

SUPPORTING INFORMATION

A Telescopic One-Pot Synthesis of β -Lactam Rings Using Amines as a Convenient Source of Imines

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1. GENERAL METHODS AND MATERIALS

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa-Aesar, TCI Europe and used as received. The solvents were purchased from Aldrich or VWR International in sure/sealed™ bottles over molecular sieves. Flash column chromatography was performed with Merck silica gel 60, particle size 0.040–0.063 mm (230–400 mesh). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade and distilled prior to use. ^1H NMR spectra were recorded at 25 °C. ^1H and ^{13}C liquid NMR spectra were recorded on a Bruker Avance III (400 MHz) NMR spectrometer at 25 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent (CHCl_3 , 7.27 ppm or DMSO-d_6 2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br s = broad singlet), coupling constant (J) in Hertz and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent (CDCl_3 , δ 77.0 ppm or δ DMSO-d_6 δ 40.45 ppm). Deuterated NMR solvents were obtained from Aldrich. High resolution mass spectra (HRMS) were obtained by using electron impact (EI) or electrospray (ES). Analysis of reaction mixture was determined by GC-MS (GC Agilent 6850, MS Agilent 5973) and equipped with HP5 universal capillary column (30 m length and 0.20 mm diameter, 0.11 film thickness) and a flame ionization detector (FID). GC oven temperature was programmed from 80 °C to 250 °C at the rate of 10 °C/min. He gas was used as a carrier gas. Temperatures of injection port and FID were kept constant at 300 °C. Retention times of different compounds were determined by injecting pure compound under identical conditions. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data.

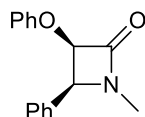
2.GENERAL PROCEDURES FOR THE PREPARATION OF β -LACTAMS 4-30

Method A: To a mixture of *N*-chlorosuccinimide (147 mg, 1.1 mmol) in MeCN (10 mL), *N*-benzylmethylamine **1** (121 mg, 129 μ L, 1 mmol), was dropwise added at room temperature and under Ar. The reaction is left under stirring until amine **1** was totally consumed (TLC analysis, about 1 h) and triethylamine (354 mg, 488 μ L, 3.5 mmol) was dropwise added; whereupon the reaction mixture was stirred at rt for further 3h. Afterwards, a solution of phenoxyacetyl chloride (342 mg, 276 μ L, 2 mmol) in MeCN (10 mL) was slowly added and the resulting reaction mixture was stirred at rt overnight. Then, the reaction mixture was diluted with EtOAc (35 mL), filtered on Celite, washed with H₂O (3 x 15 mL), and brine (15 mL), dried over Na₂SO₄ and concentrated. Finally, the crude product was purified by column chromatography (30-60% EtOAc in hexane) to give β -lactam **4** as a pure white solid (215 mg, 85 %).

Method B: To a mixture of *N*-chlorosuccinimide (147 mg, 1.1 mmol) in MeCN (10 mL), *N*-benzylmethylamine **1** (121 mg, 129 μ L, 1 mmol), was dropwise added at room temperature and under Ar. The reaction is left under stirring until amine **1** was totally consumed (TLC analysis, about 1 h) and NEt₃ (354 mg, 488 μ L, 3.5 mmol) was dropwise added; whereupon the reaction mixture was stirred at rt for further 3h. Afterwards, the reaction mixture was heated to 60 °C over 15 min, phenylacetyl chloride (309 mg, 264 μ L, 2 mmol) was added dropwise and the reaction mixture was stirred at 60 °C for 3 h and at rt overnight. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, washed with water and brine, dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (30-60% EtOAc in hexane) to give β -lactam **20** as a yellow oil (178 mg, 75 %).

CHEMICAL CHARACTERIZATION FOR β -LACTAMS 4-28

(3R,4S)-1-methyl-3-phenoxy-4-phenylazetidin-2-one (4)



Method A gave the product as a white solid, 215 mg, 85%. M.p 99-100 °C.

R_f = 0.40 (1:1 Hexane/AcOEt).

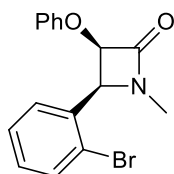
IR (liq. film), cm^{-1} : 3419, 3064, 2917, 1761, 1599, 1495, 1235, 1047, 867, 755, 701.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.30-7.26 (5H, m, Ar), 7.12 (2H, d, J = 7.5 Hz, Ar), 6.87 (1H, t, J = 7.3 Hz, Ar), 6.73 (2H, d, J = 8.0 Hz, Ar), 5.44 (1H, d, J = 4.3 Hz, CH), 4.87 (1H, d, J = 4.3 Hz, CH), 2.85 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 166.1 (0), 156.9 (0), 132.8 (0), 129.2 (1), 128.7 (1), 128.4 (1), 128.3 (1), 122.0 (1), 115.6 (1), 82.5 (1), 63.7 (1), 28.7 (3).

HRMS (ES) $\text{C}_{16}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 254.1176, found 254.1178.

(3R,4S)-4- (2-bromophenyl)-1-methyl-3-phenoxyazetidin-2-one (5)



Method A gave the product as a yellow oil, 262 mg, 79%.

R_f = 0.50 (1:1 hexane/AcOEt).

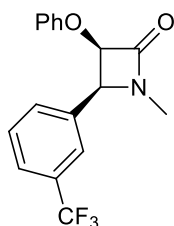
IR (liq. film), cm^{-1} : 3434, 3063, 2923, 1763, 1599, 1495, 1234, 1029, 754.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.49 (1H, d, J = 8.0 Hz, Ar), 7.37-7.32 (2H, m, Ar), 7.15 (3H, t, J = 7.3 Hz, Ar), 6.90 (1H, d, J = 7.3 Hz, Ar), 6.82 (2H, d, J = 7.9 Hz, Ar), 5.49 (1H, d, J = 4.4 Hz, CH), 5.35 (1H, d, J = 4.4 Hz, CH), 2.92 (3H, s, CH_3).

^{13}C NMR (100 MHz) δ (CDCl_3): 166.3 (0), 157.0 (0), 132.9 (1), 132.7 (0), 129.9 (1), 129.2 (1), 128.7 (1), 127.4 (1), 124.2 (0), 122.2 (1), 116.0 (1), 82.8 (1), 62.8 (1), 27.3 (3).

HRMS (ES) $\text{C}_{16}\text{H}_{15}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$ requires 332.0281, found 332.0283.

(3R,4S)-1-methyl-3-phenoxy-4- (3- (trifluoromethyl)phenyl)azetidin-2-one (6)



Method A gave the product as a white solid, 231 mg, 72%. M.p. 91-92 °C.

R_f = 0.47 (1:1 hexane/AcOEt).

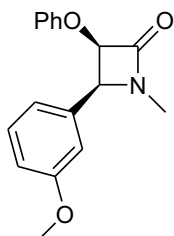
IR (liq. film), cm^{-1} : 3446, 3063, 2923, 1770, 1599, 1591, 1496, 1329, 1235, 1168, 1126, 867.

^1H -NMR (400 MHz) δ (CDCl_3): 7.47-7.24 (3H, m, Ar), 7.36 (1H, t, J = 7.9 Hz, Ar), 7.05 (2H, t, J = 7.5 Hz, Ar), 6.81 (1H, t, J = 7.3 Hz, Ar), 6.63 (2H, d, J = 8.0 Hz, Ar), 5.42 (1H, d, J = 4.3 Hz, CH), 4.86 (1H, d, J = 4.3 Hz, CH), 2.80 (3H, s, CH_3).

^{13}C NMR (100 MHz) δ (CDCl_3): 165.7 (0), 156.5 (0), 134.2 (0), 131.5 (0), 130.8 (q, J = 32 Hz, 0), 129.3 (1), 128.8 (1), 125.6 (q, J = 3.7 Hz, 0), 125.4 (q, J = 3.7 Hz, 0), 122.2 (1), 115.4 (0), 82.3 (1), 63.1 (1), 26.9 (3).

HRMS (ES) $\text{C}_{17}\text{H}_{15}\text{F}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 322.1049, found 322.1052.

(3R, 4S)-4- (3-Methoxy-phenyl)-1-methyl-3-phenoxy-azetidin-2-one (7)



Method A gave the product as a white solid, 210 mg, 74%. M.p. 149-150 °C.

R_f = 0.31 (1:1 hexane/AcOEt).

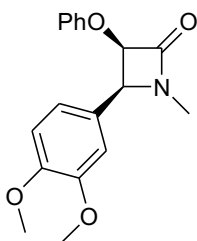
IR (liq. film), cm^{-1} : 3419, 1750, 1652, 1489, 1231, 1050, 756.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.22 (1H, t, $J = 7.7$ Hz, Ar), 7.14 (2H, t, $J = 7.4$ Hz, Ar), 6.90-6.87 (2H, m, Ar), 6.83 (1H, s, Ar), 6.82 (1H, d, $J = 8.0$ Hz, Ar), 6.76 (2H, d, $J = 8.0$ Hz, Ar), 5.44 (1H, d, $J = 4.3$ Hz, CH), 4.85 (1H, d, $J = 4.3$ Hz, CH), 3.76 (3H, s, CH_3), 2.86 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 166.0 (0), 159.6 (0), 157.0 (0), 134.5 (0), 129.3 (1), 129.2 (1), 122.0 (1), 120.8 (1), 115.7 (1), 114.4 (1), 113.8 (1), 82.5 (1), 63.6 (1), 55.3 (3), 26.7 (3).

HRMS (ES) $\text{C}_{17}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$ requires 284.1281, found 284.1285.

(3R,4S)-4- (3,4-Dimethoxy-phenyl)-1-methyl-3-phenoxy-azetidin-2-one (8)



Method A gave the product as a white solid, 241 mg, 77%. M.p. 91-92 °C.

$R_f = 0.27$ (1:1 hexane/AcOEt).

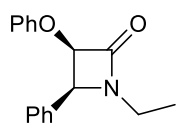
IR (liq. film), cm^{-1} : 2934, 2837, 1761, 1598, 1516, 1259, 1237, 1141, 1026, 758.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.13 (2H, t, $J = 7.3$ Hz, Ar), 6.90-6.85 (2H, m, Ar), 6.18 (1H, s, Ar), 6.79 (1H, d, $J = 8.3$ Hz, Ar), 6.75 (2H, d, $J = 7.9$ Hz, Ar), 5.43 (1H, d, $J = 4.1$ Hz, CH), 4.8 (1H, d, $J = 4.1$ Hz, CH), 3.84 (3H, s, CH_3), 3.82 (3H, s, CH_3), 2.84 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 166.1 (0), 156.9 (0), 149.4 (0), 148.9 (0), 129.2 (1), 125.1 (0), 122.0 (1), 121.3 (1), 115.5 (1), 111.1 (1), 110.7 (1), 82.4 (1), 63.5 (1), 56.0 (3), 55.8 (3), 26.6 (3).

HRMS (ES) $\text{C}_{18}\text{H}_{20}\text{NO}_4$ $[\text{M}+\text{H}]^+$ requires 314.1387, found: 314.1390.

(3R,4S)-1-ethyl-3-phenoxy-4-phenylazetidin-2-one (9)



Method A gave the product as a white solid, 215 mg, 80%. M.p. 105-106 °C.

$R_f = 0.55$ (1:1 hexane/AcOEt).

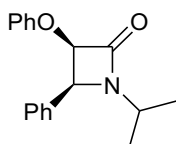
IR (liq. film), cm^{-1} : 3054, 2984, 1761, 1496, 1457, 1266, 1239, 739.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.35-7.28 (5H, m, Ar), 7.11 (2H, t, $J = 7.6$ Hz, Ar), 6.87 (1H, t, $J = 7.4$ Hz, Ar), 6.72 (2H, d, $J = 8.0$ Hz, Ar), 5.41 (1H, d, $J = 4.3$ Hz, CH), 4.94 (1H, d, $J = 4.3$ Hz, CH), 3.57 (1H, dq, $J' = 7.3$, $J^2 = 14.4$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.07 (1H, dq, $J' = 7.3$ Hz, $J^2 = 14.4$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.13 (3H, t, $J = 7.3$ Hz, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 165.6 (0), 156.9 (0), 133.3 (0), 129.2 (1), 128.7 (1), 128.6 (1), 128.2 (1), 121.9 (1), 115.6 (1), 81.8 (1), 61.7 (1), 35.3 (2), 12.6 (3).

HRMS (ES) $\text{C}_{17}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 268.1332, found: 268.1330.

(3R,4S)-1-isopropyl-3-phenoxy-4-phenylazetidin-2-one (10)¹



Method A gave the product as a white solid, 174 mg, 62%. M.p. 132-133 °C.

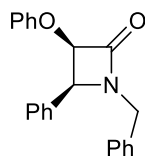
$R_f = 0.50$ (1:1 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3419, 2086, 1748, 1646, 1339, 1244, 1117, 751.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.39 (2H, d, $J = 7.5$ Hz, Ar), 7.29-7.25 (3H, m, Ar), 7.10 (2H, t, $J = 7.5$ Hz, Ar), 6.85 (1H, t, $J = 7.3$ Hz, Ar), 6.71 (2H, d, $J = 8.0$ Hz, Ar), 5.34 (1H, d, $J = 4.3$ Hz, CH), 4.94 (1H, d, $J = 4.3$ Hz, CH), 3.87 (1H, m, CH), 1.31 (3H, d, $J = 6.7$ Hz, CH_3), 1.08 (3H, d, $J = 6.7$ Hz, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 165.5 (0), 156.9 (0), 134.4 (0), 129.1 (1), 128.8 (1), 128.6 (1), 128.1 (1), 121.8 (1), 115.6 (1), 80.9 (1), 61.1 (1), 45.1 (1), 21.3 (3), 20.2 (1).

HRMS (ES) $\text{C}_{18}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 282.1489, found: 282.1492.

(3R,4S)-1-benzyl-3-phenoxy-4-phenylazetidin-2-one (11)

Method A gave the product as a white solid, 267 mg, 81%. M.p. 112-113 °C, lit.² 114-115.

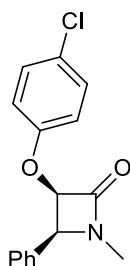
R_f = 0.80 (1: 1 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3434, 3063, 2923, 1763, 1599, 1495, 1234, 1029, 754.

¹H-NMR (400 MHz) δ (CDCl_3): 7.30-7.25 (8H, m, Ar), 7.15 (2H, d, J = 7.2Hz, Ar), 7.08 (2H, t, J = 7.4Hz, Ar), 6.83 (1H, t, J = 7.3Hz, Ar), 6.69 (2H, d, J = 8.0Hz, Ar), 5.38 (1H, d, J = 4.3Hz, CH), 4.88 (1H, d, J = 14.8Hz, CH), 4.74 (1H, d, J = 4.3Hz, CH), 3.86 (1H, d, J = 14.8 Hz, CH).

¹³C NMR (100 MHz) δ (CDCl_3): 165.6 (0), 156.9 (0), 134.8 (1), 132.7 (1), 129.2 (1), 128.9 (1), 128.73 (1), 128.70 (1), 128.69 (1), 128.3 (1), 128.0 (1), 122.0 (1), 115.6 (1), 82.1 (1), 61.5 (1), 44.2 (2).

HRMS (ES) $\text{C}_{22}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 330.1489, found 330.1491.

(3R,4S)-3- (4-chlorophenoxy)-1-methyl-4-phenylazetidin-2-one (14)

Method A gave the product as a white solid, 207 mg, 72%. M.p. 135-136 °C.

R_f = 0.49 (1:1 hexane/AcOEt).

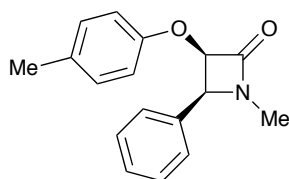
IR (liq. film), cm^{-1} : 3424, 2305, 1757, 1646, 1489, 1265, 1240, 826.

¹H-NMR (400 MHz) δ (CDCl₃): 7.33-7.28 (6H, 5H, m, Ar), 7.07 (2H, d, J = 8.6Hz, Ar), 6.67 (2H, d, J = 8.6Hz, Ar), 5.39 (1H, d, J = 4.3Hz, CH), 4.87 (1H, d, J = 4.3Hz, CH), 2.86 (3H, s, CH₃).

¹³C NMR (100 MHz) δ (CDCl₃): 165.7 (0), 155.5 (0), 132.5 (0), 129.1 (1), 128.9 (1), 128.4 (1), 128.35 (1), 127.0 (0), 116.9 (1), 82.5 (1), 63.5 (1), 26.7 (3).

HRMS (ES) C₁₆H₁₅ClNO₂ [M+H]⁺ requires 288.0786, found: 288.0790.

(3R,4S)-1-Methyl-4-phenyl-3-(*p*-tolylloxy)azetidin-2-one, (15).



Method A gave the product as a white solid, 232 mg, 87%. M.p. 131-132 °C

R_f = 0.77 (1: 1 hexane/AcOEt).

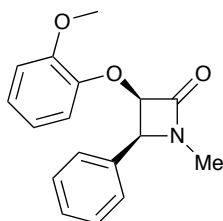
IR (liq. film), cm⁻¹: 3486, 3065, 2970, 2910, 1753, 1610, 1585, 1508, 1246, 1047, 817.

¹H-NMR (400 MHz) δ (CDCl₃): 7.27 (s, 5H), 6.87 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 5.35 (d, J = 4.3 Hz, 1H), 4.81 (d, J = 4.3 Hz, 1H), 2.80 (s, 3H), 2.16 (s, 3H).

¹³C NMR (100 MHz) δ (CDCl₃): 166.2, 154.9, 132.9, 131.3, 129.6, 128.6, 128.4, 128.3, 115.5, 82.84, 63.7, 26.6, 20.4.

HRMS (ES) C₁₇H₁₈NO₂ [M+H]⁺ requires 268.1332, found 268.1335.

(3R,4S)-3-(2-methoxyphenoxy)-1-methyl-4-phenylazetidin-2-one, (16).



Method A gave the product as a pale colourless oil, 255 mg, 90%.

R_f = 0.34 (1:1 hexane/AcOEt).

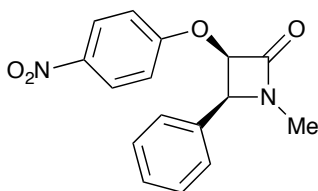
IR (liq. film), cm^{-1} : 3071, 3030, 2962, 2912, 2836, 1762, , 1640, 1500, 1260, 1216, 1047, 755.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.36–7.20 (m, 5H), 6.83 (td, $J = 7.7, 1.6$ Hz, 1H), 6.68 (ddd, $J = 15.4, 7.9, 1.6$ Hz, 2H), 6.58 (dd, $J = 7.9, 1.6$ Hz, 1H), 5.42 (d, $J = 4.4$ Hz, 1H), 4.79 (d, $J = 4.4$ Hz, 1H), 3.61 (s, 3H), 2.81 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 166.4, 150.1, 147.0, 133.5, 128.8, 128.7, 128.5, 123.3, 120.9, 117.7, 113.4, 84.2, 64.1, 56.4, 26.8.

HRMS (ES) $\text{C}_{17}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$ requires 284.1281, found: 284.1279.

(3*R*,4*S*)-1-methyl-3-(4-nitrophenoxy)-4-phenylazetidin-2-one, (17)



Method A gave the product as a white solid, 185 mg (62%), M.p. 115-117.

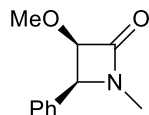
R_f = 0.15 (2:3 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3117, 3087, 3049, 2929, 2858, 1765, 1661, 1593, 1517, 1342, 1258, 1107, 1044, 842, 746.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 8.01 (d, $J = 9.4$ Hz, 2H), 7.26 (dt, $J = 13.7, 6.1$ Hz, 5H), 6.82 (d, $J = 9.4$ Hz, 2H), 5.49 (d, $J = 4.4$ Hz, 1H), 4.91 (d, $J = 4.4$ Hz, 1H), 2.85 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 164.6, 161.4, 142.4, 131.9, 129.2, 128.5, 128.3, 125.5, 115.4, 81.9, 63.1, 26.8.

HRMS (ES) $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ requires 299.1026, found: 299.11025.

(3R,4S)-3-methoxy-1-methyl-4-phenylazetidin-2-one (18)

Method A gave the product as a white solid, 136 mg, 71%. M.p. 66-67 °C.

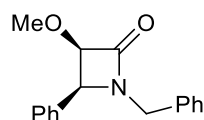
$R_f = 0.54$ (1:1 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3495, 3034, 2991, 2930, 2834, 1755, 1456, 1393, 1361, 1210, 1061, 997, 703.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.42-7.31 (5H, m, Ar), 4.69-4.68 (2H, m, 2CH), 3.11 (3H, s, CH_3), 2.78 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 167.2 (0), 133.5 (0), 128.6 (1), 128.5 (1), 128.2 (1), 86.1 (1), 63.3 (1), 58.1 (3), 26.4 (3).

HRMS (ES) $\text{C}_{11}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 192.1019, found: 192.1018.

(3R,4S)-1-benzyl-3-methoxy-4-phenylazetidin-2-one (19)

Method A gave the product as a colourless oil, 155 mg, 58%.

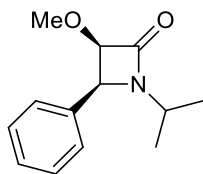
$R_f = 0.51$ (1:1 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3032, 2928, 1759, 1496, 1456, 1399, 1360, 1266, 1211, 1037, 736, 700.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.40-7.32 (3H, m, Ar), 7.32-7.23 (5H, m, Ar), 7.12 (2H, d, $J = 7.0$ Hz, Ar), 4.82 (1H, d, $J = 14.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.66 (1H, d, $J = 4.3$ Hz, CH), 4.56 (1H, d, $J = 4.3$ Hz, CH), 3.81 (1H, d, $J = 14.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.09 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 166.8 (0), 135.0 (0), 133.4 (0), 128.8 (1), 128.61 (1), 128.59 (1), 128.5 (1), 128.4 (1), 127.9 (1), 85.8 (1), 61.1 (1), 58.2 (3), 43.9 (2).

HRMS (ES) $\text{C}_{17}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 268.1332, found: 268.1334.

(3R,4S)-1-methyl-3-phenoxy-4- (3- (trifluoromethyl)phenyl)azetidin-2-one (20)

Method A gave the product as a white solid, 96 mg, 44%. M.p. 67-68 °C.

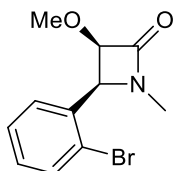
R_f = 0.38 (1:1 hexane/AcOEt).

IR (liq. film), cm^{-1} : 2974, 2926, 1752, 1392, 1349, 1128, 1028.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.46-7.36 (5H, m, Ar), 4.74 (1H, d, J = 4.3 Hz, CH), 4.59 (1H, d, J = 4.3 Hz, CH), 3.81 (1H, quint., J = 6.7 Hz, CH), 3.06 (3H, s, CH_3), 1.26 (3H, d, J = 6.5 Hz, CH_3), 1.04 (3H, d, J = 6.5 Hz, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 166.7 (0), 135.2 (0), 128.6 (1), 128.5 (1), 128.2 (1), 84.6 (1), 60.6 (1), 58.0 (3), 44.8 (1), 21.4 (3), 20.2 (3).

HRMS (ES) $\text{C}_{13}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 220.1332, found: 220.1337.

(3R,4S)-4- (2-bromophenyl)-3-methoxy-1-methylazetidin-2-one (21)

Method A gave the product as a yellow oil, 184 mg, 68%.

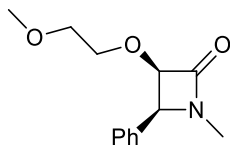
R_f = 0.43 (1:1 hexane/AcOEt).

IR (liq. film), cm^{-1} : 2930, 1763, 1469, 1442, 1390, 1209, 1060, 996, 754.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.60 (1H, d, J = 8.0 Hz, Ar), 7.39 (1H, t, J = 7.5 Hz, Ar), 7.28 (1H, d, J = 7.7 Hz, Ar), 7.23 (1H, t, J = 7.6 Hz, Ar), 5.14 (1H, d, J = 4.3 Hz, CH), 4.79 (1H, d, J = 4.3 Hz, CH), 3.21 (3H, s, CH_3), 2.87 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 167.2 (0), 133.4 (0), 133.0 (1), 129.7 (1), 128.6 (1), 127.5 (1), 123.6 (0), 86.3 (1), 63.2 (1), 58.9 (3), 27.0 (3).

HRMS (ES) $\text{C}_{11}\text{H}_{13}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$ requires 270.0124, found 270.0129.

(3R,4S)-3- (2-methoxyethoxy)-1-methyl-4-phenylazetidin-2-one (22)

Method A gave the product as a yellow oil, 125 mg, 53%.

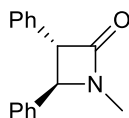
$R_f = 0.24$ (1:3 hexane/AcOEt).

IR (liq. film), cm^{-1} : 2923, 1756, 1457, 1395, 1125, 1069, 703.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.41-7.32 (5H, m, Ar), 4.89 (1H, d, $J = 4$ Hz, CH), 4.68 (1H, d, $J = 4$ Hz, CH), 3.49 (1H, m, $\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 3.28-3.11 (3H, m, $\text{CH}^{\text{A}}\text{H}^{\text{B}}$, CH_2), 3.14 (3H, s, CH_3), 2.78 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 167.1 (0), 133.8 (0), 128.5 (1), 128.4 (1), 128.3 (1), 85.6 (1), 71.4 (2), 69.9 (2), 63.8 (1), 58.8 (3), 26.4 (3).

HRMS (ES) $\text{C}_{13}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$ requires 236.1281, found: 236.1284.

(3S,4R)-1-methyl-3,4-diphenylazetidin-2-one (23).

Method B gave the product as a yellow oil, 178 mg, 75%.

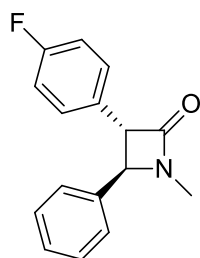
$R_f = 0.55$ (1:1 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3446, 1756, 1653, 1496, 1456, 1388, 698.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.5-7.25 (10H, m, Ar), 4.45 (1H, s, CH), 4.17 (1H, s, CH), 2.87 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 168.5 (0), 137.4 (0), 135.1 (0), 129.2 (1), 128.9 (1), 128.7 (1), 127.7 (1), 127.4 (1), 126.3 (1), 65.7 (1), 65.4 (1), 27.1 (3).

Spectroscopic data agrees with Paul et al.³

(3S,4R)-3- (4-fluorophenyl)-1-methyl-4-phenylazetidin-2-one (24)

Method B gave the product as colourless oil, 125 mg, 49%.

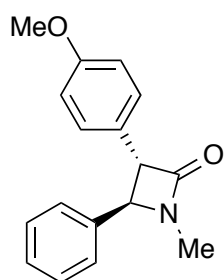
$R_f = 0.48$ (7:3 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3064, 3034, 2921, 2852, 1755, 1658, 1604, 1510, 1456, 1421, 1389, 1225, 1159, 700.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.44-7.38 (3H, m, Ar), 7.33-7.32 (2H, m, Ar), 7.28-7.25 (2H, m, Ar), 7.04 (2H, t, $J = 8$ Hz, Ar), 4.44 (1H, s, CH), 4.14 (1H, s, CH), 2.86 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 168.2 (0), 162.3 (d, $J = 246$ Hz, 0), 137.2 (0), 130.9 (d, $J = 3$ Hz, 0), 129.2 (1), 129.0 (d, $J = 8$ Hz, 1), 128.8 (1), 126.3 (1), 115.8 (d, $J = 22$ Hz, 1), 65.5 (1), 64.9 (1), 27.1 (3).

HRMS (ES) $\text{C}_{16}\text{H}_{15}\text{FNO}$ $[\text{M}+\text{H}]^+$ requires 256.1132, found 256.1137.

(3S,4R)-3- (4-methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (25).

Method B gave the product as a yellow oil, 233 mg, 87%.

$R_f = 0.53$ (1:1 hexane/AcOEt).

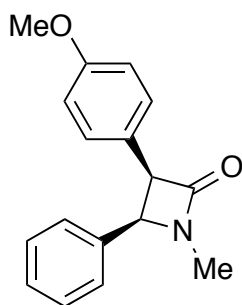
IR (liq. film), cm^{-1} : 2908, 2839, 1753, 1513, 1388, 1250, 1179, 1031, 700.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.44-7.31 (5H, m, Ar), 7.21 (2H, d, $J = 7.9$ Hz, Ar), 6.89 (2H, d, $J = 7.9$ Hz, Ar), 4.40 (1H, s, CH), 4.10 (1H, s, CH), 3.80 (3H, s, CH_3), 2.86 (3H, s, CH_3).

¹³C NMR (100 MHz) δ (CDCl₃): 168.9 (0), 159.1 (0), 137.5 (0), 129.2 (1), 128.6 (1), 128.5 (1), 127.2 (0), 126.3 (1), 114.3 (1), 65.7 (1), 65.2 (1), 55.3 (3), 27.0 (3).

Spectroscopical data agrees with Wang et al.²

(3R,4R)-3- (4-Methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (26)



Method B gave the product as a yellow oil, 16 mg, 6%.

R_f = 0.38 (1:1 hexane/AcOEt).

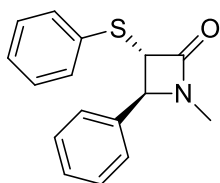
IR (liq. film), cm⁻¹: 2924, 2854, 1750, 1611, 1514, 1249, 1179, 1032, 764, 701.

¹H-NMR (400 MHz) δ (CDCl₃): 7.18-7.10 (3H, m, Ar), 7.00 (2H, d, *J* = 7.0 Hz, Ar), 6.91 (2H, d, *J* = 8.0 Hz, Ar), 6.59 (2H, d, *J* = 8.0 Hz, Ar), 4.92 (1H, d, *J* = 5.3 Hz, CH), 4.81 (1H, d, *J* = 5.2 Hz, CH), 3.66 (3H, s, CH₃), 2.91 (3H, s, CH₃).

¹³C NMR (100 MHz) δ (CDCl₃): 168.8 (0), 158.4 (0), 135.0 (0), 129.8 (1), 128.2 (1), 127.9 (1), 127.3 (1), 124.8 (0), 113.5 (1), 62.4 (1), 60.7 (1), 55.1 (3), 27.3 (3).

Spectroscopical data agrees with Wang *et al.*⁴

(3S,4S)-1-methyl-4-phenyl-3- (phenylthio)azetidin-2-one (28)



Method B gave the product as yellow oil, 162 mg, 60%.

$R_f = 0.34$ (7:3 hexane/AcOEt).

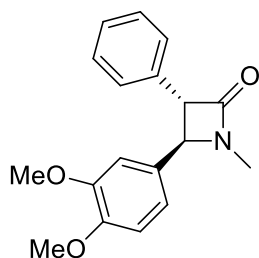
IR (liq. film), cm^{-1} : 3060, 2916, 1761, 1647, 1582, 1456, 1439, 1419, 1386, 1070, 986, 739, 699.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.47-7.45 (2H, m, Ar), 7.40-7.33 (3H, m, Ar), 7.28-7.24 (5H, m, Ar), 4.30 (1H, s, CH), 4.15 (1H, s, CH), 2.71 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 166.14 (0), 136.19 (0), 132.6 (0), 132.1 (1), 129.2 (1), 129.1 (1), 129.0 (1), 127.8 (1), 126.3 (1), 64.7 (1), 61.9 (1), 27.3 (3).

HRMS (ES) $\text{C}_{16}\text{H}_{16}\text{NOS}$ $[\text{M}+\text{H}]^+$ requires 270.0947, found 270.0950.

(3S,4R)-4- (3,4-dimethoxyphenyl)-1-methyl-3-phenylazetidin-2-one (29)



Method B gave the product as yellow solid, 193 mg, 65%. M.p. 128-129 °C.

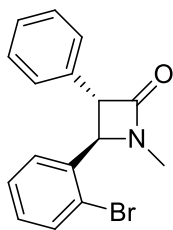
$R_f = 0.32$ (1:1 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3060, 3028, 3001, 2935, 2836, 1753, 1517, 1454, 1426, 1388, 1261, 1236, 1161, 1139, 1026, 699.

$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.37-7.34 (2H, m, Ar), 7.30-7.29 (3H, m, Ar), 6.90 (2H, s, Ar), 6.82 (1H, s, Ar), 4.39 (1H, s, CH), 4.16 (1H, s, CH), 3.90 (6H, s, $2 \times \text{CH}_3$), 2.86 (3H, s, CH_3).

$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 168.6 (0), 149.8 (0), 149.4 (0), 135.1 (0), 129.7 (0), 128.9 (1), 127.6 (1), 127.4 (1), 119.1 (1), 111.6 (1), 108.7 (1), 65.7 (1), 65.3 (1), 56.06 (3), 56.02 (3), 27.0 (3).

HRMS (ES) $\text{C}_{18}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$ requires 298.1438, found: 298.1444.

(3S,4R)-4- (2-bromophenyl)-1-methyl-3-phenylazetidin-2-one (30)

Method B gave the product as yellow oil, 187 mg, 59%.

R_f = 0.34 (7:3 hexane/AcOEt).

IR (liq. film), cm^{-1} : 3061, 3030, 2944, 1754, 1651, 1568, 1469, 1441, 1389, 1028, 990, 755, 733, 698.

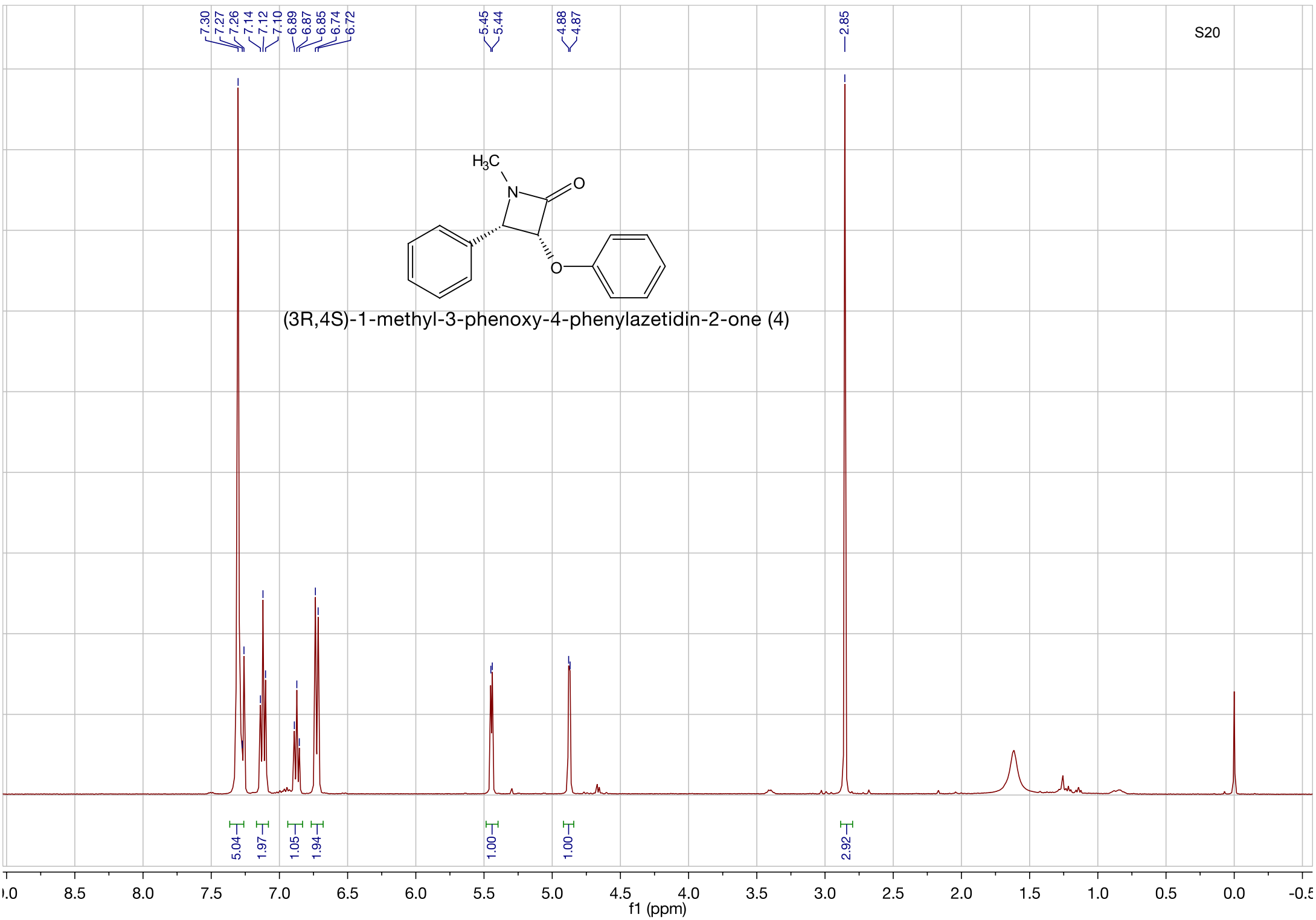
$^1\text{H-NMR}$ (400 MHz) δ (CDCl_3): 7.60 (1H, d, J = 8.0 Hz, Ar), 7.43-7.26 (7H, m, Ar), 7.21 (1H, t, J = 7.5 Hz, Ar), 5.01 (1H, s, CH), 4.12 (1H, s, CH), 2.92 (3H, s, CH_3).

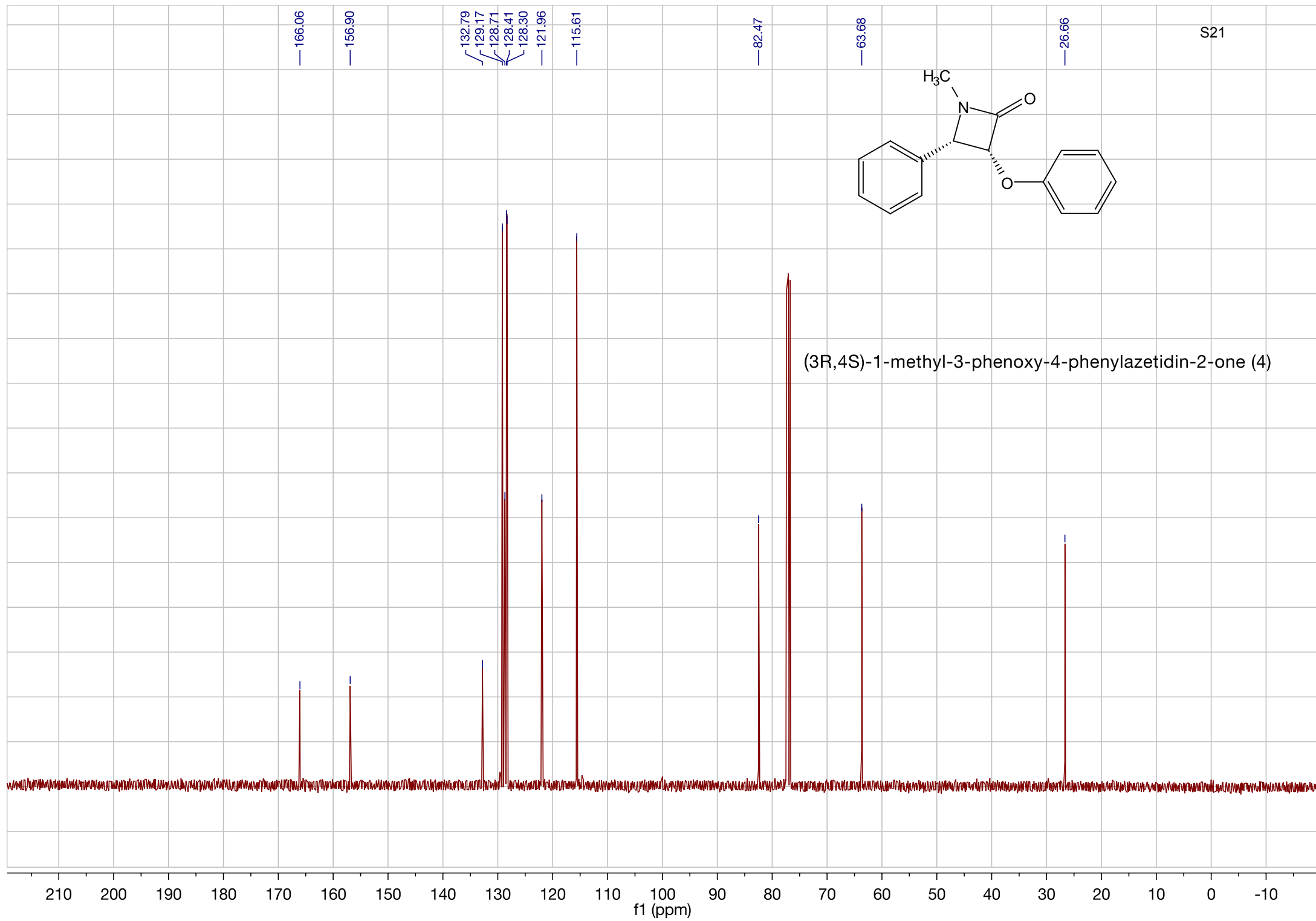
$^{13}\text{C NMR}$ (100 MHz) δ (CDCl_3): 168.6 (0), 137.0 (0), 134.9 (0), 133.5 (1), 129.8 (1), 128.8 (1), 128.2 (1), 127.7 (1), 127.6 (1), 126.5 (1), 123.3 (0), 65.7 (1), 63.6 (1), 27.5 (3).

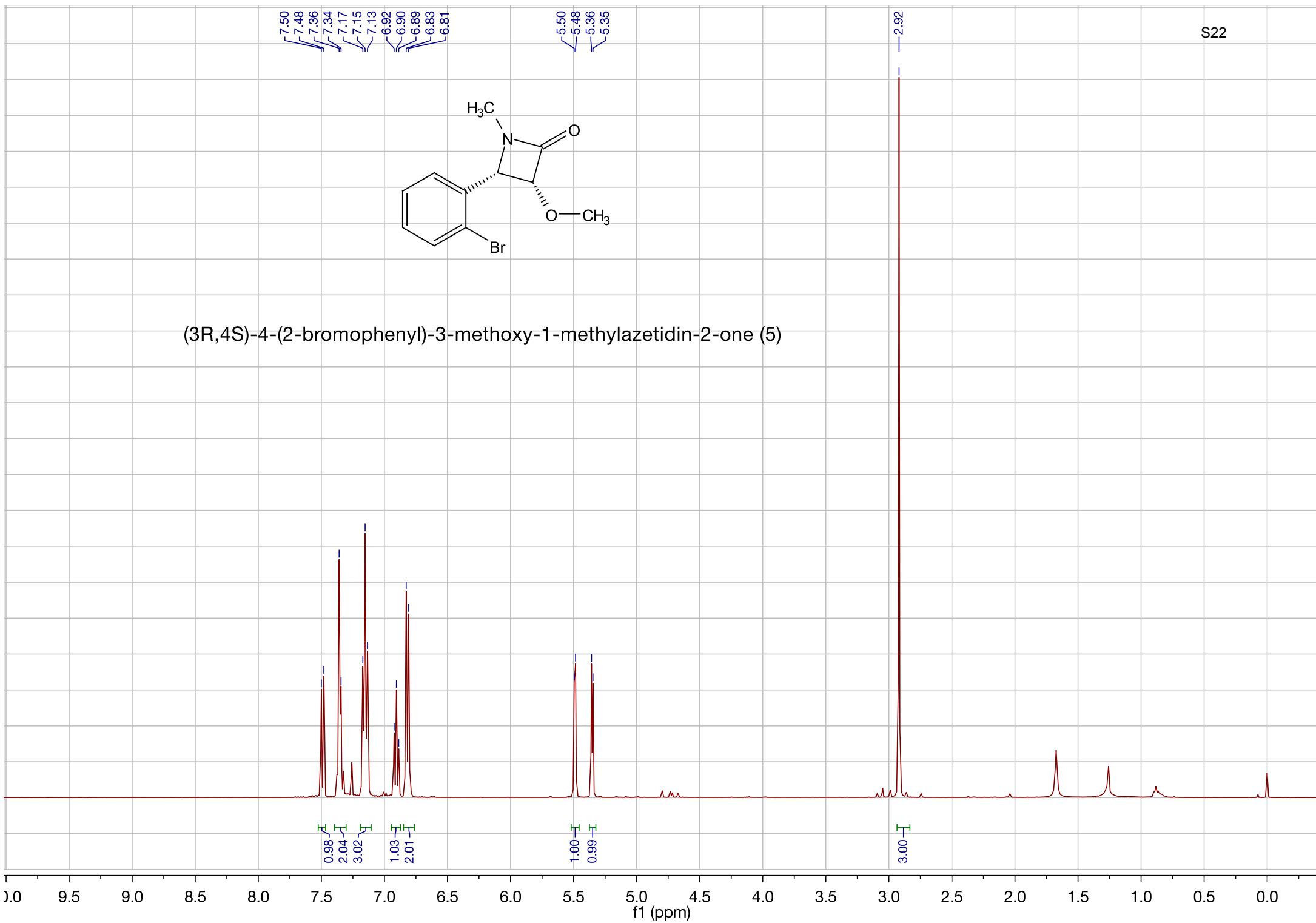
HRMS (ES) $\text{C}_{16}\text{H}_{14}\text{BrNO}$ $[\text{M}+\text{H}]^+$ requires 316.0332, found 317.0329.

REFERENCES

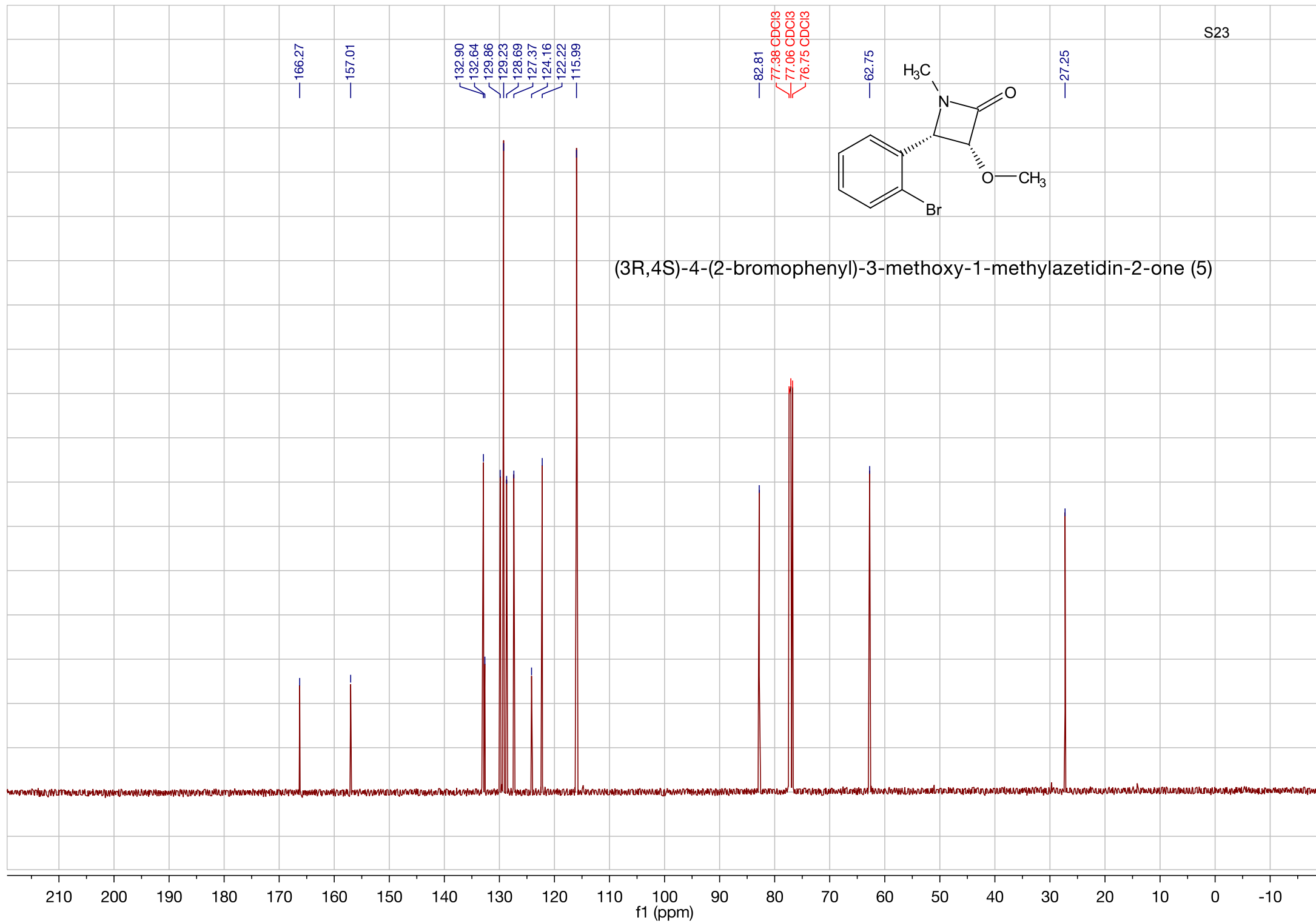
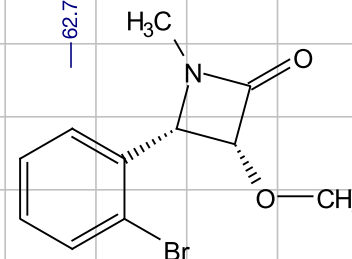
-
1. For chemical characterization data of *trans*-regioisomer, see Wang, Y.; Liang, Y; Jiao, L.; Du, D.-M.; Xu J. *J. Org. Chem.*, **2006**, *71*, 6983.
 2. Matsui, S.; Hashimoto, Y.; Saigo, K. *Synthesis*, **1998**, 1161.
 3. Paul, N. D.; Chirila, A.; Lu, H.; Zhang, X. P.; de Bruin, B. *Chem. Eur. J.* **2013**, *19*, 12953.
 4. Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330.

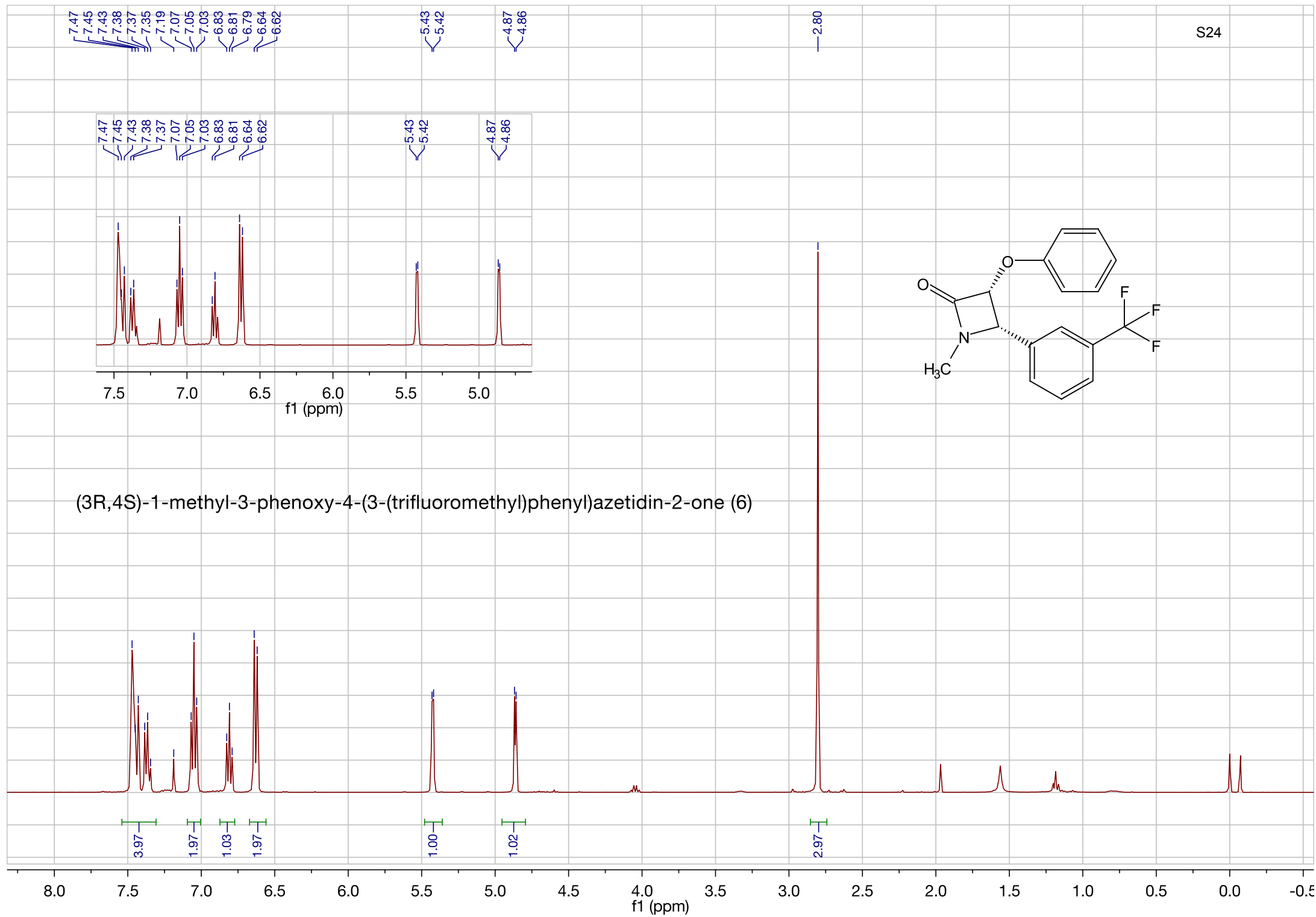


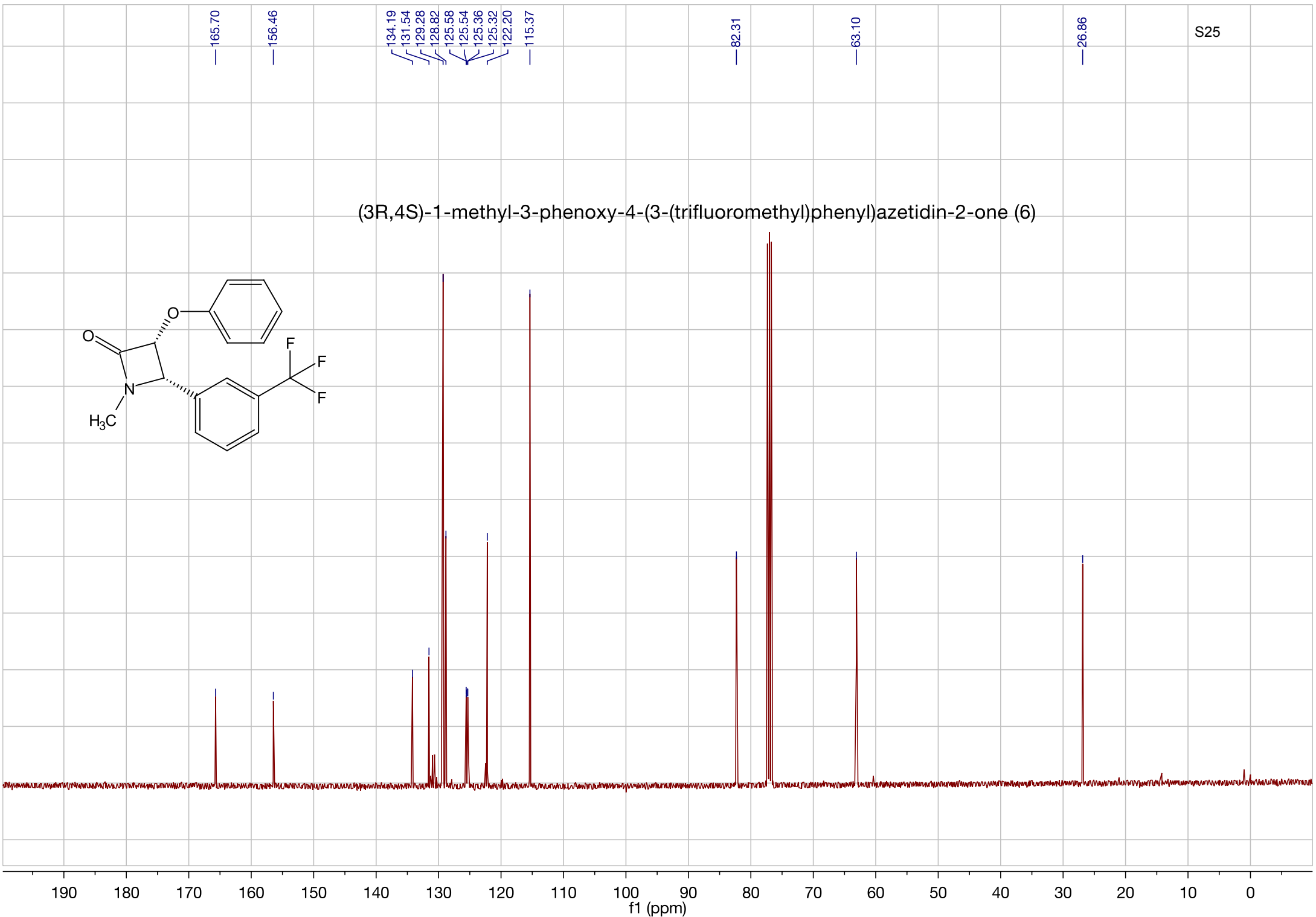


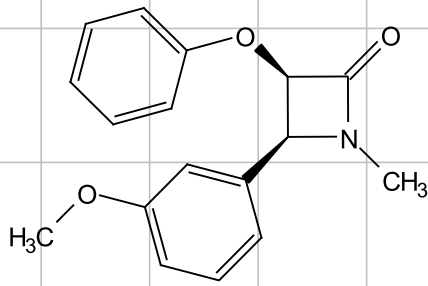


(3R,4S)-4-(2-bromophenyl)-3-methoxy-1-methylazetidin-2-one (5)

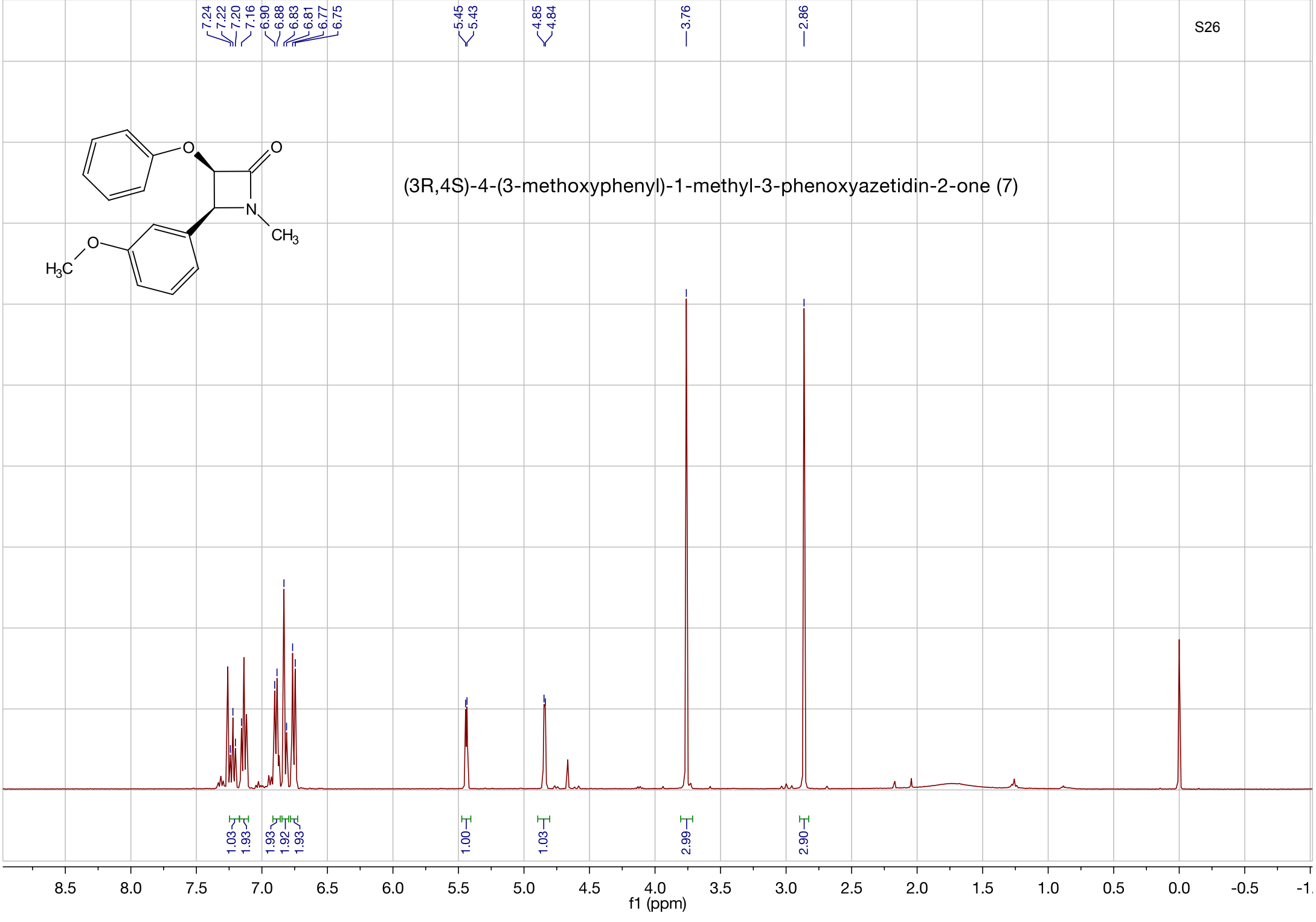


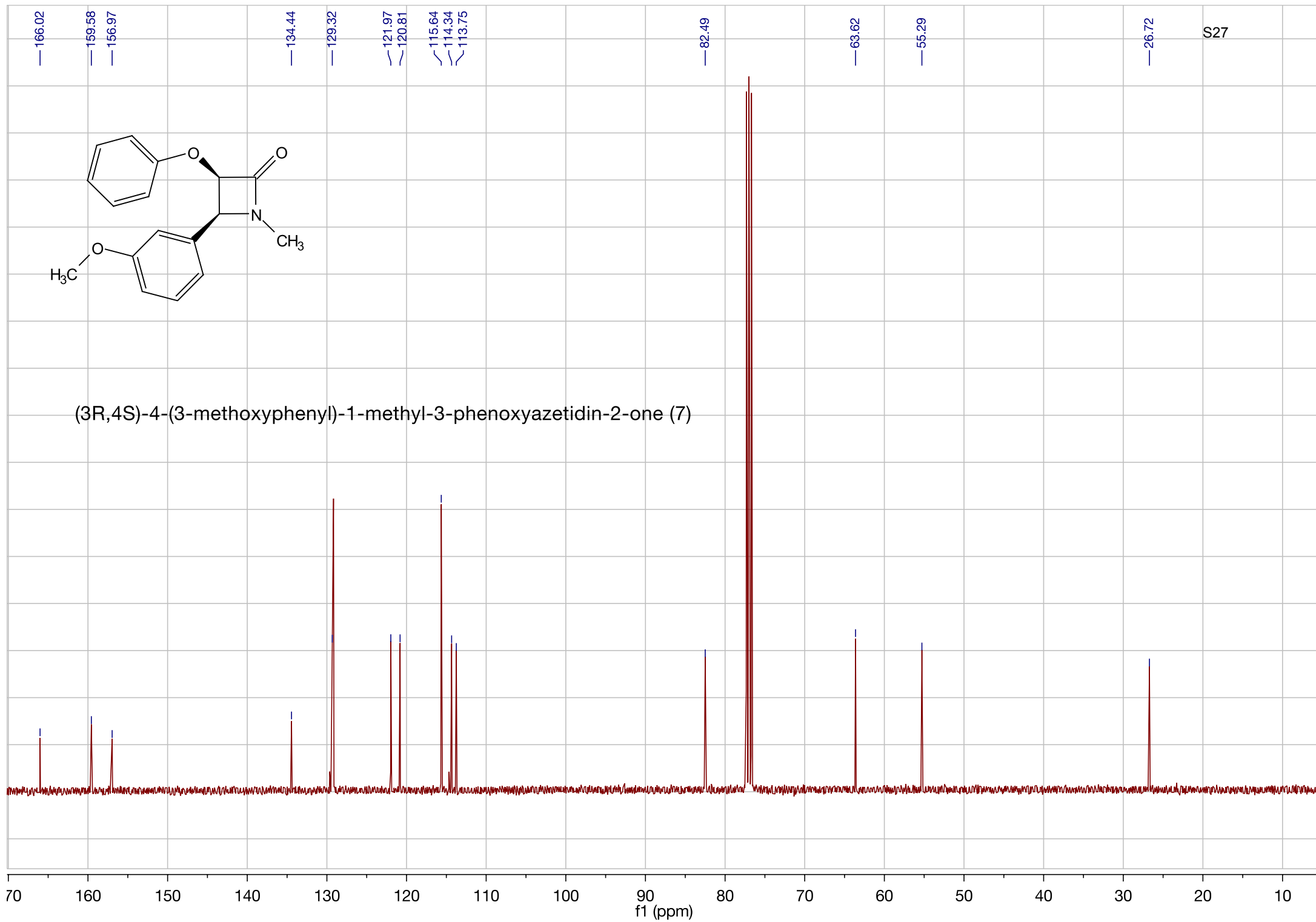




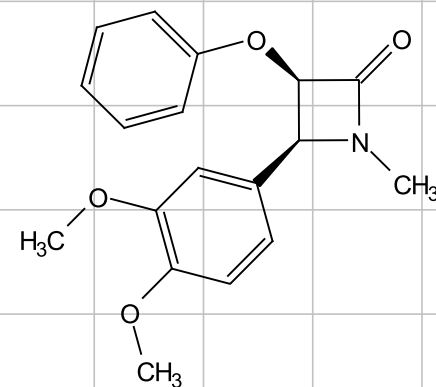


(3R,4S)-4-(3-methoxyphenyl)-1-methyl-3-phenoxyazetidin-2-one (7)

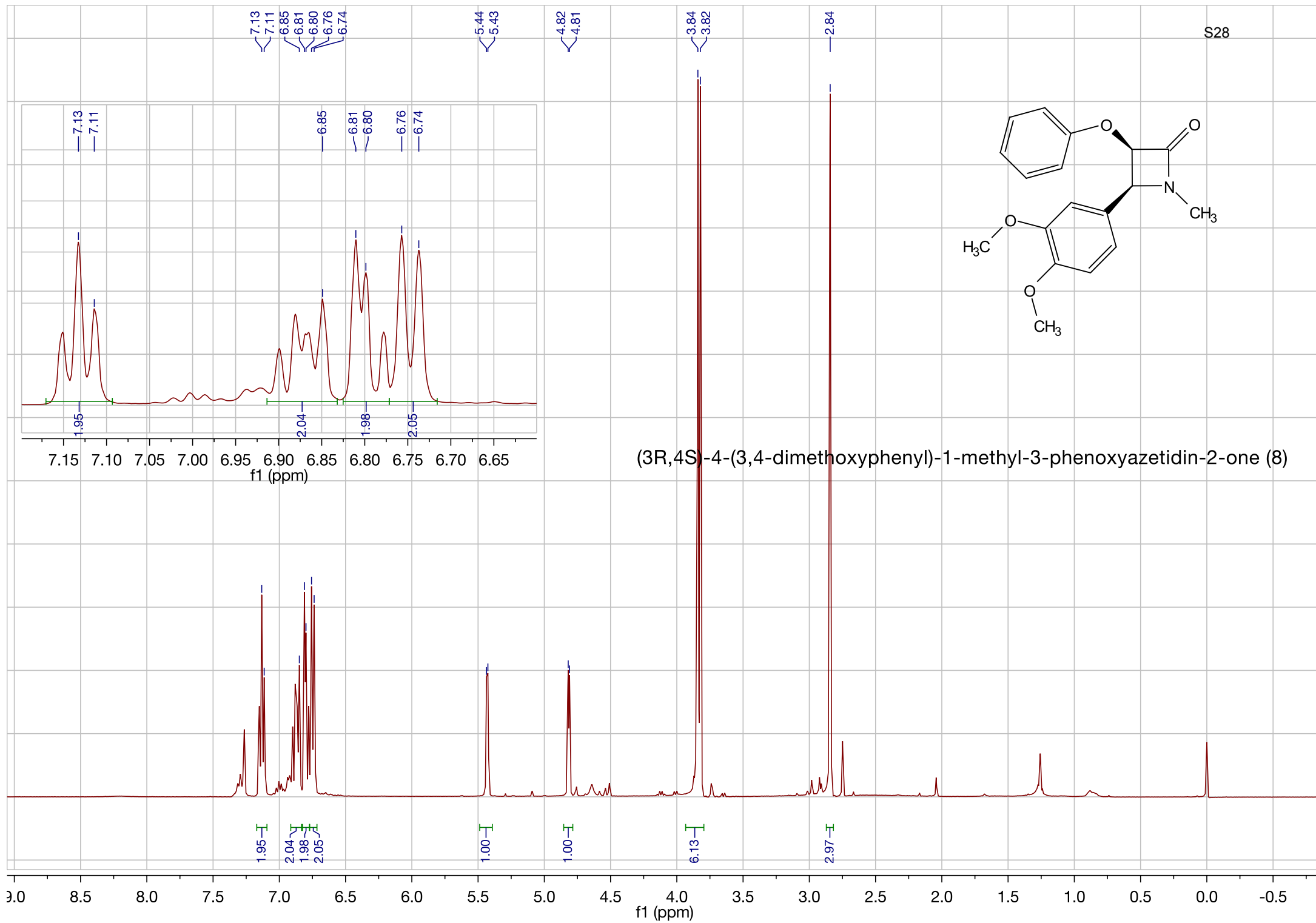




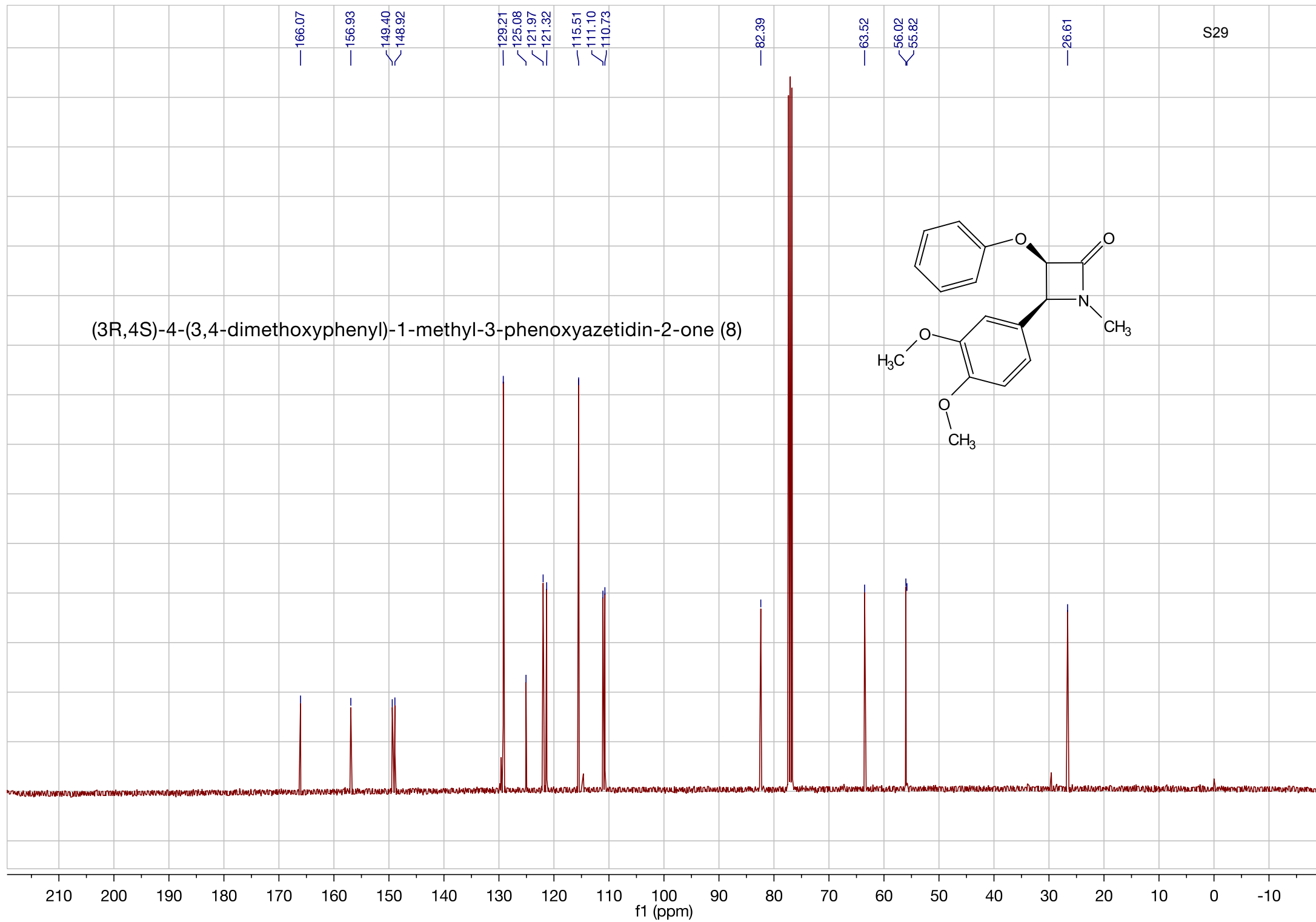
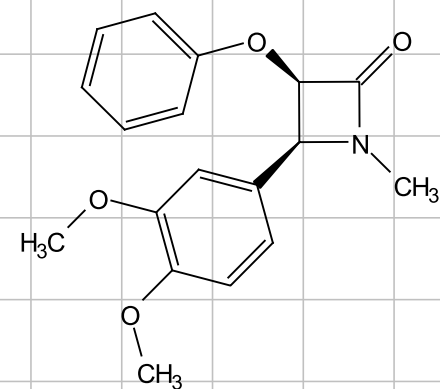
S28

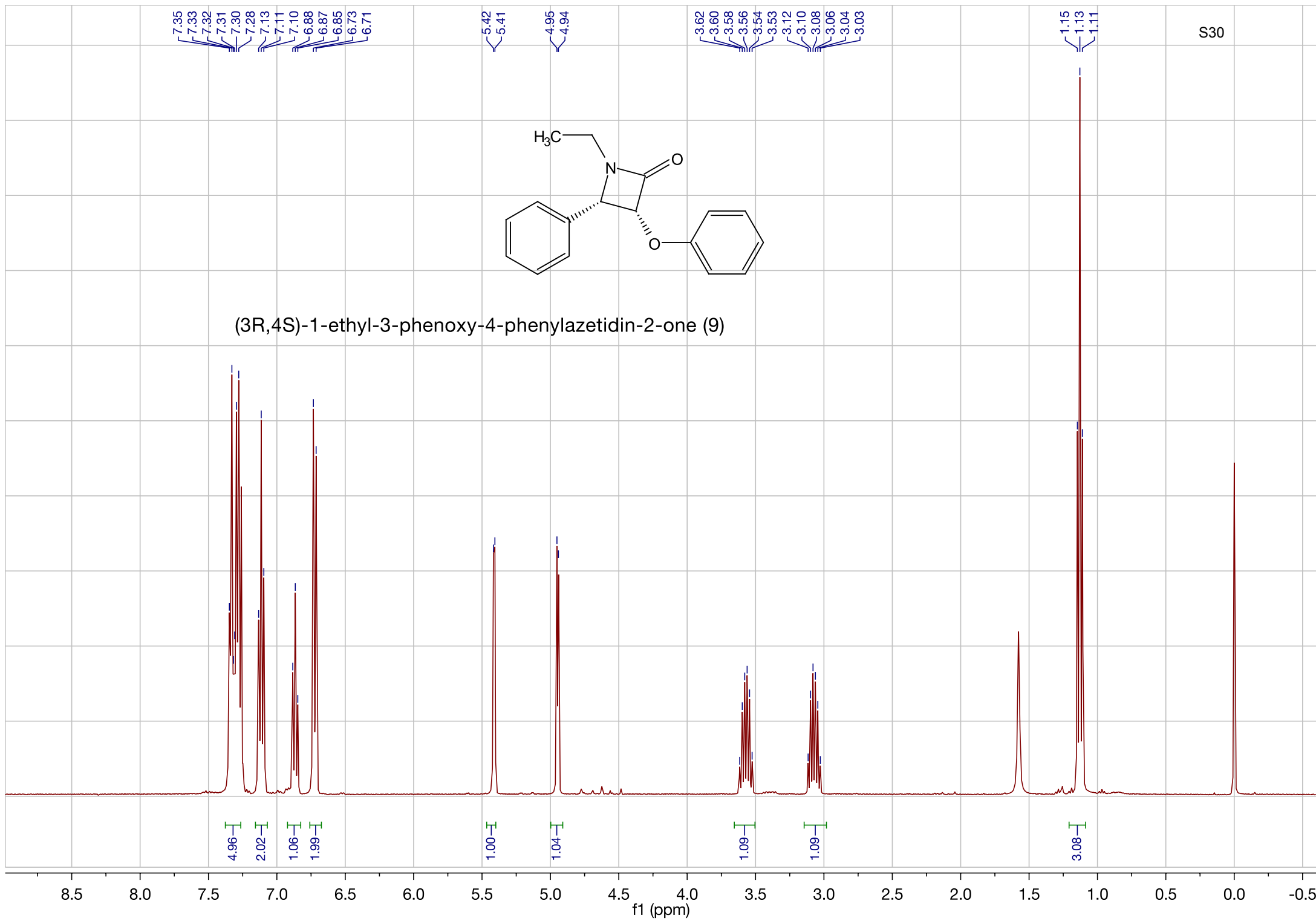


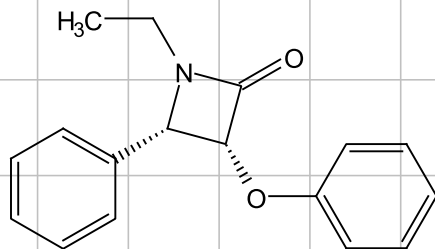
(3R,4S)-4-(3,4-dimethoxyphenyl)-1-methyl-3-phenoxyazetidin-2-one (8)



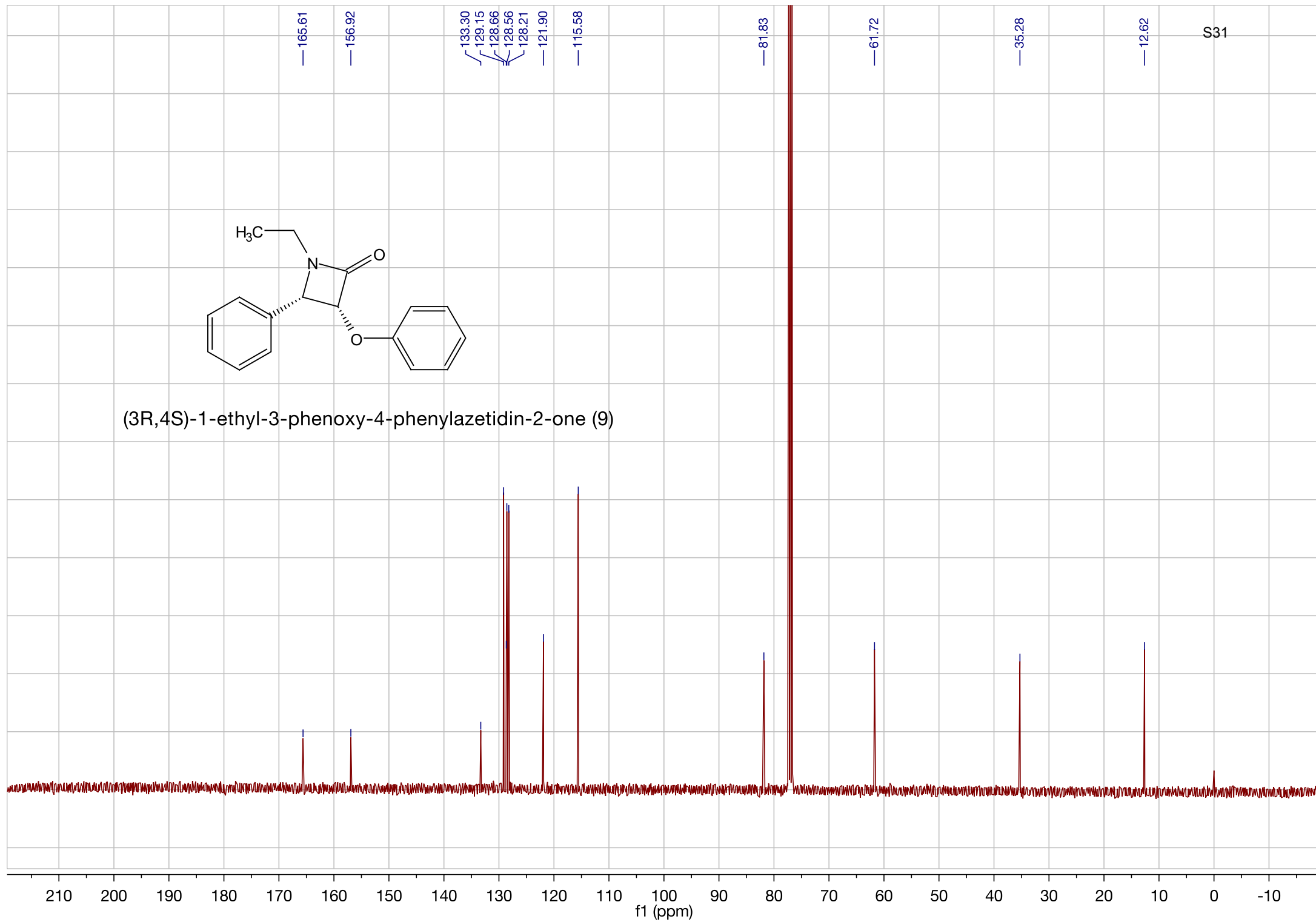
(3R,4S)-4-(3,4-dimethoxyphenyl)-1-methyl-3-phenoxyazetidin-2-one (8)

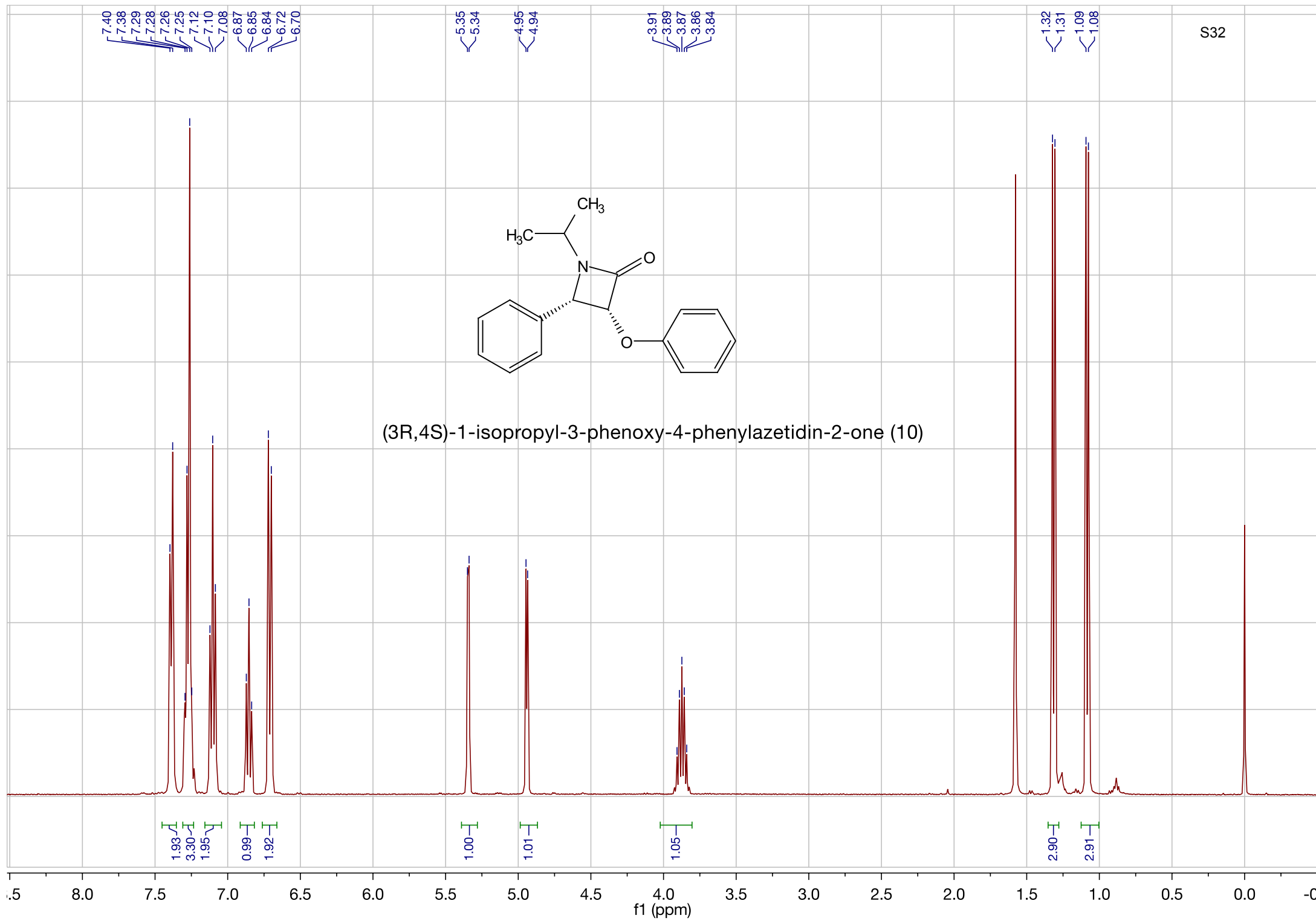


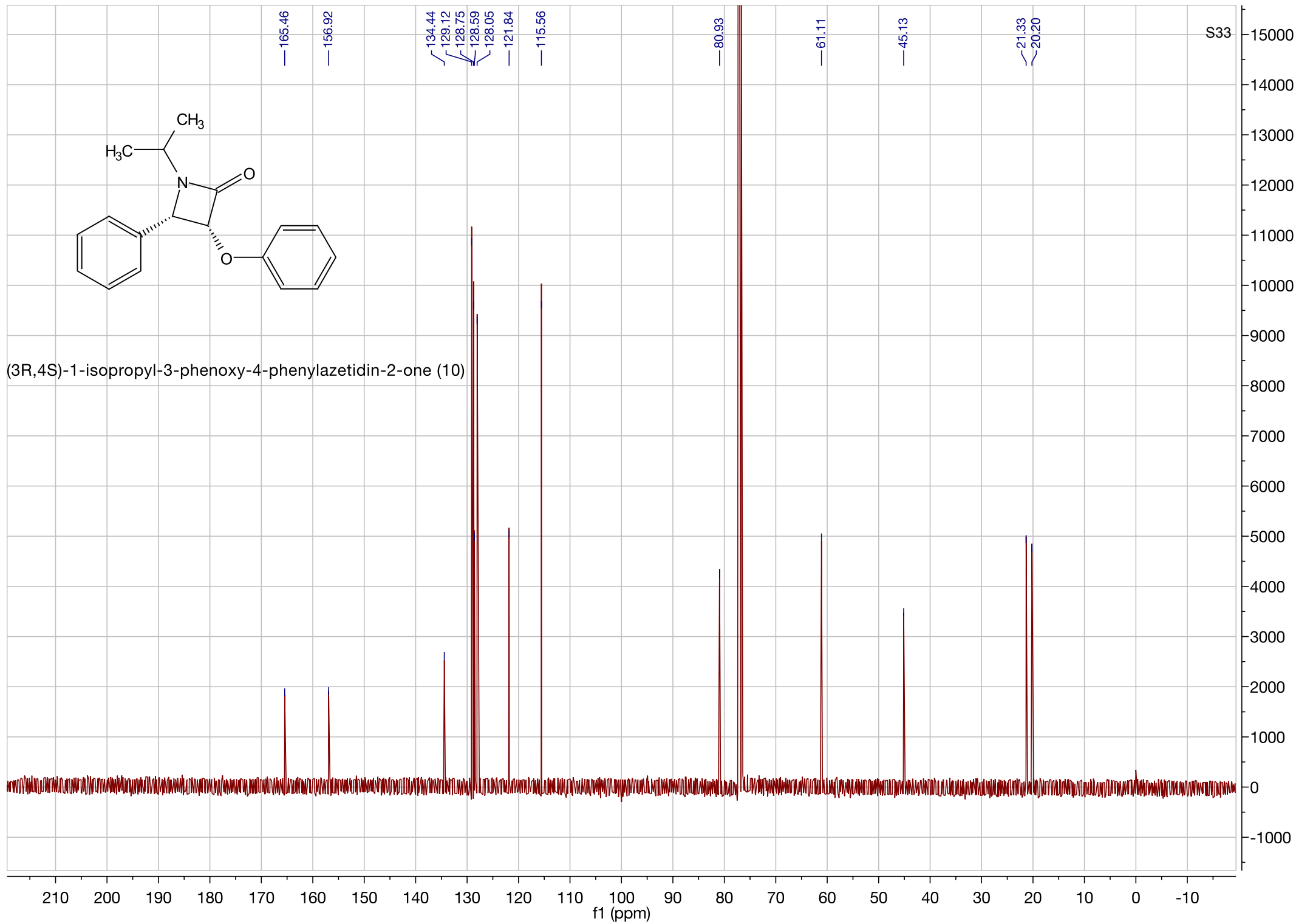


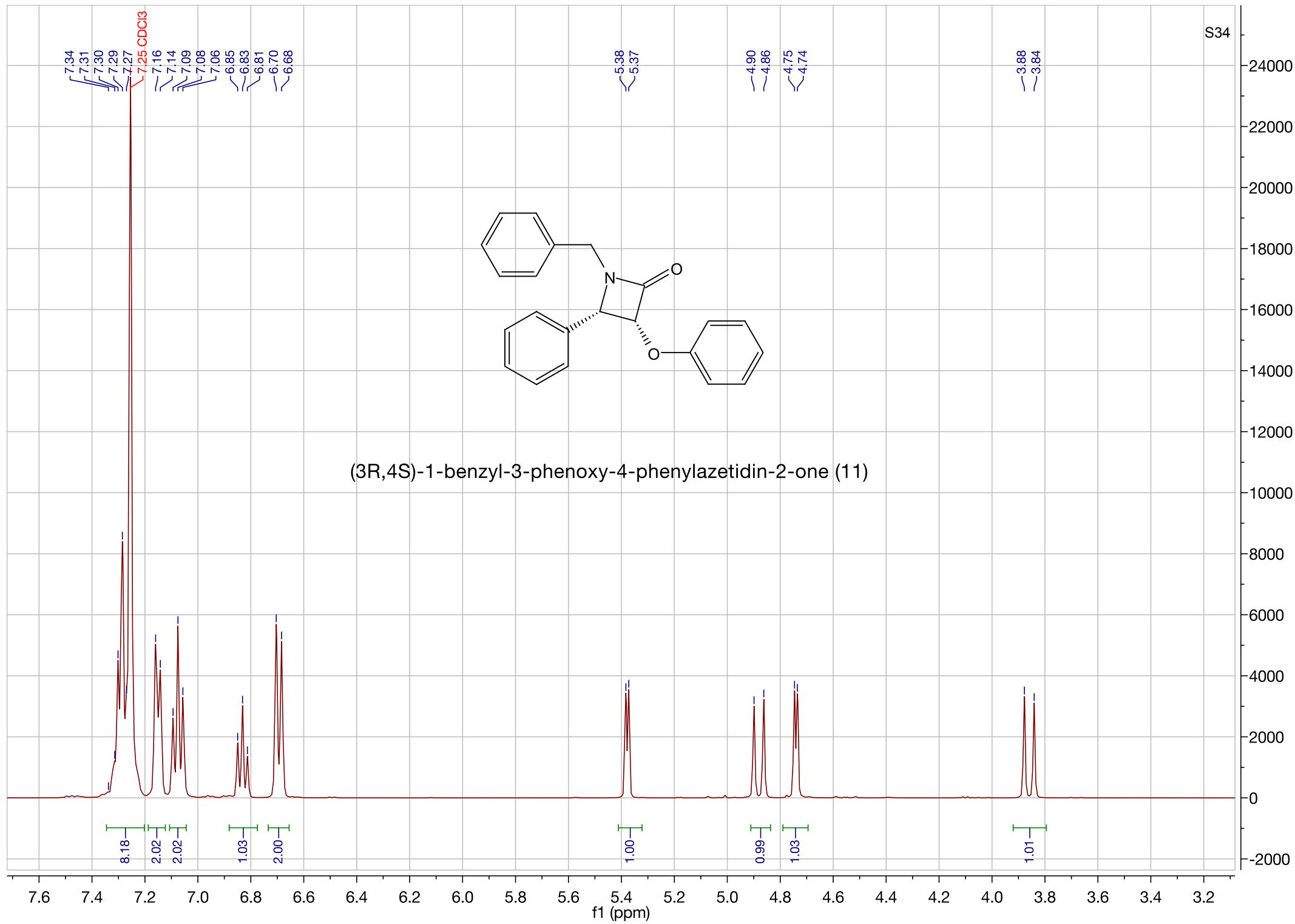


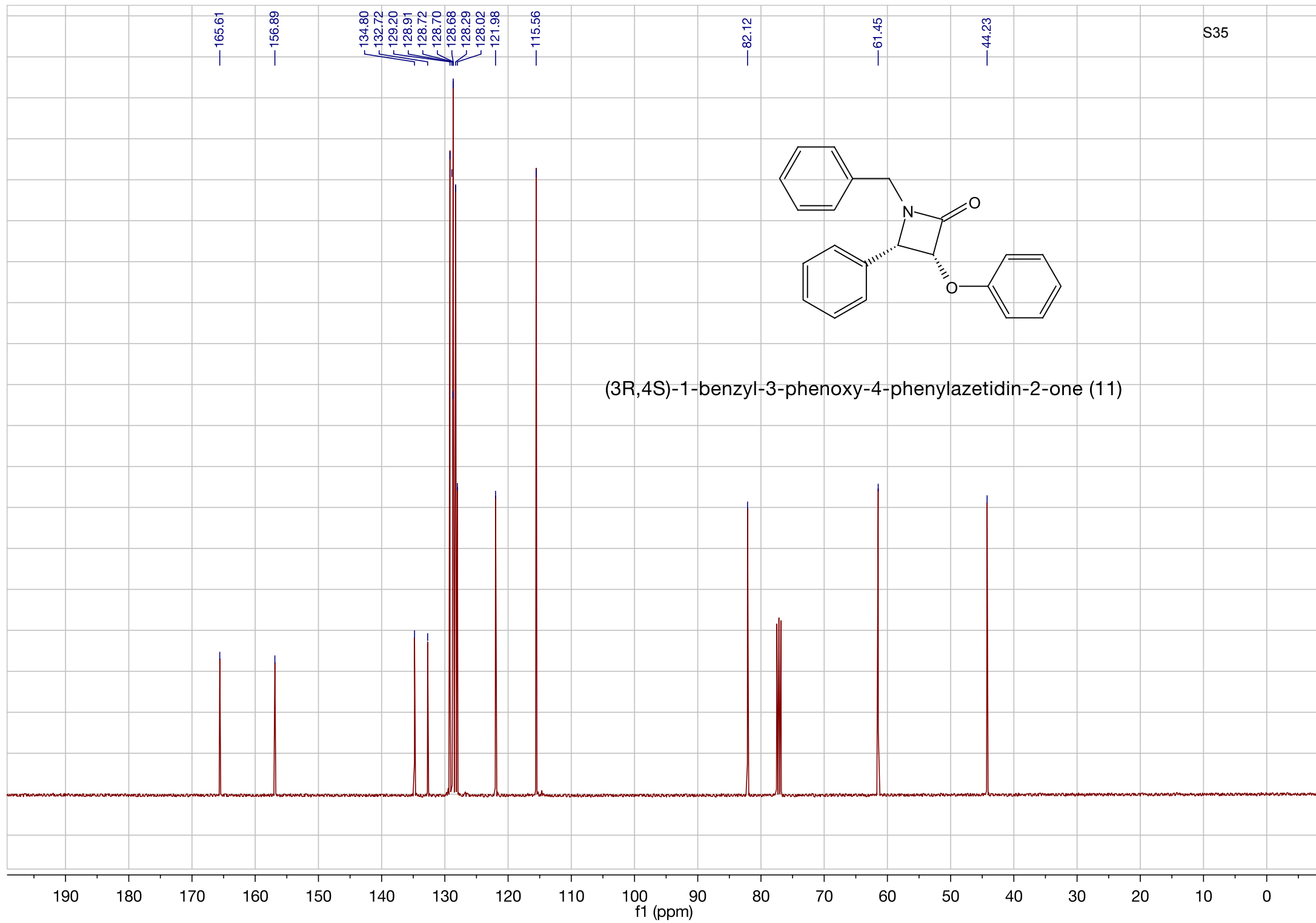
(3R,4S)-1-ethyl-3-phenoxy-4-phenylazetidin-2-one (9)



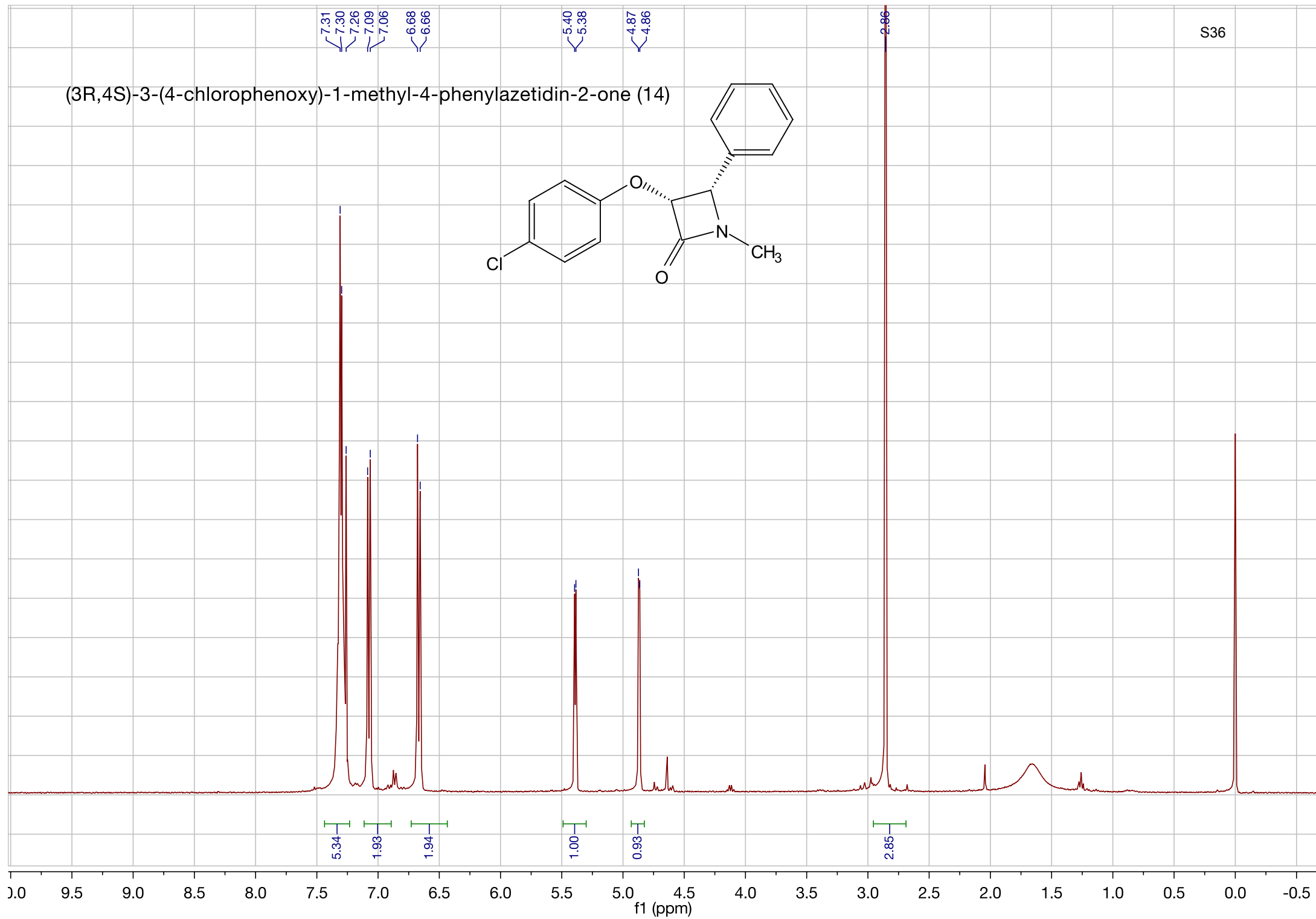
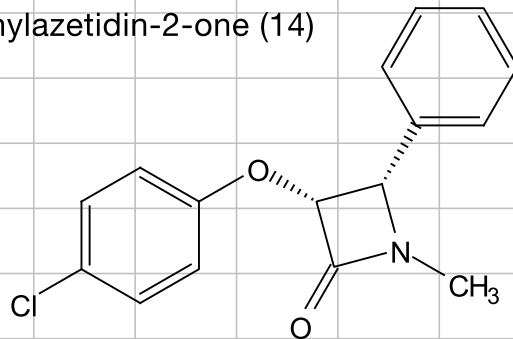


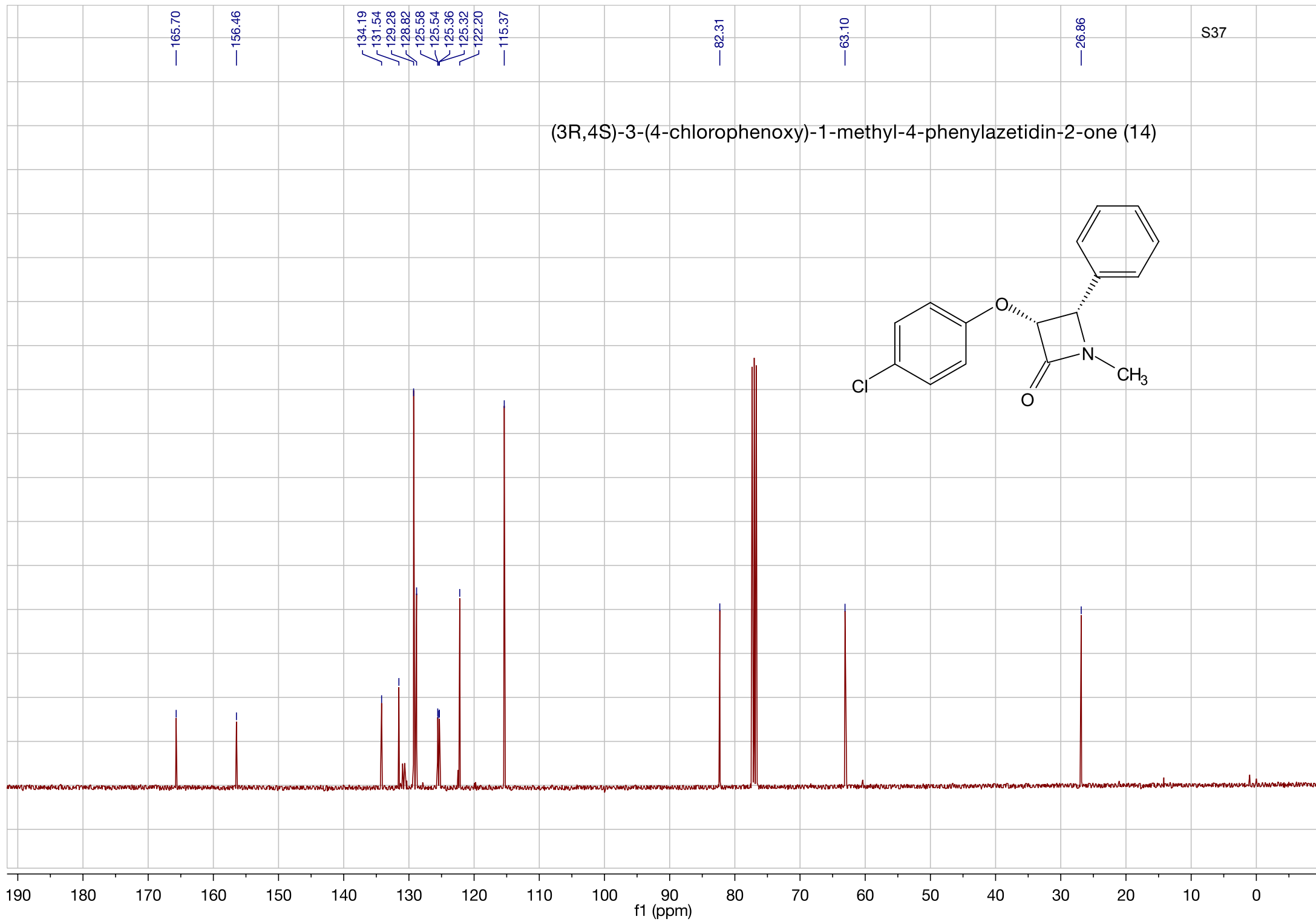


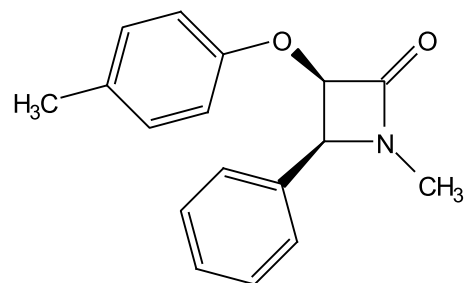




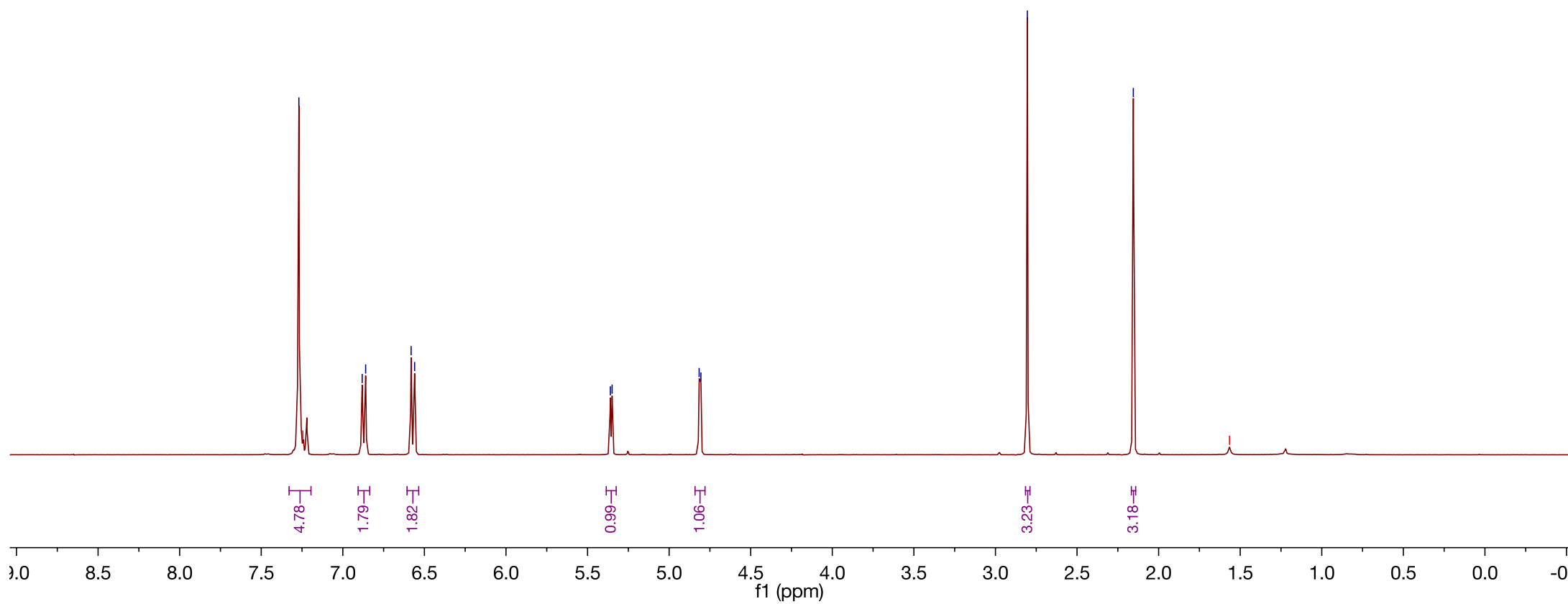
(3R,4S)-3-(4-chlorophenoxy)-1-methyl-4-phenylazetidin-2-one (14)

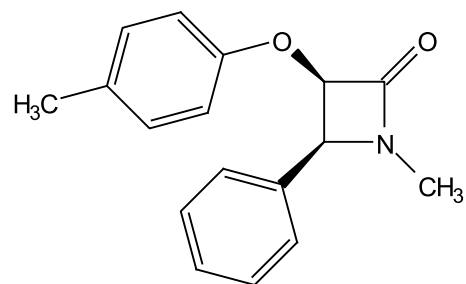




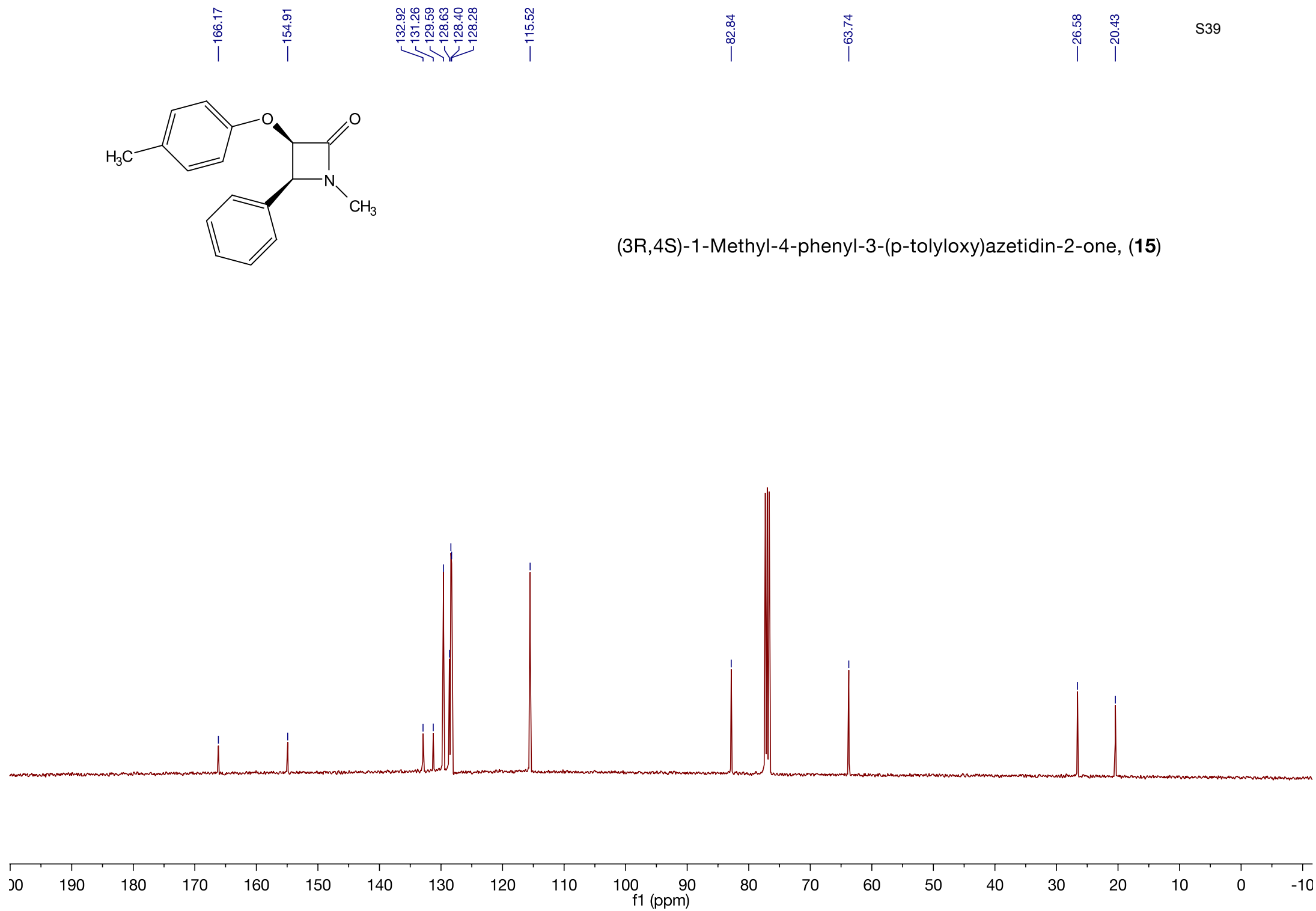


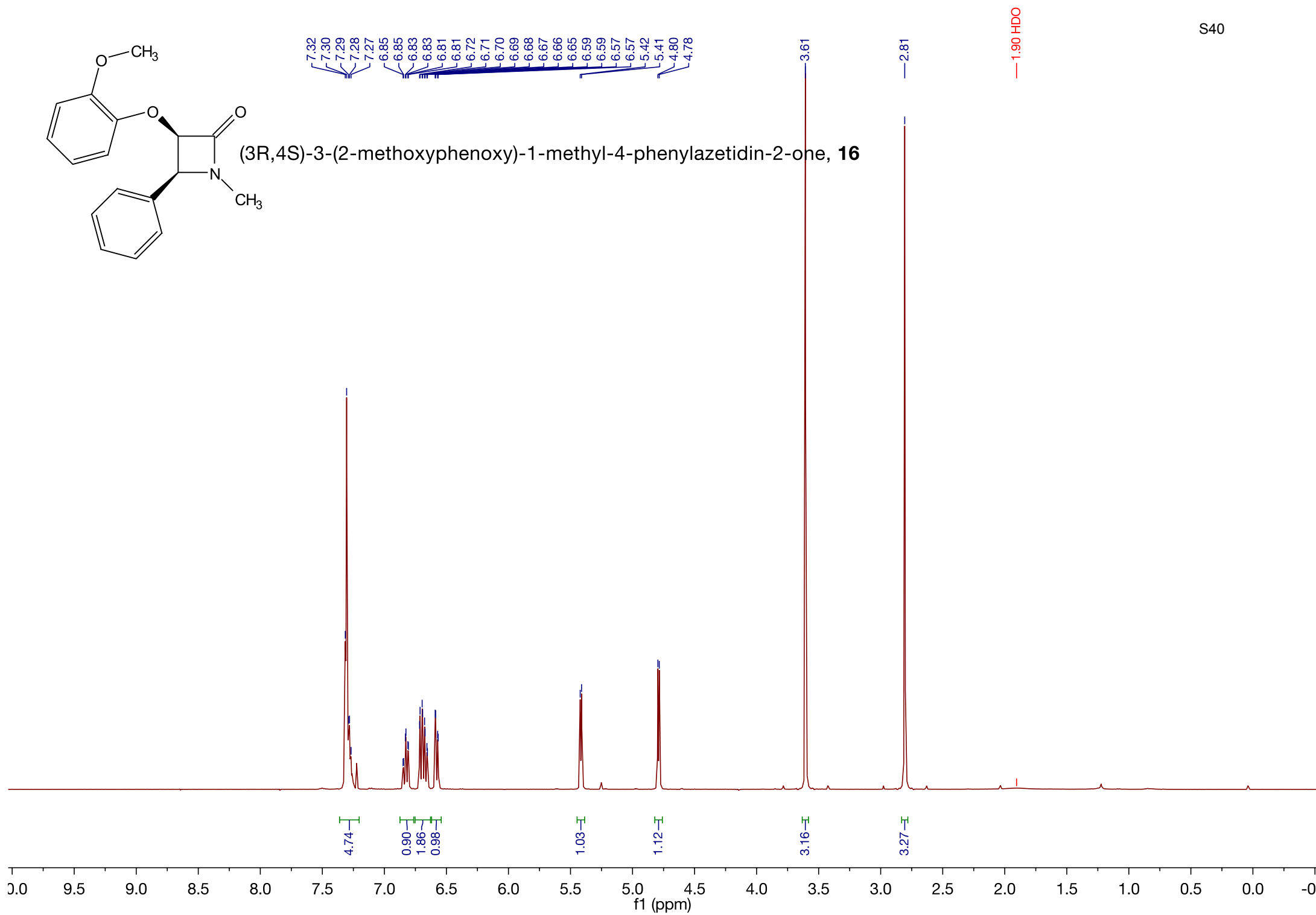
(3R,4S)-1-Methyl-4-phenyl-3-(p-tolyloxy)azetidin-2-one, (**15**)

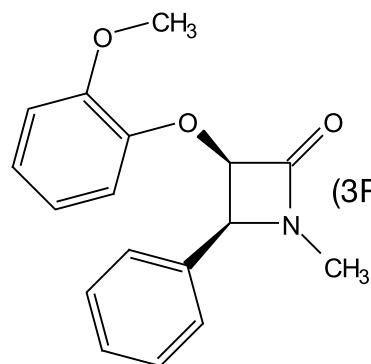




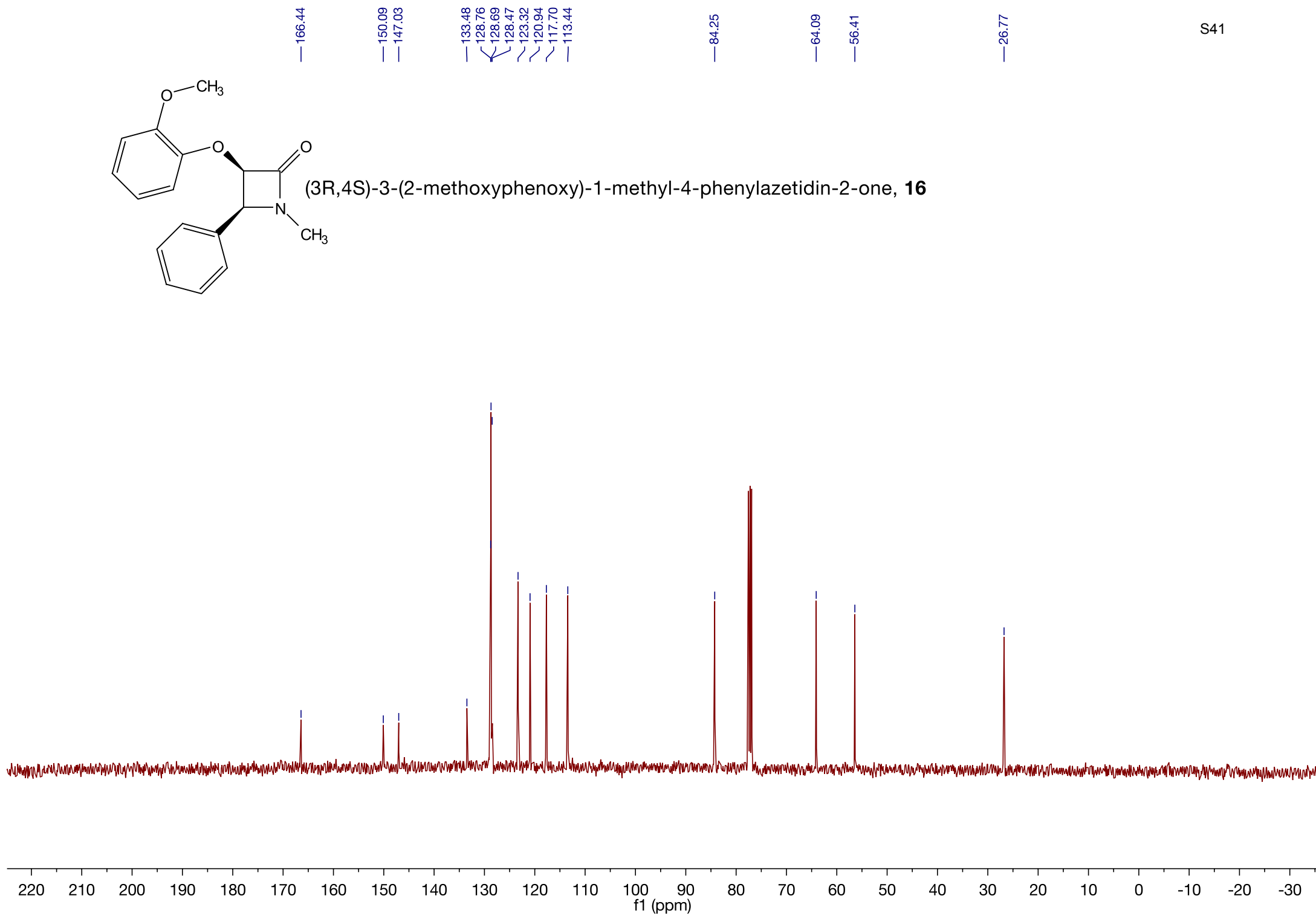
(3R,4S)-1-Methyl-4-phenyl-3-(p-tolyloxy)azetidin-2-one, (**15**)

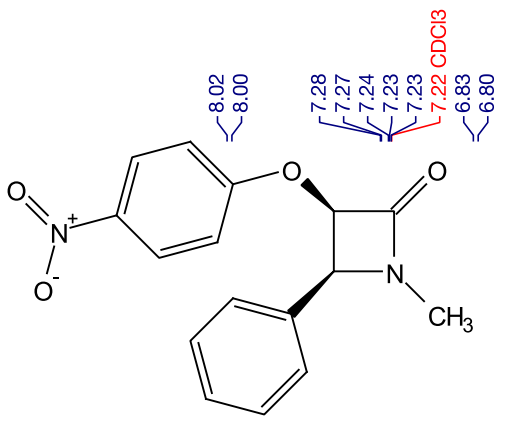




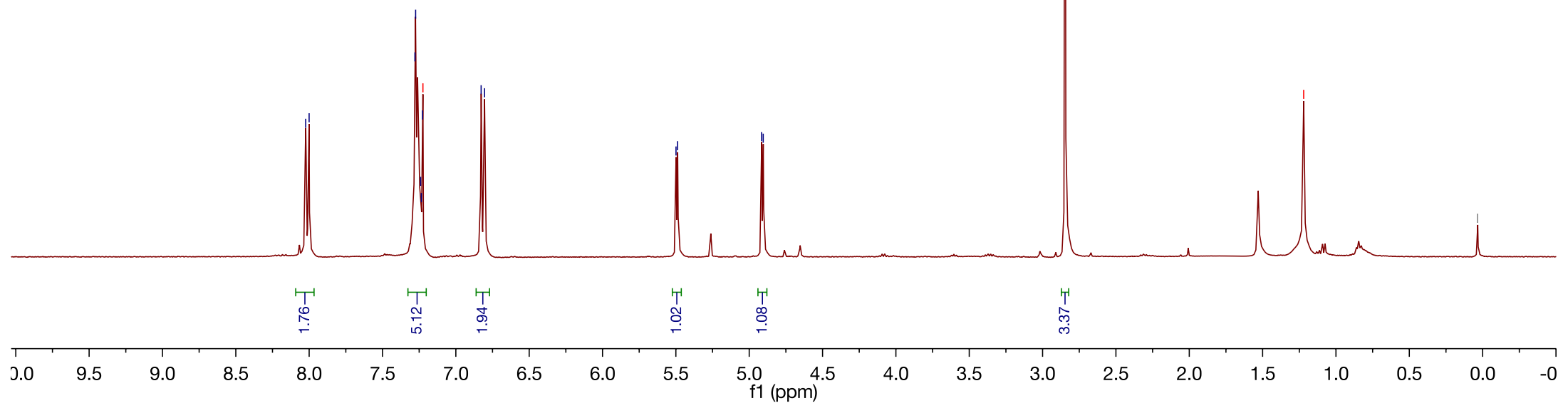


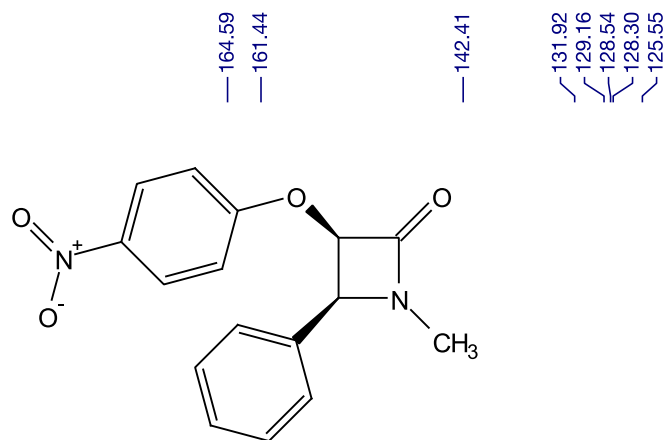
(3R,4S)-3-(2-methoxyphenoxy)-1-methyl-4-phenylazetidin-2-one, **16**



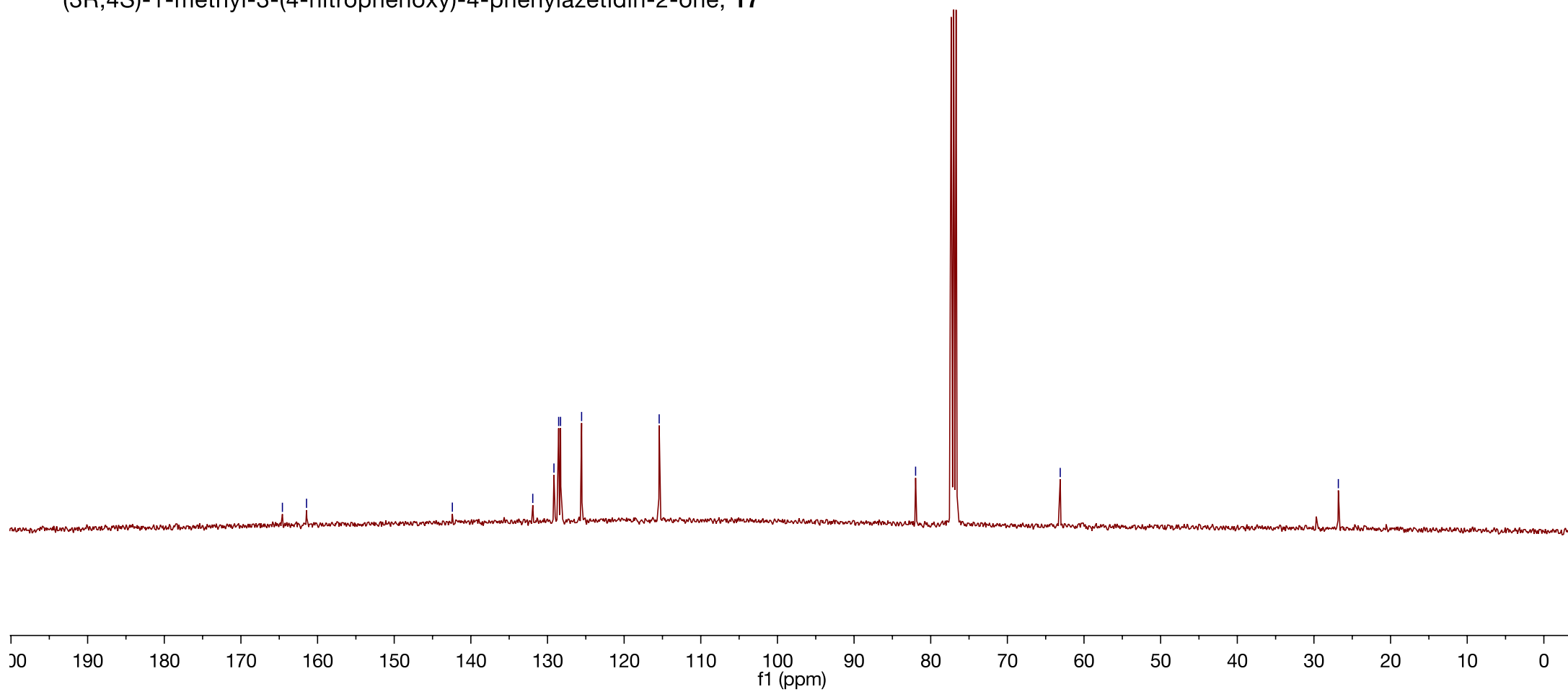


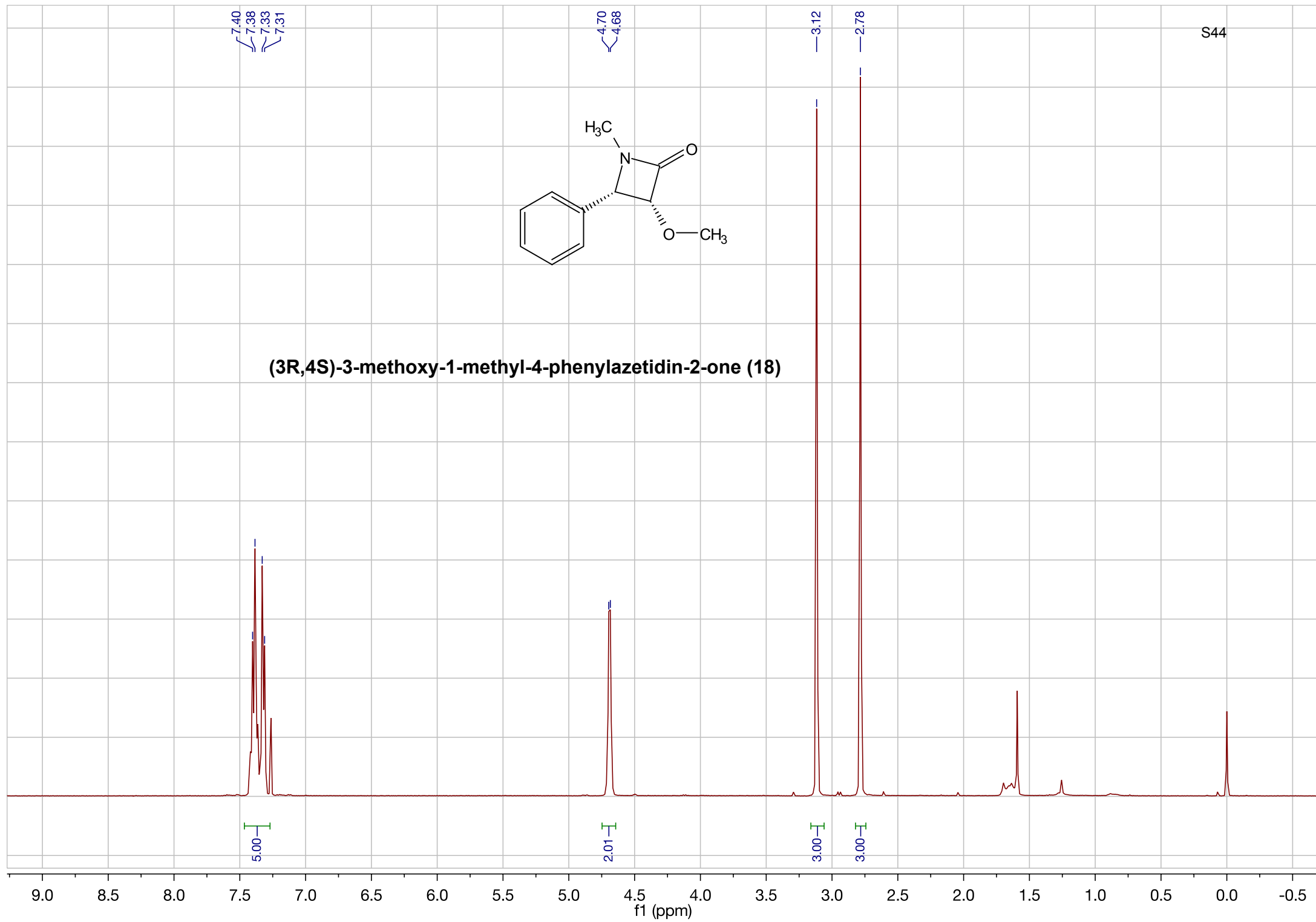
(3R,4S)-1-methyl-3-(4-nitrophenoxy)-4-phenylazetidin-2-one, **17**



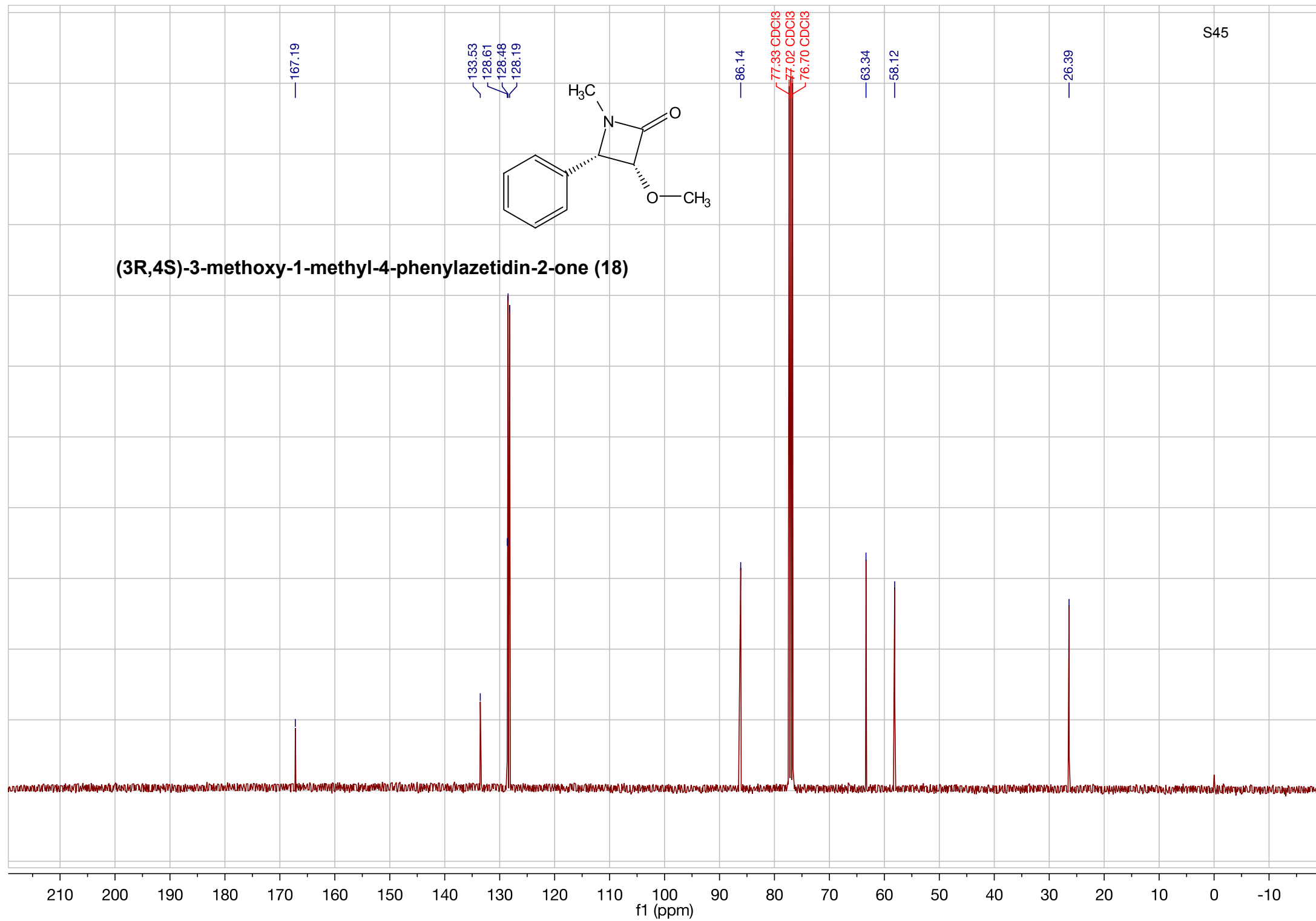
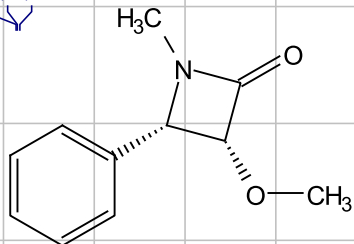


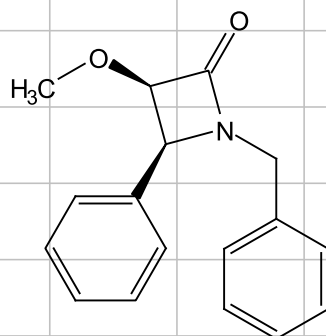
(3R,4S)-1-methyl-3-(4-nitrophenoxy)-4-phenylazetidin-2-one, **17**



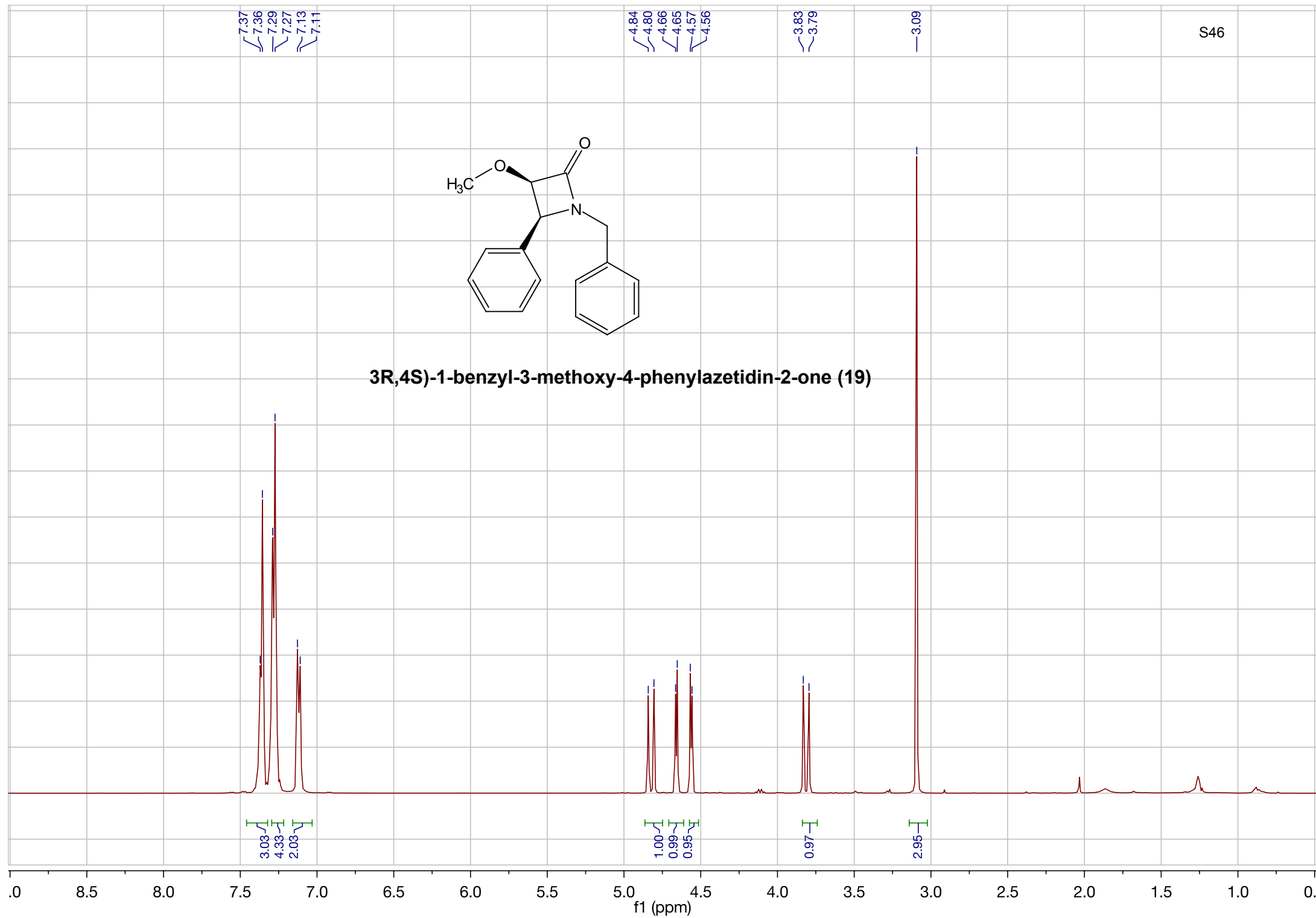


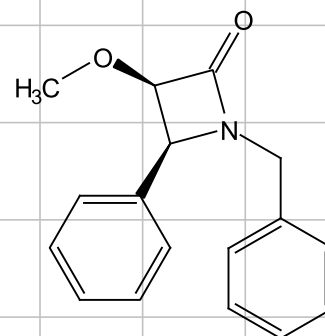
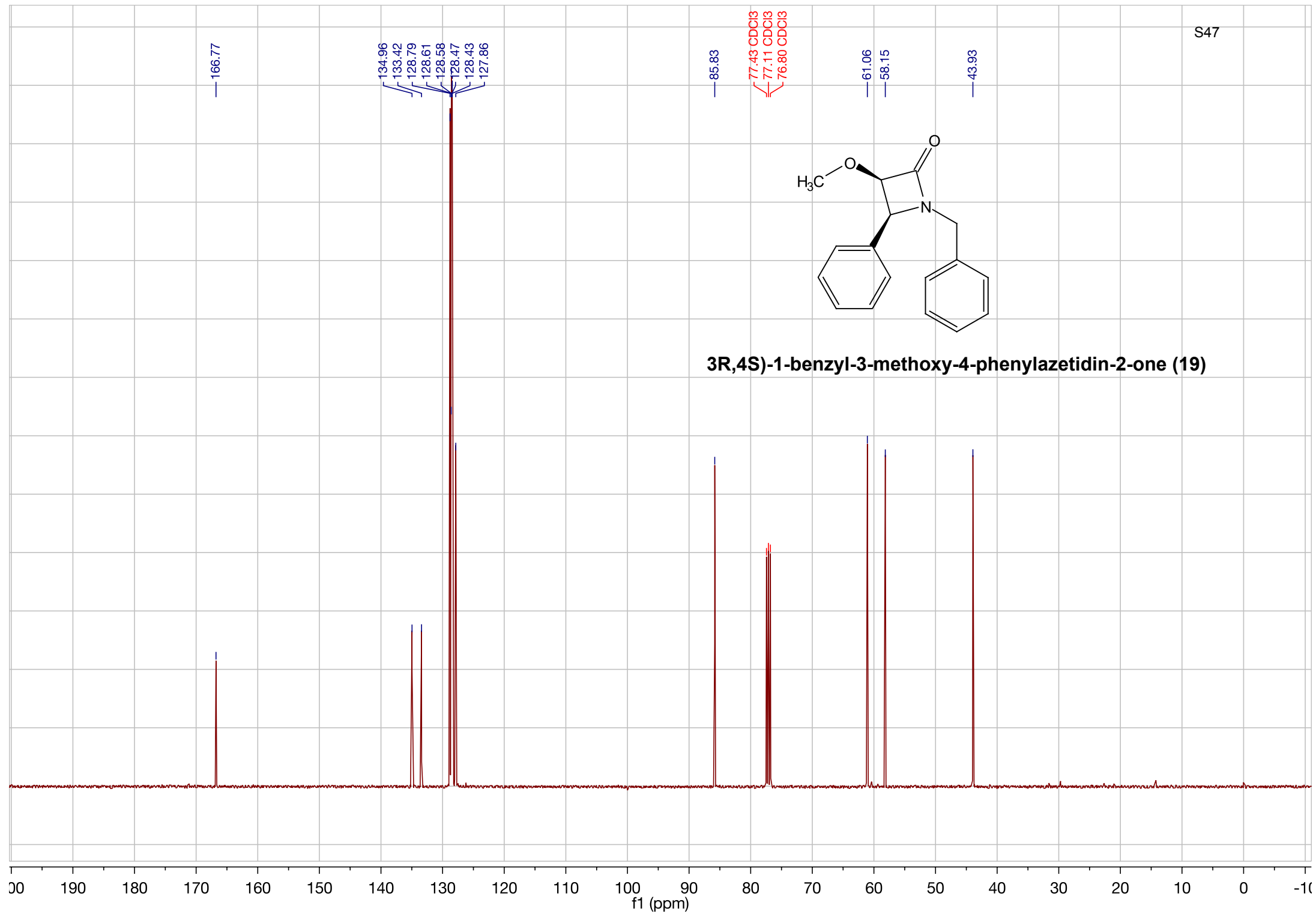
(3R,4S)-3-methoxy-1-methyl-4-phenylazetidin-2-one (18)

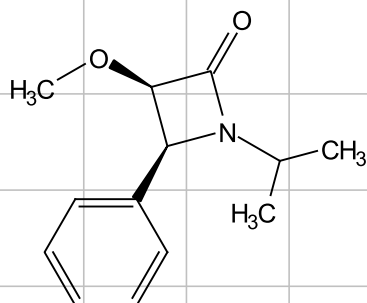




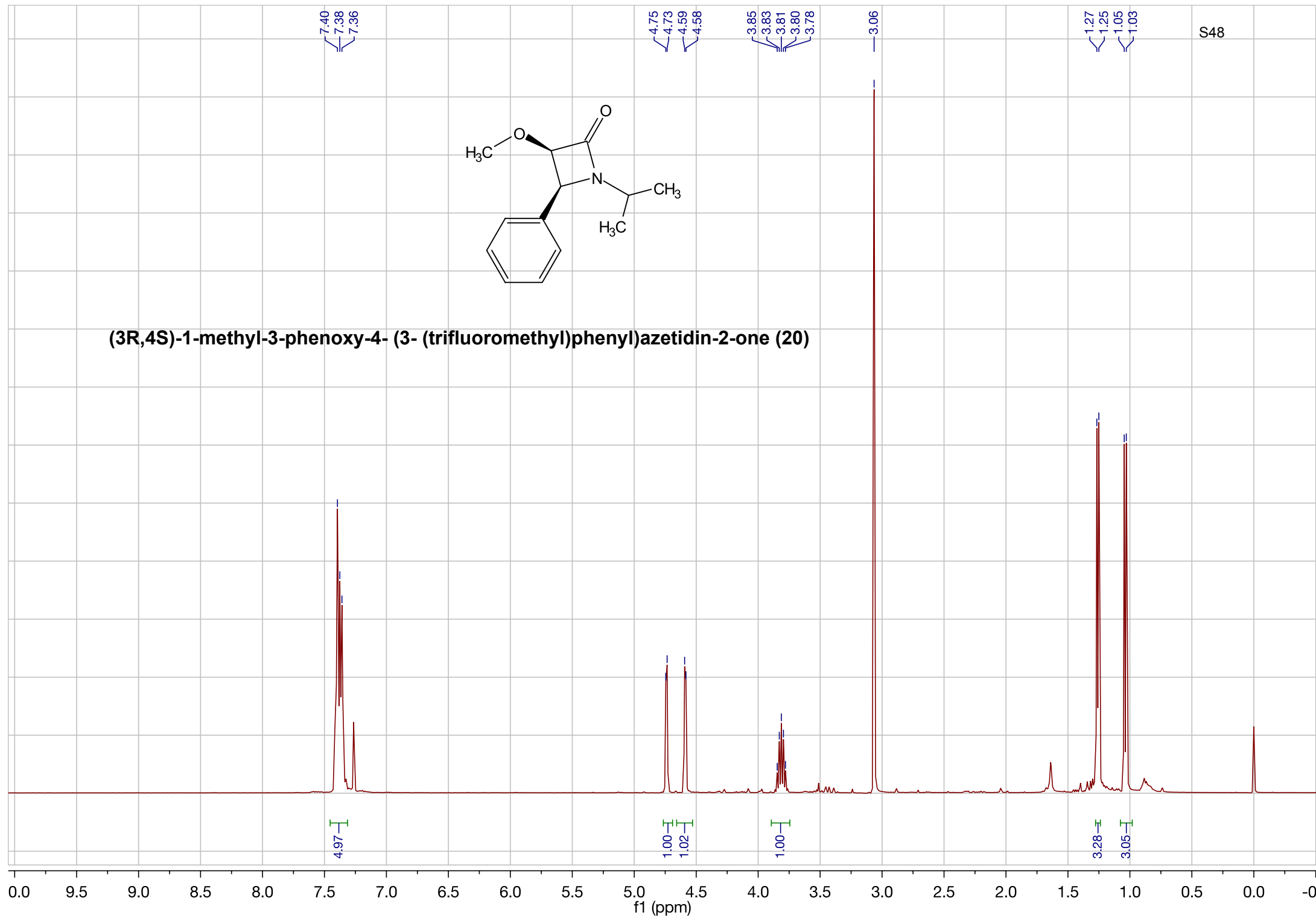
3R,4S)-1-benzyl-3-methoxy-4-phenylazetidin-2-one (19)



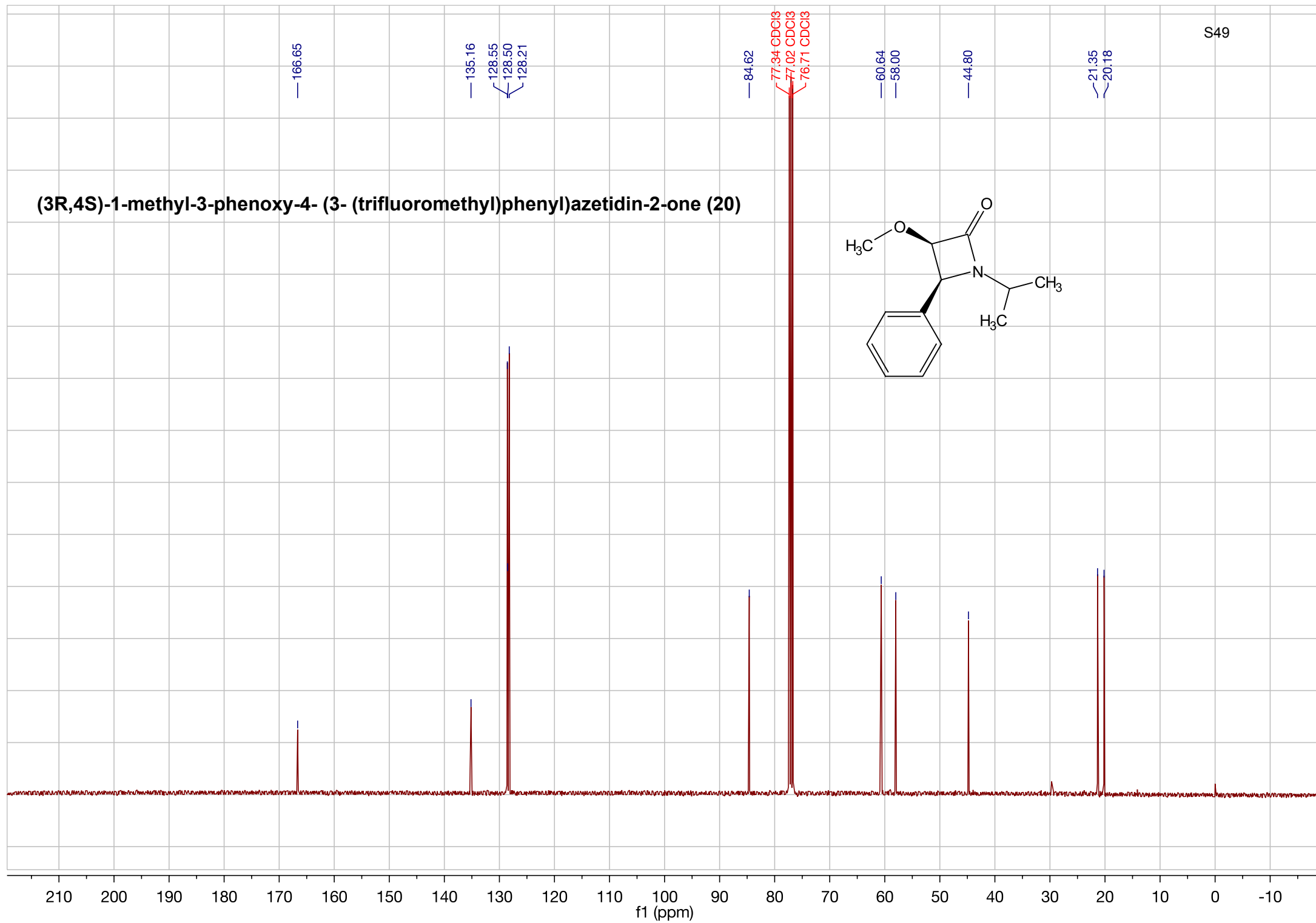
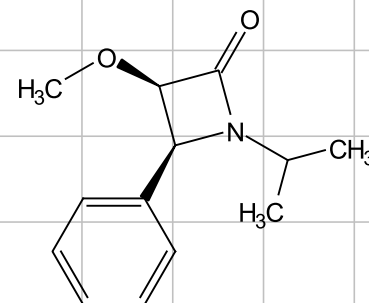
**3R,4S)-1-benzyl-3-methoxy-4-phenylazetidin-2-one (19)**

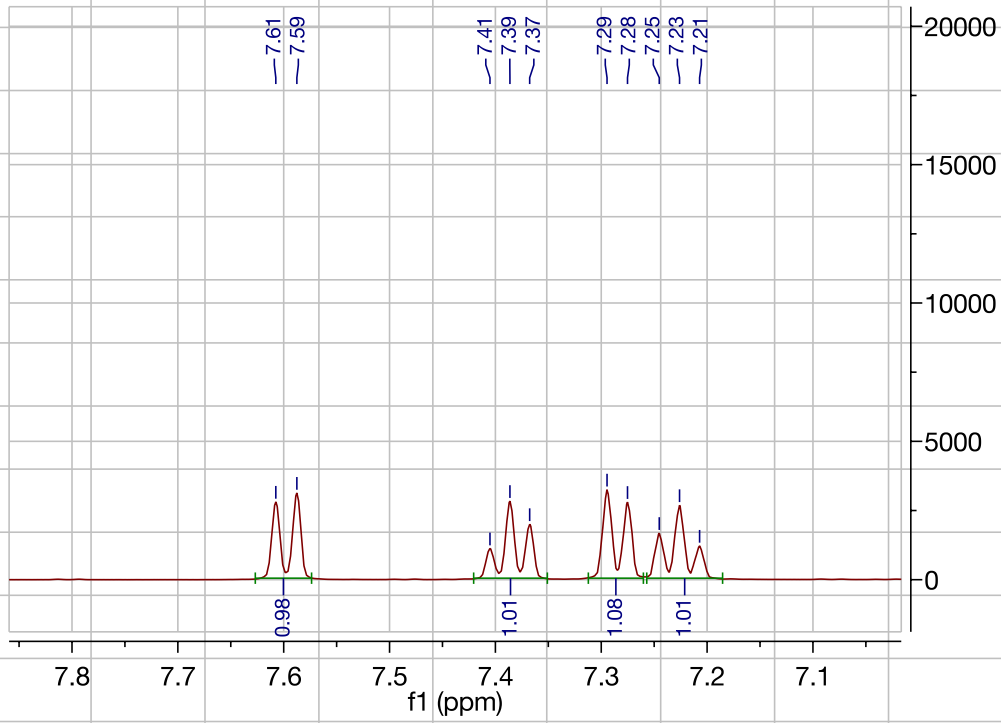
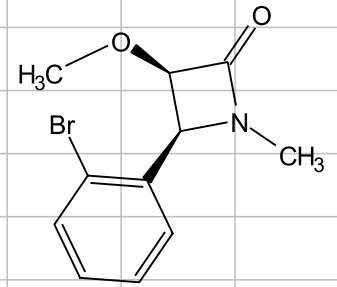


(3R,4S)-1-methyl-3-phenoxy-4-(3-(trifluoromethyl)phenyl)azetidin-2-one (20)

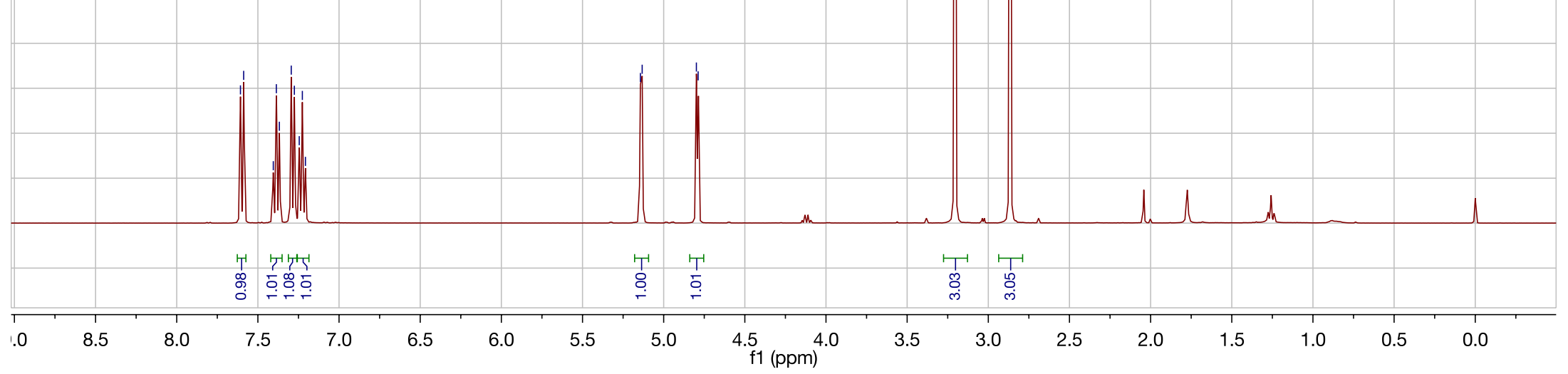


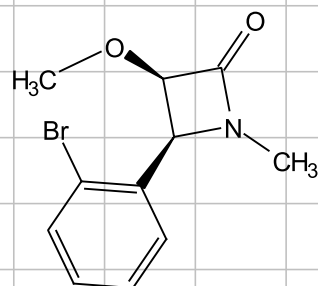
(3R,4S)-1-methyl-3-phenoxy-4- (3- (trifluoromethyl)phenyl)azetidin-2-one (20)



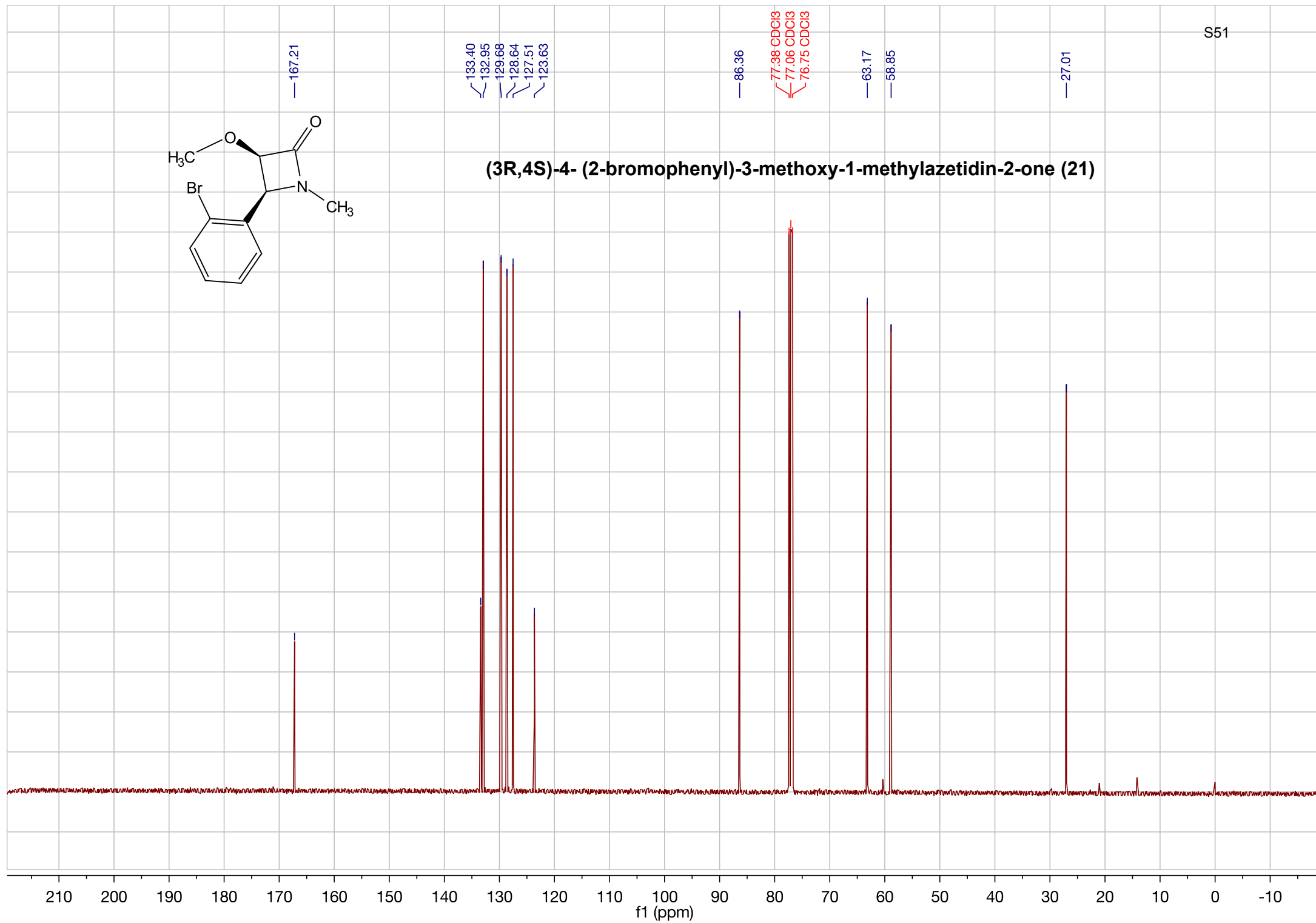


(3R,4S)-4-(2-bromophenyl)-3-methoxy-1-methylazetidin-2-one (21)

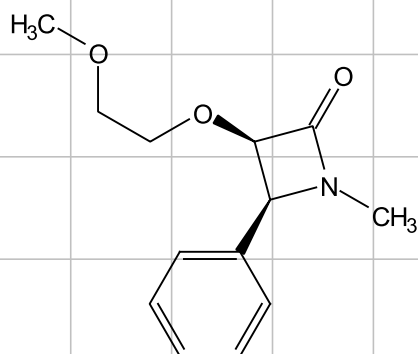




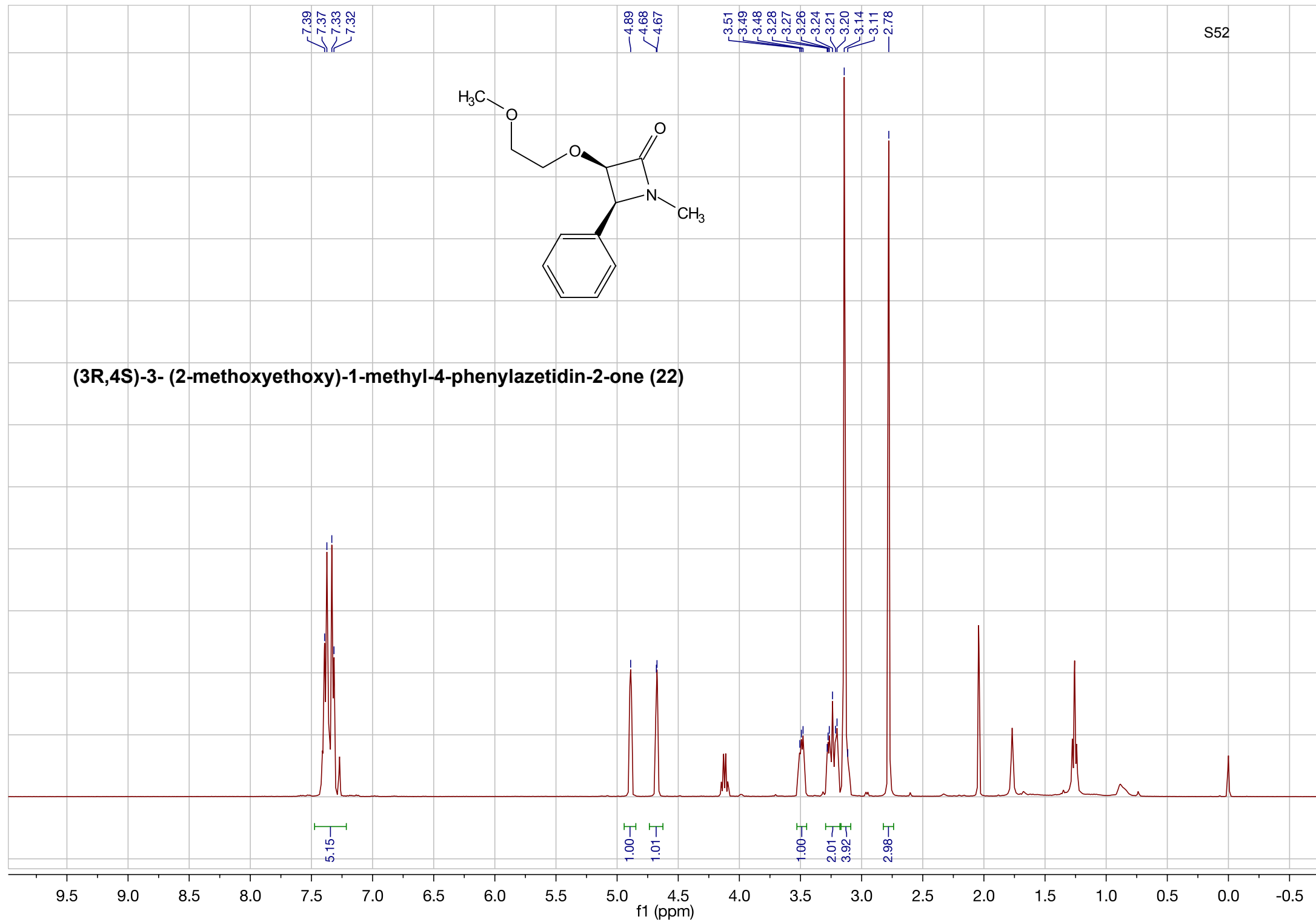
(3R,4S)-4-(2-bromophenyl)-3-methoxy-1-methylazetidin-2-one (21)

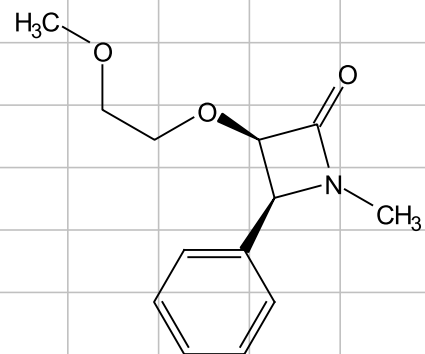
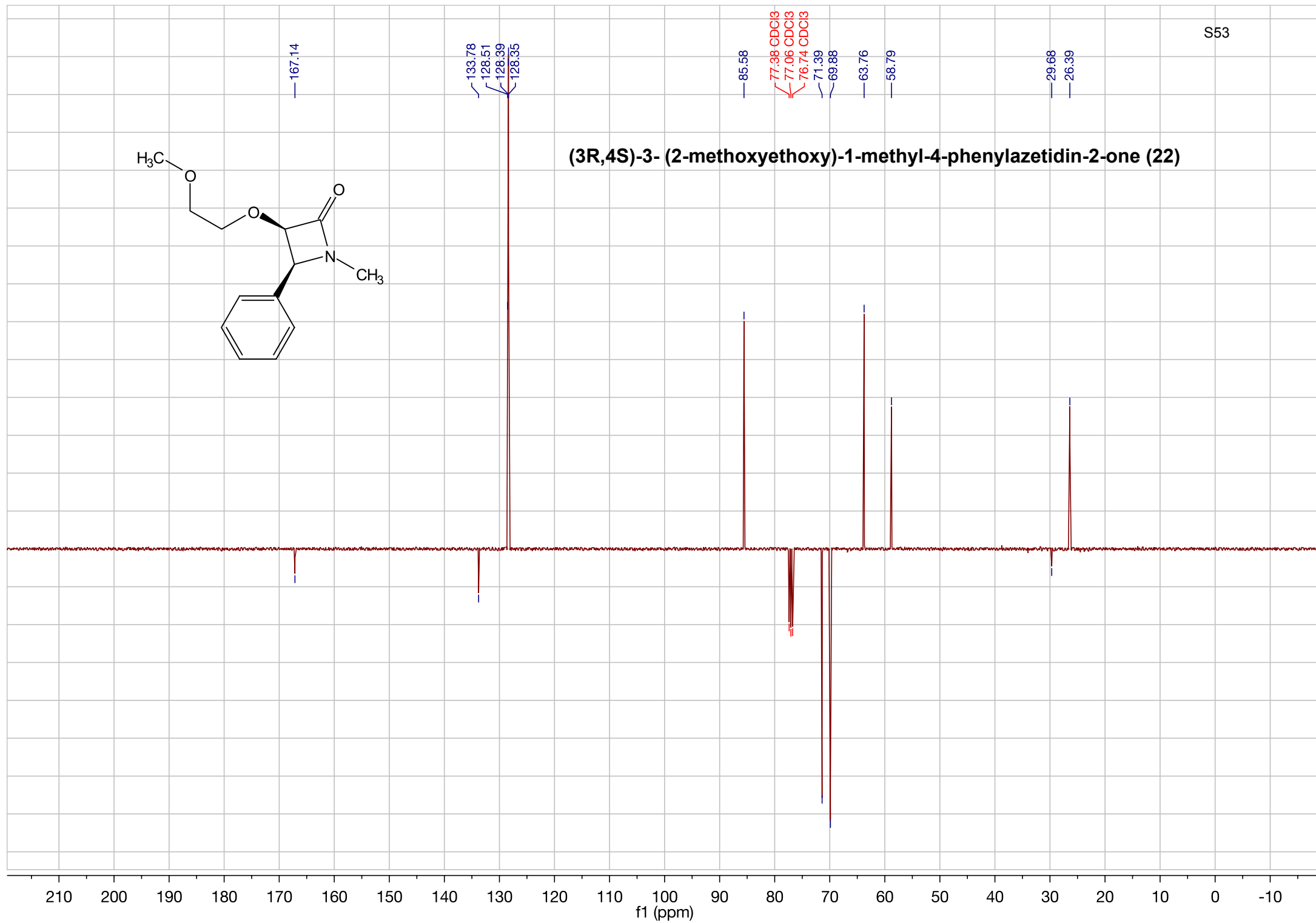


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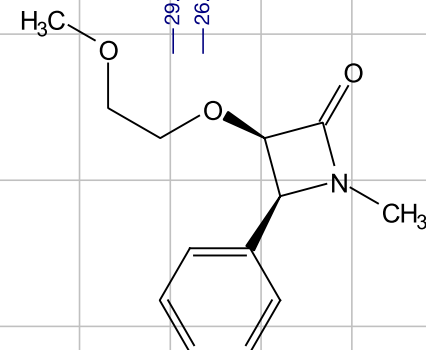


(3R,4S)-3-(2-methoxyethoxy)-1-methyl-4-phenylazetidin-2-one (22)

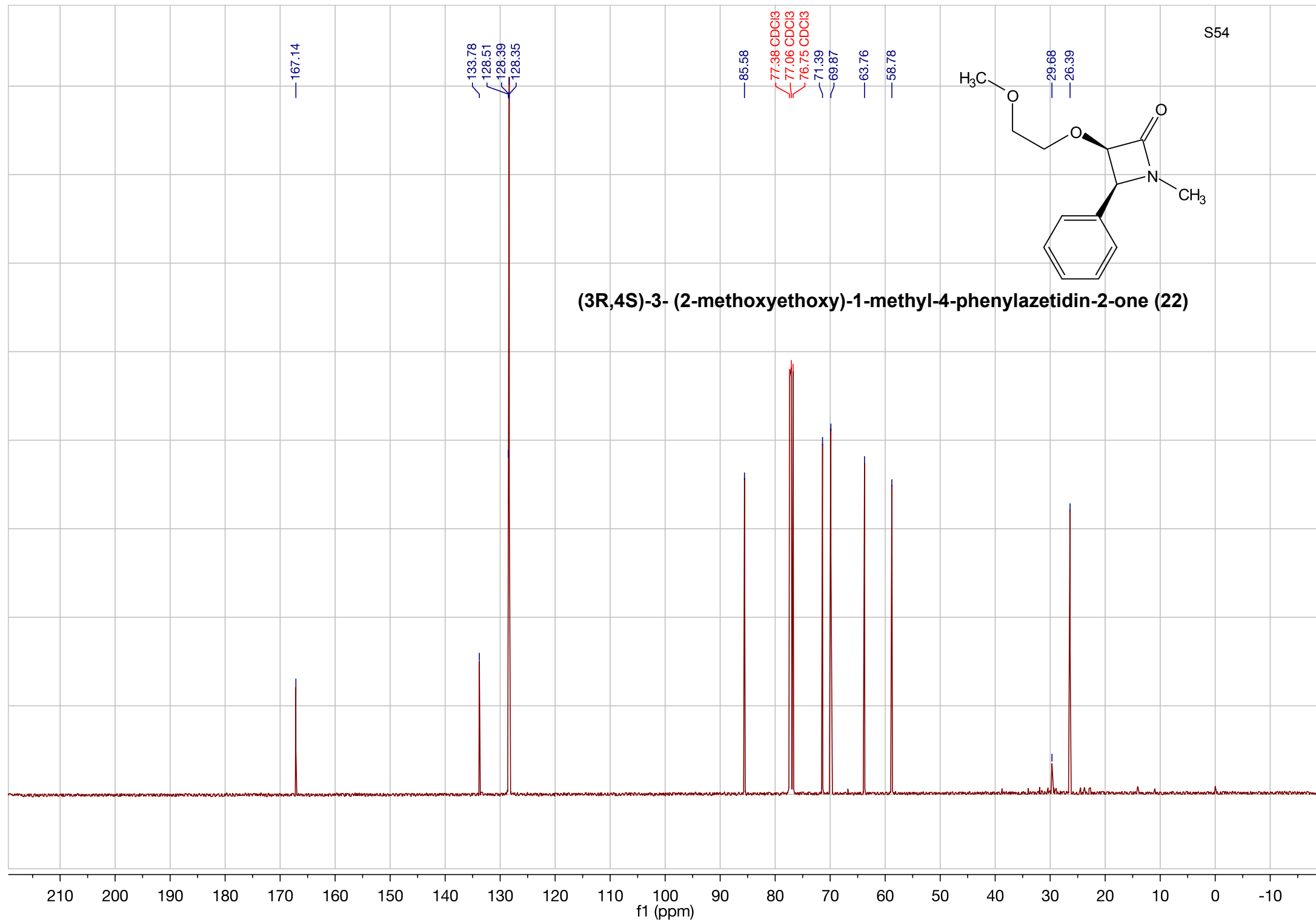


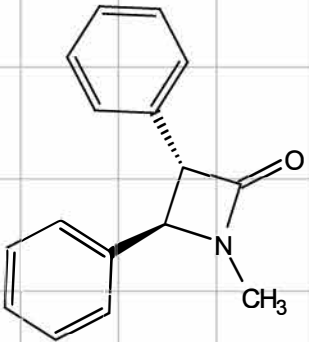
**(3R,4S)-3-(2-methoxyethoxy)-1-methyl-4-phenylazetidin-2-one (22)**

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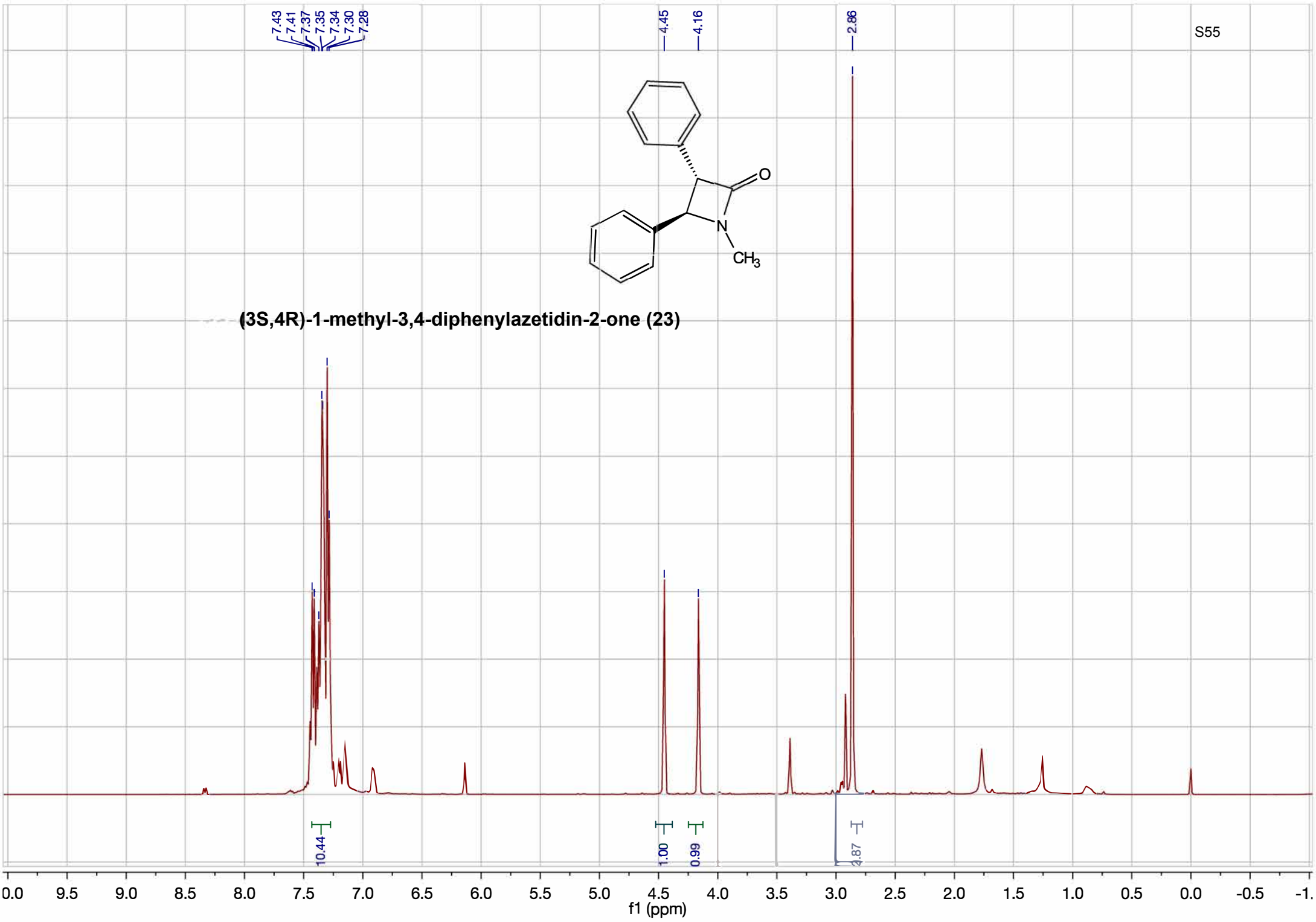


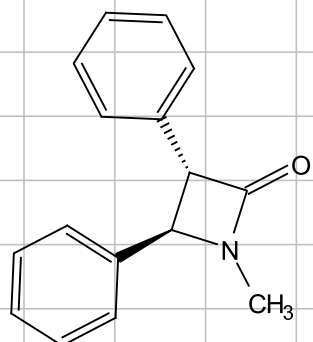
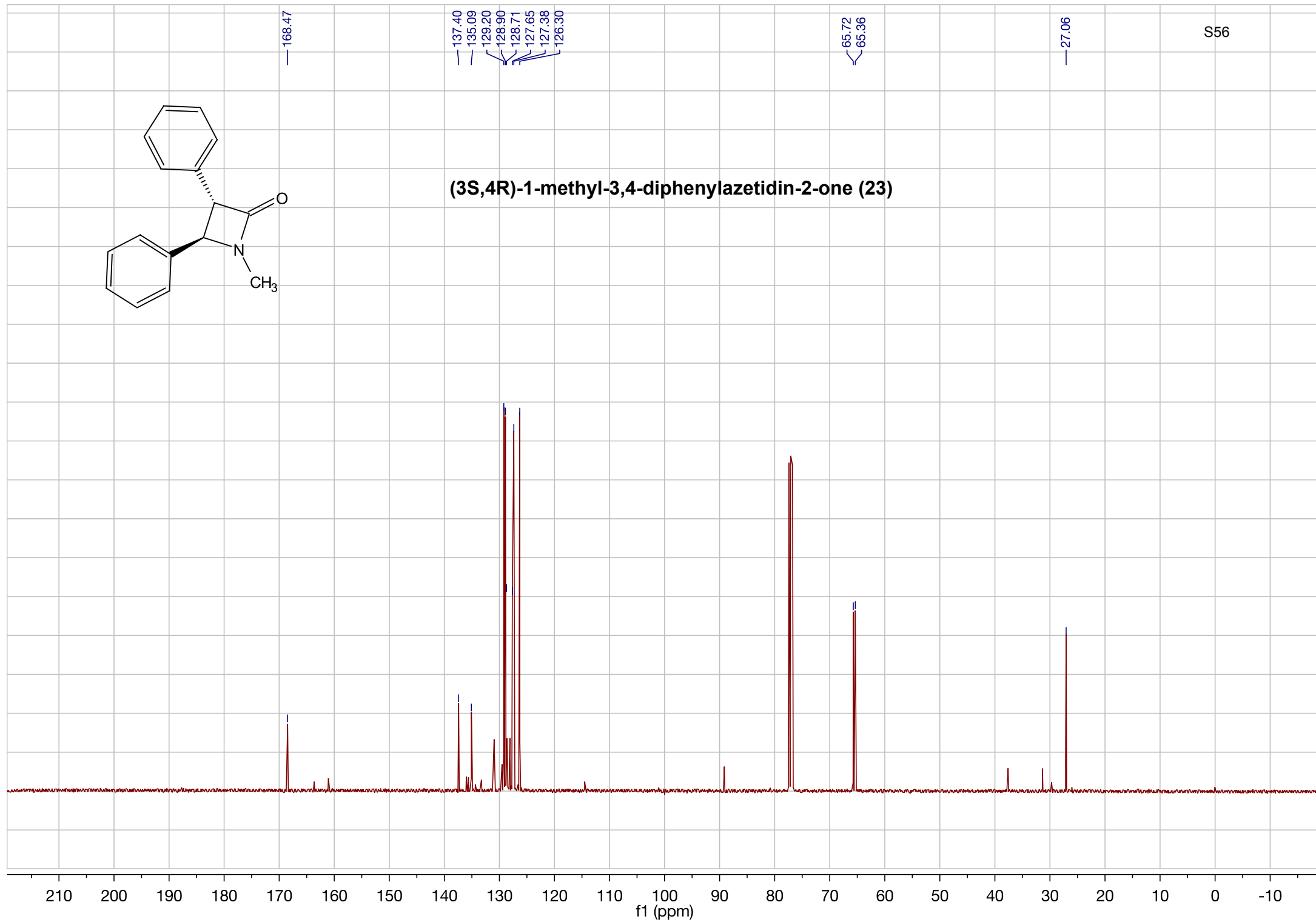
(3R,4S)-3-(2-methoxyethoxy)-1-methyl-4-phenylazetidin-2-one (22)

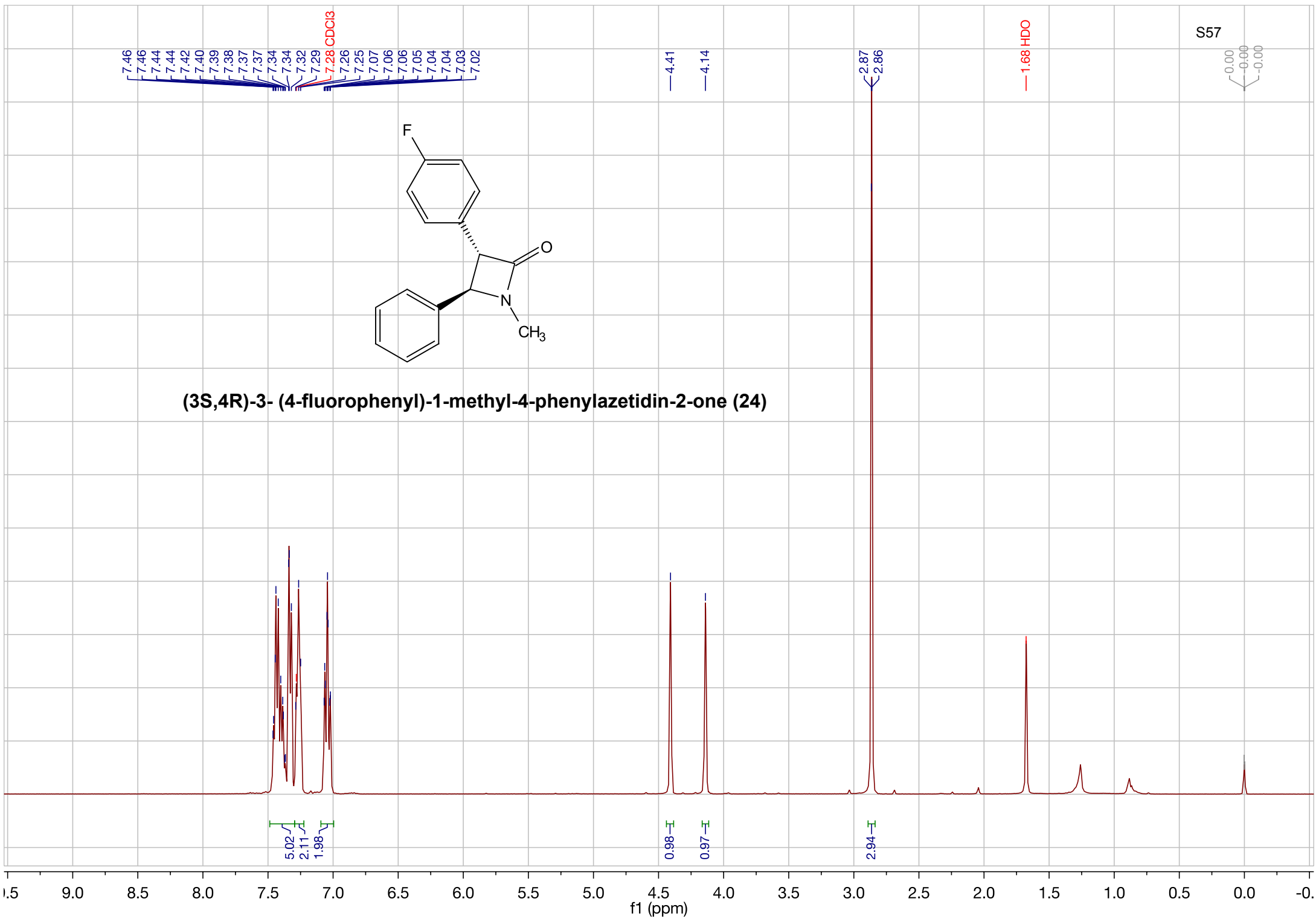


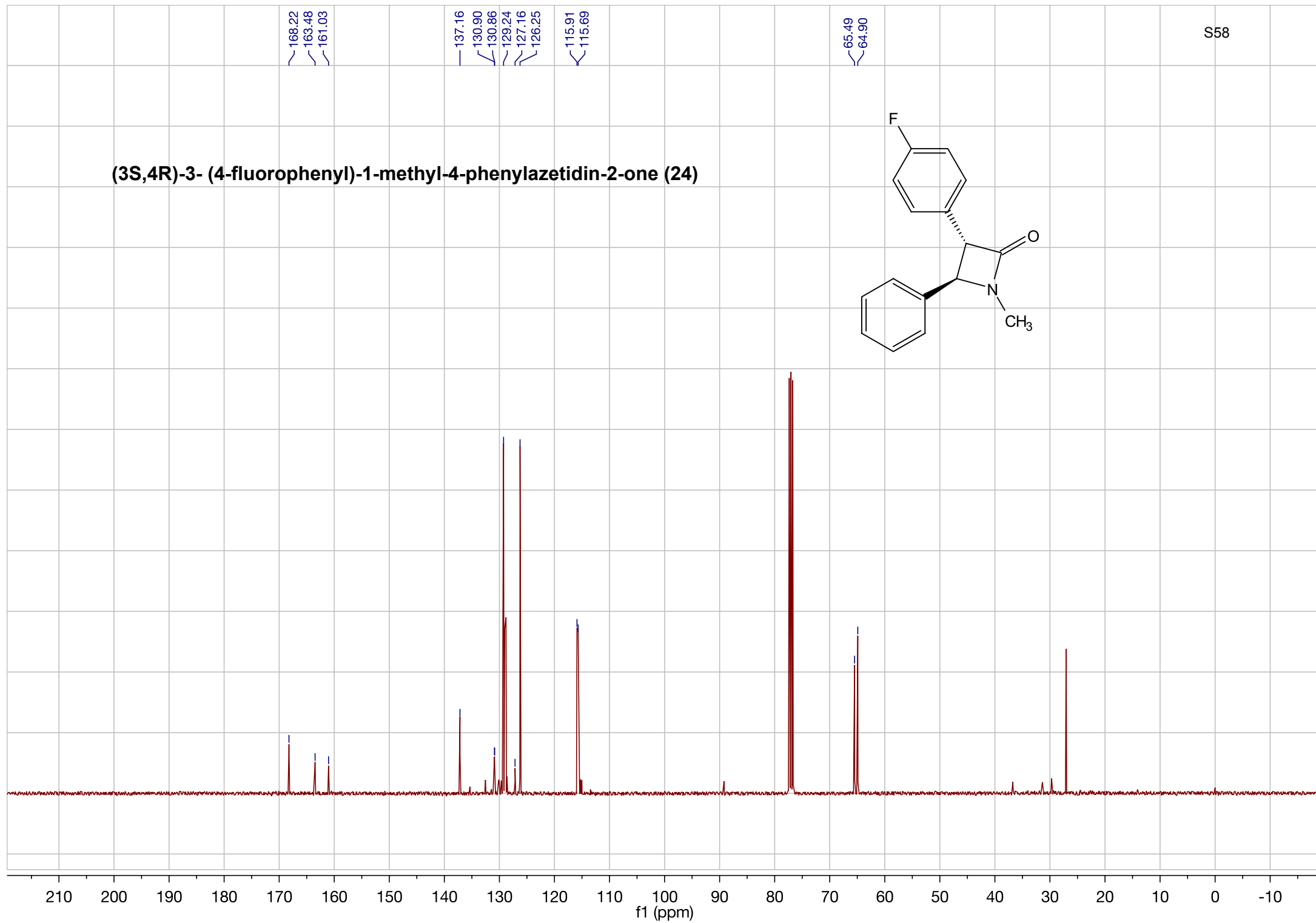
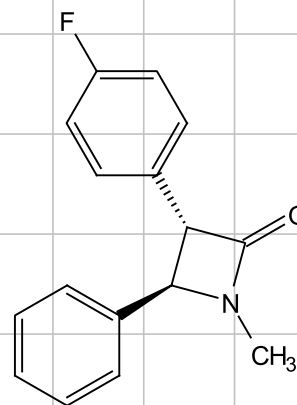


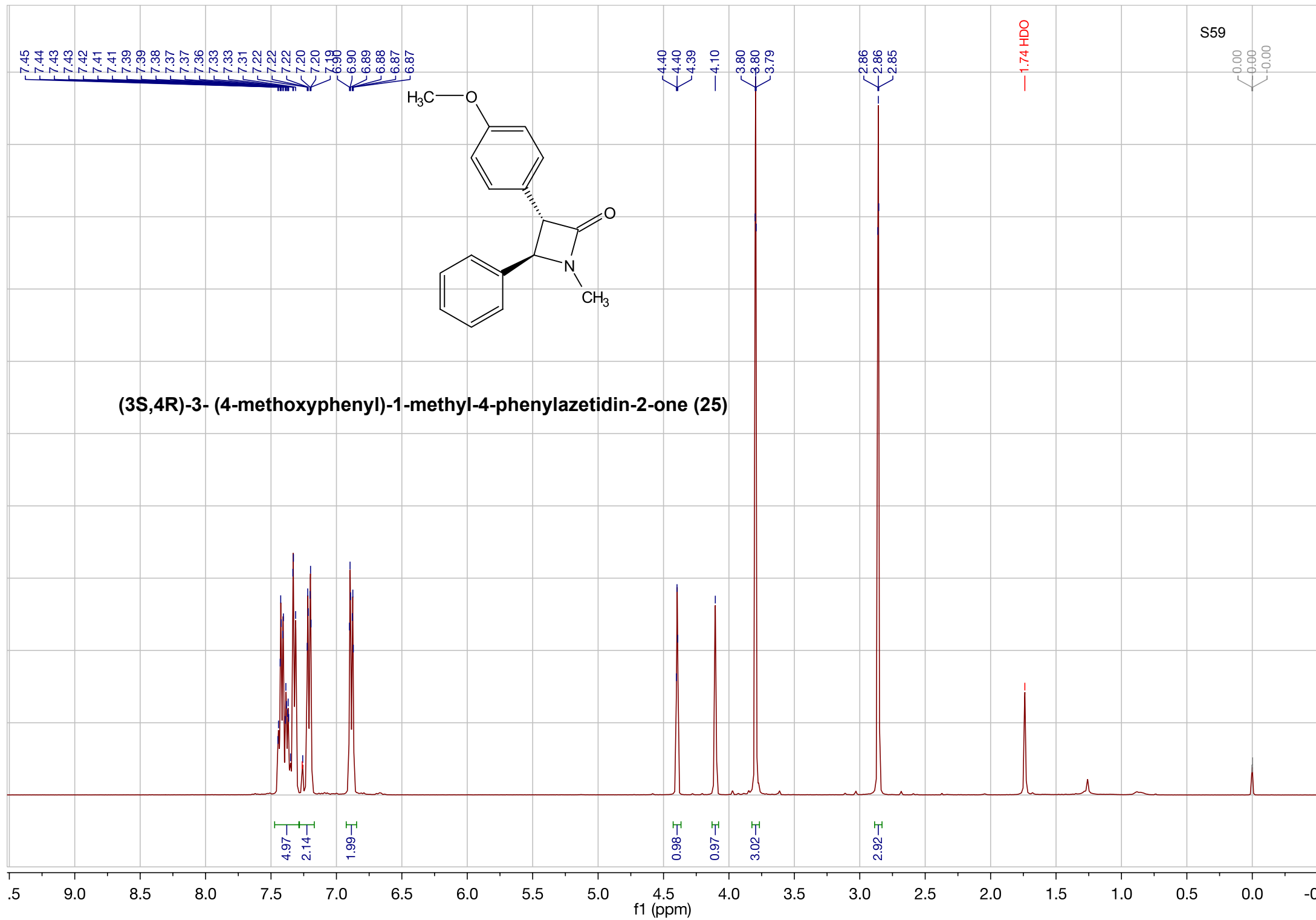
(3S,4R)-1-methyl-3,4-diphenylazetidin-2-one (23)

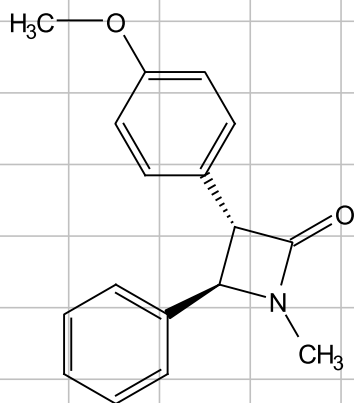


**(3S,4R)-1-methyl-3,4-diphenylazetidin-2-one (23)**

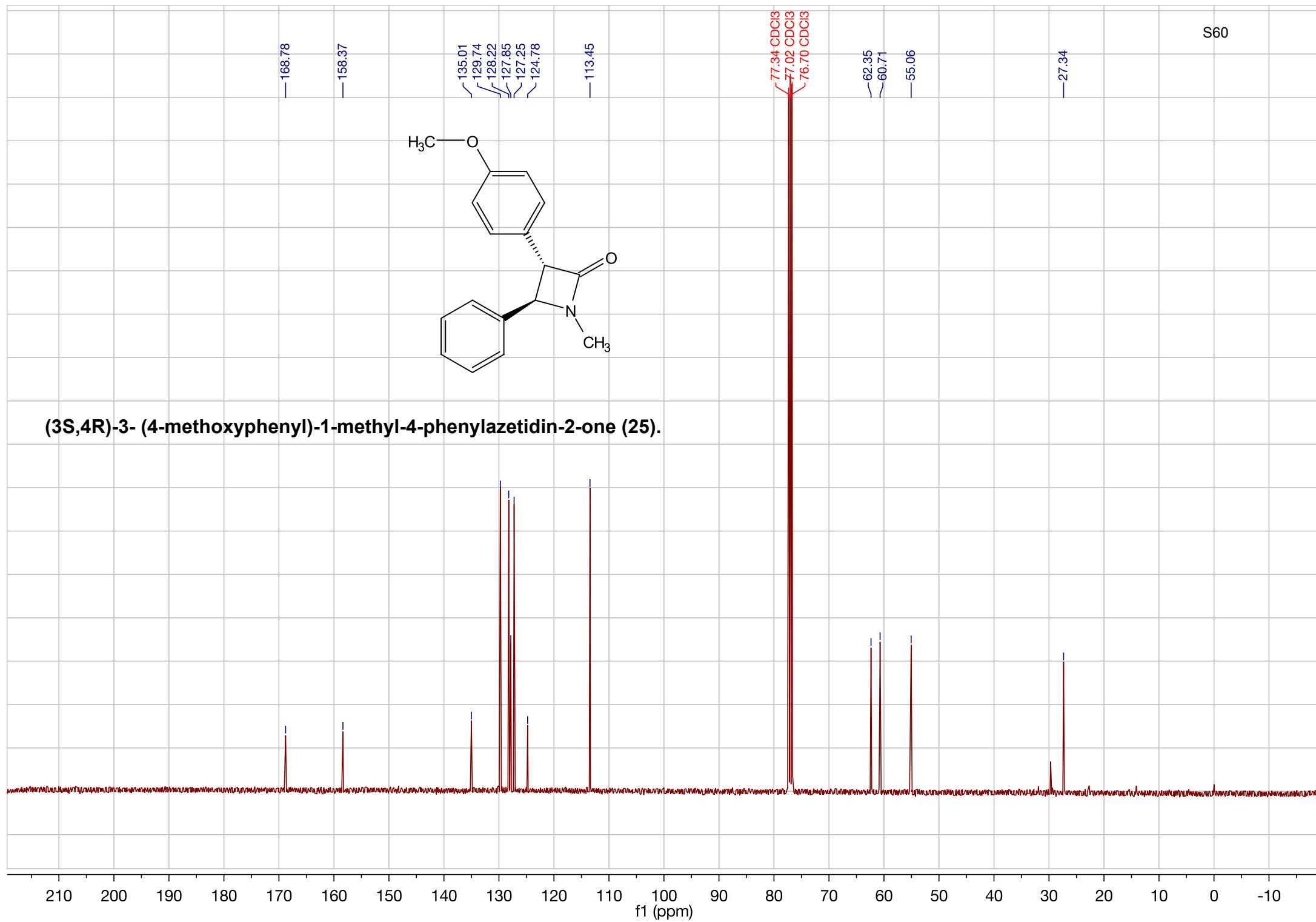


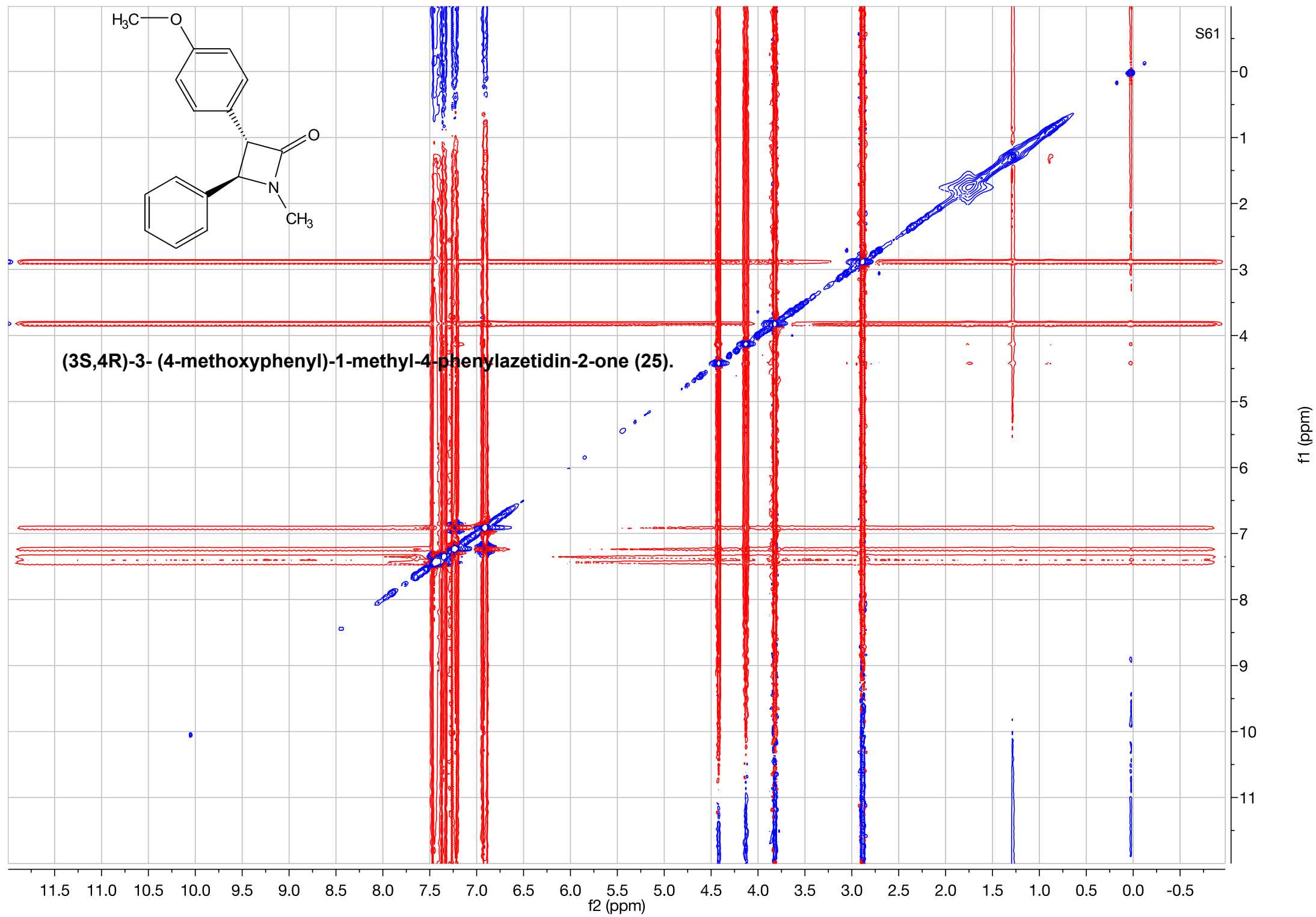
(3S,4R)-3- (4-fluorophenyl)-1-methyl-4-phenylazetidin-2-one (24)

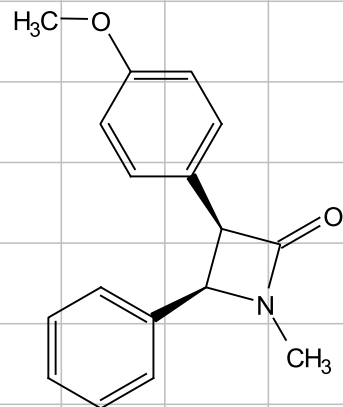




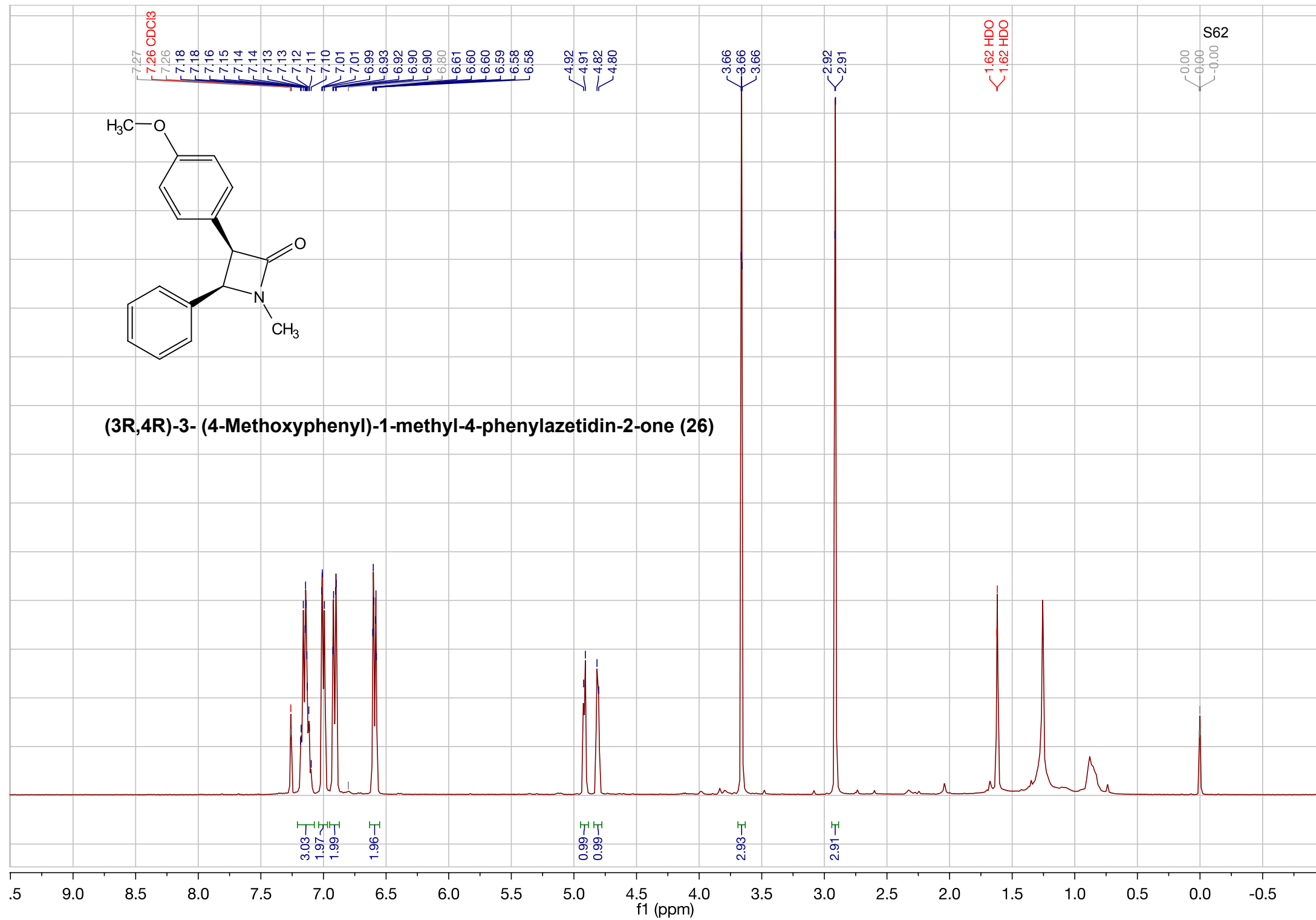
(3S,4R)-3-(4-methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (25).

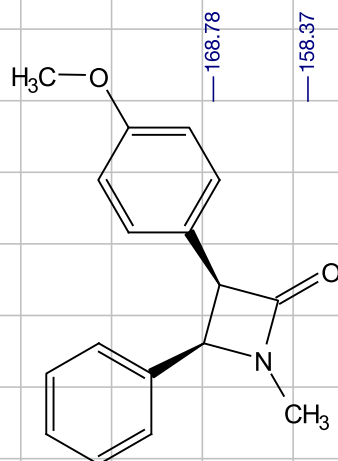




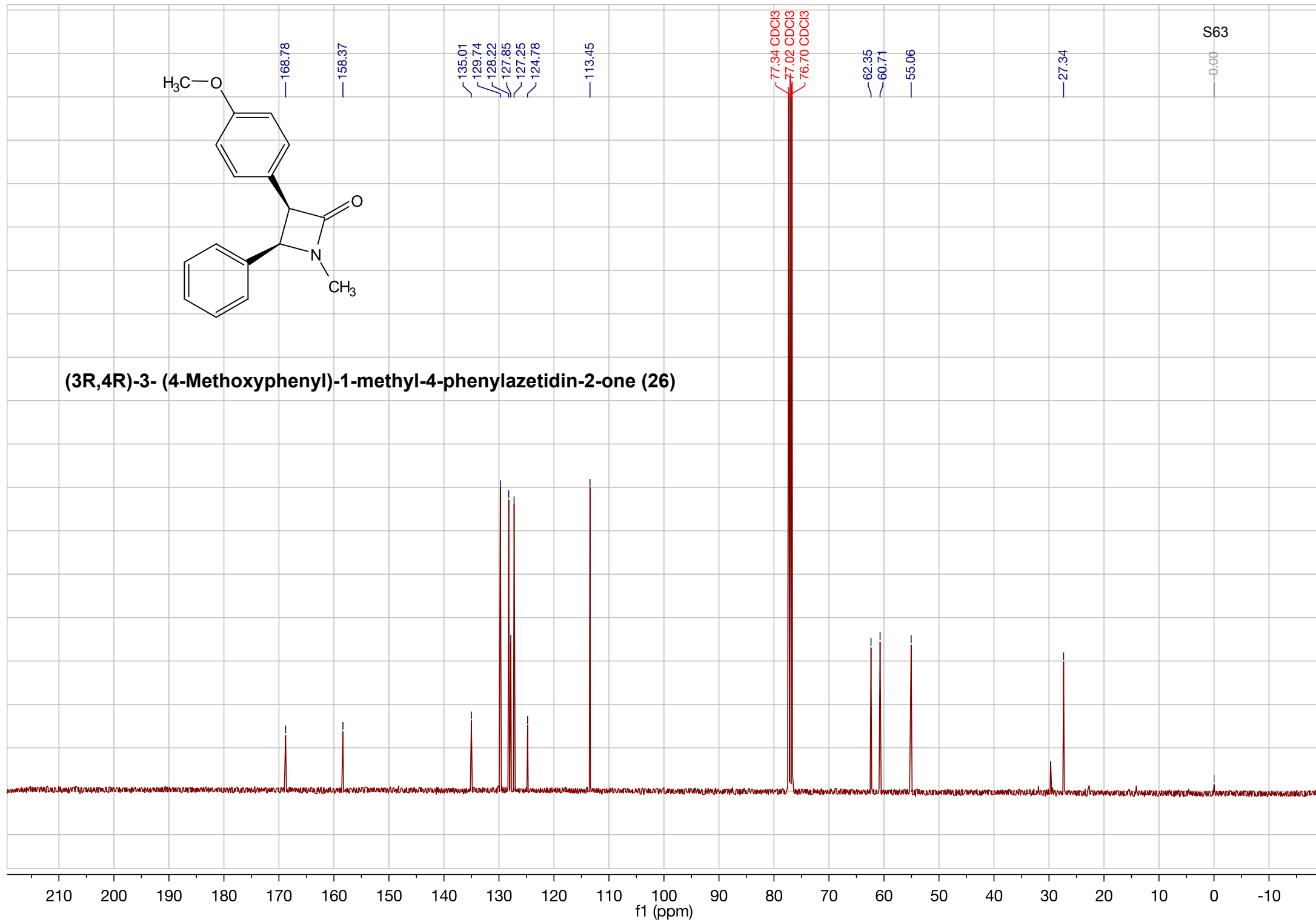


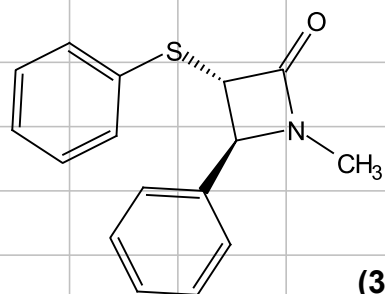
(3R,4R)-3- (4-Methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (26)



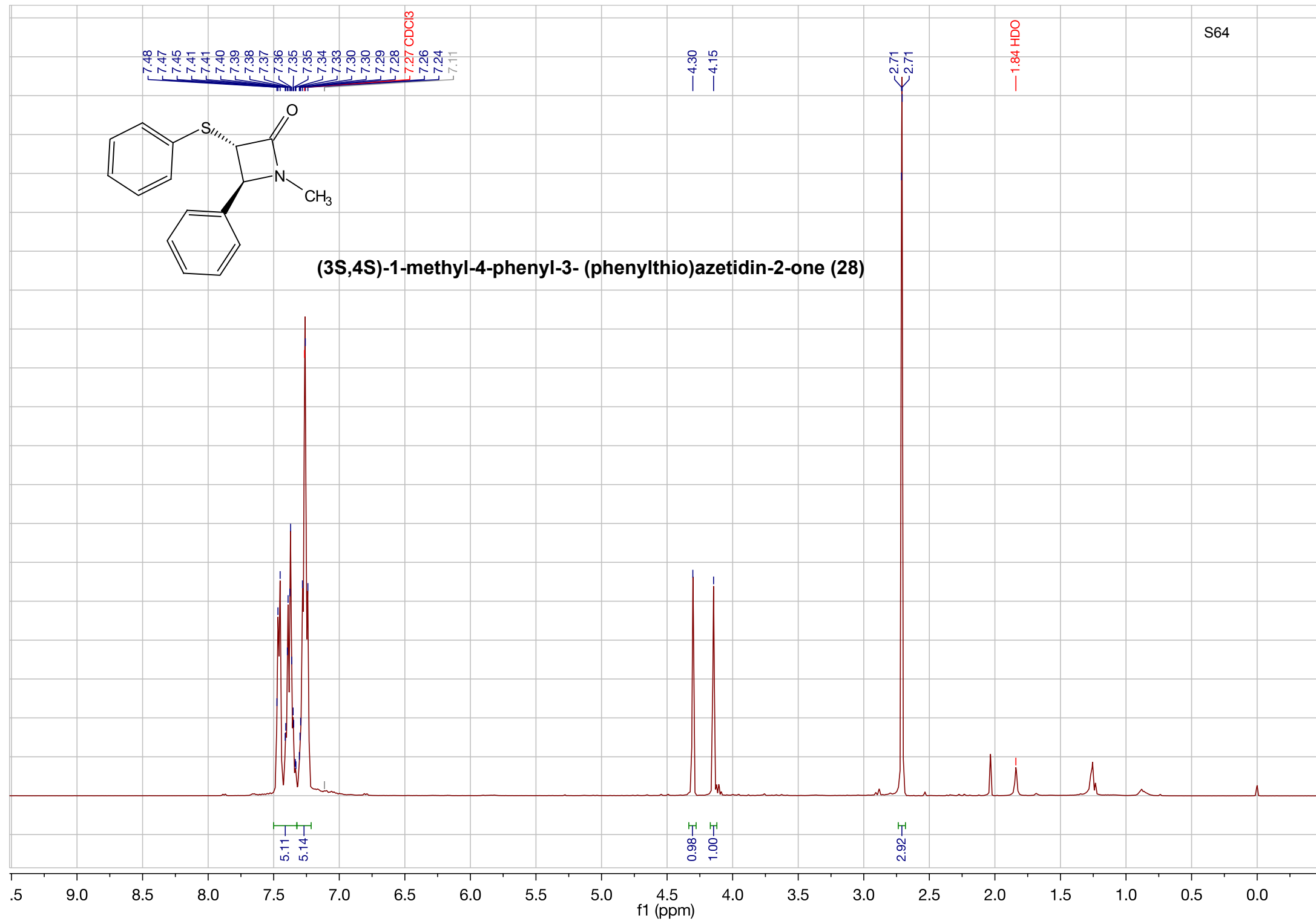


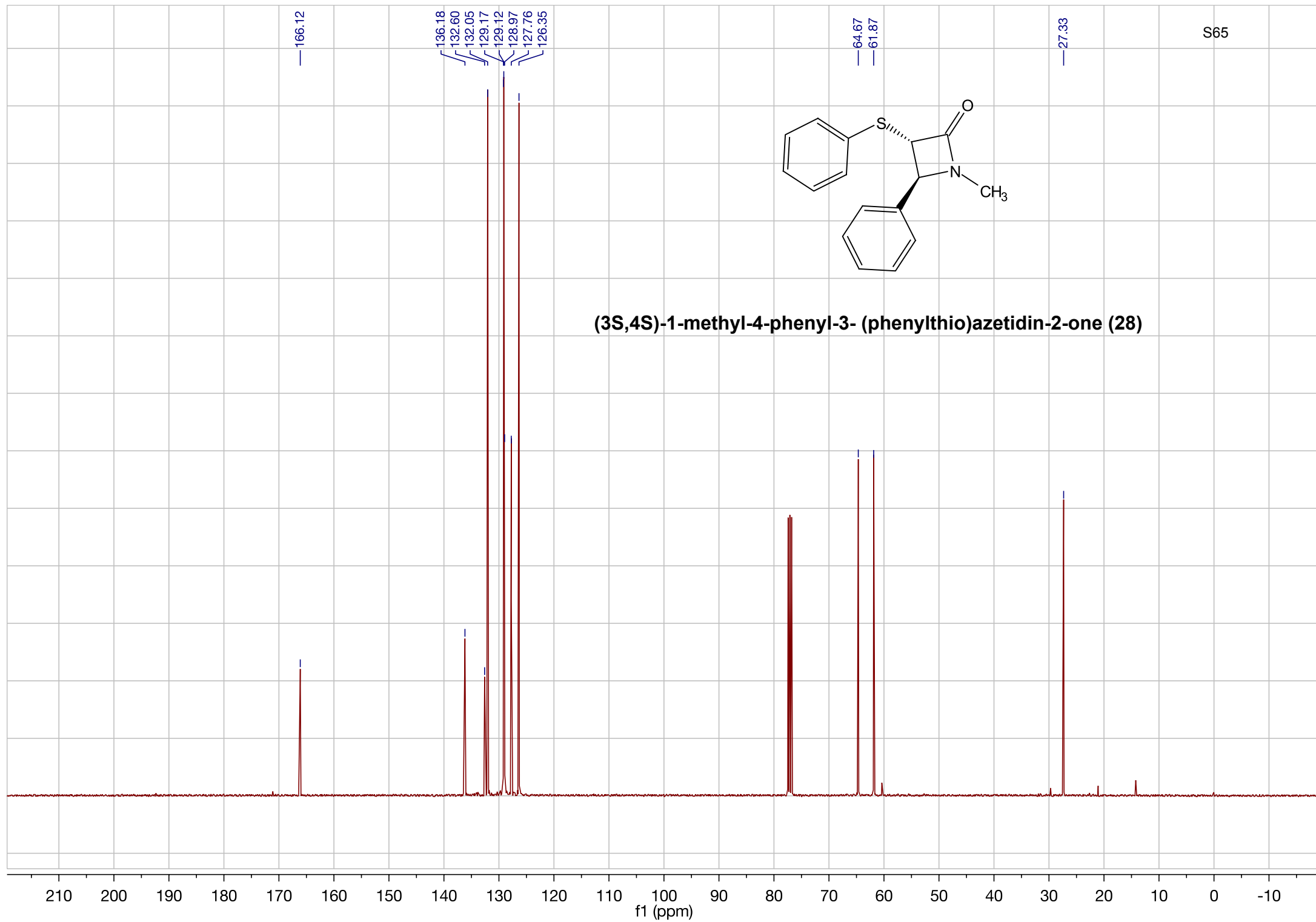
(3R,4R)-3- (4-Methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (26)

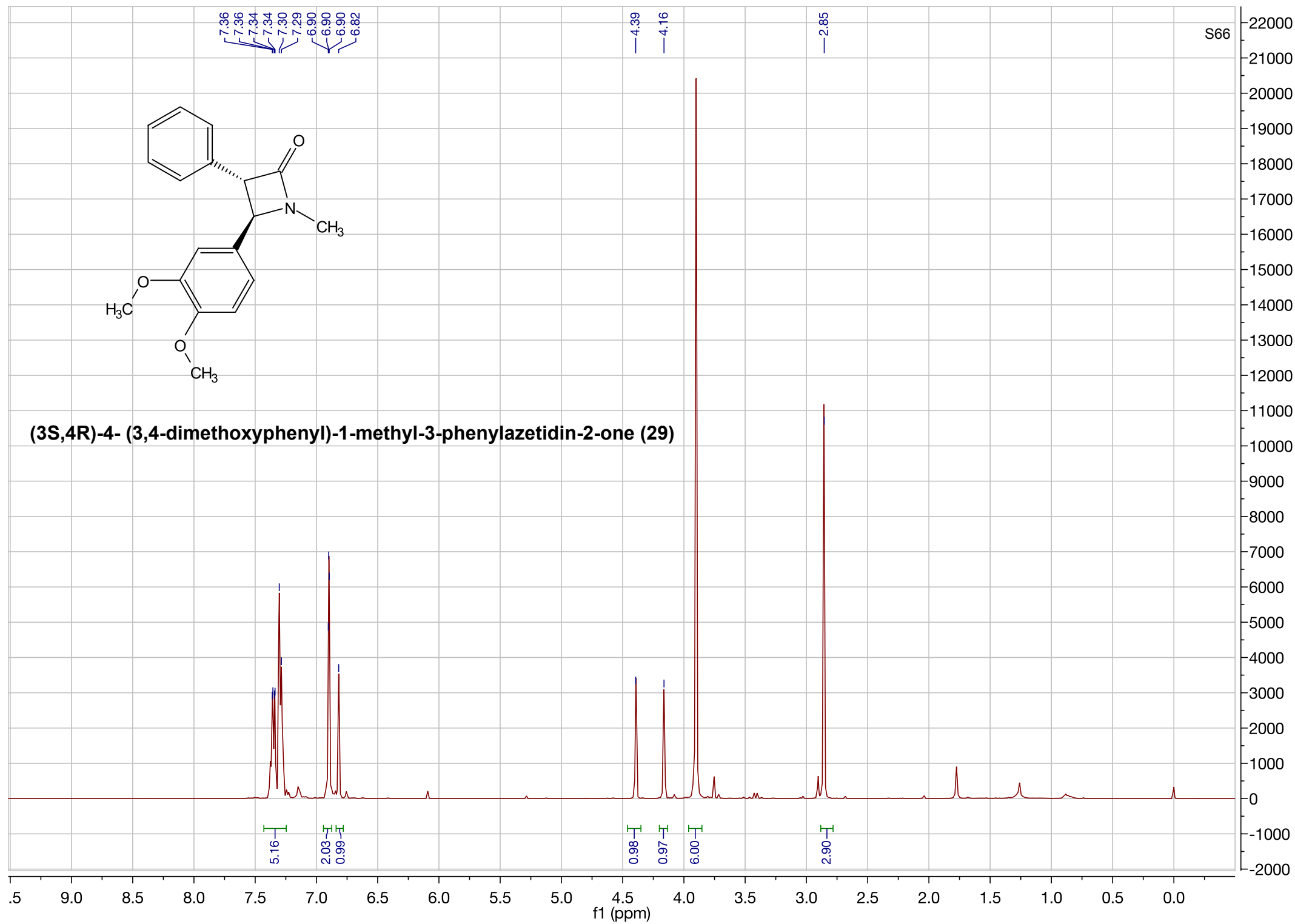


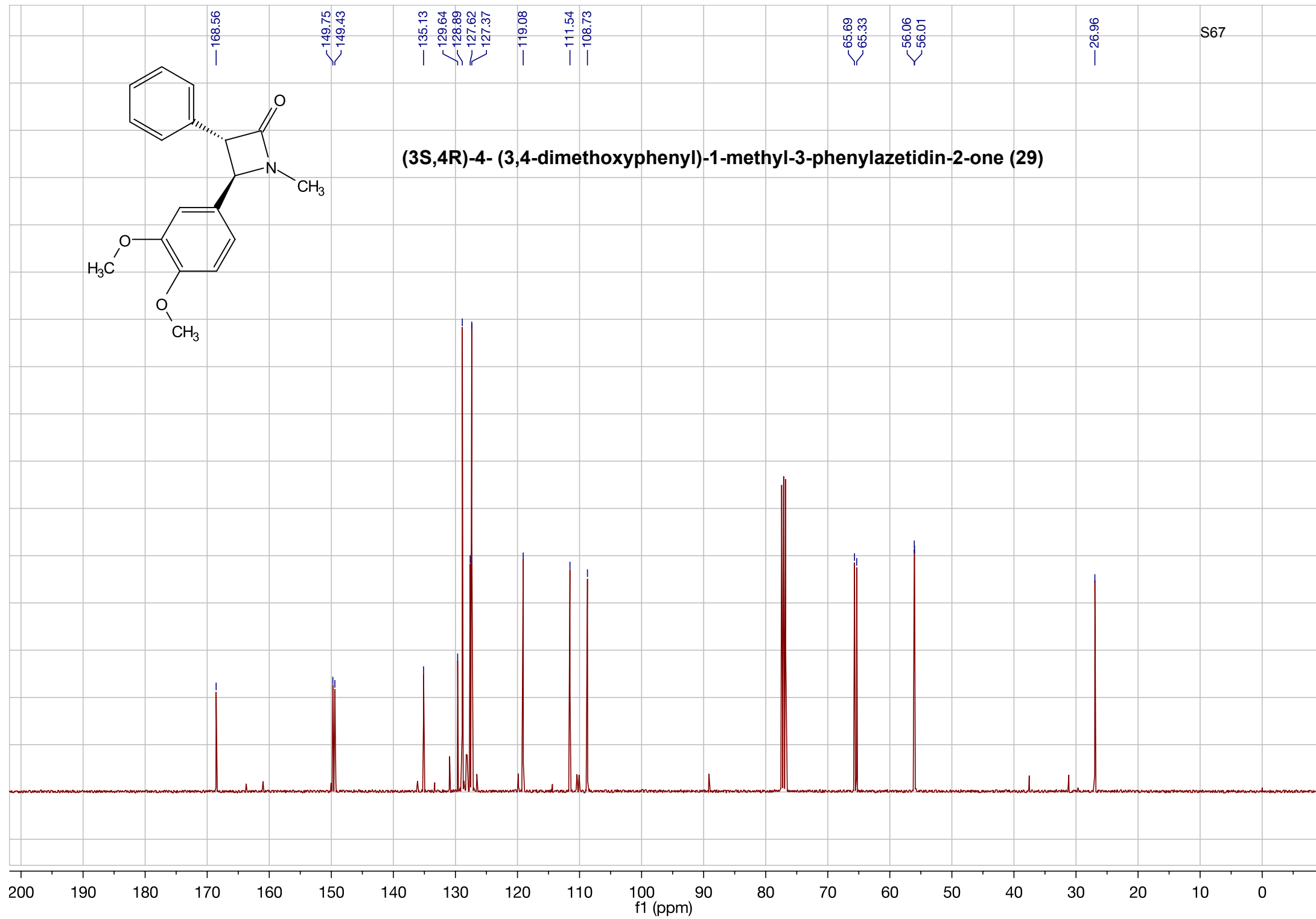


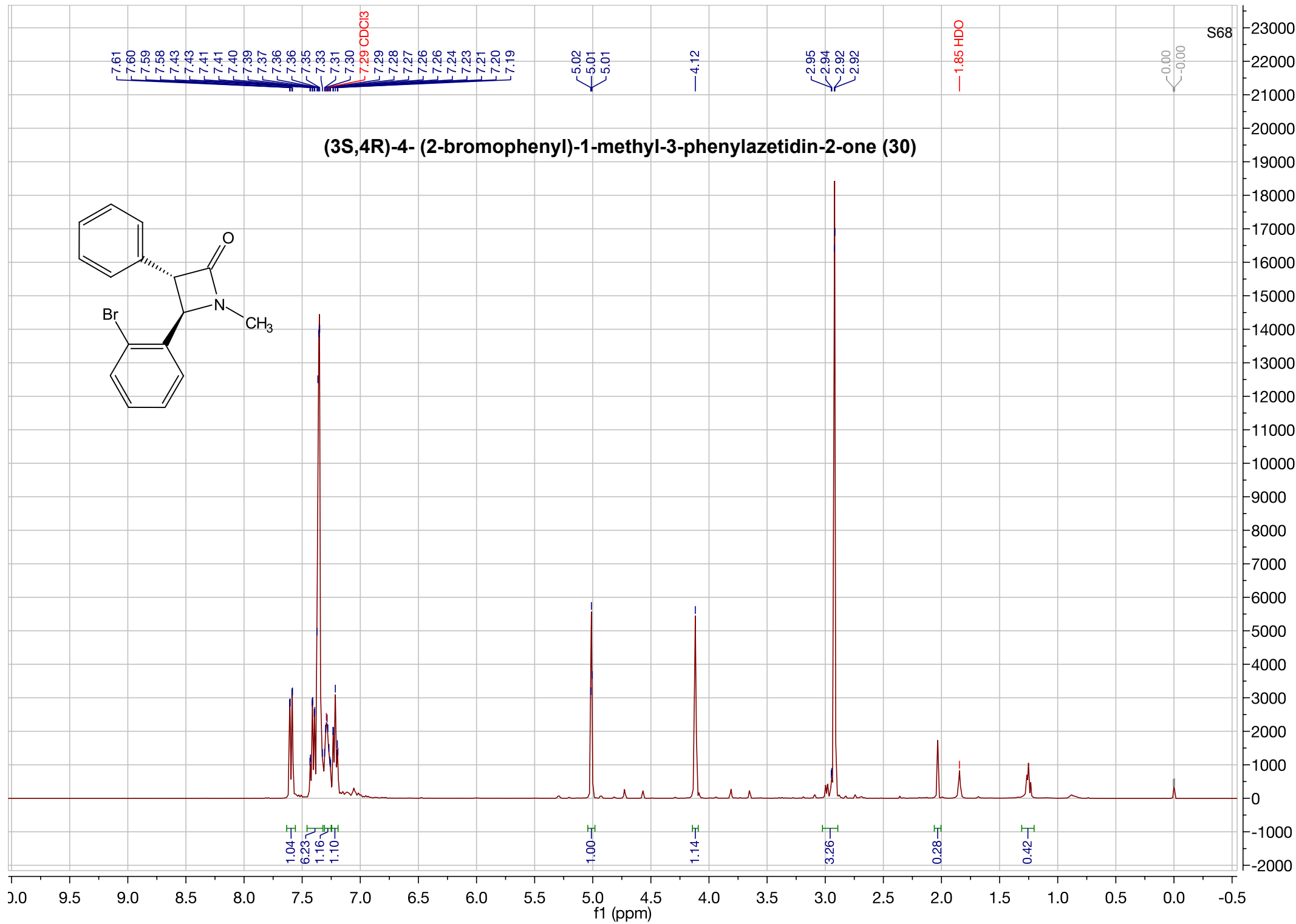
(3S,4S)-1-methyl-4-phenyl-3-(phenylthio)azetidin-2-one (28)

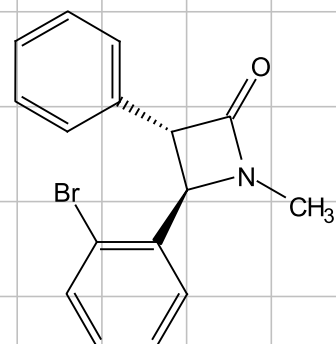












(3S,4R)-4- (2-bromophenyl)-1-methyl-3-phenylazetidin-2-one (30)

