A continuous-flow protocol for the synthesis of enantiomerically pure intermediates of anti epilepsy and anti tuberculosis Active Pharmaceutical Ingredients

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CONTENTS EXPERIMENTAL SECTION AND SPECTRAL DATA FOR COMPOUNDS:

1. General Methods: Unless otherwise stated, reagents were obtained from commercial sources and used without further purification. All reactions were monitored by HPLC, following the method described below (Purity Analysis).

1.1. Chromatographic Analysis

All chromatography analyses were performed at room temperature using the SHIMADZU HPLC system, with automatic injector.

1.1.1. HPLC Purity Analysis

All HPLC Purity analyses were performed using the OPA-MCE derivatization methodology.[1] For this a derivatization a solution containing 40 mM o-phthalaldehyde (OPA) and 1% (v/v) 2-mercaptoethanol (MCE) in a saturated solution of $Na_2B_2O_4$ (pH 10) with 20% methanol, was used. The sample for analysis was prepared with 250 µL from the reaction, 250 µL of water and 750 µL of the derivatization solution. 10 µL of the derivatized sample was directly injected into the HPLC. The chromatography was performed at room temperature using the HPLC column Eclipe XDB-C18 5 µm 150 mm. Phase A was composed of phosphate buffer (40 mM, pH 7.8) and phase B was composed of AcCN:MeOH:H_2O (45:45:10). The analysis was performed at 1 mL/min at 338 nm.

Table S1: Gradient of aqueous phase to HPLC analysis with OPA-MCE derivatization.

Time (min)	A (%)	B (%)
0	80	20
4	80	20
15	40	60
17	20	80
19	20	80
21	80	20
23	80	20

1.1.2. HPLC Chiral Analysis

All HPLC Chiral Analysis were performed using an Amazon SL (Bruker) ESI - ion trap (positive mode) as analyzer and SHIMADZU HPLC system, with automatic injector.[2]

The chromatography was performed at room temperature using the HPLC column Astec Chirobiotic T 250 x 4.6 mm with water/methanol/formic acid (30:70:0,02) isocratic mobile phase and 0,5 mL/min flow during 20 min. (*R*)- and (*S*)-aminobutyric acid were detected with EIC mode at 58.25±0.1.

1.2. NMR Spectroscopy

^{1}H and ^{13}C NMR data were recorded at 25 °C using Varian 300 MHz and 500 MHz spectrometer; Chemical shifts values (δ) are reported in part per million (ppm). Peak multiplicity is summarized as br (broad), s (singlet), d (doublet), t (triplet), m (multiplet).

1.3. Flow Equipment

1.3.1. Desulfurization

All desulfurization reactions using Nickel Raney under continuous flow were performed using an Asia system, which consists of a syringe pump, liquid phase PTFE coil, a solid phase glass column reactor (Omnifit column; 900 PSI) and a heater. All equipment's were purchased from Syrris.

1.3.2. Desulfurization with Hydrogen Pressure

All desulfurization reactions using Pd/C under continuous flow were performed using an H-Cube® system from ThalesNano, with an HPLC pump. All equipment's were purchased from ThalesNano.

1.3.3. Photo-desulfurization

All desulfurization reactions using UVC-light under continuous flow were performed using an Asia system, which consists of a syringe pump, liquid phase PFA coiled direct attached to the lamp. All equipments were purchased from Syrris.

1.4. Residual Metal Analysis

The residual metal analysis was performed in an Analytic Jena atomic absorption spectrometer, model contrAA300.

2. EXPERIMENTAL SECTION

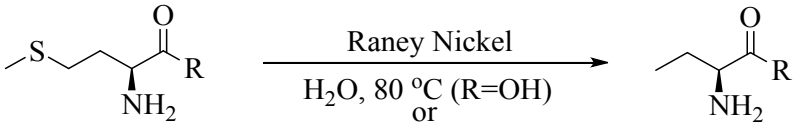
2.1 RANEY NICKEL PREPARATION [3]

In a 500 mL Erlenmeyer, 200 mL of water was heated to 50 ºC. Then 5 g of Ni-Al alloy (50 : 50) fine powder was added. To the suspension under stirring, 40mL of aqueous NaOH 40% was added in small portions for 30 min, in order to control the hydrogen evolution. After addition was complete, the mixture was allowed to stir for more 15 min (final pH 14). To the suspension, lactic acid was added until pH=7 (40 mL). The suspension was cooled to 0ºC (ice bath), then the solid was decanted, washed 2 x 100 mL of cold water. Then the catalyst was rinsed with 2 x 30 mL of ethanol for water removal and afterwards it was stored at room temperature in ethanol.

This catalyst was used in batch and flow reactions.

2.2 BATCH REACTIONS

2.2.1. Desulfurization using Raney Nickel in batch



R= OH (**7**), OMe (**8**), NH_2 (**9**) R= OH (**1**), OMe (**10**), NH_2 (**2**)

In a 20 mL reactor, around 2 g of the wet catalyst is weighted and rinsed with 2 x 5 mL of the corresponding solvent. Separately, a solution of the substrate in the solvent is prepared (60-70 mM), and then this solution is transferred to the reactor containing the catalyst. The resulting mixture is heated to set temperature and stirred until reaction is finished. After cooling to room temperature, the reaction medium is filtered to remove the catalyst and washed with solvent. After solvent removal in

vacuum, the crude greenish white solid is re-crystallized by solubilizing in 1 mL of water and precipitated with the addition of 20 mL of acetone.

2-amino-butanoic acid (**1**), (Yield= 60%): ^{1}H NMR (500 MHz, D_2O) δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.92 – 1.79 (m, 2H), 3.67 (t, *J* = 5.9 Hz, 1H). ^{13}C NMR (126 MHz, D_2O) δ 8.46, 23.61, 55.82, 174.83 (C=O).

Methyl (*S*)-2-amino-butanoate (**10**), (Yield= 64%): ^{1}H NMR (500 MHz, MeOD) δ 1.05 (t, *J* = 7.6 Hz, 3H), 2.06 – 1.93 (m, 2H), 3.85 (s, 3H), 4.05 (t, *J* = 6.2 Hz, 1H), 4.87 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 8.32, 23.44, 52.33, 53.79, 169.54 (C=O).

(*S*)-2-amino-butyramide (**2**), (Yield= 62%): ^{1}H NMR (400 MHz, DMSO) δ 0.88 (t, *J* = 7.5 Hz, 3H), 1.79 – 1.69 (m, 2H), 3.69 (t, *J* = 6.1 Hz, 1H), 7.52 (s, 1H), 7.88 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 9.04, 24.22, 53.22, 170.34 (C=O).

Table S1: Process development in Batch 2-amino-butanoic acid (**1**):

Entry	Catalyst	S/C (ratio)	Time (h)	Conv. (%)* 1	Conv. (%)* 7
1	Raney Ni (Aldrich 2800) pH 10	0.1	4	99	1
2		**0.17**	**4**	**36**	**64**
3		**0.33**	**4**	**24**	**76**
4	Fresh Raney Nickel Final pH 7	0.1	0.83	>99	0,1
5		0.2	1.5	99	1
6		**1**	**4**	**16**	**84**

*HPLC: Purity Analysis

Table S2: Process development in Batch Methyl (*S*)-2-amino-butanoate (**10**).

Entry	Catalyst	S/C	Time (h)	Conv. (%)* 10	Conv. (%)* 8	Conv. (%)* 1	Conv. (%)* 7
1	Raney Ni (Aldrich 2800) pH 10	**0.05**	**7**	**84**	**14**	**4**	**ND**
2		**0.11**	**4**	**47**	**19**	**15**	**17**
3	Fresh Raney Nickel Final pH 7	0.11	0.5	98	0.5	1	0.1
4		0.14	4	97	0.2	2	ND
5		**0.2**	**4**	**67**	**29**	**1**	**2**

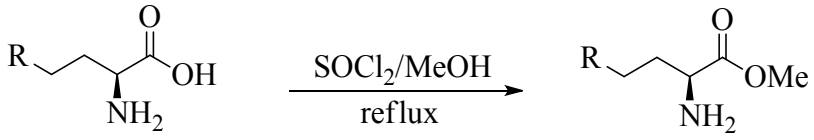
*HPLC: Purity Analysis

Table S3: Process development in Batch (*S*)-2-amino-butyramide (**2**).

Entry	Catalyst	S/C	Time (h)	Conv. (%)* 2	Conv. (%)* 9	Conv. (%)* 1	Conv. (%)* 7
1	Raney Nickel (Aldrich 2800) pH 10	**0.15**	**20**	**34**	**65**	**0.5**	**1**
2		0.05	4	97	1	0.5	1
3	Fresh Raney Nickel Final pH 7	0.15	4	97	1	1	1

*HPLC: Purity Analysis

2.2.2. Esterification of the amino acid



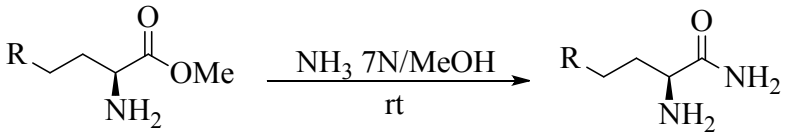
R=SMe (**7**), H (**1**) R=SMe (**8**), H (**10**)

In a 20 mL reactor, 10 mmol of the substrate was suspended in 10 mL of methanol and cooled to 0°C. Then thionyl chloride (20 mmol) is slowly added, and the resulting solution is heated to reflux until reaction is finished. After volatiles removal in vacuum, the crude oil is used in the next step.

L-methionine methyl ester (**8**), **(**Yield= 99%): ^{1}H NMR (500 MHz, D_2O) δ 2.12 (s, 3H), 2.23 (td, *J* = 14.5, 7.0 Hz, 1H), 2.36 – 2.29 (m, 1H), 2.74 – 2.66 (m, 2H), 3.86 (s, 3H), 4.32 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR (126 MHz, D_2O) δ 14.03, 28.55, 28.84, 51.85, 53.80,170.53 (C=O).

Methyl (*S*)-2-amino-butanoate (**10**), (Yield= 99%): ^{1}H NMR (500 MHz, MeOD) δ 1.05 (t, *J* = 7.6 Hz, 3H), 2.06 – 1.93 (m, 2H), 3.85 (s, 3H), 4.05 (t, *J* = 6.2 Hz, 1H), 4.87 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 8.32, 23.44, 52.33, 53.79, 169.54 (C=O).

2.2.3. Preparation of the Amide



R=SMe (**8**), H (**10**) R=SMe (**9**), H (**2**)

In a 20 mL reactor, 6 mmol of the substrate is added, then 70 mmol of ammonia (sol. in methanol 7 N) is added. The resulting solution is stirred at room temperature until end of the reaction. After solvent removal in vacuum, the crude sticky white solid is re-crystallized by solubilizing in 1 mL of water and precipitated with the addition of 20 mL of acetone (90% yield).

L-methionamide (**9**), **(**Yield= 90%): ^{1}H NMR (400 MHz, D_2O) δ 2.19 – 2.05 (m, 5H), 2.65 (t, *J* = 7.6 Hz, 2H), 3.95 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (101 MHz, D_2O) δ 14.05, 28.62, 31.29, 52.60, 174.72 (C=O).

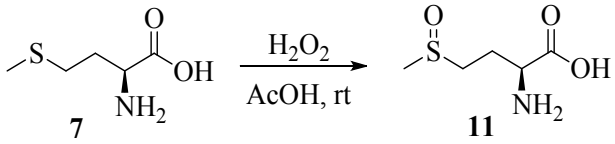
(*S*)-2-amino-butyramide (**2**), (Yield= 85%): ^{1}H NMR (400 MHz, DMSO) δ 0.88 (t, *J* = 7.5 Hz, 3H), 1.79 – 1.69 (m, 2H), 3.69 (t, *J* = 6.1 Hz, 1H), 7.52 (s, 1H), 7.88 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 9.04, 24.22, 53.22, 170.34 (C=O).

Table S4: Batch trials to test the eq NH_3 vs. conversion L-Methionine Methyl Ester (**8**) into L-Methionamide (**9**).

NH_3 eq. (~7N)	**Conv. (%)***					
	8 h	**24 h**	**33 h**	**48h**	**55h**	**71h**
11.7	46	77	83	91	93	95
23.4	53	81	88	93	95	97
46.8	58	83	89	95	97	97

*HPLC: Purity Analysis

2.2.4. L-Methionine Oxide (Impurity) Preparation[4]



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In a 20 mL reactor, 3 mmol of L-methionine is added, then 9 mL of acetic acid is added. The mixture is cooled with an ice bath, then 3.6 mmol of H_2O_2 (30% aqueous) was added slowly. The resulting solution was allowed to raise to room temperature until end of the reaction. After solvent removal in vacuum, the crude sticky white solid is re-crystallized by solubilizing in 1 mL of water and precipitated with the addition of 20 mL of acetone (90% yield). ^{1}H NMR (300 MHz, D2O) δ 2.32 – 2.24 (m, 2H), 2.72 (s, 3H), 3.15 – 2.85 (m, 2H), 3.90 – 3.82 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ 23.80, 36.48, 48.29, 53.39, 173.28 (C=O).

2.3. FLOW REACTIONS

2.3.1. Desulfurization with Raney Nickel in flow

The following set-up was prepared for desulfurization in flow:

R=OH (**7**), OMe (**8**), NH_2 (**9**) R=OH (**1**), OMe (**10**), NH_2 (**2**)

Scheme 1: Desulfurization of L-methionine (**7**), L-methionine methyl ester (**8**) and L-methionamide (**9**).

The column (1.2 mL) was pre-packed with the chosen catalyst (around 2.2 g of wet Raney Nickel) and washed with the corresponding solvent. The column was warmed up until the reaction temperature and then the solution containing the substrate was pumped through this column. The flow rate was adjusted to desired residence time.

Table S5: Process development for desulfurization of L-methionine (**7**) and L-methionamide (**9**).

	7 (H_2O, 80 ºC)		**9** (Methanol, 60 ºC)	
	Raney Ni Aldrich 2800	**Raney Ni prepared**	**Raney Ni Aldrich 2800**	**Raney Ni prepared**
Residence Time (min)	1	1	1	1
Selectivity (HPLC Area %)	99	99	97	97
Productivity ($mmol_{product}.h^{-1}.mmol_{catalyst}^{-1}$)	0.06	0.32	0.09	0.11

Reaction conditions: 40 mM, water, T=80ºC (R=OH) or 24 mM, methanol, T=60ºC ($R=NH_2$); Reactor Vol= 1,2 mL, BPR=6,9bar.

Table S6: Process development for desulfurization of L-methionine methyl ester (**8**).

	Raney Ni Aldrich 2800	**Raney Ni prepared**
Residence Time (minute)	1	1
Conversion (Selectivity) (HPLC Area %)	99 (52)*	97

*52% of methyl 2-amino-butanoate (**10**), 43% of *S*-2-amino-butan-1-ol (**3**), 4% of 2-aminobutanoic acid (**1**)

2.3.2. Desulfurization with Pd/C and hydrogen pressure in flow

The H-CUBE (ThalesNano Inc.) system was used for this procedure. The H-CUBE has an internal hydrogen generator, then this hydrogen is introduced into the reactional mixture, that is pumped by a HPLC pump, prior to catalyst contact. The pressure of the system is dictated by the adjustable BPR (back-pressure regulator). The product is isolated by solvent evaporation. The system can be summarized by the following scheme:

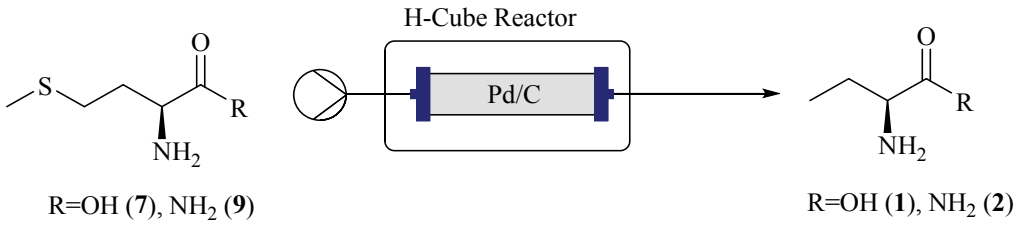


Table S7: Process development for desulfurization of L-methionine (**7**).

	10%Pd/C H_2/20 bar	10%Pd/C H_2/40 bar	10%Pd/C H_2/80 bar	10%Pd/C H_2/80 bar
Concentration L-Met (mg/mL)	1	1	1	1
Temperature (ºC)	80			25
Flow (mL/min)	0.2	0.5		
Reactor volume (mL)	0.131			
Residence Time (s)	39	15		
Catalyst Amount (g)	0.101			
Productivity ($mmol_{product}$. h^{-1}. $mmol^{-1}_{catalyst}$)	Maximum Conversion = 10%	4.3	4.3	4.3

2.3.3. Preparation of *S*-2-amino-butan-1-ol (3)

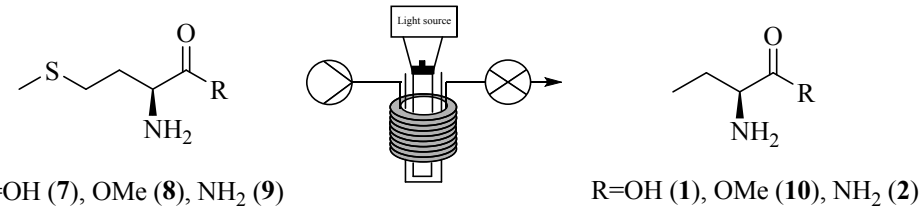
The following set-up was prepared for desulfurization/reduction in flow (same as for only desulfurization):

The column (1.2 mL) was pre-packed with the chosen catalyst (around 2.2 g of wet Raney Nickel from Aldrich W.R. Grace and Co. Raney® 2800) and rinsed with methanol. The column was warmed up until 60°C and then the solution containing the substrate (3 mM) was pumped through this column. The flow rate was adjusted to improve the conversion of L-methionine methyl ester into *S*-2-amino-butan-1-ol (**3**).

Table S8: Process development for desulfurization of L-methionine methyl ester to *S*-2-amino-butan-1-ol (**3**).

Entry	Substrate (mM)	R. T. (min)	Conv. (%)
1	6	1.2	43
2	3	1.2	69
3	3	2.4	74
4	3	6	90
5	3	12	97

2.3.4. Desulfurization using UV-light in flow



R=OH (**7**), OMe (**8**), NH_2 (**9**) 11 mL coil R=OH (**1**), OMe (**10**), NH_2 (**2**)

All trials were performed using an 8W-UVC lamp, T=50°C.

2.3.4.1. Solvent Screening trials for desulfurization of L-methionine (7) and L-methionamide (9)

Because of poor solubility of L-methionine (**1**), it was not possible to test any pure solvent. No solvent screening was performed for **8**, since it was already known that it hydrolyses in water.

The solvents tested gave moderate selectivity in the production of the desired product. And methanol was the chosen solvent for process improvement due to its best results on the balance between conversion and selectivity.

Table S9: Solvent Screening trials for desulfurization of L-methionine (**7**).

	Reactor Volume (mL)	Flow (µL/min)	Residence Time (min)	Conv.(%)*
H_2O	2	50	40	57 (**1**, 19)
H_2O		25	80	76 (**1**, 21)
H_2O:ACN (1:4)				71 (**1**, 28)
HCl 0.05M				86 (**1**, 33)
H_2O:MeOH (1:4)	11	91.5	120	35 (**1**, 25)

* Conversions were obtained by HPLC analysis and selectivity towards the desired product is presented in parenthesis.

Table S10: Solvent Screening trials for desulfurization of L-methionamide (**9**).

	Reactor Volume (mL)	Flow (µL/min)	Residence Time (min)	Conv. (%)*
MeOH	2	25	80	77 (**2**, 40)
MeOH:ACN (1:4)				85 (**2**, 21)
H_2O	11	91.5	120	66 (**2**, 37)

* Conversions were obtained by HPLC analysis and selectivity towards the desired product is presented in parenthesis.

2.3.4.2. Residence time screening trials for desulfurization of L-methionine (7), L-methionine methyl ester (8) and L-methionamide (9)

The substrate solution (6 mM in methanol or H_2O:MeOH (1:4) when L-methionine (**7**)) flow was adjusted to vary the residence time and the impact in the conversion and selectivity. For every substrate tested, the best result was archived for 180 min of residence time.

Table S11: Residence time screening trials for desulfurization of L-methionine (**7**).

	Reactor Volume (mL)	Flow (μL/min)	Residence Time (min)	Conv. (%)*
1	11	183	60	32 (**1**, 20)
2		91.6	120	48 (**1**, 34)
3		61.1	180	60 (**1**, 42)

* Conversions were obtained by HPLC analysis and selectivity towards the desired product is presented in parenthesis.

Table S12: Residence time screening trials for desulfurization of L-methionine methyl ester (**8**).

	Reactor Volume (mL)	Flow (μL/min)	Residence Time (min)	Conv. (%)*
1	11	183	60	52 (**10**, 26)
2		91.6	120	80 (**10**, 51)
3		61.1	180	88 (**10**, 59)

* Conversions were obtained by HPLC analysis and selectivity towards the desired product is presented in parenthesis.

Table S13: Residence time screening trials for desulfurization of L-methionamide (**9**).

	Reactor Volume (mL)	Flow (μL/min)	Residence Time (min)	Conv.(%)*
1	11	366	30	45 (**2**, 25)
2		183	60	70 (**2**, 45)
3		91.6	120	85 (**2**, 65)
4		61.1	180	89 (**2**, 71)
5		46.8	240	88 (**2**, 60)

* Conversions were obtained by HPLC analysis and selectivity towards the desired product is presented in parenthesis.

2.3.4.3. Concentration screening trials for desulfurization of L-methionamide (9).

Since the best results were obtained for L-methionamide, further trials were done only for this substrate to see if it was possible to improve the process even more. The substrate solution concentration was prepared at 6 mM, 30 mM and 60 mM in methanol, the flow was adjusted to set the residence time to 120 min and the impact in the conversion and selectivity was observed. Additionally, 2 in-sequence reactors (2 coils rolled up in 2 identical lamps) were also tested. The best result was achieved for 6 mM using only one reactor. The second reactor gave higher content of the impurities.

Table S14: Concentration screening trials for desulfurization of L-methionamide (**9**).

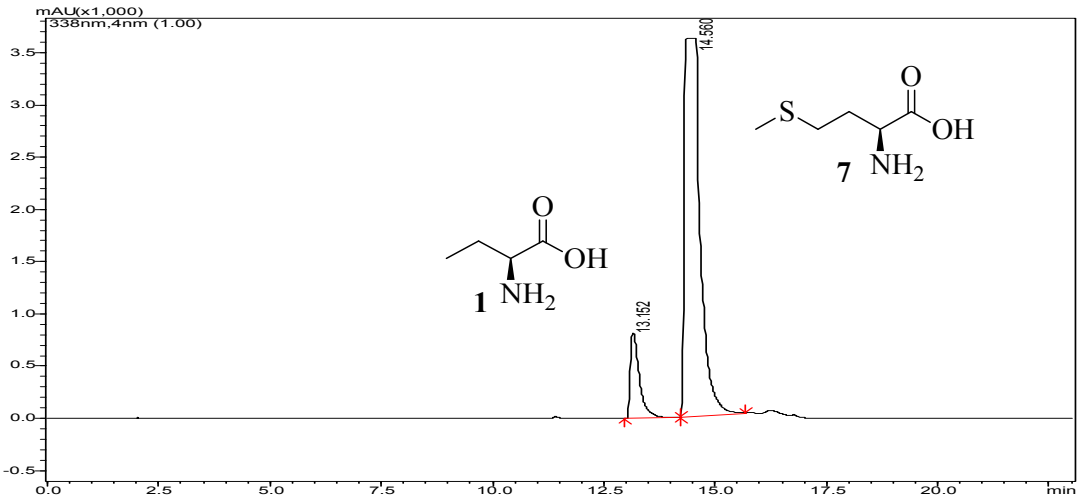
Concentration (mM)	Reactor Volume (mL)	Flow (µL/min)	Residence Time (min)	Conv.(%)*
6	11	91.6	120	85 (**2**, 65)
30				61 (**2**, 50)
60				35 (**2**, 20)
6	11 x 2 (in-sequence)		240	92 (**2**, 56)
30	11 x 2 (in-sequence)		240	59 (**2**, 42)

* Conversions were obtained by HPLC analysis and selectivity towards the desired product is presented in parenthesis.

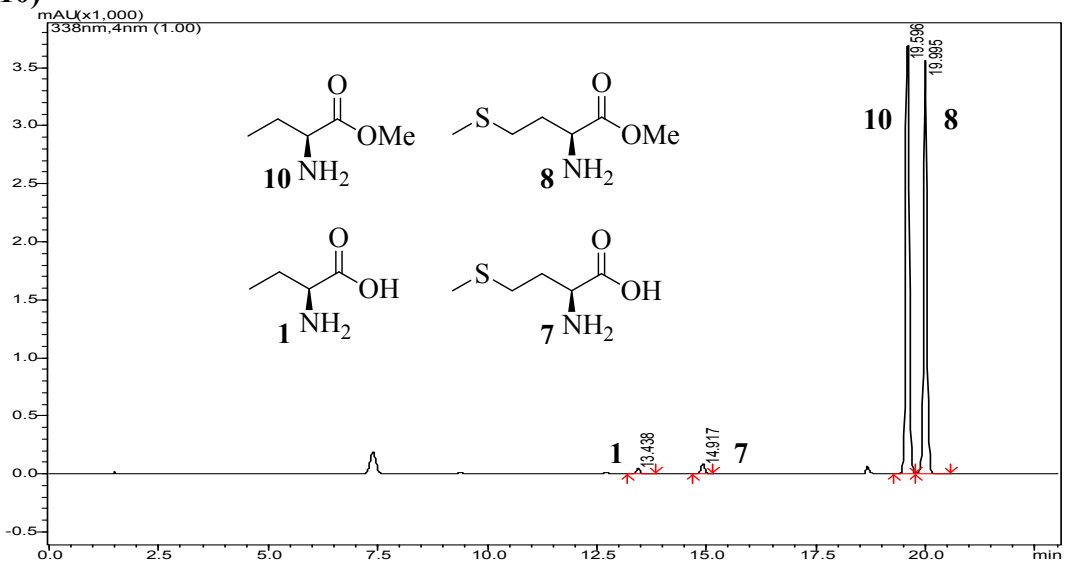
3. CHROMATOGRAPHIC DATA

3.1. Chromatograms for reaction conversions

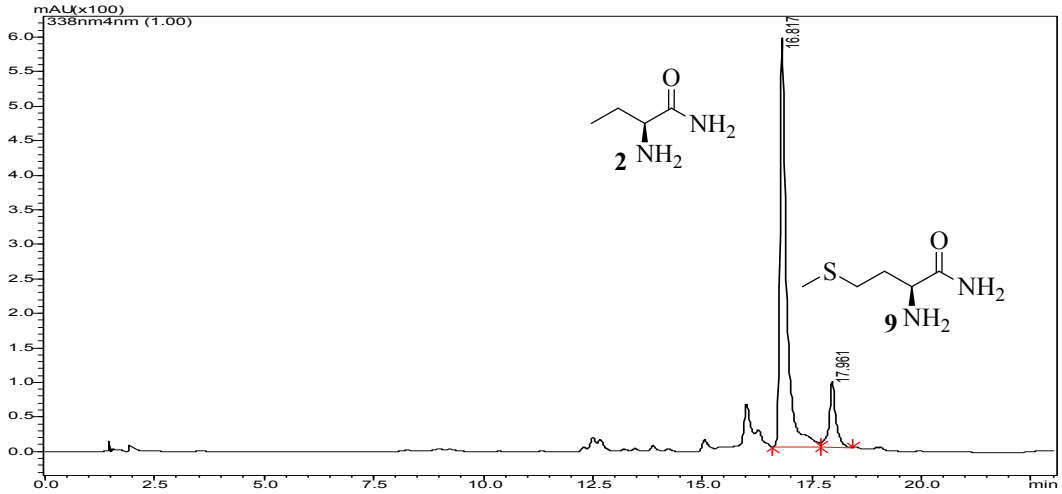
3.1.1. Conversion L-methionine (7) into 2-amino-butanoic acid (1)



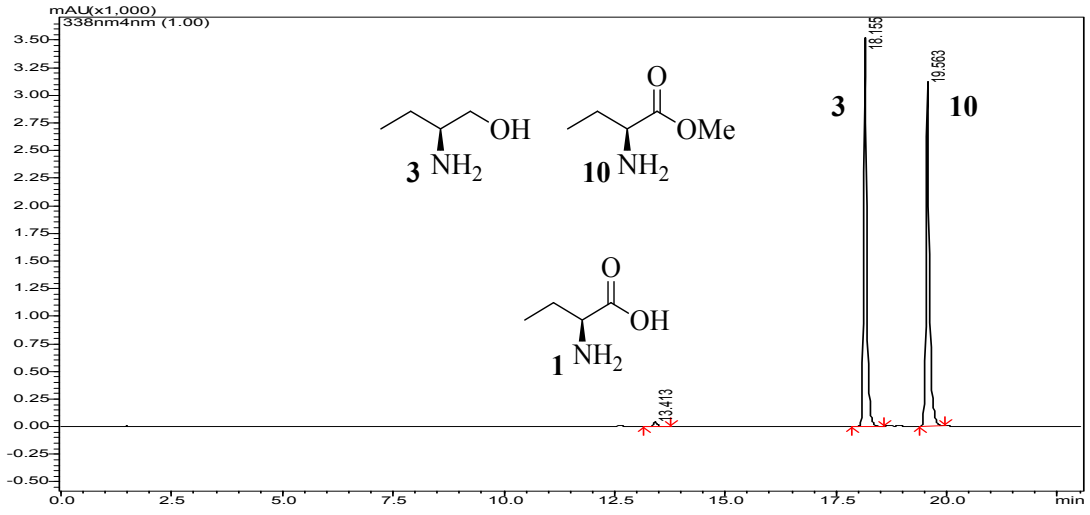
3.1.2. Conversion L-methionine methyl ester (8) into methyl 2-amino-butanoate (10)



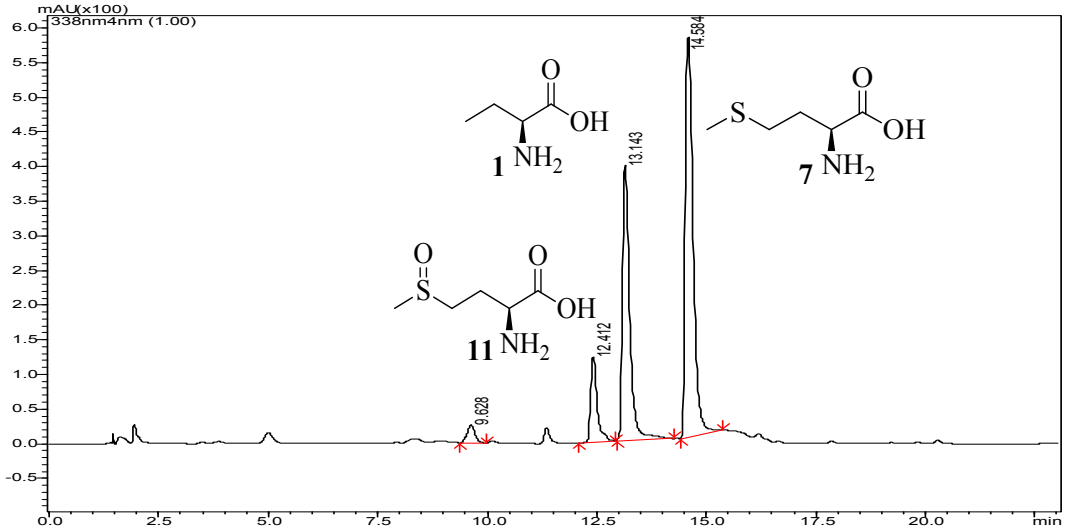
3.1.3. Conversion L-methionamide (9) into 2-amino-butanamide (2)



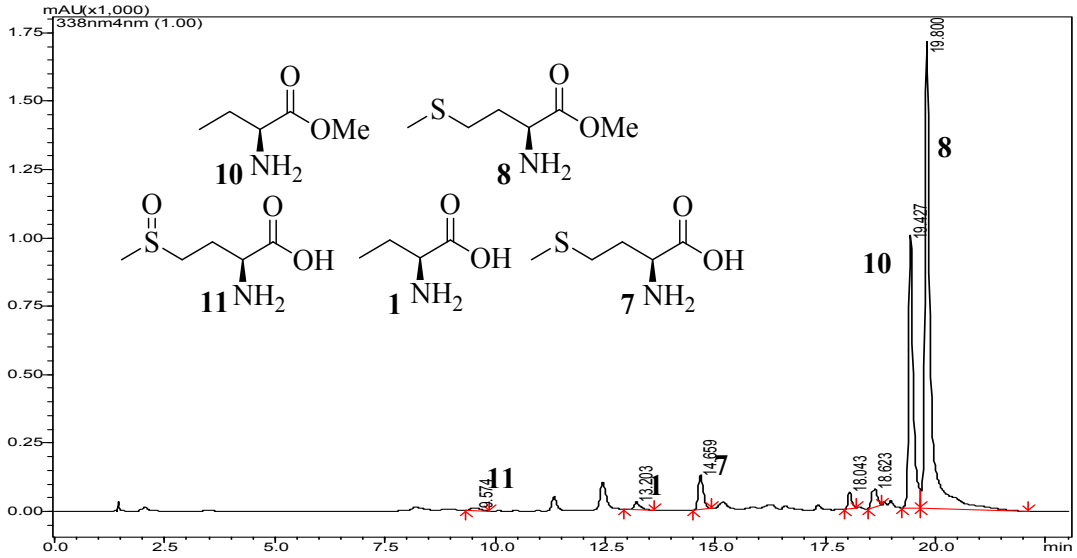
3.1.4. Preparation of *S*-2-amino-butan-1-ol (3)



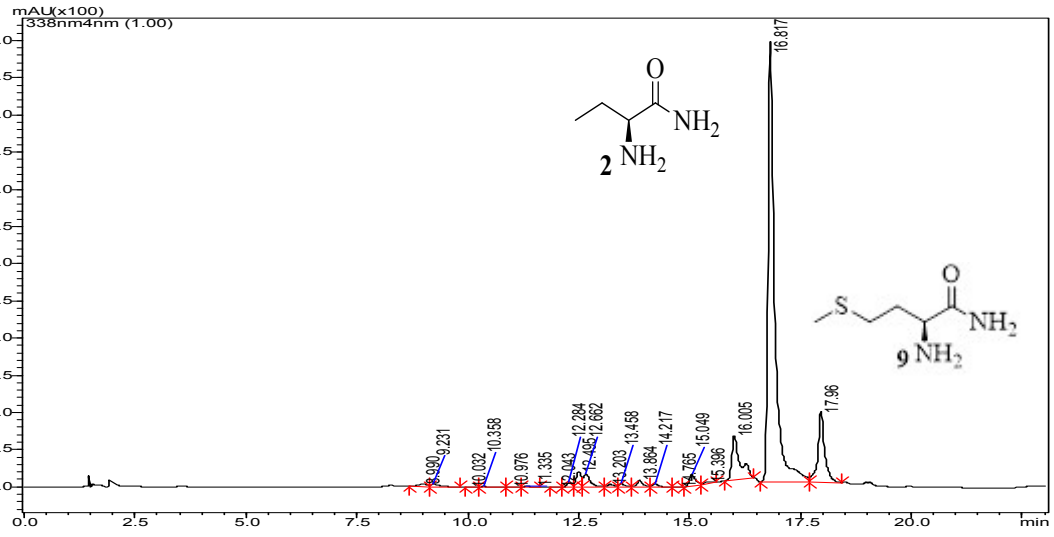
3.1.5. Photodesulfurization of L-methionine (10) (6 mM, H_2O:MeOH 1:4)



3.1.6. Photodesulfurization of L-methionine methyl ester (8) (6mM, methanol)

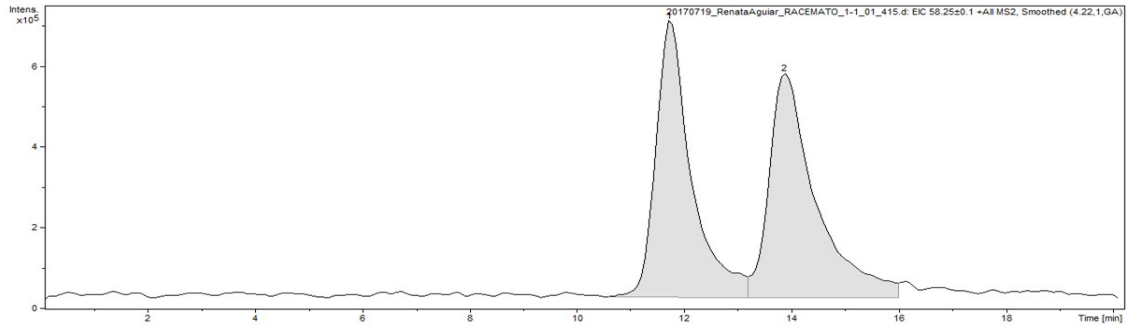


3.1.7. Photodesulfurization of L-methionamide (3) (6 mM, methanol)

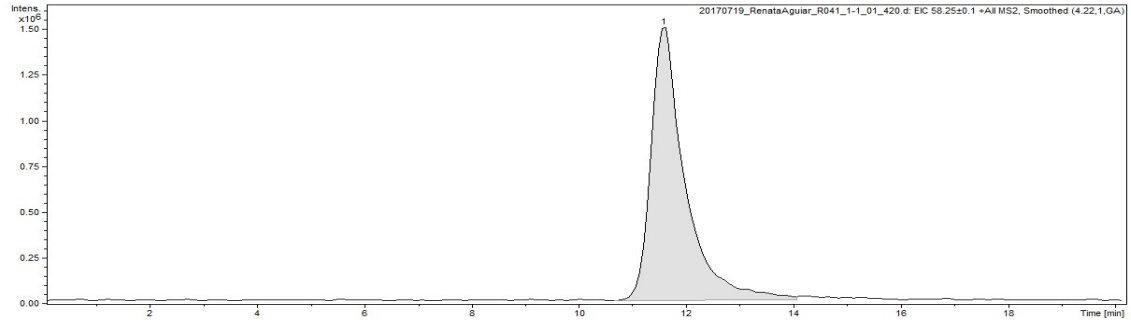


3.2. HPLC Chiral Chromatograms

3.2.1. Chromatogram from 2-amino-butanoic acid (1) (Racemate)

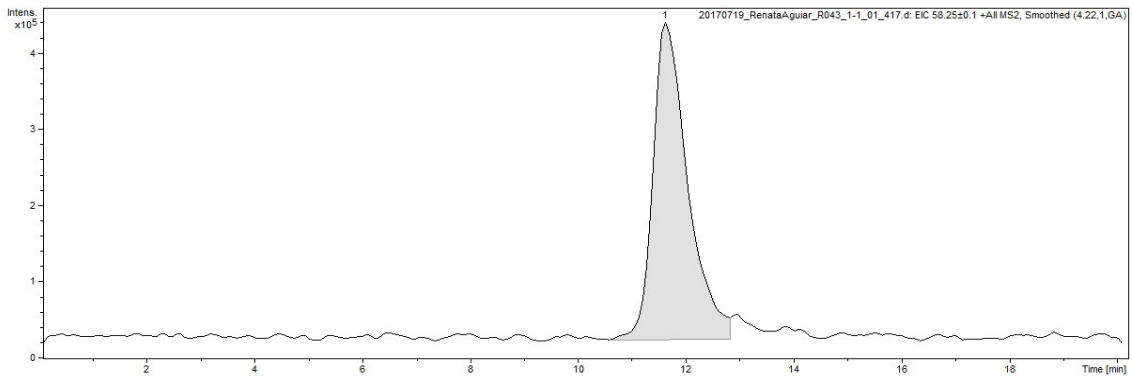


3.2.2. Chromatogram from 2-amino-butanoic acid (1) prepared with Nickel Raney



3.2.3. Chromatogram from 2-amino-butanoic acid (1) prepared with Pd/C and 40 bar hydrogen

3.2.3. Chromatogram from 2-amino-butanoic acid (1) prepared with Pd/C and 80 bar hydrogen

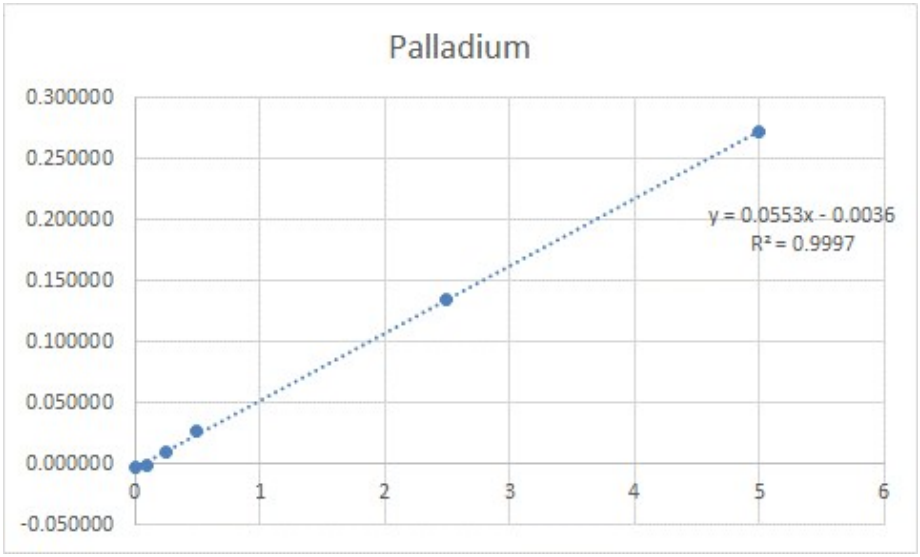


4. Residual Metal Analysis (Atomic Absorption Spectrometry)

4.1. Palladium

A calibration curve was performed using a $PdCl_2$ solution:

Conc. (mg/L)	Result
0	-0.002850
0.1	-0.001150
0.25	0.009728
0.5	0.027058
2.5	0.134650
5	0.272790

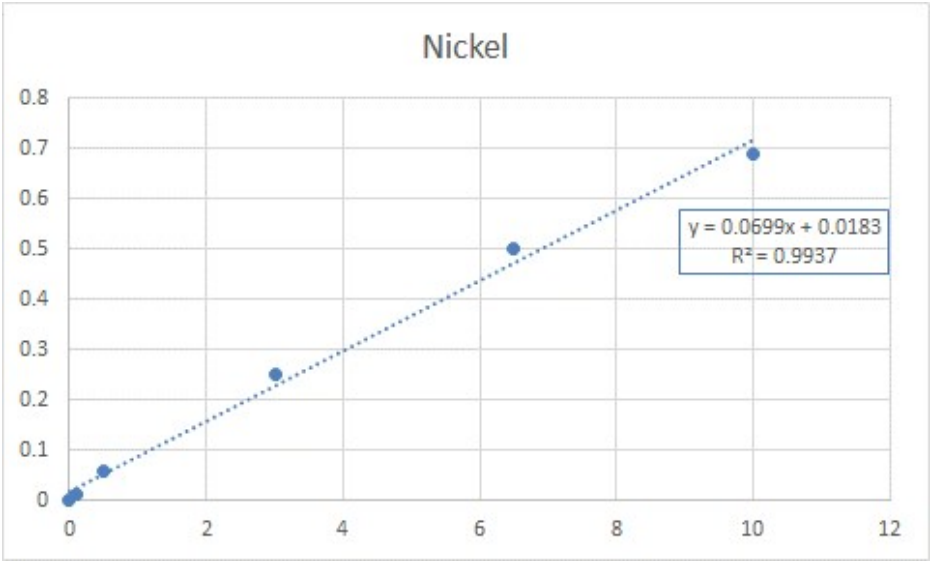


The palladium content in (*S*)-2-amino-butyric acid (**1**) was 70 ppm in the isolated product.

4.2. Nickel

A calibration curve was performed using a $NiCl_2$ solution:

Conc. (mg/L)	Result
0	0.0009
0.1	0.01084
0.5	0.05946
3	0.24989
6.5	0.50246
10	0.69100



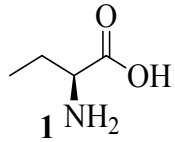
The nickel content in the (*S*)-2-amino-butyric acid (**1**) was 135 ppm in the isolated product.

5. SPECTRA DATA

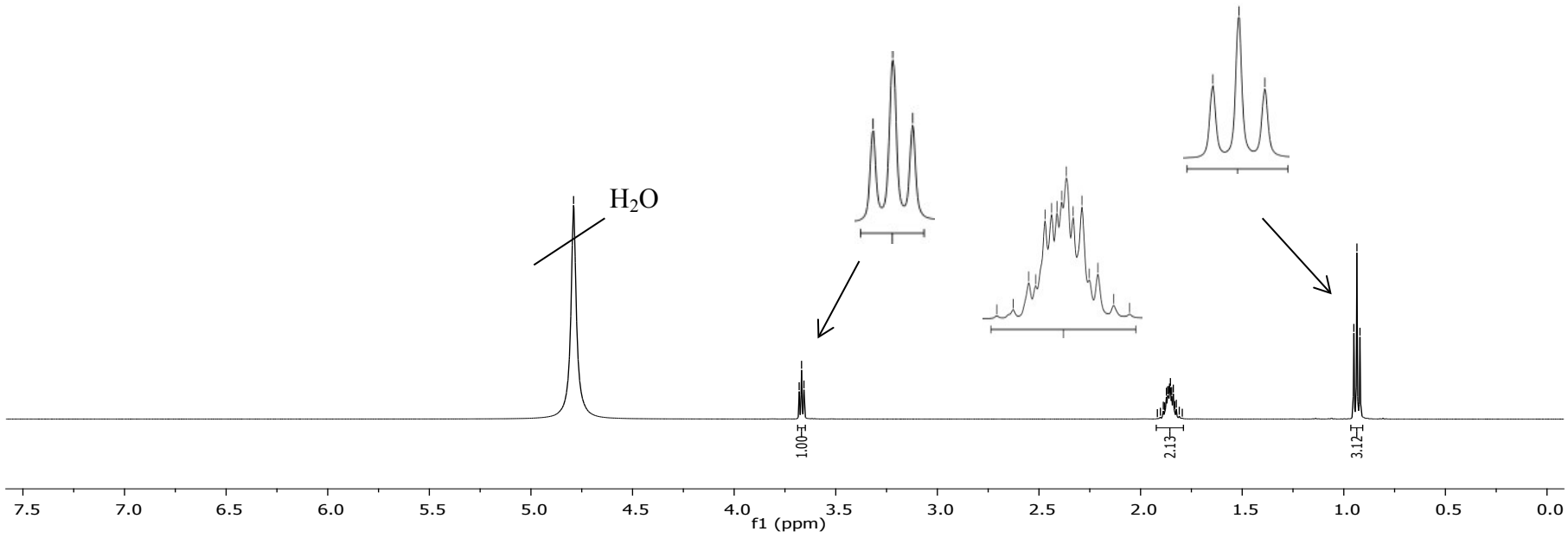
4.1. ^{1}H and ^{13}C NMR

5.1.1. 2-amino-butanoic acid (1)[5]

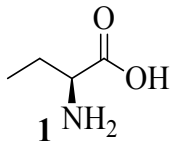
^{1}H NMR (500 MHz, D_2O) δ 0.94 (t, J = 7.5 Hz, 3H), 1.92 – 1.79 (m, 2H), 3.67 (t, J = 5.9 Hz, 1H).



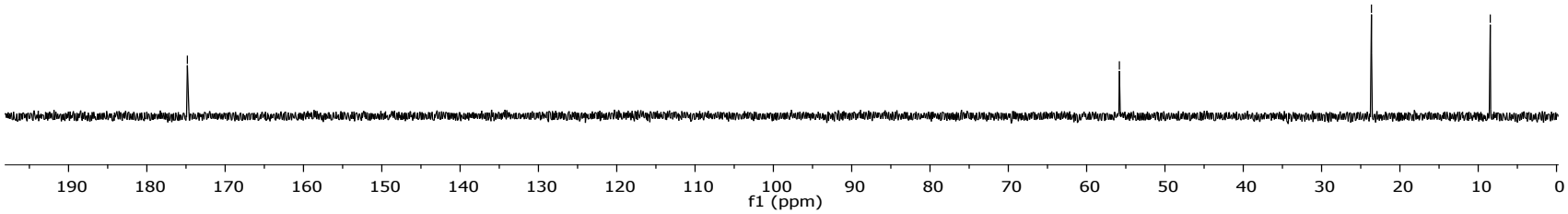
1



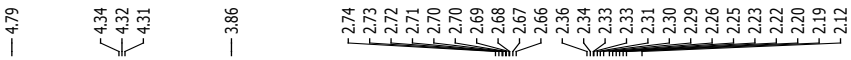
^{13}C NMR (126 MHz, D_2O) δ 8.46, 23.61, 55.82, 174.83 (C=O).



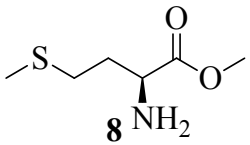
1



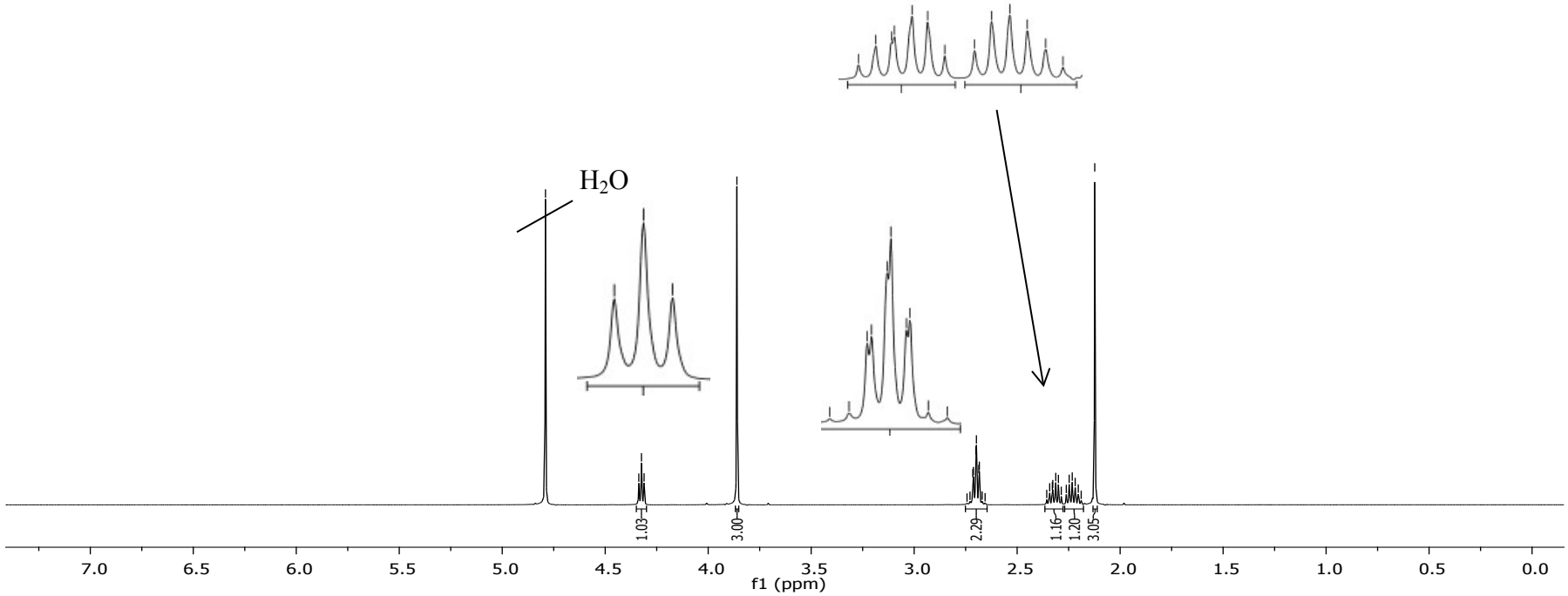
5.1.2. L-Methionine Methyl Ester (8)[6]



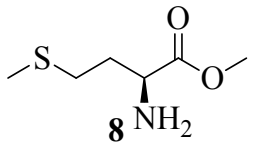
^{1}H NMR (500 MHz, D_2O) δ 2.12 (s, 3H), 2.23 (td, *J* = 14.5, 7.0 Hz, 1H), 2.36 – 2.29 (m, 1H), 2.74 – 2.66 (m, 2H), 3.86 (s, 3H), 4.32 (t, *J* = 6.4 Hz, 1H).



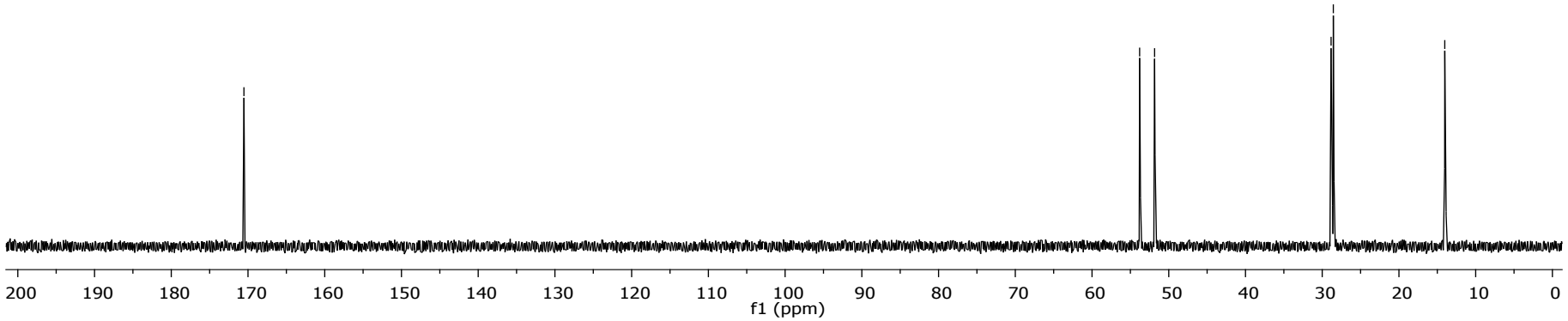
8



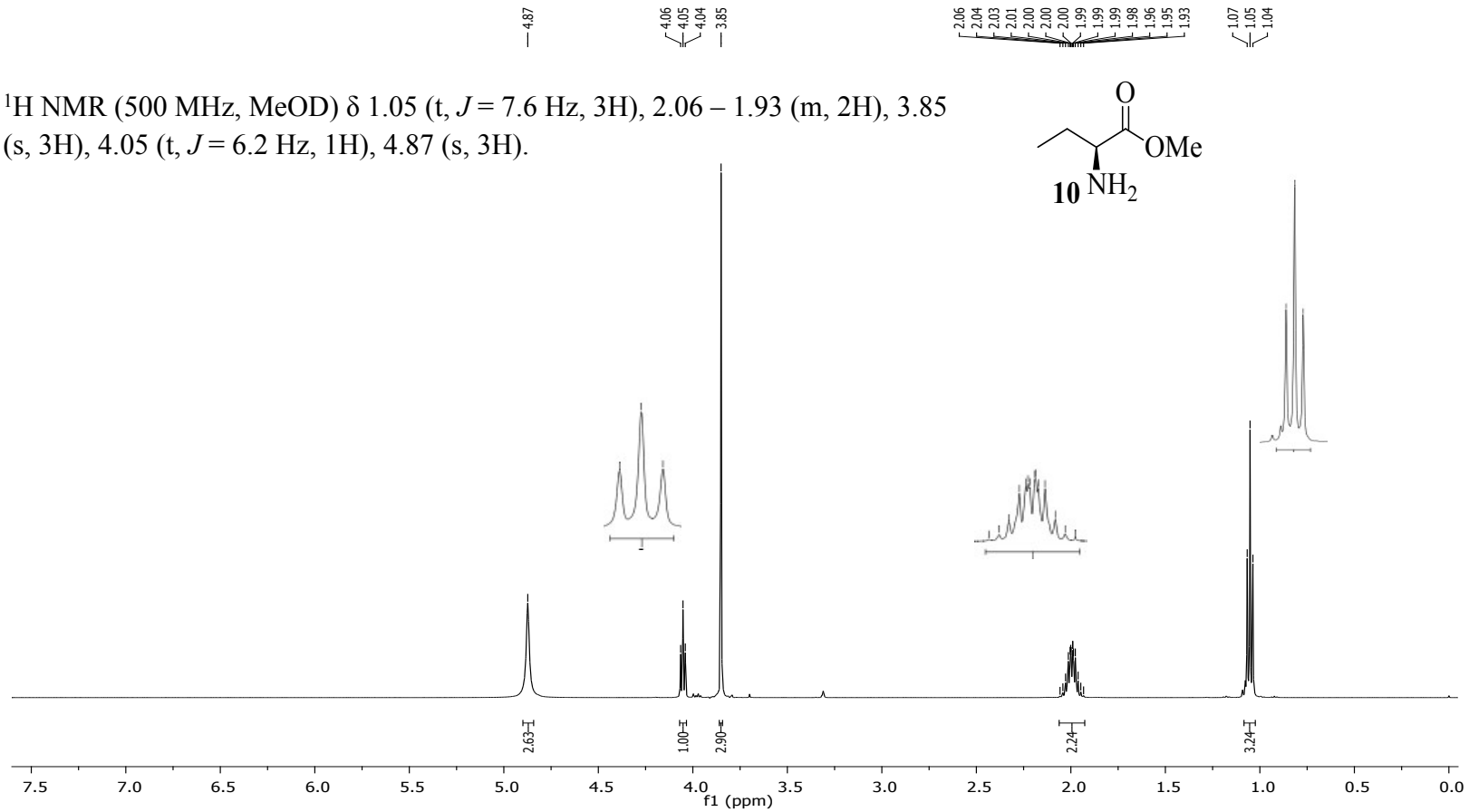
^{13}C NMR (126 MHz, D_2O) δ 14.03, 28.55, 28.84, 51.85, 53.80,170.53 (C=O).



8



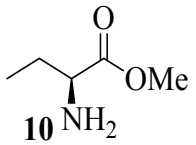
5.1.3. Methyl (*S*)-2-amino-butanoate (10) [7]



^{1}H NMR (500 MHz, MeOD) δ 1.05 (t, *J* = 7.6 Hz, 3H), 2.06 – 1.93 (m, 2H), 3.85 (s, 3H), 4.05 (t, *J* = 6.2 Hz, 1H), 4.87 (s, 3H).

10

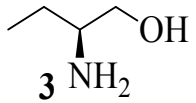
^{13}C NMR (126 MHz, MeOD) δ 8.32, 23.44, 52.33, 53.79, 169.54 (C=O).



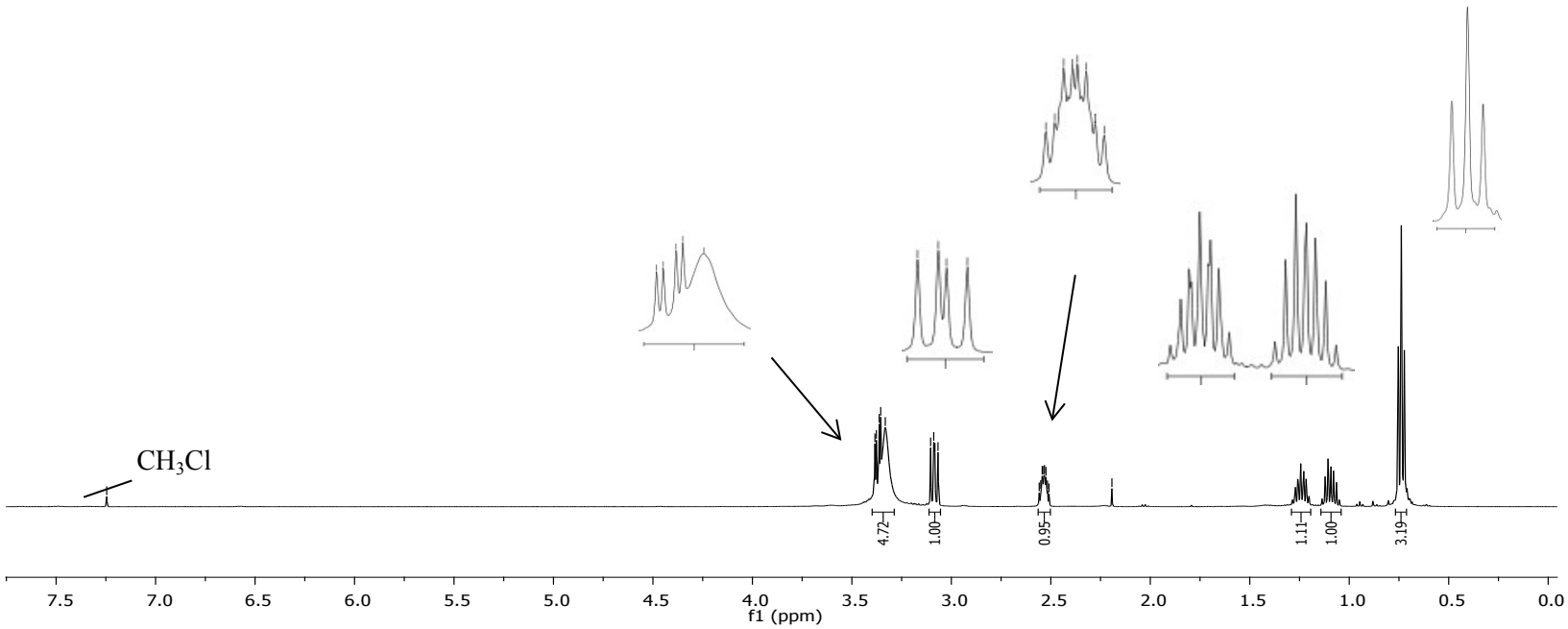
10

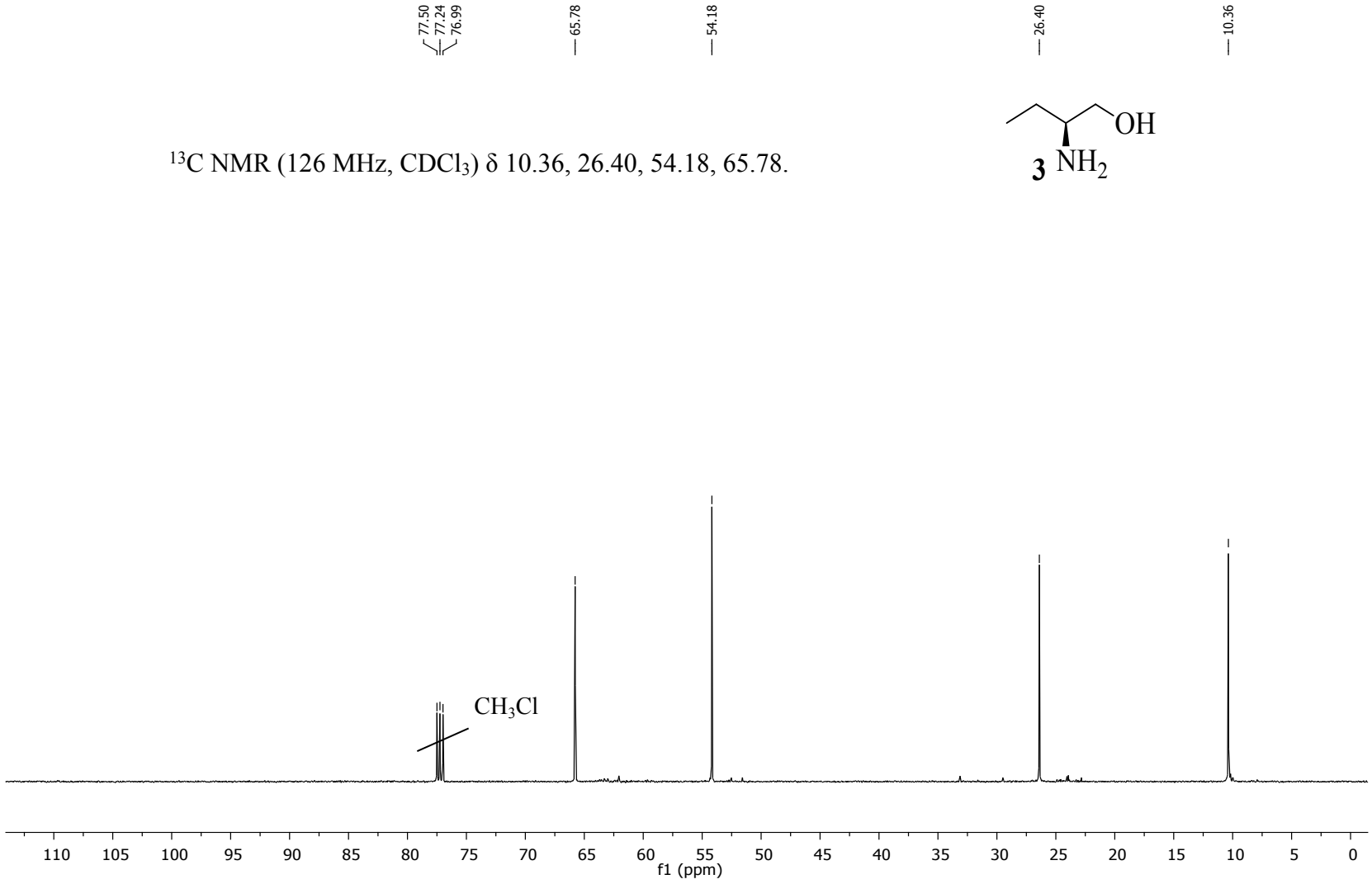
5.1.4. (*S*)-2-aminobutan-1-ol (3)[8]

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (dt, *J* = 5.4, 4.9 Hz, 3H), 1.14 – 1.04 (m, 1H), 1.29 – 1.19 (m, 1H), 2.53 (ddd, *J* = 13.3, 7.6, 3.8 Hz, 1H), 3.09 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.40 – 3.29 (m, 5H).



3



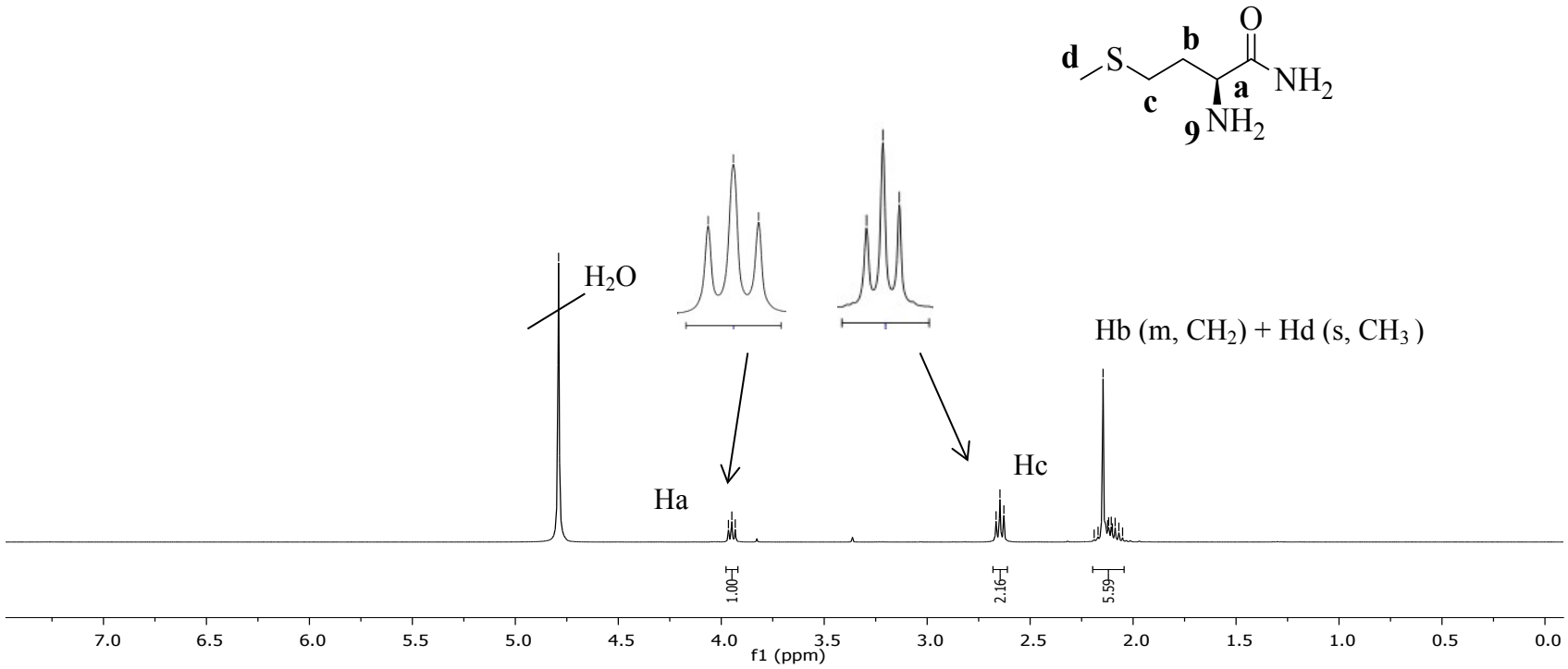


^{13}C NMR (126 MHz, $CDCl_3$) δ 10.36, 26.40, 54.18, 65.78.

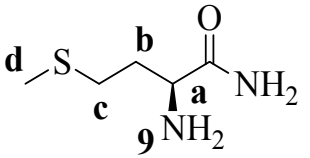
3

5.1.5. L-Methionamide (9)[9]

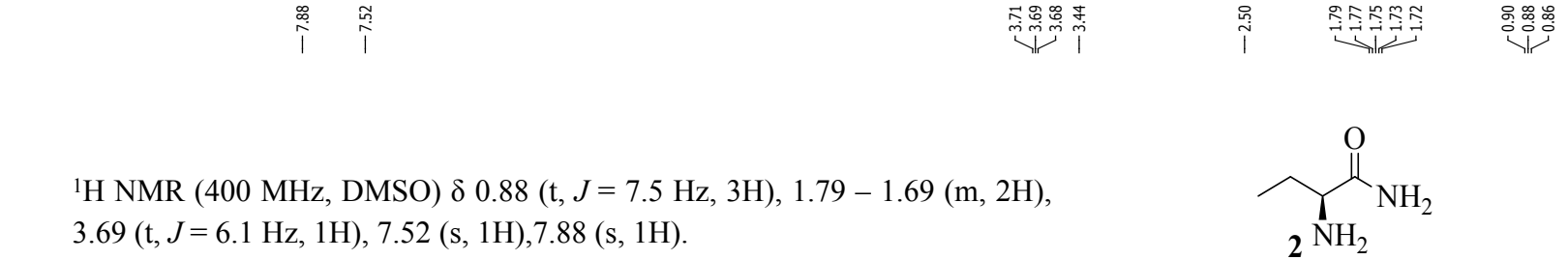
^{1}H NMR (400 MHz, D_2O) δ 2.19 – 2.05 (m, 5H), 2.65 (t, J = 7.6 Hz, 2H), 3.95 (t, J = 6.6 Hz, 1H).



^{13}C NMR (101 MHz, D_2O) δ 14.05, 28.62, 31.29, 52.60, 174.72 (C=O).

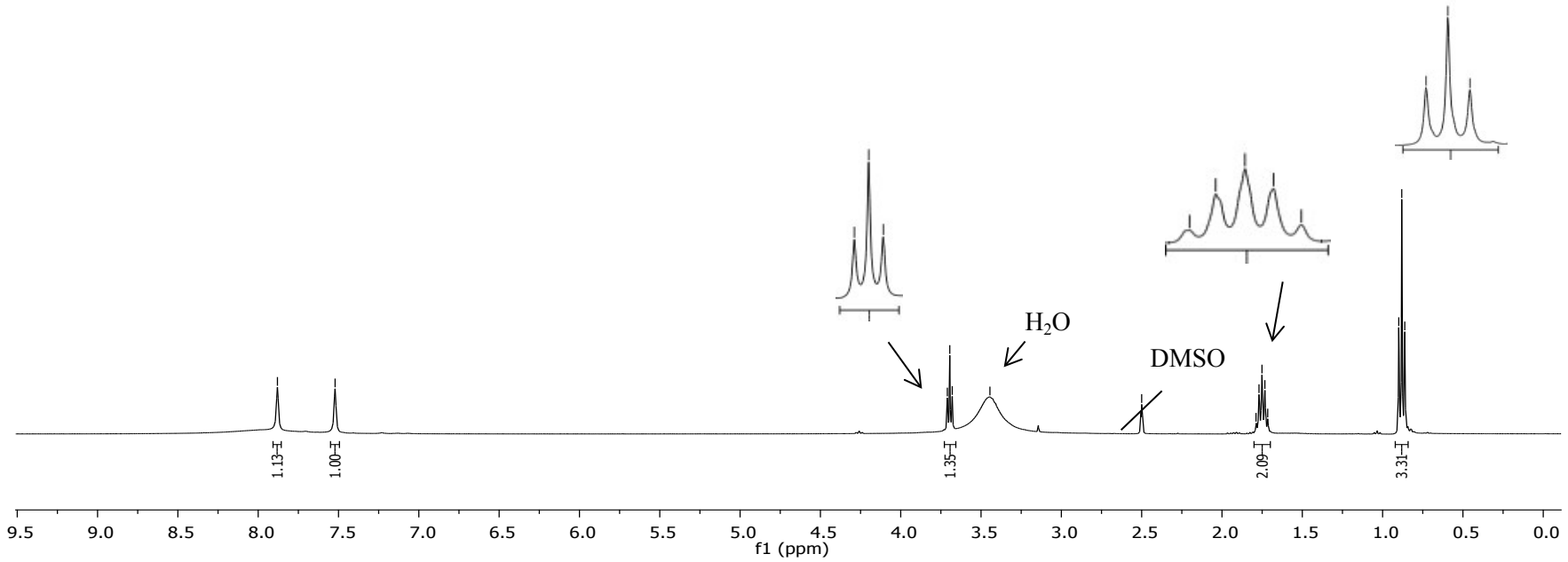


5.1.6. 2-Amino-butanamide (2)[10]

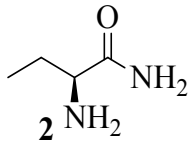


^{1}H NMR (400 MHz, DMSO) δ 0.88 (t, *J* = 7.5 Hz, 3H), 1.79 – 1.69 (m, 2H), 3.69 (t, *J* = 6.1 Hz, 1H), 7.52 (s, 1H),7.88 (s, 1H).

2

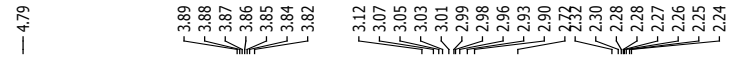


^{13}C NMR (101 MHz, DMSO) δ 9.04, 24.22, 53.22,170.34 (C=O).

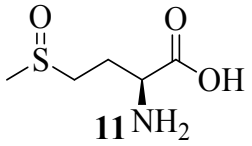


2

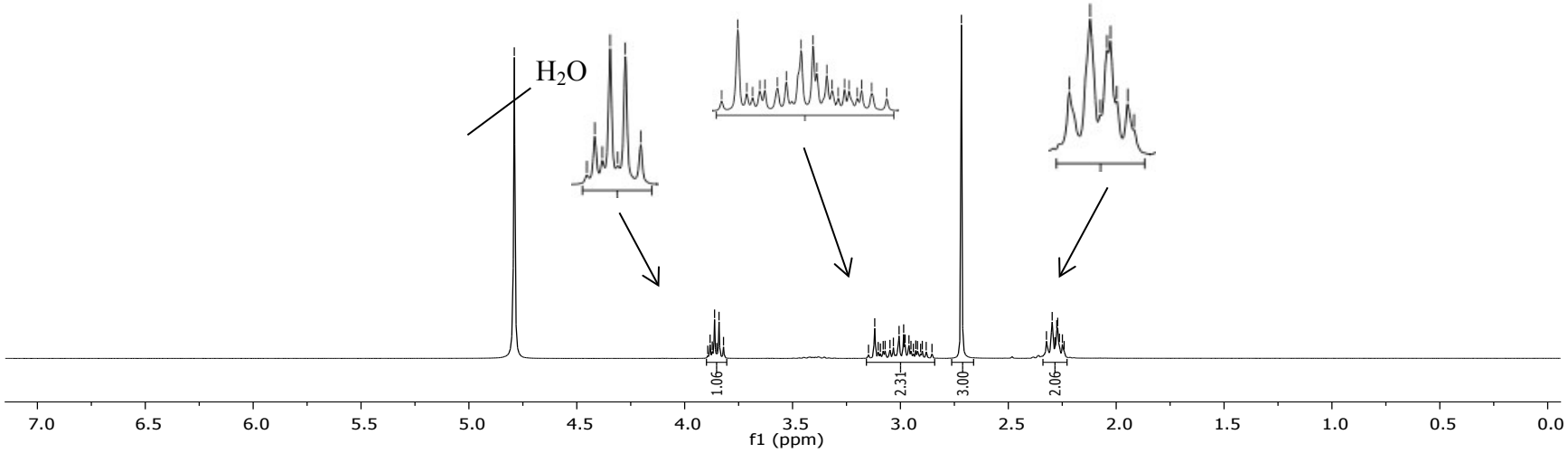
5.1.7. L-Methionine Oxide (11)[11]



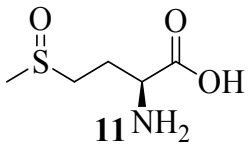
^{1}H NMR (300 MHz, D_2O) δ 2.32 – 2.24 (m, 2H), 2.72 (s, 3H), 3.15 – 2.85 (m, 2H), 3.90 – 3.82 (m, 1H).



11



^{13}C NMR (75 MHz, D_2O) δ 23.80, 36.48, 48.29, 53.39, 173.28 (C=O).



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