Continuous-Flow Thermolysis for the Preparation of Vinylglycine Derivatives

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Supporting Information

Contents

1. Experimental section

Compounds **1a-c** and **1e-g** were synthesized according to reported procedures. [S1] The preparation and characterization of compounds L-**1d** and **L-2d** are described hereafter.

1.1 Continuous-flow setup

1.1.1 Pumps

FLOM HPLC pumps (Intelligent Pump AI 12 Series) were selected for handling the feed solutions of compounds **1a-g** and the extraction solvent (water).

1.1.2 Connectors, ferrules and tubing

PFA/PEEK tubing, and PEEK/ETFE connectors and ferrules were utilized for the sections of the reactor exposed to low temperature and pressure (feed inlets, extraction module). SS tubing, connectors and ferrules were utilized for the sections of the reactor exposed to high temperature and pressure (Table S1).

Table S1. Tubing, Junctions, Nuts and Ferules

Equipment	Material	Specifications
Tubing	High-purity PFA tubing	1/16'' i.d., 1/8" o.d.
	PEEK tubing	1/32" i.d., 1/16" o.d.
	SS tubing	500 µm i.d., 1/16" o.d.
Mixers	Upchurch Scientific Tee, natural PEEK	1/4-28 thread for 1/8" o.d. tubing, 0.05" (1.25 mm) thru hole
Nuts	Upchurch Scientific Super Flangeless Nuts, natural PEEK	1/4-28 thread for 1/8" o.d. tubing; 1/4-28 thread for 1/16" o.d. tubing
	Upchurch Scientific fingertight Nuts, natural PEEK	10/32 thread for 1/16" o.d. tubing
	SS Valco internal nut	For 1/16" o.d. tubing
Ferrules	Upchurch Scientific Super Flangeless Ferrules, yellow ETFE	1/8" and 1/16" o.d. tubing
	Valco Type 303 stainless ferrules	For 1/16" o.d. tubing
Unions	SS Valco internal unions	1/16'' standard with 0.15 mm bore

1.1.3 Back pressure regulators

Upchurch Scientific back pressure regulators (BPRs) were utilized. 250 PSI BPRs were inserted after the pressure transducer of the HPLC pumps to ensure steady pump operation. A 1000 PSI BPR was inserted after the thermolysis reactor to sustain superheated conditions.

1.1.4 Membrane separator

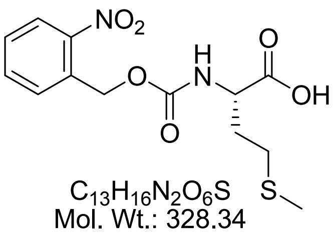
A continuous-flow liquid-liquid membrane separator (Zaiput Flow Technologies®) with a PTFE membrane (0.5 µm pores) was utilized after the extraction loop.

1.2 HPLC method

HPLC analyses were performed on a Waters setup (Alliance 2695 system, Empower software) with a 996 PDA UV detector (190 – 400 nm) using a X-Terra® RP18 column (150 x 4.6 mm, 3.5 µm) with a 70:30 mixture acetonitrile/H_2O containing 0.1% TFA. Conversions were measured at 210 nm.

1.3 General procedure for the preparation of L-1d

1.3.1 NBOC-L-methionine



$C_{13}H_{16}N_2O_6S$
Mol. Wt.: 328.34

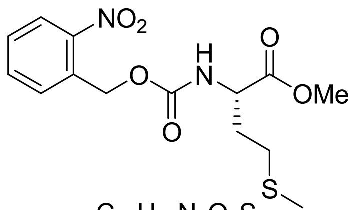
To a solution of L-methionine (2.98 g, 20 mmol, 1.0 equiv.) in 20 mL of $NaOH_{aq}$ (1 M, 1.0 equiv.) were added dropwise a solution of 2-nitrobenzyl chloroformate [S2] (6.47 g, 30 mmol, 1.5 equiv.) in toluene (30 mL) and 30 mL of $NaOH_{aq}$ (1 M, 1.5 equiv.) at 0 °C under vigorous stirring. After 12 h of reaction at room temperature, the organic phase was discarded and the aqueous phase was washed with diethyl ether (3x 50 mL). The pH of the aqueous phase was then adjusted to 1 with aqueous $KHSO_4$ (10% wt.), and the title compound was extracted with dichloromethane (3x 50 mL). The combined dichloromethane fractions were then dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a yellow oil (5.39 g, yield = 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (br s, 1H), 8.08 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.71-7.52 (m, 2H), 7.51-7.41 (m, 1H), 5.66 (d, *J* = 8.2 Hz, 1H), 5.54 (s, 2H), 4.56-4.45 (m, 1H), 2.66-2.50 (m, 2H), 2.28-2.13 (m, 1H), 2.10 (s, 3H), 2.06-1.95 (m, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 176.8, 156.0, 147.6, 134.2, 132.9, 129.0, 125.4, 64.2, 53.4, 31.6, 30.3, 15.7.

ESI HRMS m/z $C_{13}H_{17}O_6N_2S$ [M+H]: calcd 329.08018. Found 329.08020.

1.3.2 2-Nitrobenzyl (*S*)-1-(methoxycarbonyl)-3-(methylthio)propylcarbamate (NBOC-L-methionine methyl ester)

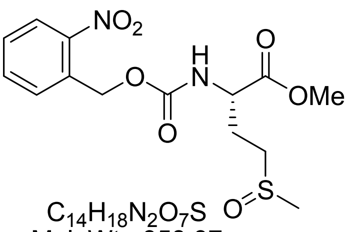


$C_{14}H_{18}N_2O_6S$
Mol. Wt.: 342.37

NBOC-L-methionine (5.23 g, 15.93 mmol, 1.0 equiv.) was mixed with trimethylsilyl chloride (6.92 g, 63.71 mmol, 4 equiv.) at 0 °C. Methanol (100 mL) was added in one portion, and to the mixture was stirred for 12 h at room temperature. The volatile compounds were removed under reduced pressure to afford essentially pure NBOC-L-methionine methyl ester as a yellow oil (5.38 g, yield = 99%). No further purification was needed.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.09 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.67-7.56 (m, 2H), 7.50-7.43 (m, 1H), 5.55 (d, *J* = 9.0 Hz, 1H), 5.52 (s, 2H), 4.50 (dt, *J* = 7.8, 4.9 Hz, 1H), 3.75 (s, 3H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.23-2.12 (m, 1H), 2.08 (s, 3H), 2.04-1.93 (m, 1H).
^{13}C NMR (100.6 MHz, CDCl$_3$) δ: 172.7, 155.7, 147.6, 134.1, 133.2, 129.1, 129.0, 125.4, 64.0, 53.6, 53.0, 32.1, 30.2, 15.8.
ESI HRMS m/z $C_{14}H_{19}O_6N_2S$ [M+H]: calcd 343.09583. Found 329.09623

1.3.3 2-Nitrobenzyl (*S*)-1-(methoxycarbonyl)-3-methylsulfinyl) propylcarbamate (L-**1d**)

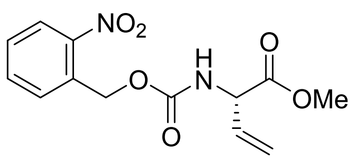


$C_{14}H_{18}N_2O_7S$
Mol. Wt.: 358.37
L-**1d**

To a solution of NBOC-L-methionine methyl ester (5.21 g, 15.22 mmol, 1.0 equiv.) in methanol (125 mL) was added an aqueous solution of $NaIO_4$ (15.22 mmol, 1 equiv. in 25 mL H_2O) dropwise at room temperature under vigorous stirring. After 12 h, the salts were filtered off, and the solvent was evaporated under reduced pressure. The remaining aqueous solution was extracted with dichloromethane (3x 50 mL). The combined organic phases were then washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the title compound as a yellow oil (5.04 g, yield = 92%). No further purification was needed.

^{1}H NMR (400 MHz, CDCl$_3$) δ: (mixture of diasteromers) 8.09 (d, *J* = 8.1 Hz, 1H), 7.69-7.55 (m, 2H), 7.52-7.45 (m, 1H), 6.03-5.87 (two d, *J* = 7.5 Hz, 1H), 5.57-5.43 (m, 2H), 4.50 (dq, *J* = 8.5, 8.4, 4.6 Hz, 1H), 3.78 (s, 3H), 2.92-2.76 (m, 2H), 2.65-2,60 (two s, 3H), 2.49-2.36 (m, 1H), 2.28-2.12 (m, 1H).
^{13}C NMR (100.6 MHz, CDCl$_3$) δ: (mixture of diasteromers) 172.0 (171.9), 155.8 (155.9), 147.6 (147.5), 134.1, 133.1 (133.0), 129.1 (129.0), 129.0 (128.9), 125.3 (125.2), 64.0 (63.9), 53.5, 53.1 (53.0), 50.5 (50.4), 38.9 (38.8), 26.2 (25.9).
ESI HRMS m/z $C_{14}H_{19}O_7N_2S$ [M+H]: calcd 329.09075. Found 329.09072.

1.4 Preparation and characterization of L-2d



$C_{13}H_{14}N_2O_6$
Mol. Wt.: 294.26
L-**2d**

A feed solution of L-**1d** (5 g L^{-1}, 0.375 g, 1.05 mmol, 1.0 equiv.) and DMAD (0.1487 g, 1.05 mmol, 1.0 equiv.) was prepared in toluene, and conveyed to the thermolysis reactor (T = 270 °C, back pressure P = 1000 psi) via a HPLC pump set at 1 mL min^{-1}, with a 1.7 min residence time in the thermolysis reactor. The reactor effluents were directed to a waste tank until the reactor reached steady state. After 5 min, the reactor effluents were collected and sampled every 10 min for quality control. Toluene was then evaporated and the resulting oil purified on silica gel column (petroleum ether/EtOAc 70:30, Rf = 0.45). 2-Nitrobenzyl (*S)*-1-(methoxycarbonyl)allylcarbamate (L-**2d**) was isolated as a yellow oil (74% after purification).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 8.6 Hz, 1H), 7.71-7.60 (m, 2H), 7.52-7.47 (m, 1H), 5.94 (ddd, *J* = 17.1, 10.3, 5.5 Hz, 1H), 5.66 (br d, *J* = 7.3 Hz, 1H), 5.57 (s, 2H), 5.41 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.32 (dd, *J* = 10.3, 1.4 Hz, 1H), 4.99-4.92 (m, 1H), 3.80 (s, 3H).
^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 171.1, 155.3, 147.6, 134.1, 133.2, 132.4, 128.9, 125.3, 118.3, 63.9, 56.4, 53.1.
ESI HRMS m/z $C_{13}H_{15}O_6N_2$ [M+H]: calcd 295.09246. Found 295.09257.

1.5 Copy of representative NMR spectra

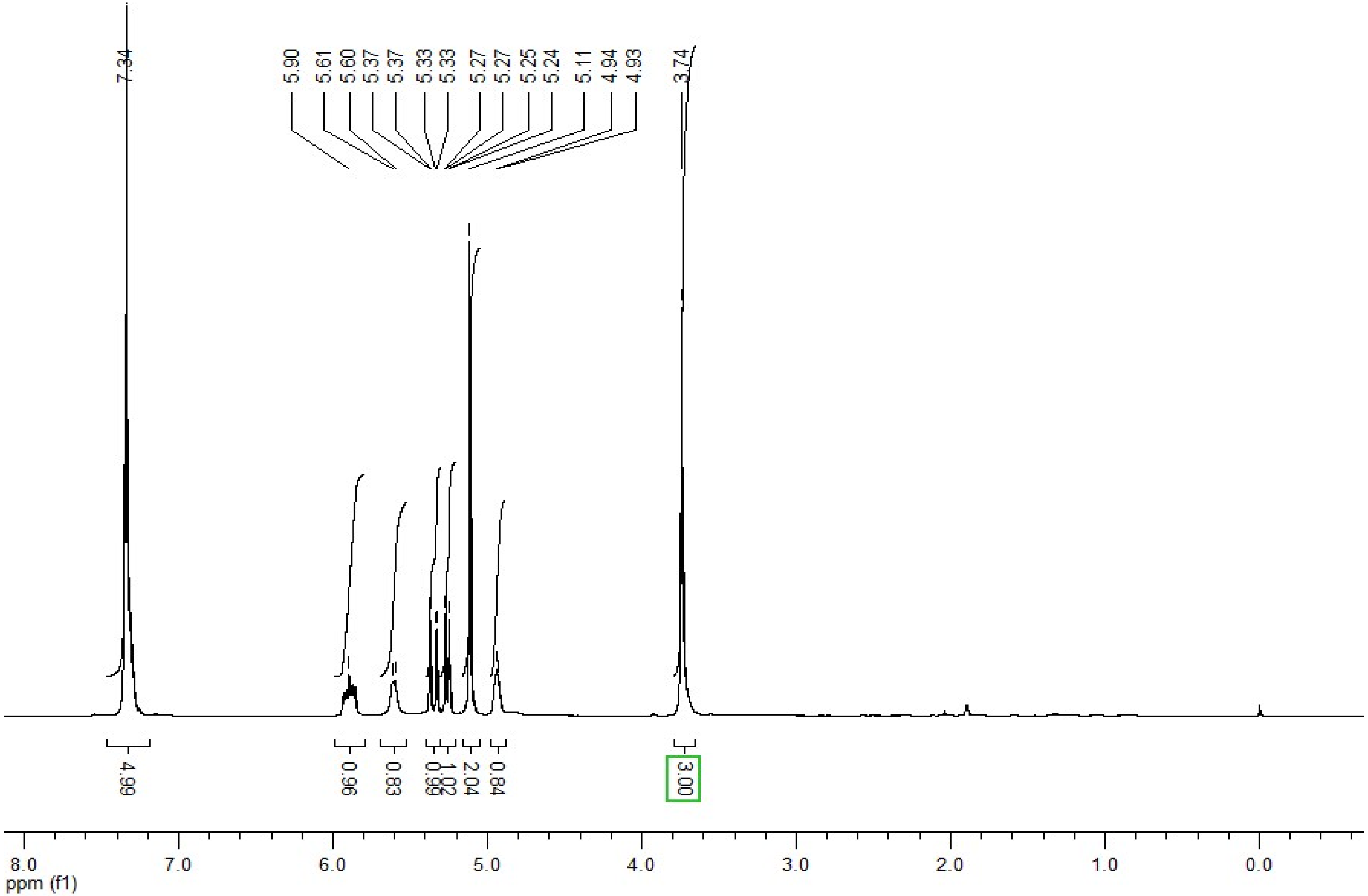


Figure S1. ^{1}H NMR of L-*N*-Cbz-vinylglycine methyl ester (L-**2a**)

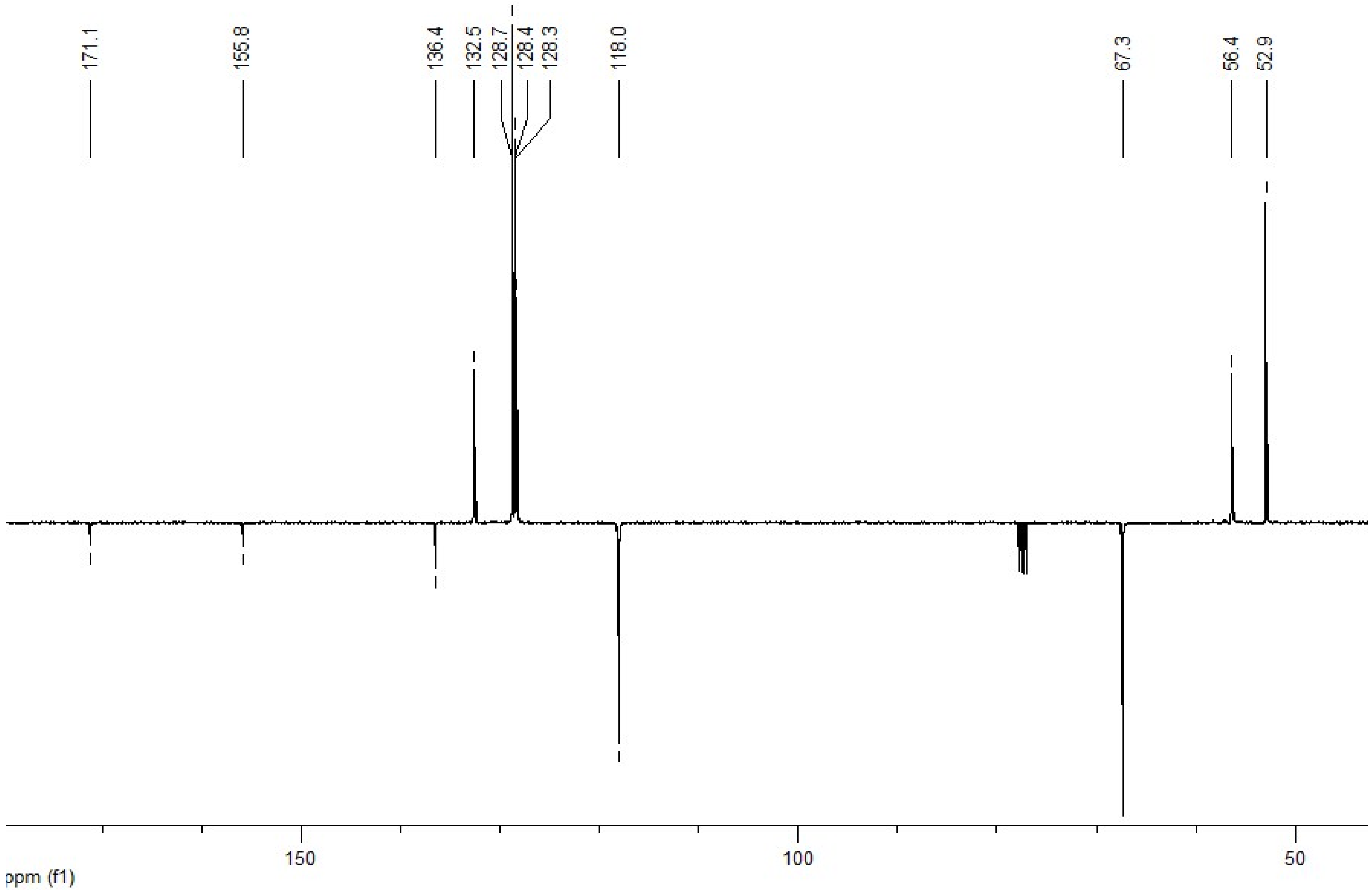


Figure S2. ^{13}C NMR of L-*N*-Cbz-vinylglycine methyl ester (L-**2a**)

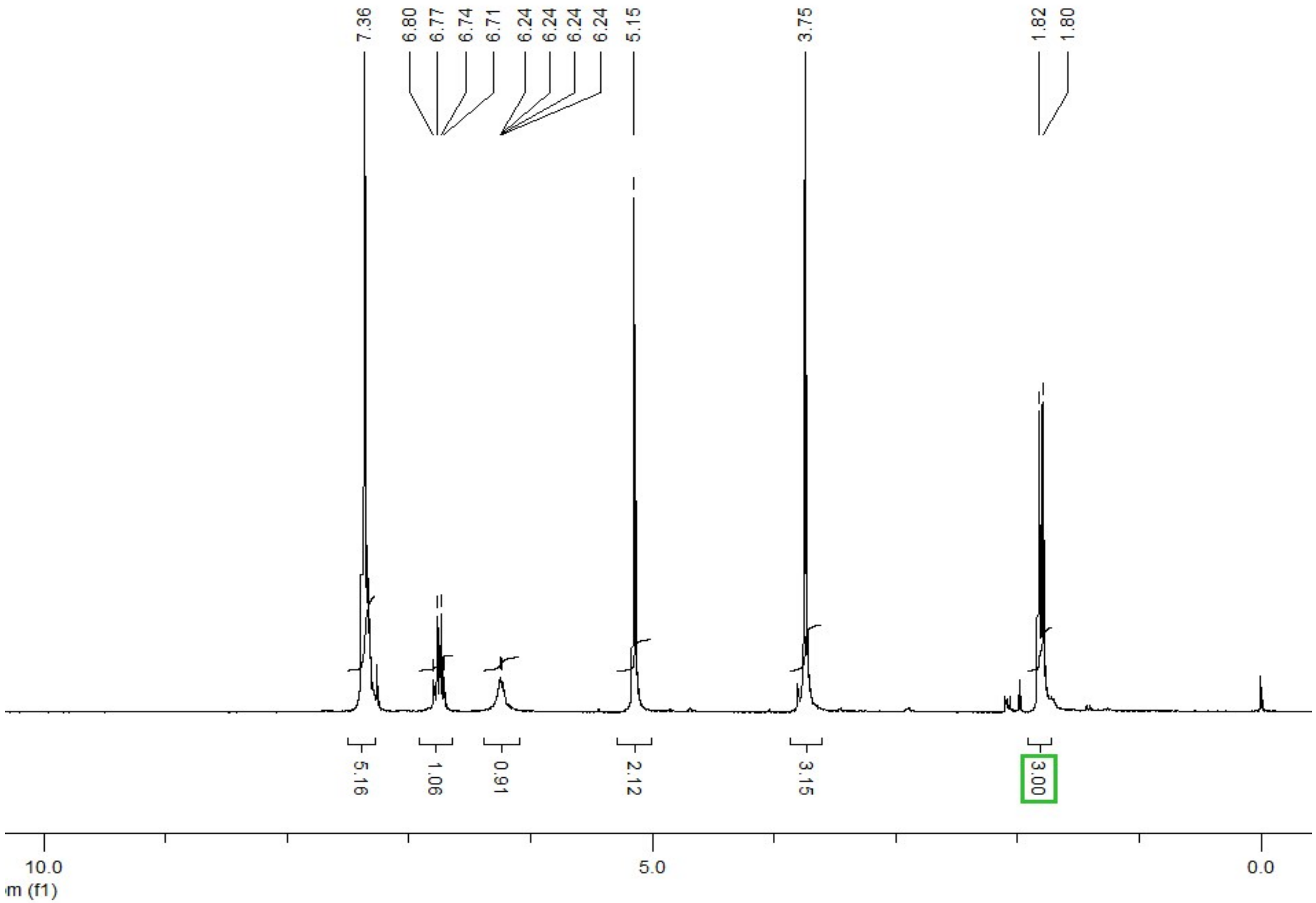


Figure S3. [1]H NMR of dehydrobutyrin derivative *E,Z*-**3a**

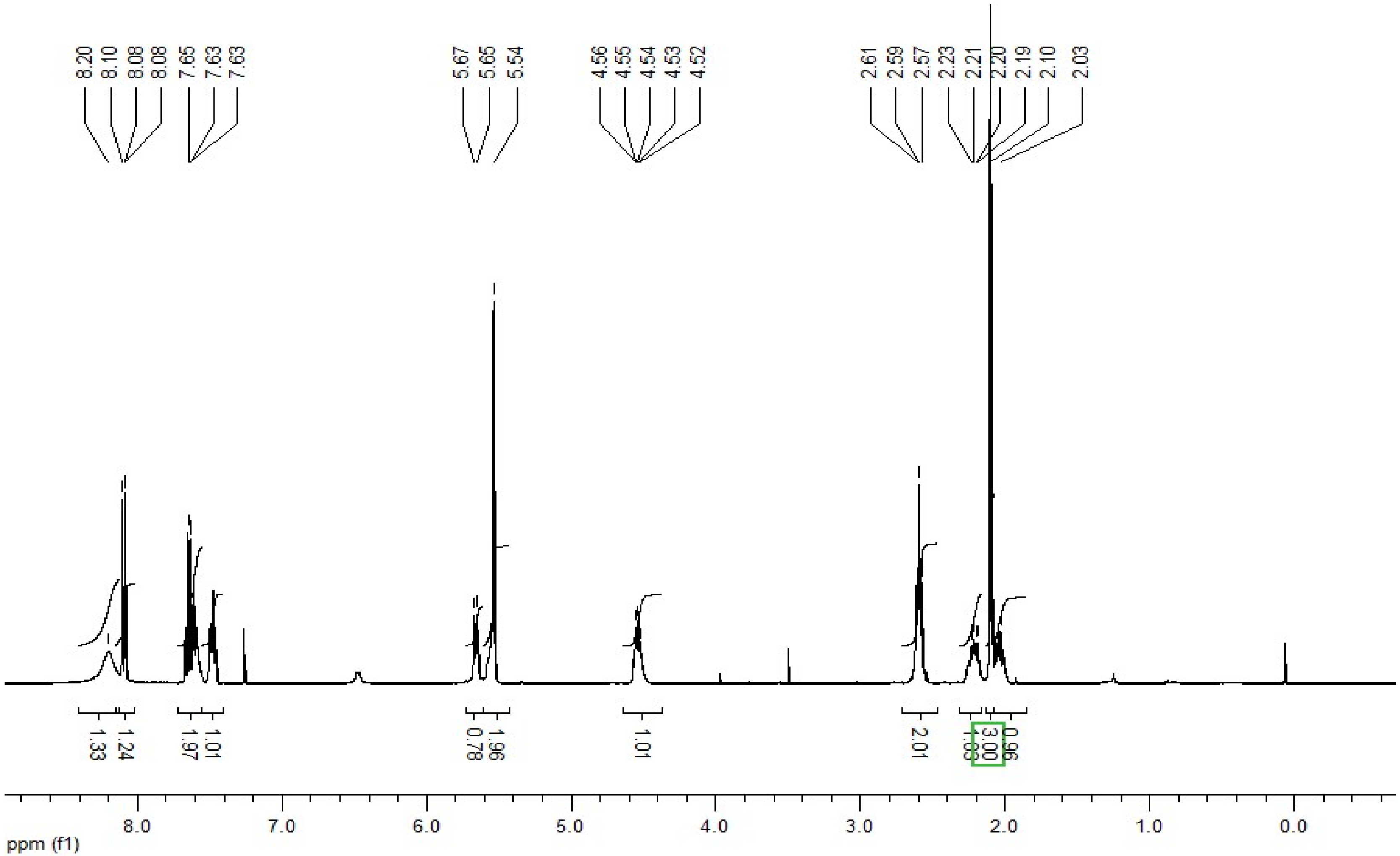


Figure S4. ^{1}H NMR of NBOC-L-methionine

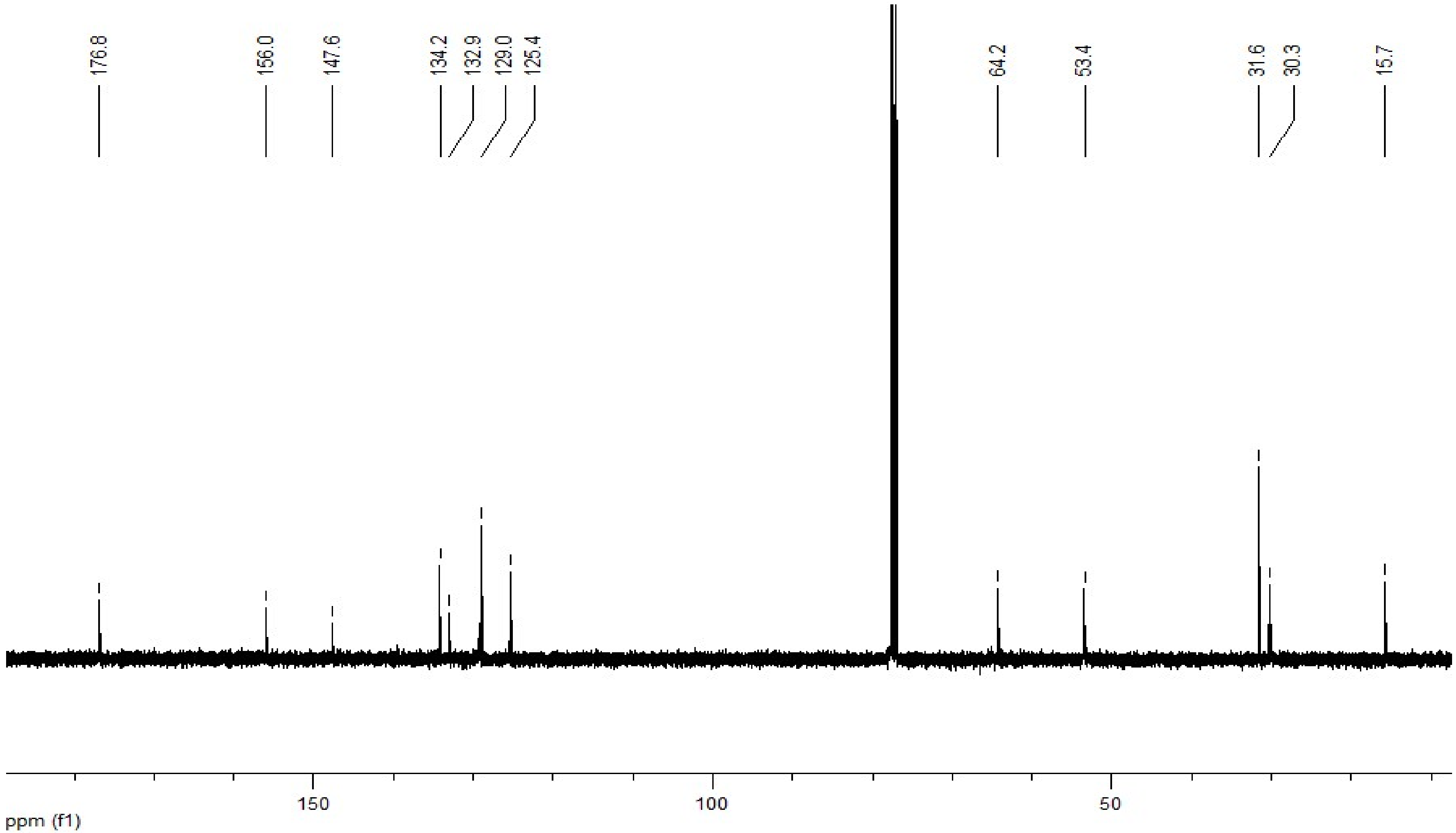


Figure S5. ^{13}C NMR of NBOC-L-methionine

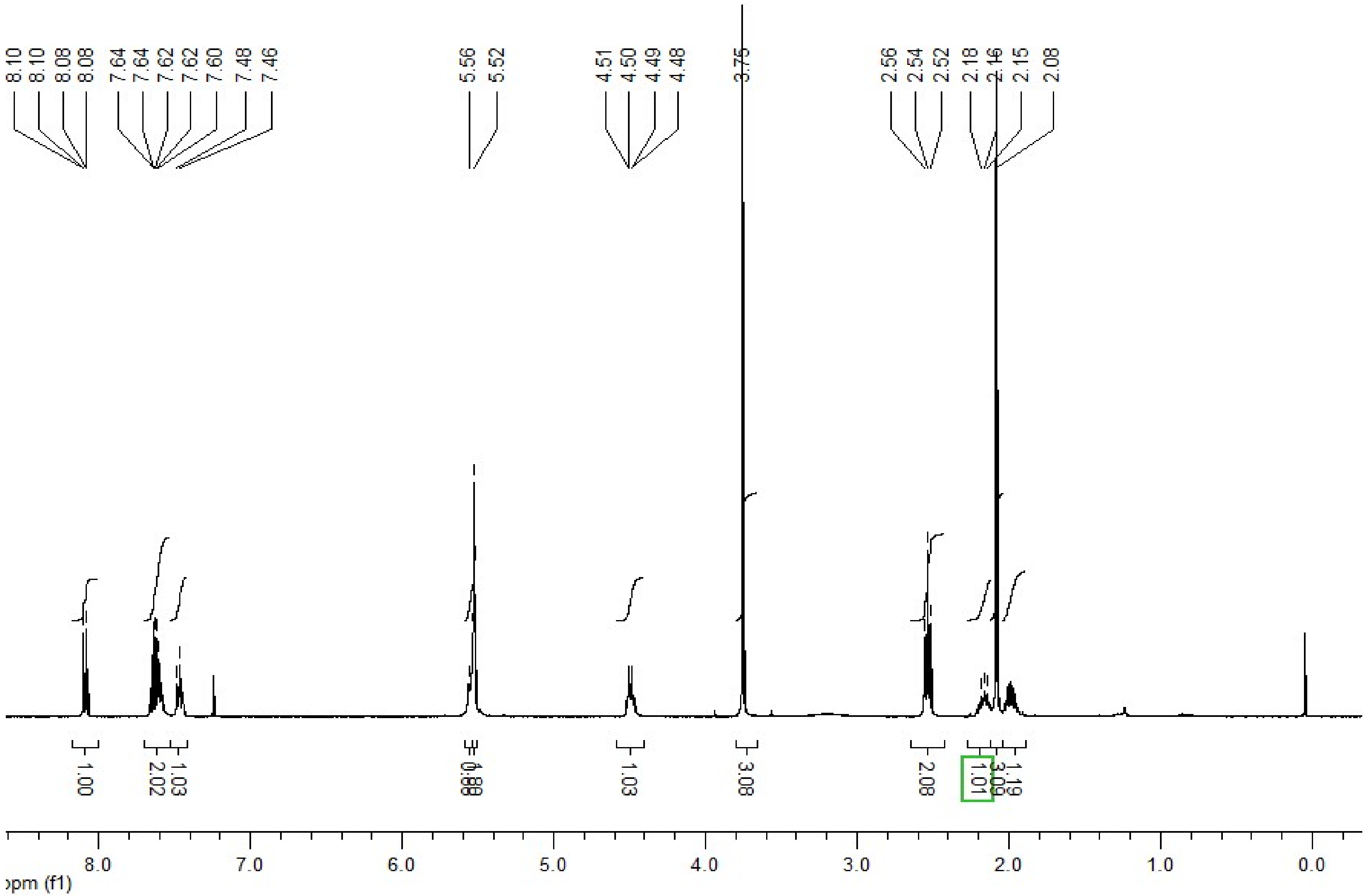


Figure S6. ^{1}H NMR of NBOC-L-methionine methyl ester

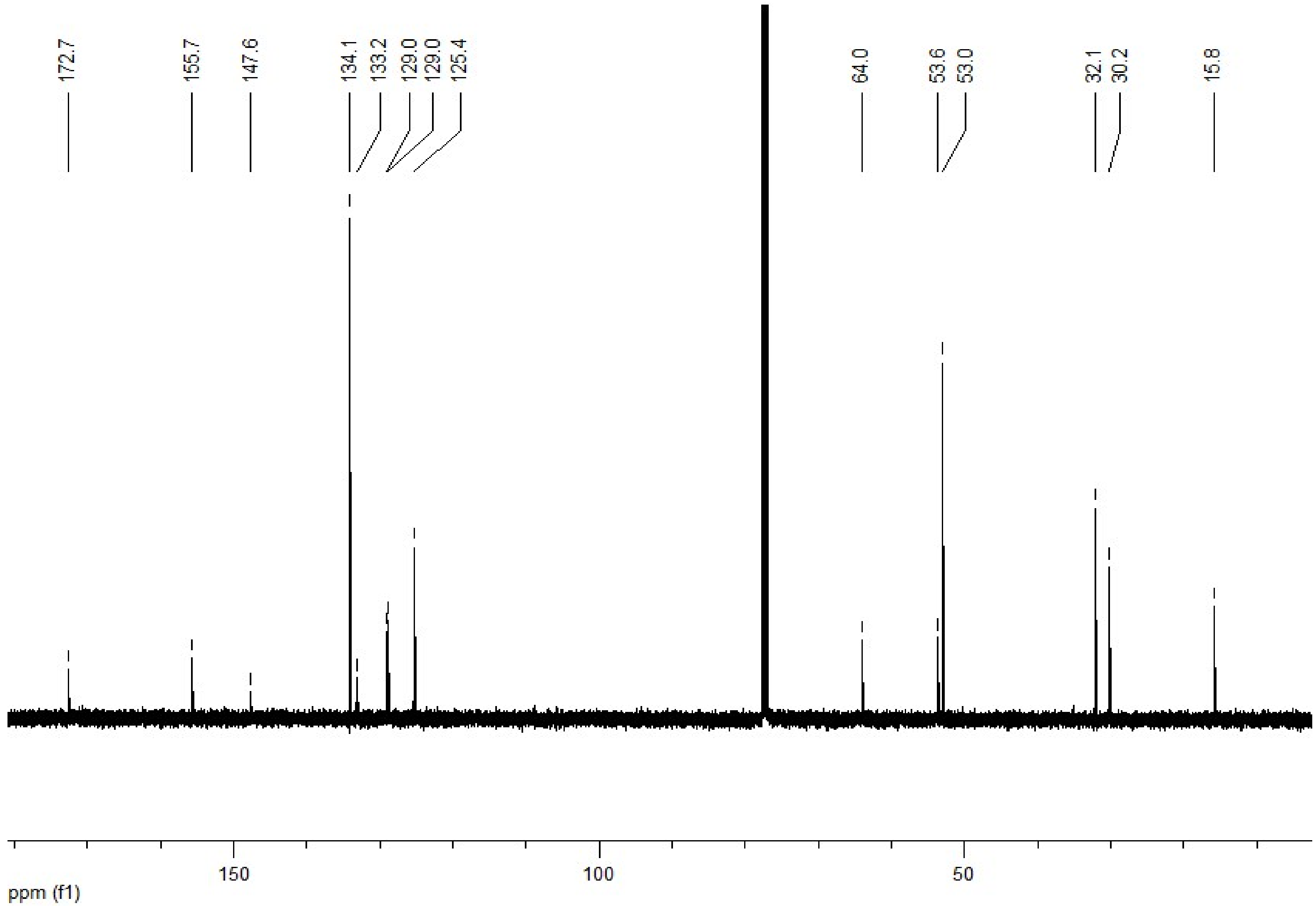


Figure S7. ^{13}C NMR of NBOC-L-methionine methyl ester

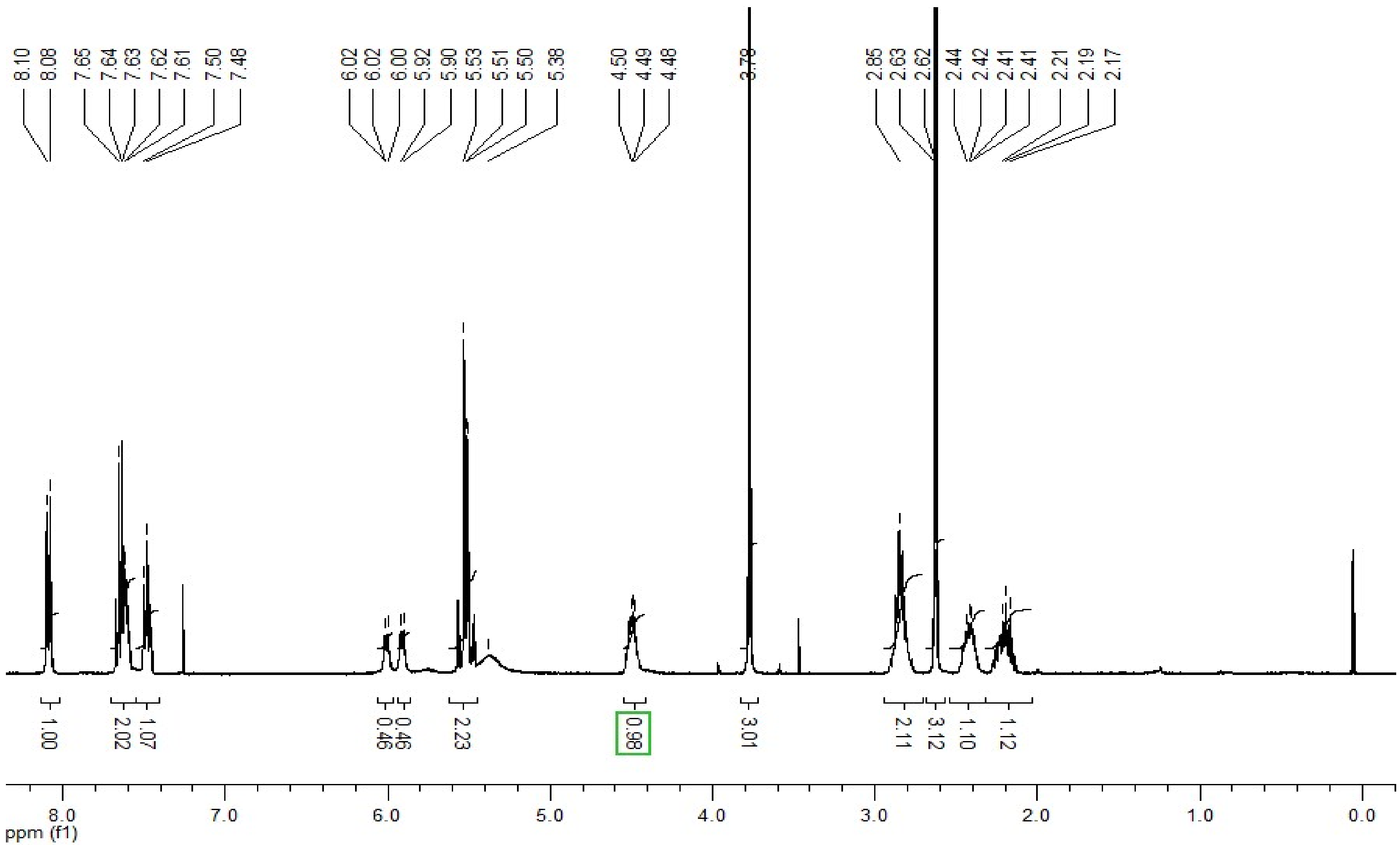


Figure S8. ^{1}H NMR of 2-nitrobenzyl (*S*)-1-(methoxycarbonyl)-3-methylsulfinyl) propylcarbamate (L-1d)

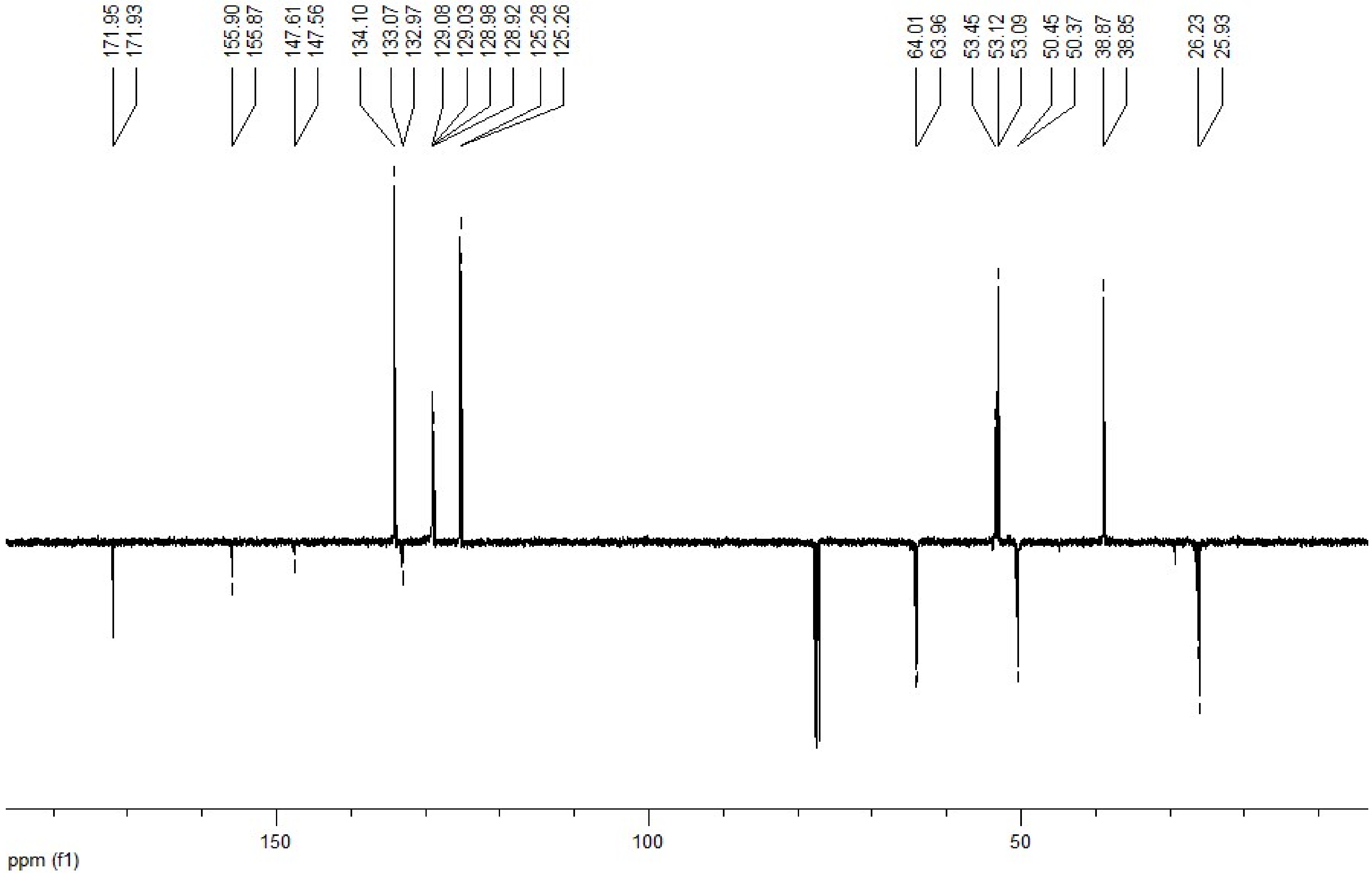


Figure S9. ^{13}C NMR of 2-nitrobenzyl (*S*)-1-(methoxycarbonyl)-3-methylsulfinyl) propylcarbamate (L-1d)

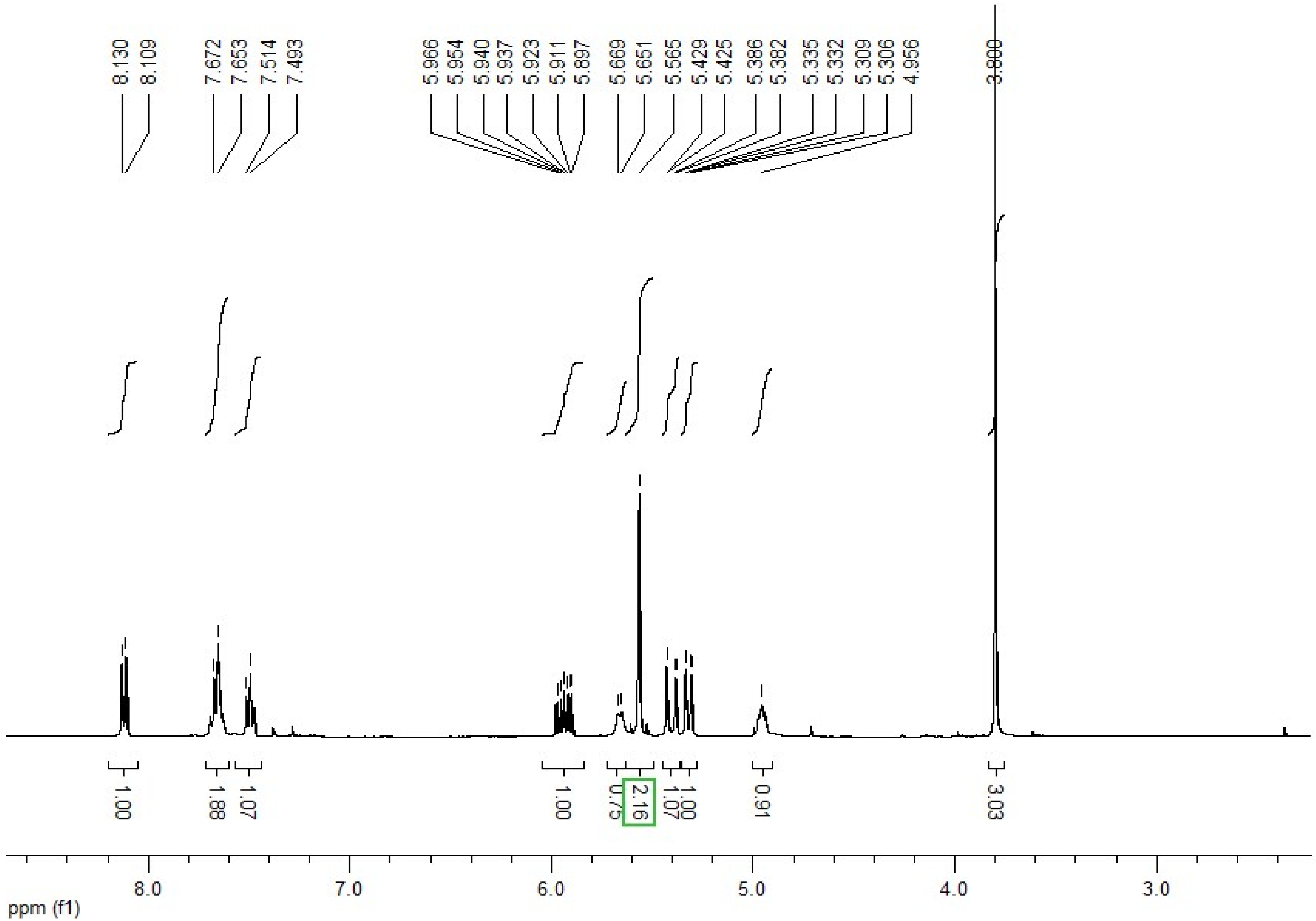


Figure S10. ^{1}H NMR of **L-2d**

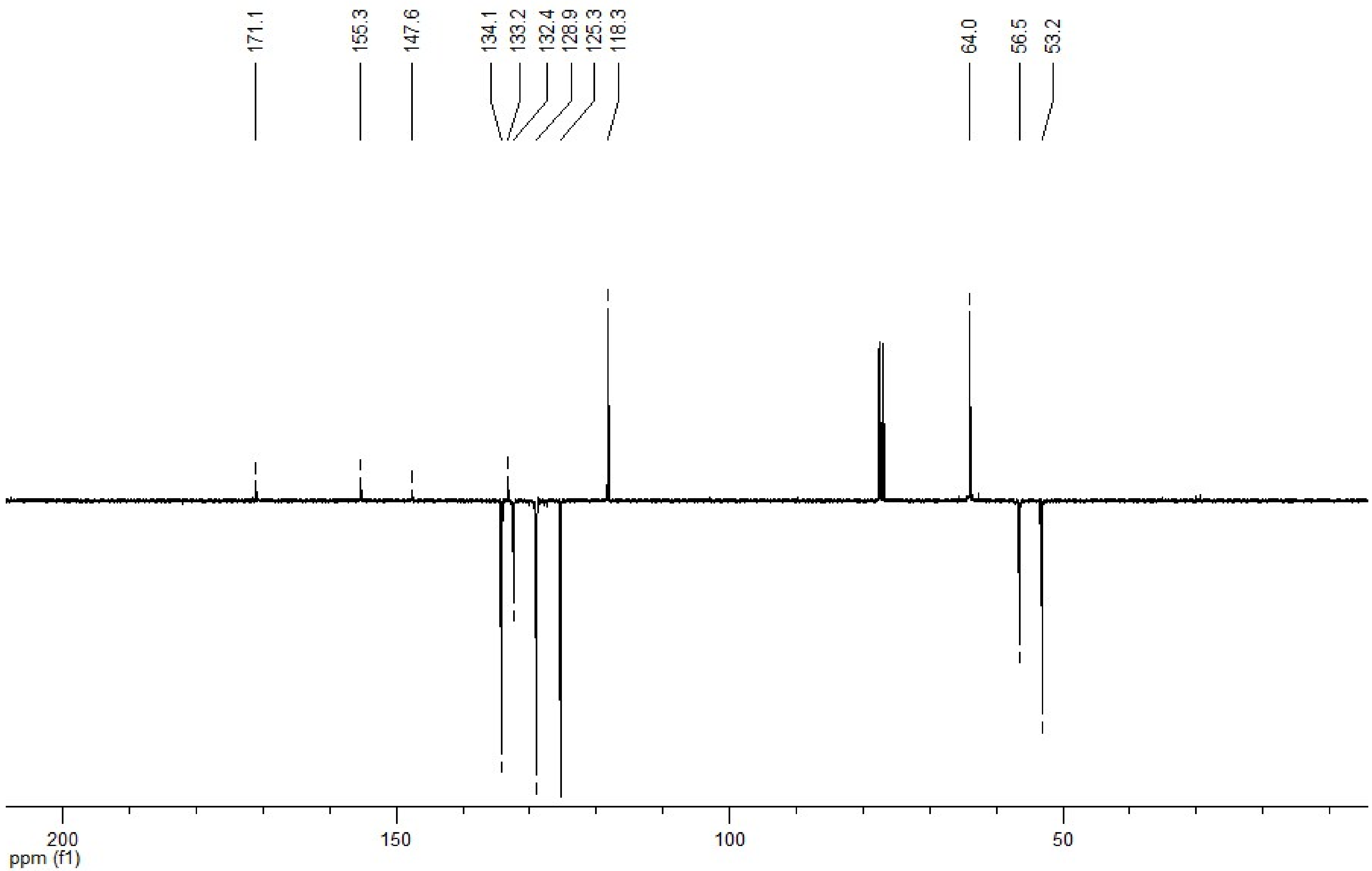


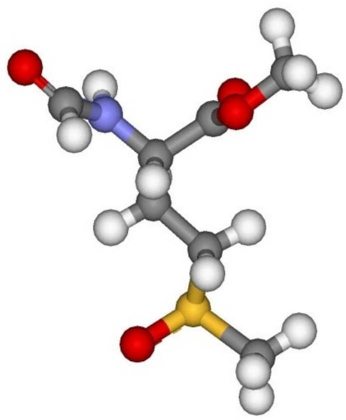
Figure S11. ^{13}C NMR of **L-2d**

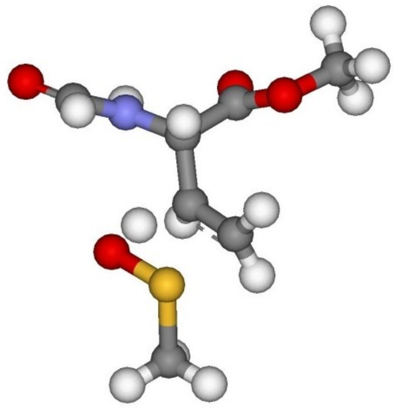
2. Computational section

2.1 Generalities

Quantum chemical calculations were performed using the Gaussian 09 package of programs (Revision A.02). [S3] DFT computations were carried out using the B3LYP hybrid functional employing the 6-31+G* basis set with 5 pure d functions. Gradient techniques using internal coordinates with very tight optimization convergence criteria (each component of the first energy derivative below 2.0 10-6 Hartree/Bohr or radian) were used for both geometry optimization and computation of vibrational properties. The transitions states were localized using the Newton-Raphson algorithm, and the nature of the stationary points was determined by analysis of the Hessian. The activation and reaction energies were calculated from the thermochemical output (298.150 Kelvin, 1 atm) computed for the reagents, transition states and products, using standard thermochemistry as implemented in Gaussian 09. Intrinsic reaction coordinate (IRC) calculations were performed in the gas phase on the neutral pathway to localize the nearest local minima on the reactant and product sides of the reaction coordinate. [S4]

2.2 Cartesian coordinates and absolute energies for all intermediates and transitions states

Thermolysis	
1	**B3LYP/6-31+G***
26 scf done: -1028.391158 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.535234 N 1.380469 0.000000 -0.461631 C -0.771294 -1.237175 -0.507096 O 0.404904 -0.921424 2.214026 O -0.505249 1.146676 2.032340 C -0.485752 1.282915 3.471638 C 1.991175 1.050471 -1.070361 O 3.166832 1.076998 -1.397182 C -2.247142 -1.199096 -0.098322 S -3.072514 -2.757169 -0.687775 O -2.935444 -2.770987 -2.201007 C -4.805676 -2.299033 -0.295708 H -0.466667 0.917381 -0.367017 H -1.084494 0.493772 3.933869 H 0.540469 1.223685 3.841592 H -0.913763 2.264759 3.673023 H 1.961257 -0.803826 -0.239539 H 1.304643 1.899018 -1.254168 H -0.694334 -1.274918 -1.598141	H = -1028.168178 Hartree G = -1028.231570 Hartree 

H -0.288286 -2.138565 -0.108774 H -2.773322 -0.371161 -0.588950 H -2.379873 -1.118512 0.986491 H -5.118907 -1.403381 -0.843467 H -4.880168 -2.144491 0.785668 H -5.424545 -3.150253 -0.591100	
TS[1-2]	**B3LYP/6-31+G***
26 scf done: -1028.346687 S 0.000000 0.000000 0.000000 O 0.000000 0.000000 1.590381 C 2.420839 0.000000 0.113783 C 2.552045 0.039488 1.517710 H 1.210405 0.073968 1.836968 C -0.226976 1.760626 -0.433954 C 3.031321 -1.210753 2.279047 C 4.534245 -1.396739 2.058558 O 5.392028 -0.914027 2.769939 O 4.788199 -2.120312 0.953066 C 6.180946 -2.283547 0.608621 N 2.796691 -1.133198 3.710584 C 1.731031 -1.684212 4.359050 O 1.546051 -1.620176 5.564946 H 2.559897 -0.929730 -0.431247 H 2.568129 0.899488 -0.478224 H 2.902065 0.977925 1.954815 H 0.525902 2.376173 0.066065 H -1.226982 2.079902 -0.129444 H -0.126015 1.853153 -1.521326 H 2.511472 -2.090122 1.883620 H 6.712977 -2.786217 1.419918 H 6.183616 -2.894614 -0.293961 H 6.639443 -1.309227 0.420586 H 3.496323 -0.661123 4.276484 H 1.033492 -2.207531 3.678478	H = -1028.129262 Hartree G = -1028.191445 Hartree 
2+MeSOH	**B3LYP/6-31+G***
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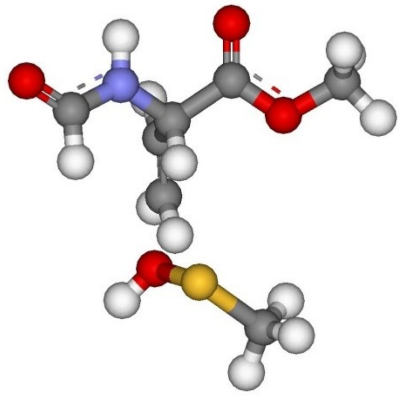
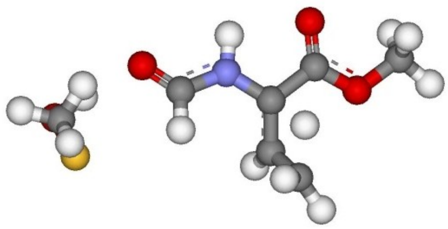
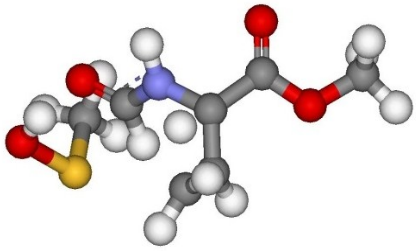
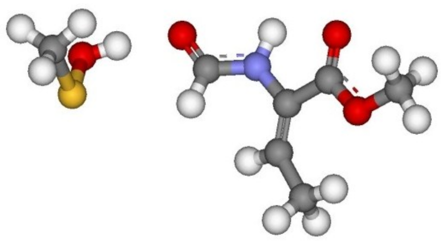
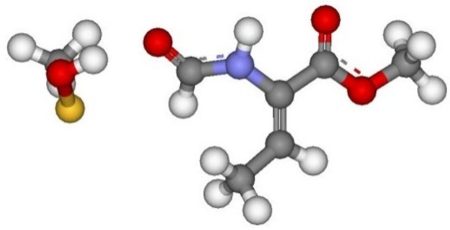
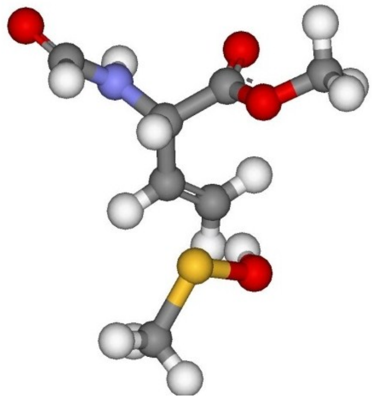
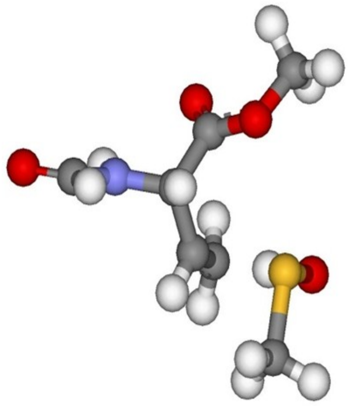
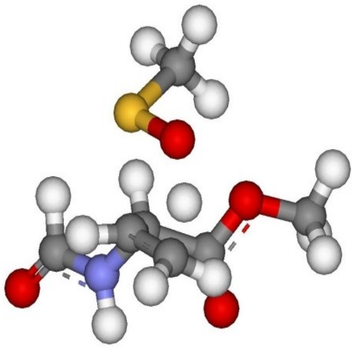
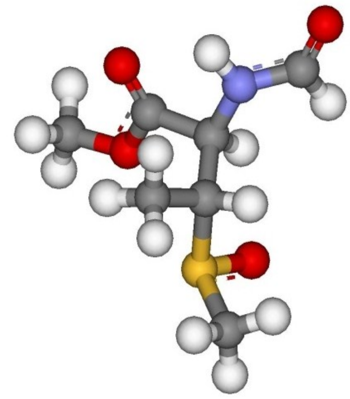
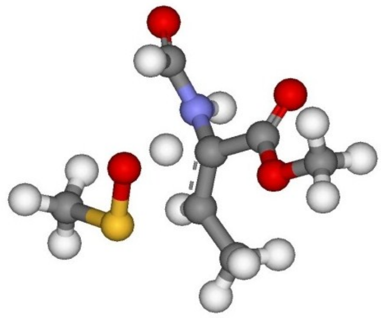
O 1.016030 1.826053 3.774192 O 2.287998 -2.439967 -0.151950 S 3.101865 -3.870424 -0.604112 C 3.558349 -3.457150 -2.313711 H 2.114297 -0.287813 1.575513 H 1.467091 4.052524 2.327899 H 2.941179 3.592345 3.224253 H 3.042474 3.958139 1.467368 H 0.670642 -0.583736 4.150859 H 2.302555 -2.399614 2.463344 H -0.936407 0.013859 1.893459 H 0.926502 -0.000420 -0.570813 H -0.929179 0.017079 -0.564201 H 2.681488 -3.369592 -2.962451 H 4.179938 -4.289142 -2.666938 H 4.148125 -2.536589 -2.343195 H 1.334199 -2.571769 -0.296808	
Thermal isomerization from 1	
TS^{2-E3}	**B3LYP/6-31+G***
26 scf done: -1028.274511 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.401536 C 1.370868 0.000000 1.819324 H 1.465036 0.093003 0.283948 C 2.186986 1.266175 1.850365 O 3.214278 1.335126 2.506135 O 1.673253 2.294991 1.158874 C 2.467145 3.498576 1.149474 N 1.800367 -0.865450 2.849653 C 1.349185 -2.139573 3.022103 O 1.741032 -2.878809 3.921628 O 0.473073 -5.383037 4.019786 S 0.282983 -5.740686 2.381659 C 1.785612 -6.718146 2.064163 H 0.407317 -0.868269 -0.522016 H -0.767908 0.513857 -0.587620 H -0.859039 0.084214 2.067153 H 2.597147 3.876068 2.166647 H 3.446630 3.305047 0.704130 H 1.900349 4.205646 0.543676 H 2.586556 -0.560282 3.422180 H 0.598906 -2.457260 2.282052 H 2.691779 -6.114360 2.173422 H 1.712575 -7.075387 1.029526 H 1.825570 -7.579169 2.737813 H 0.958773 -4.526205 4.078825	H = -514.208849 Hartree G = -514.256691 Hartree 

TS^{2-Z3}	**B3LYP/6-31+G***
26 scf done: -1028.274511 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.401536 C 1.370868 0.000000 1.819324 H 1.465036 0.093003 0.283948 C 2.186986 1.266175 1.850365 O 3.214278 1.335126 2.506135 O 1.673253 2.294991 1.158874 C 2.467145 3.498576 1.149474 N 1.800367 -0.865450 2.849653 C 1.349185 -2.139573 3.022103 O 1.741032 -2.878809 3.921628 O 0.473073 -5.383037 4.019786 S 0.282983 -5.740686 2.381659 C 1.785612 -6.718146 2.064163 H 0.407317 -0.868269 -0.522016 H -0.767908 0.513857 -0.587620 H -0.859039 0.084214 2.067153 H 2.597147 3.876068 2.166647 H 3.446630 3.305047 0.704130 H 1.900349 4.205646 0.543676 H 2.586556 -0.560282 3.422180 H 0.598906 -2.457260 2.282052 H 2.691779 -6.114360 2.173422 H 1.712575 -7.075387 1.029526 H 1.825570 -7.579169 2.737813 H 0.958773 -4.526205 4.078825	H = -514.187170 Hartree G = -514.236153 Hartree 
***E*-3** (kinetic product)	**B3LYP/6-31+G***
26 scf done: -1028.400179 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.351177 C 1.136246 0.000000 2.327613 C 1.158068 -0.181701 -0.932467 O 0.992238 -0.371978 -2.126174 O 2.368099 -0.146327 -0.353536 C 3.491858 -0.361245 -1.235275 N -1.208046 0.109515 -0.735734 C -2.271288 0.892820 -0.415039 O -3.288864 0.964654 -1.102174 H -4.696810 1.944070 -0.482484 O -5.359906 2.524878 -0.038174 S -4.502613 3.709196 0.803870 C -4.384527 5.015690 -0.458545 H -0.984785 0.010177 1.817438	H = -514.327097 Hartree G = -514.377310 Hartree 

H 2.115975 -0.033031 1.856037 H 1.036642 -0.857147 3.007638 H 1.078900 0.899169 2.957389 H 3.514935 0.408111 -2.010673 H 3.422676 -1.347336 -1.700858 H 4.371402 -0.294112 -0.595094 H -1.204574 -0.293061 -1.669945 H -2.150581 1.473391 0.511720 H -3.781691 4.696750 -1.314405 H -3.899971 5.873217 0.024414 H -5.383533 5.310401 -0.793094	
***Z*-3** (thermodynamic product)	**B3LYP/6-31+G***
26 scf done: -1028.403950 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.348616 C 1.186998 0.000000 2.263825 C -1.246327 -0.177338 -0.806632 O -1.223411 -0.341166 -2.015131 O -2.373091 -0.169525 -0.074713 C -3.599124 -0.378230 -0.805348 N 1.146853 0.093005 -0.820998 C 2.186555 0.955312 -0.648848 O 3.121513 1.047588 -1.441231 O 5.244451 2.678692 -0.595729 S 4.443893 3.793473 0.385470 C 4.128138 5.137574 -0.801132 H -0.978492 -0.023779 1.818602 H 2.103577 -0.326771 1.762810 H 0.999263 -0.668993 3.112016 H 1.373348 0.996966 2.687401 H -3.584162 -1.353941 -1.297553 H -3.730794 0.406260 -1.554697 H -4.388655 -0.334277 -0.055224 H 1.077150 -0.341803 -1.738676 H 2.124882 1.576038 0.255816 H 4.559098 2.080906 -0.978710 H 3.677020 5.958131 -0.229680 H 3.437618 4.826900 -1.591232 H 5.068958 5.482202 -1.240209	H = -514.330892 Hartree G = -514.380197 Hartree 
Addition of MeSOH on 2 towards intermediate 4 (competitive path)	
Van Der Waals complex	**B3LYP/6-31+G***
26 scf done: -1028.378927 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.521554 C 1.073127 0.000000 2.320304	H = -1028.156397 Hartree G = -1028.225862 Hartree

C 1.401531 0.234785 -0.576879 O 2.203829 -0.647632 -0.799340 O 1.628764 1.542351 -0.773665 C 2.936911 1.901885 -1.270067 N -0.554654 -1.243993 -0.507264 C -1.664615 -1.332309 -1.298450 O -2.099445 -2.368559 -1.772305 O 0.364239 3.384800 2.159283 S -1.151347 3.600736 1.428798 C -2.224936 3.654477 2.896147 H -0.649988 0.814704 -0.338450 H -0.999873 -0.042826 1.952003 H 2.090360 0.010166 1.935515 H 0.963710 -0.038186 3.401072 H 2.924006 2.988613 -1.345777 H 3.709203 1.569798 -0.571719 H 3.105463 1.442600 -2.247217 H -0.017679 -2.095056 -0.367217 H -2.152513 -0.351750 -1.462969 H 0.561349 2.427367 2.148485 H -1.903443 4.450447 3.573691 H -2.245867 2.695871 3.423425 H -3.232825 3.883077 2.528760	
TS$^{2-4(exo)}$	**B3LYP/6-31+G***
26 scf done: -1028.346554 S 0.000000 0.000000 0.000000 O 0.000000 0.000000 1.587859 C 2.480151 0.000000 0.138871 C 2.554291 -0.140947 1.540476 H 1.240526 -0.079448 1.847185 C -0.199403 -1.766309 -0.429548 C 2.859784 1.282448 -0.603336 C 2.552040 2.536509 0.224136 O 1.310418 2.984544 -0.006341 O 3.333199 3.036357 1.007031 C 0.875850 4.109325 0.791103 N 4.277178 1.261463 -0.935578 C 4.776025 1.133766 -2.198907 O 5.962754 1.116079 -2.481977 H 2.953886 0.692059 2.120400 H 2.826934 -1.124517 1.925055 H 2.580330 -0.882960 -0.489713 H -0.126453 -1.859182 -1.519307 H 0.578499 -2.368067 0.049152 H -1.183746 -2.107554 -0.098202 H 2.301019 1.339473 -1.541985	H = -1028.129237 Hartree G = -1028.190739 Hartree 

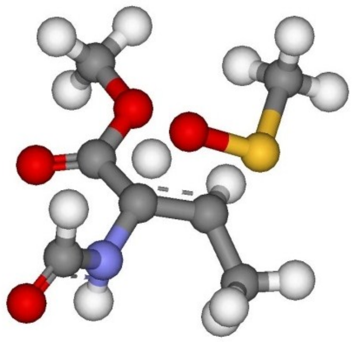
H -0.139816 4.319057 0.457282 H 0.888214 3.841618 1.850227 H 1.530469 4.966845 0.618030 H 4.943794 1.396054 -0.180766 H 3.981808 1.042052 -2.965996	
TS$^{2-4(endo)}$	**B3LYP/6-31+G***
26 scf done: -1028.341098 S 0.000000 0.000000 0.000000 O 0.000000 0.000000 1.583078 C 2.549543 0.000000 0.171476 C 2.558964 -0.021484 1.585851 H 1.282572 0.060128 1.855342 C -0.413990 1.721716 -0.459215 C 3.086135 1.146554 -0.695310 C 3.541571 2.346233 0.148674 O 4.684653 2.525265 0.508761 O 2.515576 3.156967 0.455949 C 2.829623 4.296316 1.290220 N 4.214963 0.686197 -1.487861 C 4.189326 0.504564 -2.840562 O 5.138850 0.138655 -3.512516 H 2.777694 -0.985040 2.051211 H 3.005717 0.824009 2.110451 H 2.561621 -0.943368 -0.366661 H 0.323389 2.423945 -0.065087 H -1.406848 1.955904 -0.065388 H -0.440260 1.773580 -1.554007 H 2.319044 1.491000 -1.396664 H 1.883823 4.819656 1.427779 H 3.231013 3.960135 2.249101 H 3.560874 4.935106 0.789602 H 5.107979 0.568838 -1.017278 H 3.197186 0.722062 -3.283612	H = -1028.123654 Hartree G = -1028.184912 Hartree 
4	**B3LYP/6-31+G***
26 scf done: -1028.390053 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.560560 C 1.387109 0.000000 2.201738 S -1.055185 1.439274 2.161498 O -2.345819 1.358518 1.357993 C -1.447842 0.740341 3.814095 C 1.002335 1.003061 -0.576386 O 2.059302 0.694379 -1.088718 O 0.578987 2.262807 -0.408937 C 1.455043 3.307739 -0.885998	H = -1028.166464 Hartree G = -1028.228373 Hartree

N 0.312364 -1.314324 -0.527836 C -0.624808 -2.215757 -0.946791 O -0.367047 -3.301491 -1.441441 H -1.008473 0.287642 -0.319089 H -0.561034 -0.895560 1.851167 H 1.916367 0.945452 2.035426 H 1.333131 -0.173270 3.281013 H 1.996374 -0.804591 1.774082 H -1.935710 -0.231518 3.692018 H -0.542302 0.657965 4.422267 H -2.141765 1.442477 4.283461 H 2.419127 3.256003 -0.373818 H 0.939358 4.238968 -0.653896 H 1.606910 3.204314 -1.963061 H 1.282826 -1.516766 -0.751259 H -1.662733 -1.867565 -0.783887	
Sulfoxide elimination from intermediate 4 (competitive path)	
TS^{4_E3}	**B3LYP/6-31+G***
26 scf done: -1028.353361 S 0.000000 0.000000 0.000000 O 0.000000 0.000000 1.591567 C 2.272114 0.000000 -0.023503 C 2.536567 0.208579 1.382799 H 1.171881 0.079839 1.811844 C -0.279695 1.749499 -0.442779 C 2.608737 -1.250250 -0.806337 C 3.226650 -0.818854 2.228786 O 4.035490 -0.556765 3.098402 O 2.806408 -2.081557 1.968411 C 3.377971 -3.113349 2.795333 N 2.898796 1.569308 1.709035 C 2.420069 2.249622 2.798868 O 2.864691 3.317346 3.188817 H 2.388880 0.914470 -0.605755 H 2.218222 -2.156694 -0.342443 H 2.218585 -1.174952 -1.827089 H 3.700519 -1.357719 -0.873439 H -1.298135 2.026729 -0.159181 H 0.442048 2.388010 0.071869 H -0.162938 1.841658 -1.528550 H 4.464575 -3.140716 2.678426 H 3.132207 -2.936108 3.845566 H 2.928000 -4.043573 2.446556 H 3.788774 1.925845 1.367864 H 1.558016 1.751751 3.278387	H = -1028.135718 Hartree G = -1028.195829 Hartree 
TS^{4_Z3}	**B3LYP/6-31+G***

26
scf done: -1028.356940

S	0.000000	0.000000	0.000000
O	0.000000	0.000000	1.591567
C	2.272114	0.000000	-0.023517
C	2.536573	0.208585	1.382785
H	1.171880	0.079829	1.811854
C	-0.240140	-1.757093	-0.435044
C	2.618188	1.047852	-1.055187
C	3.163639	-0.911229	2.154347
O	3.888328	-0.770041	3.119328
O	2.792016	-2.135113	1.682535
C	3.306055	-3.263319	2.415494
N	2.962589	1.522602	1.776364
C	2.459131	2.210270	2.850033
O	2.942970	3.241278	3.288155
H	2.399390	-1.026315	-0.358760
H	0.466052	-2.373871	0.125993
H	-1.267120	-2.044655	-0.196469
H	-0.070574	-1.863333	-1.512623
H	2.167112	0.814937	-2.025997
H	3.708342	1.077308	-1.199190
H	2.297380	2.046881	-0.748026
H	4.398975	-3.267253	2.394487
H	2.965342	-3.229632	3.453597
H	2.908617	-4.143562	1.908355
H	3.873216	1.855675	1.468357
H	1.544991	1.753211	3.269119

H = -1028.140015 Hartree
G = -1028.199963 Hartree



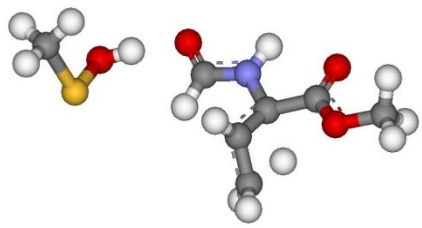
Thermal epimerization

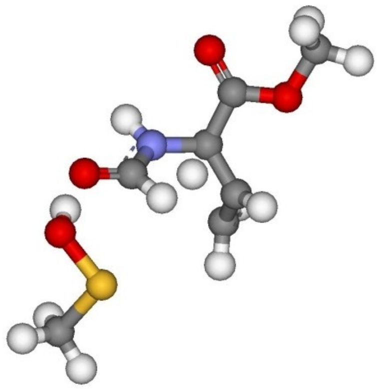
TS^{E3_epi2} — **B3LYP/6-31+G***

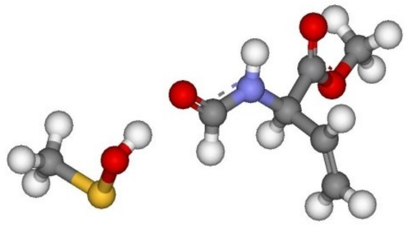
26
scf done: -1028.274451

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.401514
C	1.370729	0.000000	1.819480
H	1.464886	-0.092686	0.284130
C	2.187453	-1.265790	1.850190
O	3.214201	-1.334667	2.506733
O	1.674947	-2.294354	1.157340
C	2.470830	-3.496630	1.145794
N	1.800457	0.865950	2.849381
C	1.343378	2.137537	3.025274
O	1.735435	2.878195	3.923621
H	0.407449	0.867960	-0.522476
H	-0.767673	-0.514147	-0.587704
H	-0.859351	-0.083434	2.066802
H	2.601308	-3.875880	2.162259

H = -1028.058105 Hartree
G = -1028.125125 Hartree



H 3.450059 -3.300589 0.701012 H 1.905338 -4.203466 0.538501 H 2.592250 0.564500 3.416167 H 0.581324 2.448994 2.294611 O 0.674860 5.480283 3.877819 S -0.890087 5.194144 3.315726 C -1.796182 5.021290 4.885343 H 1.120718 4.604084 3.960895 H -1.470251 4.139369 5.445415 H -1.670316 5.920180 5.496030 H -2.855713 4.911188 4.623172	
TS^{Z3_epi2}	**B3LYP/6-31+G***
26 scf done: -1028.253123 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.406632 C 1.393209 0.000000 1.801490 H 1.417963 0.020503 0.286984 C 1.933588 -0.952388 2.824040 O 3.056480 -0.903670 3.290625 O 1.037318 -1.922977 3.103202 C 1.459244 -2.917337 4.058070 N 2.077224 1.270347 1.822307 C 1.521406 2.444560 2.214792 O 2.128306 3.514591 2.221926 H 0.357044 -0.912045 -0.486798 H -0.757043 0.514120 -0.603494 H -0.866611 0.012459 2.067215 H 1.700246 -2.446448 5.014658 H 2.338281 -3.447973 3.683189 H 0.611970 -3.595245 4.161876 H 3.073712 1.287680 1.626445 H 0.464309 2.362739 2.511809 O 0.684847 5.683106 3.246511 S -0.873085 5.362498 2.686084 C -0.876900 6.292533 1.120908 H -0.166042 5.875033 0.401118 H -1.892336 6.213944 0.713146 H -0.646538 7.345803 1.306364 H 1.275881 4.972440 2.898467	H = -1028.036952 Hartree G = -1028.104035 Hartree 
epi2	**B3LYP/6-31+G***
26 scf done: -1028.389281 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.520018 C 1.106473 0.000000 2.266709 C -0.584135 1.322097 -0.509116	H = -1028.166507 Hartree G = -1028.235243 Hartree

O	-1.756337	1.480022	-0.784837	
O	0.349661	2.280340	-0.571001	
C	-0.109574	3.593259	-0.961233	
N	-0.799356	-1.082163	-0.559587	
C	-0.347199	-2.354234	-0.743252	
O	-1.025076	-3.281095	-1.159356	
O	0.280184	-5.754886	-1.252636	
S	1.843441	-5.308913	-1.701163	
C	1.740721	-5.458492	-3.512763	
H	1.030975	-0.081085	-0.359404	
H	-0.986839	-0.018724	1.981992	
H	1.057212	-0.013191	3.352172	
H	2.099900	0.012471	1.822064	
H	0.780931	4.221226	-0.952738	
H	-0.550845	3.555702	-1.960135	
H	-0.850981	3.959077	-0.246506	
H	-1.774739	-0.886931	-0.769066	
H	0.722655	-2.473389	-0.484900	
H	-0.265315	-4.931895	-1.225262	
H	1.046094	-4.728471	-3.939725	
H	1.436901	-6.471724	-3.791865	
H	2.749227	-5.267077	-3.899854	

2.3 Summary of relevant thermochemistry data

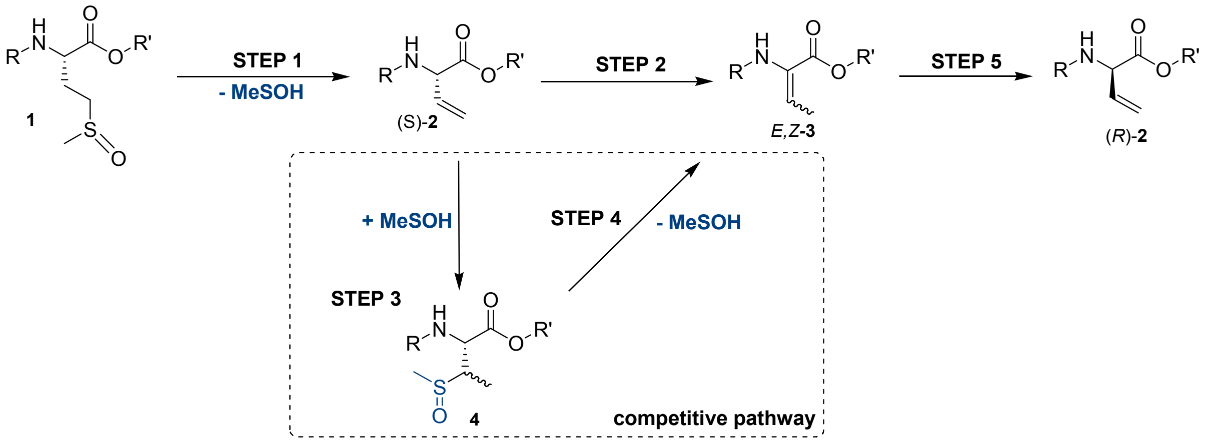


Figure S12. Overview of the competitive pathways for the thermolysis of **1**

Table S2. Summary of relevant thermochemistry data (see Figure S9)

Activation/reaction parameters (kcal mol^{-1})	Step 1	Step 2	Step 3	Step 4	Step 5
$\Delta G^{\neq}$	25.2	69.4	22.0	17.8	75.4
$\Delta H^{\neq}$	24.4	68.0	17.0	16.6	74.5
$\Delta G°$	1.3	-6.3	-1.6	-12.4	6.3
$\Delta H°$	6.6	-6.5	-6.3	-8.8	6.5

3 References

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