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Stereoselective synthesis of spirocyclic derivatives of functionalized 2,3,4,7-tetrahydro-1*H*-azepines

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1. General information

NMR spectra were recorded on Bruker Avance 400 instrument with operating frequency of 400 and 100.6 MHz, respectively, and calibrated using residual non-deuterated chloroform (δ_H = 7.27 ppm) and $CDCl_3$ (δ_C = 77.16 ppm) or undeuterated dimethyl sulfoxide (DMSO) (δ_H = 2.50 ppm) and DMSO-d_6 (δ_C = 39.51 ppm) as internal references. The following abbreviations are used to set multiplicities: s = singlet, d =doublet, t = triplet, q = quartet, m = multiplet, br = broad. The purity of the final compounds was checked by liquid chromatography-mass-spectrometry (LCMS) in a Shimadzu LCMS-2010A using three types of detection systems such as EDAD, ELSD, and UV. High Resolution Mass Spectra (HRMS) were registered on a Sciex TripleTOF 5600+ machine. We used commercial reagents and solvents without further purification. Reactions were monitored by thin-layer chromatography (TLC) performed on Merck TLC Silica gel plates (60 F254), using a UV light for visualization and basic aqueous potassium permanganate or iodine fumes as a developing agent.

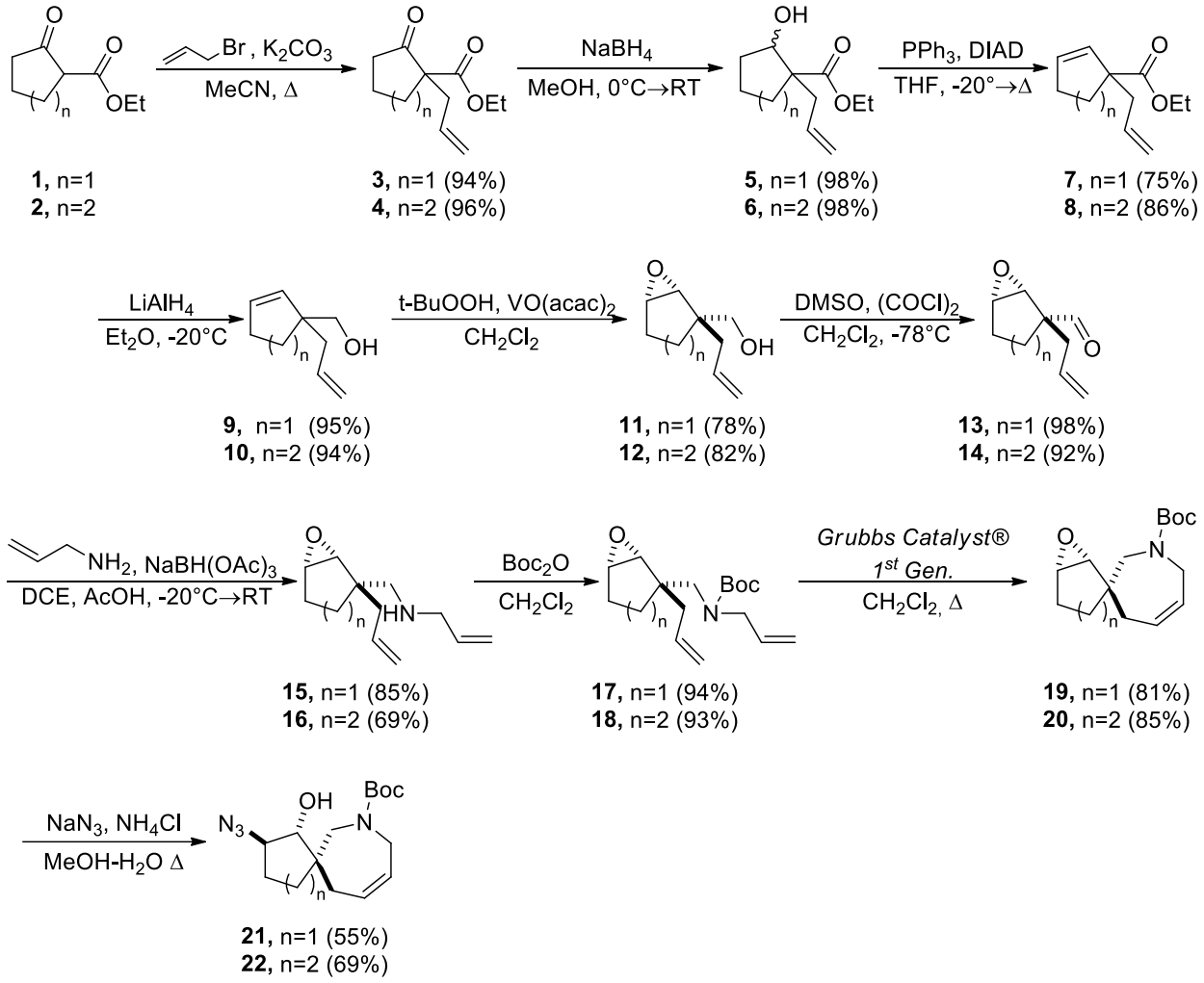
Table S1 Optimization of metathesis reaction conditions for obtaining compound **20**.

Entry	Conditions	Yield, %
1	[Ru] (0.2 mol. %), CH_2Cl_2 (0.1M), Δ (12 h)	42
2	[Ru] (0.4 mol. %), CH_2Cl_2 (0.1M), Δ (12 h)	68
3	[Ru] (0.5 mol. %), CH_2Cl_2 (0.2M), Δ (12 h)	85

Table S2 Optimization of metathesis reaction conditions for obtaining compound **19**.

Entry	Conditions	Yield, %
1	[Ru] (0.5 mol. %), CH_2Cl_2 (0.2M), Δ (12 h)	53
2	[Ru] (0.5 mol. %), CH_2Cl_2 (0.2M), Δ (24 h)	59
3	[Ru] (1 mol. %), CH_2Cl_2 (0.2M), Δ (12 h)	74
4	[Ru] (1 mol. %), CH_2Cl_2 (0.2M), Δ (24 h)	81

2. *Synthesis and characterization of compounds 3-22.*



1, n=1
2, n=2

3, n=1 (94%)
4, n=2 (96%)

5, n=1 (98%)
6, n=2 (98%)

7, n=1 (75%)
8, n=2 (86%)

9, n=1 (95%)
10, n=2 (94%)

11, n=1 (78%)
12, n=2 (82%)

13, n=1 (98%)
14, n=2 (92%)

15, n=1 (85%)
16, n=2 (69%)

17, n=1 (94%)
18, n=2 (93%)

19, n=1 (81%)
20, n=2 (85%)

21, n=1 (55%)
22, n=2 (69%)

Characterization and spectral data of compounds **1-12** were described in our previous work [I. R. Iusupov, E. R. Lukyanenko, A. Altieri and A. V. Kurkin, *ChemMedChem*, 2022, **17**, e202200394. https://doi.org/10.1002/cmdc.202200394].

*General procedure for synthesis compounds **3**, **4**:*

Starting compound **1** or **2** (1 equiv.) was dissolved in MeCN (0.5 M). Then solid potassium carbonate (2.5 equiv.) and allyl bromide (1.5 equiv.) were added successively. The reaction mixture was refluxed for 5-8 h (TLC-control) and then cooled to room temperature. Solids were filtered, washed with MeCN (2 × 200 mL); the filtrate was evaporated. The crude product was purified by distillation under reduced pressure, after which pure product was obtained as colorless liquid.

3: b.p. = 110-113 °C at 3-4 Torr, M = 184.5 g. Yield = 94%.

4: b.p. = 119-122 °C at 3-4 Torr, M = 201.4 g. Yield = 96%.

*General procedure for synthesis compounds **5**, **6**:*

Ketone **3** or **4** (1 equiv.) was dissolved in MeOH (0.5M) and it was cooled to 0 – -10 °C. Then $NaBH_4$ (1.1 equiv.) was added carefully in small portions. The mixture was stirred for 1 h at 0 °C and warmed to room temperature and stirred for another 3-4 h. After that 2/3 of the solvent volume was evaporated, and water (500 mL) was added to the residue followed by aqueous HCl (12M, 4 equiv.) addition. The resulting mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by distillation under reduced pressure to afford alcohol **5** or **6** as a colorless liquid.

5: b.p. = 115-125 °C at 3-4 Torr, M = 58.1 g. Yield = 98%.

6: b.p. = 135-146 °C at 3-4 Torr, M = 156 g. Yield 98%.

*General procedure for synthesis compounds **7**, **8**:*

To a solution of alcohol **5** or **6** (1 equiv.) in THF (0.5M), Ph_3P (1.2 equiv.) was added. After dissolving of Ph_3P, the solution was cooled to -20°C. Then DIAD (diisopropyl azodicarboxylate; 1.21 equiv.) was added dropwise (at the end of addition, a precipitate forms), and the mixture was warmed (for ~1 h) to room temperature and then refluxed for 10-15 h (TLC-control). The solvent was evaporated and the residue was triturated in hexane (500 mL). The precipitate was filtered and washed with hexane (3 × 150 mL). The filtrate was evaporated and the crude product was purified by distillation under reduced pressure to afford alkene **7** or **8** as a colorless liquid.

7: b.p. = 78-80 °C at 3-4 Torr, M = 39.6 g. Yield = 75%.

8: b.p. = 75-77 °C at 3-4 Torr, M = 89.3 g. Yield = 86%.

*General procedure for synthesis compounds **9**, **10**:*

A suspension of $LiAlH_4$ (1.2 equiv.) in Et_2O (1M) was cooled to -20°C, and a solution of ethyl ester **7,8** (1 equiv.) in Et_2O (1M) was added dropwise (the temperature should not exceed -15°C). The mixture was stirred for 1 h at 0°C and again cooled to -20 – -15 °C. Water (1 mL per 1 g of $LiAlH_4$), 10% aqueous NaOH (1 mL per 1 g of $LiAlH_4$) and once more water (1 mL per 1 g of $LiAlH_4$) were added successively. The resulting precipitate was filtered, washed with Et_2O (4 × 150 mL); the filtrate was evaporated. Crude product was purified by distillation under reduced pressure to afford alcohol **9** or **10** as a colorless liquid.

9: b.p. = 78-80 °C at 13-15 Torr, M = 28.8 g. Yield = 95%.

10: b.p. = 110-112 °C at 10-12 Torr, M = 68.9 g. Yield = 94%.

*General procedure for synthesis compounds **11**, **12**:*

Starting compound **9** or **10** (1 equiv.) was dissolved in CH_2Cl_2 (0.2M), $VO(acac)_2$ (0.05 equiv.) was added in a one portion followed by dropwise addition (~1 min) of Bu^tOOH (5.5M in decane, 1.5 equiv.). The mixture was stirred for 3-6 h (TLC-control) at the room temperature, then it was cooled to 0°C. A solution of mixture of $FeSO_4 \times 7H_2O$ (1.5 equiv.) and tartaric acid (1 equiv.) in water (300 mL) was added in several portions, and the resulting biphasic mixture was stirred for 30 min for neutralization of excess Bu^tOOH. The organic layer was separated; the water phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography on silica gel to afford desired compound **11** or **12** as a colorless oil.

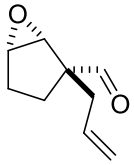
11: eluent: hexane-EtOAc, 5:1 → 3:1, Rf = 0.4 in hexane-EtOAc 3:1, M = 8.7 g. Yield = 78%.

12: eluent: hexane-EtOAc, 5:1 → 3:1, Rf = 0.3-0.4 in hexane-EtOAc 3:1, M = 9.1 g. Yield = 82%.

General procedure for the Swern oxidation:

A solution of DMSO (2.5 equiv.) in CH_2Cl_2 (1M solution) was added dropwise to a solution of oxalyl chloride (1.5 equiv.) in CH_2Cl_2 (1M solution) at−70 to−80°C. The resulting solution was stirred for 10 min, and a solution of epoxy alcohol **11** or **12** (1 equiv.) in CH_2Cl_2 (1M solution) was added dropwise at the same temperature. After 15 min, Et_3N (4 equiv.) was added dropwise, and 5 min later, the reaction mixture was allowed to warm to rt. The reaction mixture was quenched with water (200 mL), and the organic layer was separated and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* (bath temperature not exceeding 45−50°C). The purification by flash chromatography using hexanes/EtOAc (10:1→5:1,) as eluent afforded aldehyde **13** or **14**.

(1RS,2SR,5SR)-2-Allyl-6-oxabicyclo[3.1.0]hexane-2-carbaldehyde (13)



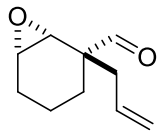
Rf = 0.6 in 5:1 hexanes/EtOAc, yellow liquid. M=7.3 g. Yield=98%.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.44 - 1.53 (m, 1 H), 1.70 - 1.84 (m, 2 H), 2.09 - 2.19 (m, 1 H), 2.24 - 2.37 (m, 2 H), 3.40 (d, J=2.6 Hz, 1 H), 3.54 - 3.59 (m, 1 H), 5.05 - 5.13 (m, 2 H), 5.65 - 5.78 (m, 1 H), 9.69 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.3, 26.3, 35.2, 57.0, 57.1, 60.5, 118.9, 132.8, 203.4.

HRMS (ESI) m/z: calcd for $C_9H_{13}O_2$ $[M+H]^+$ 153.0910, found 153.0910.

(1RS,2SR,6SR)-2-Allyl-7-oxabicyclo[4.1.0]heptane-2-carbaldehyde (14)



Rf = 0.6 in 5:1 hexanes/EtOAc, yellow liquid. M=6.2 g. Yield=92%.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.00 - 1.09 (m, 1 H), 1.30 - 1.39 (m, 2 H), 1.64 - 1.74 (m, 1 H), 1.88 (dt, J=13.6, 4.4 Hz, 1 H), 1.96 - 2.05 (m, 1 H), 2.34 (d, J=7.3 Hz, 2 H), 3.15 (d, J=3.7 Hz, 1 H), 3.22 (dt, J=3.7, 1.9 Hz, 1 H), 5.07 - 5.11 (m, 1 H), 5.13 (c, 1 H), 5.61 - 5.75 (m, 1 H), 9.69 (c, 1 H).

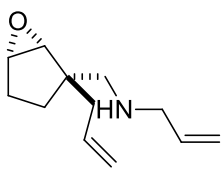
^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.5, 23.8, 25.5, 38.8, 48.2, 51.6, 54.7, 119.5, 131.9, 202.5.

HRMS (ESI) m/z: calcd for $C_{10}H_{15}O_2$ $[M+H]^+$ 167.1067, found 167.1066.

*General procedure for synthesis of compounds **15-16**:*

To a solution of aldehyde **13** or **14** (1 equiv.) and allylamine (1.2 equiv.) in 1,2-dichloroethane DCE (0.5M solution), AcOH (0.5 mL) was added, and the solution was stirred for 10-15 min. Then $NaBH(OAc)_3$ (2.5 equiv.) was added portionwise for 10 min. The resulting mixture was stirred overnight at room temperature and quenched with saturated aqueous $NaHCO_3$ (200 mL). The organic layer was separated; the water layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The purification by flash chromatography using hexanes/EtOAc (10:1→5:1→1:1) as eluent afforded desired compound.

N-(((1RS,2RS,5SR)-2-Allyl-6-oxabicyclo[3.1.0]hex-2-yl)methyl)prop-2-en-1-amine (15)



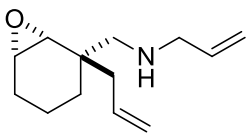
Rf = 0.1-0.6 in 2:1 hexanes/EtOAc, colorless oil. M=7.8 g. Yield=85%.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.12 - 1.27 (m, 2 H), 1.40 (dd, J=12.9, 8.8 Hz, 1 H), 1.62 - 1.73 (m, 1 H), 1.93 - 2.10 (m, 2 H), 2.12 - 2.21 (m, 1 H), 2.60 - 2.68 (m, 2 H), 3.20 - 3.31 (m, 3 H), 3.44 (s, 1 H), 5.04 - 5.11 (m, 3 H), 5.17 (dd, J=17.2, 1.6 Hz, 1 H), 5.72 - 5.95 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 28.2, 37.8, 46.1, 53.3, 53.6, 57.2, 62.1, 115.8, 117.8, 134.3, 137.3.

HRMS (ESI) m/z: calcd for $C_{12}H_{20}NO$ $[M+H]^+$ 194.1539, found 194.1540.

N-(((1RS,2RS,6SR)-2-Allyl-7-oxabicyclo[4.1.0]hept-2-yl)methyl)prop-2-en-1-amine (16)



Rf = 0.3-0.6 in 2:1 hexanes/EtOAc, slightly yellow oil. M=5.2 g. Yield=69%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 - 1.13 (m, 1 H), 1.20 - 1.34 (m, 3 H), 1.34 - 1.45 (m, 1 H), 1.69 (dddd, *J*=14.8, 8.8, 5.8, 2.6 Hz, 1 H), 1.91 - 1.99 (m, 1 H), 2.19 - 2.29 (m, 2 H), 2.38 (d, *J*=11.7 Hz, 1 H), 2.70 (d, *J*=11.9 Hz, 1 H), 2.89 (d, *J*=3.9 Hz, 1 H), 3.17 - 3.32 (m, 3 H), 5.04 - 5.12 (m, 3 H), 5.17 (dd, *J*=17.2, 1.5 Hz, 1 H), 5.74 - 5.94 (m, 2 H).

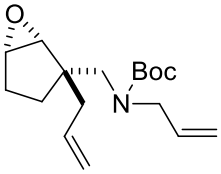
^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 24.6, 28.9, 36.0, 40.4, 53.3, 53.3, 54.6, 57.9, 115.7, 118.0, 134.1, 137.5.

HRMS (ESI) m/z: calcd for $C_{13}H_{22}NO$ $[M+H]^+$ 208.1696, found 208.1697.

*General procedure for synthesis of compounds **17-18**:*

To a solution of amine **15** or **16** (1 equiv.) in CH_2Cl_2 (0.5M solution), Boc_2O (1.2 equiv.) was added portionwise on water bath. The resulting solution was stirred for 5-6 h (TLC-control). Then the solvent was evaporated. The crude product was purified by flash chromatography using hexanes/EtOAc (20:1→10:1) as eluent afforded Boc-protected compound.

tert-Butyl N-ally-N-l(((1R,2R,5S)-2-allyl-6-oxabicyclo[3.1.0]hex-2-yl)methyl)carbamate (17)



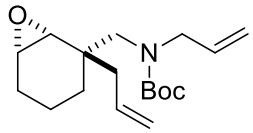
Rf = 0.5 in 10:1 hexanes/EtOAc, colorless oil. M=11.05 g. Yield=81%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (dt, J=12.9, 9.3 Hz, 1 H), 1.35 - 1.43 (m, 1 H), 1.45 (s, 9 H), 1.59 - 1.71 (m, 1 H), 1.94 (dd, J=14.2, 8.4 Hz, 1 H), 2.04 - 2.19 (m, 2 H), 3.02 - 3.26 (m, 2 H), 3.34 - 3.59 (m, 2 H), 3.76 - 4.07 (m, 2 H), 5.01 - 5.17 (m, 4 H), 5.71 - 5.95 (m, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 28.2 (br.), 28.5 (3 C), 38.7 (br.), 47.0, 51.0, 51.1 (br.), 58.6, 62.2, 80.0 (br.), 116.2 (br.), 117.8, 134.0 (br.), 134.5 (br.), 156.4 (br.).

HRMS (ESI) m/z: calcd for $C_{17}H_{28}NO_3$ $[M+H]^+$ 294.2063, found 294.2066.

tert-Butyl N-allyl-N-(((1RS,2RS,6SR)-2-allyl-7-oxabicyclo[4.1.0]hept-2-yl)methyl)carbamate (18)



Rf = 0.6 in 10:1 hexanes/EtOAc, colorless oil. M=7.0 g. Yield=93%.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.13 - 1.20 (m, 2 H), 1.25 - 1.37 (m, 2 H), 1.44 (c, 9 H), 1.65 - 1.75 (m, 1 H), 1.86 - 1.97 (m, 1 H), 2.19 (d, *J*=7.0 Hz, 2 H), 2.76 - 2.89 (m, 1 H), 3.01 - 3.19 (m, 1 H), 3.20 - 3.26 (m, 1 H), 3.29 - 3.49 (m, 1 H), 3.82 - 3.90 (m, 1 H), 3.95 - 4.17 (m, 1 H), 5.01 - 5.17 (m, 4 H), 5.66 - 6.03 (m, 2 H).

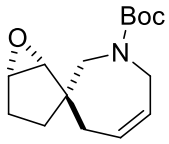
^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.5, 24.1, (27.6, 27.8), 28.5 (3 C), 37.5, (39.8, 40.0), (50.9, 51.5), (52.3, 52.5), 54.1, 57.7, (79.5, 80.1), (115.8, 115.9), 118.0, 133.9 (br., 2 C), (156.7, 157.0).

HRMS (ESI) m/z: calcd for $C_{18}H_{30}NO_3$ $[M+H]^+$ 308.2220, found 308.2223.

*General procedure for synthesis **19-20*** (see Tables S1 and S2)*:*

Diallyl derivative **17** or **18** (1 equiv.) was dissolved in CH_2Cl_2 (0.1M solution). The flask was purged with argon for 10–15 min, and the Grubbs Catalyst® 1st Generation (0.5 or 1 mol. %) was added. The resulting solution was refluxed for 24 or 12 h (TLC-control) under argon atmosphere. The solvent was evaporated, and the crude product was purified by flash chromatography on silica using hexanes/EtOAc (20:1→5:1) as eluent to afford the desired compound.

tert-Butyl (1'RS,2'RS,5'SR)-4,7-dihydro-6'-oxaspiro[azepine-3,2'-bicyclo[3.1.0]hexane]-1(2H)-carboxylate (19)



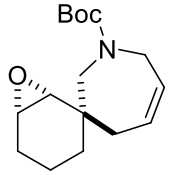
Rf = 0.4 in 5:1 hexanes/EtOAc, slightly yellow oil. M=6.55 g. Yield=81%.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.03 - 1.21 (m, 1 H), 1.35 (dd, J=12.8, 8.5 Hz, 1 H), 1.42 - 1.52 (m, 9 H), 1.63 (dt, J=14.2, 9.4 Hz, 1 H), 1.80 - 2.05 (m, 2 H), 2.08 - 2.24 (m, 1 H), 3.02 - 3.46 (m, 3 H), 3.65 - 4.43 (m, 3 H), 5.59 - 5.74 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm), 25.6, 28.6 (3 C), 29.3, 30.5, 47.5, 47.9, 51.9, 57.4, 62.2, 80.0, 126.1, 129.4, 155.6.

HRMS (ESI) m/z: calcd for $C_{15}H_{24}NO_3$ $[M+H]^+$ 266.1751, found 266.1754.

tert-Butyl (1'RS,2'RS,6'SR)-4,7-dihydro-7'-oxaspiro[azepine-3,2'-bicyclo[4.1.0]heptane]-1(2H)-carboxylate (20)



Rf = 0.3 in 10:1 hexanes/EtOAc, slightly yellow oil. M=3.8 g. Yield=85%.

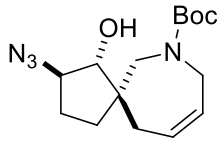
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.85 - 0.96 (m, 1 H), 1.22 - 1.34 (m, 1 H), 1.35 - 1.55 (m, 11 H), 1.66 - 1.79 (m, 1 H), 1.88 - 2.00 (m, 1 H), 2.09 - 2.21 (m, 2 H), 2.82 - 2.93 (m, 1 H), 3.11 - 3.20 (m, 1 H), 3.38 (d, *J*=14.7 Hz, 1 H), 3.51 - 3.69 (m, 1 H), 3.71 - 3.95 (m, 1 H), 4.06 - 4.22 (m, 1 H), 5.61 - 5.78 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.9, 24.3, 28.5 (3 C), (29.5, 30.1), (33.8, 33.9), (37.9, 38.5), (47.7, 48.5), 52.9, 53.1, (58.4, 58.5), (79.4, 79.8), (126.8, 127.1), (129.1, 129.2), 155.9.

HRMS (ESI) m/z: calcd for $C_{16}H_{26}NO_3$ $[M+H]^+$ 280.1907, found 280.1919.

*General procedure for synthesis **21-22**:*

Starting epoxide **19** or **20** (1 equiv.) was dissolved in MeOH-H_2O mixture (10:1, 0.5 M), then NaN_3 (3 equiv.) and NH_4Cl (2 equiv.) were added to the solution. The resulting mixture was refluxed for 20–25 h (TLC-control). After cooling to room temperature, water (150 mL) was added, and the mixture was extracted with EtOAc (4 × 100 mL); the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography on silica gel using hexanes/EtOAc (10:1→5:1) as eluent afforded to desired product.



tert-Butyl (1RS,2RS,5RS)-2-azido-1-hydroxy-7-azaspiro[4.6]undec-9-ene-7-carboxylate (21)

Rf = 0.2-0.3 in 5:1 hexanes/EtOAc, colorless oil. M=1.9 g. Yield=55%.

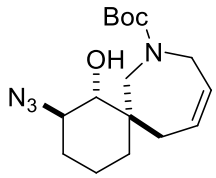
^{1}H NMR (400 MHz, $CDCl_3$): ***δ*** 1.47 (s, 9 H), 1.53 - 1.66 (m, 3 H), 1.97 (dd, J=14.3, 7.5 Hz, 1 H), 2.08 - 2.18 (m, 1 H), 2.40 (dd, J=14.2, 6.1 Hz, 1 H), 2.81 (d, J=14.9 Hz, 1 H), 3.51 - 3.60 (m, 2 H), 3.83 - 3.91 (m, 1 H), 3.99 (d, J=14.9 Hz, 1 H), 4.44 (dd, J=17.3, 1.3 Hz, 1 H), 5.29 (d, J=4.2 Hz, 1 H), 5.60 - 5.68 (m, 1 H), 5.70 - 5.79 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): ***δ*** 27.5, 28.5 (3 C), 33.1, 33.5, 48.6, 50.8, 51.1, 68.3, 81.1, 82.6, 128.2, 128.2, 156.7.

HRMS (ESI) m/z: calcd for $C_{15}H_{25}N_4O_3$ $[M+H]^+$ 309.1921, found 309.1924.

tert-Butyl (1RS,2RS,6RS)-2-azido-1-hydroxy-8-azaspiro[5.6]dodec-10-ene-8-carboxylate (22)

Rf = 0.3 in 5:1 hexanes/EtOAc, white powder. M=1.4 g. Yield=69%. mp = 68-70 °C.

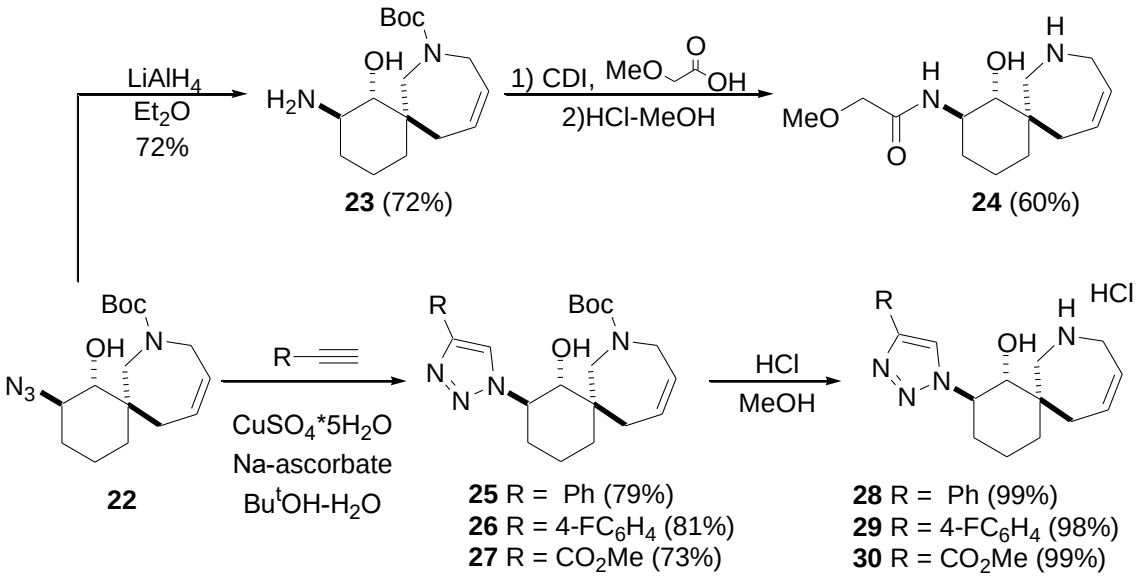


^{1}H NMR (400 MHz, $CDCl_3$): ***δ*** 1.13 (td, J=12.9, 3.5 Hz, 1 H), 1.22 - 1.36 (m, 2 H), 1.45 - 1.52 (m, 9 H), 1.53 - 1.63 (m, 2 H), 1.83 (dd, J=14.7, 2.4 Hz, 1 H), 1.94 - 2.05 (m, 1 H), 2.79 (d, J=15.0 Hz, 1 H), 2.95 - 3.10 (m, 2 H), 3.52 (td, J=10.0, 4.8 Hz, 1 H), 3.60 (dt, J=18.0, 1.8 Hz, 1 H), 3.95 (d, J=14.9 Hz, 1 H), 4.52 (d, J=18.0 Hz, 1 H), 4.64 (d, J=10.5 Hz, 1 H), 5.38 - 5.51 (ddt, J=11.0, 3.2, 2.8, 2.8 Hz, 1 H), 5.66 - 5.75 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$): ***δ*** 19.5, 28.5 (3 C), 30.7, 34.1, 36.2, 46.6, 50.1, 50.7, 63.5, 79.3, 81.4, 126.3, 127.3, 157.0.

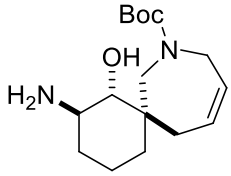
HRMS (ESI) m/z: calcd for $C_{16}H_{26}N_4NaO_3$ $[M+H]^+$ 345.1897, found 345.1895.

3. Synthesis and characterization of compounds 23-30.



tert-Butyl (1RS,2RS,6RS)-2-amino-1-hydroxy-8-azaspiro[5.6]dodec-10-ene-8-carboxylate (23)

A solution of azide **22** (300 mg, 0.93 mmol, 1 equiv.) in Et_2O (10 mL) was added dropwise to a suspension of $LiAlH_4$ (42.4 mg, 1.12 mmol, 1.2 equiv.) in Et_2O (10 mL) at −10°C. The reaction mixture was stirred for 3-4 h at −10°C (TLC-control). It was then quenched by successive addition of water (0.05 mL), 10% NaOH (0.05 mL) solution, and water (0.1 mL) (the temperature should not exceed 0°C). The precipitate was filtered off and washed several times with Et_2O. The filtrate was evaporated to give crude amine, which was purified by flash chromatography using CH_2Cl_2-MeOH (20:1→10:1) as eluent (Rf = 0.3 in CH_2Cl_2-MeOH 10:1). White powder, M = 203 mg. Yield = 72%. mp = 91-93 °C.



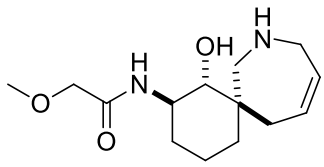
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.01 - 1.32 (m, 3 H), 1.40 - 1.54 (m, 11 H), 1.58 - 2.16 (m, 5 H), 2.66 (d J=9.7 Hz, 1 H), 2.75 - 2.84 (m, 2 H), 2.97 - 3.06 (m, 1 H), 3.58 (dddd, J=18.3, 3.6, 2.1, 1.9 Hz, 1 H), 3.94 (d, J=14.9 Hz, 1 H), 4.54 (dt, J=18.2, 2.0 Hz, 1 H), 5.34 - 5.41 (m, 1 H), 5.64 - 5.74 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.3, 28.5 (3 C), 34.3, 34.5, 37.7, 46.9, 50.4, 50.6, 53.1, 81.1, 82.9, 125.7, 127.3, 156.9.

HRMS (ESI) m/z: calcd for $C_{16}H_{29}N_2O_3$ $[M+H]^+$ 297.2173, found 297.2172.

N-((1RS,2RS,6RS)-1-Hydroxy-8-azaspiro[5.6]dodec-10-en-2-yl)-2-methoxyacetamide (24)

To a solution of methoxyacetic acid (0.057 mL, 0.74 mmol, 1.1 equiv.) in MeCN (10 mL), CDI (0.12 g, 0.74 mmol, 1.1 equiv.) was added in one portion. After stirring for 5 min, amine **23** (0.2 g, 0.67 mmol, 1 equiv.) was added. The resulting mixture was stirred overnight at room temperature. Then the solvent was evaporated, water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was used without further purification and analysis.



To the above Boc-protected compound in MeOH (10 mL), 10 mL of 1 M HCl in methanol (prepared by dropwise addition of AcCl to MeOH) was added. The resulting solution was stirred overnight at room temperature, and the solvent was evaporated. After that 10% aqueous K_2CO_3 (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 30 mL). The crude product was purified by flash chromatography using CH_2Cl_2-(MeOH sat. NH_3) (20:1→10:1) as eluent (Rf = 0.3 in CH_2Cl_2-(MeOH sat. NH_3 10:1)). White powder, M = 107 mg. Yield = 60%. mp = 89-92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): ***δ*** 1.05 - 1.19 (m, 2 H), 1.36 - 1.64 (m, 3 H), 1.93 (dd, *J*=16.0, 5.5 Hz, 1 H), 2.16 (d, *J*=14.3 Hz, 1 H), 2.67 (d, *J*=13.8 Hz, 1 H), 2.75 (dd, *J*=15.8, 6.2 Hz, 1 H), 3.12 - 3.45 (m, 7 H), 3.55 (dd, *J*=16.1, 4.8 Hz, 1 H), 3.69 (d, *J*=13.8 Hz, 1 H), 3.84 - 3.97 (m, 3 H), 5.54 - 5.61 (m, 1 H), 5.75 - 5.83 (m, 1 H), 6.65 (d, *J*=6.1 Hz, 1 H).

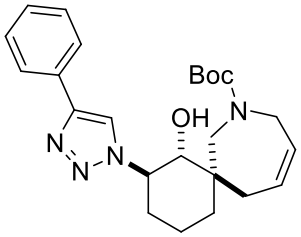
^{13}C NMR (100 MHz, $CDCl_3$): ***δ*** 20.3, 31.9, 36.6, 41.0, 42.0, 50.5, 52.1, 54.3, 59.3, 72.1, 82.8, 127.6, 128.6, 170.6.

HRMS (ESI) m/z: calcd for $C_{14}H_{25}N_2O_3$ $[M+H]^+$ 269.1860, found 269.1860.

*General procedure for synthesis **25-27**:*

Azide **22** (1 equiv.) was dissolved in a mixture of Bu^{t}OH-H_2O (1:1, 0.2M solution). Then the appropriate quantity of acetylene (1.2 equiv.) was added followed by sodium ascorbate (0.1 equiv.) and $CuSO_4$×5H_2O (0.02 equiv.). The resulting mixture was stirred at the room temperature for 5–10 h (TLC-control). After the end of the reaction, water (50 mL per each gram of azide) was added; the mixture was extracted with EtOAc (3 × 50 mL); the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography on silica gel to give desired triazoles.

tert-Butyl (1RS,2RS,6RS)-1-hydroxy-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-8-azaspiro[5.6]dodec-10-ene-8-carboxylate (25)



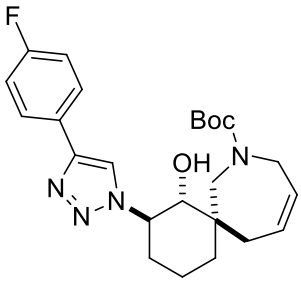
Rf = 0.4 in 2:1 hexanes/EtOAc, white powder. M=0.206 g. Yield=79%. mp = 103-105 °C

^{1}H NMR (400 MHz, $CDCl_3$): ***δ*** 1.30 - 1.52 (m, 11 H), 1.59 (dd, J=14.3, 8.9 Hz, 1 H), 1.68 - 1.77 (m, 1 H), 1.93 - 2.34 (m, 3 H), 2.93 (d, J=15.1 Hz, 1 H), 3.06 (ddd, J=14.2, 4.9, 2.4 Hz, 1 H), 3.48 - 3.70 (m, 2 H), 4.07 (d, J=15.0 Hz, 1 H), 4.51 - 4.62 (m, 2 H), 4.82 (d, J=11.2 Hz, 1 H), 5.41 - 5.48 (m, 1 H), 5.67 - 5.77 (m, 1 H), 7.27 - 7.33 (m, 1 H), 7.41 (t, J=7.6 Hz, 2 H), 7.85 (d, J=7.4 Hz, 2 H), 7.93 (s, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$): ***δ*** 20.2, 28.4 (3 C), 32.6, 34.2, 36.8, 47.6, 49.9, 50.6, 63.7, 78.3, 81.6, 120.0, 125.8 (2 C), 126.2, 126.7, 127.8, 128.8 (2 C), 131.2, 146.9, 157.1

HRMS (ESI) m/z: calcd for $C_{24}H_{33}N_4O_3$ $[M+H]^+$ 425.2547, found 425.2557.

tert-Butyl (1RS,2RS,6RS)-2-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)-1-hydroxy-8-azaspiro[5.6]dodec-10-ene-8-carboxylate (26)



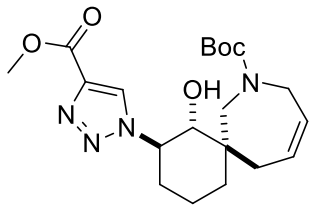
Rf = 0.4 in 2:1 hexanes/EtOAc, white powder. M=0.55 g. Yield=81%. mp = 106-109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): ***δ*** 1.32 - 1.53 (m, 11 H), 1.60 (dd, J=14.4, 8.9 Hz, 1 H), 1.72 - 1.77 (m, 1 H), 1.98 - 2.13 (m, 2 H), 2.26 - 2.34 (m, 1 H), 2.92 (d, J=15.1 Hz, 1 H), 3.07 (ddd, J=14.2, 5.1, 2.4 Hz, 1 H), 3.52 (t, J=10.9 Hz, 1 H), 3.65 (dt, J=18.3, 1.6 Hz, 1 H), 4.08 (d, J=14.9 Hz, 1 H), 4.51 - 4.64 (m, 2 H), 4.83 (d, J=11.3 Hz, 1 H), 5.41 - 5.49 (m, 1 H), 5.68 - 5.77 (m, 1 H), 7.06 - 7.13 (m, 2 H), 7.78 - 7.85 (m, 2 H), 7.89 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): ***δ*** 20.2, 28.5 (3 C), 32.6, 34.2, 37.0, 47.7, 49.9, 50.7, 63.8, 78.4, 81.7, 115.7 (d, J=21.7 Hz), 119.8, 126.2, 126.7, 127.5, 127.6 (d, J=8.1 Hz), 146.1, 157.1, 162.6 (d, J=246.4 Hz).

HRMS (ESI) m/z: calcd for $C_{24}H_{32}FN_4O_3$ $[M+H]^+$ 443.2453, found 443.2449.

tert-Butyl (1RS,2RS,6RS)-1-hydroxy-2-(4-(methoxycarbonyl)-1H-1,2,3-triazol-1-yl)-8-azaspiro[5.6]dodec-10-ene-8-carboxylate (27)



Rf = 0.5 in 1:1 hexanes/EtOAc, white powder. M=0.64 g. Yield=73%. mp = 101-104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): ***δ*** 1.35 - 1.49 (m, 10 H), 1.57 (dd J=14.3, 9.0 Hz, 1 H), 1.74 (d, J=12.3 Hz, 2 H), 1.97 - 2.14 (m, 2 H), 2.28 (d, J=13.8 Hz, 1 H), 2.87 (d, J=15.2 Hz, 1 H), 3.01 - 3.10 (m, 1 H), 3.46 (t, J=11.0 Hz, 1 H), 3.62 (d, J=18.2 Hz, 1 H), 3.93 (s, 3 H), 4.05 (d, J=15.0 Hz, 1 H), 4.49 - 4.64 (m, 2 H), 4.88 (d, J=11.5 Hz, 1 H), 5.40 - 5.47 (m, 1 H), 5.66 - 5.77 (m, 1 H), 8.26 (s, 1 H).

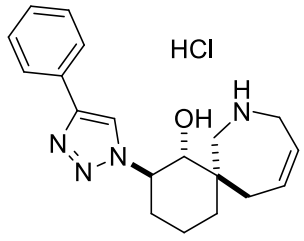
^{13}C NMR (100 MHz, $CDCl_3$): ***δ*** 20.1, 28.4 (3 C), 32.3, 33.9, 37.0, 47.7, 49.9, 50.7, 52.1, 64.3, 78.1, 81.8, 126.2, 126.5, 128.2, 139.1, 157.2, 161.6.

HRMS (ESI) m/z: calcd for $C_{20}H_{31}N_4O_5$ $[M+H]^+$ 407.2289, found 407.2290.

*General procedure for synthesis **28-30**:*

To the Boc-protected compound **25-27** in MeOH (1M), 1 M HCl in methanol (50 mL) (prepared by dropwise addition of AcCl to MeOH) was added. The resulting solution was stirred overnight at the room temperature and then the solvent was evaporated. The precipitate was triturated in Et_2O (50 mL) and filtered. The product was washed with Et_2O (30 mL) and CH_2Cl_2 (30 mL), then dried on rotary evaporator under reduced pressure.

(1RS,2RS,6RS)-2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-8-azaspiro[5.6]dodec-10-en-1-ol hydrochloride (28)



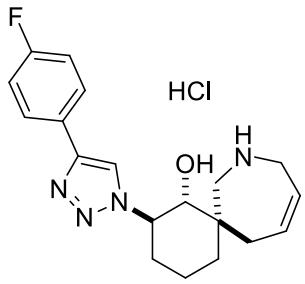
White powder, M=0.173 g. Yield=99%. mp = 173-174 °C.

^{1}H NMR (400 MHz, DMSO-d6): ***δ*** 1.19 - 1.30 (m, 1 H), 1.44 - 1.65 (m, 2 H), 1.87 - 2.09 (m, 4 H), 2.93 (d, J=14.5 Hz, 1 H), 3.25 - 3.34 (m, 1 H), 3.35 - 3.44 (m, 1 H), 3.53 - 3.77 (m, 3 H), 4.51 - 4.60 (m, 1 H), 5.60 - 5.68 (m, 1 H), 5.88 - 5.97 (m, 1 H), 7.32 (t, J=7.4 Hz, 1 H), 7.44 (t, J=7.6 Hz, 2 H), 7.84 (d, J=7.2 Hz, 2 H), 8.63 (s, 1 H), 9.05 - 9.29 (m, 2 H)

^{13}C NMR (100 MHz, DMSO-*d_6*): ***δ*** 19.4, 31.9, 32.0, 36.4, 42.5, 46.1, 48.3, 61.6, 77.7, 120.9, 123.2, 125.0 (2 C), 127.7, 128.9 (2 C), 131.1, 131.2, 145.6

HRMS (ESI) m/z: calcd for $C_{19}H_{25}N_4O$ $[M+H]^+$ 325.2023, found 325.2031.

(1RS,2RS,6RS)-2-(4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)-8-azaspiro[5.6]dodec-10-en-1-ol hydrochloride (29)



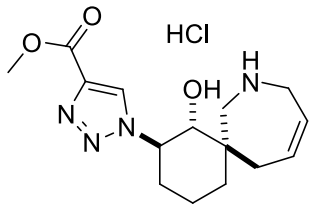
White powder, M=0.251 g. Yield=98%. mp = 183-185 °C.

^{1}H NMR (400 MHz, DMSO-d6): ***δ*** 1.24 (td, J=13.5, 4.0 Hz, 1 H), 1.44 - 1.66 (m, 2 H), 1.86 - 2.11 (m, 4 H), 2.93 (d, J=14.5 Hz, 1 H), 3.25 - 3.43 (m, 2 H), 3.52 - 3.75 (m, 3 H), 4.49 - 4.59 (m, 1 H), 5.58 - 5.68 (m, 1 H), 5.87 - 5.97 (m, 1 H), 7.23 - 7.32 (m, 2 H), 7.83 - 7.92 (m, 2 H), 8.64 (s, 1 H), 9.07 - 9.42 (m, 2 H).

^{13}C NMR (100 MHz, DMSO- ***d_6*****):** ***δ*** 19.4, 31.9, 32.0, 36.5, 42.5, 46.0, 48.2, 61.6, 77.7, 115.8 (d, J=21.7 Hz) 120.9, 123.2, 127.0 (d, J=8.1 Hz), 127.6 (d, J=3.0 Hz), 131.2, 144.7, 161.7 (d, J=244.2 Hz).

HRMS (ESI) m/z: calcd for $C_{19}H_{24}FN_4O$ $[M+H]^+$ 343.1929, found 343.1933.

Methyl 1-((1RS,2RS,6RS)-1-hydroxy-8-azaspiro[5.6]dodec-10-en-2-yl)-1H-1,2,3-triazole-4-carboxylate hydrochloride (30)



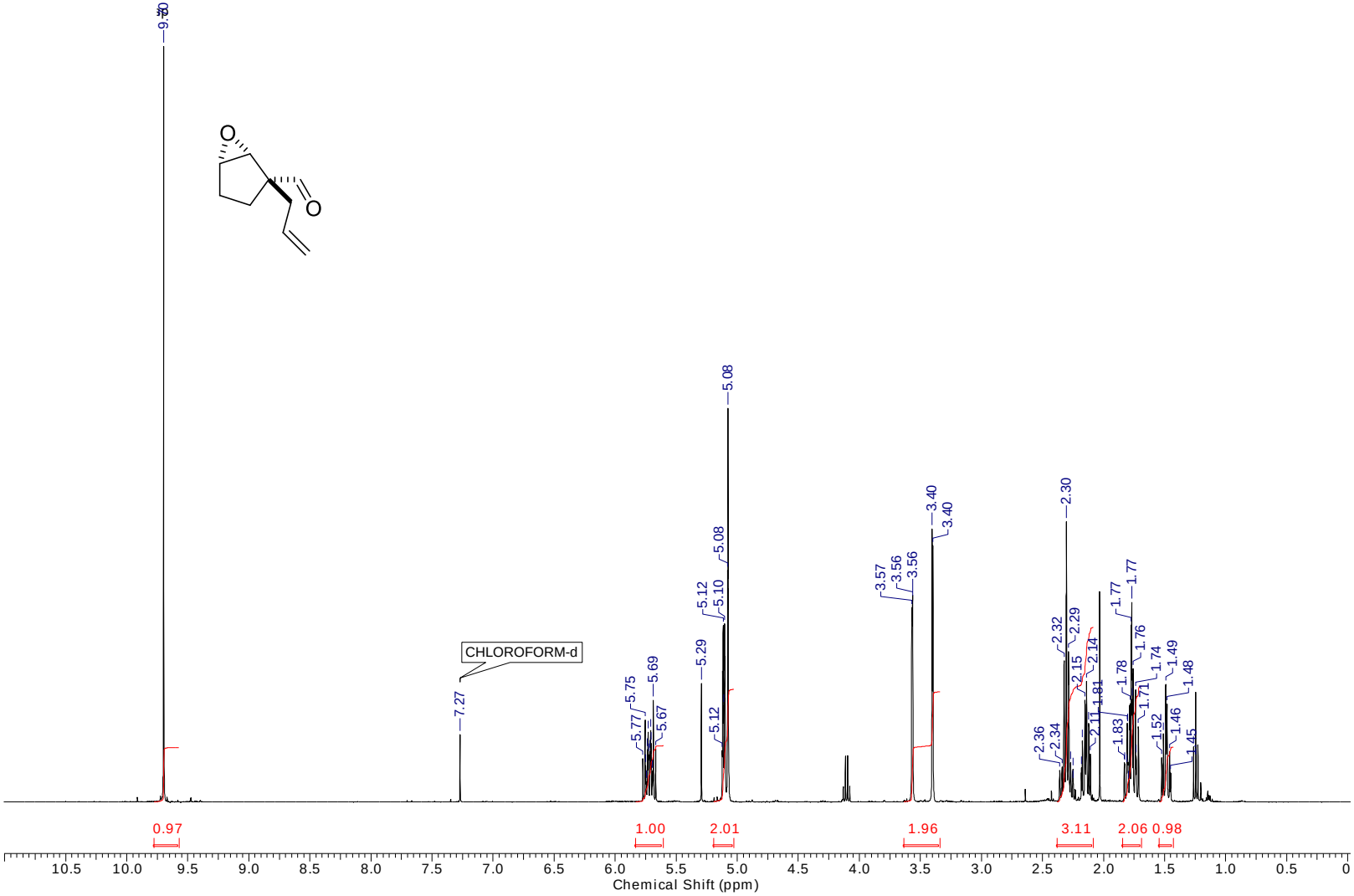
White powder, M=0.293 g. Yield=99%. mp > 170 °C (decomp.).

^{1}H NMR (400 MHz, DMSO-d6): ***δ*** 1.24 (td, J=13.7, 3.6 Hz, 1 H), 1.39 - 1.63 (m, 2 H), 1.86 - 2.06 (m, 4 H), 2.91 (d, J=15.5 Hz, 1 H), 3.22 - 3.30 (m, 1 H), 3.33 - 3.41 (m, 1 H), 3.54 - 3.63 (m, 1 H), 3.69 (d, J=10.5 Hz, 2 H), 3.83 (s, 3 H), 4.63 (td, J=11.1, 5.0 Hz, 1 H), 5.39 - 6.02 (m, 3 H), 8.82 (s, 1 H), 9.03 - 9.24 (m, 2 H).

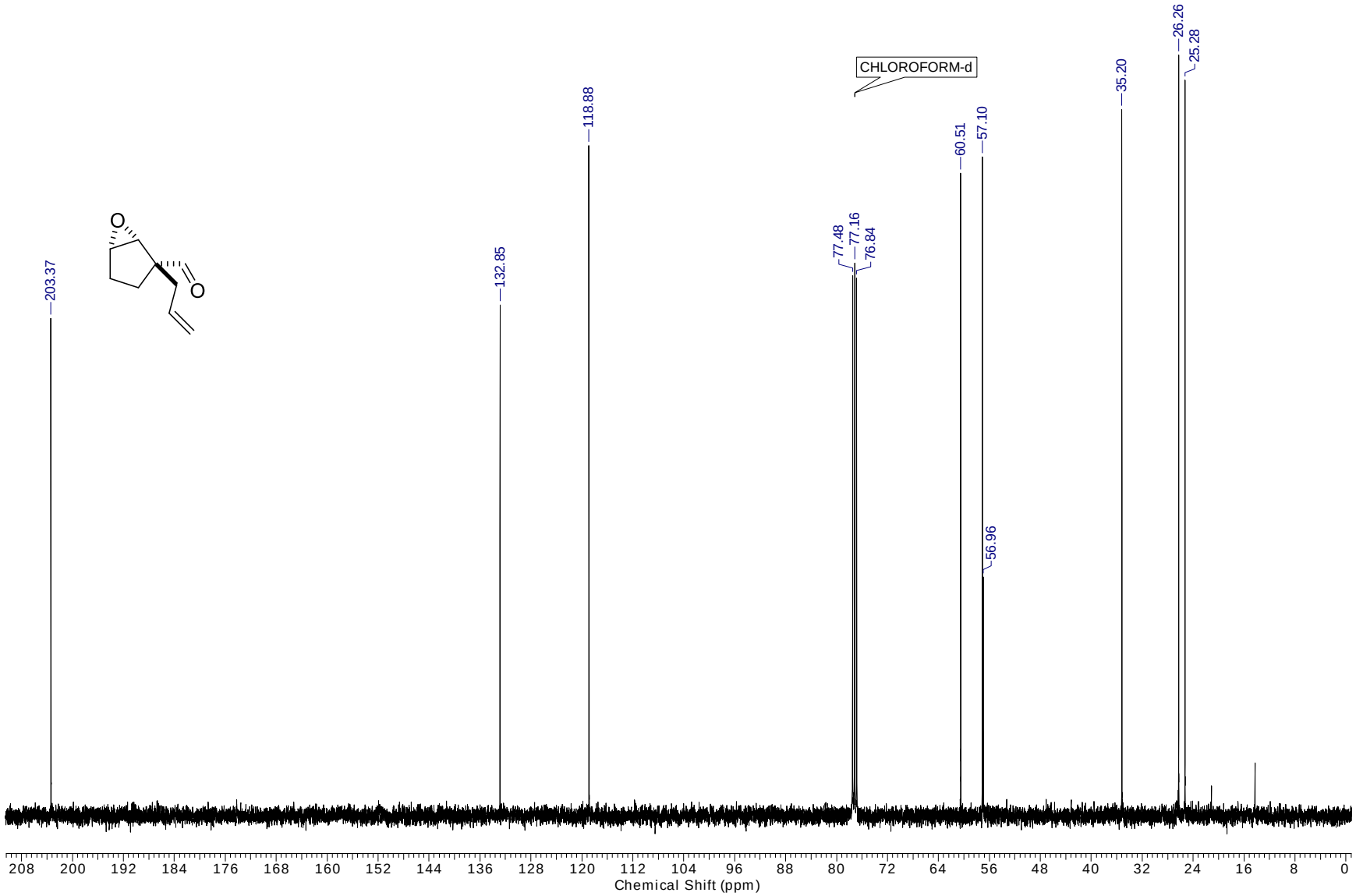
^{13}C NMR (100 MHz, DMSO- ***d_6*****):** ***δ*** 19.3, 31.5, 31.8, 36.3, 42.5, 46.1, 48.1, 51.7, 61.9, 77.4, 123.2, 128.6, 131.2, 138.1, 160.9.

HRMS (ESI) m/z: calcd for $C_{15}H_{23}N_4O_3$ $[M+H]^+$ 307.1765, found 307.1766.

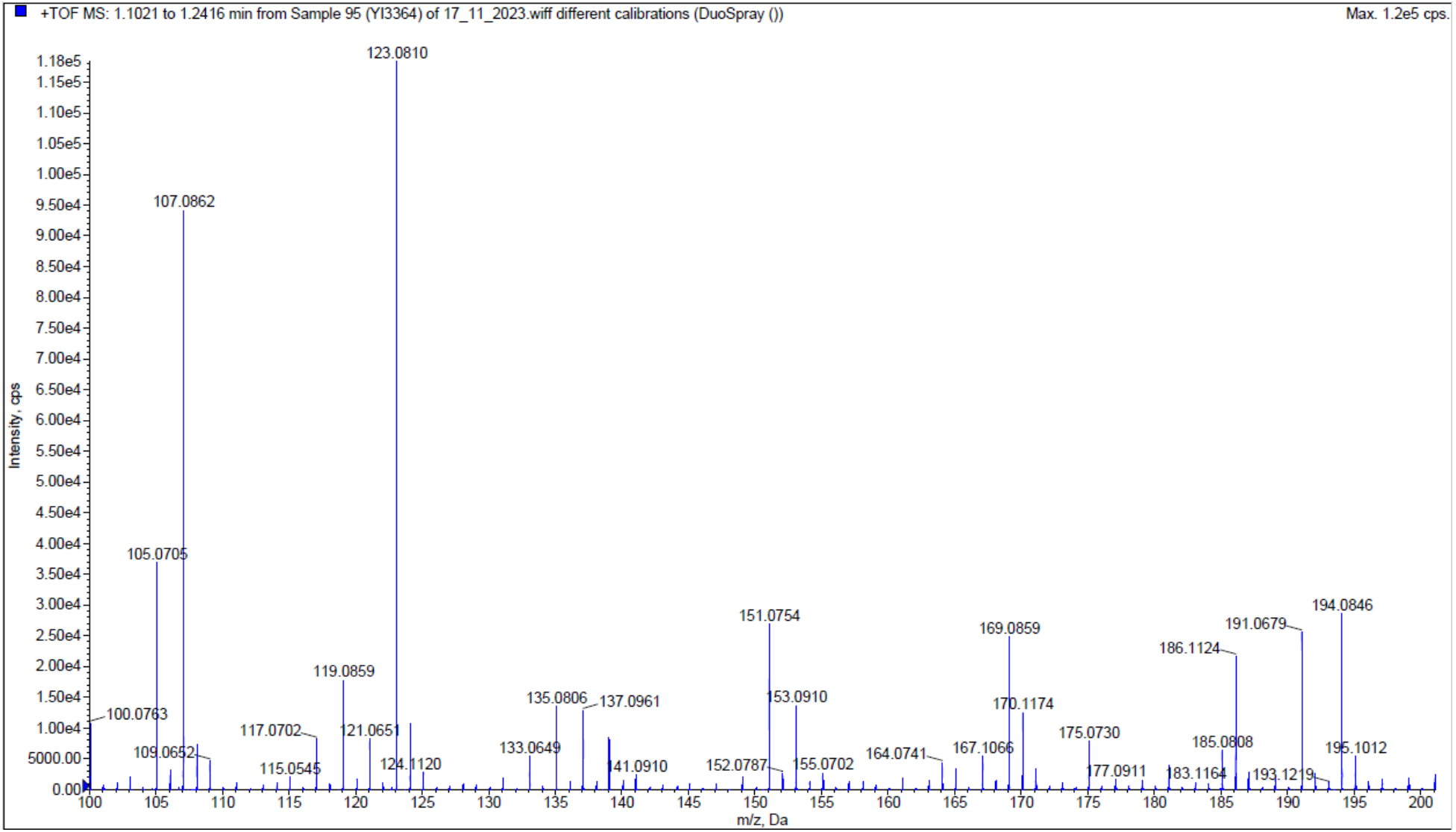
4. Spectral data of synthesized compounds



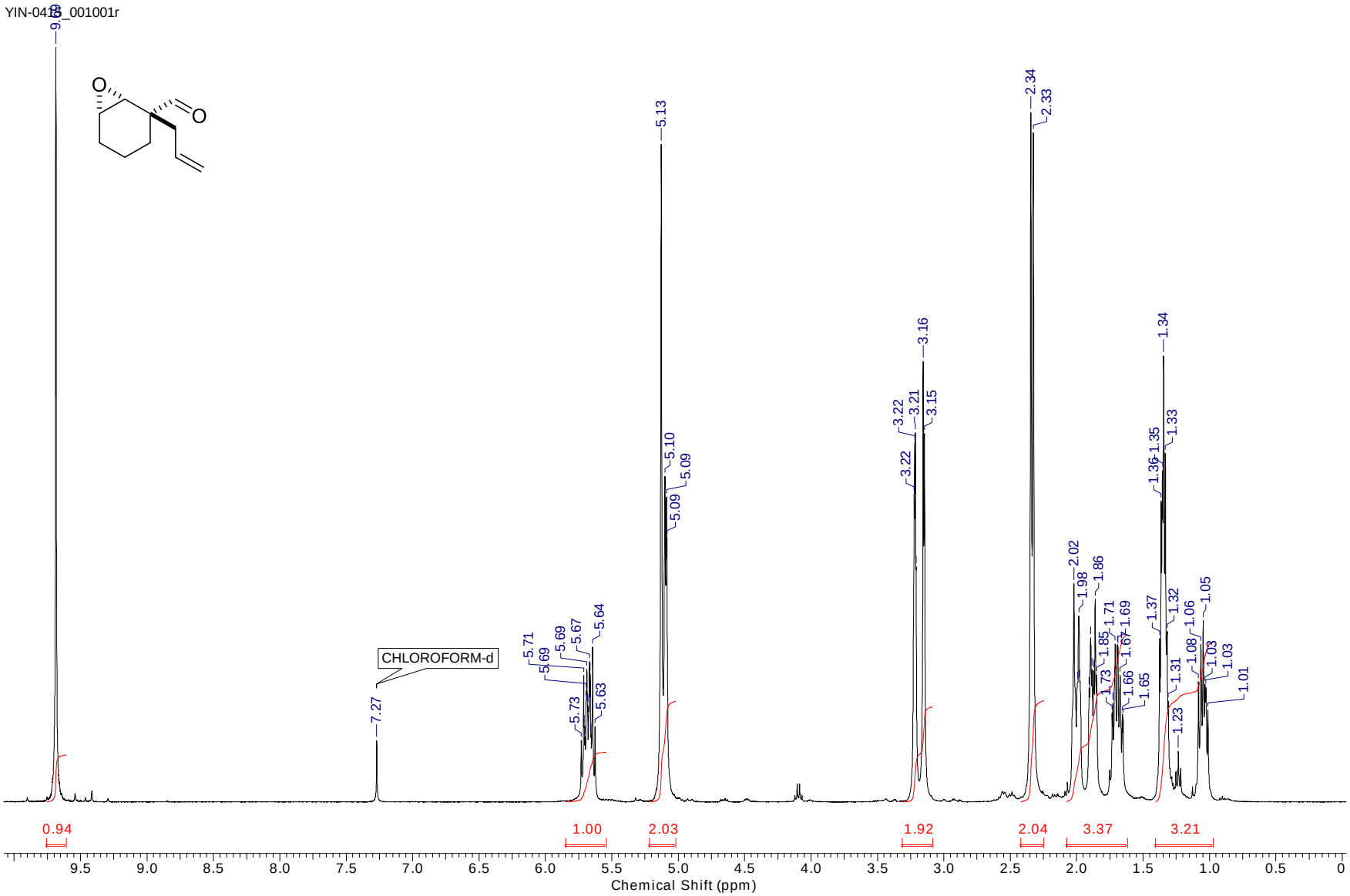
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 13



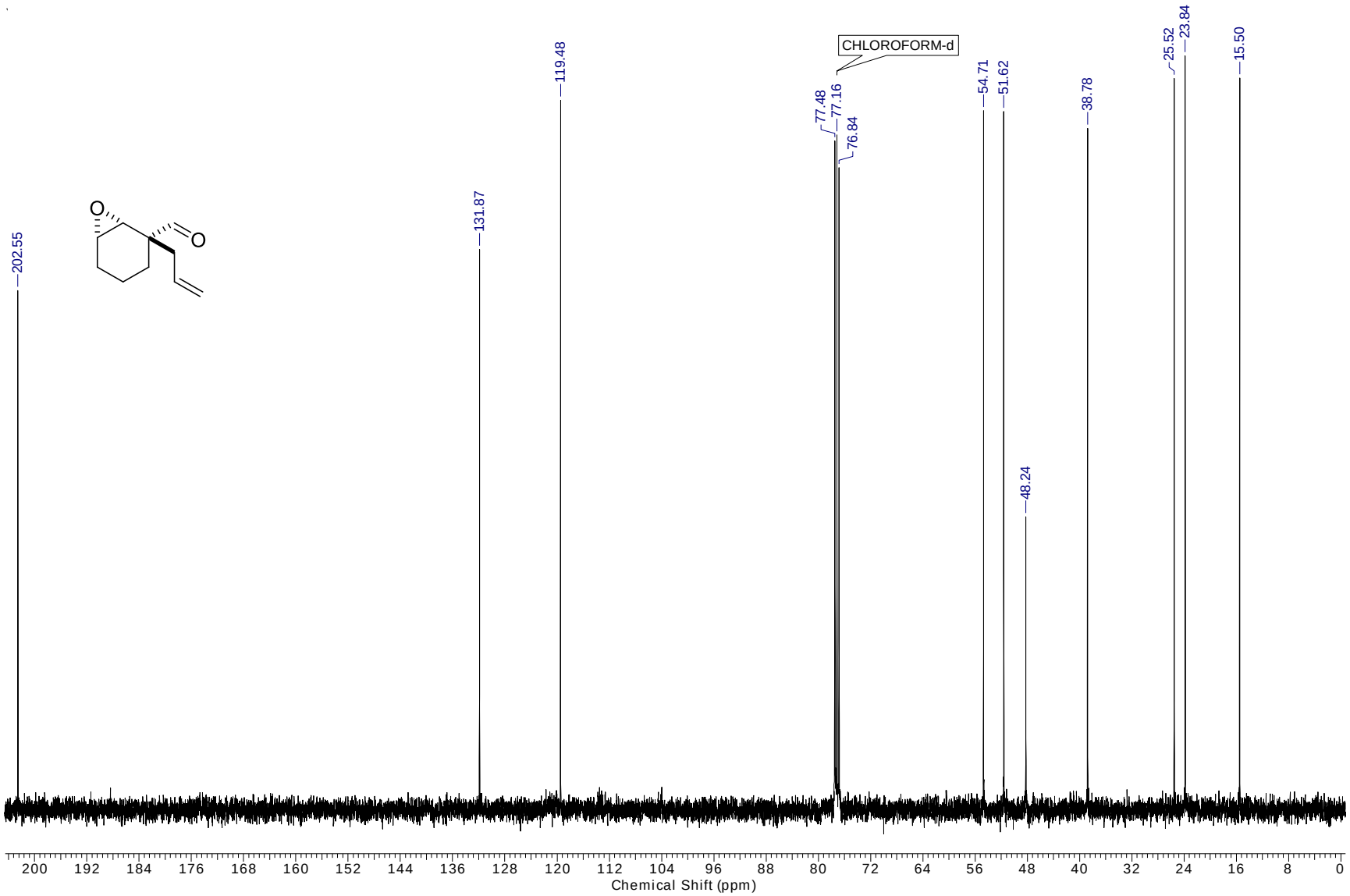
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 13



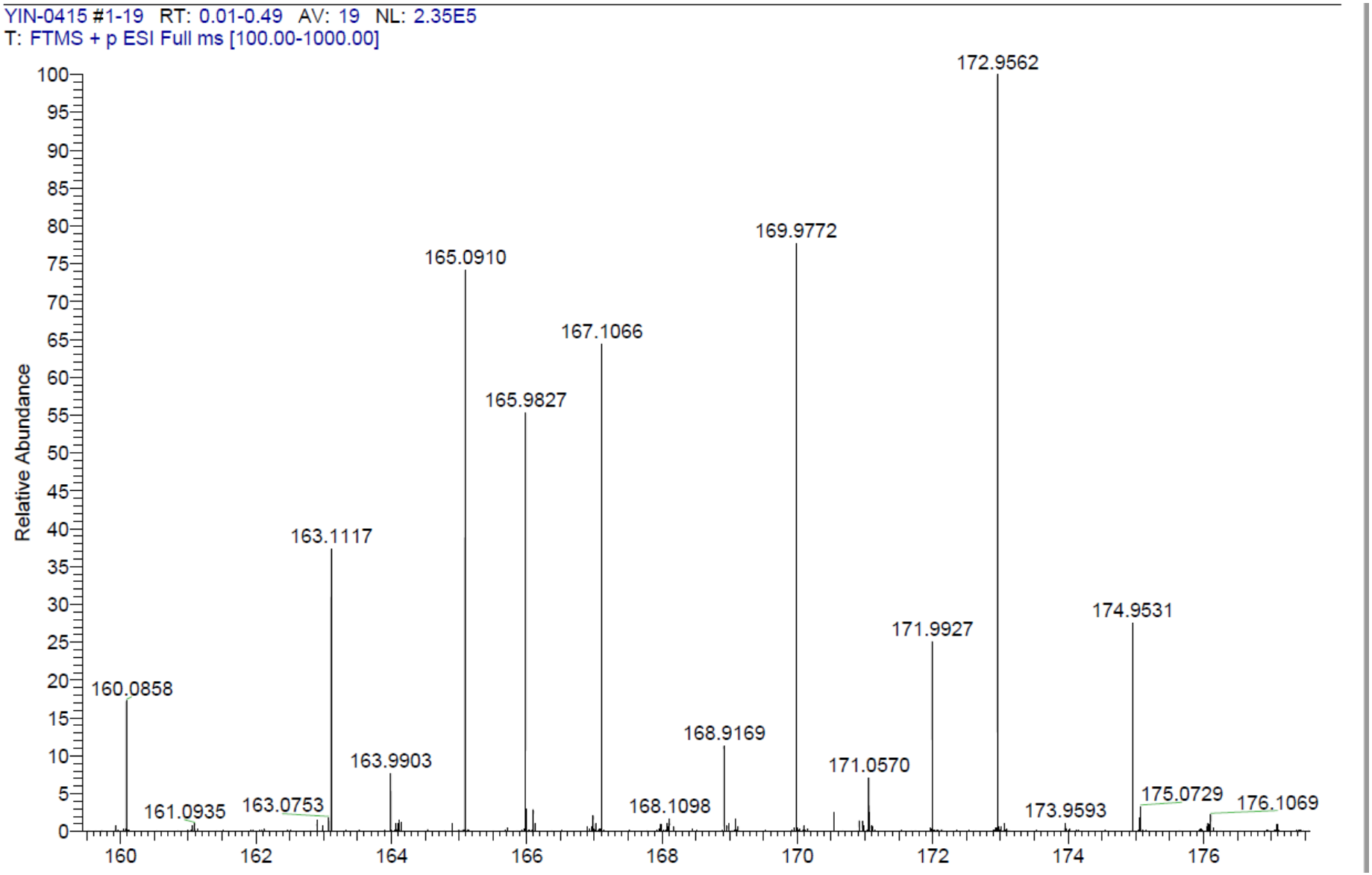
HRMS spectrum of 13



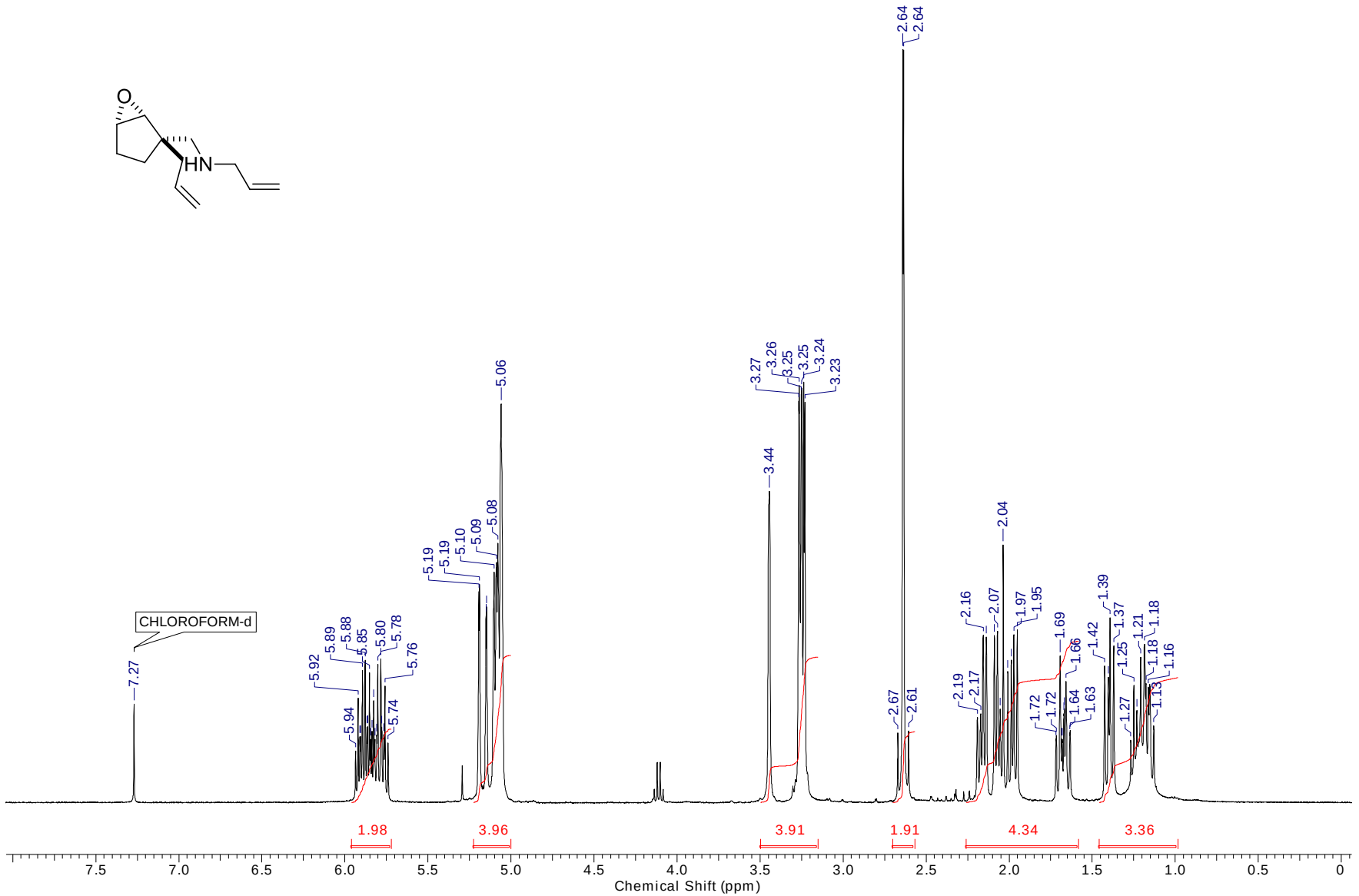
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 14



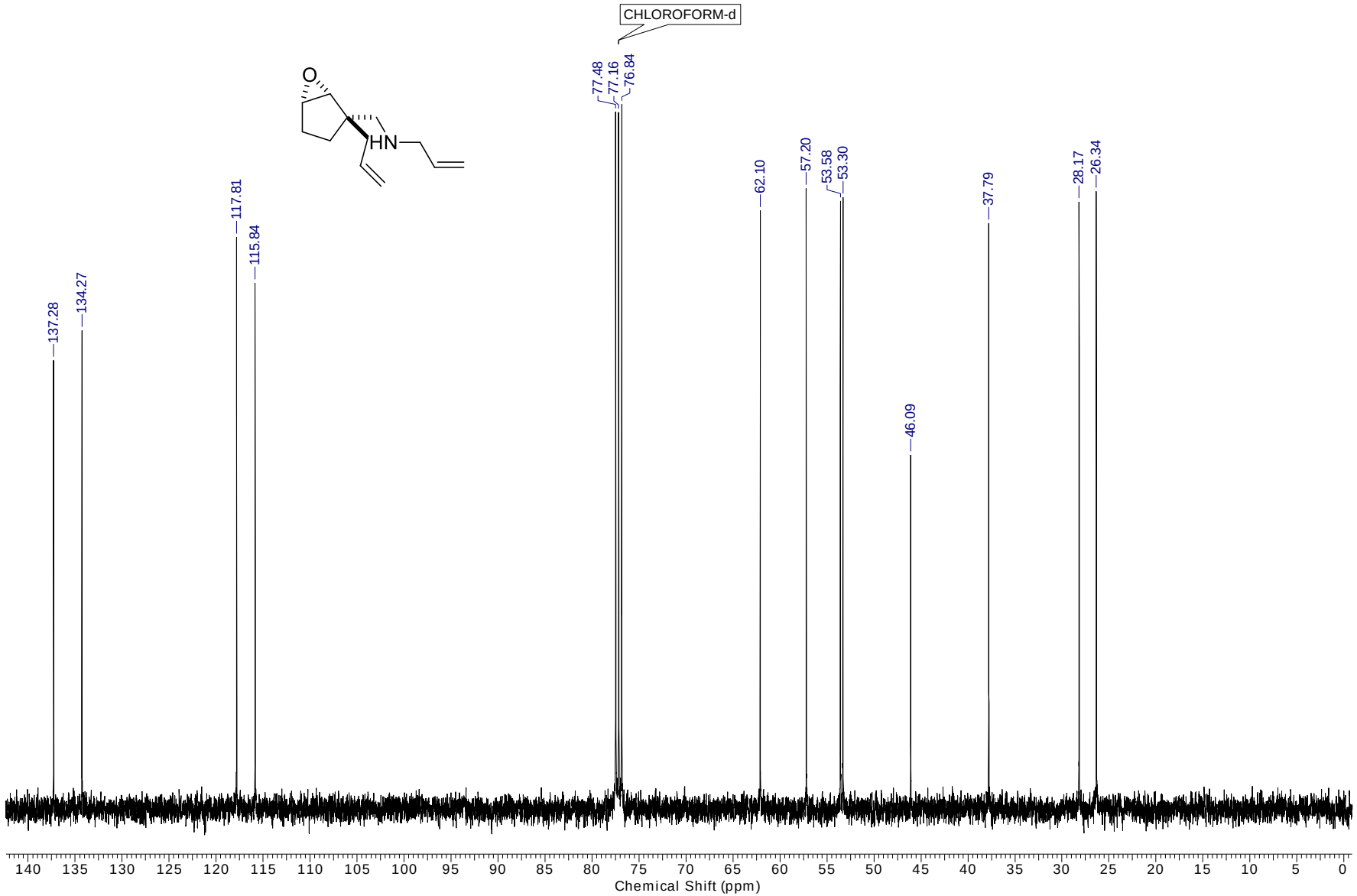
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 14



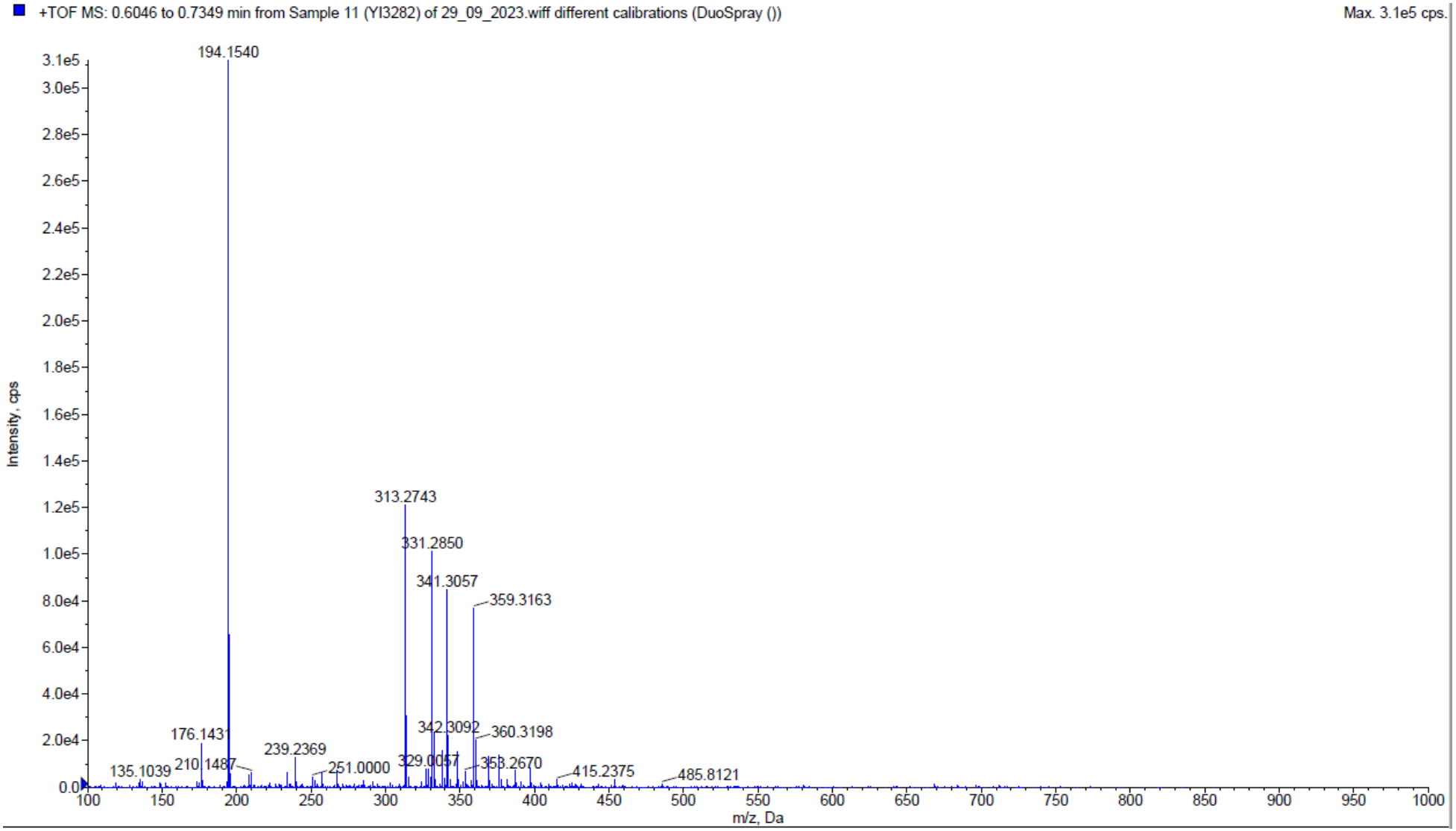
HRMS spectrum of 14



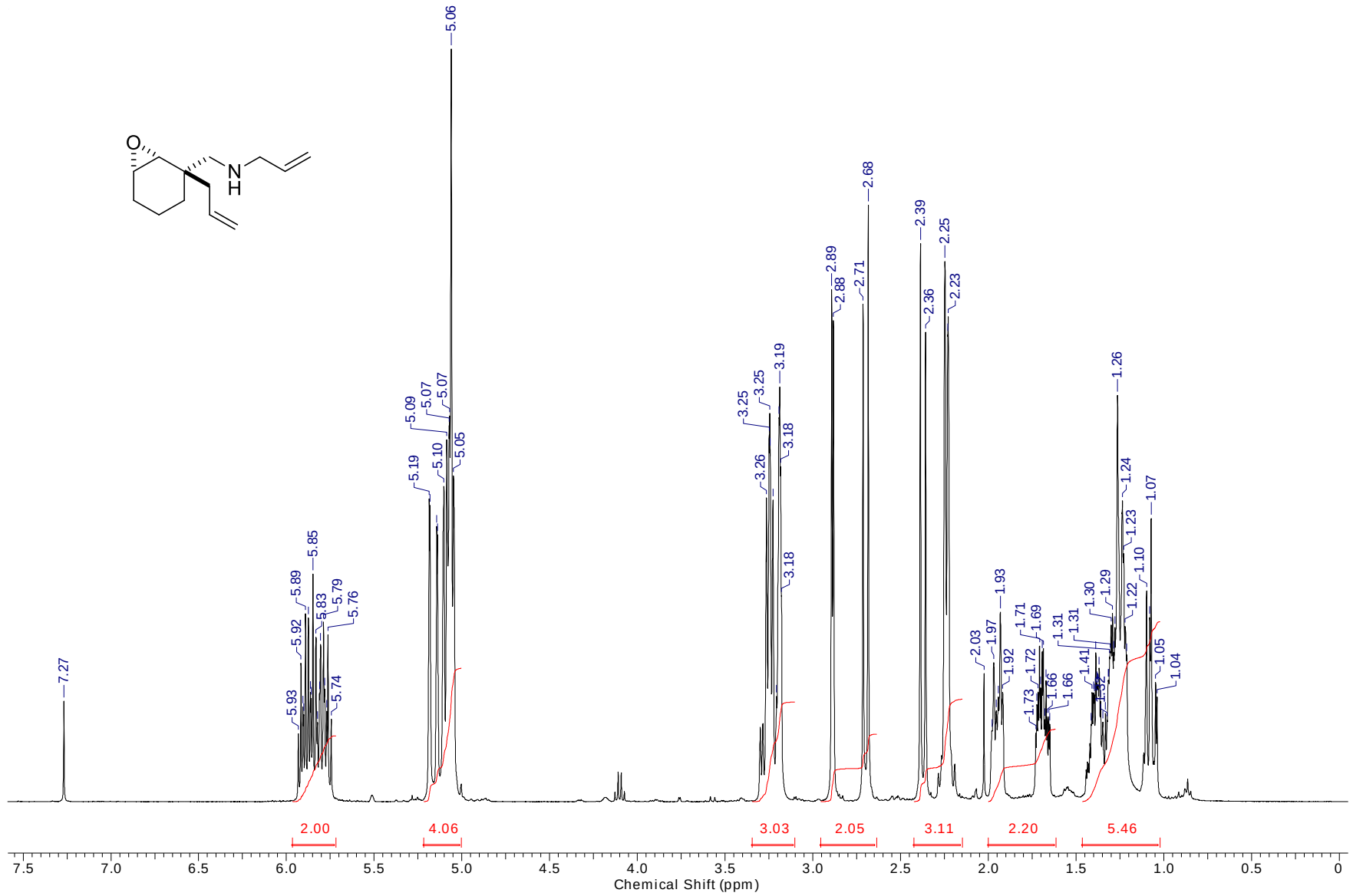
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 15



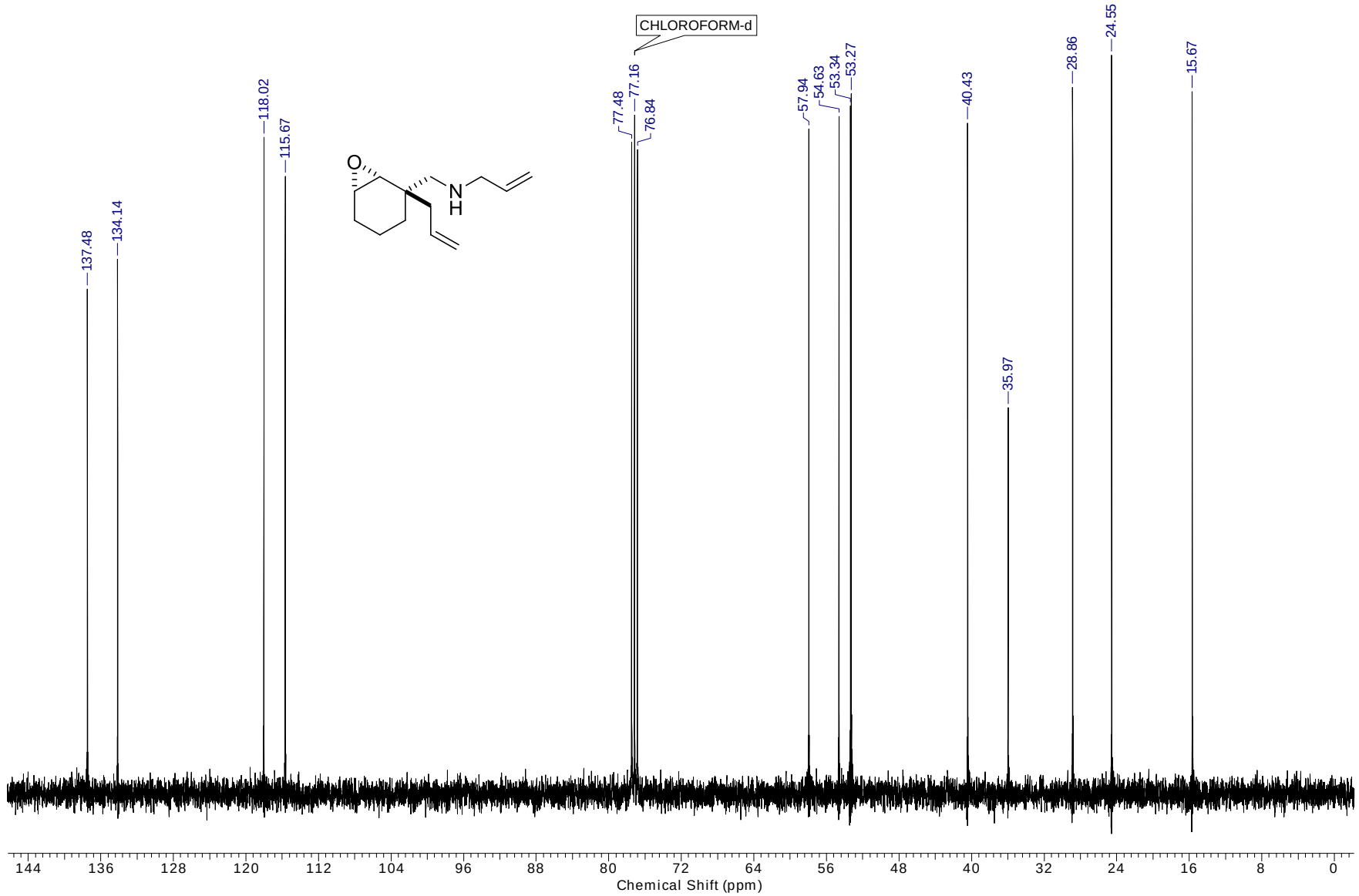
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 15



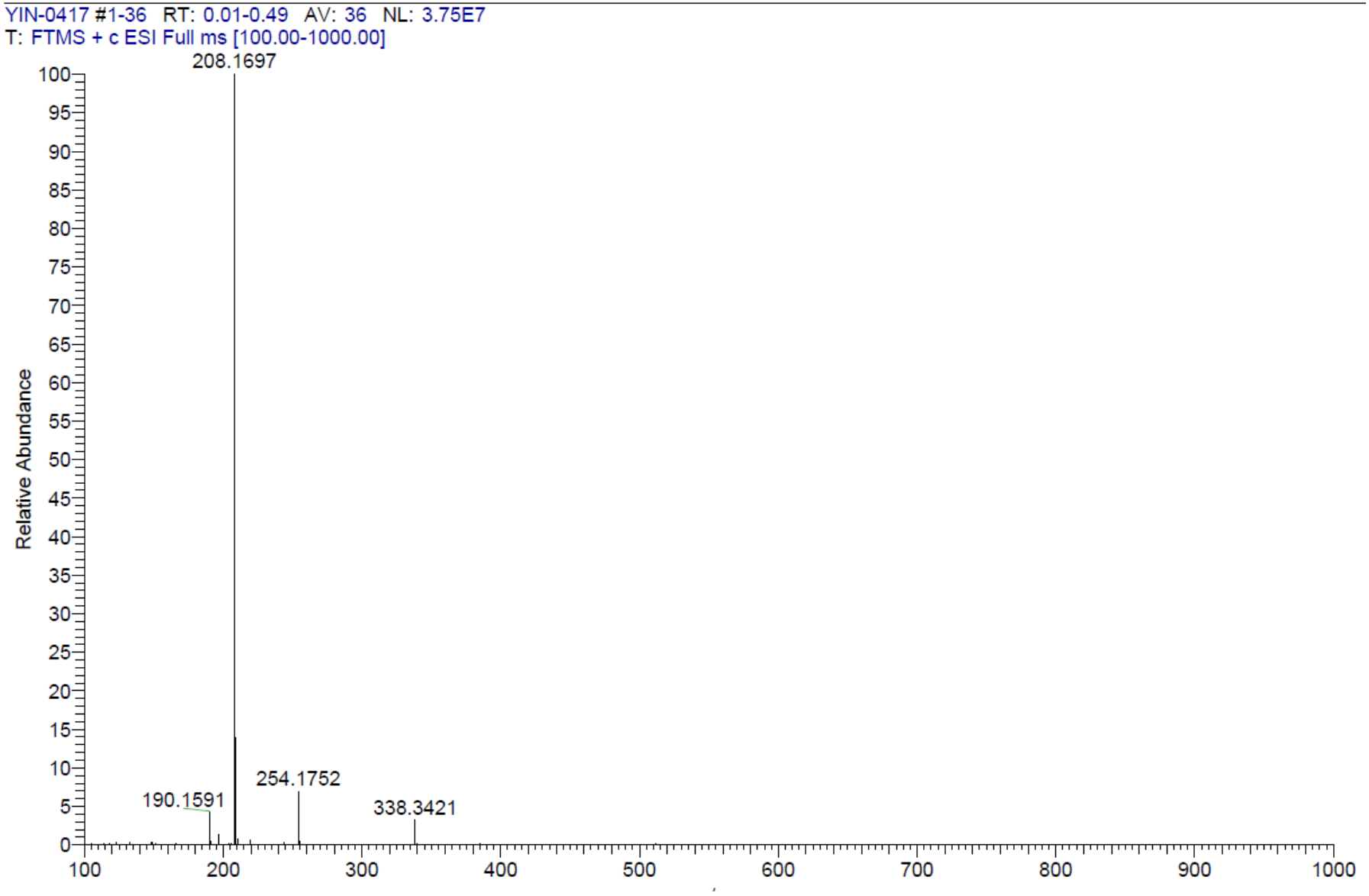
HRMS spectrum of 15



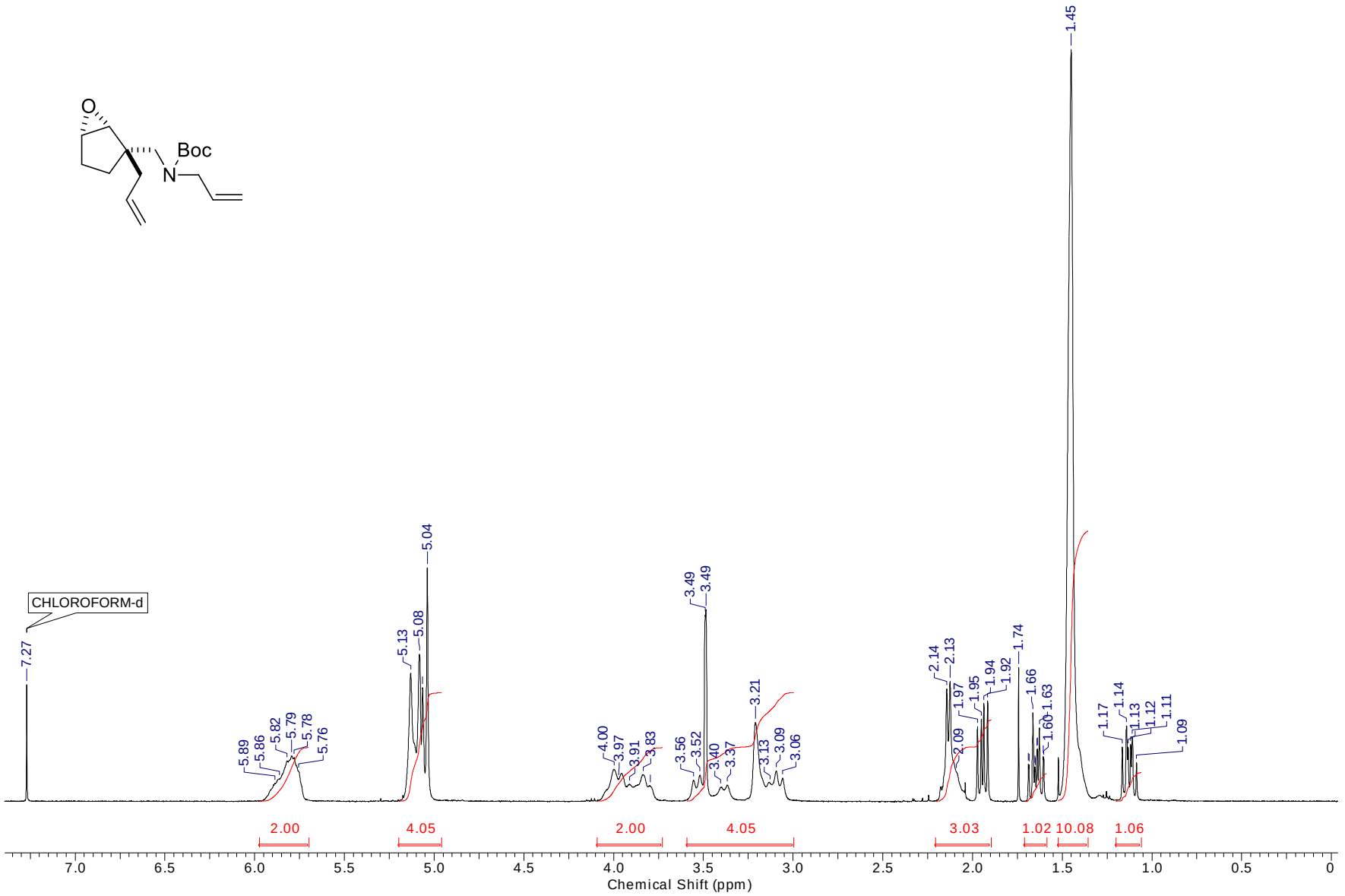
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 16



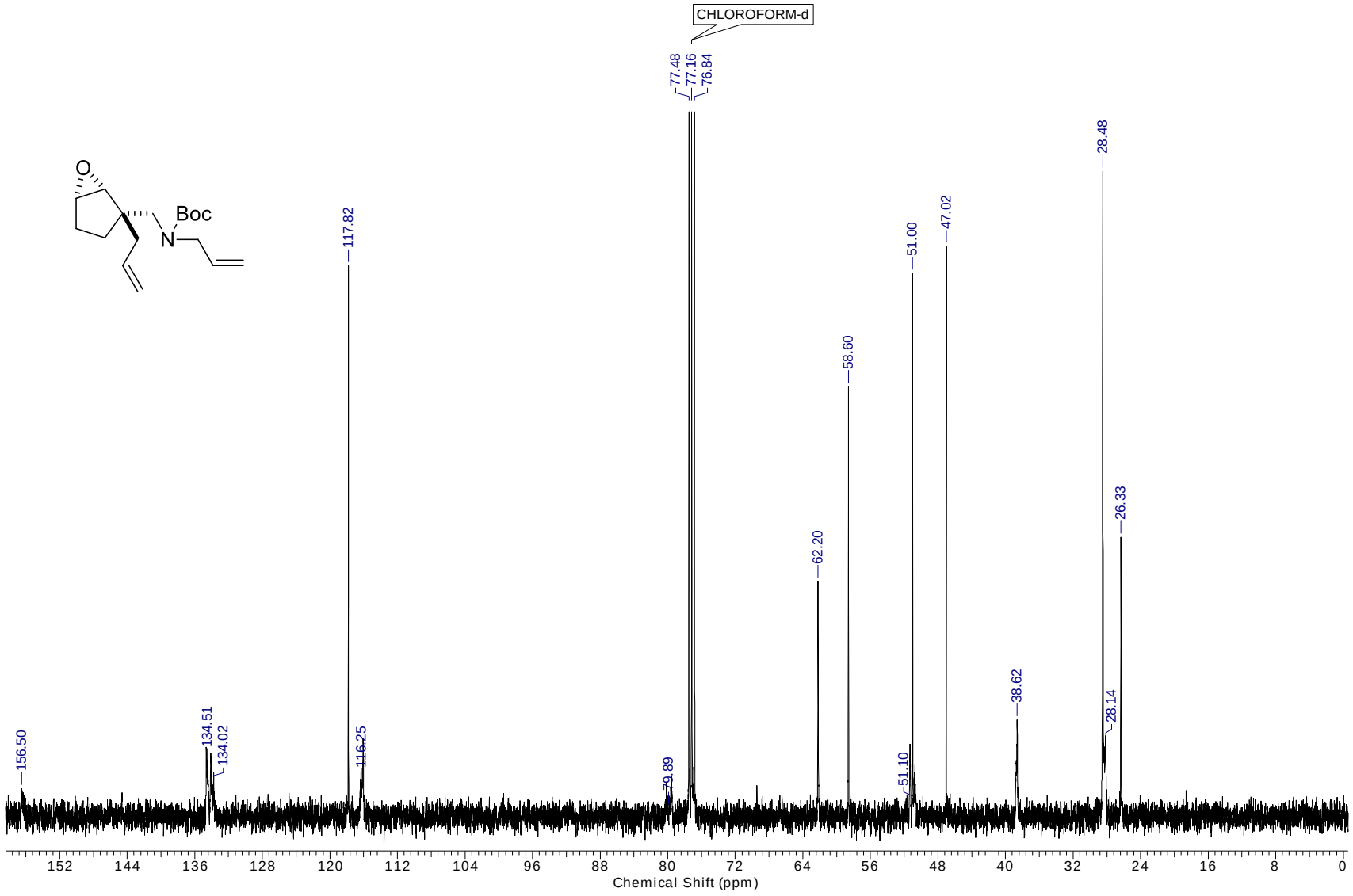
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 16



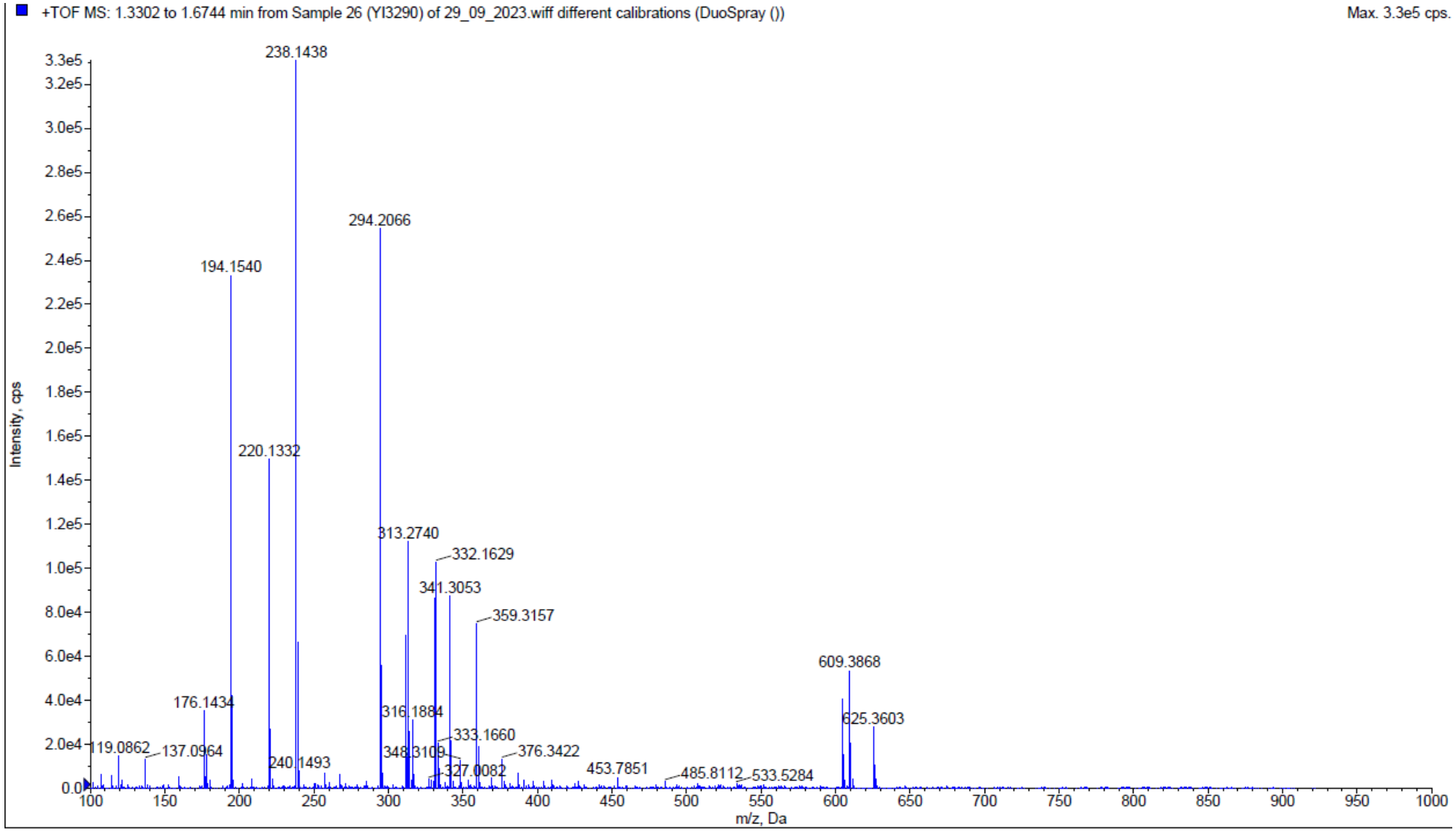
HRMS spectrum of 16



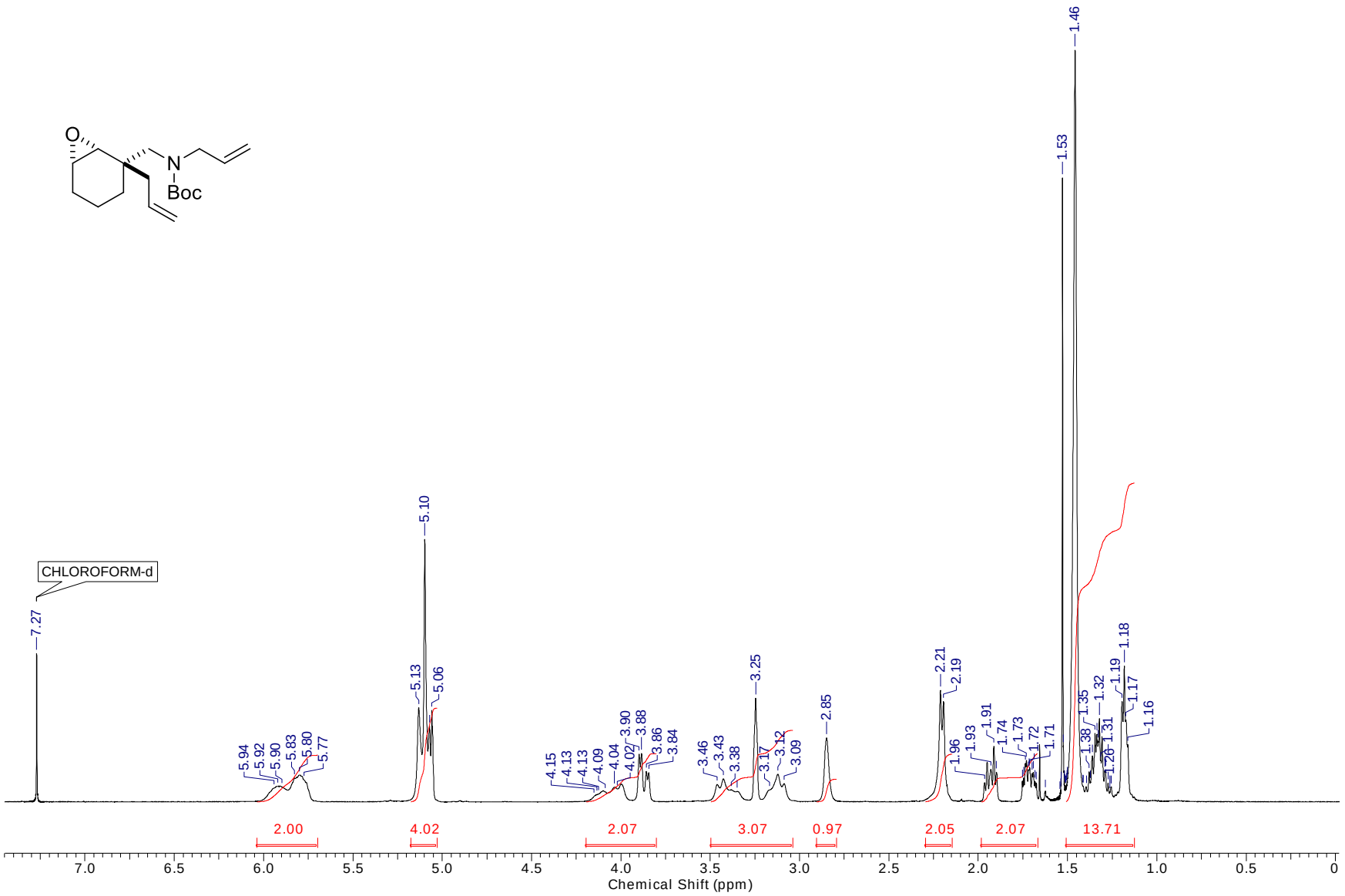
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 17



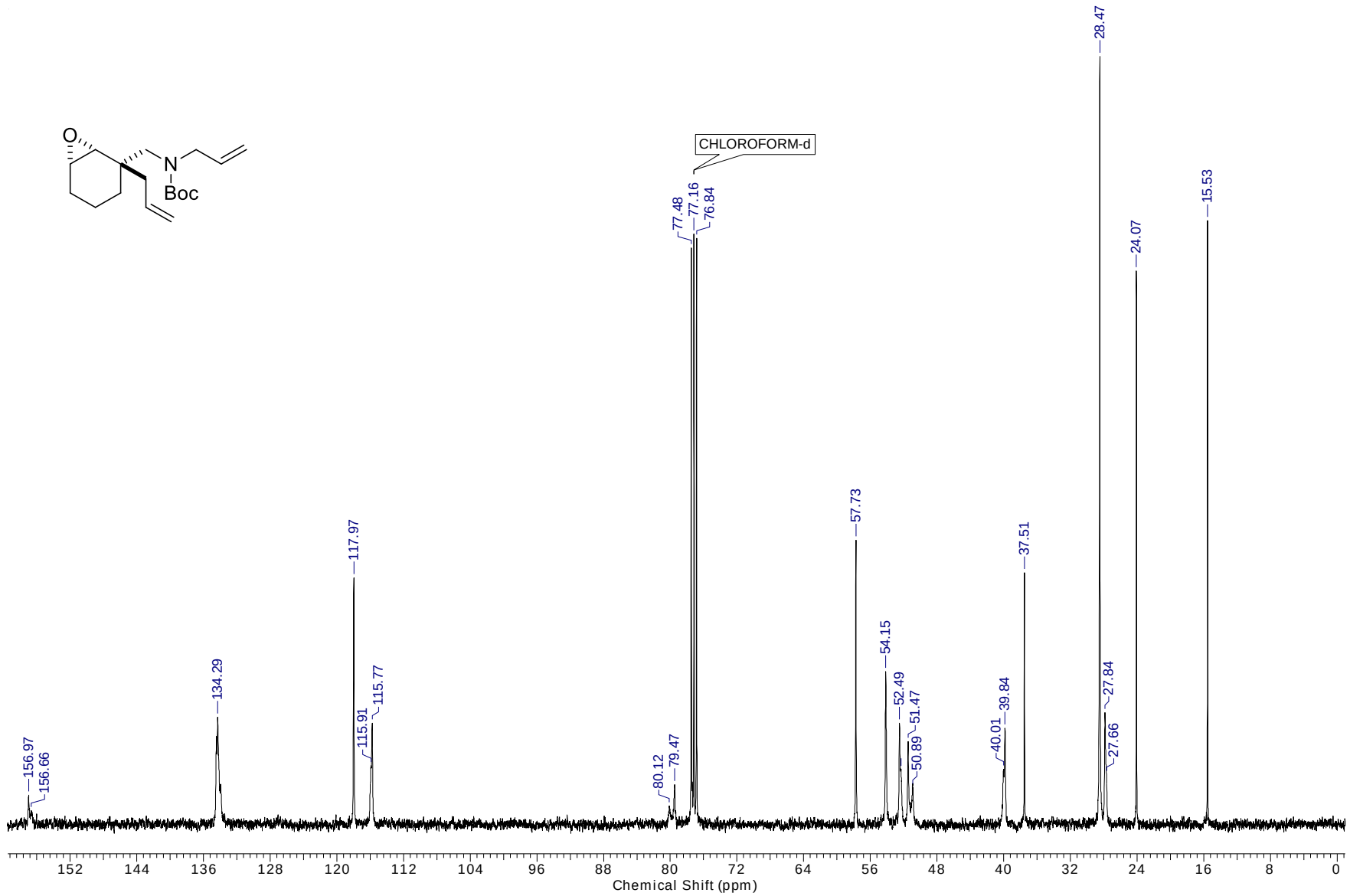
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 17



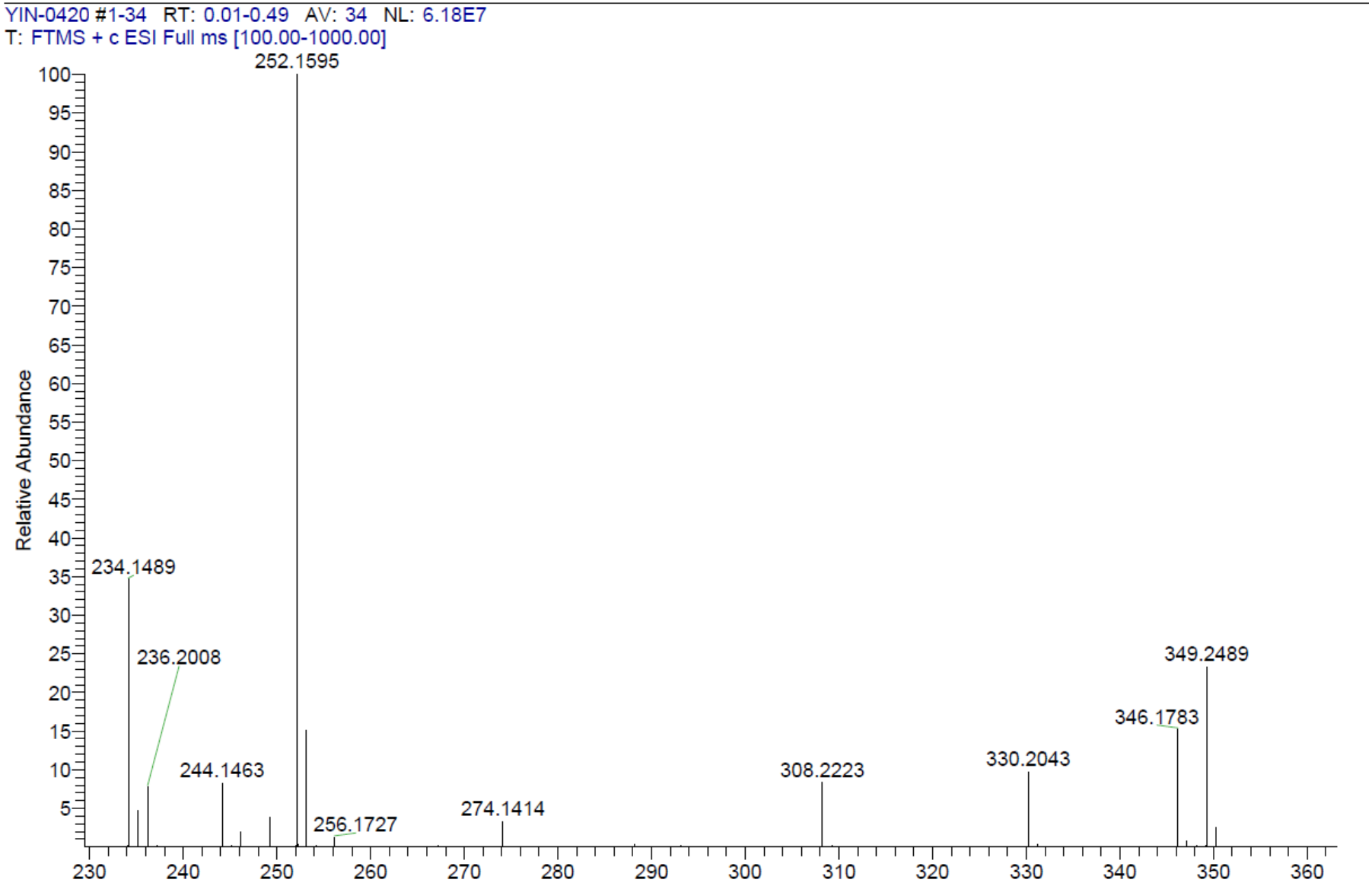
HRMS spectrum of 17



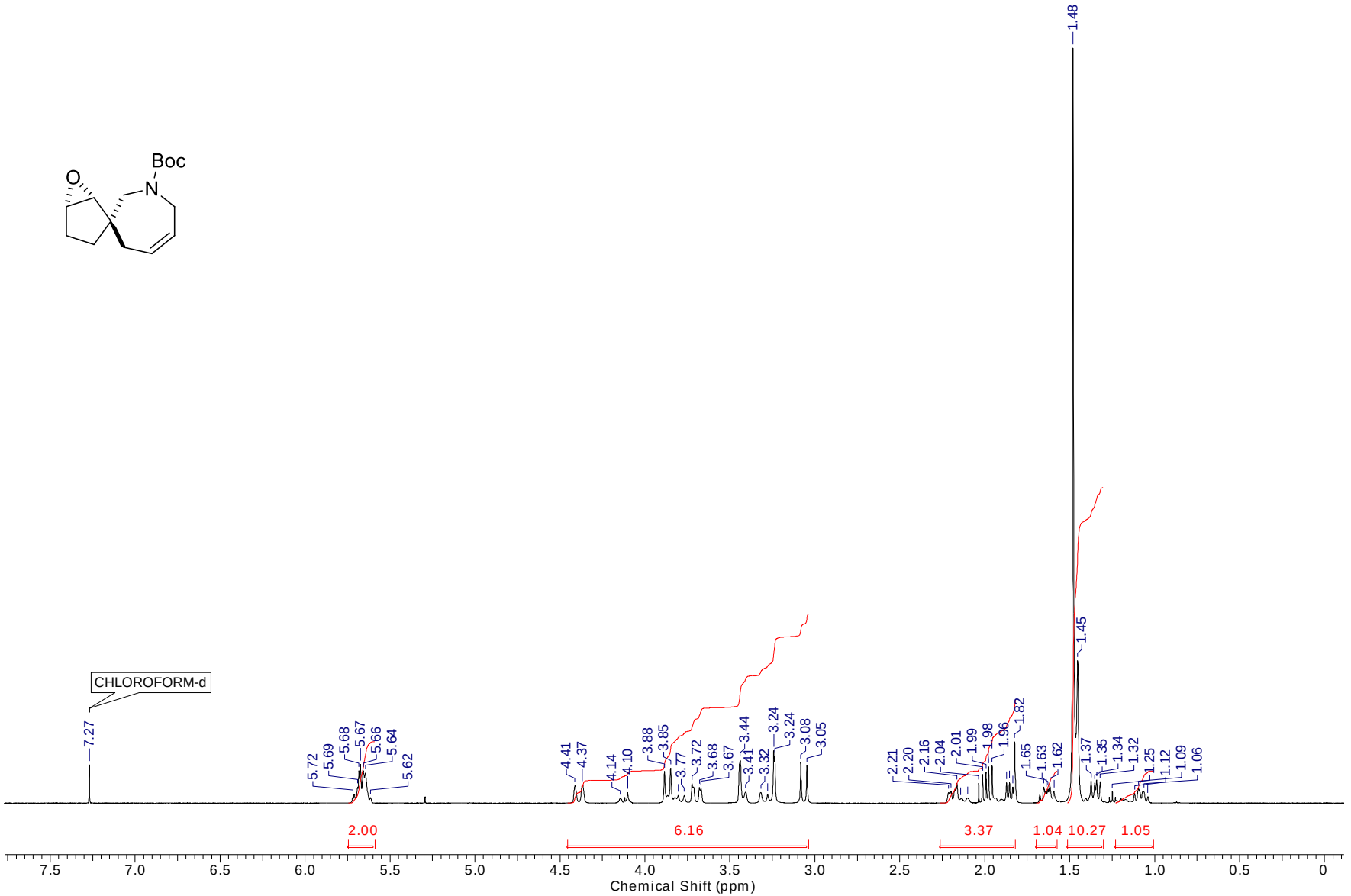
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 18



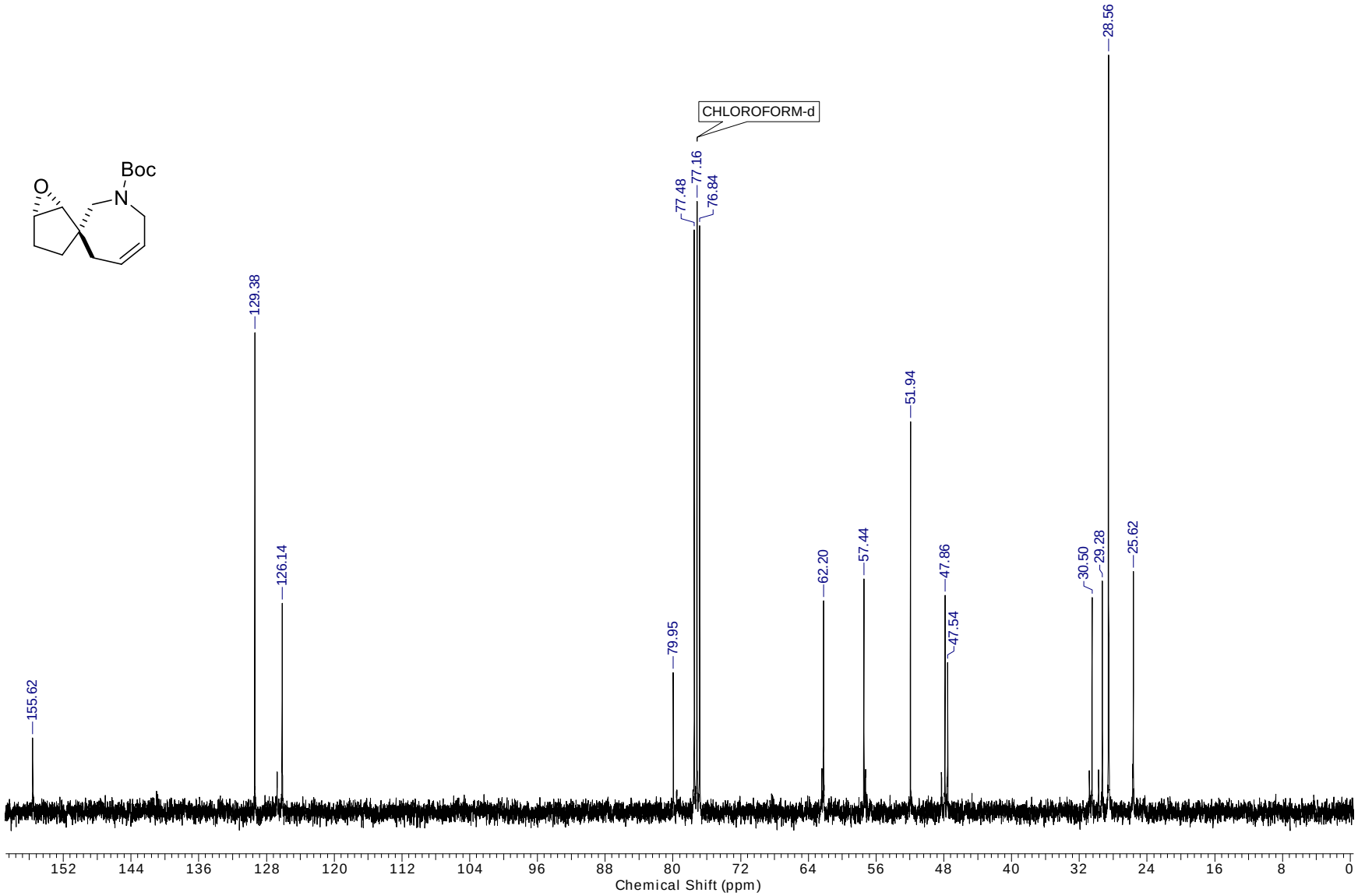
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 18



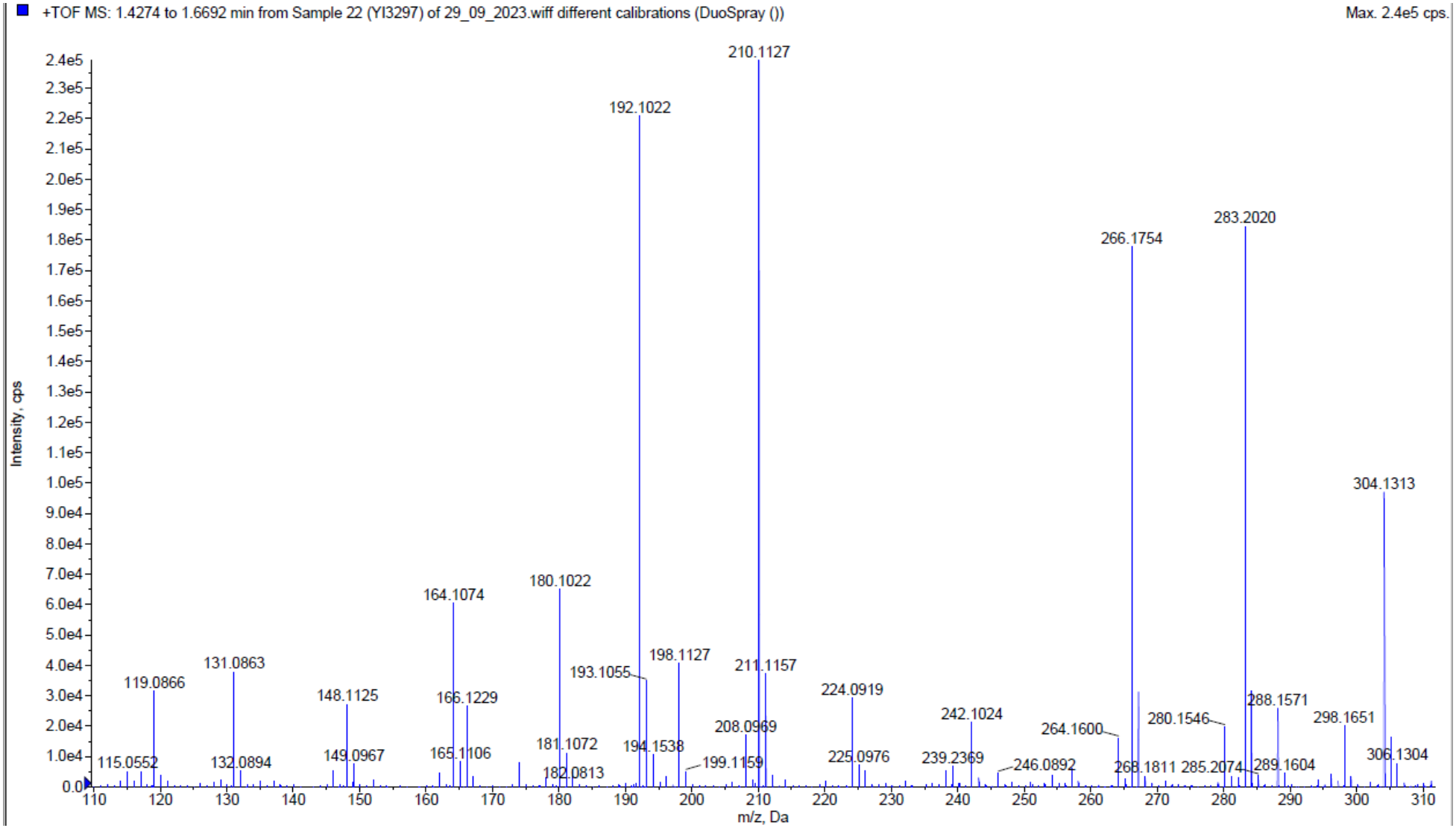
HRMS spectrum of 18



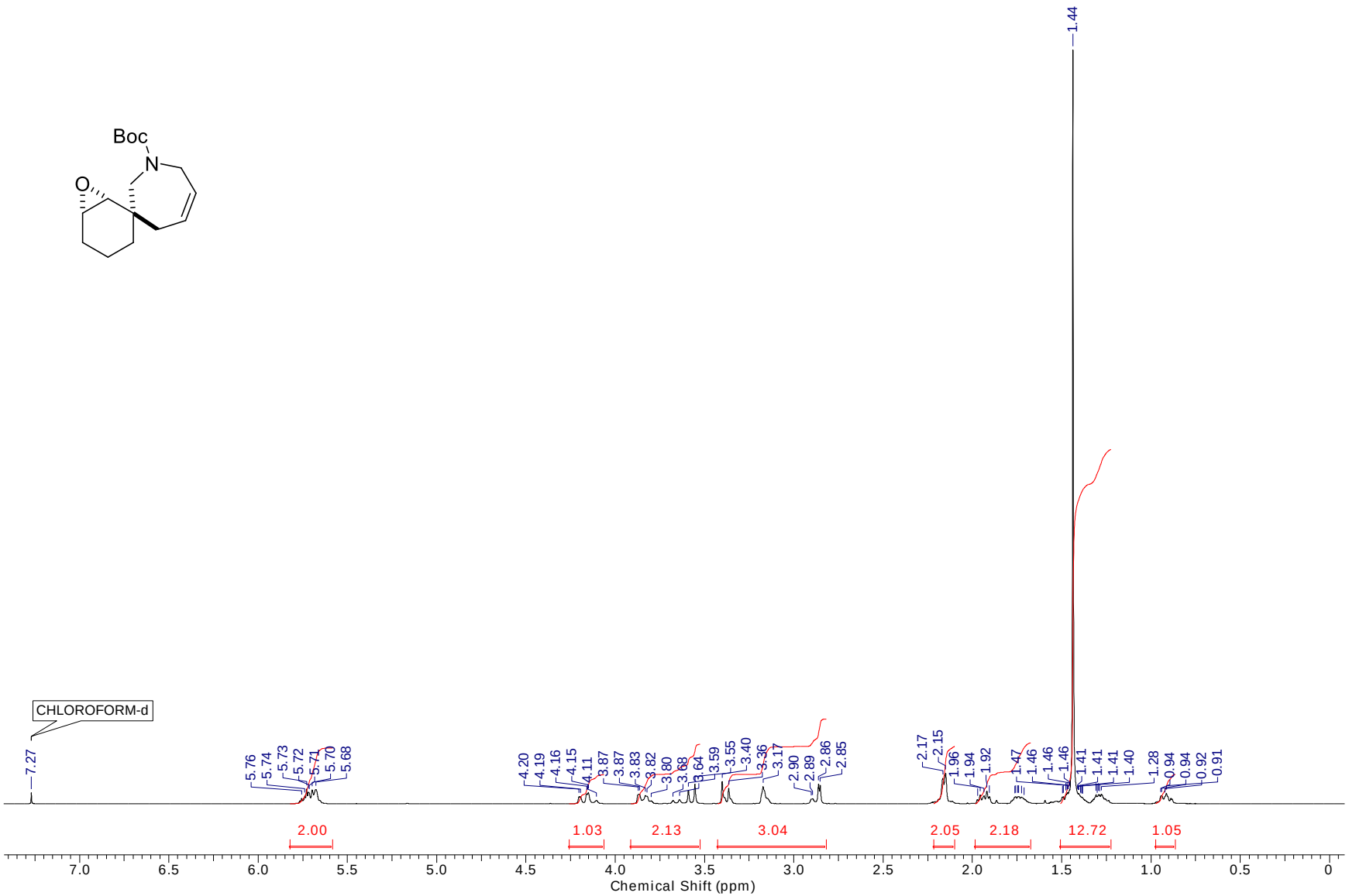
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 19



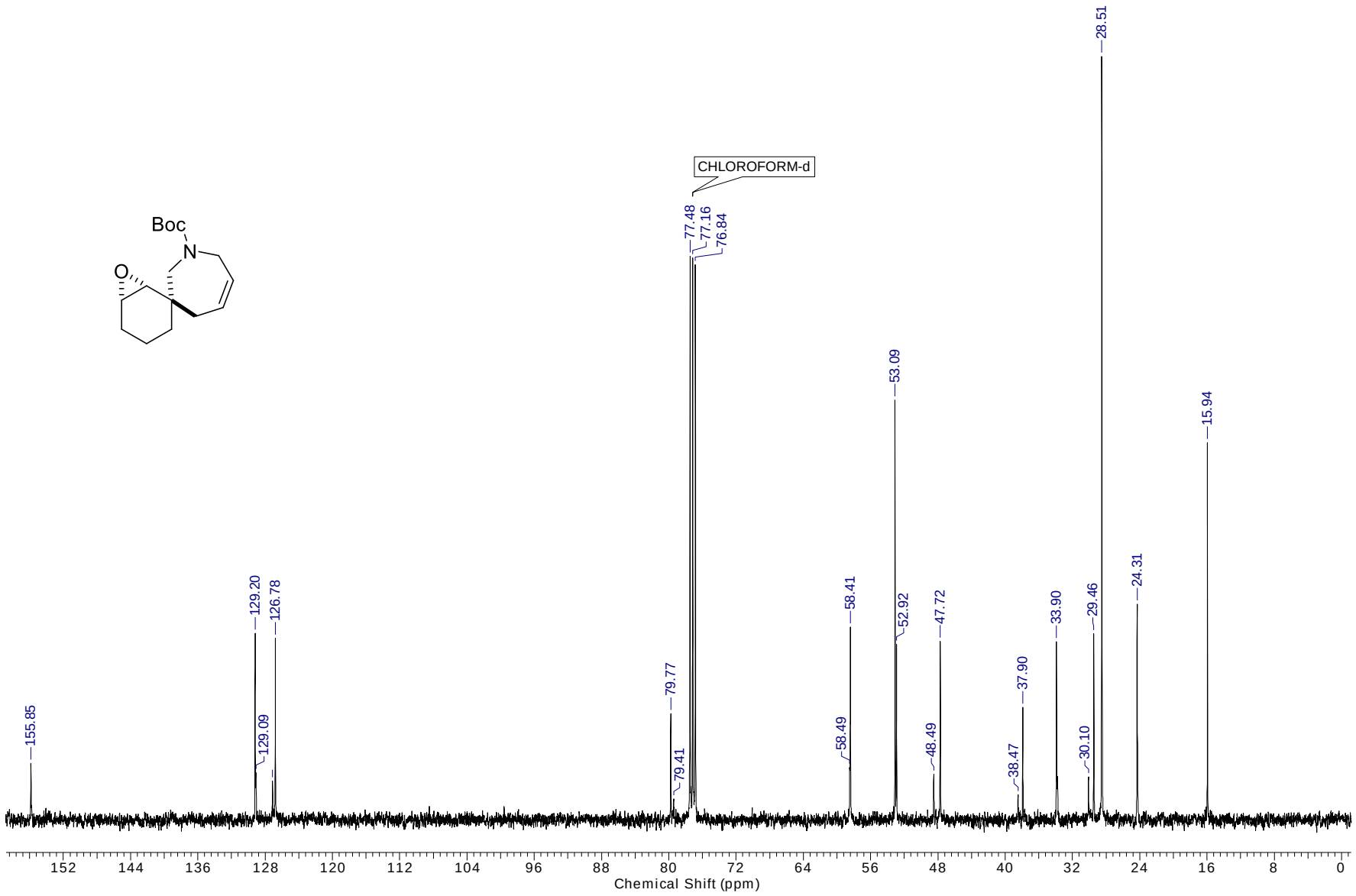
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 19



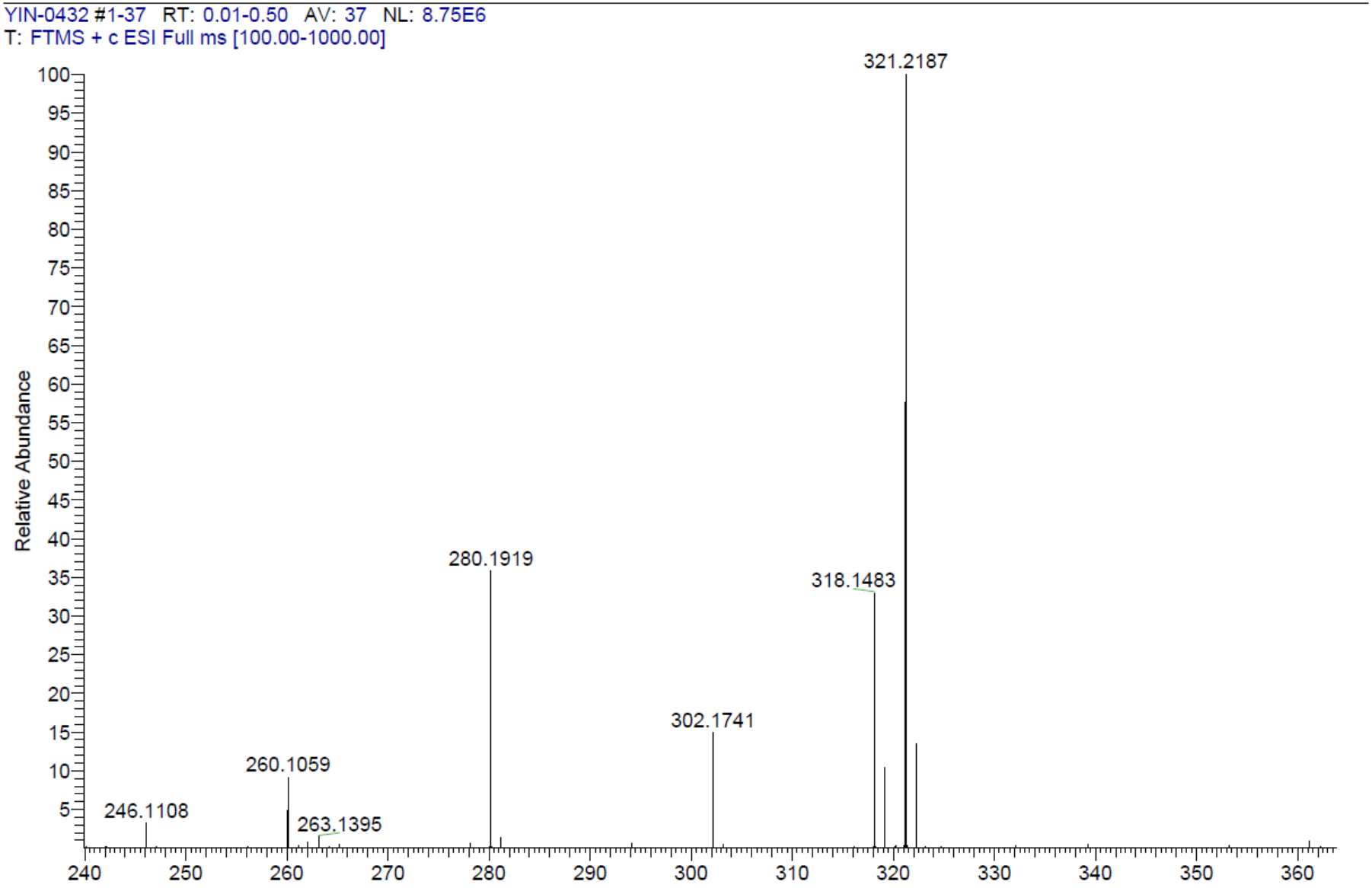
HRMS spectrum of 19



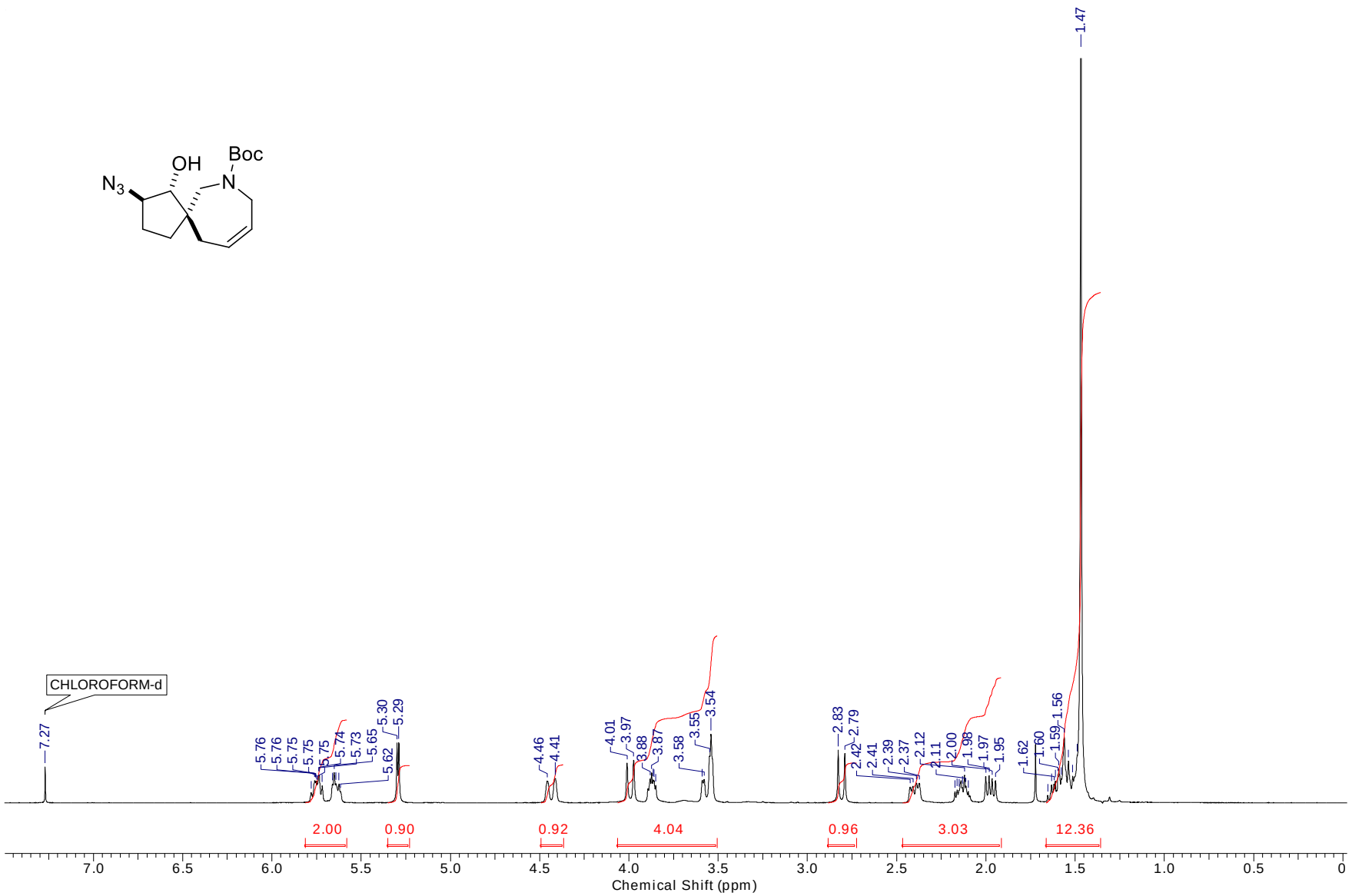
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 20



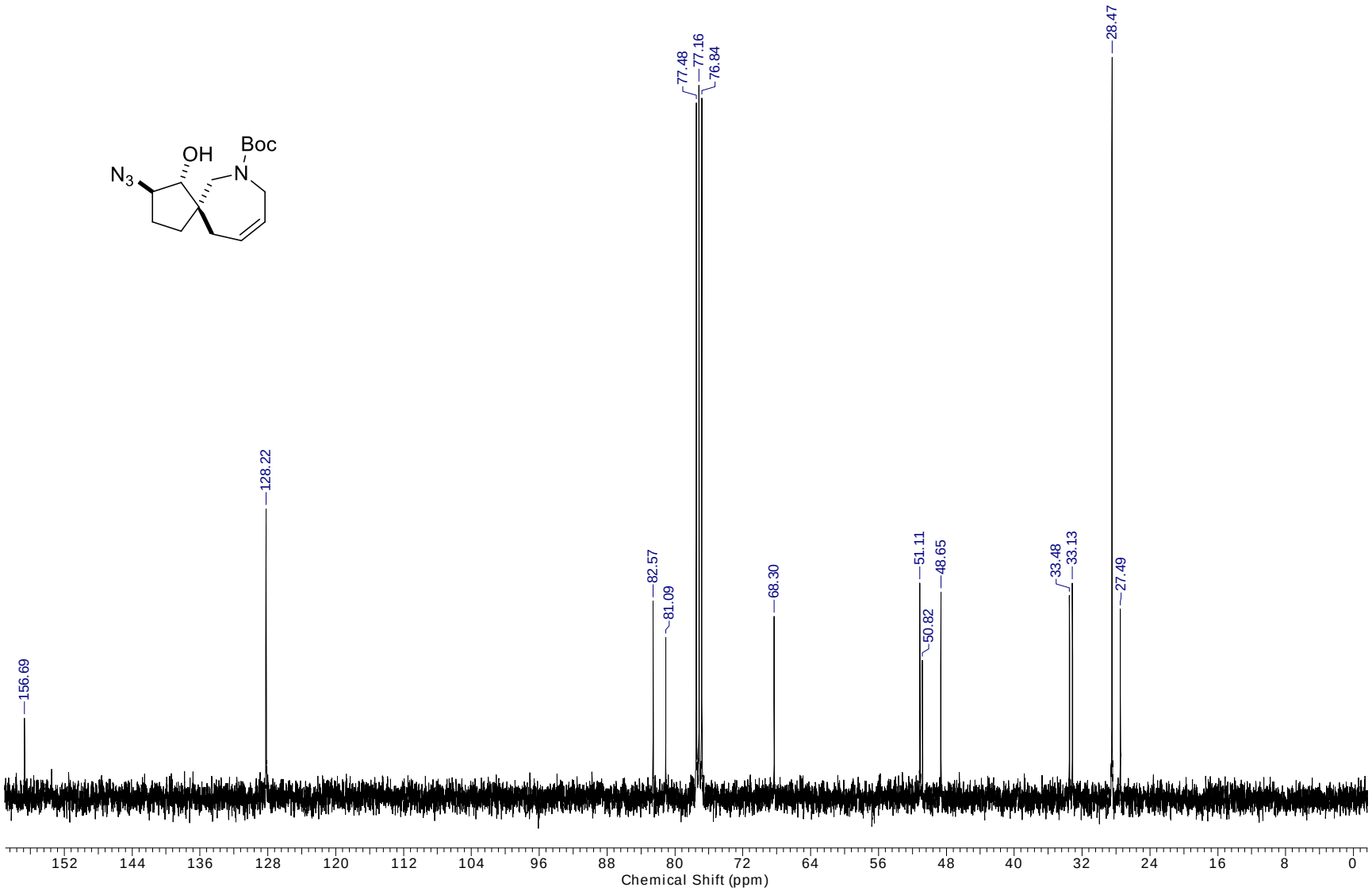
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 20



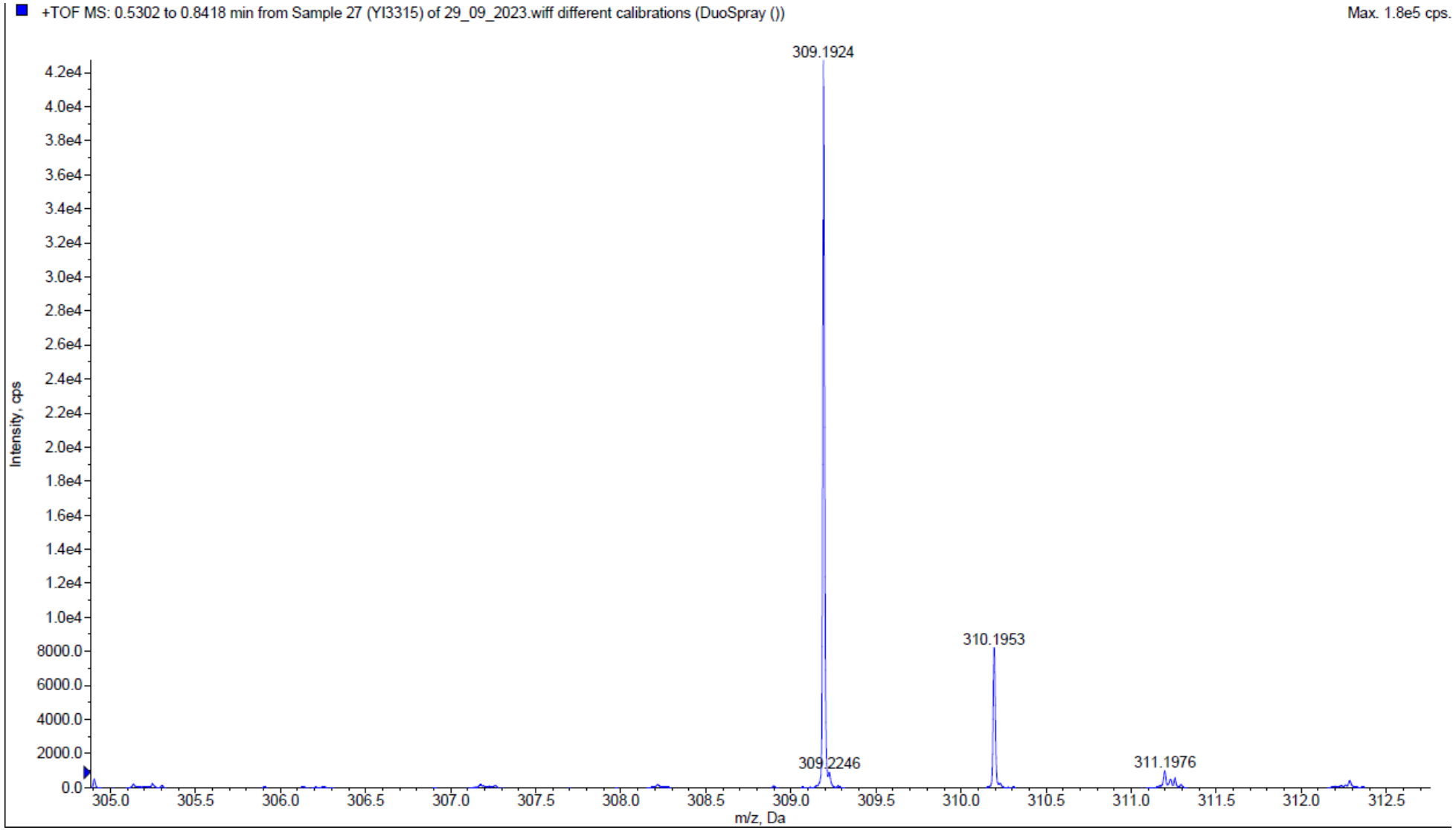
HRMS spectrum of 20



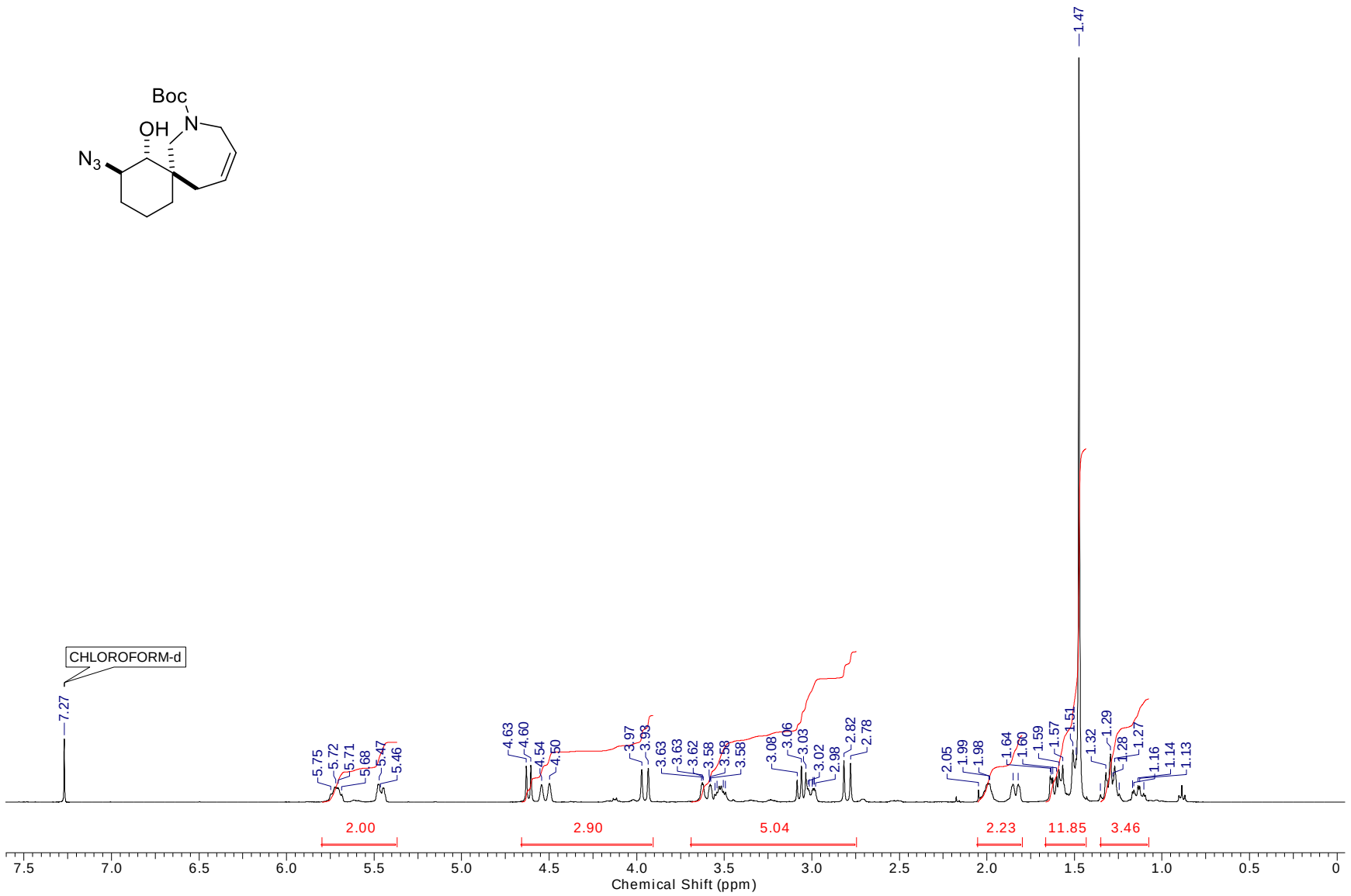
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 21



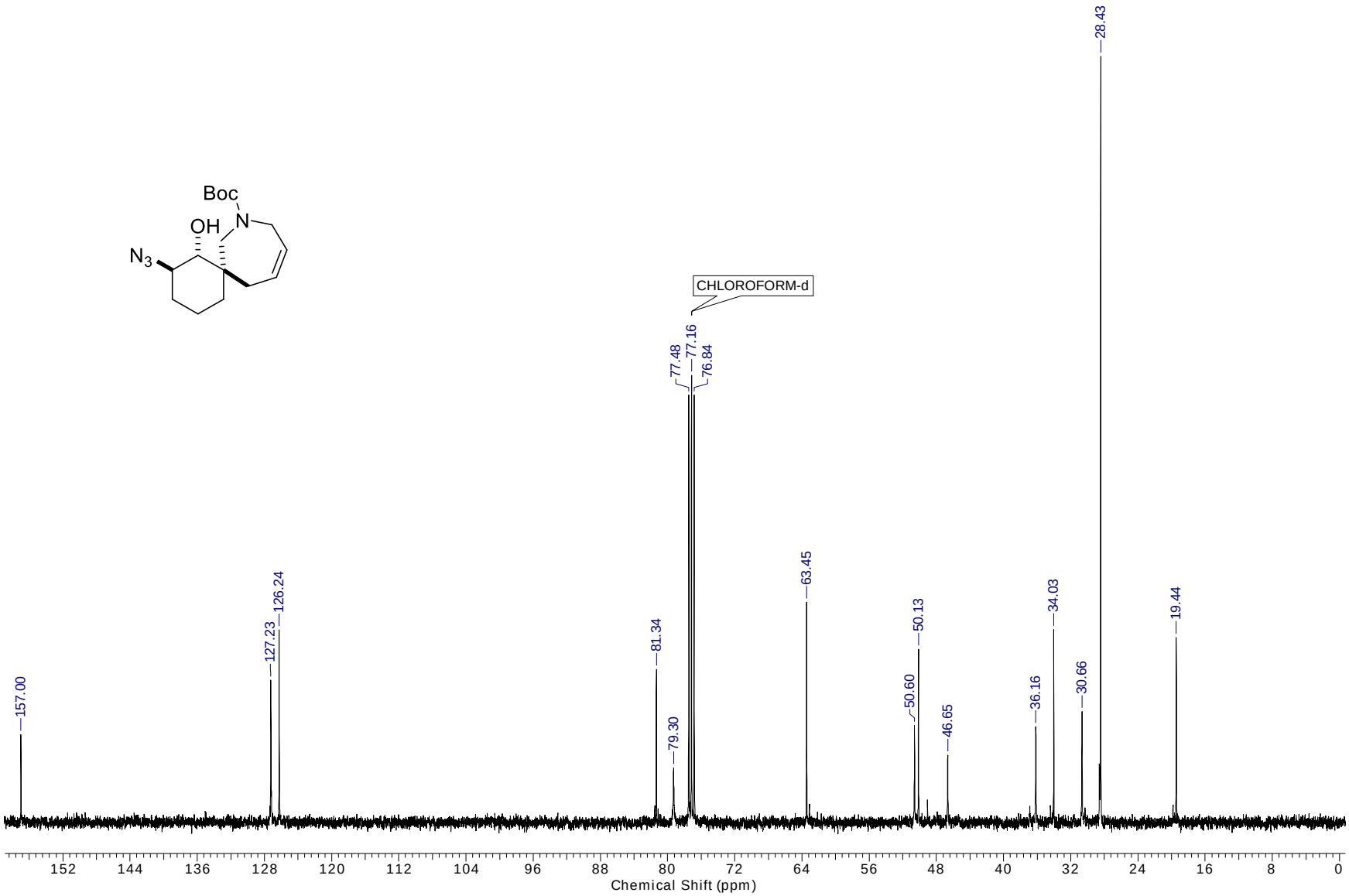
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 21



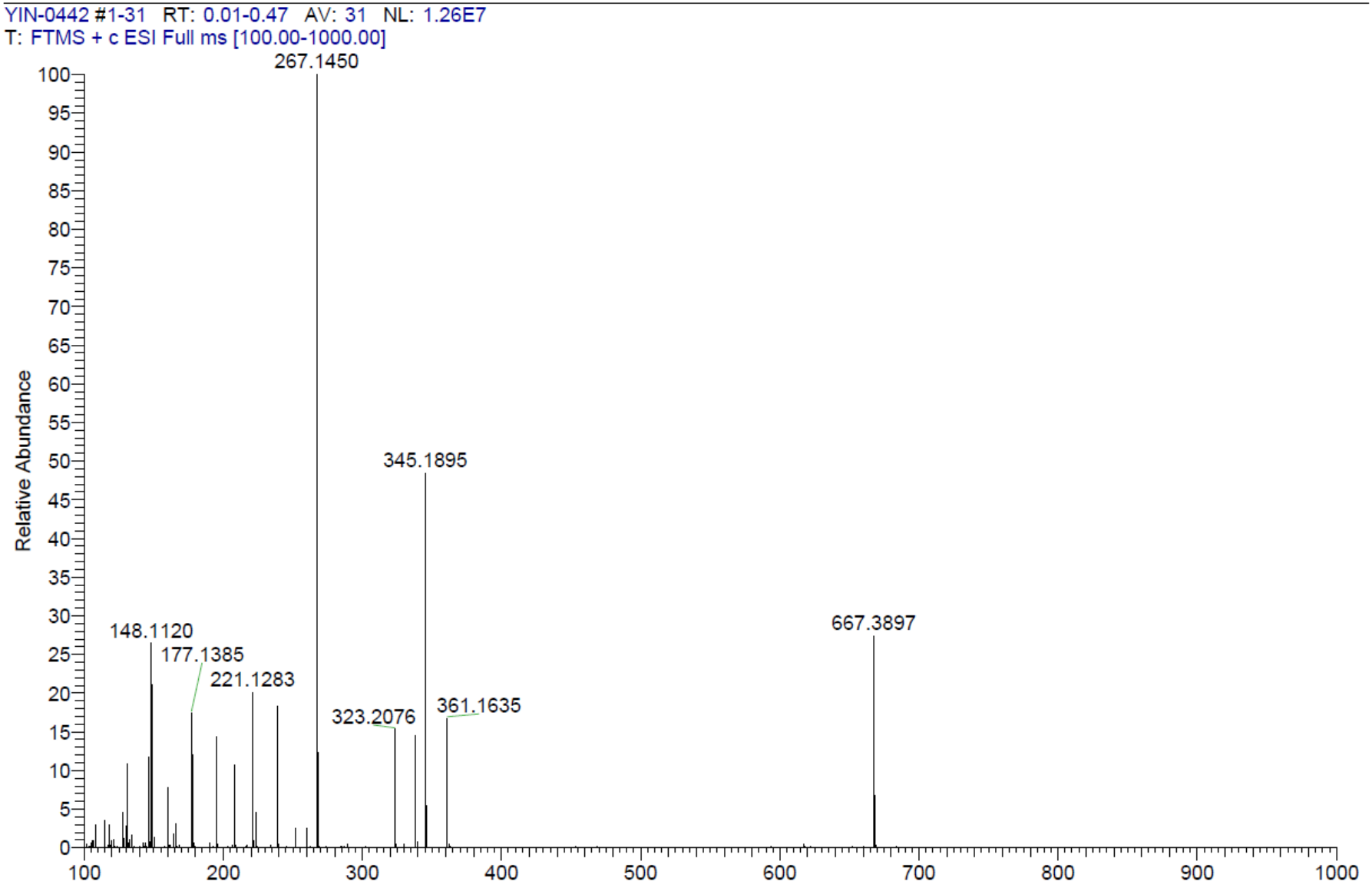
HRMS spectrum of 21



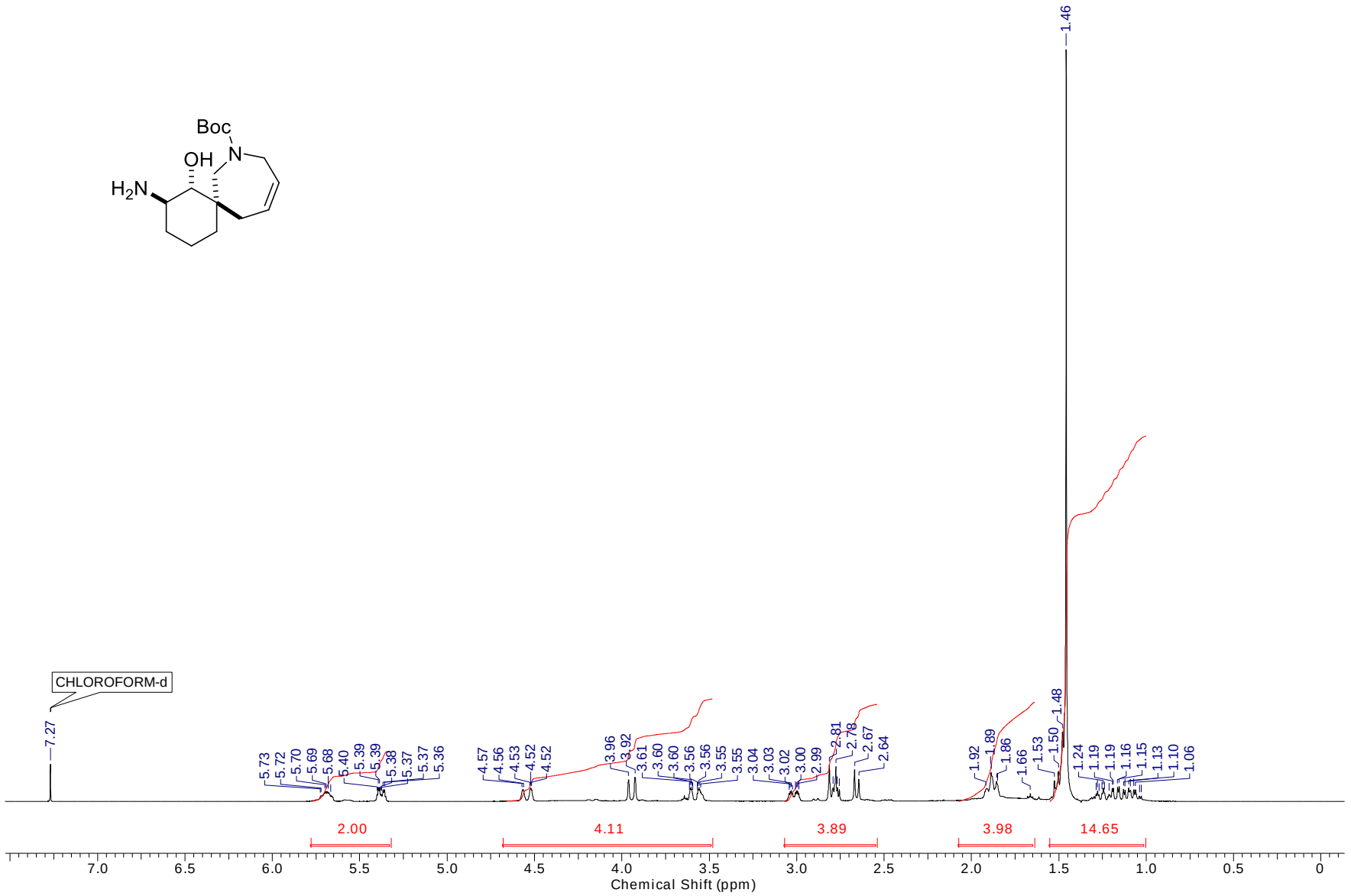
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 22



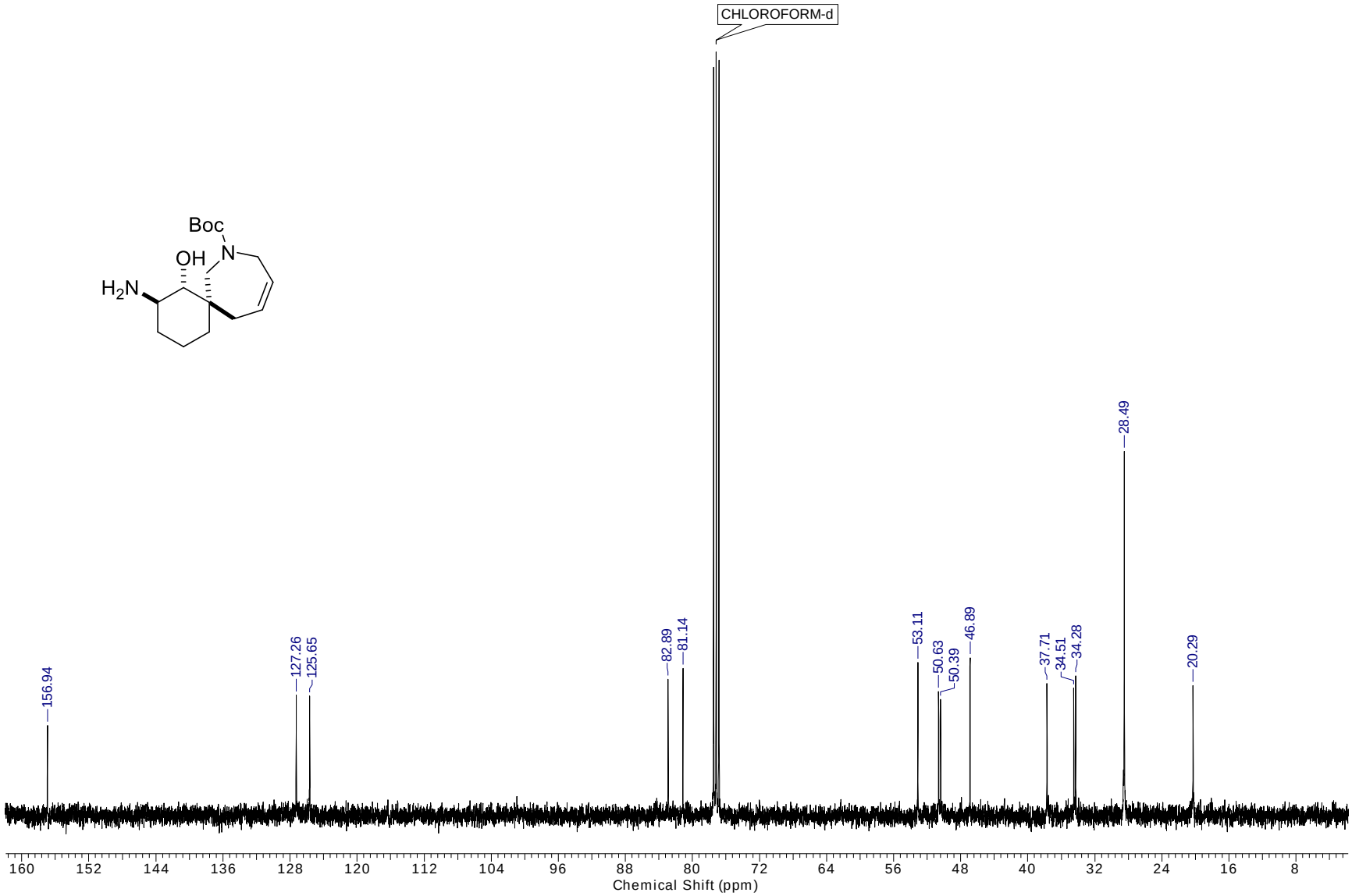
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 22



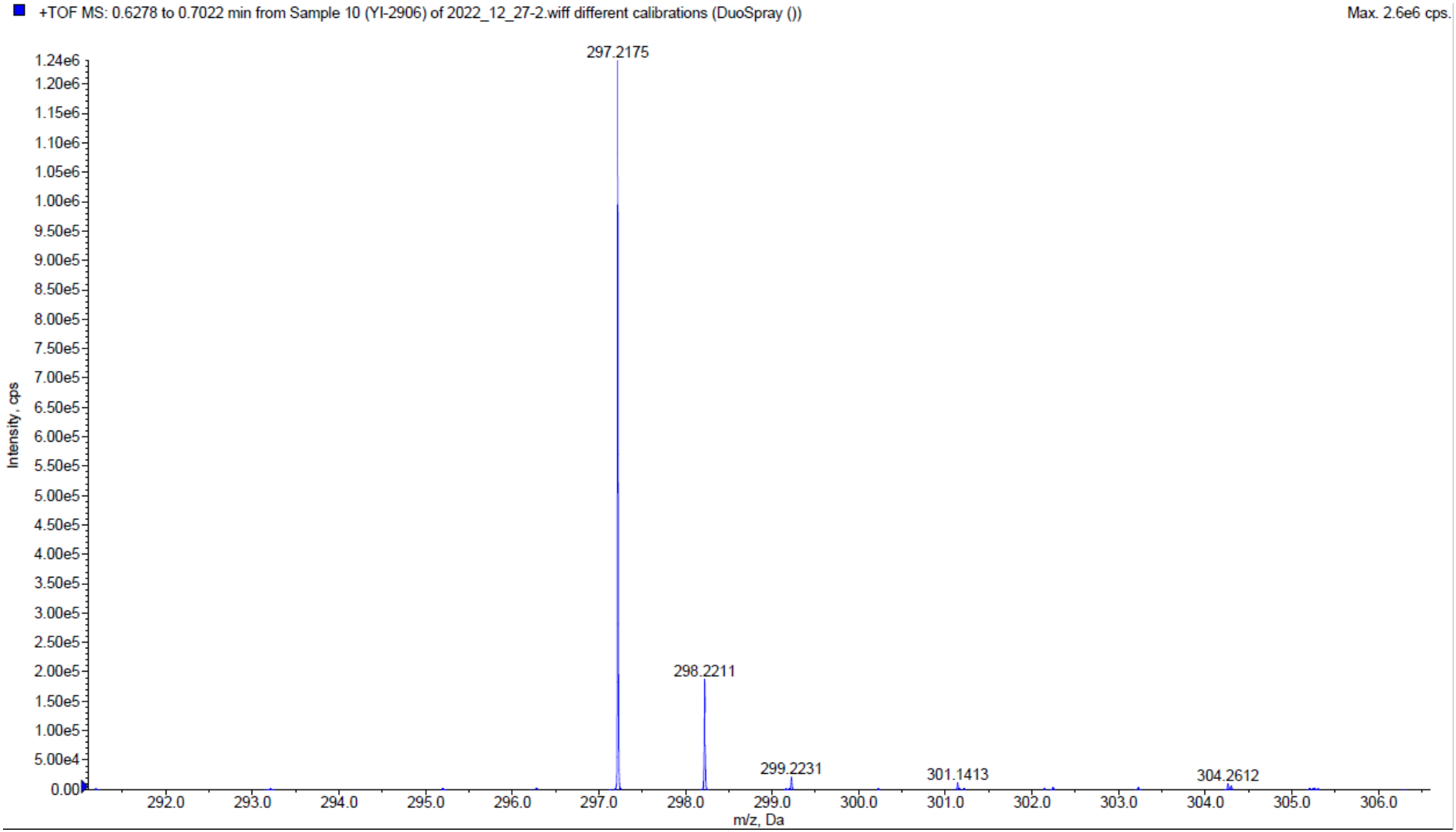
HRMS spectrum of 22



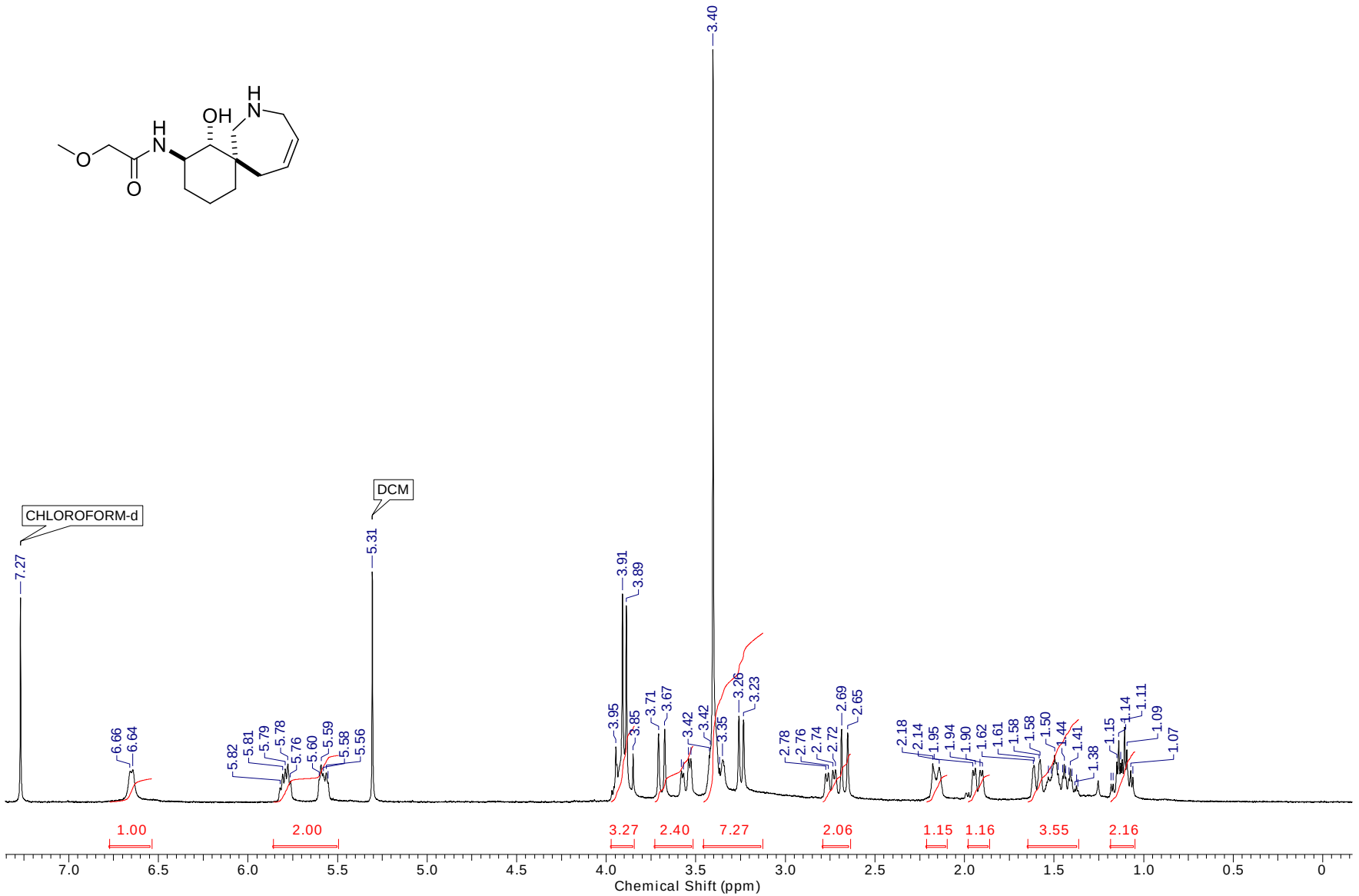
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 23



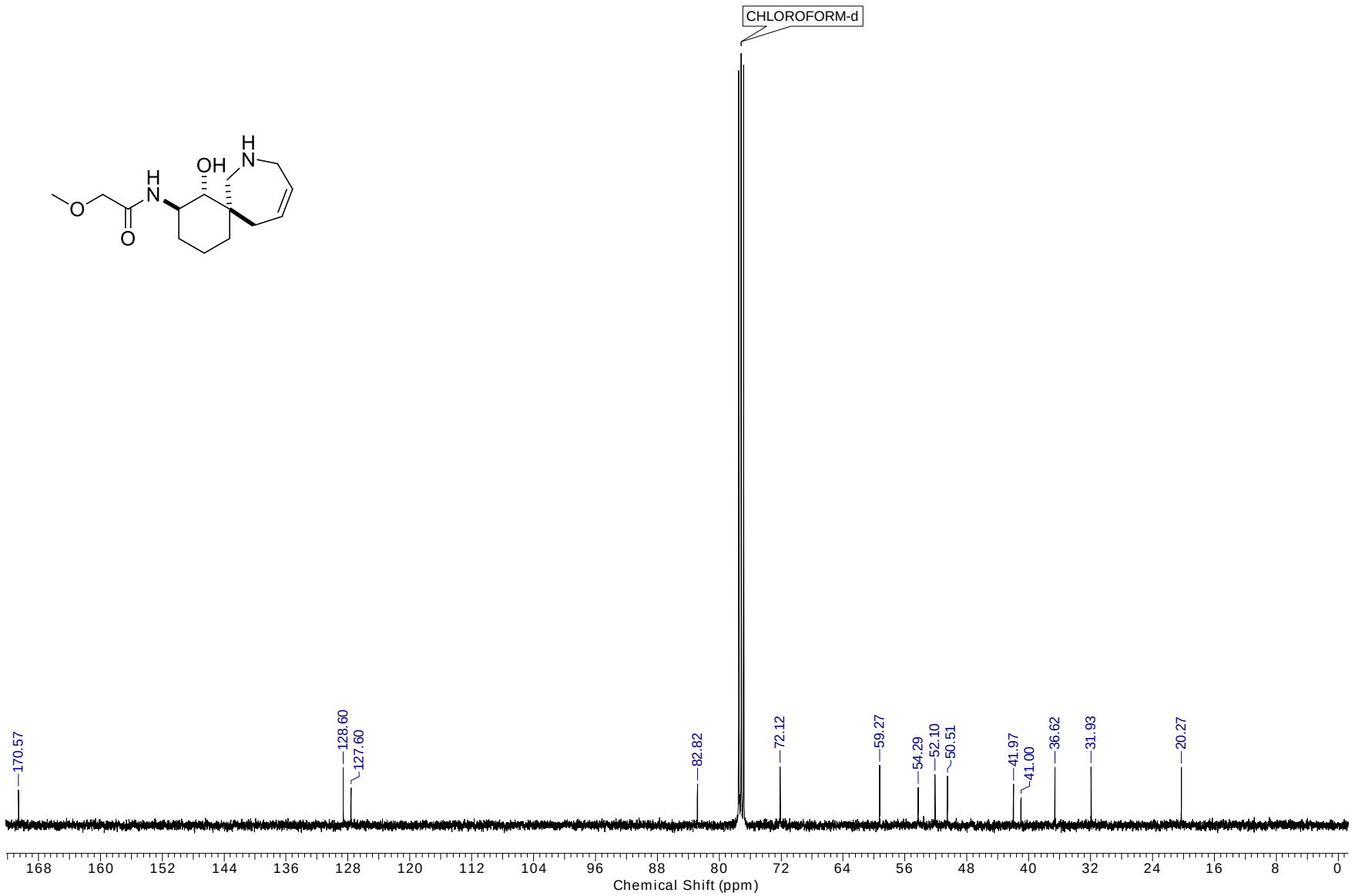
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 23



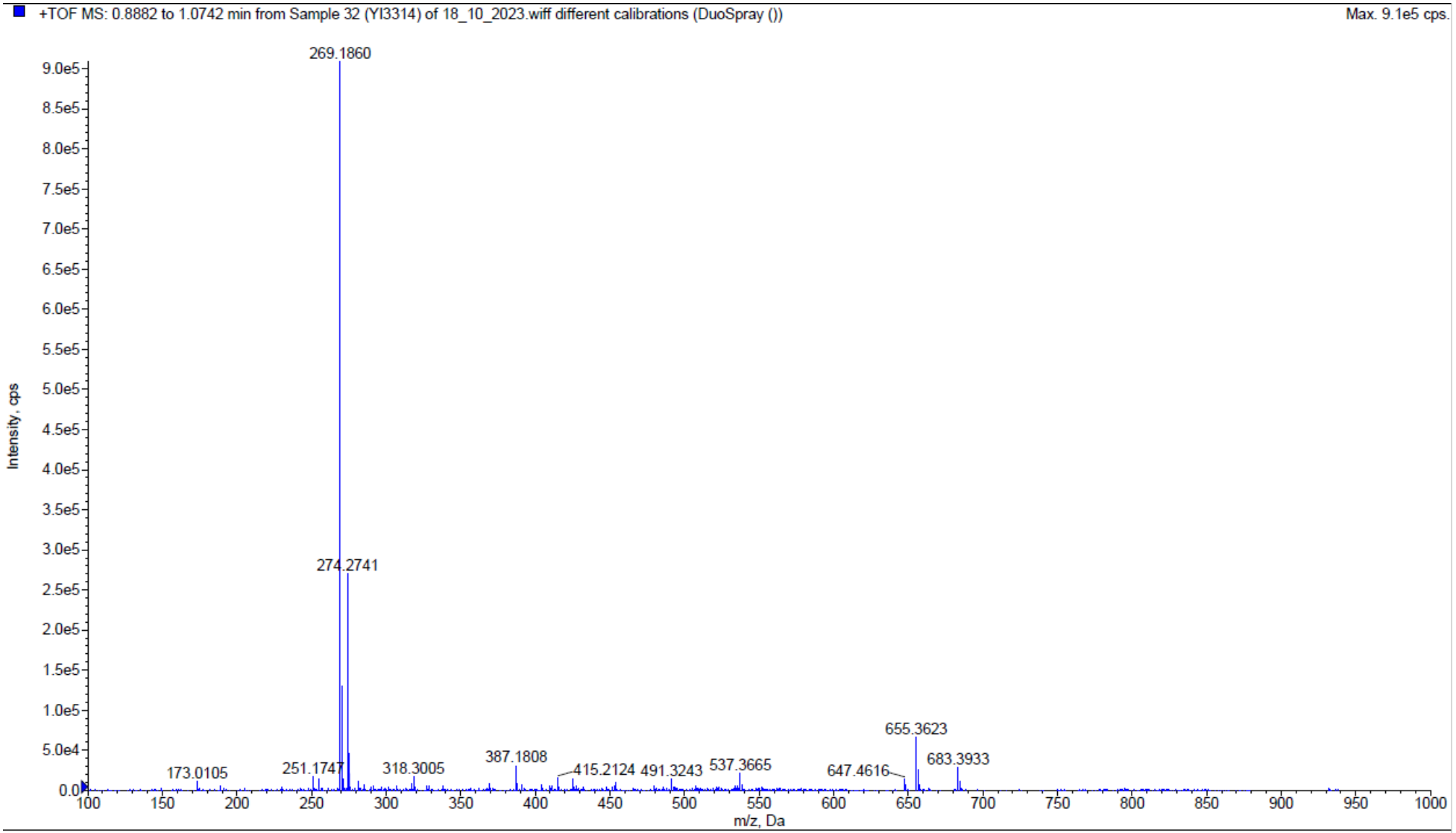
HRMS spectrum of 23



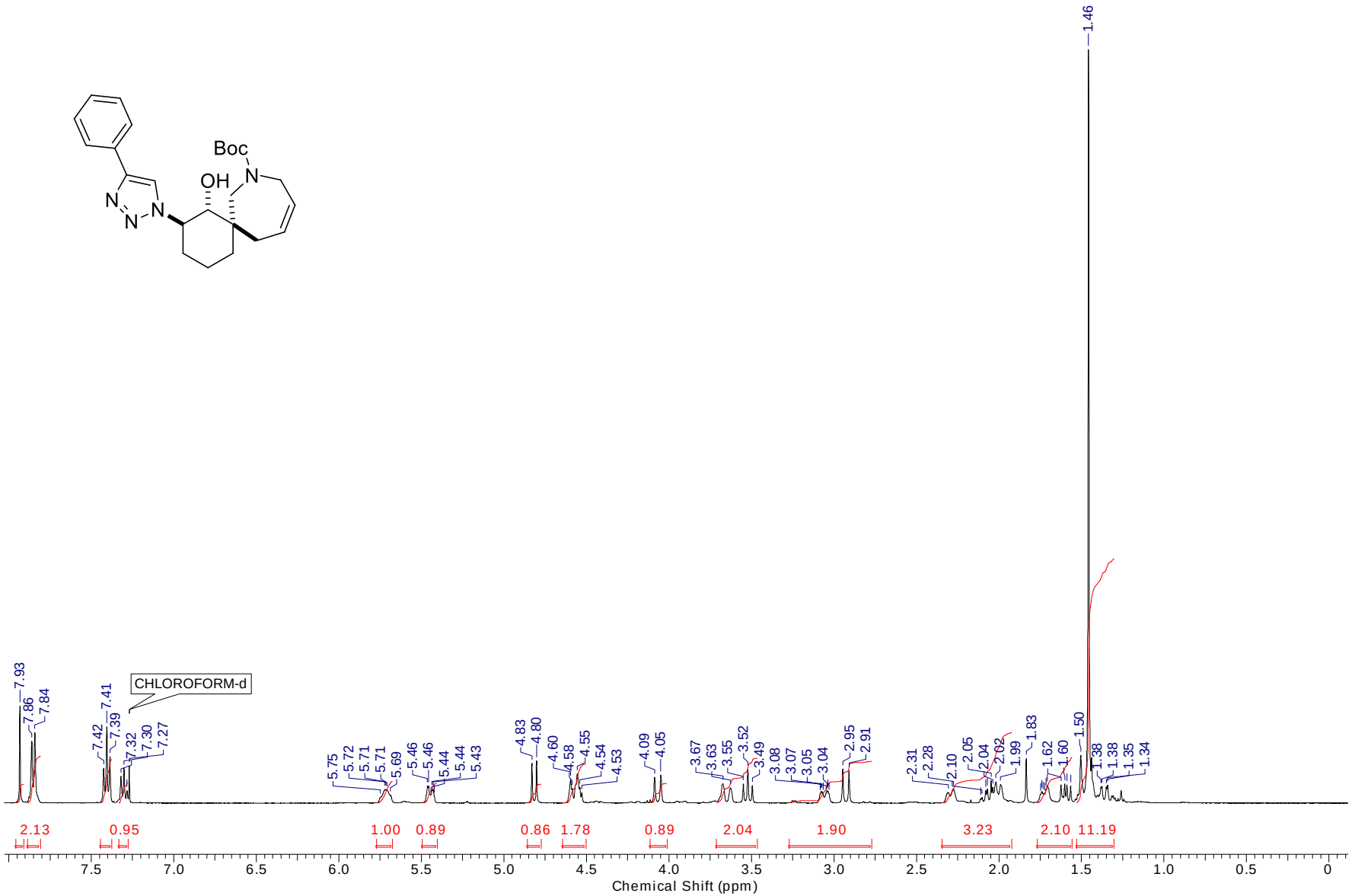
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 24



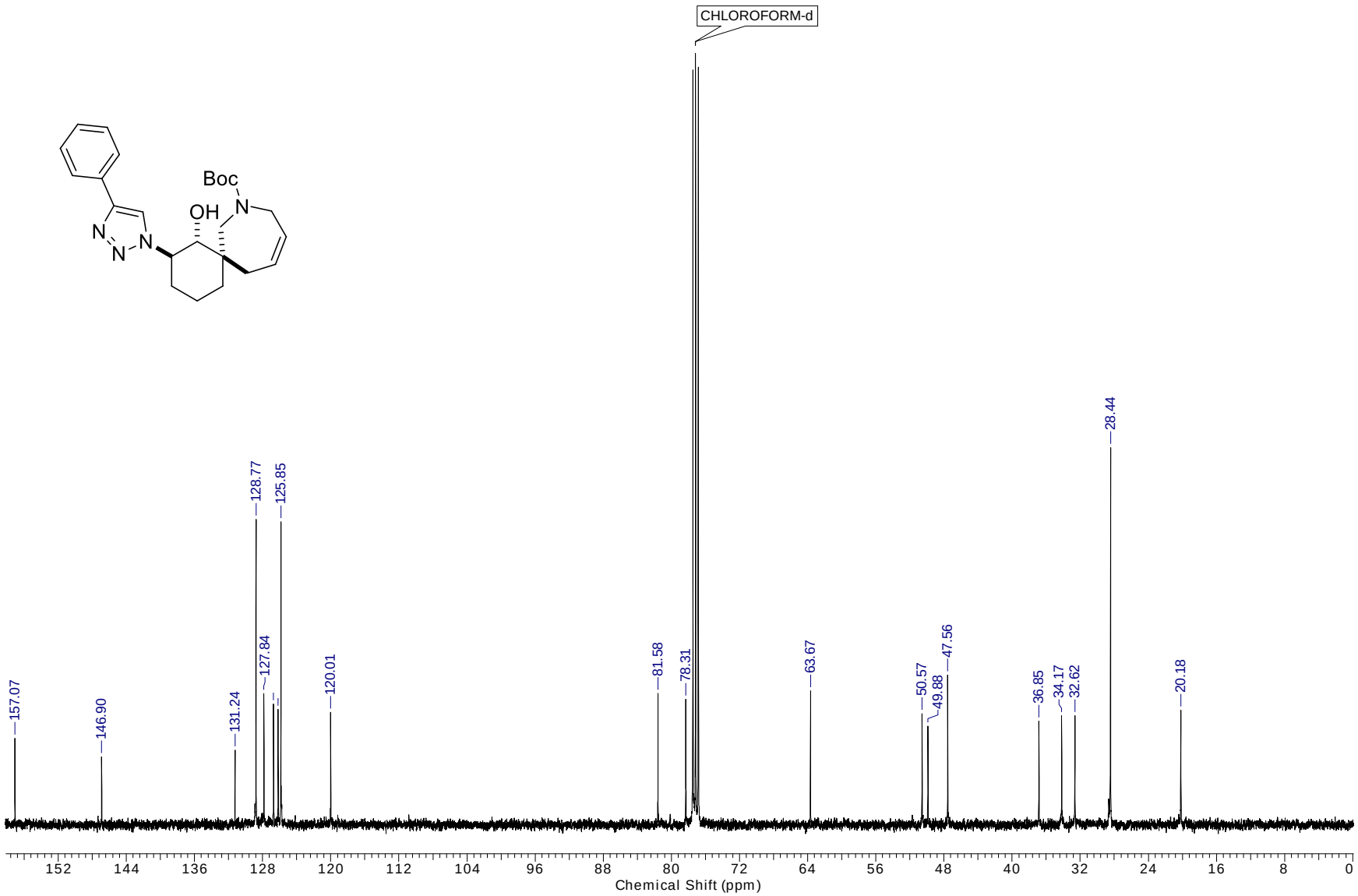
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 24



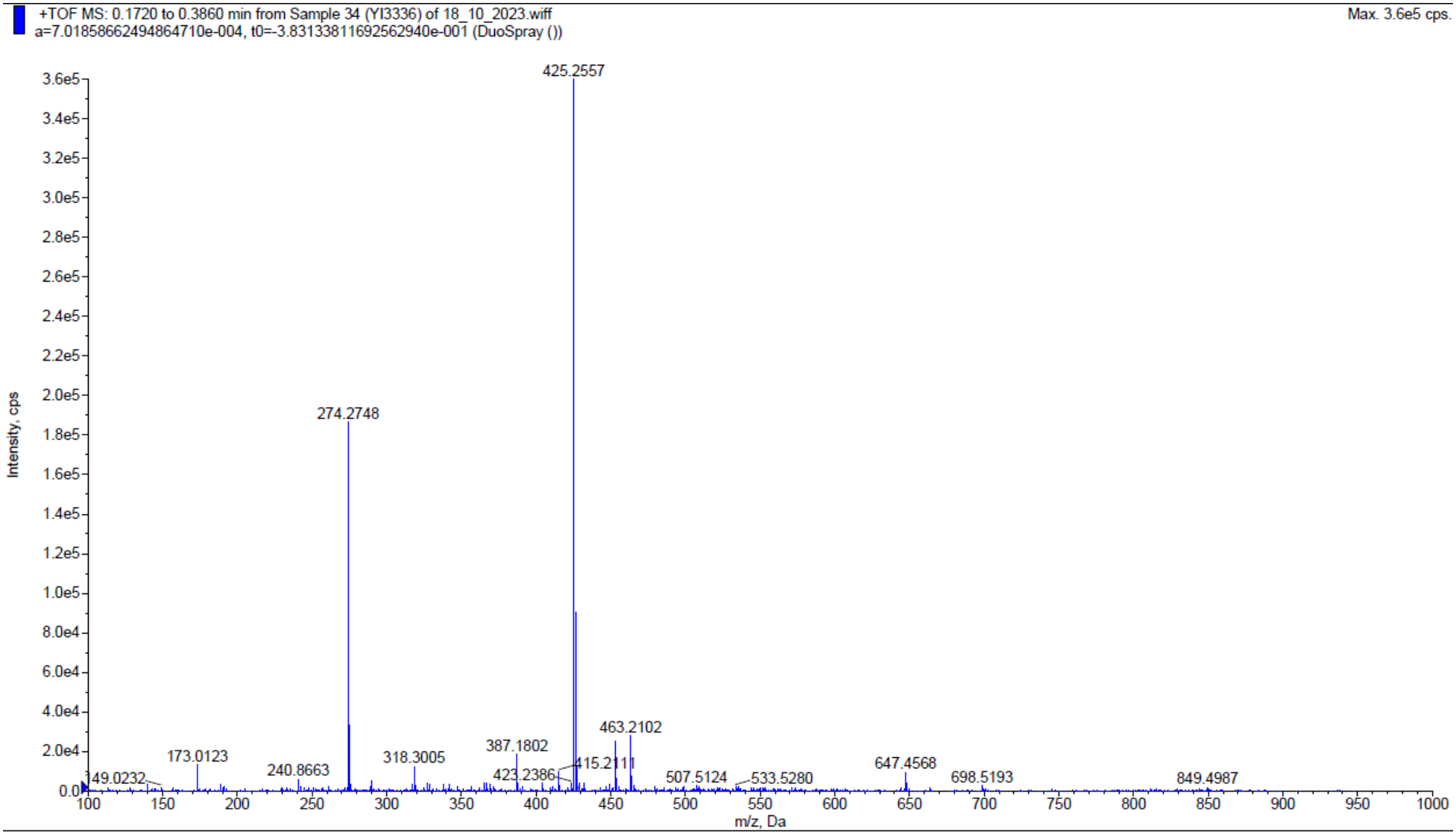
HRMS spectrum of 24



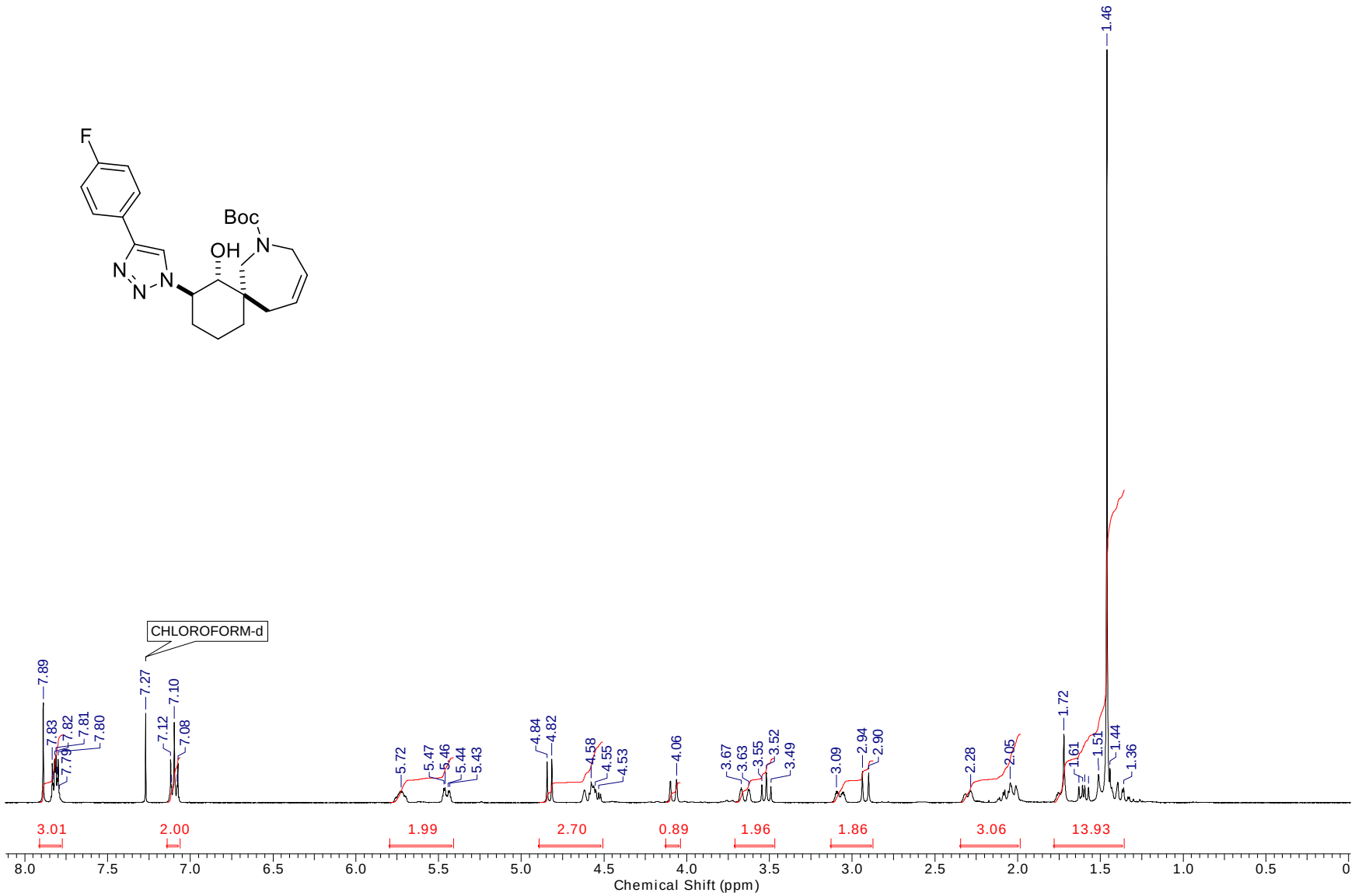
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 25



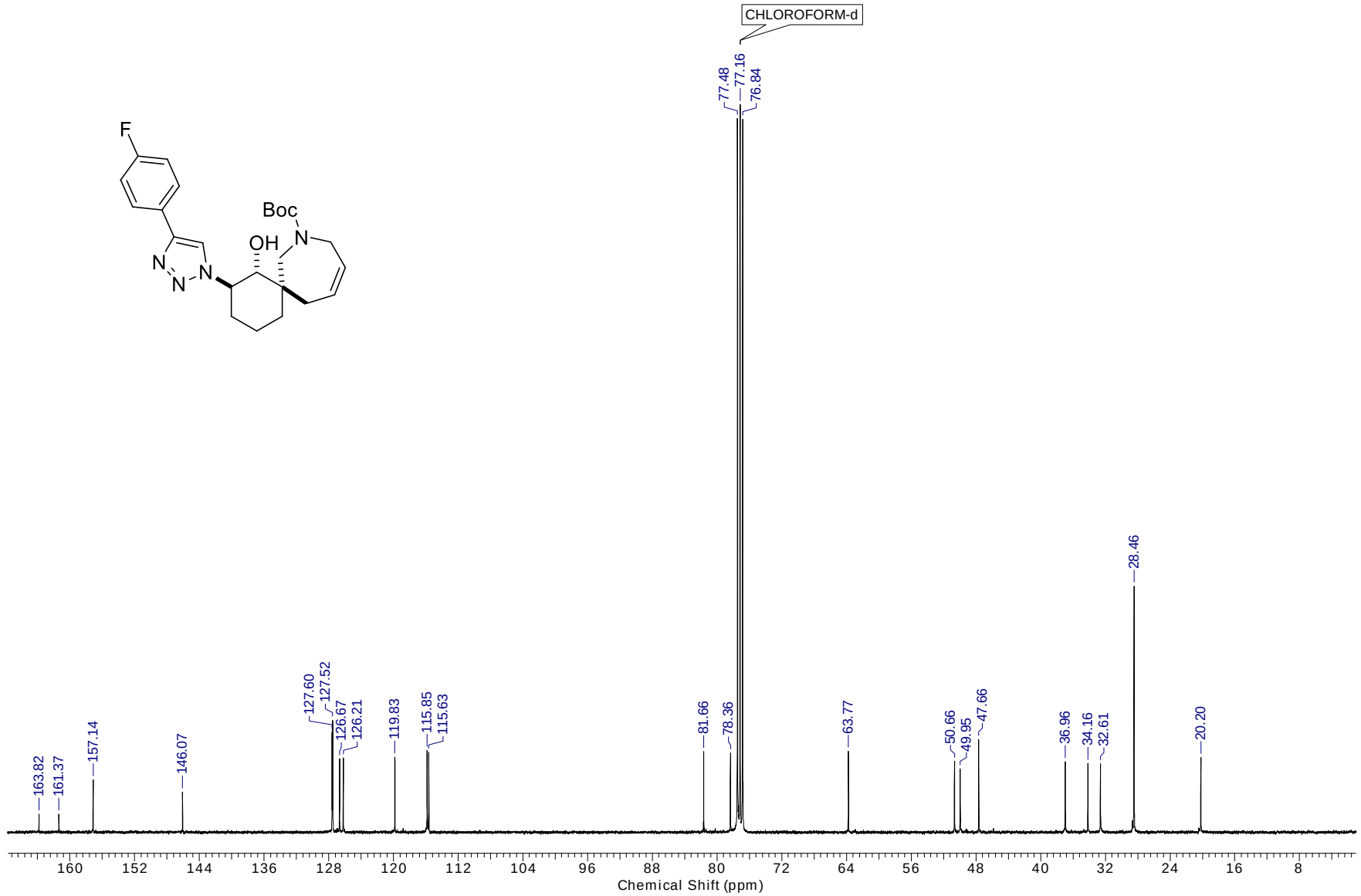
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 25



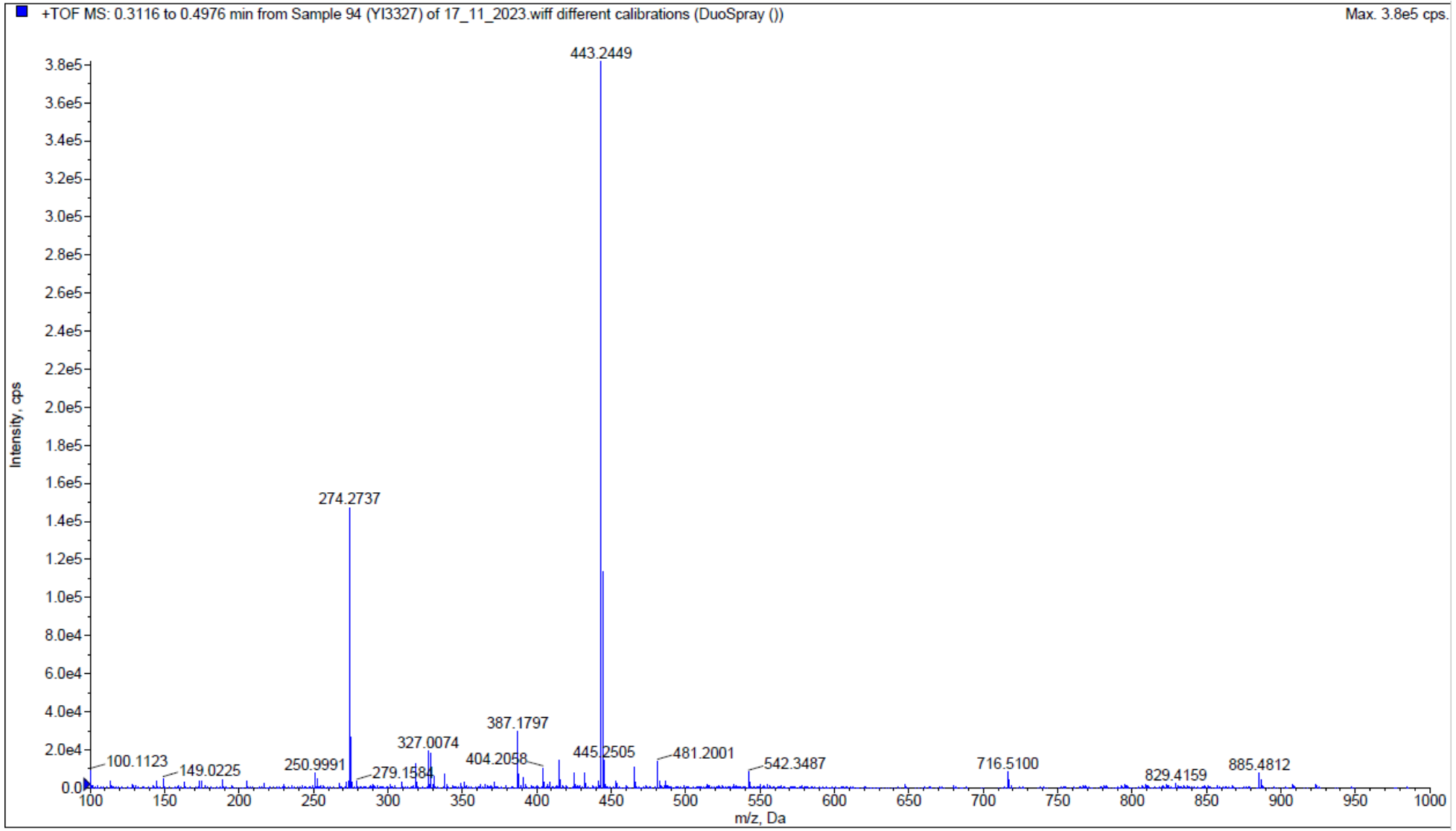
HRMS spectrum of 25



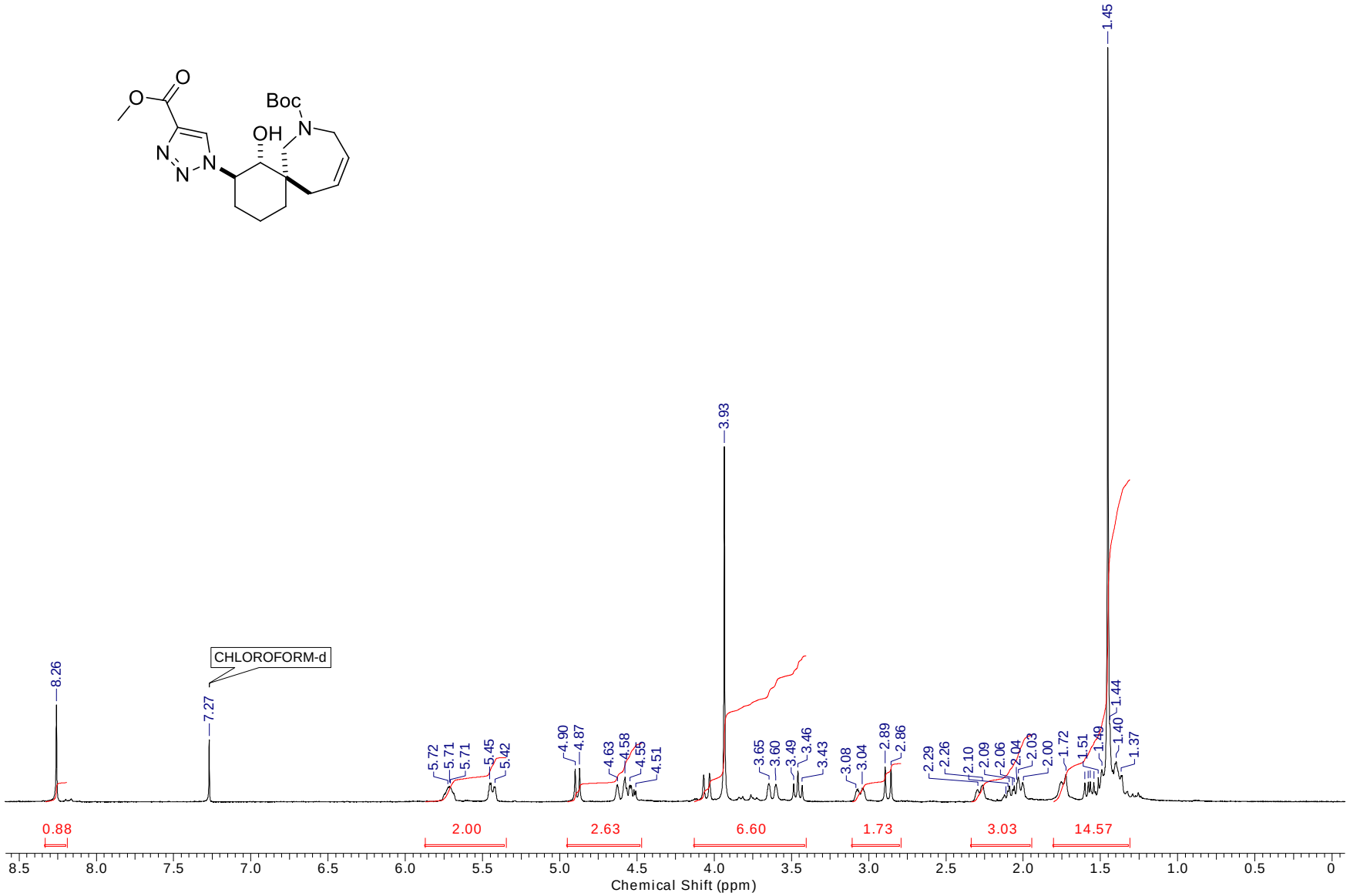
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 26



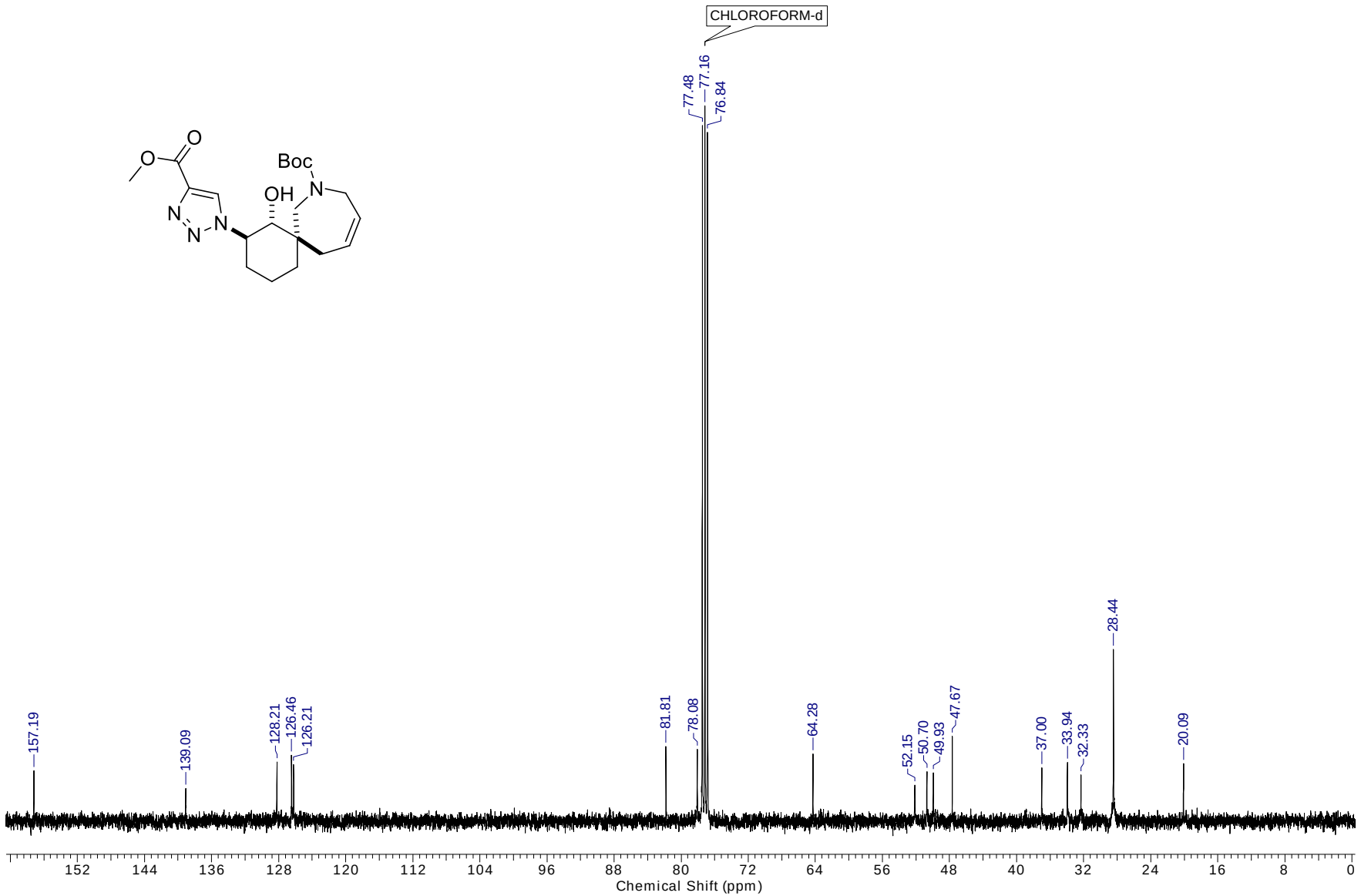
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 26



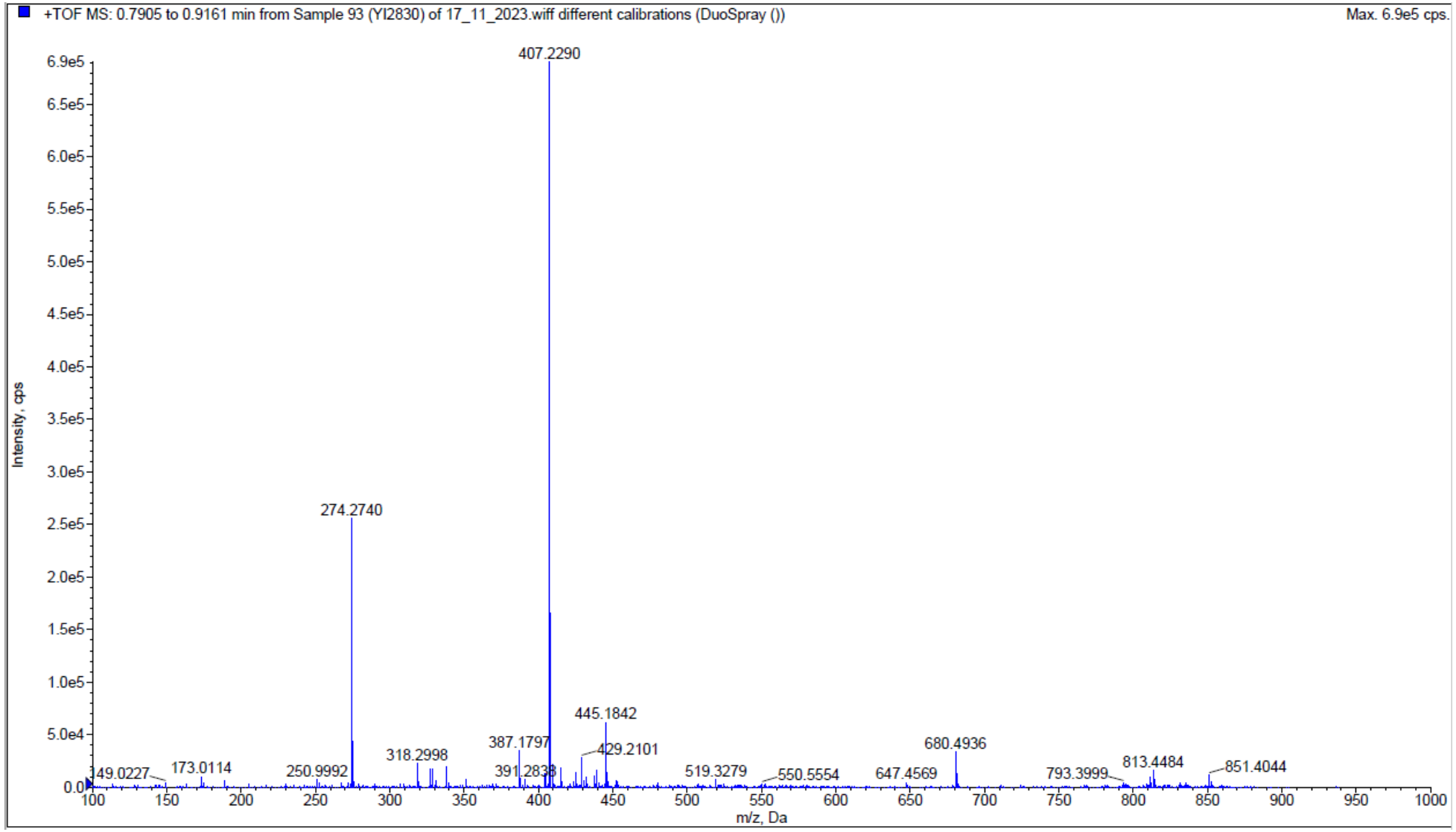
HRMS spectrum of 26



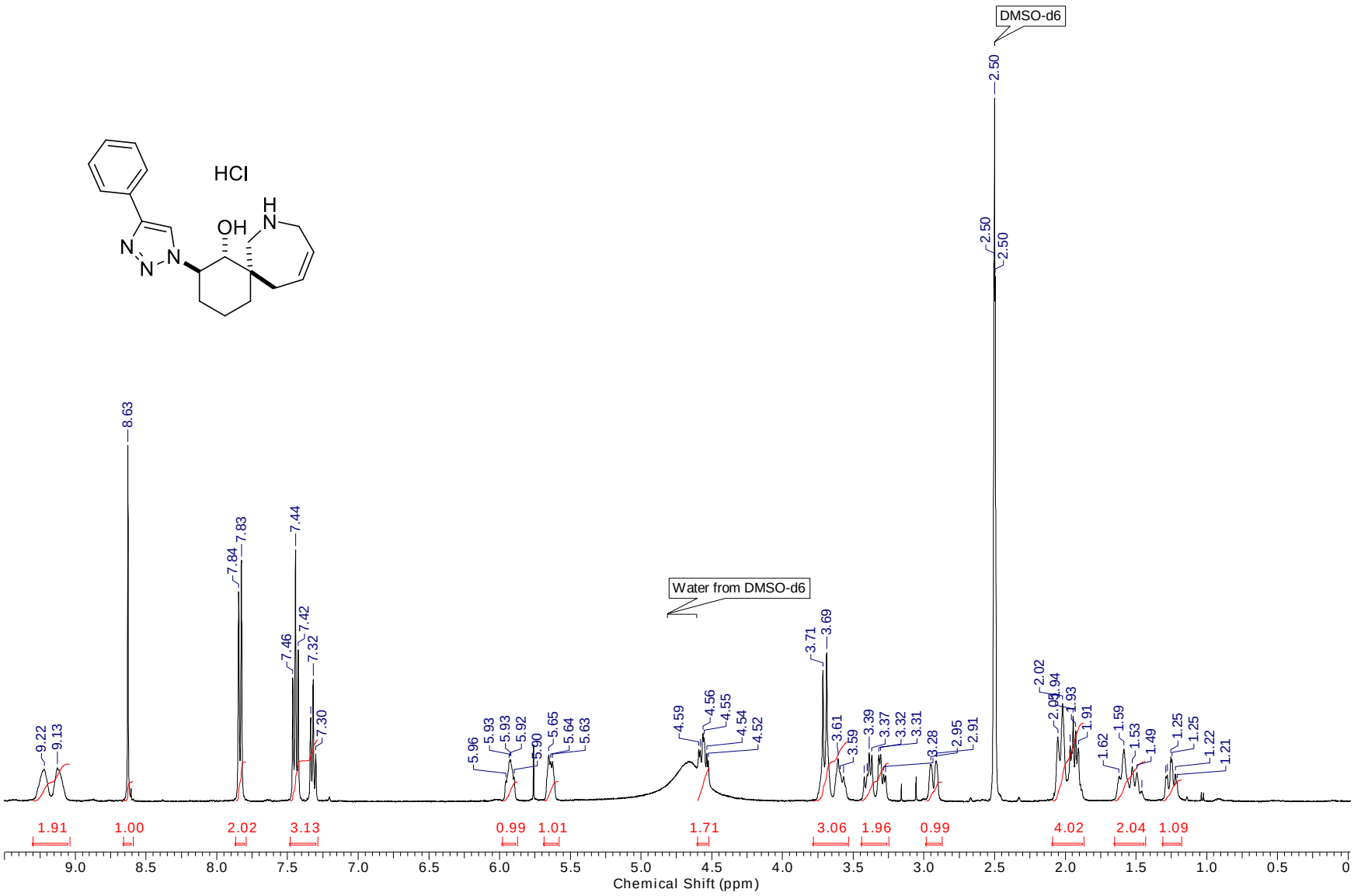
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 27



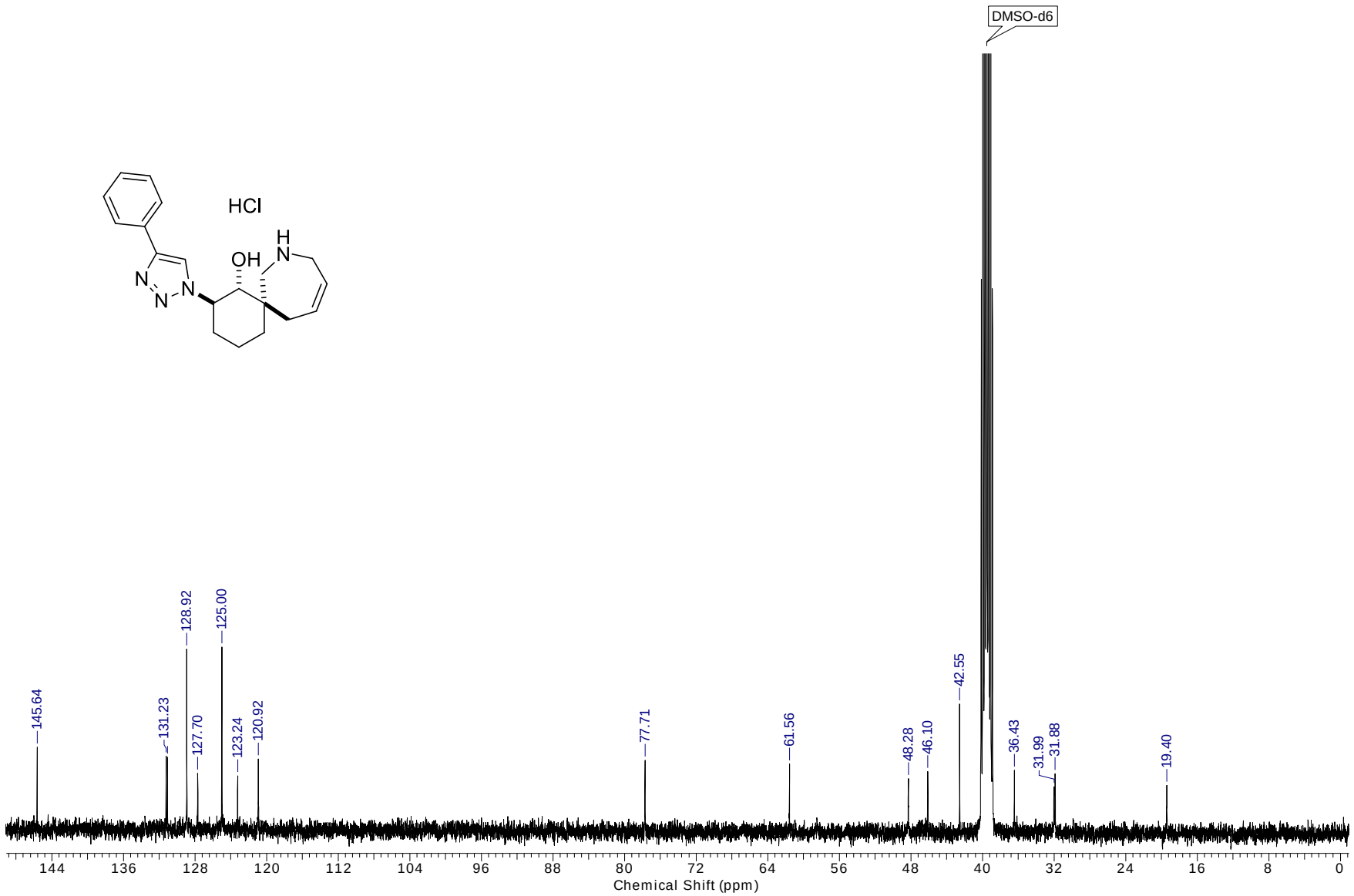
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 27



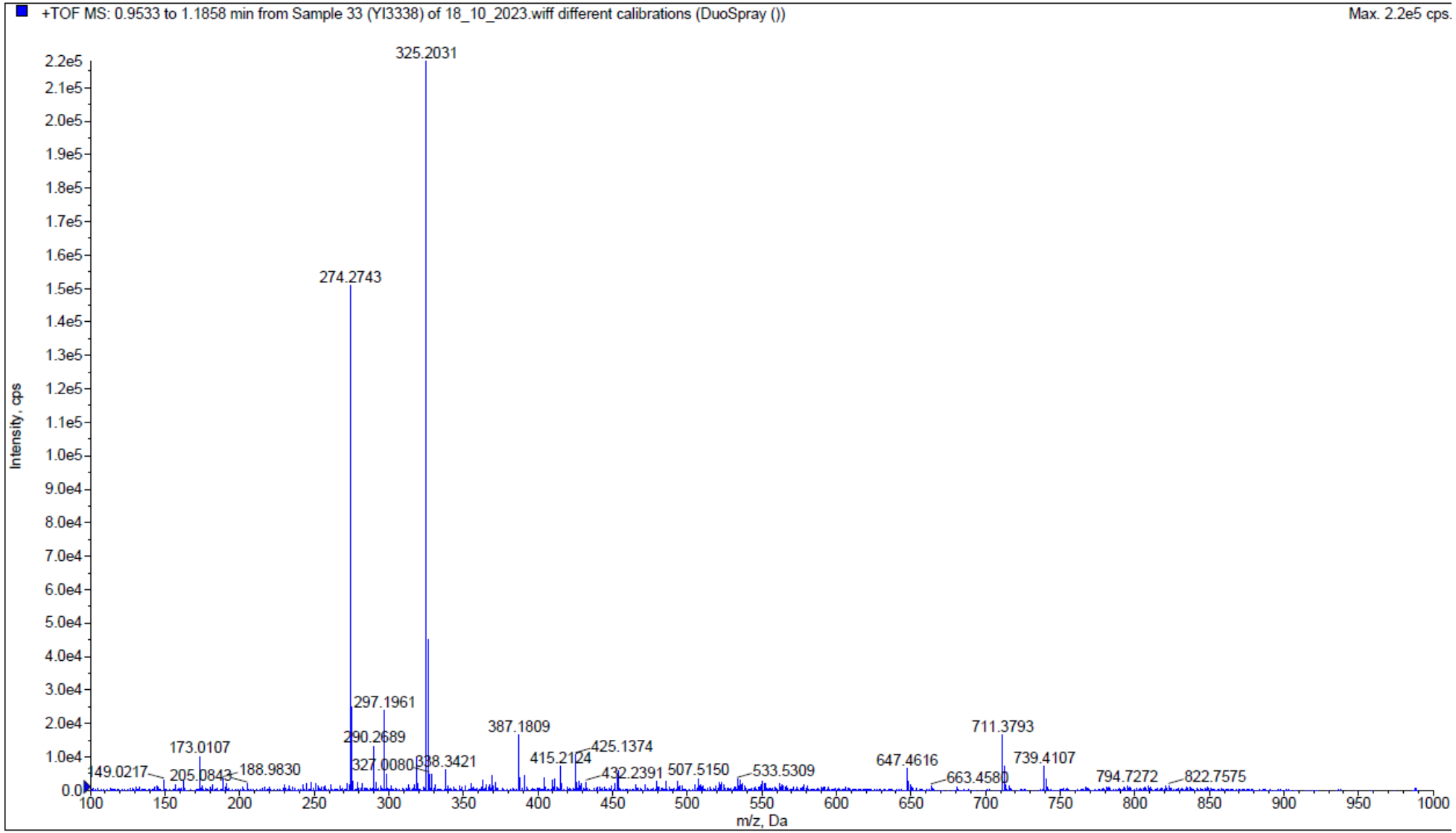
HRMS spectrum of 27



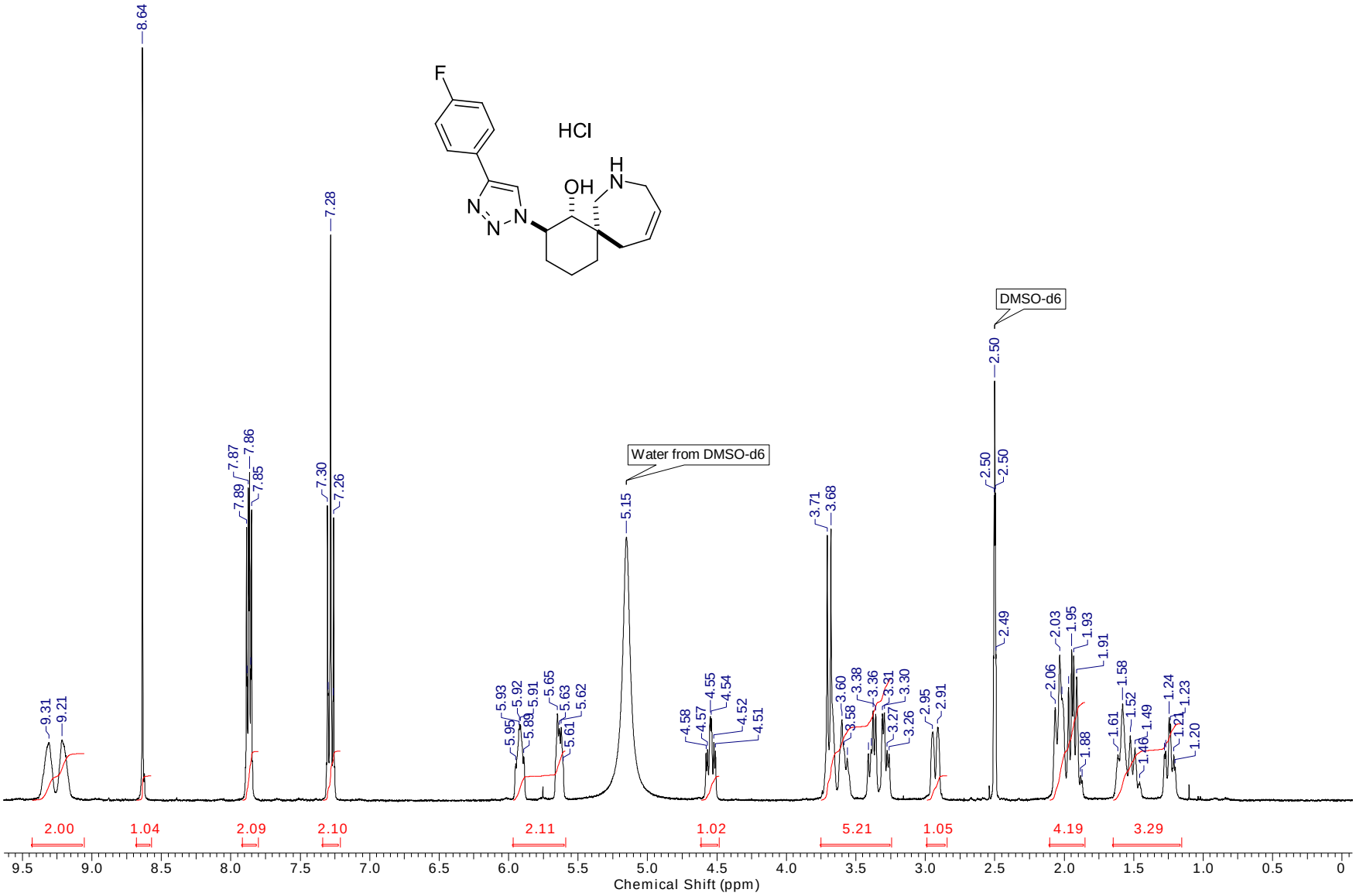
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 28



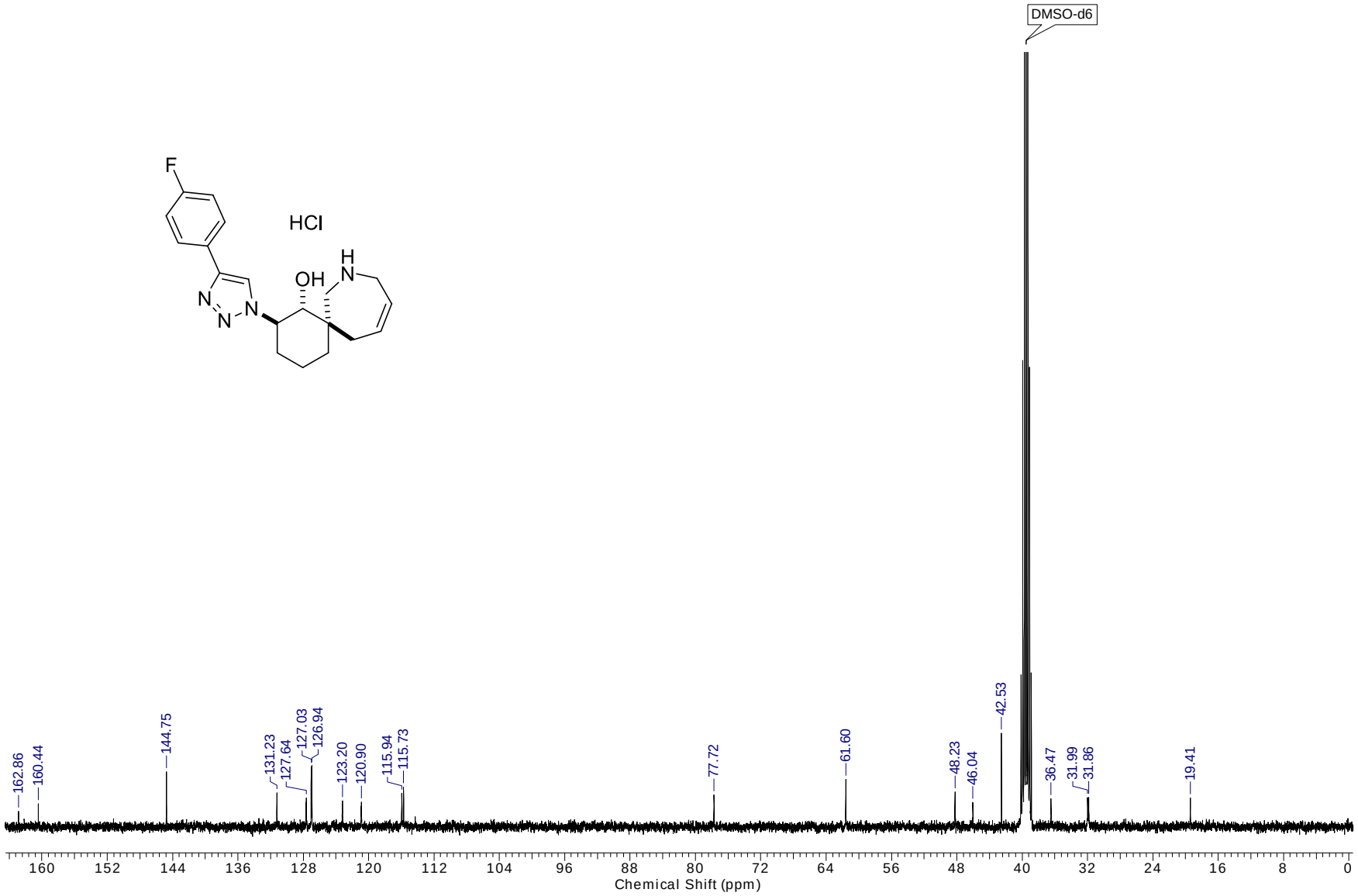
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of 28



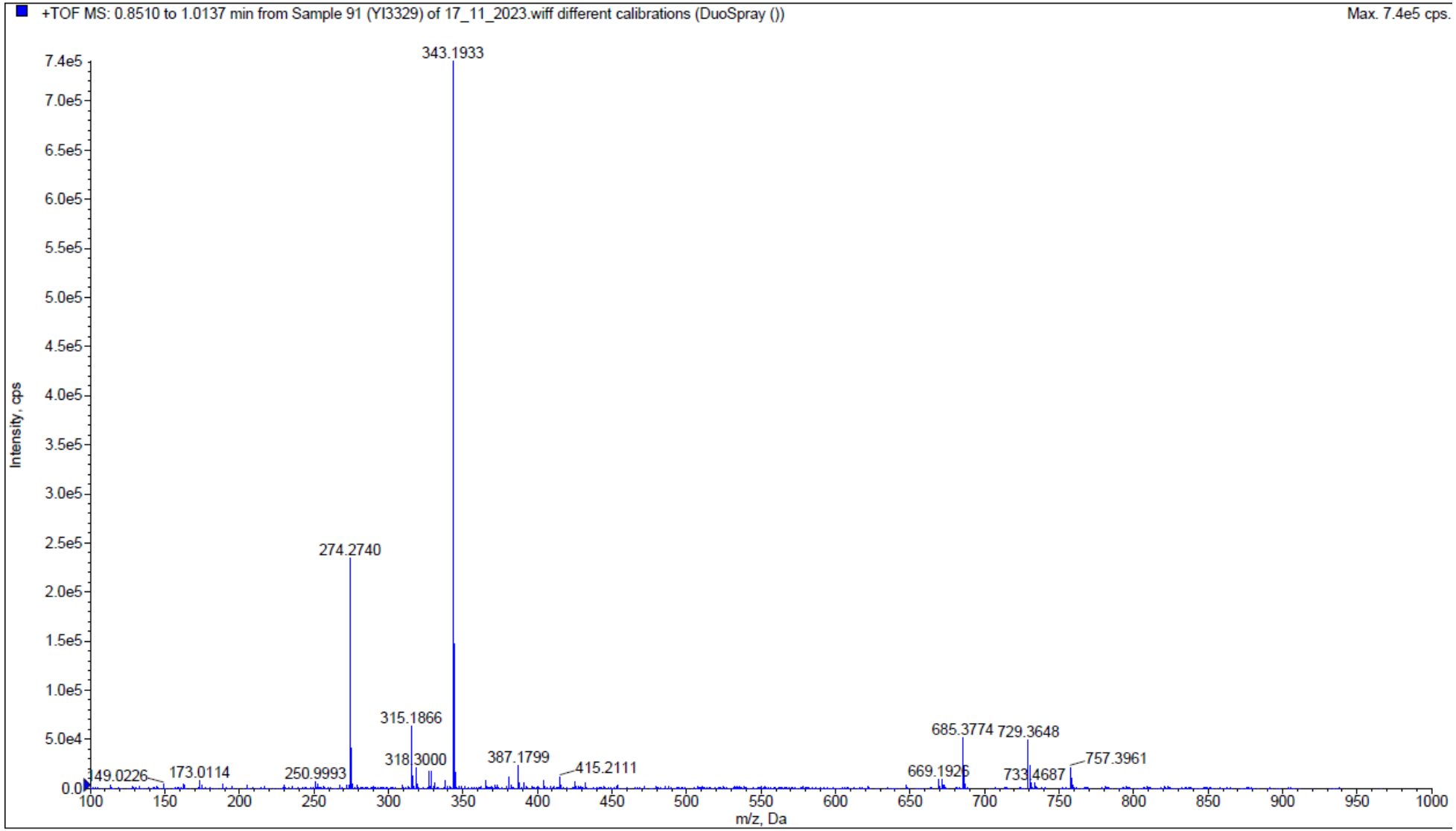
HRMS spectrum of 28



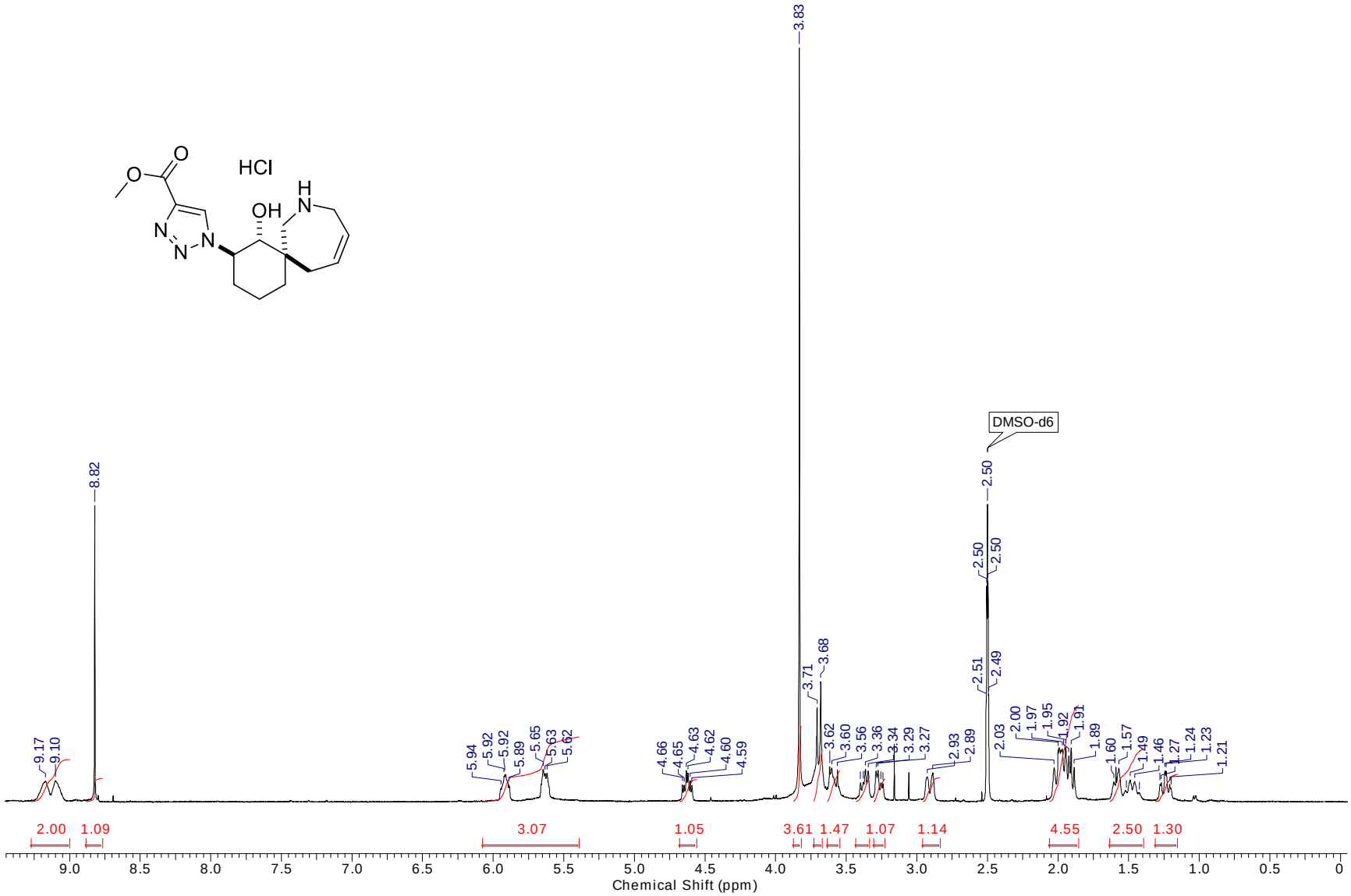
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 29



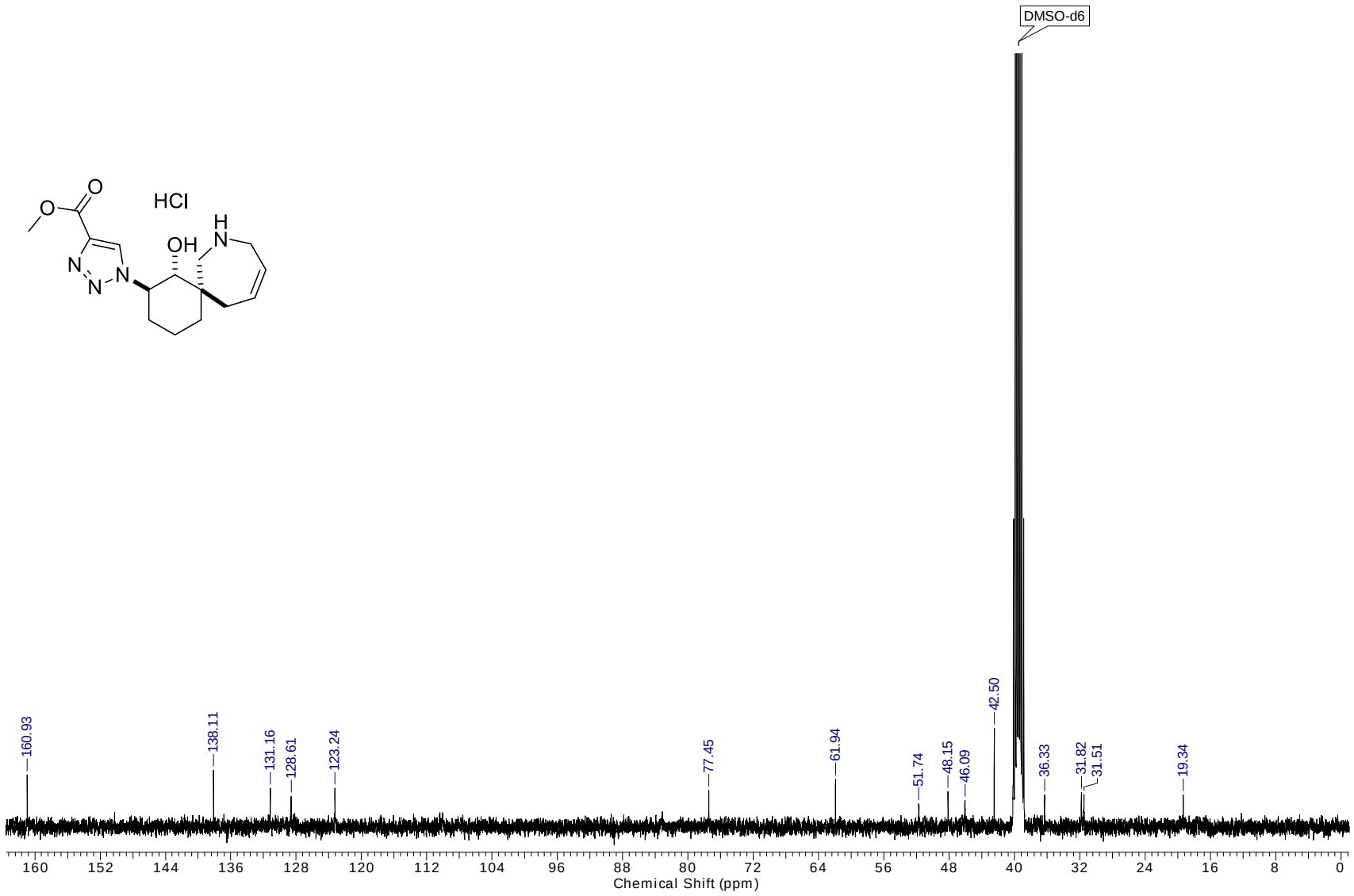
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of 29



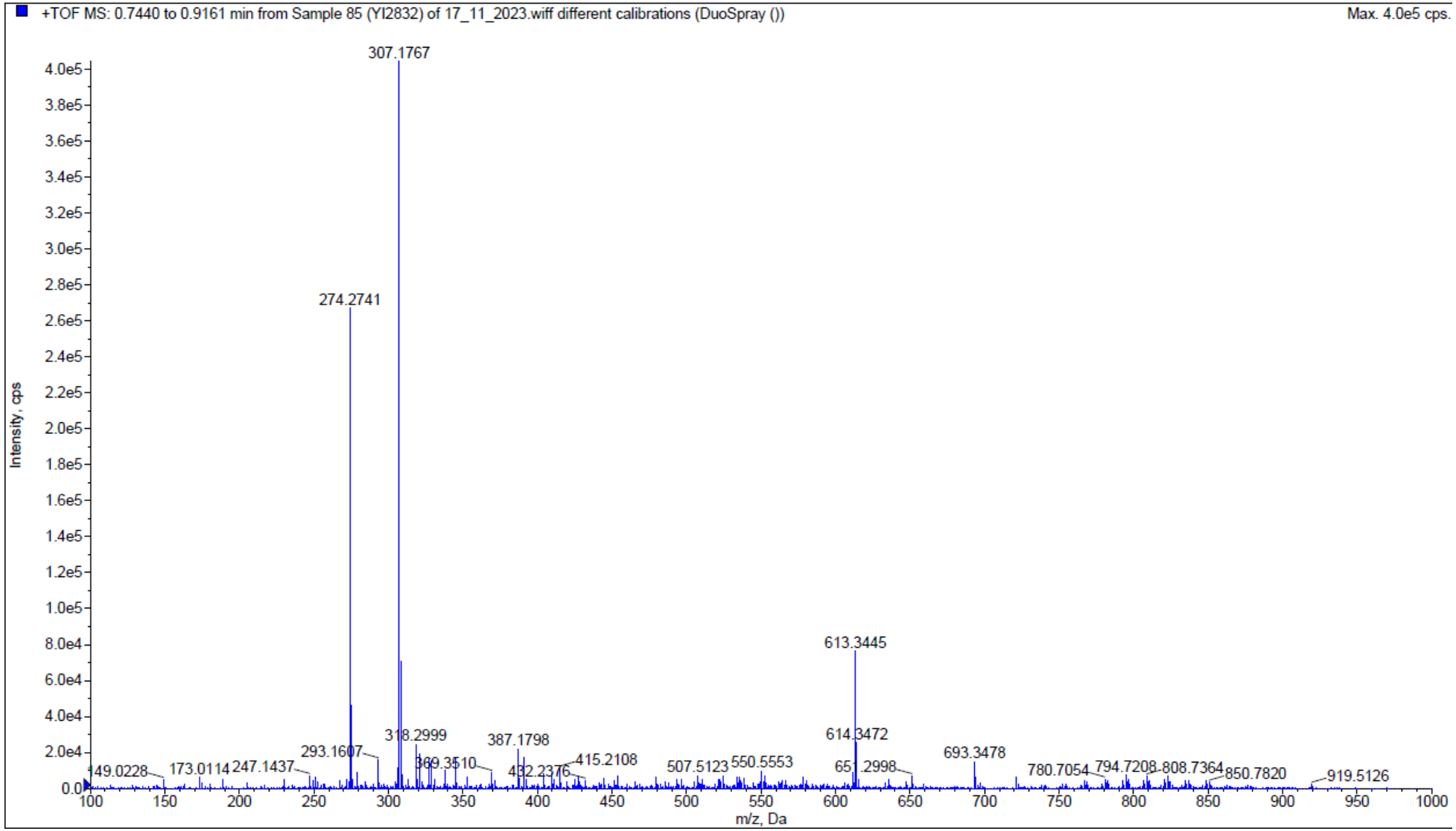
HRMS spectrum of 29



^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 30



^{13}C NMR (100 MHz, DMSO-d_6) spectrum of 30



HRMS spectrum of 30