SUPPORTING INFORMATION

Organocatalytic Enantioselective Synthesis of 2,5,5-Trisubstituted Piperidines Bearing a Quaternary Stereocenter. Vinyl Sulfonamides as New Amine Protecting Groups.

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Contents

GENERAL REMARKS

Reactions involving moisture-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere. The following solvents were purified prior to use: THF, diethyl ether and toluene were distilled from sodium/benzophenone, CH_2Cl_2 was distilled from calcium hydride. All other solvents and reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stains. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040-0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a 300 or 500 MHz spectrometer. Chemical shifts are given in ppm (δ), with reference to the residual proton resonances of the solvents. Coupling constants (J) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. The letters br indicate that the signal is broad. High-resolution mass spectra were carried out on VGmAutospec (VG Analytical, Micromass Instruments) by the Universidad de Valencia Mass Spectrometry Service. Enantiomeric ratios were determined with the aid of HPLC analysis with an appropriate chiral column (25cm x 0.46 cm) with mixtures of n-hexane: i-propanol as eluents. The starting monoalkylmalonitriles **6**, were synthesized following literature procedures.[1,2,3,4]

[1] M. K. Ghorai, R. Talukdar, D. P. Tiwari, *Org. Lett.* 2014**, *16***, 2204.

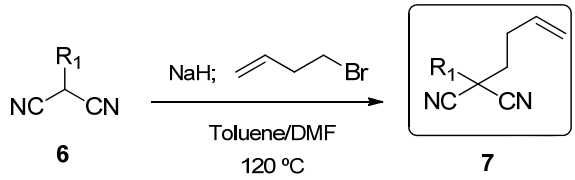
[2] C. Hu, G.Hong, X.Qian, K. R.Kim, X.Zhu, L. Wang, *Org. Biomol. Chem.* 2017, ***15***, 4984.

[3] C. Chen, Y. Luo, L. Fu, P. Chen, Y. Lan, G. Liu, *J. Am. Chem. Soc.* 2018, ***140***, 1207.

[4] F. Tayyari, D.E. Wood, P.E. Fanwick, R.E. Sammelson, *Synthesis* 2008, ***2***, 279

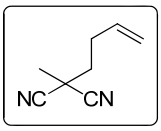
SYNTHESIS OF DIALKYLMALONITRILES 7:

Dialkylmalonitriles **7a-f** were synthesized by homoallylation reaction of malonitriles **6a-f**:



To a solution of the corresponding monoalkylmalonitrile **6** in toluene (0.5 M), sodium hydride (60% dispersion in mineral oil, 1,05 equiv) and N,N-dimethylformamide (1:4 toluene) were added. The mixture was stirred at room temperature for 15 minutes, and 4-bromo-1-butene was added dropwise (1.05 equiv). Upon complete addition, the reaction mixture was heated to reflux for 12 hours (monitored by TLC). Then, it was cooled to room temperature before quenching with water and extracting with diethyl ether. The combined organic layers were washed with water three times, and dried over anhydrous Na_2SO_4, before filtration and concentration under reduced pressure. The crude residue was purified by silica gel column chromatography.

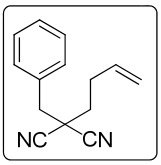
2-(3-Butenyl)-2-methylmalononitrile (7a).



7a

By means of the general procedure described above, compound **7a** (912 mg, 78% yield) was obtained as a colorless oil starting from 700 mg (8.75 mmol) of **6a** after flash chromatography with 20:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.21-5.10 (m, 2H), 2.48 – 2.39 (m, 2H), 2.06 – 2.00 (m, 2H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6 (s), 117.6 (s), 116.1 (s), 38.5 (s), 31.6 (s), 29.9 (s), 25.1 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_8H_{10}N_2$: 135.0844; found: 135.0841.

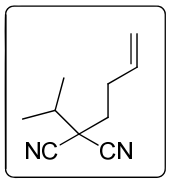
2-Benzyl-2-(3-Butenyl)malononitrile (7b).



7b

By means of the general procedure described above, compound **7b** (203 mg, 54% yield) was obtained as a colorless oil starting from 305 mg (1.79 mmol) of **6b** after flash chromatography with 15:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 5H), 5.81 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.20 – 5.09 (m, 2H), 3.23 (s, 2H), 2.53 – 2.44 (m, 2H), 2.06 – 2.02 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7 (s), 132.00 (s), 130.4 (s), 129.1 (s), 129.0 (s), 117.5 (s), 115.3 (s), 43.6 (s), 39.1 (s), 36.8 (s), 29.9 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{14}N_2$: 210.1157; found: 210.1152.

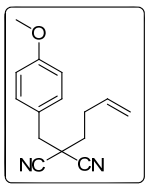
2-(3-Butenyl)-2-isopropylmalononitrile (7c).



7c

By means of the general procedure described above, compound **7c** (230 mg, 77% yield) was obtained as a colorless oil starting from 200 g (1.85 mmol) of **6c** after flash chromatography with 15:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.21 – 5.09 (m, 2H), 2.49 – 2.41 (m, 2H), 2.18 (hept, *J* = 6.7 Hz, 1H), 2.01 – 1.95 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9 (s), 117.4 (s), 115.1 (s), 43.6 (s), 35.8 (s), 34.7 (s), 30.1 (s), 18.4 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{10}H_{14}N_2$: 163.1235; found: 163.1230.

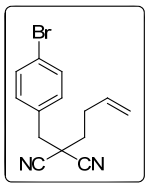
2-(3-Butenyl)-2-(4-methoxybenzyl)malononitrile (7d).



7d

By means of the general procedure described above, compound **7d** (772 mg, 57% yield) was obtained as a yellow oil starting from 1,053 g (5.65 mmol) of **6d** after flash chromatography with 15:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.95 – 6.90 (m, 2H), 5.81 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.20 – 5.09 (m, 2H), 3.82 (s, 3H), 3.18 (s, 2H), 2.51 – 2.43 (m, 2H), 2.04 – 1.99 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 134.7, 131.5, 124.0, 117.5, 115.4, 114.5, 55.4, 43.0, 39.3, 36.6, 29.9. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{17}N_2O$: 241.1342; found: 241.1340.

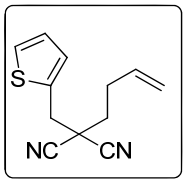
2-(4-Bromobenzyl)-2-(3-butenyl)malononitrile (7e).



7e

By means of the general procedure described above, compound **7e** (962 mg, 78% yield) was obtained as a yellow solid starting from 1 g (4.25 mmol) of **6e** after flash chromatography with 15:1 n-hexane: ethyl acetate. Mp = 64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.28 – 7.23 (m, 2H), 5.81 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 0H), 5.21 – 5.10 (m, 2H), 3.18 (s, 3H), 2.52 – 2.43 (m, 2H), 2.06 – 2.01 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 132.3, 131.9, 131.0, 123.4, 117.7, 115.0, 43.0, 38.9, 36.8, 29.9. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{13}BrN_2$: 289,0340; found: 289.0341.

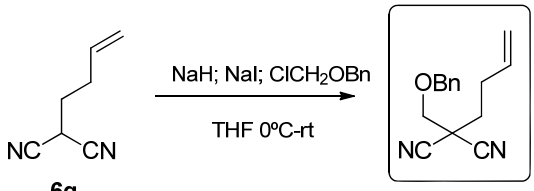
2-(3-Butenyl)-2-(thiophen-2-ylmethyl)malononitrile (7f).



7f

By means of the general procedure described above, compound **7f** (1,239 g, 93% yield) was obtained as a yellow solid starting from 1 g (6.2 mmol) of **6f** after flash chromatography with 10:1 n-hexane: ethyl acetate. Mp = 78 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.16 – 7.15 (m, 1H), 7.06 (dd, *J* = 5.2, 3.5 Hz, 1H), 5.81 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.21 – 5.10 (m, 2H), 3.49 (s, 2H), 2.52 – 2.43 (m, 2H), 2.08 – 2.02 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 132.7, 129.3, 127.8, 126.8, 117.6, 115.2, 39.1, 37.8, 36.3, 29.9. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{12}N_2S$: 217.0799; found: 217.0796.

2-[(Benzyloxy)methyl]-2-(3-butenyl)malononitrile (**7g)** was synthesized according to literature procedure[5]:

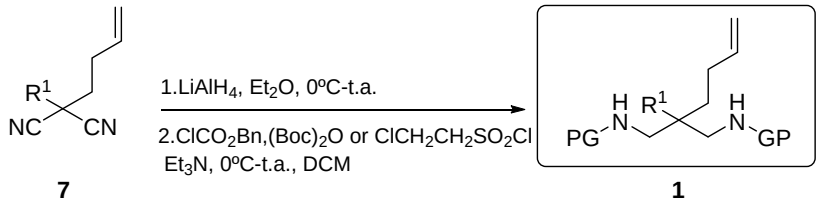


6g **7g**

To a solution of monoalkylmalonitrile **6g** (111 mg, 0.92 mmol) in THF (1mL, 0.9M), benzyl chloromethyl ether (0,24 mL 60 % solution; 1 mmol; 1.1 equiv) and sodium iodide (4 mg; 0.03 mmol; 0.03 equiv) were added. The yellow suspension was cooled with an ice bath and sodium hydride (44 mg; 1.1 mmol; 1.2 equiv) was added in small portions. The mixture was stirred for 2 hours at room temperature (monitored by TLC), diluted with ether, and extracted with 5% aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtrated and concentrated. The crude residue was purified by flash chromatography with 20:1 n-hexane: ethyl acetate as eluent to afford **7d** (155 mg, 70 % yield) as a color less oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 5H), 5.80 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.19 – 5.09 (m, 2H), 4.70 (s, 2H), 3.77 (s, 2H), 2.45 – 2.37 (m, 2H), 2.09 – 2.04 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2 (s), 134.6 (s), 128.9 (s), 128.6 (s), 128.1 (s), 117.6 (s), 114.4 (s), 74.2 (s), 71.2 (s), 38.2 (s), 33.5 (s), 29.5 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{16}N_2O$ $[M+NH_4]^+$: 258.1601; found: 258.1603.

[5] Iwema Bakker, Wouter I. et al, PCT Int. Appl., 2008034863, 2008.

GENERAL PROCEDURE FOR THE SYNTHESIS OF N-PROTECTED DIAMINES 1:



7 **1**

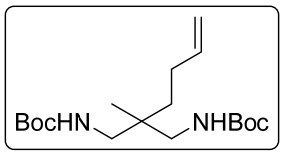
To a solution of the corresponding dialkylmalonitrile **7** in diethyl ether (0.2M), $LiAlH_4$ (3 equiv) was added at 0°C under N_2 atmosphere. The reaction mixture was stirred for 2 hours at room temperature (monitored by TLC), then $Na_2SO_4 \cdot 10H_20$ was added with vigorous stirring until grey aluminum salts turned white. The suspension was filtered through a short pad of Celite washing with small portions of diethyl ether. The filtrate was dried with Na_2SO_4, filtered and concentrated under vacuum, obtaining a yellow oil that was employed without further purification. The crude primary amine was dissolved in CH_2Cl_2 (0.5 M), then H_2O (0.5 equiv.) and Et_3N (4.0 equiv) were added at 0 °C, followed by benzyl chloroformate, di-tert-butyl dicarbonate or 2-chloroethanesulfonyl chloride (2.0 equiv) (depending of the desired protecting group). The reaction mixture was allowed to reach room temperature for 12 hours (monitored by TLC) and then it was hydrolyzed with 3M HCl solution, extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. Finally, solvents were removed and the crude mixture was purified by flash chromatography on silica gel using mixtures of n-hexane and ethyl acetate as eluents.

Dibenzyl [2-(3-butenyl)-2-methylpropane-1,3-diyl]dicarbamate (1a).

1a

By means of the general procedure described above, dicarbamate **1a** (653 mg, 54% yield) was obtained as a colorless oil starting from 395 mg (2.95 mmol) of **7a** after flash chromatography with 6:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 10H), 5.78 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.50 (t, *J* = 6.7 Hz, 2H), 5.15 – 5.10 (m, 6H), 5.04 – 4.92 (m, 2H), 3.00 (qd, *J* = 14.4, 6.9 Hz, 4H), 2,09 – 2.02 (m, 2H), 1.29 – 1.23 (m, 2H), 0.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4 (s), 138.8 (s), 128.7 (s), 128.6 (s), 128.2 (s), 114.6 (s), 66.9 (s), 46.1 (s), 39.0 (s), 34.9 (s), 27.7 (s), 19.9 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{26}H_{32}N_2O_5$: 411.2278; found: 411.2279.

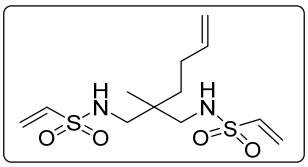
Di-tert-Butyl [2-(3-butenyl)-2-methylpropane-1,3-diyl]dicarbamate (1b).



1b

By means of the general procedure described above, dicarbamate **1b** (231 mg, 60% yield) was obtained as a white solid starting from 150 mg (1.12 mmol) of **7a** after flash chromatography with 10:1 n-hexane: ethyl acetate. Mp = 103-105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 1H), 5.26 – 5.22 (m, 2H), 4.97 (d, *J* = 17.8 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 2.95 – 2.80 (m, 4H), 2.05 – 1.95 (m, 2H), 1.40 (s, 18H), 1.23 – 1.17 (m, 2H), 0.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8 (s), 139.0 (s), 114.4 (s), 79.1 (s), 45.7 (s), 38.9 (s), 35.0 (s), 28.5 (s), 27.8 (s), 20.0 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{31}H_{36}N_2O_5$: 343.2597; found: 343.2591.

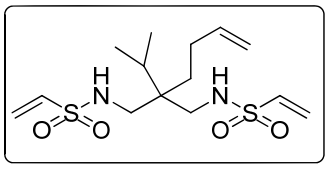
***N,N'*-[2-(3-Butenyl)-2-methylpropane-1,3-diyl]diethenesulfonamide (1c).**



1c

By means of the general procedure described above, sulfonamide **1c** (206 mg, 43% yield) was obtained as a yellow oil starting from 200 mg (1.49 mmol) of **7a** after flash chromatography with 3:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 16.5, 9.9 Hz, 4H), 6.23 (d, *J* = 16.6 Hz, 2H), 5.96 (d, *J* = 9.9 Hz, 2H), 5.77 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.09 – 4.93 (m, 4H), 2.90 – 2.76 (m, 4H), 2.05 – 1.97 (m, 2H), 1.36 – 1.30 (m, 2H), 0.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (s), 135.7 (s), 127.1 (s), 115.1 (s), 47.9 (s), 38.2 (s), 34.5 (s), 27.5 (s), 20.0 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{22}N_2O_4S_2$: 323.1094; found:323.1098.

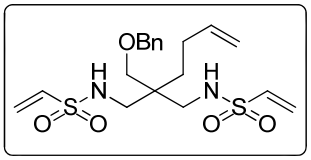
***N,N'*-[2-(3-Butenyl)-2-isopropylpropane-1,3-di yl]diethenesulfonamide (1d).**



1d

By means of the general procedure described above, sulfonamide **1d** (651 mg, 34% yield) was obtained as a yellow oil starting from 900 mg (5.5 mmol) of **7c** after flash chromatography with 4:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 16.6, 9.9 Hz, 2H), 6.26 (d, *J* = 16.6 Hz, 2H), 5.99 (d, *J* = 9.9 Hz, 2H), 5.76 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.06 – 4.93 (m, 4H), 3.00 (dd, *J* = 13.6, 7.1 Hz, 2H), 2.92 (dd, *J* = 13.6, 7.5 Hz, 2H), 2.07 – 1.99 (m, 2H), 1.88 – 1.70 (m, 1H), 1.78 (hept, *J* = 6.9 Hz, 1H), 1.40 – 1.34 (m, 2H), 0.93 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 135.5, 127.5, 115.1, 46.3, 41.8, 30.8, 30.5, 27.9, 17.5. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{26}N_2O_4S_2$: 351.1412; found: 351.1414.

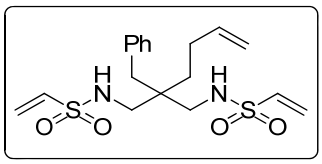
***N,N'*-[2-(Benzyloxymethyl)-2-(3-butenyl)propane-1,3-diyl]diethenesulfonamide (1e).**



1e

By means of the general procedure described above, sulfonamide **1e** (156 mg, 31% yield) was obtained as a colorless oil starting from 287 mg (1.2 mmol) of **7g** after flash chromatography with 2:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.27 (m, 5H), 6.49 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.23 (d, *J* = 16.6 Hz, 2H), 5.95 (d, *J* = 9.9 Hz, 2H), 5.75 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H), 5.04 – 4.89 (m, 4H), 4.47 (s, 2H), 3.32 (s, 2H), 3.03 (dd, *J* = 13.5, 5.5 Hz, 2H), 2.91 (dd, *J* = 13.5, 8.6 Hz, 2H), 2.02 – 1.95 (m, 2H), 1.48 – 1.39 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.5, 135.7, 128.8, 128.3, 128.0, 127.1, 115.2, 73.7, 72.7, 45.3, 41.7, 30.9, 27.3. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{28}N_2O_5S_2$: 429.1518; found: 429.1520.

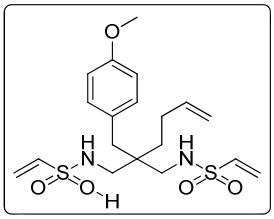
***N,N'*-[2-Benzyl-2-(3-butenyl)propane-1,3-diyl]diethenesulfonamide (1f).**



1f

By means of the general procedure described above, sulfonamide **1f** (197 mg, 32% yield) was obtained as a colorless oil starting from 333 mg (1.58 mmol) of **7b** after flash chromatography with 3:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 3H), 7.14 – 7.11 (m, 2H), 6.52 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.25 (d, *J* = 16.6 Hz, 2H), 5.98 (d, *J* = 9.9 Hz, 2H), 5.79 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H), 5.11 – 4.97 (m, 2H), 4.80 (t, *J* = 7.3 Hz, 2H), 2.95 – 2.81 (m, 4H), 2.64 (s, 2H), 2.23 – 2.15 (m, 2H), 1.35 – 1.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 136.5, 135.5, 130.2, 128.8, 127.5, 127.1, 115.3, 46.5, 42.0, 38.4, 31.1, 27.3. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{26}N_2O_4S_2$: 399.1412; found: 399.1412.

***N,N'*-[2-(3-Butenyl)-2-(4-methoxybenzyl)propane-1,3-diyl]diethenesulfonamide (1g).**

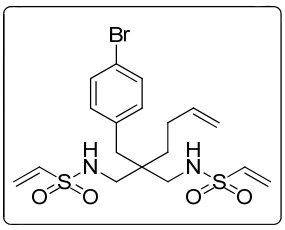


1g

By means of the general procedure described above, sulfonamide **1g** (277 mg, 31% yield) was obtained as a yellow oil starting from 500 mg (2.08 mmol) of **7d** after flash chromatography with 2:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.52 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.25 (d, *J* = 16.6 Hz, 2H), 5.98 (d, *J* = 9.9 Hz, 2H), 5.79 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.10 – 4.97 (m, 2H), 4.79 (t, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 2.89 (dd, *J* = 13.2, 6.7 Hz, 2H), 2.83 (dd, *J* = 13.2, 7.1 Hz, 1H),2.58 (s, 2H), 2.24 – 2.11 (m, 2H), 1.34 – 1.28 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 137.9, 135.5, 131.2, 128.2, 127., 115.3, 114.2, 55.4, 46.5,

42.0, 37.4, 31.0, 27.3. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{28}N_2O_5S_2$: 429.1518; found: 429.1515.

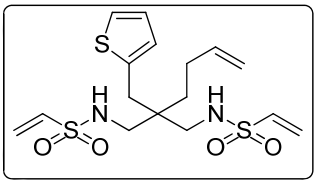
***N,N'*-[2-(4-Bromobenzyl)-2-(3-Butenyl)propane-1,3-diyl]diethenesulfonamide (1h).**



1h

By means of the general procedure described above, sulfonamide **1h** (252 mg, 31% yield) was obtained as a colorless oil starting from 500 mg (1.72 mmol) of **7e** after flash chromatography with 2:1 n-hexane: ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.52 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.26 (d, *J* = 16.6 Hz, 2H), 5.99 (d, *J* = 9.9 Hz, 2H), 5.76 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.09 – 4.99 (m, 2H), 4.87 (t, *J* = 7.3 Hz, 2H), 2.91 – 2.80 (m, 4H), 2.62 (s, 2H), 2.18 – 2.12 (m, 2H), 1.29 – 1.25 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 135.5, 135.4, 132.0, 131.8, 127.6, 121.1, 115.6, 46.4, 42.0, 37.3, 30.7, 27.3. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{18}H_{25}BrN_2O_4S_2$: 477.0517; found: 477.0519.

***N,N'*-[2-(3-Butenyl)-2-(thiophen-2-ylmethyl)propane-1,3-diyl]diethenesulfonamide (1i).**

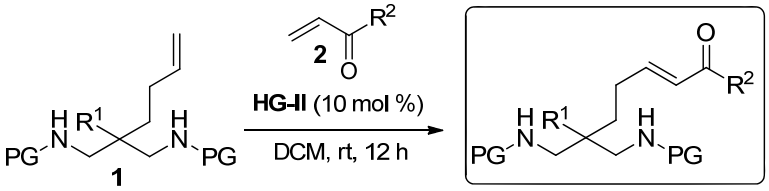


1i

By means of the general procedure described above, sulfonamide **1f** (301 mg, 32% yield) was obtained as a yellow oil starting from 500 mg (2.31 mmol) of **7f** after flash chromatography with 2:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 5.2, 1.1 Hz, 1H), 6.97 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.85 (dd, *J* = 3.4, 1.0 Hz, 1H), 6.53 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.26 (d, *J* = 16.6 Hz, 2H), 5.98 (d, *J* = 9.9 Hz, 2H), 5.80 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.12 – 4.92 (m, 4H), 2.93 – 2.85 (m, 4H), 2.83 (s, 2H), 2.22 – 2.13 (m, 2H), 1.41 – 1.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 135.5, 127.6, 127.5, 127.4, 124.7, 115.4, 46.2, 42.0, 32.0, 30.7, 27.2. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{16}H_{24}N_2O_4S_3$: 405.0976; found: 405.0977.

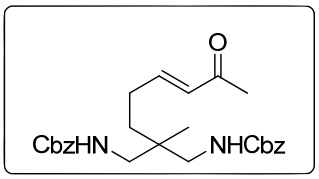
GENERAL PROCEDURE FOR THE CROSS-METATHESIS REACTON. SYNTHESIS OF SYMMETRICAL ENONES 3:

To a solution of the corresponding *N*-protected diamines **1** in dichloromethane (0.3 M), the appropiate vinyl ketone **2** (3.0 equiv) and second generation Hoveyda-Grubbs catalyst (10 mol %) were successively added. The resulting mixture was stirred for 12 h at room temperature (monitored by TLC) and then concentrated to dryness and purified by means of flash column chromatography on silica gel using mixtures of n-hexane and ethyl acetate as eluents. (In the case of substrates **1c-m** reaction was performed with 20 mol % of $Ti(iPrO)_4$ as co-catalyst)



HG-II = Cl_2(**I**Mes)Ru=CH(*o*-*i*PrC_6H_4)

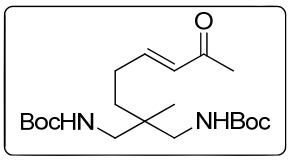
(*E*)-Dibenzyl [2-methyl-2-(5-oxohex-3-en-1-yl)propane-1,3-diyl]dicarbamate (3a).



3a

By means of the general procedure described above, compound **3a** (102 mg, 96% yield) was obtained as a brown oil starting from 96 mg (0.23 mmol) of **1a** after flash chromatography with 1:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 10H), 6.74 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.06 (d, J = 16.0 Hz, 1H), 5.58 (t, *J* = 6.7 Hz, 2H), 5.10 (s, 4H), 3.08 (dd, *J* = 14.5, 7.4 Hz, 2H), 2.91 (dd, *J* = 14.4, 6.4 Hz, 2H), 2.30 – 2.25 (m, 2H), 2.21 (s, 3H), 1.33 – 1.26 (m, 2H), 0.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8 (s), 157.5 (s), 148.2 (s), 136.6 (s), 131.4 (s), 128.6 (s), 128.3 (s), 128.2 (s), 67.0 (s), 46.1 (s), 39.1 (s), 33.9 (s), 27.0 (s), 26.7 (s), 20.0 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{26}H_{32}N_2O_5$: 453.2384; found: 453.2389.

(*E*)-Di-tert-butyl [2-methyl-2-(5-oxohex-3-en-1-yl)propane-1,3-diyl]dicarbamate (3b).

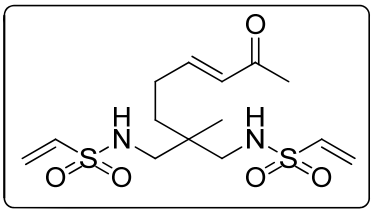


3b

By means of the general procedure described above, compound **3b** (94 mg, 84% yield) was obtained as a brown oil starting from 100 mg (0.29 mmol) of **1b** after flash chromatography with 2:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.07 (dt, *J* = 15.9, 1.3 Hz, 1H), 5.24 (t, *J* = 6.0 Hz, 2H), 2.99 (dd, *J* = 14.4, 7.4 Hz, 2H), 2.83 (dd, *J* = 14.3, 6.4

Hz, 2H), 2.30 – 2.23 (m, 2H), 2.21 (s, 3H), 1.43 (s, 18H), 1.30 – 1.24 (m, 2H), 0.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8 (s), 156.9 (s), 148.6 (s), 131.3 (s), 79.5 (s), 45.6 (s), 39.1 (s), 33.9 (s), 28.5 (s), 27.0 (s), 26.7 (s), 20.0 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{36}N_2O_5$: 385.2697; found: 385.2694.

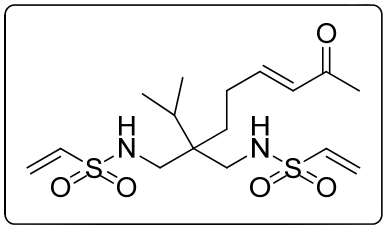
(*E*)-*N,N'*-[2-Methyl-2-(5-oxohex-3-en-1-yl)propane-1,3-diyl]diethenesulfonamide (3c).



3c

By means of the general procedure described above, compound **3c** (92 mg, 87% yield) was obtained as a brown oil starting from 94 mg (0.29 mmol) of **1c** after flash chromatography with 1:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.48 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.25 – 5.89 (m, 5H), 5.25 (t, *J* = 7.1 Hz, 2H), 2.85 – 2.72 (m, 4H), 2.20 – 2.14 (m, 5H), 1.38 – 1.33 (m, 2H), 0.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1 (s), 147.9 (s), 135.6 (s), 131.4 (s), 127.0 (s), 47.7 (s), 38.2 (s), 33.3 (s), 26.9 (s), 26.2 (s), 19.8 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{24}N_2O_5S_2$: 365.1199; found: 365.1209.

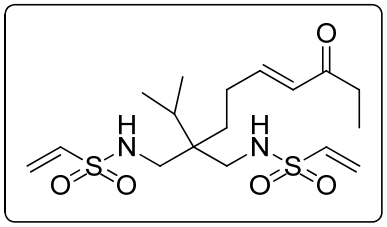
(*E*)-*N,N'*-[2-Isopropyl-2-(5-oxohex-3-en-1-yl)propane-1,3-diyl]diethenesulfonamide (3d).



3d

By means of the general procedure described above, compound **3d** (254 mg, 82% yield) was obtained as a brown oil starting from 277 mg (0.79 mmol) of **1d** after flash chromatography with 1:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 15.9, 6.6 Hz, 1H), 6.54 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.24 (d, *J* = 16.5 Hz, 2H), 6.07 (d, *J* = 16.0 Hz, 1H), 5.99 (d, *J* = 9.8 Hz, 2H), 5.28 (bs, 2H), δ 3.02 (dd, *J* = 13.6, 6.4 Hz, 2H), 2.92 (dd, *J* = 13.6, 7.8 Hz, 2H), 2.33 – 2.13 (m, 5H), 1.75 (hept, *J* = 6.9 Hz, 1H), 1.49 – 1.43 (m, 2H), 0.92 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 148.2, 135.5, 131.4, 127.5, 46.2, 41.9, 30.5, 29.7, 27.0, 26.6, 17.5. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{16}H_{28}N_2O_5S_2$: 393.1518; found: 393.1521.

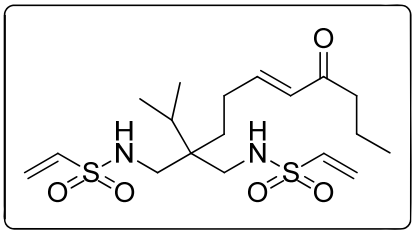
(*E*)-*N,N'*-[2-Isopropyl-2-(5-oxohept-3-en-1-yl)propane-1,3-diyl]diethenesulfonamide (3e).



3e

By means of the general procedure described above, compound **3e** (81 mg, 69% yield) was obtained as a brown oil starting from 100 mg (0.29 mmol) of **1d** after flash chromatography with 1:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 15.8, 6.7 Hz, 1H), 6.54 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.27 (d, *J* = 16.6 Hz, 2H), 6.12 (d, *J* = 15.9 Hz, 1H), 6.00 (d, *J* = 9.9 Hz, 2H), 4.99 (t, *J* = 7.3 Hz, 2H), 3.03 (dd, *J* = 13.7, 6.4 Hz, 2H), 2.94 (dd, *J* = 13.7, 8.3 Hz, 2H), 2.29 – 2.19 (m, 1H), 2.56 (q, *J* = 7.3 Hz, 2H) 1.75 (hept, *J* = 6.9 Hz, 1H), 1.48 – 1.42 (m, 2H), 1.09 (t, *J* = 7.3 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 146.2, 135.5, 130.4, 127.6, 46.1, 42.0, 33.4, 30.6, 29.9, 26.6, 17.6, 8.2. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{30}N_2O_5S_2$: 407.1674; found: 407.1671.

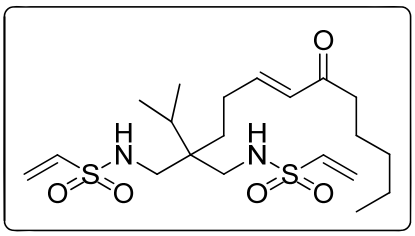
(*E*)-*N,N'*-[2-Isopropyl-2-(5-oxooct-3-en-1-yl)propane-1,3-diyl]diethenesulfonamide (3f).



3f

By means of the general procedure described above, compound **3f** (87 mg, 61% yield) was obtained as a brown oil starting from 119 mg (0.35 mmol) of **1d** after flash chromatography with 2:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.54 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.27 (d, *J* = 16.6 Hz, 2H), 6.11 (d, *J* = 15.9 Hz, 1H), 6.00 (d, *J* = 9.9 Hz, 2H), 5.02 (t, *J* = 7.3 Hz, 2H), 3.03 (dd, *J* = 13.7, 6.5 Hz, 2H), 2.94 (dd, *J* = 13.7, 8.2 Hz, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.29 – 2.20 (m, 2H), 1.75 (hept, *J* = 6.9 Hz, 1H), 1.62 (h, *J* = 7.4 Hz, 2H), 1.48 – 1.42 (m, 2H), 0.98 – 0.88 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 146.2, 135.3, 130.6, 127.4, 46.0, 42.0, 41.9, 30.5, 29.7, 26.5, 17.7, 17.4, 13.8. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{32}N_2O_5S_2$: 421.1831; found: 421.1831.

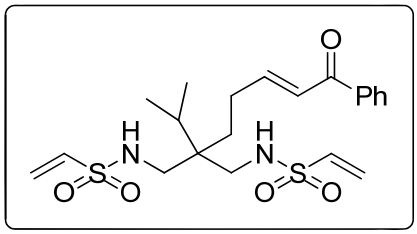
(*E*)-*N,N'*-[2-Isopropyl-2-(5-oxodec-3-en-1-yl)propane-1,3-diyl]diethenesulfonamide (3g).



3g

By means of the general procedure described above, compound **3g** (93 mg, 61% yield) was obtained as a brown oil starting from 119 mg (0.35 mmol) of **1d** after flash chromatography with 2:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 15.8, 6.8 Hz, 1H), 6.54 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.27 (d, *J* = 16.6 Hz, 2H), 6.11 (d, *J* = 15.9 Hz, 1H), 6.00 (d, *J* = 9.9 Hz, 2H), 4.98 (t, *J* = 7.3 Hz, 2H), 3.03 (dd, *J* = 13.7, 6.5 Hz, 2H), 2.94 (dd, *J* = 13.7, 8.3 Hz, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.28 – 2.21 (m, 2H), 1.75 (hept, *J* = 6.8 Hz, 1H), 1.59 (quint, *J* = 7.4 Hz, 2H), 1.48 – 1.42 (m, 2H), 1.37 – 1.22 (m, 4H), 0.93 (d, *J* = 7.0 Hz, 6H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 146.3, 135.5, 130.7, 127.6, 46.1, 42.0, 40.3, 31.6, 30.6, 29.9, 26.7, 24.0, 22.6, 17.6, 14.1. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{36}N_2O_5S_2$: 449.2144; found: 449.2144.

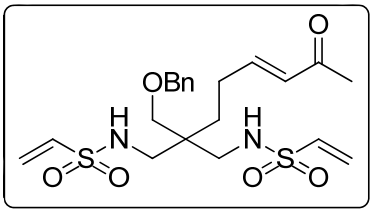
(*E*)-*N,N'*-[2-Isopropyl-2-(5-oxo-5-phenylpent-3-en-1-yl)propane-1,3-diyl] diethene sulfonamide (3h).



3h

By means of the general procedure described above, compound **3h** (50 mg, 32% yield) was obtained as a brown oil starting from 119 mg (0.35 mmol) of **1d** after flash chromatography with 1:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.57 – 7.44 (m, 3H), 7.04 – 6.9 (m, 2H), 6.55 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.27 (d, *J* = 16.5 Hz, 2H), 5.99 (d, *J* = 9.9 Hz, 2H), 4.99 (t, *J* = 7.3 Hz, 2H), 3.05 (dd, *J* = 13.8, 6.4 Hz, 2H), 2.97 (dd, *J* = 13.8, 8.2 Hz, 2H), 2.49 – 2.32 (m, 2H), 1.78 (hept, *J* = 6.9 Hz, 1H), 1.54 – 1.49 (m, 2H), 0.95 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.9, 148.7, 137.7, 135.4, 132.8, 128.6, 128.6, 127.4, 126.3, 46.0, 42.0, 30.5, 29.9, 26.9, 17.5. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{21}H_{30}N_2O_5S_2$: 455.1644; found: 455.1641.

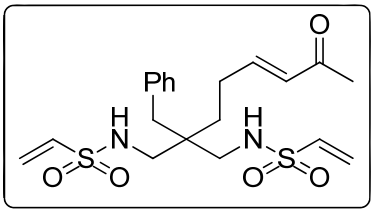
(*E*)-*N,N'*-[2-((Benzyloxy)methyl)-2-(5-oxohex-3-en-1-yl)propane-1,3-diyl] diethene sulfonamide (3i).



3i

By means of the general procedure described above, compound **3i** (86 mg, 70% yield) was obtained as a brown oil starting from 111 mg (0.26 mmol) of **1e** after flash chromatography with 1:1 n-hexane: ethyl acetate. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 3H), 7.29 – 7.27 (m, 2H), 6.73 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.49 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.22 (d, *J* = 16.6 Hz, 2H), 6.05 (d, *J* = 16.0 Hz, 1H), 5.96 (d, *J* = 9.9 Hz, 2H), 4.93 – 4.91 (m, 2H), 4.46 (s, 2H), 3.28 (s, 2H), 3.01 (dd, *J* = 13.6, 5.4 Hz, 2H), 2.87 (dd, *J* = 13.6, 9.0 Hz, 2H), 2.22 (s, 3H), 2.22 – 2.15 (m, 2H), 1.50 – 1.46 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8, 147.4, 137.4, 135.6, 131.7, 128.9, 128.5, 128.1, 127.2, 73.7, 71.6, 44.8, 42.0, 29.6, 27.0, 26.1. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{21}H_{30}N_2O_6S_2$: 471.1624; found:471.1626.

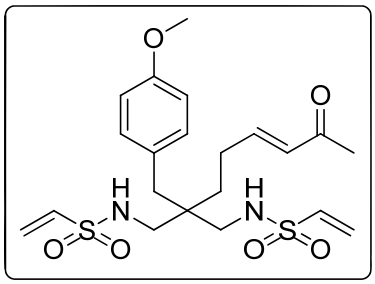
(*E*)-*N,N'*-[2-Benzyl-2-(5-oxohex-3-en-1-yl)propane-1,3-diyl]diethenesulfonamide (3j).



3j

By means of the general procedure described above, compound **3j** (127 mg, 72% yield) was obtained as a brown oil starting from 159 mg (0.39 mmol) of **1f** after flash chromatography with 1:1 n-hexane: ethyl acetate. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 3H), 7.09 (d, *J* = 6.9 Hz, 2H), 6.77 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.52 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.25 (d, *J* = 16.6 Hz, 2H), 6.11 (d, *J* = 16.0 Hz, 1H), 5.98 (d, *J* = 9.9 Hz, 2H), 4.96 (t, *J* = 7.2 Hz, 2H), 2.92 (dd, *J* = 13.8, 6.4 Hz, 2H), 2.85 (dd, *J* = 13.8, 8.3 Hz, 2H), 2.62 (s, 2H), 2.41 – 2.37 (m, 2H), 2.24 (s, 3H), 1.42 – 1.39 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 146.9, 136.1, 135.3, 131.5, 129.8, 128.9, 127.4, 127.2, 46.2, 42.0, 38.3, 30.1, 27.0, 25.9. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{28}N_2O_5S_2$: 441.1518; found: 441.1516.

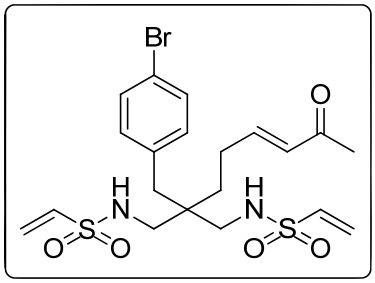
(*E*)-*N,N'*-[2-(4-Methoxybenzyl)-2-(5-oxohex-3-en-1-yl)propane-1,3-diyl] diethenesulfonamide (3k).



3k

By means of the general procedure described above, compound **3k** (195 mg, 71% yield) was obtained as a brown oil starting from 250 mg (0.58 mmol) of **1g** after flash chromatography with 1:1 n-hexane: ethyl acetate.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.6 Hz, 2H), 6.85 – 6.72 (m, 3H), 6.52 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.24 (d, *J* = 16.5 Hz, 2H), 6.10 (d, *J* = 16.0 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 2H), 5.09 (t, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.93 – 2.79 (m, 4H), 2.55 (s, 2H), 2.40 – 2.32 (m, 2H), 2.23 (s, 3H), 1.40 – 1.34 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 158.7, 147.3, 135.4, 131.6, 131.0, 127.9, 127.5, 114.3, 55.4, 46.4, 42.0, 37.4, 30.1, 27.1, 26.0. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{21}H_{30}N_2O_6S_2$: 471.1624; found: 471.1626.

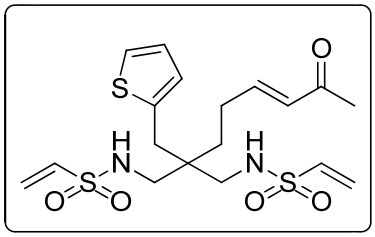
(*E*)-*N,N'*-[2-(4-Bromobenzyl)-2-(5-oxohex-3-en-1-yl)propane-1,3-diyl] diethenesulfonamide (3l).



3l

By means of the general procedure described above, compound **3l** (169 mg, 66% yield) was obtained as a brown oil starting from 236 mg (0.49 mmol) of **1h** after flash chromatography with 1:1 n-hexane: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.74 (dt, *J* = 15.9, 6.6 Hz, 1H), 6.53 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.26 (d, *J* = 16.5 Hz, 2H), 6.10 (d, *J* = 16.0 Hz, 1H), 6.00 (d, *J* = 9.8 Hz, 2H), 5.07 (t, *J* = 7.3 Hz, 2H), 2.90 (dd, *J* = 12.6, 5.8 Hz, 2H), 2.83 (dd, *J* = 12.7, 6.4 Hz, 2H), 2.59 (s, 2H), 2.39 – 2.31 (m, 2H), 2.24 (s, 3H), 1.39 – 1.33 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 146.7, 135.4, 135.1, 132.1, 131.8, 131.7, 127.7, 121.3, 46.3, 42.0, 37.5, 30.0, 27.2, 26.0. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{27}BrN_2O_5S_2$: 519.0623; found: 519.0627.

(*E*)-*N,N'*-[2-(5-Oxohex-3-en-1-yl)-2-(thiophen-2-ylmethyl)propane-1,3-diyl] diethene sulfonamide (3m).

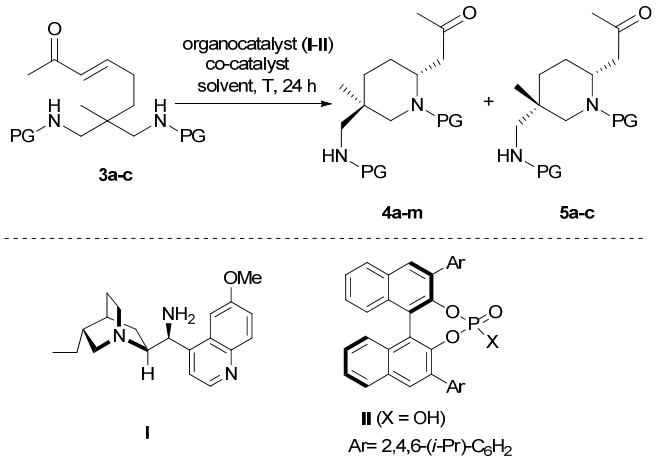


3m

By means of the general procedure described above, compound **3m** (207 mg, 70% yield) was obtained as a brown oil starting from 268 mg (0.66 mmol) of **1g** after flash chromatography with 1:1 n-hexane: ethyl acetate.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 5.2, 1.1 Hz, 1H), 6.98 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.85 – 6.75 (m, 2H), 6.53 (dd, *J* = 16.5, 9.9 Hz, 2H), 6.26 (d, *J* = 16.5 Hz, 2H), 6.14 (d, *J* = 16.0 Hz, 1H), 6.00 (d, *J* = 9.8 Hz, 2H), 4.97 (t, *J* = 7.4 Hz, 2H), 2.93 – 2.80 (m, 4H), 2.80 (s, 2H), 2.46 – 2.33 (m, 2H), 2.25 (s, 3H), 1.49 – 1.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 147.0, 137.4, 131.9, 127.6, 127.6, 127.4, 124.9, 45.9, 42.3, 31.8, 29.6, 27.1, 26.1. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{26}N_2O_5S_3$: 447.1082; found:447.1083.

GENERAL PROCEDURE FOR THE INTRAMOLECULAR AZA-MICHAEL REACTION. SYNTHESIS OF 2,5,5-TRISUBSTITUTED PIPERIDINES 4,5

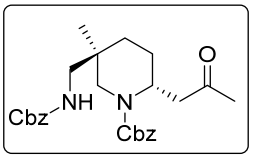
In a 10 mL round bottomed flask, the corresponding enone **3** was dissolved in chloroform (0.1 M). Catalyst **I** (10 mol %) (or catalyst **II** in the case of substrate **3h**) and trifluoroacetic acid (TFA) (10 mol %) were added and the resulting solution was stirred at room temperature for 24 hours (monitored by TLC). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel.



Compounds **4a-b** and **5a-b** showed in ^{1}NMR and ^{13}CNMR the presence or rotamers about the carbamate bond. Therefore, NMR spectra of these piperidines were recorded in DMSO above the temperature of coalescence (at 75 °C), avoiding the duplication of signals due to the presence of rotamers.

By means of the general procedure described above, 2,5,5-trisubstituted piperidines **4a** and **5a** (30 mg, >99% yield) were obtained from 30 mg (0.07 mmol) of **3a** as a separable 2:1 mixture of diastereoisomers.

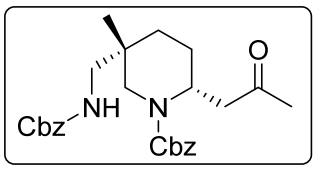
(2*R*,5*R*)-*N*-Benzyloxycarbonyl-5-benzyloxycarbonylaminomethyl-5-methyl-2-(2-oxopropyl)piperidine (4a).



4a (major)

Diastereoisomer **4a (major)**: was obtained as a colorless oil (20 mg) in 99% ee after flash chromatography with 3:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Phenomenex Celulose 4 column (hexane: isopropanol 80:20); flow rate = 1.0 mL/min, t_{major}= 39.2 min, t_{minor}= 57.0 min. $[\alpha]_D^{25}$ = -17.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-D_6) δ 7.37– 7.31 (m, 10H), 5.06 (s, 2H), 5.04 (s, 2H), 4.67 – 4.63 (m, 1H), 3.55 (d, J = 13.6 Hz, 1H), 2.90 (d, J = 6.4 Hz, 2H), 2.79 – 2.52 (m, 4H), 2.06 (s, 3H), 1.79 – 1.70 (m, 1H), 1.52 – 1.44 (m, 1H), 1.37 – 1.10 (m, 2H), 0.77 (s, 3H). ^{13}C NMR (126 MHz, DMSO-D_6) δ 205.9 (s), 154.5 (s), 137.0 (s), 136.7 (s), 127.9 (s), 127.9 (s), 127.3 (s), 127.3 (s), 127.2 (s), 127.0 (s), 127.0 (s), 65.8 (s), 65.0 (s), 49.8 (s), 46.4 (s), 46.3 (s), 43.2 (s), 34.7 (s), 29.5 (s), 27.5 (s), 23.4 (s), 18.8 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{26}H_{32}N_2O_5$: 453.2384; found: 453.2392.

(2*R*,5*S*)-*N*-Benzyloxycarbonyl-5-benzyloxycarbonylaminomethyl-5-methyl-2-(2-oxopropyl) piperidine (5a).

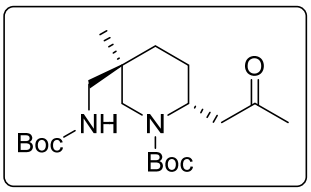


5a (minor)

Diastereoisomer **5a (minor)**: was obtained as a colorless oil (10 mg) in 99% ee after flash chromatography with 3:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Chiralpack ODH column (hexane: isopropanol 80:20); flow rate = 1.0 mL/min, t_{major}= 19.7 min, t_{minor}= 22.4 min. $[\alpha]_D^{25}$ = -16.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-D_6) δ 7.38– 7.27 (m, 10H), 5.05 (s, 2H), 5.02 (s, 2H), 4.65 – 4.56 (m, 1H), 3.61 (d, *J* = 13.9 Hz, 1H), 3.14 – 3.11 (m, 2H), 2.82– 2.75 (m, 2H), 2.71 – 2.60 (m, 2H), 2.06 (s, 3H), 1.48– 1.26 (m, 4H), 0.82 (s, 3H). ^{13}C NMR (126 MHz, DMSO-D_6) δ 205.9 (s), 154.4 (s), 136.9 (s), 136.6 (s), 127.9 (s), 127.8 (s), 127.2 (s), 127.2 (s), 127.1 (s), 126.9 (s), 126.9 (s), 65.9 (s), 65.0 (s), 46.7 (s), 46.5 (s), 44.4 (s), 43.3 (s), 33.9 (s), 29.4 (s), 27.0 (s), 23.5 (s), 23.5 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{26}H_{32}N_2O_5$: 453.2384; found: 453.2389.

By means of the general procedure described above, 2,5,5-trisubstituted piperidines **4b** and **5b** (43 mg, 86% yield) were obtained from 50 mg (0.13 mmol) of **3b** as a separable 1.5:1 mixture of diastereoisomers.

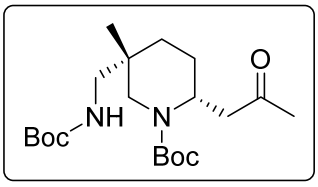
***(*2R*,5R)-N-*^{t}Butoxycarbonyl-5-^{t}butoxycarbonylaminomethyl-5-methyl-2-(2-oxopropyl) piperidine (4b).**



4b (major)

Diastereoisomer **4b (major)**: was obtained as a colorless oil (26 mg) in 98% ee after flash chromatography with 4:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Phenomenex Celulose 2 column (hexane: isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}= 14.8 min, t_{minor}= 19.0 min. $[\alpha]_D^{25}$ = -22.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-D_6) δ 4.63 – 4.55 (m, 1H), 3.48 (d, *J* = 13.5 Hz, 1H), 2.86– 2.78 (m, 2H), 2.68 – 2.56 (m, 2H), 2.10 (s, 3H), 1.79 – 1.69 (m, 1H), 1.41 – 1.39 (m, 22H), 1.15 – 1.07 (m, 1H), 0.79 (s, 3H). ^{13}C NMR (126 MHz, DMSO-D_6) δ 205.8 (s), 155,0 (s), 153.8 (s), 78.2 (s), 77.2 (s), 49.5 (s), 46.1 (s), 46.0 (s), 43.4 (s), 34.8 (s), 29.3 (s), 27.9 (s), 27.8 (s), 27.7 (s), 23.5 (s), 18.8 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{36}N_2O_5$: 385.2697;found: 385.2694.

***(*2R*,5S)-N-*^{t}Butoxycarbonyl-5-^{t}butoxycarbonylaminomethyl-5-methyl-2-(2-oxopropyl) piperidine (5b).**

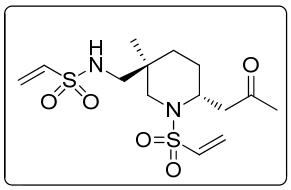


5b (minor)

Diastereoisomer **5b (minor)**: was obtained as a colorless oil (17 mg) in 92% ee after flash chromatography with 4:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Chiralpack IC column (hexane: isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}= 56.9 min, t_{minor}= 47.6 min. $[\alpha]_D^{25}$ = -17.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-D_6) δ 4.56 – 4.52 (m, 1H), 3.53 (d, *J* = 14.0 Hz, 1H), 2.74 – 2.67(m, 2H), 2.63 – 2.56 (m, 2H), 2.10 (s, 3H), 1.87– 1.78 (m, 1H), 1.41 – 1.39 (m, 20H), 1.32 – 1.25 (m, 3H), 0.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-D_6) δ 205.9 (s), 155.5 (s), 153.7 (s), 78.5 (s), 77.3 (s), 46.4 (s), 46.3 (s), 44.0 (s), 43.5 (s), 34.0 (s), 29.4 (s), 27.9 (s), 27.7 (s), 27.3 (s), 23.6 (s), 23.6 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{36}N_2O_5$: 385,2697; found: 385,2694.

By means of the general procedure described above, 2,5,5-trisubstituted piperidines **4c** and **5c** (81 mg, 81% yield) were obtained from 100 mg (0.27 mmol) of **3c** as a separable 4:1 mixture of diastereoisomers.

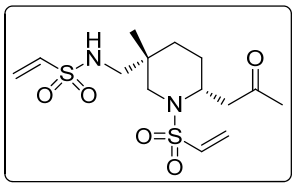
(2*R*,5*R*)-*N*-*Vinylsulfonyl*-5-methyl-2-(2-oxopropyl)-5-vinylsulfonylaminomethyl piperidine (4c).



4c (major)

Diastereoisomer **4c (major)**: was obtained as a colorless solid (65 mg) in 99% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. M. p. = 115-117 °C. The ee value was determined by HPLC analysis using a Chiralpack AYH column (hexane: isopropanol 60:40); flow rate = 1.0 mL/min, t_{major}= 20.9 min, t_{minor}= 9.3 min. $[\alpha]_D^{25}$ = -7.6 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.43 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.24 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H), 5.92 (d, *J* = 9.8 Hz, 1H), 4.75 (t, *J* = 7.1 Hz, 1H), 4.27 – 4.20 (m, 1H), 3.10 (d, *J* = 13.3 Hz, 1H), 2.95 – 2.83 (m, 3H), 2.82 – 2.68 (m, 2H), 2.17 (s, 3H), 1.87 – 1.76 (m, 1H), 1.59 – 1.41 (m, 2H), 1.36 – 1.28 (m, 1H), 1.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2 (s), 135.9 (s), 135.3 (s), 127.1 (s), 51.4 (s), 49.8 (s), 49.6 (s), 44.5 (s), 34.4 (s), 30.5 (s), 29.3 (s), 25.7 (s), 20.6 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{24}N_2O_5S_2$: 365.1199; found: 365.1203.

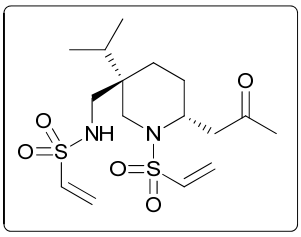
(2*R*,5*S*)-*N*-*Vinylsulfonyl*-5-methyl-2-(2-oxopropyl)-5-vinylsulfonylaminomethyl piperidine (5c).



5c (minor)

Diastereoisomer **5c (minor)**: was obtained as a colorless oil (16 mg) in 80% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Chiralpack AYH column (hexane: isopropanol 60:40); flow rate = 1.0 mL/min, t_{major}= 27.8 min, t_{minor}= 14.5 min. $[\alpha]_D^{25}$ = -5.8 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.42 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.21 (d, *J* = 16.6 Hz, 1H), δ 6.19 (d, *J* = 16.5 Hz, 1H), 5.93 (d, *J* = 9.9 Hz, 1H), 5.89 (d, *J* = 9.8 Hz, 1H), 5.02 (dd, *J* = 9.3, 5.1 Hz, 1H), 4.54 (q, *J* = 6.5 Hz, 1H), 3.34 – 3.22 (m, 2H), 2.78 – 2.65 (m, 3H), 2.60 (d, *J* = 14.4 Hz, 1H), 2.17 (s, 3H), 2.01 – 1.86 (m, 1H), 1.50 – 1.41 (m, 1H), 1.32 – 1.21 (m, 2H), 0.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7 (s), 136.2 (s), 135.8 (s), 126.7 (s), 126.5 (s), 47.9 (s), 46.5 (s), 46.3 (s), 43.5 (s), 34.0 (s), 30.6 (s), 29.7 (s), 25.4 (s), 23.9 (s) HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{24}N_2O_5S_2$: 365.1199; found: 365.1205.

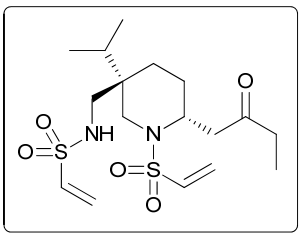
(2*R*,5*S*)-*N*-Vinylsulfonyl-5-isopropyl-2-(2-oxopropyl)-5-vinylsulfonylaminomethyl piperidine (4d).



4d

By means of the general procedure described above, piperidine **4d** (43 mg, 86% yield) was obtained from 50 mg (0.13 mmol) of **3d** as a colorless oil separable 10:1 mixture of diastereoisomers in 98% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Chiralpack IC column (hexane: isopropanol 60:40); flow rate = 1.0 mL/min, t_{major}= 83.1 min, t_{minor}= 39.0 min. $[\alpha]_D^{25}$ = 15.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.45 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.24 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 4.76 (dd, *J* = 8.5, 5.8 Hz, 1H), 4.05 – 3.95 (m, 1H), 3.1 (dd, *J* = 17.7, 6.3 Hz, 1H), 3.06 (s, 2H), 3.02 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.92 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.64 (dd, *J* = 17.7, 6.3 Hz, 1H), 3.17 (s, 3H), 2.04 (hept, *J* = 6.4 Hz, 1H), 1.72 – 1.46 (m, 4H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 135.9, 134.5, 127.6, 127.1, 51.8, 48.0, 45.9, 44.6, 38.5, 30.4, 28.2, 26.9, 25.2, 17.0, 16.5. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{16}H_{28}N_2O_5S_2$: 393.1518; found: 393.1520.

(2*R*,5*S*)-*N*-Vinylsulfonyl-5-isopropyl-2-(2-oxobutyl)-5-vinylsulfonylaminomethyl piperidine (4e).

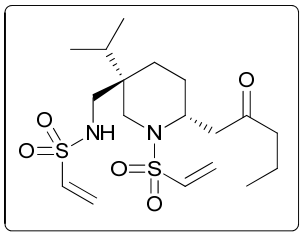


4e

By means of the general procedure described above, piperidine **4e** (36 mg, 89% yield) was obtained from 40 mg (0.1 mmol) of **3e** as a colorless oil separable 10:1 mixture of diastereoisomers in 98% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Phenomenex Celulose 4 column (hexane: isopropanol 70:30); flow rate = 1.0 mL/min, t_{major}= 51.5 min, t_{minor}= 77.3 min. $[\alpha]_D^{25}$ = 11.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.45 (dd, *J* = 16.5, 9.8 Hz, 1H) 6.25 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 4.67 (dd, *J* = 8.7, 5.8 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.12 – 3.01 (m, 4H), 2.93 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.60 (dd, *J* = 17.5, 6.3 Hz, 1H), 2.53 – 2.37 (m, 2H), 2.04 (hept, *J* = 7.0 Hz, 1H), 1.72 – 1.60 (m, 2H), 1.52 – 1.46 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 7.0 Hz,

3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 135.9, 134.5, 127.6, 127.1, 52.1, 49.1, 44.8, 44.6, 38.6, 36.3, 28.3, 27.1, 25.3, 17.1, 16.5, 7.7. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{30}N_2O_5S_2$: 407.1674; found: 407.1676.

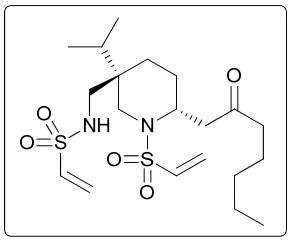
(2*R*,5*S*)-*N*-Vinylsulfonyl-5-isopropyl-2-(2-oxopentyl)-5-vinylsulfonylaminomethyl piperidine (4f).



4f

By means of the general procedure described above, piperidine **4f** (34 mg, 86% yield) was obtained from 40 mg (0.09 mmol) of **3f** as a white solid separable 12:1 mixture of diastereoisomers in 98% ee after flash chromatography with 2:1 n-hexane: ethyl acetate. Mp= 96 °C. The ee value was determined by HPLC analysis using a Phenomenex Celulose 4 column (hexane: isopropanol 70:30); flow rate = 1.0 mL/min, t_{major}= 19.9 min, t_{minor}= 16.0 min. $[\alpha]_D^{25}$ = 13.7 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.46 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.25 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 5.97 (d, *J* = 9.8 Hz, 1H), δ 5.94 (d, *J* = 9.8 Hz, 1H), 4.66 (dd, *J* = 8.7, 5.7 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.11 – 3.01 (m, 4H), 2.93 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.60 (dd, *J* = 17.5, 6.3 Hz, 1H), 2.46 – 2.32 (m, 2H), 2.04 (hept, *J* = 6.8 Hz, 1H), 1.74 – 1.61 (m, 4H), 1.51 – 1.43 (m, 2H), 0.96 – 0.88 (m, 6H), 0.86 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 135.9, 134.5, 127.6, 127.1, 52.0, 49.1, 45.1, 45.0, 44.6, 38.6, 28.3, 27.1, 25.3, 17.1, 17.1, 16.5, 13.8. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{32}N_2O_5S_2$: 421.1831; found: 421.1833.

(2*R*,5*S*)-*N*-Vinylsulfonyl-5-isopropyl-2-(2-oxoheptyl)-5-vinylsulfonylaminomethyl piperidine (4g).

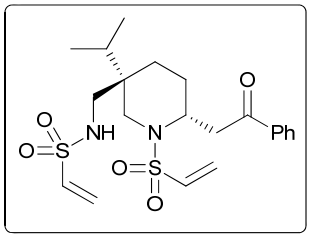


4g

By means of the general procedure described above, piperidine **4g** (29 mg, 72% yield) was obtained from 40 mg (0.09 mmol) of **3g** as a colorless oil separable 10:1 mixture of diastereoisomers in 96% ee after flash chromatography with 2:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Phenomenex Celulose 4 column (hexane: isopropanol 70:30); flow rate = 1.0 mL/min, t_{major}= 19.0 min, t_{minor}= 14.5 min. $[\alpha]_D^{25}$ = 13.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.45 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.25 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 5.97 (d, *J* = 9.8 Hz, 1H), 5.94 (d, *J* = 9.8 Hz, 1H),

4.69 (dd, *J* = 8.6, 5.8 Hz, 1H), 4.03 – 3.96 (m, 1H), 3.11 – 3.00 (m, 4H), 2.92 (dd, *J* = 13.5, 8.8 Hz, 1H), 2.61 (dd, *J* = 17.5, 6.4 Hz, 1H), 2.52 – 2.33 (m, 2H), 2.04 (hept, *J* = 7.1 Hz, 1H), 1.74 – 1.63 (m, 1H), 1.59 – 1.43 (m, 5H), 1.32 – 1.25 (m, 4H), 0.92 – 0.84 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 135.9, 134.5, 127.5, 127.1, 51.9, 49.0, 45.0, 44.6, 43.1, 38.6, 31.5, 28.2, 27.0, 25.2, 23.4, 22.6, 17.1, 16.5, 14.1. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{36}N_2O_5S_2$: 449.2144; found: 449.2144.

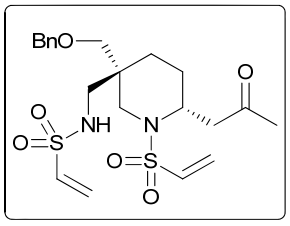
(2*R*,5*S*)-*N*-Vinylsulfonyl-5-isopropyl-2-(2-oxo2-phenylethyl)-5-vinylsulfonylaminomethyl piperidine (4h).



4h

By means of the general procedure described above, piperidine **4h** (27 mg, 67% yield) was obtained from 40 mg (0.09 mmol) of **3h** as a colorless oil separable 7:1 mixture of diastereoisomers in 76% ee after flash chromatography with 2:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Phenomenex Celulose 4 column (hexane: isopropanol 70:30); flow rate = 1.0 mL/min, t_{major}= 51.5 min, t_{minor}= 77.3 min. $[\alpha]_D^{25}$ = 9.2 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.92 (m, 2H), 7.64 – 7.58 (m, 1H), 7.52 – 7.46 (m, 2H), 6.55 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.43 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.23 (d, *J* = 16.6 Hz, 1H), 6.17 (d, *J* = 16.5 Hz, 1H), 5.95 (d, *J* = 9.9 Hz, 1H), 5.83 (d, *J* = 9.8 Hz, 1H), 5.00 (dd, *J* = 9.8, 4.7 Hz, 1H), 4.71 – 4.65 (m, 1H), 3.32 – 3.21 (m, 4H), 3.02 – 2.94 (m, 2H), 2.04 – 1.86 (m, 2H), 1.65 – 1.56 (m, 2H), 1.42 – 1.34 (m, 1H), 0.97 (d, *J* = 2.6 Hz, 3H), 0.95 (d, *J* = 2.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 136.4, 136.0, 135.7, 133.9, 129.0, 128.3, 126.9, 126.8, 48.9, 44.1, 42.8, 38.4, 38.4, 30.9, 24.9, 22.3, 17.1, 16.8. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{21}H_{30}N_2O_5S_2$: 455.1644; found: 455.1648

(2*R*,5*S*)-*N*-Vinylsulfonyl-5-(benzyloxy)methyl-2-(2-oxopropyl)-5-vinylsulfonylaminomethyl piperidine (4i).

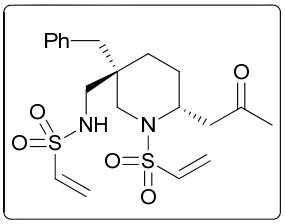


4i

By means of the general procedure described above, piperidine **4i** (40 mg, >99% yield) was obtained from 40 mg (0.09 mmol) of **3i** as a colorless oil separable 4:1 mixture of diastereoisomers in 98% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. The ee

value was determined by HPLC analysis using a Phenomenex Celulose 4 column (hexane: isopropanol 70:30); flow rate = 1.0 mL/min, t_{major}= 55.5 min, t_{minor}= 50.9 min. $[\alpha]_D^{25}$ = -3.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 6.44 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.31 (dd, *J* = 16.5, 9.4 Hz, 1H), 6.19 (d, *J* = 16.5 Hz, 1H), 6.17 (d, *J* = 16.5 Hz, 1H), 5.92 (d, *J* = 9.8 Hz, 1H), 5.85 (d, *J* = 9.4 Hz, 1H), 4.93 (t, *J* = 6.5 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.37 – 4.29 (m, 1H), 3.57 – 3.50 (m, 2H), 3.39 (d, *J* = 9.5 Hz, 1H), 2.96 – 2.89 (m, 2H), 2.78 – 2.73 (m, 3H), 2.16 (s, 3H), 1.77 – 1.63 (m, 1H), 1.55 – 1.46 (m, 2H), 1.40 – 1.30 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 137.7, 135.8, 135.4, 128.8, 128.3, 128.1, 127.1, 126.8, 73.8, 71.3, 49.8, 48.9, 45.1, 44.0, 37.6, 30.6, 25.0, 25.0. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{21}H_{30}N_2O_6S_2$: 471.1624; found: 471.1624.

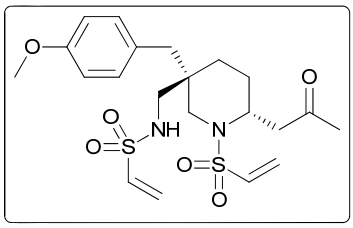
(2*R*,5*S*)-*N*-Vinylsulfonyl-5-benzyl-2-(2-oxopropyl)-5-vinylsulfonylaminomethylpiperidine (4j).



4j

By means of the general procedure described above, piperidine **4j** (40 mg, 93% yield) was obtained from 40 mg (0.09 mmol) of **3j** as a colorless oil separable 7:1 mixture of diastereoisomers in 98% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. The ee value was determined by HPLC analysis using a Phenomenex Celulose 4 column (hexane: isopropanol 70:30); flow rate = 1.0 mL/min, t_{major}= 37.4 min, t_{minor}= 41.1 min. $[\alpha]_D^{25}$ = 14.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.26 – 7.22 (m, 1H), 7.17 – 7.15 (m, 2H), 6.49 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.48 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.24 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 5.96 (d, *J* = 9.9 Hz, 1H), 5.95 (d, *J* = 9.9 Hz, 1H), 4.64 (t, *J* = 7.0 Hz, 1H), 4.13 (p, *J* = 5.8 Hz, 1H), 3.15 – 3.07 (m, 2H), 3.00 (dd, *J* = 17.5, 5.9 Hz, 1H), 2.90 – 2.78 (m, 3H), 2.72 – 2.63 (m, 2H), 2.17 (s, 3H), 1.93 – 1.84 (m, 1H), 1.63 – 1.58 (m, 1H), 1.49 – 1.43 (m, 1H), 1.39 – 1.28 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1, 136.5, 135.7, 134.8, 130.5, 128.6, 127.7, 127.3, 127.0, 51.0, 50.1, 47.8, 45.1, 39.1, 37.7, 30.4, 27.5, 26.6. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{28}N_2O_5S_2$: 441.1518; found: 441.1515.

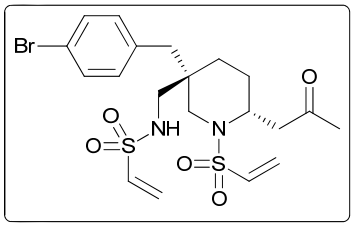
(2*R*,5*S*)-*N*-Vinylsulfonyl-5-(4-methoxybenzyl)-2-(2-oxopropyl)-5-vinylsulfonylaminomethyl piperidine (4k).



4k

By means of the general procedure described above, piperidine **4k** (55 mg, >99% yield) was obtained from 55 mg (0.12 mmol) of **3k** as a white solid separable 7:1 mixture of diastereoisomers in 97% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. Mp=134-135 °C. The ee value was determined by HPLC analysis using a Chiralpack IC column (hexane: isopropanol 70:30); flow rate = 1.0 mL/min, t_{major}= 90.9 min, t_{minor}= 70.5 min. $[\alpha]_D^{25}$ = 18.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.49 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.48 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.23 (d, *J* = 16.5 Hz, 1H), 6.21 (d, *J* = 16.5 Hz, 1H), 5.96 (d, *J* = 9.8 Hz, 1H), 5.95 (d, *J* = 9.8 Hz, 1H),4.65 (t, *J* = 7.0 Hz, 1H), 4.12 (p, *J* = 5.9 Hz, 1H), 3.78 (s, 3H), 3.13 – 2.96 (m, 3H), 2.90 – 2.80 (m, 2H), 2.75 – 2.62 (m, 3H), 2.16 (s, 3H), 1.92 – 1.81 (m, 1H), 1.62 – 1.55 (m, 1H), 1.48 – 1.28 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 158.6, 135.7, 134.8, 131.4, 128.3, 127.7, 127.3, 114.0, 55.4, 51.0, 50.1, 47.7, 45.1, 38.2, 37.7, 30.4, 27.5, 26.6. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{21}H_{30}N_2O_6S_2$: 471.1624; found: 471.1623.

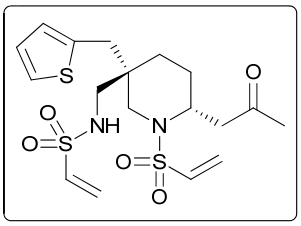
(2*R*,5*S*)-*N*-Vinylsulfonyl-5-(4-bromobenzyl)-2-(2-oxopropyl)-5-vinylsulfonylaminomethyl piperidine (4l).



4l

By means of the general procedure described above, piperidine **4i** (55 mg, >99% yield) was obtained from 55 mg (0.1 mmol) of **3i** as a white solid separable 8:1 mixture of diastereoisomers in 95% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. Mp=181-183 °C. The ee value was determined by HPLC analysis using a Chiralpack IC column (hexane: isopropanol 60:40); flow rate = 1.0 mL/min, t_{major}= 27.9 min, t_{minor}= 22.9 min. $[\alpha]_D^{25}$ = 31.5 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.52 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.48 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.23 (d, *J* = 16.6 Hz, 1H), 6.22 (d, *J* = 16.6 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H), 5.96 (d, *J* = 9.9 Hz, 1H), 4.91 (dd, *J* = 8.1, 6.0 Hz, 1H), 4.13 – 4.06 (m, 1H), 3.14 – 2.98 (m, 3H), 2.87 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.78 (dd, *J* = 13.2, 8.3 Hz, 1H), 2.71 – 2.59 (m, 3H), 2.16 (s, 3H), 1.89 – 1.78 (m, 1H), 1.64 – 1.53 (m, 1H), 1.44 – 1.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 135.6, 135.4, 134.7, 132.3, 131.6, 127.8, 127.5, 121.0, 51.3, 50.3, 47.2, 45.1, 38.3, 37.6, 30.4, 27.5, 26.9. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{27}BrN_2O_5S_2$: 519.0623; found: 519.0624.

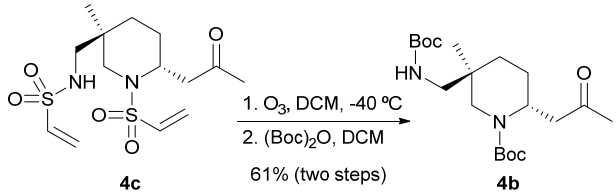
(2*R*,5*S*)-*N*-Vinylsulfonyl-5-(thiphen-2-ylmethyl)-2-(2-oxopropyl)-5-vinylsulfonylaminomethyl piperidine (4m).



4m

By means of the general procedure described above, piperidine **4i** (53 mg, 97% yield) was obtained from 55 mg (0.12 mmol) of **3i** as a yellow solid separable 7:1 mixture of diastereoisomers in 97% ee after flash chromatography with 1:1 n-hexane: ethyl acetate. Mp=145 °C. The ee value was determined by HPLC analysis using a Chiralpack IC column (hexane: isopropanol 70:30); flow rate = 1.0 mL/min, t_{major}= 74.5 min, t_{minor}= 55.2 min. $[\alpha]_D^{25}$ = 19.5 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 5.2, 1.1 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.89 – 6.88 (m, 1H), 6.51 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.48 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.23 (d, *J* = 16.5 Hz, 1H), 6.21 (d, *J* = 16.5 Hz, 1H), 5.96 (d, *J* = 9.8 Hz, 1H), 5.95 (d, *J* = 9.8 Hz, 1H), 4.82 (t, *J* = 7.1 Hz, 1H), 4.31 – 4.24 (m, 1H), 3.29 (d, *J* = 13.4 Hz, 1H), 3.08 – 2.85 (m, 6H), 2.74 (dd, *J* = 17.2, 7.7 Hz, 1H), 2.16 (s, 3H), 1.98 – 1.87 (m, 1H), 1.63 – 1.47 (m, 2H), 1.41 – 1.32 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 137.9, 135.6, 135.1, 127.7, 127.6, 127.4, 127.35, 124.6, 49.9, 48.9, 48.2, 44.4, 37.6, 32.2, 30.5, 26.5, 25.7. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{26}N_2O_5S_3$: 447.1082; found: 447.1083.

GENERAL PROCEDURE FOR THE DESPROTECTION OF PIPERIDINE 4C:



4c **4b**

To a solution of piperidine **4c** (100 mg, 0.27 mmol) in dichloromethane (5,4 mL, 0.05 M) at -40 °C, O_3 was bubbled. The reaction mixture was stirred until solution was turned to pale blue colour (10 minutes monitored by TLC). Then H_2O was added, and the mixture was stirred for 5 hours at room temperature. Afterwards solvents were removed, the crude amine was dissolved in CH_2Cl_2 (2.8 mL, 0.1 M), and Et_3N (0.23 mL, 6.0 equiv) was added at 0 °C, followed by di-tert-butyl dicarbonate (178 mg, 3.0 equiv). The reaction mixture was allowed to reach room temperature for 12 hours (monitored by TLC) and then it was hydrolyzed with saturated NH_4Cl solution, extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. Finally, solvents were removed and the crude mixture was purified by flash chromatography on siilica gel with 4:1 n-hexane: ethyl acetate to afford piperidine **4b** (65 mg, 61 % yield) as a colorless oil. NMR data are in agreement with those we previously reported.

X-RAY STRUCTURE OF COMPOUND 4C[6]

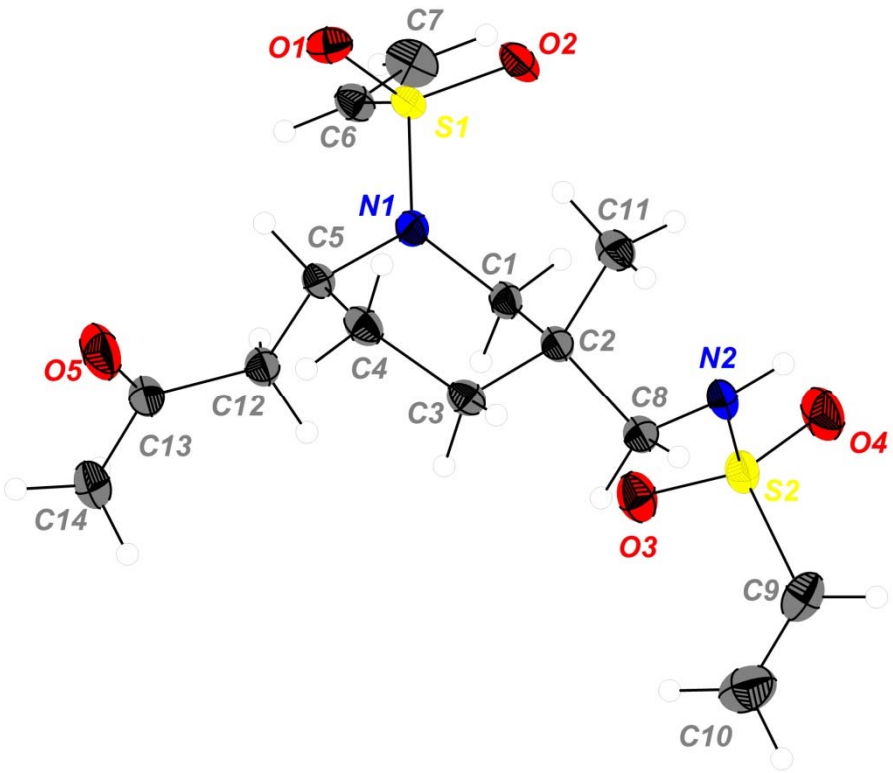
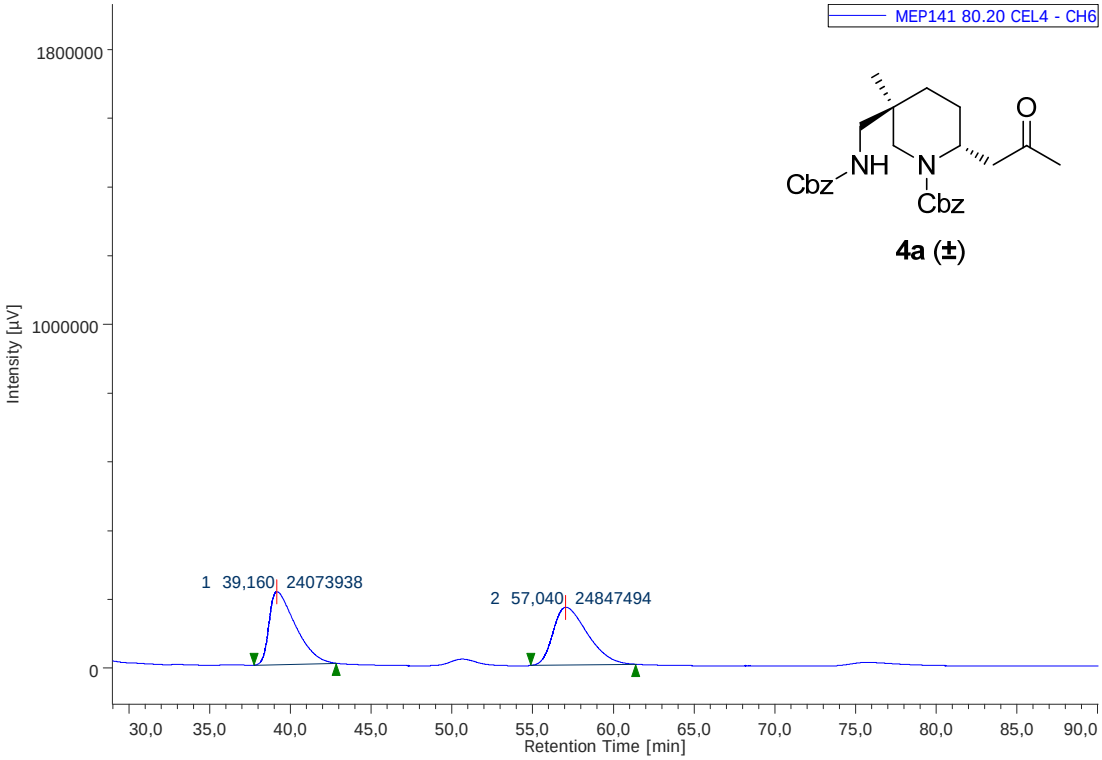


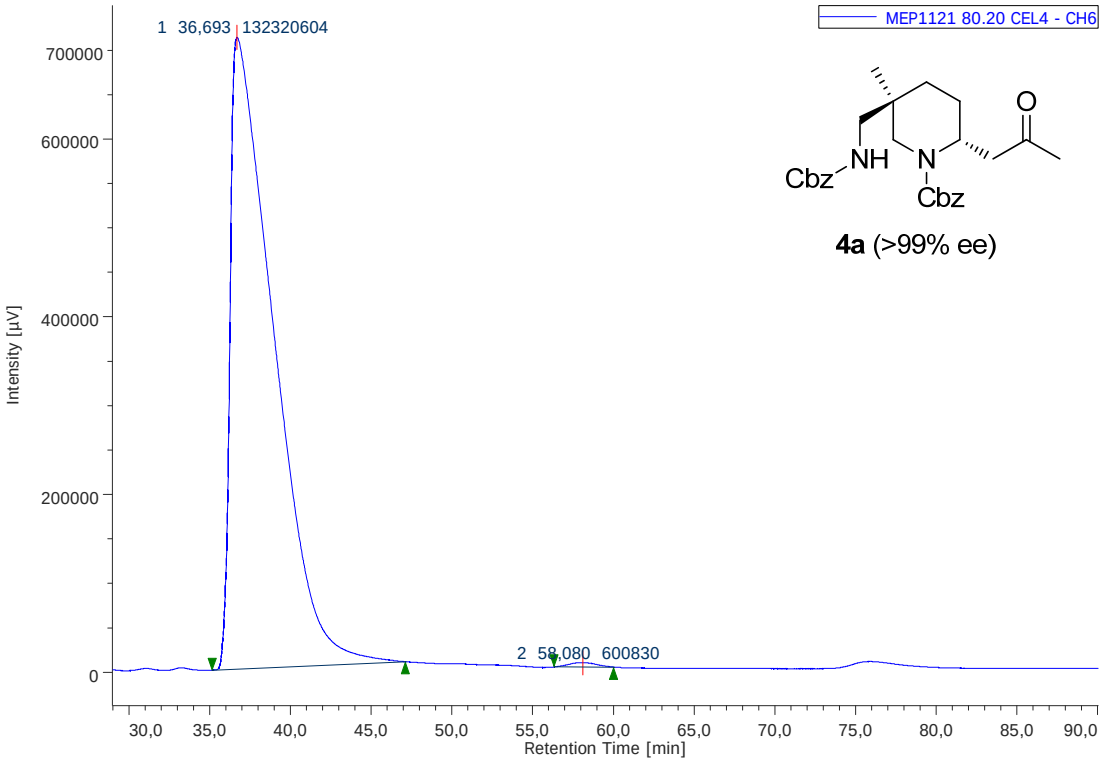
Figure S1. Ortep diagram for compound **4c**

[6] CCDC 1891128 contains the supplementary crystallographic data of compound **4c**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

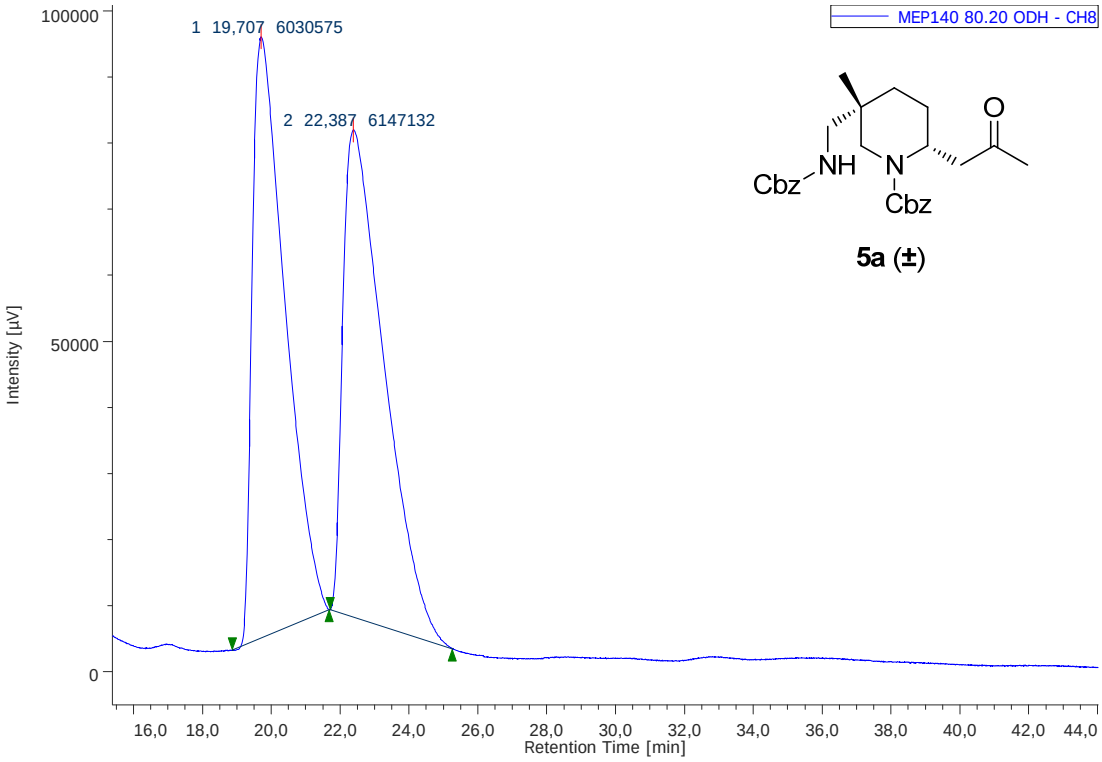
HPLC TRACES OF ENANTIOENRICHED 2,5,5 TRISUBSTITUTED PIPERIDINES 4,5:

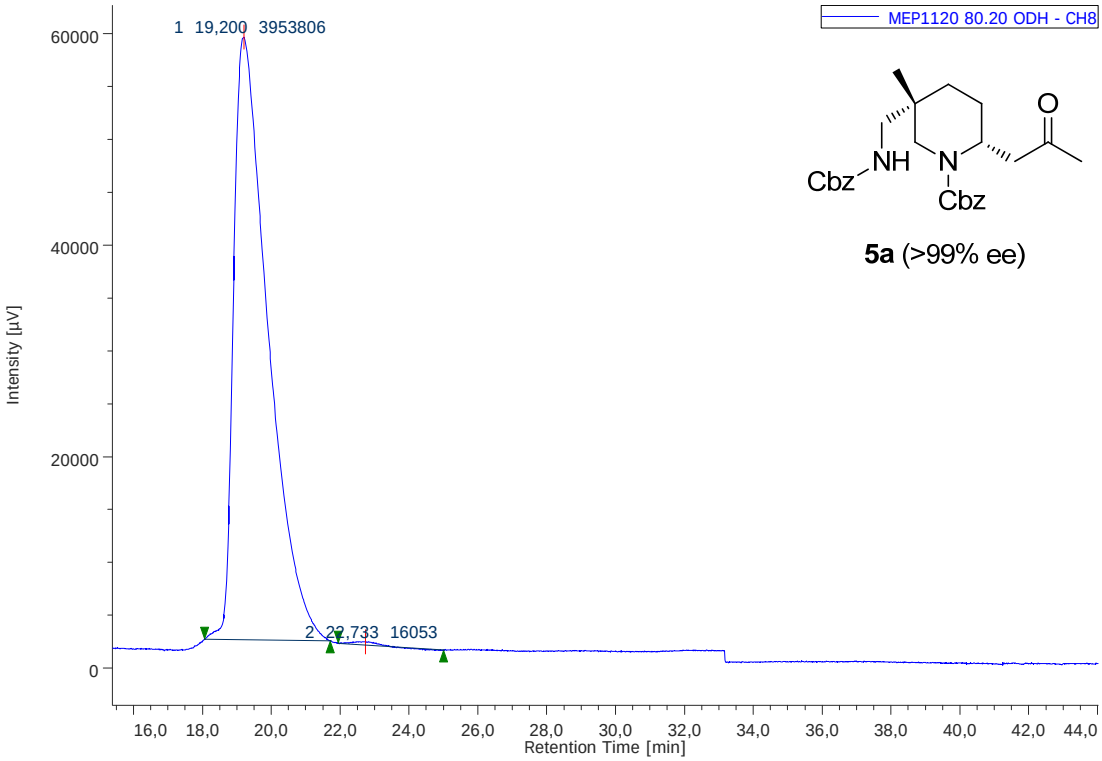


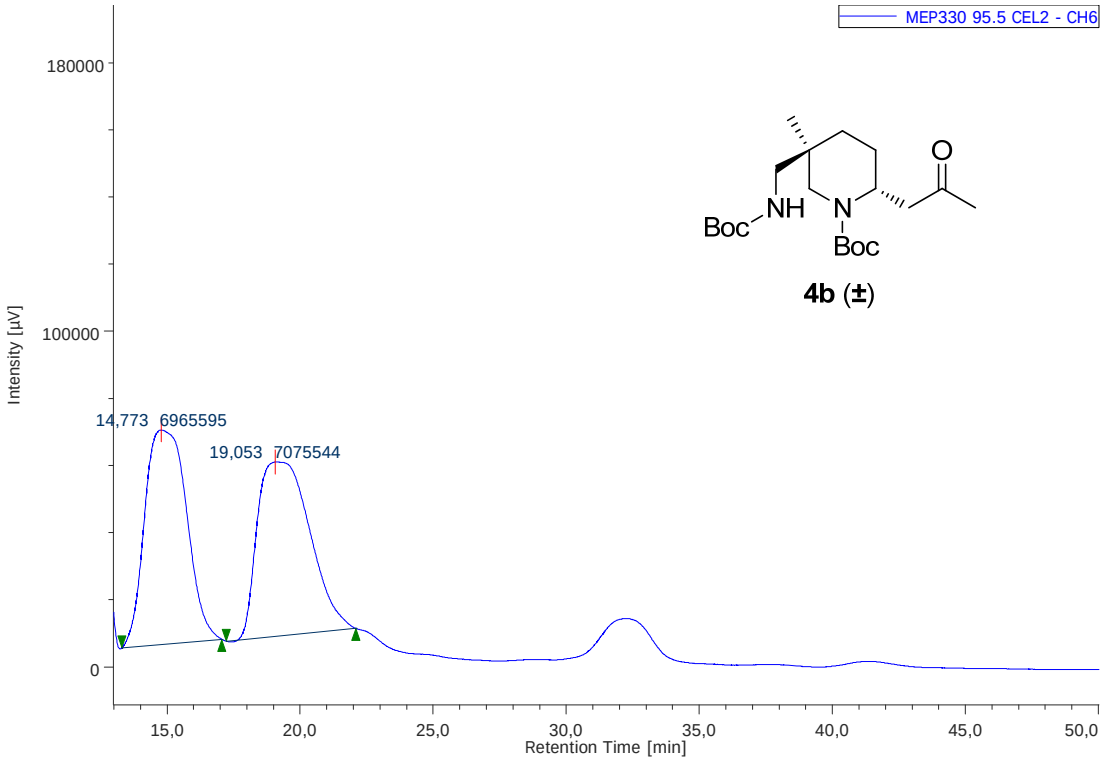
4a (±)

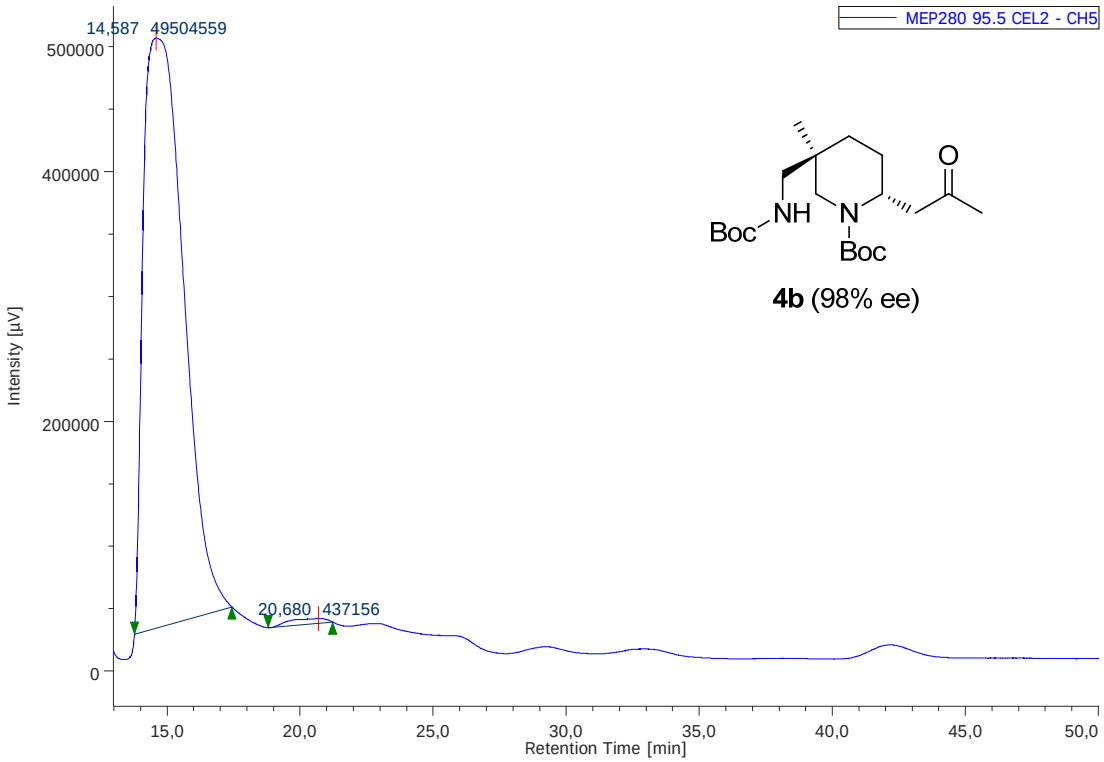


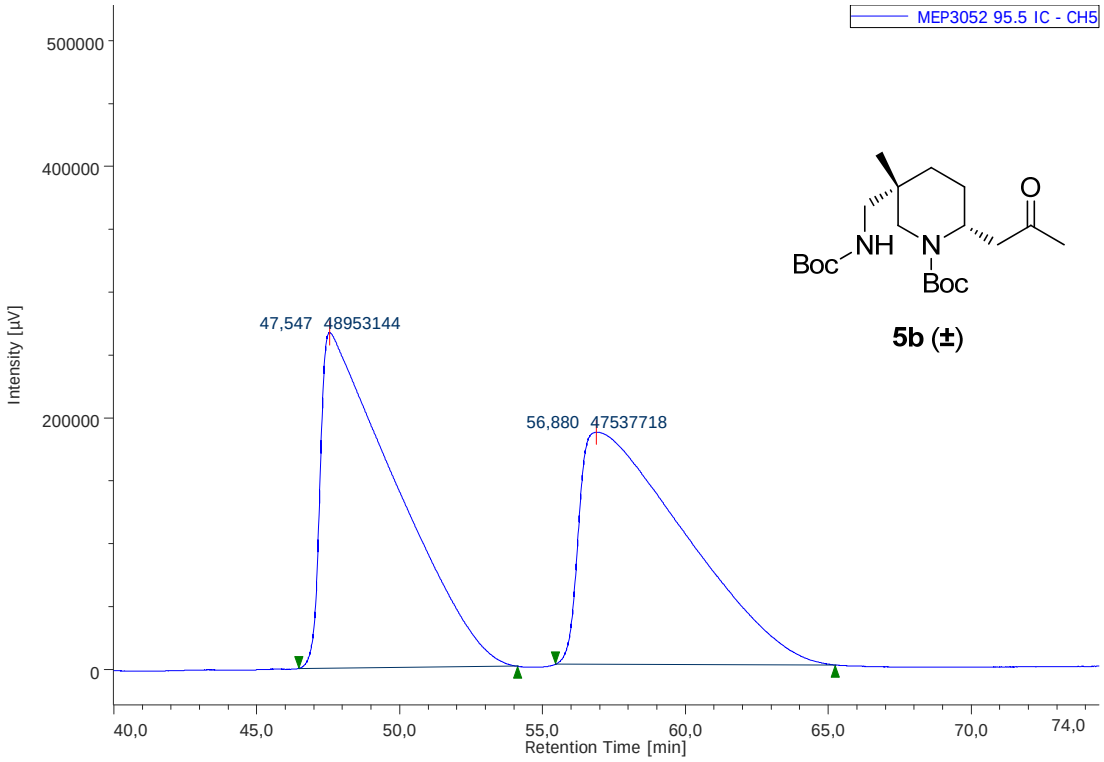
4a (>99% ee)


MEP140 80.20 ODH - CH8
1 19,707 6030575
2 22,387 6147132
Intensity [µV]
Retention Time [min]
5a (±)

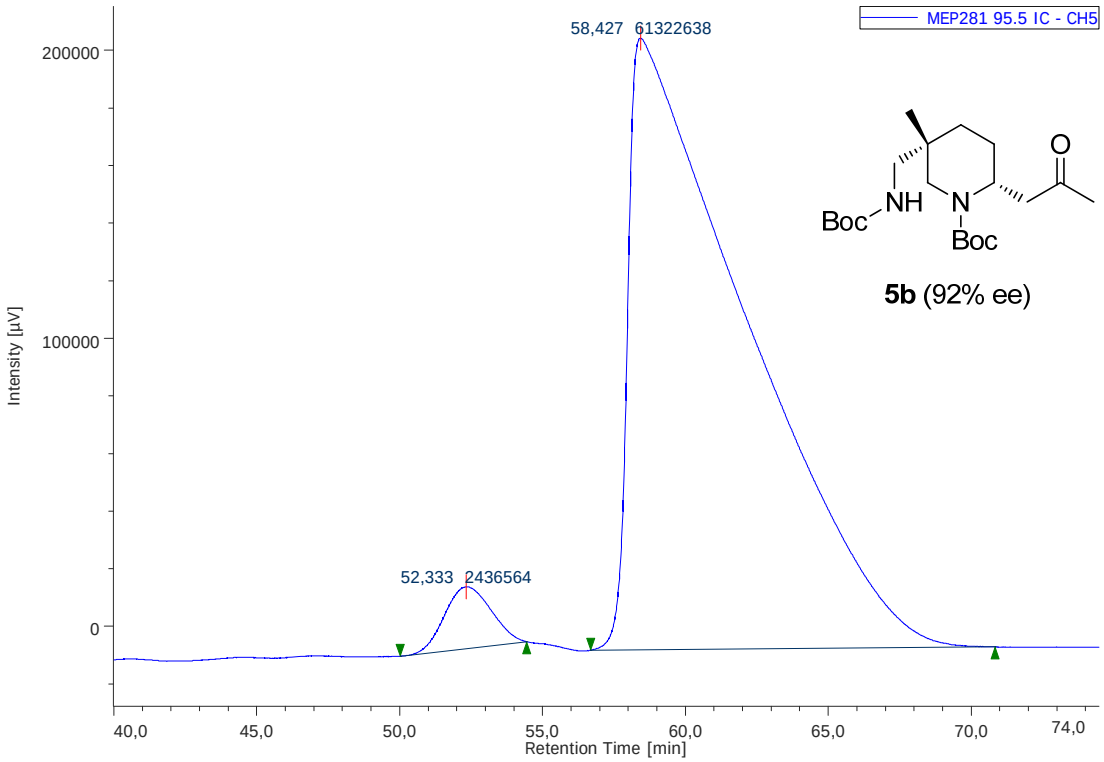

MEP1120 80.20 ODH - CH8
1 19,200 3953806
2 22,733 16053
Intensity [µV]
Retention Time [min]
5a (>99% ee)


MEP330 95.5 CEL2 - CH6
Intensity [µV]
180000
100000
0
14,773 6965595
19,053 7075544
15,0
20,0
25,0
30,0
35,0
40,0
45,0
50,0
Retention Time [min]
NH
N
Boc
Boc
O
4b (±)

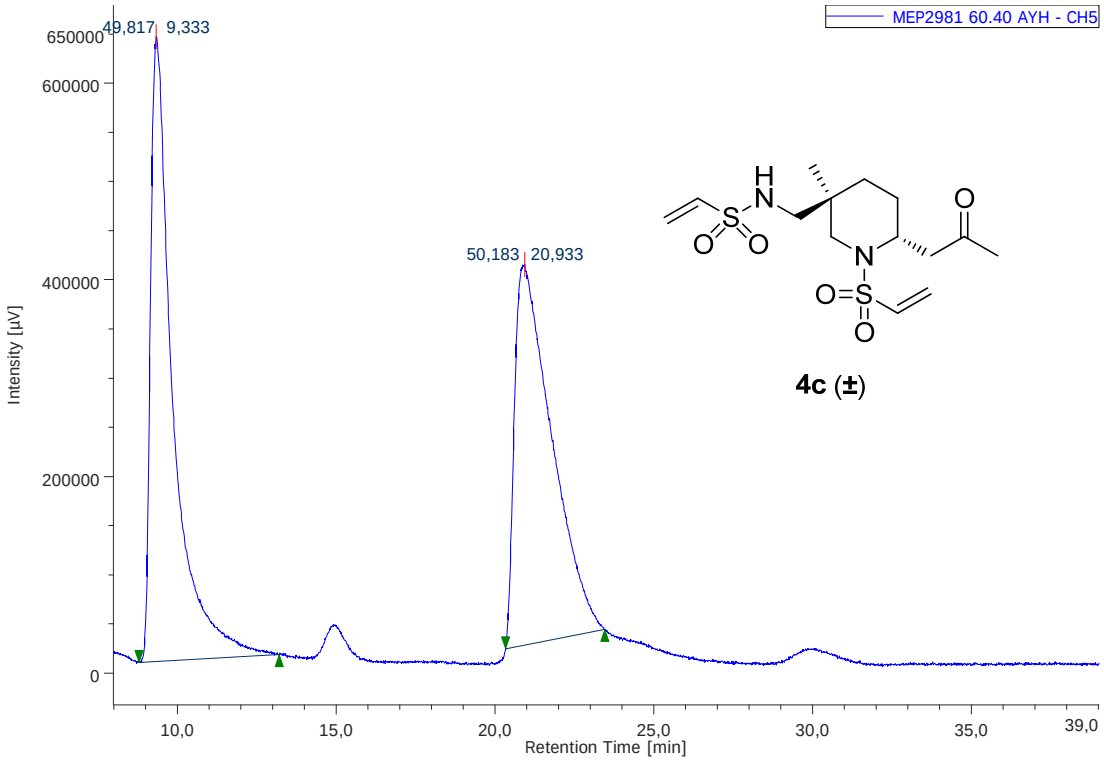

MEP280 95.5 CEL2 - CH5
Intensity [µV]
500000
400000
200000
0
14,587 49504559
20,680 437156
15,0
20,0
25,0
30,0
35,0
40,0
45,0
50,0
Retention Time [min]
NH
N
Boc
Boc
O
4b (98% ee)


MEP3052 95.5 IC - CH5
500000
400000
200000
0
Intensity [µV]
47,547 48953144
56,880 47537718
40,0
45,0
50,0
55,0
60,0
65,0
70,0
74,0
Retention Time [min]
NH
N
Boc
Boc
O

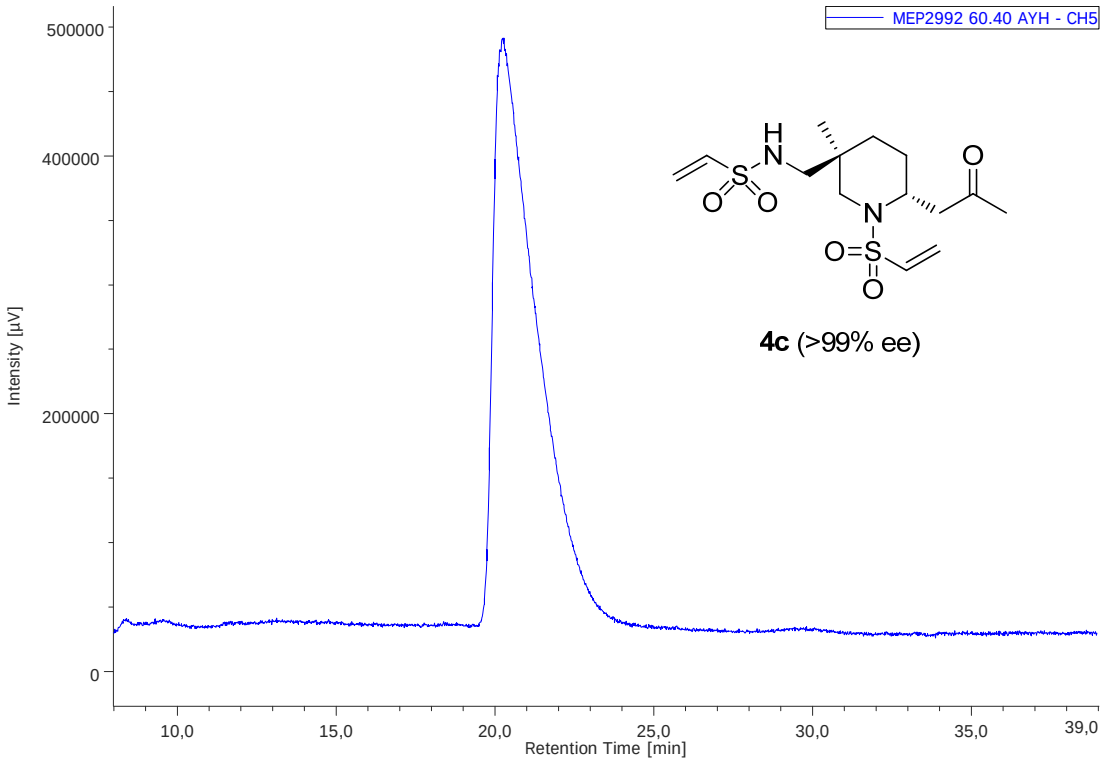
5b (±)


MEP281 95.5 IC - CH5
200000
100000
0
Intensity [µV]
58,427 61322638
52,333 2436564
40,0
45,0
50,0
55,0
60,0
65,0
70,0
74,0
Retention Time [min]
NH
N
Boc
Boc
O

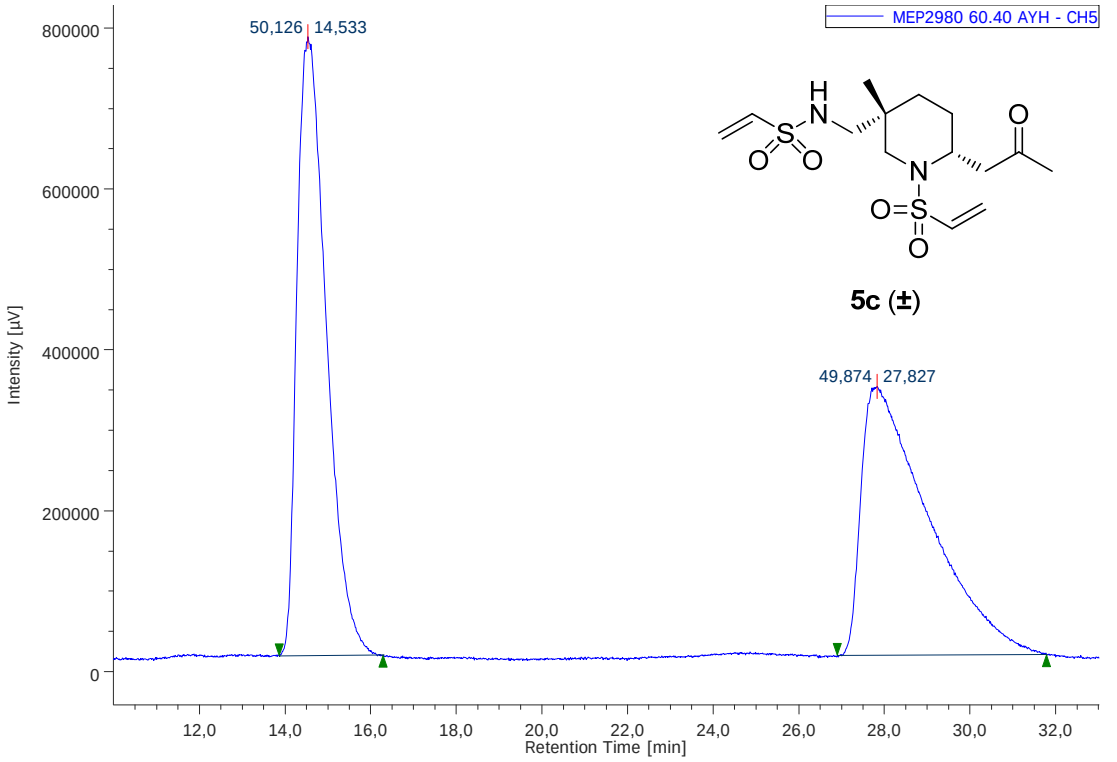
5b (92% ee)


MEP2981 60.40 AYH - CH5
49,817
9,333
50,183
20,933
650000
600000
400000
200000
0
Intensity [µV]
10,0
15,0
20,0
25,0
30,0
35,0
39,0
Retention Time [min]

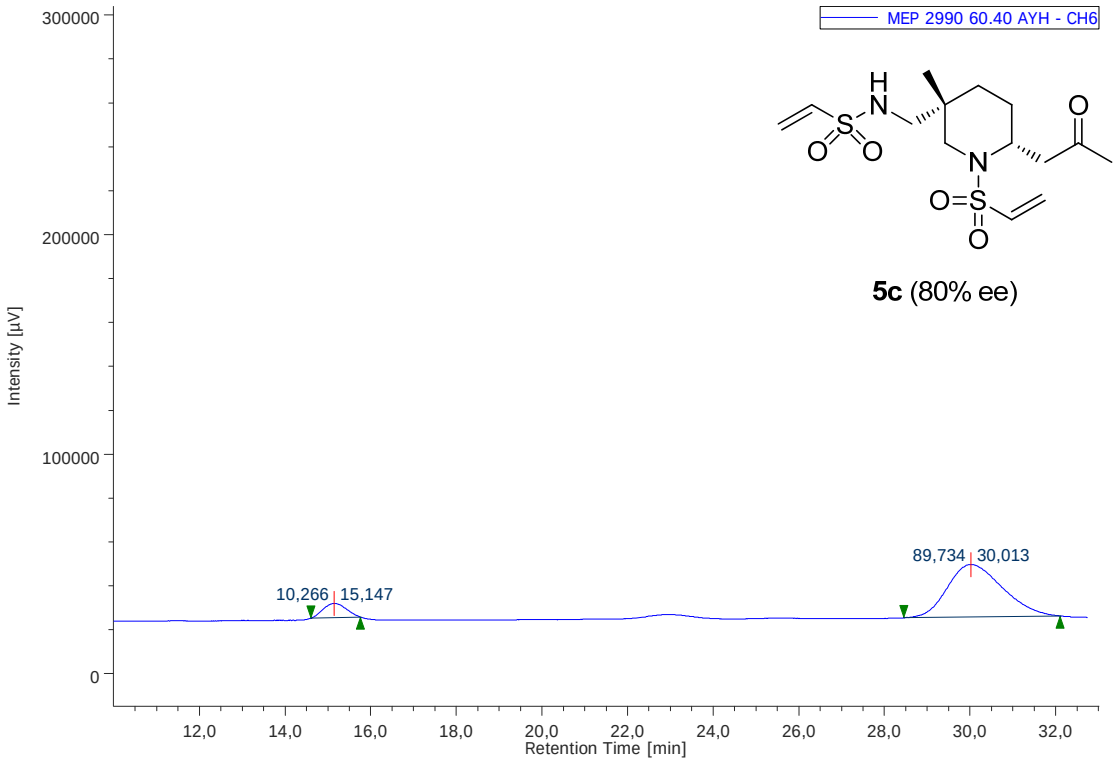
4c (±)


MEP2992 60.40 AYH - CH5
500000
400000
200000
0
Intensity [µV]
10,0
15,0
20,0
25,0
30,0
35,0
39,0
Retention Time [min]

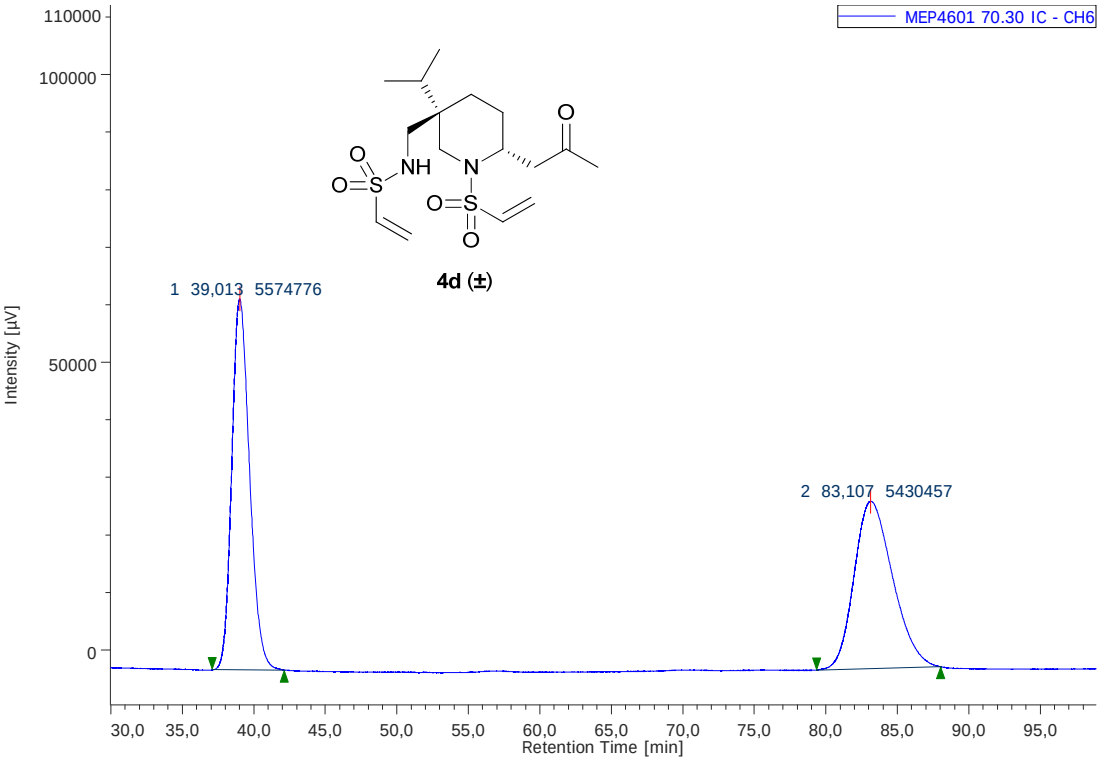
4c (>99% ee)

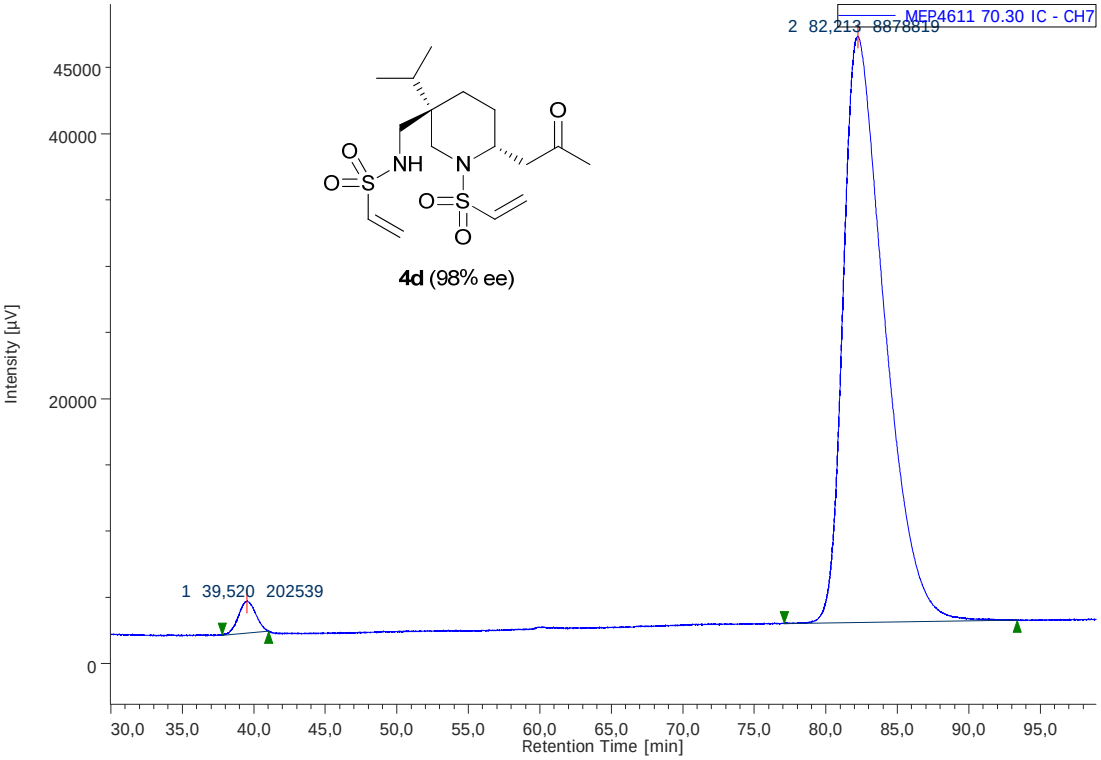

MEP2980 60.40 AYH - CH5
50,126
14,533
49,874
27,827
Intensity [µV]
800000
600000
400000
200000
0
12,0
14,0
16,0
18,0
20,0
22,0
24,0
26,0
28,0
30,0
32,0
Retention Time [min]

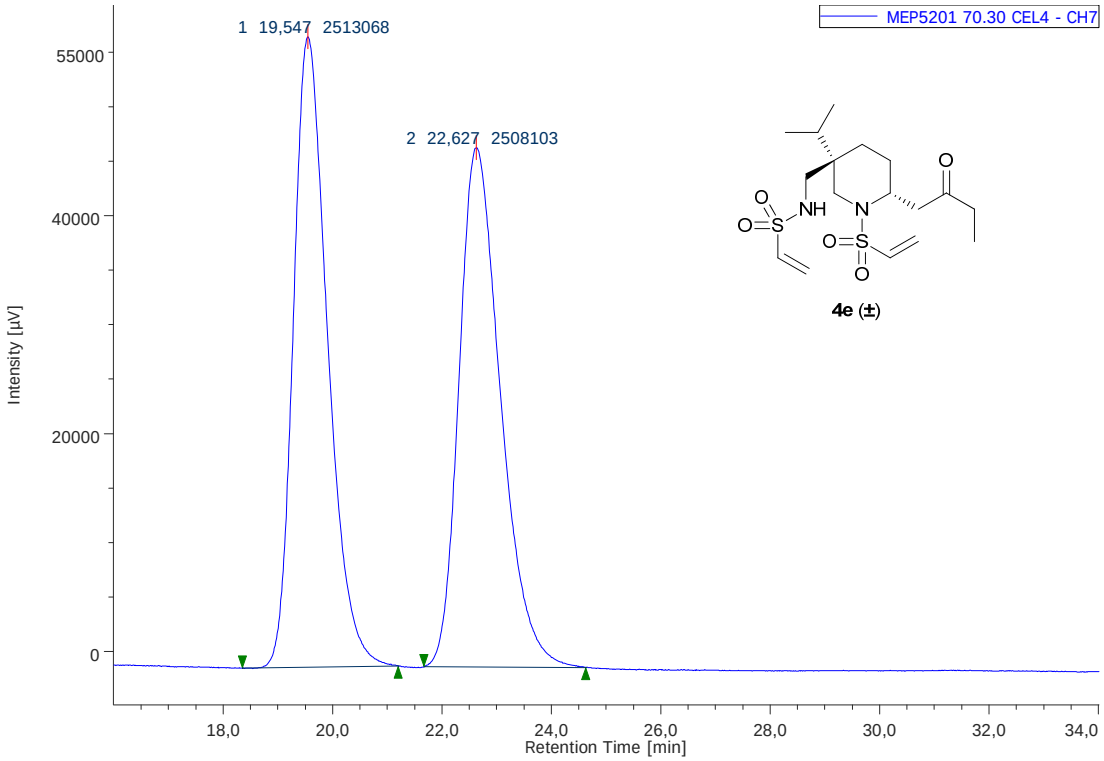
5c (±)

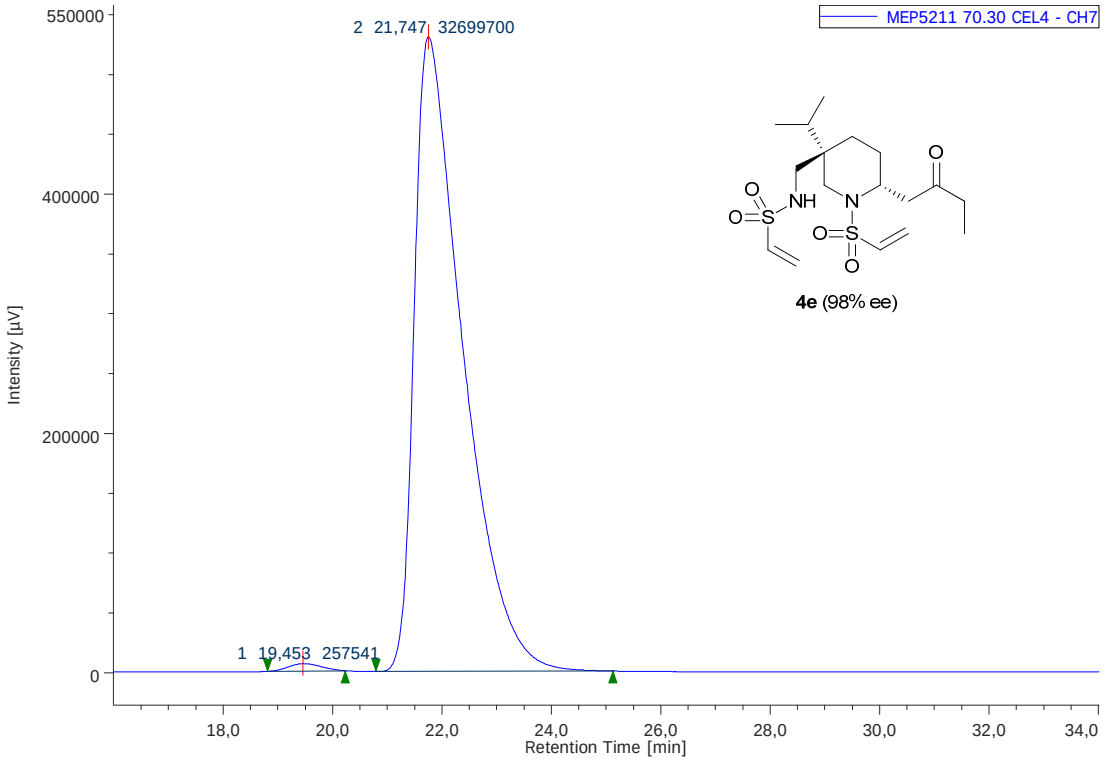

MEP 2990 60.40 AYH - CH6
89,734
30,013
10,266
15,147
Intensity [µV]
300000
200000
100000
0
12,0
14,0
16,0
18,0
20,0
22,0
24,0
26,0
28,0
30,0
32,0
Retention Time [min]

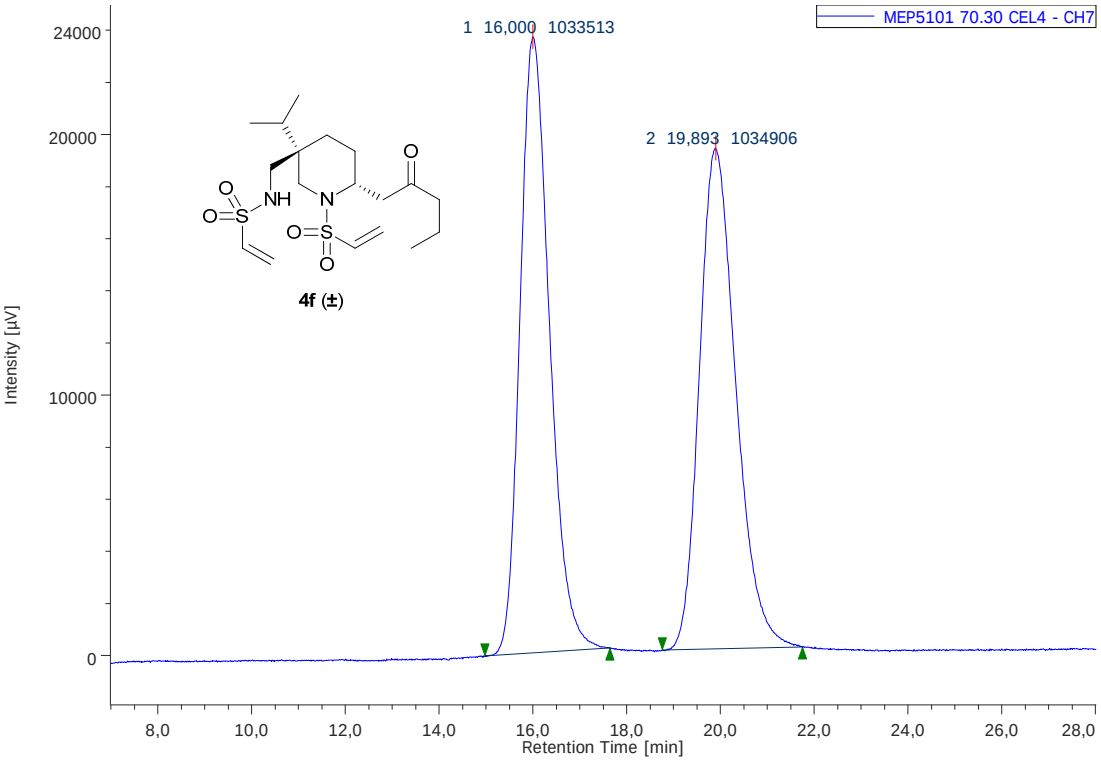
5c (80% ee)

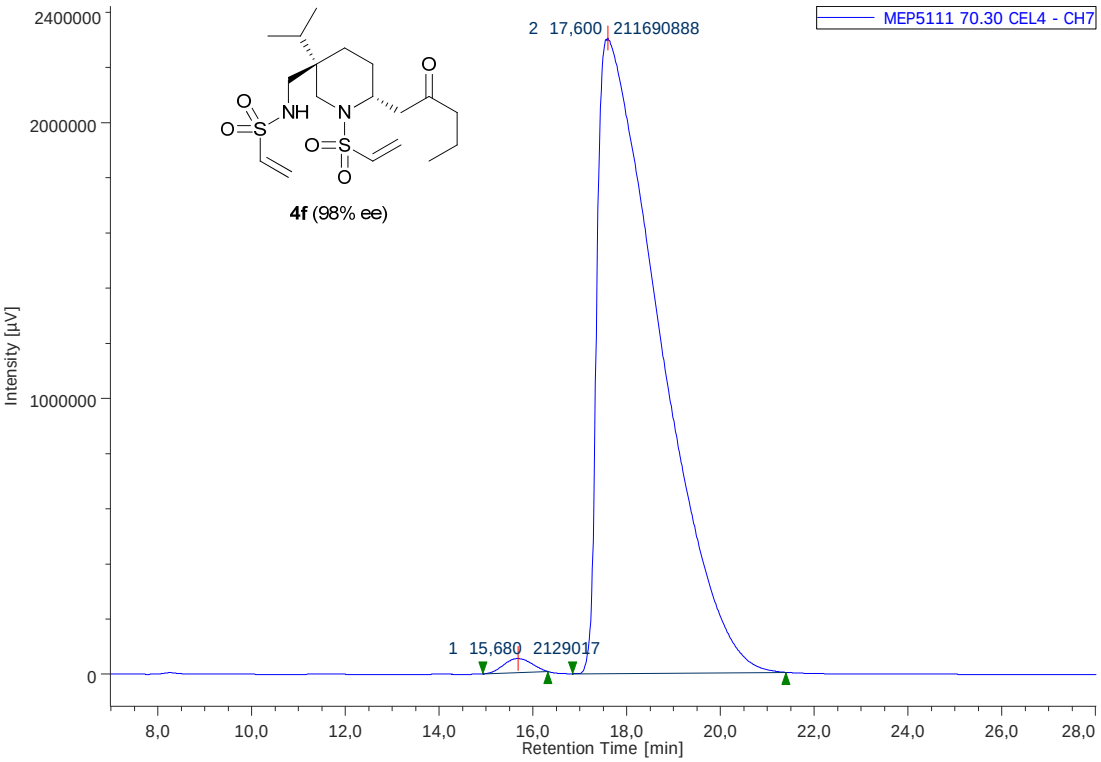

MEP4601 70.30 IC - CH6
110000
100000
50000
0
Intensity [µV]
1 39,013 5574776
2 83,107 5430457
4d (±)
30,0 35,0 40,0 45,0 50,0 55,0 60,0 65,0 70,0 75,0 80,0 85,0 90,0 95,0
Retention Time [min]

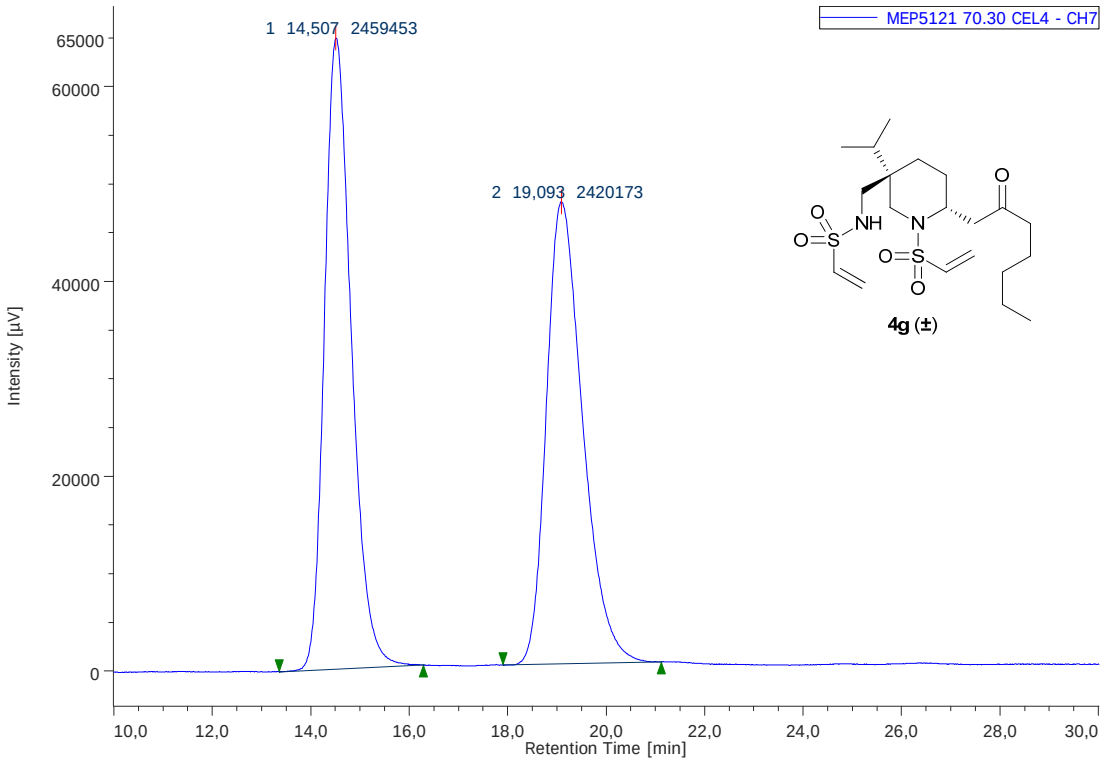

MEP4611 70.30 IC - CH7
45000
40000
20000
0
Intensity [µV]
2 82,213 8878819
1 39,520 202539
4d (98% ee)
30,0 35,0 40,0 45,0 50,0 55,0 60,0 65,0 70,0 75,0 80,0 85,0 90,0 95,0
Retention Time [min]

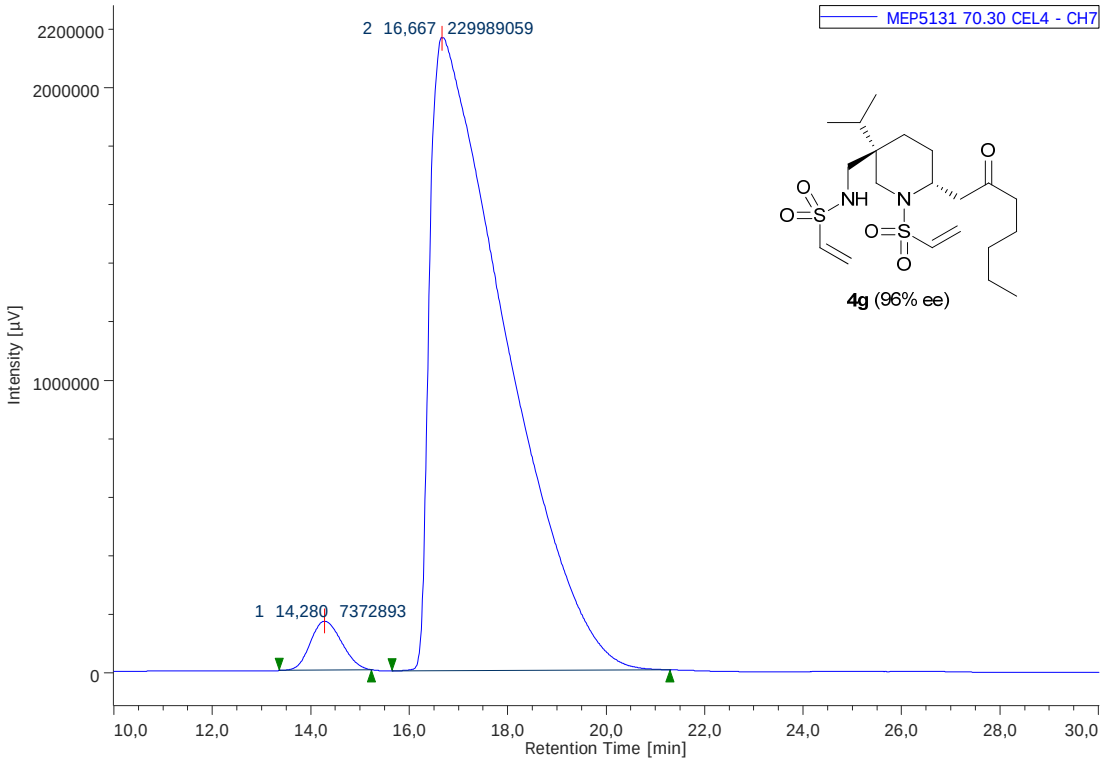

MEP5201 70.30 CEL4 - CH7
1 19,547 2513068
2 22,627 2508103
55000
40000
20000
0
Intensity [µV]
18,0
20,0
22,0
24,0
26,0
28,0
30,0
32,0
34,0
Retention Time [min]
4e (±)

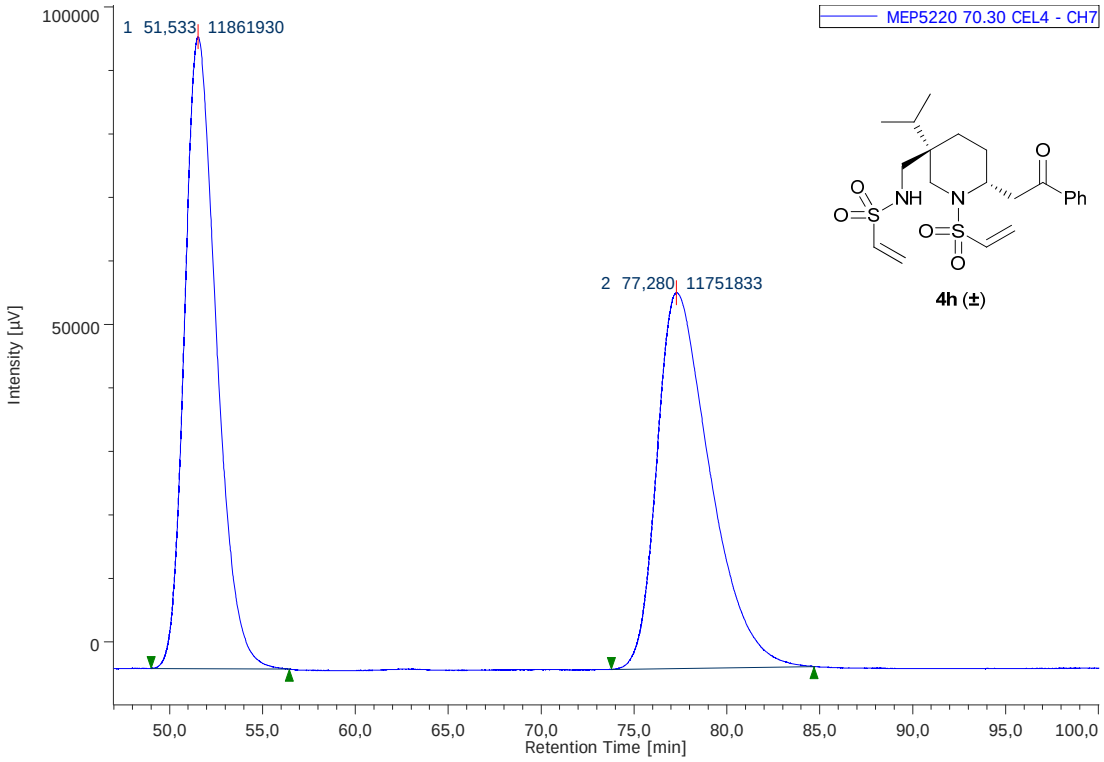

MEP5211 70.30 CEL4 - CH7
2 21,747 32699700
1 19,453 257541
550000
400000
200000
0
Intensity [µV]
18,0
20,0
22,0
24,0
26,0
28,0
30,0
32,0
34,0
Retention Time [min]
4e (98% ee)

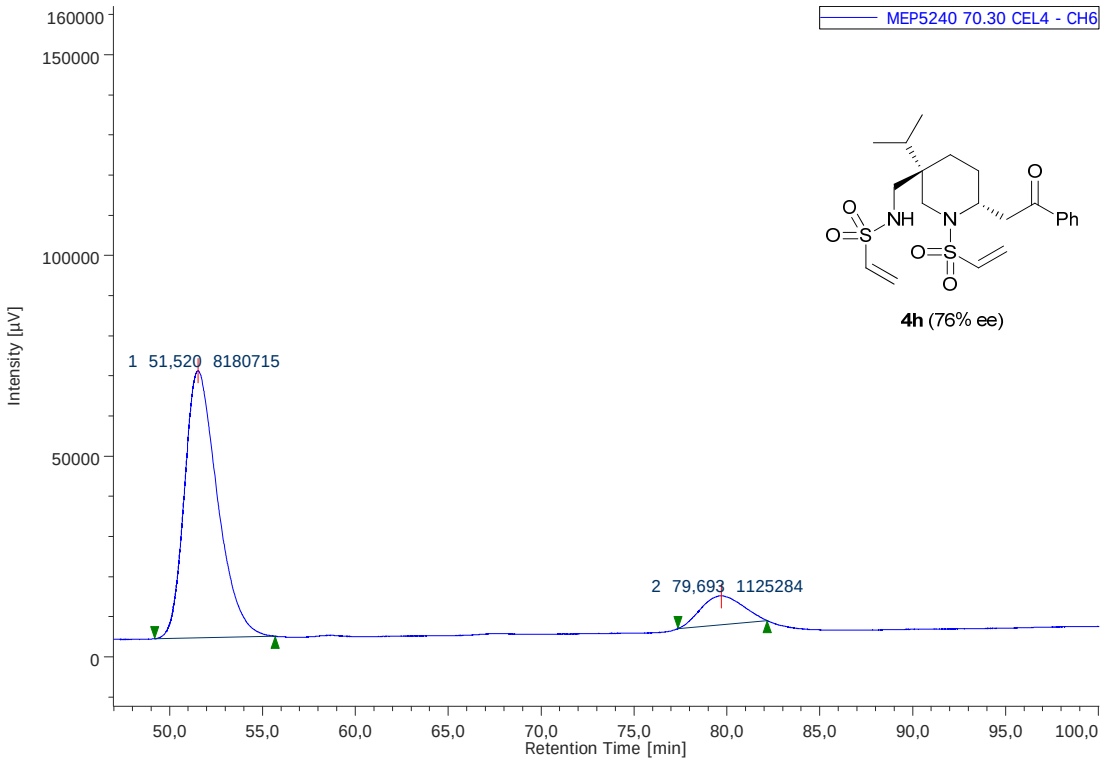

MEP5101 70.30 CEL4 - CH7
1 16,000 1033513
2 19,893 1034906
4f (±)
Intensity [µV]
Retention Time [min]

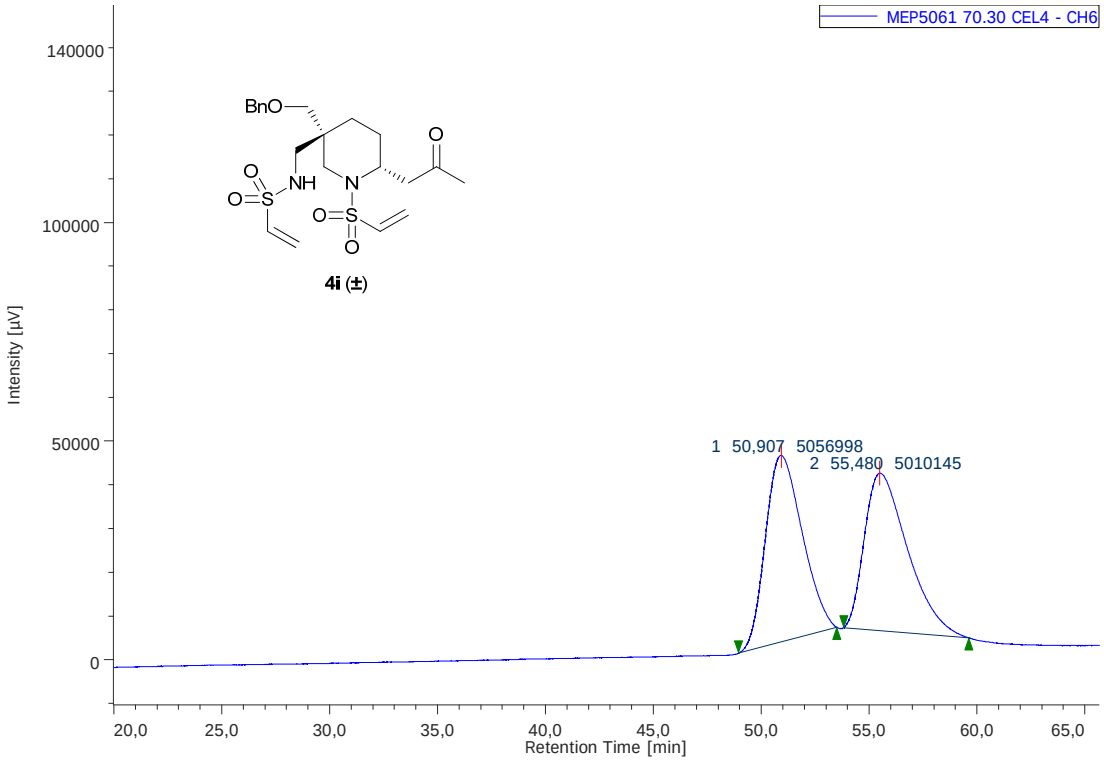

MEP5111 70.30 CEL4 - CH7
2 17,600 211690888
1 15,680 2129017
4f (98% ee)
Intensity [µV]
Retention Time [min]

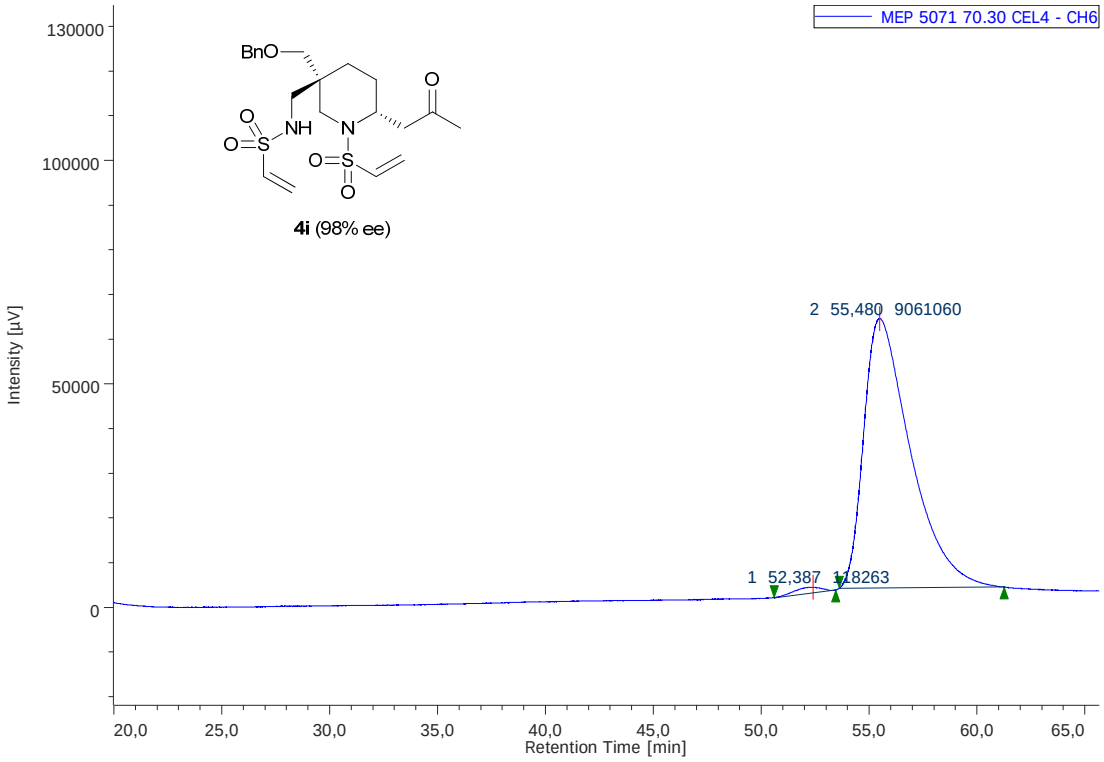

MEP5121 70.30 CEL4 - CH7
1 14,507 2459453
2 19,093 2420173
65000
60000
40000
20000
0
Intensity [µV]
10,0
12,0
14,0
16,0
18,0
20,0
22,0
24,0
26,0
28,0
30,0
Retention Time [min]
4g (±)

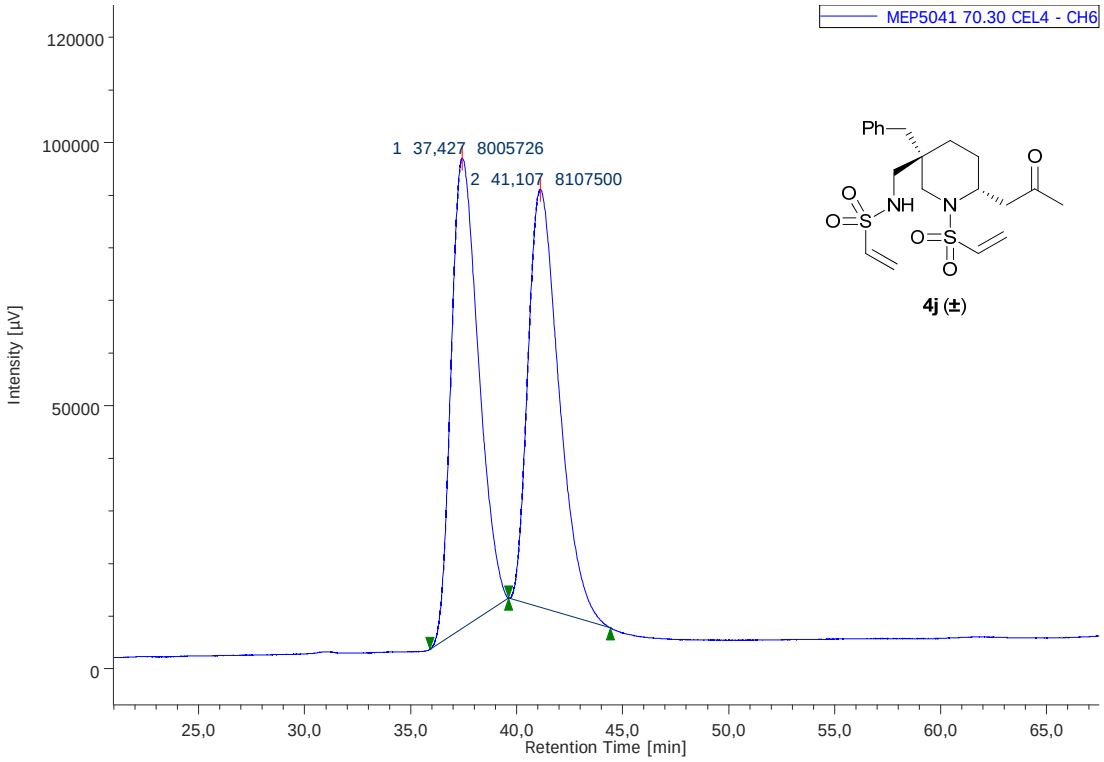

MEP5131 70.30 CEL4 - CH7
2 16,667 229989059
1 14,280 7372893
2200000
2000000
1000000
0
Intensity [µV]
10,0
12,0
14,0
16,0
18,0
20,0
22,0
24,0
26,0
28,0
30,0
Retention Time [min]
4g (96% ee)

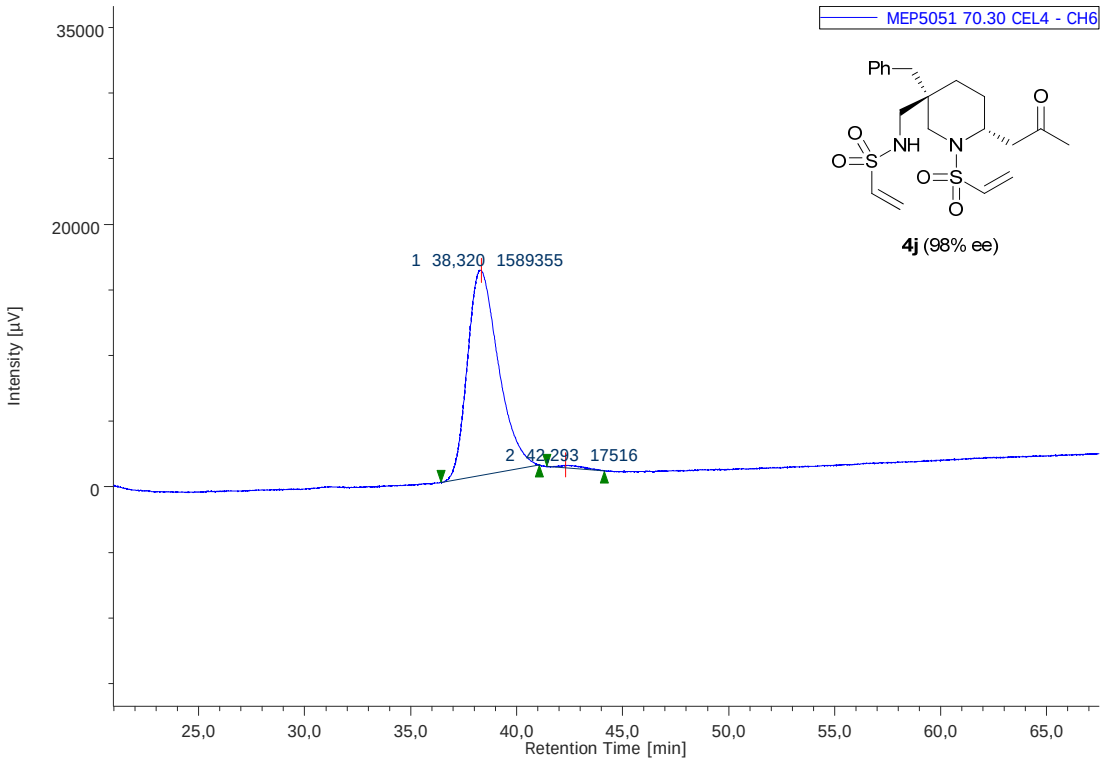

MEP5220 70.30 CEL4 - CH7
1 51,533 11861930
2 77,280 11751833
4h (±)
Intensity [µV]
Retention Time [min]

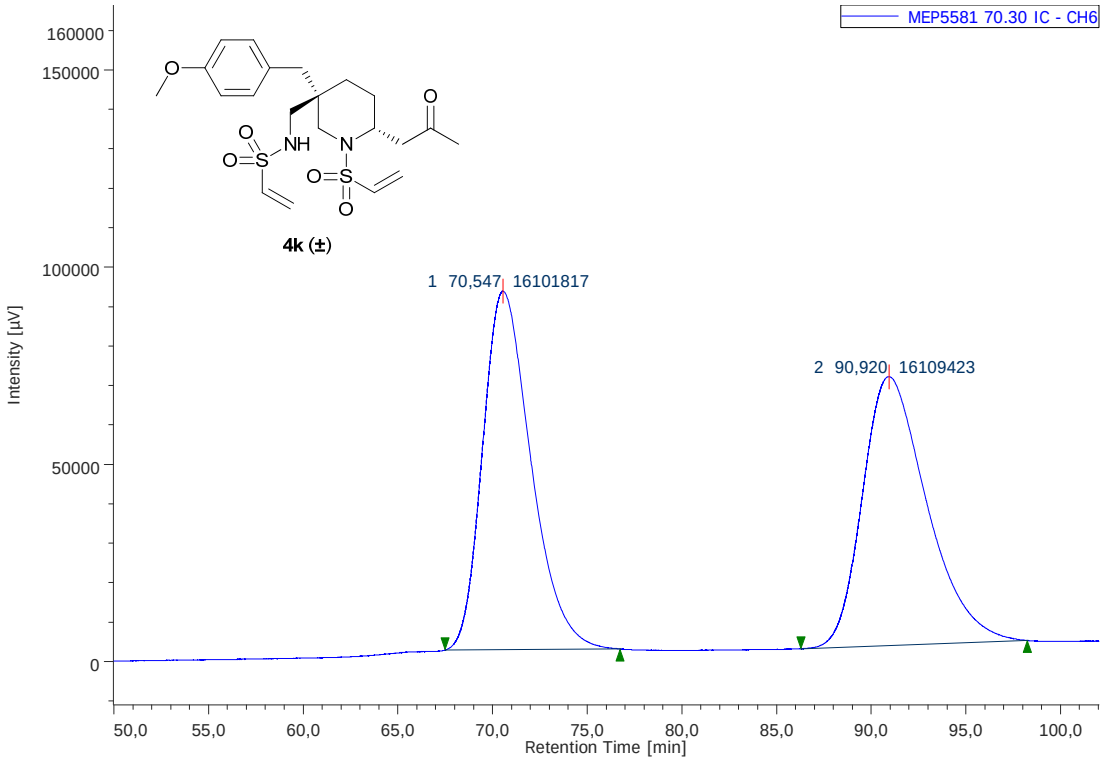

MEP5240 70.30 CEL4 - CH6
1 51,520 8180715
2 79,693 1125284
4h (76% ee)
Intensity [µV]
Retention Time [min]

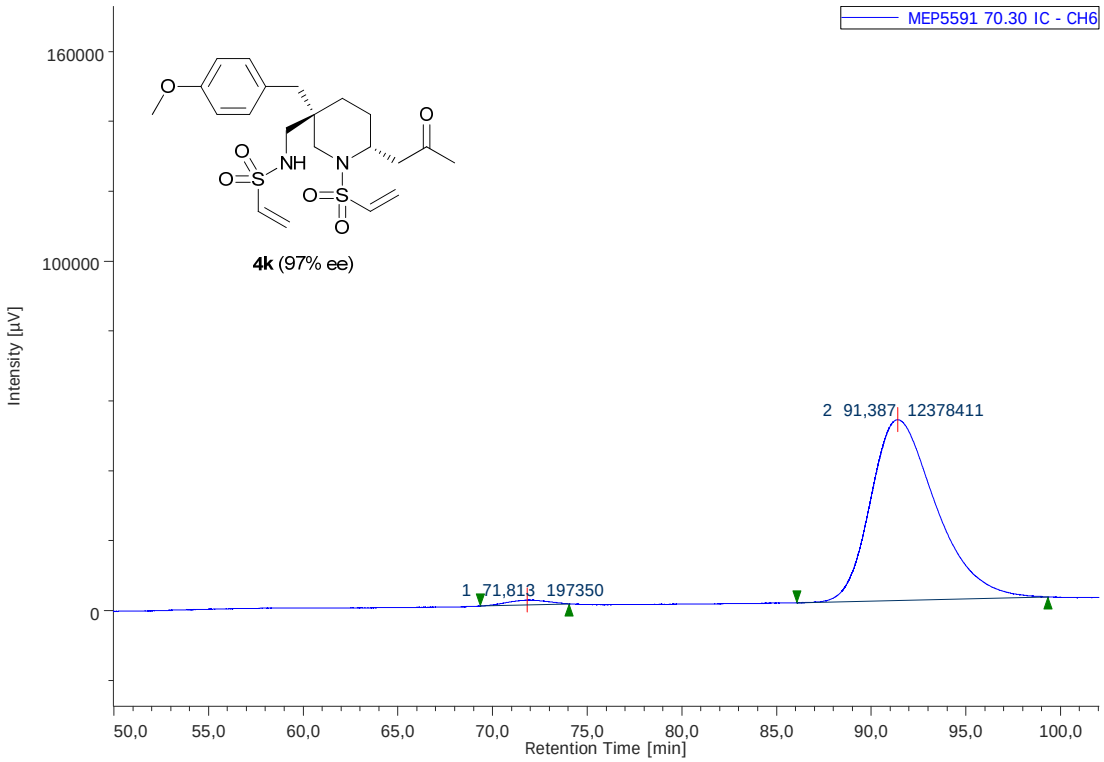

MEP5061 70.30 CEL4 - CH6
140000
100000
50000
0
Intensity [µV]
BnO
O
NH
N
O=S
O=S
O
O
4i (±)
1 50,907 5056998
2 55,480 5010145
20,0
25,0
30,0
35,0
40,0
45,0
50,0
55,0
60,0
65,0
Retention Time [min]

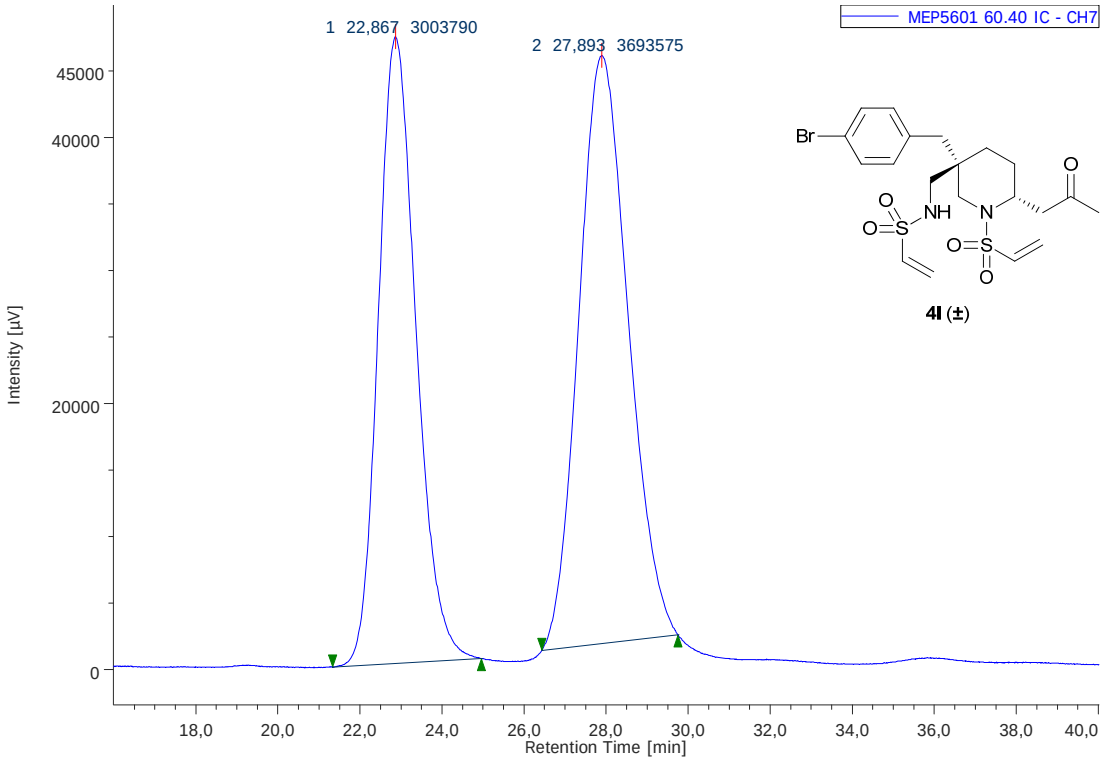

MEP 5071 70.30 CEL4 - CH6
130000
100000
50000
0
Intensity [µV]
BnO
O
NH
N
O=S
O=S
O
O
4i (98% ee)
2 55,480 9061060
1 52,387 118263
20,0
25,0
30,0
35,0
40,0
45,0
50,0
55,0
60,0
65,0
Retention Time [min]

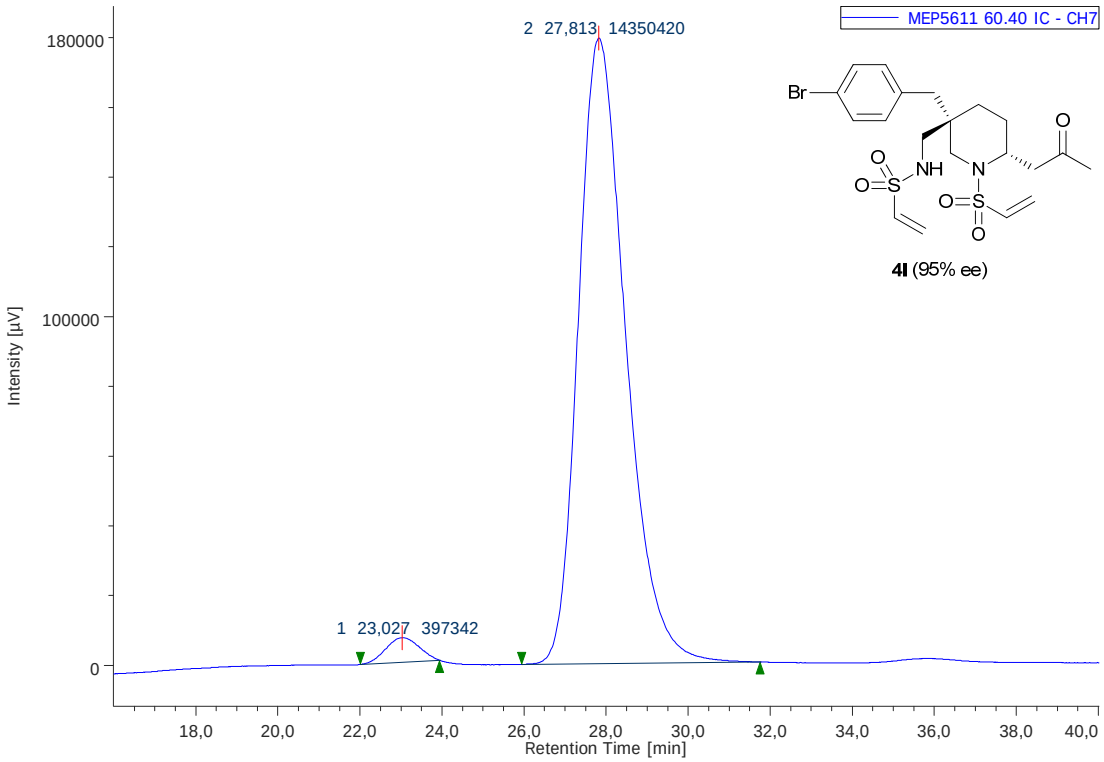

MEP5041 70.30 CEL4 - CH6
120000
100000
50000
0
Intensity [µV]
1 37,427 8005726
2 41,107 8107500
25,0
30,0
35,0
40,0
45,0
50,0
55,0
60,0
65,0
Retention Time [min]
Ph
NH
N
O
S
4j (±)

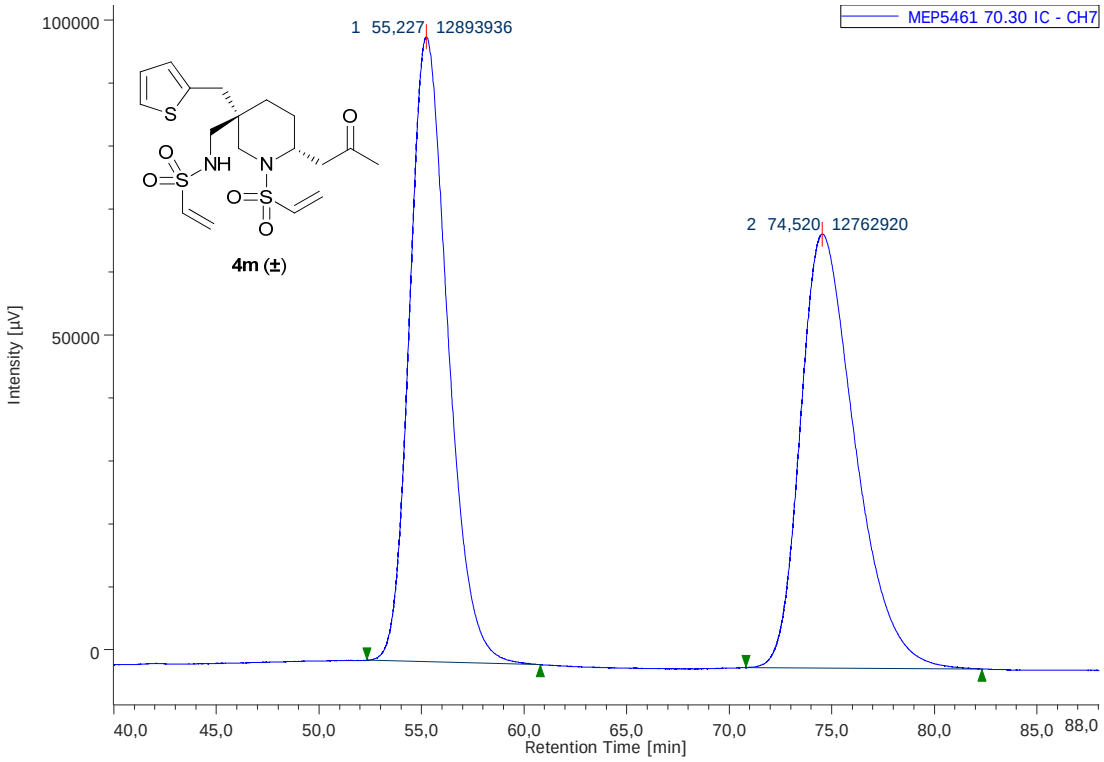

MEP5051 70.30 CEL4 - CH6
35000
20000
0
Intensity [µV]
1 38,320 1589355
2 42,293 17516
25,0
30,0
35,0
40,0
45,0
50,0
55,0
60,0
65,0
Retention Time [min]
Ph
NH
N
O
S
4j (98% ee)

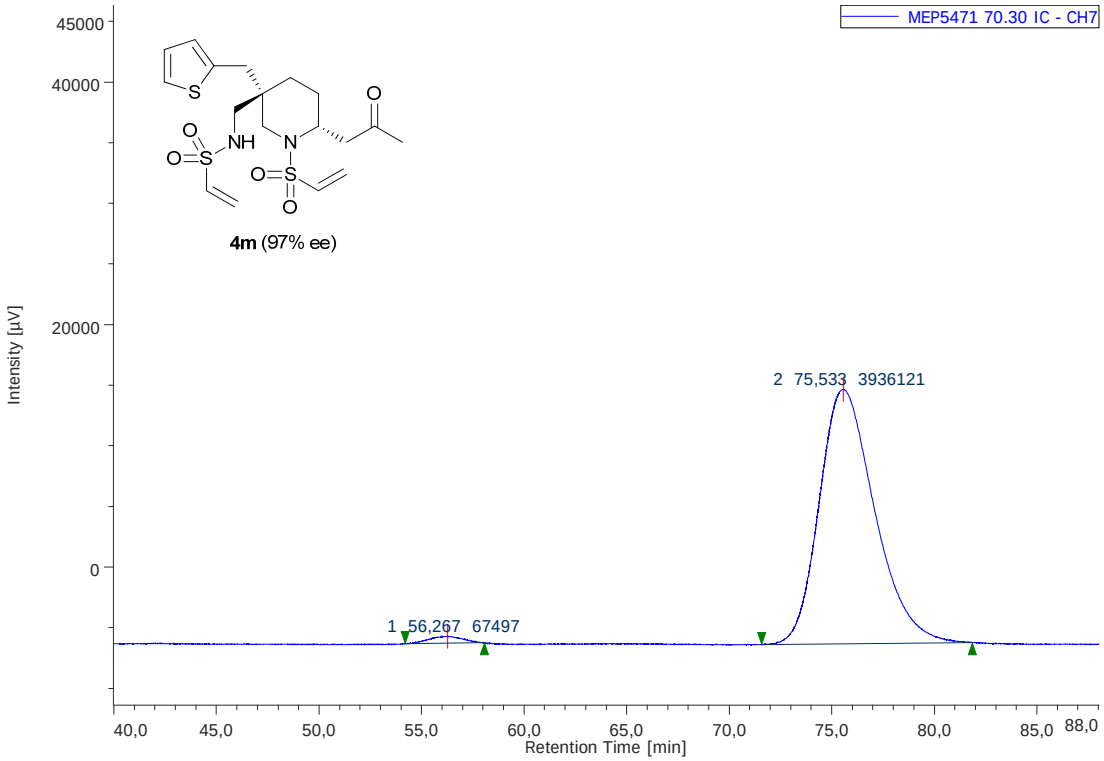

MEP5581 70.30 IC - CH6
4k (±)
1 70,547 16101817
2 90,920 16109423
Intensity [µV]
Retention Time [min]


MEP5591 70.30 IC - CH6
4k (97% ee)
1 71,813 197350
2 91,387 12378411
Intensity [µV]
Retention Time [min]


MEP5601 60.40 IC - CH7
1 22,867 3003790
2 27,893 3693575
45000
40000
20000
0
Intensity [µV]
18,0
20,0
22,0
24,0
26,0
28,0
30,0
32,0
34,0
36,0
38,0
40,0
Retention Time [min]
Br
NH
N
O
O=S
O=S
O
4l (±)

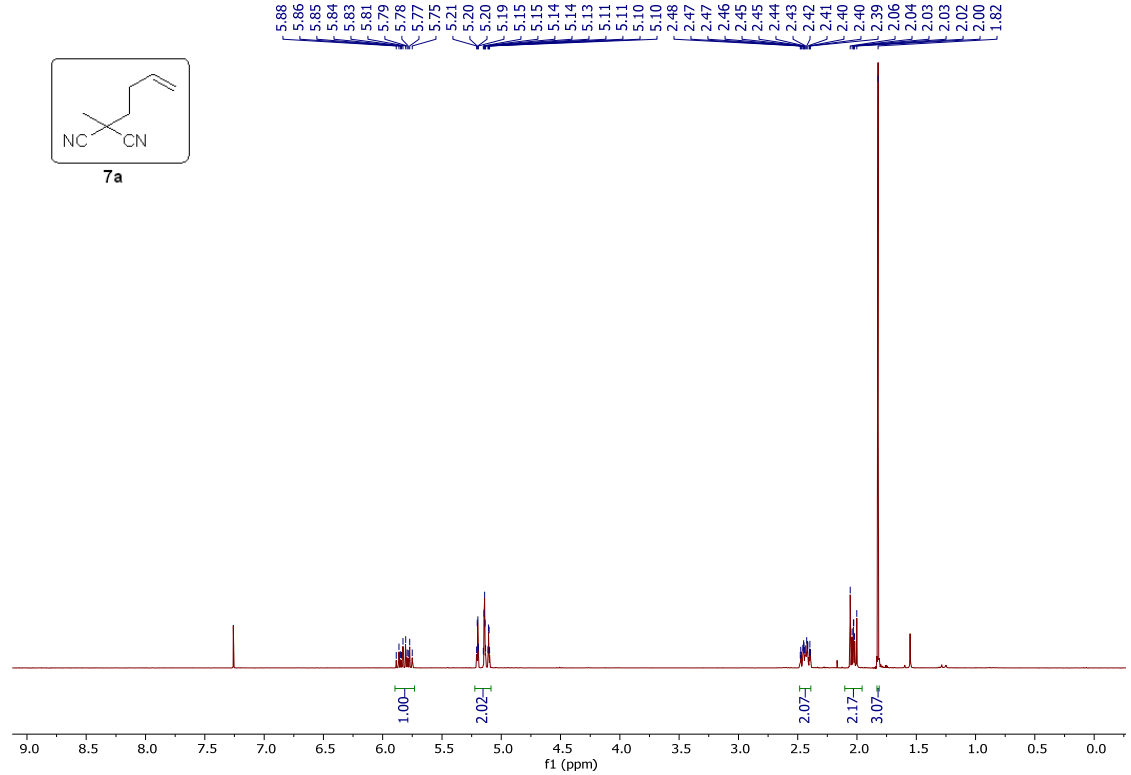

MEP5611 60.40 IC - CH7
2 27,813 14350420
1 23,027 397342
180000
100000
0
Intensity [µV]
18,0
20,0
22,0
24,0
26,0
28,0
30,0
32,0
34,0
36,0
38,0
40,0
Retention Time [min]
Br
NH
N
O
O=S
O=S
O
4l (95% ee)

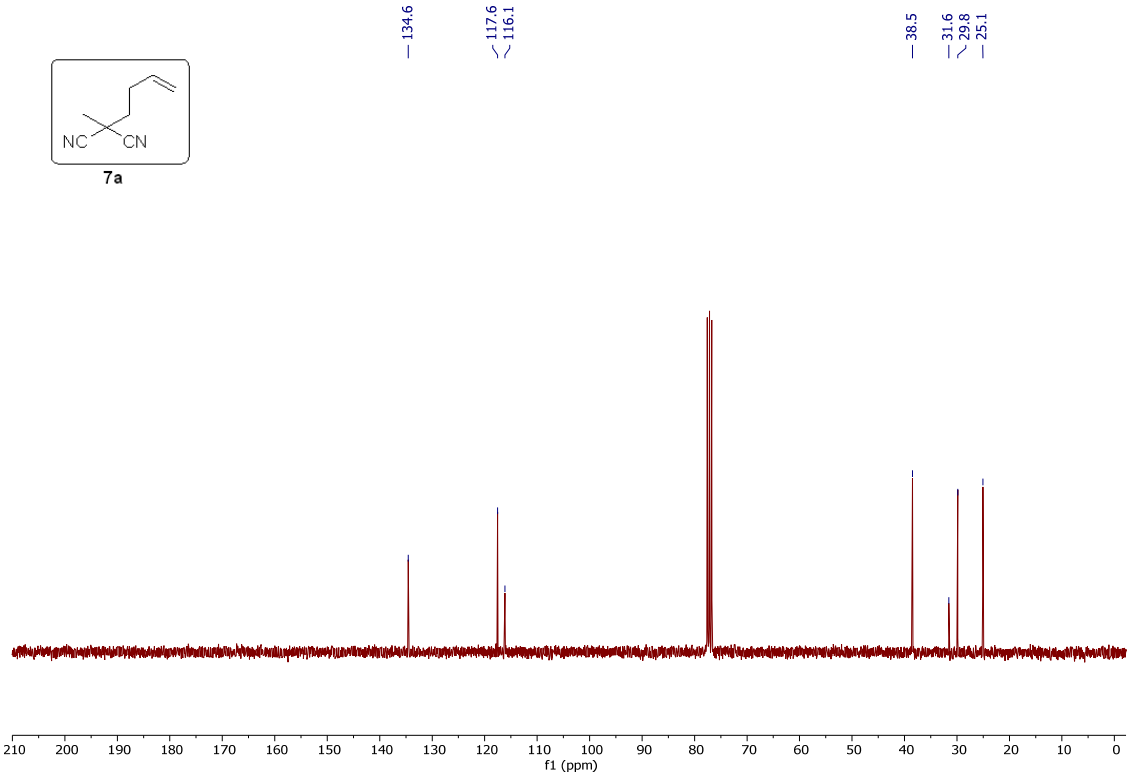

MEP5461 70.30 IC - CH7
1 55,227 12893936
2 74,520 12762920
4m (±)
Intensity [µV]
Retention Time [min]


MEP5471 70.30 IC - CH7
4m (97% ee)
1 56,267 67497
2 75,533 3936121
Intensity [µV]
Retention Time [min]

NMR SPECTRA OF NEW COMPOUNDS:

^{1}H and ^{13}C NMR spectra of compounds **4a,b** and **5a,b**, were carried out in DMSO-d_6 at 75 °C because of the presence of rotamers.






7.42
7.42
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7.40
7.39
7.39
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7.38
7.37
7.37
7.36
7.36
7.35
5.88
5.86
5.84
5.83
5.82
5.80
5.79
5.78
5.76
5.74
5.20
5.20
5.19
5.19
5.14
5.14
5.13
5.13
5.13
5.10
5.10
5.10
5.09
3.23
2.53
2.52
2.51
2.50
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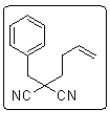
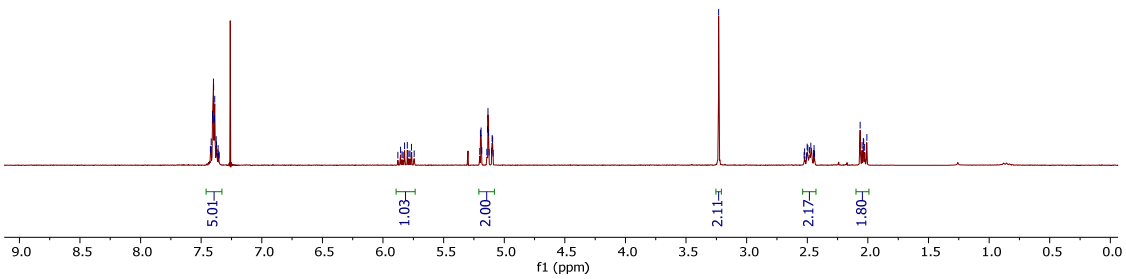
2.06
2.05
2.04
2.03
2.03
2.01


NC
CN

7b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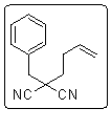
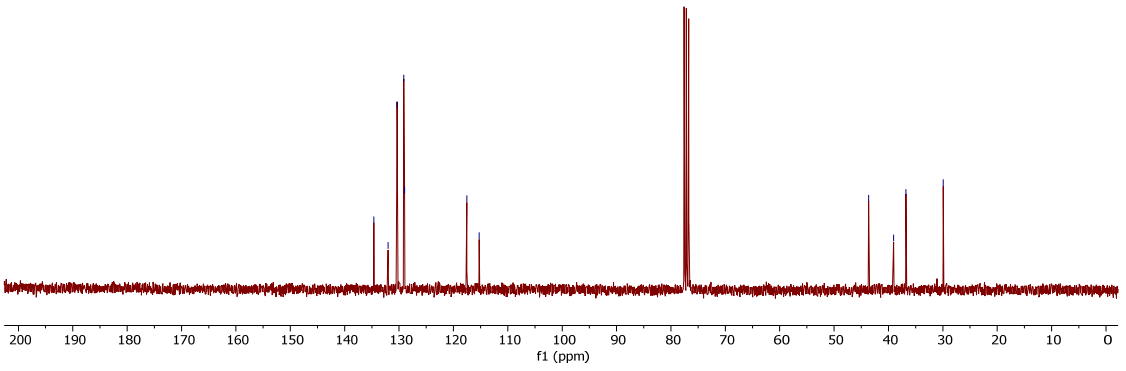
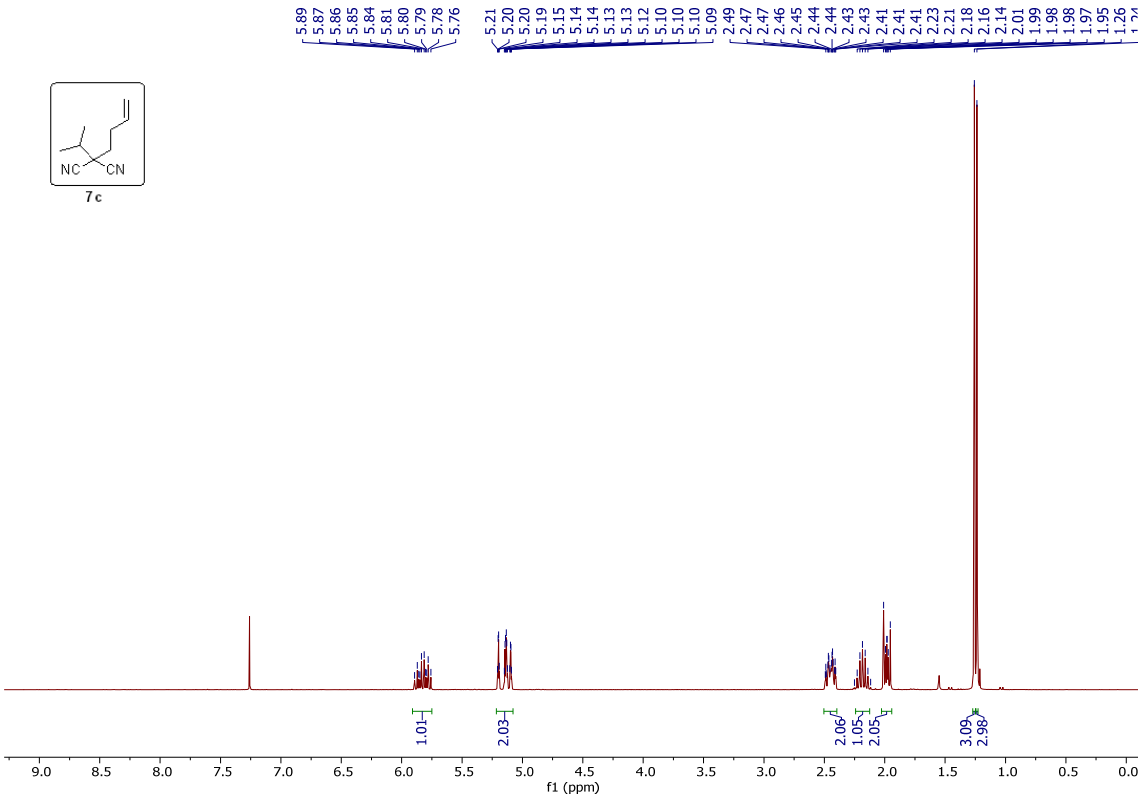
1.03
2.00
2.11
2.17
1.80
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


134.7
132.0
130.4
129.1
129.0
117.5
115.3
43.6
39.1
36.8
29.9


NC
CN

7b


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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5.87
5.86
5.85
5.84
5.81
5.80
5.79
5.78
5.76
5.21
5.20
5.20
5.19
5.15
5.14
5.14
5.13
5.13
5.12
5.10
5.10
5.10
5.09
2.49
2.47
2.47
2.46
2.45
2.44
2.44
2.43
2.43
2.41
2.41
2.41
2.23
2.21
2.18
2.16
2.14
2.01
1.99
1.98
1.98
1.97
1.95
1.26
NC
CN
7c
1.01
2.03
2.06
1.05
2.05
3.09
2.98
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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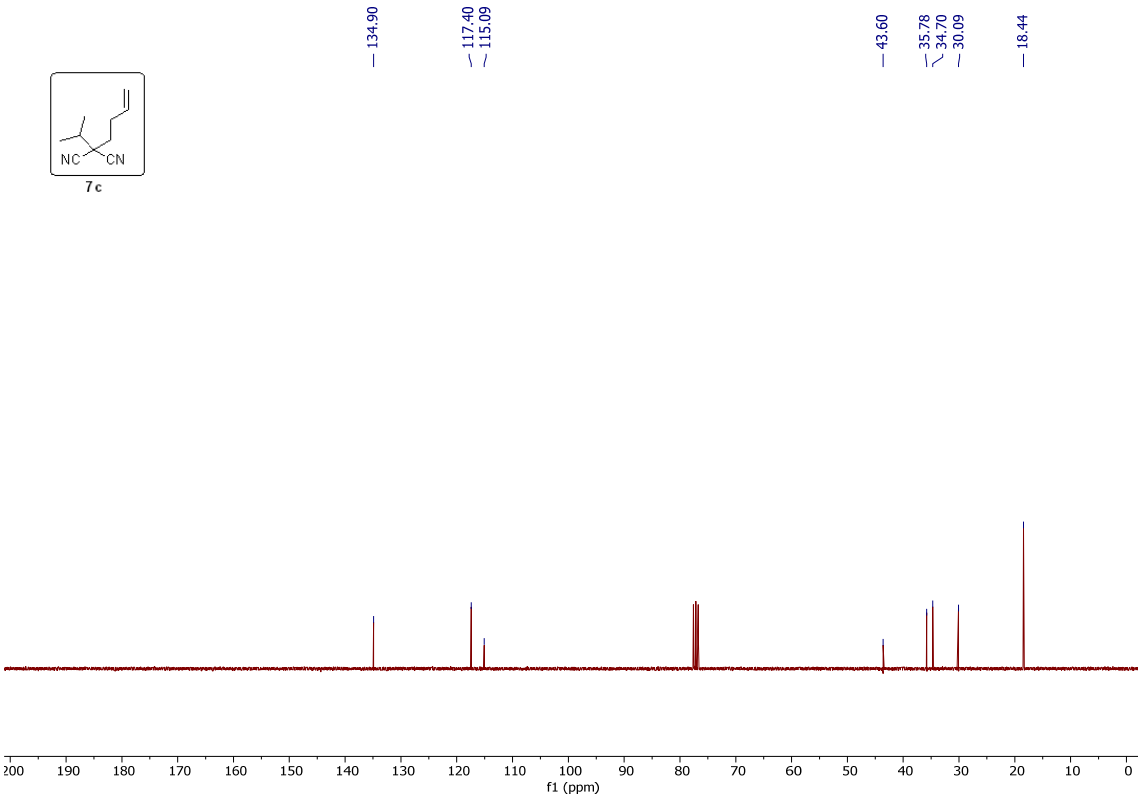
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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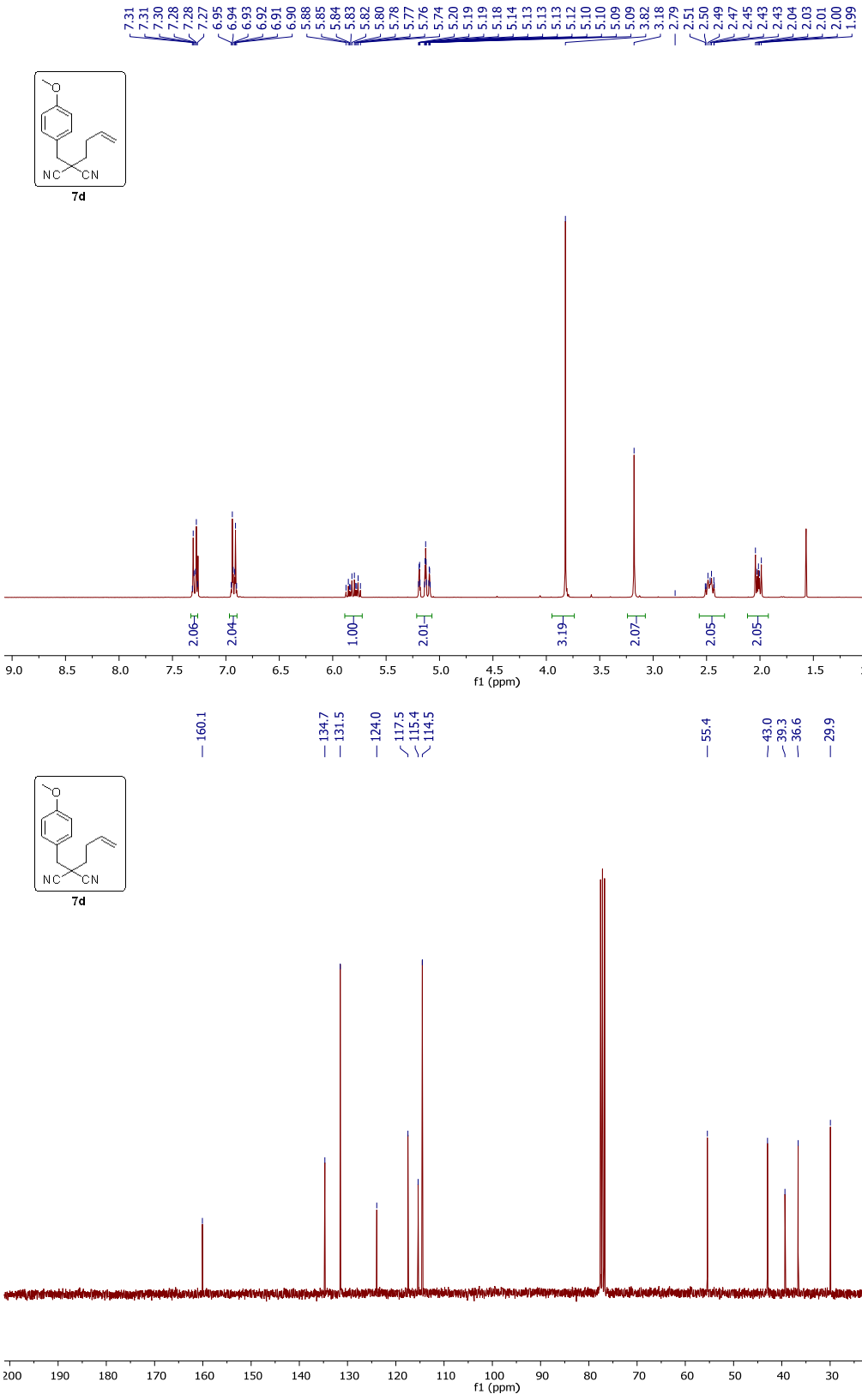
117.40
115.09
43.60
35.78
34.70
30.09
18.44
NC
CN
7c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.30
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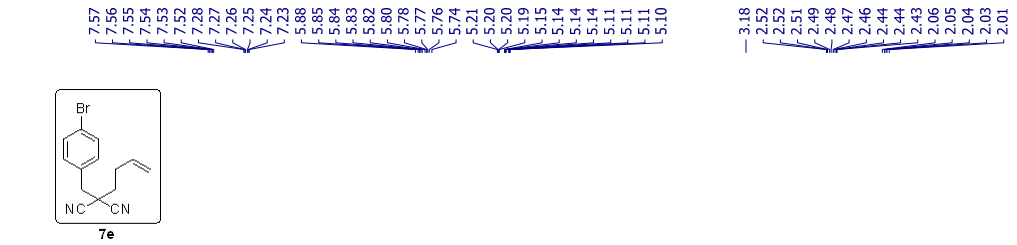
7.28
7.27
6.95
6.94
6.93
6.92
6.91
6.90
5.88
5.85
5.84
5.83
5.82
5.80
5.78
5.77
5.76
5.74
5.20
5.19
5.19
5.18
5.14
5.13
5.13
5.13
5.12
5.10
5.10
5.09
5.09
3.82
3.18
2.79
2.51
2.50
2.49
2.47
2.45
2.43
2.43
2.04
2.03
2.01
2.00
1.99
NC
CN
7d
2.06
2.04
1.00
2.01
3.19
2.07
2.05
2.05
f1 (ppm)
160.1
134.7
131.5
124.0
117.5
115.4
114.5
55.4
43.0
39.3
36.6
29.9
NC
CN
7d
f1 (ppm)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7.52
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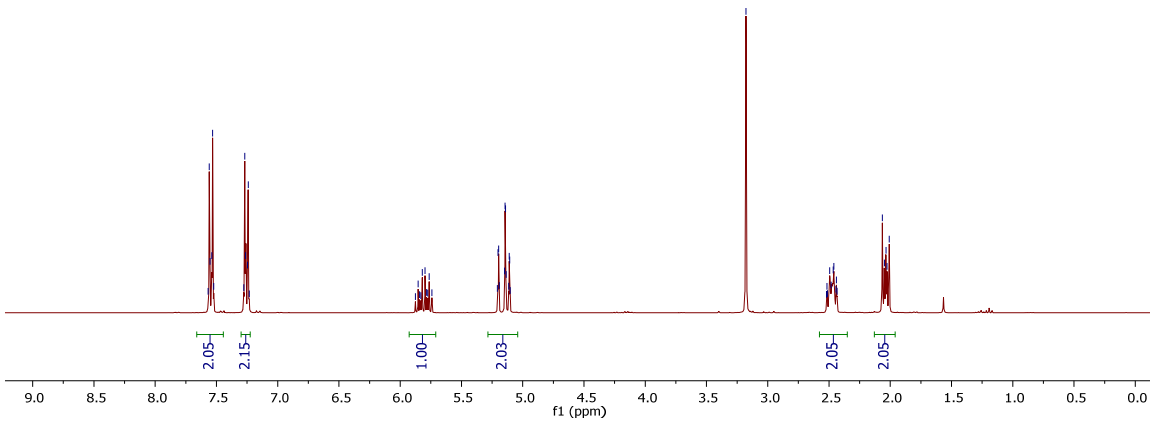
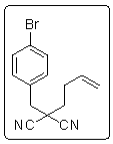
7.26
7.25
7.24
7.23
5.88
5.85
5.84
5.83
5.82
5.80
5.78
5.77
5.76
5.74
5.21
5.20
5.19
5.15
5.14
5.14
5.11
5.11
5.11
5.10
3.18
2.52
2.52
2.51
2.49
2.48
2.47
2.46
2.44
2.44
2.43
2.06
2.05
2.04
2.03
2.01

Br
NC
CN

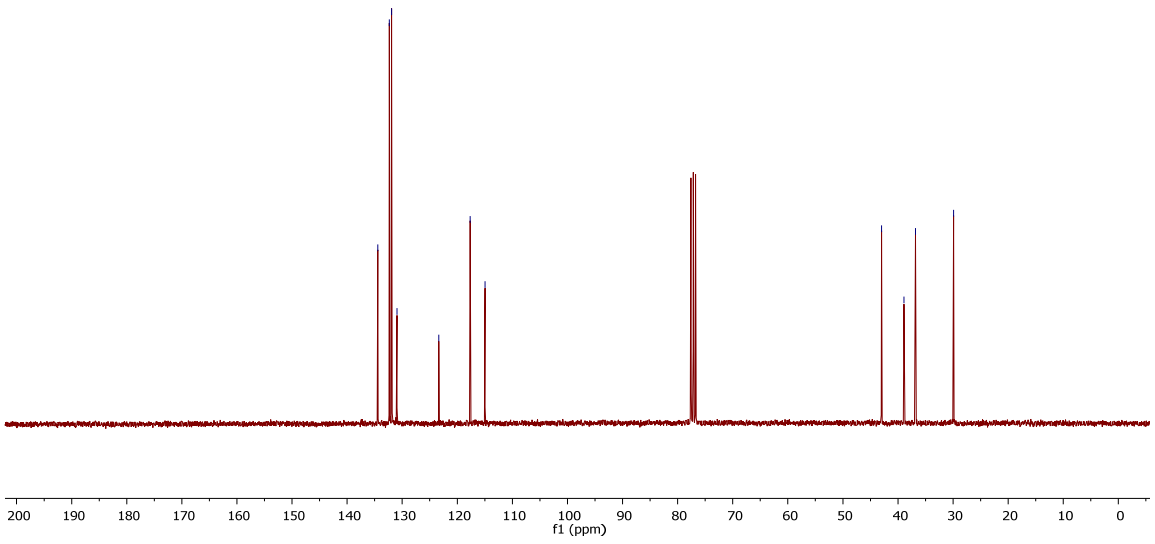
7e


2.05
2.15
1.00
2.03
2.05
2.05
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
0.0
f1 (ppm)


134.4
132.3
131.9
131.0
123.4
117.7
115.0
43.0
38.9
36.8
29.9


Br
NC
CN

7e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190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.34
7.34
7.33
7.32
7.16
7.16
7.16
7.15
7.15
7.15
7.07
7.06
7.05
7.04
5.88
5.86
5.84
5.83
5.82
5.80
5.79
5.78
5.77
5.74
5.21
5.20
5.20
5.19
5.15
5.15
5.14
5.14
5.13
5.11
5.11
5.10
5.10
3.49
2.52
2.51
2.51
2.49
2.47
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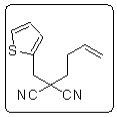
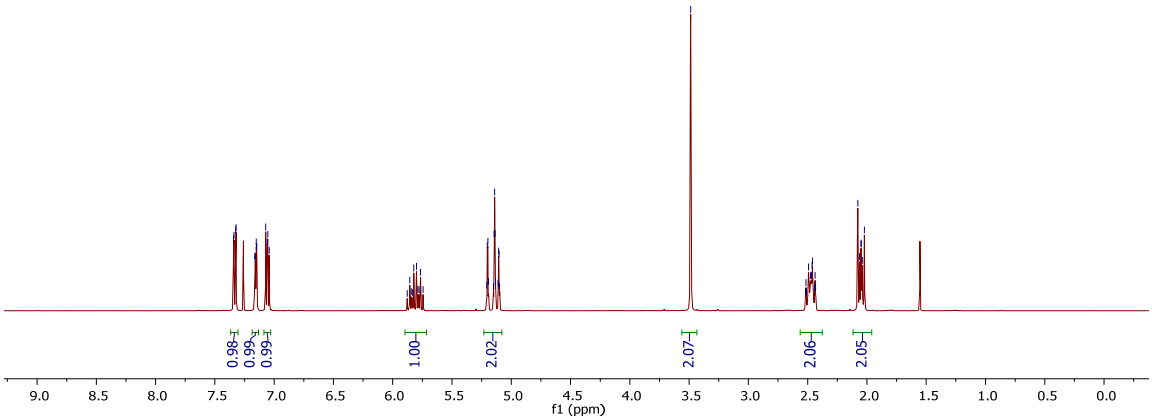
2.08
2.06
2.05
2.05
2.04
2.02


S
NC
CN

7f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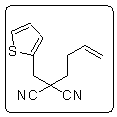
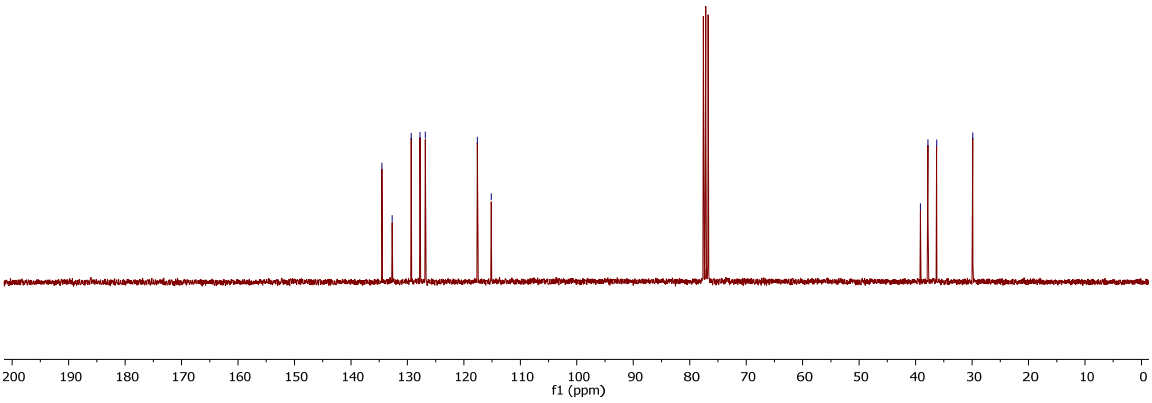
0.99
0.99
1.00
2.02
2.07
2.06
2.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

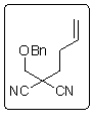

134.5
132.7
129.3
127.8
126.8
117.6
115.2
39.1
37.8
36.3
29.9


S
NC
CN

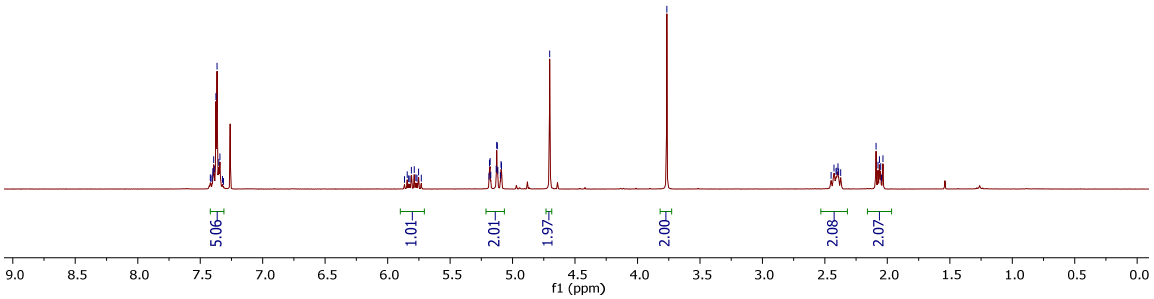
7f

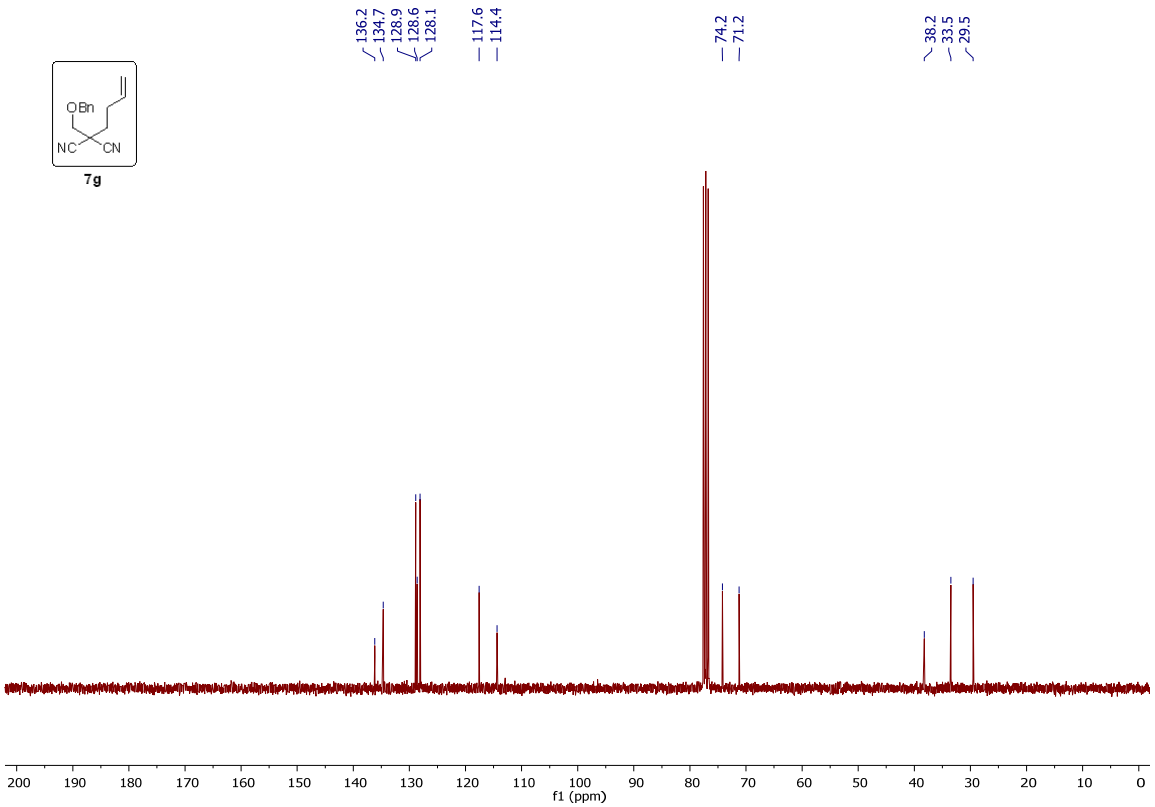

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.42
7.41
7.40
7.40
7.39
7.39
7.37
7.37
7.35
7.34
7.32
7.31
5.87
5.84
5.83
5.82
5.81
5.79
5.77
5.76
5.75
5.73
5.19
5.18
5.18
5.17
5.13
5.13
5.12
5.12
5.10
5.09
5.09
4.70
3.77
2.45
2.43
2.41
2.40
2.40
2.39
2.37
2.09
2.07
2.06
2.05
2.05
2.04


OBn
NC
CN

7g

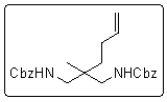

5.06
1.01
2.01
1.97
2.00
2.08
2.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


136.2
134.7
128.9
128.6
128.1
117.6
114.4
74.2
71.2
38.2
33.5
29.5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

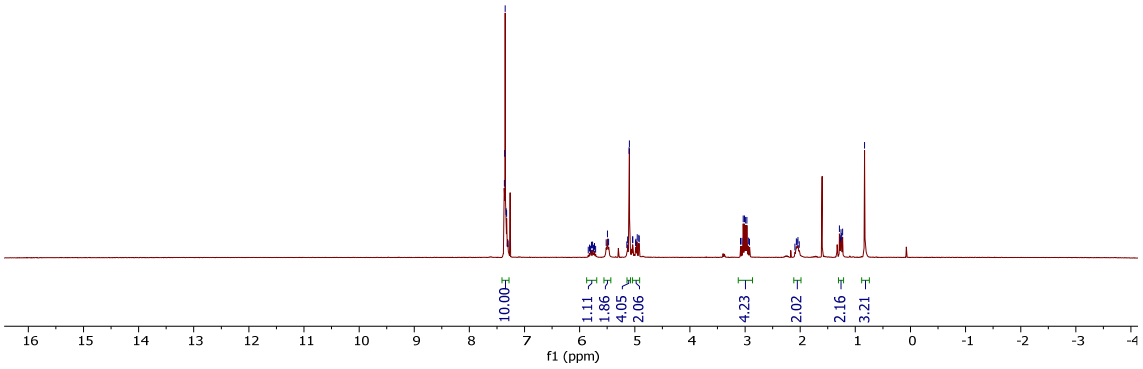
OBn
NC
CN

7g

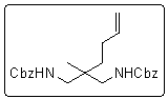

7.37
7.36
7.35
7.33
7.32
7.30
5.84
5.82
5.81
5.80
5.79
5.77
5.75
5.74
5.73
5.71
5.52
5.50
5.47
5.15
5.13
5.10
5.10
5.04
5.04
4.98
4.98
4.96
4.93
4.92
3.08
3.06
3.03
3.01
2.99
2.97
2.94
2.92
2.09
2.07
2.06
2.04
2.02
1.29
1.27
1.26
1.25
1.23
0.83


CbzHN
NHCbz

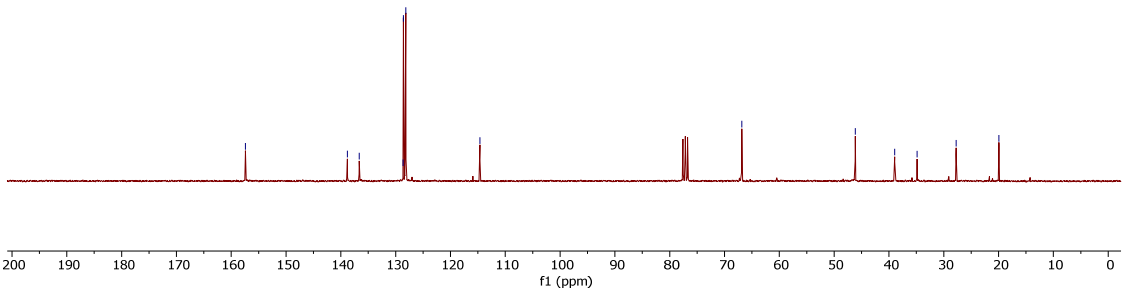
1a

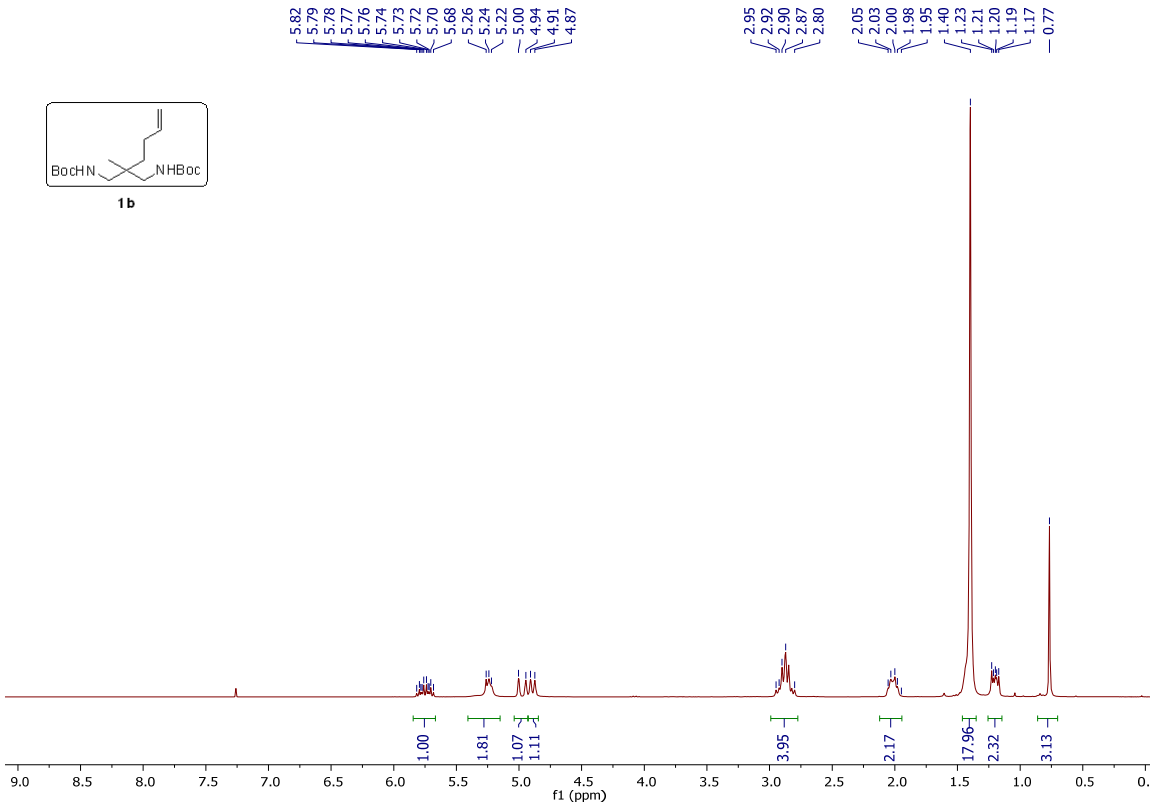

10.00
1.11
1.86
4.05
2.06
4.23
2.02
2.16
3.21
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

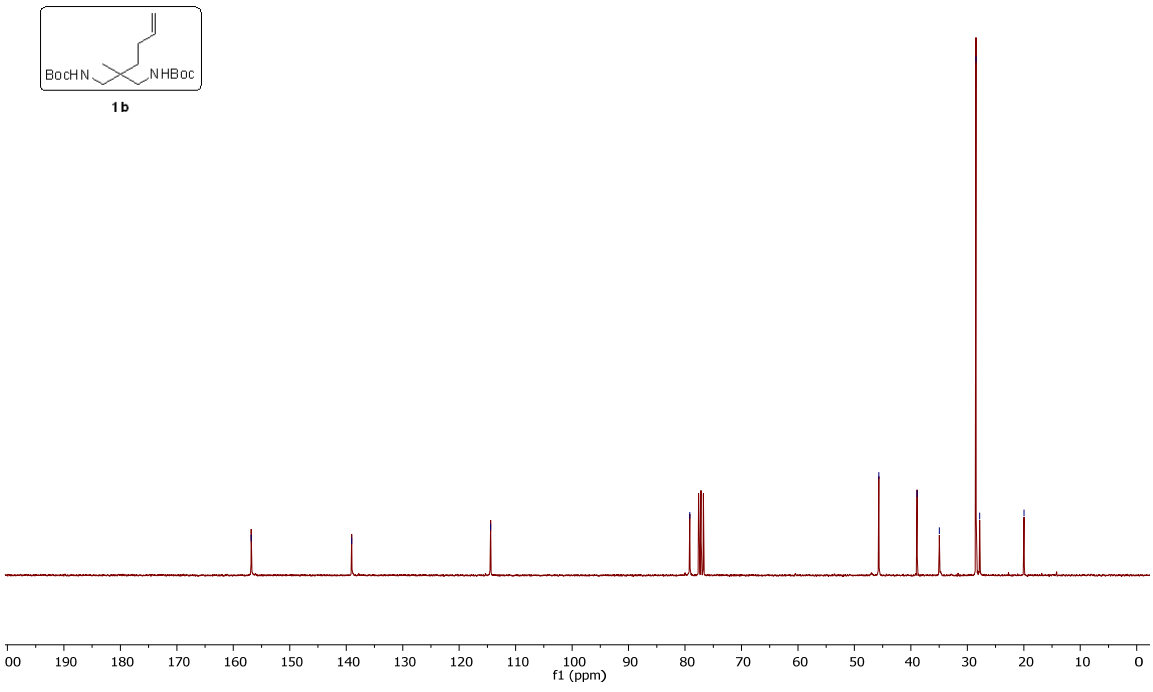

157.4
138.8
136.7
128.7
128.6
128.2
114.6
66.9
46.1
39.0
34.9
27.7
19.9


CbzHN
NHCbz

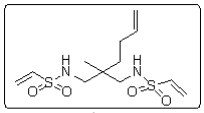
1a


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

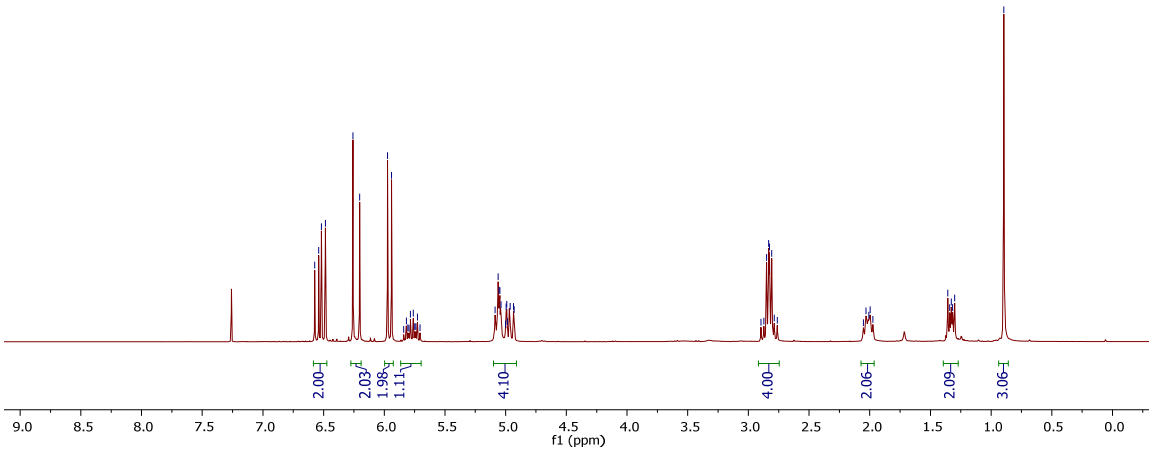

5.82
5.79
5.78
5.77
5.76
5.74
5.73
5.72
5.70
5.68
5.26
5.24
5.22
5.00
4.94
4.91
4.87
2.95
2.92
2.90
2.87
2.80
2.05
2.03
2.00
1.98
1.95
1.40
1.23
1.21
1.20
1.19
1.17
0.77
BocHN
NHBoc
1b
1.00
1.81
1.07
1.11
3.95
2.17
17.96
2.32
3.13
f1 (ppm)
156.8
139.0
114.4
79.1
45.7
38.9
35.0
28.5
27.8
20.0

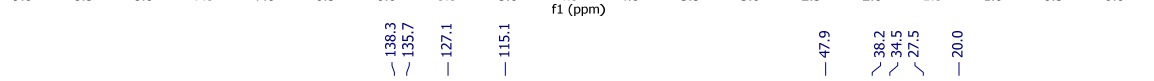

BocHN
NHBoc
1b
f1 (ppm)

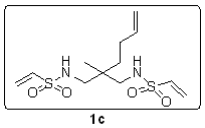

6.57
6.54
6.52
6.49
6.26
6.20
5.97
5.94
5.84
5.82
5.81
5.80
5.78
5.76
5.75
5.74
5.73
5.71
5.09
5.06
5.05
5.05
5.04
5.00
5.00
4.99
4.99
4.96
4.94
4.93
2.90
2.87
2.85
2.83
2.83
2.81
2.79
2.76
2.05
2.03
2.01
2.00
1.97
1.36
1.34
1.33
1.32
1.30
0.90



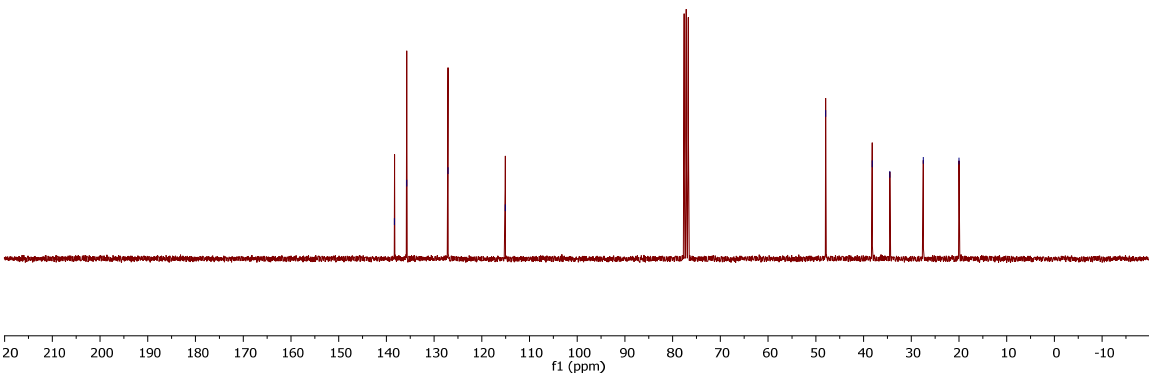
1c

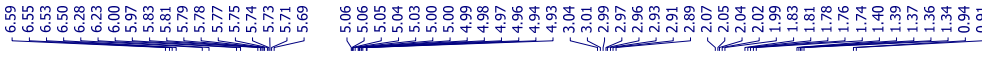

2.00
2.03
1.98
1.11
4.10
4.00
2.06
2.09
3.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

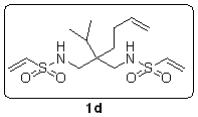

138.3
135.7
127.1
115.1
47.9
38.2
34.5
27.5
20.0



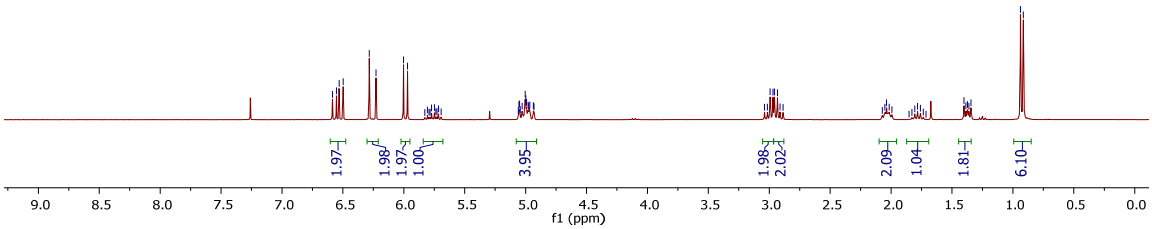
1c


20
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)

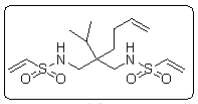

6.59
6.55
6.53
6.50
6.28
6.23
6.00
5.97
5.83
5.81
5.79
5.78
5.77
5.75
5.74
5.73
5.71
5.69
5.06
5.06
5.05
5.04
5.03
5.00
5.00
4.99
4.98
4.97
4.96
4.94
4.93
3.04
3.01
2.99
2.97
2.96
2.93
2.91
2.89
2.07
2.05
2.04
2.02
1.99
1.83
1.81
1.78
1.76
1.74
1.40
1.39
1.37
1.36
1.34
0.94



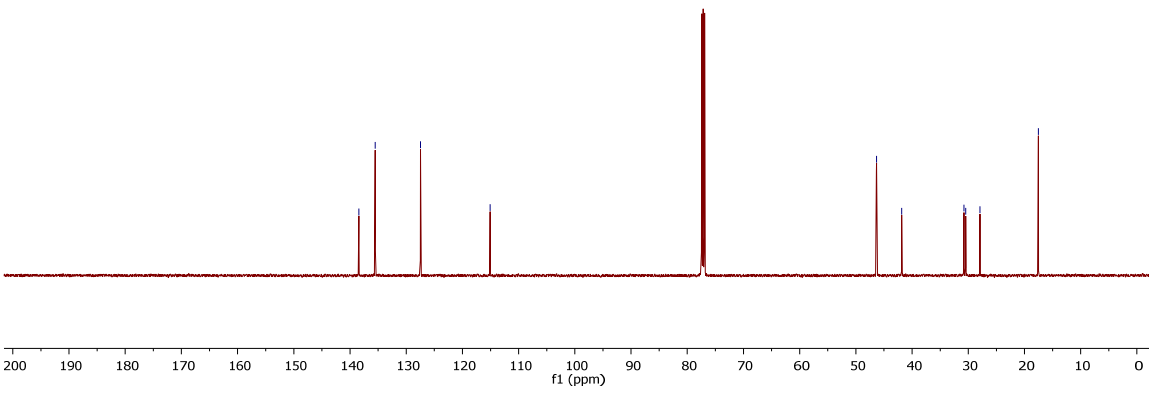
1d


1.97
1.98
1.97
1.00
3.95
1.98
2.02
2.09
1.04
1.81
6.10
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
0.0
f1 (ppm)

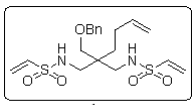

138.4
135.5
127.5
115.1
46.3
41.8
30.8
30.5
27.9
17.5



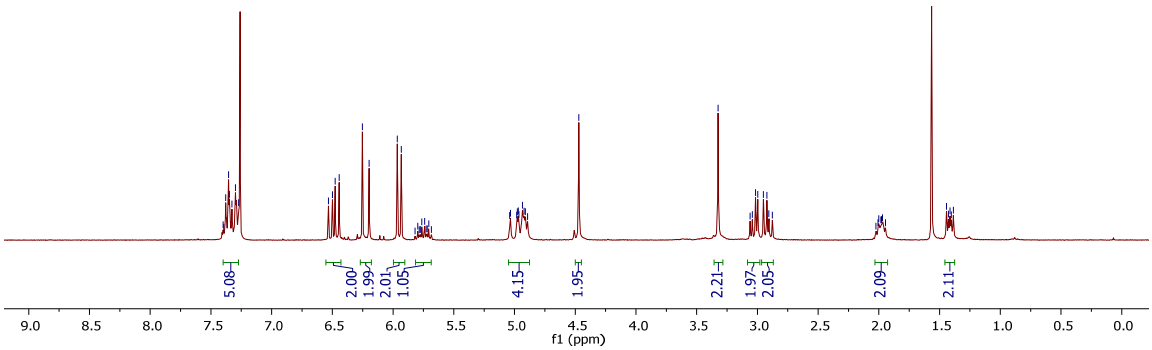
1d


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

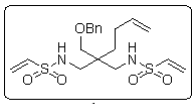

7.40
7.39
7.38
7.35
7.35
7.33
7.30
7.27
6.53
6.50
6.48
6.44
6.25
6.20
5.97
5.93
5.82
5.80
5.79
5.78
5.76
5.74
5.73
5.72
5.71
5.68
5.04
5.03
4.98
4.98
4.97
4.96
4.94
4.92
4.91
4.89
4.47
3.32
3.06
3.04
3.02
3.00
2.95
2.92
2.91
2.88
2.02
2.01
2.00
1.98
1.98
1.97
1.95
1.44
1.43
1.41
1.40
1.39


OBn
H
N
S
O
O
H
N
S
O
O

1e


5.08
2.00
1.99
2.01
1.05
4.15
1.95
2.21
1.97
2.05
2.09
2.11
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
0.0
f1 (ppm)

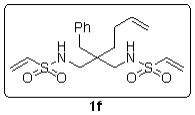

138.1
137.5
135.7
128.8
128.3
128.0
127.1
115.2
73.7
72.7
45.3
41.7
30.9
27.3


OBn
H
N
S
O
O
H
N
S
O
O

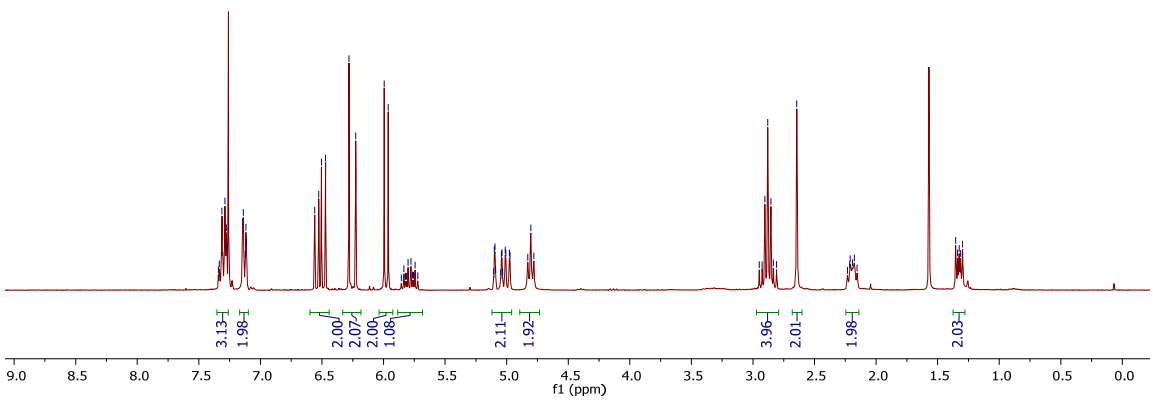
1e

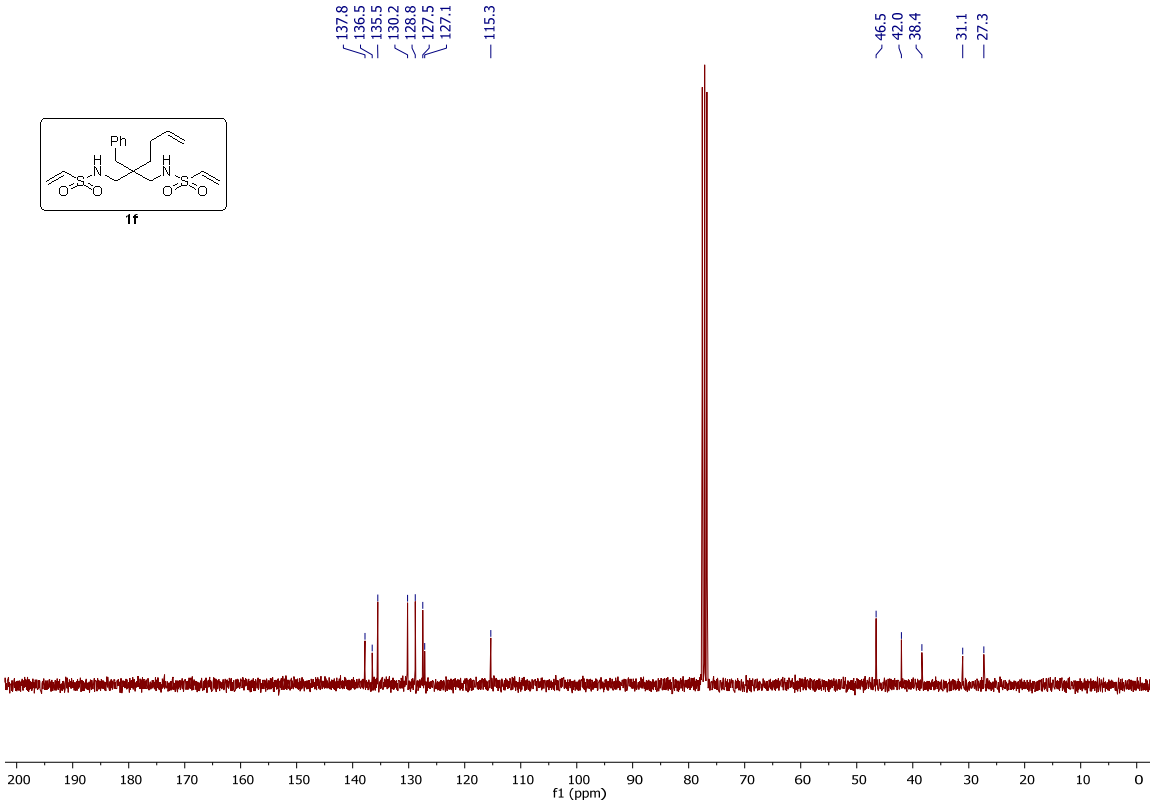
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.34
7.33
7.31
7.29
7.28
7.27
7.14
7.14
7.12
7.12
7.11
6.56
6.53
6.50
6.47
6.28
6.23
5.99
5.96
5.83
5.82
5.80
5.78
5.77
5.76
5.74
5.72
5.11
5.10
5.09
5.09
5.05
5.04
5.04
5.03
5.01
5.01
4.98
4.97
4.83
4.80
4.78
2.95
2.93
2.90
2.88
2.85
2.83
2.81
2.64
2.23
2.21
2.21
2.19
2.18
2.15
1.35
1.34
1.33
1.31


Ph
H
N
H
N
O
S
O
O
S
O

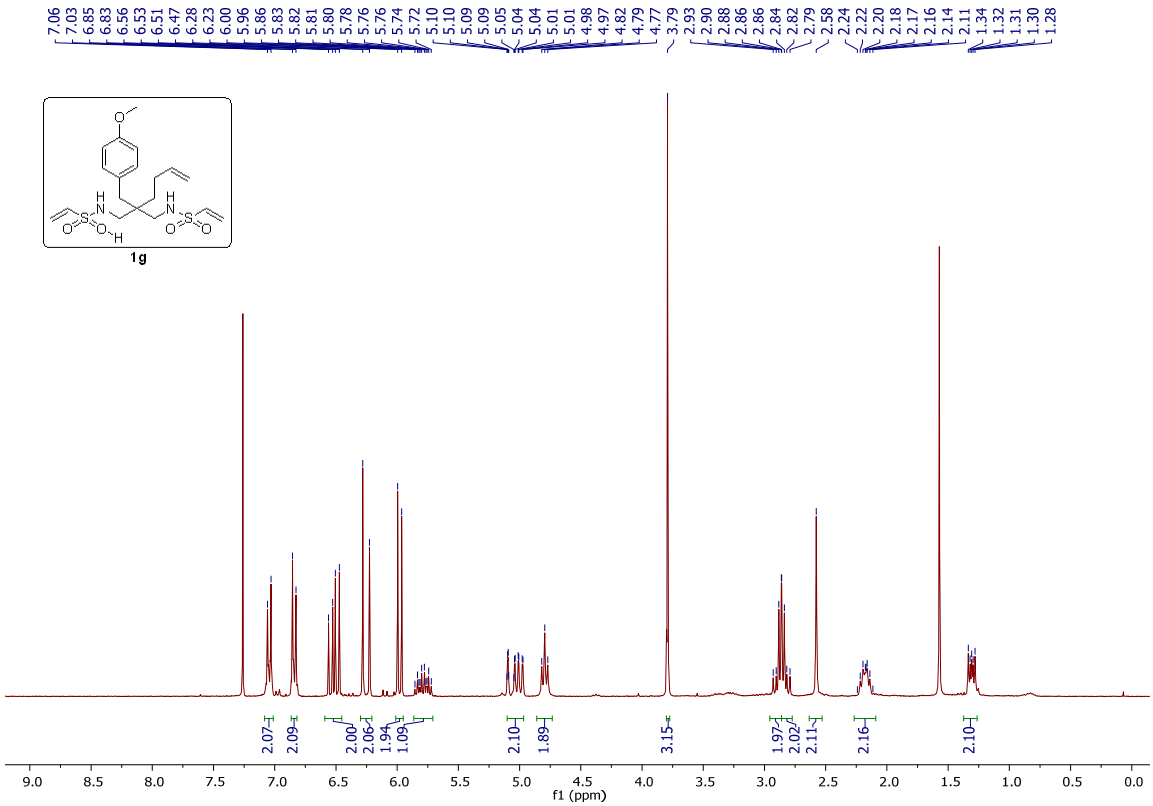
1f

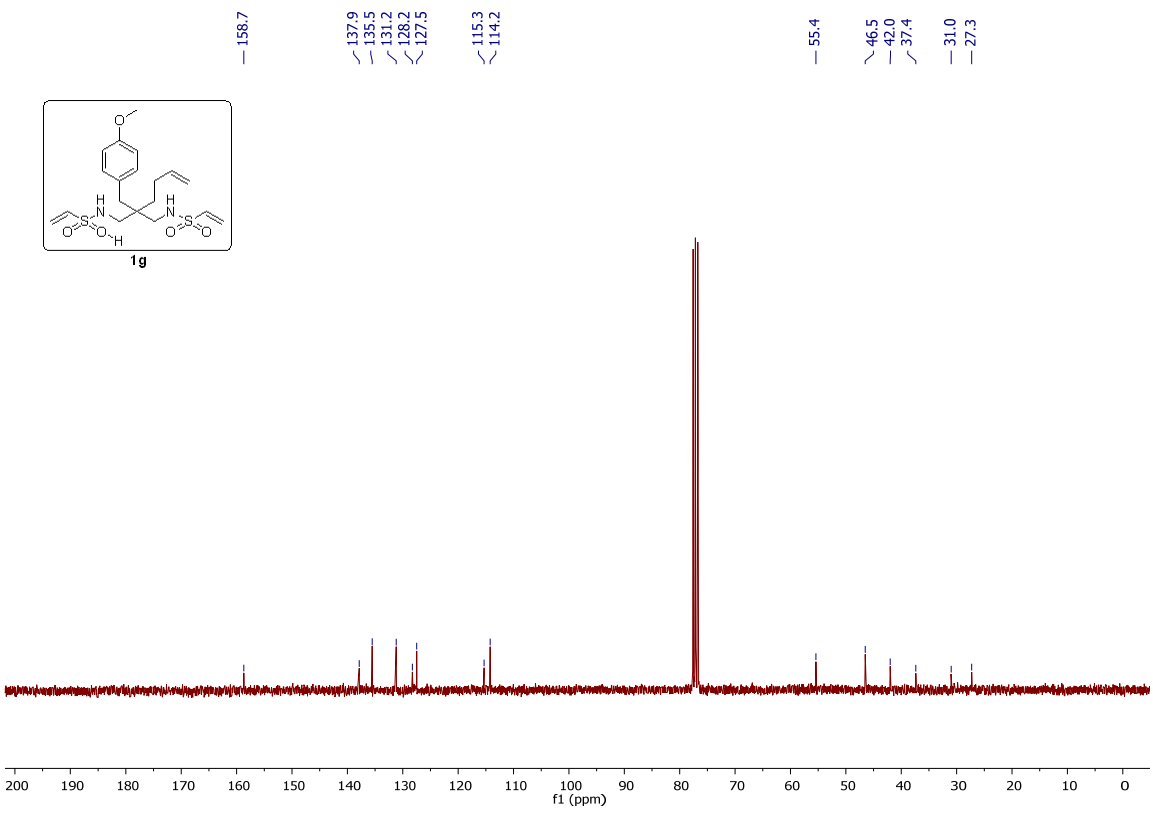

3.13
1.98
2.00
2.07
2.00
1.08
2.11
1.92
3.96
2.01
1.98
2.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

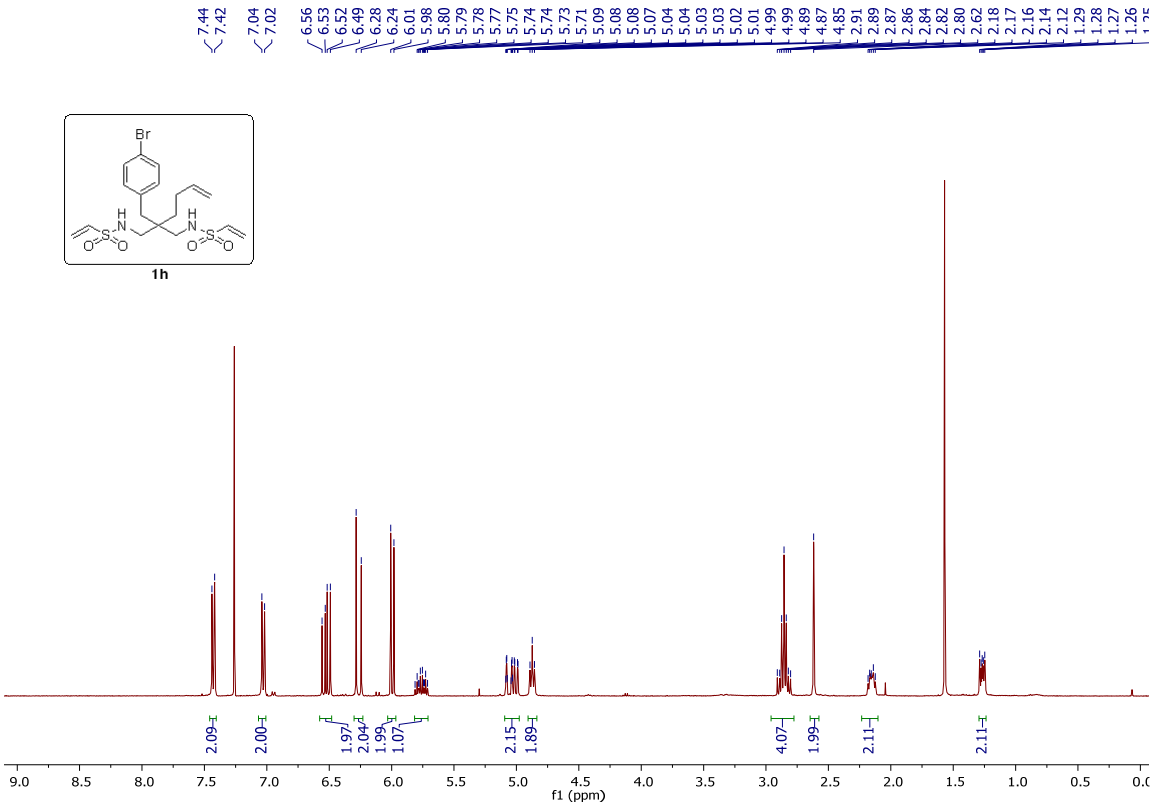

137.8
136.5
135.5
130.2
128.8
127.5
127.1
115.3
46.5
42.0
38.4
31.1
27.3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Ph
H
N
H
N
O
S
O
O
S
O

1f


7.06 7.03 6.85 6.83 6.56 6.53 6.51 6.47 6.28 6.23 6.00 5.96 5.86 5.83 5.82 5.81 5.80 5.78 5.76 5.76 5.74 5.72 5.10 5.10 5.09 5.09 5.05 5.04 5.04 5.01 5.01 4.98 4.97 4.82 4.79 4.77 3.79 2.93 2.90 2.88 2.86 2.86 2.84 2.82 2.79 2.58 2.24 2.22 2.20 2.18 2.17 2.16 2.14 2.11 1.34 1.32 1.31 1.30 1.28
1g
2.07 2.09 2.00 2.06 1.94 1.09 2.10 1.89 3.15 1.97 2.02 2.11 2.16 2.10
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 0.0
f1 (ppm)


158.7 137.9 135.5 131.2 128.2 127.5 115.3 114.2 55.4 46.5 42.0 37.4 31.0 27.3
1g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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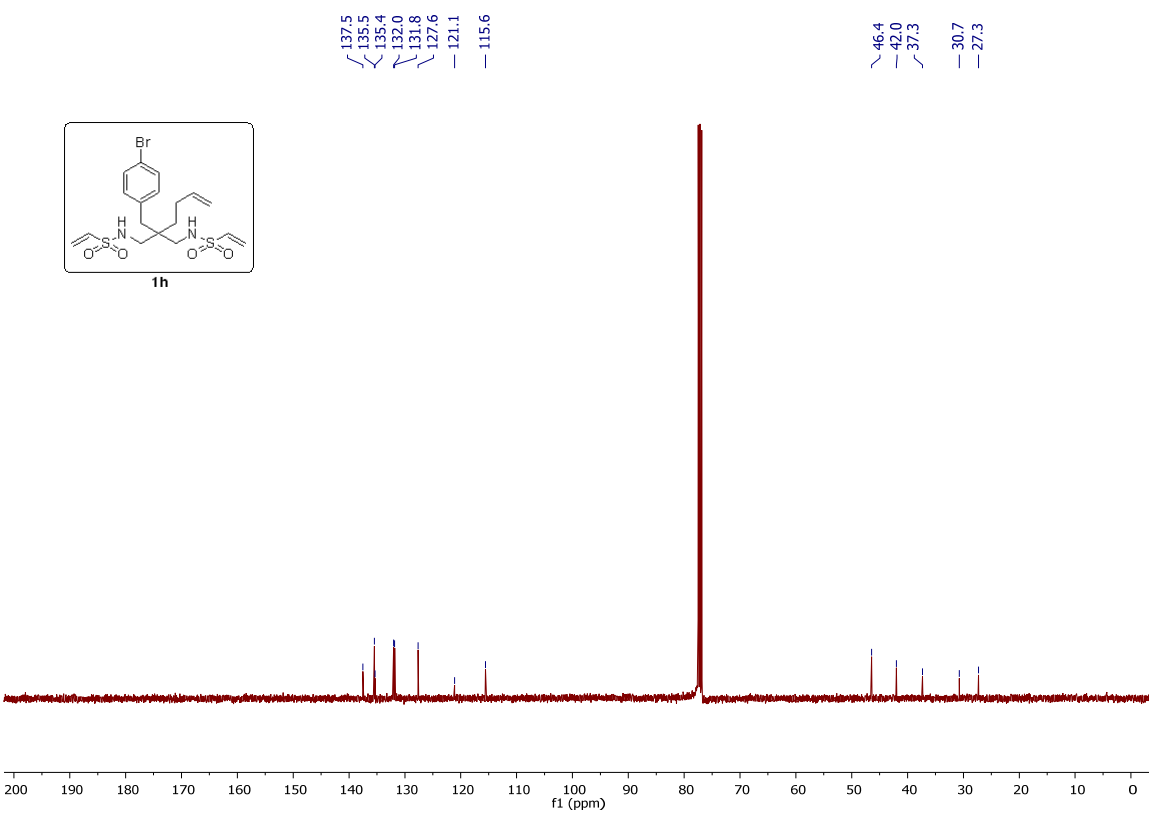
7.42
7.04
7.02
6.56
6.53
6.52
6.49
6.28
6.24
6.01
5.98
5.80
5.79
5.78
5.77
5.75
5.74
5.74
5.73
5.71
5.09
5.08
5.08
5.07
5.04
5.04
5.03
5.03
5.02
5.01
4.99
4.99
4.89
4.87
4.85
2.91
2.89
2.87
2.86
2.84
2.82
2.80
2.62
2.18
2.17
2.16
2.14
2.12
1.29
1.28
1.27
1.26
Br
1h
2.09
2.00
1.97
2.04
1.99
1.07
2.15
1.89
4.07
1.99
2.11
2.11
f1 (ppm)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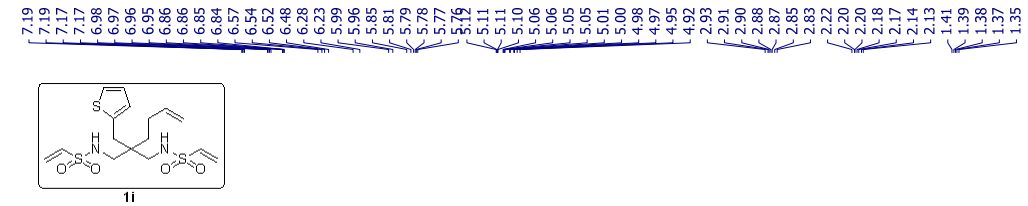
135.5
135.4
132.0
131.8
127.6
121.1
115.6
46.4
42.0
37.3
30.7
27.3
Br
1h
f1 (ppm)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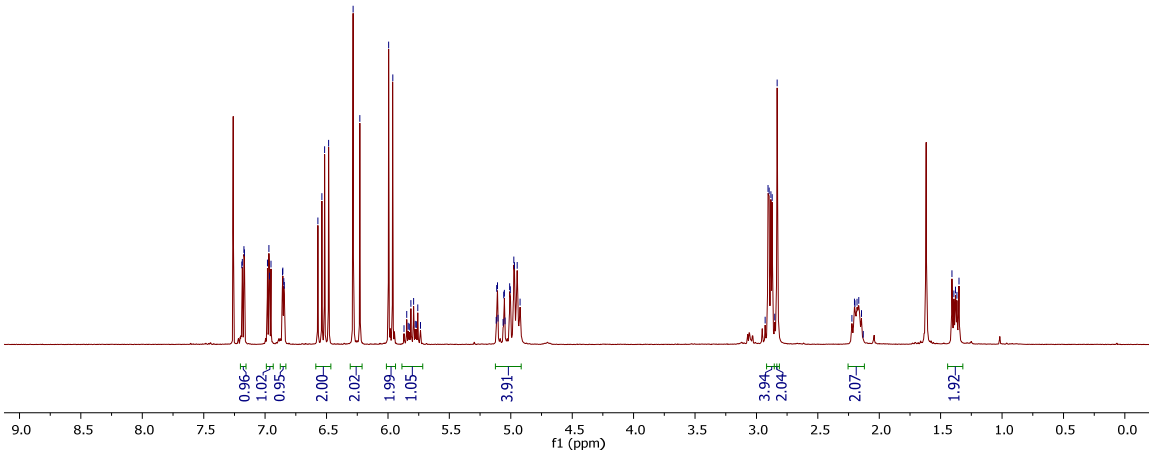
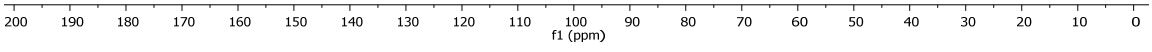
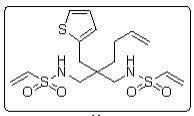
7.19
7.17
7.17
6.98
6.97
6.96
6.95
6.86
6.86
6.85
6.84
6.57
6.54
6.52
6.48
6.28
6.23
5.99
5.96
5.85
5.81
5.79
5.78
5.77
5.76
5.12
5.11
5.11
5.10
5.06
5.06
5.05
5.05
5.01
5.00
4.98
4.97
4.95
4.92
2.93
2.91
2.90
2.88
2.87
2.85
2.83
2.22
2.20
2.20
2.18
2.17
2.14
2.13
1.41
1.39
1.38
1.37
1.35

1i

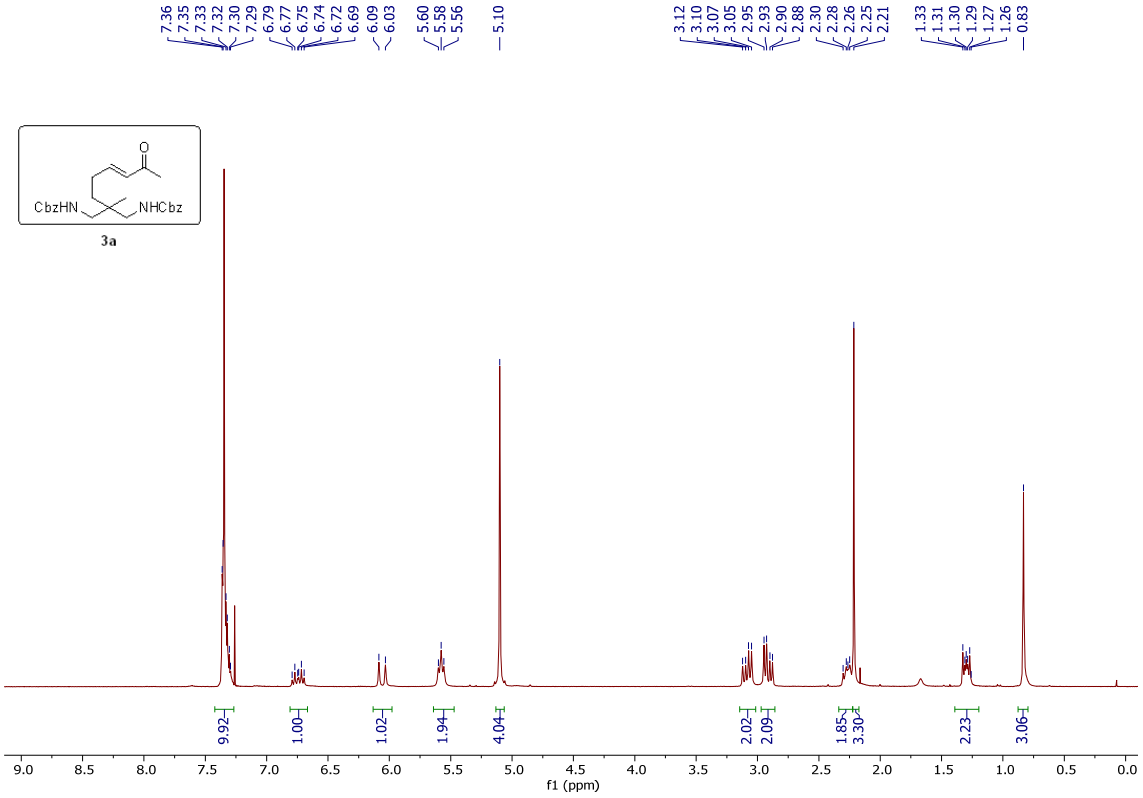

0.96
1.02
0.95
2.00
2.02
1.99
1.05
3.91
3.94
2.04
2.07
1.92
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

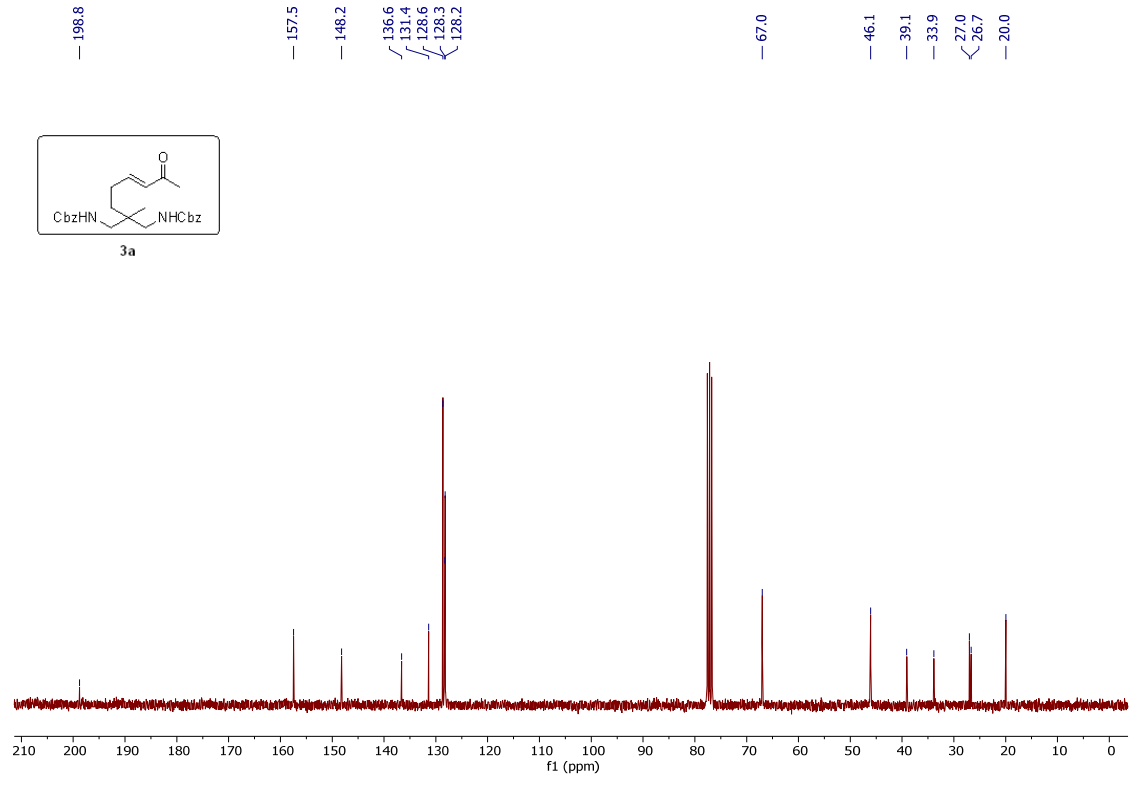

137.7
135.5
127.6
127.5
127.4
124.7
115.4
46.2
42.0
32.0
30.7
27.2



1i

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


7.36
7.35
7.33
7.32
7.30
7.29
6.79
6.77
6.75
6.74
6.72
6.69
6.09
6.03
5.60
5.58
5.56
5.10
3.12
3.10
3.07
3.05
2.95
2.93
2.90
2.88
2.30
2.28
2.26
2.25
2.21
1.33
1.31
1.30
1.29
1.27
1.26
0.83
CbzHN
NHCbz
3a
9.92
1.00
1.02
1.94
4.04
2.02
2.09
1.85
3.30
2.23
3.06
f1 (ppm)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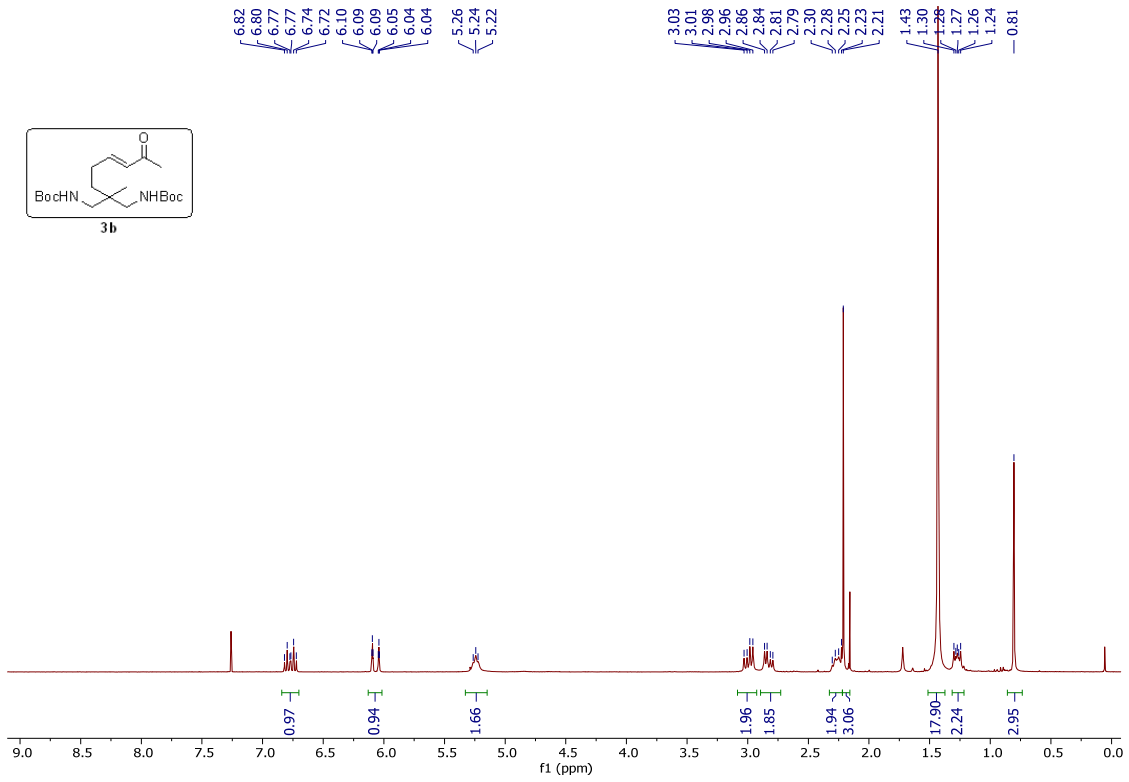
157.5
148.2
136.6
131.4
128.6
128.3
128.2
67.0
46.1
39.1
33.9
27.0
26.7
20.0
CbzHN
NHCbz
3a
f1 (ppm)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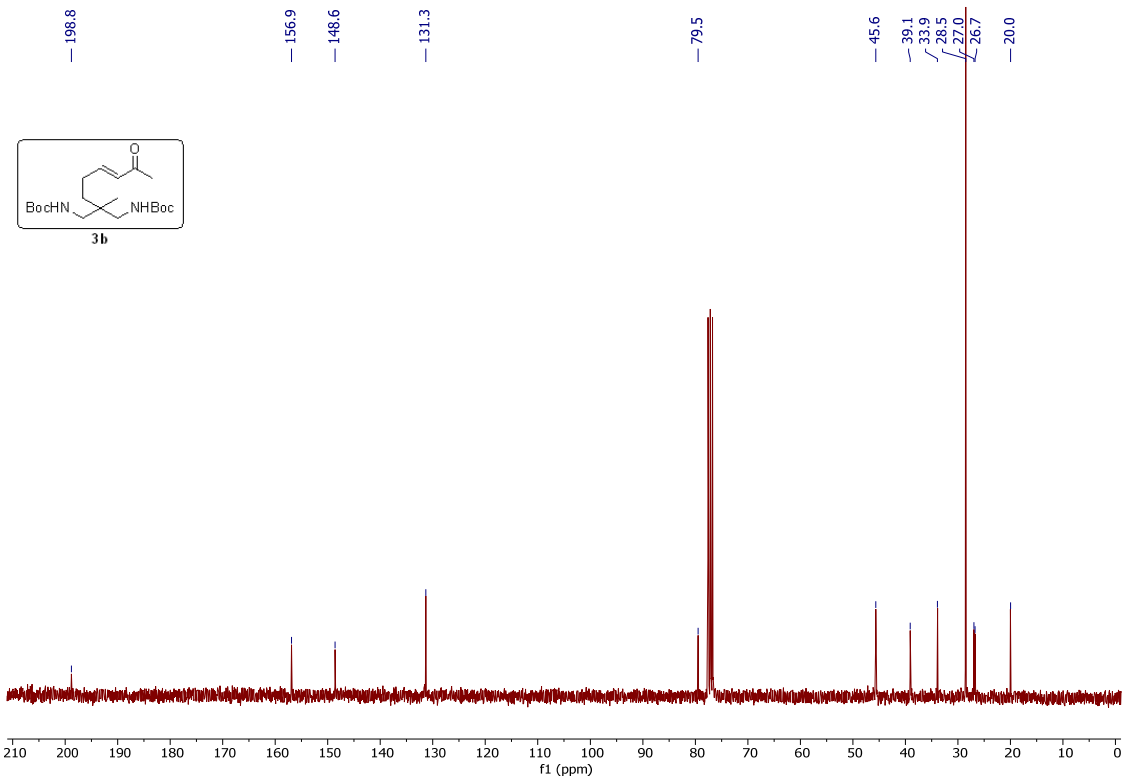
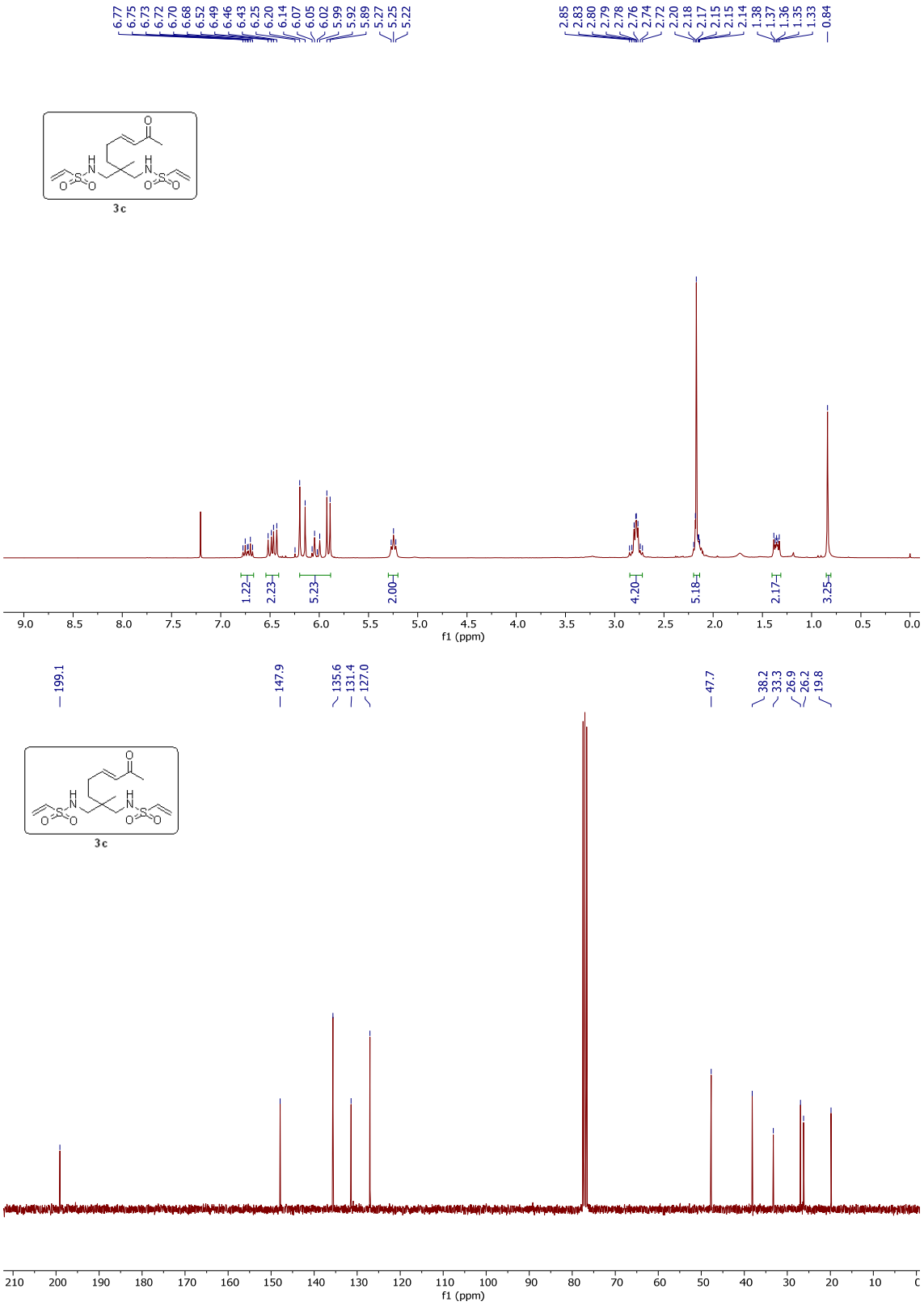
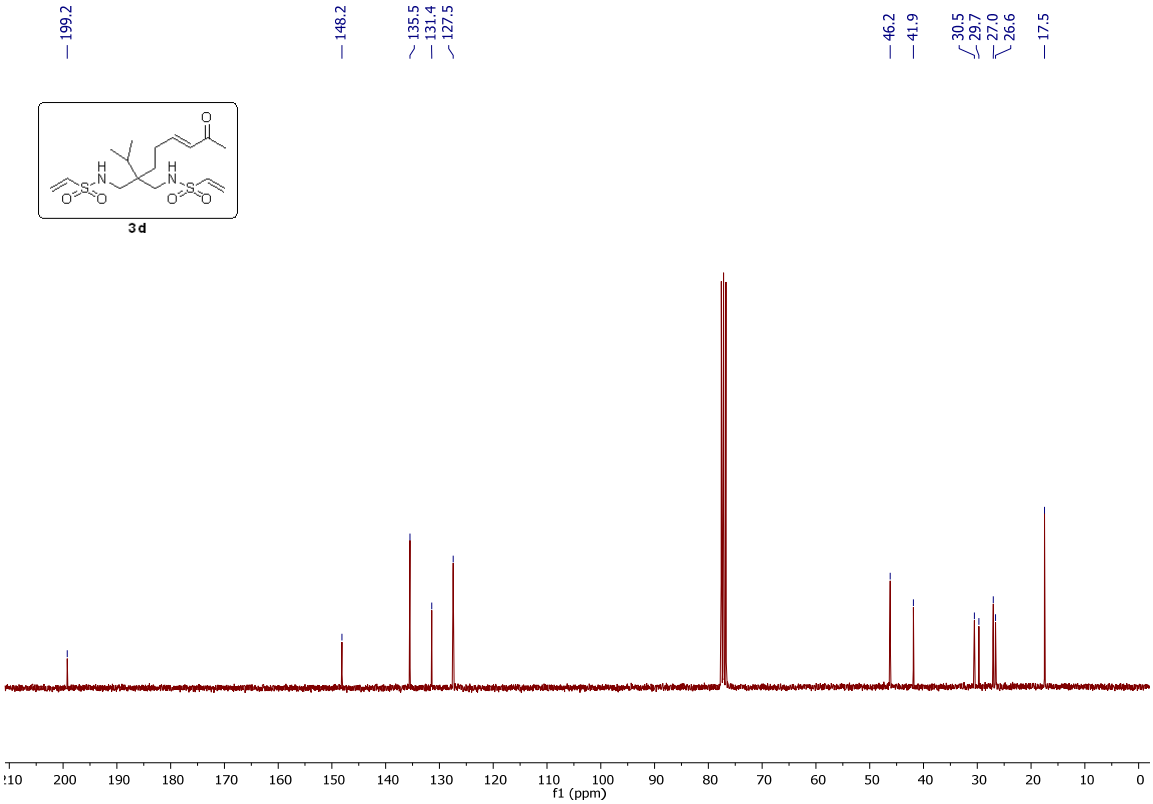
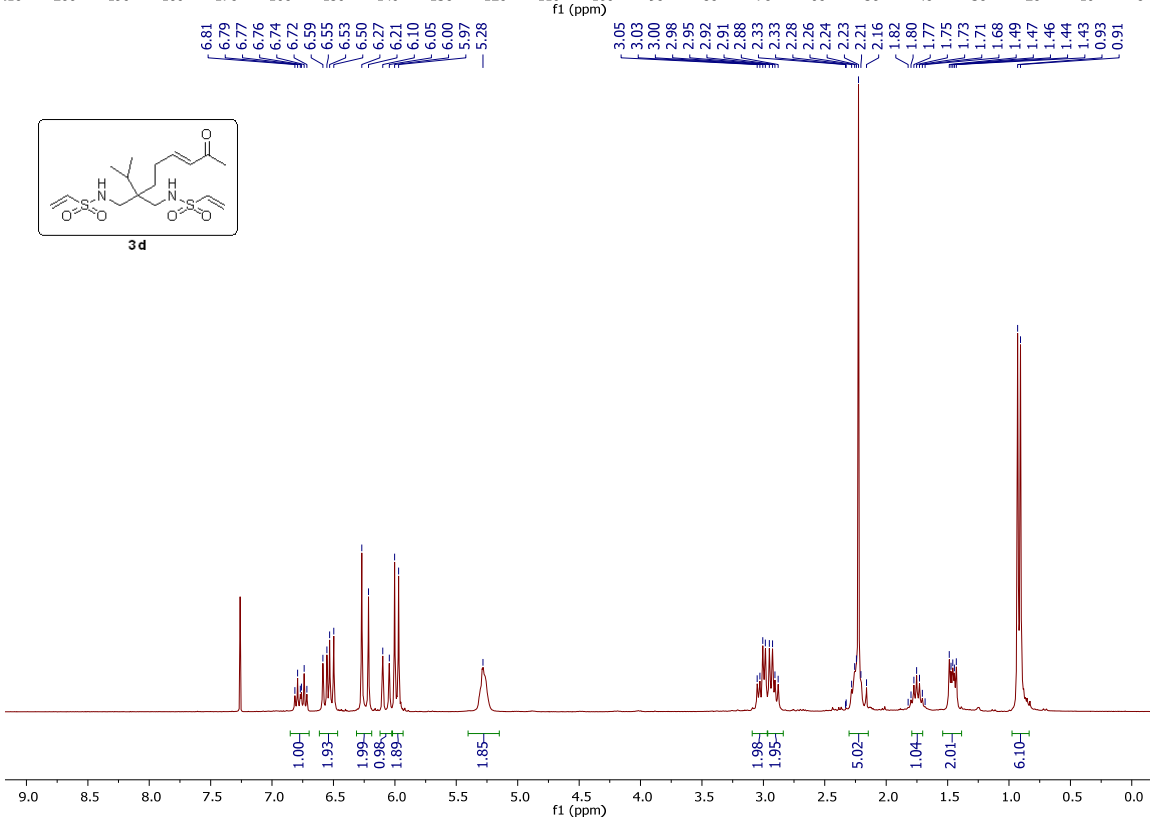
6.80
6.77
6.77
6.74
6.72
6.10
6.09
6.09
6.05
6.04
6.04
5.26
5.24
5.22
3.03
3.01
2.98
2.96
2.86
2.84
2.81
2.79
2.30
2.28
2.25
2.23
2.21
1.43
1.30
1.28
1.27
1.26
1.24
0.81
BocHN
NHBoc
3b
0.97
0.94
1.66
1.96
1.85
1.94
3.06
17.90
2.24
2.95
f1 (ppm)


198.8
156.9
148.6
131.3
79.5
45.6
39.1
33.9
28.5
27.0
26.7
20.0
BocHN
NHBoc
3b
f1 (ppm)


6.77
6.75
6.73
6.72
6.70
6.68
6.52
6.49
6.46
6.43
6.25
6.20
6.14
6.07
6.05
6.02
5.99
5.92
5.89
5.27
5.25
5.22
2.85
2.83
2.80
2.79
2.78
2.76
2.74
2.72
2.20
2.18
2.17
2.15
2.15
2.14
1.38
1.37
1.36
1.35
1.33
0.84
3c
1.22
2.23
5.23
2.00
4.20
5.18
2.17
3.25
f1 (ppm)
199.1
147.9
135.6
131.4
127.0
47.7
38.2
33.3
26.9
26.2
19.8
3c
f1 (ppm)


199.2
148.2
135.5
131.4
127.5
46.2
41.9
30.5
29.7
27.0
26.6
17.5
3d
f1 (ppm)


6.81
6.79
6.77
6.76
6.74
6.72
6.59
6.55
6.53
6.50
6.27
6.21
6.10
6.05
6.00
5.97
5.28
3.05
3.03
3.00
2.98
2.95
2.92
2.91
2.88
2.33
2.33
2.28
2.26
2.24
2.23
2.21
2.16
1.82
1.80
1.77
1.75
1.73
1.71
1.68
1.49
1.47
1.46
1.44
1.43
0.93
0.91
3d
1.00
1.93
1.99
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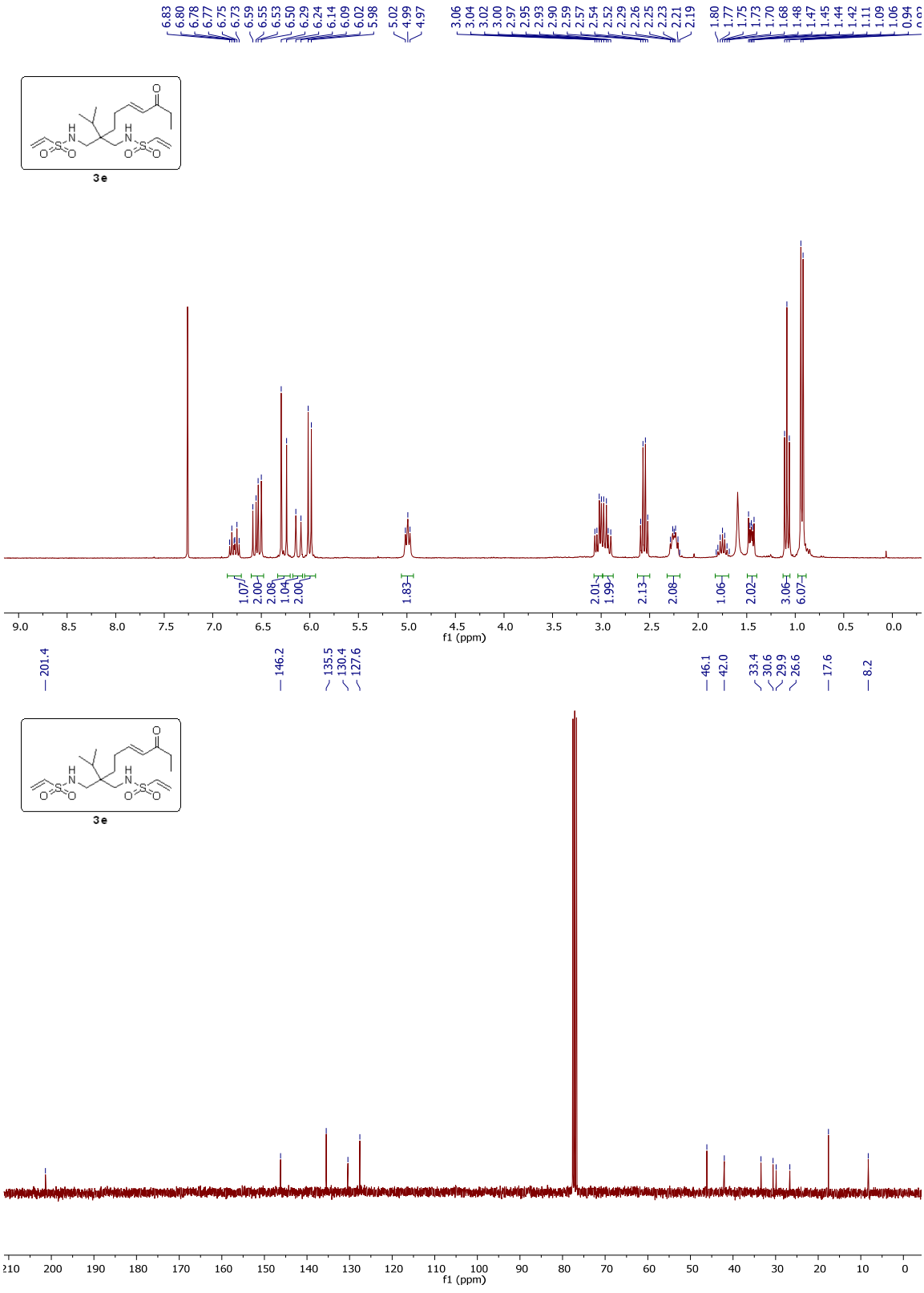
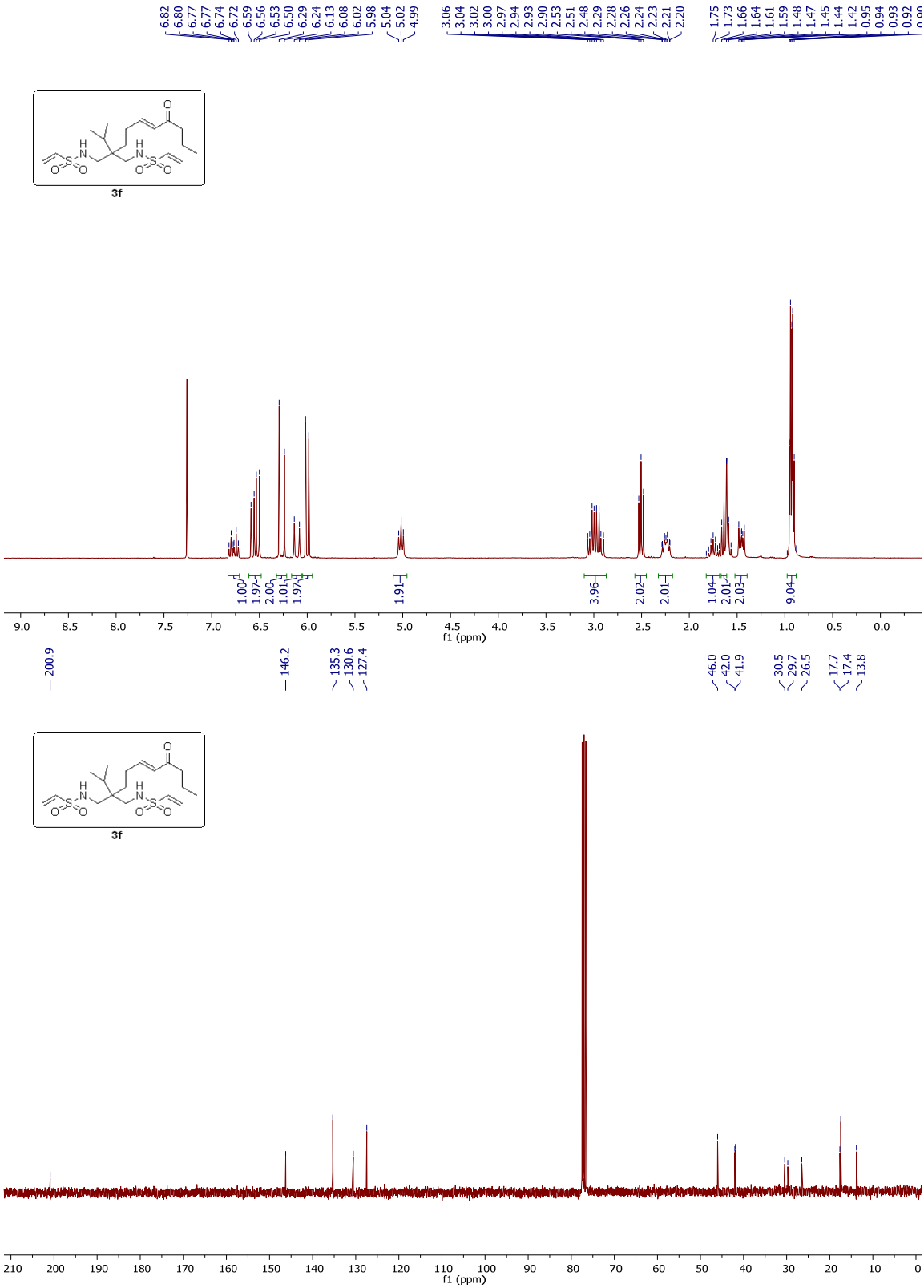
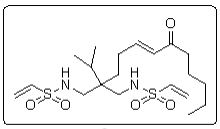
1.85
1.98
1.95
5.02
1.04
2.01
6.10
f1 (ppm)

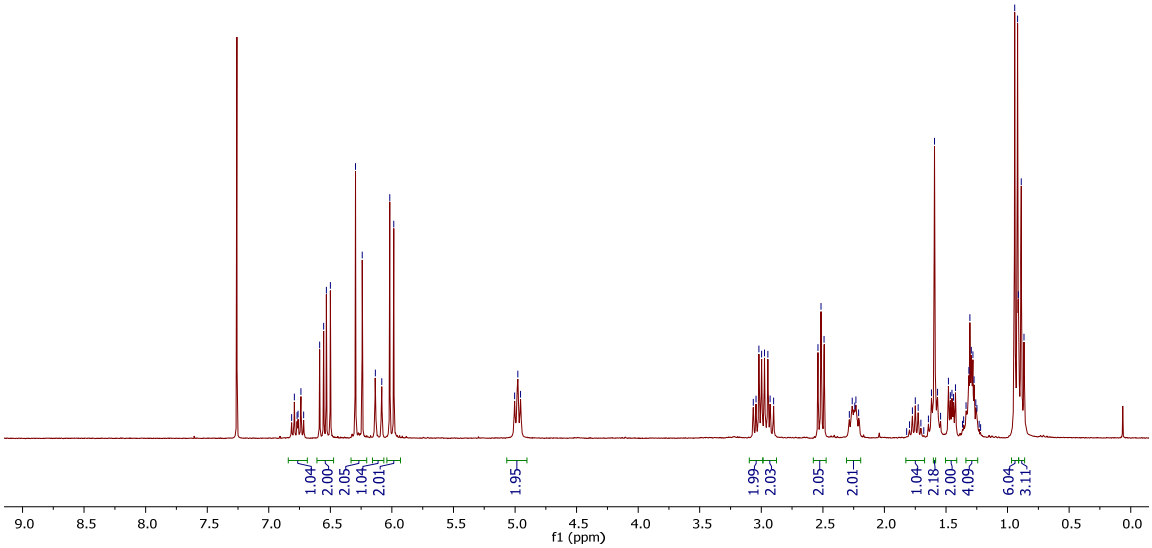

6.83 6.80 6.78 6.77 6.75 6.73 6.59 6.55 6.53 6.50 6.29 6.24 6.14 6.09 6.02 5.98 5.02 4.99 4.97
3.06 3.04 3.02 3.00 2.97 2.95 2.93 2.90 2.59 2.57 2.54 2.52 2.29 2.26 2.25 2.23 2.21 2.19
1.80 1.77 1.75 1.73 1.70 1.68 1.48 1.47 1.45 1.44 1.42 1.11 1.09 1.06 0.94
3e
1.07 2.00 2.08 1.04 2.00 1.83 2.01 1.99 2.13 2.08 1.06 2.02 3.06 6.07
f1 (ppm)
201.4 146.2 135.5 130.4 127.6 46.1 42.0 33.4 30.6 29.9 26.6 17.6 8.2
3e
f1 (ppm)

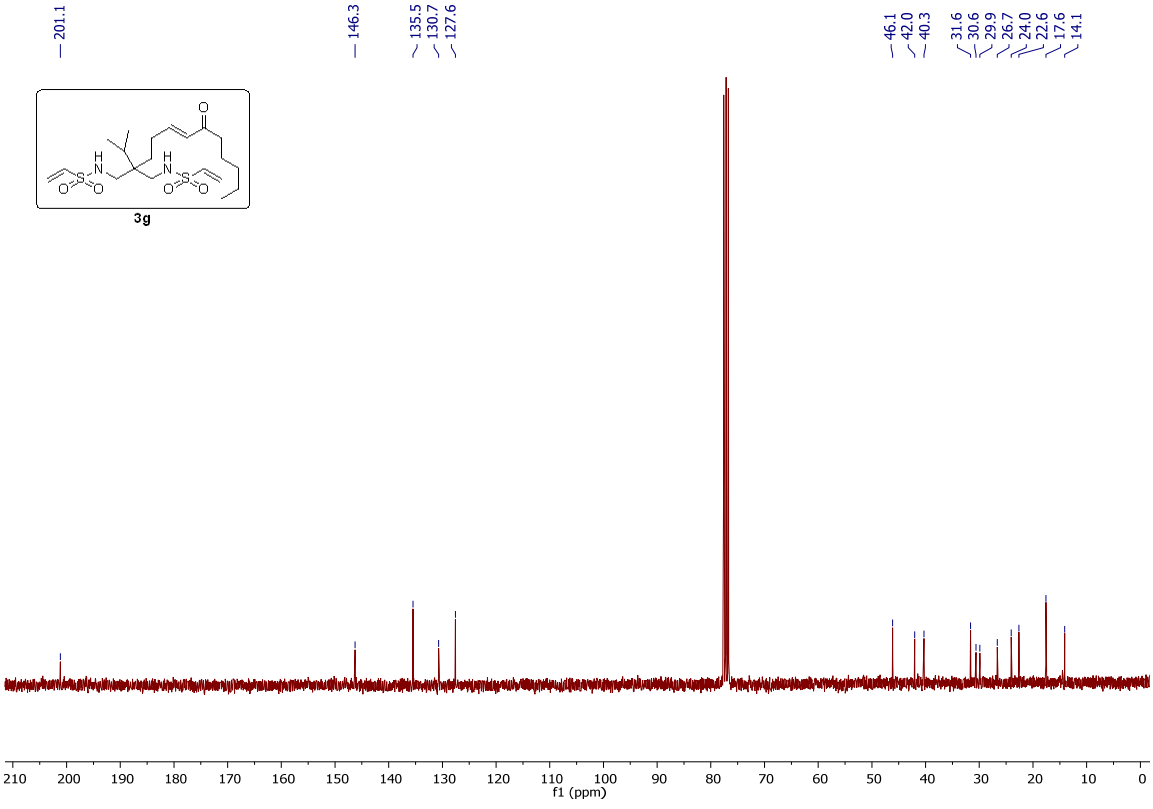

6.82 6.80 6.77 6.74 6.72 6.59 6.56 6.53 6.50 6.29 6.24 6.13 6.08 6.02 5.98 5.04 5.02 4.99
3.06 3.04 3.02 3.00 2.97 2.94 2.93 2.90 2.53 2.51 2.48 2.29 2.28 2.26 2.24 2.23 2.21 2.20
1.75 1.73 1.66 1.64 1.61 1.59 1.48 1.47 1.45 1.44 1.42 0.95 0.94 0.93 0.92
3f
1.00 1.97 2.00 1.01 1.97 1.91 3.96 2.02 2.01 1.04 2.01 2.03 9.04
f1 (ppm)
200.9 146.2 135.3 130.6 127.4 46.0 42.0 41.9 30.5 29.7 26.5 17.7 17.4 13.8
3f
f1 (ppm)


6.81 6.79 6.77 6.76 6.74 6.72 6.59 6.55 6.53 6.50 6.30 6.24 6.13 6.08 6.02 5.98 5.00 4.98 4.95 3.06 3.04 3.02 3.00 2.97 2.95 2.93 2.90 2.54 2.52 2.49 2.28 2.26 2.24 2.23 2.21 1.80 1.77 1.75 1.73 1.70 1.64 1.62 1.59 1.57 1.54 1.48 1.47 1.45 1.44 1.42 1.37 1.36 1.34 1.31 1.31 1.29 1.28 1.27 1.26 1.25 1.23 0.94 0.92 0.91 0.89 0.87



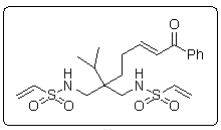
3g


1.04 2.00 2.05 1.04 2.01 1.95 1.99 2.03 2.05 2.01 1.04 2.18 2.00 4.09 6.04 3.11
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 0.0
f1 (ppm)

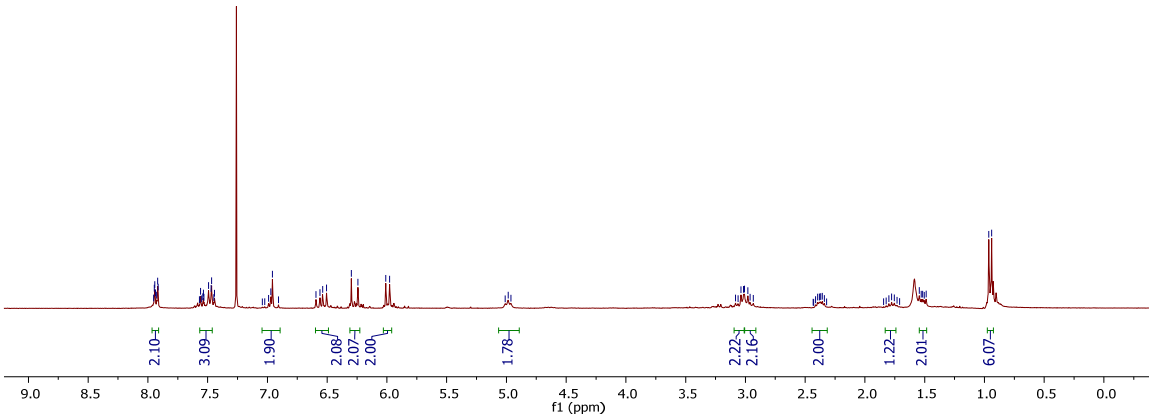

201.1
146.3
135.5
130.7
127.6
46.1
42.0
40.3
31.6
30.6
29.9
26.7
24.0
22.6
17.6
14.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

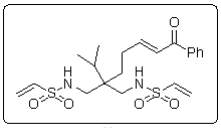
3g


7.95
7.95
7.94
7.94
7.93
7.92
7.91
7.57
7.56
7.55
7.54
7.54
7.53
7.49
7.47
7.47
7.45
7.44
7.04
7.02
6.99
6.97
6.96
6.91
6.59
6.56
6.54
6.50
6.30
6.24
6.01
5.98
5.01
4.99
4.96
3.08
3.06
3.04
3.02
3.01
2.98
2.96
2.93
2.41
2.40
2.38
2.37
2.36
2.34
1.84
1.82
1.80
1.78
1.75
1.73
1.71
1.54
1.53
1.52
1.50
1.49
0.96


O
Ph
H
N
S
O
O
H
N
S
O
O

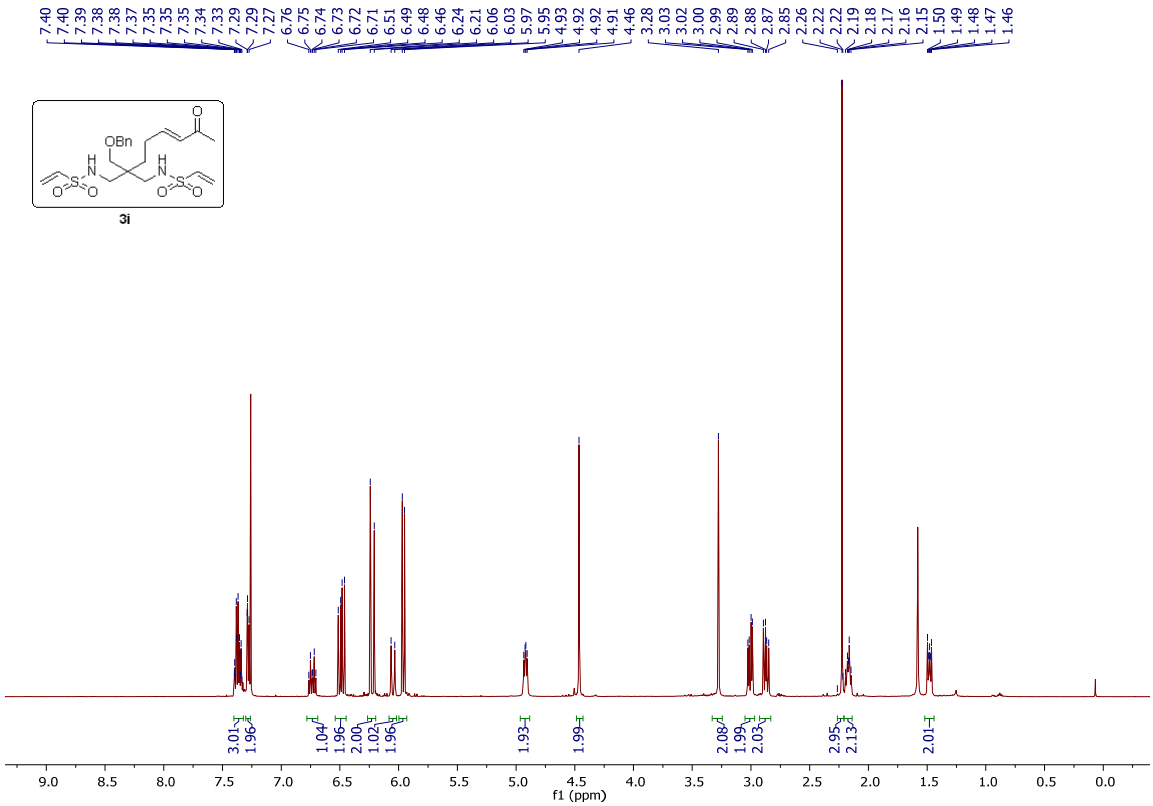
3h

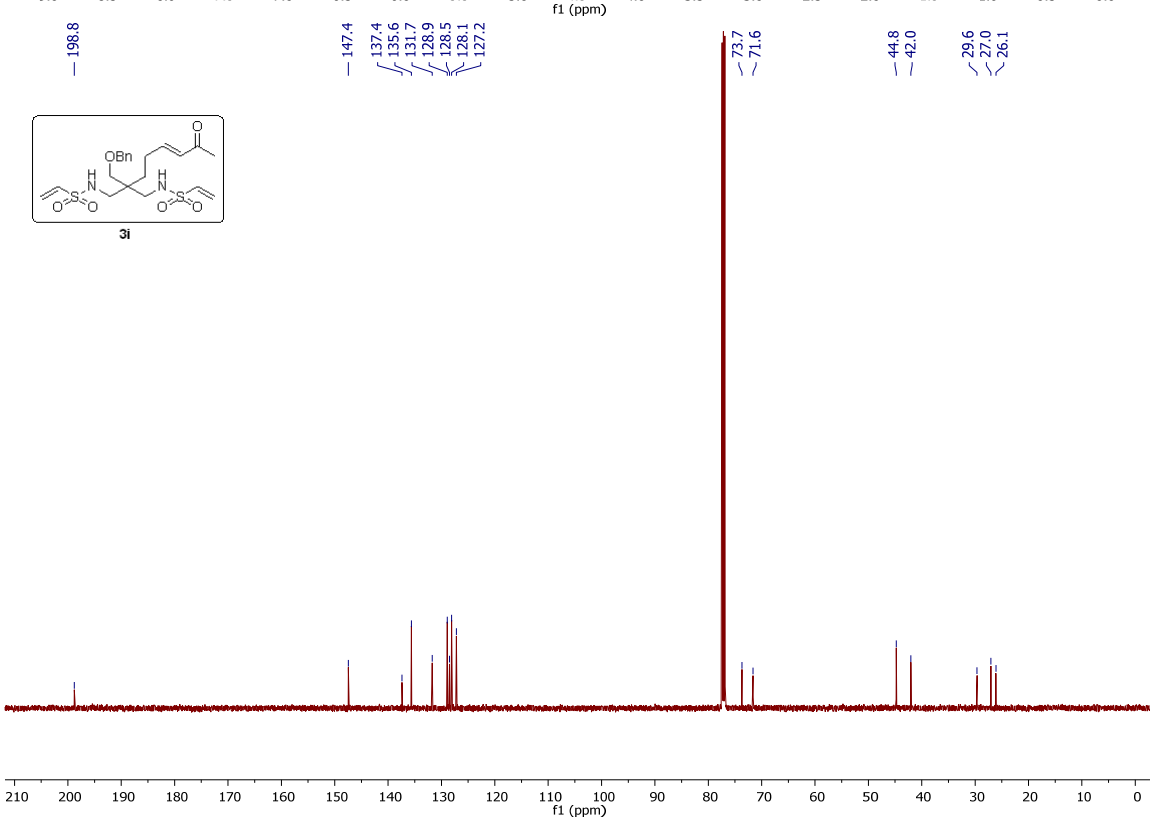

2.10
3.09
1.90
2.08
2.07
2.00
1.78
2.22
2.16
2.00
1.22
2.01
6.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

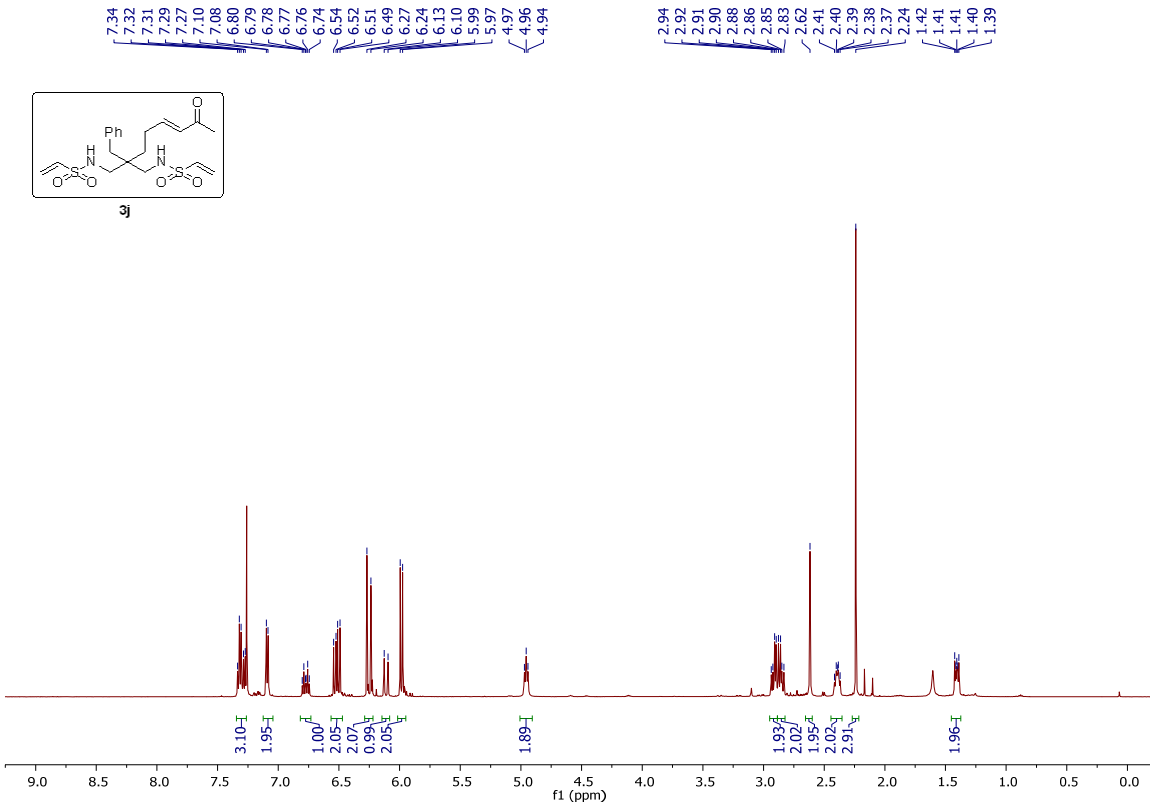

O
Ph
H
N
S
O
O
H
N
S
O
O

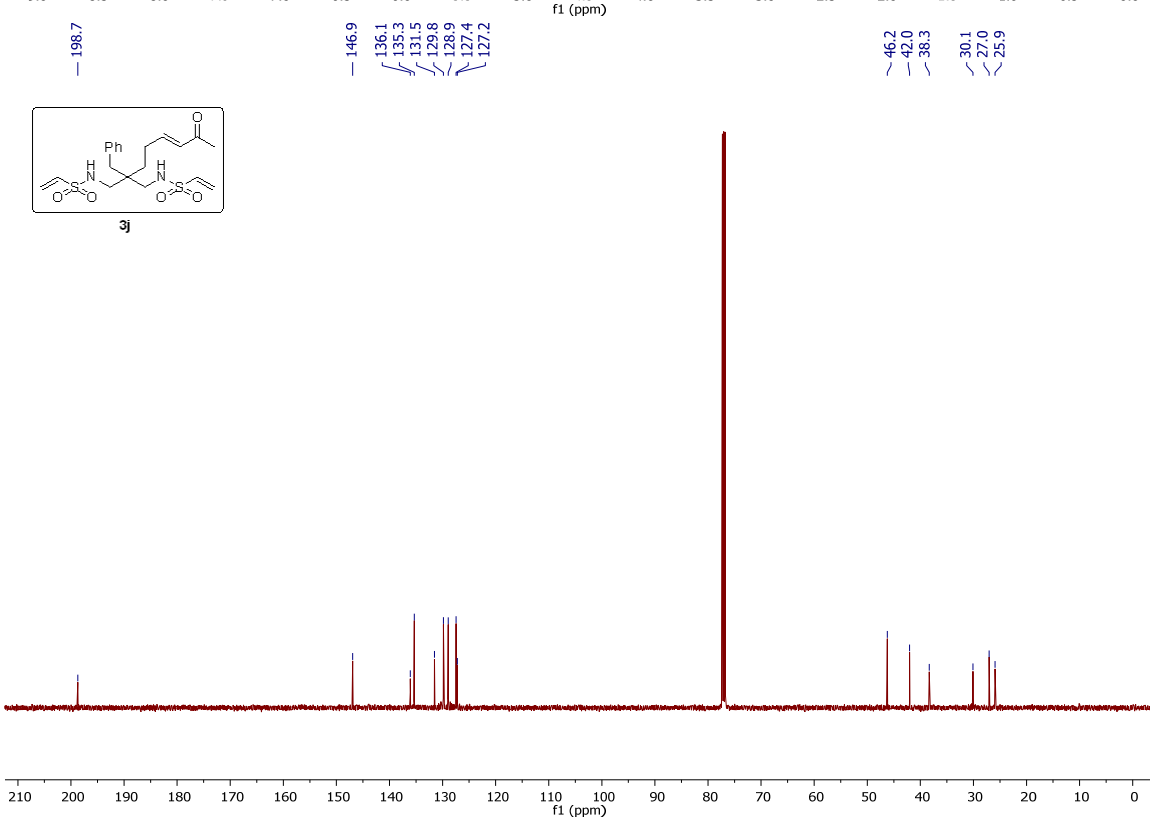
3h

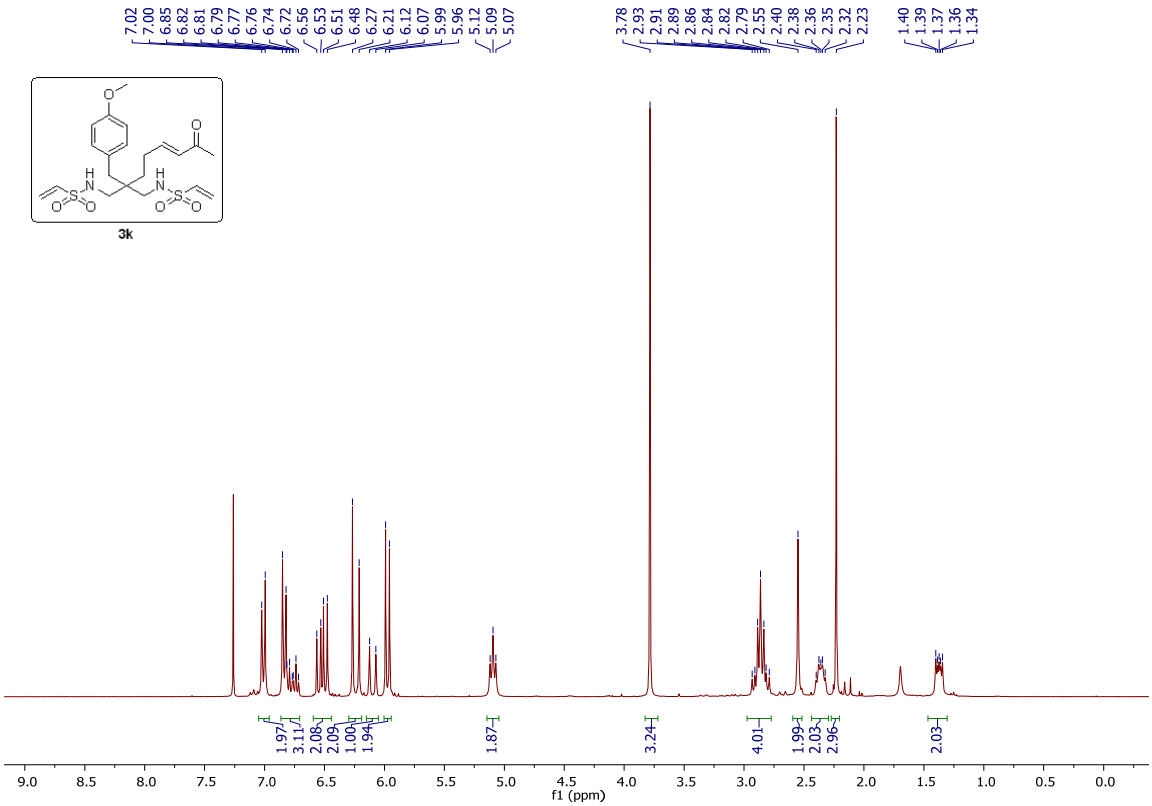
190.9
148.7
137.7
135.4
132.8
128.6
128.6
127.4
126.3
46.0
42.0
30.5
29.9
26.9
17.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

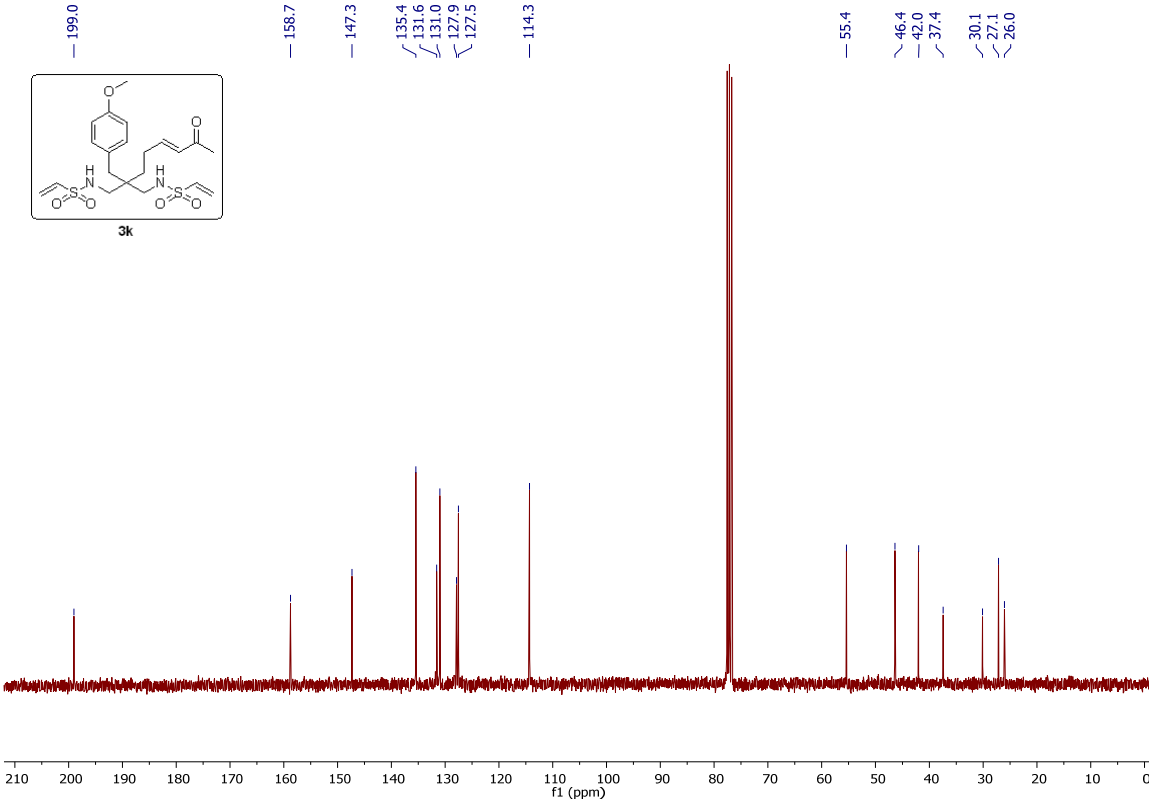

7.40 7.40 7.39 7.38 7.38 7.37 7.35 7.35 7.35 7.34 7.33 7.29 7.29 7.27 6.76 6.75 6.74 6.73 6.72 6.71 6.51 6.49 6.48 6.46 6.24 6.21 6.06 6.03 5.97 5.95 4.93 4.92 4.92 4.91 4.46 3.28 3.03 3.02 3.00 2.99 2.89 2.88 2.87 2.85 2.26 2.22 2.22 2.19 2.18 2.17 2.16 2.15 1.50 1.49 1.48 1.47 1.46
OBn
3i
3.01 1.96 1.04 1.96 2.00 1.02 1.96 1.93 1.99 2.08 1.99 2.03 2.95 2.13 2.01
f1 (ppm)

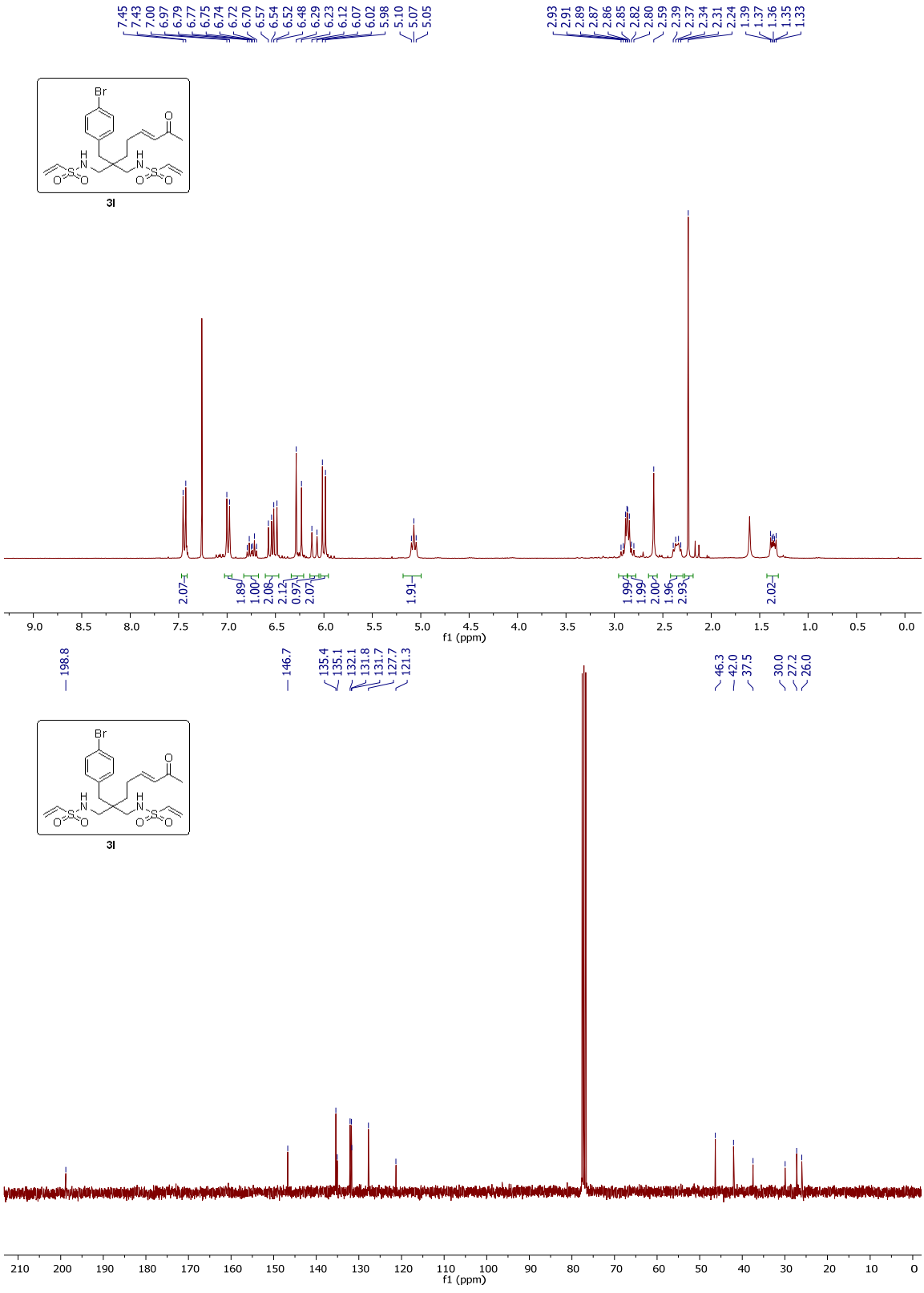

198.8 147.4 137.4 135.6 131.7 128.9 128.5 128.1 127.2 73.7 71.6 44.8 42.0 29.6 27.0 26.1
OBn
3i
f1 (ppm)


7.34
7.32
7.31
7.29
7.27
7.10
7.08
6.80
6.79
6.78
6.77
6.76
6.74
6.54
6.52
6.51
6.49
6.27
6.24
6.13
6.10
5.99
5.97
4.97
4.96
4.94
2.94
2.92
2.91
2.90
2.88
2.86
2.85
2.83
2.62
2.41
2.40
2.39
2.38
2.37
2.24
1.42
1.41
1.41
1.40
1.39
Ph
O
H
N
S
O
O
3j
3.10
1.95
1.00
2.05
2.07
0.99
2.05
1.89
1.93
2.02
1.95
2.02
2.91
1.96
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
0.0
f1 (ppm)


198.7
146.9
136.1
135.3
131.5
129.8
128.9
127.4
127.2
46.2
42.0
38.3
30.1
27.0
25.9
Ph
O
H
N
S
O
O
3j
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.02
7.00
6.85
6.82
6.81
6.79
6.77
6.76
6.74
6.72
6.56
6.53
6.51
6.48
6.27
6.21
6.12
6.07
5.99
5.96
5.12
5.09
5.07
3.78
2.93
2.91
2.89
2.86
2.84
2.82
2.79
2.55
2.40
2.38
2.36
2.35
2.32
2.23
1.40
1.39
1.37
1.36
1.34
3k
1.97
3.11
2.08
2.09
1.00
1.94
1.87
3.24
4.01
1.99
2.03
2.96
2.03
f1 (ppm)


199.0
158.7
147.3
135.4
131.6
131.0
127.9
127.5
114.3
55.4
46.4
42.0
37.4
30.1
27.1
26.0
3k
f1 (ppm)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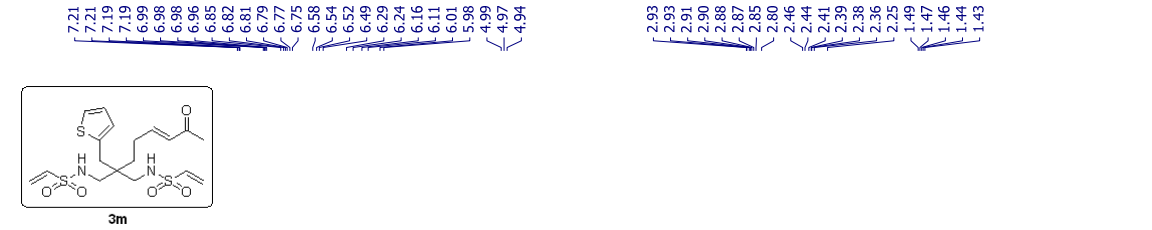
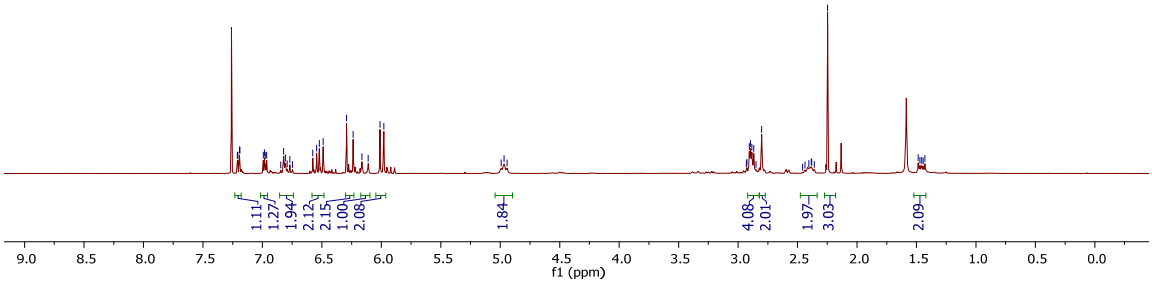
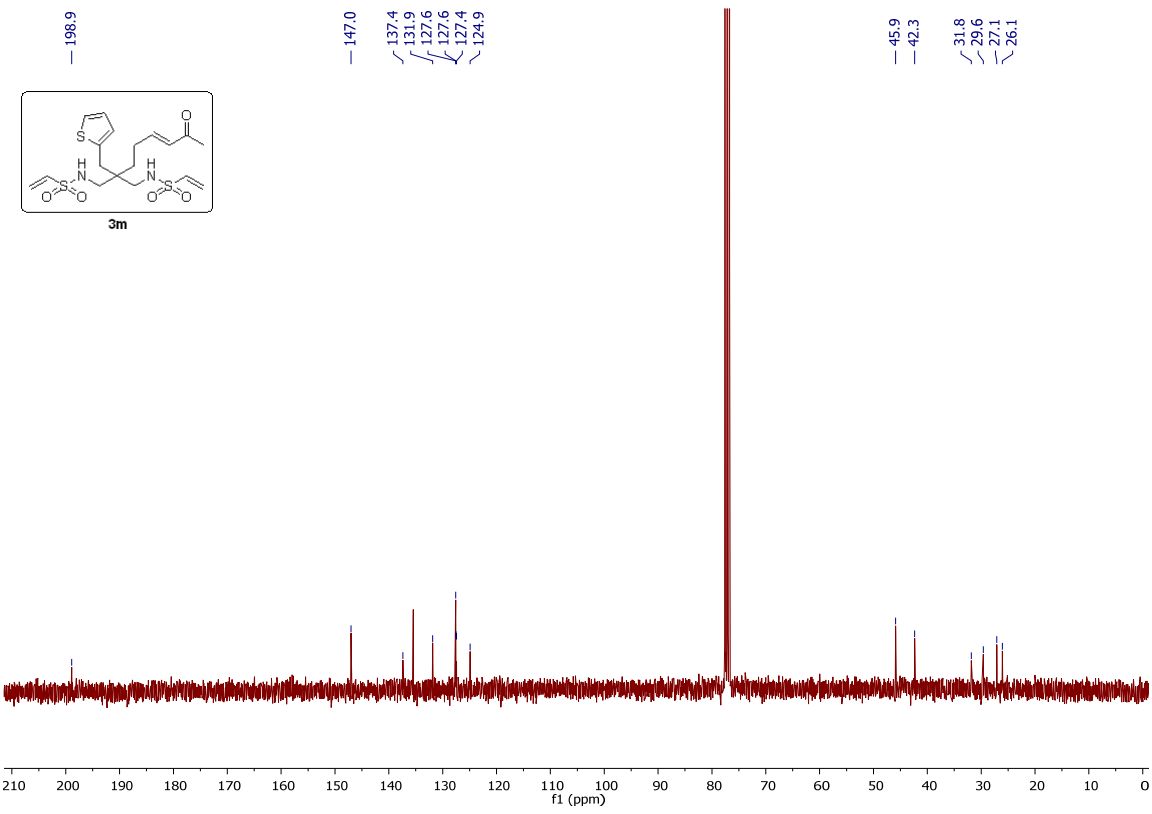
7.43
7.00
6.97
6.79
6.77
6.75
6.74
6.72
6.70
6.57
6.54
6.52
6.48
6.29
6.23
6.12
6.07
6.02
5.98
5.10
5.07
5.05
2.93
2.91
2.89
2.87
2.86
2.85
2.82
2.80
2.59
2.39
2.37
2.34
2.31
2.24
1.39
1.37
1.36
1.35
1.33
Br
O
H
N
S
O
O
3l
2.07
1.89
1.00
2.08
2.12
0.97
2.07
1.91
1.99
1.99
2.00
1.96
2.93
2.02
9.0
8.5
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
0.0
f1 (ppm)
198.8
146.7
135.4
135.1
132.1
131.8
131.7
127.7
121.3
46.3
42.0
37.5
30.0
27.2
26.0
Br
O
H
N
S
O
O
3l
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

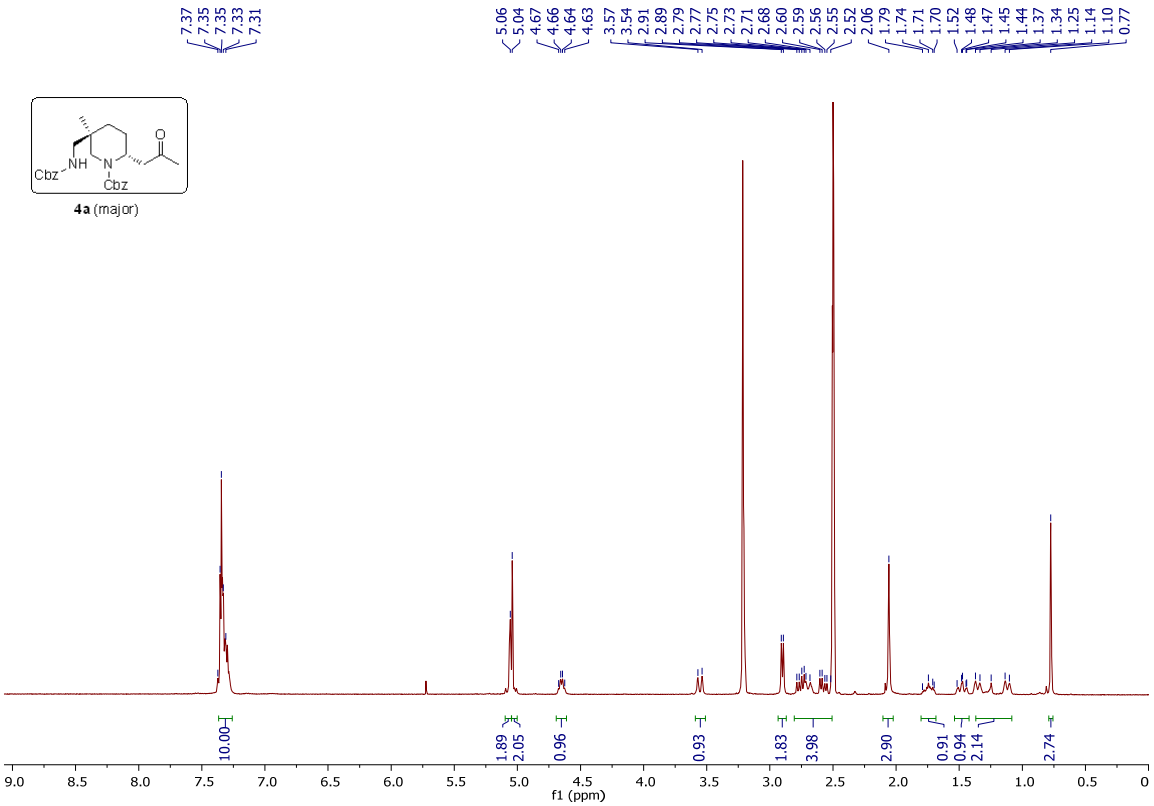

7.21
7.21
7.19
7.19
6.99
6.98
6.98
6.96
6.85
6.82
6.81
6.79
6.77
6.75
6.58
6.54
6.52
6.49
6.29
6.24
6.16
6.11
6.01
5.98
4.99
4.97
4.94
2.93
2.93
2.91
2.90
2.88
2.87
2.85
2.80
2.46
2.44
2.41
2.39
2.38
2.36
2.25
1.49
1.47
1.46
1.44
1.43

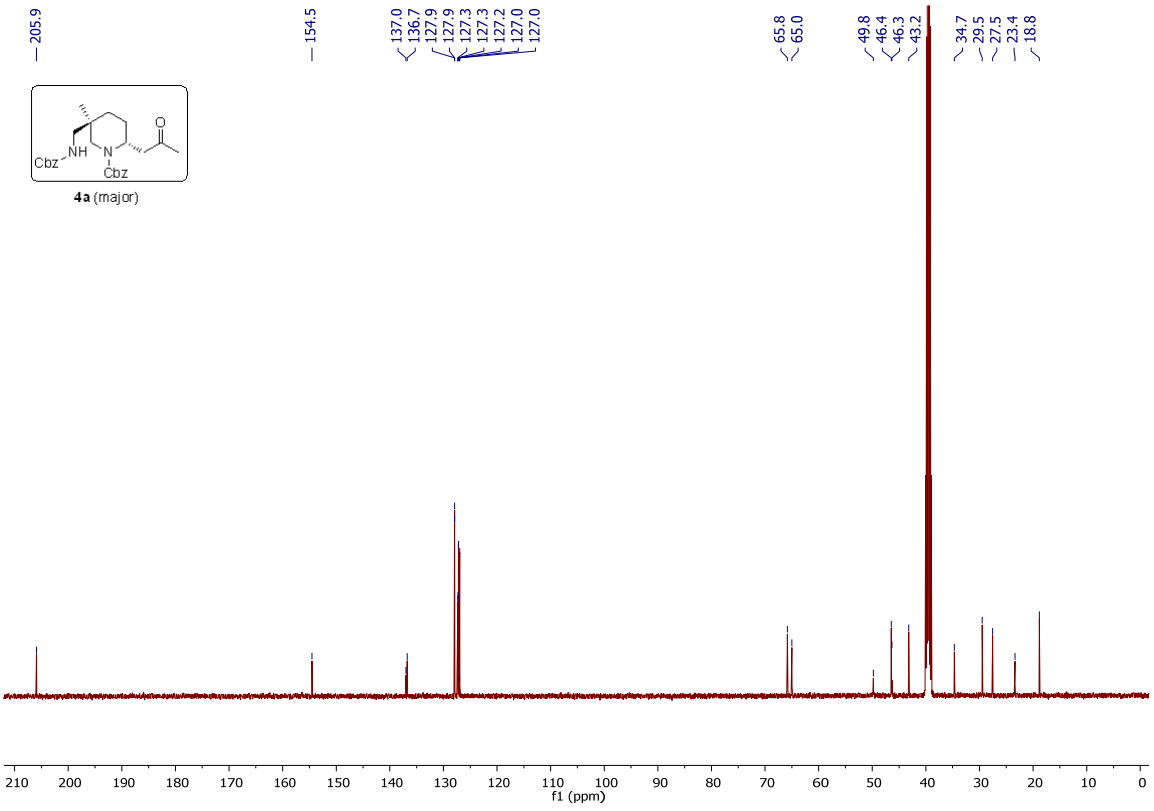
3m

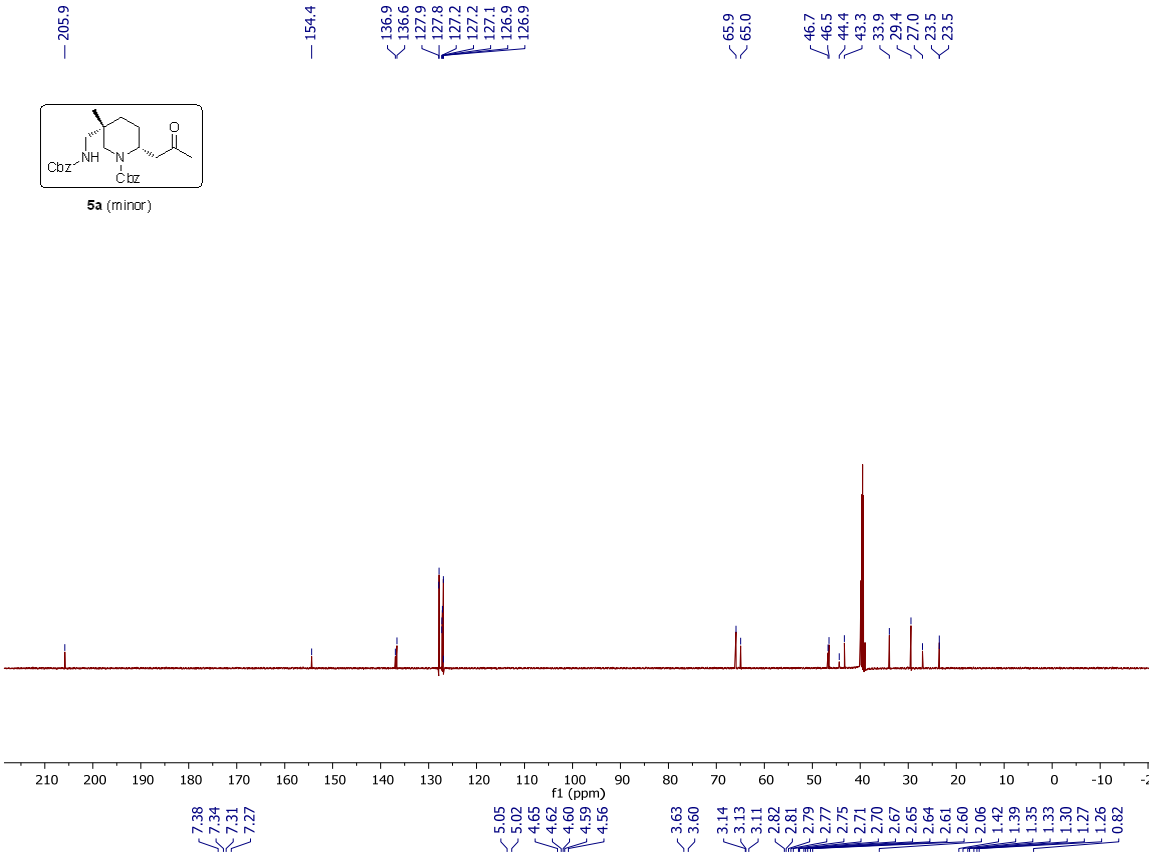

1.11
1.27
1.94
2.12
2.15
1.00
2.08
1.84
4.08
2.01
1.97
3.03
2.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


198.9
147.0
137.4
131.9
127.6
127.6
127.4
124.9
45.9
42.3
31.8
29.6
27.1
26.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

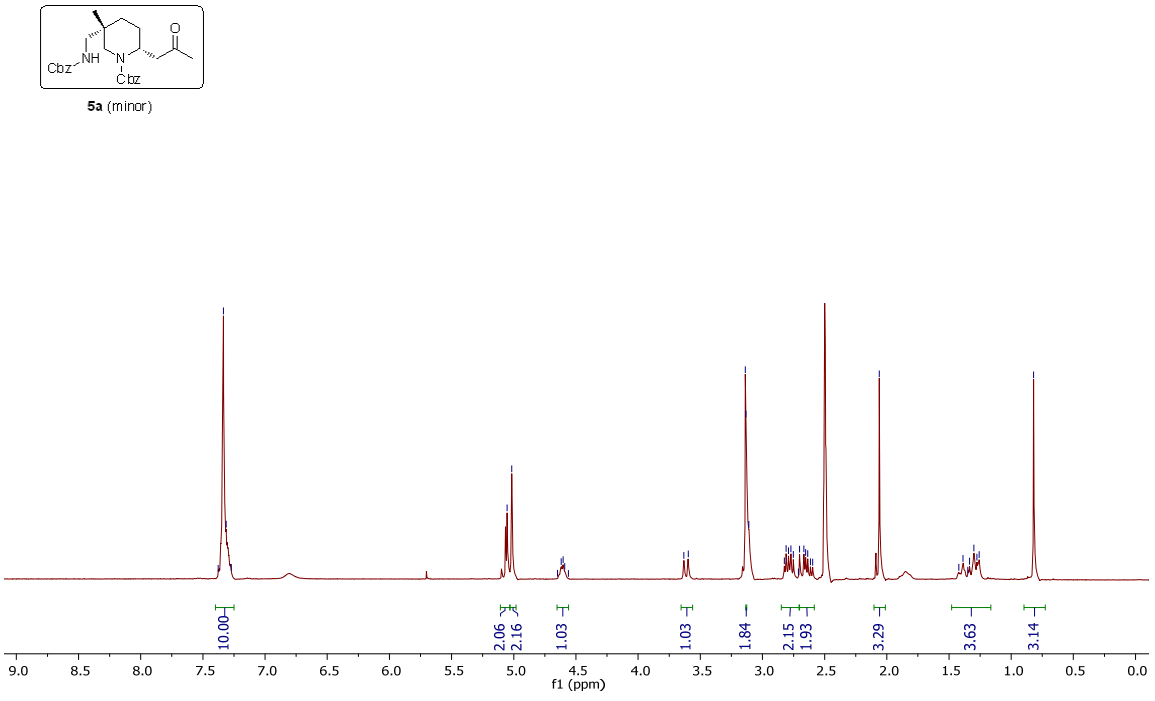
3m


7.37
7.35
7.35
7.33
7.31
5.06
5.04
4.67
4.66
4.64
4.63
3.57
3.54
2.91
2.89
2.79
2.77
2.75
2.73
2.71
2.68
2.60
2.59
2.56
2.55
2.52
2.06
1.79
1.74
1.71
1.70
1.52
1.48
1.47
1.45
1.44
1.37
1.34
1.25
1.14
1.10
0.77
Cbz
NH
N
Cbz
O
4a (major)
10.00
1.89
2.05
0.96
0.93
1.83
3.98
2.90
0.91
0.94
2.14
2.74
f1 (ppm)

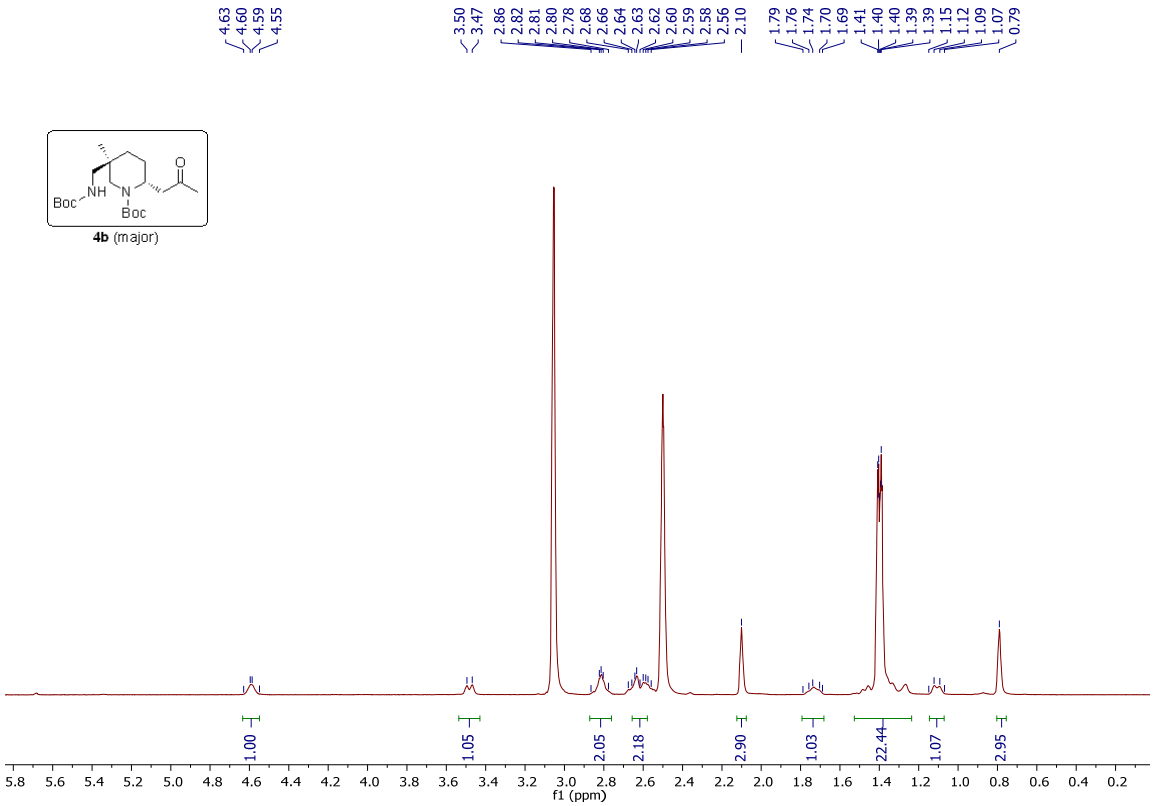

205.9
154.5
137.0
136.7
127.9
127.9
127.3
127.3
127.2
127.0
127.0
65.8
65.0
49.8
46.4
46.3
43.2
34.7
29.5
27.5
23.4
18.8
Cbz
NH
N
Cbz
O
4a (major)
f1 (ppm)



5a (minor)



5a (minor)


4.63
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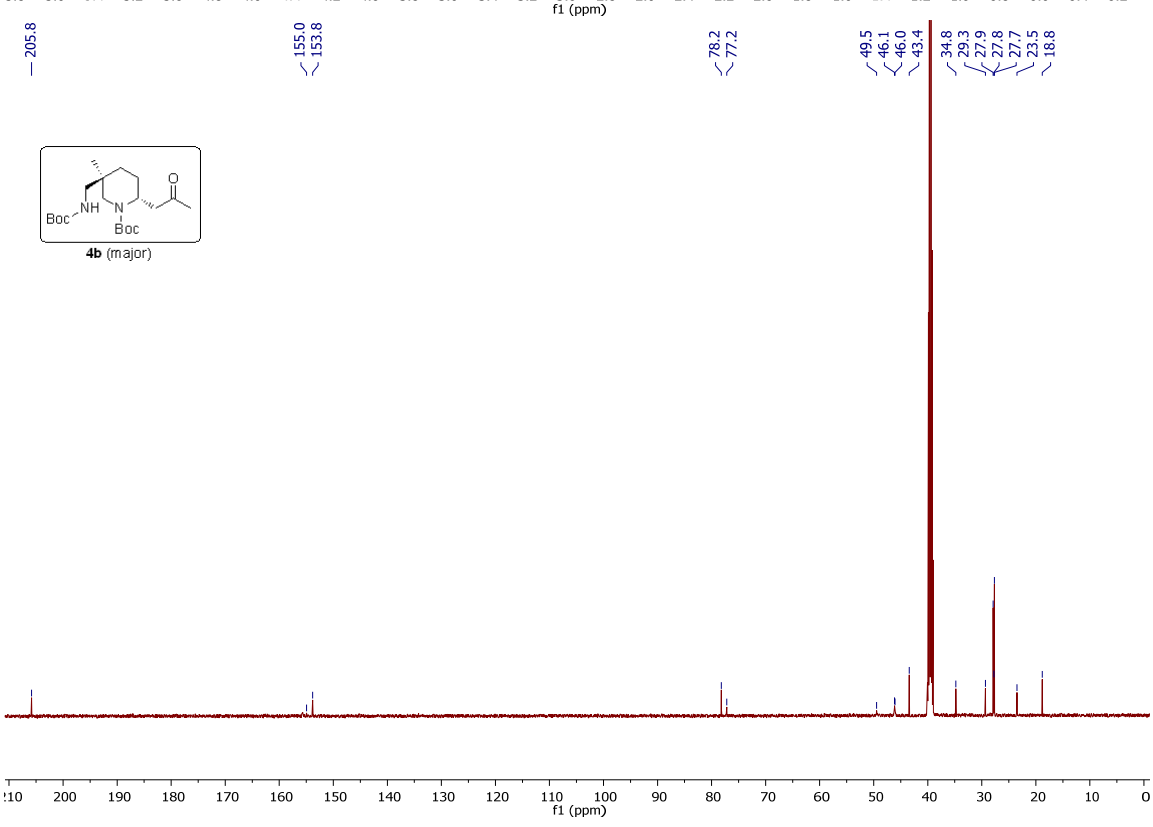
4.59
4.55
3.50
3.47
2.86
2.82
2.81
2.80
2.78
2.68
2.66
2.64
2.63
2.62
2.60
2.59
2.58
2.56
2.10
1.79
1.76
1.74
1.70
1.69
1.41
1.40
1.40
1.39
1.15
1.12
1.09
1.07
0.79
Boc
NH
N
Boc
O
4b (major)
1.00
1.05
2.05
2.18
2.90
1.03
22.44
1.07
2.95
f1 (ppm)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153.8
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46.0
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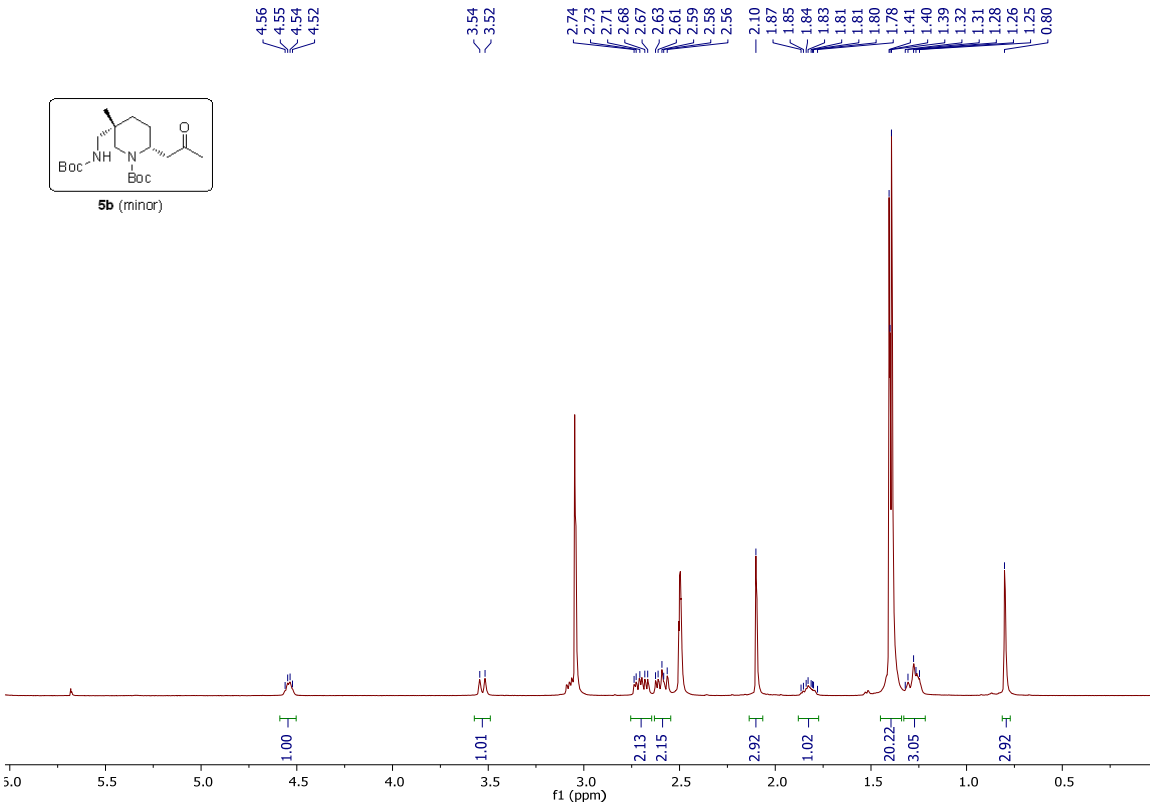
27.7
23.5
18.8
Boc
NH
N
Boc
O
4b (major)
f1 (ppm)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2.61
2.59
2.58
2.56
2.10
1.87
1.85
1.84
1.83
1.81
1.81
1.80
1.78
1.41
1.40
1.39
1.32
1.31
1.28
1.26
1.25
0.80
Boc
NH
N
Boc
O
5b (minor)
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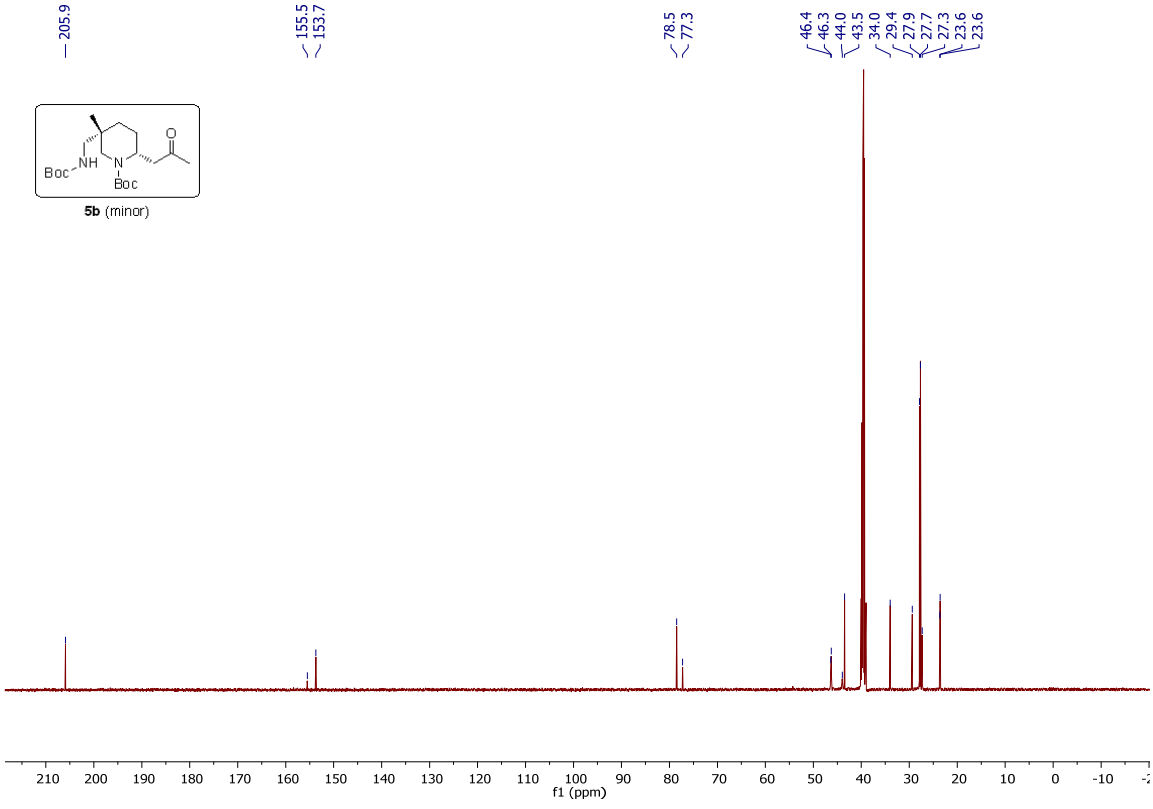
1.01
2.13
2.15
2.92
1.02
20.22
3.05
2.92
f1 (ppm)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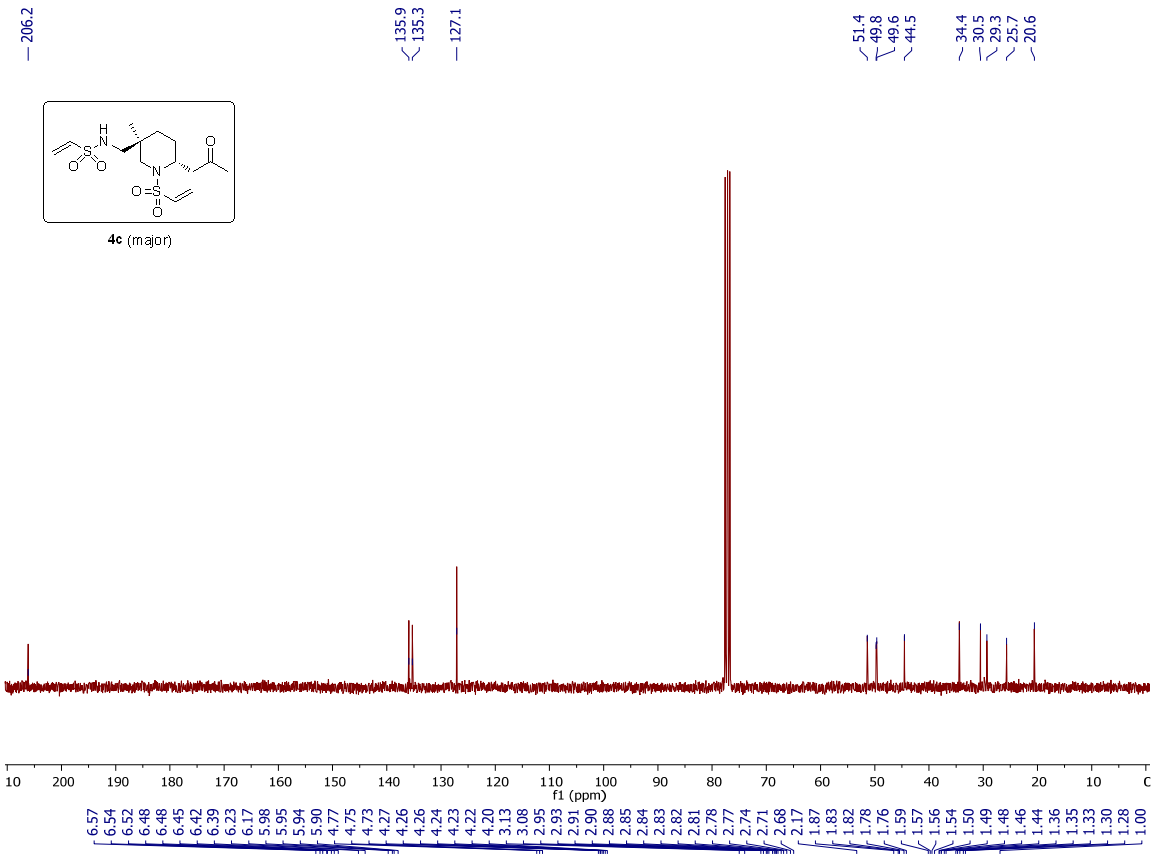
155.5
153.7
78.5
77.3
46.4
46.3
44.0
43.5
34.0
29.4
27.9
27.7
27.3
23.6
23.6
Boc
NH
N
Boc
O
5b (minor)
f1 (ppm)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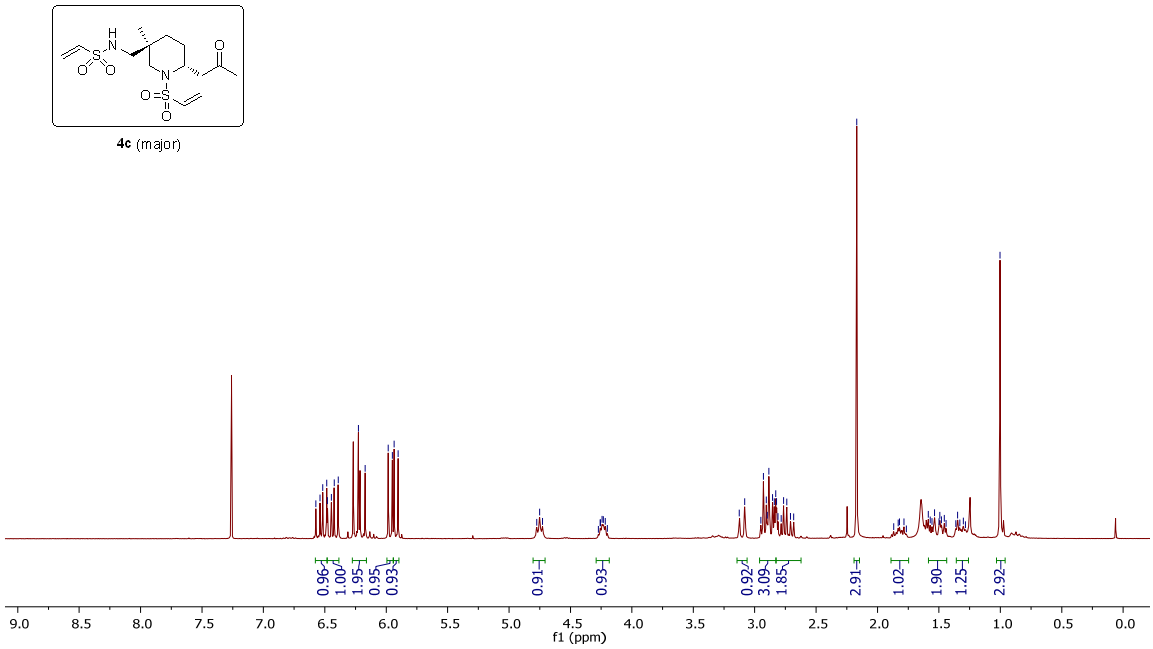
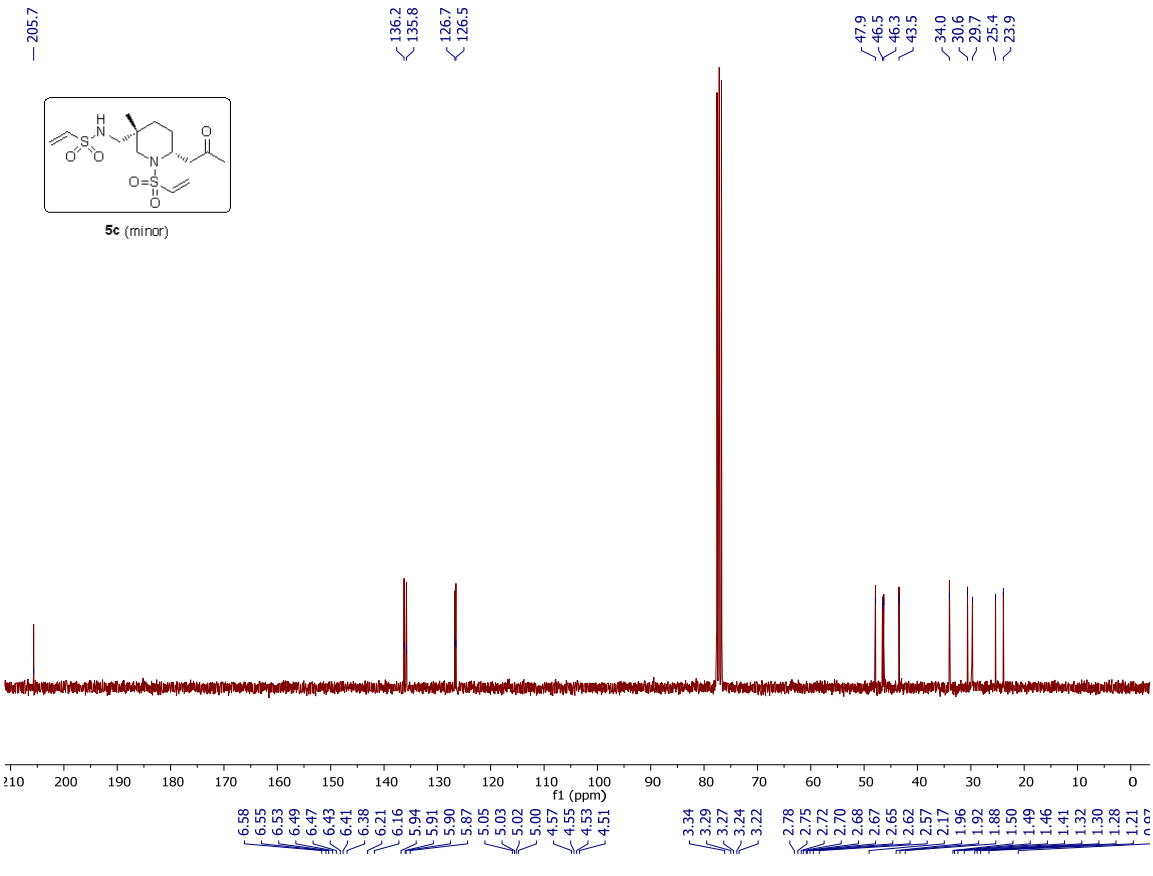
135.9
135.3
127.1
51.4
49.8
49.6
44.5
34.4
30.5
29.3
25.7
20.6
4c (major)
f1 (ppm)


4c (major)
0.96
1.00
1.95
0.95
0.93
0.91
0.93
0.92
3.09
1.85
2.91
1.02
1.90
1.25
2.92
f1 (ppm)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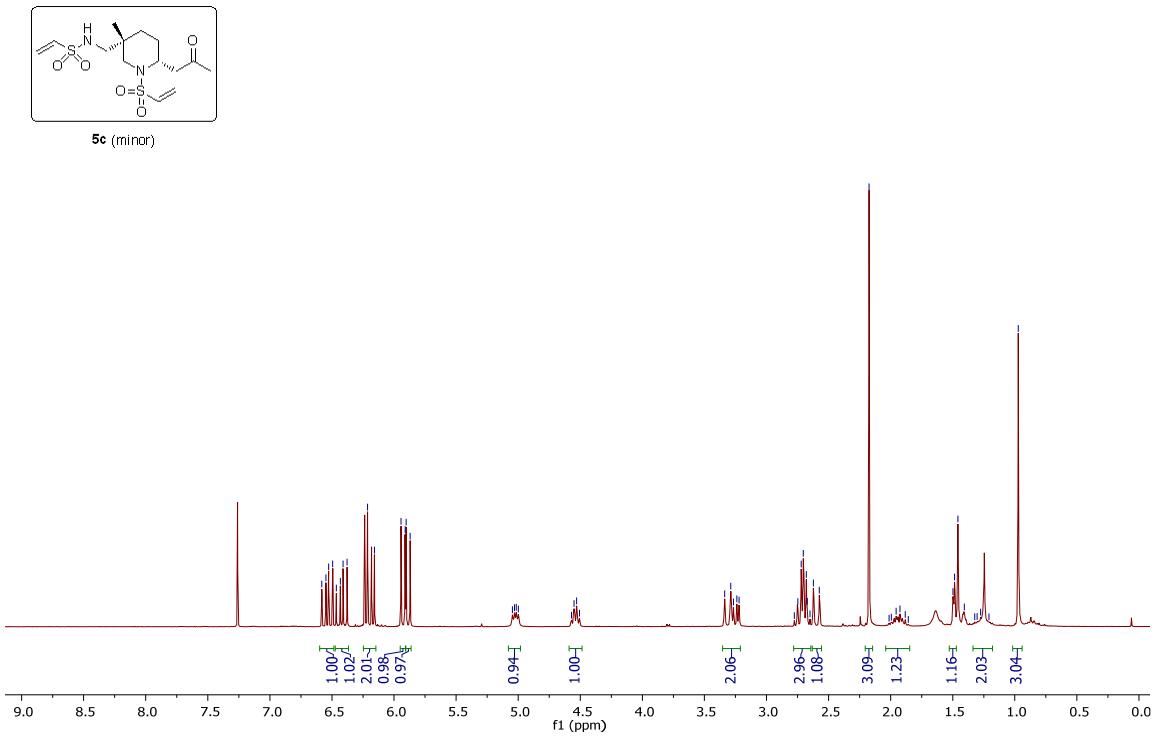
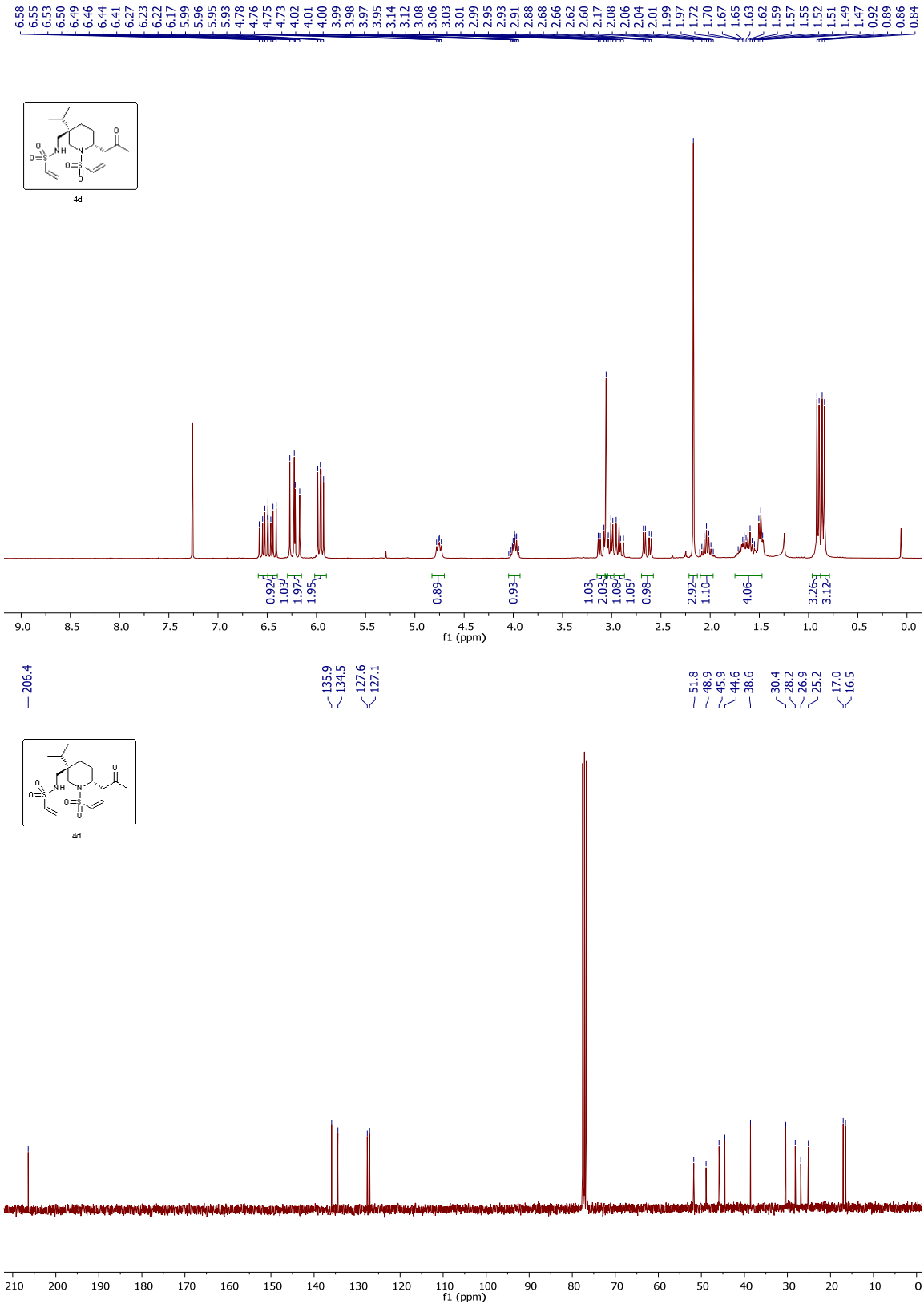
136.2
135.8
126.7
126.5
47.9
46.5
46.3
43.5
34.0
30.6
29.7
25.4
23.9
5c (minor)
f1 (ppm)


5c (minor)
f1 (ppm)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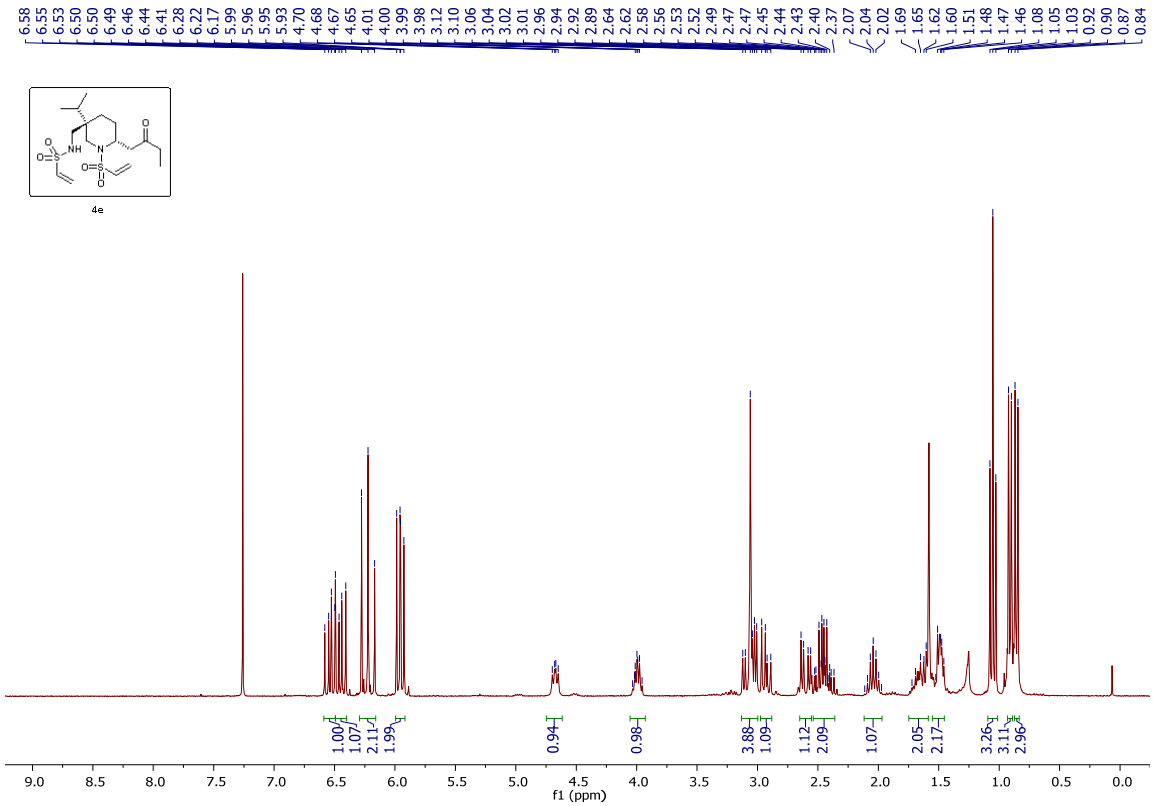
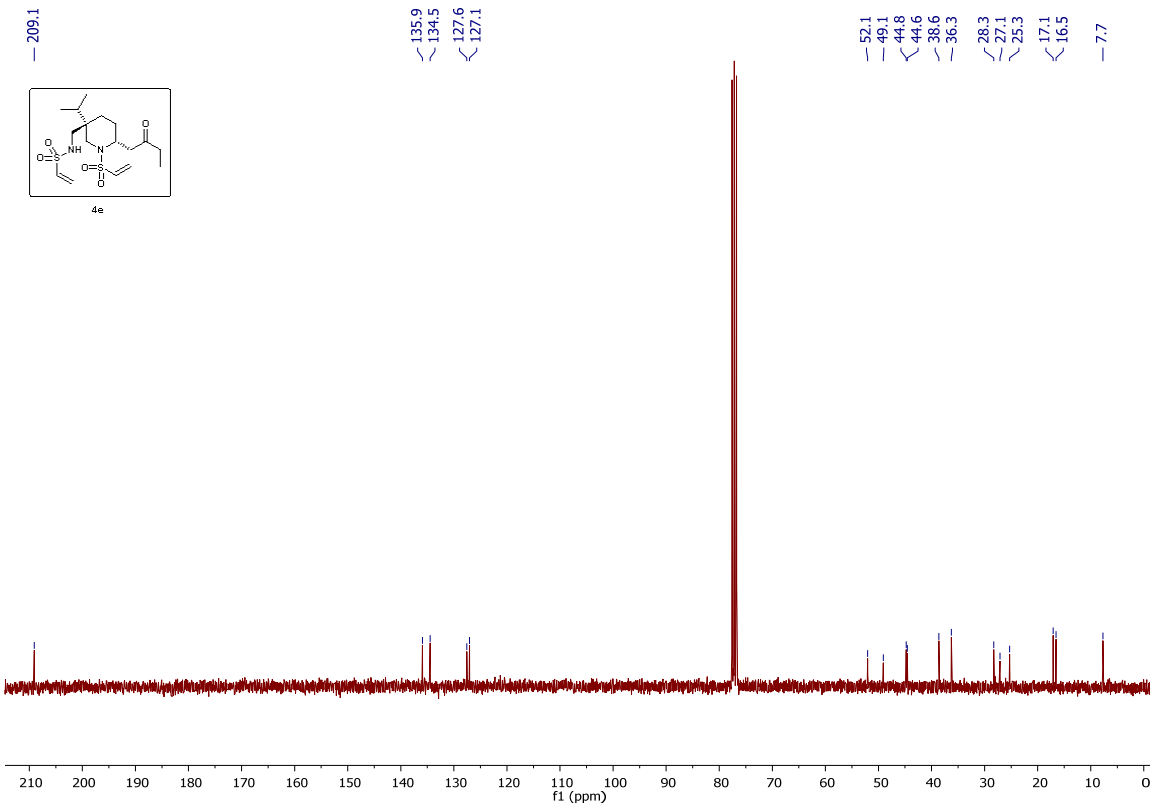
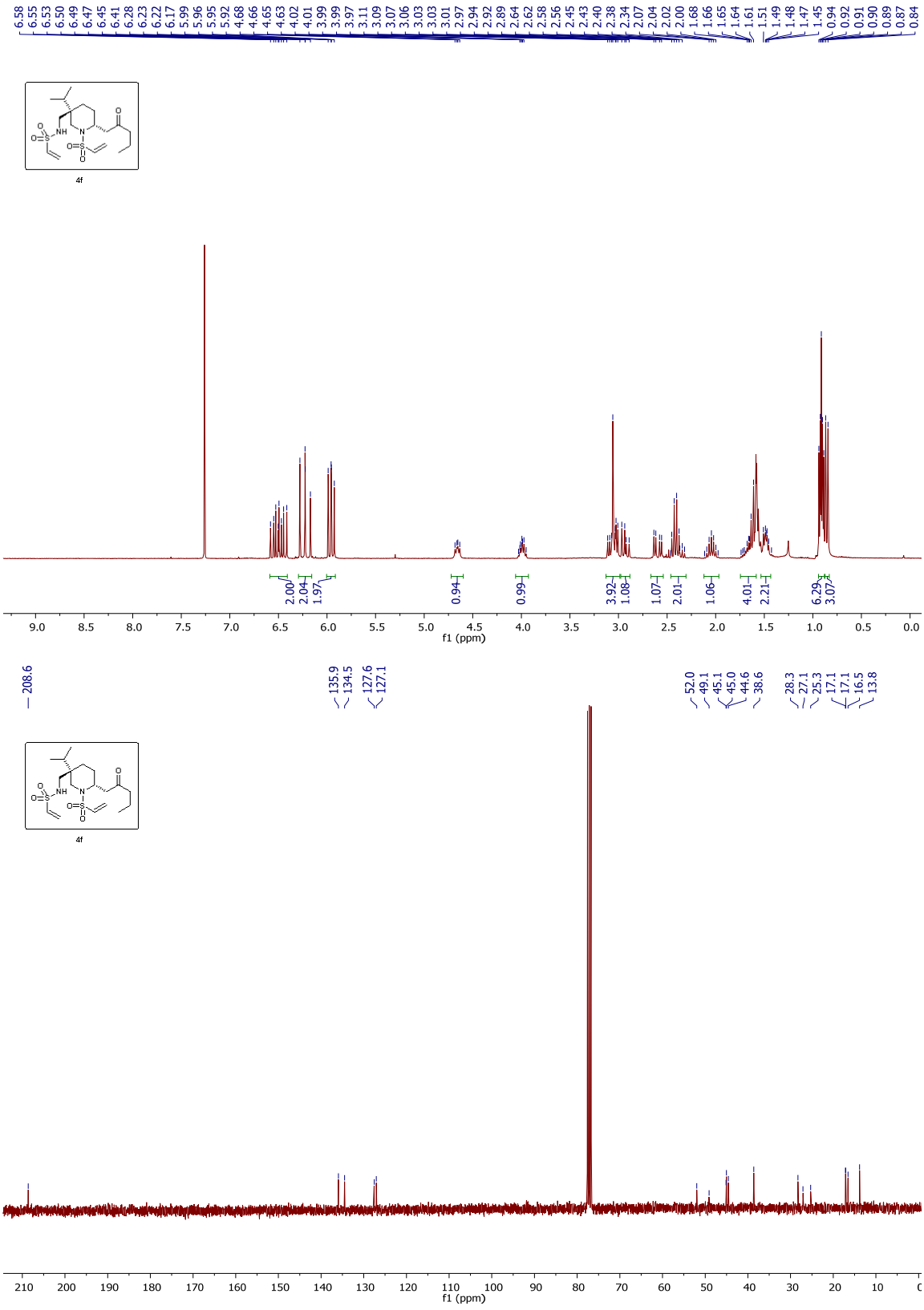
4d
0.92 1.03 1.97 1.95 0.89 0.93 1.03 2.03 1.08 1.05 0.98 2.92 1.10 4.06 3.26 3.12
f1 (ppm)
206.4 135.9 134.5 127.6 127.1 51.8 48.9 45.9 44.6 38.6 30.4 28.2 26.9 25.2 17.0 16.5
4d
f1 (ppm)


6.58 6.55 6.53 6.50 6.50 6.49 6.46 6.44 6.41 6.28 6.22 6.17 5.99 5.96 5.95 5.93 4.70 4.68 4.67 4.65 4.01 4.00 3.99 3.98 3.12 3.10 3.06 3.04 3.02 3.01 2.96 2.94 2.92 2.89 2.64 2.62 2.58 2.56 2.53 2.52 2.49 2.47 2.47 2.45 2.44 2.43 2.40 2.37 2.07 2.04 2.02 1.69 1.65 1.62 1.60 1.51 1.48 1.47 1.46 1.08 1.05 1.03 0.92 0.90 0.87 0.84
4e
1.00 1.07 2.11 1.99 0.94 0.98 3.88 1.09 1.12 2.09 1.07 2.05 2.17 3.26 3.11 2.96
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 0.0
f1 (ppm)


209.1
135.9 134.5 127.6 127.1
52.1 49.1 44.8 44.6 38.6 36.3 28.3 27.1 25.3 17.1 16.5 7.7
4e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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4f
2.00 2.04 1.97 0.94 0.99 3.92 1.08 1.07 2.01 1.06 4.01 2.21 6.29 3.07
f1 (ppm)
208.6 135.9 134.5 127.6 127.1 52.0 49.1 45.1 45.0 44.6 38.6 28.3 27.1 25.3 17.1 17.1 16.5 13.8
4f
f1 (ppm)


6.58
6.55
6.52
6.50
6.49
6.47
6.44
6.41
6.27
6.22
6.22
6.17
5.99
5.95
5.92
4.71
4.70
4.69
4.67
4.01
4.00
3.99
3.98
3.10
3.07
3.06
3.04
3.02
3.00
2.96
2.93
2.91
2.88
2.65
2.63
2.59
2.57
2.46
2.43
2.41
2.38
2.07
2.04
2.02
1.68
1.67
1.65
1.63
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1.56
1.54
1.51
1.49
1.47
1.45
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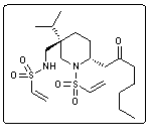
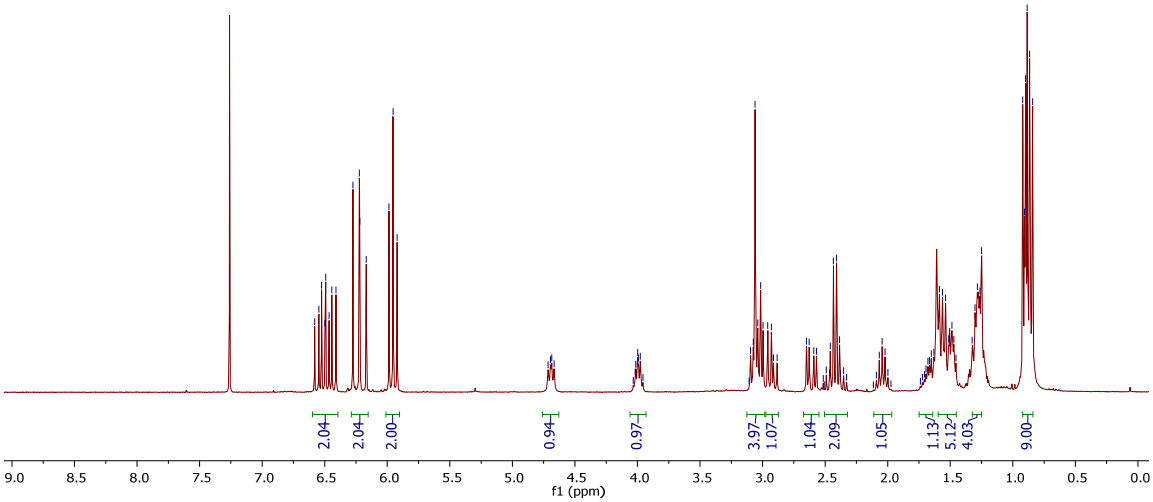
1.30
1.28
1.26
1.25
0.92
0.91
0.90
0.88
0.87
0.84


4g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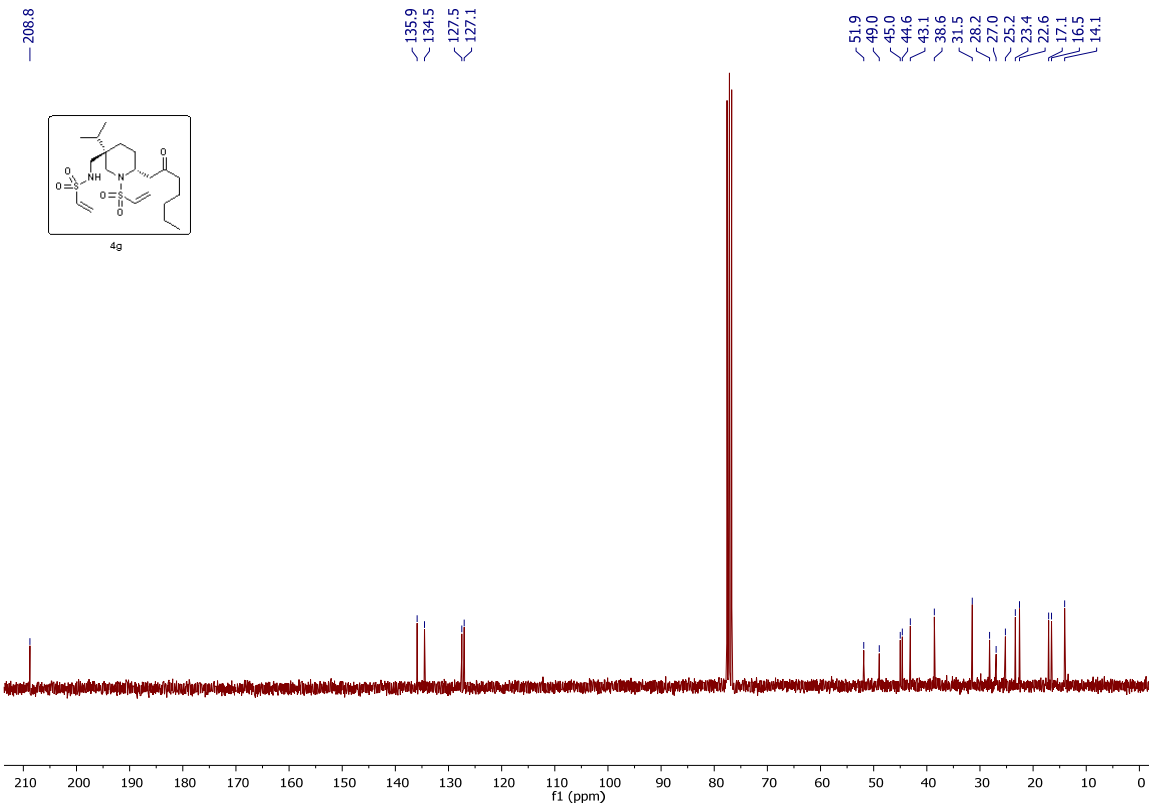
3.97
1.07
1.04
2.09
1.05
1.13
5.12
4.03
9.00
f1 (ppm)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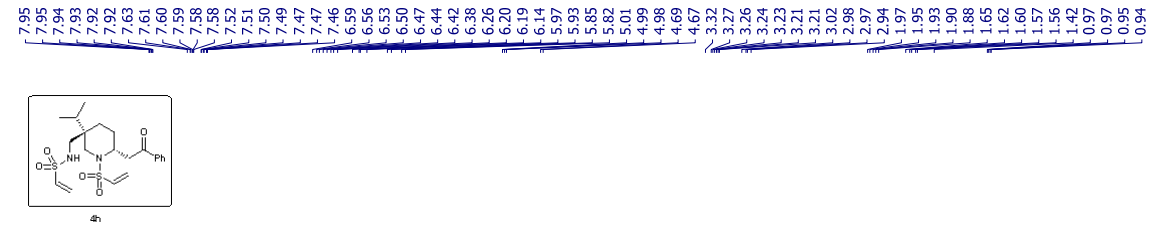
134.5
127.5
127.1
51.9
49.0
45.0
44.6
43.1
38.6
31.5
28.2
27.0
25.2
23.4
22.6
17.1
16.5
14.1
f1 (ppm)

4g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7.94
7.93
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7.92
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7.58
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7.50
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7.47
7.47
7.46
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6.56
6.53
6.50
6.47
6.44
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6.38
6.26
6.20
6.19
6.14
5.97
5.93
5.85
5.82
5.01
4.99
4.98
4.69
4.67
3.32
3.27
3.26
3.24
3.23
3.21
3.02
2.98
2.97
2.94
1.97
1.95
1.93
1.90
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1.62
1.60
1.57
1.56
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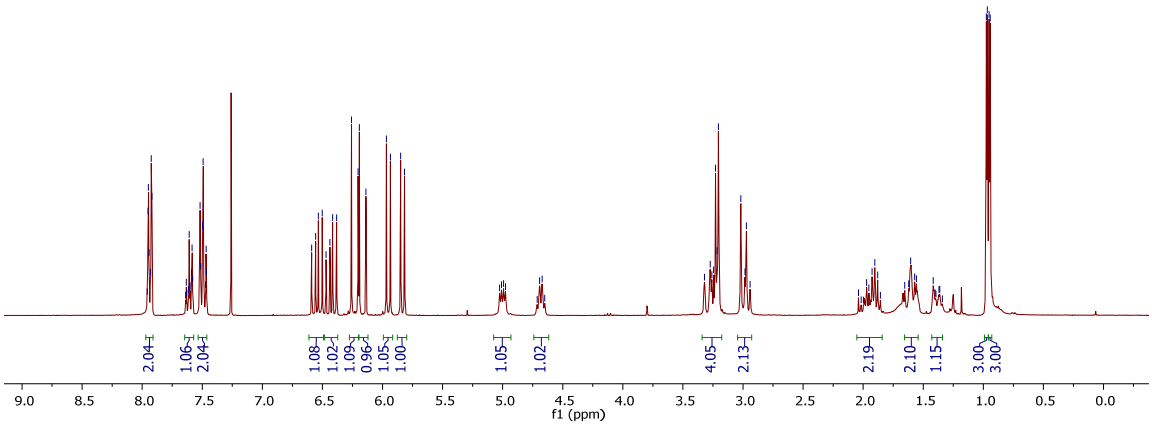
0.97
0.97
0.95
0.94

4h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2.04
1.08
1.02
1.09
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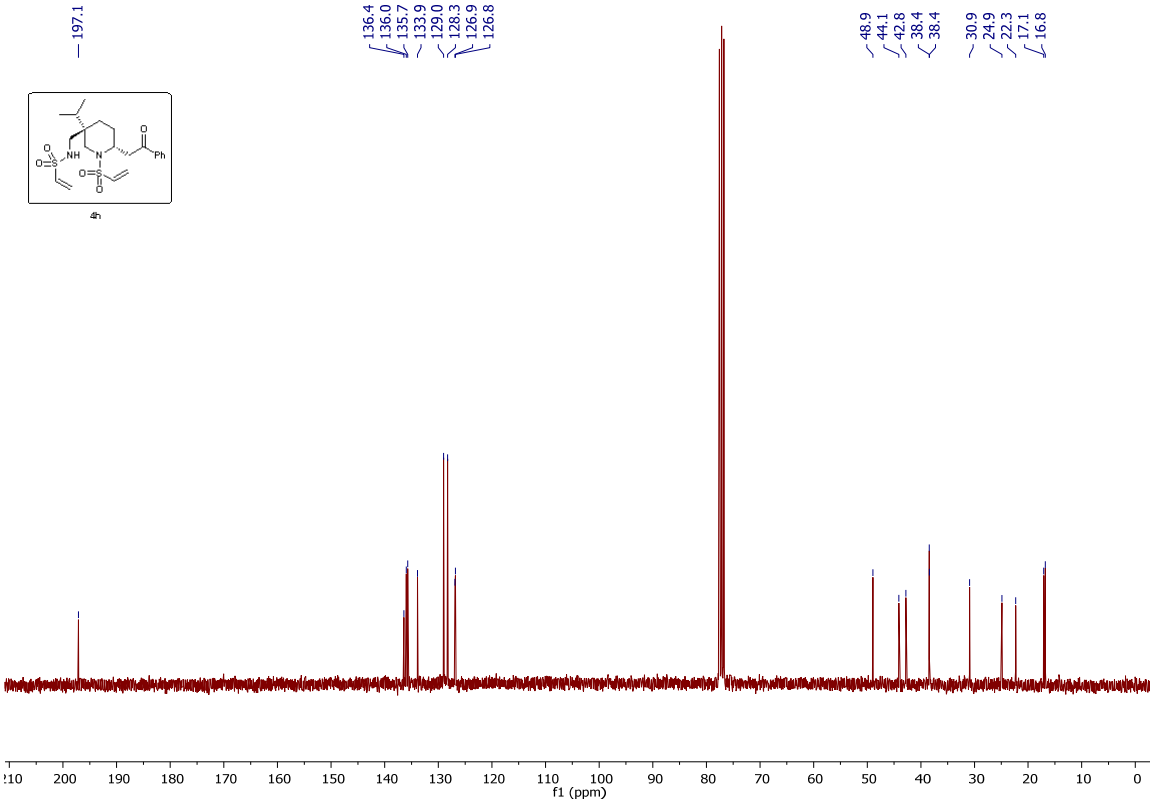
1.05
1.00
1.05
1.02
4.05
2.13
2.19
2.10
1.15
3.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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135.7
133.9
129.0
128.3
126.9
126.8
48.9
44.1
42.8
38.4
38.4
30.9
24.9
22.3
17.1
16.8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

4h


7.40
7.39
7.37
7.37
7.36
7.35
7.34
7.34
7.33
7.32
7.31
7.29
7.28
6.49
6.45
6.43
6.40
6.35
6.32
6.29
6.26
6.22
6.16
6.15
5.94
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4.95
4.92
4.90
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4.54
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4.32
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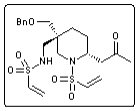
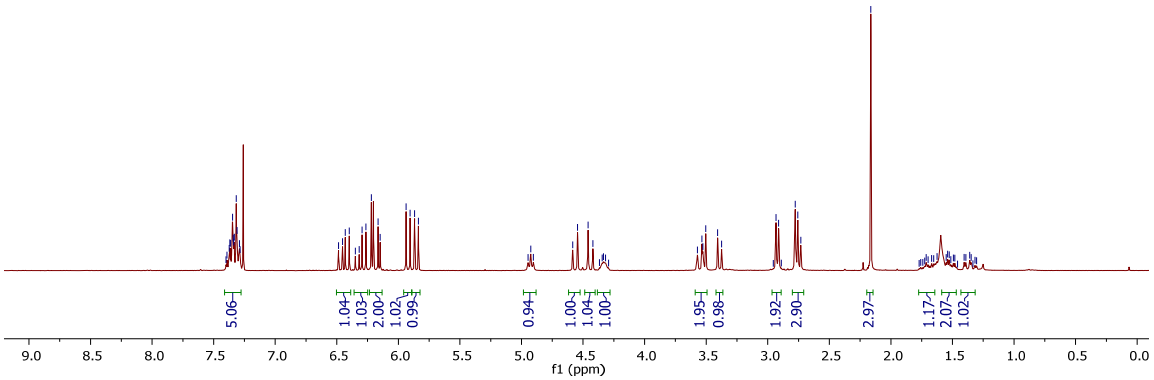
1.32


BnO
NH
N
O
S
O
O
O
O
S
O
O

4i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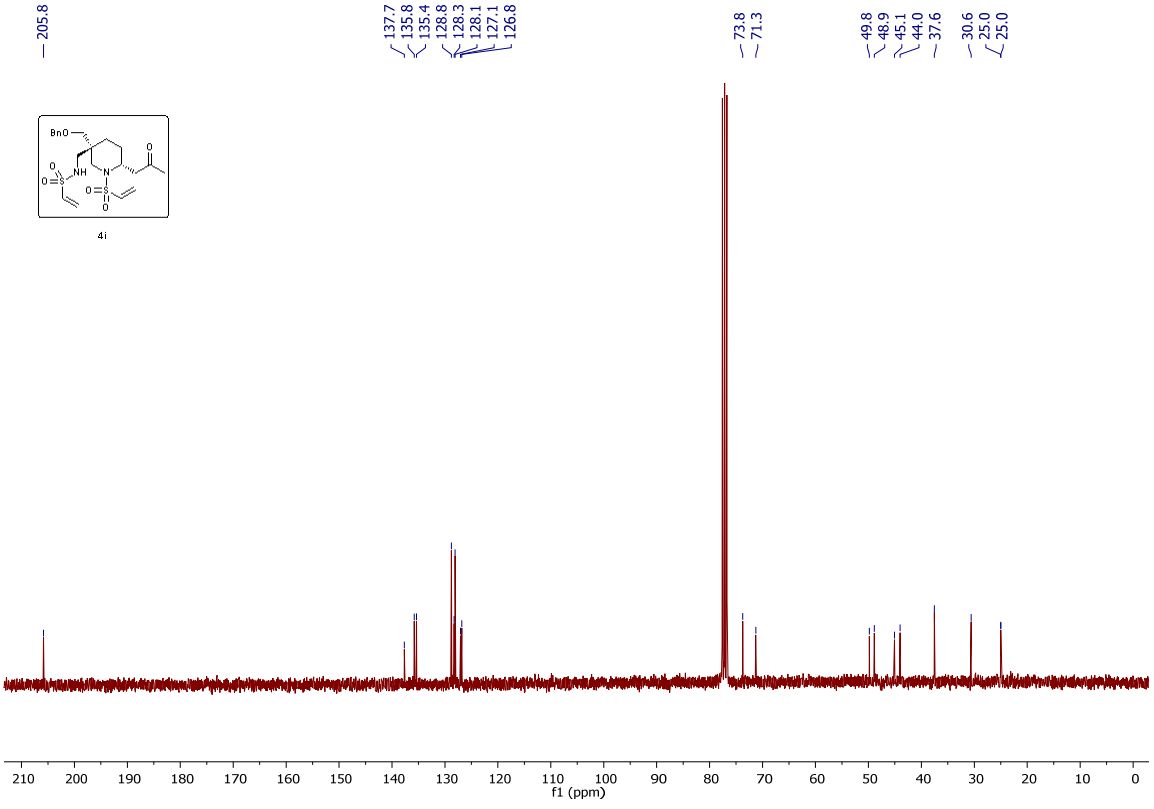
1.02
0.99
0.94
1.00
1.04
1.00
1.95
0.98
1.92
2.90
2.97
1.17
2.07
1.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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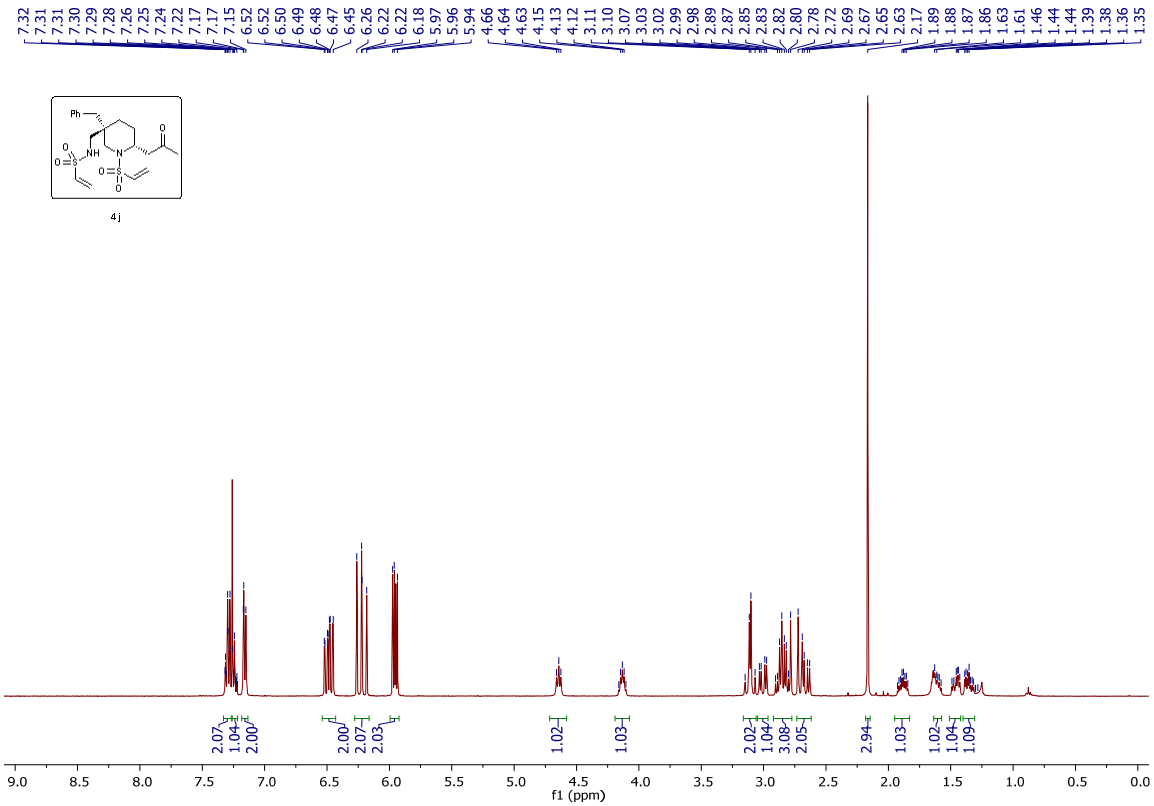
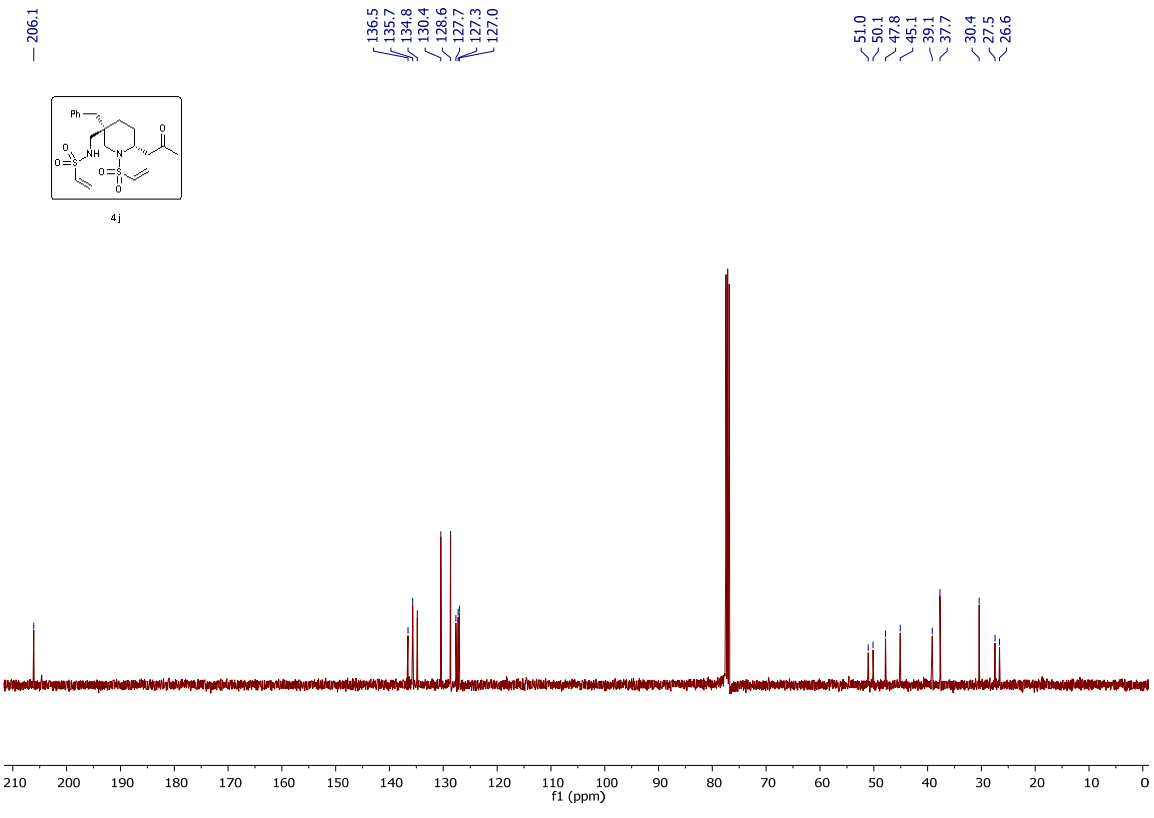
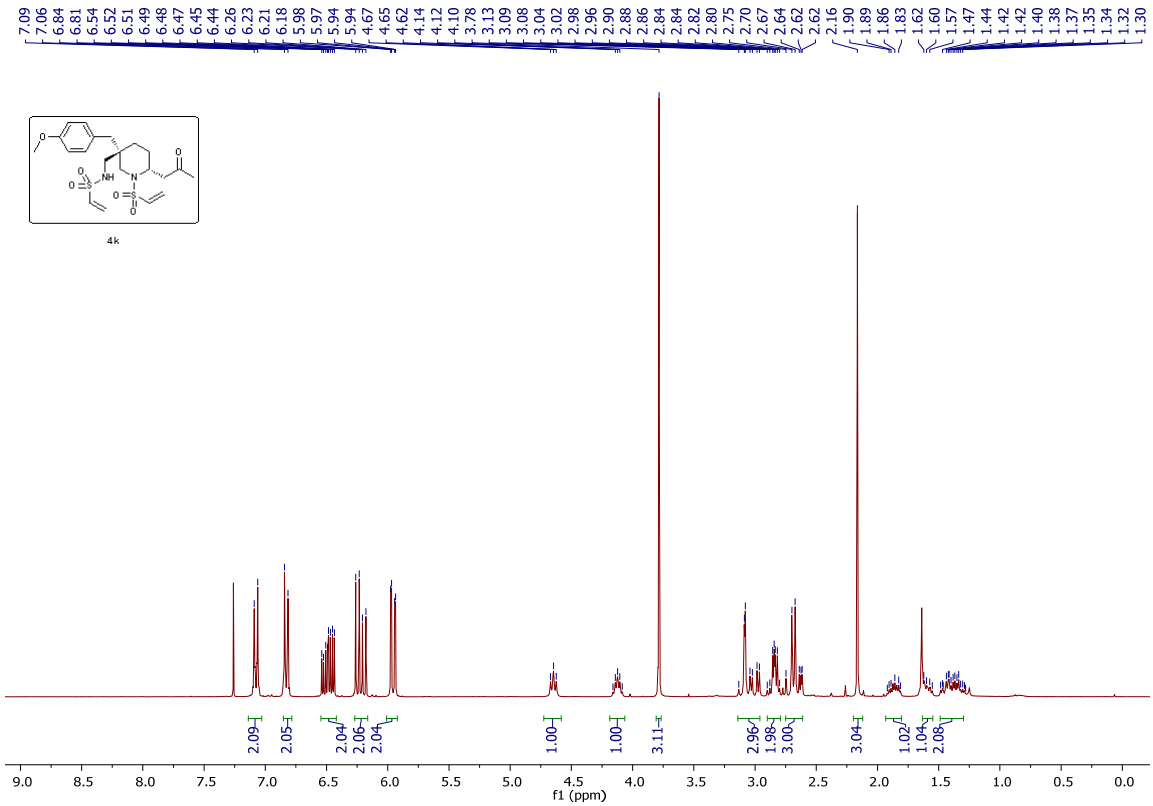
135.4
128.8
128.3
128.1
127.1
126.8
73.8
71.3
49.8
48.9
45.1
44.0
37.6
30.6
25.0
25.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

BnO
NH
N
O
S
O
O
O
O
S
O
O

4i


7.32 7.31 7.31 7.30 7.29 7.28 7.26 7.25 7.24 7.22 7.17 7.17 7.15 6.52 6.52 6.50 6.49 6.48 6.47 6.45 6.26 6.22 6.22 6.18 5.97 5.96 5.94 4.66 4.64 4.63 4.15 4.13 4.12 3.11 3.10 3.07 3.03 3.02 2.99 2.98 2.89 2.87 2.85 2.83 2.82 2.80 2.78 2.72 2.69 2.67 2.65 2.63 2.17 1.89 1.88 1.87 1.86 1.63 1.61 1.46 1.44 1.44 1.39 1.38 1.36 1.35
Ph
NH
N
4j
2.07 1.04 2.00 2.00 2.07 2.03 1.02 1.03 2.02 1.04 3.08 2.05 2.94 1.03 1.02 1.04 1.09
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 0.0
f1 (ppm)


206.1
136.5 135.7 134.8 130.4 128.6 127.7 127.3 127.0
51.0 50.1 47.8 45.1 39.1 37.7 30.4 27.5 26.6
Ph
NH
N
4j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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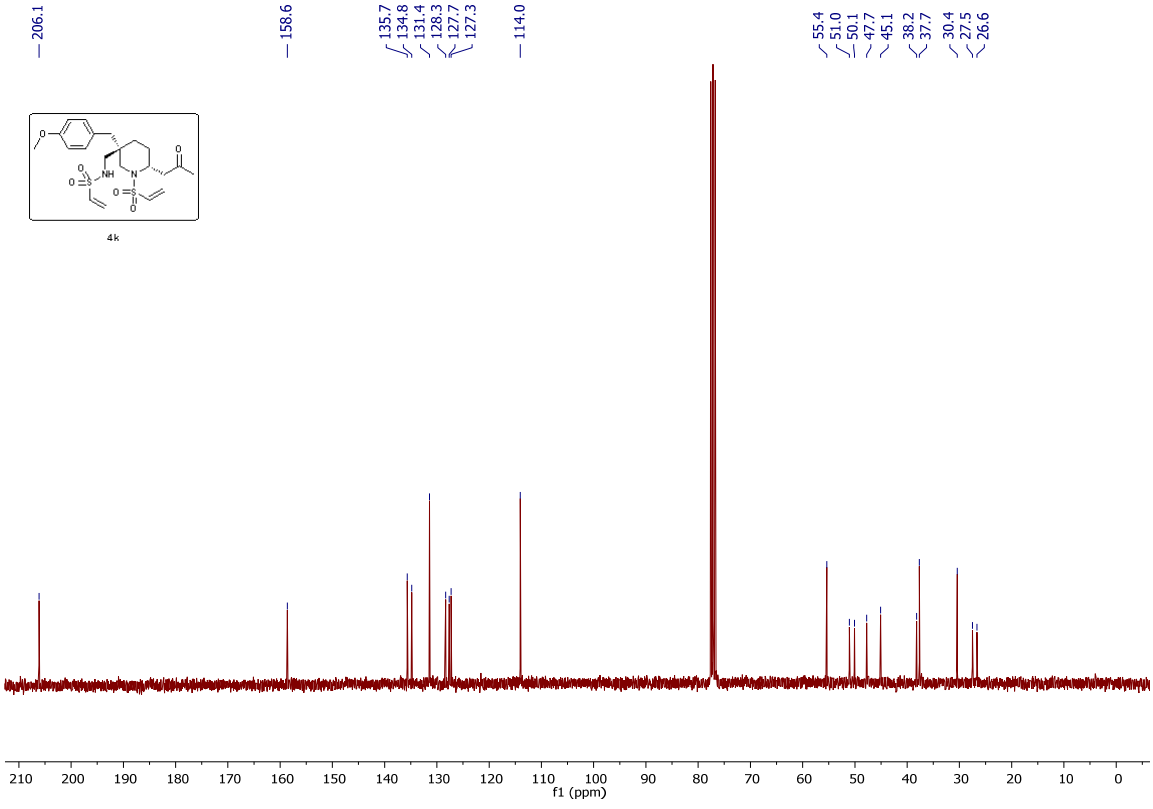
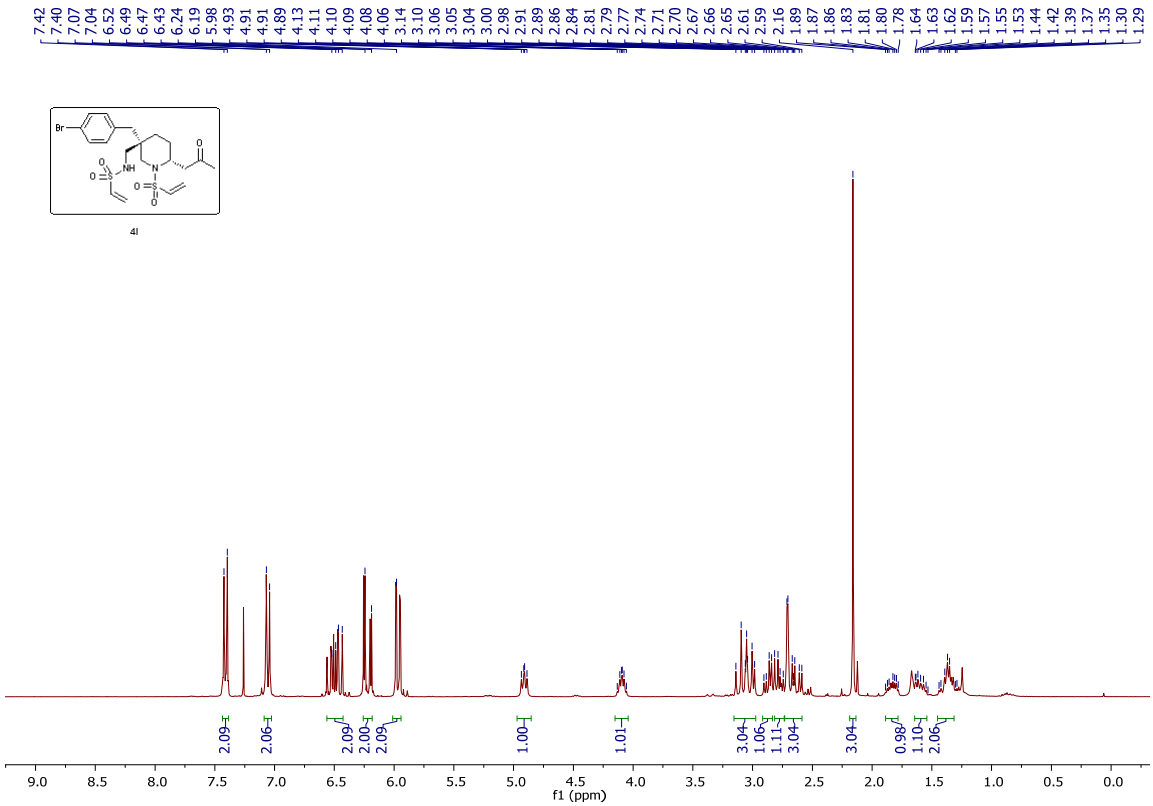
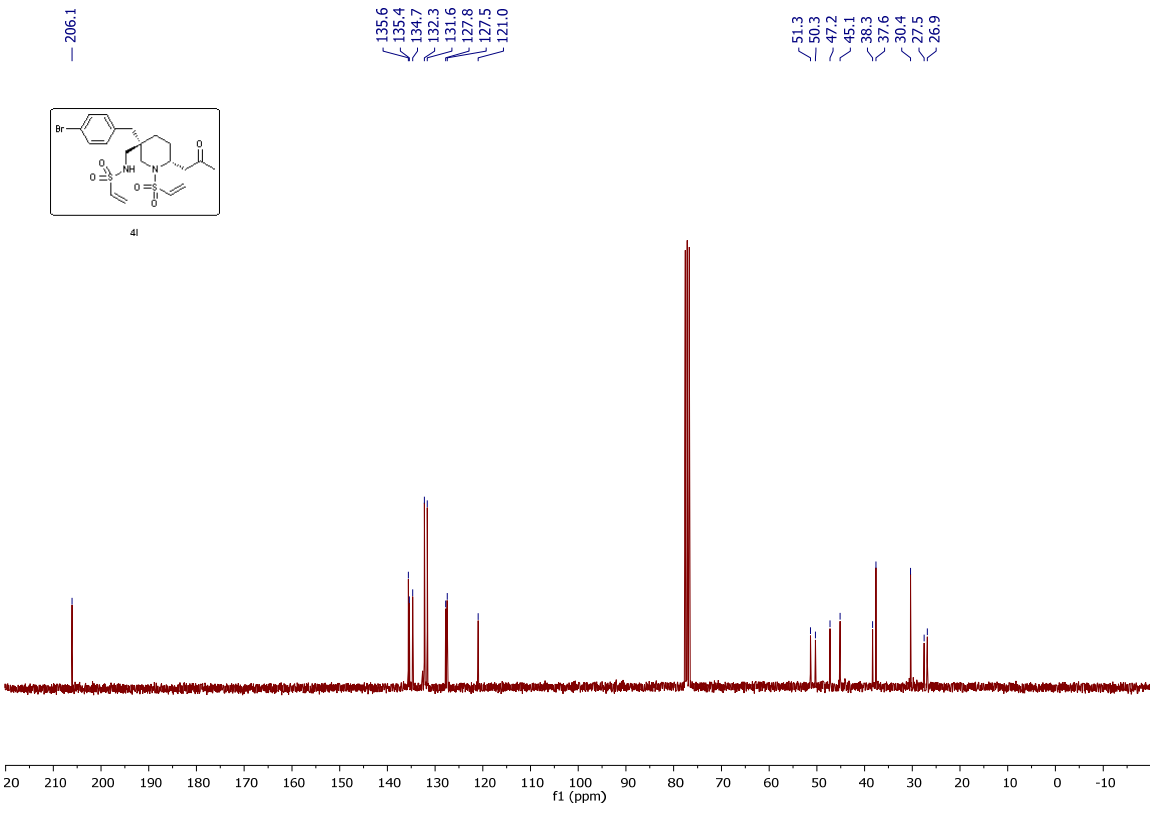
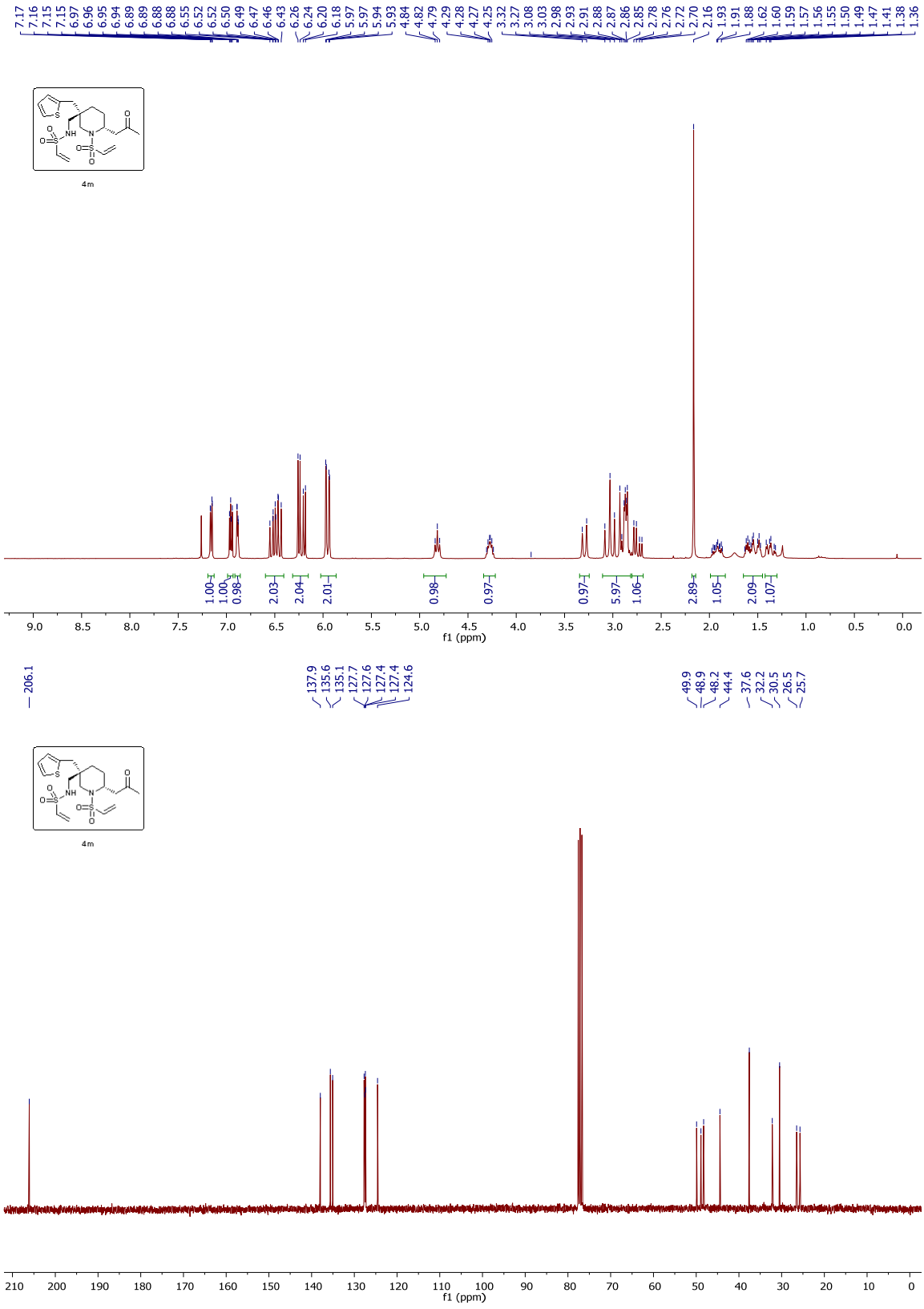
4k
2.09 2.05 2.04 2.06 2.04 1.00 1.00 3.11 2.96 1.98 3.00 3.04 1.02 1.04 2.08
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


206.1 158.6 135.7 134.8 131.4 128.3 127.7 127.3 114.0 55.4 51.0 50.1 47.7 45.1 38.2 37.7 30.4 27.5 26.6
4k
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.42 7.40 7.07 7.04 6.52 6.49 6.47 6.43 6.24 6.19 5.98 4.93 4.91 4.91 4.89 4.13 4.11 4.10 4.09 4.08 4.06 3.14 3.10 3.06 3.05 3.04 3.00 2.98 2.91 2.89 2.86 2.84 2.81 2.79 2.77 2.74 2.71 2.70 2.67 2.66 2.65 2.61 2.59 2.16 1.89 1.87 1.86 1.83 1.81 1.80 1.78 1.64 1.63 1.62 1.59 1.57 1.55 1.53 1.44 1.42 1.39 1.37 1.35 1.30 1.29
Br
O
NH
N
O
S
O
O
O
S
O
O
4l
2.09 2.06 2.09 2.00 2.09 1.00 1.01 3.04 1.06 1.11 3.04 3.04 0.98 1.10 2.06
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 0.0
f1 (ppm)


206.1
135.6 135.4 134.7 132.3 131.6 127.8 127.5 121.0
51.3 50.3 47.2 45.1 38.3 37.6 30.4 27.5 26.9
Br
O
NH
N
O
S
O
O
O
S
O
O
4l
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.17 7.16 7.15 7.15 6.97 6.96 6.95 6.94 6.89 6.89 6.88 6.88 6.55 6.52 6.52 6.50 6.49 6.47 6.46 6.43 6.26 6.24 6.20 6.18 5.97 5.97 5.94 5.93 4.84 4.82 4.79 4.29 4.28 4.27 4.25 3.32 3.27 3.08 3.03 2.98 2.93 2.91 2.88 2.87 2.86 2.85 2.78 2.76 2.72 2.70 2.16 1.93 1.91 1.88 1.62 1.60 1.59 1.57 1.56 1.55 1.50 1.49 1.47 1.41 1.38 1.36
4m
1.00 1.00 0.98 2.03 2.04 2.01 0.98 0.97 0.97 5.97 1.06 2.89 1.05 2.09 1.07
f1 (ppm)
206.1
137.9 135.6 135.1 127.7 127.6 127.4 127.4 124.6
49.9 48.9 48.2 44.4 37.6 32.2 30.5 26.5 25.7
4m
f1 (ppm)