Z-Selective Copper-Catalyzed Asymmetric Allylic Alkylation with Grignard Reagents

Giannerini, Massimo; Fananas-Mastral, Martin; Feringa, B.L.; Fañanás-Mastral, Martín

Published in:
Journal of the American Chemical Society

DOI:
10.1021/ja300743t

Publication date:
2012

SUPPORTING INFORMATION

Z-Selective Copper-Catalyzed Asymmetric Allylic Alkylation with Grignard Reagents

Massimo Giannerini, Martín Fañanás-Mastral and Ben L. Feringa*

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands.

Table of Contents

General Methods:

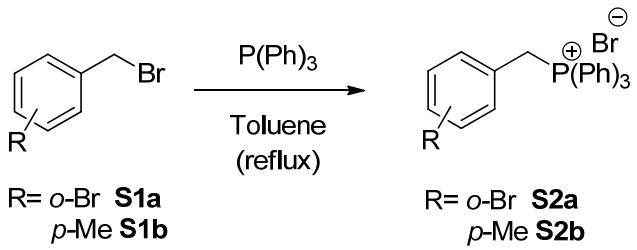
Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) or a Varian Mercury Plus (200 and 50 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Carbon assignments are based on APT ^{13}C-NMR experiments. Optical rotations were measured on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Enantiomeric ratios were determined by HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector or by capillary GC analysis (HP 6890, CP-Chiralsil-Dex-CB column (25 m x 0.25 mm) or Chiraldex B-PM (30 m x 0.25 mm x 0.25 μm)) using flame ionization detector.

All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. Dichloromethane was dried and distilled over calcium hydride; toluene was dried and distilled over sodium. Benzyl bromides **S1**, *trans*-cinnamaldehyde **S3**, the phosphorus ylides **S4** and copper salts (CuI and copper thiophene-2-carboxylate (CuTC)) were purchased from Aldrich, and used without further purification. Grignard reagents were purchased from Aldrich (MeMgBr (3.0 M in Et_2O), EtMgBr (3.0 M in Et_2O), *n*-HexMgBr (2.0 M in Et_2O), *i*-BuMgBr (2.0 M in Et_2O), Ligands **DavePhos** and **XPhos**, cesium fluoride, 9-BBN, palladium salts (tris-(dibenzylideneacetone)dipalladium(0) ($Pd_{2(}dba)_{3)}$ and palladium acetate ($Pd(OAc)_2$) and boronic acids were purchased from Aldrich. 1,1-Dichloroacetaldehyde hydrate **S5** was purchased from TCI. Phosphoramidite ligands **L1,2**[1] and **L3,4**[2] were prepared as reported in the literature. Racemic products were synthesized by reaction of the *gem*-dichlorides (**1**) and the

[1] Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623.
[2] Tissot-Croset, K.; Polet, D.; Gille, S.; Hawner, C.; Alexakis, A. *Synthesis* **2004**, 2586–2590.

corresponding Grignard reagent at -78°C in CH_2Cl_2 in the presence of CuI (10 mol%) and PPh_3 (20 mol%).

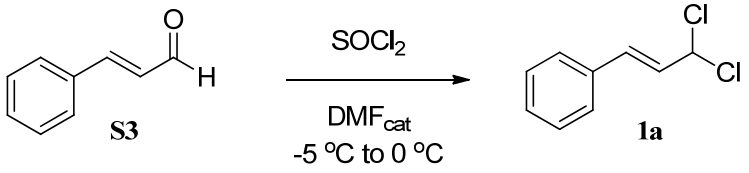
Synthesis of phosphonium salts S2:



The corresponding benzyl bromide (12 mmol) and triphenylphosphine (3.54 g, 13.5 mmol) were dissolved in toluene (60 mL) and the mixture was heated at reflux with vigorous stirring for 3 h (**S1a**) or 12 h (**S1b**). During this time a white crystalline solid precipitated from solution. The reaction mixture was cooled to room temperature and then filtered. The solid was washed with hexane to afford the products in 93% (**S2a**) and 95% (**S2b**) yield as white powders. The resulting salts were used in the next step without additional purification.

General procedure for the synthesis of *gem*-dichlorides 1:

-Method A: [3]

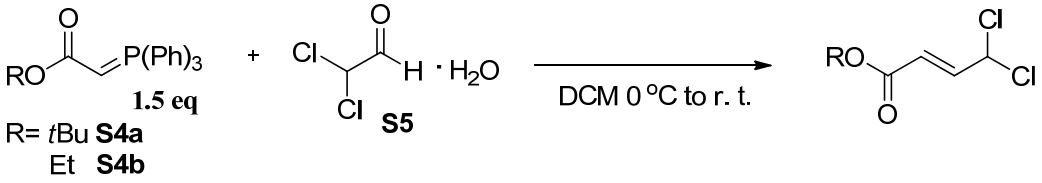


To a solution of $SOCl_2$ (35 ml, 0.48 mol) and DMF (1 ml, 13 mmol), *trans*-cinnamaldehyde **S3** (7 g, 53 mmol) was added dropwise at -5 °C. After 4 hours the reaction was carefully quenched

[3] Newman, M. S.; Sujeeth, P. K. *J. Org. Chem.* **1978**, *43*, 4367–4369

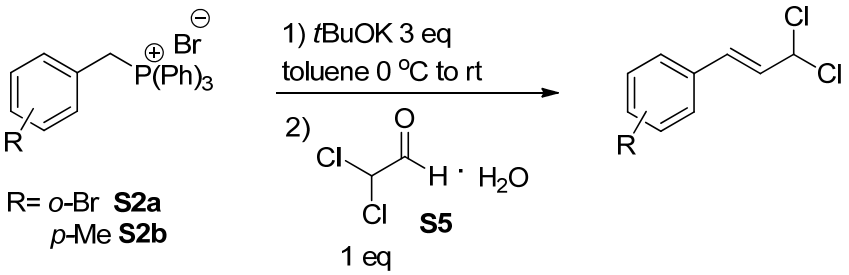
by pouring it on ice and the mixture was extracted with diethylether when still cold. The organic phase was dried over $MgSO_4$ and th solvent evaporated under reduced pressure. The resultant brown solid was purified by column chromatography using a mixture of *n*-pentane/NEt_3 200:1 to afford the desired compound as a white solid (8.52 g 86%).

-Method B:



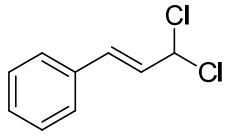
In a Schlenk flask equipped with magnetic stirring bar, dried under vacuum and then purged with nitrogen, 1,1-dichloroacetaldehyde hydrate **S5** (1 equiv.) was added to a solution of the corresponding commercially available phosphorous ylide **S4** (1.5 equiv.) in dry DCM at 0 °C. Then the solution was allowed to reach room temperature and was stirred for 4 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with dichloromethane. The organic phase was dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude mixture was then purified by column chromatography using a mixture of *n*-pentane/AcOEt. .

-Method C:

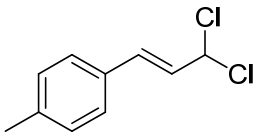


In a Schlenk equipped with magnetic stirring bar, dried under vacuum and then purged with nitrogen the corresponding phosphonium salt **S2** (3 equiv.) and *t*BuOK (3 equiv.) were placed. The flask was then put under vacuum and the content allowed to stir for 10 min. Then the flask was filled with nitrogen and toluene was added. The suspension was allowed to stir for 30 min. **S5** (1 equiv.) was added and the reaction mixture was allowed to stir for 4 more hours. The reaction was quenched with an aqueous saturated solution of NH_4Cl and the mixture was extracted with DCM. The organic phase was dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude mixture was then purified by column chromatography using a mixture of *n*-pentane/NEt_3

Characterization of *gem*-dichlorides 1:

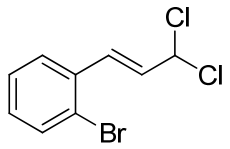


(*E*)-1-(3,3-dichloroprop-1-en-1-yl)-benzene (1a): Synthesized according to **Method A**. White solid [8.52 g, 86% yield] obtained as pure *E* isomer after column chromatography (SiO_2, *n*-pentane/ NEt_3 200:1. ^{1}H NMR (400 MHz, $CDCl_3$) 7.48 – 7.28 (m, 5H), 6.73 (d, *J* = 15.5 Hz, 1H), 6.46 (dd, *J* = 15.5, 7.9 Hz, 1H), 6.35 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 132.2, 129.1, 128.8, 127.9, 127.3, 71.3.

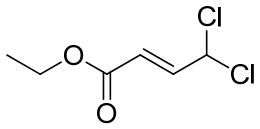


(*E*)-1-(3,3-dichloroprop-1-en-1-yl)-4methylbenzene (1b): Synthesized according to **Method C** (**S2b** 4.2 g, 9 mmol; 1,1-dichloroacetaldehyde hydrate **S5** 393 mg, 3 mmol; *t*BuOK 1g, 9 mmol). Colorless oil [247 mg, 41% yield] obtained as pure *E* isomer after column chromatography (SiO_2, the silica was flushed with *n*-pentane/ NEt_3 1:1 and then *n*-pentane was used as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.21 – 7.15 (m,

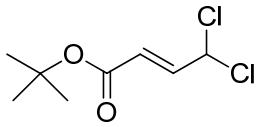
1H), 6.69 (d, J = 15.3 Hz, 1H), 6.43 (dd, J = 15.3, 8.0 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 132.1, 131.5, 129.5, 127.2, 126.9, 71.5, 21.3.



(*E*)-1-Bromo-2-(3,3-dichloroprop-1-en-1-yl)benzene (1c): Synthesized according to **Method C** (**S2a** 4.6 g, 9 mmol; 1,1-dichloroacetaldehyde hydrate **S5** 393 mg, 3 mmol; *t*BuOK 1g, 9 mmol). Yellow oil [391 mg, 49% yield] obtained as pure *E* isomer after column chromatography (SiO_2, the silica was flushed with *n*-pentane/ NEt_3 1:1 and then *n*-pentane was used as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.51(m, 2H), 7.36 – 7.23 (m, 1H), 7.21 – 7.15 (m, 1H), 7.10 (d, J = 13.8 Hz, 1H), 6.48 – 6.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 133.2, 130.8, 130.3, 130.3, 127.7, 127.5, 124.5, 70.8.



(*E*)-Ethyl-4,4-dichlorobut-2-enoate (1d): Synthesized according to **Method B** (**S4b** 1.04 g, 3 mmol; 1,1-dichloroacetaldehyde hydrate **S5** 196.5 mg, 1.5 mmol). Colorless oil [121 mg, 44% yield] obtained after column chromatography (SiO_2, *n*-pentane/EtOAc 200:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd J = 15.3, 6.9 Hz, 1H), 6.24 (d, J = 6.9 Hz, 1H), 6.12 (dd, J = 15.3, 0.8 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.9, 142.4, 123.1, 68.0, 61.2, 14.1.



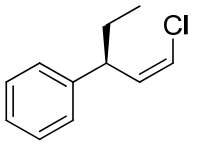
(*E*)-*tert*-Butyl-4,4-dichlorobut-2-enoate (1e): Synthetized according to **Method B** (**S4a** 1.13 g, 3 mmol; 1,1-dichloroacetaldehyde hydrate **S5** 196.5 mg, 1.5 mmol). White solid [136 mg, 43% yield] obtained after column chromatography (SiO_2, *n*-pentane/EtOAc 200:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 15.2, 6.9 Hz, 1H), 6.22 (d, *J* = 6.9 Hz, 1H), 6.05 (d, *J* = 15.2 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.1, 141.4, 124.9, 81.7, 68.2, 28.0.

General procedure for the copper-catalyzed allylic alkylation of *gem*-dichlorides 1 with Grignards reagents:

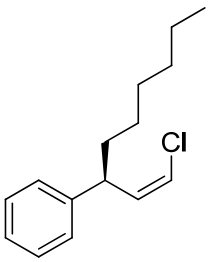
A Schlenk tube equipped with septum and stirring bar was charged with CuTC (0.015 mmol, 2.86 mg, 5 mol%) and the appropriate ligand (0.0165 mmol, 5.5 mol%). Dry dichloromethane (1 mL) was added and the solution was stirred under nitrogen at room temperature for 20 min. Then the corresponding *gem*-dichloride **1** (0.3 mmol), was dissolved in 1 ml of dichloromethane, was added and the resulting solution was cooled to -78°C. The corresponding Grignard reagent (0.45 mmol, 1.5 equiv.) was diluted with dichloromethane (combined volume of 0.9 mL) under nitrogen and added dropwise to the reaction mixture over 6 h using a syringe pump. Once the addition was complete, the mixture was stirred for two hours at -78°C. The reaction was quenched with a saturated aqueous NH_4Cl solution (2 mL) and the mixture was warmed up to room temperature, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried with anhydrous Mg_2SO_4, filtered and the the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using different mixtures of *n*-pentane:AcOEt as eluent.

Note: Gas chromatography analysis was carried out to determine the *Z*/*E* and S_N2'/ S_N2 product ratio on a sample obtained after aqueous extraction with dichloromethane, which has been passed through a short plug of silica gel to remove transition metal residues.

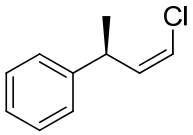
Characterization of optically active *Z*-vinyl chlorides 2:



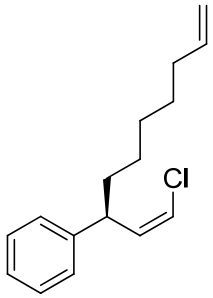
(+)-(*Z*)-1-Chloropent-1-en-3-ylbenzene (2a): Colorless oil obtained as pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [74% yield, 99:1 er]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39 – 7.09 (m, 5H), 6.09 (dd, *J* = 7.1, 0.8 Hz, 1H), 5.89 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.82 (dt, *J* = 9.6, 7.5 Hz, 1H), 1.91 – 1.60 (m, 2H), 0.97 – 0.84 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.3, 135.2, 128.5, 127.4, 126.4, 117.8, 45.0, 28.7, 11.9. $[\alpha]_D^{20}$ = +246.0 (*c* = 1.0, $CHCl_3$). HRMS (APCI+, *m/z*): calculated for $C_{11}H_{13}Cl$ [M+H$^+$]: 181.07785; found: 181.07803. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak OJ-H column, Heptane/*i*-PrOH 100:0, 40 °C, 210 nm, retention times (min): 15.3 (minor enantiomer), 16.4 (major enantiomer).



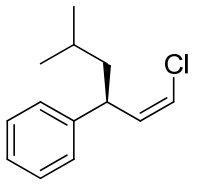
(+)-(*Z*)-1-Chloronon-1-en-3-ylbenzene (2b): Colorless oil obtained as pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [77% yield, 97:3 er]. ^{1}H NMR (201 MHz, $CDCl_3$) δ 7.35 – 7.02 (m, 5H), 5.98 (dd, *J* = 7.1, 0.7 Hz, 1H), 5.80 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.82 (dt, *J* = 9.6 7.6 Hz, 1H), 1.77-1.51 (m, 2H), 1.34-1.03 (m, 8H), 0.87-0.71 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.7, 135.5, 128.5, 127.4, 126.3, 117.5, 43.2, 35.7, 31.7, 29.2, 27.2, 22.6, 14.1. $[\alpha]_D^{20}$ = +142.8 (*c* = 1.0, $CHCl_3$). HRMS (APCI+, *m/z*): calculated for $C_{15}H_{22}Cl$ [M+H$^+$]: 237.14045; found: 237.14057. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak OJ-H column, Heptane/*i*-PrOH 100:0, 40 °C, 210 nm, retention times (min): 11.08 (minor enantiomer), 11.72 (major enantiomer).



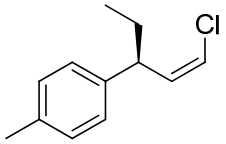
(+)-(*Z*)-1-Chlorobut-1-en-3-ylbenzene (2c): Colorless oil obtained as pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [56% yield, 95:5 er]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 4H), 6.05 (d, *J* = 7.1, 0.9 Hz, 1H), 5.90 (dd, *J* = 9.4, 7.1 Hz, 1H), 3.78 (dt, *J* = 9.4, 7.0 Hz, 1H), 1.40 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 136.4, 128.4, 126.9, 126.4, 117.1, 37.2, 20.5. $[\alpha]_D^{20}$ = +184.5 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak OB-H column, Heptane/*i*-PrOH 100:0, 40 °C, 210 nm retention times (min): 9.6 (major enantiomer), 10.1 (minor enantiomer).



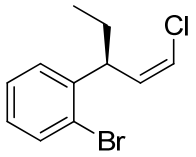
(+)-(*Z*)-1-Chlorodeca-1,9-dien-3-ylbenzene (2d): Colorless oil obtained as pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [72% yield, 98:2 er]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 – 7.10 (m, 5H), 6.07 (dd, *J* = 7.1, 0.7 Hz 1H), 5.95 – 5.65 (m, 2H), 5.08 – 4.83 (m, 2H), 3.90 (dt, *J* = 9.4, 7.6 Hz, 1H), 2.15 – 1.94 (m, 2H), 1.87 – 1.58 (m, 2H), 1.49 – 1.15 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.5, 139.0, 135.4, 128.5, 127.3, 126.3, 117.6, 114.2, 43.2, 35.6, 33.7, 28.9, 28.7, 27.1. $[\alpha]_D^{20}$ = +150.2 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak OJ-H column, Heptane/*i*-PrOH 100:0, 40 °C, 210 nm, retention times (min): 14.0 (minor), 14.9 (major). HRMS (APCI+, *m/z*): calculated for $C_{16}H_{22}Cl$ [M+H$^+$]: 249.14043; found: 249.14017.



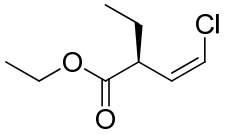
(+)-(*Z*)-1-Chloronon-1-en-3-ylbenzene (2e): Colorless oil obtained as pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [74% yield, 90:10 er]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 – 7.09 (m, 5H), 6.05 (dd, *J* = 7.1, 0.7 Hz, 1H), 5.86 (dd, *J* = 9.6, 7.1 Hz, 1H), 4.02 (dt, *J* = 9.6, 7.6 Hz, 1H), 1.78 – 1.39 (m, 3H), 1.06 – 0.81 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.7, 135.6, 128.5, 127.4, 126.3, 117.4, 44.9, 41.2, 25.6, 22.8, 22.5. $[\alpha]_D^{20}$ = +169.4 (*c* = 1.0, $CHCl_3$). HRMS (APCI+, *m/z*): calculated for $C_{11}H_{14}Cl$ $[M+H^+]$: 209.10915; found: 209.10943. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak OJ-H column, Heptane/*i*-PrOH 100:0, 40 °C, 210 nm, retention times (min): 12.1 (minor enantiomer), 12.9 (major enantiomer).



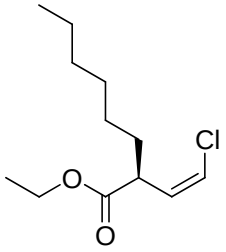
(+)-(*Z*)-1-(1-Chloropent-1-en-3-yl)-4-methylbenzene (2f): Colorless oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [75% yield, 95:5 er]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 6.99 (m, 4H), 6.07 (dd, *J* = 7.1, 0.7 Hz, 1H), 5.87 (dd, *J* = 9.7, 7.1 Hz, 1H), 3.78 (dt, *J* = 8.8, 7.6, 1H), 2.32 (s, 3H), 1.83 – 1.64 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.8, 135.4, 129.2, 127.2, 117.6, 44.5, 28.7, 21.0, 11.9. $[\alpha]_D^{20}$ = +194.3 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak OJ-H column, Heptane/*i*-PrOH 100:0, 40 °C, 210 nm, retention times (min): 14.0 (minor), 14.9 (major). HRMS (APCI+, *m/z*): calculated for $C_{12}H_{16}Cl$ $[M+H^+]$: 195.09350; found: 195.08643.



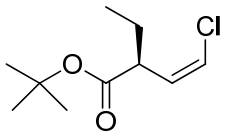
(+)-(*Z*)-1-Bromo-2-(1-chloropent-1-en-3-yl)benzene (2g): Colorless oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [78% yield, 98:2 er]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.11 – 7.02 (m, 1H), 6.15 (dd, *J* = 7.1, 0.8 Hz, 1H), 5.93 (dd, *J* = 9.2, 7.1 Hz, 1H), 4.30 (dt, *J* = 8.6, 7.5 Hz, 1H), 1.87 – 1.63 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 133.8, 133.1, 128.2, 127.7, 127.6, 124.6, 119.2, 43.9, 28.9, 11.7. Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 105 ºC for 100 min, then 10 ºC/min to 175 ºC (hold for 5 min), then 10 ºC/min to 105 ºC, retention times (min): 105.2 (minor) and 105.5 (major). $[\alpha]_D^{20}$ = +77.6 (*c* = 1.0, $CHCl_3$). HRMS (APCI+, *m/z*): calculated for $C_{11}H_{13}BrCl$ [M+H$^+$]: 258.98837; found: 258.98852.



(+)-(*Z*)-Ethyl-2(2-chlorovinyl)butanoate (2h): Colorless oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane/EtOAc 30:1), [71% yield, 97:3 er]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.11 (d, *J* = 7.2 Hz, 1H), 5.81 (dd, *J* = 9.4, 7.2 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.50 (dt, *J* = 9.4, 7.1 Hz, 1H), 1.90 – 1.43 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 129.3, 120.1, 60.7, 45.3, 25.6, 14.2, 11.3. $[\alpha]_D^{20}$ = +33.2 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 85 ºC for 60 min, then 5 ºC/min to 175 ºC (hold for 2 min), then 10 ºC/min to 80 ºC, retention times (min.): 24.3 (major) and 25.9 (minor). HRMS (APCI+, *m/z*): calculated for $C_8H_{14}O_2Cl$ [M+H$^+$]: 177.06768; found: 177.06741.



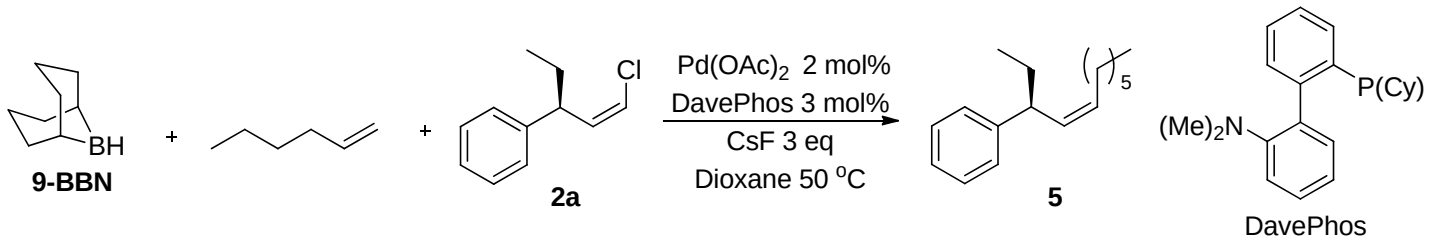
(+)-(*Z*)-Ethyl-2(2-chlorovinyl)octanoate (2i): Colorless oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [72% yield, 97:3 er]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (d, *J* = 7.2 Hz, 1H), 5.79 (dd, *J* = 9.5, 7.2 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.55 (dt, *J* = 9.5, 7.3 Hz, 1H), 1.79 – 1.37 (m, 2H), 1.35 – 1,03 (m, 11H), 0.81 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.4, 129.7, 119.8, 60.7, 43.8, 32.3, 31.6, 28.9, 26.7, 22.5, 14.2, 14.0. $[\alpha]_D^{20}$ = +31.2 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 105 ºC for 100 min, then 10 ºC/min to 175 ºC (hold for 5 min), then 10 ºC/min to 105 ºC, retention times (min.): 72.8 (major) and 75.6 (minor). HRMS (APCI+, *m/z*): calculated for $C_{12}H_{22}O_2Cl$ [M+H$^+$]: 233.13028; found: 233.13021.



(+)-(*Z*)-Ethyl-2(2-chlorovinyl)butanoate (2j): Colorless oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane/EtOAc 10:0.5), [67% yield, 98:2 er]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, *J* = 7.2 Hz, 1H), 5.85 (dd, *J* = 9.3, 7.2 Hz, 1H), 3.45 (dt, *J* = 9.3, 8.1 Hz, 1H), 1.85 – 1.72 (m, 1H), 1.66 – 1.53 (m, 1H), 1.44 (s, 9H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 129.8, 119.6, 80.8, 46.2, 28.0, 25.6, 11.2. $[\alpha]_D^{20}$ = +68.7 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 85 ºC for 60 min, then 5 ºC/min to 175 ºC (hold for 2 min), then 10 ºC/min to 80 ºC, retention times (min.): 25.2 (minor) and 26.9 (major). HRMS (APCI+, *m/z*): calculated for $C_{10}H_{18}O_2Cl$ [M+H$^+$]: 205.09171; found: 205.09192.

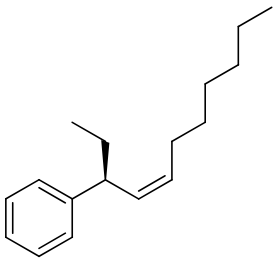
Synthesis and characterization of *Z*-alkenes 5, 6, 7 and 8:

-Synthesis of *Z*-olefin 5:



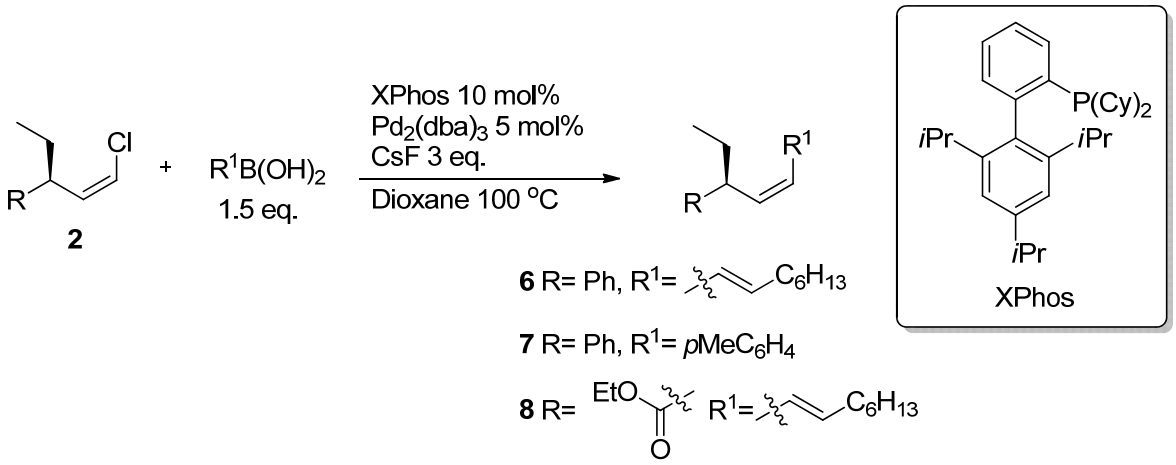
Compound **5** was synthetized via a modified protocol described for the Suzuki coupling of aryl chlorides.[4] In a Schlenk tube (previously dried under vacuum and then purged with nitrogen) 1-hexene (0.32 mmol 40 μL) was placed and cooled to 0 °C. A solution of 9-BBN in THF (0.32 mmol, 0.64 mL 0.5 M) was added and the mixture was stirred for 5 more minutes at 0 °C and then for 5h at room temperature. Compound number **2a** was added (0.20 mmol, 35 mg), followed by palladium acetate (0.004 mmol, 0.9 mg 2 mol%), DavePhos (0.006 mmol, 2.36 mg, 3 mol%) and cesium fluoride (0.6 mmol, 91.4 mg). Dioxane was added (1 ml) and the reaction mixture was heated to 50 °C for 18 hours. The mixture was allowed to cool to room temperature and diluted with ether (20 ml) and . The mixture was washed with 1 M aqueous NaOH (20 ml) the layers were separated, and the aqueous phase was extracted with ether (20 ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography.

[4] Buchwald, S. L.; Wolfe, J. P.; Old, D. W. *J. Am. Chem. Soc.* **1998,** *120,* 9722-9723



(+)-(*Z*)-Undec-4-en-3-ylbenzene (5): Colorless oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [70% yield, 98:2 er]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.12 (m, 5H), 5.49 (dd, *J* = 10.8, 9.5 Hz, 1H), 5.43 (dt, *J* = 10.8, 6.8 Hz, 1H), 3.47 (dt, *J* = 8.6, 6.8 Hz, 1H), 2.22 – 1.95 (m, 2H), 1.82 – 1.57 (m, 2H), 1.40 – 1.20 (m, 8H), 0.93 – 0.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 133.5, 130.0, 128.3, 127.3, 125.8, 45.2, 31.7, 29.8, 29.6, 29.0, 27.6, 22.6, 14.1, 12.2. $[\alpha]_D^{20}$ = +139.8 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 130 ºC for 60 min, then 10 ºC/min to 175 ºC (hold for 5 min), then 10 ºC/min to 130 ºC, retention times (min.): 40.9 (minor) and 42.0 (major). HRMS (APCI+, *m/z*): calculated for $C_{17}H_{27}$ [M+H$^+$]: 231.21073; found: 231.21034.

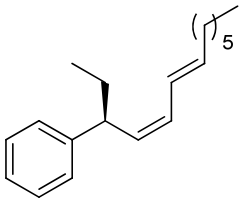
-Synthesis of *Z* olefin 6, 7 and 8:



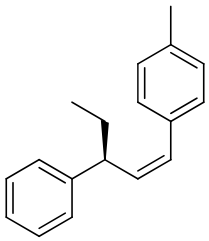
Compounds **6**, **7** and **8** were synthetized via a modified protocol described for the Suzuki coupling of dichloroethylenes.[5] In a dry Schlenk flask under nitrogen atmosphere dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) (10 mol%, 0.02 mmol, 9.53 mg),

[5] Barluenga, J.; Moriel, P.; Aznar, F.; Valdés, C.; *Adv. Synth. Catal.* **2006,** *348,* 347.

tris(dibenzylideneacetone)dipalladium(0) (5 mol%, 0.01 mmol, 9.2 mg) cesium fluoride (3 eq. 0.6 mmol, 91 mg) and the corresponding boronic acid (1.5 eq) were placed and dioxane (2 ml) was added. The suspension was then stirred for 1 min and the substrate (0.2 mmol.) was added, the Schlenk tube was sealed and the mixture was heated at 100 ^{o}C for 16 h. The mixture was allowed to cool to room temperature, diluted with ether (20 ml). The mixture was washed with 1 M aqueous NaOH (20 ml), the layers were separated and the aqueous phase was extracted with ether (20 ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography.

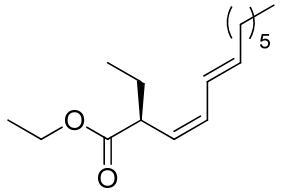


(+)-(4*Z*, 6*E*)-Trideca-4,6-dien-3-ylbenzene (6): Colorless oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [77% yield, 98:2 er]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41 – 7.09 (m, 5H), 6.39 (dd, *J* = 14.5, 10.9, Hz, 1H), 6.02 (t, *J* = 10.9 Hz, 1H), 5.83 – 5.57 (m, 1H), 5.41 (t, *J* = 10.4 Hz, 1H), 3.63 (dd, *J* = 17.0, 7.6 Hz, 1H), 2.11 (q, *J* = 6.7 Hz, 2H), 1.88 – 1.09 (m, 11H), 0.89 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 135.8, 133.1, 128.5, 128.4, 127.3, 125.9, 125.5, 45.5, 32.9, 31.7, 29.7, 29.3, 28.9, 22.7, 14.1, 12.2. $[\alpha]_D^{20}$ = +236.7 (*c* = 1.0, $CHCl_3$). HRMS (APCI+, *m/z*): calculated for $C_{19}H_{29}$ [M+H$^+$]: 257.2263; found: 257.2253.



(+)-(Z)-1-methyl-4-(3-phenylpent-1-en-1-yl)benzene (7): Colorless oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane), [75% yield, 98:2 er]. ^{1}H NMR (400

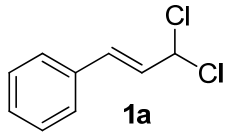
MHz, $CDCl_3$) δ 7.38 – 7.12 (m, 9H), 6.52 (d, *J* = 11.6 Hz, 1H), 5.83 (t, *J* = 11.6 Hz, 1H), 3.74 (dt, *J* = 10.4, 7.3 Hz, 1H), 3.74 (dt, *J* = 10.4, 7.3 Hz, 6H), 2.37 (s, 3H), 1.85 – 1.65 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 136.3, 135.3, 134.6, 128.8, 128.7, 128.6, 128.5, 127.4, 126.0, 45.5, 30.7, 21.2, 11.9. $[\alpha]_D^{20}$ = +331.2 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 130 ºC for 60 min, then 10 ºC/min to 175 ºC (hold for 5 min), then 10 ºC/min to 130 ºC, retention times (min.): 68.8 (major) and 69.0 (minor).



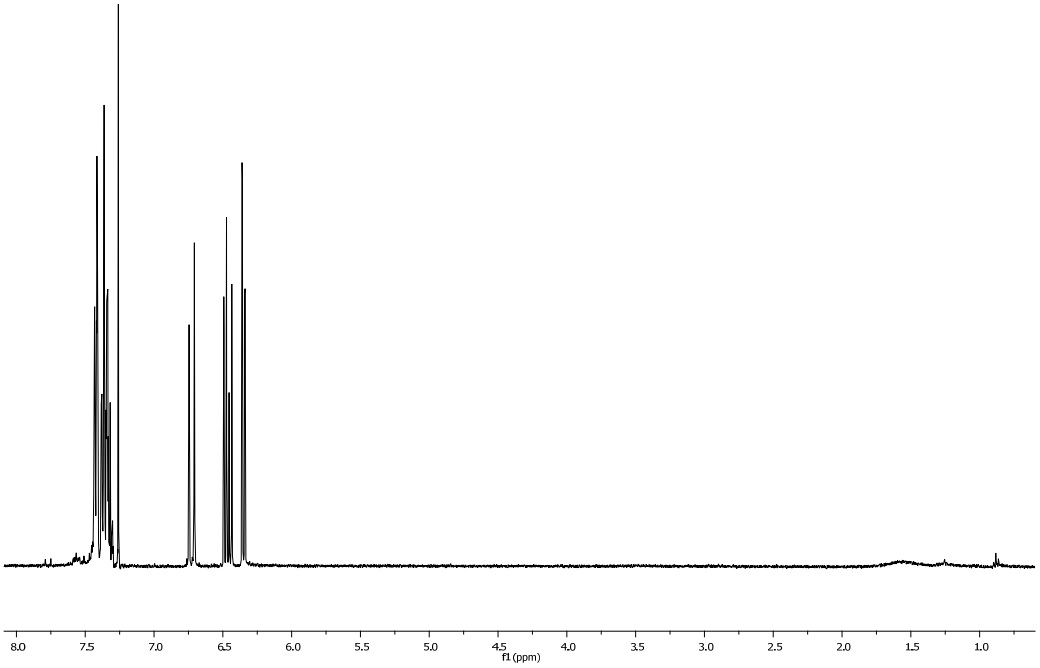
(+)-(3*Z*, 5*E*)-Ethyl-2-ethyldodeca-3,5-dienoate (8):

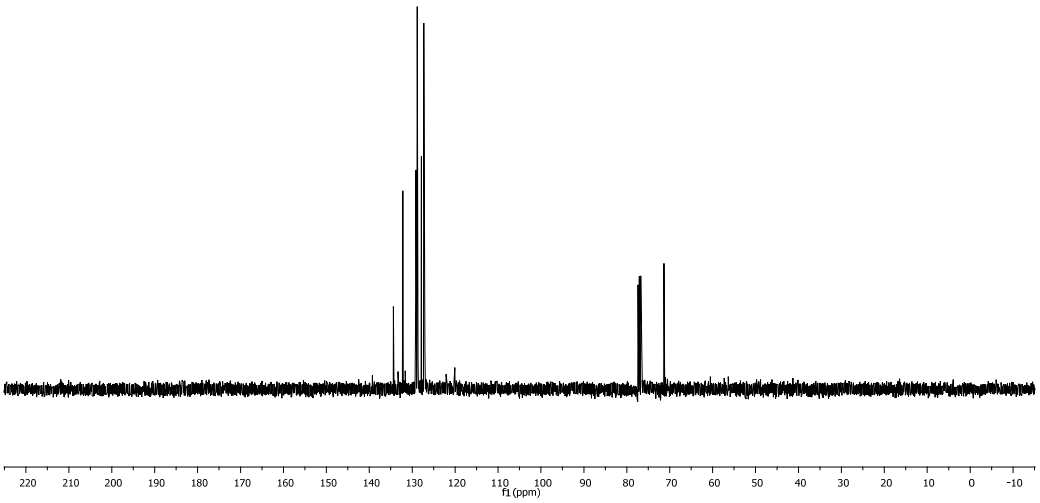
Yellowish oil obtained as the pure *Z* isomer after column chromatography (SiO_2, *n*-pentane/EtOAc 50:1), [72% yield, 96:4 er]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, *J* = 14.7, 11.3 Hz, 1H), 6.07 (t, *J* = 10.9 Hz, 1H), 5.73 (dt, *J* = 14.7, 6.9 Hz, 1H), 5.27 (t, *J* = 10.2 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.35 (dt, *J* = 9.2, 7.6 Hz, 1H), 2.10 (dt, *J* = 7.4, 6.9 Hz, 2H), 1.87 – 1.71 (m, 1H), 1.87 – 1.71 (m, 1H), 1.61 – 1.46 (m, 1H), 1.41 – 1.17 (m, 10H) 0.94 – 0.81 (m, 6H) . ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 137.0, 131.0, 126.3, 125.1, 60.4, 46.0, 32.8, 31.7, 29.2, 28.9, 26.3, 22.6, 14.2, 14.1, 11.6. $[\alpha]_D^{20}$ = +102.6 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 35 ºC for 0 min, then 10 ºC/min to 105 ºC (hold for 60 min), then 10 ºC/min to 175 ºC (hold for 10 min) then 10 ºC/min to 35 ºC, retention times (min.): 97.7 (minor) and 97.8 (major).HRMS (APCI+, *m/z*): calculated for $C_{16}H_{29}O_2$ [$M+H^+$]: 253.221603; found: 253.21621.

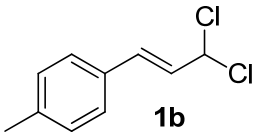
NMR spectra of new compounds


Cl
Cl

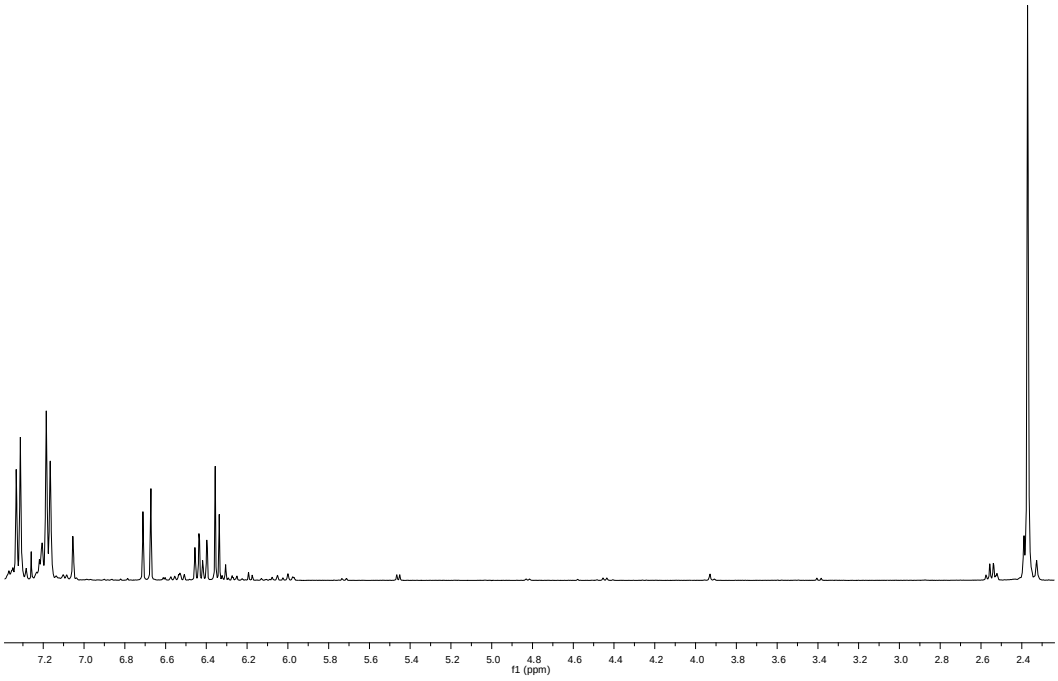
1a

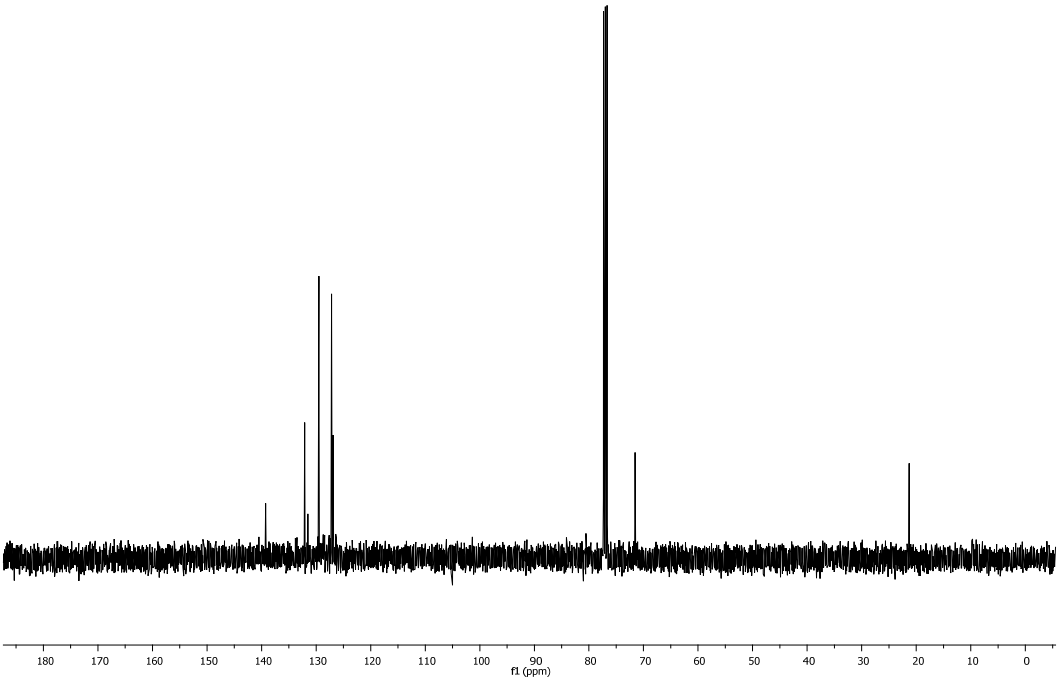

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

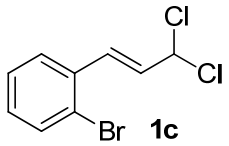

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Cl
Cl

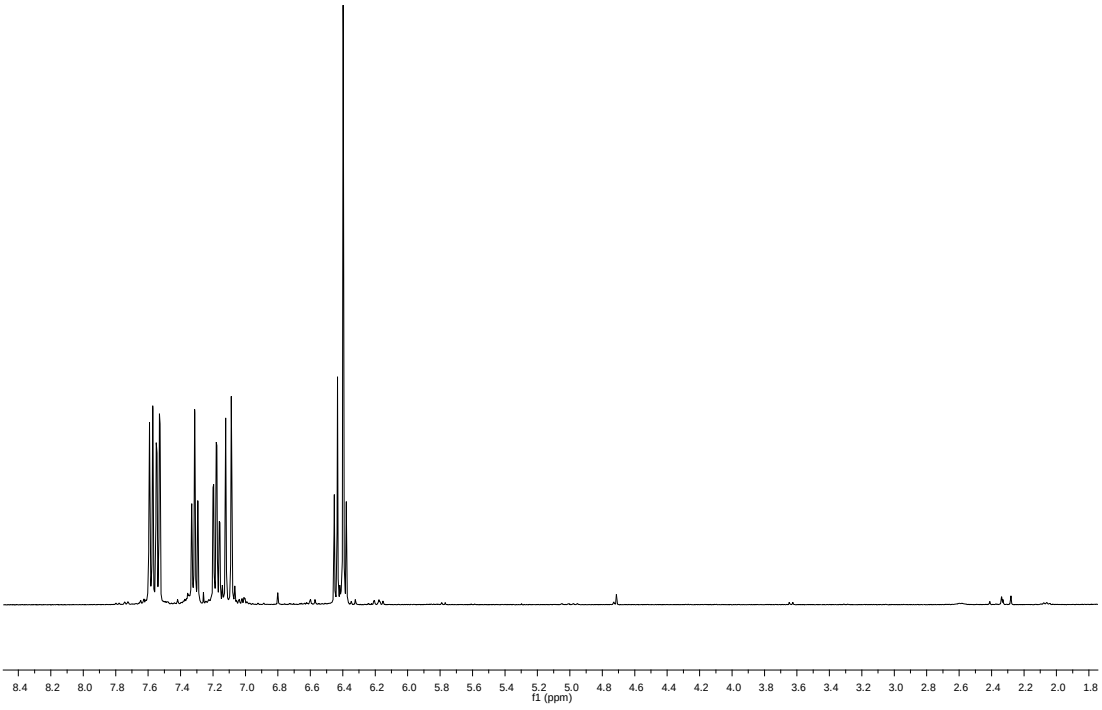
1b

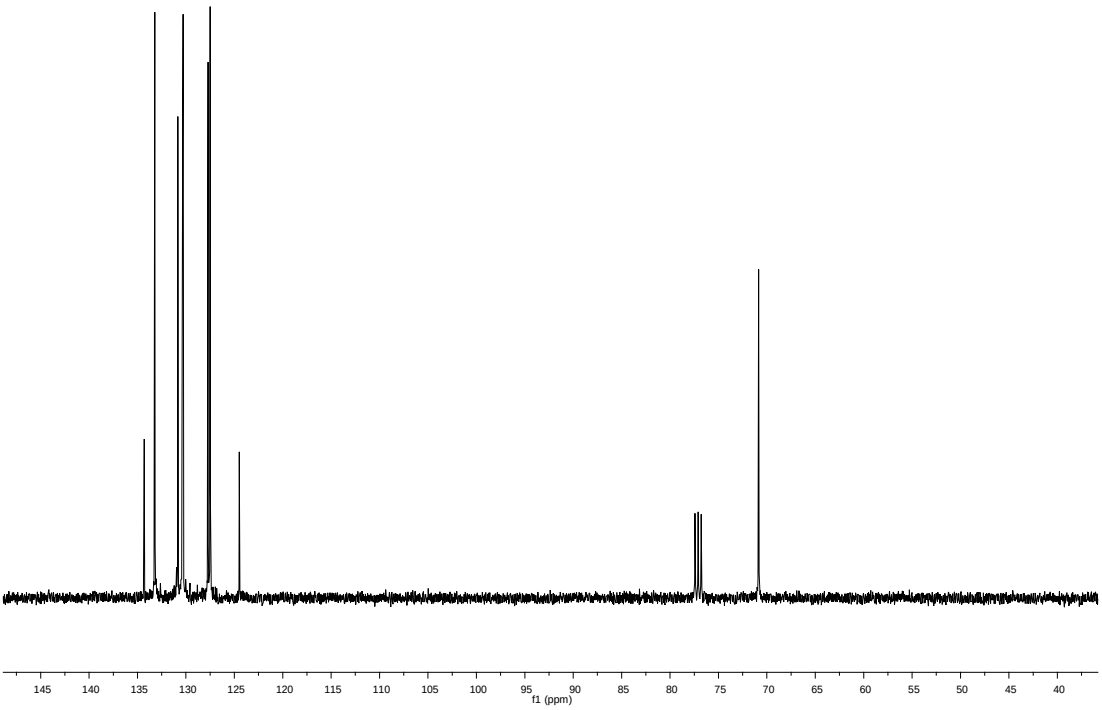

7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4
f1 (ppm)

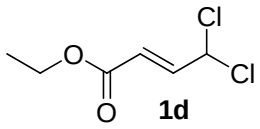

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Cl
Cl
Br

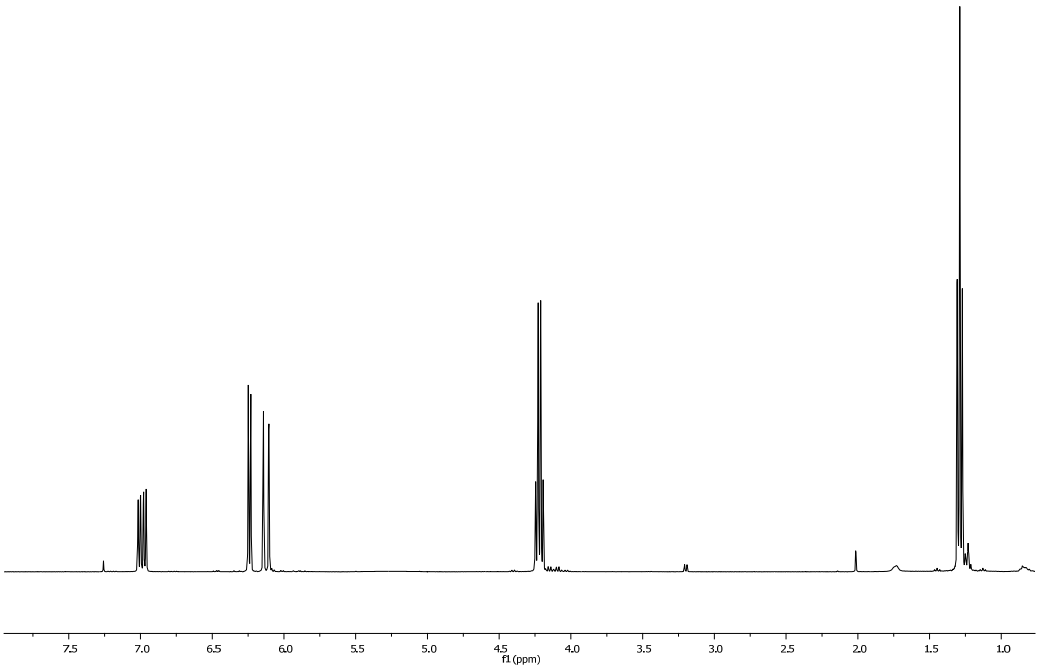
1c

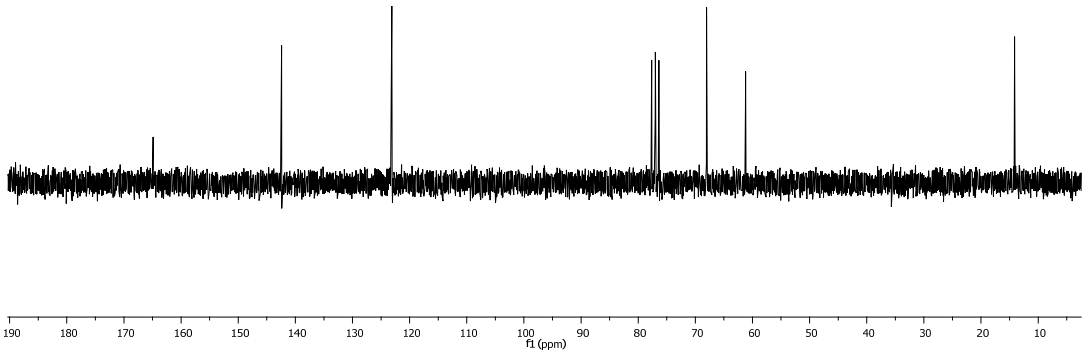

8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)

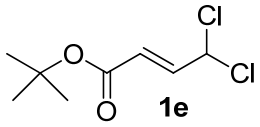

145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40
f1 (ppm)


Cl
O
Cl
O

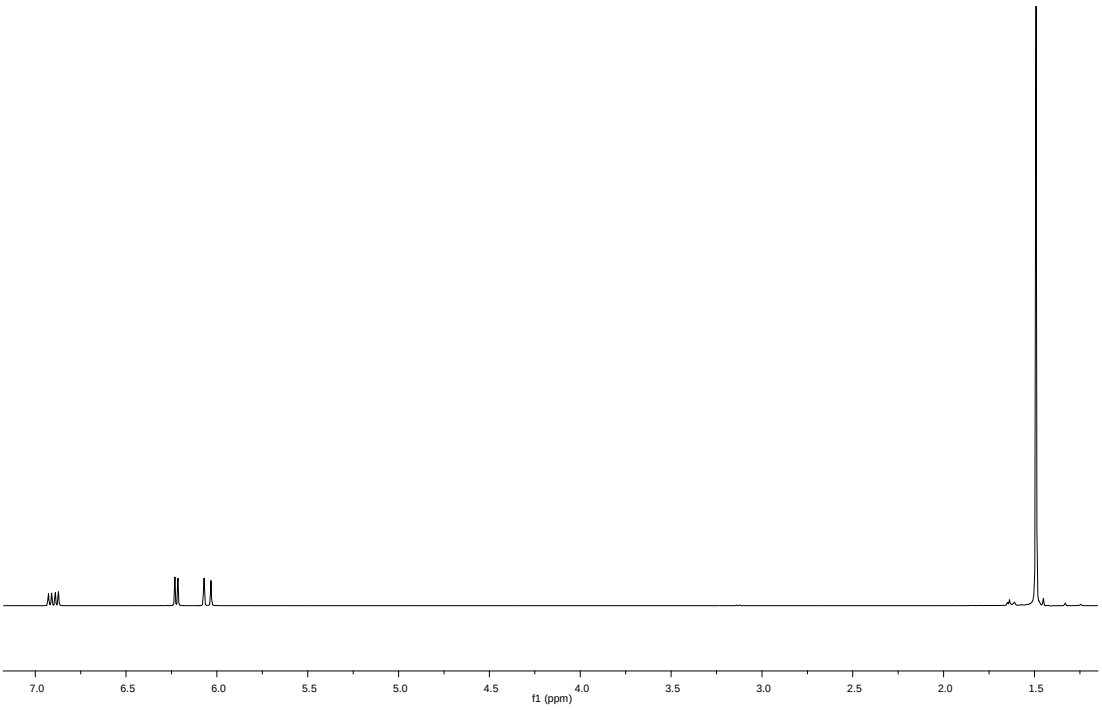
1d

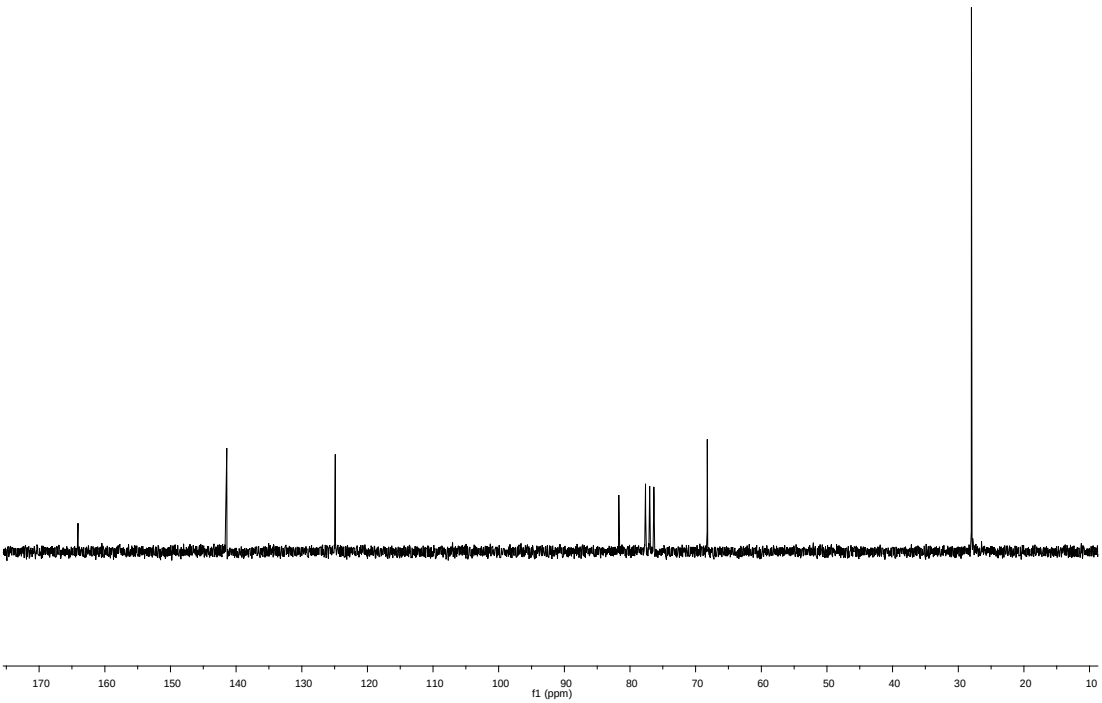

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

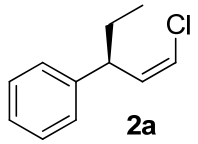

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Cl
O
Cl
O

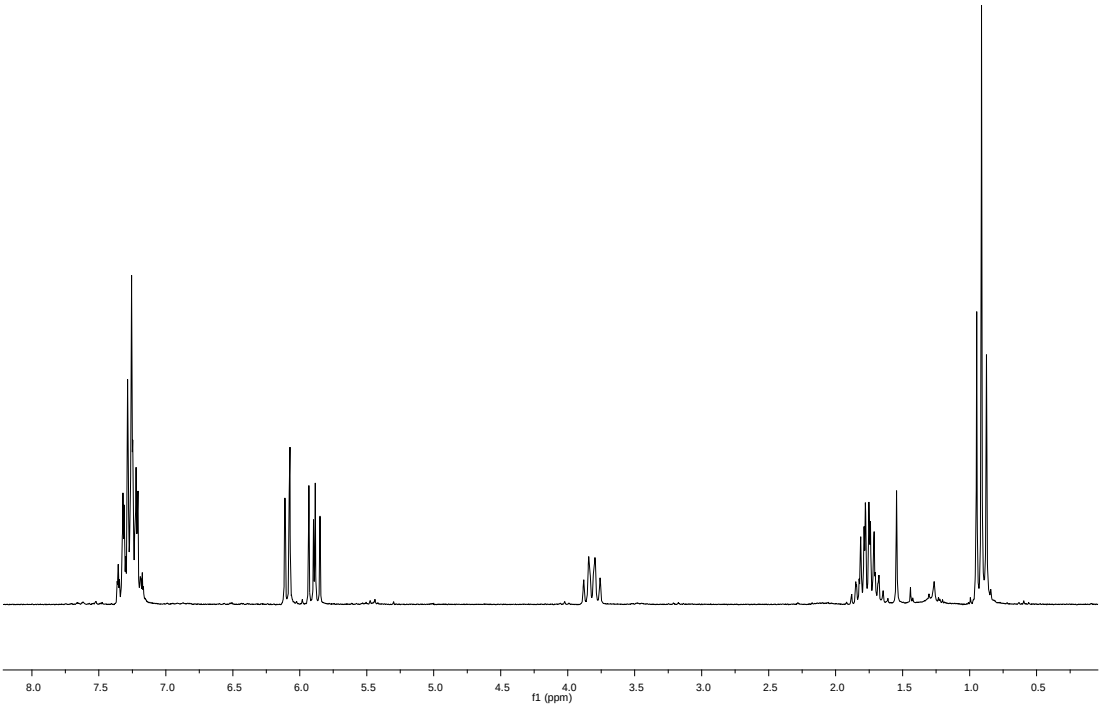
1e

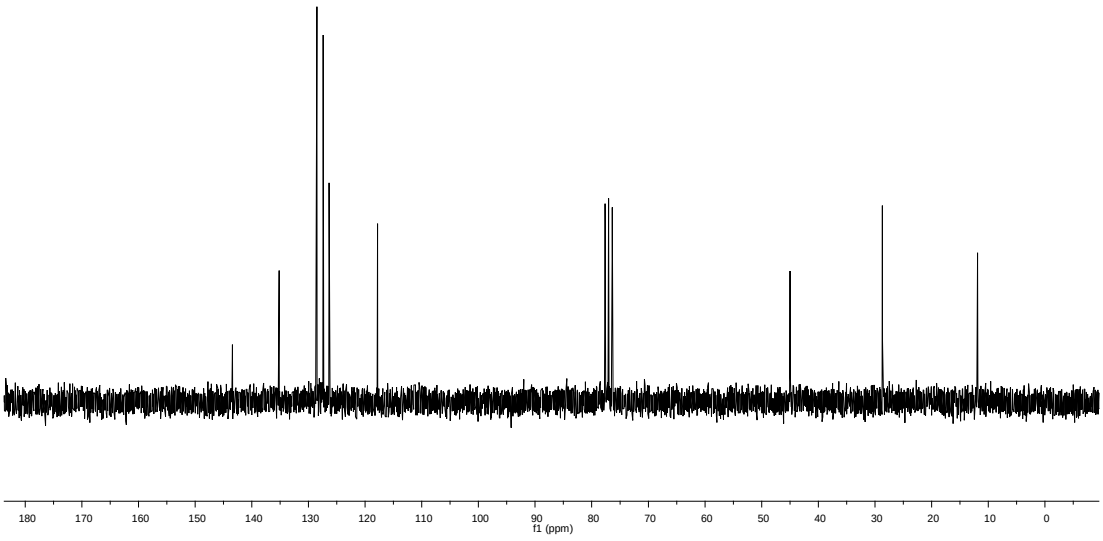

7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

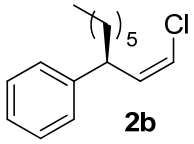

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Cl

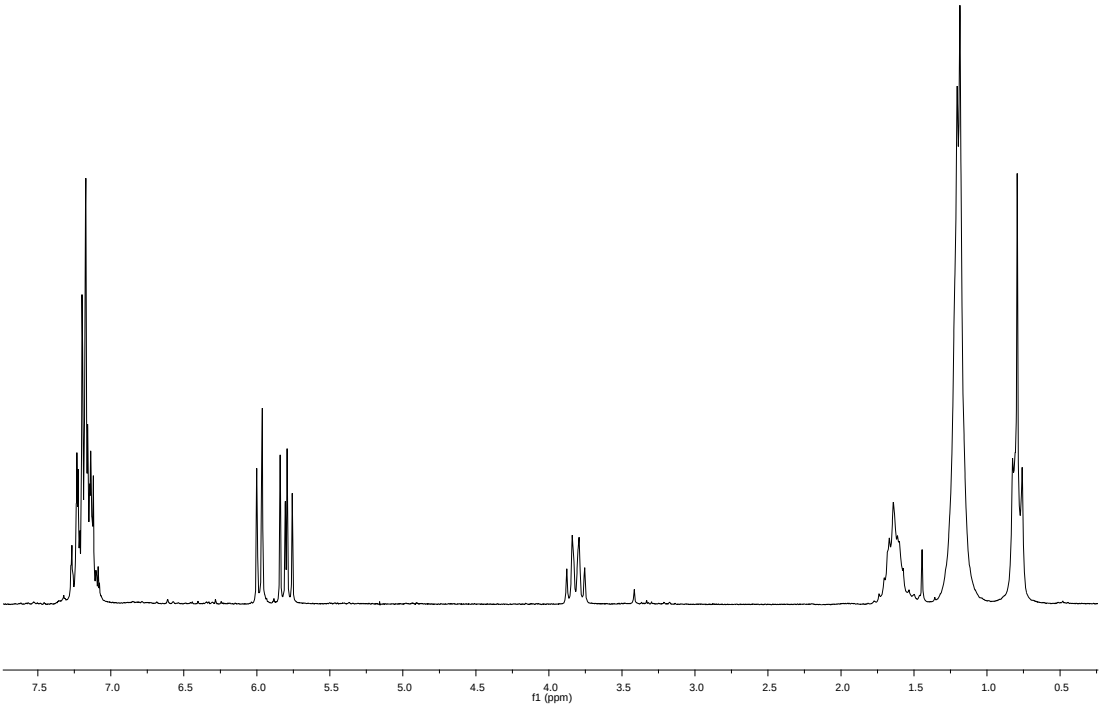
2a

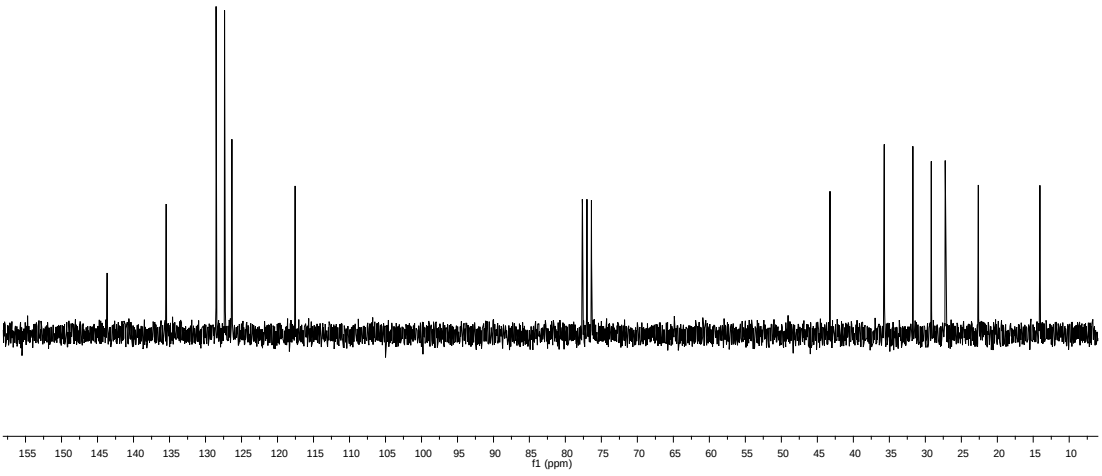

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

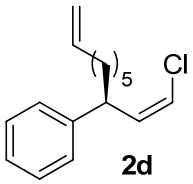

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
5

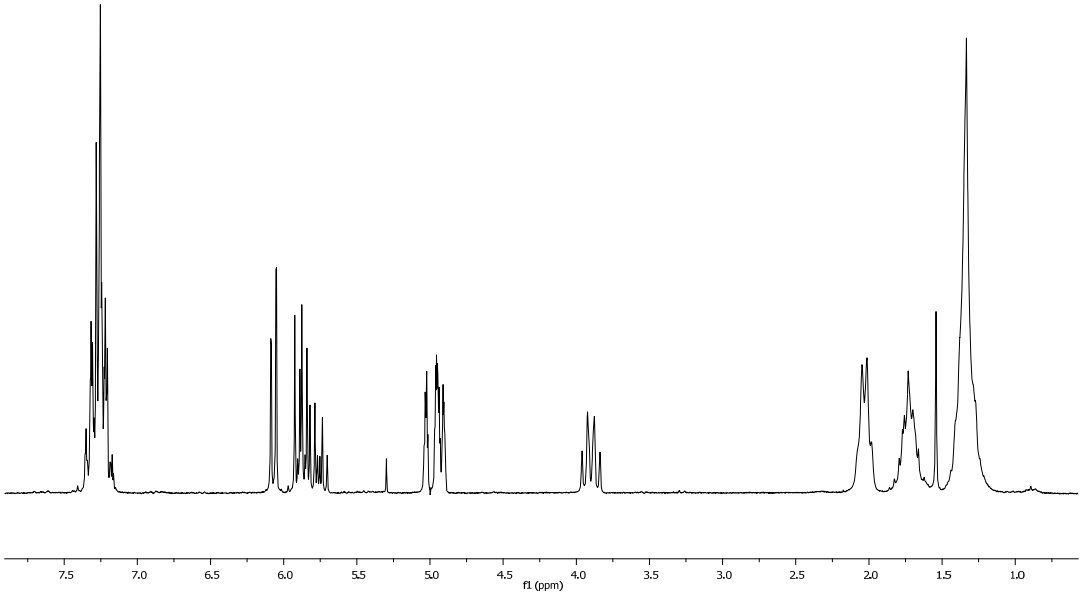
2b

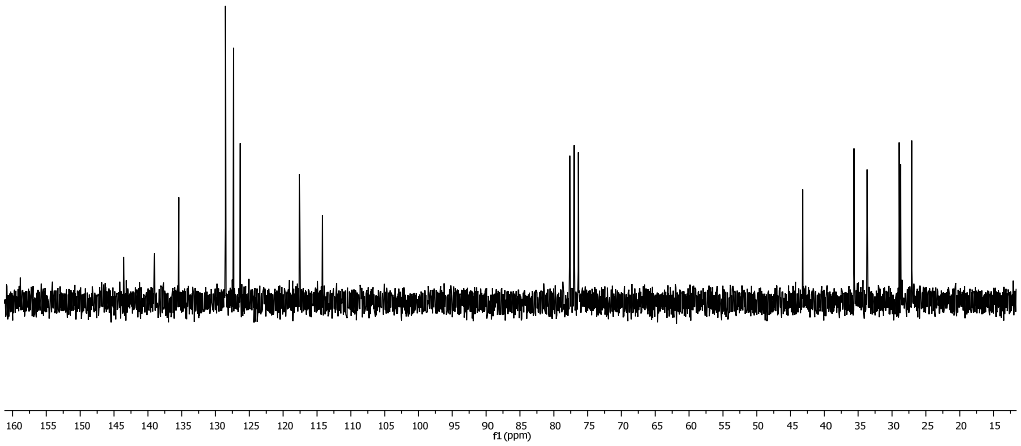

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

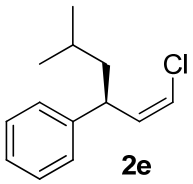

155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)


Cl
5

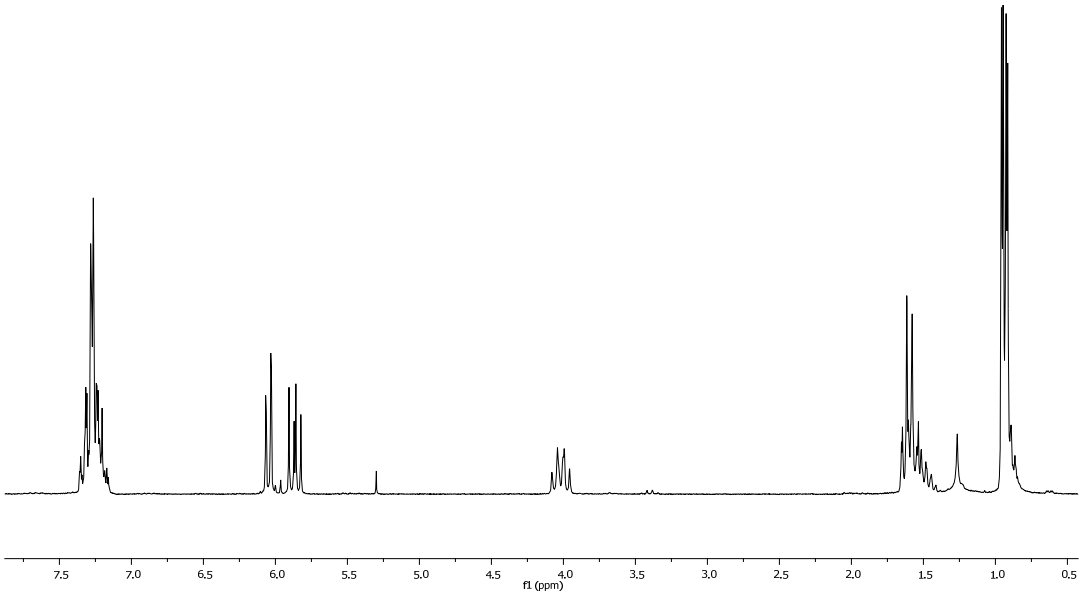
2d

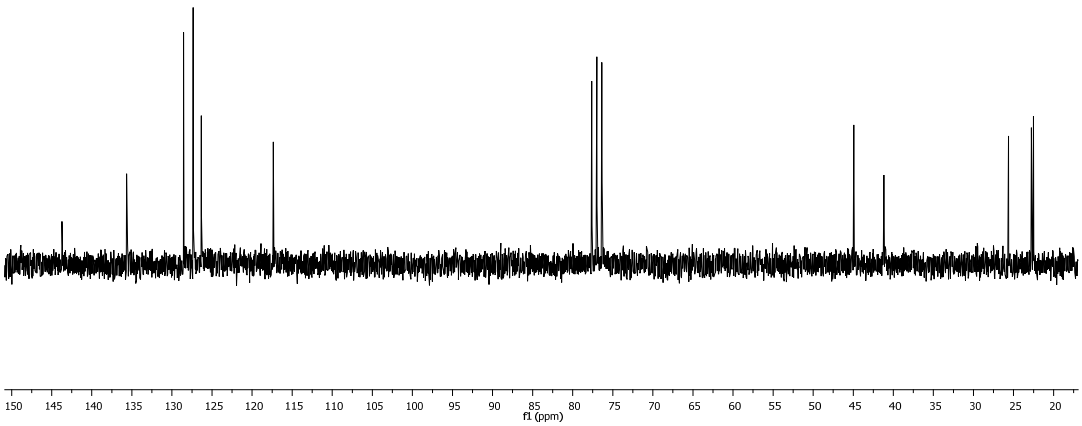

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

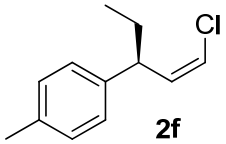

160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)


Cl

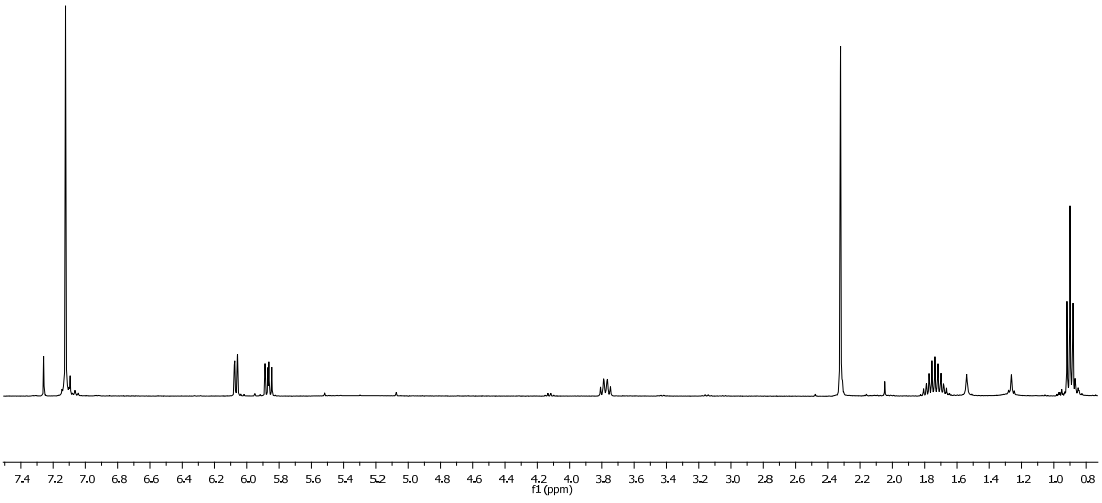
2e

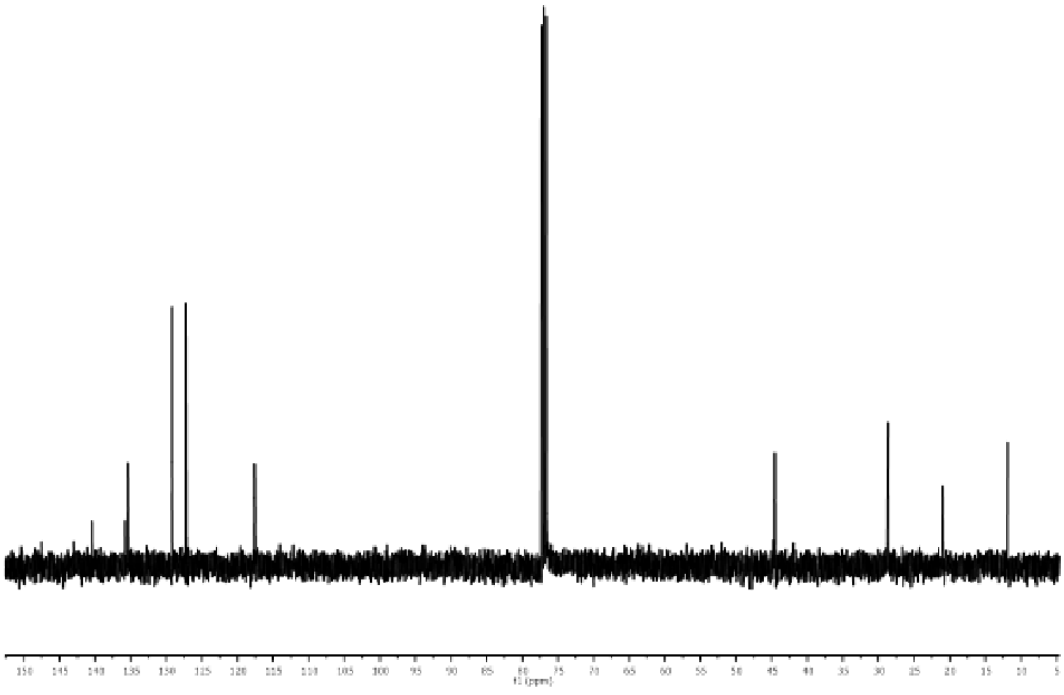

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

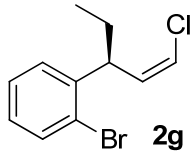

150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
f1 (ppm)


Cl

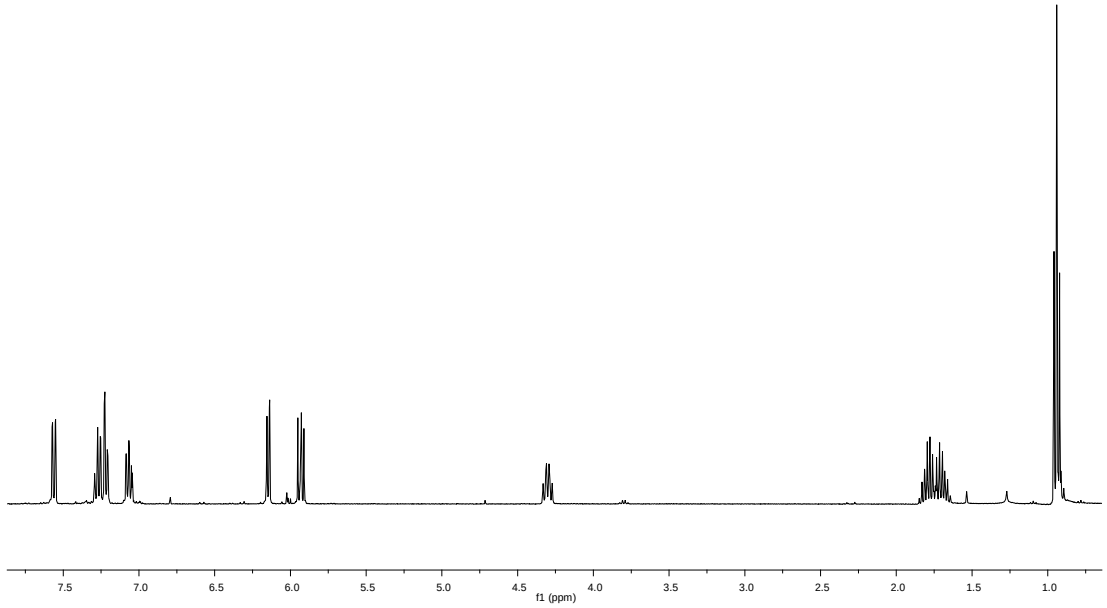
2f

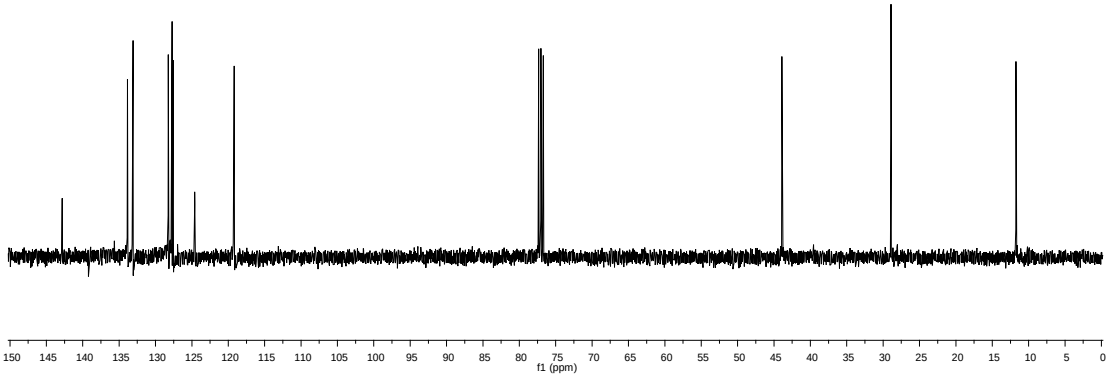

7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)

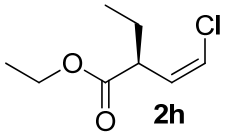

f1 (ppm)


Cl
Br

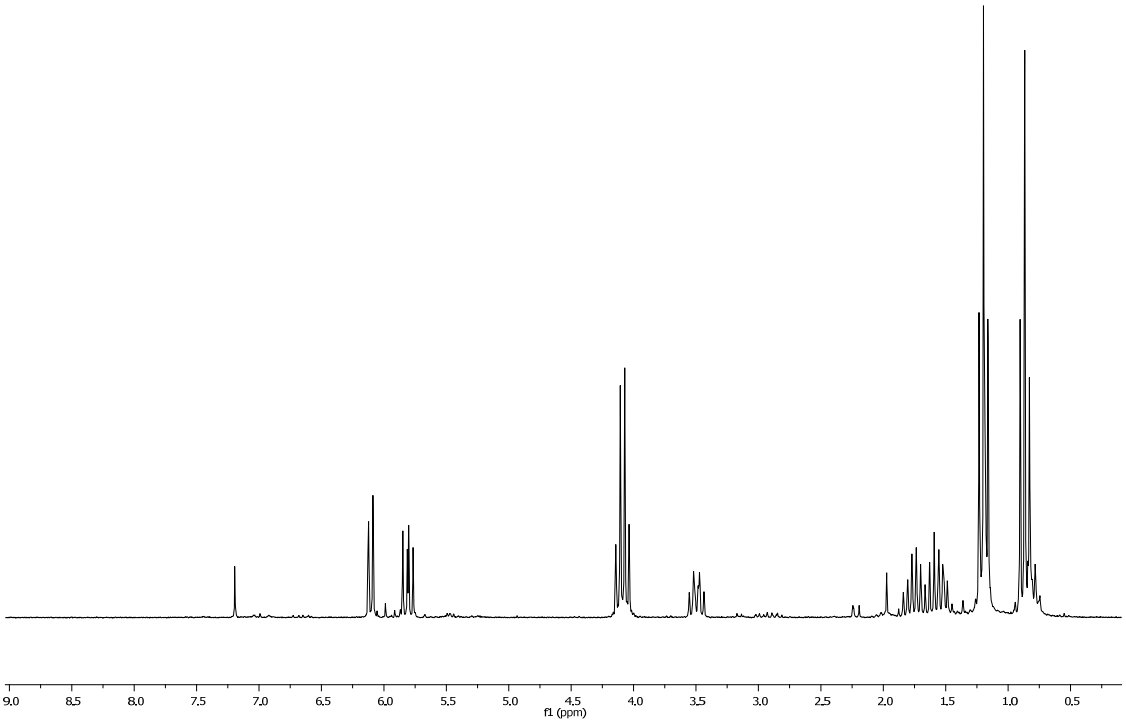
2g

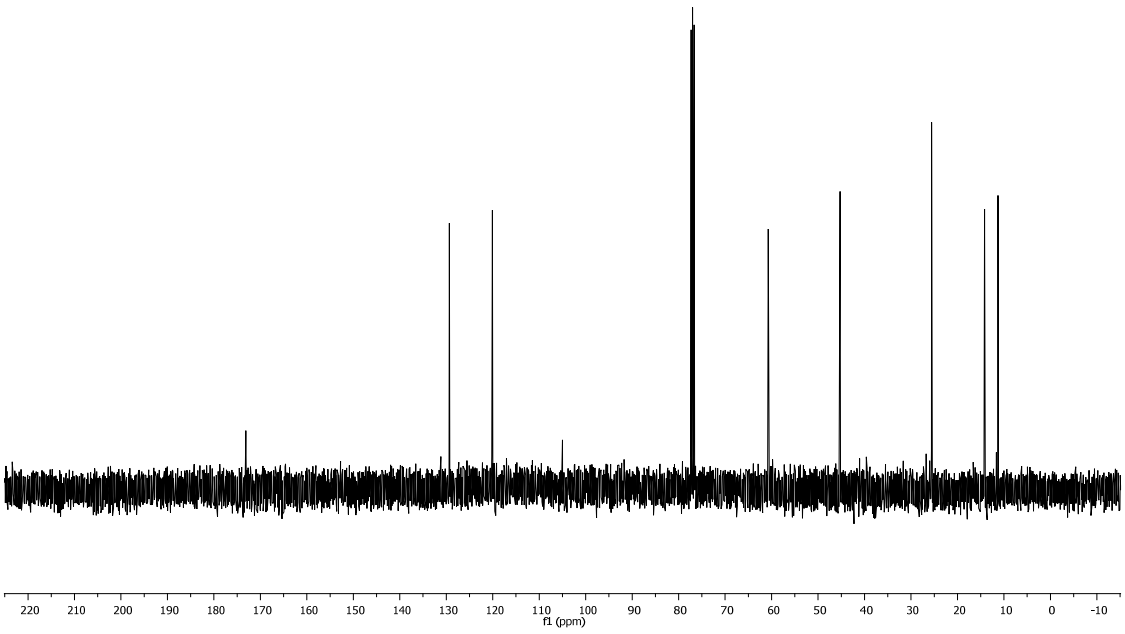

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

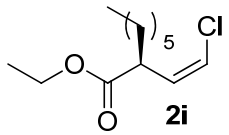

150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)


Cl
O
O

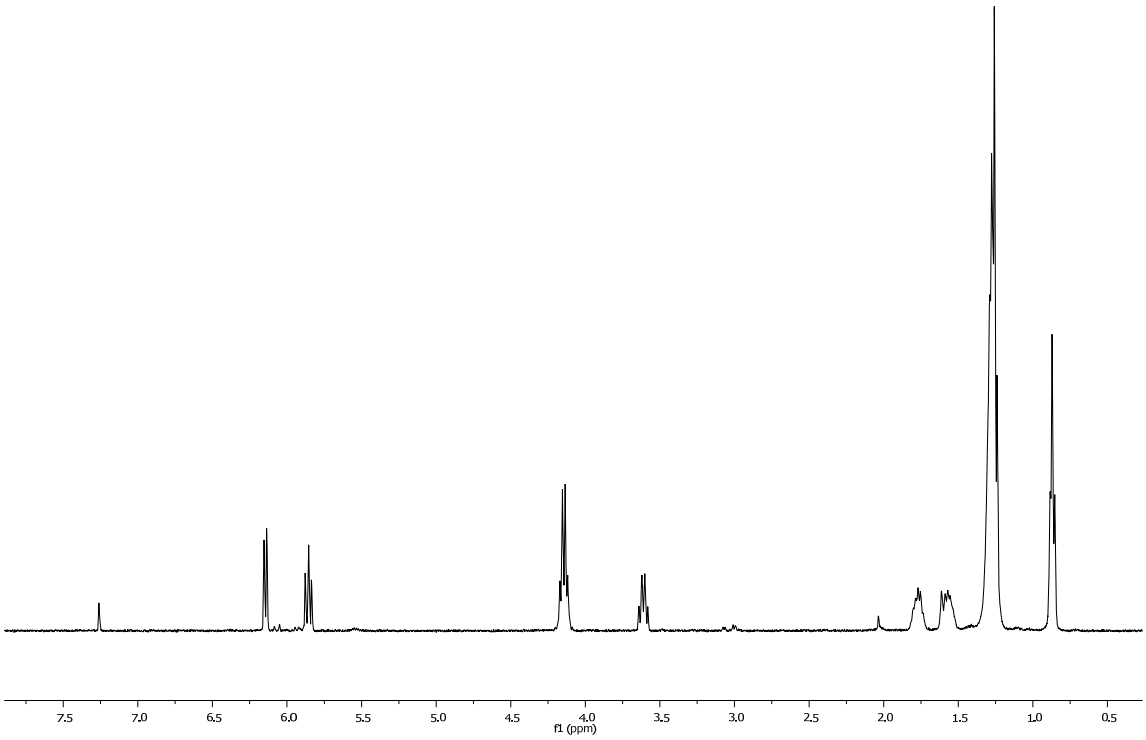
2h

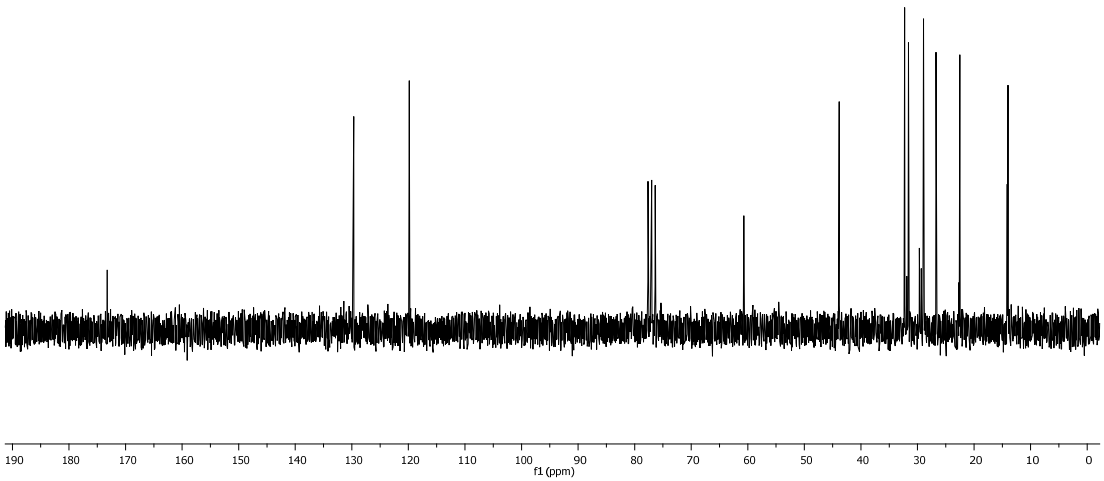

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

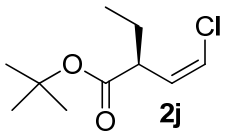

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Cl
5
O
O

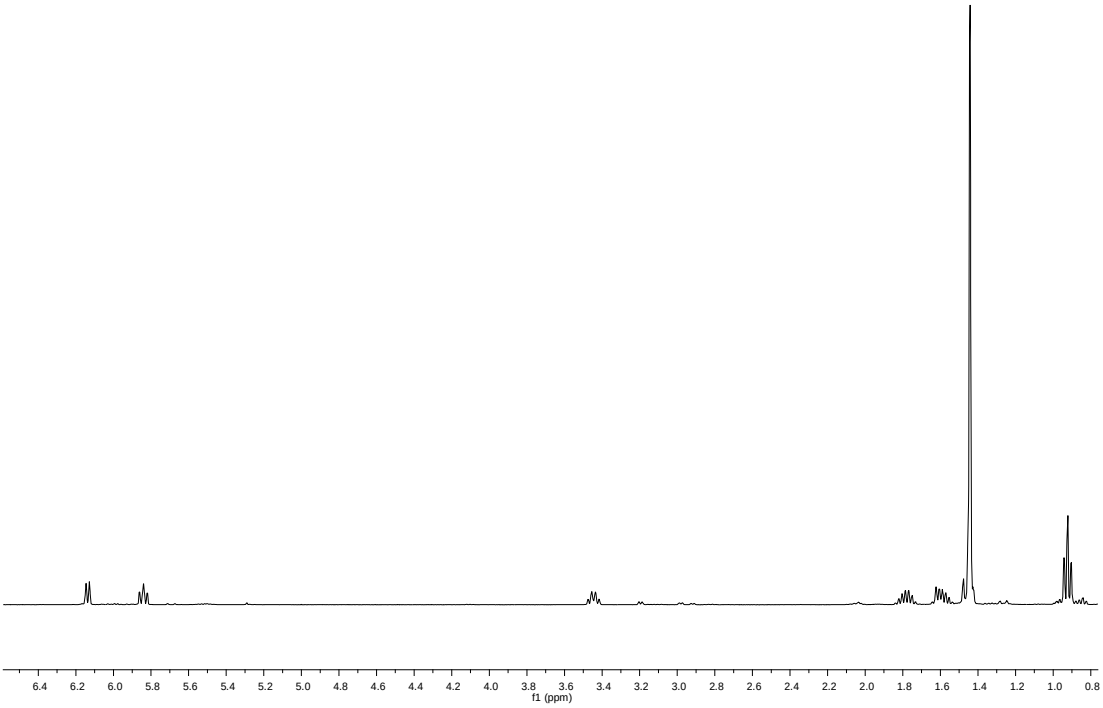
2i

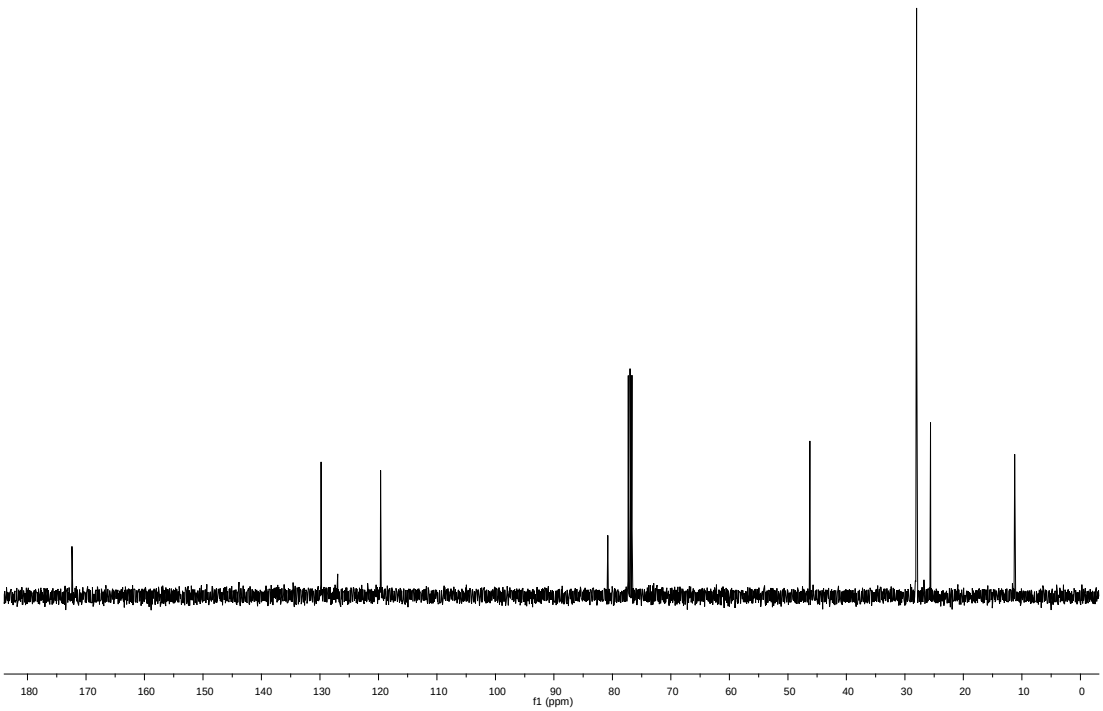

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

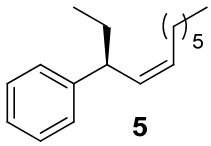

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
O
O

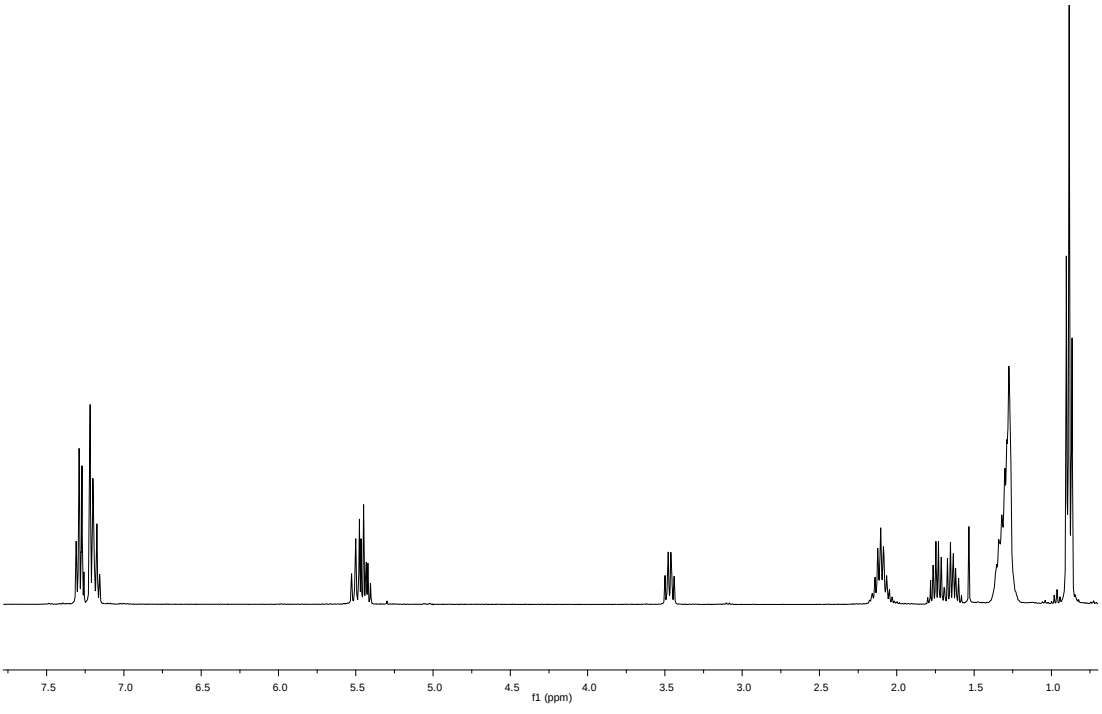
2j

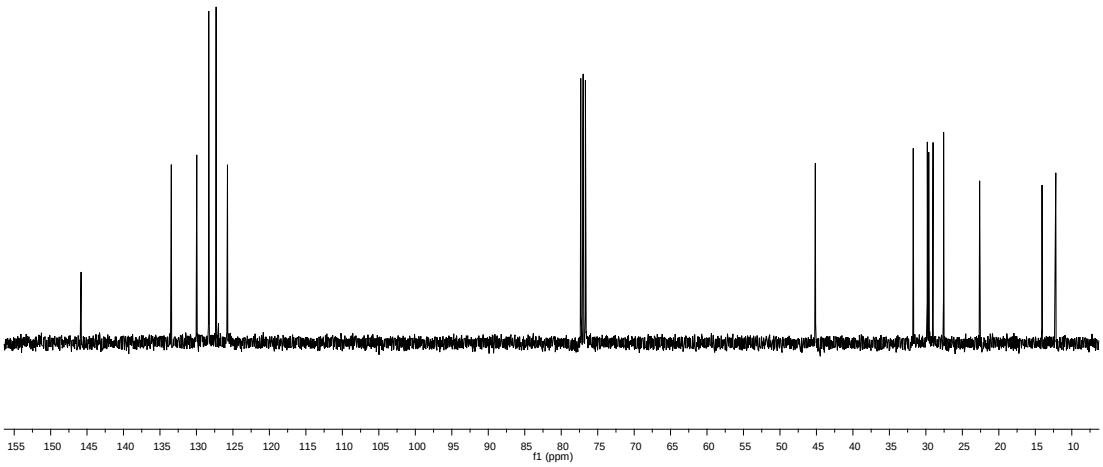

6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)

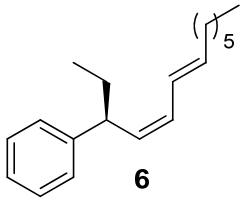

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


5

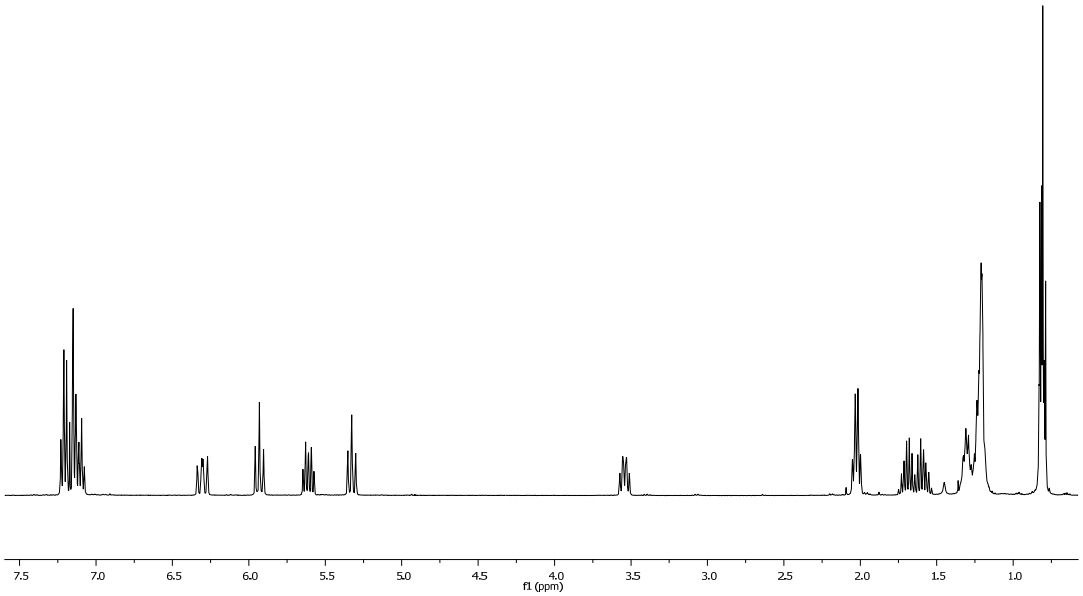
5

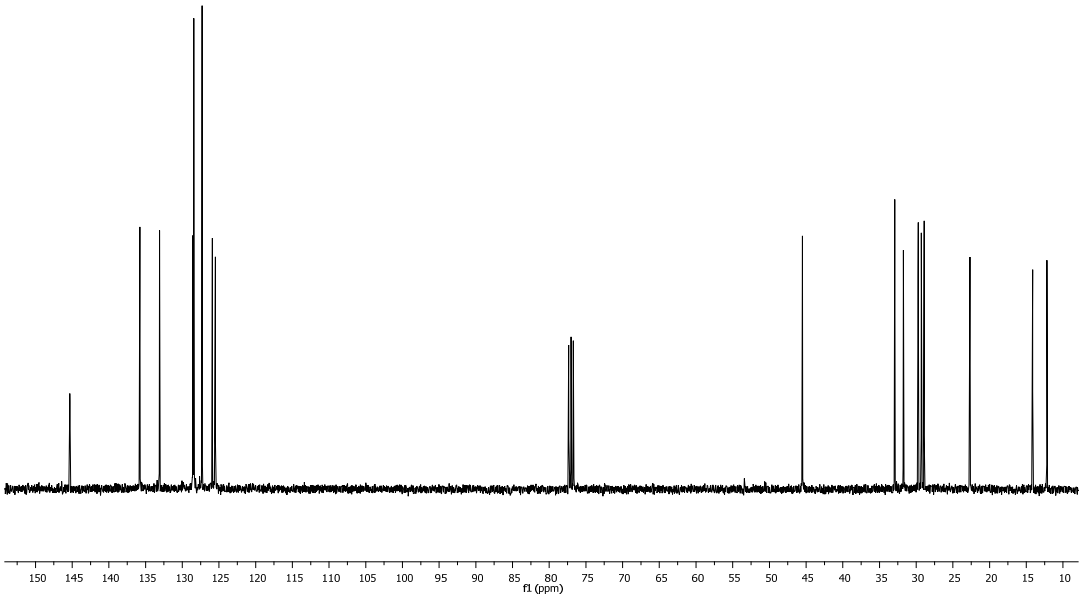

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

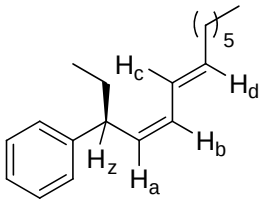

5

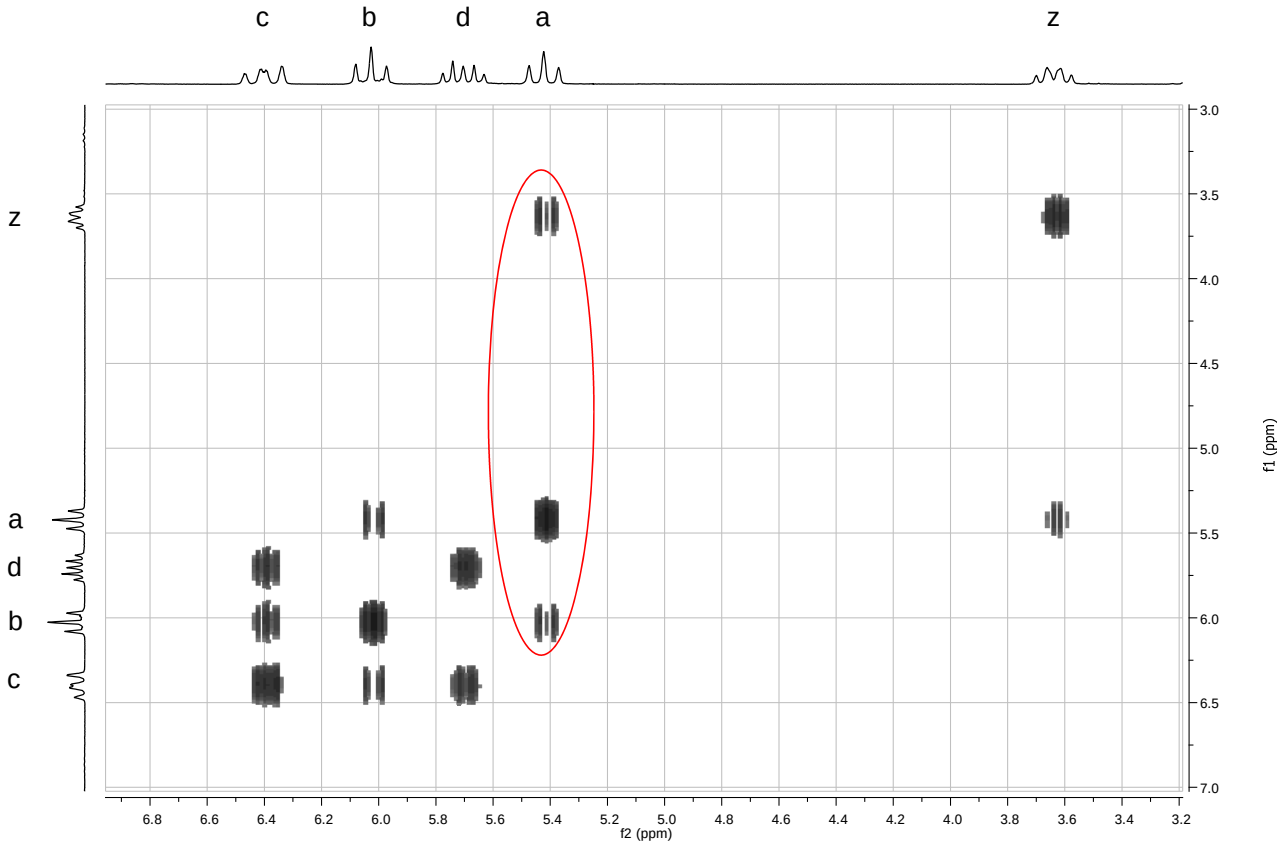
6

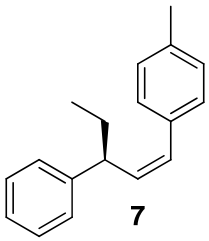

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

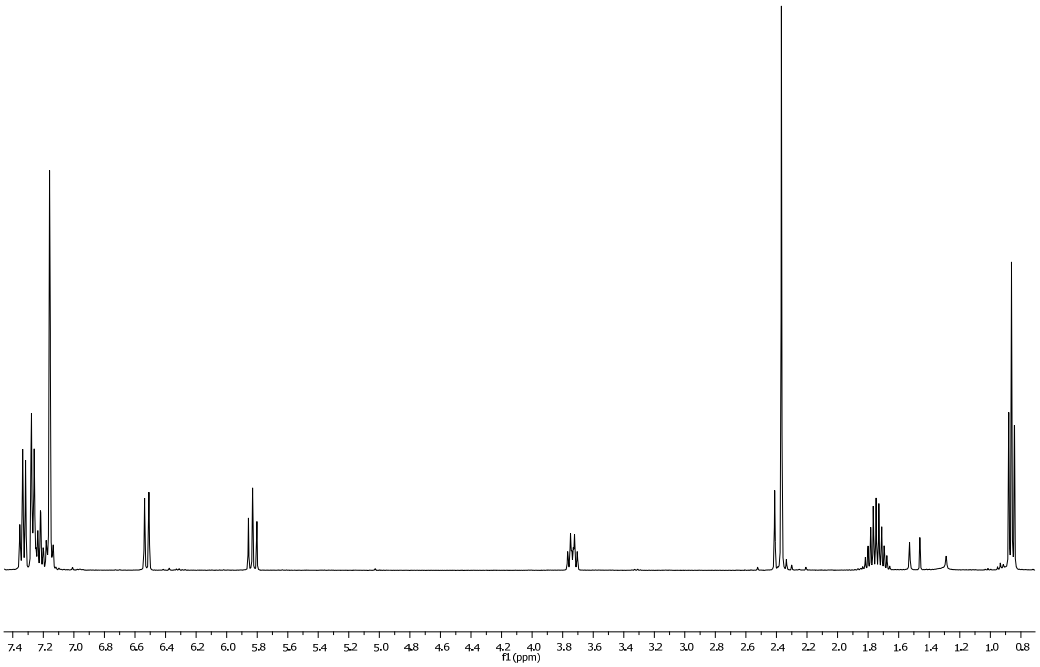
COSY (6)

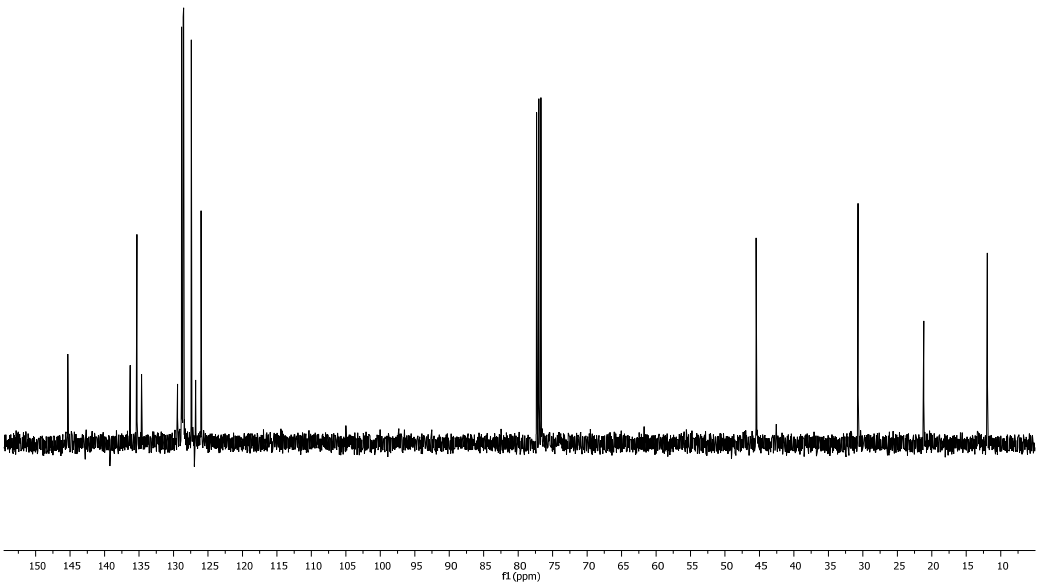


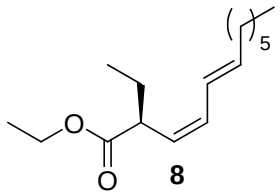




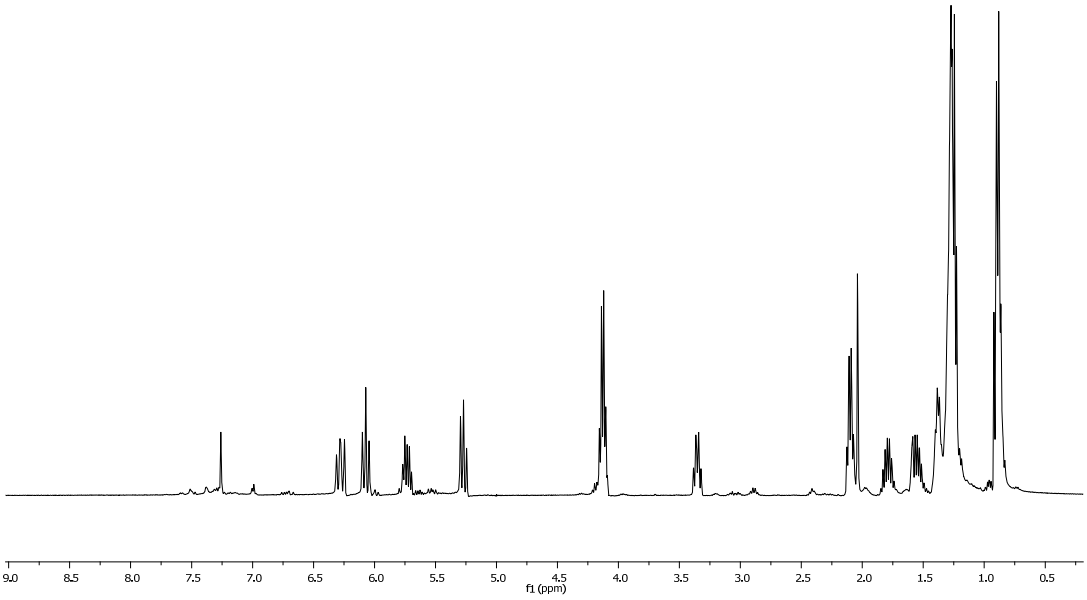
7

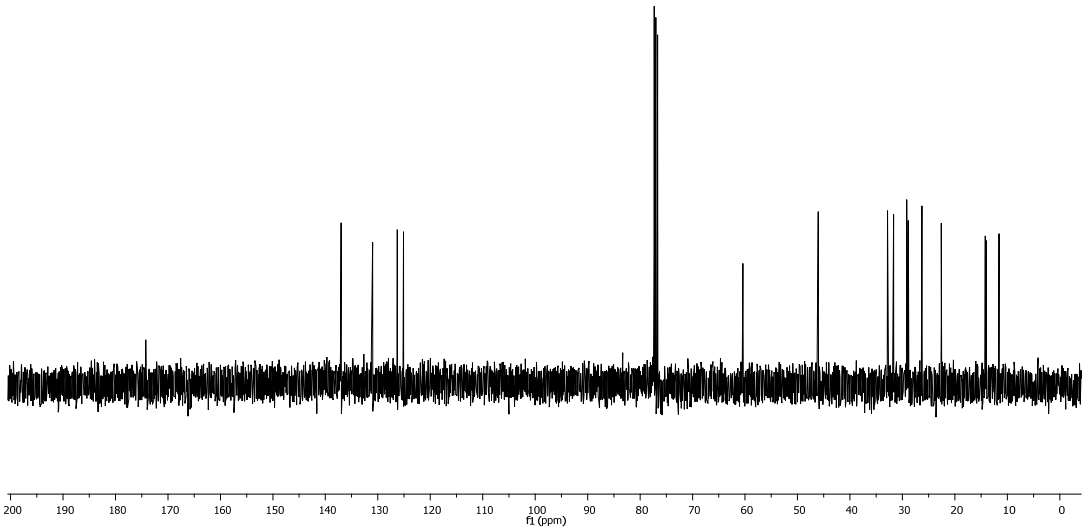

7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)


150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)


O
O
5

8


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)