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SUPPORTING INFORMATION

Supporting Information
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Thieme

Direct Domino Synthesis of Azido-dienoic Acids: Potential Linkers Units

Caroline Souris, Frédéric Frébault, Davide Audisio, Christophe Farès and Nuno Maulide*

Max-Planck-Institut für Kohlenforschung Kaiser-Wilhelm-Platz 1
45470 Mülheim an der Ruhr, Germany

E-mail: maulide@mpi-muelheim.mpg.de

Supporting Information

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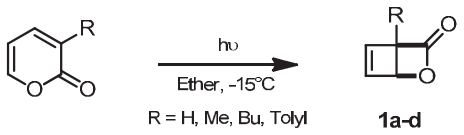
General Methods: All glassware was oven dried at 80 ºC before use and all reactions were performed under an atmosphere of argon unless otherwise stated. All solvents were distilled from appropriate drying agents prior to use. All reagents were used as received from commercial suppliers unless otherwise stated. Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-FTIR spectrometer. Wavelengths (ν) are reported in cm^{-1}. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). Accurate mass determinations were obtained on a Brucker APEX III FT-MS (7 T magnet). All ^{1}H-NMR and ^{13}C-NMR experiments were recorded using Bruker DPX-300, AV-400, AV-500 and AV-600 spectrometers at 300 K. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are quoted in Hz. The 7.27 and 2.05 ppm resonance of residual $CDCl_3$ and CD_3COCD_2H for proton spectra and 77.16 and 29.84 ppm resonance of $CDCl_3$ and CD_3COCD_3 for carbon spectra were used as internal references. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with keiselgel F_{254} with 0.2 mm thickness. Visualisation was achieved by a combination of ultraviolet light (254 nm) and acidic potassium permanganate or anisaldehyde. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.).

All the reactions were performed using a stock ethereal solution of bicyclic lactone **1** prepared according to the literature in a concentration typically ranging from 0.15M to 0.25M. No significant change in yields depending on the concentration of **1** was noted in the reactions reported on this study (provided that the concentration is in the range 0.15-0.25M).

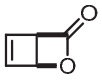
1. General procedure for lactone preparation:



2-pyrone (500 mg, 5.2 mmol) was dissolved in degassed Et_2O (150 mL) and the resulting solution was irradiated at – 10 ºC using a water-cooled mercury arc lamp (Hanovia, 450 W) with a quartz filter. The reaction progress was followed by ^{1}H-NMR and usually 24 to 36h was required to reach completion. After warming to room temperature, the solution was concentrated under vacuum in a cold bath to reach a volume of 5-10 mL and the concentration of **1** was repeatedly assayed by ^{1}H-NMR. Solutions of **1** were stored at 4 ºC and did not show any signs of decomposition after several weeks.

The synthesis of 3-substituted-2-pyrone was performed in accordance to the reported literature.[1]

2-oxabicyclo[2.2.0]hex-5-en-3-one (1a)

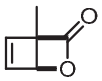


1a

Data of the ^{1}H-NMR spectra of **1a** matches those reported in the literature.[2] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.73 (app t., *J* 3.5, 1H), 6.54 (app. t, *J* 1.9, 1H), 5.29 (dd, *J* 4.5, 1.9, 1H).

[1] F. Frebault, M. T. Oliveira, E. Wostefeld, N. Maulide *J. Org. Chem.* **2010**, *75*, 7962.
[2] E. J. Corey; J. Streith *J. Am. Chem. Soc.* **1964**, *86*, 950.

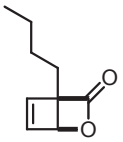
4-methyl-2-oxabicyclo[2.2.0]hex-5-en-3-one (1b)



1b

Data of the ^{1}H-NMR spectra of **1b** matches those reported in the literature.[3] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.73 (dd, *J* 4.5, 2.5, 1H), 6.55 (d, *J* 2.5, 1H), 5.15 (d, *J* 4.5, 1H), 1.45 (s, 3H).

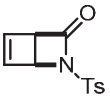
4-butyl-2-oxabicyclo[2.2.0]hex-5-en-3-one (1c)



1c

Compound **1c** was obtained as a yellow solution in diethyl ether in quantitative yield according to the general procedure. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* 4.4, 2.4, 1H), 6.51 (d, *J* 2.4, 1H), 5.13 (d, *J* 4.4, 1H), 1.88-1.81 (m, 2H), 1.45-1.33 (m, 4H), 0.91 (t, *J* 7.1, 3H).

2-tosyl-2-azabicyclo[2.2.0]hex-5-en-3-one (1e)



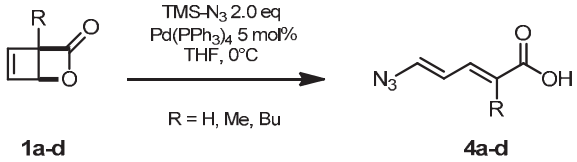
1e

The lactam **1e** was prepared according to the literature. Data of the ^{1}H- and ^{13}C-NMR spectra of **1e** matches those reported in the literature.[4]

[3] M. Luparia, M. T. Oliveira, D. Audisio, F. Frébault, R. Goddard, N. Maulide *Angew. Chem. Int. Ed.*, **2011**, *50*, 12631.
[4] N. Gauvry, F. Huet, *J. Org. Chem.* **2001**, *66*, 583.

2. General procedure for azido dienoic acids preparation:

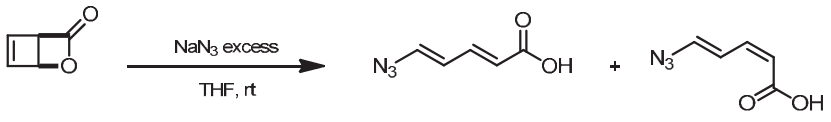
5-azidopenta-2,4-dienoic acid synthesis 4a-d:



1a-d **4a-d**

In a schlenk flask, $Pd(PPh_3)_4$ (9.0 mg, 8 μmol, 5 mol%) was evacuated/backfilled with Argon three times and dissolved in THF (3.1 mL). TMS-N_3 (36 μL, 0.312 mmol, 2.0 equiv.) was added to the stirred solution of $Pd(PPh_3)_4$ and the mixture was cooled to 0 °C. After 5 min, an etheral solution of lactone **1** (0.20 M in Et_2O, 0.78 mL, 0.156 mmol, 1.0 equiv.) was added dropwise to the mixture and the mixture was then stirred at 0 °C for 2 days. The solution was quenched with water and Et_2O was added to the mixture. The organic phase was extracted three times with saturated $NaHCO_3$. The aqueous phases were acidified using 1M HCl, extracted three times with EtOAc and the combined extracts were evaporated to give the azido diene.

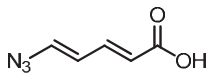
Reaction was performed using both NaN_3 and TMS-N_3 as nucleophile in absence or presence of Pd. NaN_3 proved to be a suitable nucleophile for the reaction. It afforded diene **4a** in 65% yield as a mixture of *E,E*/*Z,E* in a 1:1 ratio. On the other hand, TMS-N_3 led to complete formation of the desired product **4a** as single isomer. Moreover, in the absence of Pd^0, a notoriously slow background reaction leading to the same product takes place.



1a-d **4a** **4a'**

1 : 1

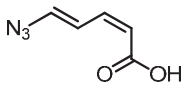
(2*E*,4*E*)-5-azidopenta-2,4-dienoic acid (4a)



4a

The reaction was performed up to 3.0 mmol scale affording the desired dienoic acid **4a** in 350 mg. Compound **4a** was obtained as a yellow powder in 81% yield according to the general procedure. FTIR (neat) ν_{max} 2926, 2567, 2283, 2103, 1673, 1619, 989; ^{1}H-NMR (300 MHz, CD_3COCD_3) δ 7.30 (dd, *J* 15.4, 11.4, 1H), 7.01 (d, *J* 13.2, 1H), 6.18 (dd, *J* 13.2, 11.4, 1H), 5.90 (d, *J* 15.4, 1H); ^{13}C-NMR (75 MHz, CD_3COCD_3) δ 167.8, 142.6, 138.8, 120.7, 118.2; HRMS (ESI) exact mass calculated for $[M]^+$ ($C_5H_5N_3O_2$) requires *m/z* 139.0380, found *m/z* 139.0382.

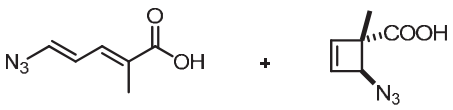
(2*Z*,4*E*)-5-azido-*N*-tosylpenta-2,4-dienamide (4a')



4'a

Compound **4a'** was obtained together with its *E,E*-isomer **4a** when the reaction was performed at room temperature using NaN_3 as nucleophile. ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 7.30 (dd, *J* 13.3, 11.5, 1H), 6.90 (d, *J* 13.3, 1H), 6.71 (d, *J* 11.5, 1H), 5.62 (d, *J* 11.2, 1H).

(2*E*,4*E*)-5-azido-2-methylpenta-2,4-dienoic acid (4b)

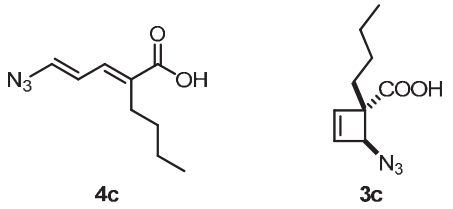


4b **3b**

Compound **3b** was obtained in quantitative yield according to the general procedure. The cyclobutene slowly ring opens at room temperature to give to diene **4b**. After the reaction the mixture contains **3b** and **4b** in a 1:1 ratio. ^{1}H-NMR (500 MHz, CD_3COCD_3) **4b**: δ 7.21 (d, *J* 12.1, 1H), 6.94 (d, *J* 13.1, 1H), 6.25 (dd, *J* 13.1, 12.1, 1H), 1.89 (d, *J* 1.4, 3H); **3b**: 6.44 (d, *J* 2.8, 1H), 6.32 (dd, *J* 2.8, 0.9, 1H), 4.62 (s, 1H), 1.44 (s, 3H); ^{13}C-NMR (125 MHz,

CD_3COCD_3) **4b**: δ 169.3, 137.2, 135.9, 116.1, 58.2, 12.5; **3b**:δ 174.6, 145.1, 136.7, 126.5, 65.7, 18.9; HRMS (ESI) exact mass calculated for [M] ($C_6H_7N_3O_2$) requires *m/z* 153.0538, found *m/z* 153.0538.

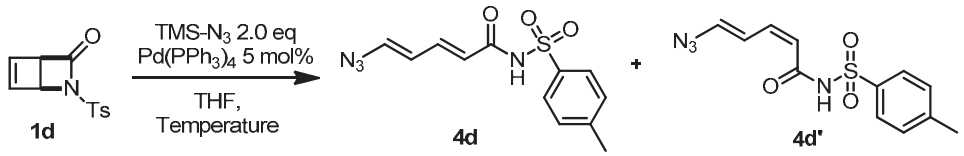
(*E*)-2-((*E*)-3-azidoallylidene)hexanoic acid (4c)



4c **3c**

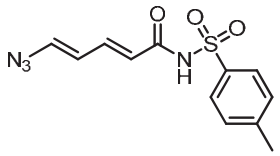
Compound **3c** was obtained in 47% yield according to the general procedure. The cyclobutene slowly ring opens at room temperature to give to diene **4c**. After the reaction the mixture contains **3c** and **4c** in a 1:2.8 ratio. ^{1}H-NMR (500 MHz, CD_3COCD_3) **4c**: δ 7.21 (d, *J* 12.3, 1H), 6.97 (d, *J* 13.1, 1H), 6.27 (app. t, *J* 12.3, 1H), 2.41 (m, 2H), 1.43-1.29 (m, 5H), 0.92-0.88 (m, 2H); **3c**: δ 6.49 (d, *J* 2.8, 1H), 6.33 (d, *J* 2.8, 1H), 4.62 (s, 1H), 2.41-2.38 (m, 2H), 1.43-1.29 (m ,5H), 0.92-0.88 (m, 2H); ^{13}C-NMR (125 MHz, CD_3COCD_3) **3c**: δ 167.7, 137.6, 137.0, 135.9, 115.9, 32.8, 23.3, 14.4, 14.3.

<u>5-azido-*N*-tosylpenta-2,4-dienamide 4d:</u>



T = RT E,E-**4d** / E,Z-**4d'** ratio: 4.4:1
T = 0°C E,E-**4d** / E,Z-**4d'** ratio: 1:0

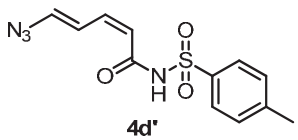
(2*E*,4*E*)-5-azido-*N*-tosylpenta-2,4-dienamide (4d)



4d

Compound **4d** was obtained as a brown oil in 62% yield according to the general procedure. FTIR (neat) ν_{max} 3155, 2102, 1669, 1600, 1447, 1080; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 7.92 (d, *J* 8.2, 2H), 7.41 (d, *J* 8.2, 2H), 7.25 (dd, *J* 15.0, 11.7, 1H), 7.03 (d, *J* 13.3, 1H), 6.11-6.03 (m, 2H), 2.42 (s, 3H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 164.0, 145.5, 142.5, 140.5, 138.0, 130.2 (2C), 129.1 (2C), 120.7, 117.9, 21.5.

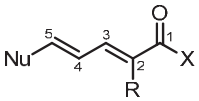
(2*Z*,4*E*)-5-azido-*N*-tosylpenta-2,4-dienamide (4d')



4d'

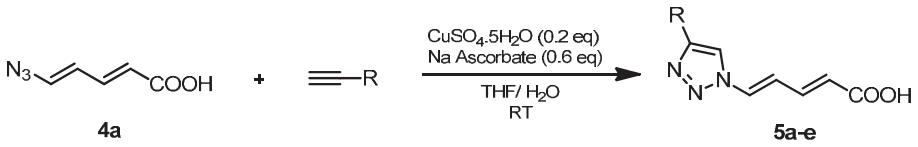
Compound **4d'** was obtained together with its *E,E*-isomer **4d** when the reaction was performed at room temperature, a mixture of *E,E*- and *Z,E*-5-azido-*N*-tosylpenta-2,4-dienamide **4d** and **4d'** were obtained in a 4.4:1 ratio. **4d'**: ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 7.96 (d, *J* 8.0, 2H), 7.35 (d, *J* 8.0, 2H), 7.29 – 7.24 (m, 1H), 6.49 (app. t, *J* 11.5, 1H), 6.39 (d, *J* 13.8, 1H), 5.49 (d, *J* 10.9, 1H), 2.45 (s, 3H).

3. Coupling constants comparison



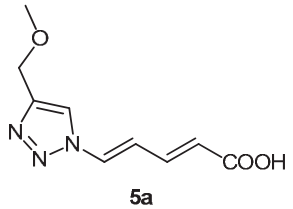
Diene	X	R	Nu	Solvent	$\delta(H_2)$ (ppm)	$\delta(H_3)$ (ppm)	$\delta(H_4)$ (ppm)	$\delta(H_5)$ (ppm)	$^{3}J(H_3H_2)$ (Hz)	$^{3}J(H_4H_3)$ (Hz)	$^{3}J(H_5H_4)$ (Hz)	Geometry
4a	-OH	-H	N_3-	Acetone	5.9	7.3	6.2	7.0	15.4	11.4	13.2	E,E
4b	-OH	-Me	N_3-	Acetone	--	7.2	6.3	7.0	--	12.0	13.1	E,E
4c	-OH	-Bu	N_3-	Acetone	--	7.2	6.3	7.0	--	12.3	13.1	E,E
4d	-NHTs	-H	N_3-	Acetone	6.0	7.3	6.1	7.0	15.0	11.7	13.3	E,E
4a'	-OH	-H	N_3-	Acetone	5.6	6.7	7.3	6.9	11.5	11.5	13.3	Z,E
4d'	-NHTs	-H	N_3-	Acetone	5.5	6.5	7.2	6.4	11.5	11.5	13.8	Z,E

4. Click reactions of azido dienes



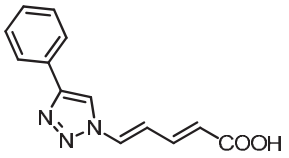
General procedure: To a mixture of azido diene **4a** (15 mg, 0.11 mmol, 1.0 equiv.) and the corresponding acetylene (0.21 mmol, 2.0 equiv.) in THF (0.5 mL) was added a solution of $CuSO_4$•$5H_2O$ (5.4 mg, 0.02 mmol, 0.2 equiv.) in water (0.25 mL) followed by a solution of sodium ascorbate (13 mg, 0.06 mmol, 0.6 equiv.) in water (0.25 mL). The reaction mixture was stirred at room temperature for 12h. Ethyl acetate was added to the mixture and the resulting solution was washed with three times with 1M HCl. The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum to afford the desired 1-4 triazole **5**.

(2*E*,4*E*)-5-(4-(methoxymethyl)-1*H*-1,2,3-triazol-1-yl)penta-2,4-dienoic acid (5a)



Compound **20a** was obtained as a yellow paste in 80% yield. FTIR (neat) ν_{max} 3094, 2931, 2887, 1677, 1644, 1619, 1044, 993; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 8.35 (s, 1H), 7.94 (d, *J* 14.2, 1H), 7.50 (dd, *J* 15.1, 11.4, 1H), 7.21 (dd, *J* 14.2, 11.4, 1H), 6.17 (d, *J* 15.1, 1H), 4.55 (s, 2H), 3.35 (s, 3H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 167.3, 146.5, 141.8, 132.4, 128.8, 122.1, 119.2, 66.0, 58.1; HRMS (ESI) exact mass calculated for $[M-H]^-$ ($C_9H_{10}N_3O_3$) requires *m/z* 208.0726, found *m/z* 208.0728.

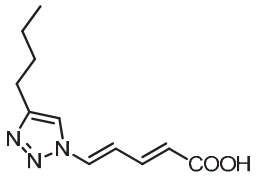
(2*E*,4*E*)-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)penta-2,4-dienoic acid (5b)



5b

Compound **5b** was obtained as a beige solid in 79%. FTIR (neat) ν_{max} 3127, 2932, 2531, 1671, 987, 937; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 8.82 (s, 1H), 8.01 (d, *J* 14.0, 1H), 7.95 (dd, *J* 8.3, 1.2, 2H), 7.55 (dd, *J* 15.4, 11.5, 1H), 7.47 (t, *J* 7.6, 2H), 7.38 (t, *J* 7.5, 1H), 7.23 (dd, *J* 14.0, 11.5 Hz, 1H), 6.18 (d, *J* 15.4, 1H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 167.2, 148.6, 141.7, 132.5, 131.3, 129.9 (2C), 129.3, 126.5 (2C), 124.9, 119.3, 119.2; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}N_3O_2$) requires *m/z* 242.0923, found *m/z* 242.0924.

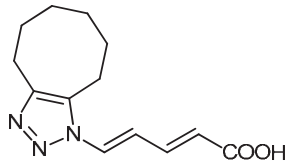
(2*E*,4*E*)-5-(4-butyl-1H-1,2,3-triazol-1-yl)penta-2,4-dienoic acid (5c)



5c

Compound **5c** was obtained as a white solid in 81% yield. FTIR (neat) ν_{max} 3123, 2930, 1672, 1643, 989; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 8.14 (s, 1H), 7.91 (d, *J* 14.2, 1H), 7.49 (dd, *J* 15.2, 11.5, 1H), 7.13 (dd, *J* 14.2, 11.5, 1H), 6.14 (d, *J* 15.2, 1H), 2.71 (t, *J* 7.6, 2H), 1.69-1.63 (m, 2H), 1.42-1.35 (m, 2H), 0.91 (t, *J* 7.3, 3H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 167.4, 149.6, 142.0, 132.7, 124.3, 120.1, 118.3, 32.1, 25.7, 22.9, 14.07; HRMS (ESI) exact mass calculated for $[M-H]^-$ ($C_{11}H_{14}N_3O_2$) requires *m/z* 220.1090, found *m/z* 220.1091.

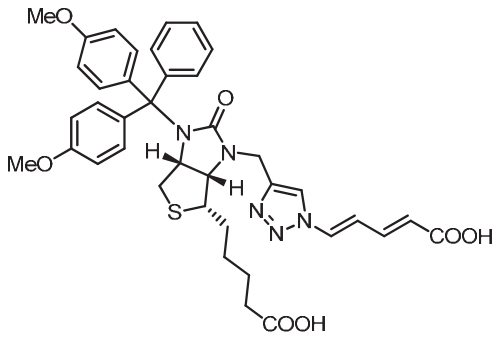
(2E,4E)-5-(4,5,6,7,8,9-hexahydro-1H-cycloocta[d][1,2,3]triazol-1-yl)penta-2,4-dienoic acid (5d)



5d

Compound **5d** was obtained as a yellow powder in quantitative yield following a modified procedure: $CuSO_4 \bullet 5H_2O$ and sodium ascorbate were not added to the mixture and after completion of the reaction, the solvent was simply removed to afford **5d**. The alkyne substrate used for was synthetised (Hydrobromination/elimination) according to the reported literature. [5] FTIR (neat) ν_{max} 2922, 2859, 1683, 1619, 1049, 995; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 7.71 (d, *J* 13.6, 1H), 7.50 (dd, *J* 15.4, 11.9, 1H), 7.26 (dd, *J* 13.6, 11.9, 1H), 6.20 (d, *J* 15.4, 1H), 2.96 (t, *J* 6.7, 2H), 2.88 (t, *J* 6.7, 2H), 1.89-0.86 (m, 8H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 167.7, 145.7, 142.4, 134.5, 130.4, 124.2, 119.4, 29.5, 26.9, 26.8, 25.4, 25.1, 21.7. HRMS (ESI) exact mass calculated for $[M-H]^-$ ($C_{13}H_{16}N_3O_2$) requires *m/z* 246.1259, found *m/z* 246.1248.

(2*E*,4*E*)-5-(4-(((3aR,6S,6aS)-3-(bis(4-methoxyphenyl)(phenyl)methyl)-6-(4-carboxybutyl)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)penta-2,4-dienoic acid (5e)



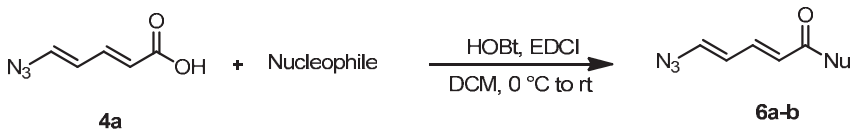
5e

Compound **5e** was obtained as a colourless oil in 63% yield. The biotin substrate used for was synthetised (methyl ester formation, protection and alkylation) according to the reported

[5] H. D. Verkruijsse, L. Brandsma *Synthesis*, **1978**, 290.

literature.[6] Upon work-up conditions, saponification of the methyl ester was observed yielding the diacid **5e**. FTIR (neat) ν_{max} 2950, 1733, 1712, 1650, 1603, 1238, 702; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 8.16 (s, 1H), 8.03 (d, *J* 14.3, 1H), 7.56 (dd, *J* 15.3, 11.3, 1H), 7.28 (dd, *J* 14.3, 11.3, 1H), 7.27-7.22 (m, 5H), 7.08 (d, *J* 8.8, 2H), 7.03 (d, *J* 8.8, 2H), 6.81 (d, *J* 9.1, 2H), 6.78 (d, *J* 9.1, 2H), 6.22 (d, *J* 15.3, 1H), 4.75 (d, *J* 15.2, 1H), 4.55 (dd, *J* 9.4, 4.9, 1H), 4.45 (m, 1H), 4.19 (d, *J* 15.2, 1H), 3.77 (s, 3H), 3.77 (s, 3H), 3.40 (m, 1H), 2.38-2.33 (m, 2H), 2.28 (dd, *J* 12.8, 4.0, 1H), 1.95 (dd, *J* 12.8, 6.1, 1H), 1.73-1.63 (m, 5H), 1.51 (m, 1H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 174.8, 167.4, 161.3, 159.3, 159.2, 145.0, 144.6, 141.7, 136.5, 136.3, 132.4, 132.3 (2C), 132.2 (2C), 130.6 (2C), 128.0 (2C), 127.3, 124.8, 122.7, 119.3, 113.3 (2C), 113.2 (2C), 73.6, 63.8, 63.7, 55.4 (2C), 55.2, 39.7, 38.3, 34.0, 29.7, 29.4, 25.3. HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{39}H_{41}N_5O_7S$) requires *m/z* 746.2611, found *m/z* 746.2619.

5. Coupling reactions of azido dienes

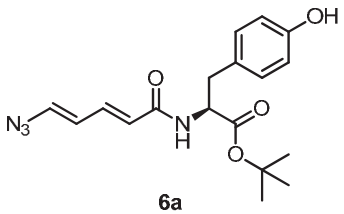


4a **6a-b**

General procedure for coupling of *N*-nucleophiles: To a solution of azido diene **4a** (15 mg, 0.11 mmol, 1.0 equiv.) and amine (0.12 mmol, 1.1 equiv.) in DCM (2 mL) were added HOBt (1-Hydroxybenzotriazole, 16 mg, 0.12 mmol, 1.1 equiv.) and EDCI (23 mg, 0.12 mmol, 1.1 equiv.) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 12h. H_2O (5 mL) and DCM (5mL) were added and the organic layer was washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was removed under vacuum and the product was purified by column chromatography on silica gel (pentane/EtOAc: 95/5) to afford the desired amides **6**.

[6] A. D. Pehere, A. D. Abell, , *J. Org. Chem.* **2011**, *76*, 9514.

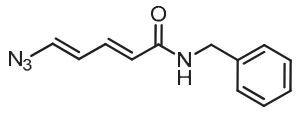
(*S*)-*tert*-butyl 2-((2*E*,4*E*)-5-azidopenta-2,4-dienamido)-3-(4-hydroxyphenyl)propanoate (6a)



6a

Compound **6a** was obtained as a pale yellow oil in 55% yield. FTIR (neat) ν_{max} 3303, 2978, 2939, 2106, 1719, 1513, 1147; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 8.23 (s, 1H), 7.28 (br d, *J* 8.5, 1H), 7.15 (app. t, *J* 12.7, 1H), 7.05 (d, *J* 7.5, 2H), 6.87 (d, *J* 12.7, 1H), 6.74 (d, *J* 7.5, 2H), 6.11 (d, *J* 14.8, 1H), 6.05 (app. t, *J* 12.7, 1H), 4.62 (m, 1H), 2.98 (dd, *J* 13.9, 6.1, 1H), 2.91 (d, *J* 13.9, 8.1, 1H), 1.39 (s, 9H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 171.7, 165.8, 157.1, 137.8, 136.9, 131.3 (2C), 128.7, 124.1, 118.6, 115.9 (2C), 81.6, 55.4, 37.8, 28.1 (3C); HRMS (ESI) exact mass calculated for [M+Na$^+$] ($C_{18}H_{22}N_4O_4Na$) requires *m/z* 381.1534, found *m/z* 381.1533.

(2*E*,4*E*)-5-azido-*N*-benzylpenta-2,4-dienamide (6b)



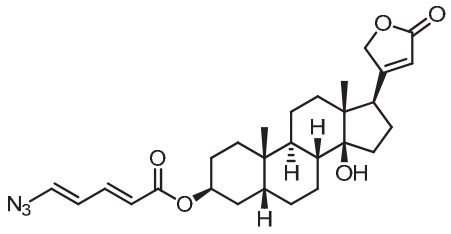
6b

Compound **6b** was obtained as a white solid in 71% yield. ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 7.65 (br s, 1H), 7.31-7.28 (m, 4H), 7.35-7.17 (m, 2H), 6.88 (d, *J* 13.2, 1H), 6.11-6.06 (m, 2H), 4.46 (d, *J* 6.1, 2H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 166.1, 140.7, 137.5, 136.7, 129.2 (2C), 128.5 (2C), 127.8, 124.6, 118.7, 43.6; HRMS (ESI) exact mass calculated for [M+Na]$^+$ ($C_{12}H_{12}N_4ONa$) requires *m/z* 251.0900, found *m/z* 251.0903.

General procedure for coupling of *O*-nucleophiles: To a stirred solution of azido diene **4a** (0.07 mmol, 1.0 eq) in DCM (1 mL) were added DMF (1 drop) followed by oxalyl chloride (0.01 mmol, 1.5 eq) at 0 °C. After 30 min, the solution was added to a mixture of alcohol

(0.09 mmol, 1.1 eq) and NaH (60% in mineral oil, 0.09 mmol, 1.1 eq) in DCM (1 mL). The resulting mixture was stirred for 12h at room temperature. H_2O (5 mL) and DCM (5mL) were added to the reaction mixture and the layers were separated. The organic phase was washed three times with H_2O, brine and dried over $MgSO_4$. The solvent was removed under vacuum and the product was purified by column chromatography on silica gel (pentane/EtOAc: 6/4) to afford the desired ester **6**.

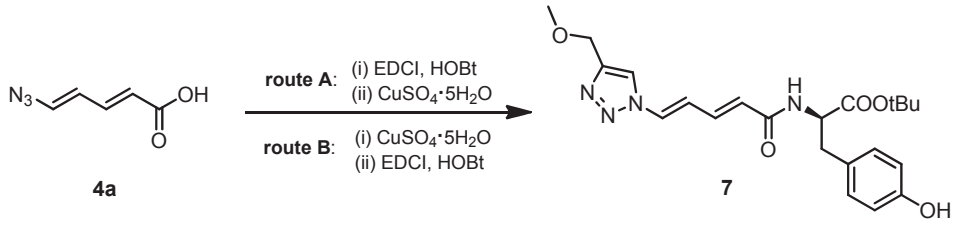
(2*E*,4*E*)-(3S,10S,13R,14S,17R)-14-hydroxy-10,13-dimethyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthren-3-yl 5-azidopenta-2,4-dienoate (6c)



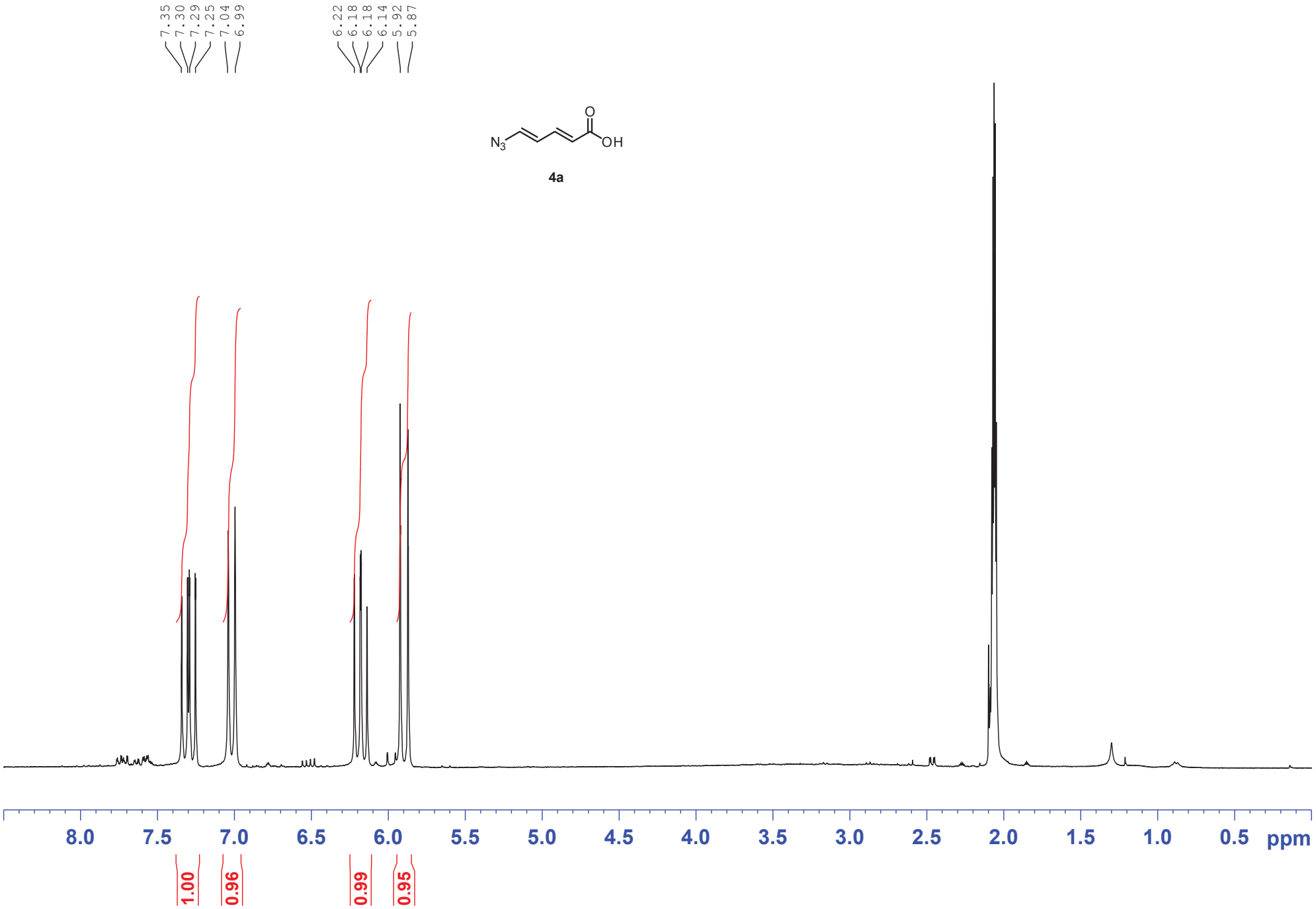
6c

Compound **6c** was obtained as a colorless solid in 22% yield. FTIR (neat) ν_{max} 2929, 2101, 1746, 1701, 1602, 1165, 989; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 7.29 (m, 1H), 7.01 (t, *J* 11.3, 1H), 6.17 (t, *J* 11.8, 1H), 5.93-5.87 (m, 2H), 5.01 (d, *J* 18.5, 1H), 4.85 (d, *J* 18.5, 1H), 3.28 (s, 1H), 2.27-2.11 (m, 2H), 2.09-2.08 (m, 3H), 1.96-1.20 (m, 18H), 0.98 (s, 3H), 0.91 (s, 3H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 176.3, 174.6, 160.8, 124.4, 123.9, 117.8, 115.6, 110.5, 85.5, 74.1, 70.7, 51.8, 50.6, 42.5, 40.4, 40.3, 36.2, 36.0, 33.6, 31.4, 31.4, 27.6, 27.4, 25.8, 24.1, 22.1, 22.0, 16.2; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{28}H_{38}N_3O_5$) requires *m/z* 496.2806, found *m/z* 496.2809.

(S)-tert-butyl 3-(4-hydroxyphenyl)-2-((2*E*,4*E*)-5-(4-(methoxymethyl)-1*H*-1,2,3-triazol-1-yl)penta-2,4-dienamido)propanoate (7)



Compound **7** was obtained as a white solid in an overall yield of 26% and 48% *via* route A and B, respectively. FTIR (neat) ν_{max} 3280, 2928, 1726, 1514, 1366, 1227, 1155; ^{1}H-NMR (500 MHz, CD_3COCD_3) δ 8.31 (s, 1H), 8.22 (s, 1H), 7.83 (d, *J* 14.3, 2H), 7.43 (d, *J* 8.1, 1H), 7.34 (dd, *J* 14.9, 11.5, 1H), 7.13 (dd, *J* 13.8, 11.5, 1H), 7.05 (d, *J* 8.4, 2H), 6.74 (d, *J* 8.5, 2H), 6.42 (d, *J* 14.9, 2H), 4.65 (q, *J* 7.5, 1H), 4.52 (s, 2H), 3.31 (s, 3H), 3.03-2.91 (m, 2H), 1.39 (s, 9H); ^{13}C-NMR (125 MHz, CD_3COCD_3) δ 171.86, 165.61, 157.43, 146.60, 137.22, 131.45, 128.81, 128.08, 122.07, 119.67, 116.30, 81.90, 66.15, 58.09, 55.44, 40.77, 37.76, 28.26; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{28}N_4O_5Na$) requires *m/z* 451.1956, found *m/z* 451.1952.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6.22
6.18
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N3
OH
4a
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7.5
7.0
6.5
6.0
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5.0
4.5
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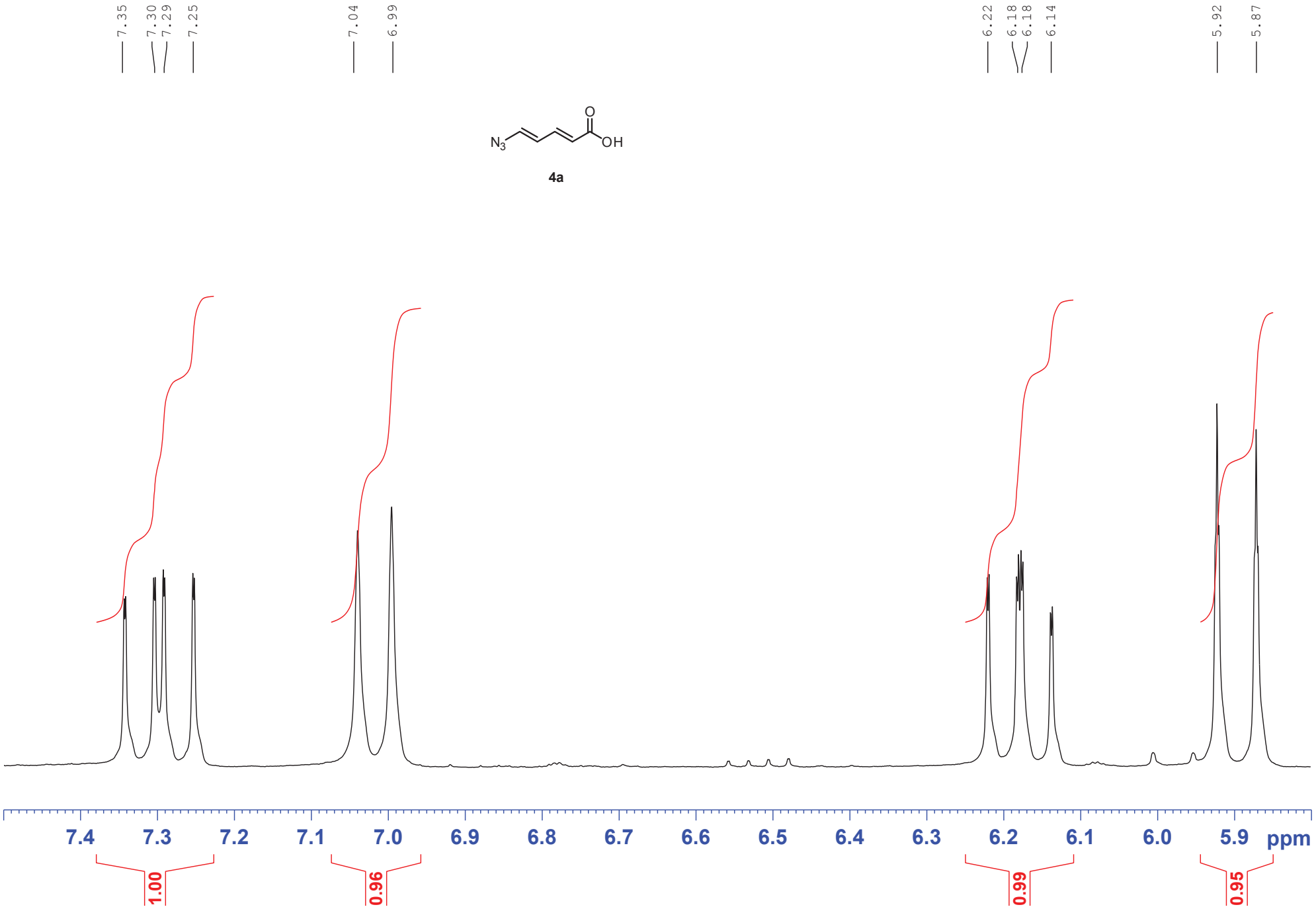
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N3
O
OH
4a
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7.3
7.2
7.1
7.0
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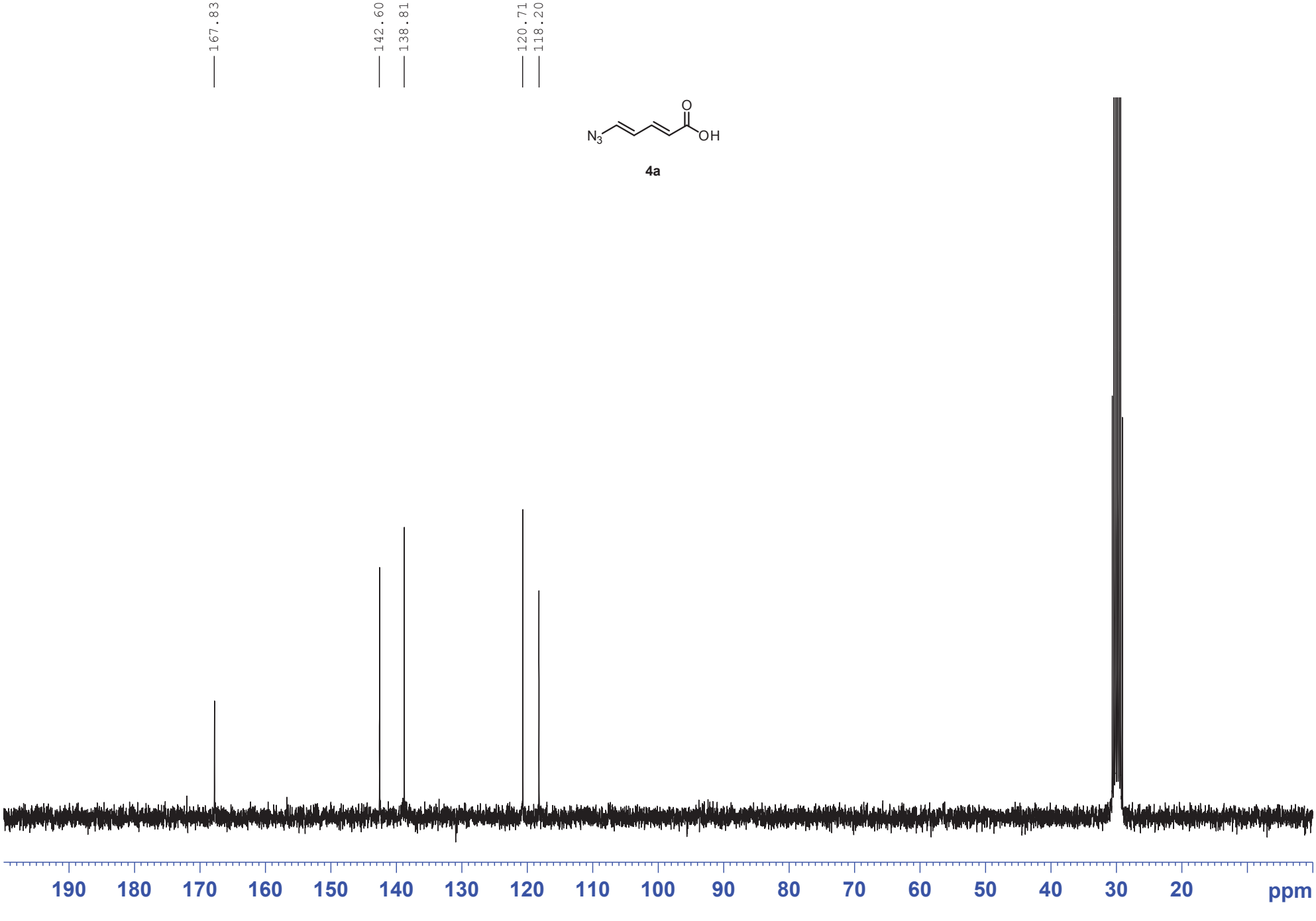
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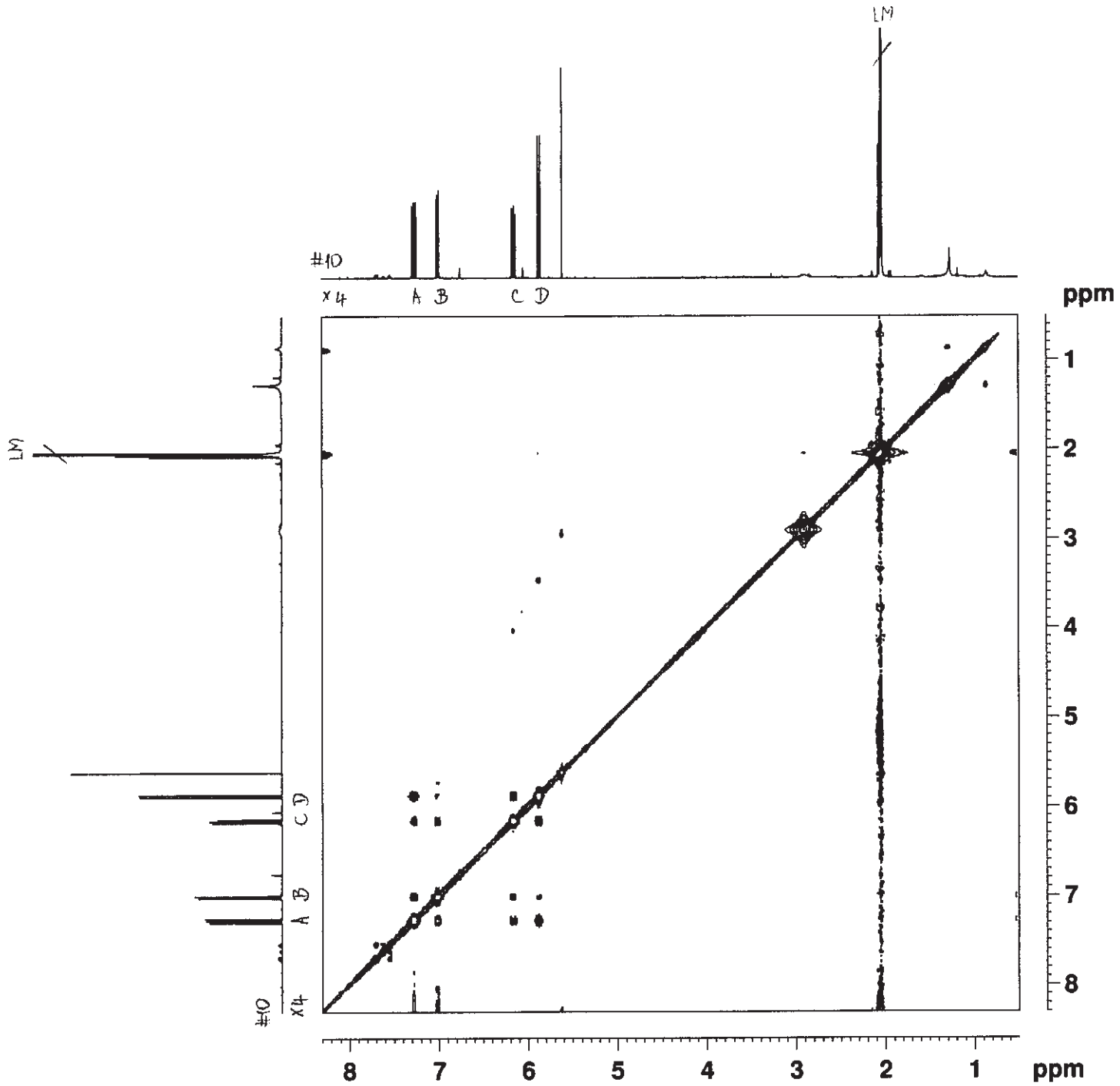
ppm



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18.65

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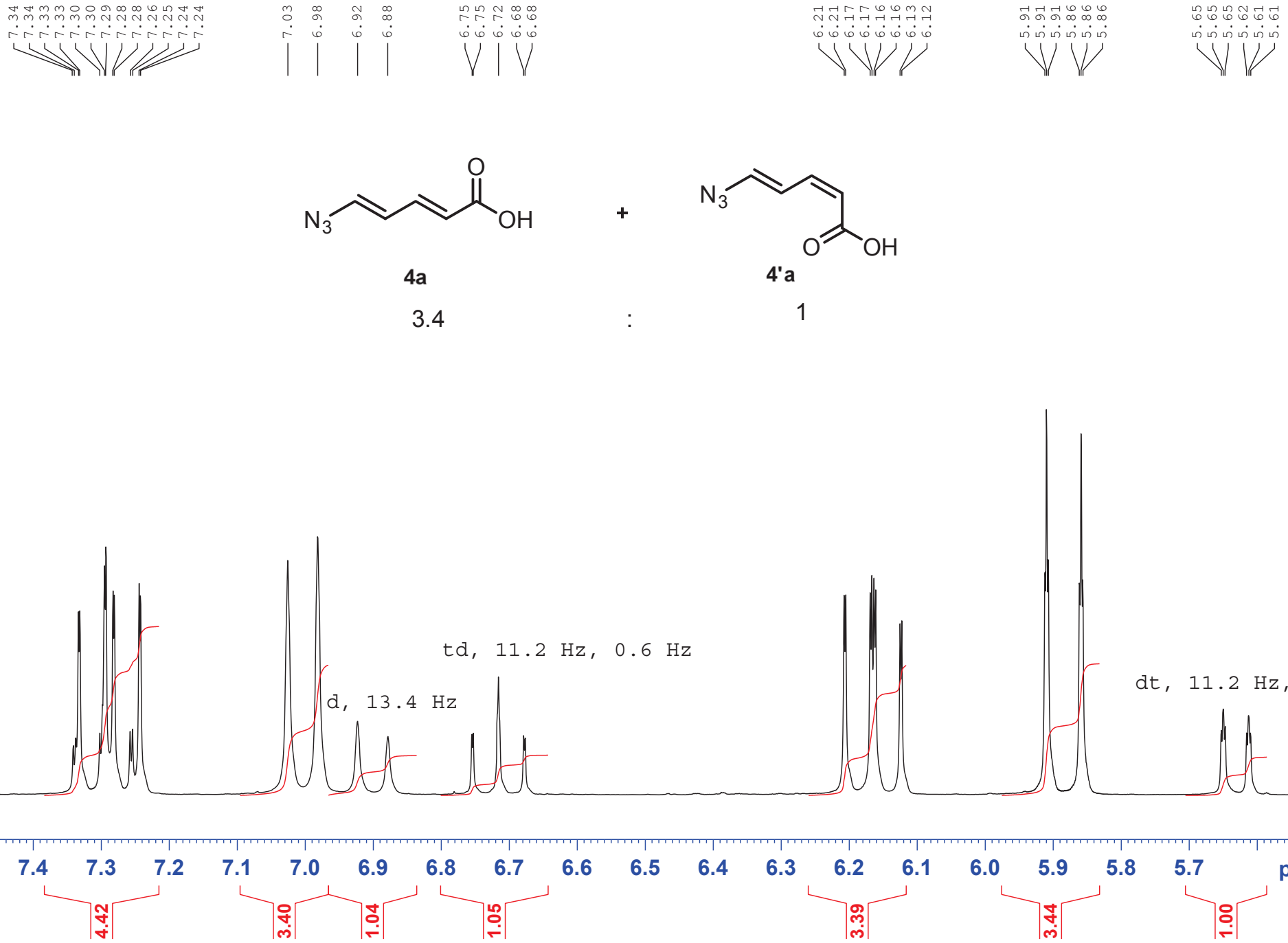
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+
N3
O
OH
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3.4
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d, 13.4 Hz
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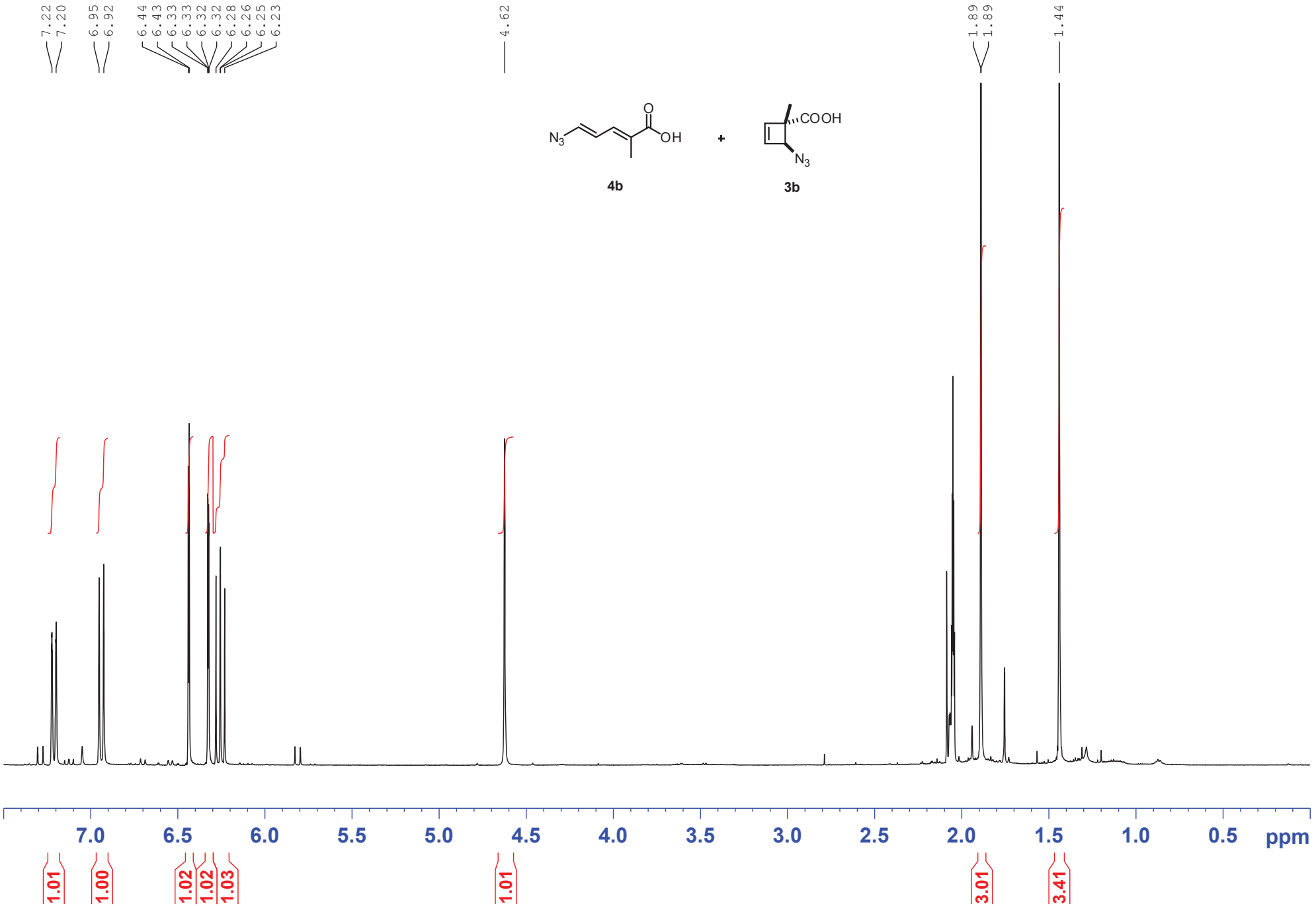
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6.23
4.62
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+
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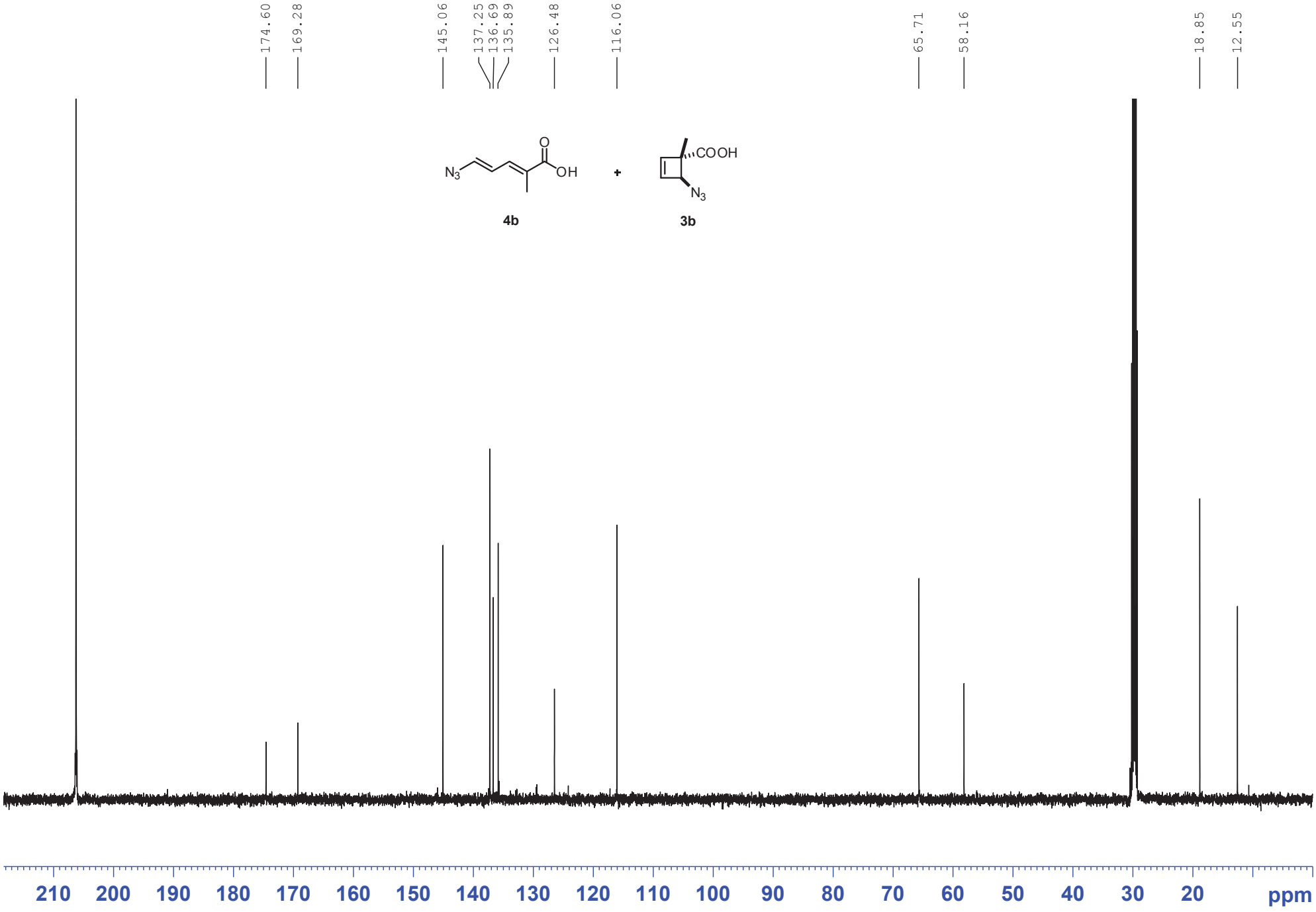
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OH
N3
4b
+
COOH
N3
3b
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ppm

sou-sa-142-01

Key NOES

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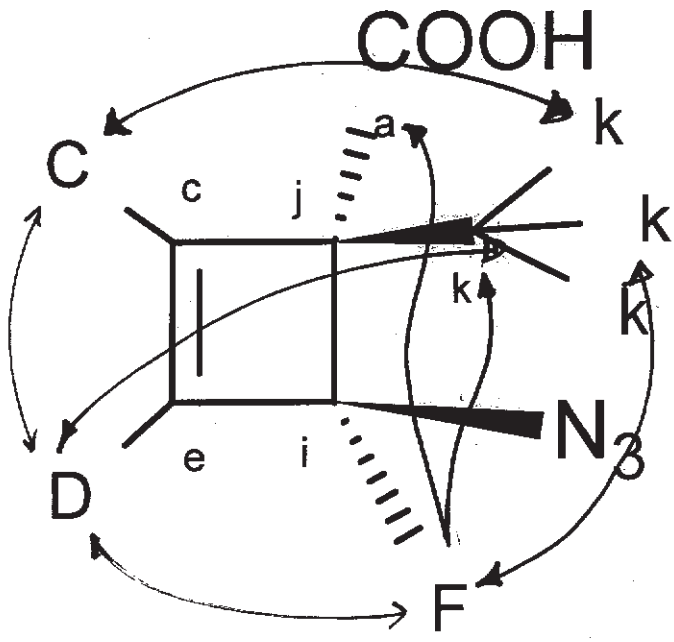
$NOE_{FK} = 0.52$

$NOE_{DK} = 0.155$



Key $^3J_{CH}$

$^3J_{Fk}$ = (undetected)

$^3J_{Fa} = 4.8$ Hz

or enantiomer

Key $^3J_{HH}$

$J_{CD} = 2.9$ Hz

$J_{DF} < 1$ Hz

Key NOES

$NOE_{AB} = 0.97$

$NOE_{BA} = 1.00$

$NOE_{BE} = 0.08$

$NOE_{EB} = 0.08$

$NOE_{AE} = 0.11$

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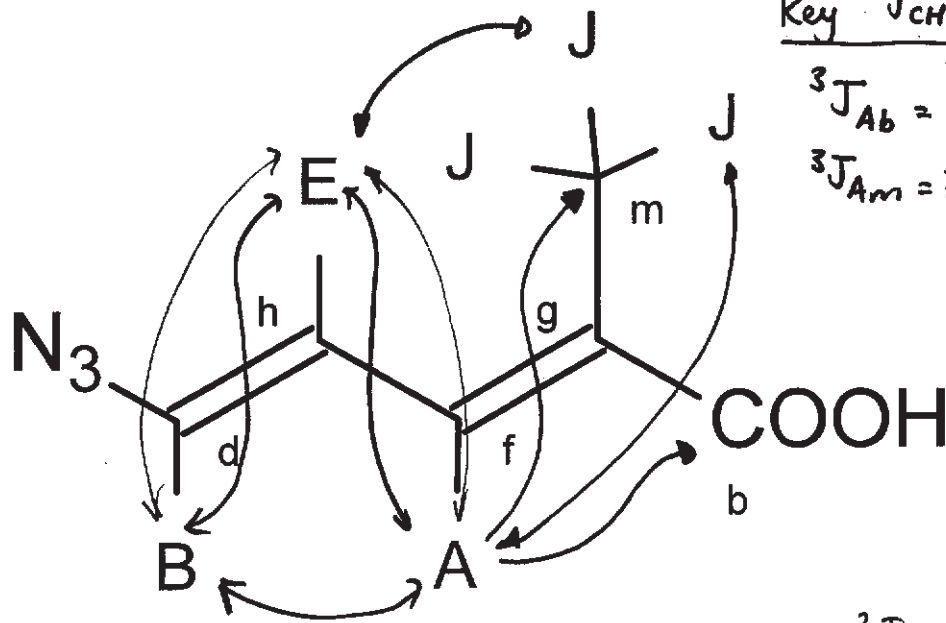
$NOE_{AJ} = 0.05$

$NOE_{JA} = 0.05$



Key $^3J_{CH}$

$^3J_{Ab} = 7.0$ Hz (cis)

$^3J_{Am} = 7.3$ Hz (trans)

Key $^3J_{HH}$

$J_{AE} = 11.9$ Hz (trans)

$J_{BE} = 13.1$ Hz (trans)

sou-sa-142-01
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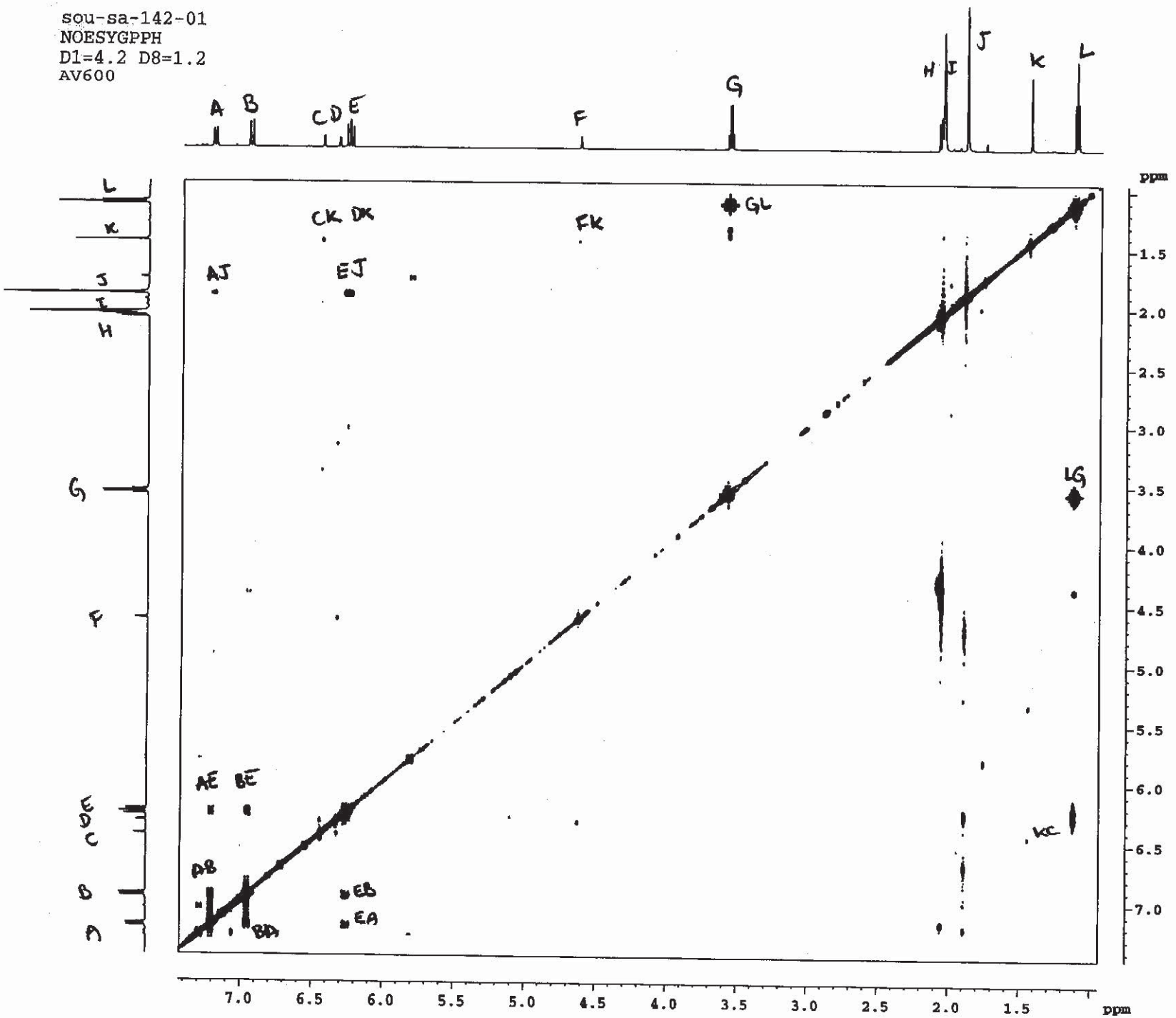
AV600



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GPZ1	
GPZ2	
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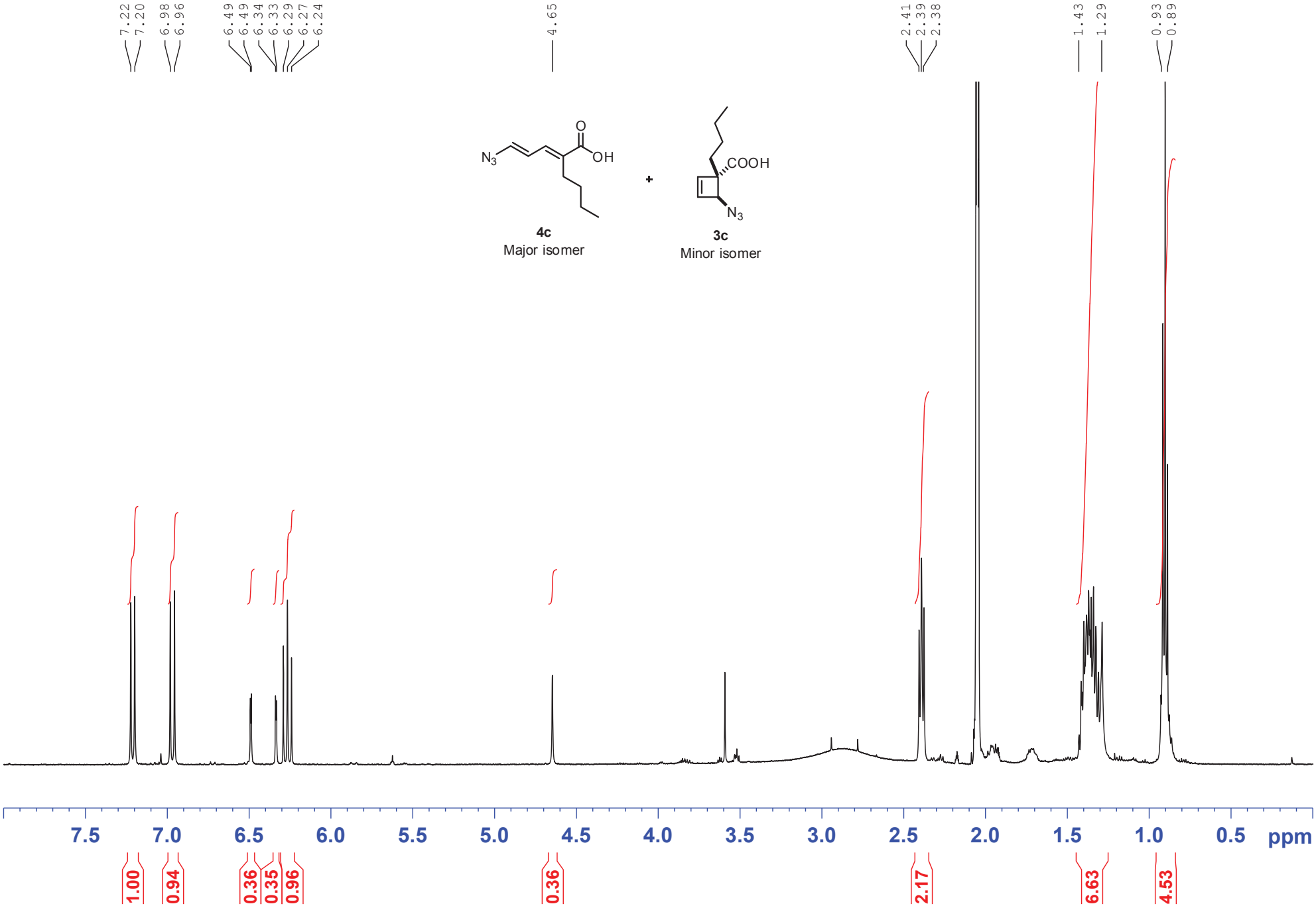
ND0	
TD	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6.27
6.24
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2.41
2.39
2.38
1.43
1.29
0.93
0.89
N3
O
OH
4c
Major isomer
+
COOH
N3
3c
Minor isomer
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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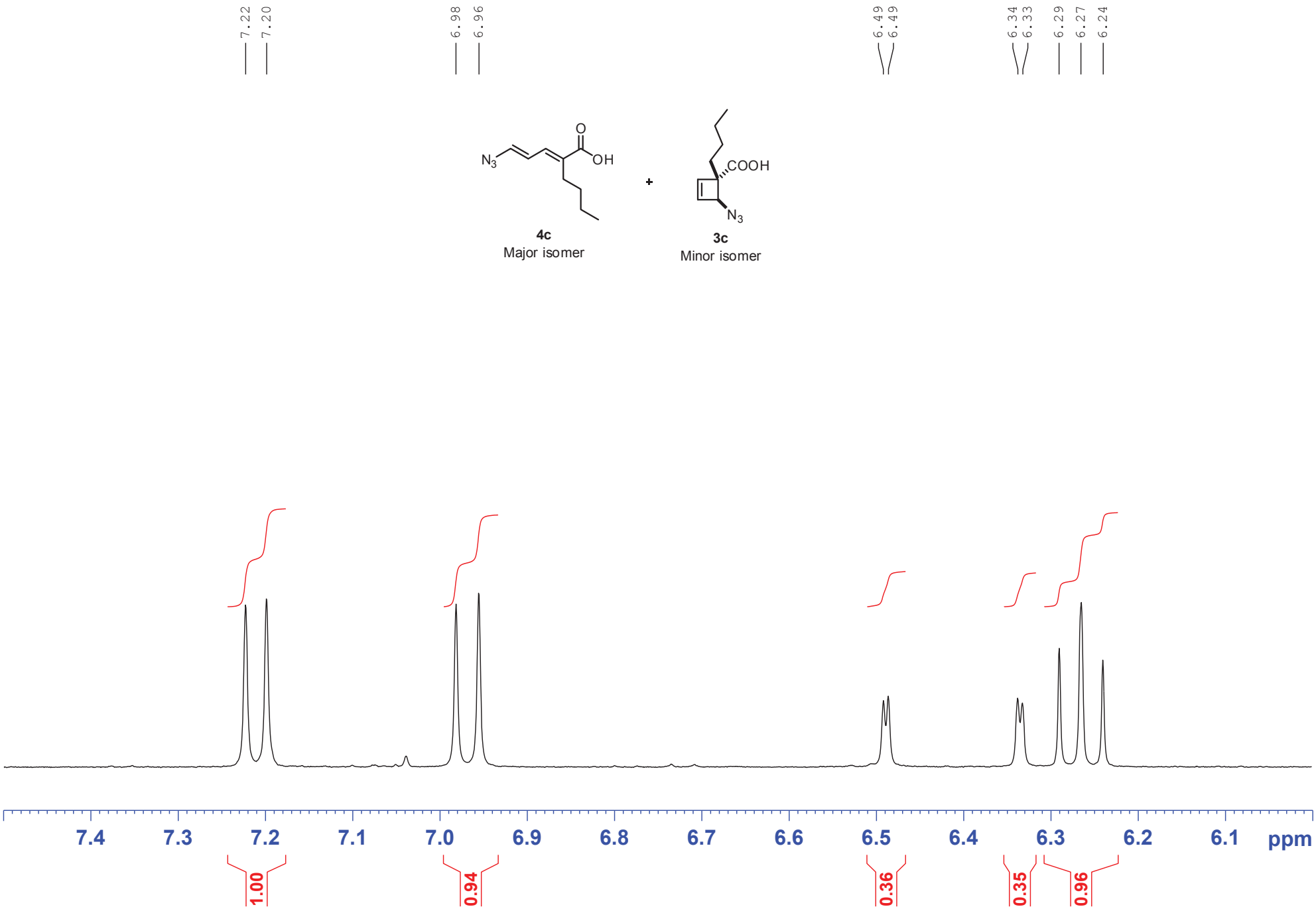
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6.49
6.34
6.33
6.29
6.27
6.24
N3
O
OH
4c
Major isomer
+
COOH
N3
3c
Minor isomer
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
ppm
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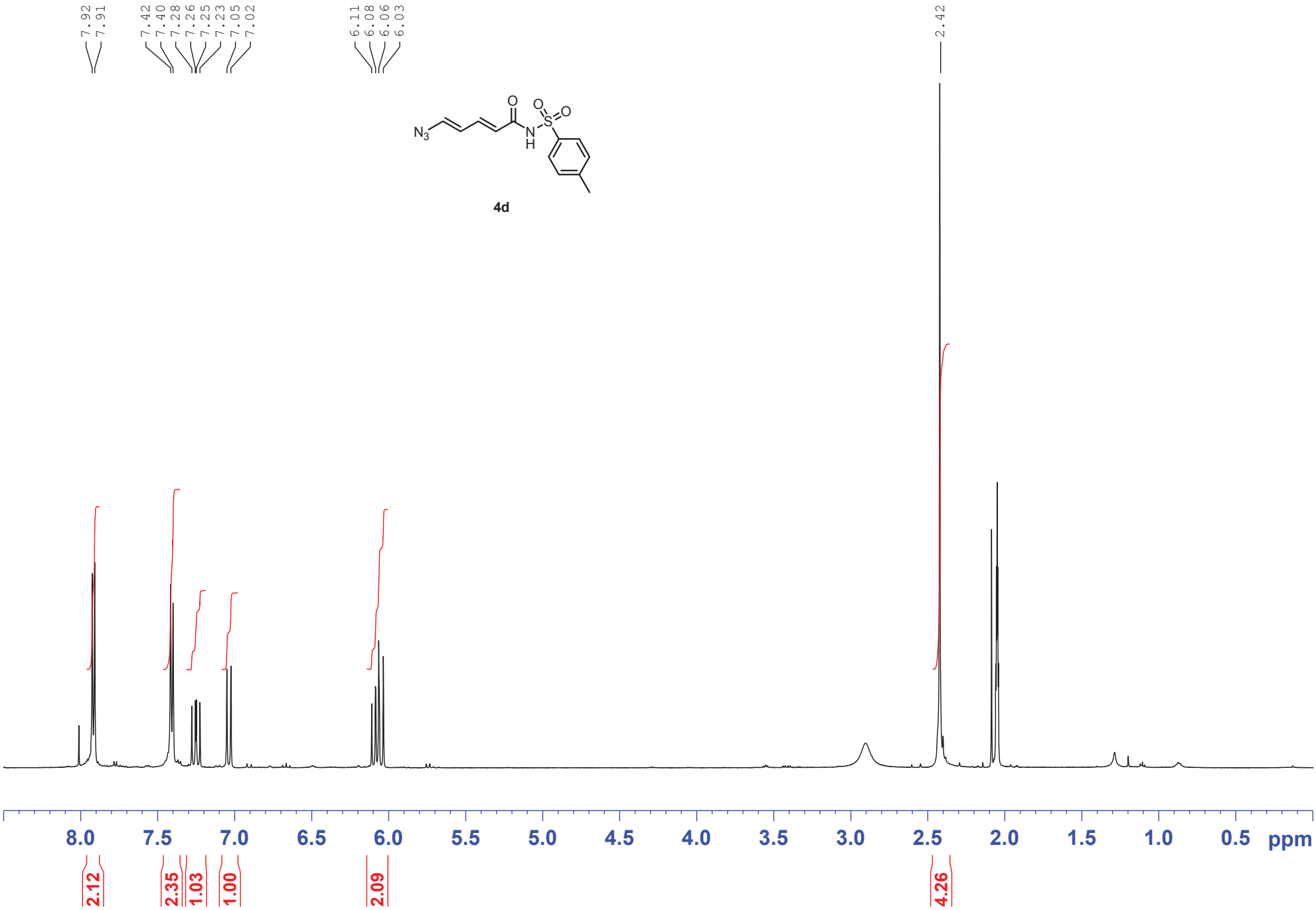
0.35
0.96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7.91
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7.26
7.25
7.23
7.05
7.02
6.11
6.08
6.06
6.03
2.42
4d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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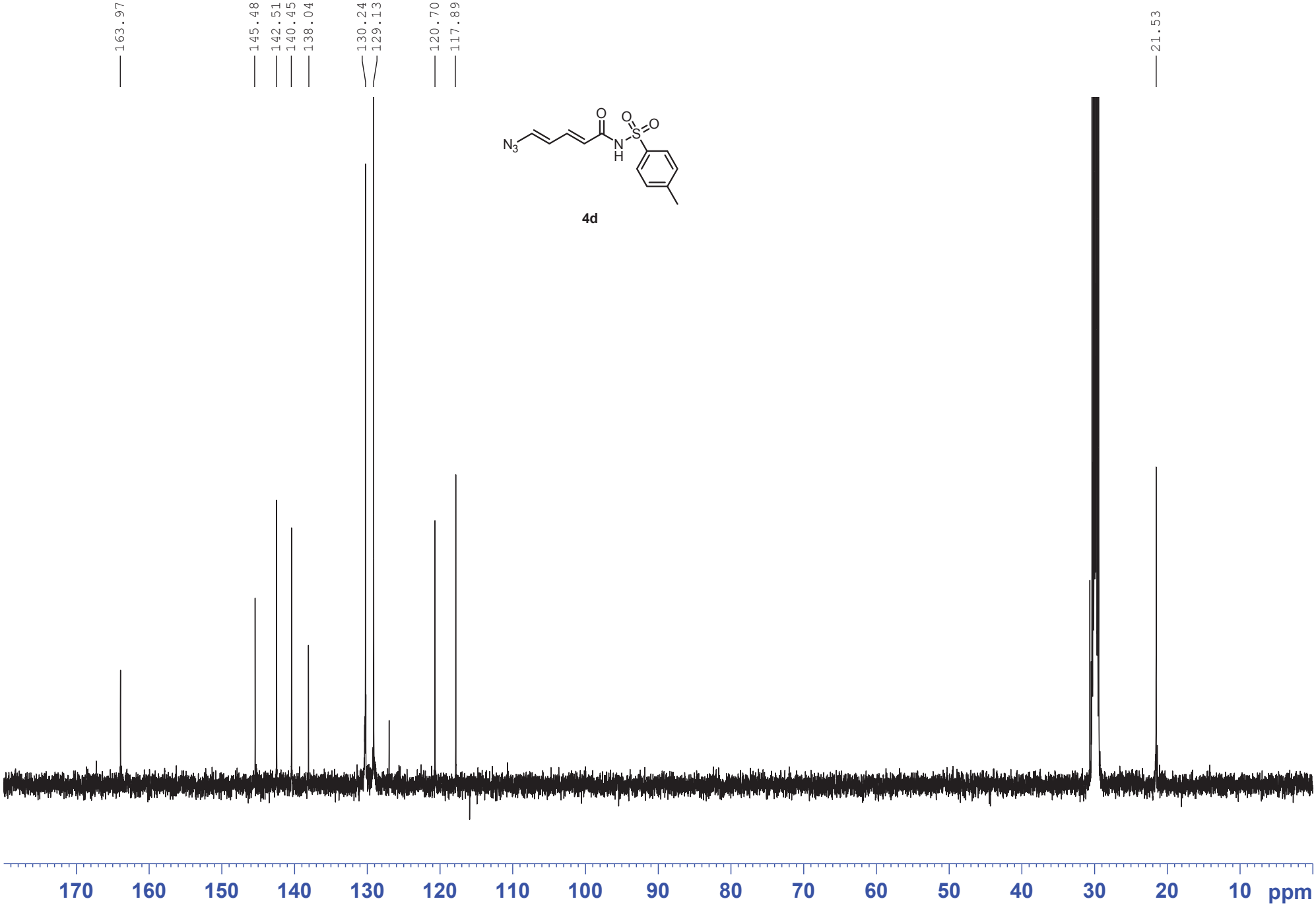
2.09
4.26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142.51
140.45
138.04
130.24
129.13
120.70
117.89
21.53
O
O
S
O
N
H
N3
4d
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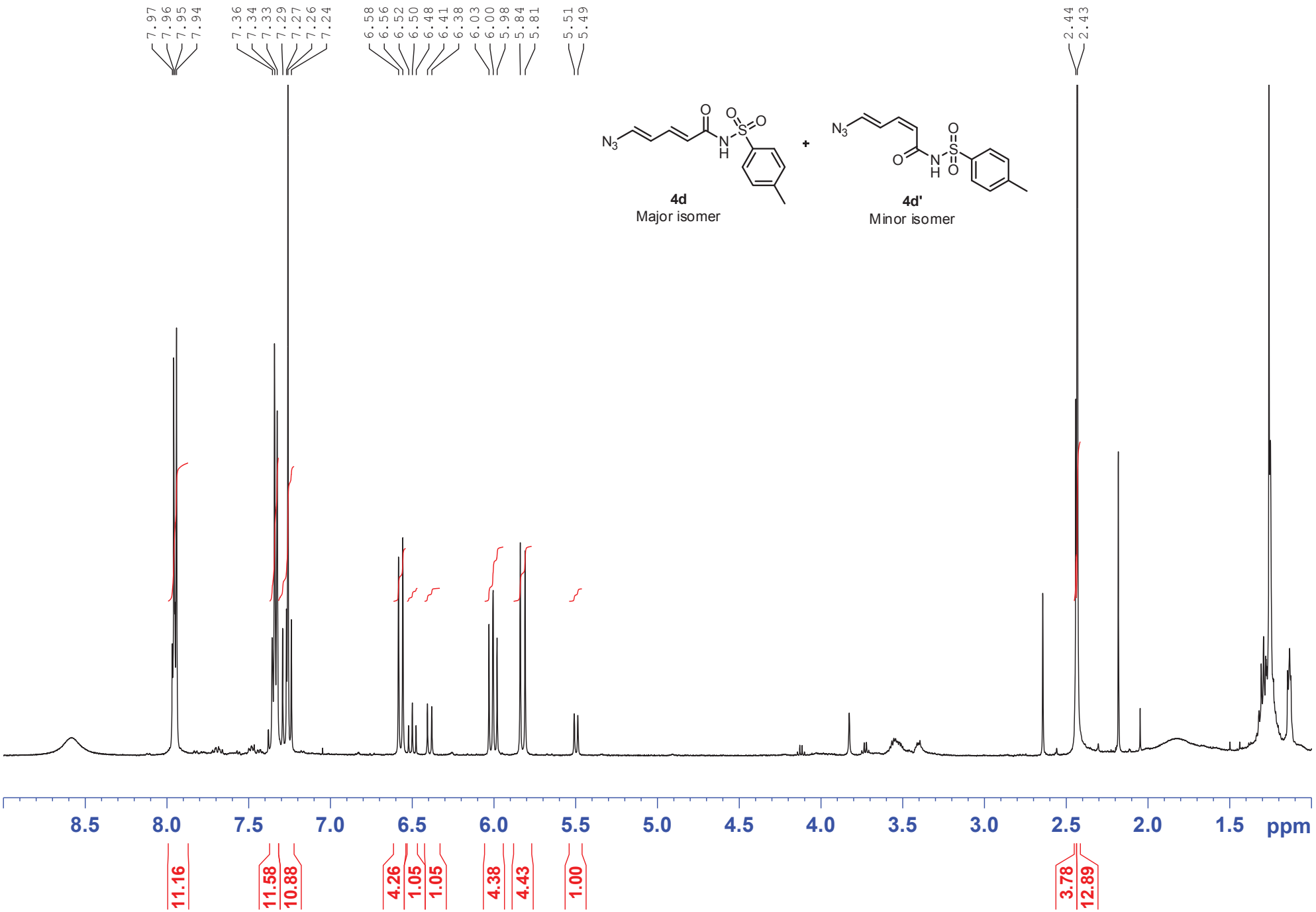
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.95
7.94
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7.33
7.29
7.27
7.26
7.24
6.58
6.56
6.52
6.50
6.48
6.41
6.38
6.03
6.00
5.98
5.84
5.81
5.51
5.49
2.44
2.43
4d
Major isomer
4d'
Minor isomer
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
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11.58
10.88
4.26
1.05
1.05
4.38
4.43
1.00
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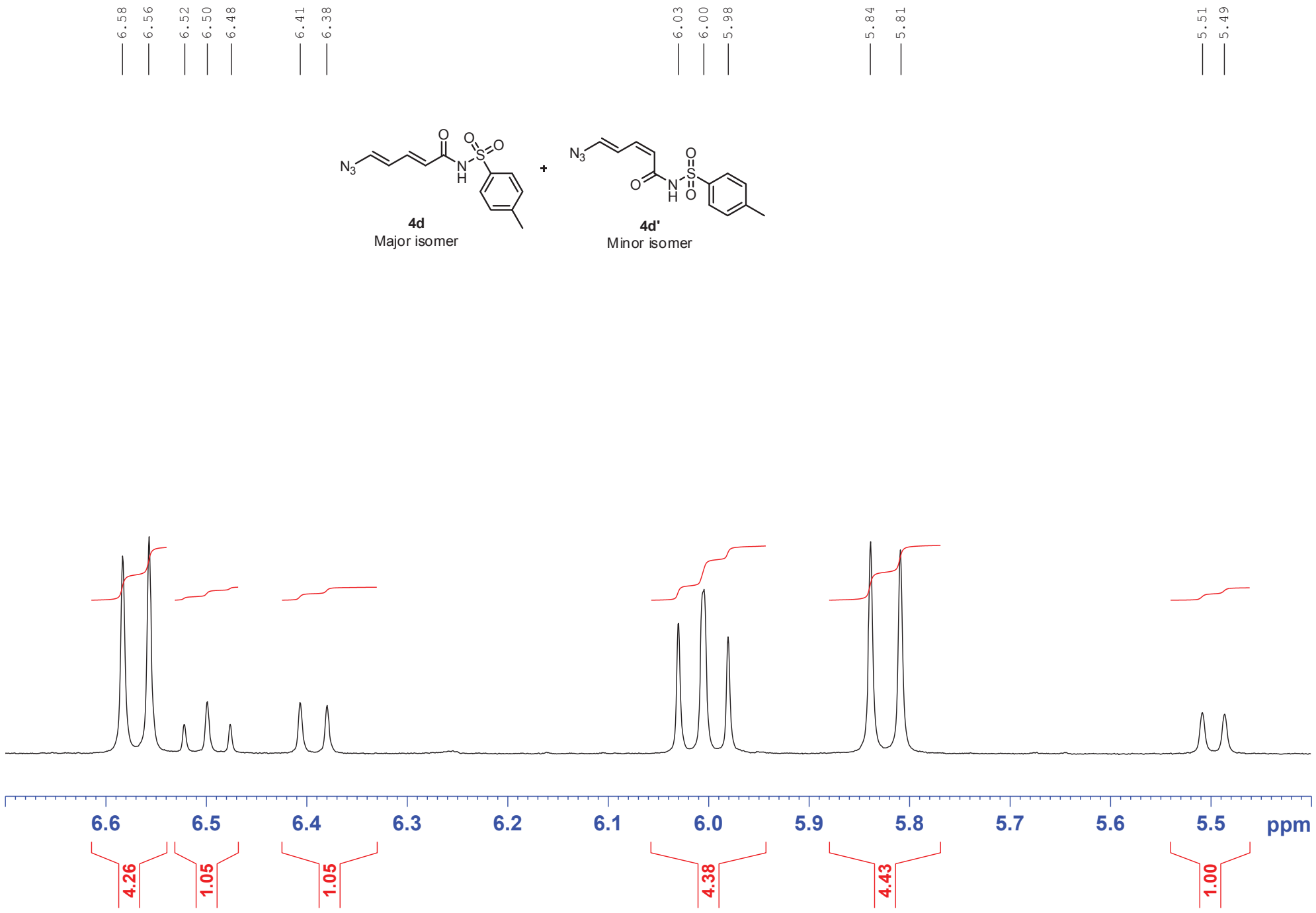
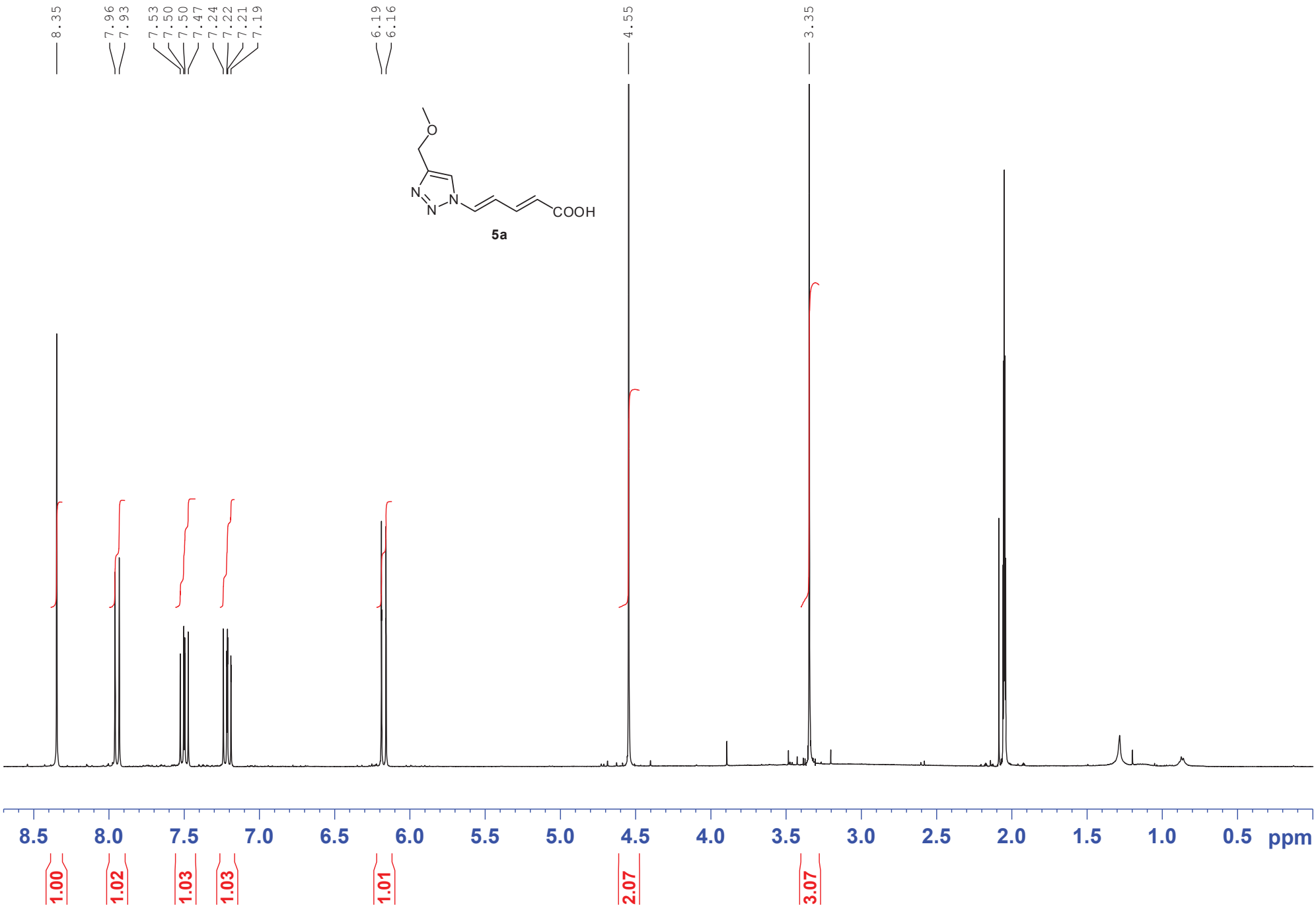
12.89


6.58
6.56
6.52
6.50
6.48
6.41
6.38
6.03
6.00
5.98
5.84
5.81
5.51
5.49
4d
Major isomer
4d'
Minor isomer
6.6
6.5
6.4
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
ppm
4.26
1.05
1.05
4.38
4.43
1.00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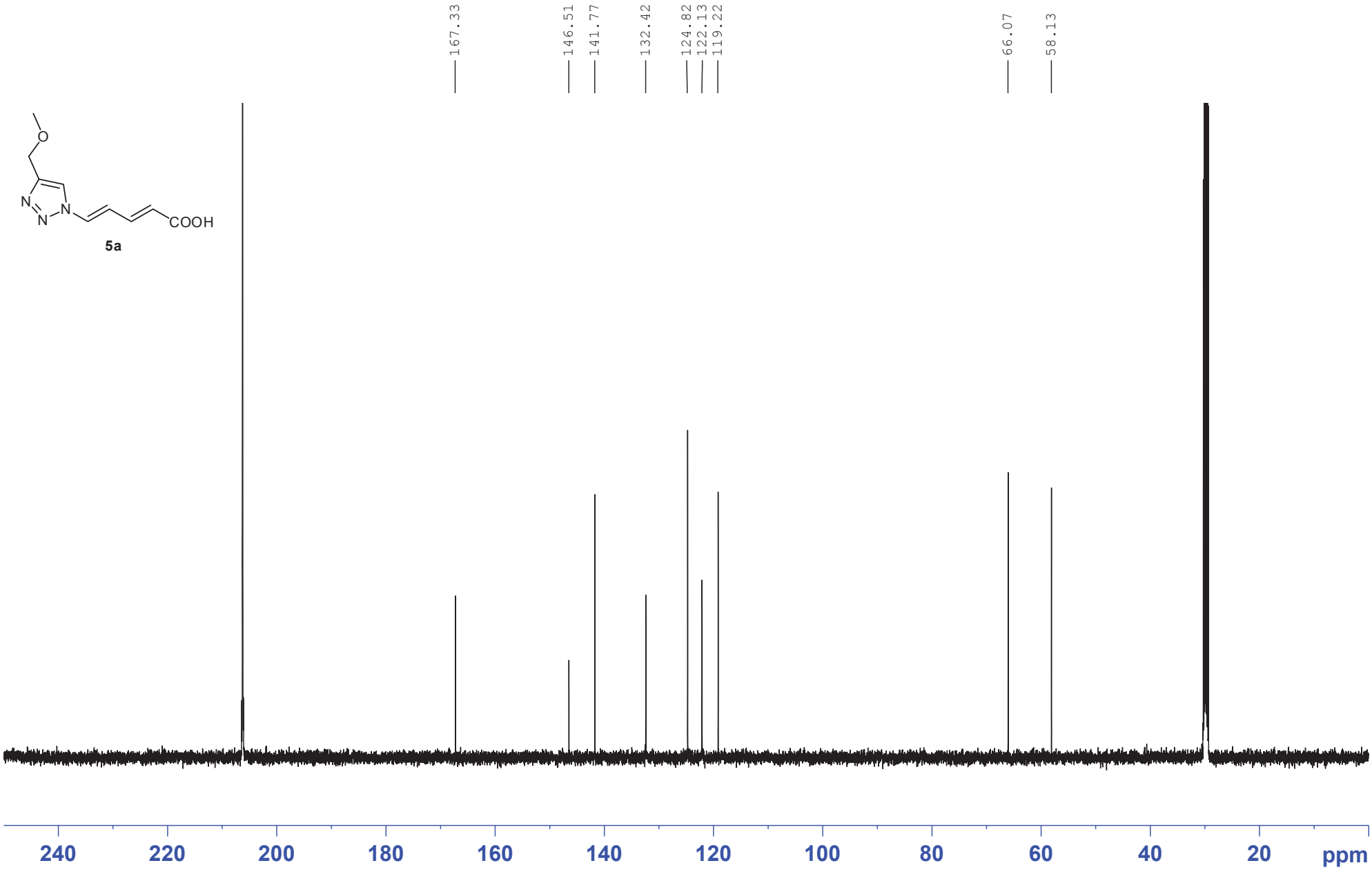
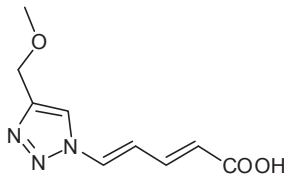
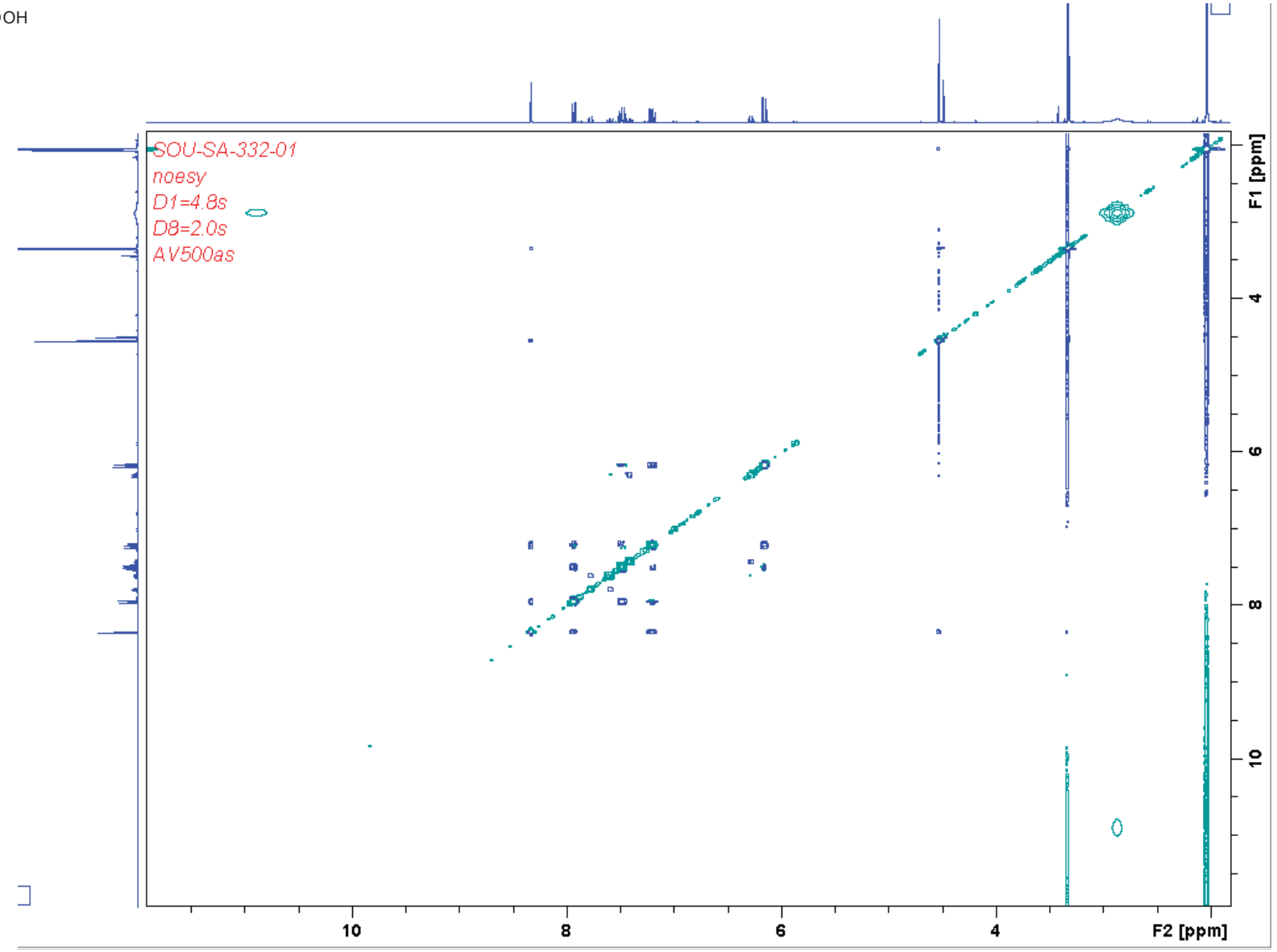
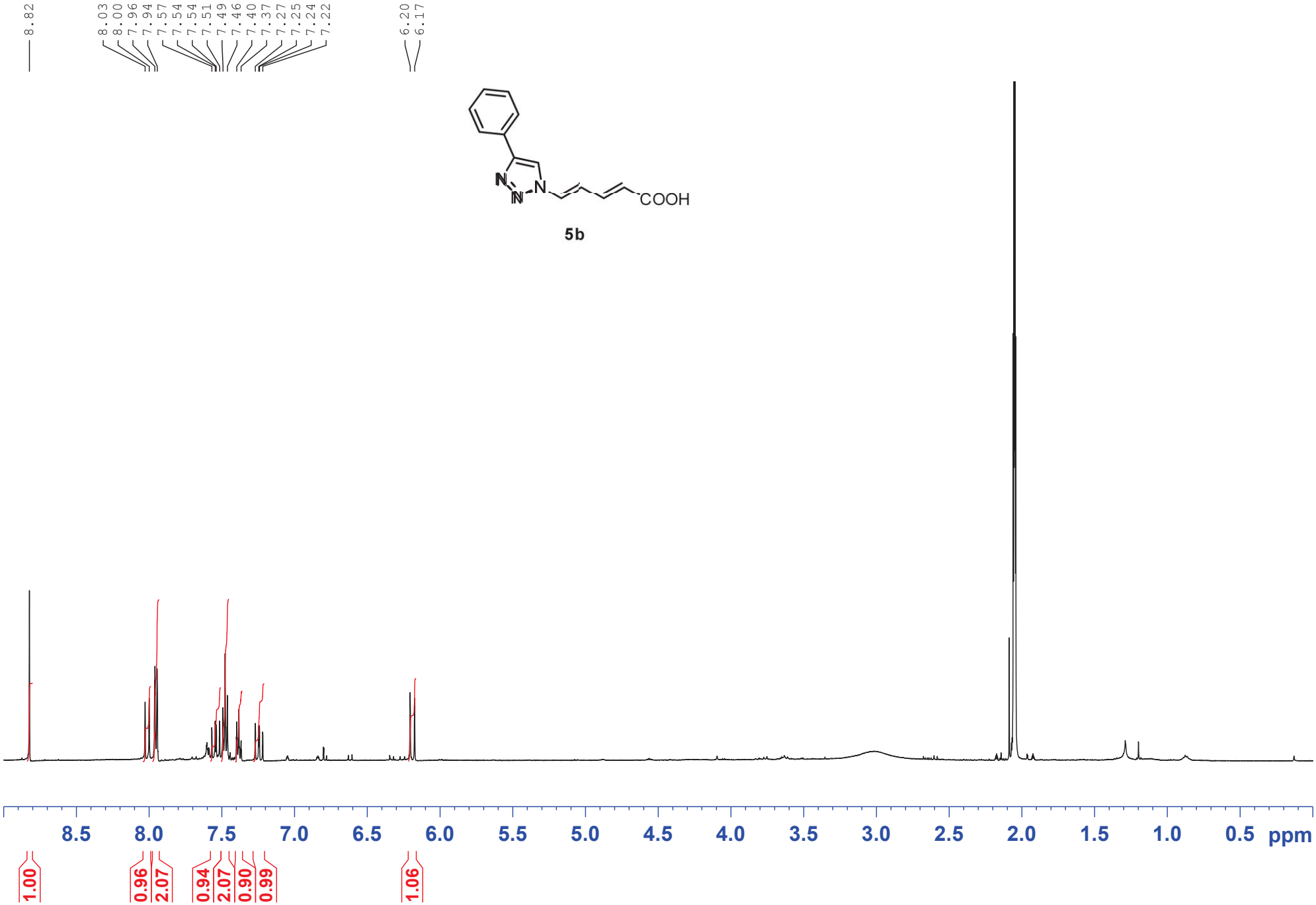
7.96
7.93
7.53
7.50
7.50
7.47
7.24
7.22
7.21
7.19
6.19
6.16
4.55
3.35
O
N
N
N
COOH
5a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.02
1.03
1.03
1.01
2.07
3.07


167.33
146.51
141.77
132.42
124.82
122.13
119.22
66.07
58.13
O
N
N
N
COOH
5a
240
220
200
180
160
140
120
100
80
60
40
20
ppm


O
N
N
N
COOH

5a


SOU-SA-332-01
noesy
D1=4.8s
D8=2.0s
AV500as
F1 [ppm]
F2 [ppm]
10
8
6
4
2
10
8
6
4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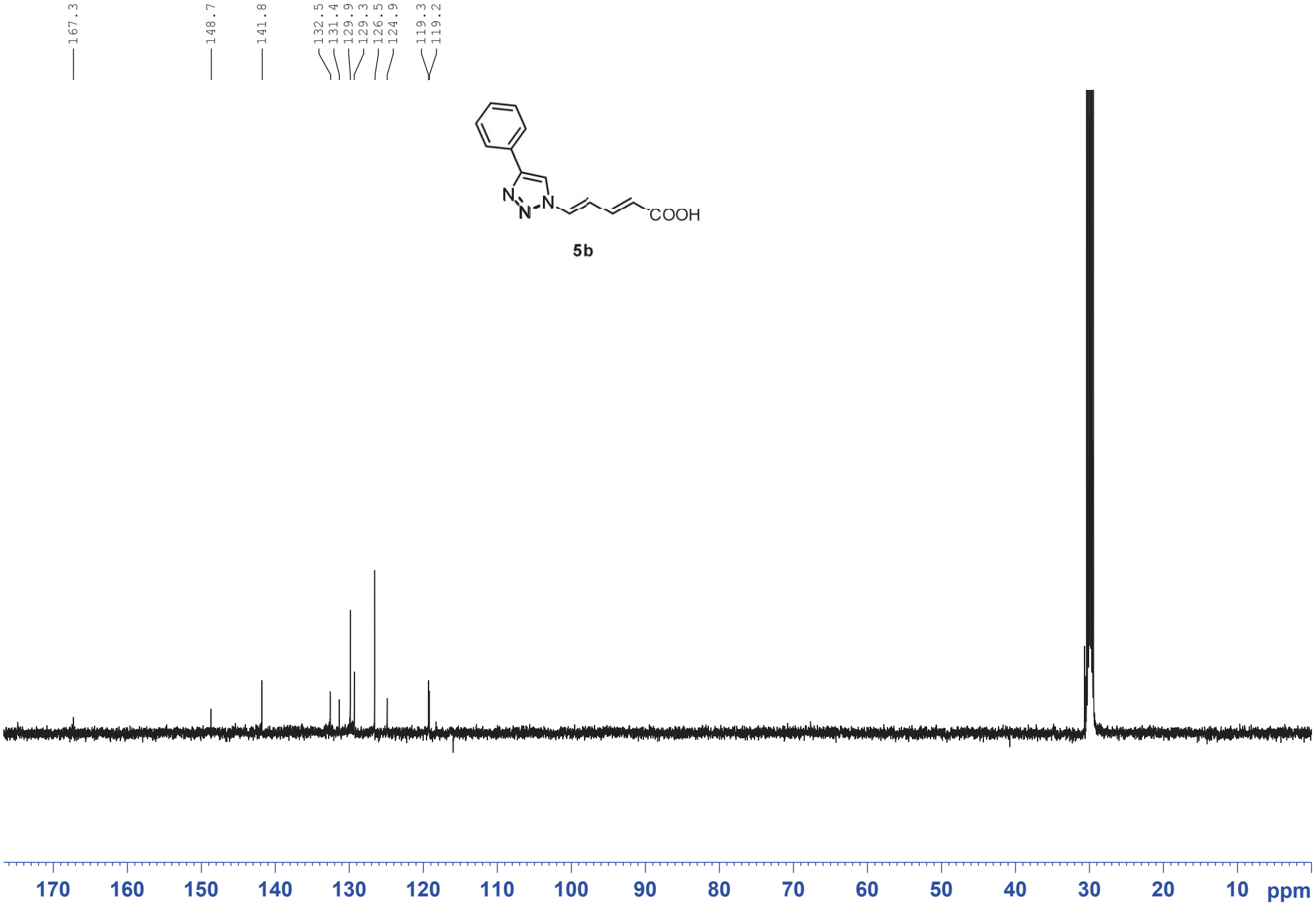
8.03
8.00
7.96
7.94
7.57
7.54
7.54
7.51
7.49
7.46
7.40
7.37
7.27
7.25
7.24
7.22
6.20
6.17
COOH
5b
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.96
2.07
0.94
2.07
0.90
0.99
1.06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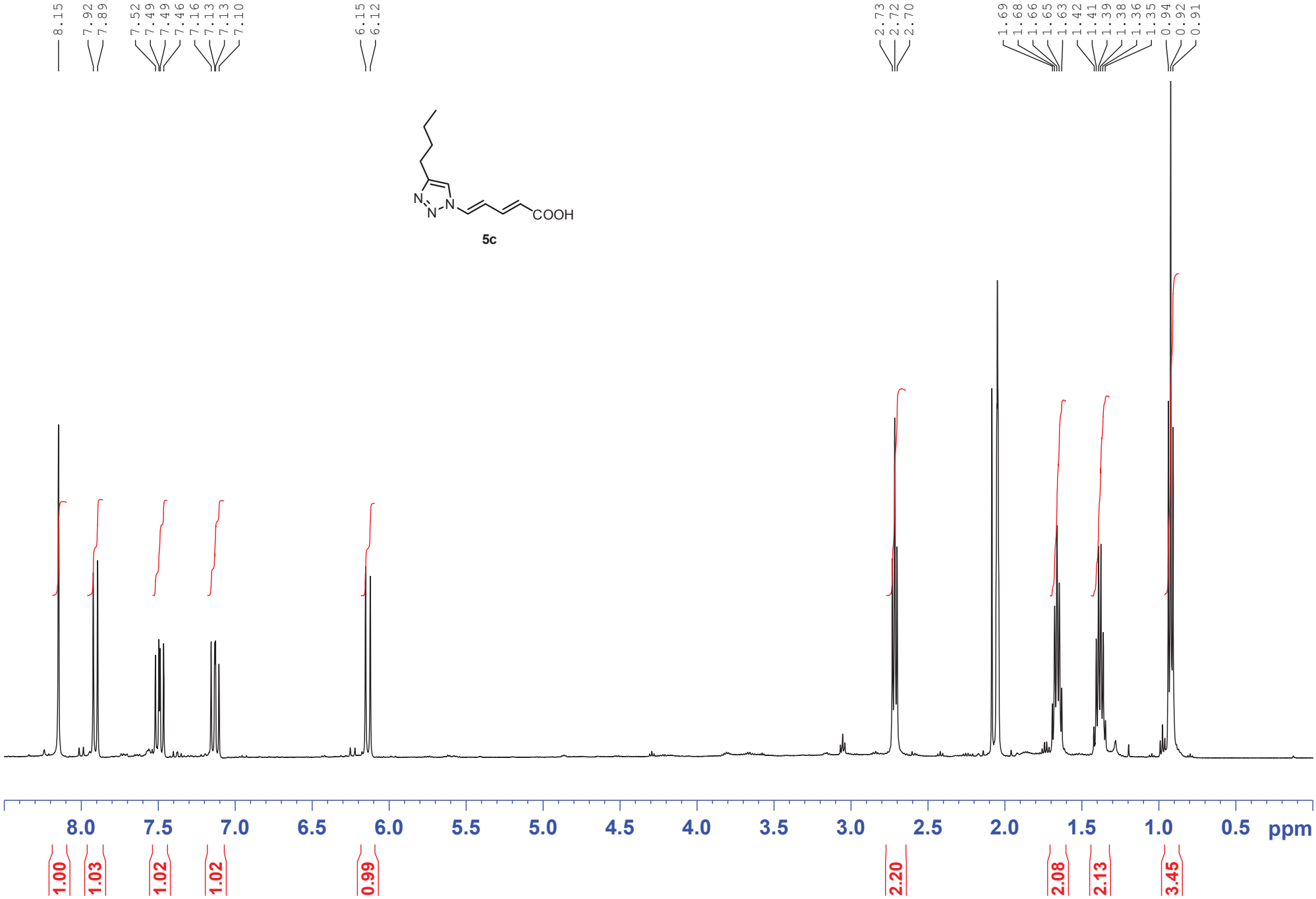
148.7
141.8
132.5
131.4
129.9
129.3
126.5
124.9
119.3
119.2
N
N
N
COOH
5b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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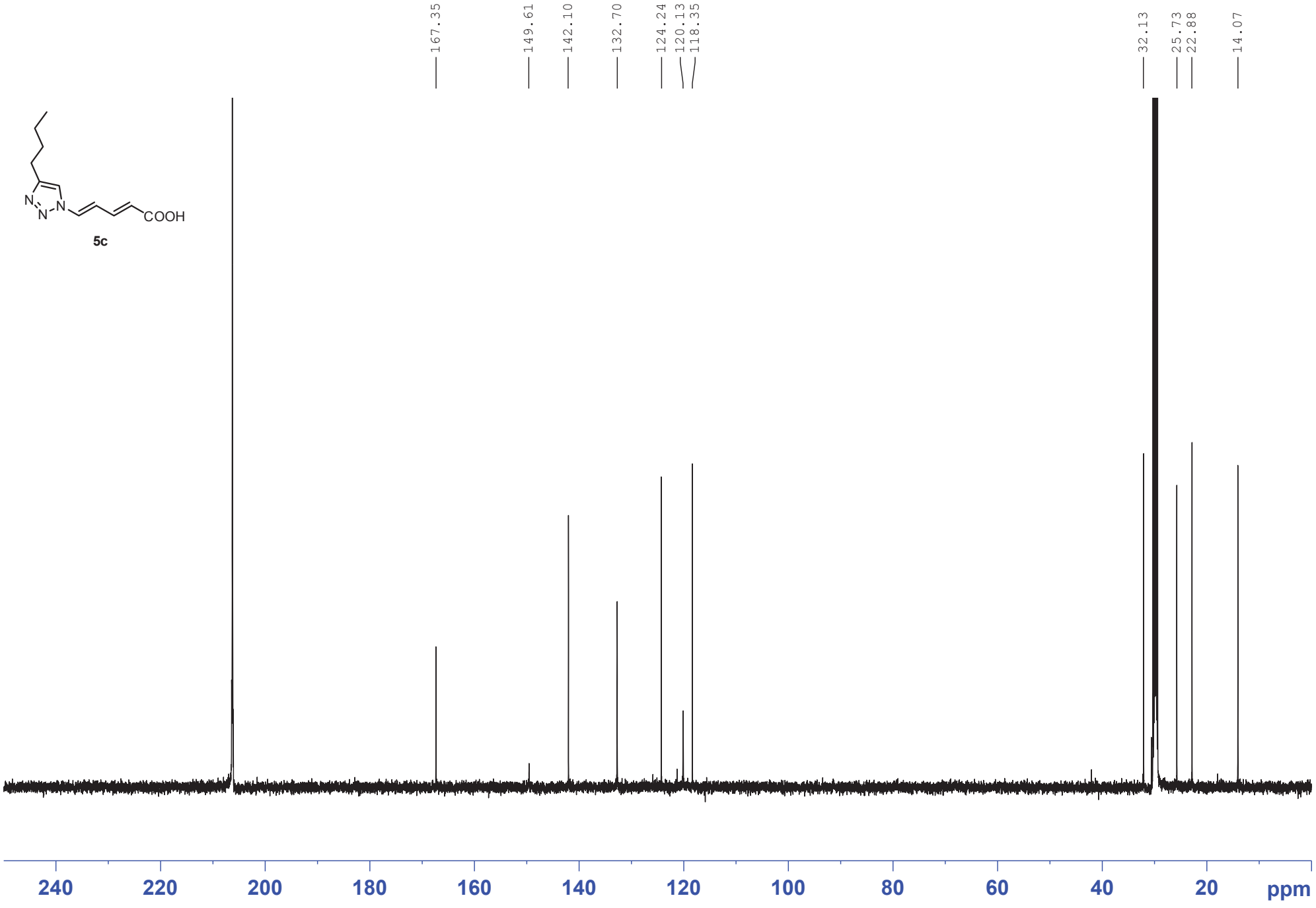
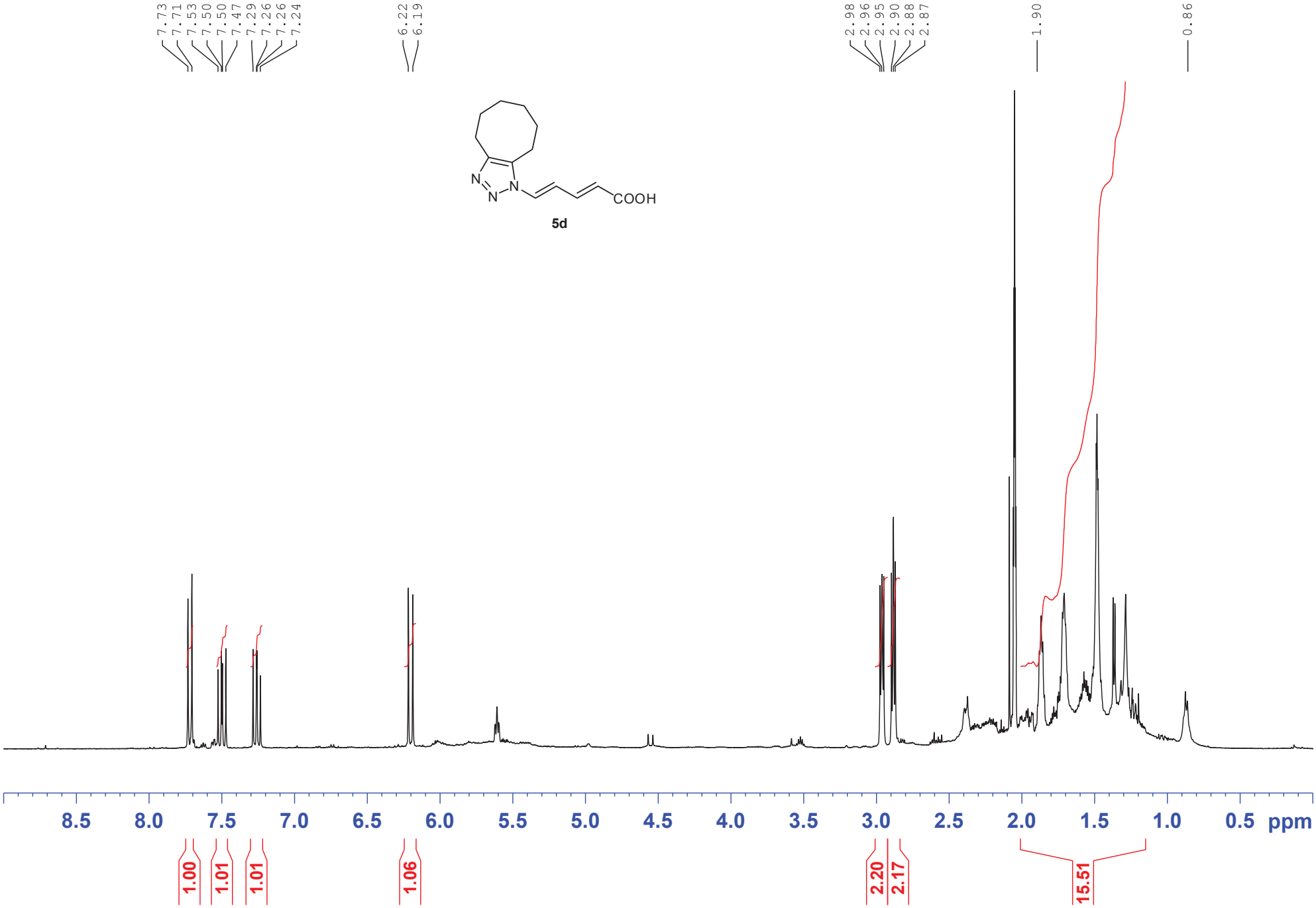
7.92
7.89
7.52
7.49
7.49
7.46
7.16
7.13
7.13
7.10
6.15
6.12
2.73
2.72
2.70
1.69
1.68
1.66
1.65
1.63
1.42
1.41
1.39
1.38
1.36
1.35
0.94
0.92
0.91
N
N
N
COOH
5c
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.03
1.02
1.02
0.99
2.20
2.08
2.13
3.45


167.35
149.61
142.10
132.70
124.24
120.13
118.35
32.13
25.73
22.88
14.07
N
N
N
COOH
5c
240
220
200
180
160
140
120
100
80
60
40
20
ppm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7.71
7.53
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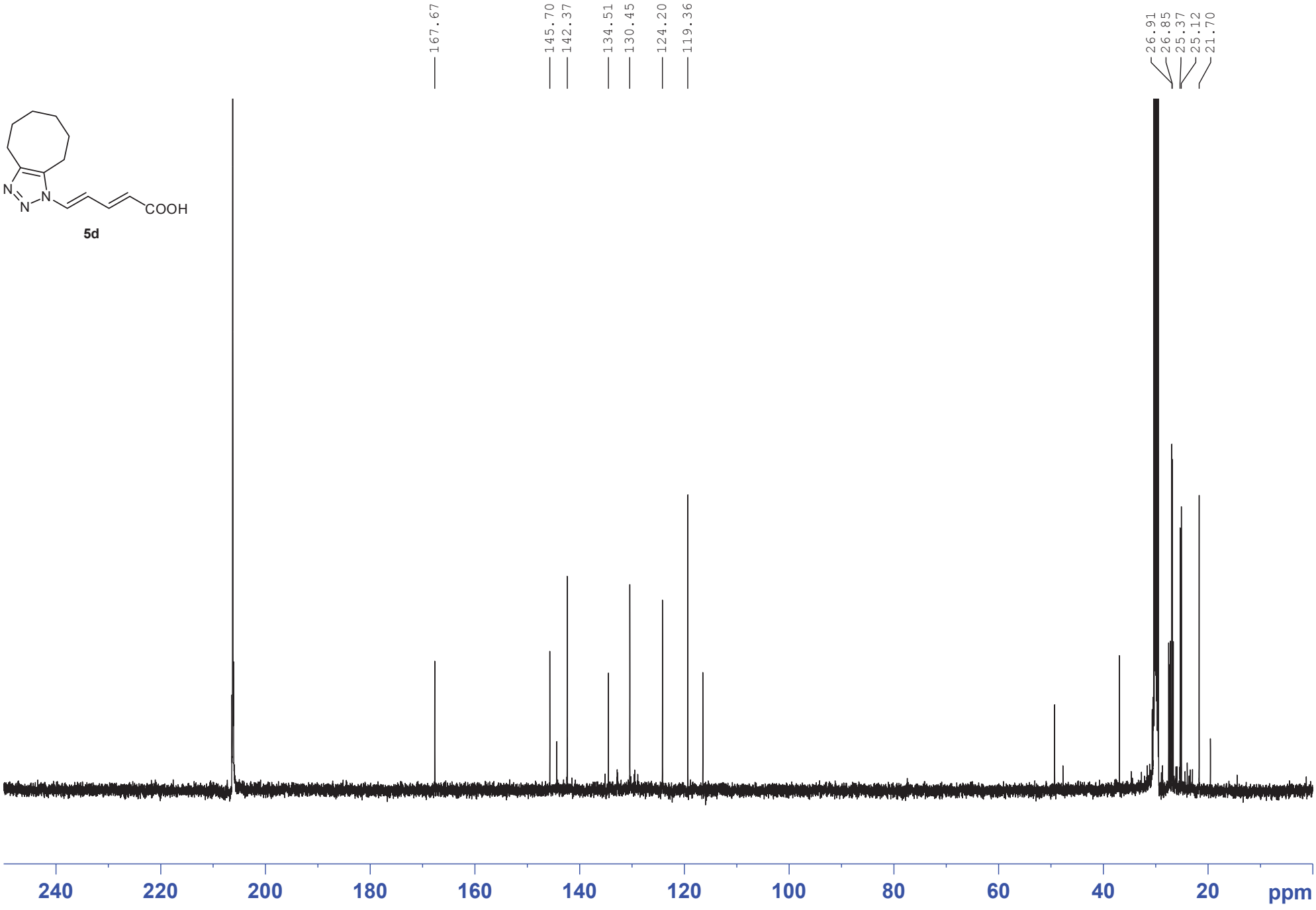
7.50
7.47
7.29
7.26
7.26
7.24
6.22
6.19
2.98
2.96
2.95
2.90
2.88
2.87
1.90
0.86
N
N
N
COOH
5d
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.01
1.01
1.06
2.20
2.17
15.51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145.70
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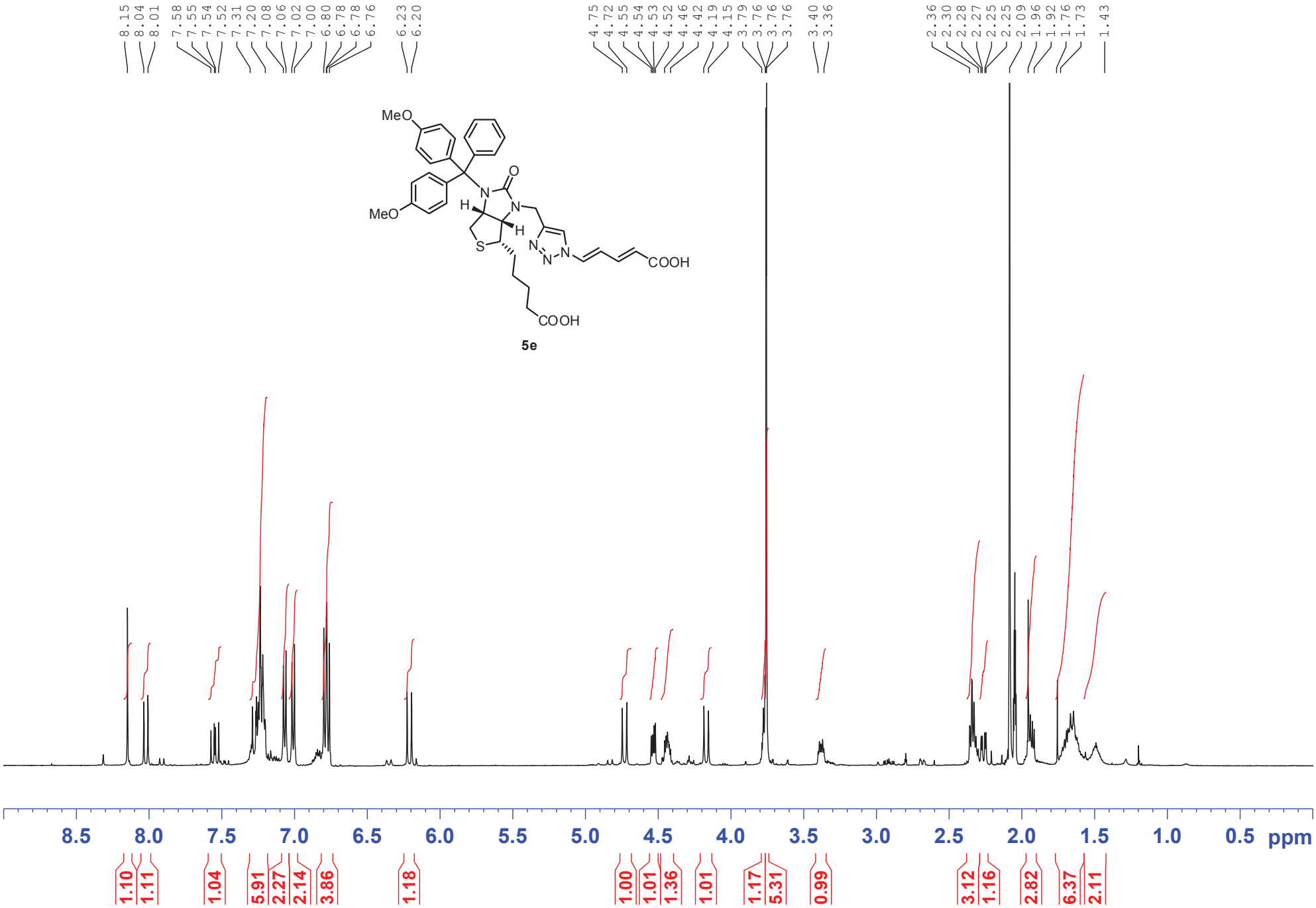
134.51
130.45
124.20
119.36
26.91
26.85
25.37
25.12
21.70
N
N
N
COOH
5d
240
220
200
180
160
140
120
100
80
60
40
20
ppm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7.02
7.00
6.80
6.78
6.78
6.76
6.23
6.20
4.75
4.72
4.55
4.54
4.53
4.52
4.46
4.42
4.19
4.15
3.79
3.76
3.76
3.76
3.40
3.36
2.36
2.30
2.28
2.27
2.25
2.25
2.09
1.96
1.92
1.76
1.73
1.43
MeO
MeO
O
N
H
N
H
S
N
N
N
COOH
COOH
5e
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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1.11
1.04
5.91
2.27
2.14
3.86
1.18
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1.01
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3.12
1.16
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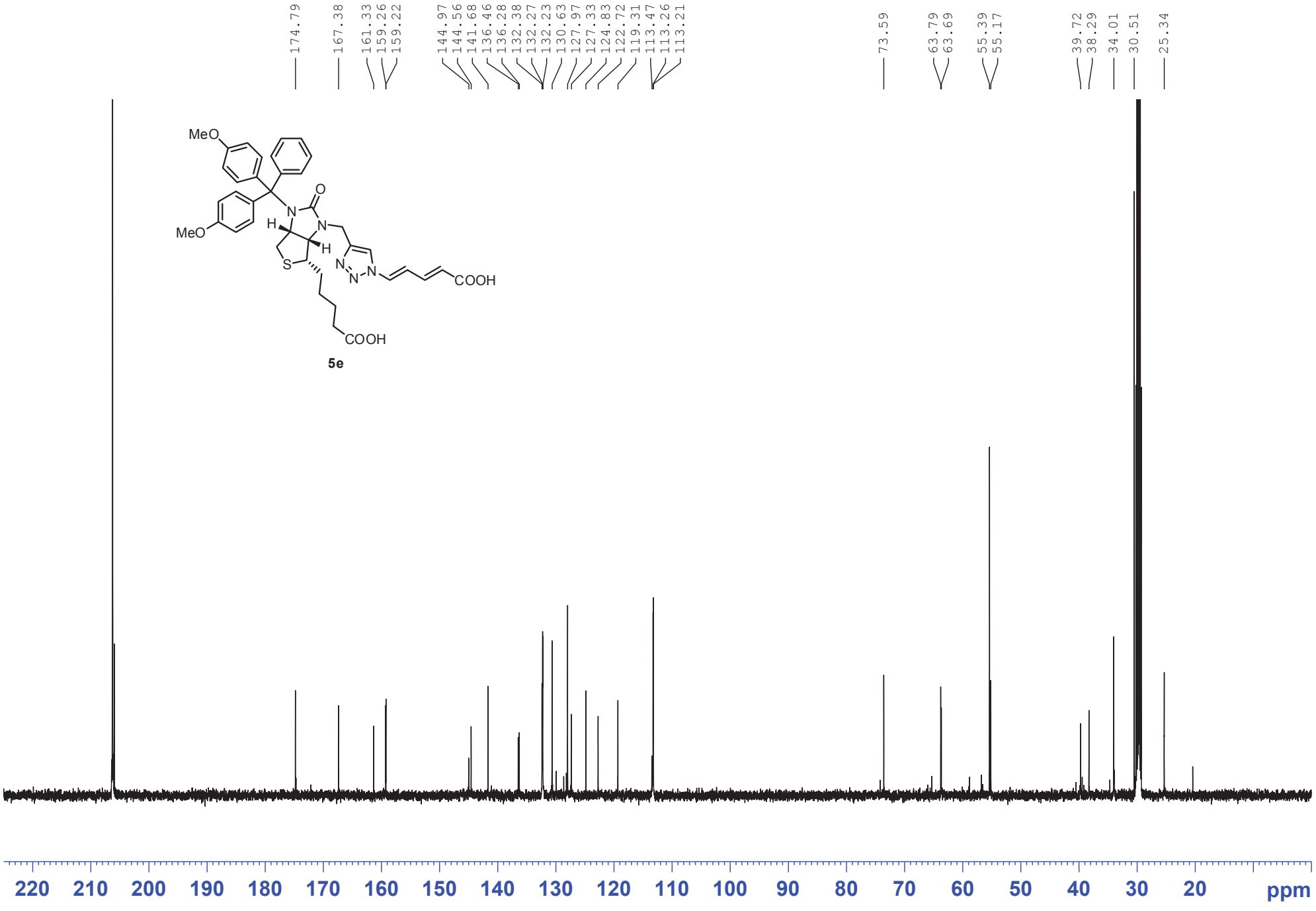
6.37
2.11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161.33
159.26
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144.97
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141.68
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136.28
132.38
132.27
132.23
130.63
127.97
127.33
124.83
122.72
119.31
113.47
113.26
113.21
73.59
63.79
63.69
55.39
55.17
39.72
38.29
34.01
30.51
25.34
MeO
MeO
O
N
H
N
H
S
N
N
N
COOH
COOH
5e
220
210
200
190
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160
150
140
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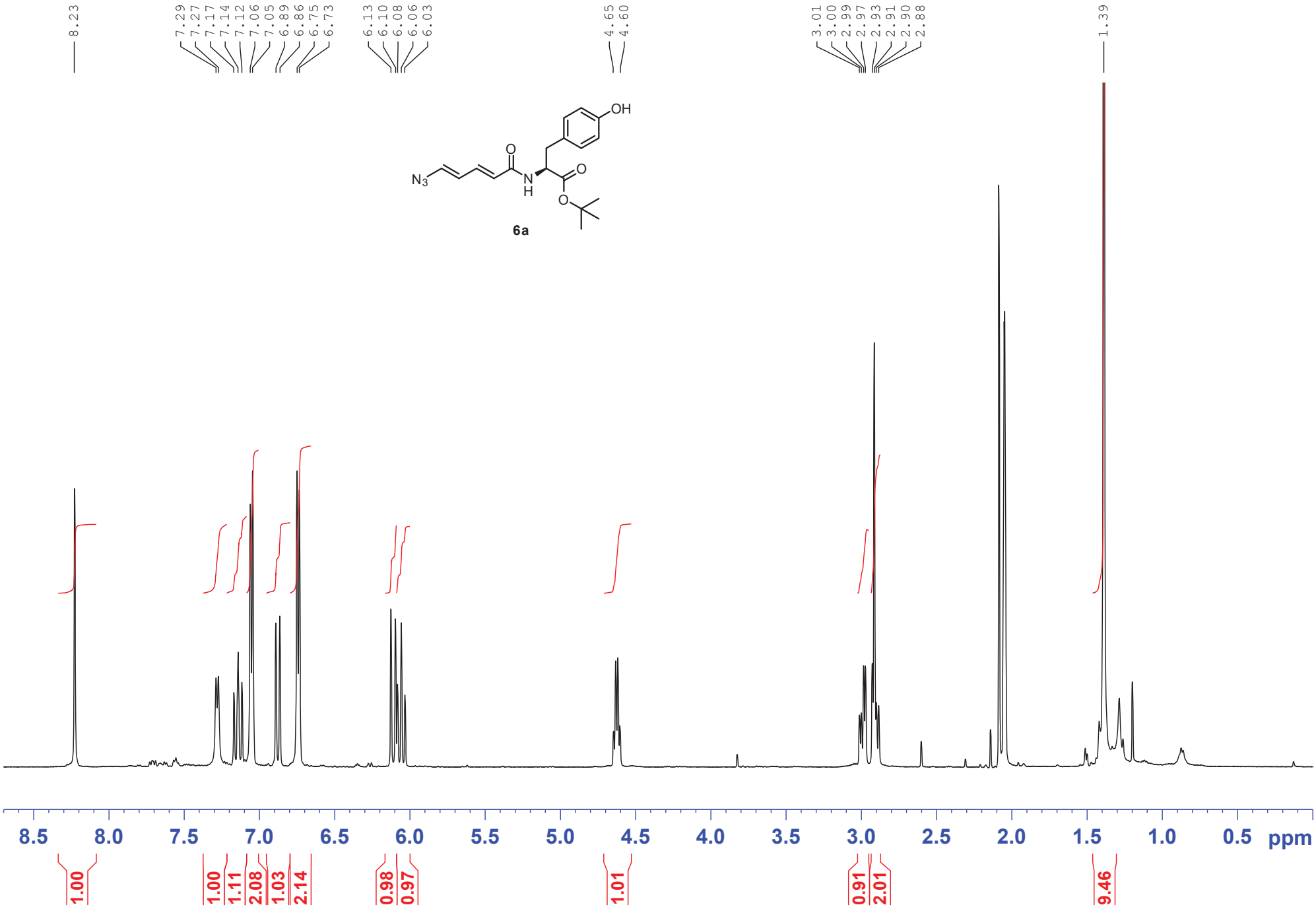
120
110
100
90
80
70
60
50
40
30
20
ppm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7.27
7.17
7.14
7.12
7.06
7.05
6.89
6.86
6.75
6.73
6.13
6.10
6.08
6.06
6.03
4.65
4.60
3.01
3.00
2.99
2.97
2.93
2.91
2.90
2.88
1.39
OH
O
N
H
O
O
N3
6a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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1.00
1.11
2.08
1.03
2.14
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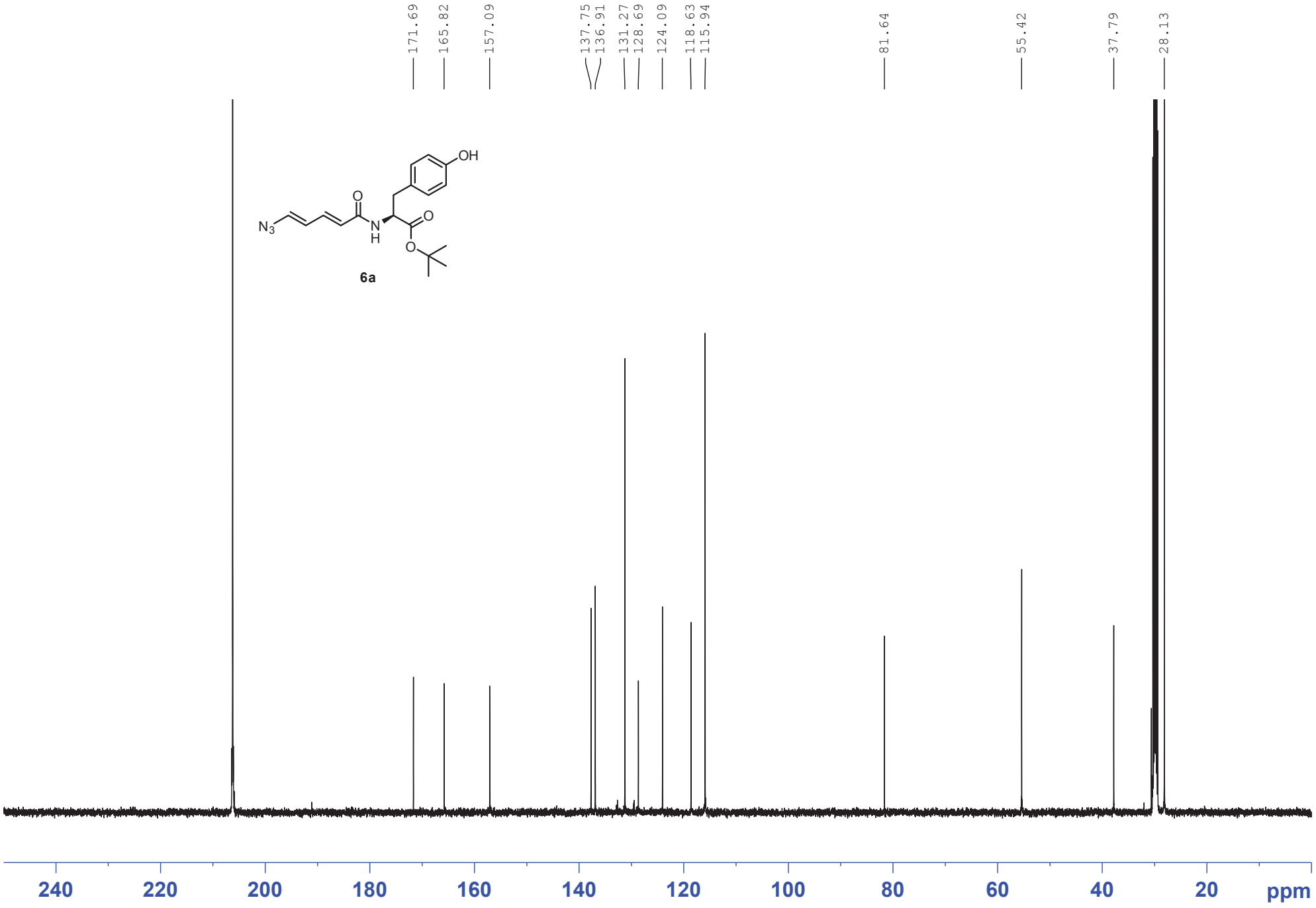
0.97
1.01
0.91
2.01
9.46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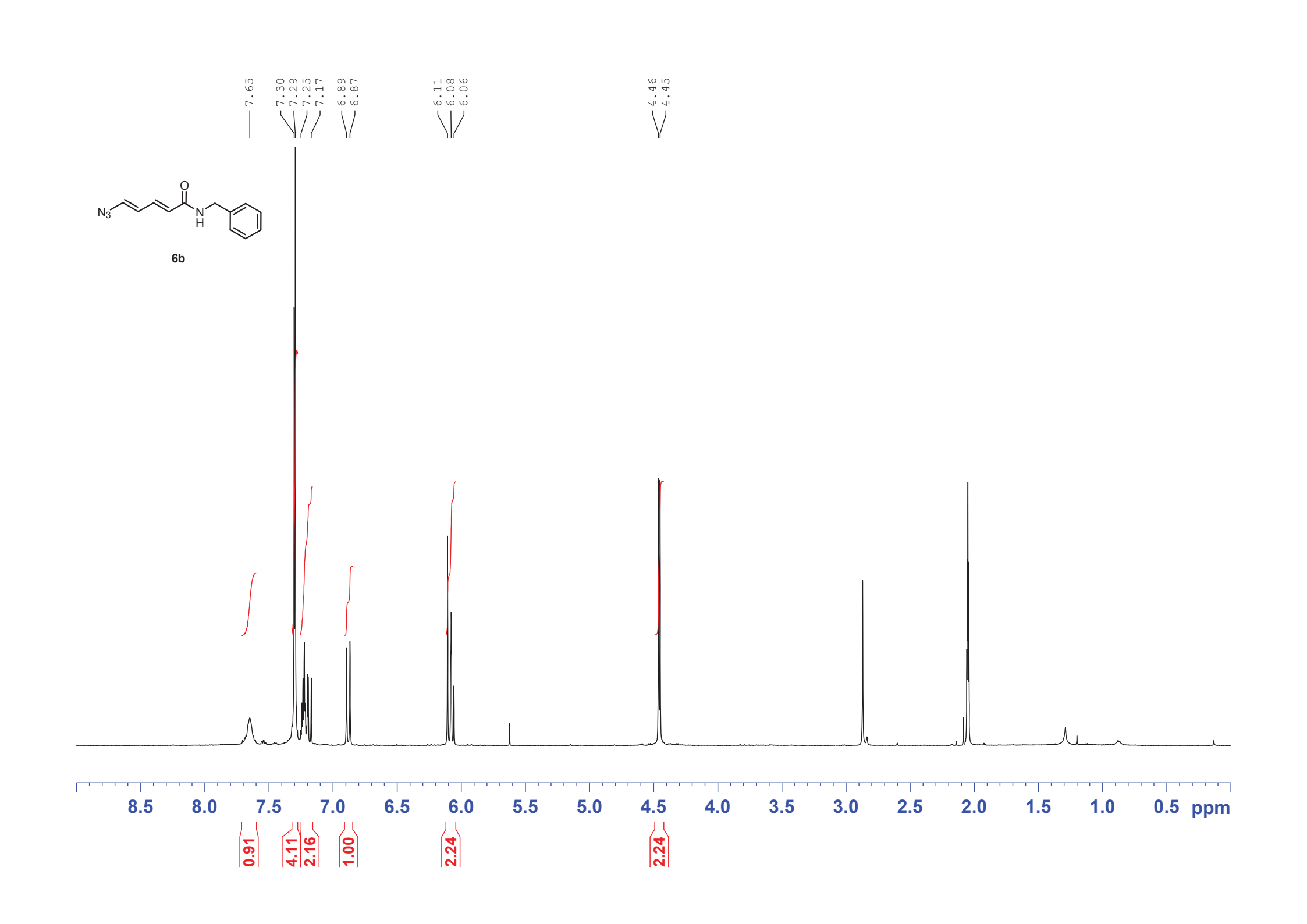
131.27
128.69
124.09
118.63
115.94
81.64
55.42
37.79
28.13
OH
O
N
H
O
O
N3
6a
240
220
200
180
160
140
120
100
80
60
40
20
ppm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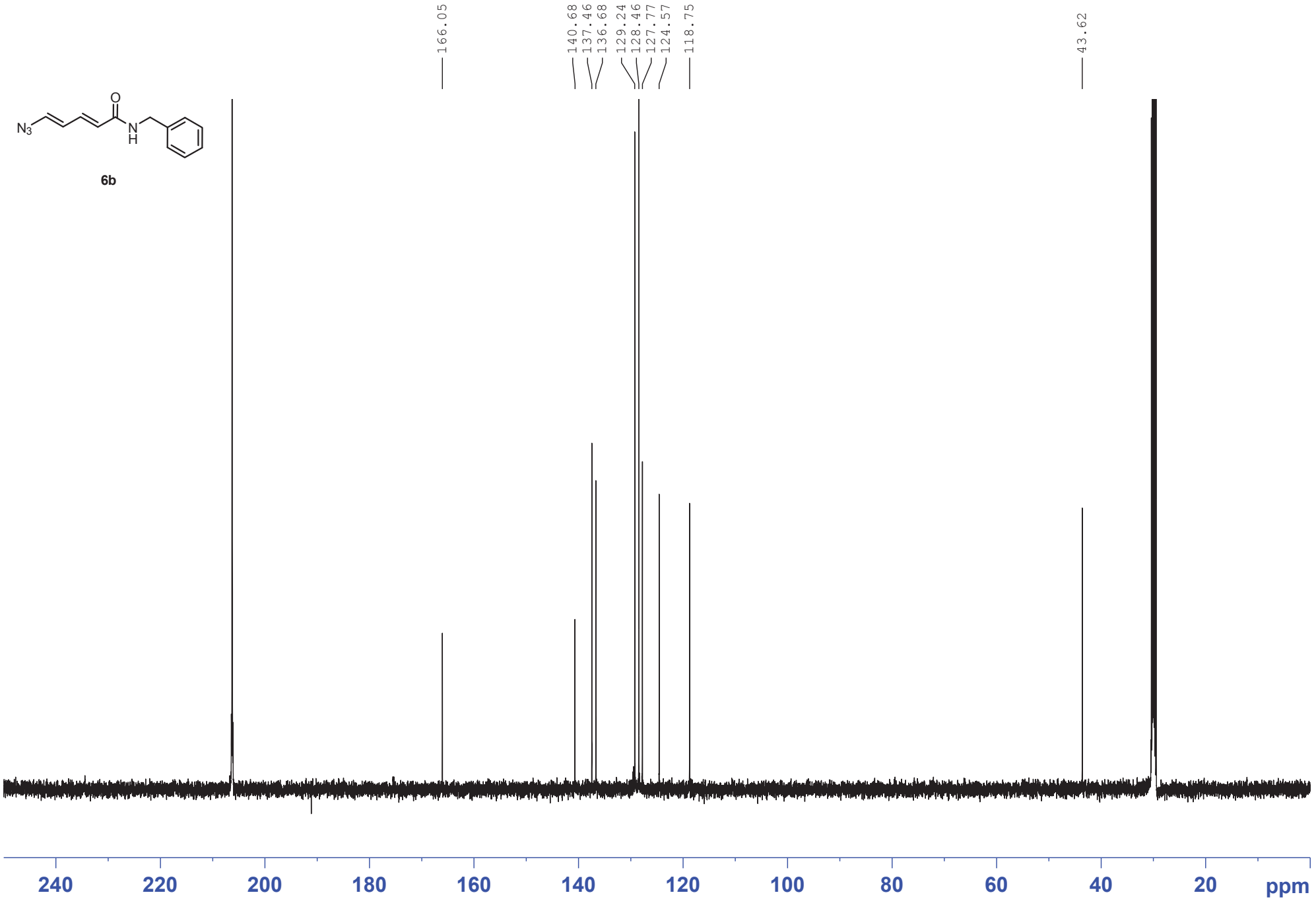
7.25
7.17
6.89
6.87
6.11
6.08
6.06
4.46
4.45
O
N3
N
H
6b
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.91
4.11
2.16
1.00
2.24
2.24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136.68
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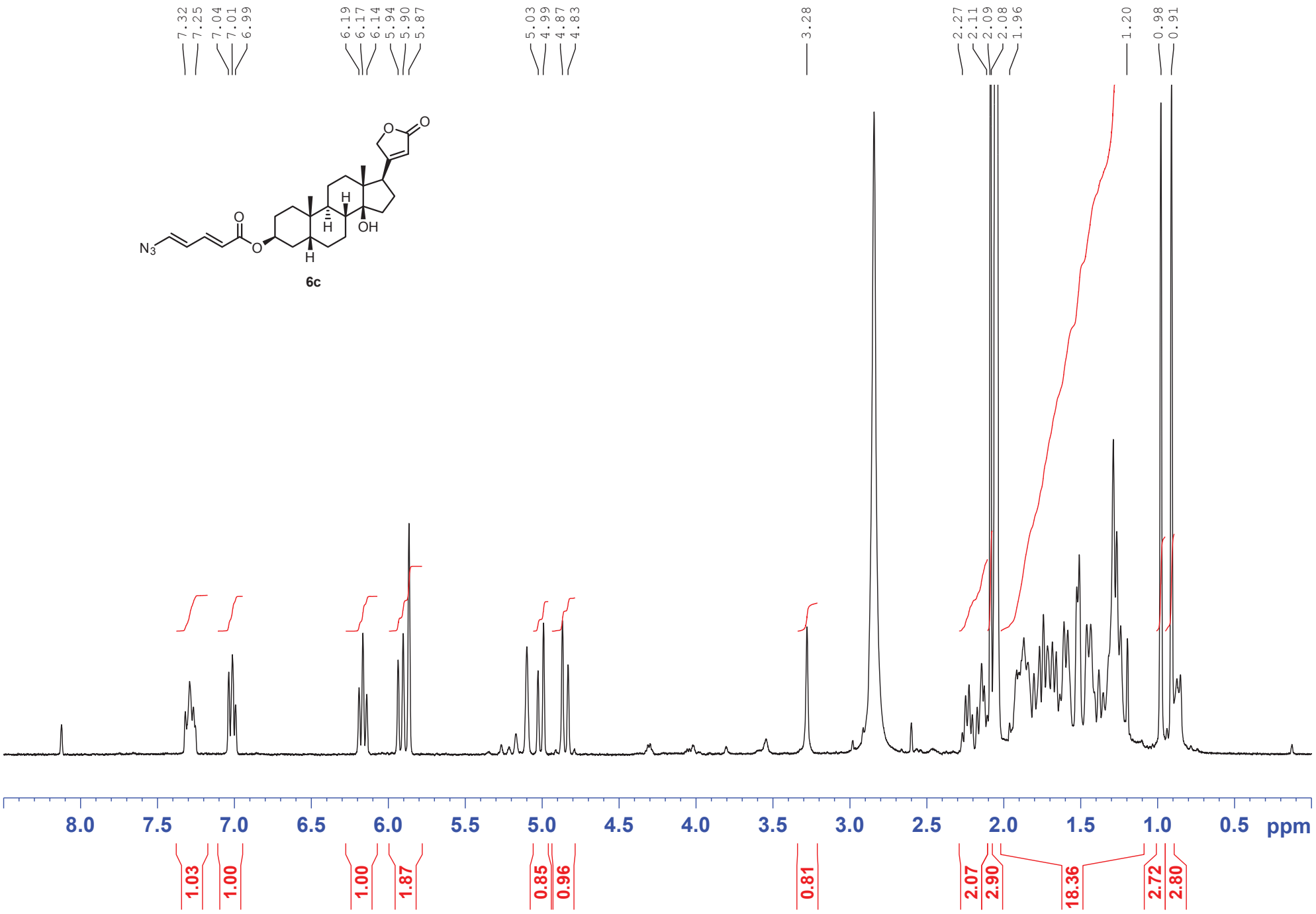
128.46
127.77
124.57
118.75
43.62
O
N3
N
H
6b
240
220
200
180
160
140
120
100
80
60
40
20
ppm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7.25
7.04
7.01
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6.19
6.17
6.14
5.94
5.90
5.87
5.03
4.99
4.87
4.83
3.28
2.27
2.11
2.09
2.08
1.96
1.20
0.98
0.91
O
O
O
O
H
H
OH
H
N3
6c
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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1.00
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0.96
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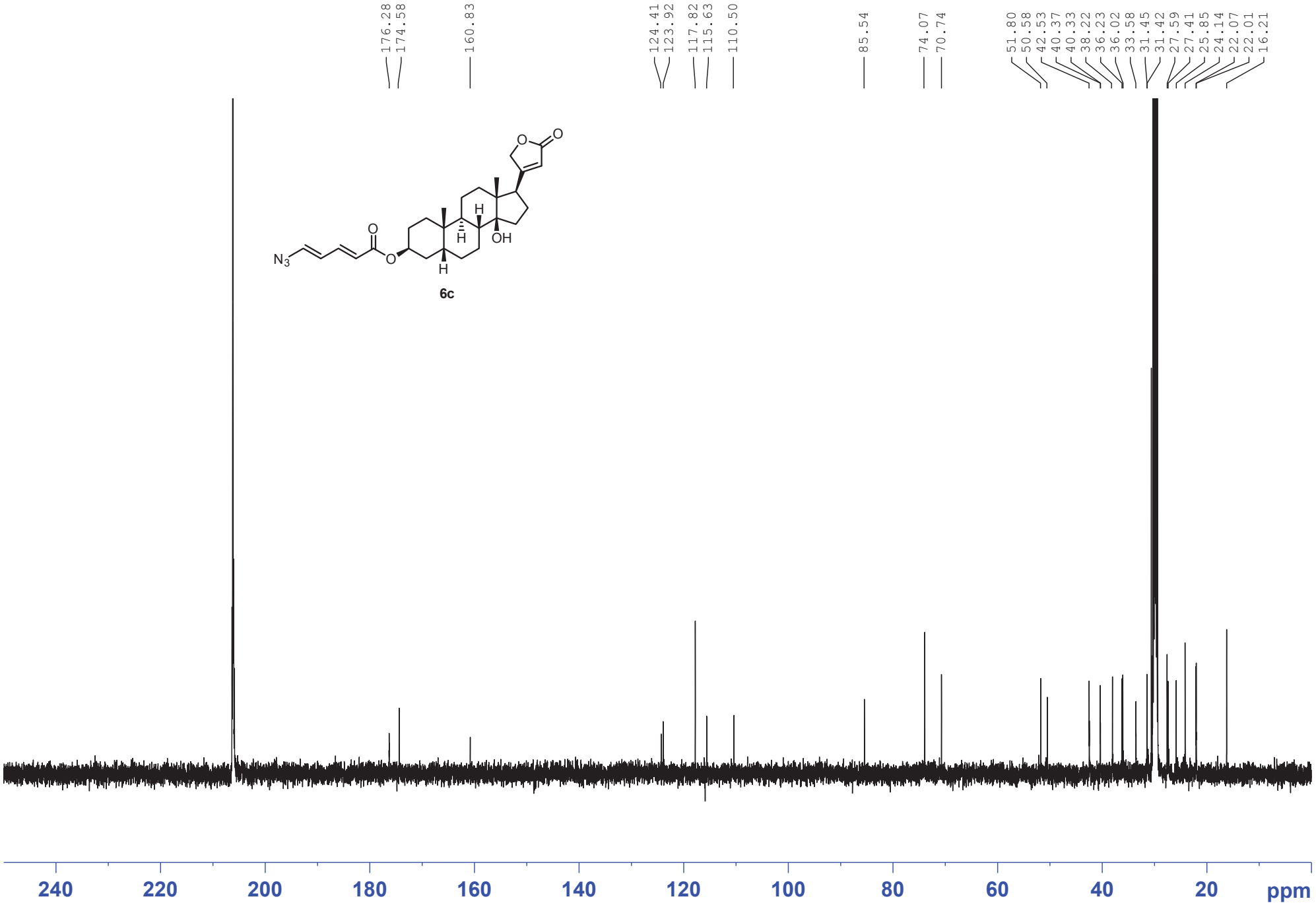
2.07
2.90
18.36
2.72
2.80


176.28
174.58
160.83
124.41
123.92
117.82
115.63
110.50
85.54
74.07
70.74
51.80
50.58
42.53
40.37
40.33
38.22
36.23
36.02
33.58
31.45
31.42
27.59
27.41
25.85
24.14
22.07
22.01
16.21
O
O
H
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OH
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N3
6c
240
220
200
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140
120
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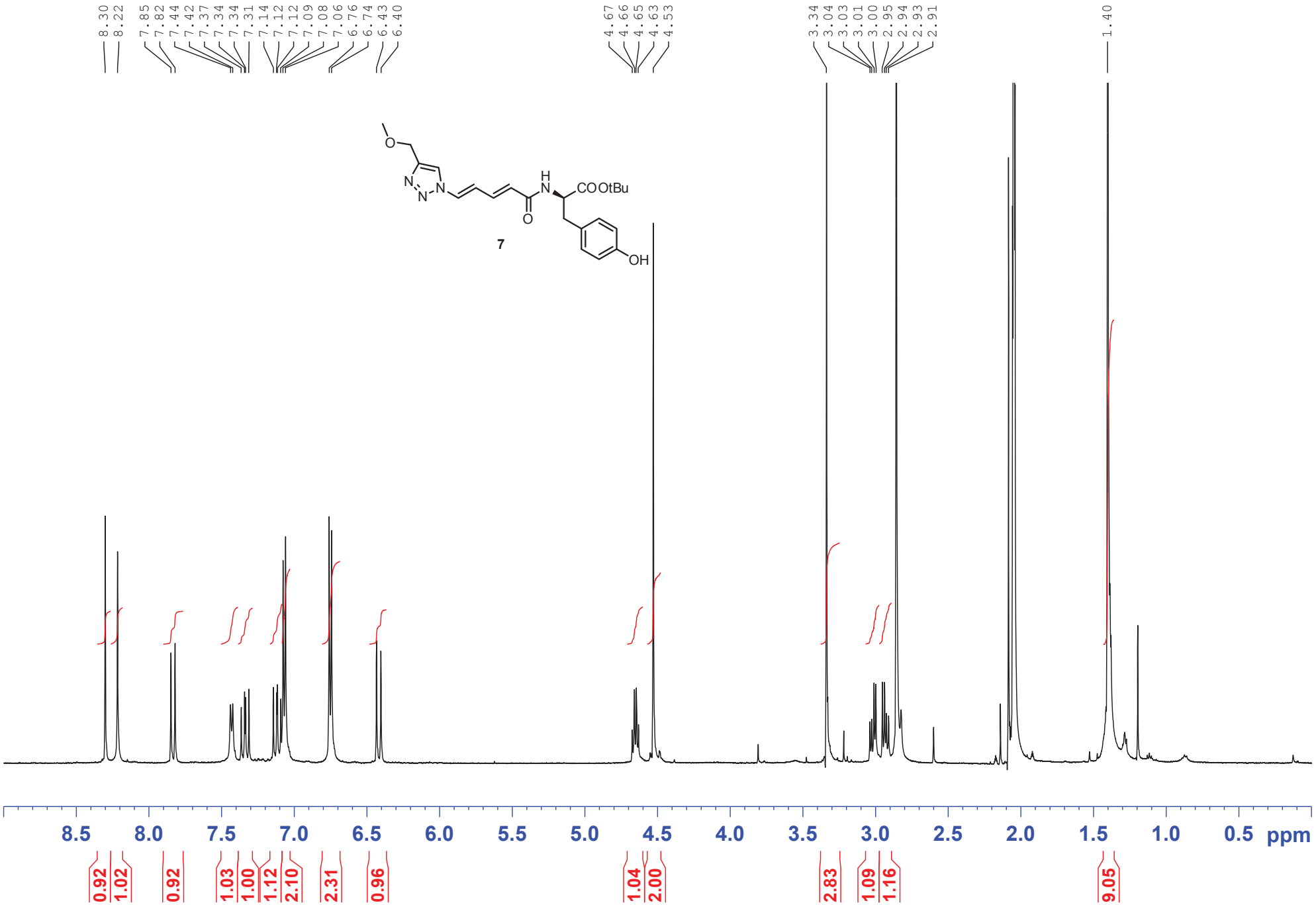
60
40
20
ppm


8.30
8.22
7.85
7.82
7.44
7.42
7.37
7.34
7.34
7.31
7.14
7.12
7.12
7.09
7.08
7.06
6.76
6.74
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3.03
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3.00
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2.94
2.93
2.91
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N
N
N
H
N
CO OtBu
O
OH
7
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6.5
6.0
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4.0
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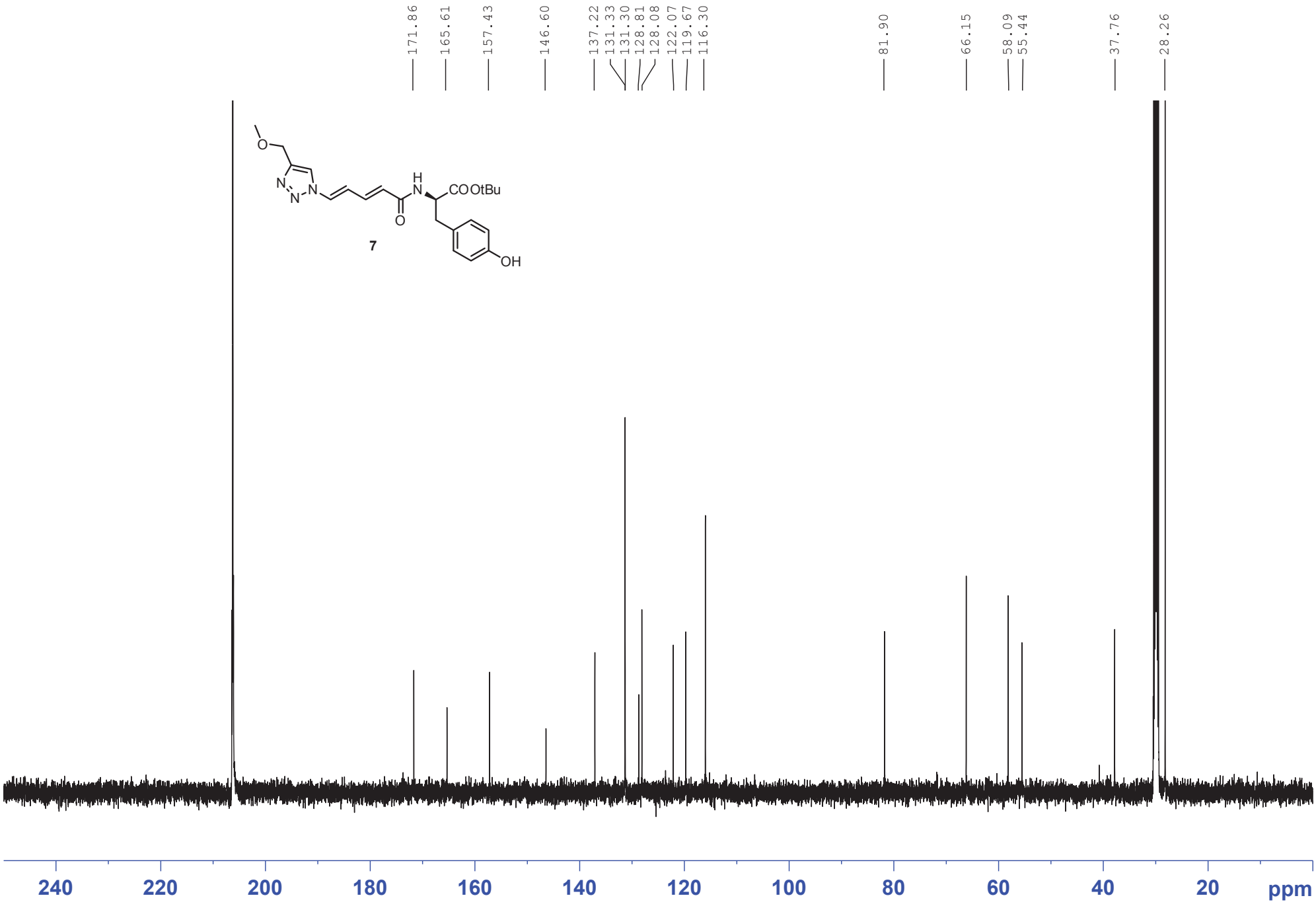
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ppm