Supplementary Information (SI) for Organic Chemistry Frontiers.

Oxetane as a part of modern medicinal chemistry toolbox: the case of 3,3-disubstituted building blocks (Supporting Information File)

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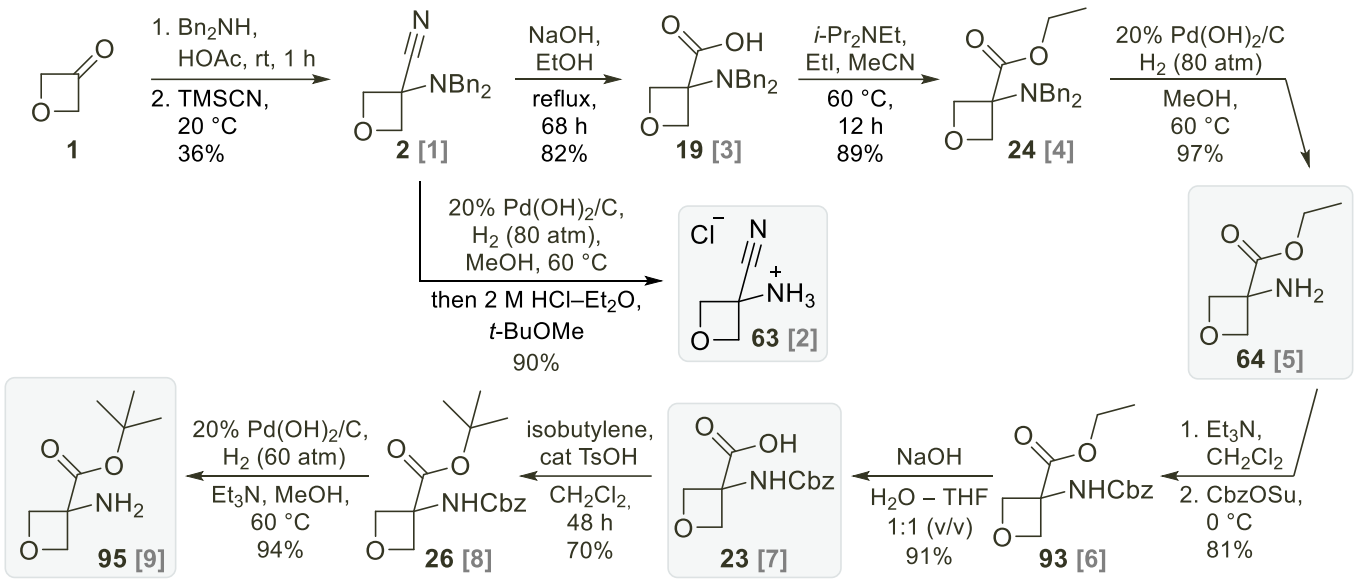
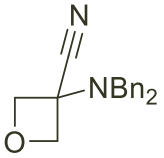


Scheme S1. Preparation of derivatives of oxetane-containing amino acids 23, 63, 64, and 95

3-Aminooxetane-3-carbonitrile (2). [1]

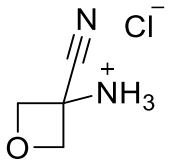


Pre–cooled solution dibenzylamine (42.8 g,0.217 mol) in HOAc (50 mL) was added at rt to a solution of oxetan–3–one (15.6 g, 0.217 mol) in HOAc (50 mL). The reaction mixture was stirred at rt for 1 h, then TMSCN (21.5 g, 217 mmol) was added dropwise at 20 °C. NOTE: due to significant exothermicity and heat generation, additional cooling was required prior to the dropwise addition when the reaction is performed on a larger scale. The resulting mixture was stirred at rt overnight (ca. 16 h), then evaporated in vacuo on a rotary evaporator. The residue was partitioned between H_2O (100 mL) and EtOAc (500 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (2 × 300 mL), and brine (2 × 300 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo to give the crude product, which was purified by column flash chromatography on silica gel (EtOAc – petroleum ether, 3:100, v/v).

NOTE: in the case of synthesis on up to 1 kg scale, the product could be separated by evaporation and then used directly in the subsequent hydrolysis step without additional purification. The residual amount of HOAc is neutralized with an excess of aq NaOH.

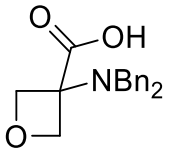
Yield 21.3 g (36%). Yellowish fusible crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 10H), 4.36 – 4.27 (m, 4H), 3.52 (d, J = 2.4 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 128.7, 128.1, 127.6, 117.3, 77.9, 60.3, 55.1. LC/MS (ES–API) m/z: 326 $[M+H]^+$. Anal. calcd. for $C_{18}H_{18}N_2O$: C 77.67; H 6.52; N 10.06, found C 77.93; H 6.66; N 10.12.

3-Aminooxetane-3-carbonitrile hydrochloride (63). [2]



Compound **2** (153 g, 0.550 mol) was dissolved in MeOH (1.7 L), the solution was placed in a high–pressure autoclave, and 20% $Pd(OH)_2/C$ (18.0 g) was added. The autoclave was sealed and hydrogenated with H_2 (80 atm) at 60 °C overnight (ca. 16 h). filtered, and the filtrate was evaporated in vacuo. If necessary, additional purification could be achieved by the addition of *t*-BuOMe, then titration with 2 M HCl – Et_2O until pH 7 was reached, followed by the filtration and drying. Yield 66.3 g (90%). Beige solid, mp 147–150 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 3H), 4.90 (d, J = 7.8 Hz, 2H), 4.85 (d, J = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 117.4, 76.4, 47.1. (ESI–TOF) *m/z*: $[M–HCl+H]^+$ calcd. for $C_4H_7N_2O$ 99.0553, found 99.0557.

3-(Dibenzylamino)oxetane-3-carboxylic acid (19). [3]



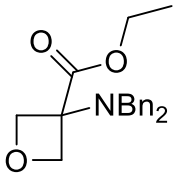
A solution of compound **2** (35.1 g, 0.126 mol) in EtOH (300 mL) was added to a solution of NaOH (20.1 g, 0.503 mol) in H_2O (200 mL), and the resulting mixture was refluxed overnight (ca. 16 h). Then the mixture was cooled to rt, and another portion of NaOH (10.0 g, 0.251 mol) was added. The resulting mixture was refluxed for 48 h, and then most of EtOH was evaporated in vacuo. NOTE: according to ^{1}H NMR, after 24 h the reaction mixture consisted of 17% of the starting nitrile **2**, 50% of the corresponding amide, and 35% of the carboxylic acid **3**. The residue was diluted with H_2O (200 mL) and washed with *t*–BuOMe (2 × 100 mL). Then, 10% aq $NaHSO_4$ was added at 0 °C to the aqueous layer until pH 4 was reached, and a colorless solid was precipitated. The precipitate was filtered, washed with H_2O (2 × 100 mL), and dried in vacuo.

NOTE: in the case of large–scale synthesis (up to 1 kg of the product in a single run), after the evaporation of EtOH, the residue was transferred into a separatory funnel. The upper layer containing the sodium carboxylate of **19** was separated. The bottom layer contained a concentrated alkali solution, and residual amounts of the product. The lower layer was discarded, and the upper layer was triturated with *t*–BuOMe to obtain a pure sodium carboxylate

of **3**, which was then subjected to an esterification reaction in DMF with EtI at 60 °C for the preparation of **24** (detailed procedure is given below). This approach shortens the amount of time needed to complete the procedure and increases the yield of the target products.

Yield 30.7 g (82%). Colorless solid, mp 171–172 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 3H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.25 (q, *J* = 4.9 Hz, 4H), 4.57 (d, *J* = 6.2 Hz, 2H), 4.45 (d, *J* = 6.2 Hz, 2H), 3.69 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.4, 138.8, 129.2, 128.5, 127.6, 78.1, 67.7, 54.9. HRMS (ESI–TOF) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{20}NO_3$ 298.1438, found 298.1429.

Ethyl 3-(dibenzylamino)oxetane-3-carboxylate (24). [4]

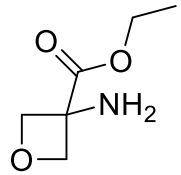


Compound **19** (9.10 g, 0.0306 mol) was dissolved in MeCN (90 mL), and *i*-Pr_2NEt (4.65 g, 0.0360 mol) was added. EtI (5.61 g, 0.0360 mol) was added, and the mixture was heated at 60 °C overnight (ca. 16 h) (ca. 16 h). Then the solution was cooled to rt, evaporated in vacuo, and the residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (50 mL). The organic layer was separated, washed with H_2O (50 mL), and brine (50 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo.

Alternative approach: sodium carboxylate of **3** (9.92 g, 0.0311 mol) was dissolved in DMF (90 mL), and EtI (13.8 g, 0.0880 mol) was added. The mixture was heated at 60 °C overnight (ca. 16 h). Then the solution was cooled, evaporated to dryness, and the residue was partitioned between EtOAc (100 mL) and H_2O (50 mL). The organic layer was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo.

Yield 8.87 g (89%). Yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.16 (m, 10H), 4.47 (d, *J* = 6.2 Hz, 2H), 4.41 – 4.32 (m, 4H), 3.59 (s, 4H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.9, 138.8, 129.0, 128.2, 127.3, 78.0, 67.5, 61.1, 54.7, 14.6. LC/MS (ES–API) m/z: 326 $[M+H]^+$. Anal. calcd. for $C_{20}H_{23}NO_3$: C 73.82; H 7.12; N 4.30, found C 73.89; H 7.44; N 4.34.

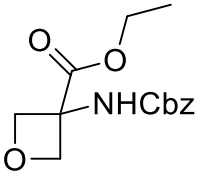
Ethyl 3-aminooxetane-3-carboxylate (64). [5]



Compound **24** (179 g, 0.550 mol) was dissolved in EtOH, the solution was placed in a high–pressure autoclave, and 20% $Pd(OH)_2/C$ (18.0 g) was added. The autoclave was sealed and hydrogenated with H_2 (80 atm) at 60 °C overnight (ca. 16 h). The resulting mixture was filtered, and the filtrate was evaporated in vacuo.

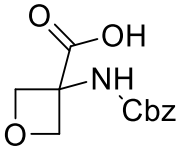
NOTE: In case of incomplete conversion, the mixture should be stirred for an additional 24 h upon the same conditions, or should be filtered following by the addition of the initial amount of $Pd(OH)_2/C$. Attempted use of 10% Pd/C was unsuccessful. Yield 77.6 g (97%). Yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 6.4 Hz, 2H), 4.48 (d, *J* = 6.2 Hz, 2H), 4.28 (q, *J* = 1.4 Hz, 2H), 2.08 (s, 2H), 1.33 (t, *J* = 1.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 82.1, 61.9, 59.0, 14.2. LC/MS (ES–API) m/z: 146 $[M+H]^+$. Anal. calcd. for $C_6H_{11}NO_3$: C 49.65; H 7.64; N 9.65, found C 49.71; H 7.87; N 9.27.

Ethyl 3-(((benzyloxy)carbonyl)amino)oxetane-3-carboxylate (93). [6]



Compound **64** (50.8 g, 0.350 mol) was dissolved in CH_2Cl_2 (500 mL), and Et_3N (71.8 g, 0.710 mol) was added. Then, the reaction mixture was cooled with ice to 0 °C, and CbzOSu (1–{[(Benzyloxy)carbonyl]oxy}–2,5–pyrrolidinedione, 87.2 g, 0.350 mol) was slowly added. The resulting mixture was stirred overnight (ca. 16 h), then washed with H_2O (300 mL) and brine (200 mL), passed through a layer of Na_2SO_4 – silica gel – Na_2SO_4 (1:1:1, v/v/v), and the organic layer was evaporated. NOTE: temperature is to be maintained under 50 °C, due to substance degradation. Yield ca. 79.2 g (ca. 81%). The compound was used in the next step immediately after the preparation without additional purification, which allowed the synthesis of the target compounds in higher yields.

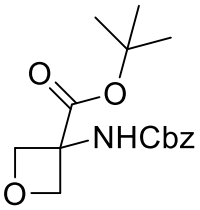
3-(((Benzyloxy)carbonyl)amino)oxetane-3-carboxylic acid (23). [7]



Compound **93** (88.0 g, 0.315 mol) was dissolved in 500 mL of H_2O and 500 mL of THF, then NaOH (37.8 g, 1.11 mol) was added at vigorous stirring and the mixture was left overnight (ca. 16 h). Then THF was evaporated, the aqueous layer was washed with *t*–BuOMe (2 × 150 mL), and 10% aq $NaHSO_4$ was added to the aqueous layer until pH 5 was reached. The resulting mixture was extracted with EtOAc (3 × 300 mL), the combined organic

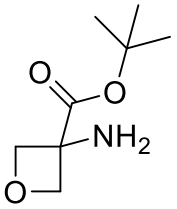
layers were dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. Yield 80.1 g (91%). Colorless solid, mp 106–108 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.38 (s, 1H), 7.39 – 7.27 (m, 5H), 5.09 – 4.94 (m, 2H), 4.79 (d, J = 6.5 Hz, 2H), 4.50 (d, J = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.1, 155.3, 136.7, 128.3, 127.8, 127.7, 76.9, 65.5, 57.4. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_{12}H_{14}NO_5$ 252.0866, found 252.0872.

tert-Butyl 3-(((benzyloxy)carbonyl)amino)oxetane-3-carboxylate (26). [8]

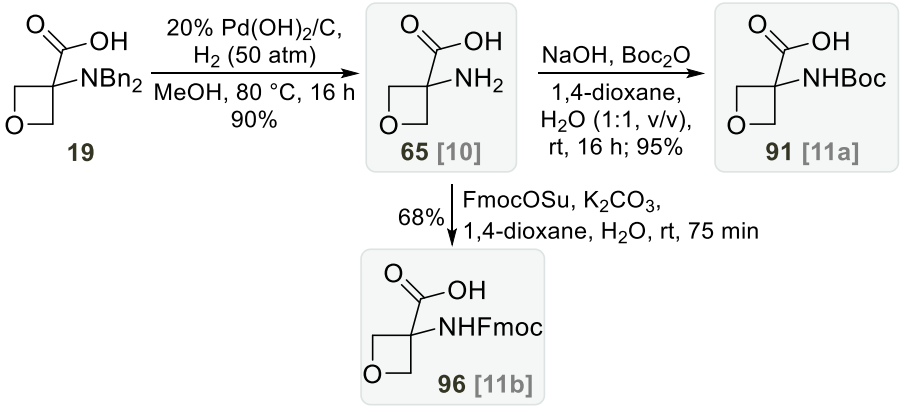


Compound **23** (40.0 g, 0.159 mol) was dissolved in CH_2Cl_2 (400 mL), and a catalytic amount of TsOH (5mol %) was added. Gaseous isobutylene (26.8 g, 0.477 mol) was condensed separately from a gas cylinder, and the resulting mixture was stirred in a high–pressure autoclave for 72 h. Then the autoclave was opened, and aq $NaHCO_3$ (200 mL) was added. The organic layer was separated, washed with brine (200 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. Yield ca. 34.2 g (ca. 70%). The compound was used in the next step immediately after the preparation without additional purification, which allowed the synthesis of the target compounds in higher yields.

tert-Butyl 3-aminooxetane-3-carboxylate (95). [9]

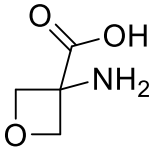


Compound **26** (28.0 g, 90.0 mmol) was dissolved in MeOH (500 mL), then 20% $Pd(OH)_2/C$ (2.80 g) and Et_3N (18.6 g, 180.0 mmol) were added. The mixture was stirred at 60 °C in a high–pressure autoclave under H_2 (60 atm) overnight (ca. 16 h). The resulting mixture was filtered, and the filtrate was evaporated in vacuo. Yield 14.7 g (94%). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (d, J = 6.3 Hz, 2H), 4.47 (d, J = 6.3 Hz, 2H), 2.19 (br s, 2H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 82.4, 82.4, 59.6, 28.1. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_8H_{16}NO_3$ 174.1125, found 174.1119.



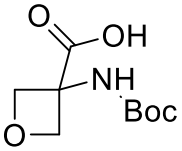
Scheme S2. Preparation of oxetane-containing derivatives of amino acids 65, 91, and 96

3-Aminooxetane-3-carboxylic acid (65). [10]



Compound **19** (10.0 g, 33.7 mmol) was dissolved in MeOH (100 mL), and 20% $Pd(OH)_2/C$ (1.00 g) was added. The mixture was stirred at 80 °C in a high–pressure autoclave under H_2 (50 atm) overnight (ca. 16 h). Then, the solution was filtered, and the precipitate was washed with H_2O. NOTE: compound **66** is insoluble in MeOH, and the filtrate was evaporated in vacuo. Yield 3.58 g (90%). Colorless solid, mp 201–203 °C. ^{1}H NMR (500 MHz, D_2O) δ 4.88 (s, 2H), 4.71 – 4.63 (m, 5H). ^{13}C NMR (151 MHz, D_2O) δ 172.3, 77.2, 58.4. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_4H_8NO_3$ 118.0499, found 118.0499.

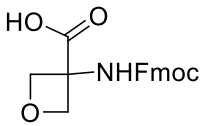
3-{[(*tert*-Butoxy)carbonyl]amino}oxetane-3-carboxylic acid (91). [11a]



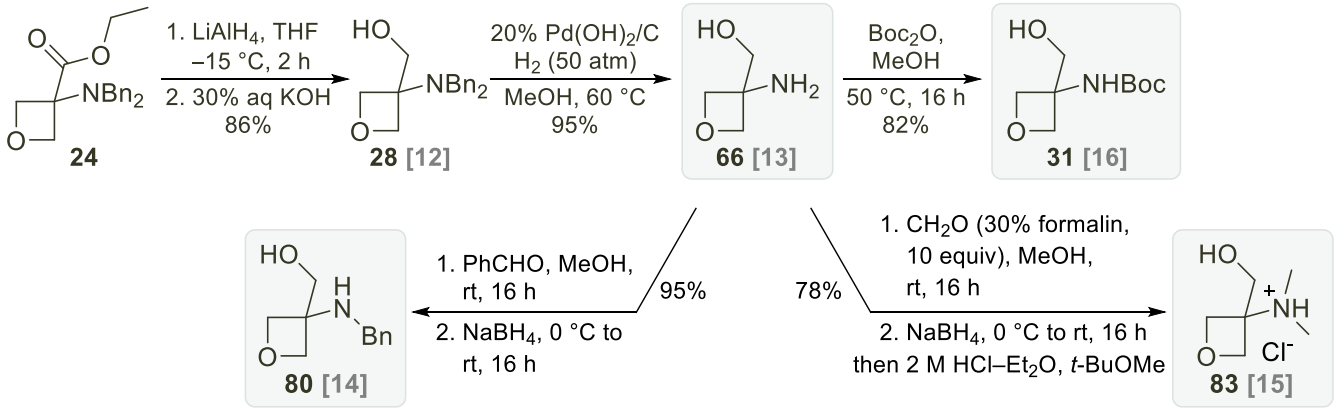
Compound **65** (10.2 g, 87.1 mmol) was dissolved in 1,4–dioxane – H_2O (100 mL, 1:1, v/v). Then NaOH (10.4 g, 0.262 mol) and Boc_2O (22.9 g, 0.104 mol) were added at rt, and the mixture was stirred overnight (ca. 16 h). Then, the solution was evaporated, and the residue was diluted with H_2O (50

mL). The solution was extracted with *t*–BuOMe (2 × 25 mL), and 10% aq $NaHSO_4$ was added to the aqueous layer until pH 4 was reached. The resulting mixture was extracted with EtOAc (3 × 25 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The compound existed as a mixture of rotamers. Yield 17.9 g (95%). Colorless solid, mp 129–132 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 7.92 (br s, 1H), 4.73 (d, J = 9.5 Hz, 2H), 4.45 (d, J = 6.4 Hz, 2H), 1.38 (s, 7H) and 1.30 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.4, 154.8, 78.6 and 77.3, 77.0, 57.2, 28.1 and 27.8. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_9H_{16}NO_5$ 218.1023, found 218.1018.

3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)oxetane-3-carboxylic acid (96). [11b]

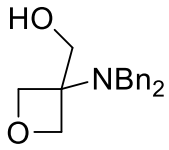


A solution of FmocOSu (3.20 g, 9.50 mmol) in 1,4-dioxane (30 mL) was added to a solution of 3-amino-oxetane-3-carboxylic acid (**65**, 1.17 g, 10.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) in H_2O (30 mL). The light yellow opaque solution was stirred at rt for 75 min. During that time, a colorless solid precipitated. The mixture was diluted with H_2O (20 mL), and extracted with Et_2O (2 × 25 mL). The colorless solid did not dissolve and was kept therefore in the aqueous layer, which was acidified to pH 2 by the addition of 1 M HC1 and extracted with EtOAc (3 × 20 mL). The combined EtOAc layers were washed with brine, dried with Na_2SO_4, and evaporated. Yield 2.31 g (68%). Colorless solid, mp 169–171 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.05 (br s, 1H), 8.39 (s, 1H), 7.90 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 4.80 (d, J = 6.5 Hz, 2H), 4.51 (d, J = 6.5 Hz, 2H), 4.34 (d, J = 6.8 Hz, 2H), 4.25 (t, J = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.2, 155.3, 143.7, 140.8, 127.7, 127.1, 125.2, 120.2, 77.0, 65.6, 57.4, 46.6. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_{19}H_{17}NO_5$ 340.1179, found 340.1175.



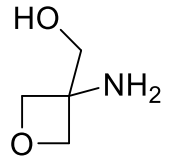
Scheme S3. Synthesis of oxetane ethanolamines 31, 66, 80, and 83

(3-(Dibenzylamino)oxetan-3-yl)methanol (28). [12]



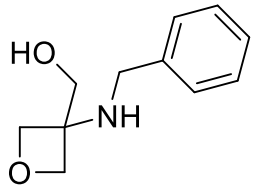
$LiAlH_4$ (4.41 g, 0.116 mol) was added to THF (350 mL), and the mixture was cooled to –15 °C. Then compound **24** (34.5 g, 0.106 mol) in THF (50 mL) was added dropwise at –15 °C. The mixture was stirred at –15 °C for 2 h, and then 30 % aq KOH (9.50 g, 0.169 mol) was added at –15 °C. The mixture was warmed up to rt, stirred for an additional 2 h, then filtered and evaporated, and used in the next step without any purification needed. Yield 25.7 g (86%). Colorless fusible solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 10H), 4.58 (d, *J* = 6.2 Hz, 2H), 4.21 (s, 2H), 4.12 (d, *J* = 6.3 Hz, 2H), 3.77 (s, 4H), 2.46 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 128.0, 127.8, 126.7, 77.0, 63.9, 63.5, 53.5. LC/MS (ES–API) m/z: 284 $[M+H]^+$. Anal. calcd. for $C_{18}H_{21}NO_2$: C 76.30; H 7.47; N 4.94, found C 76.40; H 7.23; N 4.96.

(3-Aminooxetan-3-yl)methanol (66). [13]



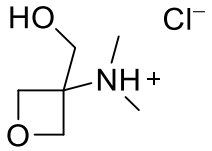
Compound **28** (12.2 g, 0.0431 mol) was dissolved in MeOH (120 mL), and 20% $Pd(OH)_2$/C (1.20 g) was added. The mixture was stirred at 60 °C in a high-pressure autoclave under H_2 (50 atm) overnight (ca. 16 h). Then, the solution was filtered and evaporated in vacuo. The residue was dissolved in $CHCl_3$ (50 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. Yield 4.21 g (95%). Grey solid, mp 92–94 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (d, *J* = 6.5 Hz, 2H), 4.43 (d, *J* = 6.5 Hz, 2H), 3.81 (s, 2H), 2.18 – 1.90 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.5, 66.7, 56.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_4H_{10}NO_2$ 104.0706, found 104.0708.

[3-(Benzylamino)oxetan-3-yl]methanol (80). [14]



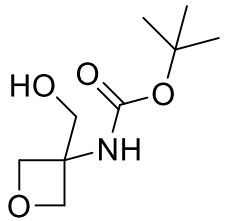
Amine **66** (14.4 g, 0.139 mol) was dissolved in MeOH (145 mL), and benzaldehyde (14.7 g, 0.139 mol) was added. The reaction mixture was stirred at rt overnight (ca. 16 h). Then, $NaBH_4$ (5.70 g, 0.153 mol) was added in portions at 0 °C, and the reaction mixture was warmed up to rt, and stirred overnight (ca. 16 h). The resulting mixture was poured into H_2O (100 mL), and most of MeOH was evaporated in vacuo. The aqueous residue was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 25.3 g (95%). Colorless solid, mp 58–59 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 4H), 7.31 – 7.24 (m, 1H), 4.57 (d, *J* = 6.7 Hz, 2H), 4.41 (d, *J* = 6.7 Hz, 2H), 3.88 (s, 2H), 3.78 (s, 2H), 2.20 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 128.2, 127.5, 127.0, 78.4, 63.7, 60.3, 46.6. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_{11}H_{16}NO_2$ 194.1176, found 194.1169.

[3-(Dimethylamino)oxetan-3-yl]methanol hydrochloride (83). [15]



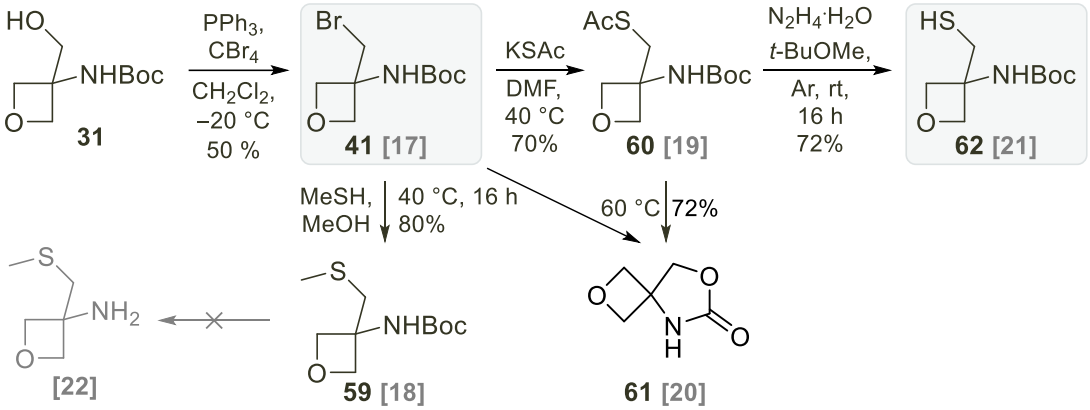
Amine **66** (14.4 g, 0.139 mol) was dissolved in MeOH (145 mL), and 30% formalin (58.4 g) was added. The reaction mixture was stirred at rt overnight (ca. 16 h). Then, $NaBH_4$ (5.78 g, 0.153 mol) was added in portions at 0 °C, and the reaction mixture was warmed up to rt and stirred overnight (ca. 16 h). The resulting mixture was poured into H_2O (100 mL), and most of MeOH was evaporated in vacuo. The aqueous residue was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo. The product was obtained as a hydrochloride by the addition of *t*-BuOMe, then titration with 2 M HCl – Et_2O until pH 7 was reached, followed by the filtration and drying. Yield 18.2 g (78%). Beige solid, mp 173–176 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.00 (br s, 1H), 5.86 (br s, 1H) 4.81 (d, *J* = 7.3 Hz, 2H), 4.36 (d, *J* = 7.3 Hz, 2H), 4.01 (s, 2H), 2.71 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 73.2, 65.5, 59.5, 38.0. HRMS (ESI–TOF) m/z: $[M–HCl+H]^+$ calcd. for $C_6H_{14}NO_2$132.1019, found 132.1026.

***tert*-Butyl *N*-[3-(hydroxymethyl)oxetan-3-yl]carbamate (31). [16]**



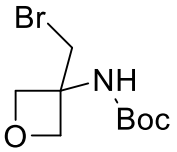
Amine **66** (12.6 g, 0.123 mol) was dissolved in MeOH (130 mL), and Boc_2O (27.7 g, 0.127 mol) was added over 30 min. The mixture was heated at 50 °C overnight (ca. 16 h), then cooled and evaporated in vacuo. In the case when Boc_2O remained after the reaction, it could be removed by triturating

with hexanes. Yield 20.1 (82%). Beige solid, mp 128–129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (s, 1H), 4.66 (d, *J* = 6.5 Hz, 2H), 4.53 (d, *J* = 6.5 Hz, 2H), 4.02 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 80.1, 77.7, 65.4, 56.4, 27.8. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_9H_{18}NO_4$ 204.1230, found 204.1225.



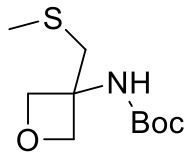
Scheme S4. Synthesis of oxetane-containing bromide 41 and thiol 62

***tert*-Butyl (3-(bromomethyl)oxetan-3-yl)carbamate (41). [17]**



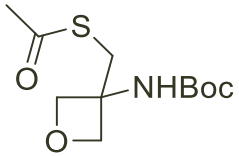
Compound **31** (9.00 g, 44.3 mmol) was dissolved in CH_2Cl_2 (90 mL), and PPh_3 (17.6 g, 67.0 mmol) was added. The reaction mixture was cooled to –20 °C, and CBr_4 (22.3 g, 67.0 mmol) in CH_2Cl_2 (90 mL) was added dropwise at –20 °C. The mixture was stirred at rt overnight (ca. 16 h). Then, the solution was evaporated, and the residue was purified by column chromatography on silica gel using hexanes – EtOAc (4:1, v/v) as an eluent. NOTE: PPh_3 is eluted first, followed by the pure compound **41**. The compound existed as a mixture of rotamers. Yield 5.85 g (50%). Colorless powder, mp 124–125 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (s, 1H), 4.46 (d, *J* = 6.6 Hz, 2H), 4.35 (d, *J* = 6.6 Hz, 2H), 3.96 (s, 2H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.1, 78.6 and 77.8, 69.2, 64.3 and 63.8, 60.9 and 55.6, 28.1 and 27.1. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_9H_{17}BrNO_3$ 266.0387 / 268.0366, found 266.0377 / 268.0357.

tert-Butyl (3-((methylthio)methyl)oxetan-3-yl)carbamate (59). [18]



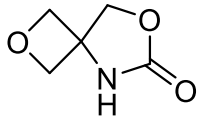
MeSH (2.40 g, 50.4 mmol) in H_2O was added to compound **41** (11.0 g, 42.0 mmol) in MeOH (100 mL), and the mixture was stirred at 40 °C overnight (ca. 16 h). Then, MeOH was evaporated, the residue was diluted with H_2O (100 mL), and the mixture was extracted with *t*–BuOMe (3 × 50 mL). Combined extracts were passed through a layer of Na_2SO_4 – silica gel – Na_2SO_4 (1:1:1, v/v/v), and evaporated in *vacuo*. Yield 7.75 g (80%). Colorless fusible solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 4.68 (d, J = 6.6 Hz, 2H), 4.47 (d, J = 6.6 Hz, 2H), 3.21 (s, 2H), 2.18 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 79.7, 56.3, 42.0, 40.1, 27.8, 16.8. LC/MS (ES–API) m/z: 234 $[M\text{-}H_2C{=}C(CH_3)_2{+}H]^+$. Anal. calcd. for $C_{10}H_{19}NO_3S$: C 51.48; H 8.21; N 6.00; S 13.74, found C 51.38; H 8.05; N 6.29; S 13.96.

***S*-((3-((*tert*-Butoxycarbonyl)amino)oxetan-3-yl)methyl) ethanethioate (60). [19]**



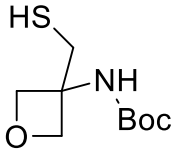
Compound **41** (10.0 g, 37.7 mmol) was dissolved in DMF (150 mL), and KSAc (21.9 g, 189 mmol) was added. The mixture was stirred at 40 °C overnight (ca. 16 h). NOTE: the reaction does not proceed at at 20 °C, and by-products are formed at 60 °C – cyclic byproduct, isolated by the evaporation of aqueous mixture **62**. For isolation, the mixture was diluted with H_2O (300 mL), extracted with EtOAc (3 × 150 mL), and the combined organic layers were washed with H_2O (150 mL), brine (150 mL), passed through a layer of Na_2SO_4 – silica gel – Na_2SO_4 (1:1:1, v/v/v), and evaporate. NOTE: the resulting substance has an unpleasant smell. The compound was quickly analyzed by ^{1}H NMR and used in the next step immediately after the preparation without additional purification, which allowed the synthesis of the target compounds in higher yields. Yield ca. 6.94 (ca. 70%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (s, 1H), 4.67 (s, 2H), 4.44 – 4.39 (m, 2H), 3.58 (s, 2H), 2.39 – 2.35 (m, 3H), 1.44 (s, 9H).

2,7-Dioxa-5-azaspiro[3.4]octan-6-one (61). [20]

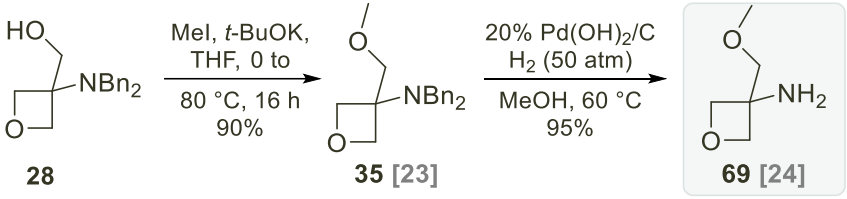


The product could be obtained according to the procedure for the preparation of thioacetate **60**, when the reaction is performed at 60 °C. Yield 350 mg (72% from **41** (1.00 g, 3.77 mmol). Beige solid, mp 111–112 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (br s, 1H), 4.63 (d, J = 7.0 Hz, 2H), 4.61 (d, J = 7.0 Hz, 2H), 4.55 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 157.3, 82.1, 72.7, 58.4. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_5H_8NO_3$ 130.0499, found 130.0498.

tert-Butyl (3-(mercaptomethyl)oxetan-3-yl)carbamate (62). [21]

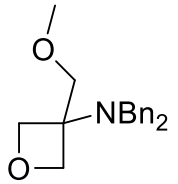


Hydrazine monohydrate (3.40 g, 68.0 mmol) was added to compound **60** (11.9 g, 45.6 mmol) in *t*–BuOMe (150 mL) in argon atmosphere. The reaction mixture was stirred overnight (ca. 16 h) at rt. NOTE: an inert atmosphere prevents the side formation of disulfide). The reaction mixture was passed through a layer of Na_2SO_4 – silica gel – Na_2SO_4 (1:1:1, v/v/v), washed with *t*–BuOMe (4 × 100 mL), evaporated, and the flask with the product was filled with argon. The compound existed as a mixture of rotamers. Yield 7.13 g (72%). Yellowish solid, mp 86–87 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (s, 1H), 4.45 (d, J = 6.3 Hz, 2H), 4.33 (d, J = 6.3 Hz, 2H), 2.99 (d, J = 7.7 Hz, 2H), 2.23 (d, J = 8.0 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.0, 78.9 and 78.3, 78.1, 56.1, 29.6 and 27.2, 28.1. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_9H_{18}NO_3S$ 220.1002, found 220.0998.



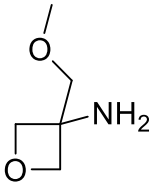
Scheme S5. Synthesis of methoxymethyl oxetan-3-amine 69

N,N-Dibenzyl-3-(methoxymethyl)oxetan-3-amine (35). [23]

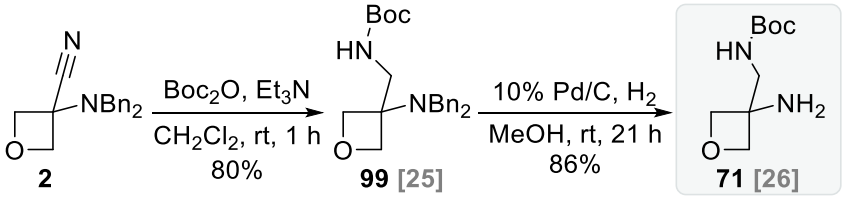


Alcohol **28** (28.8 g, 0.102 mol) was dissolved in THF (300 mL), and *t*-BuOK (17.2 g, 0.153 mol) was added. The mixture was cooled to 0 °C, and MeI (43.6 g, 0.307 mol) was added dropwise. The resulting mixture was stirred at 80 °C overnight (ca. 16 h). If the reaction is incomplete, an additional 30% of the initial amount of *t*-BuOK and MeI should be added, and the reaction should be heated for another night (ca. 16 h). The reaction mixture was then poured onto a saturated NH_4Cl solution. The organic phase was separated, and the aqueous phase was extracted with *t*-BuOMe (3 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (300 mL), dried over Na_2SO_4, filtered, and evaporated again. Yield 27.4 g (90%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.37 – 7.30 (m, 4H), 7.28 – 7.22 (m, 4H), 7.22 – 7.13 (m, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 4.05 – 3.97 (m, 4H), 3.62 (s, 4H), 3.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 128.8, 128.1, 127.0, 78.7, 73.7, 63.4, 59.5, 54.4. LC/MS (ES-API) m/z: 298 $[M+H]^+$. Anal. calcd. for $C_{19}H_{23}NO_2$: C 76.74; H 7.80; N 4.71, found C 76.72; H 7.63; N 5.05.

3-(Methoxymethyl)oxetan-3-amine (69). [24]

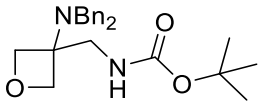


Compound **35** (18.0 g, 0.0605 mol) was dissolved in MeOH (200 mL), the solution was placed in a high–pressure autoclave, and 20% $Pd(OH)_2/C$ (1.7 g) was added. The autoclave was sealed and hydrogenated with H_2 (80 atm) at 60 °C overnight (ca. 16 h). The resulting mixture was filtered, and the filtrate was evaporated in vacuo. Yield 6.67 g (95%). Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 – 4.43 (m, 4H), 3.62 (s, 2H), 3.43 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.4, 59.4, 59.4, 56.2. LC/MS (ES-API) m/z: 118 $[M+H]^+$. Anal. calcd. for $C_5H_{11}NO_2$: C 51.26; H 9.46; N 11.96, found C 51.11; H 9.40; N 12.32.



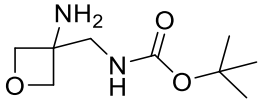
Scheme S6. Synthesis of mono-protected oxetane diamine 71

tert-Butyl ((3-(dibenzylamino)oxetan-3-yl)methyl)carbamate (99). [25]

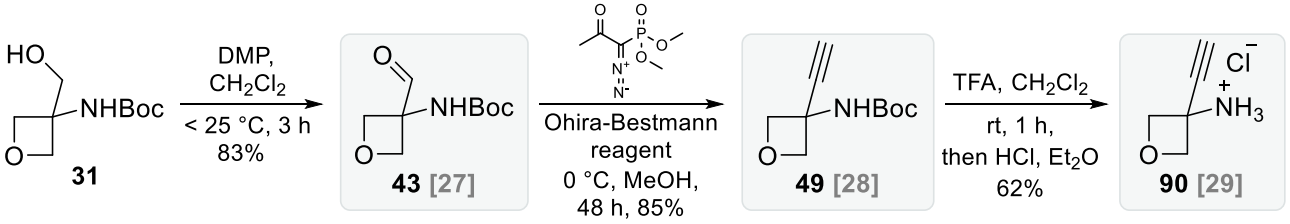


$NaBH_4$ (815 mg, 21.6 mmol) was added in portions to a solution of compound **2** (1.00 g, 3.59 mmol) and $CoCl_2 \times 6H_2O$ (256 mg, 1.08 mmol) in MeOH (10 mL) at 0 °C, and the resulting mixture was stirred at rt for 30 min. After that, Boc_2O (0.941 g, 4.31 mmol) was added dropwise at 0 °C, and the resulting mixture was stirred at rt for 16 h. Then, the solution was poured into sat. aq NH_4Cl (500 mL), and the target product was extracted with EtOAc (3 × 500 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The mixture was concentrated, the residue was purified by column chromatography using silica gel (pentane: EtOAc = 10:1 to 5:1, v/v, gradient). The compound was used in the next step immediately after the purification. Yield ca. 1.09 g (ca. 80%). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 10H), 4.48 (d, J = 6.3 Hz, 2H), 4.03 (d, J = 6.1 Hz, 2H), 3.77 (d, J = 5.6 Hz, 2H), 3.66 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 128.1, 127.8, 126.7, 79.1, 77.7, 63.1, 53.1, 41.4, 27.9.

tert-Butyl _N_-[(3-aminooxetan-3-yl)methyl]carbamate (71). [26]

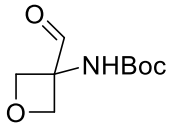


10% Pd/C (100 mg) was added to a solution of **99** (800 mg, 2.08 mmol) in MeOH (20 mL) and the mixture was stirred under H_2 (balloon, slight excess of 1 atm) for 9 h. Then, more 10% Pd/C (100 mg) was added, and the resulting mixture was stirred overnight (13 h) under an atmophere of H_2 (balloon). The mixture was filtered over Celite®, and washed with EtOAc, and the filtrate was concentrated in vacuo to dryness. Yield 365 mg (86%). Spectral and physical data were in accordance with that reported.[1] Beige crystals 74–77 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (t, J = 6.0 Hz, 1H), 4.48 (d, J = 6.5 Hz, 2H), 4.39 (d, J = 6.5 Hz, 2H), 3.44 (d, J = 6.0 Hz, 2H), 1.91 (br s, 2H), 1.43 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.5, 82.6, 79.6, 56.5, 47.0, 28.3. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_9H_{19}N_2O_3$ 203.1390, found 203.1389.



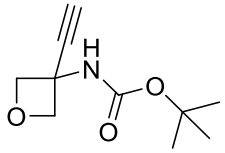
Scheme S7. Synthesis of oxetane amino aldehyde 43 and its conversion to acetylenes 49, and 90

tert-Butyl _N_-(3-formyloxetan-3-yl)carbamate (43). [27]



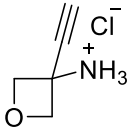
Compound **31** (74.0 g, 0.364 mol) was dissolved in CH_2Cl_2 (1.1 L), the reaction mixture was placed in a cooling bath, and DMP (187 g, 0.441 mol) was added in portions at 20 °C. NOTE: temperature elevation over 25–37 °C leads to substance degradation. The reaction mixture was stirred for 3 h, then poured into aq $NaHCO_3$ (123.6 g, 1.47 mol) and aq $Na_2S_2O_3$•$5H_2O$ (273 g, 1.10 mol) in H_2O (1.5 L). The resulting mixture was stirred for 1 h. Then the organic layer was separated, washed with H_2O (700 mL), brine (700 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. Yield 60.6 g (83%). Colorless solid, mp 87–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 4.90 (d, J = 6.7 Hz, 1H), 5.00 – 4.64 (m, 4H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.7, 154.7, 81.1, 75.6, 62.0, 28.2. HRMS (ESI–TOF) m/z: $[M–H_2C=C(CH_3)_2 +H]^+$ calcd. for $C_5H_8NO_4$ 146.0448, found 146.0445.

tert-Butyl _N_-(3-ethynyloxetan-3-yl)carbamate (49). [28]

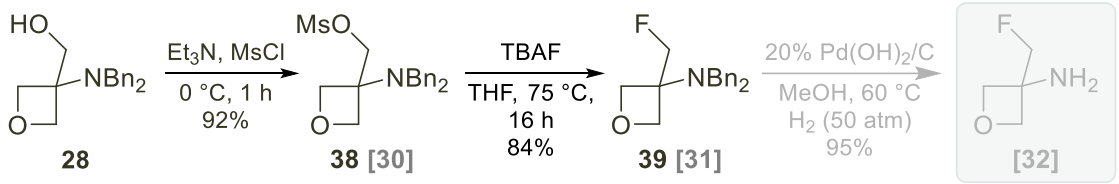


Compound **43** (22.4 g, 0.111 mol) was dissolved in MeOH (200 mL) and cooled with ice to 0 °C. The Ohira–Bestmann reagent (29.7 g, 0.155 mol), and K_2CO_3 (38.1 g, 0.276 mol) were added. The reaction mixture was warmed up to rt, stirred for 48 h, then diluted with H_2O (100 mL). Most of MeOH was evaporated in vacuo, and the resulting solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were passed through a layer of Na_2SO_4 – silica gel – Na_2SO_4 (1:1:1, v/v/v), and the solution was evaporated. The product was then crystallized from hexanes–_t_–BuOMe (100 mL, 2:1, v/v). Yield 18.6 g (85%). Beige crystals, 97–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (s, 1H), 4.83 (d, J = 6.4 Hz, 3H), 4.73 (d, J = 6.3 Hz, 3H), 2.56 (s, 1H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 82.5, 80.8, 80.4, 71.8, 48.8, 27.8. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_{10}H_{16}NO_3$ 198.1125, found 198.1122.

3-Ethynyloxetan-3-amine hydrochloride (90). [29][2]

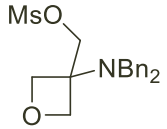


The corresponding *N*-Boc amine **49** (10.0 g, 50.7 mmol) was dissolved in CH_2Cl_2 (150 mL), and TFA (5.78 g, 3.90 mL, 50.7 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 1 h, and then 2 M HCl in Et_2O (25.4 mL) was added. NOTE: hydrochloride is crystalline in contrast to trifluoroacetate. The precipitate formed was filtered and dried on air. Yield 4.18 g (62%). Beige solid, 179–182 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (br s, 3H), 4.81 (d, J = 7.0 Hz, 2H), 4.65 (d, J = 7.1 Hz, 2H), 4.10 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 79.9, 79.4, 78.6, 47.8. HRMS (ESI–TOF) m/z: [M–HCl+H]+ calcd. for C_5H_8NO 98.0600, found 98.0602.



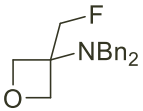
Scheme S8. Synthesis of fluoromethyl-substituted oxetan-3-amine 39

(3-(Dibenzylamino)oxetan-3-yl)methyl methanesulfonate (38). [30]



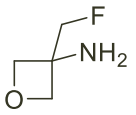
Compound **28** (14.2 g, 50.0 mmol) was dissolved in CH_2Cl_2 (150 mL), and Et_3N (6.58 g, 65.0 mmol) was added. The mixture was cooled with ice to 0 °C, and MsCl (6.01 g, 53.0 mmol) was added dropwise. The mixture was warmed to rt, stirred for 1 h, then poured into saturated aq $NaHCO_3$ (150 mL). The organic phase was separated, washed with saturated aq $NaHCO_3$ (75 mL), brine (75 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo at 30 °C (the compound should not be evaporated to dryness). The product was rapidly used in the next step without further purification due to its inherent instability and polymerization side reaction. Yield 18.2 g (92%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 10H), 4.82 (s, 2H), 4.41 (d, J = 6.3 Hz, 2H), 4.01 – 3.95 (m, 2H), 3.67 (s, 4H), 3.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 128.8, 128.3, 127.4, 77.5, 68.9, 62.9, 54.2, 37.5. LC/MS (ES-API) m/z: 362 $[M+H]^+$. Anal. calcd. for $C_{19}H_{23}NO_4S$: C 63.14; H 6.41; N 3.88; S 8.87, found C 63.53; H 6.16; N 3.64; S 9.19.

N,N-Dibenzyl-3-(fluoromethyl)oxetan-3-amine (39). [31]

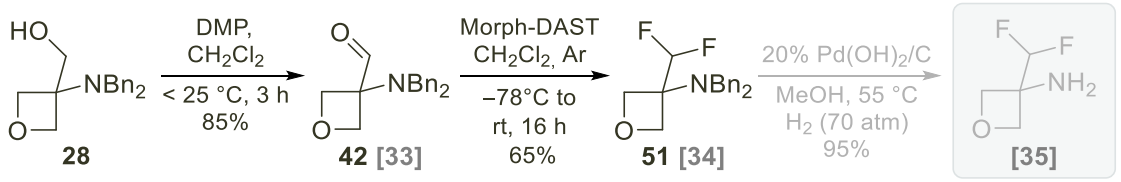


Compound **38** (17.1 g, 49.0 mmol) was dissolved in 1 M TBAF in THF (10.2 g, 49.0 mmol) and the resulting mixture was refluxed overnight (ca. 16 h) at 75 °C. Then, the THF was evaporated and *t*-BuOMe (200 mL) was added. The mixture of TBAF and *t*-BuOMe was separated, and the *t*-BuOMe was washed with H_2O (150 mL) and dried over Na_2SO_4. The solution was evaporated in vacuo. Yield 11.5 g (84%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.20 (m, 10H), 5.12 (d, *J* = 47.6 Hz, 2H), 4.40 (dd, *J* = 6.2, 4.0 Hz, 2H), 4.03 (d, *J* = 6.1 Hz, 2H), 3.68 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 128.3, 127.7, 126.8, 83.2 (d, *J* = 175.6 Hz), 76.8 (d, *J* = 8.3 Hz), 62.83 (d, *J* = 16.9 Hz), 53.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -225.03. LC/MS (ES-API) m/z: 286 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{20}FNO$: C 75.76; H 7.06; N 4.91, found C 75.36; H 6.84; N 5.29.

3-(Fluoromethyl)oxetan-3-amine [32]

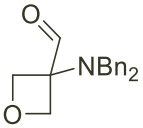


Compound **39** (11.2 g, 39.3 mmol) was dissolved in MeOH (110 mL), and 20% $Pd(OH)_2/C$ (1.20 g) was added. The mixture was heated at 60 °C overnight (ca. 16 h) under H_2 (50 atm) in a high–pressure autoclave. Then, the solution was filtered and evaporated in vacuo. NOTE: H_2O formed during the reaction. Moreover, during filtration, catalyst particles pass through the filter. Therefore, to obtain a pure product, it could be dissolved in $CHCl_3$, dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 3.91 g (95%). Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (d, *J* = 47.2 Hz, 2H), 4.52 (d, *J* = 6.7 Hz, 2H), 4.46 (dd, *J* = 6.8, 3.6 Hz, 2H), 1.77 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 87.1 (d, *J* = 172.5 Hz), 81.0 (d, *J* = 7.6 Hz), 56.2 (d, *J* = 19.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -229.7. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for C_4H_9FNO 106.0663, found 106.0664.



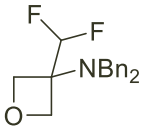
Scheme S9. Synthesis of CHF_2-substituted oxetan-3-amine 51

3-(Dibenzylamino)oxetane-3-carbaldehyde (42). [33]



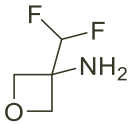
Compound **28** (60.2 g, 0.213 mol) was dissolved in CH_2Cl_2 (900 mL) and DMP (108.2 g, 0.255 mol) was gradually added. The reaction mixture was kept in a cooling bath to ensure that the temperature did not exceed 25 °C. The mixture was stirred for 3 h, then poured onto an aq $NaHCO_3$ (107.1 g, 1.28 mol) and $Na_2S_2O_3$•$5H_2O$ (210.9 g, 0.850 mol) and stirred for 1 h. After 1 h, the layers were separated and the organic layer was washed with H_2O (500 mL) and brine (500 mL). The solution was dried over Na_2SO_4 and evaporated in vacuo at 30 °C (the compound should not be evaporated to dryness). Yield 50.8 g (85%).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.38 – 7.27 (m, 10H), 4.56 – 4.50 (m, 2H), 4.45 – 4.39 (m, 2H), 3.83 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.1, 138.0, 128.3, 128.0, 127.1, 74.5, 69.8, 53.3. LC/MS (ES-API) m/z: 282 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{19}NO_2$: C 76.84; H 6.81; N 4.98, found C 76.94; H 6.48; N 4.93.

N,N-Dibenzyl-3-(difluoromethyl)oxetan-3-amine (51). [34]



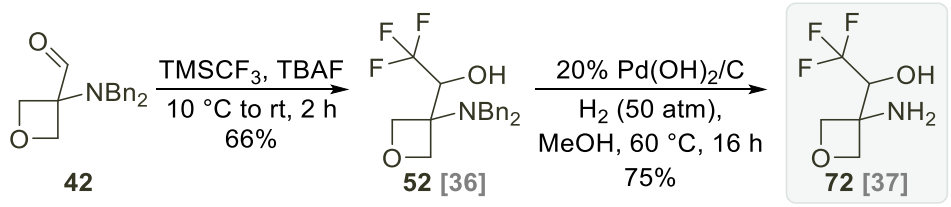
Compound **42** (21.3 g, 0.0758 mol) was dissolved in CH_2Cl_2 (200 mL) and cooled to –78 °C using a MeOH–liquid nitrogen bath. Morph–DAST (19.9 g, 0.114 mol) was slowly added under Ar, and the mixture was stirred at rt overnight (ca. 16 h). Then, the mixture was carefully poured onto a concentrated aq $NaHCO_3$ and stirred for 40 min. The solution was dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. NOTE: during the quenching process, extensive gas release is observed, therefore, a beaker of a larger volume is advised. The crude product was purified with column chromatography on silica gel using hexanes–EtOAc (7:3, v/v) as an eluent, and immediately used in the next step without additional purification. Yield ca. 14.1 g (ca. 65%). Yellow fusible crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 4H), 7.30 – 7.18 (m, 6H), 6.29 (t, J = 55.0 Hz, 1H), 4.48 – 4.42 (m, 2H), 4.29 (d, J = 6.7 Hz, 2H), 3.75 (s, 4H).

3-(Difluoromethyl)oxetan-3-amine [35]



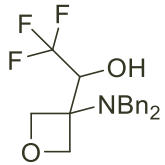
Compound **51** (44.4 g, 0.146 mol) was dissolved in MeOH (450 mL), and 20% $Pd(OH)_2$/C (4.40 g) was added. The mixture was heated at 55 °C overnight (ca. 16 h) under H_2 (70 atm) in a high–pressure autoclave, then filtered and evaporated in vacuo. NOTE: H_2O formed during the reaction. Moreover, during filtration, catalyst particles pass through the filter. To obtain a pure product, it could be dissolved in $CHCl_3$, dried over Na_2SO_4, filtered, and evaporated in vacuo. Note 2: due to the reaction with Morph–DAST in the previous step, residual amounts of sulfur-containing derivatives sometimes remained, so the reaction may not proceed at all overnight (ca. 16 h). In this case, *t*-BuOMe solution could be mixed in the presence of 10% aq $AgNO_3$ (10.0 g) at rt over 30 min to give a dark-colored precipitate separated directly on a separatory funnel. Then, another portion of $Pd(OH)_2$ is added to

complete the conversion of the hydrogenation. Yield 17.0 g (95%). Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (t, *J* = 56.2 Hz, 1H), 4.70 (d, *J* = 7.0 Hz, 2H), 4.45 (dt, *J* = 7.2, 2.5 Hz, 2H), 1.73 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 115.9 (t, *J* = 243.6 Hz), 78.3 (t, *J* = 5.0 Hz), 57.5 (t, *J* = 23.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -133.45. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_4H_8F_2NO$ 124.0568, found 124.0568.



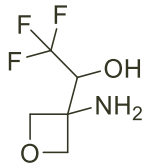
Scheme S10. Performing the Ruppert-Prakash reaction for the preparation of oxetane-containing amino ethanol 72

1-(3-(Dibenzylamino)oxetan-3-yl)-2,2,2-trifluoroethan-1-ol (52). [36]



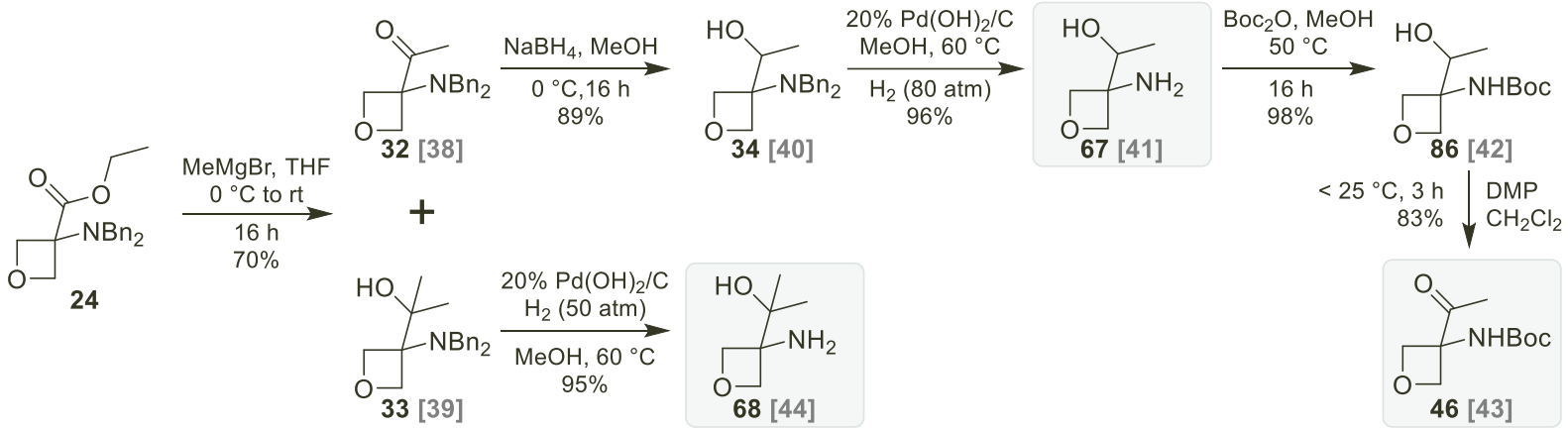
$TMSCF_3$ (39.6 g, 0.279 mol) was slowly added dropwise at 10 °C to a solution of aldehyde **42** (39.2 g, 0.139 mol). NOTE: the reaction is highly exothermic. Then, 10% TBAF (38.3 g, 0.146 mol) in THF was added via syringe. The mixture was stirred at rt for 1 h, and 10% TBAF (38.3 g, 0.146 mol) in THF was added. The mixture was stirred at rt for 1 h, then evaporated in vacuo. The residue was purified by column flash chromatography on silica gel (EtOAc – petroleum ether, 3:100, v/v), and immediately used in the next step. Yield ca. 32.2 g (ca. 66%). Yellowish oil.

-(3-Aminooxetan-3-yl)-2,2,2-trifluoroethan-1-ol (72). [37]



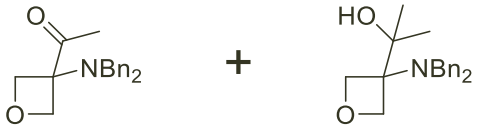
Compound **52** (11.2 g, 31.9 mmol) was dissolved in MeOH (110 mL), and 20% $Pd(OH)_2/C$ (1.20 g) was added. The mixture was heated at 60 °C overnight (ca. 16 h) under H_2 (50 atm) in a high–pressure autoclave. Then, the solution was filtered and evaporated in vacuo. NOTE: H_2O formed during

the reaction. Moreover, during filtration, catalyst particles pass through the filter. To obtain a pure product, it could be dissolved in $CHCl_3$, dried over Na_2SO_4,iltered, and evaporated in vacuo. Yield 4.09 g (75%). Colorless crystals, 111–112 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.52 (d, J = 6.3 Hz, 1H), 4.57 (dd, J = 22.9, 6.0 Hz, 2H), 4.26 – 4.09 (m, 3H), 2.12 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 125.7 (q, J = 284.2 Hz), 81.2, 79.9, 71.2 (q, J = 26.9 Hz), 57.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ -72.1. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_5H_9F_3NO_2$ 172.0580, found 172.0576.



Scheme S11. Derivatisation of oxetane amino ester using MeMgBr: synthesis of oxetane-containing alcohols and ketones

1-(3-(Dibenzylamino)oxetan-3-yl)ethan-1-one (32) [38] + 2-(3-(dibenzylamino)oxetan-3-yl)propan-2-ol (33). [39]

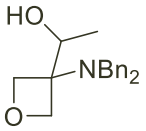


A solution of MeMgBr (735 g, 6.17 mol) in THF (6 L) was cooled with ice to 0 °C, and compound **24** (626.0 g, 1.90 mol) was added dropwise. The mixture was then warmed to rt and stirred overnight (ca. 16 h). Then, the reaction was quenched with an aq NH_4Cl (371.0 g, 6.93 mol) in 4 L of H_2O. The aqueous layer was extracted with EtOAc (4 × 1.5L). The combined organic layers were dried over Na_2SO_4 and evaporated. Yield (mixture of **32** and **33**) 404.1 g (70%). A mixture of compounds **32** and **33** was formed in a ratio of 3:7, respectively. The compounds were separated by column chromatography using hexanes–EtOAc (8:2, v/v) as an eluent with the ketone eluting first, followed by the alcohol. NOTE: the ratio of products depends on the amount of MeMgBr. In the case of using 1 equiv, a ca. 3:3:4 mixture of products and the starting material **32**:**33**:**24**, respectively, was formed. In the case of using 2 equiv, a ca. 2:3 mixture of products **32**:**33**, respectively, was formed. In the case of using 4 equiv, a ca. 3:7 mixture of products **32**:**33**, respectively, was formed.

Ketone **32** (118 g, 21% yield): Beige oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 10H), 4.55 (d, *J* = 6.8 Hz, 2H), 4.44 (d, *J* = 6.9 Hz, 2H), 3.76 (s, 4H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 139.0, 128.6, 128.4, 127.4, 75.9, 72.6, 54.1, 25.9. LC/MS (ES-API): m/z: 296 $[M+H]^+$. Anal. calcd. for $C_{19}H_{21}NO_2$: C 77.26; H 7.17; N 4.74, found C 77.16; H 7.45; N 4.89.

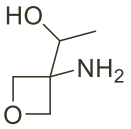
Alcohol **33** (289 g, 49% yield): Beige oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.16 (s, 10H), 4.94 (d, *J* = 6.7 Hz, 2H), 4.43 (d, *J* = 6.5 Hz, 2H), 3.89 (s, 4H), 2.07 (s, 1H), 1.41 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.7, 128.3, 128.2, 126.9, 75.2, 74.8, 69.4, 55.6, 25.9. LC/MS (ES-API): m/z: 312 $[M+H]^+$. Anal. calcd. for $C_{20}H_{25}NO_2$: C 77.14; H 8.09; N 4.50, found C 77.42; H 7.98; N 4.31.

1-(3-(Dibenzylamino)oxetan-3-yl)ethan-1-ol (34). [40]



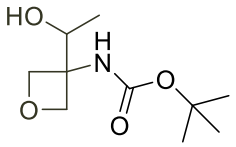
Compound **32** (100 g, 0.338 mol) was dissolved in MeOH at 0 °C, and $NaBH_4$ (14.0 g, 0.370 mol) was added. The mixture was stirred overnight (ca. 16 h). Then, the MeOH was evaporated, the formed precipitate was dissolved in 400 mL of H_2O, and the solution was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The compound was used in the next step after the preparation without additional purification. Yield 89.1 g (89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 8H), 7.20 (td, *J* = 5.5, 2.8 Hz, 2H), 4.74 (t, *J* = 6.1 Hz, 2H), 4.31 (dd, *J* = 10.4, 6.6 Hz, 2H), 4.15 (d, *J* = 6.7 Hz, 1H), 3.83 (s, 4H), 2.67 (s, 1H), 1.51 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 139.3, 127.9, 127.8, 126.6, 125.1, 76.8, 76.5, 76.2, 73.9, 67.2, 66.8, 53.6, 17.0. LC/MS (ES-API): m/z: 298 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{23}NO_2$: C 76.74; H 7.80; N 4.71, found C 76.91; H 8.07; N 4.65.

1-(3-Aminooxetan-3-yl)ethan-1-ol (67). [41]



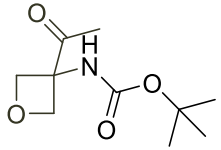
Compound **34** (154 g, 0.519 mol) was dissolved in MeOH (1.5 L), and 20% $Pd(OH)_2/C$ (16.0 g) was added. The mixture was heated at 60 °C overnight (ca. 16 h) under H_2 (80 atm) in an autoclave. Then, the solution was filtered and evaporated in vacuo. Yield 58.1 g (96%). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (d, *J* = 6.5 Hz, 1H), 4.51 (d, *J* = 6.6 Hz, 1H), 4.37 (dd, *J* = 12.7, 6.6 Hz, 2H), 4.04 (q, *J* = 6.4 Hz, 1H), 2.02 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.3, 80.3, 76.8, 76.5, 76.3, 70.0, 58.8, 16.3. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_5H_{12}NO_2$ 118.0863, found 118.0862.

tert-Butyl _N_-[3-(1-hydroxyethyl)oxetan-3-yl]carbamate (86). [42]



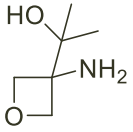
Compound **67** (40.0 g, 0.128 mol) was dissolved in MeOH (150 mL), and Boc_2O (28.4 g, 0.130 mol) was added over 30 min. The mixture was heated at 50 °C overnight (ca. 16 h). Then, the solution was cooled and evaporated in vacuo. NOTE: residual Boc_2O after the reaction can be removed by washing with hexane. The compound existed as a mixture of rotamers. Yield 27.3 g (98%). Colorless solid, mp 144-145 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.95 (d, J = 5.5 Hz, 1H), 4.55 (d, J = 6.2 Hz, 1H), 4.48 (d, J = 6.2 Hz, 1H), 4.42 (d, J = 6.2 Hz, 1H), 4.35 (d, J = 6.1 Hz, 1H), 3.87 (d, J = 5.9 Hz, 1H), 1.36 (s, 9H), 0.95 (d, J = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.7, 78.5, 76.5, 75.0, 66.5, 59.6, 28.6, 17.8. GC/MS (EI) *m/z*: 144 [M-O*t*Bu]$^+$. Anal. calcd. for $C_{10}H_{19}NO_4$: C 55.28; H 8.82; N 6.45, found C 55.22; H 8.84; N 6.30.

tert-Butyl _N_-(3-acetyloxetan-3-yl)carbamate (46). [43]

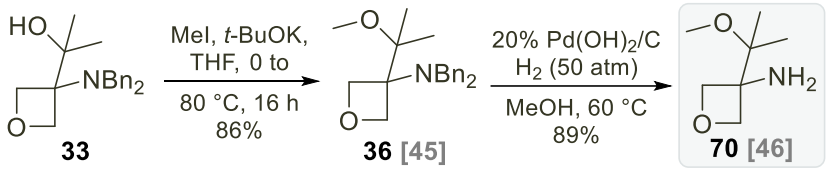


Compound **86** (26.2 g, 0.120 mol) was dissolved in CH_2Cl_2 (400 mL), and DMP (61.0 g, 0.144 mol) was added in portions. The reaction mixture was kept in a cooling bath to ensure the temperature did not exceed 25 °C. The mixture was stirred for 3 h, then poured onto an aq $NaHCO_3$ (40.5 g, 0.480 mol) and $Na_2S_2O_3$•$5H_2O$ (89.0 g, 0.360 mol), and stirred for 1 h. After 1 h, the layers were separated, and the organic layer was washed with H_2O (500 mL) and brine (300 mL). The solution was dried over Na_2SO_4, and evaporated in vacuo. The compound was used in the next step immediately after the synthesis. Yield ca. 21.4 g (ca. 83%). Yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (s, 1H), 4.78 – 4.33 (m, 4H), 3.30 (s, 3H), 1.37 (s, 9H). GC/MS (EI) *m/z*: 142 [M-O*t*Bu]$^+$.

2-(3-Aminooxetan-3-yl)propan-2-ol (68). [44]

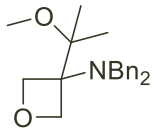


Compound **33** (166 g, 0.530 mol) was dissolved in MeOH (1.5 L), and 20% $Pd(OH)_2/C$ (16.0 g) was added. The mixture was heated at 60 °C overnight (ca. 16 h) under H_2 (50 atm) in an autoclave. Then, the solution was filtered and evaporated in vacuo. NOTE: H_2O formed during the reaction. Moreover, during filtration, catalyst particles pass through the filter. To obtain a pure product, it could be dissolved in $CHCl_3$, dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 60.1 g (95%). Colorless crystals, mp 88-90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (d, *J* = 6.8 Hz, 2H), 4.33 (d, *J* = 6.7 Hz, 2H), 2.01 (br s, 3H), 1.29 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.0, 71.6, 61.9, 24.1. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_6H_{14}NO_2$ 132.1019, found 132.1018.



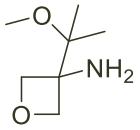
Scheme S12. Preparation of amino oxetane-containing ether 70

N,N-Dibenzyl-3-(2-methoxypropan-2-yl)oxetan-3-amine (36). [45]



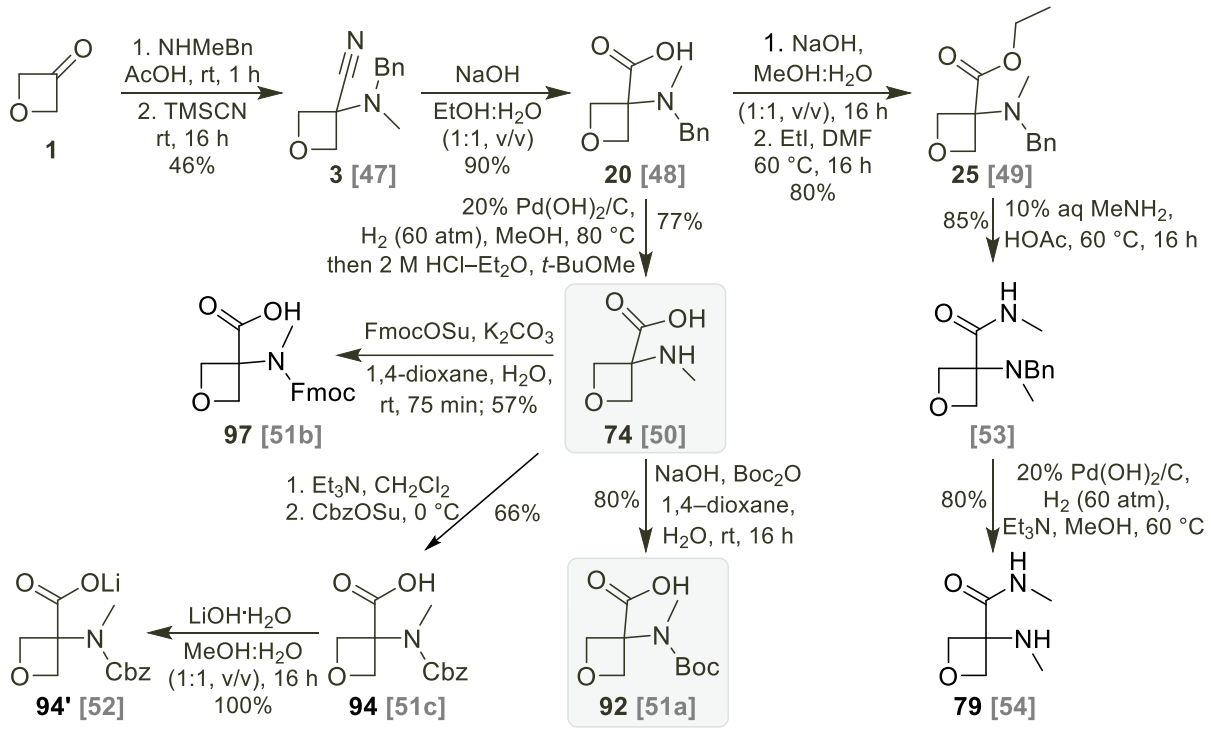
The compound was obtained from alcohol **33** according to the procedure for the synthesis *N,N*-dibenzyl-3-(methoxymethyl)oxetan-3-amine (**37**). The compound was used immediately in the next step after the preparation without additional purification. Yield ca. 13.3 g (ca. 86%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.09 (m, 10H), 4.94 (d, *J* = 6.7 Hz, 1H), 4.77 (d, *J* = 6.4 Hz, 1H), 4.55 (d, *J* = 6.4 Hz, 1H), 4.42 (d, *J* = 6.7 Hz, 1H), 4.37 – 4.28 (m, 1.5H) and 3.94 – 3.84 (m, 4H) and 3.33 – 3.28 (m, 1.5H), 1.41 (s, 3H), 1.33 (s, 3H). LC/MS (ES-API) m/z: 326 $[M+H]^+$.

3-(2-Methoxypropan-2-yl)oxetan-3-amine (70). [46]



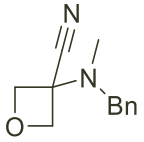
The compound was obtained from compound **36** (16.0 g, 49.2 mmol) according to the procedure for the synthesis 3-(methoxymethyl)oxetan-3-amine (**70**). Yield 6.32 g (89%). Fusible yellowish crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (d, *J* = 6.7 Hz, 2H), 4.33 (d, *J* = 6.7 Hz, 2H), 3.21 (s, 3H), 1.90

(s, 2H), 1.23 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.5, 76.7, 62.2, 49.6, 18.8. LC/MS (ES-API) m/z: 146 $[M+H]^+$. Anal. calcd. for $C_7H_{15}NO_2$: C 57.90; H 10.41; N 9.65, found C 57.51; H 10.39; N 9.31.



Scheme S13. Preparation of oxetane-containing *N*-methyl amino acids 74, 92, and their derivatives

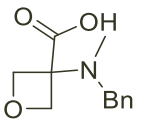
3-(Benzyl(methyl)amino)oxetane-3-carbonitrile (3). [47]



Oxetan-3-one (**1**, 71.0 g, 0.986 mol) was dissolved in, and pre-cooled methylbenzylamine (120 g, 0.986 mol) in HOAc (75 mL) was added at rt. After stirring the mixture at rt for 1 h, TMSCN (97.7 g, 0.986 mol) was added dropwise at 20 °C, and the mixture was stirred at rt overnight (ca. 16 h). NOTE: when scaling–up, the solution should be cooled prior to the addition of the next component, as the temperature rises significantly during this process. The mixture was evaporated on a rotary evaporator. The residue was partitioned between H_2O (250 mL) and EtOAc (600 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (2 × 600 mL) and brine (2 × 600 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in vacuo to give the crude product, which was purified by flash column chromatography on silica gel (EtOAc – petroleum ether, 3:97, v/v).

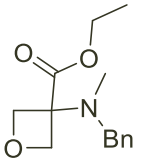
Yield 90.4 g (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 4.72 (d, *J* = 6.4 Hz, 2H), 4.63 (d, *J* = 6.4 Hz, 2H), 3.44 (s, 2H), 2.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 128.5, 128.1, 127.4, 116.2, 81.0, 77.4, 59.7, 56.3, 35.7. LC/MS (ES-API) m/z: 203 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}N_2O$: C 71.26; H 6.98; N 13.85, found C 71.01; H 6.97; N 13.98.

3-(Benzyl(methyl)amino)oxetane-3-carboxylic acid (20). [48]



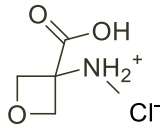
A solution of compound **3** (83.4 g, 0.411 mol) in EtOH (850 mL) was treated with an aq NaOH (98.7 g, 2.47 mol) in H_2O (900 mL) and the resulting mixture was refluxed overnight (ca. 16 h). NOTE: with methylbenzyl substitution, the hydrolysis proceeds completely in one day, unlike the dibenzyl analog. Then, the mixture was cooled to rt and most of the EtOH was evaporated. The residue was diluted with H_2O (700 mL) and washed with t–BuOMe (2 × 350 mL). Then10 % aq $NaHSO_4$ was added at 0 °C to the aqueous layer until pH 4 was reached, resulting in the precipitation of a colorless solid. The precipitate was filtered, washed with H_2O (2 × 300 mL), and dried in vacuo. NOTE: in the case of large–scale synthesis (up to 1 kg of the product in a single run) the product could be separated by evaporation of EtOH, resulting in a precipitate that can be triturated with *t*-BuOMe – this is the sodium salt of the acid. This process is considerably more time-efficient). The compound was used in the next step immediately after the synthesis. Yield ca. 81.2 (ca. 90%). Colorless fusible solid.

Ethyl 3-(benzyl(methyl)amino)oxetane-3-carboxylate (25). [49]



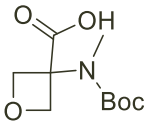
Carboxylic acid **20** (8.87 g, 0.0401 mol) was dissolved in MeOH – H_2O (100 mL, 1:1, v/v), and NaOH (1.60 g, 0.0401 mol)) was added at rt. The resulting mixture was stirred at rt overnight (ca. 16 h), then evaporated in vacuo to dryness. The residue was triturated from acetone (ca. 50 mL). The resulting sodium salt of compound **20** (9.75 g, 0.0401 mol) was dissolved in DMF (100 mL), and EtI (18.8 g, 0.123 mol) was added. The mixture was refluxed overnight (ca. 16 h) at 60° C. Then, the DMF was evaporated, H_2O (100 mL) was added, and the solution was extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with H_2O (2 × 100 mL) and once with brine (150 mL). The solution was dried over Na_2SO_4 and evaporated in vacuo. The compound was used in the next step immediately after the preparation without additional purification. Yield ca. 7.96 g (ca. 80%). The compound could be obtained from nitrile **3** (83.4 g, 0.411 mol) in one-pot manner; yield ca. 70.3 g (ca. 69%).

3-(Methylamino)oxetane-3-carboxylic acid hydrochloride (74). [50]



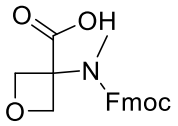
Compound **20** (22.1 g, 0.100 mol) was dissolved in MeOH (300 L), the solution was placed in a high–pressure autoclave, and 20% $Pd(OH)_2/C$ (3.00 g) was added. The autoclave was sealed and hydrogenated with H_2 (80 atm) at 60 °C overnight (ca. 16 h). filtered, and the filtrate was evaporated in vacuo. Additional purification was achieved by the addition of *t*-BuOMe, the titration with 2 M HCl – Et_2O until pH 7 was reached, followed by the filtration and drying. Yield 12.8 g (77%). Colorless crystals, mp 150–154 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.80 (d, J = 7.5 Hz, 2H), 4.75 (d, J = 7.6 Hz, 2H), 2.61 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.6, 73.6, 61.9, 28.4. HRMS (ESI–TOF) m/z: [M–HCl+H]+ calcd. for $C_5H_{10}NO_3$ 132.0661, found 132.0654.

3-((*tert*-Butoxycarbonyl)(methyl)amino)oxetane-3-carboxylic acid (92). [51a]



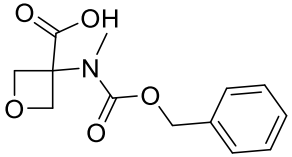
Hydrochloride **74**·HCl (14.5 g, 87.0 mmol) was dissolved in 1,4–dioxane – H_2O (100 mL, 1:1, v/v). Then NaOH (10.4 g, 0.262 mol) and Boc_2O (22.9 g, 0.104 mol) were added at rt, and the mixture was stirred overnight (ca. 16 h). Then, the solution was evaporated, and the residue was diluted with H_2O (50 mL). The solution was extracted with *t*–BuOMe (2 × 25 mL), and 10% aq $NaHSO_4$ was added to the aqueous layer until pH 4 was reached. The resulting mixture was extracted with EtOAc (3 × 25 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The compound existed as a mixture of rotamers. Yield 16.1 g (80%). Colorless crystals, mp 92–93 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.22 (s, 1H), 4.78 – 4.52 (m, 4H), 2.70 (s, 3H), 1.37 (s, 3H) and 1.28 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.9, 154.6, 79.5, 75.8 and 75.5, 62.2, 31.7 and 31.2, 27.9 and 27.4, 27.7. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_{10}H_{18}NO_5$ 232.1179, found 232.1172.

3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}(methyl)amino)oxetane-3-carboxylic acid (97). [51b]



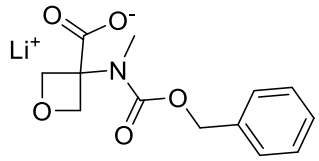
A solution of FmocOSu (3.20 g, 9.50 mmol) in 1,4-dioxane (30 mL) was added to a solution of hydrochloride **74**·HCl (1.67 g, 10.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) in H_2O (30 mL). The light yellow solution was stirred at rt for 75 min. During that time, a colorless solid precipitated. The mixture was diluted with water and extracted with Et_2O (2 × 25 mL). The colorless solid did not dissolve and was kept therefore in the aqueous layer, which was acidified to pH 2 by the addition of 1 M HCl and extracted with EtOAc (3 × 20 mL). The combined EtOAc layers were washed with brine, dried with Na_2SO_4, and evaporated in vacuo. The compound existed as a mixture of rotamers. Yield 2.00 g (57%). Colorless crystals, mp 144–146 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.19 (br s, 1H), 7.87 (dd, J = 18.1, 7.5 Hz, 2H), 7.64 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.39 (dt, J = 12.0, 7.4 Hz, 2H), 7.32 (dt, J = 11.1, 7.4 Hz, 2H), 4.65 (d, J = 2.6 Hz, 2H), 4.56 (d, J = 4.4 Hz, 1H), 4.35 – 4.19 (m, 1.5H) and 4.19 – 4.10 (m, 1.5H), 4.01 (d, J = 6.8 Hz, 1H), 2.77 (s, 1.5H) and 2.59 (s, 1.5H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3 and 172.1, 155.7 and 155.4, 143.7 and 143.6, 140.8 and 140.7, 127.6 and 127.5, 127.1 and 127.0, 125.0 and 124.4, 120.1 and 119.9, 75.2 and 75.1, 66.8 and 65.8, 62.7 and 61.9, 46.6 and 46.5, 31.7 and 31.4. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_{20}H_{20}NO_5$ 354.1336, found 354.1328.

3-{[(Benzyloxy)carbonyl](methyl)amino}oxetane-3-carboxylic acid (94). [51c]



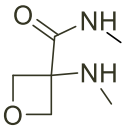
Hydrochloride **74**·HCl (5.93 g, 0.0355 mol) was dissolved in CH_2Cl_2 (50 mL), and Et_3N (3.59 g, 0.0355 mol) was added. Then, the reaction mixture was cooled with ice to 0 °C, and CbzOSu (1–{[(Benzyloxy)carbonyl]oxy}–2,5–pyrrolidinedione, 4.43 g, 0.0355 mol) was slowly added. The resulting mixture was stirred overnight (ca. 16 h), then washed with H_2O (15 mL) and brine (10 mL), passed through a layer of Na_2SO_4 – silica gel – Na_2SO_4 (1:1:1, v/v/v), and the organic layer was evaporated. NOTE: temperature should be maintained under 50 °C due to substance degradation. The compound showed limited stability, therefore it was transformed to the corresponding lithium carboxylate as given below. The compound existed as a mixture of rotamers. Yield 6.21 g (66%). Yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.33 (br s, 1H), 7.36 – 7.23 (m, 5H), 5.07 (s, 1H) and 4.98 (s, 1H), 4.74 – 4.53 (m, 4H), 2.81 (s, 1.5H) and 2.78 (s, 1.5H). LC/MS (ES-API) m/z: 266 $[M+H]^+$.

Lithium 3-{[(benzyloxy)carbonyl](methyl)amino}oxetane-3-carboxylate (94'). [52]

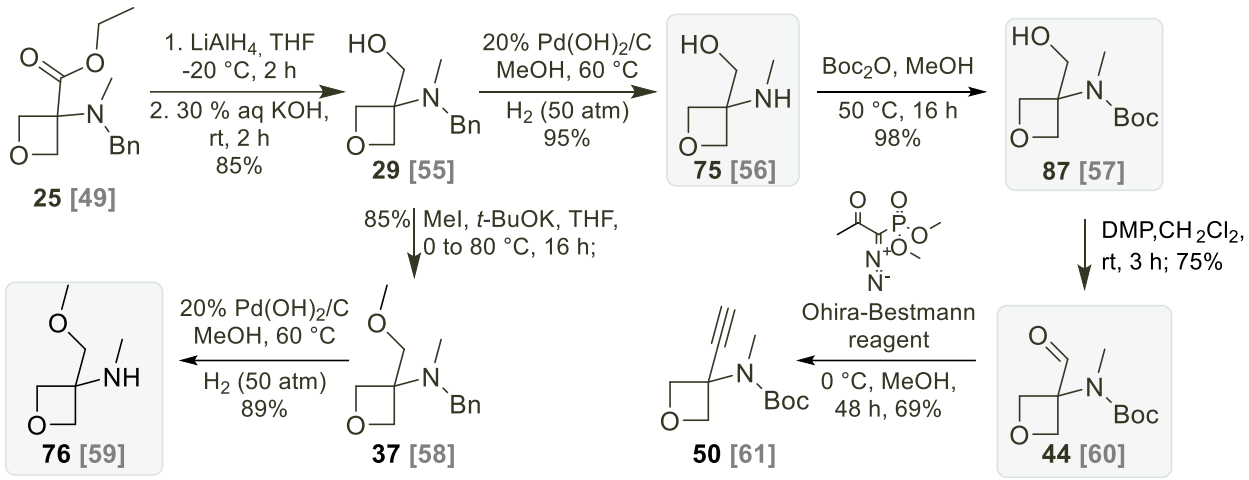


Carboxylic acid **94** (5.00 g, 18.9 mmol) was dissolved in MeOH (50 mL), and $LiOH \cdot H_2O$ (832 mg, 19.8 mmol) in H_2O (50 mL) was added. The solution was stirred at rt overnight (ca. 16 h), then evaporated in vacuo to dryness. The residue was triturated from acetone. Yield 5.12 g (100%). The compound could be obtained from the corresponding methyl ester (108 g, 0.369 mol). The latter derivative could be dissolved in THF (500 mL), and $LiOH \cdot H_2O$ (15.5 g, 0.370 mol) in H_2O (500 mL) was added. The solution was stirred at rt for 3 h, then the aqueous layer was separated, washed with *t*-BuOMe (3 × 100 mL), and evaporated in vacuo to dryness. The compound existed as a mixture of rotamers. Yield 3.58 g (70%). Colorless crystals, mp 60–61 °C. ^{1}H NMR (500 MHz, D_2O) δ 7.37 – 7.19 (m, 5H), 4.98 (d, *J* = 36.1 Hz, 2H), 4.83 – 4.70 (m, 2H), 4.60 (d, *J* = 7.3 Hz, 2H), 2.82 – 2.68 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.7, 156.8, 137.2 and 137.0, 128.3 and 128.1, 127.6 and 127.4, 127.2 and 127.2, 77.3 and 76.8, 65.9 and 65.5, 64.2 and 63.5, 32.1 and 31.7. HRMS (ESI–TOF) m/z: [M–Li+2H]+ calcd. for $C_{13}H_{16}NO_5$ 266.1023, found 266.1012.

***N*-Methyl-3-(methylamino)oxetane-3-carboxamide (79). [54]**

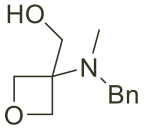


Ester **25** (5.95 g, 0.0239 mol) was dissolved in 10% aq $MeNH_2$ (10 mL), and HOAc (1.44 g, 0.0239 mol) was added art rt. The resulting mixture was stirred at 60 °C overnight (ca. 16 h), then evaporated in vacuo. The residue was diluted with H_2O (20 mL), and $NaHCO_3$ (2.00 g, 0.0239 mol) was added. The resulting mixture was extracted with *t*-BuOMe (3 × 15 mL). The combined extracts were evaporated in vacuo, the residue was triturated from hexanes to give 3-(benzyl(methyl)amino)-*N*-methyloxetane-3-carboxamide (ca. 4.75 g, ca. 85%). Then, the latter compound **[53]** (ca. 4.75 g, ca. 0.0203 mol) was dissolved in MeOH (60 L), the solution was placed in a high–pressure autoclave, and 20% $Pd(OH)_2/C$ (500 mg) was added. The autoclave was sealed and hydrogenated with H_2 (80 atm) at 60 °C overnight (ca. 16 h). filtered, and the filtrate was evaporated in vacuo. The compound existed as a mixture of rotamers. Yield 3.80 g (80%). Beige solid, mp 117–119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (s, 1H), 4.97 (d, *J* = 6.5 Hz, 2H), 4.42 (d, *J* = 6.5 Hz, 2H), 2.84 (d, *J* = 4.9 Hz, 3H), 2.31 (s, 3H), 2.02 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 77.8 and 77.8, 64.3, 30.3, 26.2. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_6H_{13}N_2O_2$ 145.0972, found 145.0970.



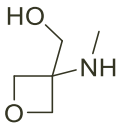
Scheme S14. Preparation of oxetane-containing *N*-methyl amino alcohols 75, 87, and their derivatives

(3-(Benzyl(methyl)amino)oxetan-3-yl)methanol (29). [55]



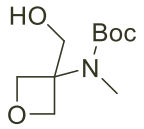
$LiAlH_4$ (3.63 g, 95.0 mmol) was added to THF (210 mL) under Ar. The mixture was cooled to –20 °C using a MeOH–nitrogen bath, and a solution of compound **25** (21.7 g, 87.0 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at –20 °C for 2 h, and then 30% aq KOH (7.82 g) was added dropwise. The mixture was warmed to rt, stirred for 2 h, then filtered and evaporated in vacuo. Yield 15.2 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 5H), 4.73 (d, *J* = 6.6 Hz, 2H), 4.57 (br s, 1H) 4.49 (d, *J* = 6.7 Hz, 2H), 3.60 (s, 2H), 2.84 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.7, 129.0, 128.5, 127.5, 83.8, 71.2, 62.8, 62.7, 41.9. LC/MS (ES-API) m/z: 208 $[M+H]^+$. Anal. calcd. for $C_{12}H_{17}NO_2$: C 69.54; H 8.27; N 6.76, found C 69.69; H 8.21; N 6.54.

[3-(Methylamino)oxetan-3-yl]methanol (75). [56]



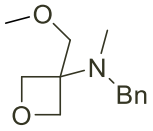
Compound **29** (8.30 g, 40.0 mmol) was dissolved in MeOH (90 mL), and 20% $Pd(OH)_2/C$ (100 mg) was added. The mixture was heated at 60 °C overnight (ca. 16 h) under H_2 (50 atm) in an autoclave. Then, the solution was filtered and evaporated in vacuo. NOTE: H_2O formed during the reaction. Moreover, during filtration, catalyst particles pass through the filter. To obtain a pure product, it could be dissolved in $CHCl_3$, dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 4.45 g (95%). Fusible yellowish crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 – 4.49 (m, 2H), 4.37 (d, *J* = 6.7 Hz, 2H), 3.81 (s, 2H), 2.38 (d, *J* = 1.6 Hz, 3H), 2.33 (br s, 1H), 2.29 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 78.1, 63.8, 60.9, 28.9. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_5H_{12}NO_2$ 118.0863, found 118.0863.

tert-Butyl *N*-[3-(hydroxymethyl)oxetan-3-yl]-*N*-methylcarbamate (87). [57]



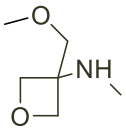
Compound **75** (8.30 g, 70.9 mmol) was dissolved in MeOH (90 mL), and Boc_2O (15.8 g, 72.0 mmol) was added for 30 min. The mixture was heated at 50 °C overnight (ca. 16 h). Then, the solution was cooled and evaporated in vacuo. NOTE: if residual Boc_2O remains after the reaction; it can be removed by washing with hexane. Yield 15.1 g (98%). Colorless solid, mp 92–93 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.13 (t, *J* = 5.9 Hz, 1H), 4.53 (d, *J* = 6.3 Hz, 2H), 4.31 – 4.11 (m, 2H), 3.73 (d, *J* = 5.9 Hz, 2H), 2.64 (s, 3H) , 1.37 (s, 3H), 1.33 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.8, 78.9, 75.2, 64.0, 60.3, 39.0, 31.6, 28.0. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_{10}H_{20}NO_4$ 218.1387, found 218.1382.

N-Benzyl-3-(methoxymethyl)-*N*-methyloxetan-3-amine (37). [58]



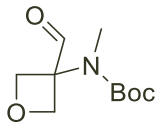
The compound was obtained from alcohol **29** according to the procedure for the synthesis *N,N*-dibenzyl-3-(methoxymethyl)oxetan-3-amine (**35**). The compound was used immediately in the next step after the preparation without additional purification. Yield ca. 9.55 g (ca. 85%).

3-(Methoxymethyl)-*N*-methyloxetan-3-amine (76). [59]



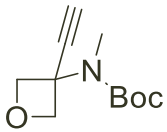
The compound was obtained from compound **37** according to the procedure for the synthesis 3-(methoxymethyl)oxetan-3-amine (**69**). Yield 7.78 g (89%). Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (d, *J* = 6.5 Hz, 2H), 4.35 (d, *J* = 6.5 Hz, 2H), 3.64 (s, 2H), 3.39 (s, 3H), 2.46 (s, 3H), 2.00 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 76.7, 75.1, 59.7, 58.9, 28.7. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_6H_{14}NO_2$ 132.1019, found 132.1021.

tert-Butyl (3-formyloxetan-3-yl)(methyl)carbamate (44). [60]

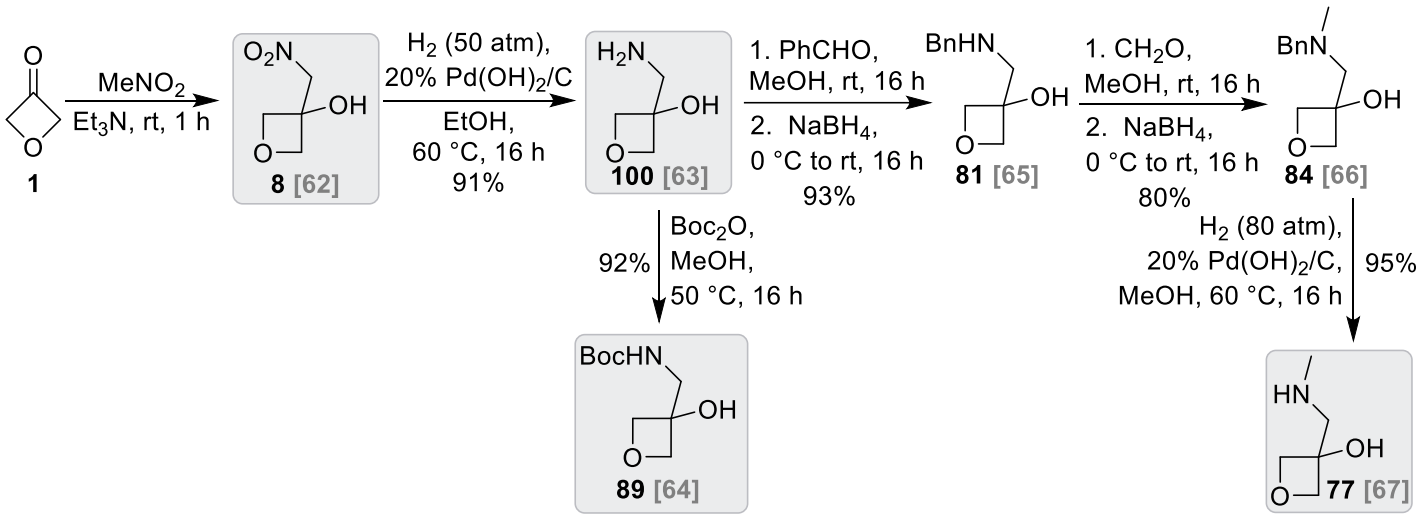


Dess-Martin periodinane (307 g, 0.723 mol) was added in portions to compound **87** (131 g, 0.603 mol) in CH_2Cl_2 (2 L) at a temperature below 25°C and the resulting mixture was stirred at the same temperature for 3 hours. Then, saturated aq $NaHCO_3$ (304 g, 3.62 mol) and $Na_2S_2O_3 \cdot 5H_2O$ (600 g, 2.41 mol) were added, and the obtained mixture was stirred for 1 h. After that, the organic layer was separated, washed with H_2O (500 mL) and brine (500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The compound existed as a mixture of rotamers. Yield 97.1 g (75%). Colorless crystals, mp 92–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 0.33H) and 9.92 (s, 0.67H), 4.85 (d, *J* = 6.5 Hz, 2H), 4.69 (dd, *J* = 50.9, 6.9 Hz, 2H), 2.80 (s, 2H) and 2.77 (s, 1H), 1.45 (s, 3H) and 1.37 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.5, 154.2, 80.8, 76.7, 76.5, 76.2, 73.7, 66.5 and 66.0, 31.2 and 30.8, 27.7. GC/MS (EI) *m/z*: 159 $[M–CH_2=C(CH_3)]^+$. HRMS (ESI–TOF) m/z: $[M–H_2C=C(CH_3)_2+H]$+ calcd. for $C_6H_{10}NO_4$ 160.0604, found 160.0603.

tert-Butyl (3-ethynyloxetan-3-yl)(methyl)carbamate (50). [61]

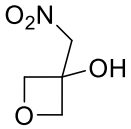


Compound **44** (22.5 g, 0.105 mol) was dissolved in MeOH (200 mL) and cooled with ice to 0 °C. The Ohira–Bestmann reagent (27.1 g, 0.141 mol), and K_2CO_3 (36.1 g, 0.261 mol) were added. The reaction mixture was warmed up to rt, stirred for 48 h, then diluted with H_2O (100 mL). Most of MeOH was evaporated in vacuo, and the resulting solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were passed through a layer of Na_2SO_4 – silica gel – Na_2SO_4 (1:1:1, v/v/v), and the solution was evaporated. The product was then crystallized from hexanes–*t*–BuOMe (100 mL, 2:1, v/v). Yield 15.2 g (69%). Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (d, *J* = 6.1 Hz, 2H), 4.71 – 4.49 (m, 2H), 2.71 (s, 3H), 2.48 (s, 1H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 82.5, 80.5, 79.4, 71.0, 54.2, 29.9, 27.8. GC/MS (EI) *m/z*: 155 $[M–CH_2=C(CH_3)]^+$. Anal. calcd. for $C_{11}H_{17}NO_3$: C 62.54; H 8.11; N 6.63, found C 62.60; H 8.34; N 6.45.



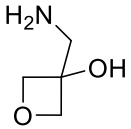
Scheme S15. Synthesis of isomeric oxetane-containing amino alcohols 77, 89, and 100

3-(Nitromethyl)oxetan-3-ol (8). [62]



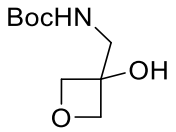
$MeNO_2$ (14.4 g, 0.236 mol) and Et_3N (47.8 g, 0.472 mol) were added dropwise to a solution of oxetan-3-on (16.2 g, 0.225 mol) in CH_2Cl_2 (500 mL), and the resulting mixture was stirred at rt for 1 h. Then, H_2O (500 mL) was added, and the organic phase was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo. Yield 27.3 g (91%). Yellow fusible crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (s, 2H), 4.73 (d, J = 7.5 Hz, 2H), 4.59 (d, J = 7.5 Hz, 2H), 3.26 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.7, 79.7, 72.2. GC/MS (EI) *m/z*: 69 $[M–NO_2–H_2O]^+$. Anal. calcd. for $C_4H_7NO_4$: C 36.10; H 5.30; N 10.52, found C 36.20; H 5.62; N 10.26.

3-(Aminomethyl)oxetan-3-ol (100). [63]



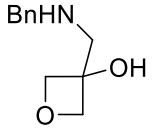
Compound **8** (30.0 g, 0.225 mol) was dissolved in EtOH (300 mL), the solution was placed in a high–pressure autoclave, and 20% $Pd(OH)_2/C$ (3.00 g) was added. The autoclave was sealed and hydrogenated with H_2 (50 atm) at 60 °C overnight (ca. 16 h). The resulting mixture was filtered and concentrated in *vacuo.* Obtained residue was dissolved in $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Yield 21.2 g (91%). Beige crystals, mp 104–107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (d, *J* = 6.6 Hz, 2H), 4.45 – 4.39 (m, 2H), 3.08 (s, 2H), 1.75 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.0, 73.1, 47.8. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_4H_{10}NO_2$ 104.0706, found 104.0708.

tert-Butyl *N*-[(3-hydroxyoxetan-3-yl)methyl]carbamate (91). [64]



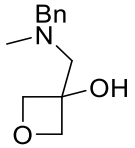
Compound **100** (12.6 g, 0.122 mol) was dissolved in MeOH (130 mL), and Boc_2O (28.0 g, 0.128 mol) was added over 30 min. The mixture was heated at 50 °C overnight (ca. 16 h), then cooled and evaporated in vacuo. In the case when Boc_2O remained after the reaction, it could be removed by triturating with hexanes. Yield 22.9 g (92%). Colorless solid, mp 93–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (s, 1H), 4.69 (s, 1H), 4.59 (d, *J* = 6.6 Hz, 2H), 4.40 (d, *J* = 6.7 Hz, 2H), 3.54 (d, *J* = 5.9 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 81.7, 80.7, 74.4, 47.3, 28.3. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_9H_{18}NO_4$ 204.1230, found 204.1225.

3-((Benzylamino)methyl)oxetan-3-ol (81). [78]



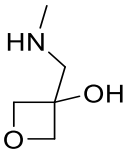
Compound **100** (14.3 g, 0.139 mol) was dissolved in dry MeOH (145 mL), and PhCHO (14.7 g, 0.139 mol) was added. The mixture was stirred at rt overnight (ca. 16 h). The next day, $NaBH_4$ (5.8 g, 0.153 mol) was added in portions at 0 °C. The mixture was warmed to rt and stirred overnight. The reaction mixture was then poured into water, and MeOH was concentrated in vacuo. The aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford compound **23**. The compound was used immediately in the next step after the preparation without additional purification. Yield. ca. 24.3 g (ca. 91%). Yellow oil.

3-((Benzyl(methyl)amino)methyl)oxetan-3-ol (84). [66]

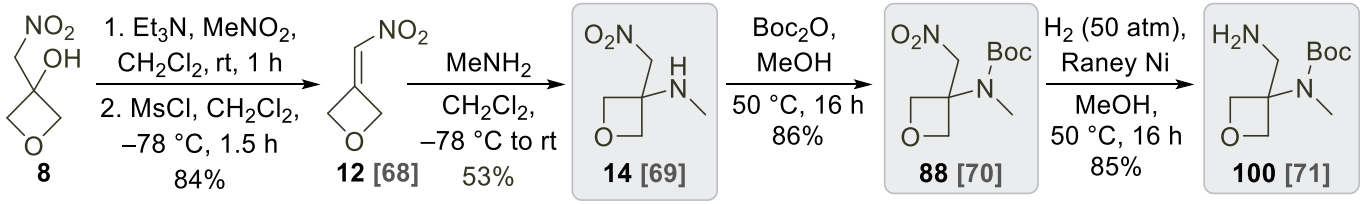


Compound **81** (41.0 g, 0.212 mol) was dissolved in dry MeOH (300 mL), and 30% formalin (22 mL) was added. The mixture was stirred at rt overnight (ca. 16 h). The next day, $NaBH_4$ (8.84 g, 0.234 mol) was added in portions at 0 °C. The mixture was warmed to rt and stirred overnight. The reaction mixture was then poured into water, and MeOH was concentrated in vacuo. The aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford compound **23**. The compound was used immediately in the next step after the preparation without additional purification. Yield ca. 35.1 g (ca. 80%). Yellow oil.

3-((Methylamino)methyl)oxetan-3-ol (77). [67]

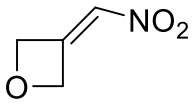


Compound **84** (37.2 g, 0.179 mol) was dissolved in MeOH (370 mL), the solution was placed in a high–pressure autoclave, and 20% $Pd(OH)_2/C$ (3.7 g) was added. The autoclave was sealed and hydrogenated with H_2 (80 atm) at 60 °C overnight (ca. 16 h). The resulting mixture was filtered and concentrated in *vacuo.* Obtained residue was dissolved in $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Yield 19.9 g (95%). Colorless solid, mp 124–126 °C °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (d, *J* = 6.6 Hz, 2H), 4.45 (d, *J* = 6.6 Hz, 2H), 2.96 (s, 2H), 2.82 (br s, 2H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.8, 72.1, 57.5, 36.6. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_5H_{12}NO_2$ 118.0863, found 118.0862



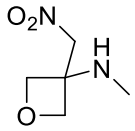
Scheme S16. Synthesis of oxetane-containing vicinal diamine 101 via Henry reaction

3-(Nitromethylene)oxetane (12). [68]



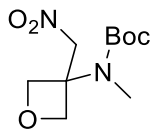
Et_3N (157 g, 1.55 mol) was added dropwise to a solution of oxetane-3-one (50.8 g, 0.703 mol) in $MeNO_2$ (60.2 g, 0.991 mol), and the resulting mixture was stirred at rt for 1 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2800 mL), and MsCl (80.7 g, 0.703 mol) was added at –78 °C. The reaction mixture was stirred for 1.5 h, then used directly in the next step or subjected to the column chromatography on silica gel using pentane - Et_2O (1:1, v/v) as eluent, the isolation of compound is required. Spectral and physical data were in accordance with that reported.[3] Yield 67.9 g (84%). Colorless solid; mp 41-43 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 5.66 (d, *J* = 2.3 Hz, 2H), 5.39 (d, *J* = 2.3 Hz, 2H).

***N*-Methyl-3-(nitromethyl)oxetan-3-amine (14). [69]**



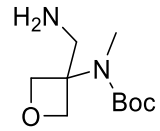
Et_3N (143 g, 1.41 mol) was dissolved in CH_2Cl_2 (2800 mL), and $MeNH_2$·HCl (94.7 g, 1.40 mol) was added. The resulting mixture was added dropwise to a solution of **12** in CH_2Cl_2 (2800 mL, or the reaction mixture from the previous step) at –78 °C. The resulting mixture was stirred at rt for 16 h, then concentrated in *vacuo* (to ca. 1000 mL residual volume) the residue was washed with H_2O (1500 mL), brine (150 L), dried over Na_2SO_4, filtered, and concentrated in *vacuo* giving a target compound. Yield 46.3 g (54%). Yellowish liquid. The compound was used immediately in the next step after the preparation without additional purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (s, 2H), 4.63 – 4.52 (m, 4H), 2.41 (s, 3H), 1.72 (br s, 1H).

***tert*-Butyl methyl(3-(nitromethyl)oxetan-3-yl)carbamate (88). [70]**

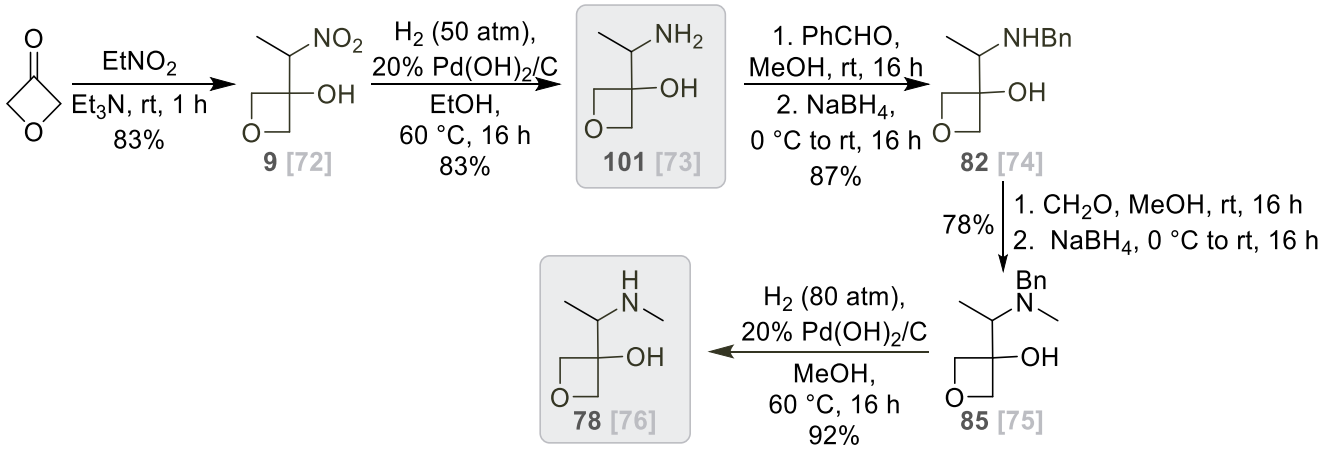


The compound was obtained from amine **14** (46.3 g, 0.317 mol) according to the procedure for the synthesis of *tert*-butyl *N*-[(3-hydroxyoxetan-3-yl)methyl]carbamate (**91**). Yield 67.1 g (86%). Yellowish liquid. The compound was used immediately in the next step after the preparation without additional purification. The compound existed as a mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.93 (s, 1H), 4.79 (d, *J* = 7.5 Hz, 2H), 4.56 (d, *J* = 7.1 Hz, 1H), 4.46 (d, *J* = 6.8 Hz, 1H), 2.73 (d, *J* = 2.7 Hz, 3H), 1.46 – 1.40 (m, 9H).

tert-Butyl *N*-[3-(aminomethyl)oxetan-3-yl]-*N*-methylcarbamate (100). [71]

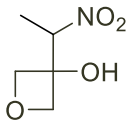


Compound **88** (65.0 g. 0.264 mol) was dissolved in MeOH (700 mL), the solution was placed in a high–pressure autoclave, and Raney Ni (7.00 g) was added. The autoclave was sealed and hydrogenated with H_2 (50 atm) at 50 °C overnight (ca. 16 h). The resulting mixture was filtered through SiO_2 and concentrated in vacuo. Yield 48.5 g (85%). Yellowish liquid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.53 (d, J = 6.3 Hz, 2H), 4.23 (s, 2H), 2.95 (s, 2H), 2.66 (s, 3H), 1.61 (s, 2H), 1.35 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.7, 80.3, 78.4, 61.1, 46.5, 31.6, 28.4. LC/MS (ES-API) m/z: 161 [M-H_2C=$C(CH_3)_2$+H]$^+$. Anal. calcd. for $C_{10}H_{20}N_2O_3$: C 55.53; H 9.32; N 12.95, found C 55.78; H 9.01; N 12.99.



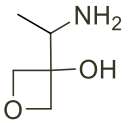
Scheme S17. Synthesis of oxetane-containing methyl-substituted vicinal amino alcohols 78 and 101

3-(Nitroethyl)oxetan-3-ol (9). [72]



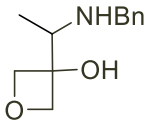
The compound was obtained from oxetan-3-one (46.0 g, 0.638 mol) according to the procedure for the synthesis of 3-(Nitromethyl)oxetan-3-ol (**8**). Yield 78.2 g (83%). Specstral and physical data were analogous to that reported.[4]

3-(1-Aminoethyl)oxetan-3-ol (101). [73]



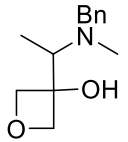
The compound was obtained from compound **9** (78.0 g, 0,530 mol) according to the procedure for the synthesis of 3-(aminomethyl)oxetan-3-ol (**63**). Yield 51.6 g (83%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 – 4.53 (m, 2H), 4.52 – 4.44 (m, 2H), 3.34 (q, *J* = 6.5 Hz, 1H), 2.14 (br s, 3H), 1.12 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.5, 80.3, 75.7, 51.2, 17.1. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_5H_{12}NO_2$ 118.0863, found 118.0862.

3-(1-(Benzylamino)ethyl)oxetan-3-ol (82). [74]



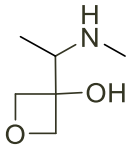
The compound was obtained from compound **101** (51.6 g, 0.441 mol) according to the procedure for the synthesis of 3-((benzylamino)methyl)oxetan-3-ol (**81**). The compound was used in the next step in a one-pot manner immediately after the preparation without additional purification, which allowed the synthesis of the target compounds in higher yields. Yield ca. 79.5 g (ca. 87%). Yellow oil.

3-(1-(Benzyl(methyl)amino)ethyl)oxetan-3-ol (85). [75]

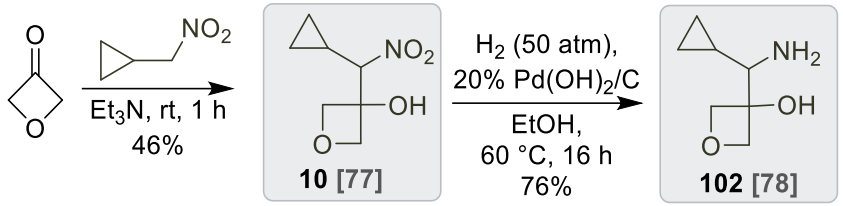


The compound was obtained from compound **82** (83.1 g, 0.400 mol) according to the procedure for the synthesis of 3-((benzyl(methyl)-amino)methyl)oxetan-3-ol (**84**). The compound was used in the next step in a one-pot manner immediately after the preparation without additional purification, which allowed the synthesis of the target compounds in higher yields. ca. 69.3 g (ca. 78%). Yellow oil.

3-(1-(Methylamino)ethyl)oxetan-3-ol (78). [76]

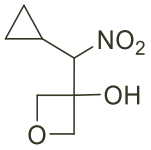


The compound was obtained from compound **85** (69.3 g, 0.313 mol) according to the procedure for the synthesis of 3-((methylamino)methyl)oxetan-3-ol (**77**). Yield 37.8 g (92%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 – 4.59 (m, 2H), 4.56 (dd, *J* = 6.8, 3.7 Hz, 2H), 2.96 (q, *J* = 6.5 Hz, 1H), 2.36 (s and br s, 3H and 2H), 1.11 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 83.6, 80.6, 75.0, 59.4, 34.7, 14.2. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_6H_{14}NO_2$ 132.1019, found 132.1024.



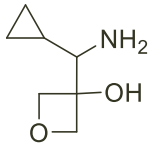
Scheme S18. Synthesis of oxetane-containing cyclopropyl-substituted vicinal amino alcohol 102

3-(Cyclopropyl(nitro)methyl)oxetan-3-ol (10). [77]

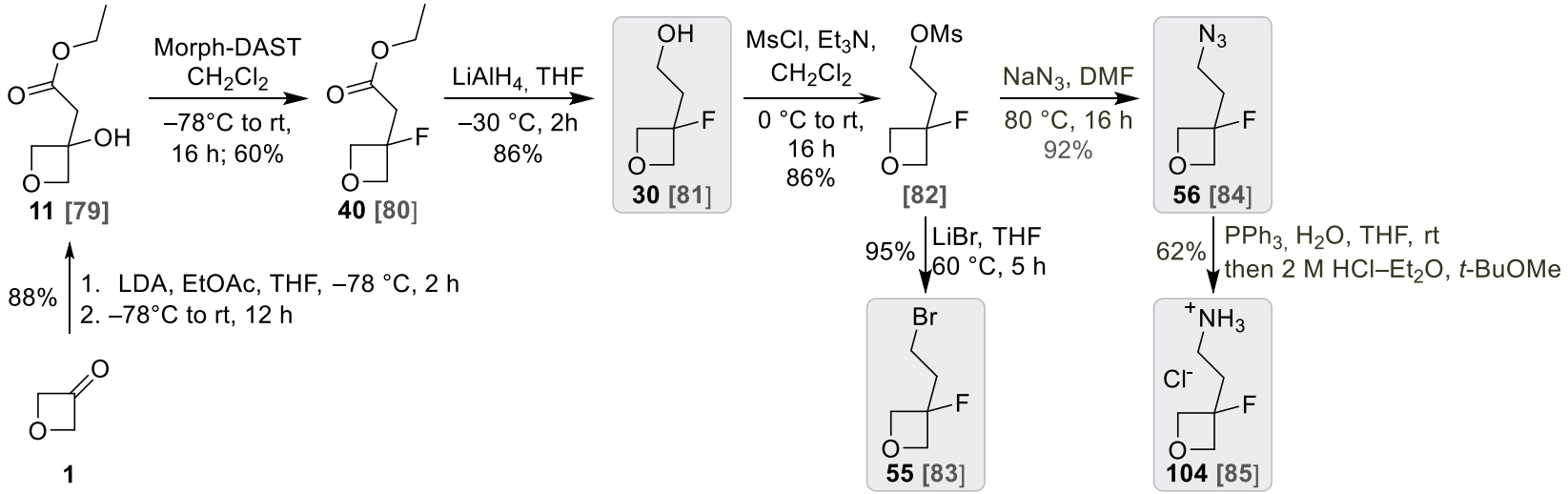


The compound was obtained from oxetan-3-one (23.0 g, 0.319 mol) according to the procedure for the synthesis of 3-(nitromethyl)oxetan-3-ol (**8**). Yield 25.3 g (46%). Yellowish oil. The compound was used in the next step immediately after the preparation without additional purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (d, *J* = 7.6 Hz, 1H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.62 (d, *J* = 7.6 Hz, 1H), 4.56 (d, *J* = 7.2 Hz, 1H), 4.16 – 3.92 (m, 2H), 1.62 – 1.39 (m, 1H), 0.93 – 0.83 (m, 1H), 0.73 – 0.67 (m, 2H), 0.54 (d, *J* = 4.4 Hz, 1H), 0.41 – 0.37 (m, 1H).

3-[Amino(cyclopropyl)methyl]oxetan-3-ol (102). [78]

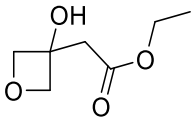


The compound was obtained from compound **10** (25.3 g, 0.146 mol) according to the procedure for the synthesis of 3-(aminomethyl)oxetan-3-ol (**100**). Yield 16.1 g (76%). Yellowish solid, 62–63 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 – 4.67 (m, 2H), 4.64 – 4.55 (m, 2H), 2.49 (s, 1H), 1.46 (br s, 3H), 1.02 – 0.91 (m, 1H), 0.65 (tdd, *J* = 8.6, 5.7, 4.4 Hz, 1H), 0.52 (ddt, *J* = 13.4, 8.6, 4.9 Hz, 1H), 0.48 – 0.40 (m, 1H), 0.21 – 0.13 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.9, 80.2, 76.2, 60.8, 13.1, 4.9, 1.3. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_7H_{14}NO_2$ 144.1019, found 144.1017.



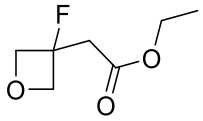
Scheme S19. Accessing oxetan-3-one derivatives employing aldol reaction and deoxyfluorination

Ethyl 2-(3-hydroxyoxetan-3-yl)acetate (11). [79]



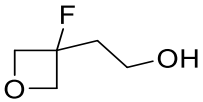
In a reactor equipped with a mechanical stirrer, *n*-BuLi (2.5 M in hexanes, 200 mL) and dry THF (3 L) were added. The solution was cooled with ice to 0 °C and *i*-Pr_2NH (77.0 mL, 55.2 g, 0.546 mol) was added. The resulting solution was stirred at 0 °C for 30 min, then cooled to –78 °C. EtOAc (48.1 g, 0.546 mol) was added dropwise through a cannula, yielding a bright yellow solution. The mixture was stirred at –78 °C for 2 h, followed by the dropwise addition of a solution of 3–oxetanone (39.3 g, 0.546 mmol), forming a colorless precipitate. The reaction mixture was allowed to slowly warm to rt and was stirred additionally for 12 h. The reaction was quenched with a saturated aq NH_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. Yield 78.1 g (88%). Physical and spectral data were analogous to that reported[5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (d, *J* = 6.8 Hz, 2H), 4.46 (d, *J* = 6.8 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 1H), 2.91 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 83.0, 72.0, 61.3, 42.1, 14.2. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_7H_{13}O_4$ 161.0808, found 161.0804.

Ethyl 2-(3-fluorooxetan-3-yl)acetate (40). [80]



Compound **11** (112 g, 0.692 mol) was dissolved in CH_2Cl_2 (1250 mL) and cooled to –78 °C using a MeOH–nitrogen bath. Morph–DAST (122 g, 0.692 mol) was slowly added under Ar, and the mixture was stirred at rt overnight (ca. 16 h). Then, the mixture was carefully poured onto a concentrated $NaHCO_3$ (58.2 g, 0.692 mol) and stirred for 40 min. The solution was dried over Na_2SO_4, separated, and evaporated in vacuo to obtain a mixture of compound **40** and the acrylate product of the side elimination reaction in a ratio of 2:1 respectively. NOTE: compound **40** is unstable and can proceed in the elimination reaction to give the corresponding acrylate for the separation of acrylate by-product, a mixture should be dissolved in THF: H_2O (4:1, v/v), then treated with NMO (1.1 equiv) and OsO_4 (1 mol%) and stirred for 2 days. After 2 days, an aq Na_2SO_3 (1.3 equiv) in H_2O was added, and the mixture was stirred for 1.5 h. Then, the mixture was extracted with *t*–BuOMe, and dried over Na_2SO_4. Product **40** should be stored in a freezer or used immediately after the preparation in the next step, which was found to be the best approach. Yield ca. 68.3 g (ca. 60%). Dark brown liquid.

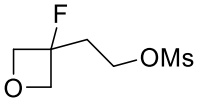
2-(3-Fluorooxetan-3-yl)ethan-1-ol (30) [81][6]



$LiAlH_4$ (47.0 g, 1.24 mol) was added to THF (2 L), and the solution was cooled to –30 °C. Compound **39** (181 g, 1.12 mol) was added dropwise in a solution of THF (500 mL), and the mixture was stirred at –30 °C for 2 h. At the same temperature, 30% aq KOH (79.2 g, 1.41 mol) was added. The mixture was warmed up to rt, and stirred for 2 h. Then, the mixture was filtered, and evaporated in vacuo. Yield 115 g (86%). Yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 20.7, 7.8 Hz, 2H), 4.70 – 4.61 (m, 2H), 3.84 – 3.81 (m, 2H), 2.19 (dt, *J* = 22.4, 6.1 Hz, 2H), 1.88 – 1.77 (m, 1H). ^{13}C

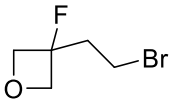
NMR (151 MHz, $CDCl_3$) δ 94.9 (d, *J* = 205.5 Hz), 81.3 (d, *J* = 24.5 Hz), 57.9 (d, *J* = 4.3 Hz), 37.2 (d, *J* = 22.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -151.1. GC/MS (EI) *m/z*: 100 $[M–HF]^+$. Anal. Calcd. for $C_5H_9FO_2$: C 49.99; H 7.55. Found: C 50.20; H 7.95.

3-(3-Fluorooxetan-3-yl)ethyl methanesulfonate [82]



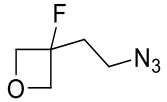
MsCl (36.7 g, 0.320 mmol) was carefully added to a solution of **30** (35.0 g, 0.291 mmol) and Et_3N (44.2 g, 0.437 mmol) in CH_2Cl_2 (500 mL) at 0 °C. Then, the reaction mixture was warmed to rt and stirred for 16 h. After that, the reaction mixture was washed with H_2O (4 ×100 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield ca. 48.9 g (ca. 85%). Yellowish oil. Due to the limited stability, the compound was used in the next step immediately after the preparation.

3-(2-Bromoethyl)-3-fluorooxetane (55). [83]



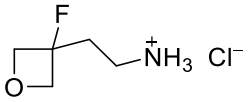
LiBr (66.2 g, 0.763 mol) was added to mesylate **[82]** (48.9 g, 0.254 mol) in THF (480 mL), and the mixture was heated at 60 °C for 5 h. Then, the resulting mixture was evaporated in vacuo, the residue was dissolved in H_2O (300 mL), and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting liquid was purified by column chromatography on silica gel using hexanes–EtOAc (9:1, v/v) as eluent. Yield 43.0 g (95%). Brown liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 20.5, 8.0 Hz, 2H), 4.67 (dd, *J* = 21.2, 8.0 Hz, 2H), 3.46 (t, *J* = 7.0 Hz, 2H), 2.53 (dt, *J* = 21.2, 7.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 94.8 (d, *J* = 208.3 Hz), 80.7 (d, *J* = 24.4 Hz), 37.9 (d, *J* = 23.4 Hz), 25.2 (d, *J* = 5.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -153.6. GC/MS (EI) *m/z*: 152/154 $[M\text{-}CH_2O]^+$. Anal. Calcd. for C_5H_8BrFO: C 32.81; H 4.41; Br 43.66, found C 32.60; H 4.39; Br 43.32.

3-(2-Azidoethyl)-3-fluorooxetane (56) [84]

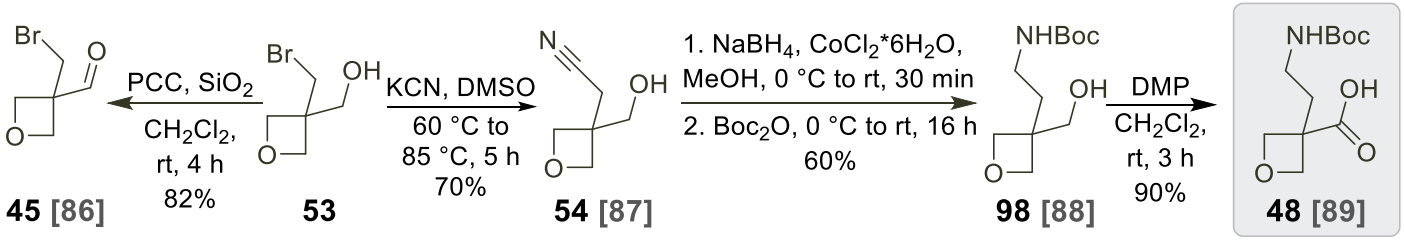


NaN_3 (35.8 g, 0.550 mol) was added to a solution of compound **[82]** (23.2 g, 0.128 mol) in DMF (100 mL), and the resulting mixture stirred at 80 °C overnight (ca. 16 h). After that, the reaction mixture was poured into H_2O (300 mL), and the target product was extracted with *t*-BuOMe (3 × 150 mL). Combined organic layers were washed with H_2O (100 mL), brine (100 mL), and carefully evaporated in vacuo. The compound was used in the next step as a solution after the isolation without additional purification due to safety concerns. Yield ca. 17.1 g (ca. 92%).

2-(3-Fluorooxetan-3-yl)ethan-1-amine hydrochloride (104). [85]

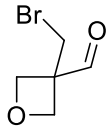


To the solution of PPh_3 (69.5 g, 0.265 mol) in THF (250 mL), distilled H_2O (9.55 g, 0.53 mol) was added, followed by slow addition of the azide (31.1 g, 0.255 mol). The mixture was heated for 4 h at 50 °C. Then, the mixture was evaporated in vacuo. The resulting solution was concentrated and purified by column chromatography on silica gel. Additional purification was achieved by the addition of *t*-BuOMe, the titration with 2 M HCl – Et_2O until pH 7 was reached, followed by the filtration and drying. Yield 21.5 g (62%). Yellow solid, mp 84-86 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (br s, 3H), 4.61 (dd, J = 17.9, 6.0 Hz, 2H), 4.56 (dd, J = 19.3, 5.8 Hz, 2H), 2.83 (t, J = 8.1 Hz, 2H), 2.28 (dt, J = 23.3, 7.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 94.9 (d, J = 205.2 Hz), 79.9 (d, J = 23.6 Hz), 34.0 (d, J = 4.4 Hz), 32.6 (d, J = 23.5 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -149.1. HRMS (ESI–TOF) m/z: [M–HCl+H]+ calcd. for $C_5H_{11}FNO$ 120.0819, found 120.0820.



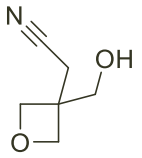
Scheme S20. Synthesis of 3-(aminoethyl)oxetane-3-carboxylic acid 48

3-(Bromomethyl)oxetane-3-carbaldehyde (45). [86]



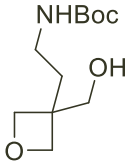
PCC (452 g, 2.09 mol) and SiO_2 (600 g) were carefully added in portions to a solution of alcohol **53**[7,8] (253 g, 1.40 mol) in CH_2Cl_2 (2800 mL). The resulting mixture was stirred at rt for 4 h, then filtered throught SiO_2 and concentrated in *vacuo*. NOTE: distillation is unsuitable for the purification due to high risk of explosion; it is advised to use this product in the next step immediately after the prapration without additional purification. Yield 204 g (82%). Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 4.83 (d, *J* = 6.8 Hz, 2H), 4.56 (d, *J* = 6.8 Hz, 2H), 3.87 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 74.7, 53.3, 31.5. ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 74.7, 53.3, 31.5. GC/MS (EI) *m/z*: 149/151 $[M–CHO]^+$. Anal. calcd. for $C_5H_7BrO_2$: C 33.55; H 3.94; Br 44.64, found C 33.94; H 4.18; Br 44.67.

2-(3-(Hydroxymethyl)oxetan-3-yl)acetonitrile (54). [87]



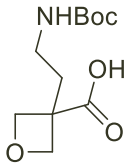
Alcohol **53** (123 g, 0.679 mol) was dissolved in EtOH (1000 mL), and KCN (177.0 g, 2.71 mol) was added. The reaction mixture was stirred at 85 °C for 16 h, then filtered and concentrated in *vacuo*. Yield 60.5 g (70%). Yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (s, 4H), 3.98 – 3.94 (m, 2H), 2.83 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 116.7, 76.7, 64.6, 41.7, 22.0. GC/MS (EI) *m/z*: 127 $[M]^+$. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_6H_{10}NO_2$ 128.0706, found 128.0706.

***tert*-Butyl (2-(3-(hydroxymethyl)oxetan-3-yl)ethyl)carbamate (98). [88]**



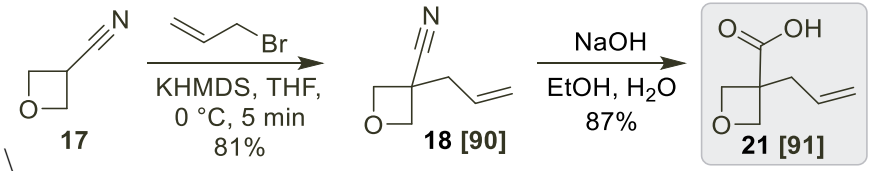
$NaBH_4$ (108 g, 2.85 mol) was added in portions to a solution of compound **54** (60.5 g, 0.476 mol) and $CoCl_2 \times 6H_2O$ (33.9 g, 0.142 mol) in MeOH (1 L) at 0 °C, and the resulting mixture was stirred at rt for 30 min. After that, Boc_2O (125 g, 0.57 mol) was added dropwise at 0 °C, and the resulting mixture was stirred at rt for 16 h. Then, the solution was poured into sat. aq NH_4Cl (500 mL), and the target product was extracted with EtOAc (3 × 500 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Yield 66.0 g (60%). Yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.45 (d, J = 6.5 Hz, 2H), 4.42 (d, J = 5.9 Hz, 2H), 3.88 (s, 2H), 3.22 – 3.06 (m, 2H), 2.83 (s, 1H), 1.95 (t, J = 7.4 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 79.8, 78.9, 66.0, 43.1, 36.7, 34.4, 28.6. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_{11}H_{22}NO_4$ 232.1543, found 232.1536.

3-(2-((*tert*-Butoxycarbonyl)amino)ethyl)oxetane-3-carboxylic acid (48). [89]



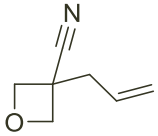
Oxidation with $KMnO_4$ (the procedure is suitable only for 3,3-bisalkyl-substituted oxetanes). Alcohol **98** (66.0 g, 0.285 mol) was dissolved in a solution of KOH (32.0 g, 0.570 mol) in H_2O (300 mL), and the reaction mixture was cooled to 0 °C. Then, $KMnO_4$ (135 g, 0.856 mol) was carefully added in portions at 0 °C, and the resulting mixture was stirred at rt for 2 h. NOTE: the reaction is highly exothermic. The reaction mixture was washed with EtOAc (2 × 300 mL), and *t*-BuOMe (3 × 300 mL), acidified to pH 4 with $NaHSO_4$, and extracted with EtOAc (3 × 500 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The residue was triturated in Et_2O. Yield 62.9 g (90%).

Oxidation with PIDA/TEMPO((the procedure is also suitable for 3-oxy- and 3-amino-subtituted oxetanes). Alcohol **90** (1.41 g, 6.12 mmol) was dissolved in CH_2Cl_2 – H_2O (2:1, v/v, 30 mL), and the reaction mixture was cooled to 10 °C. Then, PIDA (3.94 g, 12.2 mmol) and TEMP (192 mg, 1.22 mmol) were added in portions. The reaction mixture was stirred overnight (ca. 16 h), and the proceeding of the reaction was monitored by ^{1}H NMR. Then, CH_2Cl_2 was evaporated in vacuo, the aqueous residue was diluted with *t*-BuOMe (50 mL), and K_2CO_3 (340 mg) was added. The aqueous layer was washed with *t*-BuOMe (2 × 15 mL), and then $NaHSO_4$ was added until pH 4 was reached. The resulting mixture was extracted with $CHCl_3$ (3 × 15 mL), combined organic extracts were dried over Na_2SO_4, filtered, and evaporated in vacuo at 30 °C. Yield 1.27 g (85%). Colorless solid, mp 123–126 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.81 (s, 1H), 6.80 (t, J = 5.7 Hz, 1H), 4.67 (d, J = 6.0 Hz, 2H), 4.35 (d, J = 6.0 Hz, 2H), 2.88 – 2.82 (m, 2H), 2.05 – 1.99 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.7, 155.4, 77.6, 77.1, 46.4, 36.0, 35.0, 28.2. HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_{11}H_{20}NO_5$ 246.1336, found 246.1334.



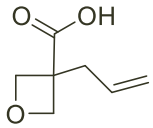
Scheme S21. Synthesis of allyl-susbtituted oxetane carboxylic acid 21

3-Allyloxetane-3-carbonitrile (18). [90]

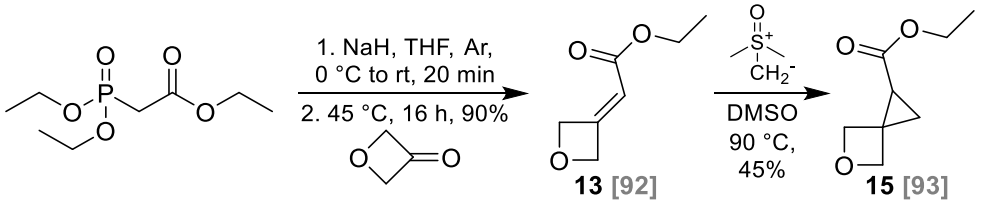


Allyl bromide (403 mg, 3.33 mmol) and oxetane-3-carbonitrile **17** (277 mg, 3.33 mmol) were dissolved in toluene (3 mL) under Ar. The mixture was cooled to 0 °C, and 1.0 M KHMDS in THF (504 mL, 1.2 mmol) was slowly added dropwise at 0 °C. The mixture was stirred for 5 min, then quenched with MeOH (1 mL). The resulting mixture was filtered via a thin pad SiO_2, rinsing with EtOAc. The filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2, and concentrated in vacuo one more time. Yield 332 mg (81%). Yellowish oil. The compound was used in the next step without additional purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (d, *J* = 10.7 Hz, 1H), 5.27 (d, *J* = 13.6 Hz, 2H), 4.92 (dd, *J* = 6.3, 3.8 Hz, 2H), 4.46 (dd, *J* = 6.3, 3.8 Hz, 2H), 2.75 (d, *J* = 5.1 Hz, 2H).

3-(Prop-2-en-1-yl)oxetane-3-carboxylic acid (21). [91]

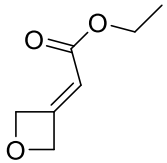


NaOH (431 mg, 10.8 mmol) was added to a solution of nitrile **18** (332 mg, 2.70 mol) in EtOH/H_2O (6 mL; 2/1), and the resulting solution was refluxed for 20 h. Then, EtOH was evaporated, and the solution was acidified to pH 4 with aq $NaHSO_4$. Then, extraction was done EtOAc (3 × 100 mL) giving the pure target product. Yield 333 mg (87%). Fusible colorless crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51 (br s, 1H), 5.86 – 5.69 (m, 1H), 5.24 – 5.10 (m, 2H), 4.95 (dd, *J* = 6.2, 1.8 Hz, 2H), 4.51 (dd, *J* = 6.2, 1.8 Hz, 2H), 2.78 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 131.9, 119.3, 77.4, 47.9, 39.4. GC/MS (EI) *m/z*: 97 $[M–CO_2H]^+$. HRMS (ESI–TOF) m/z: $[M–H]^-$ calcd. for $C_7H_9O_3$ 141.0557, found 141.0559.



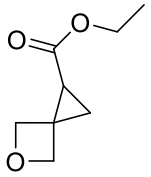
Scheme S22. Modification of oxetan-3-one via Corey-Chaykovsky cyclopropanation

Ethyl 2-(oxetan-3-ylidene)acetate (13). [92]

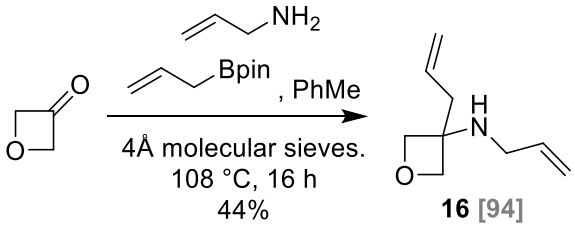


Ethyl 2–(diethoxyphosphoryl)acetate (568 g, 2.53 mol) was added dropwise to a suspension of NaH (92.7 g, 3.86 mol) in THF (1.5 L) under Ar at 0 °C for 1 h. The reaction mixture was stirred at rt for 20 min. Then, the reaction mixture was heated to 45 °C, and oxetan–3–one (152 g, 2.11 mol) was added dropwise over 30 min. The reaction mixture was stirred overnight (ca. 16 h) at 45 °C, then poured onto a solution of NH_4Cl (339 g, 6.33 mol). The mixture was extracted with EtOAc (2 × 800 mL), and the combined organic layers were washed with brine (400 mL). The organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 301 g (90%). Spectral and physical data were analogous to that reported.[9]

Ethyl 5-oxaspiro[2.3]hexane-1-carboxylate (15). [93]



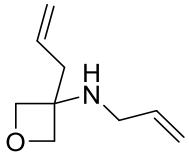
Compound **13** (419 g, 2.95 mol) was dissolved in DMSO (1260 mL) and heated to 90 °C. Simultaneously, to a suspension of NaH (167 g, 6.95 mol) in DMSO (2940 mL) at 13–18 °C under an Ar atmosphere, $Me_3S(O)I$ (778 g, 3.54 mol) was added in portions and stirred at 13–18 °C for 40 min under an Ar atmosphere. The solution was then added dropwise to the already heated (90 °C) solution of compound 2. NOTE: Heating overnight (ca. 16 h) destroys the product; the 2 h duration is crucial). After the addition was complete, the reaction mixture was left for 2 h at 90 °C. After 2 h, the reaction mixture was cooled to rt and poured onto a solution of NH_4Cl (473 g, 8.83 mol). The mixture was extracted with *t*-BuOMe (3 × 500 mL), and the combined organic layers were washed with brine. The organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. Purification was done by chromatography. Yield 207 g (45%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 – 4.65 (m, 4H), 4.13 (q, *J* = 7.1 Hz, 2H), 1.77 (dd, *J* = 8.8, 5.6 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.15 (dd, *J* = 8.8, 5.6 Hz, 1H). HRMS (ESI–TOF) m/z: [M+H]+ calcd. for $C_8H_{13}O_3$ 157.0859, found 157.0857.



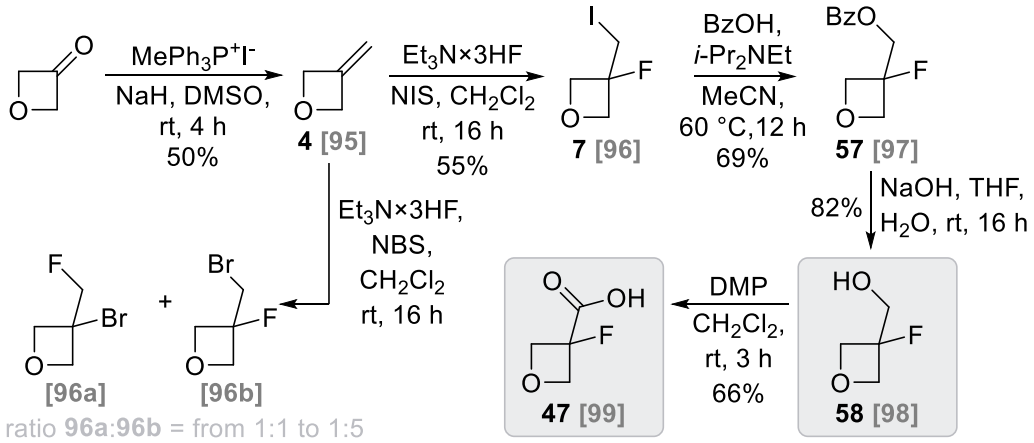
16 [94]

Scheme S23. Petasis reaction for the preparation of *N*,3-diallyloxetan-3-amine (16)

_N_,3-diallyloxetan-3-amine (16). [94]



Allylamine (8.00 g, 0.140 mol), allylboronpinacolate (23.5 g, 0.140 mol), and oxetanone (10.0 g, 0.140 mol) were mixed in toluene (100 mL) with 4Å molecular sieves (a few pellets). The mixture was heated at 108 °C overnight (ca. 16 h). After cooling, the reaction mixture was poured into EtOAc (200 mL) and saturated $NaHCO_3$ solution (200 mL), then extracted again with $NaHCO_3$ solution. The combined organic layers were washed with brine, passed through a short silica column (SiO_2), and evaporated in *vacuo*. Yield 9.38 g (44%). Yellowish oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 – 5.75 (m, 2H), 5.27 – 5.19 (m, 2H), 5.19 – 5.07 (m, 2H), 4.58 (d, *J* = 6.4 Hz, 2H), 4.42 (d, *J* = 6.4 Hz, 2H), 3.31 (dt, *J* = 6.0, 1.5 Hz, 2H), 2.61 (d, *J* = 7.2 Hz, 2H), 1.55 (br s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.8, 132.7, 118.8, 116.0, 80.8, 77.2, 77.0, 76.8, 59.3, 45.7, 40.6. LC/MS (ES-API) m/z 154 $[M+H]^+$. Anal. calcd. for $C_9H_{15}NO$: C 70.55; H 9.87; N 9.14, found C 70.84; H 9.58; N 9.48.

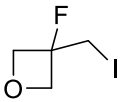


Scheme S24. Synthesis 3-fluorooxetanes building blocks 47 and 58

3-Methyleneoxetane (4). [95]

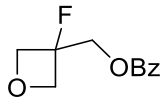
NaH (71.9 g, 3.00 mol) was carefully added to the methyltriphenylphosphonium iodide (865 g, 2.14 mol) in DMSO at a temperature below 25 °C, and the resulting mixture was stirred at rt for 4 h. Then, oxetan-3-one (103 g, 1.43 mol) was slowly added to the reaction mixture at 0 °C, and the resulting mixture was stirred overnight (ca. 16 h). Then, the title compound was obtained using distillation. Yield 50.3 g (50%). Spectral data were in accordance with that reported.[10]

3-(Iodomethyl)-3-fluorooxetane (7). [96]



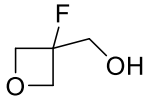
$Et_3N{\times}3HF$ (560 g, 3.47 mol) was added in portions to a solution of alkene **4** (97.4 g, 1.39 mol) in CH_2Cl_2, and then NIS (344 g, 1.53 mol) was added at 0 °C. The resulting solution was stirred at rt for 16 h. After that, it was poured into ice water. The organic phase was separated, washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 165 g (55%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 18.2, 8.5 Hz, 2H), 4.50 (dd, *J* = 18.2, 8.5 Hz, 2H), 3.61 (d, *J* = 22.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 92.8 (d, *J* = 212.6 Hz), 80.3 (d, *J* = 23.8 Hz), 6.8 (d, *J* = 27.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -144.7. GC/MS (EI) *m/z*: 216 $[M]^+$. Anal. Calcd. for C_4H_6FIO: C 22.24; H 2.80; I 58.75; Found C 22.43; H 2.80; I 59.10.

(3-Fluorooxetan-3-yl)methyl benzoate (57). [97]



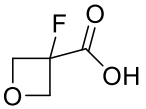
Compound **7** (255 g, 1.18 mol), $PhCO_2H$ (173 g, 1.42 mol), and i-Pr_2NEt (229 g, 1.77 mol) were dissolved in MeCN (3 L) and left stirring at 60 °C for 12 h. Then, the reaction mixture was concentrated in *vacuo*, diluted with EtOAc (2 L) and washed with saturated aq Na_2CO_3 (1 L), saturated aq $NaHSO_4$ (1 L), and brine (1 L). The organic layer was dried over Na_2SO_4 and evaporated in *vacuo*. The compound was characterized by ^{1}H NMR and used in the next step immediately after the preparation. Yield 171 g (69%). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dt, *J* = 8.2, 1.6 Hz, 2H), 7.58 (td, *J* = 7.4, 1.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 4.87 (dd, *J* = 18.9, 7.4 Hz, 2H), 4.73 – 4.61 (m, 4H).

(3-Fluorooxetan-3-yl)methanol (58). [98]

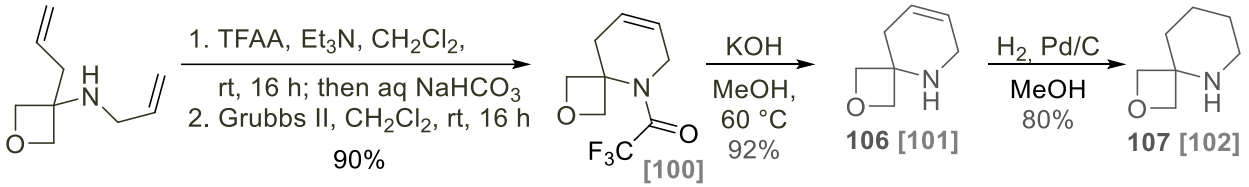


Benzoate **57** (170 g, 0.809 mol) was dissolved in THF-H_2O (2 L, 1:1 v/v), NaOH (97.0 g, 2.42 mol) was added and reaction mixture was left stirring at rt for 16 h. THF was evaporated in *vacuo*, residual aqueous solution was extracted with *t*-BuOMe (3 × 1 L), dried over Na_2SO_4, and evaporated in *vacuo*. Spectral and physical data were analogous to that reported.[11] Yield 70.3 g (82%). Yellow liquid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.01 – 4.49 (m, 4H), 3.70 (d, J = 21.5 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 95.0 (d, J = 208 Hz), 77.4 (d, J = 23.4 Hz), 62.0 (d, J = 26.2 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -155.9. GC/MS (EI) *m/z*: 106 $[M]^+$. Anal. calcd. for $C_4H_7FO_2$: C 45.28; H 6.65, found C 45.51; H 6.62.

3-Fluorooxetane-3-carboxylic acid (47). [99]

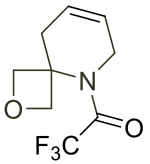


Alcohol **58** (9.12 g, 0.0860 mol) was dissolved in a solution of KOH (9.66 g, 0.172 mol) in H_2O (100 mL), and the reaction mixture was cooled to 0 °C. Then, $KMnO_4$ (40.8 g, 0.258 mol) was carefully added in portions at 0 °C, and the resulting mixture was stirred at rt for 2 h. NOTE: the reaction is highly exothermic. The reaction mixture was washed with EtOAc (2 × 80 mL), and *t*-BuOMe (3 × 30 mL), acidified to pH 4 with $NaHSO_4$, and extracted with EtOAc (3 × 100 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The residue was triturated in Et_2O. Yield 6.84 g (66%). Colorless solid, 107–109 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.87 (br s, 1H), 4.87 (dd, J = 22.1, 8.2 Hz, 2H), 4.71 (dd, J = 21.6, 8.2 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.6 (d, J = 28.2 Hz), 91.4 (d, J = 217 Hz), 78.1 (d, J = 24.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -159.7. HRMS (ESI–TOF) m/z: $[M-H]^-$ calcd. for $C_4H_4FO_3$ 119.0150, found 119.0151.



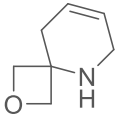
Scheme S25. Synthesis of 2-oxa-5-azaspiro[3.5]nonane 107

2,2,2-Trifluoro-1-(2-oxa-5-azaspiro[3.5]non-7-en-5-yl)ethan-1-one [100]



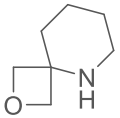
Et_3N (351 mL, 2.54 mol) was added to a solution of diene (393 g, 2.12 mol) in CH_2Cl_2 (4 L) at rt, then $(CF_3CO)_2O$ (324 mL, 2.33 mol) was added at rt. The resulting solution was stirred at rt overnight (ca. 16 h). Then, the solution was washed with saturated aq $NaHCO_3$ (2×2 L), brine (2 L), dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The obtained *N*-trifluoroacetyl derivative (250 g, 0.890 mol) in CH_2Cl_2 (9.5 L) was degassed 3 times and placed under the Ar atmosphere. Then, Grubbs II catalyst (37.8 g, 44.5 mmol) was added, and the resulting mixture was stirred at rt overnight (ca. 16 h). Then, reaction mixture was concentrated in vacuo, and subjected to flash chromatography. The obtained product was immediately used in the next step. Yield ca. 203 g (ca. 90%).

2-Oxa-5-azaspiro[3.5]non-7-ene (106). [101]

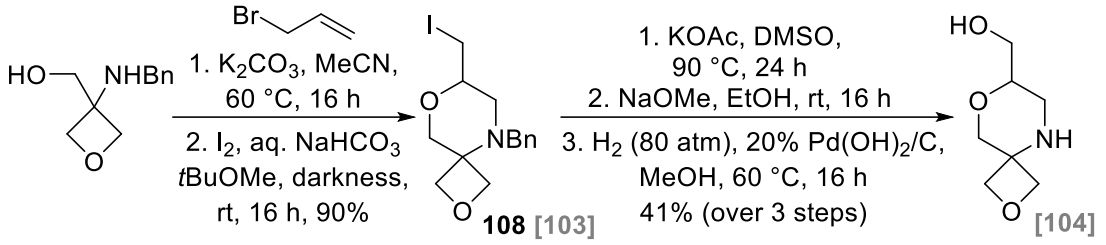


KOH (31.0 g, 0.554 mol) in MeOH (350 mL) was added to a solution of compound **[100]** (70.0 g, 0.277 mol) in MeOH (350 mL), and the resulting solution was stirred at 60 °C overnight (ca. 16 h). After that, the reaction mixture was concentrated in *vacuo*. Then, H_2O (350 mL) was added to an obtained residue, and the target was extracted with CH_2Cl_2 (3 × 150 mL). Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Yield 31.9 g (92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 – 5.58 (m, 2H), 4.47 (d, J = 6.3 Hz, 2H), 4.45 (d, J = 6.3 Hz, 2H), 3.52 – 3.37 (m, 2H), 2.44 – 2.34 (m, 2H), 1.93 (br s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 126.0, 123.3, 83.3, 55.6, 42.2, 34.6. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_7H_{12}NO$ 126.0913, found 126.0913.

2-Oxa-5-azaspiro[3.5]nonane (107) [102]

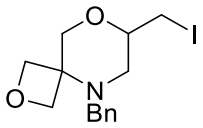


10% Pd/C (3.00 g) was added to a solution of compound **106** (30.0 g, 0.240 mol) in MeOH (300 mL), and the resulting mixture was stirred under H_2 (1 atm) at rt overnight (ca. 16 h). Then, Pd/C was filtered, and obtained filtrate was concentrated in *vacuo* giving the target compound. Yield 24.2 g (80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (d, J = 6.3 Hz, 2H), 4.38 (d, J = 6.3 Hz, 2H), 2.74 (t, J = 5.5 Hz, 2H), 1.97 (br s, 1H), 1.78 (t, J = 5.5 Hz, 2H), 1.55 – 1.36 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 83.6, 58.0, 43.2, 34.1, 25.4, 21.6. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for 128.1070, found 128.1070.



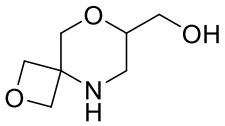
Scheme S26. Iodocyclization reaction for the preparation of spirocyclic oxetanes

5-benzyl-7-(iodomethyl)-2,8-dioxa-5-azaspiro[3.5]nonane (108). [103]



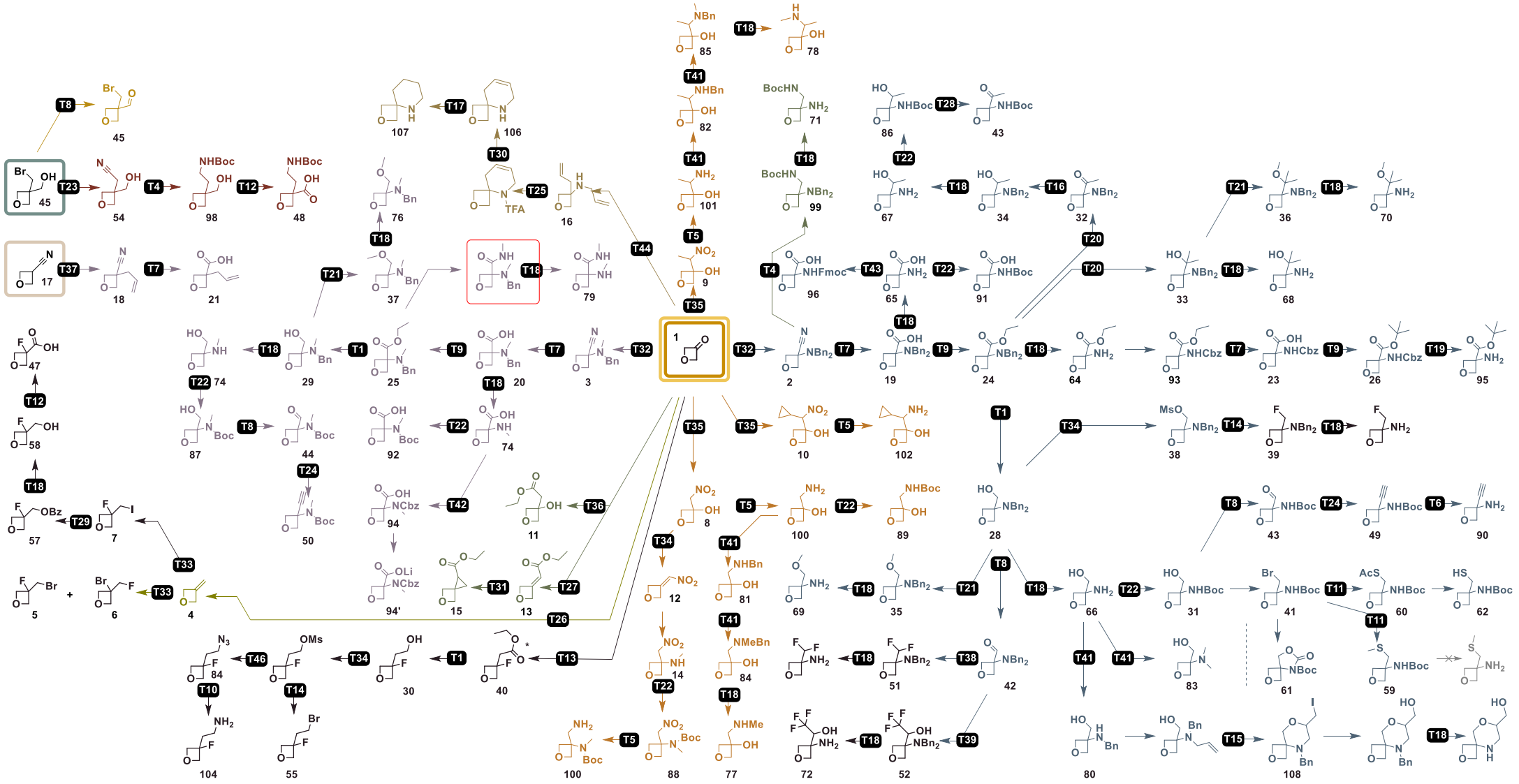
K_2CO_3 (195 g, 1.41 mol) was added to amine (136 g, 0.705 mol) in MeCN (1.4 L), then allyl bromide (73.2 mL, 0.846 mol) was added, and the resulting mixture was stirred at 60°C overnight (ca. 16 h). Then, the solution was cooled to rt, H_2O (1 L) was added, and MeCN (ca. 1.4 L) was evaporated in vacuo. Then, aqueous residue was extracted with *t*-BuOMe (4×250 mL). Combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo giving 157 g of the amber oil. Then, 1 M aq $NaHCO_3$ (1.48 L, 1.48 mol) followed by I_2 (188 g, 0.741 mol) were added to the obtained crude compound (157 g, 0.674 mol) in *t*-BuOMe (1.5 L), and the resulting solution was stirred in the darkness at rt overnight (ca 16 h). After that, saturated aq $Na_2S_2O_3$ was added until the solution become yellowish. The organic layer was separated, washed with brine (1 L), dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Yield 228 g (90%). Amber oil. The compound was used in the next step immediately after the preparation.

(2,8-Dioxa-5-azaspiro[3.5]nonan-7-yl)methanol [104]



KOAc (353 g, 3.60 mol) was added to a solution of compound **108** (432 g, 1.20 mol) in DMSO (2.4 L), and the resulting mixture was stirred at 90 °C overnight (ca. 16 h). Then, the reaction mixture was cooled to rt and poured into H_2O (4.8 L). The aqueous layer was extracted with EtOAc (5×700 mL). Combined organic layers were, washed with brine (400 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo* resulting in 210 g of amber oil (5-benzyl-2,8-dioxa-5-azaspiro[3.5]nonan-7-yl)methyl acetate). Then, NaOMe (117 g, 2.17 mol) was added to the obtained acetate (210 g, 0.722 mol) in

EtOH (1.5 L) at 5–10 °C, and the resulting mixture was stirred at rt overnight (ca. 16 h). After that, the solution was cooled to rt, H_2O (1 L) was added, and the organic layer (ca. 1 L) was evaporated in *vacuo*. Then, aqua layers was extracted with EtOAc (3×350 mL). Organic layers were combined and washed with brine (250 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The obtained orange oil was purified using column chromatography using hexanes - EtOAc (4:1, v/v) as eluent, giving 127 g of the amber oil. Then, 20% $Pd(OH)_2/C$ (18,9 g) was added to a solution of obtained *N*-benzyl amino alcohol (127 g, 0.51 mol) in MeOH, and the resulting solution was the solution was placed in a high–pressure autoclave. The autoclave was sealed and hydrogenated with H_2 (80 atm) at 60 °C overnight (ca. 16 h). After that, $Pd(OH)_2/C$ was filtered, and the filtrate was concentrated in *vacuo*. Yield 77.5 g (41% over 3 steps) amber solid. NOTE: the product is highly hydrophilic. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (d, J = 6.3 Hz, 1H), 4.54 (dd, J = 6.3, 1.9 Hz, 1H), 4.35 (d, J = 7.2 Hz, 1H), 4.33 (d, J = 7.2 Hz, 1H), 4.27 (d, J = 11.1 Hz, 1H), 3.70 – 3.47 (m, 4H), 2.81 (dd, J = 11.8, 2.4 Hz, 1H), 2.70 (dd, J = 11.8, 9.8 Hz, 1H), 1.94 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 83.0, 79.0, 76.3, 72.6, 63.7, 56.0, 43.9. HRMS (ESI–TOF) m/z: $[M+H]^+$ calcd. for $C_7H_{14}NO_3$ 160.0968, found 160.0963.



Scheme S27. The scope of this study

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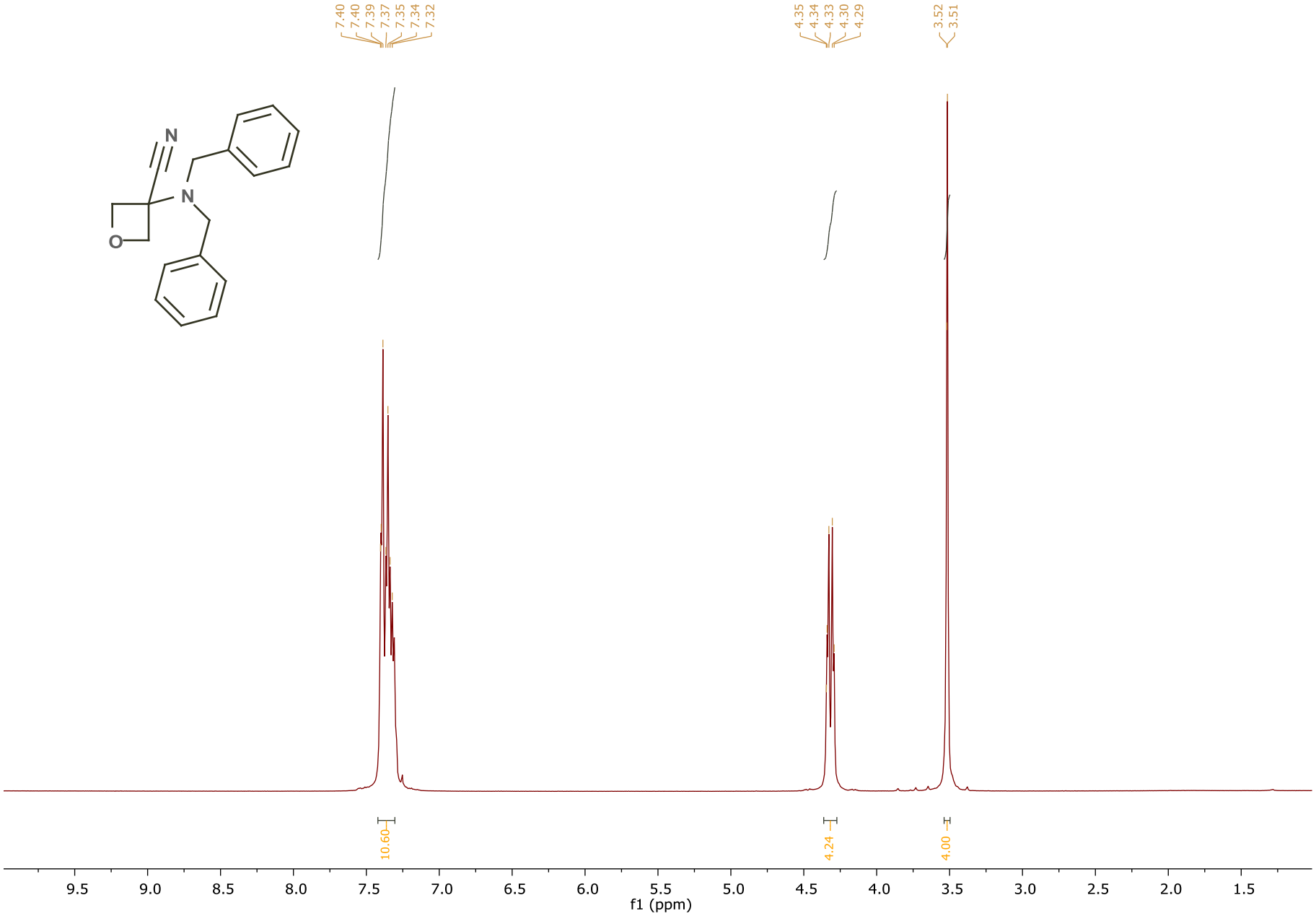
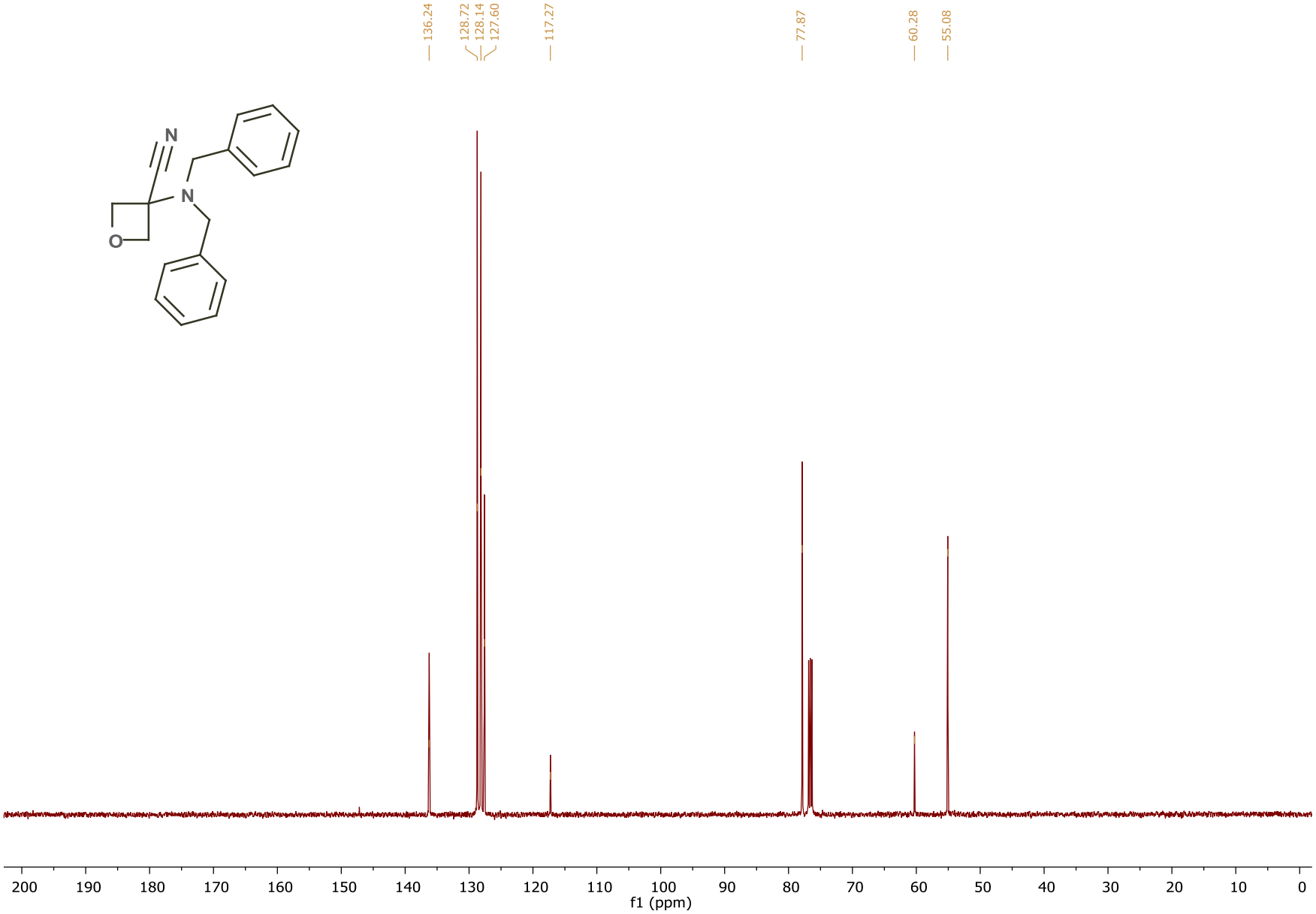
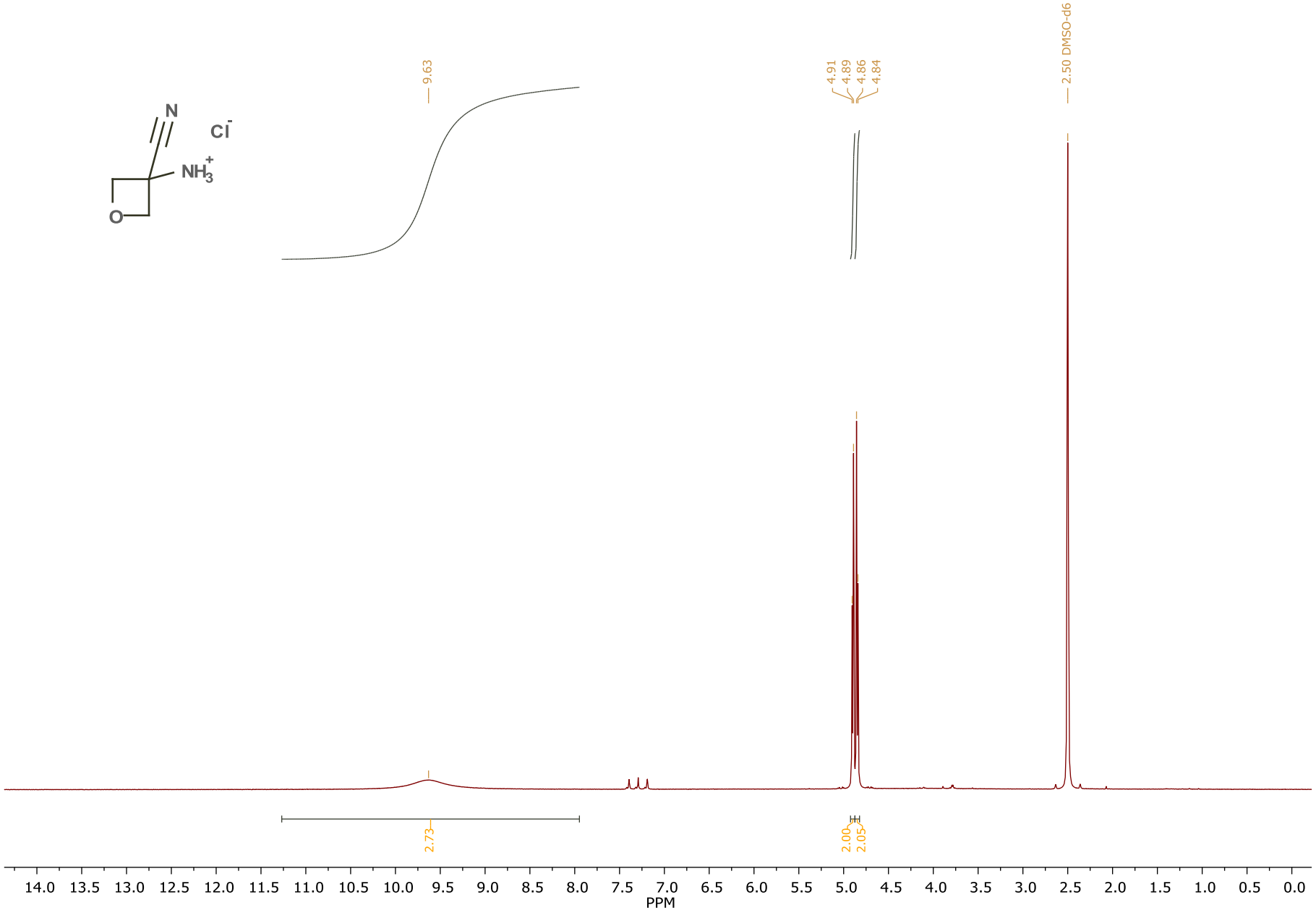


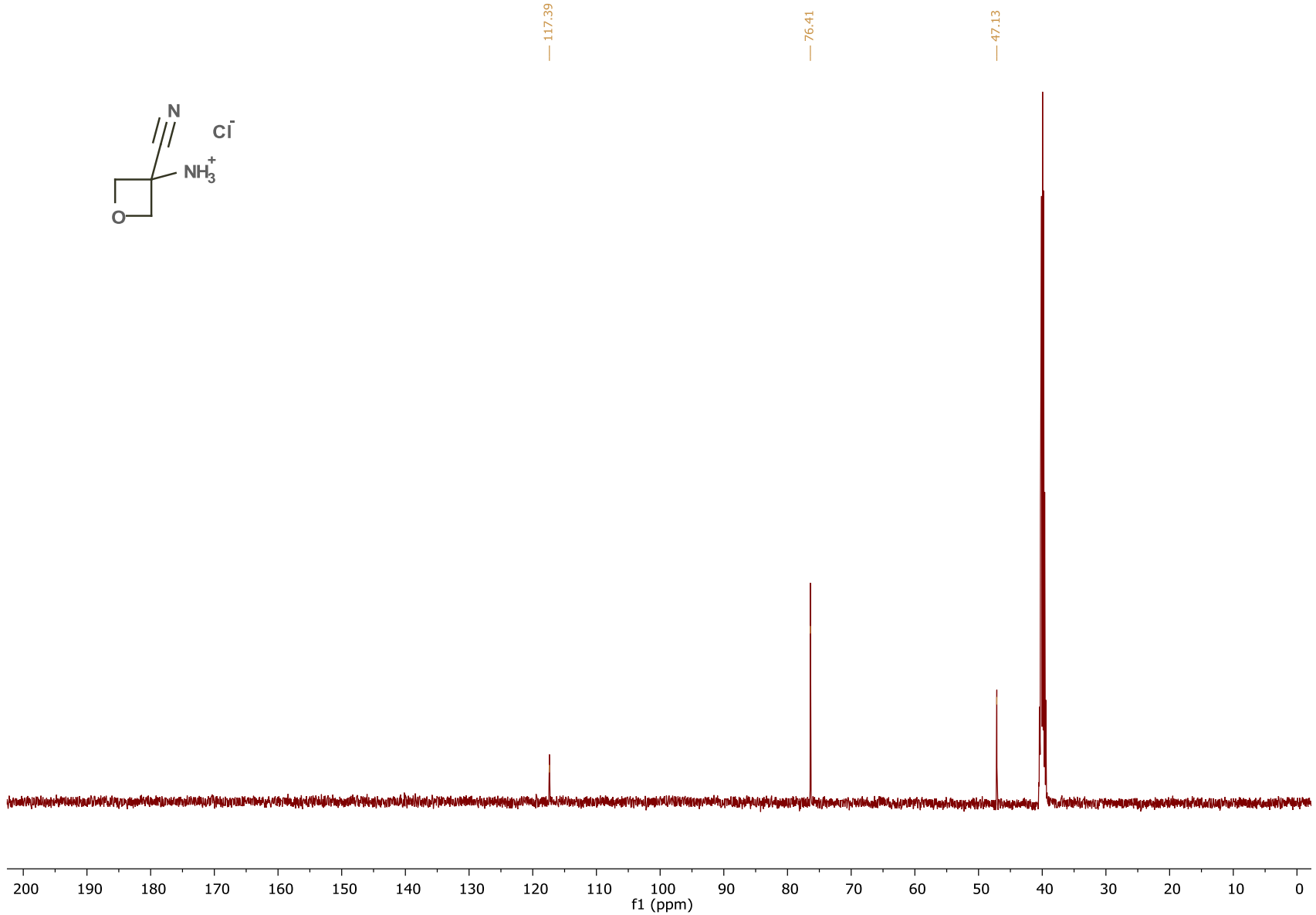
3-Aminooxetane-3-carbonitrile (1) ^{1}H NMR



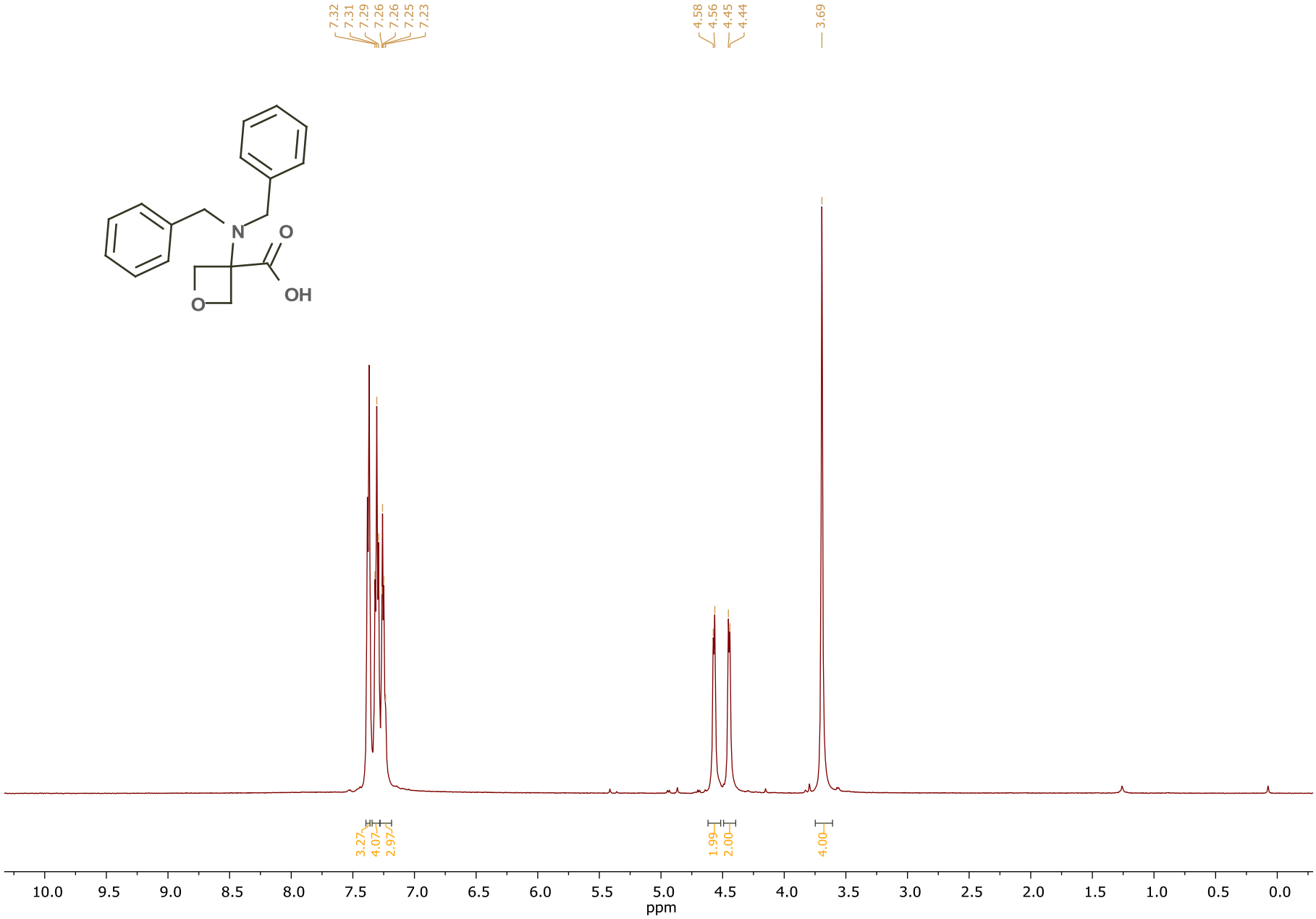
3-Aminooxetane-3-carbonitrile (1) $^{13}C\{H\}$ NMR



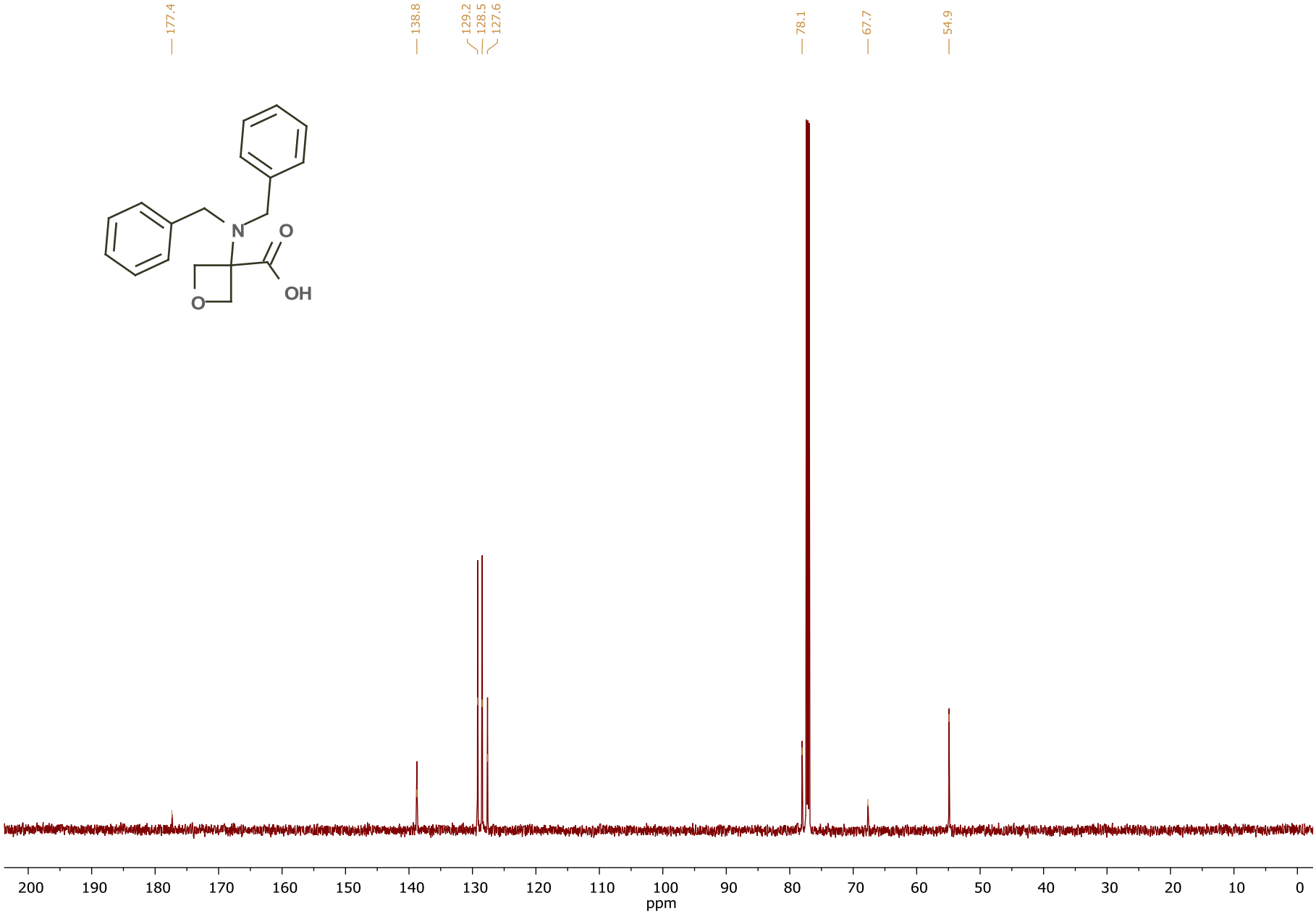
3-Aminooxetane-3-carbonitrile hydrochloride (2) ^{1}H NMR



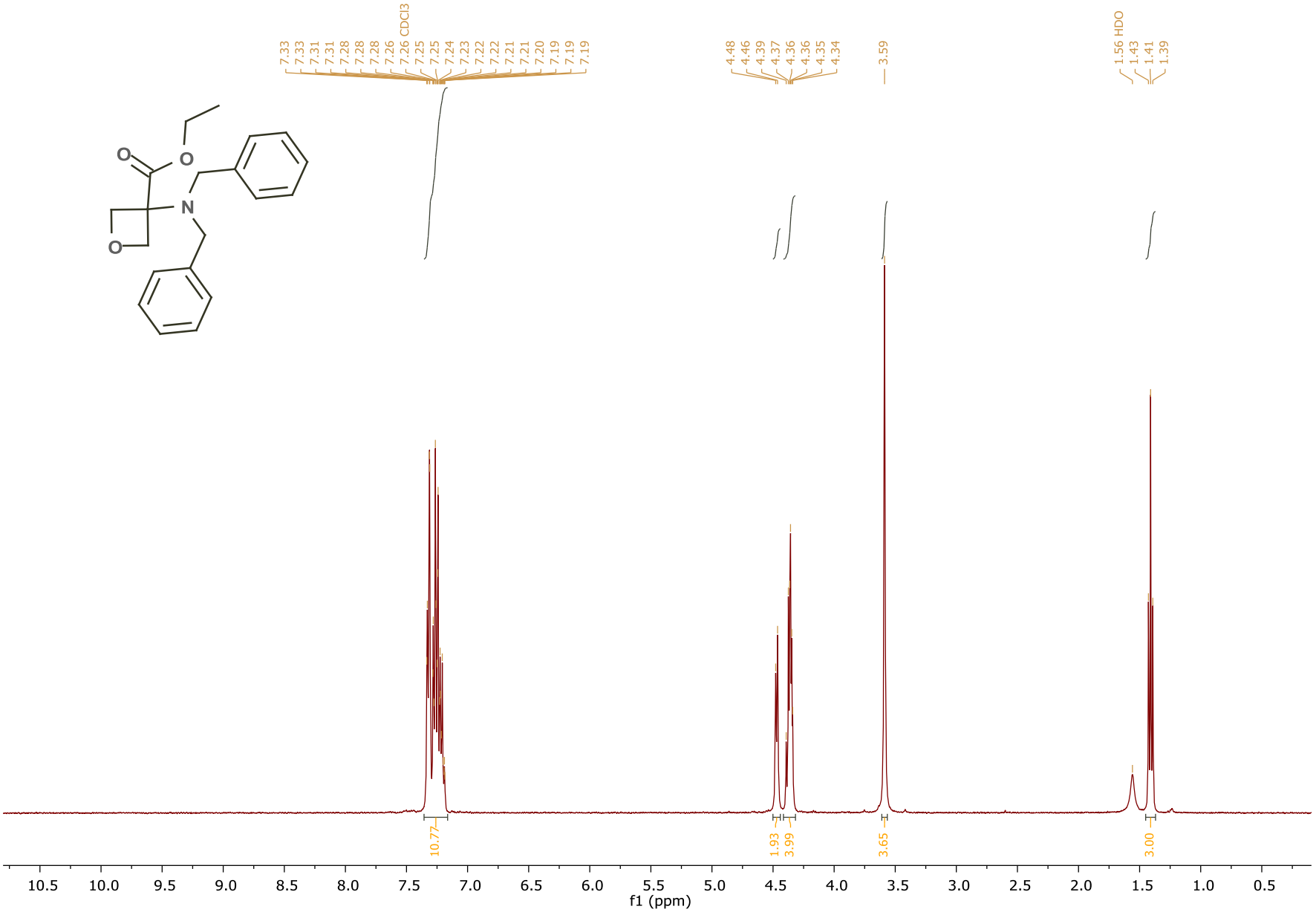
3-Aminooxetane-3-carbonitrile hydrochloride (2) $^{13}C\{H\}$ NMR



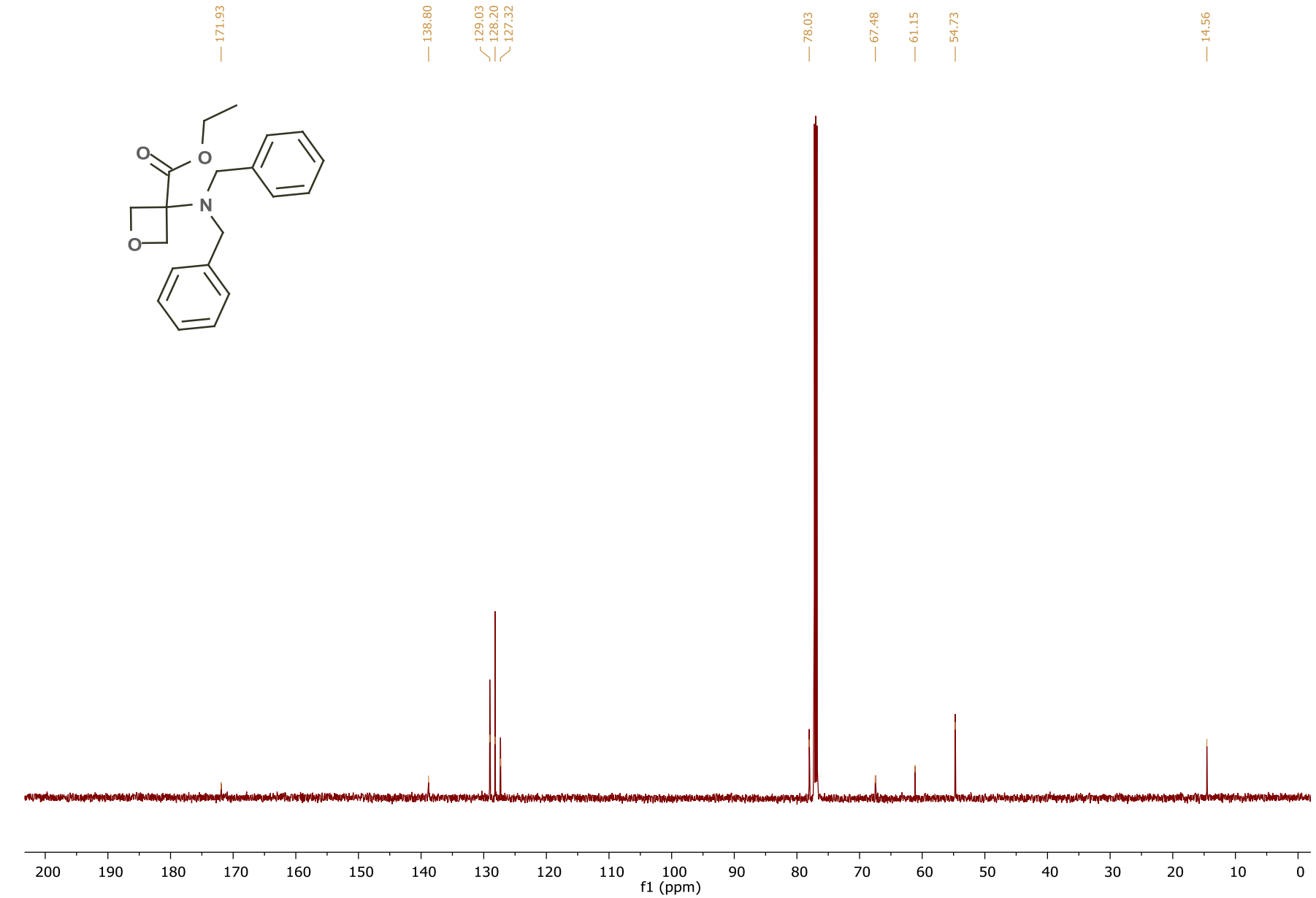
3-(Dibenzylamino)oxetane-3-carboxylic acid (3) ^{1}H NMR



3-(Dibenzylamino)oxetane-3-carboxylic acid (3) $^{13}C\{H\}$ NMR



Ethyl 3-(dibenzylamino)oxetane-3-carboxylate (4) ^{1}H NMR



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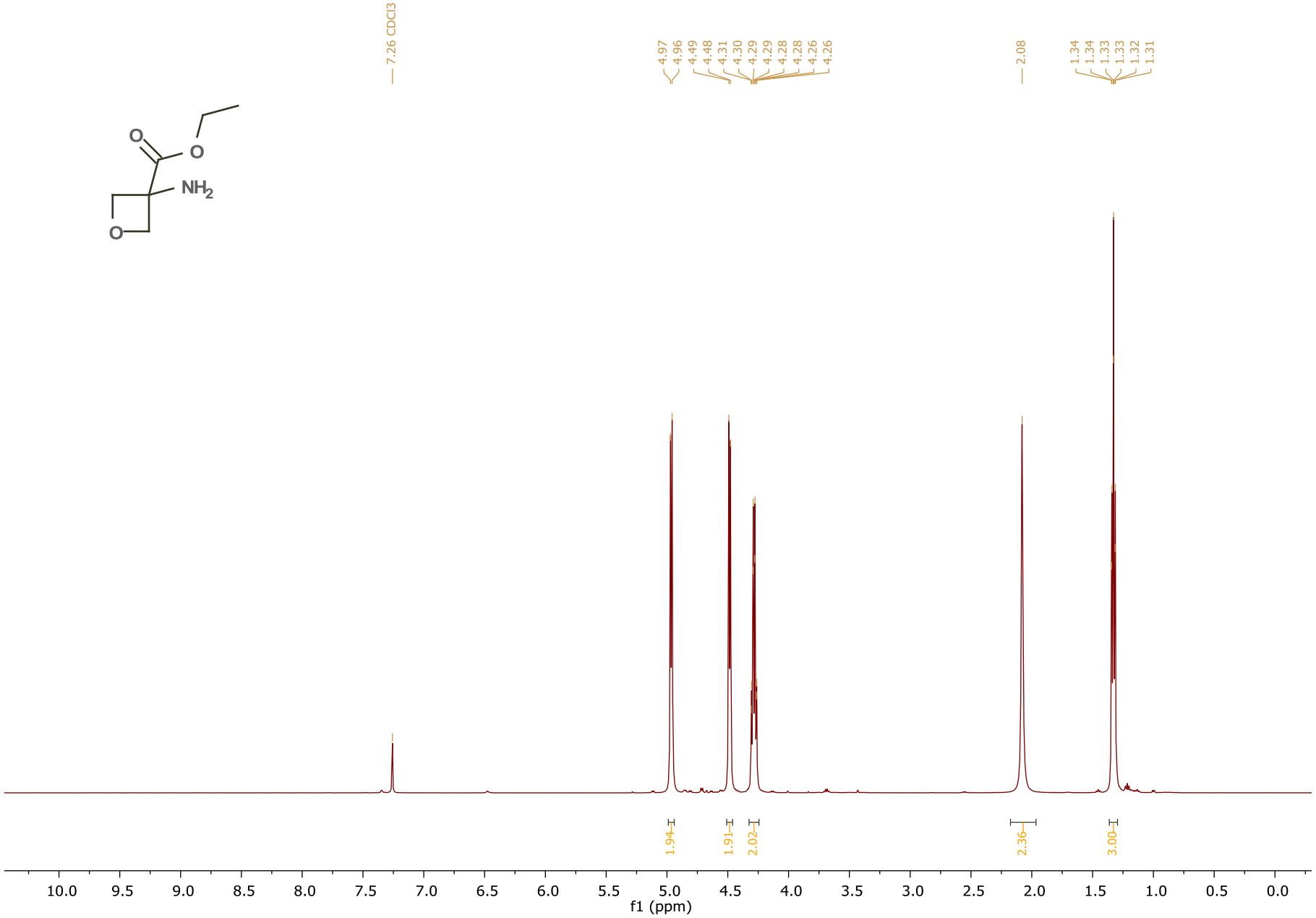
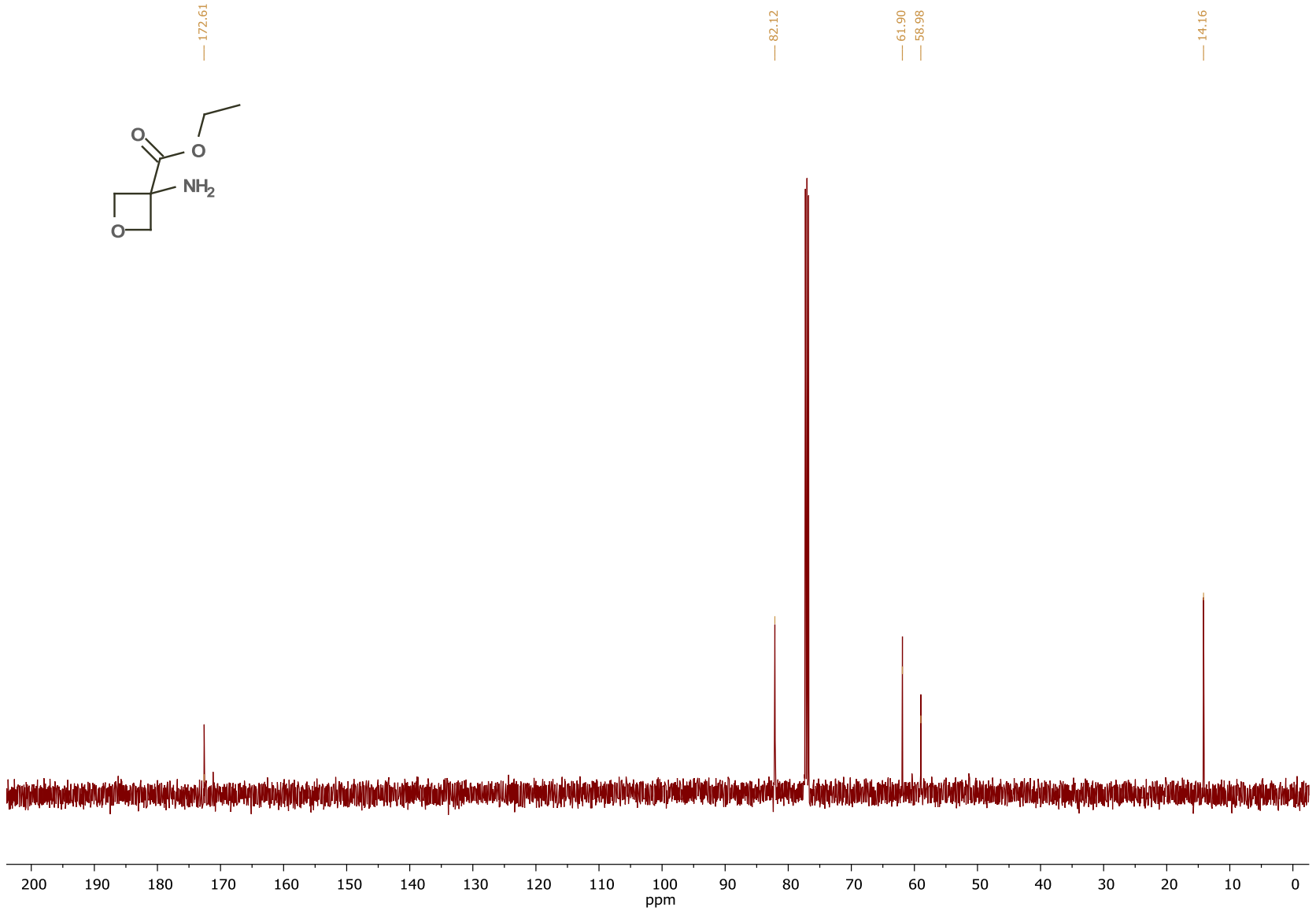
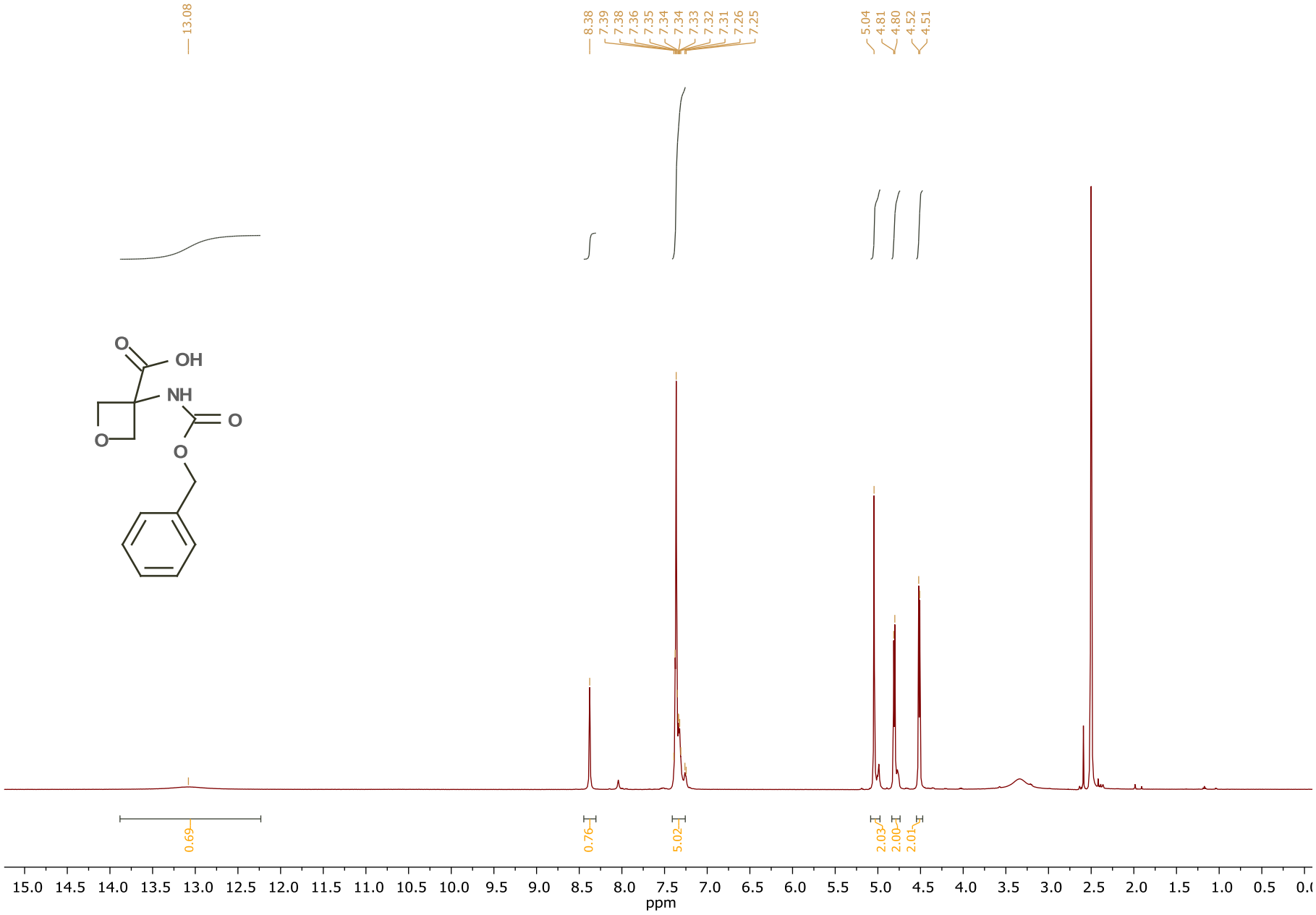
Ethyl 3-(dibenzylamino)oxetane-3-carboxylate (4) $^{13}C\{H\}$ NMR



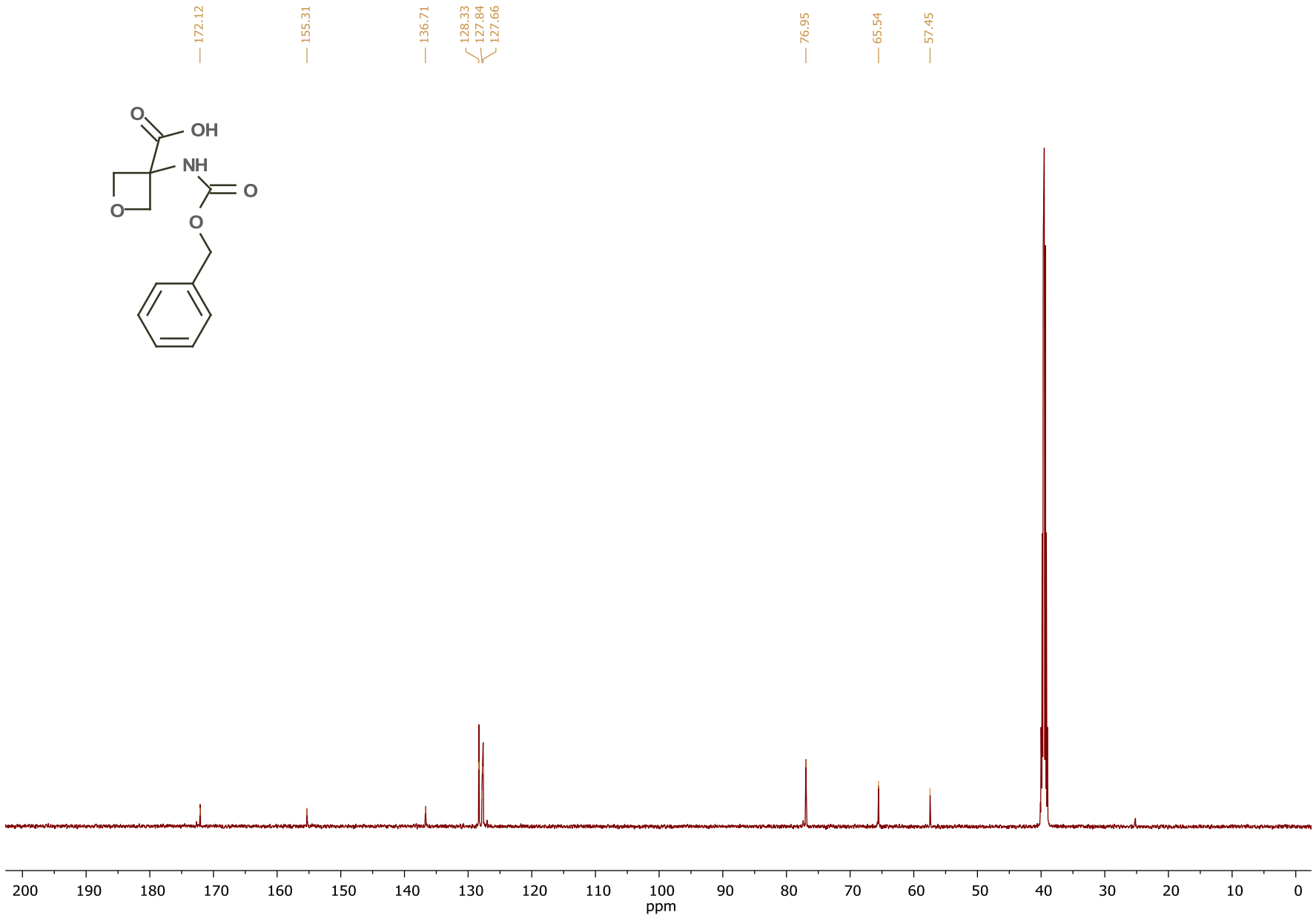
Ethyl 3-aminooxetane-3-carboxylate (5) ^{1}H NMR



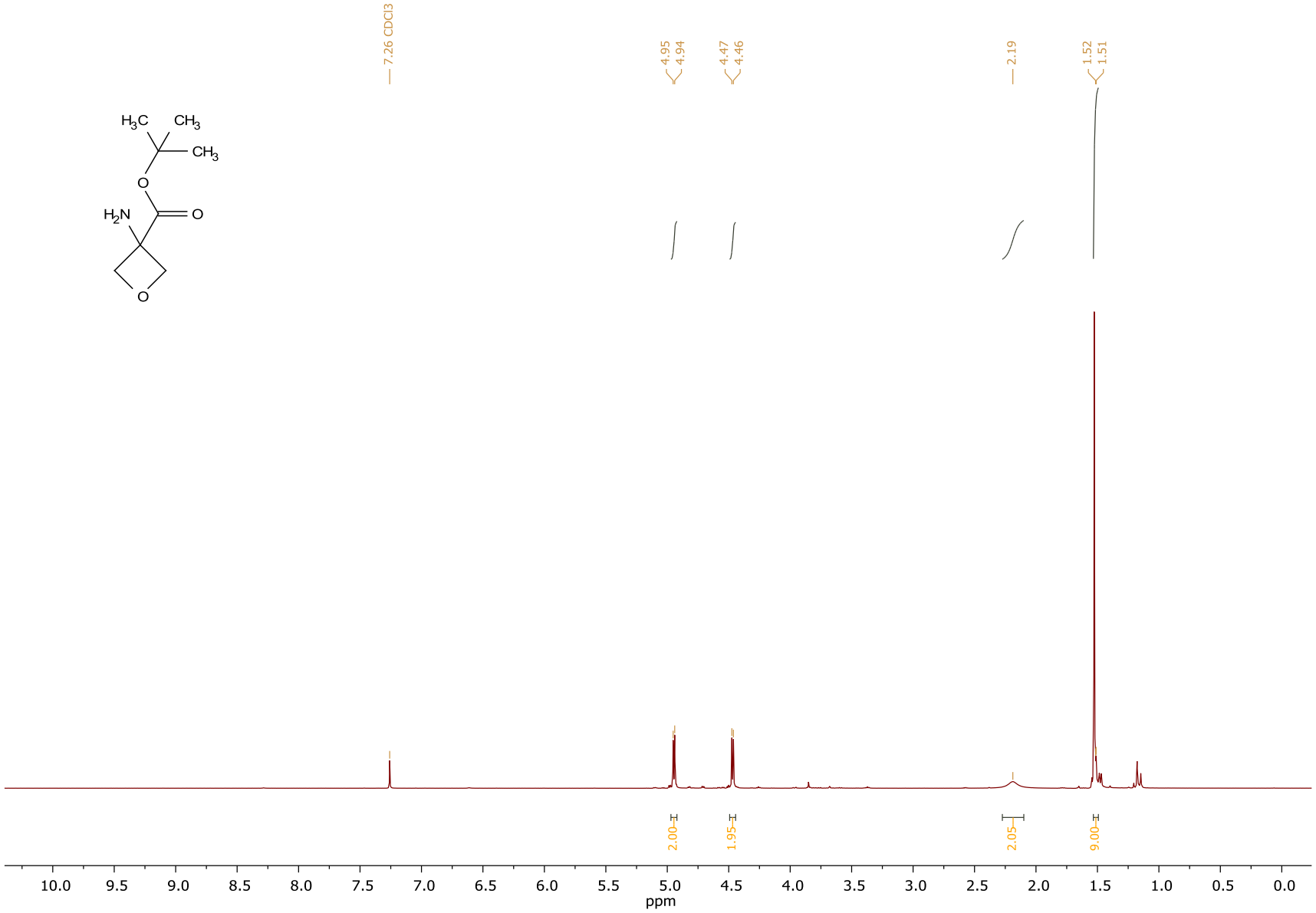
Ethyl 3-aminooxetane-3-carboxylate (5) $^{13}C\{H\}$ NMR



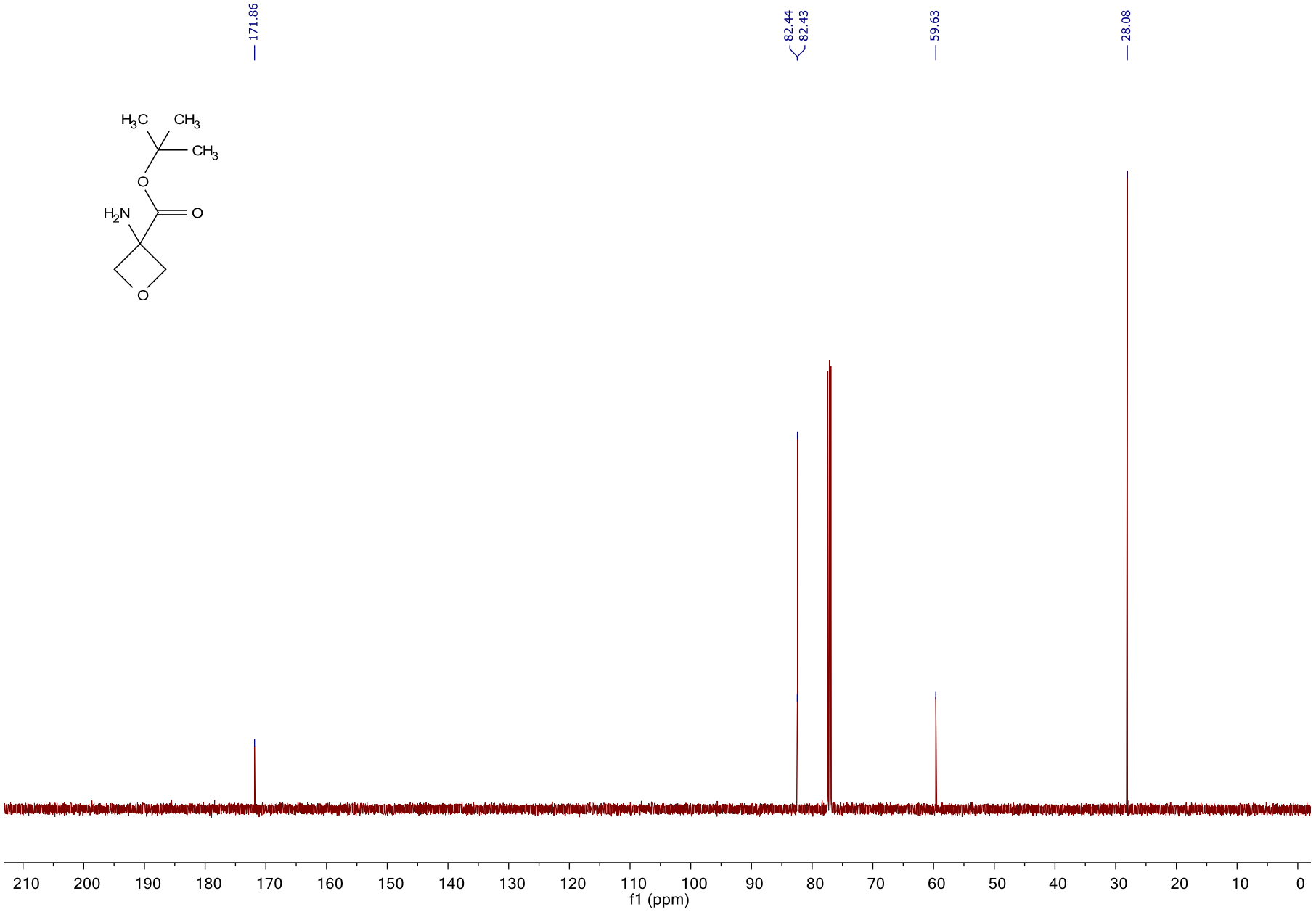
3-(((Benzyloxy)carbonyl)amino)oxetane-3-carboxylic acid (7) ^{1}H NMR



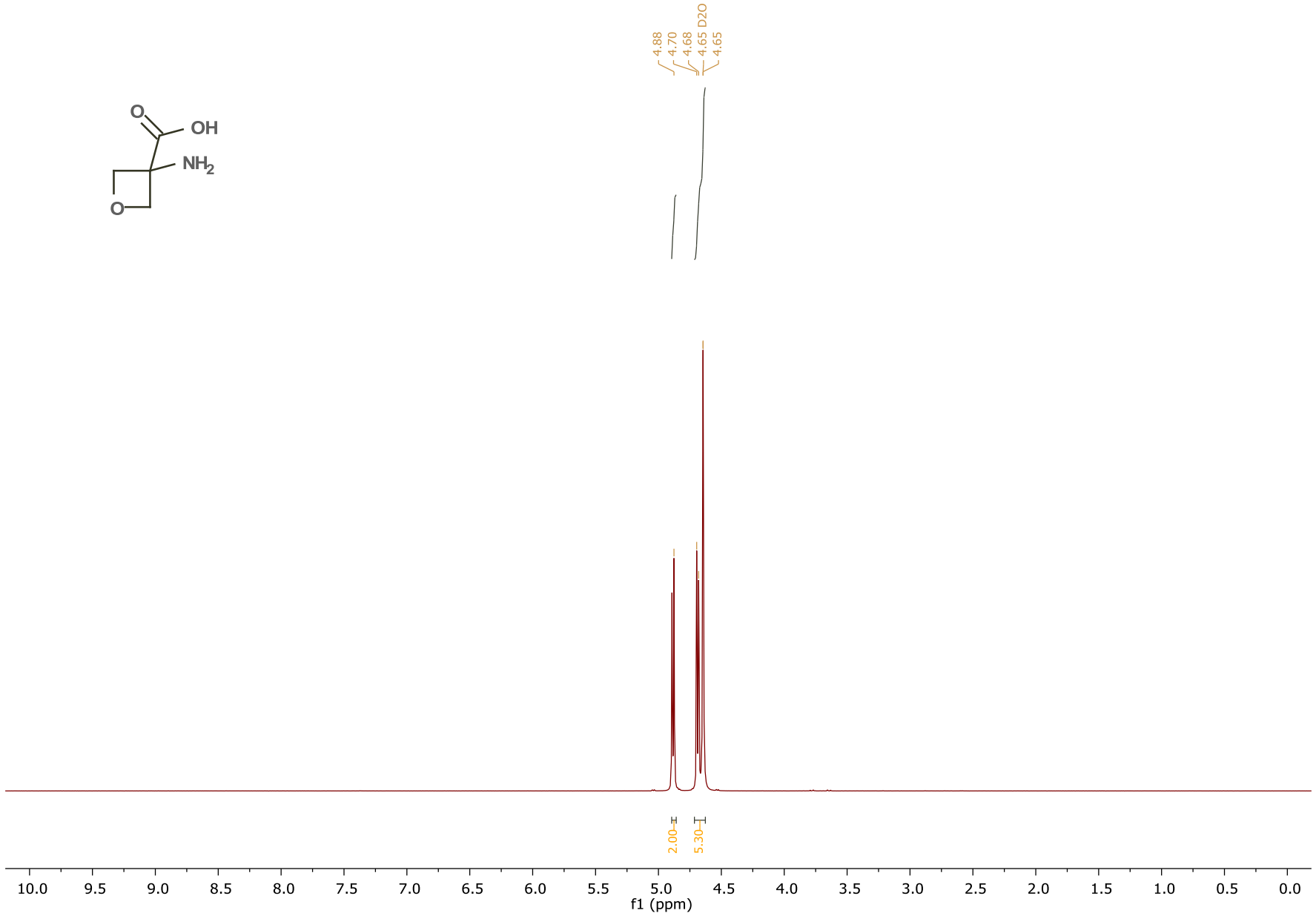
3-(((Benzyloxy)carbonyl)amino)oxetane-3-carboxylic (7) $^{13}C\{H\}$ NMR



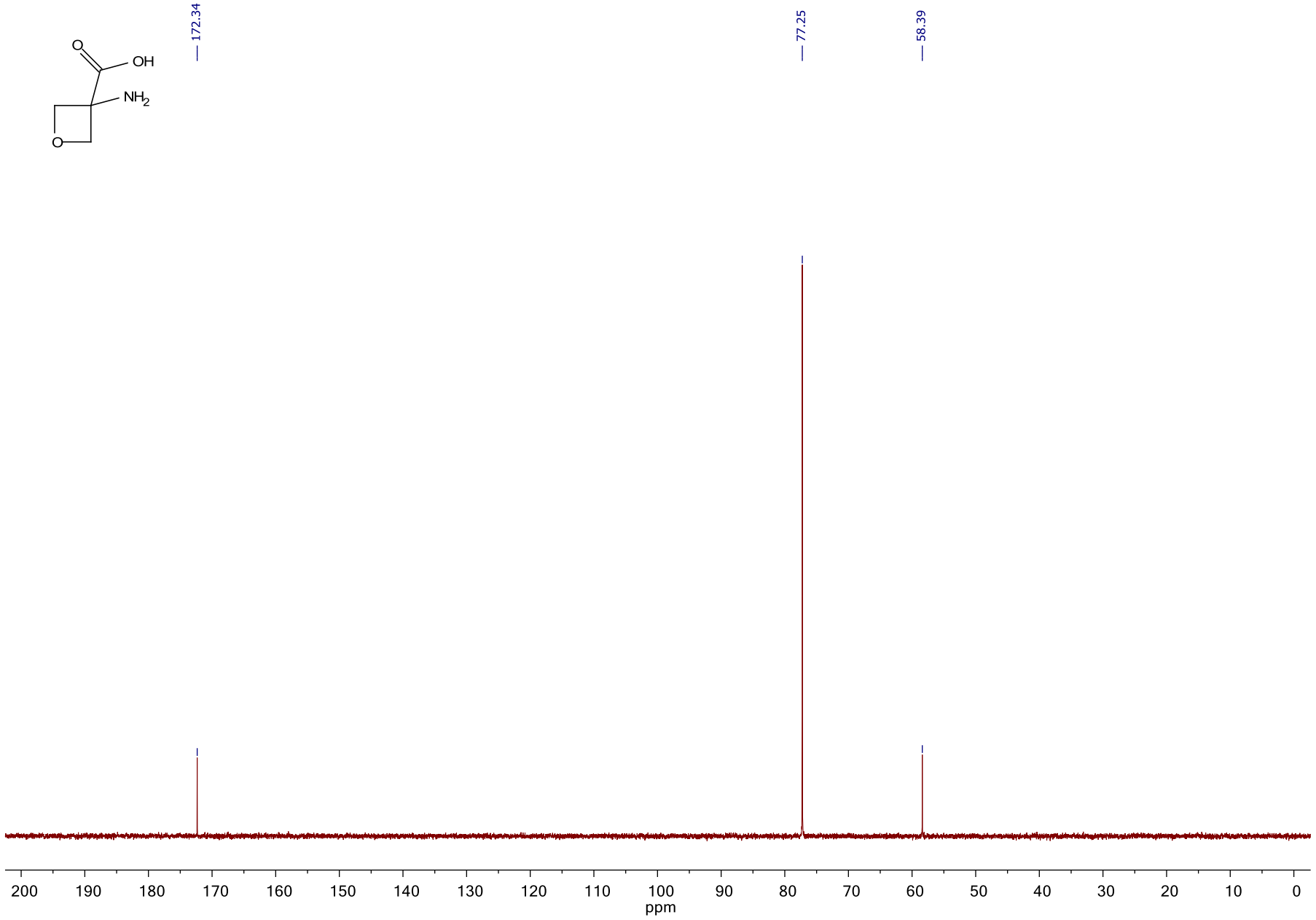
***tert*-Butyl 3-aminooxetane-3-carboxylate (9) ^{1}H NMR**



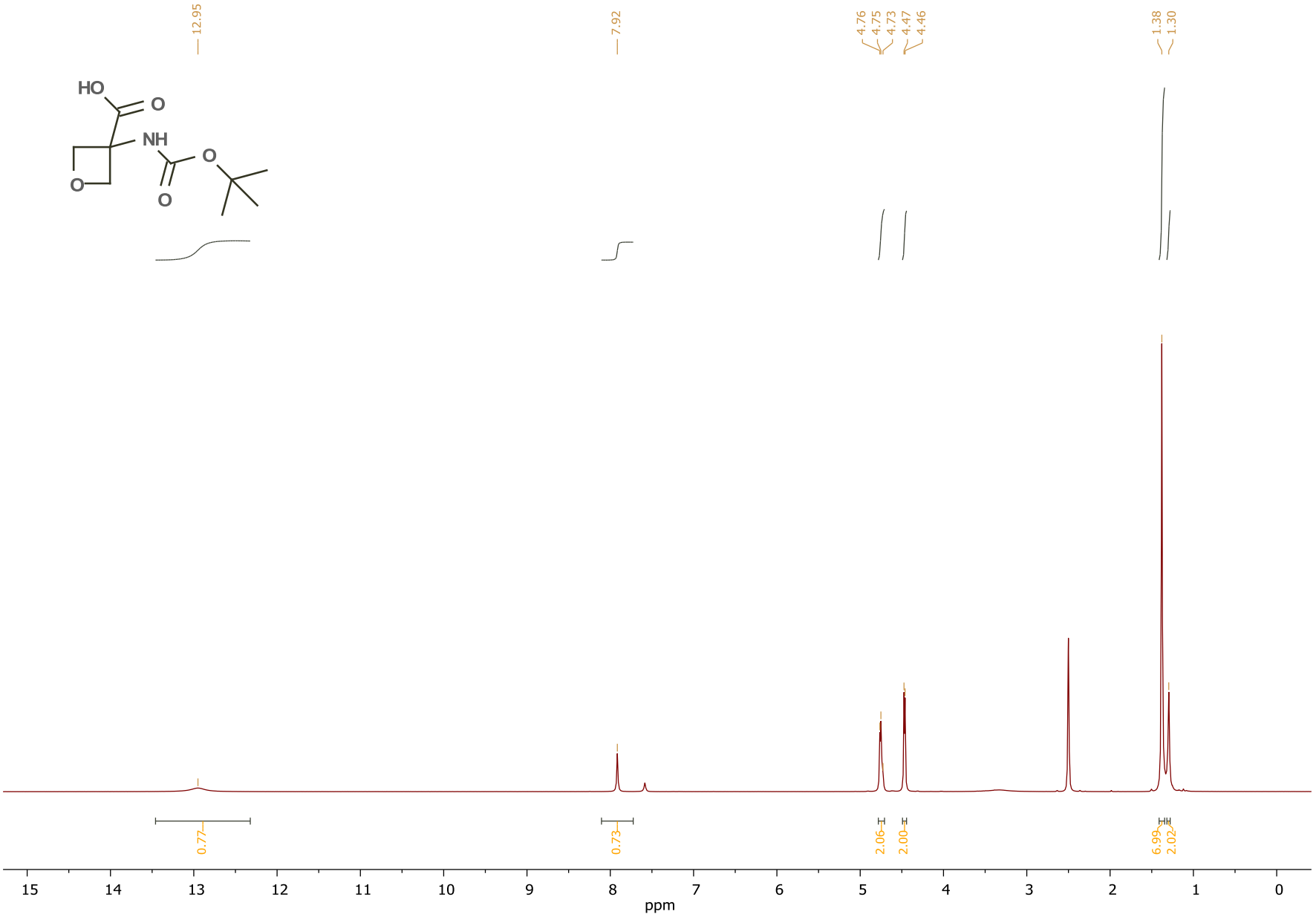
***tert*-Butyl 3-aminooxetane-3-carboxylate (9) ^{13}C{H} NMR**



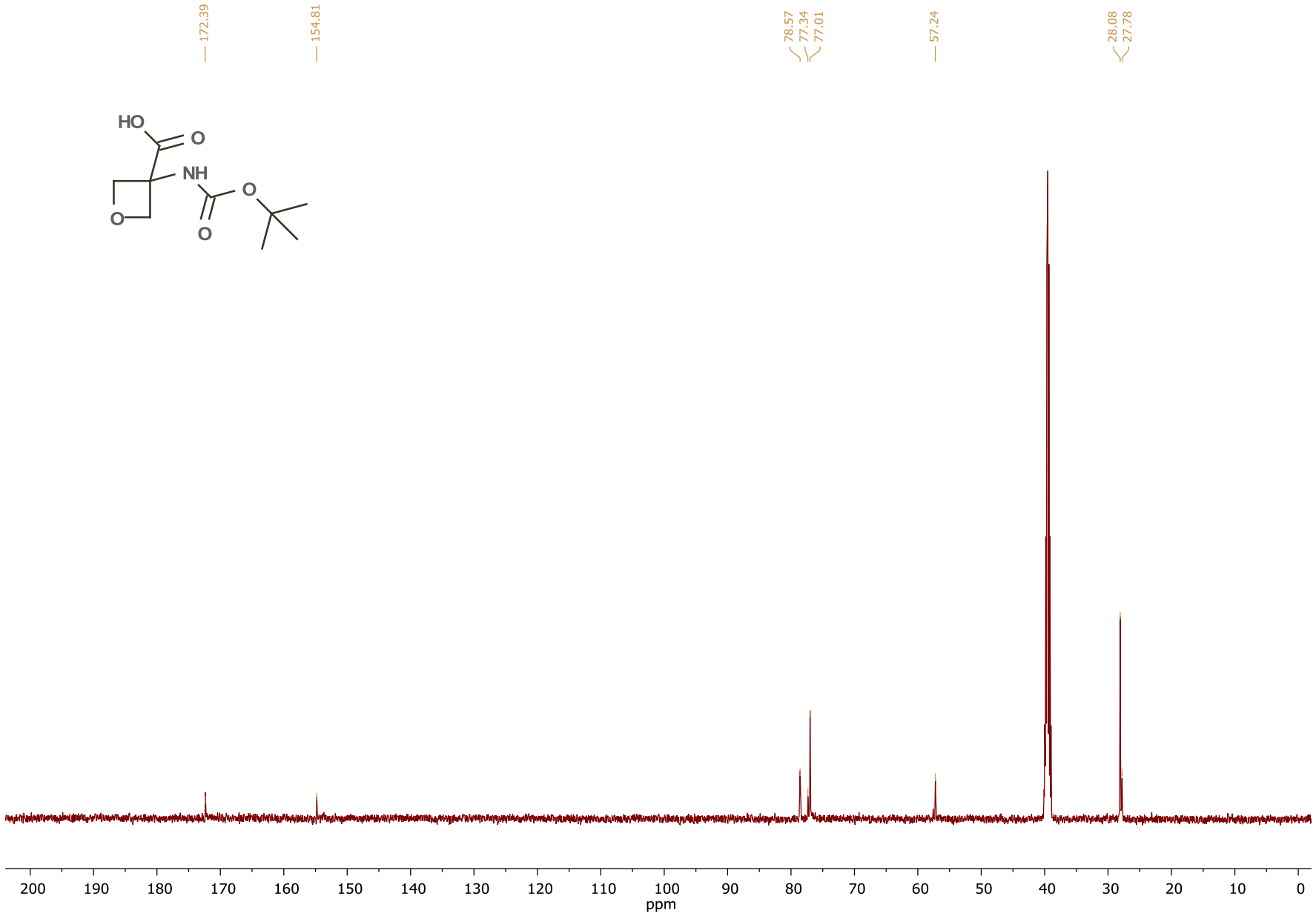
3-Aminooxetane-3-carboxylic acid (10) ^{1}H NMR



3-Aminooxetane-3-carboxylic acid (10) $^{13}C\{H\}$ NMR



3-{[(*tert*-Butoxy)carbonyl]amino}oxetane-3-carboxylic acid (11a) ^{1}H NMR



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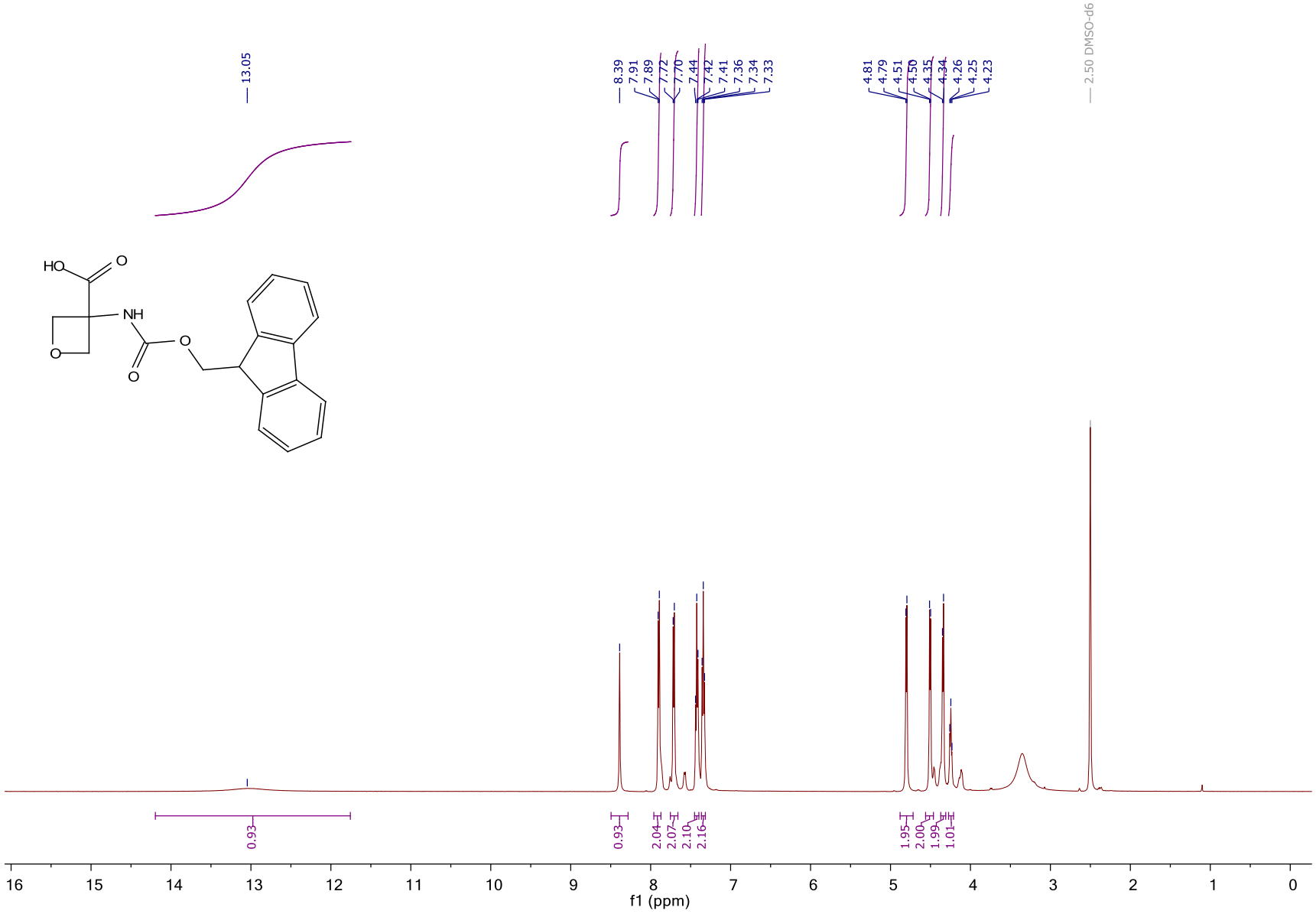

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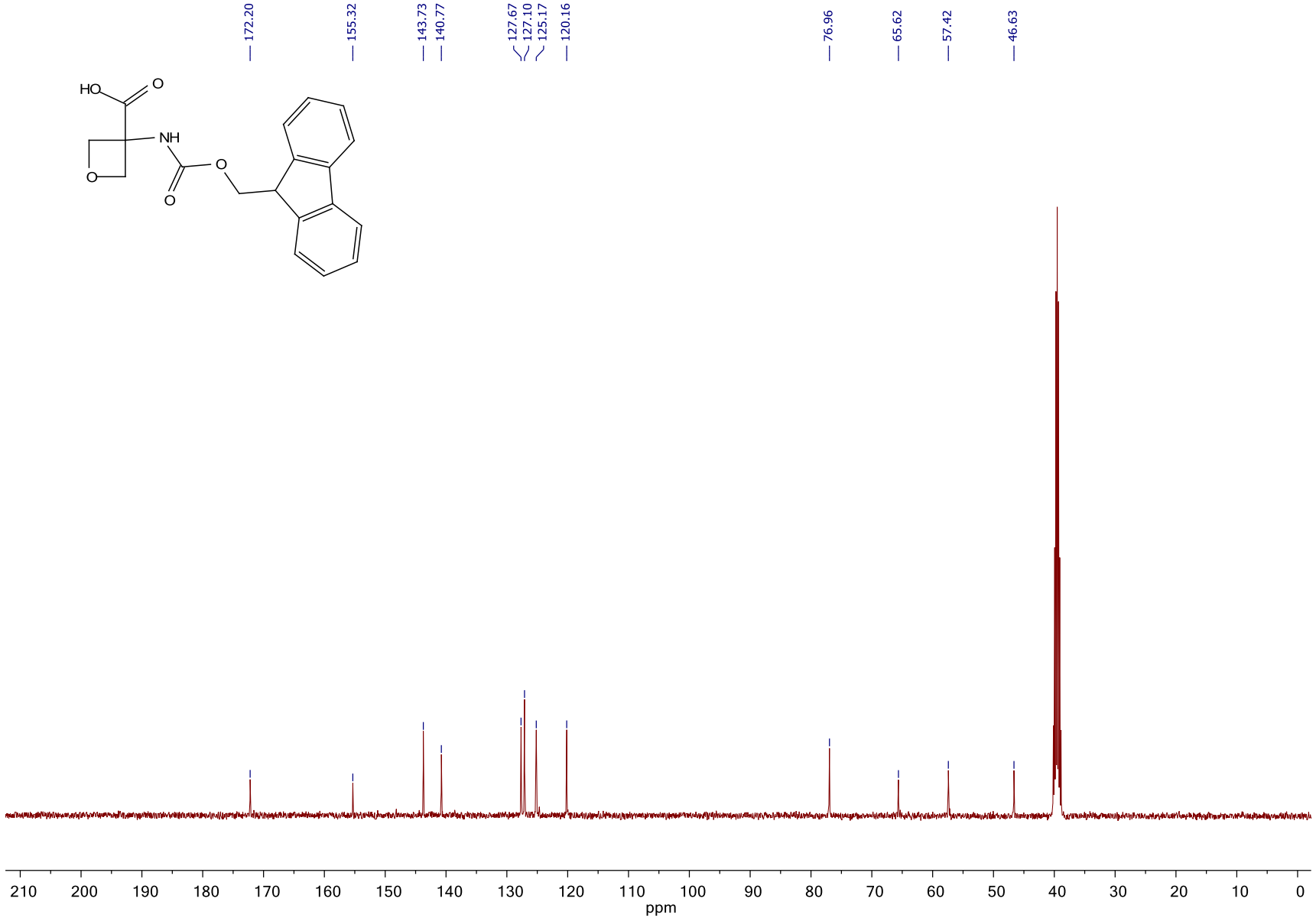

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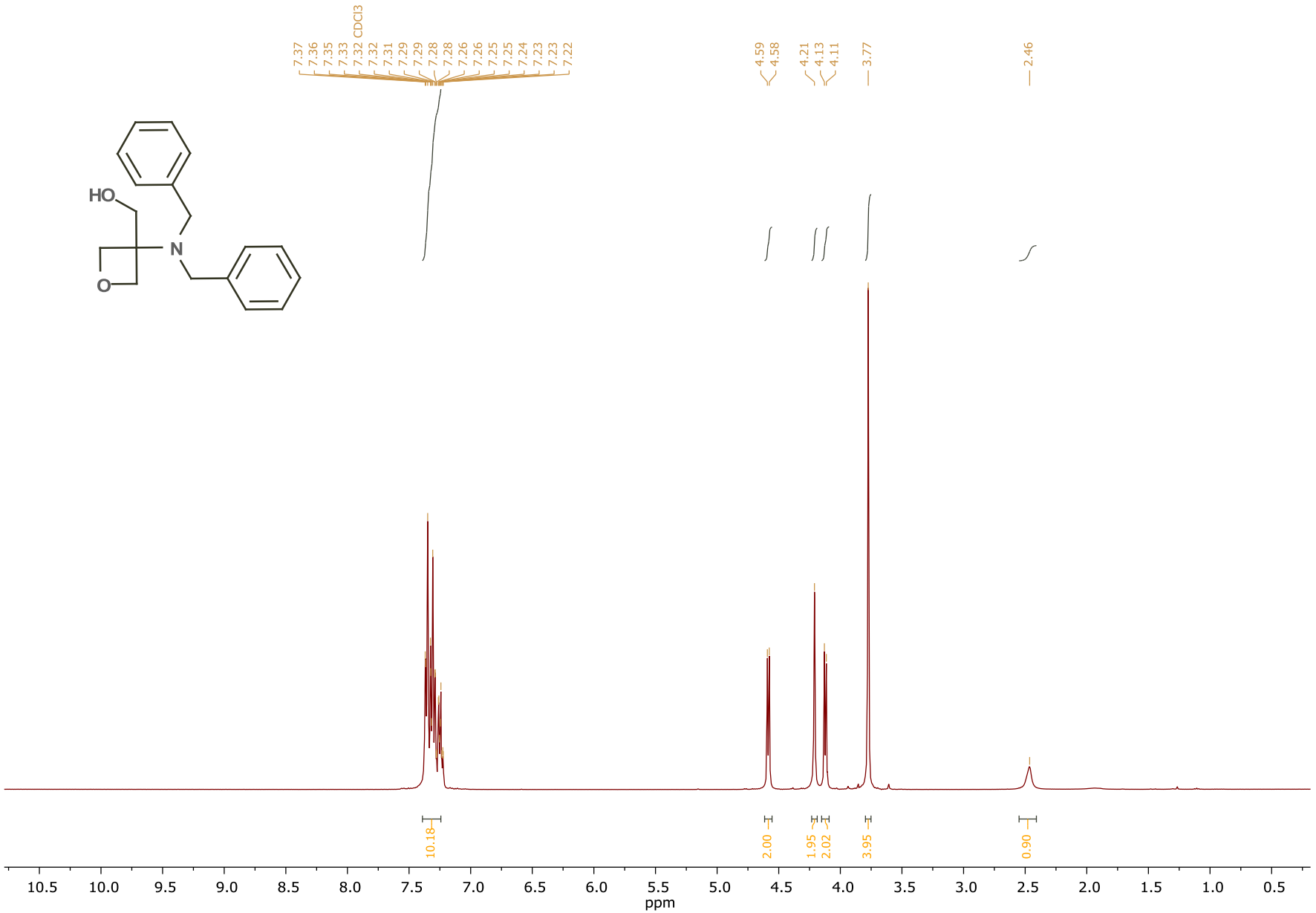
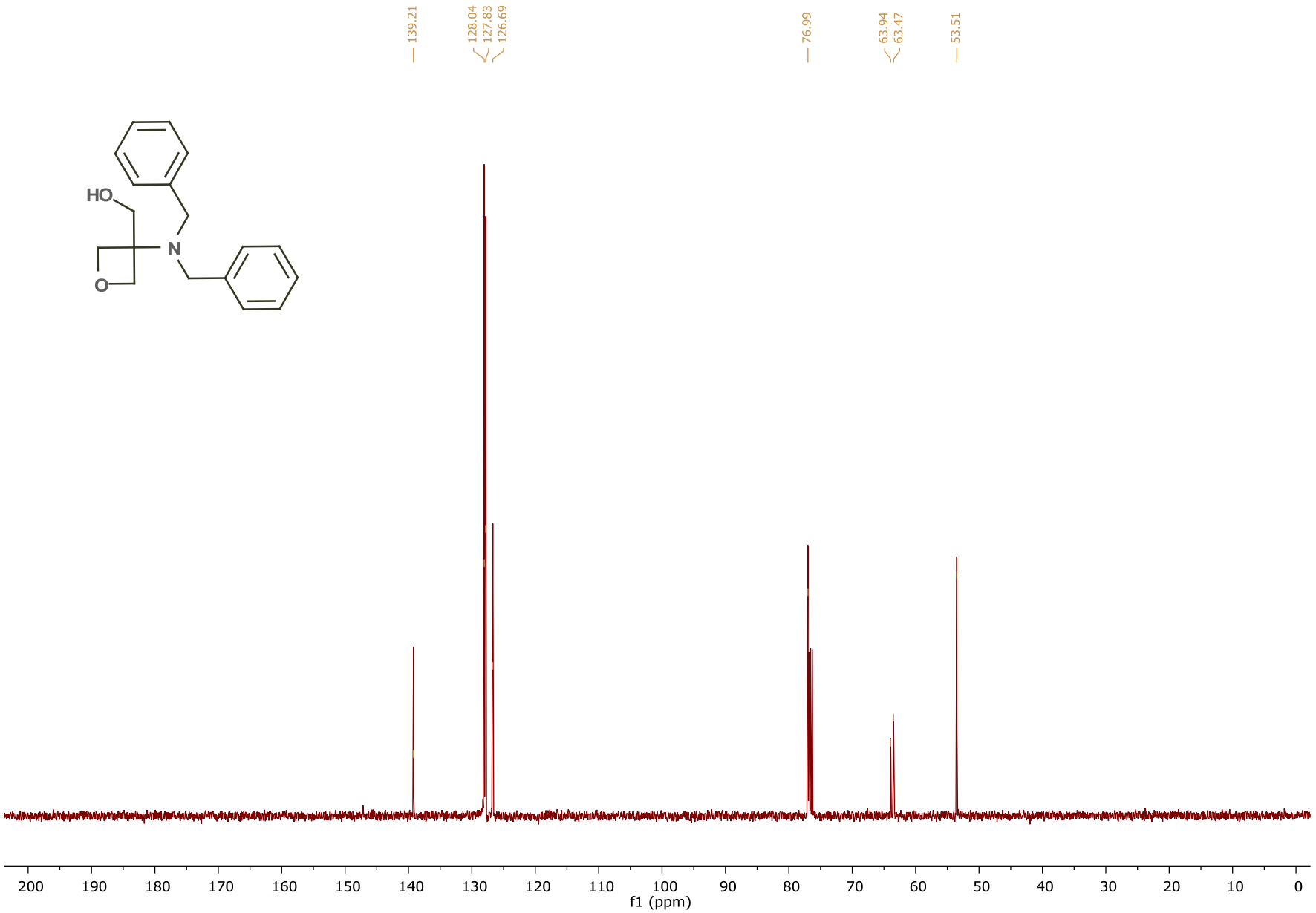
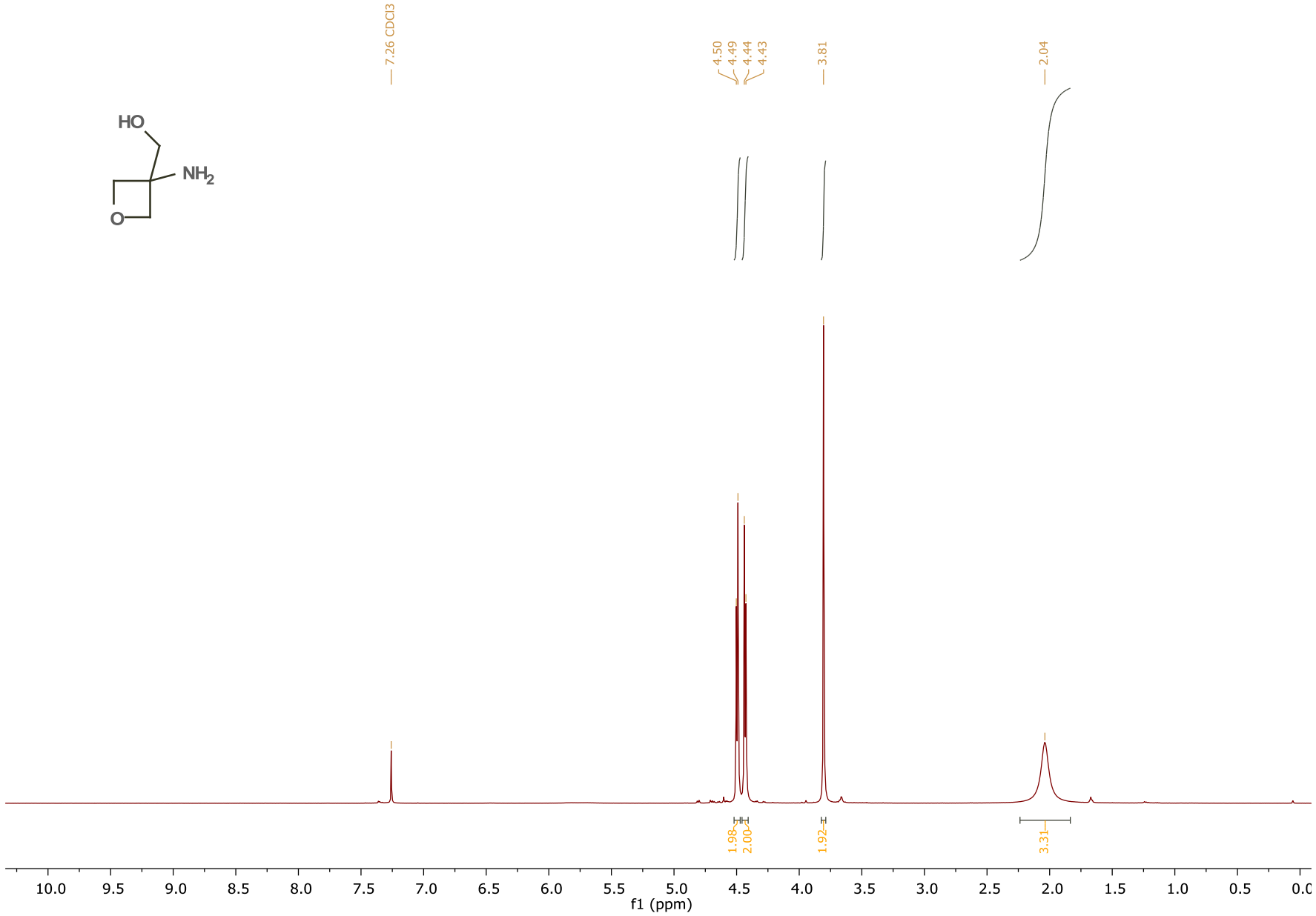


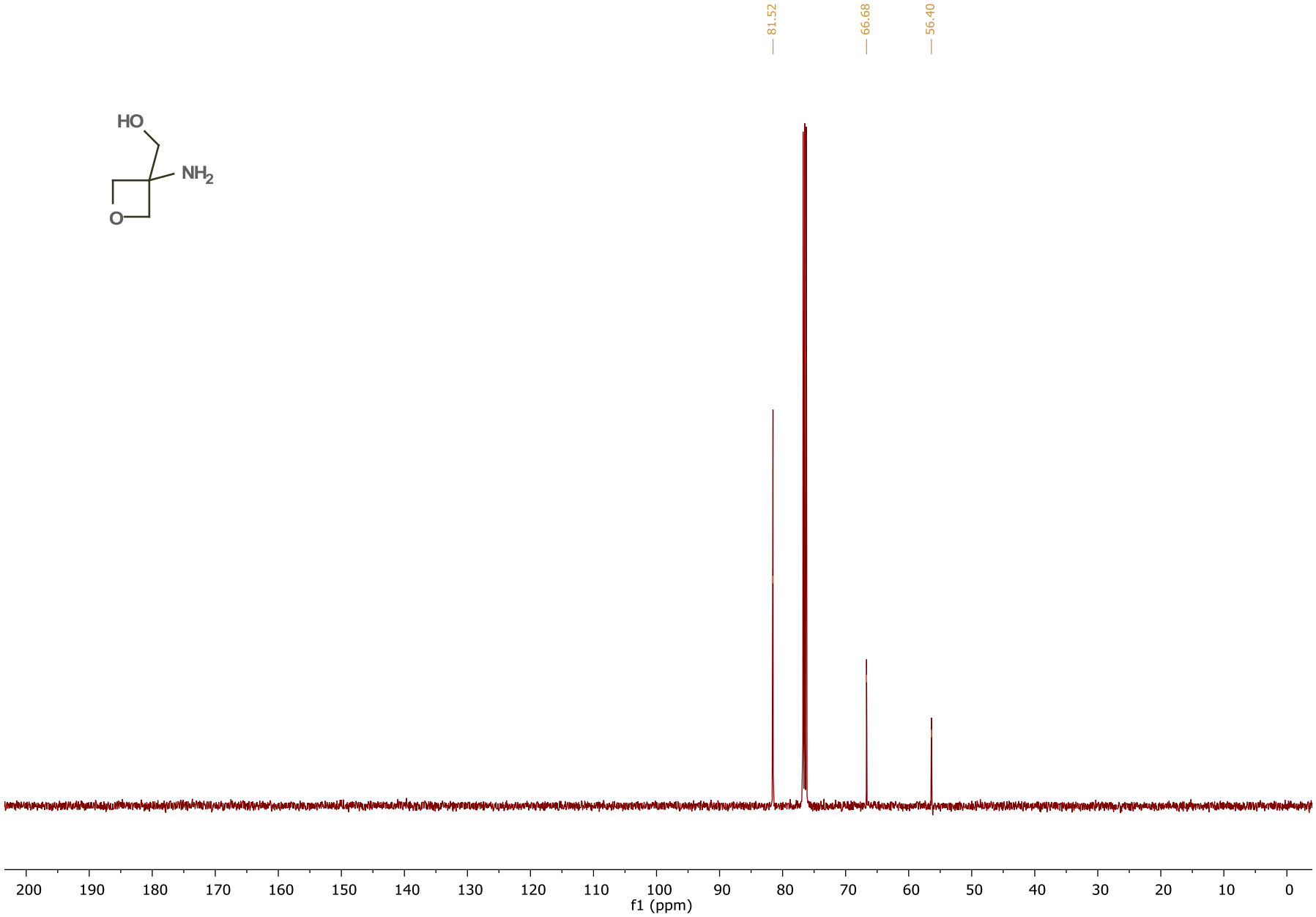
(3-(Dibenzylamino)oxetan-3-yl)methanol (12) ^{1}H NMR



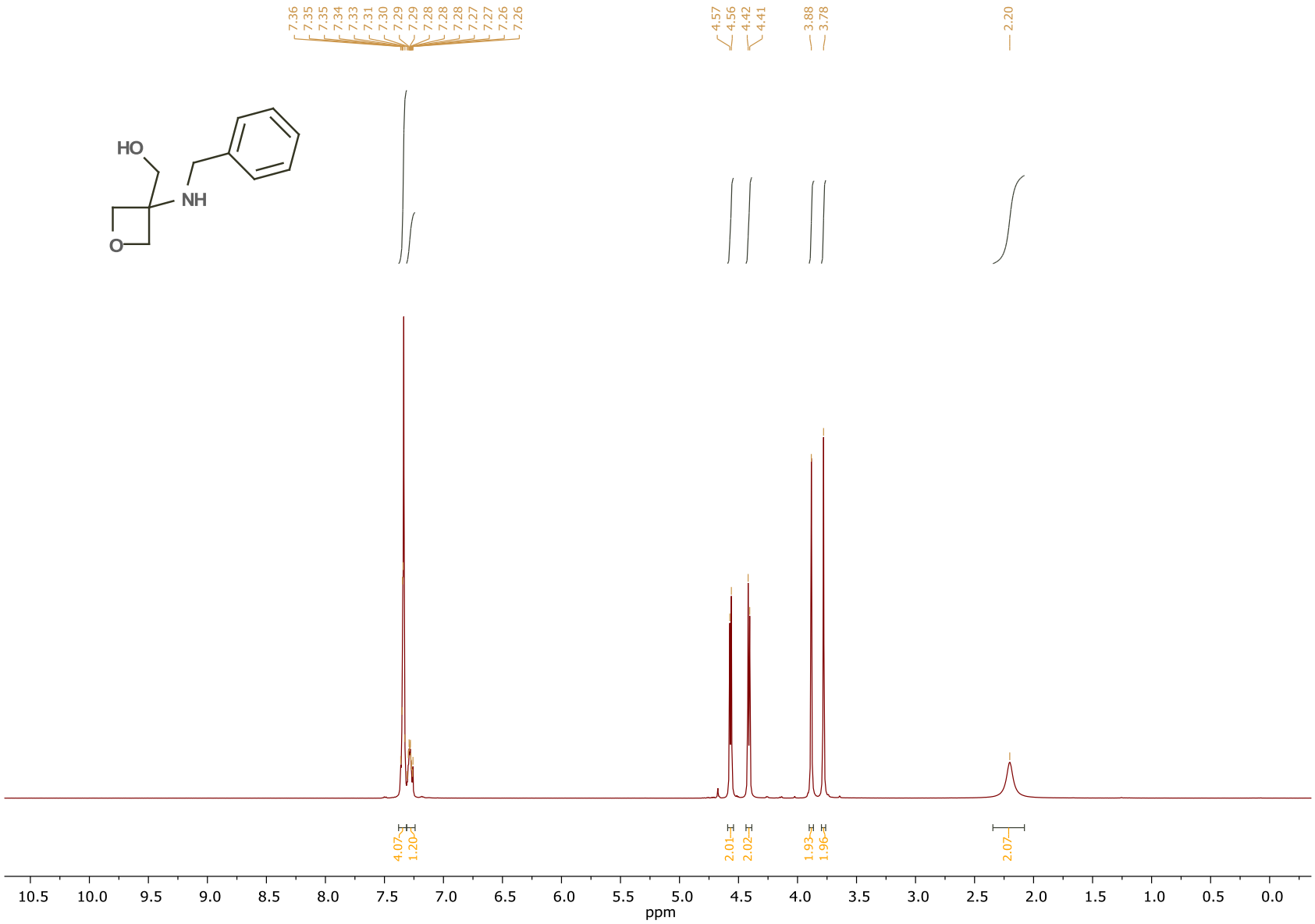
(3-(Dibenzylamino)oxetan-3-yl)methanol (12) $^{13}C\{H\}$ NMR



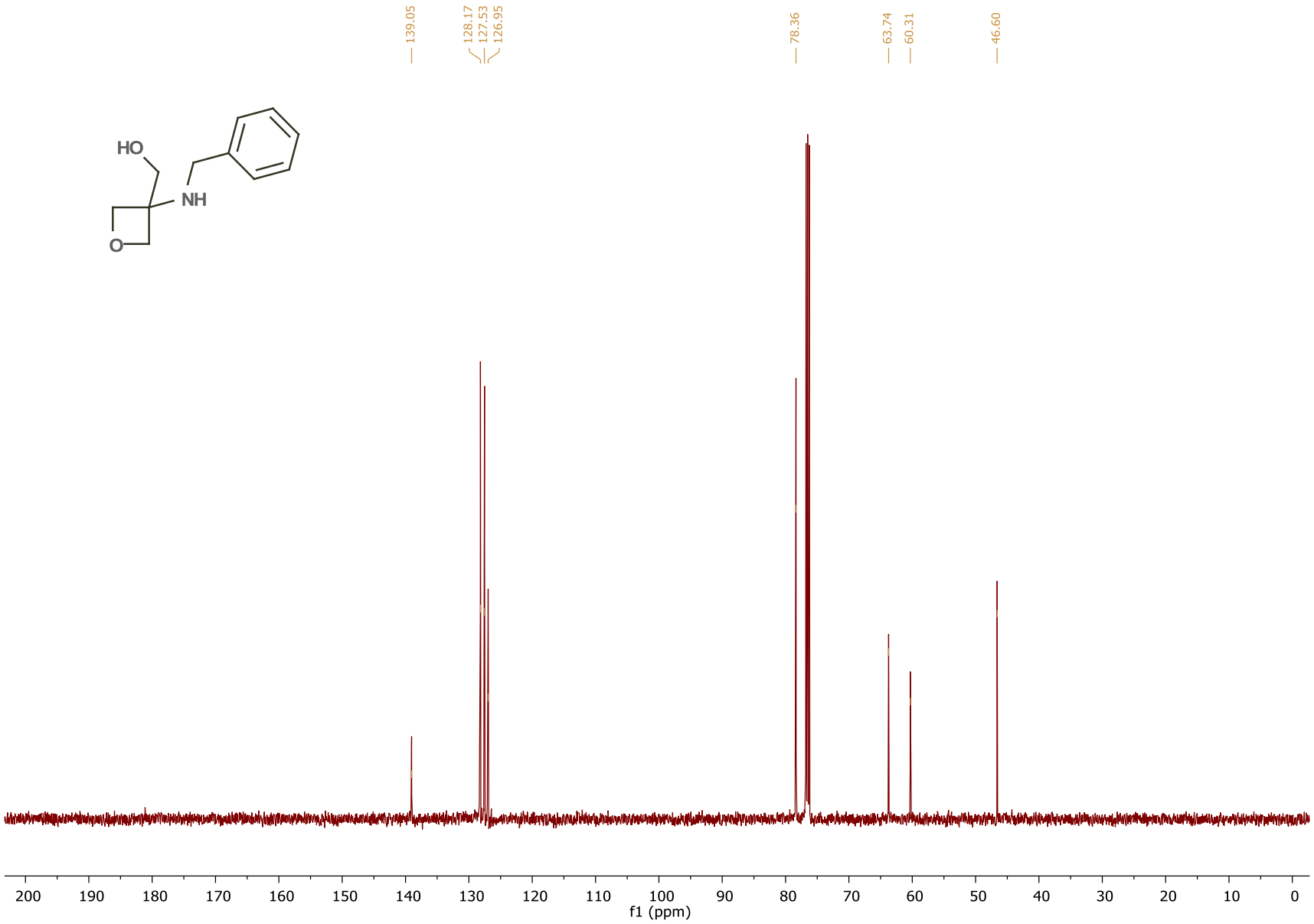
(3-Aminooxetan-3-yl)methanol (13) ^{1}H NMR



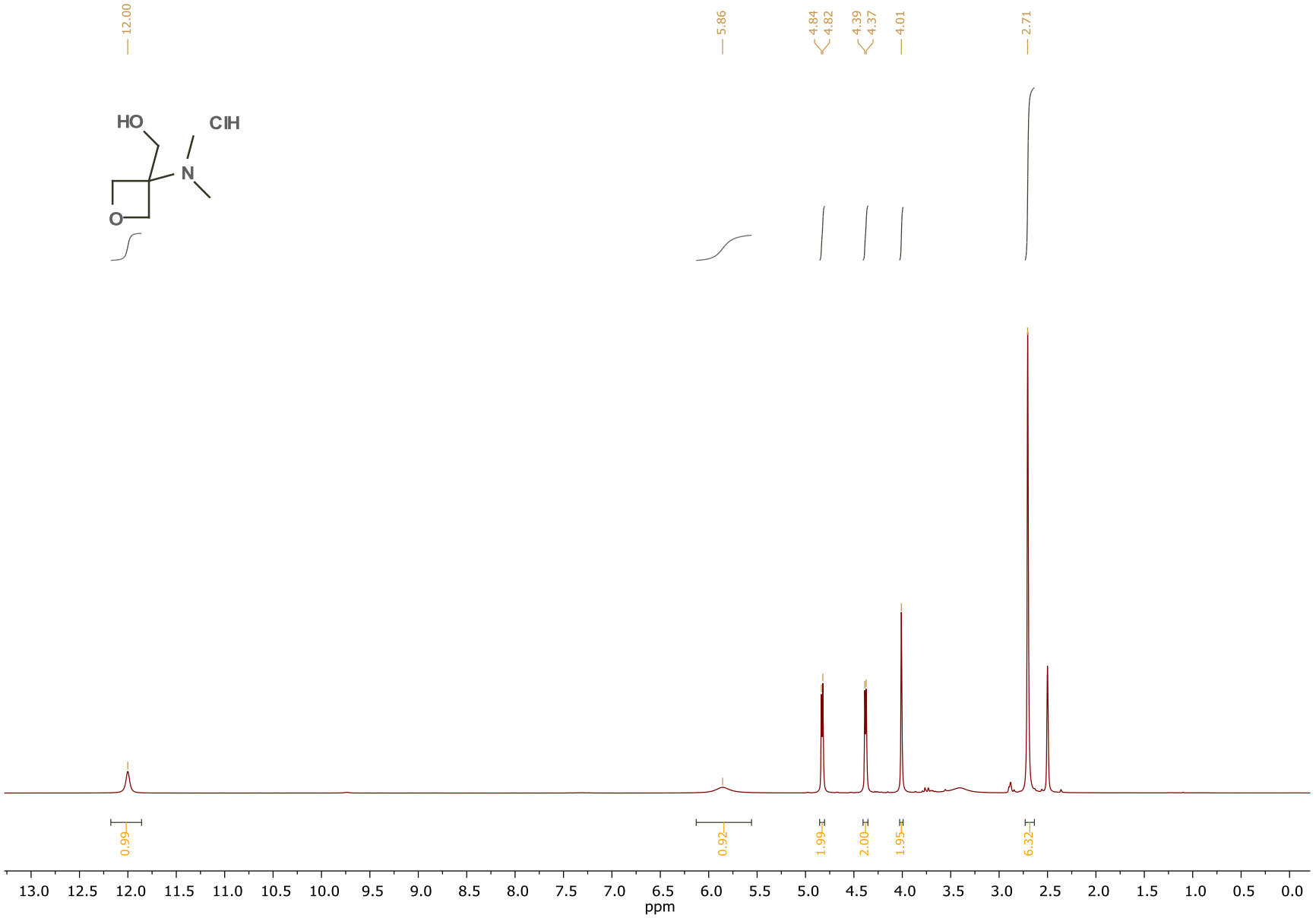
(3-Aminooxetan-3-yl)methanol (13) $^{13}C\{H\}$ NMR



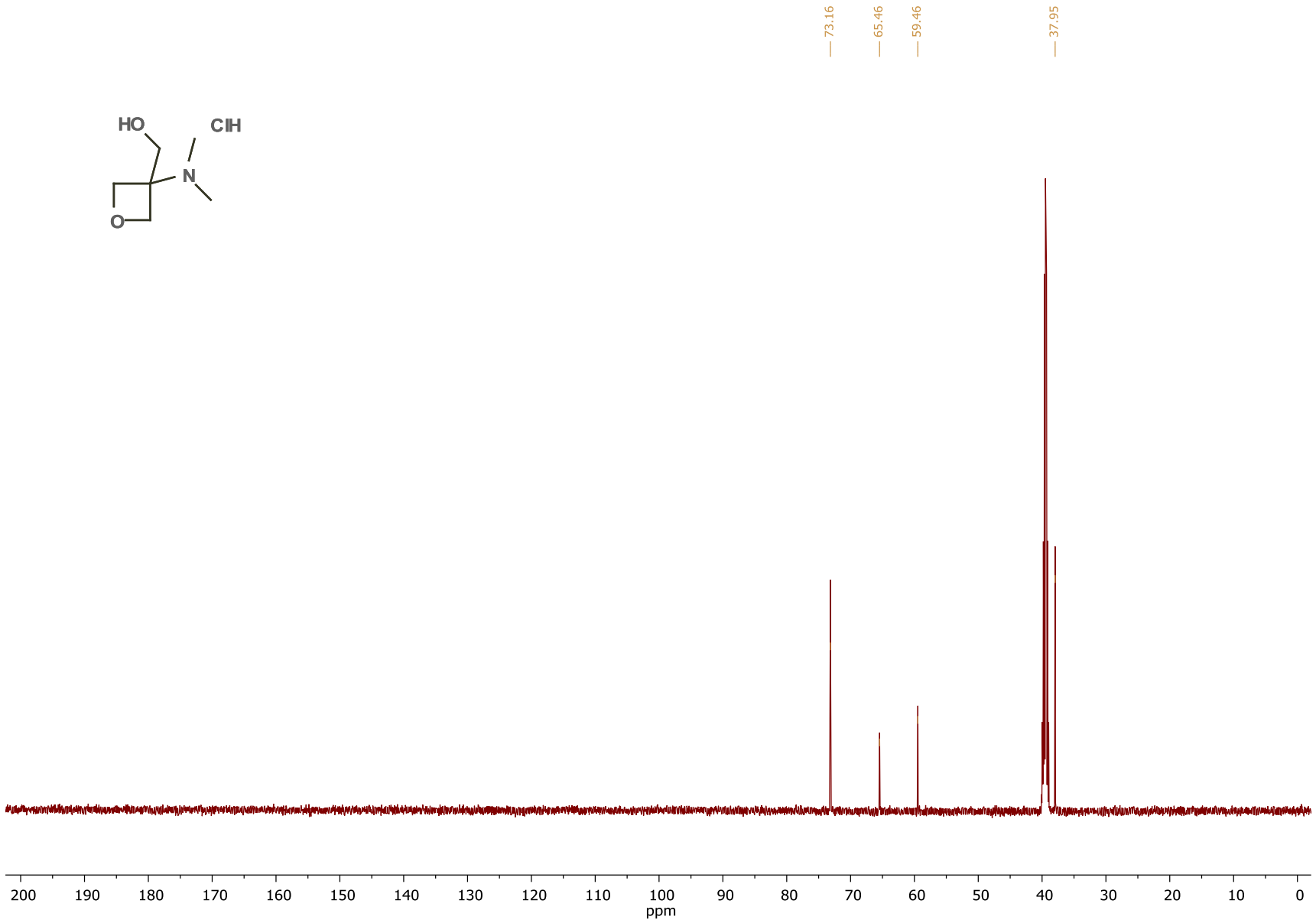
[3-(Benzylamino)oxetan-3-yl]methanol (14) ^{1}H NMR



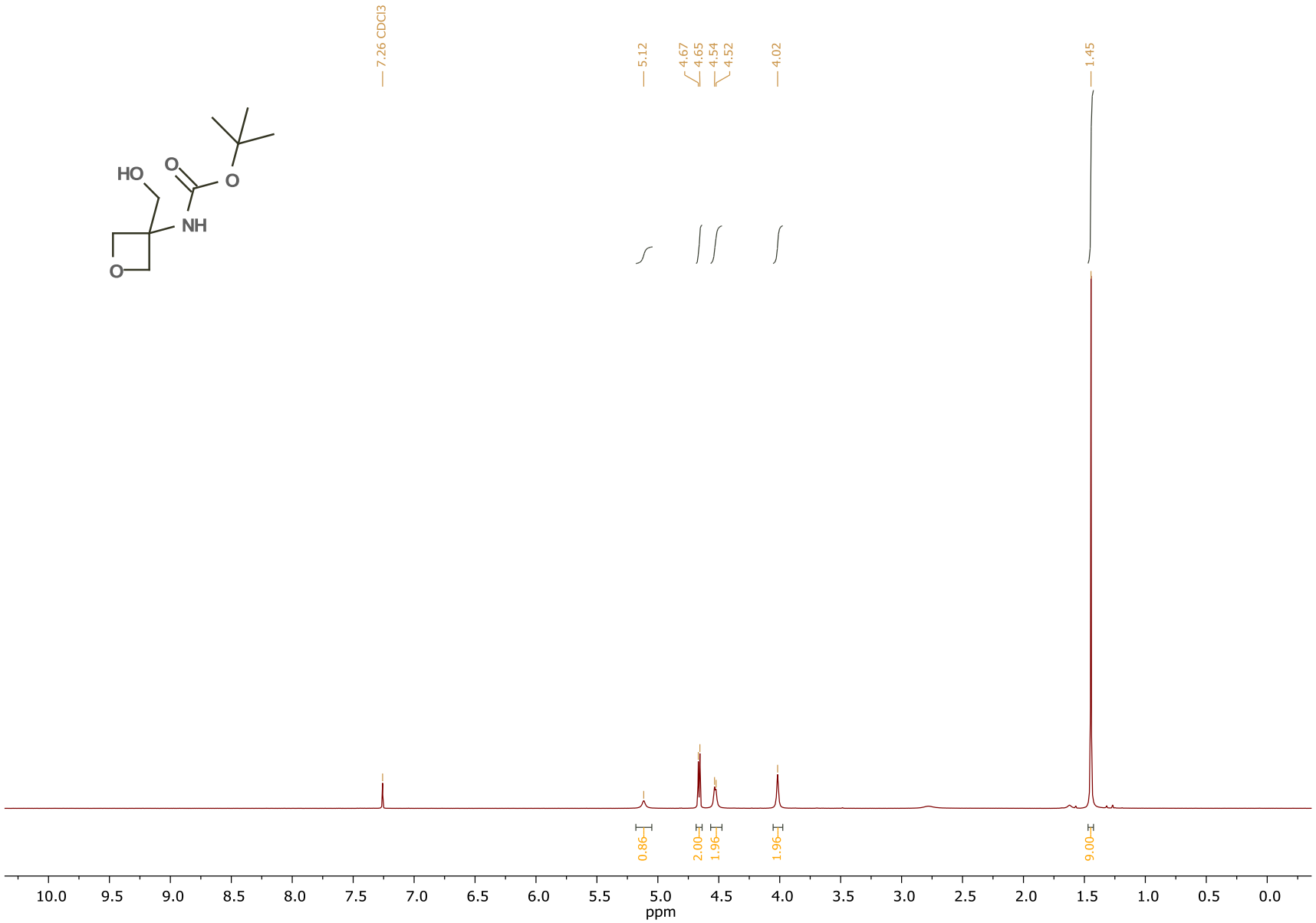
[3-(Benzylamino)oxetan-3-yl]methanol (14) $^{13}C\{H\}$ NMR



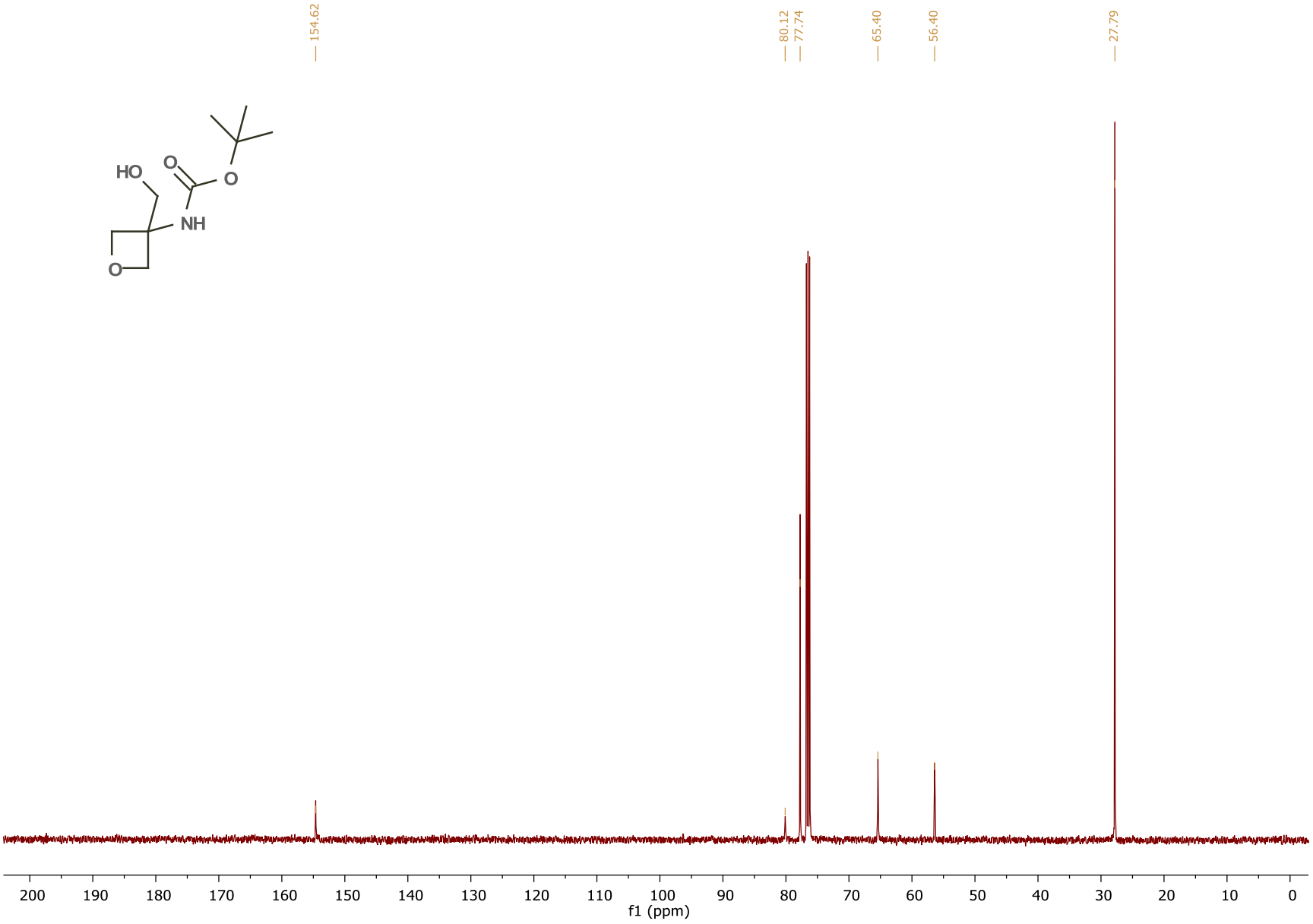
[3-(Dimethylamino)oxetan-3-yl]methanol hydrochloride (15) ^{1}H NMR



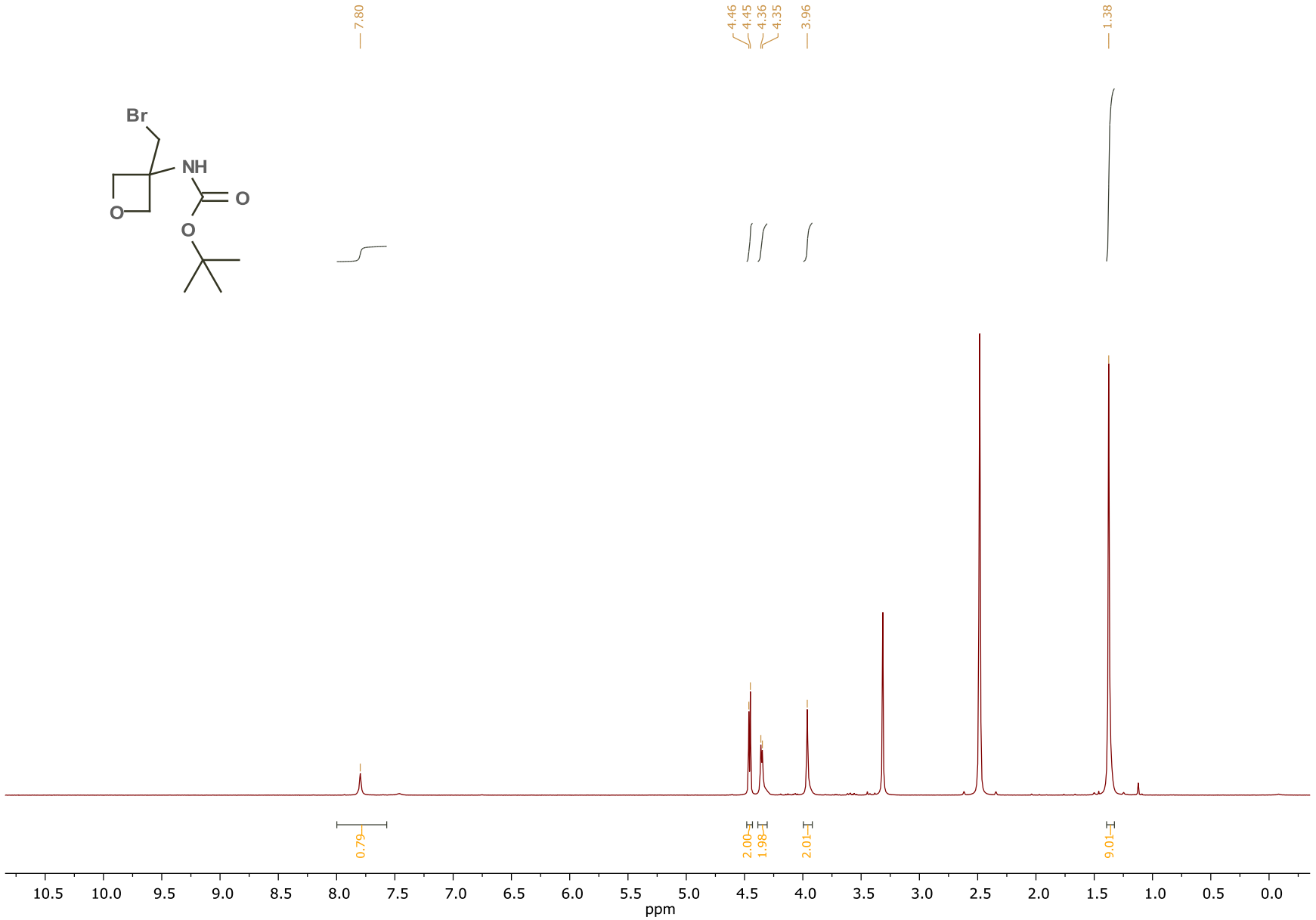
[3-(Dimethylamino)oxetan-3-yl]methanol hydrochloride (15) $^{13}C\{H\}$ NMR



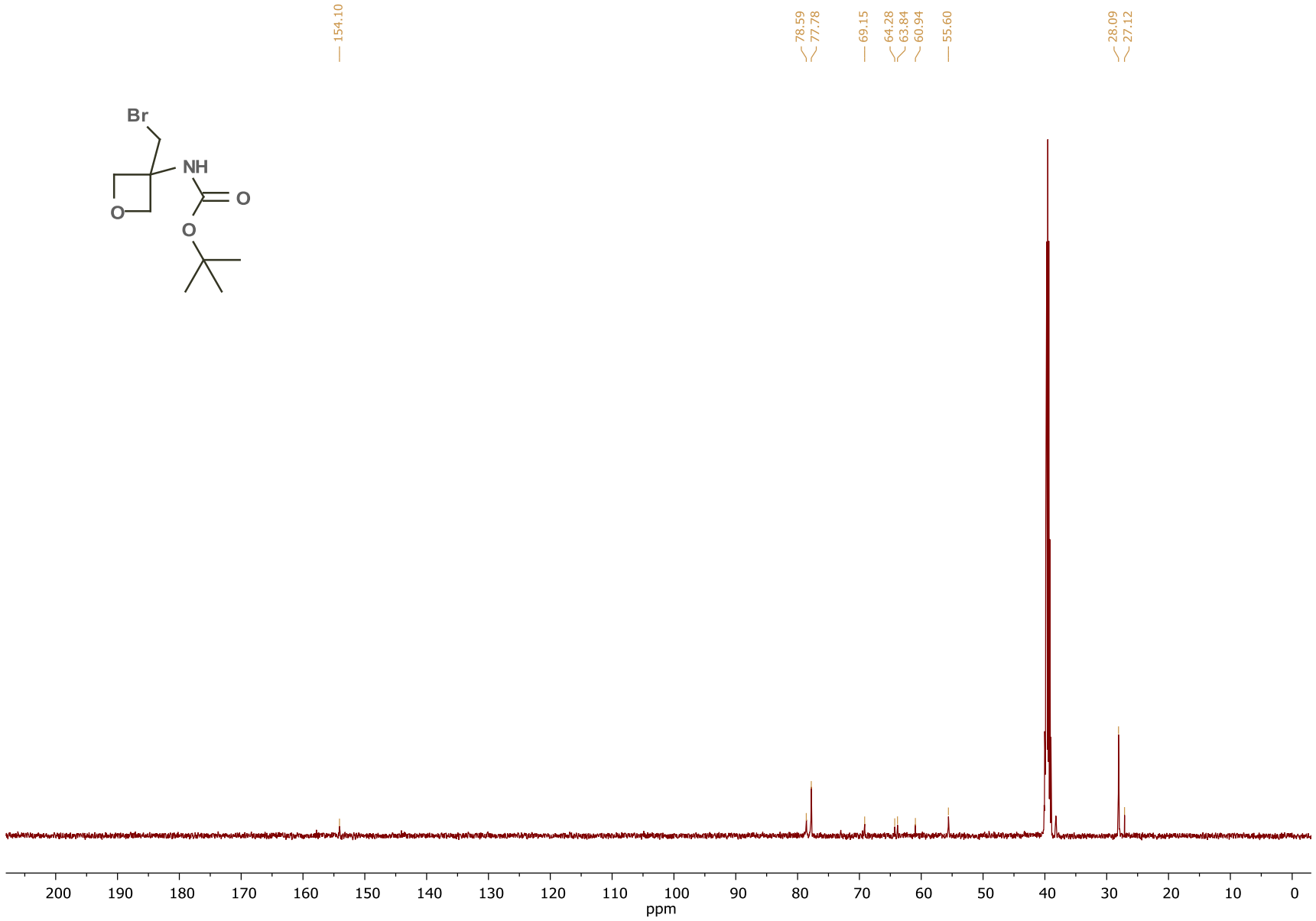
***tert*-Butyl *N*-[3-(hydroxymethyl)oxetan-3-yl]carbamate (16) ^{1}H NMR**



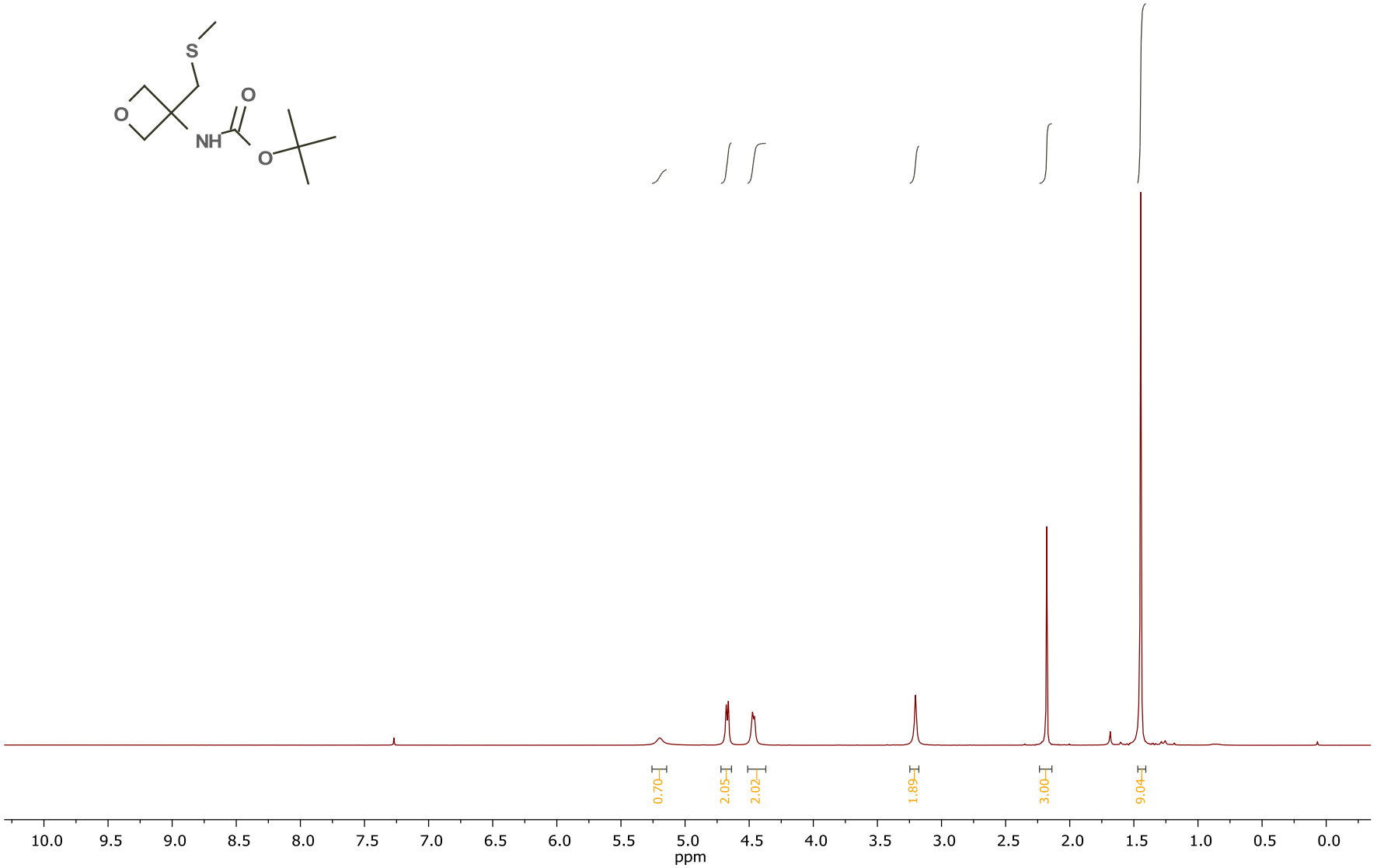
***tert*-Butyl *N*-[3-(hydroxymethyl)oxetan-3-yl]carbamate (16) $^{13}C\{H\}$ NMR**



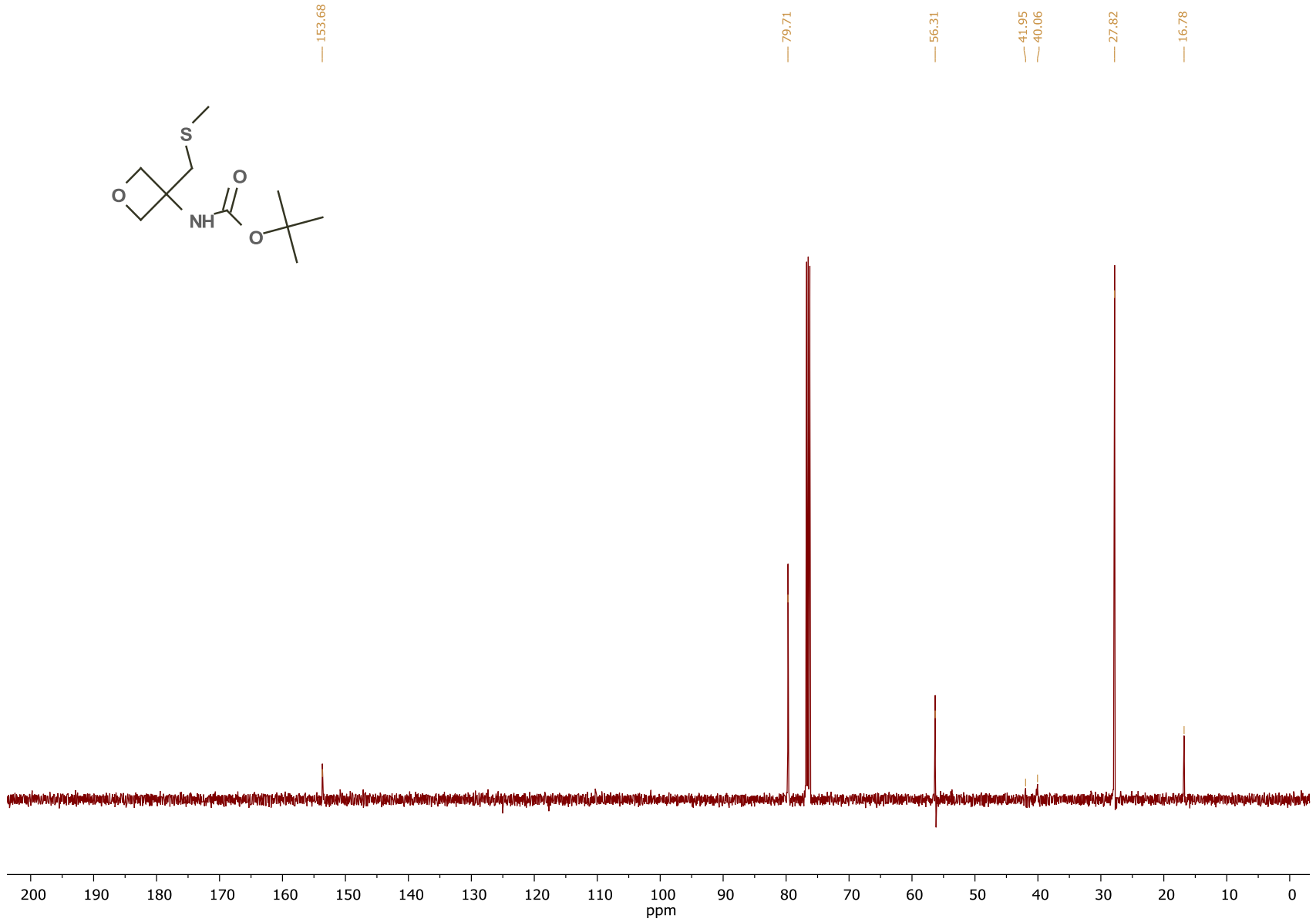
***tert*-Butyl (3-(bromomethyl)oxetan-3-yl)carbamate (17) ^{1}H NMR**



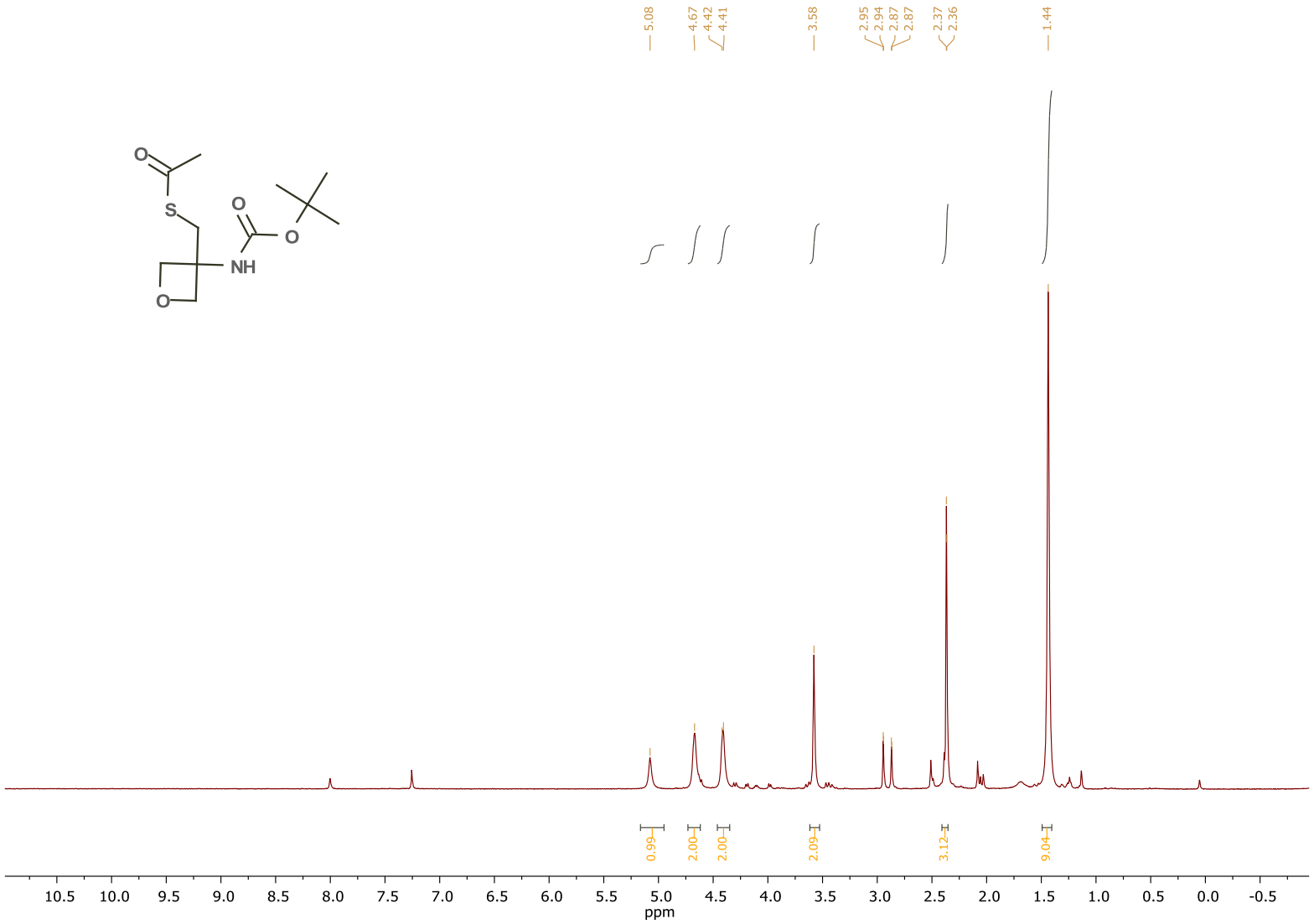
***tert*-Butyl (3-(bromomethyl)oxetan-3-yl)carbamate (17) $^{13}C\{H\}$ NMR**



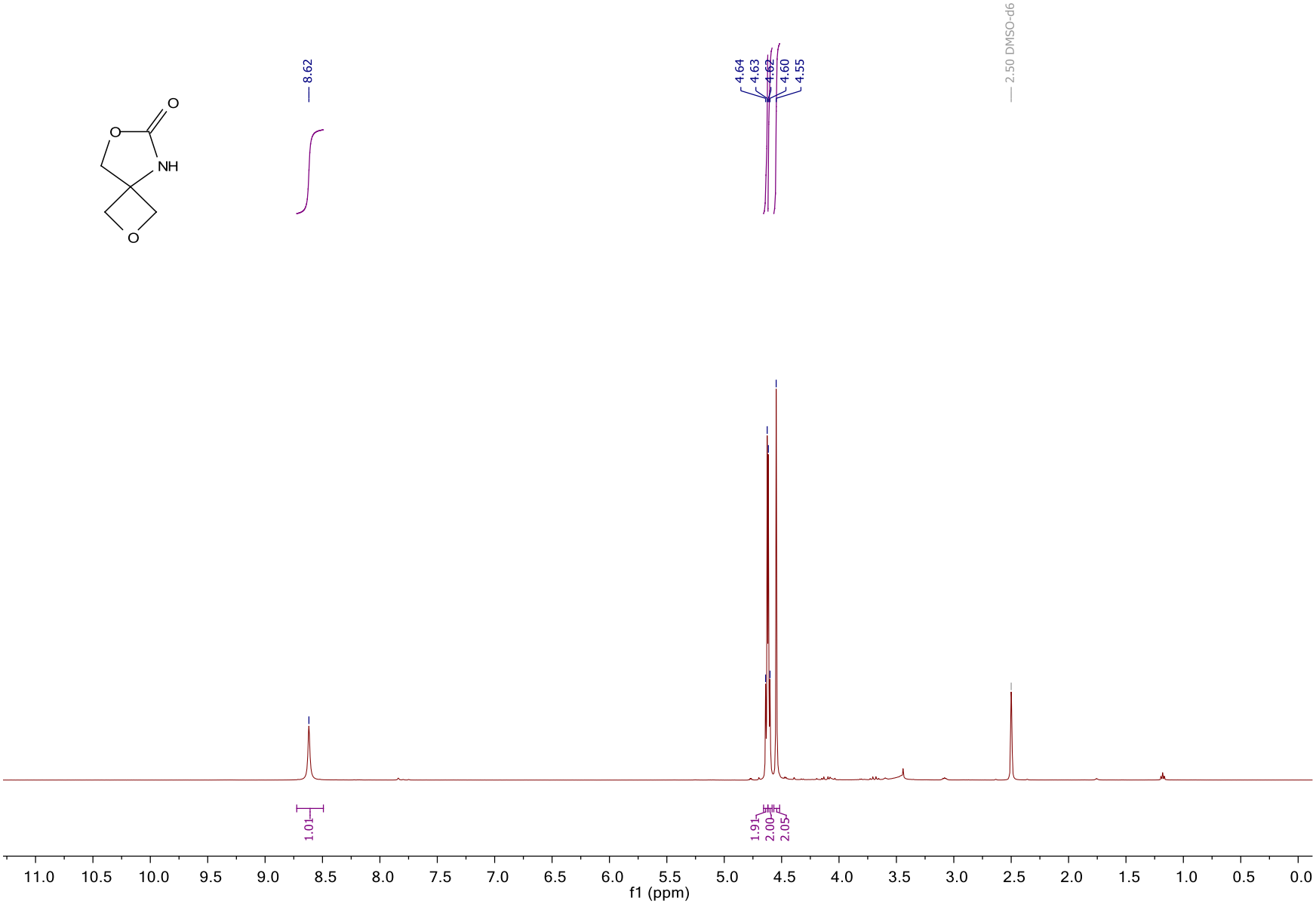
***tert*-Butyl (3-((methylthio)methyl)oxetan-3-yl)carbamate (18) ^{1}H NMR**



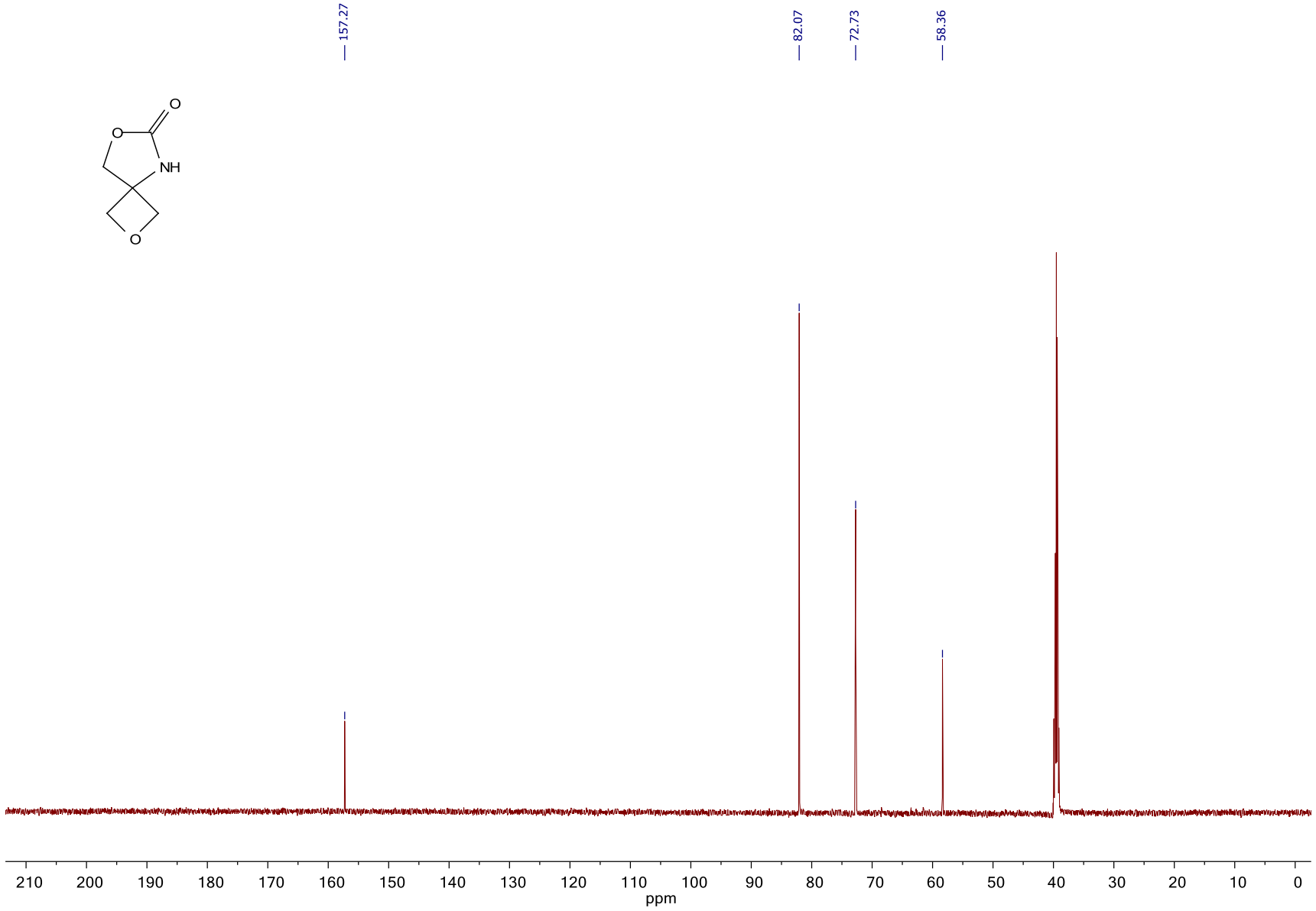
***tert*-Butyl (3-((methylthio)methyl)oxetan-3-yl)carbamate (18) $^{13}C\{H\}$ NMR**



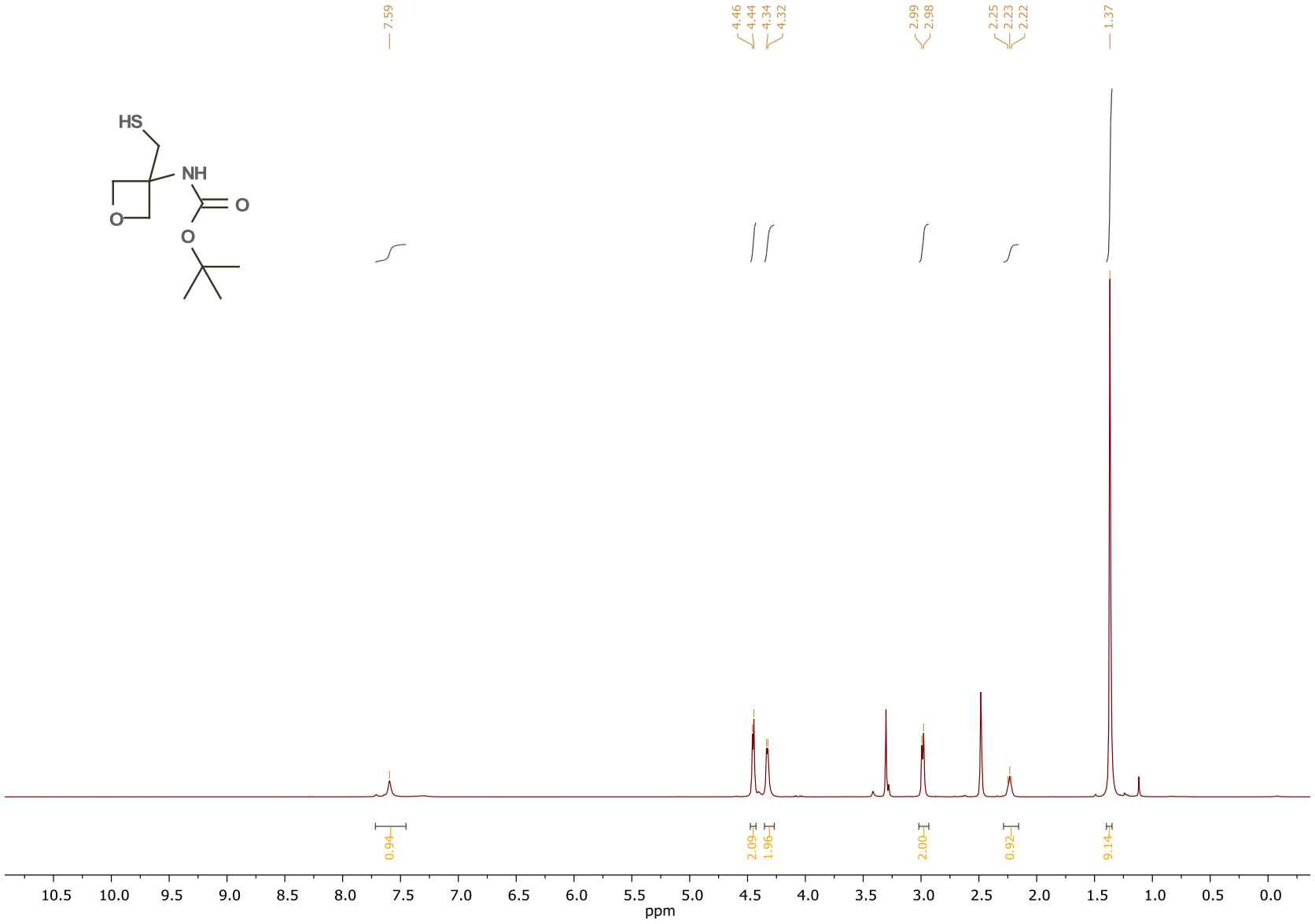
_S_-((3-((tert-Butoxycarbonyl)amino)oxetan-3-yl)methyl) ethanethioate (19) ^{1}H NMR (crude)



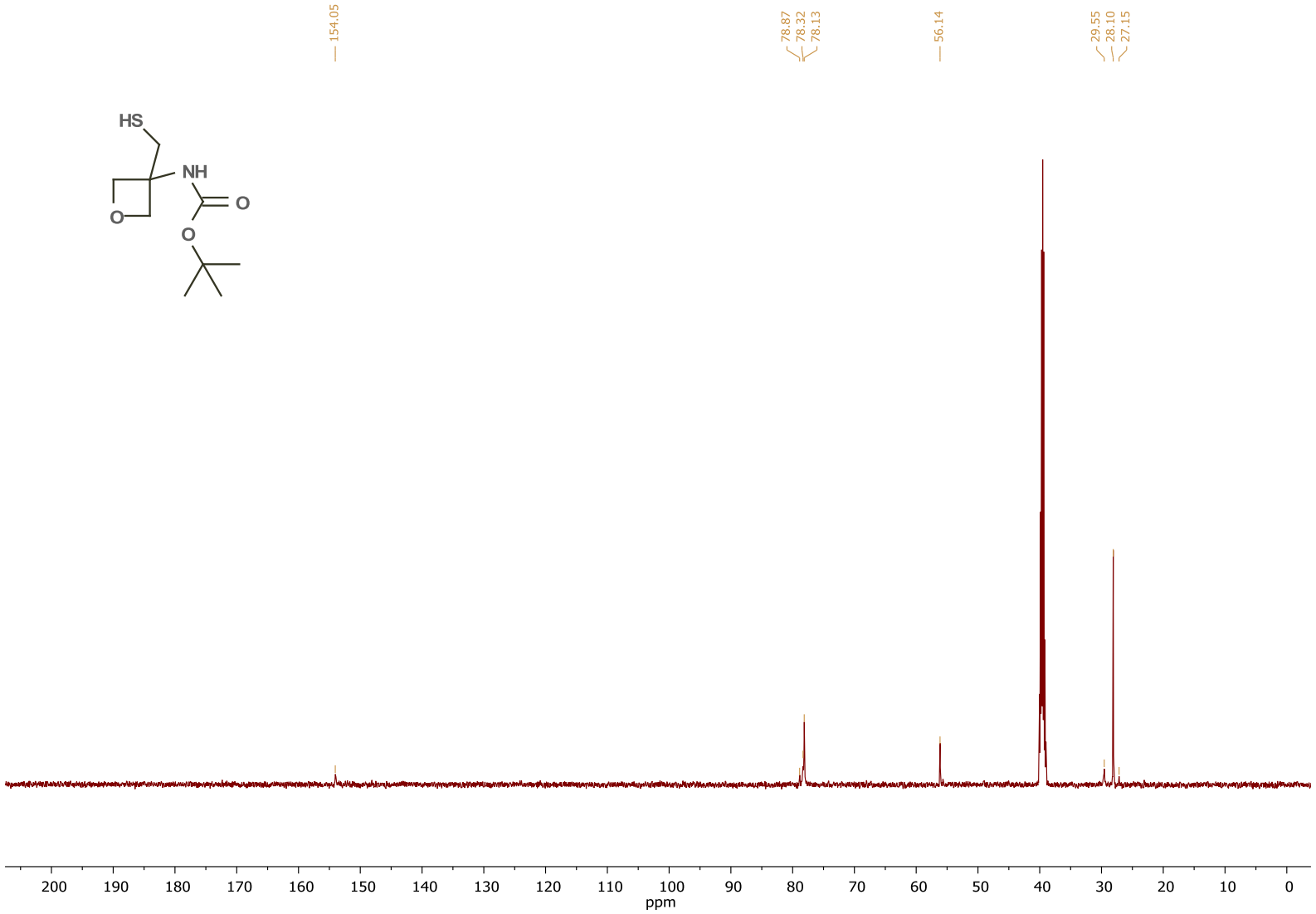
2,7-Dioxa-5-azaspiro[3.4]octan-6-one (20) ^{1}H NMR (500 MHz, DMSO-d_6)



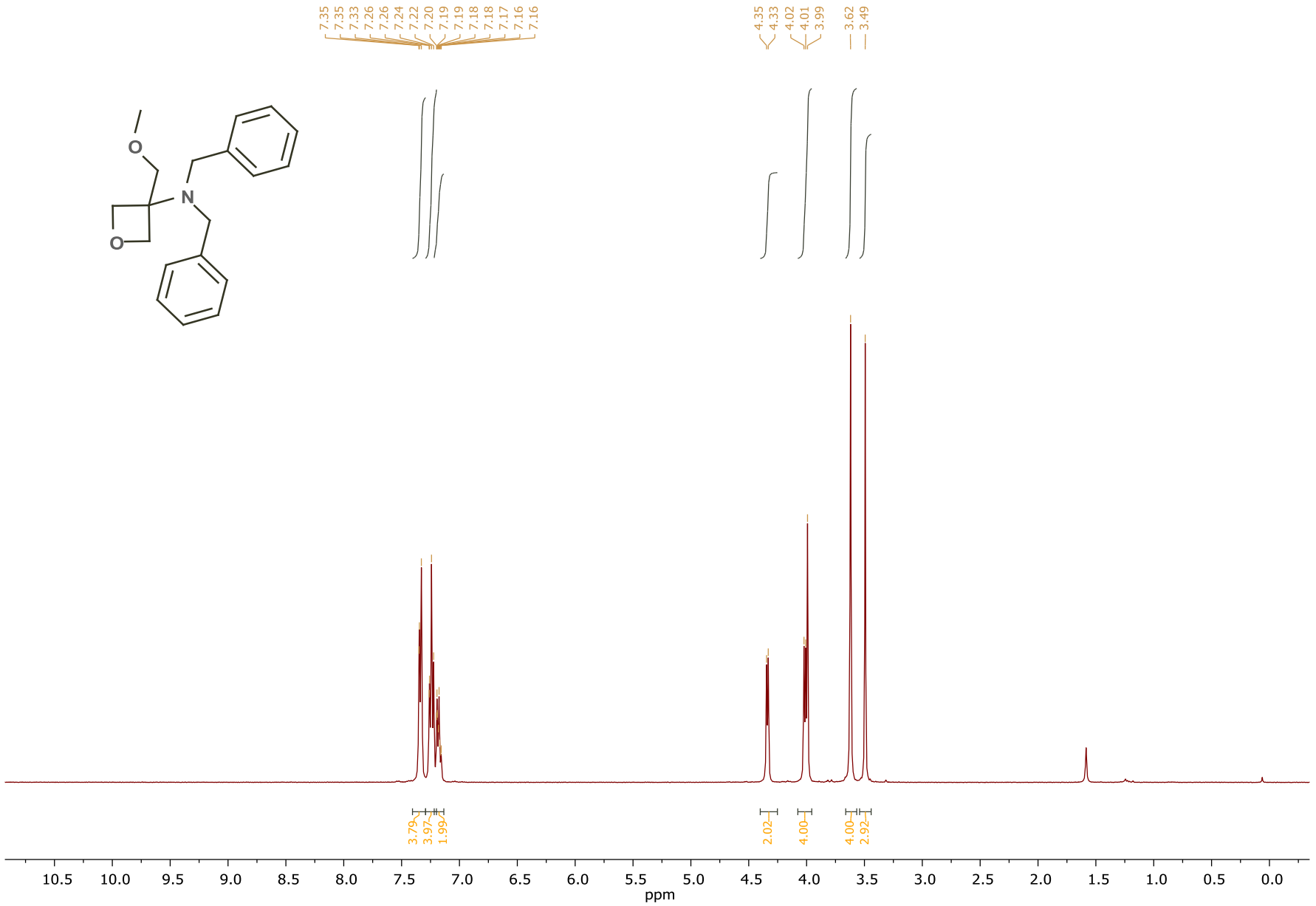
2,7-Dioxa-5-azaspiro[3.4]octan-6-one (20) ^{13}C NMR (151 MHz, DMSO-d_6)



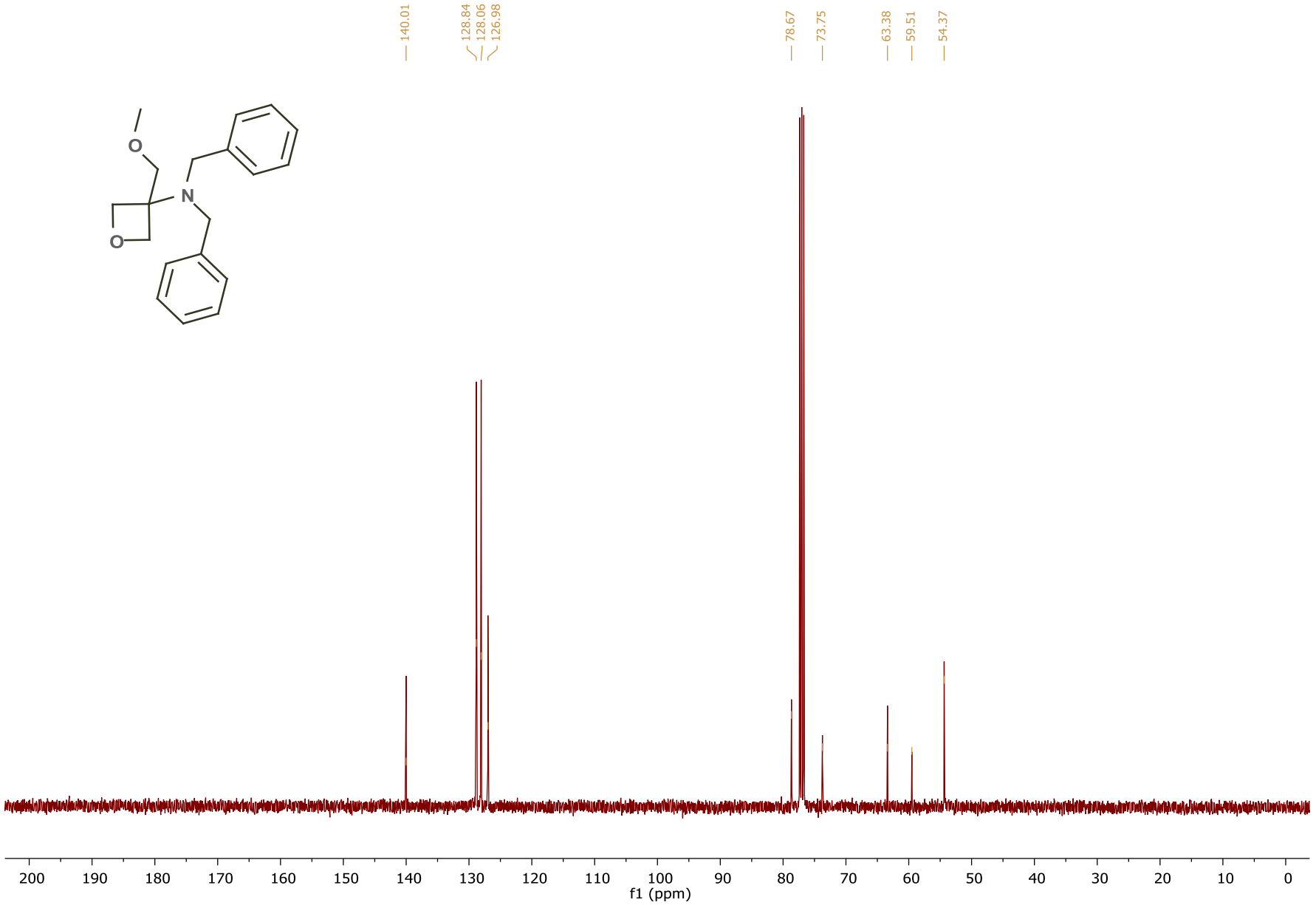
tert-Butyl (3-(mercaptomethyl)oxetan-3-yl)carbamate (21) ^{1}H NMR



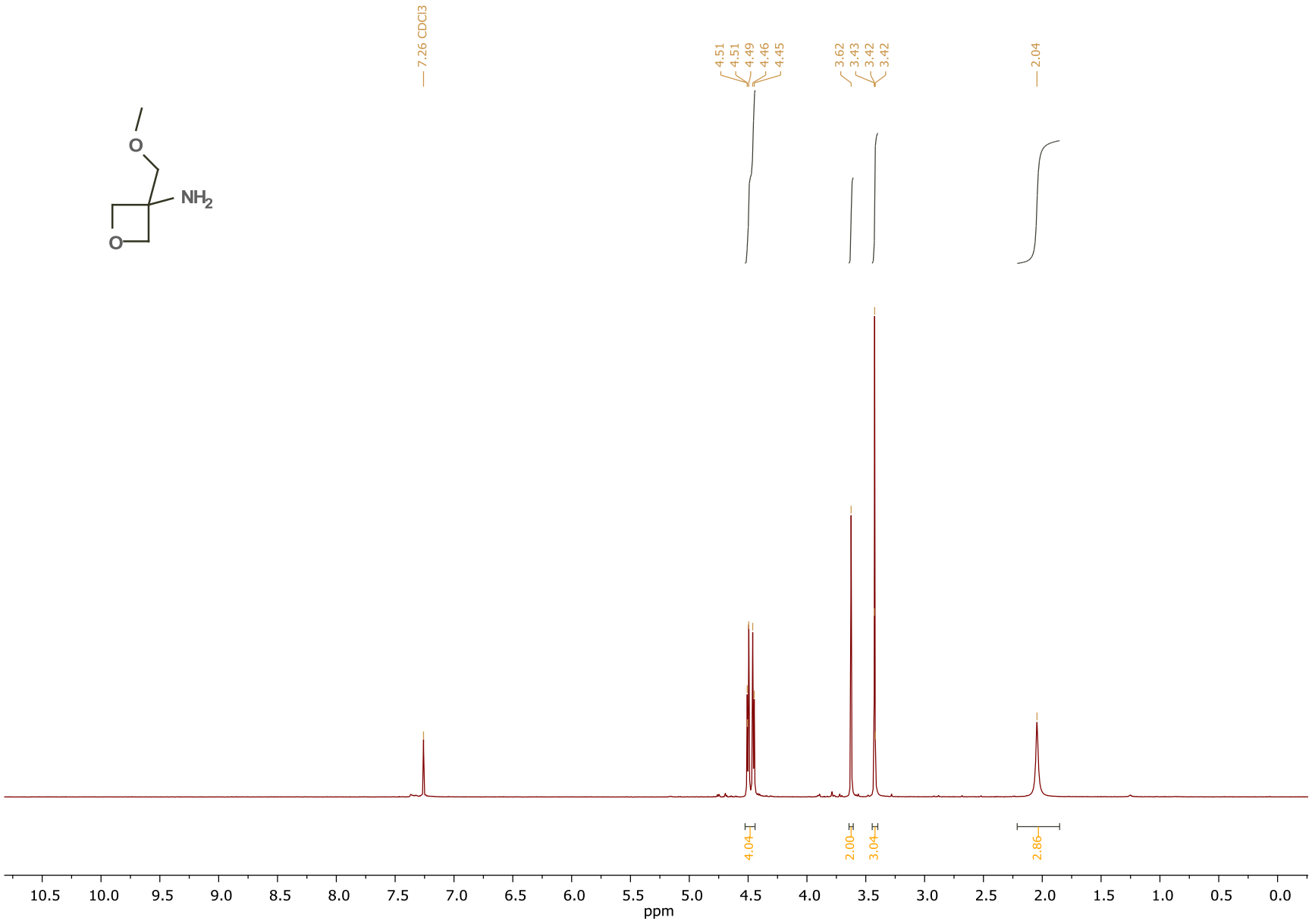
***tert*-Butyl (3-(mercaptomethyl)oxetan-3-yl)carbamate (21) $^{13}C\{H\}$ NMR**



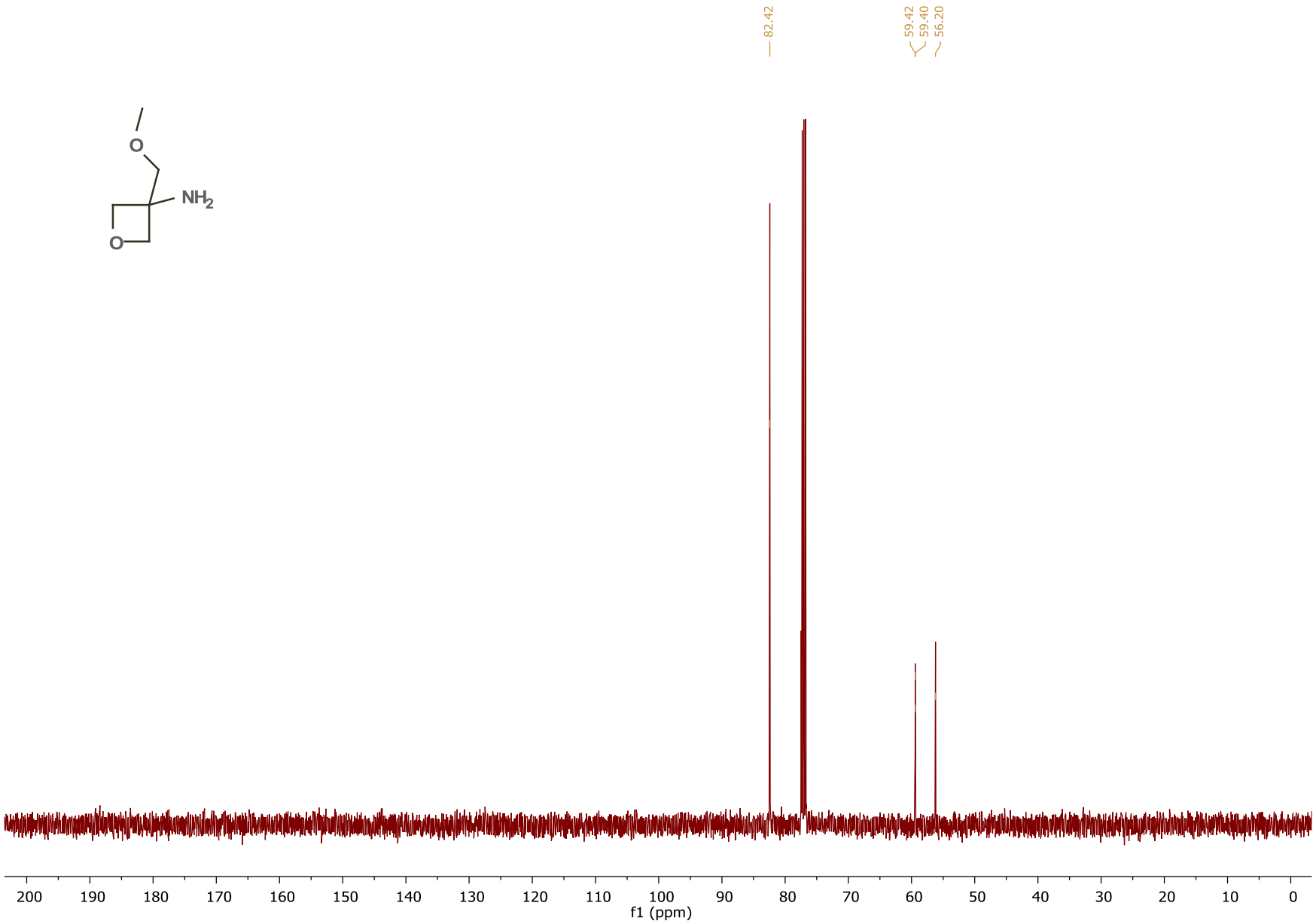
***N,N*-Dibenzyl-3-(methoxymethyl)oxetan-3-amine (23) ^{1}H NMR**



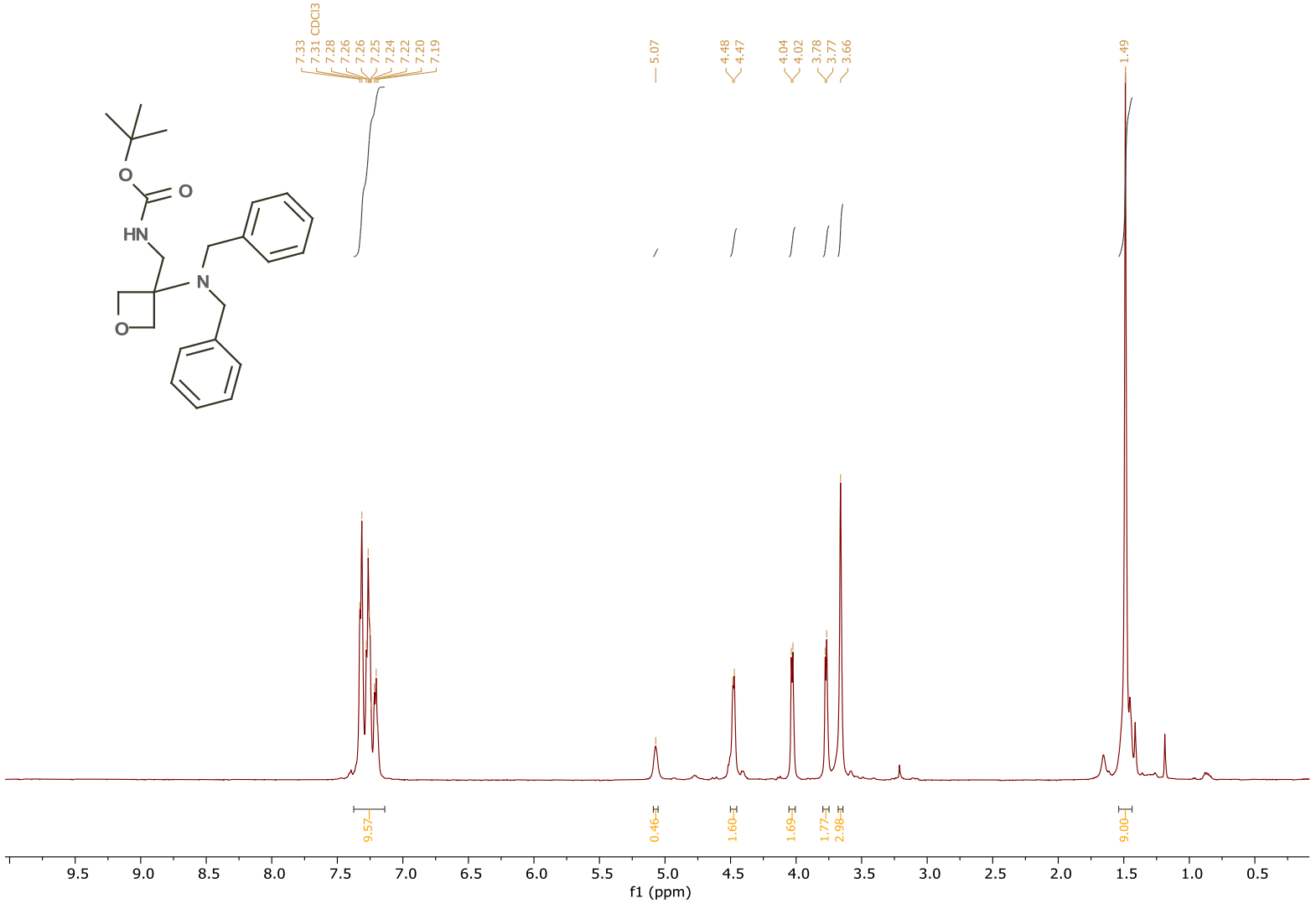
_N,N_-Dibenzyl-3-(methoxymethyl)oxetan-3-amine (23) ^{1}H NMR



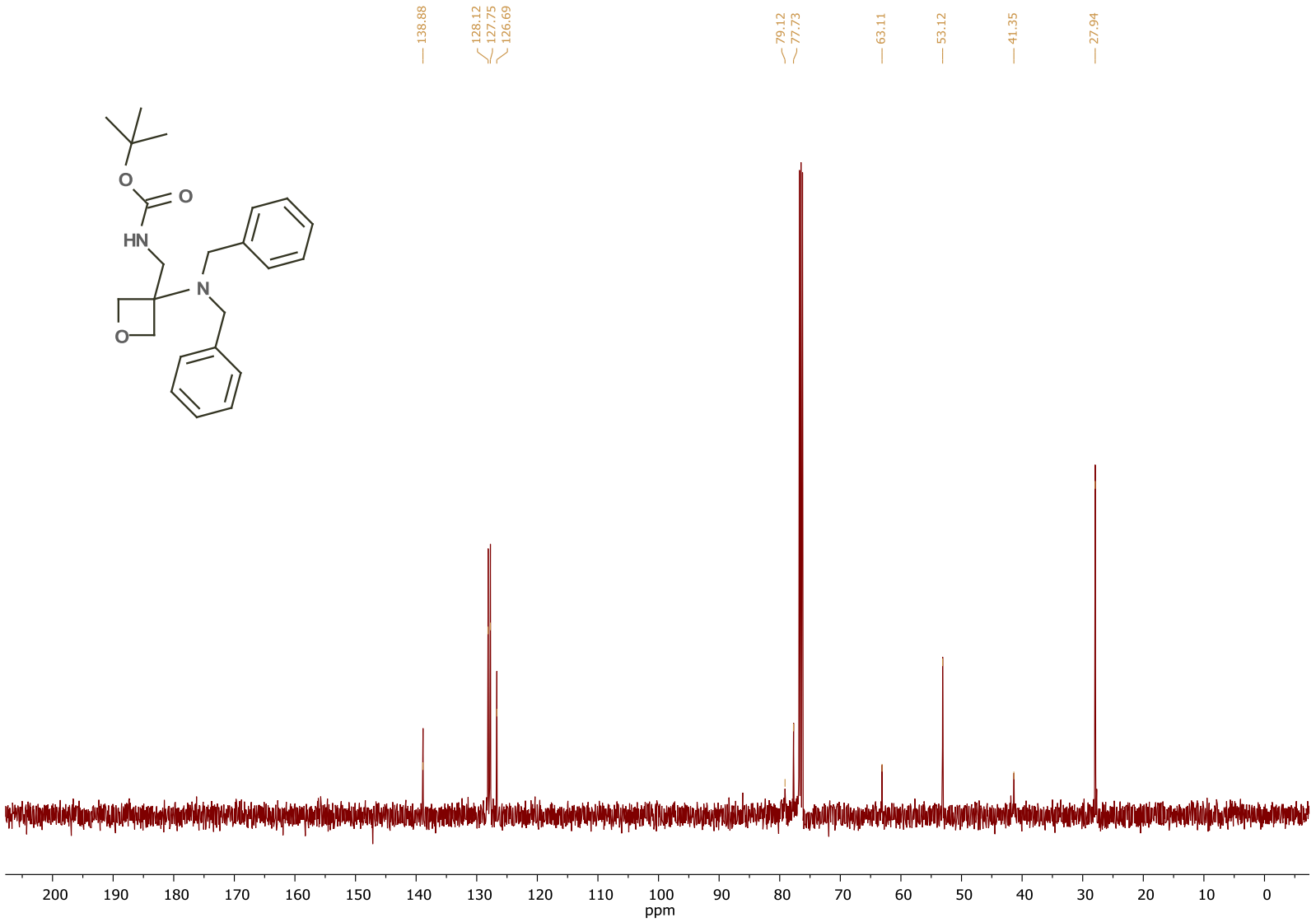
3-(Methoxymethyl)oxetan-3-amine (24) ^{1}H NMR



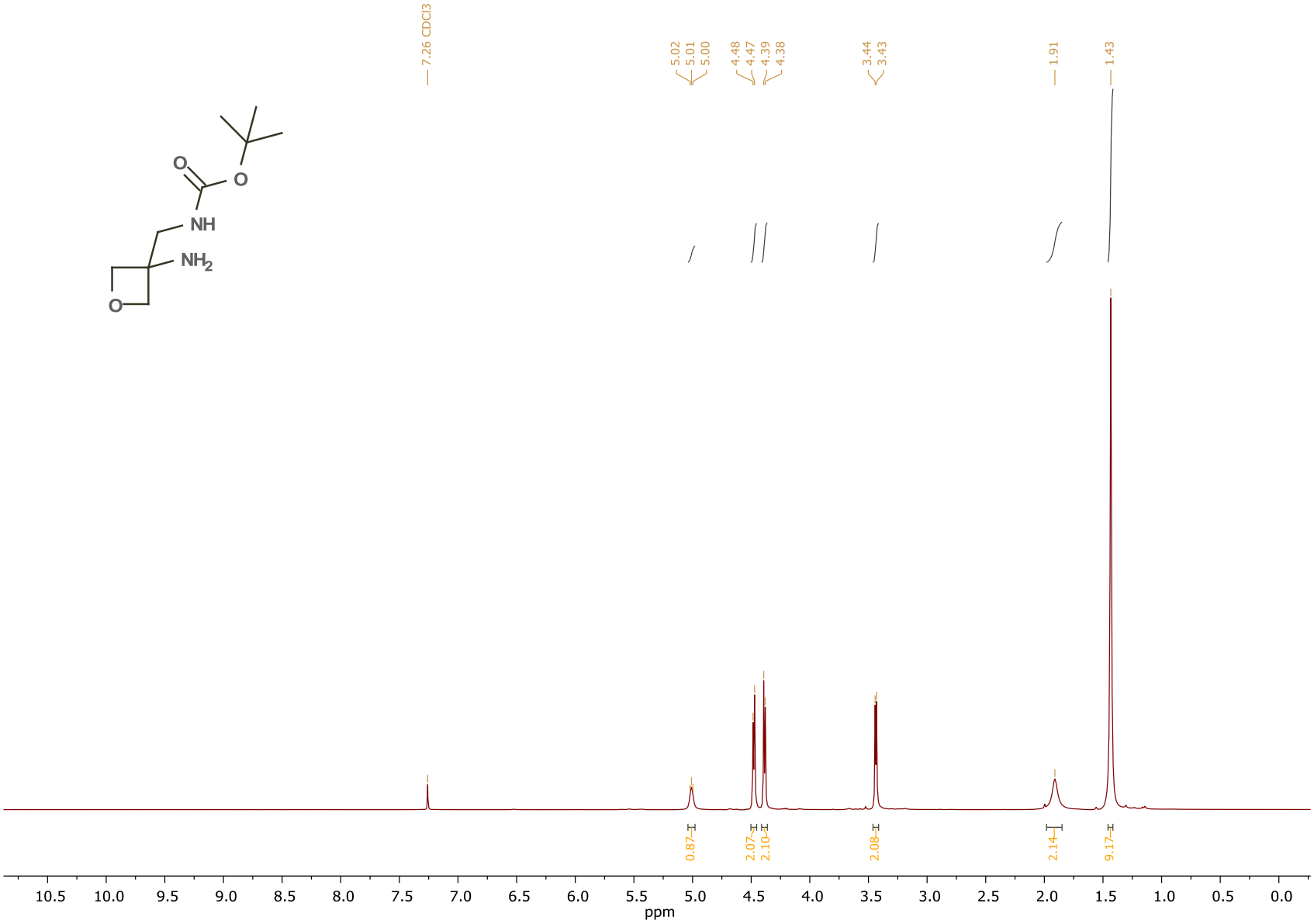
3-(Methoxymethyl)oxetan-3-amine (24) $^{13}C\{H\}$ NMR



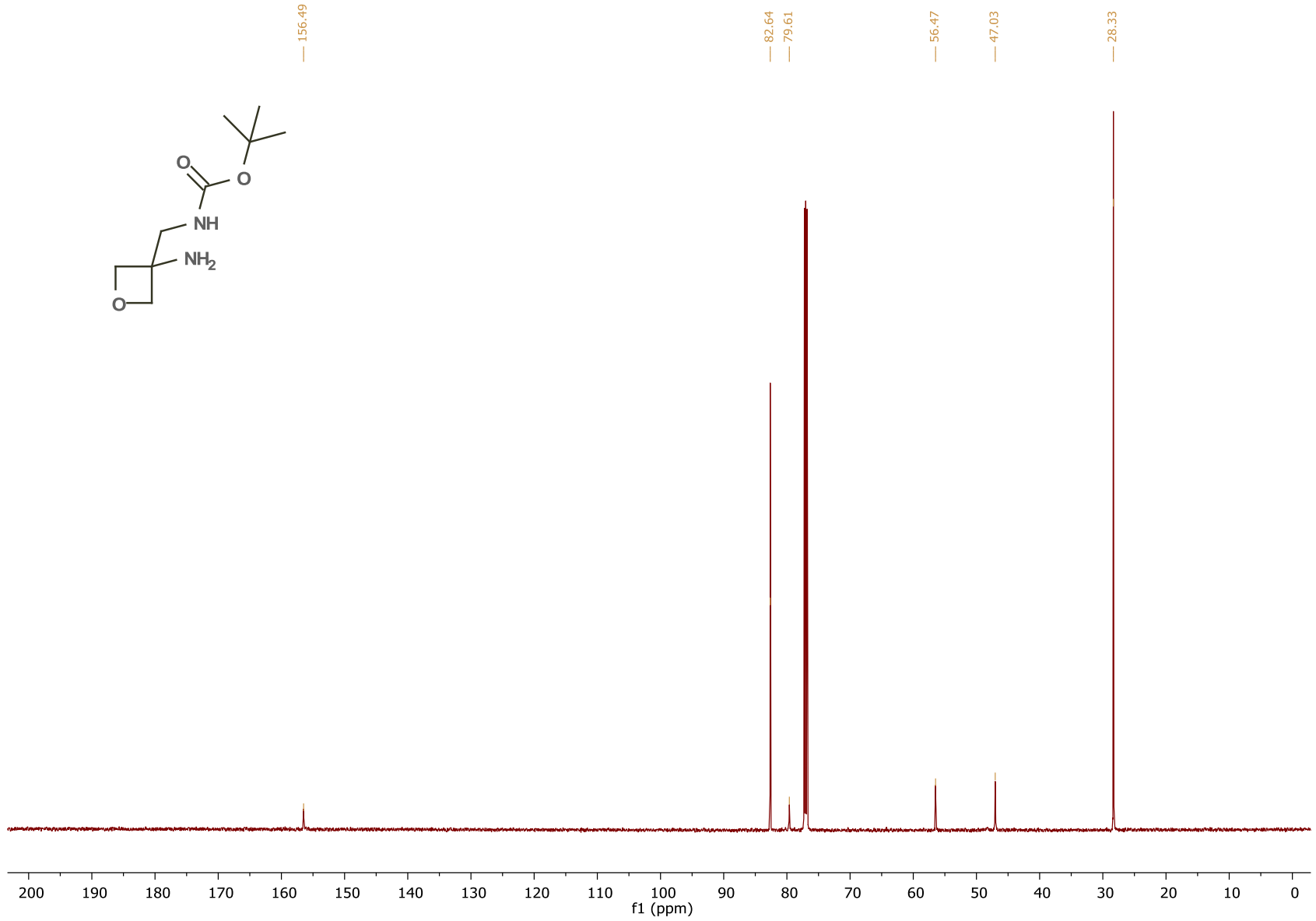
***tert*-Butyl ((3-(dibenzylamino)oxetan-3-yl)methyl)carbamate (25) ^{1}H NMR**



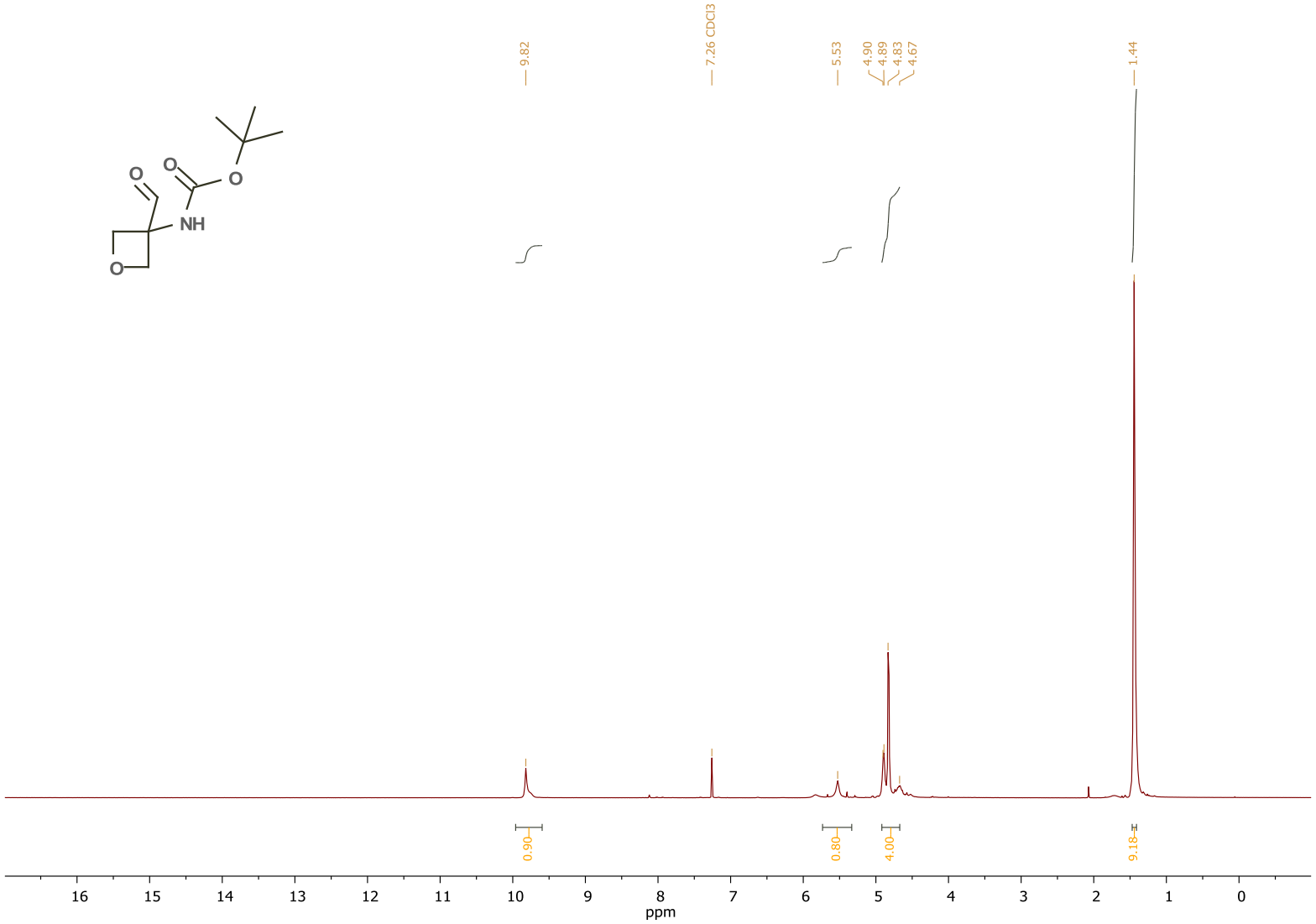
***tert*-Butyl ((3-(dibenzylamino)oxetan-3-yl)methyl)carbamate (25) $^{13}C\{H\}$ NMR**



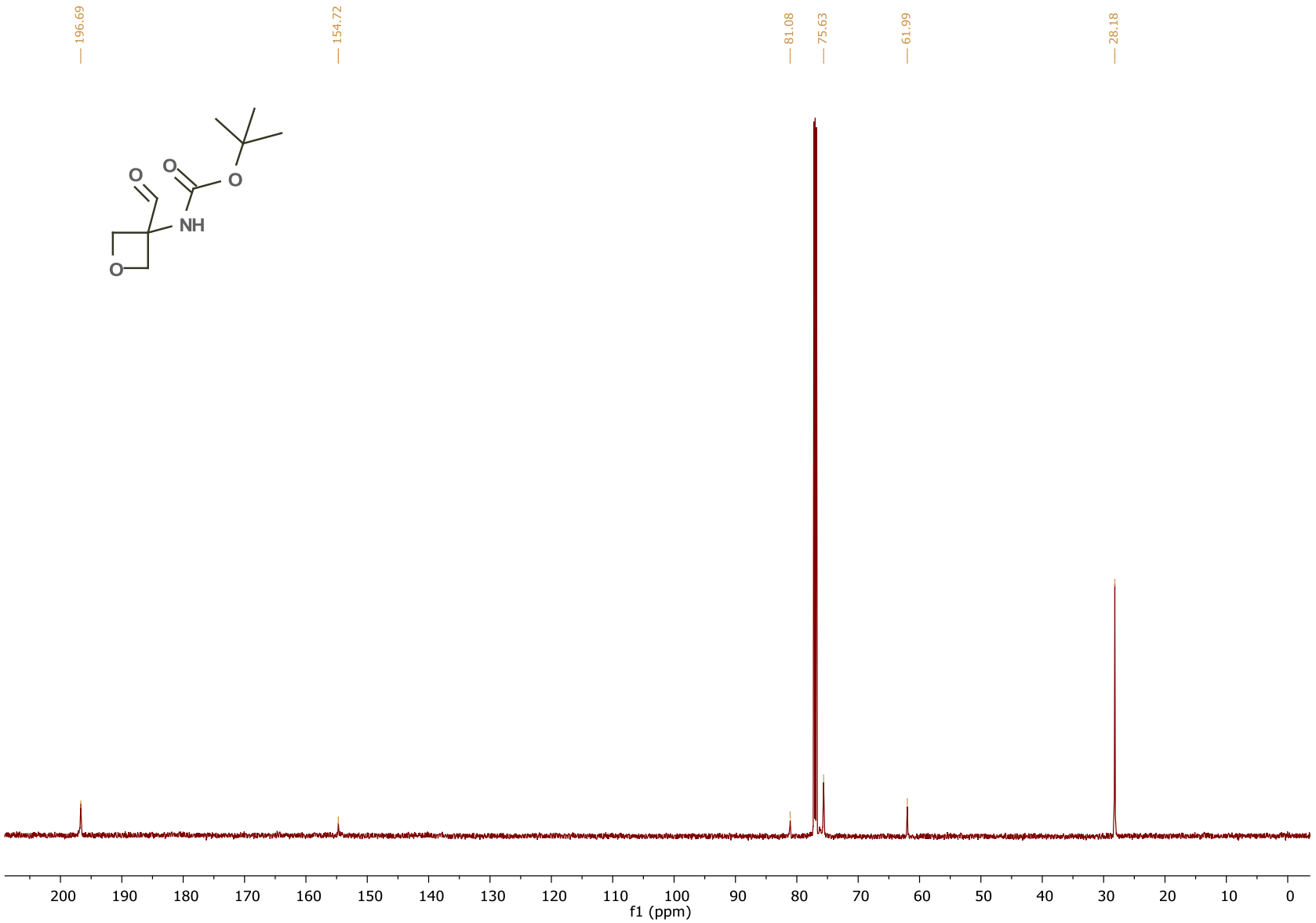
***tert*-Butyl *N*-[(3-aminooxetan-3-yl)methyl]carbamate (26) ^{1}H NMR**



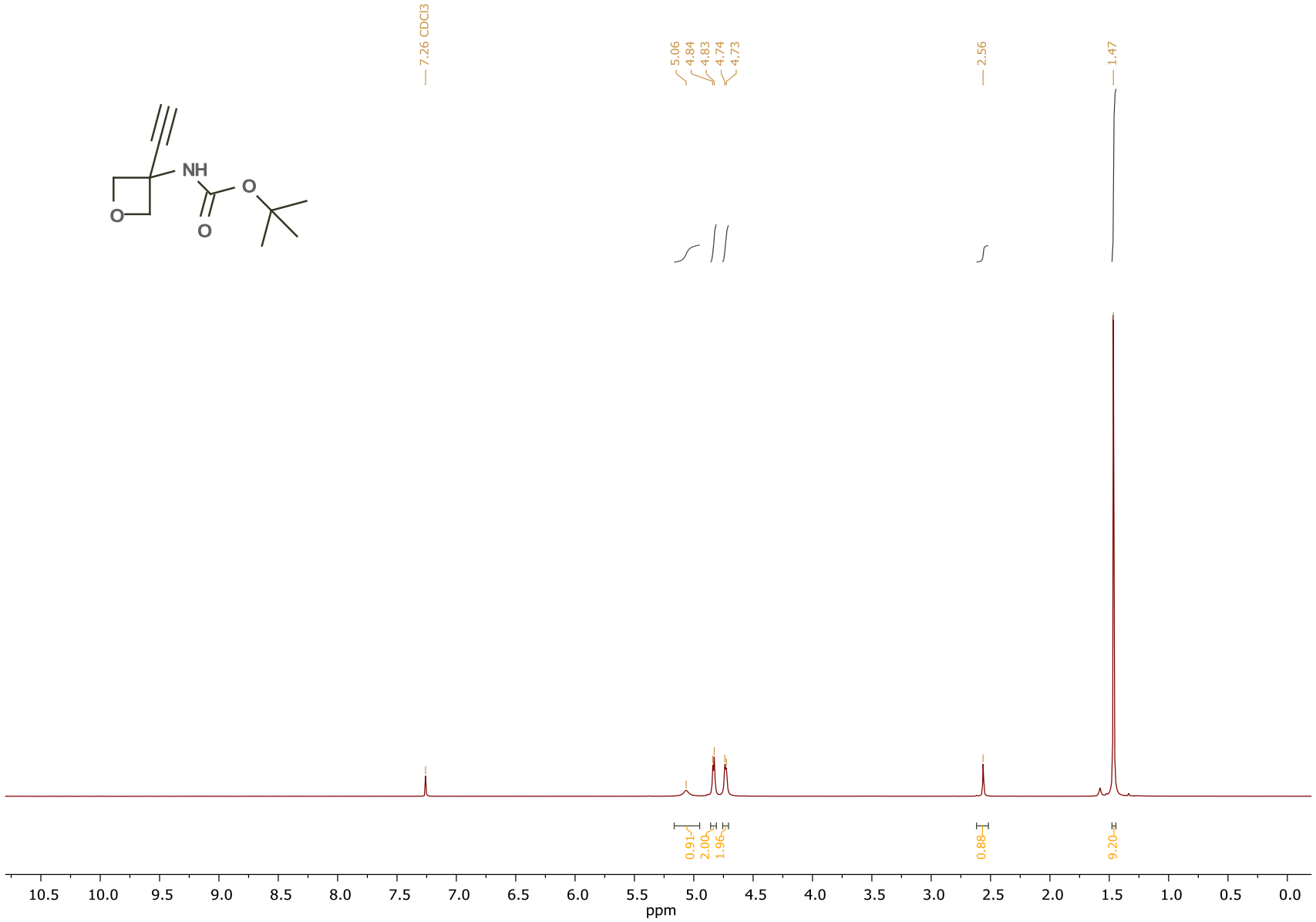
tert-Butyl _N_-[(3-aminooxetan-3-yl)methyl]carbamate (26) $^{13}C\{H\}$ NMR



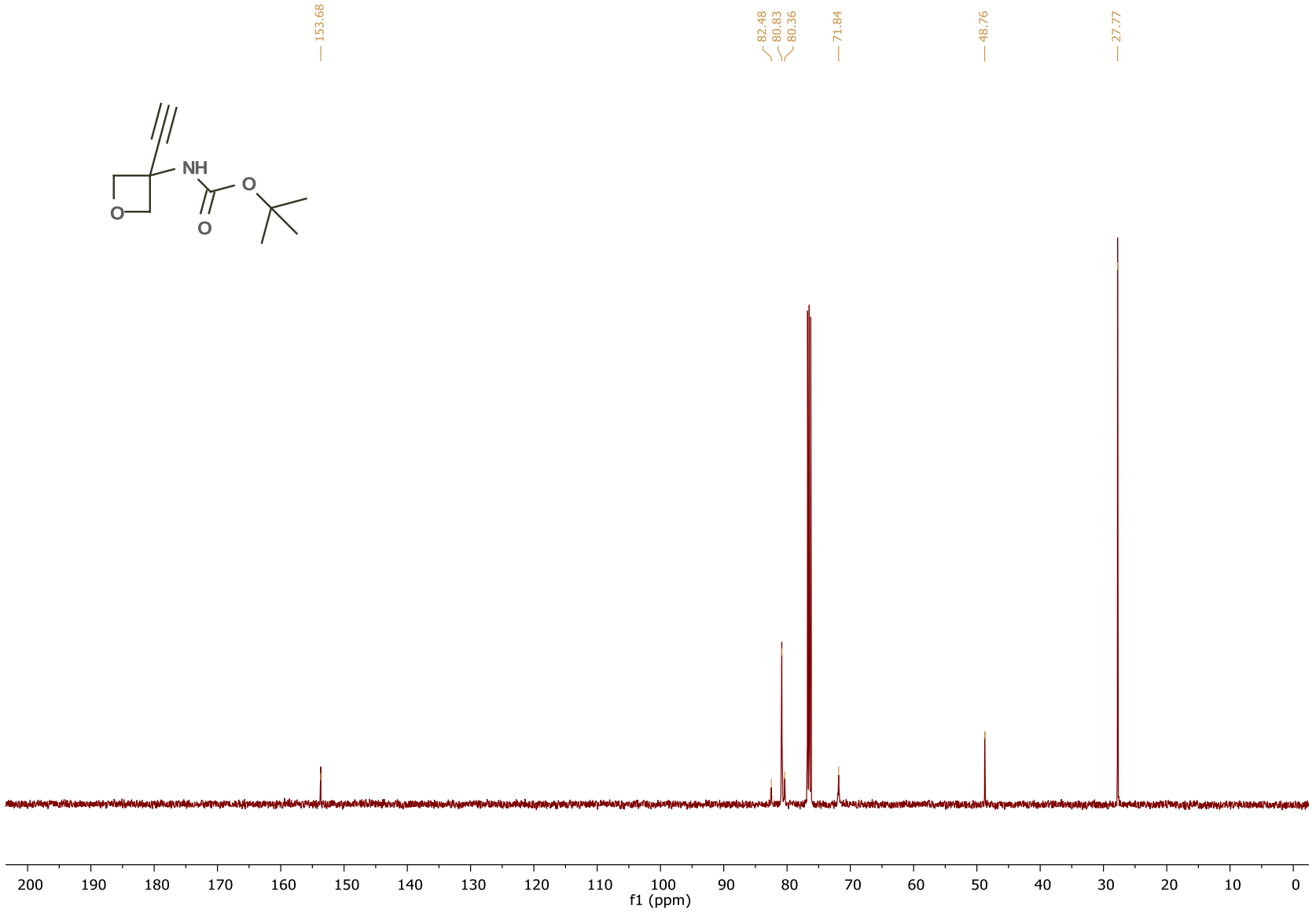
***tert*-Butyl *N*-(3-formyloxetan-3-yl)carbamate (27) ^{1}H NMR**



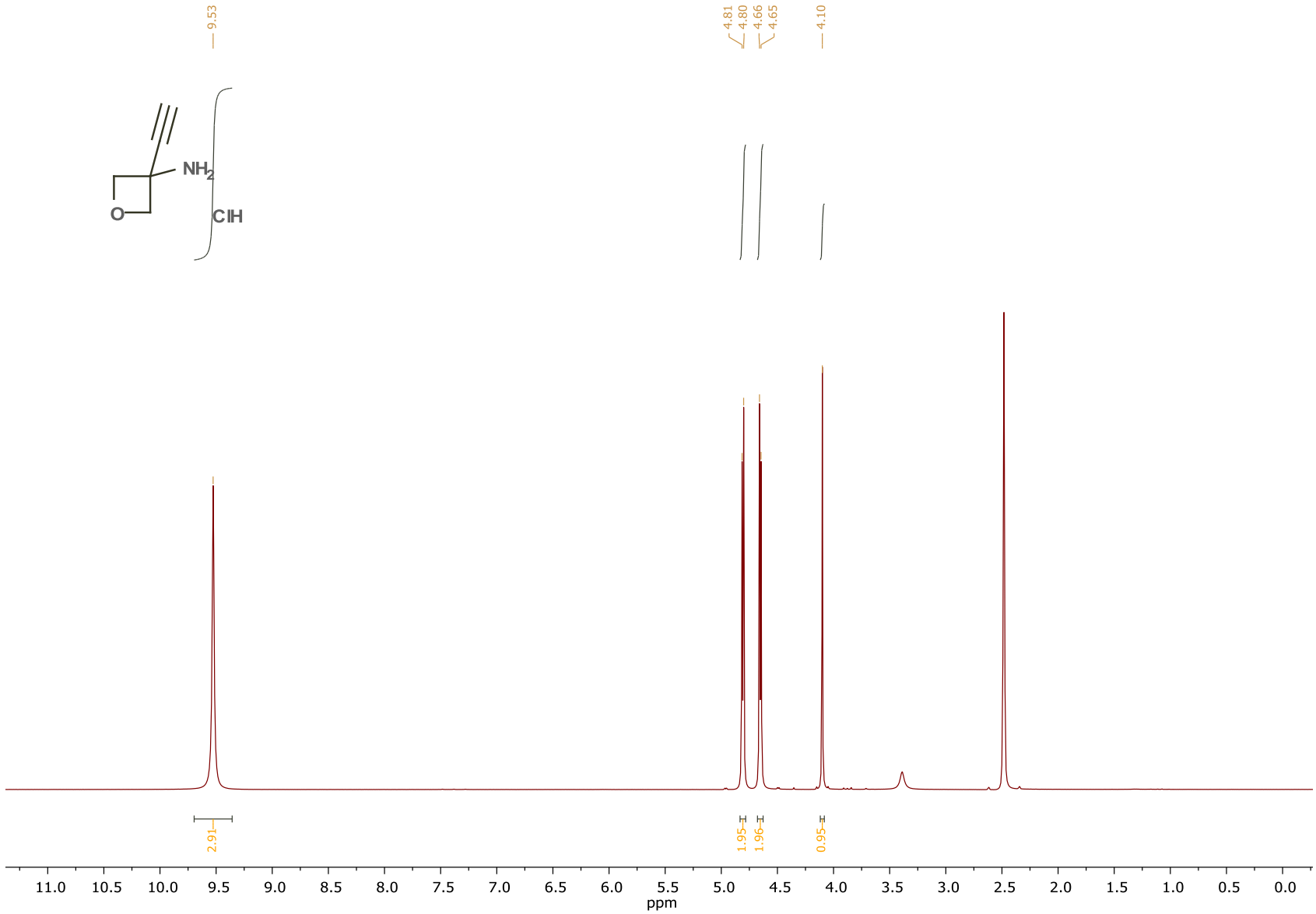
tert-Butyl _N_-(3-formyloxetan-3-yl)carbamate (27) ^{13}C{H} NMR



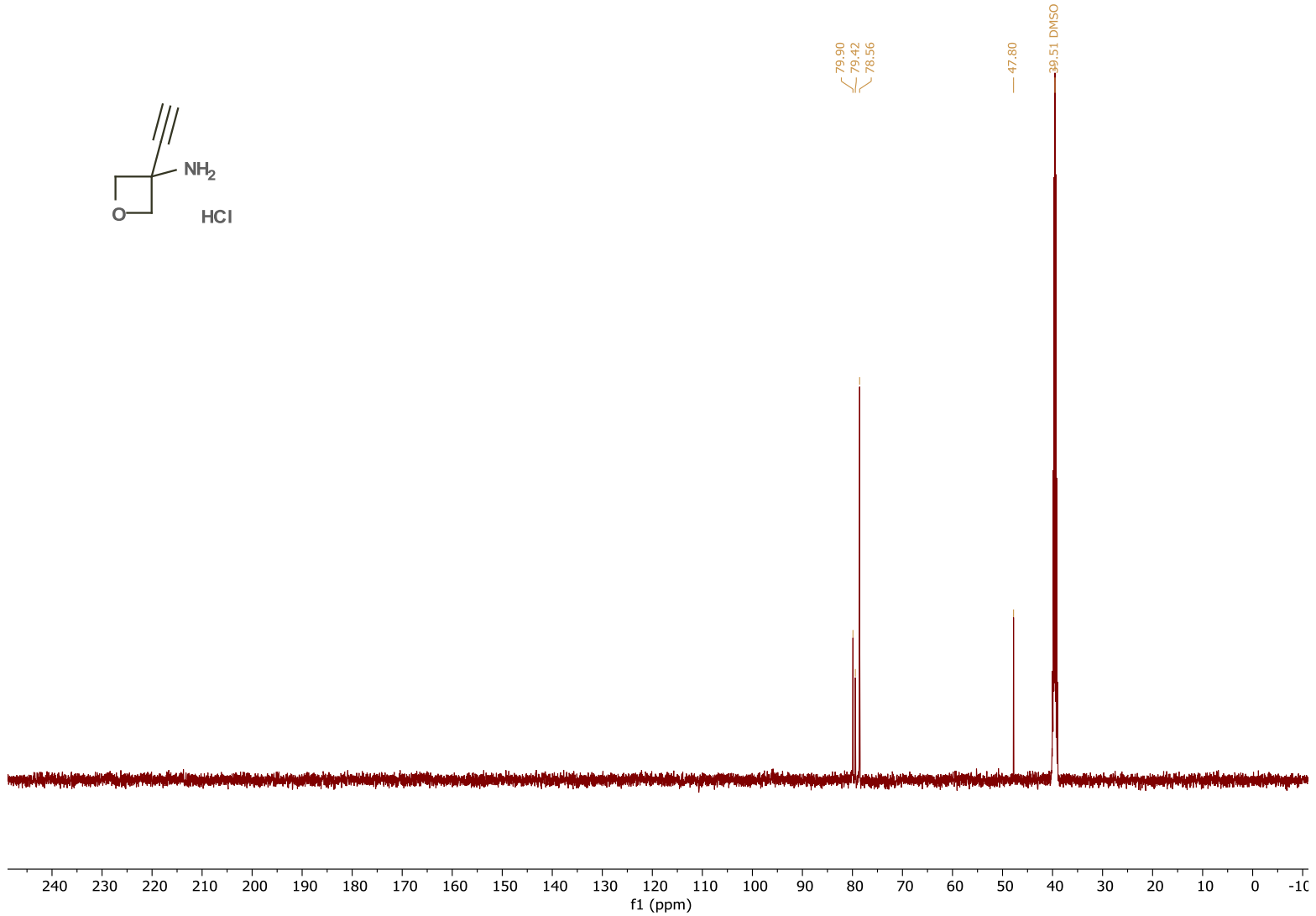
***tert*-Butyl *N*-(3-ethynyloxetan-3-yl)carbamate (28) ^{1}H NMR**



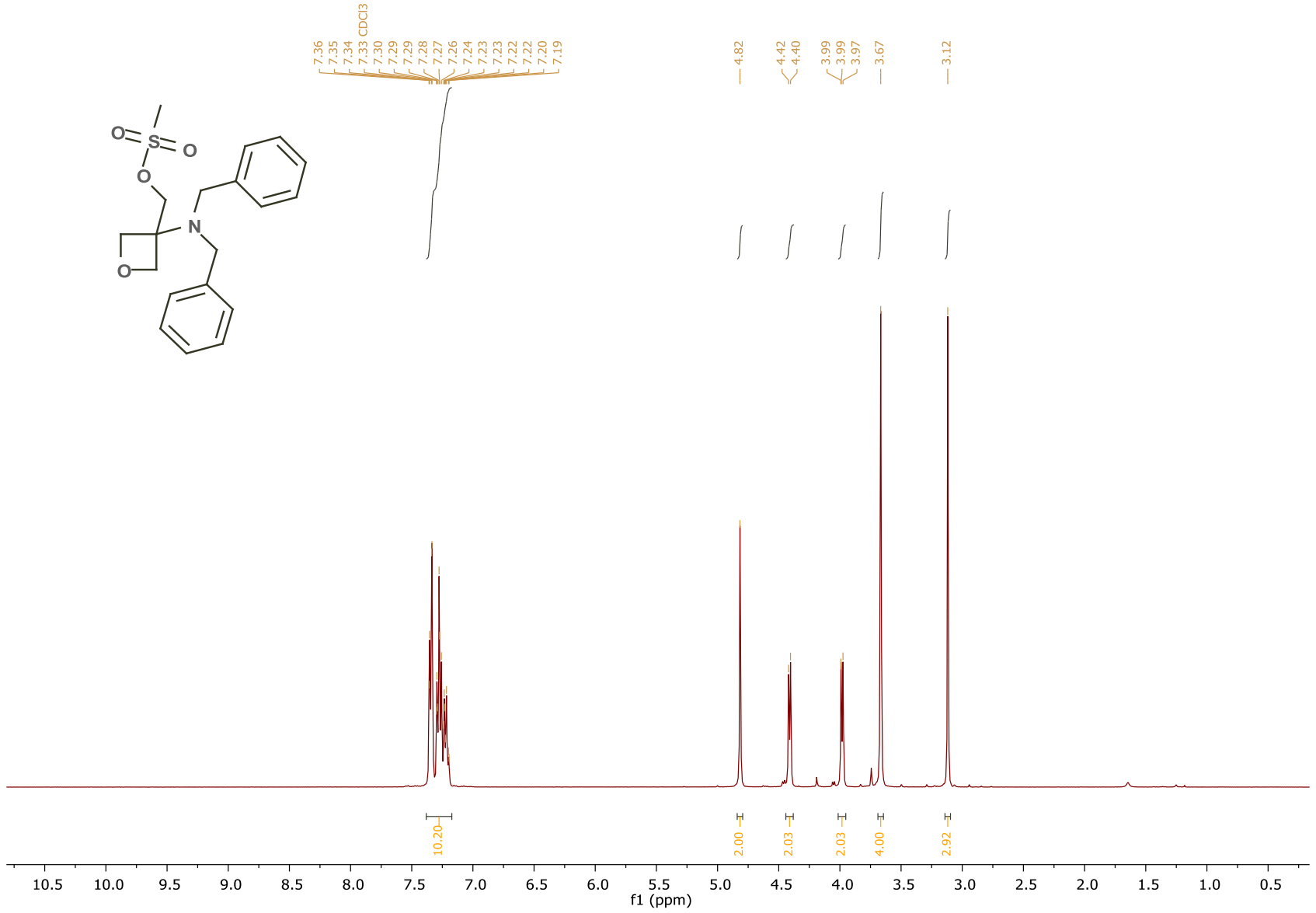
tert-Butyl _N_-(3-ethynyloxetan-3-yl)carbamate (28) $^{13}C\{H\}$ NMR



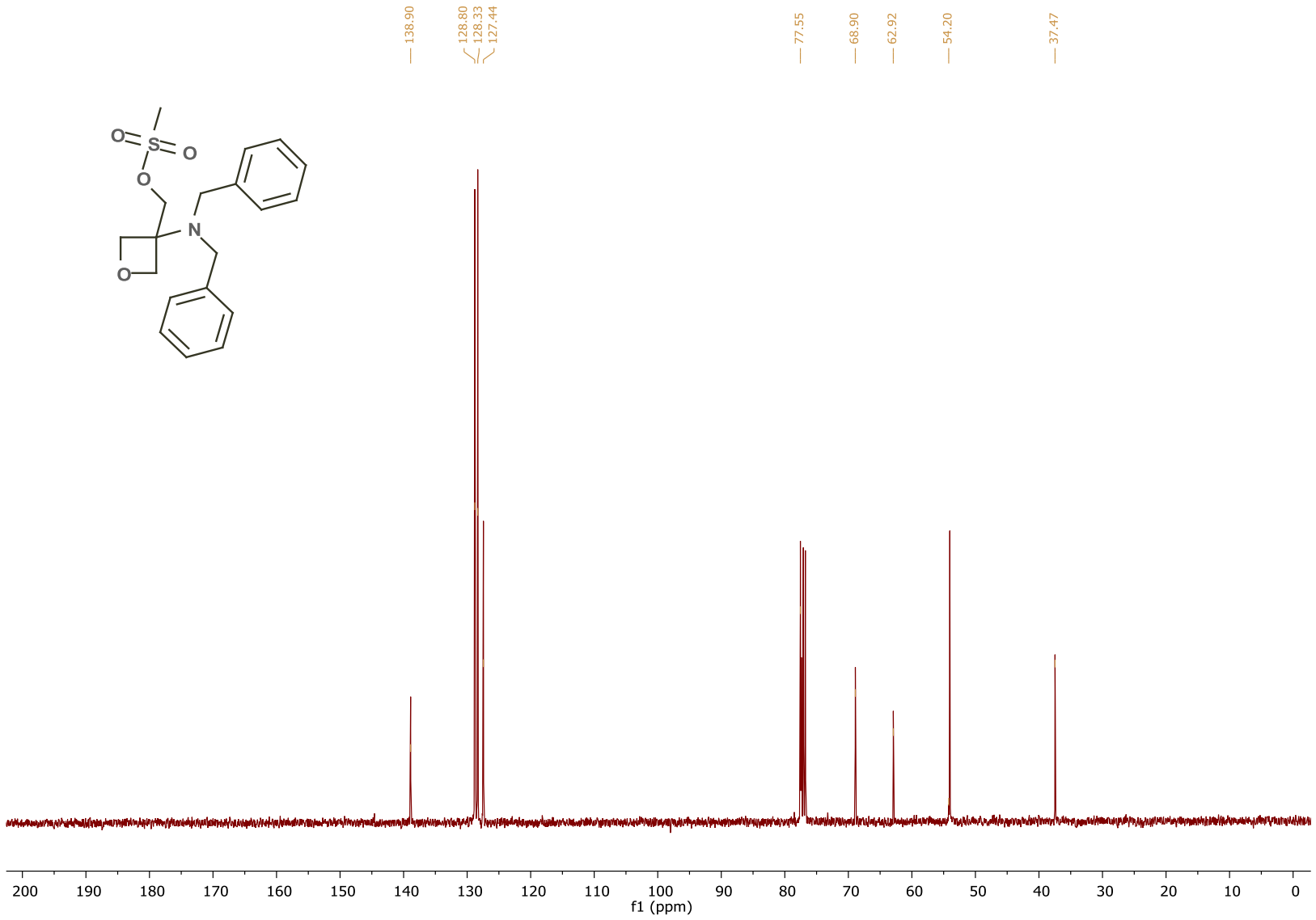
3-Ethynyloxetan-3-amine hydrochloride (29) ^{1}H NMR



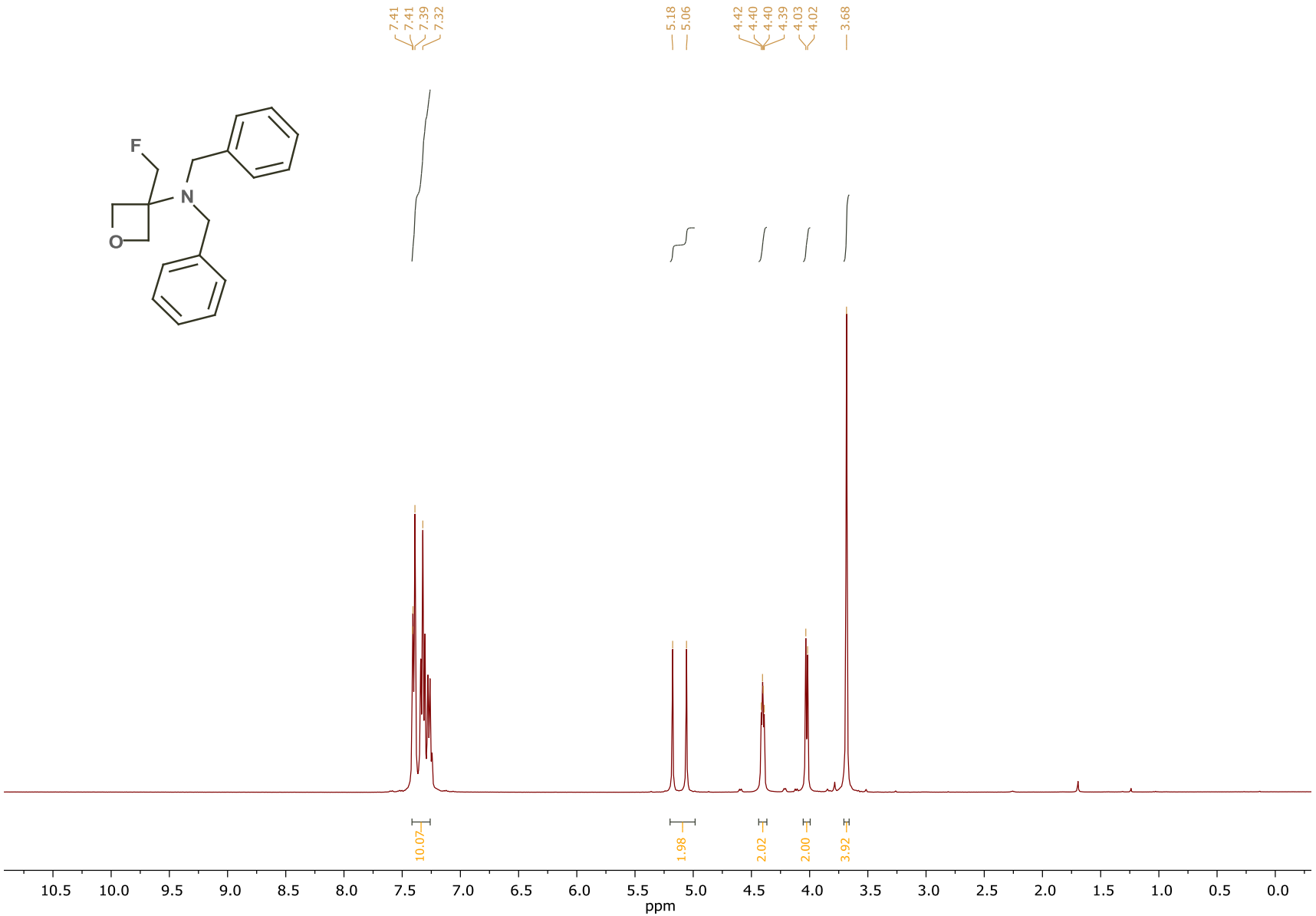
3-Ethynyloxetan-3-amine hydrochloride (29) $^{13}C\{H\}$ NMR



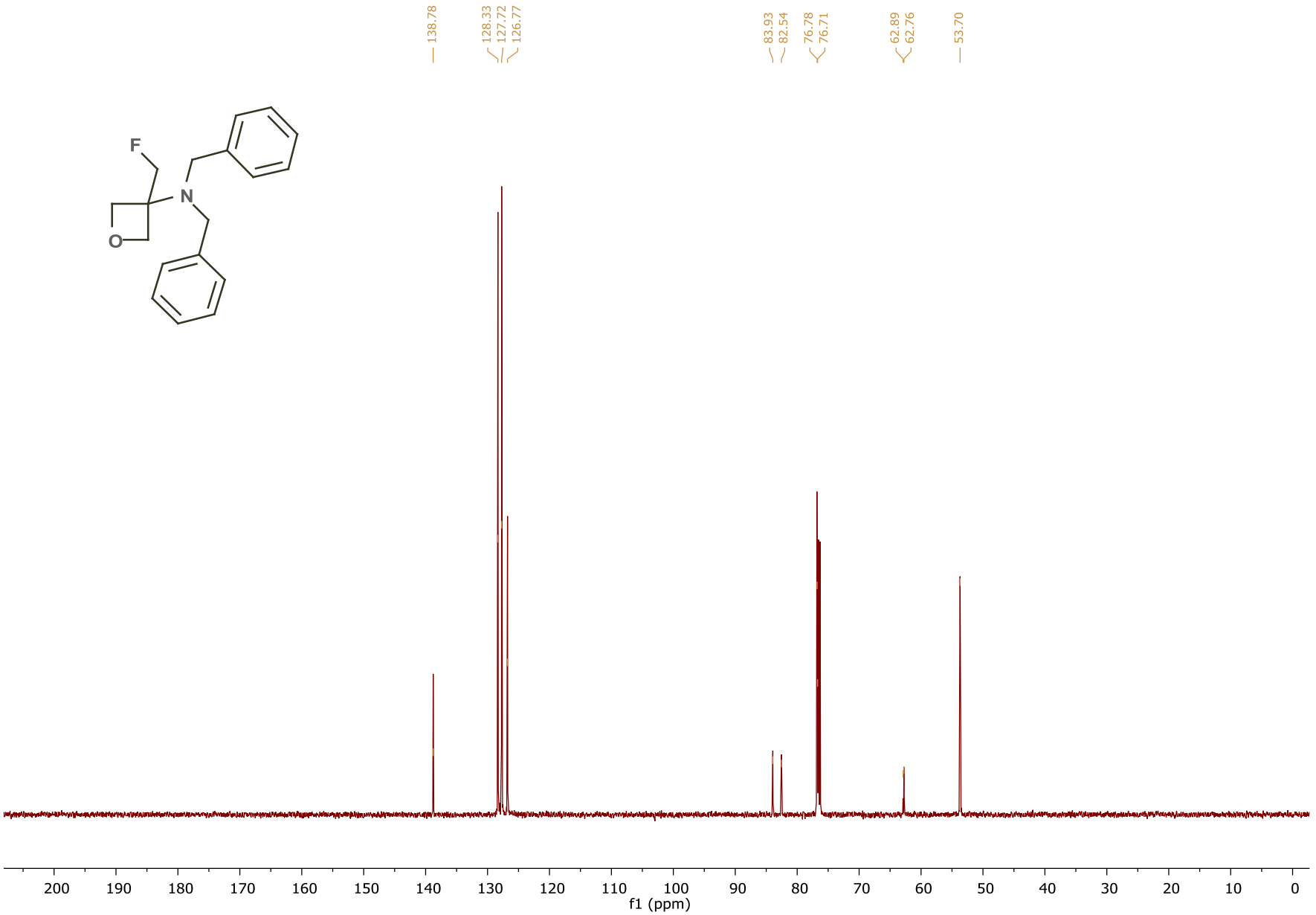
(3-(Dibenzylamino)oxetan-3-yl)methyl methanesulfonate (30) ^{1}H NMR



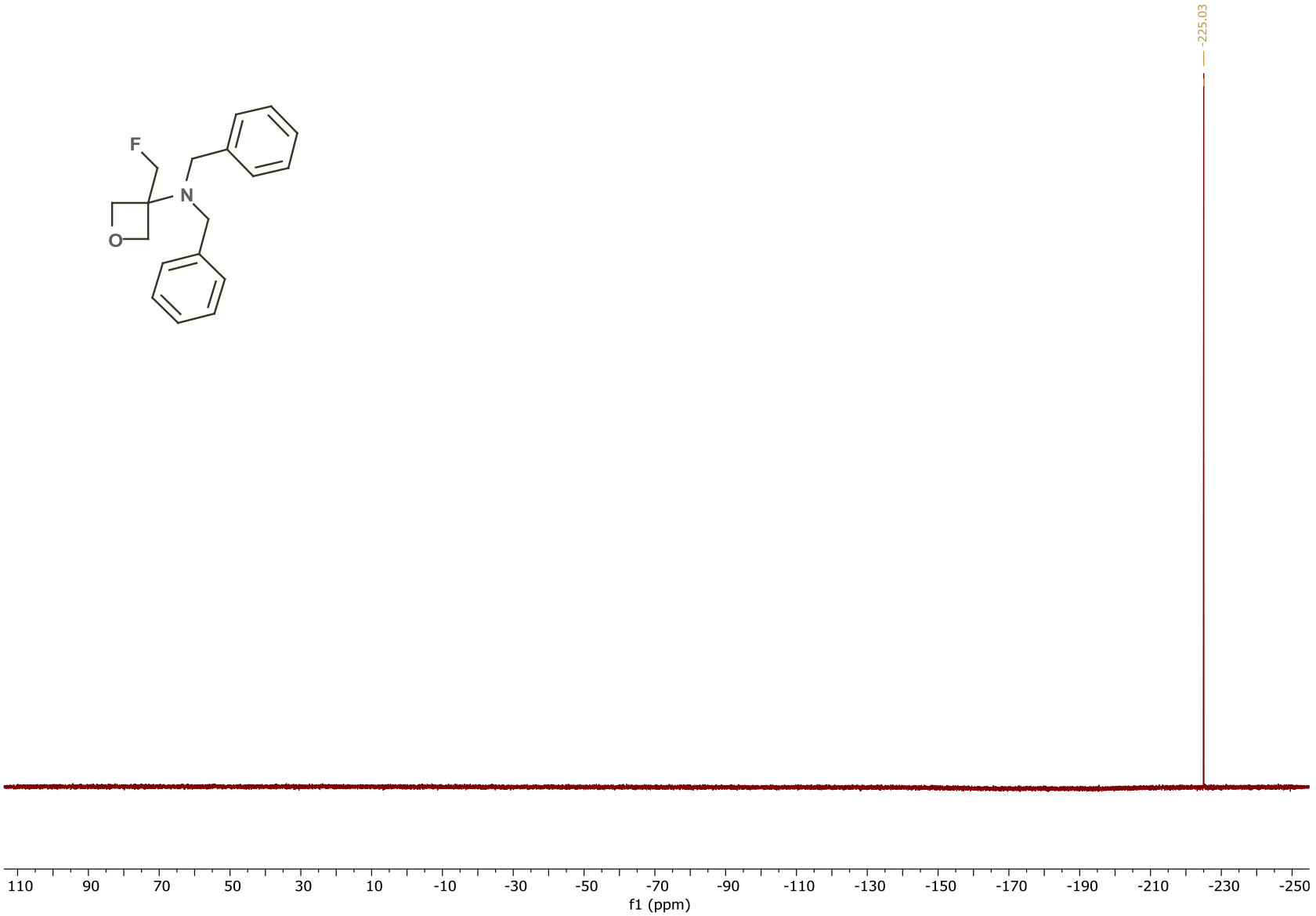
(3-(Dibenzylamino)oxetan-3-yl)methyl methanesulfonate (30) $^{13}C\{H\}$ NMR



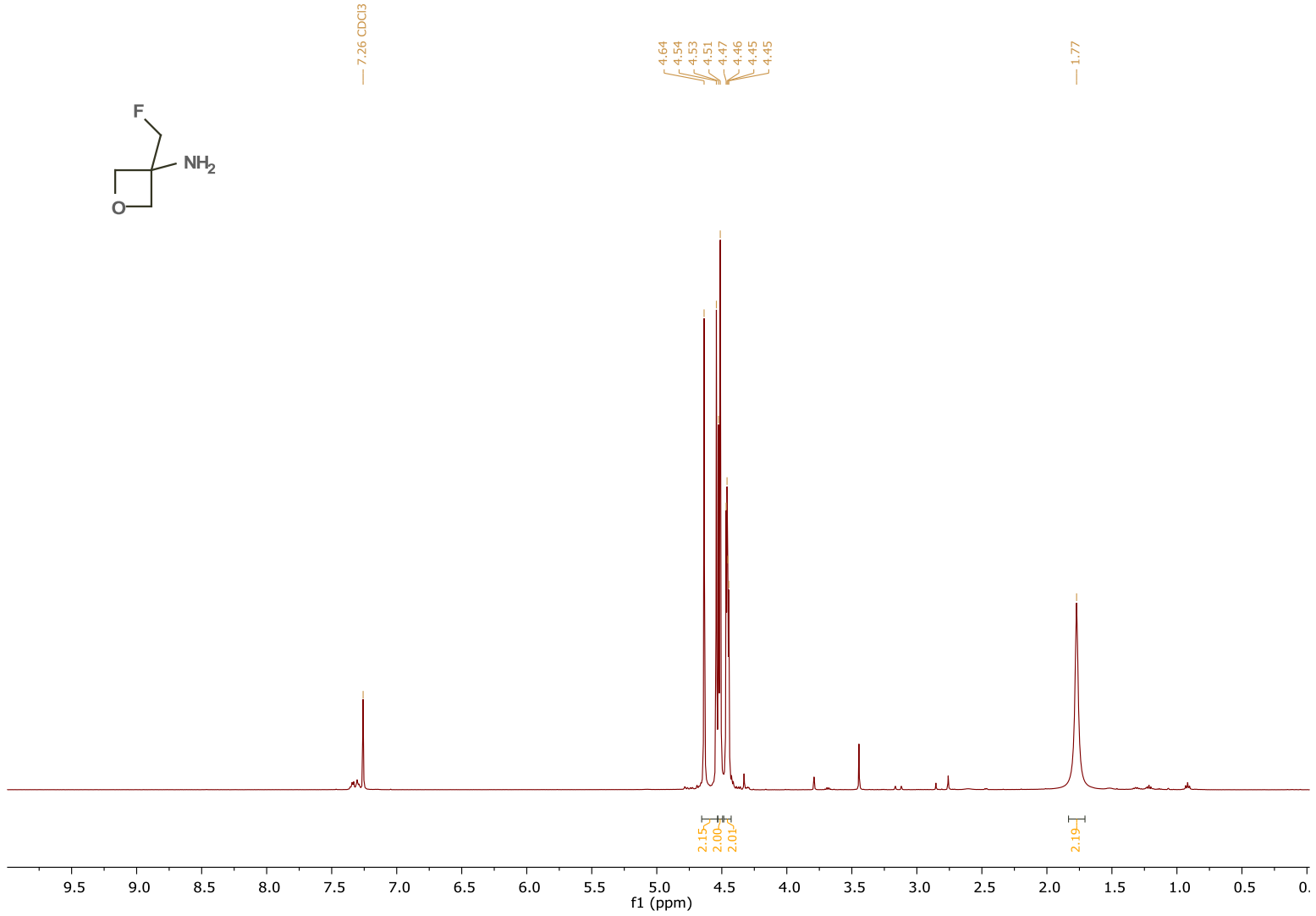
_N,N_-Dibenzyl-3-(fluoromethyl)oxetan-3-amine (31) ^{1}H NMR



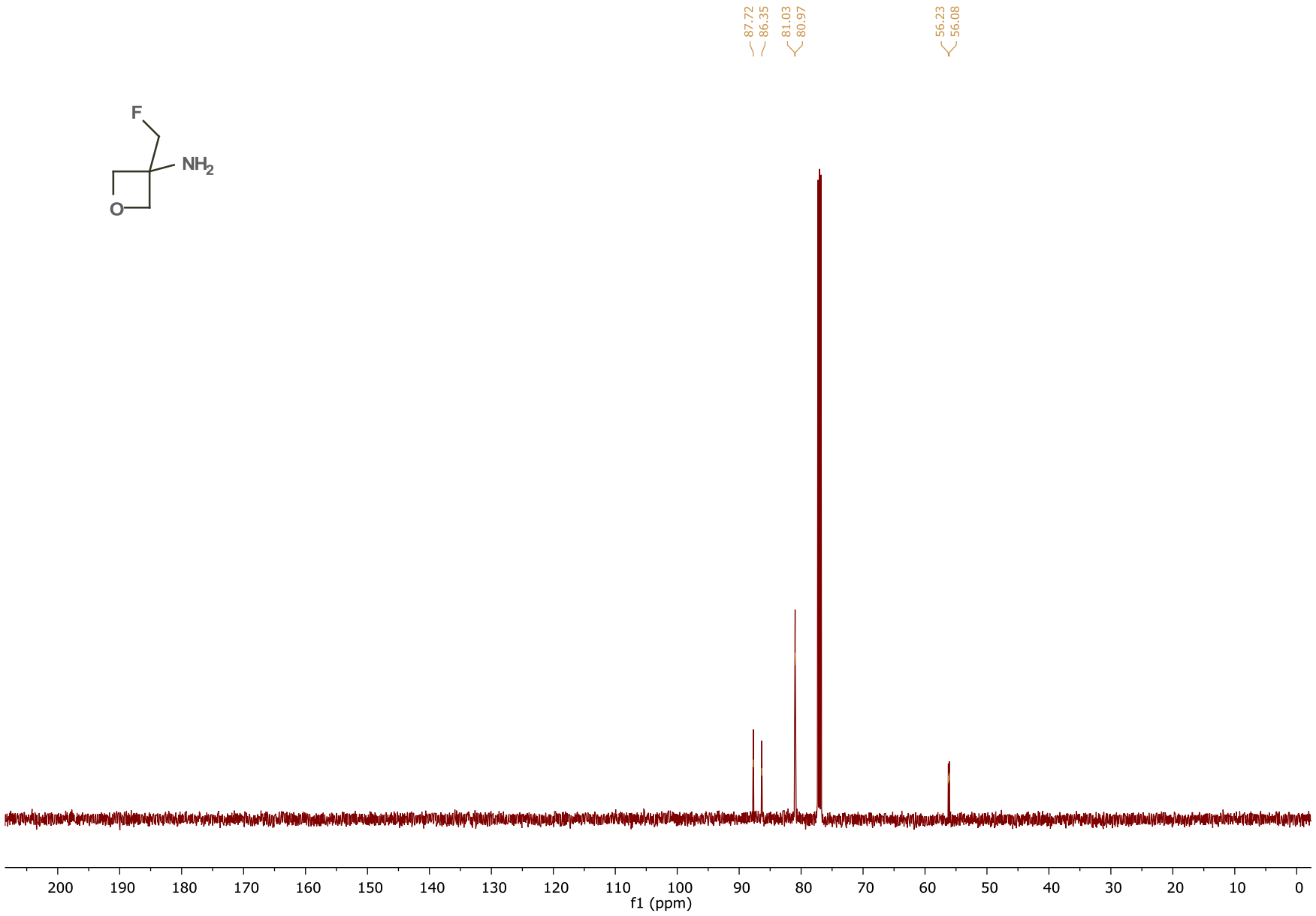
_N,N_-Dibenzyl-3-(fluoromethyl)oxetan-3-amine (31) $^{13}C\{H\}$ NMR



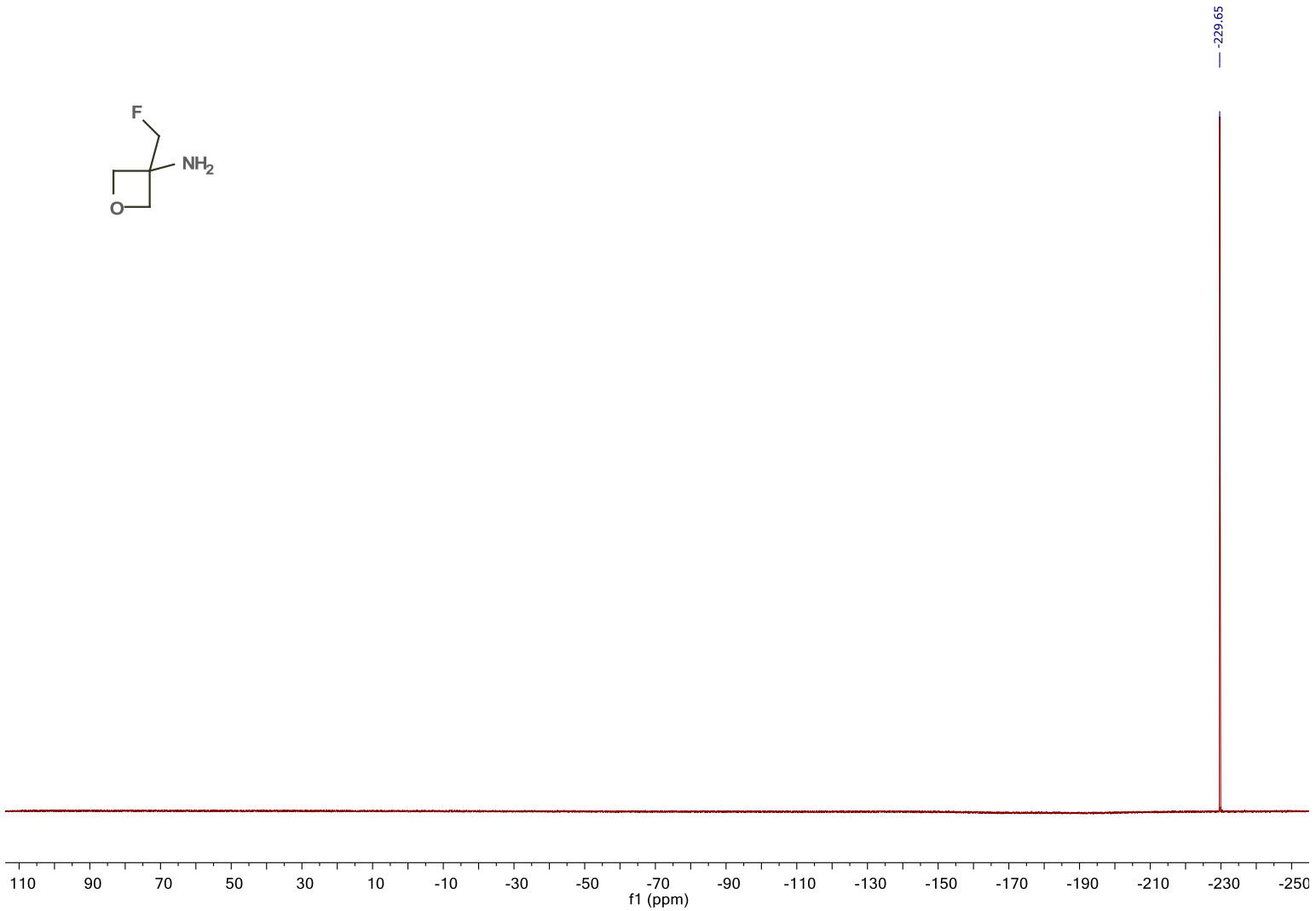
_N,N_-Dibenzyl-3-(fluoromethyl)oxetan-3-amine (31) ^{19}F NMR



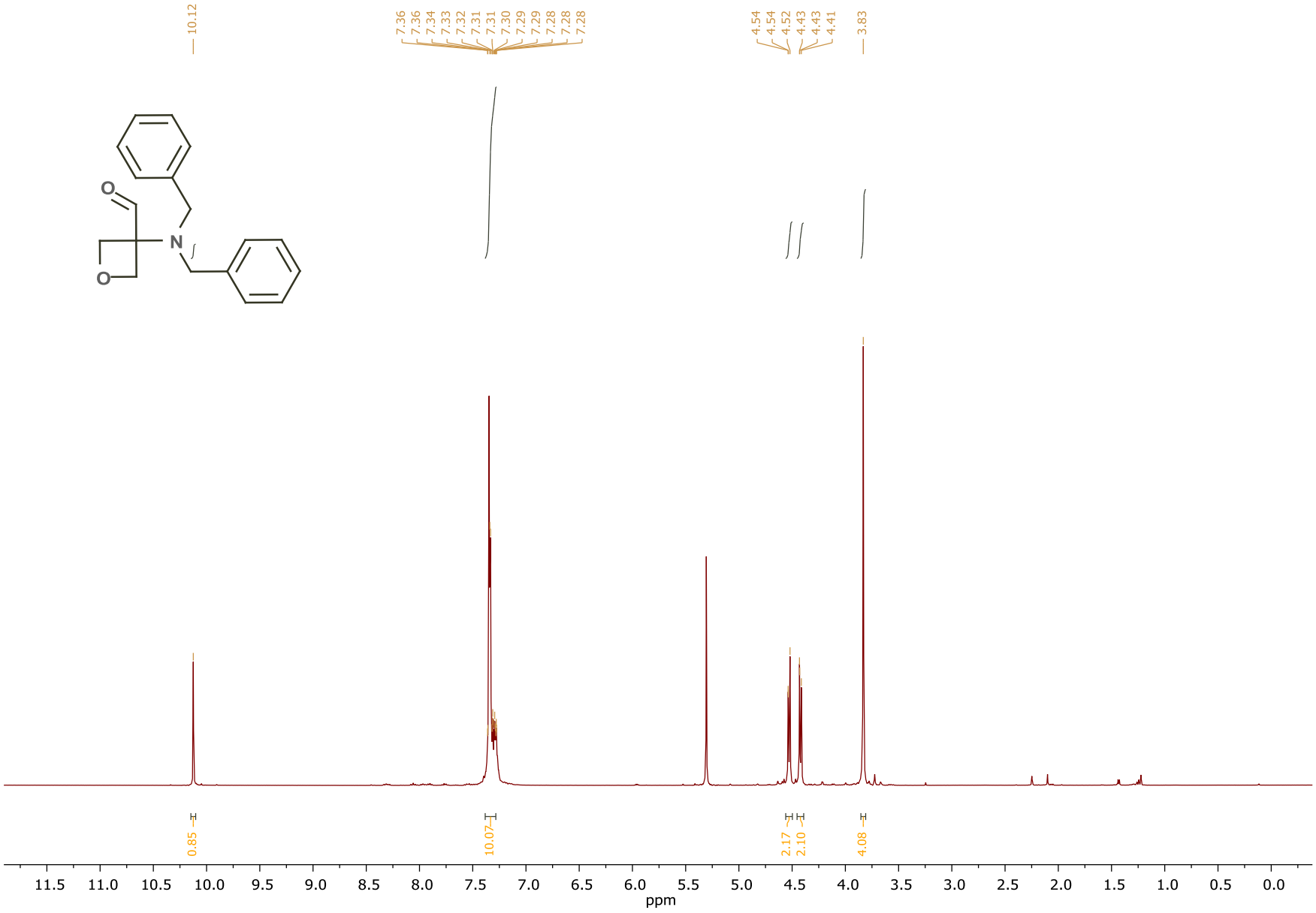
3-(Fluoromethyl)oxetan-3-amine (32) ^{1}H NMR



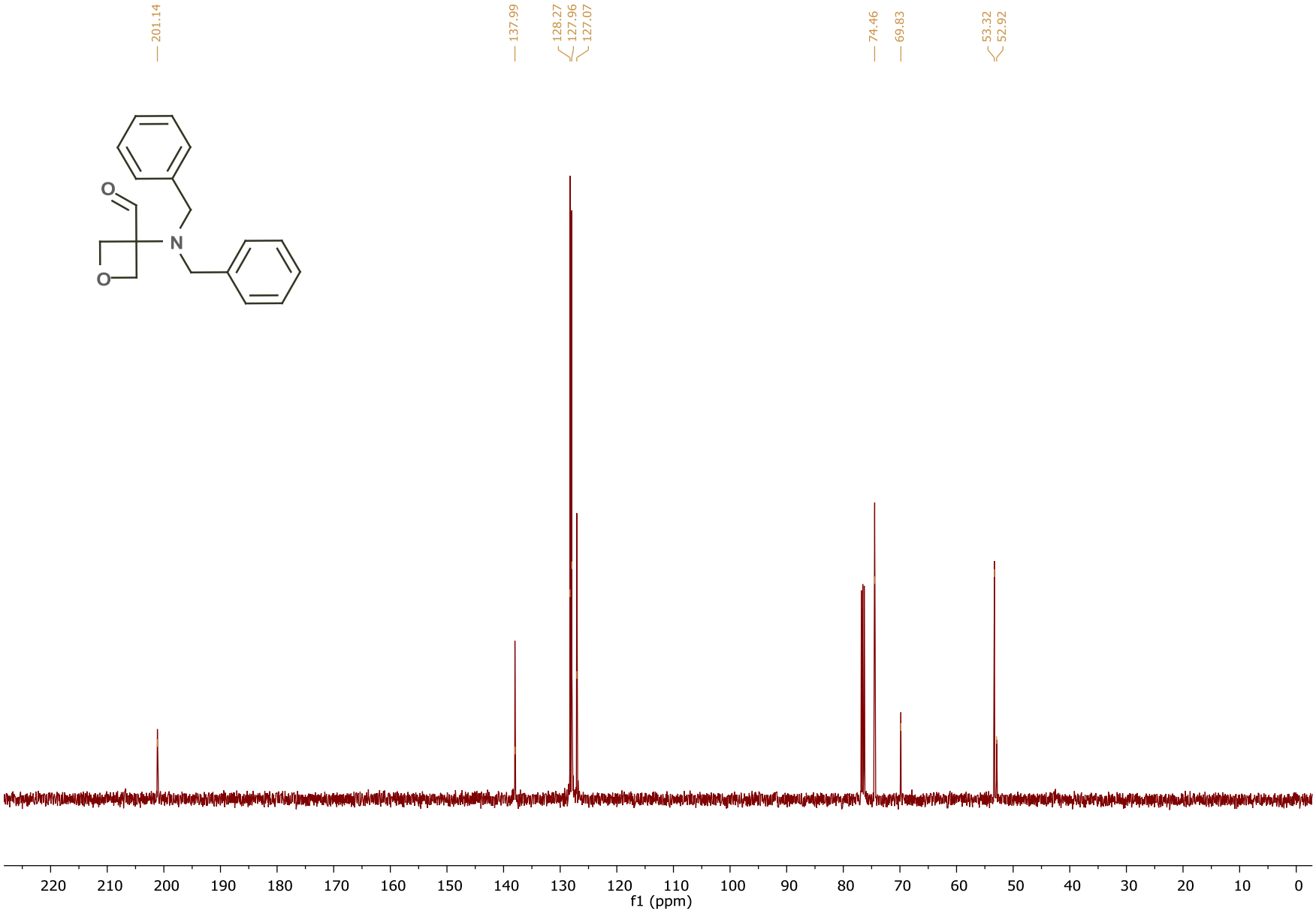
3-(Fluoromethyl)oxetan-3-amine (32) ^{13}C NMR



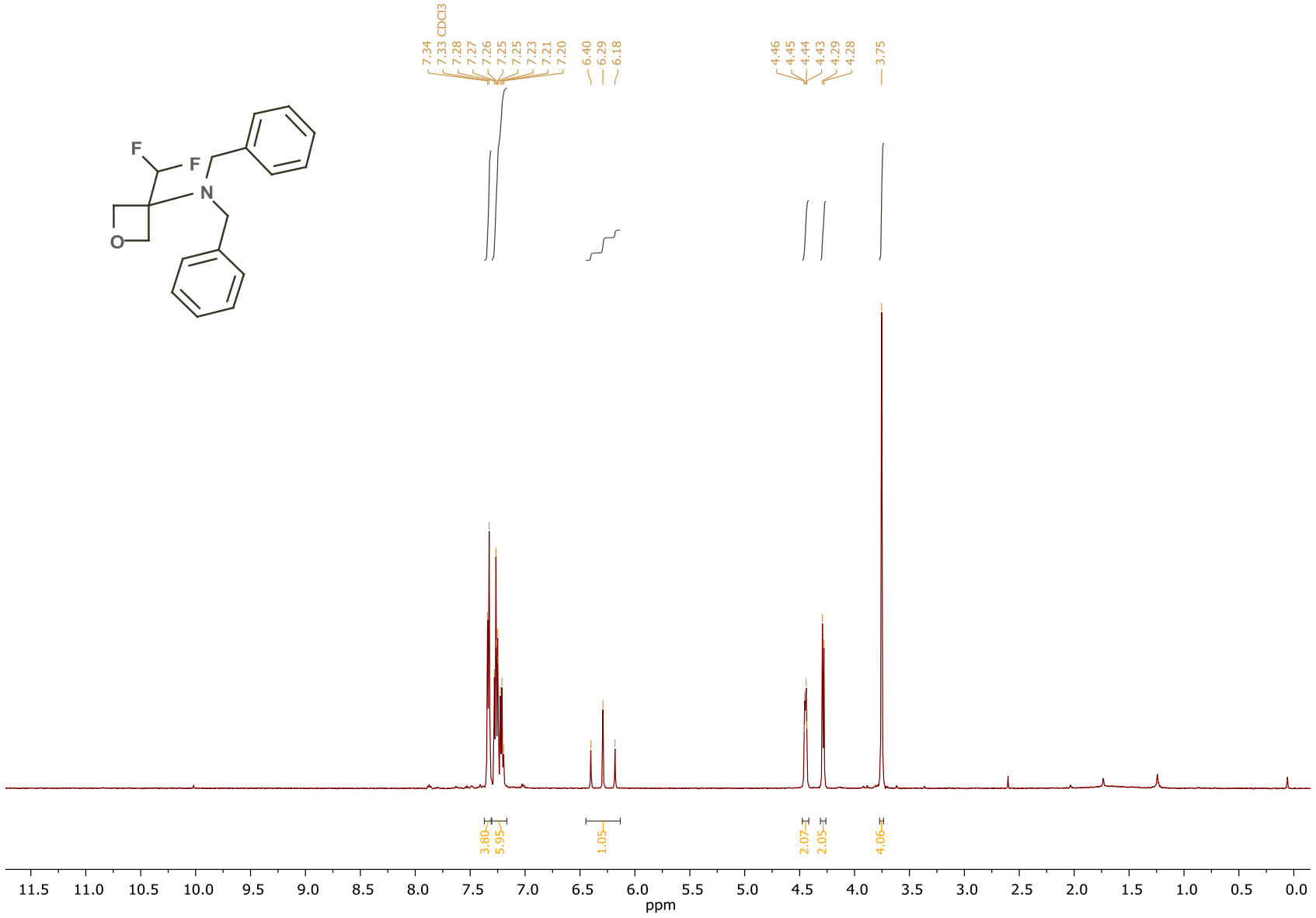
3-(Fluoromethyl)oxetan-3-amine (32) ^{19}F NMR



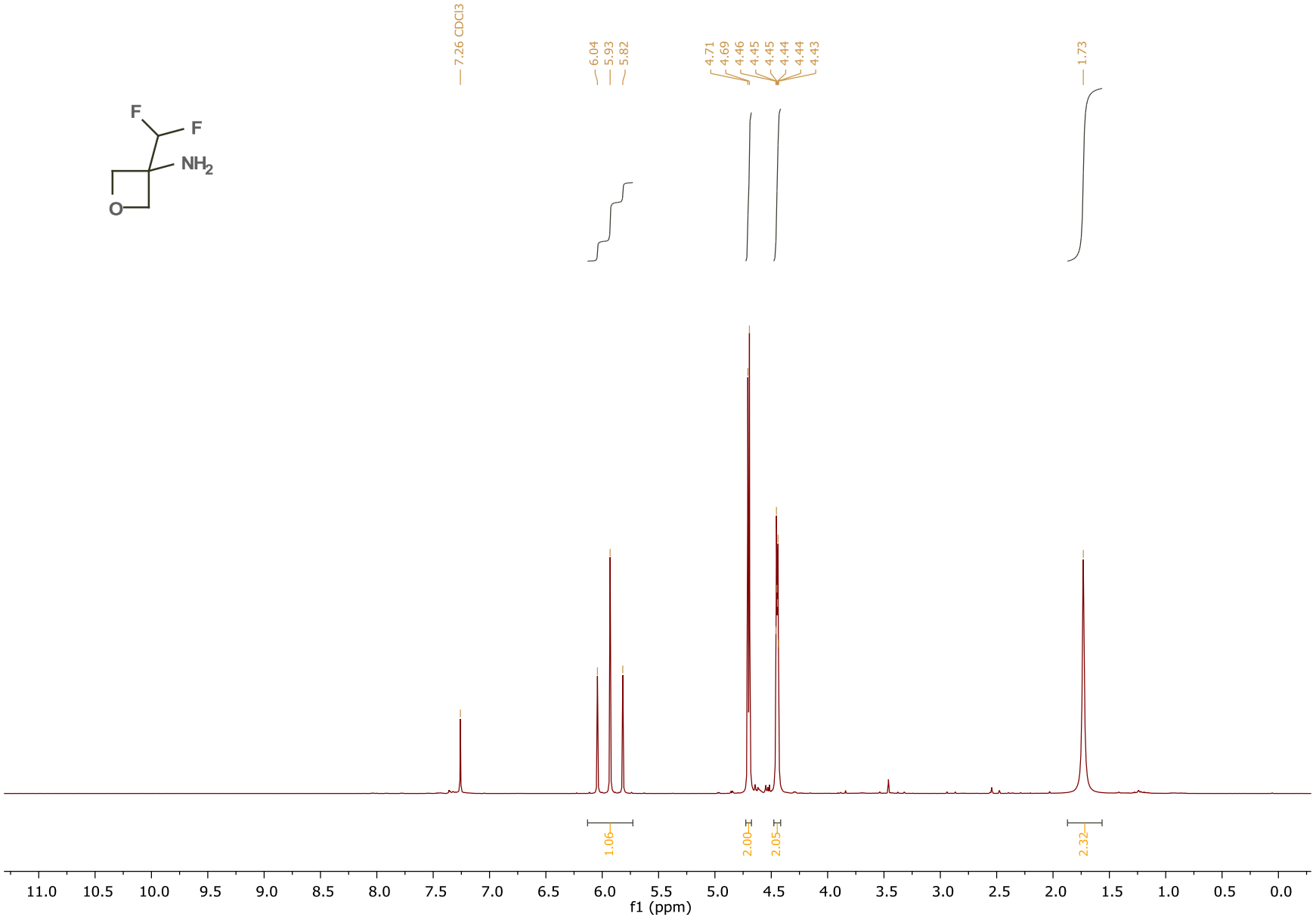
3-(Dibenzylamino)oxetane-3-carbaldehyde (33) ^{1}H NMR



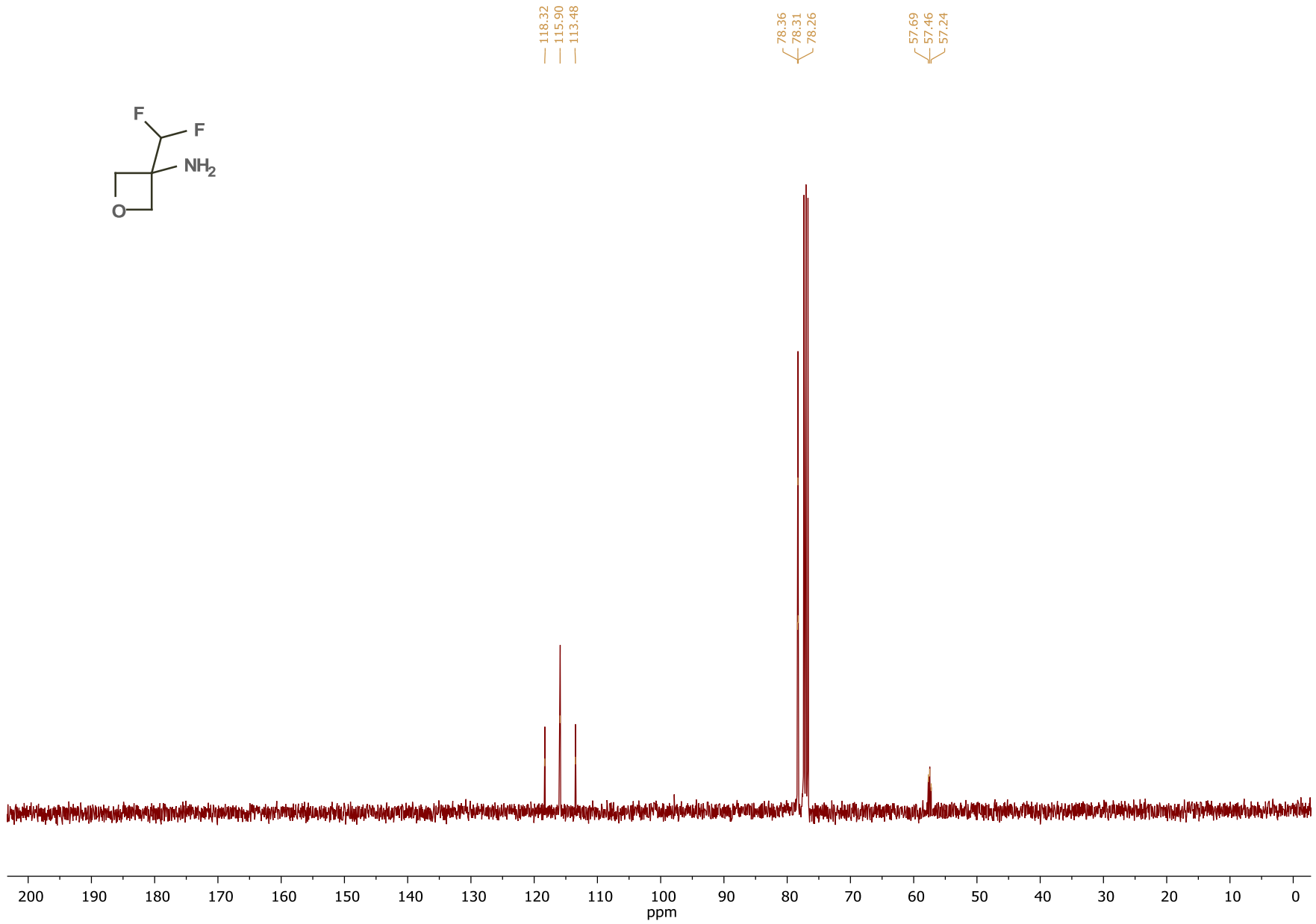
3-(Dibenzylamino)oxetane-3-carbaldehyde (33) ^{1}H NMR



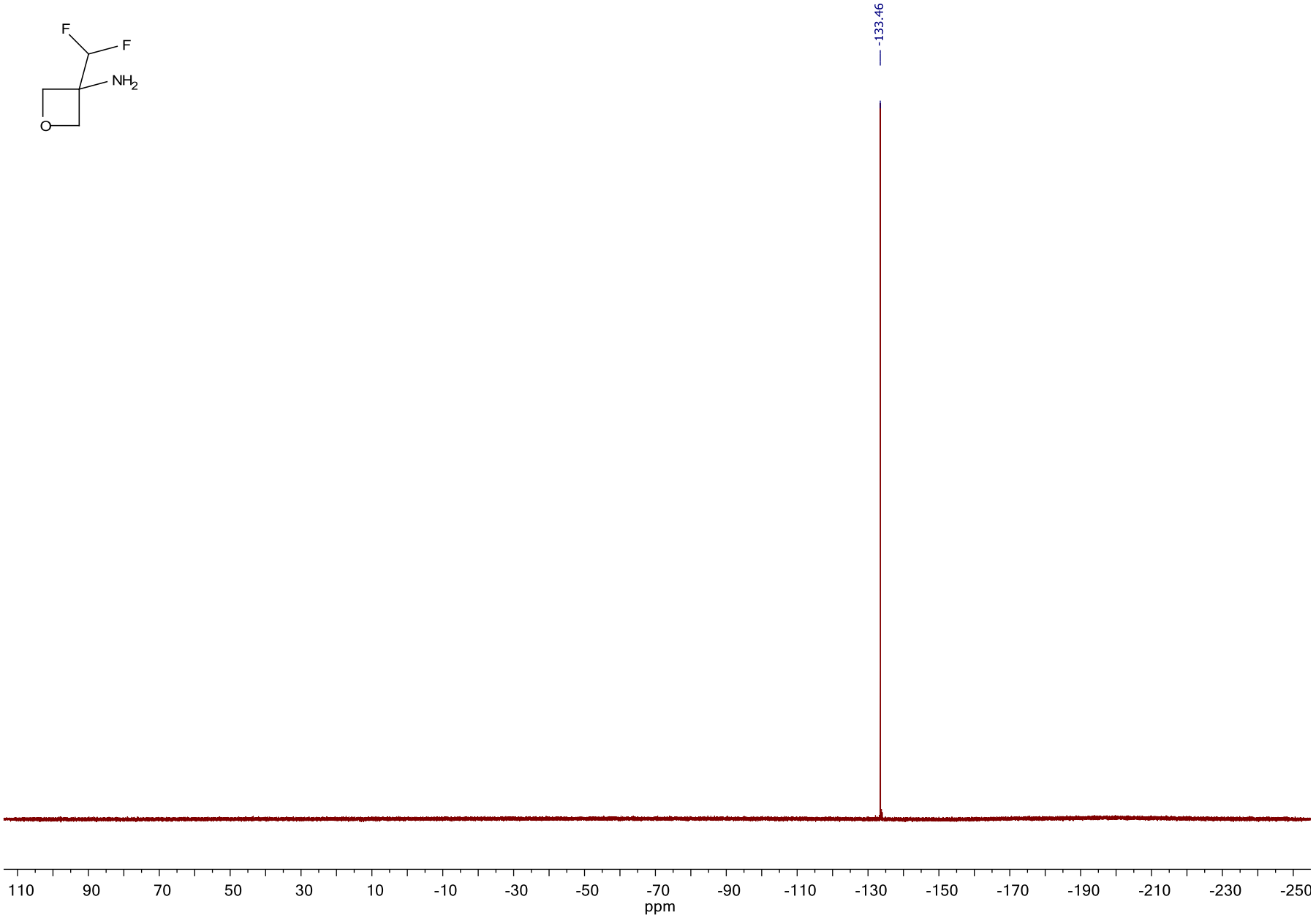
_N,N_-Dibenzyl-3-(difluoromethyl)oxetan-3-amine (34) ^{1}H NMR



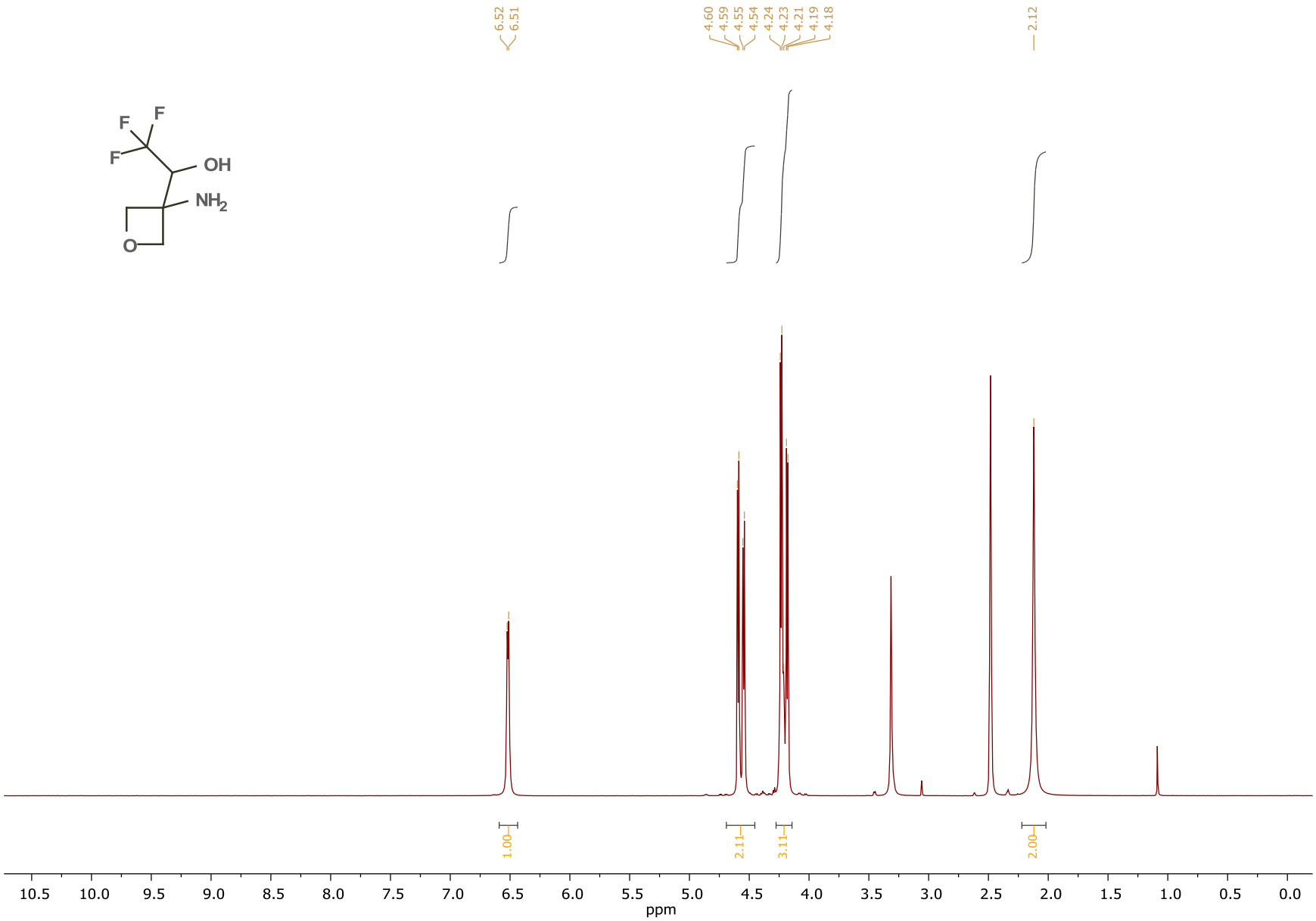
3-(Difluoromethyl)oxetan-3-amine (35) ^{1}H NMR



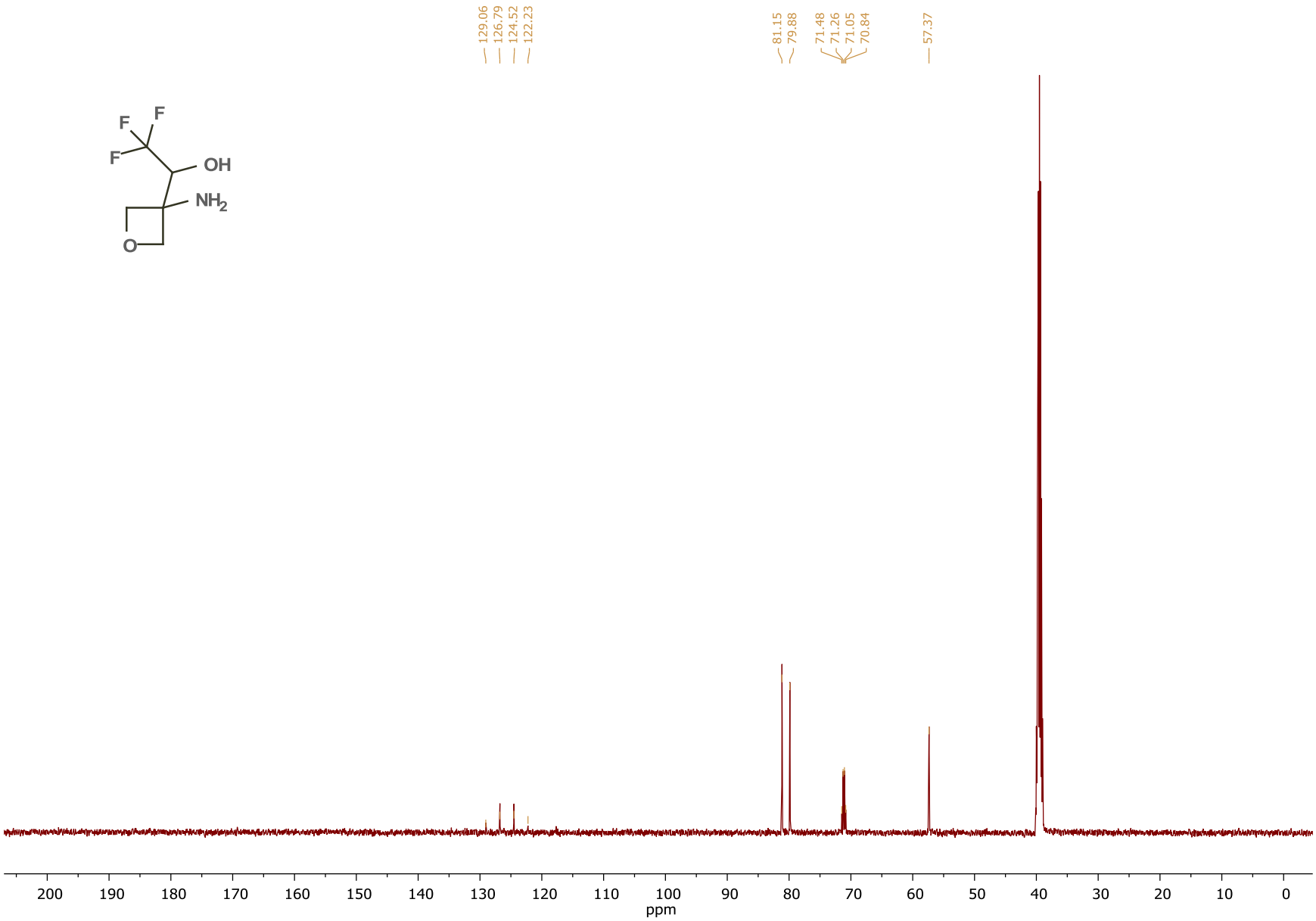
3-(Difluoromethyl)oxetan-3-amine (35) $^{13}C\{H\}$ NMR



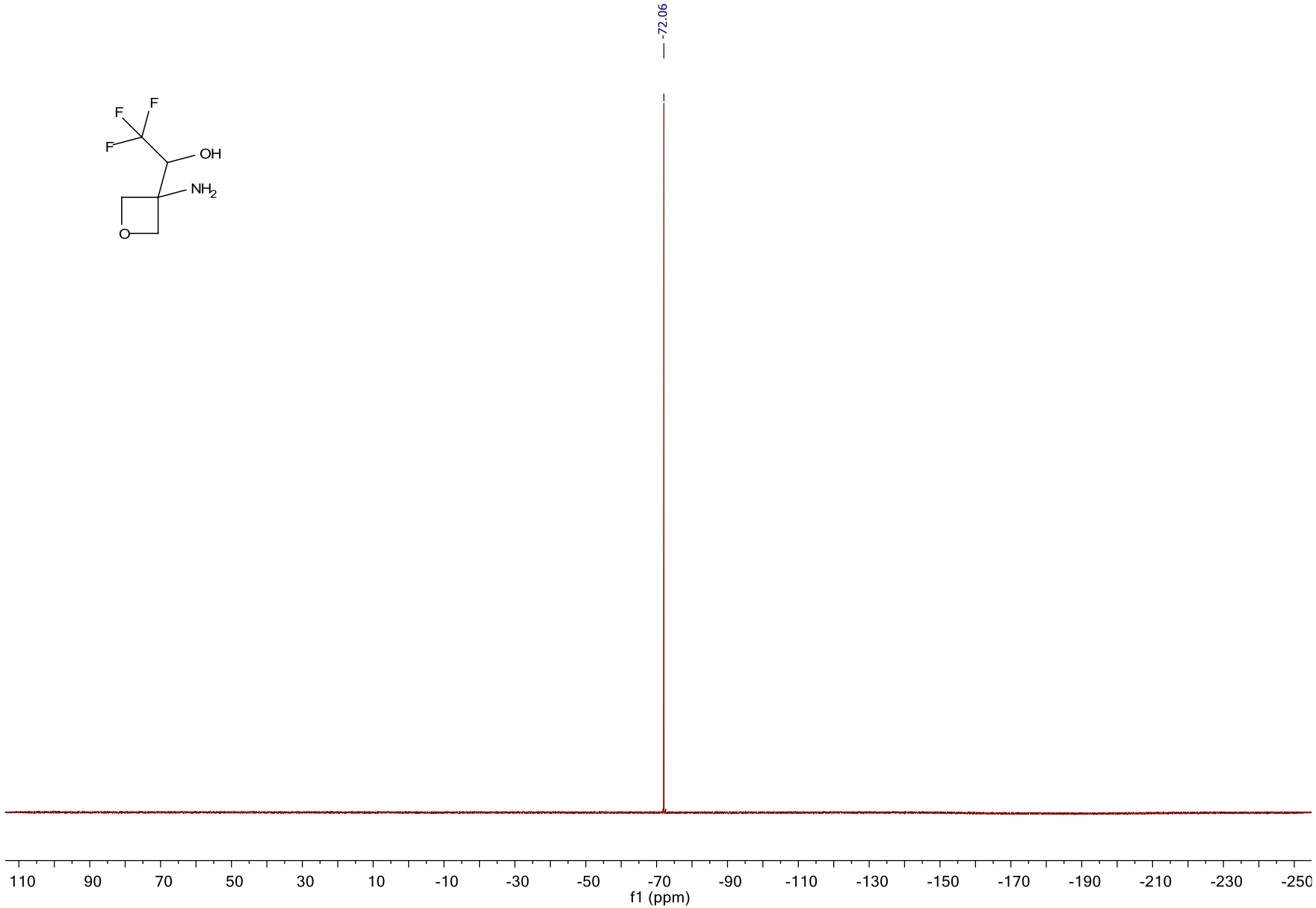
3-(Difluoromethyl)oxetan-3-amine (35) $^{19}F\{H\}$ NMR



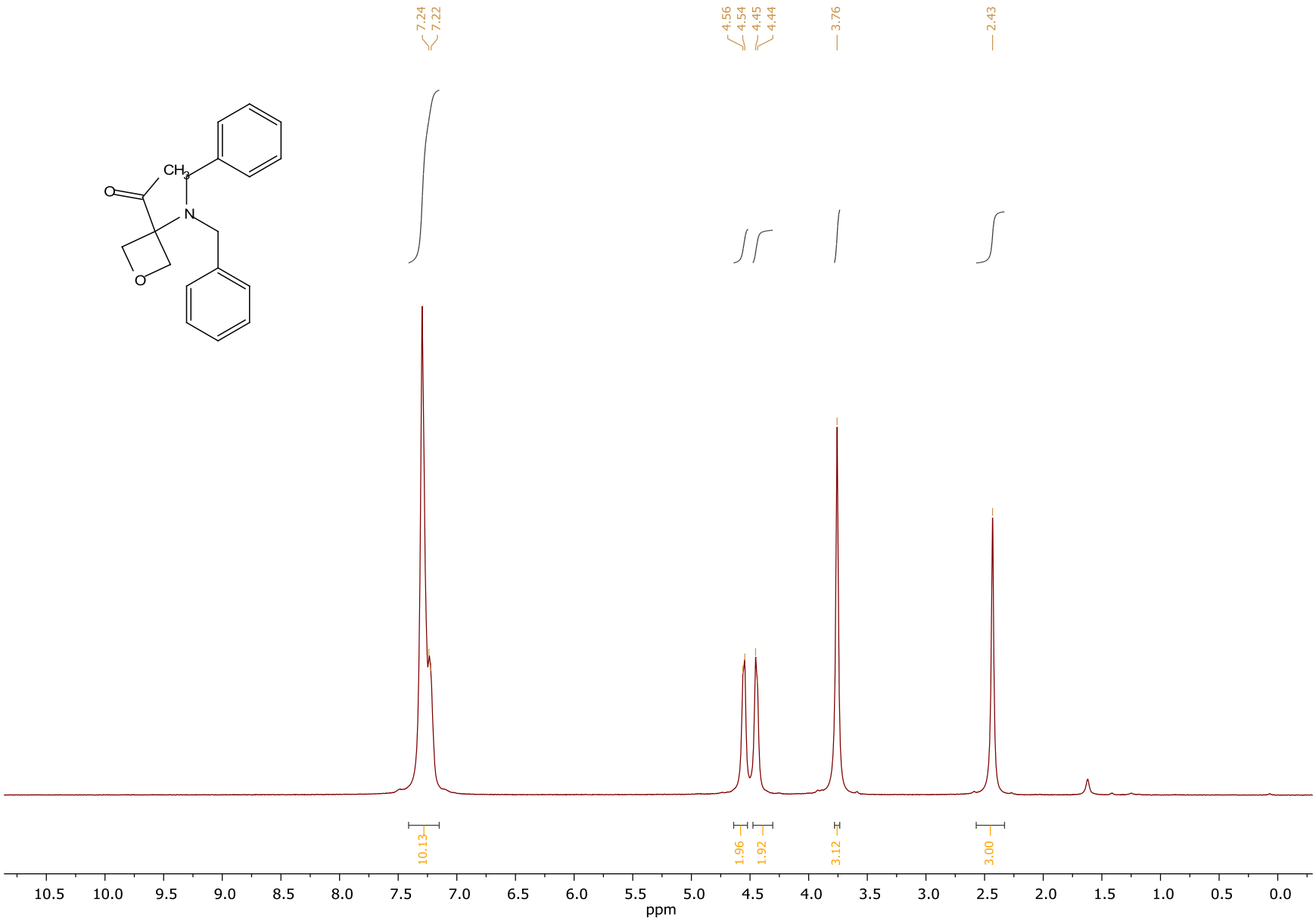
1-(3-Aminooxetan-3-yl)-2,2,2-trifluoroethan-1-ol (37) ^{1}H NMR



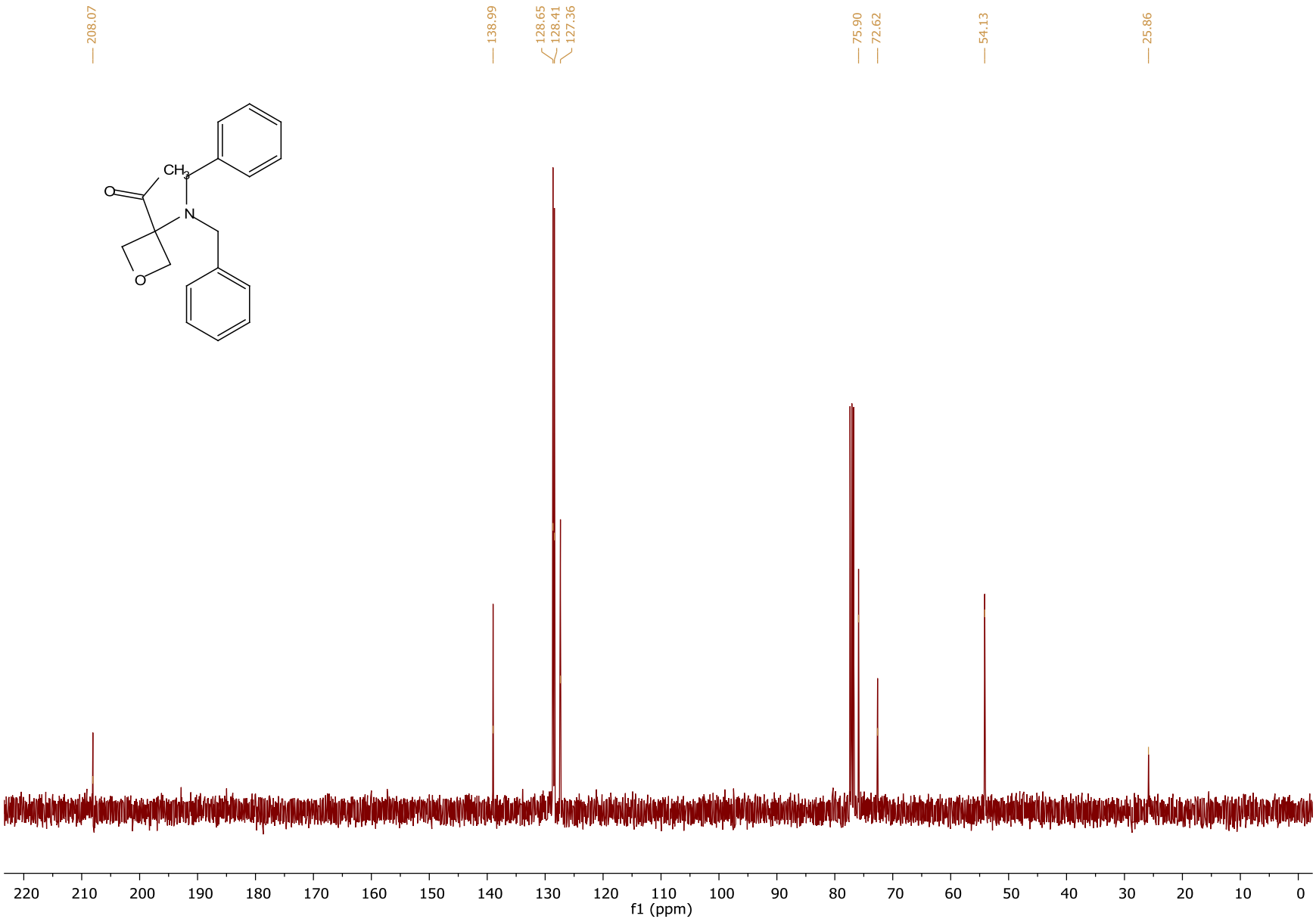
1-(3-Aminooxetan-3-yl)-2,2,2-trifluoroethan-1-ol (37) $^{13}C\{H\}$ NMR



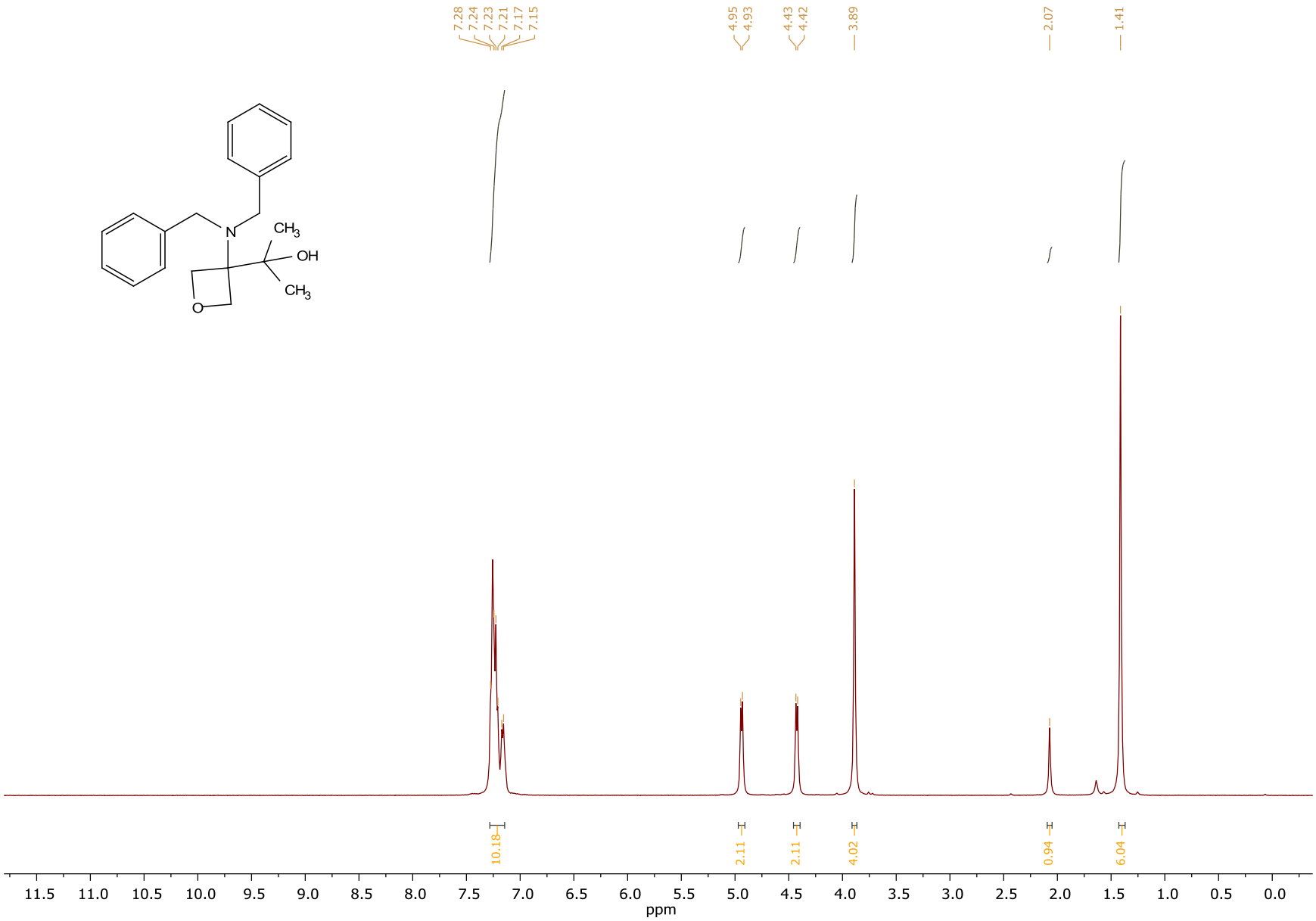
1-(3-Aminooxetan-3-yl)-2,2,2-trifluoroethan-1-ol (37) ^{19}F NMR (376 MHz, DMSO-d_6)



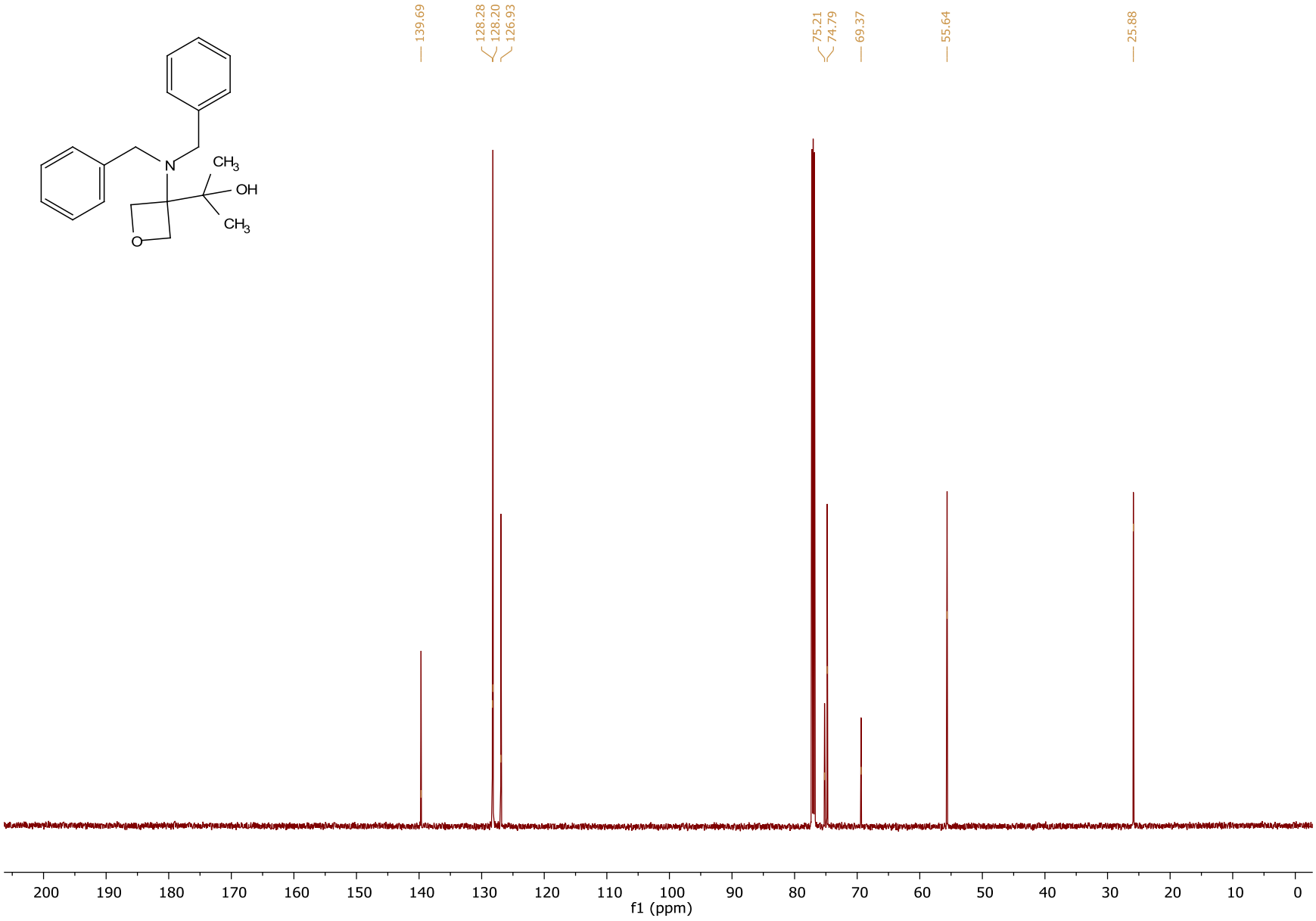
1-(3-(Dibenzylamino)oxetan-3-yl)ethan-1-one (38) ^{1}H NMR



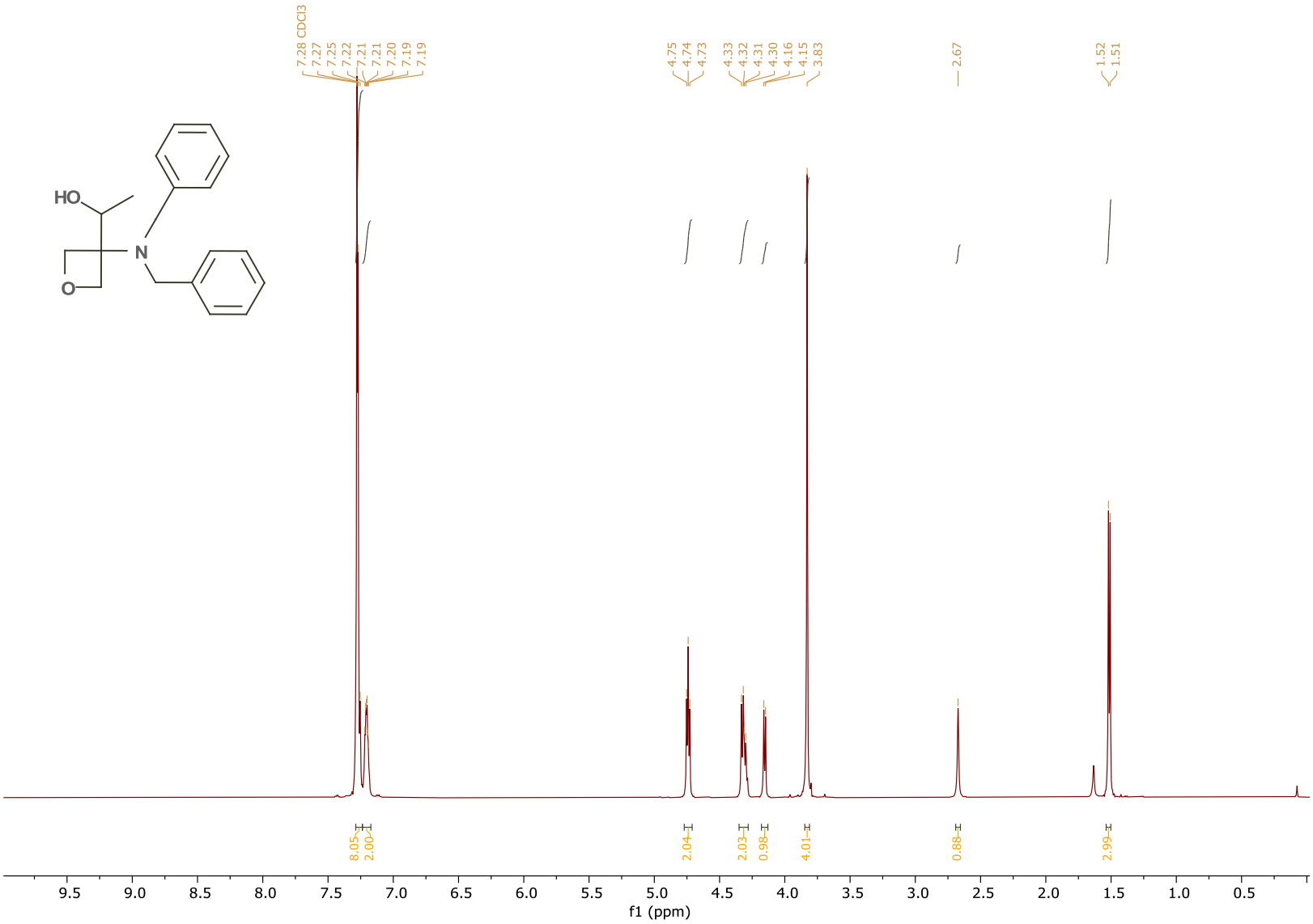
1-(3-(Dibenzylamino)oxetan-3-yl)ethan-1-one (38) ^{1}H NMR



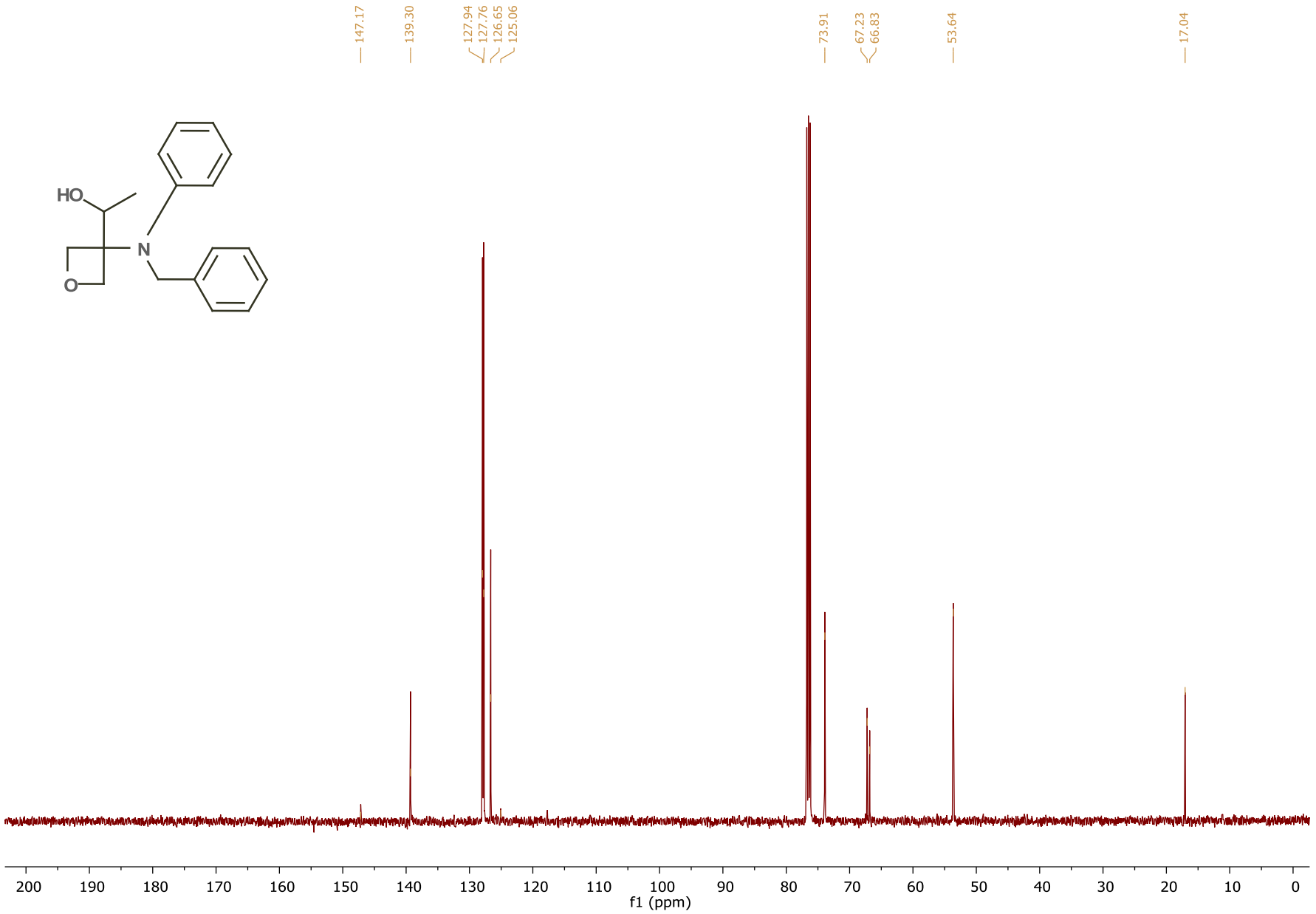
2-(3-(dibenzylamino)oxetan-3-yl)propan-2-ol (39) ^{1}H NMR



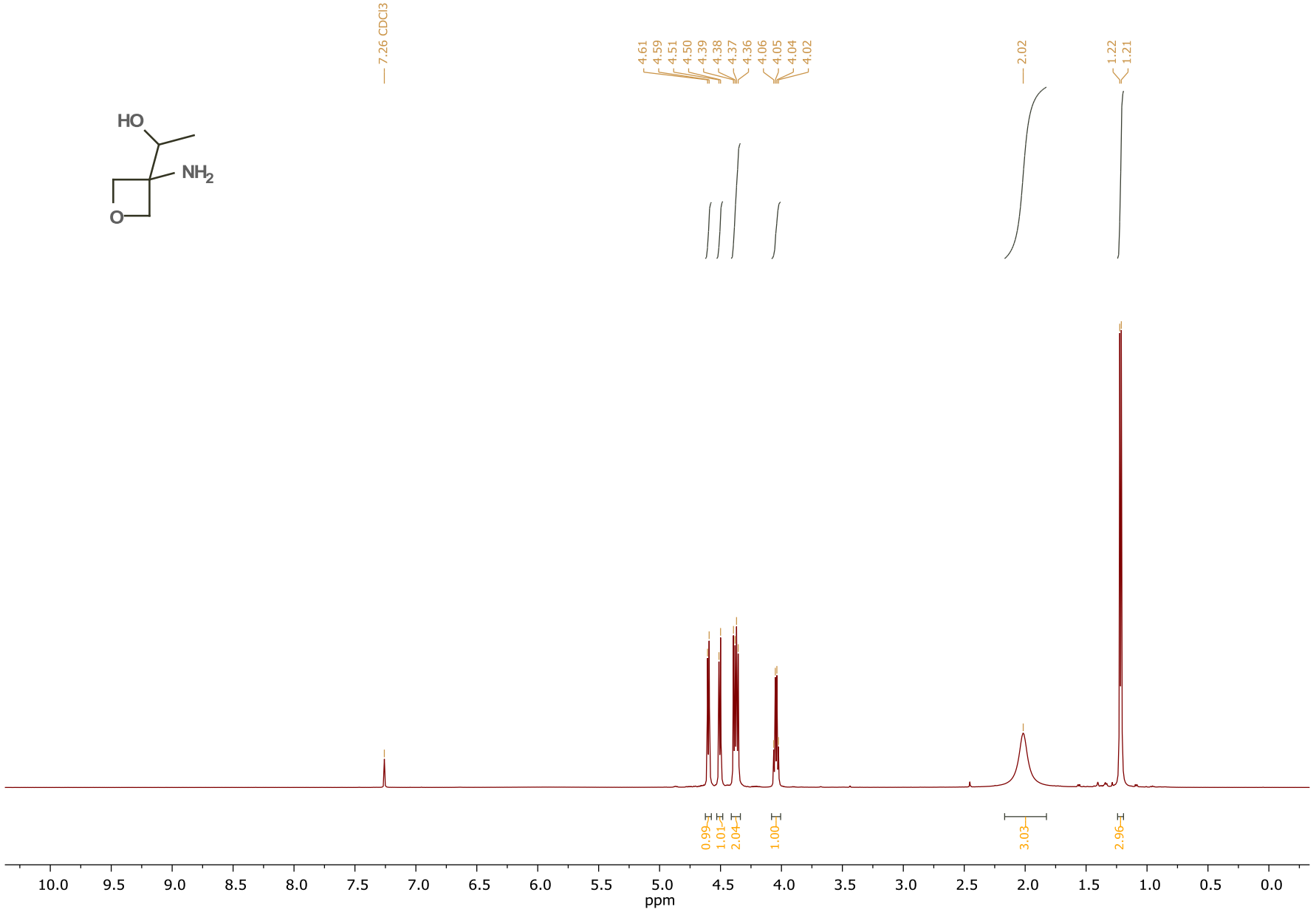
2-(3-(dibenzylamino)oxetan-3-yl)propan-2-ol (39) ^{13}C NMR



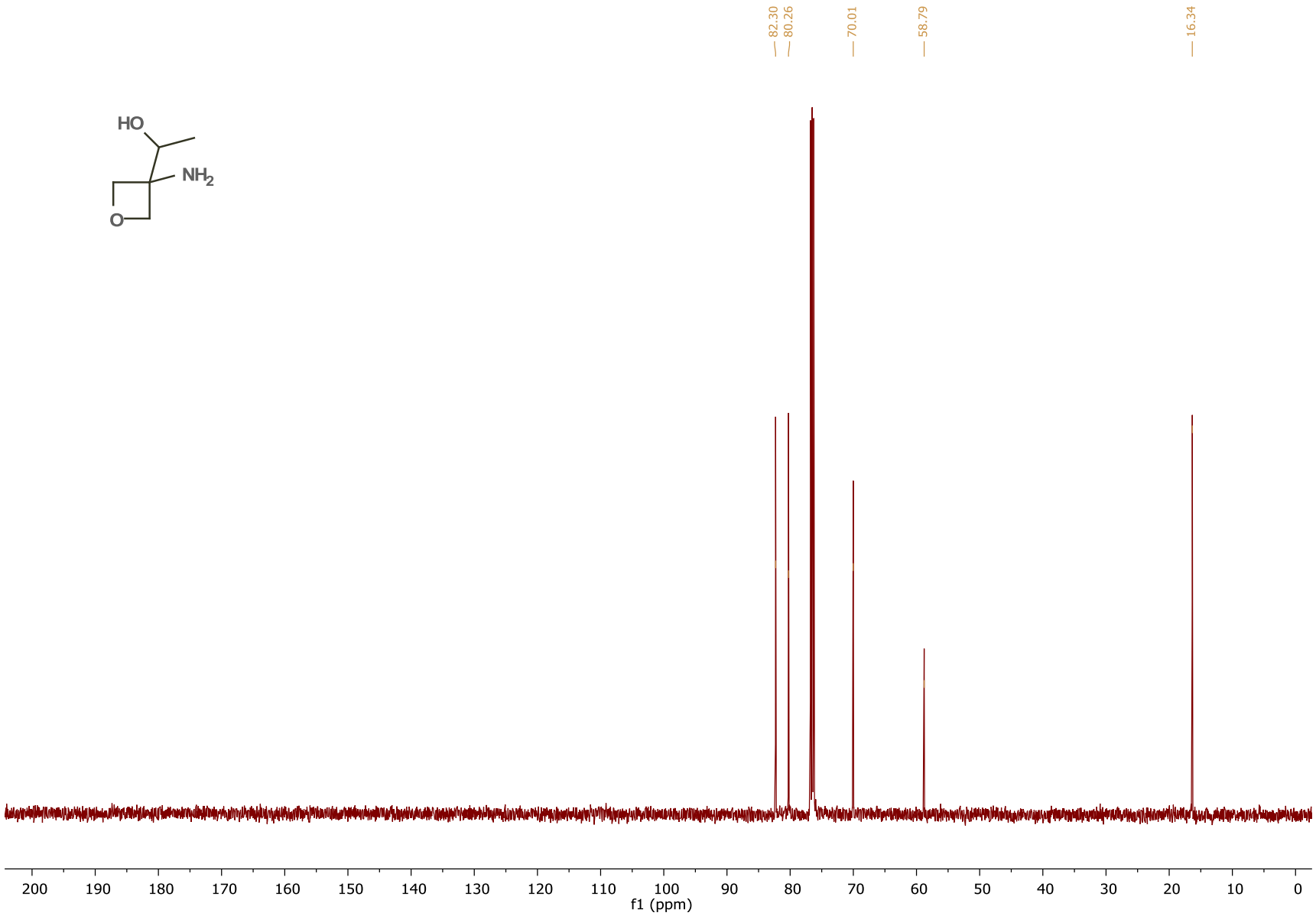
1-(3-(Dibenzylamino)oxetan-3-yl)ethan-1-ol (40) ^{1}H NMR



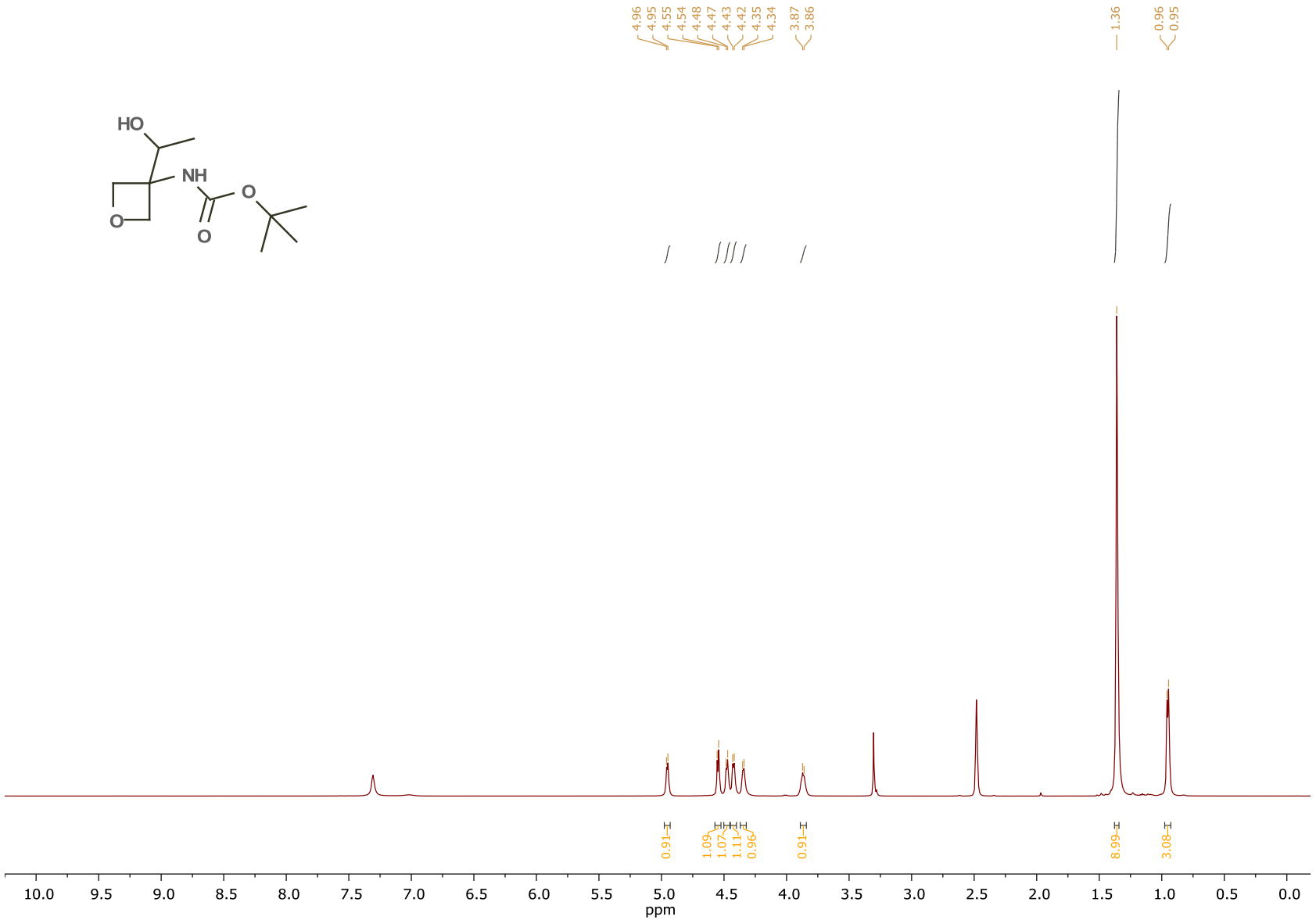
1-(3-(Dibenzylamino)oxetan-3-yl)ethan-1-ol (40) ^{13}C NMR



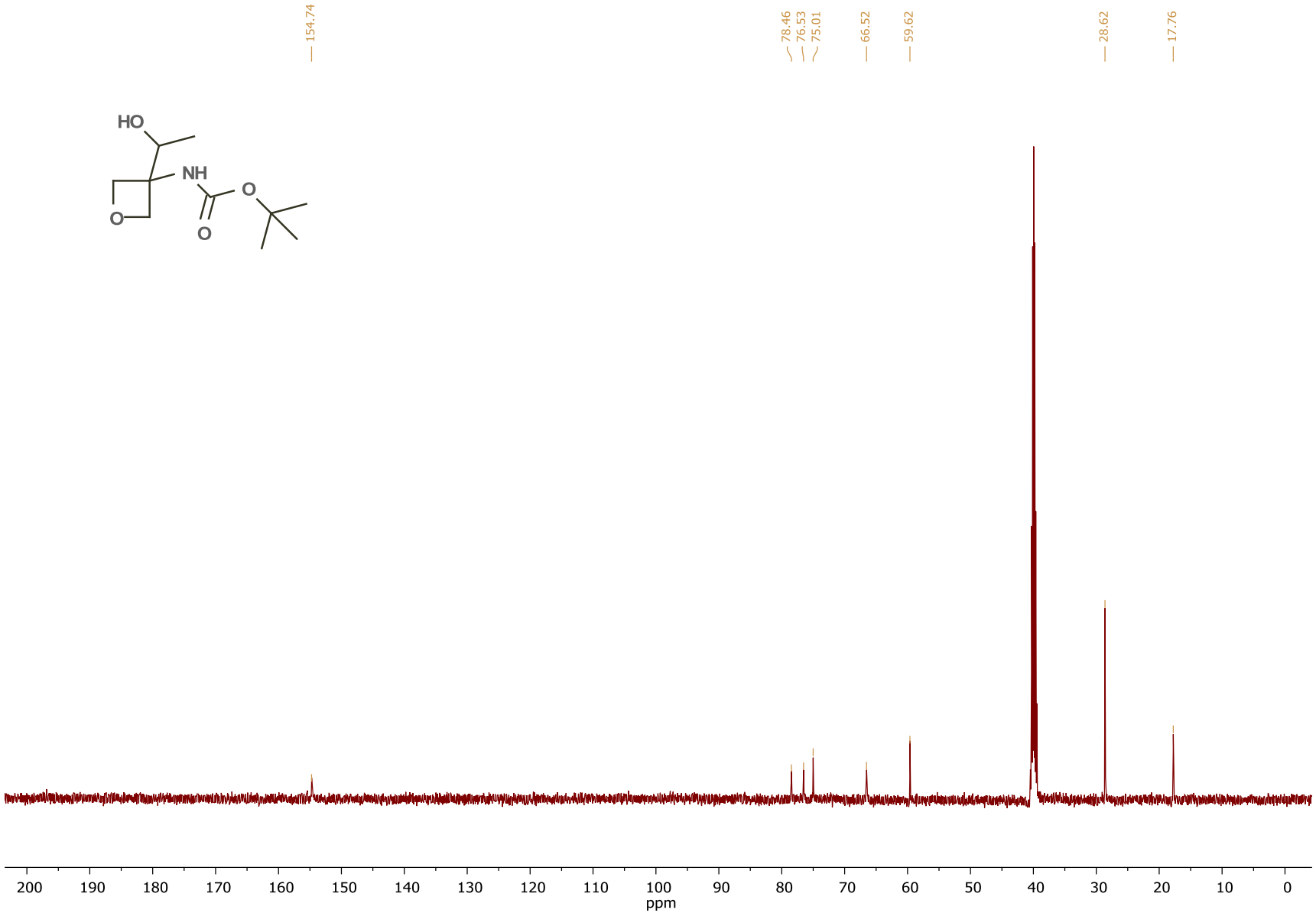
1-(3-Aminooxetan-3-yl)ethan-1-ol (41) ^{1}H NMR



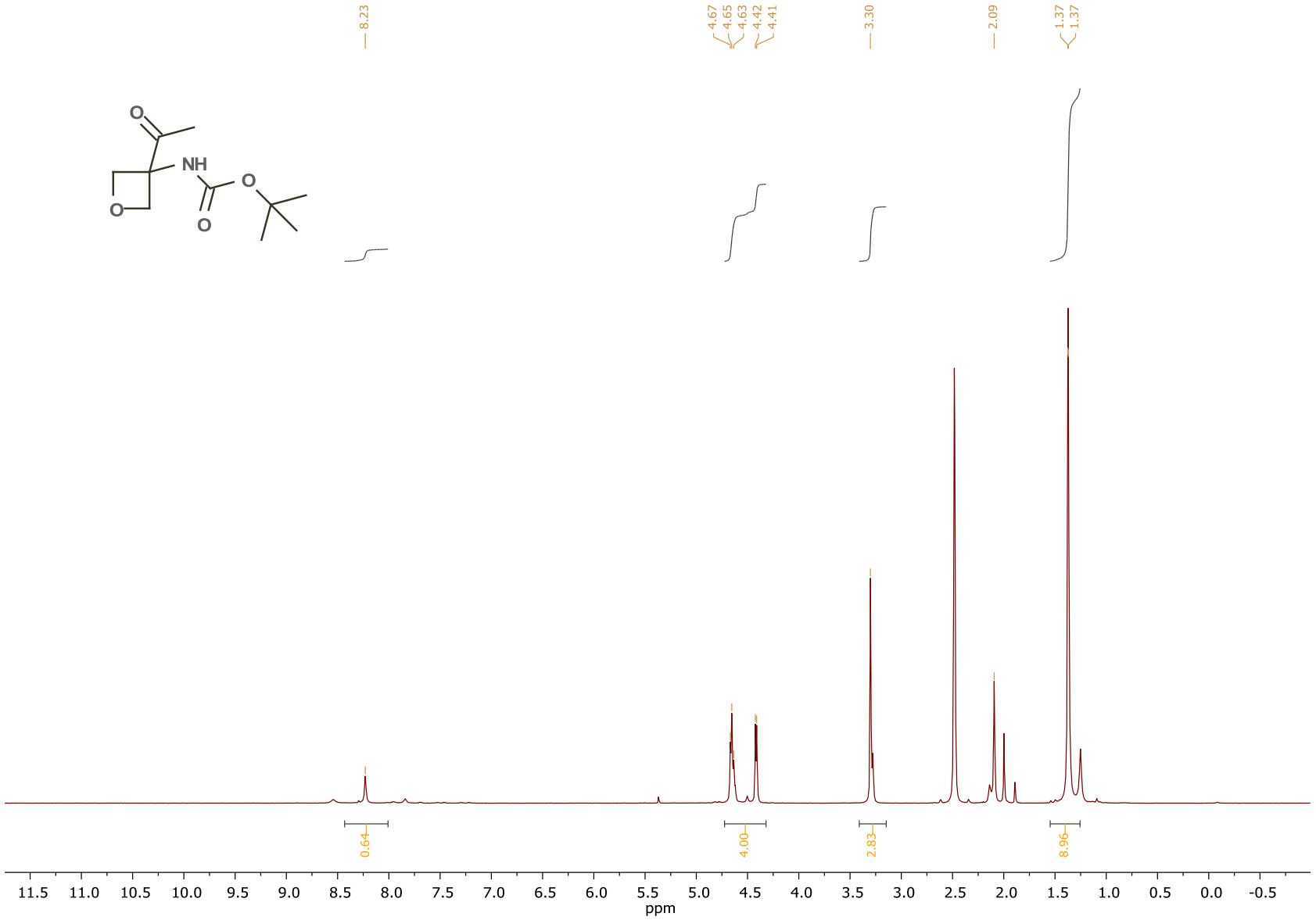
1-(3-Aminooxetan-3-yl)ethan-1-ol (41) $^{13}C\{H\}$ NMR



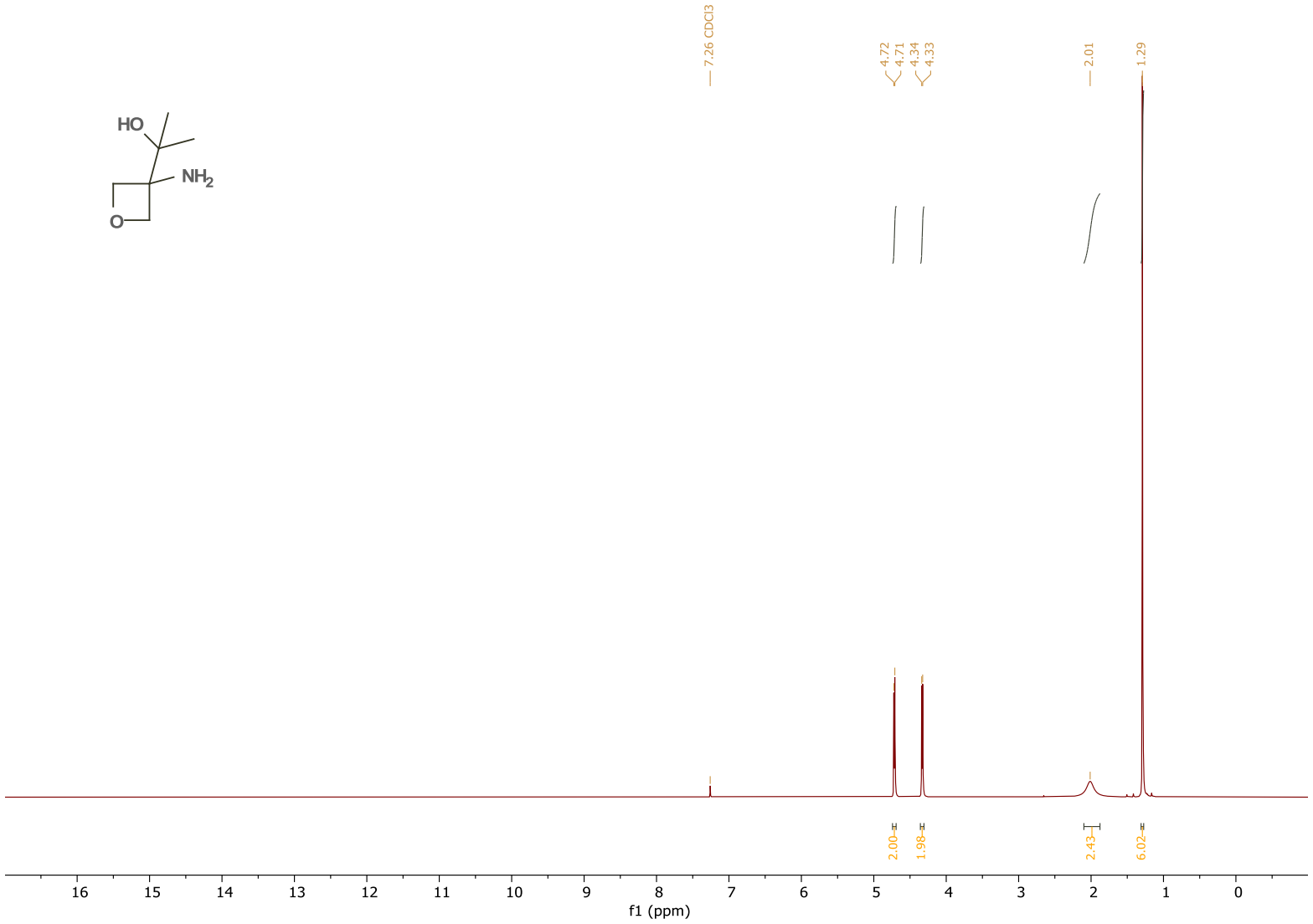
tert-Butyl _N_-[3-(1-hydroxyethyl)oxetan-3-yl]carbamate (42) ^{1}H NMR



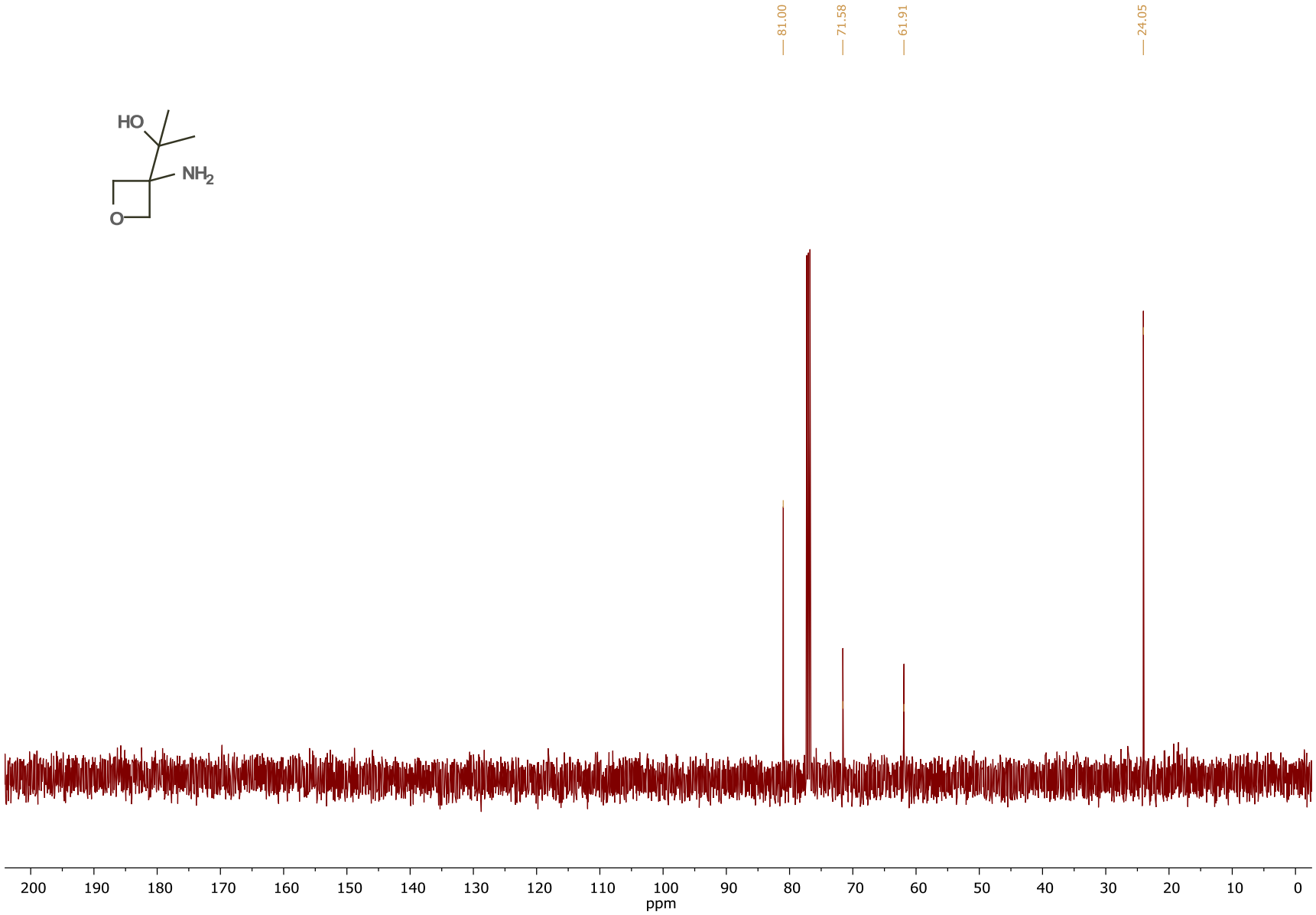
tert-Butyl _N_-[3-(1-hydroxyethyl)oxetan-3-yl]carbamate (42) $^{13}C\{H\}$ NMR



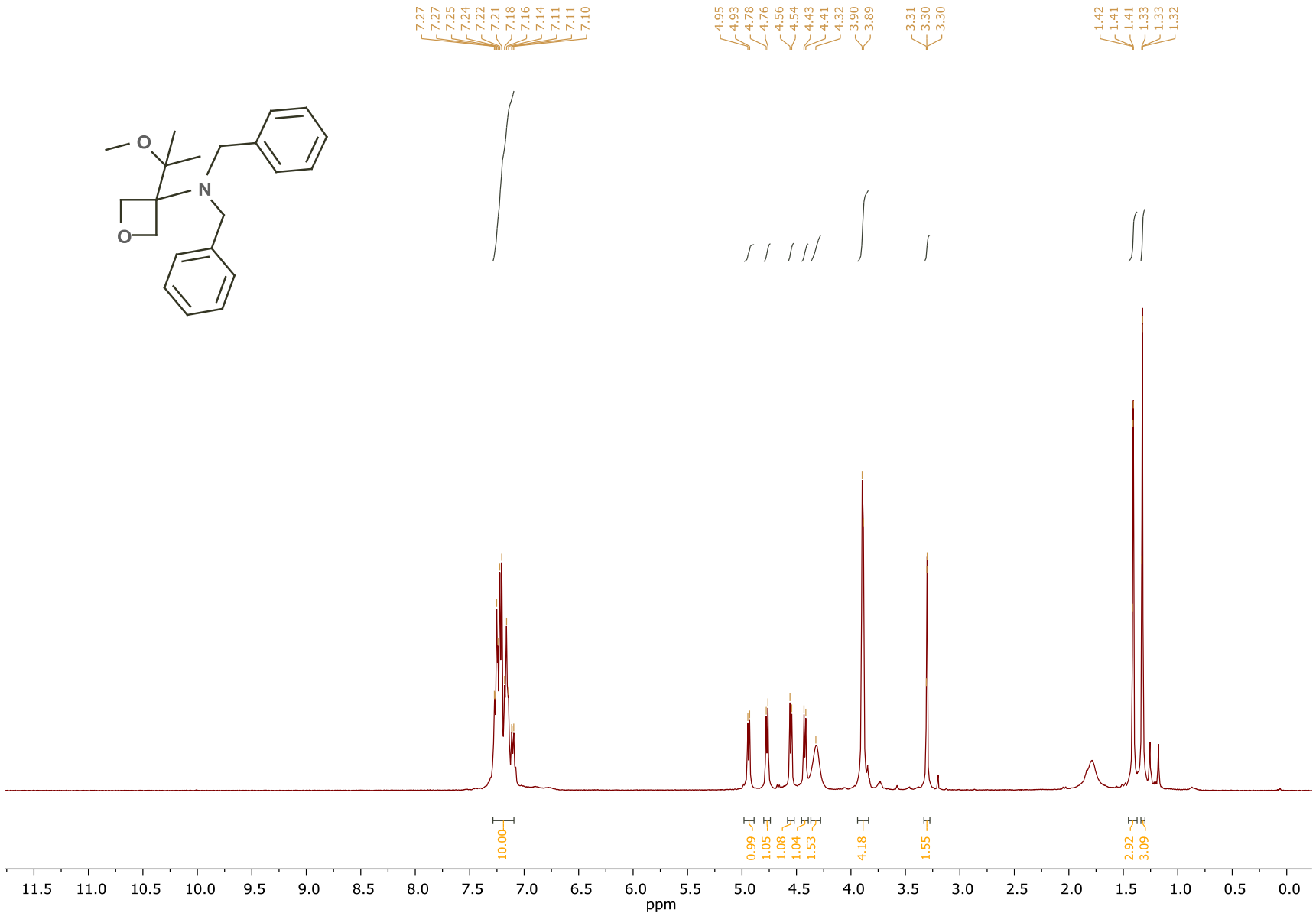
tert-Butyl _N_-(3-acetyloxetan-3-yl)carbamate (43) ^{1}H NMR (crude)



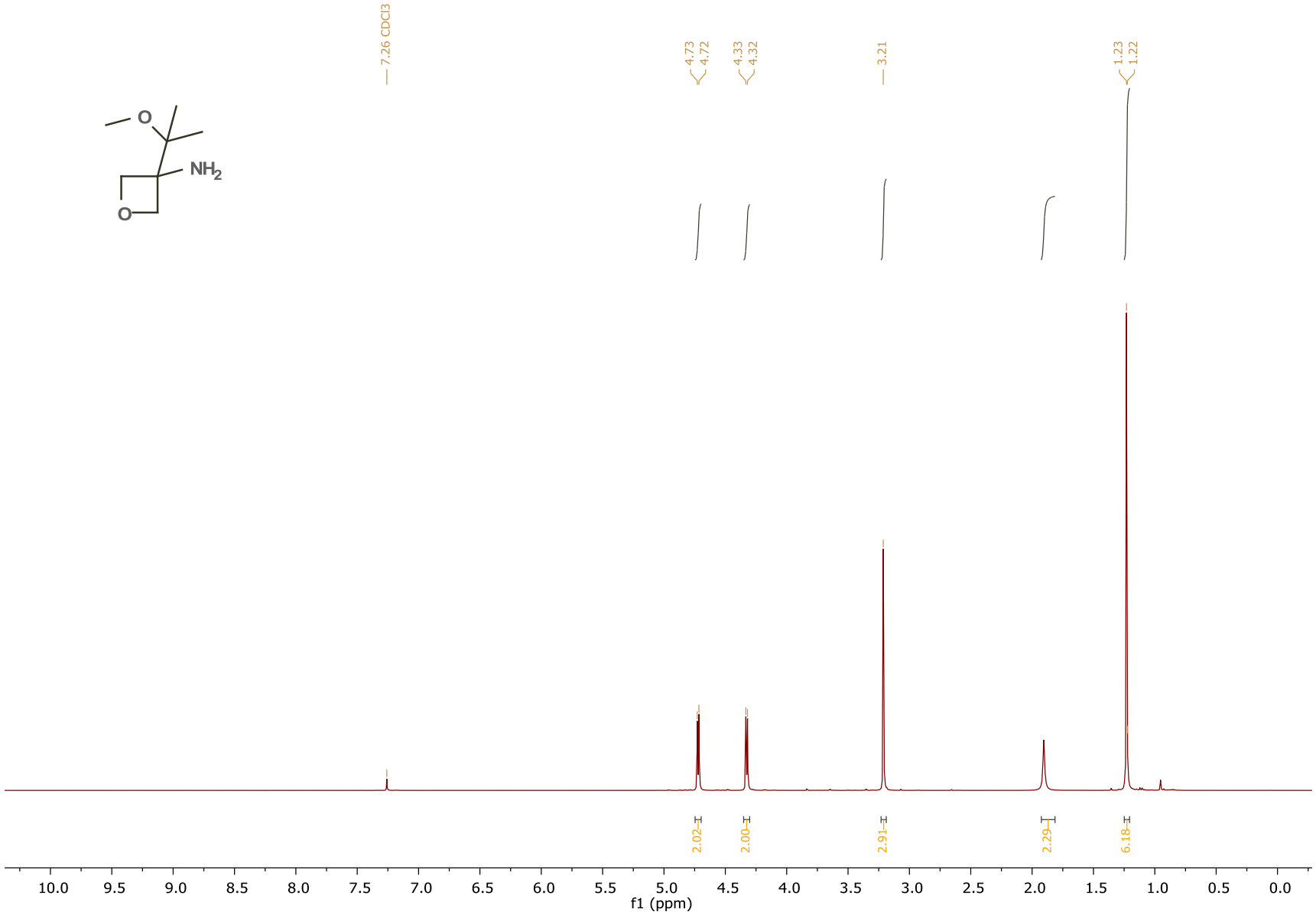
2-(3-Aminooxetan-3-yl)propan-2-ol (44) ^{1}H NMR



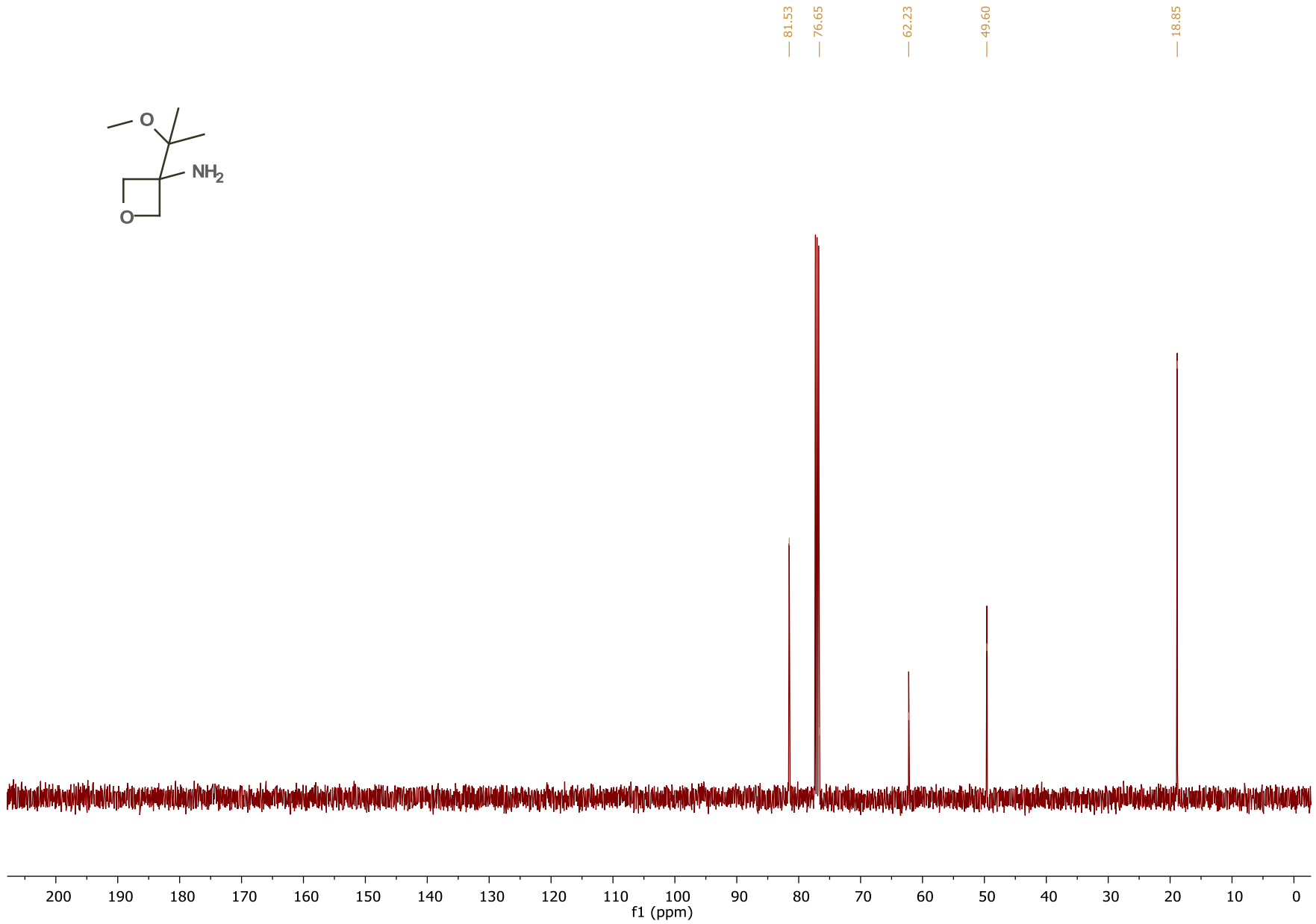
2-(3-Aminooxetan-3-yl)propan-2-ol (44) $^{13}C\{H\}$ NMR



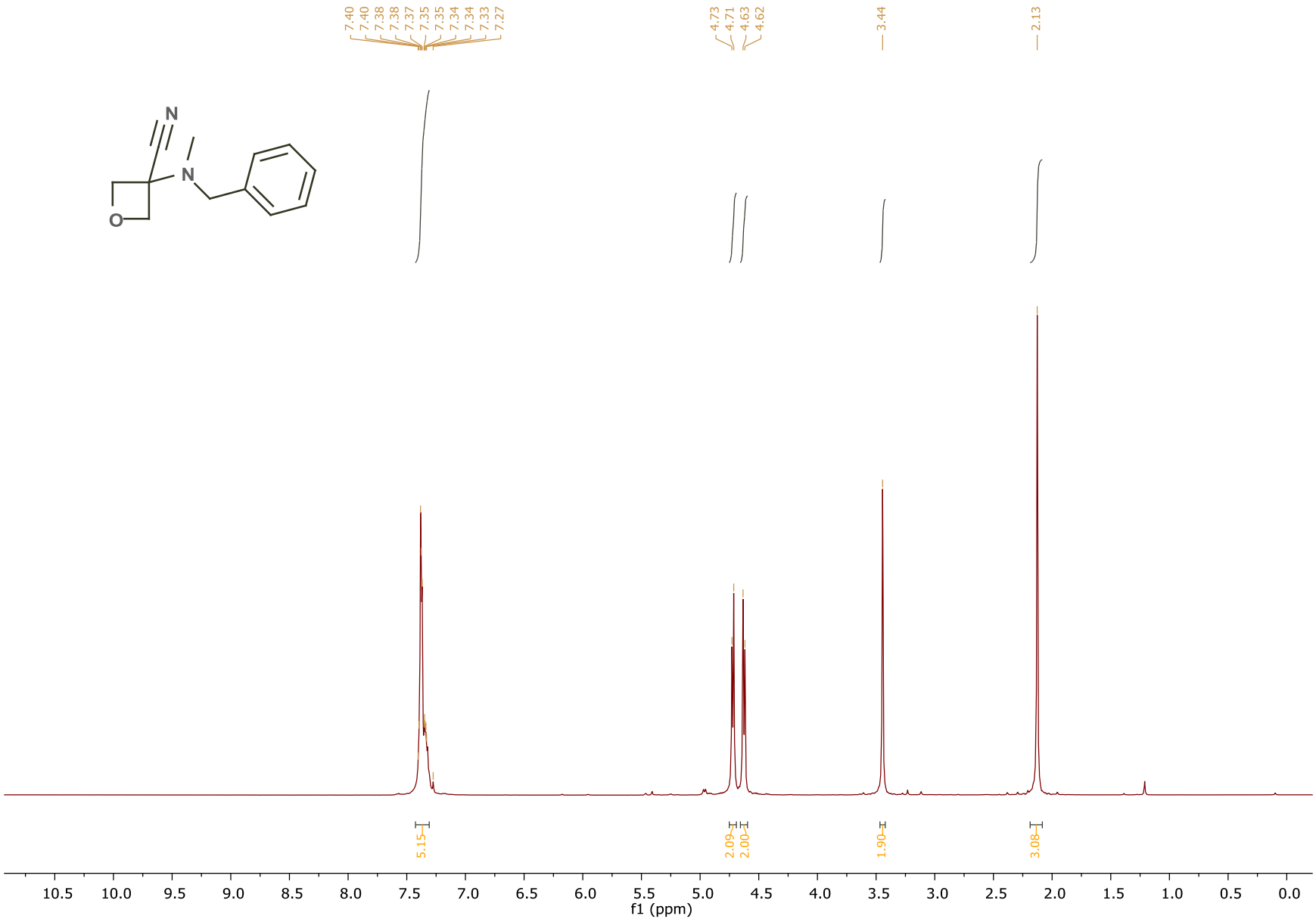
_N,N_-Dibenzyl-3-(2-methoxypropan-2-yl)oxetan-3-amine (45) ^{1}H NMR



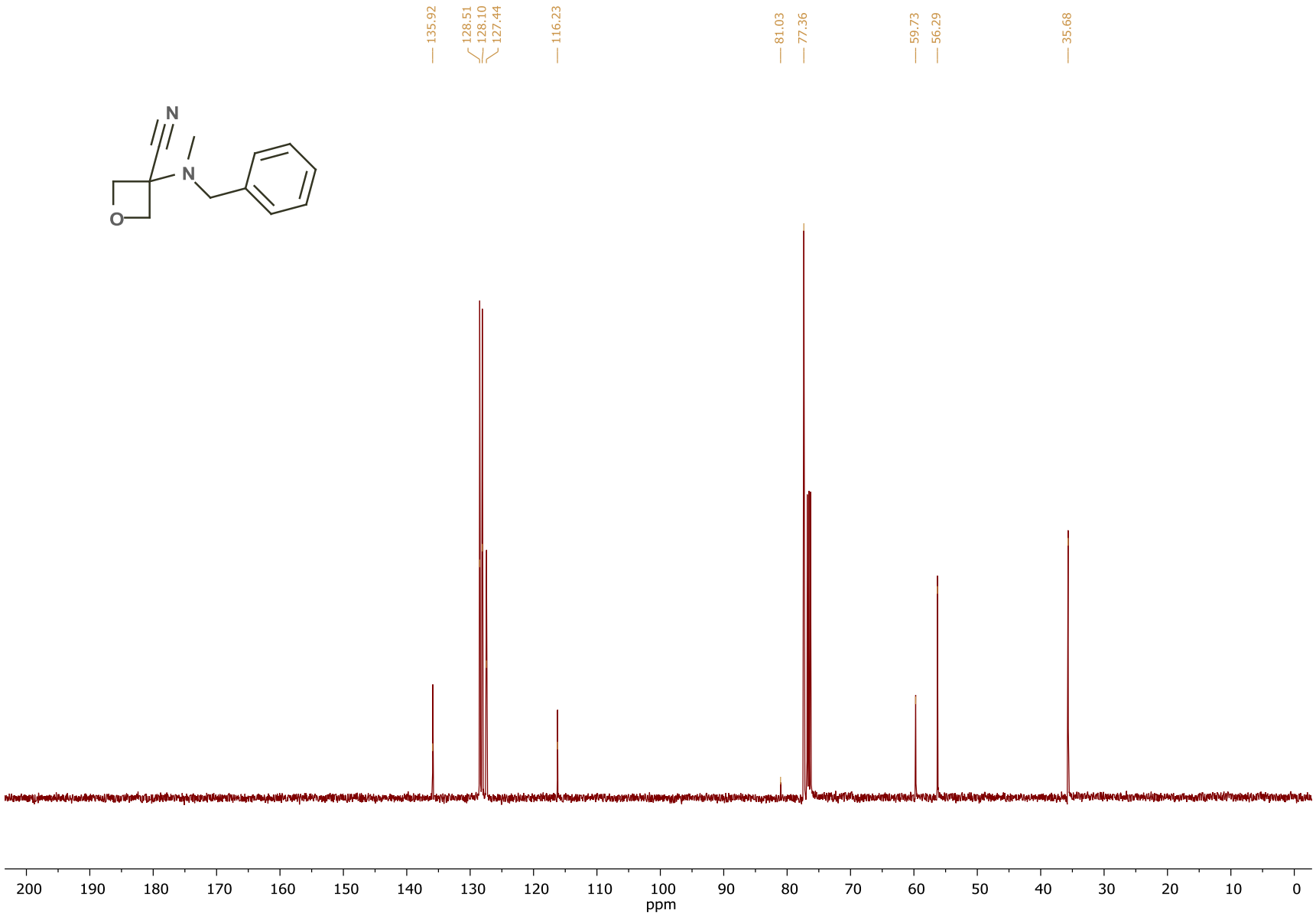
3-(2-Methoxypropan-2-yl)oxetan-3-amine (46) ^{1}H NMR



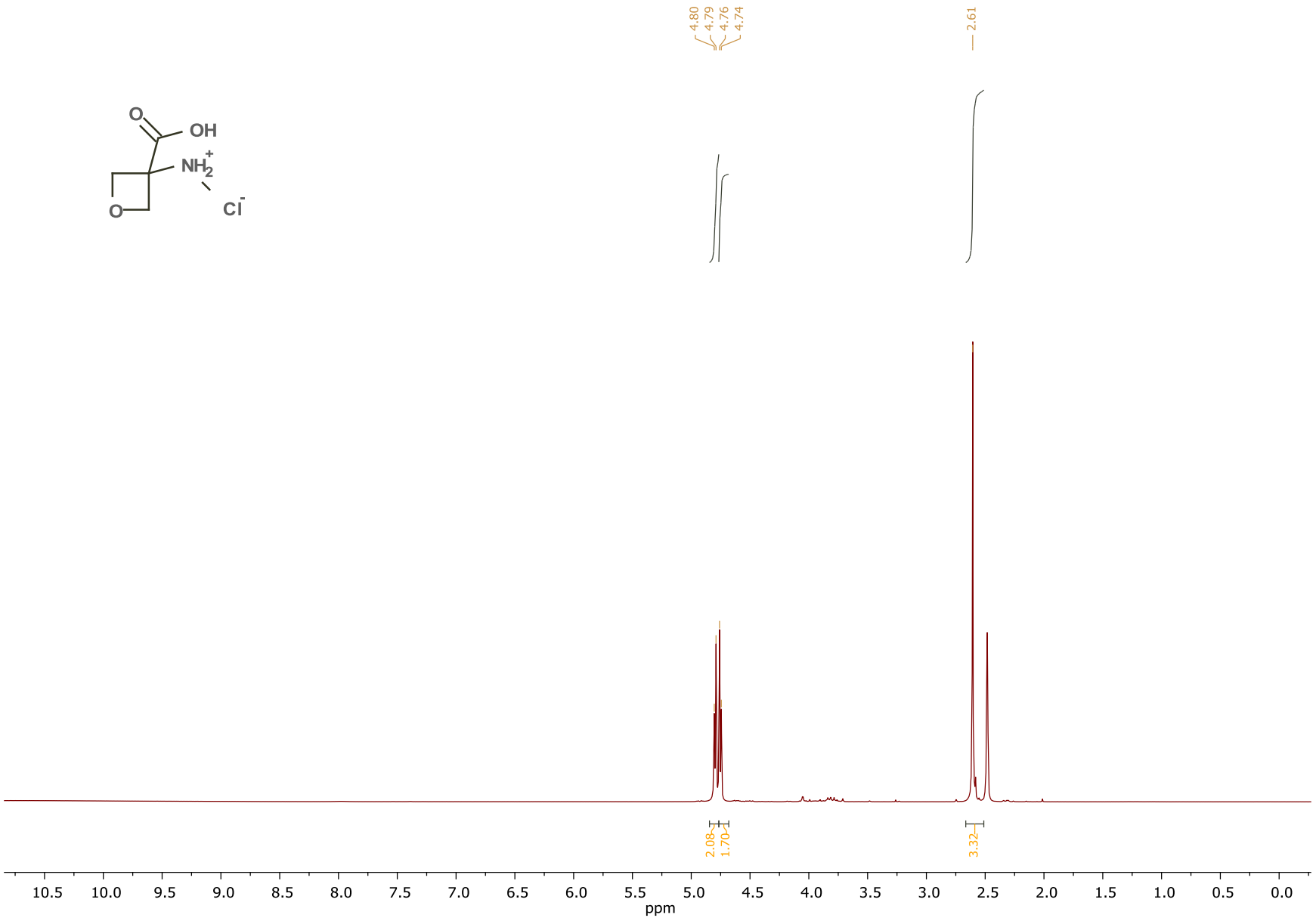
3-(2-Methoxypropan-2-yl)oxetan-3-amine (46) $^{13}C\{H\}$ NMR



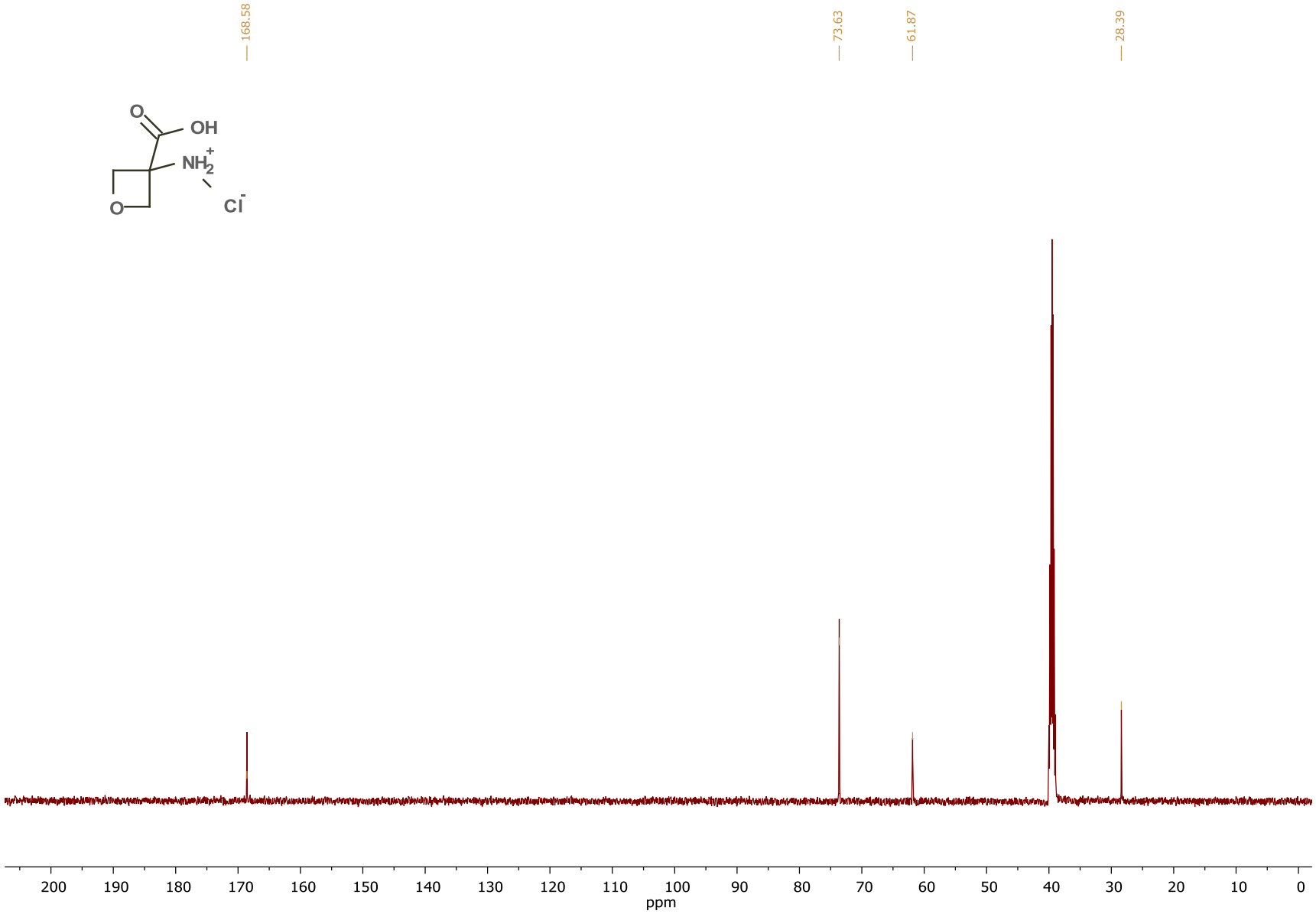
3-(Benzyl(methyl)amino)oxetane-3-carbonitrile (47) ^{1}H NMR



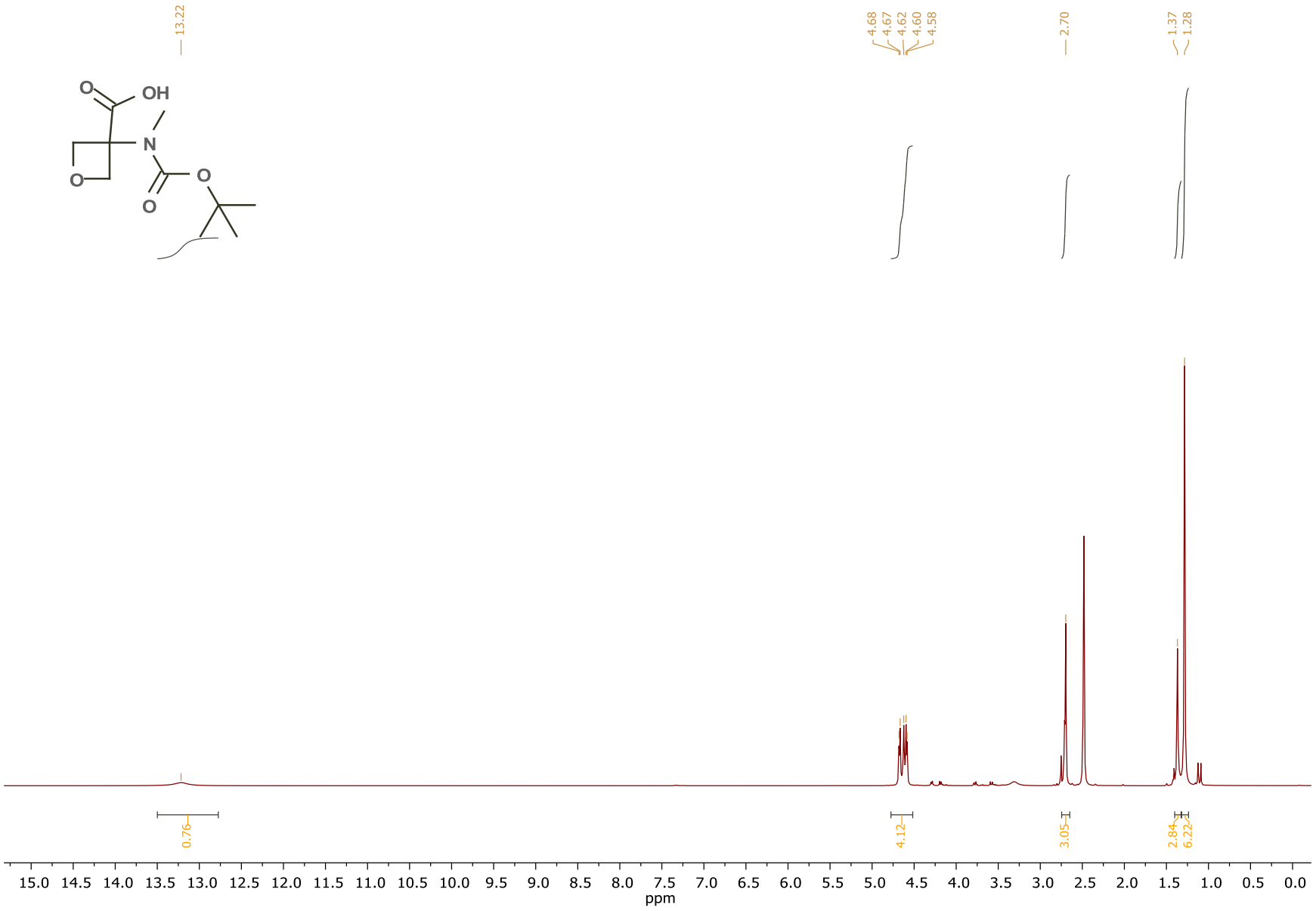
3-(Benzyl(methyl)amino)oxetane-3-carbonitrile (47) $^{13}C\{H\}$ NMR



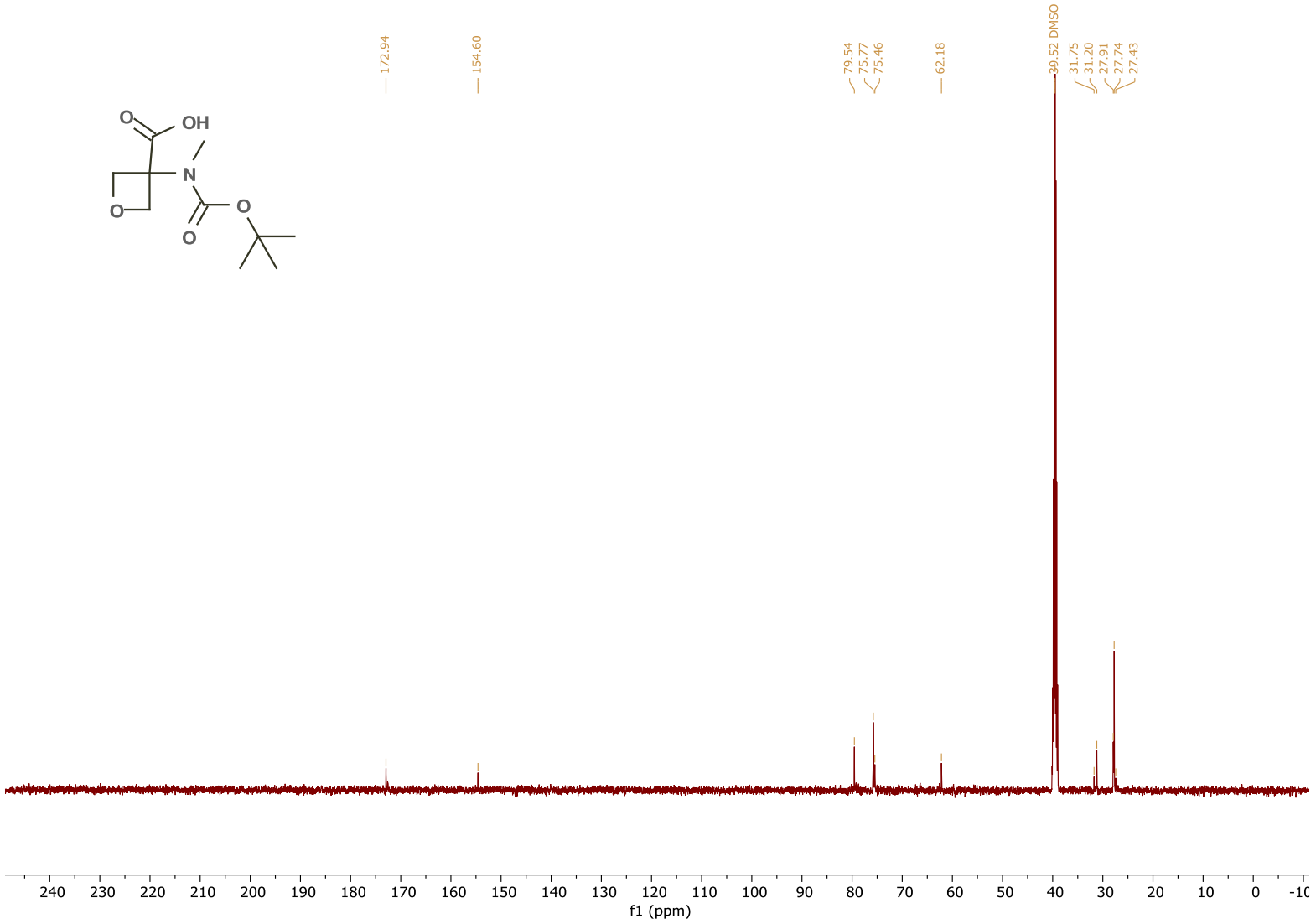
3-(Methylamino)oxetane-3-carboxylic acid hydrochloride (50) ^{1}H NMR



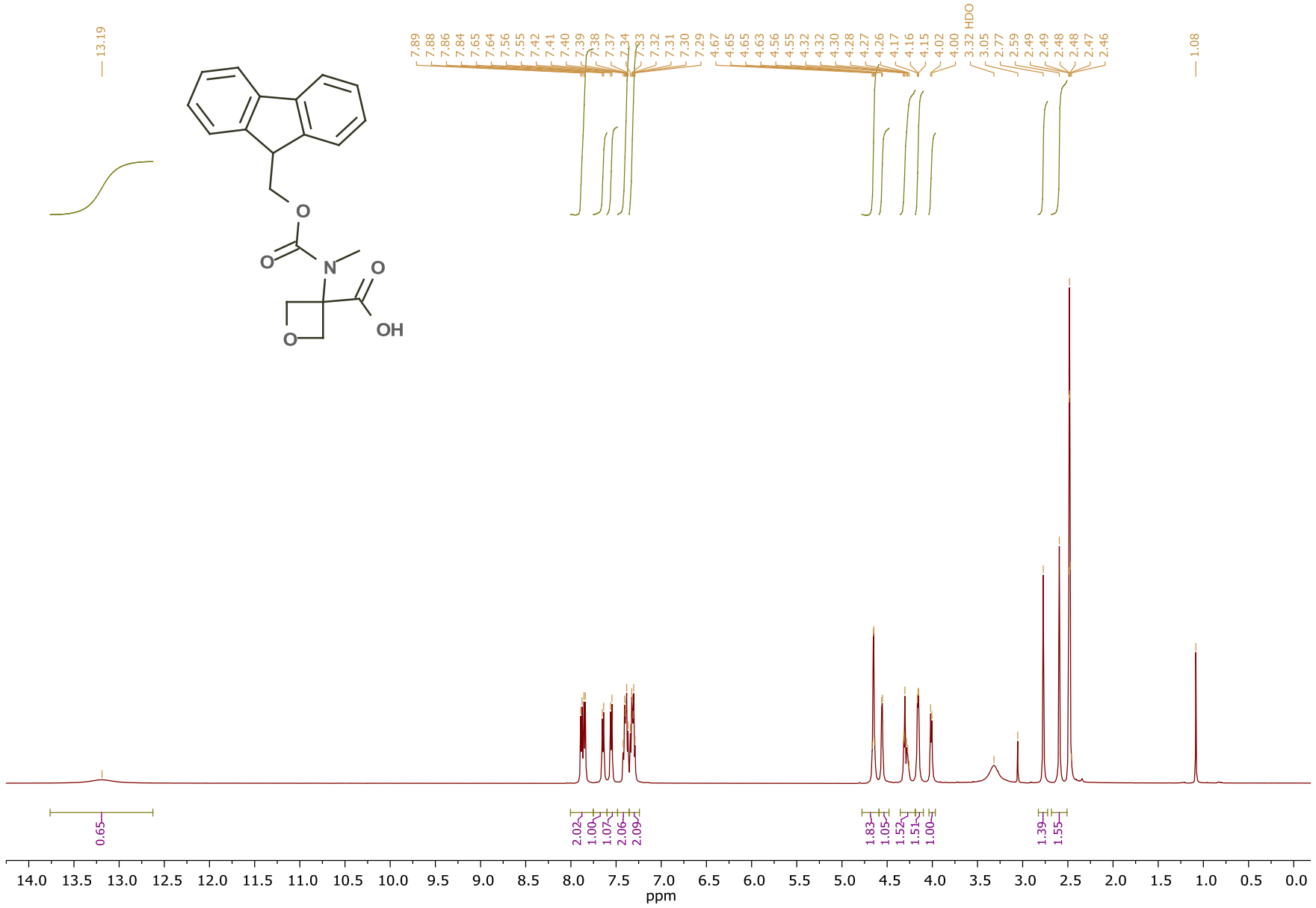
3-(Methylamino)oxetane-3-carboxylic acid hydrochloride (50) $^{13}C\{H\}$ NMR



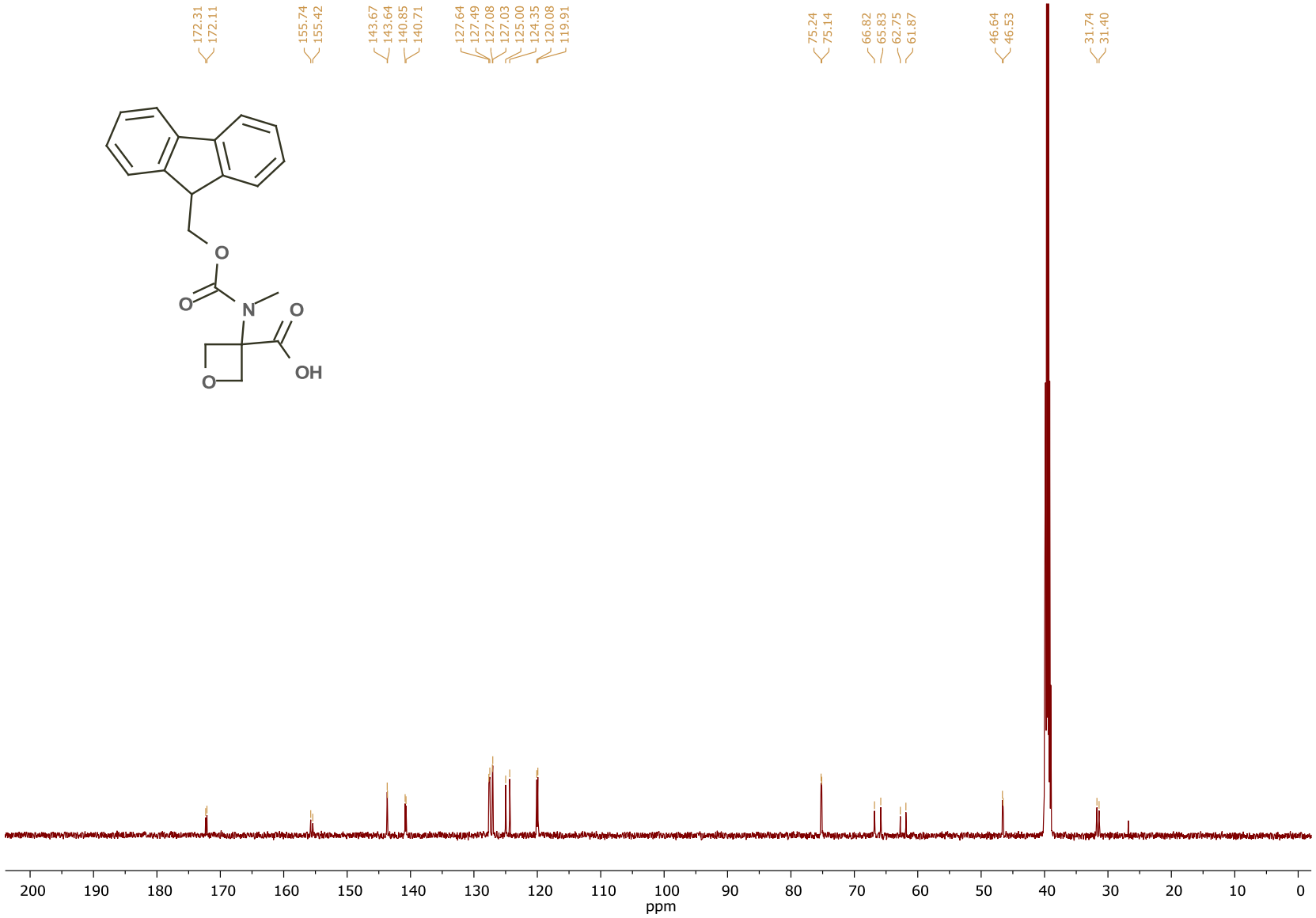
3-((*tert*-Butoxycarbonyl)(methyl)amino)oxetane-3-carboxylic acid (51a) ^{1}H NMR



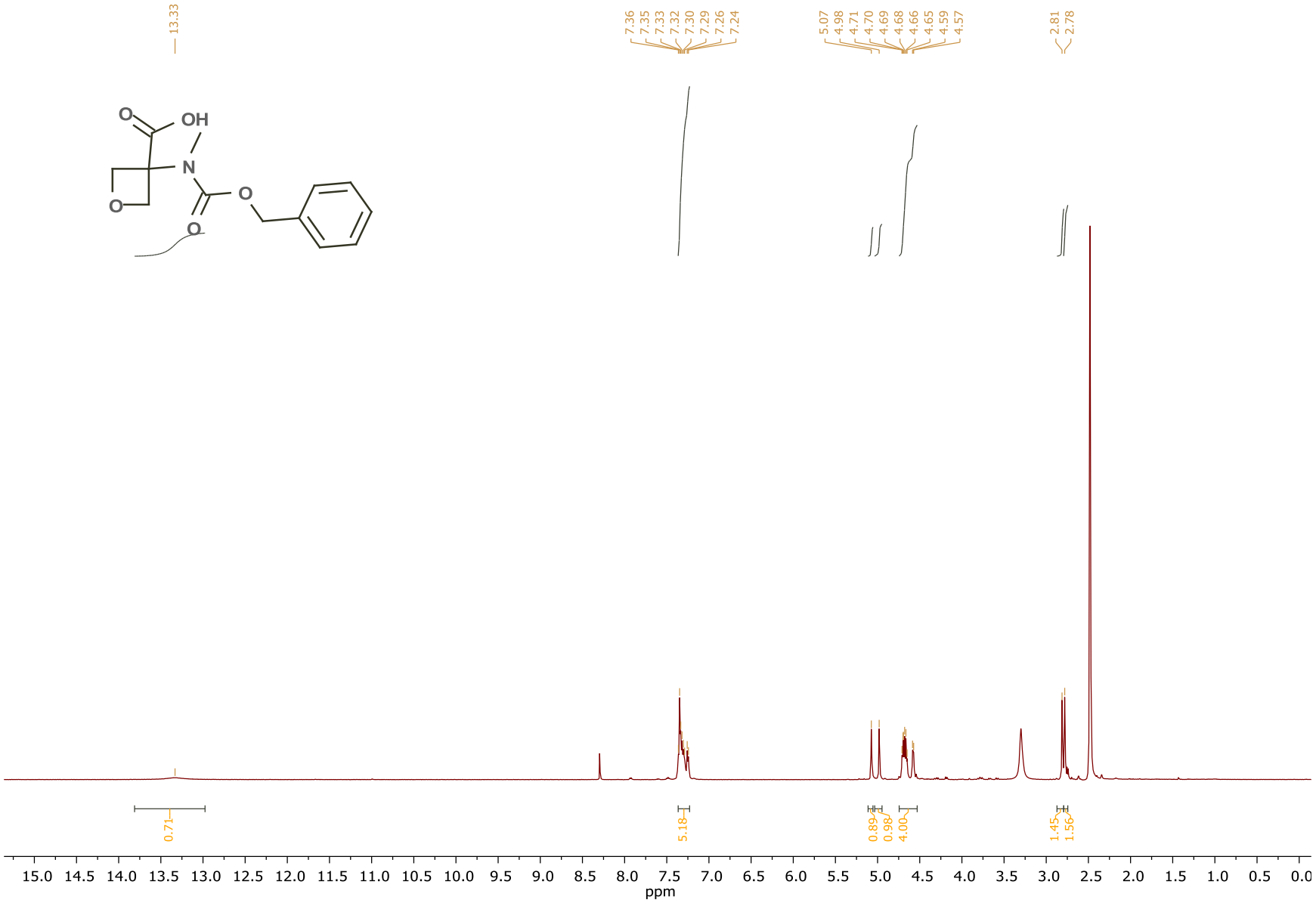
3-((*tert*-Butoxycarbonyl)(methyl)amino)oxetane-3-carboxylic acid (51a) $^{13}C\{H\}$ NMR



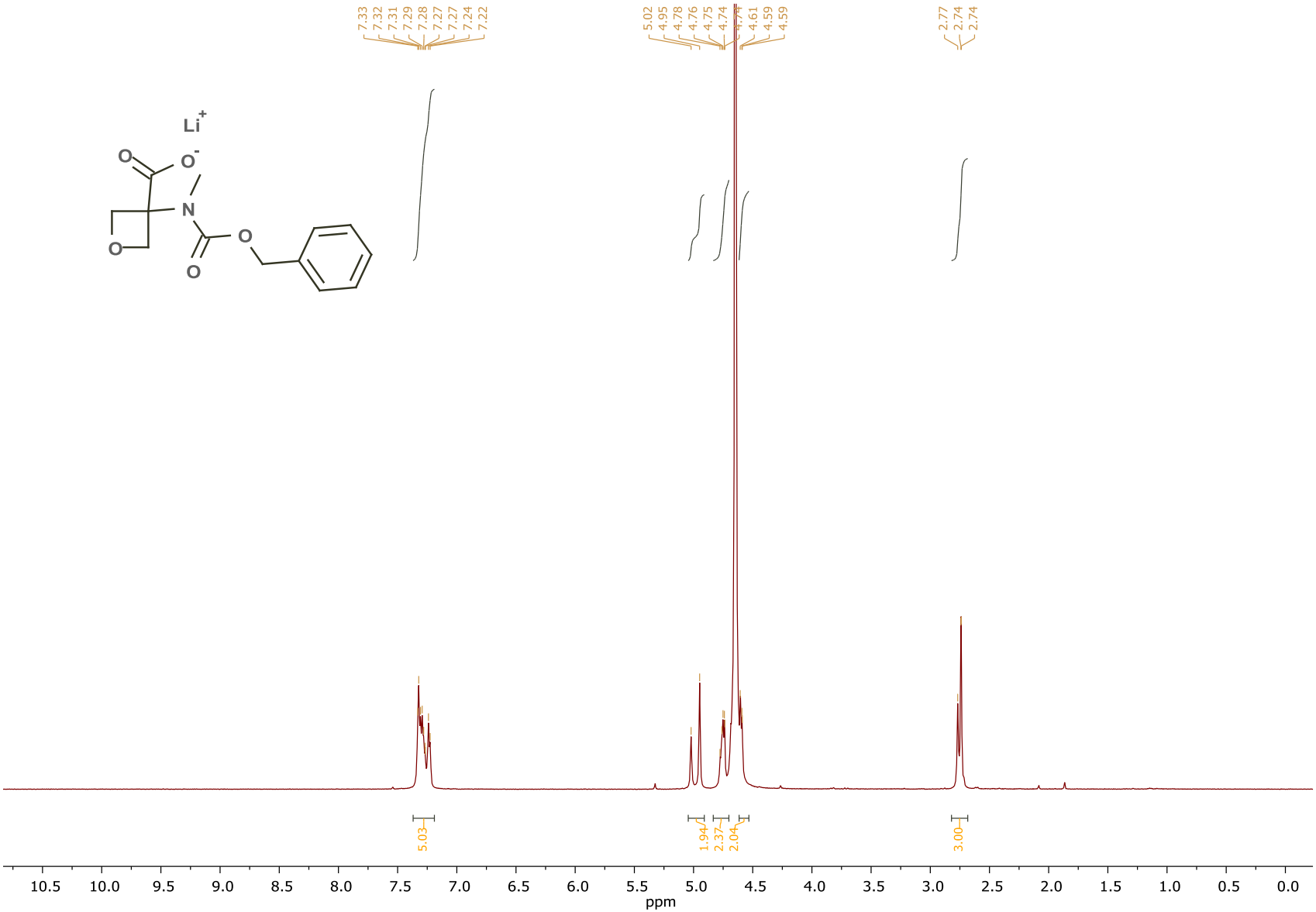
3-({[(9H-Fluoren-9-yl)methoxy]carbonyl}(methyl)amino)oxetane-3-carboxylic acid (51b) ^{1}H NMR



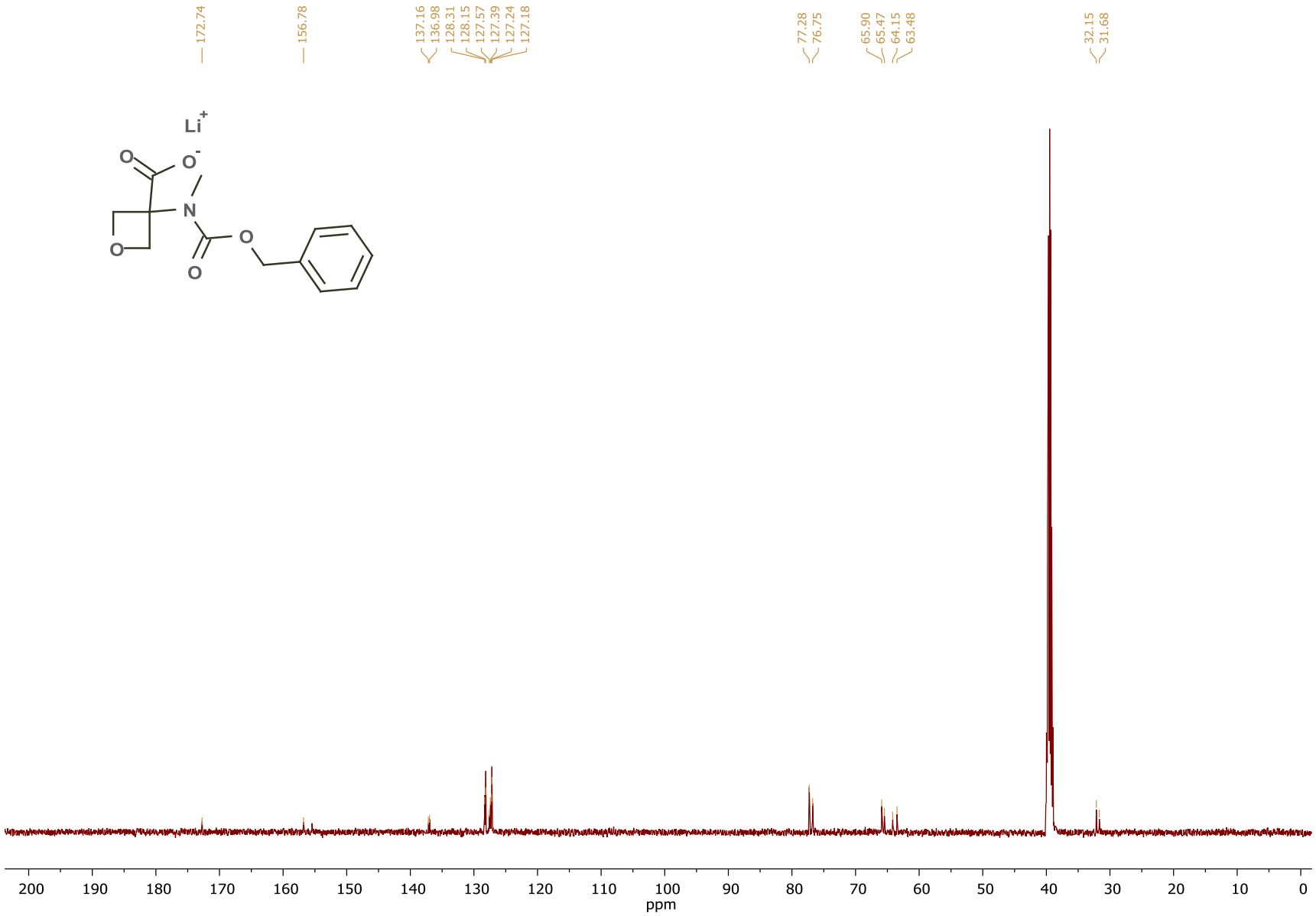
3-({[(9H-Fluoren-9-yl)methoxy]carbonyl}(methyl)amino)oxetane-3-carboxylic acid (51b) ^{13}C NMR



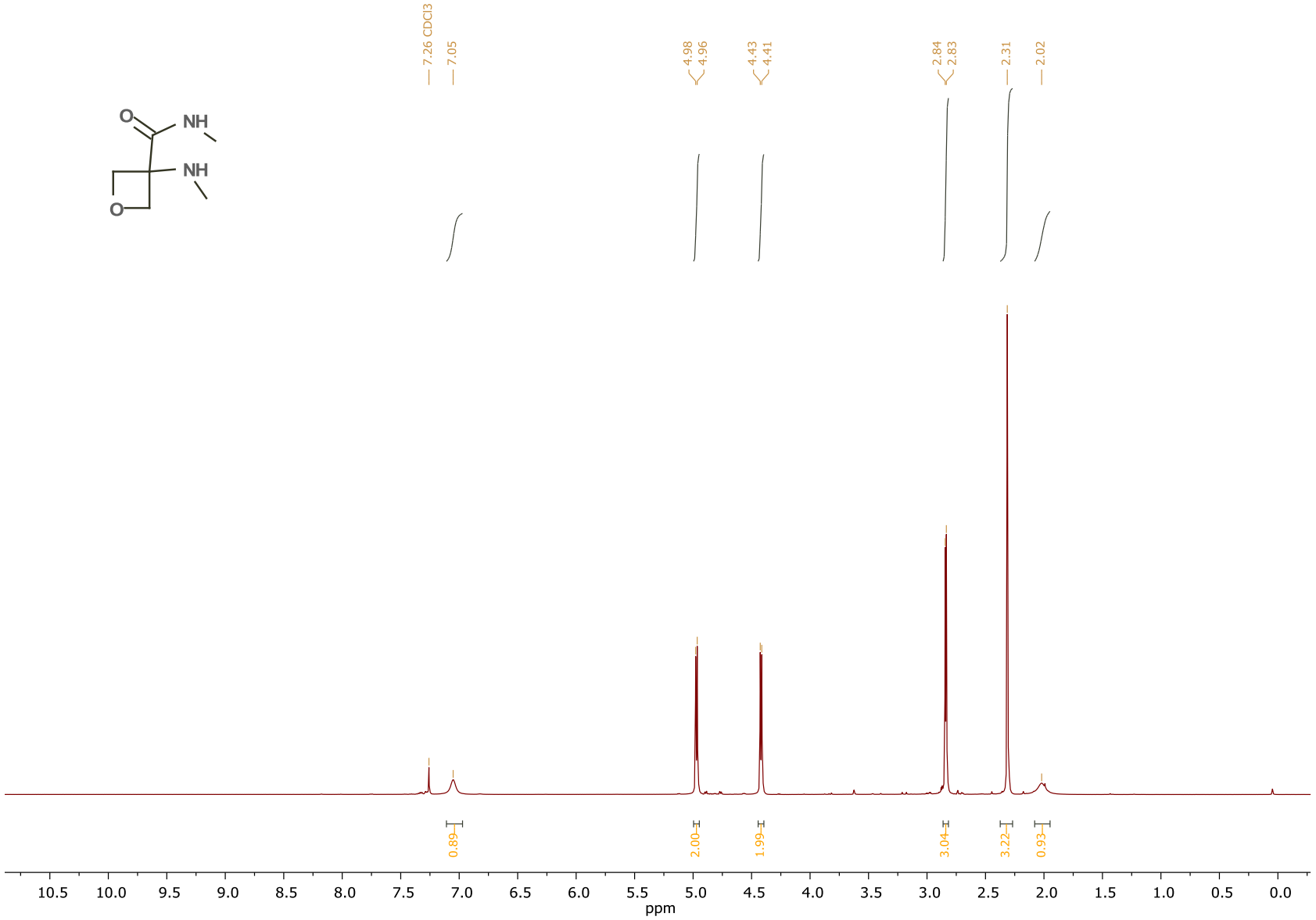
3-{[(benzyloxy)carbonyl](methyl)amino}oxetane-3-carboxylic acid (51c) ^{1}H NMR



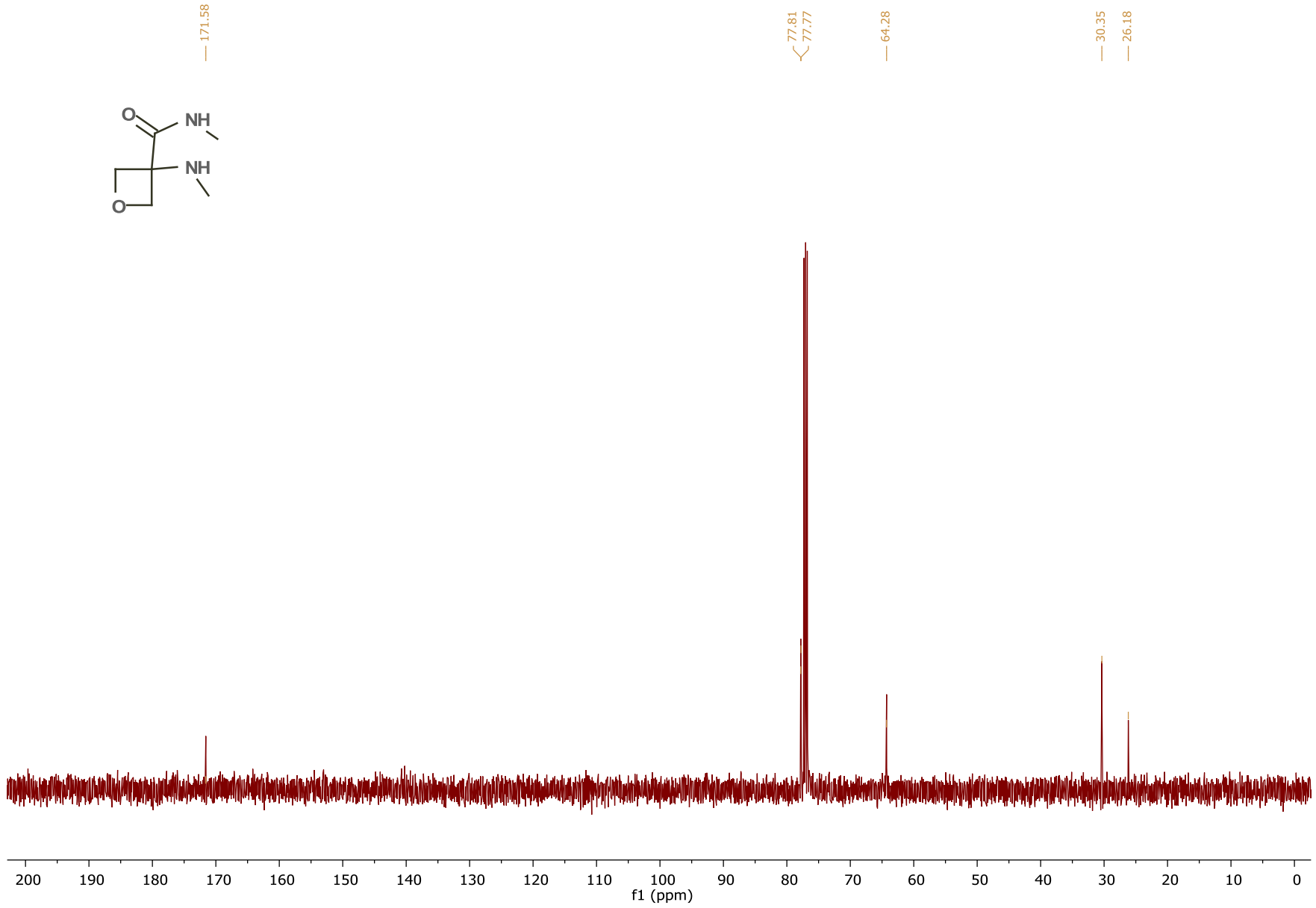
Lithium 3-{[(benzyloxy)carbonyl](methyl)amino}oxetane-3-carboxylate (52) ^{1}H NMR



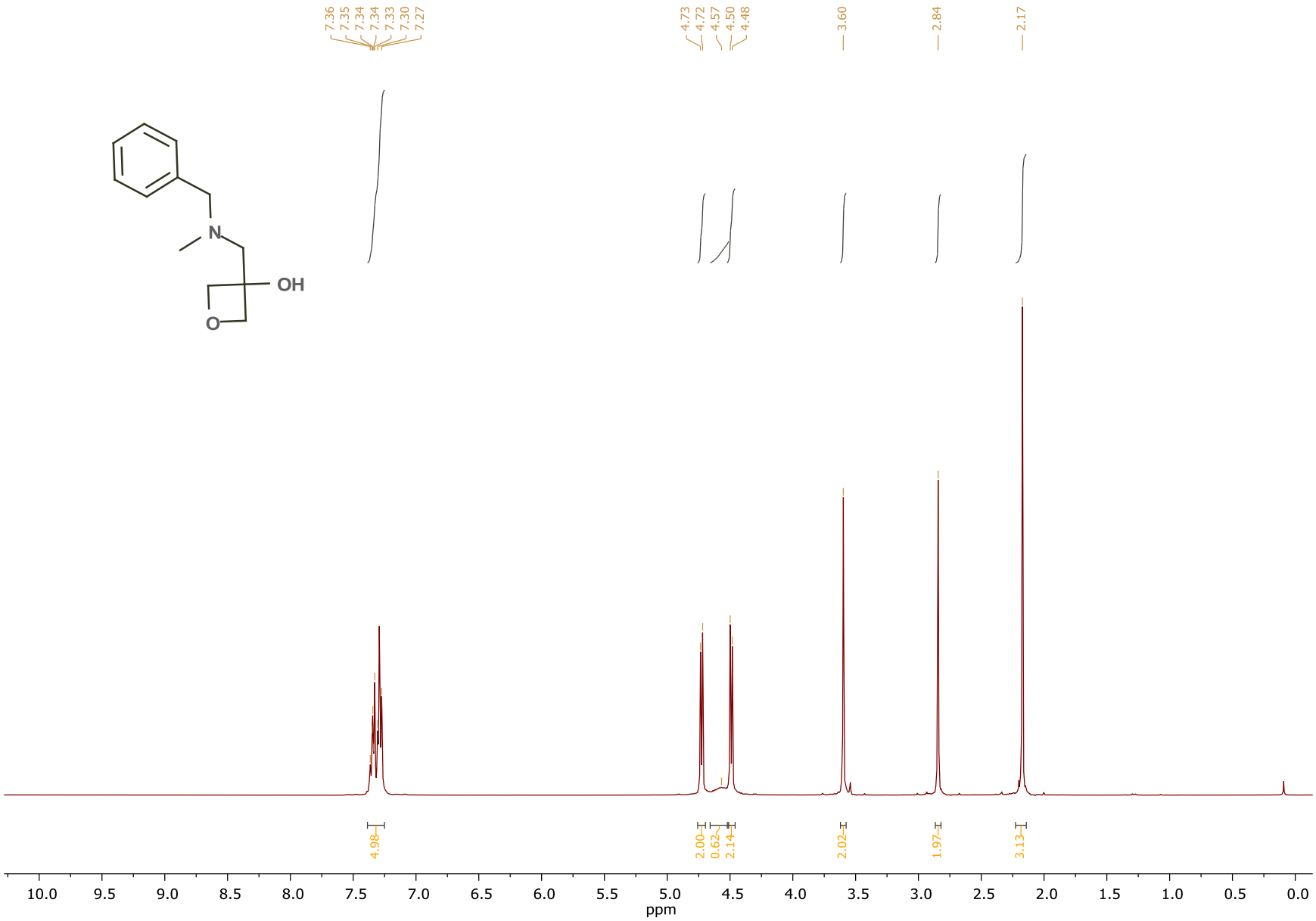
Lithium 3-{[(benzyloxy)carbonyl](methyl)amino}oxetane-3-carboxylate (52) $^{13}C\{H\}$ NMR



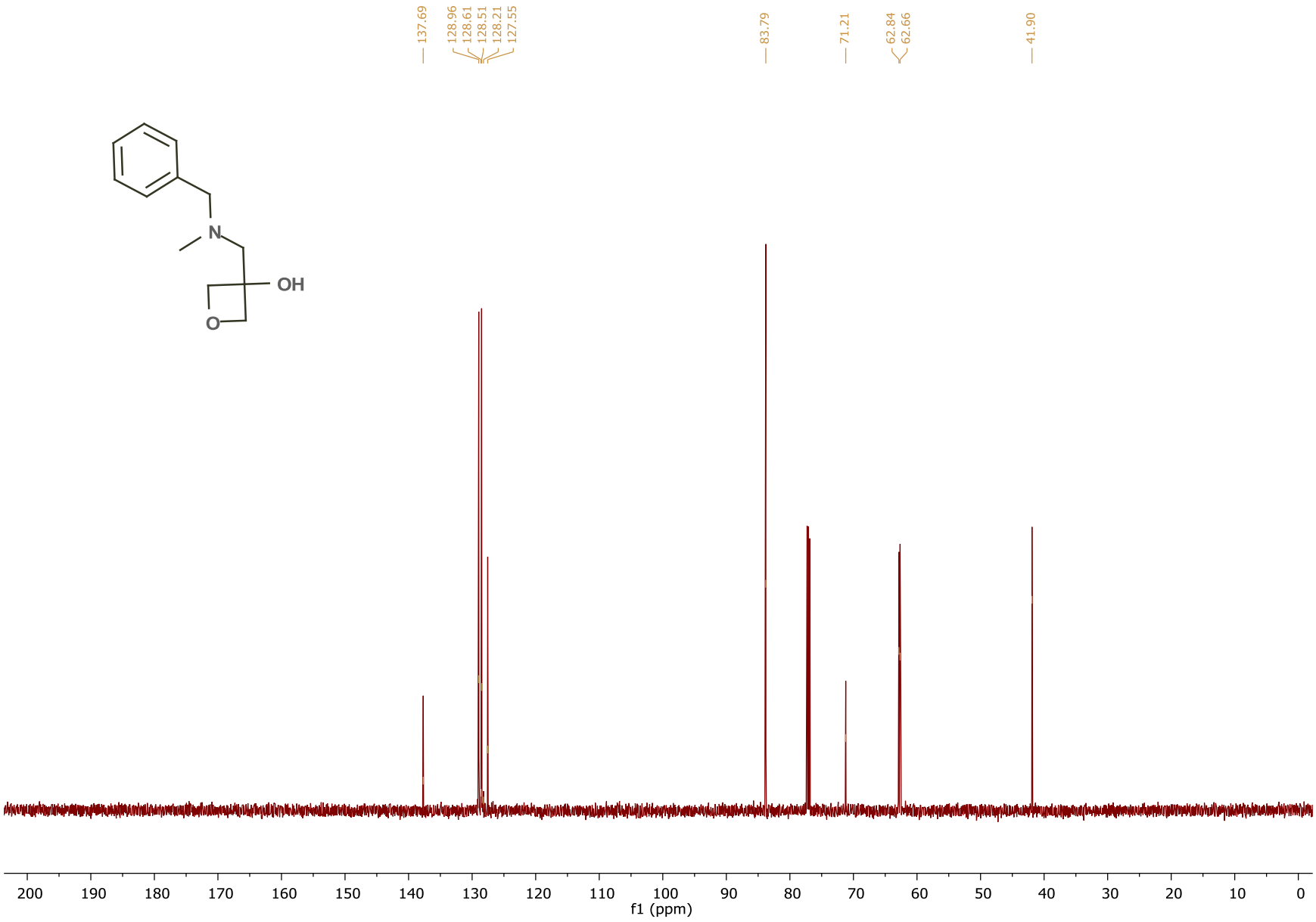
_N_-Methyl-3-(methylamino)oxetane-3-carboxamide (54) ^{1}H NMR



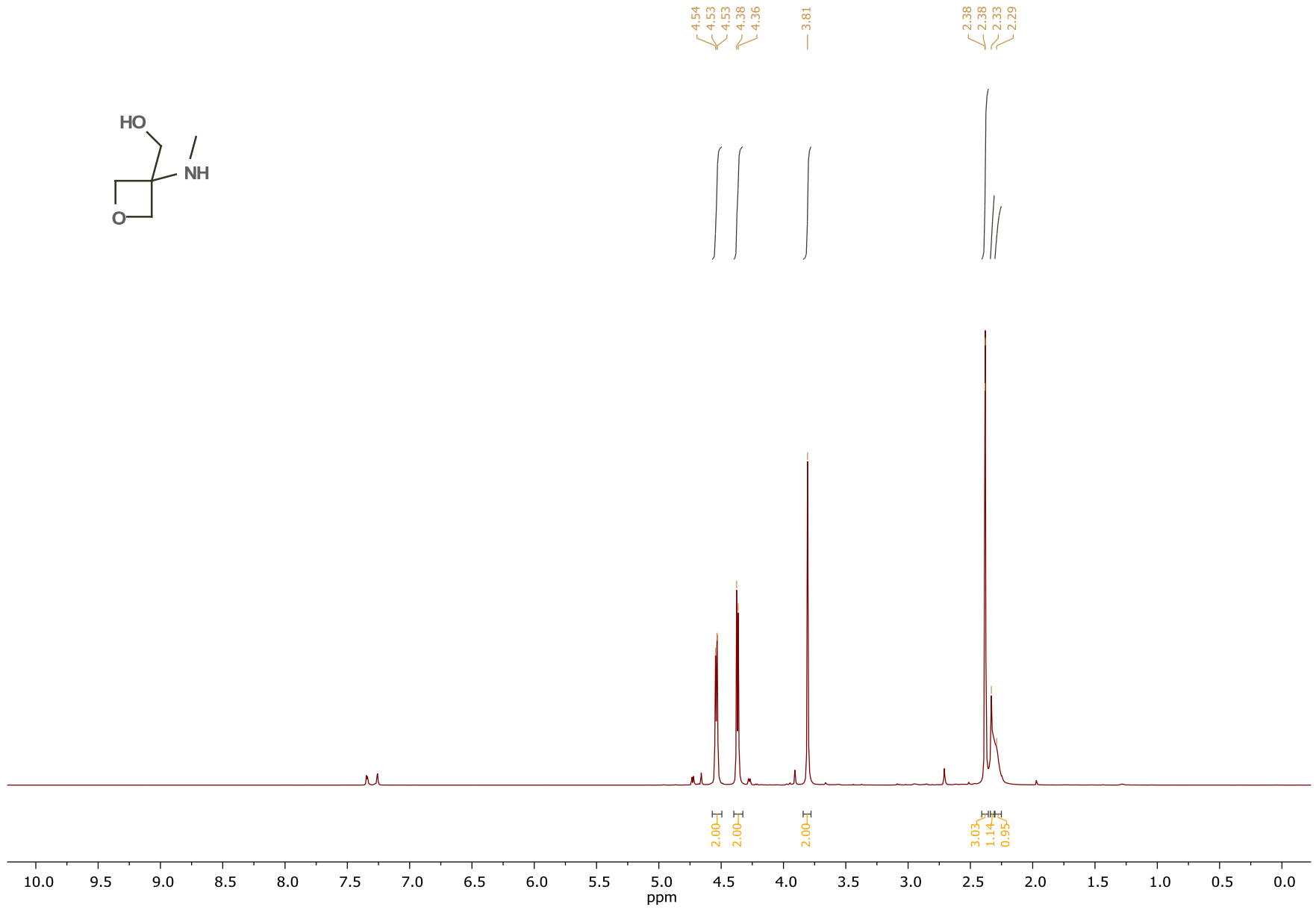
***N*-Methyl-3-(methylamino)oxetane-3-carboxamide (54) $^{13}C\{H\}$ NMR**



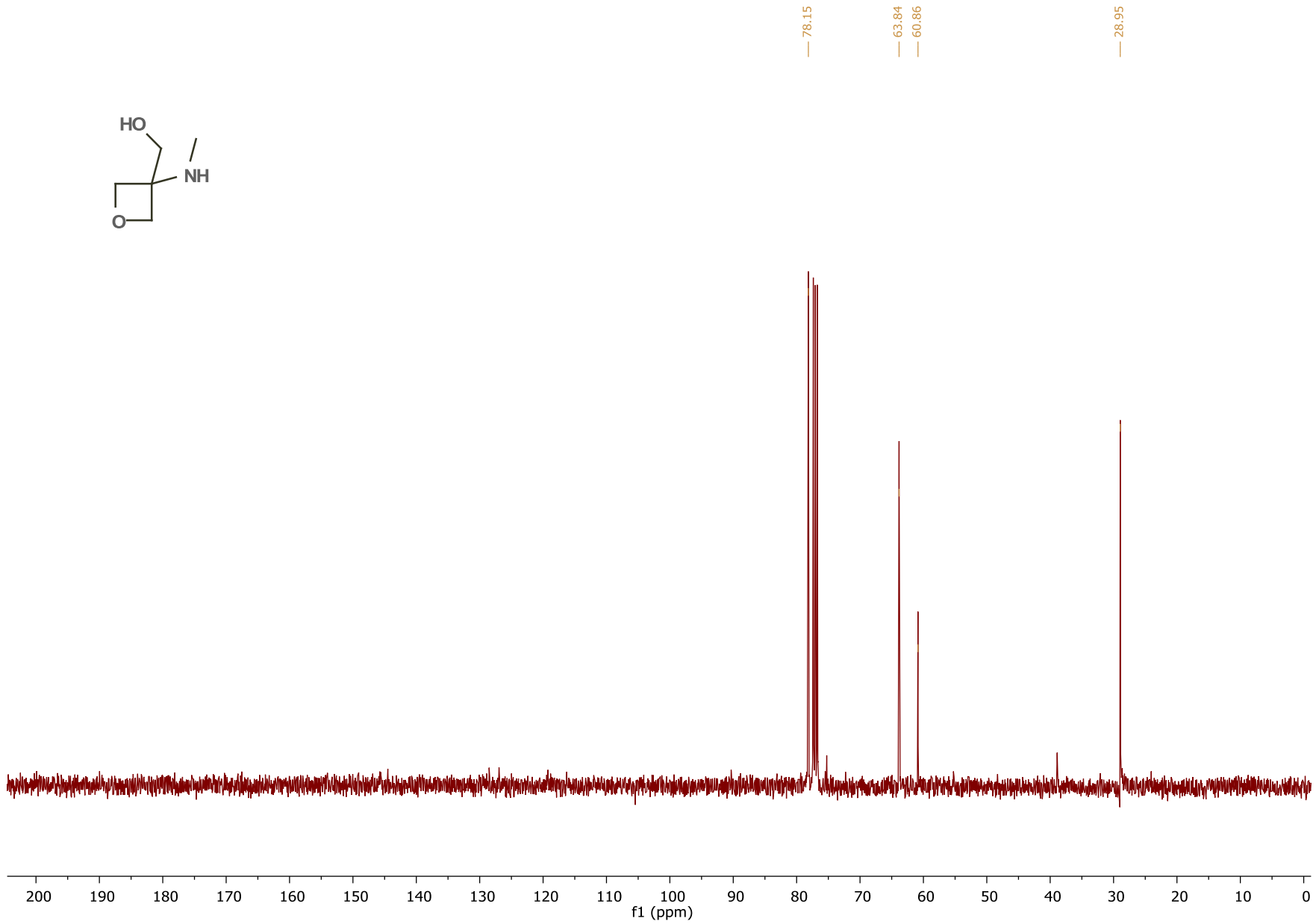
(3-(Benzyl(methyl)amino)oxetan-3-yl)methanol (55) ^{1}H NMR



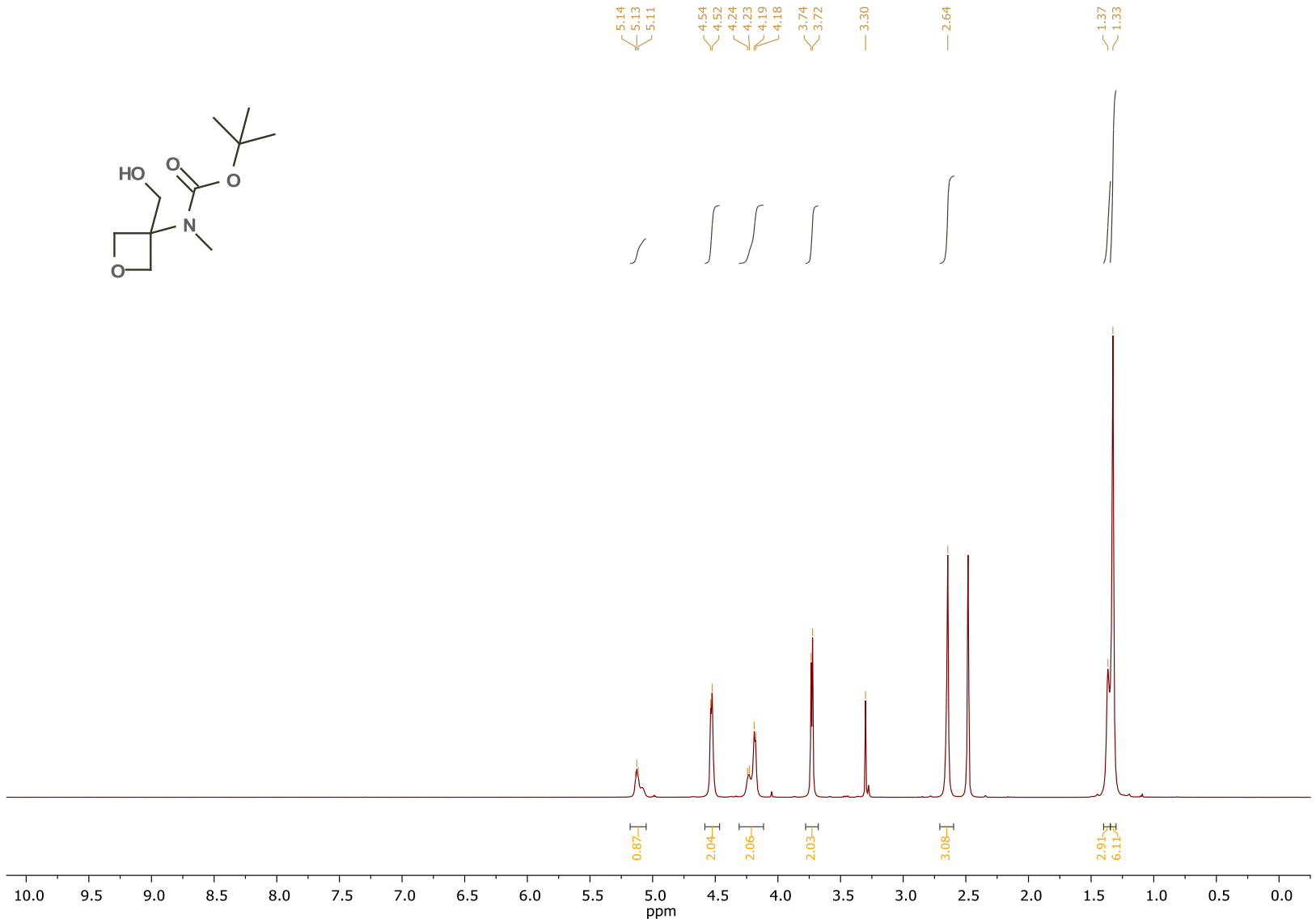
(3-(Benzyl(methyl)amino)oxetan-3-yl)methanol (55) $^{13}C\{H\}$ NMR



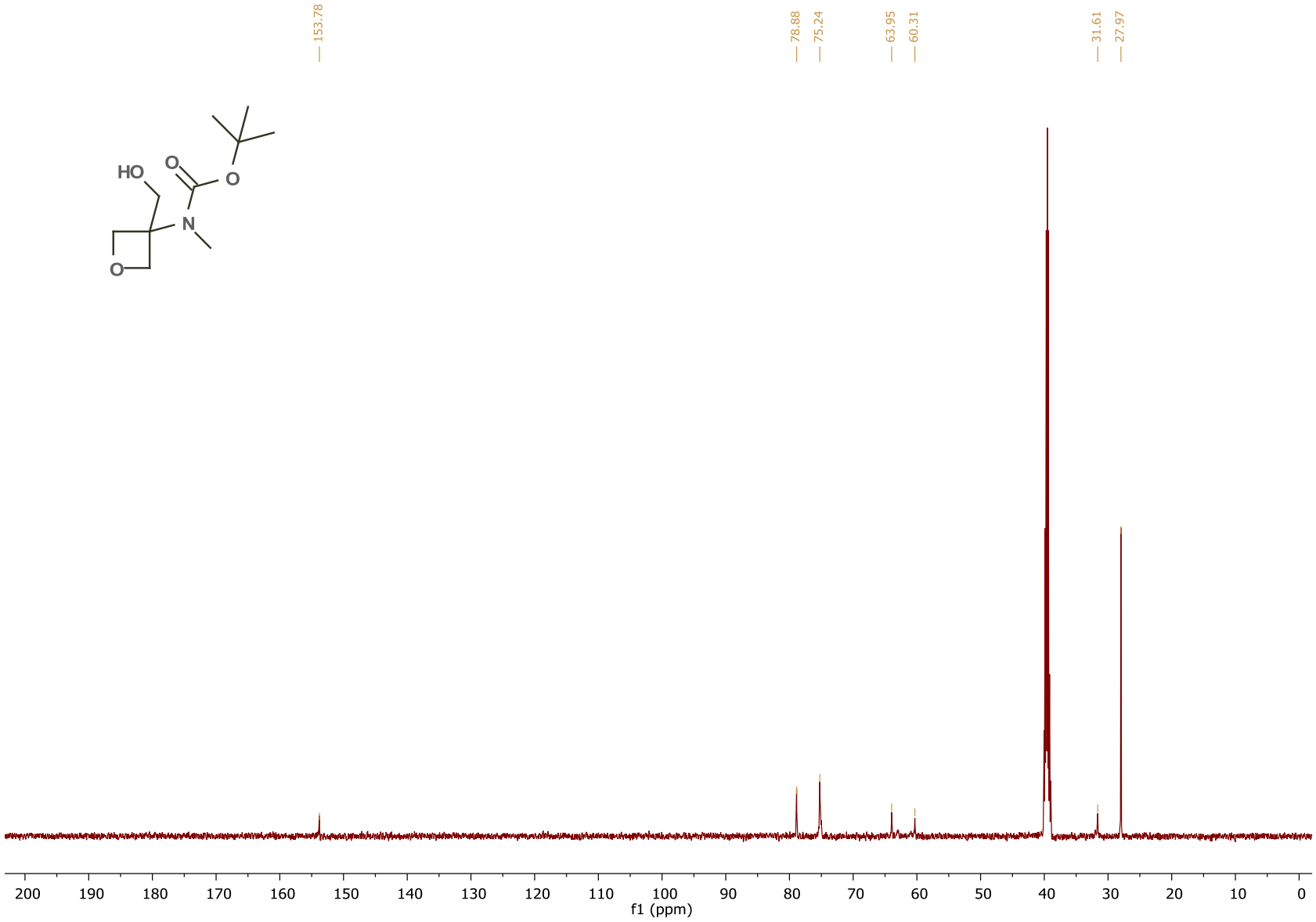
[3-(Methylamino)oxetan-3-yl]methanol (56) ^{1}H NMR



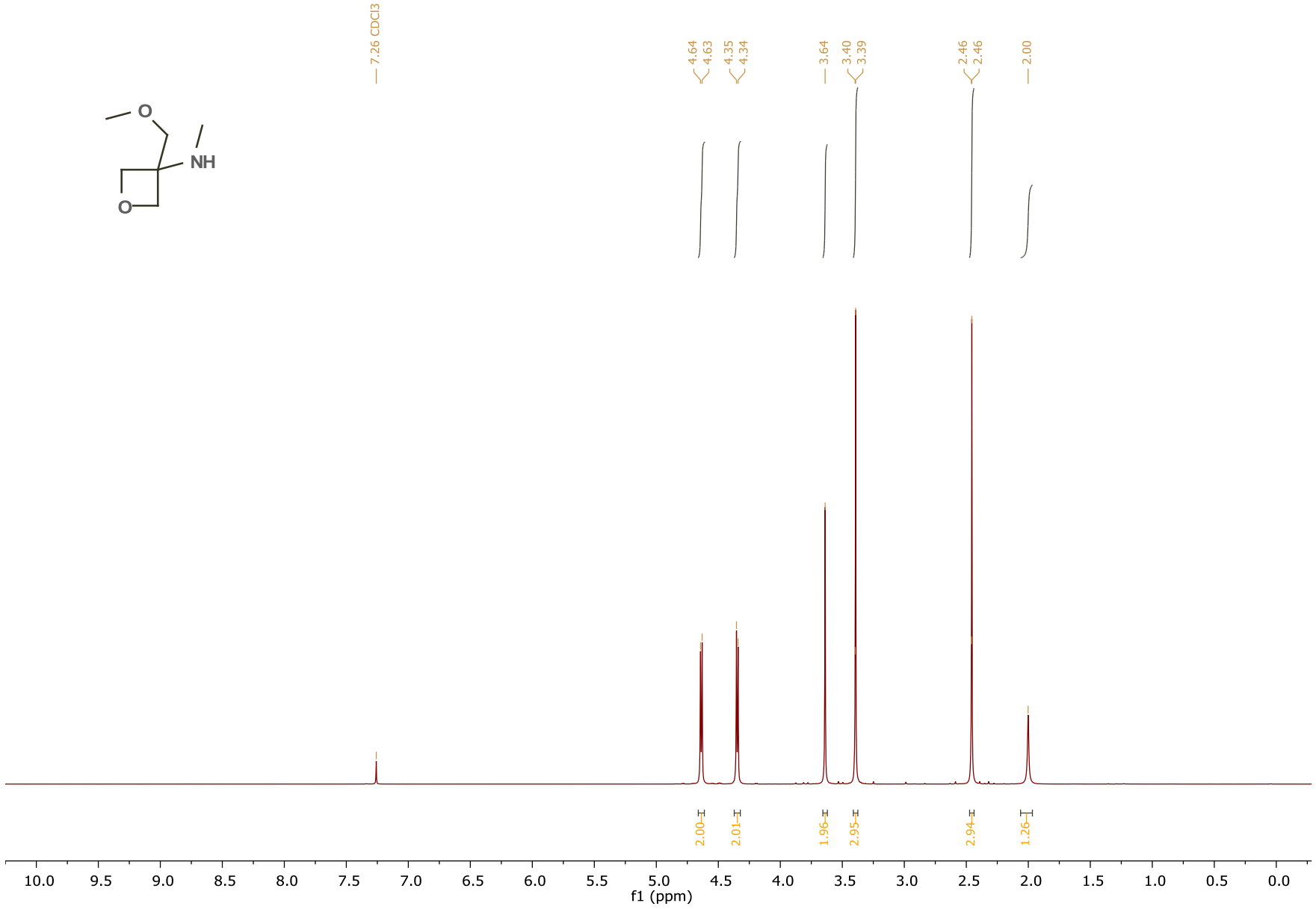
[3-(Methylamino)oxetan-3-yl]methanol (56) $^{13}C\{H\}$ NMR



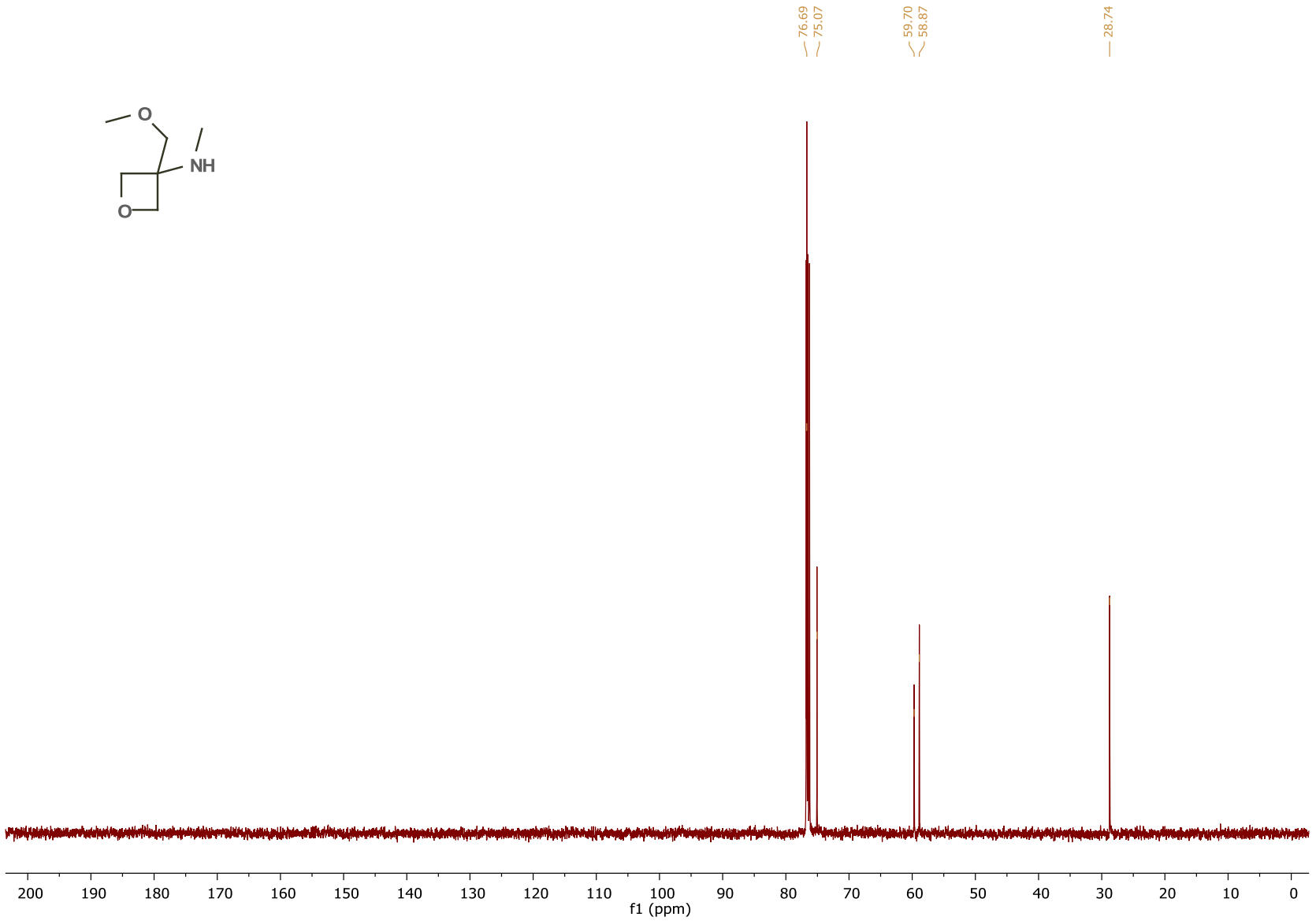
***tert*-Butyl *N*-[3-(hydroxymethyl)oxetan-3-yl]-*N*-methylcarbamate (57) ^{1}H NMR**



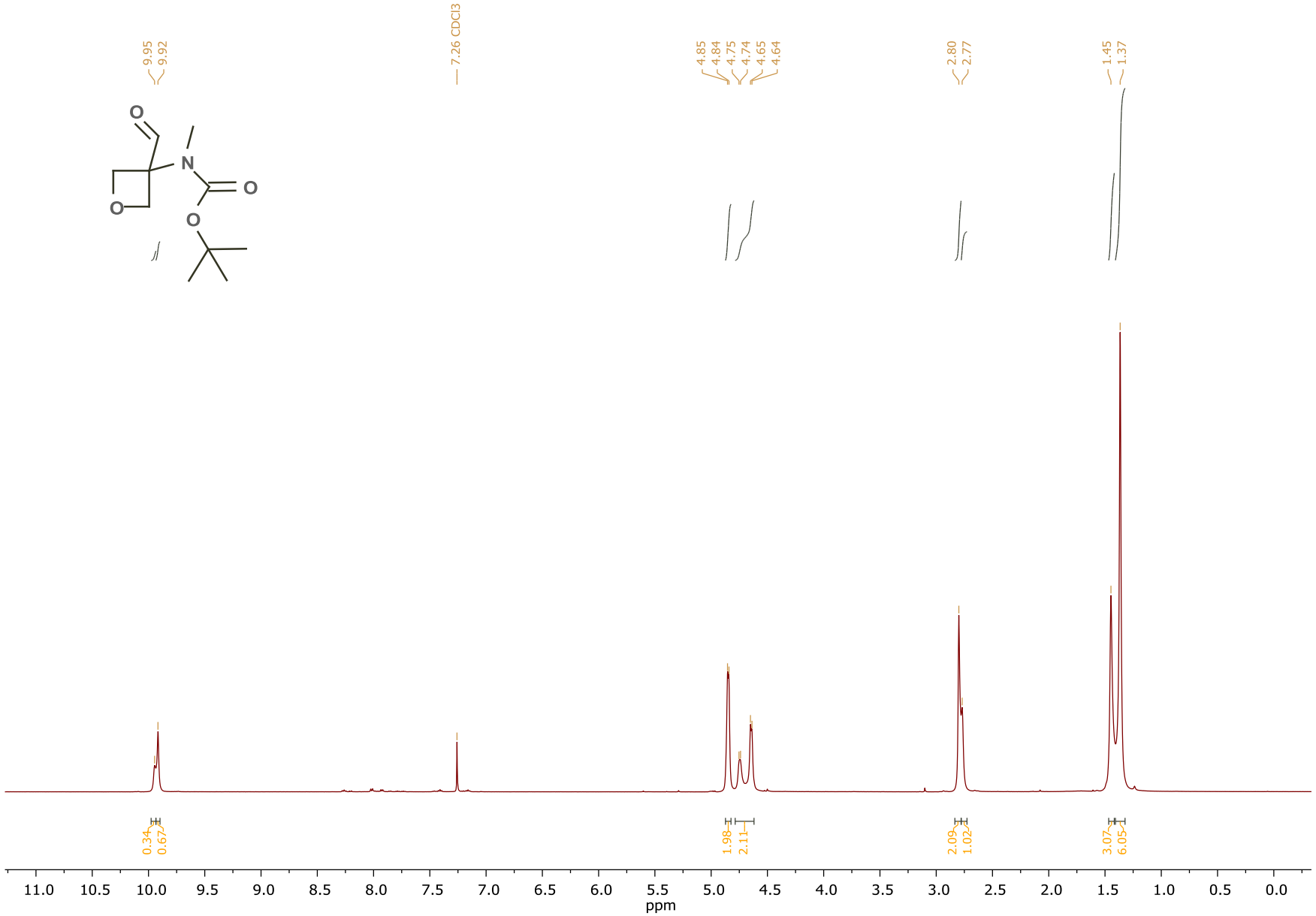
tert-Butyl _N_-[3-(hydroxymethyl)oxetan-3-yl]-_N_-methylcarbamate (57) $^{13}C\{H\}$ NMR



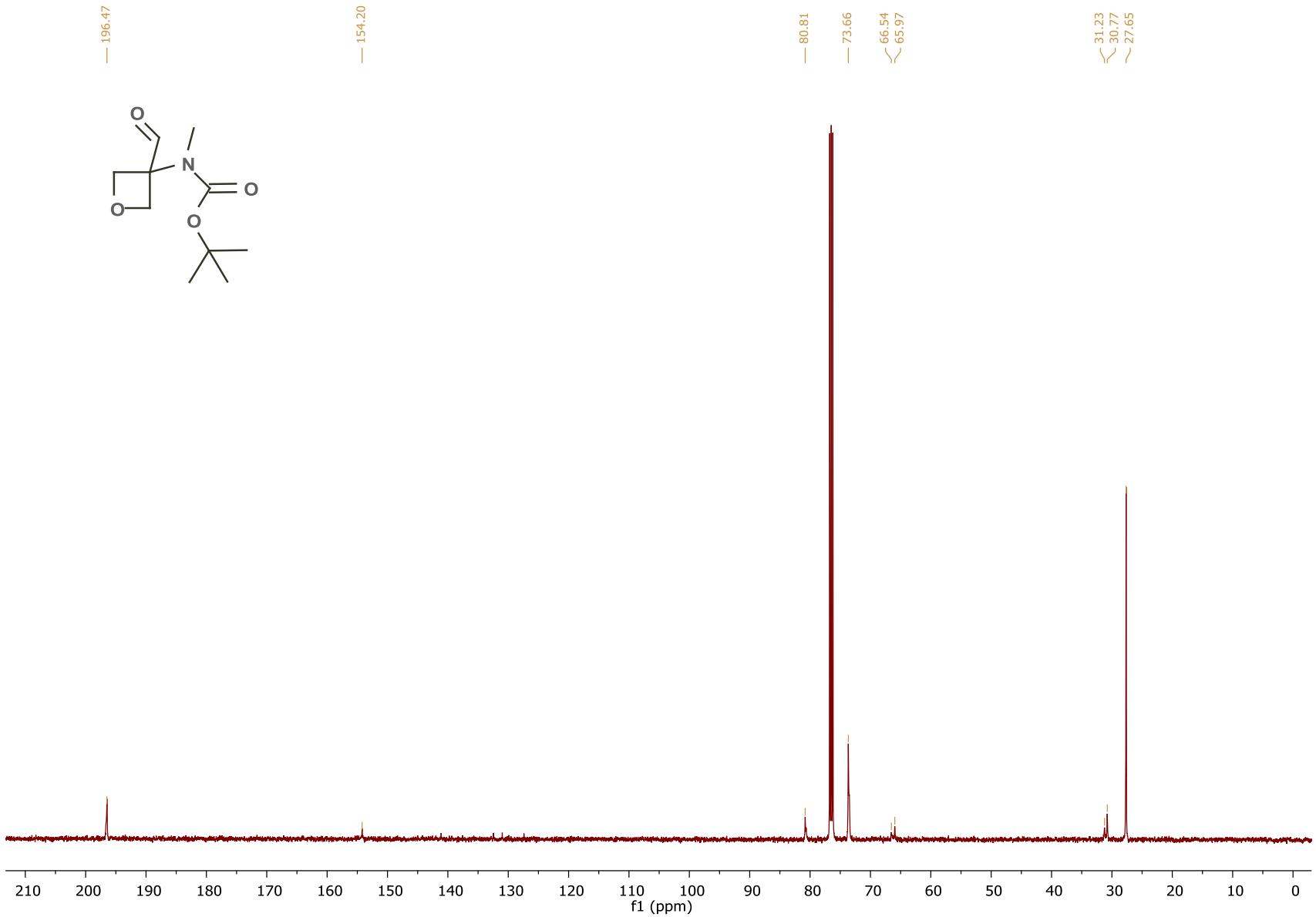
3-(Methoxymethyl)-*N*-methyloxetan-3-amine (59) ^{1}H NMR



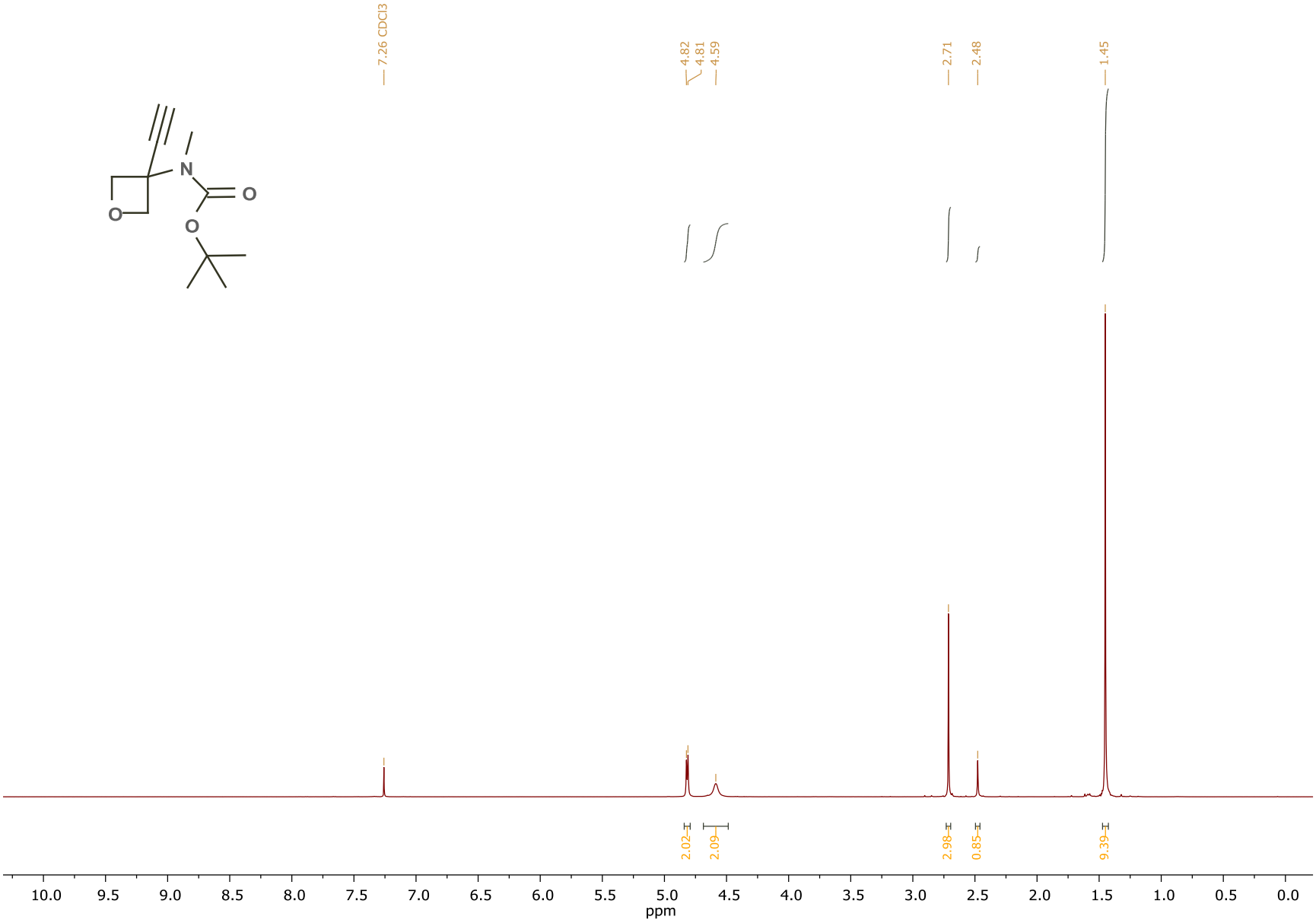
3-(Methoxymethyl)-*N*-methyloxetan-3-amine (59) ^{13}C{H} NMR



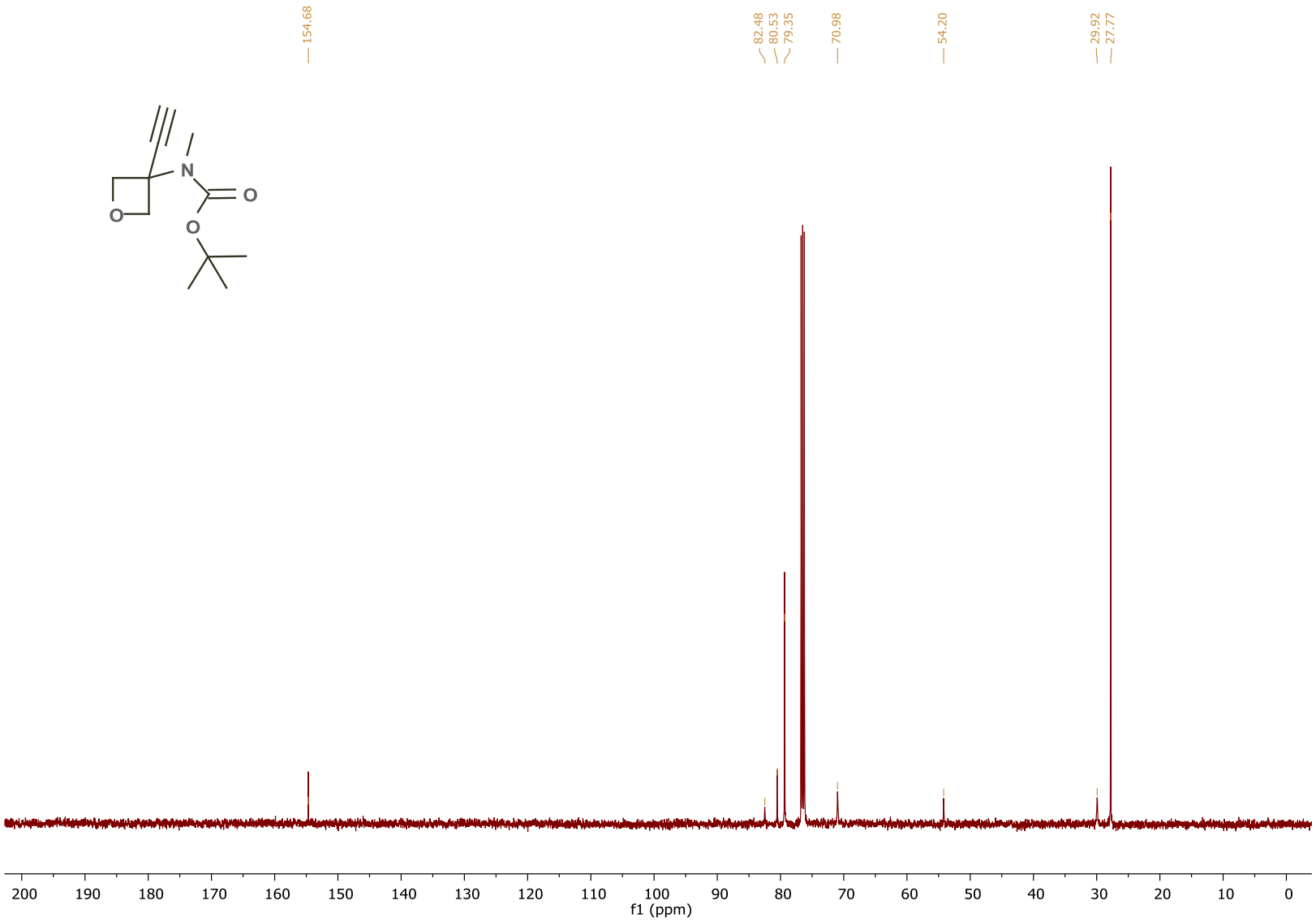
tert-Butyl (3-formyloxetan-3-yl)(methyl)carbamate (60) ^{1}H NMR



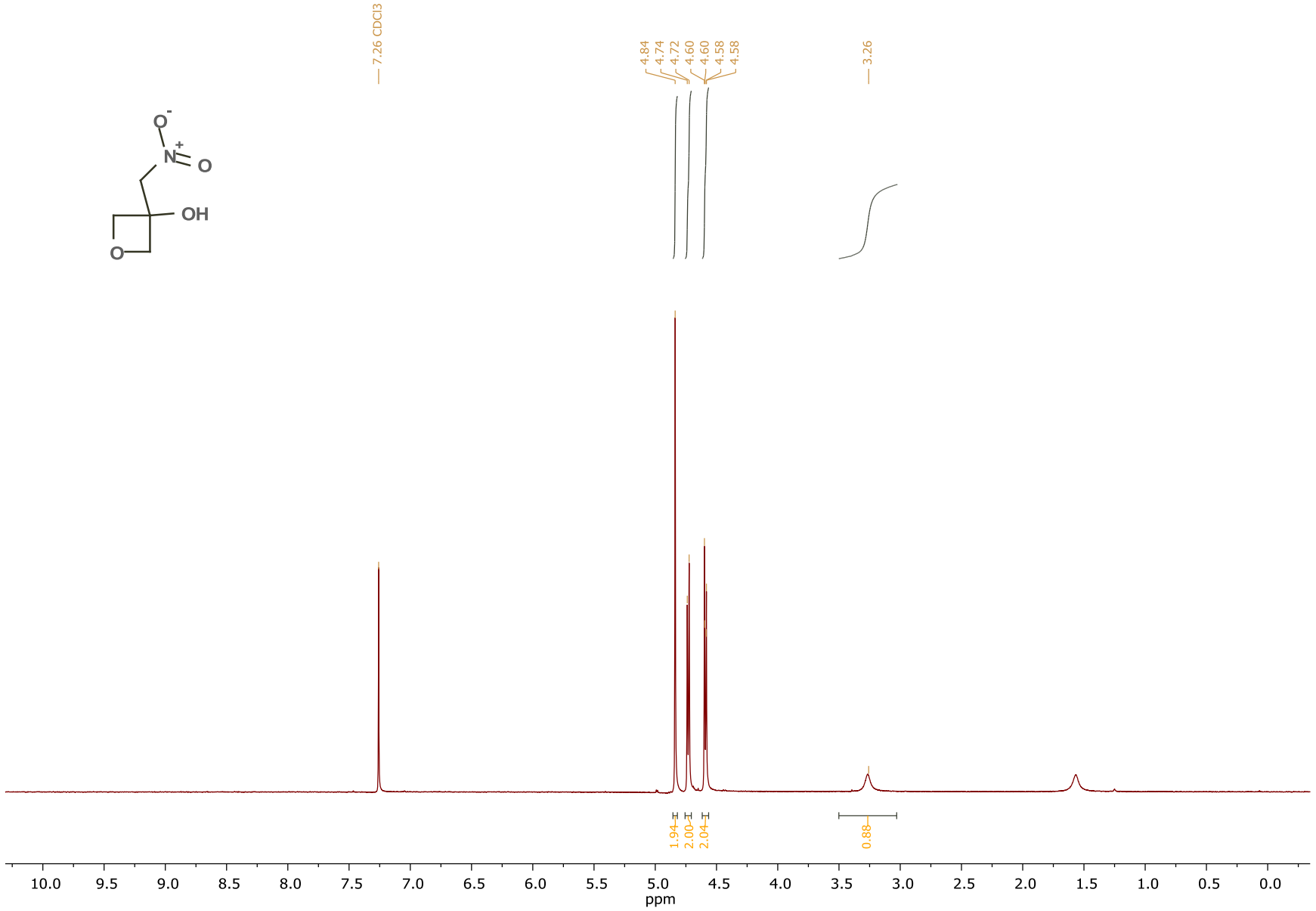
tert-Butyl (3-formyloxetan-3-yl)(methyl)carbamate (60) $^{13}C\{H\}$ NMR



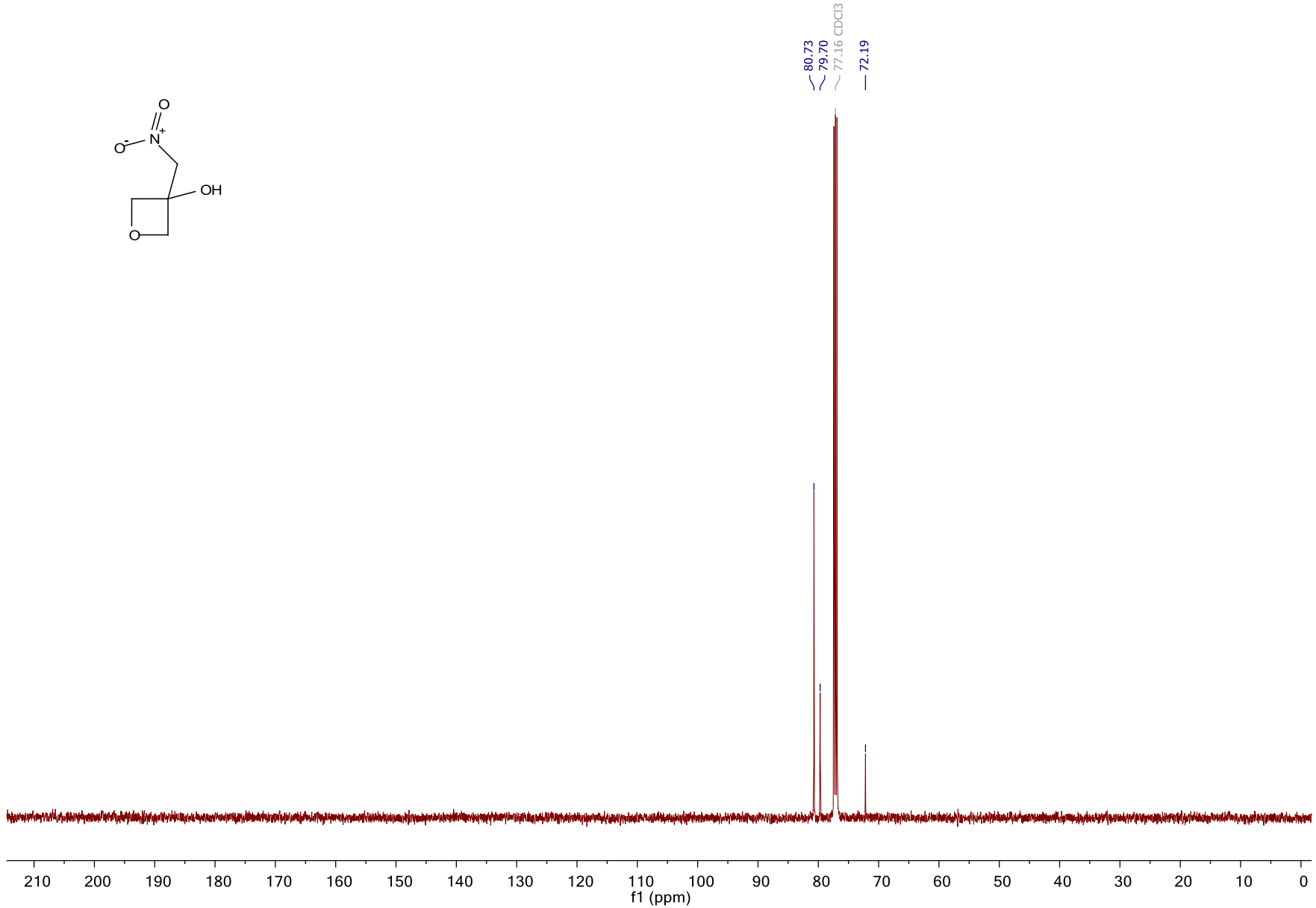
tert-Butyl (3-ethynyloxetan-3-yl)(methyl)carbamate (61) ^{1}H NMR



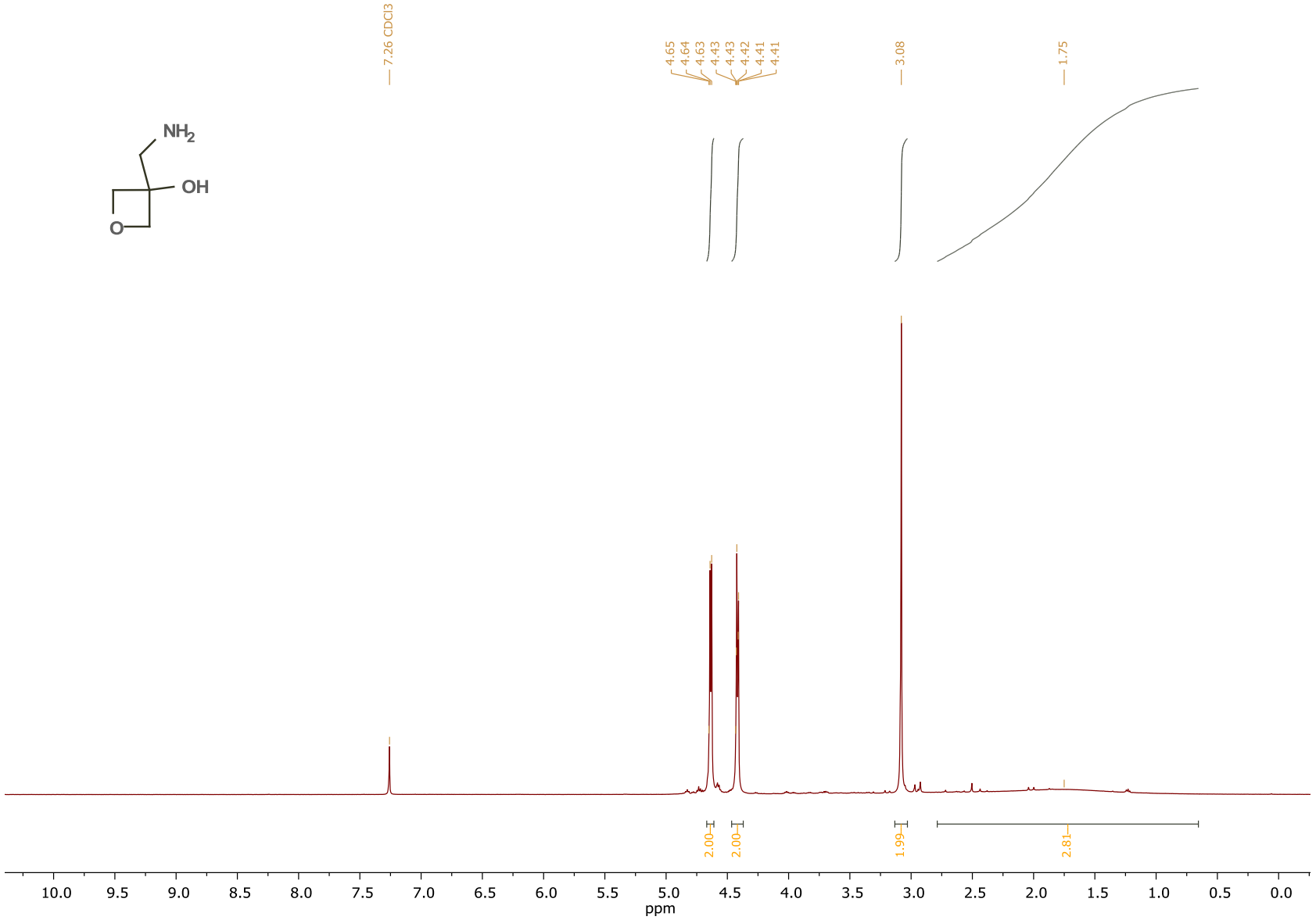
tert-Butyl (3-ethynyloxetan-3-yl)(methyl)carbamate (61) $^{13}C\{H\}$ NMR



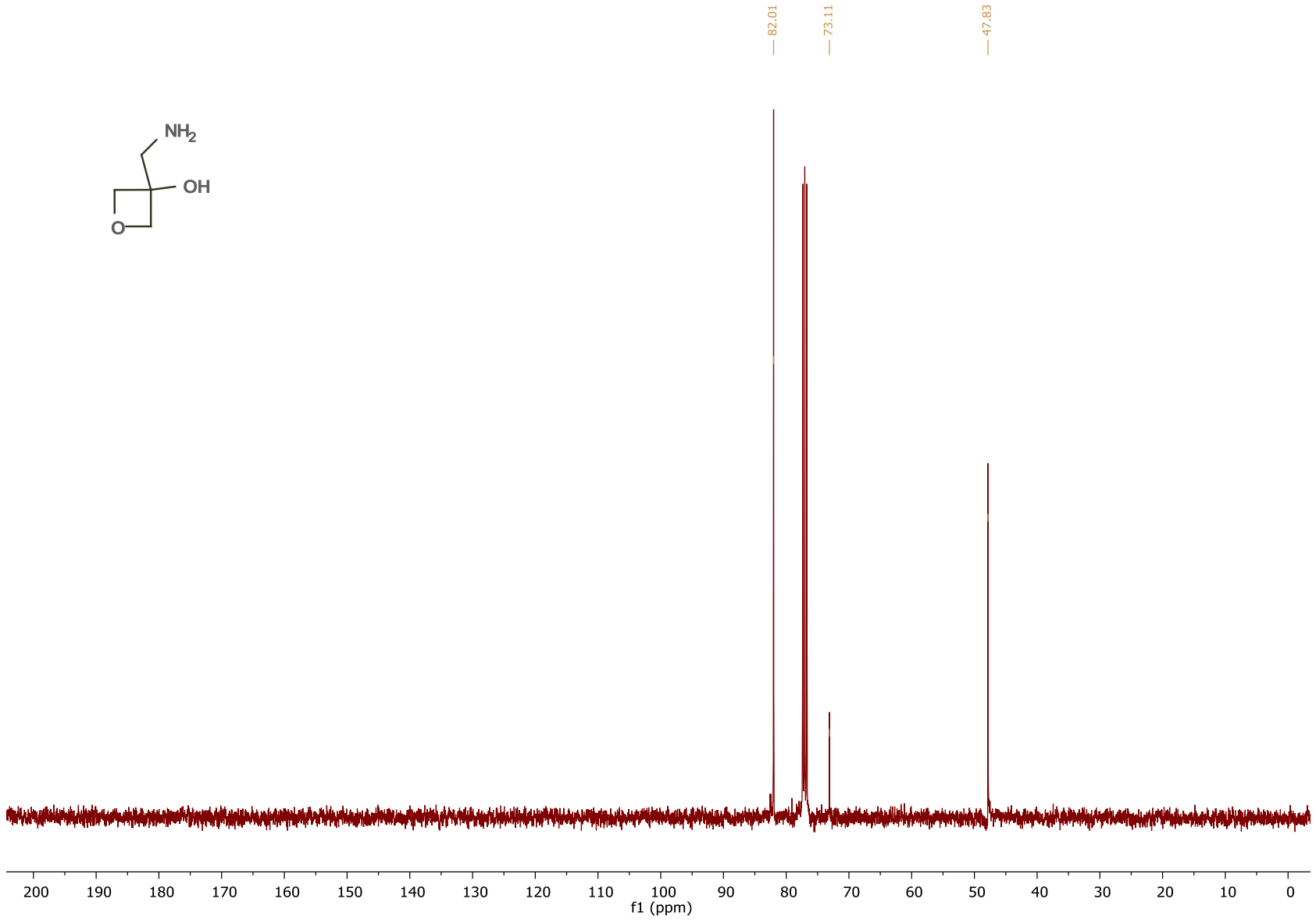
3-(Nitromethyl)oxetan-3-ol (62) ^{1}H NMR



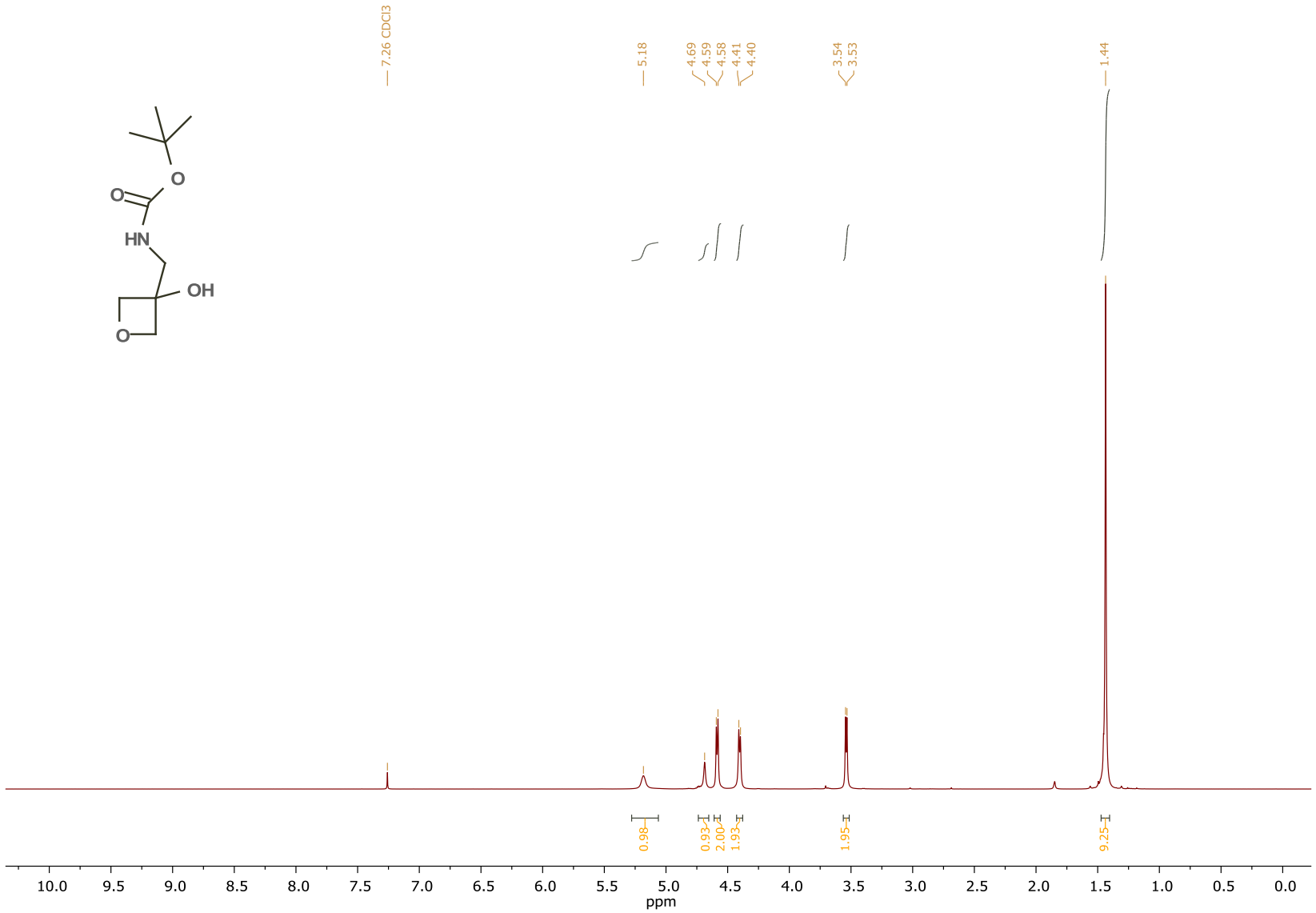
3-(Nitromethyl)oxetan-3-ol (62) $^{13}C\{H\}$ NMR



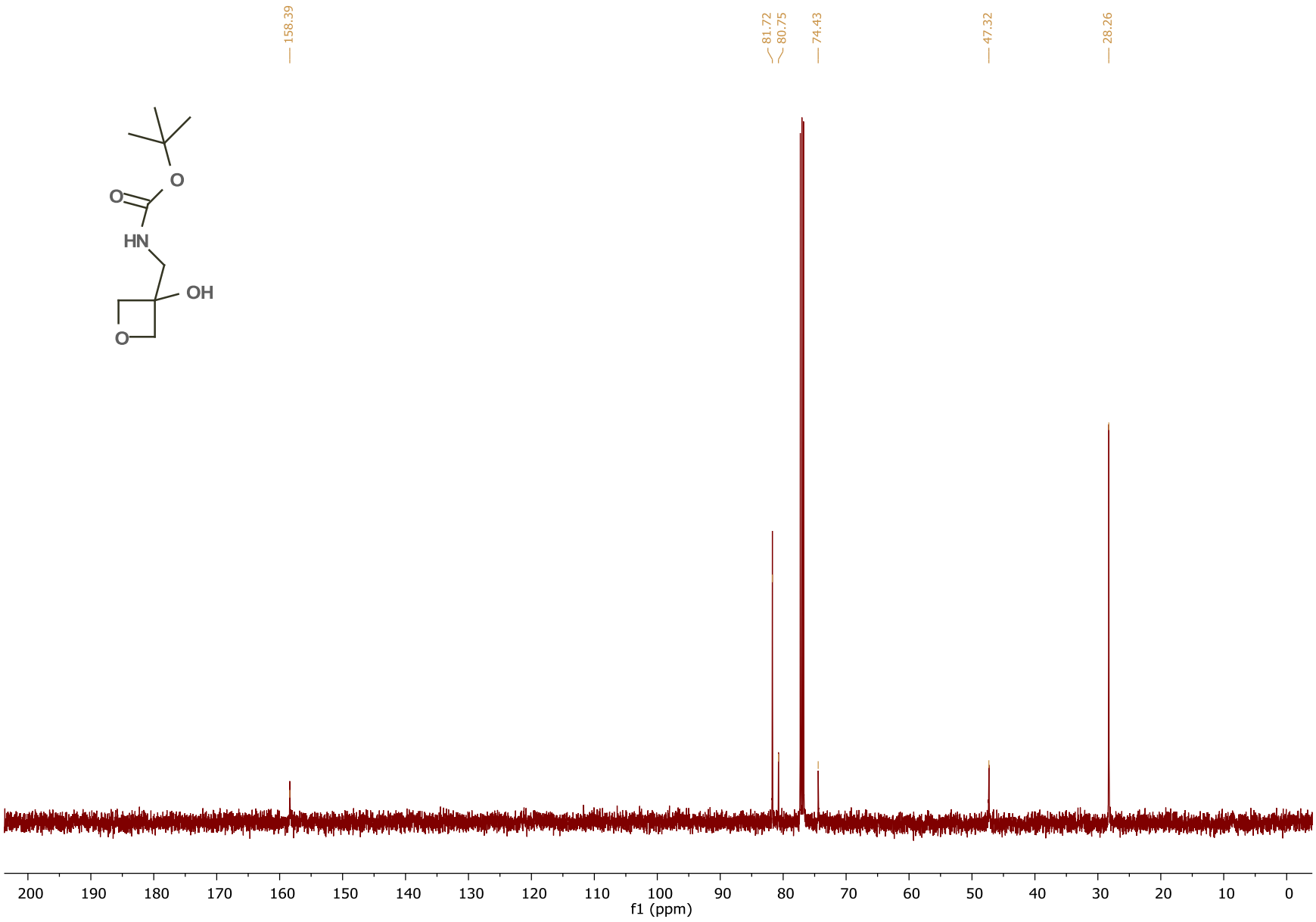
3-(Aminomethyl)oxetan-3-ol (63) ^{1}H NMR



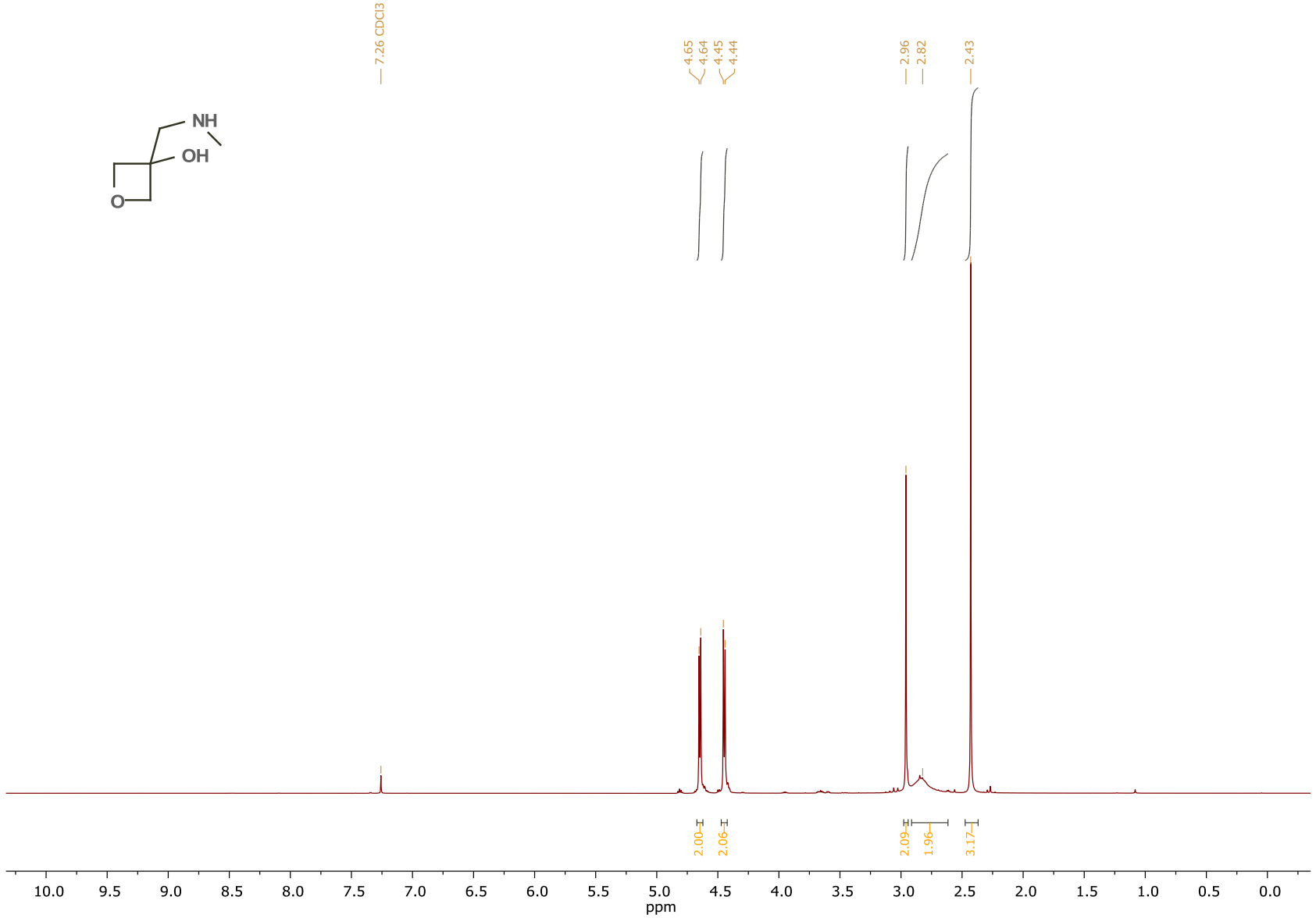
3-(Aminomethyl)oxetan-3-ol (63) $^{13}C\{H\}$ NMR



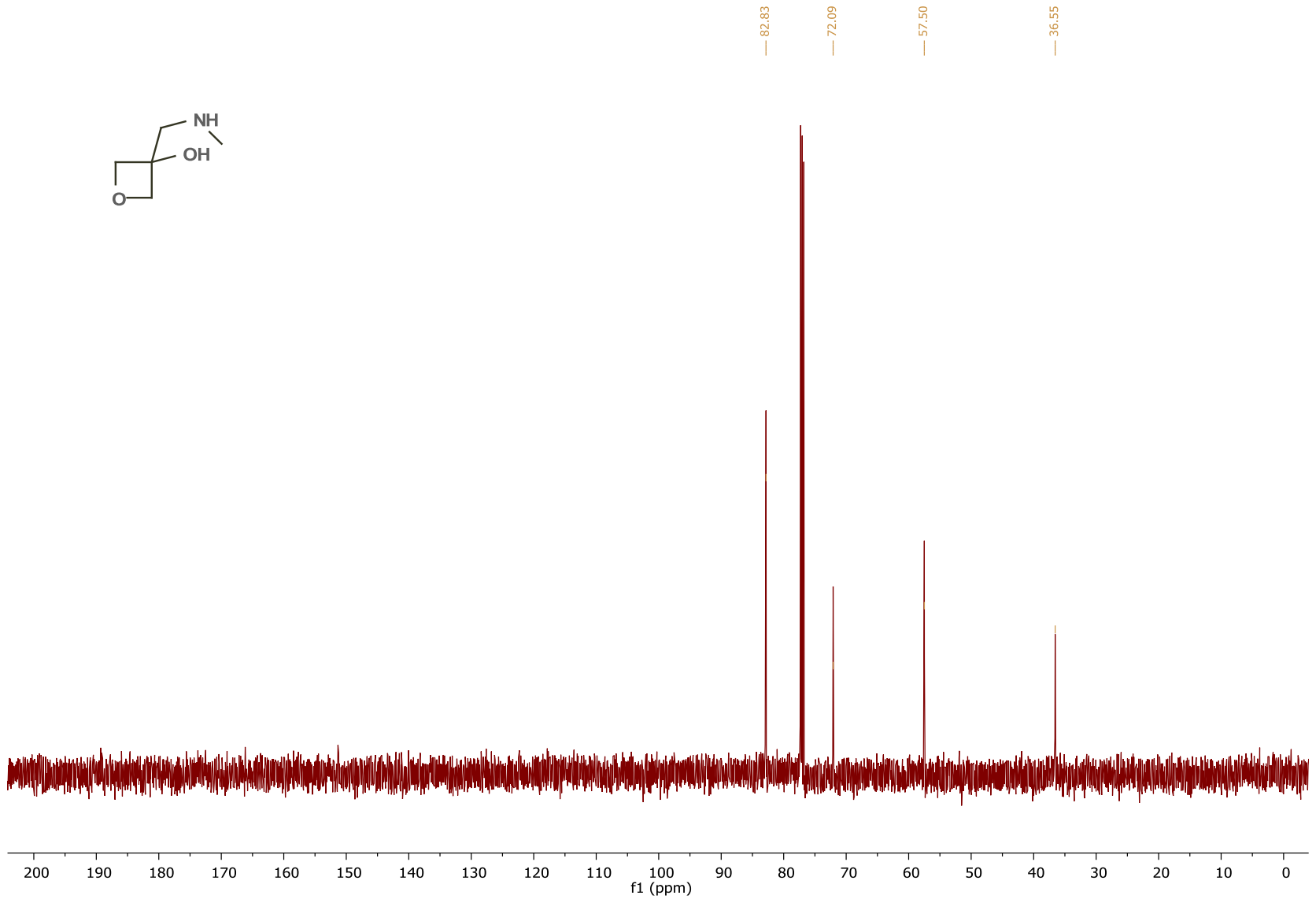
tert-Butyl _N_-[(3-hydroxyoxetan-3-yl)methyl]carbamate (64) ^{1}H NMR



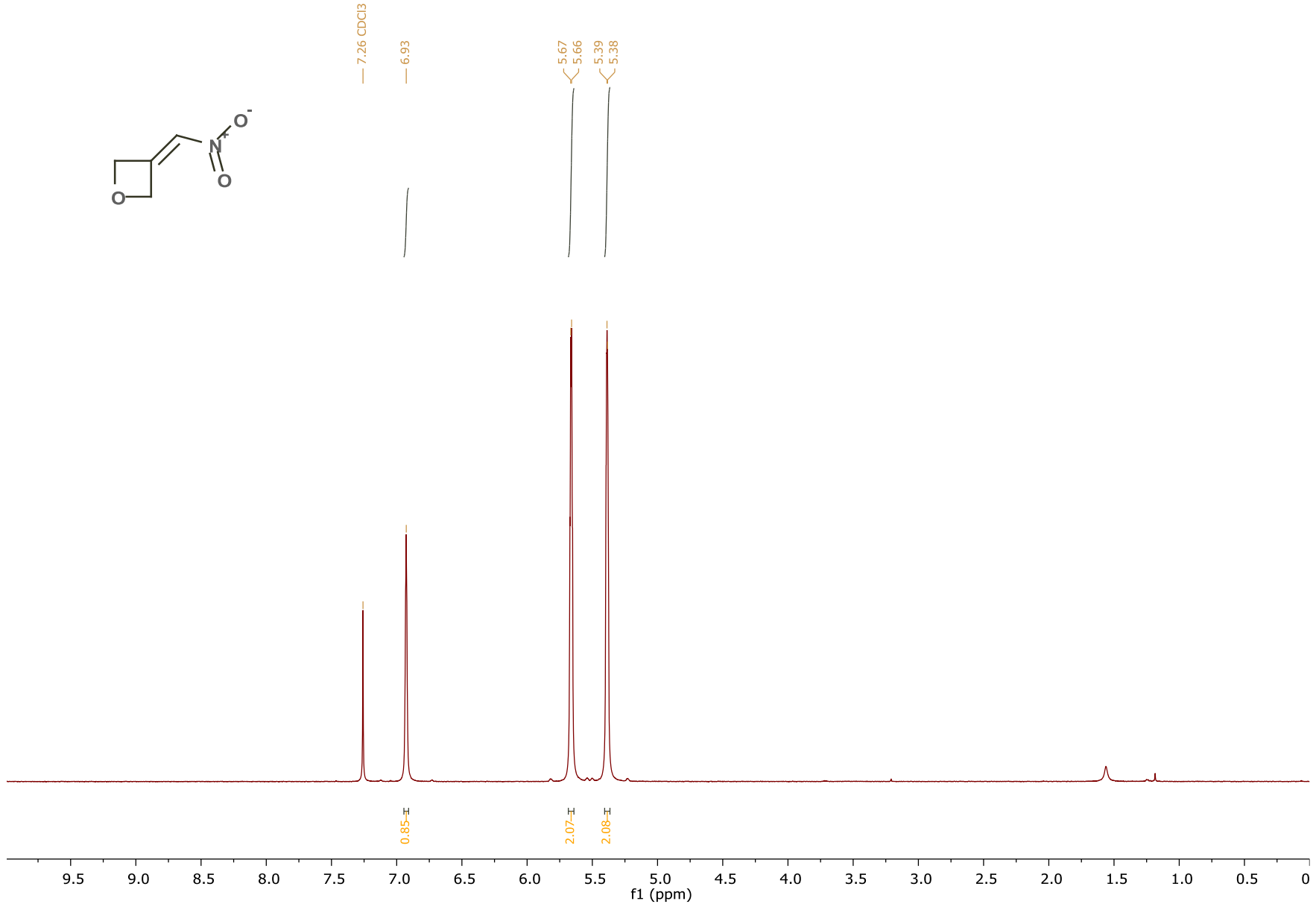
***tert*-Butyl *N*-[(3-hydroxyoxetan-3-yl)methyl]carbamate (64) $^{13}C\{H\}$ NMR**



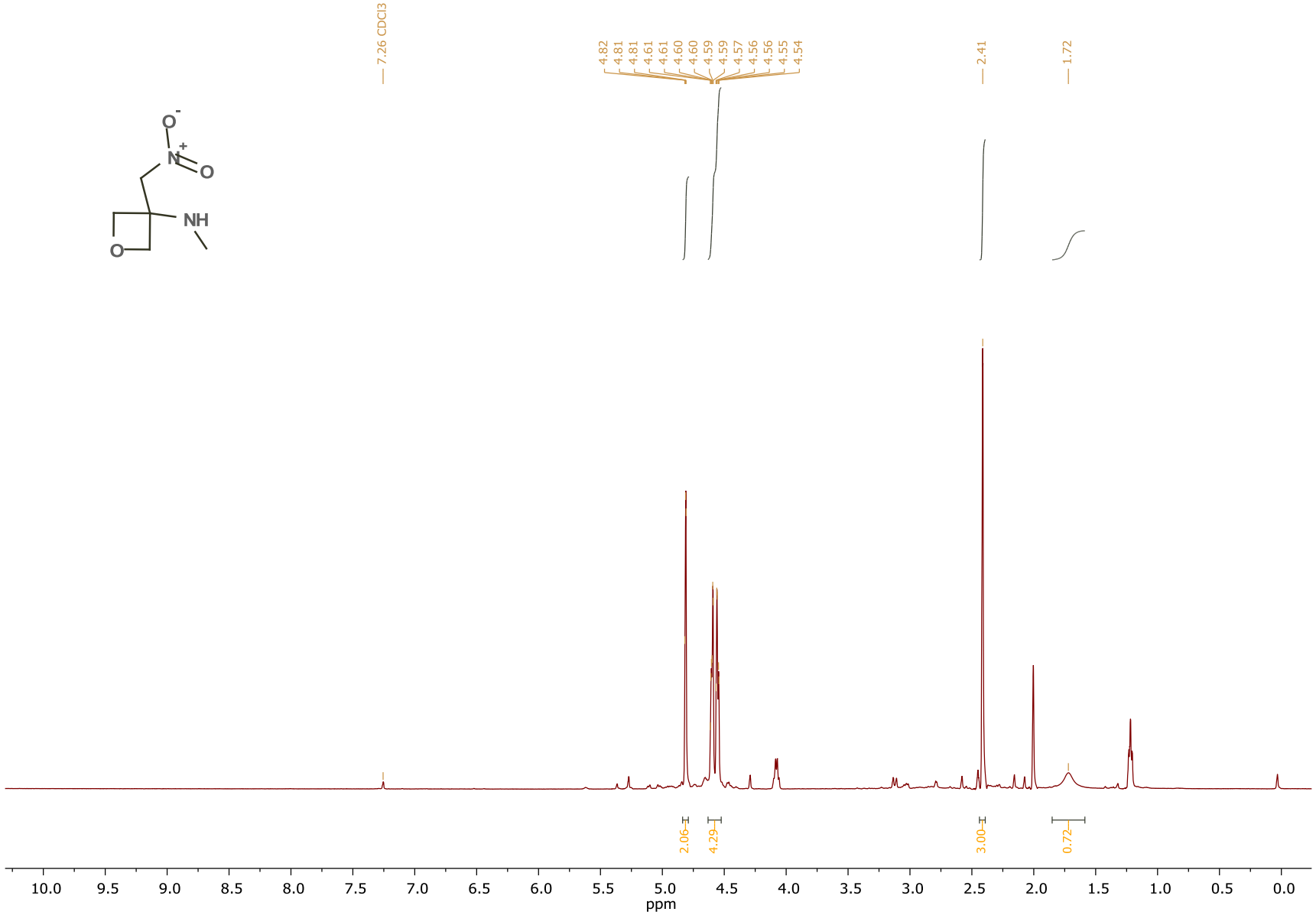
3-((Methylamino)methyl)oxetan-3-ol (67) ^{1}H NMR



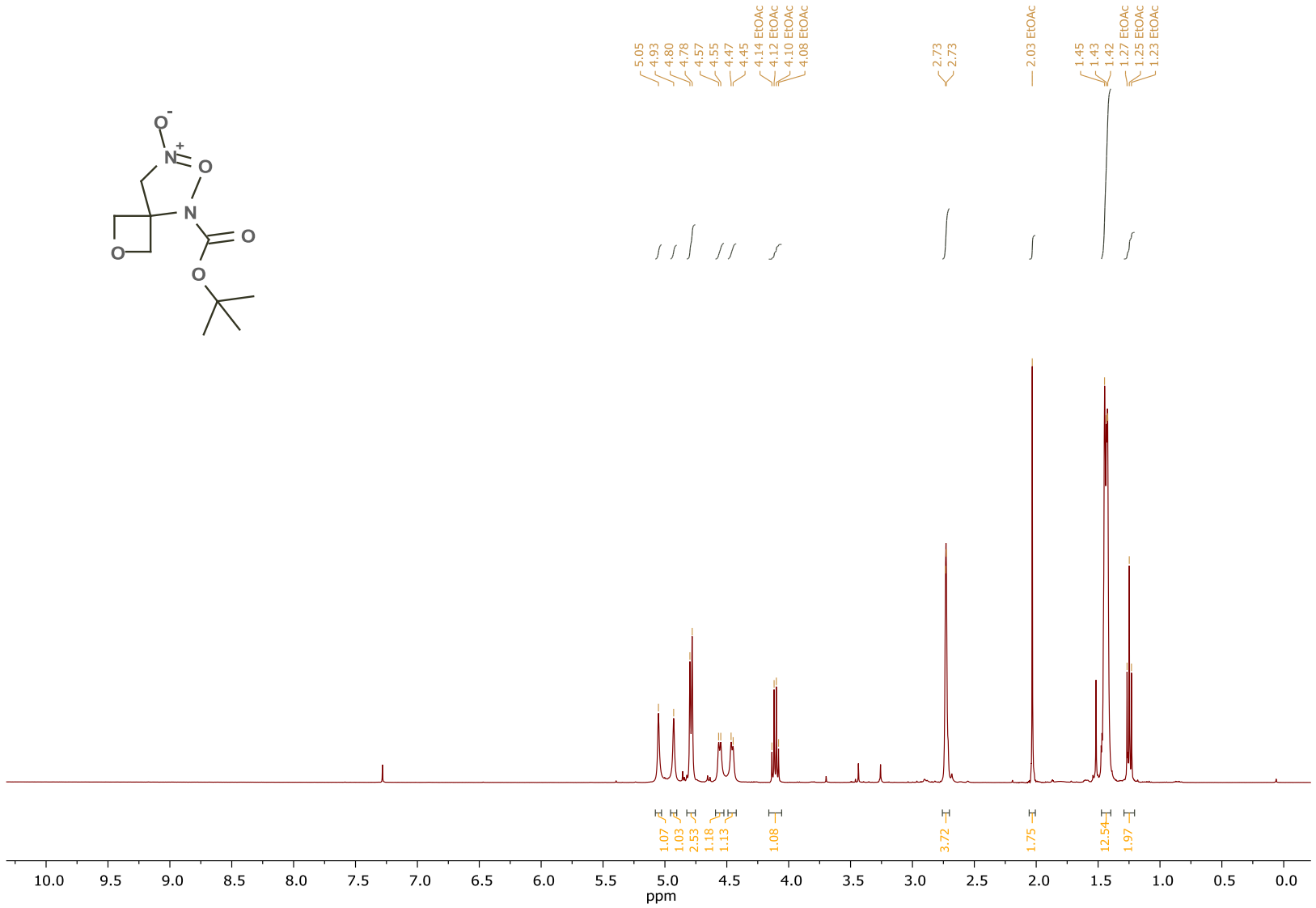
3-((Methylamino)methyl)oxetan-3-ol (67) $^{13}C\{H\}$ NMR



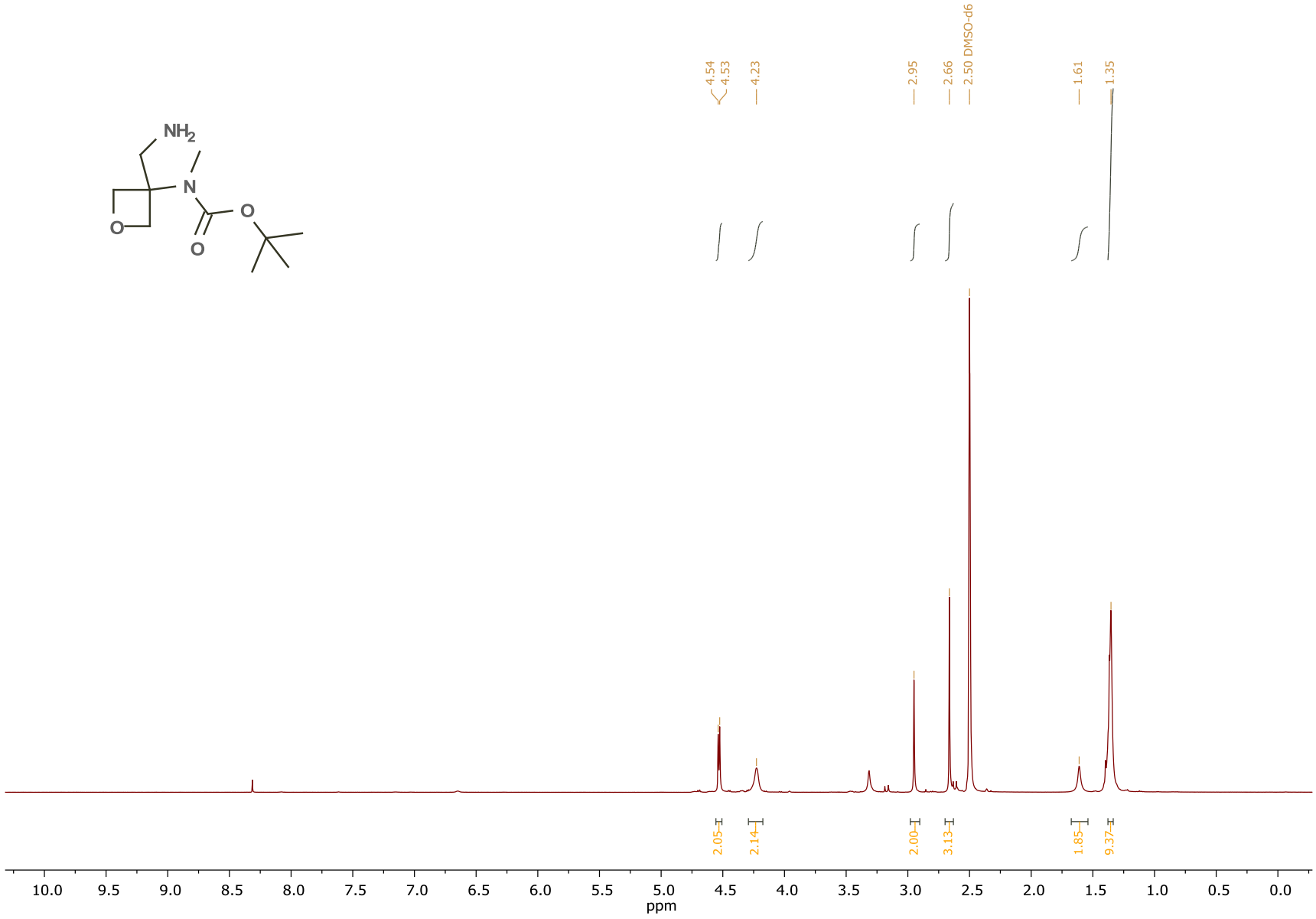
3-(Nitromethylene)oxetane (68) ^{1}H NMR



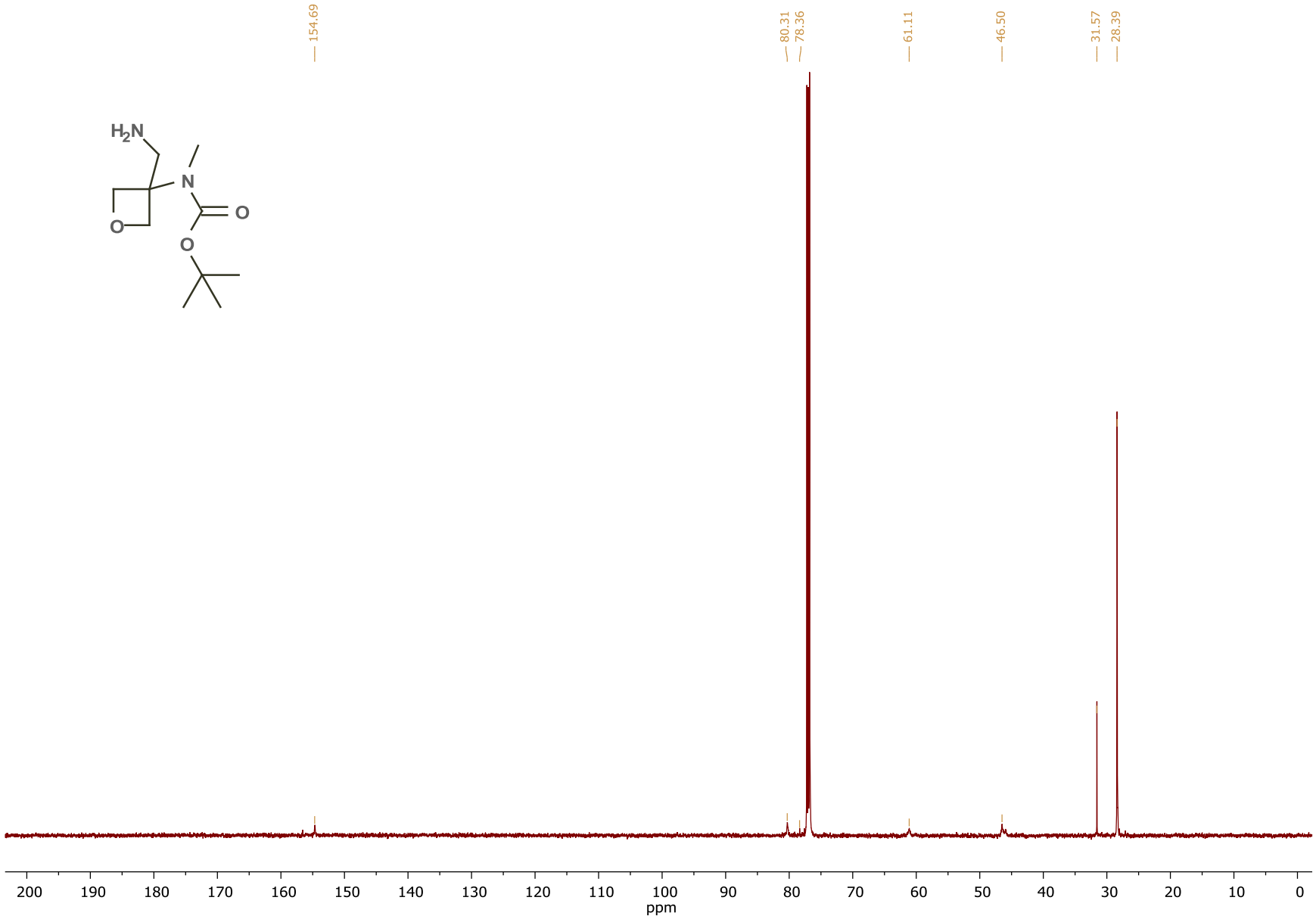
_N_-Methyl-3-(nitromethyl)oxetan-3-amine (69) ^{1}H NMR (crude)



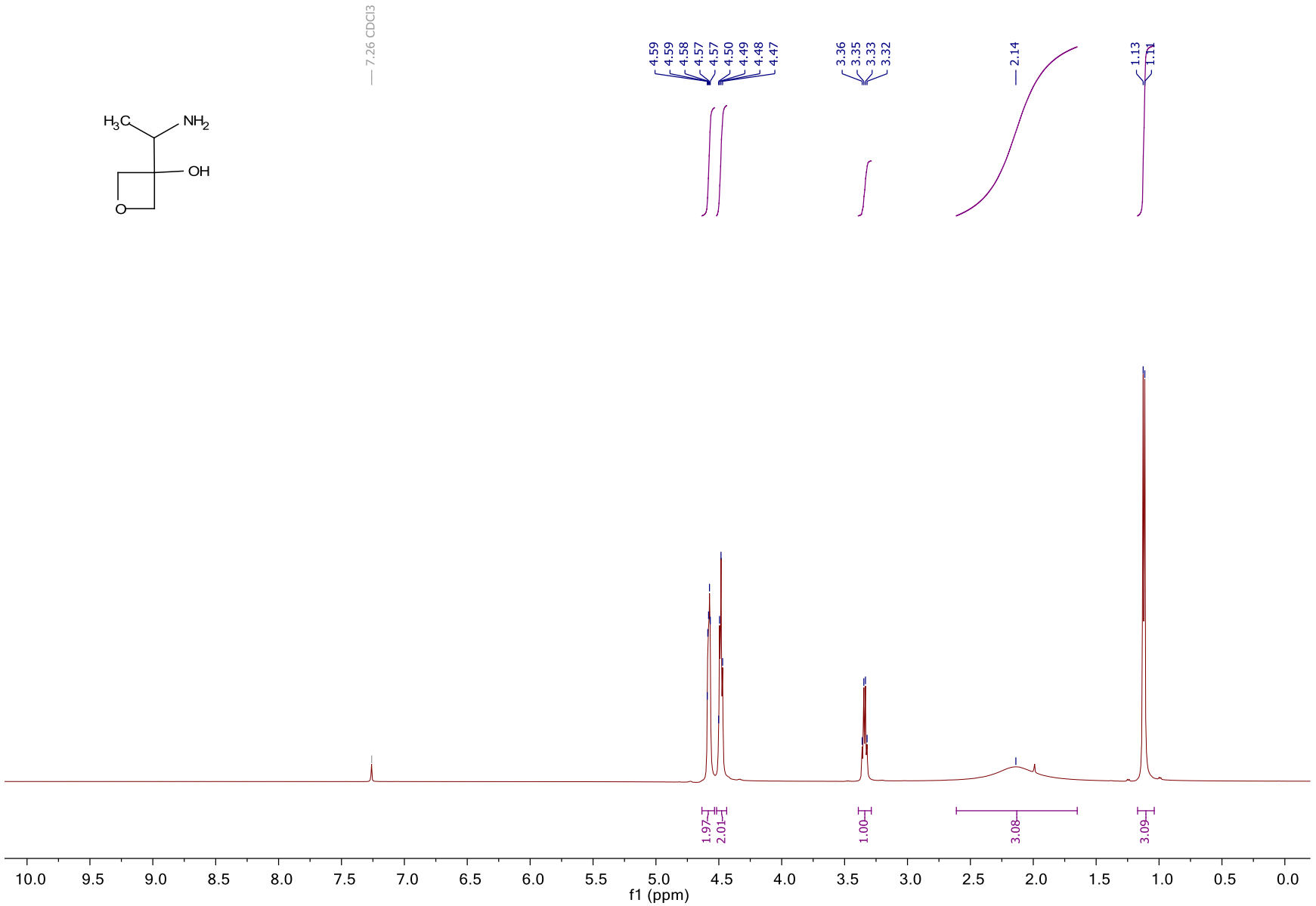
tert-Butyl methyl(3-(nitromethyl)oxetan-3-yl)carbamate (70) ^{1}H NMR (crude)



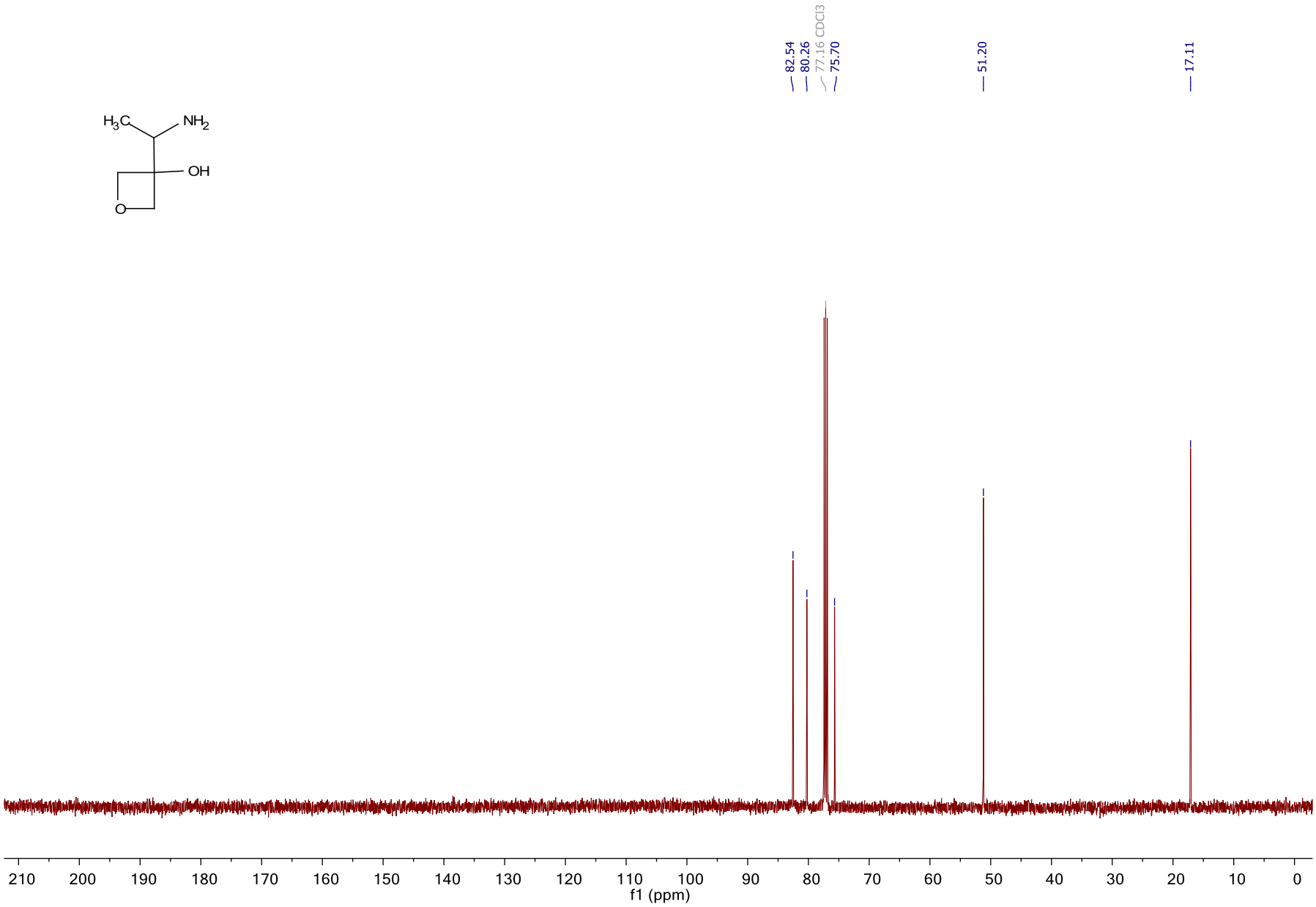
tert-Butyl _N_-[3-(aminomethyl)oxetan-3-yl]-_N_-methylcarbamate (71) ^{1}H NMR



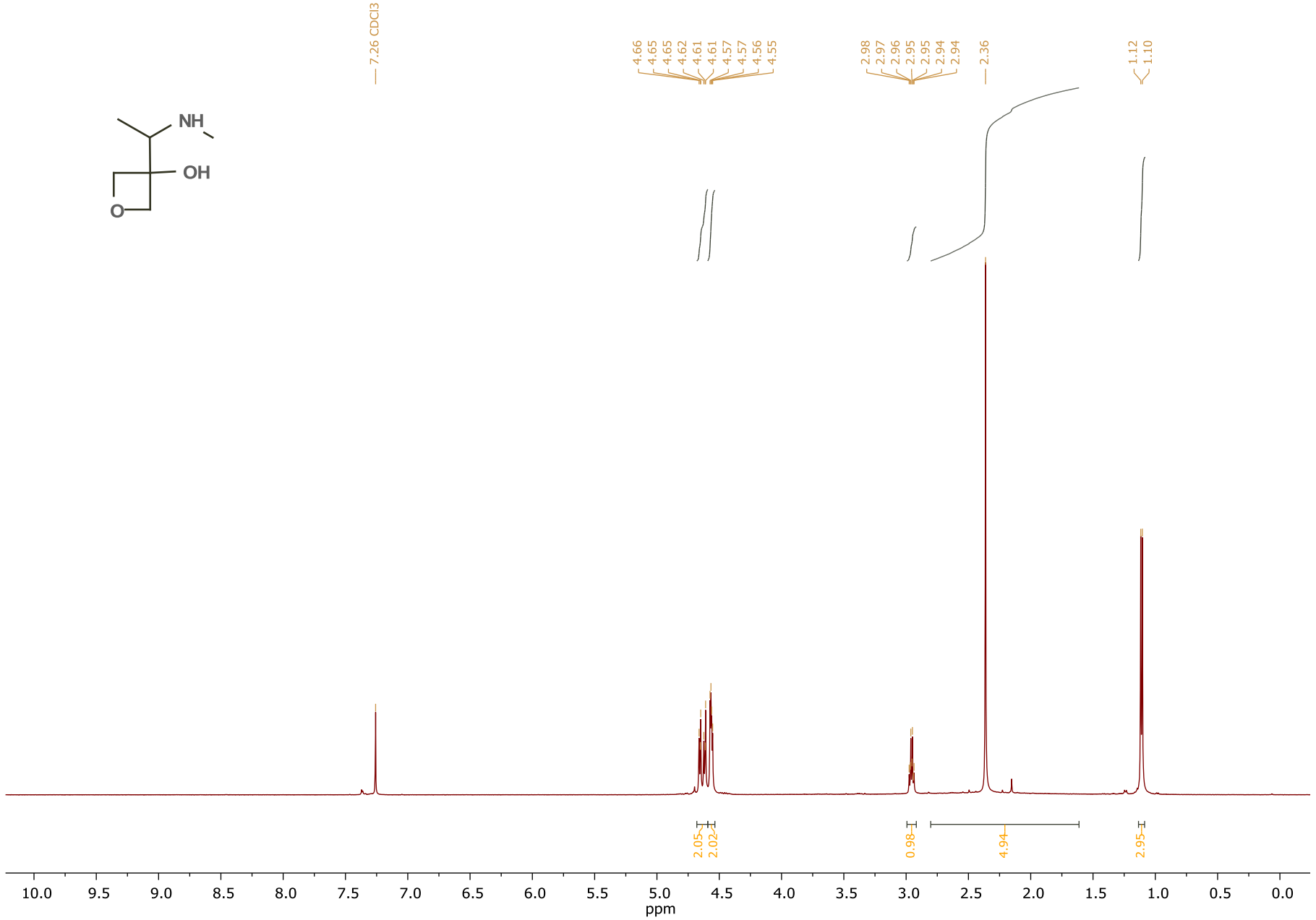
tert-Butyl _N_-[3-(aminomethyl)oxetan-3-yl]-_N_-methylcarbamate (71) ^{13}C{H} NMR



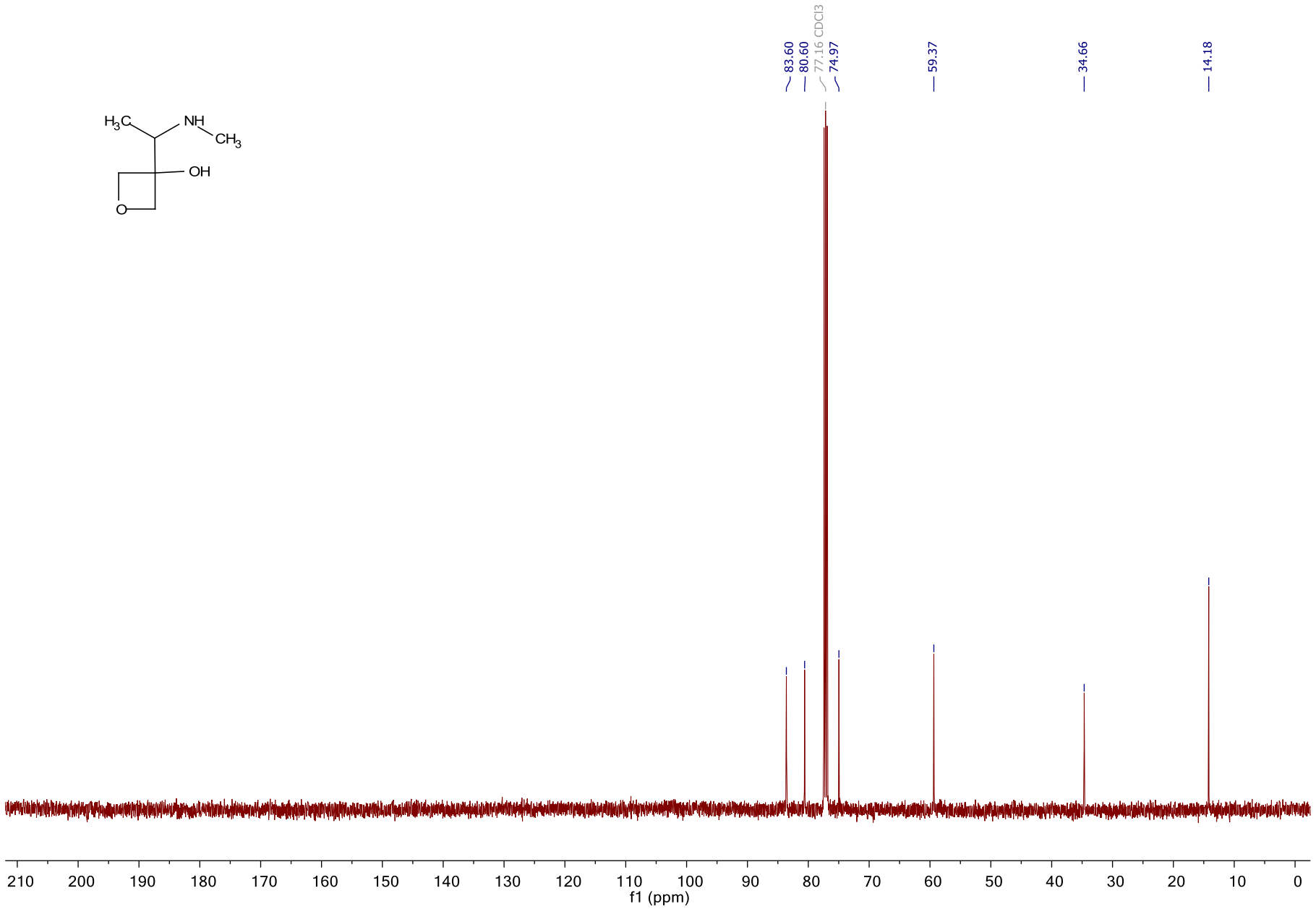
3-(1-Aminoethyl)oxetan-3-ol (73) ^{1}H NMR



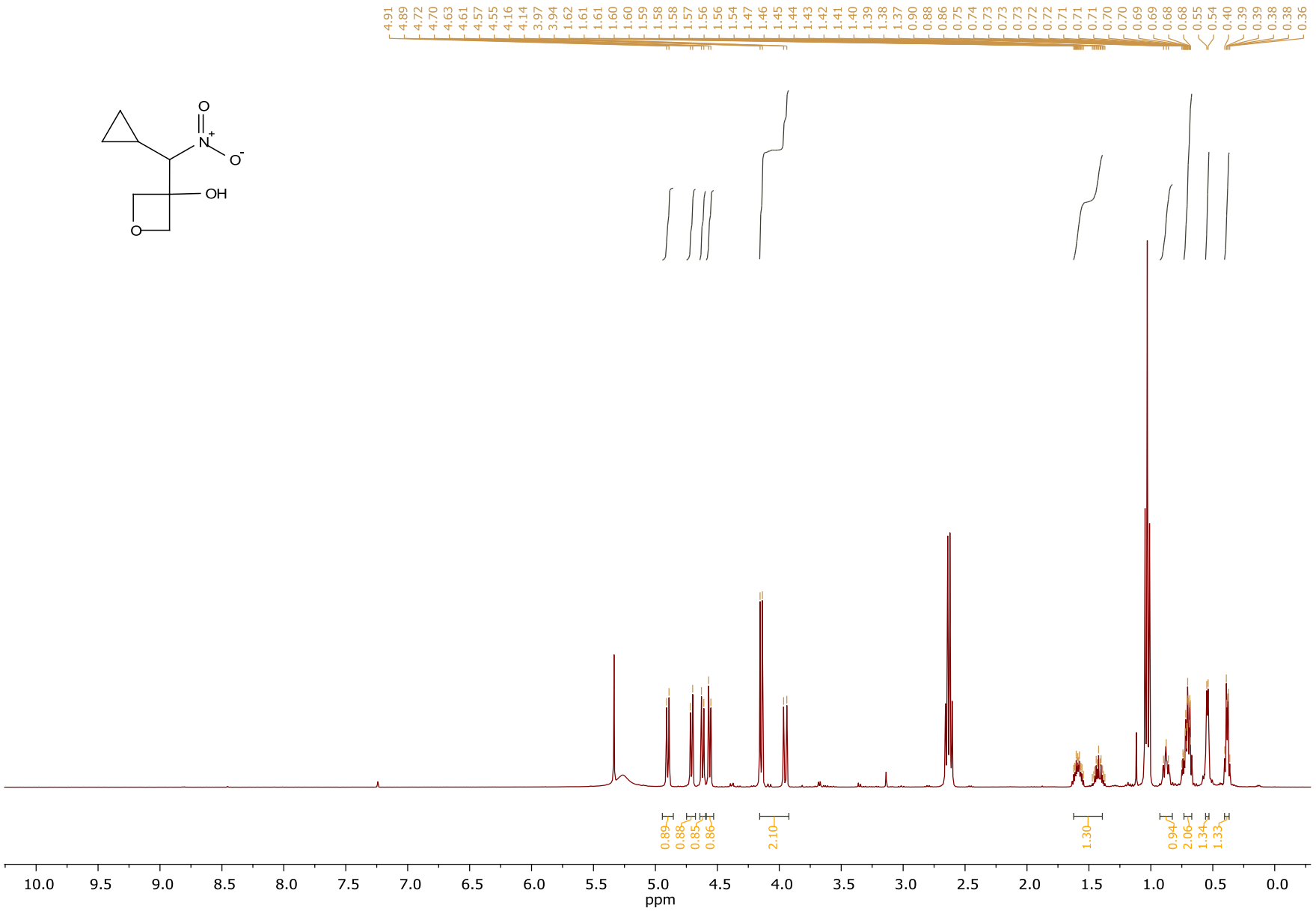
3-(1-Aminoethyl)oxetan-3-ol (73) ^{13}C NMR



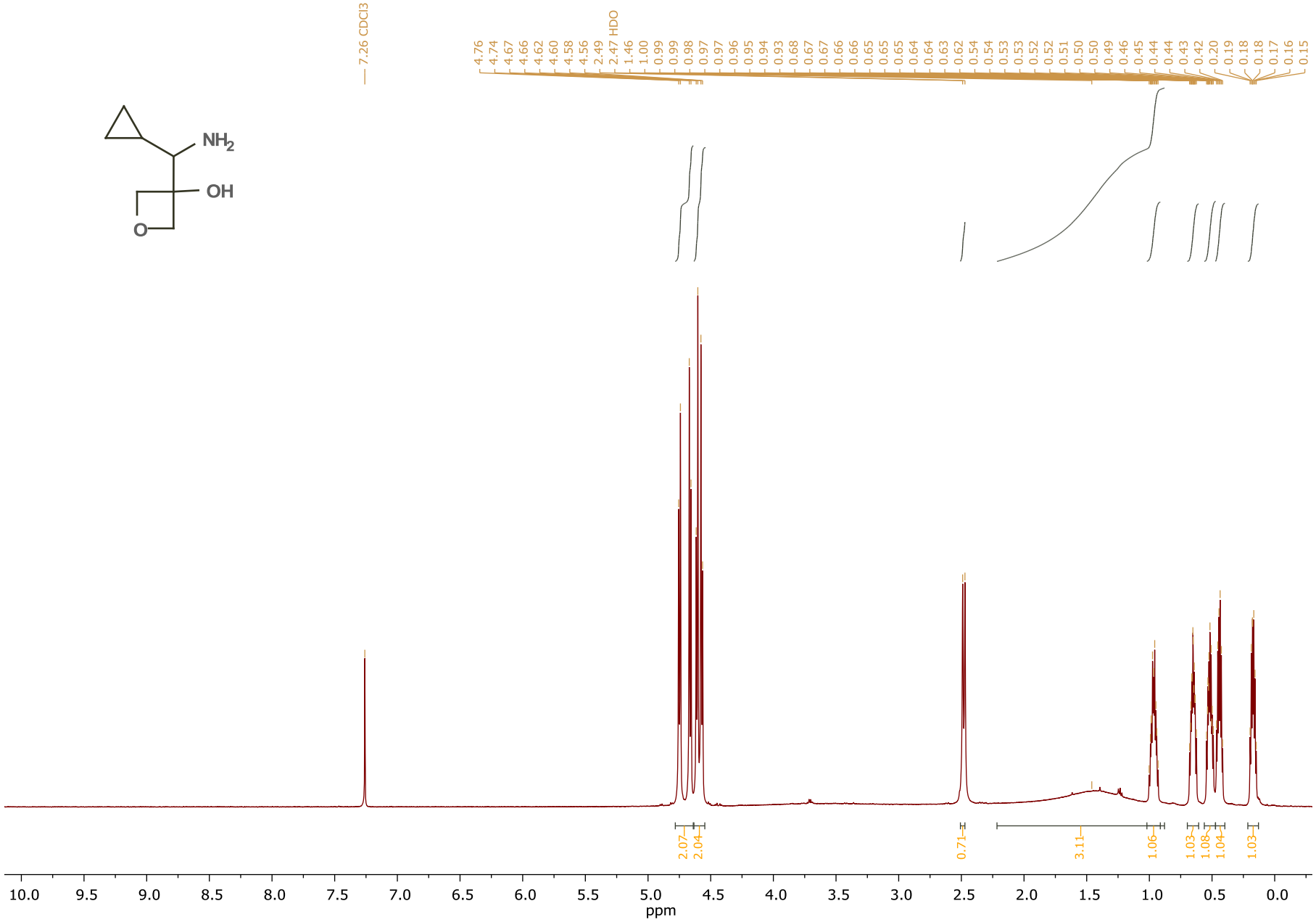
3-(1-(Methylamino)ethyl)oxetan-3-ol (74) ^{1}H NMR



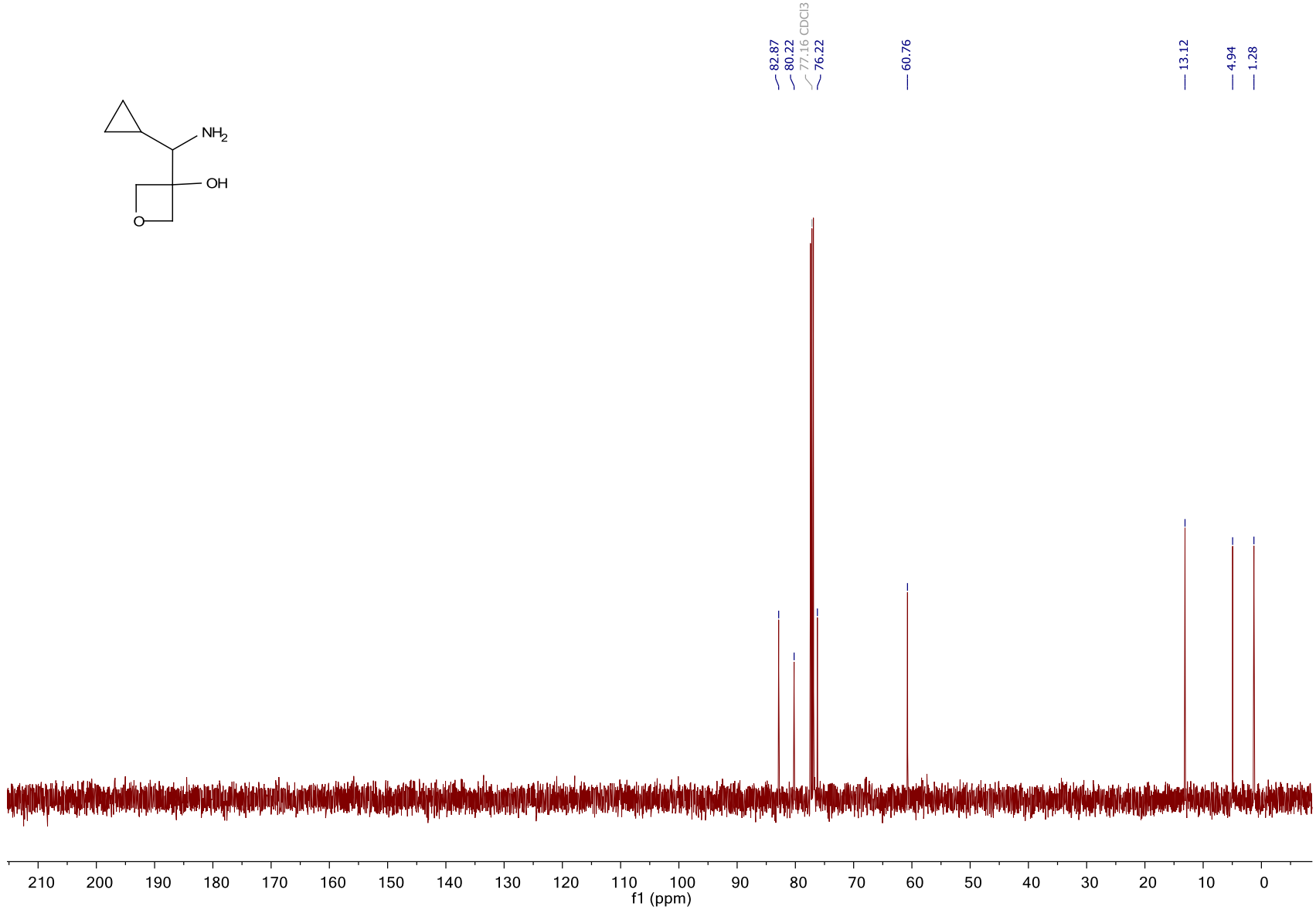
3-(1-(Methylamino)ethyl)oxetan-3-ol (74) $^{13}C\{H\}$ NMR



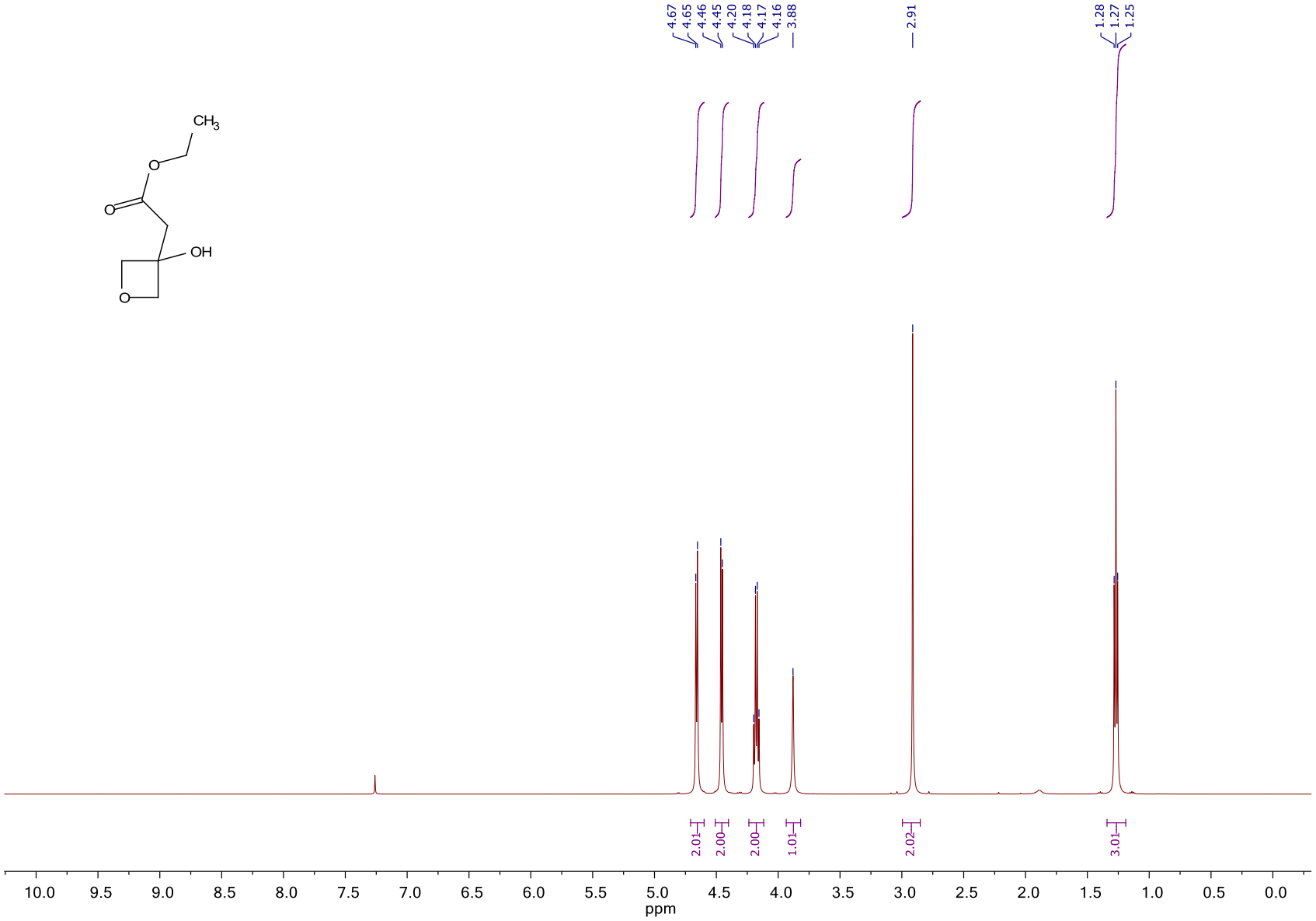
3-(Cyclopropyl(nitro)methyl)oxetan-3-ol (77) ^{1}H NMR (crude)



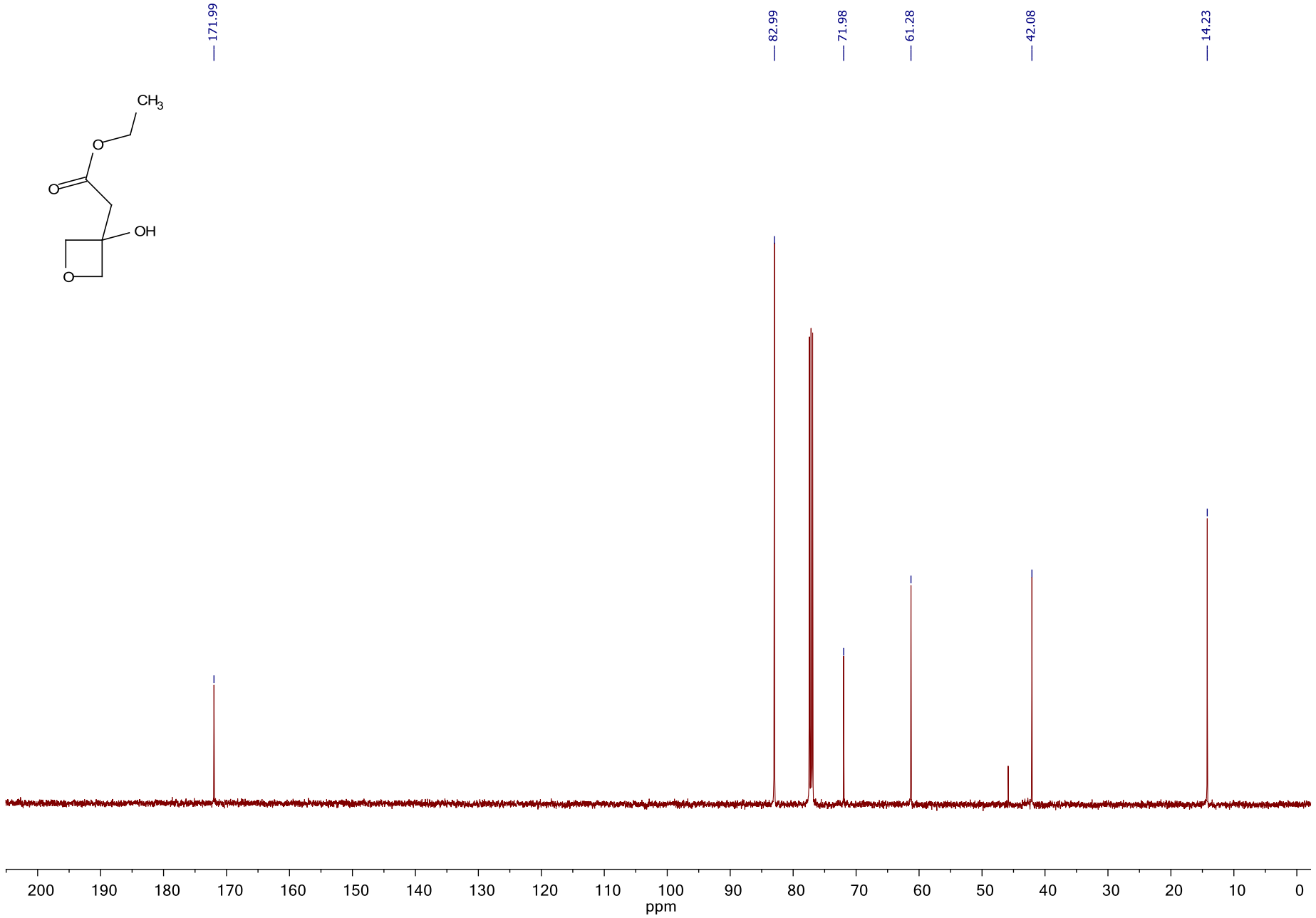
3-[Amino(cyclopropyl)methyl]oxetan-3-ol (78) ^{1}H NMR



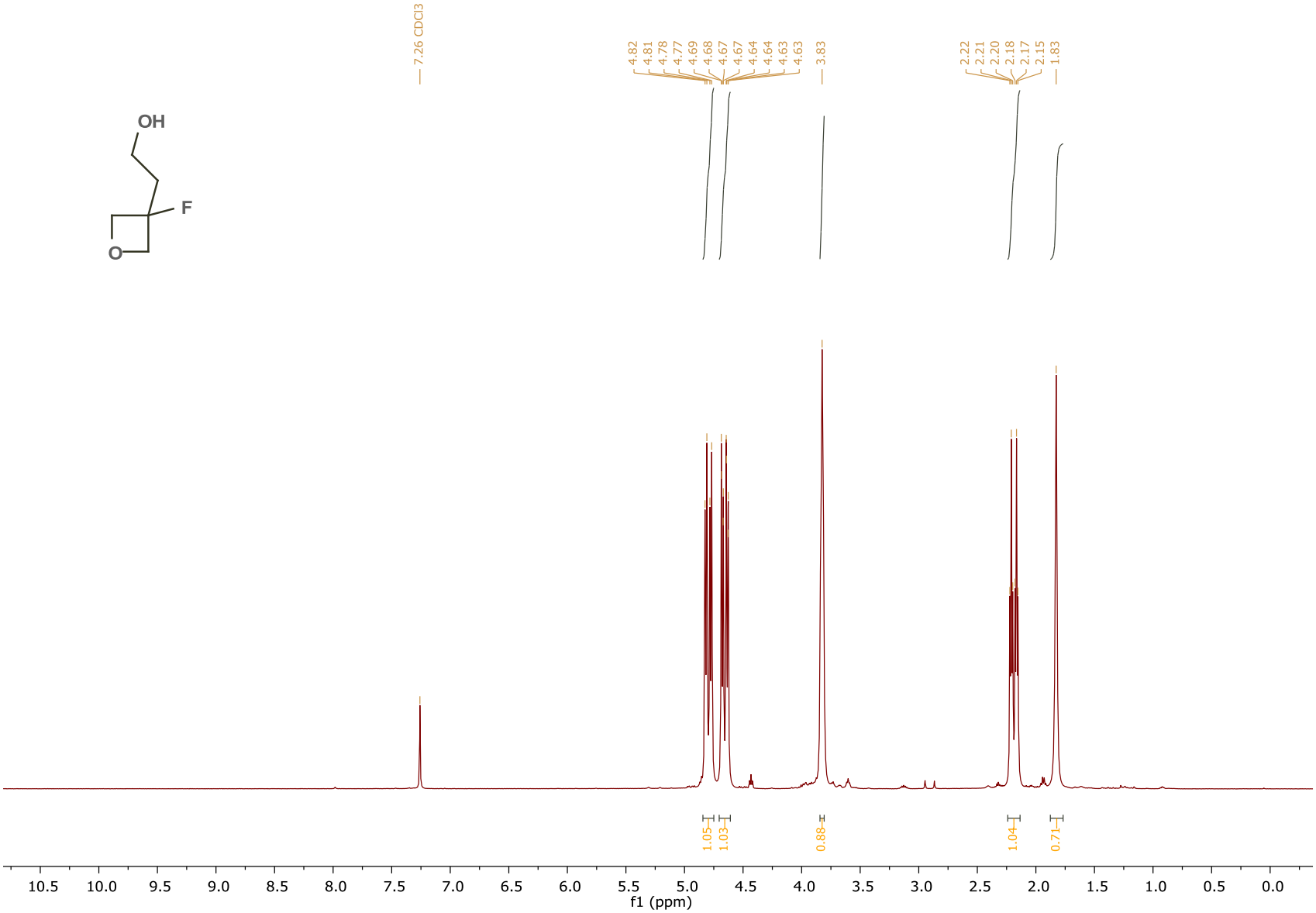
3-[Amino(cyclopropyl)methyl]oxetan-3-ol (78) $^{13}C\{H\}$ NMR



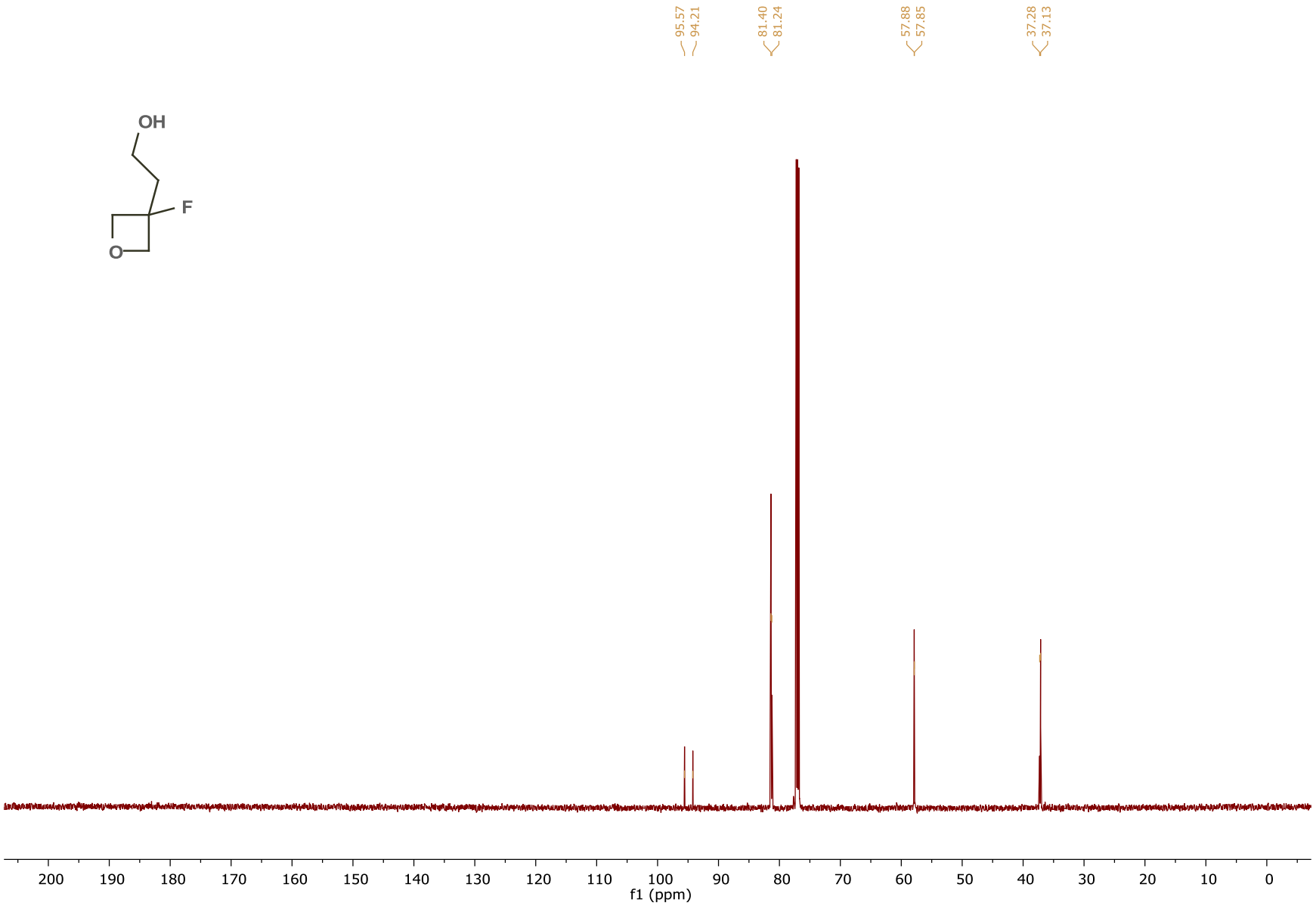
Ethyl 2-(3-hydroxyoxetan-3-yl)acetate (79) ^{1}H NMR



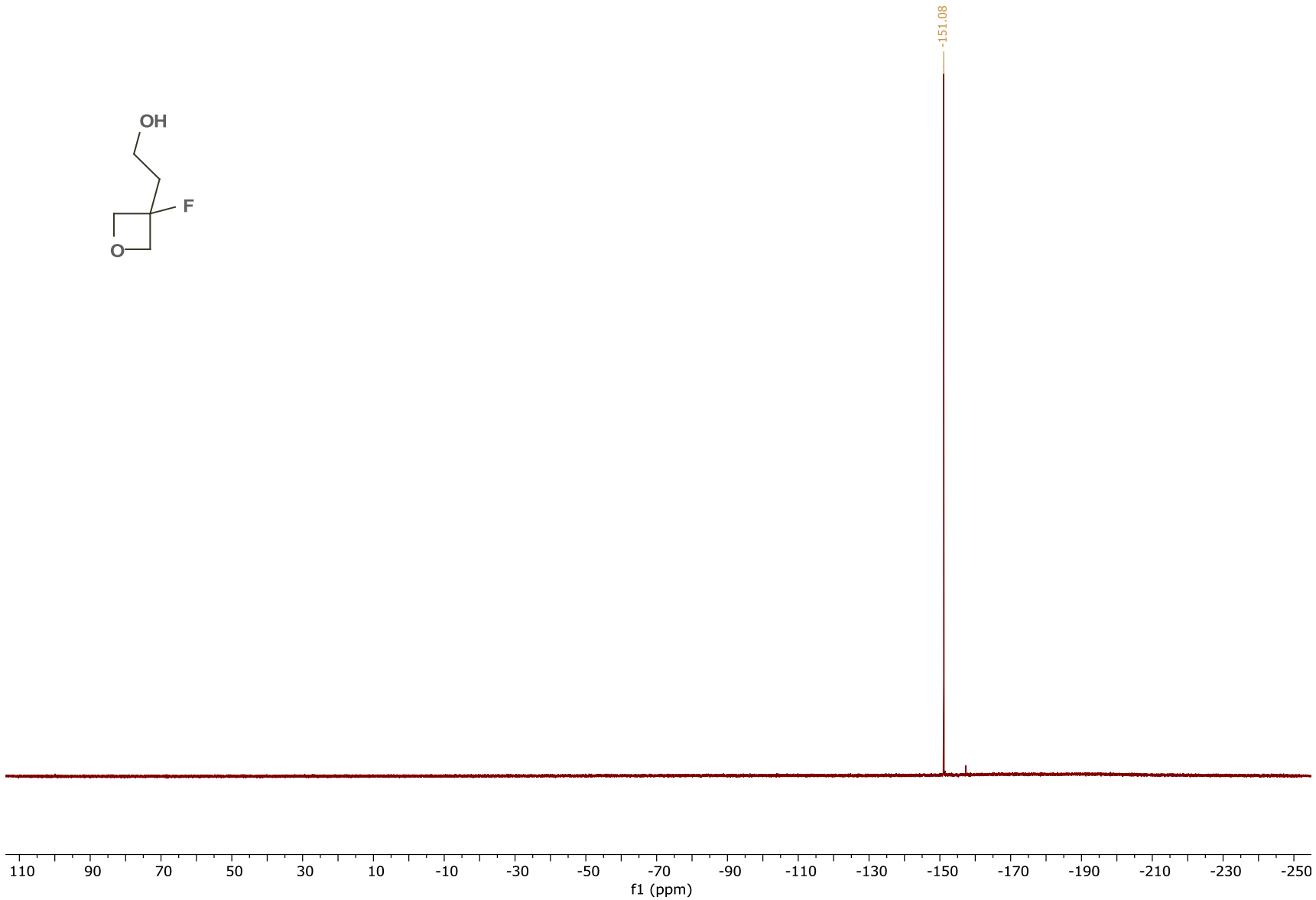
Ethyl 2-(3-hydroxyoxetan-3-yl)acetate (79) $^{13}C\{H\}$ NMR



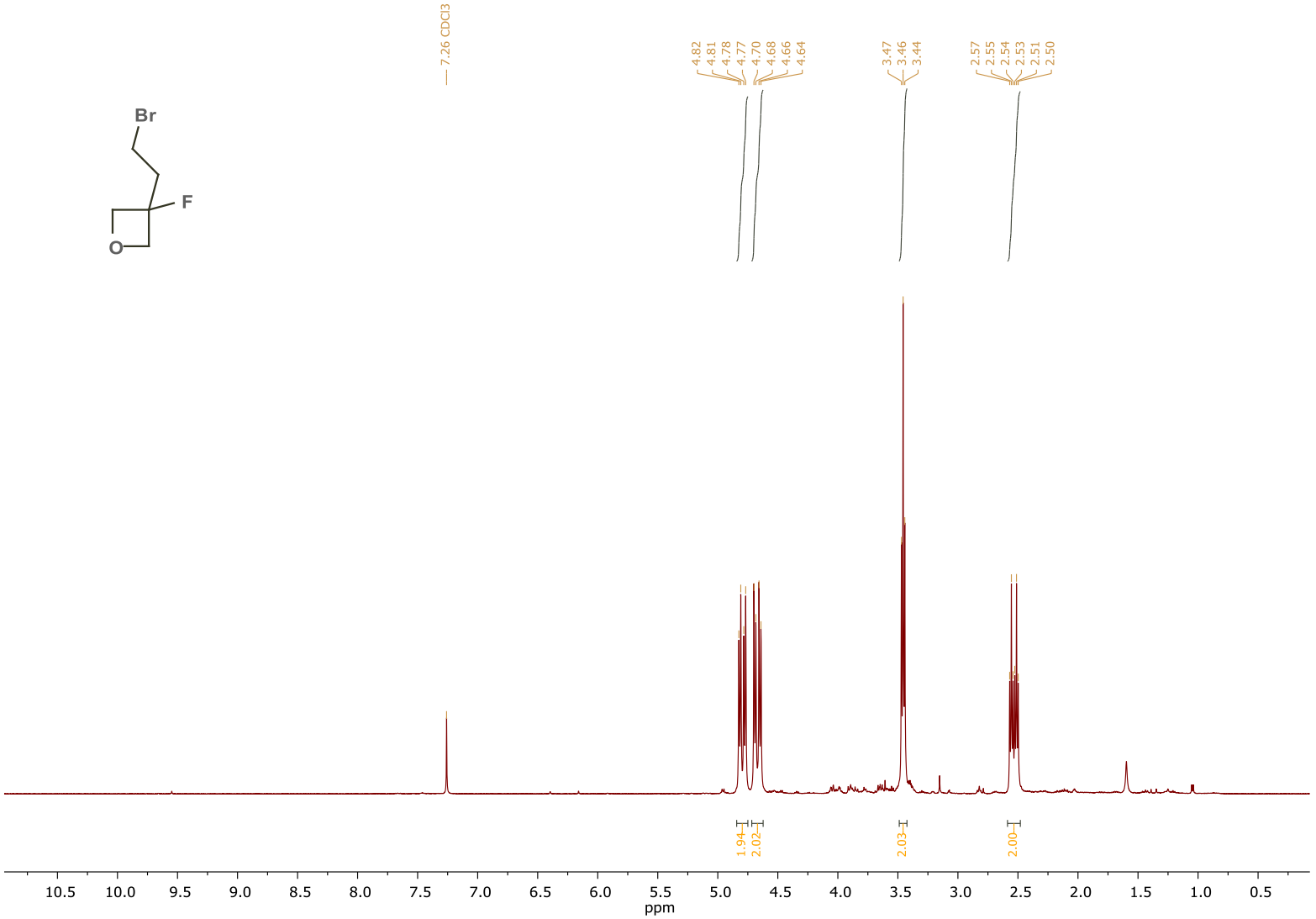
2-(3-Fluorooxetan-3-yl)ethan-1-ol (81) ^{1}H NMR



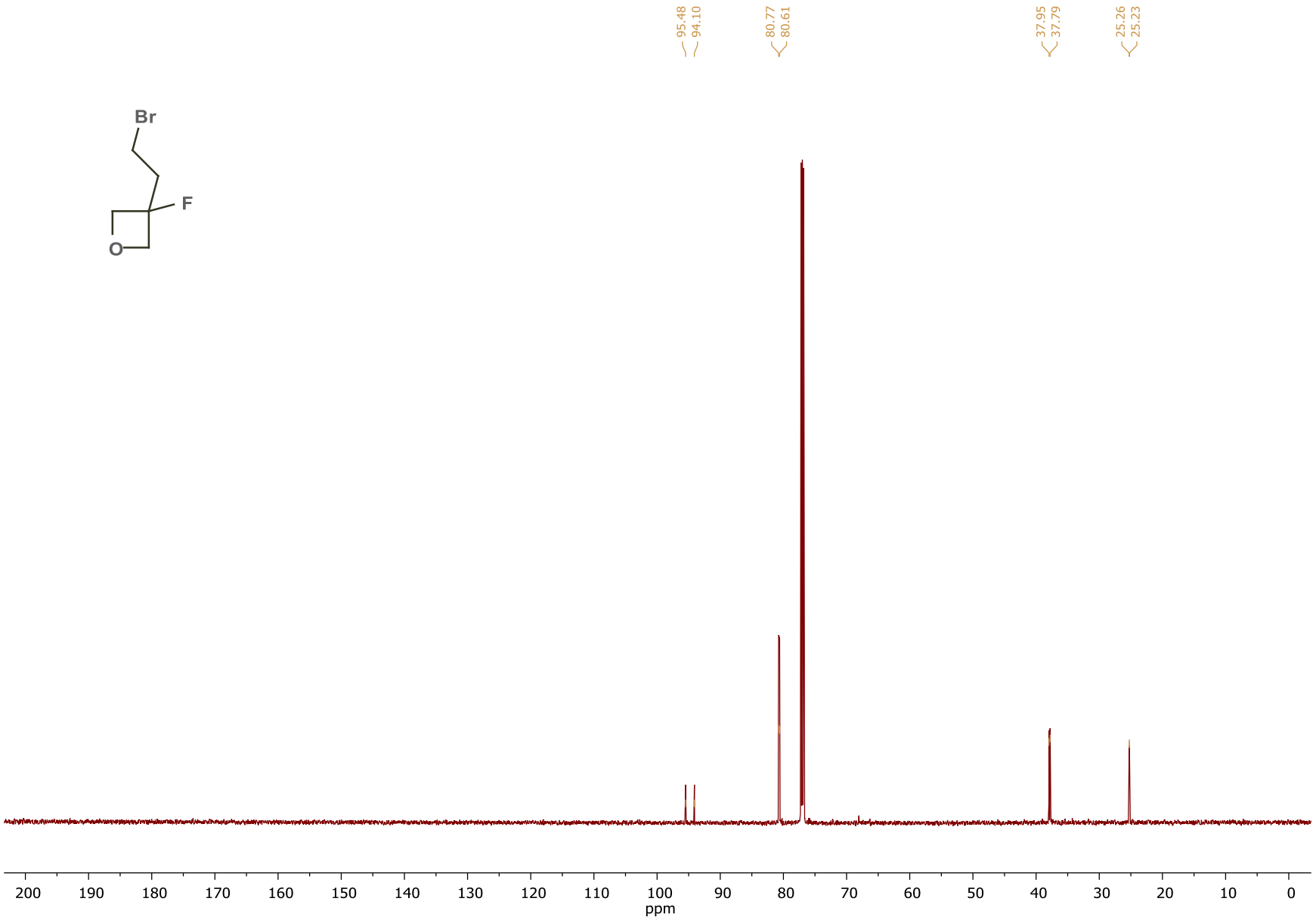
2-(3-Fluorooxetan-3-yl)ethan-1-ol (81) $^{13}C\{H\}$ NMR



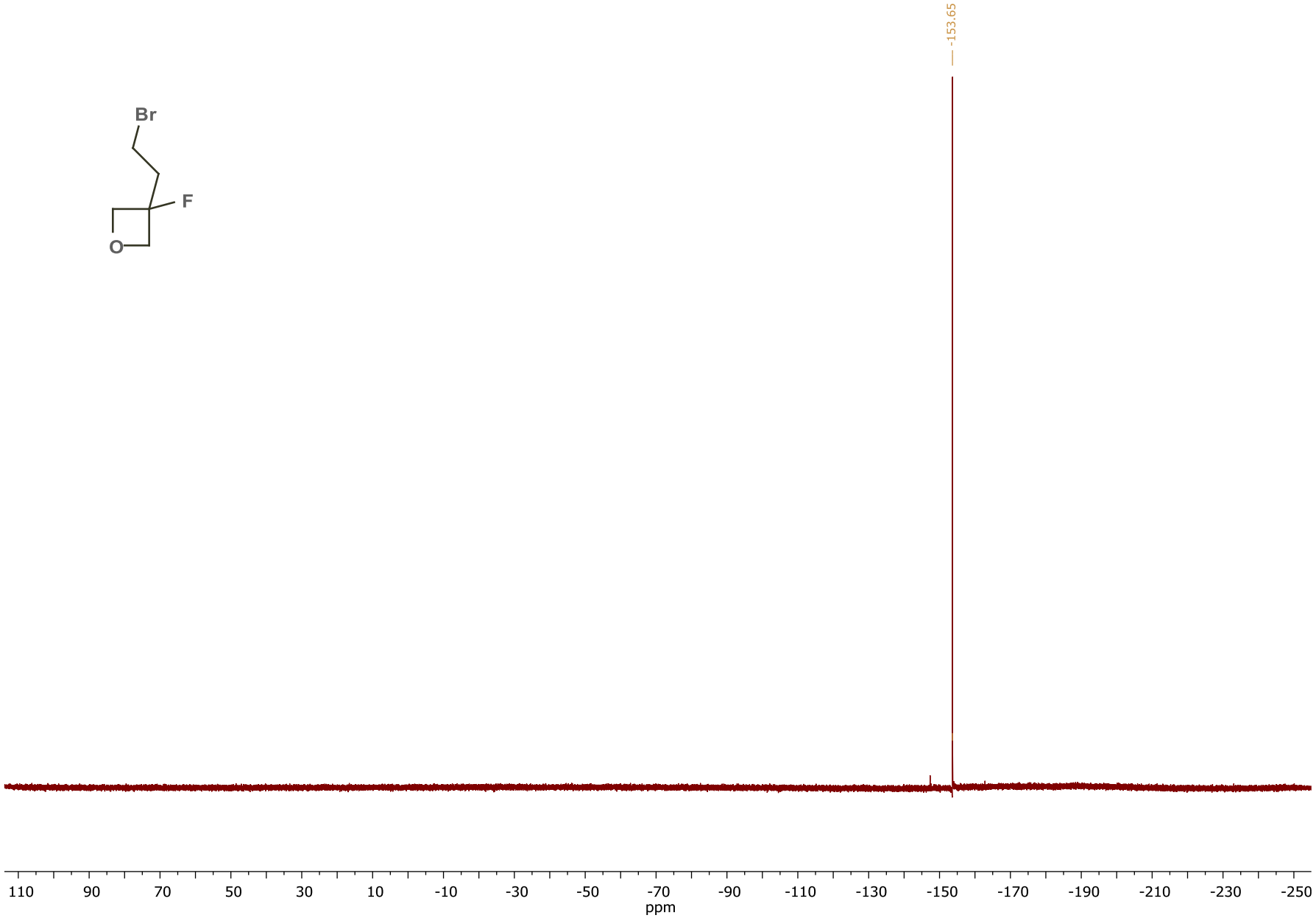
2-(3-Fluorooxetan-3-yl)ethan-1-ol (81) $^{19}F\{H\}$ NMR



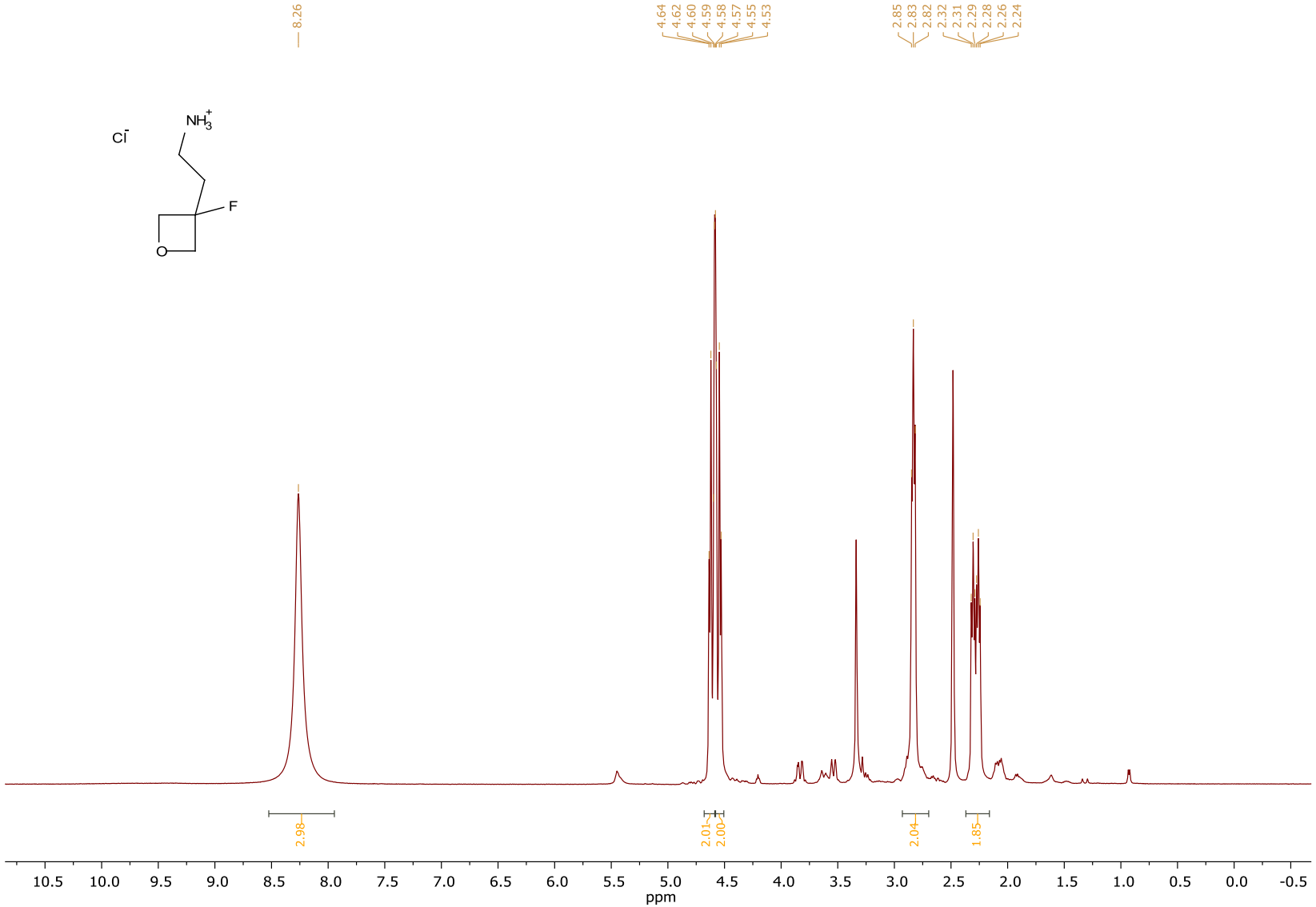
3-(2-Bromoethyl)-3-fluorooxetane (83) ^{1}H NMR



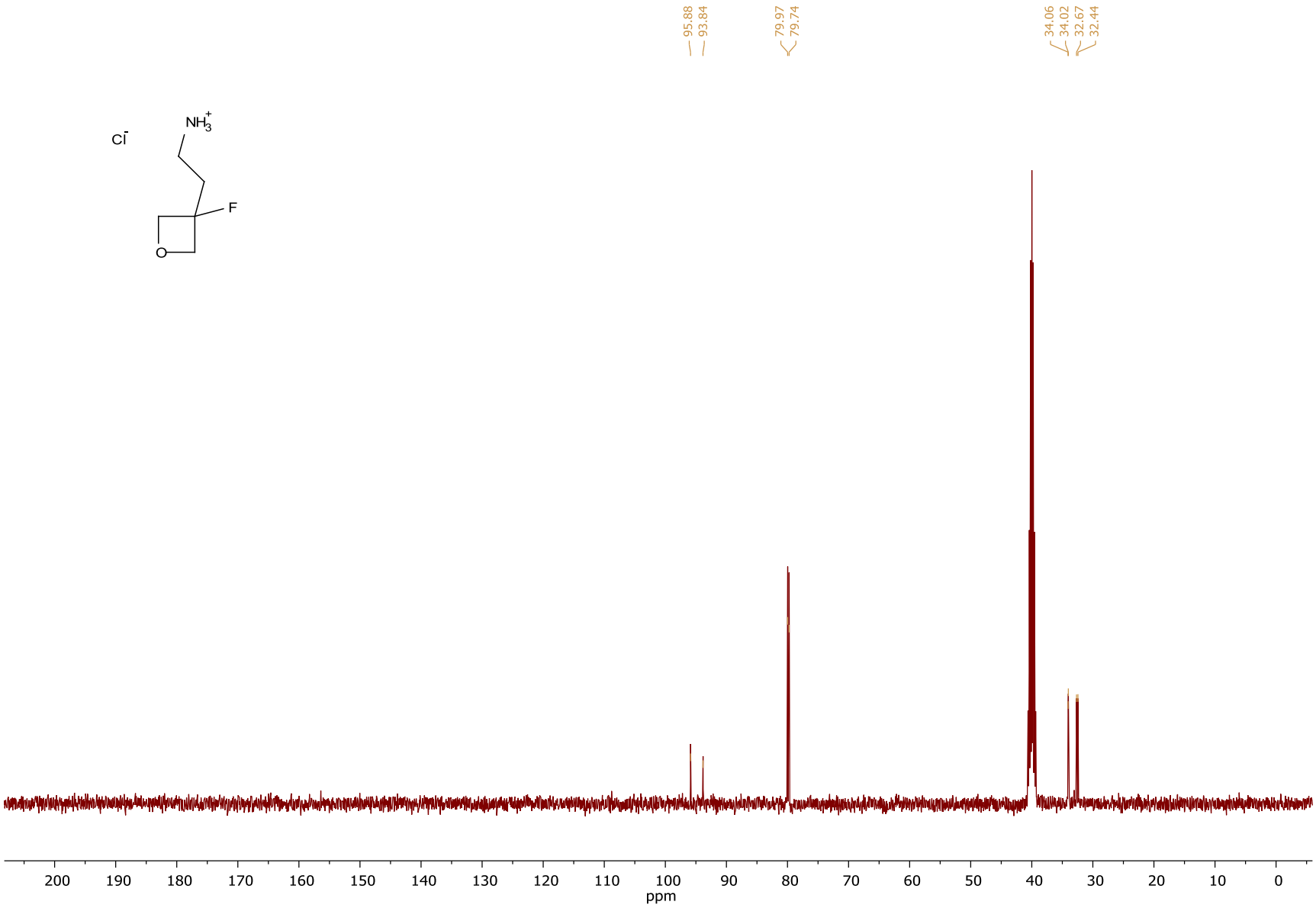
3-(2-Bromoethyl)-3-fluorooxetane (83) $^{13}C\{H\}$ NMR



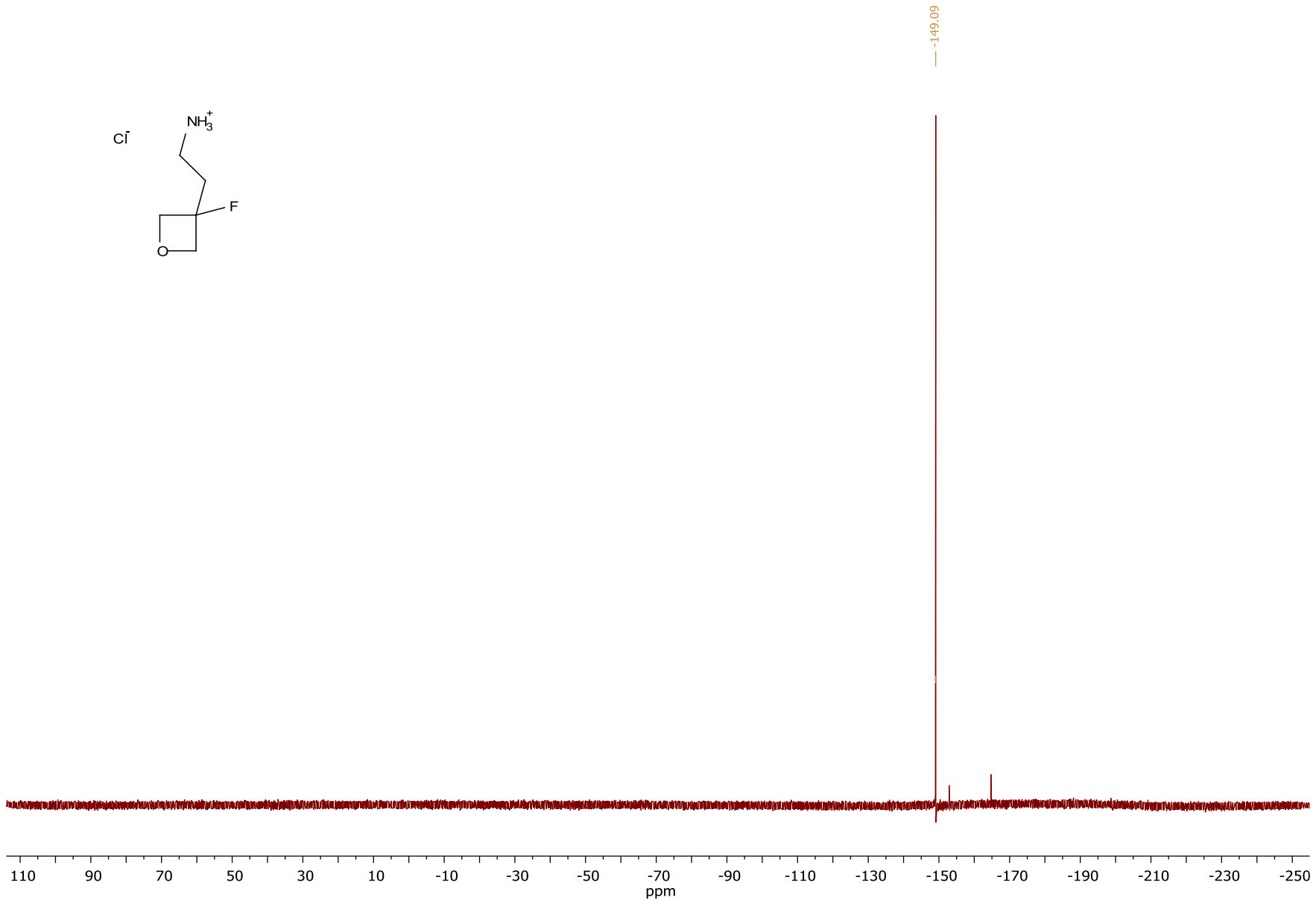
3-(2-Bromoethyl)-3-fluorooxetane (83) $^{19}F\{H\}$ NMR



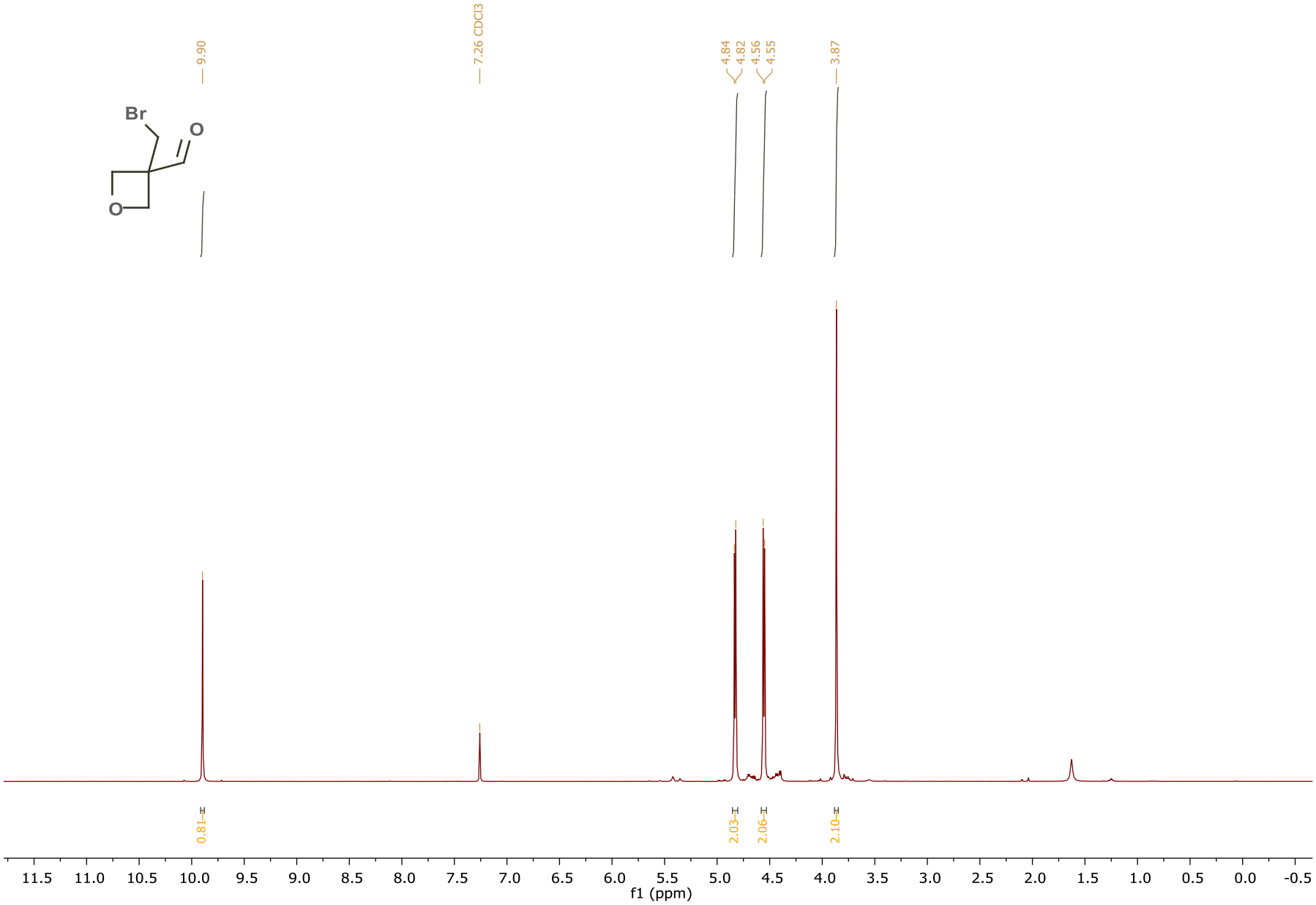
2-(3-Fluorooxetan-3-yl)ethan-1-amine hydrochloride (85) ^{1}H NMR



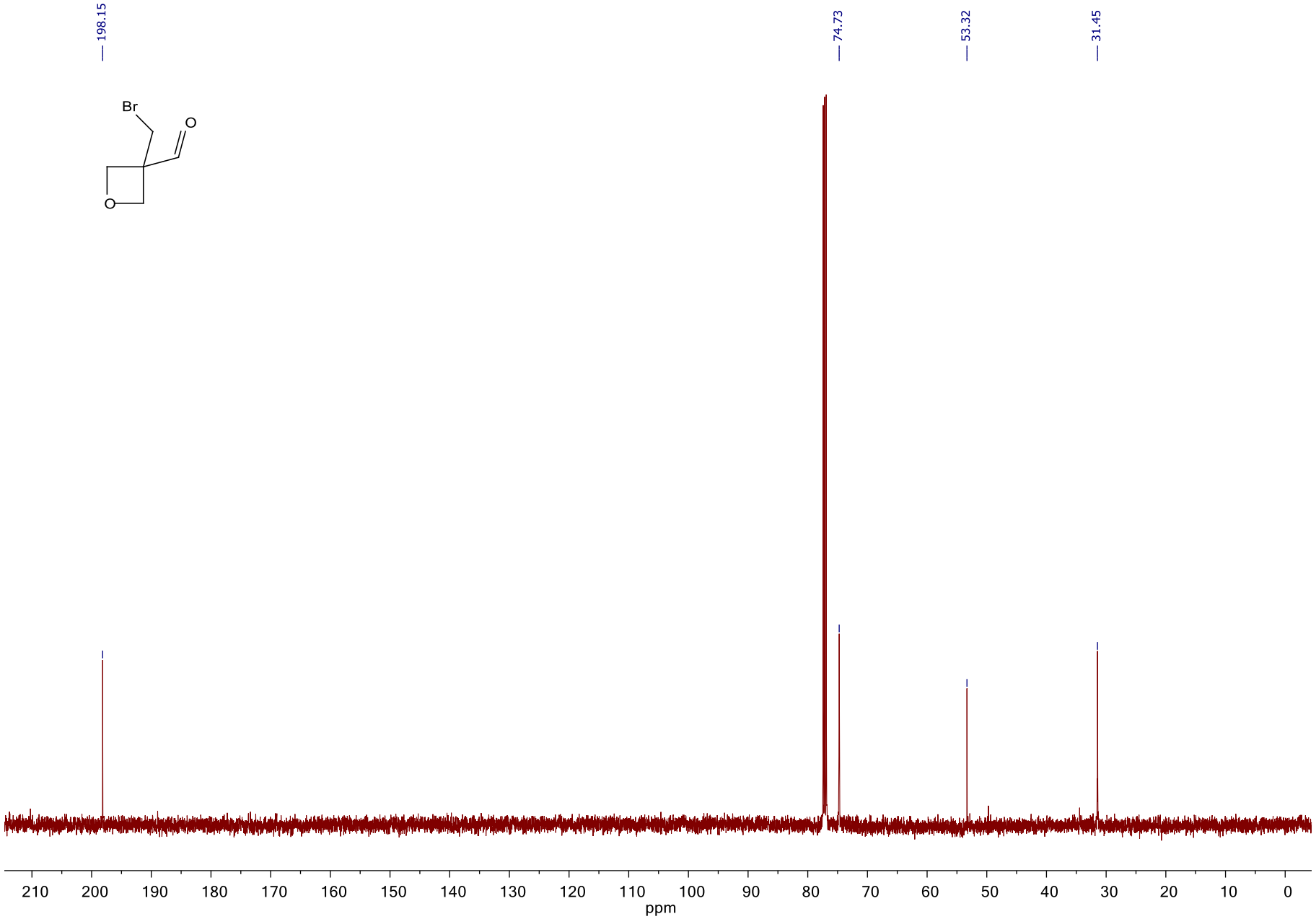
2-(3-Fluorooxetan-3-yl)ethan-1-amine hydrochloride (85) $^{13}C\{H\}$ NMR



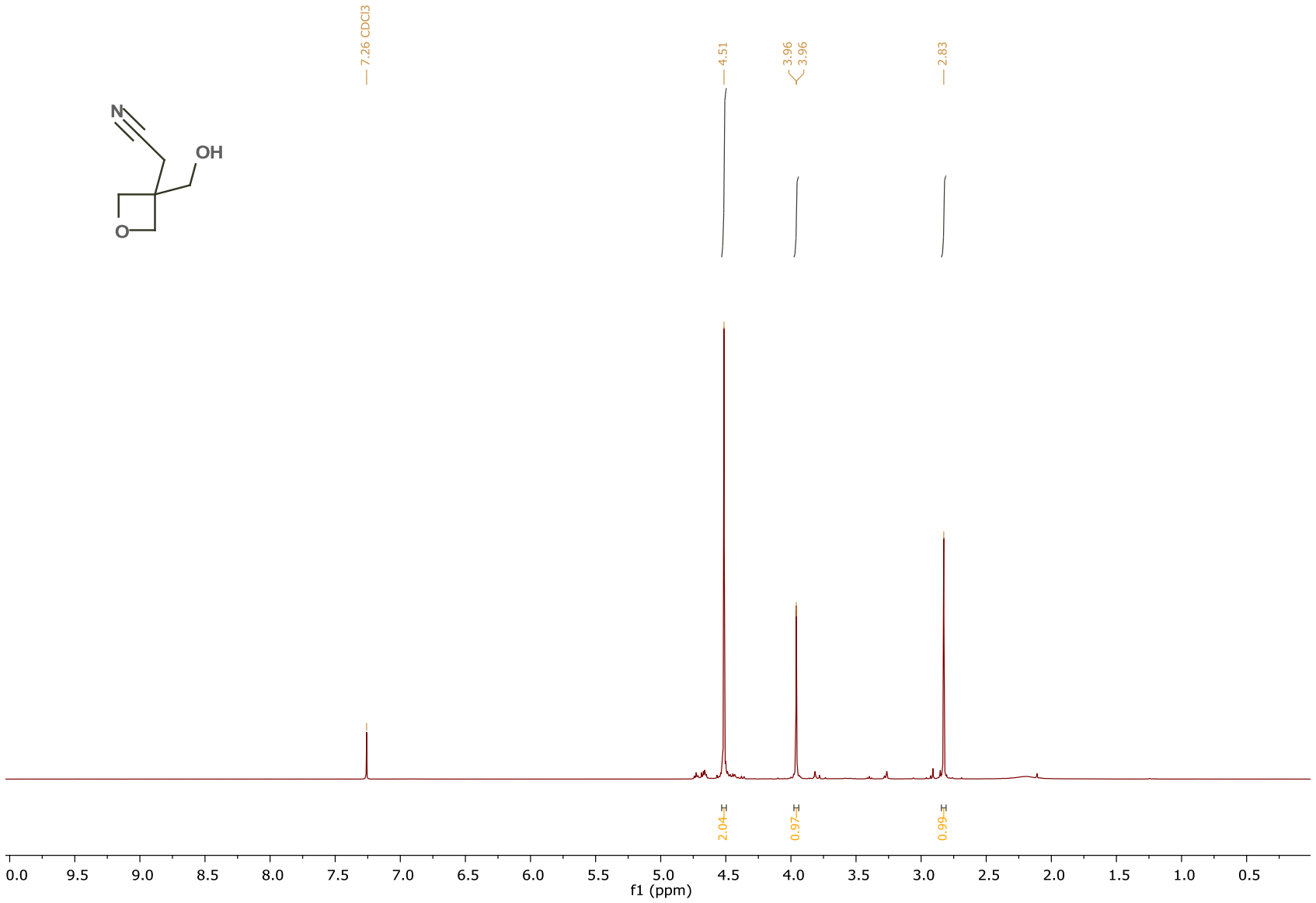
2-(3-Fluorooxetan-3-yl)ethan-1-amine hydrochloride (85) $^{19}F\{H\}$ NMR



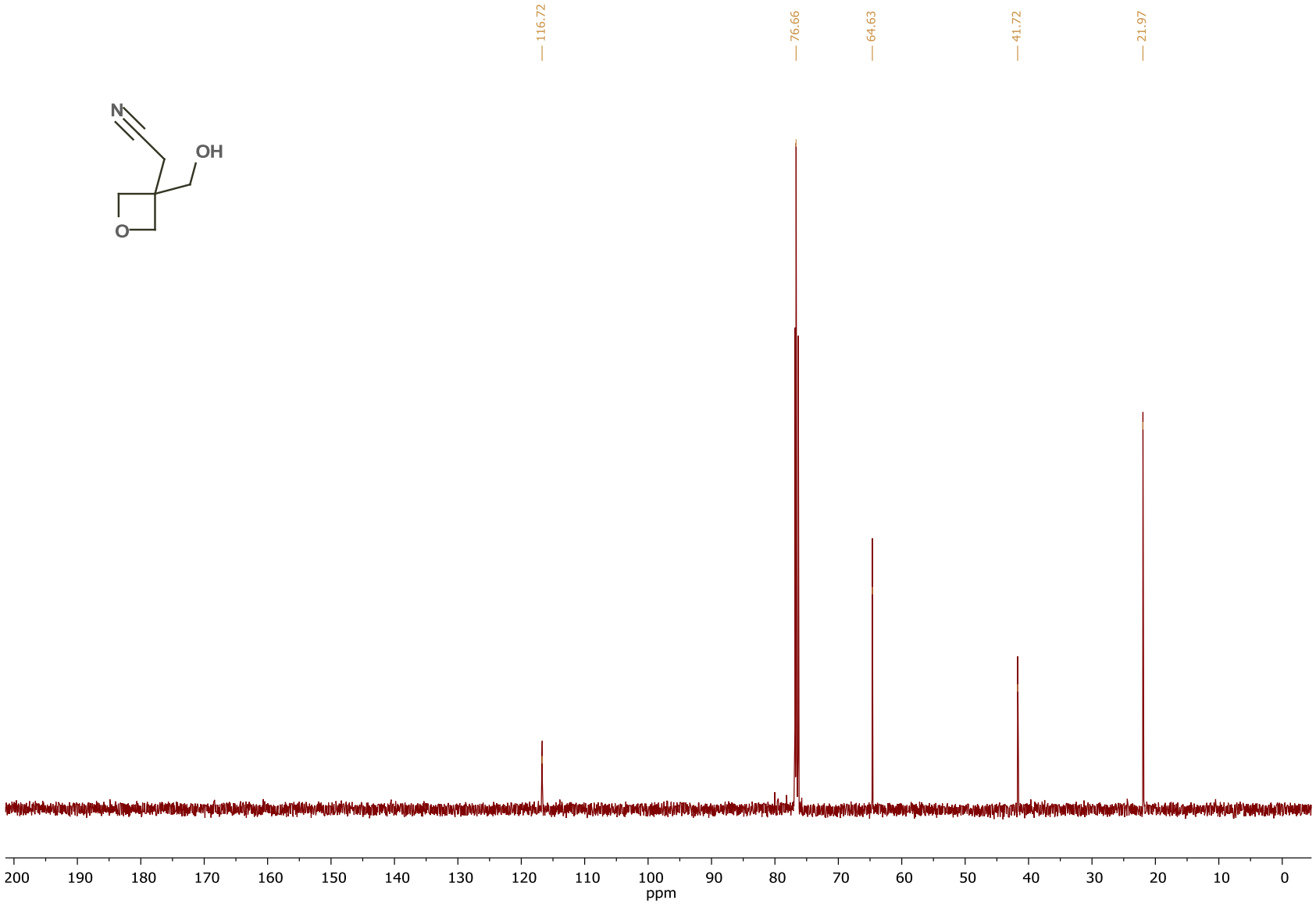
3-(Bromomethyl)oxetane-3-carbaldehyde (86) ^{1}H NMR



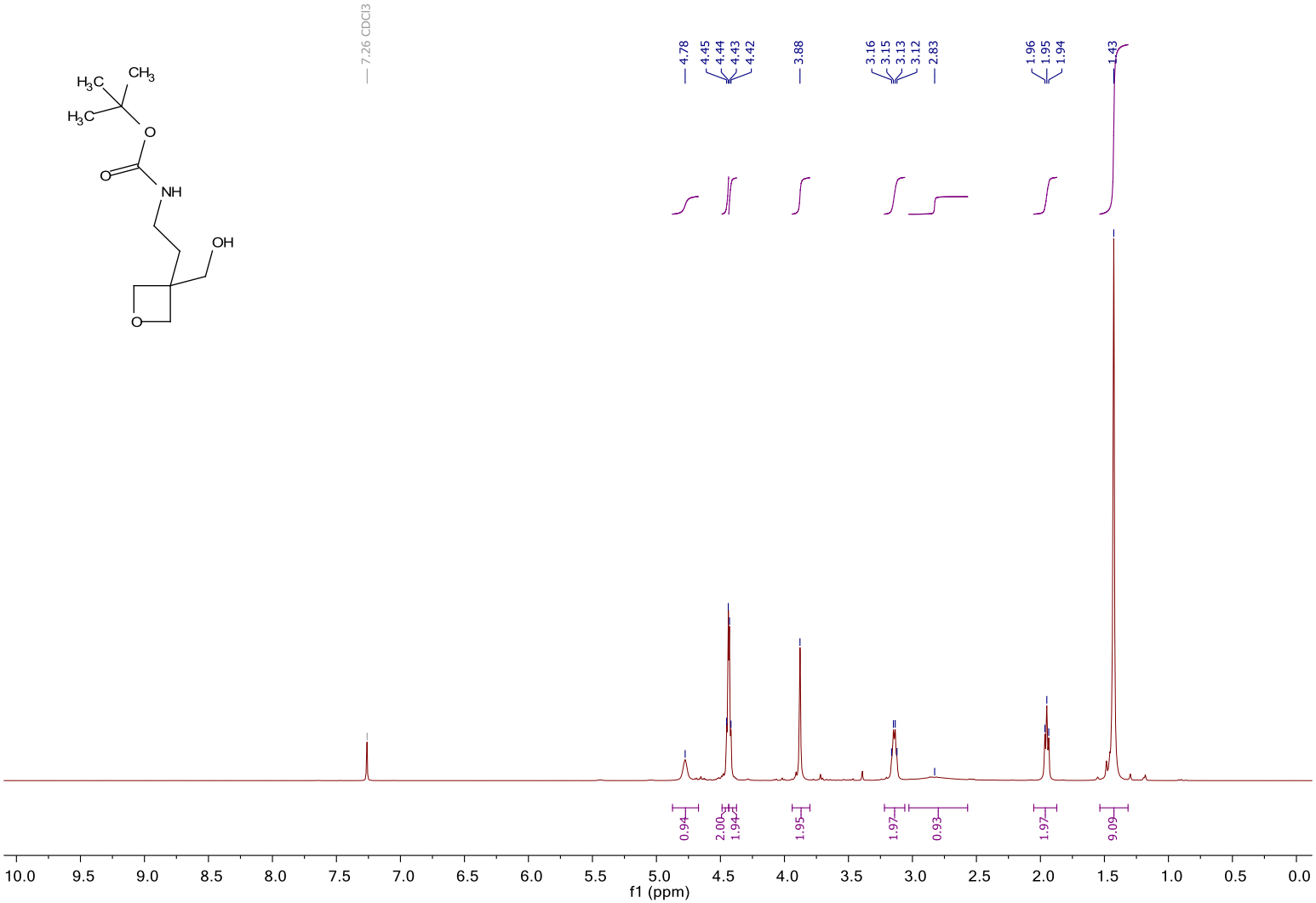
3-(Bromomethyl)oxetane-3-carbaldehyde (86) $^{13}C\{H\}$ NMR



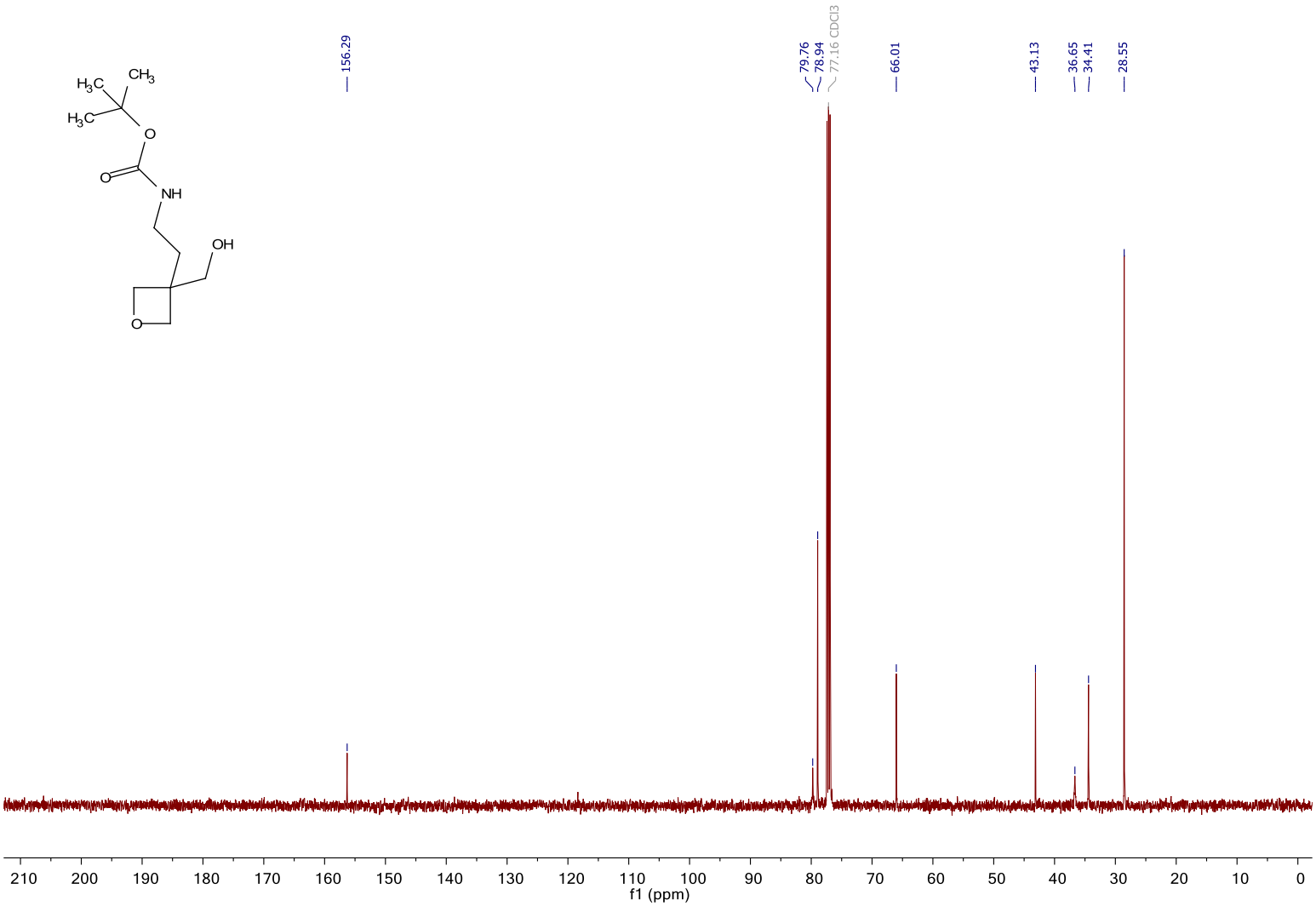
2-(3-(Hydroxymethyl)oxetan-3-yl)acetonitrile (87) ^{1}H NMR



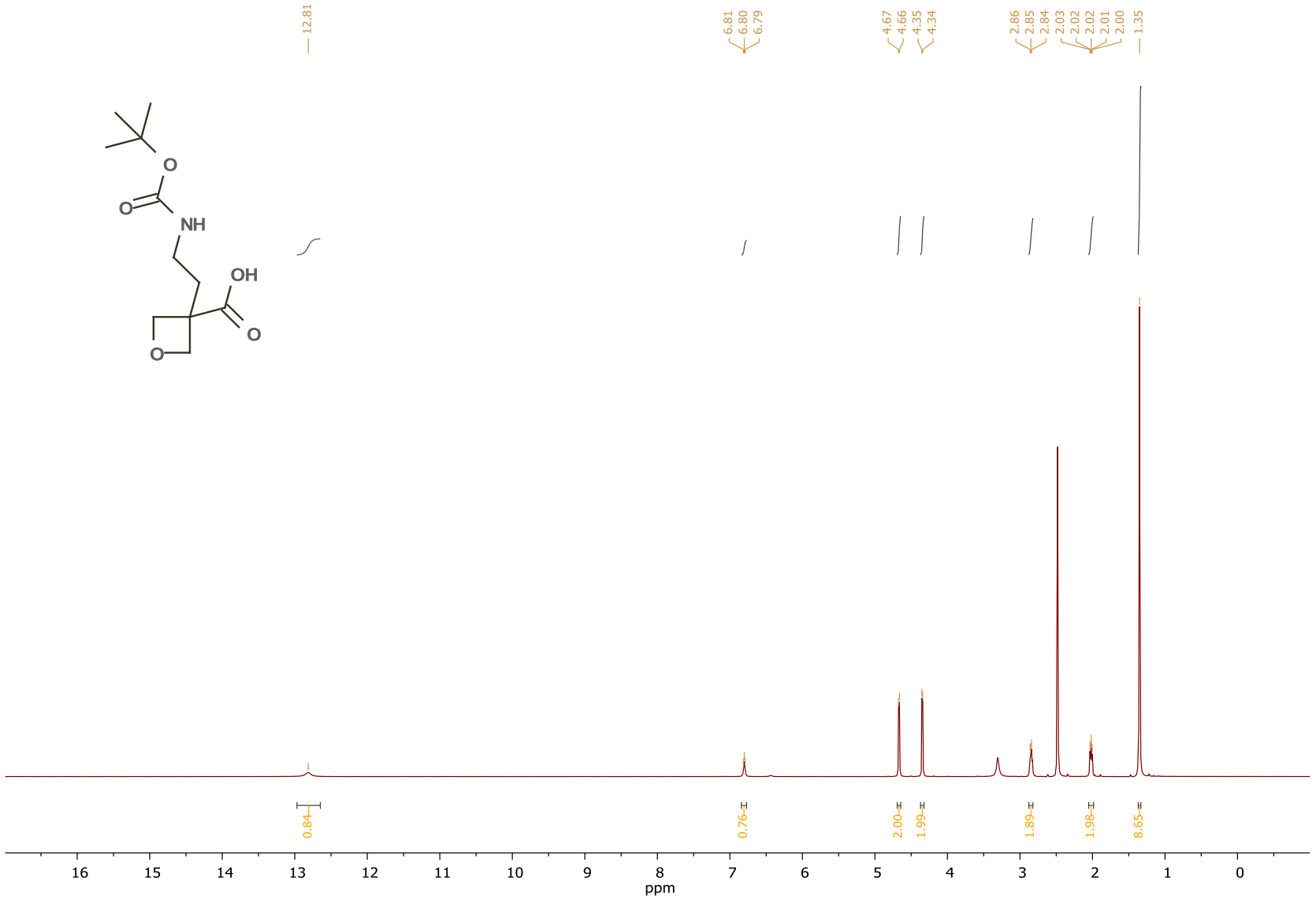
2-(3-(Hydroxymethyl)oxetan-3-yl)acetonitrile (87) $^{13}C\{H\}$ NMR



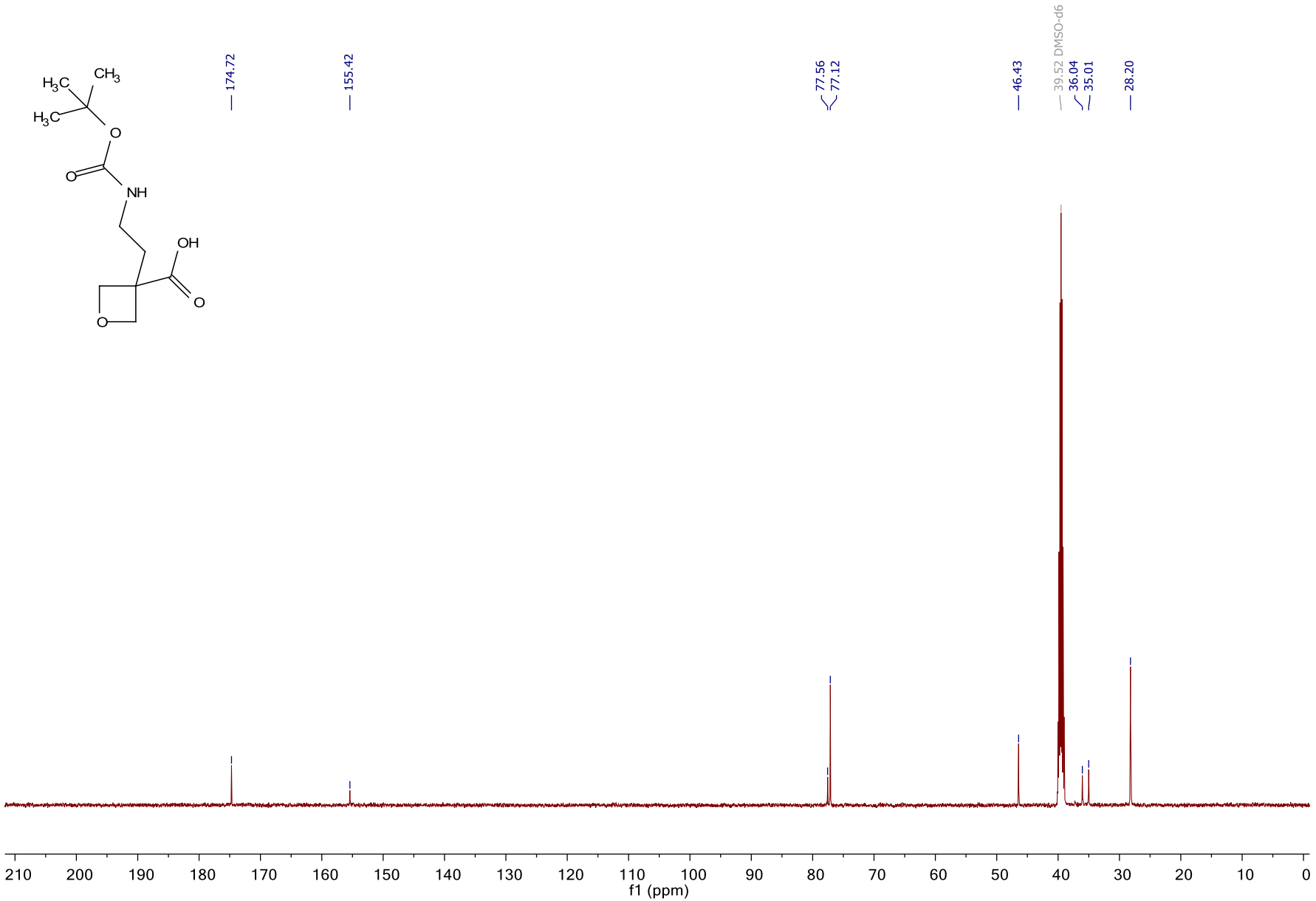
***tert*-Butyl (2-(3-(hydroxymethyl)oxetan-3-yl)ethyl)carbamate (88) ^{1}H NMR (500 MHz, $CDCl_3$)**



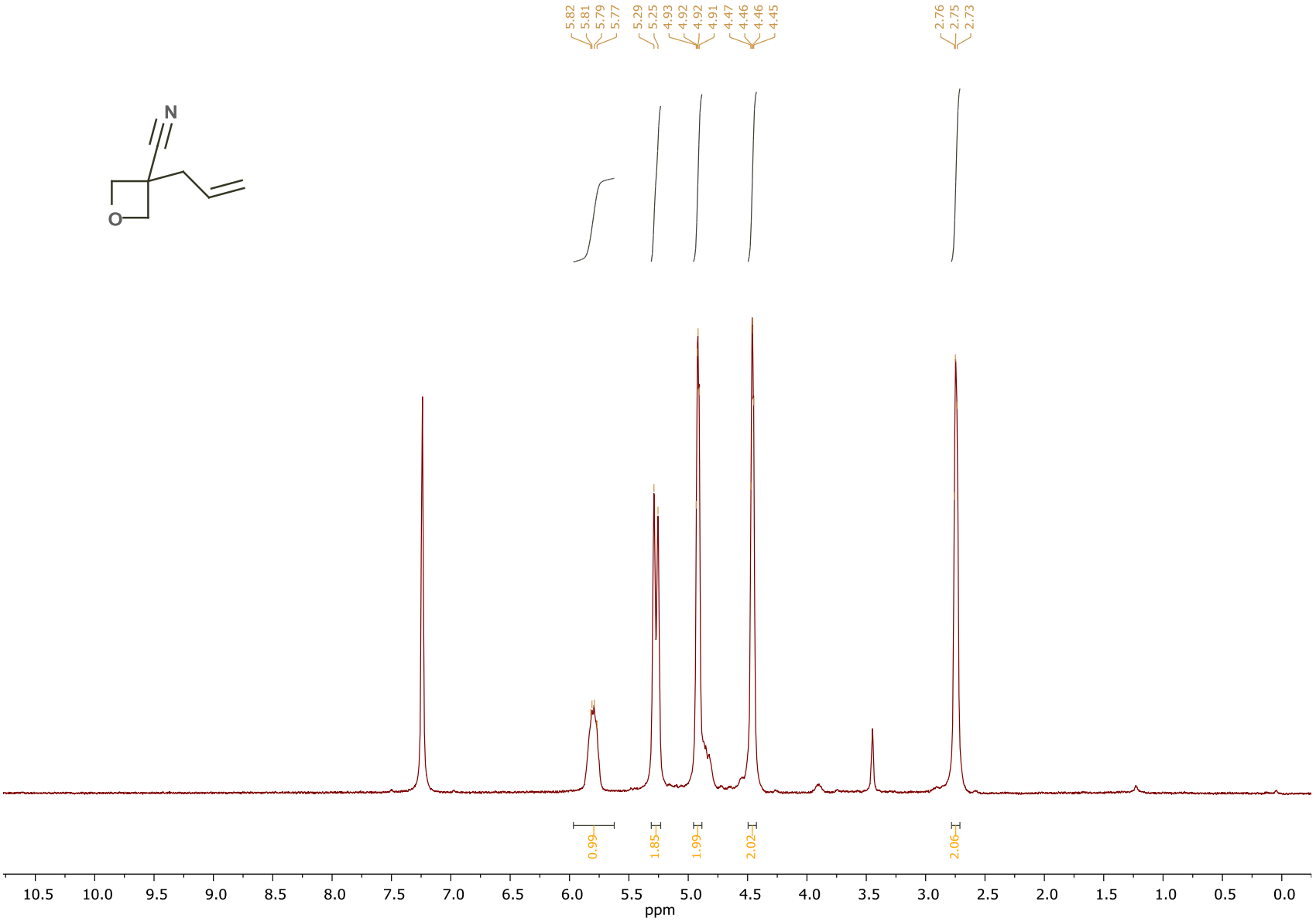
***tert*-Butyl (2-(3-(hydroxymethyl)oxetan-3-yl)ethyl)carbamate (88) ^{13}C NMR (126 MHz, $CDCl_3$)**



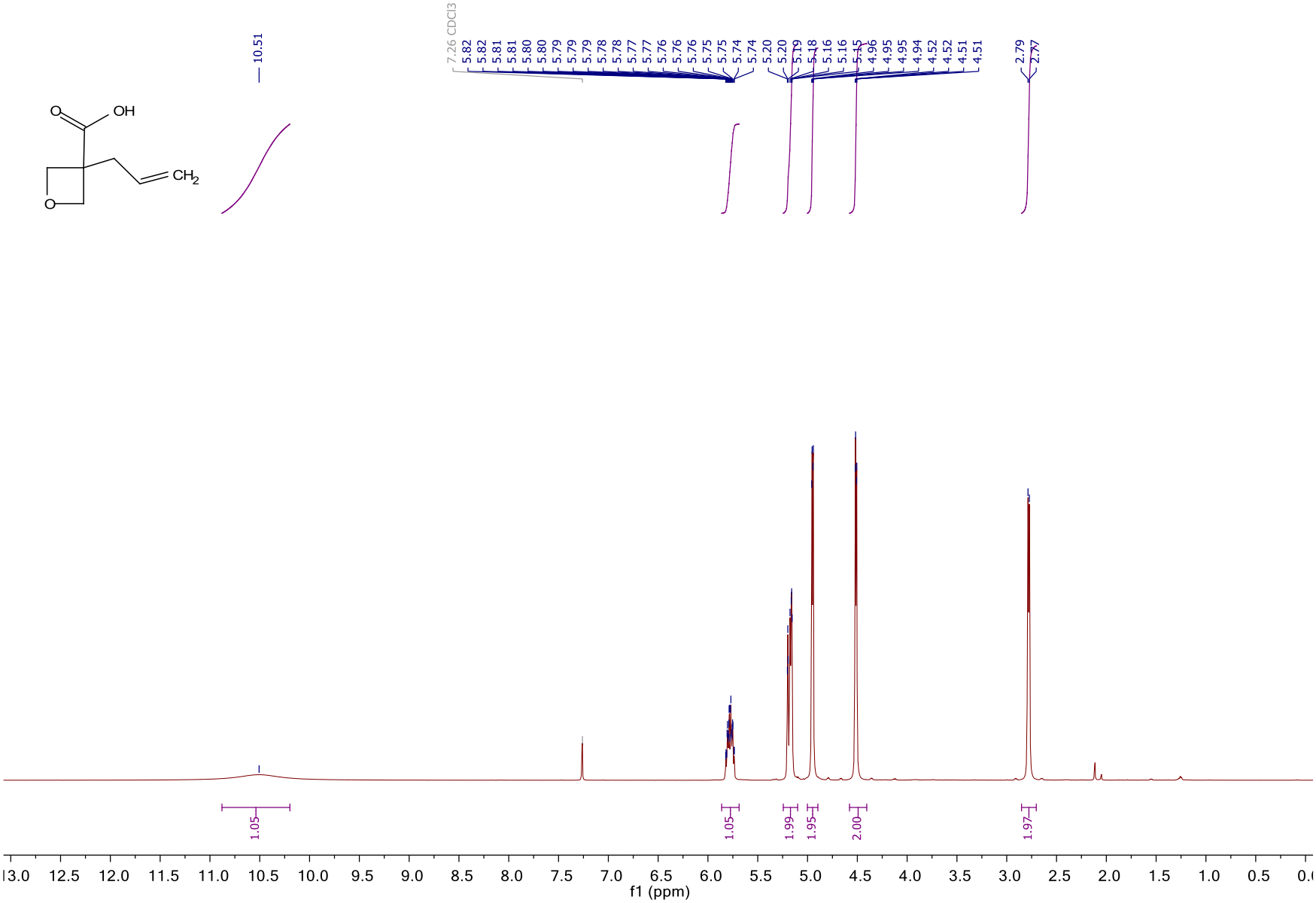
3-(2-((*tert*-Butoxycarbonyl)amino)ethyl)oxetane-3-carboxylic acid (89) ^{1}H NMR



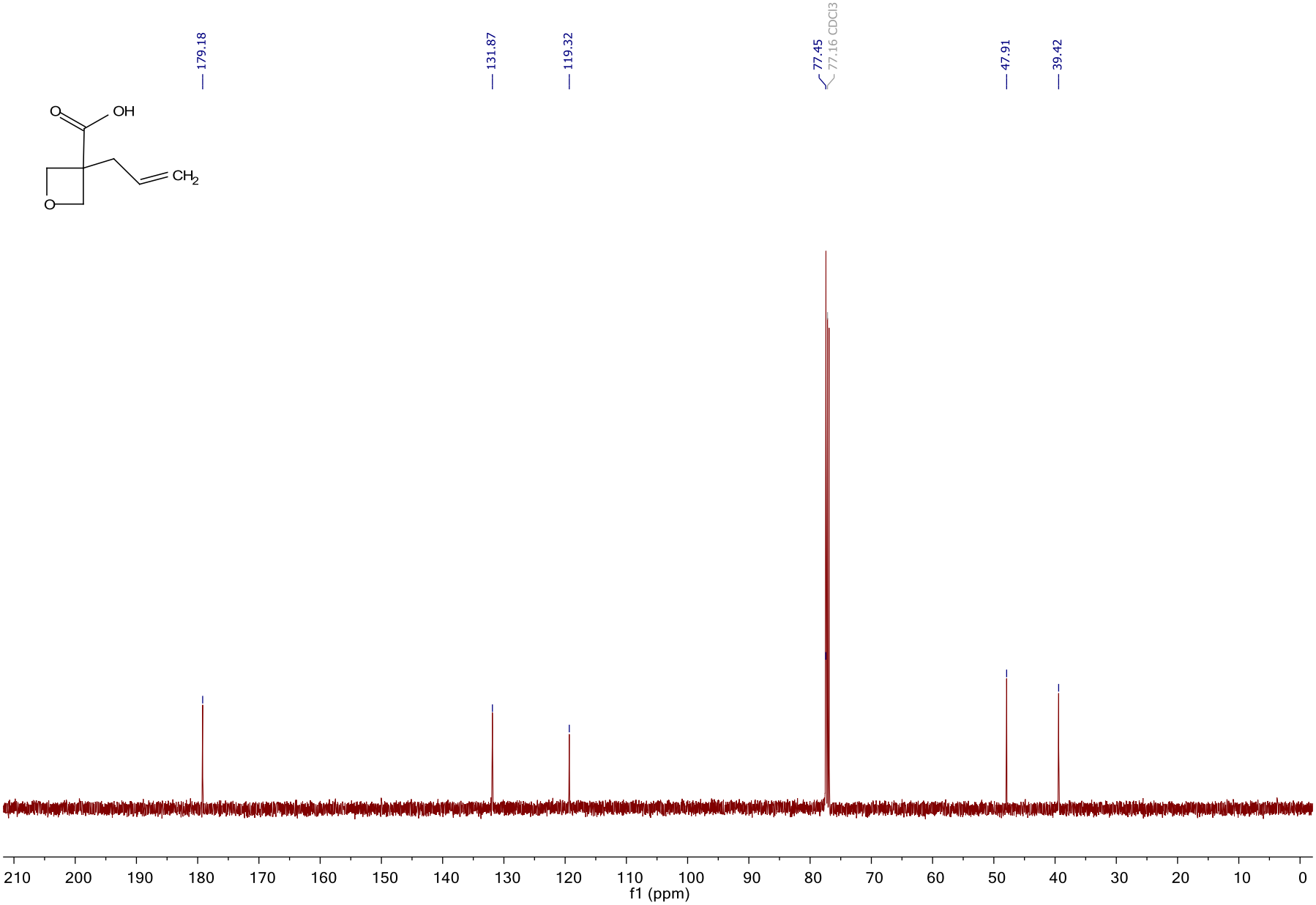
3-(2-((*tert*-Butoxycarbonyl)amino)ethyl)oxetane-3-carboxylic acid (89) $^{13}C\{H\}$ NMR



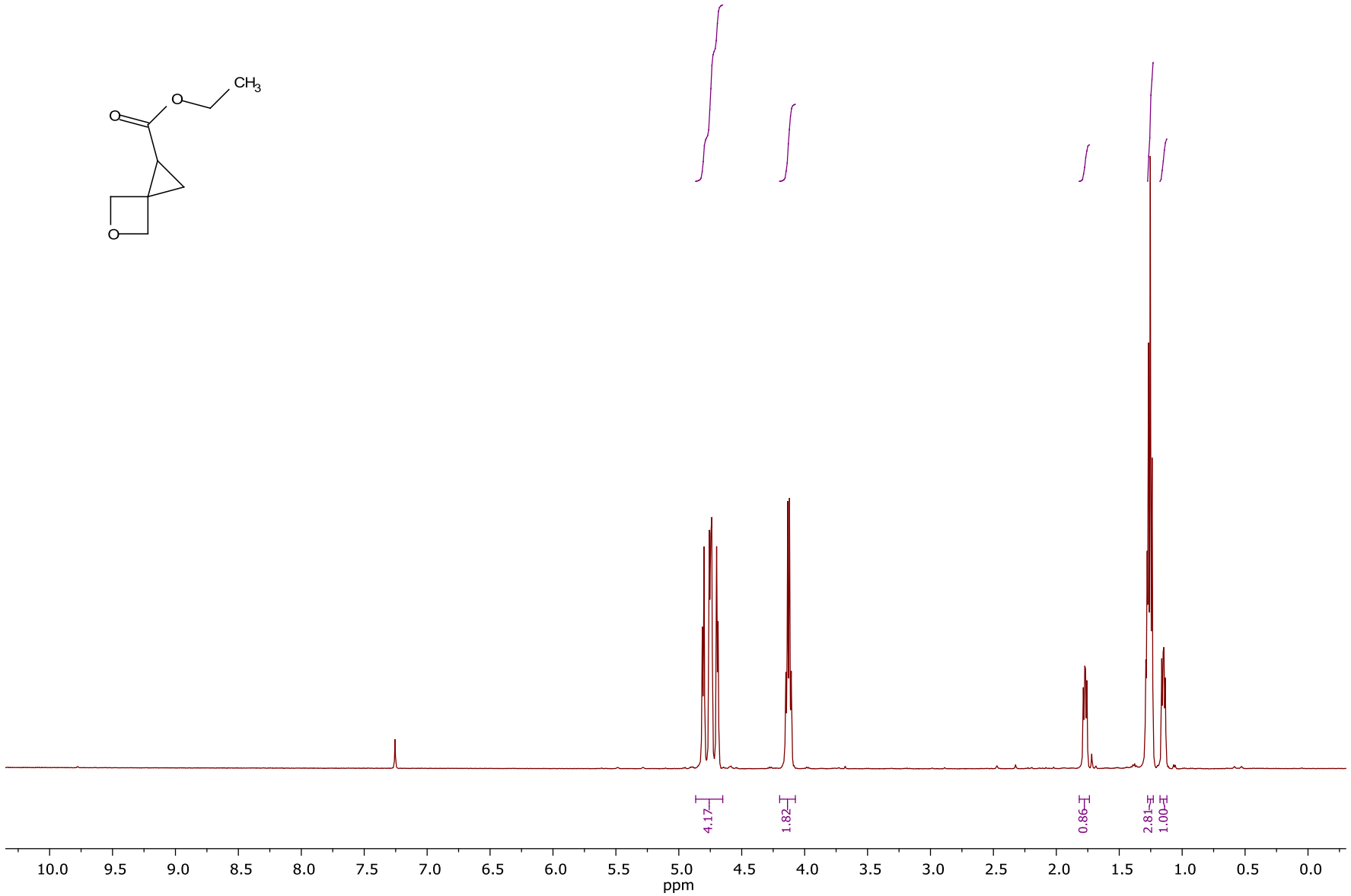
3-Allyloxetane-3-carbonitrile (90) ^{1}H NMR



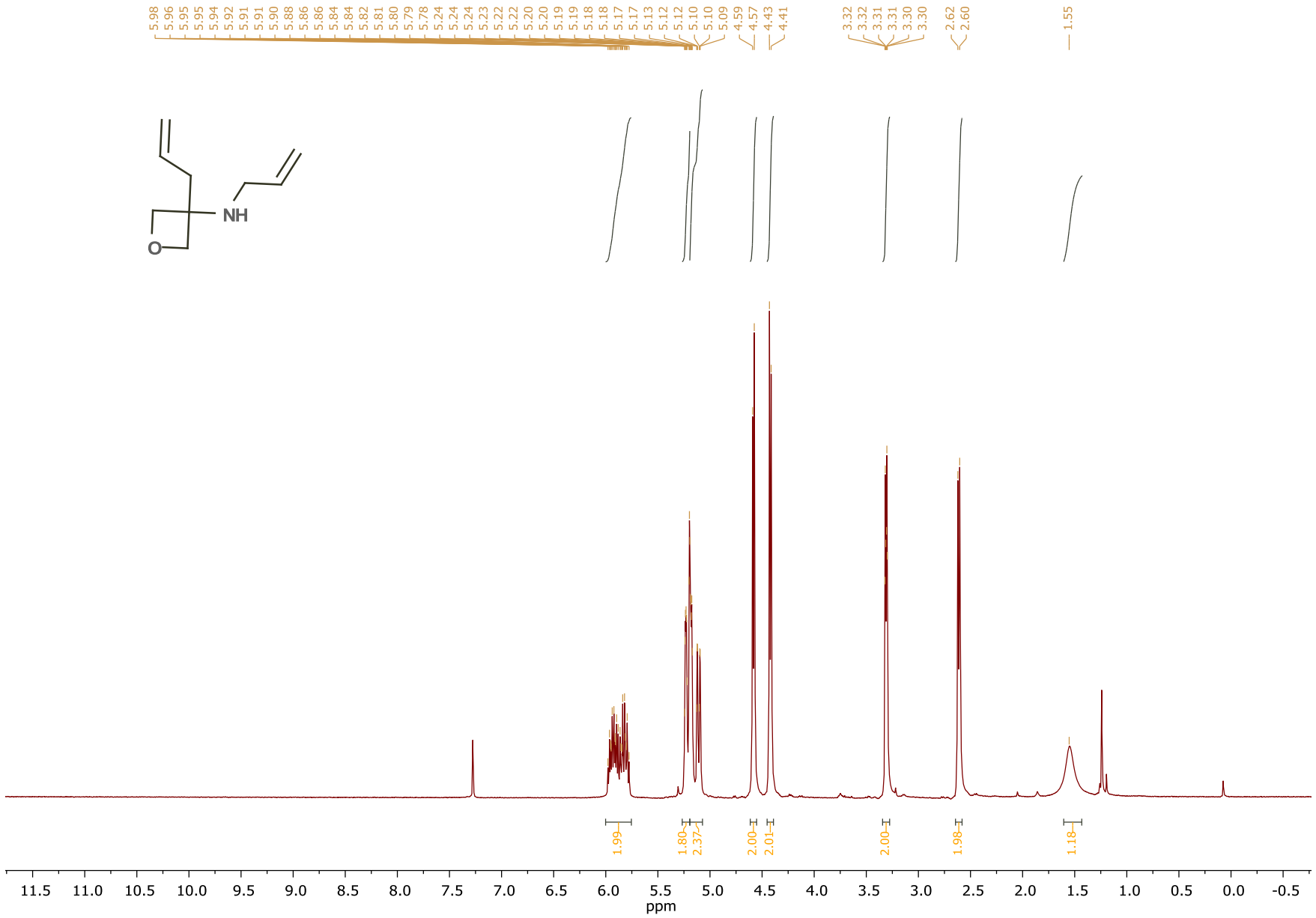
3-(Prop-2-en-1-yl)oxetane-3-carboxylic acid (91) ^{1}H NMR (500 MHz, $CDCl_3$)



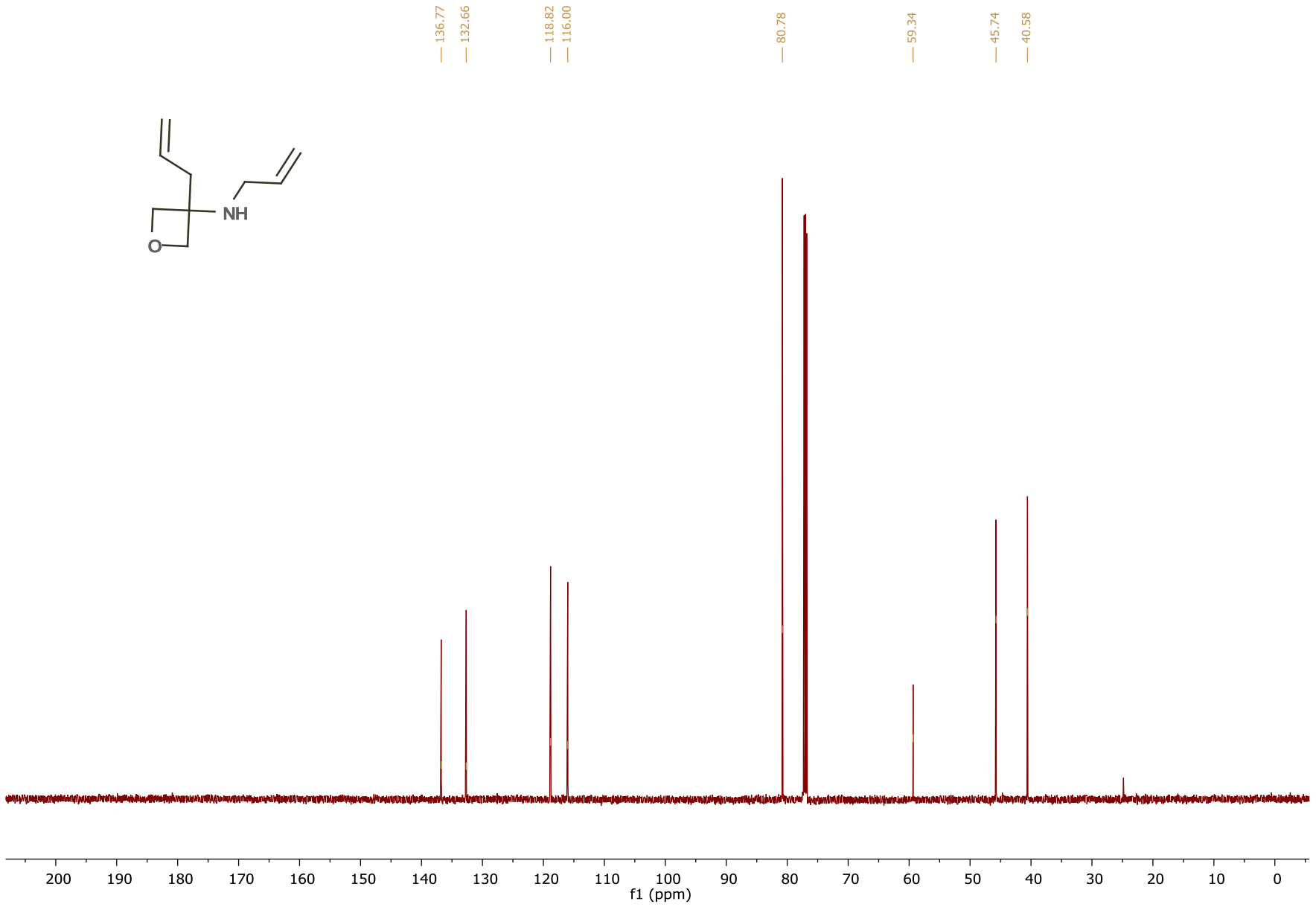
3-(Prop-2-en-1-yl)oxetane-3-carboxylic acid (91) $^{13}C\{H\}$ NMR



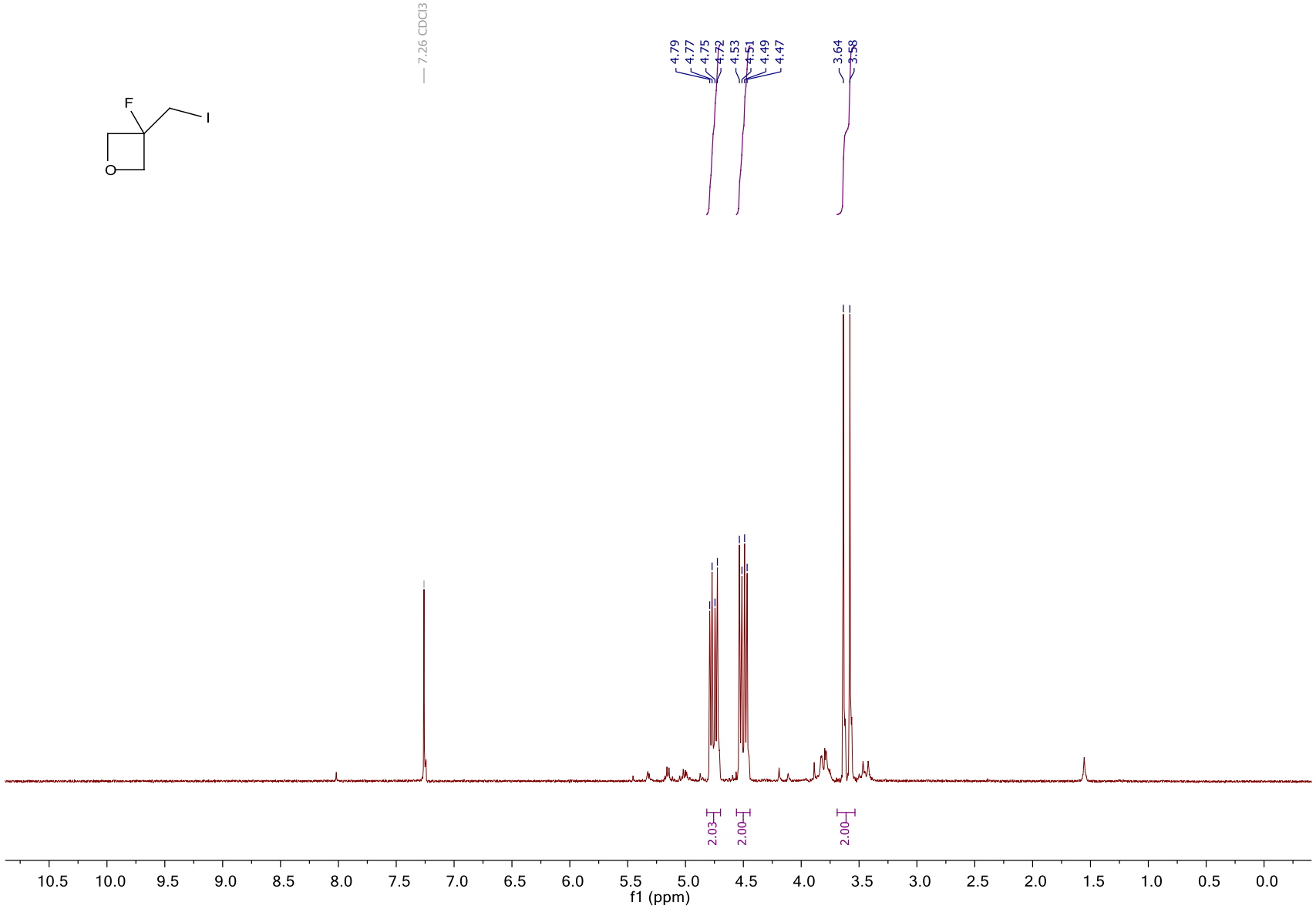
Ethyl 5-oxaspiro[2.3]hexane-1-carboxylate (93) ^{1}H NMR



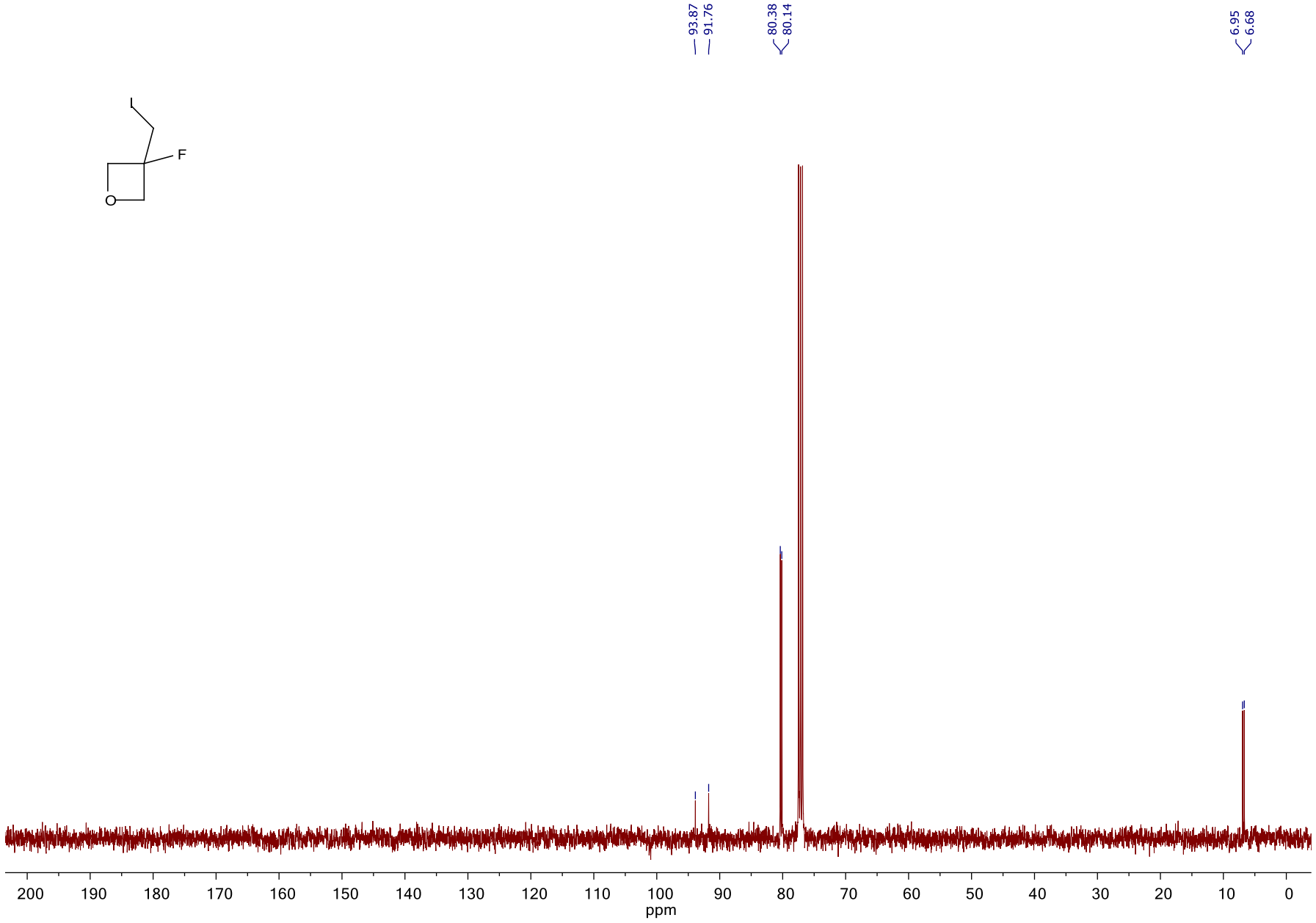
***N*,3-diallyloxetan-3-amine (94) ^{1}H NMR**



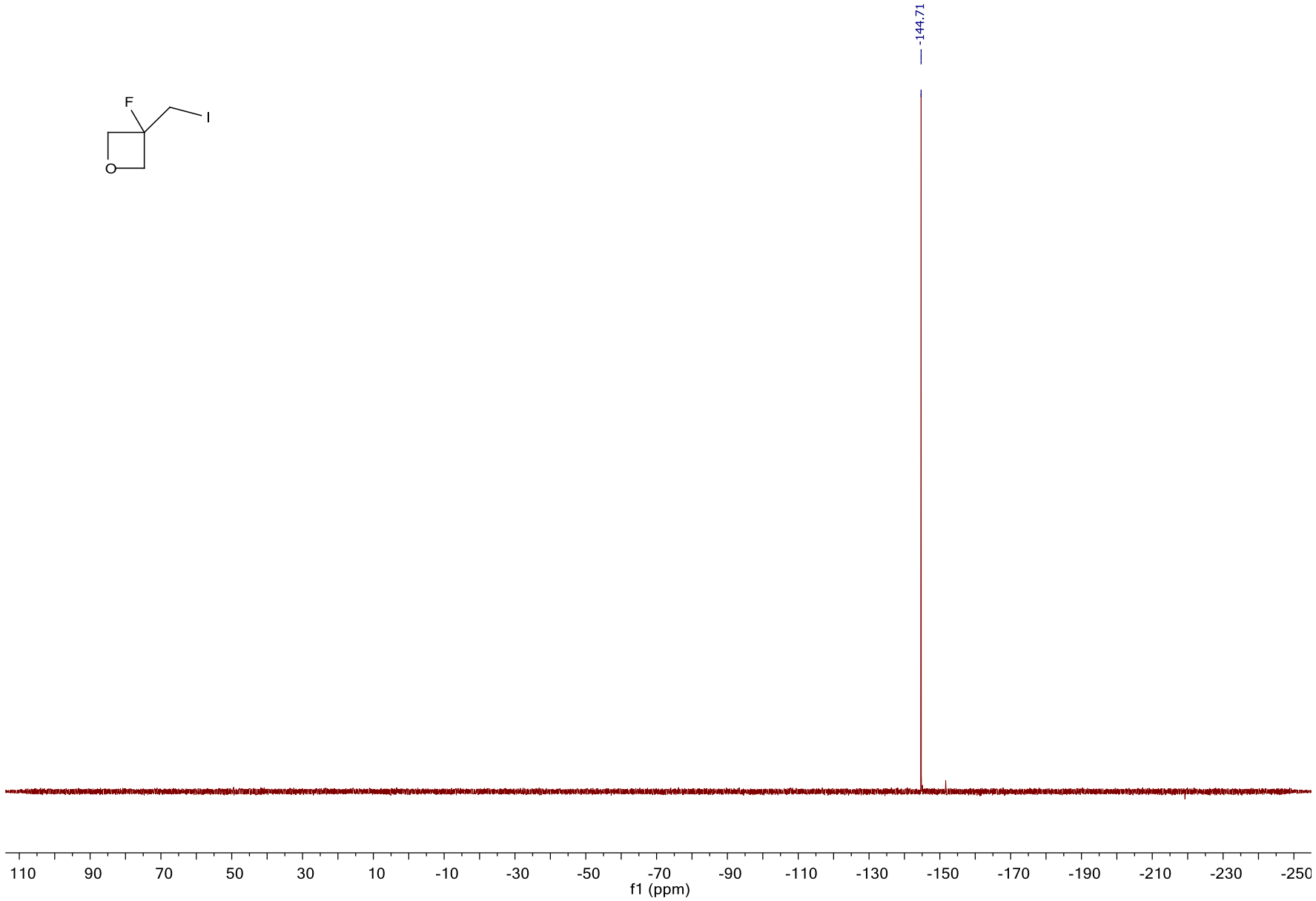
_N_,3-diallyloxetan-3-amine (94) $^{13}C\{H\}$ NMR



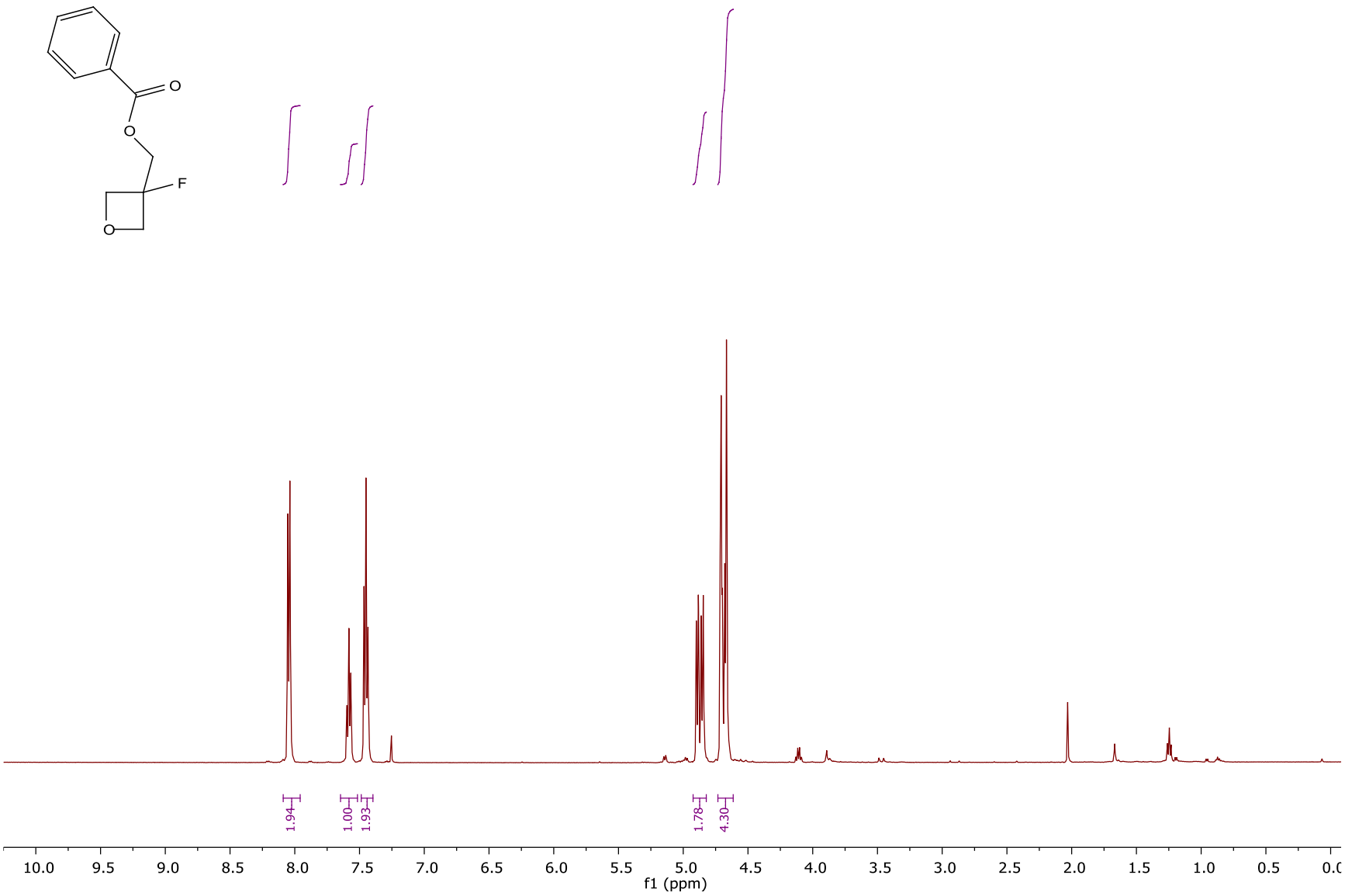
3-(Iodomethyl)-3-fluorooxetane (96) ^{1}H NMR



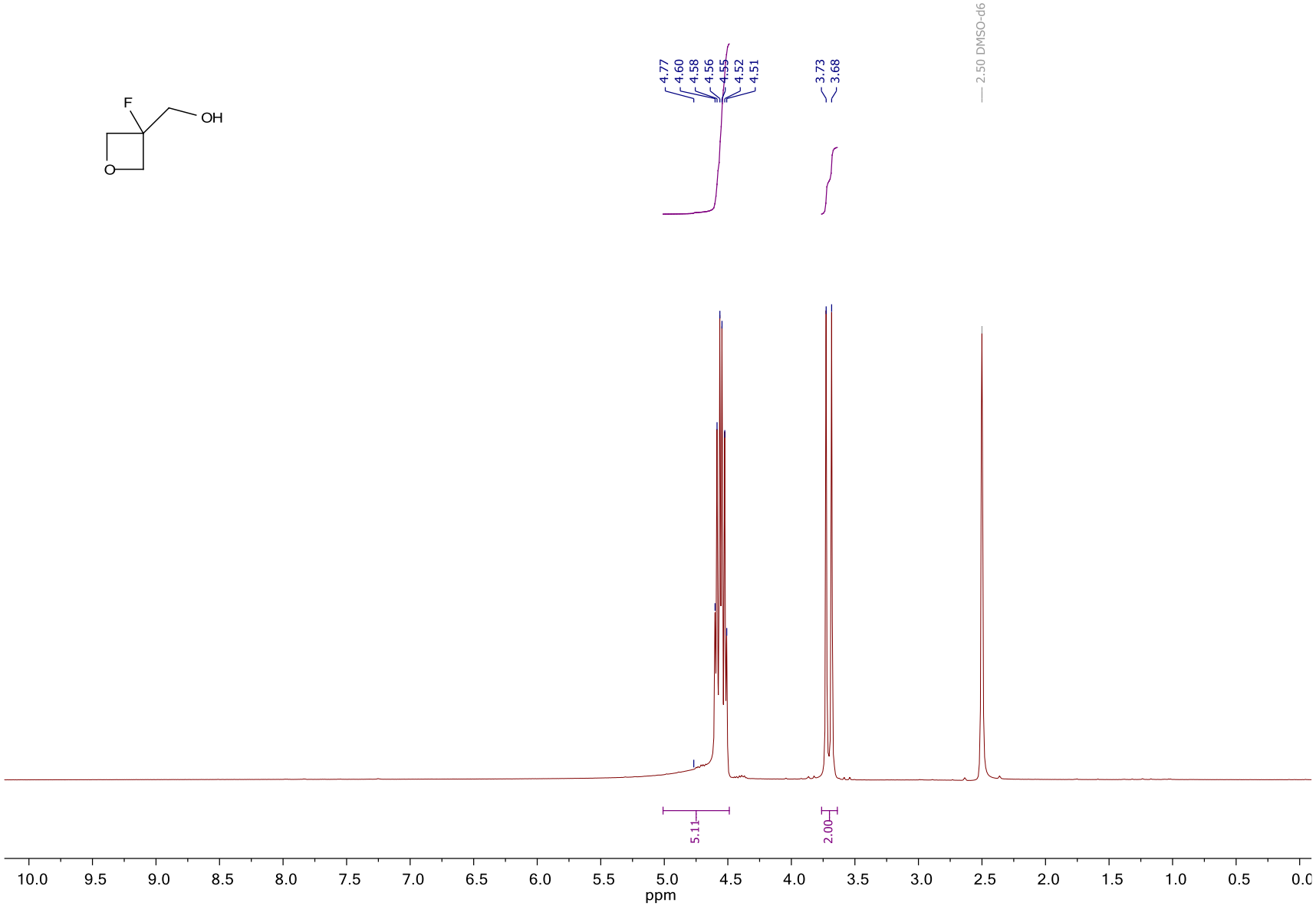
3-(Iodomethyl)-3-fluorooxetane (96) $^{13}C\{H\}$ NMR



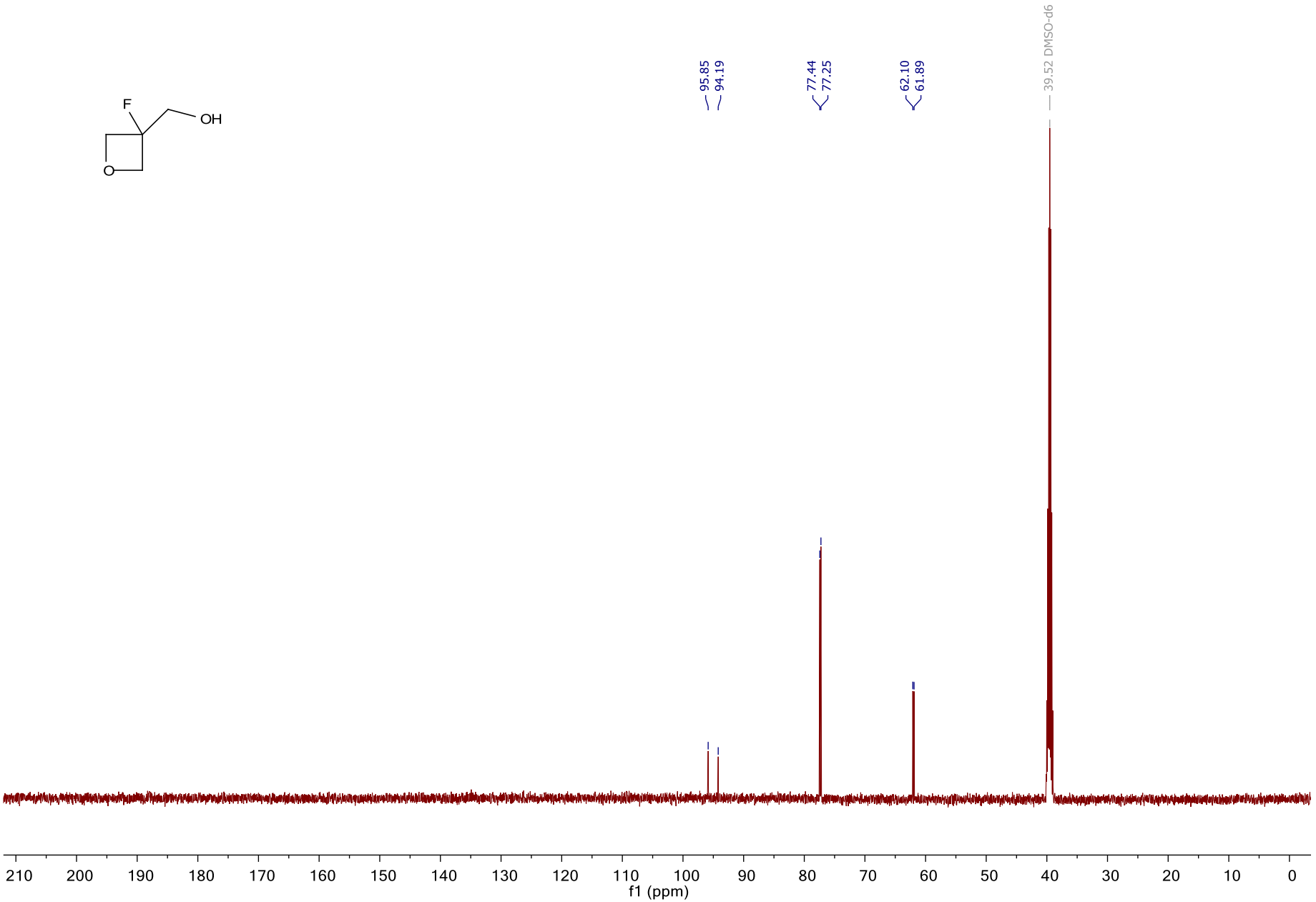
3-(Iodomethyl)-3-fluorooxetane (96) $^{19}F\{H\}$ NMR



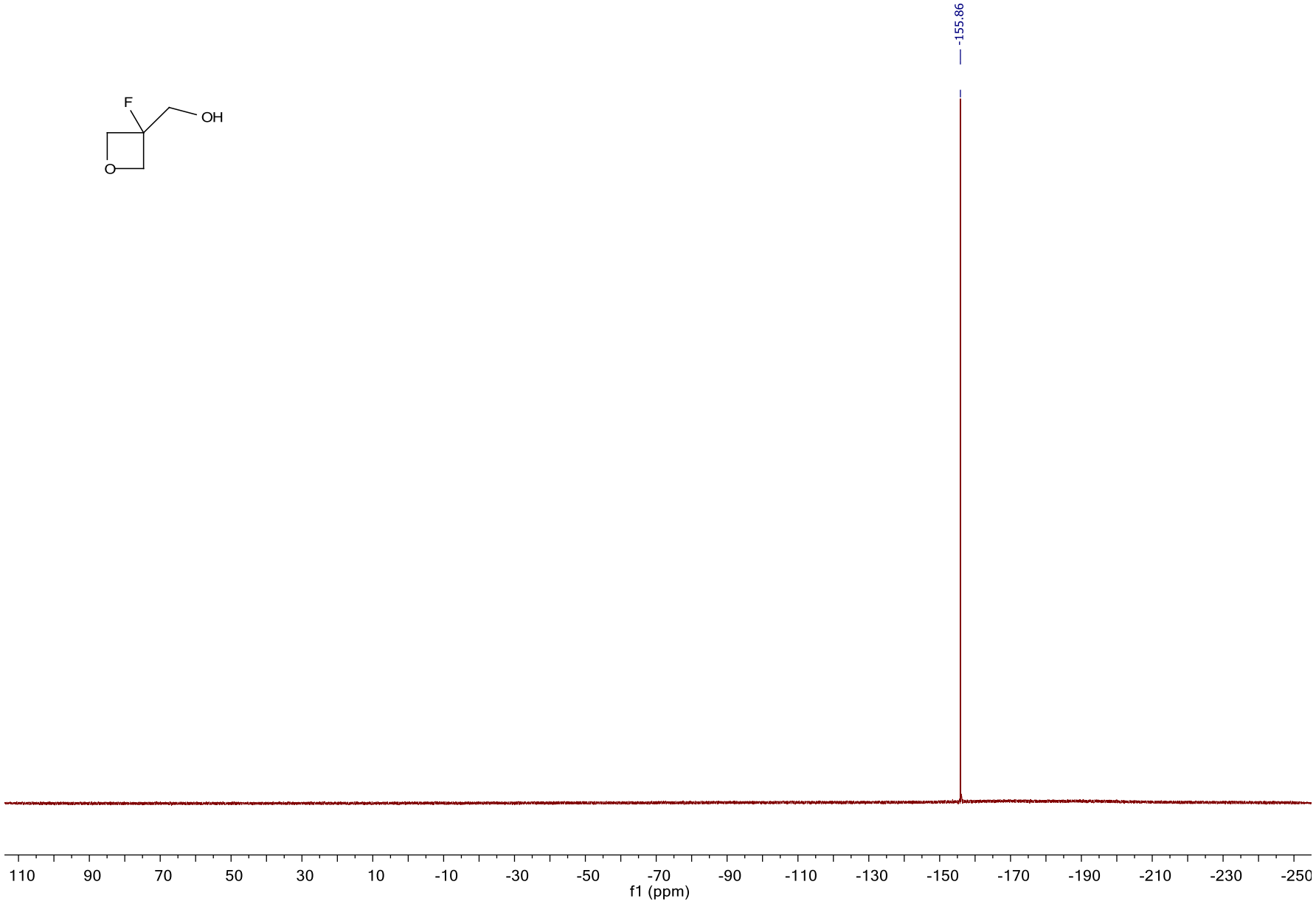
(3-Fluorooxetan-3-yl)methyl benzoate (97) ^{1}H NMR



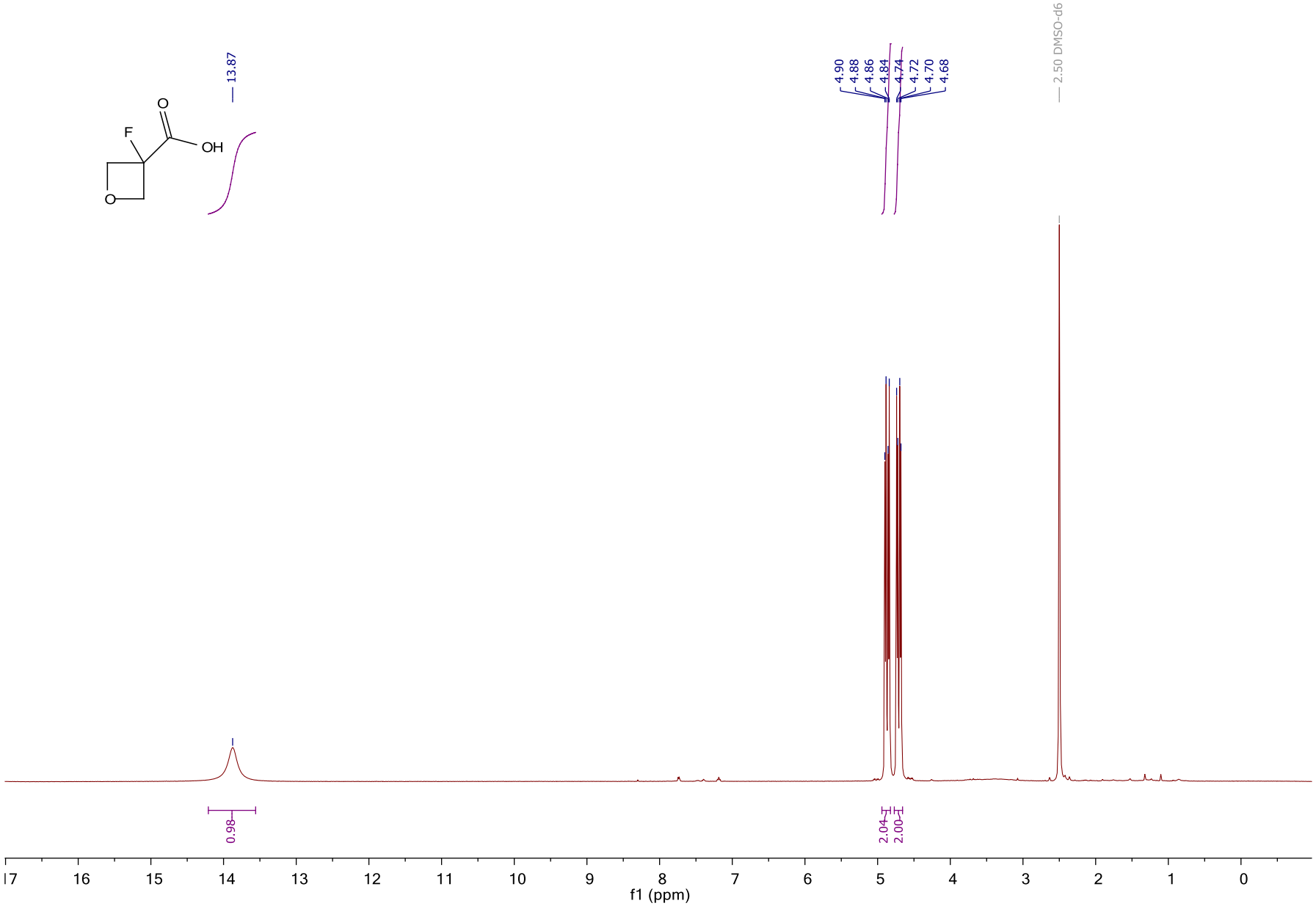
(3-Fluorooxetan-3-yl)methanol (98) ^{1}H NMR



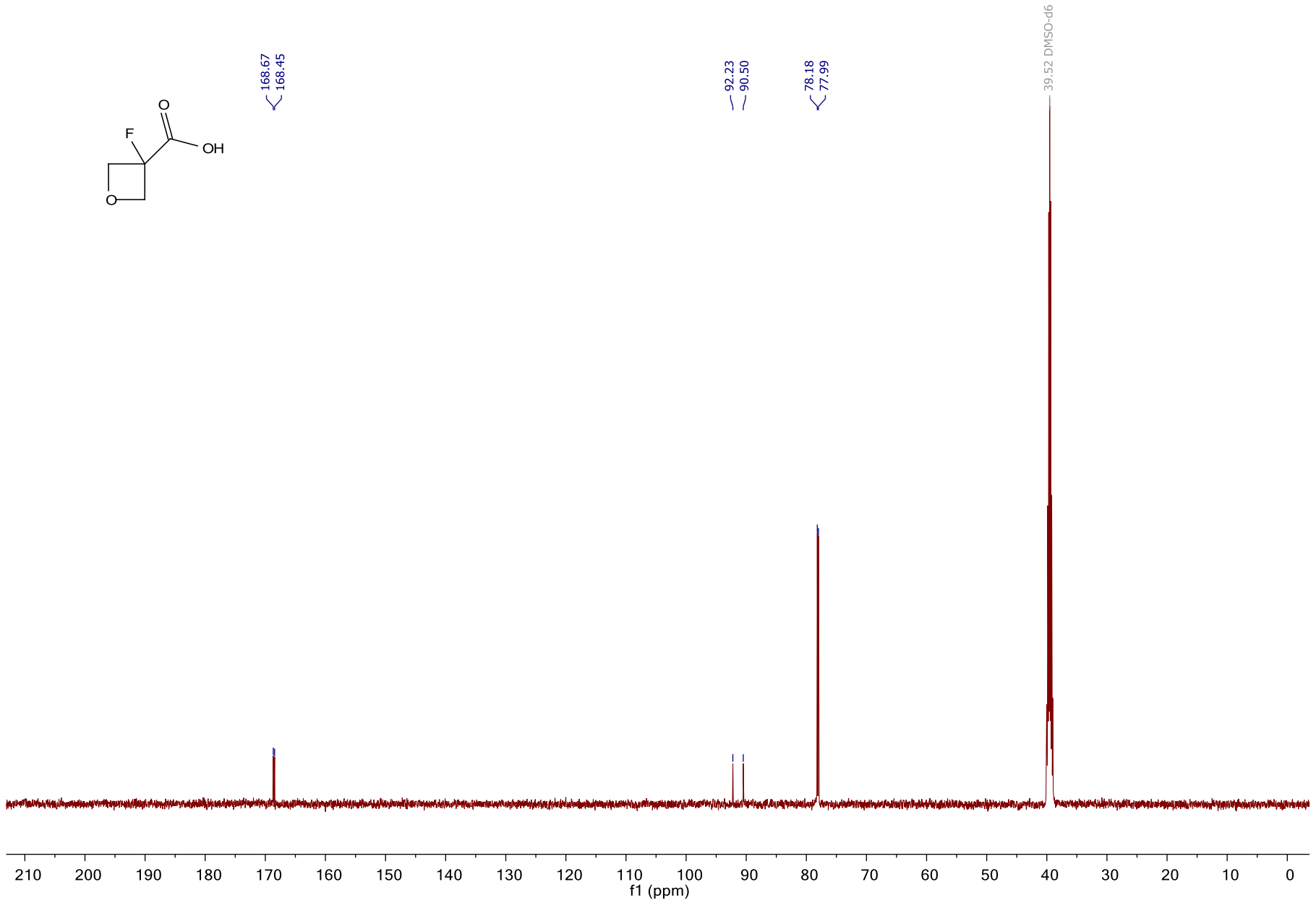
(3-Fluorooxetan-3-yl)methanol (98) $^{13}C\{H\}$ NMR



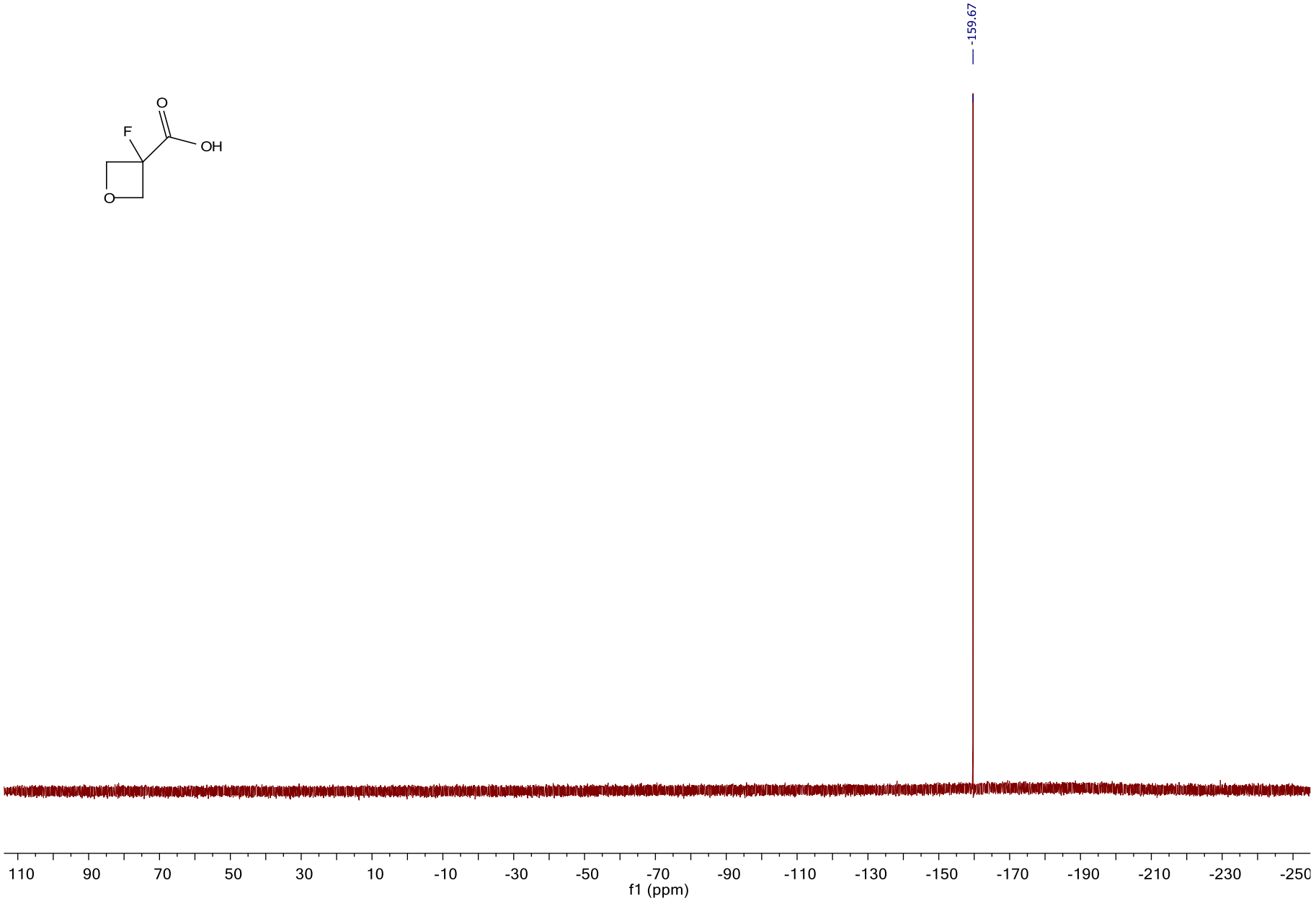
(3-Fluorooxetan-3-yl)methanol (98) $^{19}F\{H\}$ NMR



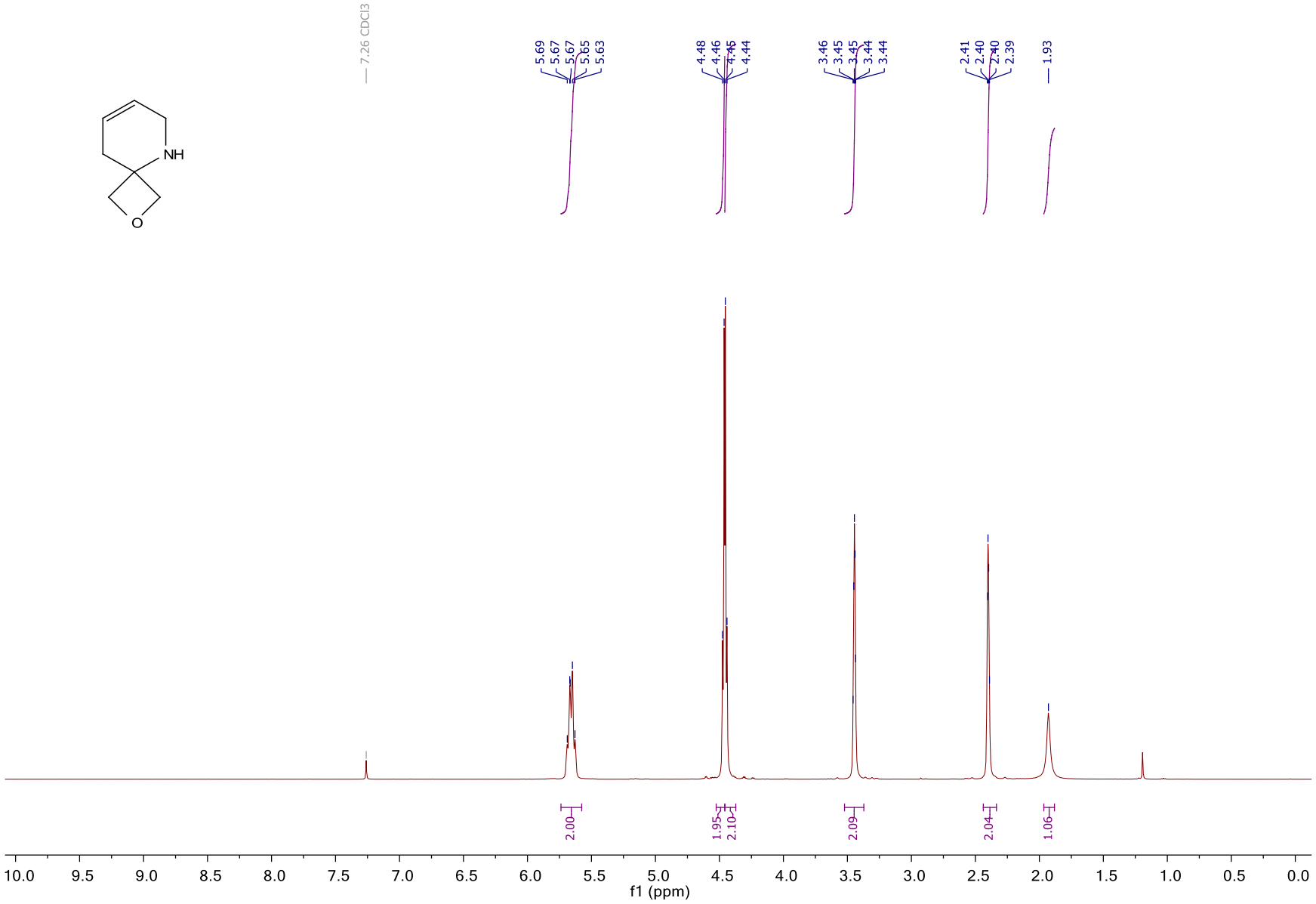
3-Fluorooxetane-3-carboxylic acid (99) ^{1}H NMR



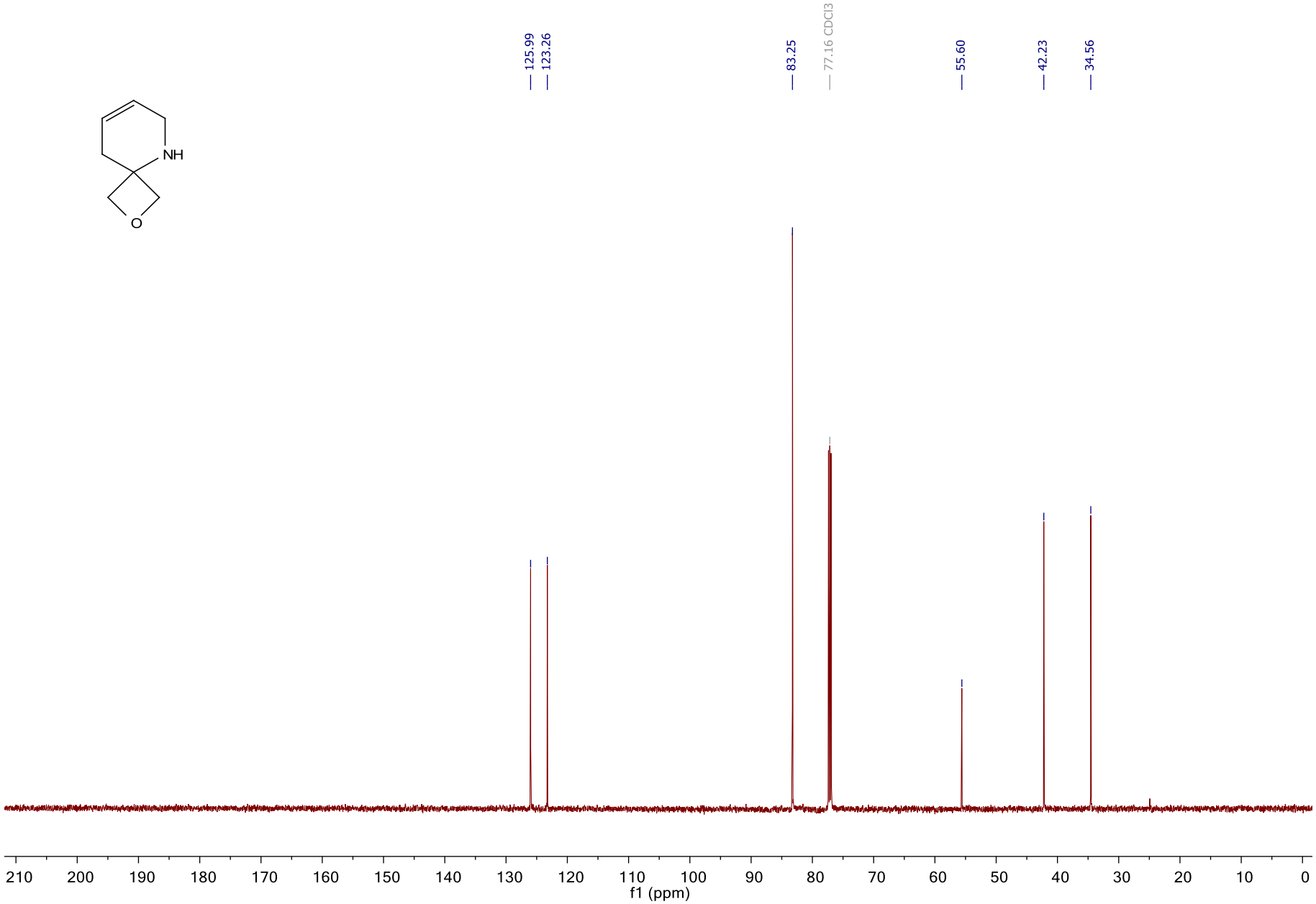
3-Fluorooxetane-3-carboxylic acid (99) ^{13}C NMR



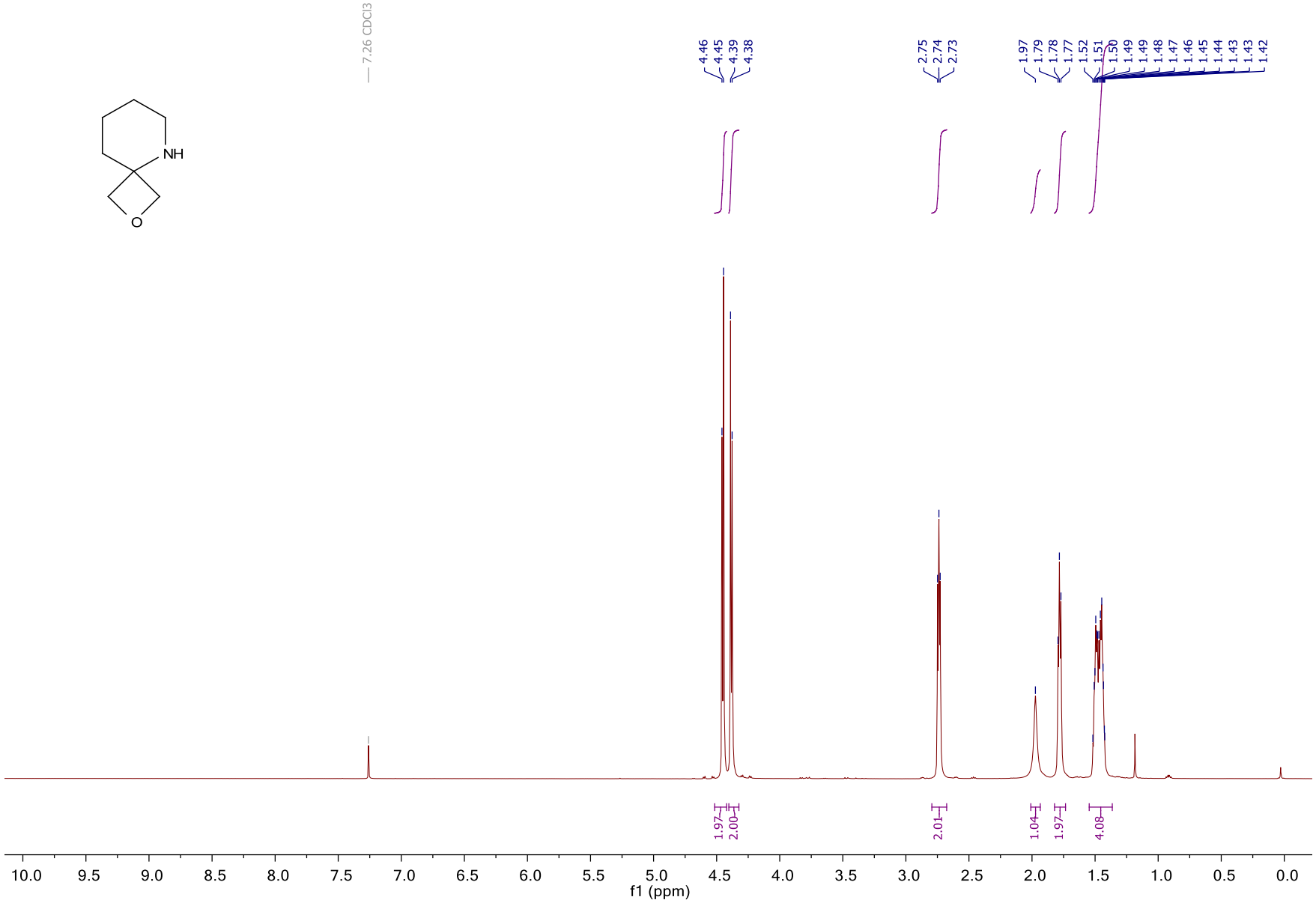
3-Fluorooxetane-3-carboxylic acid (99) ^{19}F NMR



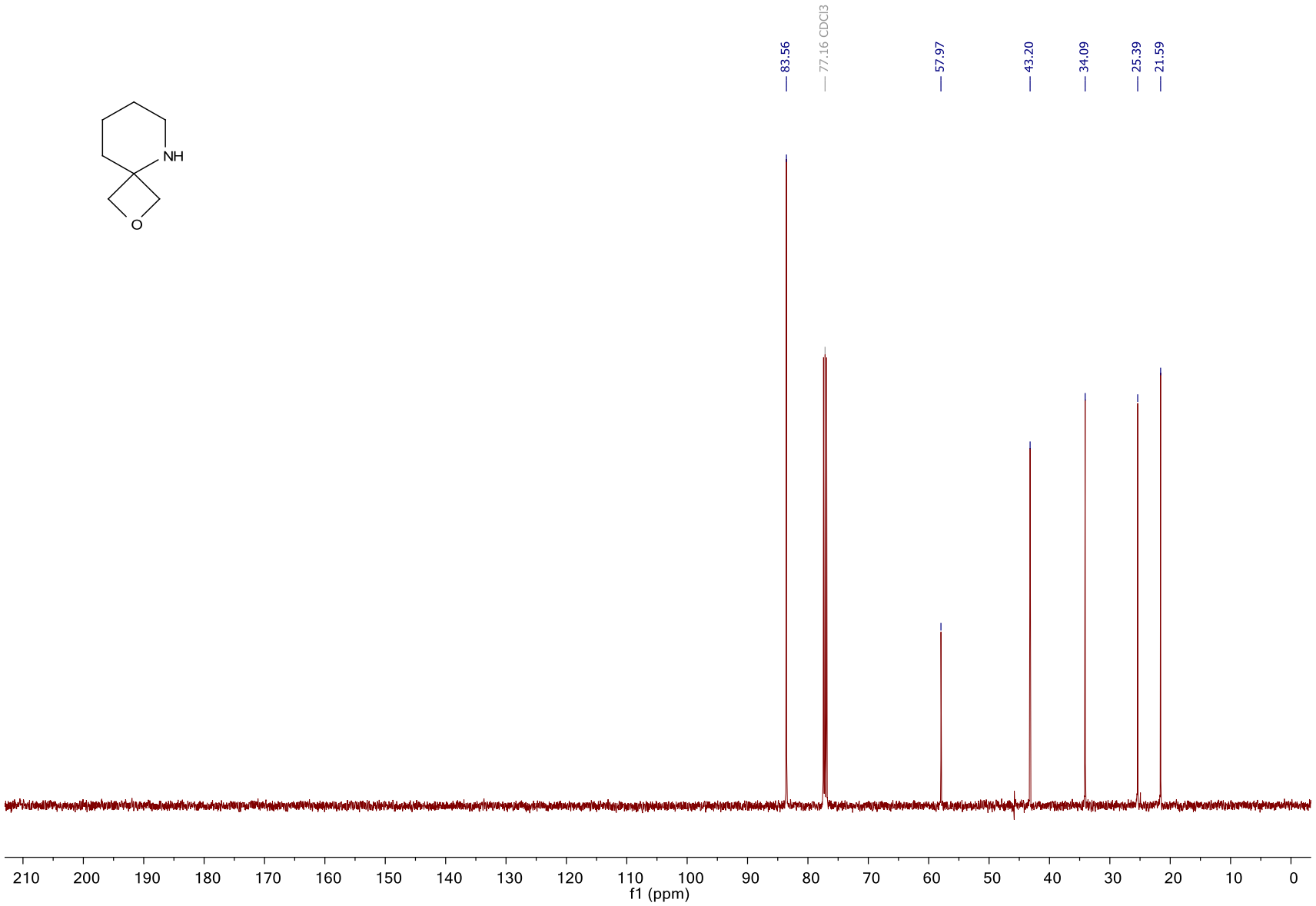
2-Oxa-5-azaspiro[3.5]non-7-ene (101) ^{1}H NMR



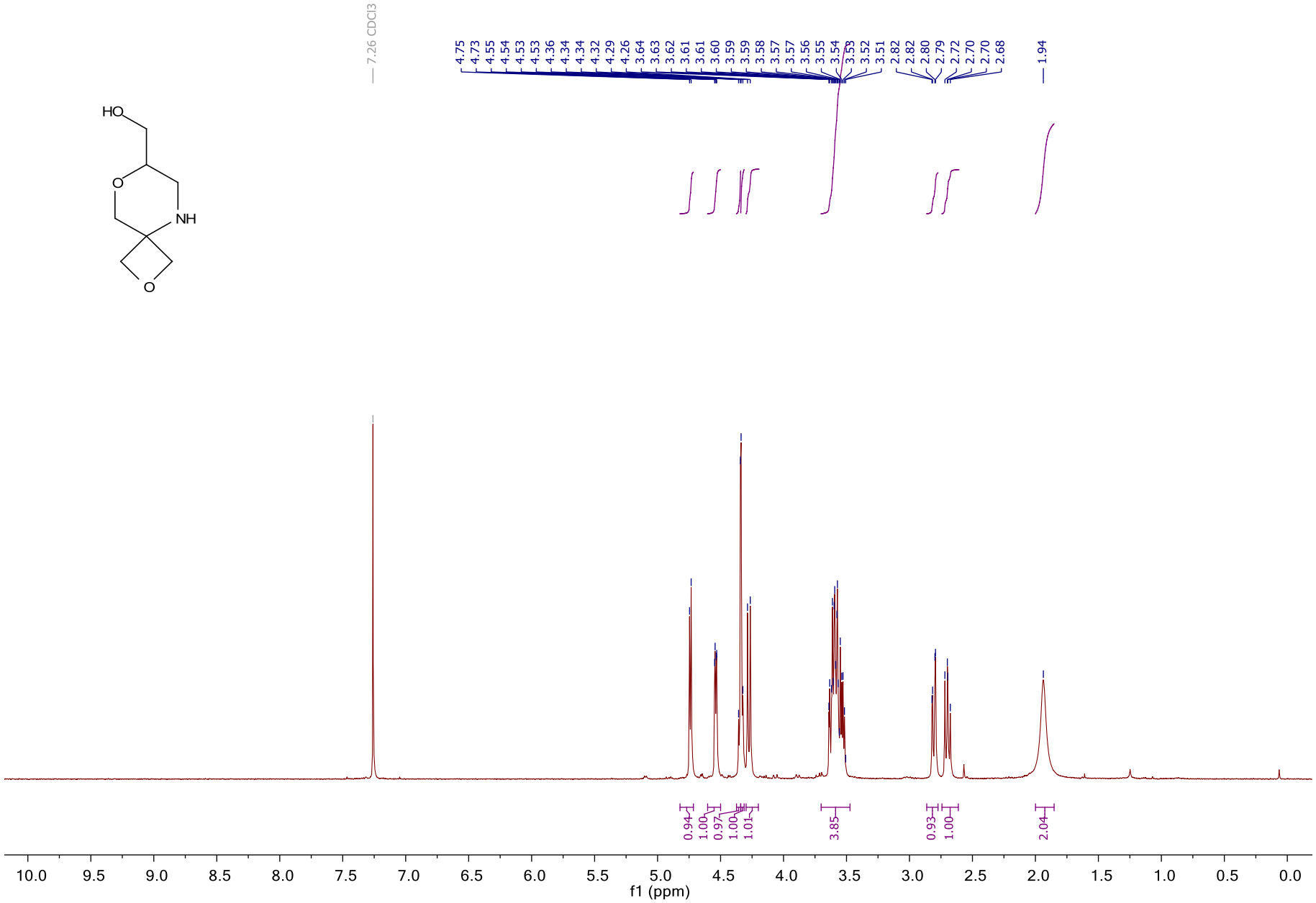
2-Oxa-5-azaspiro[3.5]non-7-ene (101) ^{13}C NMR



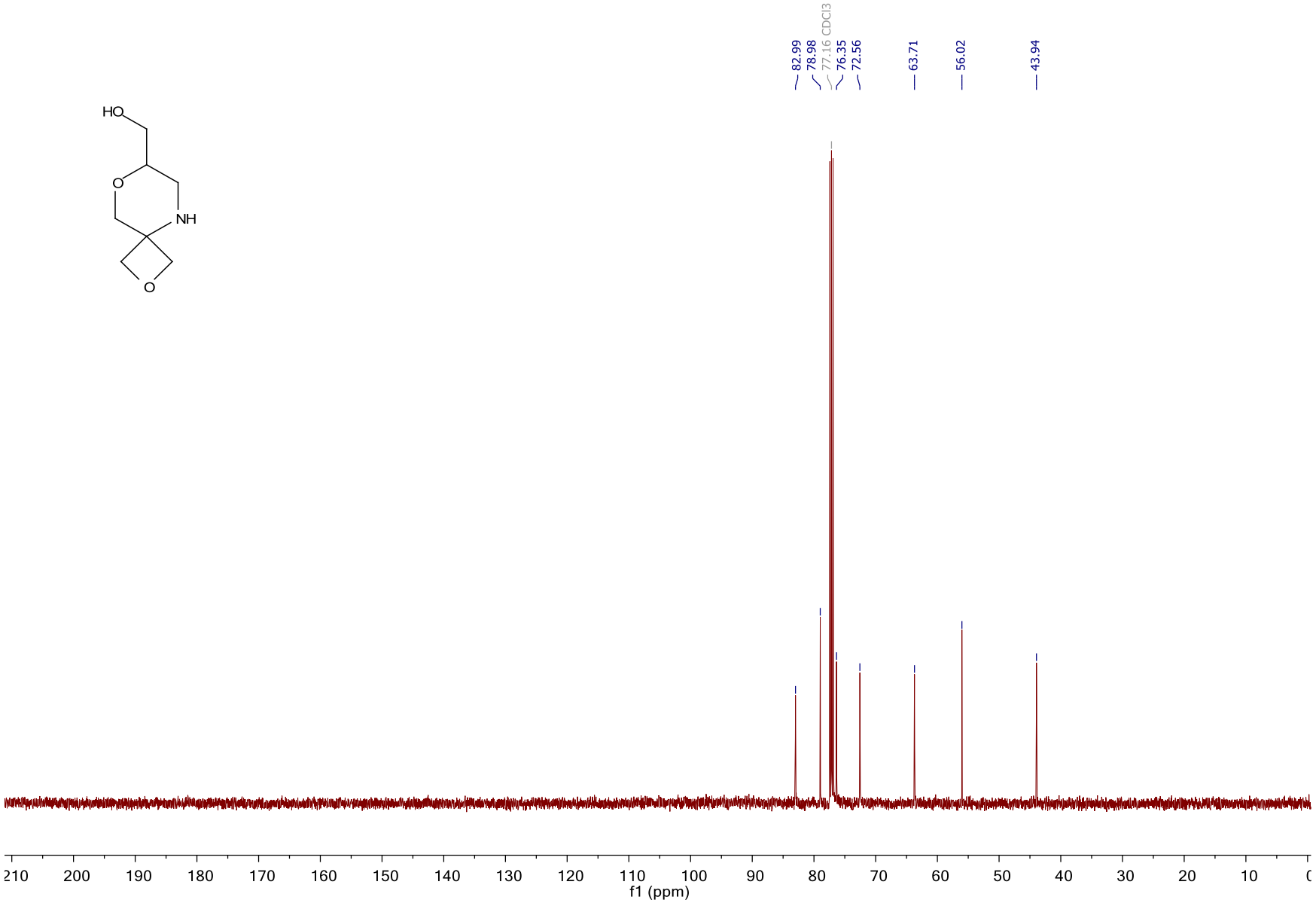
2-Oxa-5-azaspiro[3.5]nonane (102) ^{1}H NMR



2-Oxa-5-azaspiro[3.5]nonane (102) ^{13}C NMR



(2,8-Dioxa-5-azaspiro[3.5]nonan-7-yl)methanol (104) ^{1}H NMR



(2,8-Dioxa-5-azaspiro[3.5]nonan-7-yl)methanol (104) ^{13}C NMR