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Synthesis of chiral *N*-trifluoroacetyl-methionine derivatives and applying them as acyl donors for Friedel-Crafts acylation

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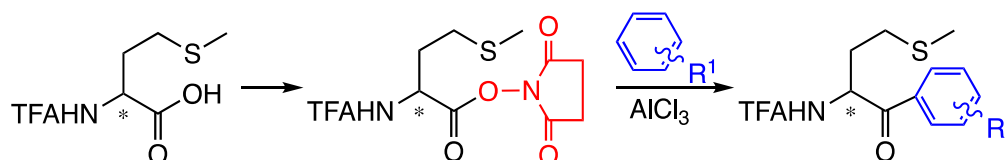
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Abstract

A chiral *N*-protected α -amino acid *N*-hydroxysuccinimide ester (OSu) is a common useful reagent for peptide bond formation. Recently, *N*-trifluoroacetyl (TFA) α -amino acid OSu esters have been reported as acyl donors for Friedel–Crafts reactions to synthesize chiral α -amino phenyl ketones retaining the configurations of the starting α -amino acids. There are few reports for chiral TFA protected methionine, which has methylthioethyl structure in the side-chain of the α -amino acid. The detailed synthesis of chiral TFA-Met-OSu and its application as an acyl donor for Friedel–Crafts acylation is reported.



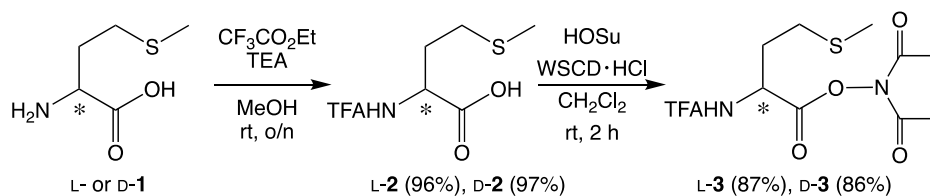
Keywords: Trifluoroacetamide, α -amino acid, *N*-hydroxysuccinimide ester, Friedel–Crafts acylation, α -amino phenyl ketone

Introduction

Chiral *N*-protected α -amino aryl-ketones are often used as precursors in the synthesis of various biologically active compounds.^{1,2} The most favourable strategy to synthesize α -amino aryl-ketone is by Friedel–Crafts acylation³ of arenes, which is known as a reliable method that results in satisfactory product yields⁴ and can utilize convenient optically pure α -amino acid derivatives as skeletons.⁵ *N*-Hydroxysuccinimide ester (OSu) derivatives of α -amino acids have high storage stability⁶ and have sufficient reactivity with amines under moderate conditions for peptide synthesis.⁷ This utility indicated that α -amino acid OSu derivatives may act as acyl donors for Friedel–Crafts reactions. Protecting groups for the *N*-terminal are one of the important factors to achieve the reactions. The Boc protecting group, which is commonly used for peptide formation in the solid phase, is unstable in the presence of a Lewis acid. Fmoc and Z protecting groups, which are stable under acidic condition, react easily as acyl acceptors in the Friedel–Crafts acylation. Acetyl protecting group sometimes promote racemization during the reaction. The trifluoroacetyl group, which is moderately stable in acid conditions and easily deprotected under alkaline conditions, is one of the most suitable amine protecting groups for Friedel–Crafts acylation.⁸ Methionine, which has methylthioethyl structure in the side-chain, would afford very rare structures, chiral α -amino α -methylthioethyl phenyl ketones, from Friedel–Crafts acylation, but only few examples of the synthesis of TFA protected methionine derivatives, including both *L*- and *D*-isomers, have been reported. The detailed synthesis of TFA-Met derivatives and application of them for Friedel–Crafts acylations are reported in this paper.

Results and Discussion

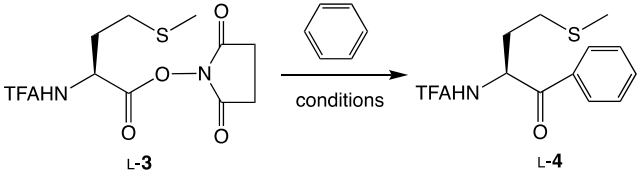
There are several methods for trifluoromethylation of chiral *L*-methionine **L-1** by *S*-ethyl trifluoroacetate/NaOH,⁹ methyl trifluoroacetate/1,1,3,3-tetramethylguanidine¹⁰ and trifluoroacetic anhydride/trifluoroacetic acid.¹¹ Ethyl trifluoroacetate is utilized commonly as a trifluoroacetylating reagent with various bases, sodium methoxide, potassium methoxide¹² and triethylamine.¹³ Triethylamine is an easier base to handle than the metal methoxides, however the paper¹³ did not give details of the synthesis (chemical yield, optical rotation, etc.). Furthermore, trifluoromethylation of *D*-methionine (**D-1**) has not been reported. Chiral methionine *L*/*D*-**1** were separately subjected to trifluoroacetylation with ethyl trifluoroacetate (1.3 eq) and triethylamine (1.5 eq) in methanol at rt to afford chiral TFA-Met-OH *L*- and *D*-**2** in near quantitative yields. The optical rotation of the *L*- and *D*-isomers of TFA-Met-OH was found to be +30.0 and -30.0 in CHCl₃, respectively. To date, an *N*-hydroxysuccinimide ester of chiral TFA-Met had not been reported. Chiral TFA-Met-OH and *N*-hydroxysuccinimide (1.6 eq) were reacted with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl, 1 eq) at rt in CH₂Cl₂ to afford chiral TFA-Met-OSu *L*/*D*-**3** with good yields (Scheme 1).



Scheme 1. Synthesis of chiral TFA-Met-OSu (*L*- and *D*-**3**).

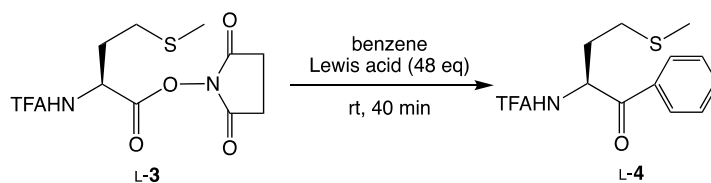
It has been reported that chiral TFA- α -amino acid-OSu was subjected to Friedel–Crafts acylation with AlCl_3 (3 eq) in benzene at 70 °C afforded TFA- α -amino acid-Ph with moderate yield.⁸ The chirality of the amino acid skeleton was retained during the reaction using four isoleucine isomers (L- and D-isoleucine and L- and D-allo-isoleucine). Similarly, TFA-L-Met-OSu **L-3** was treated under the identical conditions (AlCl_3 , 3 eq, 70 °C, 120 min) for Friedel–Crafts acylation to afford TFA-Met-Ph **L-4** but in less than 10% yield (Table 1, Entry 1). Improvement of chemical yield of **L-4** was observed by increasing the amount of AlCl_3 (Table 1 Entry 2). A lower temperature (40 °C and rt) with six equivalents of AlCl_3 also improved the chemical yield (Table 1, Entries 3 and 4). Detailed analysis indicated that the reaction time can be shortened to 40 minutes at rt. Changing the amount of acyl acceptor did not improve the selectivity (Table 1, entries 4, 5, 8 and 9). Increasing the amount of AlCl_3 at rt improved the chemical yield of Friedel–Crafts acylation. Finally, 48 equivalents of AlCl_3 afforded 84% of **L-4** selectively at rt (Table 1, entry 10). The large excess of AlCl_3 required for the Friedel–Crafts acylation to give TFA-L-Met-Ph **L-4** might be due to coordination of the AlCl_3 to the lone pairs of the starting material **L-3**. TFA-D-Met-OSu **D-3** was also reacted in benzene with established condition to afford TFA-D-Met-Ph **D-4** in good yield.

Table 1. Friedel-Crafts acylation of TFA-Met-OSu **L-3** with benzene

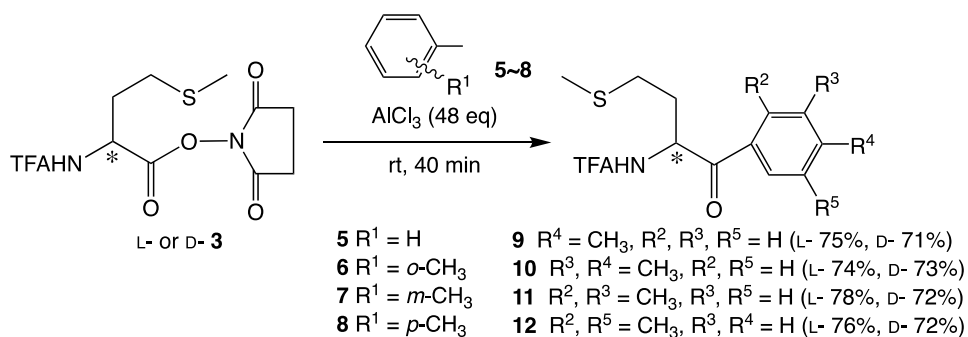


Entry	Temp (°C)	AlCl_3 (eq)	Time (min)	benzene (mL)	Yield (%)
1	70	3	120	4.5	10
2	70	6	120	4.5	31
3	40	6	120	4.5	40
4	40	6	40	4.5	48
5	40	6	40	18	43
6	40	12	40	18	57
7	rt	24	40	18	71
8	rt	36	40	4.5	72
9	rt	36	40	18	74
10	rt	48	40	18	84

In Table 2, Lewis acids were screened for Friedel–Crafts acylation utilizing TFA-L-Met-OSu **L-4**. In the presence of 48 equivalents of Lewis acid, AlCl_3 is superior for conducting the reaction compared with AlBr_3 , GaCl_3 , GaBr_3 , TiCl_3 , TiBr_4 and FeCl_3 . Other Lewis acids did not afford a Friedel–Crafts acylated product (Table 2).

Table 2. Screening of Lewis acid for the Friedel-Crafts acylation of L-3 with benzene

Lewis acid	L-4 Yield (%)	Lewis acid	L-4 Yield (%)
AlCl ₃	84	SnCl ₄	0
AlBr ₃	65	ZnCl ₂	0
GaCl ₃	57	ZrCl ₄	9
GaBr ₃	16	InCl ₃	0
TiCl ₄	17	InBr ₃	0
TiBr ₄	19	FeCl ₃	14

**Figure 2.** Friedel-Crafts acylation of various aromatics with TFA-Met-OSu (L- or D-3).

Chiral TFA-Met-OSu L- and D-3 were used for Friedel–Crafts acylation of several aromatics. Reaction with toluene (5) afforded an acyl product mainly at the *p*-position (9) with respect to the methyl group. Main products from xylenes (6–8) are based on the orientations of methyl substitutions. There is no big difference for the reactivity between chiral centers. Other isomers 9, 10 and 11 were detected less than 5% by NMR analysis.

Conclusions

Synthetic details of chiral trifluoroacetyl protected methionine and their *N*-hydroxysuccinimide derivatives are reported. These derivatives are utilized as acyl donor for Friedel–Crafts acylation to form α -trifluoroacetamide α -methylthioethyl phenyl ketone derivatives in good yields. Excess amounts of Lewis acid are needed to perform Friedel–Crafts acylation due to coordination between the Lewis acid and the lone pairs of TFA-methionine derivatives. These derivatives of methionine will be utilized not only for peptide and protein chemistry but also for other thioether chemistry in further work.

Experimental Section

General. All reagents used were analytical grade. FTIR spectra were recorded on a FT-IR 4100 spectrometer (JASCO, Tokyo, Japan). NMR spectra were measured by a EX 270 spectrometer (JEOL, Tokyo, Japan). Optical rotations were measured at 23 °C on a JASCO DIP370 polarimeter (JASCO, Tokyo, Japan). HRMS-ESI spectra were obtained with a Waters UPLC ESI-TOF mass spectrometer (Waters, Milford, CT, USA).

(S)-6-(Methylthio)-2-(2,2,2-trifluoroacetamido) hexanoic acid (L-2). To L-methionine L-1 (500 mg, 3.35 mmol) in dry MeOH (1.68 mL), Et₃N (508 mg, 5.03 mmol) was added at rt. After the reaction mixture was stirred for 15 min at rt, ethyl trifluoroacetate (619 mg, 4.36 mmol) was slowly added at same temperature. The reaction mixture was stirred overnight at rt. After H₂O (100 mL) and 12 M HCl (4 mL) were added, the reaction mixture was stirred 15 min at rt. The reaction mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was precipitated by petroleum ether to give a colorless solid (791 mg, 79 %). ¹H-NMR (270 MHz, CDCl₃) δ: 4.81 (1H, dd, *J* 12.5, 7.3 Hz), 2.60 (2H, m), 2.28 (2H, m), 2.13 (3H, s). ¹³C-NMR (67.8 MHz, CDCl₃) δ: 174.9, 157.4 (q, ²*J*_{CF} 38.2 Hz), 115.5 (q, ¹*J*_{CF} 289.4 Hz), 51.9, 30.0, 29.7, 15.2. [α]_D +30.0 (c 1.0, CHCl₃). HRMS-ESI (*m/z*) [M+H]⁺ calcd for C₇H₁₁F₃NO₃S⁺ 246.0406, found 246.0415.

Compound D-2 was obtained from D-methionine D-1 in the same manner as L-2 (97 %). ¹H-NMR (270 MHz, CDCl₃) δ: 4.81 (1H, dd, *J* 12.4, 7.1 Hz), 2.59 (2H, m), 2.28 (2H, m), 2.11 (3H, s). ¹³C-NMR (CDCl₃) δ: 174.8, 157.8 (q, ²*J*_{CF} 37.6 Hz), 115.9 (q, ¹*J*_{CF} 287.3 Hz), 52.4, 30.4, 30.1, 15.5. [α]_D -30.0 (c 1.0, CHCl₃). HRMS-ESI (*m/z*) [M+H]⁺ calcd for C₇H₁₁F₃NO₃S⁺ 246.0406, found 246.0392.

2,5-Dioxopyrrolidin-1-yl (S)-6-(methylthio)-2-(2,2,2-trifluoroacetamido)hexanoate (L-3). To TFA-L-methionine L-2 (200 mg, 0.816 mmol) and *N*-hydroxysuccinimide (156.4 mg, 1.36 mmol) in dry CH₂Cl₂ (8.2 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, hydrochloride (WSCD·HCl, 156.4 mg, 0.816 mmol) in dry CH₂Cl₂ (8.2 mL) was added on ice. The reaction mixture was stirred 2 at rt and partitioned between water and CH₂Cl₂. The organic layer was washed with brine, NaHCO₃, and brine, dried over MgSO₄, filtered and concentrated. The residue was precipitated by petroleum ether to give colorless solid (242 mg, 87 %). ¹H-NMR (270 MHz, CDCl₃) δ: 7.56 (1H, br s), 5.18 (1H, dd, *J* 13.2, 6.9 Hz), 2.84 (4H, s), 2.68 (2H, m), 2.30 (2H, m), 2.11 (3H, s). ¹³C-NMR (67.8 MHz, CDCl₃) 168.8, 166.3, 157.0 (q, ²*J*_{CF} 38.0 Hz), 115.4 (q, ¹*J*_{CF} 288.3 Hz), 50.3, 30.4, 29.4, 25.5, 15.1. [α]_D -13.0 (c 1.0, CHCl₃). HRMS-ESI (*m/z*) [M+Na]⁺ calcd for C₁₁H₁₃F₃N₂NaO₅S⁺ 365.0389, found 365.0381.

Compound D-3 was obtained from D-2 in the same manner as L-3 (86 %). ¹H-NMR (270 MHz, CDCl₃) δ: 7.65 (1H, br s), 5.12 (1H, dd, *J* 12.9, 7.3 Hz), 2.79 (4H, s), 2.63 (2H, m), 2.26 (2H, m), 2.07 (3H, s). ¹³C-NMR (67.8 MHz, CDCl₃) δ: 168.6, 166.4, 157.0 (q, ²*J*_{CF} 38.0 Hz), 115.5 (q, ¹*J*_{CF} 288.8 Hz), 50.3, 30.5, 29.4, 25.5, 15.2. [α]_D +13.0 (c 1.0, CHCl₃). HRMS-ESI (*m/z*) [M+Na]⁺ calcd for C₁₁H₁₃F₃N₂NaO₅S⁺ 365.0389, found 365.0387.

(S)-2,2,2-Trifluoro-*N*-(6-(methylthio)-1-oxo-1-phenylhexan-2-yl) acetamide (L-4). To TFA-L-methionine-OSu L-3 (57.5 mg, 0.168 mmol) in benzene (4.5 mL, 1.01 mmol), AlCl₃ (1.07 g, 8.02 mmol) was added at rt. The reaction mixture was stirred 40 min at rt and partitioned between water and EtOAc. The organic layer was washed with H₂O, NaHCO₃, and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography (EtOAc: n-hexane, 1:1) to give colorless solid (43.2 mg, 84 %). ¹H-NMR (270 MHz, CDCl₃) δ: 7.94 (2H, d, *J* 7.6 Hz), 7.57 (2H, t, *J* 7.6 Hz), 7.44 (2H, t, *J* 7.6 Hz), 5.72 (1H, td, *J* 7.6, 4.0 Hz), 2.43 (2H, m), 2.21 (1H, m), 1.94 (3H, s), 1.87 (1H, m). ¹³C-NMR (67.8 MHz, CDCl₃) δ: 196.3, 156.9 (q, ²*J*_{CF} 36.9 Hz), 134.5, 133.3, 129.0, 128.7, 115.7 (q, *J* 288.8 Hz), 53.6, 32.4, 29.8, 15.40. [α]_D +27.0 (c 1.0, CHCl₃). HRMS-ESI (*m/z*) [M+Na]⁺ calcd for C₁₃H₁₄F₃NNaO₂S⁺ 328.0590, found 328.0604.

Compound **D-4** was obtained from **D-3** in the same manner as **L-4** (83 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.94 (2H, d, J 7.4 Hz), 7.57 (1H, t, J 7.4 Hz), 7.44 (2H, t, J 7.4 Hz), 5.72 (1H, td, J 7.7, 3.8 Hz), 2.43 (2H, m), 2.23 (1H, m), 1.94 (3H, s), 1.87 (1H, m). $^{13}\text{C-NMR}$ (67.8 MHz, CDCl_3) δ : 196.3, 156.9 (q, $^2J_{\text{CF}}$ 37.6 Hz), 134.5, 133.3, 129.0, 128.7, 115.7 (q, $^1J_{\text{CF}}$ 287.8 Hz), 53.6, 32.4, 29.8, 15.3. $[\alpha]_{\text{D}} -27.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NNaO}_2\text{S}^+$ 328.0590, found 328.0583.

(S)-2,2,2-Trifluoro-N-(4-(methylthio)-1-oxo-1-(*p*-tolyl)butan-2-yl)acetamide (L-9). To TFA-L-methionine-OSu **L-3** (57.5 mg, 0.168 mmol) in toluene (**5**, 5.4 ml, 1.01 mmol), AlCl_3 (1.07 g, 8.02 mmol) was added at rt. The reaction mixture was stirred 40 min at rt and partitioned between water and EtOAc. The organic layer was washed with H_2O , NaHCO_3 , and brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography (EtOAc: hexane = 1: 3) to give pale yellow solid **L-9** (40.1 mg, 75 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.93 (2H, d, J 8.2 Hz), 7.71 (1H, br s), 7.33 (2H, d, J 8.2 Hz), 5.78 (1H, td, J 7.7, 3.7 Hz), 2.60-2.47 (2H, m), 2.44 (3H, s), 2.29 (1H, m), 2.04 (4H, s), 1.95 (1H, m). $^{13}\text{C-NMR}$ (67.8 MHz, CDCl_3) δ : 195.8, 156.9 (q, $^2J_{\text{CF}}$ 37.8 Hz), 145.8, 130.7, 129.7, 128.8, 115.7 (q, $^1J_{\text{CF}}$ 287.5 Hz), 53.5, 32.6, 29.8, 21.7, 15.4. $[\alpha]_{\text{D}} +28.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{F}_3\text{NO}_2\text{S}^+$ 320.0927, found 320.0925.

Compound **D-9** was obtained from **D-3** in the same manner as **L-9** (71 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.92 (2H, d, J 8.2 Hz), 7.58 (1H, br s), 7.34 (2H, d, J 8.2 Hz), 5.75 (1H, td, J 7.5, 4.1 Hz), 2.54 (2H, m), 2.45 (5H, s), 2.35-2.26 (1H, m), 2.04 (3H, s), 1.97 (1H, dd, J 13.8, 5.9 Hz). $^{13}\text{C-NMR}$ (67.8 MHz, CDCl_3) δ : 195.8, 157.0 (q, $^2J_{\text{CF}}$ 37.4 Hz), 145.9, 130.7, 129.9, 128.9, 115.7 (q, $^1J_{\text{CF}}$ 288.3 Hz), 53.5, 32.8, 29.8, 21.8, 15.5. $[\alpha]_{\text{D}} -28.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{F}_3\text{NO}_2\text{S}^+$ 320.0927, found 320.0922.

(S)-N-(1-(3,4-Dimethylphenyl)-4-(methylthio)-1-oxobutan-2-yl)-2,2,2-trifluoroacetamide (L-10). To TFA-L-methionine-OSu **L-3** (57.5 mg, 0.168 mmol) in *o*-xylene (**6**, 6.1 ml, 1.01 mmol), AlCl_3 (1.07 g, 8.02 mmol) was added on rt. The reaction mixture was stirred 40 min at rt and partitioned between water and EtOAc. The organic layer was washed with H_2O , NaHCO_3 , and brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography (EtOAc: hexane = 1: 3) to give light yellow solid **L-10** (41.1 mg, 74 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.79 (1H, s), 7.75 (1H, d, J 7.9 Hz), 7.55 (1H, br s), 7.28 (1H, d, J 7.9 Hz), 5.75 (1H, td, J 7.5, 4.1 Hz), 2.48 (2H, m), 2.34 (6H, s), 2.30 (1H, m), 2.04 (3H, s), 1.96 (1H, m). $^{13}\text{C-NMR}$ (67.8 MHz, CDCl_3) δ : 196.0, 156.9 (q, $^2J_{\text{CF}}$ 37.6 Hz), 144.6, 137.6, 131.1, 130.3, 129.8, 126.5, 115.7 (q, $^1J_{\text{CF}}$ 288.1 Hz), 53.5, 32.3, 29.8, 20.1, 19.7, 15.40. $[\alpha]_{\text{D}} +21.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_2\text{S}^+$ 334.1083, found 334.1057.

Compound **D-10** was obtained from **D-3** in the same manner as **L-10** (73 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.79 (1H, s), 7.75 (1H, d, J 8.2 Hz), 7.56 (1H, br s), 7.28 (1H, d, J 8.2 Hz), 5.75 (1H, td, J 7.5, 4.1 Hz), 2.48 (2H, m), 2.34 (6H, s), 2.04 (3H, s), 1.96 (1H, m). $^{13}\text{C-NMR}$ (67.8 MHz, CDCl_3) δ : 196.0, 157.0 (q, $^2J_{\text{CF}}$ 38.5 Hz), 144.6, 137.7, 131.2, 130.3, 129.8, 126.5, 115.7 (q, $^1J_{\text{CF}}$ 290.0 Hz), 53.5, 32.8, 29.8, 20.1, 19.7, 15.4. $[\alpha]_{\text{D}} -22.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_2\text{S}^+$ 334.1083, found 334.1074.

(S)-N-(1-(2,4-Dimethylphenyl)-4-(methylthio)-1-oxobutan-2-yl)-2,2,2-trifluoroacetamide (L-11). To TFA-L-methionine-OSu **L-3** (57.5 mg, 0.168 mmol) in *m*-xylene (**7**, 6.1 ml, 1.01 mmol), AlCl_3 (1.07 g, 8.02 mmol) was added on rt. The reaction mixture was stirred 40 min at rt and partitioned between water and EtOAc. The organic layer was washed with H_2O , NaHCO_3 , and brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography (EtOAc: hexane = 1: 3) to give dark green liquid **L-11** (43.5 mg, 78 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.69 (1H, d, J 8.2 Hz), 7.58 (1H, s), 7.16-7.12 (2H, m), 5.65 (1H, td, J 7.6, 4.3 Hz), 2.52 (3H, s), 2.46 (3H, t, J 7.7 Hz), 2.39 (4H, s), 2.28-2.16 (2H, m), 1.99 (3H, s), 1.92 (2H, dd, J 14.2, 6.3 Hz). $^{13}\text{C-NMR}$ (CDCl_3) δ : 199.0, 157.8 (q, $^2J_{\text{CF}}$ 38.0 Hz), 144.9, 141.4, 134.4, 131.2, 130.3, 127.7, 116.6 (q, $^1J_{\text{CF}}$ 288.8 Hz), 55.8, 33.0, 30.5, 22.4, 22.3, 16.3. $[\alpha]_{\text{D}} +11.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_2\text{S}^+$ 334.1083, found 334.1055.

Compound D-**11** was obtained from D-**3** in the same manner as L-**11** (72 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.69 (1H, d, J 8.2 Hz), 7.60 (1H, br s), 7.14 (2H, m), 5.66 (1H, td, J 7.5, 4.4 Hz), 2.51 (3H, s), 2.45 (2H, m), 2.39 (3H, s), 2.24 (1H, m), 1.99 (3H, s), 1.92 (1H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 198.2, 157.0 (q, $^2J_{\text{CF}}$ 37.2 Hz) 144.1, 140.6, 133.6, 130.4, 129.5, 126.8, 115.8 (q, $^1J_{\text{CF}}$ 286.0 Hz), 55.0, 32.2, 29.7, 21.5, 21.5, 15.4. $[\alpha]_{\text{D}} -11.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_2\text{S}^+$ 334.1083, found 334.1064.

(S)-N-(1-(2,5-Dimethylphenyl)-4-(methylthio)-1-oxobutan-2-yl)-2,2,2-trifluoroacetamide (L-12). To TFA-L-methionine-OSu L-**3** (57.5 mg, 0.168 mmol) in *p*-Xylene (**8**, 6.1 ml, 1.01 mmol), AlCl_3 (1.07 g, 8.02 mmol) was added on rt. The reaction mixture was stirred 40 min at rt and partitioned between water and EtOAc. The organic layer was washed with H_2O , NaHCO_3 , and brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography (EtOAc: hexane = 1: 3) to give colorless solid L-**12** (42.3 mg, 76 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.65 (1H, br s), 7.57 (1H, s), 7.28 (1H, d, J 7.2 Hz), 7.20 (1H, d, J 7.2 Hz), 5.68 (1H, td, J 7.5, 4.1 Hz), 2.48 (2H, m), 2.46 (3H, s), 2.38 (3H, s), 2.21 (1H, s), 1.98 (3H, s), 1.92 (1H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 199.1, 157.0 (q, $^2J_{\text{CF}}$ 37.6 Hz), 136.8, 135.8, 133.7, 133.3, 132.4, 129.5, 115.8 (q, $^1J_{\text{CF}}$ 287.5 Hz), 55.3, 31.7, 29.8, 20.8, 15.3. $[\alpha]_{\text{D}} +6.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_2\text{S}^+$ 334.1083, found 334.1086.

Compound D-**12** was obtained from D-**3** in the same manner as L-**12** (72 %). $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 7.56 (1H, s), 7.29 (1H, d, J 7.6 Hz), 7.21 (1H, d, J 7.6 Hz), 5.66 (1H, td, J 7.3, 4.3 Hz), 2.48 (2H, m), 2.47 (3H, s), 2.39 (3H, s), 2.20 (1H, m), 1.99 (3H, s), 1.91 (1H, m). $^{13}\text{C-NMR}$ (67.8 MHz, CDCl_3) δ : 199.0, 157.0 (q, $^2J_{\text{CF}}$ 37.4 Hz), 136.8, 135.8, 133.7, 133.2, 132.4, 129.4, 115.7 (q, $^1J_{\text{CF}}$ 288.6 Hz), 55.2, 31.7, 29.7, 20.8, 15.3. $[\alpha]_{\text{D}} -6.0$ (c 1.0, CHCl_3). HRMS-ESI (m/z) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_2\text{S}^+$ 334.1083, found 334.1081.

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Supplementary Material

Nuclear magnetic resonance (^1H and ^{13}C NMR) figures for all synthetic compounds are available online.

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Supplementary Material

Synthesis of chiral *N*-trifluoroacetyl-methionine derivatives and applying them as acyl donors for Friedel-Crafts acylation

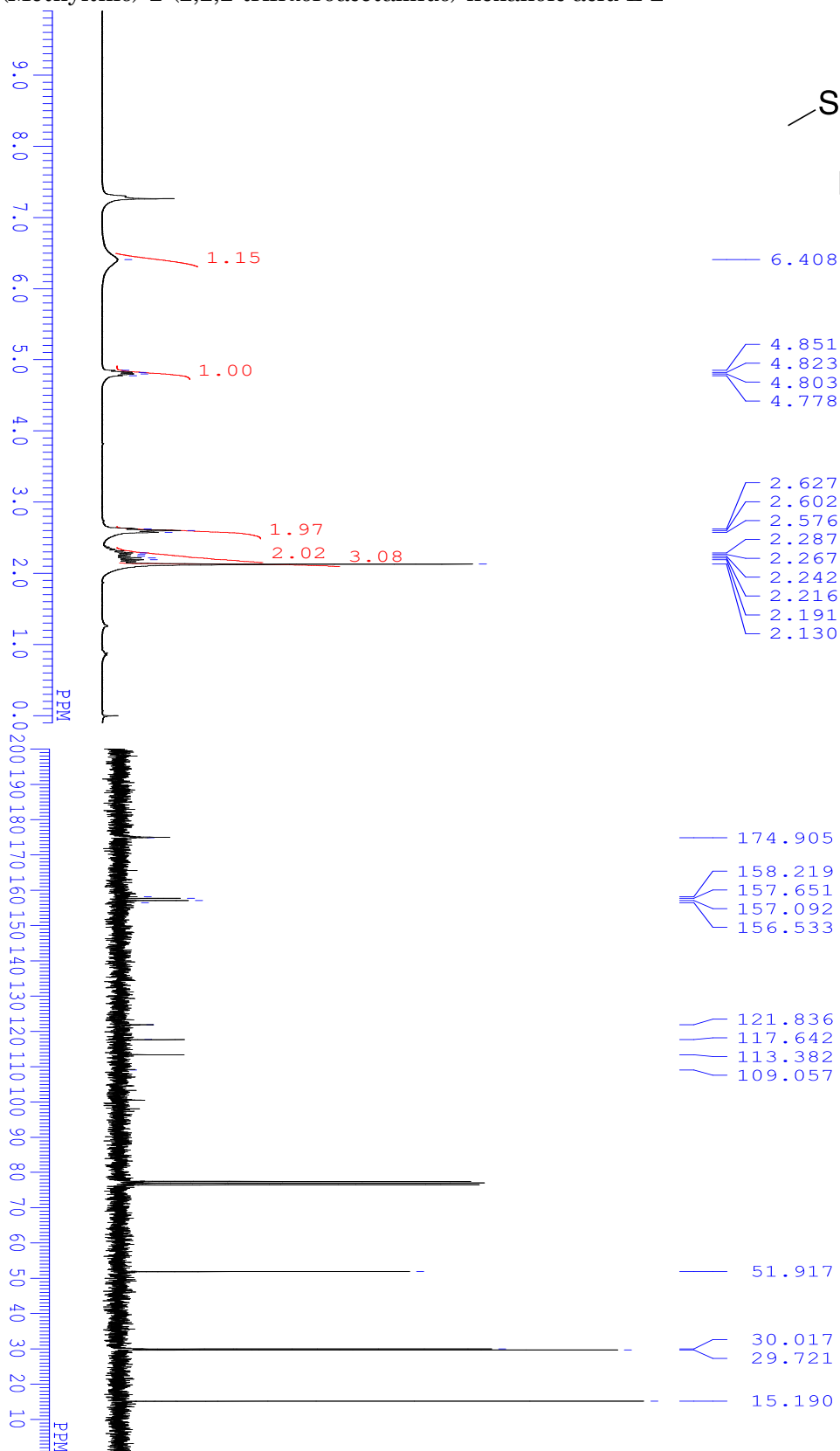
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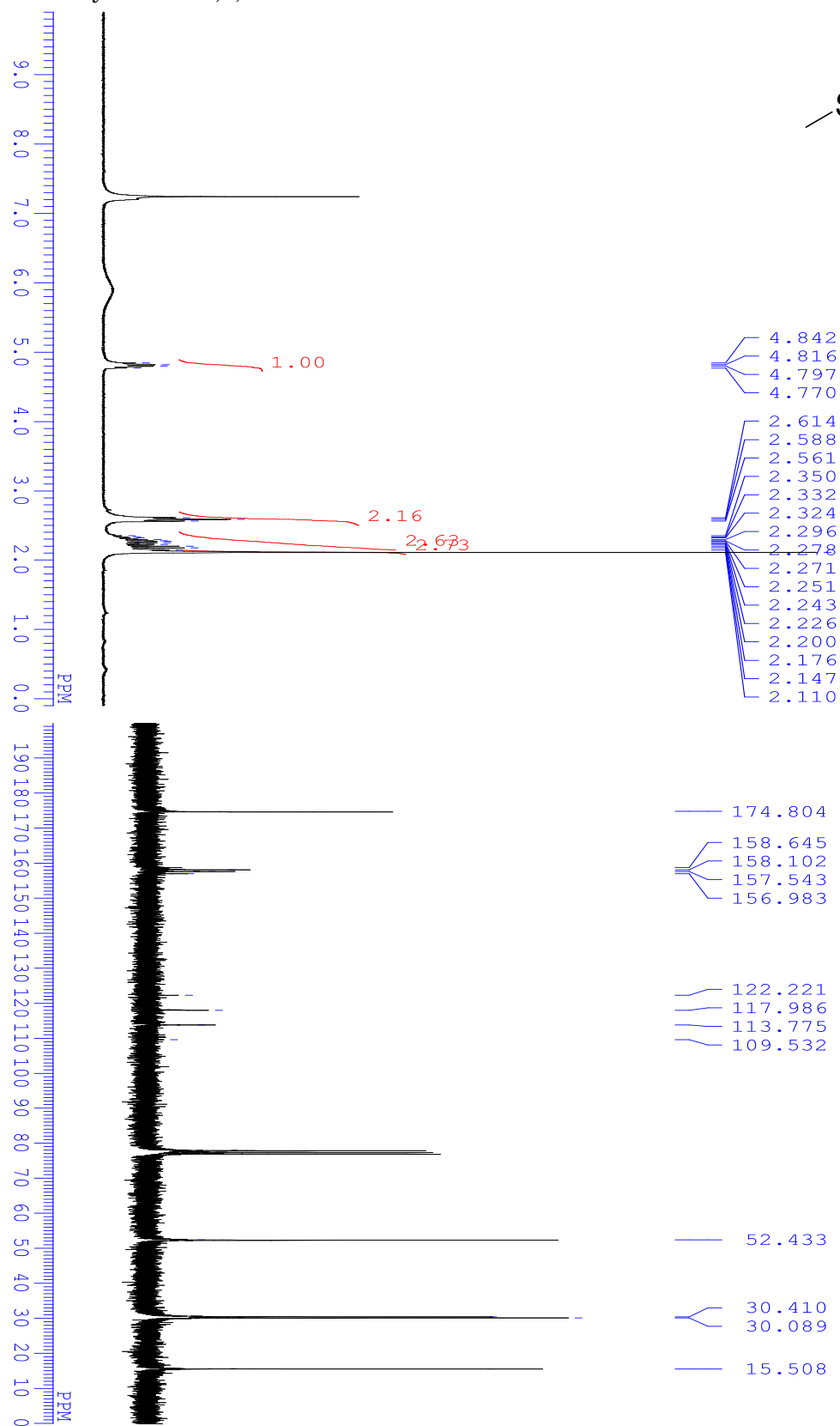
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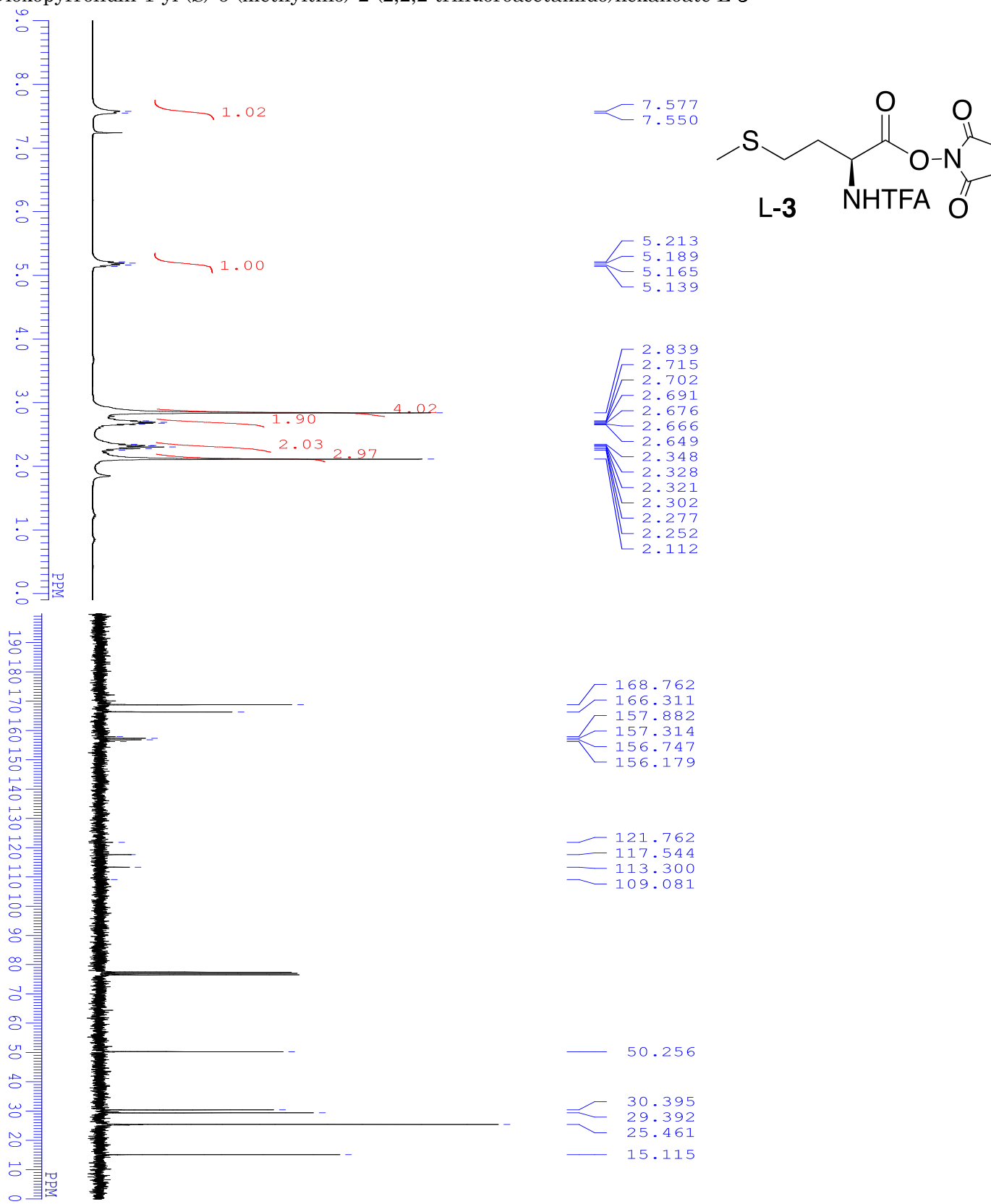
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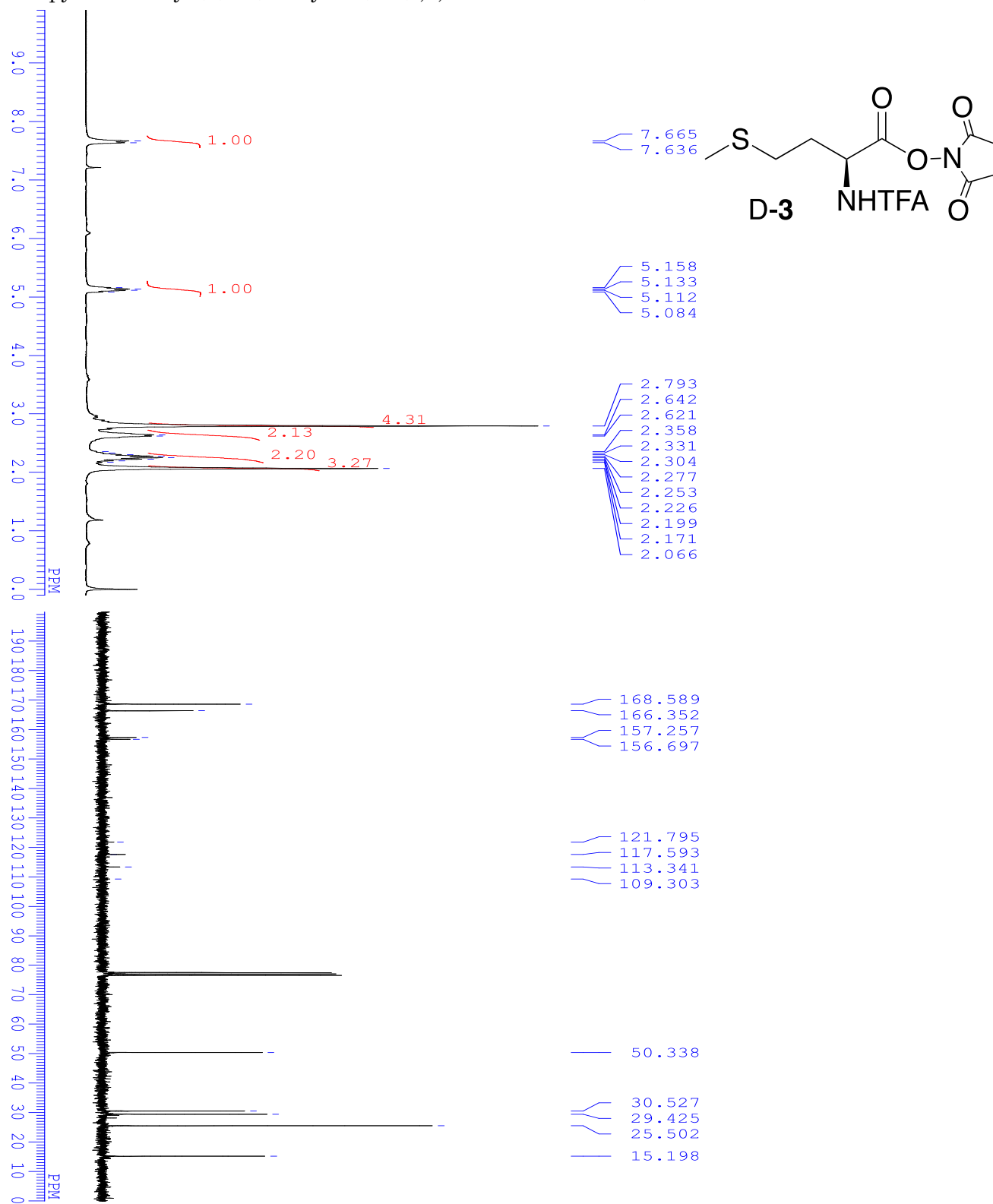
Table of Contents

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| 1. ^1H and ^{13}C NMR figures for all synthetic compounds | S2 |
|---|----|

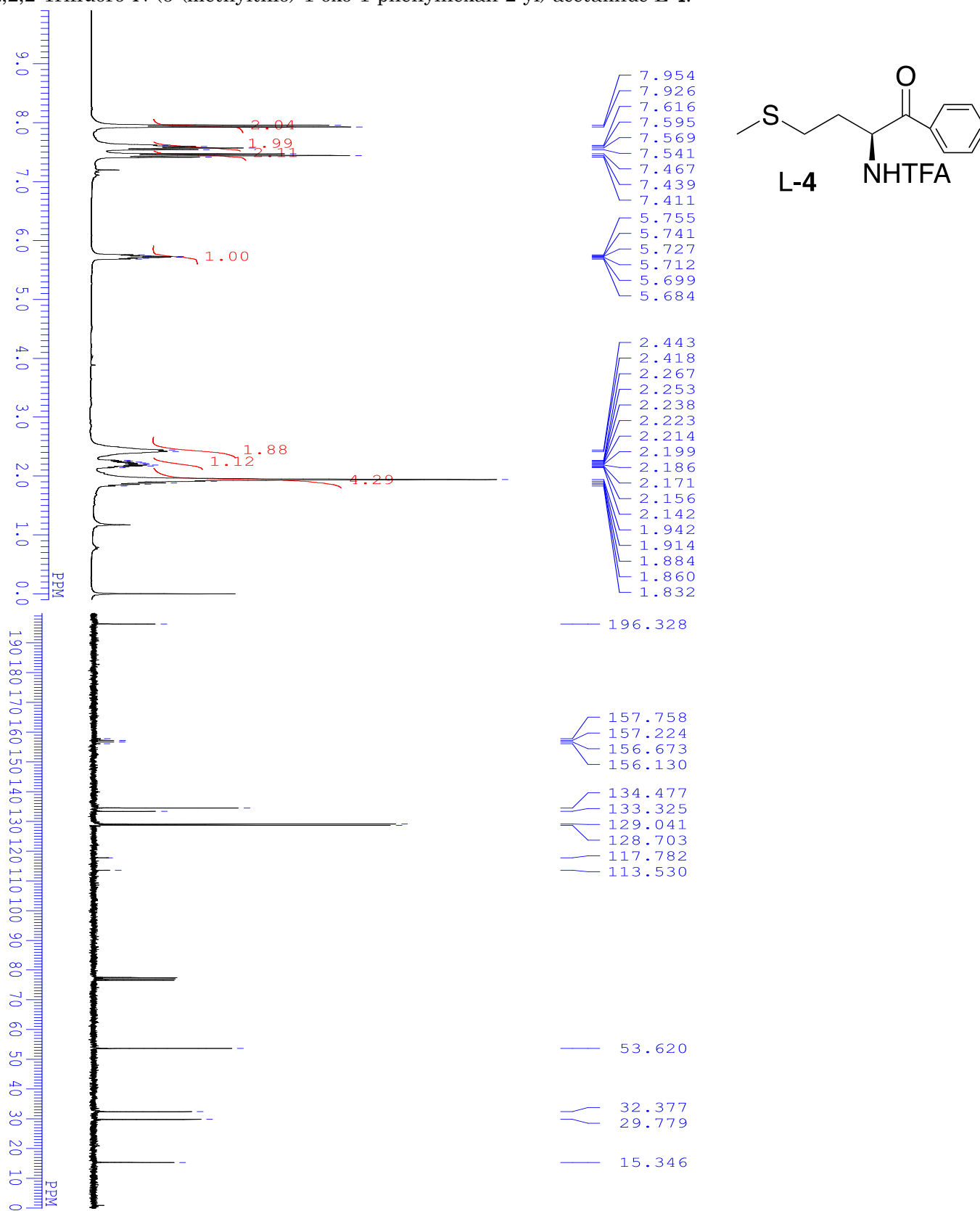
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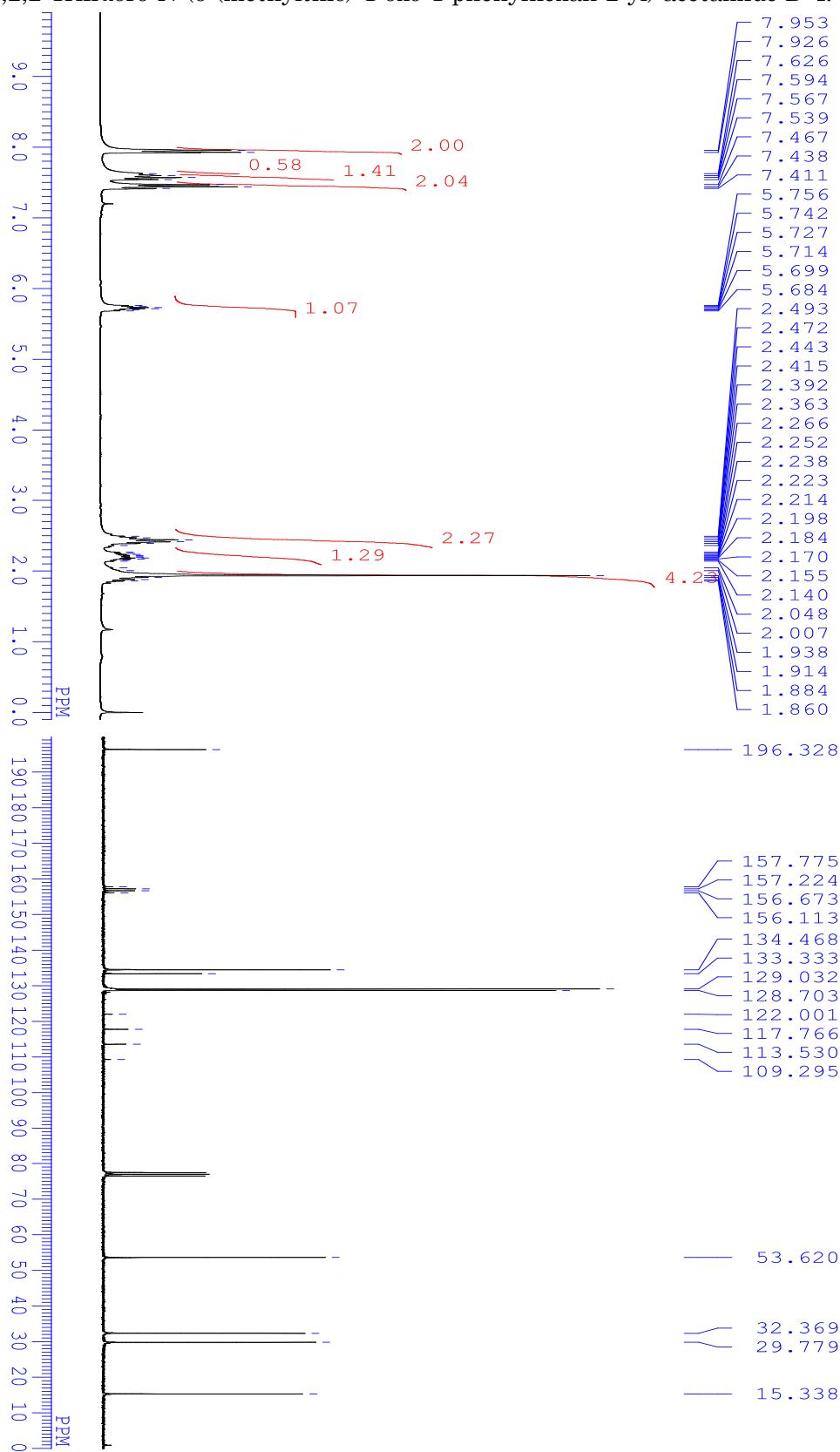
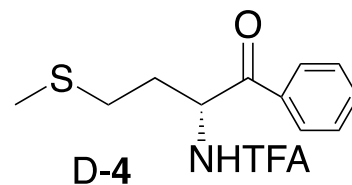
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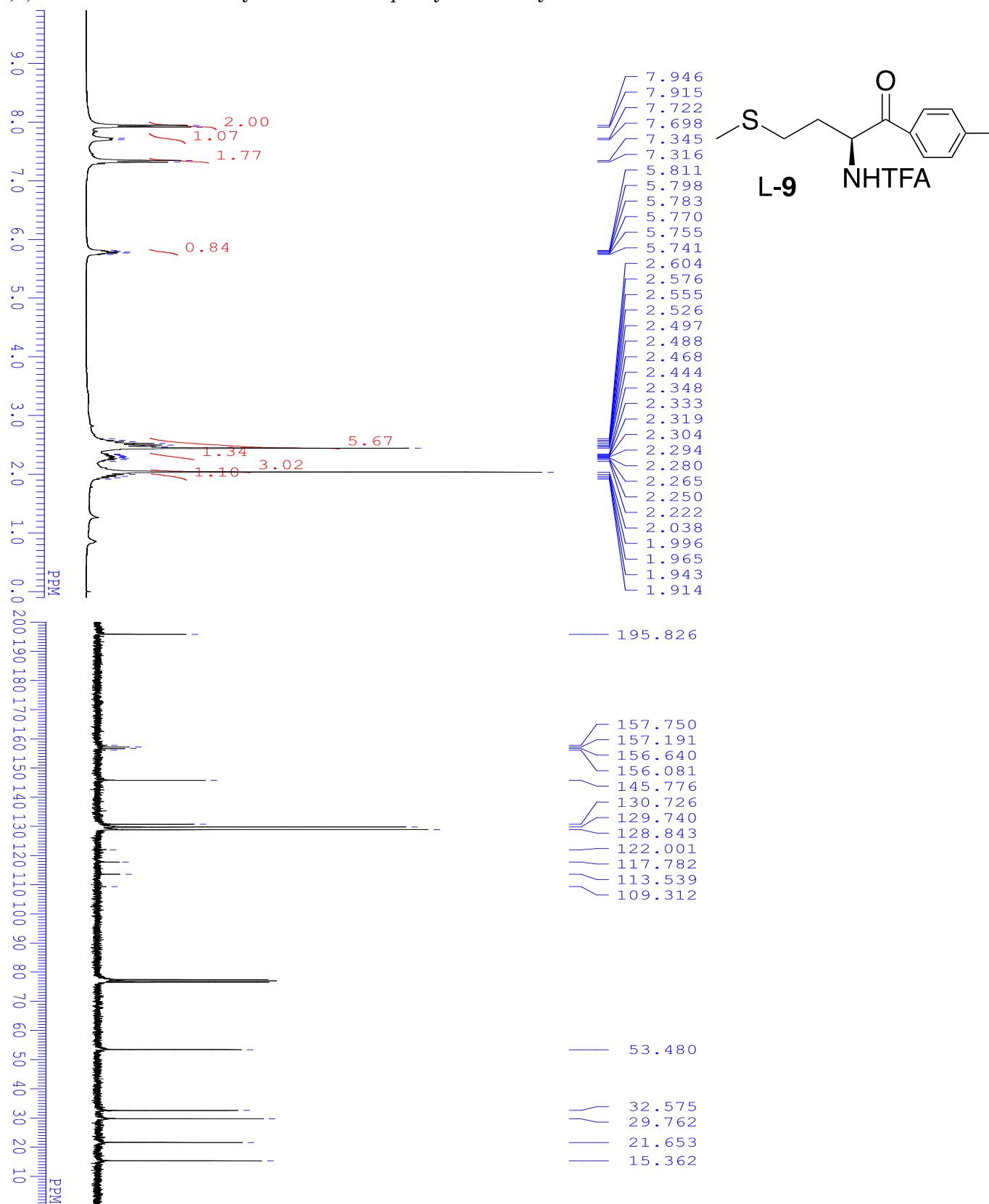
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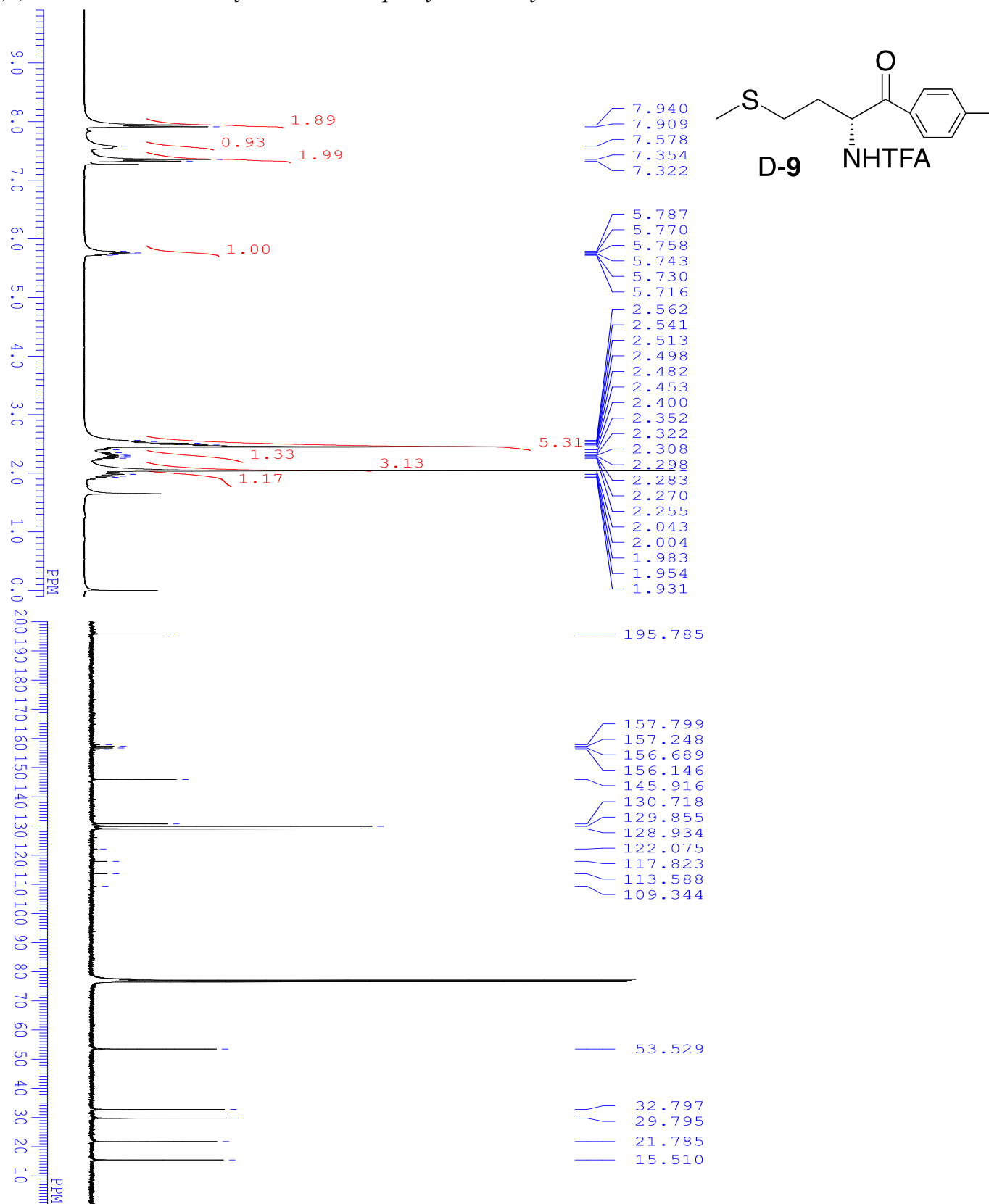
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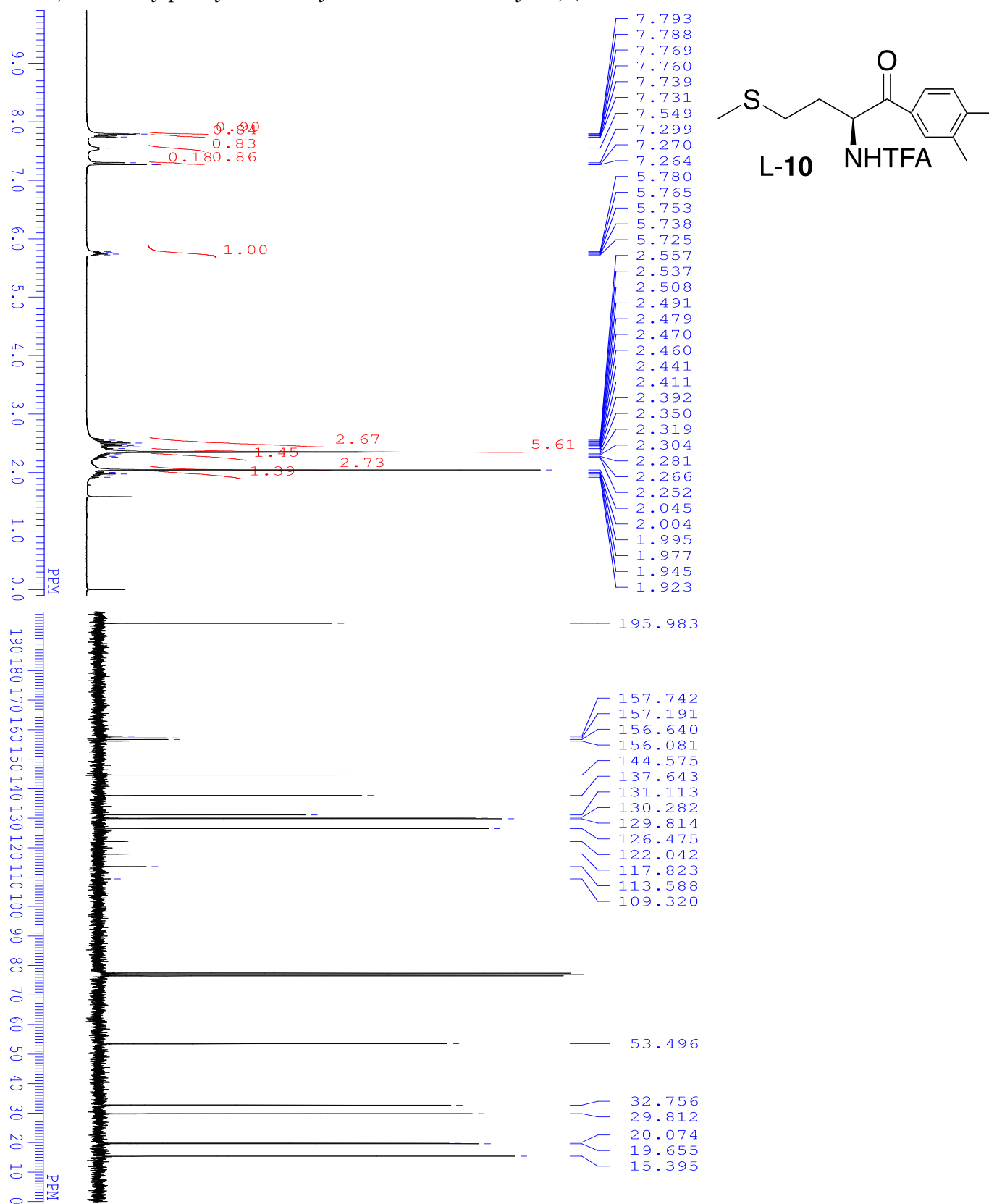
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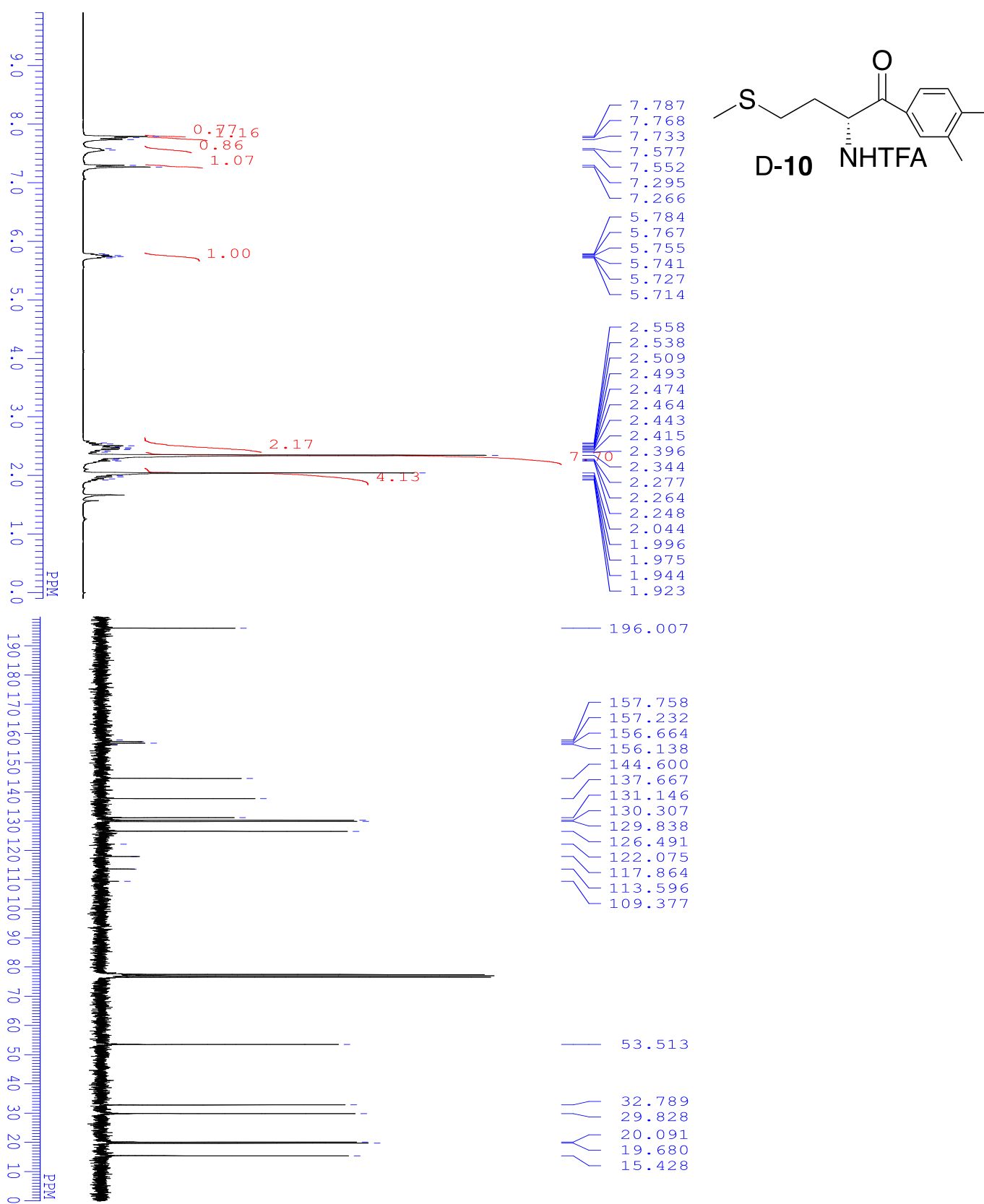
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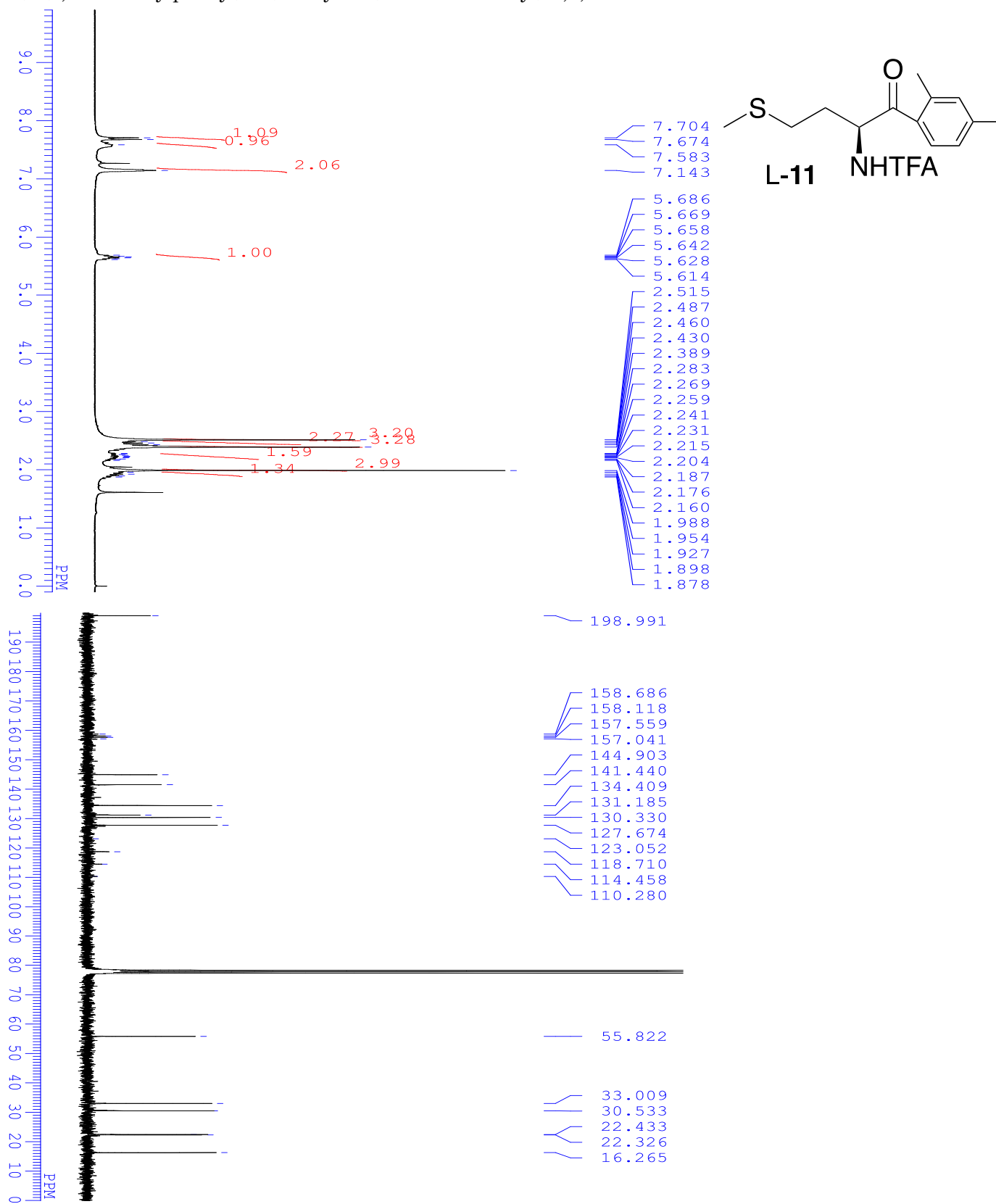
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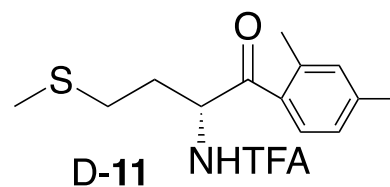
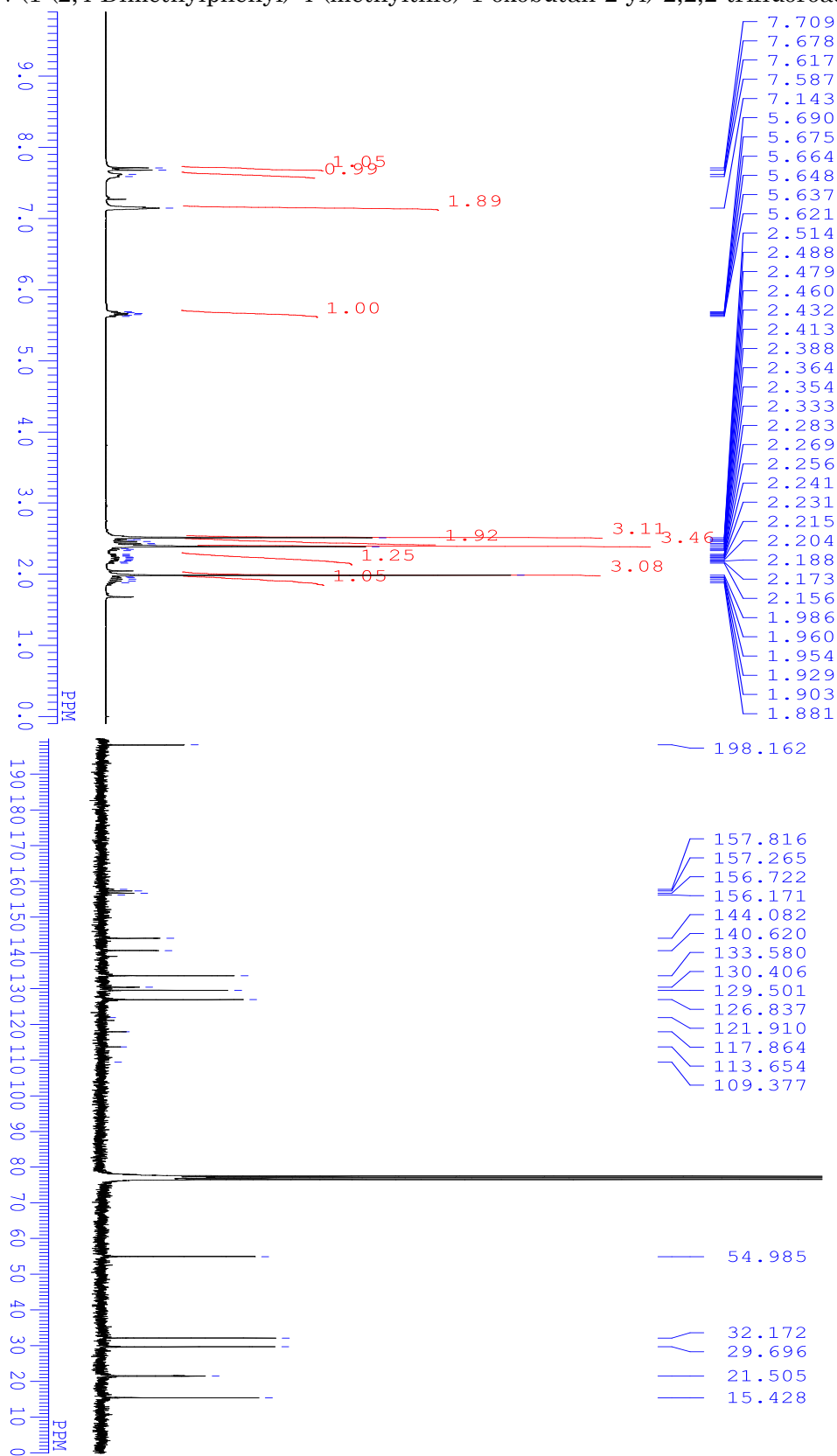


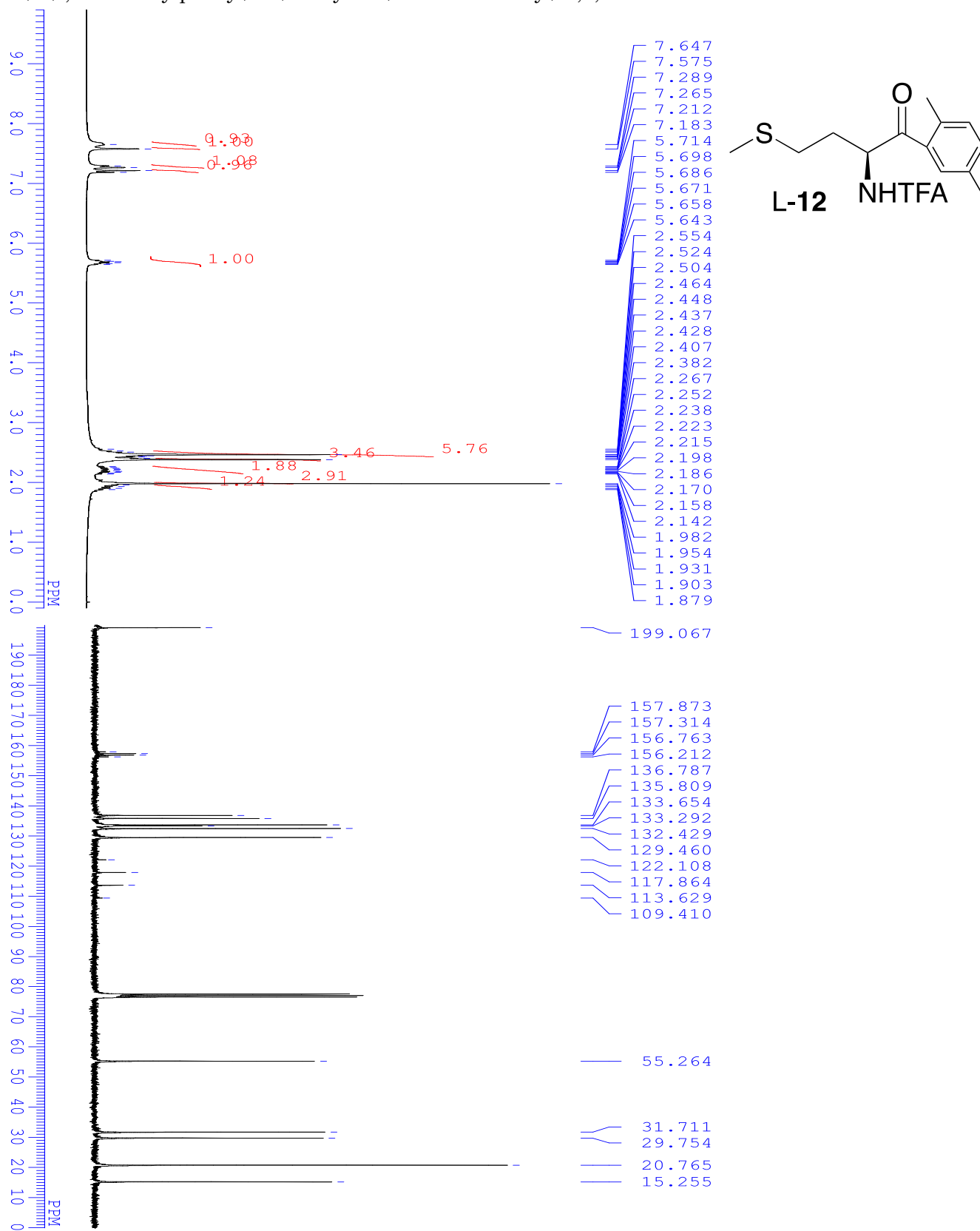
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(S)-*N*-(1-(2,5-Dimethylphenyl)-4-(methylthio)-1-oxobutan-2-yl)-2,2,2-trifluoroacetamide L-12

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