Supporting Information

Click-based Synthesis and Proteomic Profiling of Lipstatin Analogues

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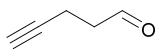
1. General information

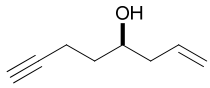
Dry tetrahydrofuran (THF) were obtained by drying over Na/benzophenone and methylene chloride (CH_2Cl_2) was obtained by drying over CaH_2. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F_{254}), and compounds were visualised with UV light and acidic *p*-anisaldehyde. Merck silica gel 60 (0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or 500 MHz Spectrometer using $CDCl_3$ as solvents. Chemicals shifts are reported in ppm with reference to residual solvent [^{1}H NMR, $CHCl_3$ (7.26); ^{13}C NMR, $CDCl_3$ (77.0)]. Mass spectra were recorded on a Finnigan LCQ mass spectrometer, or a Shimadzu LC-IT-TOF spectrometer. Analytical HPLC was carried out on Shimadzu LC-IT-TOF system equipped with an autosampler, using reverse-phase Phenomenex Luna 5μm C18 100 Å 50 X 3.0 mm column. 0.1% TFA/H_2O and 0.1% TFA/acetonitrile were used as eluents. The flow rate was 0.6 mL/min.

2. Synthesis and Characterizations



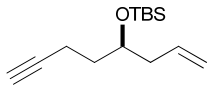
4

pent-4-ynal (4). DMSO (5.58 g, 71.4 mmol) was added to a solution of oxalyl chloride (4.53 g, 35.7 mmol) in CH_2Cl_2 (90 mL) cooled at -78 °C. After 15 min, 3-pentyn-1-ol (2.0 g, 23.8 mmol) in CH_2Cl_2 (30 mL) was added dropwise to the reaction mixture and left to stir for 15 min. Et_3N (10.84 g, 107.1 mmol) was added to the reaction mixture and left to stir for an additional 15 min, then the reaction mixture was warmed to 0 °C and quenched with water. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic phase was washed with water (2 x 30 mL), brine (30 mL) and dried over Na_2SO_4, concentrated under reduced pressure to give crude **4** (1.77 g) as a pale yellow oil. Crude **4** was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (t, *J* = 1.2 Hz, 1H), 2.69 (t, *J* = 7.1 Hz, 2H), 2.50 (dt, *J* = 6.6, 2.5 Hz, 2H), 1.98 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 82.2, 69.2, 42.3, 11.6.



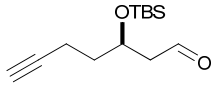
5

(*R*)-oct-1-en-7-yn-4-ol (5): A solution of (*S*)-BINOL (349 mg, 1.22 mmol), $Ti(O^iPr)_4$ (173 mg, 0.61 mmol) and 4Å molecular sieve in CH_2Cl_2 (15 mL) was refluxed for 1 h. The red-brown mixture was cooled to rt and a solution of 4-pentynal (500 mg) in CH_2Cl_2 (4 mL) was added. The solution was stirred for 10 min at rt and cooled to -78 °C, and allyltributylstannane (2.42 g, 7.31 mmol) was added. The reaction mixture was stirred at -18 °C for 26 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (7 mL) and stirred for 1 h and was filtered through a pad of celite. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), then the combined organic phase was washed with brine (30 mL), dried over Na_2SO_4. The residue was chromatographed on silica gel (hexanes/EtOAc, 1:0 to 93:7) to give homoallylic alcohol **5** (356 mg, 43% over two step, *ee* > 97%) as an colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (m, 1H), 5.16 (m, 1H), 5.13 (m, 1H), 3.81 (m, 1H), 2.35 (dt, *J* = 7.6, 2.5 Hz, 2H), 2.29-2.32 (m, 1H), 2.20 (dt, *J* = 14.9, 7.6 Hz, 1H), 1.97 (t, *J* = 2.5 Hz, 1H), 1.79 (d, *J* = 4.5 Hz, 1H), 1.63-1.75 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.4, 118.4, 84.1, 69.4, 68.7, 41.8, 35.2, 15.0.



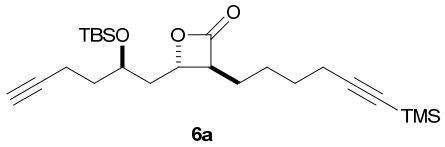
5a

(*R*)-tert-butyldimethyl(oct-1-en-7-yn-4-yloxy)silane (5a): TBSCl (428 mg, 2.84 mmol), imidazole (211 mg, 3.10 mmol) and DMAP (32 mg, 0.26 mmol) was added to a solution of homoallylic alcohol **5** (320 mg, 2.58 mmol) in DCM (10 mL) cooled at 0 °C. The reaction mixture was warmed to rt and left to stir for 23 h. The reaction mixture was diluted with CH_2Cl_2 and extracted with water (2 x 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The residue was chromatographed on silica gel (hexanes/EtOAc, 1:0 to 98:2) to give silyl **5a** (595 mg, 97%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76-5.84 (m, 1H), 5.06 (br d, *J* = 5.1 Hz, 1H), 5.04 (br s, 1H), 3.81-3.86 (m, 1H), 2.22-2.26 (m, 4H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.59-1.73 (m, 3H), 0.89 (s, 9H), 0.076 (s, 3H), 0.071 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.7, 117.1, 84.5, 70.4, 68.3, 41.8, 35.3, 31.6, 25.9, 22.7, 18.1, 14.6, 14.1, -4.4, -4.7.



6

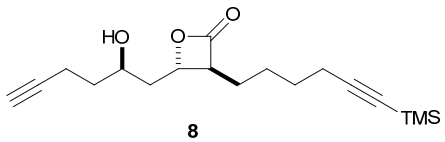
(*R*)-3-(tert-butyldimethylsilyloxy)hept-6-ynal (6): Potassium osmate dihydrate (20 mg, 0.05 mmol) was added to a solution of silyl ether **5a** (370 mg, 1.55 mmol) and $NaIO_4$ (994 mg, 4.65 mmol) in THF:H_2O (3:1, 35 mL). The reaction mixture was left to stir at rt for 4 h. The reaction mixture was diluted with water and extracted with Et_2O (3 x 10 mL). The combined organic layer was washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4. The residue was chromatographed on silica gel (hexanes/EtOAc, 1:0 to 95:5) to give aldehyde **6** (224 mg, 60%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (t, *J* = 2.5 Hz, 1H), 4.34 (quin, *J* = 5.7 Hz, 1H), 2.57 (dt, *J* = 5.7, 2.5 Hz, 2H), 2.25-2.29 (m, 2H), 1.96 (t, *J* = 2.5 hz, 1H), 1.72-1.82 (m, 2H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.6, 83.6, 68.9, 66.7, 50.7, 36.1, 29.4, 25.7, 18.0, 14.4, -4.59, -4.64.



6a

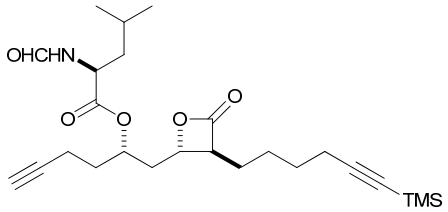
(3*S*,4*S*)-4-((*R*)-2-(tert-butyldimethylsilyloxy)hex-5-ynyl)-3-(6-(trimethylsilyl)hex-5-ynyl)oxetan-2-one (6a): Aldehyde **6** (300 mg, 1.25 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a suspension of $ZnCl_2$ (340 mg, 2.5 mmol, freshly fused under vacuum) in

CH_2Cl_2 (6 mL) at rt. After 10 min, ketene acetal **7** (789 mg, 1.88 mmol) in CH_2Cl_2 (1 mL) was added dropwise to the reaction mixture. The reaction was left to stir at rt for 47 h. An PBS buffer (*p*H 7; 10 mL) was added to the reaction mixture and stirred for 25 min. The organic phase was extracted with CH_2Cl_2 (3 x 15 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. Flash chromatography (Hex:EtOAc, 1:0 to 9:1) yielded silyloxy-β-lactone diastereomers **6a** (362 mg) as a pale yellow oil. ^{1}H NMR (500 MHz) analysis of the mixture of diastereomers indicated a diastereomeric ratio of 9:1. Without further purification, the mixture was used directly in the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.38-4.41 (m, 1H), 3.98 (quin, *J* = 5.7 Hz, 1H), 3.20 (dt, *J* = 7.0, 3.8 Hz, 1H), 2.23-2.26 (m, 4H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.89 (t, *J* = 7.0 Hz, 3H), 1.70-1.77 (m, 4H), 1.50-1.60 (m, 4H), 0.90 (s, 9H), 0.15 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 106.6, 85.0, 83.8, 74.8, 68.9, 67.4, 56.2, 41.9, 36.3, 31.6, 28.2, 27.3, 26.0, 25.83, 25.80, 25.6, 22.6, 19.6, 18.0, 14.1, 14.0, 0.14, -3.6, -4.4, -4.7. ESI-MS (*m/z*) calcd for $C_{24}H_{42}O_3Si_2$ $[M + Na]^+$ 457.3, found 457.0.



8

(3*S*,4*S*)-4-((*R*)-2-hydroxyhex-5-ynyl)-3-(6-(trimethylsilyl)hex-5-ynyl)oxetan-2-one (8):
40% HF (162 mg, 8.1 mmol) was added to a solution of β-lactone **8** (350 mg, 0.81 mmol) in CH_3CN (3 mL) at 0 °C. The reaction mixture was stirred at rt for 18 h. Water was added to the reaction mixture and quenched with solid $NaHCO_3$ (820 mg, 9.7 mmol). The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography on SiO_2 (10:1, hexanes:EtOAc) to provide the hydroxy-β-lactone **8** (134 mg, 33%) and a mixture of the two diastereomers (22.1 mg, 6%) as white solids (39% overall, 2 steps). Spectroscopic data are reported for the major diastereomeric-β-lactone **8**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.51 (m, 1H), 4.01 (m, 1H), 3.32 (dt, *J* = 8.2, 3.8 Hz, 1H), 2.36 (ddd, *J* = 17.7, 6.9, 2.5 Hz, 2H), 2.24 (t, *J* = 6.7 Hz, 2H), 2.01 (t, *J* = 2.5 Hz, 1H), 1.54-1.95 (m, 10H), 0.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 106.7, 85.0, 83.4, 75.3, 69.6, 67.6, 56.5, 41.7, 35.9, 28.1, 27.2, 25.9, 19.6, 14.9, 14.2, 0.1. ESI-MS (*m/z*) calcd for $C_{25}H_{39}O_5Si$ $[M + Na]^+$ 343.2, found 342.9.



9

(*S*)-((*S*)-1-((2*S*,3*S*)-4-oxo-3-(6-(trimethylsilyl)hex-5-ynyl)oxetan-2-yl)hex-5-yn-2-yl) 2-formamido-4-methylpentanoate (9): DIAD (138 mg, 0.68 mmol) was added to a solution of β-lactone **8** (166 mg, 0.52 mml), *N*-formyl-L-Leu (108 mg, 0.68 mmol), and PPh_3 (178 mg, 0.68 mmol) in THF (3 mL). The reaction mixture was left to stir at rt for 21 h. The solvent was evaporated *in vacuo*, the residue was chromatographed on silica gel (hexanes/EtOAc, 95:5 to 7:3) to give β-lactone **9** (177 mg, 74%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 5.89 (d, *J* = 8.2 Hz, 1H), 5.18-5.23 (m, 1H), 5.18-5.23 (m, 1H), 4.65-4.70 (m, 1H), 4.30-4.34 (m, 1H), 3.25 (dt, *J* = 7.6, 4.4 Hz, 1H), 2.23-2.30 (m, 4H), 2.17 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.09 (dt, *J* = 15.1, 4.4 Hz, 1H), 2.00 (t, *J* = 2.5 Hz, 1H), 1.65-1.95 (m, 6H), 1.56 (br s, 5 H), 0.97 (d, *J* = 6.3 Hz, 6H), 0.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 170.3, 160.6, 106.6, 85.0, 82.5, 74.5, 71.5, 69.6, 57.0, 49.6, 41.4, 38.7, 32.6, 28.2, 27.2, 25.9, 24.9, 22.9, 21.7, 19.6, 14.7, 0.13. ESI-MS (*m/z*) calcd for $C_{25}H_{39}O_5Si$ $[M + Na]^+$ 484.3, found 484.1.

Optimization of click reaction

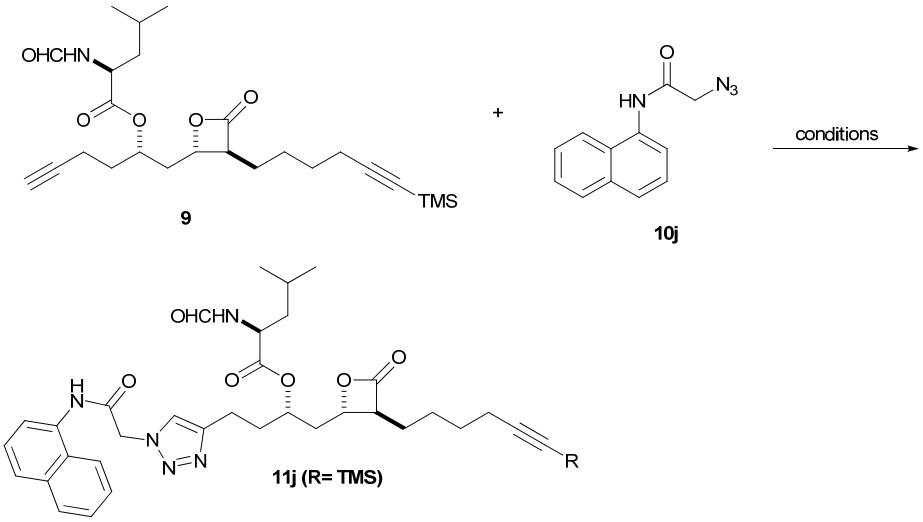


Table S1. Optimization of click chemistry

Entry	Catalyst	Base/additive	Solvent	Remarks
1	$CuSO_4.5H_2O$ (0.4 eq)	NaAsc (1.6 eq)	DMSO:H_2O (1:1)	50%
2	$CuSO_4.5H_2O$ (0.4 eq)	NaAsc (1.6 eq)	DCM:H_2O (1:1)	30%
3	$CuSO_4.5H_2O$ (0.4 eq)	NaAsc (1.6 eq)	DCE:H_2O (1:1)	~10%
4	$CuSO_4.5H_2O$ (0.4 eq)	NaAsc (1.6 eq)	*t*BuOH:H_2O (1:1)	~10%
5	CuI (0.4 eq)	DIEA (0.8 eq)	DMSO:H_2O (1:1)	~10%
6	CuI (0.4 eq)	DIEA (0.8 eq)	DCM:H_2O (1:1)	~10%
7	CuI (0.4 eq)	DIEA (0.8 eq)	DCE:H_2O (1:1)	Complete consumption of azide **10j**

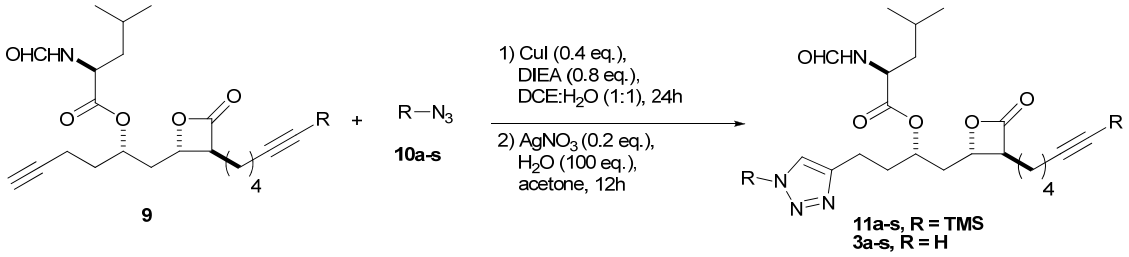
[a] All reactions were carried out with 1 equiv of alkyne **9** and 1 equiv of azide **10j** at rt.

To a 60 µL solution of the solvent in 1 mL eppendof tube, were added 4 µL of azide **10j** (50 mM), 4 µL of alkyne 9 (50 mM), 4 µL of $CuSO_4{\cdot}5H_2O$ (10 mM) with 8 µL of sodium ascorbate (20 mM) or 4 µL of CuI (10 mM) with 4 µL of DIEA (20 mM). The tube were sealed with parafilm and shaken at rt for 24 h. The solvent was removed under reduced pressure with Genevac evaporator, the product was then redissolved in DMSO and analysed by LCMS.

The most suitable conditions (entry 7) was chosen for all subsequent click reactions.

General procedure for click reaction

Table S2. "Click" assembly of THL analogues



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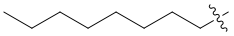
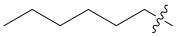
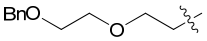
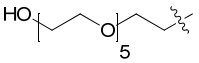
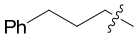
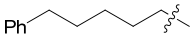
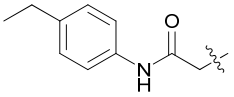
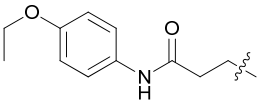
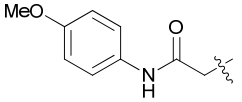
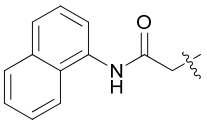
a		40%
b		79%
c		22%
d		33%
e		49%
f		49%
g		24%
h		12%
i		46%
j		70%

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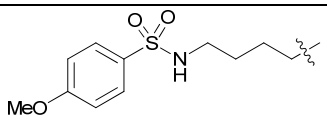
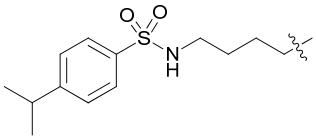
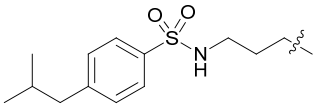
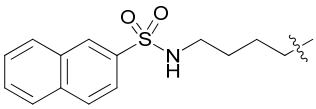
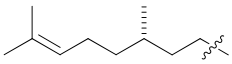
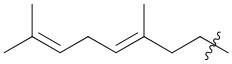
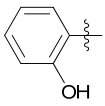
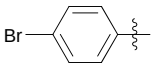
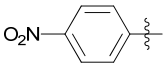
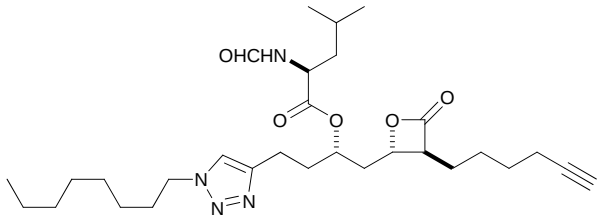
k		63%
l		33%
m		65%
n		46%
o		48%
p		41%
q		30%
r		30%
s		35%

To a mixture of alkyne **9** (10 mg, 0.022 mmol) and azide (0.024 mmol) in a mixture of DCE:H_2O (1:1, 200 µL) was added CuI (22 µL, 400 mM in DMSO, 0.009 mmol) and DIPEA (22, µL, 800 mM in DMSO, 0.018 mmol). The reaction mixture was stirred at rt for 24 h. The reaction mixture was then diluted with water (1 mL) and extracted with EtOAc (3 x 1 mL). The combined organic phase was extracted with an EDTA solution (1 M; 2 x 1 mL), brine (2 mL) and dried over anhydrous Na_2SO_4. The residue was used for next step without further purification.

General procedure for desilylation.

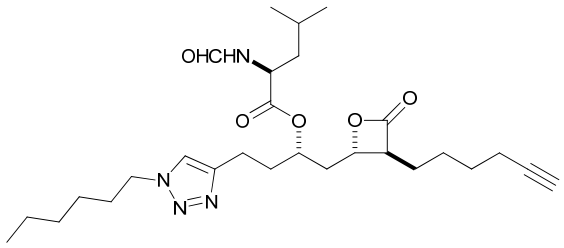
$AgNO_3$ (0.7 mg, 0.004 mmol) and H_2O (10 µL, 0.55 mmol) was added to a solution of crude click product **11** in acetone (150 µL). The reaction mixture was left to stir at rt for 12 h. Brine (1 mL) was added to the reaction mixture and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The residue was chromatographed on silica gel to give **3** as a colourless oil.

3a



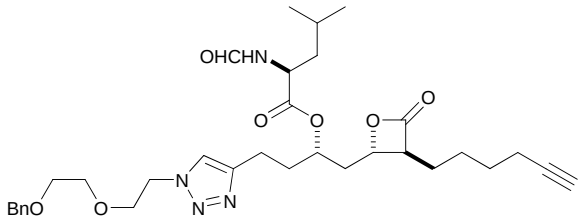
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.35 (s, 1H), 5.98 (d, *J* = 7.6 Hz, 1H), 5.05 (m, 1H), 4.64 (m, 1H), 4.30 (t, *J* = 6.3 Hz, 3H), 3.24 (dt, *J* = 7.6, 4.4 Hz, 1H), 2.77 (m, 2H), 2.21 (br s, 2H), 2.14-1.17 (m, 2H), 2.06-2.10 (m, 2H), 1.96 (br s, 1H), 1.69-1.87 (m, 6H), 1.26-1.31 (m, 12H), 0.98 (m, 6H), 0.88 (t, *J* = 5.7 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{30}H_{48}N_4O_5$ $[M+H]^+$ 545, found 545. HRMS (ESI) (*m/z*) calcd for $C_{30}H_{48}N_4O_5$ $[M-H]^-$ 543.3546, found 543.3545.

3b



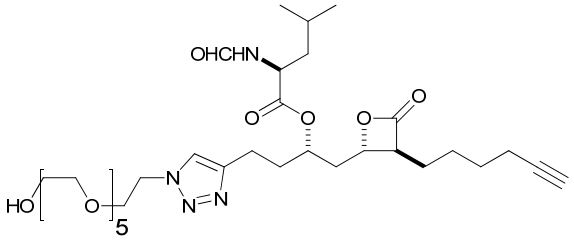
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.35 (s, 1H), 6.01 (d, *J* = 8.6 Hz, 1H), 5.02-5.03 (m, 1H), 4.64 (dt, *J* = 8.9, 4.3 Hz, 1H), 4.61-4.67 (m, 3H), 3.24 (dt, 7.4, 4.1 Hz, 1H), 2.68-2.84 (m, 2H), 2.21 (m, 2H), 2.04-2.15 (m, 4H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.53-1.87 (m, 13H), 1.31 (br s, 6H), 0.97 (d, *J* = 4.5 Hz, 6H), 0.90 (t, *J* = 6.7 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{28}H_{44}N_4O_5$ $[M + Na]^+$ 539.3, found 539.2. HRMS (ESI) (*m/z*) calcd for $C_{28}H_{44}N_4O_5$ $[M - H]^-$ 515.3233, found 515.3231.

3c



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.61 (br s, 1H), 6.42 (d, *J* = 7.6 Hz, 1H), 5.03 (br s, 1H), 4.63 (dt, *J* = 8.9, 4.5 Hz, 1H), 4.53 (t, *J* = 4.8 Hz, 2H), 4.31 (dt, *J* = 8.2, 3.8 Hz, 1H), 3.86 (t, *J* = 5.1 Hz, 2H), 3.59-3.65 (m, 12H), 3.25 (dt, *J* = 7.6, 3.8 Hz, 1H), 2.80 (m, 2H), 2.21 (dt, *J* = 6.3, 2.3 Hz, 2H), 2.10 (m, 2H), 1.97 (t, *J* = 2.5 Hz, 1H), 1.78-1.83 (m, 8H), 1.67-1.70 (m, 2H), 1.54-1.59 (m, 4H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.96 (d, *J* = 6.3 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{33}H_{46}N_4O_7$ $[M + H]^+$ 611.3, found 611.3. HRMS (ESI) (*m/z*) calcd for $C_{33}H_{46}N_4O_7$ $[M - H]^-$ 609.3287, found 609.3289.

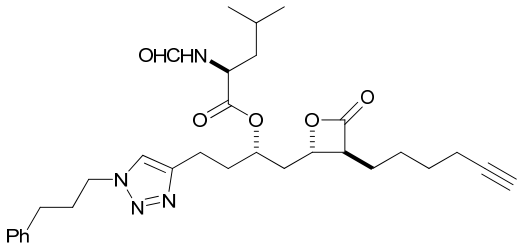
3d



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.55 (br s, 1H), 7.29-7.37 (m, 5H), 6.05 (br d, *J* = 7.0 Hz, 1H), 5.03 (br s, 1H), 4.64 (m, 1H), 4.54 (s, 2H), 4.51 (t, *J* = 5.1 Hz, 2H), 4.29

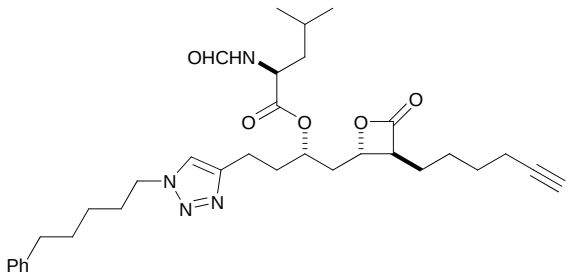
(m, 1H), 3.87 (t, *J* = 4.5 Hz, 2H), 3.63 (br d, *J* = 5.7 Hz, 4H), 3.23 (dt, *J* = 7.6, 3.8 Hz, 1H), 2.21 (m, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.60 (br s, 13H), 0.91-0.97 (m, 6H). ESI-MS (*m/z*) calcd for $C_{34}H_{56}N_4O_{11}$ $[M + Na]^+$ 719.4, found 719.3. HRMS (ESI) (*m/z*) calcd for $C_{34}H_{56}N_4O_{11}$ $[M - H]^-$ 695.3867, found 695.4152.

3e



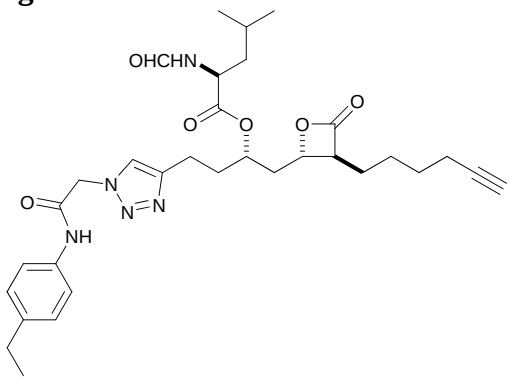
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.29-7.31 (m, 2H), 7.17-7.23 (m, 3H), 5.97 (br s, 1H), 5.03 (br s, 1H), 4.62 (br s , 1H), 4.34 (br s, 1H), 4.31 (br s, 1H), 3.25 (br s, 1H), 2.65 (t, *J* = 7.0 Hz, 2H), 2.10-2.25 (m, 6H), 1.95 (br s, 1H), 1.53-1.71 (m, 17H), 0.97 (m, 6H). ESI-MS (*m/z*) calcd for $C_{31}H_{42}N_4O_5$ $[M + H]^+$ 551.2, found 551.2. HRMS (ESI) (*m/z*) calcd for $C_{31}H_{42}N_4O_5$ $[M - H]^-$ 549.3076, found 549.3077.

3f



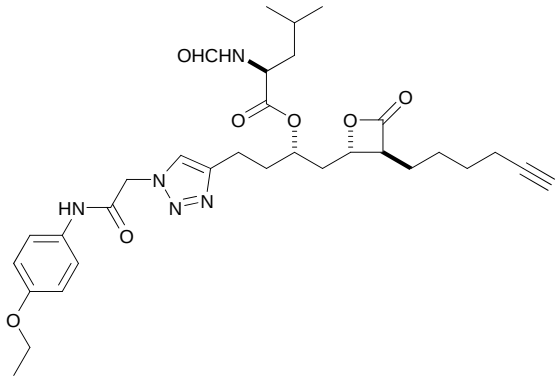
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.37 (br s, 1H), 7.27-7.29 (m, 2H), 7.15-7.20 (m, 3H), 5.99 (d, *J* = 7.6 Hz, 1H), 4.62 (dt, *J* = 9.5, 3.8 Hz, 1H), 4.31 (t, *J* = 6.9 Hz, 3H), 3.25 (dt, *J* = 7.6, 3.8 Hz, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.21 (dt, *J* = 6.9, 2.5 Hz, 2H), 2.06-2.17 (m, 2H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.92 (t, *J* = 7.6 Hz, 2H), 1.54-1.71 (br m, 18H), 1.33-1.39 (m, 2H), 0.98 (d, *J* = 5.7 Hz, 3H), 0.97 (d, *J* = 5.7 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{33}H_{46}N_4O_5$ $[M + H]^+$ 579.4, found 579.3. HRMS (ESI) (*m/z*) calcd for $C_{33}H_{46}N_4O_5$ $[M - H]^-$ 577.3389, found 577.3388.

3g



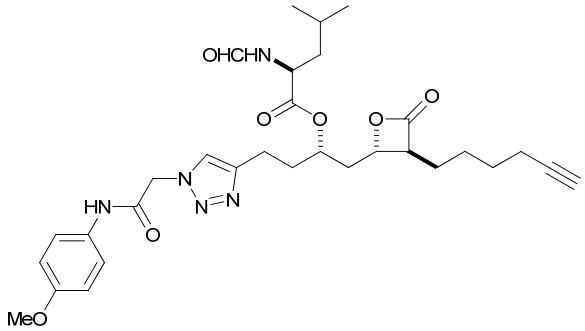
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.86 (br s, 1H), 7.61 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.79 (br d, *J* = 8.2 Hz, 1H), 5.19 (d, *J* = 16.4 Hz, 1H), 5.12 (d, *J* = 16.4 Hz, 1H), 5.08 (m, 1H), 4.52 (dt, *J* = 10.1, 3.8 Hz, 1H), 4.29 (dt, *J* = 8.8. 3.8 Hz, 1H), 3.25 (dt, *J* = 7.6, 3.8 Hz, 1H), 2.85 (m, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 2.10-2.21 (m, 6H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.72-1.80 (m, 2H), 1.50-1.67 (m, 10H), 1.21 (t, *J* = 7.6 Hz, 3H), 0.95 (t-like, *J* = 6.0 Hz, 6H). ESI-MS (*m/z*) calcd for $C_{32}H_{43}N_5O_6$ $[M - H]^-$ 592.3, found 592.3. HRMS (ESI) (*m/z*) calcd for $C_{32}H_{43}N_5O_6$ $[M - H]^-$ 592.3134, found 592.3125.

3h



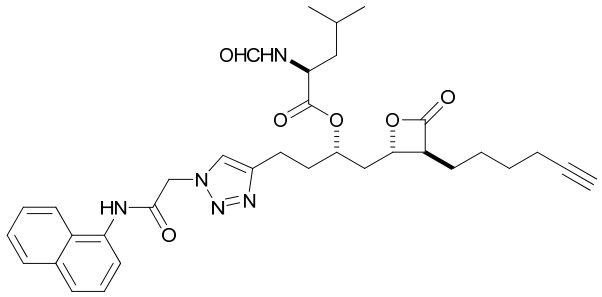
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.81 (s, 1H), 7.61 (s, 1H), 7.37 (d, *J* = 9.5 Hz, 2H), 6.84 (d, *J* = 9.5 Hz, 2H), 5.82 (d, *J* = 7.6 Hz, 1H), 5.18 (d, *J* = 16.4 Hz, 1H), 5.11 (d, *J* = 16.4 Hz, 1H), 4.52 (m, 1H), 4.29 (m, 1H), 4.00 (q, J = 6.9 Hz, 2H), 3.24 (dt, *J* = 7.6, 3.2 Hz, 1H), 2.85 (m, 2H), 2.05-2.21 (m, 6H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.57-1.67 (m, 8H), 1.39 (t, *J* = 6.9 Hz, 3H), 0.95 (t-like, *J* = 7.0 Hz, 6H). ESI-MS (*m/z*) calcd for $C_{32}H_{43}N_5O_7$ $[M + Na]^+$ 632.3, found 632.2. HRMS (ESI) (*m/z*) calcd for $C_{32}H_{43}N_5O_7$ $[M - H]^-$ 608.3083, found 608.3075.

3i



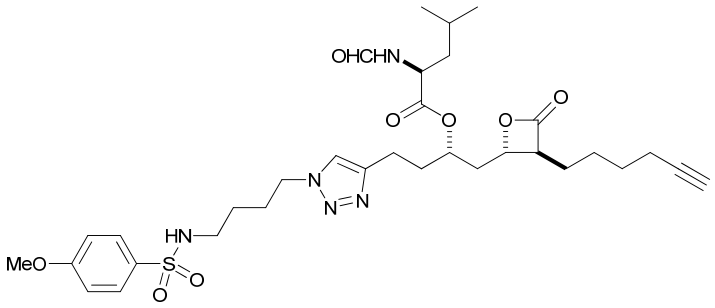
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.03 (br s, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.91 (br s, 1H), 5.20 (br s, 2H), 5.07 (br s, 1H), 4,52 (br s, 1H), 4.30 (br s, 1H), 3.78 (s, 3H), 3.25 (br s, 1H), 2.86 (br s, 2H), 2.21 (br s, 2H), 2.09 (br s, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.54-1.64 (m, 24H), 0.95 (t, *J* = 6.3 Hz, 3H), 0.94 (t, *J* = 6.3 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{31}H_{41}N_5O_7$ $[M + Na]^+$ 618.3, found 618.2. HRMS (ESI) (*m/z*) calcd for $C_{31}H_{41}N_5O_7$ $[M - H]^-$ 594.2927, found 594.2921.

3j



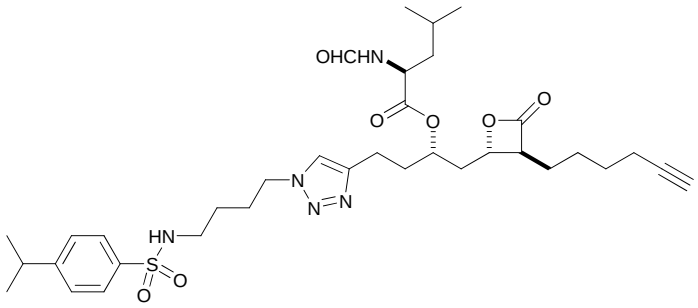
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (br s, 1H), 8.12 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.70-7.74 (m, 2H), 7.46-7.55 (m, 3H), 5.63 (d, *J* = 6.9 Hz, 1H), 5.34 (d, *J* = 16.4 Hz, 1H), 5.29 (d, *J* = 16.4 Hz), 5.04 (m, 1H), 4.49 (m, 1H), 4.24 (m, 1H), 3.21 (m, 1H), 2.88 (m, 2H), 2.04-2.22 (m, 6H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.24-1.27 (m, 6H), 0.92 (m, 6H). ESI-MS (*m/z*) calcd for $C_{34}H_{41}N_5O_6$ $[M + Na]^+$ 638.3, found 638.2. HRMS (ESI) (*m/z*) calcd for $C_{34}H_{41}N_5O_6$ $[M - H]^-$ 614.2978, found 614.2972.

3k



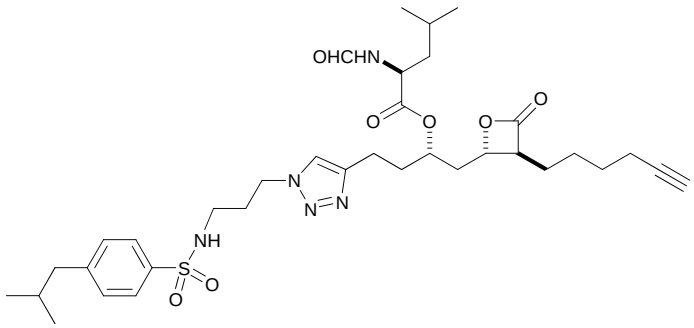
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.59 (s. 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 5.96 (d, *J* = 7.6 Hz, 1H), 4.79 (br s, 1H), 4.59 (dt, *J* = 10.2, 4.5 Hz, 1H), 4.46 (m, 1H), 4.30 (dt, *J* = 13.2, 4.5 Hz, 1H), 4.18-4.22 (m, 1H), 3.20 (dt, *J* = 7.6, 3.8 Hz, 1H), 3.00 (m, 1H), 2.86 (m, 2H), 2,79 (m, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.63 (m, 1H), 2.19 (m, 2H), 2.04 (m, 4H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.63-1.75 (m, 10H), 1.50 (m, 6H), 1.26 (m, 6H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.3 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{33}H_{47}N_5O_8S$ $[M + Na]^+$ 696.3, found 696.2. HRMS (ESI) (*m/z*) calcd for $C_{33}H_{47}N_5O_8S$ $[M - H]^-$ 672.3066, found 672.3058.

3l



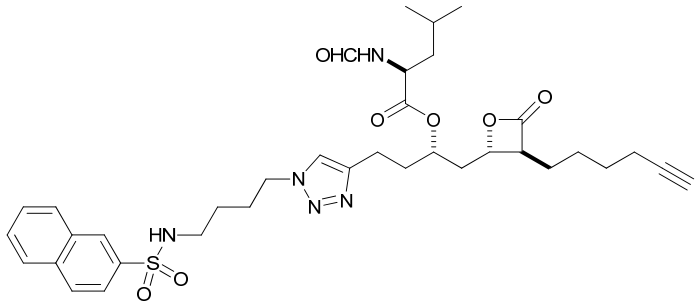
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.59 (s, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 1H), 5.98 (d, *J* = 6.9 Hz, 1H), 4.79 (m, 1H), 4.59 (dt, *J* = 10.1, 3.8 Hz, 1H), 4.46 (ddd, *J* = 14.5, 10.7, 3.8 Hz, 1H), 4.30 (dt, *J* = 13.9, 4.5 Hz, 1H), 4.20 (dt, *J* = 8.8, 3.8 Hz, 1H), 3.21 (dt, *J* = 8.8, 3.8 Hz, 1H), 2.98-3.04 (m, 1H), 2.97 (sept, *J* = 6.9 Hz, 1H), 2.86 (m, 2H), 2.77-2.80 (m, 1H), 2.31 (m, 1H), 2.18 (m, 2H), 2.01-2.13 (m, 4H), 1.60-1.78 (m, 10H), 1.49-1.51 (m, 6H), 1.26 (2xd, *J* = 6.3 Hz, 6H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.96 (d, *J* = 6.3 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{35}H_{51}N_5O_7S$ $[M + H]^+$ 686.9, found 686.3. HRMS (ESI) (*m/z*) calcd for $C_{35}H_{51}N_5O_7S$ $[M - H]^-$ 684.3430, found 684.3421.

3m



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.59 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 1H), 5.96 (d, *J* = 7.6 Hz, 1H), 4.79 (br s, 1H), 4.59 (dt, *J* = 10.2, 4.5 Hz, 1H), 4.46 (m, 1H), 4.30 (dt, *J* = 13.2, 4.5 Hz, 1H), 4.18-4.23 (m, 1H), 3.20 (dt, *J* = 7.6, 3.8 Hz, 1H), 3.00 (m, 1H), 2.86 (m, 2H), 2.79 (m, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.32 (m, 2H), 2.04 (m, 4H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.63-1.76 (m, 10H), 1.50 (m, 6H), 1.26 (br s, 6H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{35}H_{51}N_5O_7S$ $[M + Na]^+$ 708.3, found 708.2. HRMS (ESI) (*m/z*) calcd for $C_{35}H_{51}N_5O_7S$ $[M - H]^-$ 684.3430, found 684.3425.

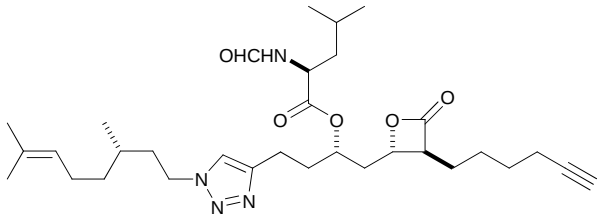
3n



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.36 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.70 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.65 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.60 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.57 (s, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.16 (d, *J* = 7.6 Hz, 1H), 4.76 (m, 1H), 4.62 (m, 1H), 4.45 (ddd, *J* = 13.9, 10.7, 3.8 Hz, 1H), 4.29 (dt, *J* = 13.9, 4.4 Hz, 1H), 4.15 (dt, *J* = 8.8, 3.8 Hz, 1H), 3.19 (dt, *J* = 7.6, 4.4 Hz, 1H), 3.06 (ddd, *J* = 15.1, 10.7, 5.1 Hz, 1H), 2.84-2.87 (m, 2H), 2.78-2.80 (m, 1H), 2.24-2.30 (m, 1H), 1.98-2.16 (m, 6H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.68-1.81 (m, 5H), 1.41-1.45 (m, 5H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 1H). ESI-MS (*m/z*) calcd for $C_{36}H_{47}N_5O_7S$ $[M + Na]^+$

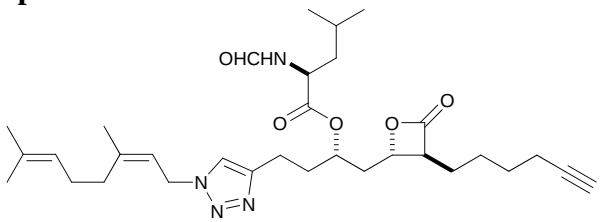
716.3, found 716.2. HRMS (ESI) (*m/z*) calcd for $C_{36}H_{47}N_5O_7S$ $[M - H]^-$ 693.3117, found 693.3105.

3o



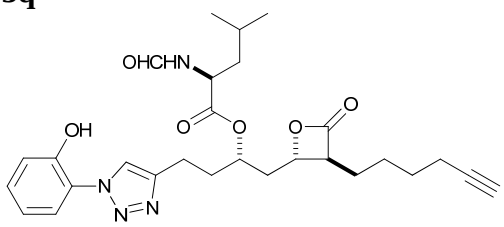
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.35 (s, 1H), 6.04 (d, *J* = 7.6 Hz, 1H), 5.04-5.07 (m, 2H), 4.65 (dt, *J* = 8.9, 5.1 Hz, 1H), 4.29-4.34 (m, H-4, 3H), 3.74 (t, *J* = 6.4 Hz, 1H), 3.24 (dt, *J* = 7.6, 3.8 Hz, 1H), 2.70-2.83 (m, 2H), 2.13-2.21 (m, 2H), 2.04-2.09 (m, 8H), 1.96 (t, *J* = 1.9 Hz, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.33-1.48 (m, 5H), 1.20-1.24 (m, 5H), 0.97 (d, *J* = 5.7 Hz, 6H), 0.95 (d, *J* = 6.9 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{32}H_{50}N_4O_5$ $[M + Na]^+$ 593.4, found 593.2. HRMS (ESI) (*m/z*) calcd for $C_{32}H_{50}N_4O_5$ $[M - H]^-$ 569.3702, found 569.3699.

3p



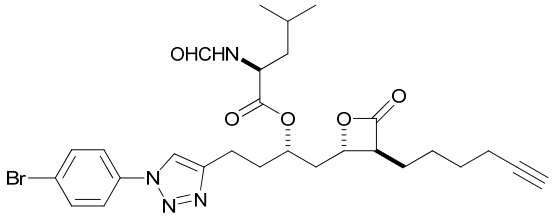
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.31 (s, 1H), 5.99 (br s, 1H), 5.41 (t, *J* = 8.0 Hz, 1H), 5.67 (m, 2H), 4.92 (t, *J* = 7.6 Hz, 2H), 4.66 (m, 1H), 4.30 (dt, *J* = 8.7, 4.5 Hz, 1H), 3.23-3.27 (m, 1H), 2.71-2.81 (m, 2H), 2.04-2.21 (m, 10H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.78 (s, 3H), 1.68 (s, 3H), 1.57 (br s, 8H), 0.97 (d, *J* = 5.1 Hz, 6H). ESI-MS (*m/z*) calcd for $C_{32}H_{50}N_4O_5$ $[M - H]^-$ 567.3, found 567.4. HRMS (ESI) (*m/z*) calcd for $C_{32}H_{50}N_4O_5$ $[M - H]^-$ 567.3546, found 567.3548.

3q



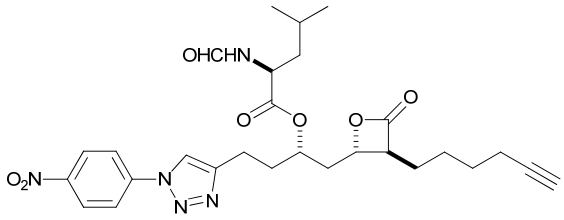
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.02 (s, 1H), 7.42 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 5.96 (br s, 1H), 5.06-5.11 (m, 1H), 4.61 (dt, *J* = 9.5, 4.4 Hz, 1H), 4.31 (dt, *J* = 8.2, 4.4 Hz, 1H), 3.25 (dt, *J* = 7.6, 4.4 Hz, 1H), 2.87-2.95 (m, 2H), 2.12-2.23 (m, 5H), 2.09 (dt, *J* = 10.8, 3.8 Hz, 1H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.69-1.83 (m, 4H), 1.53-1.62 (m, 7H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.3 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{28}H_{36}N_4O_6$ $[M + H]^+$ 525.3, found 525.2. HRMS (ESI) (*m/z*) calcd for $C_{28}H_{36}N_4O_6$ $[M - H]^-$ 523.2556, found 523.2546.

3r



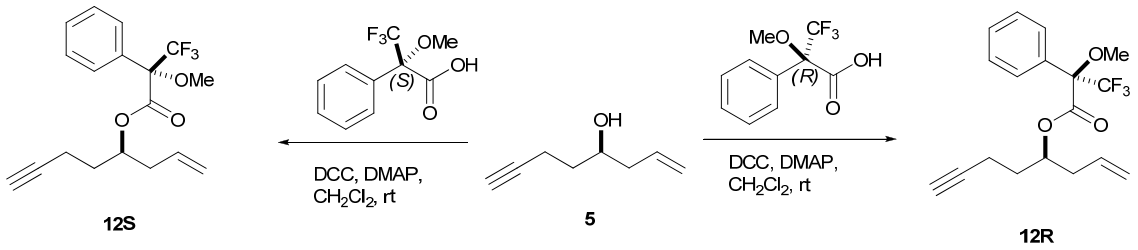
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.87 (s, 1H), 7.64 9s, 4H), 5.93 (d, *J* = 7.6 Hz, 1H), 5.05-5.09 (m, 1H), 4.61 (dt, *J* = 8.8, 3.8 Hz, 1H), 4.31 (dt, *J* = 8.8, 4.5 Hz, 1H), 3.25 (dt, *J* = 7.6, 4.4 Hz, 1H), 2.81-2.92 (m, 2H), 2.07-2.20 (m, 6H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.70-1.72 (m, 4H), 1.53-1.60 (m, 5H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.3 Hz, 3H). ESI-MS (*m/z*) calcd for $C_{28}H_{35}BrN_4O_5$ $[M]^-$ 587.2, found 587.2. HRMS (ESI) (*m/z*) calcd for $C_{28}H_{35}BrN_4O_5$ $[M - H]^-$ 585.1713, found 585.1713.

3s



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, *J* = 8.9 Hz, 2H), 8.26 (s, 1H), 8.09 (s, 1H), 8.01 (d, *J* = 8.9 Hz, 2H), 5.92 (br s, 1H), 5.01-5.06 (m, 1H), 4.55-4.60 (m, 1H), 4.30 (dt, *J* = 8.2, 3.8 Hz, 1H), 3.24 (dt, 7.6, 4.4 Hz, 1H), 2.86-2.96 (m, 2H), 2.12-2.21 (m, 5H), 2.08 (dt, *J* = 11.4, 3.8 Hz, 1H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.71-1.82 (m, 4H), 1.52-1.60 (m, 5H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 712.1, 170.3, 161.2, 125.5, 120.3, 83.8, 74.7, 71.2, 68.8, 57.0, 50.0, 40.4, 39.3, 33.4, 27.9, 27.0, 25.7, 25.0, 22.9, 21.5, 21.0, 18.1. ESI-MS (*m/z*) calcd for $C_{28}H_{35}N_5O_7$ $[M - H]^-$ 552.3, found 552.4. HRMS (ESI) (*m/z*) calcd for $C_{28}H_{35}N_5O_7$ $[M - H]^-$ 552.2457, found 552.2455.

Synthesis of (*S*)- and (*R*)-Mosher esters for determination of *ee* and absolute configuration of homoallylic alcohol 5



Scheme S1: Synthesis of (*S*)- and (*R*)-Mosher esters

(*S*)-((*R*)-oct-1-en-7-yn-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (12S): DCC (21 mg, 0.102 mmol) and DMAP (2 mg, 0.015 mmol) was added to a mixture of (*S*)-Mosher acid (22 mg, 0.095 mmol) and homoallylic alcohol **5** (9 mg, 0.073 mmol) in CH_2Cl_2. The reaction mixture was stirred at rt overnight. The precipitate was filtered through a pad of celite, the filtrate was evaporated under reduced pressure. Purification by flash chromatography on SiO_2 (95:5, hexanes:EtOAc) to provide the (*S*)-Mosher ester **12S** (21.2 mg, 85%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.54 (m, 2H), 7.40-7.41 (m, 3H), 5.61-5.63 (m 1H), 5.25-5.30 (m, 1H), 5.07 (br d, *J* = 3.8 Hz, 1H), 5.04 (s, 1H), 3.54 (s, 3H), 2.41 (br t, *J* = 6.3 Hz, 2H), 2.22-2.29 (m, 1H), 2.19 (ddd, *J* = 17.1, 7.6, 2.6 Hz, 1H), 2.00 (t, *J* = 2.5 Hz, 1H), 1.83-1.91 (m, 2H).

(*R*)-((*R*)-oct-1-en-7-yn-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (12R): The title compound was prepared from (*R*)-Mosher acid following the same procedure that was used for the synthesis of **12S**; yield 54%; pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.55 (m, 2H), 7.39-7.41 (m, 3H), 5.72-5.81 (m, 1H), 5.30 (m, 1H), 5.14 (dd, *J* = 6.3, 1.3 Hz, 1H), 5.11 (br s, 1H), 3.57 (d, *J* = 1.3 Hz, 3H), 2.47 (t, J = 6.3 Hz, 2H), 2.09-2.15 (m, 1H), 2.01 (ddd, *J* = 15.1, 7.6, 2.5 Hz, 1H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.80-1.84 (m, 2H).

Fig. S1(a) shows the $\Delta\delta_{SR}$ values from the ^{1}H NMR spectra of the (*S*)- and (*R*)-MTPA esters of homoallylic alcohol **5**. Based on model[1] (**Fig. S1(b)**), the absolute configuration of homoallylic alcohol **5** was determined to be *R*.

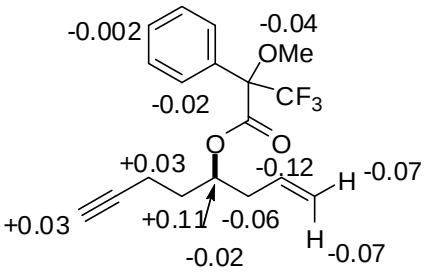


Fig. S1(a)

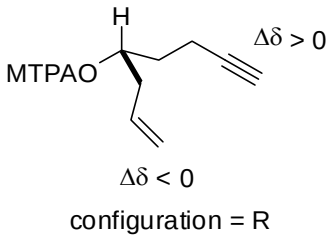
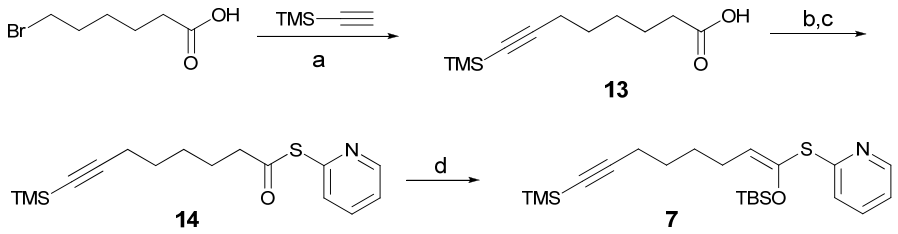


Fig. S1(b)

Synthesis of thiopyridyl ketene acetal 7



Scheme S2. Reagents and conditions: (a) ethynyltrimethylsilane (1.8 equiv), nBuLi (2.0 equiv), DMSO:THF, -78 °C, 2h, 82%; (b) $(COCl)_2$ (1.5 equiv), DMF (cat.), 0 °C, rt; c) 2-mercaptopyridine (1.2 equiv), Et_3N (2.0 equiv), 0 °C to rt, 2 h, 78%; (d) LiHMDS (1.2 equiv), DMF (4.0 equiv), TBSCl (1.0 equiv), THF, -78 °C, 15 min, 74%.

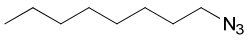
8-(trimethylsilyl)-oct-7-ynoic acid (13): nBuLi in hexane (1.5 M, 38 mL, 49.22 mmol), was added dropwise to a solution of TMS-acetylene (4.029 g, 41.02 mmol) in THF (50 mL) cooled at -78 °C. After 20 min, 6-bromohexanoic acid (4.0 g, 20.51 mmol) in THF:DMSO (3:1, 60 mL), was added dropwise via cannula. The reaction mixture was stirred at -78 °C for 1.5 h. The reaction mixture was warmed to 0 °C and stirred for 1 h, then stirred at rt for 1 h. The reaction mixture was then cooled to 0 °C and quenched with saturated NH_4Cl solution (80 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic phase was washed with brine (2 x 30 mL) and dried over Na_2SO_4. Purification by flash chromatography (Hexanes/EtOAc, 1:1) gave acid **13** (1.5115 g, 35%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (t, J = 7.4 Hz, 2H), 2.23 (t, J = 6.72 Hz, 2H), 1.44-1.68 (m, 6H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 107.2, 84.7, 33.9, 28.2, 28.1, 24.2, 19.7, 0.2.

S-pyridin-2-yl 8-(trimethylsilyl)-oct-7-ynethioate (14): Oxalyl chloride (1.34 g, 10.59 mmol) was added to a solution of acid **13** (1.5 g, 6.59 mmol) in CH_2Cl_2 (20 mL) cooled at 0 °C and one drop of DMF was added to the reaction mixture. The reaction mixture was stirred at 0 °C for 2 h. The solvent was evaporated in vacuo and the crude product was used for next step without any purification.

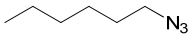
The crude acyl chloride was redissolved in CH_2Cl_2, then 2-mercaptopyridine (879 mg, 7.91 mmol) was added followed by Et_3N (1.335 g, 13.18 mmol). The reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was extracted with 1M HCl (3 x 10 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give crude thioester **14** (1.7447 g) as a pale yellow oil, which was used for next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61-8.63 (m, 1H), 7.71-7.77 (m, 1H), 7.31-7.60 (m, 1H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.32 (t, *J* = 6.9 Hz, 2H), 1.70-1.80 (m, 1H), 1.44-1.57 (m, 4H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 151.6, 150.3, 137.0, 130.1, 123.4, 107.5, 84.3, 44.1, 28.7, 25.3, 19.8, 0.1.

(*E*)-2-(1-(tert-butyldimethylsilyloxy)-8-(trimethylsilyl)oct-1-en-7-ynylthio)pyridine (7): *n*BuLi (1.6 M, 5.2 mL, 7.78 mmol) was added to a solution of hexamethyldisilane (1.205 g, 1.47 mmol) in THF (18 mL) cooled at 0 °C and stirred for 15 min. The LiHMDS solution was cooled to -78 °C, DMF (1.818 g, 24.9 mmol), TBSCl (0.937 g, 6.22 mmol) in THF (7 mL) and thioester **13** (1.9 g, 6.22 mmol) in THF (7 mL) were added sequentially to the solution. The reaction mixture was stirred at -78 °C for 15 min and then quenched with EtOAc (30 mL). Water was added to the reaction mixture and the resulting aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4.The solvent was removed under reduced pressure and the crude product was purified with flash chromatography (hexanes/EtOAc, 95:5) to give thiopyridyl ketene acetal **7** (1.4977 g, 57%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40-8.50 (m, 1H), 7.54 (dt, *J* = 1.9, 7.6, Hz, 1H), 7.31-7.33 (d, *J* = 8.2 Hz, 1H), 6.98-7.01 (m, 1H), 5.39 (t, *J* = 7.0 Hz, 1H), 2.34 (dd, *J* = 6.9, 13.8 Hz, 2H), 2.20 (dd, *J* = 5.7, 12.6 Hz, 2H), 1.50-1.56 (m, 4H), 0.88 (s, 9H), 0.14 (s, 9H), 0.08(s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 160.4, 149.4, 139.7, 136.5, 123.4, 121.5, 119.6, 107.3, 84.5, 35.9, 28.4, 28.3, 26.3, 25.7, 25.6, 25.0, 19.7, 18.1, 17.6, 0.2. -4.8; TOF-MS (*m/z*) calcd for $C_{22}H_{37}NOSSi_2$ $[M + H]^-$ 420.221, found 420.244.

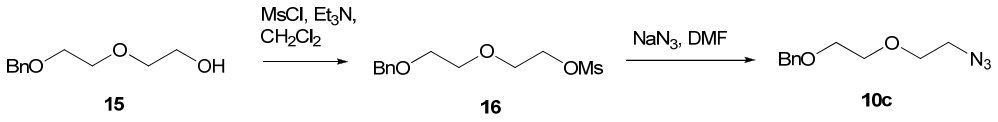
General procedure for the synthesis of azides from alkyl bromides or mesylates



1-azidooctane (10a)[2]: NaN_3 (505 mg, 7.77 mmol) was added to a solution of 1-bromooctane (1 g, 5.18 mmol) in DMF (2 mL). The reaction mixture was stirred at rt for 4 h. Water (20 mL) was added to the reaction mixture and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give azide **10a** (793 mg, 99%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.25 (t, *J* = 6.9 Hz, 2H), 1.60 (quin, *J* = 6.7 Hz, 2H), 1.28 (br s, 10H), 0.80 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.5, 31.7, 29.13, 29.10, 28.8, 26.7, 22.6, 14.0. ^{13}C NMR (125 MHz, $CDCl_3$): δ 72.6, 70.60, 70.57, 70.55, 70.49, 70.44, 70.2, 70.0, 61.7, 50.6.



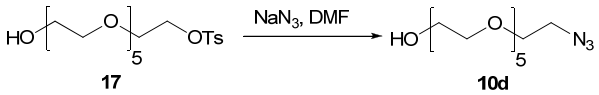
1-azidohexane (10b)[3]: The title compound was prepared from hexyl bromide following the same procedure that was used for the synthesis of **10b**; yield 89%; colouless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.26 (t, *J* = 6.9 Hz, 2H), 1.55-1.64 (m, 2H), 1.26-1.39 (m, 6H), 0.90 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.5, 31.3, 28.8, 26.4, 22.5, 13.9. ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 128.4, 127.74, 127.72, 73.3, 70.7, 69.4, 69.2, 69.0, 37.7.



Scheme S4: Synthesis of azide **10c**

((2-(2-azidoethoxy)ethoxy)methyl)benzene (10c): The mesylate was prepared from ethyleneglycol **15** following the same procedure that was used for synthesis of mesylate **16**; colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.35 (m, 5H), 4.55 (s, 2H), 3.76-3.78 (m, 2H), 3.69-3.70 (m, 2H), 3.63-3.65 (m, 2H), 3.02 (s, 3H).

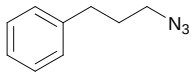
The azide was prepared from mesylate **16** following the same procedure that was used for synthesis of azide **10c**; colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.35 (m, 5H), 4.58 (s, 2H), 3.64-3.70 (m, 6H), 3.40 (t, *J* = 5.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 128.4, 127.7, 127.6, 73.3, 70.8, 70.1, 69.5, 50.7.



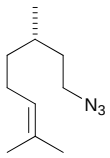
17 10d

Scheme S5: Synthesis of hexaethyleneglycol azide **10d**

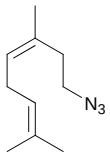
17-azido-3,6,9,12,15-pentaoxaheptadecan-1-ol (10d)[7]: The title compound was prepared from monotosylate **17** following the same procedure that was used for the synthesis of **10c**; yield 99%; colouless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64-3.72 (m, 20 H), 3.58-3.60 (m, 2H), 3.37 (t, *J* = 5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.6, 70.60, 70.57, 70.55, 70.49, 70.44, 70.2, 70.0, 61.7, 50.6.



(3-azidopropyl)benzene (10e)[4]: The title compound was prepared from (3-bromopropyl)benzene following the same procedure that was used for the synthesis of **10c**; yield 99%; colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 2H), 7.21 (m, 3H), 3.29 (t, *J* = 6.9 Hz, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 1.92 (pent, *J* = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.5, 128.4, 126.1, 50.6, 32.7, 30.4.

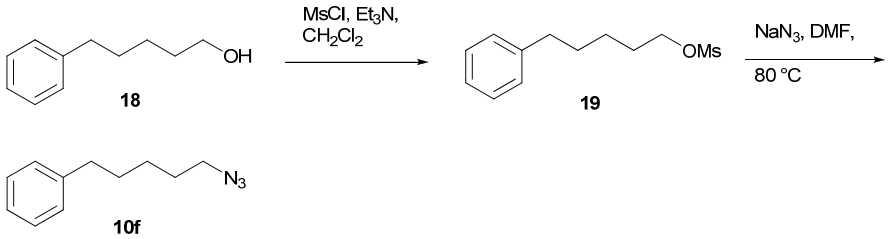


Citronellyl azide (10o)[5]: The title compound was prepared from citronellyl bromide following the same procedure that was used for the synthesis of **10c**; yield 75%; pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.09 (t, *J* = 7.0 Hz, 1H), 3.23-3.34 (m, 2H), 1.94-2.06 (m, 2H), 1.69 (s, 3H), 1.61-1.66 (m, 4H), 1.61 (s, 3H), 1.54 (m, 1H), 1.31-1.45 (m, 2H), 1.17-1.22 (m, 1H), 0.91 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.5, 124.4, 49.5, 36.9, 35.6, 30.0, 25.7, 25.4, 19.2, 17.6



Geranyl azide (10p)[6]: The title compound was prepared from geranyl bromide following the same procedure that was used for the synthesis of **10c**; yield 65%; pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34 (m, 1H), 5.10 (m, 1H), 3.77 (t, *J* = 7.6 Hz, 1H), 2.11 (m, 4H), 1.71 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H).

General procedure for the synthesis of azides from alcohols

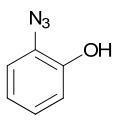


Scheme S6: Synthesis of azide **10f**

(5-azidopentyl)benzene (10f): Methanesulfonyl chloride (696 mg, 6.08 mmol) was added to a solution of alcohol **18** (500 mg, 3.04 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C, followed by Et_3N (922 mg, 9.12 mmol). The reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and extracted with H_2O (2 x 10 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to give a colourless oil. The product was used for next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 2H), 7.18 (m, 3H), 4.22 (t, *J* = 6.6 Hz, 2H), 2.98 (s, 3H), 2.63 (t, *J* = 7.4 Hz, 2H), 1.73-1.83 (m, 2H), 1.62-1.72 (m, 2H), 1.41-1.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.4, 128.3, 125.8, 69.9, 37.4, 35.6, 30.8, 29.0, 25.0.

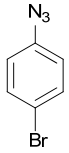
NaN_3 (293 mg, 4.5 mmol) was added to a solution of crude **19** in DMF (5 mL). The reaction mixture was heated at 80 °C for 4 h. The reaction mixture was cooled to rt and diluted with water (20 mL) and the organic phase was extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (hexanes/EtOAc, 1:0 to 98:2) to give azide **10f** (560 mg, 97%, 2 steps) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.28 (m, 2H), 7.17-7.21 (m, 3H), 3.26 (t, *J* = 6.9 Hz, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 1.59-1.72 (m, 4H), 1.38-1.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.4, 128.3, 125.7, 51.4, 35.8, 31.0, 28.7, 26.3.

General procedure for the synthesis of aromatic azides

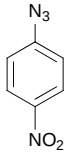


2-azidophenol (10q)[8]: Concentreated HCl (2.3 mL) was added to a suspension of 2-aminophenol (1.09 g, 10 mmol) in water (25 mL) cooled at 0 °C. $NaNO_2$ (690 mg, 10 mmol) in water (3 mL) was added to the reaction mixture. After 10 min, NaN_3 (780 mL, 12

mmol) was added portionwise. The reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to give a colourless oil (1.283 g, 95%). The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.04 (dd, 7.4, 1.3 Hz, 1H), 6.91-6.97 (m, 2H), 5.33 (br s, 1H).



1-azido-4-bromobenzene (10r)[9]**:** The title compound was prepared from *p*-bromoaminobenzene following the same procedure that was used for the synthesis of **10q**; yield 87%; pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H).



1-azido-4-nitrobenzene (10s)[10]**:** The title compound was prepared from *p*-nitroaminobenzene following the same procedure that was used for the synthesis of **10q**; yield 97%; pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 hz, 2H).

3. Cell biological experiments

3.1 Chemicals and Antibodies

Orlistat (98%), tris(2-carboxyethyl) phosphine (TCEP), and the click chemistry ligand, tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine ("ligand"), were purchased from Sigma-Aldrich. Antibodies against eIf2α (#9722), phospho-eIf2α (#9721), and cleaved caspase-8 (#9746) were from Cell Signaling Technologies (Beverly, MA).

3.2 Cell lines and culture conditions

Cell lines were obtained from the National Cancer Institute Developmental Therapeutics Program (NCI60 cell line panel). HepG2 was grown in DMEM (Invitrogen, Carlsbad, CA) containing 10% heat-inactivated fetal bovine serum (FBS; Gibco Invitrogen), 100 U/mL penicillin and 100 μg/mL streptomycin (Thermo Scientific, Rockford, IL) and maintained in a humidified 37 ^{o}C incubator with 5% CO_2. MCF-7 and PC-3 were maintained in RPMI 1640 medium supplemented with 10% FBS and 100 U/mL penicillin and 100 μg/mL streptomycin. To generate protein lysates, cells were washed twice with cold phosphate-buffered saline (PBS), and harvested with a cell scraper, and collected by centrifugation. Cell pellets were resuspended in PBS and lysed by sonication. Protein concentration was determined by the Bradford assay. Cell lysates were diluted with PBS to achieve final concentration of ~ 1 mg/mL for labeling reactions.

3.3 Cell proliferation assay

Cell viability was determined using the XTT colorimetric cell proliferation kit (Roche) following manufacturer's guidelines. Briefly, cells were grown to 20-30% confluence (since they will reach ~ 90% confluence within 48 to 72 h in the absence of drugs) in 96-well plates under the conditions described above. The medium was aspirated, and then washed with PBS, and then treated, in duplicate, with 0.1 mL of the medium containing different concentrations of triazole-modified Orlistat analogues (1-50 μM) or Orlistat and THL-R (1-50 μM; as a positive control). Probes were applied from DMSO stocks whereby DMSO never exceeded 1% in the final solution. The same volume of DMSO was used as a negative control. Fresh medium, along with the probes and Orlistat, were added every 24 h. After a total treatment time of 72 h, proliferation was assayed using the XTT colorimetric cell proliferation kit (Roche) following manufacturer's guidelines (read at 450 nm).

3.4 Western Blotting

To monitor the effects of triazole-modified Orlistat analogues on inducing phosphorylation of eIf2α, PC-3 cells were treated with indicated concentrations of Orlistat and analogues for 16 h. Samples from treated cells were then separated on 12% SDS PAGE gel and further transferred to PVDF membranes. Membranes were blocked with 5% BSA in TBS. After blocking, membranes were incubated with anti-eIf2α (#9722 from cell signaling, 1/5000) or anti-phospho-eIf2α (#9721 from Cell Signaling, 1/2000). After incubation, membranes were washed with TBST for three times and then incubated with an appropriate secondary antibody [anti-mouse conjugated HRP (1/5000) or anti-rabbit conjugated HRP (1/5000)]. After secondary incubation, blots were washed again with TBST before development with the SuperSignal West Pico kit (Pierce).

To monitor the effects of triazole-modified Orlistat analogues on inducing activation of caspase-8 pathway, MCF-7 cells were treated with indicated concentrations of THL-R and triazole-modified Orlistat analogues for 36 h. Samples from treated cells were then separated on a 12% SDS-PAGE gel and further transferred to PVDF membranes. Membranes were blocked with 5% BSA in TBS. After blocking, membranes were incubated with anti-caspase 8 (#9746 from Cell Signaling, 1/2000). After incubation, membranes were washed with TBST for three times, and then incubated with anti-mouse conjugated HRP (1/5000). After secondary incubation, blots were washed again with TBST before development with the SuperSignal West Pico kit (Pierce).

3.5 *In vitro* and *in situ* proteome labeling and analysis

For *in vitro* proteome labeling, probes were added to cell lysates (50 μg) in 50 μL PBS at a final concentration of 1-20 μM. Unless indicated otherwise, samples were incubated for 2 h with varying concentrations of probe at room temperature. After incubation, 10 μL of the freshly premixed click chemistry reaction cocktail in PBS [rho-azide (100 μM, 10 mM stock solution in DMSO), tris(2-carboxyethyl)phosphine hydrochloride (TCEP) (1 mM, 50 mM freshly prepared stock solution in deionized water), tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl] amine (TBTA) (100 μM, 10 mM stock solution in DMSO) and $CuSO_4$ (1 mM, 50 mM freshly prepared stock solution in

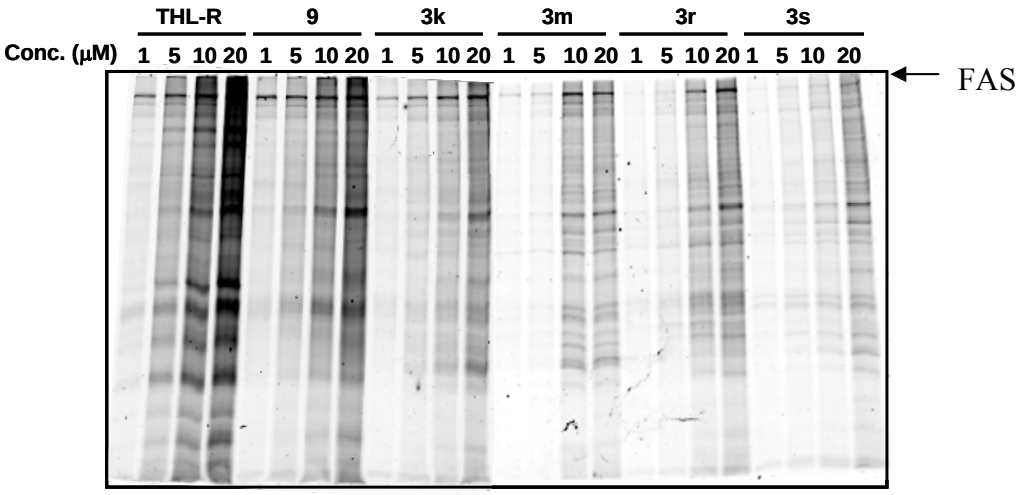
deionized water)] was added and vortexed, then incubated for 2 h at room temperature with gentle mixing. The reactions were terminated by the addition of pre-chilled acetone (0.5 mL), placed at -20 °C for 30 min and centrifuged at 13000 rpm for 10 min at 4 °C to precipitate proteins. The supernatant was discarded and the pellet washed two times with 200 μL of pre-chilled methanol. The protein pellets were allowed to air-dry for 10 min, resuspended in 25 μL 1× standard reducing SDS-loading buffer and heated for 10 min at 95 °C; ~ 20 μg of protein was loaded per gel lane for separation by SDS-PAGE (12% gel), then visualized by in-gel fluorescent scanning using a Typhoon 9410 Variable Mode Imager scanner.

For *in situ* labeling, Cells were grown to 80-90% confluence in 24-well plates under the conditions described above. The medium was removed, and then cells were washed twice with cold PBS, and treated with 0.5 mL of DMEM-containing probe (1-20 μM). Probes were applied from DMSO stocks whereby DMSO never exceeded 1% in the final solution. The same volume of DMSO was used as a negative control. After 4 h of incubation at 37 ^{o}C/5% CO_2, the growth medium was aspirated, and cells were washed twice with PBS to remove the excessive probe, trypsined, and pelleted by centrifugation. The cell pellet was resuspended in PBS (50 μL), homogenized by sonication, and diluted to ~1 mg/mL with PBS. Probe targets were detected by click chemistry with a rhodamine-azide tag, SDS/PAGE analysis, and in-gel fluorescence scanning.

3.6 Hydroxylamine Treatment of Gels.

After the proteins were separated by SDS-PAGE gel, the gel was soaked in 40% MeOH, 10% acetic acid, shaken overnight at room temperature, washed with deionized water (2 × 5 min), and scanned for the prehydroxylamine treatment fluorescence. The gel was then soaked in PBS, followed by shaking for 1 h at room temperature, boiling in neutralized hydroxylamine (Alfa Aesar) (2.5% final concentration) for 5 min, washing with deionized water (2 × 5 min), and soaking in 40% MeOH, 10% acetic acid, shaking overnight at room temperature. The gel was washed with deionized water (2 × 5 min) and scanned for the post-hydroxylamine fluorescence.

A



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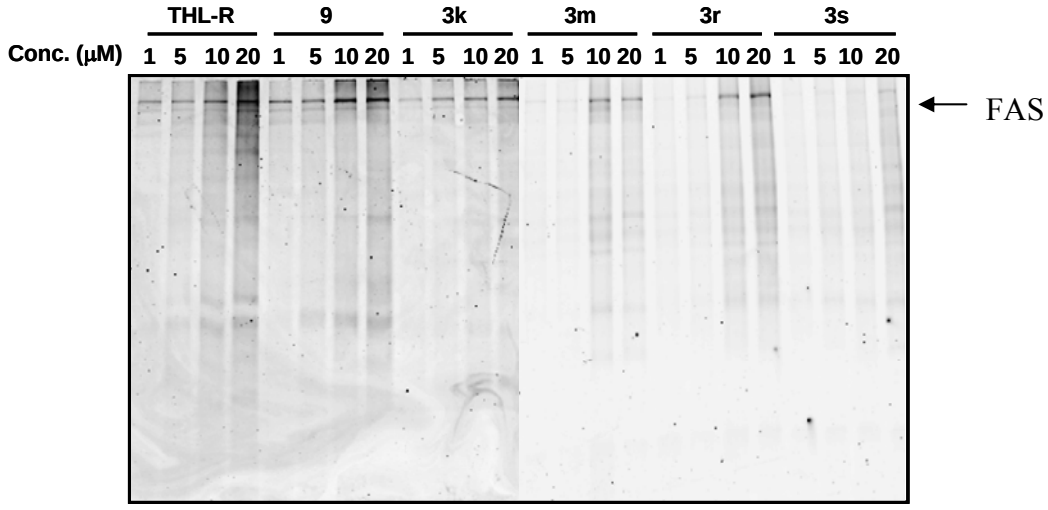

Fig. S2. Fluorescent profiles of the gel upon treatment with hydroxylamine. (A) before hydroxylamine treatment; (B) after hydroxylamine treatment.

References:

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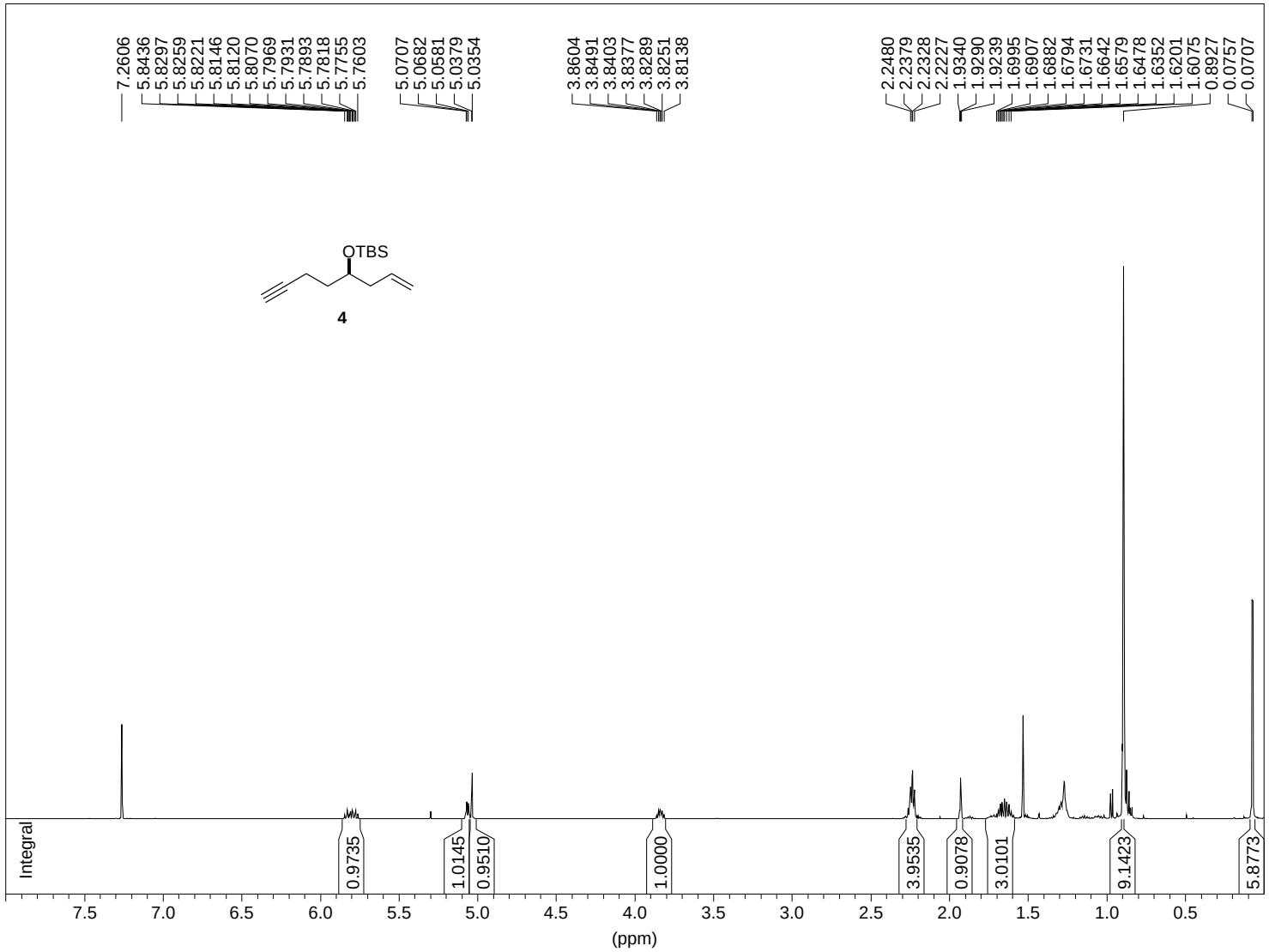
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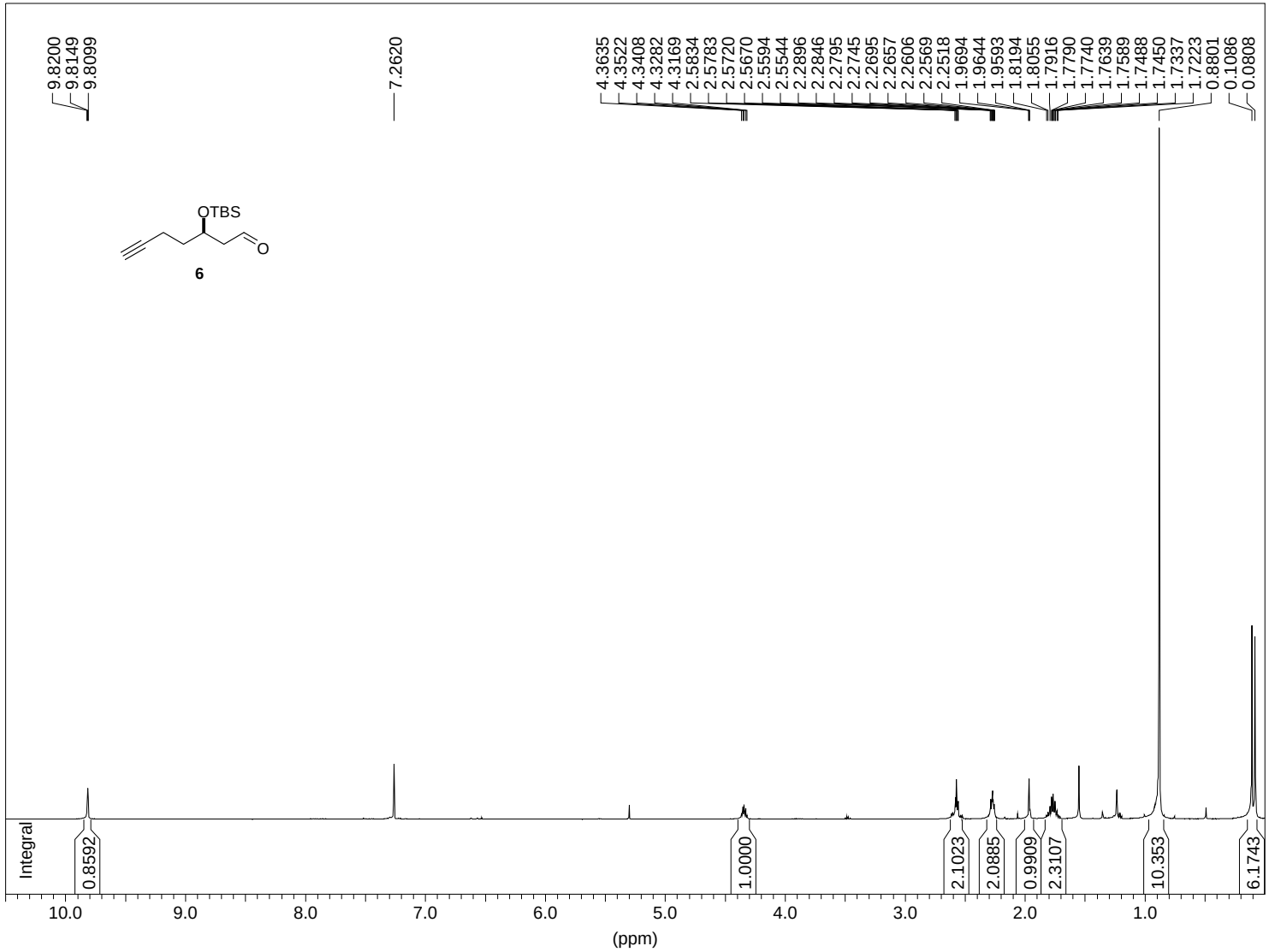
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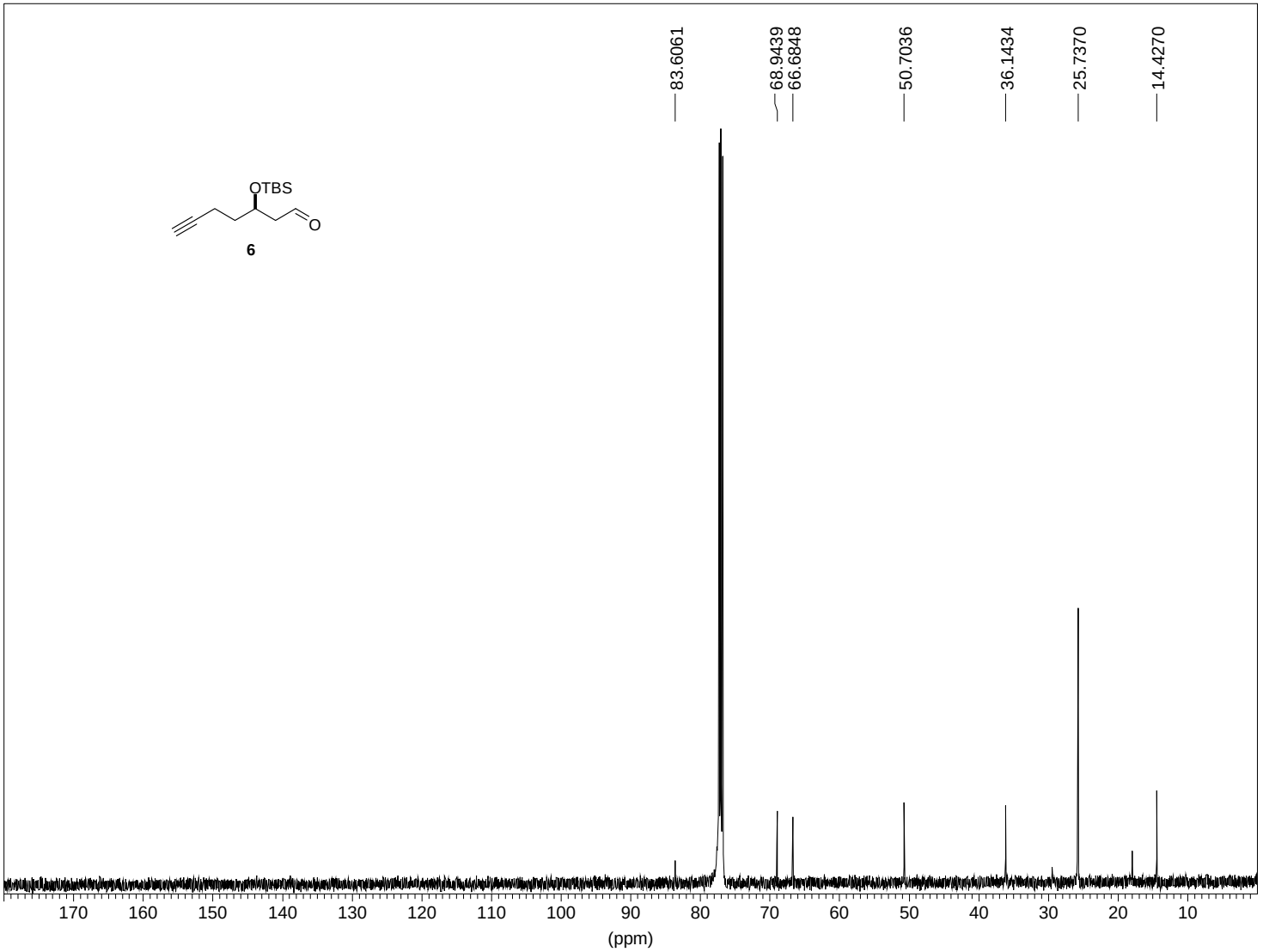
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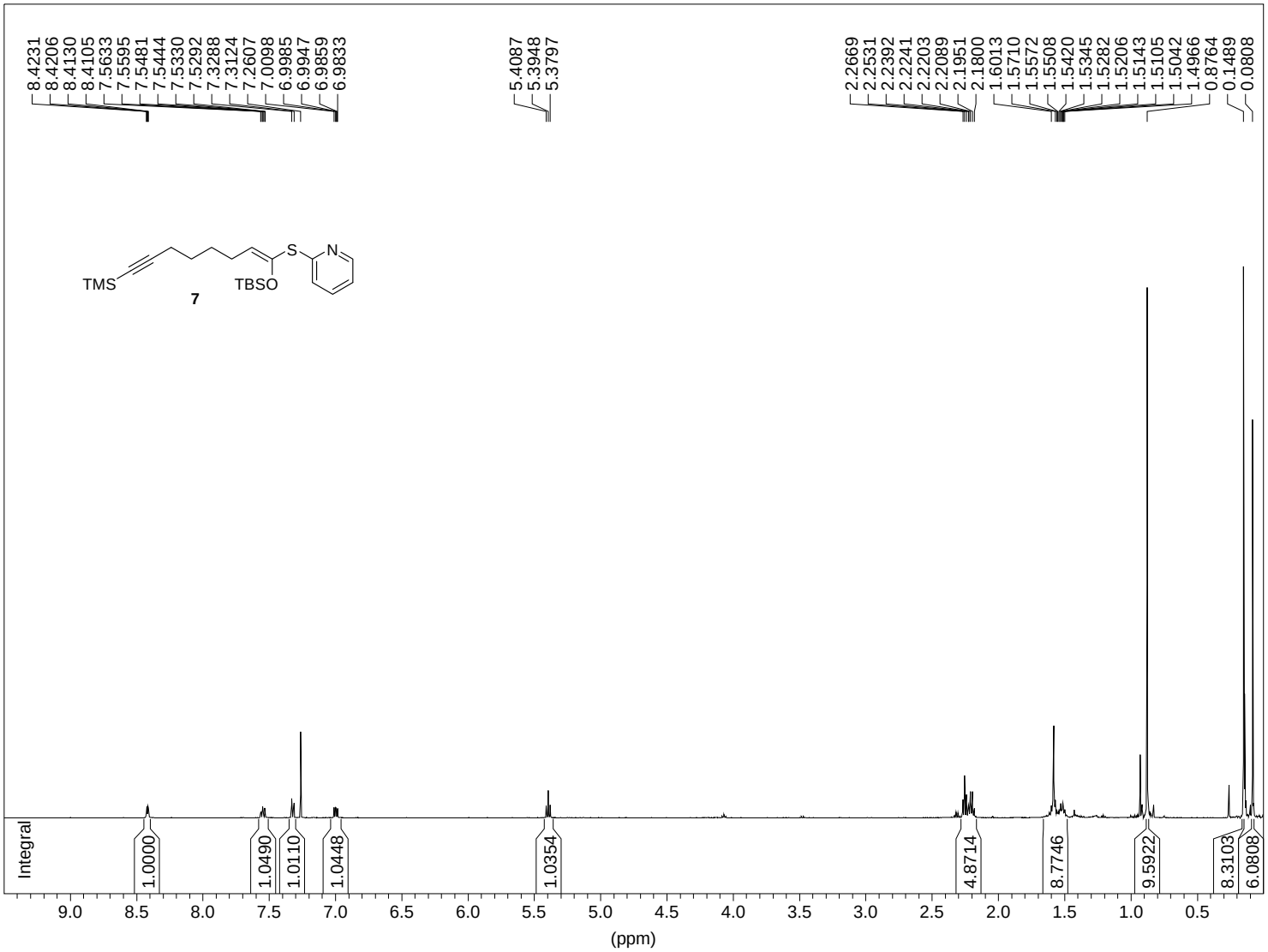
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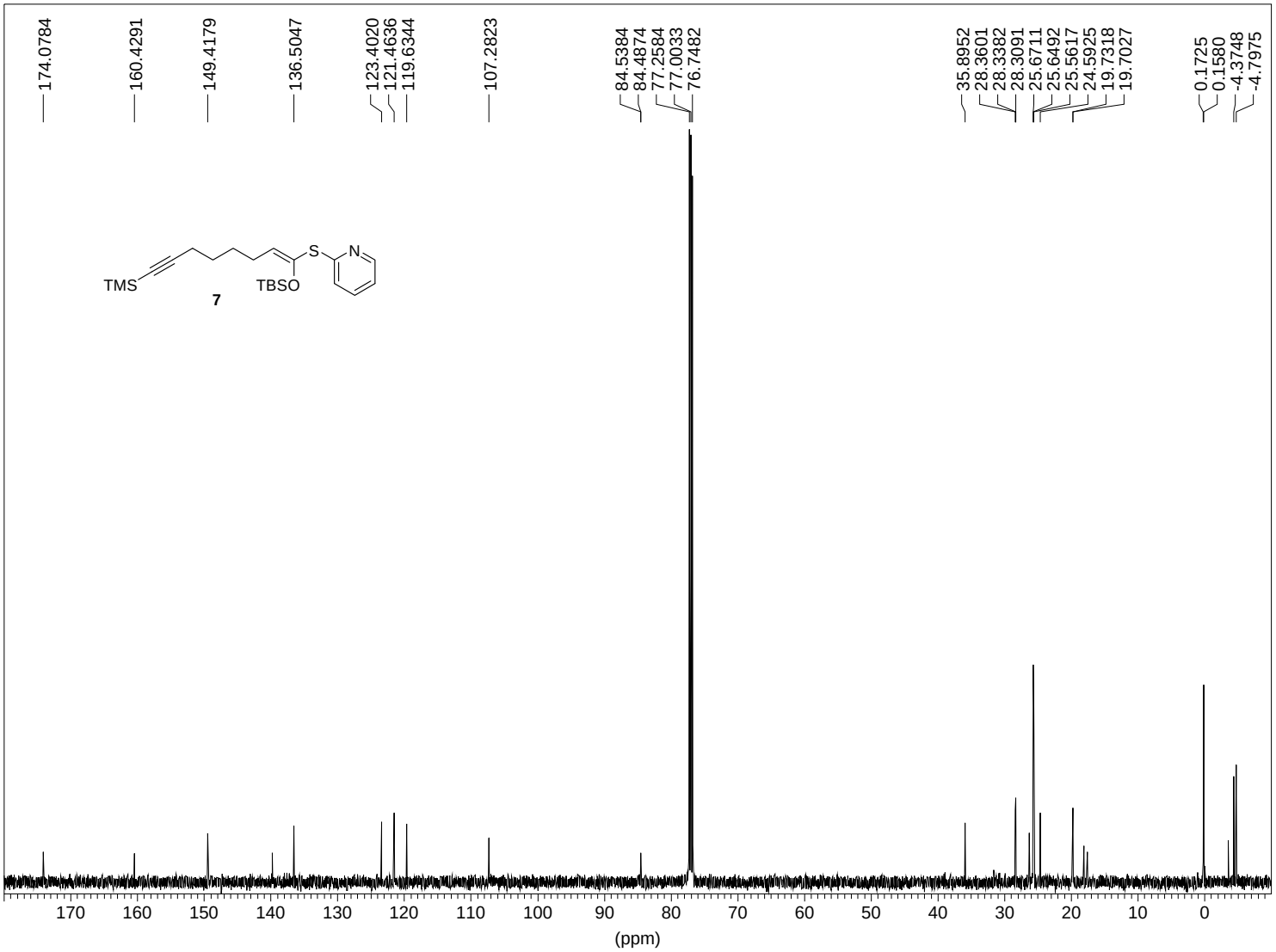
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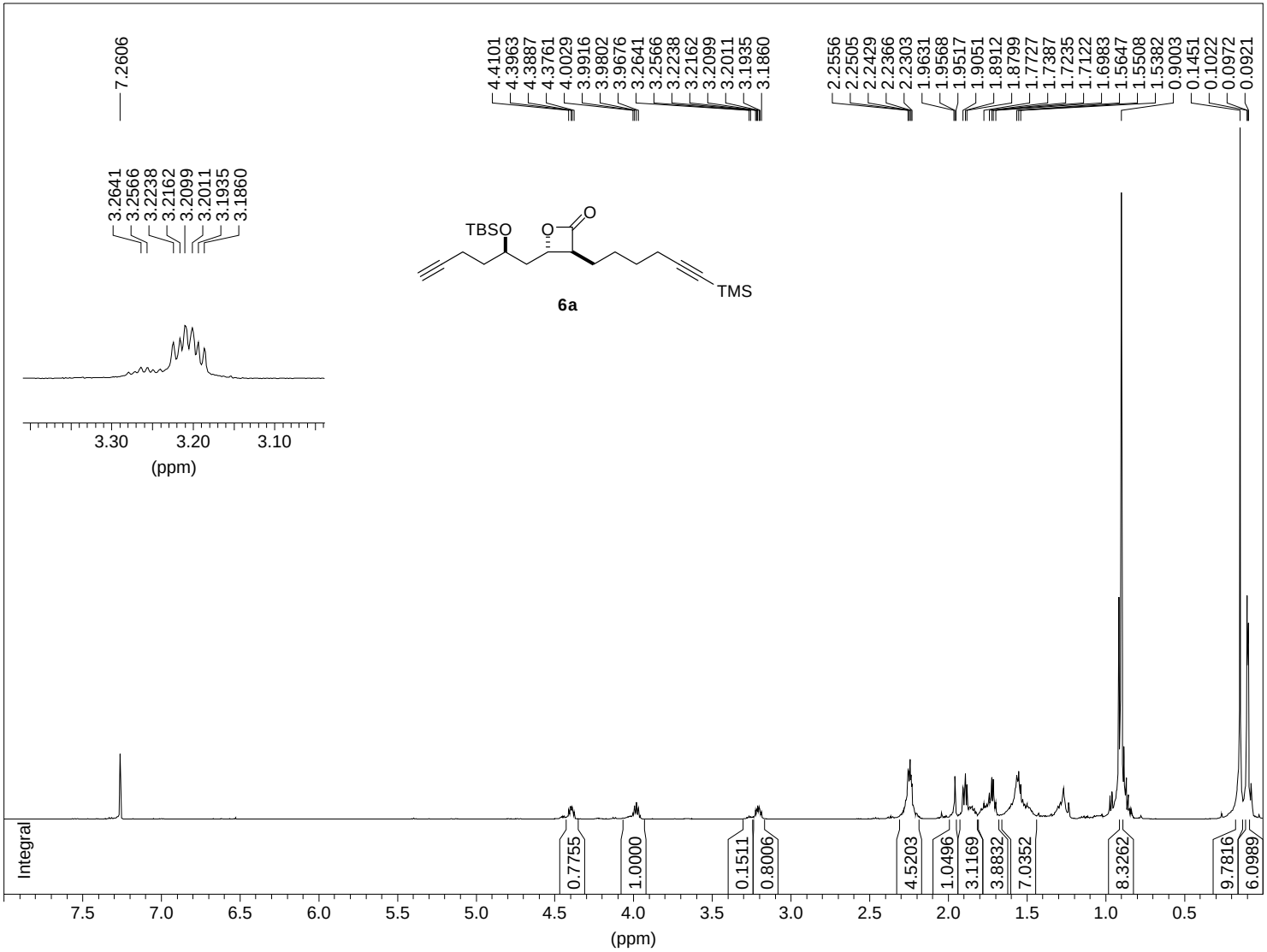
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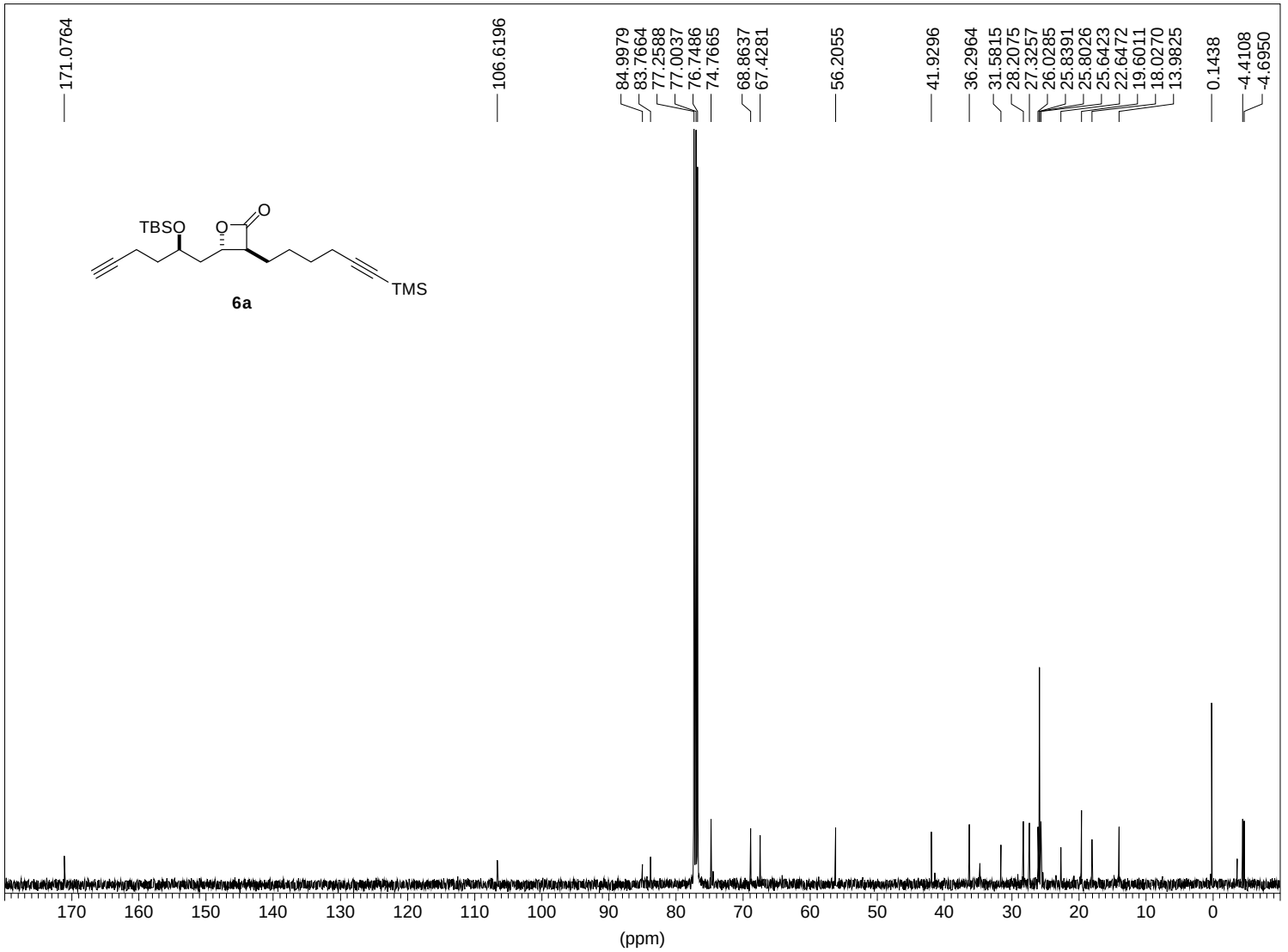
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84.9979
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56.2055
41.9296
36.2964
31.5815
28.2075
27.3257
26.0285
25.8391
25.8026
25.6423
22.6472
19.6011
18.0270
13.9825
0.1438
-4.4108
-4.6950
TBSO
O
O
TMS
6a
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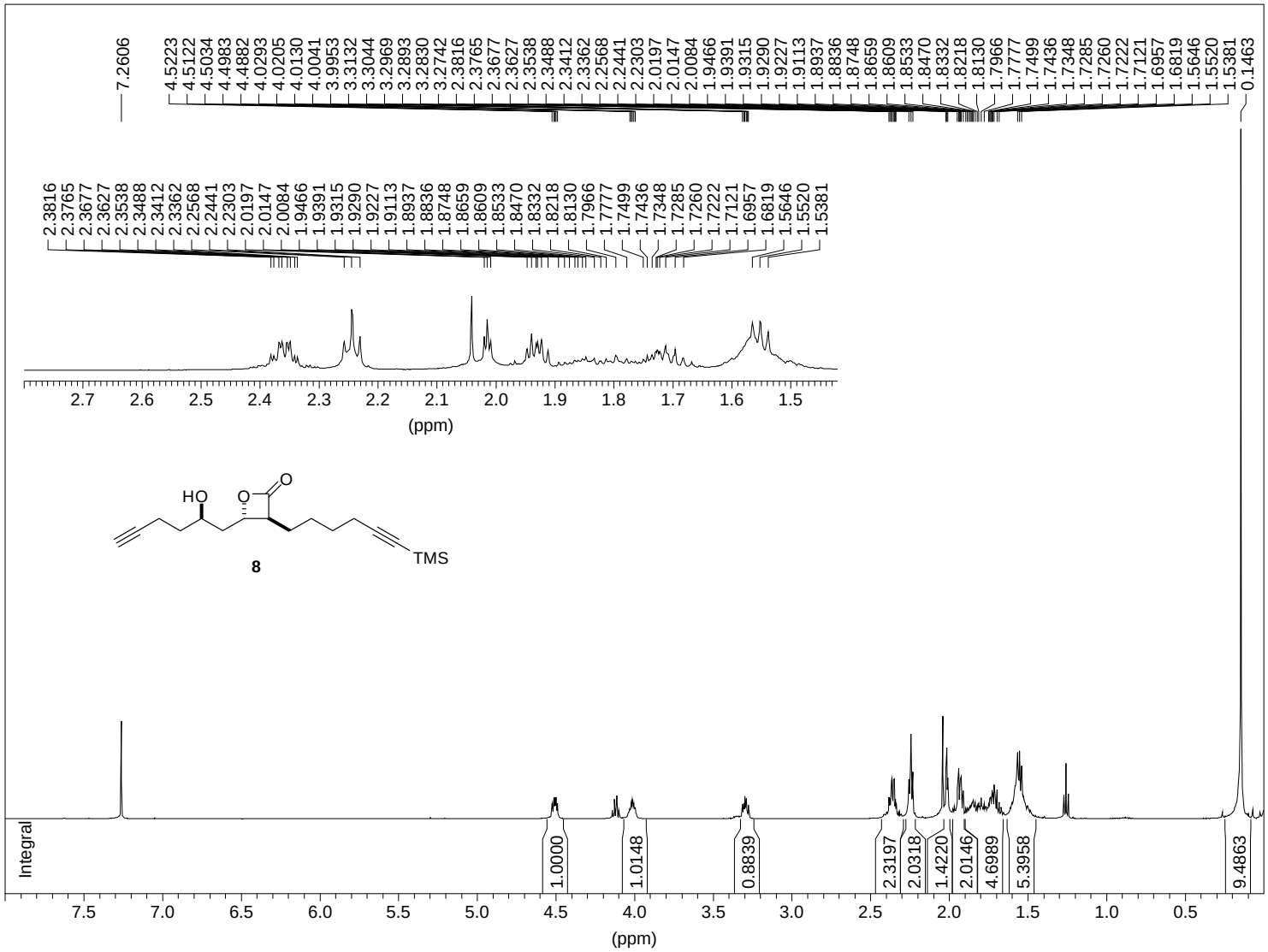
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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4.5122
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4.0293
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4.0130
4.0041
3.9953
3.3132
3.3044
3.2969
3.2893
3.2830
3.2742
2.3816
2.3765
2.3677
2.3627
2.3538
2.3488
2.3412
2.3362
2.2568
2.2441
2.2303
2.0197
2.0147
2.0084
1.9466
1.9391
1.9315
1.9290
1.9227
1.9113
1.8937
1.8836
1.8748
1.8659
1.8609
1.8533
1.8470
1.8332
1.8218
1.8130
1.7966
1.7777
1.7499
1.7436
1.7348
1.7285
1.7260
1.7222
1.7121
1.6957
1.6819
1.6646
1.5520
1.5381
0.1463
2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5
(ppm)
HO
O
O
TMS
8
Integral
1.0000
1.0148
0.8839
2.3197
2.0318
1.4220
2.0146
4.6989
5.3958
9.4863
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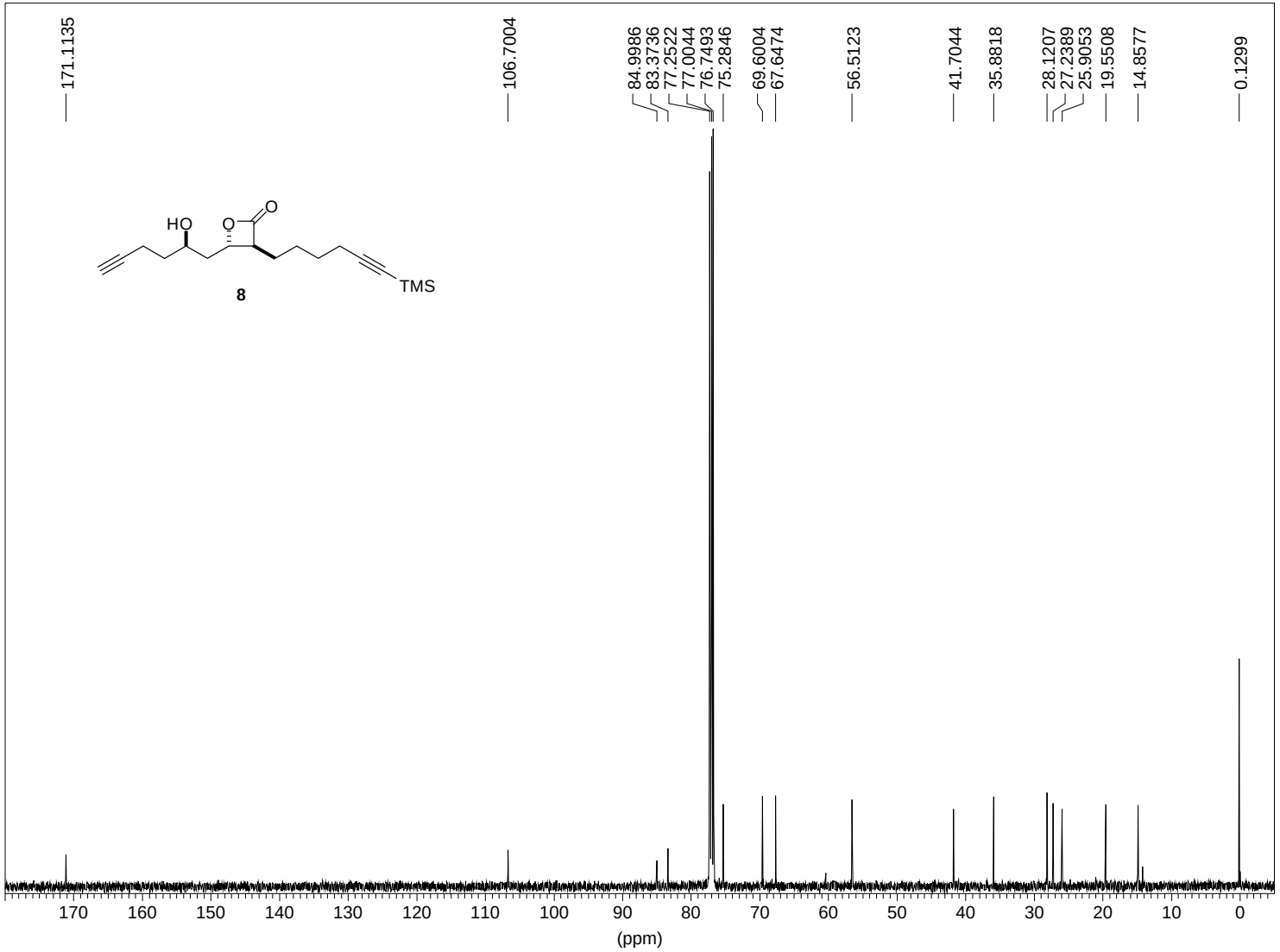
(ppm)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77.2522
77.0044
76.7493
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69.6004
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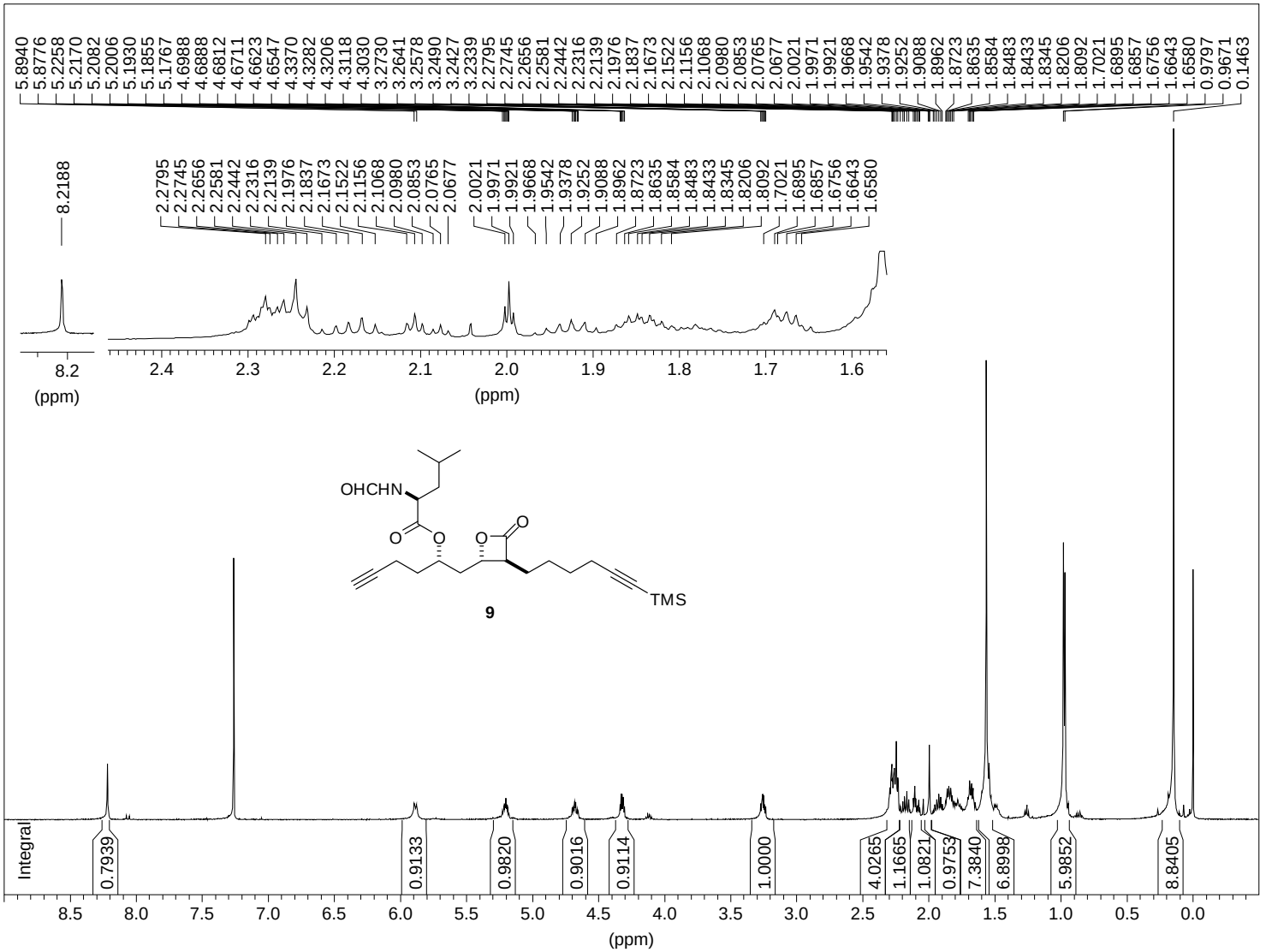
56.5123
41.7044
35.8818
28.1207
27.2389
25.9053
19.5508
14.8577
0.1299
HO
O
O
TMS
8
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


OHCHN
O
O
O
O
TMS
9
(ppm)
Integral
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0.9820
0.9016
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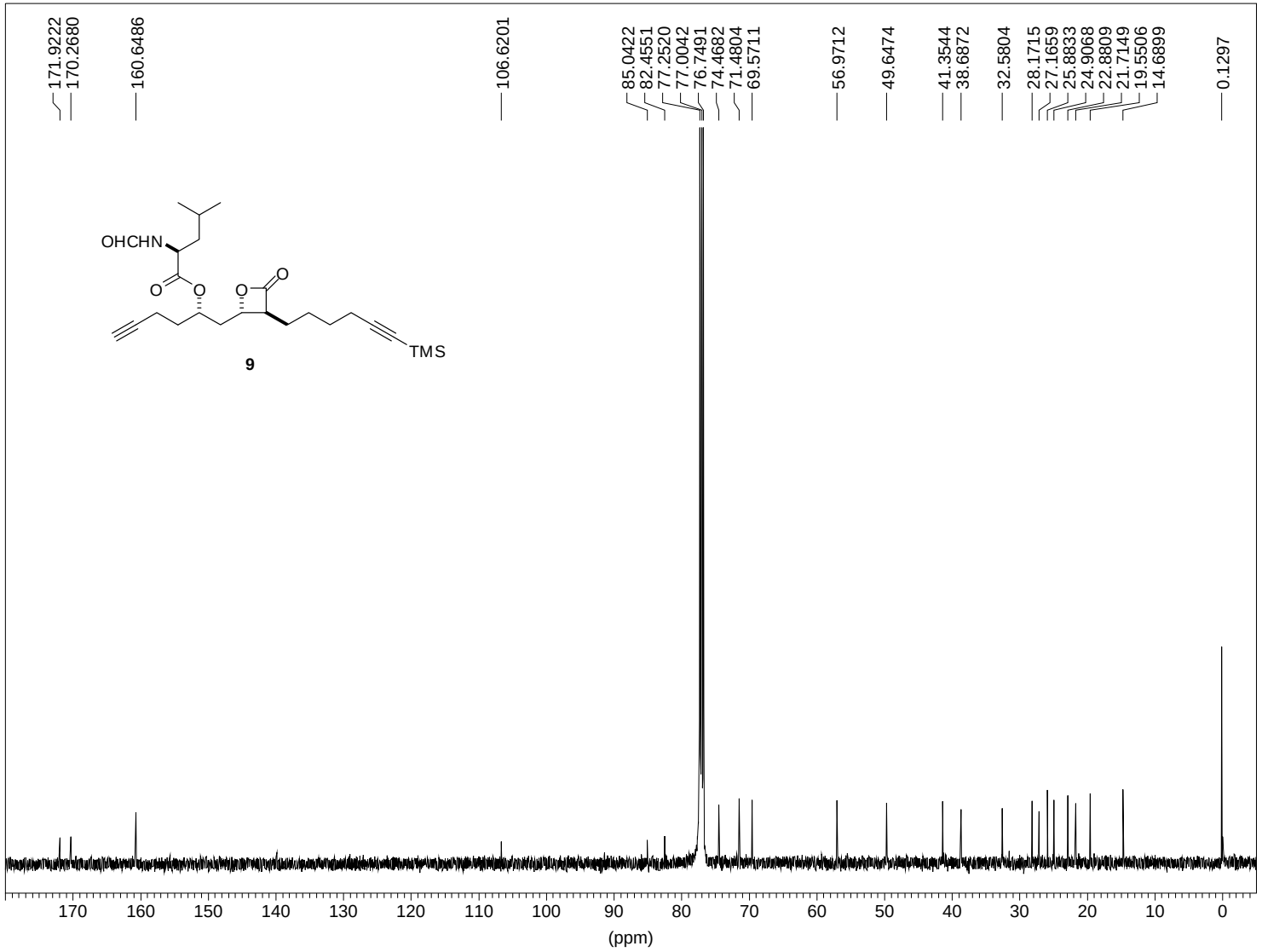
4.0265
1.1665
1.0821
0.9753
7.3840
6.8998
5.9852
8.8405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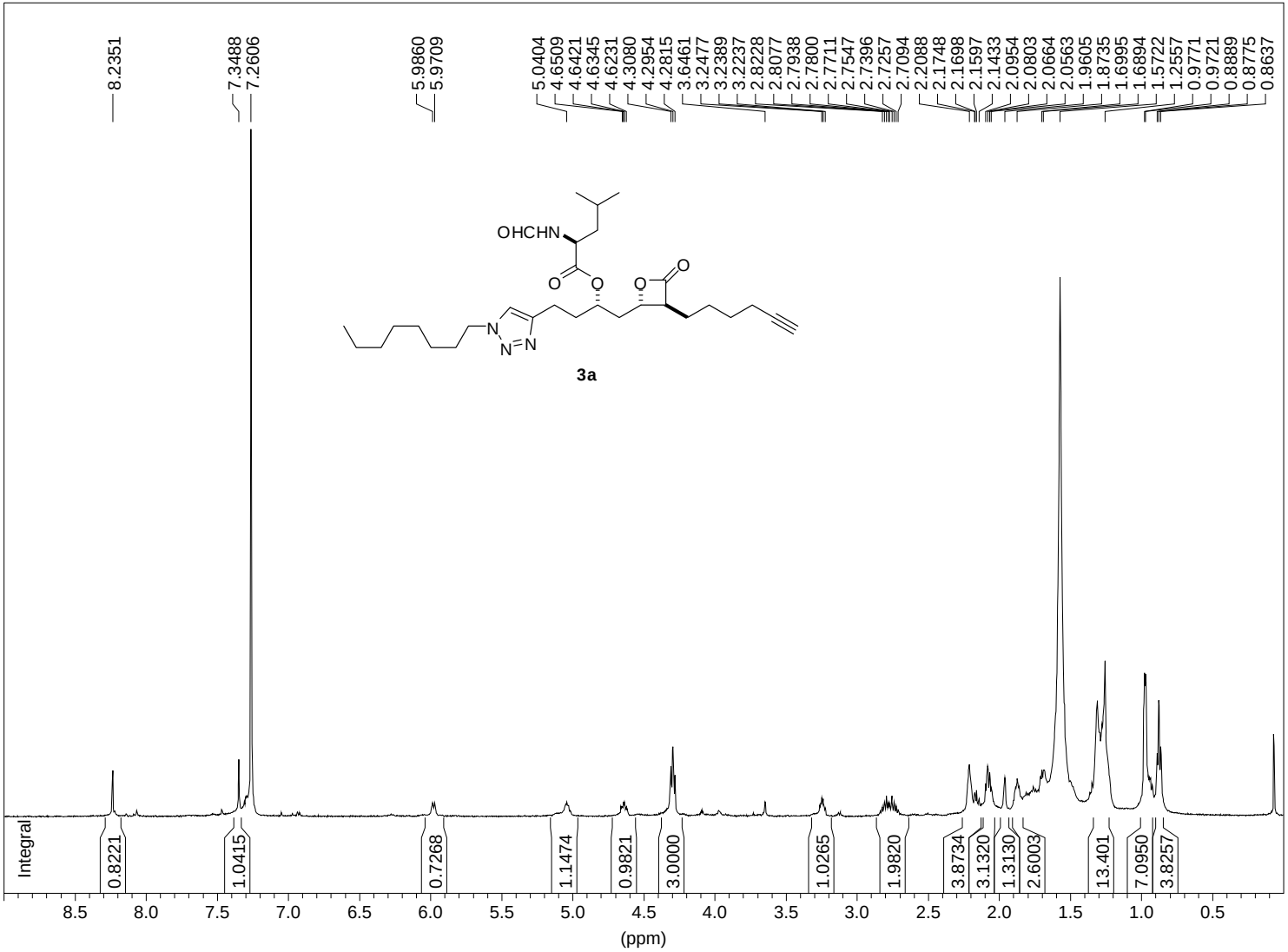
170.2680
160.6486
106.6201
85.0422
82.4551
77.2520
77.0042
76.7491
74.4682
71.4804
69.5711
56.9712
49.6474
41.3544
38.6872
32.5804
28.1715
27.1659
25.8833
24.9068
22.8809
21.7149
19.5506
14.6899
0.1297
OHCHN
O
O
O
O
TMS
9
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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5.9709
5.0404
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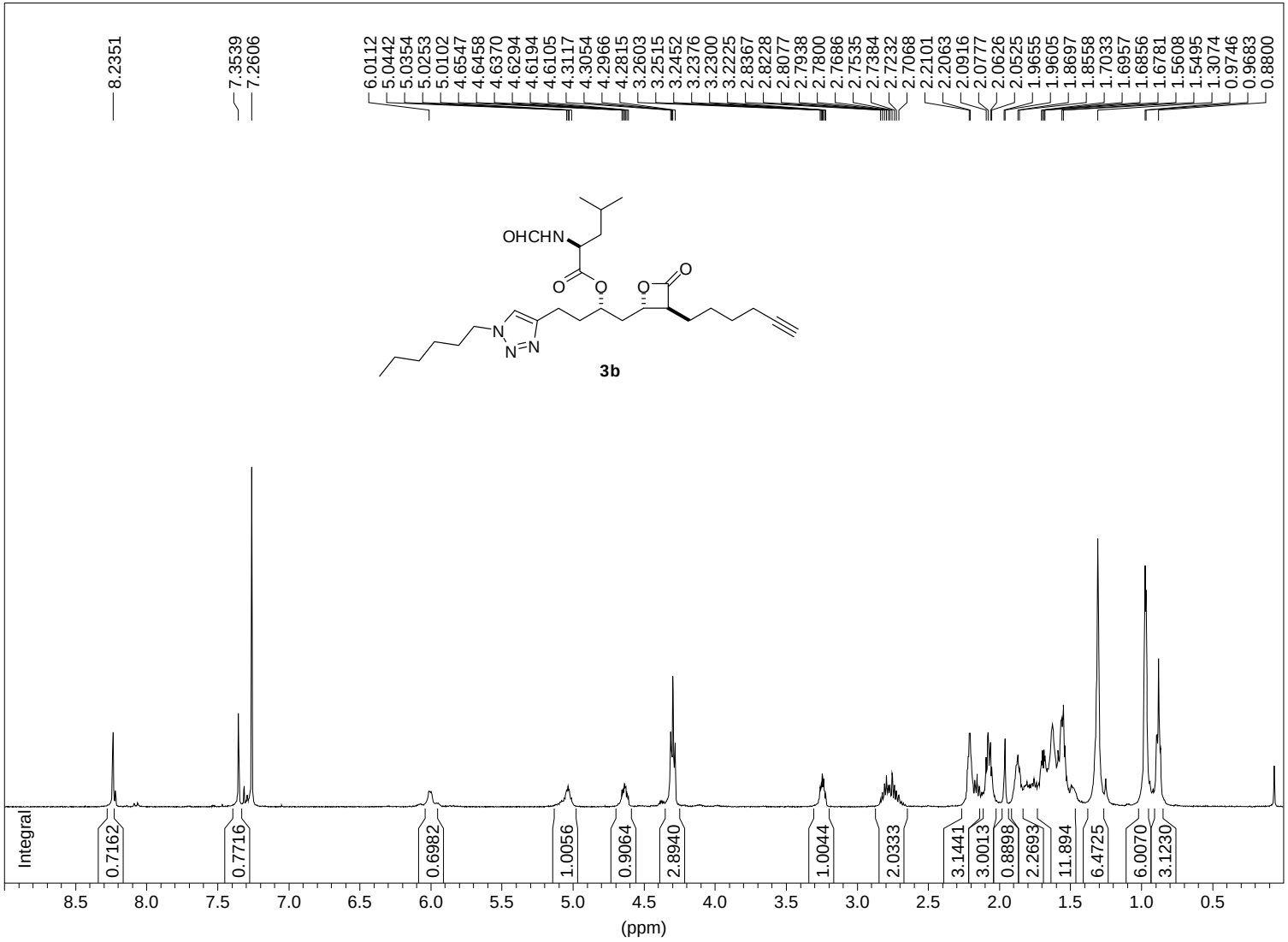
4.6421
4.6345
4.6231
4.3080
4.2954
4.2815
3.6461
3.2477
3.2389
3.2237
2.8228
2.8077
2.7938
2.7800
2.7711
2.7547
2.7396
2.7257
2.7094
2.2088
2.1748
2.1698
2.1597
2.1433
2.0954
2.0803
2.0664
2.0563
1.9605
1.8735
1.6995
1.6894
1.5722
1.2557
0.9771
0.9721
0.8889
0.8775
0.8637
OHCHN
O
O
O
O
N
N
N
3a
Integral
0.8221
1.0415
0.7268
1.1474
0.9821
3.0000
1.0265
1.9820
3.8734
3.1320
1.3130
2.6003
13.401
7.0950
3.8257
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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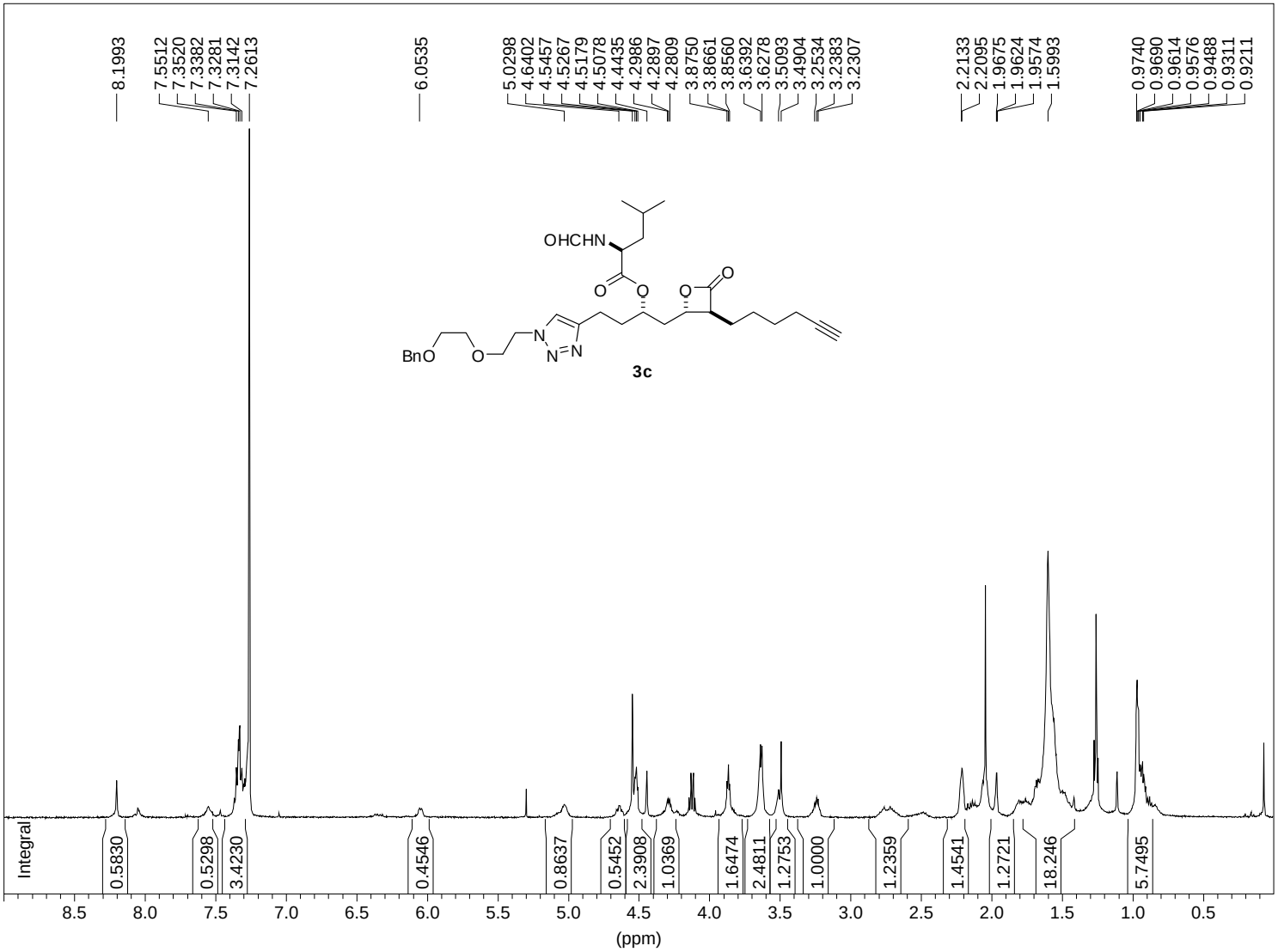
7.2606
6.0112
5.0442
5.0354
5.0253
5.0102
4.6547
4.6458
4.6370
4.6294
4.6194
4.6105
4.3117
4.3054
4.2966
4.2815
3.2603
3.2515
3.2452
3.2376
3.2300
3.2225
2.8367
2.8228
2.8077
2.7938
2.7800
2.7686
2.7535
2.7384
2.7232
2.7068
2.2101
2.2063
2.0916
2.0777
2.0626
2.0525
1.9655
1.9605
1.8697
1.8558
1.7033
1.6957
1.6856
1.6781
1.5608
1.5495
1.3074
0.9746
0.9683
0.8800
OHCHN
O
O
O
O
N
N
N
3b
Integral
0.7162
0.7716
0.6982
1.0056
0.9064
2.8940
1.0044
2.0333
3.1441
3.0013
0.8898
2.2693
11.894
6.4725
6.0070
3.1230
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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7.3281
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7.2613
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5.0298
4.6402
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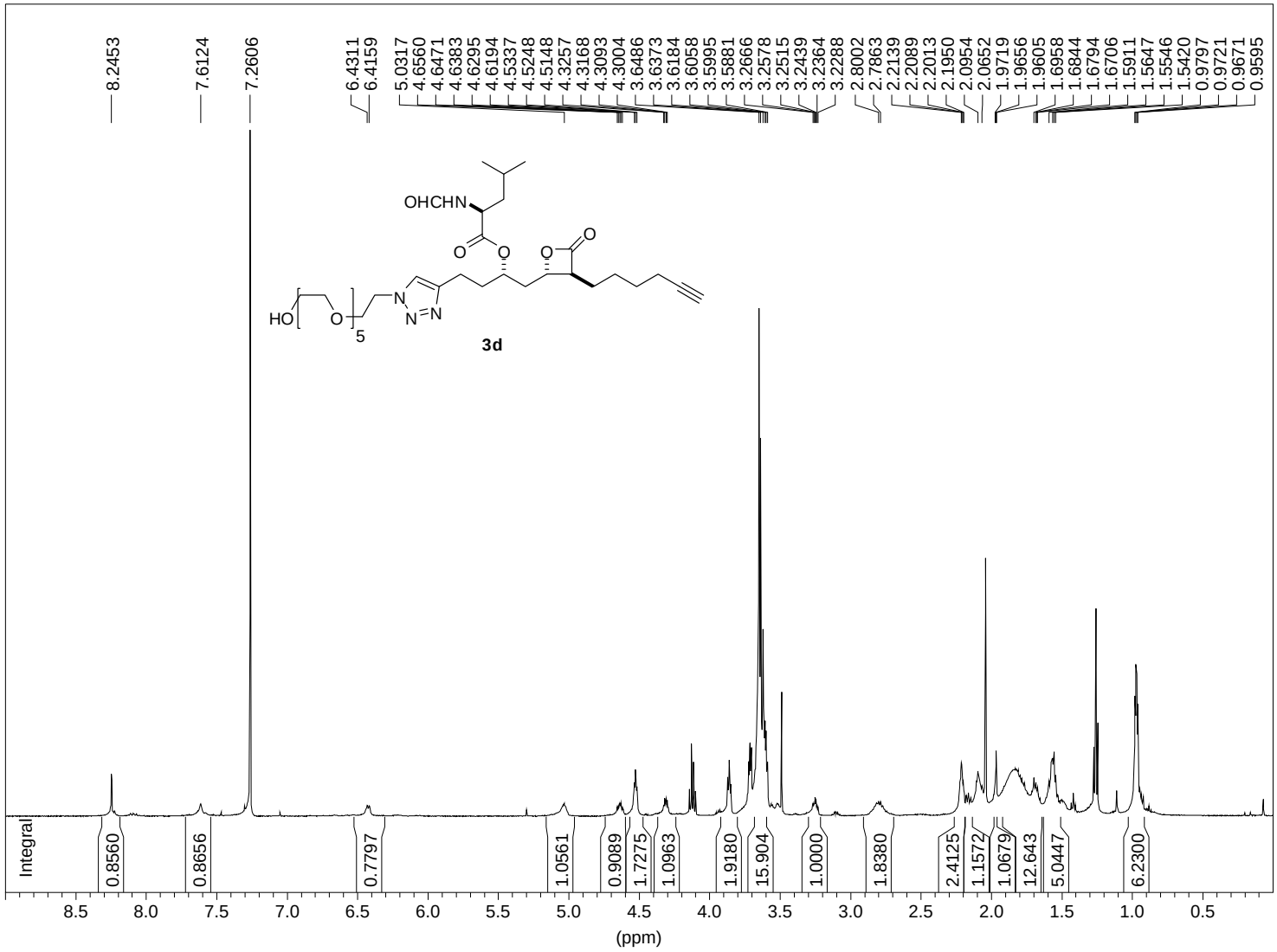
4.5267
4.5179
4.5078
4.4435
4.2986
4.2897
4.2809
3.8750
3.8661
3.8560
3.6392
3.6278
3.5093
3.4904
3.2534
3.2383
3.2307
2.2133
2.2095
1.9675
1.9624
1.9574
1.5993
0.9740
0.9690
0.9614
0.9576
0.9488
0.9311
0.9211
OHCHN
O
O
O
O
N
N
N
BnO
O
3c
Integral
0.5830
0.5298
3.4230
0.4546
0.8637
0.5452
2.3908
1.0369
1.6474
2.4811
1.2753
1.0000
1.2359
1.4541
1.2721
18.246
5.7495
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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6.4159
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4.6560
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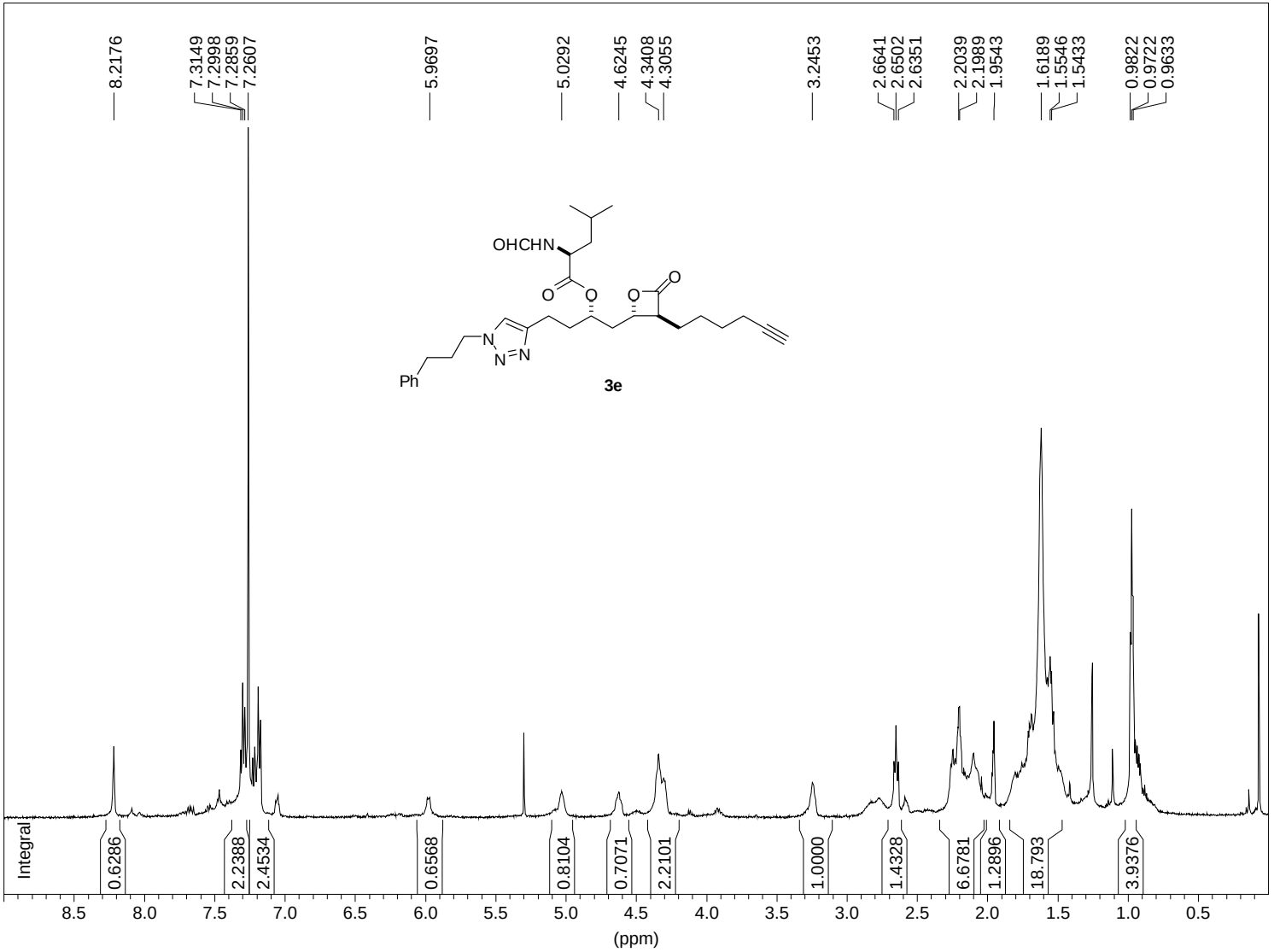
4.6383
4.6295
4.6194
4.5337
4.5248
4.5148
4.3257
4.3168
4.3093
4.3004
3.6486
3.6373
3.6184
3.6058
3.5995
3.5881
3.2666
3.2578
3.2515
3.2439
3.2364
3.2288
2.8002
2.7863
2.2139
2.2089
2.2013
2.1950
2.0954
2.0652
1.9719
1.9656
1.9605
1.6958
1.6844
1.6794
1.6706
1.5911
1.5647
1.5546
1.5420
0.9797
0.9721
0.9671
0.9595
OHCHN
HO
O
5
N
N=N
3d
Integral
0.8560
0.8656
0.7797
1.0561
0.9089
1.7275
1.0963
1.9180
15.904
1.0000
1.8380
2.4125
1.1572
1.0679
12.643
5.0447
6.2300
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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4.3408
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3.2453
2.6641
2.6502
2.6351
2.2039
2.1989
1.9543
1.6189
1.5546
1.5433
0.9822
0.9722
0.9633
OHCHN
O
O
O
O
N
N
N
Ph
3e
Integral
0.6286
2.2388
2.4534
0.6568
0.8104
0.7071
2.2101
1.0000
1.4328
6.6781
1.2896
18.793
3.9376
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
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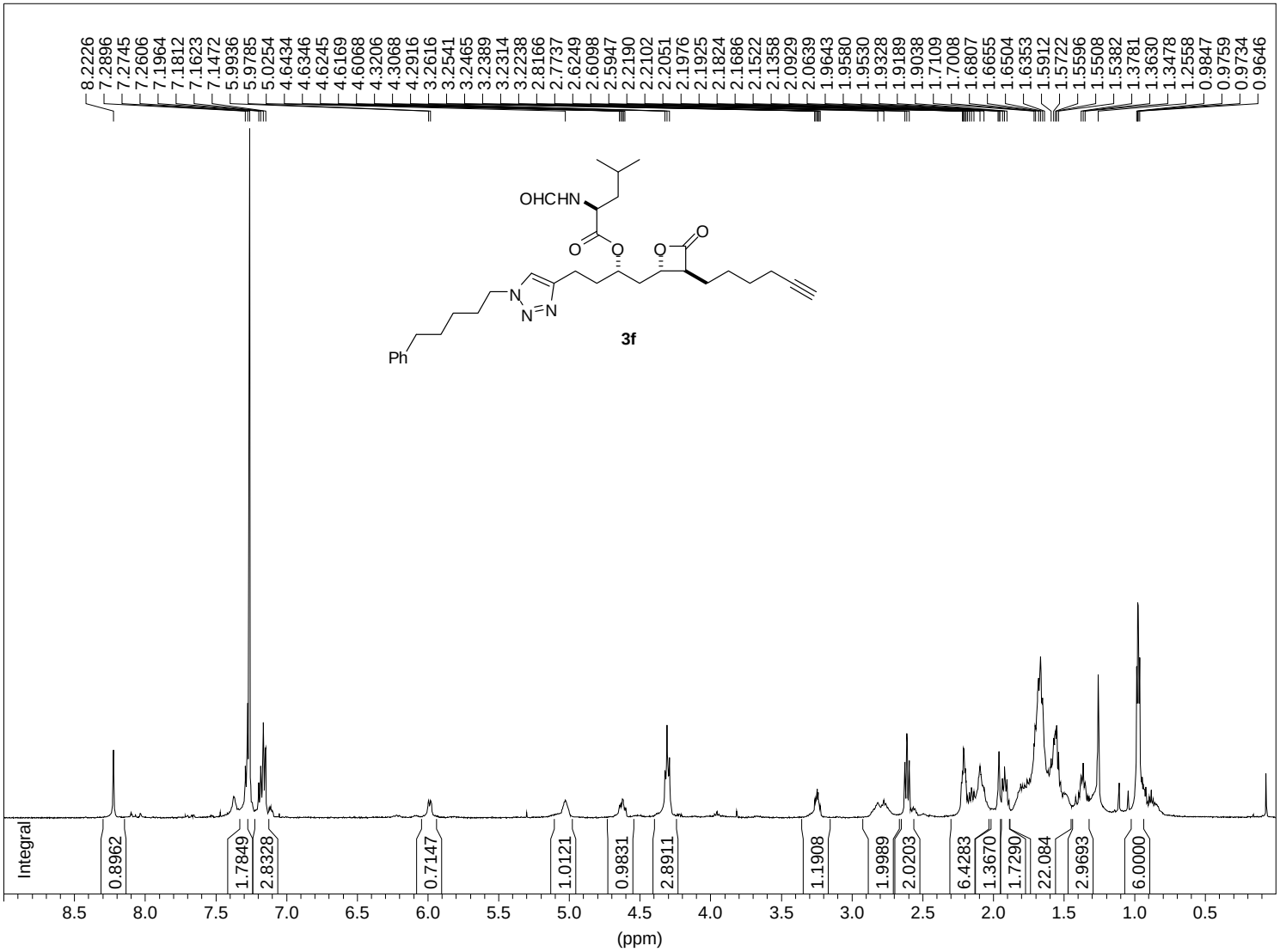
(ppm)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5.9785
5.0254
4.6434
4.6346
4.6245
4.6169
4.6068
4.3206
4.3068
4.2916
3.2616
3.2541
3.2465
3.2389
3.2314
3.2238
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2.7737
2.6249
2.6098
2.5947
2.2190
2.2102
2.2051
2.1976
2.1925
2.1824
2.1686
2.1522
2.1358
2.0929
2.0639
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1.9580
1.9530
1.9328
1.9189
1.9038
1.7109
1.7008
1.6807
1.6655
1.6504
1.6353
1.5912
1.5722
1.5596
1.5508
1.5382
1.3781
1.3630
1.3478
1.2558
0.9847
0.9759
0.9734
0.9646
OHCHN
O
O
O
O
N
N=N
Ph
3f
Integral
0.8962
1.7849
2.8328
0.7147
1.0121
0.9831
2.8911
1.1908
1.9989
2.0203
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1.3670
1.7290
22.084
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6.0000
8.5
8.0
7.5
7.0
6.5
6.0
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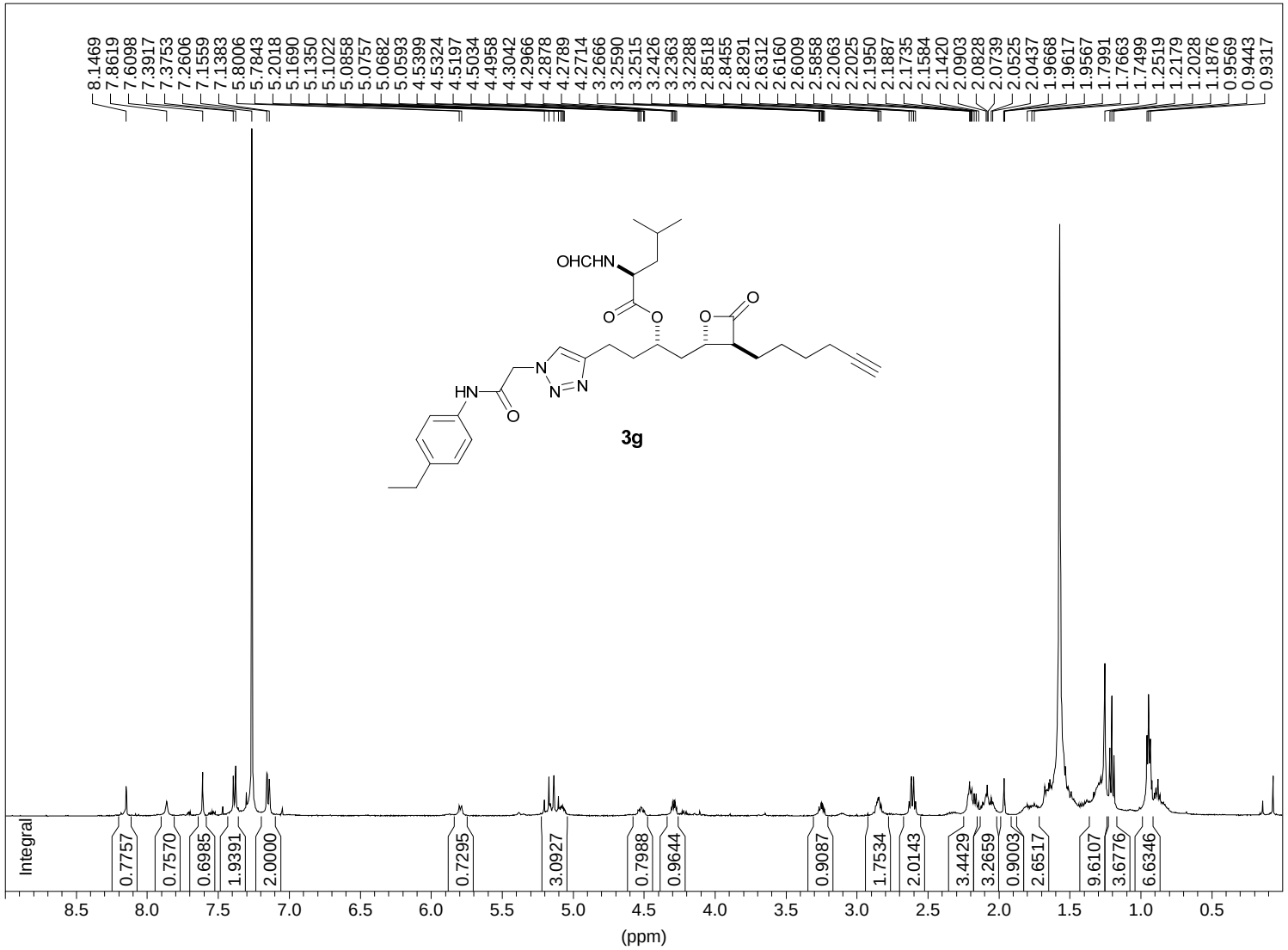
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)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5.2018
5.1690
5.1350
5.1022
5.0858
5.0757
5.0682
5.0593
4.5399
4.5324
4.5197
4.5034
4.4958
4.3042
4.2966
4.2878
4.2789
4.2714
3.2666
3.2590
3.2515
3.2426
3.2363
3.2288
2.8518
2.8455
2.8291
2.6312
2.6160
2.6009
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2.2025
2.1950
2.1887
2.1735
2.1584
2.1420
2.0903
2.0828
2.0739
2.0525
2.0437
1.9668
1.9617
1.9567
1.7991
1.7663
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1.2519
1.2179
1.2028
1.1876
0.9569
0.9443
0.9317
OHCHN
O
O
O
O
N
N
N
HN
O
3g
Integral
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1.9391
2.0000
0.7295
3.0927
0.7988
0.9644
0.9087
1.7534
2.0143
3.4429
3.2659
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9.6107
3.6776
6.6346
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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2.5
2.0
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1.0
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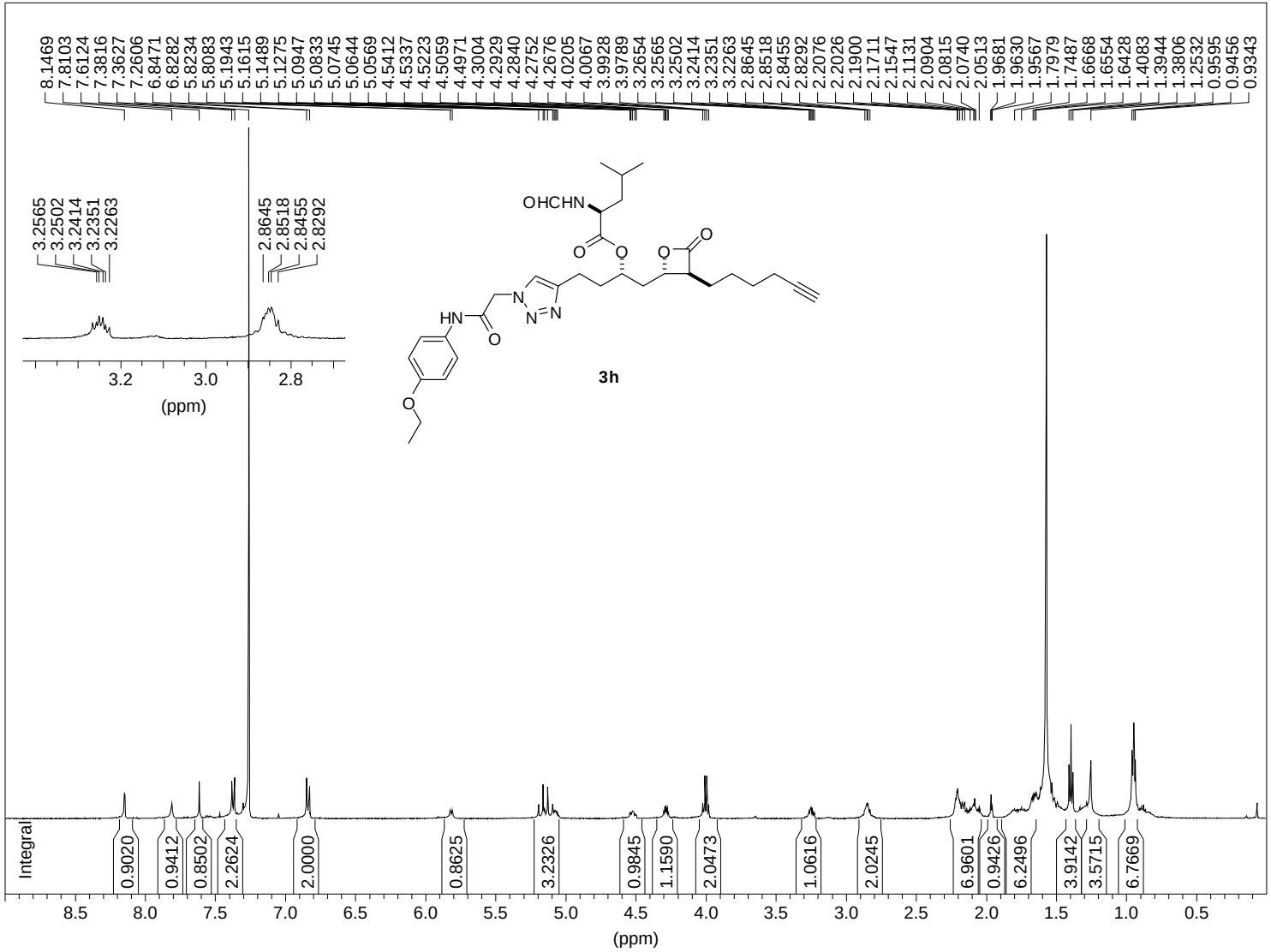
(ppm)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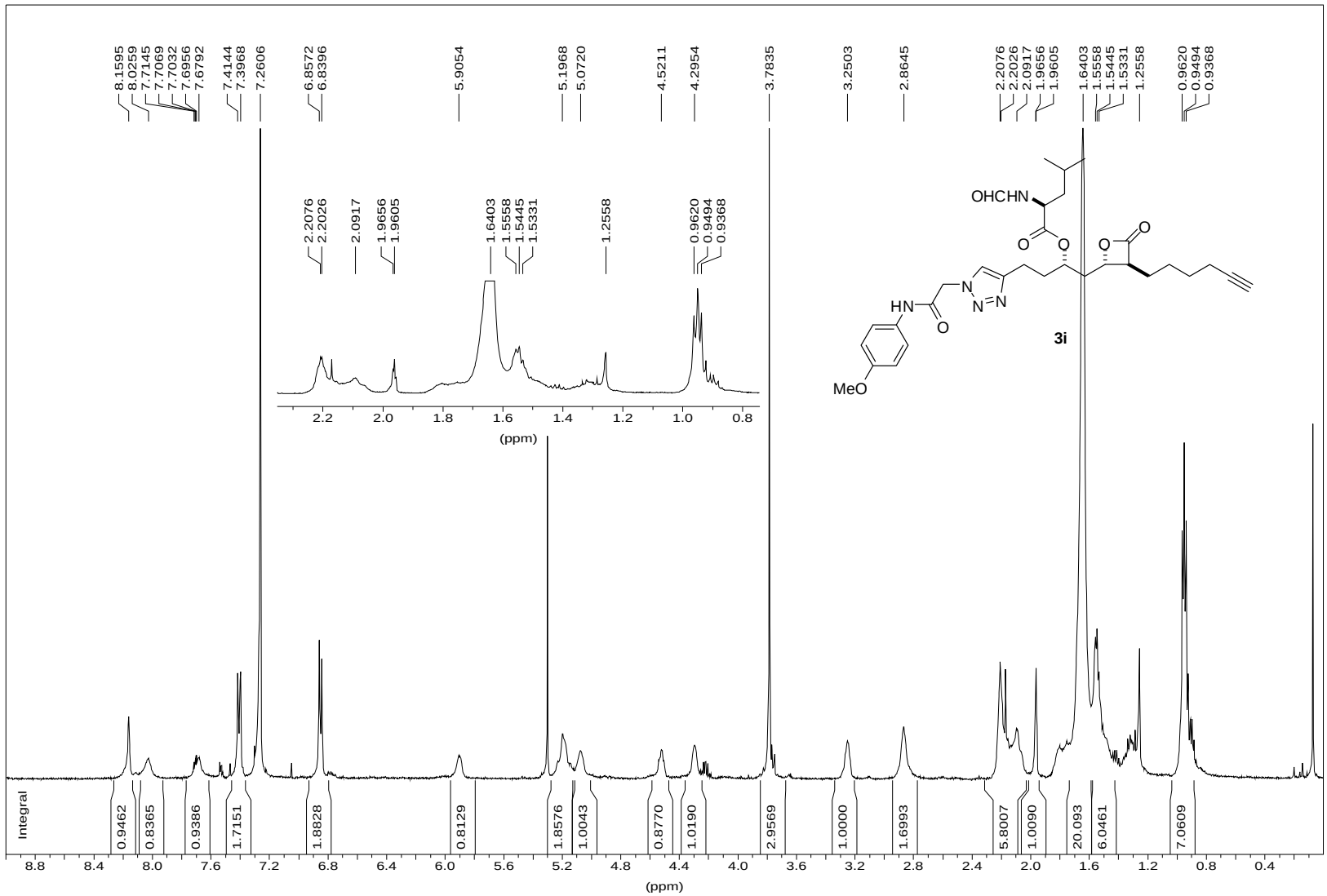
5.1943
5.1615
5.1489
5.1275
5.0947
5.0833
5.0745
5.0644
5.0569
4.5412
4.5337
4.5223
4.5059
4.4971
4.3004
4.2929
4.2840
4.2752
4.2676
4.0205
4.0067
3.9928
3.9789
3.2654
3.2565
3.2502
3.2414
3.2351
3.2263
2.8645
2.8518
2.8455
2.8292
2.2076
2.2026
2.1900
2.1711
2.1547
2.1131
2.0904
2.0815
2.0740
2.0513
1.9681
1.9630
1.9567
1.7979
1.7487
1.6668
1.6554
1.6428
1.4083
1.3944
1.3806
1.2532
0.9595
0.9456
0.9343
3.2
3.0
2.8
(ppm)
OHCHN
HN
N
N=N
O
3h
Integral
0.9020
0.9412
0.8502
2.2624
2.0000
0.8625
3.2326
0.9845
1.1590
2.0473
1.0616
2.0245
6.9601
0.9426
6.2496
3.9142
3.5715
6.7669
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)


1H AMX500 mh6009db
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7.3968
7.2606
6.8572
6.8396
5.9054
5.1968
5.0720
4.5211
4.2954
3.7835
3.2503
2.8645
2.2076
2.2026
2.0917
1.9656
1.9605
1.6403
1.5558
1.5445
1.5331
1.2558
0.9620
0.9494
0.9368
OHCHN
HN
MeO
3i
Integral
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0.8365
0.9386
1.7151
1.8828
0.8129
1.8576
1.0043
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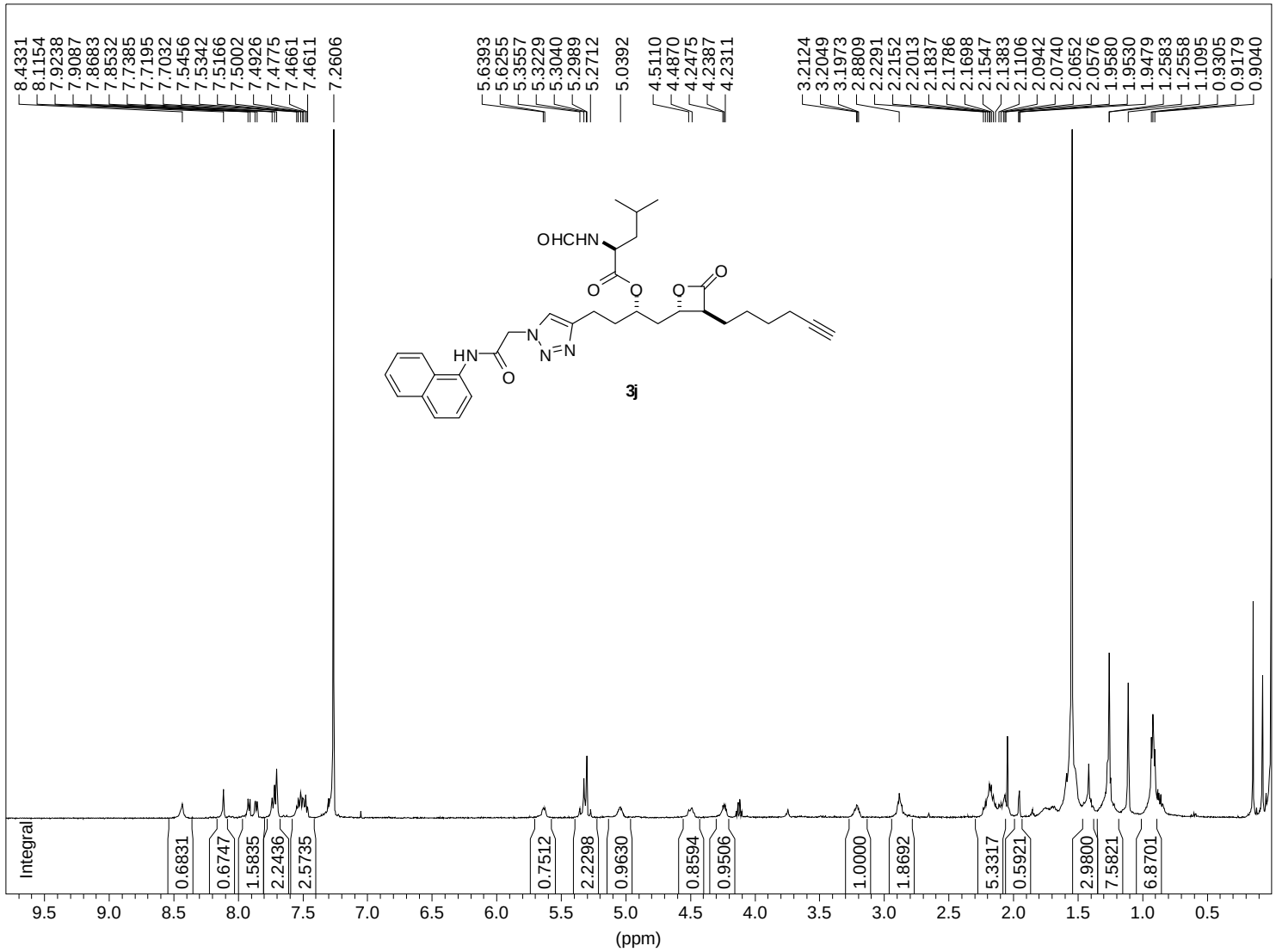
7.0609
(ppm)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7.7385
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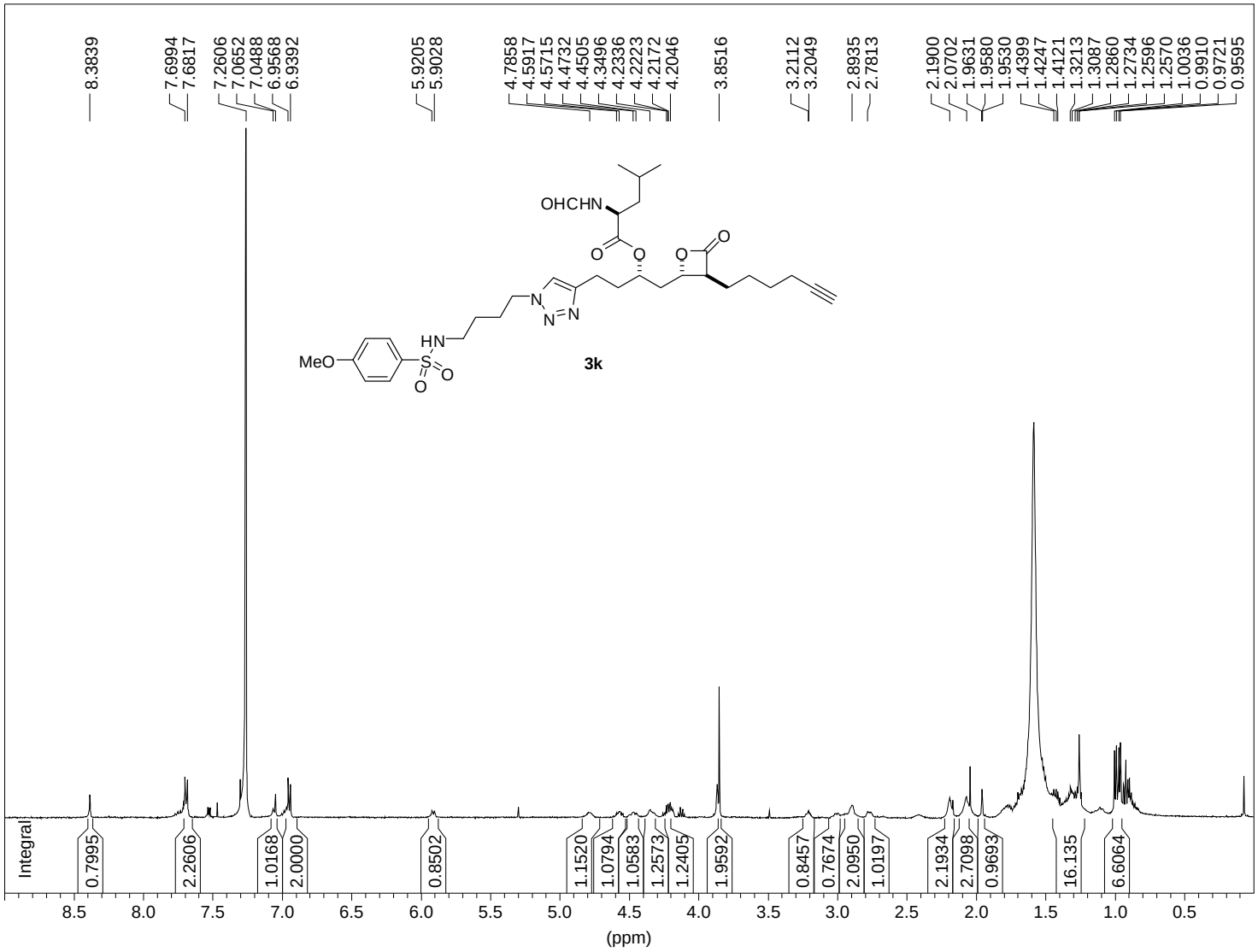
7.7032
7.5456
7.5342
7.5166
7.5002
7.4926
7.4775
7.4661
7.4611
7.2606
5.6393
5.6255
5.3557
5.3229
5.3040
5.2989
5.2712
5.0392
4.5110
4.4870
4.2475
4.2387
4.2311
3.2124
3.2049
3.1973
2.8809
2.2291
2.2152
2.2013
2.1837
2.1786
2.1698
2.1547
2.1383
2.1106
2.0942
2.0740
2.0652
2.0576
1.9580
1.9530
1.9479
1.2583
1.2558
1.1095
0.9305
0.9179
0.9040
OHCHN
O
O
O
O
N
N
N
HN
O
3j
Integral
0.6831
0.6747
1.5835
2.2436
2.5735
0.7512
2.2298
0.9630
0.8594
0.9506
1.0000
1.8692
5.3317
0.5921
2.9800
7.5821
6.8701
9.5
9.0
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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7.6994
7.6817
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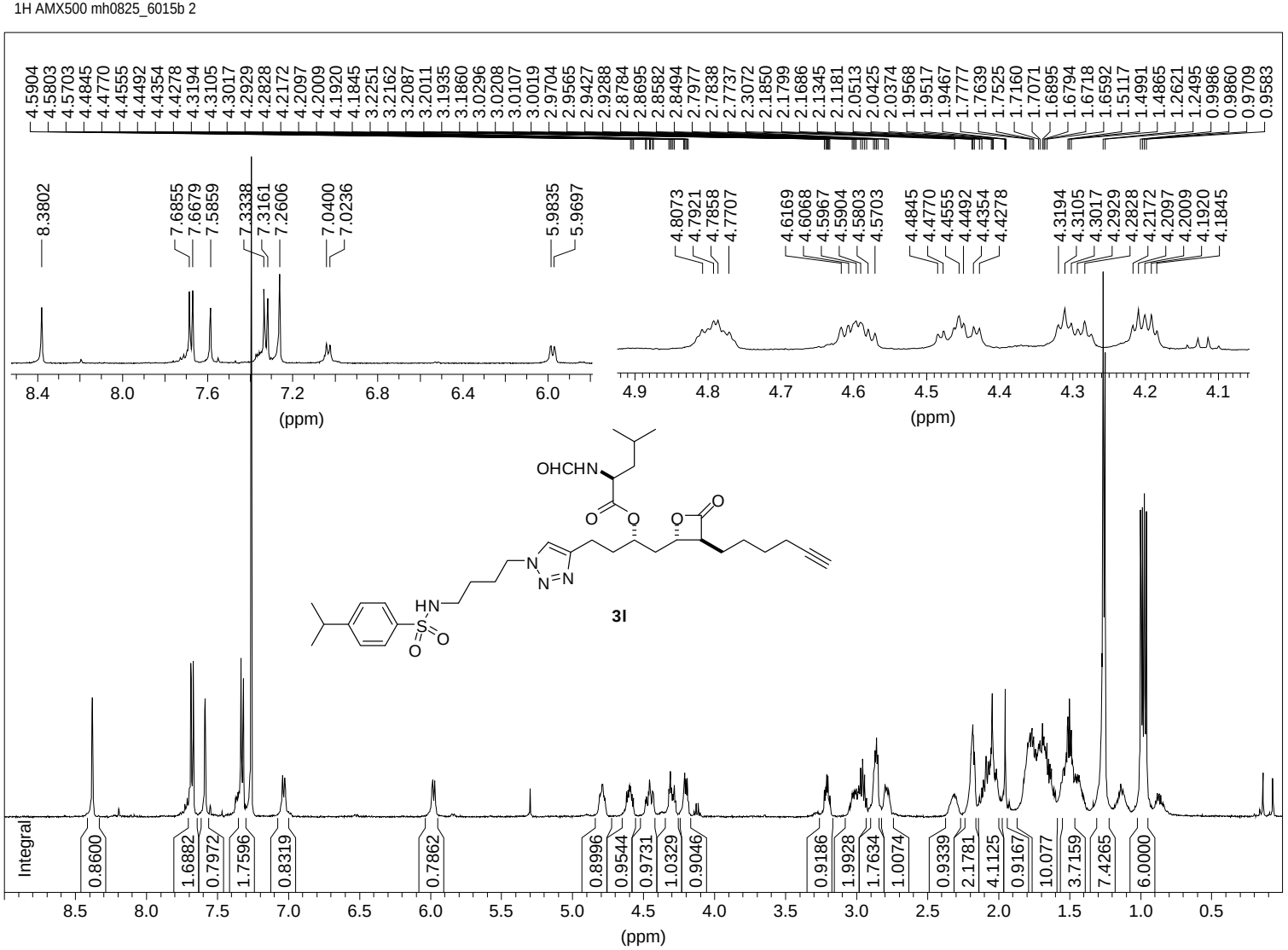
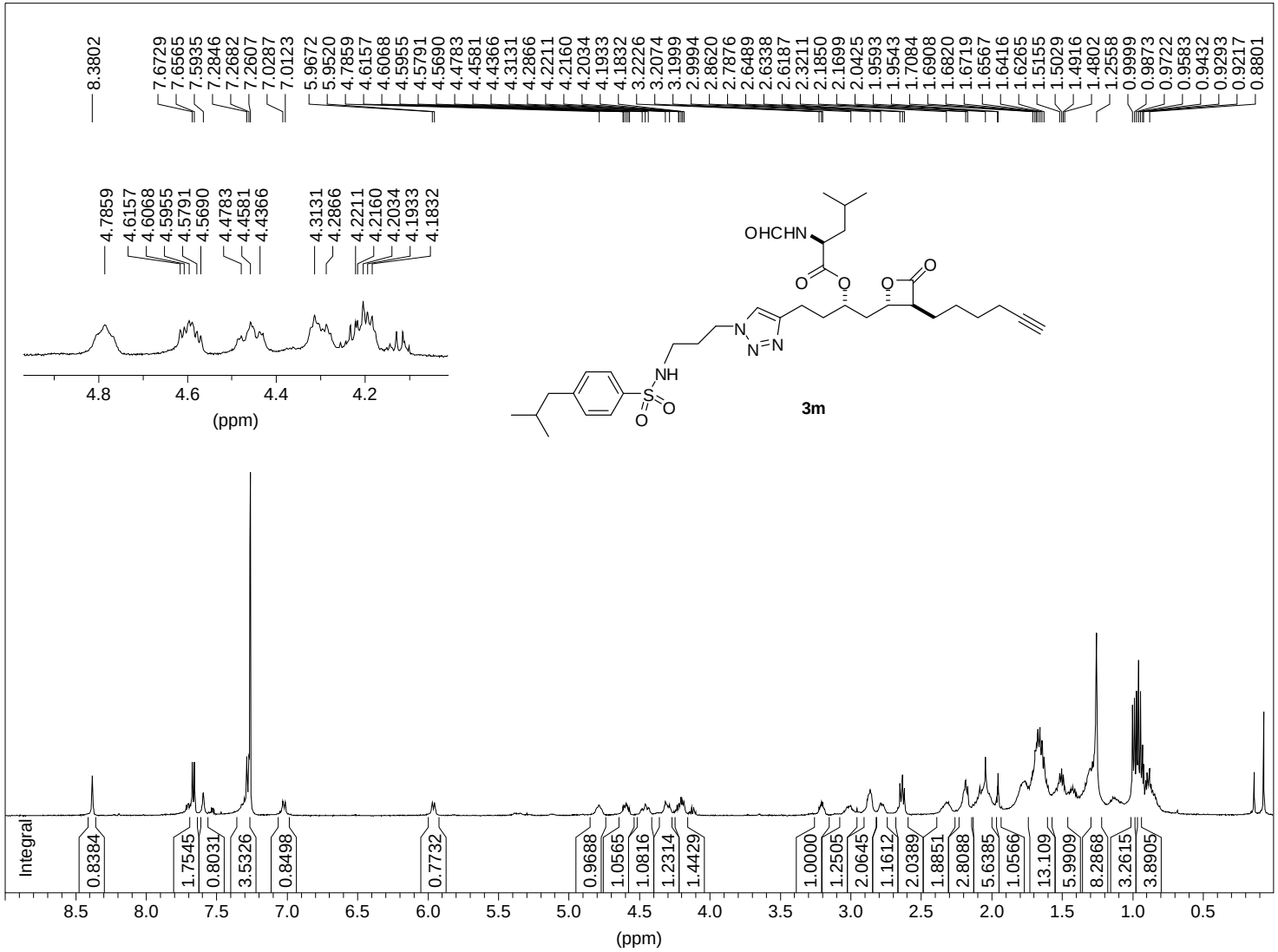
7.0652
7.0488
6.9568
6.9392
5.9205
5.9028
4.7858
4.5917
4.5715
4.4732
4.4505
4.3496
4.2336
4.2223
4.2172
4.2046
3.8516
3.2112
3.2049
2.8935
2.7813
2.1900
2.0702
1.9631
1.9580
1.9530
1.4399
1.4247
1.4121
1.3213
1.3087
1.2860
1.2734
1.2596
1.2570
1.0036
0.9910
0.9721
0.9595
OHCHN
O
O
O
O
N
N
N
HN
MeO
S
O
O
3k
Integral
0.7995
2.2606
1.0168
2.0000
0.8502
1.1520
1.0794
1.0583
1.2573
1.2405
1.9592
0.8457
0.7674
2.0950
1.0197
2.1934
2.7098
0.9693
16.135
6.6064
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)


1H AMX500 mh0825_6015b 2
OHCHN
O
O
O
O
N
N
N
HN
S
O
O
3l
Integral
0.8600
1.6882
0.7972
1.7596
0.8319
0.7862
0.8996
0.9544
0.9731
1.0329
0.9046
0.9186
1.9928
1.7634
1.0074
0.9339
2.1781
4.1125
0.9167
10.077
3.7159
7.4265
6.0000
(ppm)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7.6565
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7.2846
7.2682
7.2607
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7.0123
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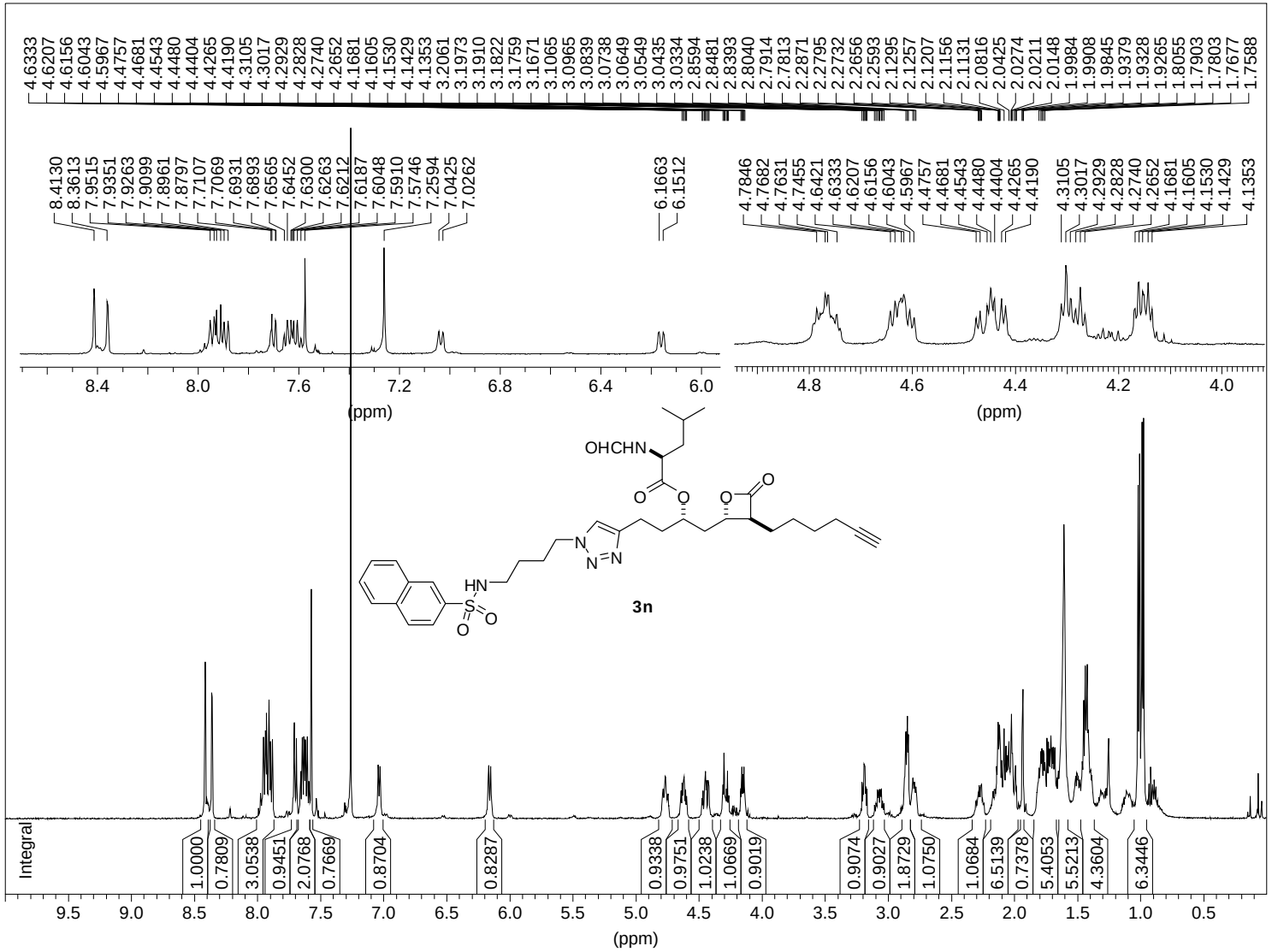
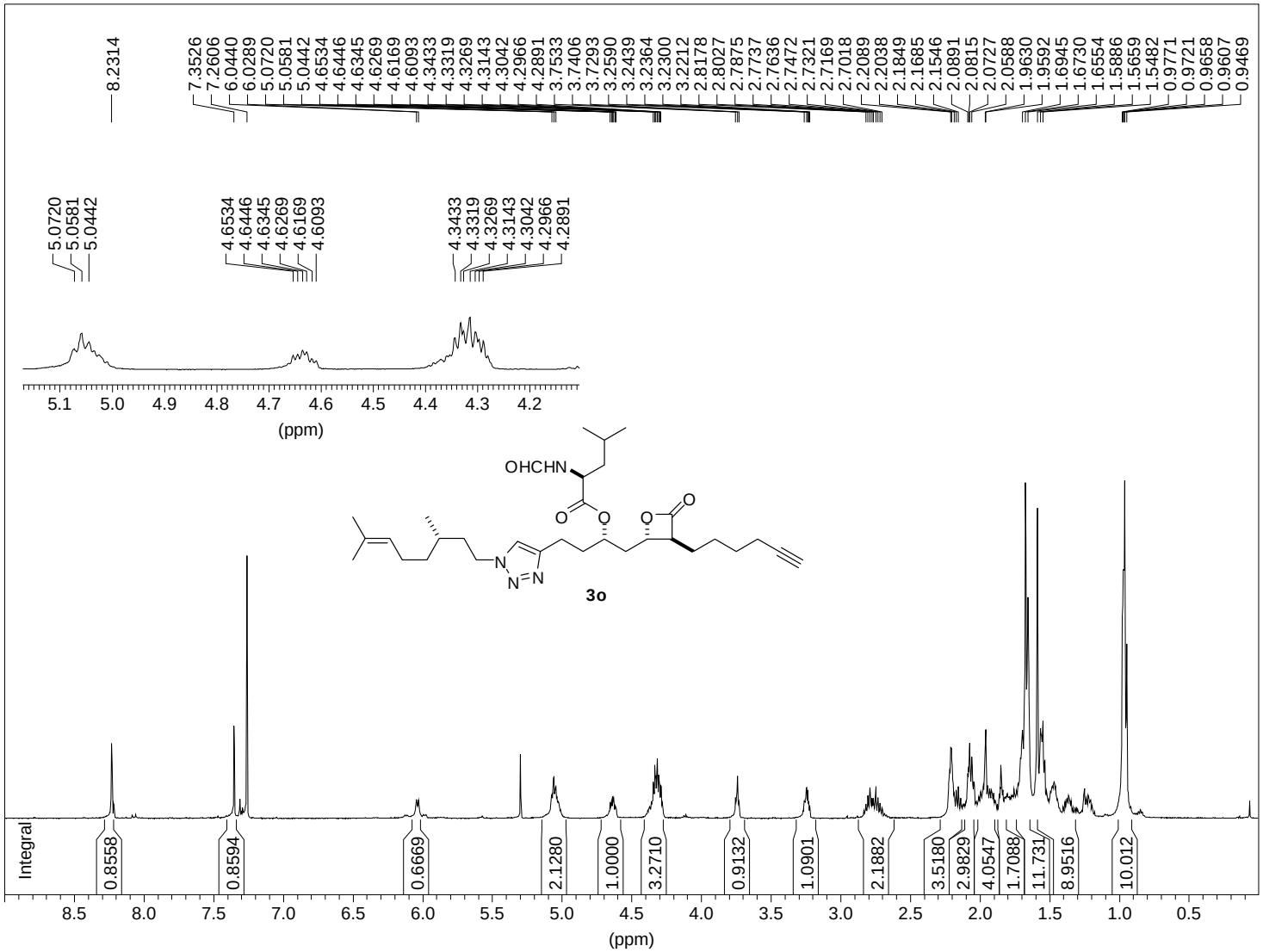
5.9520
4.7859
4.6157
4.6068
4.5955
4.5791
4.5690
4.4783
4.4581
4.4366
4.3131
4.2866
4.2211
4.2160
4.2034
4.1933
4.1832
3.2226
3.2074
3.1999
2.9994
2.8620
2.7876
2.6489
2.6338
2.6187
2.3211
2.1850
2.1699
2.0425
1.9593
1.9543
1.7084
1.6908
1.6820
1.6719
1.6567
1.6416
1.6265
1.5155
1.5029
1.4916
1.4802
1.2558
0.9999
0.9873
0.9722
0.9583
0.9432
0.9293
0.9217
0.8801
4.8
4.6
4.4
4.2
(ppm)
OHCHN
NH
3m
Integral
0.8384
1.7545
0.8031
3.5326
0.8498
0.7732
0.9688
1.0565
1.0816
1.2314
1.4429
1.0000
1.2505
2.0645
1.1612
2.0389
1.8851
2.8088
5.6385
1.0566
13.109
5.9909
8.2868
3.2615
3.8905
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)


OHCHN
HN
N
N=N
3n
(ppm)
Integral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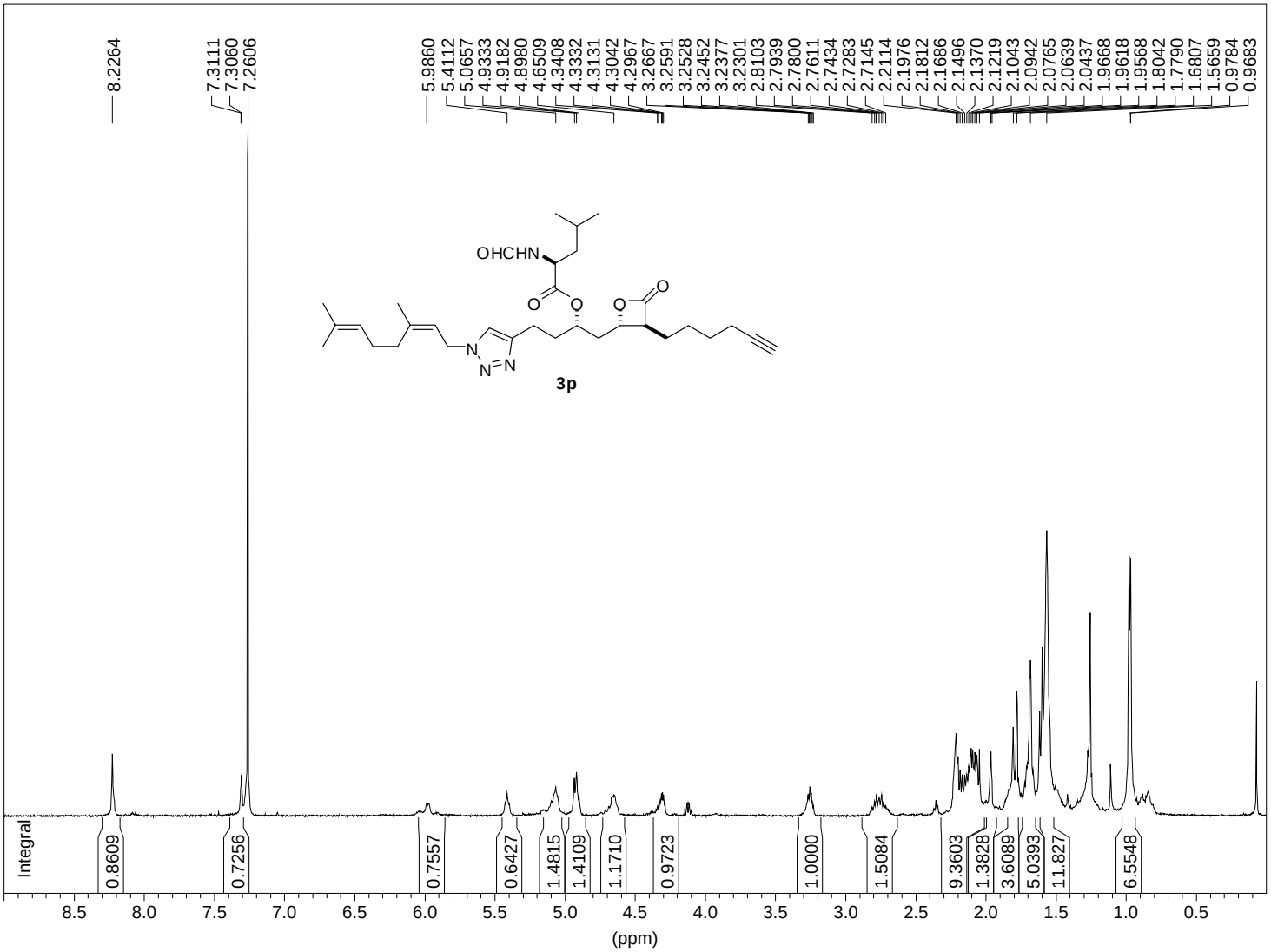
7.2606
6.0440
6.0289
5.0720
5.0581
5.0442
4.6534
4.6446
4.6345
4.6269
4.6169
4.6093
4.3433
4.3319
4.3269
4.3143
4.3042
4.2966
4.2891
3.7533
3.7406
3.7293
3.2590
3.2439
3.2364
3.2300
3.2212
2.8178
2.8027
2.7875
2.7737
2.7636
2.7472
2.7321
2.7169
2.7018
2.2089
2.2038
2.1849
2.1685
2.1546
2.0891
2.0815
2.0727
2.0588
1.9630
1.9592
1.6945
1.6730
1.6554
1.5886
1.5659
1.5482
0.9771
0.9721
0.9658
0.9607
0.9469
5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2
(ppm)
OHCHN
O
O
O
O
N
N=N
3o
Integral
0.8558
0.8594
0.6669
2.1280
1.0000
3.2710
0.9132
1.0901
2.1882
3.5180
2.9829
4.0547
1.7088
11.731
8.9516
10.012
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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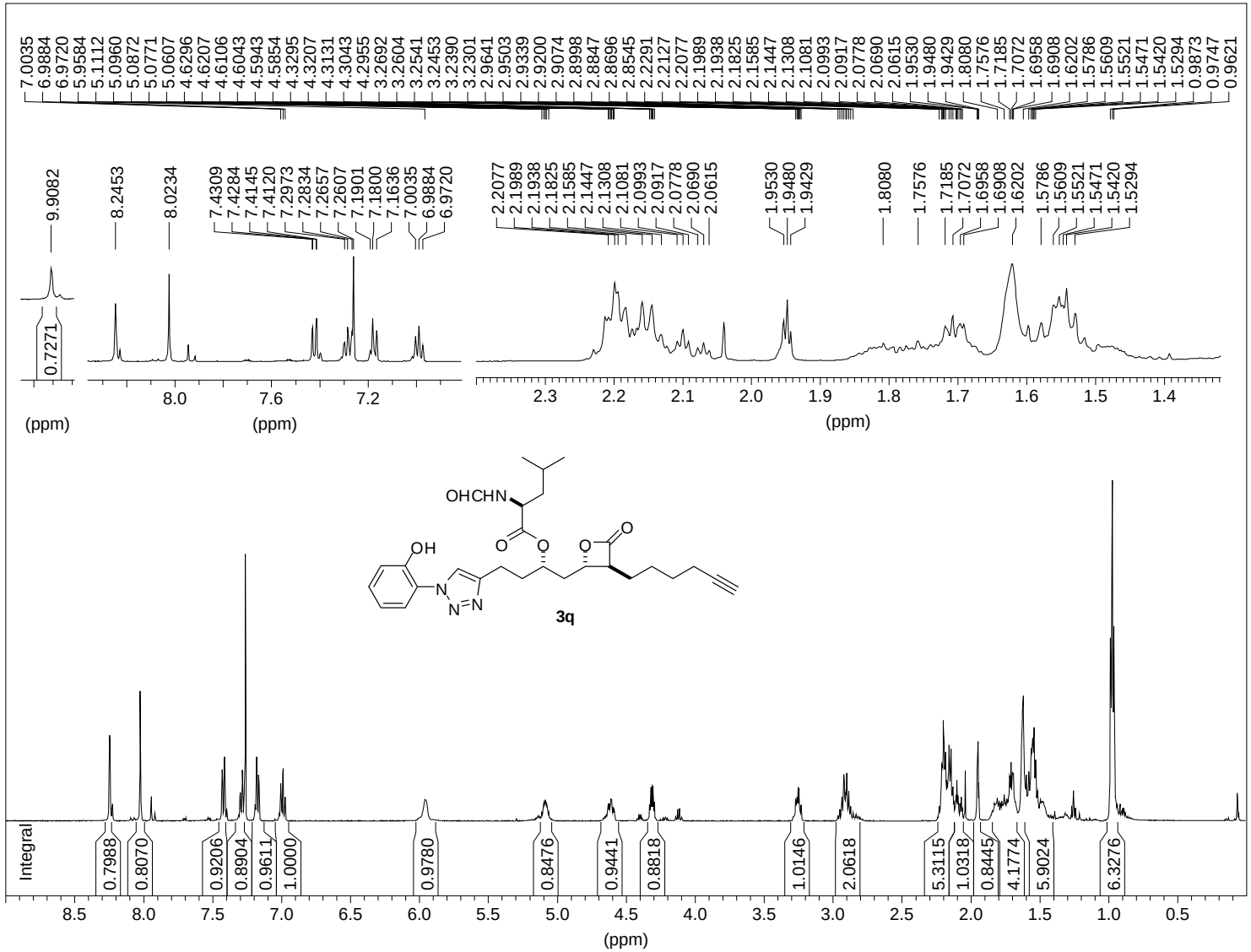
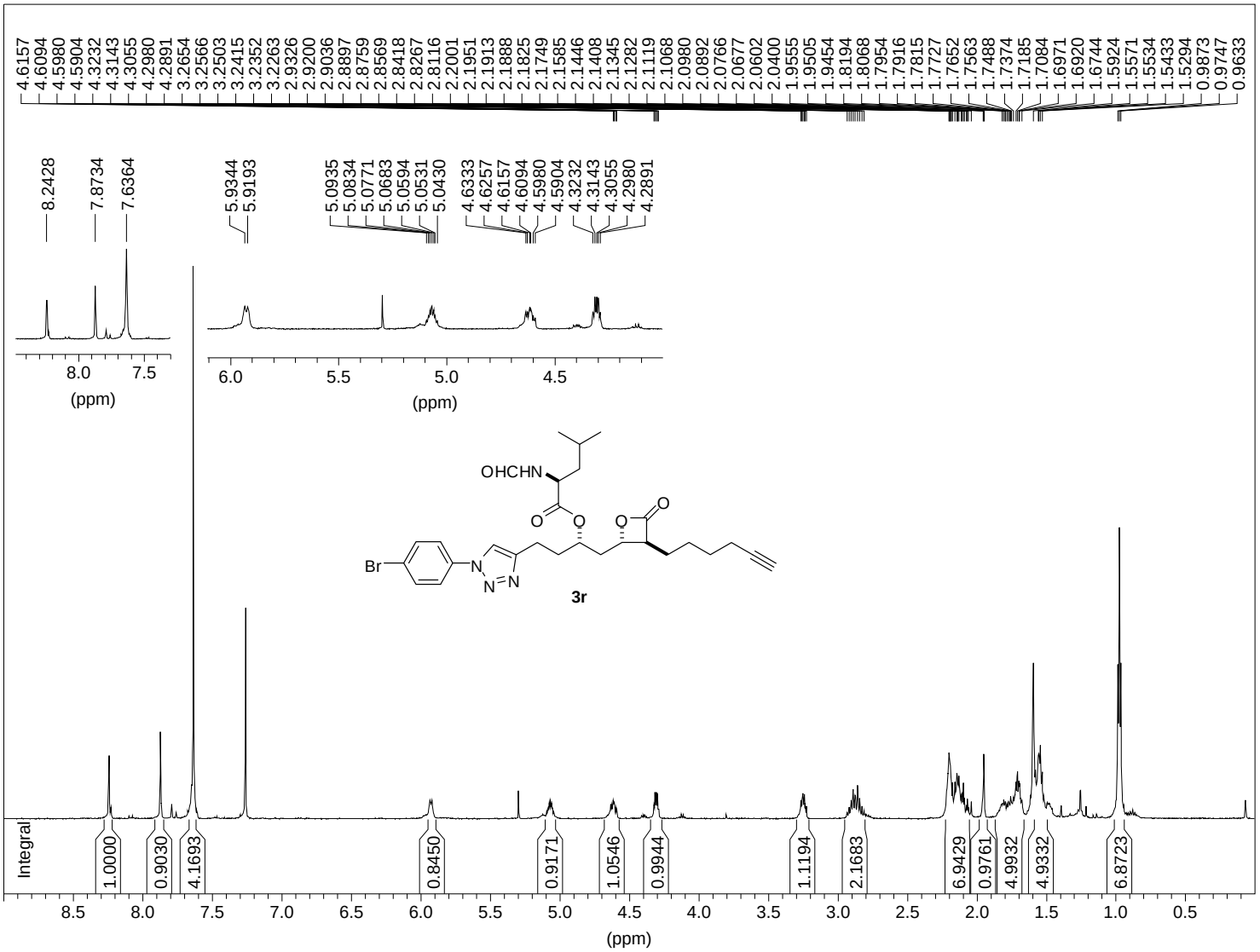
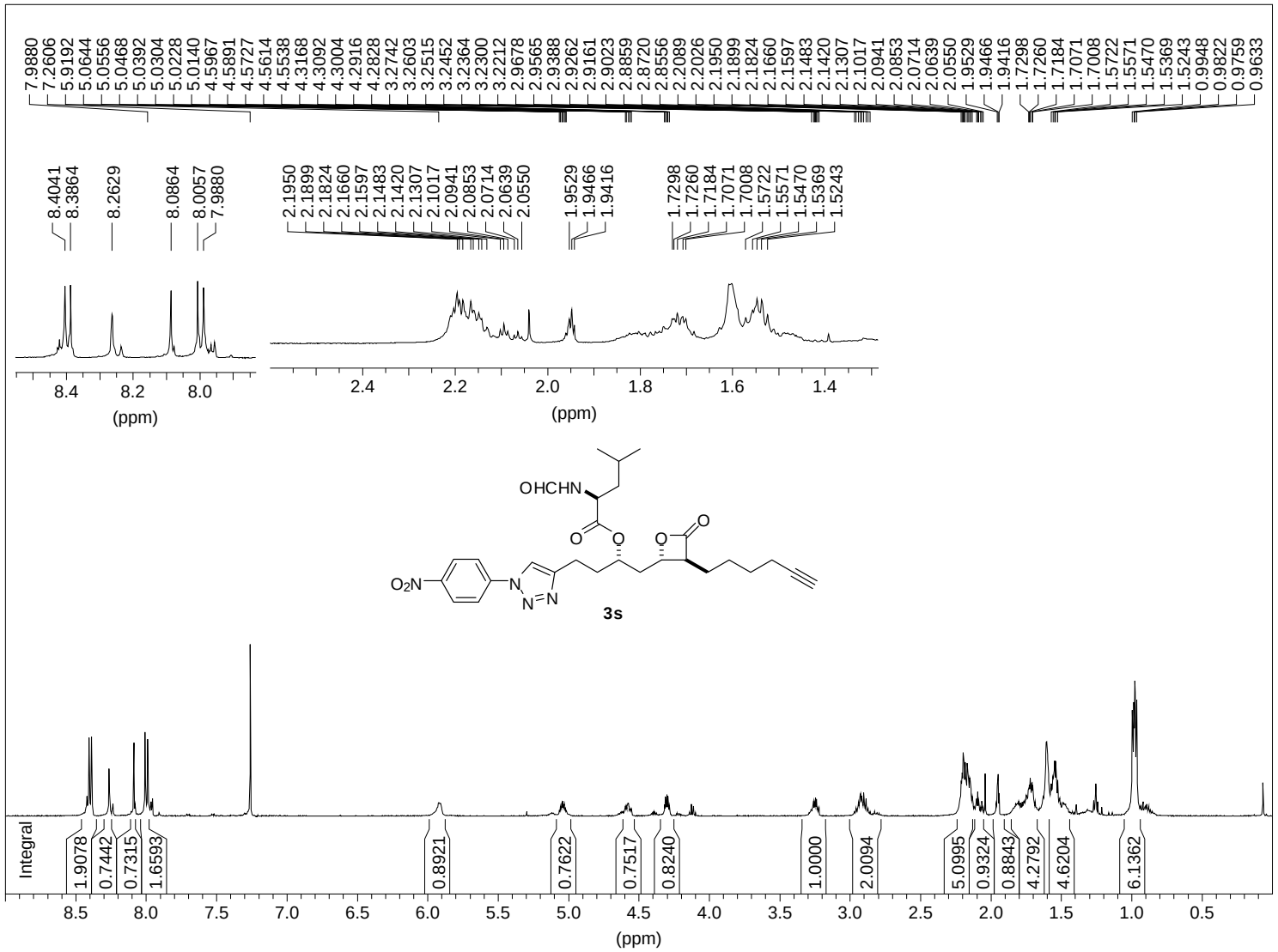
7.3060
7.2606
5.9860
5.4112
5.0657
4.9333
4.9182
4.8980
4.6509
4.3408
4.3332
4.3131
4.3042
4.2967
3.2667
3.2591
3.2528
3.2452
3.2377
3.2301
2.8103
2.7939
2.7800
2.7611
2.7434
2.7283
2.7145
2.2114
2.1976
2.1812
2.1686
2.1496
2.1370
2.1219
2.1043
2.0942
2.0765
2.0639
2.0437
1.9668
1.9618
1.9568
1.8042
1.7790
1.6807
1.5659
0.9784
0.9683
OHCHN
O
O
O
O
N
N=N
3p
Integral
0.8609
0.7256
0.7557
0.6427
1.4815
1.4109
1.1710
0.9723
1.0000
1.5084
9.3603
1.3828
3.6089
5.0393
11.827
6.5548
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)


OHCHN
OH
O
O
O
O
N
N
N
3q
Integral
0.7988
0.8070
0.9206
0.8904
0.9611
1.0000
0.9780
0.8476
0.9441
0.8818
1.0146
2.0618
5.3115
1.0318
0.8445
4.1774
5.9024
6.3276
(ppm)


OHCHN
O
O
O
O
Br
N
N
N
3r
Integral
1.0000
0.9030
4.1693
0.8450
0.9171
1.0546
0.9944
1.1194
2.1683
6.9429
0.9761
4.9932
4.9332
6.8723
(ppm)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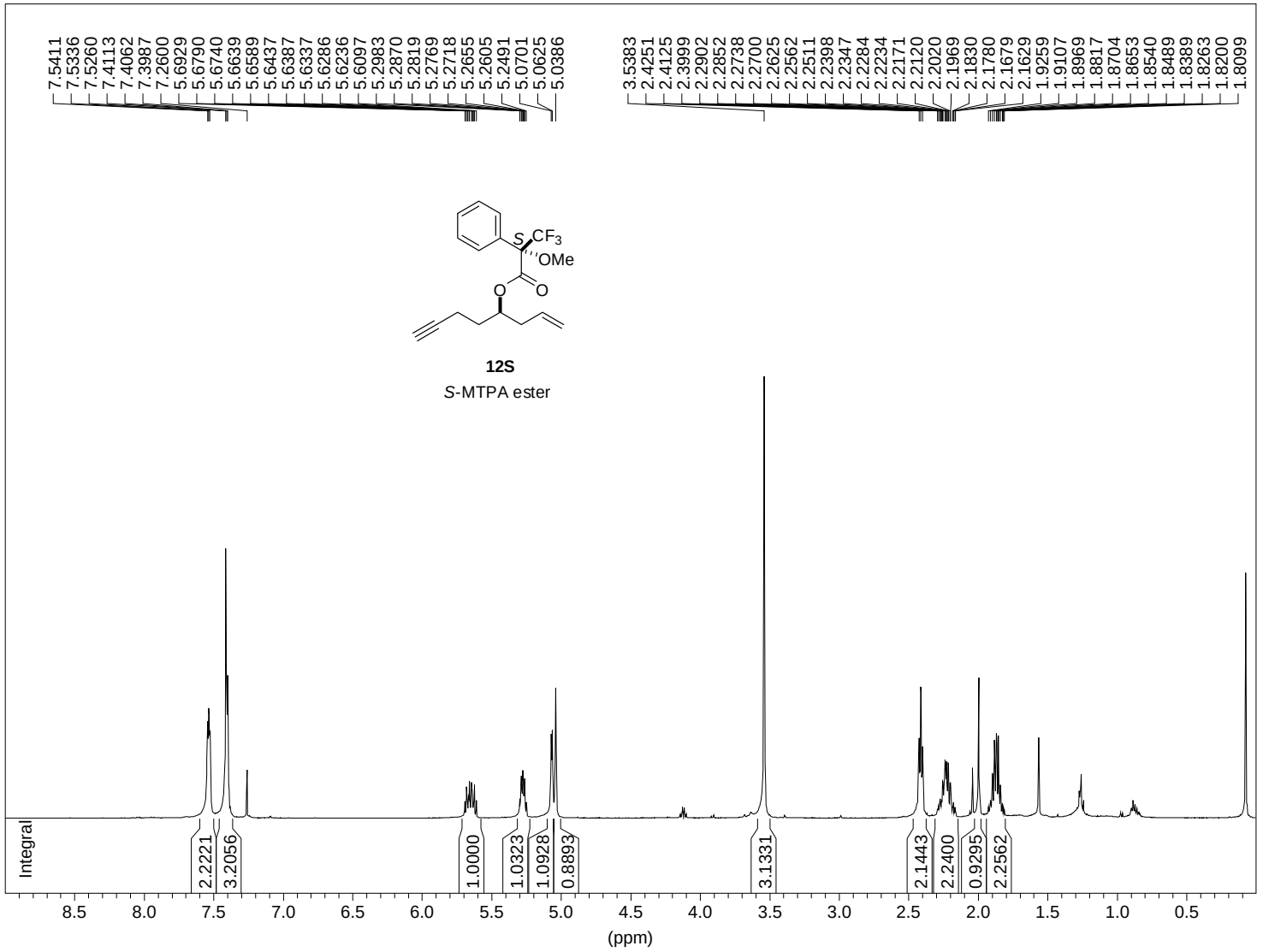
7.2606
5.9192
5.0644
5.0556
5.0468
5.0392
5.0304
5.0228
5.0140
4.5967
4.5891
4.5727
4.5614
4.5538
4.3168
4.3092
4.3004
4.2916
4.2828
3.2742
3.2603
3.2515
3.2452
3.2364
3.2300
3.2212
2.9678
2.9565
2.9388
2.9262
2.9161
2.9023
2.8859
2.8720
2.8556
2.2089
2.2026
2.1950
2.1899
2.1824
2.1660
2.1597
2.1483
2.1420
2.1307
2.1017
2.0941
2.0853
2.0714
2.0639
2.0550
1.9529
1.9466
1.9416
1.7298
1.7260
1.7184
1.7071
1.7008
1.5722
1.5571
1.5470
1.5369
1.5243
0.9948
0.9822
0.9759
0.9633
8.4041
8.3864
8.2629
8.0864
8.0057
7.9880
2.1950
2.1899
2.1824
2.1660
2.1597
2.1483
2.1420
2.1307
2.1017
2.0941
2.0853
2.0714
2.0639
2.0550
1.9529
1.9466
1.9416
1.7298
1.7260
1.7184
1.7071
1.7008
1.5722
1.5571
1.5470
1.5369
1.5243
8.4
8.2
8.0
(ppm)
2.4
2.2
2.0
1.8
1.6
1.4
(ppm)
OHCHN
O
O
O
O
O2N
N
N
N
3s
Integral
1.9078
0.7442
0.7315
1.6593
0.8921
0.7622
0.7517
0.8240
1.0000
2.0094
5.0995
0.9324
0.8843
4.2792
4.6204
6.1362
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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7.4062
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7.2600
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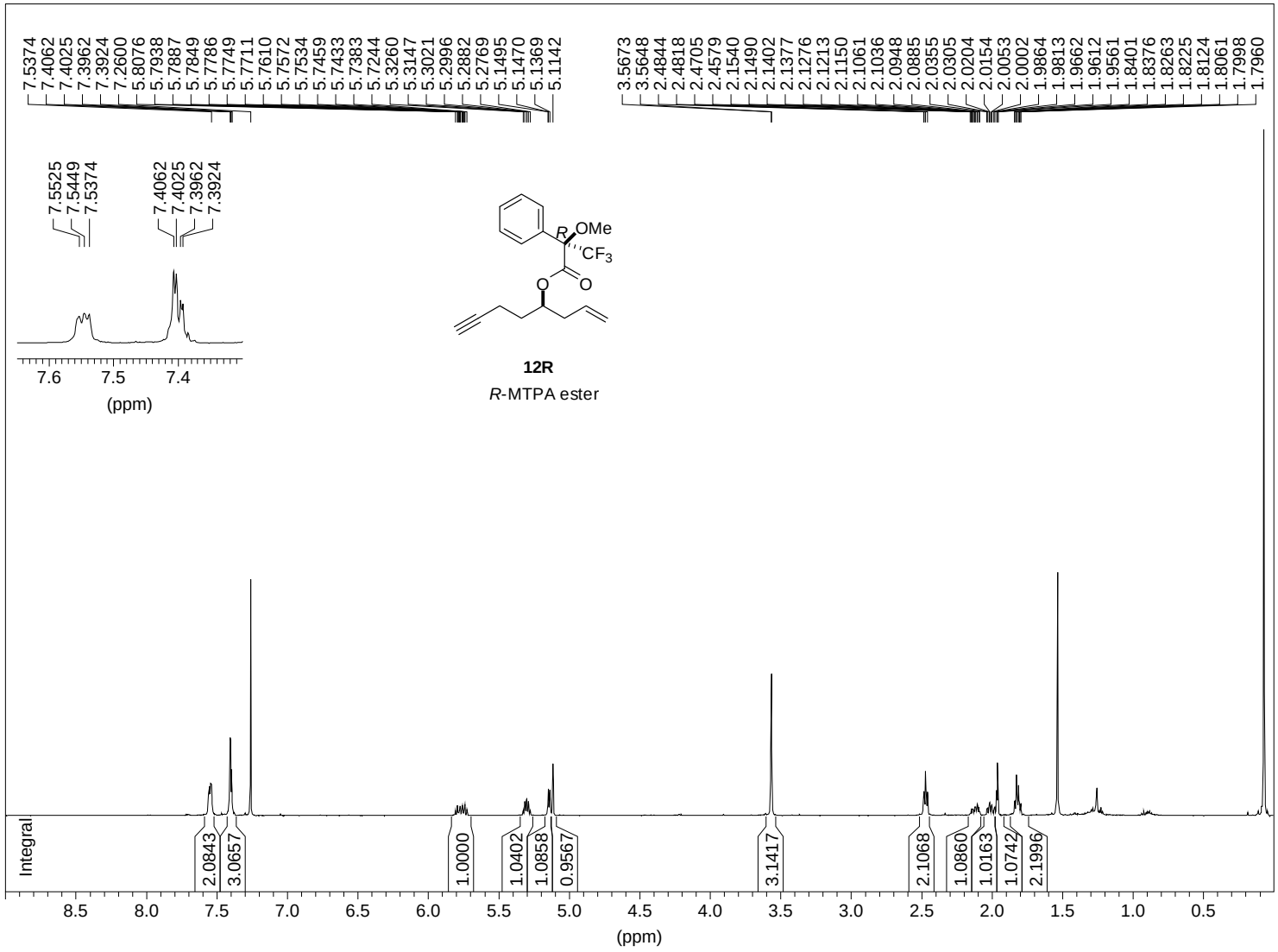
5.6790
5.6740
5.6639
5.6589
5.6437
5.6387
5.6337
5.6286
5.6236
5.6097
5.2983
5.2870
5.2819
5.2769
5.2718
5.2655
5.2605
5.2491
5.0701
5.0625
5.0386
3.5383
2.4251
2.4125
2.3999
2.2902
2.2852
2.2738
2.2700
2.2625
2.2562
2.2511
2.2398
2.2347
2.2284
2.2234
2.2171
2.2120
2.2020
2.1969
2.1830
2.1780
2.1679
2.1629
1.9259
1.9107
1.8969
1.8817
1.8704
1.8653
1.8540
1.8489
1.8389
1.8263
1.8200
1.8099
S
CF3
OMe
O
O
12S
S-MTPA ester
Integral
2.2221
3.2056
1.0000
1.0323
1.0928
0.8893
3.1331
2.1443
2.2400
0.9295
2.2562
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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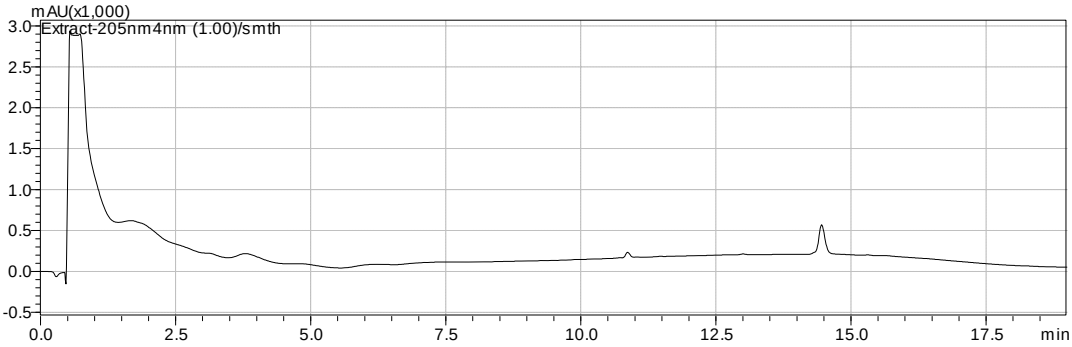
7.3924
7.2600
5.8076
5.7938
5.7887
5.7849
5.7786
5.7749
5.7711
5.7610
5.7572
5.7534
5.7459
5.7433
5.7383
5.7244
5.3260
5.3147
5.3021
5.2996
5.2882
5.2769
5.1495
5.1470
5.1369
5.1142
3.5673
3.5648
2.4844
2.4818
2.4705
2.4579
2.1540
2.1490
2.1402
2.1377
2.1276
2.1213
2.1150
2.1061
2.1036
2.0948
2.0885
2.0355
2.0305
2.0204
2.0154
2.0053
2.0002
1.9864
1.9813
1.9662
1.9612
1.9561
1.8401
1.8376
1.8263
1.8225
1.8124
1.8061
1.7998
1.7960
7.5525
7.5449
7.5374
7.4062
7.4025
7.3962
7.3924
7.6
7.5
7.4
(ppm)
R
OMe
CF3
O
O
12R
R-MTPA ester
Integral
2.0843
3.0657
1.0000
1.0402
1.0858
0.9567
3.1417
2.1068
1.0860
1.0163
1.0742
2.1996
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)

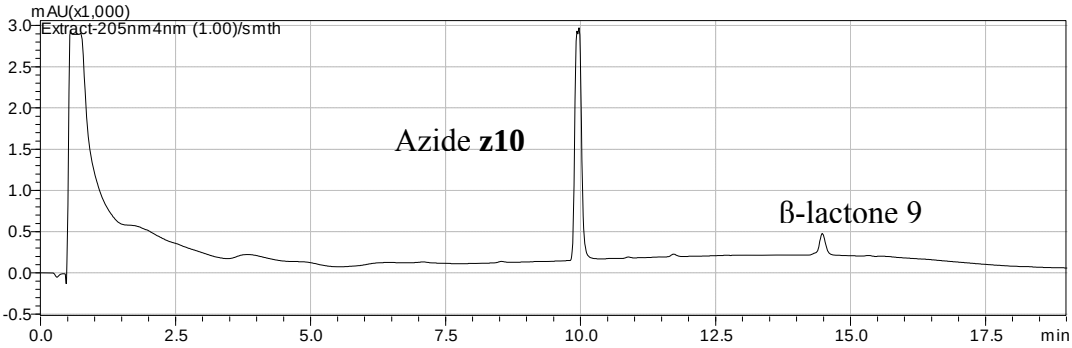
LC profile for click chemistry optimization

LC condition: 10-80% CH_3CN in 10 min, 80-100% CH_3CN in 10-12 min, 100% CH_3CN in 12-15 min. Flow rate = 0.6 mL min^{-1}.

β-lactone **9**

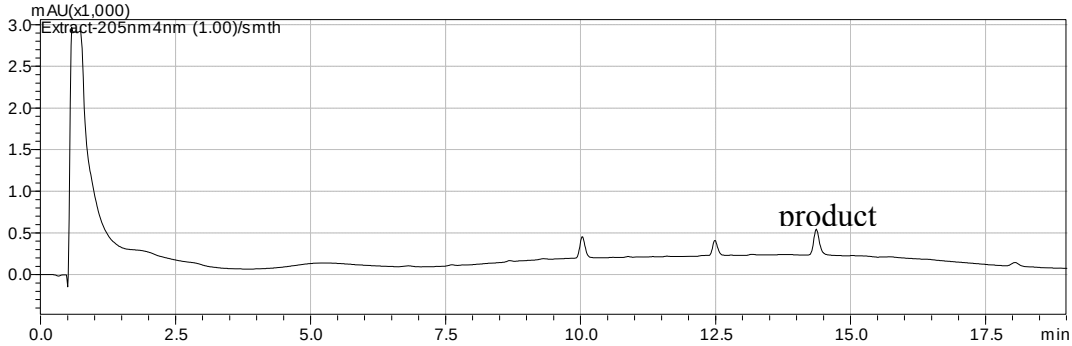


β-lactone **9** + azide **10j**

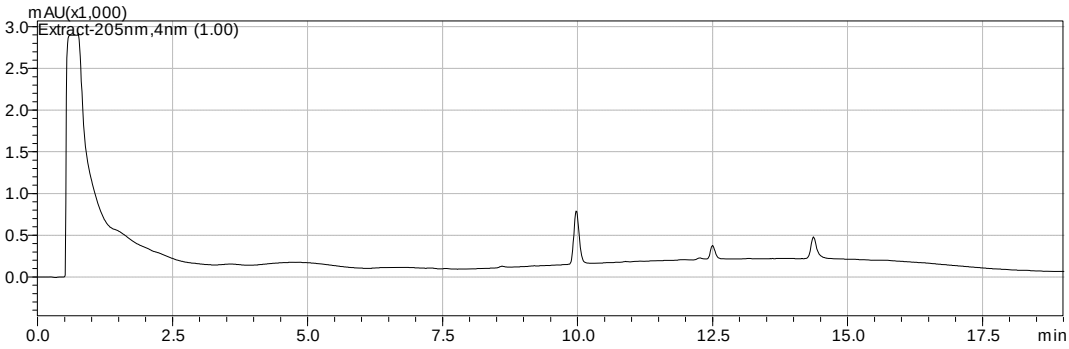


$CuSO_4.5H_2O$ (0.4 eq) + NaAsc (1.6 eq)

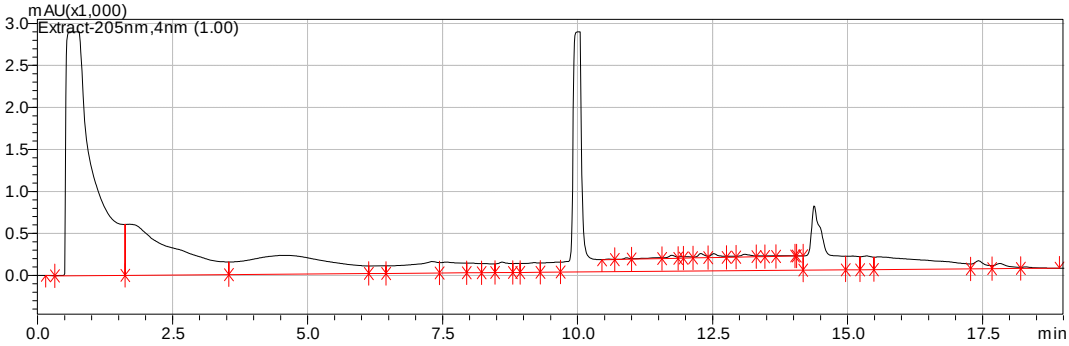
1. DMSO:H_2O (1:1)



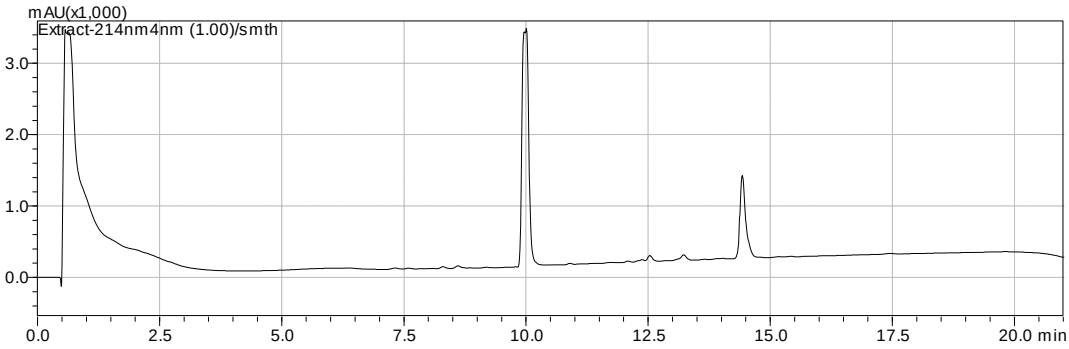
2. DCM:H_2O (1:1)



3. DCE:H_2O (1:1)

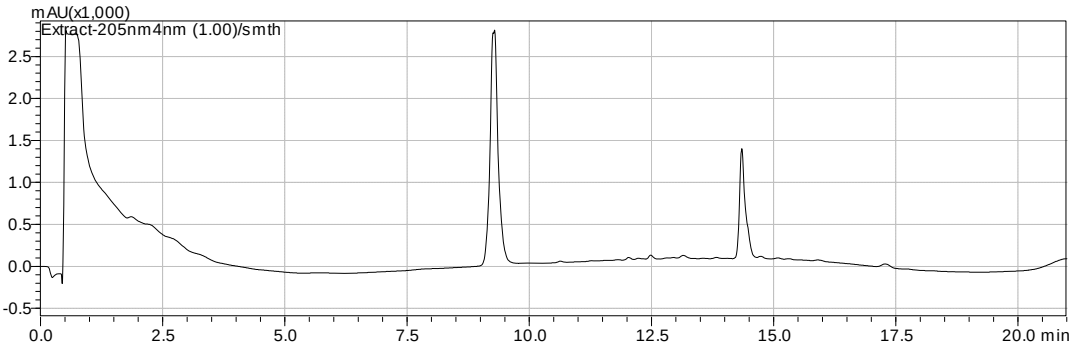


4. *t*BuOH:H_2O (1:1)

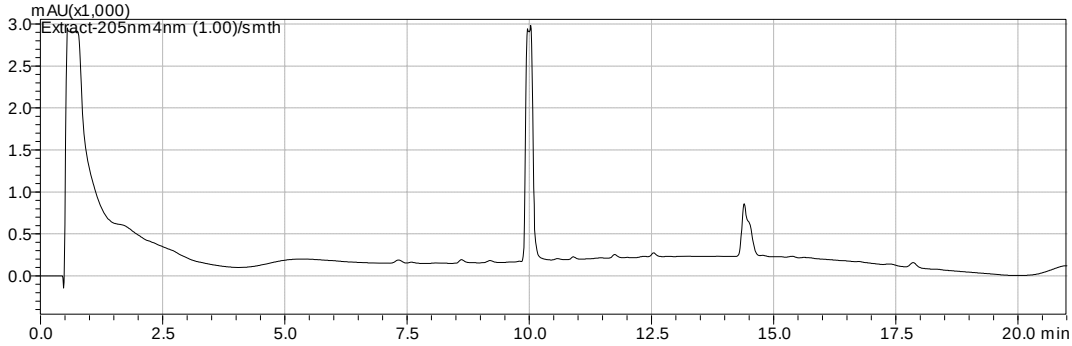


CuI (0.4 eq) + DIEA (0.8 eq)

5. DMSO:H_2O (1:1)



6. DCM:H_2O (1:1)



7. DCE:H_2O (1:1)