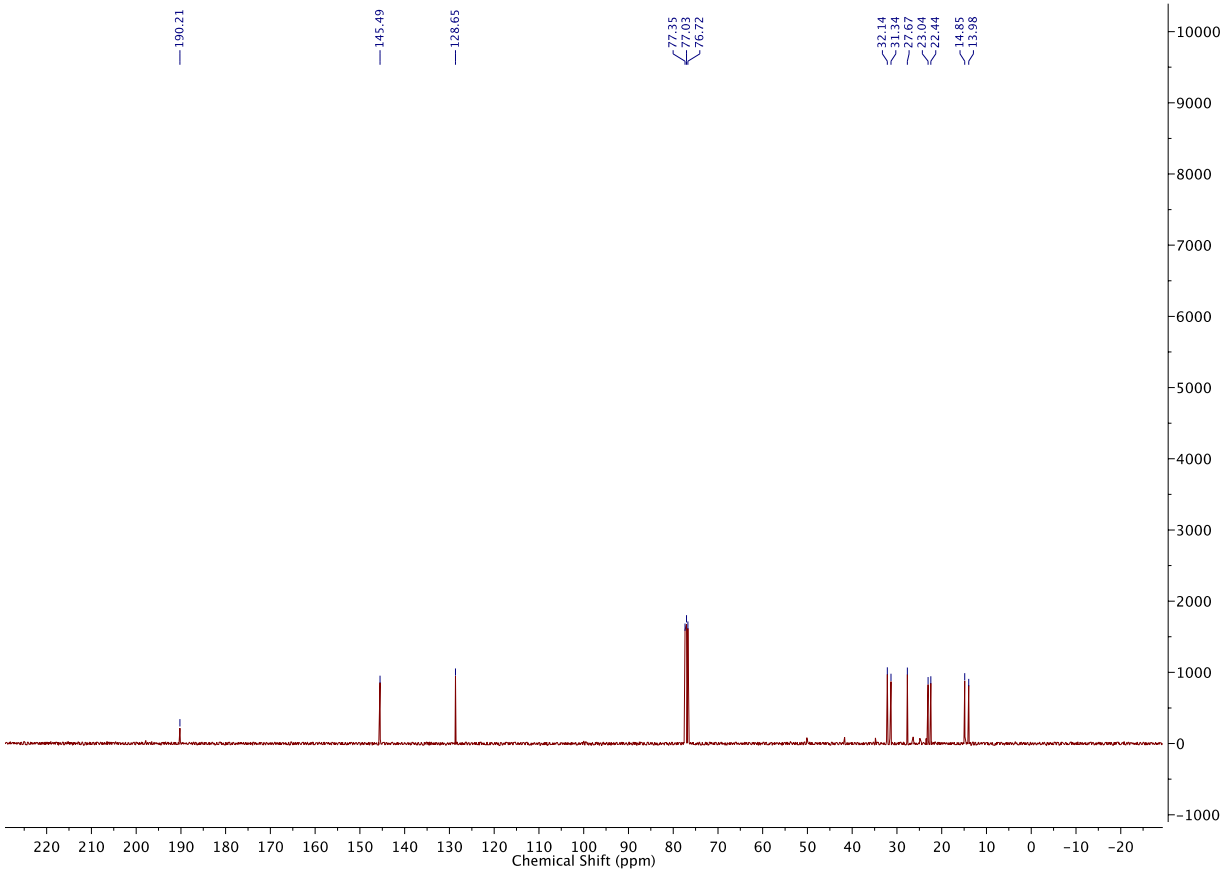
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 190.2, 145.5, 128.7, 32.1, 31.3, 27.7, 23.0, 22.4, 14.9, 14.0.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980,1673,1633,1457,1391,1263,1117,941,773

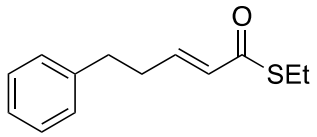
HRMS (ESI) m/z calc. for $C_{10}H_{19}O^{32}S$ $[M+H]^+$: 187.1151, found: 187.1153

This data was concordant with literature values[8].


B (dt) 6.88
A (dt) 6.09
C (q) 2.92
D (qd) 2.18
E (p) 1.46
F (m) 1.28
G (t) 0.89
0.97
0.88
2.30
2.17
2.38
7.91
3.45
Chemical Shift (ppm)


190.21
145.49
128.65
77.35
77.03
76.72
32.14
31.34
27.67
23.04
22.44
14.85
13.98
Chemical Shift (ppm)

_S_-ethyl (_E_)-5-phenylpent-2-enethioate (2c)



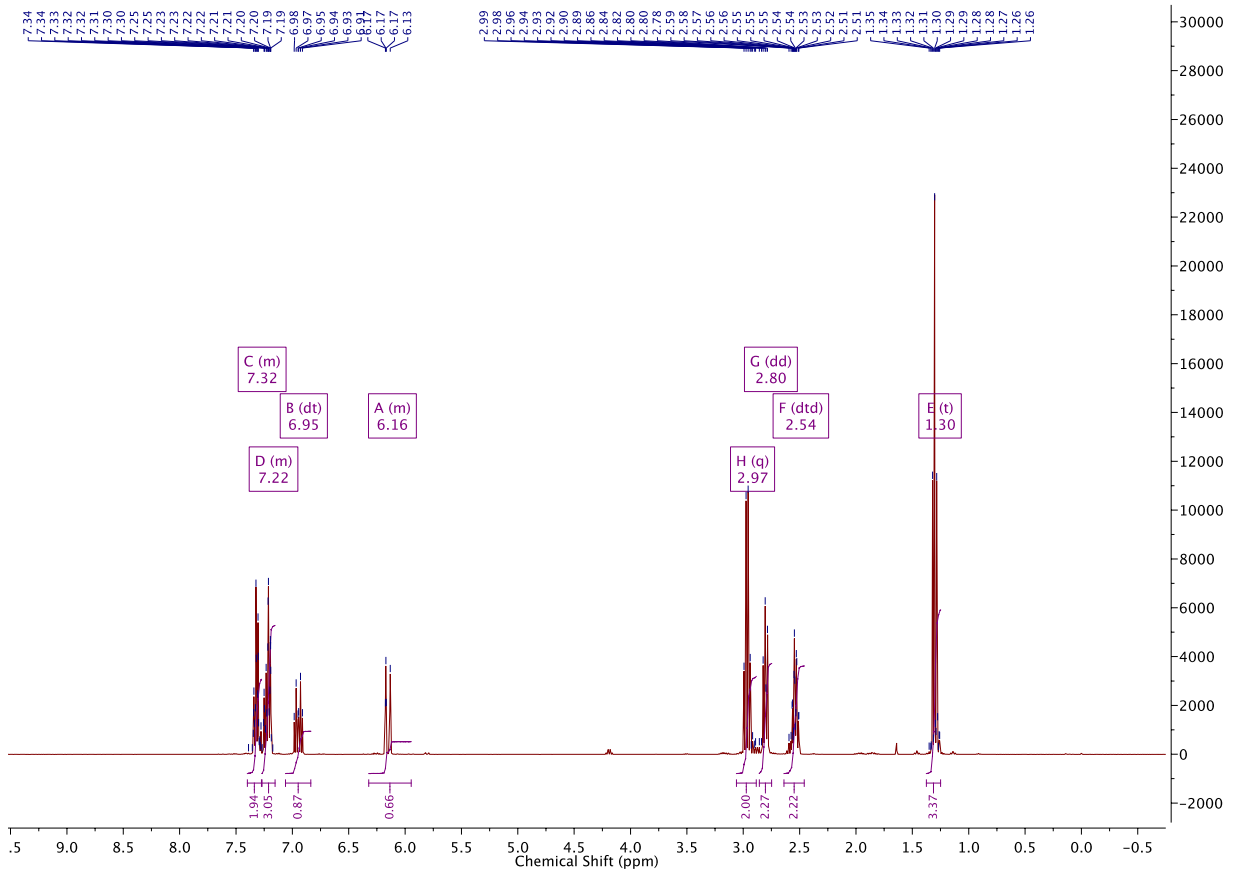
1.6 M n-BuLi in hexane (9.4 ml, 15 mmol, 1.5 eq.) was added to a stirring solution of $(EtO)_2POCHCOSEt$ (4.8 g ,20mmol, 2.0 eq.) in 60 ml THF at 0°C under argon. The mixture was stirred for another 20 min. A solution of 3-phenylpropanal (1.34 g, 10mmol, 1.0 eq.) in 5 ml THF was added dropwise. The mixture was slowly warmed to room temperature and was continued overnight. The mixture was quenched with aqueous NH_4Cl (sat.). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried ($MgSO_4$), filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired α, β-unsaturated thioester (1.83g, 8.3mmol, 83% yield).

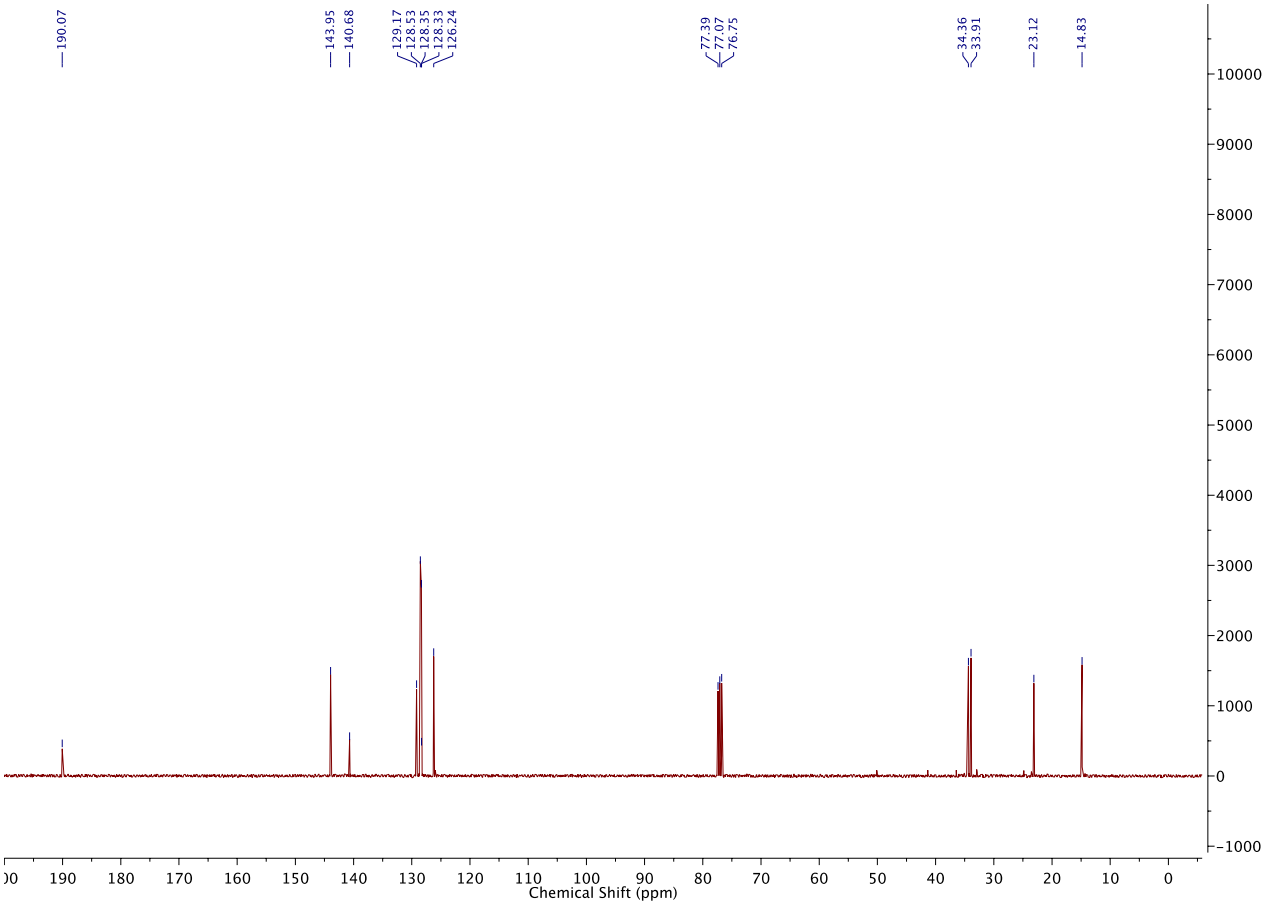
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.40 – 7.27 (m, 2H, Ar-*H*), 7.27 – 7.15 (m, 3H, Ar-*H*), 6.95 (dt, *J* = 15.5 Hz, 6.8 Hz, 1H, C*H*COSEt), 6.32 – 5.95 (m, 1H, C*H*=CH), 2.97 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.80 (dd, *J* = 8.8 Hz, 6.7 Hz, 2H, C*H*$_2$Ph), 2.54 (dtd, *J* = 8.7 Hz, 6.9 Hz, 1.5 Hz, 2H, C*H*$_2$CH=CH), 1.30 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 190.1, 144.0, 140.7, 129.2, 128.5(2C), 128.4(2C), 126.2, 34.4, 33.9, 23.1, 14.8.

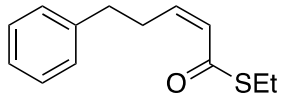
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3697, 2929,1670,1632,1453,1029,937,748,699

HRMS (ESI) m/z calc. for $C_{13}H_{17}O^{32}S$ $[M+H]^+$: 221.0995 , found 221.0994.


C (m)
7.32
B (dt)
6.95
A (m)
6.16
D (m)
7.22
G (dd)
2.80
F (dtd)
2.54
H (q)
2.97
E (t)
1.30
1.94
3.05
0.87
0.66
2.00
2.27
2.22
3.37
Chemical Shift (ppm)


190.07
143.95
140.68
129.17
128.53
128.35
128.33
126.24
77.39
77.07
76.75
34.36
33.91
23.12
14.83
Chemical Shift (ppm)

_S_-ethyl (_Z_)-5-phenylpent-2-enethioate (2d)



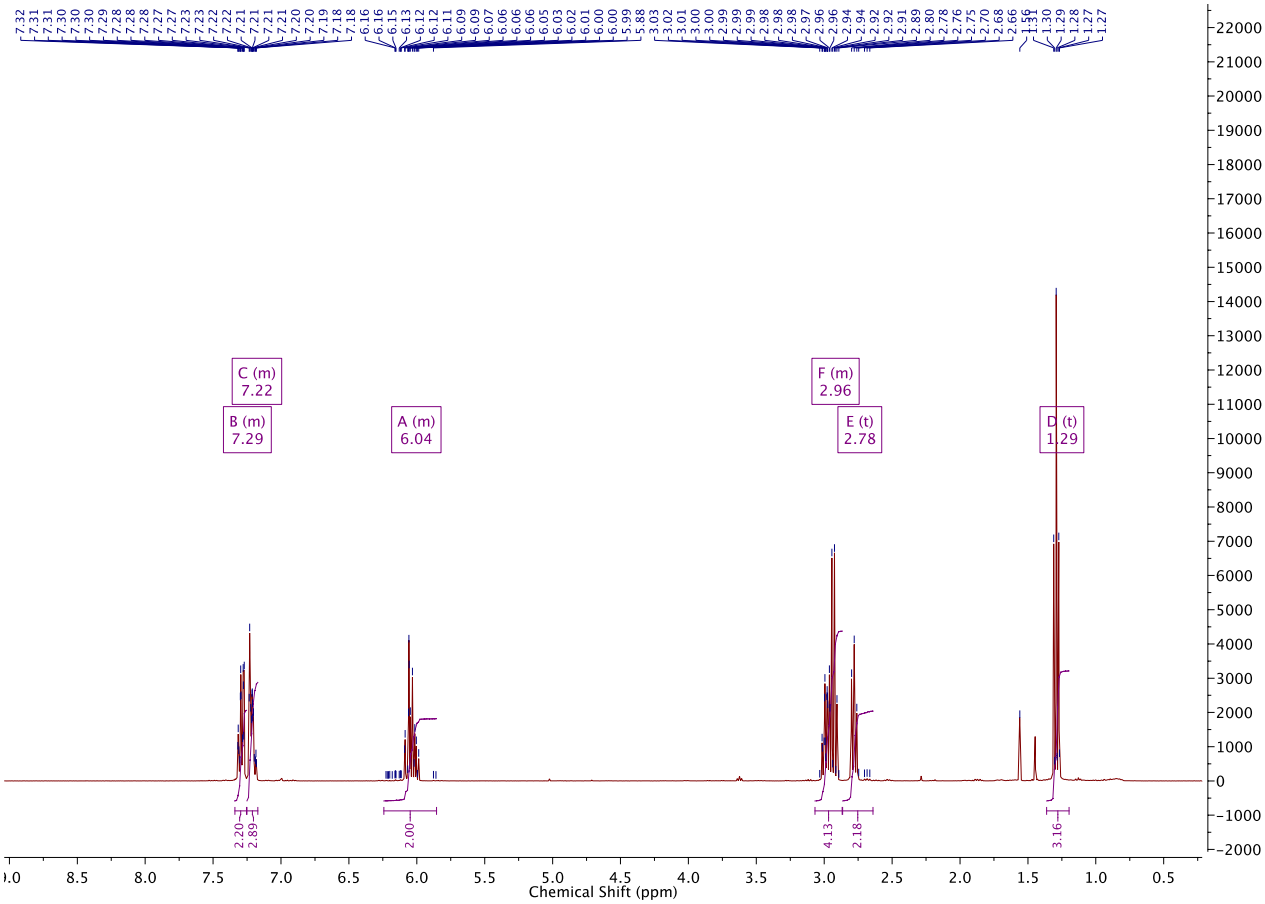
1.6 M n-BuLi in hexane (9.4 ml, 15 mmol, 1.5 eq.) was added to a stirring solution of $(EtO)_2POCHCOSEt$ (4.8 g ,20mmol, 2.0 eq.) in 60 ml THF at 0°C under argon. The mixture was stirred for another 20 min. A solution of 3-phenylpropanal (1.34 g, 10mmol, 1.0 eq.) in 5 ml THF was added dropwise. The mixture was slowly warmed to room temperature and was continued overnight. The mixture was quenched with aqueous NH_4Cl (sat.). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried ($MgSO_4$), filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired α, β-unsaturated thioester (76mg, 0.3 mmol, 3% yield).

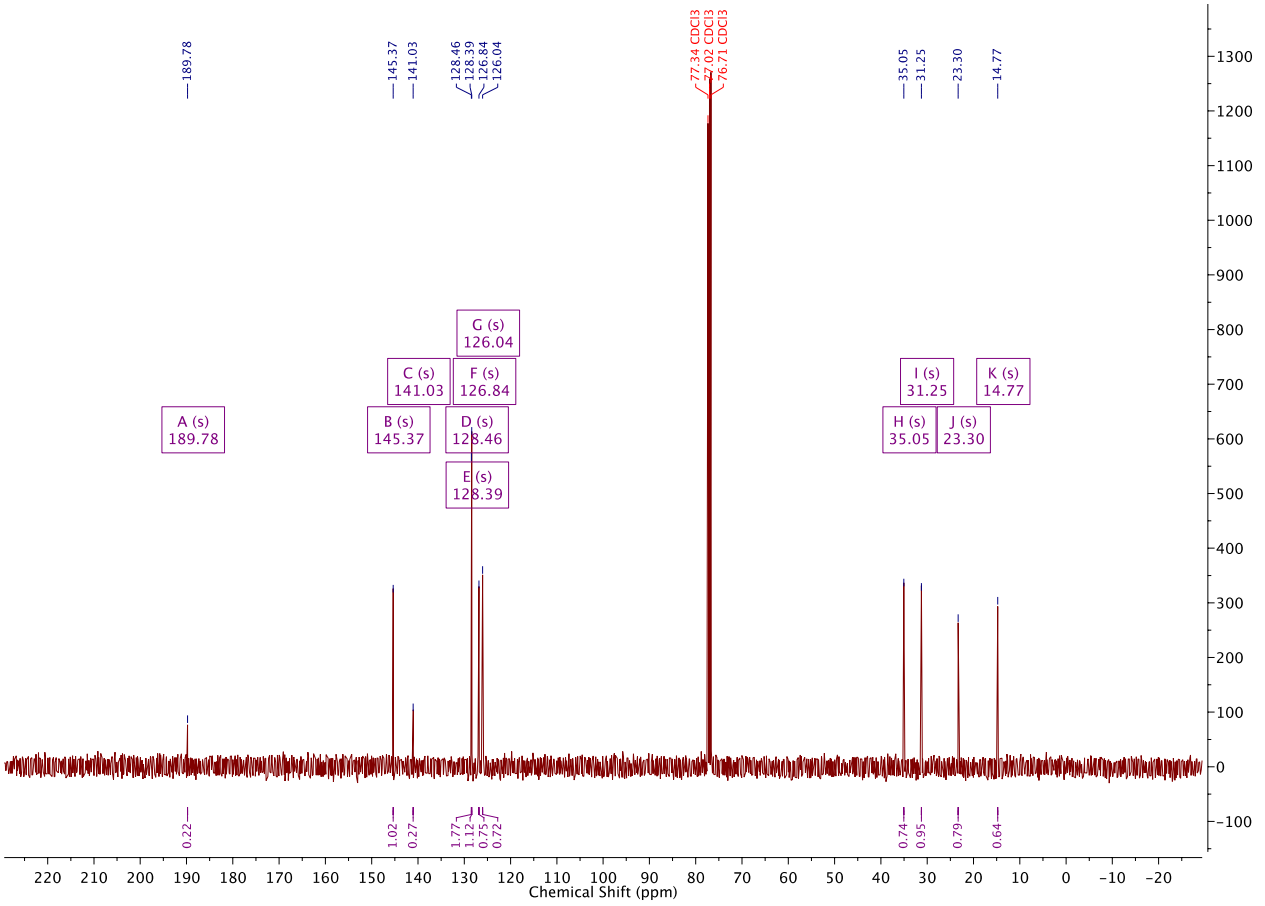
^1H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.34 – 7.25 (m, 2H, Ar-*H*), 7.25 – 7.17 (m, 3H, Ar-*H*), 6.24 – 5.86 (m, 2H, C*H*=C*H*), 3.07 – 2.87 (m, 4H, CH_2CH_2Ph), 2.78 (t, *J*=7.7 Hz, 2H, SCH_2CH_3), 1.29 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 189.8, 145.4, 141.0, 128.5(2C), 128.4(2C), 126.8, 126.0, 35.1, 31.3, 23.3, 14.8.

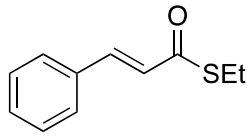
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980,1670,1619,1473,1152,1073,953,699

HRMS (ESI) m/z calc. for $C_{13}H_{17}O^{32}S$ $[M+H]^+$: 221.0995 found 221.0994.


C (m)
7.22
B (m)
7.29
A (m)
6.04
F (m)
2.96
E (t)
2.78
D (t)
1.29
2.20
2.89
2.00
4.13
2.18
3.16
Chemical Shift (ppm)


189.78
145.37
141.03
128.46
128.39
126.84
126.04
77.34 CDCl3
77.02 CDCl3
76.71 CDCl3
35.05
31.25
23.30
14.77
G (s)
126.04
C (s)
141.03
F (s)
126.84
I (s)
31.25
K (s)
14.77
A (s)
189.78
B (s)
145.37
D (s)
128.46
H (s)
35.05
J (s)
23.30
E (s)
128.39
0.22
1.02
0.27
1.77
1.12
0.75
0.72
0.74
0.95
0.79
0.64
Chemical Shift (ppm)

_S_-ethyl (_E_)-3-phenylprop-2-enethioate (2e)



Me_3SiSEt (3.60ml, 22mmol, 2.0 eq.) and $AlCl_3$ (1.80g, 13.2mmol, 1.2 eq.) were added to a solution of methyl cinnamate (1.78g, 11mmol, 1.0 eq) in 30 ml THF. The resulting mixture was stirred at reflux for 3.5 hours and the quenched at rt by addition of aqueous phosphate buffer solution (pH 7). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried over $MgSO_4$, filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired α, β-unsaturated thioester (2.03g, 10.6mmol, 96% yield).

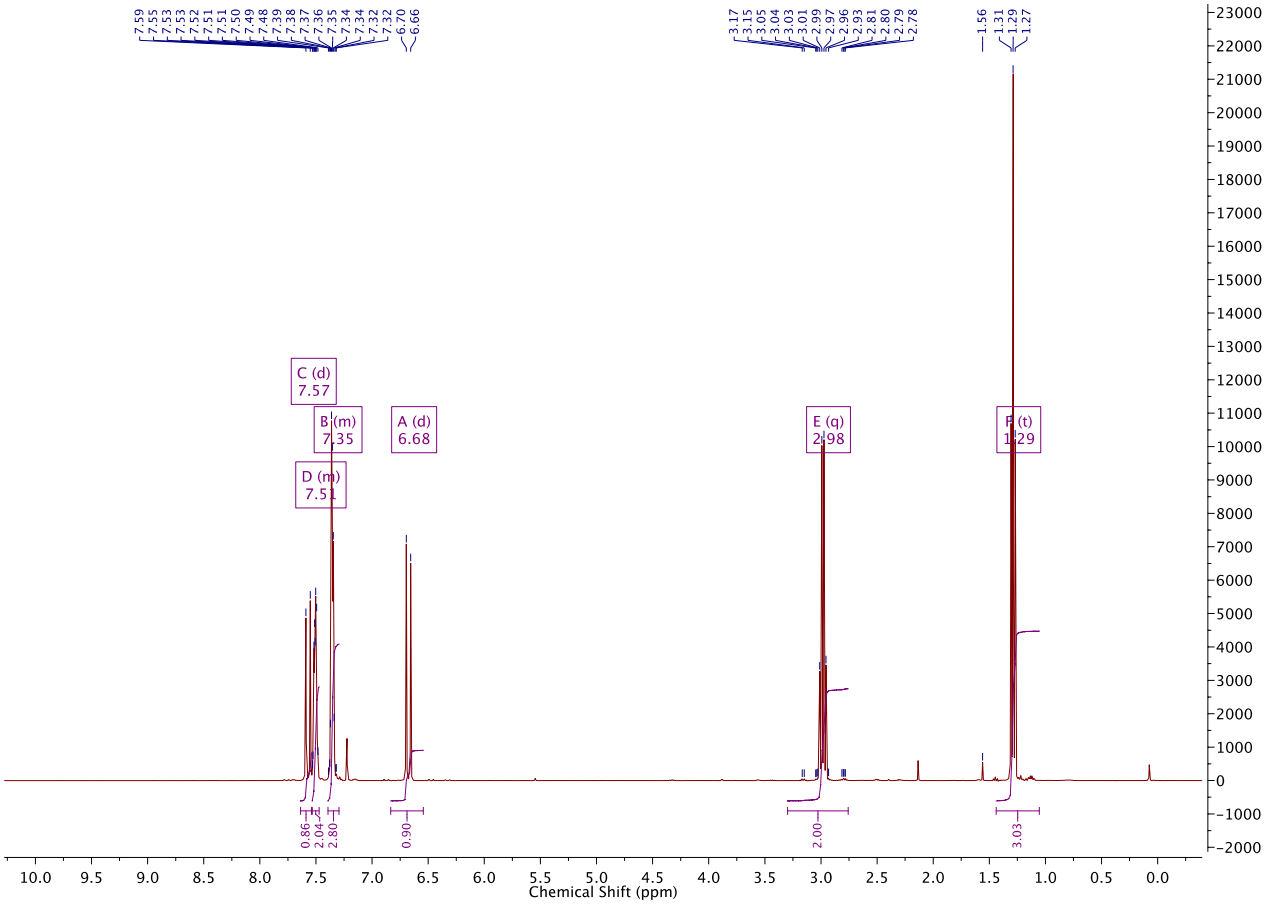
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.57 (d, *J* = 15.8 Hz, 1H,C*H*COSEt), 7.53 – 7.47 (m, 2H, Ar-*H*), 7.39 – 7.30 (m, 3H, Ar-*H*), 6.68 (d, *J* =15.8 Hz, 1H, C*H*=CH), 2.98 (q, *J* = 7.4 Hz, 2H, CH_2CH$_3$), 1.29 (t, *J* = 7.4 Hz, 3H, CH$_2$CH_3).

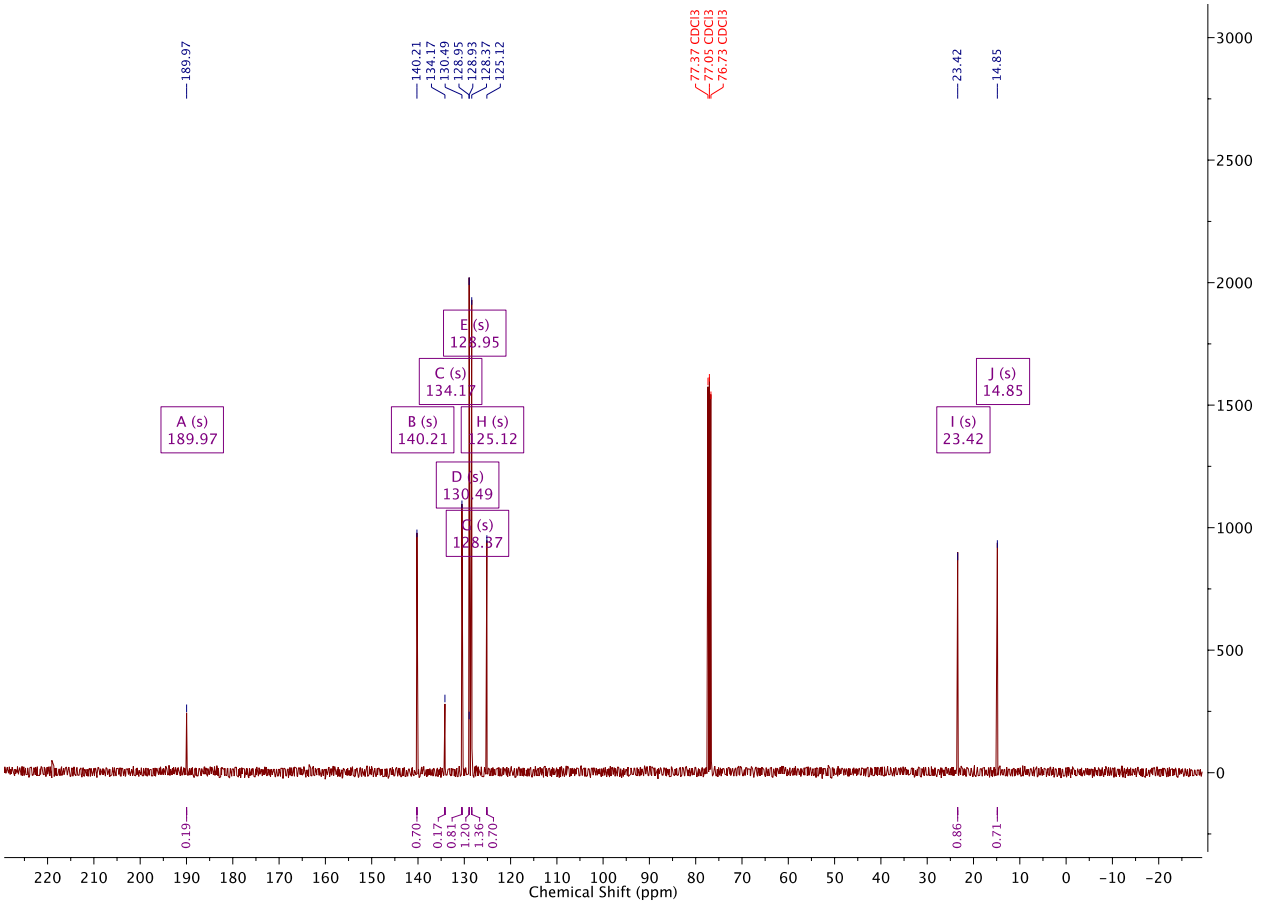
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 190.0, 140.2, 134.2, 130.5, 129.0 (2C), 128.4 (2C), 125.1, 23.4, 14.9.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3028, 1655,1615,1449,1138,999,753

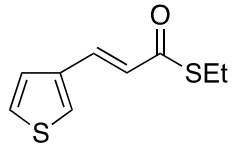
HRMS (ESI) m/z calc. for $C_{11}H_{13}O^{32}S$ $[M+H]^+$: 193.0682, found: 193.0684.

This data was concordant with literature values[9].


C (d)
7.57
B (m)
7.35
A (d)
6.68
D (m)
7.51
E (q)
2.98
F (t)
1.29
Chemical Shift (ppm)


A (s)
189.97
B (s)
140.21
C (s)
134.17
D (s)
130.49
E (s)
128.95
G (s)
128.37
H (s)
125.12
I (s)
23.42
J (s)
14.85
77.37 CDCl3
77.05 CDCl3
76.73 CDCl3
Chemical Shift (ppm)

_S_-ethyl (_E_)-3-(thiophen-3-yl)prop-2-enethioate (2f)



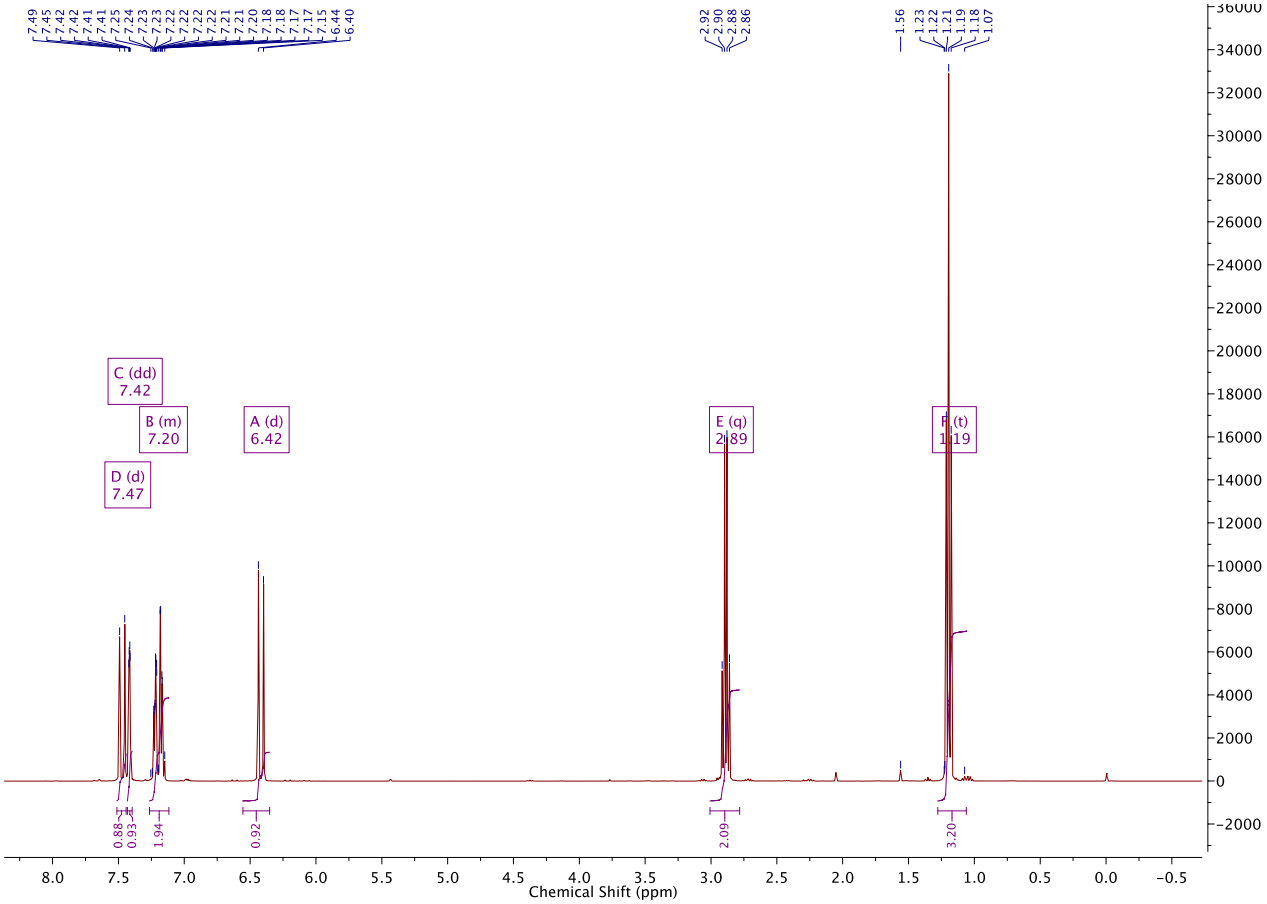
Me_3SiSEt (3.60 ml, 22mmol, 2.0 eq.) and $AlCl_3$ (1.80g, 13.2 mmol, 1.2 eq.) were added to a solution of ethyl (*E*)-3-(thiophen-3-yl) acrylate (2.00 g, 11mmol, 1.0 eq) in 30 ml THF. The resulting mixture was stirred at reflux for 3.5 hours and the quenched at rt. by addition of aqueous phosphate buffer solution (pH 7). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried over $MgSO_4$, filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired α, β-unsaturated thioester (1.85g, 9.3mmol, 85% yield).

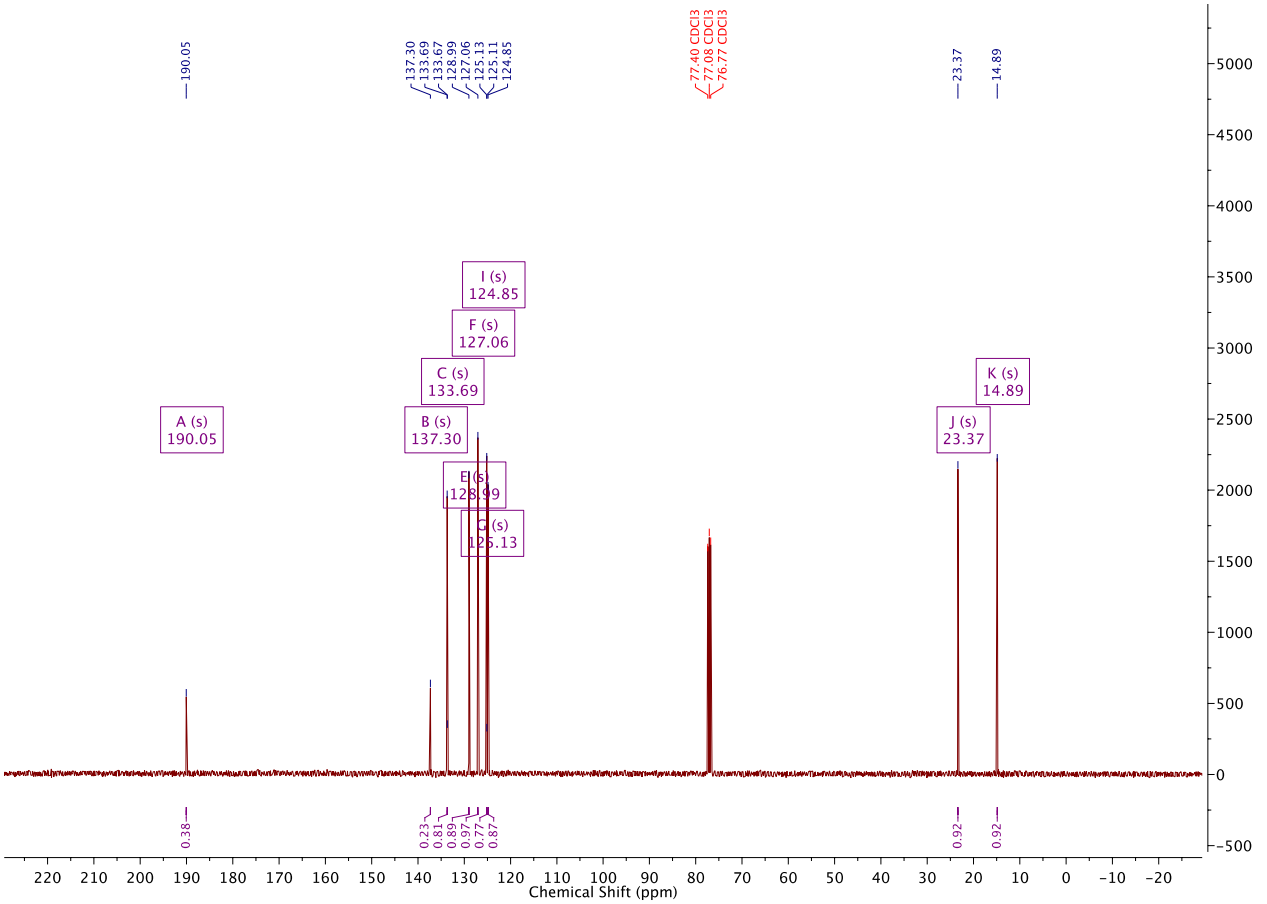
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.47 (d, *J* = 15.7 Hz, 1H, C*H*COSEt), 7.43-7.40 (m, 1H, Ar-*H*), 7.26 – 7.12 (m, 2H, Ar-*H*), 6.42 (d, *J* = 15.7 Hz, 1H, C*H*=CH), 2.89 (q, *J* = 7.4 Hz, 2H, CH_2CH$_3$), 1.19 (t, *J* = 7.4 Hz, 3H, CH$_2$CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 190.1, 137.3, 133.7, 129.0, 127.1, 125.1, 124.9, 23.4, 14.9.

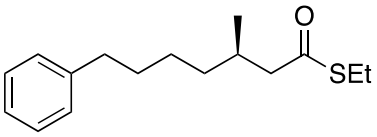
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3097, 1656,1604,1245,1131,1024,776

HRMS (ESI) m/z calc. for $C_9H_{11}O^{32}S_2$ $[M+H]^+$: 199.0246, found: 199.0247.


C (dd)
7.42
B (m)
7.20
A (d)
6.42
D (d)
7.47
E (q)
2.89
F (t)
1.19
Chemical Shift (ppm)


I (s)
124.85
F (s)
127.06
C (s)
133.69
A (s)
190.05
B (s)
137.30
K (s)
14.89
J (s)
23.37
Chemical Shift (ppm)

(+)-*S*-ethyl (*R*)-3-methyl-7-phenylheptanethioate (3a)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of but-3-en-1-ylbenzene (66 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained. The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone(26.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (45 mg, 0.17mmol, 85% yield).

HPLC analysis indicated an enantiomeric excess of 98 % [Chiralpak® IC; flow: 0.8 mL/min; hexane/i-PrOH: 99.7:0.3; λ = 210 nm; major enantiomer tR = 9.48 min; minor enantiomer, tR = 9.27 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.34 – 7.23 (m, 2H, Ar-*H*), 7.22 – 6.99 (m, 3H, Ar-*H*), 2.87 (q, *J* = 7.4 Hz, 2H, S*CH*$_2$CH$_3$), 2.60 (t, *J* = 7.8 Hz, 2H, C*H*$_2$Ph), 2.51 (dd, *J* = 14.4 Hz, 6.1 Hz, 1H, C*H*$_2$COSEt), 2.34 (dd, *J* = 14.4 Hz, 8.0 Hz, 1H, C*H*$_2$COSEt)), 2.12 – 1.89 (m, 1H, C*H*), 1.69 – 1.53 (m, 3H,C*H*$_2$), 1.41 – 1.28 (m, 2H, C*H*$_2$), 1.24 (t, *J* = 7.4 Hz, 4H, C*H*$_2$, SCH$_2$C*H*$_3$), 0.92 (d, *J* = 6.6 Hz, 3H CHC*H*$_3$).

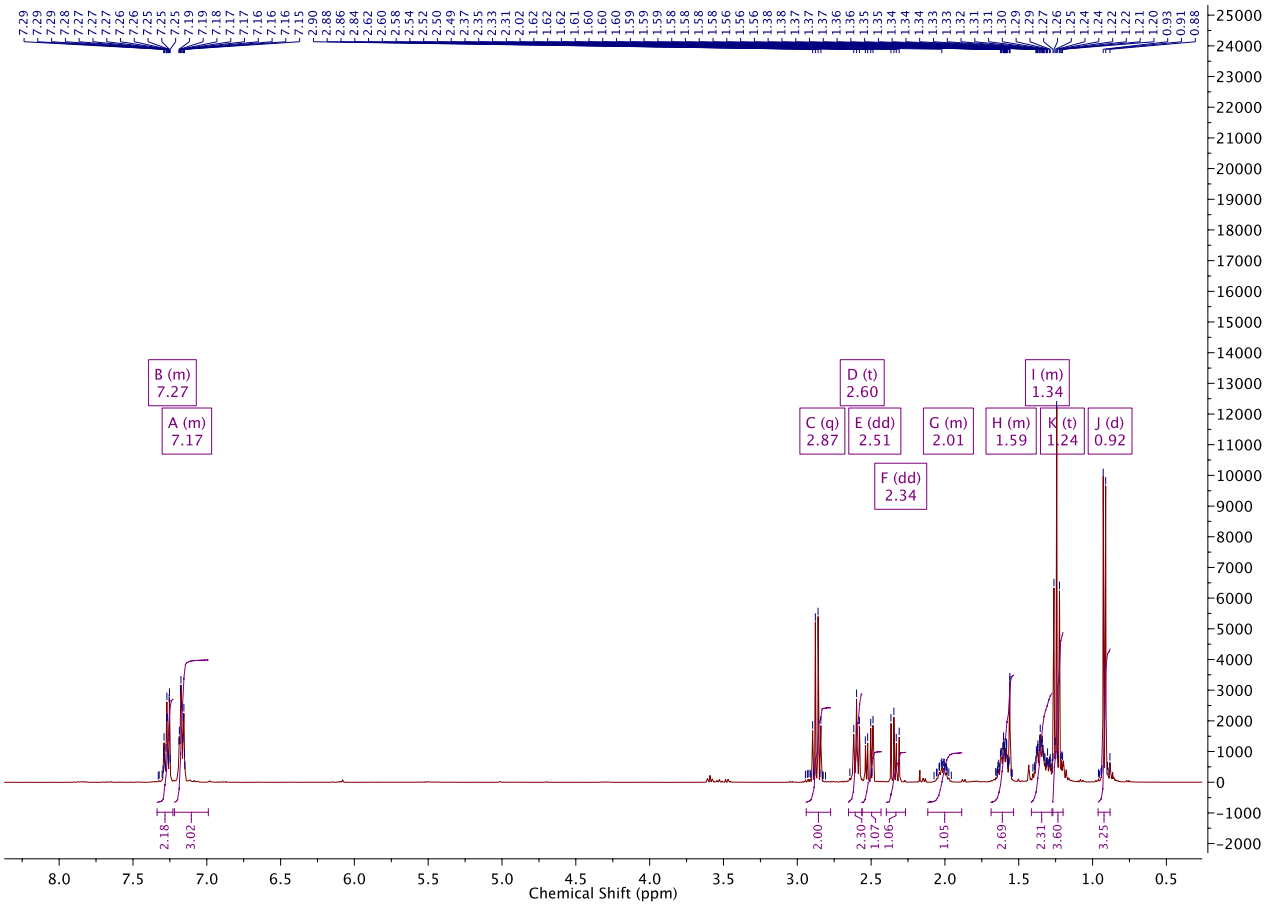
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.3, 142.7, 128.4 (2C), 128.3(2C), 125.6, 51.4, 36.4, 35.9, 31.5, 31.0, 26.5, 23.3, 19.5, 14.8.

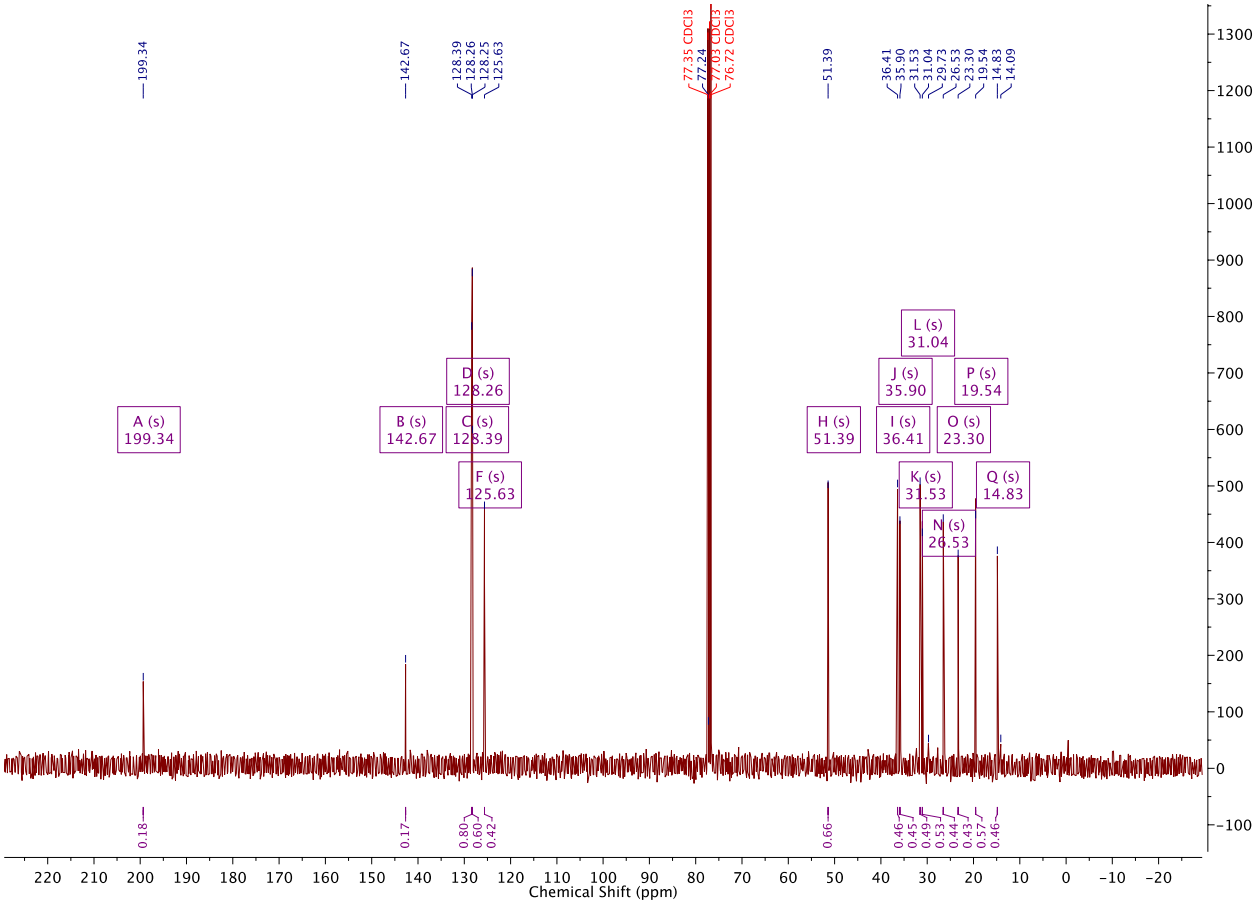
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980,1688,1384,1252,1151,1072,966

HRMS (ESI) m/z calc. for $C_{16}H_{24}O^{23}Na^{32}S$ $[M+Na]^+$: 287.1440, found: 287.1440

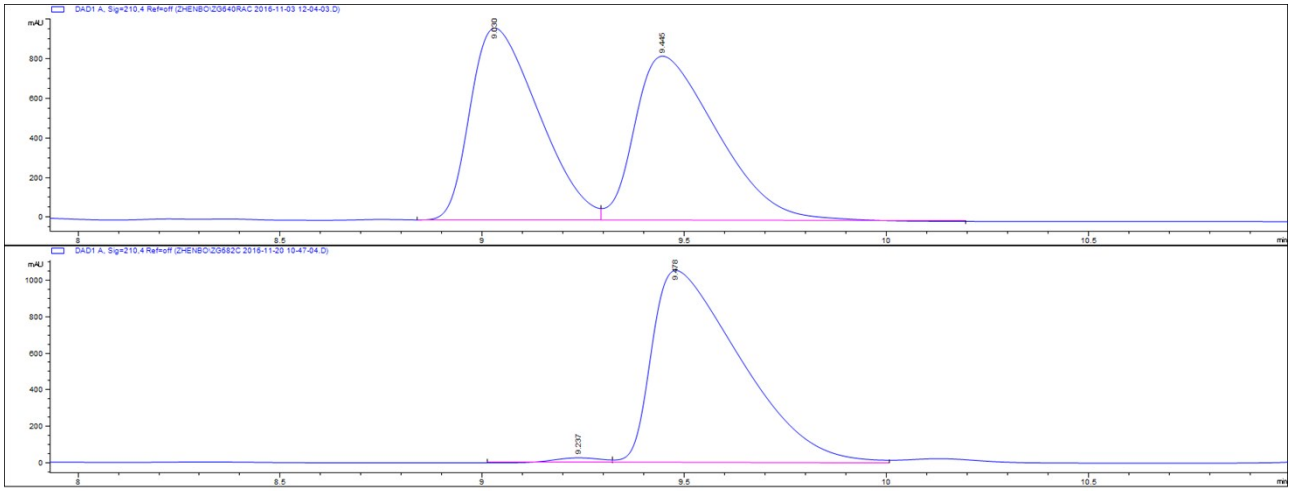
$[\alpha]^{20}_{589}$ = +2.3 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.




199.34
142.67
128.39
128.26
128.25
125.63
77.35 CDCl3
77.24
77.03 CDCl3
76.72 CDCl3
51.39
36.41
35.90
31.53
31.04
29.73
26.53
23.30
19.54
14.83
14.09
A (s) 199.34
B (s) 142.67
C (s) 128.39
D (s) 128.26
F (s) 125.63
H (s) 51.39
I (s) 36.41
J (s) 35.90
K (s) 31.53
L (s) 31.04
N (s) 26.53
O (s) 23.30
P (s) 19.54
Q (s) 14.83
0.18
0.17
0.80
0.60
0.42
0.66
0.46
0.45
0.49
0.53
0.44
0.43
0.57
0.46
Chemical Shift (ppm)

HPLC trace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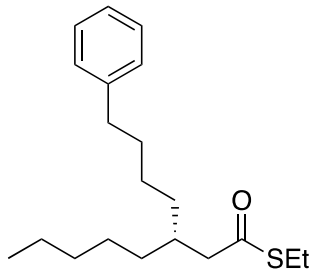
9.030
9.445
DAD1 A, Sig=210,4 Ref=off (ZHENBO\ZG682C 2016-11-20 10-47-04.D)
9.478
9.237

(+)-*S*-ethyl (*R*)-3-(4-phenylbutyl)octanethioate (3b)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of but-3-en-1-ylbenzene (66 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained. The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-oct-2-enethioate (37.2 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (47 mg, 0.15mmol, 73% yield).

HPLC analysis indicated an enantiomeric excess of 97 % [Chiralpak® IB; flow: 1.0 mL/min; 100% hexane; λ = 210 nm; major enantiomer tR = 13.22 min; minor enantiomer, tR = 12.17 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.33 – 7.22 (m, 2H, Ar-*H*), 7.17 (ddt, *J* = 7.0 Hz, 3.8 Hz, 2.2 Hz, 3H, Ar-*H*), 2.86 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.59 (dd, *J* = 8.7 Hz, 6.8 Hz, 2H, C*H*$_2$Ph), 2.46 (dd, *J* = 6.9 Hz, 0.9 Hz, 2H, C*H*$_2$COSEt), 2.04 – 1.83 (m, 1H, C*H*), 1.65-1.48 (m, 2H, C*H*$_2$), 1.39 – 1.19 (m, 15H, C*H*$_2$, SCH$_2$C*H*$_3$), 0.88 (td, *J* = 7.0 Hz, 2.5 Hz, 3H, CH$_2$C*H*$_3$).

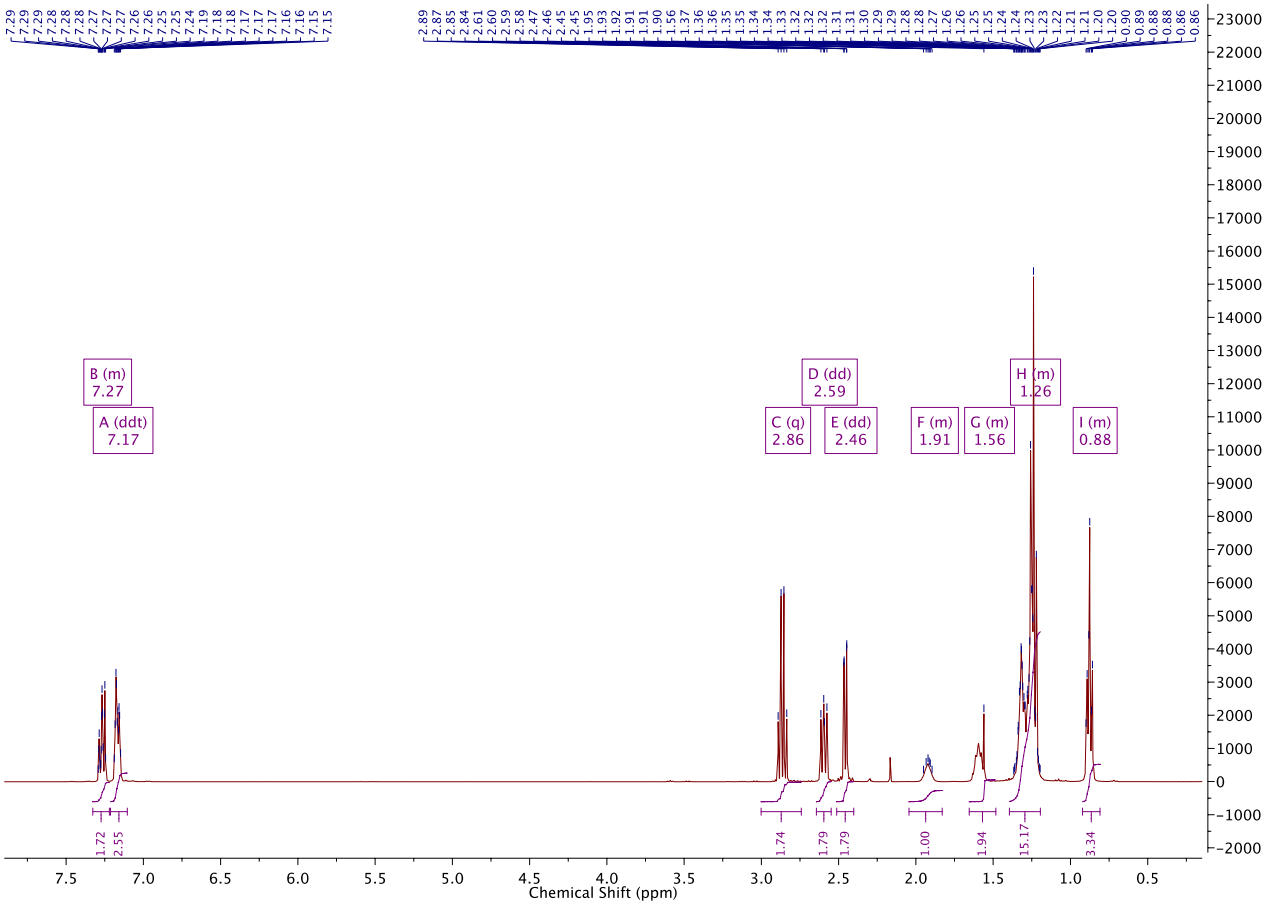
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.6, 142.7, 128.4(2C), 128.3(2C), 125.6, 48.9, 35.9, 35.7, 33.6, 33.5, 32.1, 31.7, 26.2, 23.3, 22.6, 22.4, 14.8, 14.1.

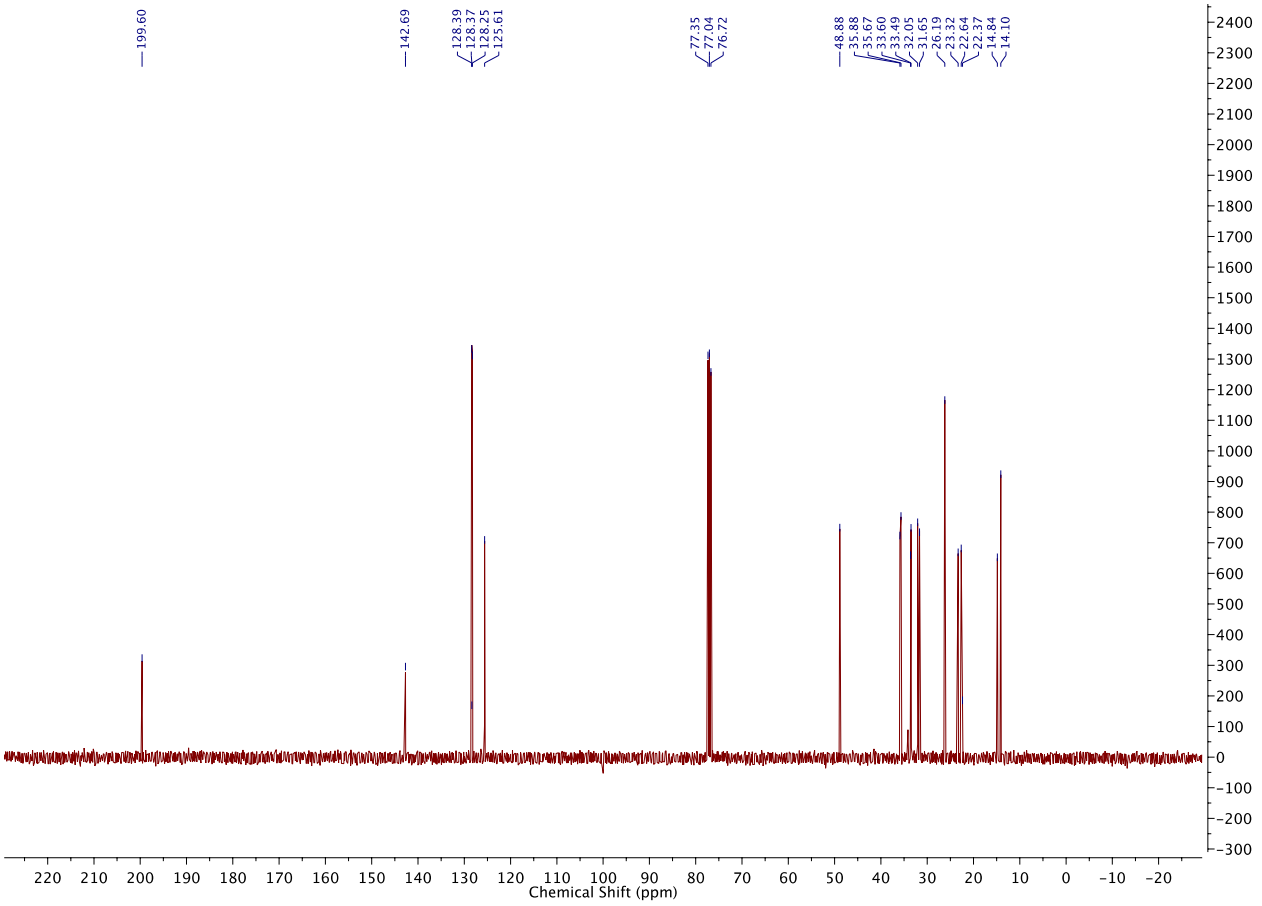
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980,1689,1382,1152,955,774

HRMS (ESI) m/z calc. for $C_{20}H_{33}O^{32}S$ $[M+H]^+$: 321.2247 found 321.2247

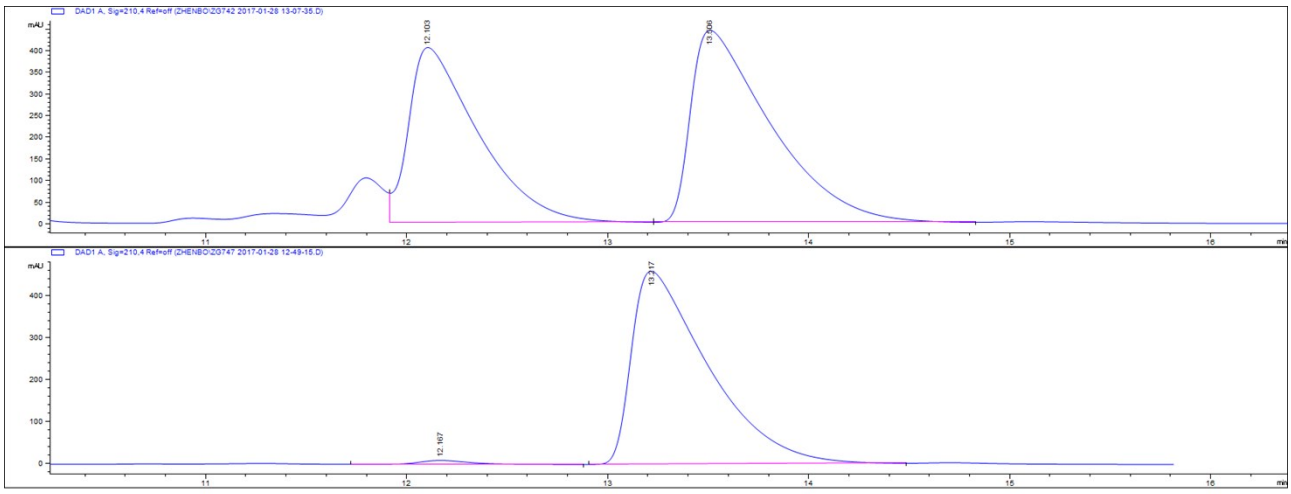
$[\alpha]^{20}_{589}$ = +3.6 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.




199.60
142.69
128.39
128.37
128.25
125.61
77.35
77.04
76.72
48.88
35.88
35.67
33.60
33.49
32.05
31.65
26.19
23.32
22.64
22.37
14.84
14.10
Chemical Shift (ppm)

HPLC trace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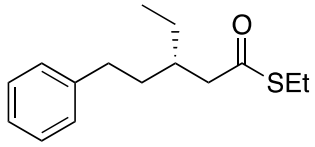
12.603
13.309
DAD1 A, Sig=210,4 Ref=off (ZHENBO-ZG747 2017-01-28 12-49-15.D)
12.167
13.317

(+)-*S*-ethyl (*S*)-3-ethyl-5-phenylpentanethioate (3c)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. A balloon filled with ethylene was used to purge the flask with ethylene for 5 min, and then DCM (0.2 mL) was added. After stirring for 15 min under an ethylene atmosphere (balloon), a clear yellow solution was obtained. To a second, flame dried, round bottom flask was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), a balloon filled with ethylene was used to purge the flask with ethylene for 5 min, and then DCM (0.2 mL) was added. After stirring for 15 min under an ethylene atmosphere (balloon), a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-5-phenylpent-2-enethioate (44.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (40 mg, 0.16mmol, 80% yield).

HPLC analysis indicated an enantiomeric excess of 97 % [Chiralpak® IB; flow: 1.0 mL/min; hexane: ipa 99.6:0.4; λ = 210 nm; major enantiomer tR = 6.17 min; minor enantiomer, tR = 7.03 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.32 – 7.24 (m, 2H, Ar-*H*), 7.21 – 7.12 (m, 3H, Ar-*H*), 2.88 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.60 (dd, *J* = 9.5 Hz, 7.1Hz, 2H, C*H*$_2$Ph), 2.54 (d, *J* = 6.9 Hz, 2H, C*H*$_2$COSEt), 1.96 (hept, *J* = 6.5 Hz, 1H, C*H*), 1.71 – 1.57 (m, 2H, C*H*$_2$CH$_2$Ph), 1.42 (dtd, *J* =

13.6Hz, 7.5 Hz, 6.2 Hz, 2H, CH_2CH$_3$), 1.25 (t, J = 7.4 Hz, 3H, SCH$_2$CH_3), 0.90 (t, J = 7.4 Hz, 3H, CH$_2$CH_3).

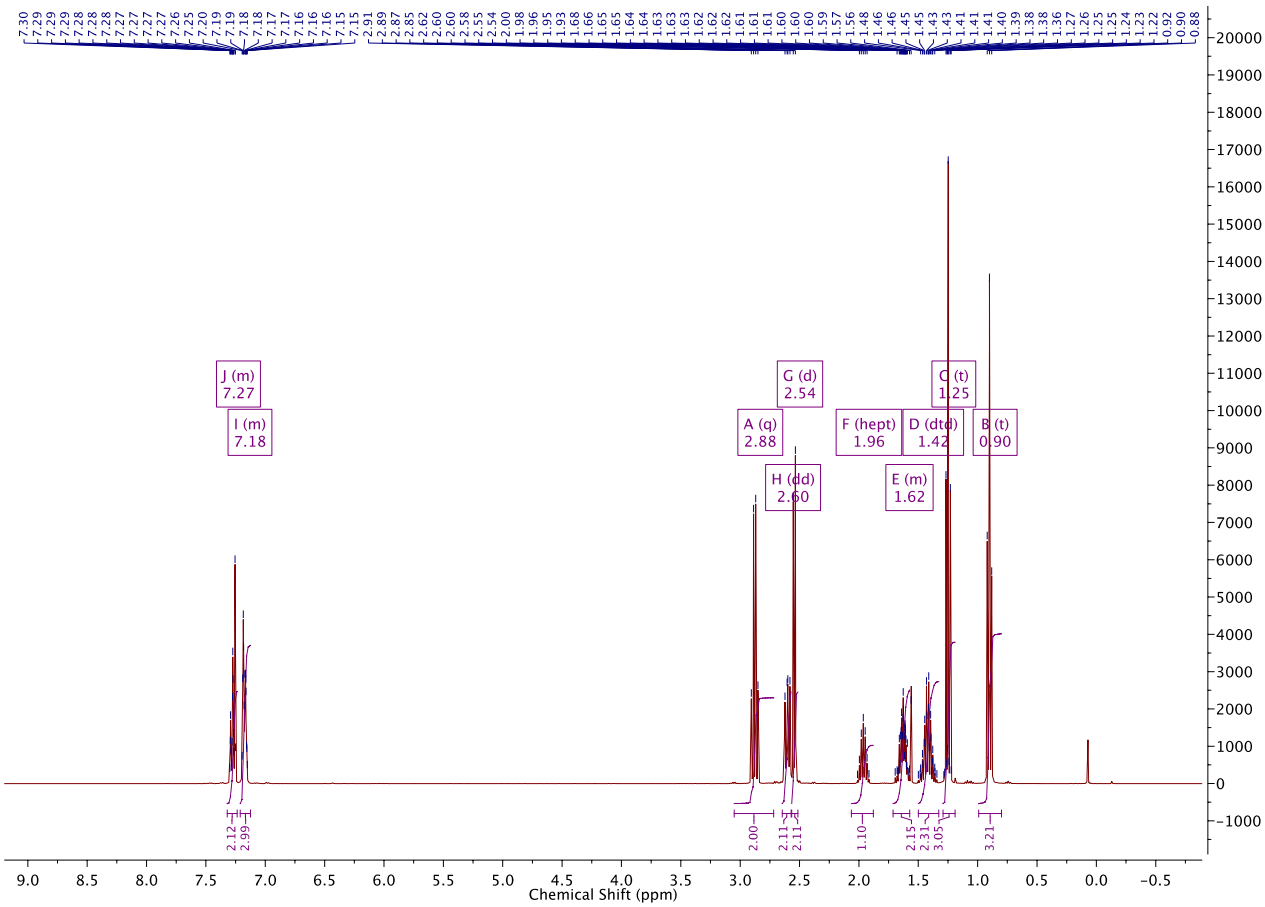
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.4, 142.5, 128.4(2C), 128.3(2C), 125.7, 48.2, 36.9, 35.1, 33.0, 26.1, 23.4, 14.8, 10.7.

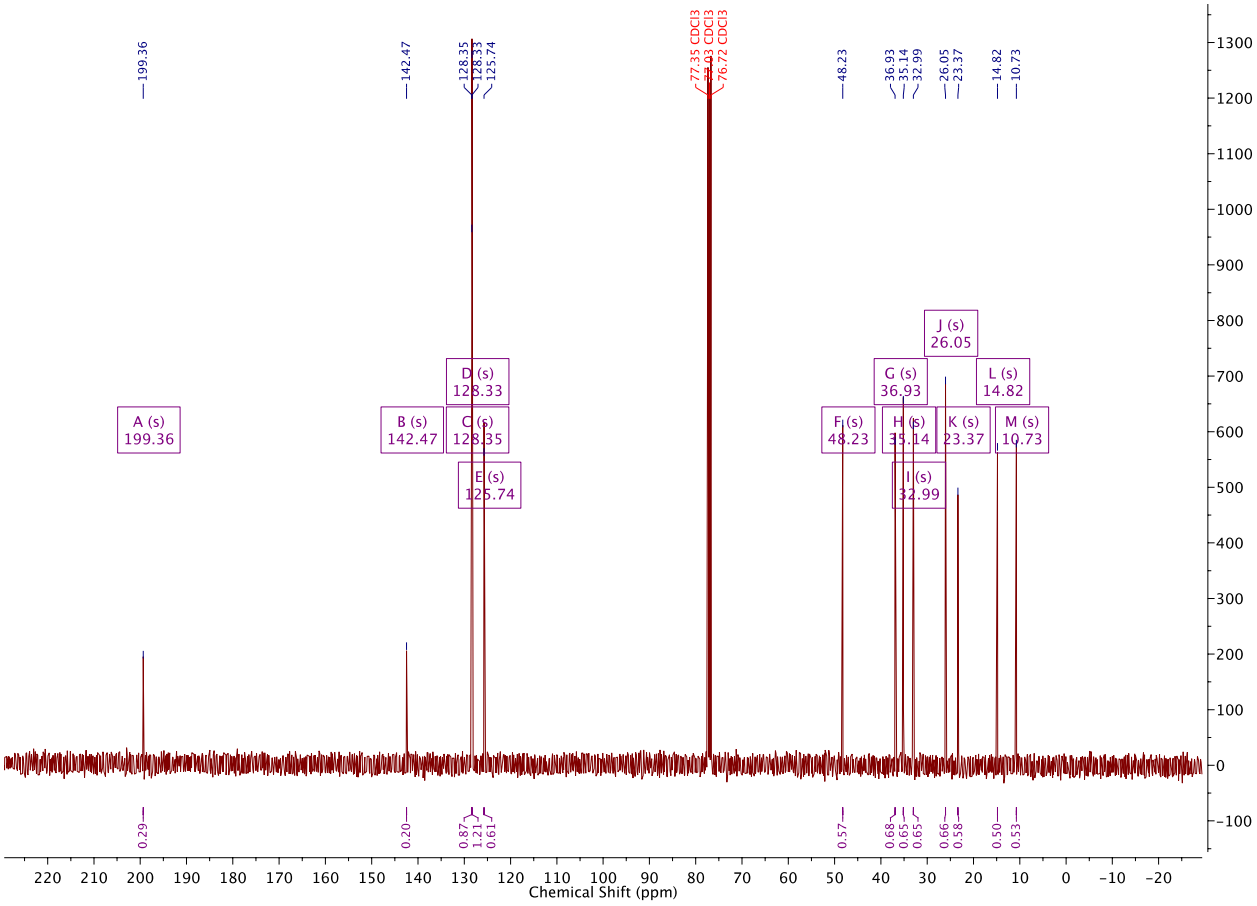
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3660, 2980,1688,1382,1251,1152,954

HRMS (ESI) m/z calc. for $C_{15}H_{23}O^{32}S$ $[M+H]^+$: 251.1464 found 251.1465

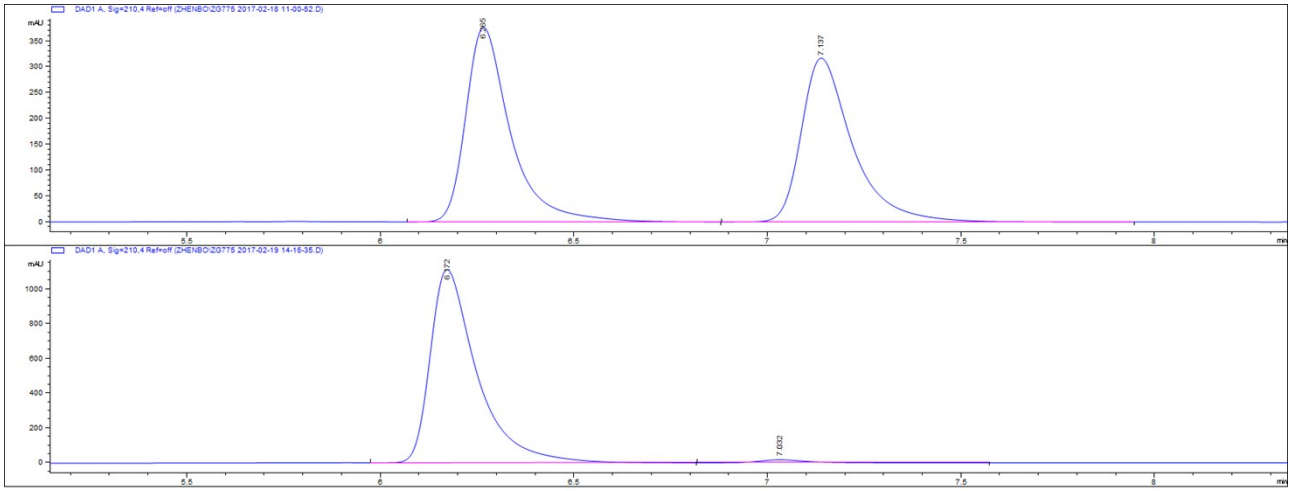
$[\alpha]^{20}_{589}$ = +5.7 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.




199.36
142.47
128.35
128.33
125.74
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
48.23
36.93
35.14
32.99
26.05
23.37
14.82
10.73
A (s) 199.36
B (s) 142.47
C (s) 128.35
D (s) 128.33
E (s) 125.74
F (s) 48.23
G (s) 36.93
H (s) 35.14
I (s) 32.99
J (s) 26.05
K (s) 23.37
L (s) 14.82
M (s) 10.73
0.29
0.20
0.87
1.21
0.61
0.57
0.68
0.65
0.65
0.66
0.58
0.50
0.53
Chemical Shift (ppm)

HPLC trace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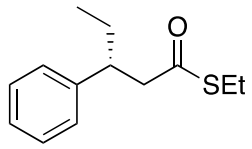
6.905
7.137
DAD1 A, Sig=210,4 Ref=off (ZHENBO\ZG775 2017-02-19 14-16-36.D)
6.972
7.002

(–)-*S*-ethyl (*R*)-3-phenylpentanethioate (3d)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. A balloon filled with ethylene was used to purge the flask with ethylene for 5 min, and then DCM (0.2 mL) was added. After stirring for 15 min under an ethylene atmosphere (balloon), a clear yellow solution was obtained. To a second, flame dried, round bottom flask was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), a balloon filled with ethylene was used to purge the flask with ethylene for 5 min, and then DCM (0.2 mL) was added. After stirring for 15 min under an ethylene atmosphere (balloon), a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-3-phenylprop-2-enethioate (38.4 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (28 mg, 0.13mmol, 63% yield).

HPLC analysis indicated an enantiomeric excess of 71 % [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.70 min; minor enantiomer, tR = 8.24 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.34 – 7.25 (m, 2H, Ar-*H*), 7.24 – 7.12 (m, 3H, Ar-*H*), 3.07 (dtd, *J* = 9.4 Hz, 7.4 Hz, 5.2 Hz, 1H, C*H*), 2.93 – 2.72 (m, 4H, SCH_2CH$_3$, CH_2COSEt), 1.90 – 1.46 (m, 2H, CH_2CH$_3$), 1.17 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3), 0.78 (t, *J* = 7.3 Hz, 3H, CH$_2$CH_3).

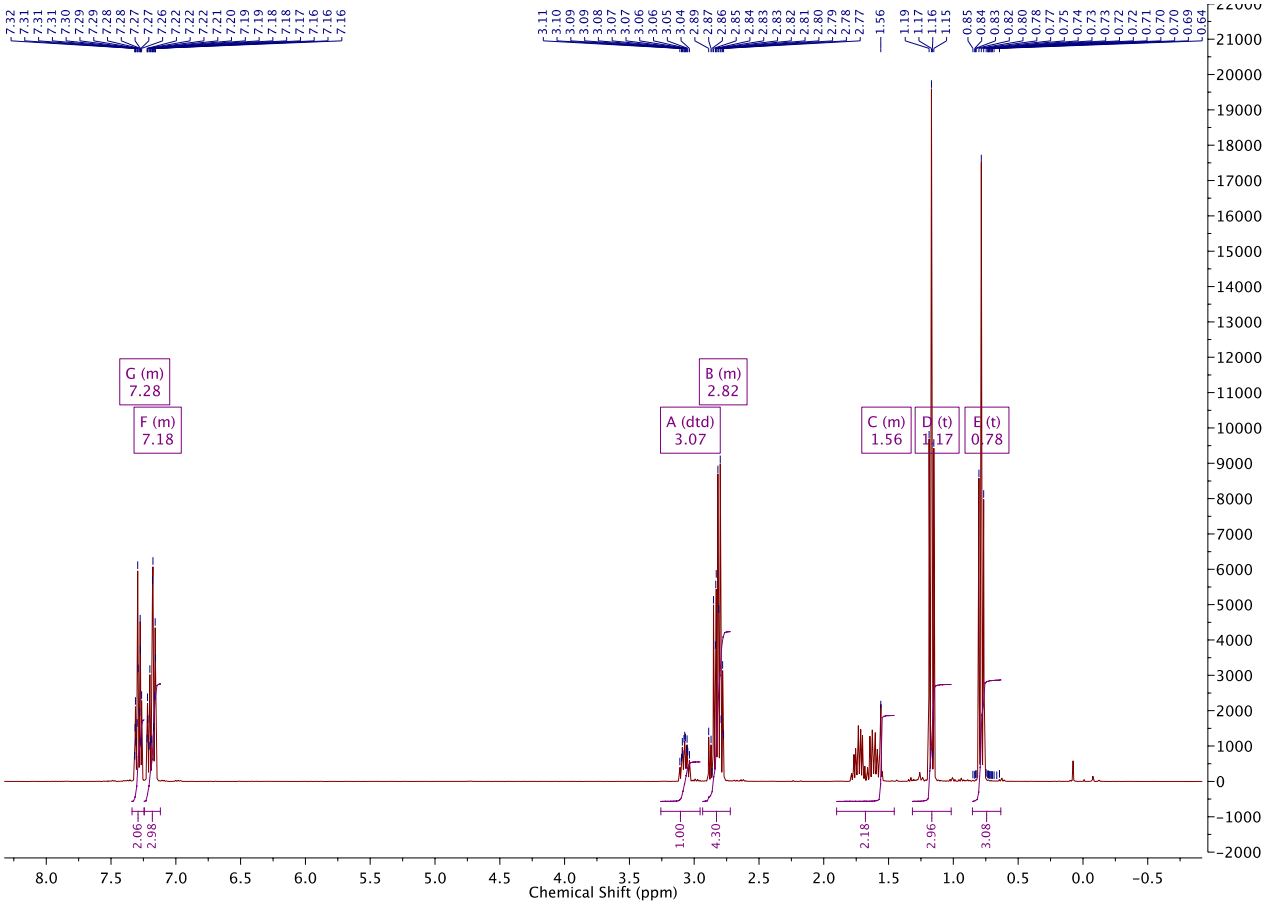
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 198.5, 143.5, 128.4(2C), 127.6(2C), 126.4, 50.8, 44.4, 28.8, 23.3, 14.7, 11.9.

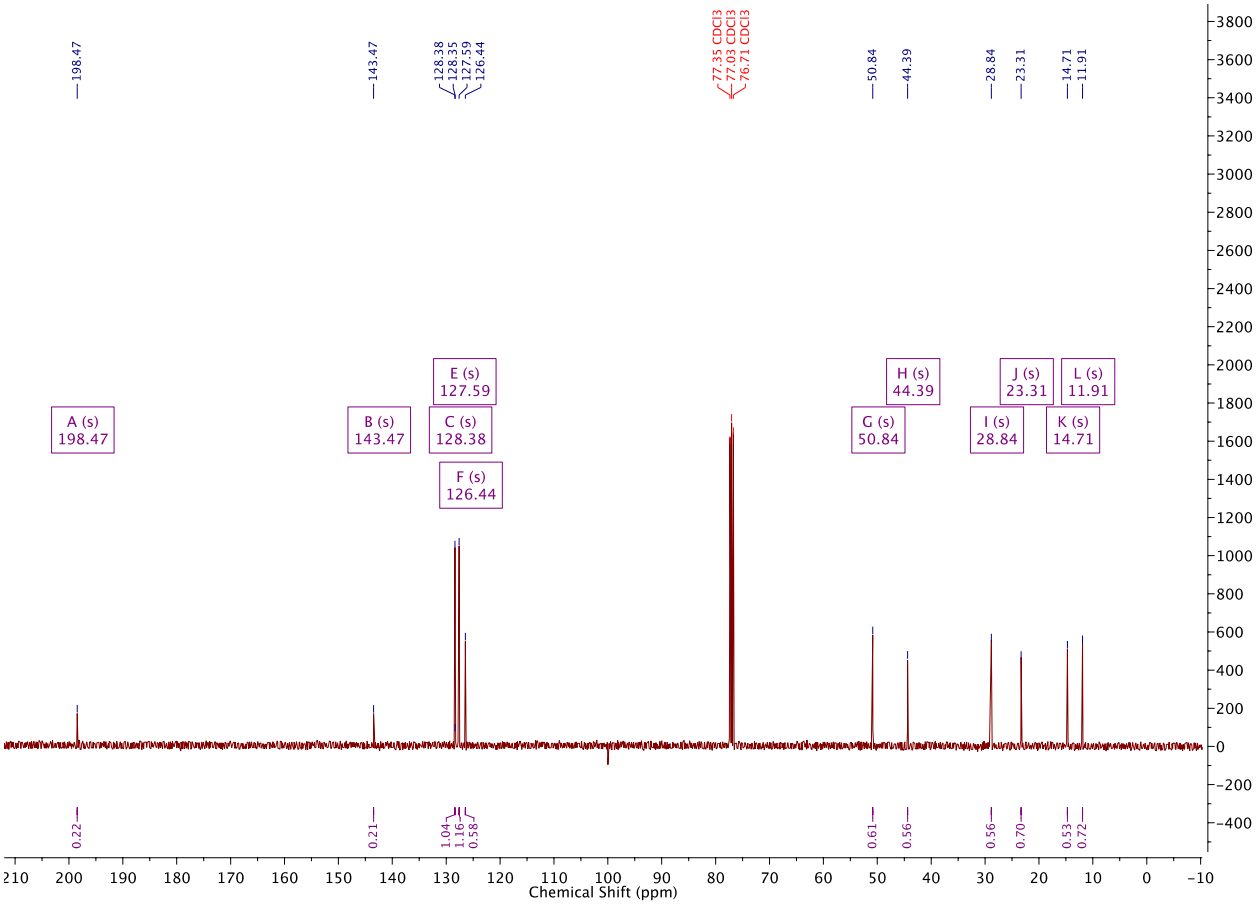
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3650, 2980,1687,1380,1153,966,700

HRMS (ESI) m/z calc. for $C_{13}H_{19}O^{32}S$ $[M+H]^+$: 223.1151 found 223.1153

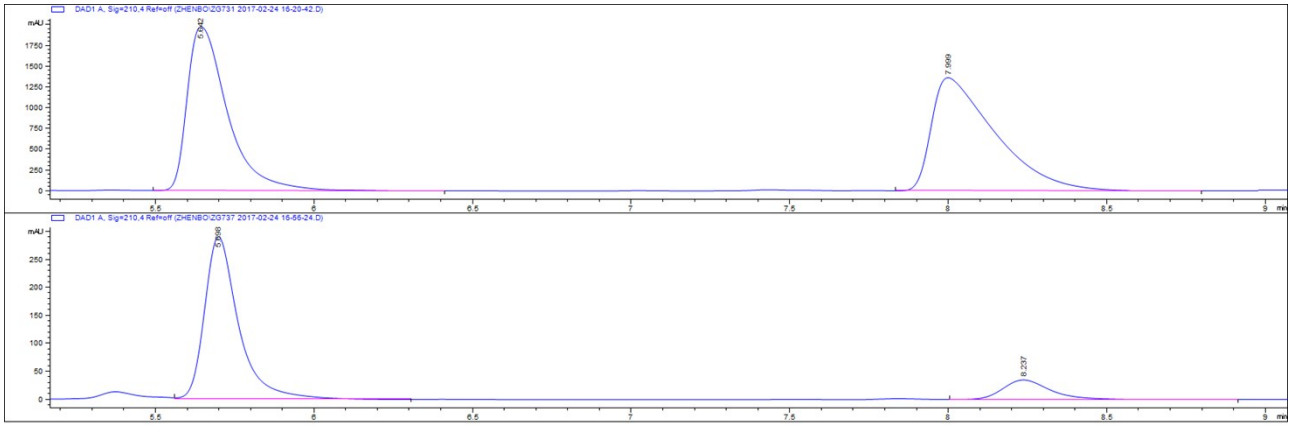
$[\alpha]^{20}_{589}$ = -25.1 ° (c 1.0, $CHCl_3$)

Absolute configuration was assigned by comparison to literature[8]optical rotation values.




198.47
143.47
128.38
128.35
127.59
126.44
77.35 CDCl3
77.03 CDCl3
76.71 CDCl3
50.84
44.39
28.84
23.31
14.71
11.91
A (s) 198.47
B (s) 143.47
C (s) 128.38
E (s) 127.59
F (s) 126.44
G (s) 50.84
H (s) 44.39
I (s) 28.84
J (s) 23.31
K (s) 14.71
L (s) 11.91
0.22
0.21
1.04
1.16
0.58
0.61
0.56
0.56
0.70
0.53
0.72
Chemical Shift (ppm)

HPLC trace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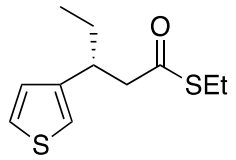
5.980
8.237

(–)-*S*-ethyl (*R*)-3-(thiophen-3-yl)pentanethioate(3e)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. A balloon filled with ethylene was used to purge the flask with ethylene for 5 min, and then DCM (0.2 mL) was added. After stirring for 15 min under an ethylene atmosphere (balloon), a clear yellow solution was obtained. To a second, flame dried, round bottom flask was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), a balloon filled with ethylene was used to purge the flask with ethylene for 5 min, and then DCM (0.2 mL) was added. After stirring for 15 min under an ethylene atmosphere (balloon), a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-3-(thiophen-3-yl) prop-2-enethioate (40.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (27 mg, 0.12mmol, 60% yield).

HPLC analysis indicated an enantiomeric excess of 66 % [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.17 min; minor enantiomer, tR = 5.94 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.37 – 7.08 (m, 1H, Ar-*H*), 7.06 – 6.77 (m, 2H, Ar-*H*), 3.23 (dtd, *J* = 8.8 Hz, 7.4 Hz, 5.2 Hz, 1H, C*H*), 2.92 – 2.66 (m, 4H, SCH_2CH$_3$, CH_2COSEt), 1.91 – 1.38 (m, 2H, CH_2CH$_3$), 1.18 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3), 0.81 (t, *J* = 7.3 Hz, 3H, CH$_2$CH_3).

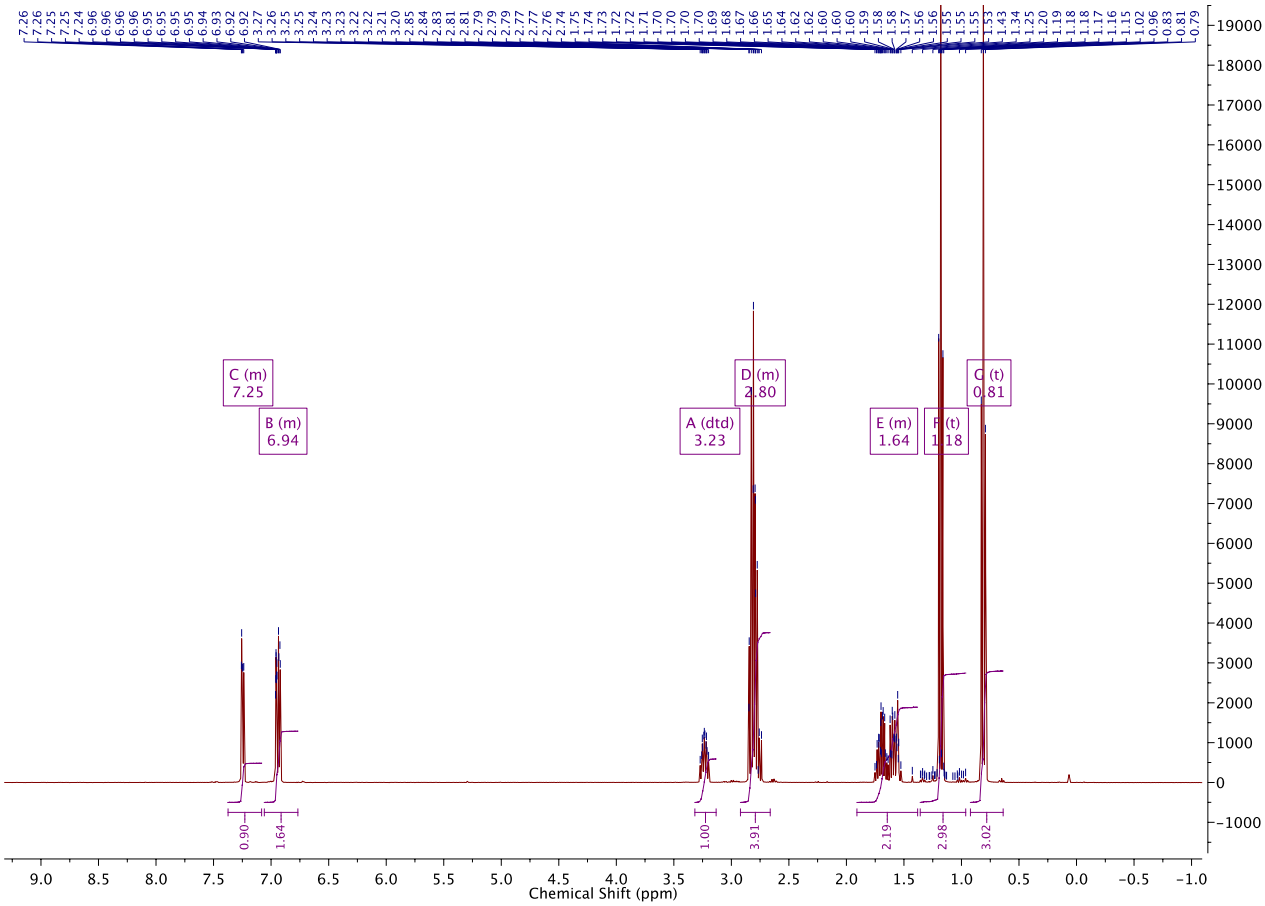
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 198.5, 144.3, 126.6, 125.5, 120.5, 50.5, 39.6, 28.70, 23.3, 14.7, 11.8.

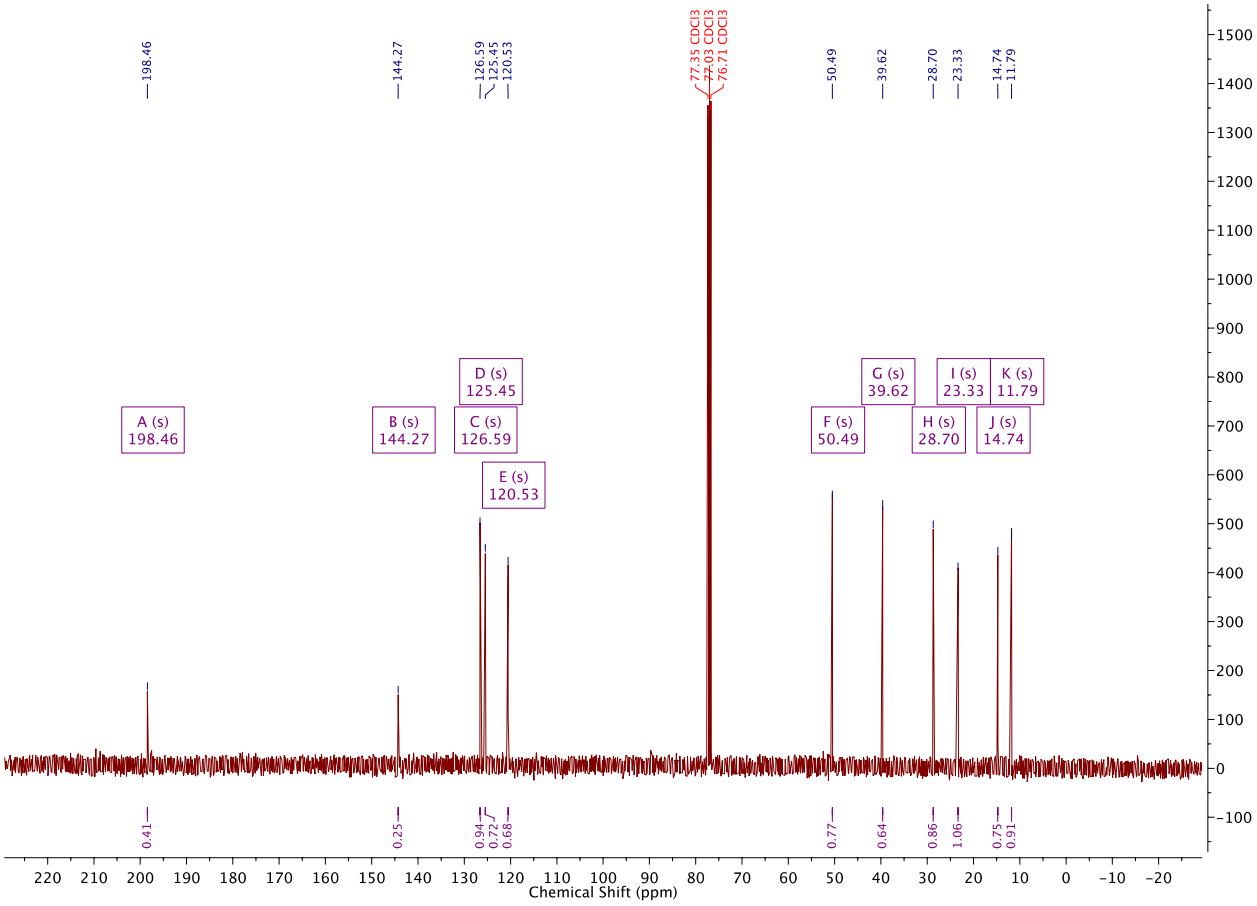
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3650, 2980,1686,1381,1153,955,774

HRMS (ESI) m/z calc. for $C_{11}H_{17}O^{32}S_2$ $[M+H]^+$: 229.0715, found 229.0716

$[\alpha]^{20}_{589}$ = -29.2 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.

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144.27
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125.45
120.53
77.35 CDCl3
77.03 CDCl3
76.71 CDCl3
50.49
39.62
28.70
23.33
14.74
11.79
A (s) 198.46
B (s) 144.27
C (s) 126.59
D (s) 125.45
E (s) 120.53
F (s) 50.49
G (s) 39.62
H (s) 28.70
I (s) 23.33
J (s) 14.74
K (s) 11.79
0.41
0.25
0.94
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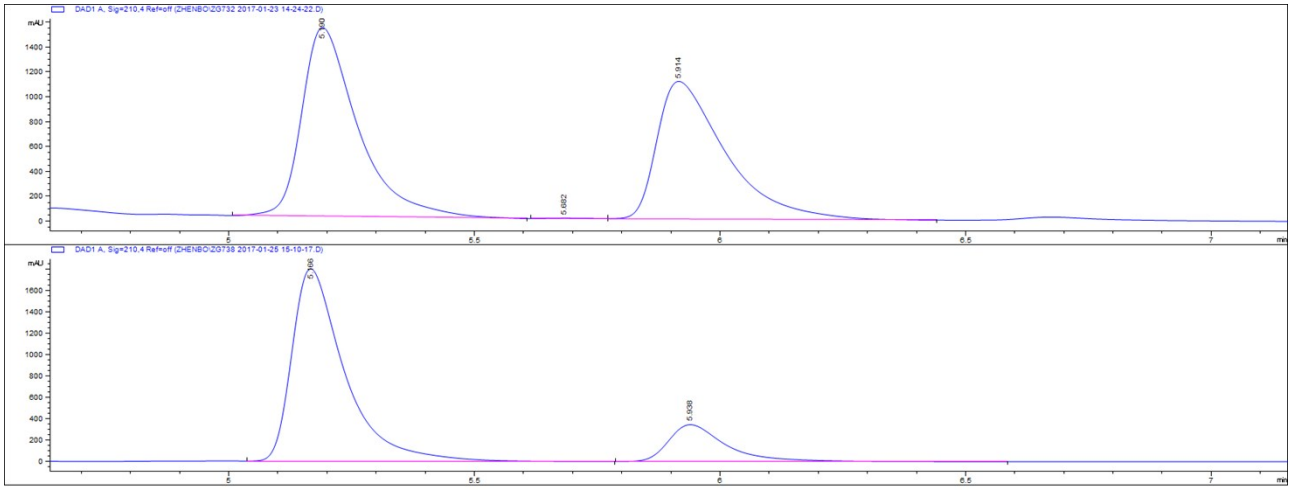
0.68
0.77
0.64
0.86
1.06
0.75
0.91
Chemical Shift (ppm)

HPLC trace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6.682
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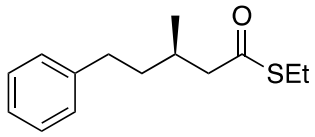
6.038

(+)-*S*-ethyl (*R*)-3-methyl-5-phenylpentanethioate (3f)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of styrene (52 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.
The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone(26.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (33 mg, 0.14mmol, 70% yield).

HPLC analysis indicated an enantiomeric excess of 97 % [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.8:0.2; λ = 210 nm; major enantiomer tR = 9.37 min; minor enantiomer, tR = 8.03 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.32 – 7.24 (m, 2H, Ar-*H*), 7.22-7.12 (m, 3H, Ar-*H*), 2.88 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.70 – 2.59 (m, 2H, C*H*$_2$Ph), 2.56 (t, *J* = 6.5 Hz, 1H, C*H*$_2$COSEt), 2.41 (dd, *J* = 14.5 Hz, 8.0 Hz, 1H, C*H*$_2$COSEt), 2.20 – 1.96 (m, 1H, C*H*), 1.67 (ddt, *J* = 13.5 Hz, 10.5, 5.9, 1H, C*H*$_2$), 1.55 – 1.39 (m, 1H, C*H*$_2$), 1.25 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$), 1.01 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$).

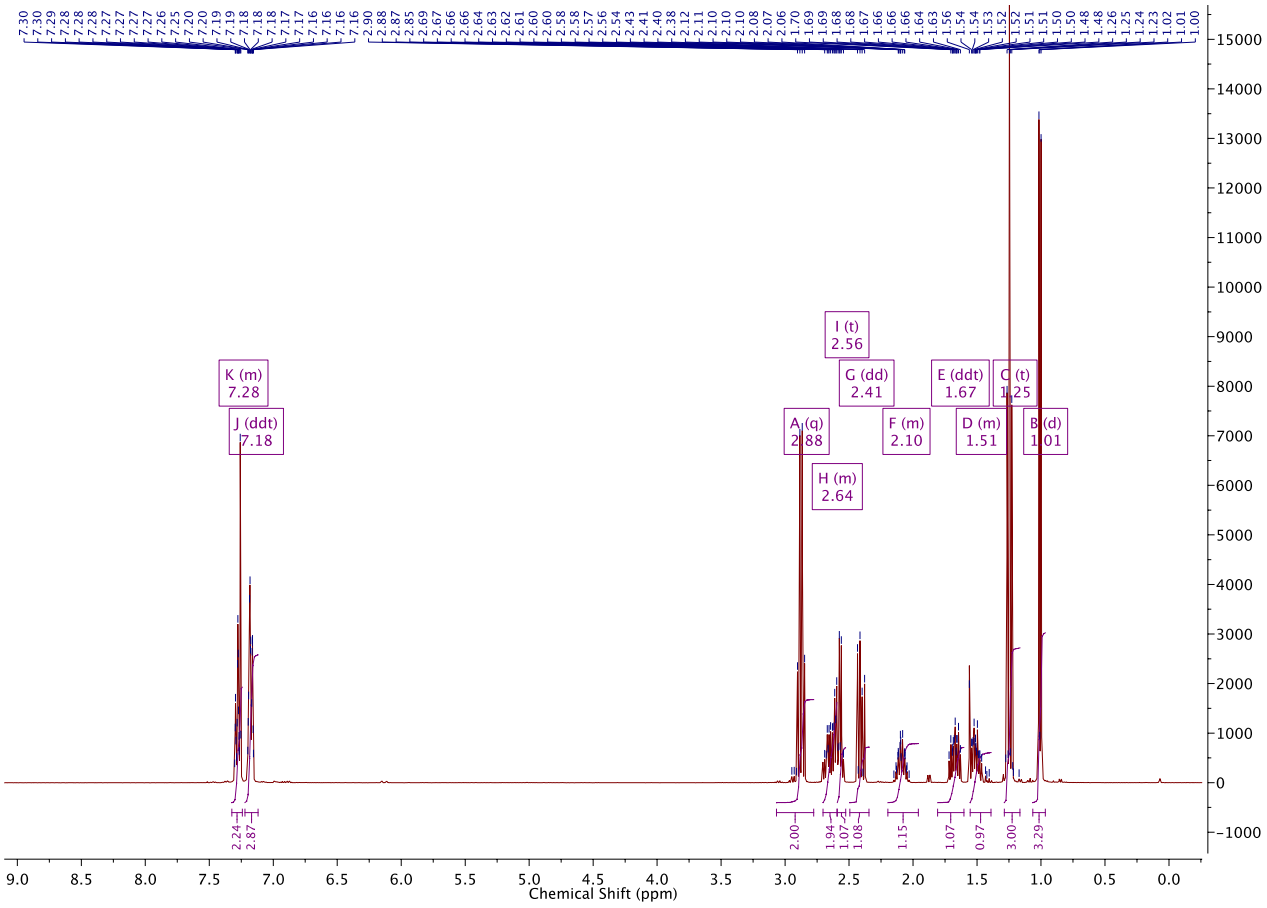
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.1, 142.3, 128.4(2C), 128.3(2C), 125.8, 51.2, 38.5, 33.3, 30.9, 23.3, 19.5, 14.8.

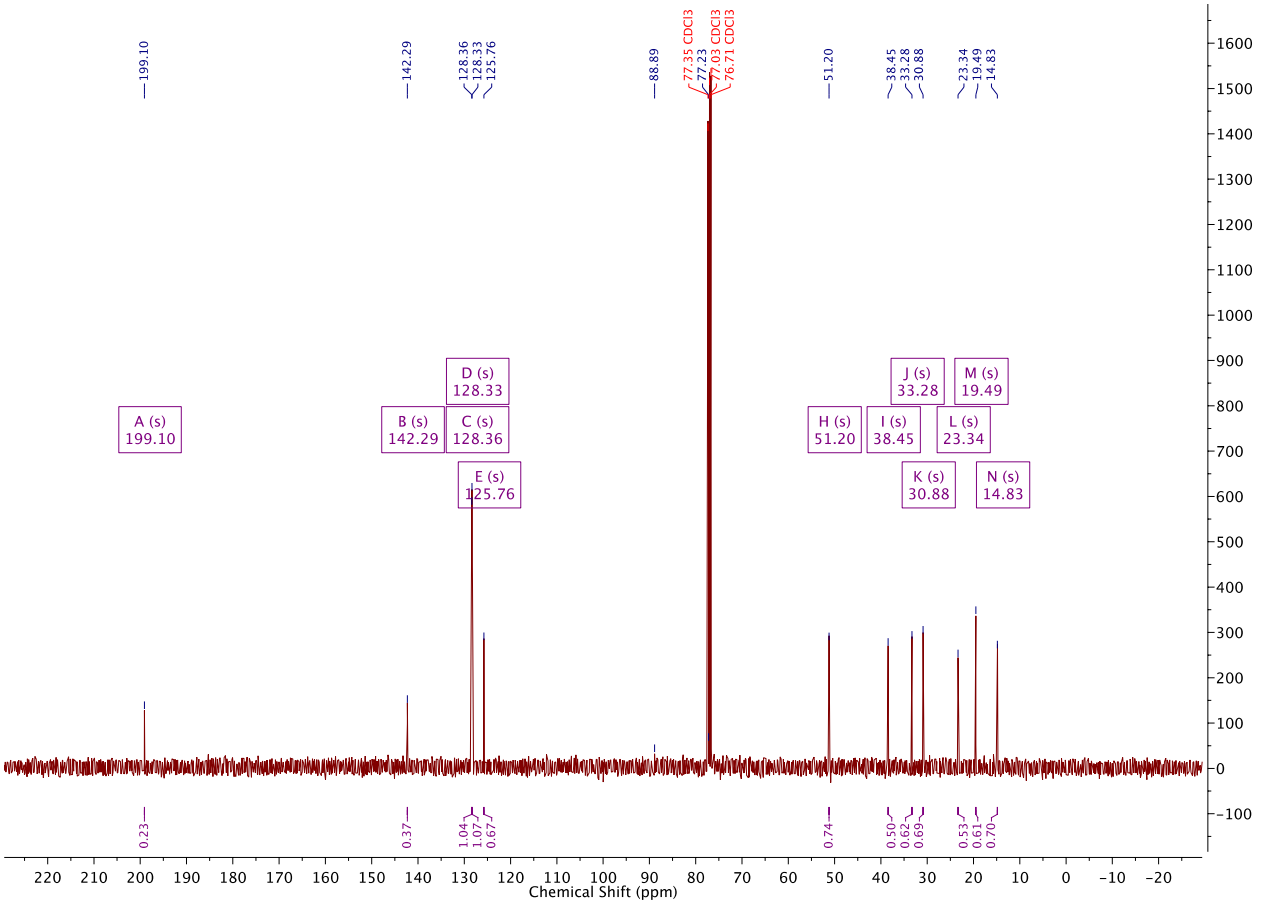
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980,1687,1382,1152,954

HRMS (ESI) m/z calc. for $C_{14}H_{21}O^{32}S$ $[M+H]^+$: 237.1308, found: 237.1309

$[\alpha]^{20}_{589}$ = +9.1 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.

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128.33
125.76
88.89
77.35 CDCl3
77.23
77.03 CDCl3
76.71 CDCl3
51.20
38.45
33.28
30.88
23.34
19.49
14.83
A (s) 199.10
B (s) 142.29
C (s) 128.36
D (s) 128.33
E (s) 125.76
H (s) 51.20
I (s) 38.45
J (s) 33.28
K (s) 30.88
L (s) 23.34
M (s) 19.49
N (s) 14.83
0.23
0.37
1.04
1.07
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0.74
0.50
0.62
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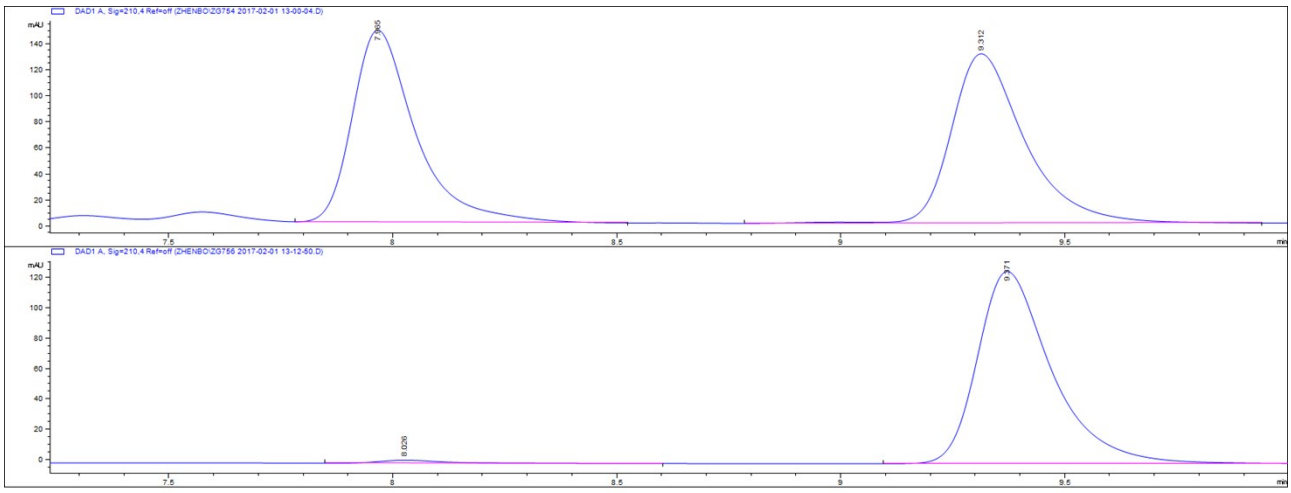
0.53
0.61
0.70
Chemical Shift (ppm)

HPLC trace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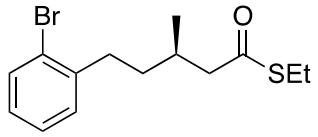
8.026
9.371

(+)-*S*-ethyl (*R*)-5-(2-bromophenyl)-3-methylpentanethioate(3g)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of 1-bromo-2-vinylbenzene (91 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone(26.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (44 mg, 0.14mmol, 70% yield).

HPLC analysis indicated an enantiomeric excess of 99 % [Chiralpak® AYH; flow: 1.0 mL/min; hexane/i-PrOH: 99.7:0.3; λ = 210 nm; major enantiomer tR = 10.10 min; minor enantiomer, tR = 8.92 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.63 – 7.44 (m, 1H, Ar-*H*), 7.24 – 7.16 (m, 2H, Ar-*H*), 7.04 (ddd, *J* = 7.9 Hz, 6.1 Hz, 2.9 Hz, 1H, Ar-*H*), 2.88 (q, *J* = 7.4 Hz, 2H, S$CH_2$$CH_3$), 2.81 – 2.65 (m, 2H, CH_2Ph), 2.62 (dd, *J* = 14.6 Hz, 6.0 Hz, 1H, CH_2COSEt), 2.43 (dd, *J* = 14.5 Hz, 8.1 Hz, 1H, CH_2COSEt), 2.13 (ddt, *J* = 14.1 Hz, 8.0 H, 6.4 Hz, 1H, C*H*), 1.64 (ddt, *J* = 13.4 Hz, 11.1 Hz, 5.6 Hz, 1H, CH_2), 1.49 (dddd, *J*=13.2 Hz, 10.9 Hz, 7.6 Hz, 5.5 Hz, 1H, CH_2), 1.24 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 1.04 (d, *J* = 6.7 Hz, 3H, $CHCH_3$).

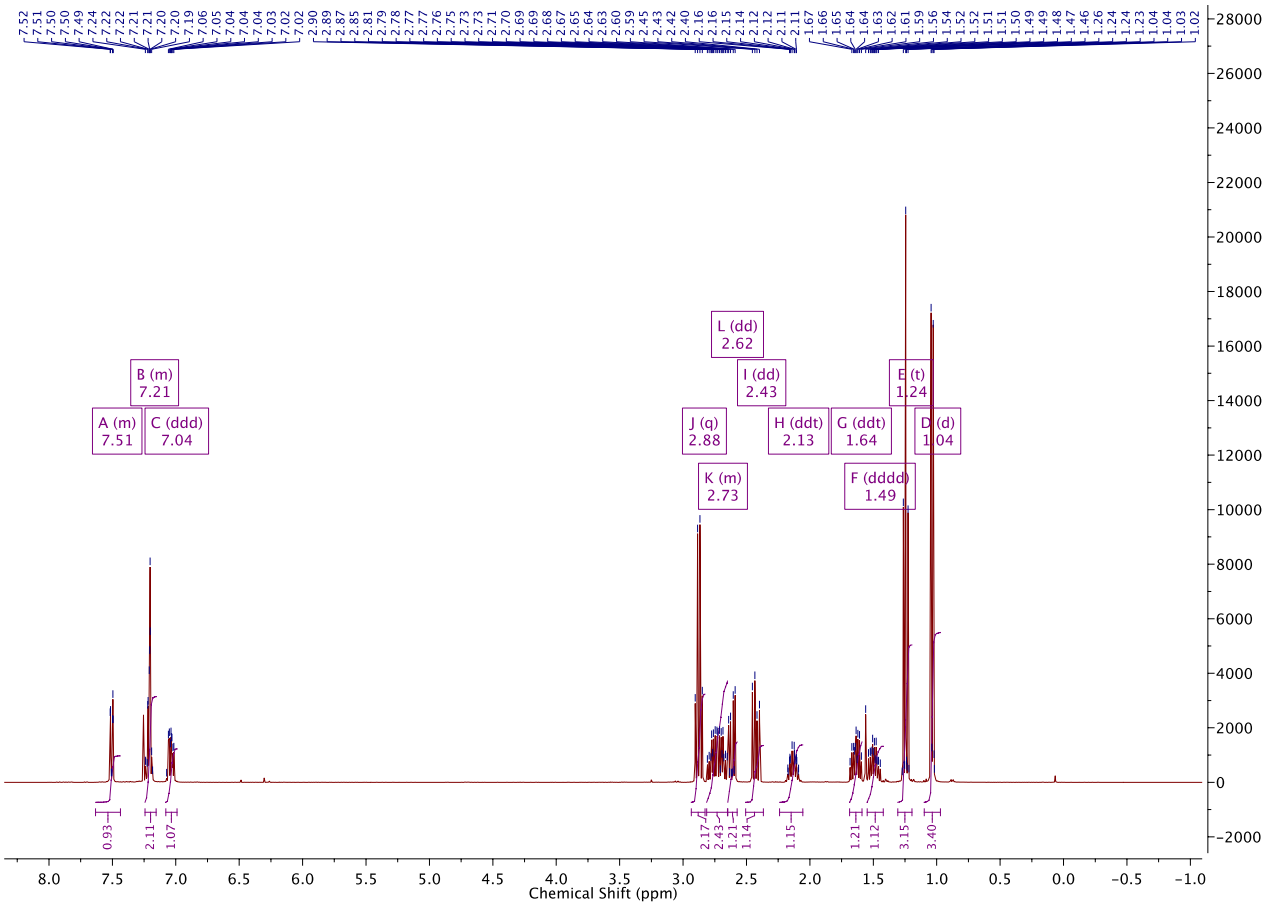
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.1, 141.6, 132.8, 130.2, 127.6, 127.5, 124.3, 51.1, 36.8, 33.7, 31.1, 23.4, 19.5, 14.8.

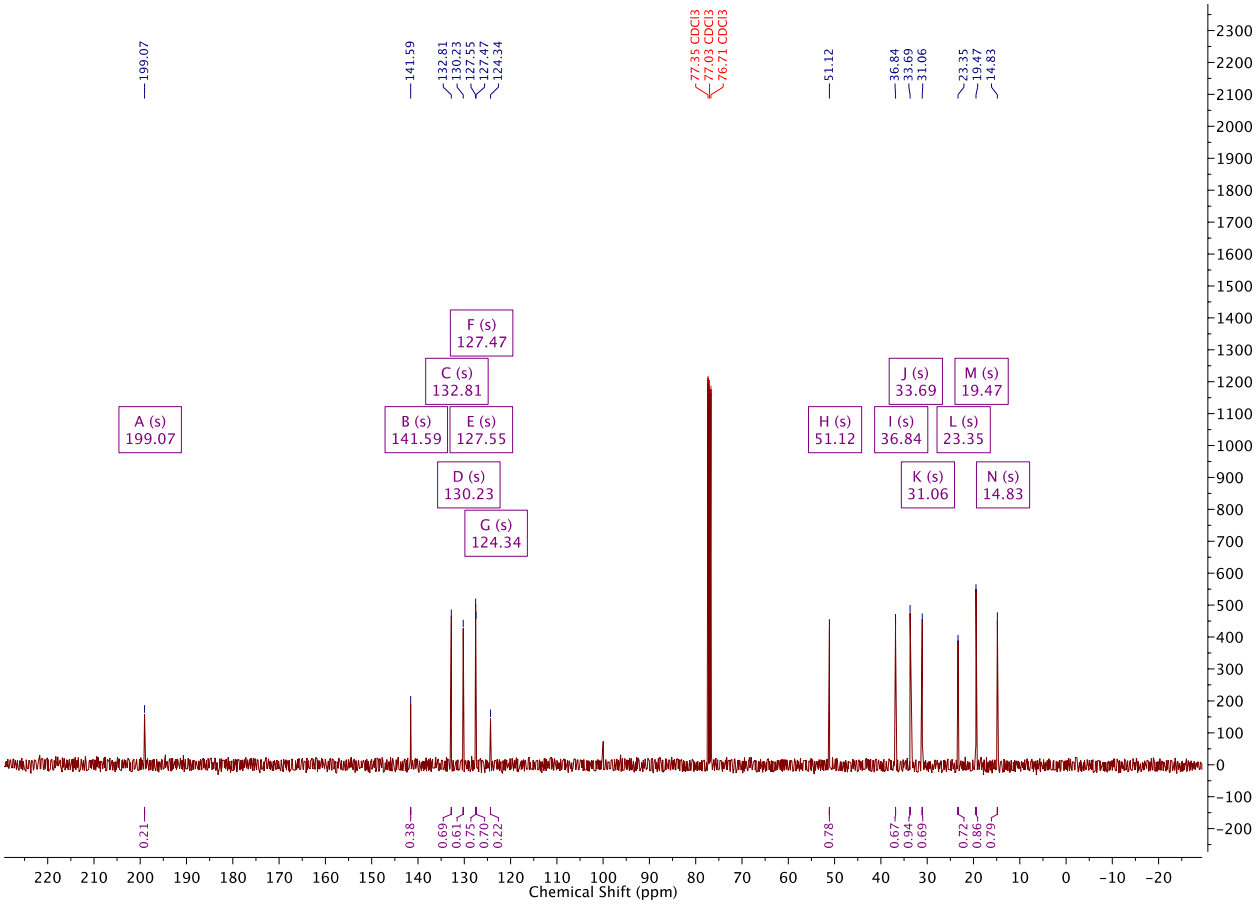
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980,1687,1382,1152,954

HRMS (ESI) m/z calc. for $C_{14}H_{20}O^{79}Br^{32}S$ $[M+H]^+$: 315.0413, 317.0392, found: 315.0415, 317.0393

$[\alpha]^{20}_{589}$ = +9.4 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.

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127.47
124.34
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77.03 CDCl3
76.71 CDCl3
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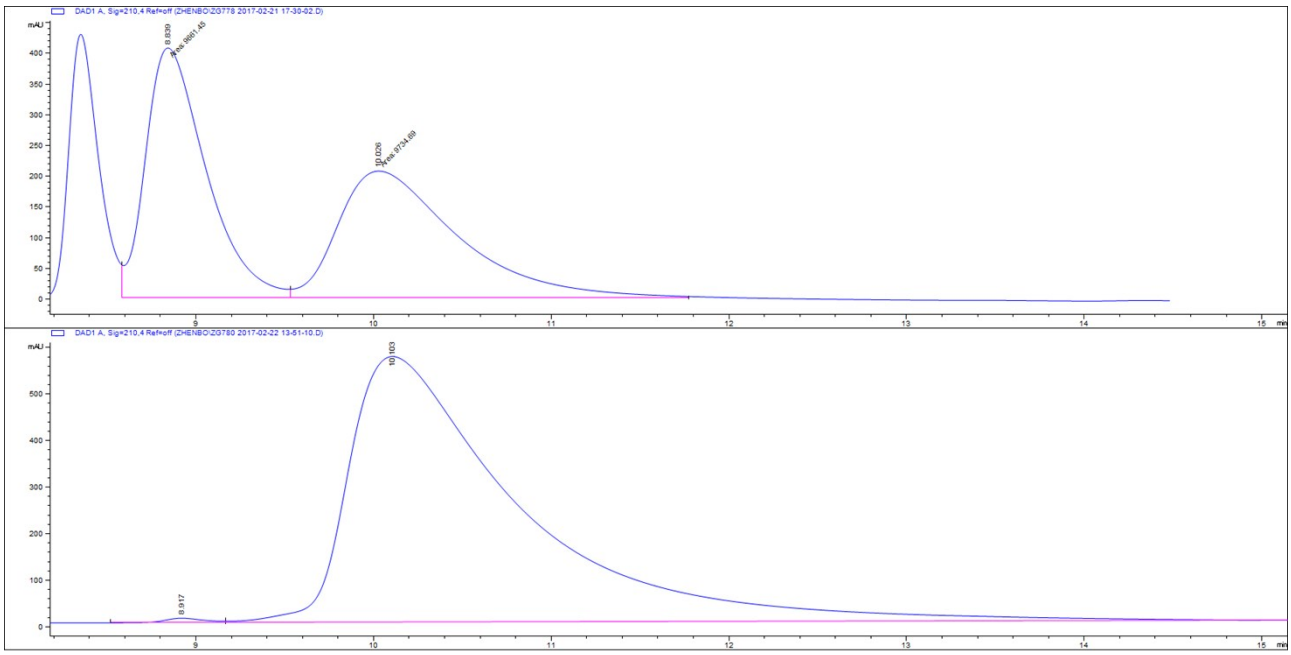
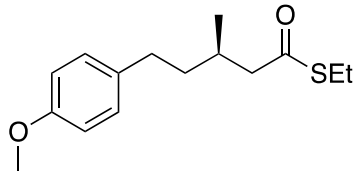
36.84
33.69
31.06
23.35
19.47
14.83
A (s) 199.07
B (s) 141.59
C (s) 132.81
D (s) 130.23
E (s) 127.55
F (s) 127.47
G (s) 124.34
H (s) 51.12
I (s) 36.84
J (s) 33.69
K (s) 31.06
L (s) 23.35
M (s) 19.47
N (s) 14.83
0.21
0.38
0.69
0.61
0.75
0.70
0.22
0.78
0.67
0.94
0.69
0.72
0.86
0.79
Chemical Shift (ppm)

HPLC trace



(+)-*S*-ethyl (*R*)-5-(4-methoxyphenyl)-3-methylpentanethioate (3h)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of 1-methoxy-4-vinylbenzene (67 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear red solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone(26.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (34 mg, 0.13mmol, 64% yield).

HPLC analysis indicated an enantiomeric excess of 97 % [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.3:0.7; λ = 210 nm; major enantiomer tR = 6.67 min; minor enantiomer, tR = 6.08 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.18 – 7.00 (m, 2H, Ar-*H*), 6.97 – 6.73 (m, 2H, Ar-*H*), 3.79 (s, 3H, OCH_3), 2.87 (q, *J* = 7.4 Hz, 2H, SCH_2CH$_3$), 2.68 – 2.46 (m, 3H, CH_2Ph, CH_2COSEt), 2.40 (dd, *J* = 14.4 Hz, 8.0 Hz, 1H, CH_2COSEt), 2.18 – 1.96 (m, 1H, C*H*), 1.80 – 1.57 (m, 1H, CH_2CH$_2$Ph), 1.47 (dddd, *J* = 13.5 Hz, 10.3Hz, 7.7 Hz, 5.8 Hz, 1H, CH_2CH$_2$Ph), 1.25 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3), 1.00 (d, *J* = 6.6 Hz, 3H, CHCH_3).

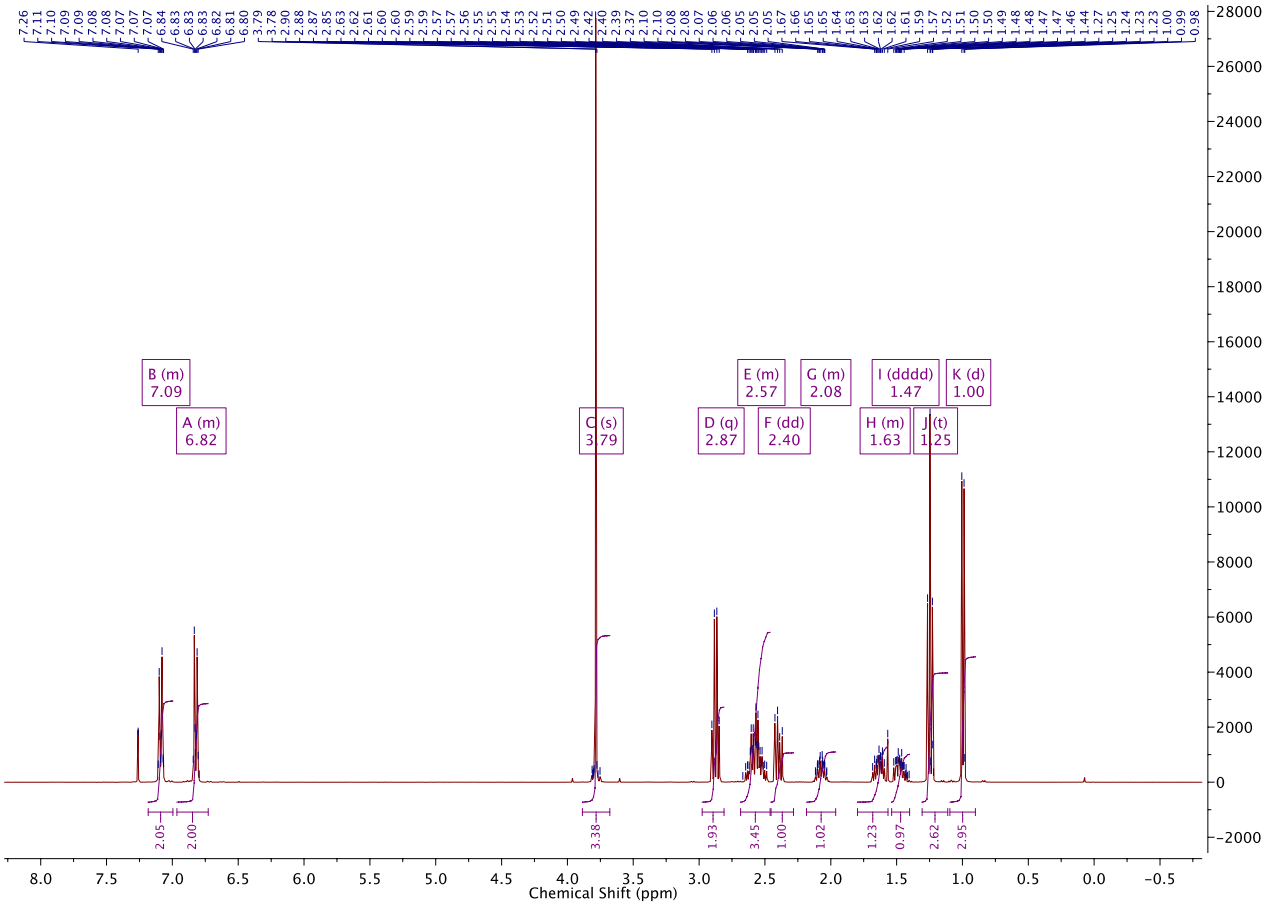
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.1, 157.7, 134.4, 129.2(2C), 113.8(2C), 55.3, 51.2, 38.7, 32.3, 30.8, 23.3, 19.5, 14.8.

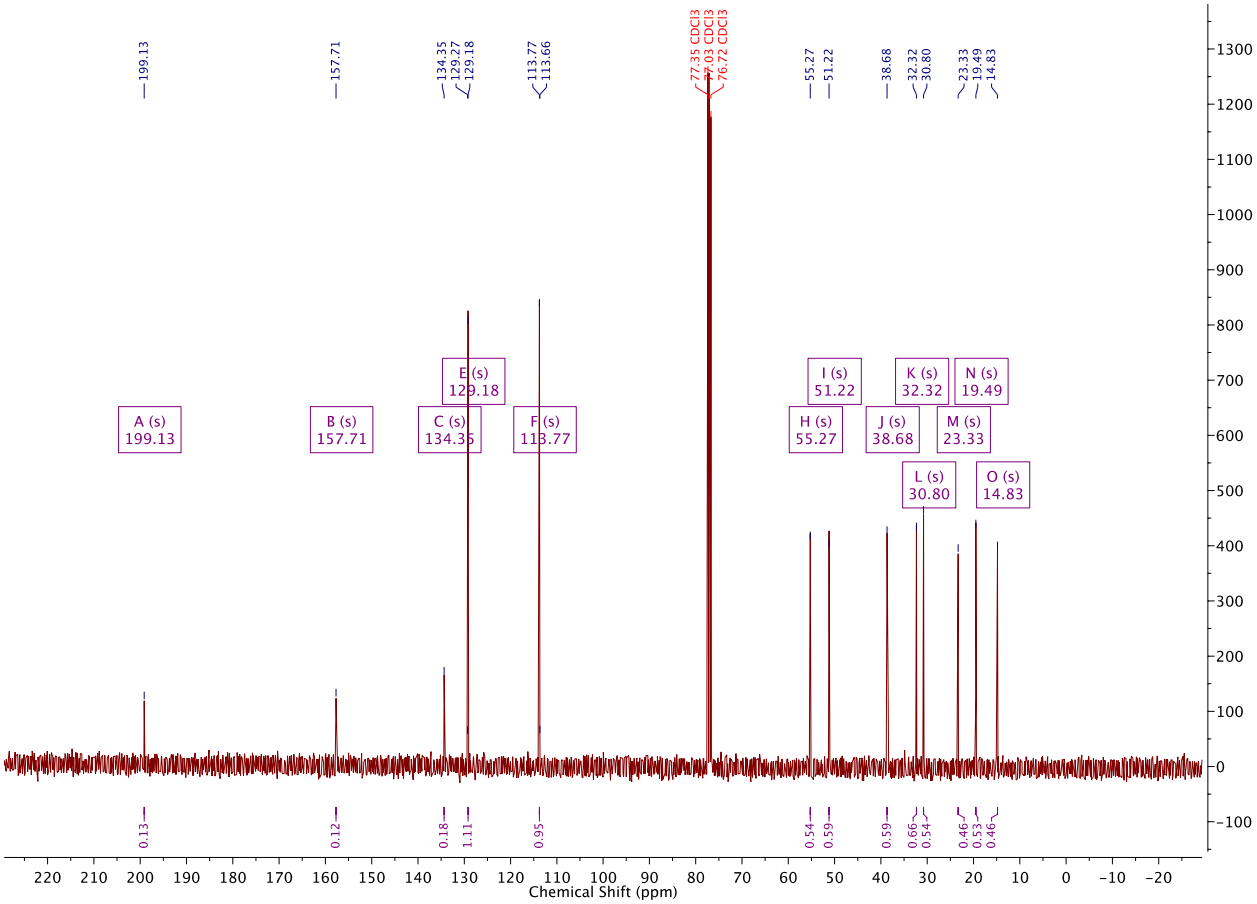
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2889,1686,1382,1248, 1152,954

HRMS (ESI) m/z calc. for $C_{15}H_{22}O_2{}^{23}Na^{32}S$ $[M+Na]^+$: 289.1233 found: 289.1233

$[\alpha]^{20}_{589}$ = +14.5 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.




199.13
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129.27
129.18
113.77
113.66
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
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51.22
38.68
32.32
30.80
23.33
19.49
14.83
A (s) 199.13
B (s) 157.71
C (s) 134.35
E (s) 129.18
F (s) 113.77
H (s) 55.27
I (s) 51.22
J (s) 38.68
K (s) 32.32
L (s) 30.80
M (s) 23.33
N (s) 19.49
O (s) 14.83
0.13
0.12
0.18
1.11
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0.59
0.59
0.66
0.54
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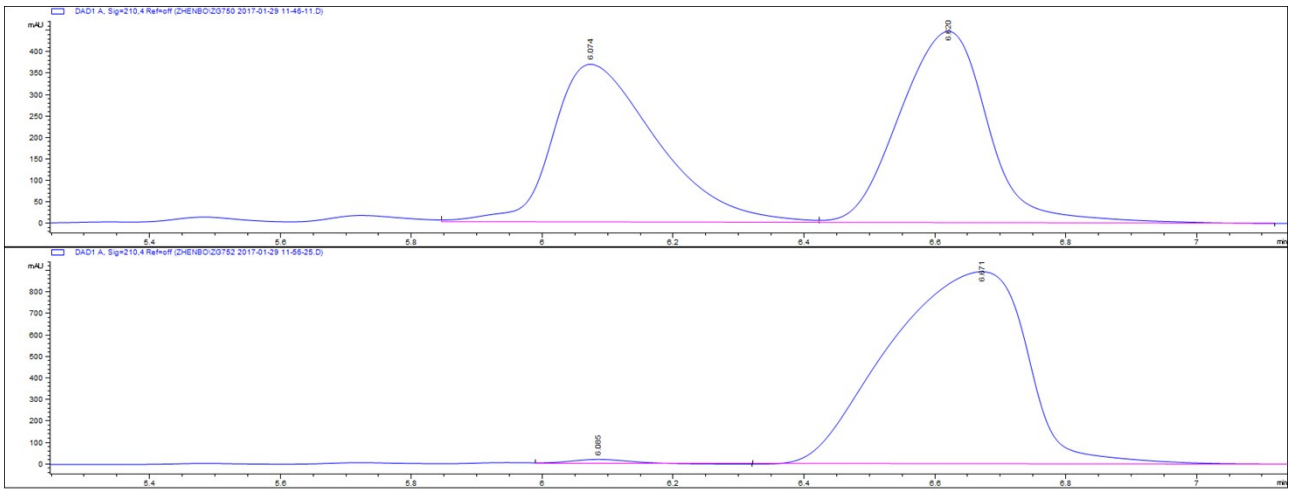
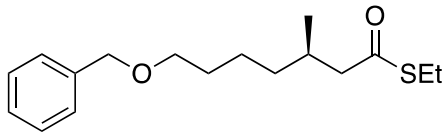
0.53
0.46
Chemical Shift (ppm)

HPLC trace



(+)-*S*-ethyl (*R*)-7-(benzyloxy)-3-methylheptanethioate(3i)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of ((but-3-en-1-yloxy) methyl) benzene (81 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear red solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone(26.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (44 mg, 0.15mmol, 75% yield).

HPLC analysis indicated an enantiomeric excess of 98 % [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 6.09 min; minor enantiomer, tR = 5.53 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.38 – 7.29 (m, 4H, Ar-*H*), 7.29 – 7.23 (m, 1H, Ar-*H*), 4.48 (s, 2H, OC*H*$_2$Ph), 3.44 (t, *J* = 6.5 Hz, 2H, C*H*$_2$OCH$_2$Ph), 2.85 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.50 (dd, *J* = 14.4 Hz, 6.0 Hz, 1H, C*H*$_2$COSEt), 2.32 (dd, *J* = 14.4 Hz, 8.1 Hz, 1H, C*H*$_2$COSEt), 2.11 – 1.93 (m, 1H, C*H*), 1.72-1.53 (m, 3H, C*H*$_2$), 1.35 (ddtd, *J* = 19.1 Hz, 12.8 Hz, 10.4 Hz, 4.9 Hz, 3H, C*H*$_2$), 1.22 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$), 0.91 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$).

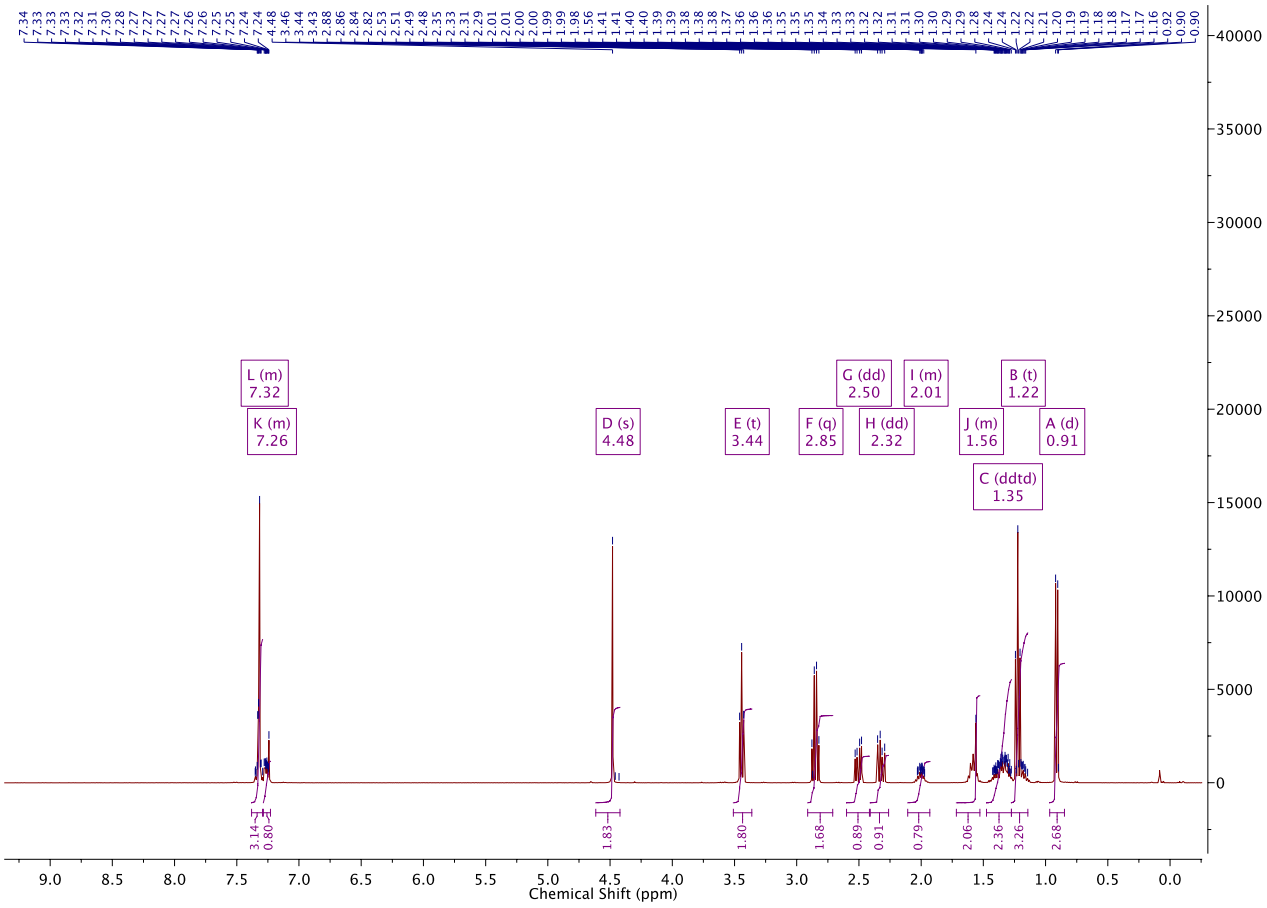
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.3, 138.6, 128.4(2C), 127.6(2C), 127.5, 72.9, 70.2, 51.4, 36.4, 31.1, 29.8, 23.5, 23.3, 19.5, 14.8.

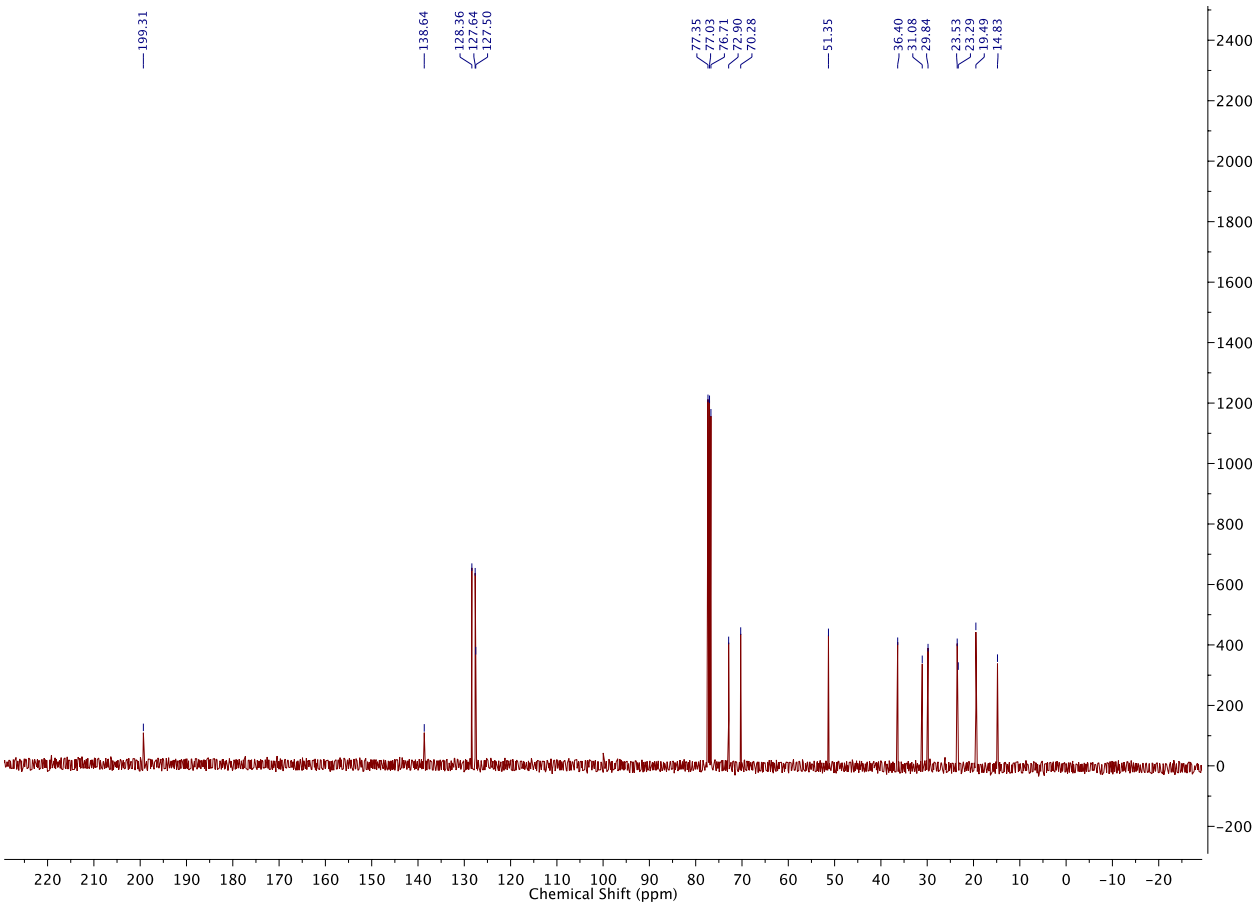
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980,1687,1382,1251,1152,954,772

HRMS (ESI) m/z calc. for $C_{17}H_{27}O_2{}^{32}S$ $[M+H]^+$: 295.1726, found: 295.1727

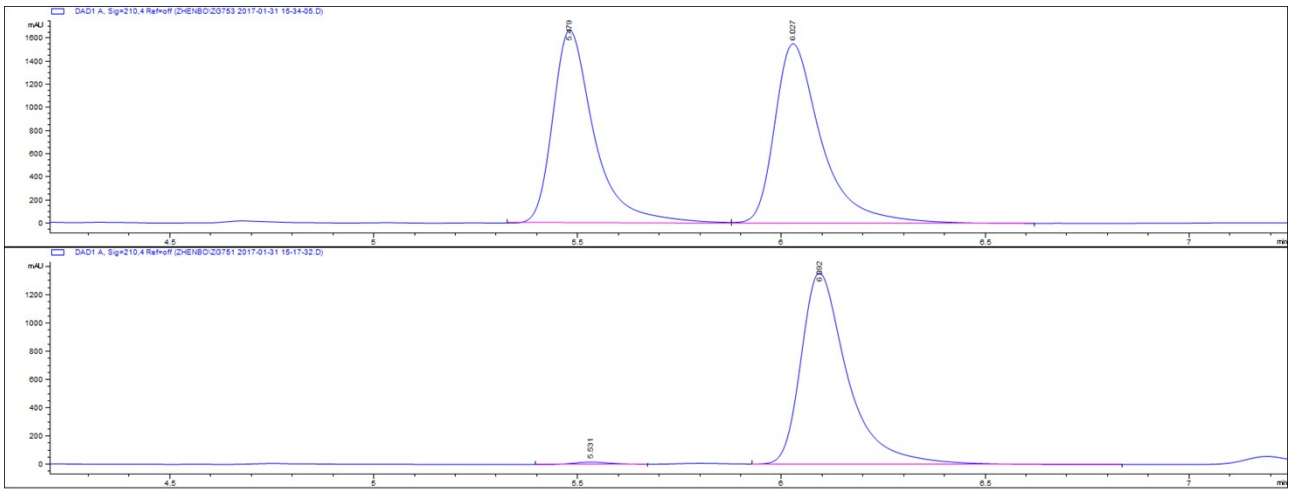
$[\alpha]^{20}_{589}$ = +14.6 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.





HPLC trace



Large-scale reactions

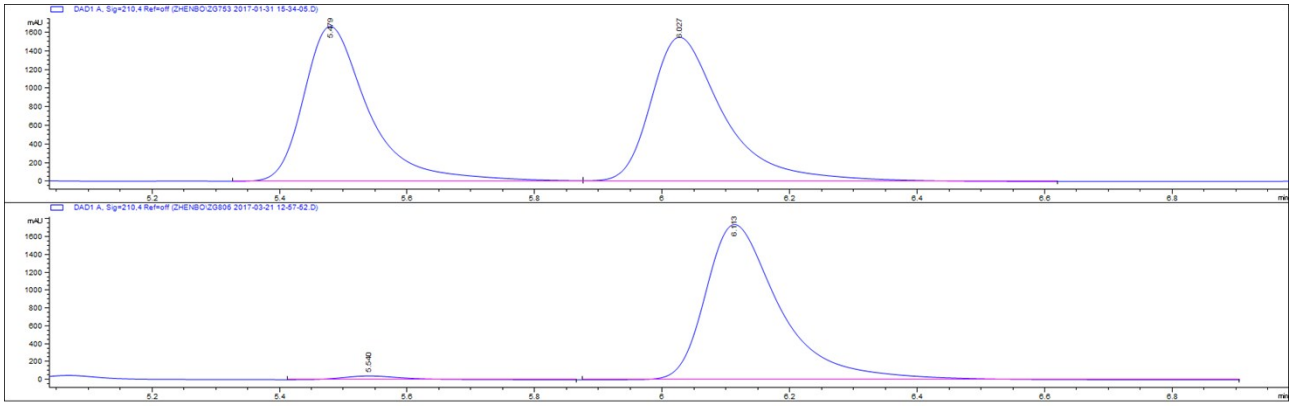
CuCl (50.0 mg, 0.5 mmol, 0.1 eq.), and the phosphoramidite ligand (280 mg, 0.5 mmol 0.1 eq.) were added to a flame dried round bottom flask containing 20 ml DCM/Et_2O (1/1) under

argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (140 mg, 0.55mmol, 0.11 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of ((but-3-en-1-yloxy)methyl)benzene (2.02 g, 12.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (2.58 g, 10 mmol, 2.0 eq.), and after stirring for 15 min, a clear red solution was obtained.

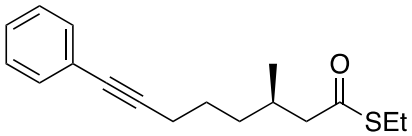
The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone(0.75 ml, 5.0 mmol, 1.0 eq.) and TMSCl (3.2 ml, 25mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (10 ml sat. aq.) and then Et_2O (10 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (1.04 g, 3.5 mmol, 70% yield).

HPLC analysis indicated an enantiomeric excess of 96 % [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 6.11 min; minor enantiomer, tR = 5.54 min].

HPLC trace



(+)-*S*-ethyl (*R*)-3-methyl-8-phenyloct-7-ynethioate (3j)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of pent-4-en-1-yn-1-ylbenzene (71 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear red solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before enone (26.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow

residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (40 mg, 0.15mmol, 73% yield).

HPLC analysis indicated an enantiomeric excess of 93 % [Chiralpak® ID; flow: 1.2 mL/min; hexane/i-PrOH: 99.8:0.2; λ = 210 nm; major enantiomer tR = 10.12 min; minor enantiomer, tR = 12.12 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.55 – 7.47 (m, 2H, Ar-*H*), 7.44 – 7.36 (m, 3H, Ar-*H*), 2.99 (q, *J* = 7.5 Hz, 2H, SC*H*$_2$CH$_3$), 2.84 – 2.61 (m, 1H, C*H*$_2$COSEt), 2.61 – 2.44 (m, 3H, C*H*$_2$COSEt, C*H*$_2$CCPh), 2.31 – 2.09 (m, 1H,C*H*), 1.88 – 1.42 (m, 4H), 1.36 (t, 3H, SCH$_2$C*H*$_3$), 1.09 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$).

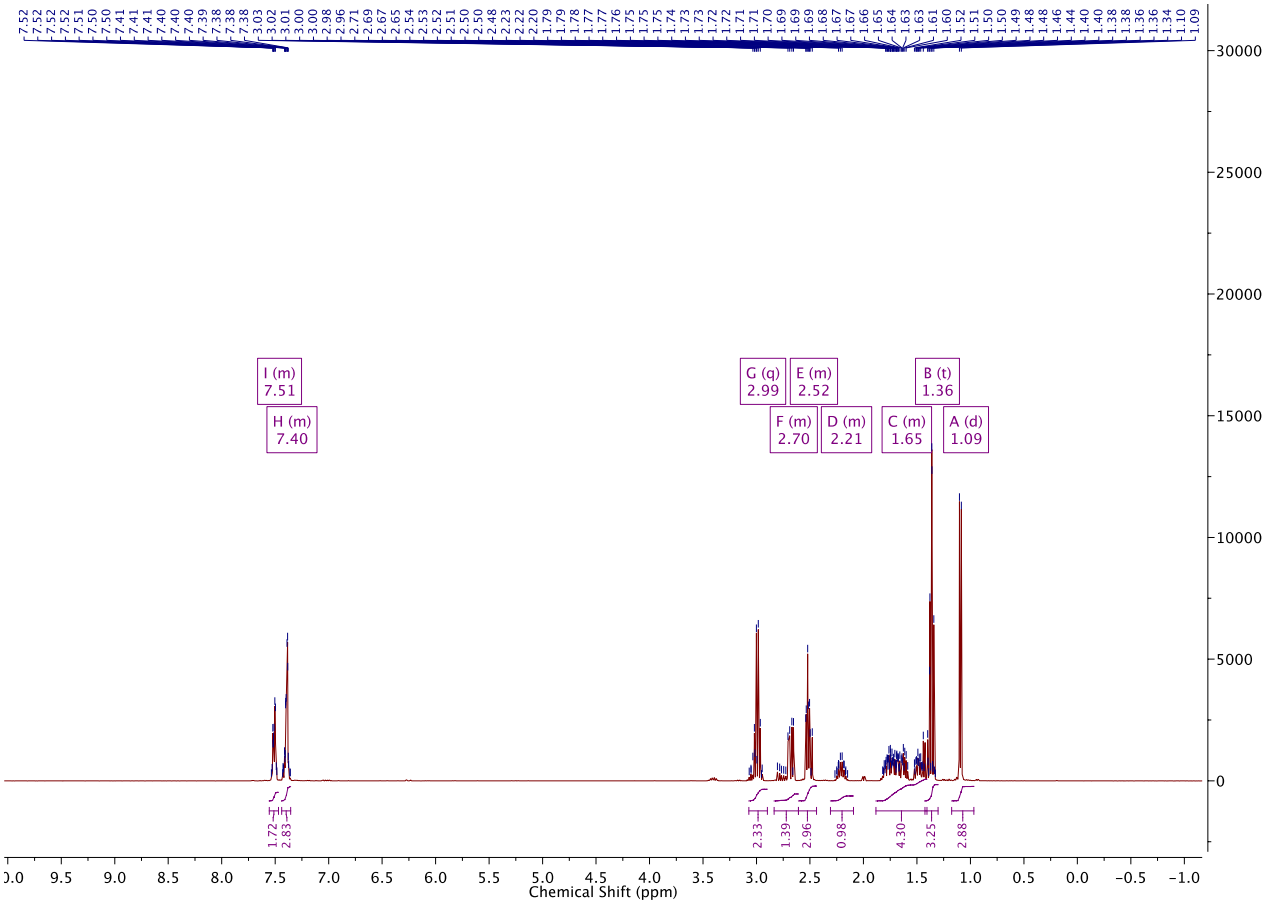
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.2, 131.5, 128.2, 127.5(2C), 124.0, 100.00, 90.0, 80.8, 51.3, 35.8, 30.8, 26.2, 23.3, 19.5, 19.5, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3690, 2930,1687,1633,1490,1391,1218,1017,941,771

HRMS (ESI) m/z calc. for $C_{17}H_{23}O^{32}S$ $[M+H]^+$: 275.1464, found: 275.1465

$[\alpha]^{20}_{589}$ = +8.8 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.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F (m)
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B (t)
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C (m)
1.65
A (d)
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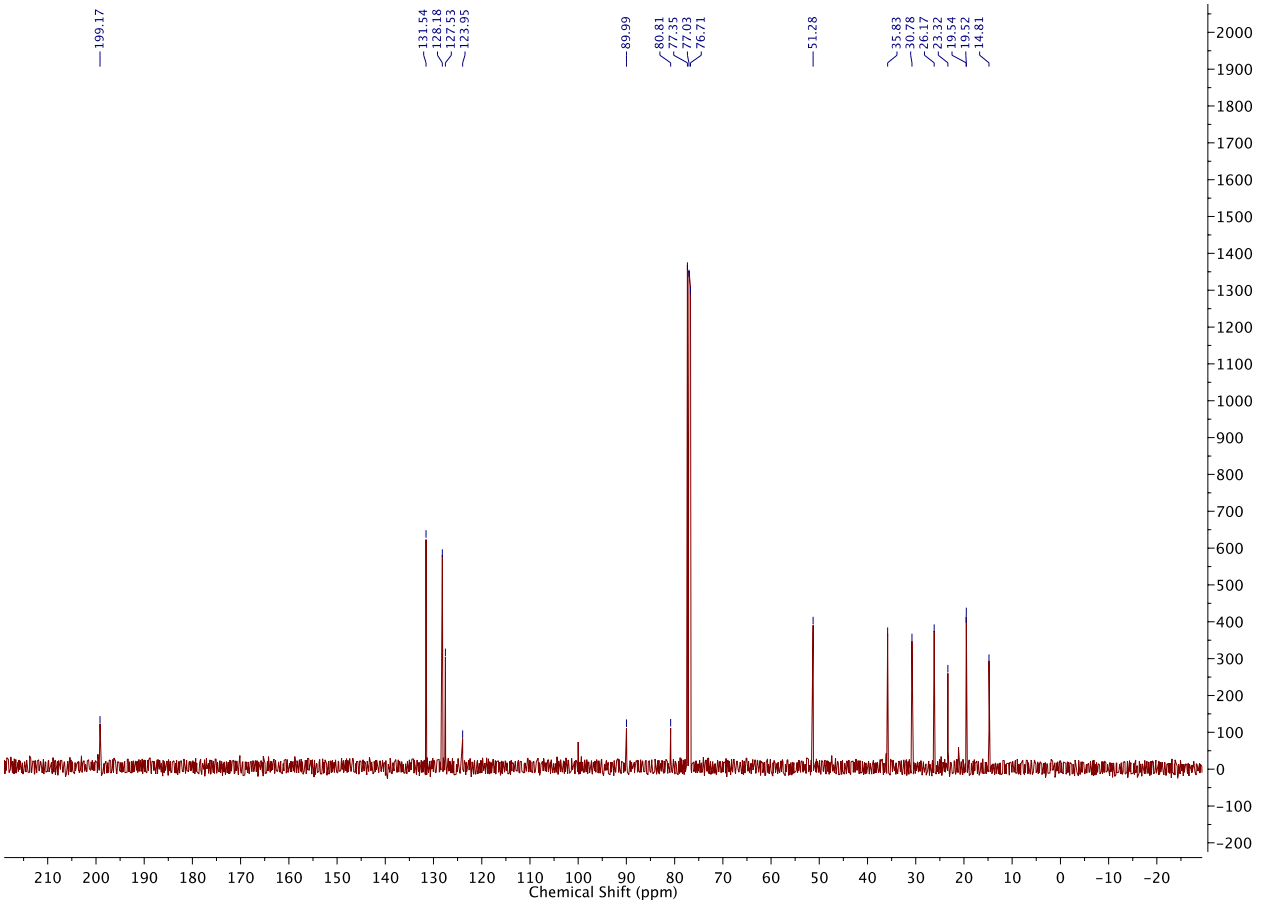
Chemical Shift (ppm)


199.17
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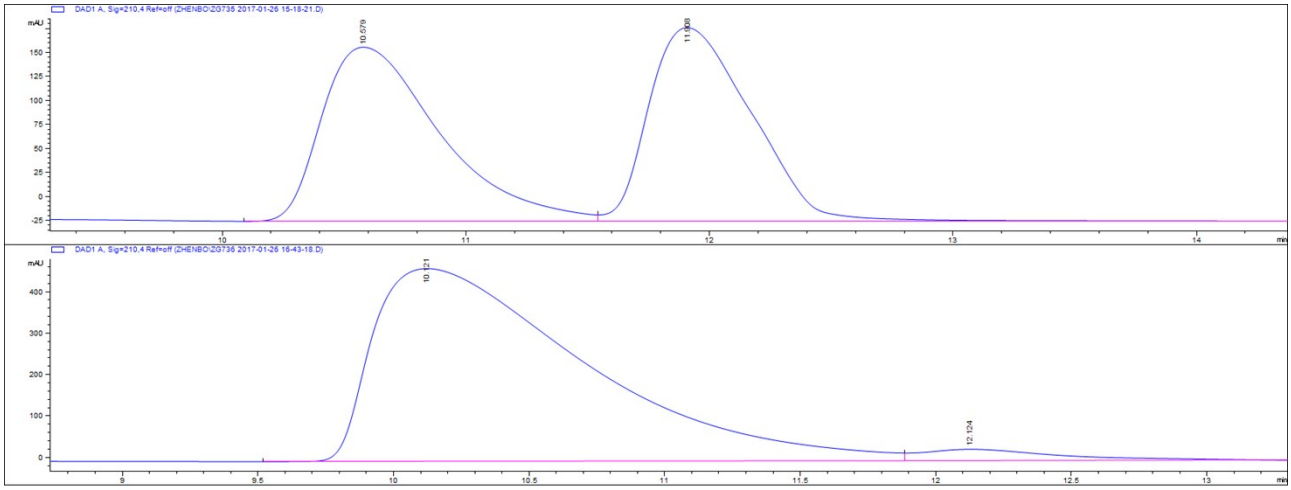
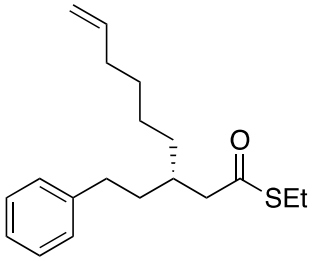
30.78
26.17
23.32
19.54
19.52
14.81
Chemical Shift (ppm)

HPLC trace



(–)-*S*-ethyl (*S*)-3-phenethylnon-8-enethioate (3k)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of hexa-1, 5-diene (41 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-5-phenylpent-2-enethioate (44.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the

reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (39 mg, 0.13mmol, 64% yield).

HPLC analysis indicated an enantiomeric excess of 92 % [Chiralpak® IB; flow: 1.0 mL/min; hexane: ipa 99.5:0.5; λ = 210 nm; major enantiomer tR = 6.17 min; minor enantiomer, tR = 6.93 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.34 – 7.23 (m, 2H, Ar-*H*), 7.19 (tq, *J* = 4.4 Hz, 1.5 Hz, 3H, Ar-*H*), 5.81 (ddt, *J* = 16.9 Hz, 10.2 Hz, 6.7 Hz, 1H,C*H*=CH_2), 5.09 – 4.82 (m, 2H, CH=CH_2), 2.89 (q, *J* = 7.4 Hz, 2H, SC$H_2$$CH_3$), 2.65 – 2.58 (m, 2H, C$H_2$Ph), 2.57 – 2.53 (m, 2H, CH_2COSEt), 2.22 – 1.94 (m, 3H, CH_2CH=CH_2, C*H*), 1.72 – 1.58 (m, 2H, CH_2), 1.48 – 1.27 (m, 6H, CH_2), 1.26 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3).

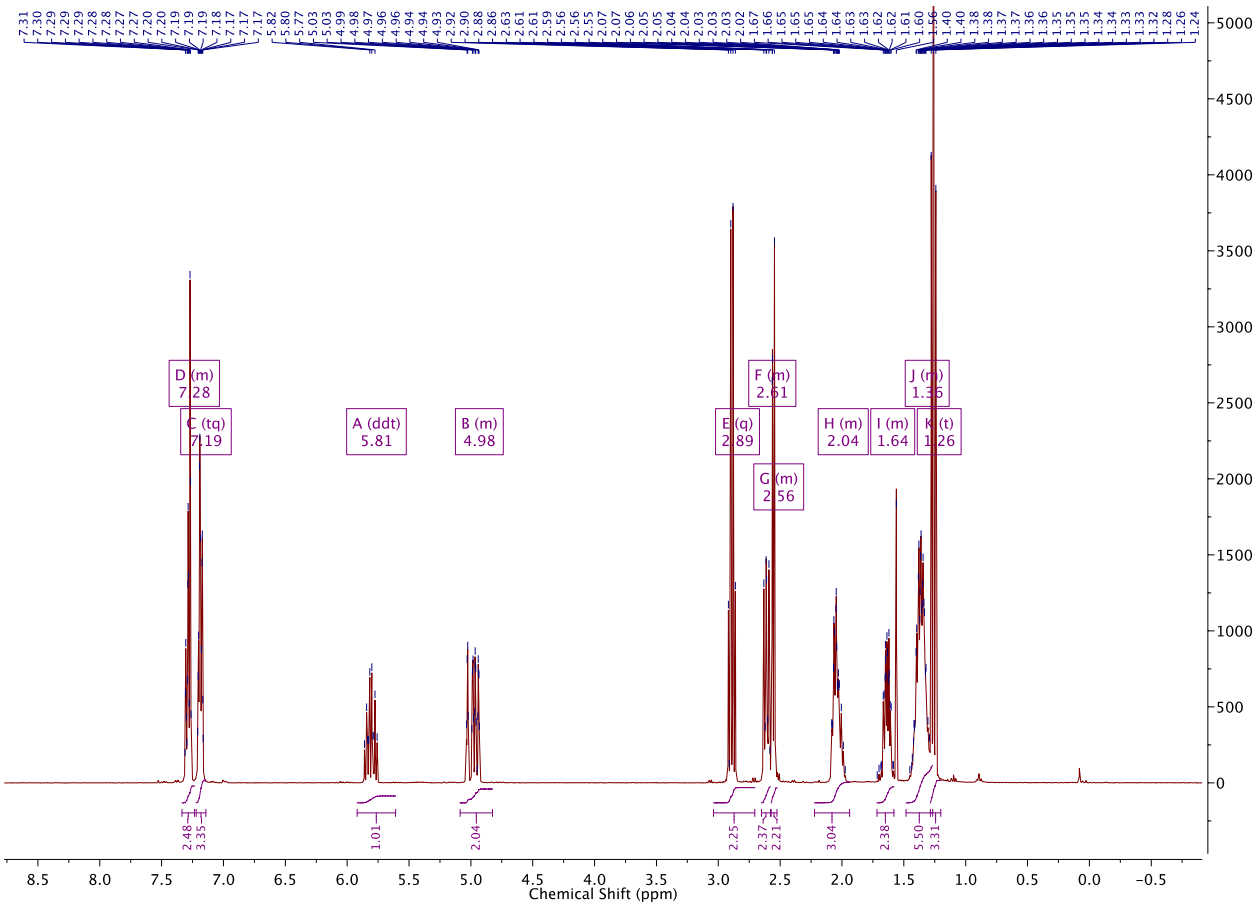
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.3, 142.4, 138.9, 128.4(2C), 128.3(2C), 125.8, 114.4, 48.6, 35.6, 35.5, 33.5, 33.4, 33.0, 29.0, 25.9, 23.4, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980,1687,1382,1152,1072,955

HRMS (ESI) m/z calc. for $C_{19}H_{28}O^{23}Na^{32}S$ $[M+Na]^+$: 327.1753, found 327.1752

$[\alpha]^{20}_{589}$ = -2.9 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.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A (ddt)
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B (m)
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E (q)
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F (m)
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G (m)
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2.04
I (m)
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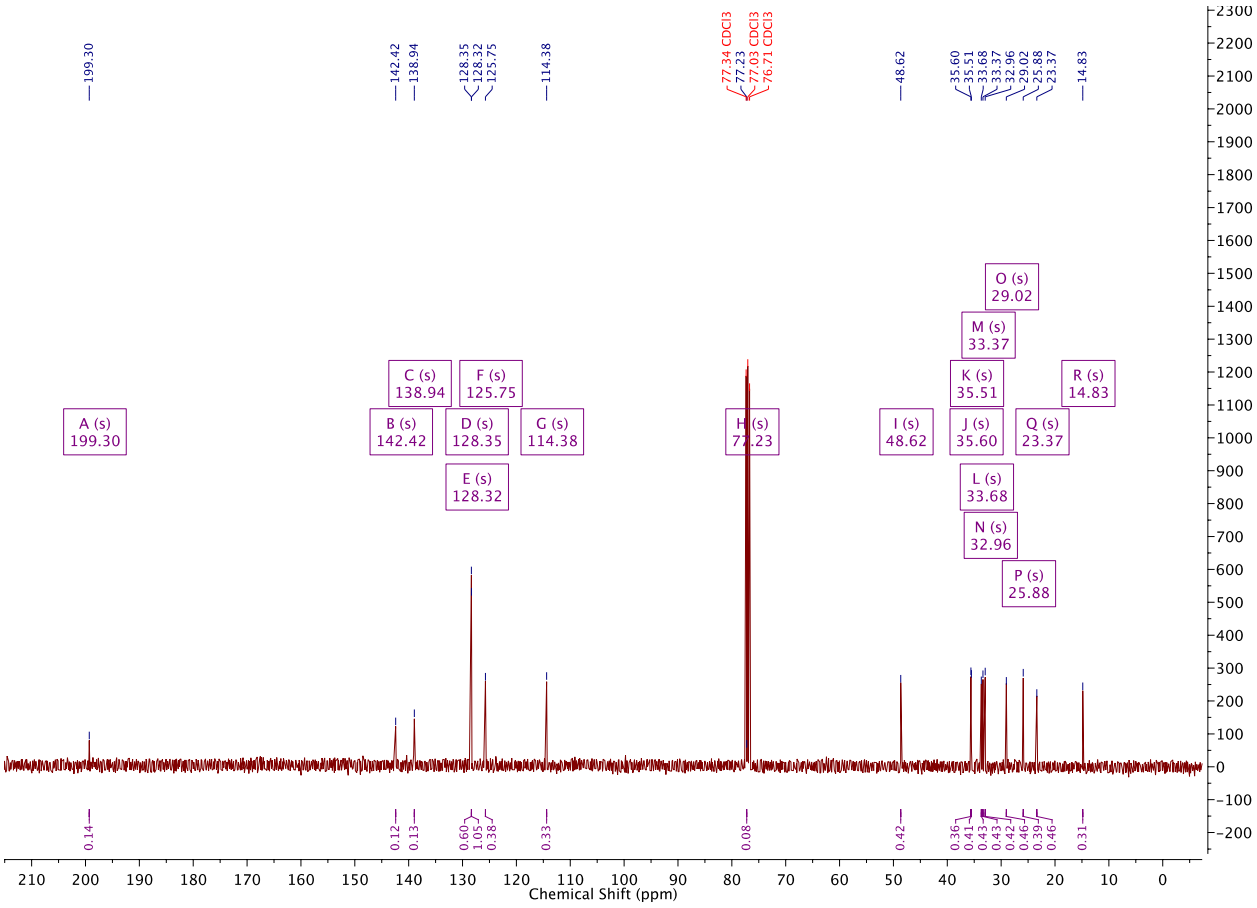
J (m)
1.35
K (t)
1.26
Chemical Shift (ppm)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C (s)
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D (s)
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E (s)
128.32
F (s)
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G (s)
114.38
H (s)
77.23
I (s)
48.62
J (s)
35.60
K (s)
35.51
L (s)
33.68
M (s)
33.37
N (s)
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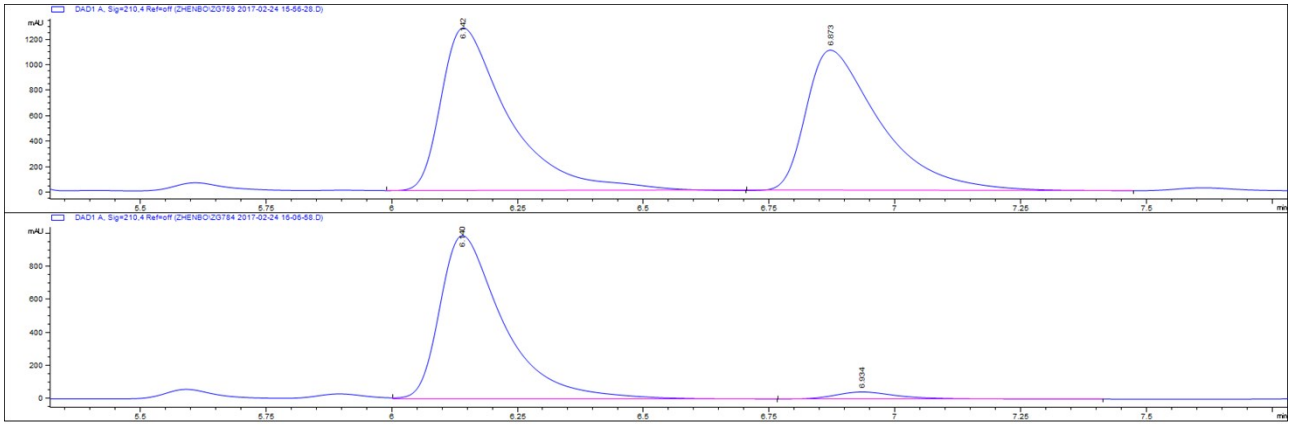
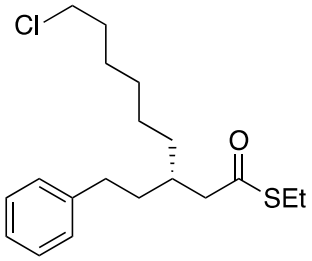
O (s)
29.02
P (s)
25.88
Q (s)
23.37
R (s)
14.83
Chemical Shift (ppm)

HPLC trace



(–)-*S*-ethyl (*S*)-9-chloro-3-phenethylnonanethioate (3l)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of 6-chlorohex-1-ene (59 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained. The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-5-phenylpent-2-enethioate (44.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the

reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (42 mg, 0.12mmol, 62% yield).

HPLC analysis indicated an enantiomeric excess of 97 % [Chiralpak® IB; flow: 1.0 mL/min; hexane: ipa 99.5:0.5; λ = 210 nm; major enantiomer tR = 8.56 min; minor enantiomer, tR = 9.73 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.32 – 7.23 (m, 2H, Ar-*H*), 7.22 – 7.12 (m, 3H, Ar-*H*), 3.53 (t, *J* = 6.7 Hz, 2H,CH_2Cl), 2.89 (q, *J* = 7.4 Hz, 2H, SCH_2CH$_3$), 2.61 (t, *J* = 8.2 Hz, 2H, CH_2Ph), 2.55 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H, CH_2COSEt), 2.01 (p, *J* = 6.3 Hz, 1H, C*H*), 1.76 (dq, *J* = 7.9 Hz, 6.8 Hz, 2H, CH_2), 1.69 – 1.57 (m, 2H, CH_2), 1.48 – 1.28 (m, 8H, CH_2), 1.26 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3).

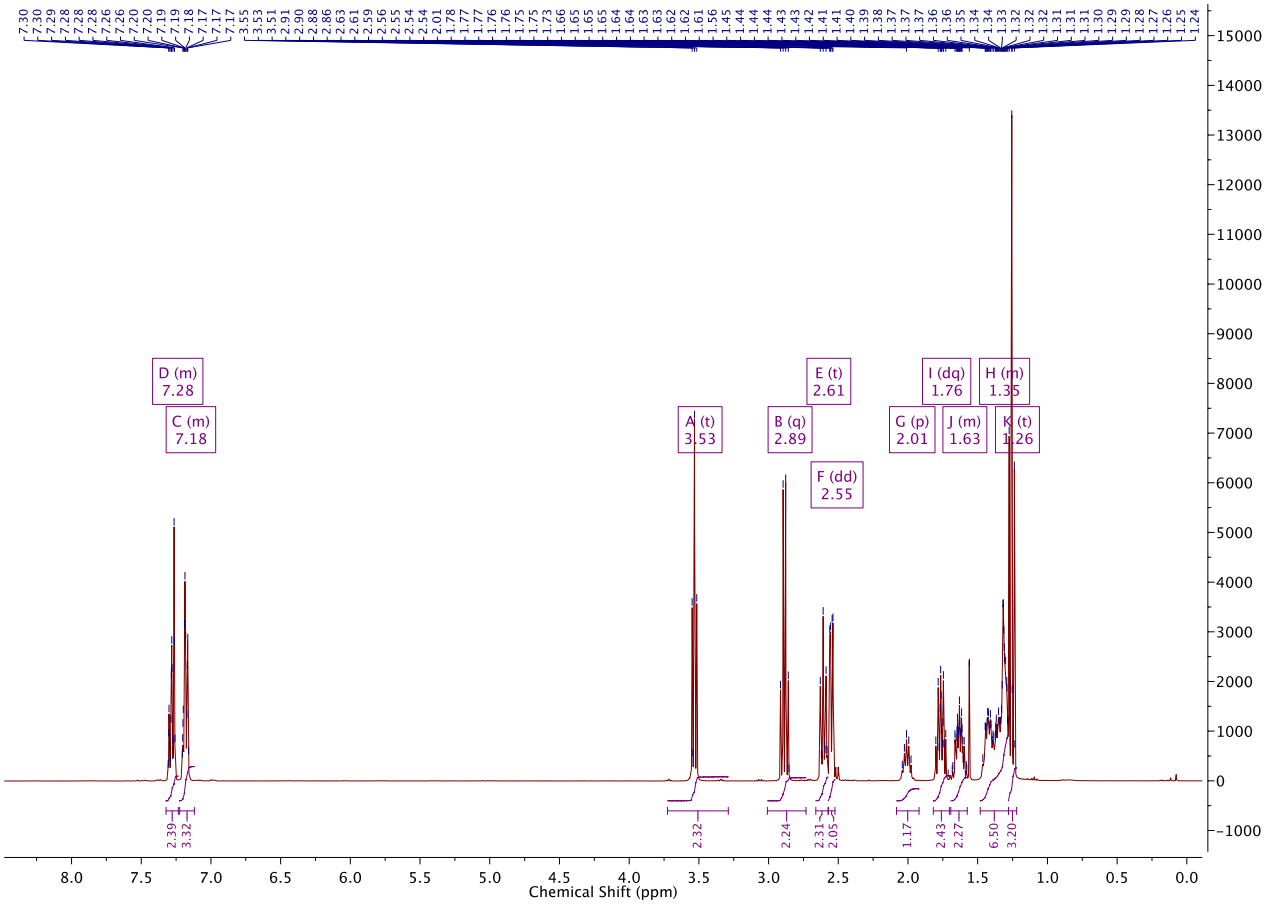
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.3, 142.4, 128.4(2C), 128.3(2C), 125.8, 48.6, 45.1, 35.6, 35.5, 33.5, 33.0, 32.6, 29.0, 26.8, 26.3, 23.4, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980,1686,1382,1252,1152,1073,954

HRMS (ESI) m/z calc. for $C_{19}H_{29}O^{35}Cl^{23}Na^{32}S$ $[M+Na]^+$: 363.1520 found 363.1520

$[\alpha]^{20}_{589}$ = -3.9 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.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E (t) 2.61
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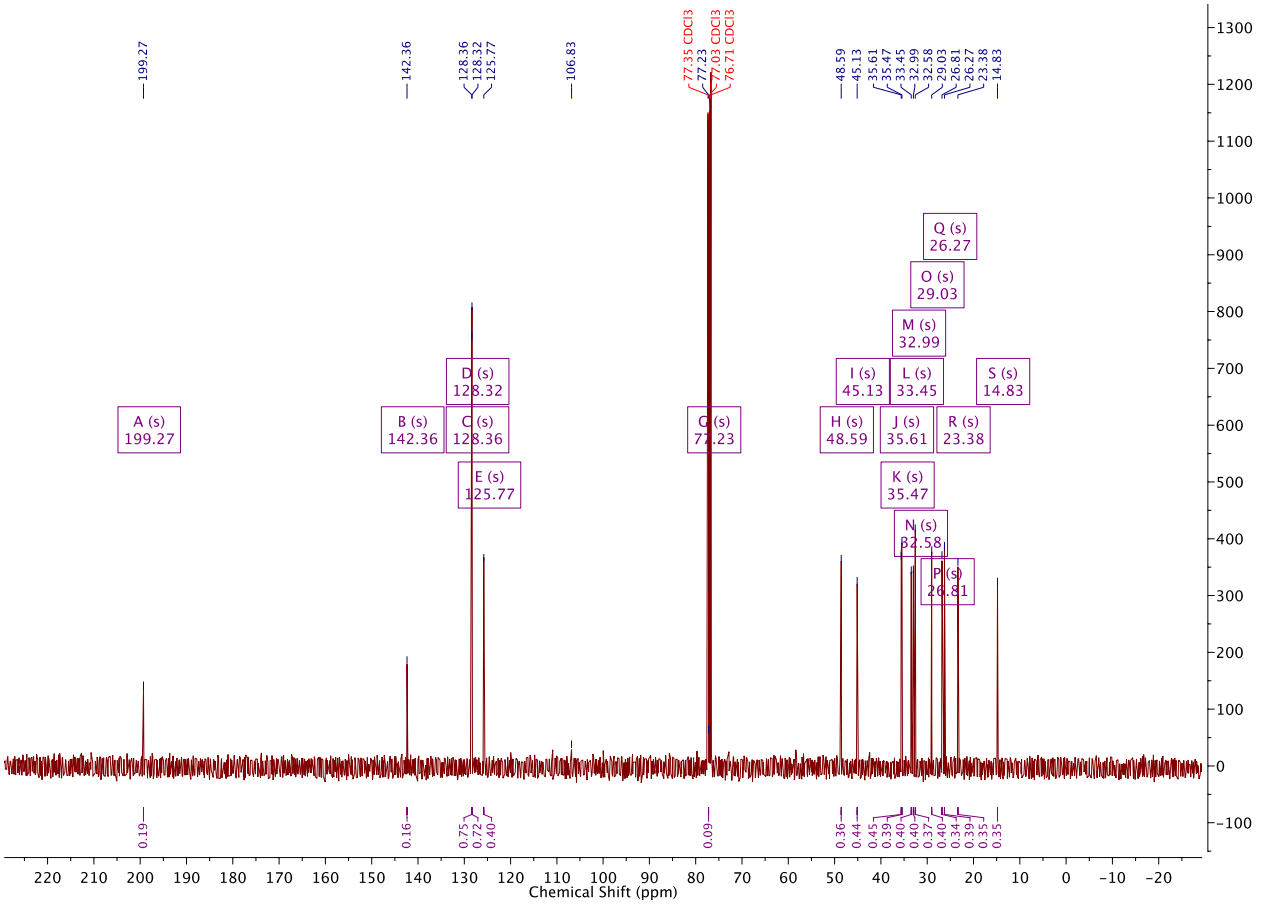
I (dq) 1.76
J (m) 1.63
H (m) 1.35
K (t) 1.26
Chemical Shift (ppm)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C (s) 128.36
D (s) 128.32
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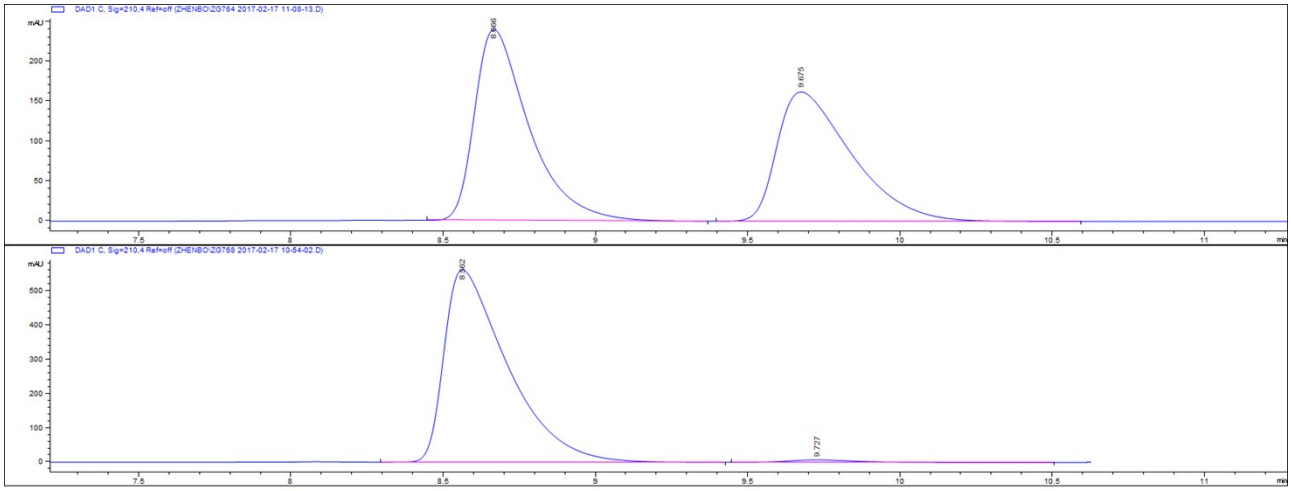
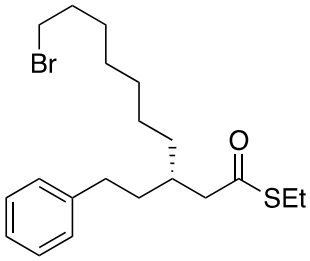
I (s) 45.13
J (s) 35.61
K (s) 35.47
L (s) 33.45
M (s) 32.99
N (s) 32.58
O (s) 29.03
P (s) 26.81
Q (s) 26.27
R (s) 23.38
S (s) 14.83
Chemical Shift (ppm)

HPLC trace



(–)-*S*-ethyl (*S*)-10-bromo-3-phenethyldecanethioate (3m)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of 7-bromohept-1-ene (88 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained. The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-5-phenylpent-2-enethioate (44.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O. The reaction

mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (59 mg, 0.15mmol, 74% yield).

HPLC analysis indicated an enantiomeric excess of 97 % [Chiralpak® IB; flow: 1.0 mL/min; hexane: ipa 99.5:0.5; λ = 210 nm; major enantiomer tR = 8.45 min; minor enantiomer, tR = 9.38 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.35 – 7.23 (m, 2H, Ar-*H*), 7.18 (tq, *J* = 4.5 Hz, 1.6 Hz, 3H, Ar-*H*), 3.41 (t, *J* = 6.9 Hz, 2H, C*H*$_2$Br), 2.89 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.65 – 2.57 (m, 2H, C*H*$_2$Ph), 2.55 (dd, *J* = 6.8 Hz, 1.3, 2H, C*H*$_2$COSEt), 2.07-1.94 (m, 1H, C*H*), 1.85 (dq, *J* = 8.7 Hz, 6.9 Hz, 2H,C*H*$_2$), 1.71 – 1.57 (m, 2H, C*H*$_2$), 1.48 – 1.28 (m, 8H,C*H*$_2$), 1.25 (t, *J* = 7.4 Hz, 5H, C*H*$_2$, SCH$_2$C*H*$_3$)

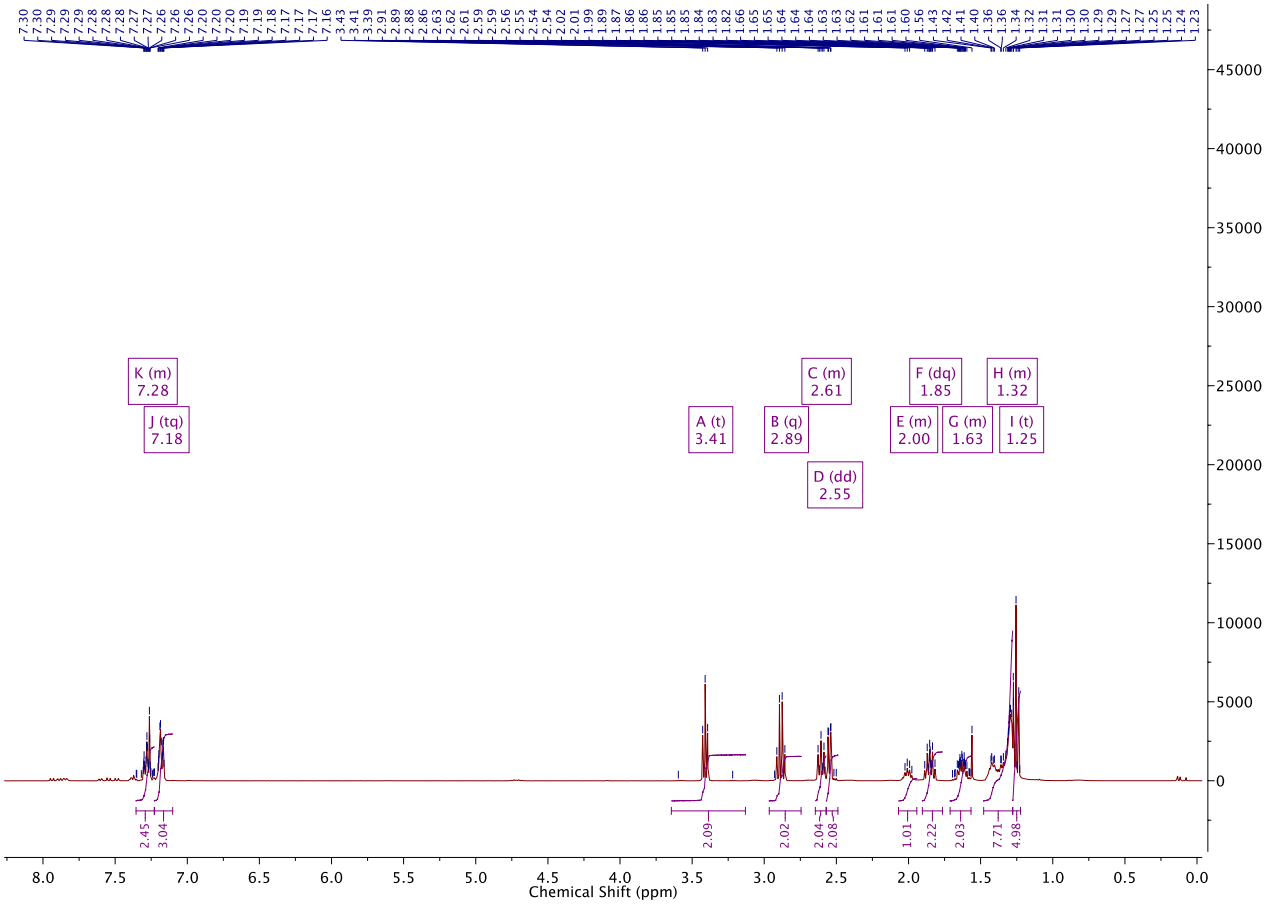
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.3, 142.4, 128.4(2C), 128.3(2C), 125.8, 48.6, 35.6, 35.5, 34.0, 33.5, 33.0, 32.8, 29.6, 28.7, 28.1, 26.3, 23.4, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3660, 2981,1688,1381,1252,1152,1072,953

HRMS (ESI) m/z calc. for $C_{20}H_{31}O^{79}Br^{23}Na^{32}S$ $[M+Na]^+$: 421.1171, 423.1151 found 421.1170, 423.1148

$[\alpha]^{20}_{589}$ = -15.0 ° (c 1.3, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.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J (tq)
7.18
A (t)
3.41
B (q)
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C (m)
2.61
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2.55
E (m)
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F (dq)
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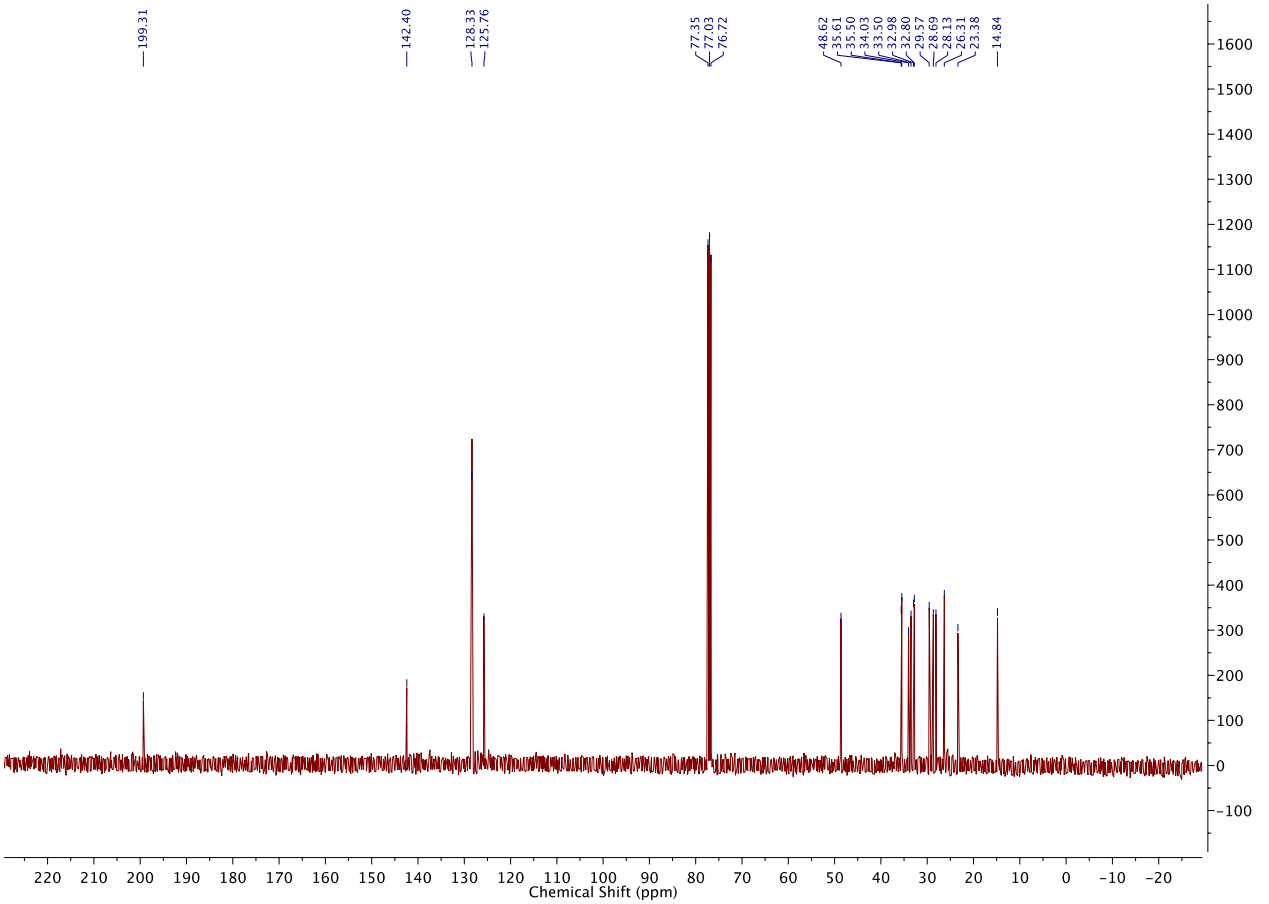
G (m)
1.63
H (m)
1.32
I (t)
1.25
Chemical Shift (ppm)


199.31
142.40
128.33
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76.72
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35.50
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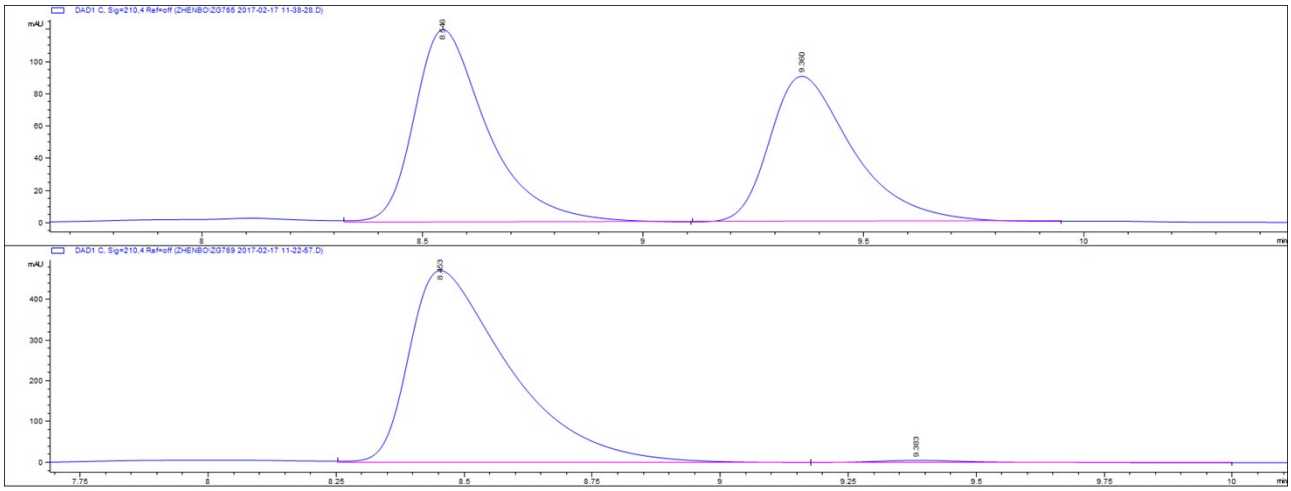
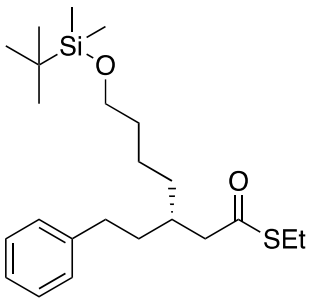
26.31
23.38
14.84
Chemical Shift (ppm)

HPLC trace



(–)-*S*-ethyl (*S*)-7-((*tert*-butyldimethylsilyl)oxy)-3-phenethylheptanethioate (3n)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of (but-3-en-1-yloxy)(tert-butyl) dimethylsilane (93 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-5-phenylpent-2-enethioate (44.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise

over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (60 mg, 0.15mmol, 74% yield).

HPLC analysis indicated an enantiomeric excess of 96 % [Chiralpak® IB; flow: 1.0 mL/min; hexane: ipa 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.13 min; minor enantiomer, tR = 5.54 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.32 – 7.22 (m, 2H), 7.17 (ddd, *J* = 7.9 Hz, 3.5 Hz, 1.2 Hz, 3H,Ar-*H*), 3.59 (t, *J* = 6.4 Hz, 2H, OC*H*$_2$), 2.87 (q, *J* = 7.5 Hz, 2H, SC*H*$_2$CH$_3$), 2.63 – 2.56 (m, 2H,PhC*H*$_2$), 2.54 (d, *J* = 6.8 Hz, 2H,C*H*$_2$CO), 2.11 – 1.90 (m, 1H,C*H*), 1.62 (tdd, *J* = 7.6 Hz, 6.3 Hz, 3.1 Hz, 2H, C*H*$_2$), 1.54 – 1.43 (m, 2H, C*H*$_2$), 1.42 – 1.28 (m, 4H, C*H*$_2$), 1.24 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H,C (C*H*$_3$)$_3$), 0.04 (s, 6H, SiC*H*$_3$).

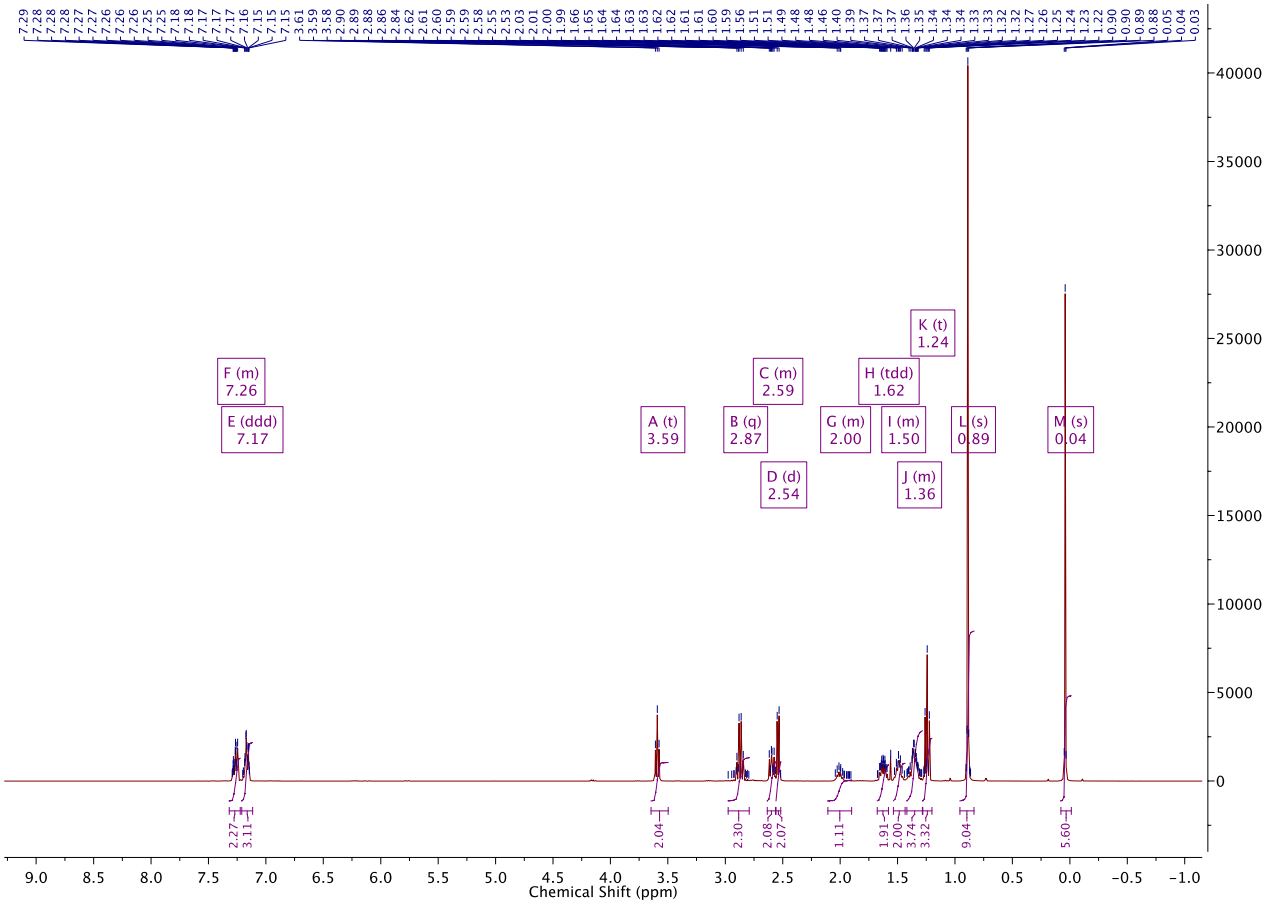
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.3, 142.4, 128.3(4C), 125.7, 63.1, 48.6, 35.5, 33.4, 33.0, 32.9, 26.0(3C), 23.4, 22.7, 18.4, 14.8, -5.23(2C).

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980,1688,1382,1152,1073,954

HRMS (ESI) m/z calc. for $C_{23}H_{40}O_2SSi$ $[M+H]^+$: 409.2588, found: 409.2588

$[\alpha]^{20}_{589}$ = -2.1 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.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B (q)
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C (m)
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D (d)
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G (m)
2.00
H (tdd)
1.62
I (m)
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K (t)
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J (m)
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L (s)
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M (s)
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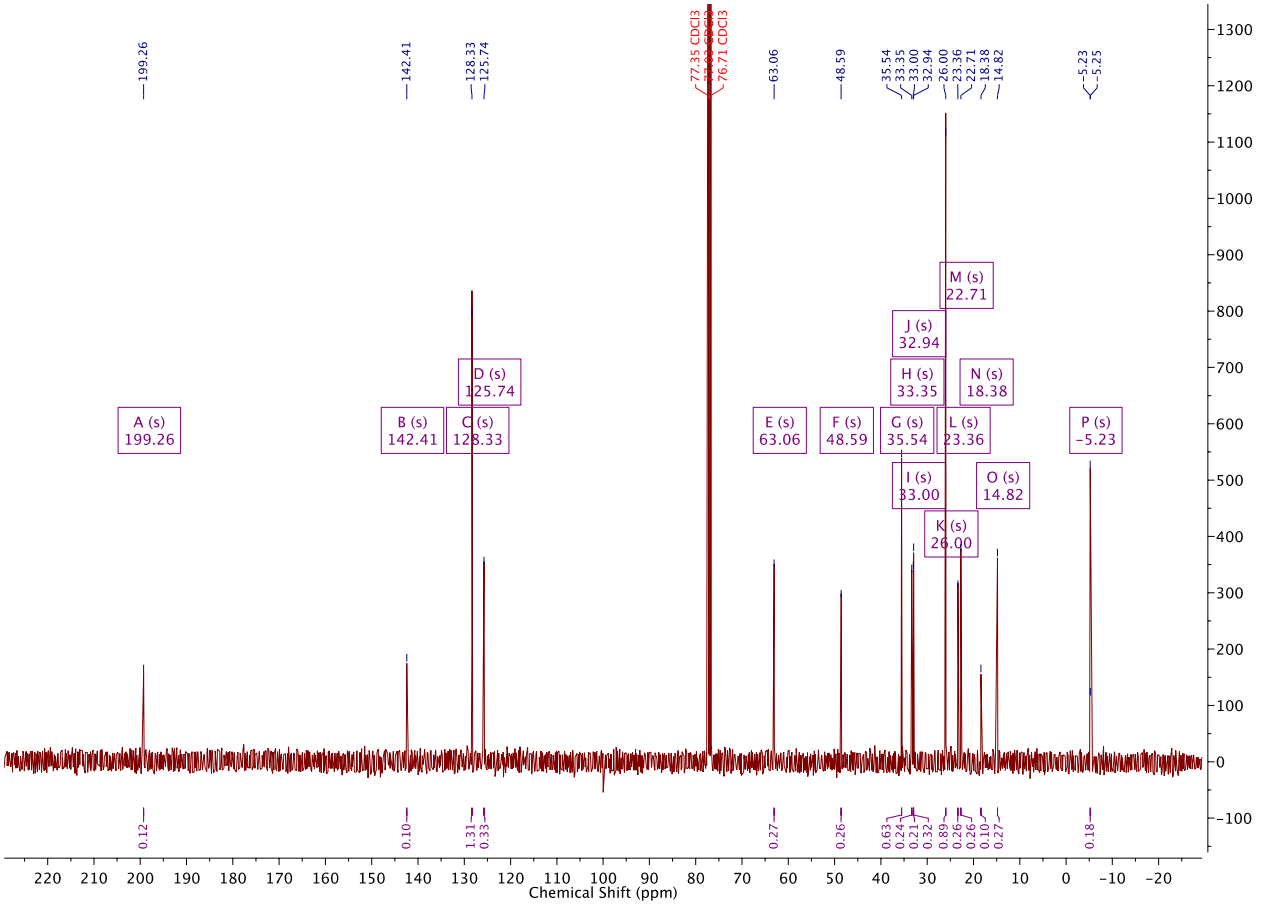
Chemical Shift (ppm)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B (s)
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C (s)
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D (s)
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E (s)
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F (s)
48.59
G (s)
35.54
H (s)
33.35
I (s)
33.00
J (s)
32.94
K (s)
26.00
L (s)
23.36
M (s)
22.71
N (s)
18.38
O (s)
14.82
P (s)
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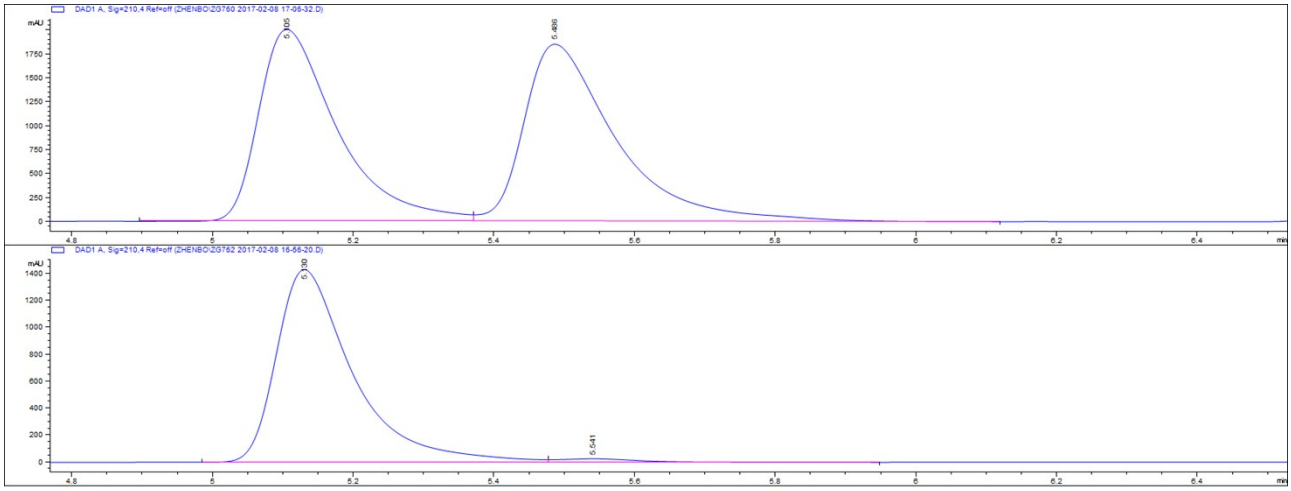
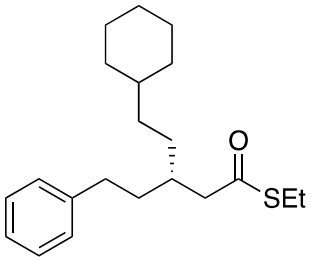
77.35 CDCl3
76.71 CDCl3
Chemical Shift (ppm)

HPLC trace



(–)-S-ethyl (S)-5-cyclohexyl-3-phenethylpentanethioate (3o)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of vinylcyclohexane (55 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-5-phenylpent-2-enethioate (44.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer

extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (55 mg, 0.17mmol, 83% yield).

HPLC analysis indicated an enantiomeric excess of 97 % [Chiralpak® IB; flow: 1.0 mL/min; hexane: ipa 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.35 min; minor enantiomer, tR = 5.91 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.35 – 7.24 (m, 2H, Ar-*H*), 7.22-7.13 (m, 3H, Ar-*H*), 2.89 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.61 (dd, *J* = 9.5 Hz, 7.1 Hz, 2H, C*H*$_2$Ph), 2.55 (d, *J* = 6.8 Hz, 2H, C*H*$_2$COSEt), 1.99 (p, *J* = 6.5, 1H, C*H*CH$_2$CH$_2$Cy), 1.84 – 1.58 (m, 8H, C*H,* C*H*$_2$), 1.50 – 1.31 (m, 2H, C*H*$_2$), 1.26 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$), 1.23 – 1.08 (m, 5H, C*H*$_2$), 0.88 (q, *J* = 10.5 Hz, 9.8 Hz, 2H, C*H*$_2$).

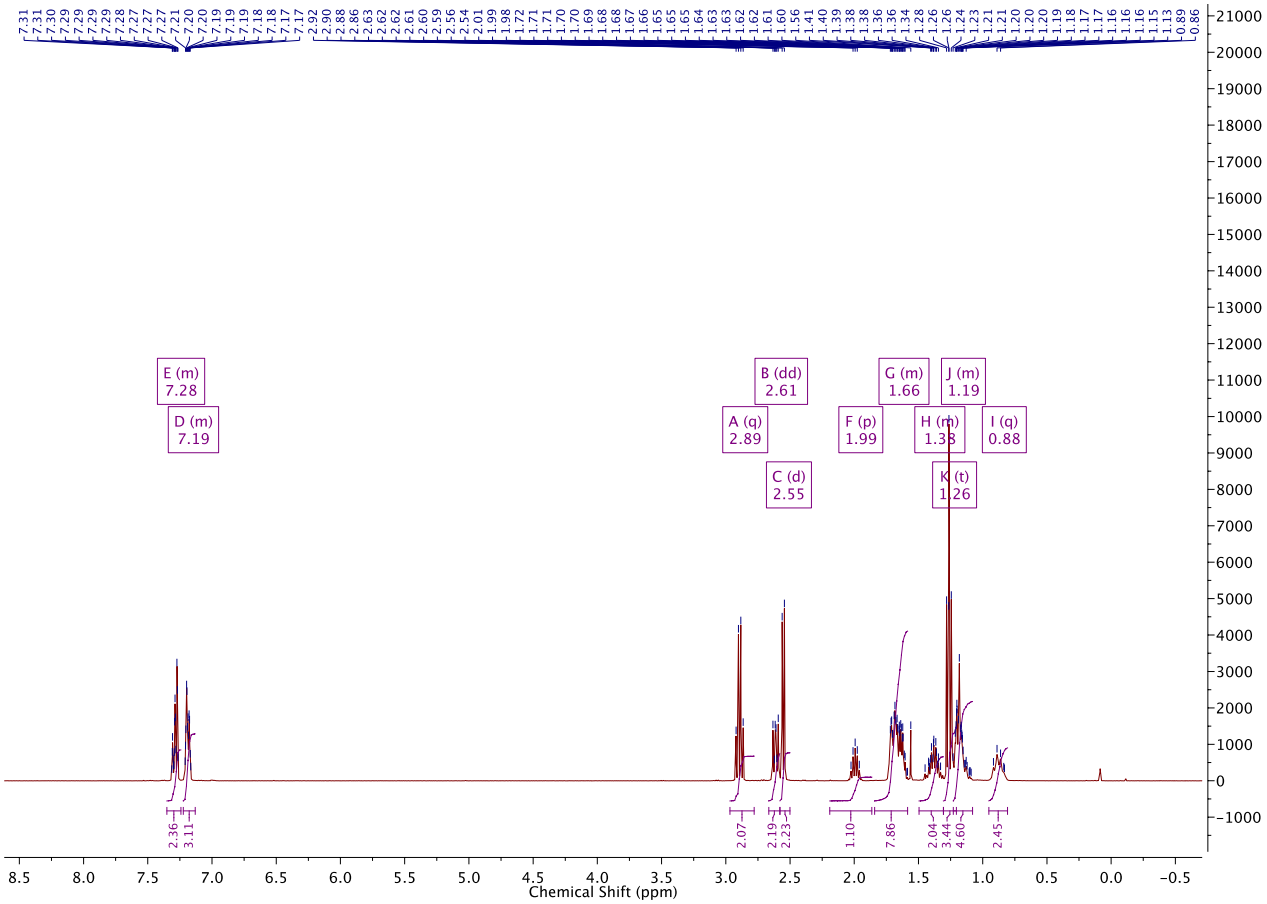
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.3, 142.5, 128.3(4C), 125.7, 48.7, 37.9, 35.8, 35.6, 34.1, 33.4, 33.4, 33.0, 30.7, 26.7, 26.4(2C), 23.4, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3660, 2981,1690,1382,1152,1073,954

HRMS (ESI) m/z calc. for $C_{21}H_{33}O^{32}S$, $[M+H]^+$: 333.2247, found: 333.2249

$[\alpha]^{20}_{589}$ = -2.8 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.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D (m)
7.19
B (dd)
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A (q)
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C (d)
2.55
G (m)
1.66
J (m)
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F (p)
1.99
H (m)
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I (q)
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K (t)
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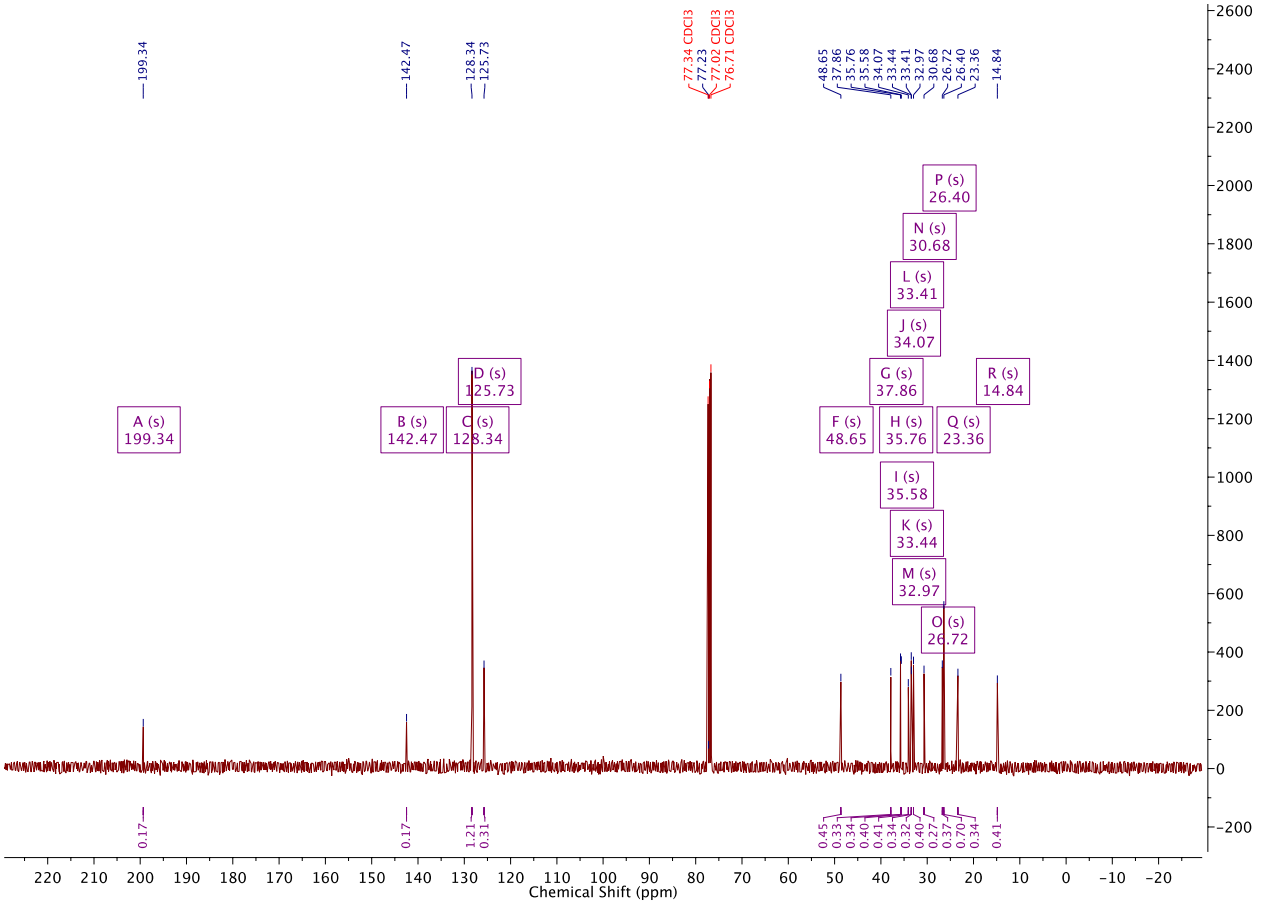
Chemical Shift (ppm)


199.34
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77.23
77.02 CDCl3
76.71 CDCl3
48.65
37.86
35.76
35.58
34.07
33.44
33.41
32.97
30.68
26.72
26.40
23.36
14.84
A (s)
199.34
B (s)
142.47
C (s)
128.34
D (s)
125.73
F (s)
48.65
G (s)
37.86
H (s)
35.76
I (s)
35.58
J (s)
34.07
K (s)
33.44
L (s)
33.41
M (s)
32.97
N (s)
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O (s)
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P (s)
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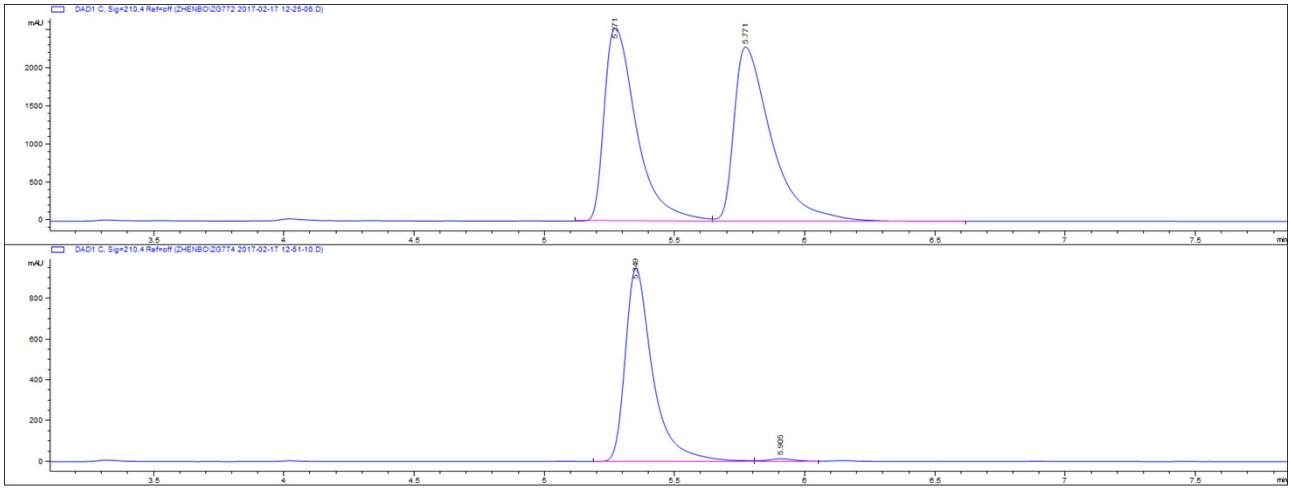
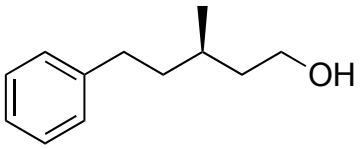
Q (s)
23.36
R (s)
14.84
Chemical Shift (ppm)

HPLC trace



(+)-(*R*)-3-methyl-5-phenylpentan-1-ol (*R*)-4a



S-ethyl (*R*)-3-methyl-5-phenylpentanethioate was obtained from S-ethyl (*E*)-but-2-enethioate and styrene by general proceduce **G 2b**.

1 mol/L $LiAlH_4$ in Et_2O (1ml, 1mmol, 1.0 eq.) was added to a stirring mixture of S-ethyl (R)-3-methyl-5-phenylpentanethioate (0.236 g, 1mmol, 1.0 eq) in DCM at 0 °C under argon. The mixture was kept stirring until the reduction was completed (ca.60min). 5ml sat. Rochelle salt solution was added to the solution and Et_2O extracted the mixture three times. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 60:40; SiO_2) to give the desired product (0.167g, 0.94mmol, 94% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.25 – 7.16 (m, 2H, Ar-*H*), 7.11 (d, *J* = 7.3 Hz, 3H, Ar-*H*), 3.60 (hept, *J* = 7.1 Hz, 6.2 Hz, 2H, CH_2OH), 2.71 – 2.28 (m, 2H, CH_2Ph), 1.67 – 1.50 (m, 3H, C*H,* CH_2), 1.46 – 1.30 (m, 1H, CH_2), 1.28 – 1.15 (m, 1H, CH_2), 0.90 (d, *J* = 6.4 Hz, 3H, CHCH_3).

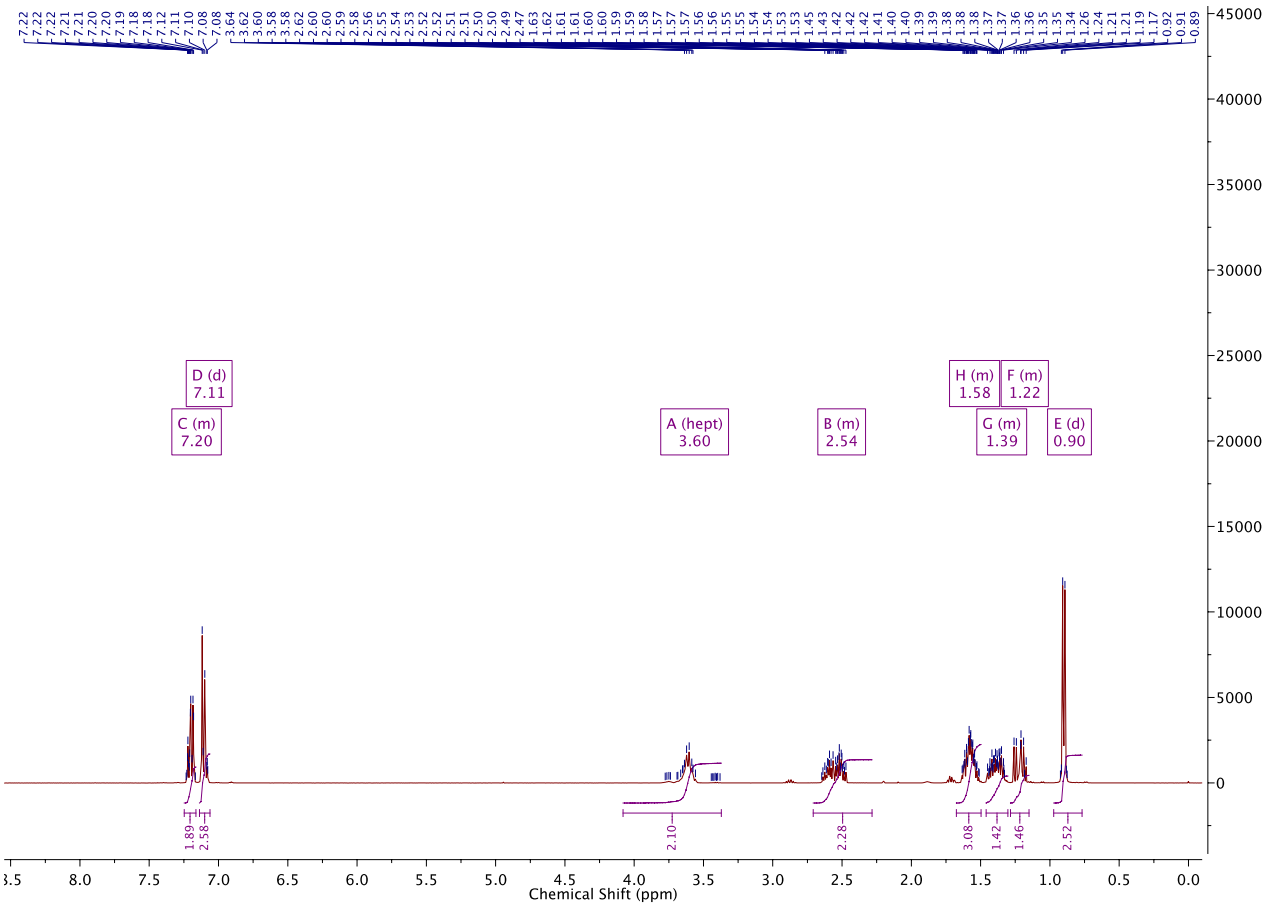
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 142.8, 128.3(4C), 125.7, 61.1, 39.8, 39.0, 33.4, 29.3, 19.6.

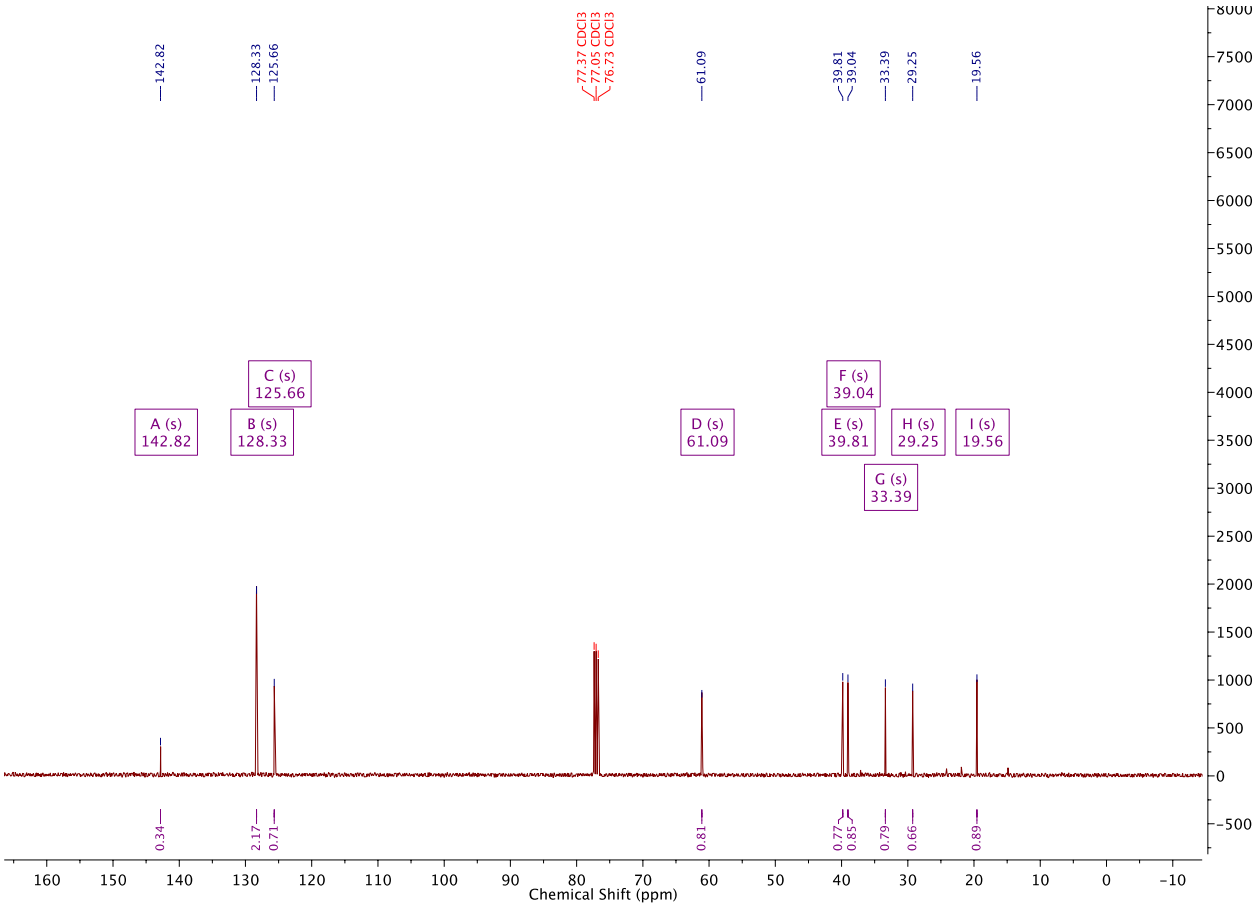
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3336, 2928,1738,1455,1378,1059,1073,698

HRMS (ESI) m/z calc. for $C_{12}H_{18}O^{23}Na$, $[M+Na]^+$: 201.1250, found: 201.1249

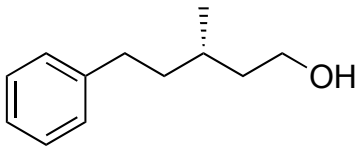
$[\alpha]^{20}_{589}$ = +10.7 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3f**.





(−)-(*S*)-3-methyl-5-phenylpentan-1-ol (*S*)-4a



S-ethyl (*S*)-3-methyl-5-phenylpentanethioate was obtained from S-ethyl (*E*)-but-2-enethioate, styrene and ***S***-ligand by general proceduce **G 2b**.

1 mol/L LiAlH4 in Et_2O (1ml, 1mmol, 1.0 eq.) was added to a stirring mixture of S-ethyl (S)-3-methyl-5-phenylpentanethioate (0.236 g, 1mmol, 1.0 eq) in DCM at 0 °C under argon. The mixture was kept stirring until the reduction was completed (ca.60min). 5ml sat. Rochelle salt solution was added to the solution and the mixture was extracted by Et_2O three times. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 60:40; SiO_2) to give the desired product (0.170g, 0.96mmol, 96% yield).

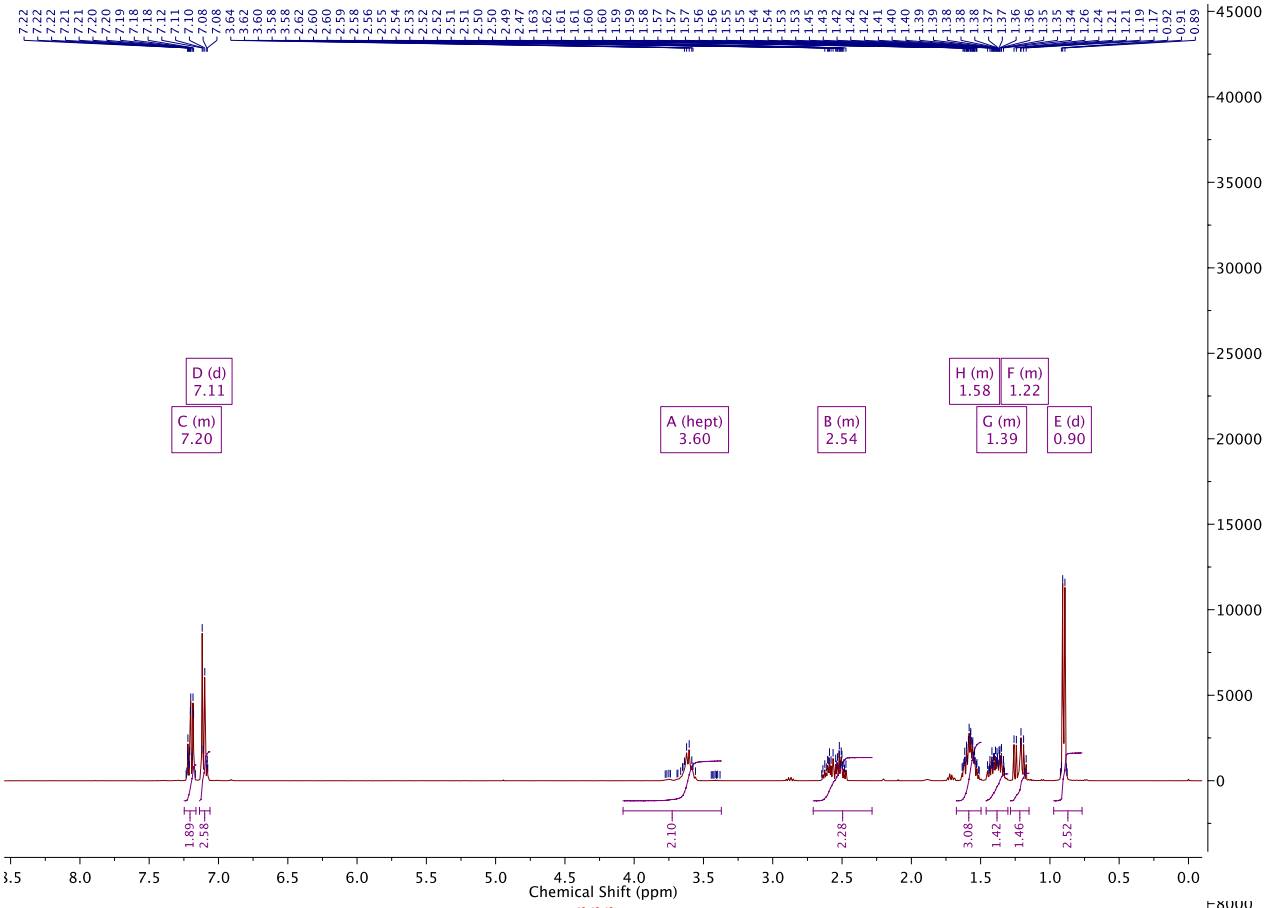
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.25 – 7.16 (m, 2H, Ar-*H*), 7.11 (d, *J* = 7.3 Hz, 3H, Ar-*H*), 3.60 (hept, *J* = 7.1 Hz, 6.2 Hz, 2H, CH_2OH), 2.71 – 2.28 (m, 2H, CH_2Ph), 1.67 – 1.50 (m, 3H, C*H,* CH_2), 1.46 – 1.30 (m, 1H, CH_2), 1.28 – 1.15 (m, 1H, CH_2), 0.90 (d, *J* = 6.4 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 142.8, 128.3(4C), 125.7, 61.1, 39.8, 39.0, 33.4, 29.3, 19.6.
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3336, 2928,1738,1455,1378,1059,1073,698

HRMS (ESI) m/z calc. for $C_{12}H_{18}O^{23}Na$, $[M+Na]^+$: 201.1250, found: 201.1249

$[\alpha]^{20}_{589}$ = -10.3 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3f**.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H (m)
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F (m)
1.22
G (m)
1.39
E (d)
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2.10
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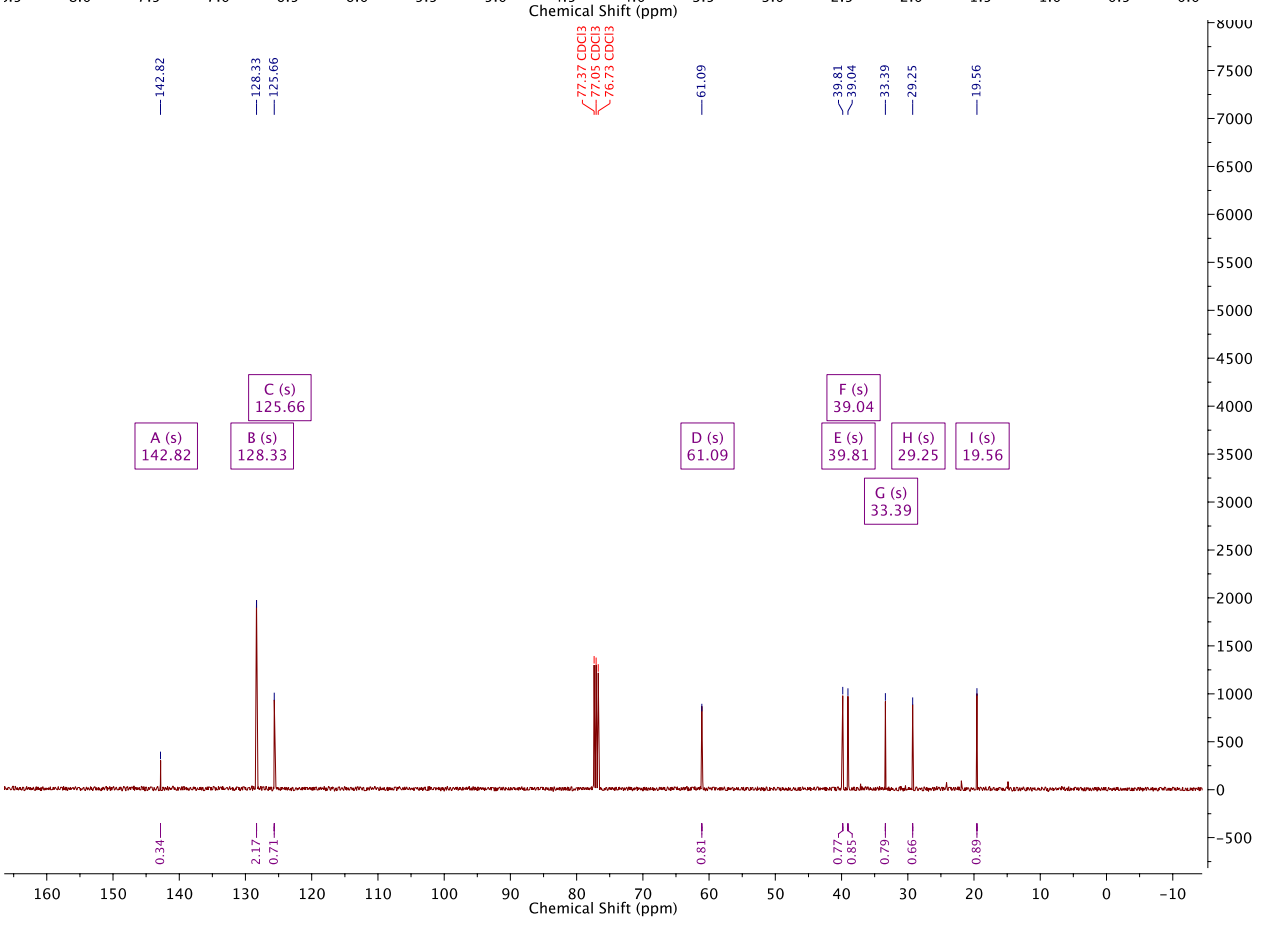
3.08
1.42
1.46
2.52
Chemical Shift (ppm)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125.66
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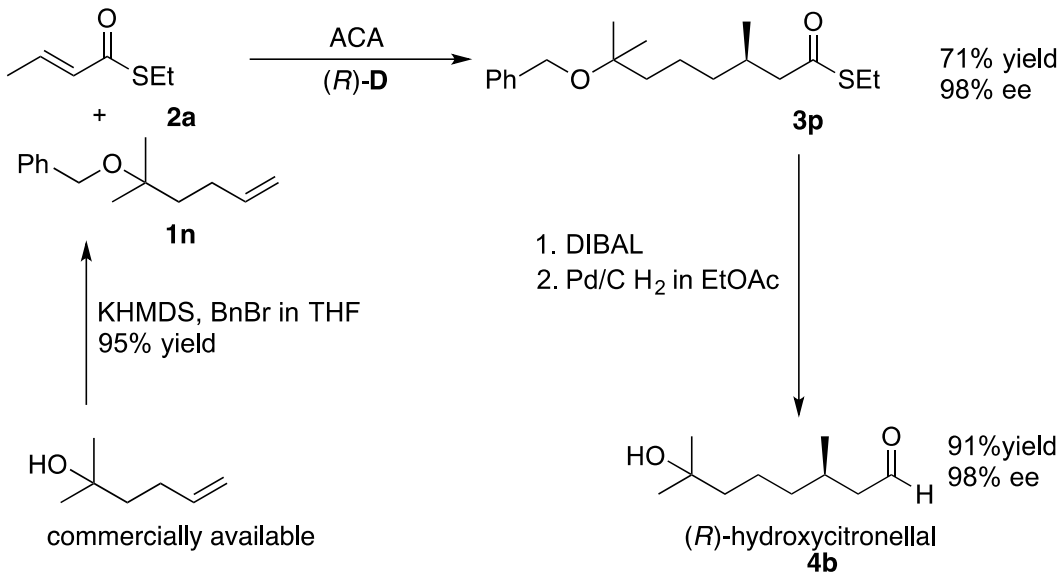
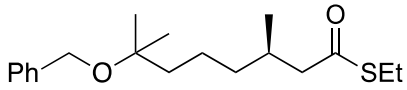
77.05 CDCl3
76.73 CDCl3
61.09
39.81
39.04
33.39
29.25
19.56
A (s)
142.82
C (s)
125.66
B (s)
128.33
D (s)
61.09
F (s)
39.04
E (s)
39.81
H (s)
29.25
I (s)
19.56
G (s)
33.39
0.34
2.17
0.71
0.81
0.77
0.85
0.79
0.66
0.89
Chemical Shift (ppm)

Synthesis of (R)-(+)- Hydroxycitronellal (4b)



(+)-*S*-ethyl (*R*)-7-(benzyloxy)-3,7-dimethyloctanethioate (3p)



CuCl (10.0 mg, 0.1 mmol, 0.1 eq.), and the phosphoramidite ligand (56 mg, 0.1 mmol 0.1 eq.) were added to a flame dried round bottom flask containing 6.0 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (28.0mg, 0.11mmol, 0.11 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of (((2-methylpent-4-en-2-yl) oxy) methyl) benzene (480 mg, 2.5mmol, 2.5 eq.) in 1.0 ml DCM, under an argon atmosphere was added Cp_2ZrHCl (515mg, 2.0mmol, 2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*E*)-but-2-enethioate (130 mg, 1.0 mmol, 1.0 eq.) and TMSCl (0.65ml, 5mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (5.0 ml sat. aq.) and then Et_2O. The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by

Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product (230 mg, 0.71mmol, 71% yield).

HPLC analysis indicated an enantiomeric excess of 98 % [Chiralpak® IA; flow: 1.0 mL/min; hexane: ipa 99.7:0.3; λ = 210 nm; major enantiomer tR = 7.54 min; minor enantiomer, tR = 10.36 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.36 – 7.26 (m, 4H, Ar-*H*), 7.26 – 7.17 (m, 1H, Ar-*H*), 4.39 (s, 2H,PhCH_2O), 2.86 (q, *J* = 7.4 Hz, 2H, SCH_2CH$_3$), 2.52 (dd, *J* = 14.4 Hz, 6.1 Hz, 1H, CH_2COSEt), 2.34 (dd, *J* = 14.4 Hz, 8.1 HZ, 1H, CH_2COSEt), 2.03 (dtdd, *J* = 14.4 Hz, 6.6 Hz, 5.5 Hz, 1.4 Hz, 1H, C*H*), 1.56 -1.47(m, 2H, CH_2), 1.47 – 1.27 (m, 3H, CH_2), 1.29 – 1.10 (m, 10H, CH_2 ,CH_3), 0.93 (d, *J* = 6.7 Hz, 3H, CHCH_3).

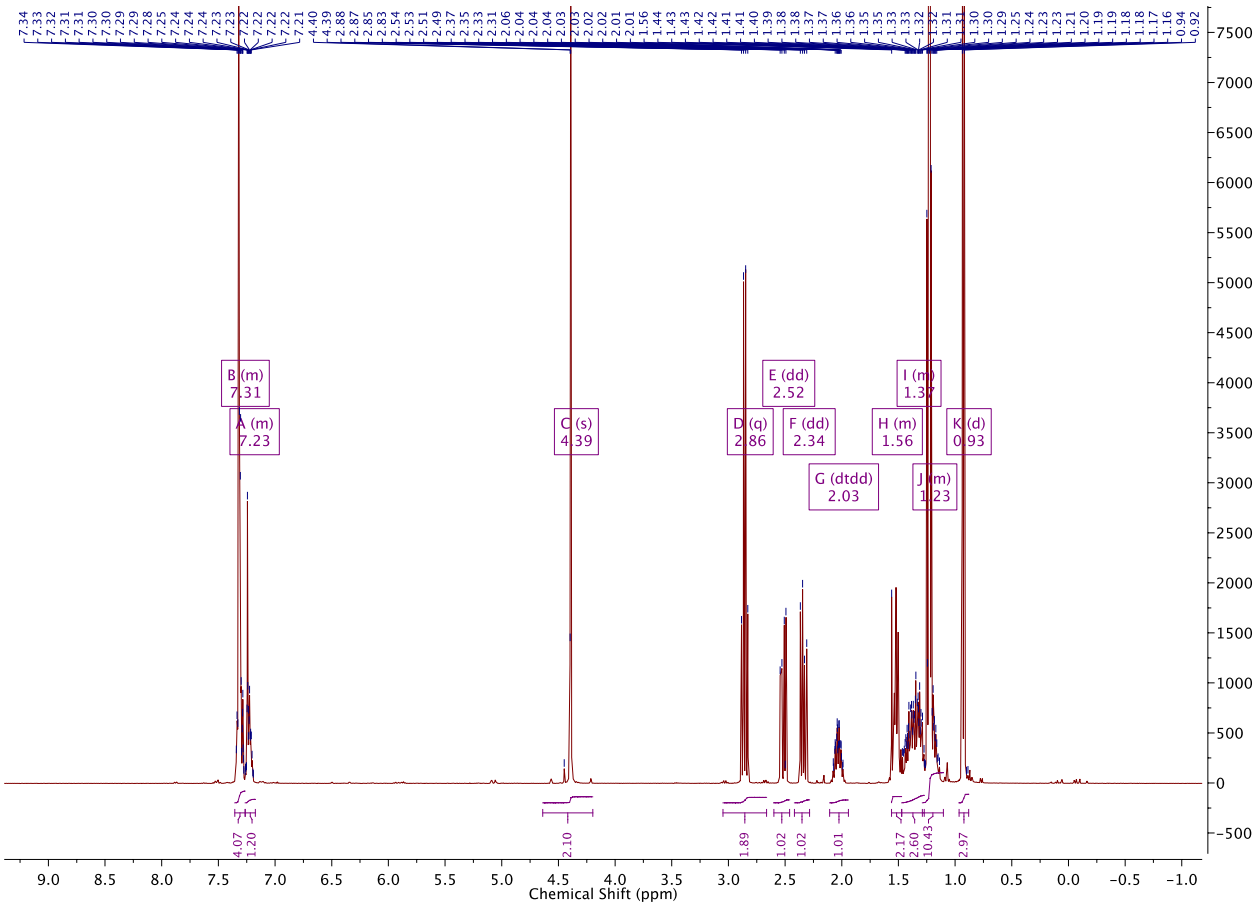
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.3, 139.9, 128.3(2C), 127.3(2C), 127.1, 75.2, 63.7, 51.4, 40.5, 37.1, 31.1, 25.7(2C), 23.3, 21.2, 19.5, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2970, 1688,1454,1381,1060,734

HRMS (ESI) m/z calc. for $C_{19}H_{30}O_2{}^{23}Na^{32}S$, $[M+Na]^+$: 345.1859, found: 345.1855

$[\alpha]^{20}_{589}$ = +6.1 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3d**.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A (m)
7.23
C (s)
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D (q)
2.86
E (dd)
2.52
F (dd)
2.34
G (dtdd)
2.03
H (m)
1.56
I (m)
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J (m)
1.23
K (d)
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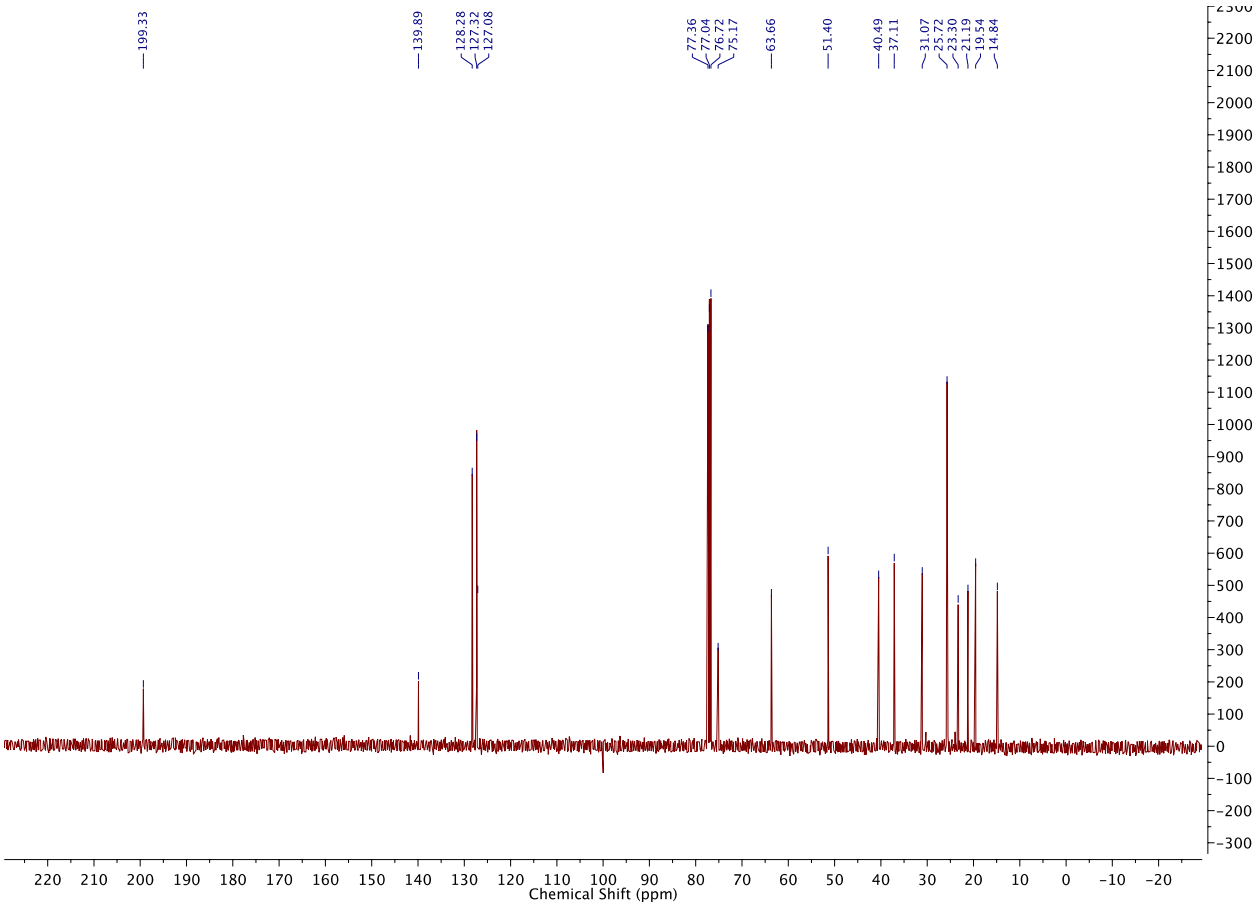
Chemical Shift (ppm)


199.33
139.89
128.28
127.32
127.08
77.36
77.04
76.72
75.17
63.66
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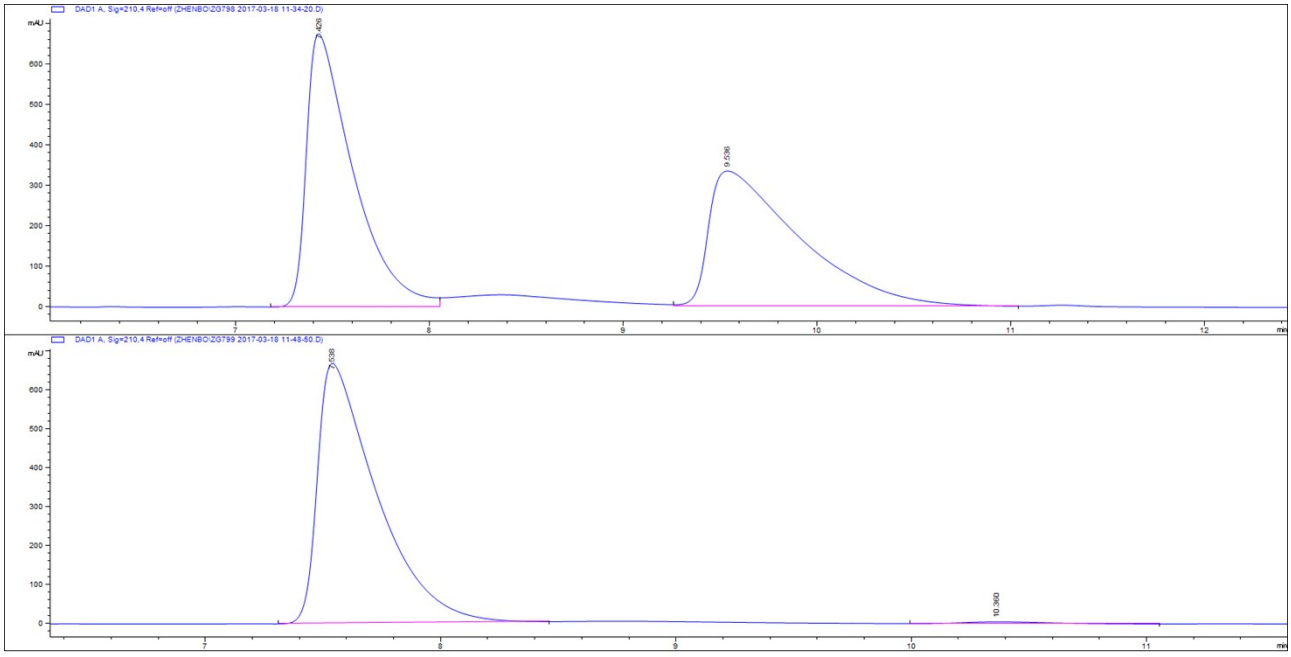
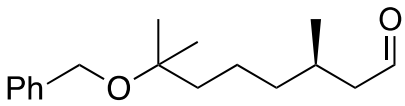
37.11
31.07
25.72
23.30
21.19
19.54
14.84
Chemical Shift (ppm)

HPLC trace



(+)-(R)-7-(benzyloxy)-3,7-dimethyloctanal (3q)



0.65 ml DIBAL (1M in DCM, 1.0 eq.) was added to a stirring mixture of S-ethyl (*R*)-7-(benzyloxy)-3,7-dimethyloctanethioate (0.20 g, 0.65mmol, 1.0 eq) in DCM at -78°C under argon. The mixture was kept stirring until the reduction was completed (30-60min). Saturated Rochelle salt solution was then added and the mixture was extracted by Et_2O three times. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product (0.165g, 0.63mmol, 97%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 9.68 (dd, *J* = 2.6 Hz, 2.0 Hz, 1H, C*H*O), 7.29 – 7.22 (m, 4H, Ar-*H*), 7.22 – 7.13 (m, 1H, Ar-*H*), 4.34 (s, 2H, PhCH_2O), 2.33 (ddd, *J* = 16.1 Hz, 5.7 Hz, 2.1 Hz, 1H, CH_2CHO), 2.16 (ddd, *J* = 16.0 Hz, 7.9 Hz, 2.6 Hz, 1H, CH_2CHO), 2.01 (tdt, *J* = 7.7 Hz, 6.6 Hz, 5.6 Hz, 1H, C*H*), 1.60 – 1.19 (m, 5H, CH_2), 1.21 – 1.10 (m, 7H, CH_2 , CH_3), 0.90 (d, *J* = 6.7 Hz, 3H, CHCH_3).

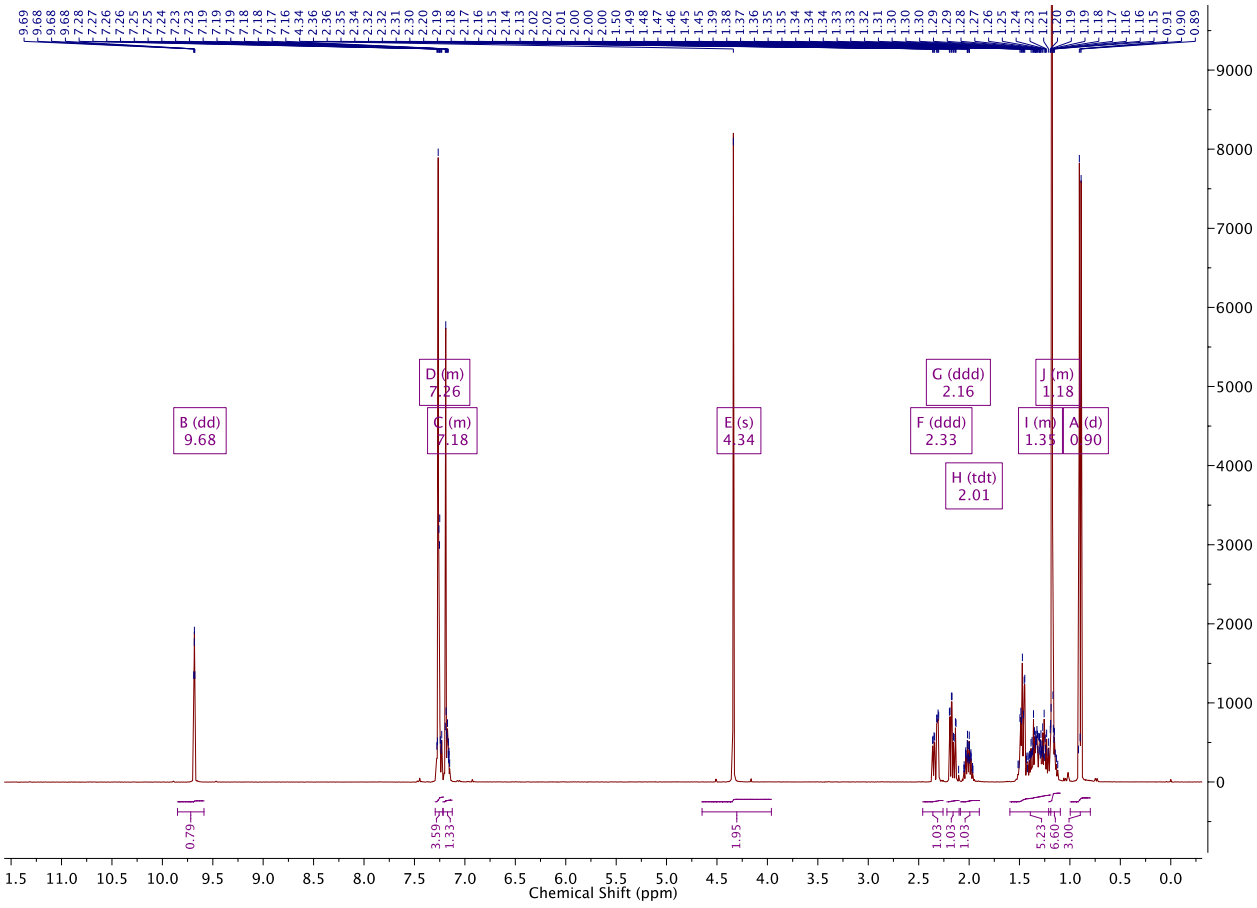
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 203.1, 139.9, 128.3(2C), 127.3(2C), 127.1, 75.1, 63.7, 51.1, 40.6, 37.4, 28.2, 25.7(2C), 21.3, 20.0.

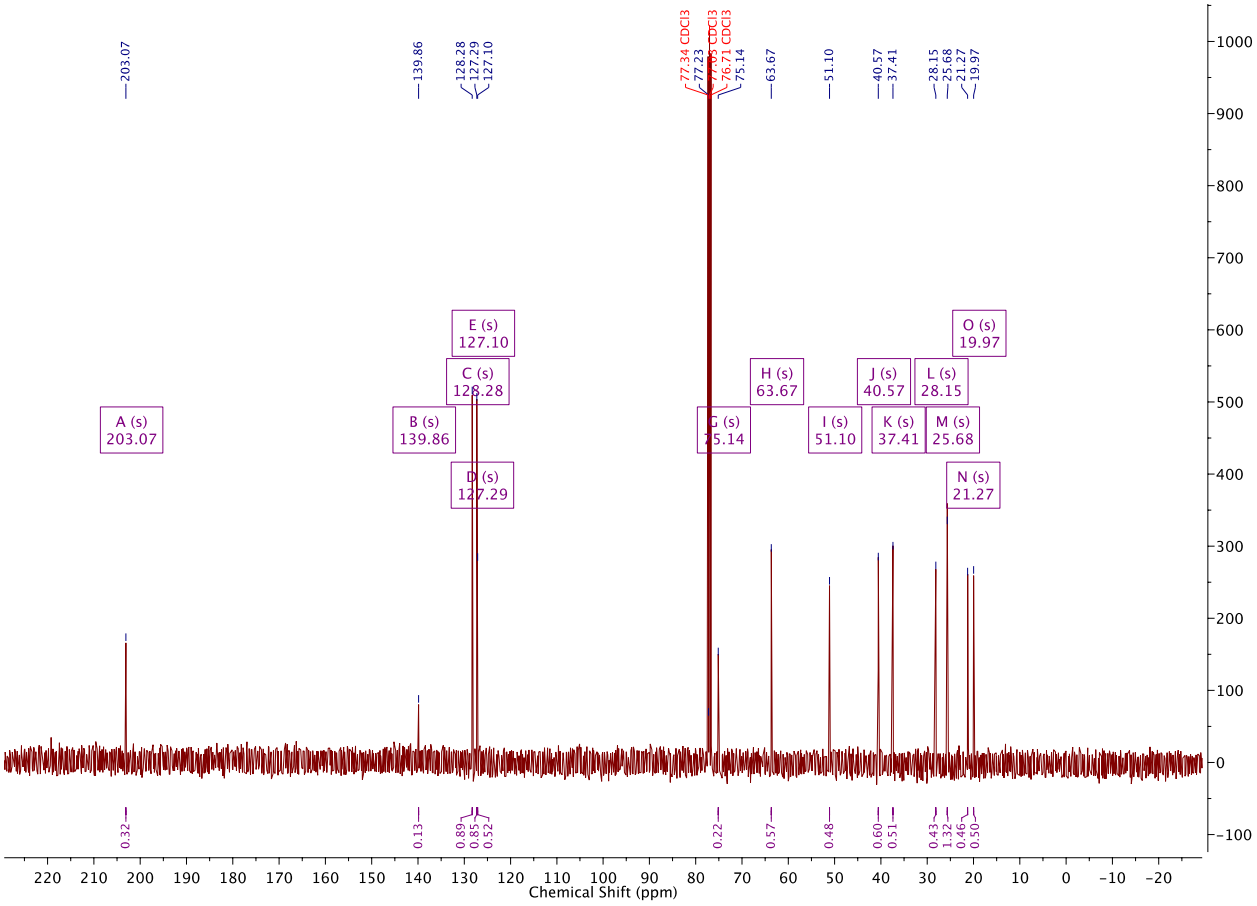
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980,1725,1382,1153,1089,954

HRMS (ESI) m/z calc. for $C_{17}H_{27}O_2$, $[M+H]^+$: 263.2006, found: 263.2008

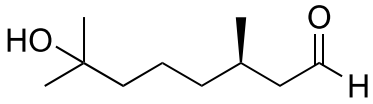
$[\alpha]^{20}_{589}$ = +4.8 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3p**.





(+)-(*R*)-7-hydroxy-3,7-dimethyloctanal (4b)



A 10 ml round bottle flask charged 10% Pd-C (30mg, 0.03mmol, 0.15 eq.) was flushed with H_2 for 5 minutes. 1 ml EtOAc and (*R*)-7-(benzyloxy)-3,7-dimethyloctanal (53mg, 0.2mmol, 1.0eq) at room temperature under H_2. The mixture was kept stirring until the reduction was completed (90min). The catalyst was filtered off through Celite and washed with the Et_2O. The filtrate was concentrated under reduced pressure and further purified by flash column chromatography (Et_2O/petane; 1:1; SiO_2) to give the pure (*R*)-(+)- Hydroxycitronellal (32mg, 0.19mmol, 94%)

HPLC analysis indicated an enantiomeric excess of 98 % [Chiralpak® IA; flow: 1.0 mL/min; hexane: ipa 95:5; λ = 275 nm; major enantiomer tR = 15.36 min; minor enantiomer, tR = 14.59 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 9.69 (t, *J* = 2.3 Hz, 1H, C*H*O), 7.20 (s, 1H, O*H*) 2.35 (ddd, *J* = 16.1 Hz, 5.8 Hz, 2.1 Hz, 1H, CH_2CHO), 2.18 (ddd, *J* = 16.1 Hz, 7.8 Hz, 2.6 Hz, 1H, CH_2CHO), 2.01 (tdt, *J* = 7.7 Hz, 6.6 Hz, 5.6 Hz, 1H, C*H*), 1.45 – 1.17 (m, 6H, CH_2), 1.15 (s, 6H, CH_3), 0.91 (d, *J* = 6.7 Hz, 3H, CHCH_3).

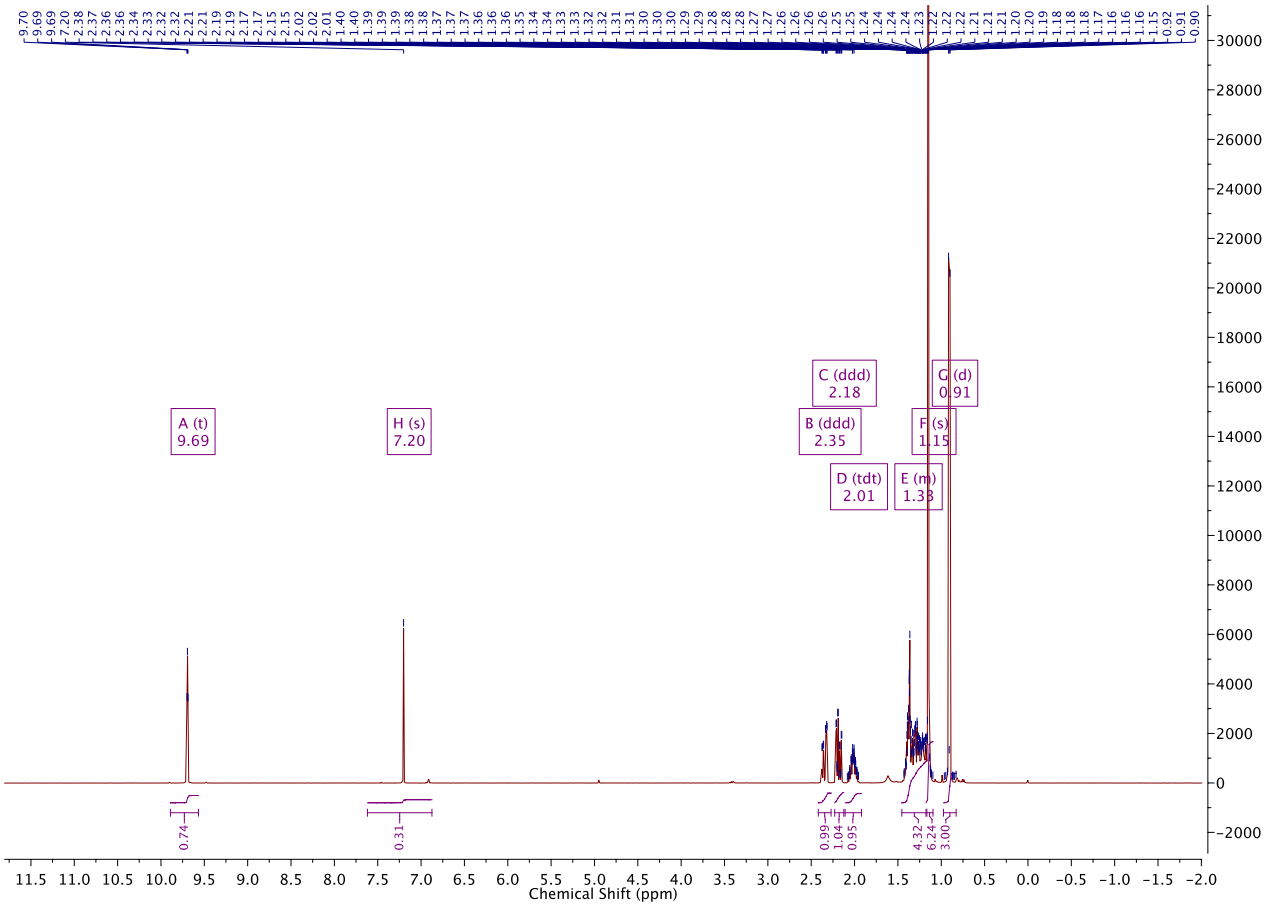
13C NMR (101 MHz, Chloroform-d) δ_C/ppm 203.0, 70.9, 51.1, 43.9, 37.3, 29.4, 29.3, 28.1, 21.7, 20.0.

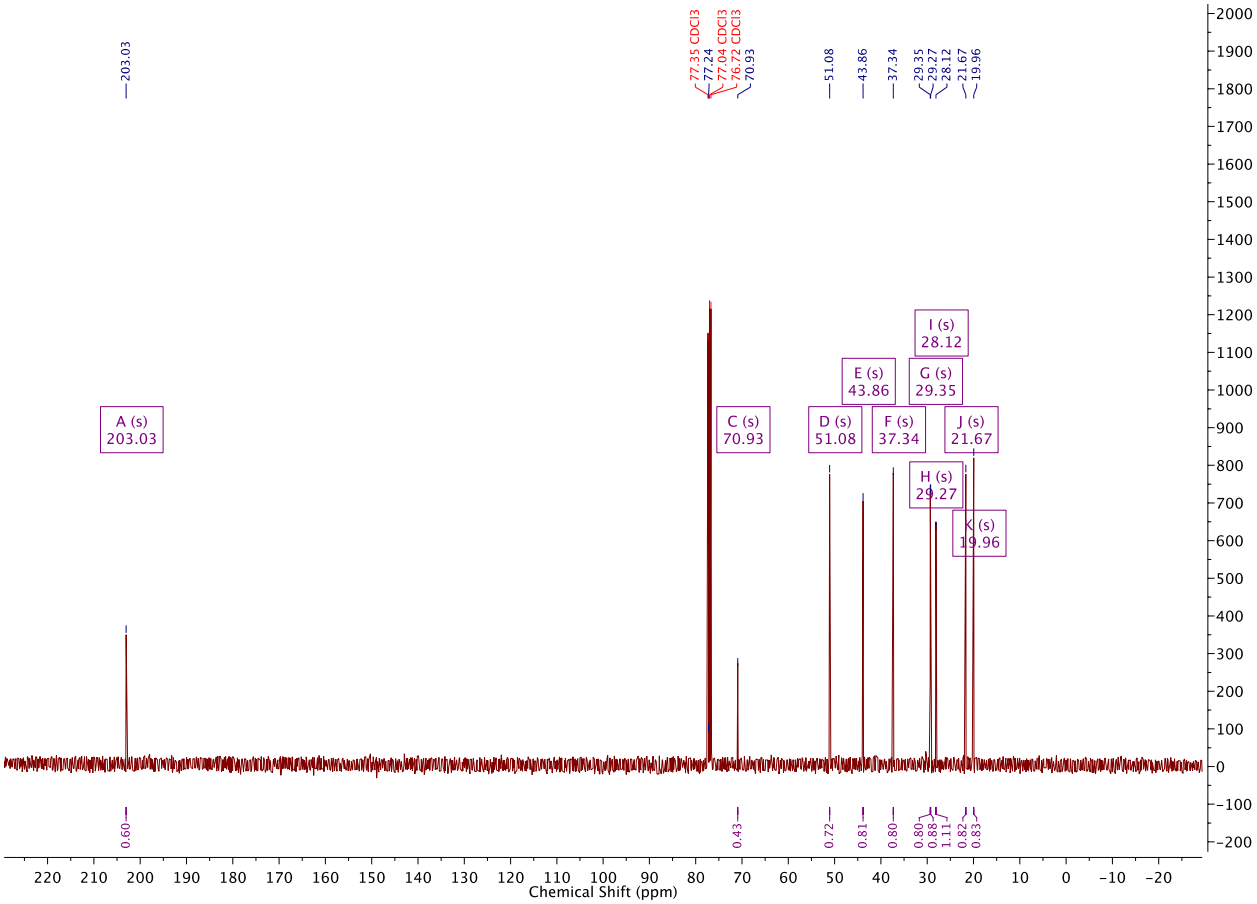
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980,1722,1382,1251,1153,954

HRMS (ESI) m/z calc. for $C_{10}H_{20}O_2{}^{23}Na$, $[M+Na]^+$: 195.1356, found: 195.1356

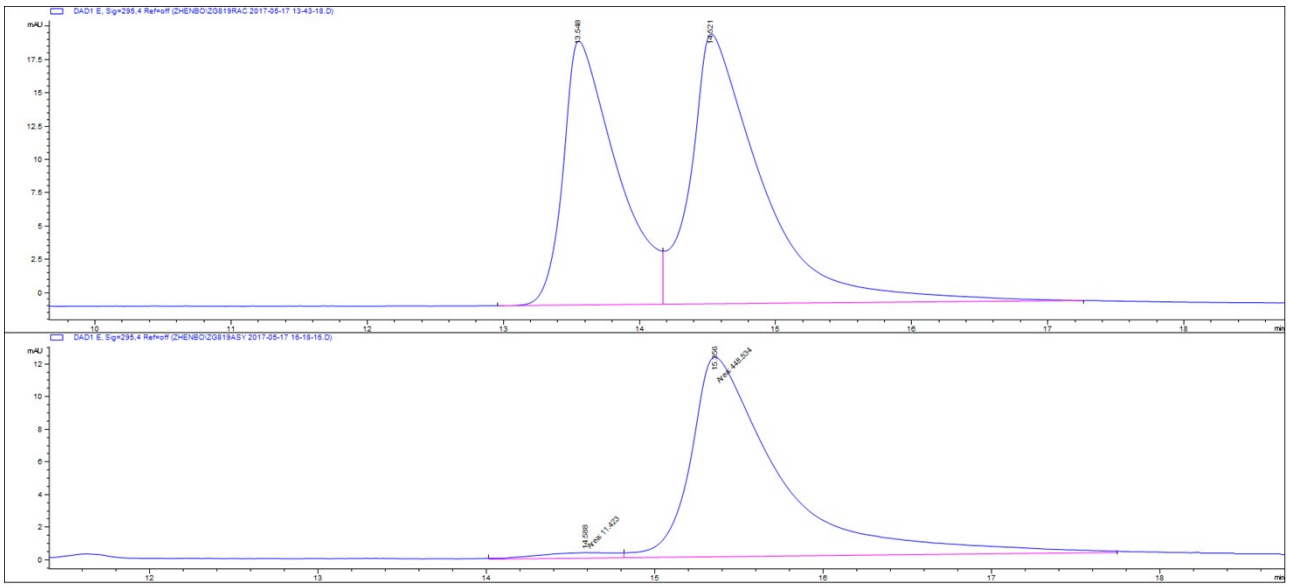
$[\alpha]^{20}_{589}$ = +8.5 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3p**.

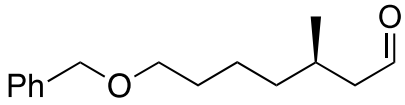




HPLC trace



(+)-(*R*)-7-(benzyloxy)-3-methylheptanal (5a)



2.5 ml DIBAL (1M in DCM, 1.0 eq.) was added to a stirring mixture of S-methyl (*R*)-7-(benzyloxy)-3-methylheptanethioate (0.701 g, 2.5mmol, 1.0 eq) in DCM at -78°C under argon. The mixture was kept stirring until the reduction was completed (30-60min). Saturated Rochelle salt solution was then added and the mixture was extracted by Et_2O three times. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product (0.574g, 2.45mmol, 98%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.75 (dd, *J* = 2.6 Hz, 2.0 Hz, 1H, C*H*O), 7.38 – 7.32 (m, 4H, Ar-*H*), 7.34 – 7.24 (m, 1H, Ar-*H*), 4.50 (s, 2H, PhCH_2O), 3.47 (t, *J* = 6.5 Hz, 2H, OCH_2), 2.39 (ddd, *J* = 16.0 Hz, 5.7 Hz, 2.0 Hz, 1H, CH_2CHO), 2.22 (ddd, *J* = 16.1 Hz, 7.8 Hz, 2.6 Hz, 1H, CH_2CHO), 2.13 – 1.98 (m, 1H, C*H*), 1.74 – 1.55 (m, 2H, CH_2), 1.52 – 1.15 (m, 4H, CH_2), 0.96 (d, *J* = 6.7 Hz, 3H, CHCH_3).

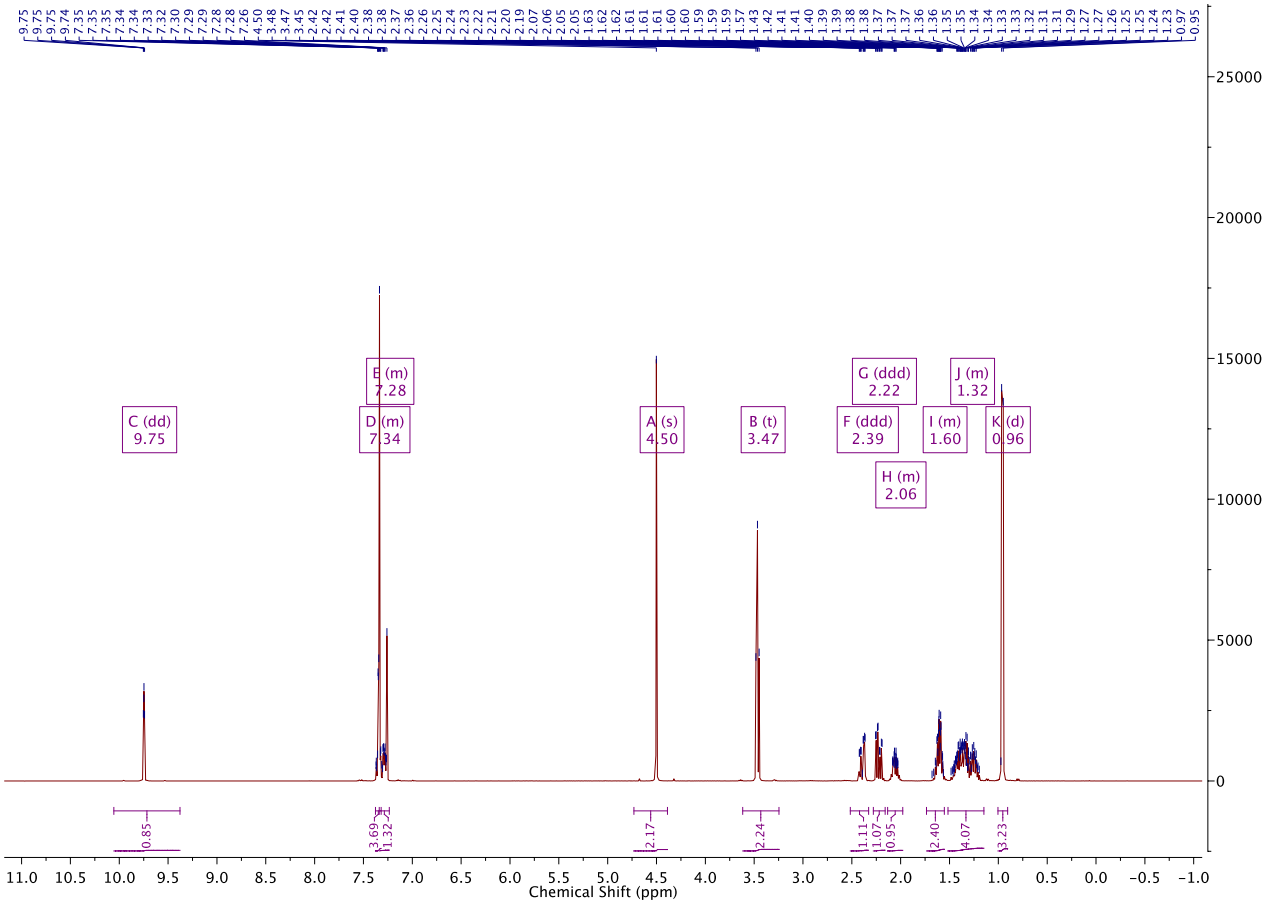
^{13}C NMR (101 MHz, Chloroform-*d*) δ = 203.1, 138.6, 128.4(2C), 127.7(2C), 127.5, 72.9, 70.2, 51.0, 36.7, 29.8, 28.1, 23.6, 20.0.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980,1724,1380,1100,1073,954,737

HRMS (ESI) m/z calc. for $C_{15}H_{23}O_2$, $[M+H]^+$: 235.1693, found: 235.1691

$[\alpha]^{20}_{589}$ = +5.1 ° (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **3i**.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D (m)
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A (s)
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B (t)
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G (ddd)
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F (ddd)
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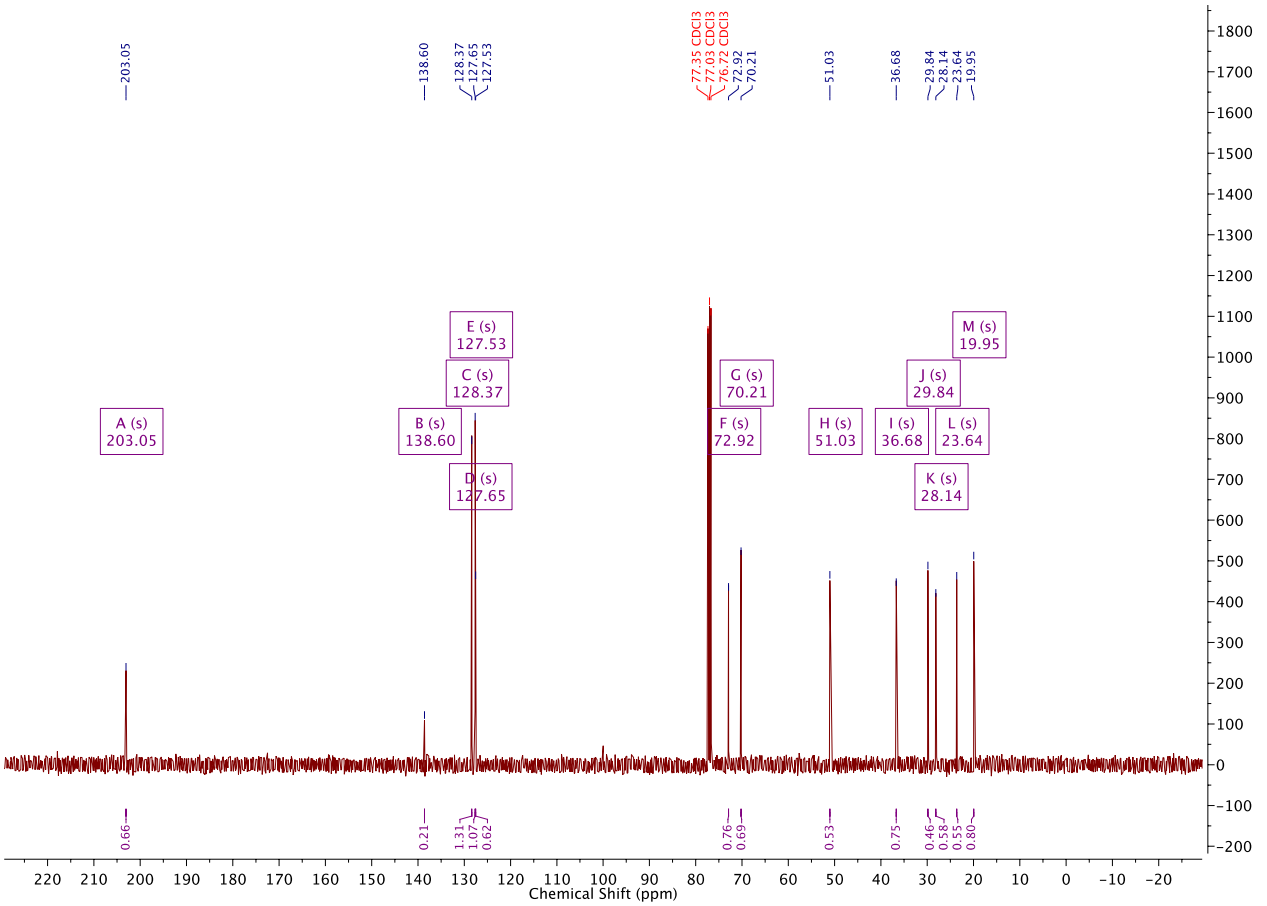
H (m)
2.06
J (m)
1.32
I (m)
1.60
K (d)
0.96
Chemical Shift (ppm)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B (s)
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C (s)
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D (s)
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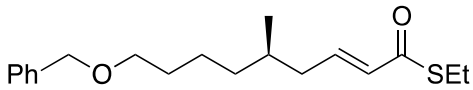
E (s)
127.53
F (s)
72.92
G (s)
70.21
H (s)
51.03
I (s)
36.68
J (s)
29.84
K (s)
28.14
L (s)
23.64
M (s)
19.95
Chemical Shift (ppm)

_S_-ethyl (_R_,_E_)-9-(benzyloxy)-5-methylnon-2-enethioate (5b)



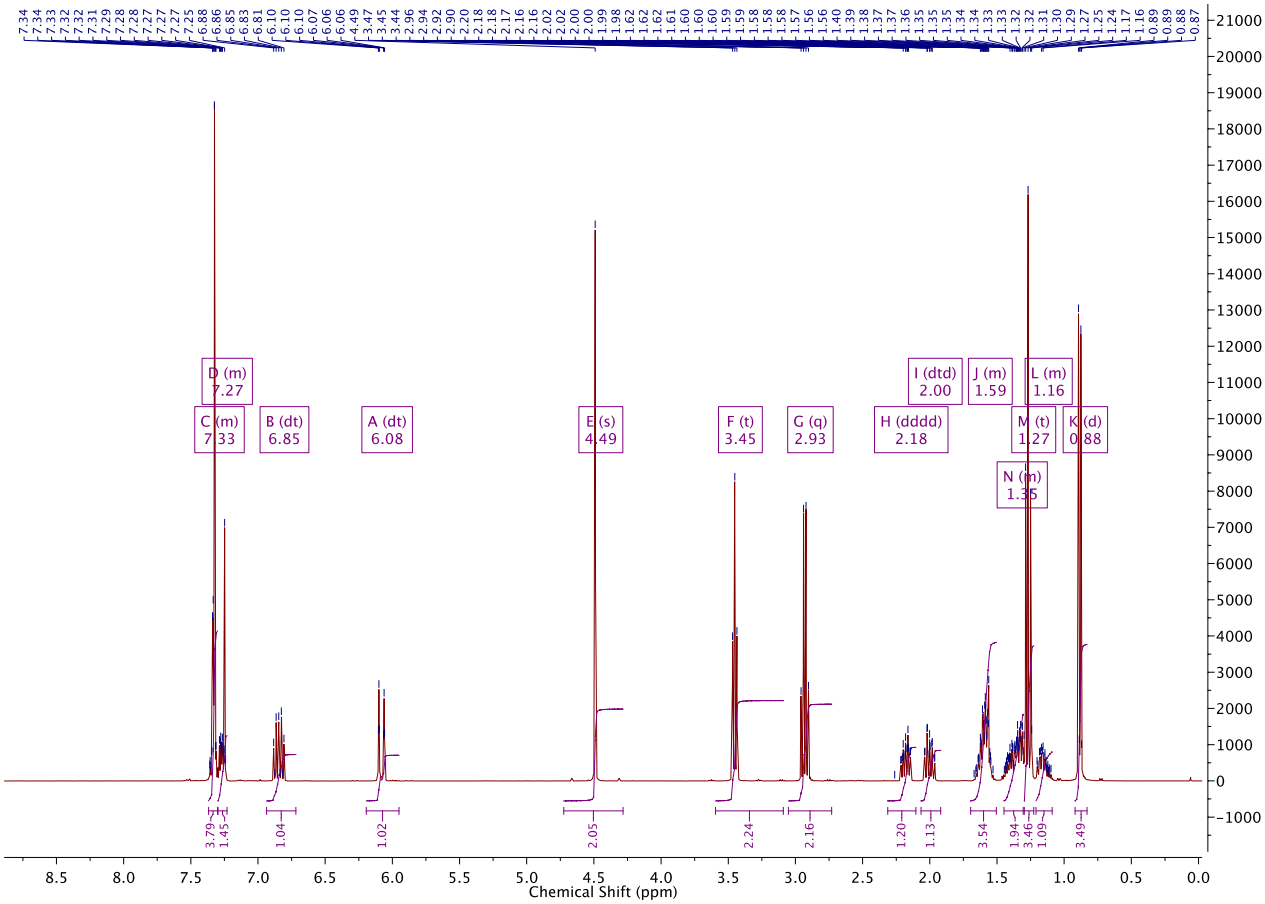
2.54 ml n-BuLi (1.5M solution in hexane, 4.05mmol, 1.5 eq.) was added to a stirring solution of $(EtO)_2POCHCOSEt$ (0.97g, 4.05 mmol, 1.5 eq.) in 15 ml THF at 0°C under argon. The mixture was stirred for another 20 min. A solution of (*R*)-7-(benzyloxy)-3-methylheptanal (0.611g, 2.6mmol, 1.0 eq.) in 2.0 ml THF was added dropwise. The mixture was slowly warmed to room temperature and was continued overnight. The mixture was quenched with aqueous NH_4Cl (sat.). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried ($MgSO_4$), filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 90:10; SiO_2) to afford the desired α, β-unsaturated thioester (0.794g, 2.47mmol, 95%)

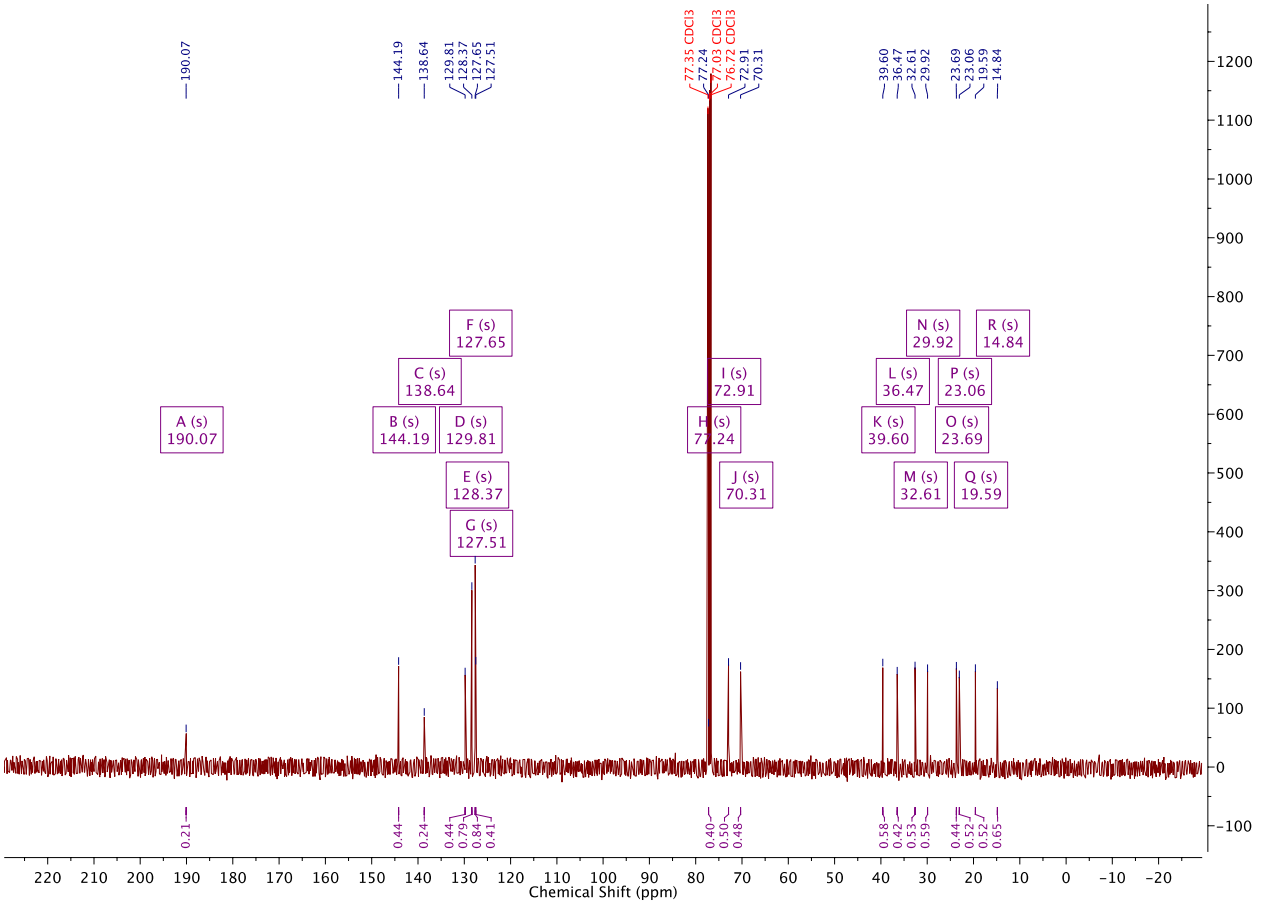
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.37 – 7.30 (m, 4H, Ar-*H*), 7.30 – 7.23 (m, 1H, Ar-*H*), 6.85 (dt, *J* = 15.3 Hz, 7.5 Hz, 1H, C*H*CH_3), 6.08 (dt, *J* = 15.4 Hz, 1.5 Hz, 1H, CH=C*H*CH_2), 4.49 (s, 2H, PhC*H*$_2$O), 3.45 (t, *J* = 6.5 Hz, 2H, OC*H*$_2$), 2.93 (q, *J* = 7.4 Hz, 2H, SC*H*$_2CH_3$), 2.18 (dddd, *J* = 14.3 Hz, 7.2 Hz, 5.6 Hz, 1.5 Hz, 1H, C*H*$_2$CH=CH), 2.00 (dtd, *J* = 14.2 Hz, 7.6 Hz, 1.4 Hz, 1H, C*H*$_2$CH=CH), 1.70 – 1.51 (m, 4H, C*H*, C*H*$_2$), 1.45 – 1.30 (m, 2H, C*H*$_2$), 1.27 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 1.21 – 1.09 (m, 1H, C*H*$_2$), 0.88 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 190.1, 144.2, 138.6, 129.8, 128.4(2C), 127.7(2C), 127.5, 72.9, 70.3, 39.6, 36.5, 32.6, 29.9, 23.7, 23.1, 19.6, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2981,1669,1632,1381,1154,970,735

HRMS (ESI) m/z calc. for $C_{19}H_{29}O_2{}^{32}S$, $[M+H]^+$: 321.1883, found: 321.1886


D (m) 7.27
C (m) 7.33
B (dt) 6.85
A (dt) 6.08
E (s) 4.49
F (t) 3.45
G (q) 2.93
H (dddd) 2.18
I (dtd) 2.00
J (m) 1.59
N (m) 1.35
M (t) 1.27
L (m) 1.16
K (d) 0.88
Chemical Shift (ppm)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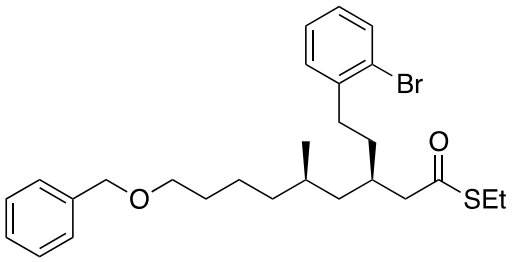
B (s) 144.19
C (s) 138.64
D (s) 129.81
E (s) 128.37
F (s) 127.65
G (s) 127.51
H (s) 77.24
I (s) 72.91
J (s) 70.31
K (s) 39.60
L (s) 36.47
M (s) 32.61
N (s) 29.92
O (s) 23.69
P (s) 23.06
Q (s) 19.59
R (s) 14.84
Chemical Shift (ppm)

(–)-*S*-ethyl (3*R*,5*R*)-9-(benzyloxy)-3-(2-bromophenethyl)-5-methylnonanethioate (5c)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of 1-bromo-2-vinylbenzene (92 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear red solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (*R*, *E*)-9-(benzyloxy)-5-methylnon-2-enethioate (64.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (85 mg, 0.17mmol, 85% yield).

HPLC analysis indicated a diastereomeric ratio of 97.5: 2.5 [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 7.21 min; minor enantiomer, tR = 7.63 min].

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.48 – 7.37 (m, 1H, Ar-*H*), 7.27 (d, *J* = 4.4 Hz, 4H, Ar-*H*), 7.23 – 7.16 (m, 1H, Ar-*H*), 7.16 – 7.11 (m, 2H, Ar-*H*), 6.96 (ddd, *J* = 8.0 Hz, 5.5 Hz, 3.6 Hz,

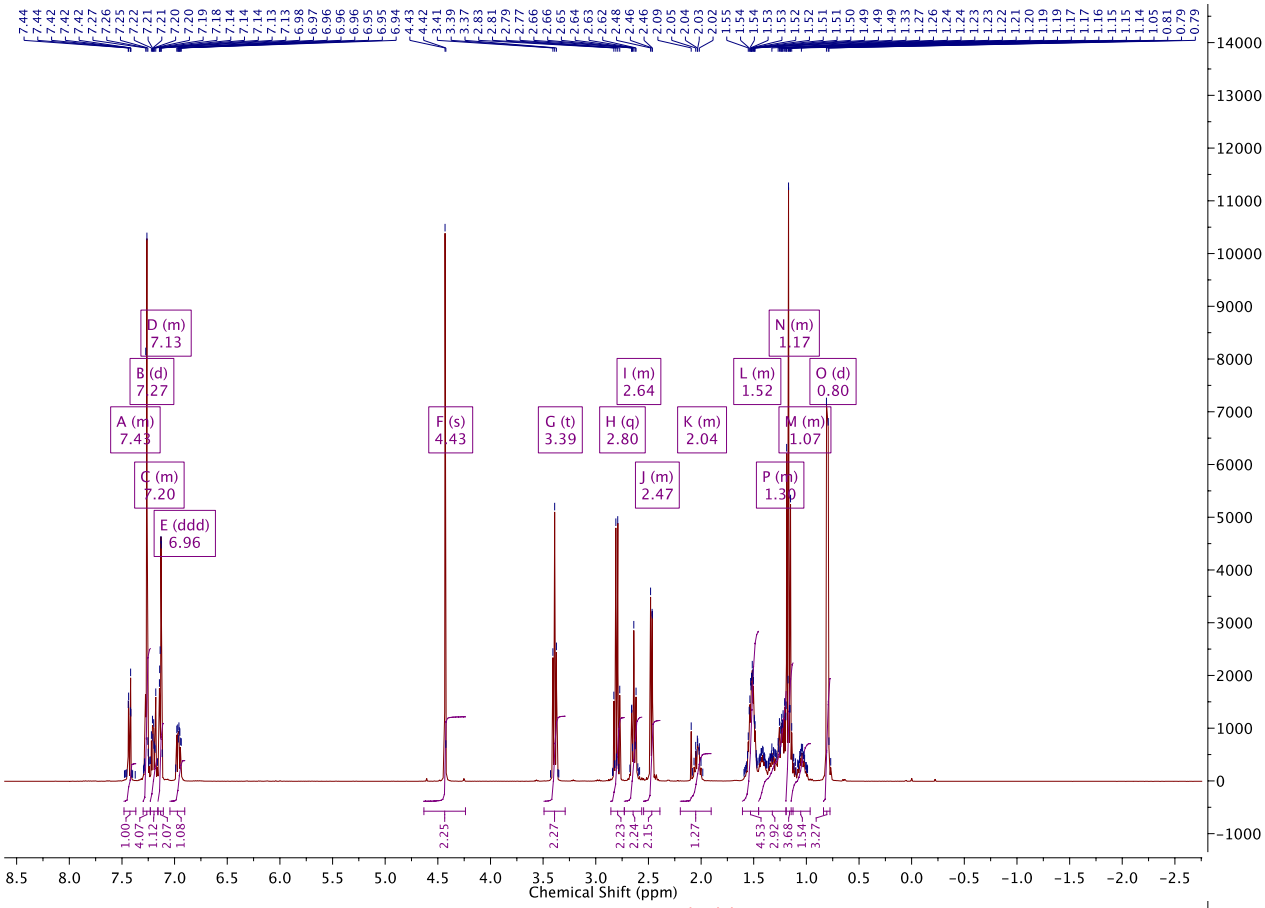
1H, Ar-*H*), 4.43 (s, 2H, PhCH_2O), 3.39 (t, *J* = 6.6 Hz, 2H, OCH_2), 2.80 (q, *J* = 7.4 Hz, 2H, SCH_2CH$_3$), 2.73 – 2.56 (m, 2H, CH_2PhBr), 2.55 – 2.39 (m, 2H, CH_2CO), 2.20 – 1.90 (m, 1H, C*H*), 1.61 – 1.45 (m, 5H, C*H,* CH_2), 1.45 – 1.19 (m, 3H, CH_2), 1.19 – 1.13 (m, 4H, SCH$_2$CH_3, CH_2), 1.15 – 0.96 (m, 2H, CH_2), 0.80 (d, J = 6.5 Hz, 3H, CH_3).

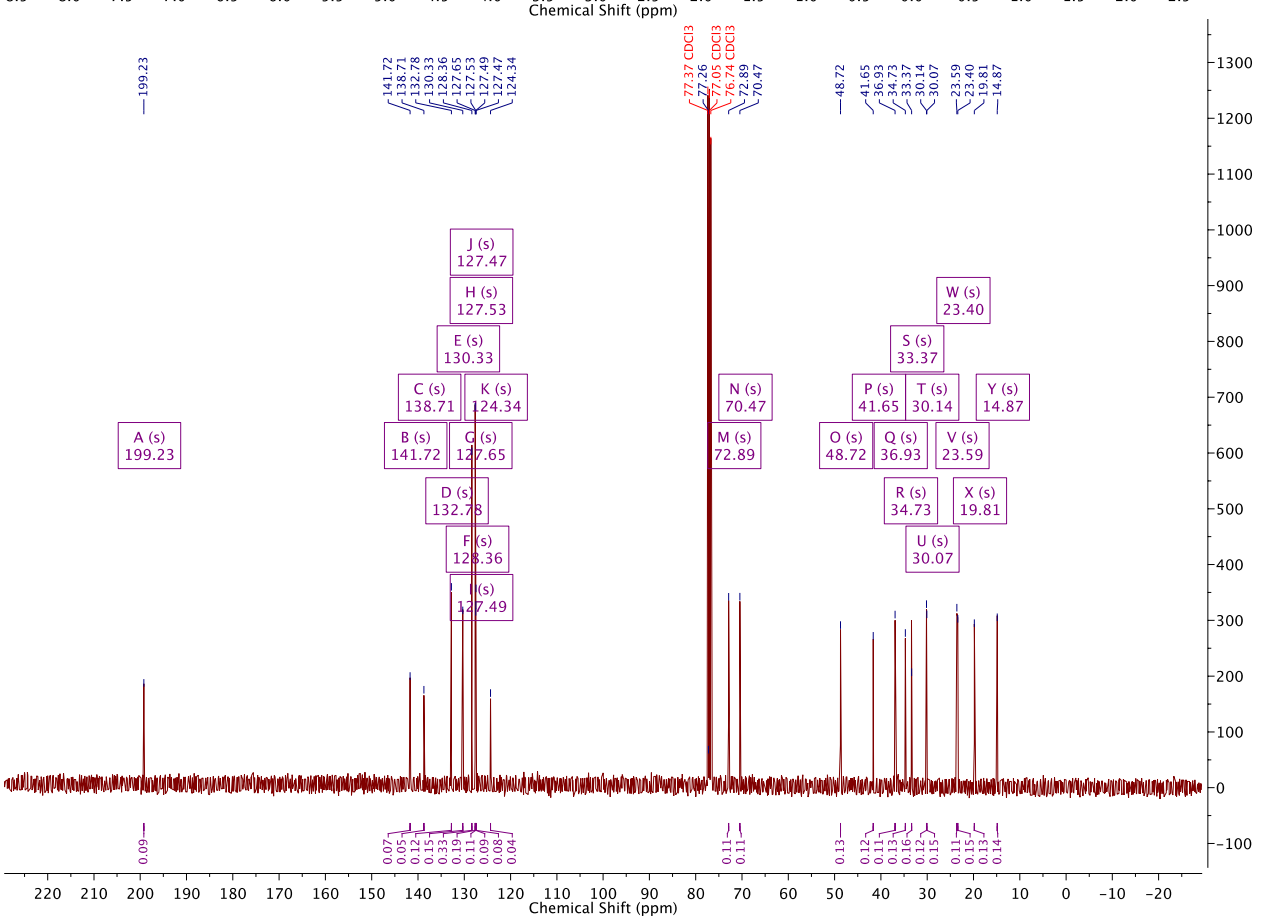
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.2, 141.7, 138.7, 132.8, 130.3, 128.4(2C), 127.7(2C), 127.5, 127.5, 127.4, 124.3, 72.9, 70.5, 48.7, 41.7, 36.9(2C), 34.7, 33.4, 30.1, 30.0, 23.6, 23.4, 19.8, 14.9.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2930, 2858,2360,1687,1455,1101,1023,749

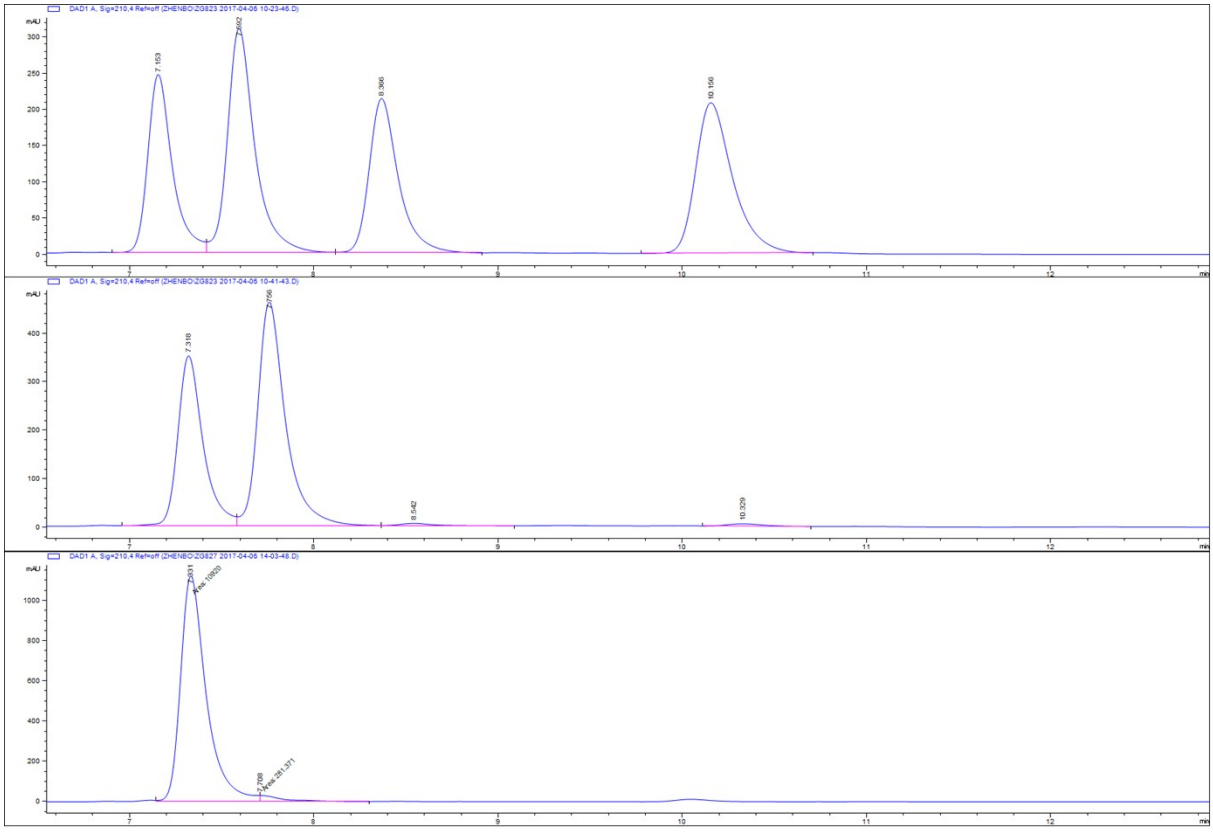
HRMS (ESI) m/z calc. for $C_{27}H_{37}O_2{}^{79}Br^{23}Na^{32}S$, $[M+Na]^+$: 527.1590, 529.1569, found: 527.1588, 529.1564

$[\alpha]^{20}_{589}$ = -6.5 ° (c 1.0, $CHCl_3$)

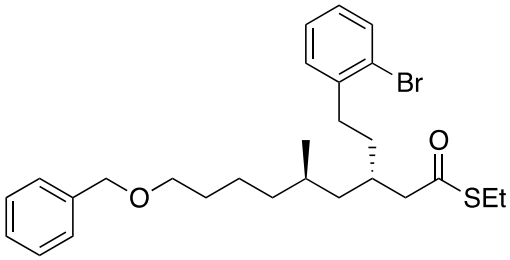

D (m) 7.13
B (d) 7.27
A (m) 7.43
C (m) 7.20
E (ddd) 6.96
F (s) 4.43
G (t) 3.39
I (m) 2.64
H (q) 2.80
K (m) 2.04
J (m) 2.47
N (m) 1.17
L (m) 1.52
O (d) 0.80
M (m) 1.07
P (m) 1.30
Chemical Shift (ppm)


A (s) 199.23
B (s) 141.72
C (s) 138.71
D (s) 132.78
E (s) 130.33
F (s) 128.36
G (s) 127.65
H (s) 127.53
J (s) 127.47
K (s) 124.34
M (s) 72.89
N (s) 70.47
O (s) 48.72
P (s) 41.65
Q (s) 36.93
R (s) 34.73
S (s) 33.37
T (s) 30.14
U (s) 30.07
V (s) 23.59
W (s) 23.40
X (s) 19.81
Y (s) 14.87
Chemical Shift (ppm)

HPLC trace



(–)-*S*-ethyl (3*S*,5*R*)-9-(benzyloxy)-3-(2-bromophenethyl)-5-methylnonanethioate (5d)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of 1-bromo-2-vinylbenzene (92 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear red solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture

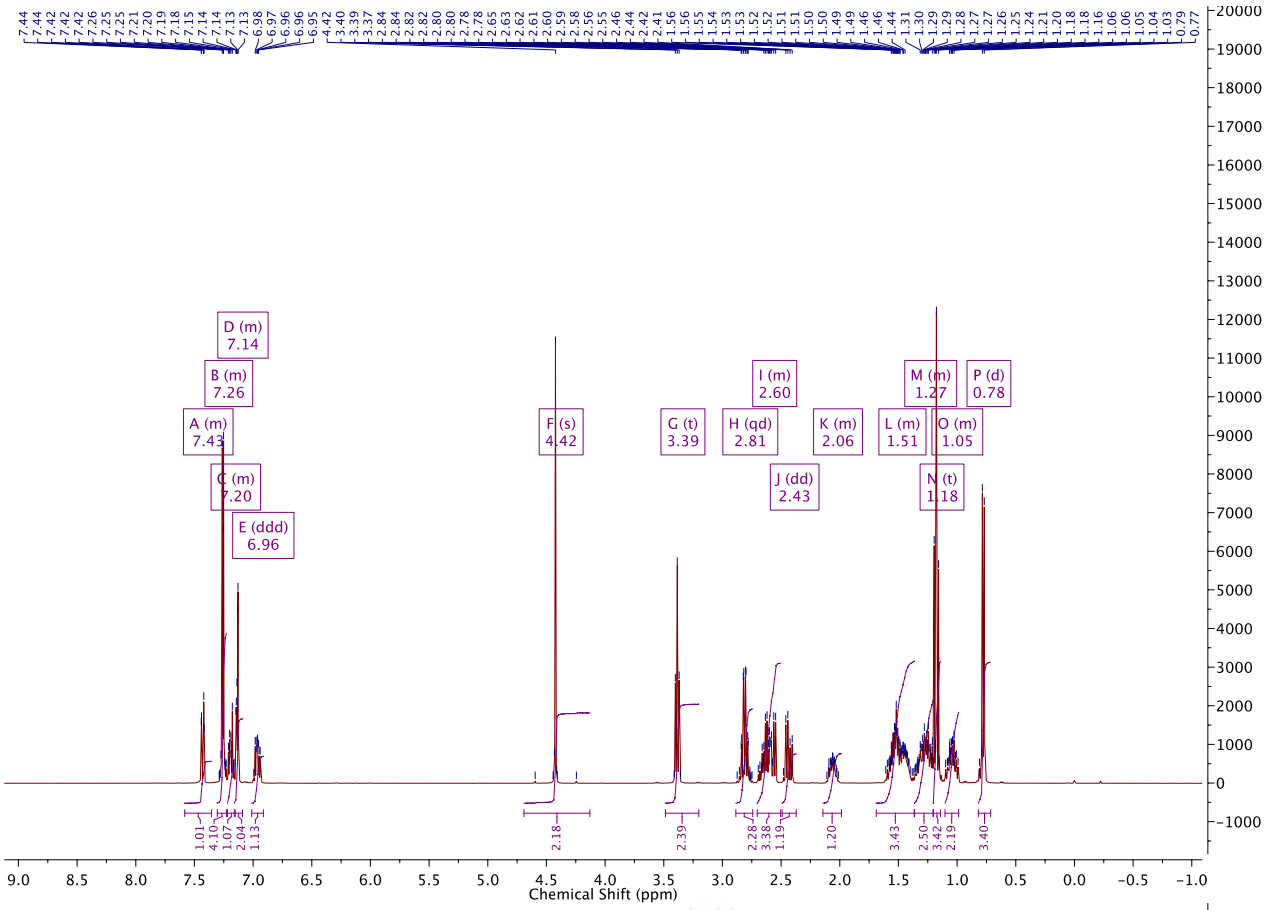
was stirred for another 10 min before S-ethyl (*R, E*)-9-(benzyloxy)-5-methylnon-2-enethioate (64.0 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (85 mg, 0.17mmol, 85% yield).
HPLC analysis indicated a diastereomeric ratio 98:2 [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 7.94 min; minor enantiomer, tR = 7.53 min].

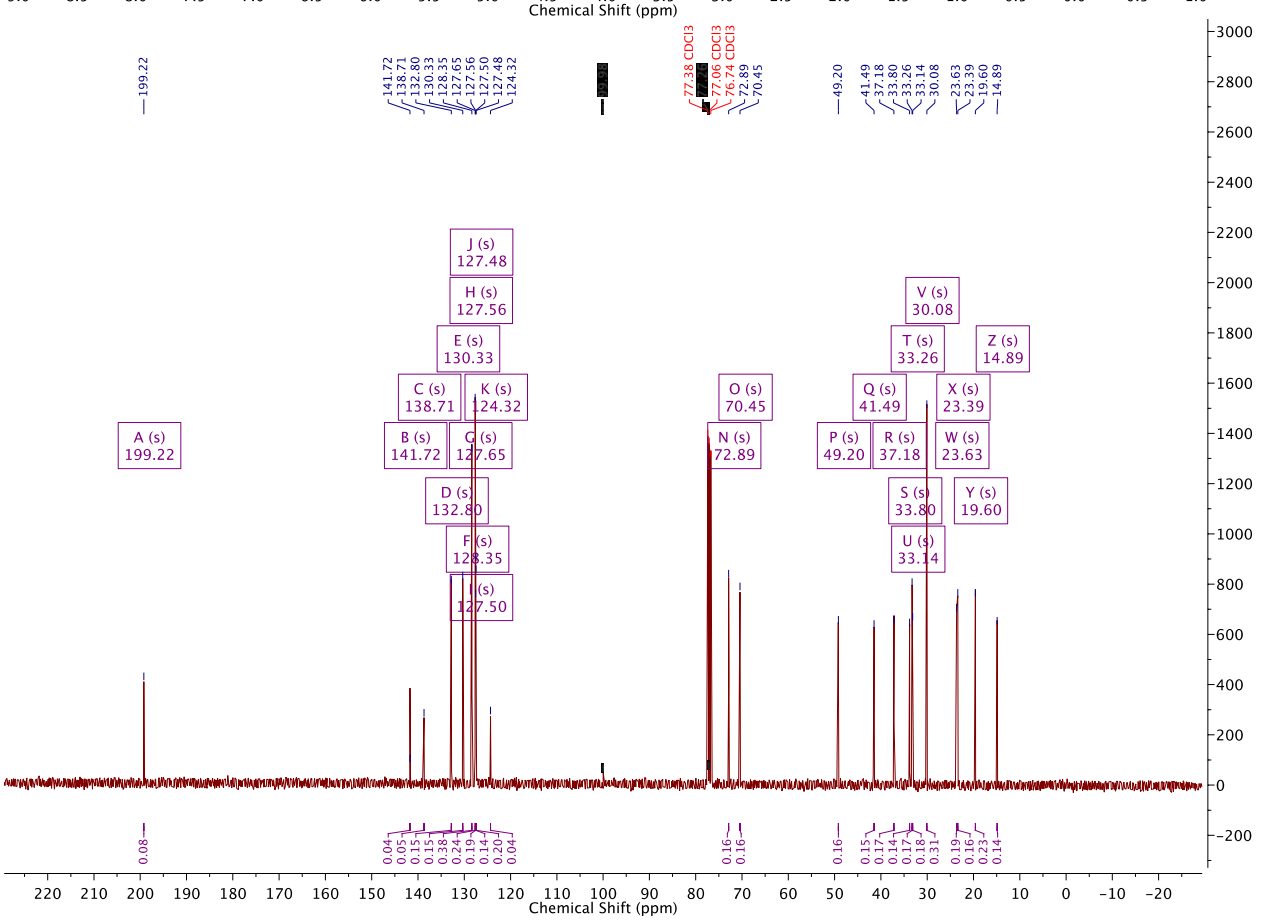
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.58 – 7.35 (m, 1H, Ar-*H*), 7.30 – 7.23 (m, 4H, Ar-*H*), 7.22 – 7.15 (m, 1H, Ar-*H*), 7.16 – 7.09 (m, 2H, Ar-*H*), 6.96 (ddd, *J* = 8.0 Hz, 5.7 Hz, 3.4 Hz, 1H, Ar-*H*), 4.42 (s, 2H, PhCH_2O), 3.39 (t, *J* = 6.6 Hz, 2H, OCH_2), 2.81 (qd, *J* = 7.4 Hz, 1.6 Hz, 2H, SCH_2CH$_3$), 2.70 – 2.50 (m, 3H, CH_2PhBr, CH_2CO), 2.43 (dd, *J* = 14.8 Hz, 7.1 Hz, 1H, CH_2CO), 2.14 – 1.99 (m, 1H, C*H*), 1.69 – 1.37 (m, 5H, C*H,* CH_2), 1.36 – 1.20 (m, 4H, CH_2), 1.18 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3), 1.10 – 0.99 (m, 2H, CH_2), 0.78 (d, *J* = 6.5 Hz, 3H, C*H*CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.2, 141.7, 138.7, 132.8, 130.3, 128.4(2C), 127.7(2C), 127.6, 127.5, 127.4, 124.3, 72.9, 70.5, 49.2, 41.5, 37.2, 33.8, 33.3, 33.1, 30.1(2C), 23.6, 23.4, 19.6, 14.9.
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2930, 2859,2360,1686,1455,1101,1023,749

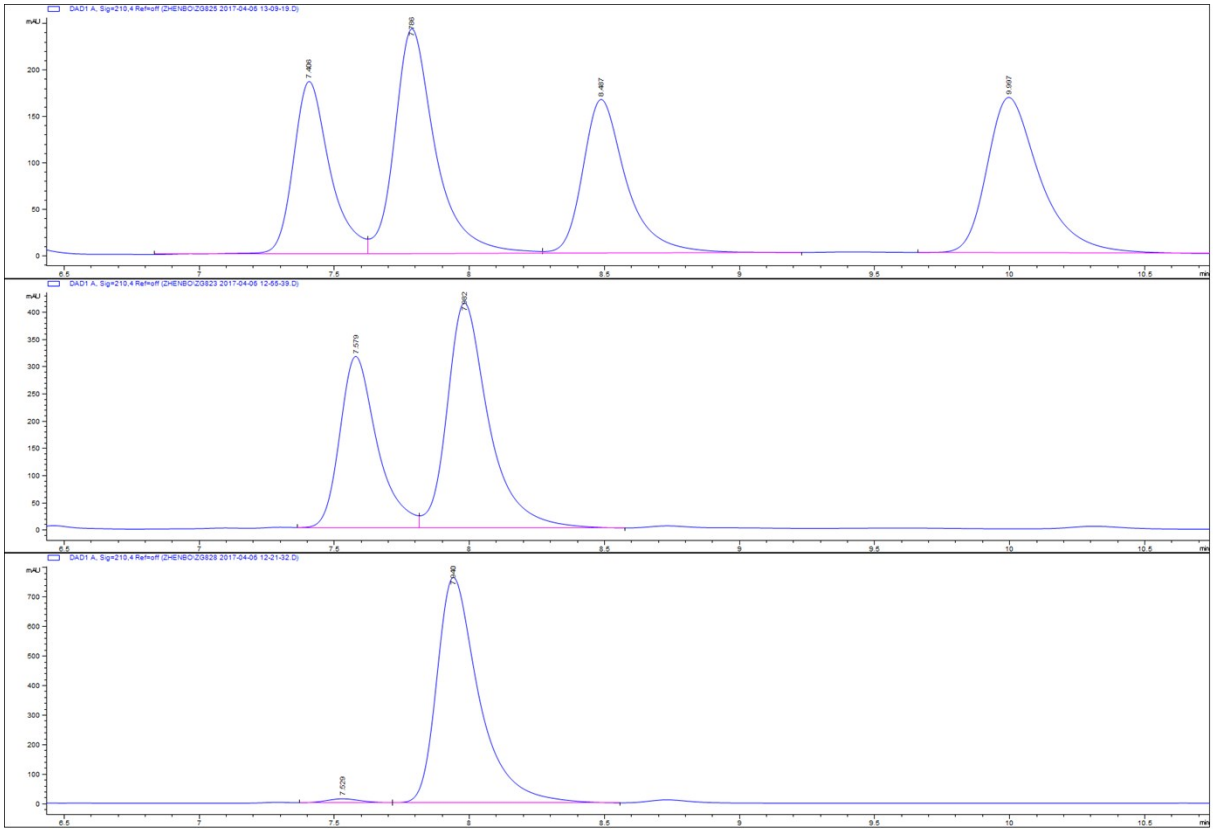
HRMS (ESI) m/z calc. for $C_{27}H_{37}O_2{}^{79}Br^{23}Na^{32}S$, $[M+Na]^+$: 527.1590, 529.1569, found: 527.1588, 529.1564

$[\alpha]^{20}_{589}$ = -7.8 ° (c 1.0, $CHCl_3$)

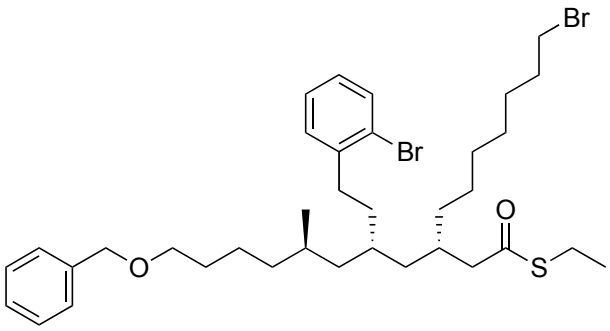

D (m) 7.14
B (m) 7.26
A (m) 7.43
C (m) 7.20
E (ddd) 6.96
F (s) 4.42
G (t) 3.39
I (m) 2.60
H (qd) 2.81
J (dd) 2.43
K (m) 2.06
M (m) 1.27
P (d) 0.78
L (m) 1.51
O (m) 1.05
N (t) 1.18
Chemical Shift (ppm)


A (s) 199.22
J (s) 127.48
H (s) 127.56
E (s) 130.33
C (s) 138.71
K (s) 124.32
B (s) 141.72
G (s) 127.65
D (s) 132.80
F (s) 128.35
I (s) 127.50
O (s) 70.45
N (s) 72.89
V (s) 30.08
T (s) 33.26
Z (s) 14.89
Q (s) 41.49
X (s) 23.39
P (s) 49.20
R (s) 37.18
W (s) 23.63
S (s) 33.80
Y (s) 19.60
U (s) 33.14
Chemical Shift (ppm)

HPLC trace



(–)-*S*-ethyl (3*S*,5*S*,7*R*)-11-(benzyloxy)-3-(7-bromoheptyl)-5-(2-bromophenethyl)-7-methylundecanethioate (5f)



CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and the phosphoramidite ligand (22.3 mg, 0.04 mmol 0.2 eq.) were added to a flame dried round bottom flask containing 1.6 ml DCM/Et_2O (1/1) under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (11.2mg, 0.44mmol, 0.22 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, containing a stirred solution of 7-bromohept-1-

ene (88 mg, 0.5mmol, 2.5 eq.) in DCM, under an argon atmosphere was added Cp_2ZrHCl (103mg, 0.4mmol, 2.0 eq.), and after stirring for 15 min, a clear red solution was obtained.
The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before S-ethyl (5S,7R,E)-11-(benzyloxy)-5-(2-bromophenethyl)-7-methylundec-2-enethioate **5e** (106 mg, 0.2mmol, 1.0 eq.) and TMSCl (0.127ml, 1mmol, 5.0eq.) were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 40 additional hours, before the reaction was quenched by the addition of NH_4Cl (1.5 ml sat. aq.) and then Et_2O (1.5 ml). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (104 mg, 0.15mmol, 73% yield).

HPLC analysis indicated a diastereomeric ratio of 98: 2 [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 7.71 min; minor enantiomer, tR = 7.17 min].

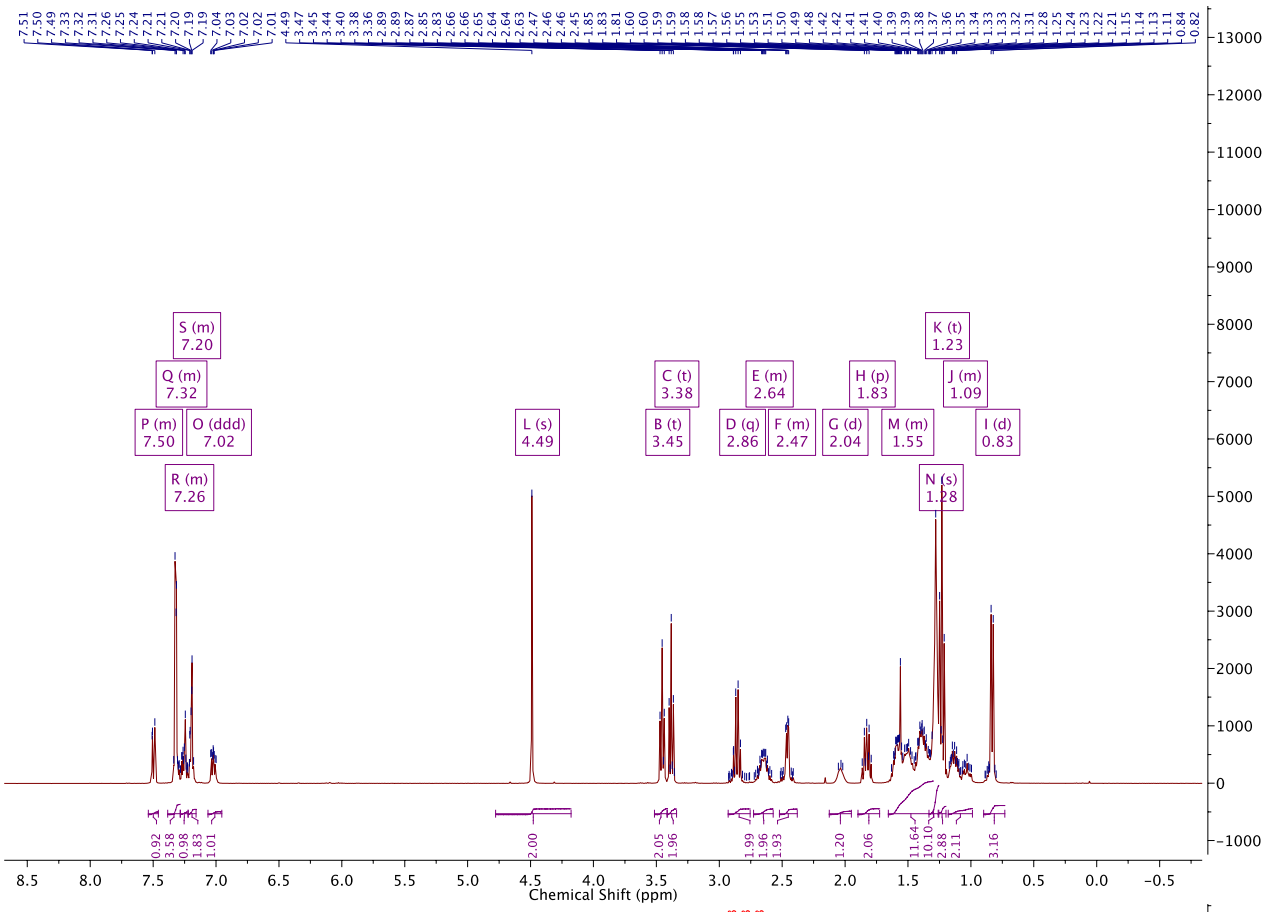
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H/ppm 7.54 – 7.46 (m, 1H, Ar-*H*), 7.38 – 7.29 (m, 4H, Ar-*H*), 7.28 – 7.22 (m, 1H, Ar-*H*), 7.22 – 7.16 (m, 2H, Ar-*H*), 7.02 (m, 1H, Ar-*H*), 4.49 (s, 2H, PhCH_2O), 3.45 (t, *J* = 6.6 Hz, 2H, OCH_2), 3.38 (t, *J* = 6.9 Hz, 2H, CH_2Br), 2.86 (q, *J* = 7.2 Hz, 2H, SCH_2CH$_3$), 2.73 – 2.57 (m, 2H, CH_2PhBr), 2.52 – 2.38 (m, 2H, CH_2CO), 2.04 (d, *J* = 8.4 Hz, 1H, C*H*), 1.83 (p, *J* = 6.9 Hz, 2H, C*H,* C*H*), 1.66 – 1.30 (m, 12H, CH_2), 1.28 (m, 10H, CH_2), 1.23 (t, *J* = 7.4 Hz, 3H, CH_2), 1.18 – 0.99 (m, 2H, CH_2), 0.83 (d, *J* = 6.6 Hz, 3H, CHCH_3).

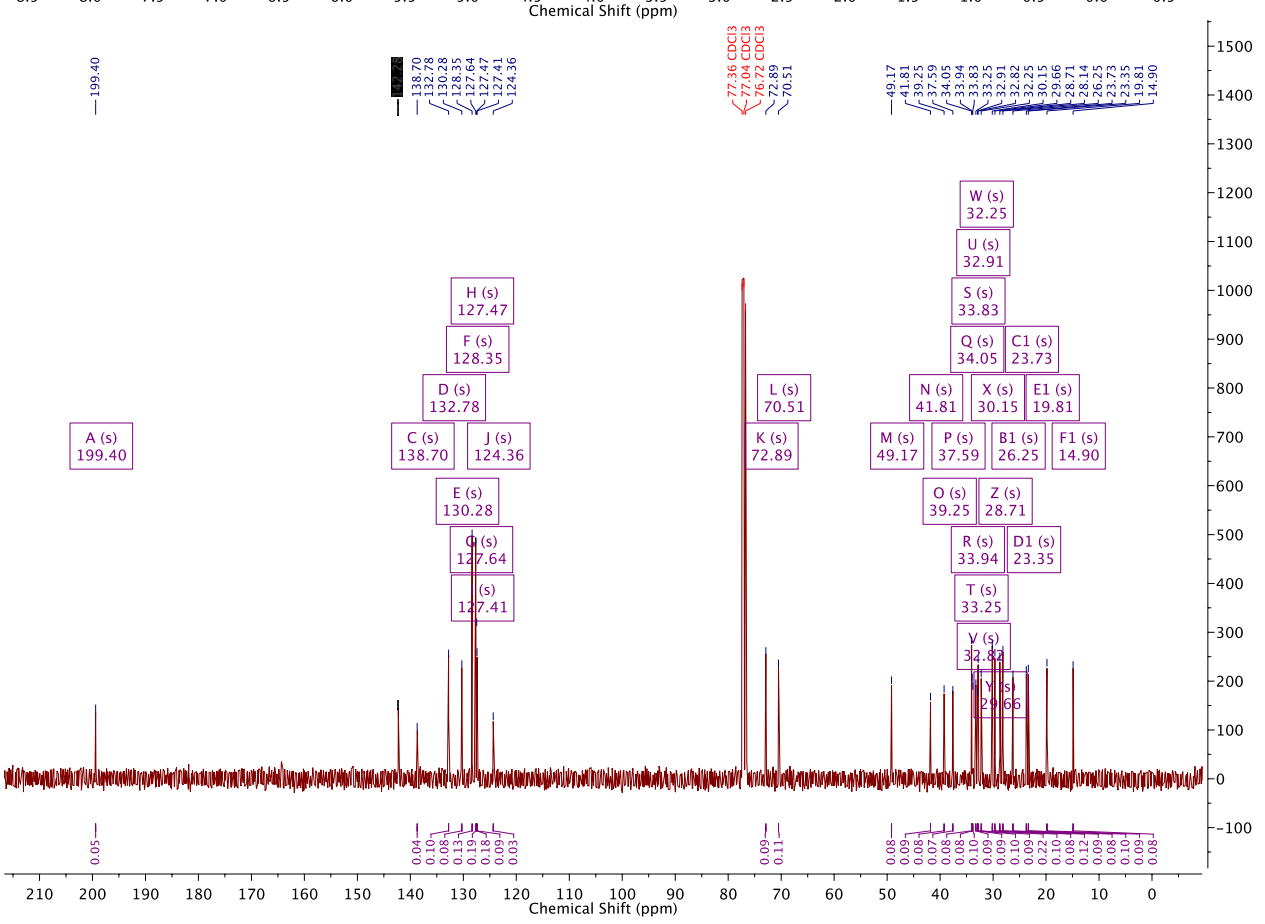
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C/ppm 199.4, 142.2, 138.7, 132.8, 130.3, 128.4(2C), 127.6(2C), 127.5 (2C), 127.4, 124.4, 72.9, 70.5, 49.2, 41.8, 39.3, 37.6, 34.1, 33.9, 33.8, 33.3, 32.9, 32.8, 32.3, 30.2(2C), 29.7, 28.7, 28.1, 26.3, 23.7, 23.4, 19.8, 14.9.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2927, 2854, 1687,1454,1101,1023,748

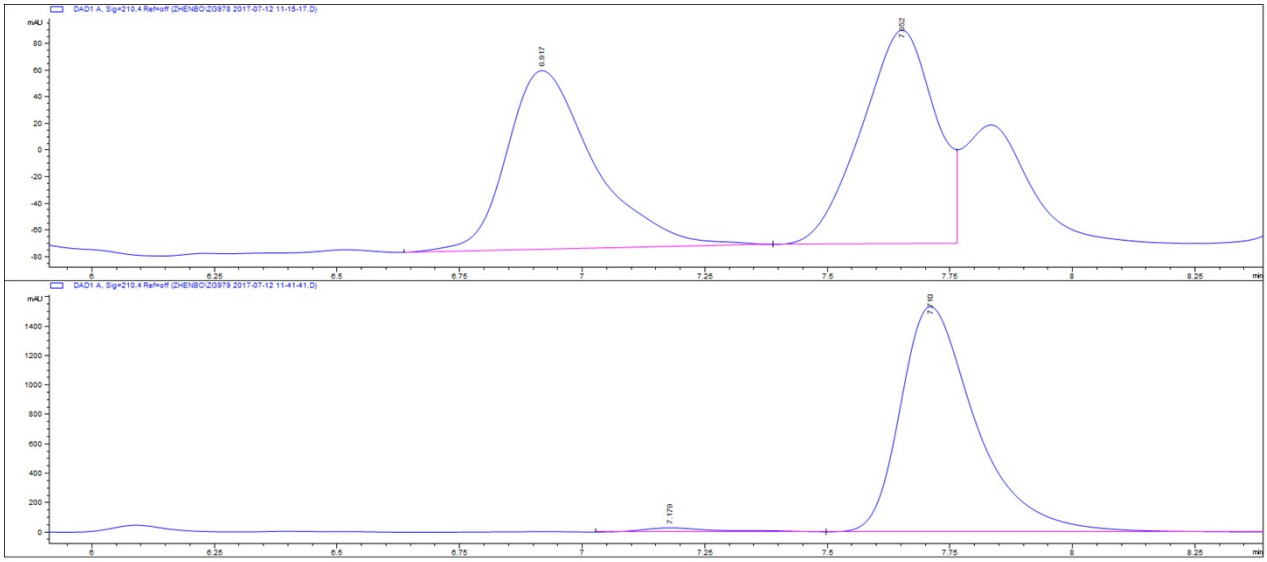
HRMS (ESI) m/z calc. for $C_{36}H_{55}O_2{}^{79}Br_2{}^{32}S$, $[M+H]^+$: 709.2284, 711.2264, 713.2243, 714.2277 found: 709.2285, 711.2261, 713.2240, 714.2274

$[\alpha]^{20}_{589}$ = -16.7 ° (c 1.0, $CHCl_3$)


S (m) 7.20
Q (m) 7.32
P (m) 7.50
O (ddd) 7.02
R (m) 7.26
L (s) 4.49
C (t) 3.38
B (t) 3.45
E (m) 2.64
D (q) 2.86
F (m) 2.47
H (p) 1.83
G (d) 2.04
M (m) 1.55
K (t) 1.23
J (m) 1.09
I (d) 0.83
N (s) 1.28
Chemical Shift (ppm)


A (s) 199.40
C (s) 138.70
D (s) 132.78
F (s) 128.35
H (s) 127.47
E (s) 130.28
J (s) 124.36
L (s) 70.51
K (s) 72.89
M (s) 49.17
N (s) 41.81
P (s) 37.59
Q (s) 34.05
S (s) 33.83
R (s) 33.94
U (s) 32.91
W (s) 32.25
T (s) 33.25
B1 (s) 26.25
F1 (s) 14.90
C1 (s) 23.73
E1 (s) 19.81
X (s) 30.15
O (s) 39.25
Z (s) 28.71
D1 (s) 23.35
Chemical Shift (ppm)

HPLC trace



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