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Supporting Information for

Ruthenium-Catalyzed Hydrogen Isotope Exchange of C(sp^3)-H Bonds Directed by a Sulfur Atom

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Reagents and General Procedures:

All operations were carried out in a Fischer-Porter glassware. Commercially available substrates were used without further purification. Ru/C was purchased from Aldrich and used as received. THF was dried over sodium and benzophenone, distilled and then thoroughly degassed before use. DMF anhydrous was purchased from Aldrich and used without further purification. ^{1}H NMR (400 MHz), ^{13}C-{^{1}H} NMR (100 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported in Hertz (Hz). Splitting patterns are designated as singlet (s), doublet (d), triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Electrospray mass spectra were recorded using an ESI/TOF Mariner Mass Spectrometer. Optical rotations were measured using a Perkin Elmer Polarimeter 341. Centrifugation was performed on a VWR Galaxy Ministar Mini Centrifuge.

Deuterium NMR:

The proton-decoupled deuterium (^{2}H-{^{1}H}) 1D NMR spectra were recorded at 14.1 T (92 MHz) on a Bruker avance II NMR spectrometer equipped by a 5-mm selective deuterium cryogenic probe. Proton signals were eliminated using the WALTZ-16 CPD sequence.

H/D exchange quantification:

Deuterium incorporation was quantified by the decrease of ^{1}H NMR integral intensities at the specified positions compared to the starting material. Integral intensities were calibrated against hydrogen signals that do not undergo H/D-exchange. Mass spectrometry quantification was performed by subtraction of the mean molecular masses of the product and substrate isotopologue clusters in order to eliminate the contribution of the natural isotope abundance to the total mass.

General Procedure A for H/D exchanges:

A 93 mL Fischer–Porter glassware was charged with Ru/C (5 wt%, 121.2 mg, 30 mol %) and a magnetic stirrer under air. The Fischer–Porter glassware was then left under vacuum for 5 min and pressurized with D_2 gas (3 bar) during 2 hours. A solution of the substrate (0.2 mmol) in degassed DMF or THF or D_2O or CD_3OD (2 mL) was added under argon. The reaction mixture was magnetically stirred at 60 °C (sand bath) under pressure of D_2 (2 bar) during 72 hours. The solution was then cooled down to room temperature, filtered through syringe filter and evaporated under vacuum. Deuterated products were obtained mostly in quantitative yield except extra mention.

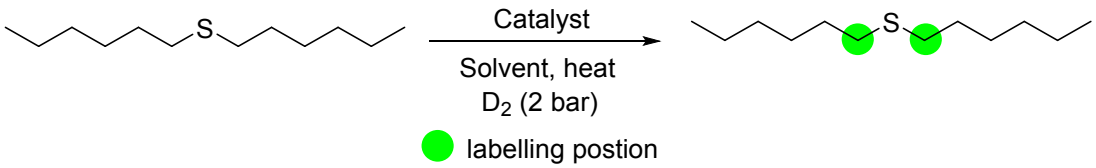
General Procedure B for H/D exchanges:

A 47 mL Fischer–Porter glassware was charged with Ru/C (5 wt%, 30 mol %) and a magnetic stirrer under air. The Fischer–Porter glassware was then left under vacuum for 5 min and pressurized with D_2 gas (3 bar) during 2 hours. A solution of the substrate (15 mg) in degassed D_2O (1 mL) was added under argon. The reaction mixture was magnetically stirred at 60 °C (sand bath) under pressure of D_2 (2 bar) during 72 hours. The solution was then cooled down to room temperature, filtered through syringe filter and evaporated under vacuum. Deuterated products were obtained mostly in quantitative yield except extra mention.

General Procedure C for H/D exchanges:

Same as General Procedure A, except that the reaction was run for 24 hours. After that, the substrate was filtered, dried and a second run of catalysis using a new batch of Ru/C catalyst was performed. The crude product was purified by HPLC. The isotopic enrichment was recorded after the purification by ^{1}H NMR and MS.

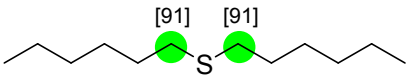
Table S1 Screening conditions for the deuteration of dihexyl sulfide



Entry	Catalyst	Solvent	T (°C)	Time (days)	Isotopic enrichment
1	10 mol% Ru/PVP	THF	55	1	3%
2	10 mol% Ru/dppb	THF	55	1	4%
3	10 mol% Ru/C	THF	55	1	11%
4	30 mol% Ru/C	THF	60	1	77%
5	30 mol% Ru/C	THF	60	3	91%
6	30 mol% Ru/PVP	THF	60	3	83%
7	30 mol% Ru-Sn/PVP	THF	60	3	14%
8	30 mol% Rh/C	THF	60	3	14%
9	30 mol% Pd/C	THF	60	3	18%
10	30 mol% Ru/C	DMF	60	3	68%
11	30 mol% Ru/C	DMA	60	3	71%
12	30 mol% Ru/C	NMP	60	3	49%
13	30 mol% Ru/C	THF	rt	3	25%

Experimental details and characterization for compounds 1 to 11:

Dihexyl sulfide (1)



Following the General Procedure A (0.2 mmol of substrate was used) and using THF as solvent. After the final evaporation an ^{1}H NMR spectrum of the residue was recorded. 41 mg (quantitative) of deuterated compound was obtained after drying by vacuum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (t, J = 7.4 Hz, 0.4H), 1.61-1.48 (m, 4H), 1.46-1.16 (m, 12H), 0.88 (t, J = 6.8 Hz, 6H). ^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$) δ 31.5-31.3 (m), 29.6-29.4 (m), 28.4 (s), 22.6 (s), 14.0 (s).

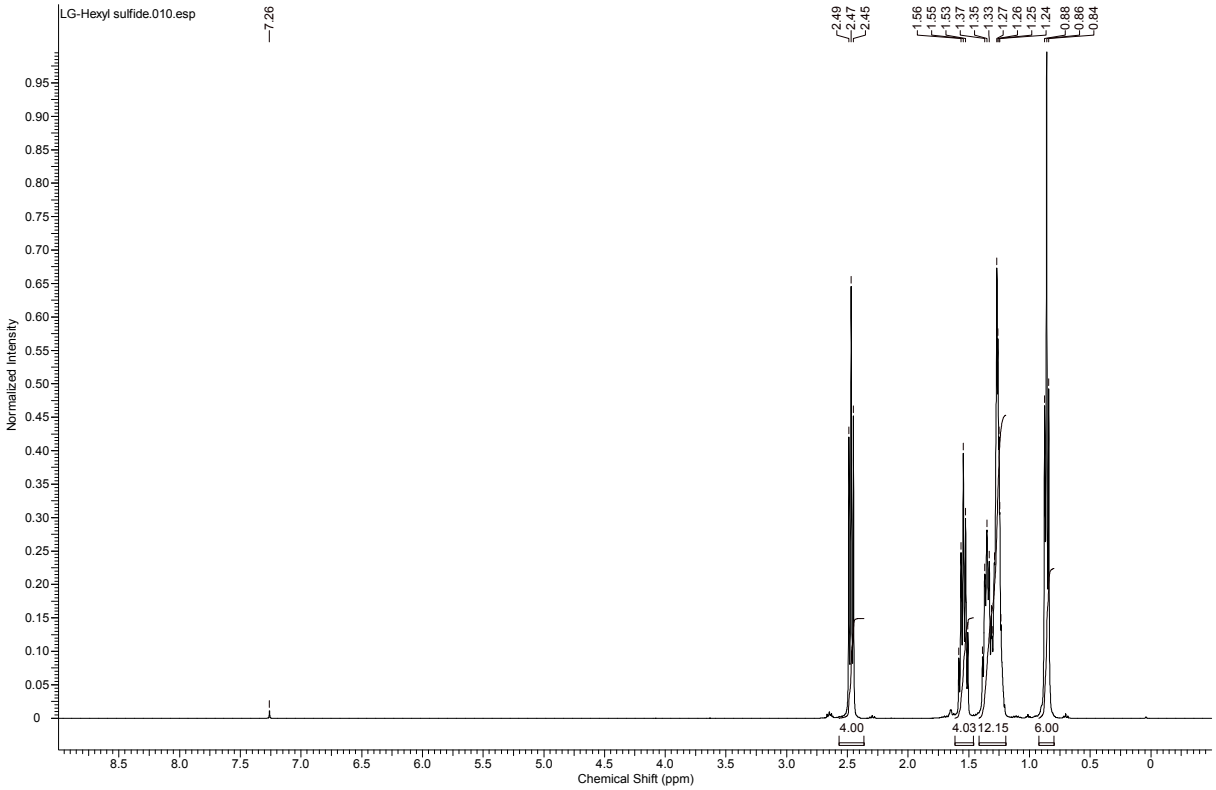


Figure S1 ^{1}H NMR spectrum of **S1 (starting material)**

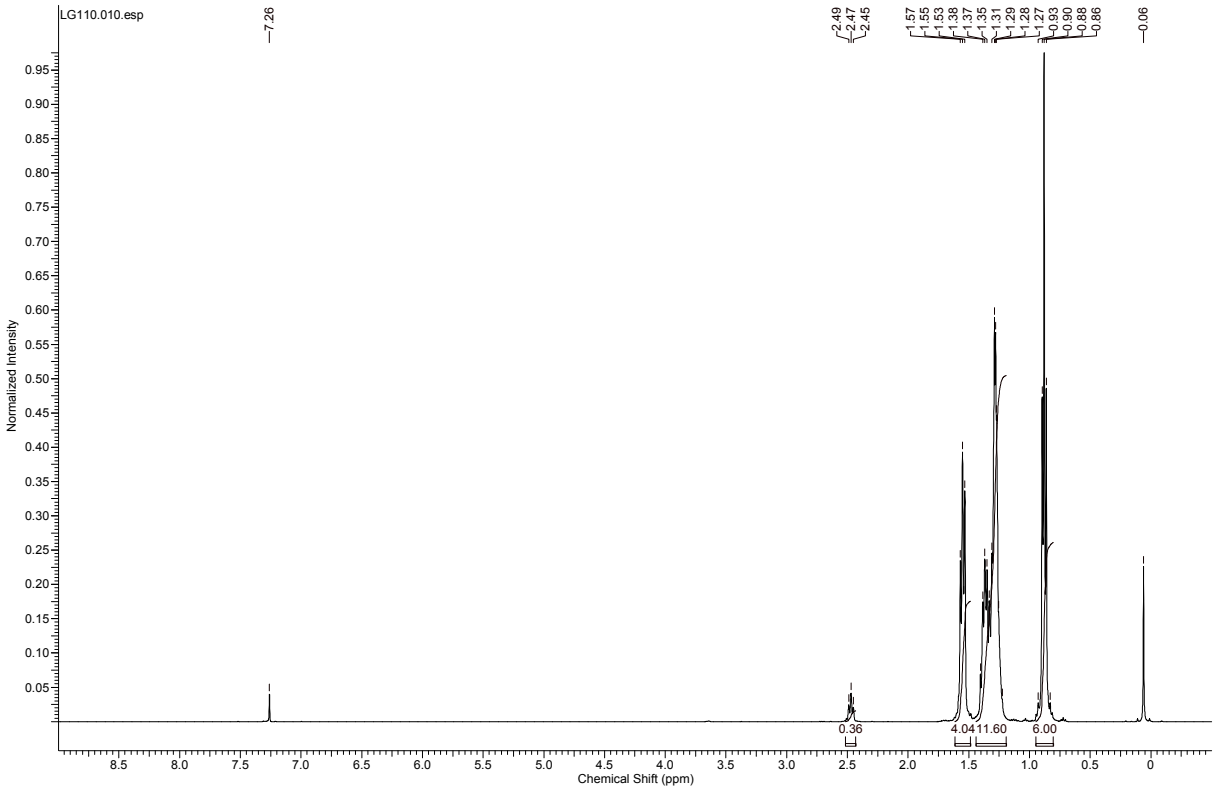


Figure S2 ^{1}H NMR spectrum of **1**

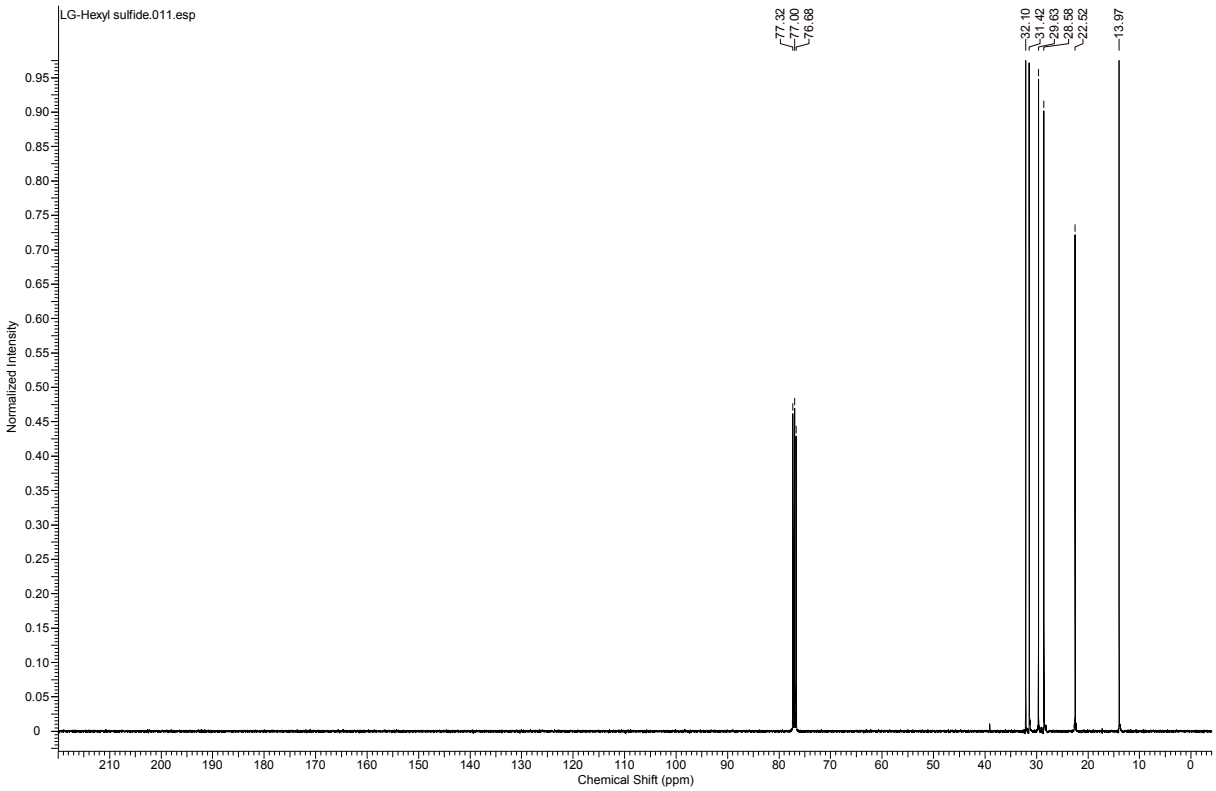


Figure S3 ^{13}C-{^{1}H} NMR spectrum of **S1 (starting material)**

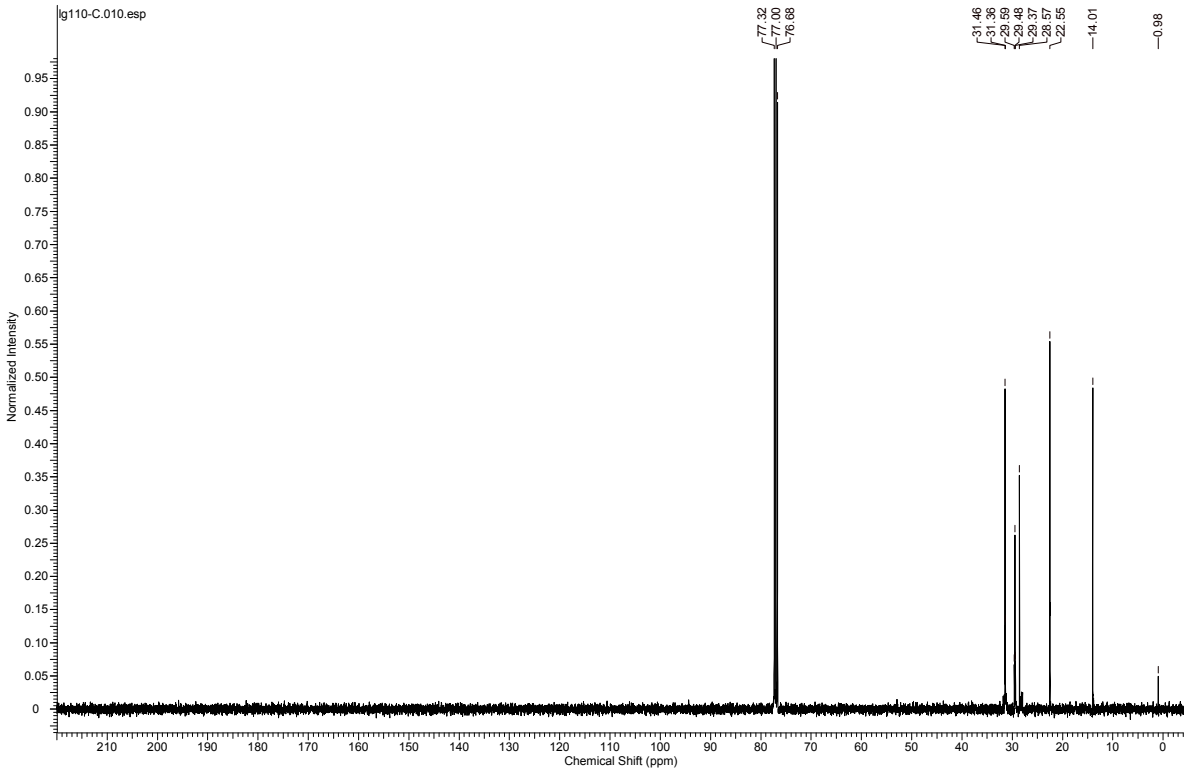


Figure S4 ^{13}C-{^{1}H} NMR spectrum of **1**

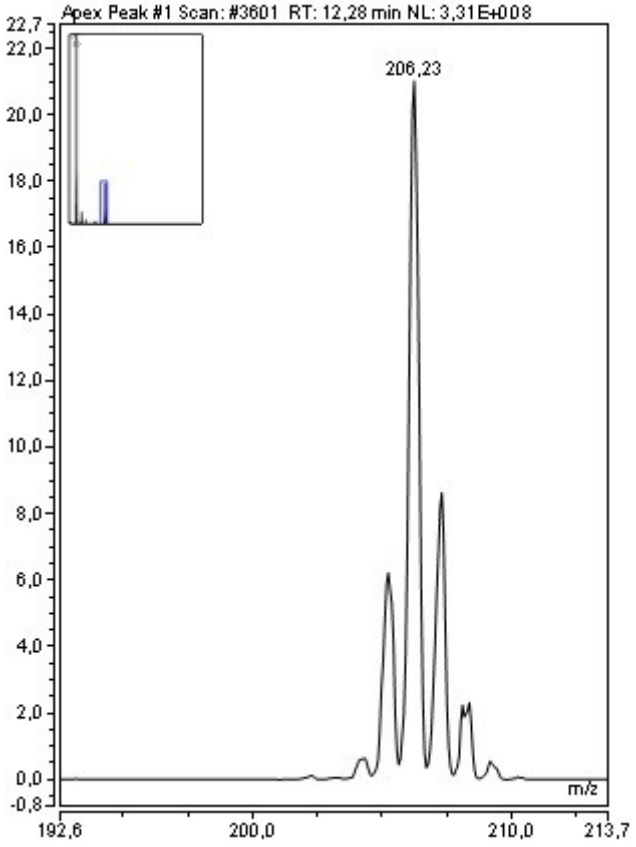
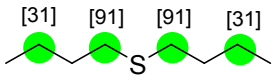


Figure S5 GC-MS analysis of **1**

Dibutyl sulfide (2)



Following the General Procedure A (0.2 mmol of substrate was used) and using THF as solvent. After the final evaporation, the ^{1}H NMR spectrum of the residue was recorded. 25 mg (86%) of deuterated compound was obtained after drying by vacuum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (t, J = 7.3 Hz, 0.4H), 1.58-1.50 (m, 4H), 1.45-1.34 (m, 2.8H), 0.91 (t, J = 7.3 Hz, 6H). ^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$) δ 31.7-31.5 (m), 22.0-21.5 (m), 13.7-13.4 (m)

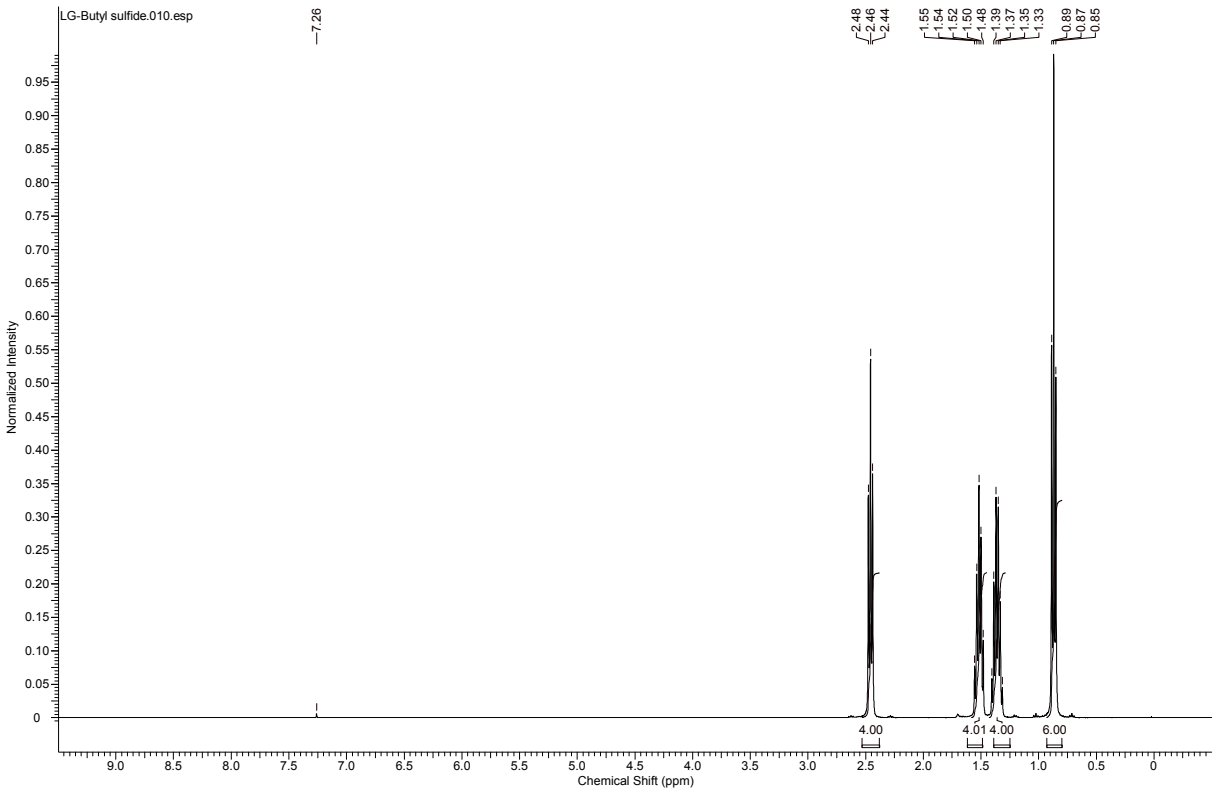


Figure S6 ^{1}H NMR spectrum of **S2 (starting material)**

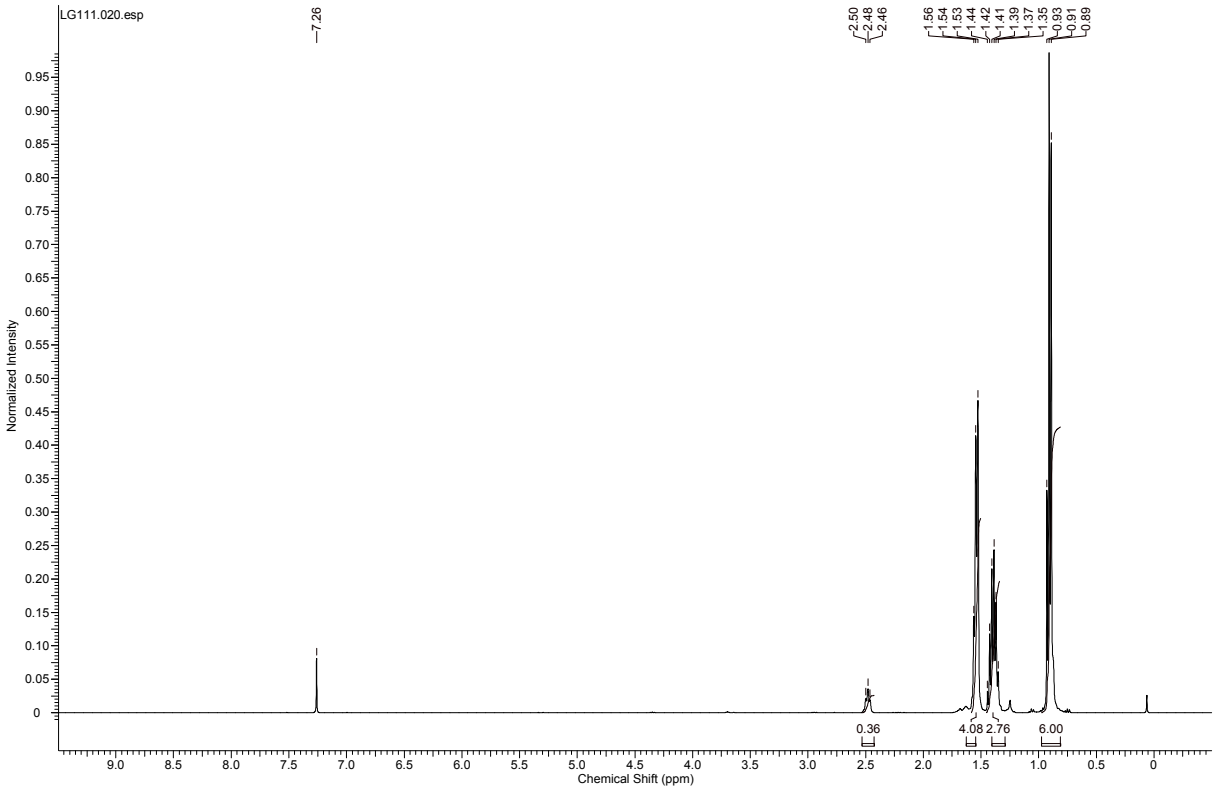


Figure S7 ^{1}H NMR spectrum of **2**

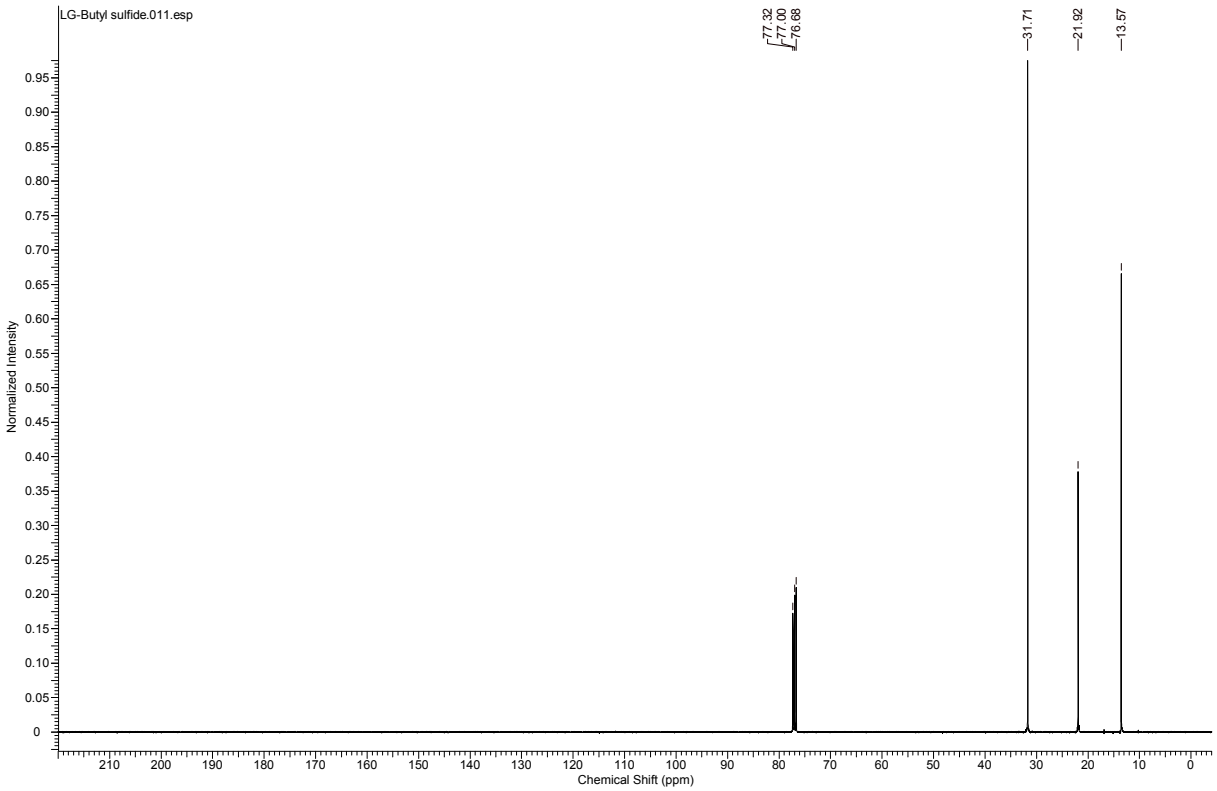


Figure S8 ^{13}C-{^{1}H} NMR spectrum of **S2 (starting material)**

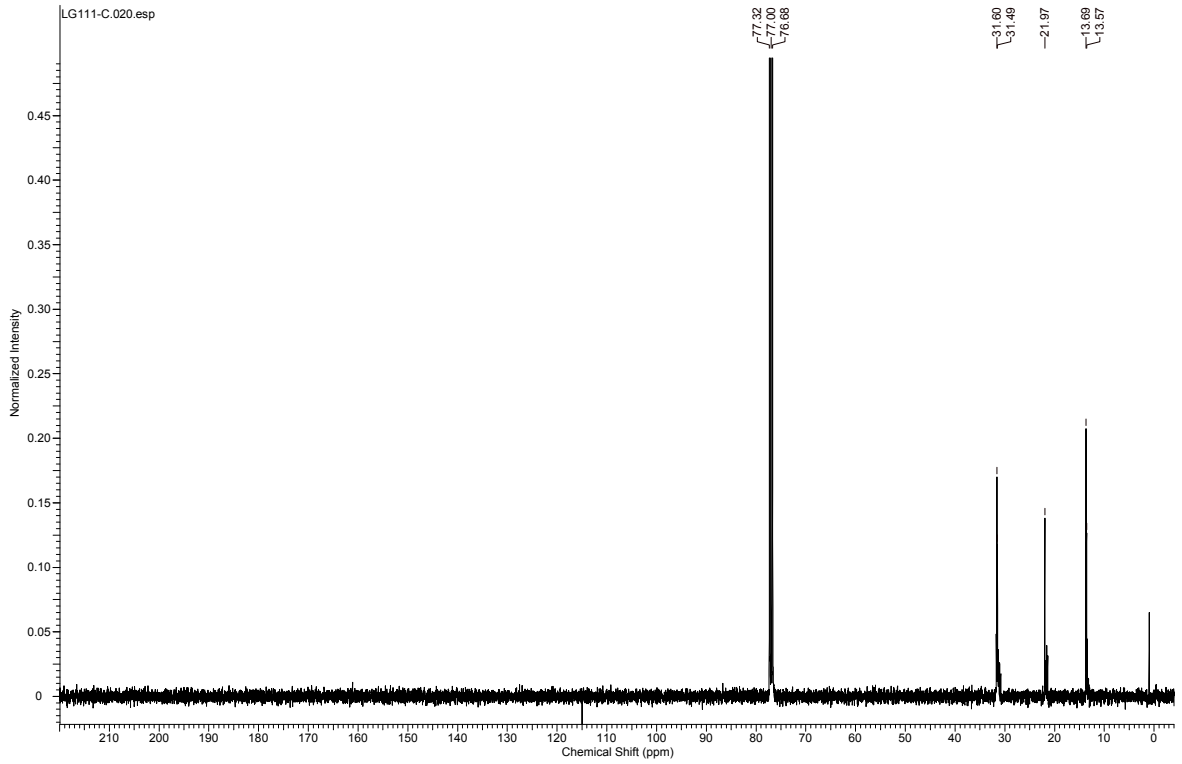


Figure S9 ^{13}C-{^{1}H} NMR spectrum of **2**

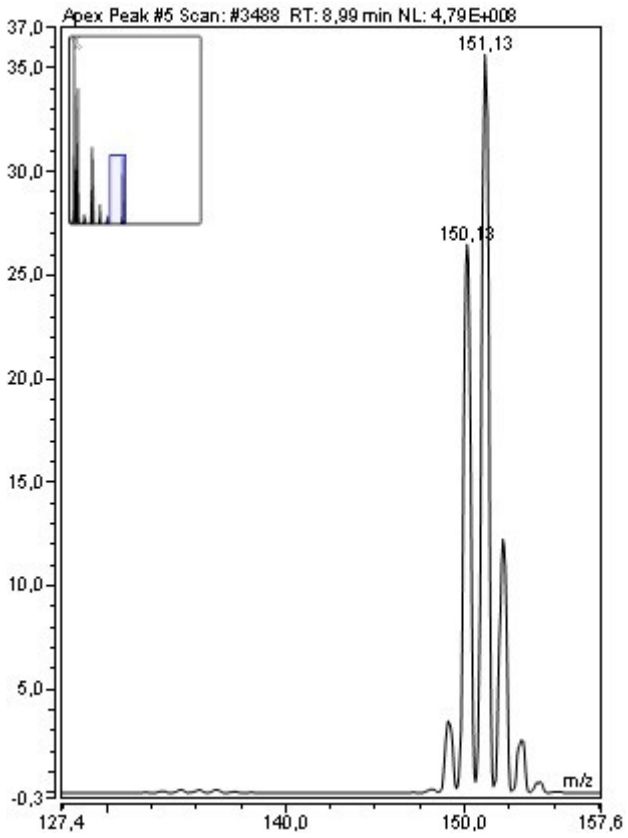
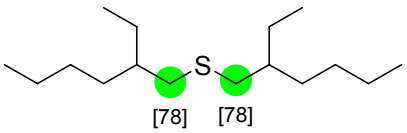


Figure S10 GC-MS analysis of **2**

Bis(2-ethylhexyl)sulfide (3)



Following the General Procedure A (0.2 mmol of substrate was used) and using THF as solvent. After the final evaporation, the ^{1}H NMR spectrum of the residue was recorded. 50 mg (97%) of deuterated compound was obtained after drying by vacuum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47-2.38 (m, 0.9H), 1.49-1.20 (m, 18H), 0.99-0.72 (m, 12H). ^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$) δ ^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$) δ 39.3-39.1 (m), 37.2-36.8 (m), 34.2 (s), 32.4 (s), 30.3 (s), 28.9-28.8 (m), 25.5 (s), 24.9 (s), 22.9 (m), 14.1 (s), 10.9 – 10.2 (m).

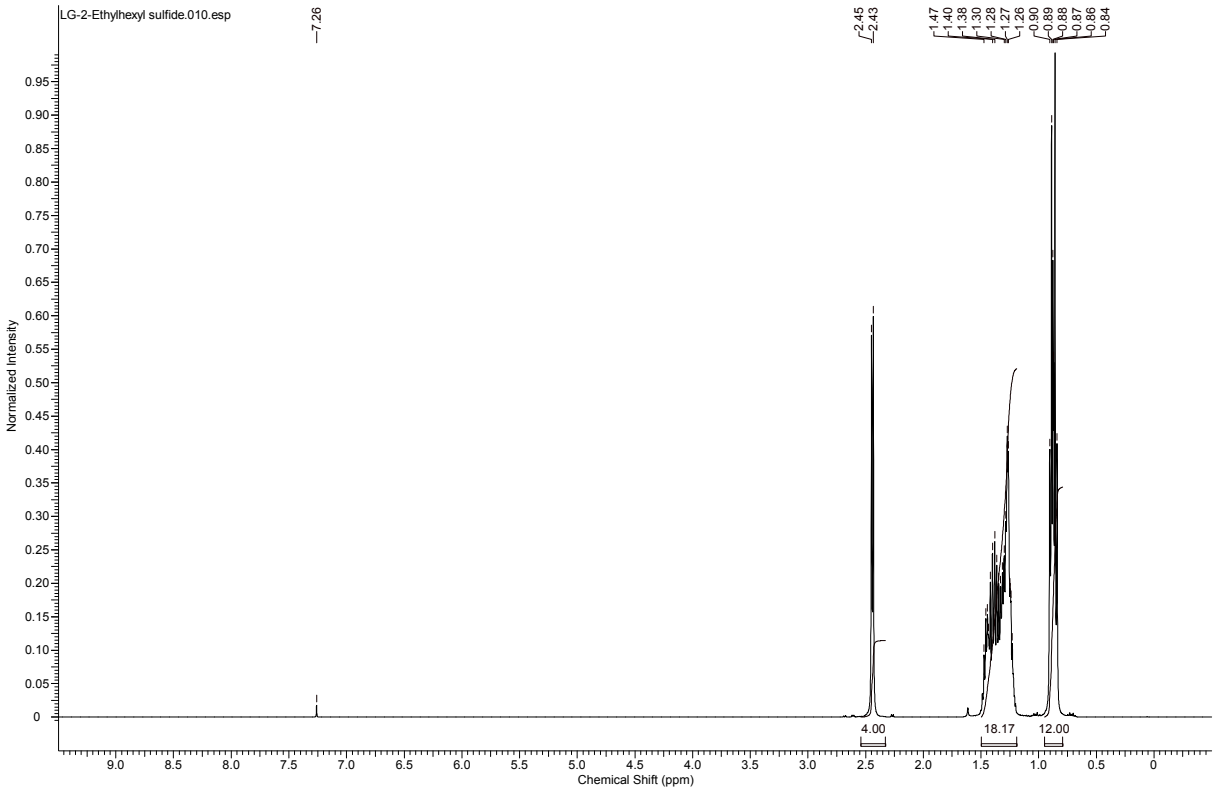


Figure S11 ^{1}H NMR spectrum of **S3 (starting material)**

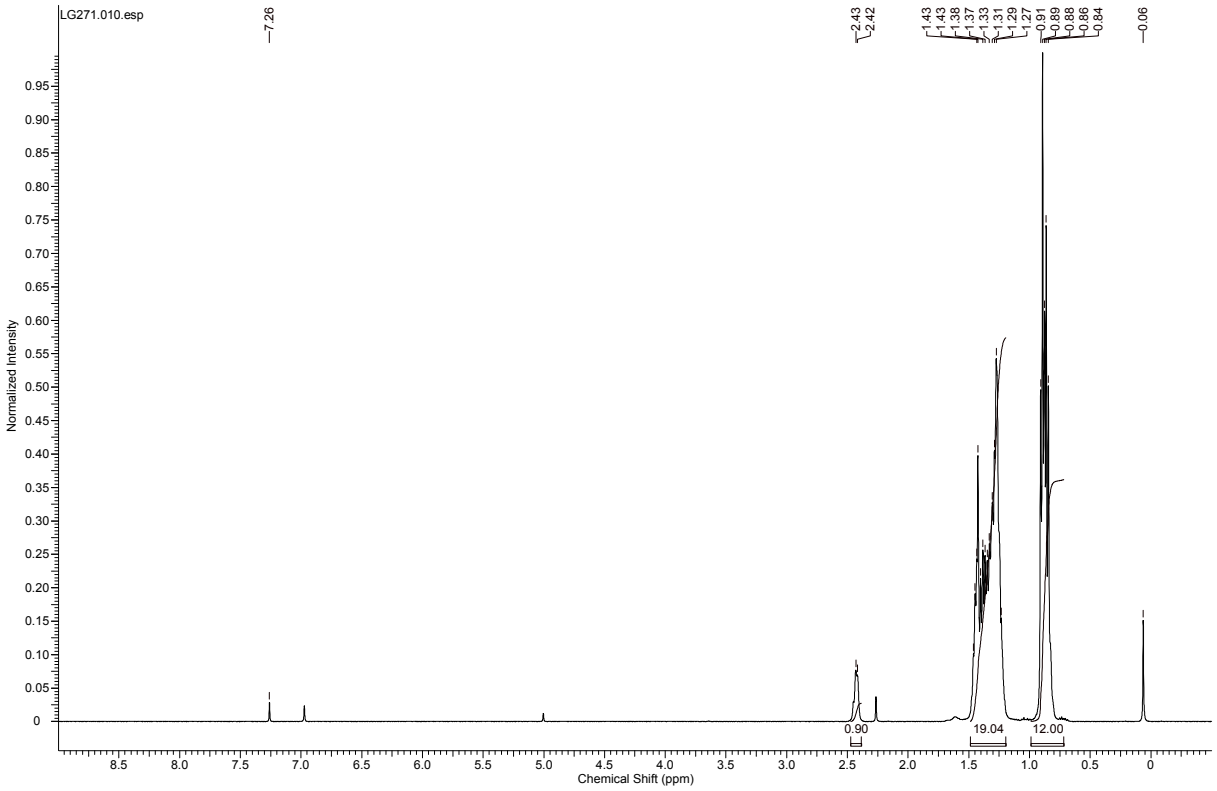


Figure S12 ^{1}H NMR spectrum of **3**

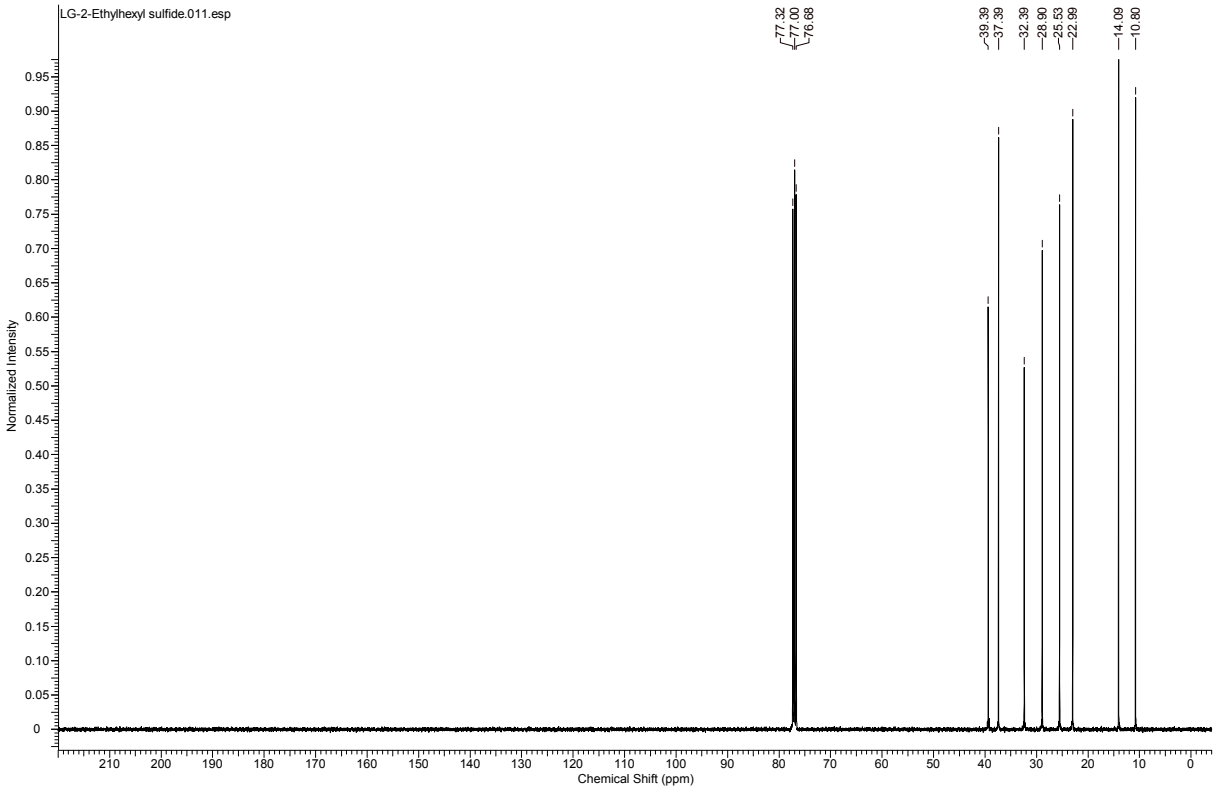


Figure S13 ^{13}C-{^{1}H} NMR spectrum of **S3 (starting material)**

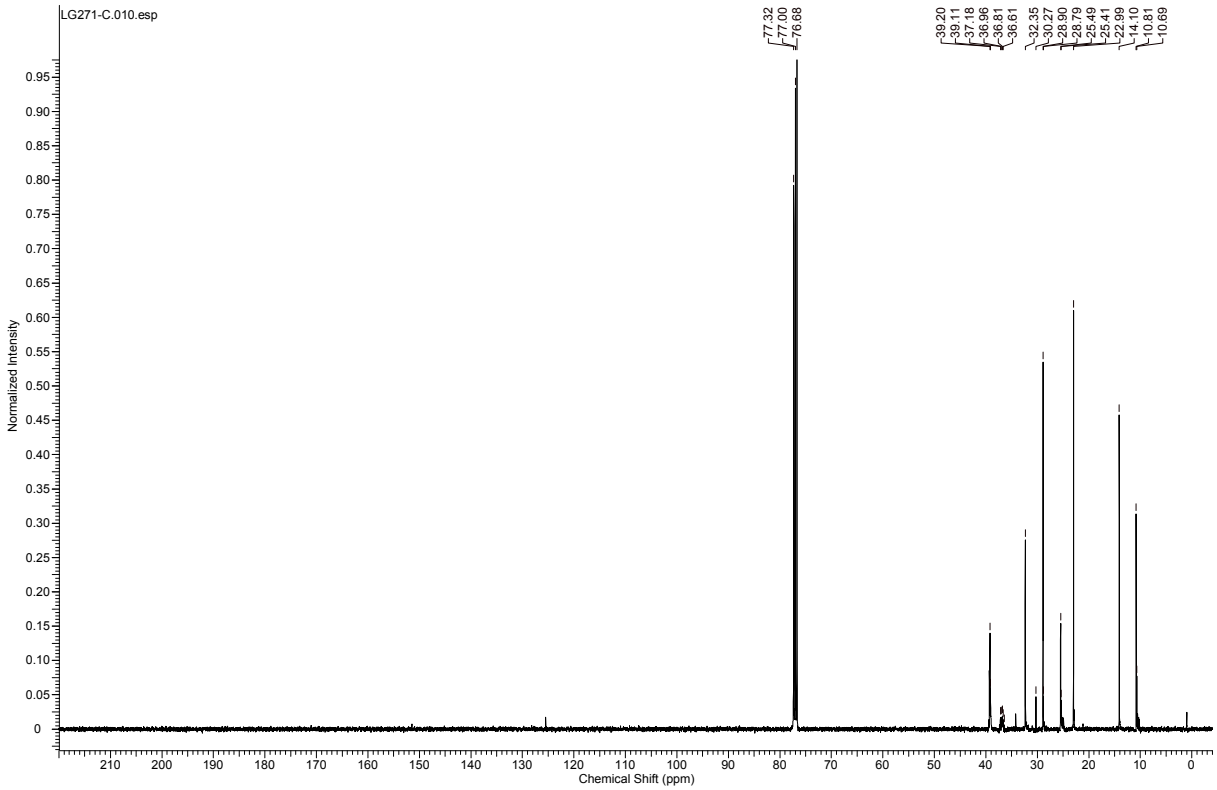


Figure S14 ^{13}C-{^{1}H} NMR spectrum of **3**

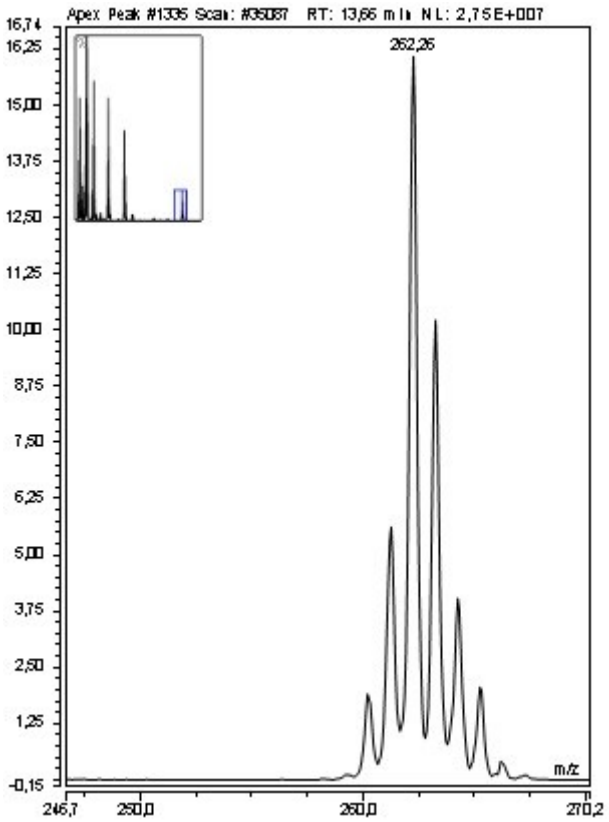
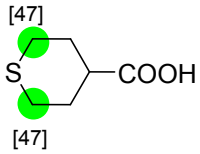


Figure S15 GC-MS analysis of **3**

Tetrahydrothiopyran-4-carboxylic acid (4)



Following the General Procedure A (0.2 mmol of substrate was used) and using THF as solvent. After the final evaporation, the ^{1}H NMR spectrum of the residue was recorded. 29 mg (quantitative) of deuterated compound was obtained after drying by vacuum. Repeating the reaction with this material (using standard conditions) has led to higher deuterium incorporation (82%, product **4'**). 27 mg (93%) of deuterated compound was obtained after drying by vacuum.

4: ^{1}H NMR (400 MHz, CD_3OD) δ 2.76-2.60 (m, 2.1H), 2.41 (tt, J = 11.0, 3.3 Hz, 1H), 2.28-2.17 (m, 2H), 1.87-1.73 (m, 2H). ^{13}C-{^{1}H} NMR (100 MHz, CD_3OD) δ 177.2 (s), 42.1 (s), 29.7 (m), 27.0 (m).

4': ^{1}H NMR (400 MHz, CD_3OD) δ 2.73-2.60 (m, 0.7H), 2.41 (tt, J = 11.0, 3.4 Hz, 1H), 2.28-2.15 (m, 2H), 1.88-1.71 (m, 2H). ^{13}C-{^{1}H} NMR (100 MHz, CD_3OD) δ 177.2 (s), 42.1 (s), 29.8-29.6 (m), 27.0-26.7 (m).

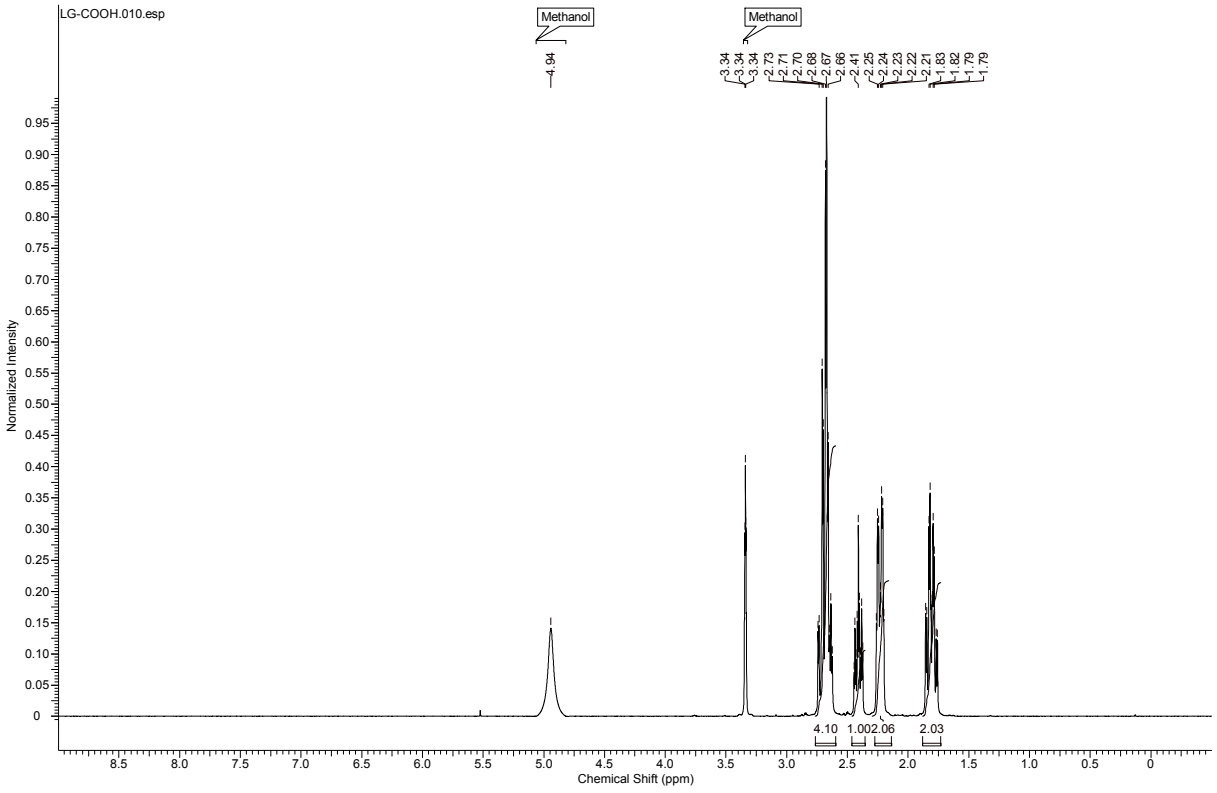


Figure S16 ^{1}H NMR spectrum of **S4 (starting material)**

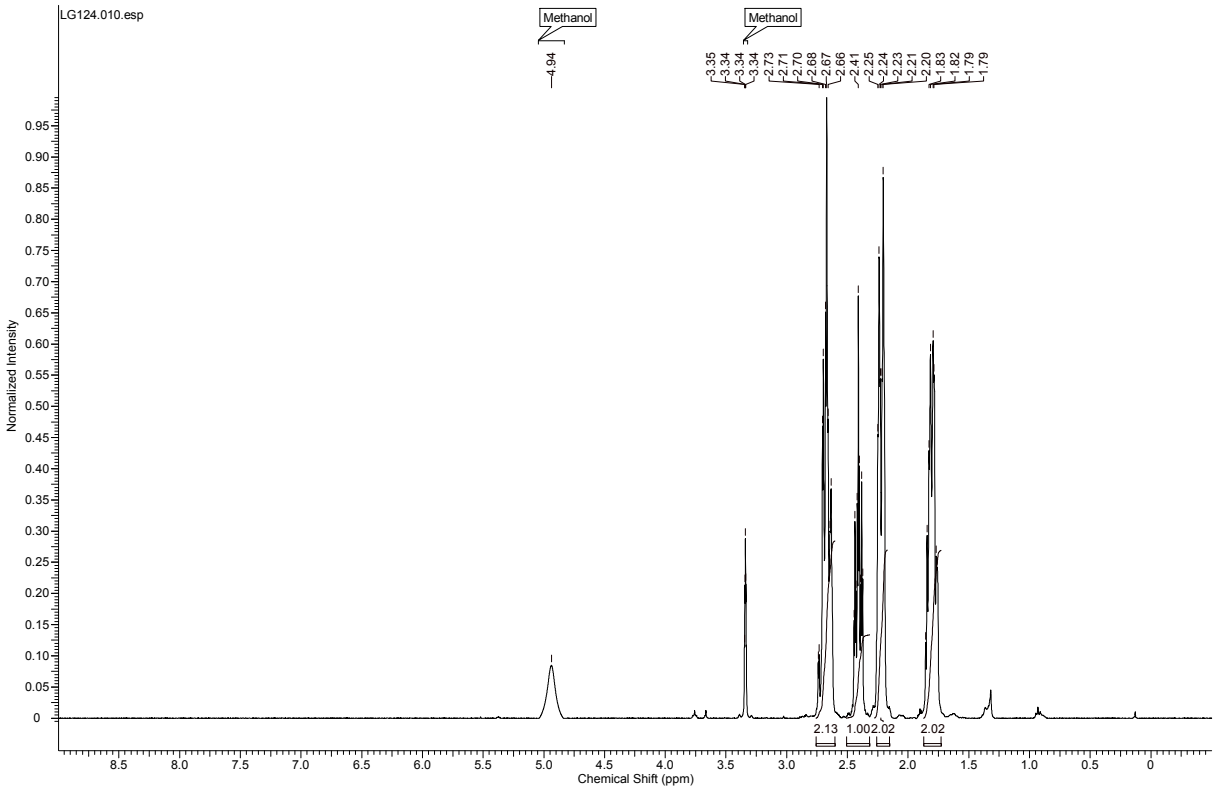


Figure S17 ^{1}H NMR spectrum of **4**

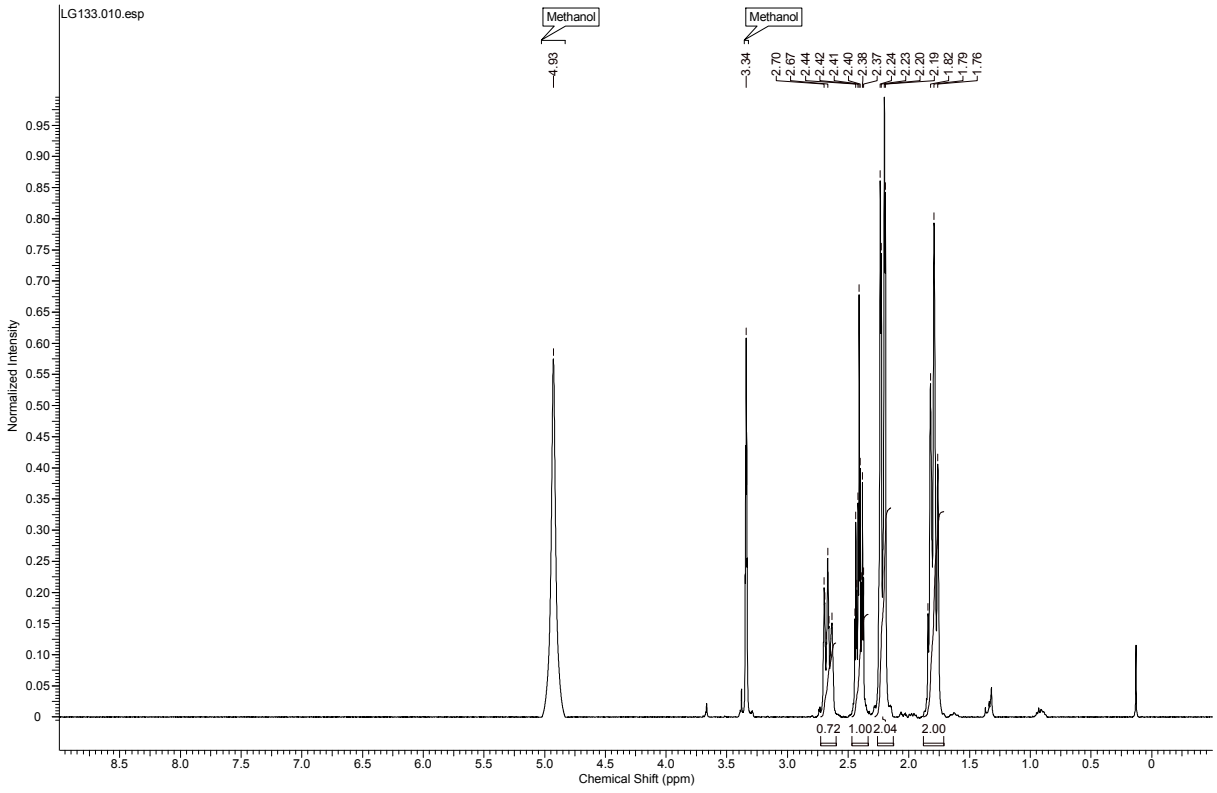


Figure S18 ^{1}H NMR spectrum of **4'**

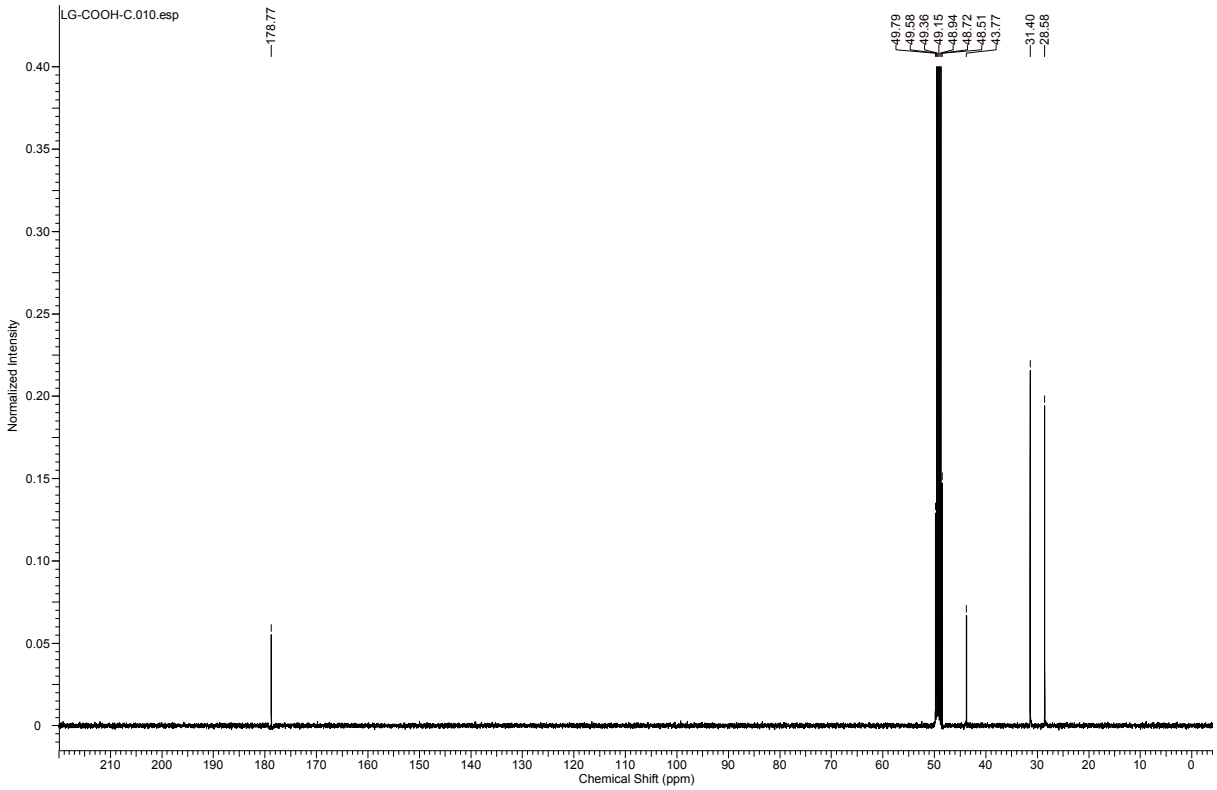


Figure S19 ^{13}C-{^{1}H} NMR spectrum of **S4 (starting material)**

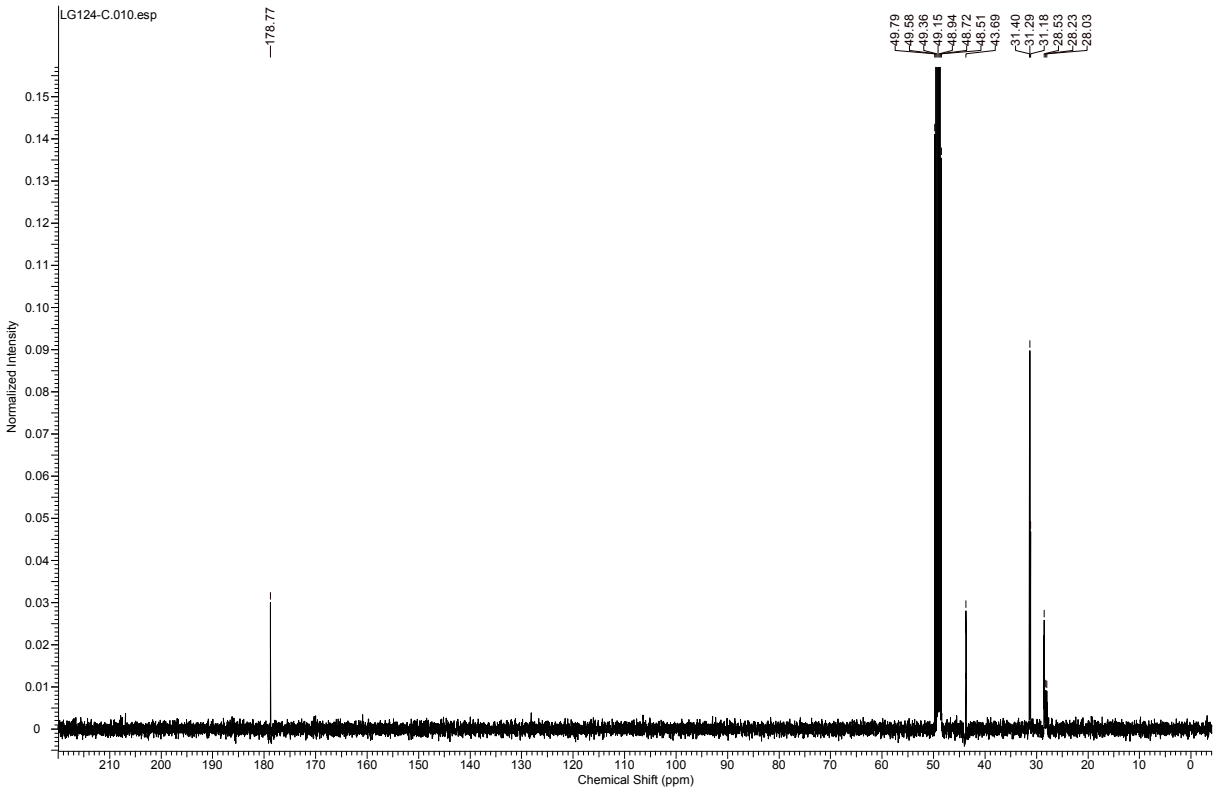


Figure S20 ^{13}C-{^{1}H} NMR spectrum of **4**

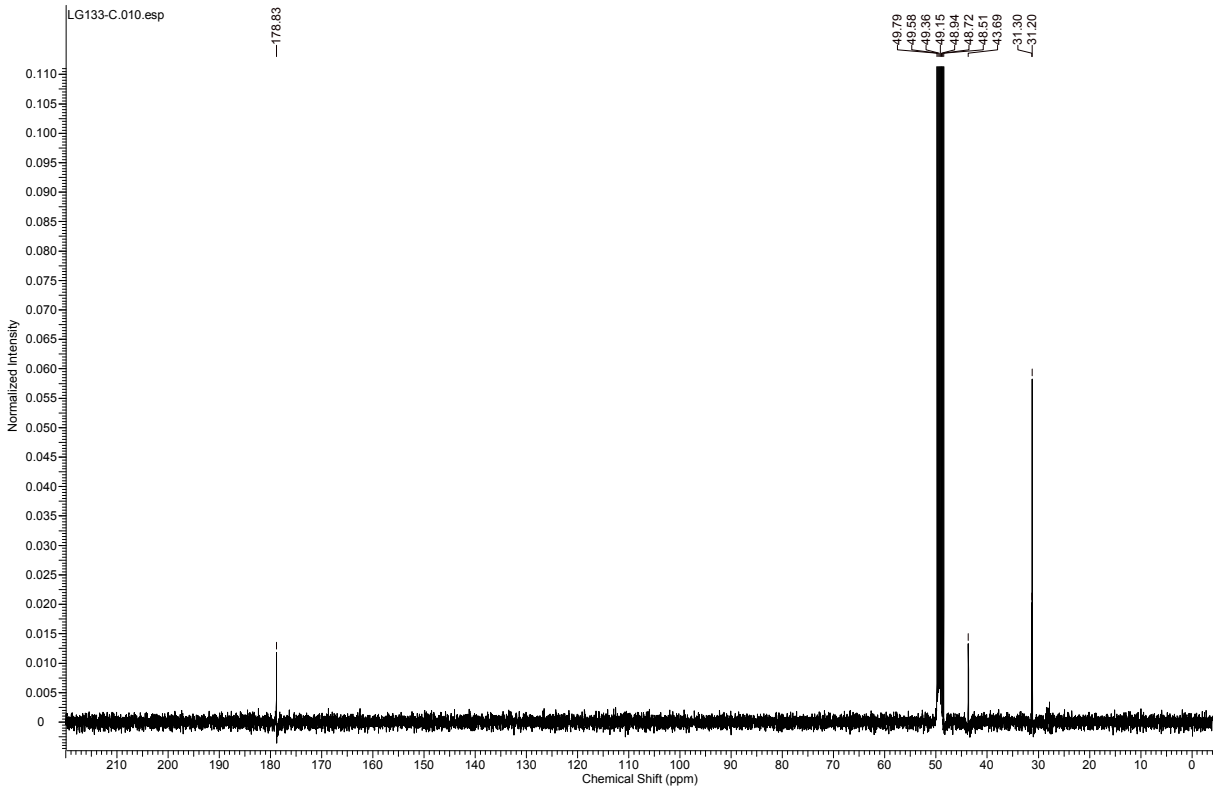


Figure S21 ^{13}C-{^{1}H} NMR spectrum of **4'**

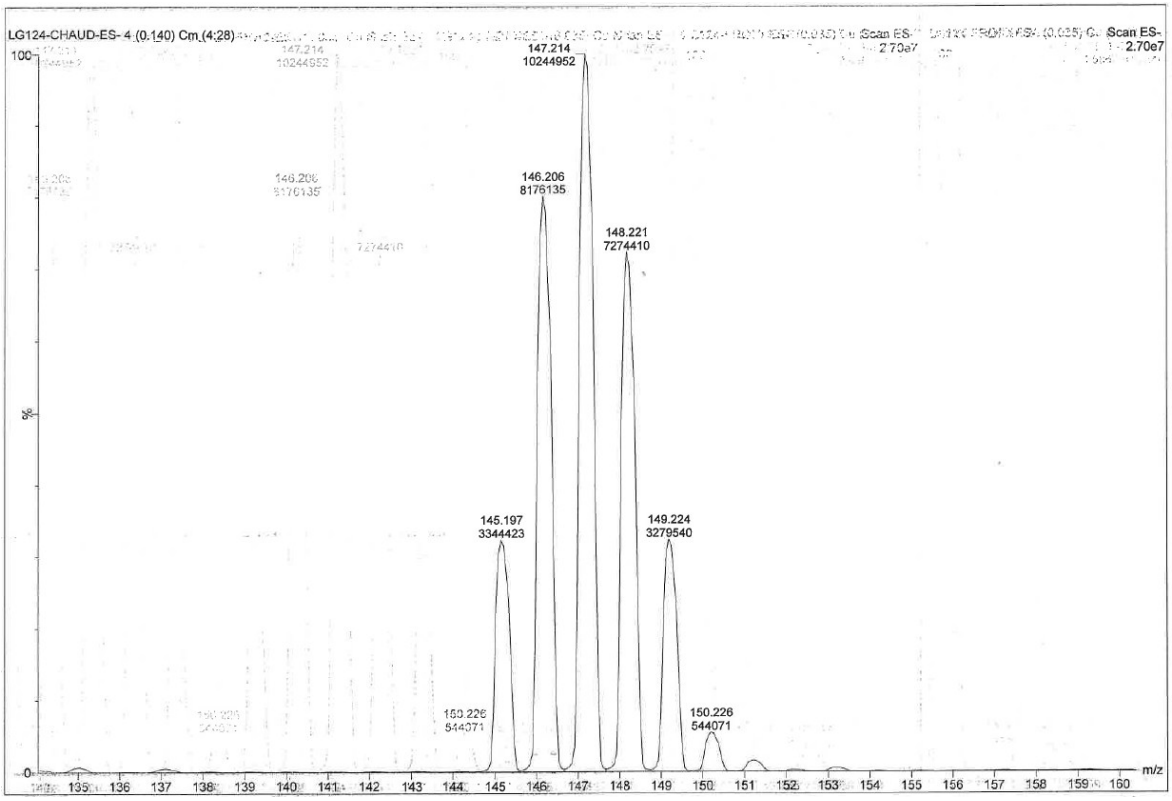


Figure S22 Mass spectrum of **4**

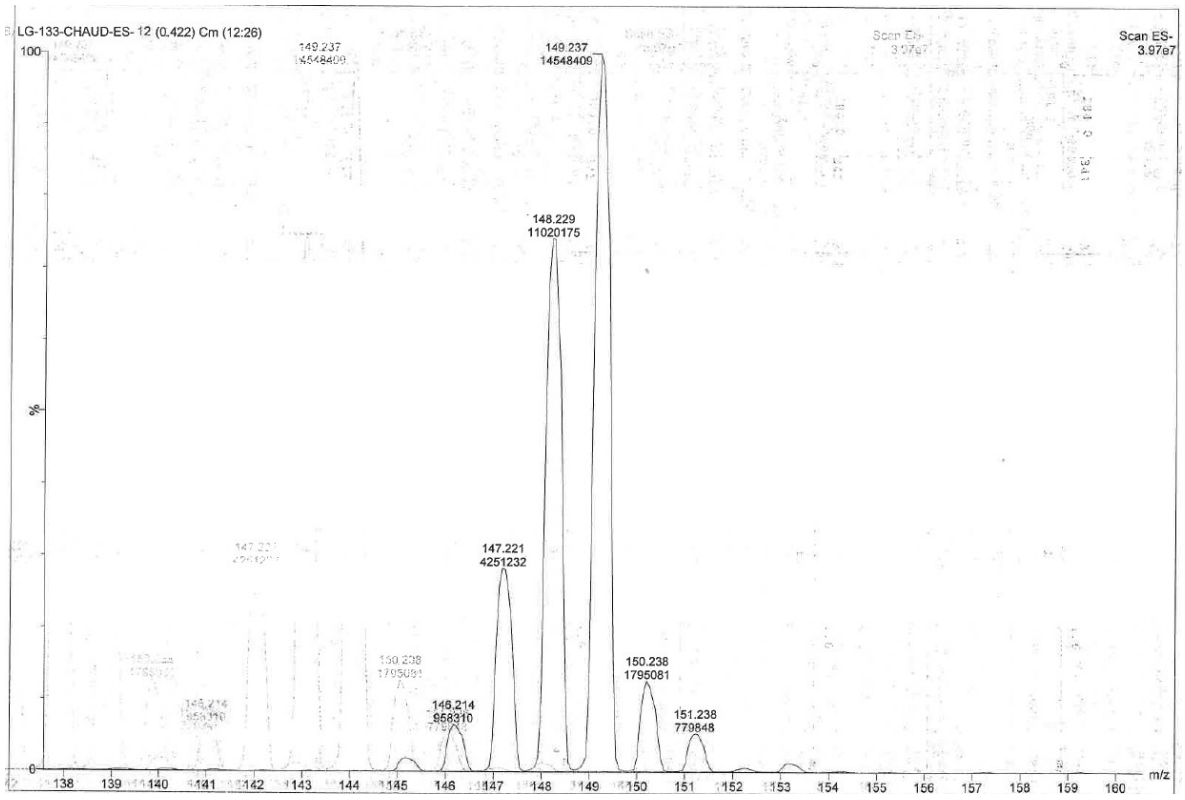
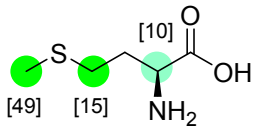


Figure S23 Mass spectrum of **4'**

L-Methionine (5)



Following the General Procedure A (0.2 mmol of substrate was used) and using D_2O as solvent. After the final evaporation, the ^1H NMR spectrum of the residue was recorded. 30 mg (quantitative) of deuterated compound was obtained after drying by vacuum. Note that HPLC purification was realized before ^2H-{^1H} NMR spectrum was recorded.

^1H NMR (400 MHz, D_2O) δ 3.85 (t, J = 6.1 Hz, 1H), 2.62 (t, J = 7.3 Hz, 1.8H), 2.25-2.02 (m, 3.9H). ^{13}C-{^1H} NMR (100 MHz, D_2O) δ ^{13}C-{^1H} NMR (100 MHz, D_2O) δ 174.2 (s), 53.8 (s), 29.7-29.5 (m), 28.8-28.6 (m), 13.9-13.5 (m).

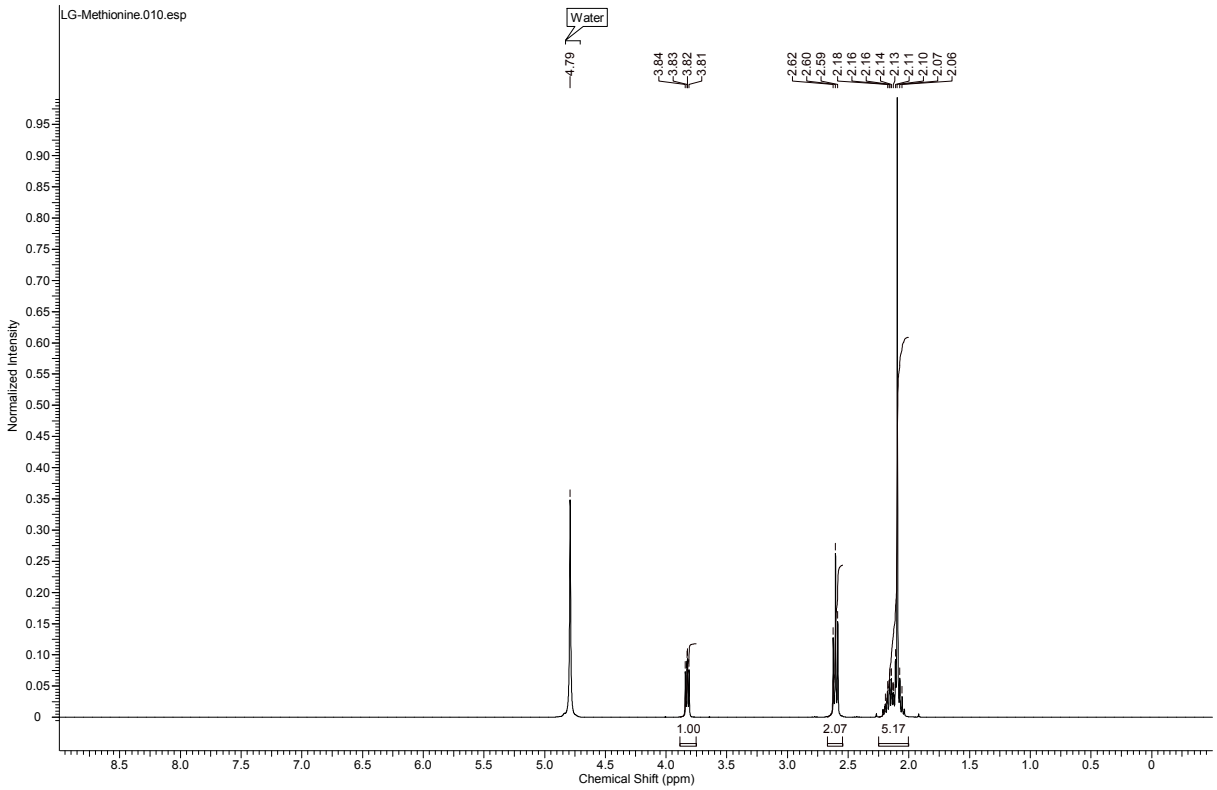


Figure S24 ^{1}H NMR spectrum of **S5 (starting material)**

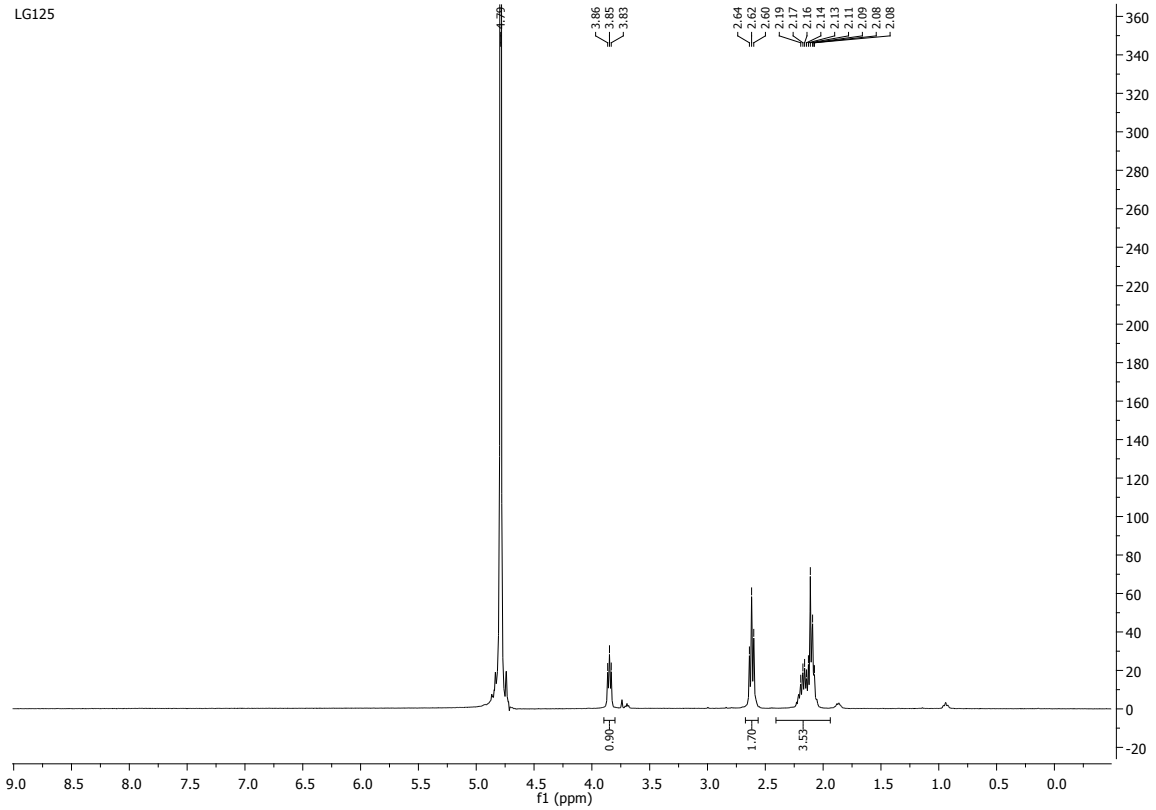


Figure S25 ^{1}H NMR spectrum of **5**

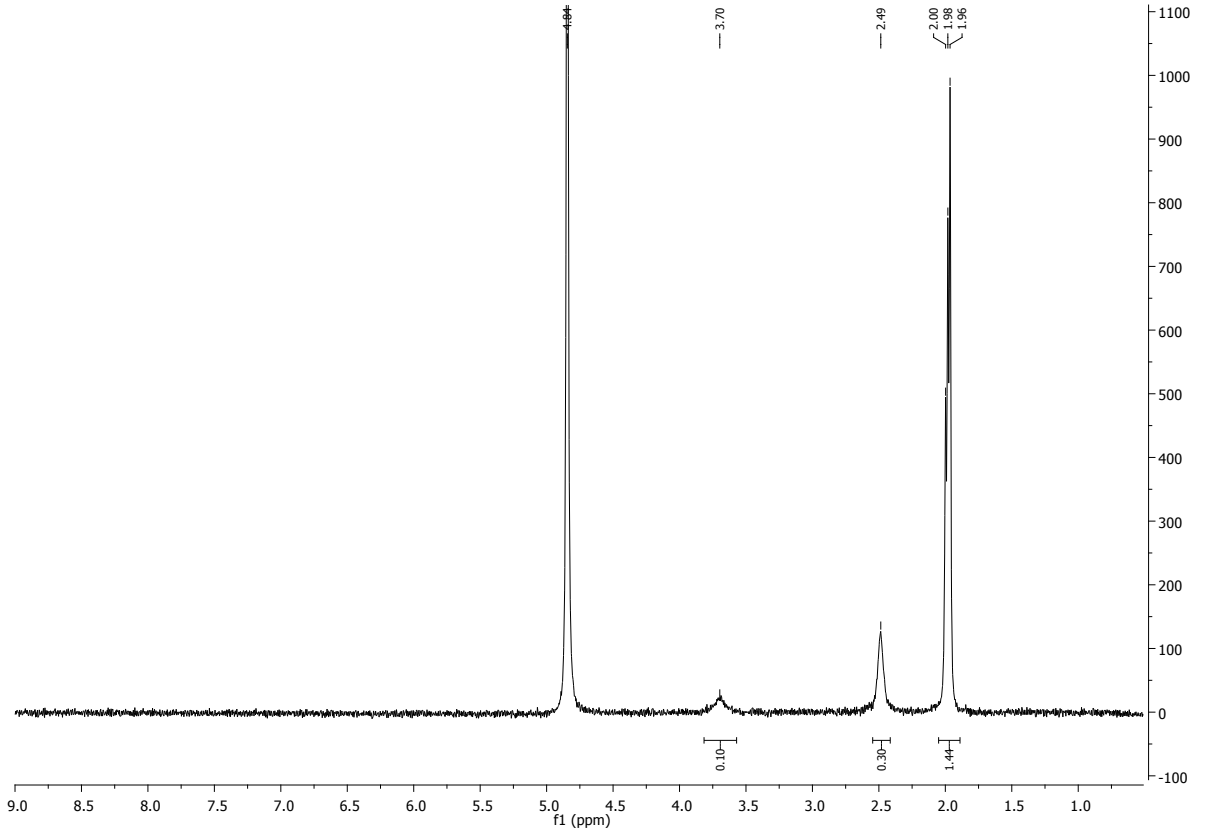


Figure S26 ^{2}H-{^{1}H} NMR spectrum of **5**

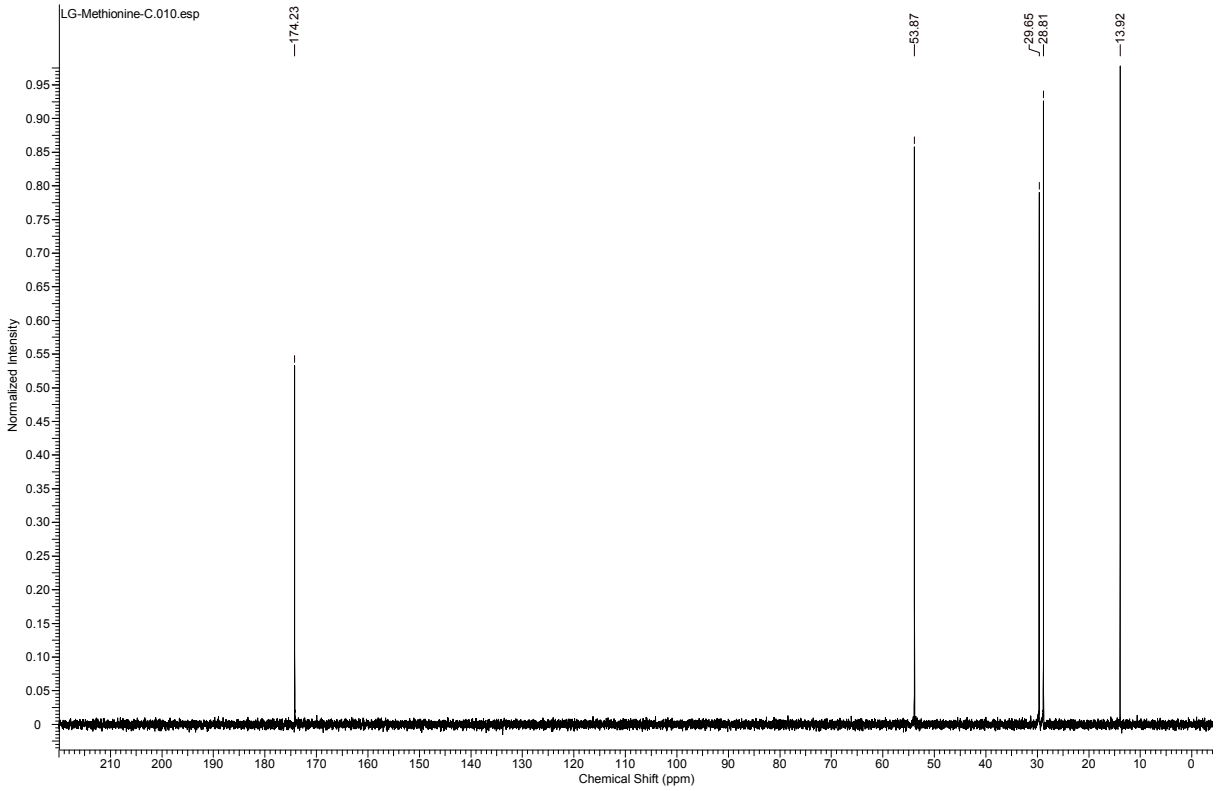


Figure S27 ^{13}C-{^{1}H} NMR spectrum of **S5 (starting material)**

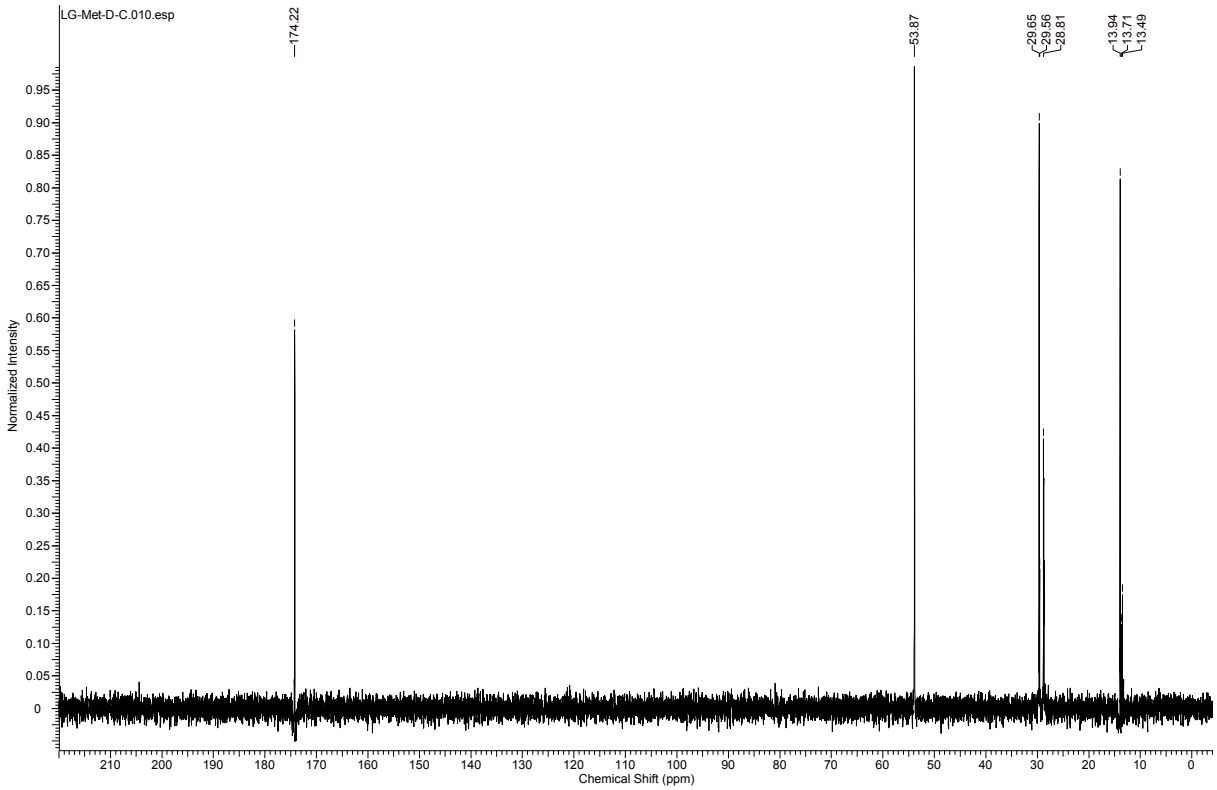


Figure S28 ^{13}C-{^{1}H} NMR spectrum of **5**

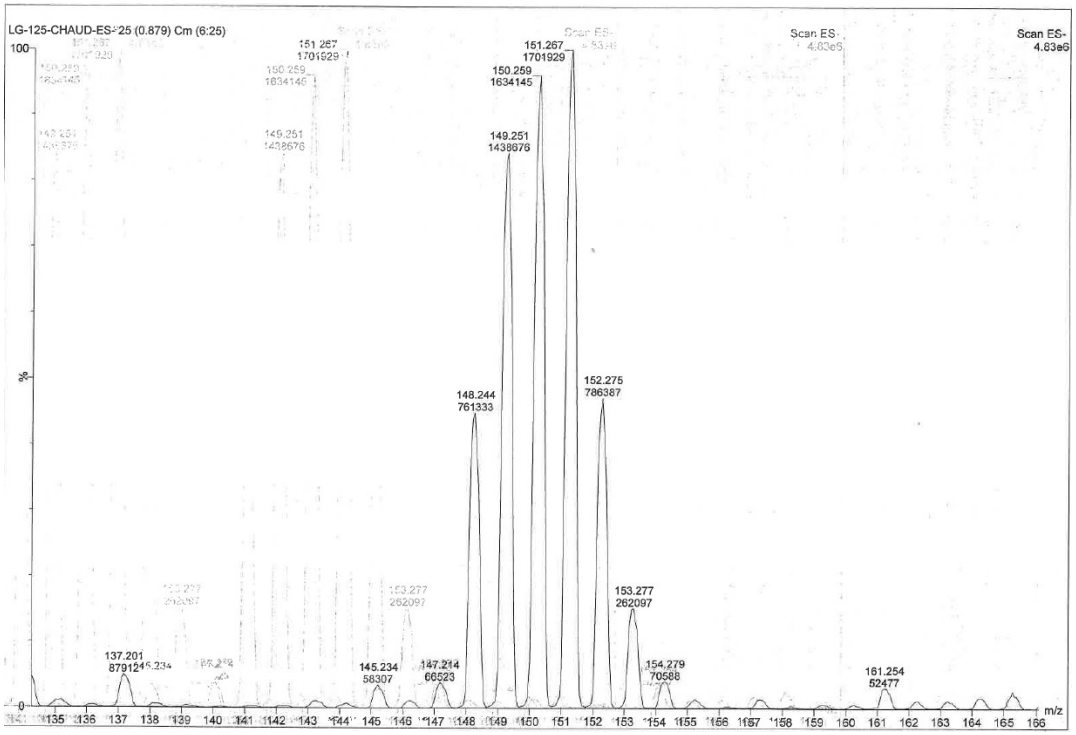


Figure S29 Mass spectrum of **5**

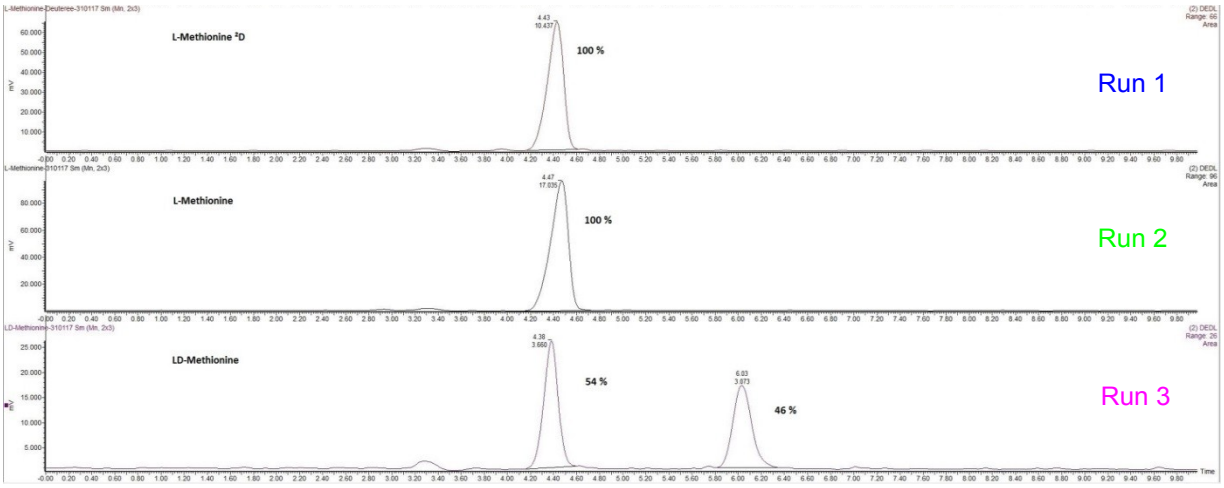


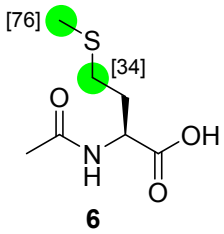
Figure S30 Chiral HPLC analysis of **5**

Run	Substrate	L-Methionine	D-Methionine
1	Deuterated L-methionine	100%	0%
2	L-Methionine	100%	0%
3	DL-Methionine	54%	46%

Conditions :

Column : Astec Chirobiotic T n° 89930-02 250mm*4.6mm*5µm
Eluent : Iso30 15min (H_2O / MeOH / HCOOH; 30 / 70 / 0.2)
Debit : 1mL/min
Temperature : Room temperature
Injection : 20µL

Acetyl-L-methionine (6)



6

Following the General Procedure A (0.2 mmol of substrate was used) and using CD_3OD as solvent. After the final evaporation, the ^1H NMR spectrum of the residue was recorded. 39 mg (quantitative) of deuterated compound was obtained after drying by vacuum. Note that HPLC purification was realized before ^2H NMR was recorded.

^1H NMR (400 MHz, CD_3OD) δ 4.53 (dd, J = 9.0, 4.6 Hz, 1H), 2.65-2.48 (m, 1.3H), 2.20-2.06 (m, 1.7H), 2.05-1.91 (m, 4H). ^{13}C-{^1H} NMR (100 MHz, CD_3OD) δ 174.3 (s), 171.9 (s), 51.7 (s), 31.0-30.9 (m), 29.7-29.4 (m), 21.0 (s), 13.7-12.8 (m).

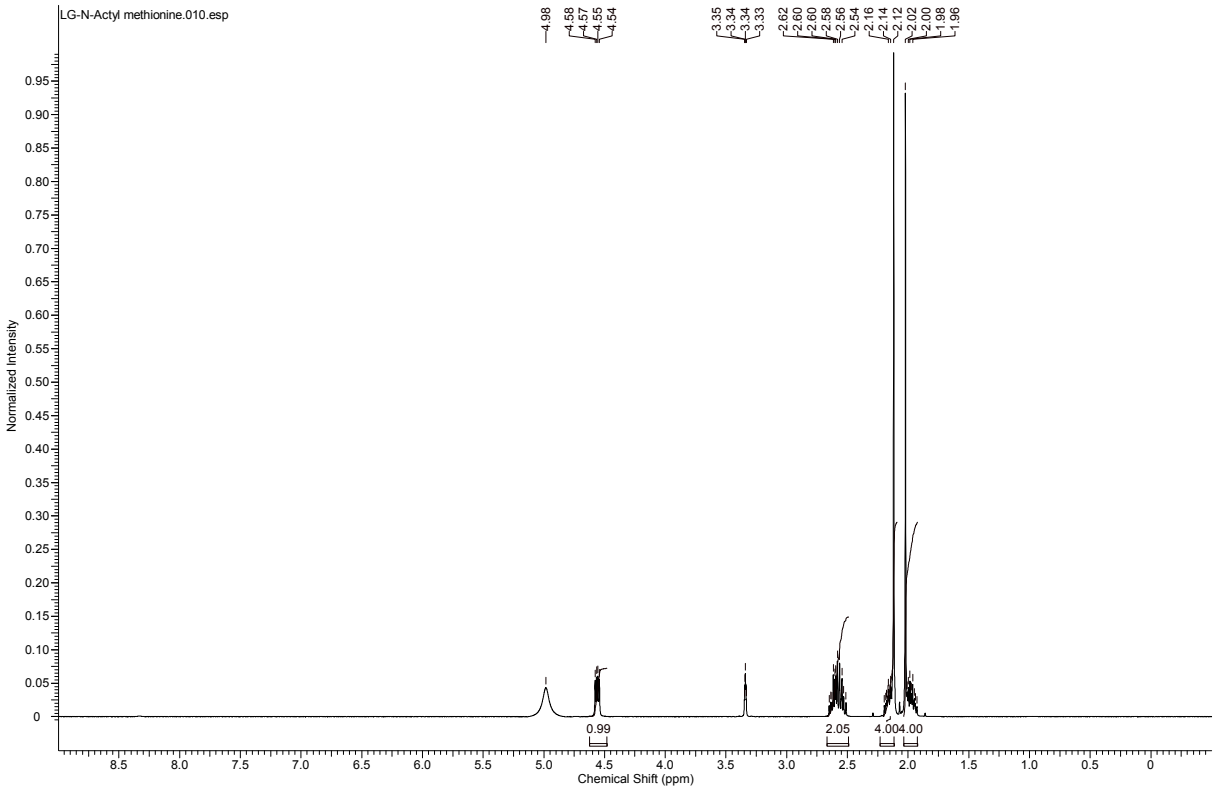


Figure S31 ^{1}H NMR spectrum of **S6 (starting material)**

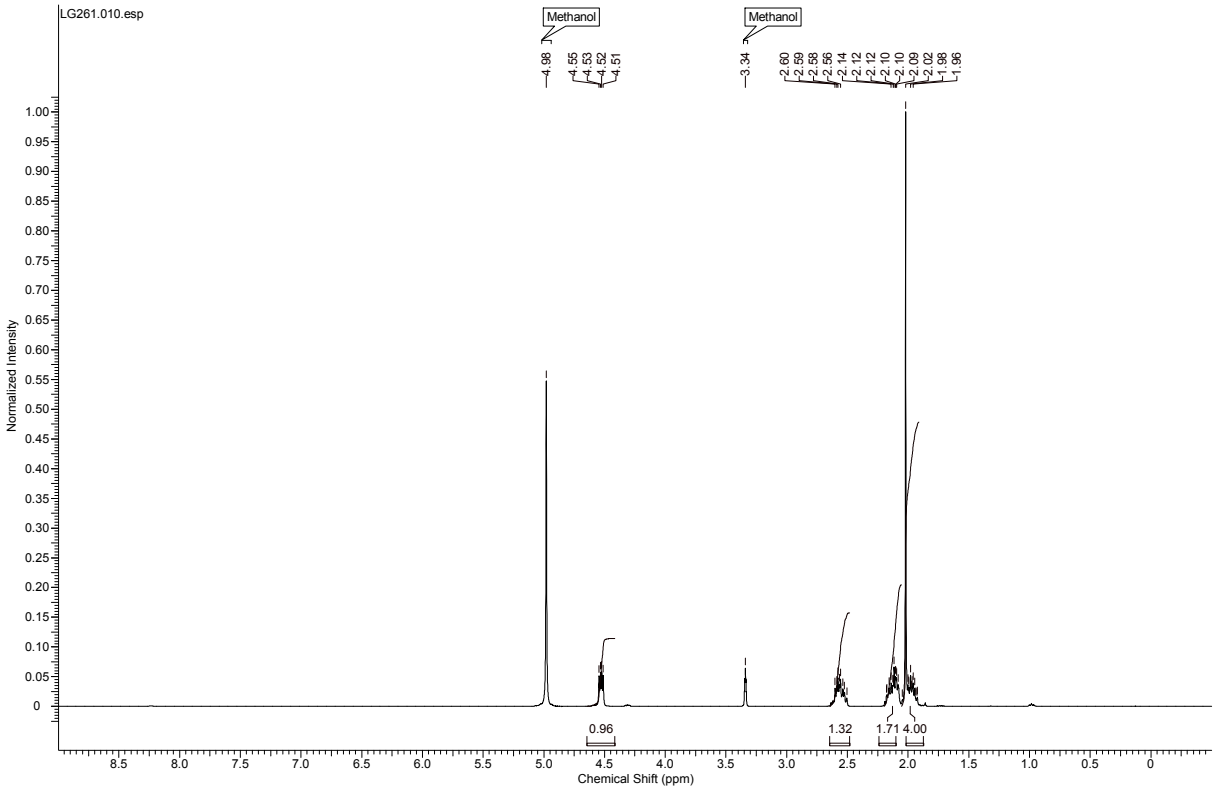


Figure S32 ^{1}H NMR spectrum of **6**

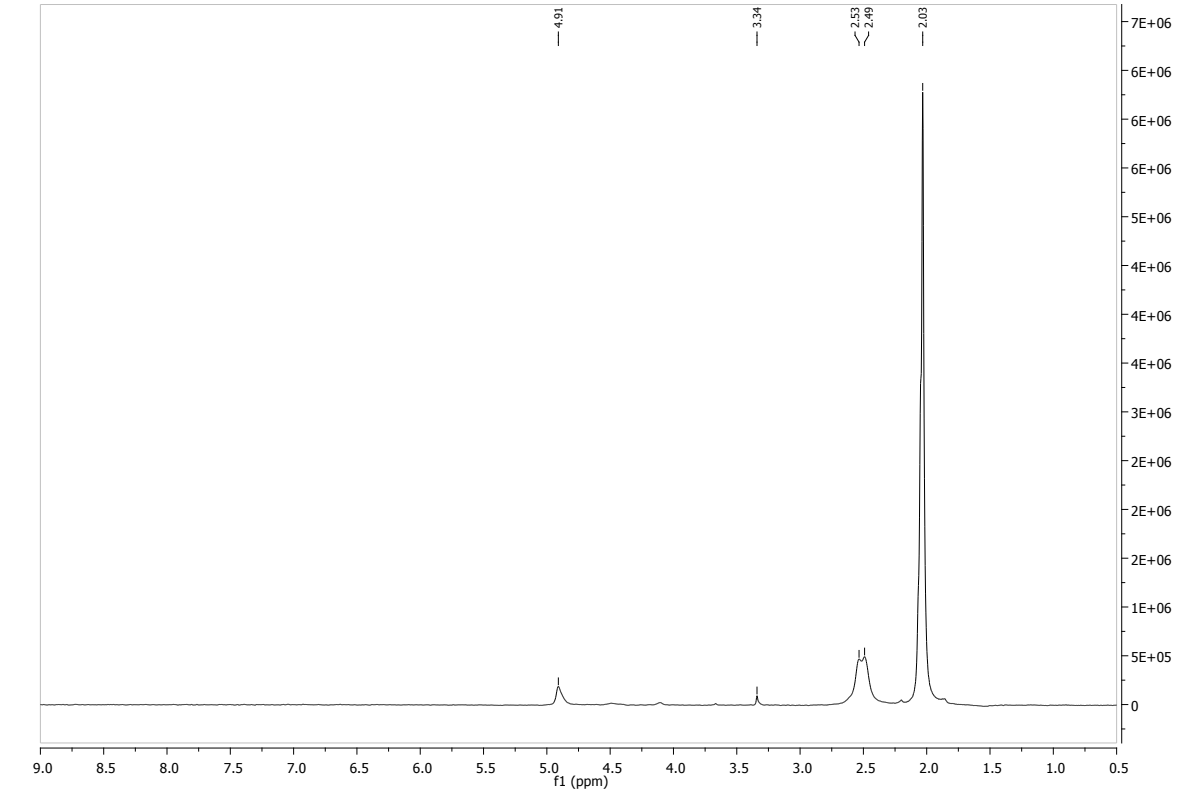


Figure S33 ^{2}H-{^{1}H} NMR spectrum of **6**

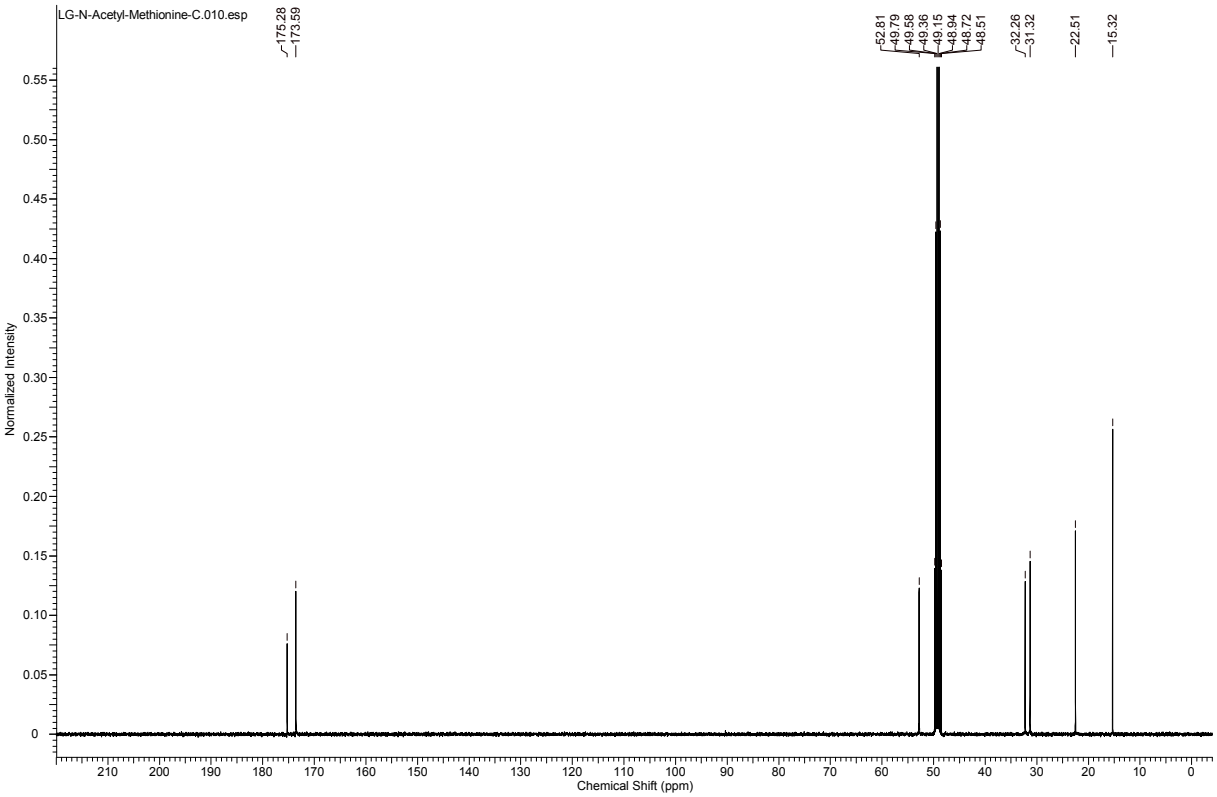


Figure S34 ^{13}C-{^{1}H} NMR spectrum of **S6 (starting material)**

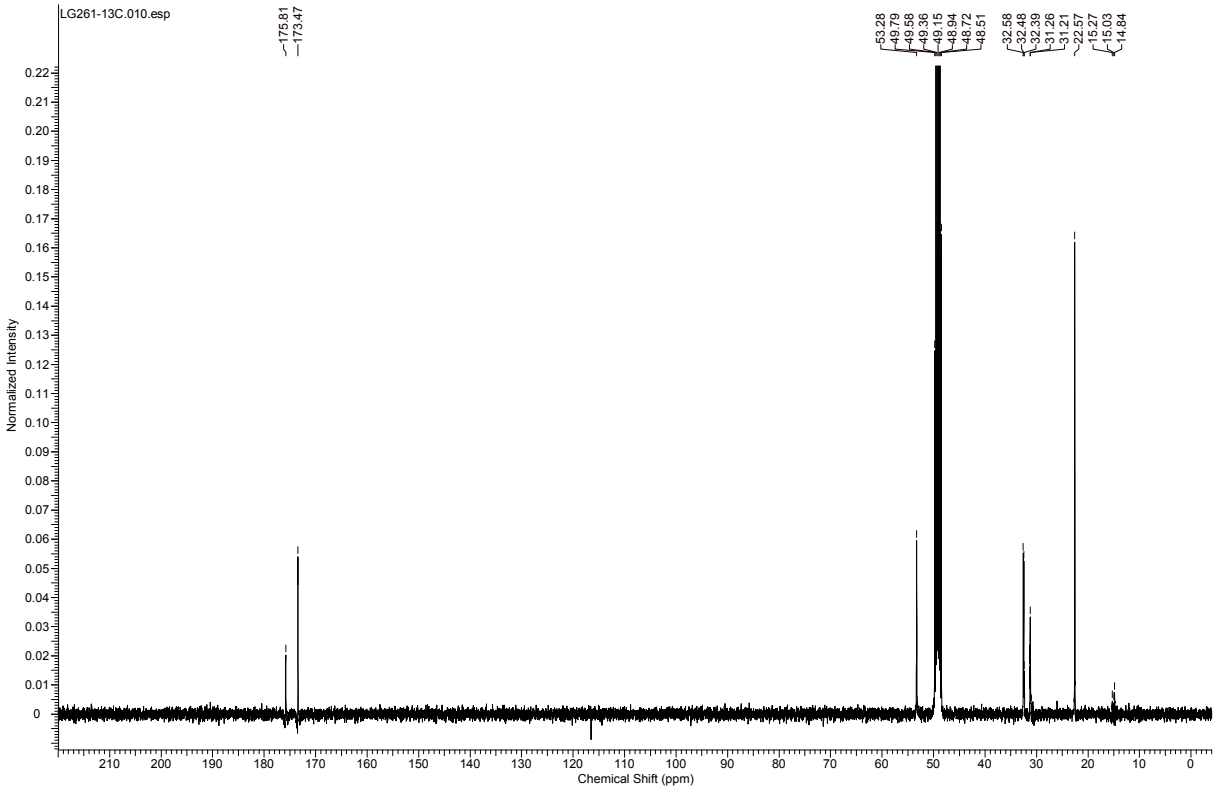


Figure S35 ^{13}C-{^{1}H} NMR spectrum of **6**

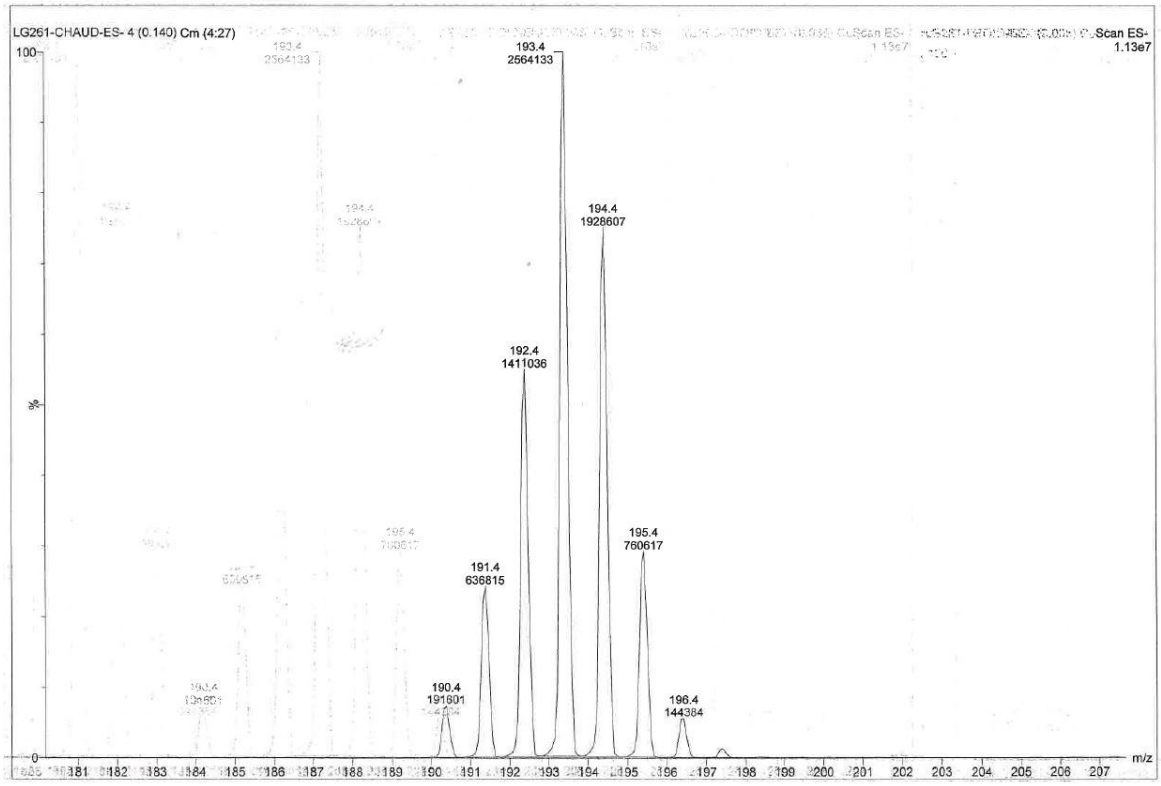
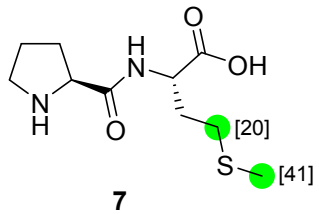


Figure S36 Mass spectrum of **6**

H-Pro-Met-OH (7)



7

Following the General Procedure B (15 mg of substrate was used) for **7** and using D_2O as solvent. After the final evaporation, the ^1H NMR spectrum of the residue was recorded. 15 mg (quantitative) of deuterated compound was obtained after drying by vacuum. Note that HPLC purification was realized before ^2H NMR was recorded.

^1H NMR (400 MHz, D_2O) δ 4.38 (dd, J = 8.4, 7.0 Hz, 1H), 4.26 (dd, J = 8.9, 4.7 Hz, 0.95H), 3.52-3.27 (m, 2H), 2.64-2.39 (m, 2.6H), 2.19-1.90 (m, 6.8H). ^{13}C-{^1H} NMR (100 MHz, D_2O) 178.0 (s), 168.9 (s), 59.7 (s), 54.8 (s), 46.4 (s), 30.7-30.5 (m), 29.8-29.4 (m), 23.7 (s), 14.1-13.6 (m).

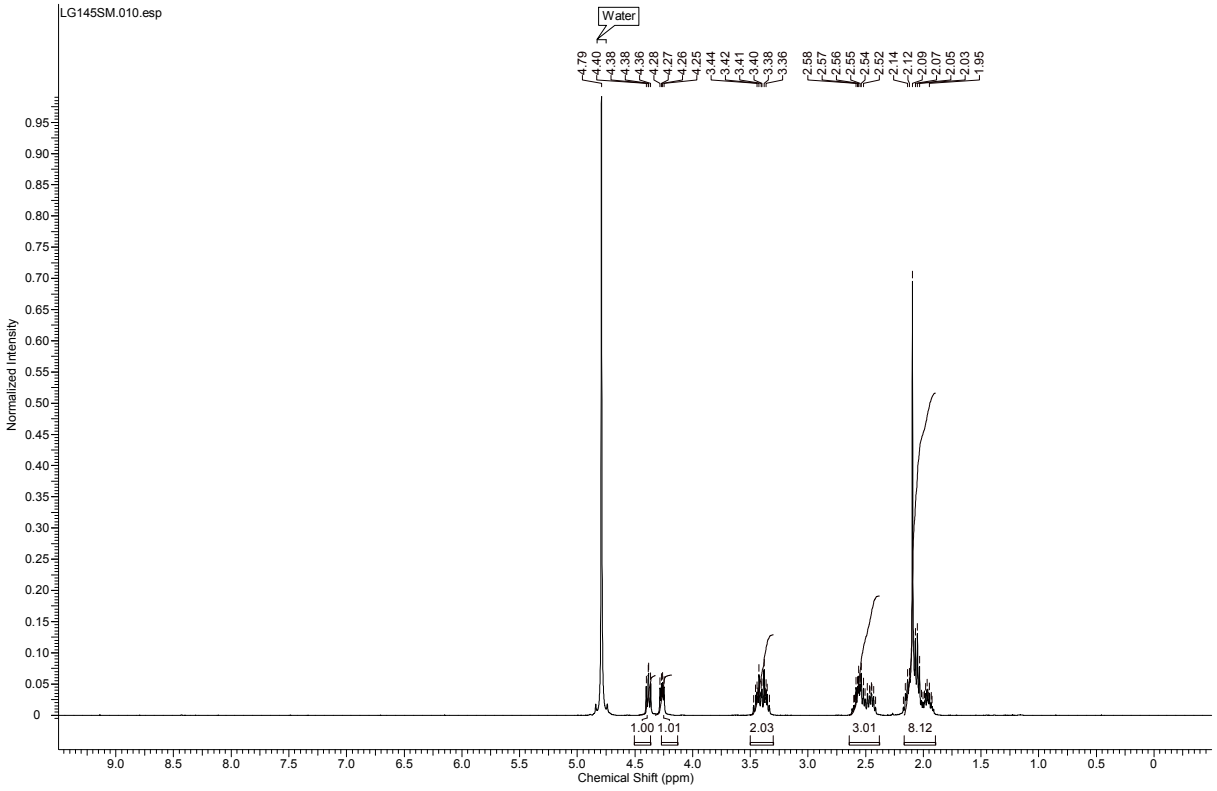


Figure S37 ^1H NMR spectrum of **S7 (starting material)**

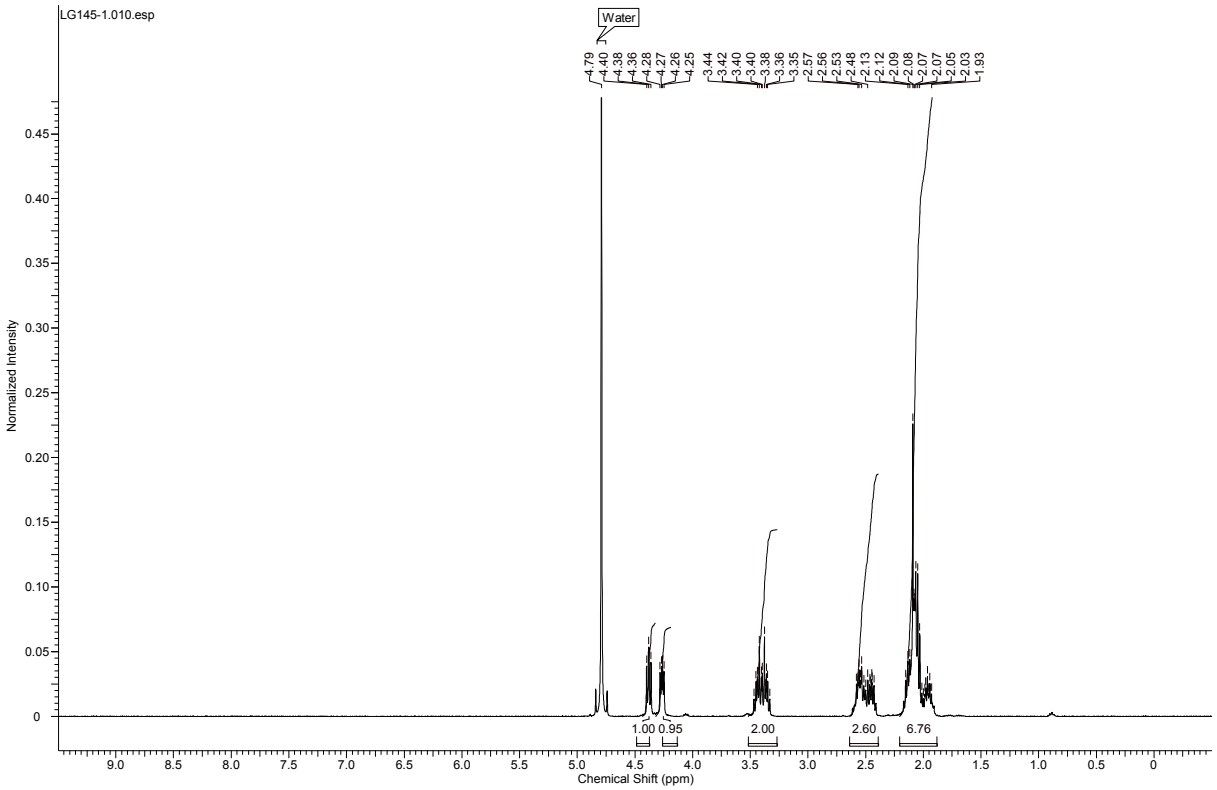


Figure S38 ^{1}H NMR spectrum of **7**

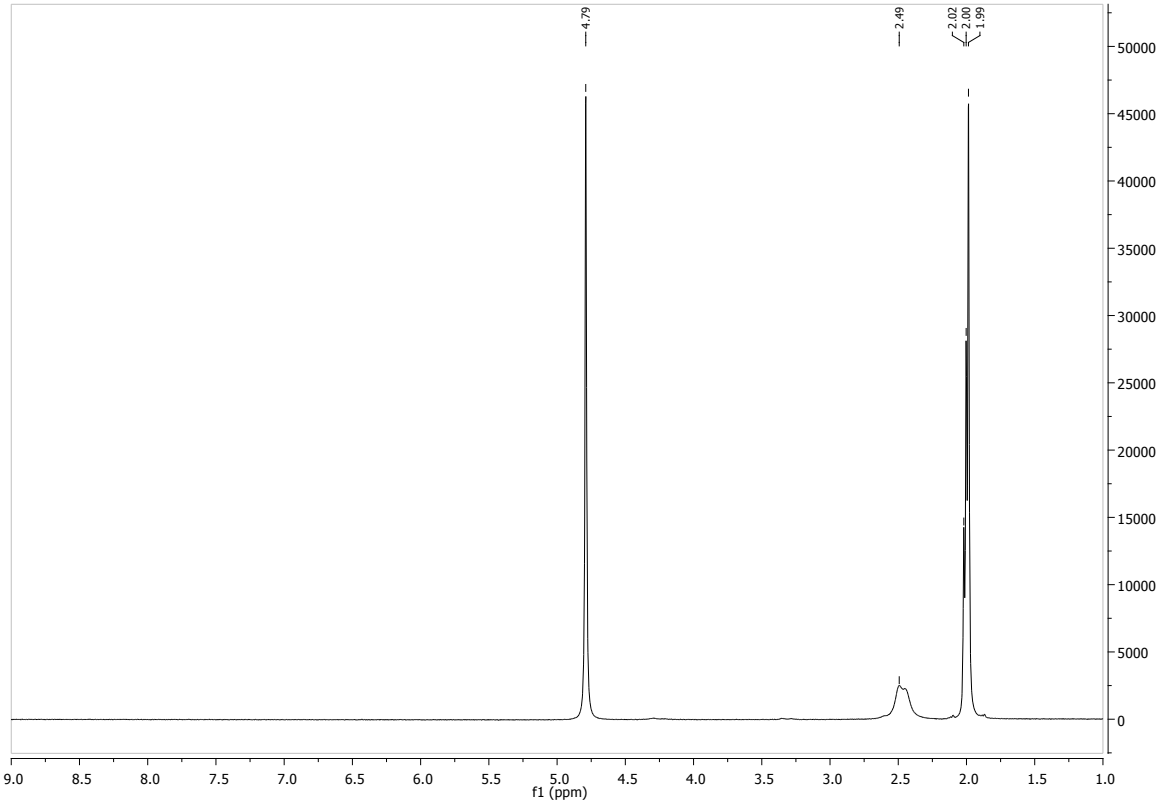


Figure S39 ^{2}H-{^{1}H} NMR spectrum of **7**

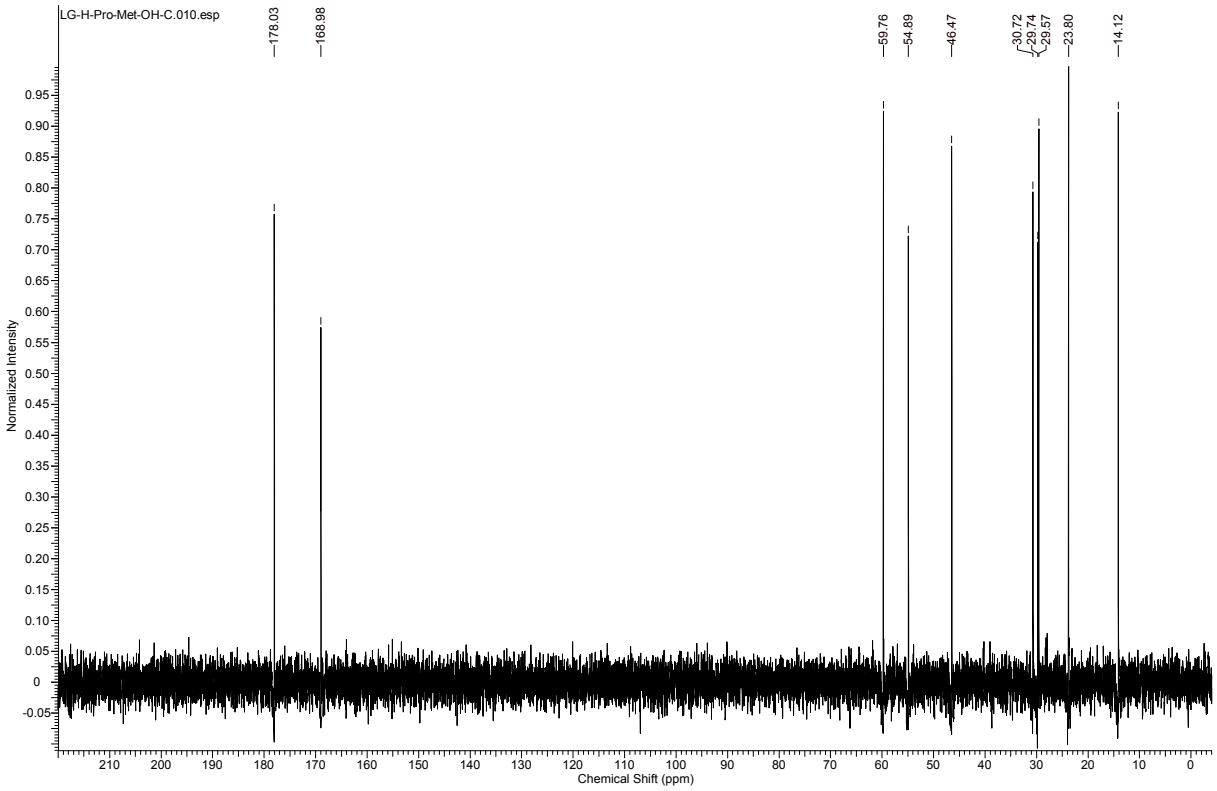


Figure S40 ^{13}C-{^{1}H} NMR spectrum of **S7 (starting material)**

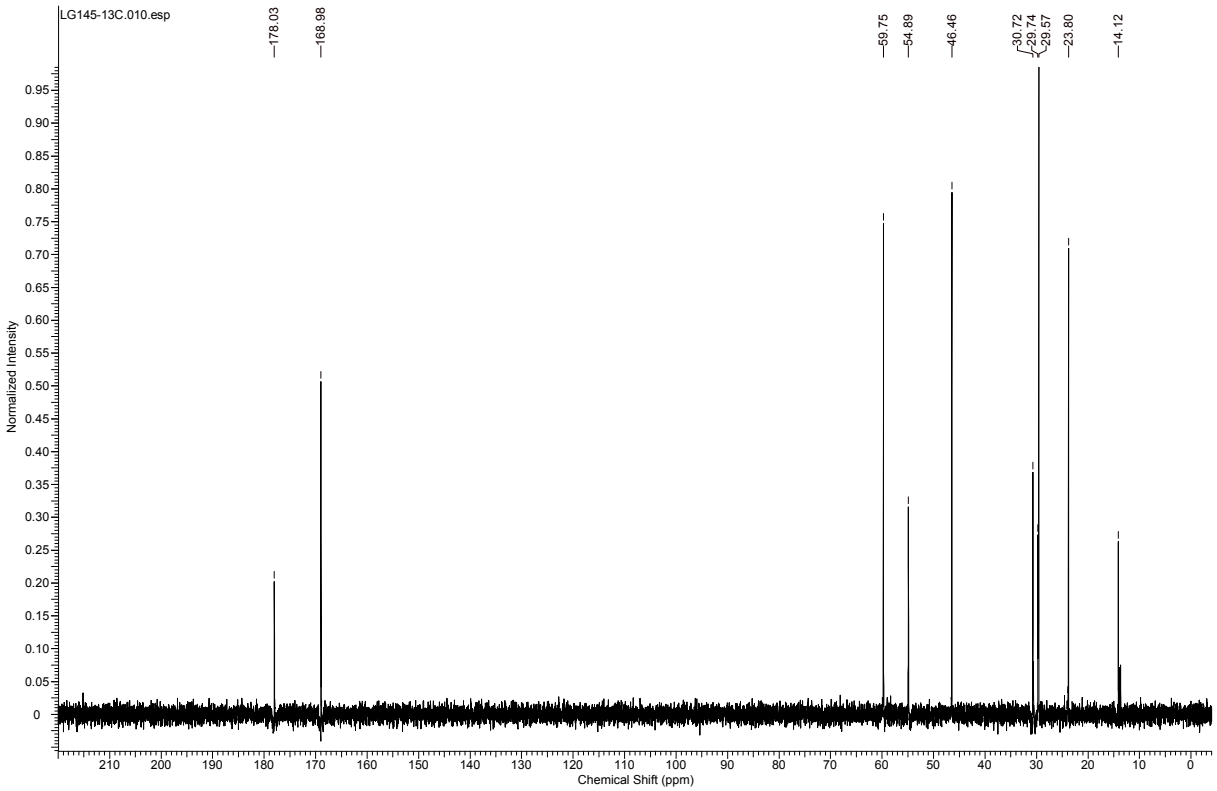


Figure S41 ^{13}C-{^{1}H} NMR spectrum of **7**

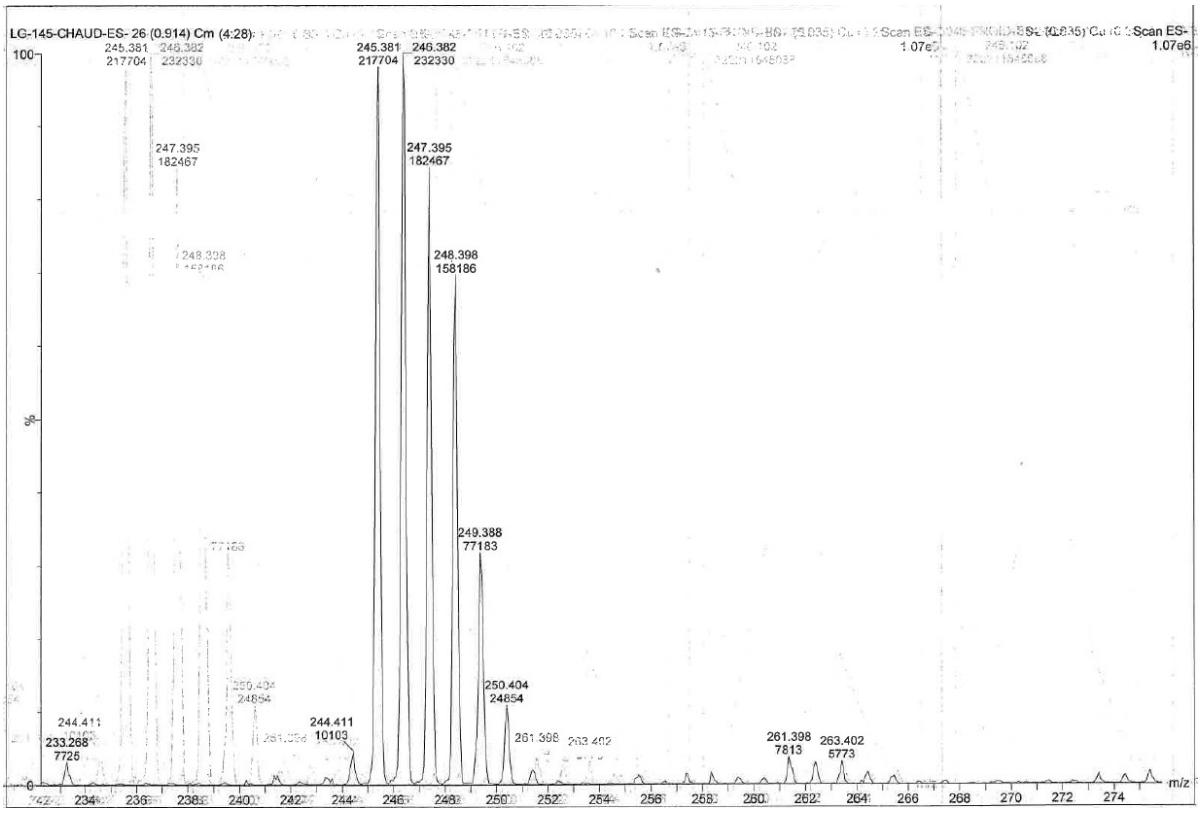


Figure S42 Mass spectrum of **7**

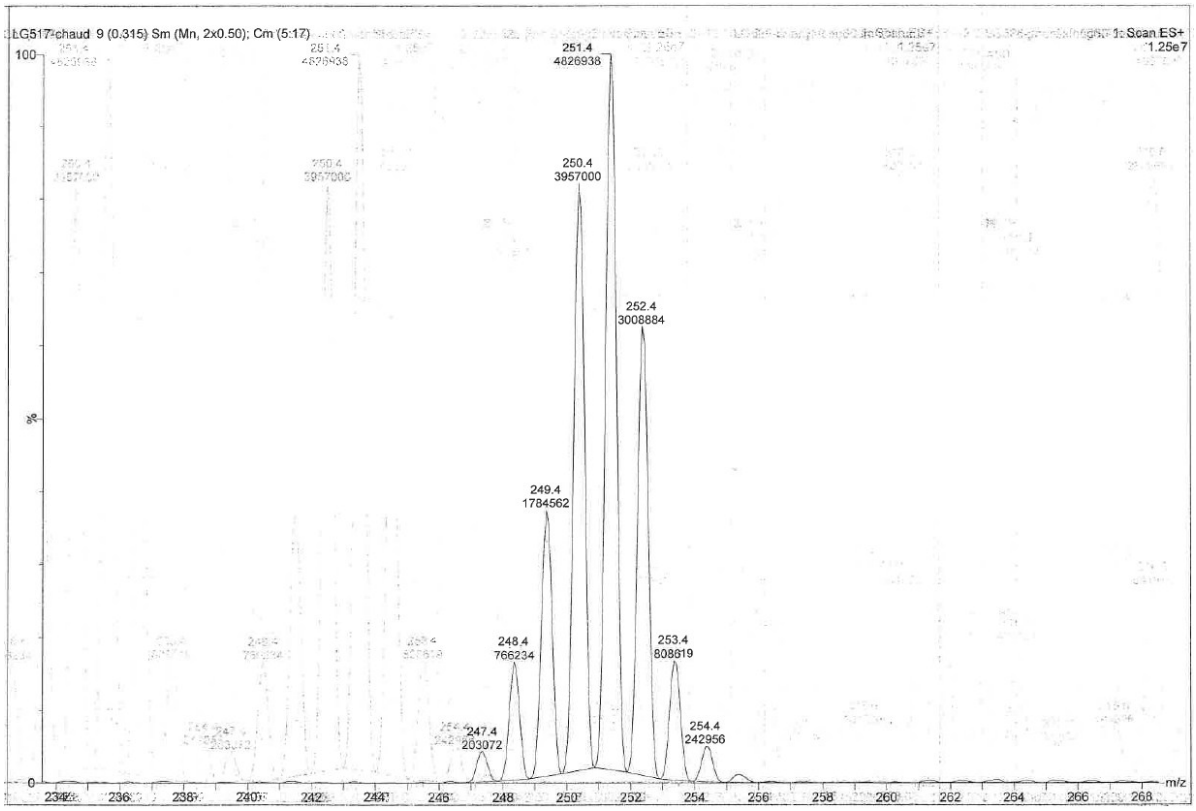


Figure S43 Mass spectrum of **7** (after the second run)

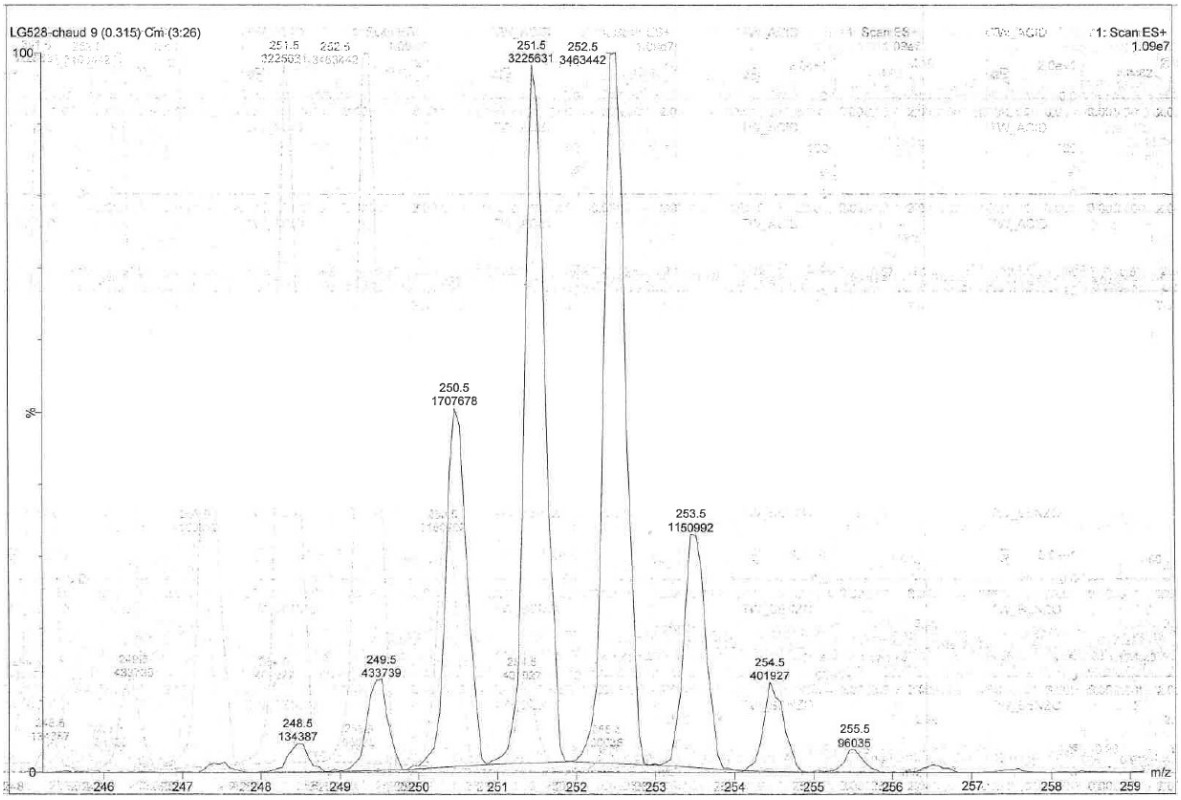


Figure S44 Mass spectrum of **7** (after the third run)

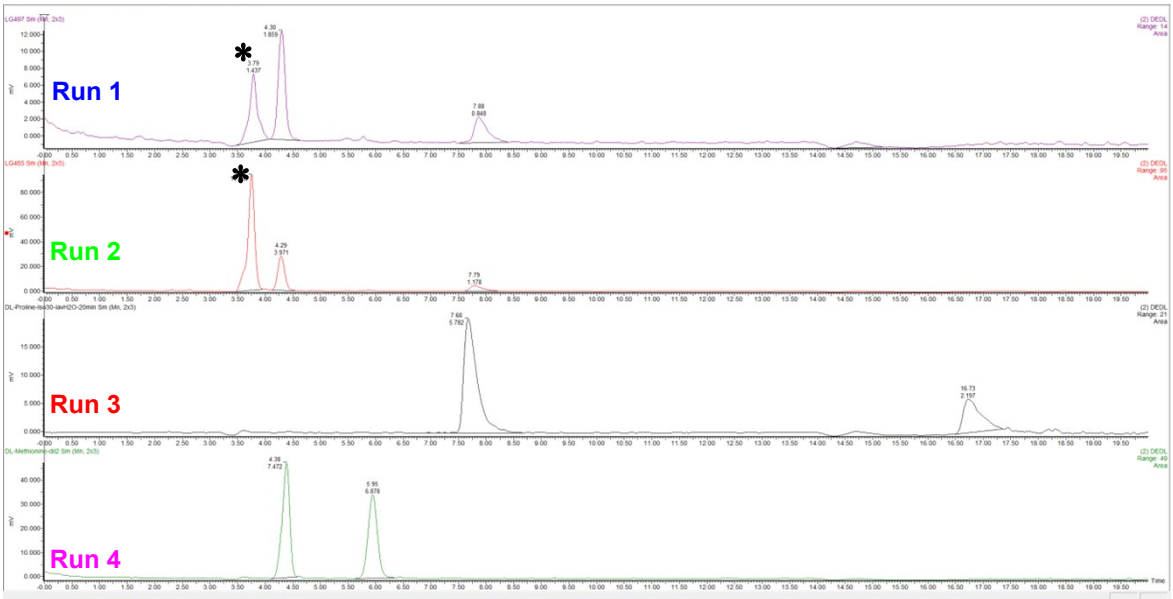


Figure S45 Chiral HPLC analyses of the amino acids obtained from the hydrolysis of **7**

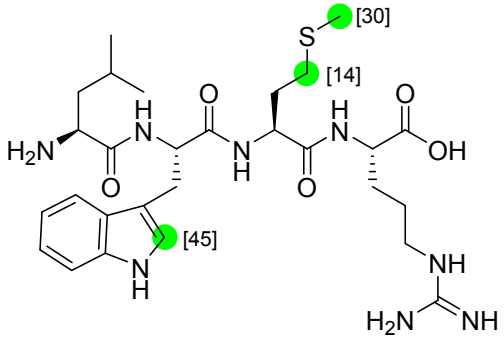
Run 1	Amino acids obtained from the hydrolysis of **7**, only deuterated L-methionine and L-proline
Run 2	Amino acids obtained from the hydrolysis of **S7**, only L-methionine and L-proline
Run 3	DL-Proline, the peak on the left is L-proline
Run 4	DL-Methionine, the peak on the left is L- methionine

*Peak of unknown compound related to the polymerization of the peptide during the hydrolysis

Conditions :

Column	:	Astec Chirobiotic T n° 89930-02 250mm*4.6mm*5µm
Eluent	:	Iso30 10min (H_2O / MeOH / HCO_2H; 30 / 70 / 0,2) + lavage 100 % H_2O 5min
Debit	:	1mL/min
Temperature	:	Room temperature
Injection	:	10µL

H-Leu-Trp-Met-Arg-OH (8)



Following the General Procedure B (15 mg of substrate was used) and using D_2O as solvent. After the final evaporation, the ^1H NMR spectrum of the residue was recorded. Note that the reaction was conducted at 100 °C. 15 mg (quantitative) of deuterated compound was obtained after drying by vacuum. Note that HPLC purification was realized before ^2H NMR was recorded.

^1H NMR (400 MHz, D_2O) δ 7.57 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.22 (s, 0.6H), 7.19 (t, J = 7.9 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 4.67 (t_{app}, J = 7.8 Hz, 1H), 4.31 (dd, J = 8.4, 5.5 Hz, 1H), 4.05-3.92 (m, 2H), 3.26-3.17 (m, 2H), 3.13-3.04 (m, 2H), 2.45-2.29 (m, 1.7H), 2.03-1.97 (m, 2.1H), 1.96-1.87 (m, 1H), 1.85-1.71 (m, 2H), 1.68-1.55 (m, 4H), 1.53-1.44 (m, 2H), 0.89 (t, J = 6.8 Hz, 6H). ^{13}C-{^1H} NMR (100 MHz, D_2O) δ 172.5, 172.0 (s, 2C), 170.0, 156.7, 136.0, 126.8, 124.3, 121.9, 119.3, 118.2, 111.9, 108.6, 54.8, 52.2, 51.7, 40.5, 39.9, 30.6, 28.9, 27.9, 26.8, 24.4, 23.8, 21.7 (s, 2C), 21.2, 14.1.

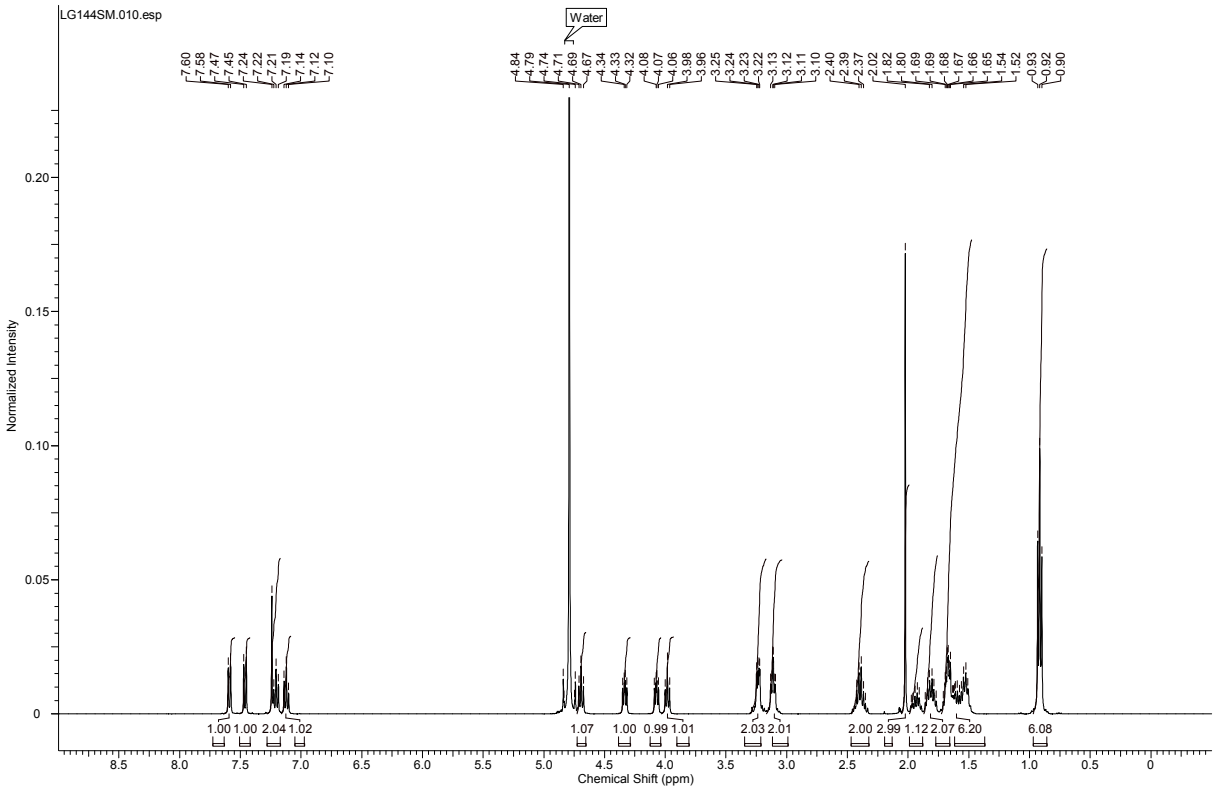


Figure S46 ^{1}H NMR spectrum of **S8 (starting material)**

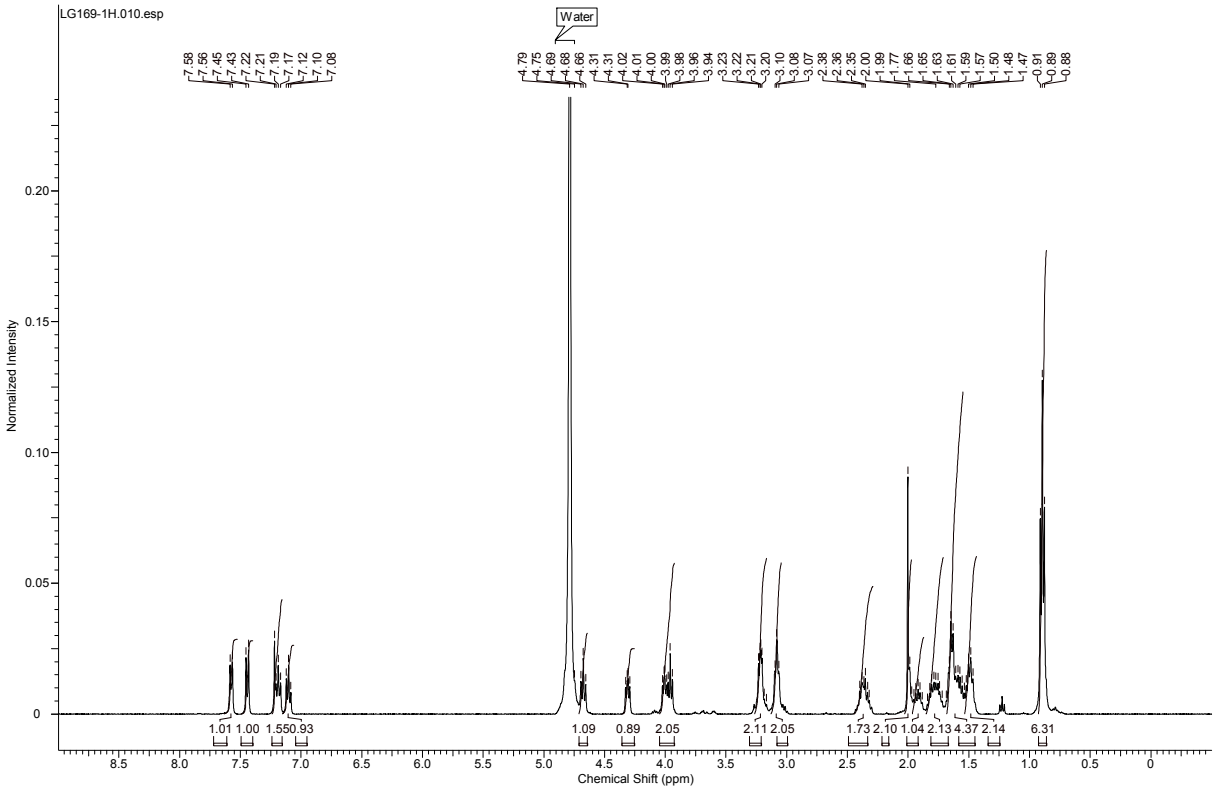


Figure S47 ^{1}H NMR spectrum of **8**

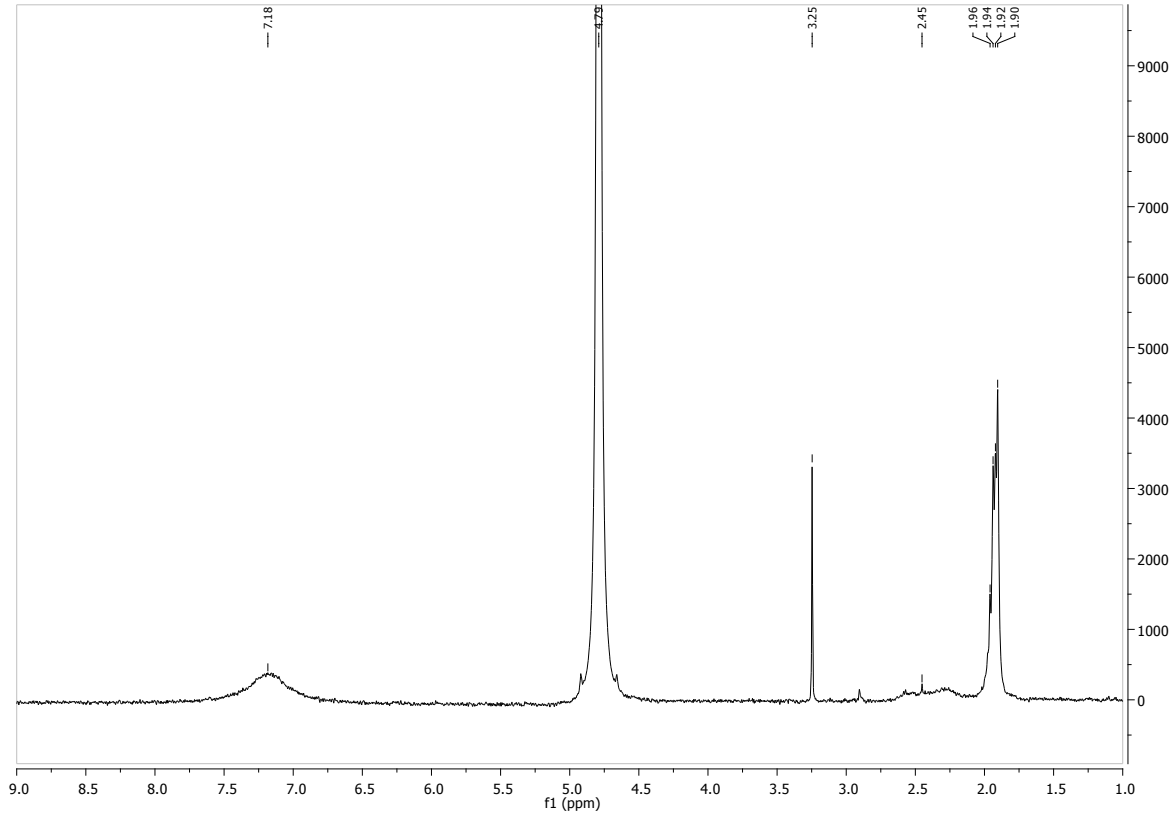


Figure S48 ^{2}H-{^{1}H} NMR spectrum of **8**

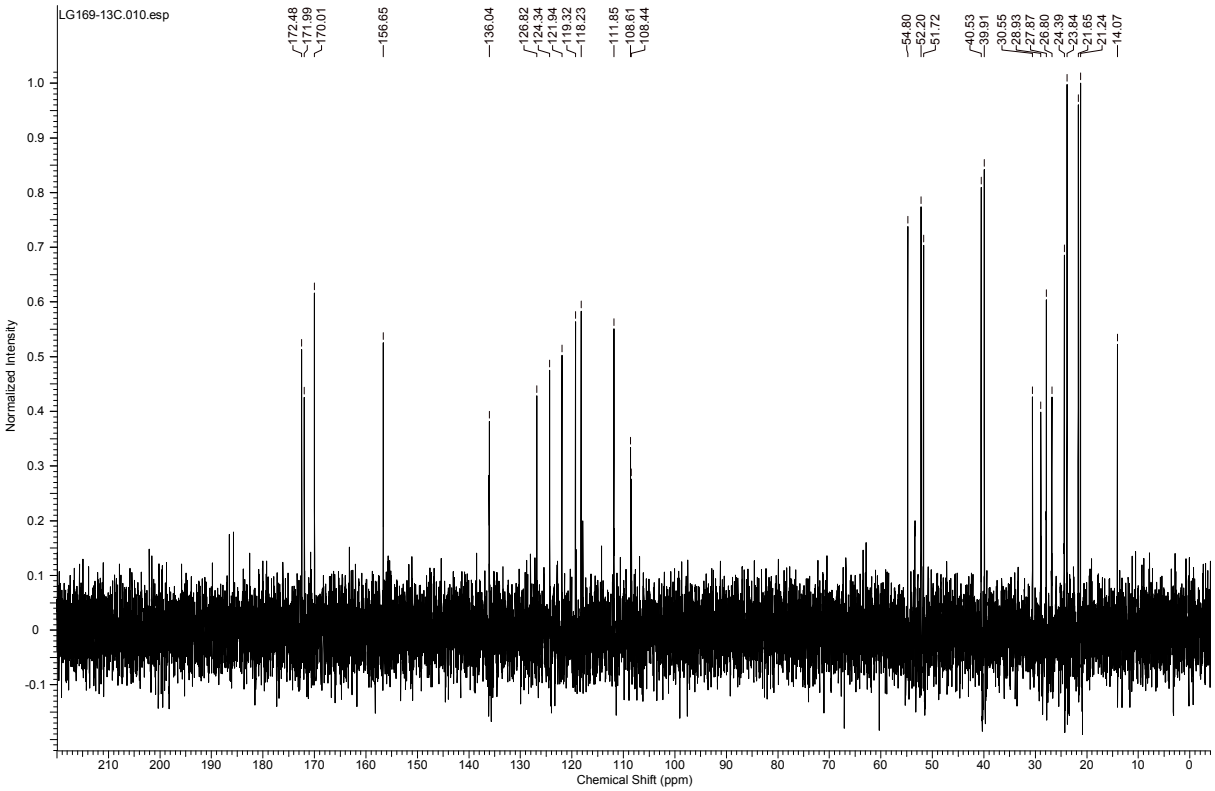


Figure S49 ^{13}C-{^{1}H} NMR spectrum of **8**

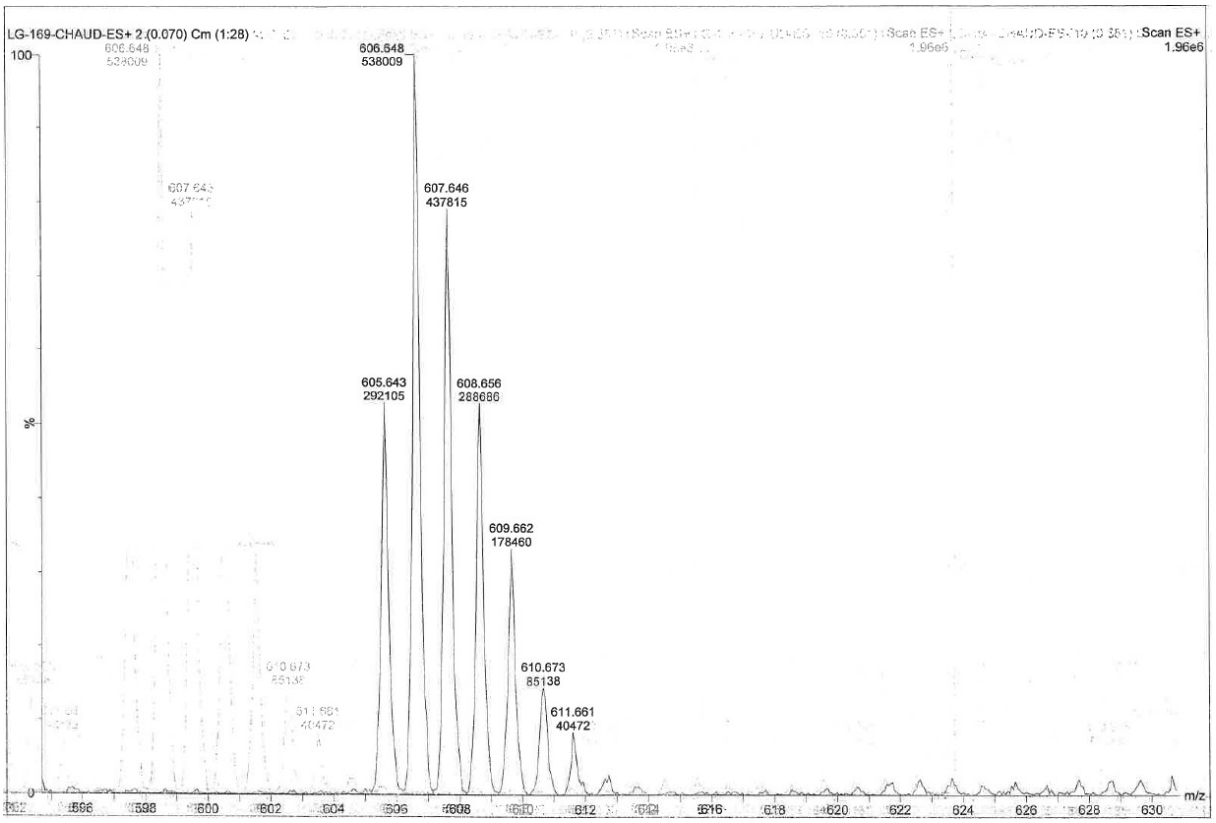


Figure S50 Mass spectrum of **8**

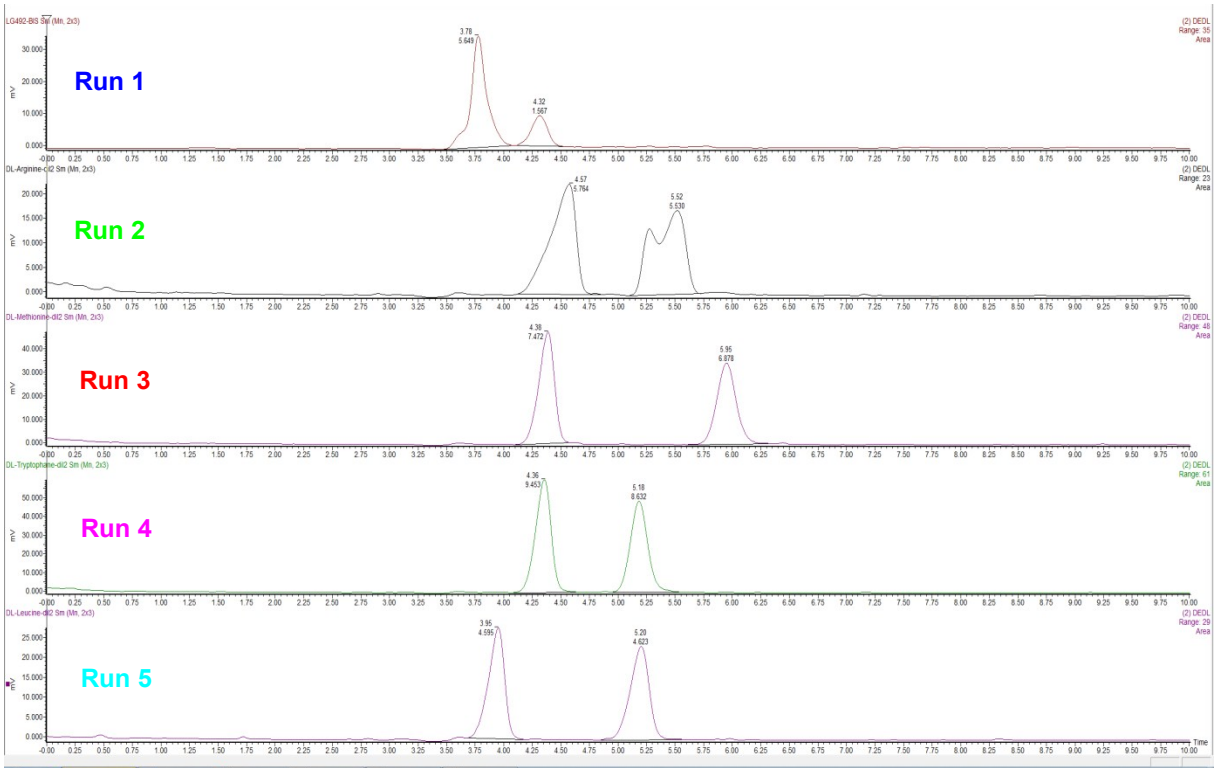


Figure S51 Chiral HPLC analysis of the amino acids obtained from the hydrolysis of **8**

Run 1	Amino acids obtained from the hydrolysis of **8**, only L-amino acids were obtained
Run 2	DL-Arginine, the peak on the left is L-arginine
Run 3	DL-Methionine, the peak on the left is L-methionine
Run 4	DL-Tryptophane, the peak on the left is L-tryptophane
Run 5	DL-Leucine, the peak on the left is L-leucine

Conditions :

Column : Astec Chirobiotic T n° 89930-02 250mm*4.6mm*5µm

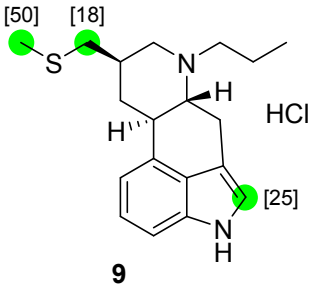
Eluent : Iso30 10min (H_2O / MeOH / HCO_2H; 30 / 70 / 0,2) + lavage 100 % H_2O 5min

Debit : 1mL/min

Temperature : Room temperature

Injection : 10µL

Pergolide hydrochloride salt (9)



9

Following the General Procedure B (15 mg of substrate was used) and using D_2O as solvent. Note that the starting compound was pergolide mesylate. In order to better analyze the result, the product was transformed into hydrochloride salt. After evaporation the crude product was dissolved in ethyl acetate and aqueous Na_2CO_3 was added. The mixture was stirred for 15 min and extracted with ethyl acetate. Then organic layer was dried over $MgSO_4$, evaporated to dryness and dissolved in THF and HCl (1M, 1 mL). After 30 min of stirring, the solution was evaporated to afford a brown solid (12 mg, 94% yield). Before deuteration $[\alpha]_D^{20}$ -31.0° (*c* 0.1, CH_3OH), after deuteration $[\alpha]_D^{20}$ -30.0° (*c* 0.1, CH_3OH).

^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.08 (s, 0.75H), 6.95 (d, J = 7.1 Hz, 1H), 3.83 (d, J = 10.8 Hz, 1H), 3.70 (dd, J = 14.2, 3.2 Hz, 1H), 3.53-3.36 (m, 4H), 3.11-2.92 (m, 3H), 2.75 (dd, J = 13.5, 6.0 Hz, 0.8H), 2.62 (dd, J = 13.5, 7.8 Hz, 0.8H), 2.43 (br s, 1H), 2.28-2.16 (m, 1.5H), 1.98-1.76 (m, 2H), 1.54-1.41 (m, 1H), 1.13 (t, J = 7.3 Hz, 3H). ^{13}C-{^{1}H} NMR (100 MHz, CD_3OD) δ 133.6 (s), 128.9 (s), 125.2 (s), 122.4 (s), 118.9 (s), 112.5 (s), 109.3 (s), 106.8 (s), 65.3 (s), 54.2 (s), 36.7-36.5 (m), 31.9-31.5 (m), 29.4 (s), 24.5 (s), 14.6 (s), 9.9 (s).

Experimental procedure for tritium labelling:

A 5 mL Fischer-Porter glassware with a magnetic stirrer was charged with pergolide mesylate (3.0 mg, 0.0073 mmol), Ru/C (11.8 mg, 80 mol %) and DMF (0.5 mL) under air. The Fischer-Porter glassware was then frozen using a liquid nitrogen bath, left under vacuum for 5 min and then pressurized with T_2 gas (0.9 bar at room temperature). The reaction mixture was magnetically stirred and heated at 80 °C (sand bath) overnight. The solution was then cooled down to room temperature, further cooled using a liquid nitrogen bath, the extra T_2 gas was then removed and replaced by N_2. Then the solution was warmed to room temperature and filtered through syringe filter and evaporated under vacuum.

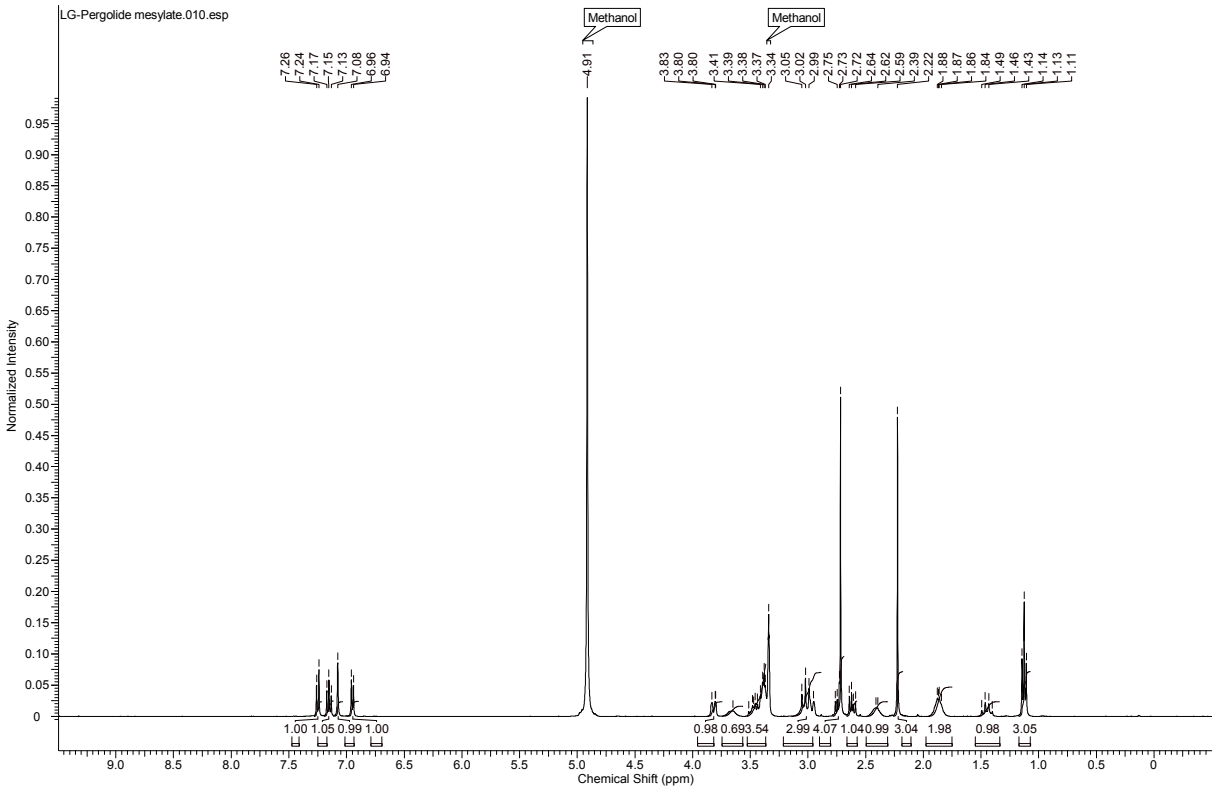


Figure S52 ^{1}H NMR spectrum of **Pergolide Mesylate**

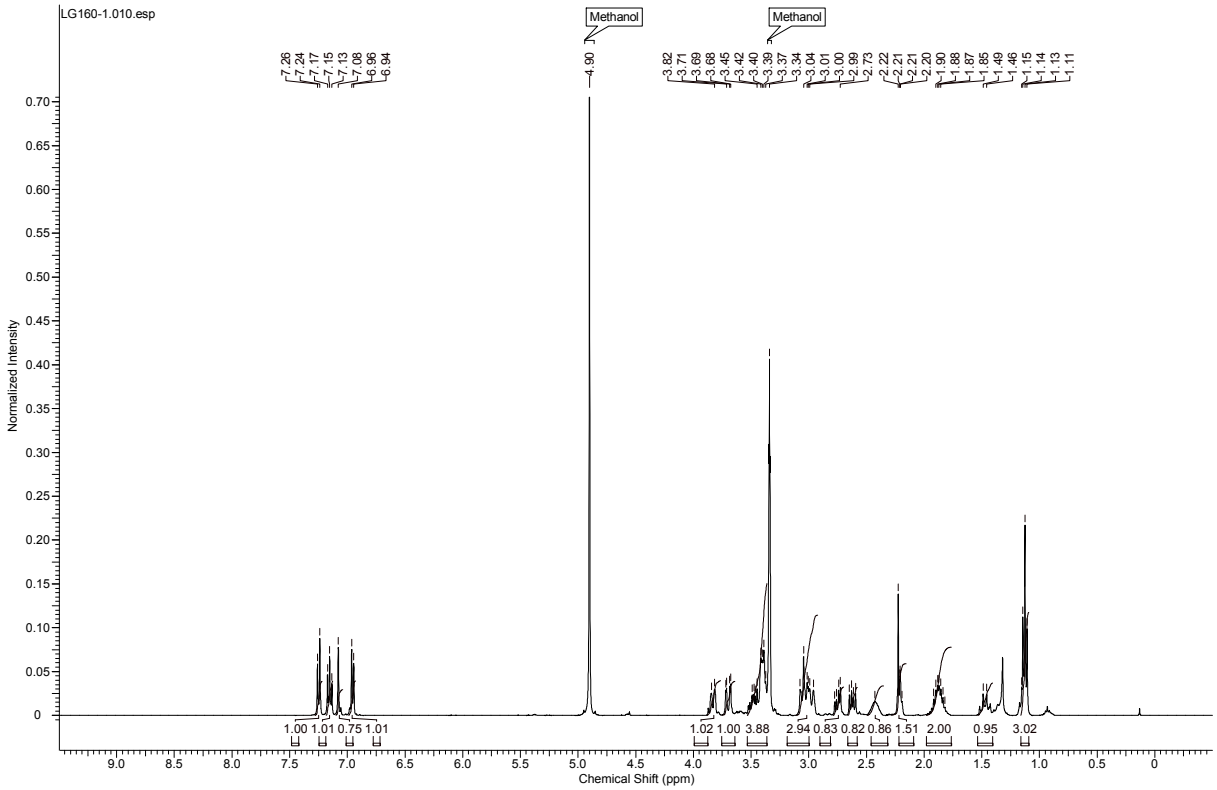


Figure S53 ^{1}H NMR spectrum of **9**

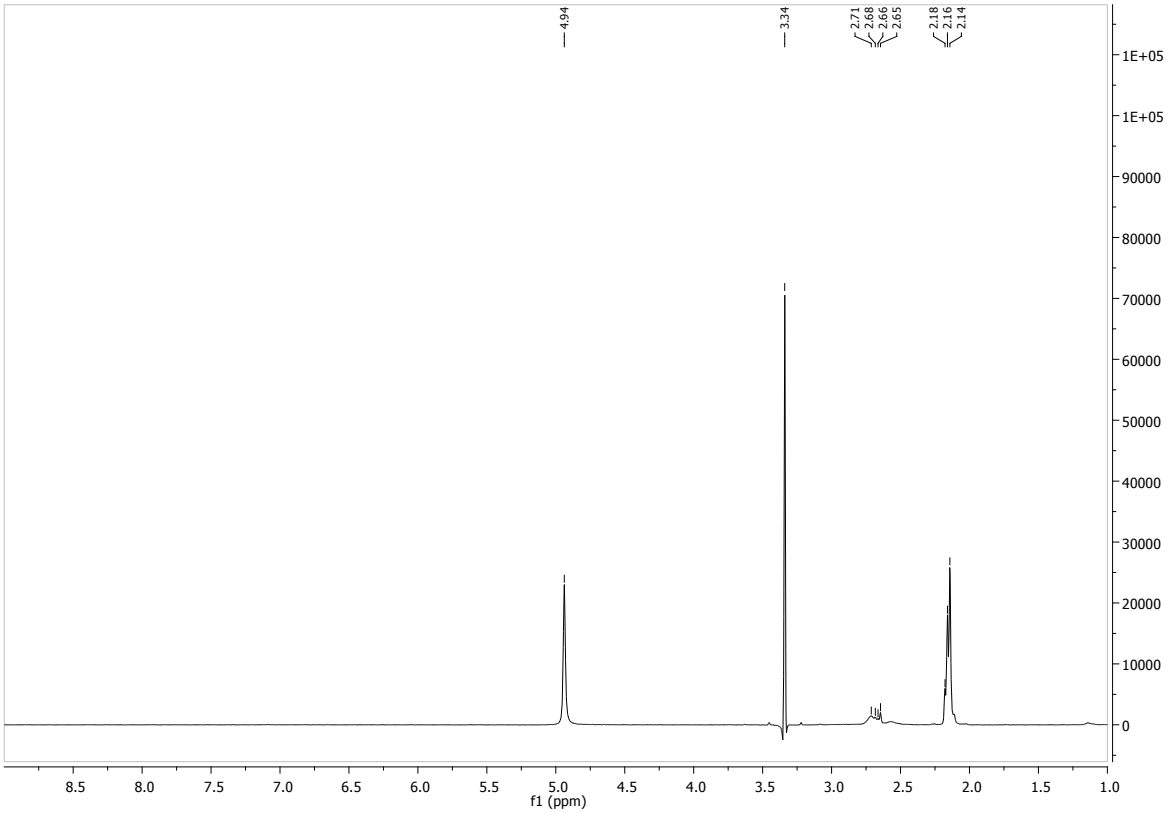


Figure S54 ^{2}H-{^{1}H} NMR spectrum of **9**

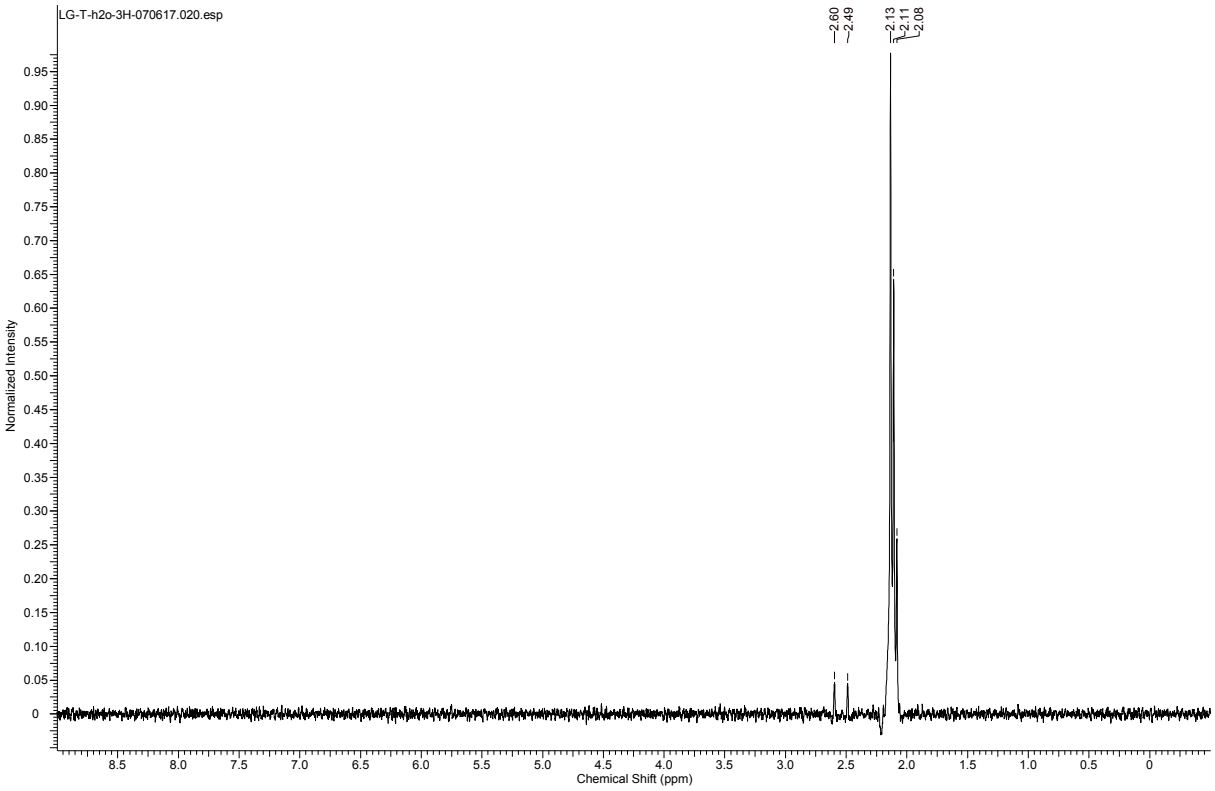


Figure S55 ^{3}H-{^{1}H} NMR spectrum of tritiated Pergolide

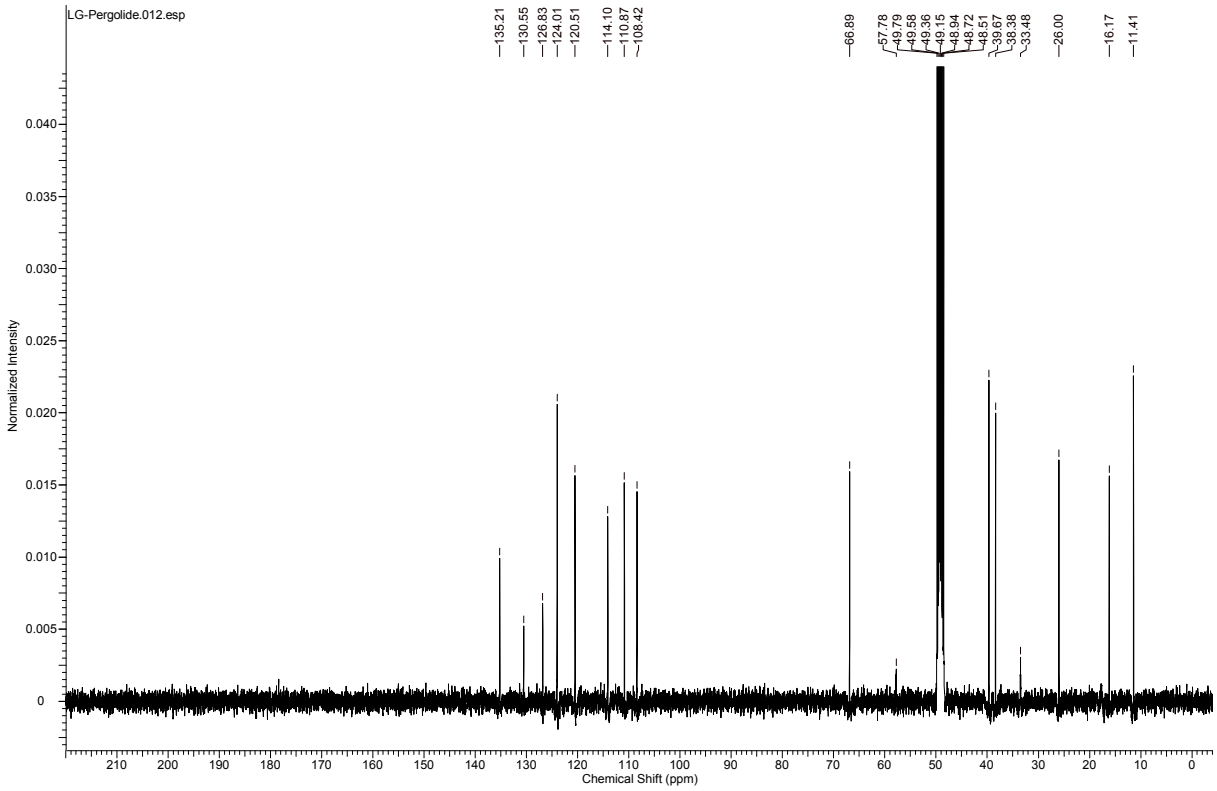


Figure S56 ^{13}C-{^{1}H} NMR spectrum of **Pergolide Mesylate**

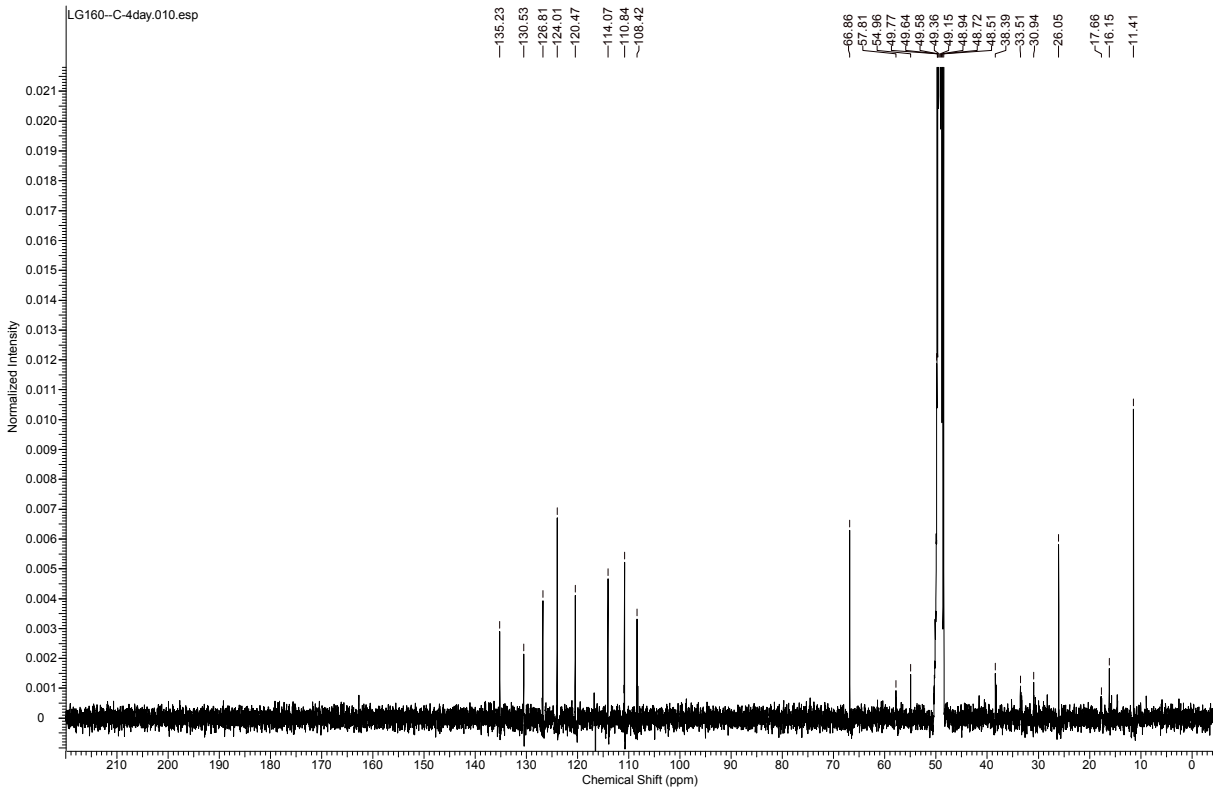


Figure S57 ^{13}C-{^{1}H} NMR spectrum of **9**

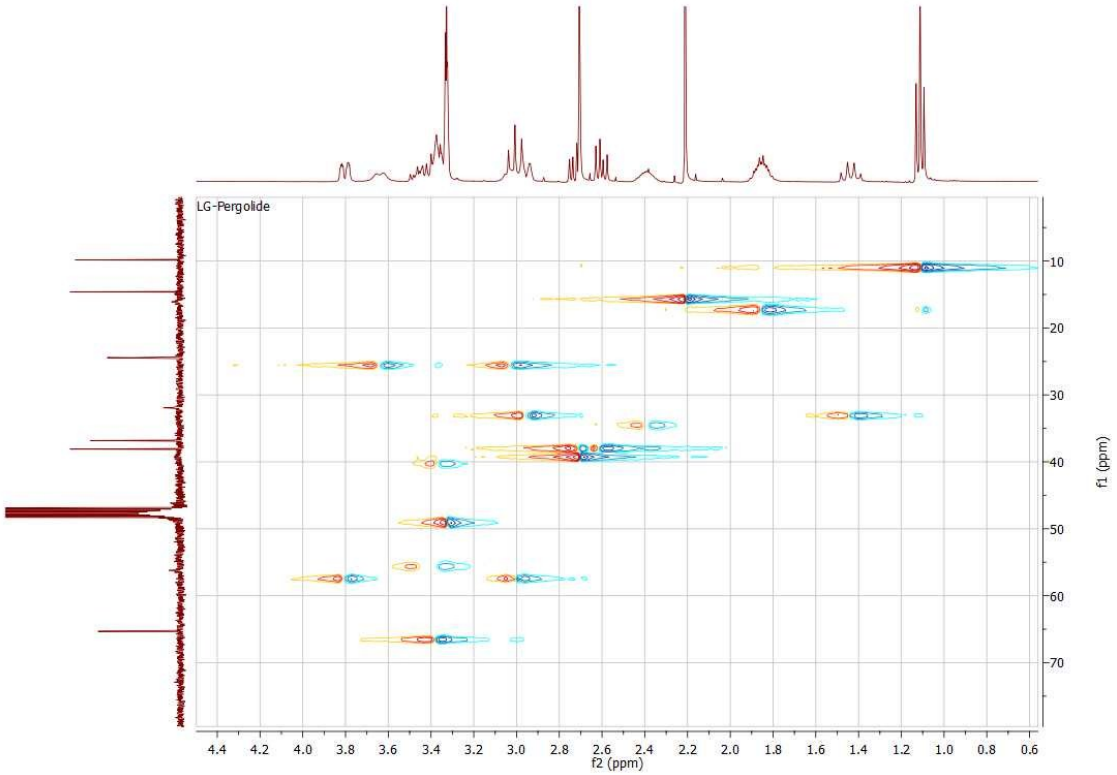


Figure S58 $^{13}C/^{1}H$ HSQC 2D NMR spectrum of **9**

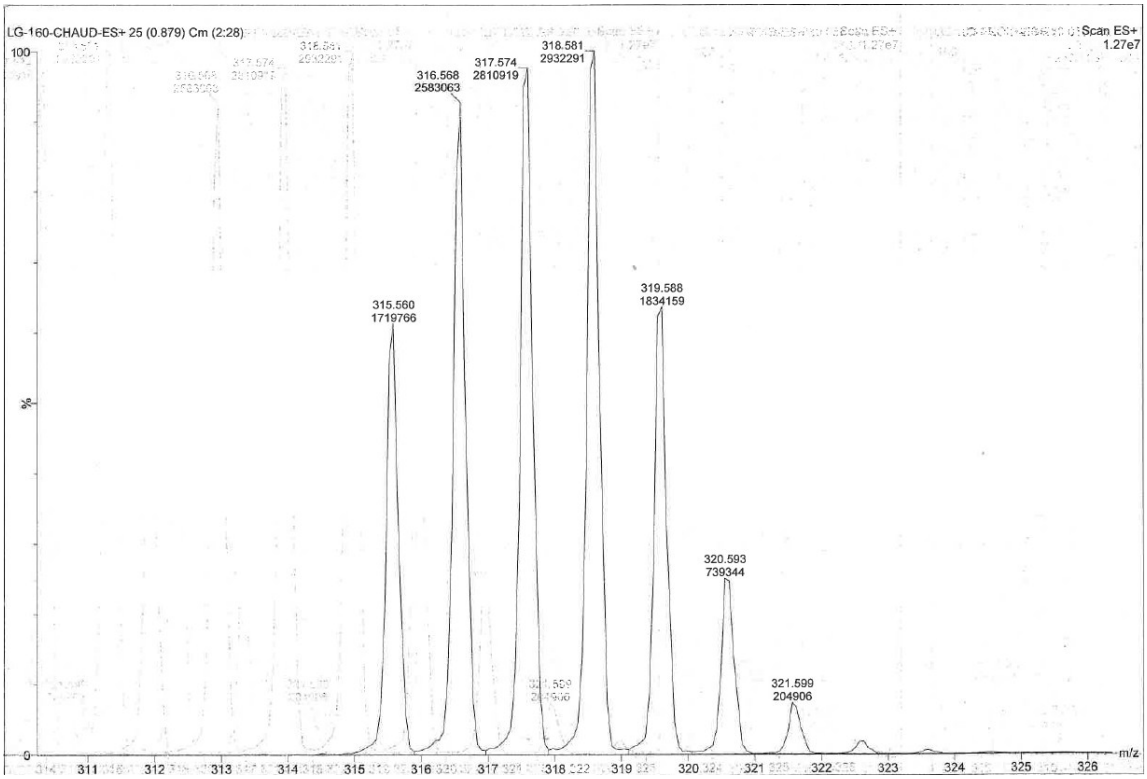


Figure S59 Mass spectrum of **9**

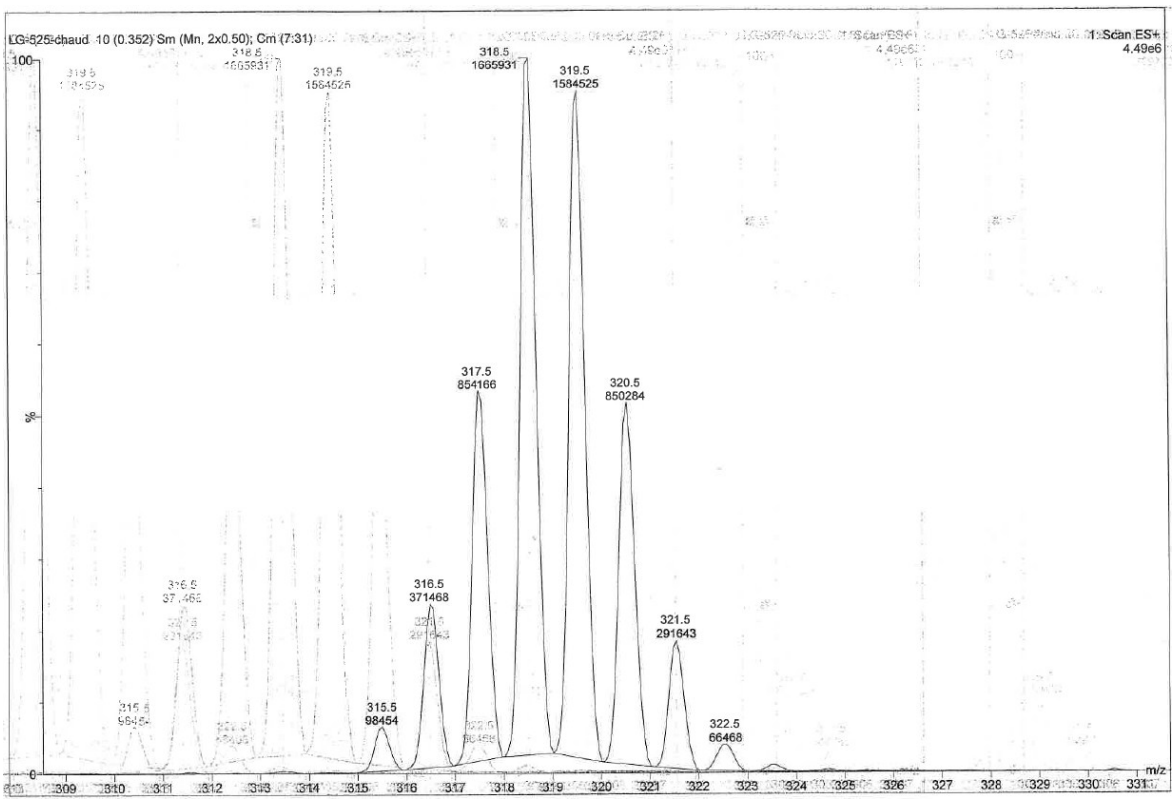


Figure S60 Mass spectrum of **9** (after the second run)

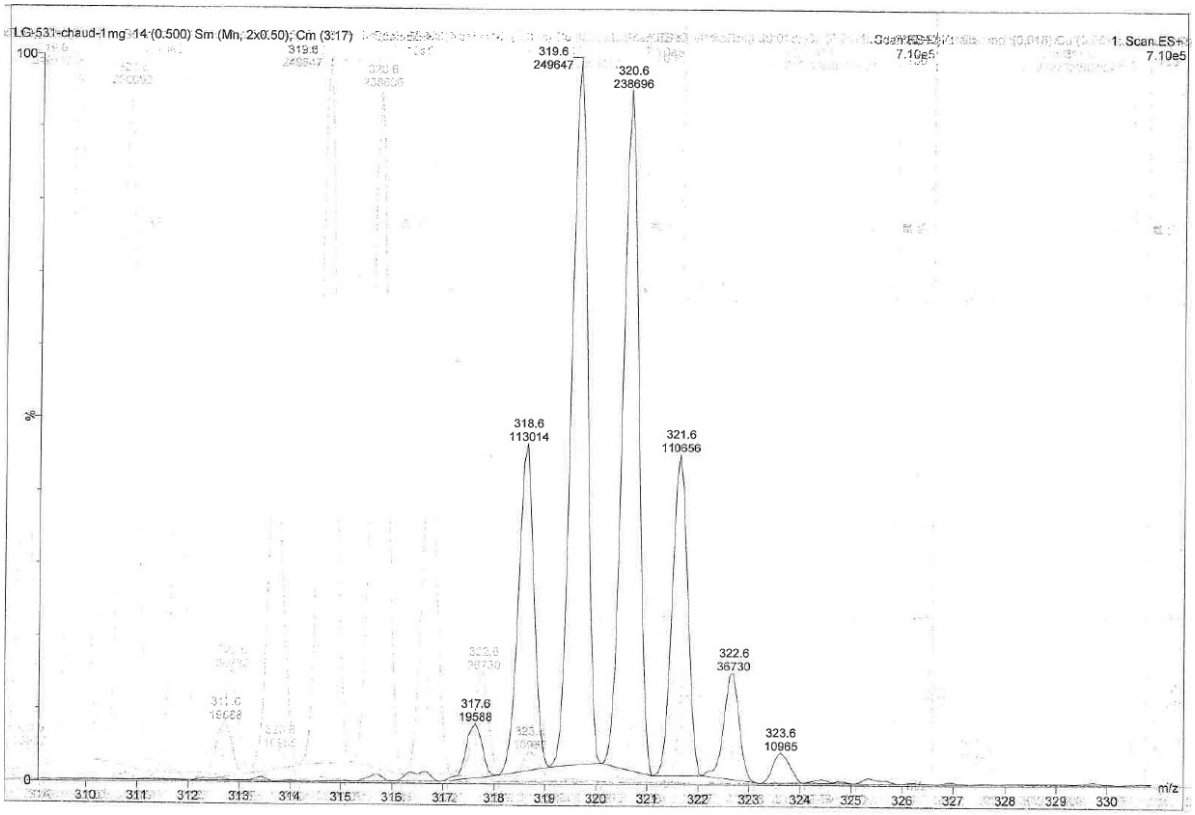


Figure S61 Mass spectrum of **9** (after the third run)

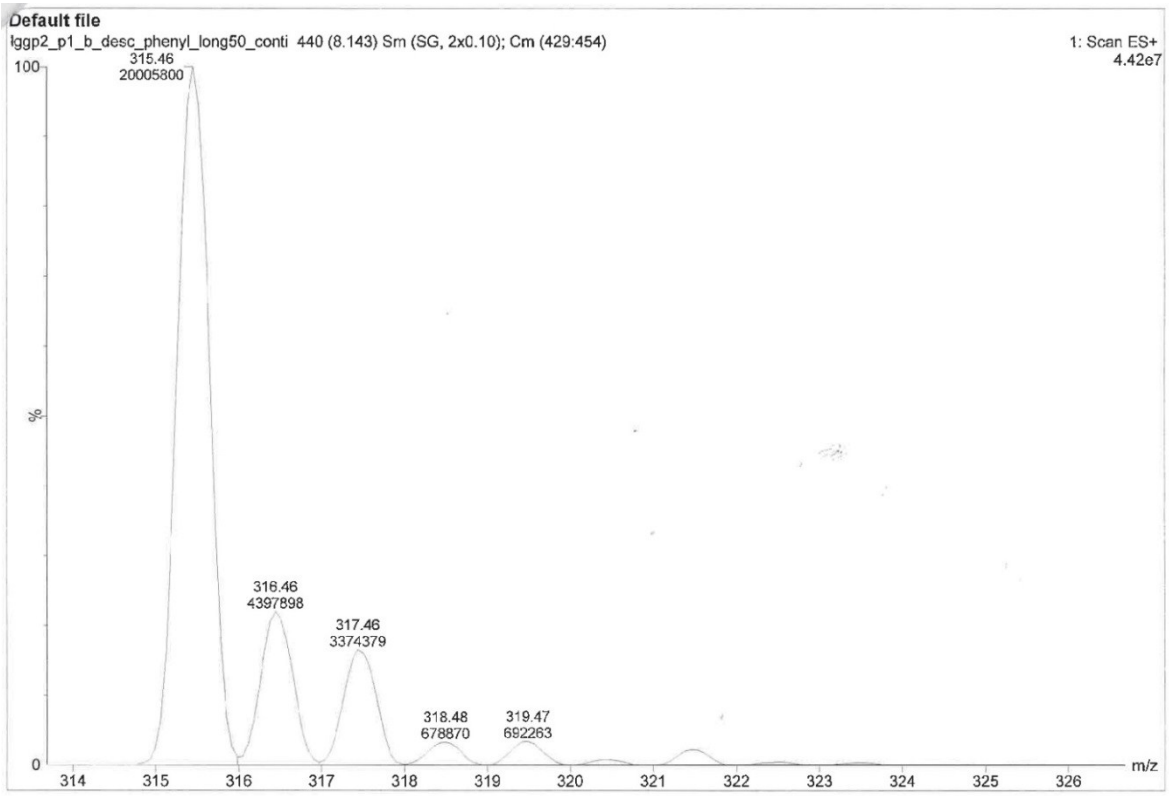
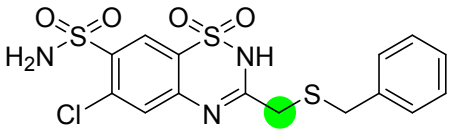
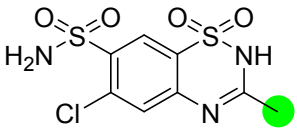


Figure S62 Mass spectrum of tritiated Pergolide

Benzthiazide (10)



[61]



10' [41]

Following the General Procedure A (0.2 mmol of substrate was used) and using THF/D_2O (1:1) as solvent. After the final evaporation, the ^{1}H NMR spectrum of the residue was recorded. Note that dethiobenzyl product (**10'**) was detected after the reaction, leading to the product that contained deuterated methyl. After purification by column chromatography (eluent: ethyl acetate/cyclohexane = 1/1), compound **10** (60 mg, 70%) and **10'** (16 mg, 26%) were obtained, and the NMR spectra were recorded.

10: ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 7.42-7.34 (m, 3H), 7.23 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 3.93 (s, 2H), 3.53-3.48 (m, 0.8H). ^{13}C-{^{1}H} NMR (100 MHz, D_2O) δ 158.9 (s), 138.7 (s), 138.5 (s), 137.5 (s), 135.5 (s), 128.8 (s), 128.1 (s), 126.6 (s), 125.6 (s), 119.7 (s), 119.1 (s), 35.7 – 35.3 (m).

10': ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 7.44 (s, 1H), 2.39 (t, J = 2.2 Hz, 1.8H).

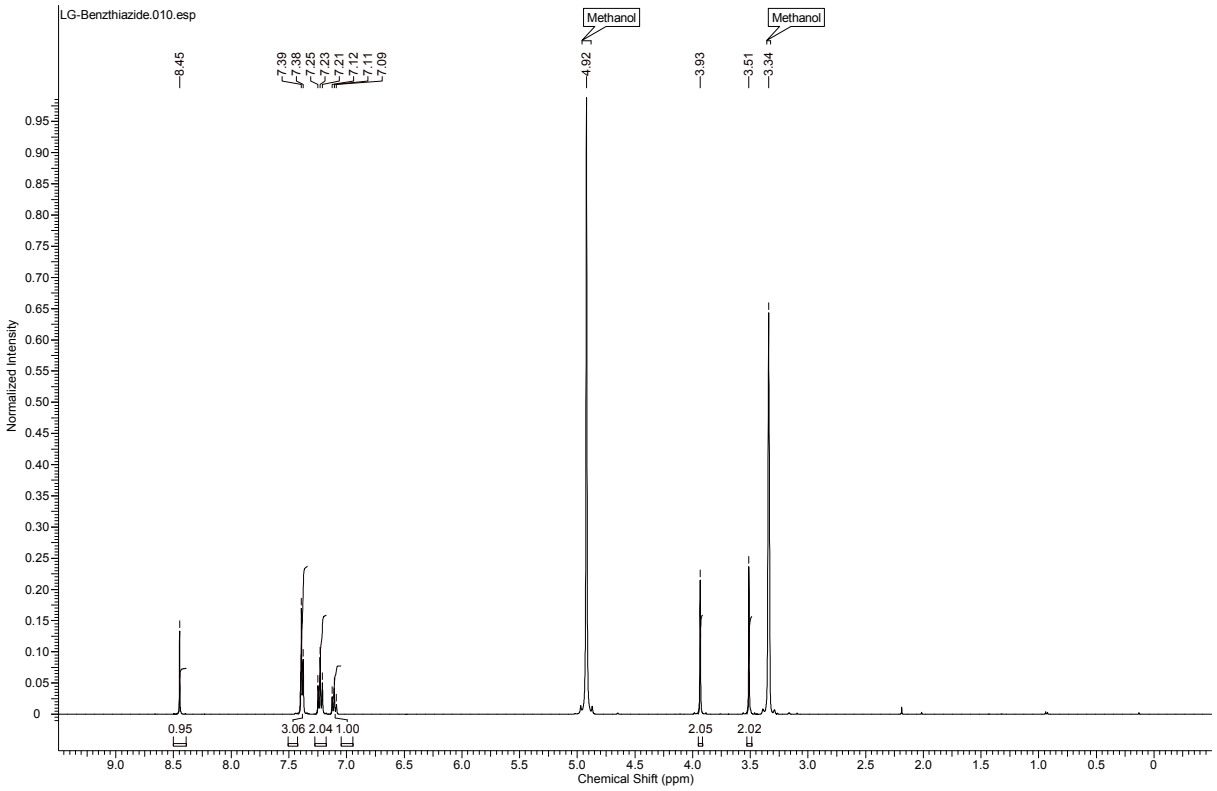


Figure S63 ^{1}H NMR spectrum of **S10 (starting material)**

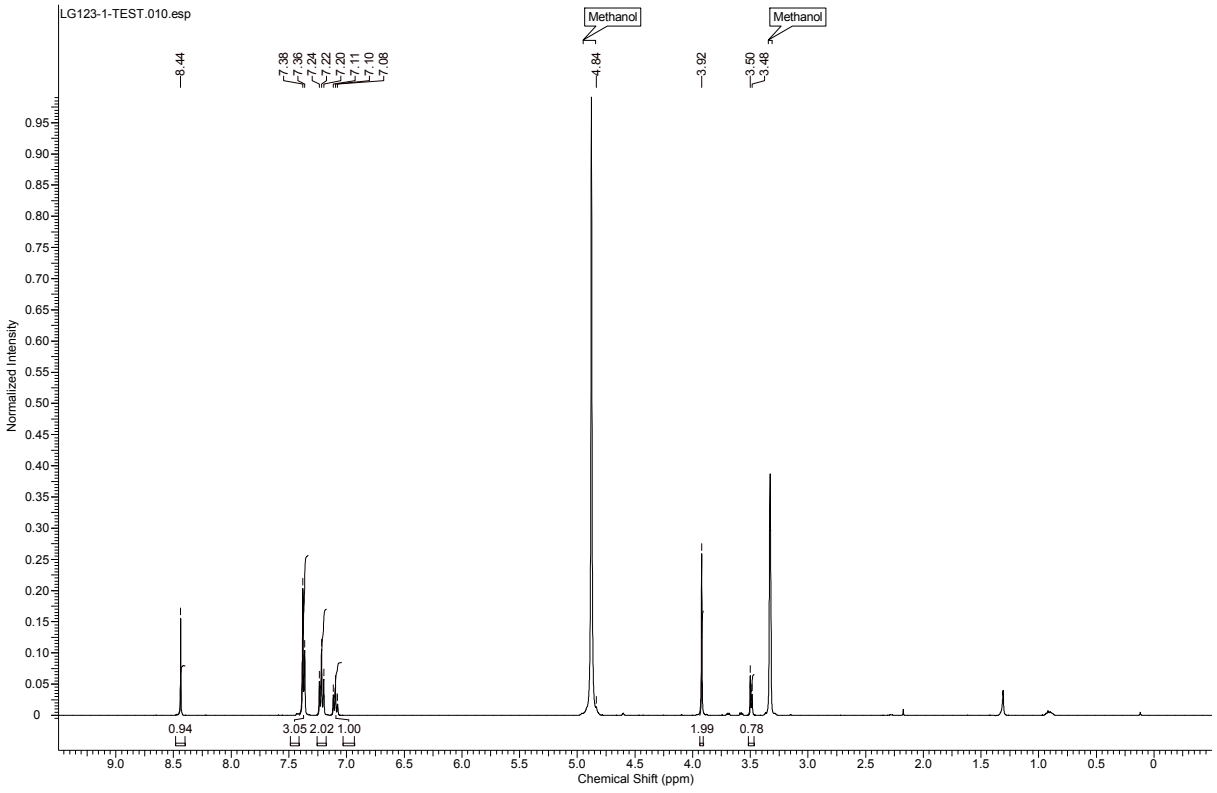


Figure S64 ^{1}H NMR spectrum of **10**

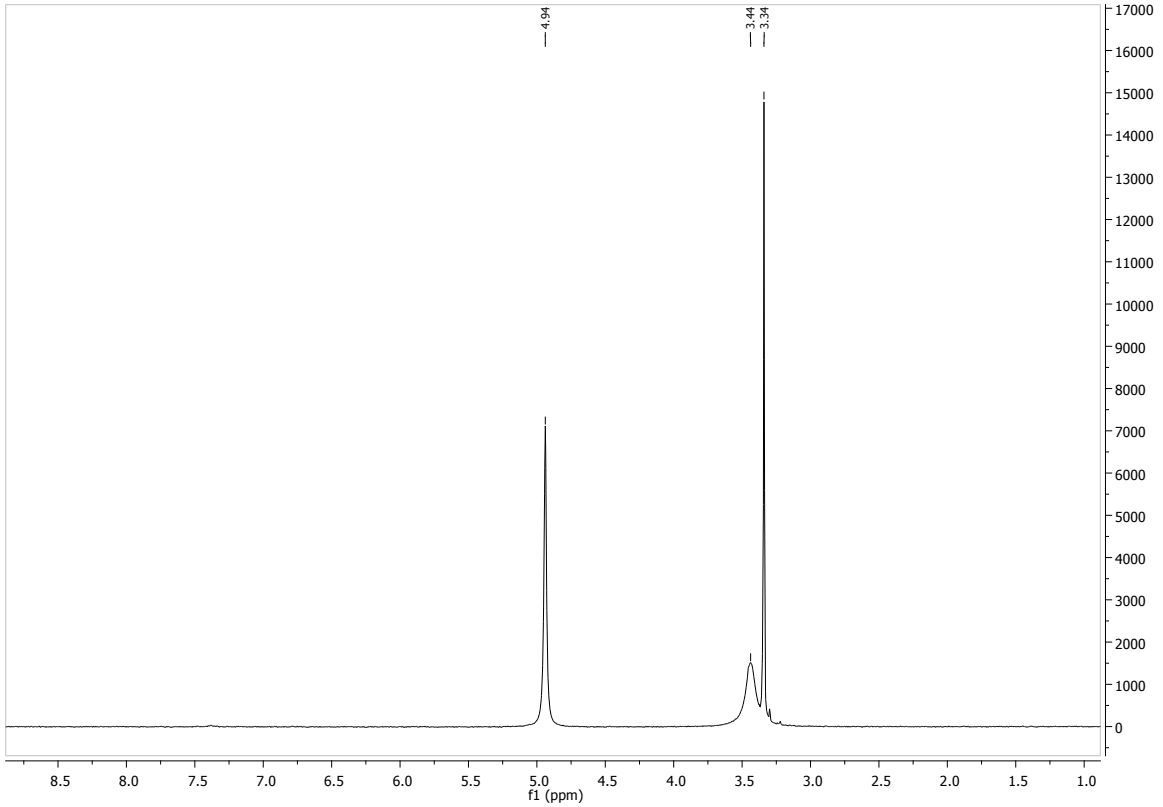


Figure S65 ^{2}H-{^{1}H} NMR spectrum of **10**

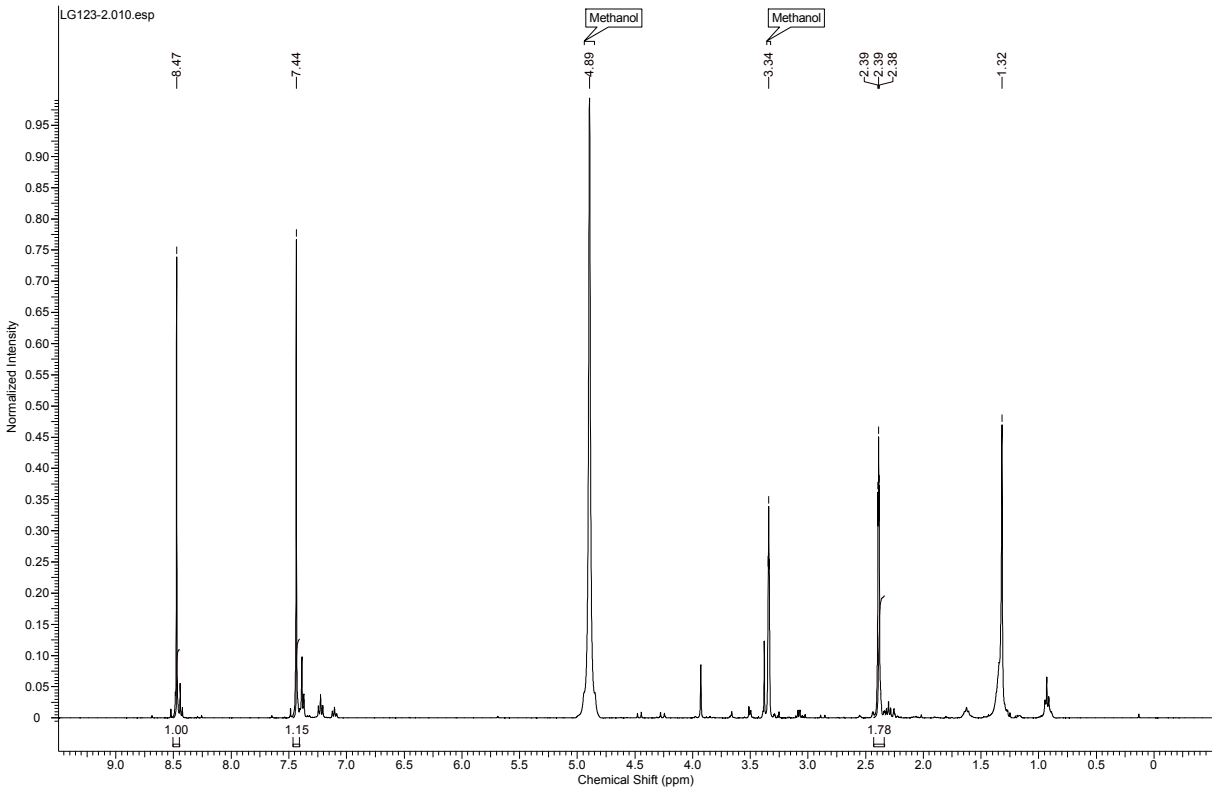


Figure S66 ^{2}H-{^{1}H} NMR spectrum of **10'**

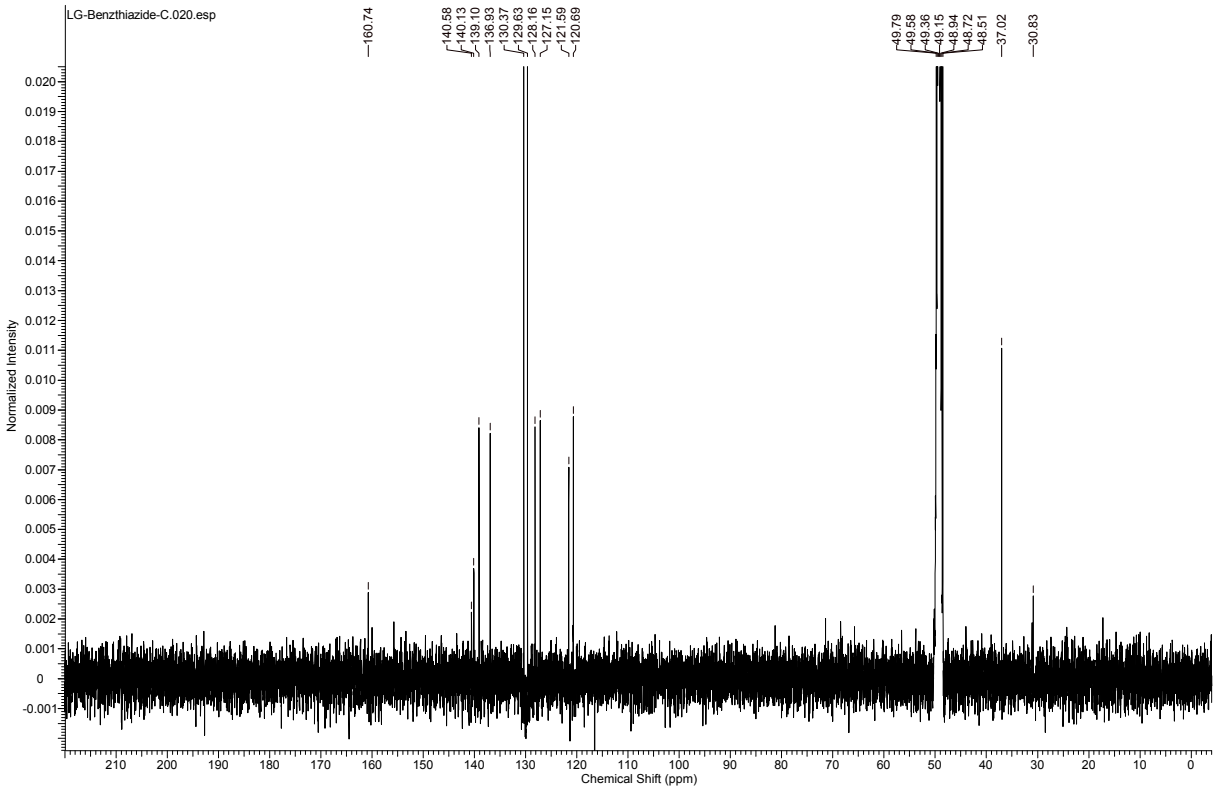


Figure S67 ^{13}C-{^{1}H} NMR spectrum of **S10 (starting material)**

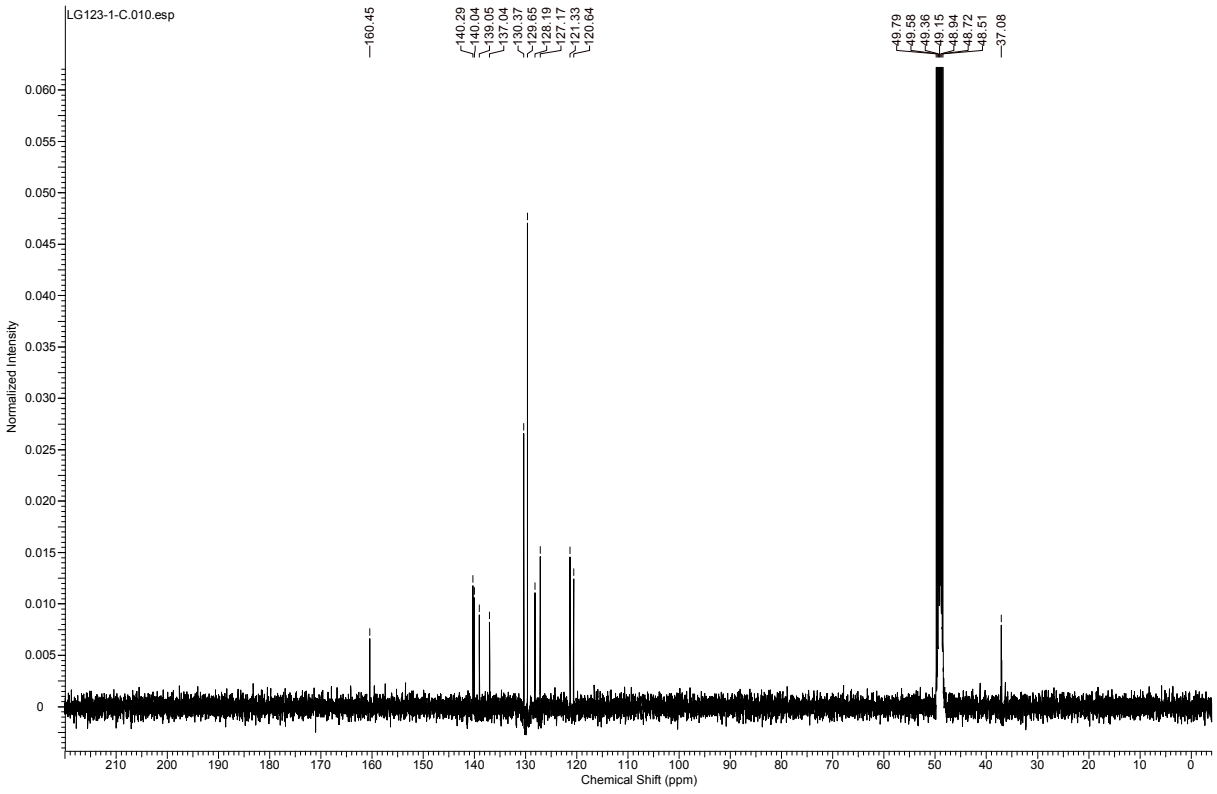


Figure S68 ^{13}C-{^{1}H} NMR spectrum of **10**

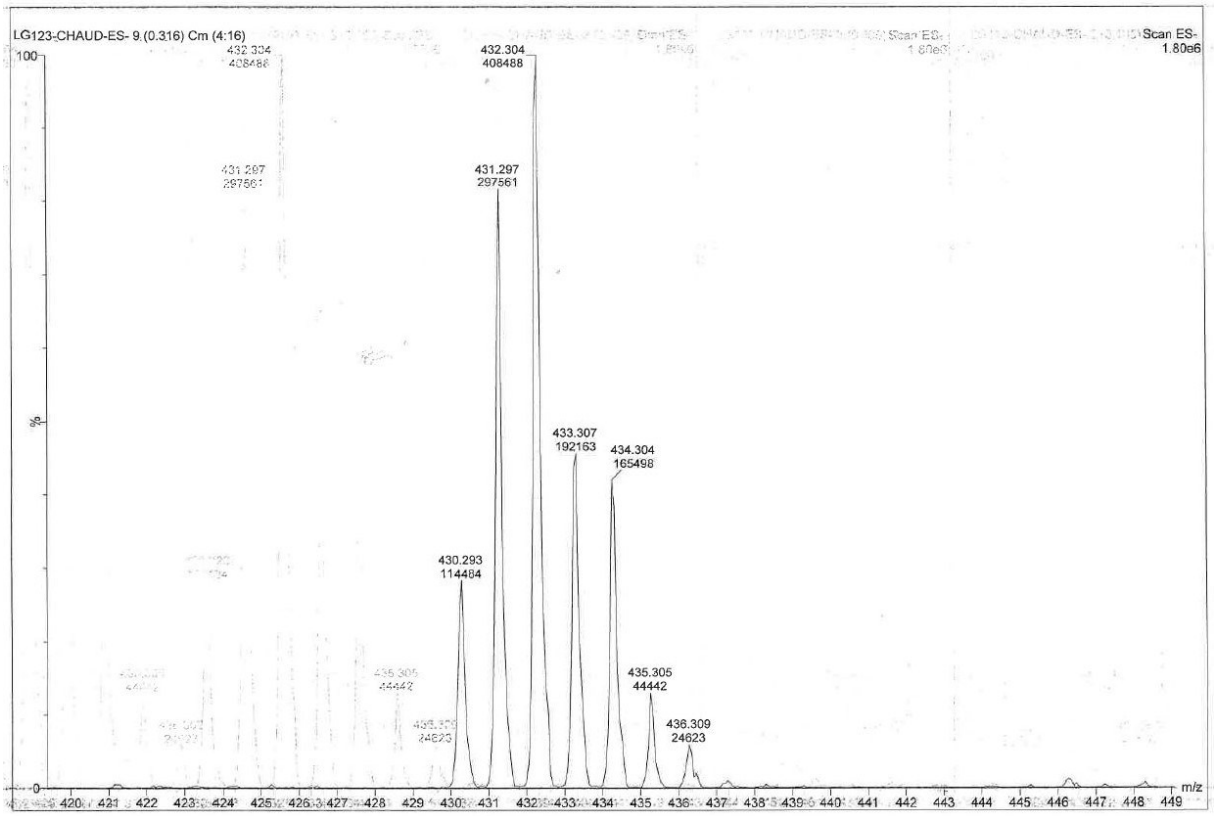
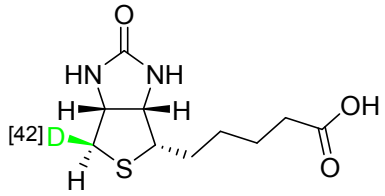


Figure S69 Mass spectrum of **10**

Biotin (11)



Following the General Procedure A (0.2 mmol of substrate was used) and using DMF as solvent. After evaporation the crude product was dissolved in methanol and centrifuged (2000 G). Supernatant was collected and evaporated *in vacuum* to afford the desired product (53 mg, quantitative). The NMR spectrum was obtained by adding 1 eq. NaOH into the D_2O solution of biotin. Before deuteration $[\alpha]_D^{20}$ +71.0° (*c* 0.1, CH_3OH), after deuteration $[\alpha]_D^{20}$ +73.0° (*c* 0.1, CH_3OH).

^{1}H NMR (400 MHz, D_2O) δ 4.56 (dd, J = 7.9, 4.6 Hz, 1H), 4.39 (dd, J = 8.0, 4.5 Hz, 1H), 3.37-3.23 (m, 1H), 2.95 (dd, J = 13.1, 5.0 Hz, 0.6H), 2.73 (d_{app}, J = 13.1 Hz, 1H), 2.14 (t, J = 8.0 Hz, 2H), 1.74-1.62 (m, 1H), 1.61-1.49 (m, 3H), 1.44-1.28 (m, 2H). ^{13}C-{^{1}H} NMR (100 MHz, D_2O) δ 183.8 (s), 165.4 (s), 62.0, 60.2-60.0 (m), 55.4 -55.2 (m), 39.8 (s), 37.4 (s), 28.3 (s), 27.7 (s), 25.7 (s).

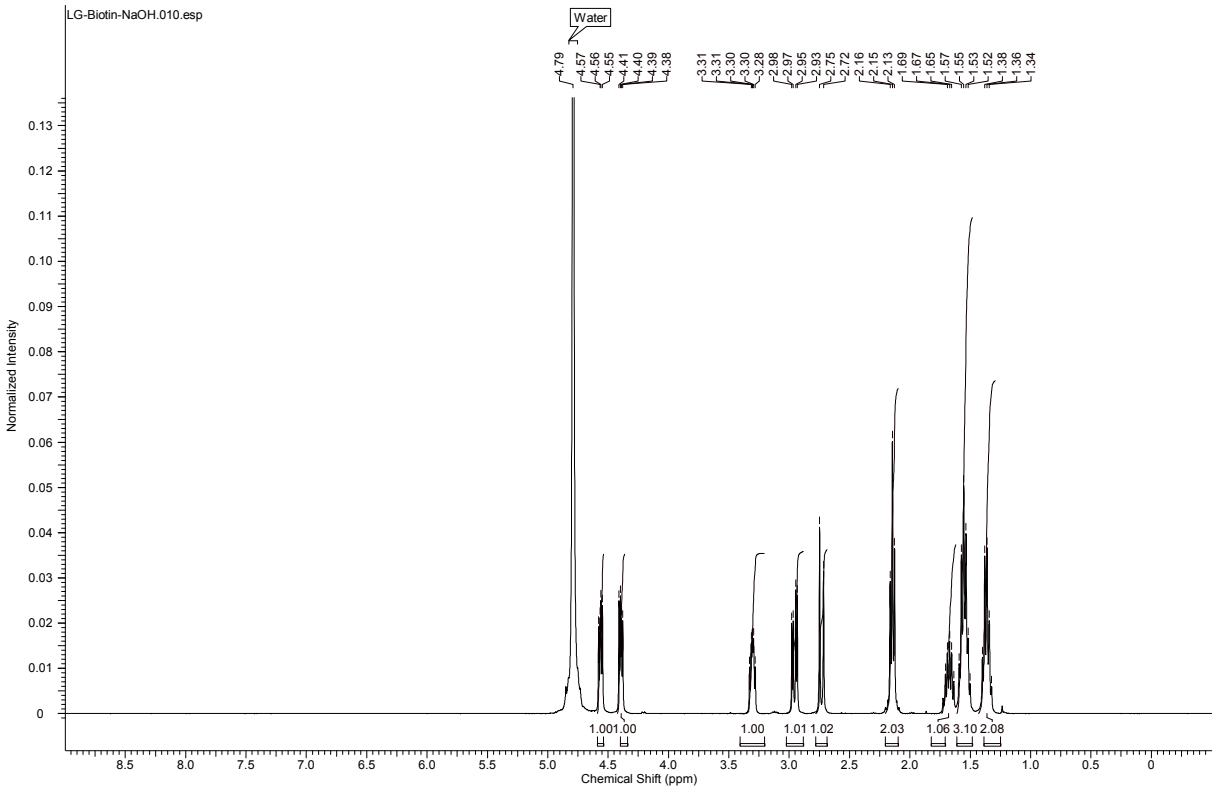


Figure S70 [1]H NMR spectrum of **S11-Na (starting material)**

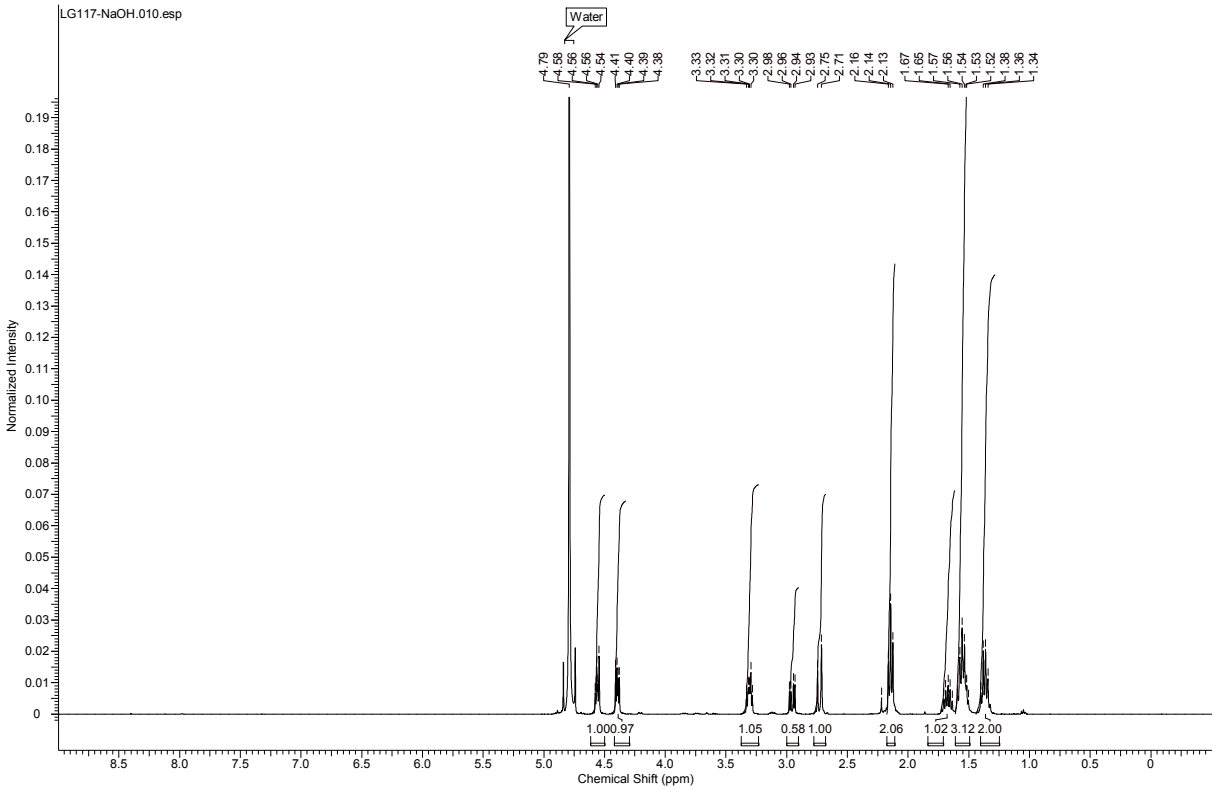


Figure S71 [1]H NMR spectrum of **11-Na**

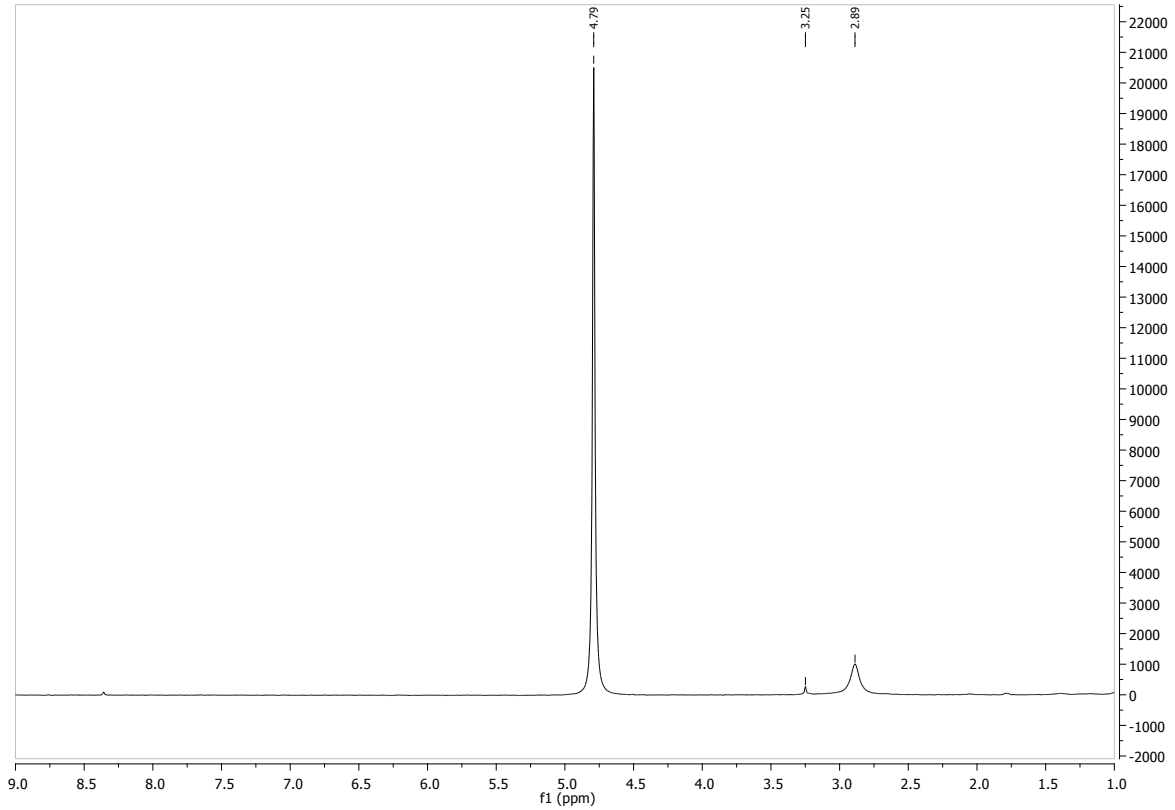


Figure S72 ^{2}H-{^{1}H} NMR spectrum of **11-Na**

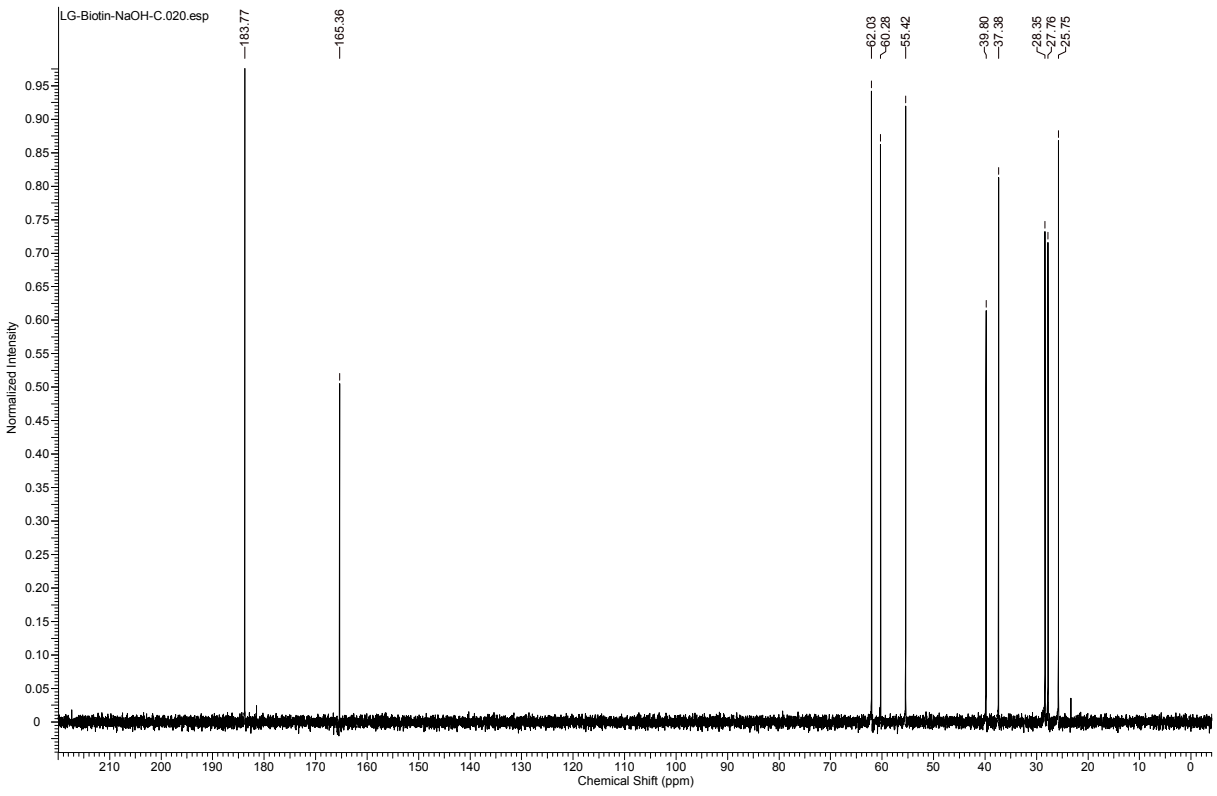


Figure S73 ^{13}C-{^{1}H} NMR spectrum of **S11-Na (starting material)**

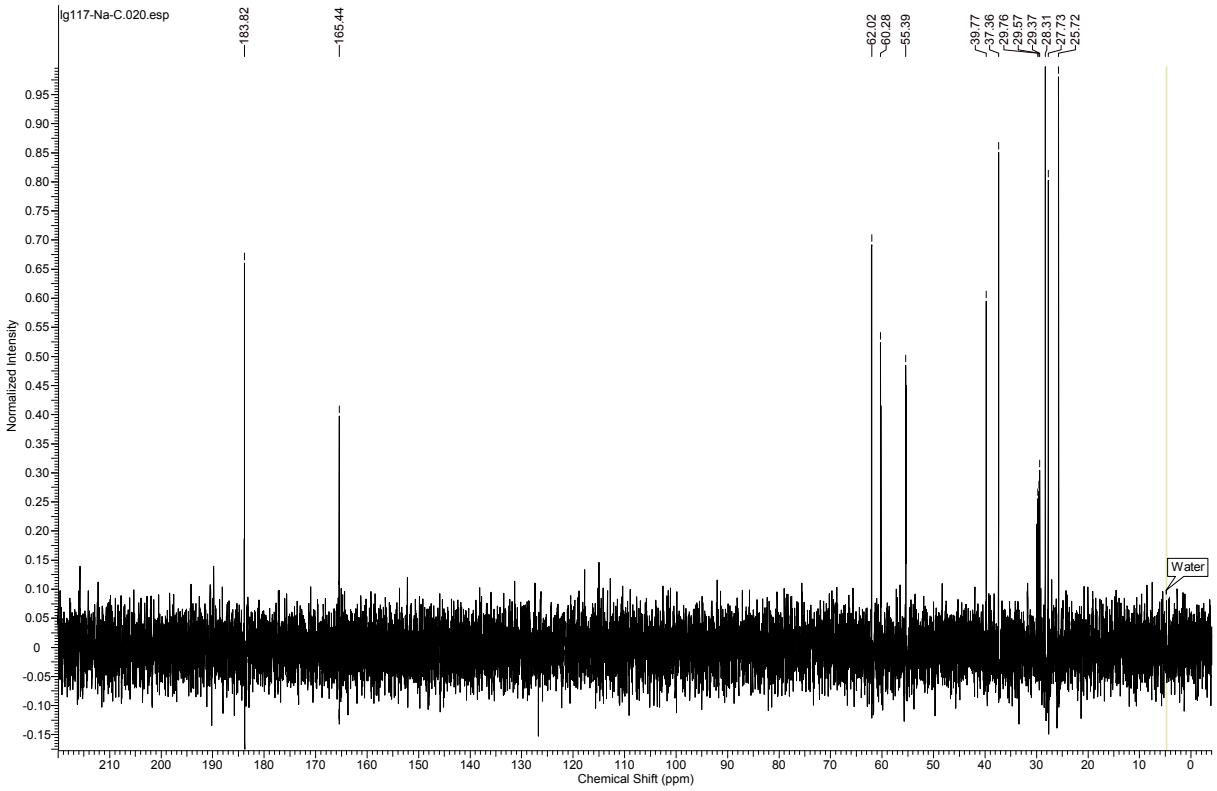


Figure S74 ^{13}C-{^{1}H} NMR spectrum of **11-Na**

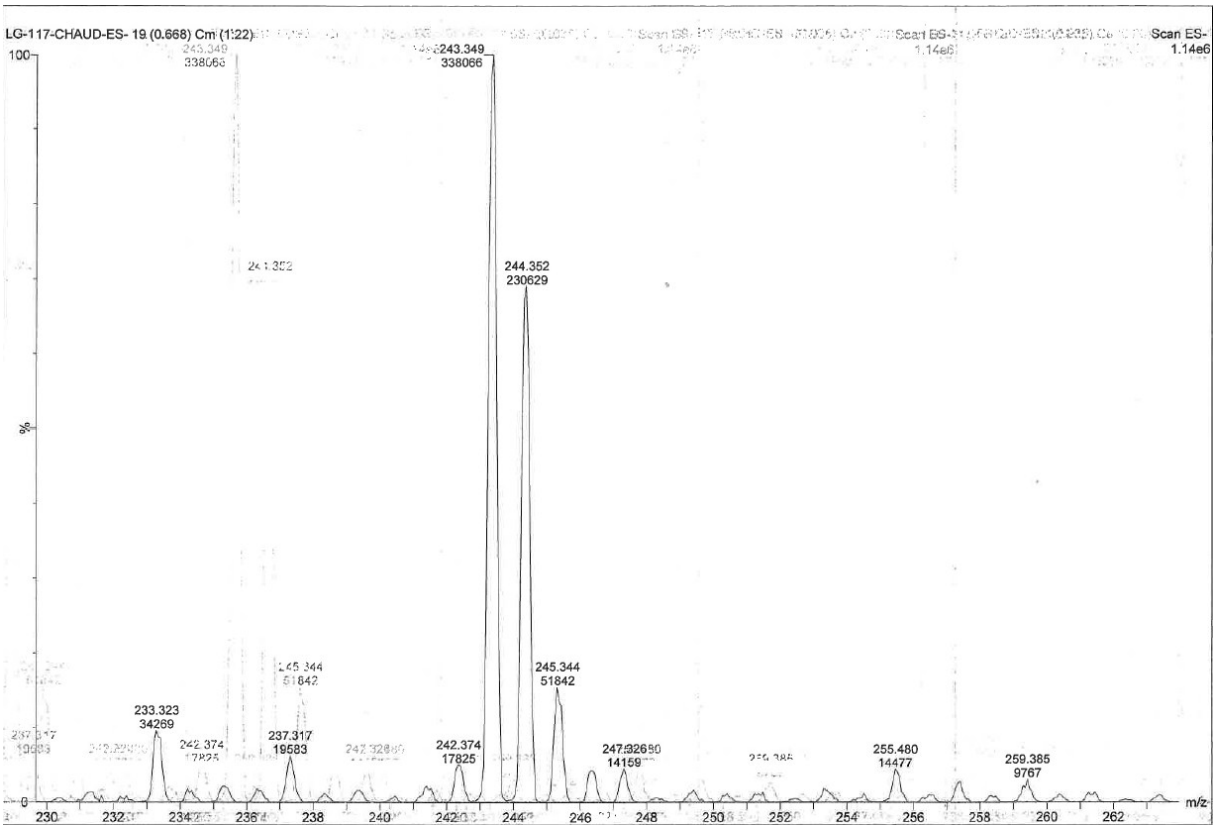


Figure S75 Mass spectrum of **11**

Table S2 Data of mass analysis for compounds 1 to 11

Compound	M_0	M_{+1}	M_{+2}	M_{+3}	M_{+4}	M_{+5}	M_{+6}	M_{+7}	M_{+8}	Total D
1	**0.3%**	**0.2%**	**2.2%**	**19.4%**	**59.7%**	**15.6%**	**2.3%**	**0.4%**		**3.9**
2	**0.0%**	**0.0%**	**0.1%**	**3.2%**	**25.8%**	**52.1%**	**17.8%**	**0.6%**	**0.4%**	**4.9**
3	**0.2%**	**0.8%**	**7.6%**	**21.1%**	**39.0%**	**22.1%**	**6.1%**	**3.7%**	**0.2%**	**4.0**
4	**11.4%**	**27.1%**	**32.4%**	**21.0%**	**8.0%**					**1.9**
4'	**0.9%**	**3.1%**	**13.9%**	**35.7%**	**45.3%**					**3.2**
5	**13.0%**	**23.4%**	**25.3%**	**25.7%**	**10.2%**	**2.4%**				**2.0**
6	**2.9%**	**9.2%**	**20.1%**	**36.0%**	**24.5%**	**7.2%**				**2.9**
7	**28.9%**	**27.1%**	**19.0%**	**16.8%**	**6.8%**	**1.3%**				**1.5**
7 (second run)	**1.6%**	**5.7%**	**12.9%**	**28.0%**	**32.0%**	**16.9%**	**2.2%**			**3.4**
7 (third run)	**0.5%**	**1.5%**	**4.7%**	**18.6%**	**33.7%**	**33.4%**	**6.0%**			**4.1**
8	**23.6%**	**34.4%**	**20.0%**	**11.4%**	**6.9%**	**2.4%**	**1.2%**			**1.6**
9	**17.4%**	**22.1%**	**22.1%**	**23.0%**	**11.7%**	**3.2%**				**2.0**
9 (second run)	**2.2%**	**7.8%**	**17.2%**	**32.9%**	**26.8%**	**10.6%**	**2.2%**			**3.1**
9 (third run)	**0.4%**	**0.7%**	**3.0%**	**17.8%**	**36.8%**	**30.0%**	**9.1%**			**4.1**
10	**11.0%**	**41.1%**	**47.9%**							**1.4**
11	**63.2%**	**35.2%**	**1.6%**							**0.4**

Identification and characterization of the compound resulting from C-S bond cleavage

Regarding the ^{1}H NMR of the acetyl-L-methionine compound **6**, a side product can be observed in a small amount (side compound peaks are indicated by a red star).

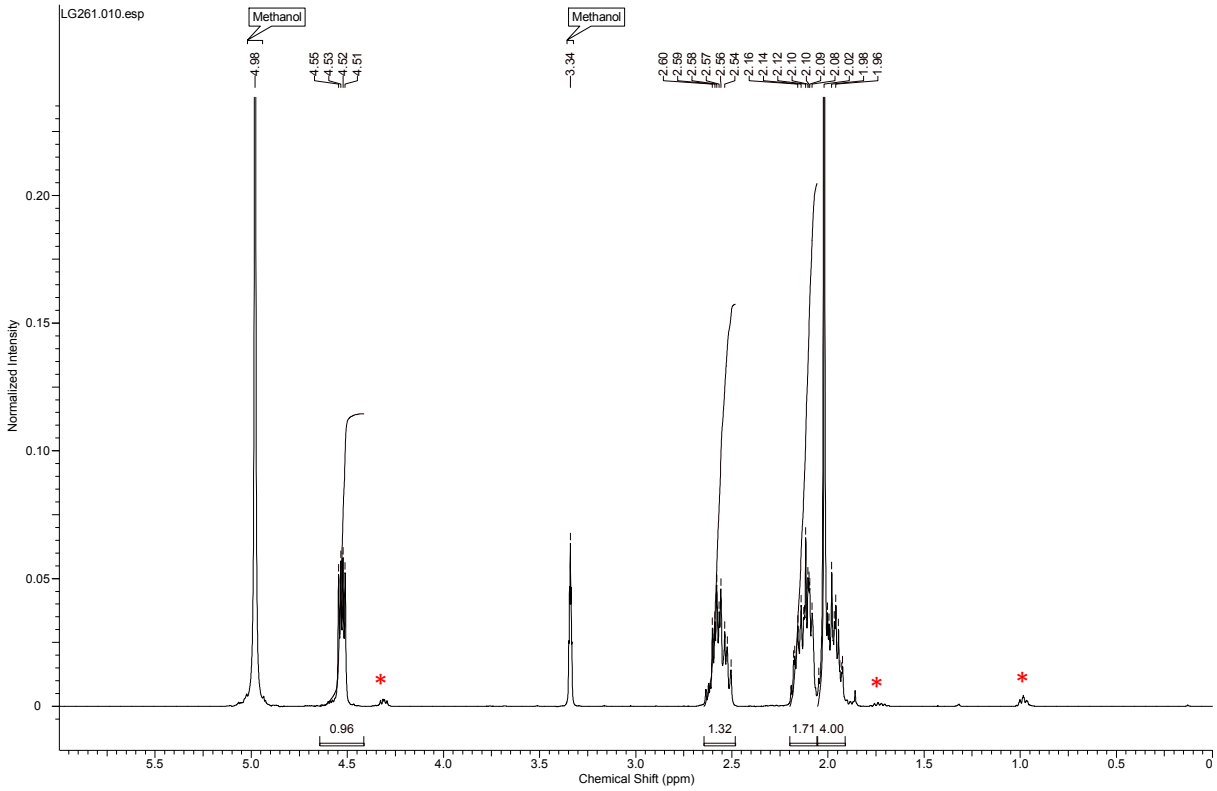


Figure S76 ^{1}H NMR spectrum of **6**

To clearly identify this compound, the following experiment was performed: a 47 mL Fischer-Porter glassware was charged with Ru/C (5 wt%, 30 mol %) and a magnetic stirrer under air. The Fischer-Porter glassware was then left under vacuum for 5 min and pressurized with H_2 gas (3 bar) during 2 hours. A solution of the substrate (15 mg) in degassed H_2O was added under argon. The reaction mixture was magnetically stirred at 60 °C (sand bath) under pressure of H_2 (2 bar) during 72 hours. The solution was then cooled down to room temperature, filtered through syringe filter and evaporated under vacuum. Preparative HPLC experiment was then performed to retrieve the desired compound which was then analyzed by ^{1}H NMR.

HPLC Preparative conditions:

Column : Waters X-Select CSH fluoro-phenyl 19×150mm×5µm

Eluent : A : H_2O + HCOOH 0.1% / B : ACN + HCOOH 0.1%

Min	A (%)	B (%)
0	95	5
16	85	15
17	0	100
30	0	100
31	95	5
35	95	5

Debit : 17 mL/min

Temperature : Room temperature

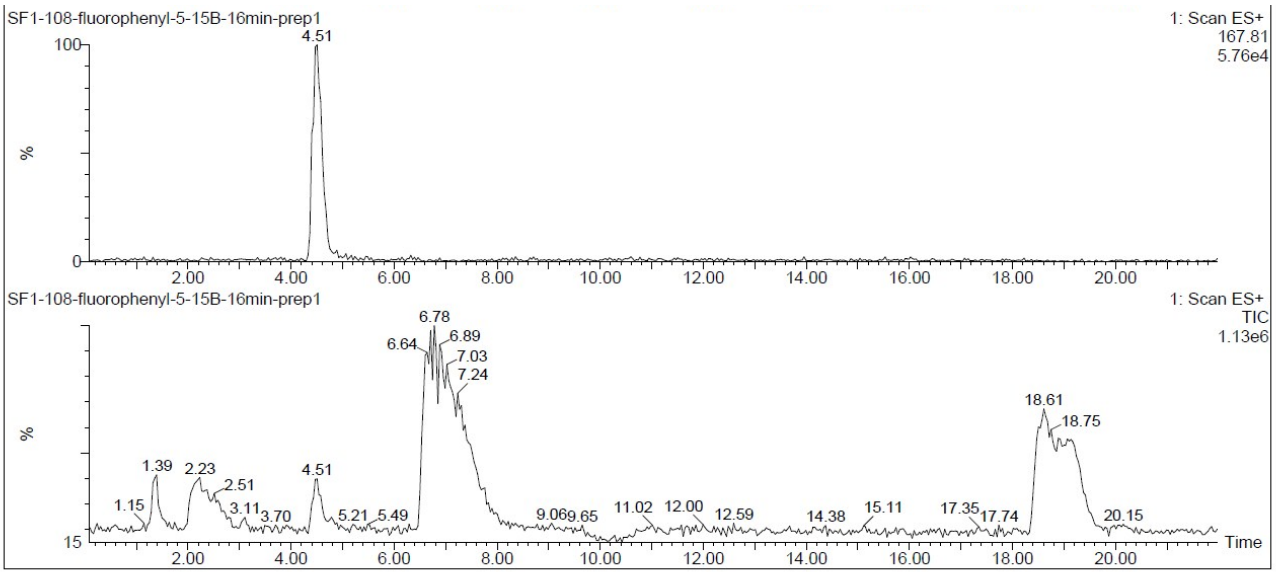


Figure S77 HPLC Chromatogram of the crude product

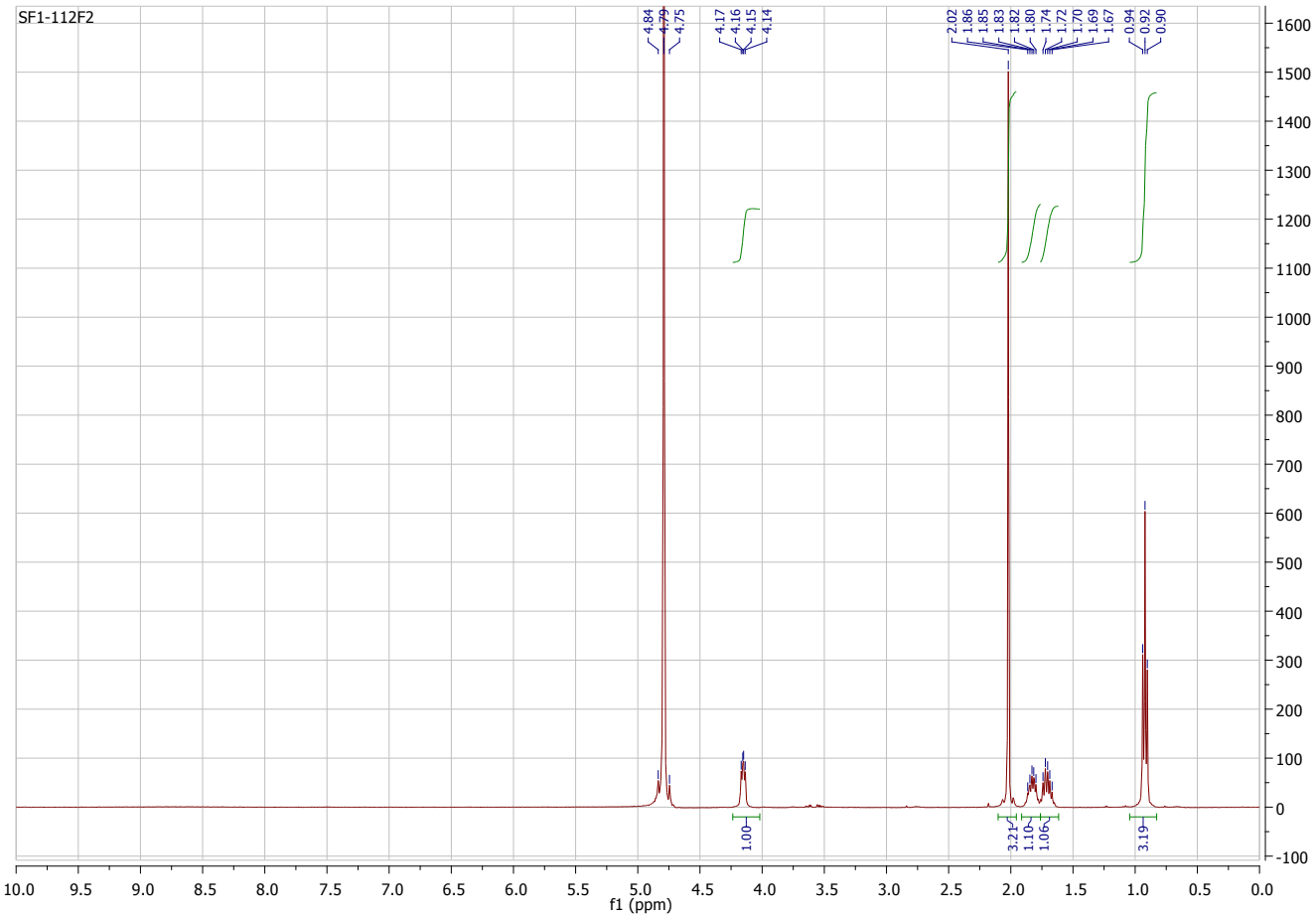
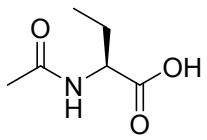


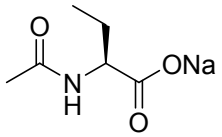
Figure S78 ^{1}H NMR spectrum of purified **12**

Structure:



12

Chemical Formula: $C_6H_{11}NO_3$



Observed in mass spectroscopy
Chemical Formula: $C_6H_{10}NNaO_3$
Exact Mass: 167,06

This compound was obtained *via* a C-S bond cleavage.

After the deuteration, ^{2}H-{^{1}H} 1D NMR analysis of the crude compound indicates also the presence of the cleavage compound.

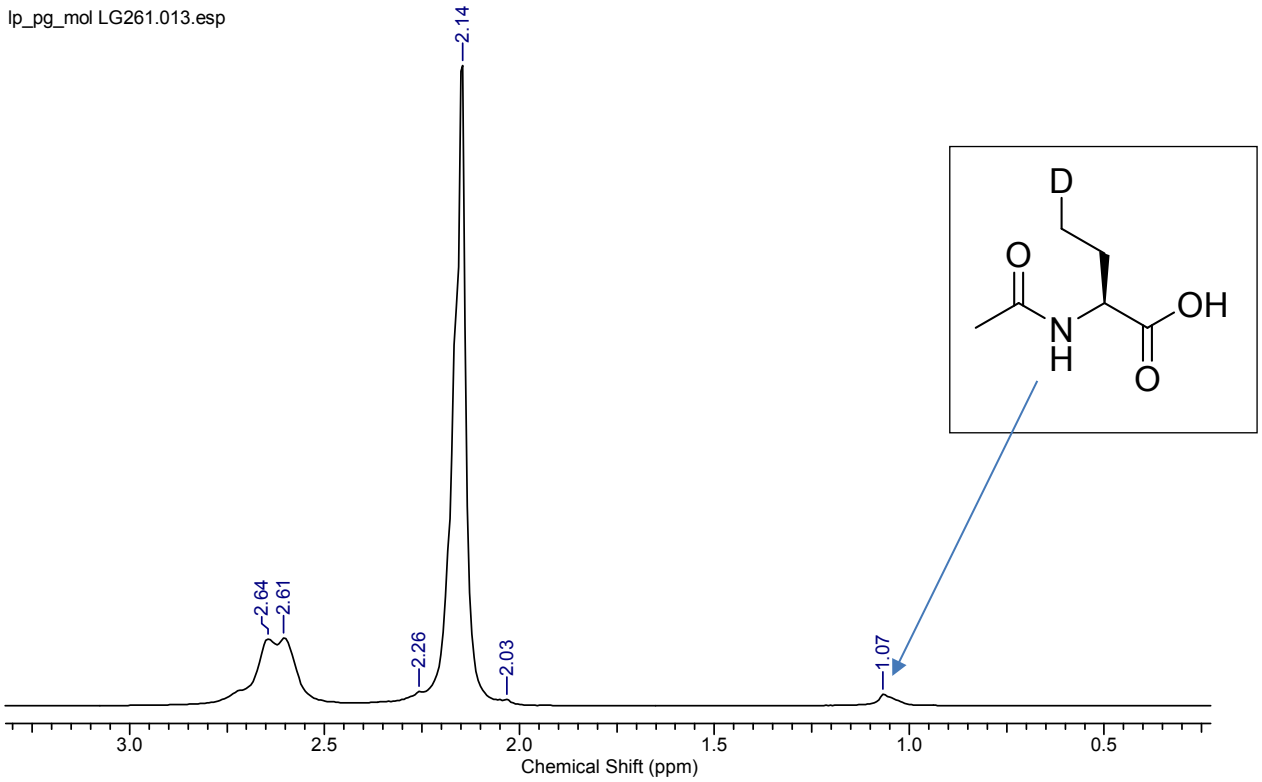


Figure S79 ^{2}H-$\{^{1}H\}$ NMR of crude **6**

Kinetic experiment:

In order to follow the deuteration of **1** in function of the time 4 experiments have been realized using standard reaction conditions (see procedure A). Reaction has been stopped after 3, 6, 22 and 66 hours and in each case the isotopic enrichment has been measured using ^{1}H NMR analysis after catalyst filtration.

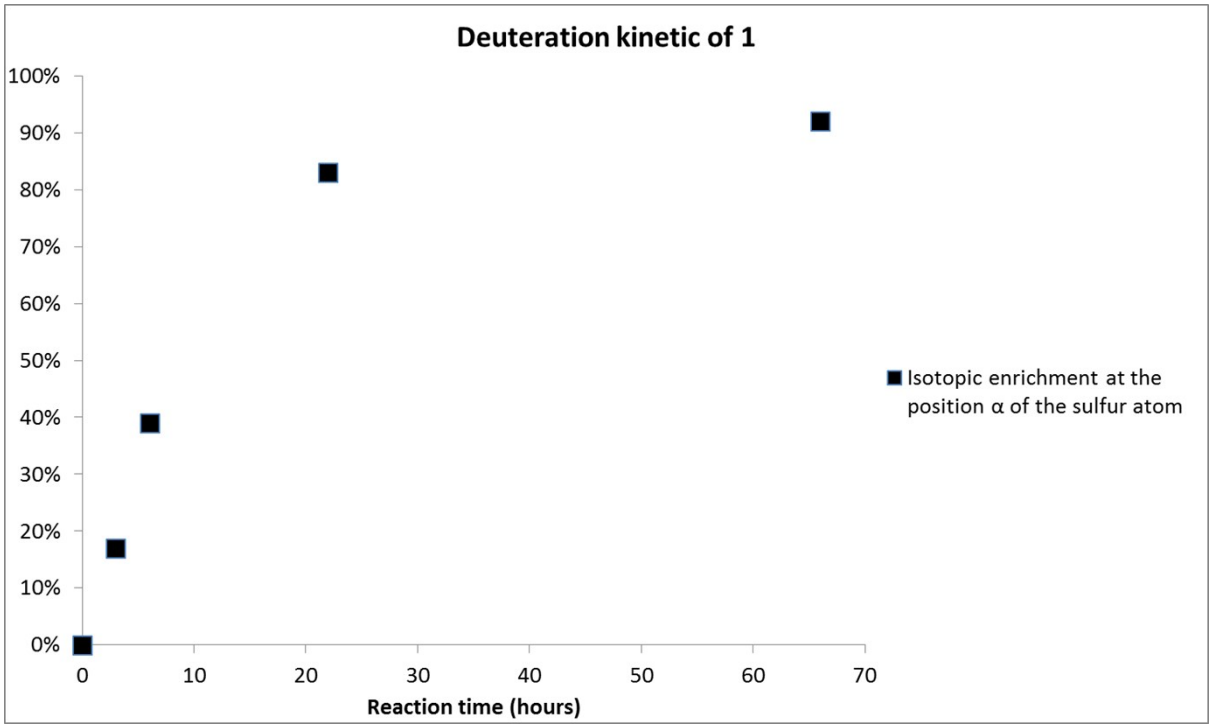


Figure S80 Kinetic experiment for the deuteration of **1**