Ephedrine-Based Diselenide: A Promiscuous catalyst suitable to mimic the enzyme glutathione peroxidase (GPx) and to Promote Enantioselective C-C Coupling Reactions

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Materials and Methods

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 MHz on a DPX-200 NMR spectrometer or at 400 MHz on DPX-400 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained either at 50 MHz on a DPX-200 NMR spectrometer or at 100 MHz on a DPX-400 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Abbreviations to denote the multiplicity of a particular signal are s (singlet), sl (singlet large), d (doublet), dd (double doublet), t (triplet), td (triplet of doublet), q (quartet), quint (quintet), sex (sextet) and m (multiplet), for selenium NMR we use $PhSe)_2$ as a internal standard (describe chemical shift 463.2 ppm)[1]. High resolution mass spectra were recorded on a MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Column chromatography was performed using Silica Gel (230-400 mesh) following the methods described by Still.[2] Thin layer chromatography (TLC) was performed using Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapour, or acidic vanillin. Most reactions were monitored by TLC for disappearance of starting material. Air- and moisture-sensitive reactions were conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. Reagents and solvents were handled using standard syringe techniques. Temperatures above room temperature were maintained by use of a mineral oil bath with an electrically heated coil connected to a Variac controller.

General procedure for synthesis of amninoalcohol (1): To one neck round bottom flask, efhedrine (6.0 mmol, 0.990g), formic acid (1.5 mL, solution 85%) and formaldehyde (0.45 mL, solution 37%) was added. The mixture was heated at 65° C for 6h, cooled at room temperature and NaOH 4N was added until obtained a white precipitated then 20 mL of diethyl ether was added, the organic layer was separated. The aqueous phase was extracted more twicely with 20 mL diethyl ether. The organic layer was dried with $MgSO_4$ and concentrated under vacuum. A white solid was obtained.

(1R,2S)-2-(dimethylamino)-1-phenylpropan-1-ol (1). Yield: 0.995g (89%)$[\alpha]^D$ = -7,0, *c* = 1, AcOEt (25ºC) . ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* (ppm): 7.39-7.30 (m, 4H), 7.27-7.19 (m, 1H), 4.94 (d, 1H, j= 3.6Hz), 3.27 (sl, 1H), 2.52-2.48 (m, 1H), 2.34 (s, 6H), 0.82 (d, 3H, j= 6.8Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), *δ* (ppm): 142.1, 127.9, 126.7, 125.8, 72.1, 65.4, 42.9, 9.91. HRMS calcd for $C_{11}H_{17}NO[M + H]^+$: 180.1388. Found: 180.1382.

General procedure for synthesis of ligands (3a-d): To a two necks flask, in argon atmosfer, aminoalcohol **1** (1mmol, 0.179g), 5mL of THF was added. The system was cooled to 0°C and Et_3N (1.2mmol, 0.121g) was added, the reaction mixture was

(1) Menezes, P. H.; Gonçalves, S. M. C.; Hallwas, F.; Silva, R. O.; Bieber, L. W; Simas, A. M. *Org. Lett.* **2003**, *5*,1601.
(2) W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. **1978**, *43,* 2923-2925.

stirred for 5 minutes, subsequently ClMS (1.2mmol, 0.141g) dissolved in 5mL of THF was added drop wise, the solution was stirred for more 30 minutes at 0°C. In a second flask, in argon atmosphere, contained the respective diselenide (1mmol), 5mL THF, $NaBH_4$ (1.2mmol, 0.046g) and 1mL of dry ethanol was added, the mixture was stirred for 30 minutes at room temperature. After complete formation of selenolate, the mixture was transferred to first flask and stirred for 2 hours at room temperature. Then the mixture was diluted in ethyl acetate (20mL) and washed with solution $NH_4Cl_{(sat)}$ (1x20 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2x20 mL) the organic layer was dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by chromatography on silica gel using hexane/ethyl acetate 90:10 as the eluent. Spectral and analytical data for:

(1S,2S)-N,N-dimethyl-1-phenyl-1-(phenylselanyl)propan-2-amine(3a). Yield: 0.263g (83%)$[\alpha]^D$ = -256, *c* = 1, AcOEt (25ºC). ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* (ppm): 7.28-7.23 (m, 2H), 7.20-7.07 (m, 8H), 4.30 (d, 1H, *j*= 8.8Hz), 3.14-3.11 (m, 1H), 2.16 (s, 6H), 1.24, (d, 3H, *j*= 6.6Hz).
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 142.0, 135.1, 129.5, 128.49, 128.47, 127.7, 127.3, 126.3. HRMS calcd for $C_{17}H_{21}NSe[M + H]^+$: 320,0917. Found: 320.0911.

(1S,2S)-1-(ethylselanyl)-N,N-dimethyl-1-phenylpropan-2-amine(3b). Yield: 0.154g (57%),$[\alpha]^D$ = -167, *c* = 1, AcOEt (25ºC). ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* (ppm): 7.33-7.25 (m, 4H), 7.2-7.15 (m, 1H), 4.14 (d, 1H, *j*= 9.0Hz), 3.07-3.0 (m, 1H), 2.2 (q, 2H, *j*= 7.5Hz), 2.16 (s, 6H), 1.2 (t, 3H, *j*=7.5Hz), 1.19 (d, 3H, *j*=6.3Hz).. ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 142.5, 128.5, 128.0, 126.4, 63.4, 48.4, 40.6, 17.6, 15.2, 11.8. HRMS calcd for $C_{13}H_{21}NSe[M + H]^+$: 272.0917. Found: 272.0911.

Se-(1S,2S)-2-(dimethylamino)-1-phenylpropyl 4-methylbenzoselenoate (3c). Yield: 0.202g (56%)$[\alpha]^D$ = -202, *c* = 1, AcOEt (25ºC). ^{1}H NMR ($CDCl_3$, 200 MHz), *δ* (ppm): 7.67 (d, 2H, *j* = 8.31Hz), 7.37 (d, 2H, *j*= 8.3Hz), 7.31-7.09 (m, 5H), 4.94 (d, 1H, *j* = 8.43 Hz), 3.22-3.02 (m, 1H), 2.30 (s, 3H), 2.22 (s, 6H), 1.19 (d, 3H, *j*= 6.48Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 221.6, 163.7, 162.0, 155.6, 148.5, 147.6, 147.4, 146.5, 145.9, 82.5, 70.5, 60.3, 40.8, 31.3.HRMS calcd for C19H23NOSe: 361.0945. Found: 361.0938

Se-(1S,2S)-2-(dimethylamino)-1-phenylpropyl 2,2-dimethylpropaneselenoate (3d). Yield: 0.189g (58%)$[\alpha]^D$ = -286, *c* = 1, AcOEt (25ºC). ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* (ppm): 7.32-7.21 (m, 4H), 7.19-7.13 (m, 1H), 4.64 (d, 1H, *j*= 8.5Hz), 3.00-2.96 (m, 1H), 2.19 (s, 6H), 1.17 (s, 9H), 1.12 (d, 3H, j= 6.6Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 209.0, 142.9, 128.15, 128.10, 126.4, 63.2, 50.5, 49.4, 40.9, 26.0, 11.3. HRMS calcd for C16H25NOSe: 327.1101. Found: 327.1096.

General procedure for synthesis of ligands (2): To a two necks flask, in argon atmosphere, aminoalcohol **1** (1mmol, 0.179g), 5mL of THF was added. The system was cooled to 0°C and Et_3N (1.2mmol, 0.121g) was added, the reaction mixture was stirred for 5 minutes, subsequently ClMS (1.2mmol, 0.141g) dissolved in 5mL of THF was added drop wise, this solution was stirred for more 30 minutes at 0°C. In a second flask, in argon atmosphere, contained elemental selenium (2mmol, 0.158g), 5mL THF, lithium triethyl-borohydride solution (2mL, solution 1M) was added slowly, the mixture was refluxed for 30 minutes. Then it was transferred to first flask, at -78°C and stirred for 1h at same temperature then solution was stirred at room temperature for overnight. After this the mixture was diluted in CH_2Cl_2 (100mL) and filtered over celite, the solution was concentrated under vacuum. The residue was

purified by chromatography on silica gel using hexane/ethyl acetate 50:50 as the eluent. Spectral and analytical data for:

(2R,3R)-3-(((1S,2S)-2-(dimethylamino)-1-phenylpropyl)diselanyl)-N,N-dimethylbutan-2-amine (2). Yield: 0.255g (53%)$[\alpha]^D$ = -430, *c* = 1, AcOEt (25ºC). ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* (ppm): 7.34-7.17 (m, 3H), 7.13-7.05 (m, 2H), 3.71 (d, 1H, *j*= 9.7Hz), 3.13-3.03 (m, 1H), 2.04 (s, 6H), 1.15 (d, 3H, *j*= 6.6Hz).^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 142.2, 128.7, 127.7, 126.5, 62.4, 53.2, 40.4, 11.5. HRMS calcd for $C_{22}H_{32}N_2Se_2[M + H]^+$: 485,0974. Found: 485.0968.

General procedure for asymmetric arylation of aldehydes: In a Schlenck tube, under argon atmosphere, boronic acid (1.2 mmol), toluene (1.5 ml) and Et_2Zn (2.7 mL, solution 1.5M in toluene) was added, the mixture was heated for 0.5 h at 60° C. The solution was cooled at room temperature and the ligand (10 mol%) diluted in toluene (0.5 mL) was added, the mixture was stirred for 15 minutes at room temperature. After that, the reaction was cooled at 0° C than aldehyde (0.5 mmol) was added and stirred for 30 minutes at same temperature. Than 10 mL of water was added in the system and the mixture was extracted with CH_2Cl_2 (3 x 20 mL), the organic layer was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by chromatography on silica gel using hexane/ethyl acetate 90:10 as the eluent. The results are summarized in the table 3. Spectral data for:

phenyl(p-tolyl)methanol (Table 3, entries 2 and 8). ^{1}H NMR ($CDCl_3$, 400MHz), *δ* (ppm): 7.35 - 7.25 (m, 4H), 7.22 – 7.18 (M, 3H), 7.10 (d, *j* = 7.8Hz), 5.35 (s, 1H), 2.29 (s, 3H), 2.2 (sl, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 144.0, 141.0, 137.1, 129.1, 128.3, 127.3, 126.5, 126.4, 76.0, 20.9. Entry 2 $[\alpha]^D$ = +7, *c* = 1, AcOEt (25ºC), Entry 8 $[\alpha]^D$ = -12, *c* = 1, AcOEt (25ºC)

phenyl(o-tolyl)methanol (Table 3, entries 1 and 7). ^{1}H NMR ($CDCl_3$, 400MHz), *δ* (ppm): 7.42 (dd, *j* = 7.09 Hz and *j* = 1.90 Hz, 1H), 7.27 – 7.23 (m, 4H), 7.22 – 7.12 (m, 3H), 7.10 – 7.05 (m, 1H), 5.88 (s, 1H), 2.33 (sl, 1H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 143.0, 141.5, 135.3, 130.4, 128.3, 127.4, 127.3, 127.0, 126.4, 126.0, 73.3, 19.1. Entry 1 $[\alpha]^D$ = +3,0, *c* = 1, AcOEt (25ºC), Entry 7$[\alpha]^D$ = -14,0, *c* = 1, AcOEt (25ºC)

(4-methoxyphenyl)(phenyl)methanol (Table 3, entries 6 and 10). ^{1}H NMR ($CDCl_3$, 400MHz), *δ* (ppm): 7.37 – 7.16 (m, 7H), 6.80 (d, *j* = 8.5 Hz), 5.69 (s, 1H), 3.71 (s, 3H), 2.48 (sl, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 159.0, 144.0, 136.2, 128.2, 127.8, 127.4, 126.3, 113.8, 75.6, 55.1. Entry 6 $[\alpha]^D$ = +3, *c* = 1, AcOEt (25ºC), Entry 10, $[\alpha]^D$ = -30, *c* = 1, AcOEt (25ºC)

(2-methoxyphenyl)(phenyl)methanol (Table 3, entries 5 and 9). ^{1}H NMR ($CDCl_3$, 400MHz), *δ* (ppm): 7.36 – 7.30 (m, 2H), 7.27 – 7.13 (m, 5H), 6.88 (td, *j* = 7.58 Hz and *j* = 0.9 Hz, 1H), 6.80 (dd, *j* = 7.58 Hz and *j* = 0.73 Hz, 1H), 6.01 (s, 1H), 3.68 (s, 3H), 3.0 (sl, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 156.6, 143.4, 132.2, 128.4, 127.9, 127.6, 126.9, 126.4, 120.7, 118.8, 71.1, 55.2. Entry 9 $[\alpha]^D$ = -34, *c* = 1, AcOEt (25ºC), Entry 5 $[\alpha]^D$ = +45,0, *c* = 1, AcOEt (25ºC)

(4-chlorophenyl)(phenyl)methanol (Table 3, entries 4 and 12). ^{1}H NMR ($CDCl_3$, 400MHz), *δ* (ppm): 7.32 – 7.20 (m, 9H), 5.70 (s, 1H), 2.41 (sl, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 143.4, 142.2, 133.2, 128.55, 128.52, 127.8, 127.7, 126.5, 75.5. Entry 4 $[\alpha]^D$ = -20, *c* = 1, AcOEt (25ºC), Entry 12 $[\alpha]^D$ = +12, *c* = 1, AcOEt (25ºC)

(2-chlorophenyl)(phenyl)methanol (Table 3, entries 3 and 11). ^{1}H NMR ($CDCl_3$, 400MHz), δ (ppm): 7.52 (dd, j = 7.5 Hz and j = 1.7Hz, 1H), 7.39 – 7.19 (m, 7H), 7.14 (td, j = 7.5Hz and j = 1.5Hz, 1H), 6.1 (s, 1H), 2.5 (sl, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm):142.3, 141.1, 132.5, 129.4, 128.6, 128.3, 128.1, 127.6, 126.9, 126,8, 77.6. Entry 3 $[\alpha]^D$ = +19, c = 1, AcOEt (25ºC), Entry 11$[\alpha]^D$ = -25, c = 1, AcOEt (25ºC)

General procedure for enantioselective addition of diethylzinc to benzaldehyde.

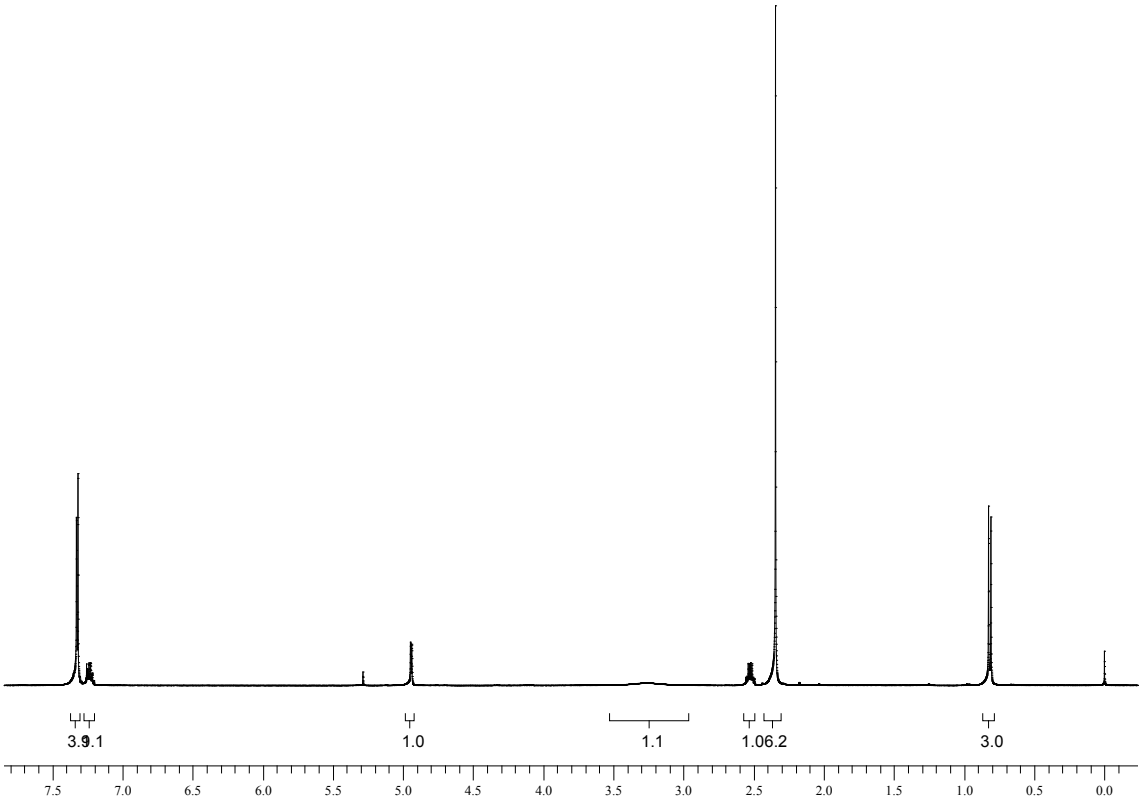
In a tube Schlenck, previously dried and purged with argon, was added to the ligand dissolved in dry toluene (5 mL) and diethylzinc (2.5 mmol solution in toluene). Left-shaking for 30 minutes at room temperature. Then cooled to the reaction system at -20 ° C and was added benzaldehyde, the system was kept under constant agitation at this temperature for 24 hours. Finally, the system was heated and at 0 ° C was added 5 mL of HCl (1M), this solution was extracted with dichloromethane (3 x 10 mL). The organic phase was separated, dried with MgSO4, filtered and the solvent was removed under vacuum. The crude product was purified by flash chromatography column, eluindo up with a solution of hexane / ethyl acetate (90:10).

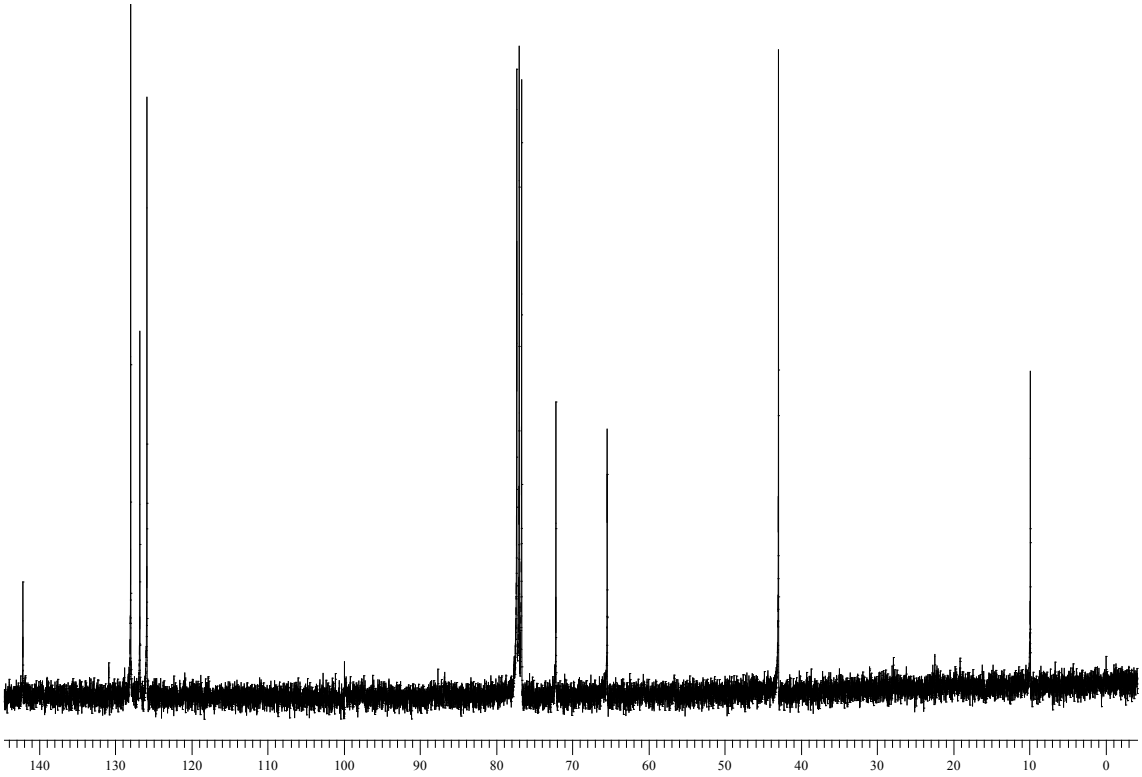
phenyl-1-propanol (Table 3).^{1}H NMR ($CDCl_3$, 400MHz), δ (ppm): 7.36 – 7.23 (m, 5H), 4.55 (t, J= 6,72Hz), 2.15 (sl, 1H), 1.76 (m, 2H), 0.89 (t, J= 7.30Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 144.51, 128.31, 127.39, 125.91, 75.91, 31.77, 10.05.

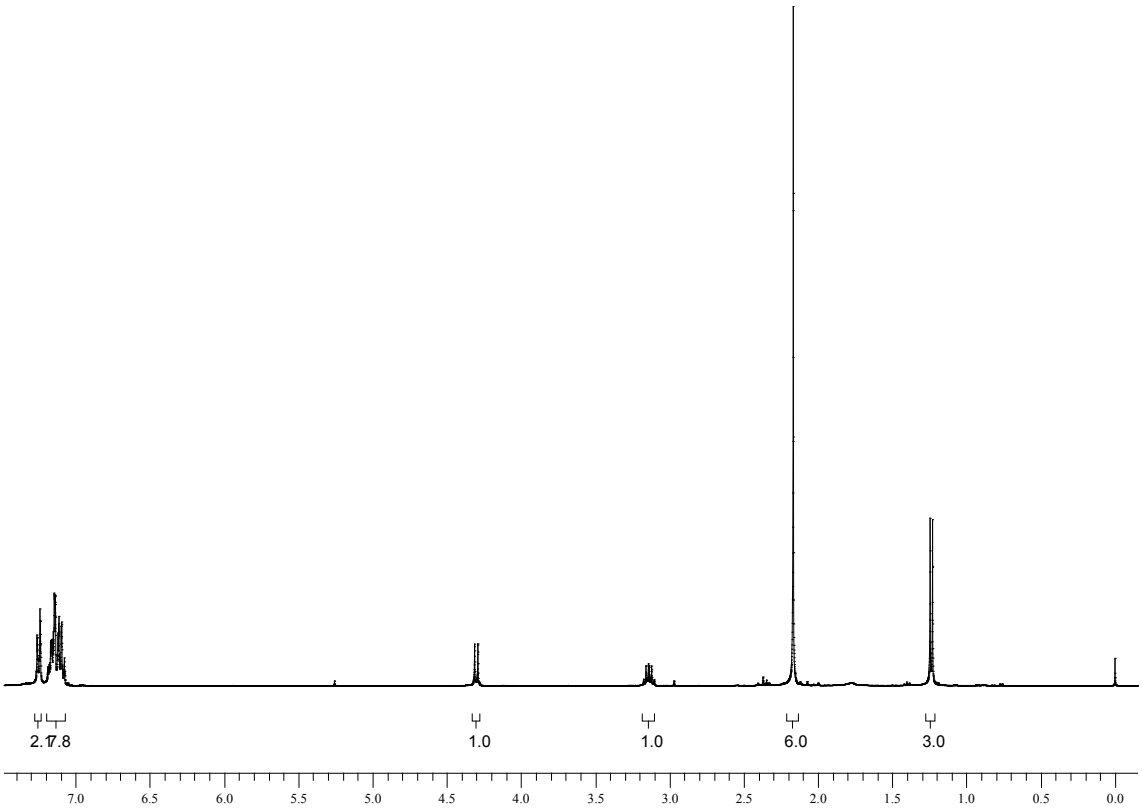
Determination of GPx-like activity.[3] The experiments were made with a diode-array spectrophotometer, with a thermostated cell holder at 30 ºC. Formation of PhSSPh was followed at 305 nm and reactions were started by the addition of an amount of H_20_2 (finalconcentration = 10 mM) to a methanol solution of PhSH (final concentration = 5 mM) containing a selenium catalyst (final concentration = 0.00005 M). Absorbance-versus time data were stored directly on a microcomputer. The reaction was monitored during six minutes, at least more than three times under the same conditions.

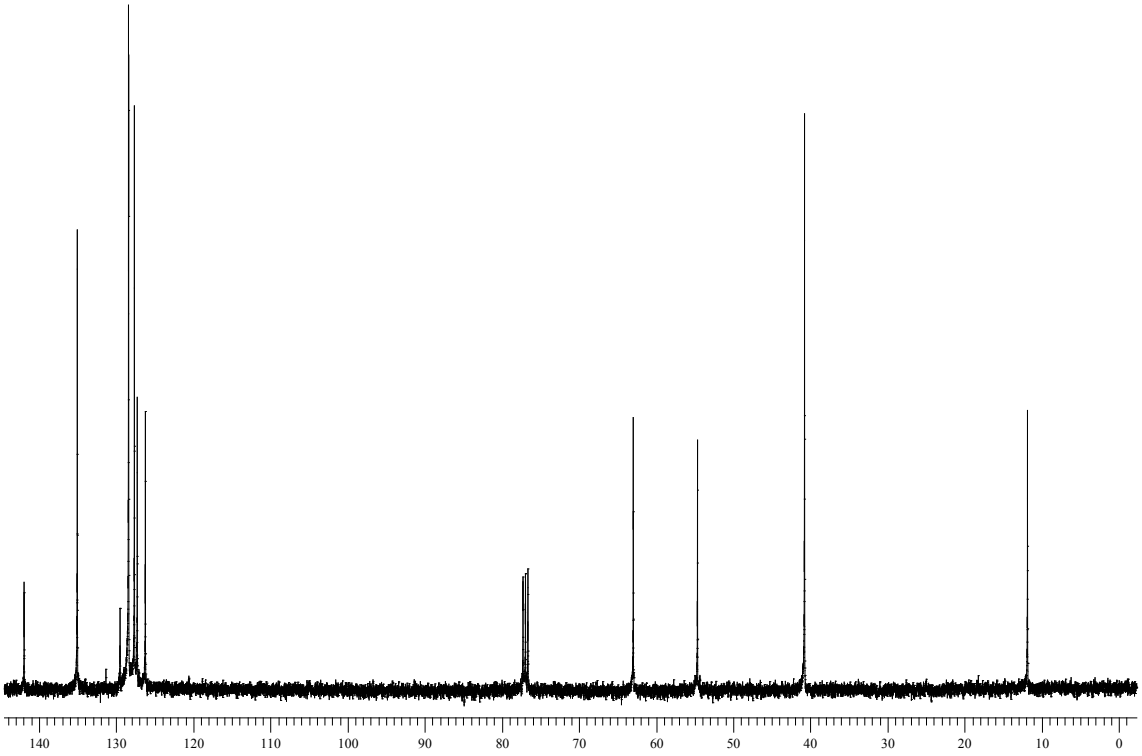
(3) Aberto, E. E.; Soares, L. C.; Sudati, J. H.; Borges, A. C. A.; Rocha, J. B. T.; Braga, A. L. *Eur. J. Org. Chem.* **2010**, 4211.

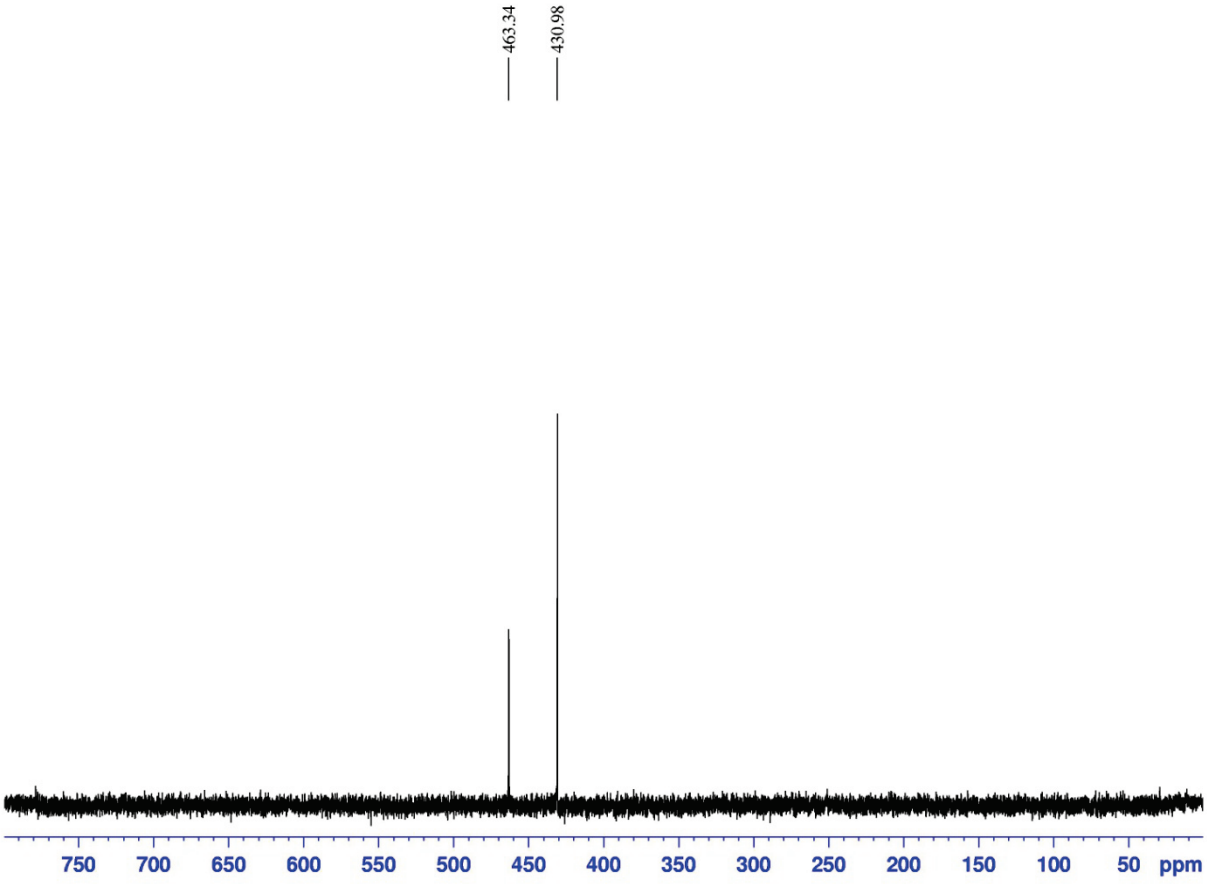
Selected Spectra

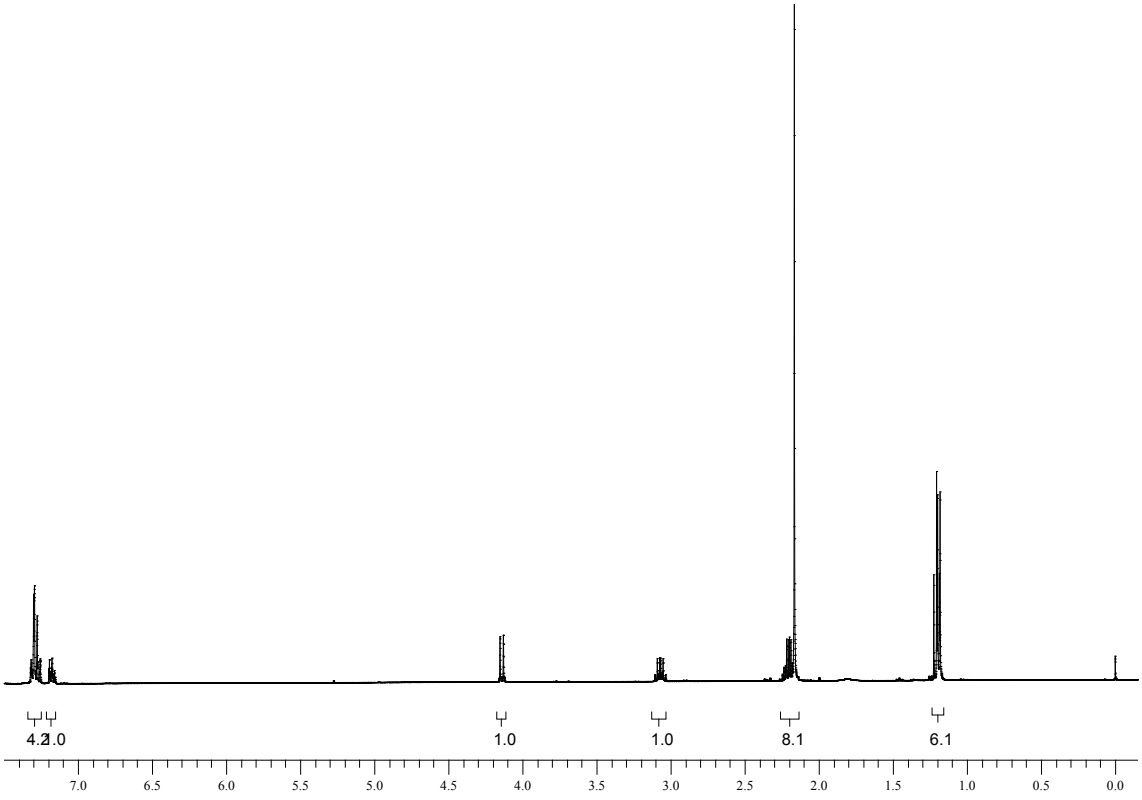


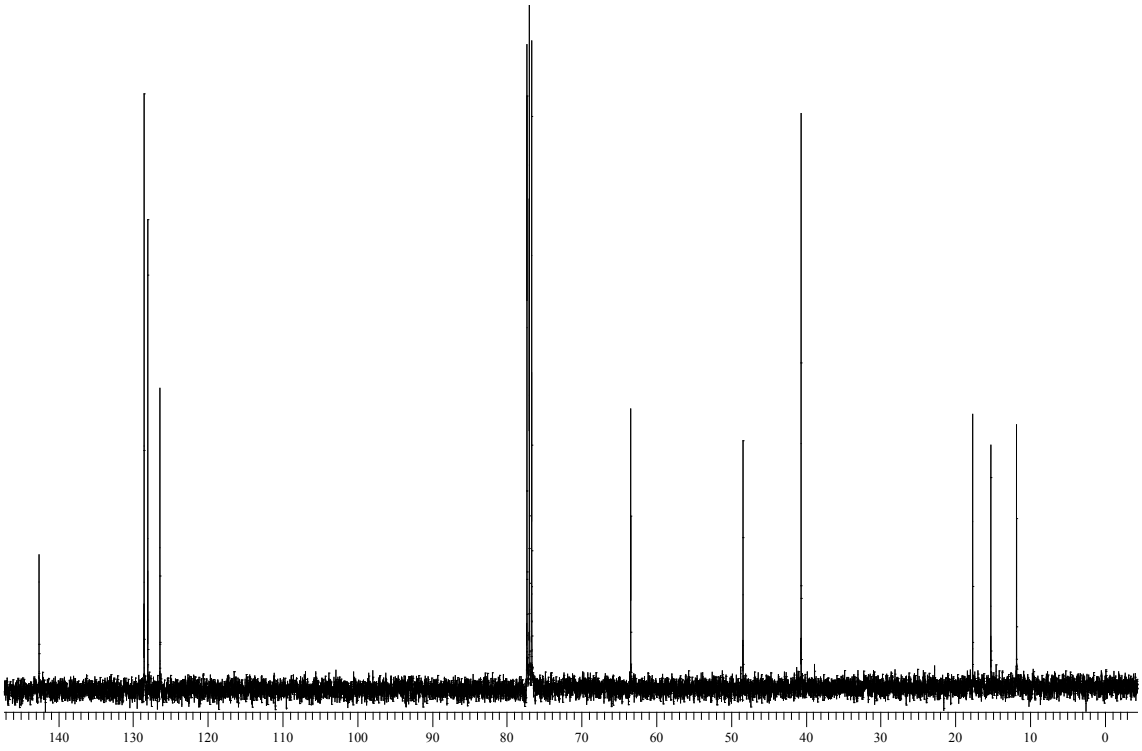


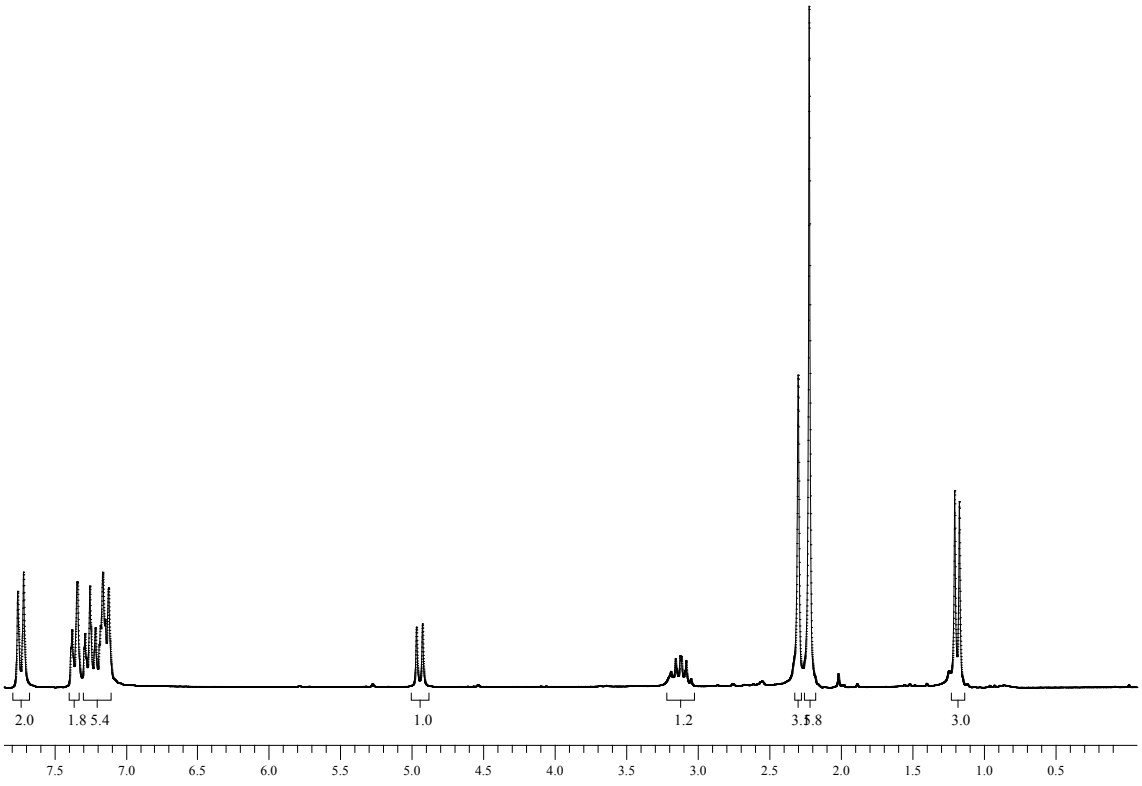


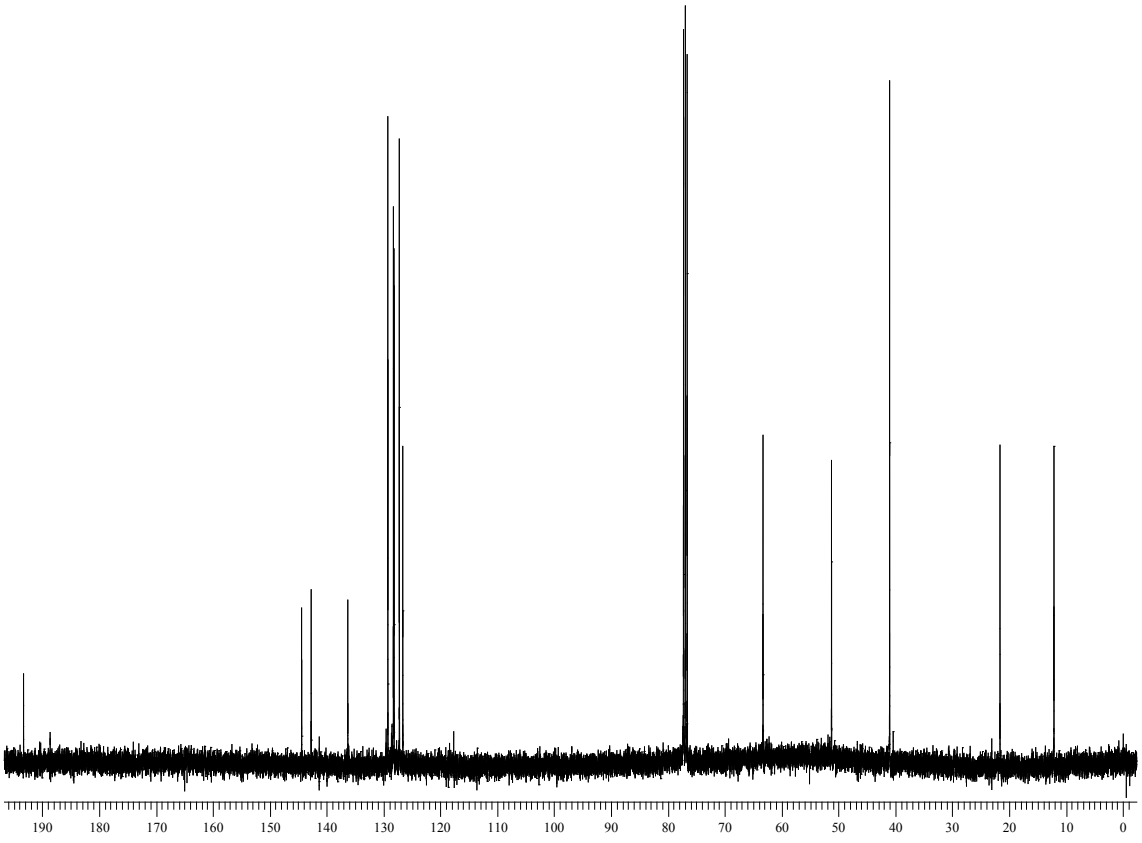


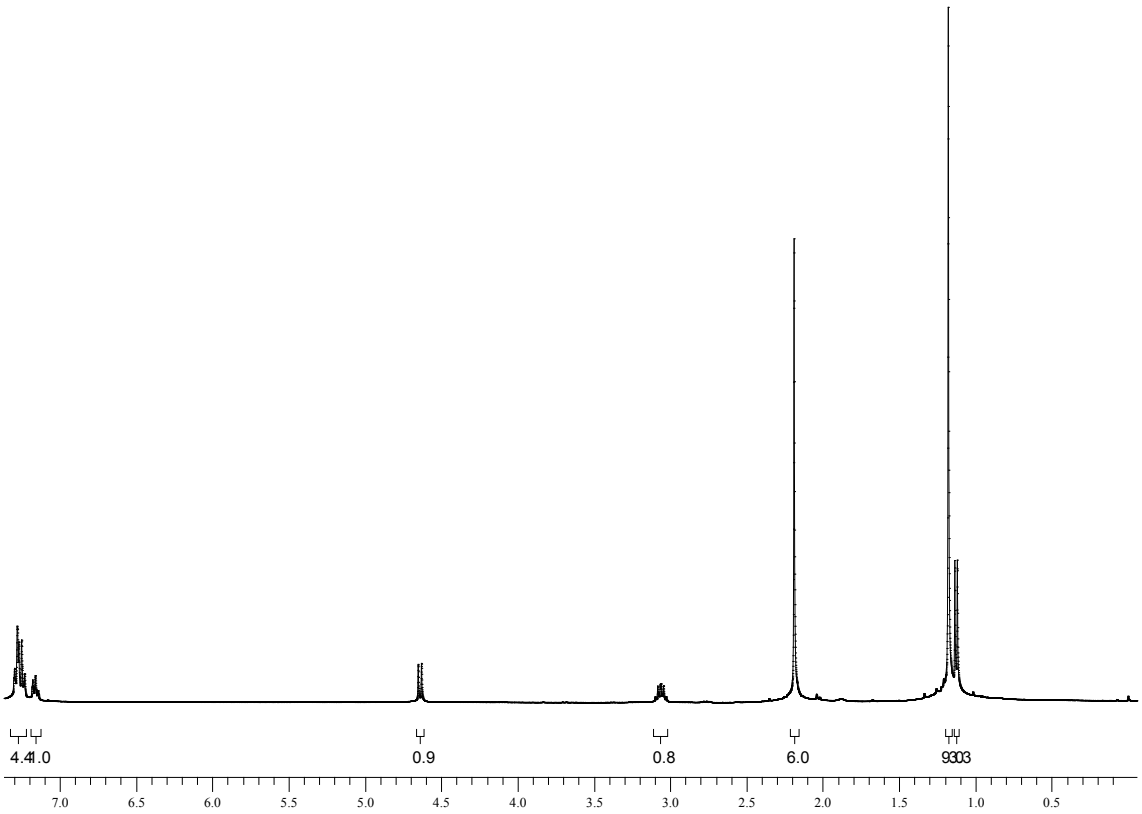


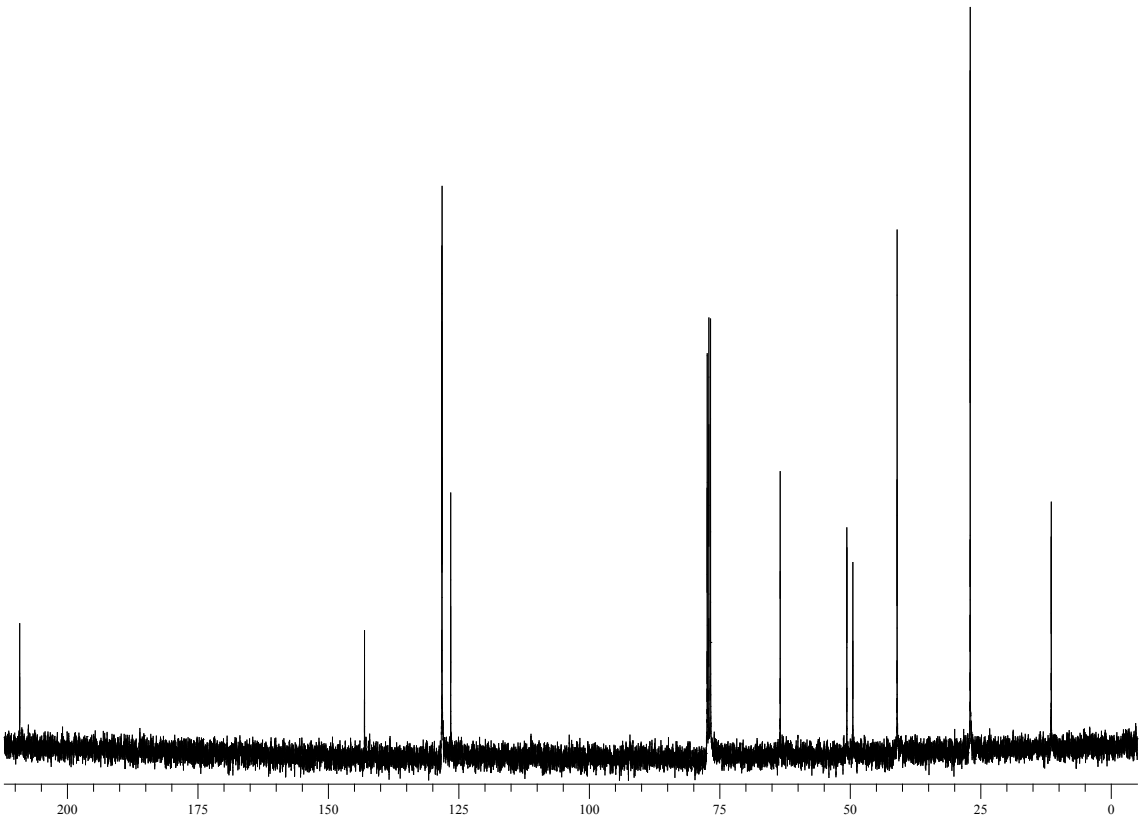


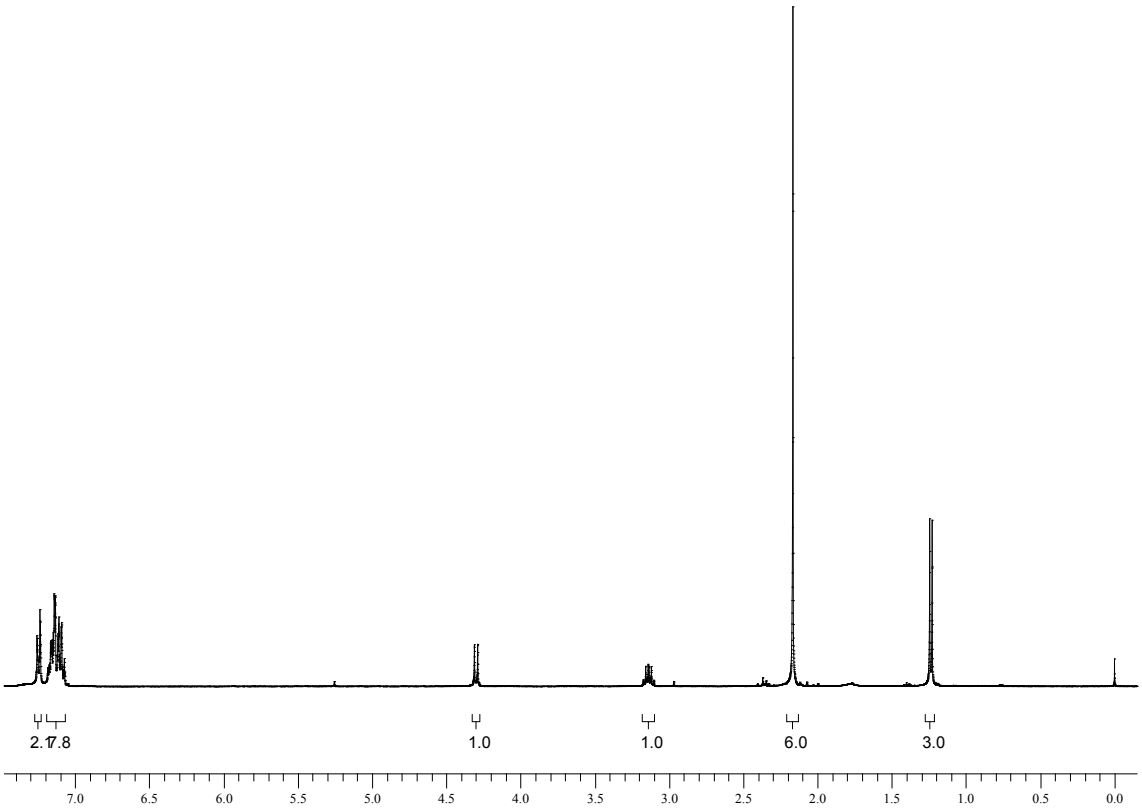


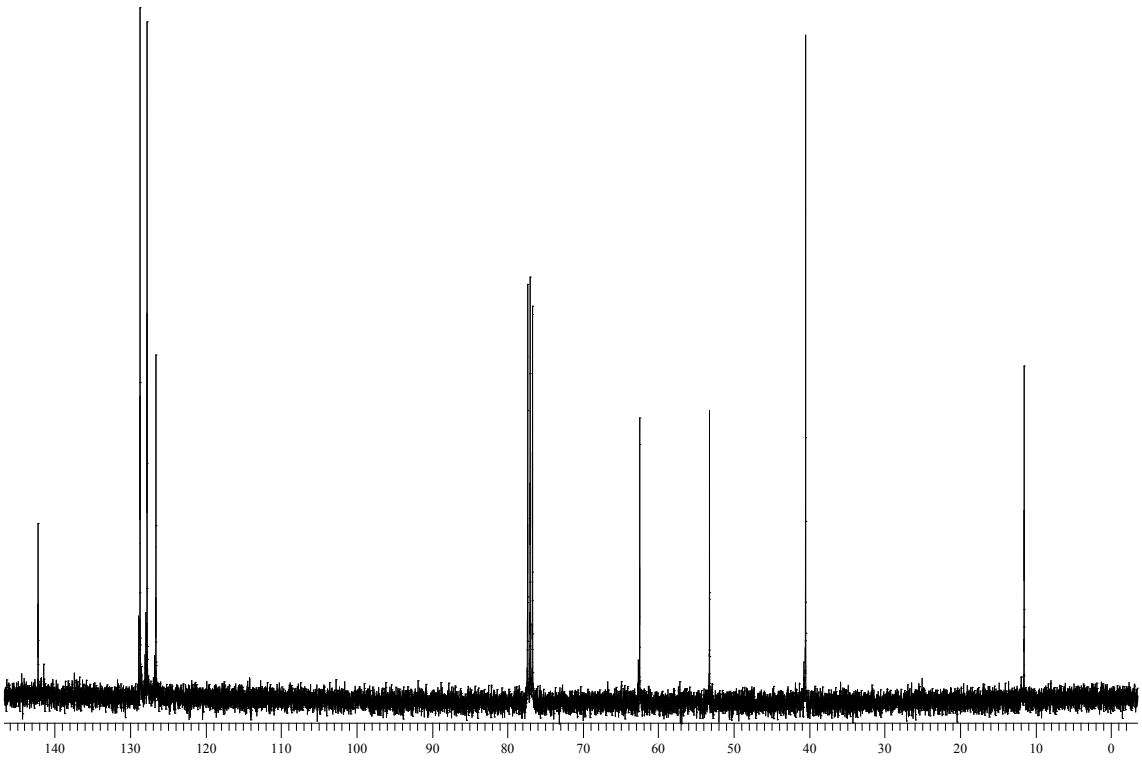


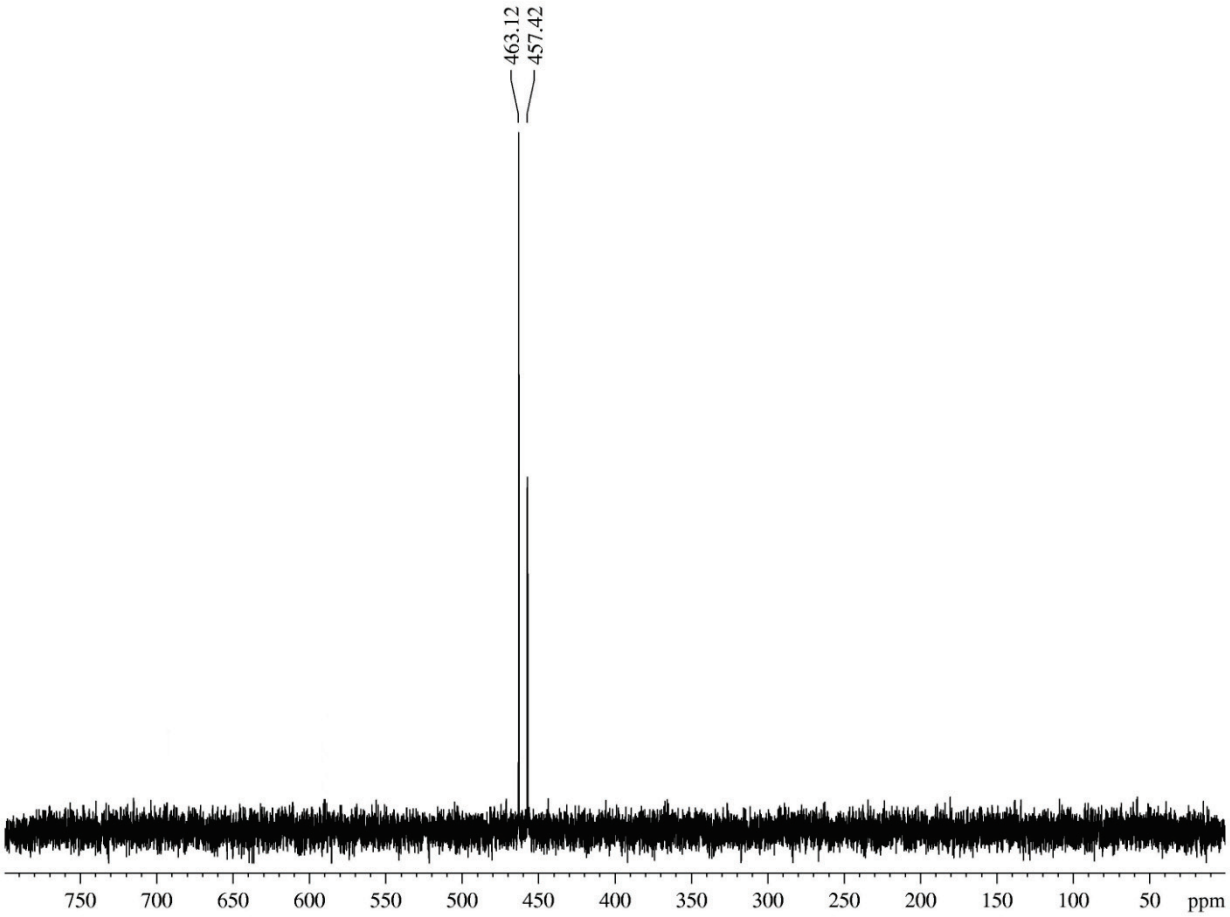


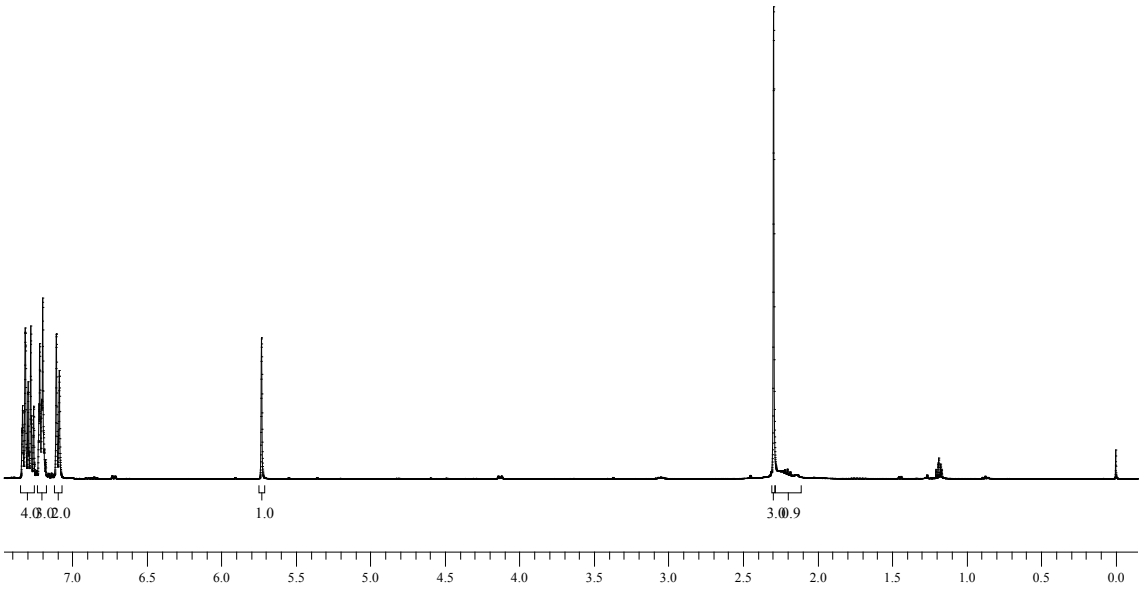


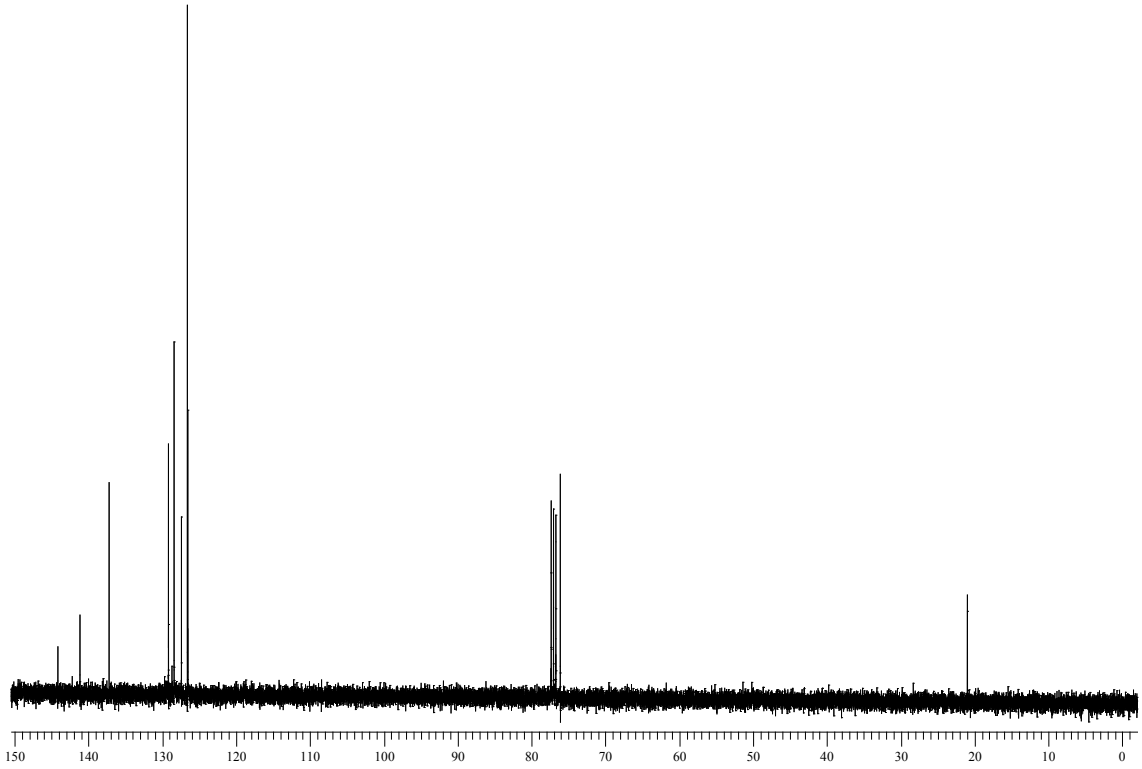


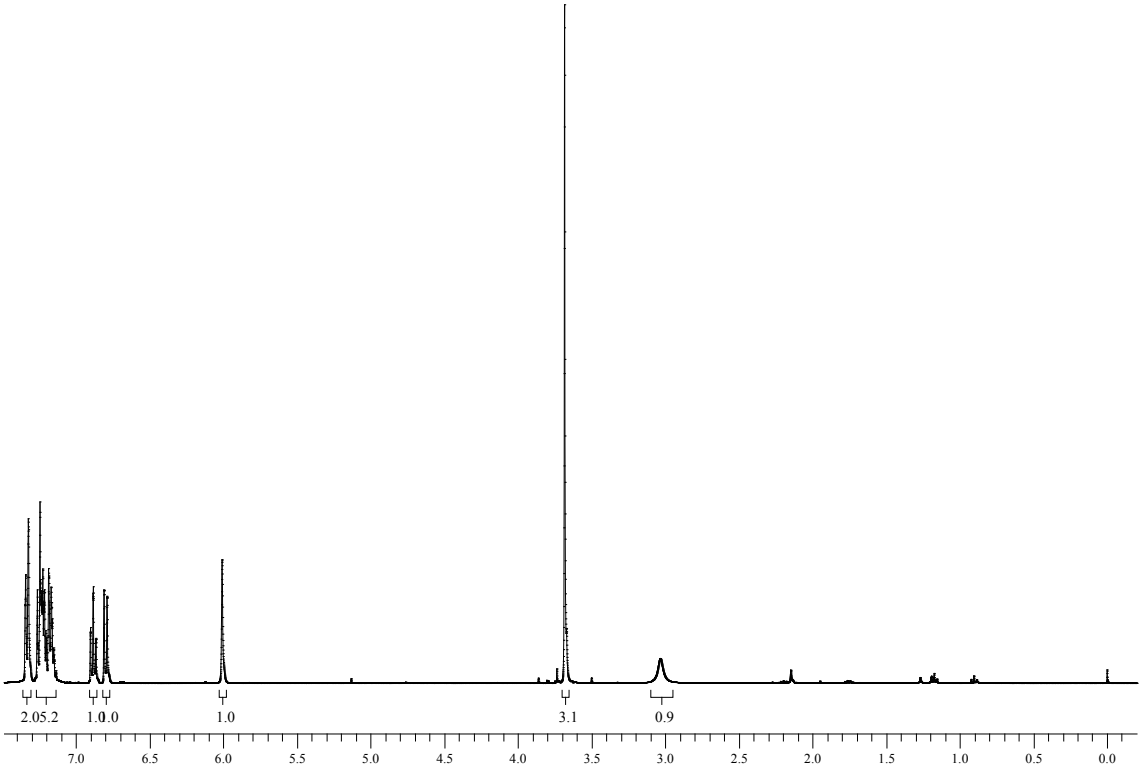


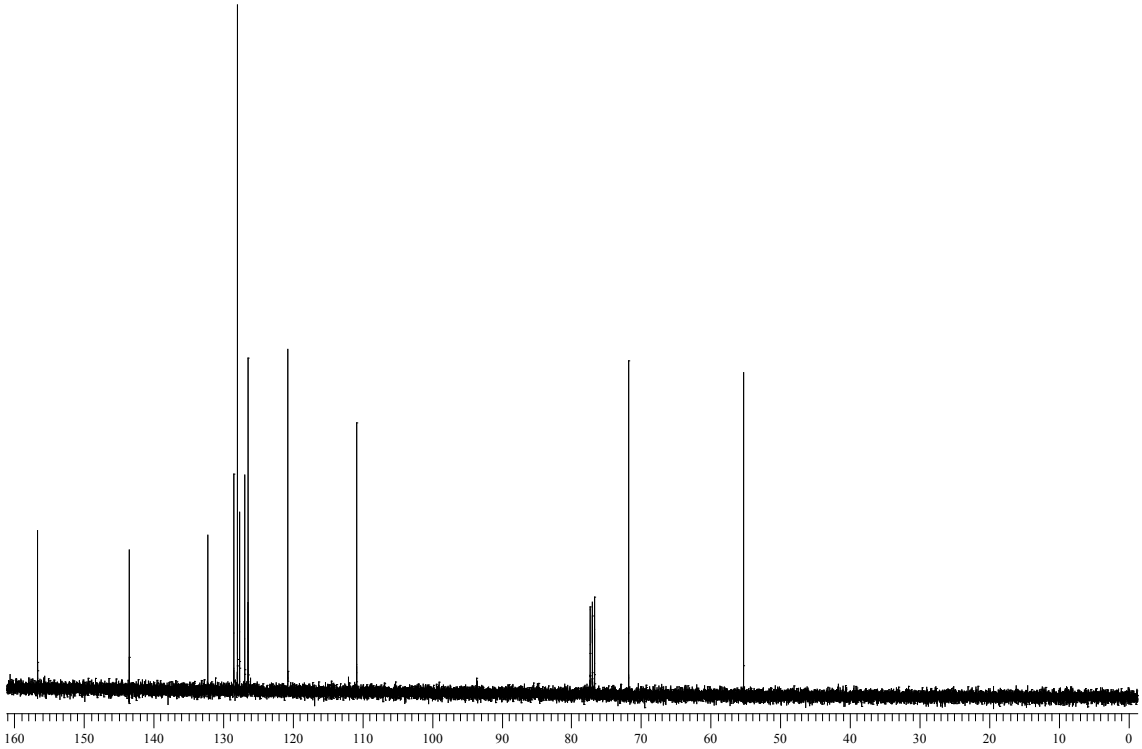


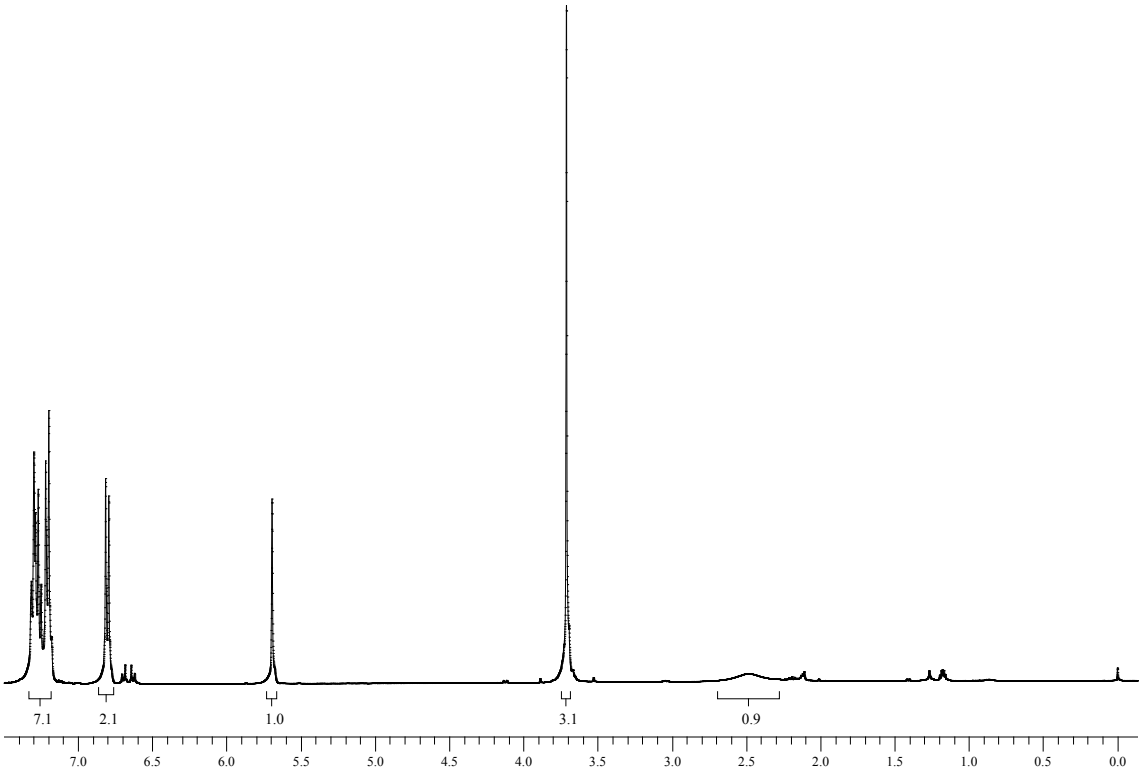


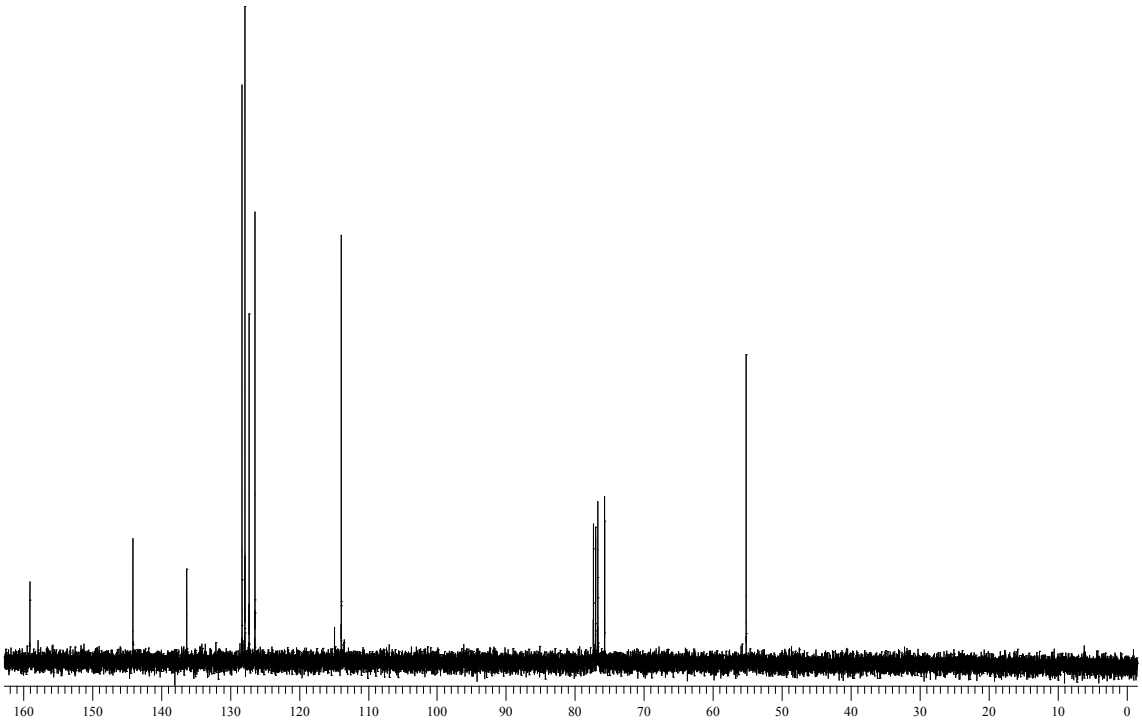


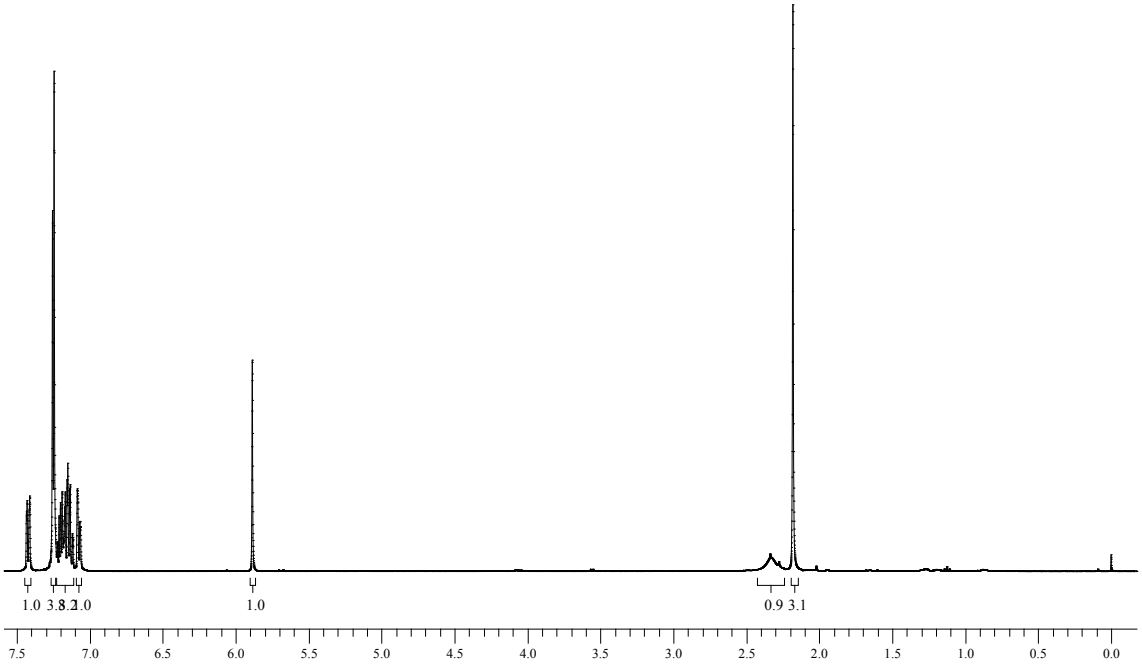


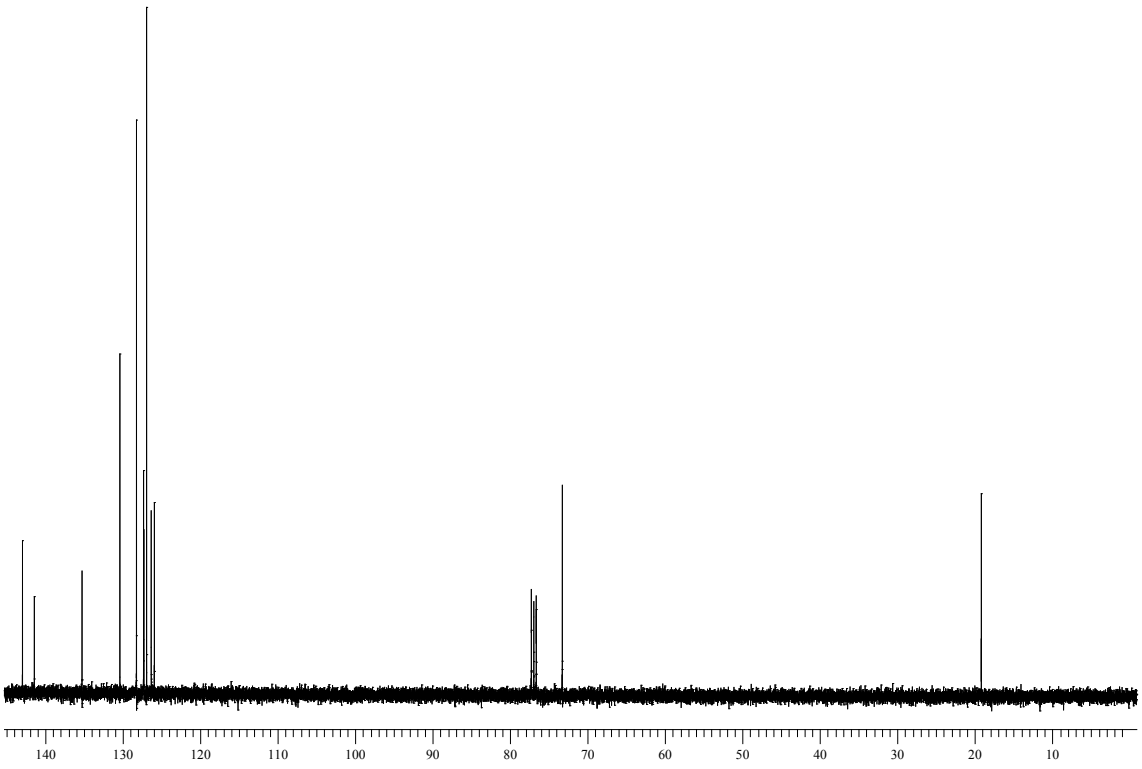


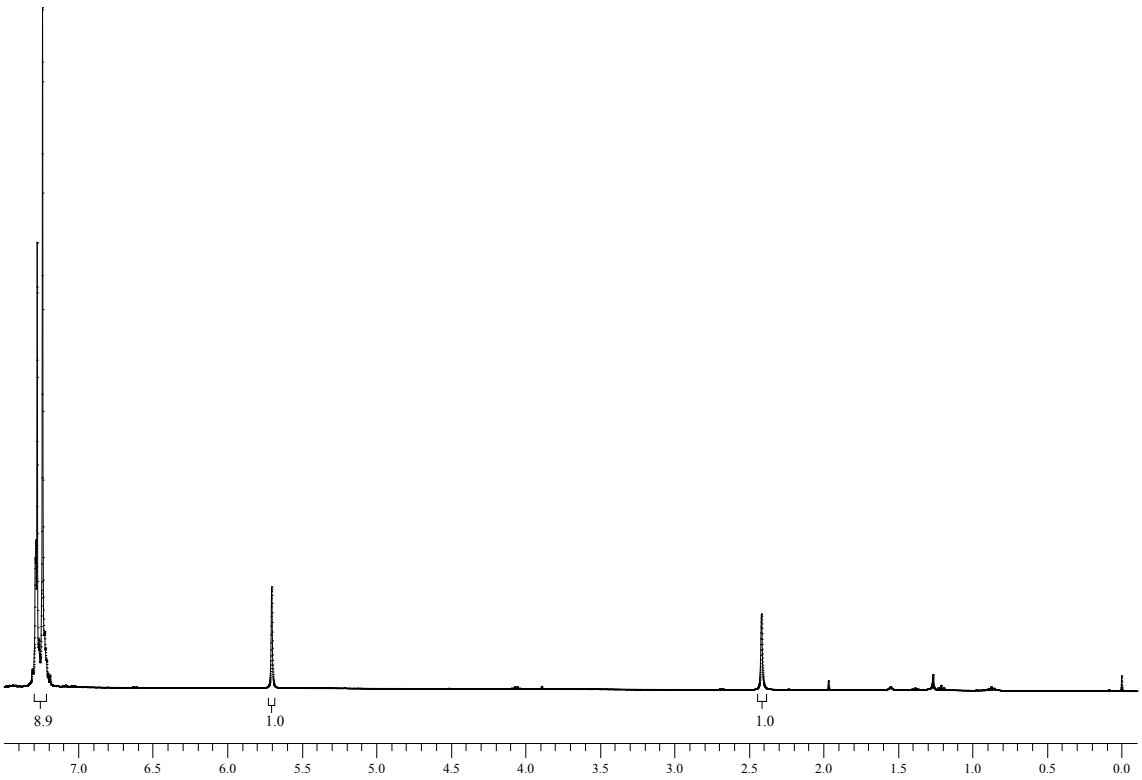


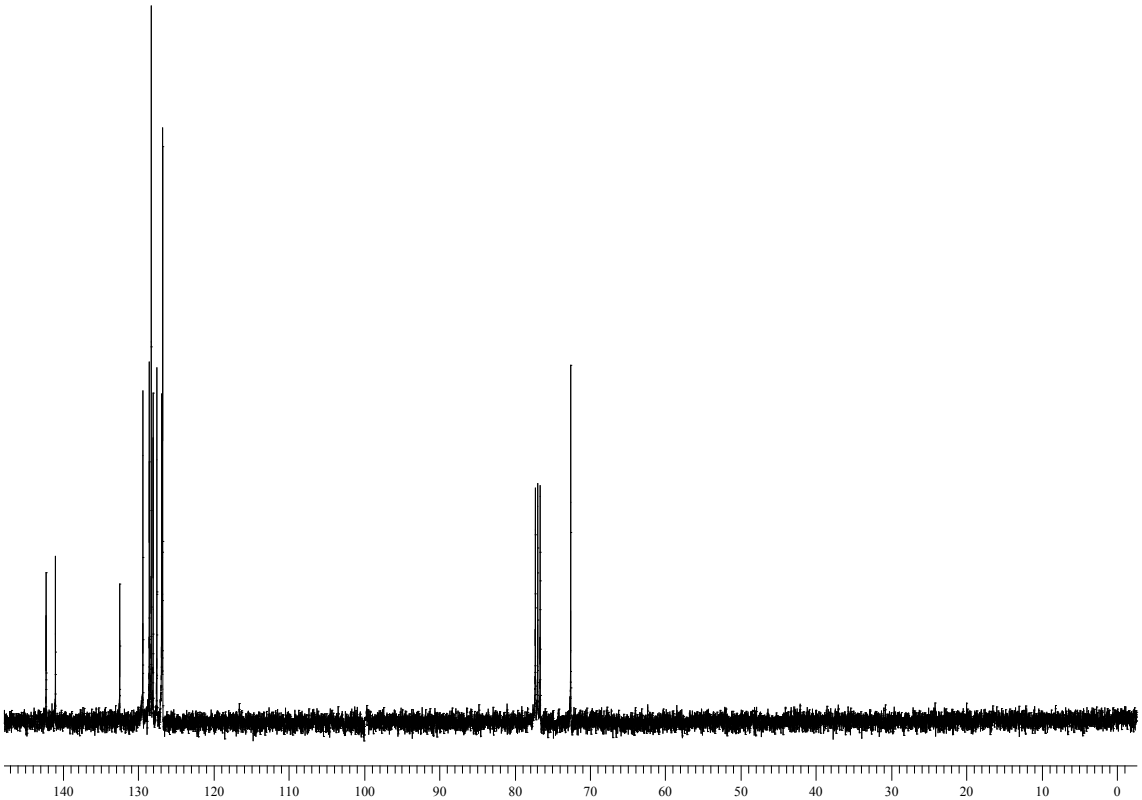


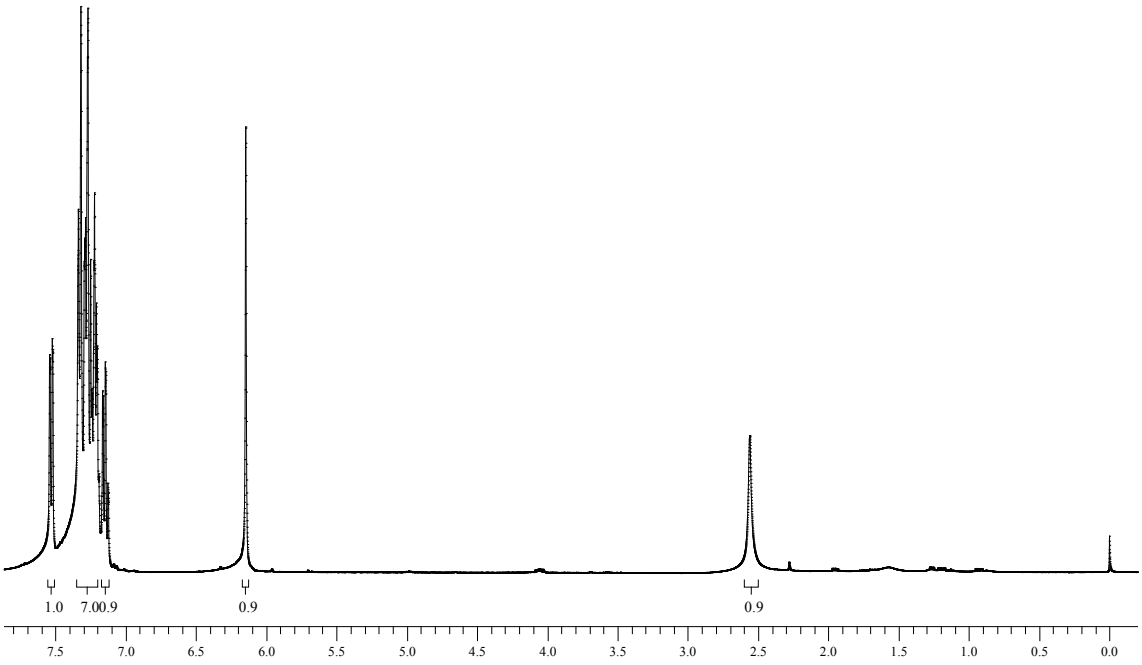


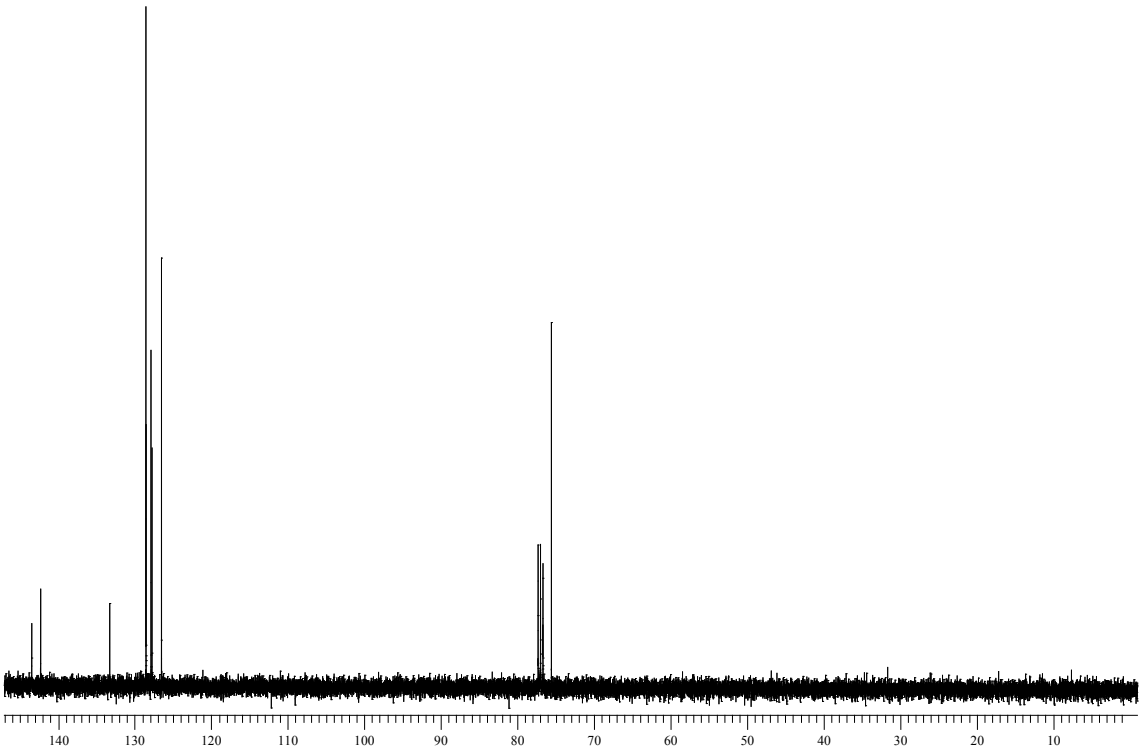


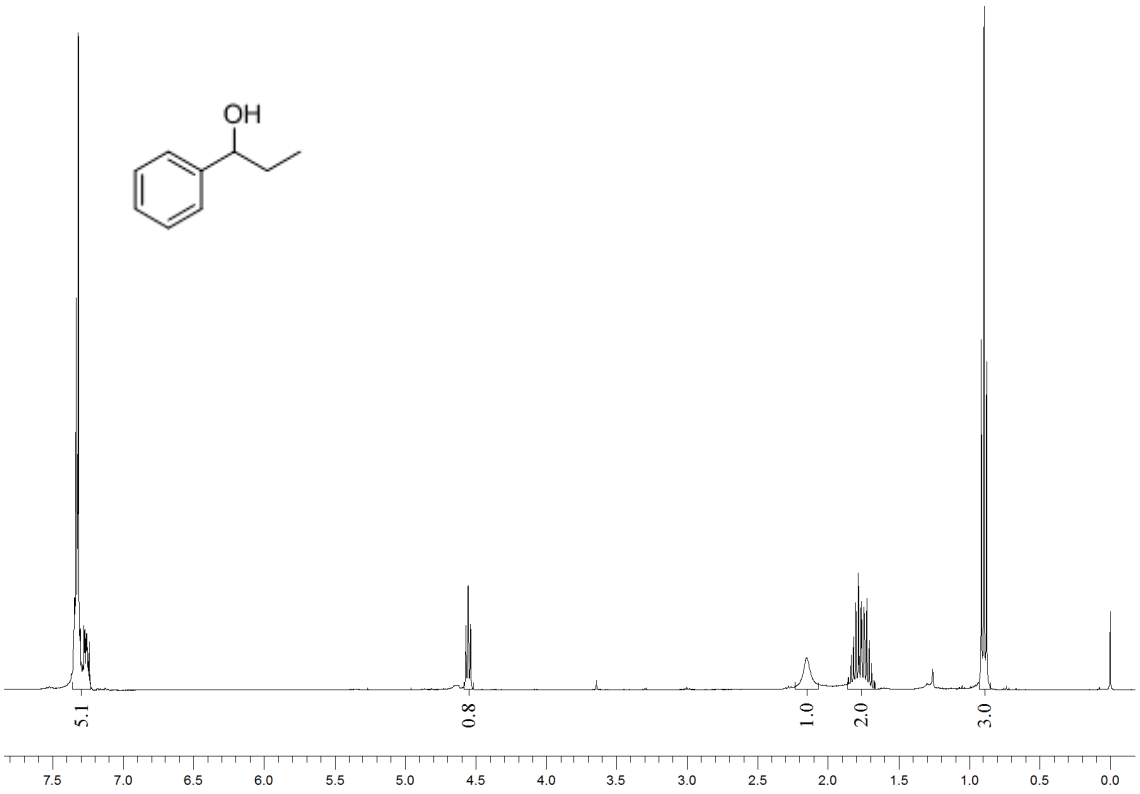


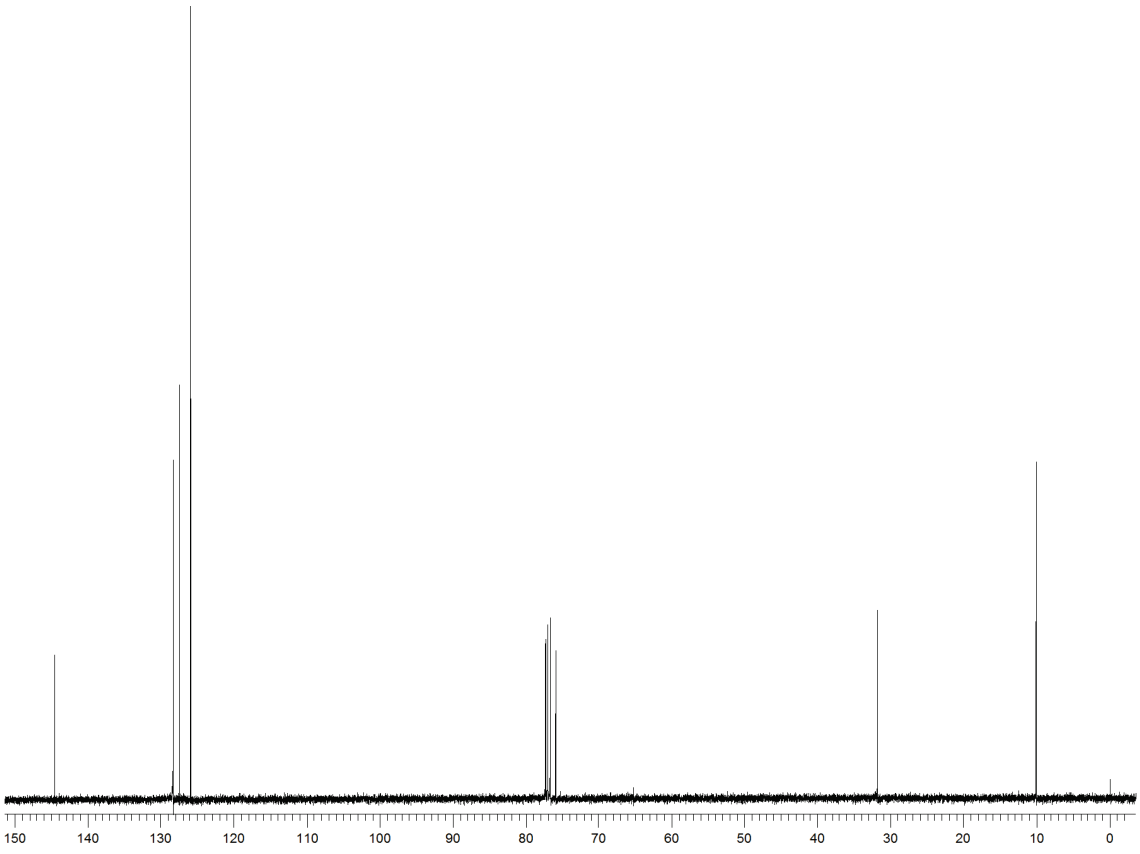






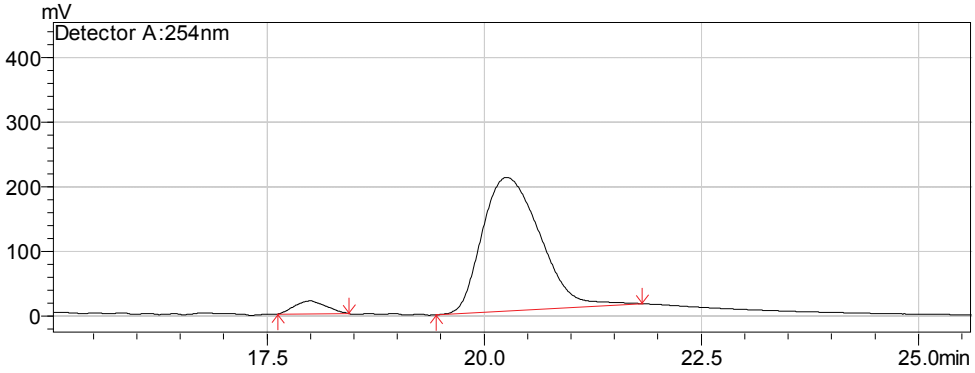






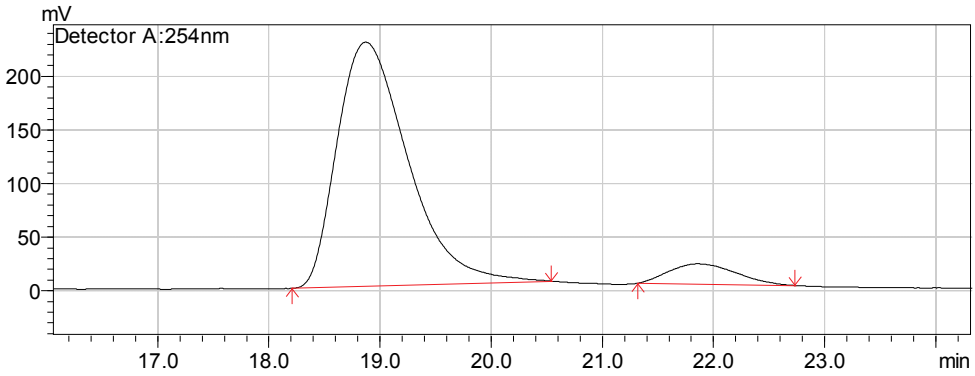
Chiral HPLC Analysis Data

(Table 2, entry 2)
phenyl(p-tolyl)methanol
ee = 91%



Peak#	*Ret. time*	*Area*	*Area%*
1	17.996	557300	4.764
2	20.250	11141725	95.236

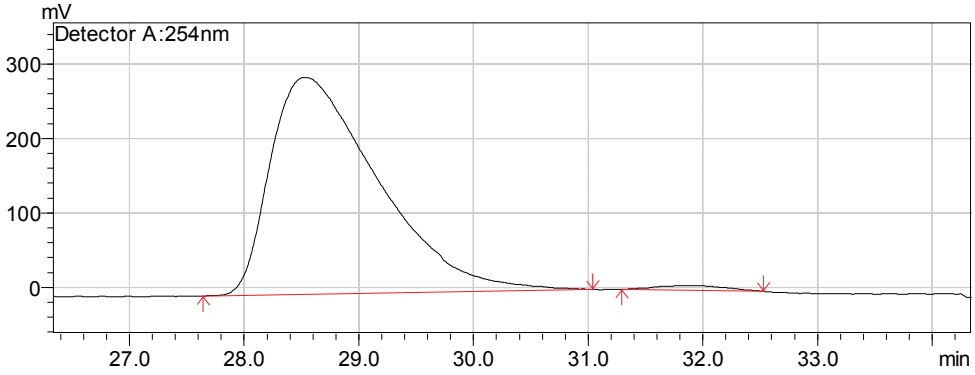
(Table 2, entry 8)
phenyl(p-tolyl)methanol
ee = 85%



Peak#	*Ret. time*	*Area*	*Area%*
1	18.867	100545332	92.736
2	21.860	787585	7.268

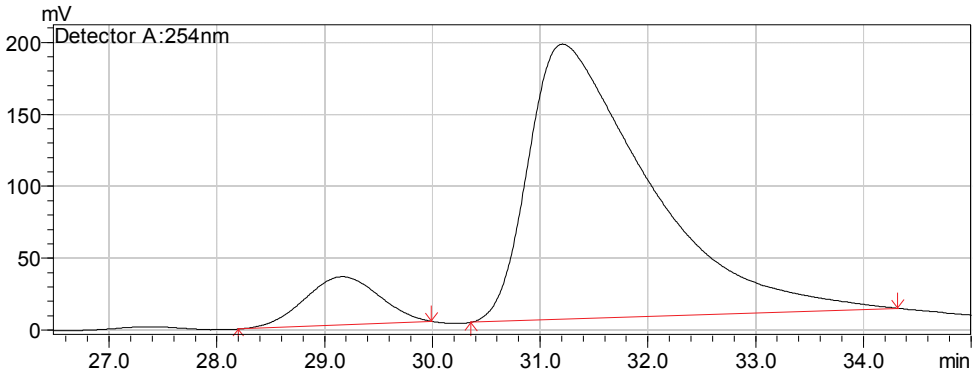
Chiralcel column OD-H (uv 254nm, 90:10 Hex/*i*-Pr, 0.5 mL/min).

(Table 2, entry 1)
phenyl(o-tolyl)methanol
ee = 97%



Peak#	*Ret.time*	*Area*	*Area%*
1	28.516	18973331	98.701
2	31.817	249790	1.299

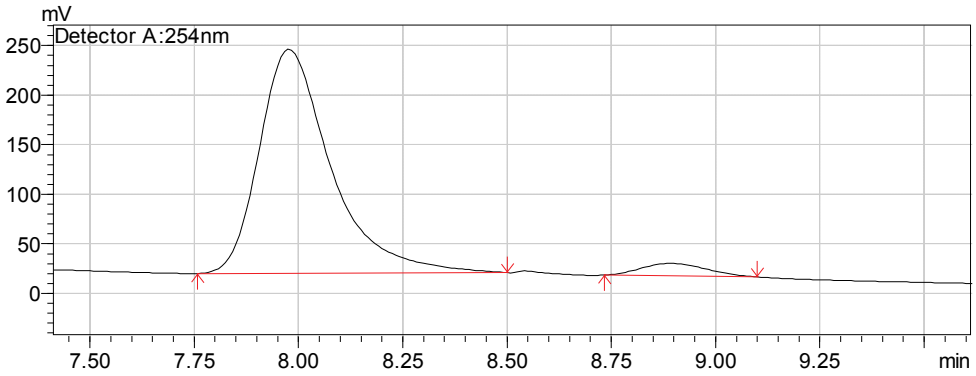
(Table 2, entry 7)
phenyl(o-tolyl)methanol
ee = 75%



$Tr_{(minor)}$ = 29.160 / $Tr_{(major)}$ = 31.211.
Chiralcel column OD-H (uv 254nm, 95:05 Hex/*i*-Pr, 0.5 mL/min).

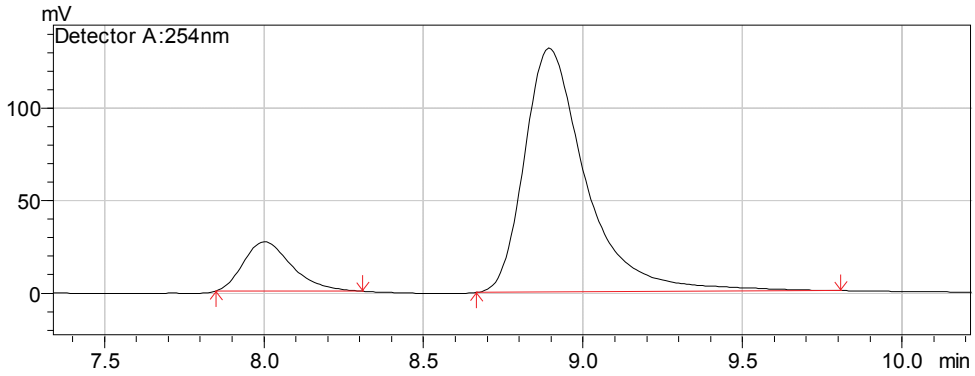
(Table 2, entry 4)

(4-chlorophenyl)(phenyl)methanol
ee = 90%



Peak#	*Ret.time*	*Area*	*Area%*
1	7.973	2678081	94.955
2	8.887	142294	5.045

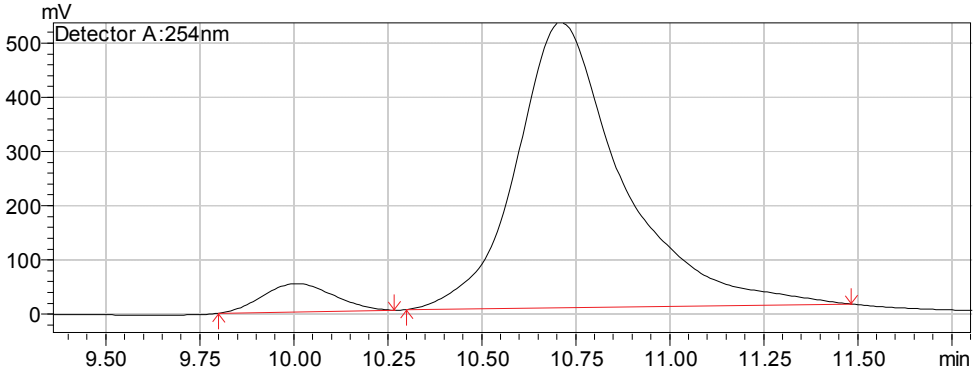
(Table 2, entry 12)
(4-chlorophenyl)(phenyl)methanol
ee = 71%



Peak#	*Ret. time*	*Area*	*Area%*
1	7.998	303195	14.546
2	8.889	1781167	85.454

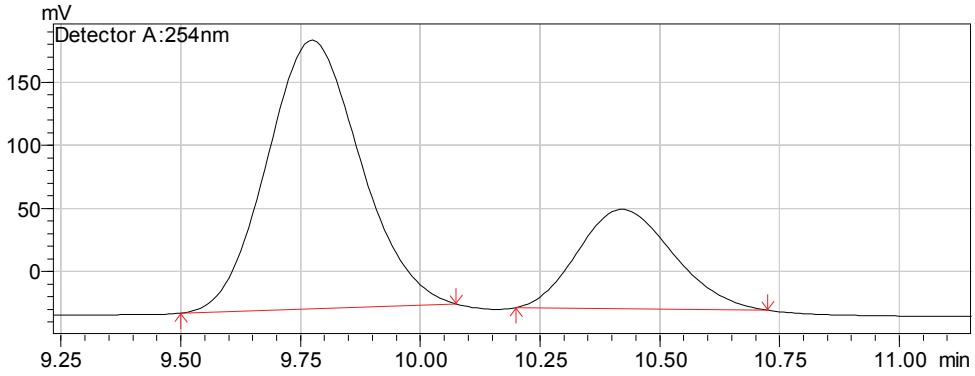
Chiralcel column AD-H (uv 254nm, 90:10 Hex/*i*-Pr, 1.0 mL/min).

(Table 2, entry 5)
(2-methoxyphenyl)(phenyl)methanol
ee = 88%



Peak#	*Ret. time*	*Area*	*Area%*
1	10.003	690497	5.935
2	10.707	10943395	94.065

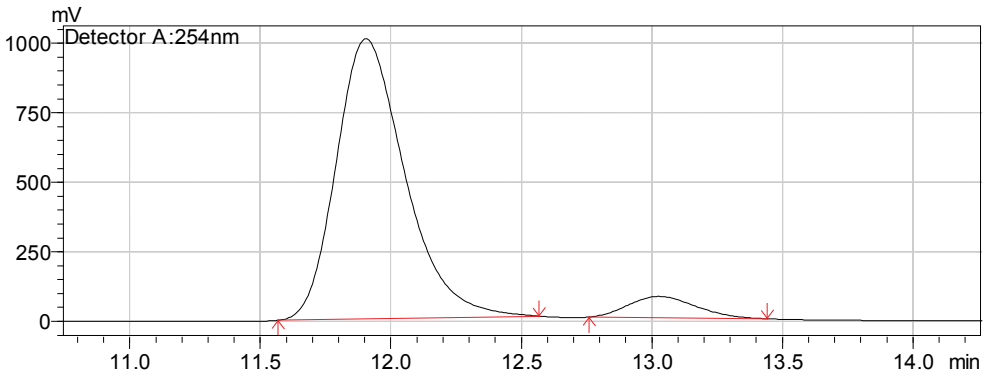
(Table 2, entry 9).
(2-methoxyphenyl)(phenyl)methanol
ee = 45%



Peak#	*Ret.time*	*Area*	*Area%*
1	9.770	2969075	72.724
2	10.417	1113590	27.276

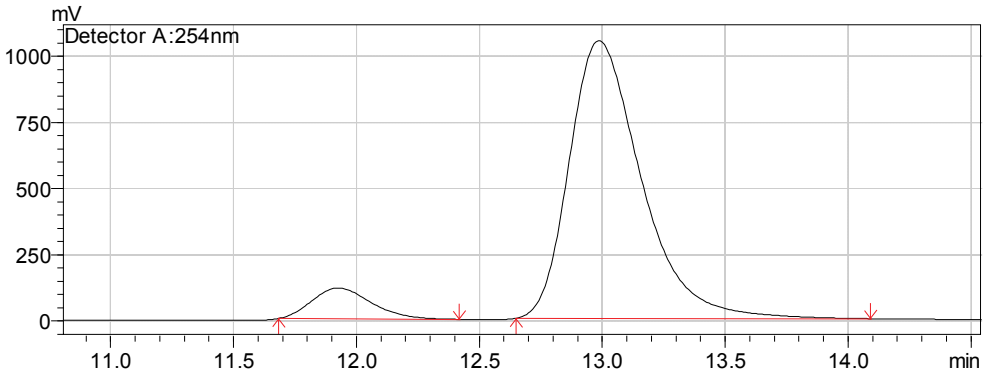
Chiralcel column AD-H (uv 254nm, 90:10 Hex/*i*-Pr, 1.0 mL/min).

(Table 2, entry 6)
(4-methoxyphenyl)(phenyl)methanol
ee = 87%



Peak#	*Ret. time*	*Area*	*Area%*
1	11.900	18320096	93.604
2	13.021	1251859	6.396

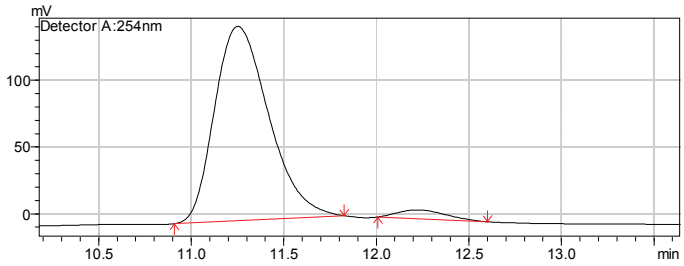
(Table 2, entry 10)
(4-methoxyphenyl)(phenyl)methanol
ee = 83%



Peak#	*Ret. time*	*Area*	*Area%*
1	11.922	1959726	8.393
2	12.982	23389859	91.607

Chiralcel column AD-H (uv 254nm, 90:10 Hex/*i*-Pr, 1.0 mL/min).

(Table 3)
phenyl-1-propanol
ee = 92%



Pico#	*Tempo ret.*	*Area*	*Area%*
1	11.248	2967375	96.128
2	12.219	119516	3.872

Coluna Chiralcel OD-H (uv 254nm, 90:10 Hex/*i*-Pr, 1.0 mL/min).