

Intramolecular hydroamidation of alkenes enabling asymmetric synthesis of β -lactams via transposed NiH catalysis

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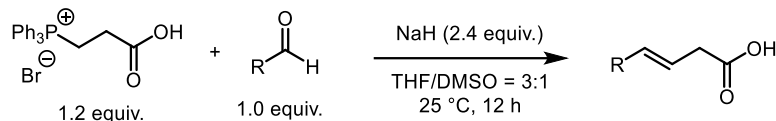
SUPPLEMENTARY METHODS

General Considerations

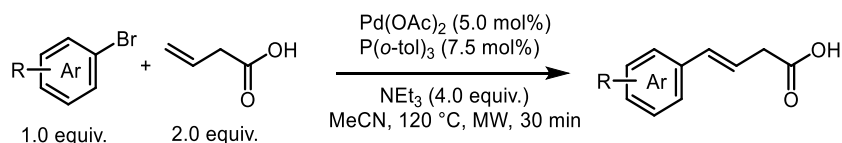
Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plates. Visualization on TLC was achieved by the use of UV light (254 nm), or treatment with potassium permanganate or ceric ammonium molybdate stain followed by heating. Flash column chromatography was undertaken using CombiFlash® *R*_f+ system with RediSep® *R*_f silica columns (230 – 400 mesh). Proton nuclear magnetic resonance spectra (¹H NMR) were recorded on Agilent Technologies DD2 (600 MHz), Bruker AV-500 (500 MHz), Bruker AVHD-400 (400 MHz), Bruker AS-400 (400 MHz), or Bruker AVNEO-400 (400 MHz) at room temperature. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak (e.g. CHCl₃ in CDCl₃: 7.26 ppm). The following abbreviations were used to describe peak splitting patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, sext = sextet, m = multiplet, br. = broad, and app. = apparent. Coupling constants, *J*, were reported in hertz (Hz) and rounded to the nearest 0.5. Carbon 13 nuclear magnetic resonance spectra (¹³C NMR) were recorded on Agilent Technologies DD2 (150 MHz), Bruker AV-500 (125 MHz), Bruker AVHD-400 (101 MHz), or Bruker AS-400 (100 MHz) and were fully decoupled by broad band decoupling. Chemical shifts were reported in ppm referenced to the appropriate solvent peak. ¹⁹F NMR spectra were recorded on Bruker AVNEO-400 (376 MHz) or Bruker AV-500 (471 MHz). Infrared (IR) spectra were recorded on Bruker Alpha FT-IR Spectrometer. Frequencies are given in wave numbers (cm⁻¹) and only selected absorbance were reported. High resolution mass spectra were obtained from the Korea Basic Science Institute (Daegu) by using FAB or EI method and from the KAIST Research Analysis Center by using ESI method. The data collection for X-ray single crystal structure analysis was performed at room temperature on a Bruker D8 QUEST diffractometer equipped with Iμs 3.0 Mo x-ray tube ($\lambda = 0.71073 \text{ \AA}$) and Photon II detector. The Parabar oil coated crystals were mounted on goniometer for diffraction experiment. The diffraction data were integrated, scaled, and reduced by using the Bruker APEX3 software. The crystal structures were solved by SHELX structure solution program and refined by full-matrix least-squares calculations with the SHELXL. The single crystals of compounds for X-ray crystal structure analysis were obtained by a diffusion method in separate vials using dichloromethane and *n*-pentane as an eluent. Melting points were measured with Buchi Melting Point M-565. Optical rotations $[\alpha]_D^{25}$ of enantioenriched compounds were recorded with Jasco P-2000 Polarimeter equipped with temperature controller.

Procedures for the Preparation of Starting Materials

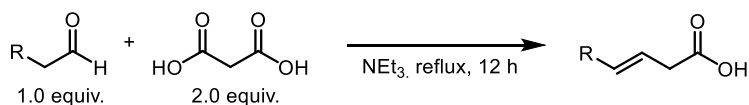
Preparation of carboxylic acids



General Procedure SM-A: To a solution of (2-carboxyethyl)triphenylphosphonium bromide (1.2 equiv.) in THF/DMSO (3:1, 0.5 M) was added NaH (2.4 equiv.) in one portion. The mixture was stirred at 25 °C until no hydrogen extrusion was observed. The corresponding aldehyde (1.0 equiv.) was then slowly added and the reaction mixture was stirred for 12 h. After completion, the reaction was quenched by 1.0 M HCl_(aq), and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: *n*-hexane/EtOAc = 10:1 to 2:1) to afford the title compounds.



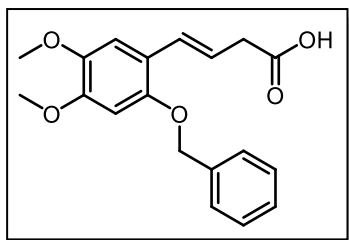
General Procedure SM-B: Modified conditions of a literature procedure¹; To a microwave vial (30 mL) equipped with a magnetic stir bar were added aryl bromide (1.0 equiv.), but-3-enoic acid (2.0 equiv.), Pd(OAc)₂ (5.0 mol%), P(*o*-tol)₃ (7.5 mol%), NEt₃ (4.0 equiv.), and MeCN (1.0 M), and the reaction mixture was heated in a microwave reactor at 120 °C for 30 min. After completion, the reaction mixture was diluted with EtOAc and 1.0 M HCl_(aq). The aqueous layer was extracted with EtOAc (20 mL x 3) and the combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: *n*-hexane/EtOAc = 10:1 to 1:1) to afford the title compounds.



General Procedure SM-C: To a round-bottom flask containing NEt₃ (0.2 M) and a magnetic stir bar were added aldehyde (1.0 equiv.) and malonic acid (2.0 equiv.), and the reaction mixture was refluxed at 100 °C for 12 h. After completion, the mixture was concentrated under reduced pressure, diluted with EtOAc, and quenched by 1.0 M HCl_(aq). The aqueous layer was extracted with EtOAc (3 times) and the combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced

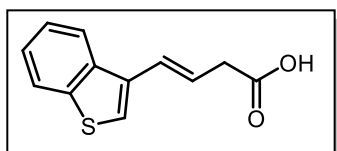
pressure. The crude mixture was purified by silica column chromatography (eluent: *n*-hexane /EtOAc = 10:1 to 1:1) to afford the desired product.

(E)-4-[2-(Benzyloxy)-4,5-dimethoxyphenyl]but-3-enoic acid



General Procedure SM-B, in 13.3 mmol scale; Pale yellow oil (3.9 g, 89%); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.71 (br. s, 1H), 7.45 – 7.35 (m, 4H), 7.33 (t, J = 7.5 Hz, 1H), 6.99 (s, 1H), 6.83 (d, J = 15.5 Hz, 1H), 6.52 (s, 1H), 6.17 (dt, J = 15.5, 7.0 Hz, 1H), 5.04 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.30 (d, J = 7.0 Hz, 2H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 177.0, 150.4, 149.5, 143.9, 137.3, 128.7, 128.4, 128.1, 127.7, 119.2, 118.5, 109.6, 100.0, 72.3, 56.6, 56.2, 38.4; **IR** (cm^{-1}) 2935, 2833, 1706, 1509, 1446, 1213, 1021, 734; **High Resolution MS** (EI): Calculated for $\text{C}_{19}\text{H}_{20}\text{O}_5$ $[\text{M}]^+$: 328.1311, Found: 328.1313.

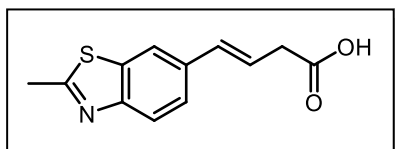
(E)-4-(Benzo[*b*]thiophen-3-yl)but-3-enoic acid



General Procedure SM-A, in 10.0 mmol scale; Yellow solid (1.0 g, 46%); **m.p.** = 91 – 93 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.91 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.42 – 7.35 (m, 2H), 6.80 (d, J = 16.0 Hz, 1H), 6.37 (dt, J = 16.0, 7.0 Hz, 1H), 3.38 (d, J = 7.0 Hz, 2H) (*OH peak not observed*); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 178.0, 140.5, 137.7, 133.5, 126.5, 124.6, 124.4, 123.0, 122.7, 122.5, 122.0, 38.4; **IR** (cm^{-1}) 2904, 1686, 1423, 1315, 1203, 960, 725; **High Resolution MS** (EI): Calculated for $\text{C}_{12}\text{H}_{10}\text{O}_2\text{S}$ $[\text{M}]^+$: 218.0402, Found: 218.0404.

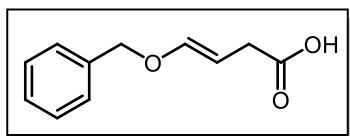
Note: Small amounts of impurities could not be removed by column chromatography. The compound was used in the following step without further purification.

(E)-4-(2-methylbenzo[*d*]thiazol-6-yl)but-3-enoic acid



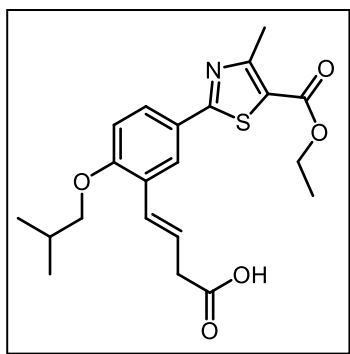
General Procedure SM-B, in 2.5 mmol scale; Yellow solid (420 mg, 72%); **m.p.** = 168 – 170 °C; $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.88 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 1.5 Hz, 1H), 7.49 (dd, J = 8.5, 1.5 Hz, 1H), 6.61 (d, J = 15.5 Hz, 1H), 6.35 (dt, J = 15.5, 7.5 Hz, 1H), 3.34 (dd, J = 7.5 Hz, 2H), 2.83 (s, 3H) (*OH peak not observed*); $^{13}\text{C NMR}$ (126 MHz, CD_2Cl_2) δ 176.1, 168.0, 153.3, 136.7, 134.2, 133.4, 124.6, 122.5, 122.3, 119.5, 38.2, 20.3; **IR** (cm^{-1}) 2919, 2684, 2500, 1711, 1518, 1404, 1177, 966; **High Resolution MS** (ESI): Calculated for $\text{C}_{12}\text{H}_{10}\text{NO}_2\text{S}$ $[\text{M}-\text{H}]^-$: 232.0438, Found: 232.0363.

(E)-4-(Benzyloxy)but-3-enoic acid



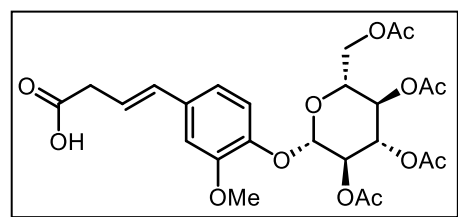
General Procedure SM-C, in 7.0 mmol scale; Pale yellow oil (990 mg, 74%); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.39 – 7.30 (m, 6H), 6.47 (d, J = 12.5 Hz, 1H), 4.97 (dt, J = 12.5, 7.5 Hz, 1H), 4.77 (s, 2H), 3.01 (d, J = 7.5 Hz, 2H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 178.5, 149.2, 136.8, 128.7, 128.2, 127.8, 96.1, 71.4, 33.3; **IR** (cm^{-1}) 3441, 3031, 2937, 2877, 1778, 1734, 1453, 1350, 1150, 1021, 945; **High Resolution MS** (EI): Calculated for $\text{C}_{11}\text{H}_{12}\text{O}_3$ $[\text{M}]^+$: 192.0786, Found: 192.0787.

(E)-4-{5-[5-(Ethoxycarbonyl)-4-methylthiazol-2-yl]-2-isobutoxyphenyl}but-3-enoic acid



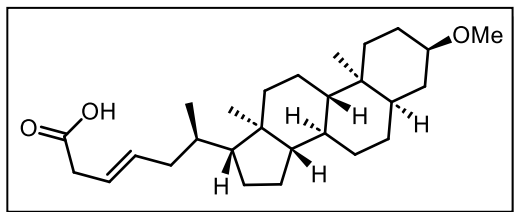
General Procedure SM-B, in 1.44 mmol scale; Yellow solid (542 mg, 93%); **m.p.** = 117 – 119 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.96 (br. s, 1H), 8.04 (d, J = 2.5 Hz, 1H), 7.80 (dd, J = 8.5, 2.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 15.5 Hz, 1H), 6.48 (dt, J = 15.5, 7.0 Hz, 1H), 4.35 (q, J = 7.0 Hz, 2H), 3.81 (d, J = 6.5 Hz, 2H), 3.36 (d, J = 7.0 Hz, 2H), 2.77 (s, 3H), 2.17 (hept, J = 6.5 Hz, 1H), 1.38 (t, J = 7.0 Hz, 3H), 1.07 (d, J = 6.5 Hz, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 177.2, 170.2, 162.5, 161.1, 158.6, 128.0, 127.6, 126.6, 125.7, 125.5, 123.1, 121.0, 112.0, 75.0, 61.3, 38.7, 28.4, 19.5, 17.6, 14.5; **IR** (cm^{-1}) 2960, 2911, 1707, 1600, 1423, 1251, 1098, 973; **High Resolution MS** (EI): Calculated for $\text{C}_{21}\text{H}_{25}\text{NO}_5\text{S}$ $[\text{M}]^+$: 403.1453, Found: 403.1456.

(E)-4-{3-Methoxy-4-[(2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl]oxy}phenyl}but-3-enoic acid



General Procedure SM-B, in 7.0 mmol scale; White solid (2.22 g, 59%); **m.p.** = 52 – 54 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.88 (br. s, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 8.5, 2.0 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 6.18 (dt, J = 16.0, 7.0 Hz, 1H), 5.30 – 5.23 (m, 2H), 5.20 – 5.13 (m, 1H), 4.98 – 4.89 (m, 1H), 4.27 (dd, J = 12.5, 5.0 Hz, 1H), 4.15 (dd, J = 12.5, 2.5 Hz, 1H), 3.82 (s, 3H), 3.82 – 3.74 (m, 1H), 3.28 (d, J = 7.0 Hz, 2H), 2.07 (s, 6H), 2.03 (s, 6H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 177.3, 170.8, 170.5, 169.6, 169.5, 150.8, 145.9, 133.6, 133.4, 120.6, 120.2, 119.3, 110.3, 100.9, 72.7, 72.2, 71.3, 68.5, 62.2, 56.1, 38.0, 20.8, 20.75 (2 $\times$ carbon peaks overlapping), 20.7; **IR** (cm^{-1}) 3249, 2944, 1739, 1510, 1367, 1210, 1030, 906; **High Resolution MS** (FAB): Calculated for $\text{C}_{25}\text{H}_{30}\text{KO}_{13}$ $[\text{M}+\text{K}]^+$: 577.1318, Found: 577.1277.

(*R,E*)-6-[(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Methoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]hept-3-enoic acid

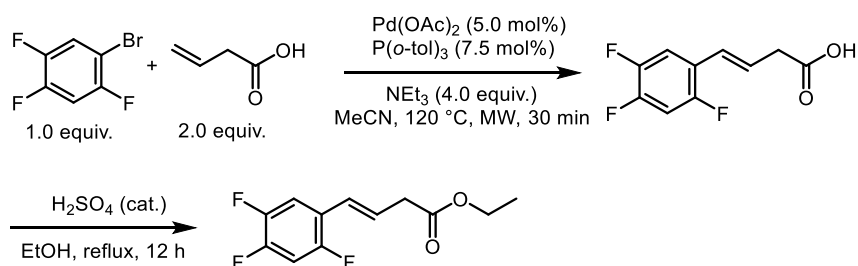


General Procedure SM-C, in 7.2 mmol scale; Pale yellow oil (1.3 g, 43%); **¹H NMR** (500 MHz, CDCl₃) δ 5.57 – 5.45 (m, 2H), 3.35 (s, 3H), 3.20 – 3.13 (m, 1H), 3.08 (d, *J* = 6.5 Hz, 2H), 2.15 (dt, *J* = 14.5, 4.0 Hz, 1H), 1.95 – 1.91 (m, 1H), 1.87 – 1.72 (m, 5H), 1.67 (t, *J* =

12.0 Hz, 1H), 1.61 – 1.53 (m, 2H), 1.43 – 1.31 (m, 6H), 1.30 – 1.15 (m, 5H), 1.14 – 1.02 (m, 5H), 0.91 (s, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.63 (s, 3H) (*OH* peak not observed); **¹³C NMR** (126 MHz, CDCl₃) δ 178.1, 133.9, 122.3, 80.7, 56.5, 56.0, 55.6, 42.8, 42.2, 40.5, 40.2, 39.3, 38.0, 36.2, 36.0, 35.4, 35.0, 32.8, 28.4, 27.5, 26.9, 26.5, 24.4, 23.6, 20.9, 18.7, 12.2; **IR** (cm⁻¹) 2928, 2864, 1709, 1447, 1373, 1098, 909, 731; **High Resolution MS** (EI): Calculated for C₂₇H₄₄O₃ [M]⁺: 416.3290, Found: 416.3293.

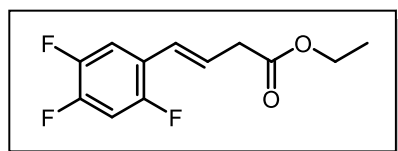
Preparation of esters

Ethyl (*E*)-4-(2,4,5-trifluorophenyl)but-3-enoate



To a microwave vial (30 mL) equipped with a magnetic stir bar were added aryl bromide (10.0 mmol, 1.0 equiv.), but-3-enoic acid (2.0 equiv.), Pd(OAc)₂ (5.0 mol%), P(*o*-tol)₃ (7.5 mol%), and MeCN (1.0 M), and the reaction mixture was heated in a microwave reactor at 120 °C for 30 min. After completion, the reaction mixture was diluted with EtOAc and quenched by 1.0 M HCl_(aq). The aqueous layer was extracted with EtOAc (20 mL x 3) and the combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was used for the next step without further purification.

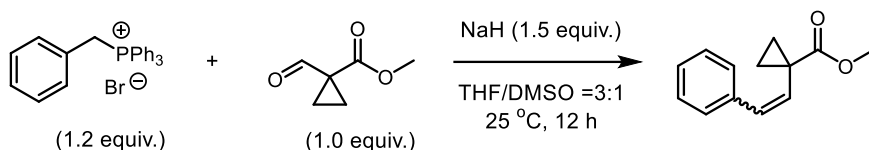
To a solution of the crude in EtOH (0.2 M) were added 2 drops of conc. H₂SO₄, and the reaction mixture was refluxed for 12 h. After completion, the reaction was cooled down to room temperature and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: *n*-hexane/EtOAc = 50:1 to 10:1) to afford the title compound as a pale yellow oil (1.1 g, 44%).



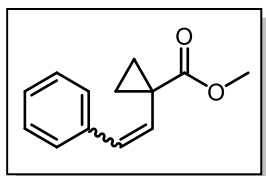
¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.21 (m, 1H), 6.89 (td, *J* = 10.0, 6.5 Hz, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.30 (dt, *J* = 16.0, 7.0 Hz, 1H), 4.18 (d, *J* = 7.0 Hz, 2H), 3.26 (dd, *J* = 7.0, 1.5 Hz, 2H), 1.29 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 171.1,

155.0 (dd, *J*_{C-F} = 248.5, 9.5 Hz), 149.3 (dd, *J*_{C-F} = 252.5, 14.0 Hz), 147.1 (dd, *J*_{C-F} = 244.5, 12.5 Hz), 125.6, 124.0, 121.3 (d, *J*_{C-F} = 27.5 Hz), 114.5 (d, *J*_{C-F} = 20.0 Hz), 105.7 (t, *J*_{C-F} = 23.0 Hz), 61.0, 38.5, 14.2; **¹⁹F NMR** (471 MHz, CDCl₃) δ –120.1 (dd, *J* = 15.0, 3.5 Hz), –134.6 (dd, *J* = 21.5, 3.5 Hz), –142.9 (dd, *J* = 21.5, 15.0 Hz); **IR** (cm^{–1}) 3063, 2984, 1731, 1513, 1428, 1153, 968, 872; **High Resolution MS** (EI): Calculated for C₁₂H₁₁F₃O₂ [M]⁺: 244.0711, Found: 244.0708.

Methyl 1-styrylcyclopropane-1-carboxylate (*Z/E* = 3:1 mixture)

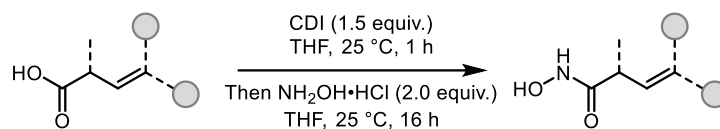


To a solution of benzyltriphenylphosphonium (1.2 equiv.) in THF/DMSO (3:1, 0.5 M) was added NaH (1.5 equiv.) in one portion. The mixture was stirred at 25 °C until no hydrogen extrusion was observed. The corresponding aldehyde (10 mmol, 1.0 equiv.) was then slowly added and the reaction mixture was stirred for 12 h. After completion, the reaction was quenched by 1.0 M HCl_{aq}, and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: n-hexane/EtOAc = 10:1) to afford the title compound as a colourless oil (1.64 g, 81%, *Z/E* = 3:1 mixture).

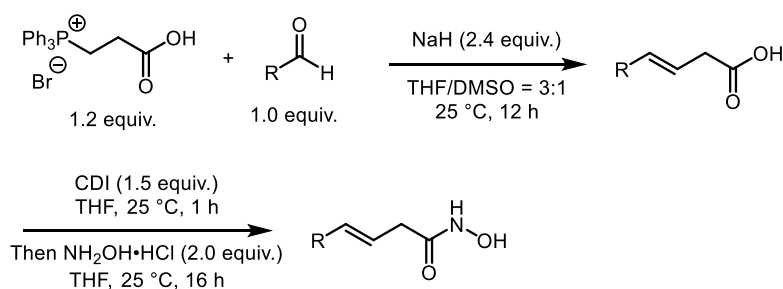


¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.17 (m, 5H), 6.83 (d, *J* = 16.0 Hz, 0.25H), 6.51 (d, *J* = 11.5 Hz, 0.75H), 6.21 (d, *J* = 16.0 Hz, 0.25H), 5.84 (d, *J* = 11.5 Hz, 0.75H), 3.68 (s, 0.75H), 3.62 (s, 2.25H), 1.51 (q, *J* = 4.0 Hz, 0.5H), 1.42 (q, *J* = 4.0 Hz, 1.5H), 1.15 (q, *J* = 4.0 Hz, 0.5H), 0.77 (q, *J* = 4.0 Hz, 1.5H); **¹³C NMR** (126 MHz, CDCl₃) δ 175.1, 174.6 (minor isomer), 137.2 (minor isomer), 136.6, 133.2, 129.0, 128.7 (minor isomer), 128.3 (minor isomer), 128.19 (minor isomer), 128.16, 127.7 (minor isomer), 127.44 (minor isomer), 127.37, 126.3, 52.5, 52.4 (minor isomer), 25.3 (minor isomer), 23.4 (minor isomer), 20.1, 19.0; **IR** (cm⁻¹) 3016, 2950, 1722, 1493, 1435, 1302, 1256, 1195; **High Resolution MS** (ESI): Calculated for C₁₃H₁₄NaO₂ [M+Na]⁺: 225.0886, Found: 225.0870.

Preparation of hydroxamic acids

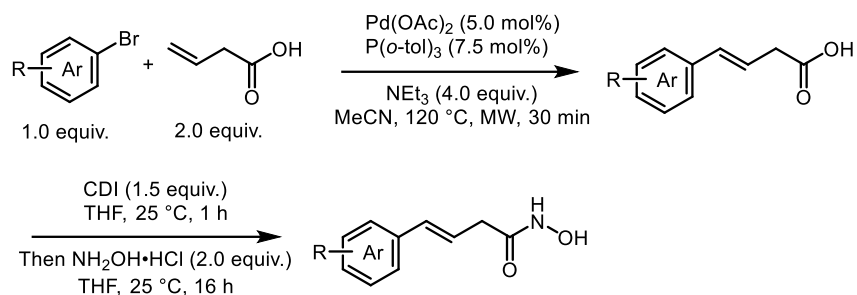


General Procedure SM-D: To a solution of carboxylic acid (1.0 equiv.) in dry tetrahydrofuran (0.33 M) was added 1,1'-carbonyldiimidazole (1.5 equiv.) under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h. While stirring, powdered hydroxylamine hydrochloride (2.0 equiv.) was added in one portion, and the resulting mixture was stirred at room temperature for additional 16 h. After completion, the mixture was diluted with 5% KHSO_{4(aq)} and extracted with EtOAc (2 times). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: CH₂Cl₂/MeOH = 10:1) to afford the desired hydroxamic acids.



General Procedure SM-E: To a solution of (2-carboxyethyl)triphenylphosphonium bromide (1.2 equiv.) in THF/DMSO (3:1, 0.5 M) was added NaH (2.4 equiv.) in one portion. The mixture was stirred at 25 °C until no hydrogen extrusion was observed. The corresponding aldehyde (1.0 equiv.) was then slowly added and the reaction mixture was stirred for 12 h. After completion, the reaction was quenched with 1.0 M HCl_(aq), and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Due to high polarity of the product, the crude acid was used for the next step without further purification.

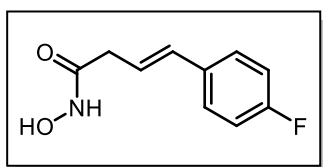
To a solution of carboxylic acid obtained from the previous step (1.0 equiv.) in dry tetrahydrofuran (0.33 M) was added 1,1'-carbonyldiimidazole (1.5 equiv.) under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h. While stirring, powdered hydroxylamine hydrochloride (2.0 equiv.) was added in one portion, and the resulting mixture was stirred at room temperature for additional 16 h. After completion, the mixture was diluted with 5% KHSO_{4(aq)} and extracted with EtOAc (2 times). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: CH₂Cl₂/MeOH = 10:1) to afford the desired hydroxamic acids.



General Procedure SM-F: To a microwave vial (30 mL) equipped with a magnetic stir bar were added aryl bromide (1.0 equiv.), but-3-enoic acid (2.0 equiv.), Pd(OAc)₂ (5.0 mol%), P(o-tol)₃ (7.5 mol%), NEt₃ (4.0 equiv.), and MeCN (1.0 M). The reaction mixture was heated in a microwave reaction at 120 °C for 30 min. After completion, the reaction mixture was diluted with EtOAc and 1.0 M HCl_(aq), and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Due to high polarity of the product, the crude acid was used for the next step without further purification.

To a solution of carboxylic acid obtained from the previous step (1.0 equiv.) in dry tetrahydrofuran (0.33 M) was added 1,1'-carbonyldiimidazole (1.5 equiv.) under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h. While stirring, powdered hydroxylamine hydrochloride (2.0 equiv.) was added in one portion, and the resulting mixture was stirred at room temperature for additional 16 h. After completion, the mixture was diluted with 5% KHSO_{4(aq)} and extracted with EtOAc (2 times). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: CH₂Cl₂/MeOH = 10:1) to afford the desired hydroxamic acids.

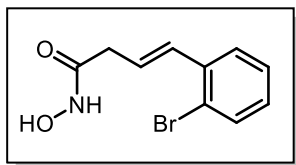
(E)-4-(4-Fluorophenyl)-N-hydroxybut-3-enamide



General Procedure SM-D, in 7.4 mmol scale; White solid (767 mg, 53%); **m.p.** = 135 – 137 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.51 (br. s, 1H), 8.79 (br. s, 1H), 7.48 – 7.41 (m, 2H), 7.19 – 7.10 (m, 2H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.24 (dt, *J* = 16.0, 7.0 Hz, 1H), 2.91 (d, *J* = 7.0 Hz,

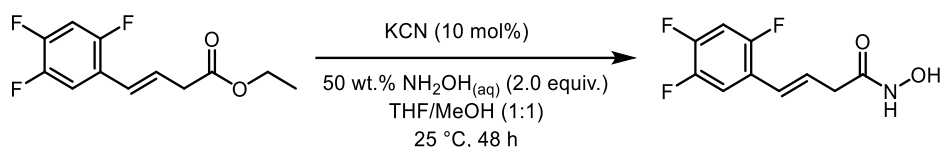
2H); ¹³C NMR (126 MHz, CD₃OD) δ 170.8, 163.7 (d, *J*_{C-F} = 245.0 Hz), 134.8, 133.5, 129.0 (d, *J*_{C-F} = 8.0 Hz), 123.4 (d, *J*_{C-F} = 2.5 Hz), 116.3 (d, *J*_{C-F} = 21.5 Hz), 37.9; ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –115.0; IR (cm⁻¹) 3169, 3017, 2886, 2311, 1622, 1508, 1241, 1056, 964; **High Resolution MS** (EI): Calculated for C₁₀H₁₀FN₂ [M]⁺: 195.0696, Found: 195.0699.

(E)-4-(2-Bromophenyl)-N-hydroxybut-3-enamide

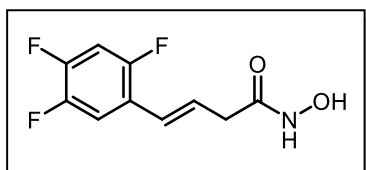


General Procedure SM-D, in 4.1 mmol scale; Pale yellow oil (670 mg, 64%); ^1H NMR (500 MHz, CD_3OD) δ 7.57 (dd, J = 7.5, 1.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.16 – 7.11 (m, 1H), 6.87 (d, J = 15.5 Hz, 1H), 6.29 (dt, J = 15.5, 7.0 Hz, 1H), 3.08 (d, J = 7.0 Hz, 2H) (*OH and NH peaks not observed*); ^{13}C NMR (126 MHz, CD_3OD) δ 170.4, 138.0, 133.9, 133.1, 130.1, 128.8, 128.2, 127.0, 124.1, 38.0; IR (cm^{-1}) 3204, 3048, 2922, 2347, 1626, 1435, 1020, 963, 744; **High Resolution MS** (EI): Calculated for $\text{C}_{10}\text{H}_9\text{BrNO}_2$ $[\text{M}]^+$: 254.9895, Found: 254.9893.

(E)-N-Hydroxy-4-(2,4,5-trifluorophenyl)but-3-enamide



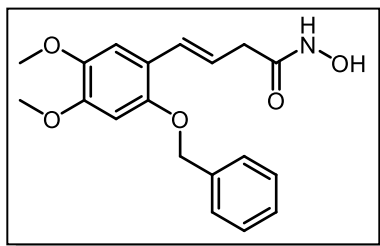
To a solution of ester (1.8 mmol, 1.0 equiv.) and 50 wt. % $\text{NH}_2\text{OH}_{(\text{aq})}$ (2.0 equiv.) in THF/MeOH (1:1, 0.2 M) was added KCN (10 mol%). The reaction mixture was stirred at 25 °C for 48 h. After completion, the mixture was concentrated under reduced pressure and the crude mixture was purified by silica column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 10:1) to afford the desired hydroxamic acids.



White solid (280 mg, 68%); **m.p.** = 105 – 108 °C; ^1H NMR (400 MHz, THF- d_8) δ 10.03 (br. s, 1H), 8.47 (br. s, 1H), 7.53 (ddd, J = 11.5, 9.0, 7.0 Hz, 1H), 7.13 (td, J = 10.5, 7.0 Hz, 1H), 6.55 (d, J = 16.0 Hz, 1H), 6.45 (dt, J = 16.0, 6.5 Hz, 1H), 3.01 (d, J = 6.5 Hz, 2H);

^{13}C NMR (126 MHz, THF- d_8) δ 167.5, 156.0 (d, $J_{\text{C-F}}$ = 246.0 Hz), 150.1 (d, $J_{\text{C-F}}$ = 248.5 Hz), 148.1 (d, $J_{\text{C-F}}$ = 240.5 Hz), 128.9, 123.7, 123.1, 115.6 (d, $J_{\text{C-F}}$ = 20.5 Hz), 106.5 (t, $J_{\text{C-F}}$ = 25.0 Hz), 38.1; ^{19}F NMR (376 MHz, THF- d_8) δ -121.5 (dd, J = 15.0, 3.5 Hz), -136.9 (dd, J = 21.5, 3.5 Hz), -144.5 (dd, J = 21.5, 15.0 Hz); IR (cm^{-1}) 3166, 3062, 2884, 1636, 1503, 1428, 1332, 1194, 1154, 968; **High Resolution MS** (EI): Calculated for $\text{C}_{10}\text{H}_8\text{F}_3\text{NO}_2$ $[\text{M}]^+$: 231.0507, Found: 231.0504.

(E)-4-[2-(Benzyloxy)-4,5-dimethoxyphenyl]-N-hydroxybut-3-enamide

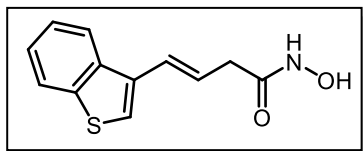


General Procedure SM-D, in 10.0 mmol scale; White solid (2.4 g, 68%); **m.p.** = 157 – 159 °C; ^1H NMR (500 MHz, CD_3OD) δ 7.45 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.05 (s, 1H), 6.82 (d, J = 15.5 Hz, 1H), 6.67 (s, 1H), 6.17 (dt, J = 15.5, 7.0 Hz, 1H), 5.07 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.00 (d, J = 7.0 Hz, 2H) (*OH and NH peaks not observed*); ^{13}C NMR (126

MHz, CD_3OD) δ 171.2, 151.8, 151.0, 145.0, 138.8, 129.5, 129.0, 128.9, 128.8, 121.7, 119.9, 111.6,

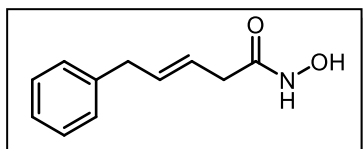
101.2, 72.8, 57.2, 56.5, 38.5; **IR** (cm⁻¹) 3317, 2831, 1663, 1514, 1196, 1012, 762; **High Resolution MS** (EI): Calculated for C₁₉H₂₁NO₅ [M]⁺: 343.1420, Found: 343.1423.

(E)-4-(Benzo[*b*]thiophen-3-yl)-*N*-hydroxybut-3-enamide



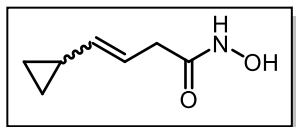
General Procedure SM-D, in 4.4 mmol scale; White solid (820 mg, 80%); **m.p.** = 122 – 124 °C; **¹H NMR** (400 MHz, CD₃OD) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 15.5 Hz, 1H), 6.39 (dt, *J* = 15.5, 7.0 Hz, 1H), 3.11 (d, *J* = 7.0 Hz, 2H) (*OH* and *NH* peaks not observed); **¹³C NMR** (101 MHz, CD₃OD) δ 170.8, 141.8, 139.0, 134.8, 126.9, 125.5, 125.3 (2 × carbon peaks overlapping), 123.8, 123.2, 122.9, 38.3; **IR** (cm⁻¹) 3173, 3034, 2880, 2362, 1625, 1421, 1048, 963, 759; **High Resolution MS** (EI): Calculated for C₁₂H₁₁NO₂S [M]⁺: 233.0510, Found: 233.0511.

(E)-*N*-Hydroxy-5-phenylpent-3-enamide



General Procedure SM-D, in 19.9 mmol scale; White solid (3.01 g, 79%); **m.p.** = 74 – 76 °C; **¹H NMR** (400 MHz, CD₃OD) δ 7.25 (t, *J* = 7.5 Hz, 2H), 7.17 – 7.13 (m, 3H), 5.76 (dt, *J* = 14.5, 7.0 Hz, 1H), 5.58 (dt, *J* = 14.5, 7.0 Hz, 1H), 3.35 (d, *J* = 7.0 Hz, 2H), 2.84 (d, *J* = 7.0 Hz, 2H) (*OH* and *NH* peaks not observed); **¹³C NMR** (101 MHz, CD₃OD) δ 171.1, 141.4, 134.7, 129.6, 129.4, 127.1, 124.9, 39.8, 37.6; **IR** (cm⁻¹) 3168, 3120, 2865, 1626, 1544, 1493, 1044, 975, 695; **High Resolution MS** (EI): Calculated for C₁₁H₁₃NO₂ [M]⁺: 191.0946, Found: 191.0948.

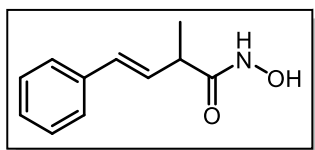
4-Cyclopropyl-*N*-hydroxybut-3-enamide (*E/Z*=1.1:1 mixture)



General Procedure SM-D, in 9.5 mmol scale; White solid (857 mg, 64%); **m.p.** = 73 – 75 °C; **¹H NMR** (500 MHz, CD₃OD) δ 5.54 (dt, *J* = 15.0, 7.0 Hz, 0.55H), 5.40 (q, *J* = 8.0 Hz, 0.45H), 5.14 (dd, *J* = 15.0, 8.5 Hz, 0.55H), 4.96 – 4.91 (m, 0.45H), 3.02 (d, *J* = 7.5 Hz, 0.9H), 2.79 (d, *J* = 7.0 Hz, 1.1H), 1.62 – 1.55 (m, 0.45H), 1.41 – 1.34 (m, 0.55H), 0.76 (d, *J* = 7.5 Hz, 0.9H), 0.68 (d, *J* = 7.5 Hz, 1.1H), 0.34 (app. d, *J* = 5.0 Hz, 2H) (*OH* and *NH* peaks not observed); **¹³C NMR** (126 MHz, CD₃OD) δ 171.4 (2 × carbon peaks overlapped), 139.6, 138.8, 120.8, 120.5, 37.6, 32.9, 14.4, 10.4, 7.3, 6.8; **IR** (cm⁻¹) 3163, 3005, 2883, 1616, 1546, 1433, 1061 961; **High Resolution MS** (ESI): Calculated for C₇H₁₀NO₂ [M-H]⁻: 140.0717, Found: 140.0676.

Note: Small amounts of impurities could not be removed by column chromatography. The title compound was used for the following step without further purification.

(E)-N-Hydroxy-2-methyl-4-phenylbut-3-enamide

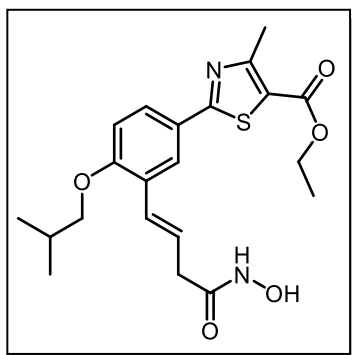


General Procedure SM-D, in 10.7 mmol scale; White solid (1.67 g, 81%);

m.p. = 134 – 136 °C; ¹H NMR (600 MHz, CD₃OD) δ 7.36 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.27 (dd, *J* = 16.0, 7.5 Hz, 1H), 3.09 (p, *J* = 7.5 Hz, 1H), 1.31 (d, *J* = 7.5 Hz, 3H) (*OH* and *NH* peaks not observed); ¹³C NMR (151 MHz, CD₃OD) δ 174.2, 138.3, 132.3,

130.4, 129.6, 128.5, 127.3, 42.7, 18.1; **IR** (cm⁻¹) 3163, 3019, 2887, 1628, 1449, 1041, 965, 697; **High Resolution MS** (EI): Calculated for C₁₁H₁₃NO₂ [M]⁺: 191.0946, Found: 191.0947.

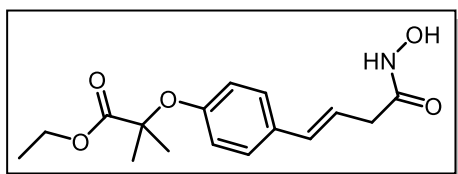
Ethyl (E)-2-{3-[4-(hydroxyamino)-4-oxobut-1-en-1-yl]-4-isobutoxyphenyl}-4-methylthiazole-5-carboxylate



General Procedure SM-D, in 1.34 mmol scale; Yellow solid (221 mg, 40%); **m.p.** = 151 – 153 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.72 (br. s, 1H), 9.11 (br. s, 1H), 7.90 (d, *J* = 2.5 Hz, 1H), 7.63 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.78 – 6.68 (m, 2H), 6.29 (dt, *J* = 15.0, 7.0 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 3.69 (d, *J* = 6.5 Hz, 2H), 3.17 (d, *J* = 7.0 Hz, 2H), 2.71 (s, 3H), 2.12 – 2.02 (m, 1H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 170.1, 169.4, 162.3, 160.8, 158.4, 128.7, 127.6, 126.3, 125.3, 125.2, 123.0, 121.0, 111.8, 74.9,

61.3, 38.1, 28.3, 19.4, 17.4, 14.4; **IR** (cm⁻¹) 3173, 2954, 2871, 1691, 1659, 1598, 1324, 1256, 1091, 1021, 967; **High Resolution MS** (FAB): Calculated for C₂₁H₂₇N₂O₅S [M+H]⁺: 419.1641, Found: 419.1645.

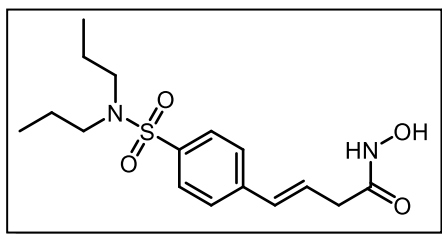
Ethyl (E)-2-[4-[4-(hydroxyamino)-4-oxobut-1-en-1-yl]phenoxy]-2-methylpropanoate



General Procedure SM-E, in 14.8 mmol scale; Red oil (840 mg, 18%); ¹H NMR (500 MHz, CDCl₃) δ 9.37 (br. s, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.34 (d, *J* = 15.5 Hz, 1H), 5.97 (dt, *J* = 15.5, 7.0 Hz, 1H), 4.20 (q, *J* =

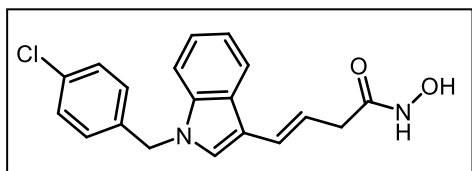
7.0 Hz, 2H), 2.98 (d, *J* = 7.0 Hz, 2H), 1.56 (s, 6H), 1.21 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.4, 169.9, 155.2, 134.2, 130.7, 127.3, 119.3, 119.2, 79.3, 61.6, 37.2, 25.4, 14.1; **IR** (cm⁻¹) 3206, 2987, 2939, 1730, 1642, 1506, 1283, 1136, 968; **High Resolution MS** (EI): Calculated for C₁₆H₂₁NO₅ [M]⁺: 307.1420, Found: 307.1423.

(E)-4-[4-(*N,N*-Dipropylsulfamoyl)phenyl]-*N*-hydroxybut-3-enamide



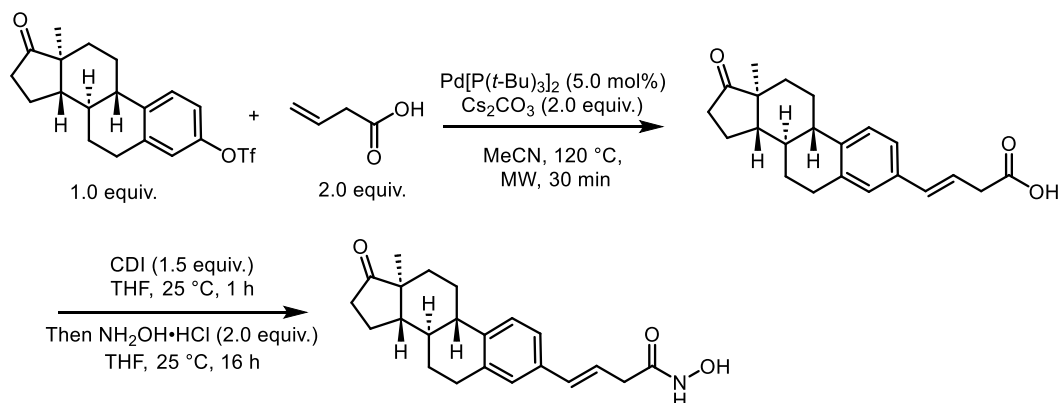
General Procedure SM-F, in 4.68 mmol scale; Yellow solid (470 mg, 39%); **m.p.** = 101 – 103 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.31 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.12 (d, *J* = 7.0 Hz, 2H), 3.08 – 3.04 (m, 4H), 1.52 (p, *J* = 7.5 Hz, 4H), 0.86 (t, *J* = 7.5 Hz, 6H) (*OH* and *NH* peaks not observed); **¹³C NMR** (126 MHz, CDCl₃) δ 168.8, 140.4, 139.1, 133.4, 127.5, 126.9, 124.4, 50.1, 37.2, 22.1, 11.3; **IR** (cm⁻¹) 2963, 2931, 1691, 1333, 1151, 971; **High Resolution MS** (ESI): Calculated for C₁₆H₂₃N₂O₃S [M-OH]⁻: 323.1435, Found: 323.1340.

(E)-4-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-*N*-hydroxybut-3-enamide



General Procedure SM-F, in 1.2 mmol scale; White solid (130 mg, 32%); **m.p.** = 133 – 135 °C; **¹H NMR** (500 MHz, CD₃OD) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H), 7.27 – 7.25 (m, 3H), 7.15 – 7.07 (m, 4H), 6.70 (d, *J* = 15.5 Hz, 1H), 6.21 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.31 (s, 2H), 3.05 (d, *J* = 7.0 Hz, 2H) (*OH* and *NH* peaks not observed); **¹³C NMR** (126 MHz, CD₃OD) δ 171.5, 138.4, 138.1, 134.3, 129.7, 129.5, 128.8, 127.8, 127.5, 123.2, 121.1, 121.0, 119.3, 115.2, 111.1, 50.0, 38.7; **IR** (cm⁻¹) 3209, 1636, 1464, 1169, 957, 738; **High Resolution MS** (FAB): Calculated for C₁₉H₁₈ClN₂O₂ [M+H]⁺: 341.1057, Found: 341.1063.

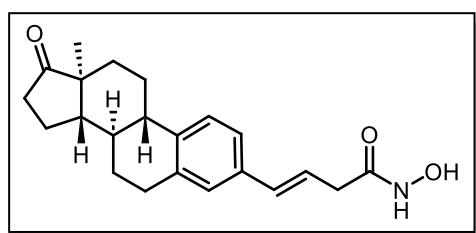
(E)-*N*-Hydroxy-4-[(8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl]but-3-enamide



To a microwave vial (30 mL) equipped with a magnetic stir bar were added aryl triflate (1.6 mmol, 1.0 equiv.), but-3-enoic acid (2.0 equiv.), Pd[P(*t*-Bu)₃]₂ (5.0 mol%), Cs₂CO₃ (2.0 equiv.), and MeCN (0.5 M). The reaction mixture was heated in a microwave reactor at 120 °C for 30 min. After completion, the reaction mixture was diluted with EtOAc and quenched with 1.0 M HCl_(aq). The aqueous layer was extracted with EtOAc (20 mL × 3) and the combined organic layers were dried over anhydrous MgSO₄,

filtered, and concentrated under reduced pressure. Due to high polarity of the carboxylic acid, the crude was used for the next step without further purification.

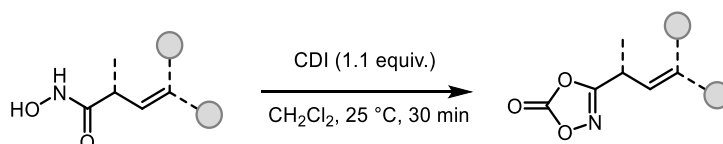
To a solution of carboxylic acid obtained from the previous step in dry tetrahydrofuran (0.33 M) was added 1,1'-carbonyldiimidazole (1.5 equiv.) under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h. While stirring, powdered hydroxylamine hydrochloride (2.0 equiv.) was added in one portion, and the resulting mixture was stirred at room temperature for additional 16 h. After completion, the mixture was diluted with 5% $\text{KHSO}_4(\text{aq})$ and extracted with EtOAc (2 times). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH} = 10:1$) to afford the desired hydroxamic acid.



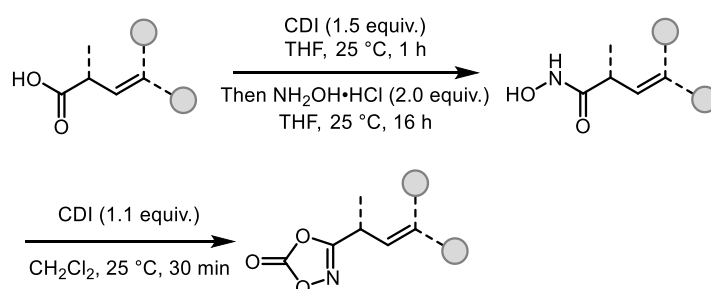
White solid (287 mg, 62%); **m.p.** = 181 – 183 °C; **^1H NMR** (500 MHz, $\text{THF}-d_8$) δ 9.90 (br. s, 1H), 9.26 (br. s, 1H), 7.19 (d, $J = 8.0$ Hz, 1H), 7.10 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.06 (d, $J = 2.0$ Hz, 1H), 6.40 (d, $J = 15.5$ Hz, 1H), 6.26 (dt, $J = 15.5, 7.0$ Hz, 1H), 2.94 (d, $J = 7.0$ Hz, 2H), 2.86 – 2.83 (m, 2H), 2.46 – 2.43 (m, 2H), 2.38 – 2.34 (m, 1H), 2.26 (td, $J = 11.0, 4.0$ Hz, 1H), 2.04 – 1.93 (m, 2H), 1.89 – 1.84 (m, 1H), 1.59 – 1.32 (m, 6H), 0.90 (s, 3H); **^{13}C NMR** (101 MHz, $\text{THF}-d_8$) δ 218.4, 167.9, 140.1, 137.3, 135.9, 133.5, 127.6, 126.3, 124.6, 123.5, 51.6, 48.5, 45.8, 39.5, 38.1, 36.2, 33.0, 30.4, 27.7, 26.8, 22.4, 14.2; **IR** (cm^{-1}) 3232, 2920, 2858, 1642, 1433, 1023, 968; **High Resolution MS** (ESI): Calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_3$ $[\text{M}-\text{H}]^-$: 352.1918, Found: 352.1911.

Preparation of 1,4,2-dioxazol-5-ones

The following 1,4,2-dioxazol-5-ones were prepared according to literature methods: 3-cinnamyl-1,4,2-dioxazol-5-one (**1**)², (*E*)-3-(4-phenylbut-3-en-1-yl)-1,4,2-dioxazol-5-one (**3**)³, (*E*)-3-(5-phenylpent-4-en-1-yl)-1,4,2-dioxazol-5-one (**5**)³, (*Z*)-3-(3-phenylallyl)-1,4,2-dioxazol-5-one², (*E*)-3-(3-phenylbut-2-en-1-yl)-1,4,2-dioxazol-5-one⁴, 3-[3-[(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-ylidene}propyl]-1,4,2-dioxazol-5-one⁴, (*E*)-3-(3-(*p*-tolyl)allyl)-1,4,2-dioxazol-5-one², (*E*)-3-(3-(4-methoxyphenyl)allyl)-1,4,2-dioxazol-5-one², (*E*)-3-(3-(4-bromophenyl)allyl)-1,4,2-dioxazol-5-one², (*E*)-3-(3-(*m*-tolyl)allyl)-1,4,2-dioxazol-5-one², (*E*)-3-(3-(2-methoxyphenyl)allyl)-1,4,2-dioxazol-5-one², (*E*)-3-(3-(3-methoxyphenyl)allyl)-1,4,2-dioxazol-5-one², (*E*)-3-(3-(naphthalen-2-yl)allyl)-1,4,2-dioxazol-5-one², (*E*)-3-(3-(furan-3-yl)allyl)-1,4,2-dioxazol-5-one², 3-(3-methylbut-2-en-1-yl)-1,4,2-dioxazol-5-one⁴, 3-(2-cyclopentylideneethyl)-1,4,2-dioxazol-5-one, 3-(2-cyclohexylideneethyl)-1,4,2-dioxazol-5-one⁴, *tert*-butyl 4-(2-(5-oxo-1,4,2-dioxazol-3-yl)ethylidene)piperidine-1-carboxylate⁴, and (*E*)-3-(3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)but-2-en-1-yl)-1,4,2-dioxazol-5-one⁴.



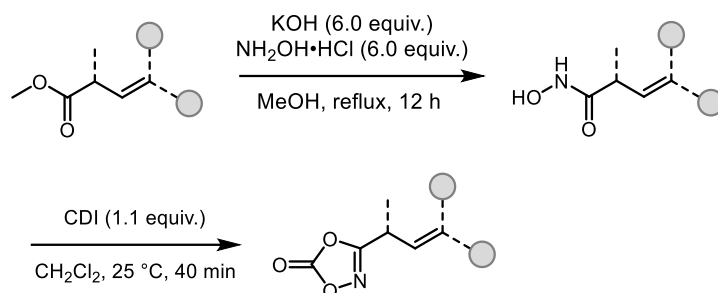
General Procedure SM-G: To a solution of hydroxamic acid (1.0 equiv.) in CH₂Cl₂ (0.1 M) was added 1,1'-carbonyldiimidazole (CDI, 1.1 equiv.) in one portion. After stirring at room temperature for 40 min, the reaction mixture was quenched with 1.0 M HCl_(aq) (20 mL), extracted with CH₂Cl₂ three times, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was filtered through a pad of silica and washed with CH₂Cl₂. The filtrate was concentrated under reduced pressure to afford the corresponding 1,4,2-dioxazol-5-ones.



General Procedure SM-H: To a solution of carboxylic acid (1.0 equiv.) in dry tetrahydrofuran (0.33 M) was added 1,1'-carbonyldiimidazole (1.5 equiv.) under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h. While stirring, powdered hydroxylamine hydrochloride (2.0 equiv.) was added in one portion, and the resulting mixture was stirred at room temperature for additional 16 h. After completion, the mixture was diluted with 5% KHSO_{4(aq)} and extracted with EtOAc (2 times).

The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude mixture was used for the next step without further purification.

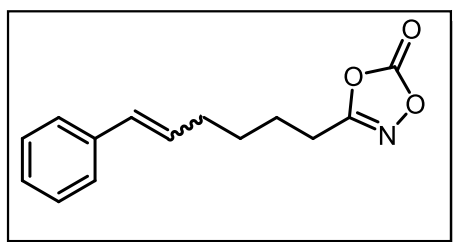
To a solution of the crude hydroxamic acid (1.0 equiv.) in CH_2Cl_2 (0.1 M) was added 1,1'-carbonyldiimidazole (CDI, 1.1 equiv.) in one portion. After stirring at room temperature for 40 min, the reaction mixture was quenched with 1.0 M $\text{HCl}_{(\text{aq})}$ (20 mL), extracted with CH_2Cl_2 three times, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude mixture was filtered through a pad of silica and washed with CH_2Cl_2 . The filtrate was concentrated under reduced pressure to afford the corresponding 1,4,2-dioxazol-5-ones.



General Procedure SM-I: To a solution of ester (1.0 equiv) in MeOH (0.2 M) were added KOH (6.0 equiv.) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (6.0 equiv.). The reaction mixture was refluxed for 12 h. After completion, the mixture was cooled to room temperature, concentrated under reduced pressure, diluted with EtOAc, quenched with 1.0 M $\text{HCl}_{(\text{aq})}$ (30 mL), and extracted with EtOAc (3×30 mL). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude hydroxamic acid was used for the next step without further purification.

To a solution of crude hydroxamic acid obtained from the previous step in CH_2Cl_2 (0.1 M) was added 1,1'-carbonyldiimidazole (CDI, 1.1 equiv) in one portion. After stirring at 25 °C for 40 min, the reaction mixture was quenched with 1.0 M $\text{HCl}_{(\text{aq})}$ (20 mL), extracted with CH_2Cl_2 (three times), dried over anhydrous MgSO_4 , filtered through a pad of silica, washed with CH_2Cl_2 , and concentrated under reduced pressure to afford the corresponding 1,4,2-dioxazol-5-ones.

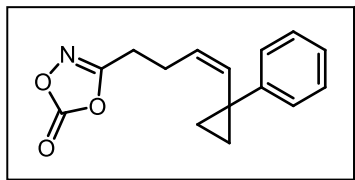
3-(6-Phenylhex-5-en-1-yl)-1,4,2-dioxazol-5-one, **12** (*E/Z* = 1.1:1 mixture)



General Procedure SM-H, in 17.0 mmol scale; Colourless oil (2.9 g, 70%, isolated as a 1.1:1 *E/Z* mixture); ^1H NMR (600 MHz, CDCl_3) δ 7.16 – 7.12 (m, 2H), 7.09 (t, J = 7.5 Hz, 1H), 7.07 – 7.03 (m, 1.4H), 7.00 (t, J = 7.5 Hz, 0.6H), 6.27 (d, J = 11.5 Hz, 0.48H), 6.20 (d, J = 16.0 Hz, 0.52H), 5.97 (dt, J = 16.0, 7.5 Hz, 0.52H), 5.41 (dt, J = 11.5, 7.5 Hz, 0.48H), 2.43 (t, J = 7.5 Hz, 1.04H), 2.36 (t, J = 7.5 Hz, 0.96H), 2.18 (q, J = 7.5 Hz, 0.96H), 2.06 (q, J = 7.5 Hz, 1.04H), 1.60 – 1.50 (m, 2H), 1.41 – 1.32 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 166.7, 166.6, 154.3, 137.52, 137.46, 131.4, 130.9, 130.0, 129.4,

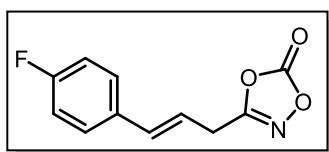
128.8, 128.6, 128.3, 127.2, 126.8, 126.1, 32.3, 28.9, 28.4, 27.8, 24.7, 24.6, 24.0; **IR** (cm⁻¹) 2934, 1827, 1634, 1493, 1357, 1151, 982; **High Resolution MS** (ESI): Calculated for C₁₄H₁₅NO₃Na [M+Na]⁺: 268.0944, Found: 268.0951.

(Z)-3-[4-(1-phenylcyclopropyl)but-3-en-1-yl]-1,4,2-dioxazol-5-one, 18



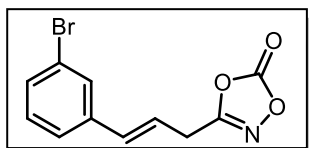
General Procedure SM-H, in 2.3 mmol scale; Colourless oil (378 mg, 63%); **¹H NMR** (500 MHz, CDCl₃) δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 5.79 (d, *J* = 10.5 Hz, 1H), 5.44 (dt, *J* = 10.5, 7.5 Hz, 1H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.37 (q, *J* = 7.5 Hz, 2H), 1.17 (q, *J* = 4.5 Hz, 2H), 0.99 (q, *J* = 4.5 Hz, 2H); **¹³C NMR** (126 MHz, CDCl₃) δ 166.2, 154.2, 144.7, 137.1, 128.9, 128.6, 126.9, 126.0, 24.5, 23.7, 23.5, 17.4; **IR** (cm⁻¹) 3008, 1867, 1825, 1636, 1495, 1362, 1146, 981; **High Resolution MS** (EI): Calculated for C₁₅H₁₅NO₃ [M]⁺: 257.1052, Found: 257.1050.

(E)-3-[3-(4-Fluorophenyl)allyl]-1,4,2-dioxazol-5-one



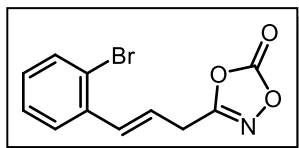
General Procedure SM-G, in 3.4 mmol scale; White solid (170 mg, 23%); **m.p.** = 58 – 60 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.35 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.03 (t, *J* = 8.5 Hz, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.07 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.55 (d, *J* = 7.0 Hz, 2H); **¹³C NMR** (126 MHz, CDCl₃) δ 165.1, 162.9 (d, *J*_{C-F} = 249.0 Hz), 154.1, 136.0, 132.0, 128.3 (d, *J*_{C-F} = 8.0 Hz), 116.9 (d, *J*_{C-F} = 2.5 Hz), 115.9 (d, *J*_{C-F} = 22.0 Hz), 28.5; **¹⁹F NMR** (471 MHz, CDCl₃) δ -112.9; **IR** (cm⁻¹) 3041, 2902, 1909, 1826, 1509, 1380, 1225, 1155, 965, 755; **High Resolution MS** (EI): Calculated for C₁₁H₈FNO₃ [M]⁺: 221.0488, Found: 221.0486.

(E)-3-[3-(3-Bromophenyl)allyl]-1,4,2-dioxazol-5-one



General Procedure SM-H, in 5.4 mmol scale; White solid (1.02 g, 67%); **m.p.** = 57 – 60 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.53 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 15.5 Hz, 1H), 6.16 (dt, *J* = 15.5, 7.0 Hz, 1H), 3.56 (d, *J* = 7.0 Hz, 2H); **¹³C NMR** (126 MHz, CDCl₃) δ 164.9, 154.0, 137.8, 135.3, 131.5, 130.4, 129.6, 125.3, 123.1, 118.8, 28.5; **IR** (cm⁻¹) 3013, 2905, 1826, 1631, 1562, 1376, 1232, 1151, 960, 756, 673; **High Resolution MS** (EI): Calculated for C₁₁H₈BrNO₃ [M]⁺: 280.9688, Found: 280.9686.

(E)-3-[3-(2-Bromophenyl)allyl]-1,4,2-dioxazol-5-one

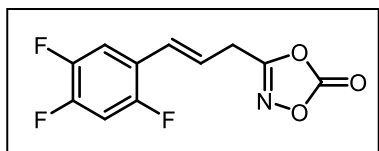


General Procedure SM-G, in 1.7 mmol scale; White solid (410 mg, 97%);

m.p. = 55 – 57 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 15.5 Hz, 1H), 6.10 (dt, *J* = 15.5, 7.5 Hz, 1H), 3.60 (d, *J* = 7.5

Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 165.0, 154.0, 135.7, 135.5, 133.1, 129.8, 127.8, 127.3, 123.7, 120.1, 28.6; **IR** (cm⁻¹) 3061, 2899, 1823, 1632, 1367, 1230, 1153, 963; **High Resolution MS** (EI): Calculated for C₁₁H₈BrNO₃ [M]⁺: 280.9688, Found: 280.9684.

(E)-3-[3-(2,4,5-Trifluorophenyl)allyl]-1,4,2-dioxazol-5-one



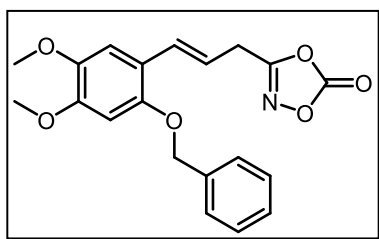
General Procedure SM-G, in 1.7 mmol scale; White solid (369 mg,

85%); **m.p.** = 101 – 102 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.28 – 7.20 (m, 1H), 6.94 (td, *J* = 10.0, 6.5 Hz, 1H), 6.71 (dd, *J* = 16.0, 1.5 Hz, 1H), 6.18 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.58 (dd, *J* = 7.0, 1.5 Hz,

2H); **¹³C NMR** (126 MHz, CDCl₃) δ 164.7, 155.4 (d, *J*_{C-F} = 250.0 Hz), 153.9, 150.0 (dd, *J*_{C-F} = 253.5, 14.0 Hz), 147.2 (dd, *J*_{C-F} = 245.0, 14.0 Hz), 127.6, 120.8, 120.1 (dt, *J*_{C-F} = 14.0, 5.0 Hz), 115.0 (d, *J*_{C-F} = 20.0 Hz), 106.2 (dd, *J*_{C-F} = 28.0, 21.0 Hz), 28.8; **¹⁹F NMR** (376 MHz, CDCl₃) δ -118.9 (dd, *J* = 14.5, 4.5 Hz), -132.6 (dd, *J* = 21.0, 4.5 Hz), -142.1 (dd, *J* = 21.0, 14.5 Hz); **IR** (cm⁻¹) 3066, 2926, 2875, 1826, 1630, 1515, 1427, 1229, 1151, 973, 851, 759; **High Resolution MS** (EI): Calculated for C₁₁H₆F₃NO₃ [M]⁺: 257.0300, Found: 257.0296.

Note: This compound was found to be unstable on silica, hence, no silica filtration was conducted after work-up with HCl_(aq).

(E)-3-[3-[2-(Benzyloxy)-4,5-dimethoxyphenyl]allyl]-1,4,2-dioxazol-5-one, 55

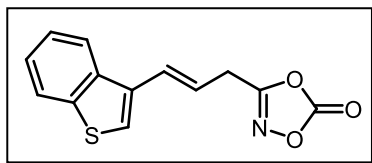


General Procedure SM-G, in 6.7 mmol scale; White solid (2.1 g, 86%); **m.p.** = 58 – 60 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.43 – 7.38

(m, 4H), 7.37 – 7.32 (m, 1H), 6.94 (d, *J* = 16.0 Hz, 1H), 6.92 (s, 1H), 6.54 (s, 1H), 6.03 (dt, *J* = 16.0, 7.0 Hz, 1H), 5.06 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.52 (d, *J* = 7.0 Hz, 2H); **¹³C NMR** (126 MHz, CDCl₃) δ 165.5, 154.2, 150.8, 150.2, 143.9, 137.0, 131.2, 128.8,

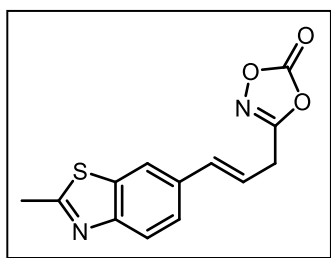
128.3, 127.7, 117.2, 115.3, 109.8, 99.6, 72.1, 56.6, 56.2, 29.0; **IR** (cm⁻¹) 2941, 1827, 1643, 1511, 1452, 1192, 970; **High Resolution MS** (EI): Calculated for C₂₀H₁₉NO₆ [M]⁺: 369.1212, Found: 369.1214.

(E)-3-[3-(Benzo[b]thiophen-3-yl)allyl]-1,4,2-dioxazol-5-one



General Procedure SM-G, in 3.4 mmol scale; Pale yellow solid (510 mg, 58%); **m.p.** = 65 – 66 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.49 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 16.0 Hz, 1H), 6.23 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.62 (d, *J* = 7.0 Hz, 2H); **¹³C NMR** (126 MHz, CDCl₃) δ 165.1, 154.1, 140.6, 137.3, 132.5, 129.2, 124.9, 124.7, 123.7, 123.2, 121.9, 118.7, 28.9; **IR** (cm⁻¹) 3069, 1825, 1627, 1408, 1353, 1232, 1149, 963, 754; **High Resolution MS** (EI): Calculated for C₁₃H₉NO₃S [M]⁺: 259.0303, Found: 259.0305.

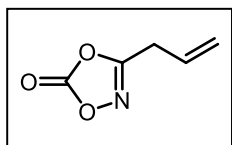
(E)-3-[3-(2-Methylbenzo[d]thiazol-6-yl)allyl]-1,4,2-dioxazol-5-one



General Procedure SM-H, in 0.95 mmol scale; White solid (118 mg, 45%); **m.p.** = 82 – 83 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 1H), 7.48 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.75 (d, *J* = 15.5 Hz, 1H), 6.19 (dt, *J* = 15.5, 7.0 Hz, 1H), 3.59 (d, *J* = 7.0 Hz, 2H), 2.83 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 168.0, 165.1, 154.1, 153.6, 136.5, 136.2, 132.6, 124.6, 122.6, 119.7, 117.5, 28.6, 20.4; **IR** (cm⁻¹)

2921, 1829, 1631, 1521, 1375, 1233, 1159, 971, 757; **High Resolution MS** (EI): Calculated for C₁₃H₁₀N₂O₃S [M]⁺: 274.0412, Found: 274.0414.

3-Allyl-1,4,2-dioxazol-5-one

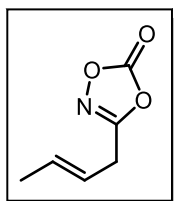


General Procedure SM-H, in 30.0 mmol scale; Colourless oil (360 mg, 10%); **¹H NMR** (500 MHz, CDCl₃) δ 5.86 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H), 5.45 – 5.36 (m, 2H), 3.42 (dt, *J* = 6.5, 1.5 Hz, 2H); **¹³C NMR** (126 MHz, CDCl₃) δ 165.1, 154.1, 126.4, 122.0, 29.3; **IR** (cm⁻¹) 2927, 1829, 1734, 1634, 1419, 1360, 1239,

985, 761; **High Resolution MS** (ESI): Calculated for C₅H₆NO₃ [M+H]⁺: 128.0342, Found: 128.0336.

Note: The title compound was found to be volatile under reduced pressure.

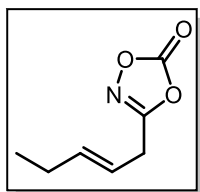
(E)-3-(But-2-en-1-yl)-1,4,2-dioxazol-5-one



General Procedure SM-H, in 1.0 mmol scale; Colourless oil (96 mg, 68%); **¹H NMR** (400 MHz, CDCl₃) δ 5.79 (dq, *J* = 13.5, 6.5 Hz, 1H), 5.45 (dt, *J* = 13.5, 6.5 Hz, 1H), 3.32 (d, *J* = 6.5 Hz, 2H), 1.74 (d, *J* = 6.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 165.7, 154.3, 133.3, 118.9, 28.3, 18.0; **IR** (cm⁻¹) 3035, 2970, 2922, 1825, 1638, 1350, 1148, 980, 761; **High Resolution MS** (EI): Calculated for C₆H₇NO₃ [M]⁺: 141.0426,

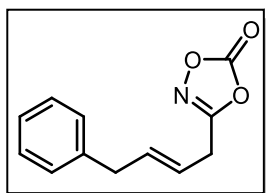
Found: 141.0423.

(E)-3-(Pent-2-en-1-yl)-1,4,2-dioxazol-5-one



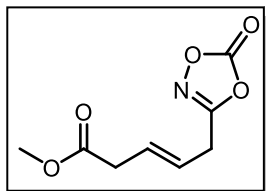
General Procedure SM-G, in 3.1 mmol scale; Colourless oil (140 mg, 30%); ^1H NMR (500 MHz, CDCl_3) δ 5.81 (dt, $J = 14.5, 6.5$ Hz, 1H), 5.42 (dt, $J = 14.5, 6.5$ Hz, 1H), 3.33 (d, $J = 6.5$ Hz, 2H), 2.09 (p, $J = 7.5$ Hz, 2H), 1.01 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.7, 154.3, 140.0, 116.8, 28.3, 25.6, 13.2; **IR** (cm^{-1}) 2967, 2935, 2876, 1827, 1634, 1336, 1147, 980, 762; **High Resolution MS** (EI): Calculated for $\text{C}_7\text{H}_9\text{NO}_3$ $[\text{M}]^+$: 155.0582, Found: 155.0581.

(E)-3-(4-Phenylbut-2-en-1-yl)-1,4,2-dioxazol-5-one



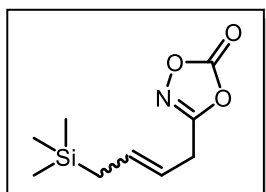
General Procedure SM-G, in 19.9 mmol scale; Colourless oil (3.43 g, 79%); ^1H NMR (400 MHz, CDCl_3) δ 7.32 (t, $J = 7.5$ Hz, 2H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.18 (d, $J = 7.5$ Hz, 2H), 5.95 (dt, $J = 14.5, 7.0$ Hz, 1H), 5.51 (dt, $J = 14.5, 7.0$ Hz, 1H), 3.42 (d, $J = 7.0$ Hz, 2H), 3.37 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.4, 154.2, 139.1, 137.0, 128.7, 128.7, 126.6, 119.1, 38.8, 28.2; **IR** (cm^{-1}) 3027, 2905, 1827, 1638, 1494, 1146, 979, 760; **High Resolution MS** (EI): Calculated for $\text{C}_{12}\text{H}_{11}\text{NO}_3$ $[\text{M}]^+$: 217.0739, Found: 217.0737.

Methyl (E)-5-(5-oxo-1,4,2-dioxazol-3-yl)pent-3-enoate



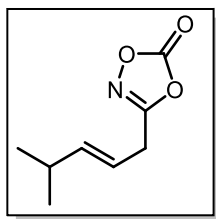
General Procedure SM-G, in 1.7 mmol scale; Colourless oil (240 mg, 71%); ^1H NMR (500 MHz, CDCl_3) δ 5.92 (dt, $J = 15.0, 7.0$ Hz, 1H), 5.60 (dt, $J = 15.0, 7.0$ Hz, 1H), 3.70 (s, 3H), 3.40 (d, $J = 7.0$ Hz, 2H), 3.14 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.4, 165.0, 154.0, 129.8, 121.9, 52.2, 37.5, 28.3; **IR** (cm^{-1}) 2956, 1828, 1732, 1634, 1149, 981, 761; **High Resolution MS** (ESI): Calculated for $\text{C}_7\text{H}_6\text{NO}_4$ $[\text{M}-\text{OCH}_3]^-$: 168.0302, Found: 168.0392.

3-[4-(Trimethylsilyl)but-2-en-1-yl]-1,4,2-dioxazol-5-one (E/Z = 1:1 mixture)



General Procedure SM-H, in 6.7 mmol scale; Pale yellow oil (1.1 g, 77%); ^1H NMR (500 MHz, CDCl_3) δ 5.84 – 5.71 (m, 1H), 5.37 – 5.30 (m, 0.5H), 5.27 – 5.17 (m, 0.5H), 3.34 (d, $J = 7.0$ Hz, 1H), 3.32 (d, $J = 7.0$ Hz, 1H), 1.56 (d, $J = 9.0$ Hz, 1H), 1.52 (d, $J = 8.5$ Hz, 1H), 0.04 (s, 4.5H), 0.01 (s, 4.5H); ^{13}C NMR (126 MHz, CDCl_3) δ 166.0, 165.7, 154.33, 154.28, 135.3, 133.6, 115.5, 114.0, 28.5, 23.4, 23.2, 19.4, -1.7, -1.9; **IR** (cm^{-1}) 2955, 1829, 1634, 1348, 1248, 1146, 981, 848; **High Resolution MS** (EI): Calculated for $\text{C}_9\text{H}_{15}\text{NO}_3\text{Si}$ $[\text{M}]^+$: 213.0821, Found: 213.0820.

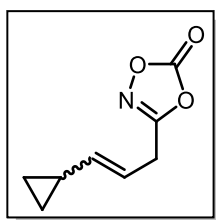
(E)-3-(4-Methylpent-2-en-1-yl)-1,4,2-dioxazol-5-one



General Procedure SM-H, in 15.6 mmol scale; Colourless oil (1.4 g, 53%); **¹H NMR** (400 MHz, CDCl₃) δ 5.73 (dd, *J* = 15.0, 6.5 Hz, 1H), 5.37 (dt, *J* = 15.0, 6.5 Hz, 1H), 3.31 (d, *J* = 6.5 Hz, 2H), 2.32 (h, *J* = 6.5 Hz, 1H), 1.00 (d, *J* = 6.5 Hz, 6H); **¹³C NMR** (126 MHz, CDCl₃) δ 165.7, 154.3, 145.3, 115.0, 31.2, 28.3, 22.0; **IR** (cm⁻¹) 2961, 2872, 1827, 1631, 1341, 1146, 972, 761; **High Resolution MS**

(EI): Calculated for C₈H₁₁NO₃ [M]⁺: 169.0739, Found: 169.0737.

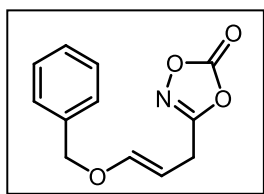
3-(3-Cyclopropylallyl)-1,4,2-dioxazol-5-one (*E/Z* = 1.2:1 mixture)



General Procedure SM-G, in 5.45 mmol scale; Colourless oil (747 mg, 82%); **¹H NMR** (500 MHz, CDCl₃) δ 5.47 (dt, *J* = 15.0, 7.0 Hz, 0.55H), 5.34 (dt, *J* = 10.5, 7.5 Hz, 0.45H), 5.26 (dd, *J* = 15.0, 9.0 Hz, 0.55H), 5.11 (t, *J* = 10.5 Hz, 0.45H), 3.51 (d, *J* = 7.5 Hz, 0.9H), 3.30 (d, *J* = 7.0 Hz, 1.1H), 1.53 – 1.46 (m, 0.45H), 0.86 – 0.81 (m, 0.55H), 0.85 – 0.82 (m, 0.9H), 0.77 – 0.71 (m, 1.1H), 0.46 – 0.37 (m,

2H); **¹³C NMR** (126 MHz, CDCl₃) δ 165.68, 165.65, 154.26, 154.23, 142.0, 141.1, 115.0, 114.6, 28.1, 23.7, 13.7, 9.9, 7.3, 6.9; **IR** (cm⁻¹) 3008, 1826, 1634, 1346, 1144, 981, 761; **High Resolution MS** (EI): Calculated for C₈H₉NO₃ [M]⁺: 167.0582, Found: 167.0580.

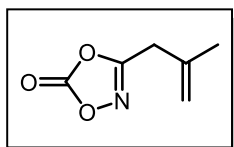
(E)-3-[3-(Benzyloxy)allyl]-1,4,2-dioxazol-5-one



General Procedure SM-G, in 4.0 mmol scale; White solid (591 mg, 64%); **m.p.** = 59 – 60 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.39 – 7.31 (m, 5H), 6.59 (dt, *J* = 13.0, 1.0 Hz, 1H), 4.85 (dt, *J* = 13.0, 7.5 Hz, 1H), 4.79 (s, 2H), 3.27 (dd, *J* = 7.5, 1.0 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 165.9, 154.1, 151.0,

136.1, 128.7, 128.3, 127.6, 92.9, 71.6, 24.1; **IR** (cm⁻¹) 2911, 2879, 1828, 1659, 1453, 1348, 1223, 1158, 978, 730; **High Resolution MS** (EI): Calculated for C₁₂H₁₁NO₄ [M]⁺: 233.0688, Found: 233.0685.

3-(2-Methylallyl)-1,4,2-dioxazol-5-one

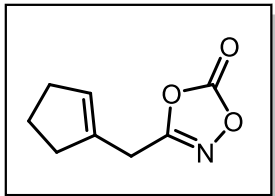


General Procedure SM-H, in 3.5 mmol scale; Colourless oil (133 mg, 27%); **¹H NMR** (400 MHz, CDCl₃) δ 5.07 (s, 1H), 4.99 (s, 1H), 3.32 (s, 2H), 1.84 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 164.9, 154.2, 135.3, 117.2, 33.4, 22.2; **IR** (cm⁻¹) 3107, 1830, 1633, 1422, 1348, 1145, 985; **High Resolution MS** (ESI):

Calculated for C₆H₈NO₃ [M+H]⁺: 142.0499, Found: 142.0498.

Note: The title compound contains some impurities that could not be removed by column chromatography (>90% purity).

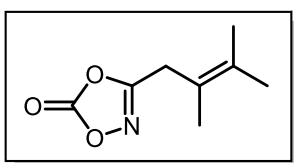
3-(Cyclopent-1-en-1-ylmethyl)-1,4,2-dioxazol-5-one



General Procedure SM-H, in 18.7 mmol scale; Colourless oil (710 mg, 67%); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.66 (s, 1H), 3.41 (s, 2H), 2.39 – 2.29 (m, 4H), 1.92 (p, $J = 7.5$ Hz, 2H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 165.1, 154.2, 133.1, 131.1, 34.9, 32.7, 27.0, 23.3; **IR** (cm^{-1}) 2956, 2851, 1826, 1632, 1374, 1334, 1145, 982; **High Resolution MS** (ESI): Calculated for $\text{C}_8\text{H}_{10}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 168.0655, Found: 168.0649.

Note: The title compound contains an inseparable α,β -unsaturated isomer (4:1) that could not be removed by column chromatography.

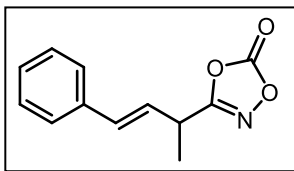
3-(2,3-Dimethylbut-2-en-1-yl)-1,4,2-dioxazol-5-one



General Procedure SM-H, in 1.6 mmol scale; Colourless oil (152 mg, 56%); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 3.34 (s, 2H), 1.75 (s, 3H), 1.74 (s, 3H), 1.73 (s, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 165.5, 154.4, 132.4, 117.3, 30.0, 21.0, 20.8, 18.7; **IR** (cm^{-1}) 2921, 1827, 1629, 1343, 1147, 980;

High Resolution MS (ESI): Calculated for $\text{C}_8\text{H}_{11}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 192.0631, Found: 192.0633.

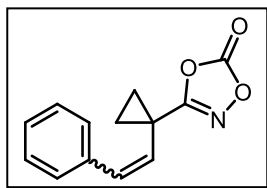
(E)-3-(4-Phenylbut-3-en-2-yl)-1,4,2-dioxazol-5-one



General Procedure SM-G, in 4.0 mmol scale; White solid (463 mg, 53%); **m.p.** = 44 – 46 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.40 – 7.27 (m, 5H), 6.63 (d, $J = 16.0$ Hz, 1H), 6.16 (dd, $J = 16.0, 7.5$ Hz, 1H), 3.70 (p, $J = 7.5$ Hz, 1H), 1.54 (d, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 168.4,

154.3, 135.8, 134.3, 128.9, 128.6, 126.7, 124.4, 34.7, 16.6; **IR** (cm^{-1}) 3029, 2988, 1819, 1619, 1450, 1255, 1035, 968, 749; **High Resolution MS** (EI): Calculated for $\text{C}_{12}\text{H}_{11}\text{NO}_3$ $[\text{M}]^+$: 217.0739, Found: 217.0736.

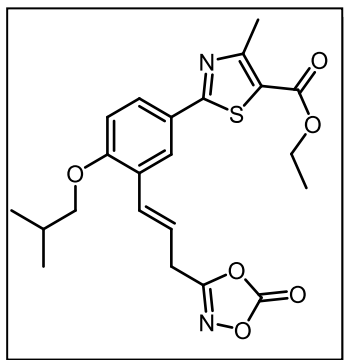
3-(1-Styrylcyclopropyl)-1,4,2-dioxazol-5-one



General Procedure SM-I, in 6.0 mmol scale; isolated as a *E/Z* mixture; Colourless oil (927 mg, 67%); the major isomer was separated for the structure characterization by NMR spectroscopy: ^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.27 (m, 5H), 6.76 (d, J = 11.0 Hz, 1H), 5.77 (d, J = 11.0 Hz, 1H), 1.53 – 1.49 (m, 2H), 1.13 – 1.08 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.5, 154.1, 136.6, 135.4, 128.9, 128.4, 128.2, 123.9, 18.3, 16.4; IR (cm^{-1}) 3025, 1831, 1611, 1381, 1195, 1113, 977, 762, 697; **High Resolution MS** (EI): Calculated for $\text{C}_{13}\text{H}_{11}\text{NO}_3$ $[\text{M}]^+$: 229.0739, Found: 229.0736.

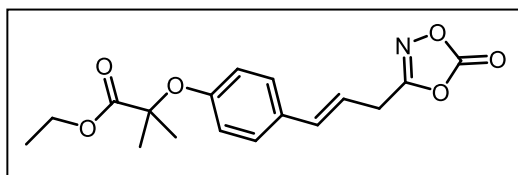
Note: The structure confirmation through NMR analysis of the E/Z mixture was difficult due to the significant overlapping of peaks. Despite the instability of the title compound on silica gel, the major isomer could still be isolated in a reasonable amount by column chromatography (~90% purity). While the separated major isomer was used for the NMR analysis, the main hydroamidation reaction was yet performed using the E/Z mixture without any purification due to its instability on silica.

Ethyl (E)-2-{4-isobutoxy-3-[3-(5-oxo-1,4,2-dioxazol-3-yl)prop-1-en-1-yl]phenyl}-4-methylthiazole-5-carboxylate



General Procedure SM-G, in 0.54 mmol scale; Yellow solid (146 mg, 61%); **m.p.** = 96 – 97 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, J = 2.5 Hz, 1H), 7.82 (dd, J = 8.5, 2.5 Hz, 1H), 6.96 (dd, J = 16.0, 1.5 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.33 (dt, J = 16.0, 7.0 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H), 3.82 (d, J = 6.5 Hz, 2H), 3.59 (dd, J = 7.0, 1.5 Hz, 2H), 2.76 (s, 3H), 2.16 (hept, J = 6.5 Hz, 1H), 1.38 (t, J = 7.0 Hz, 3H), 1.06 (d, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.6, 165.2, 162.4, 161.1, 158.7, 154.1, 130.9, 128.2, 125.84, 125.75, 125.4, 121.1, 119.1, 112.2, 75.1, 61.3, 29.0, 28.4, 19.4, 17.6, 14.5; IR (cm^{-1}) 2928, 2876, 1829, 1700, 1431, 1252, 1100, 961; **High Resolution MS** (EI): Calculated for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_6\text{S}$ $[\text{M}]^+$: 444.1355, Found: 444.1358.

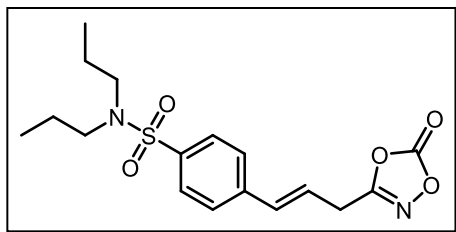
Ethyl (E)-2-methyl-2-{4-[3-(5-oxo-1,4,2-dioxazol-3-yl)prop-1-en-1-yl]phenoxy}propanoate



General Procedure SM-G, in 2.7 mmol scale; Pale yellow oil (610 mg, 68%); ^1H NMR (400 MHz, CDCl_3) δ 7.25 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.58 (dd, J = 16.0, 1.5 Hz, 1H), 6.00 (dt, J = 16.0, 7.0 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 3.52 (dd, J = 7.0, 1.5 Hz, 2H), 1.60 (s, 6H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.3, 165.3, 155.9, 154.1, 136.1, 129.7, 127.6, 119.1, 115.4, 79.4, 61.7,

28.6, 25.5, 14.2; **IR** (cm⁻¹) 2987, 2940, 1829, 1729, 1508, 1234, 1139, 981; **High Resolution MS** (EI): Calculated for C₁₇H₁₉NO₆ [M]⁺: 333.1212, Found: 333.1209.

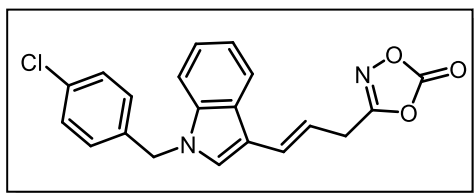
(E)-4-[3-(5-Oxo-1,4,2-dioxazol-3-yl)prop-1-en-1-yl]-N,N-dipropylbenzenesulfonamide



General Procedure SM-G, in 1.32 mmol scale; Pale yellow oil (382 mg, 79%); ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.60 (d, *J* = 7.0, 2H), 3.08 (t, *J* = 7.5 Hz, 4H), 1.57 – 1.52 (m, 4H), 0.87 (t, *J* = 7.5

Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 164.8, 153.9, 140.0, 139.5, 135.3, 127.7, 127.1, 120.4, 50.1, 28.6, 22.1, 11.3; **IR** (cm⁻¹) 2967, 2935, 1829, 1634, 1330, 1148, 1090, 981; **High Resolution MS** (EI): Calculated for C₁₇H₂₂N₂O₅S [M]⁺: 366.1249, Found: 366.1252.

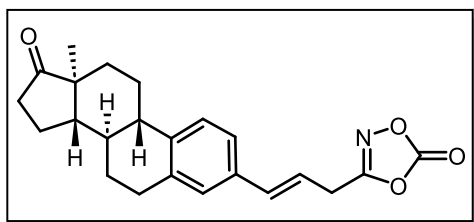
(E)-3-{3-[1-(4-Chlorobenzyl)-1H-indol-3-yl]allyl}-1,4,2-dioxazol-5-one



General Procedure SM-G, in 0.29 mmol scale; Pale yellow oil (90 mg, 85%); ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 7.0 Hz, 1H), 7.31 – 7.14 (m, 6H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 15.5 Hz, 1H), 6.09 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.25 (s, 2H), 3.55 (d, *J* = 7.0 Hz, 2H); ¹³C NMR (101 MHz,

CDCl₃) δ 165.7, 154.3, 137.2, 135.4, 133.8, 129.23, 129.19, 128.3, 128.1, 126.2, 122.9, 120.8, 120.2, 113.3, 113.2, 110.2, 49.6, 29.1; **IR** (cm⁻¹) 3051, 2926, 1827, 1634, 1466, 1349, 1147, 980, 734; **High Resolution MS** (EI): Calculated for C₂₀H₁₅ClN₂O₃ [M]⁺: 366.0771, Found: 366.0773.

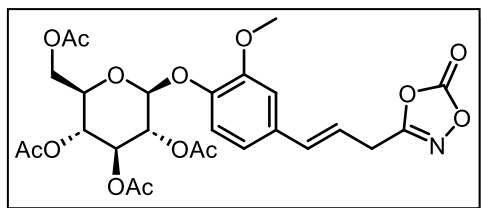
3-[(E)-3-[(8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl]allyl]-1,4,2-dioxazol-5-one



General Procedure SM-G, in 0.57 mmol scale; Pale yellow solid (104 mg, 48%); **m.p.** = 135 – 136 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.27 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.11 (s, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.10 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.54 (d, *J* = 7.0 Hz, 2H), 2.91 (dd, *J* = 9.0,

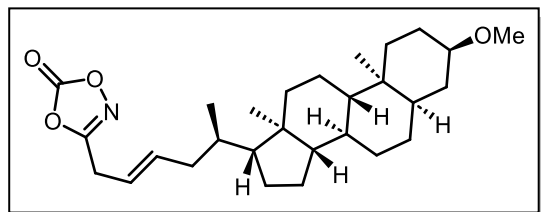
4.0 Hz, 2H), 2.51 (dd, *J* = 19.0, 8.5 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.34 – 2.25 (m, 1H), 2.20 – 1.94 (m, 4H), 1.69 – 1.40 (m, 6H), 0.91 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 220.9, 165.3, 154.1, 140.5, 137.0, 136.4, 133.4, 127.2, 125.9, 124.0, 116.4, 50.6, 48.1, 44.5, 38.2, 36.0, 31.7, 29.5, 28.6, 26.5, 25.8, 21.7, 13.9; **IR** (cm⁻¹) 2924, 2858, 1816, 1736, 1645, 1371, 1298, 1160, 981, 759; **High Resolution MS** (EI): Calculated for C₂₃H₂₅NO₄ [M]⁺: 379.1784, Found: 379.1781.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-{2-methoxy-4-[(*E*)-3-(5-oxo-1,4,2-dioxazol-3-yl)prop-1-en-1-yl]phenoxy}tetrahydro-2*H*-pyran-3,4,5-triyl triacetate



General Procedure SM-H, in 2.9 mmol scale; White solid (176 mg, 10%); **m.p.** = 51 – 52 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.05 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.57 (dt, *J* = 16.0, 1.5 Hz, 1H), 6.03 (dt, *J* = 16.0, 7.0 Hz, 1H), 5.31 – 5.19 (m, 2H), 5.19 – 5.07 (m, 1H), 4.99 – 4.89 (m, 1H), 4.25 (dd, *J* = 12.0, 5.0 Hz, 1H), 4.14 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.81 (s, 3H), 3.76 (ddt, *J* = 10.0, 5.0, 2.5 Hz, 1H), 3.52 (dd, *J* = 7.0, 1.5 Hz, 2H), 2.05 (s, 6H), 2.013 (s, 3H), 2.009 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 170.6, 170.3, 169.5, 169.4, 165.1, 154.0, 150.8, 146.4, 135.9, 132.5, 120.0, 119.6, 116.7, 110.4, 100.7, 72.6, 72.1, 71.2, 68.4, 62.0, 56.1, 28.4, 20.76, 20.69, 20.68, 20.64; **IR** (cm⁻¹) 2948, 2889, 1845, 1749, 1627, 1510, 1365, 1210, 1031, 980; **High Resolution MS** (ESI): Calculated for C₂₆H₂₉NNaO₁₄ [M+Na]⁺: 602.1480, Found: 602.1469.

3-[(*R,E*)-5-[(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Methoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]hex-2-en-1-yl]-1,4,2-dioxazol-5-one



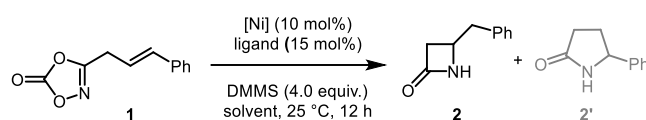
General procedure SM-H, in 3.0 mmol scale; White solid (810 mg, 59%); **m.p.** = 103 – 105 °C; **¹H NMR** (500 MHz, CDCl₃) δ 5.74 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.41 (dt, *J* = 15.0, 7.0 Hz, 1H), 3.36 (d, *J* = 4.0 Hz, 2H), 3.355 (s, 3H), 3.17 (tt, *J* = 11.0, 4.5 Hz, 1H), 2.19 (dt, *J* = 14.5, 4.0 Hz, 1H), 1.95 (dt, *J* = 12.5, 3.0 Hz, 1H), 1.90 – 1.74 (m, 5H), 1.71 – 1.66 (m, 1H), 1.64 – 1.54 (m, 2H), 1.52 – 1.33 (m, 7H), 1.32 – 1.18 (m, 4H), 1.17 – 1.01 (m, 5H), 0.93 (s, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.66 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 165.7, 154.2, 137.1, 118.8, 80.5, 56.5, 56.0, 55.6, 42.8, 42.1, 40.4, 40.2, 39.2, 35.9 (2 × carbon peaks overlapping), 35.4, 35.0, 32.9, 28.41, 28.38, 27.4, 26.9, 26.5, 24.3, 23.5, 20.9, 18.7, 12.2; **IR** (cm⁻¹) 2993, 2852, 1828, 1378, 1150, 1093, 975; **High Resolution MS** (EI): Calculated for C₂₈H₄₃NO₄ [M]⁺: 457.3192, Found: 457.3193.

Procedures for the Optimization Study

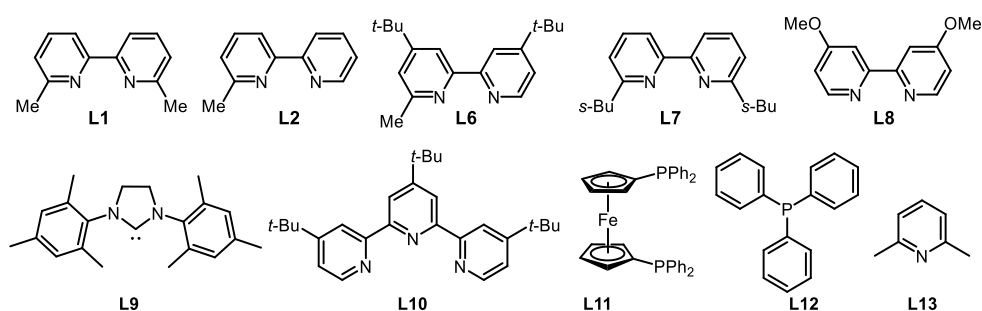
Optimization of conditions for the NiH-catalysed hydroamidation of alkenes to β -lactams

To a 4.0 mL vial equipped with a stir bar were added Ni (10.0 mol%), **ligand** (15.0 mol%), and anhydrous solvent (1.0 mL, 0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before 3-cinnamyl-1,4,2-dioxazol-5-one **1** (20.3 mg, 0.1 mmol, 1.0 equiv.) and dimethoxy(methyl)silane (DMMS, 50 μ L, 0.4 mmol, 4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at the indicated temperature for 12 h. After completion, the resulting mixture was filtered through a short pad of silica, washed by EtOAc (20 mL), and concentrated under reduced pressure. The yields of **2** and **2'** were determined by ^1H NMR of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard.

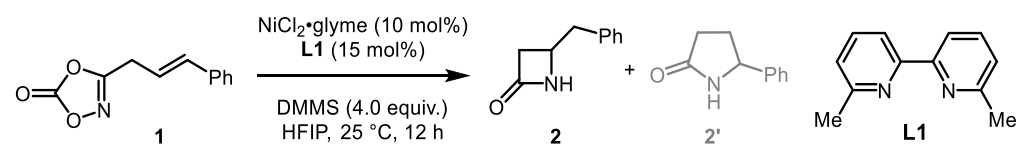
Supplementary Table 1. Ligand screening.



entry	Ligand	2 (%)	2' (%)
1	L1	90	<1
2	L2	49	<1
3	L6	49	<1
4	L7	30	<1
5	L8	<5	<1
6	L9	<1	<1
7	L10	<1	<1
8	L11	<1	<1
9	L12 , 20 mol%	<1	<1
10	L13 , 20 mol%	<1	<1

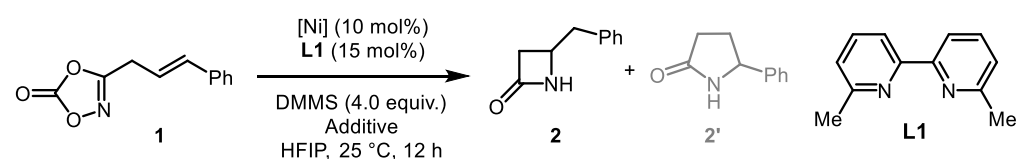


Supplementary Table 2. Screening of other parameters.



entry	variations from the above conditions	2 (%)	2' (%)
1	none	90	<1
2	using 2.0 equiv. of DMMS	45	<1
3	with H ₂ O (1.0 equiv.)	80	<1
4	DMA instead of HFIP, H ₂ O additive (1.0 equiv.)	45	<1
5	DMPU instead of HFIP, H ₂ O additive (1.0 equiv.)	36	trace
6	1,4-dioxane instead of HFIP, H ₂ O additive (1.0 equiv.)	52	12
7	Toluene instead of HFIP, H ₂ O additive (1.0 equiv.)	36	<1

Supplementary Table 3. Screening of Ni sources and additives.

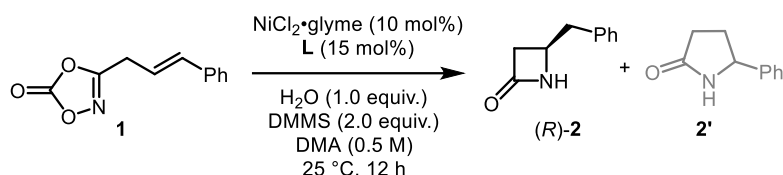


entry	$[\text{Ni}]$	Additive	2 (%)	2' (%)
1	NiBr_2	-	86	<1
2	$\text{Ni}(\text{OTf})_2$	-	<1	<1
3	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	-	5	<1
4	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	$(n\text{Bu})_4\text{NCl}$ (10 mol%)	94	4
5	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	$(n\text{Bu})_4\text{NCl}$ (1.0 equiv.)	93	3
6	$\text{Ni}(\text{COD})_2$	-	7	10
7	$\text{Ni}(\text{COD})_2$	$(n\text{Bu})_4\text{NCl}$ (1.0 equiv.)	51	2
8	$\text{Ni}(\text{COD})_2$	1.0 M HCl in MeOH (20 mol%)	40	6
9	$\text{Ni}(\text{COD})_2$	Et_4NBr (1.0 equiv.)	60	2
10	$\text{Ni}(\text{COD})_2$	$(n\text{Bu})_4\text{N}(\text{OAc})$ (1.0 equiv.)	<1	<1
11	$\text{Ni}(\text{acac})_2$	-	20	38
12	$\text{Ni}(\text{acac})_2$	$(n\text{Bu})_4\text{NCl}$ (10 mol%)	87	10
13	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	-	19	48

Optimization of conditions for the NiH-catalysed enantioselective hydroamidation leading to β -lactams

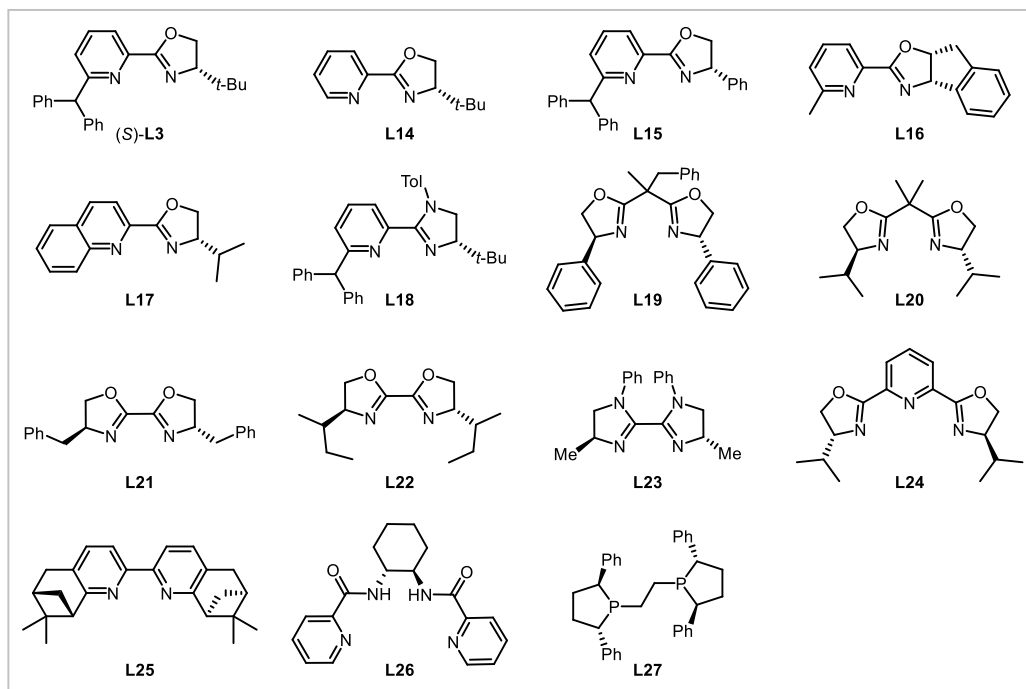
To a 4.0 mL vial equipped with a stir bar were added NiCl₂·glyme (2.2 mg, 10 mol%), ligand (15 mol%), and anhydrous solvent (0.2 mL, 0.5 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before 3-cinnamyl-1,4,2-dioxazol-5-one **1** (20.3 mg, 0.1 mmol, 1.0 equiv.), dimethoxy(methyl)silane (DMMS, indicated amount), and additives were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at the indicated temperature for 12 h. After completion, the resulting mixture was quenched with 1.0 M HCl_(aq) and extracted with *t*-BuOMe. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The yields of **2** and **2'** were determined by ¹H NMR of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard.

Supplementary Table 4. Initial ligand screening for the enantioselective reaction.

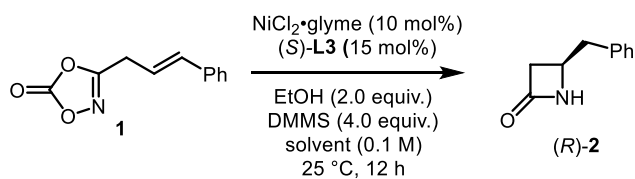


entry	Ligand	Yield of 2 (%)	e.r.	Yield of 2' (%)
1	(S)-L3	50%	91:9	<1
2	L14	<1	n.d.	<1
3	L15	34	65:35	<1
4	L16	2	n.d.	<1
5	L17	15	65:35	<1
6	L18	<1	n.d.	<1
7	L19	<1	n.d.	<1
8	L20	<1	n.d.	<1
9	L21	20	28:72	<1
10	L22	7	n.d.	2
11	L23	<1	n.d.	<1
12	L24	<1	n.d.	<1
13 ^a	L25	<1	n.d.	<1
14	L26	<1	n.d.	<1
15	L27	<1	n.d.	<1

^aUsing HFIP instead of DMA, without H₂O additive. n.d., not detected.



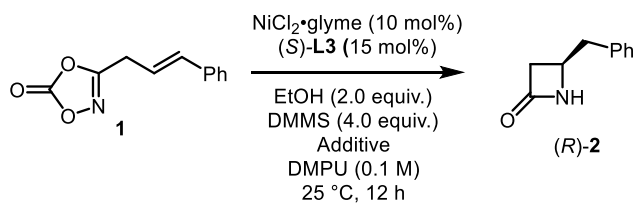
Supplementary Table 5. Solvent screening for the asymmetric hydroamidation.



entry	Solvent	Yield (%)	e.r.
1	HFIP	6	n.d.
2	DMPU	55	94:6
3	DMF	30	n.d.
4	MeCN	15	n.d.
5	THF	9	n.d.
6	1,4-dioxane	8	n.d.

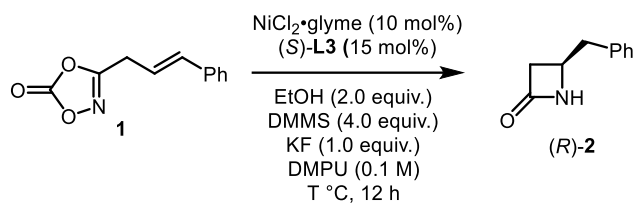
Notes: n.d. = not detected.

Supplementary Table 6. Additive screening.



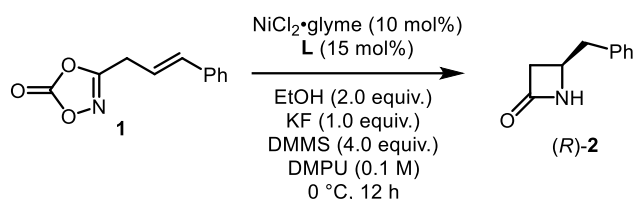
entry	Additives	Yield (%)	e.r.
1	K_3PO_4 (1.0 equiv.)	74	93:7
2	Cs_2CO_3 (1.0 equiv.)	72	94:6
3	KF (0.5 equiv.)	75	94:6
4	KF (1.0 equiv.)	82	93:7
5	KF (2.0 equiv.)	77	94:6
6	KF (1.0 equiv.) & no EtOH	19	94:6

Supplementary Table 7. Temperature screening.

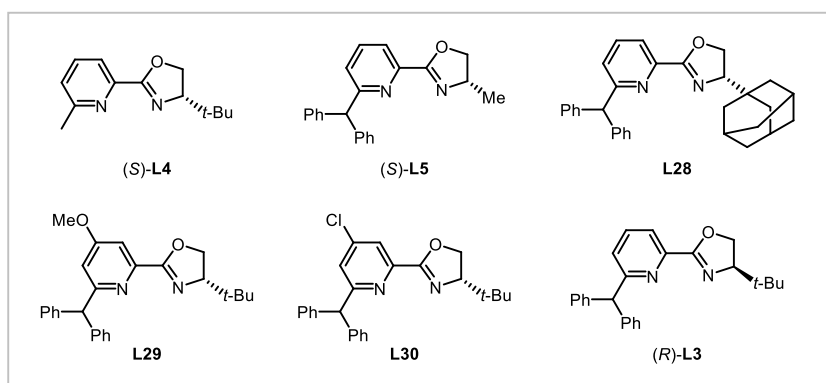


entry	Temperature	Yield (%)	e.r.
1	-10 °C	55	94:6
2	0 °C	88	94:6
3	25 °C	82	93:7
4	40 °C	68	93:7
5	60 °C	54	87:13

Supplementary Table 8. Further screening of ligands under optimized conditions.



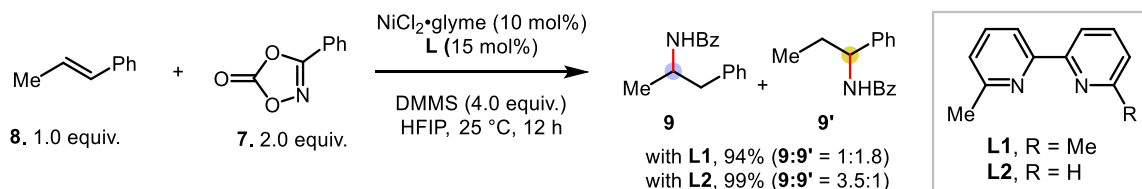
entry	Ligand	Yield (%)	e.r.
1	(S)- L4	40	83:17
2	(S)- L5	25	28:72
3	L15	34	65:35
4	L28	50	91:9
5	L29	80	96:4
6	L30	20	94:6
7	(R)- L3	84	6:94



The use of **L29** resulted in the highest e.r. for the formation of β -lactam **2**, however, the catalytic efficiency was generally lower in comparison to when (S)-**L3** was used. For this reason, (S)-**L3** was employed throughout the scope investigation and synthetic utility of the enantioselective hydroamidation. For the enantioselective reactions giving diminished yields, the major side products were found to be primary amides likely obtained via decomposition of the dioxazolone moiety. The use of alternative alcohol additives does not improve the reaction efficiency in these cases since the decomposition of dioxazolones is not associated with the product release step where alcohol is believed to play an essential role.

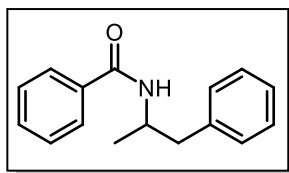
Experimental Mechanistic Studies

Intermolecular hydroamidation reaction between internal alkene and phenyl dioxazolone



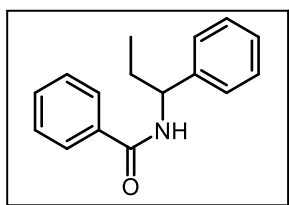
To a 4.0 mL vial equipped with a stir bar were added $\text{NiCl}_2\cdot\text{glyme}$ (2.2 mg, 10.0 mol%), ligand **L** (15.0 mol%), and anhydrous HFIP (1.0 mL, 0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before *trans*- β -methylstyrene **8** (13 μL , 0.1 mmol, 1.0 equiv.), phenyl-1,4,2-dioxazolone-5-one **7** (32.6 mg, 0.2 mmol, 2.0 equiv.), and DMMS (50 μL , 0.4 mmol, 4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at the indicated temperature for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure. The yields of **9** and **9'** were determined by ^1H NMR of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard, and each product was characterized after isolation by silica column chromatography.

N-(1-Phenylpropan-2-yl)benzamide, **9**



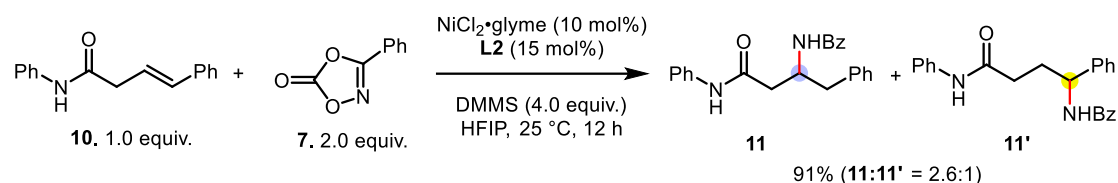
^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.26 – 7.21 (m, 3H), 5.90 (br. s, 1H), 4.48 (hept, J = 6.5 Hz, 1H), 2.95 (dd, J = 13.5, 5.5 Hz, 1H), 2.87 (dd, J = 13.5, 6.5 Hz, 1H), 1.23 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.8, 137.8, 134.8, 131.3, 129.5, 128.5, 128.4, 126.7, 126.5, 46.4, 42.3, 19.9; Data consistent with those reported in literature⁵.

N-(1-Phenylpropyl)benzamide, **9'**



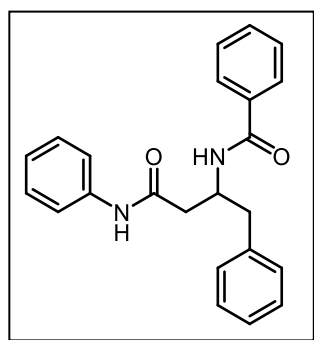
^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, J = 7.5 Hz, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.37 – 7.34 (m, 4H), 7.30 – 7.26 (m, 1H), 6.31 (br. s, 1H), 5.10 (q, J = 7.5 Hz, 1H), 2.03 – 1.89 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.0, 142.2, 134.8, 131.6, 128.8, 128.7, 127.5, 127.0, 126.8, 55.5, 29.1, 11.0; Data consistent with those reported in literature⁶.

Intermolecular hydroamidation reaction between internal alkene containing a directing group and phenyl dioxazolone



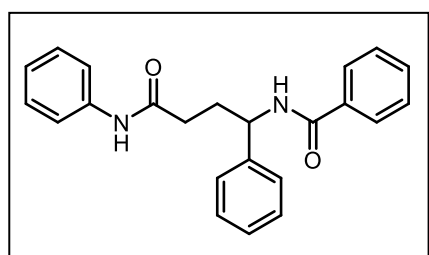
To a 4.0 mL vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (2.2 mg, 10.0 mol%), ligand **L2** (2.6 mg, 15.0 mol%), and anhydrous HFIP (1.0 mL, 0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before (*E*)-*N*,4-diphenylbut-3-enamide **10** (23.7 mg, 0.1 mmol, 1.0 equiv.), phenyl-1,4,2-dioxazol-5-one **7** (32.6 mg, 0.2 mmol, 2.0 equiv.), and DMMS (50 μL , 0.4 mmol, 4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at the indicated temperature for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure. The yields of **11** and **11'** were determined by ^1H NMR of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard, and each product was characterized after isolation by silica column chromatography.

N*-[4-Oxo-1-phenyl-4-(phenylamino)butan-2-yl]benzamide **11*



White solid, **m.p.** = 203 – 204 °C; ^1H NMR (500 MHz, THF-*d*8) δ 9.23 (br. s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.29 – 7.20 (m, 5H), 7.15 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 4.58 – 4.51 (m, 1H), 3.18 (dd, J = 13.5, 7.0 Hz, 1H), 2.99 (dd, J = 13.5, 7.5 Hz, 1H), 2.72 – 2.59 (m, 2H) (1 $\times$ NH peak not observed); ^{13}C NMR (126 MHz, THF-*d*8) δ 170.5, 167.1, 140.6, 140.4, 136.6, 131.7, 130.4, 129.4, 129.2, 129.1, 128.1, 127.1, 124.1, 120.3, 50.5, 40.7, 40.3; **IR** (cm^{-1}) 3289, 2918, 1664, 1531, 1443, 1313, 1067, 691; **High Resolution MS** (ESI): Calculated for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2\text{K}$ [$\text{M}+\text{K}$] $^+$: 397.1313, Found: 397.1321.

N*-[4-Oxo-1-phenyl-4-(phenylamino)butyl]benzamide **11'*

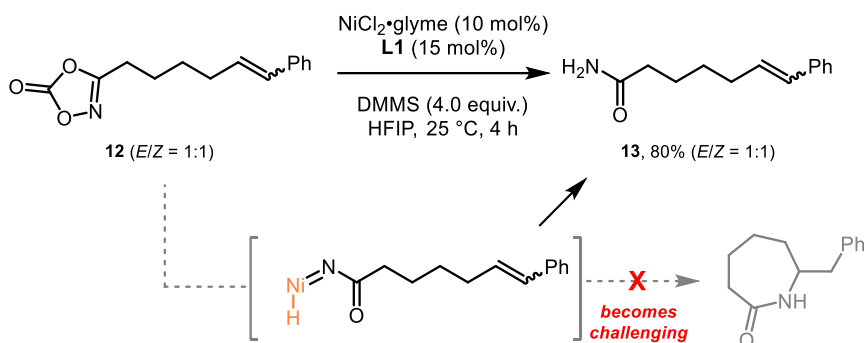


White solid, **m.p.** = 150 – 151 °C; ^1H NMR (400 MHz, THF-*d*8) δ 9.15 (br. s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 3H), 7.34 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.23 – 7.15 (m, 3H), 6.95 (t, J = 7.5 Hz, 1H), 5.25 (td, J = 8.5, 5.5 Hz, 1H), 2.45 – 2.42 (m, 2H), 2.34 – 2.18 (m, 2H); ^{13}C NMR (126 MHz, THF-*d*8) δ 171.7, 167.0, 144.6, 140.9, 136.3, 131.7, 129.4, 129.2, 128.9, 128.4, 127.76, 127.75, 123.8, 120.0,

54.3, 35.0, 32.3; **IR** (cm⁻¹) 3287, 3030, 1661, 1638, 1528, 1442, 1308, 691; High Resolution MS (ESI): Calculated for C₂₃H₂₂N₂O₂K [M+K]⁺: 397.1313, Found: 397.1327.

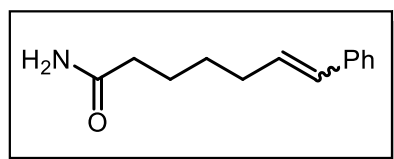
Note: The separation of the two isomers was proven difficult by silica column chromatography. Small fractions containing pure materials of each isomer were collected separately and used for the purpose of characterization.

Intramolecular hydroamidation of alkenyl dioxazolone with a longer carbon chain (**12**)



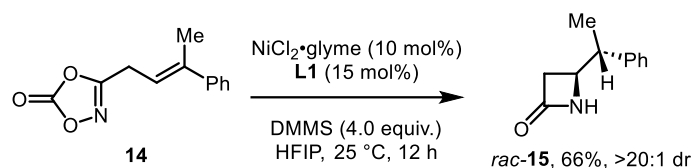
To a 4.0 mL vial equipped with a stir bar were added NiCl₂·glyme (2.2 mg, 10.0 mol%), ligand **L1** (2.8 mg, 15.0 mol%), and anhydrous HFIP (1.0 mL, 0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before 3-(6-phenylhex-5-en-1-yl)-1,4,2-dioxazol-5-one **12** (24.5 mg, 0.1 mmol, 1.0 equiv.) and DMMS (50 μL, 0.4 mmol, 4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at the indicated temperature for 4 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, concentrated under reduced pressure, and isolated after purification by silica column chromatography.

7-Phenylhept-6-enamide, 13 (*E/Z* = 1.1:1 mixture)



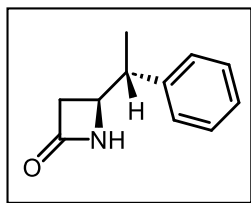
White solid (12.9 mg, 80%, *E/Z* = 1.1:1 mixture); **m.p.** = 65 – 66 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.16 (m, 5H), 6.42 (d, *J* = 11.5 Hz, 0.47H), 6.38 (d, *J* = 15.5 Hz, 0.53H), 6.19 (dt, *J* = 15.5, 7.0 Hz, 0.53H), 5.66 – 5.52 (m, 1.47H), 5.43 (br. s, 0.5H), 5.36 (br. s, 0.5H), 2.35 (q, *J* = 7.0 Hz, 1H), 2.26 – 2.16 (m, 3H), 1.73 – 1.63 (m, 2H), 1.55 – 1.46 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 175.52, 175.49, 137.83, 137.76, 132.5, 130.43, 130.36, 129.4, 128.9, 128.6, 128.3, 127.0, 126.7, 126.1, 35.9, 35.7, 32.8, 29.5, 29.0, 28.2, 25.2 (2 × carbon peaks overlapping); **IR** (cm⁻¹) 3372, 3178, 2936, 2854, 1645, 1415, 1307, 1114, 966; **High Resolution MS** (ESI): Calculated for C₁₃H₁₇NONa [M+Na]⁺: 226.1202, Found: 226.1196.

Hydroamination of tri-substituted alkene



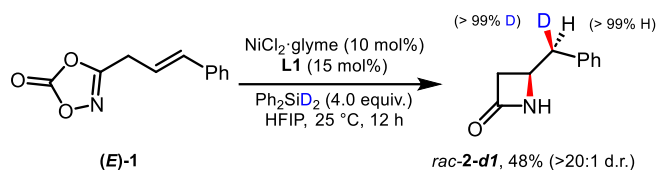
To a reaction vial equipped with a stir bar were added NiCl₂·glyme (10 mol%), 6,6'-dimethyl-2,2'-bipyridine **L1** (15 mol%), and anhydrous HFIP (0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before (E)-3-(3-phenylbut-2-en-1-yl)-1,4,2-dioxazol-5-one **14** (0.1 mmol, 1.0 equiv.) and DMMS (4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at 25 °C for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography to afford the β-lactam product *rac*-**15** as a white solid (11.6 mg, 66%, d.r. > 20:1 determined by ¹H NMR of the crude mixture).

4-(1-Phenylethyl)azetidin-2-one, *rac*-**15**



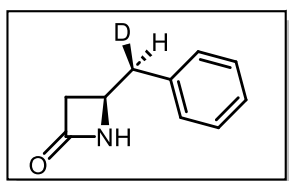
m.p. = 83 – 84 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.37 – 7.30 (m, 2H), 7.28 – 7.23 (m, 1H), 7.23 – 7.14 (m, 2H), 5.57 (br. s, 1H), 3.66 (ddd, *J* = 9.5, 5.0, 2.5 Hz, 1H), 3.11 (ddd, *J* = 15.0, 5.0, 2.5 Hz, 1H), 2.76 (dq, *J* = 9.5, 7.0 Hz, 1H), 2.69 (ddd, *J* = 15.0, 2.5, 1.5 Hz, 1H), 1.29 (d, *J* = 7.0 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 167.4, 142.9, 129.0, 127.34, 127.25, 53.7, 45.6, 42.7, 17.7; **IR** (cm⁻¹) 3179, 2920, 2850, 1705, 1378, 1196, 1024, 754; **High Resolution MS** (EI): Calculated for C₁₁H₁₃NO [M]⁺: 175.0997, Found: 175.0995.

Deuterium experiments using (*E*)-1



To a reaction vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (10 mol%), 6,6'-dimethyl-2,2'-bipyridine **L1** (15 mol%), and anhydrous HFIP (0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before 3-cinnamyl-1,4,2-dioxazol-5-one (**(E)**-1) (0.1 mmol, 1.0 equiv.) and Ph_2SiD_2 (4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at 25 °C for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography to afford the β -lactam product *rac*-2-**d1** as a white solid (7.8 mg, 48%).

4-(Phenylmethyl-*d*)azetidin-2-one, *rac*-2-**d1**



¹H NMR (500 MHz, CDCl_3) δ 7.34 (t, J = 7.5 Hz, 2H), 7.31 – 7.27 (m, 1H), 7.20 (d, J = 7.5 Hz, 2H), 6.09 (br. s, 1H), 3.85 (t, J = 6.0 Hz, 1H), 3.08 (dd, J = 15.0, 5.0 Hz, 1H), 2.96 (d, J = 6.0 Hz, 1H), 2.71 (d, J = 15.0 Hz, 1H);

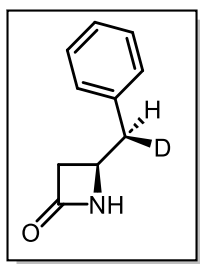
¹³C NMR (126 MHz, CDCl_3) δ 167.7, 137.6, 128.94, 128.85, 127.0, 49.0, 43.4, 41.6 (t, J = 20.0 Hz); **High Resolution MS** (EI): Calculated for $\text{C}_{10}\text{H}_{10}\text{DNO}$ $[\text{M}]^+$: 162.0903, Found: 162.0905.

Deuterium experiments using (*Z*)-1

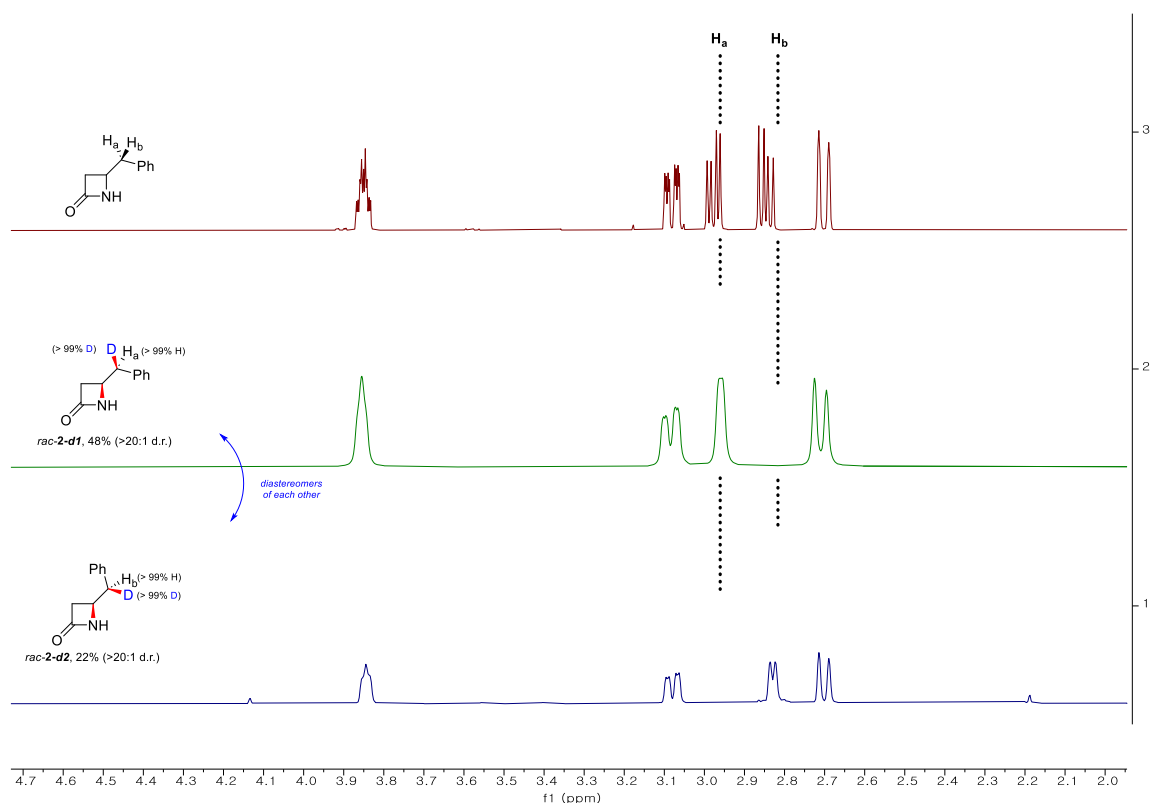


To a reaction vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (10 mol%), 6,6'-dimethyl-2,2'-bipyridine **L1** (15 mol%), and anhydrous HFIP (0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before 3-cinnamyl-1,4,2-dioxazol-5-one (**(Z)**-1) (0.1 mmol, 1.0 equiv.) and Ph_2SiD_2 (4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at 25 °C for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography to afford the β -lactam product *rac*-2-**d2** as a white solid (3.6 mg, 22%).

4-(Phenylmethyl-*d*)azetidin-2-one, *rac*-2-*d*2

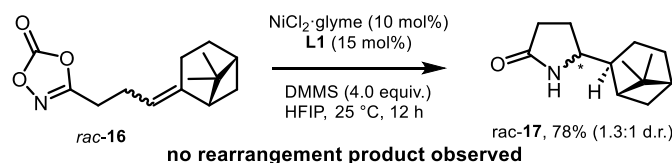


¹H NMR (600 MHz, CDCl₃) δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.25 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 5.83 (br. s, 1H), 3.84 (t, *J* = 6.5 Hz, 1H), 3.08 (ddd, *J* = 15.0, 5.0, 2.5 Hz, 1H), 2.86 – 2.81 (m, 1H), 2.70 (d, *J* = 15.0 Hz, 1H); **¹³C NMR** (126 MHz, CDCl₃) δ 167.5, 137.6, 129.0, 128.9, 127.1, 49.0, 43.5, 41.7 (t, *J* = 20.0 Hz); **High Resolution MS** (EI): Calculated for C₁₀H₁₀DNO [M]⁺: 162.0903, Found: 162.0901.



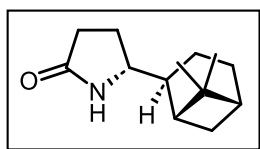
Supplementary Fig. 1 | Stacked ¹H NMR spectrum of **2**, *rac*-2-*d*1 and *rac*-2-*d*2.

Investigation toward the intermediacy of carbocation using (+)-nopinone-derived alkenyl dioxazolone

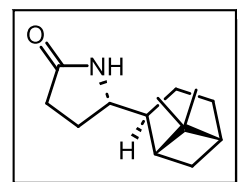


To a reaction vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (10 mol%), 6,6'-dimethyl-2,2'-bipyridine **L1** (15 mol%), and anhydrous HFIP (0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before dioxazolone *rac*-**16** (*E/Z* = 1.3:1, 0.1 mmol, 1.0 equiv.) and DMMS (4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at 25 °C for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography to afford the γ -lactam product *rac*-**17** as a white solid (16.1 mg, 78%, *d.r.* = 1.3:1 determined by ^1H NMR).

5-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)pyrrolidin-2-one, *rac*-**17**



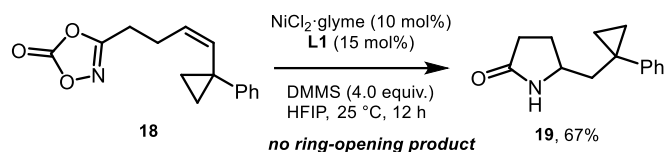
major [from (*E*)-isomer]: ^1H NMR (500 MHz, CDCl_3) δ 5.89 (br. s, 1H), 3.64 (dt, J = 11.5, 6.5 Hz, 1H), 2.39 (dd, J = 10.0, 5.5 Hz, 1H), 2.32 – 2.20 (m, 3H), 1.99 – 1.86 (m, 6H), 1.72 – 1.65 (m, 1H), 1.47 – 1.37 (m, 1H), 1.20 (s, 3H), 1.00 (s, 3H), 0.90 (d, J = 10.0 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.2, 58.5, 47.7, 43.5, 41.2, 38.8, 33.0, 29.9, 28.2, 26.7, 26.0, 23.5, 18.3; IR (cm^{-1}) 3186, 2978, 2863, 1693, 1468, 761; **High Resolution MS** (EI): Calculated for $\text{C}_{13}\text{H}_{21}\text{NO}$ [M] $^+$: 207.1623, Found: 207.1620.



minor [from (*Z*)-isomer]: ^1H NMR (500 MHz, CDCl_3) δ 6.00 (br. s, 1H), 3.69 (dt, J = 10.0, 7.0 Hz, 1H), 2.42 – 2.37 (m, 1H), 2.31 (dd, J = 9.5, 6.5 Hz, 2H), 2.18 (dq, J = 13.5, 6.5 Hz, 1H), 2.01 – 1.87 (m, 6H), 1.74 – 1.66 (m, 1H), 1.57 – 1.51 (m, 1H), 1.20 (s, 3H), 1.00 (s, 3H), 0.88 (d, J = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.1, 59.4, 48.1, 42.5, 41.2, 38.5, 33.4, 30.4, 28.0, 26.6, 26.1, 23.7, 20.3; IR (cm^{-1}) 3177, 2989, 2866, 1703, 1465, 738; **High Resolution MS** (EI): Calculated for $\text{C}_{13}\text{H}_{21}\text{NO}$ [M] $^+$: 207.1623, Found: 207.1621.

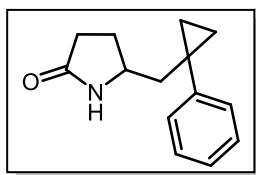
Note: The separation of the two diastereomers was proven difficult by silica column chromatography. Small fractions containing pure materials of each isomer were collected separately and used for the purpose of characterization. The relative stereochemistry of the major isomer was confirmed by X-ray crystallographic analysis (see Crystallographic Data).

Radical-clock experiment using cyclopropyl-containing alkenyl dioxazolone



To a reaction vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (10 mol%), 6,6'-dimethyl-2,2'-bipyridine **L1** (15 mol%), and anhydrous HFIP (0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before dioxazolone **18** (0.1 mmol, 1.0 equiv.) and DMMS (4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at 25 °C for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography to afford the γ -lactam product **19** as a white solid (14.4 mg, 67%).

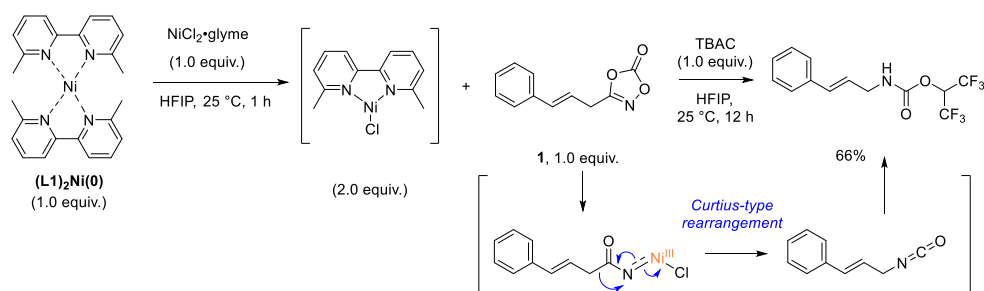
5-[(1-Phenylcyclopropyl)methyl]pyrrolidin-2-one, **19**



m.p. = 89 – 90 °C; **^1H NMR** (500 MHz, CDCl_3) δ 7.31 – 7.28 (m, 4H), 7.24 – 7.20 (m, 1H), 5.65 (br. s, 1H), 3.56 (app. qd, J = 7.5, 4.5 Hz, 1H), 2.27 – 2.19 (m, 2H), 2.17 – 2.09 (m, 1H), 1.87 (dd, J = 14.0, 4.5 Hz, 1H), 1.67 – 1.58 (m, 2H), 0.90 (dt, J = 9.0, 4.5 Hz, 1H), 0.83 (dt, J = 9.5, 4.5 Hz, 1H), 0.75 (dt, J = 9.0, 4.5 Hz, 1H), 0.69 (dt, J = 9.5, 4.5 Hz, 1H); **^{13}C NMR** (126 MHz, CDCl_3) δ 177.9, 143.9, 129.2, 128.8, 126.9, 53.6, 47.7, 30.1, 28.1, 24.3, 12.7, 12.4; **IR** (cm^{-1}) 3195, 3081, 2923, 1681, 1387, 1291, 1026, 764, 704; **High Resolution MS** (EI): Calculated for $\text{C}_{14}\text{H}_{17}\text{NO}$ $[\text{M}]^+$: 215.1310, Found: 215.1309.

Stoichiometric reaction of **(L1)Ni(I)Cl** with dioxazolone

In glovebox, to a 4.0 mL vial equipped with a stir bar were added **L1₂Ni(0)** (42.7 mg, 0.1 mmol, 1.0 equiv.), NiCl₂·glyme (22.0 mg, 0.1 mmol, 1.0 equiv.) and anhydrous HFIP (1.0 mL, 0.1 M). The resulting mixture was stirred for 1 h before dioxazolone **1** (20.3 mg, 0.1 mmol, 1.0 equiv.) and TBAC (27.8 mg, 0.1 mmol, 1.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at the 25 °C for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, concentrated under reduced pressure, and purified by silica column chromatography.

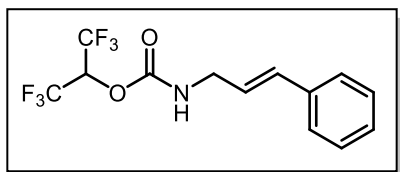


Supplementary Fig. 2 | Reaction of alkenyl dioxazolone with excess of **(L1)Ni(I)Cl**.

The reaction between dioxazolone **1** and excess of **(L1)Ni(I)Cl** should lead to the formation of the corresponding primary amide if **int-F** could be accessed by N-activation of dioxazolone with **(L1)Ni(I)Cl**. To investigate this possibility, **(L1)Ni(I)Cl** was synthesized according to the literature procedure⁷, and treated with dioxazolone **1** under argon atmosphere (Supplementary Fig. 2). Notably, a HFIP adduct was obtained as the only product under these conditions (21.6 mg, 66%), probably via the Curtius-type rearrangement followed by nucleophilic attack of HFIP. This outcome indicates that Ni(I)Cl can indeed activate the dioxazolone motif, but the resulting nitrenoid would dominantly undergo the Curtius-type rearrangement before it could react with another portion of Ni(I)Cl for comproportionation.

On the other hand, the formation of such Curtius-type rearrangement products was not observed under our catalytic conditions, nor in the analogous stoichiometric Ni(I)Cl reactions in the presence of DMMS. The dramatic reactivity change in the presence of hydride might be attributed to the fact that having H as the co-ligand would render the Ni centre more electron-rich and subsequently circumvent the Curtius-type rearrangement of the NiH nitrenoid species. While the direct reaction with Ni(I)H could not be investigated due to the difficulty of its synthesis, our previous study also supports this hypothesis that the electronic nature of ligand is essential in tuning the reactivity of metal nitrenoids³.

1,1,1,3,3,3-Hexafluoropropan-2-yl cinnamylcarbamate

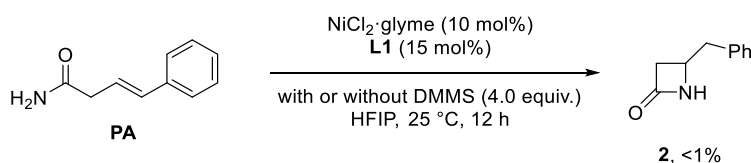


m.p. = 114 – 115°C; ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.24 (m, 5H), 6.56 (d, J = 15.5 Hz, 1H), 6.19 (dt, J = 15.5, 6.5 Hz, 1H), 5.76 – 5.66 (m, 1H), 5.21 (s, 1H), 4.05 (t, J = 6.5 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.5, 136.2, 133.2, 128.8, 128.2, 126.6, 124.1, 120.8 (d, $J_{\text{C-F}}$ = 283.5 Hz), 67.9 (p, $J_{\text{C-F}}$ = 34.5 Hz), 43.9; ^{19}F NMR (376 MHz, CDCl_3) δ –73.6. **IR** (cm^{-1}) 3324, 2969, 1733, 1549, 1384, 1244, 1186, 1106, 923, 750; **High Resolution MS** (ESI): Calculated for $\text{C}_{13}\text{H}_{11}\text{NF}_6\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 350.0586, Found: 350.0593.

Experimental investigations toward the accessibility of **int-F** by other means

Control experiments with primary amide

To a 4.0 mL vial equipped with a stir bar were added $\text{NiCl}_2\cdot\text{glyme}$ (2.2 mg, 10 mol%), **L1** (15 mol%), and anhydrous HFIP (1.0 mL, 0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before (*E*)-4-phenylbut-3-enamide **PA** (16.1 mg, 0.1 mmol, 1.0 equiv.) and DMMS (50 μL , 0.4 mmol, 4.0 equiv.) were added (or conducted without DMMS). The vial was sealed with a screw cap, removed from the glovebox, and stirred at the indicated temperature for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure.

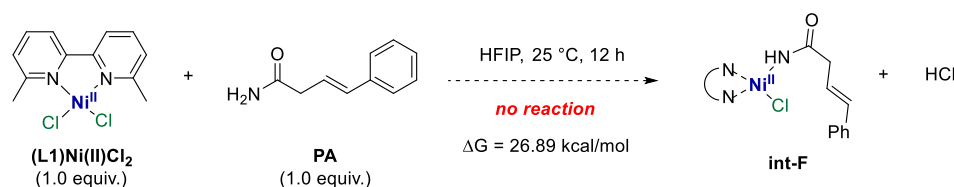


Supplementary Fig. 3 | Control experiments using primary amide as the reactant.

The formation of β -lactam **2** had not been observed when primary amide was utilized as the reactant either in the presence or absence of DMMS (Supplementary Fig. 3), suggesting that the key intermediate is not accessible from primary amides in the current system.

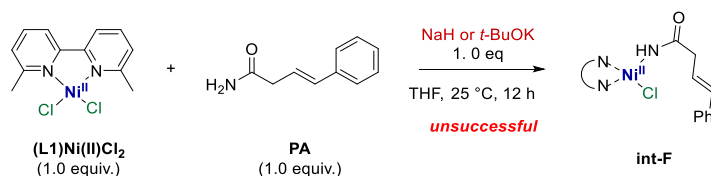
Attempts to synthesize int-F

To a 4.0 mL vial equipped with a stir bar were added **PA** (16.1 mg, 0.1 mmol, 1.0 equiv.), **L1Ni(II)Cl₂** (31.3 mg, 0.1 mmol, 1.0 equiv.), and anhydrous HFIP (1.0 mL, 0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 12 h.



Supplementary Fig. 4 | Reaction between **(L1)Ni(II)Cl₂** and primary amide.

The stoichiometric reaction between **(L1)Ni(II)Cl₂** and **PA** (Supplementary Fig. 4) was monitored by ¹H NMR, which revealed that the starting materials remain unreacted. This unsuccessful outcome was not surprising since primary amide **PA** has a low acidity. This observation was further supported by DFT calculations (see Computational Details below), which indeed proves that the formation of **int-F** from the corresponding primary amide (**PA**) is highly endergonic ($\Delta G = 26.89$ kcal/mol) and thermodynamically unfavourable.

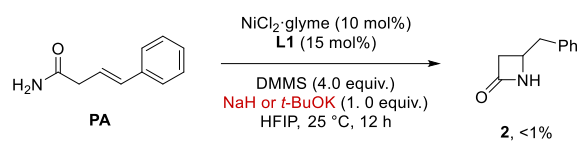


Supplementary Fig. 5 | Control experiments under basic conditions.

It could be envisioned that **int-F** might be accessible under basic conditions. However, the analogous reactions repeated under basic conditions (**NaH** or ***t*-BuOK**, 0.1 mmol, 1.0 equiv.) in THF solvent were also unsuccessful (Supplementary Fig. 5).

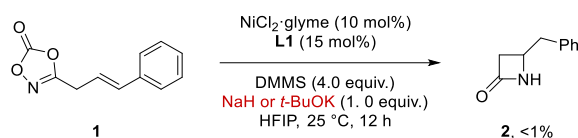
Control experiments under basic conditions

To a 4.0 mL vial equipped with a stir bar were added **NiCl₂·glyme** (2.2 mg, 10 mol%), **L1** (15 mol%), and anhydrous HFIP (1.0 mL, 0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before (*E*)-4-phenylbut-3-enamide (16.1 mg, 0.1 mmol, 1.0 equiv.), **DMMS** (50 μ L, 0.4 mmol, 4.0 equiv.), and **NaH** (4.0 mg, 0.1 mmol, 1.0 equiv., 60% dispersion in mineral oil) or ***t*-BuOK** (11.2 mg, 0.1 mmol, 1.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at the indicated temperature for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure.



Supplementary Fig. 6 | Reaction of primary amide under basic conditions.

While the above stoichiometric reactions were unsuccessful, **int-F** could still be accessed catalytically from primary amides under basic conditions. However, the reaction of primary amide **PA** under the modified catalytic conditions employing a base (NaH or *t*-BuOK, 0.1 mmol, 1.0 equiv.) did not yield the β -lactam product (Supplementary Fig. 6), indicating that **int-F** is unlikely to be accessible from primary amides under the current conditions.



Supplementary Fig. 7 | Reaction of alkenyl dioxazolone under basic conditions.

In addition, the analogous reactions of alkenyl dioxazolone **1** under basic conditions were also unsuccessful (Supplementary Fig. 7), suggesting that the utilization of a strong base would impair not only the controllable generation of **int-F** but also other mechanistic steps. The chloride ion on the Ni center could be readily replaced under basic conditions, which would be deleterious in a process where the nature of ligand is very essential for the successful conversion in each catalytic step. Therefore, incorporating primary amides in the proposed catalytic cycle would be highly challenging.

Computational Details

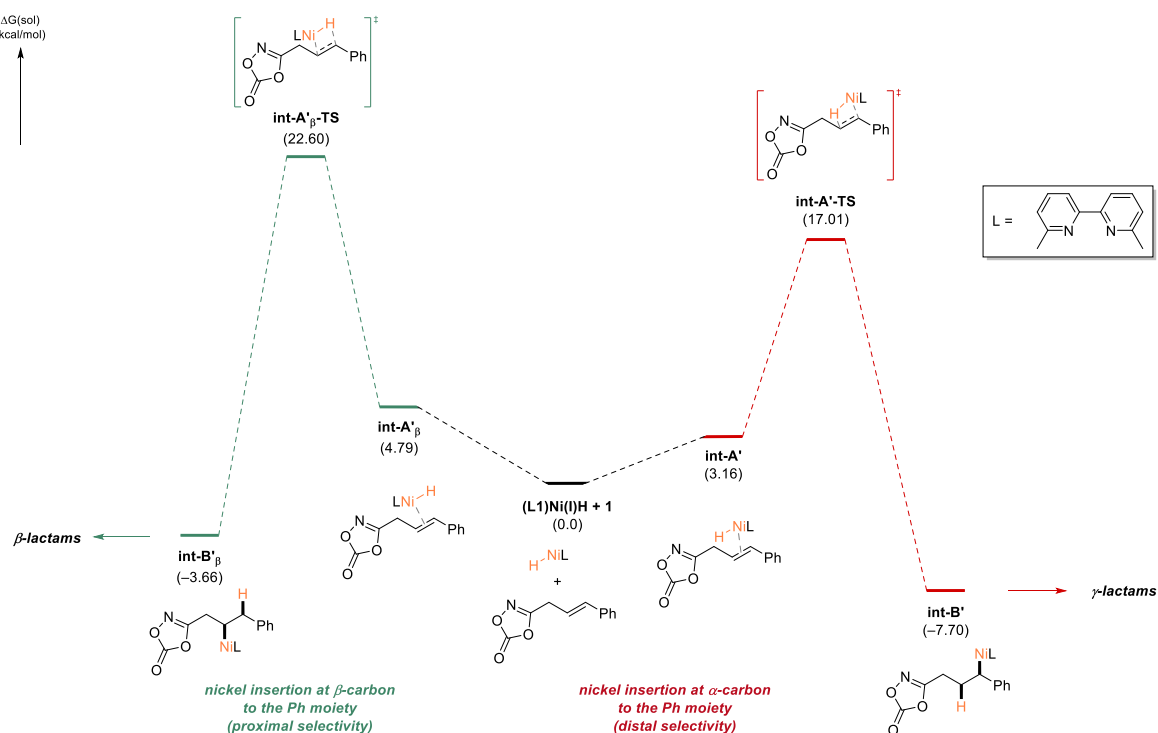
All calculations were performed using the density functional theory⁸ (DFT) as implemented in the Gaussian 09⁹ suite of programs. Geometry optimizations were performed using the M06 functional¹⁰ with Grimme's D3¹¹ correction, and a mixed basis set of SDD¹² for Ni and 6-31G**¹³ for all other atoms. Vibrational frequency calculations were carried out at the same level of theory as that used for geometry optimizations, wherein thermochemistry correction energy ($G - E$) was acquired. Transition states were realized by the presence of single imaginary frequency and confirmed by intrinsic reaction coordinate calculations (IRC). Single point energies of optimized structures were calculated with the M06 functional¹⁰ and a mixed basis set of SDD for Ni and 6-311+G** for other atoms. Solvation effects were incorporated using the SMD model¹⁴ based on the gas-phase optimized geometries, and carried out at the same level as single-point calculations. Implicit HFIP solvent for the calculations of standard racemic reactions was modelled using the parameters (solvent = generic, $\epsilon = 16.7$, $\epsilon_{\text{inf}} = 1.625625$)¹⁵, and *N,N*-dimethylacetamide (DMA) solvent for alkynyl variants and asymmetric reactions was modelled with the SMD continuum solvation¹⁴. Graphical structures were created using CYLview¹⁶. Final solution phase Gibbs free energies were calculated as follows:

$$G_{\text{sol}} = E_{\text{sol}} + (G - E) \quad (1)$$

$$\Delta G(\text{sol}) = \Sigma G(\text{sol}) \text{ for products} - \Sigma G(\text{sol}) \text{ for reactants} \quad (2)$$

Energy comparison between the two regio-pathways of hydronickelation

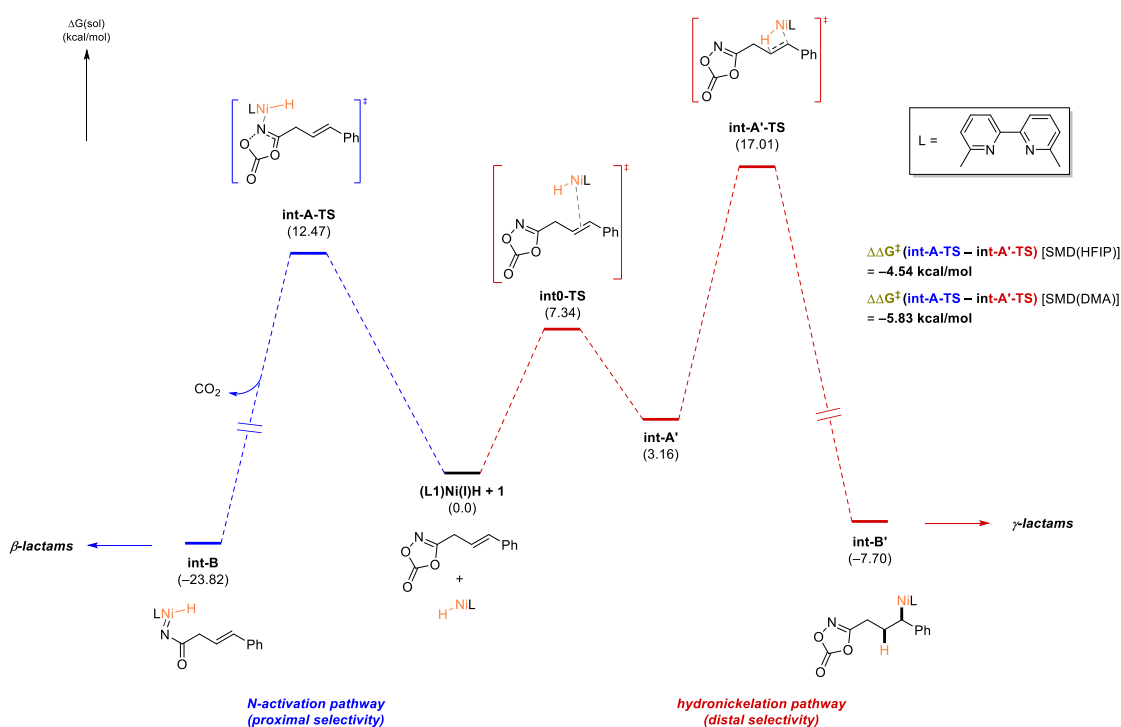
A number of previous CuH systems show that an electronegative group, such as oxygen or nitrogen substituent, in the allylic^{17,18} or homoallylic¹⁹ position could provide inductive effects to polarize the C=C double bond of aliphatic alkenes, consequently giving rise to the C–N bond formation at the proximal site to the functional group. If the dioxazolone motif causes similar influences in our case, the nickel insertion in the hydronickelation step should then be more favoured at the proximal site (β -carbon to Ph). However, opposed to this scenario, density functional theory (DFT) calculations on a model substrate **1** showed that the conventional hydronickelation rather favours the nickel addition at the distal carbon (α -carbon to Ph) with a significantly lower activation barrier ($\Delta\Delta G^\ddagger = -5.59$ kcal/mol, Supplementary Fig. 8). This computational outcome indicated that the inductive effects of dioxazolone motif, if existing, would be only marginal in comparison to the electronic perturbation elicited from a conjugated aryl substituent. Therefore, the currently observed proximal C–N bond-forming selectivity leading to β -lactams cannot be explicated by this common hydronickelation mechanism, as the computational data have proven that this process clearly prefers the opposite selectivity that would rather furnish γ -lactams.



Supplementary Fig. 8 | Energy profiles of hydronickelation with two possible regioselectivity.

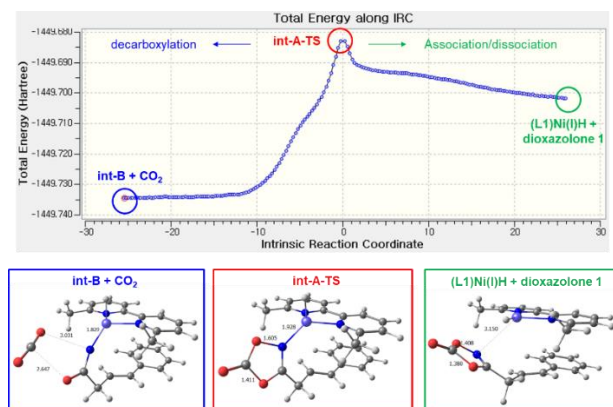
Energy comparison between the hydronicellation and alternative N-activation pathways

It was interesting to note the dependence of regioselectivity on the nature of unsaturated C–C bonds (alkene vs alkyne), since our previously reported intramolecular hydroamidation of alkynes contrarily resulted in regioselectivity commonly expected by TMH catalysis (α -carbon to Ph)²⁰. The fact that the hydrometalation of alkynes is typically more facile than that of alkenes led us to hypothesize that there might be a correlation between the selectivity and relative efficiency of activation of unsaturated C–C bonds. While the above mentioned hydronicellation process would lead to the formation of γ -lactams (Supplementary Fig. 9, red), we envisioned that there may exist an alternative pathway, presumably initiated by N-activation, to furnish the proximal selectivity (blue). In this scenario, the coordination alkene (**int-A'**) to the Ni(I)H catalytic species would be initially in equilibrium, and the subsequent activation process would then be under kinetic control.



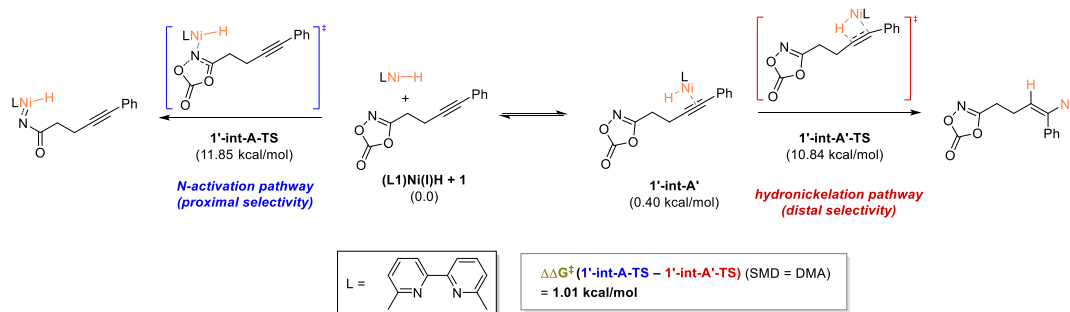
Supplementary Fig. 9 | Energy comparison between the hydronicellation and N-activation pathways for initial activation of alkenyl dioxazolone **1**.

Interestingly, the decarboxylation barrier via **int-A-TS** (Supplementary Fig. 9, blue) was found to require relatively lower energy [$\Delta\Delta G^\ddagger = -4.54$ kcal/mol; SMD(HFIP)] than the hydronicellation pathway traversing **int-A'-TS**, which supports our hypothesis that the experimentally observed proximal selectivity would be achieved through the N-activation path. A consistent result was obtained when the single-point energy calculations were performed with solvation effects incorporated using DMA [$\Delta\Delta G^\ddagger = -5.83$ kcal/mol; SMD(DMA)].



Supplementary Fig. 10 | Intrinsic reaction coordinate (IRC) trajectory from **int-A-TS**.

In this scenario, we were unable to explicitly locate the geometry of N-coordinated intermediate, presumably because such an intermediate might be very unstable so that it may rather get activated rapidly or dissociate back. An intrinsic reaction coordinate (IRC) analysis on **int-A-TS** further confirmed this outcome, as it directly leads to a pair of dissociated (**L1**)Ni(I)H intermediate and alkenyl dioxazolone **1** (Supplementary Fig. 10). Nonetheless, the kinetic preference for the N-activation pathway is clear, which should therefore be dominant in a process where the coordination event of alkene to the Ni(I)H species is in equilibrium.

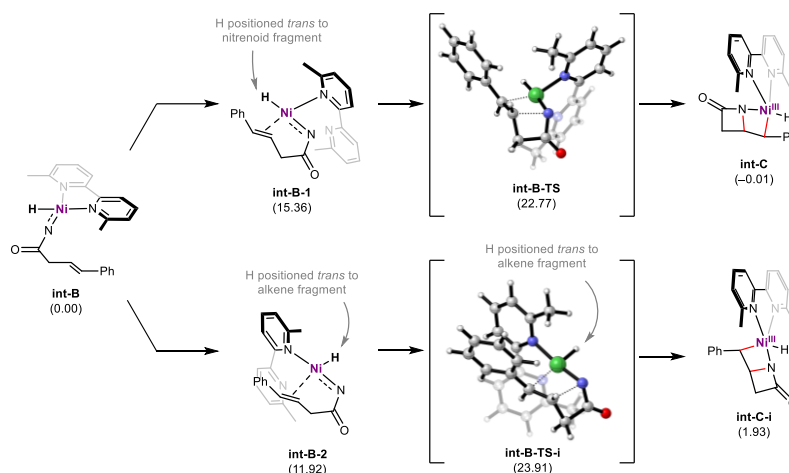


Supplementary Fig. 11 | Energy comparison between the hydronickelation and N-activation pathways for initial activation of alkynyl dioxazolone **1'**.

On the other hand, the kinetic preference is altered toward the conventional hydronickelation path for alkynyl dioxazolone **1'** [Supplementary Fig. 11, $\Delta\Delta G^\ddagger = +1.01 \text{ kcal/mol}$; SMD(DMA)], with significantly lowered hydronickelation TS. Once again, this computational result is consistent with our previous experimental outcome²⁰, in which the cyclization of alkynyl dioxazolones is delivered via distal selectivity expected by the hydronickelation mechanism. It needs to be noted that a number of possible conformers were considered in these calculations, and the reported energies are those of the lowest energies for each structure.

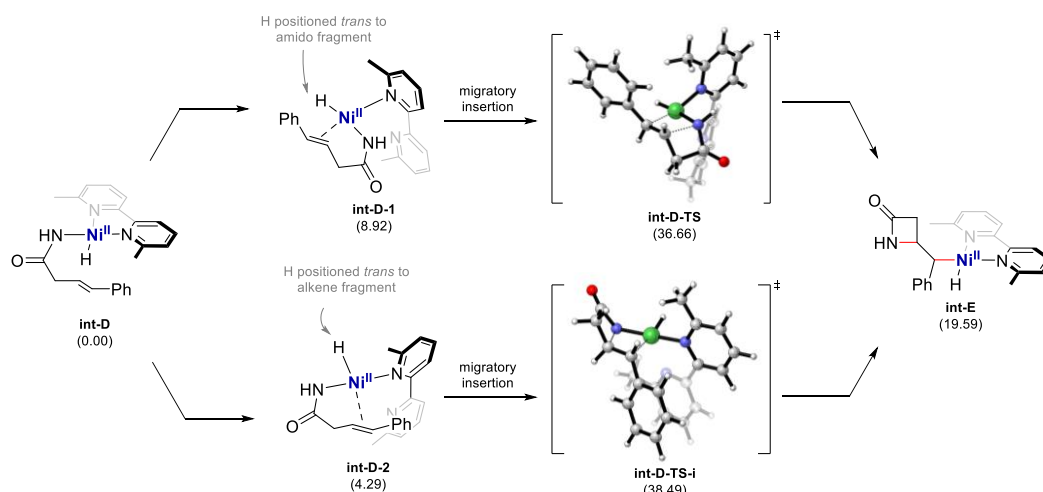
Migratory insertion of alkene into Ni–N

With the experimental results indicating that the step-wise C–N bond formation is less likely to be operative, we subsequently investigated the plausibility of concerted insertion of Ni and nitrogen across the C=C double bond. We first considered a [2+2] cycloaddition process taking place directly from NiH nitrenoid **int-B** (Supplementary Fig. 12), as previously proposed for the reactions involving imido species based on early transition metals²¹. Interestingly, this [2+2] cycloaddition reaction mode leading to fused-azametallacyclobutane **int-C** showed a reasonable activation barrier ($\Delta G^\ddagger = 22.77$ kcal/mol) via **int-B-TS**. In this case, the lowest-energy transition state structure was found to adopt hydride ligand *trans* to the nitrenoid fragment (**int-B-TS**). The other isomeric transition state with olefin positioned *trans* to the hydride ligand (**int-B-TS-i**) gave a higher barrier ($\Delta\Delta G^\ddagger = 1.14$ kcal/mol), presumably because hydride, which is a strong σ -donor, may destabilize the transition states when positioned *trans* to the approaching carbon.



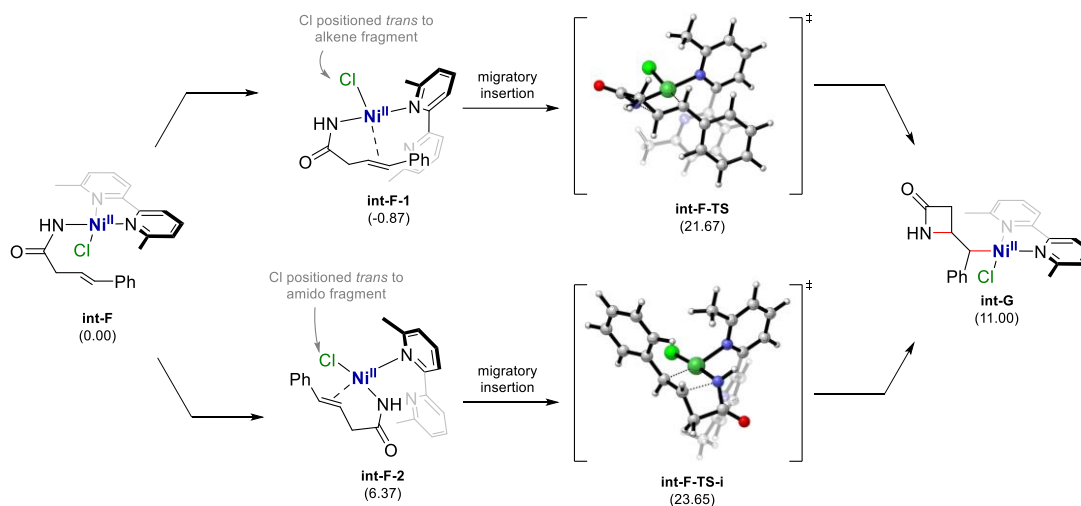
Supplementary Fig. 12 | Energy calculations on the [2+2] cycloaddition of Ni-nitrenoid **int-B**.

While this result has proven that the [2+2] cycloaddition pathway might be energetically feasible, its exergonic nature was somewhat unusual given that the resulting intermediate (**int-C**) has a highly strained structure. This adversely suggested that the four-coordinate Ni intermediate **int-B** itself might be very unstable and may consequently follow lower-energy decomposition paths instead. This led us to consider an alternative scenario where **int-B** is rapidly converted to a Ni(II)H amido species (**int-D**) through comproportionation with a fleeting Ni(I) species, which may then undergo amidonickelation (Supplementary Fig. 13). However, DFT calculations showed that this process has a higher activation barrier ($\Delta G^\ddagger = 36.66$ kcal/mol). Similar to the above mentioned [2+2] cycloaddition reaction, this nickel-hydride-based amidonickelation gave a lower transition state energy when H is positioned *trans* to the amido group (**int-D-TS**) than when it is *trans* to the approaching carbon (**int-D-TS-i**) ($\Delta\Delta G^\ddagger = 1.83$ kcal/mol).



Supplementary Fig. 13 | Energy calculations on the amidonickelation of Ni(II)H amido intermediate.

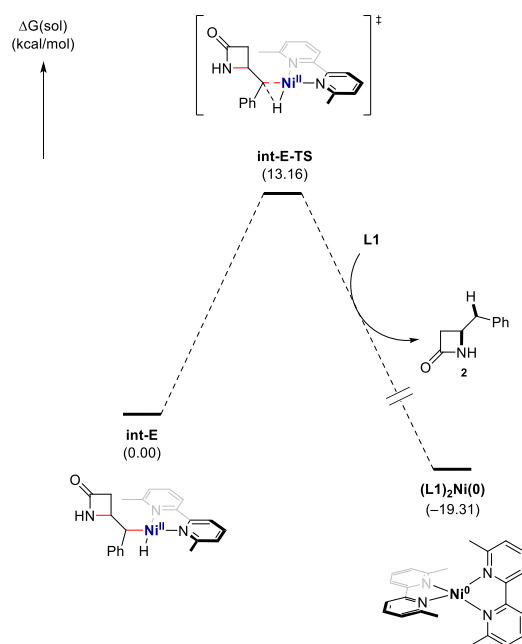
Interestingly, the analogous amidonickelation with Ni(II)Cl derivative gave a lot lower activation barrier ($\Delta G^\ddagger = 21.67$ kcal/mol), likely due to the electronic influence of chloride that renders the Ni center more electron-deficient (Supplementary Fig. 14). Notably, the geometry of transition state structure was also affected, since the *trans* effects of chloride are relatively small and would therefore rather adopt sterically the most stable structure. Consistent with this logic, the lowest-energy transition state structure for amidonickelation of **int-F** was found to be that with Cl positioned *trans* to the alkene functionality (**int-F-TS**), which is in stark contrast to the above NiH cases. The other geometrical isomer (**int-F-TS-i**) having Cl *trans* to the amido functionality gave a higher energy ($\Delta\Delta G^\ddagger = 1.98$ kcal/mol).



Supplementary Fig. 14 | Energy calculations on the amidonickelation of alkenylamido-Ni(II)Cl intermediate.

C–H bond formation via reductive elimination

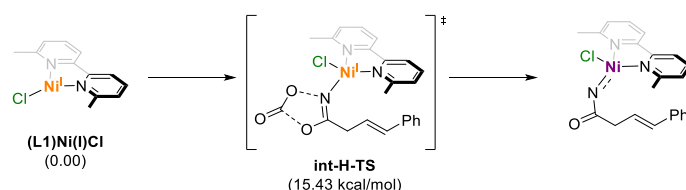
Ligand exchange of **int-G** with hydride would lead to alkyl-Ni(II)H intermediate **int-E**, which would then undergo a reductive elimination to afford the β -lactam product and Ni(0) species. DFT calculations showed that this C–H bond formation process is highly feasible (Supplementary Fig. 15). **(L1)₂Ni(0)** would then undergo a comproportionation with fleeting Ni(II) species to regenerate Ni(I)-based active catalyst.



Supplementary Fig. 15 | C–H bond formation via reductive elimination.

N-Activation of dioxazolone with **(L1)Ni(I)Cl**

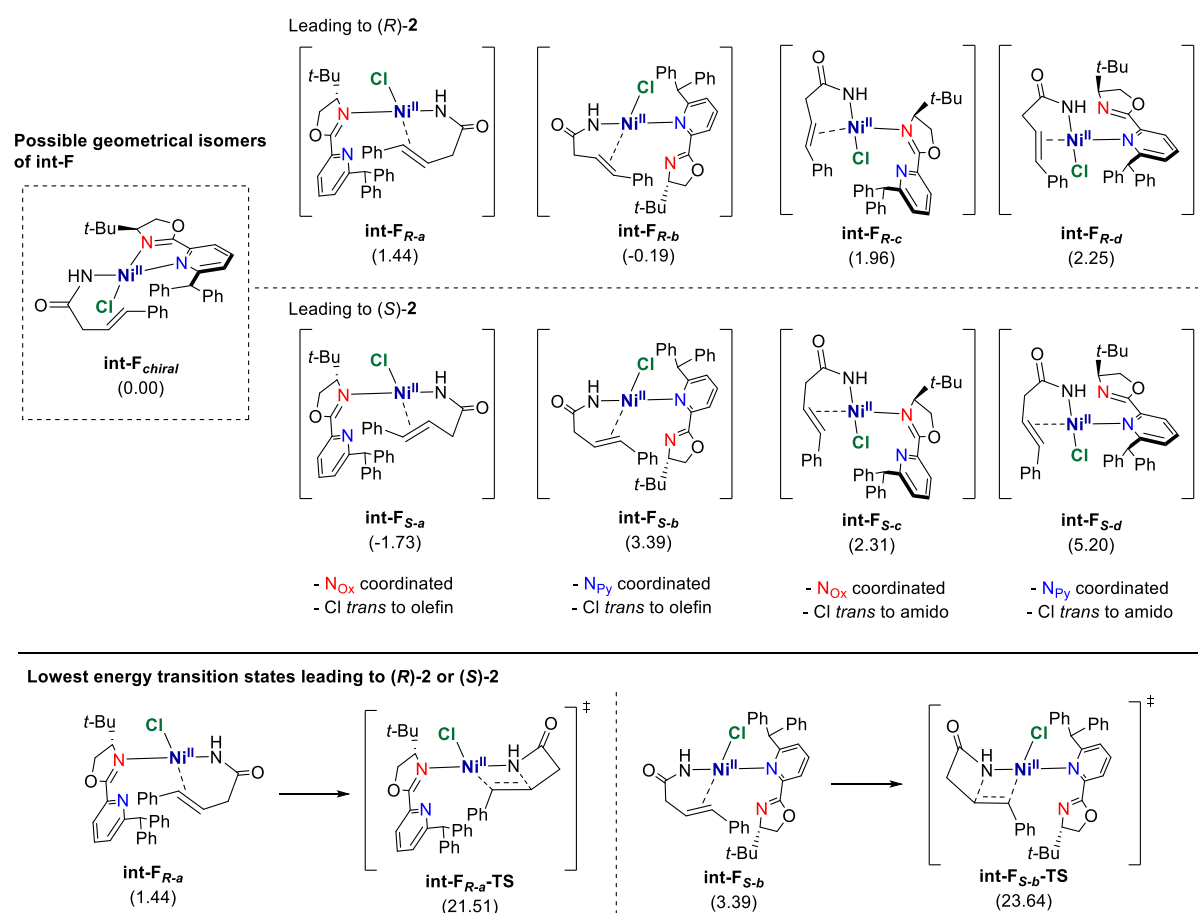
While Ni(I)H species has been proposed as the main catalytic species, the initial N-activation by Ni(I)Cl might also be feasible, which could then lead to the key Ni(II)Cl-amido intermediate **int-F** after comproportionation/protonation. DFT calculations indeed show that N-activation is also kinetically viable with **(L1)Ni(I)Cl** (Supplementary Fig. 16). Although this computational outcome indicates that this pathway cannot be completely excluded, the stoichiometric reaction with **L1Ni(I)Cl** suggests that N-activation by Ni(I)Cl is likely to lead to the undesired decompositions (see Supplementary Fig. 2).



Supplementary Fig. 16 | N-Activation of dioxazolone with **(L1)Ni(I)Cl**.

Amidonickelation of alkenylamido-Ni(II)Cl intermediate as the enantioselectivity-determining step

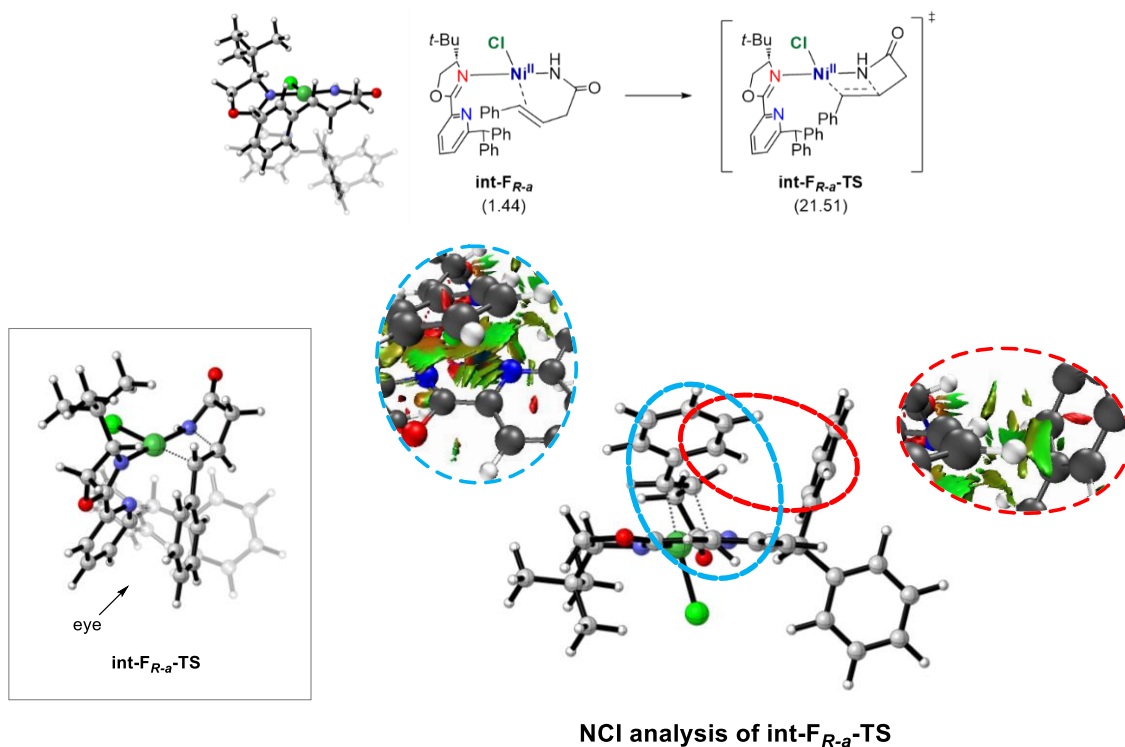
DFT calculations were carried out to better understand the origin of the enantioselectivity observed in this system. Given that amidonickelation of **int-F** is likely the enantioselectivity-determining process based on our mechanistic proposal, the corresponding transition state structures with a chiral ligand (**S**)-**L3** were obtained with considerations of a number of possible geometrical isomers (Supplementary Fig. 17). We initially searched conformers of **int-F_{chiral}** using CREST software²², and classified the geometrical isomers based on the coordination environment. From the eight geometrical isomers, we were able to locate the corresponding amidonickelation transition states, and the lowest transition state was found to be **int-F_{R-a}-TS** leading to the experimentally observed enantiomer.



Supplementary Fig. 17 | Classification of geometrical isomers of **int-F_{chiral}** and the lowest energy transition states leading to (*R*)-2 and (*S*)-2.

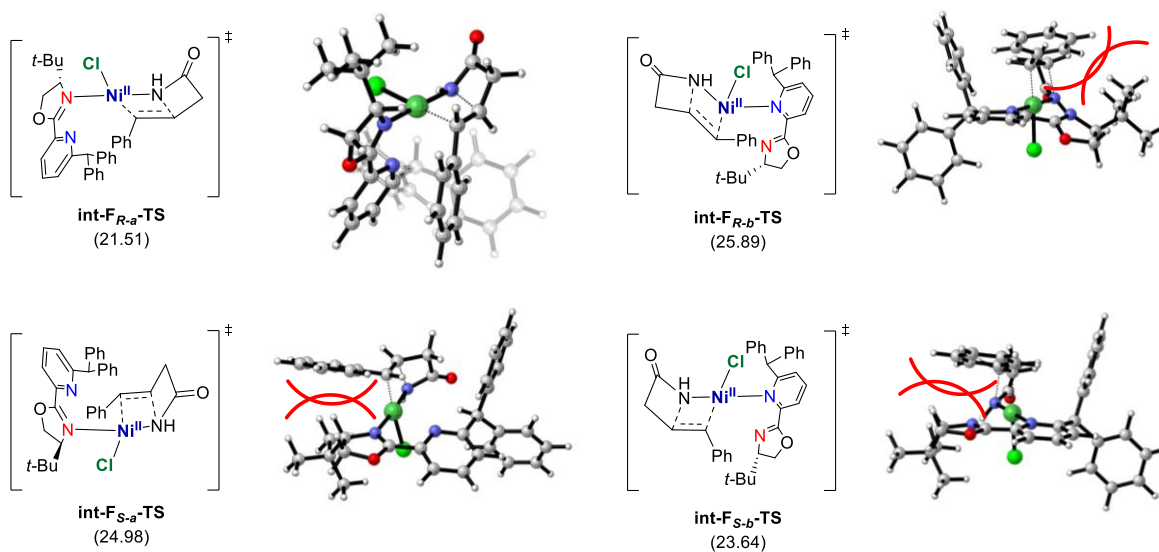
When looking at the structure of the most favourable transition state (**int-F_{R-a}-TS**) that leads to the major enantiomer, the styryl moiety shows no steric clashes between the CH-Ph₂ group as well as the *t*Bu group of (**S**)-**L3**. Also, when conducting the non-covalent interaction (NCI) analysis^{23,24}, we found C-H $\cdots$ π interaction between the diphenyl moiety of (**S**)-**L3** and the alkenyl moiety of the substrate as

well as the π - π interaction between the pyridine of ligand (*S*)-**L3** and the styryl moiety (Supplementary Fig. 18).



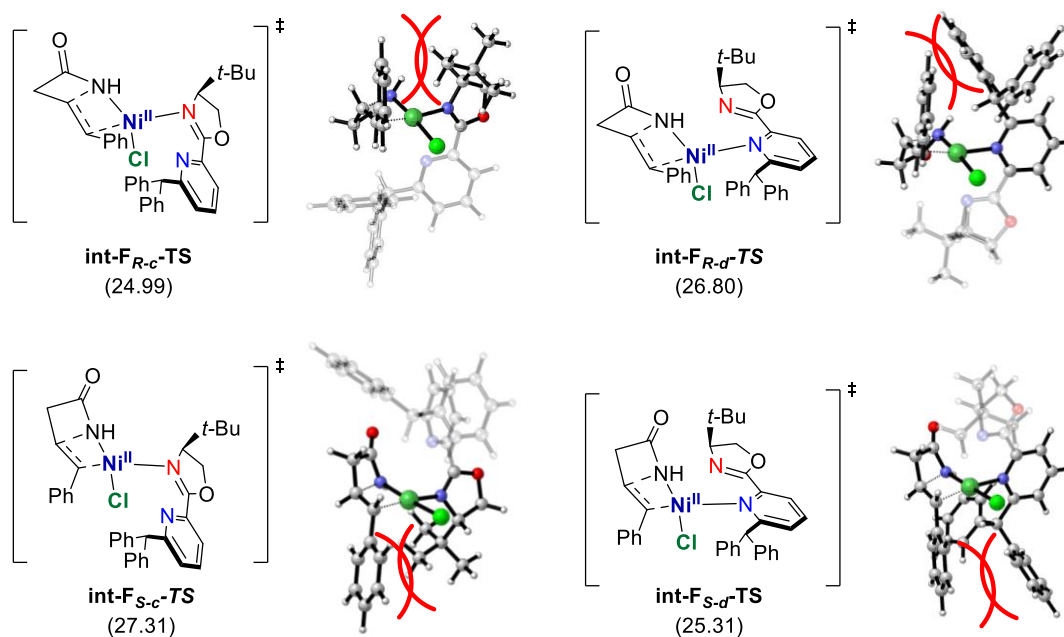
Supplementary Fig. 18 | 3D structures and identification of non-covalent interactions in **int-F_{R-a}-TS**.

In sharp contrasts, all other transition state structures show significant steric repulsions (Supplementary Fig. 19). Noteworthy is that the CH-Ph₂ and *t*-Bu groups of the ligand are not always the major components involved in such steric repulsions, but rather occupy the least hindered spaces to induce certain geometries where other parts of the ligand clashes with the substrate. For example, **int-F_{S-a}-TS** and **int-F_{S-b}-TS**, both leading to the minor enantiomer, display clear steric repulsion, most critically between the styryl moiety of the substrate and the hydrogen atoms appended at the oxazoline part of the ligand.



Supplementary Fig. 19 | 3D structures of **int-F_a-TS** and **int-F_b-TS**.

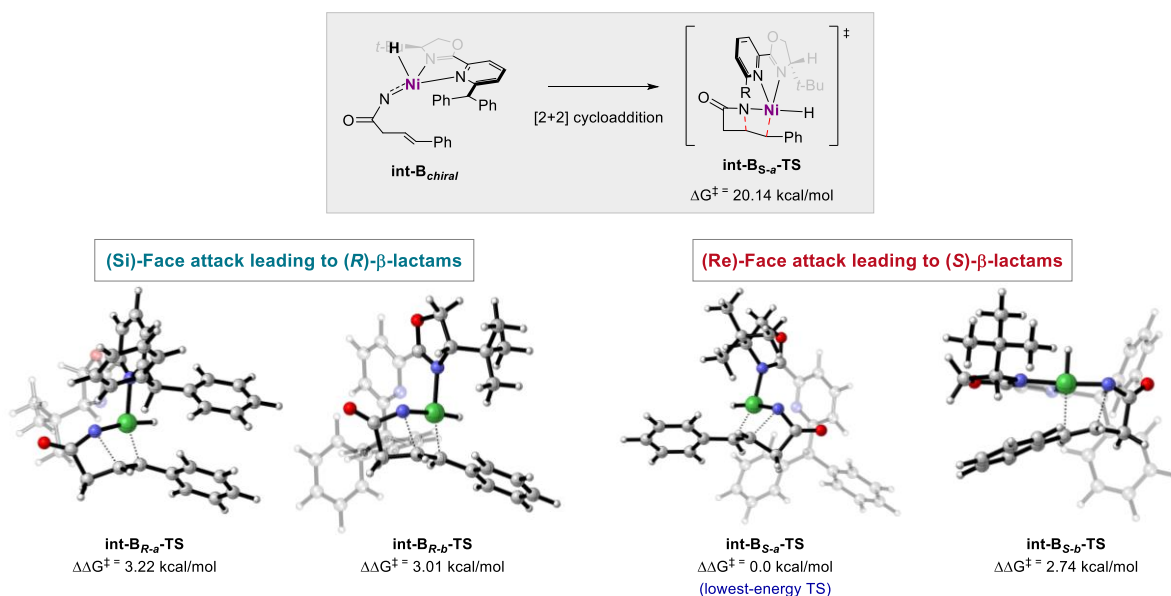
As shown in Supplementary Fig. 20, transition states from **int-F_c** and **int-F_d** encounter steric clashes between the substrate and ligand. Another notable observation is that there are no discrimination factors for the asymmetric induction in these geometries where Cl is *trans* to the amido group.



Supplementary Fig. 20 | 3D structures of **int-F_c-TS** and **int-F_d-TS**.

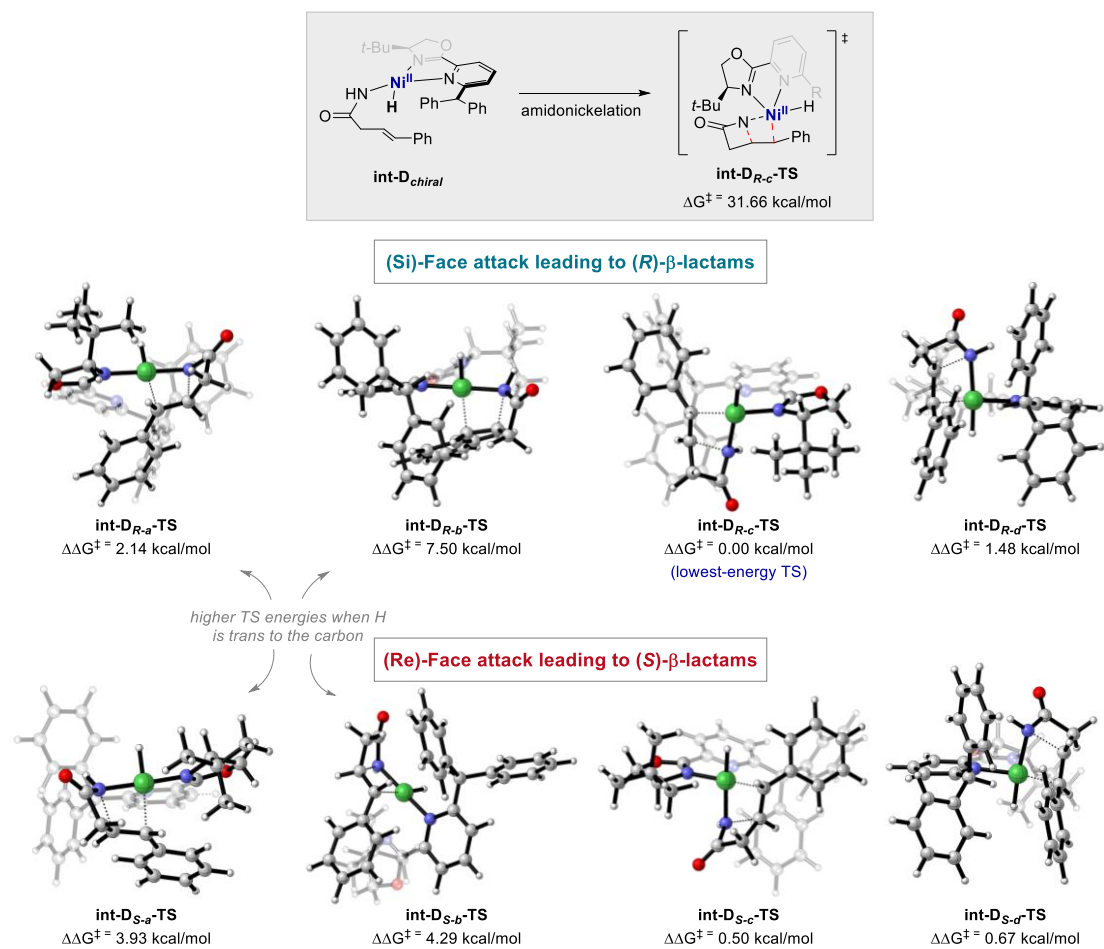
Consideration of other mechanisms for validation of the observed enantioselectivity

To investigate whether the observed enantioselectivity could be rationalized by other considered mechanisms, we further carried out DFT calculations for the key processes that are likely the enantioselectivity-determining step in each case. We first explored the [2+2] cycloaddition pathway involving NiH nitrenoid species **int-B_{chiral}**, which revealed that the computational outcome is not in agreement with the experimentally obtained enantioselectivity (Supplementary Fig. 21). This is because the nickel-hydride-based transformation gives lower-energy transition states when H is positioned *trans* to the nitrenoid group, which does not provide the necessary environments for enantio-discrimination. Indeed, the lowest-energy transition state structure in this case was found to be one that leads to (*S*)- β -lactams (**int-B_{S-a}-TS**, $\Delta G^\ddagger = 20.14$ kcal/mol), which is lower in energy compared to that of the opposite enantioselectivity path (**int-B_{R-b}-TS**, $\Delta\Delta G^\ddagger = 3.01$ kcal/mol).



Supplementary Fig. 21 | Energy comparisons of the isomeric structures of the [2+2] cycloaddition transition states with (*S*)-L3.

Likewise, the amidonickelation based on alkenylamido-Ni(II)H complex was evaluated as summarized in Supplementary Fig. 22. While DFT calculations predicted the experimentally observed enantiomer, the energy difference between the two enantioselectivity pathway was only marginal with $\Delta\Delta G^\ddagger = 0.50$ kcal/mol. These results once again indicate that the ligand orientation is essential for the asymmetric induction: hydride as the co-ligand during the amidonickelation step leads to the TS geometries that do not provide the right environments for enantio-discrimination.



Supplementary Fig. 22 | Energy comparisons of the isomeric structures of the Ni(II)H amidonickelation transition states with (S)-L3.

Summarized energy components of all DFT-optimized structures

Supplementary Table 9. Summarized energy components of DFT-optimized structures for the standard reaction.

DFT-optimized Structures	E(sol) (SCF/TZ) [eV] M06/6-311+G**, SDD(Ni)/ SMD(HFIP; eps = 16.7, epsinf = 1.625625)	G-E (Thermochemistry correction energy) [eV] M06/6-31G**, SDD(Ni)	G(sol) [eV]
1	-19176.137	3.775	-19172.361
2	-14080.444	4.144	-14076.300
PA	-45313.548	4.687	-45308.861
CO ₂	-5130.627	-0.173	-5130.800
HCl	-12538.996	-0.302	-12539.298
L1	-15612.436	4.675	-15607.761
(L1) ₂ Ni(0)	-35878.536	10.039	-35868.497
(L1)Ni(I)H	-20281.619	4.802	-20276.817
(L1)Ni(I)Cl	-32790.635	4.616	-32786.020
(L1)Ni(II)Cl ₂	-14080.720	4.035	-14076.685
int0-TS	-39458.101	9.242	-39448.860
int-A'	-39458.382	9.341	-39449.041
int-A'-TS	-39457.778	9.337	-39448.441
int-B'	-39458.824	9.312	-39449.512
int-A' _β	-39458.202	9.232	-39448.971
int-A' _β -TS	-39457.472	9.273	-39448.198
int-B' _β	-39458.718	9.381	-39449.337
int-A-TS	-39457.842	9.204	-39448.637
int-B	-34328.414	9.003	-34319.411
int-B-1	-34327.761	9.016	-34318.745
int-B-TS	-34327.446	9.023	-34318.424
int-C	-34328.493	9.081	-34319.411
int-B-2	-34327.899	9.005	-34318.894
Int-B-TS-i	-34327.391	9.017	-34318.374
Int-C-i	-34328.489	9.162	-34319.327
int-D	-34346.458	9.410	-34337.048
int-D-1	-34346.059	9.398	-34336.661
int-D-TS	-34344.822	9.364	-34335.458
int-D-2	-34346.267	9.405	-34336.862
int-D-TS-i	-34344.787	9.409	-34335.379
Int-E	-34345.567	9.368	-34336.198
Int-E-TS	-34344.907	9.279	-34335.628
int-F	-46854.294	9.211	-46845.082
int-F-1	-46854.318	9.198	-46845.120
int-F-TS	-46853.383	9.240	-46844.143
int-F-2	-46854.018	9.212	-46844.806
int-F-TS-i	-46853.187	9.130	-46844.057
int-G	-46853.764	9.158	-46844.606
int-H-TS	-51966.770	9.059	-51957.712

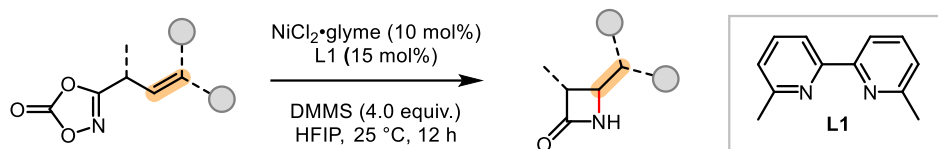
Supplementary Table 10. Summarized energy components of DFT-optimized structures for the initial competing paths in DMA (for substrates **1** and **1'**).

DFT-optimized Structures	E(sol) (SCF/TZ) [eV] M06/6-311+G**, SDD(Ni)/ SMD(DMA)	G-E (Thermochemistry correction energy) [eV] M06/6-31G**, SDD(Ni)	G(sol) [eV]
CO₂	-5130.627	-0.173	-5130.800
(L1)Ni(D)H	-20281.388	4.802	-20276.586
int-A'-TS'	-39457.454	9.337	-39448.117
int-A'_β-TS	-39457.104	9.273	-39447.831
int-A-TS	-39457.574	9.204	-39448.370
1'	-20211.360	3.858	-20207.502
1'-int-A'	-40493.413	9.342	-40484.071
1'-int-A'-TS	-40493.051	9.432	-40483.619
1'-int-A-TS	-40492.886	9.311	-40483.575

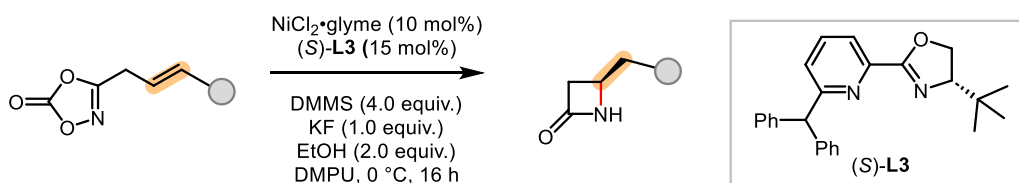
Supplementary Table 11. Summarized energy components of DFT-optimized structures for the enantioselectivity-determining process.

DFT-optimized Structures	E(sol) (SCF/TZ) [eV] M06/6-311+G**, SDD(Ni)/ SMD(DMA)	G-E (Thermochemistry correction energy) [eV] M06/6-31G**, SDD(Ni)	G(sol) [eV]
int-B _{chiral}	-50077.100	15.070	-50062.030
int-B _{R-a} -TS	-50076.084	15.067	-50061.016
int-B _{R-b} -TS	-50076.139	15.113	-50061.026
int-B _{S-a} -TS	-50076.264	15.108	-50061.156
int-B _{S-b} -TS	-50076.161	15.123	-50061.037
int-D _{chiral}	-50095.099	15.523	-50079.576
int-D _{R-a} -TS	-50093.610	15.500	-50078.110
int-D _{R-b} -TS	-50093.395	15.517	-50077.878
int-D _{R-c} -TS	-50093.688	15.485	-50078.203
int-D _{R-d} -TS	-50093.604	15.465	-50078.139
int-D _{S-a} -TS	-50093.513	15.481	-50078.032
int-D _{S-b} -TS	-50093.514	15.497	-50078.017
int-D _{S-c} -TS	-50093.642	15.460	-50078.181
int-D _{S-d} -TS	-50093.690	15.517	-50078.174
int-F _{chiral}	-62603.134	15.308	-62587.826
int-F _{R-a}	-62603.039	15.275	-62587.764
int-F _{R-b}	-62603.204	15.369	-62587.835
int-F _{R-c}	-62603.050	15.308	-62587.741
int-F _{R-d}	-62603.091	15.362	-62587.729
int-F _{R-a} -TS	-62602.207	15.313	-62586.894
int-F _{R-b} -TS	-62601.966	15.262	-62586.704
int-F _{R-c} -TS	-62602.005	15.263	-62586.743
int-F _{R-d} -TS	-62601.921	15.279	-62586.642
int-F _{S-a}	-62603.299	15.397	-62587.901
int-F _{S-b}	-62603.045	15.366	-62587.679
int-F _{S-c}	-62603.025	15.298	-62587.726
int-F _{S-d}	-62602.967	15.366	-62587.601
int-F _{S-a} -TS	-62602.040	15.297	-62586.743
int-F _{S-b} -TS	-62602.110	15.309	-62586.801
int-F _{S-c} -TS	-62601.939	15.275	-62586.664
int-F _{S-d} -TS	-62602.033	15.304	-62586.729
int-G _R	-62602.536	15.265	-62587.270
int-G _S	-62602.467	15.272	-62587.195

Procedures for the NiH-Catalysed Intramolecular Hydroamidation of Alkenes Leading to β -Lactams

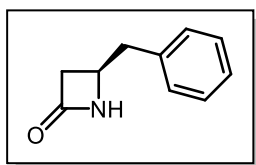


General Procedure A: To a reaction vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (10 mol%), 6,6'-dimethyl-2,2'-bipyridine **L1** (15 mol%), and anhydrous HFIP (0.1 M) in an argon-filled glovebox. The resulting mixture was stirred for 10 min before alkenyl dioxazolone (1.0 equiv.) and DMMS (4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at 25 °C for 12 h. After completion, the resulting mixture was filtered through a pad of silica, washed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: *n*-hexane/EtOAc = 10:1 to 1:1) to afford the desired product.



General Procedure B: To a reaction vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (10 mol%), $(S)\text{-L3}$ (15 mol%), and anhydrous DMPU (0.1 M) in an argon-filled glovebox. The resulting mixture was stirred over 10 min before KF (1.0 equiv.), EtOH (2.0 equiv.), and alkenyl dioxazolone (1.0 equiv.) were added. The mixture was cooled to 0 °C in a glovebox fridge, and to this was added DMMS (4.0 equiv.). The vial was sealed with a screw cap, quickly removed from the glovebox, and stirred at 0 °C for 16 h. After completion, the resulting mixture was quenched with 1.0 M $\text{HCl}_{(\text{aq})}$ and extracted with *t*-BuOMe. The combined organic layers were dried over anhydrous MgSO_4 , filtered, concentrated under reduced pressure, and purified by silica column chromatography (eluent: *n*-hexane/ EtOAc = 10:1 to 1:1) to afford the desired product.

(*R*)-4-Benzylazetidin-2-one, (*R*)-2



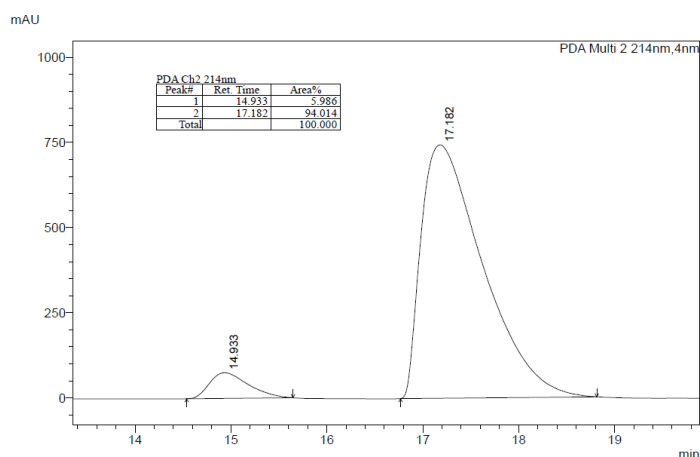
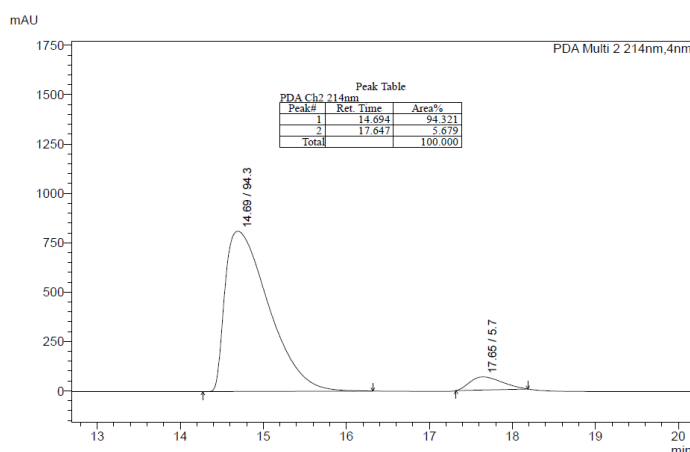
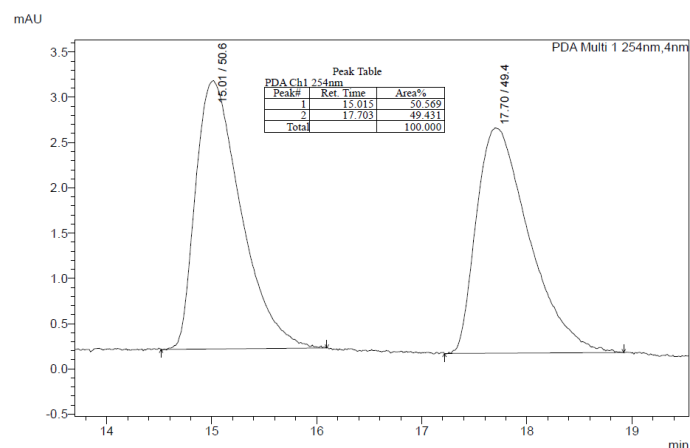
General Procedure A, in 0.1 mmol scale; White solid (14.5 mg, 90%); **General Procedure B** using $(S)\text{-L3}$, in 0.1 mmol scale; (14.0 mg, 87%); **General Procedure B** using $(R)\text{-L3}$, in 0.1 mmol scale; (13.2 mg, 82%); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.33 (t, J = 7.5 Hz, 2H), 7.26 (d, J = 15.0 Hz, 1H), 7.18 (d, J = 7.5 Hz, 2H), 5.86 (s, 1H), 3.85 (dtd, J = 8.0, 5.5, 2.5 Hz, 1H), 3.08 (ddd, J = 15.0, 5.0, 2.5 Hz, 1H), 2.98 (dd, J = 13.5, 5.5 Hz, 1H), 2.85 (dd, J = 13.5, 8.0 Hz, 1H), 2.70 (dd, J = 15.0, 2.5 Hz, 1H); ^{13}C

NMR (101 MHz, CDCl₃) δ 167.2, 137.4, 128.7, 128.6, 126.8, 48.8, 43.2, 41.7; Data consistent with those reported in literature.²⁵

(R)-2: Specific Rotation $[\alpha]_D^{21} +19.1^\circ$ ($c = 0.65$, CHCl₃); Reported $[\alpha]_D^{26} +30.1^\circ$ ($c = 0.65$, CHCl₃)²⁵;

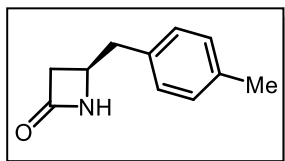
HPLC Analysis CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 5/95, 1.0 mL/min, UV 214 nm, $t_{\text{major}} = 14.7$ min, $t_{\text{minor}} = 17.7$ min, 94:6 e.r.

(S)-2: Specific Rotation $[\alpha]_D^{21} -15.8^\circ$ ($c = 0.10$, CHCl₃); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 5/95, 1.0 mL/min, UV 214 nm, $t_{\text{major}} = 17.2$ min, $t_{\text{minor}} = 14.9$ min, 94:6 e.r.



HPLC traces of racemic (**2**) and enantioenriched [(*R*)-**2** and (*S*)-**2**] products

(R)-4-(4-Methylbenzyl)azetidin-2-one, (R)-20



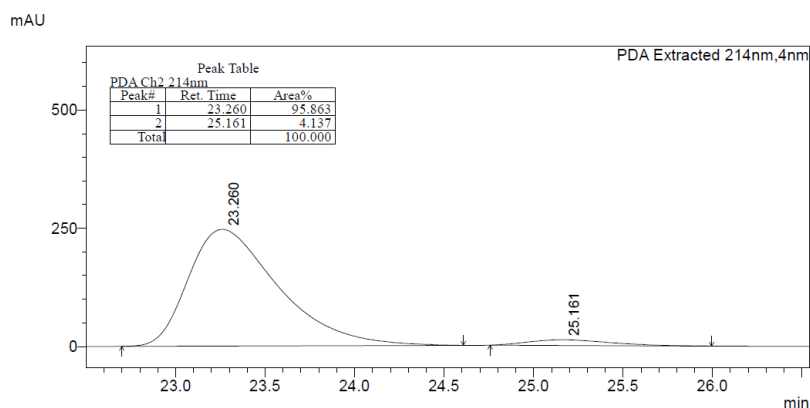
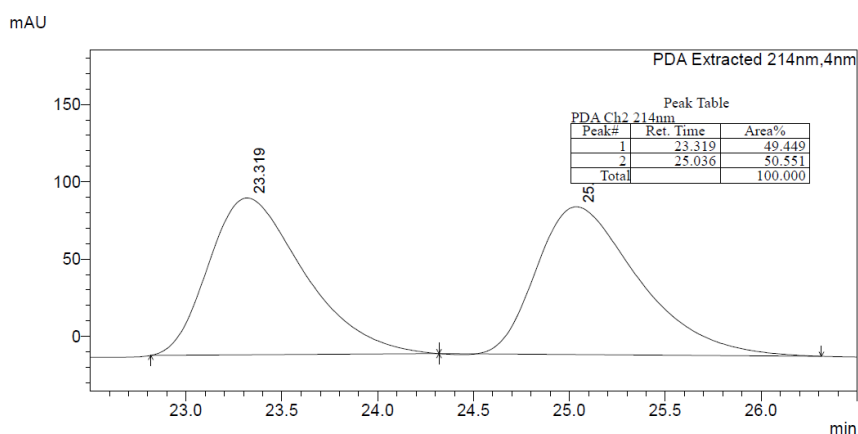
General Procedure A, in 0.1 mmol scale; White solid (11.7 mg, 67%);

General Procedure B, in 0.1 mmol scale; (13.2 mg, 75%); **m.p.** = 105 – 106

°C; ^1H NMR (500 MHz, CDCl_3) δ 7.13 (d, J = 7.5 Hz, 2H), 7.07 (d, J = 7.5 Hz, 2H), 5.87 (br. s, 1H), 3.84 – 3.80 (m, 1H), 3.06 (ddd, J = 15.0, 5.0, 2.0

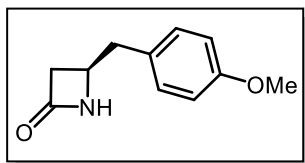
Hz, 1H), 2.93 (dd, J = 14.0, 6.0 Hz, 1H), 2.80 (dd, J = 14.0, 8.0 Hz, 1H), 2.68 (d, J = 15.0 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.6, 136.7, 134.6, 129.6, 128.8, 49.1, 43.4, 41.6, 21.2; **IR** (cm^{-1}) 3205, 2919, 1703, 1513, 1357, 1193, 965; **High Resolution MS** (EI): Calculated for $\text{C}_{11}\text{H}_{13}\text{NO}$ $[\text{M}]^+$: 175.0997, Found: 175.0998.

Specific Rotation $[\alpha]_D^{21} +29.4^\circ$ (c = 0.14, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 5/95, 0.5 mL/min, UV 214 nm, t_{major} = 23.3 min, t_{minor} = 25.2 min, 96:4 e.r.



HPLC traces of racemic (**20**) and enantioenriched [(*R*)-**20**] products

(R)-4-(4-Methoxybenzyl)azetidin-2-one, (R)-21



General Procedure A, in 0.1 mmol scale; White solid (15.3 mg, 80%);

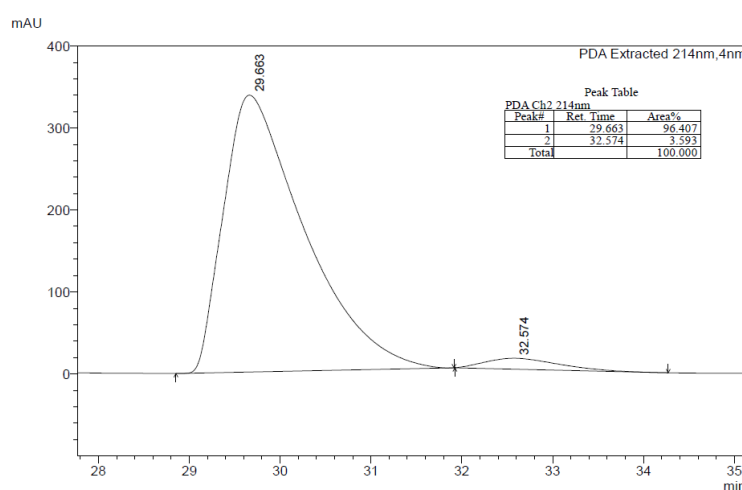
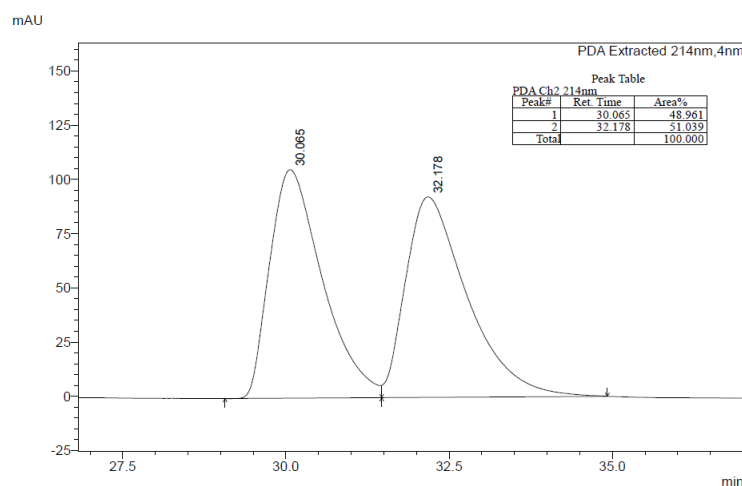
General Procedure B, in 0.1 mmol scale; (13.4 mg, 70%); **m.p.** = 45 – 46

°C; ¹H NMR (500 MHz, CDCl₃) δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.96 (br. s, 1H), 3.82 – 3.78 (m, 4H), 3.05 (ddd, *J* = 15.0, 5.0,

2.0 Hz, 1H), 2.90 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.78 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.71 – 2.61 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 167.7, 158.7, 129.9, 129.7, 114.4, 55.4, 49.2, 43.3, 41.1; IR (cm⁻¹) 3206, 2952, 2929, 1705, 1608, 1510, 1241, 1173, 1031, 976; **High Resolution MS** (EI): Calculated for C₁₁H₁₃NO₂ [M]⁺: 191.0946, Found: 191.0949.

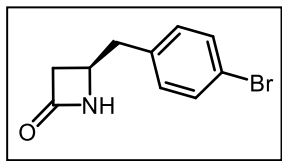
Specific Rotation [α]_D²¹ +33.0° (c = 0.16, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-

PrOH/*n*-hexane = 5/95, 0.7 mL/min, UV 214 nm, *t*_{major} = 29.7 min, *t*_{minor} = 32.6 min, 96:4 e.r.



HPLC traces of racemic (**21**) and enantioenriched [(*R*)-**21**] products

(R)-4-(4-Bromobenzyl)azetidin-2-one, (R)-22



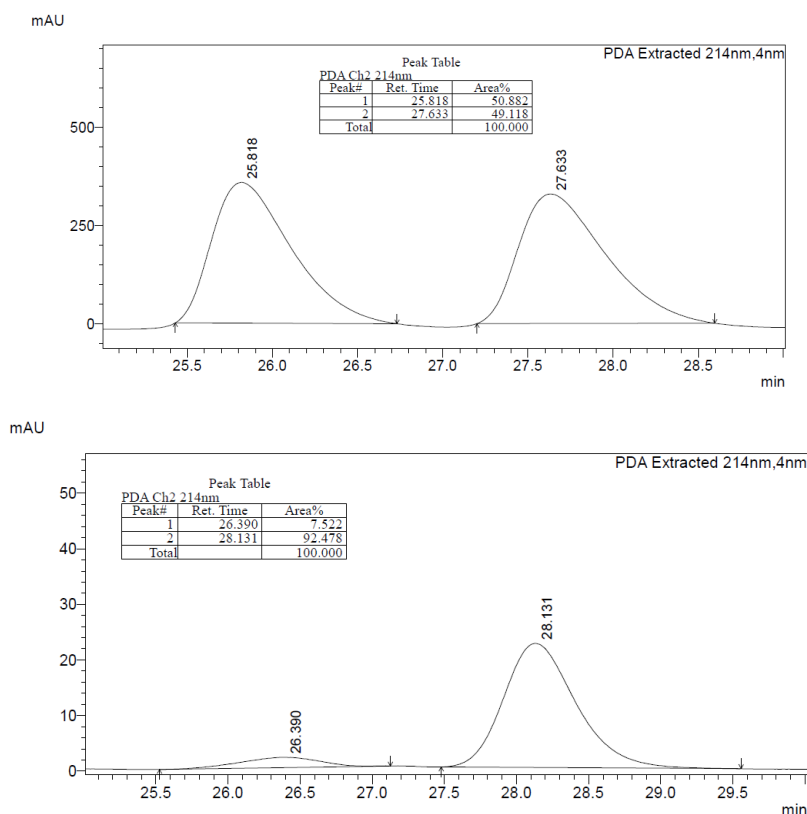
General Procedure A, in 0.1 mmol scale; White solid (9.6 mg, 40%);

General Procedure B, in 0.1 mmol scale; (13.7 mg, 57%); **m.p.** = 90 – 91

°C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.45 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 5.91 (br. s, 1H), 3.82 (dtd, J = 8.0, 5.5, 2.5 Hz, 1H), 3.08 (ddd, J =

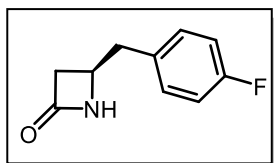
15.0, 5.5, 2.5 Hz, 1H), 2.93 (dd, J = 14.0, 5.5 Hz, 1H), 2.81 (dd, J = 14.0, 8.0 Hz, 1H), 2.67 (ddd, J = 15.0, 2.5, 1.0 Hz, 1H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 167.4, 136.6, 132.1, 130.6, 121.0, 48.8, 43.5, 41.4; **IR** (cm^{-1}) 3222, 2940, 1708, 1486, 1259, 1066, 988, 628; **High Resolution MS** (EI): Calculated for $\text{C}_{10}\text{H}_9\text{BrNO}$ $[\text{M}]^+$: 238.9946, Found: 238.9944.

Specific Rotation $[\alpha]_D^{21} +31.0^\circ$ (c = 0.10, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IF-3, 32 °C, *i*-PrOH/*n*-hexane = 5/95, 0.5 mL/min, UV 214 nm, t_{major} = 28.1 min, t_{minor} = 26.4 min, 92:8 e.r.



HPLC traces of racemic (**22**) and enantioenriched [(*R*)-**22**] products

(R)-4-(4-Fluorobenzyl)azetidin-2-one, (R)-23

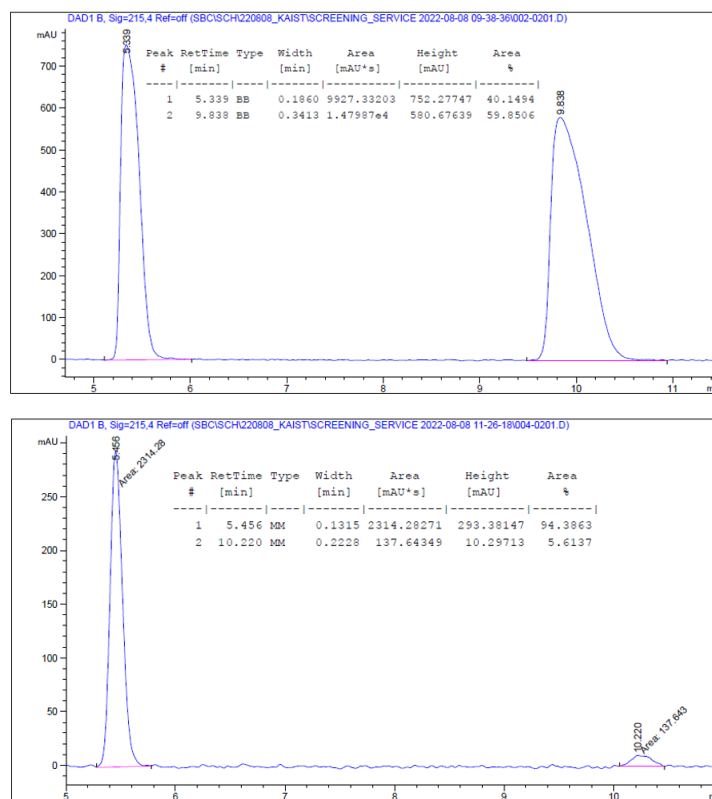


General Procedure A, in 0.1 mmol scale; White solid (17.2 mg, 96%);

General Procedure B, in 0.1 mmol scale; (12.7 mg, 71%); **m.p.** = 78 – 79 °C;

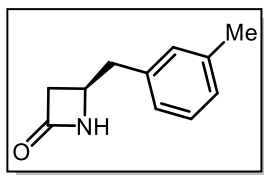
¹H NMR (400 MHz, CDCl₃) δ 7.16 – 7.12 (m, 2H), 7.05 – 6.99 (m, 2H), 5.87 (br. s, 1H), 3.85 – 3.77 (m, 1H), 3.08 (ddd, *J* = 15.0, 5.0, 2.5 Hz, 1H), 2.95 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.82 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.68 (ddd, *J* = 15.0, 2.5, 1.0 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 167.4, 162.0 (d, *J*_{C-F} = 245.0 Hz), 133.3 (d, *J*_{C-F} = 3.5 Hz), 130.34 (d, *J*_{C-F} = 8.0 Hz), 115.8 (d, *J*_{C-F} = 21.0 Hz), 49.0, 43.4, 41.2; ¹⁹F NMR (376 MHz, CDCl₃) δ –115.8; IR (cm⁻¹) 3157, 3095, 2919, 1734, 1703, 1507, 1218, 1189, 815, 692; **High Resolution MS** (EI): Calculated for C₁₀H₁₀FNO [M]⁺: 179.0746, Found: 179.0745.

Specific Rotation [α]_D²¹ +13.3° (c = 0.12, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IH-3, 32 °C, 0.1% diethylamine in EtOH/*n*-hexane = 50/50, 1.0 mL/min, UV 215 nm, t_{major} = 5.5 min, t_{minor} = 10.2 min, 94:6 e.r.



HPLC traces of racemic (**23**) and enantioenriched [(*R*)-**23**] products

(R)-4-(3-Methylbenzyl)azetidin-2-one, (R)-24



General Procedure A, in 0.1 mmol scale; White solid (16.3 mg, 93%);

General Procedure B, in 0.1 mmol scale; (13.6 mg, 78%); **m.p.** = 41 – 42 °C;

¹H NMR (500 MHz, CDCl₃) δ 7.21 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.01 – 6.95 (m, 2H), 5.91 (br. s, 1H), 3.83 (dtd, *J* = 8.0, 5.5, 2.5 Hz, 1H),

3.07 (ddd, *J* = 15.0, 5.5, 2.5 Hz, 1H), 2.93 (dd, *J* = 13.5, 5.5 Hz, 1H), 2.80 (dd, *J* = 13.5, 8.0 Hz, 1H),

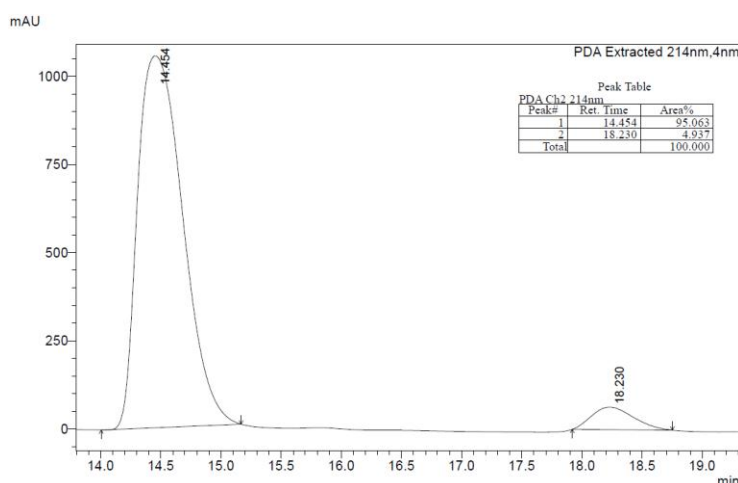
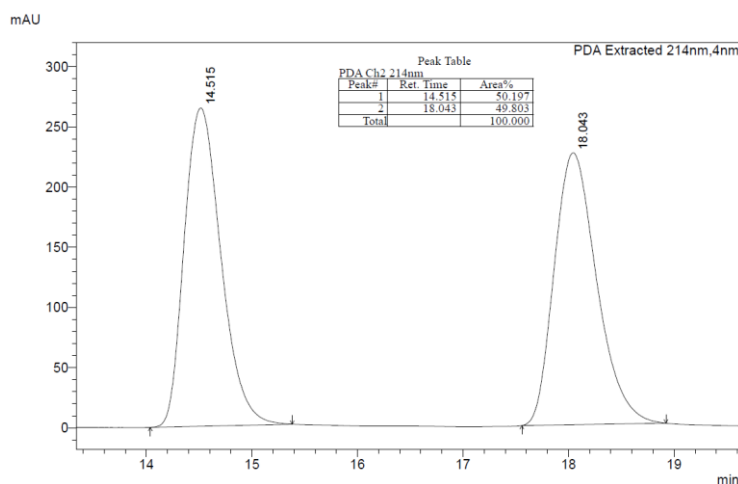
2.69 (d, *J* = 15.0 Hz, 1H), 2.34 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 167.6, 138.6, 137.6, 129.7,

128.9, 127.8, 125.9, 49.1, 43.5, 42.0, 21.5; **IR** (cm⁻¹) 3212, 3094, 2921, 1744, 1608, 1361, 1195, 699;

High Resolution MS (EI): Calculated for C₁₁H₁₃NO [M]⁺: 175.0997, Found: 175.0993.

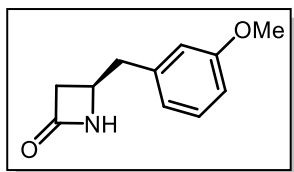
Specific Rotation [α]_D²¹ +29.4° (c = 0.10, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-

hexane = 10/90, 0.5 mL/min, UV 214 nm, *t*_{major} = 14.5 min, *t*_{minor} = 18.2 min, 95:5 e.r.



HPLC traces of racemic (**24**) and enantioenriched [(*R*)-**24**] products

(R)-4-(3-Methoxybenzyl)azetidin-2-one, (R)-25



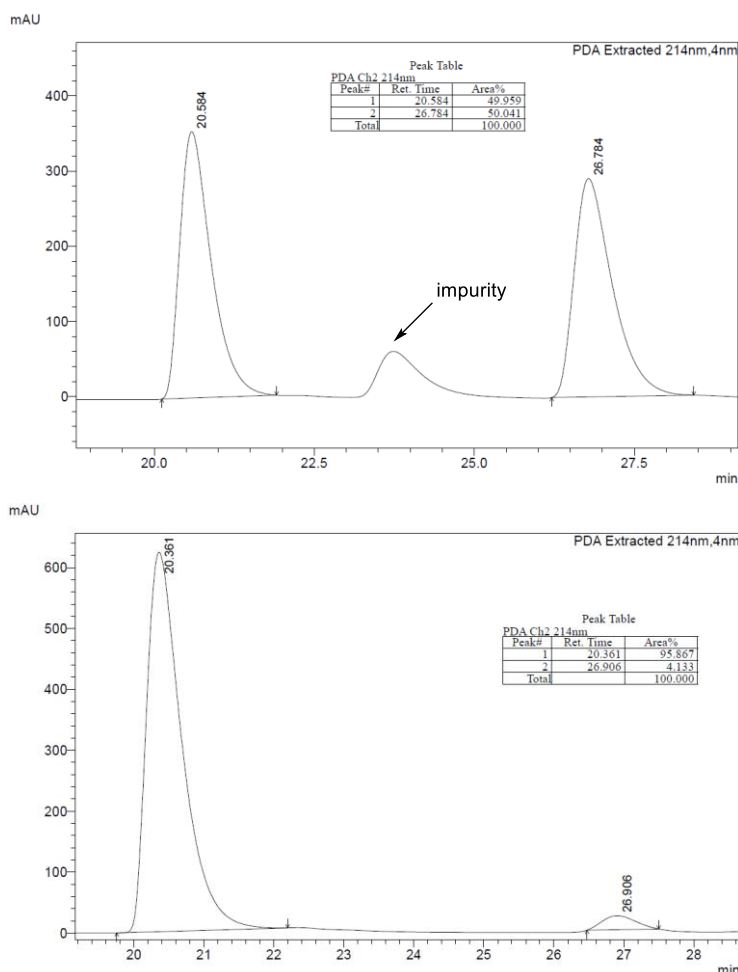
General Procedure A, in 0.1 mmol scale; White solid (15.1 mg, 79%);

General Procedure B, in 0.1 mmol scale; (10.5 mg, 55%); **m.p.** = 71 – 72

°C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.23 (t, J = 8.0 Hz, 1H), 6.80 (dd, J = 8.0, 2.5 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 5.93 (br. s, 1H),

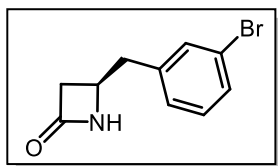
3.84 (dtd, J = 8.0, 5.0, 2.5 Hz, 1H), 3.80 (s, 3H), 3.08 (ddd, J = 15.0, 5.0, 2.5 Hz, 1H), 2.95 (dd, J = 14.0, 5.5 Hz, 1H), 2.81 (dd, J = 14.0, 8.0 Hz, 1H), 2.69 (d, J = 15.0 Hz, 1H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 167.6, 160.0, 139.3, 130.0, 121.1, 114.8, 112.1, 55.3, 49.0, 43.5, 42.1; **IR** (cm^{-1}) 3206, 2958, 1707, 1592, 1467, 1259, 1164, 1038, 698; **High Resolution MS** (EI): Calculated for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ $[\text{M}]^+$: 191.0946, Found: 191.0948.

Specific Rotation $[\alpha]_D^{21} +26.3^\circ$ (c = 0.10, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 32 °C, i -PrOH/ n -hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 20.4 min, t_{minor} = 26.9 min, 96:4 e.r.



HPLC traces of racemic (**25**) and enantioenriched [(*R*)-**25**] products

(R)-4-(3-Bromobenzyl)azetidin-2-one, (R)-26



General Procedure A, in 0.1 mmol scale; White solid (22.3 mg, 93%);

General Procedure B, in 0.1 mmol scale; (14.0 mg, 58%); **m.p.** = 72 – 74

°C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H),

7.20 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 5.89 (br. s, 1H), 3.84 (dtd,

J = 8.0, 5.5, 2.5 Hz, 1H), 3.10 (ddd, J = 15.0, 5.5, 2.5 Hz, 1H), 2.95 (dd, J = 14.0, 5.5 Hz, 1H), 2.82 (dd,

J = 14.0, 8.0 Hz, 1H), 2.69 (d, J = 15.0 Hz, 1H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 167.3, 139.9, 131.9,

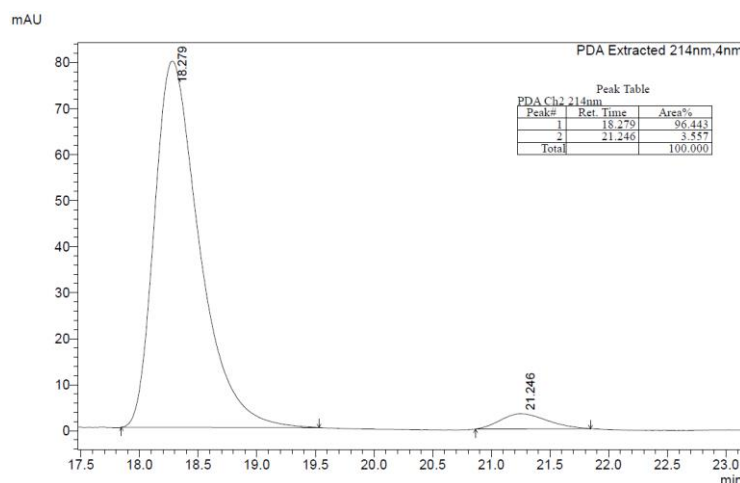
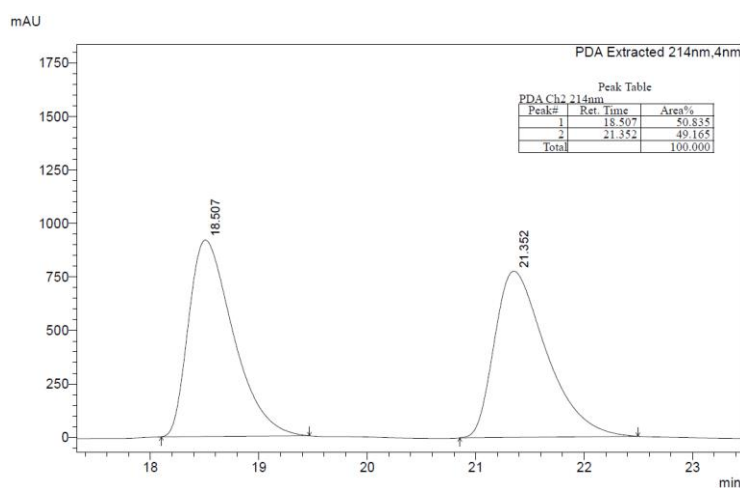
130.6, 130.3, 127.5, 123.0, 48.8, 43.5, 41.6; **IR** (cm^{-1}) 3156, 3089, 2914, 1736, 1703, 1564, 1185, 1064,

989, 782, 688; **High Resolution MS** (EI): Calculated for $\text{C}_{10}\text{H}_9\text{BrNO}$ $[\text{M}]^+$: 238.9946, Found:

238.9948.

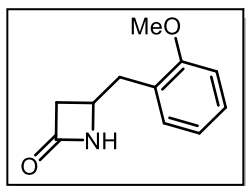
Specific Rotation $[\alpha]_D^{21} +12.6^\circ$ (c = 0.10, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-

hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 18.3 min, t_{minor} = 21.2 min, 96:4 e.r.



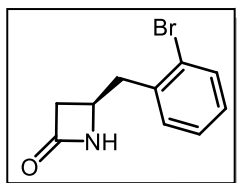
HPLC traces of racemic (**26**) and enantioenriched [(*R*)-**26**] products

4-(2-Methoxybenzyl)azetidin-2-one, 27



General Procedure A, in 0.07 mmol scale; White solid (12.3 mg, 92%); **m.p.** = 87 – 88 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.26 – 7.21 (m, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.94 – 6.84 (m, 2H), 5.87 (br. s, 1H), 3.90 (dtd, *J* = 7.5, 5.5, 2.5 Hz, 1H), 3.83 (s, 3H), 3.06 – 2.99 (m, 2H), 2.83 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.70 (d, *J* = 15.0 Hz, 1H); **¹³C NMR** (126 MHz, CDCl₃) δ 168.0, 157.6, 130.7, 128.4, 126.0, 120.8, 110.6, 55.4, 47.8, 43.4, 36.7; **IR** (cm⁻¹) 3191, 2957, 2917, 1745, 1600, 1639, 1493, 1248, 1025, 756; **High Resolution MS** (EI): Calculated for C₁₁H₁₃NO₂ [M]⁺: 191.0946, Found: 191.0947.

(R)-4-(2-Bromobenzyl)azetidin-2-one, (R)-28



General Procedure A, in 0.1 mmol scale; White solid (22.5 mg, 94%);

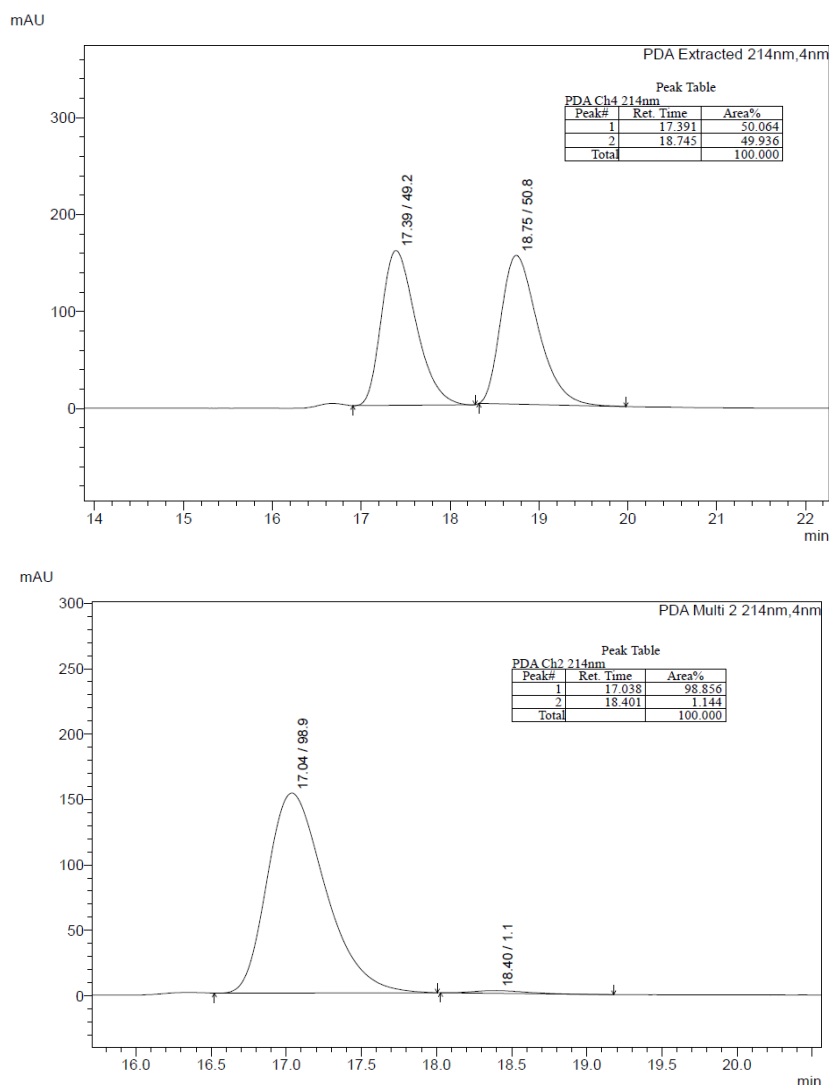
General Procedure B, in 0.1 mmol scale; (14.4 mg, 60%); **m.p.** = 73 – 74 °C; **¹H NMR**

(500 MHz, CDCl₃) δ 7.57 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.94 (br. s, 1H), 4.00 – 3.97 (m, 1H),

3.15 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.09 (ddd, *J* = 15.0, 5.0, 2.0 Hz, 1H), 2.99 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.75 (d, *J* = 15.0 Hz, 1H); **¹³C NMR** (126 MHz, CDCl₃) δ 167.5, 137.1, 133.4, 131.1, 128.9, 128.0, 124.6, 47.4, 43.4, 41.8; **IR** (cm⁻¹) 3217, 2948, 1744, 1470, 1359, 1190, 748; **High Resolution MS** (FAB): Calculated for C₁₀H₁₁BrNO [M+H]⁺: 240.0024, Found: 240.0026.

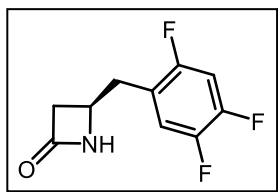
Specific Rotation [α]_D²¹ +67.5° (c = 0.13, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-

PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, *t*_{major} = 17.0 min, *t*_{minor} = 18.4 min, 99:1 e.r.



HPLC traces of racemic (**28**) and enantioenriched [(*R*)-**28**] products

(R)-4-(2,4,5-Trifluorobenzyl)azetidin-2-one, (R)-29



General Procedure A, in 0.10 mmol scale; Yellow solid (17.8 mg, 83%);

General Procedure B, in 0.78 mmol scale; (108.2 mg, 64%); **m.p.** = 106 –

108 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.07 – 6.88 (m, 2H), 5.98 (br. s, 1H),

3.93 – 3.83 (m, 1H), 3.09 (ddd, *J* = 15.0, 5.0, 2.5 Hz, 1H), 2.98 (ddd, *J* =

14.0, 6.0, 1.5 Hz, 1H), 2.85 (ddd, *J* = 14.0, 7.0, 1.5 Hz, 1H), 2.69 (ddd, *J* = 15.0, 2.5, 1.0 Hz, 1H); **¹³C**

NMR (101 MHz, CDCl₃) δ 167.0, 156.3 (d, *J*_{C-F} = 247.0 Hz), 149.2 (t, *J*_{C-F} = 247.0 Hz), 146.7 (t, *J*_{C-F}

= 247.0 Hz) 120.5 (d, *J*_{C-F} = 18.5 Hz), 118.6 (d, *J*_{C-F} = 19.0 Hz), 105.9 (dd, *J*_{C-F} = 28.5, 20.5 Hz), 47.42,

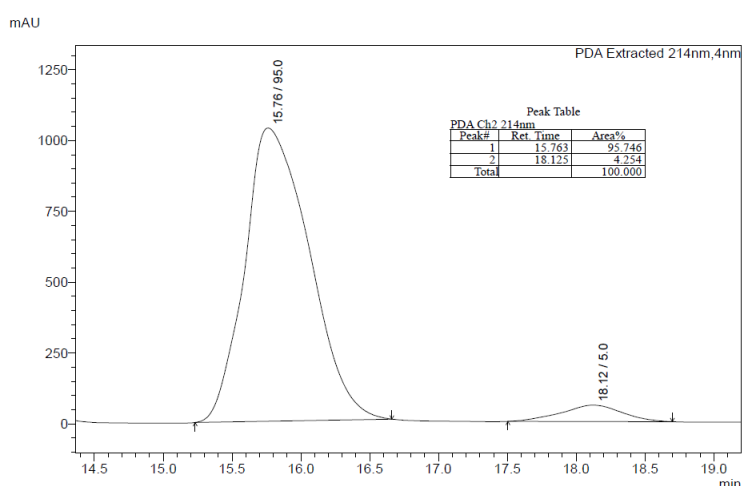
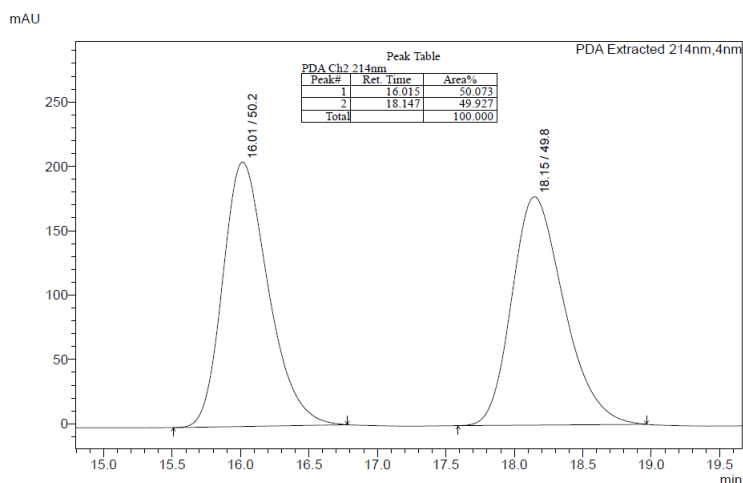
43.24, 34.54; **¹⁹F NMR** (376 MHz, CDCl₃) δ –119.2 (dd, *J* = 15.3, 3.5 Hz), –134.7 (dd, *J* = 21.2, 3.7

Hz), –142.2 (dd, *J* = 21.4, 15.4 Hz); **IR** (cm⁻¹) 3169, 3093, 2927, 1743, 1501, 1423, 1326, 1153, 837,

710; **High Resolution MS** (FAB): Calculated for C₁₀H₉F₃NO [M+H]⁺: 216.0631, Found: 216.0634.

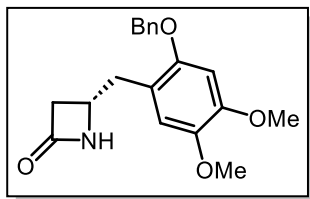
Specific Rotation [α]_D²¹ +2.7° (c = 0.15, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-

hexane = 10/90, 0.5 mL/min, UV 214 nm, *t*_{major} = 15.8 min, *t*_{minor} = 18.1 min, 96:4 e.r.



HPLC traces of racemic (**29**) and enantioenriched [(*R*)-**29**] products

(S)-4-[2-(Benzyloxy)-4,5-dimethoxybenzyl]azetidin-2-one, (S)-30



General Procedure A, in 1.0 mmol scale; White solid (251.9 mg, 77%);

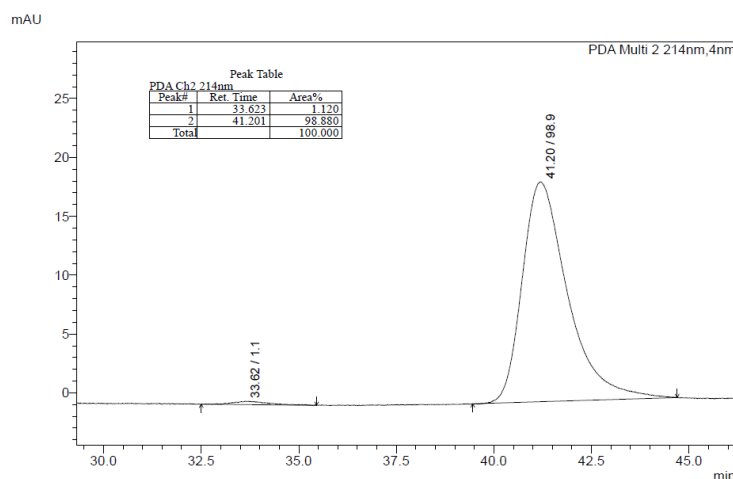
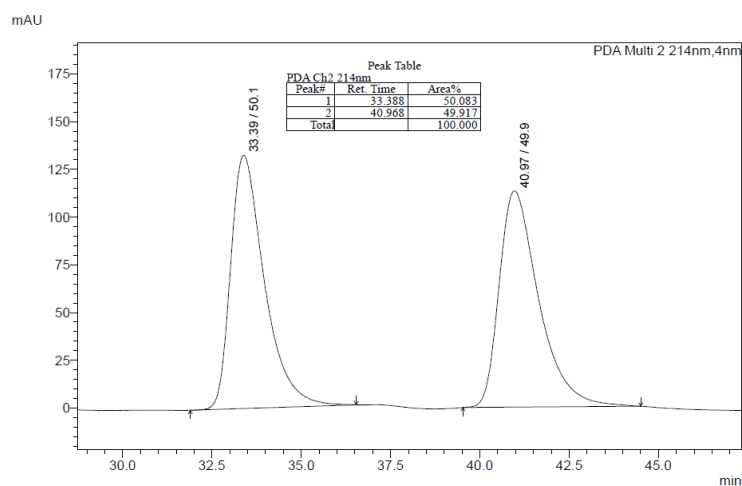
General Procedure B, using (*R*)-**L3** as ligand in 1.0 mmol scale; (270 mg,

82%); **m.p.** = 128 – 129 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.35 (m, 4H), 7.36 – 7.30 (m, 1H), 6.65 (s, 1H), 6.57 (s, 1H), 6.04 (br. s, 1H), 5.04 (s, 2H), 3.88 – 3.83 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 2.98 (dd, *J* =

13.5, 5.5 Hz, 2H), 2.76 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.66 (d, *J* = 15.0 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 168.0, 150.7, 148.6, 143.3, 137.1, 128.8, 128.2, 127.4, 117.7, 114.7, 99.3, 71.3, 56.7, 56.2, 48.0, 43.2, 36.2; **IR** (cm⁻¹) 3332, 2939, 2850, 1743, 1512, 1224, 1096, 1117, 1023, 862; **High Resolution MS** (EI): Calculated for C₁₉H₂₁NO₄ [M]⁺: 327.1471, Found: 327.1471.

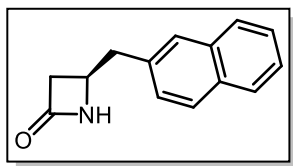
Specific Rotation [α]_D²¹ –23.2° (c = 0.18, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-

PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, *t*_{major} = 41.2 min, *t*_{minor} = 33.6 min, 99:1 e.r.



HPLC traces of racemic (**30**) and enantioenriched [(*S*)-**30**] products

(R)-4-(Naphthalen-2-ylmethyl)azetidin-2-one, (R)-31



General Procedure A, in 0.1 mmol scale; White solid (20.1 mg, 95%);

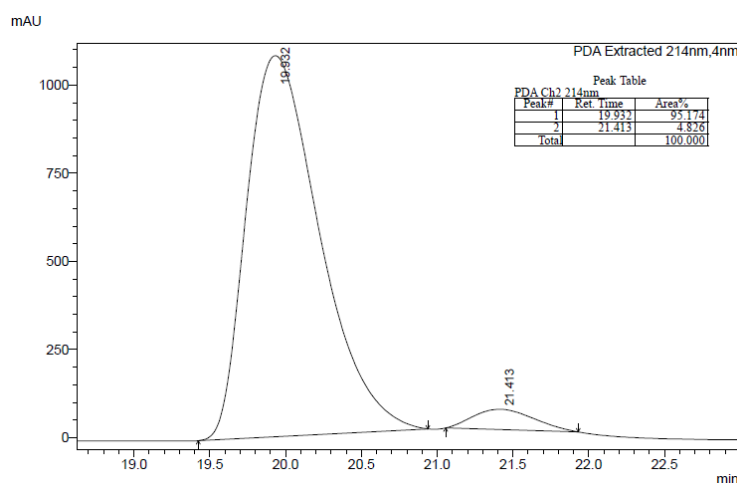
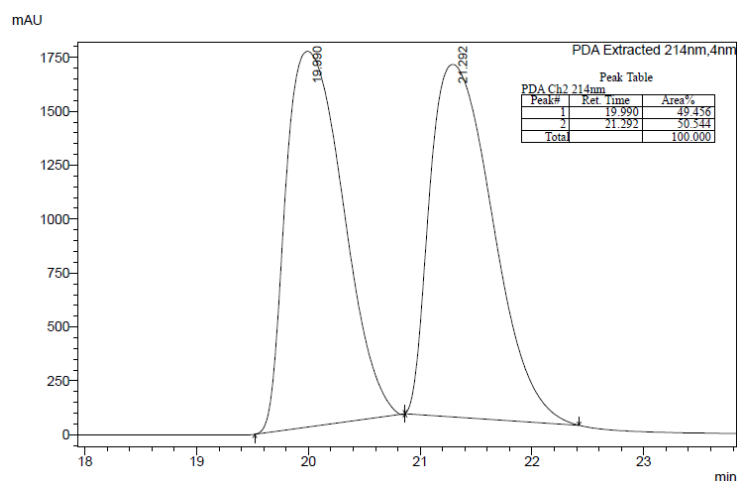
General Procedure B, in 0.1 mmol scale; (18.8 mg, 89%); **m.p.** = 126 –

128 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.88 – 7.74 (m, 3H), 7.63 (s, 1H),

7.51 – 7.45 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 5.96 (br. s, 1H), 3.98 – 3.89

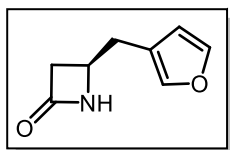
(m, 1H), 3.15 – 3.08 (m, 2H), 3.00 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.75 (d, *J* = 15.0 Hz, 1H); **¹³C NMR** (126 MHz, CDCl₃) δ 167.6, 135.2, 133.7, 132.5, 128.7, 127.8, 127.6, 127.4, 127.1, 126.5, 125.9, 49.0, 43.5, 42.2; **IR** (cm⁻¹) 3257, 3050, 2949, 1788, 1350, 1201, 738, 640; **High Resolution MS** (EI): Calculated for C₁₄H₁₃NO [M]⁺: 211.0997, Found: 211.1000.

Specific Rotation [α]_D²¹ +33.7 (*c* = 0.10, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, *t*_{major} = 19.9 min, *t*_{minor} = 21.4 min, 95:5 e.r.



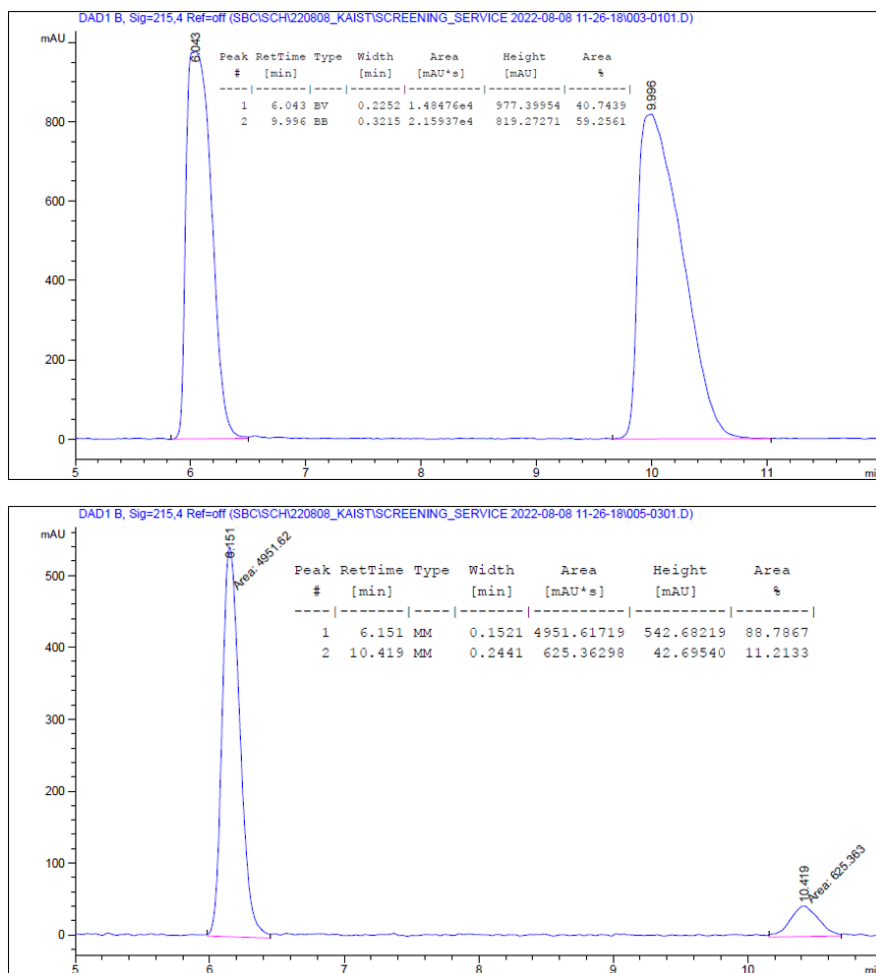
HPLC traces of racemic (**31**) and enantioenriched [(*R*)-**31**] products

(R)-4-(Furan-3-ylmethyl)azetidin-2-one, (R)-32



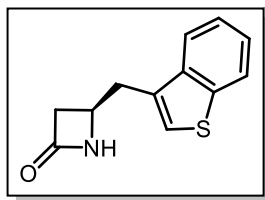
General Procedure A, in 0.1 mmol scale; White solid (12.9 mg, 85%); **General Procedure B**, in 0.1 mmol scale; (7.9 mg, 52%); **m.p.** = 41 – 42 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.38 (s, 1H), 7.28 (s, 1H), 6.28 (s, 1H), 6.15 (br. s, 1H), 3.79 (q, *J* = 6.5 Hz, 1H), 3.07 (dd, *J* = 15.0, 5.0 Hz, 1H), 2.78 – 2.69 (m, 2H), 2.64 (d, *J* = 15.0 Hz, 1H); **¹³C NMR** (126 MHz, CDCl₃) δ 167.8, 143.5, 139.8, 120.6, 110.9, 48.1, 43.4, 31.1; **IR** (cm⁻¹) 3217, 2948, 2914, 1730, 1502, 1384, 1155, 1020, 873, 596; **High Resolution MS** (EI): Calculated for C₈H₉NO₂ [M]⁺: 151.0633, Found: 151.0631.

Specific Rotation [α]_D²¹ –19.3° (c = 0.36, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IH-3, 32 °C, 0.1% diethylamine in EtOH/*n*-hexane = 50/50, 1.0 mL/min, UV 215 nm, *t*_{major} = 6.2 min, *t*_{minor} = 10.4 min, 89:11 e.r.



HPLC traces of racemic (**32**) and enantioenriched [(*R*)-**32**] products

(R)-4-(Benzo[*b*]thiophen-3-ylmethyl)azetidin-2-one, (R)-33



General Procedure A, in 0.1 mmol scale; White solid (16.7 mg, 77%);

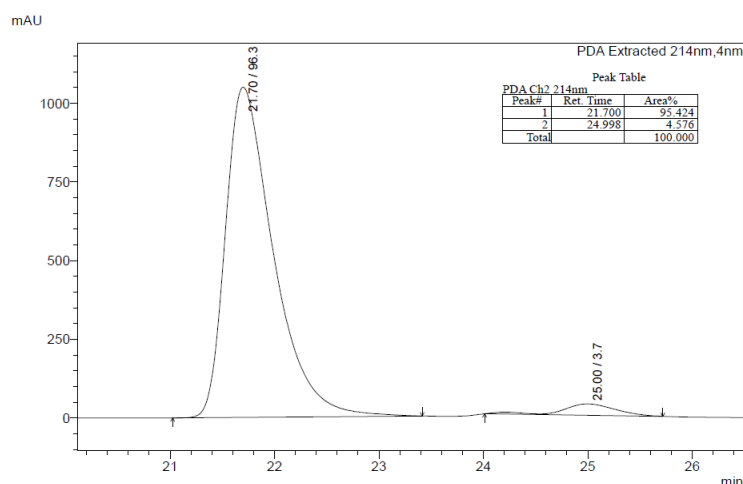
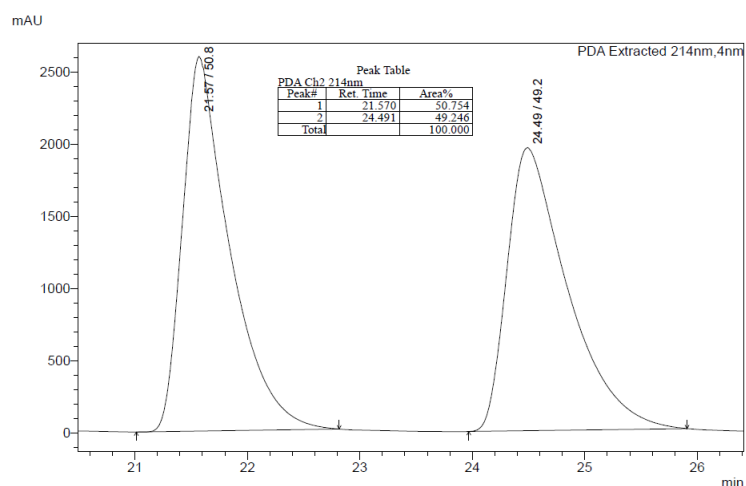
General Procedure B, in 0.1 mmol scale; (12.1 mg, 56%); **m.p.** = 84 – 86

°C; ¹H NMR (500 MHz, CDCl₃) δ 7.88 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.75 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.17 (s, 1H), 6.01 (br. s, 1H), 4.02 (dtd, *J* = 8.0, 5.5, 2.5 Hz, 1H), 3.21 (ddd, *J* = 14.5, 5.5, 1.0 Hz, 1H), 3.18 –

3.09 (m, 2H), 2.76 (ddd, *J* = 14.5, 2.5, 1.0 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 167.6, 140.7, 138.6, 132.4, 124.7, 124.4, 123.2, 123.1, 121.5, 47.6, 43.8, 34.9; IR (cm⁻¹) 3198, 3083, 2912, 2851, 1783, 1423, 1389, 1185, 1079, 829, 720; **High Resolution MS** (EI): Calculated for C₁₂H₁₁NOS [M]⁺: 217.0561, Found: 217.0562.

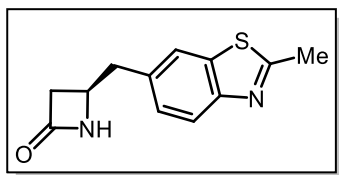
Specific Rotation [α]_D²¹ +6.4° (*c* = 0.13, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-

PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, *t*_{major} = 21.7 min, *t*_{minor} = 25.0 min, 95:5 e.r.



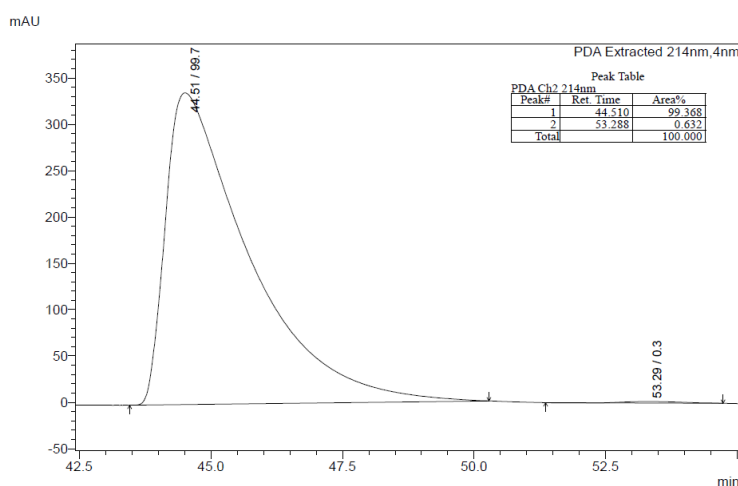
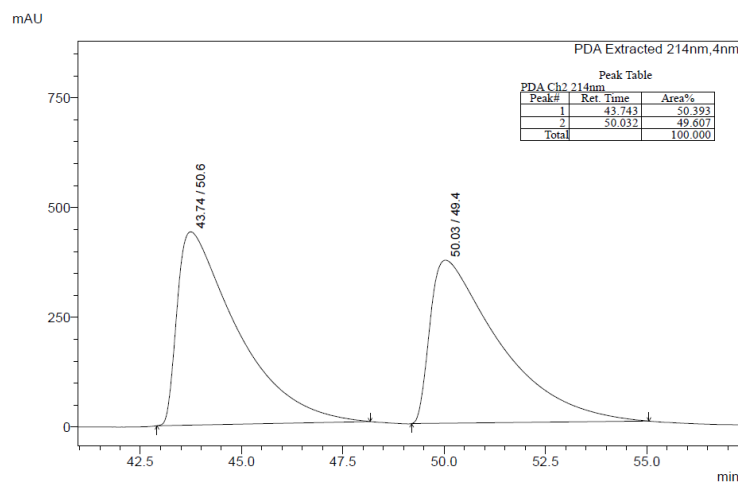
HPLC traces of racemic (**33**) and enantioenriched [(*R*)-**33**] products

(R)-4-[(2-Methylbenzo[d]thiazol-6-yl)methyl]azetidin-2-one, (R)-34



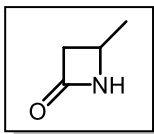
General Procedure A, in 0.1 mmol scale; Pale yellow solid (9.5 mg, 41%); **General Procedure B**, in 0.1 mmol scale; (12.8 mg, 55%); **m.p.** = 89 – 90 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.89 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.26 (dd, J = 8.5, 2.0 Hz, 1H), 5.87 (br. s, 1H), 3.90 (dtd, J = 8.0, 5.5, 2.5 Hz, 1H), 3.15 – 3.05 (m, 2H), 2.95 (dd, J = 15.0, 8.0 Hz, 1H), 2.83 (s, 3H), 2.73 (d, J = 15.0 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.4, 167.2, 152.6, 136.5, 134.4, 127.0, 122.7, 121.4, 49.2, 43.5, 42.0, 20.3; **IR** (cm^{-1}) 3217, 2923, 2852, 1744, 1420, 1169, 809; **High Resolution MS** (EI): Calculated for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{OS}$ $[\text{M}]^+$: 232.0670, Found: 232.0673.

Specific Rotation $[\alpha]_D^{21} +16.4^\circ$ (c = 0.13, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 44.5 min, t_{minor} = 53.3 min, >99:1 e.r.



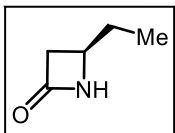
HPLC traces of racemic (**34**) and enantioenriched [(*R*)-**34**] products

4-Methylazetidin-2-one, **35**



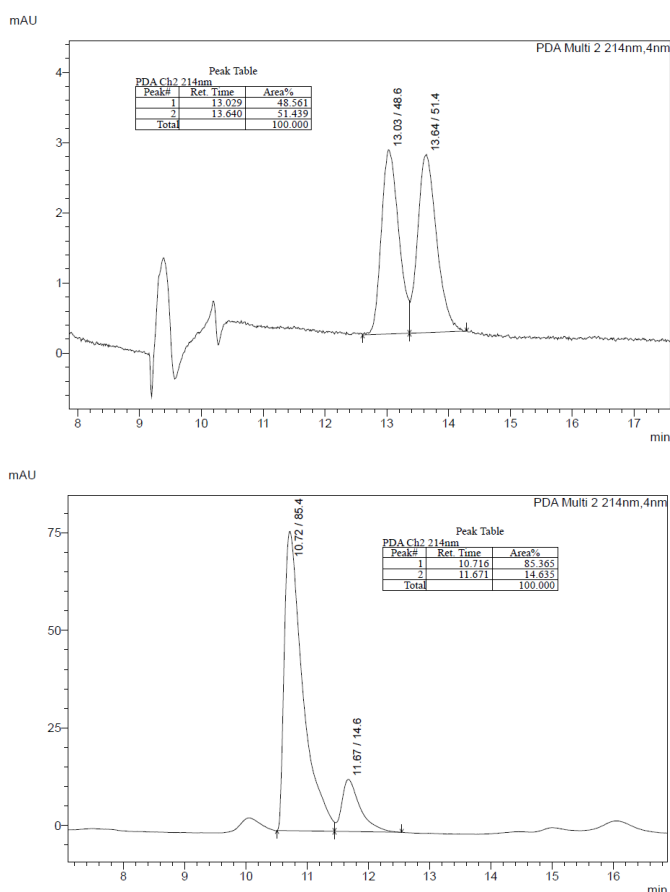
General Procedure A, in 0.1 mmol scale; Yellow oil (6.1 mg, 72%); ^1H NMR (400 MHz, CDCl_3) δ 5.80 (br. s, 1H), 3.84 – 3.73 (m, 1H), 3.11 (ddd, J = 14.5, 5.0, 2.0 Hz, 1H), 2.56 (ddd, J = 14.5, 2.5, 2.0 Hz, 1H), 1.37 (d, J = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.6, 45.2, 43.2, 22.6; Data consistent with those reported in literature²⁶.

4-Ethylazetidin-2-one, (*R*)-**36**



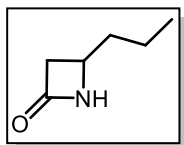
General Procedure A, in 0.1 mmol scale; Colourless oil (5.9 mg, 60%); **General Procedure B**, in 0.1 mmol scale; (3.0 mg, 30%); ^1H NMR (400 MHz, CDCl_3) δ 5.84 (br. s, 1H), 3.59 – 3.54 (m, 1H), 3.05 (dd, J = 14.5, 4.0 Hz, 1H), 2.57 (d, J = 14.5 Hz, 1H), 1.73 – 1.59 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.1, 49.6, 43.2, 28.5, 10.4; Data consistent with those reported in literature²⁷.

HPLC Analysis CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 10.7 min, t_{minor} = 11.7 min, 85:15 e.r.



HPLC traces of racemic (**36**) and enantioenriched [(*R*)-**36**] products

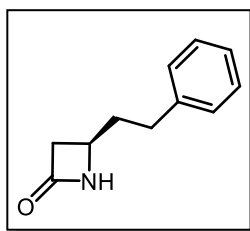
4-Propylazetidin-2-one, **37**



General Procedure A, in 0.1 mmol scale; Colourless oil (6.7 mg, 59%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.93 (br. s, 1H), 3.69 – 3.54 (m, 1H), 3.05 (ddd, J = 15.0, 5.0, 2.0 Hz, 1H), 2.56 (d, J = 15.0 Hz, 1H), 1.67 – 1.53 (m, 2H), 1.42 – 1.29 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 168.2, 48.2, 43.7, 37.7, 19.7, 14.0;

IR (cm^{-1}) 3253, 2958, 2931, 1741, 1370, 1191, 733; **High Resolution MS** (EI): Calculated for $\text{C}_6\text{H}_{11}\text{NO}$ $[\text{M}]^+$: 113.0841, Found: 113.0837.

(*R*)-4-Phenethylazetidin-2-one, (*R*)-**38**

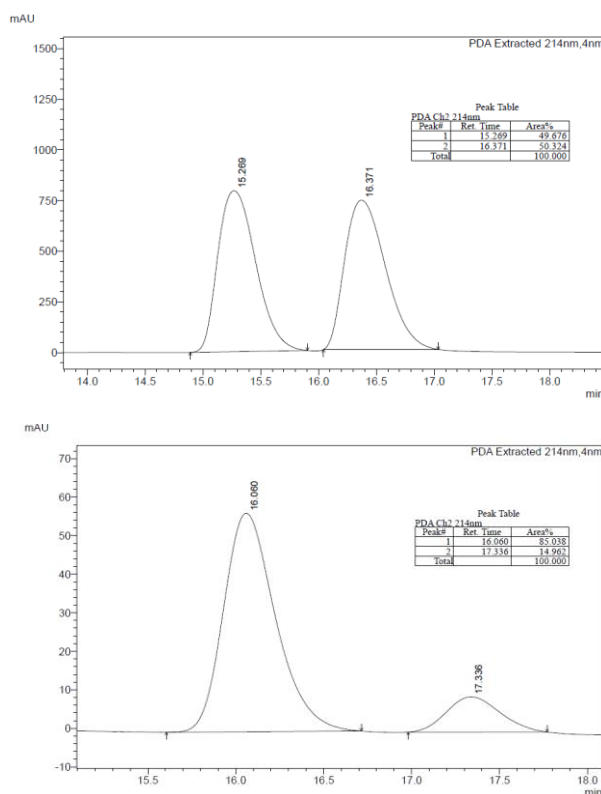


General Procedure A, in 0.1 mmol scale; Pale yellow oil (6.7 mg, 38%);

General Procedure B, in 0.1 mmol scale; (6.3 mg, 36%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.30 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 5.76 (br. s, 1H), 3.65 – 3.61 (m, 1H), 3.05 (dd, J = 14.5, 5.0 Hz, 1H), 2.74 – 2.63 (m, 2H), 2.57 (d, J = 14.5 Hz, 1H), 1.97 (q, J = 7.5 Hz, 2H); $^{13}\text{C NMR}$

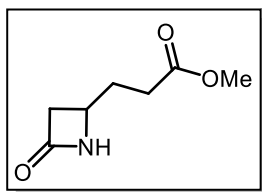
(101 MHz, CDCl_3) δ 167.9, 140.7, 128.8, 128.5, 126.5, 48.0, 43.7, 37.1, 33.1; **IR** (cm^{-1}) 3257, 2933, 1748, 1515, 1430, 1144, 700; **High Resolution MS** (EI): Calculated for $\text{C}_{11}\text{H}_{13}\text{NO}$ $[\text{M}]^+$: 175.0997, Found: 175.0998.

Specific Rotation $[\alpha]_D^{21} +1.5^\circ$ (c = 0.11, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 32 $^\circ\text{C}$, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 16.0 min, t_{minor} = 17.3 min, 85:15 e.r.



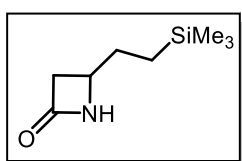
HPLC traces of racemic (**38**) and enantioenriched [(*R*)-**38**] products

Methyl 3-(4-oxoazetidin-2-yl)propanoate, 39



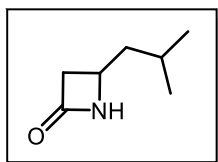
General Procedure A, in 0.5 mmol scale; White solid (61.0 mg, 78%); **m.p.** = 35 – 36 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.08 (br. s, 1H), 3.71 – 3.66 (m, 4H), 3.08 (ddd, J = 15.0, 5.0, 2.5 Hz, 1H), 2.60 (d, J = 15.0 Hz, 1H), 2.38 (t, J = 7.0 Hz, 2H), 1.96 (q, J = 7.0 Hz, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 173.2, 167.7, 52.0, 47.4, 43.5, 30.7, 30.5; **IR** (cm^{-1}) 3263, 2953, 1726, 1439, 1360, 1258, 1174; **High Resolution MS** (FAB): Calculated for $\text{C}_7\text{H}_{12}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 158.0817, Found: 158.0819.

4-[2-(Trimethylsilyl)ethyl]azetidin-2-one, 40



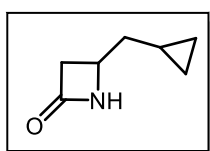
General Procedure A, in 0.1 mmol scale; White solid (8.8 mg, 51%); **m.p.** = 60 – 61 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.95 (br. s, 1H), 3.59 – 3.53 (m, 1H), 3.03 (ddd, J = 15.0, 5.0, 2.0 Hz, 1H), 2.53 (d, J = 15.0 Hz, 1H), 1.68 – 1.52 (m, 2H), 0.54 – 0.40 (m, 2H), 0.00 (s, 9H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 168.3, 50.7, 43.2, 30.0, 12.8, -1.7; **IR** (cm^{-1}) 3188, 2950, 2921, 1733, 1246, 829; **High Resolution MS** (EI): Calculated for $\text{C}_7\text{H}_{14}\text{NOSi}$ $[\text{M}-\text{CH}_3]^+$: 156.0845, Found: 156.0847.

4-Isobutylazetidin-2-one, 41



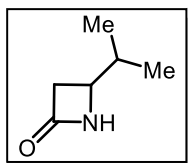
General Procedure A, in 0.1 mmol scale; Pale yellow oil (10.1 mg, 80%); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 5.93 (br. s, 1H), 3.71 – 3.64 (m, 1H), 3.08 (ddd, J = 14.5, 5.0, 2.0 Hz, 1H), 2.60 – 2.52 (m, 1H), 1.62 – 1.55 (m, 2H), 1.48 (dt, J = 13.5, 7.0 Hz, 1H), 0.94 (d, J = 4.0 Hz, 3H), 0.93 (d, J = 4.0 Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 168.2, 47.0, 44.6, 44.2, 26.5, 23.0, 22.4; **IR** (cm^{-1}) 3263, 2959, 2927, 1735, 1468, 1388, 1282, 1188; **High Resolution MS** (ESI): Calculated for $\text{C}_7\text{H}_{12}\text{NO}$ $[\text{M}-\text{H}]^-$: 126.0924, Found: 126.0946.

4-(Cyclopropylmethyl)azetidin-2-one, 42



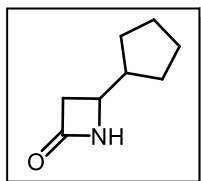
General Procedure A, in 0.1 mmol scale; Colourless oil (11.4 mg, 91%); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 6.15 (br. s, 1H), 3.77 – 3.65 (m, 1H), 3.07 (ddd, J = 15.0, 5.0, 2.0 Hz, 1H), 2.62 (dt, J = 15.0, 2.0 Hz, 1H), 1.61 (dt, J = 13.5, 6.0 Hz, 1H), 1.42 (dt, J = 13.5, 7.5 Hz, 1H), 0.71 – 0.60 (m, 1H), 0.54 – 0.42 (m, 2H), 0.13 – 0.04 (m, 2H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 168.3, 48.5, 43.5, 40.2, 7.8, 4.3, 3.8; **IR** (cm^{-1}) 3252, 3001, 2926, 1740, 1416, 1361, 1264, 1190, 1017, 961; **High Resolution MS** (FAB): Calculated for $\text{C}_7\text{H}_{12}\text{NO}$ $[\text{M}+\text{H}]^+$: 126.0919, Found: 126.0916.

4-Isopropylazetidin-2-one, 43



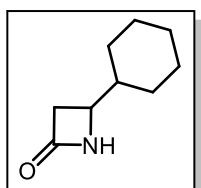
General Procedure A, in 0.1 mmol scale; Pale yellow oil (5.7 mg, 50%); **¹H NMR** (400 MHz, CDCl₃) δ 5.95 (br. s, 1H), 3.32 (ddd, *J* = 8.0, 5.0, 2.5 Hz, 1H), 2.98 (ddd, *J* = 15.0, 5.0, 2.5 Hz, 1H), 2.61 (ddd, *J* = 15.0, 2.5, 1.0 Hz, 1H), 1.77 – 1.65 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 166.8, 55.6, 40.0, 34.7, 21.7, 17.6. Data consistent with those reported in literature²⁸.

4-Cyclopentylazetidin-2-one, 44



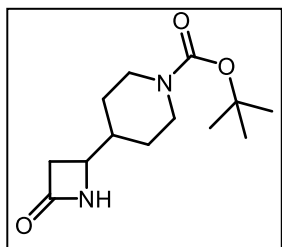
General Procedure A, in 0.1 mmol scale; Colourless oil (8.4 mg, 60%); **¹H NMR** (400 MHz, CDCl₃) δ 5.97 (br. s, 1H), 3.48 (ddd, *J* = 8.0, 5.0, 2.5 Hz, 1H), 3.00 (ddd, *J* = 15.0, 5.0, 2.0 Hz, 1H), 2.57 (dt, *J* = 15.0, 2.0 Hz, 1H), 2.01 (sext, *J* = 8.0 Hz, 1H), 1.83 – 1.69 (m, 2H), 1.65 – 1.54 (m, 4H), 1.31 – 1.11 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 168.3, 52.3, 44.5, 42.5, 29.4, 28.9, 25.82, 25.77; **IR** (cm⁻¹) 3243, 2950, 2867, 1752, 1668, 1452, 1394, 1191, 1093; **High Resolution MS** (FAB): Calculated for C₈H₁₄NO [M+H]⁺: 140.1075, Found: 140.1077.

4-Cyclohexylazetidin-2-one, 45



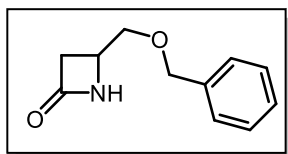
General Procedure A, in 0.1 mmol scale; White solid (10.0 mg, 65%); **m.p.** = 86 – 87 °C; **¹H NMR** (400 MHz, CDCl₃) δ 6.16 (br. s, 1H), 3.29 (ddd, *J* = 8.0, 5.0, 2.5 Hz, 1H), 2.97 (ddd, *J* = 15.0, 5.0, 2.5 Hz, 1H), 2.62 (dd, *J* = 15.0, 2.5 Hz, 1H), 1.81 – 1.63 (m, 5H), 1.40 – 1.08 (m, 4H), 1.00 – 0.85 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 168.6, 53.2, 42.7, 41.9, 29.5, 28.6, 26.2, 25.7, 25.6; **IR** (cm⁻¹) 3289, 2921, 2851, 1751, 1702, 1453, 1185, 978, 653; **High Resolution MS** (FAB): Calculated for C₉H₁₆NO [M+H]⁺: 154.1232, Found: 154.1229.

tert-Butyl 4-(4-oxoazetidin-2-yl)piperidine-1-carboxylate, 46



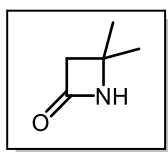
General Procedure A, in 0.1 mmol scale; White solid (18.3 mg, 72%); **m.p.** = 143 – 145 °C; **¹H NMR** (400 MHz, CDCl₃) δ 6.08 (br. s, 1H), 4.16 (app. br. s, 2H), 3.36 (ddd, *J* = 8.0, 5.0, 2.5 Hz, 1H), 3.02 (ddd, *J* = 15.0, 5.0, 2.5 Hz, 1H), 2.71 – 2.64 (m, 3H), 1.72 – 1.58 (m, 2H), 1.57 – 1.49 (m, 1H), 1.45 (s, 9H), 1.23 – 1.07 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 168.0, 154.9, 79.8, 52.4, 41.8, 41.2, 28.6, 28.5, 27.7; **IR** (cm⁻¹) 3251, 2924, 2855, 1751, 1649, 1416, 1156, 1021, 655; **High Resolution MS** (FAB): Calculated for C₁₃H₂₃N₂O₃ [M+H]⁺: 255.1709, Found: 255.1707.

4-[(Benzyloxy)methyl]azetidin-2-one, 47



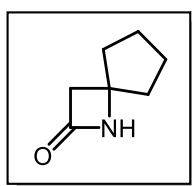
General Procedure A, in 0.1 mmol scale; Pale yellow oil (8.6 mg, 45%); ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.34 (m, 2H), 7.34 – 7.29 (m, 3H), 5.99 (br. s, 1H), 4.55 (s, 2H), 3.85 – 3.81 (m, 1H), 3.66 (dd, J = 10.0, 4.0 Hz, 1H), 3.47 (dd, J = 10.0, 8.0 Hz, 1H), 3.04 (ddd, J = 15.0, 5.0, 2.0 Hz, 1H), 2.65 (ddd, J = 15.0, 2.5, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.6, 137.7, 128.7, 128.2, 127.9, 73.7, 73.0, 47.0, 40.8; IR (cm^{-1}) 3257, 2928, 2860, 1747, 1454, 1368, 1339, 1188, 1102, 740; **High Resolution MS** (FAB): Calculated for $\text{C}_{11}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 192.1025, Found: 192.1027.

4,4-Dimethylazetidin-2-one, 48



General Procedure A, in 0.1 mmol scale; Colourless oil (2.2 mg, 23% yield); ^1H NMR (400 MHz, CDCl_3) δ 5.76 (br. s, H), 2.76 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.2, 52.0, 50.5, 27.6; Data consistent with those reported in literature²⁹.

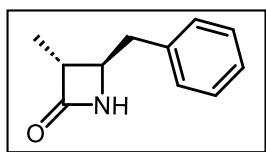
1-Azaspiro[3.4]octan-2-one, 49



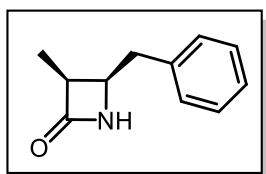
General Procedure A, in 0.1 mmol scale; Yellow oil (0.7 mg, 6%); ^1H NMR (400 MHz, CDCl_3) δ 5.71 (br. s, 1H), 2.80 (s, 2H), 1.85 – 1.71 (m, 4H), 1.68 – 1.59 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.9, 61.7, 49.2, 37.0, 23.7; Data consistent with those reported in literature³⁰.

Benzyl-3-methylazetidin-2-one, 51

General Procedure A, in 0.1 mmol scale, isolated as a diastereomeric mixture (*d.r.* = 4:1 determined by ^1H NMR); Pale yellow oil (12.8 mg, 73%);



major [*trans*]: ^1H NMR (500 MHz, CDCl_3) δ 7.35 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 2H), 5.83 (br. s, 1H), 3.48 (t, J = 6.5 Hz, 1H), 3.00 (dd, J = 13.5, 6.5 Hz, 1H), 2.93 (q, J = 7.5 Hz, 1H), 2.86 (dd, J = 13.5, 8.0 Hz, 1H), 1.28 (d, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 171.2, 137.8, 129.0, 128.8, 127.0, 57.7, 51.4, 41.4, 13.1; IR (cm^{-1}) 3233, 2910, 1738, 1460, 1377, 1041, 761; **High Resolution MS** (FAB): Calculated for $\text{C}_{11}\text{H}_{14}\text{NO}$ $[\text{M}+\text{H}]^+$: 176.1075, Found: 176.1073. Data consistent with those reported in literature³¹.

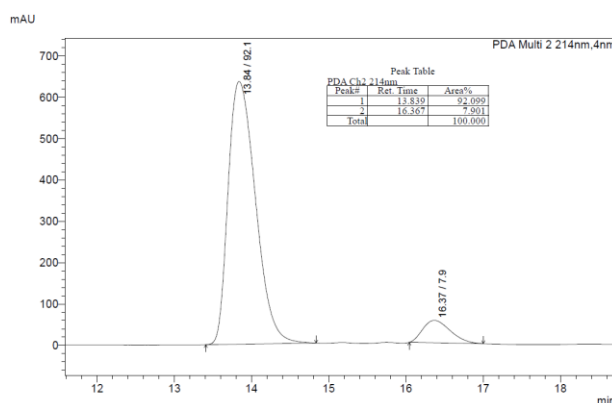
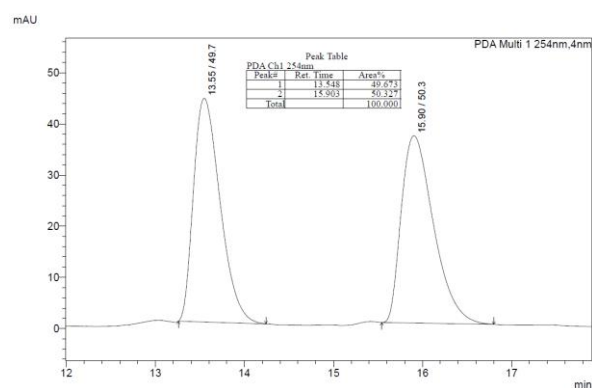
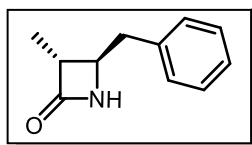


minor [*cis*]: ^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.31 (m, 2H), 7.28 – 7.24 (m, 1H), 7.21 – 7.16 (m, 2H), 5.72 (br. s, 1H), 3.93 (ddd, J = 10.0, 5.5, 4.5 Hz, 1H), 3.38 (qdd, J = 7.5, 5.5, 2.0 Hz, 1H), 2.94 (dd, J = 14.0, 4.5 Hz, 1H), 2.73 (dd, J = 14.0, 10.0 Hz, 1H), 1.31 (d, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.7, 138.0, 129.1, 128.9, 126.9, 53.3, 47.8, 37.4, 9.1; IR (cm^{-1}) 3236, 2929, 1747, 1496,

1454, 1386, 1071, 700; **High Resolution MS** (FAB): Calculated for $C_{11}H_{14}NO$ $[M+H]^+$: 176.1075, Found: 176.1073.

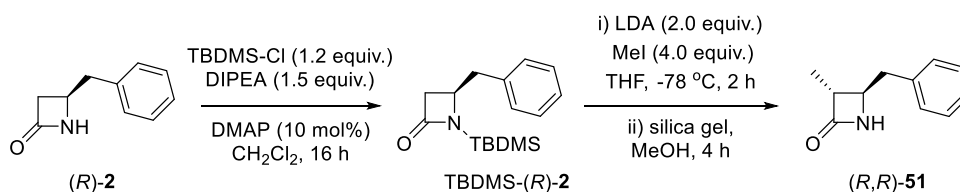
Note: The separation of the two diastereomers was proven difficult by silica column chromatography. While the reported yield is that of isolated mixture (d.r. = 4:1), small fractions containing pure materials of each isomer were collected separately and used for the purpose of structure characterization.

General Procedure B, in 0.1 mmol scale; d.r. = 4:1 determined by 1H NMR of the crude mixture; *trans* product was isolated as the major diastereomer (3.5 mg, 20%); **HPLC Analysis of the major diastereomer** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 13.8 min, t_{minor} = 16.4 min, 92:8 e.r.

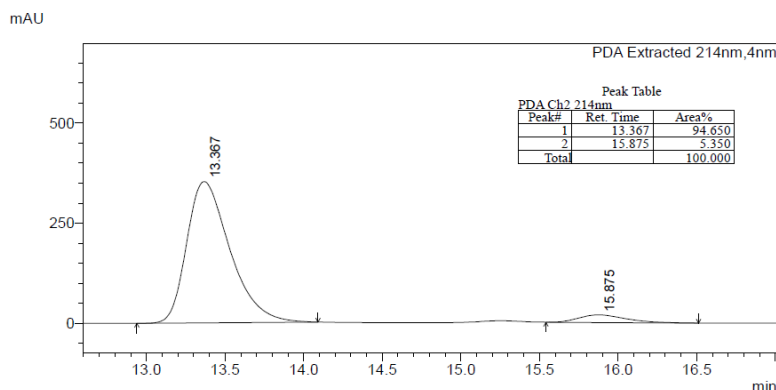


HPLC traces of racemic (**51**) and enantioenriched [(*R,R*)-**51**] products

The absolute stereochemistry of the obtained enantioenriched product was confirmed by comparing its HPLC traces to that of (*R,R*)-51 synthesized from (*R*)-2 using the following procedure:

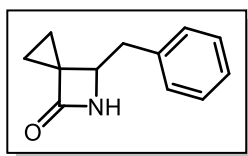


To a solution of (*R*)-**2** (32 mg, 0.2 mmol, 1.0 equiv.) in CH₂Cl₂ (5 mL) were added TBDMS-Cl (36.0 mg, 0.24 mmol, 1.2 equiv.), DIPEA (52.5 μ L, 0.3 mmol, 1.5 equiv.) and DMAP (2.4 mg, 0.02 mmol, 10 mol%). The reaction was stirred at 25 °C for 16 h. After completion, the solvent was removed under reduced pressure, and the crude mixture was purified by silica column chromatography to give TBDMS-(*R*)-**2** (19.8 mg, 36%)³¹. To a solution of TBDMS-(*R*)-**2** (19.8 mg, 0.07 mmol, 1.0 equiv.) in anhydrous THF (1.0 mL) was then added LDA (1.0 M in THF, 0.14 mL, 2.0 equiv.) at –78 °C under N₂ atmosphere. After stirring at –78 °C for 1 h, MeI (17.4 μ L, 4.0 equiv.) was added at the same temperature. The reaction mixture was stirred for 15 minutes, allowed to warm to 25 °C, and further stirred for 12 h. After completion, the resulting mixture was quenched with sat. NH₄Cl(aq) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude was dissolved in MeOH (1.0 mL) with silica gel (200 mg), stirred for additional 4 h, concentrated under reduced pressure, and purified by silica column chromatography (eluent: *n*-hexane/ EtOAc = 10:1 to 2:1) to afford (*R,R*)-**51** (2.2 mg, 18%).



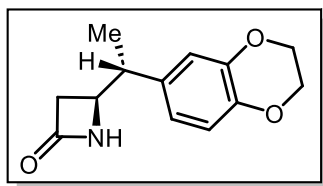
HPLC traces of (*R,R*)-**51** prepared from (*R*)-**2**

6-Benzyl-5-azaspiro[2.3]hexan-4-one, **52**



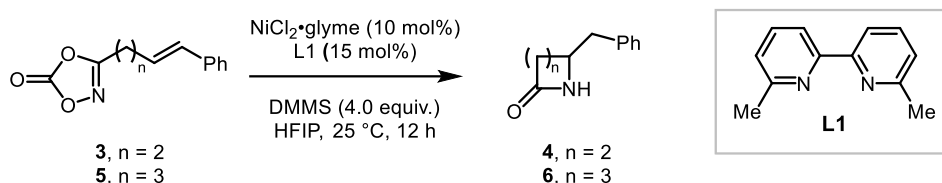
General Procedure A, in 0.1 mmol scale; White solid (9.4 mg, 50%); **m.p.** = 109 – 111 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.33 (d, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 5.81 (br. s, 1H), 3.97 (dd, *J* = 9.5, 4.5 Hz, 1H), 2.86 (dd, *J* = 14.0, 4.5 Hz, 1H), 2.77 (dd, *J* = 14.0, 9.5 Hz, 1H), 1.24 (ddd, *J* = 10.5, 6.5, 4.0 Hz, 1H), 1.15 (ddd, *J* = 10.5, 6.5, 4.5 Hz, 1H), 1.07 – 1.02 (m, 1H), 0.98 (ddd, *J* = 10.5, 6.5, 4.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.4, 137.7, 129.0, 128.8, 127.0, 56.5, 40.3, 37.8, 8.3, 6.6; **IR** (cm⁻¹) 3216, 2925, 2853, 1733, 1639, 1358, 1149, 698; **High Resolution MS** (EI): Calculated for C₁₂H₁₃NO [M]⁺: 187.0997, Found: 187.0997.

4-[1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl]azetidin-2-one, *rac*-53

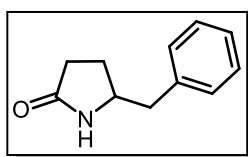


General Procedure A, in 0.1 mmol scale; White solid (20.9 mg, 90%, >20:1 d.r., determined by ^1H NMR of the crude mixture); **m.p.** = 119 – 121 °C; ^1H NMR (500 MHz, CDCl_3) δ 6.81 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.66 (dd, J = 8.0, 2.0 Hz, 1H), 5.62 (br. s, 1H), 4.24 (app. s, 4H), 3.58 (ddd, J = 9.5, 5.0, 2.0 Hz, 1H), 3.08 (ddd, J = 14.5, 5.0, 2.0 Hz, 1H), 2.68 – 2.60 (m, 2H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.4, 143.8, 142.7, 136.2, 120.3, 117.6, 115.8, 64.5, 64.4, 53.7, 44.9, 42.6, 17.7; **IR** (cm^{-1}) 3324, 2924, 1740, 1502, 1285, 1063, 907; **High Resolution MS** (EI): Calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_3$ $[\text{M}]^+$: 233.1052, Found: 233.1050.

Intramolecular hydroamidation of alkenyl dioxazolones with elongated chain length

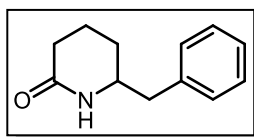


5-Benzylpyrrolidin-2-one, **4**



General Procedure A, using reactant **3** as starting material in 0.1 mmol scale; White solid (9.5 mg, 54%); ^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.12 (m, 5H), 5.97 (br. s, 1H), 3.92 – 3.88 (m, 1H), 2.87 (dd, J = 13.5, 5.5 Hz, 1H), 2.69 (dd, J = 13.5, 8.5 Hz, 1H), 2.34 – 2.20 (m, 3H), 1.89 – 1.80 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 178.1, 137.9, 129.3, 129.2, 127.1, 55.9, 43.2, 30.3, 27.2. Data consistent with those reported in literature³².

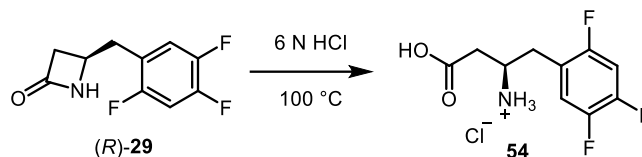
6-Benzylpiperidin-2-one, **6**



General Procedure A, using reactant **5** as starting material, in 0.1 mmol scale; White solid (5.7 mg, 30%); ^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.30 (m, 2H), 7.28 – 7.24 (m, 1H), 7.20 – 7.13 (m, 2H), 5.58 (br. s, 1H), 3.61 (tt, J = 9.5, 4.5 Hz, 1H), 2.88 (dd, J = 13.5, 5.0 Hz, 1H), 2.61 (dd, J = 13.5, 9.0 Hz, 1H), 2.45 – 2.24 (m, 2H), 2.02 – 1.88 (m, 2H), 1.78 – 1.63 (m, 1H), 1.54 – 1.39 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.4, 137.1, 129.4, 129.1, 127.2, 54.5, 43.6, 31.6, 28.9, 20.0. Data consistent with those reported in literature³³.

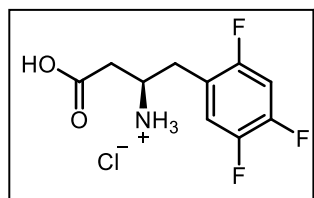
Synthetic Utility

Access to β -amino acid derivative



A solution of **(R)-29** (20.0 mg, 0.92 mmol) in 0.6 mL of 6 N HCl_(aq) was heated at 100 °C for 12 h. The reaction was then cooled to 25 °C and concentrated under reduced pressure. Ethyl acetate (1 mL) was added, then the precipitate was suspended by sonication and stirred at 25 °C for 1 h. The solid was filtered off and washed with MeOH to give the title compound in high purity without further purification.

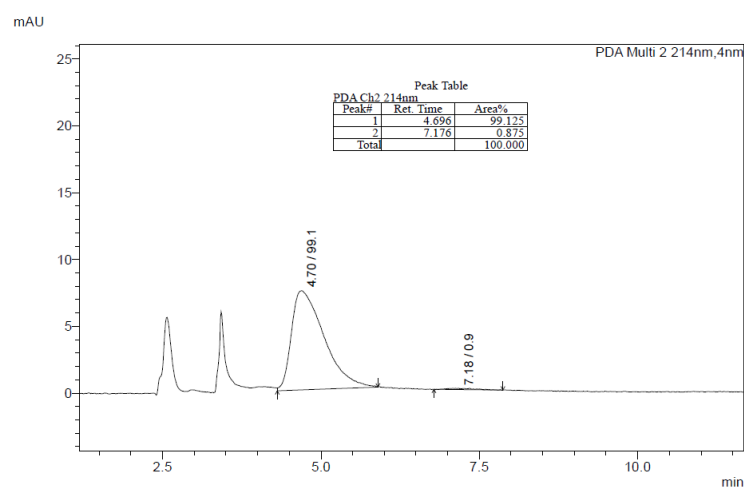
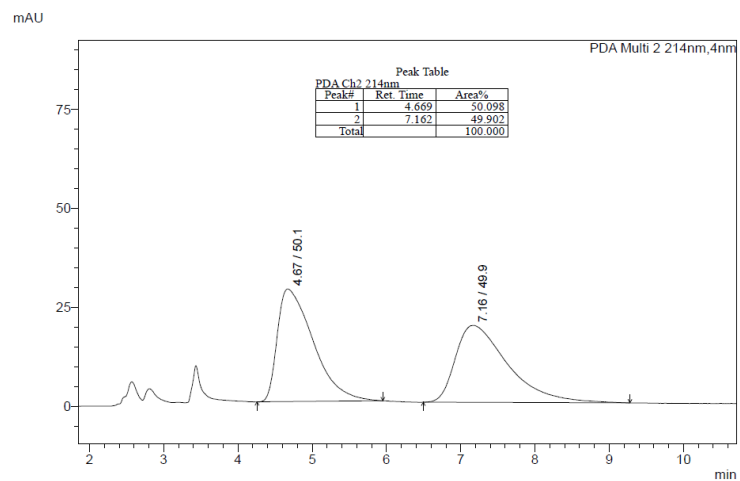
(R)-1-Carboxy-3-(2,4,5-trifluorophenyl)propan-2-aminium chloride, 54



White solid (22.1 mg, 89%); **m.p.** = 197 – 199 °C; **¹H NMR** (400 MHz, CD₃OD) δ 7.41 – 7.31 (m, 1H), 7.22 (td, J = 10.0, 6.5 Hz, 1H), 3.82 (p, J = 6.5 Hz, 1H), 3.13 – 2.99 (m, 2H), 2.76 – 2.58 (m, 2H) (*OH and NH peaks not observed*); **¹³C NMR** (151 MHz, CD₃OD) δ 173.24, 157.98 (dd, J_{C-F} = 244.0, 8.0 Hz), 150.99 (dt, J_{C-F} = 249.5, 13.5 Hz), 148.22 (dd, J_{C-F} = 240.5, 12.5 Hz), 120.61 (dd, J_{C-F} = 20.0, 5.5 Hz), 120.36 (d, J_{C-F} = 18.0 Hz), 107.00 (dd, J_{C-F} = 29.0, 21.5 Hz), 36.3, 32.3; **¹⁹F NMR** (376 MHz, CD₃OD) δ -119.79 (dd, J = 15.5, 4.0 Hz), -136.65 (dd, J = 21.0, 4.0 Hz), -144.53 (dd, J = 21.0, 15.5 Hz). Data consistent with those reported in literature³⁴.

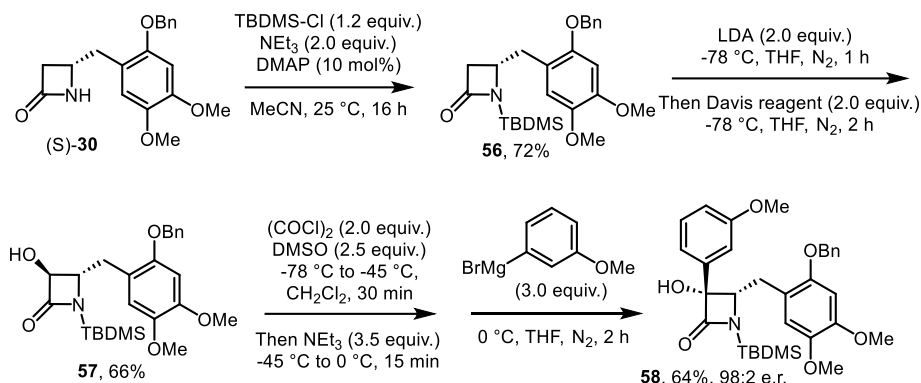
Specific Rotation $[\alpha]_D^{21}$ -39.3° (c = 0.19, CH₂Cl₂); **HPLC Analysis** CHIRALPAK AD-H, 32 °C, *i*-PrOH/*n*-hexane = 15/85, 1.2 mL/min, UV 214 nm, t_{major} = 4.7 min, t_{minor} = 7.2 min, >99:1 e.r.

Note: HPLC analysis was performed after N-Boc protection of 54, due to the encountered difficulty in separation of compound 54 on chiral HPLC. The obtained N-Boc variant of 54 (Boc-54) was confirmed by NMR data, which were consisted with those reported in literature³⁵.



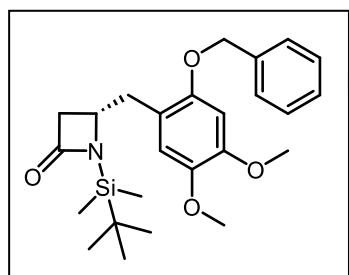
HPLC traces of racemic and enantioenriched compounds of **Boc-54**

Synthesis of β -lactam **58**



(*S*)-4-[2-(Benzyloxy)-4,5-dimethoxybenzyl]-1-(*tert*-butyldimethylsilyl)azetidin-2-one, **56**

To a solution of (*S*)-**30** (260 mg, 0.79 mmol, 1.0 equiv.) in MeCN (20 mL) were added TBDMS-Cl (143 mg, 0.95 mmol, 1.2 equiv.), NEt₃ (0.26 mL, 1.58 mmol, 2.0 equiv.), and DMAP (11.6 mg, 0.08 mmol, 10 mol%). The reaction was stirred at 25 °C for 16 h. After completion, the solvent was removed under reduced pressure, and the crude mixture was purified by silica column chromatography (eluent: *n*-hexane/EtOAc = 10:1 to 4:1) to afford the desired product **56** as a white solid (250 mg, 72%).



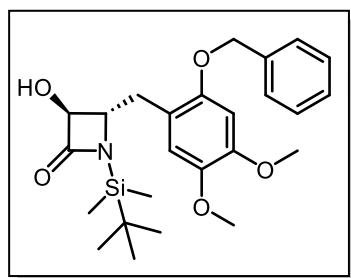
m.p. = 110 – 111 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.43 – 7.30 (m, 5H), 6.64 (s, 1H), 6.58 (s, 1H), 5.02 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.75 (dddd, *J* = 11.0, 5.5, 3.5, 2.5 Hz, 1H), 3.33 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.92 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.69 (dd, *J* = 15.5, 2.5 Hz, 1H), 2.39 (dd, *J* = 13.0, 11.0 Hz, 1H), 0.93 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); **¹³C NMR** (151 MHz, CDCl₃) δ 173.0, 151.0, 148.6, 143.2, 137.0,

128.8, 128.3, 127.9, 117.7, 114.8, 99.0, 71.4, 56.8, 56.3, 48.9, 43.8, 37.8, 26.4, 18.4, –5.2, –5.7; **IR** (cm^{–1}) 2925, 2857, 1736, 1518, 1192, 1023, 826; **High Resolution MS** (EI): Calculated for C₂₅H₃₅NO₄Si [M]⁺: 441.2335, Found: 441.2333; **Specific Rotation** [α]_D²¹ +11.4° (*c* = 0.12, CH₂Cl₂).

(3*S*,4*S*)-4-[2-(Benzyloxy)-4,5-dimethoxybenzyl]-1-(*tert*-butyldimethylsilyl)-3-hydroxyazetidin-2-one, **57**

To a solution of **56** (30 mg, 0.07 mmol, 1.0 equiv.) in anhydrous THF (0.2 mL) was added LDA dropwise (1.0 M in THF, 0.14 mL, 2.0 equiv.) at –78 °C under N₂. After stirring for 1 h, a solution of 2-(phenylsulfonyl)-3-phenyloxaziridine (*Davis reagent*, 35.2 mg, 0.14 mmol, 2.0 equiv.) in THF (0.1 mL) was slowly added to the reaction mixture at the same temperature. The reaction was further stirred for 2 h, quenched with saturated solution of NH₄Cl_(aq), and extracted with EtOAc (2 times). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: CH₂Cl₂/ EtOAc =

10:1 to 4:1) to afford the desired product **57** as a brown solid (22.0 mg, 68%; *d.r.* > 20:1 determined by ^1H NMR of the crude mixture).



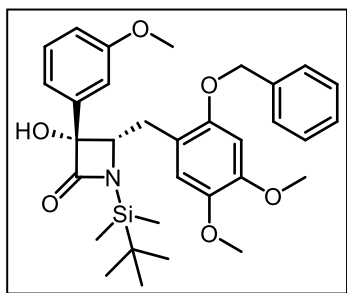
m.p. = 56 – 57 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.42 – 7.33 (m, 5H), 6.73 (s, 1H), 6.59 (s, 1H), 5.03 (s, 2H), 4.52 (br. s, 1H), 3.84 (s, 6H), 3.73 (d, J = 12.0 Hz, 1H), 3.25 (dd, J = 13.5, 3.5 Hz, 1H), 2.98 (br. s, 1H), 2.47 (t, J = 12.0 Hz, 1H), 0.94 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 174.3, 150.9, 148.6, 143.4, 137.1, 128.

8, 128.3, 127.9, 117.2, 114.3, 99.1, 81.2, 71.5, 60.4, 56.8, 56.3, 35.4, 26.3, 18.4, –5.1, –5.8; **IR** (cm^{-1}) 2928, 2856, 1716, 1517, 1452, 1253, 1194, 1022, 823; **High Resolution MS** (EI): Calculated for $\text{C}_{25}\text{H}_{35}\text{NO}_5\text{Si}$ $[\text{M}]^+$: 457.2284, Found: 457.2288; **Specific Rotation** $[\alpha]_D^{21}$ –47.5° (c = 0.12, CH_2Cl_2).

(3R,4S)-4-[2-(Benzyloxy)-4,5-dimethoxybenzyl]-1-(tert-butyldimethylsilyl)-3-hydroxy-3-(3-methoxyphenyl)azetidin-2-one, 58

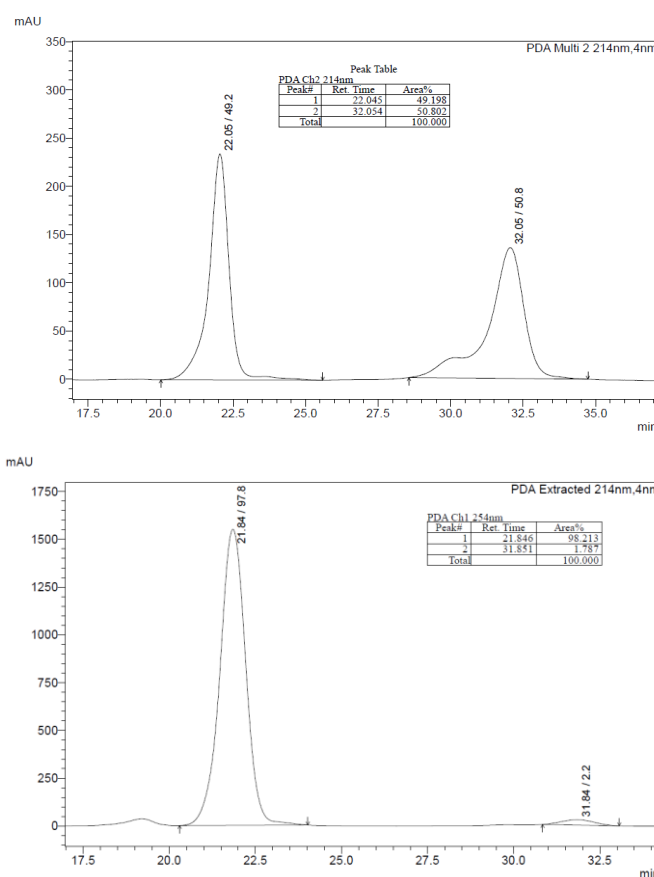
A round-bottomed flask equipped with a magnetic stirring bar was charged with DMSO (7.8 μL , 0.10 mmol, 2.5 equiv.) and CH_2Cl_2 (0.5 mL). To the colourless solution was added $(\text{COCl})_2$ (7.6 μL , 0.08 mmol, 2.0 equiv.) at –78 °C. After stirring for 10 min, a solution of **57** (20.0 mg, 0.04 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) was added dropwise over 5 min at –78 °C. After further stirring for 5 min, the suspension was warmed to –45 °C and stirred for additional 30 min. To the resulting mixture was added Et_3N (21.5 μL , 0.14 mmol, 3.5 equiv.) at –45 °C, warmed to 0 °C, and stirred for 15 min. The reaction was quenched with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$, warmed to room temperature, and extracted with CH_2Cl_2 (5 mL x 2 times). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to give α -keto- β -lactam product, which was used for the next step without further purification.

The α -keto- β -lactam was dissolved in anhydrous THF (0.5 mL). To the deep yellow solution was added 3-methoxyphenyl magnesium bromide (1.0 M in THF, 0.12 mL, 3.0 equiv.) dropwise at 0 °C. The reaction mixture was stirred for 1.5 h and quenched with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ at 0 °C. The resulting mixture was extracted with EtOAc (5 mL x 2 times), and the combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (eluent: *n*-hexane/EtOAc = 10:1 to 1:1) to afford the desired product **58** as a yellow solid (15.5 mg, 64%; *d.r.* > 20:1 determined by ^1H NMR of the crude mixture).

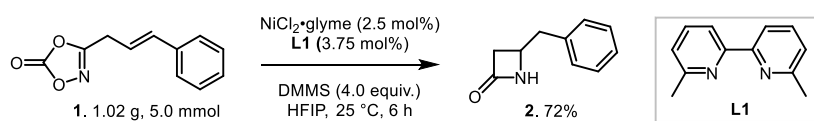


m.p. = 138 – 140 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.34 – 7.30 (m, 5H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.04 (s, 1H), 6.79 (dd, *J* = 12.0, 8.0 Hz, 2H), 6.61 (s, 1H), 6.53 (s, 1H), 5.00 (dd, *J* = 18.0, 11.5 Hz, 2H), 3.95 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 3.25 (br. s, 1H), 3.22 (dd, *J* = 13.5, 3.0 Hz, 1H), 3.05 (dd, *J* = 13.5, 11.5 Hz, 1H), 0.92 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); **¹³C NMR** (151 MHz,

CDCl₃) δ 174.6, 159.9, 150.8, 148.3, 143.1, 141.8, 136.9, 129.8, 128.8, 128.3, 128.2, 118.1, 117.8, 115.9, 114.9, 110.8, 98.7, 86.6, 71.6, 64.4, 56.6, 56.3, 55.1, 31.7, 26.4, 18.4, −5.2, −5.7; **IR** (cm^{−1}) 3380, 2931, 2855, 1711, 1518, 1288, 1222, 1194, 1112, 1021, 877; **High Resolution MS** (EI): Calculated for C₃₂H₄₁NO₆Si [M]⁺: 563.2703, Found: 563.2700.

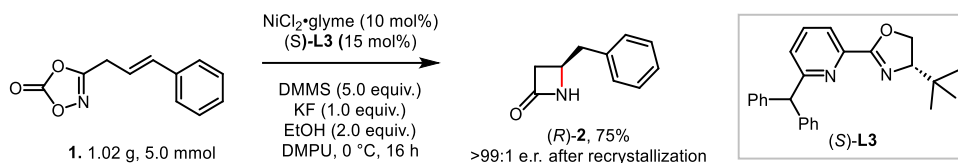


Large-scale reactions for the standard hydroamidation



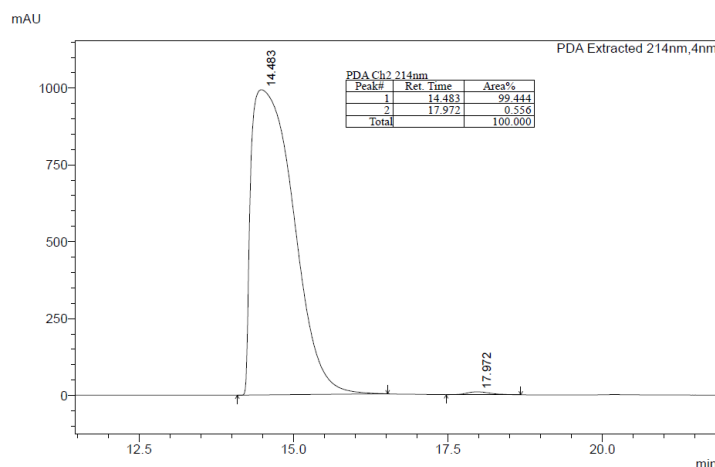
To a reaction vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (27.5 mg, 2.5 mol%), 6,6'-dimethyl-2,2'-bipyridine **L1** (34.5 mg, 3.75 mol%), and anhydrous HFIP (10.0 mL, 0.5 M) in an argon-filled glovebox. The resulting mixture was stirred over 10 min before 1,4,2-dioxazol-5-one **1** (1.02 g, 5.0 mmol, 1.0 equiv.) and DMMS (2.73 mL, 4.0 equiv.) were added. The vial was sealed with a screw cap, removed from the glovebox, and stirred at 25 °C for 6 h. After completion, the solvent was removed under reduced pressure. The crude mixture was diluted with EtOAc (30 mL) and 1.0 M $\text{HCl}_{(\text{aq})}$ (10 mL), and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude mixture was purified by silica column chromatography (eluent: *n*-hexane/EtOAc = 10:1 to 1:1) to afford the desired product **2** (580.5 mg, 72%).

Large-scale reactions for the enantioselective hydroamidation



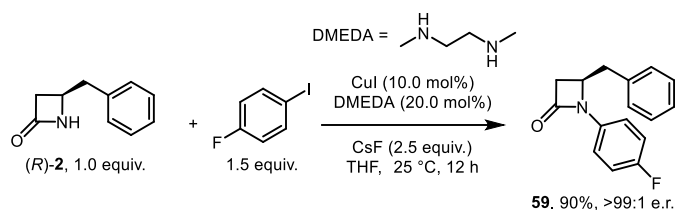
To a reaction vial equipped with a stir bar were added $\text{NiCl}_2 \cdot \text{glyme}$ (109.9 mg, 10.0 mol%), (S)-L3 (277.9 mg, 15 mol%), and anhydrous DMPU (5.0 mL, 1.0 M) in an argon-filled glovebox. The resulting mixture was stirred over 10 min before KF (290.5 mg, 1.0 equiv.), EtOH (0.58 mL, 2.0 equiv.), and 3-cinnamyl-1,4,2-dioxazol-5-one **1** (1.02 g, 5.0 mmol, 1.0 equiv.) were added. The mixture was cooled to 0 °C and DMMS (3.42 mL, 5.0 equiv.) were added. The vial was sealed with a screw cap, quickly removed from the glovebox, and stirred at 0 °C for 16 h. After completion, the resulting mixture was quenched with 1.0 M $\text{HCl}_{(\text{aq})}$ and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO_4 , filtered, concentrated under reduced pressure, and purified by silica column chromatography (eluent: *n*-hexane/ EtOAc = 10:1 to 1:1) to afford the desired product (R)-2 (606.3 mg, 75%). The obtained (R)-2 was then recrystallized in *n*-hexane with several drops of CH_2Cl_2 .

HPLC Analysis CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 5/95, 1.0 mL/min, UV 214 nm, $t_{\text{major}} = 14.5$ min, $t_{\text{minor}} = 18.0$ min, >99:1 e.r.



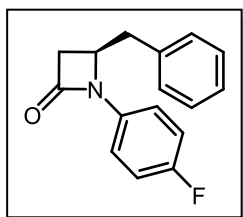
HPLC traces of (R)-2 after recrystallization

N-Arylation of compound (R)-2



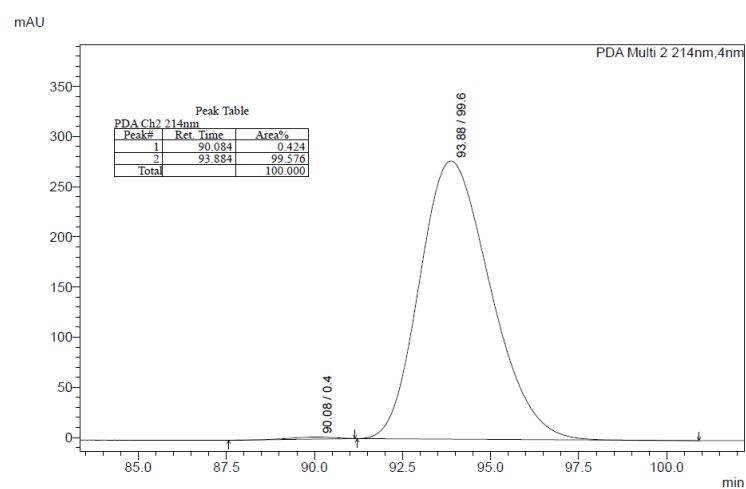
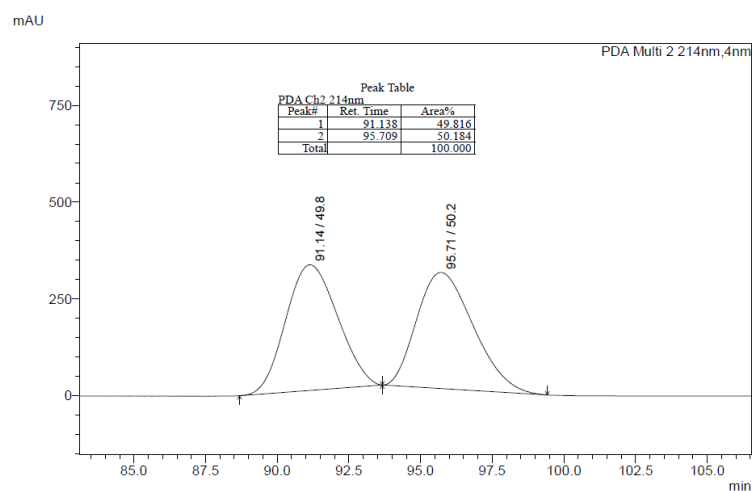
To a reaction vial equipped with a stir bar were added 4-benzylazetidin-2-one (R)-2 (200 mg, 1.24 mmol, 1.0 equiv.), CsF (471 mg, 3.10 mmol, 2.5 equiv.), CuI (23.6 mg, 0.12 mmol, 10 mol%), and *N,N'*-dimethylethylenediamine (DMEDA, 27 μL , 0.24 mmol, 20 mol%), 4-fluoroiodobenzene (215 μL , 1.86 mmol, 1.5 equiv.) and anhydrous THF (2.0 mL) in an argon-filled glovebox. The vial was sealed with a screw cap, removed from the glovebox, and stirred at 25 $^\circ\text{C}$ for 12 h. After completion, the resulting mixture was quenched with 1.0 M HCl_(aq) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, concentrated under reduced pressure, and purified by silica column chromatography (eluent: *n*-hexane/ EtOAc = 10:1 to 2:1) to afford the desired product **59** (279.3 mg, 90%, >99:1 e.r.) as a white solid.

(R)-4-Benzyl-1-(4-fluorophenyl)azetidin-2-one, 59



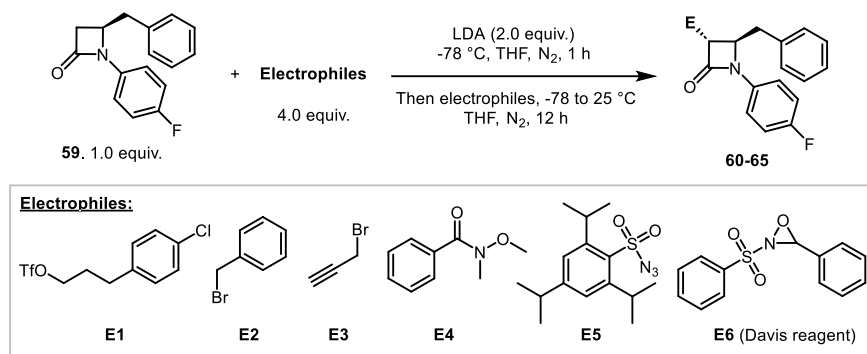
m.p. = 77 – 78 $^\circ\text{C}$; **¹H NMR** (400 MHz, CDCl₃) δ 7.49 – 7.34 (m, 5H), 7.25 (d, J = 8.5 Hz, 2H), 7.15 (t, J = 8.5 Hz, 2H), 4.40 (dddd, J = 8.0, 5.5, 4.0, 2.5 Hz, 1H), 3.44 (dd, J = 14.0, 4.0 Hz, 1H), 3.21 (dd, J = 15.0, 5.5 Hz, 1H), 3.01 (dd, J = 14.0, 8.5 Hz, 1H), 2.91 (dd, J = 15.0, 2.5 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 164.1, 159.2 (d, $J_{\text{C-F}}$ = 243.5 Hz), 136.1, 133.9 (d, $J_{\text{C-F}}$ = 3.0 Hz), 129.3, 128.9, 127.3, 118.7 (d, $J_{\text{C-F}}$ = 8.0 Hz), 116.2 (d, $J_{\text{C-F}}$ = 22.5 Hz), 52.0, 42.0, 38.4; **¹⁹F NMR** (376 MHz, CDCl₃) δ –118.0; **IR** (cm⁻¹) 2923, 1727, 1508, 1380, 1198, 1151, 1104, 809; **High Resolution MS** (EI): Calculated for C₁₆H₁₄FNO [M]⁺: 255.1059, Found: 255.1058.

Specific Rotation [α]_D²¹ –111.2 $^\circ$ (c = 0.19, CH₂Cl₂); **HPLC Analysis**. CHIRALPAK IA, 40 $^\circ\text{C}$, *i*-PrOH/*n*-hexane = 2/98, 0.5 mL/min, UV 214 nm, t_{major} = 93.9 min, t_{minor} = 90.1 min, >99:1 e.r.



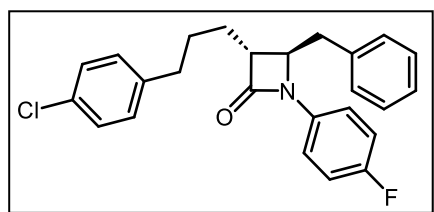
HPLC traces of racemic and enantioenriched compounds of **59**

α -Functionalization of compound **59**



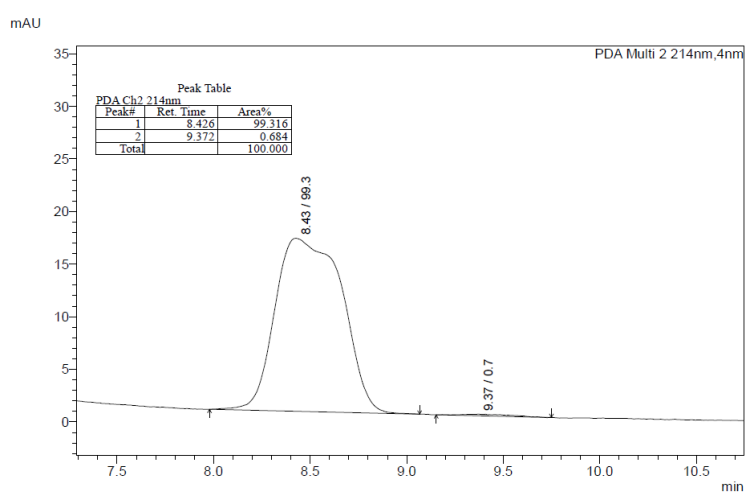
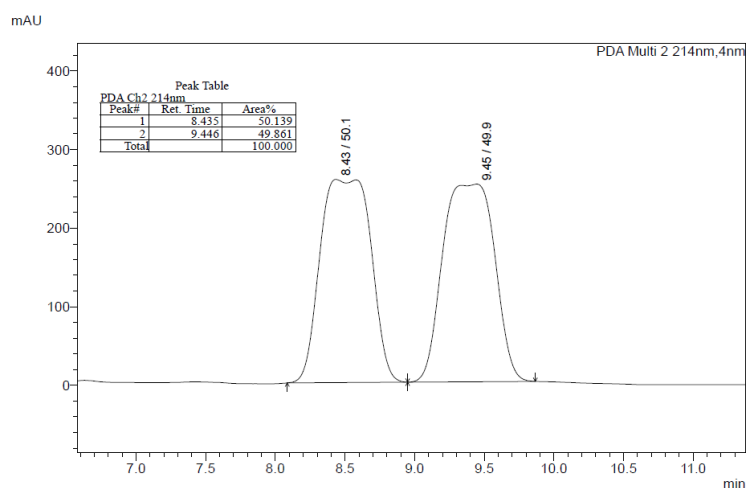
General Procedure C: To a solution of (*R*)-4-benzyl-1-(4-fluorophenyl)azetidin-2-one **59** (25.5 mg, 0.1 mmol, 1.0 equiv.) in anhydrous THF (1.0 ml) was added LDA (1.0 M in THF, 0.2 mL, 2.0 equiv.) at $-78\text{ }^{\circ}\text{C}$ under N_2 atmosphere. After stirring at $-78\text{ }^{\circ}\text{C}$ for 1 h, electrophile (4.0 equiv.) was added at the same temperature. The reaction mixture was stirred for 15 minutes, allowed to warm to $25\text{ }^{\circ}\text{C}$, and further stirred for 12 h. After completion, the resulting mixture was quenched with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, concentrated under reduced pressure, and purified by silica column chromatography (eluent: *n*-hexane/ EtOAc = 10:1 to 2:1) to afford the desired product.

(3*R*,4*R*)-4-Benzyl-3-[3-(4-chlorophenyl)propyl]-1-(4-fluorophenyl)azetidin-2-one, **60**



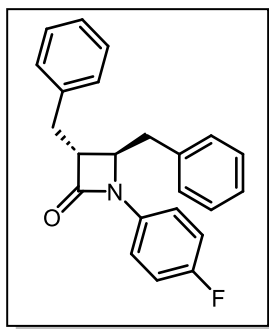
General Procedure C, using **E1** as electrophile; White solid (31.1 mg, 76%, *d.r.* > 20:1 determined by ^1H NMR of the crude mixture); **m.p.** = $57 - 58\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.32 (m, 2H), 7.32 – 7.25 (m, 3H), 7.20 (d, $J = 8.5\text{ Hz}$, 2H), 7.15 (d, $J = 7.0\text{ Hz}$, 2H), 7.05 (t, $J = 8.5\text{ Hz}$, 2H), 6.94 (d, $J = 8.5\text{ Hz}$, 2H), 3.88 (ddd, $J = 9.0, 4.0, 2.0\text{ Hz}$, 1H), 3.37 (dd, $J = 14.0, 4.0\text{ Hz}$, 1H), 2.96 (ddd, $J = 8.5, 6.0, 2.0\text{ Hz}$, 1H), 2.80 (dd, $J = 14.0, 9.0\text{ Hz}$, 1H), 2.44 (t, $J = 7.5\text{ Hz}$, 2H), 1.71 (ddt, $J = 13.0, 10.5, 5.5\text{ Hz}$, 1H), 1.56 – 1.21 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.1, 159.2 (d, $J_{\text{C-F}} = 243.5\text{ Hz}$), 140.2, 136.3, 133.8 (d, $J_{\text{C-F}} = 2.5\text{ Hz}$), 131.7, 129.8, 129.4, 129.0, 128.5, 127.3, 118.8 (d, $J_{\text{C-F}} = 8.0\text{ Hz}$), 116.2 (d, $J_{\text{C-F}} = 23.0\text{ Hz}$), 59.3, 55.0, 38.4, 34.9, 28.4, 28.1; ^{19}F NMR (376 MHz, CDCl_3) δ -118.1 ; IR (cm^{-1}) 2932, 2860, 1729, 1509, 1491, 1386, 1210, 1089, 828; **High Resolution MS** (EI): Calculated for $\text{C}_{25}\text{H}_{23}\text{ClFNO}$ $[\text{M}]^+$: 407.1452, Found: 407.1456.

Specific Rotation $[\alpha]_D^{21} -22.0^{\circ}$ ($c = 0.15$, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IB-3, $40\text{ }^{\circ}\text{C}$, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, $t_{\text{major}} = 8.4\text{ min}$, $t_{\text{minor}} = 9.4\text{ min}$, >99:1 e.r.



HPLC traces of racemic and enantioenriched compounds of **60**

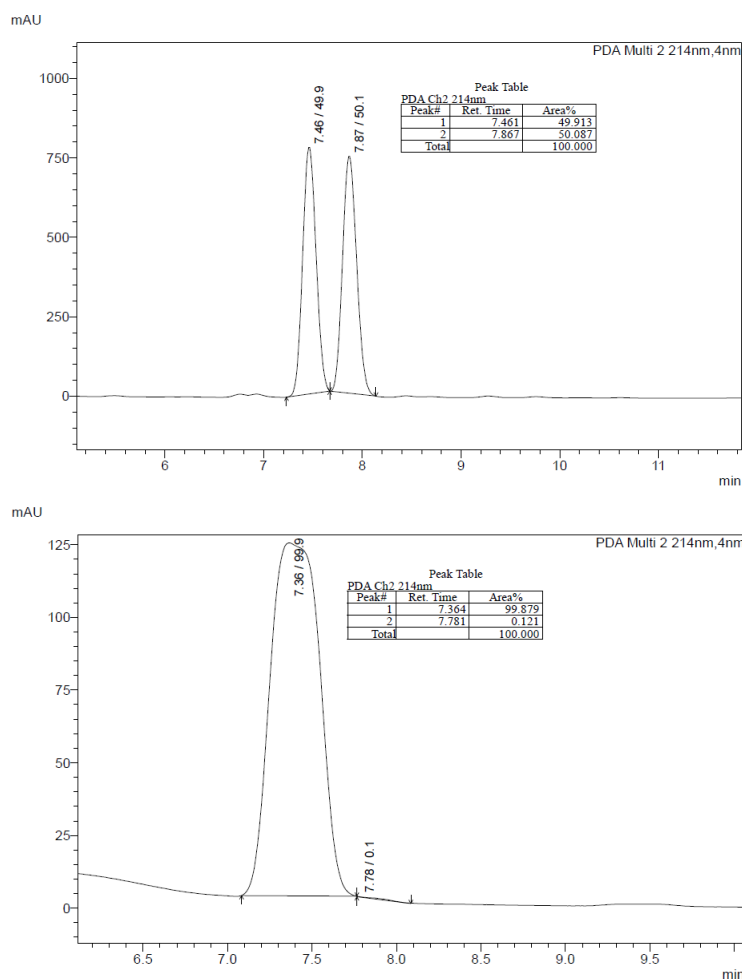
(3R,4R)-3,4-Dibenzyl-1-(4-fluorophenyl)azetidin-2-one, 61



Synthesized according to a modified **General Procedure C**; reaction was kept at $-78\text{ }^{\circ}\text{C}$ for 2 h after addition of **E2** as electrophile; Brown solid (24.8 mg, 72%, d.r. > 20:1 determined by ^1H NMR of the crude mixture); **m.p.** = 98 – 99 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.14 (m, 6H), 7.09 – 6.99 (m, 4H), 6.98 – 6.91 (m, 2H), 4.00 (ddd, J = 7.5, 4.0, 2.5 Hz, 1H), 3.25 (ddd, J = 9.0, 5.5, 2.5 Hz, 1H), 3.10 (dd, J = 14.0, 4.0 Hz, 1H), 3.02 (dd, J = 14.5, 5.5 Hz, 1H), 2.84 (ddd, J = 14.5, 10.0, 8.0 Hz, 2H); ^{13}C NMR

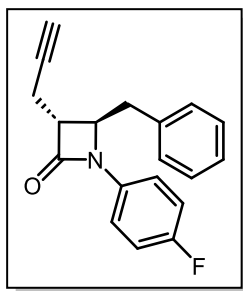
(101 MHz, CDCl_3) δ 166.7, 159.2 (d, $J_{\text{C-F}}$ = 243.5 Hz), 138.1, 135.9, 133.7 (d, $J_{\text{C-F}}$ = 2.5 Hz), 129.3, 128.81 (2 $\times$ carbon peaks overlapping), 128.76, 127.1, 126.7, 119.0 (d, $J_{\text{C-F}}$ = 8.0 Hz), 116.1 (d, $J_{\text{C-F}}$ = 22.5 Hz), 58.2, 55.9, 37.9, 34.4; ^{19}F NMR (376 MHz, CDCl_3) δ –118.0; IR (cm^{-1}) 2924, 2858, 1733, 1508, 1388, 1210, 1154, 831; **High Resolution MS** (EI): Calculated for $\text{C}_{23}\text{H}_{20}\text{FNO}$ $[\text{M}]^+$: 345.1529, Found: 345.1531.

Specific Rotation $[\alpha]_D^{21}$ –73.3 $^{\circ}$ (c = 0.10, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA-3, 40 $^{\circ}\text{C}$, i -PrOH/ n -hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 7.4 min, t_{minor} = 7.8 min, >99:1 e.r.



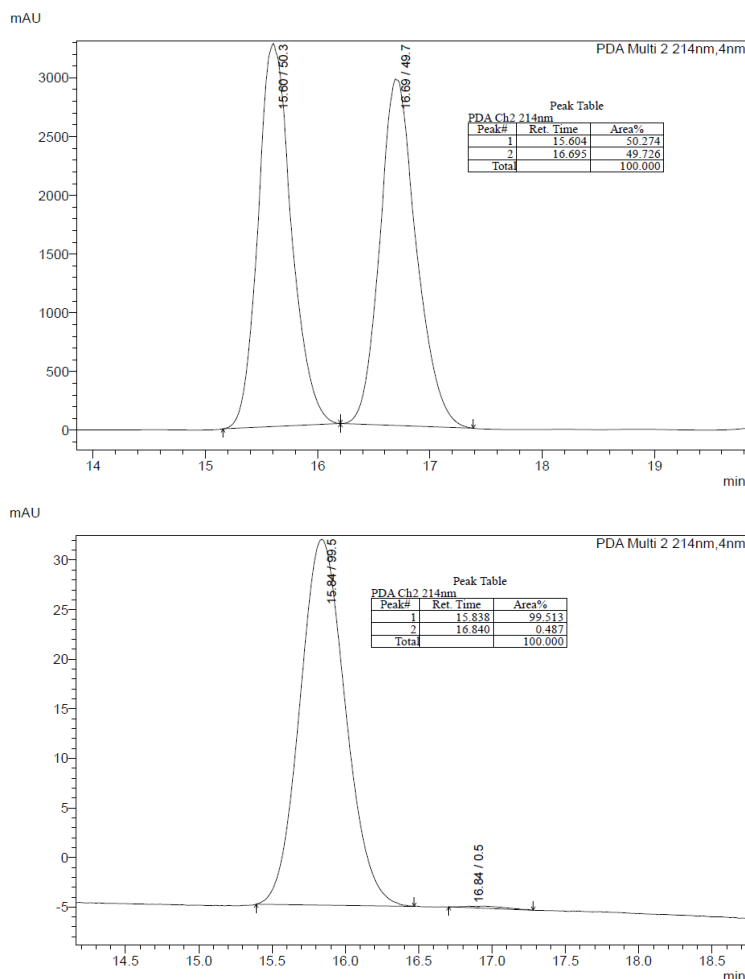
HPLC traces of racemic and enantioenriched compounds of **61**

(3R,4R)-4-Benzyl-1-(4-fluorophenyl)-3-(prop-2-yn-1-yl)azetidin-2-one, 62



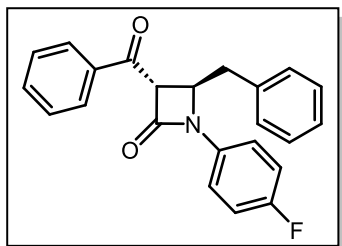
General Procedure C, using **E3** as electrophile; Colourless oil (17.4 mg, 59%, *d.r.* > 20:1 determined by ^1H NMR of the crude mixture); ^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.21 (m, 5H), 7.18 – 7.11 (m, 2H), 7.10 – 7.00 (m, 2H), 4.23 (ddd, J = 8.0, 4.5, 2.5 Hz, 1H), 3.34 (dd, J = 14.0, 4.5 Hz, 1H), 3.13 (ddd, J = 7.5, 5.0, 2.5 Hz, 1H), 2.98 (dd, J = 14.0, 8.0 Hz, 1H), 2.60 – 2.41 (m, 2H), 1.87 (d, J = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.0, 159.3 (d, $J_{\text{C-F}}$ = 243.5 Hz), 135.9, 133.5 (d, $J_{\text{C-F}}$ = 3.0 Hz), 129.5, 128.9, 127.3, 119.1 (d, $J_{\text{C-F}}$ = 8.0 Hz), 116.2 (d, $J_{\text{C-F}}$ = 23.0 Hz), 79.4, 70.6, 57.9, 52.6, 37.9, 17.6; ^{19}F NMR (376 MHz, CDCl_3) δ -117.7; IR (cm^{-1}) 3300, 2924, 1744, 1508, 1385, 1216, 1140, 831; **High Resolution MS** (EI): Calculated for $\text{C}_{19}\text{H}_{16}\text{FNO}$ $[\text{M}]^+$: 293.1216, Found: 293.1212.

Specific Rotation $[\alpha]_D^{21}$ -26.8° (c = 0.56, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 40 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 15.8 min, t_{minor} = 16.8 min, >99:1 e.r.



HPLC traces of racemic and enantioenriched compounds of **62**

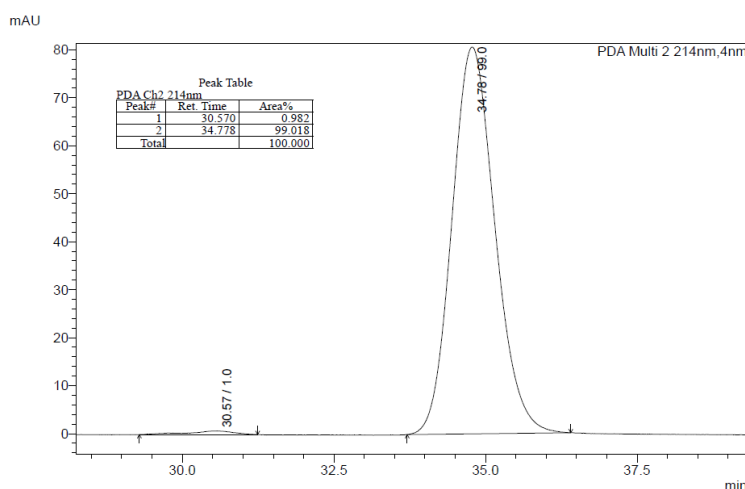
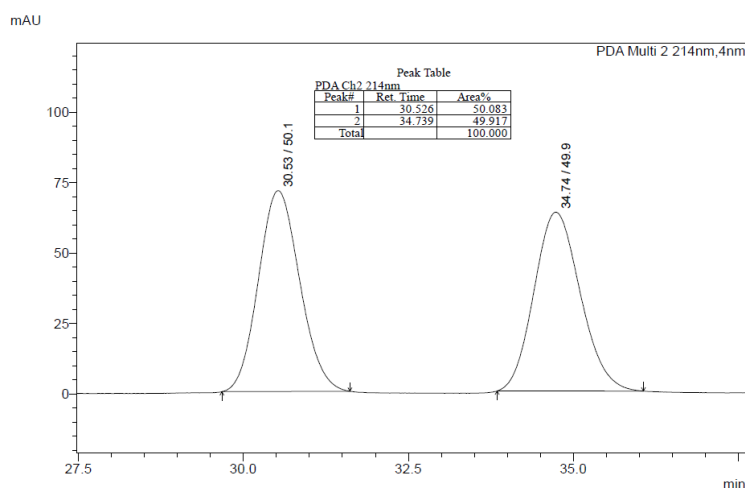
(3*S*,4*R*)-3-Benzoyl-4-benzyl-1-(4-fluorophenyl)azetidin-2-one, 63



General Procedure C, using **E4** as electrophile; White solid (26.8 mg, 75%, d.r. > 20:1 determined by ^1H NMR of the crude mixture); **m.p.** = 132 – 134 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.05 – 8.02 (m, 2H), 7.61 – 7.57 (m, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.33 – 7.19 (m, 3H), 7.17 – 7.10 (m, 2H), 7.10 – 7.03 (m, 2H), 5.14 (ddd, J = 7.5, 4.5, 2.5 Hz, 1H), 4.67 (d, J = 2.5 Hz, 1H), 3.40 (dd, J = 14.5, 4.5

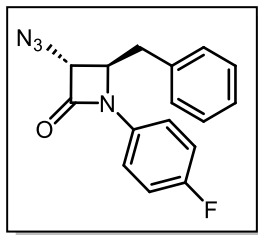
Hz, 1H), 3.13 (dd, J = 14.5, 7.5 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 191.0, 159.52, 159.51 (d, $J_{\text{C-F}}$ = 244.0 Hz), 135.9, 135.5, 134.1, 133.4 (d, $J_{\text{C-F}}$ = 3.0 Hz), 129.5, 129.3, 129.1, 128.9, 127.4, 119.2 (d, $J_{\text{C-F}}$ = 8.0 Hz), 116.3 (d, $J_{\text{C-F}}$ = 23.0 Hz), 63.7, 53.5, 37.0; ^{19}F NMR (376 MHz, CDCl_3) δ –117.2; **IR** (cm^{-1}) 2974, 1740, 1673, 1508, 1287, 1225, 1054, 833; **High Resolution MS** (EI): Calculated for $\text{C}_{23}\text{H}_{18}\text{FNO}_2$ $[\text{M}]^+$: 359.1322, Found: 359.1325.

Specific Rotation $[\alpha]_D^{21} +139.4^\circ$ (c = 0.60, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 30.6 min, t_{minor} = 34.8 min, 99:1 e.r.



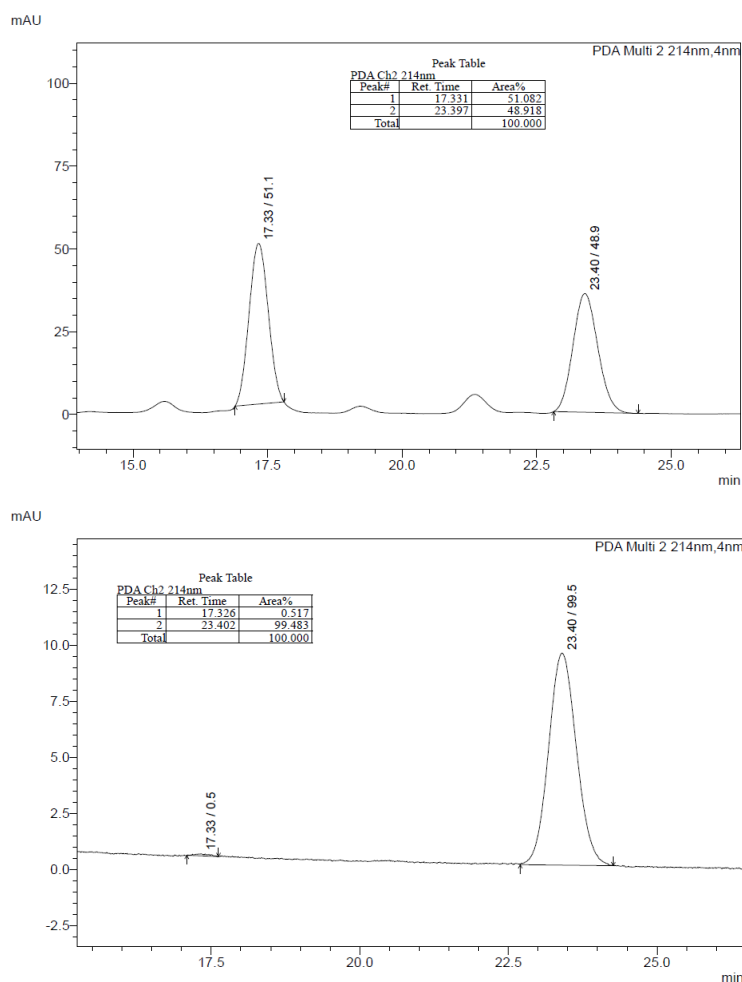
HPLC traces of racemic and enantioenriched compounds of **63**

(3R,4R)-3-Azido-4-benzyl-1-(4-fluorophenyl)azetidin-2-one, 64



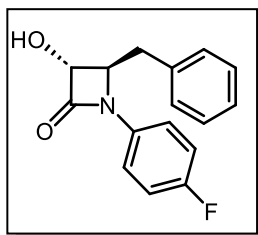
General Procedure C, using **E5** as electrophile; Yellow oil (10.3 mg, 35%, d.r. > 20:1 determined by ^1H NMR of the crude mixture); ^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.27 (m, 5H), 7.17 – 7.12 (m, 2H), 7.12 – 7.05 (m, 2H), 4.42 (d, J = 2.0 Hz, 1H), 4.20 (ddd, J = 8.5, 4.0, 2.0 Hz, 1H), 3.39 (dd, J = 14.5, 4.0 Hz, 1H), 2.97 (dd, J = 14.5, 8.5 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 160.8, 159.8 (d, $J_{\text{C-F}}$ = 245.0 Hz), 134.9, 132.7 (d, $J_{\text{C-F}}$ = 3.0 Hz), 129.3, 129.2, 127.7, 119.6 (d, $J_{\text{C-F}}$ = 8.0 Hz), 116.5 (d, $J_{\text{C-F}}$ = 23.0 Hz), 68.0, 60.7, 36.5; ^{19}F NMR (376 MHz, CDCl_3) δ –116.3; IR (cm^{-1}) 2928, 2104, 1751, 1507, 1385, 1219, 1104, 830; **High Resolution MS** (EI): Calculated for $\text{C}_{16}\text{H}_{13}\text{FN}_4\text{O}$ $[\text{M}]^+$: 296.1073, Found: 296.1075.

Specific Rotation $[\alpha]_D^{21} +85.7^\circ$ (c = 0.64, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 32 $^\circ\text{C}$, i -PrOH/ n -hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 17.3 min, t_{minor} = 23.4 min, >99:1 e.r.



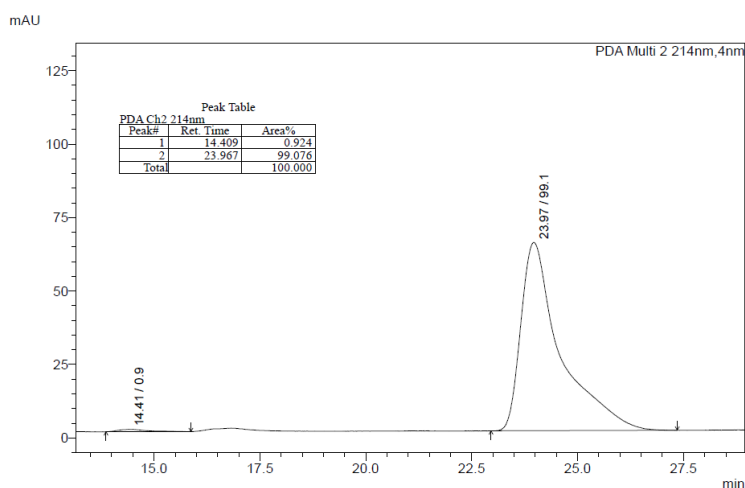
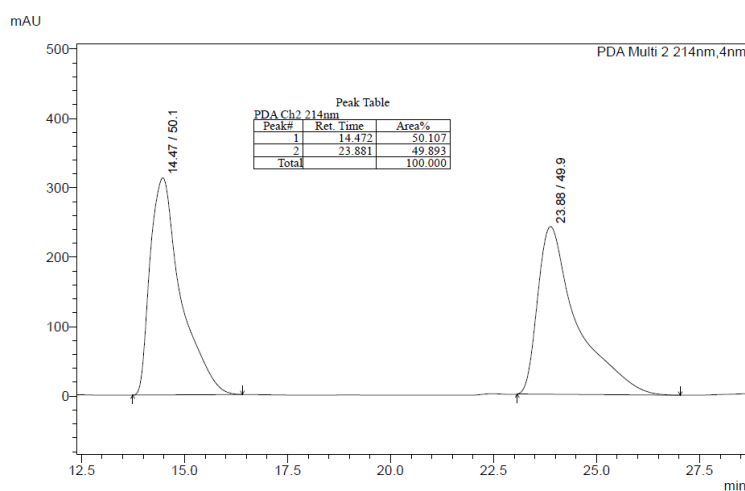
HPLC traces of racemic and enantioenriched compounds of **64**

(3R,4R)-4-Benzyl-1-(4-fluorophenyl)-3-hydroxyazetidin-2-one, 65



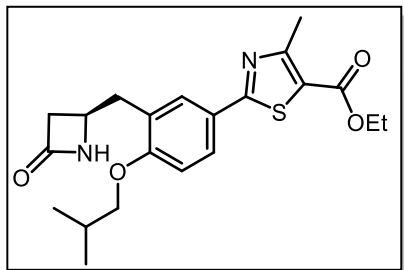
General Procedure C, using **E6** as electrophile; Pale yellow solid (9.5 mg, 35%, *d.r.* > 20:1 determined by ^1H NMR of the crude); **m.p.** = 70 – 71 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.24 (m, 5H), 7.18 – 7.13 (m, 2H), 7.13 – 6.99 (m, 2H), 4.67 (d, J = 2.0 Hz, 1H), 4.25 (ddd, J = 8.0, 4.0, 2.0 Hz, 1H), 3.33 (dd, J = 14.5, 4.0 Hz, 1H), 2.98 (dd, J = 14.5, 8.0 Hz, 1H) (*OH* peak not observed); ^{13}C NMR (101 MHz, CDCl_3) δ 165.5, 159.7 (d, $J_{\text{C-F}}$ = 244.5 Hz), 135.7, 132.8 (d, $J_{\text{C-F}}$ = 3.0 Hz), 129.2, 129.0, 127.4, 119.8 (d, $J_{\text{C-F}}$ = 8.0 Hz), 116.3 (d, $J_{\text{C-F}}$ = 23.0 Hz), 79.5, 62.7, 36.2; ^{19}F NMR (376 MHz, CDCl_3) δ –116.8; **IR** (cm^{-1}) 3244, 2917, 1735, 1508, 1347, 1216, 1144, 830; **High Resolution MS** (EI): Calculated for $\text{C}_{16}\text{H}_{14}\text{FNO}_2$ $[\text{M}]^+$: 271.1009, Found: 271.1012.

Specific Rotation $[\alpha]_D^{21}$ –96.0° (c = 0.10, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IC-3, 40 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 24.0 min, t_{minor} = 14.4 min, 99:1 e.r.



HPLC traces of racemic and enantioenriched compounds of **65**

Ethyl (R)-2-{4-isobutoxy-3-[(4-oxoazetidin-2-yl)methyl]phenyl}-4-methylthiazole-5-carboxylate, 66

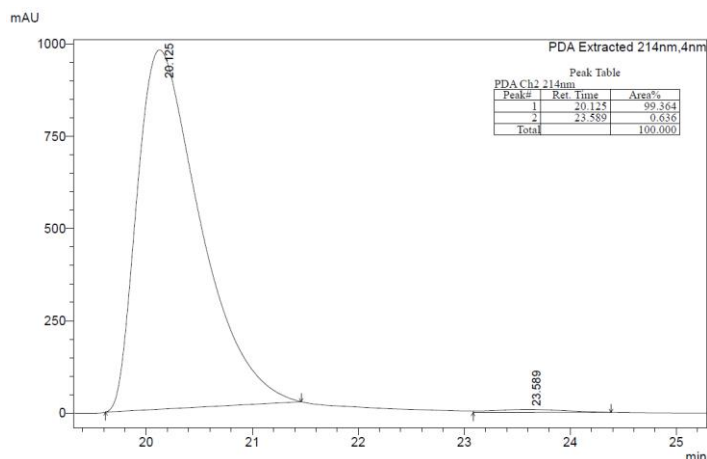
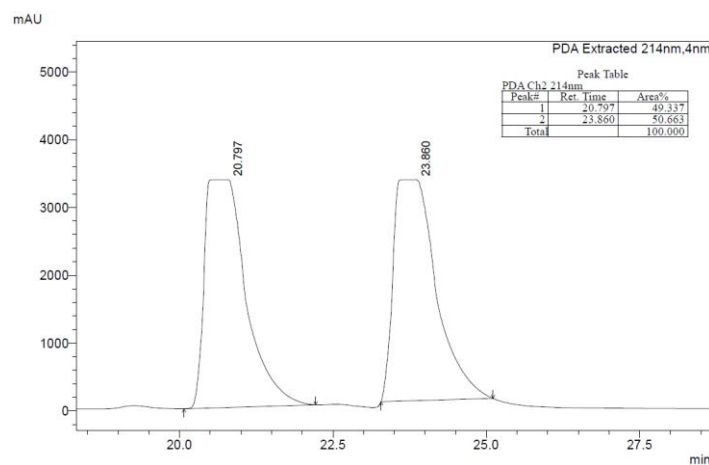


General Procedure A, 0.05 mmol scale; Yellow solid (16.1 mg, 80%); **General Procedure B**, in 0.05 mmol scale; (13.2 mg, 66%);

m.p. = 108 – 110 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.79 (dd, J = 8.5, 2.5 Hz, 1H), 7.75 (d, J = 2.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 5.92 (br. s, 1H), 4.34 (q, J = 7.0 Hz, 2H), 3.96 (dtd, J = 7.5, 5.5, 2.5 Hz, 1H), 3.84 – 3.76 (m, 2H), 3.14 – 3.02 (m, 2H), 2.88

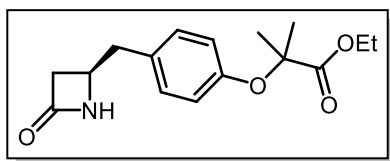
(dd, J = 13.5, 7.5 Hz, 1H), 2.78 – 2.71 (m, 4H), 2.14 (hept, J = 6.5 Hz, 1H), 1.37 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 6.5 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 169.7, 167.7, 162.5, 161.1, 159.4, 129.1, 127.4, 126.9, 125.8, 121.1, 111.6, 74.8, 61.3, 47.6, 43.5, 36.5, 28.5, 19.5, 17.7, 14.5; **IR** (cm⁻¹) 3258, 2970, 2917, 1775, 1689, 1601, 1425, 1369, 1314, 1252, 1172, 1088, 1013, 820; **High Resolution MS** (EI): Calculated for C₂₁H₂₆N₂O₄S [M]⁺: 402.1613, Found: 402.1617.

Specific Rotation [α]_D²¹ +5.0° (c = 0.14, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 20.1 min, t_{minor} = 23.6 min, >99: 1 e.r.



HPLC traces of racemic and enantioenriched compounds of **66**

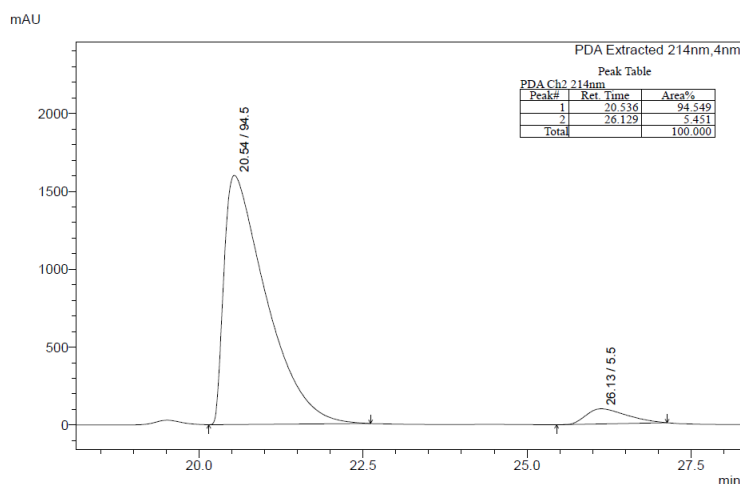
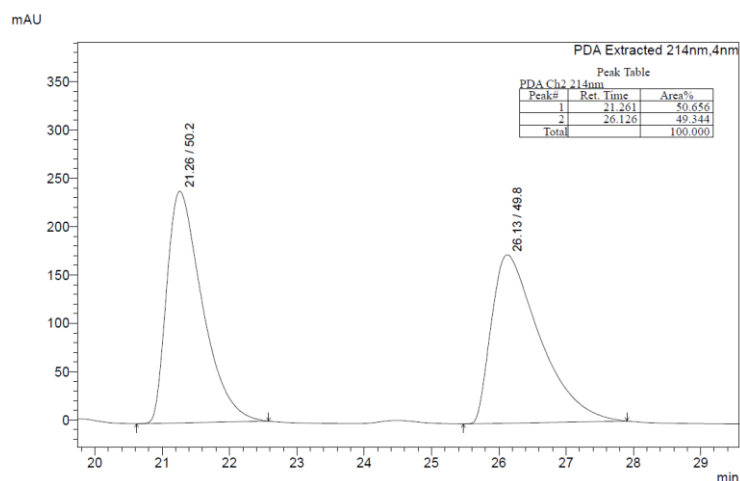
Ethyl (*R*)-2-methyl-2-{4-[(4-oxoazetidin-2-yl)methyl]phenoxy}propanoate, **67**



General Procedure A, in 0.1 mmol scale; Pale yellow oil (24.8 mg, 85%); **General Procedure B**, in 0.1 mmol scale; (19.7 mg, 68%);

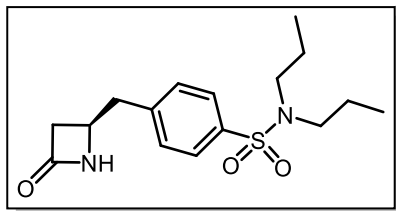
^1H NMR (500 MHz, CDCl_3) 7.03 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 5.89 (br. s, 1H), 4.23 (q, J = 7.0 Hz, 2H), 3.79 (ddt, J = 8.0, 5.5, 2.5 Hz, 1H), 3.05 (ddd, J = 15.0, 5.5, 1.5 Hz, 1H), 2.89 (dd, J = 14.0, 5.5 Hz, 1H), 2.76 (dd, J = 14.0, 8.0 Hz, 1H), 2.66 (ddd, J = 15.0, 2.5, 1.5 Hz, 1H), 1.58 (s, 6H), 1.25 (t, J = 7.0 Hz, 3H).; ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 167.6, 154.5, 131.2, 129.5, 119.6, 79.3, 61.6, 49.1, 43.4, 41.2, 25.50, 25.48, 14.2; IR (cm^{-1}) 3272, 2989, 2938, 1730, 1508, 1234, 1137, 1019, 971; **High Resolution MS** (EI): Calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_4$ $[\text{M}]^+$: 291.1471, Found: 291.1472.

Specific Rotation $[\alpha]_D^{21} +10.4^\circ$ (c = 0.75, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IA, 32 $^\circ\text{C}$, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, t_{major} = 20.5 min, t_{minor} = 26.1 min, 95:5 e.r.



HPLC traces of racemic and enantioenriched compounds of **67**

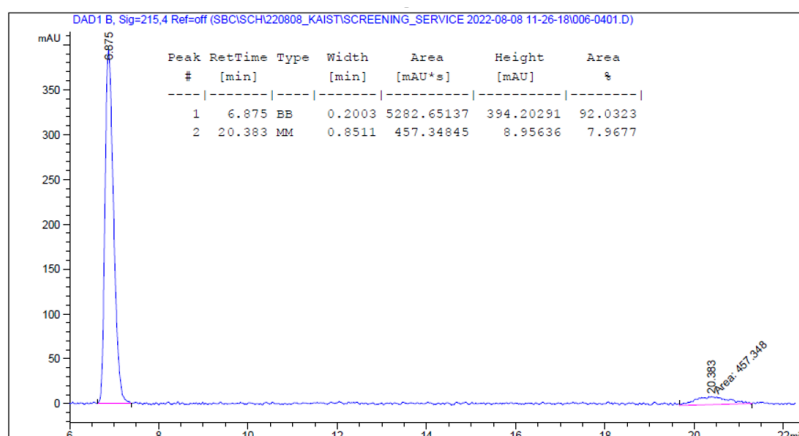
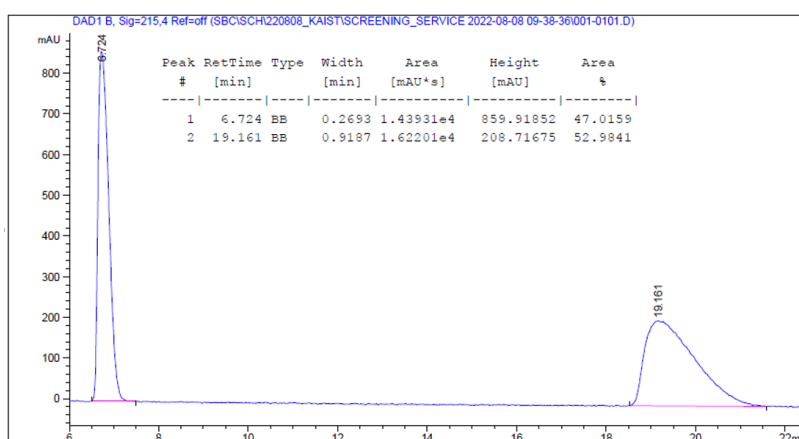
(R)-4-[(4-Oxoazetidin-2-yl)methyl]-N,N-dipropylbenzenesulfonamide, 68



General Procedure A, in 0.1 mmol scale; Yellow solid (27.6 mg, 85%); **General Procedure B**, in 0.1 mmol scale; (24.0 mg, 74%); **m.p.** = 67 – 68 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.76 (dd, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.95 (br. d, J = 15.0 Hz, 1H), 3.89 – 3.85 (m, 1H), 3.14 – 3.00 (m, 6H), 2.93 (dd, J = 14.0, 8.0

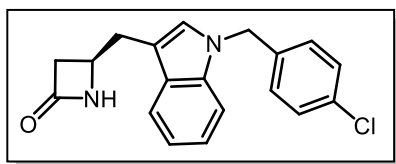
Hz, 1H), 2.70 (d, J = 15.0 Hz, 1H), 1.55 (sext, J = 7.5 Hz, 4H), 0.87 (t, J = 7.5 Hz, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 167.2, 142.3, 139.1, 129.5, 127.8, 50.2, 48.6, 43.6, 41.7, 22.2, 11.3; **IR** (cm^{-1}) 3188, 2962, 2934, 1745, 1332, 1151, 985; **High Resolution MS** (EI): Calculated for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ $[\text{M}]^+$: 324.1508, Found: 324.1510.

Specific Rotation $[\alpha]_D^{21} +2.2^\circ$ (c = 0.81, CH_2Cl_2); **HPLC Analysis** CHIRALPAK IH-3, 32 °C, 0.1% DEA in EtOH/*n*-hexane = 50/50, 1.0 mL/min, UV 215 nm, t_{major} = 6.9 min, t_{minor} = 20.4 min, 92:8 e.r.



HPLC traces of racemic and enantioenriched compounds of **68**

(R)-4-([1-(4-Chlorobenzyl)-1H-indol-3-yl]methyl)azetidin-2-one, 69

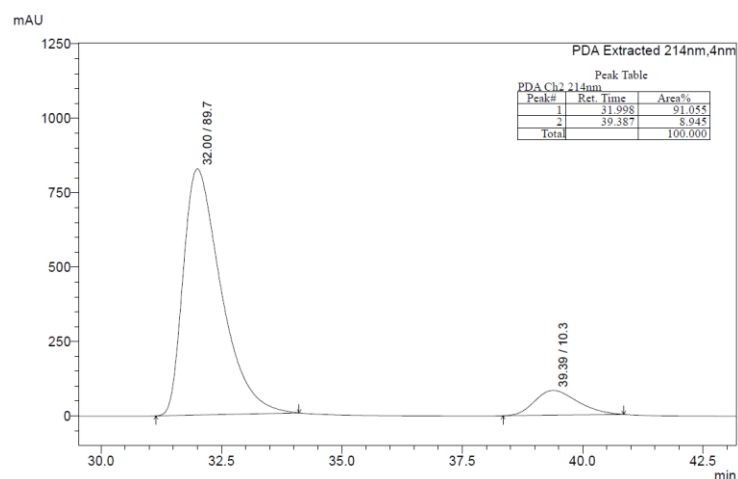
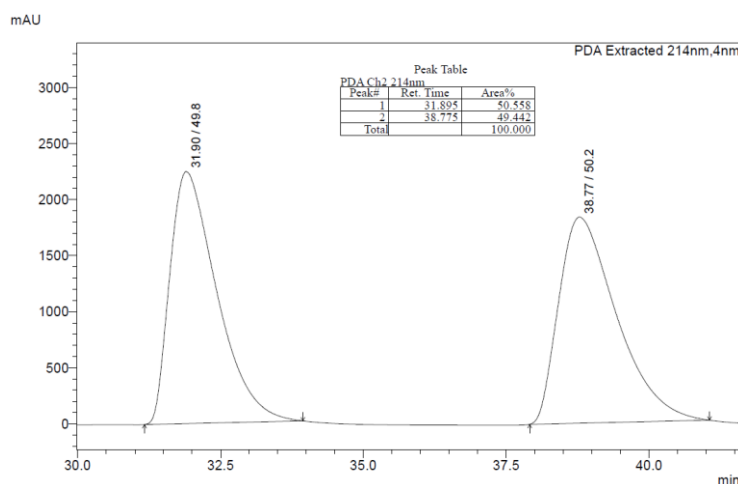


General Procedure A, in 0.05 mmol scale; Yellow solid (4.9 mg, 30%); **General Procedure B**, in 0.05 mmol scale; (6.3 mg, 39%);

m.p. = 136 – 138 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.18 (m, 4H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.93 (s, 1H), 5.83 (br. s, 1H), 5.25 (s, 2H), 3.95 (dtd, *J* = 7.5, 5.0, 2.0 Hz, 1H), 3.15 – 3.06 (m, 2H), 3.00 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.71 (d, *J* = 14.5 Hz, 1H); **¹³C NMR** (126 MHz, CDCl₃) δ 167.8, 136.8, 136.0, 133.7, 129.2, 128.3, 128.1, 126.1, 122.5, 119.8, 119.0, 111.6, 110.0, 49.5, 48.5, 43.6, 31.7; **IR** (cm⁻¹) 2923, 2852, 1727, 1466, 1245, 1175, 1010, 738; **High Resolution MS** (EI):

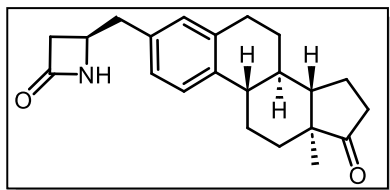
Calculated for C₁₉H₁₇ClN₂O [M]⁺: 324.1029, Found: 324.1027.

Specific Rotation [α]_D²¹ +7.4° (c = 0.18, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, *t*_{major} = 32.0 min, *t*_{minor} = 39.4 min, 91:9 e.r.



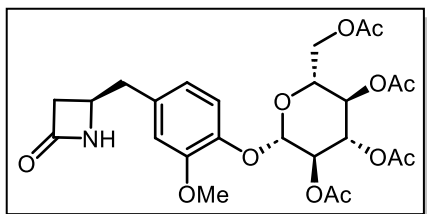
HPLC traces of racemic and enantioenriched compounds of **69**

(R)-4-[[[(8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl]methyl]azetidin-2-one, 70



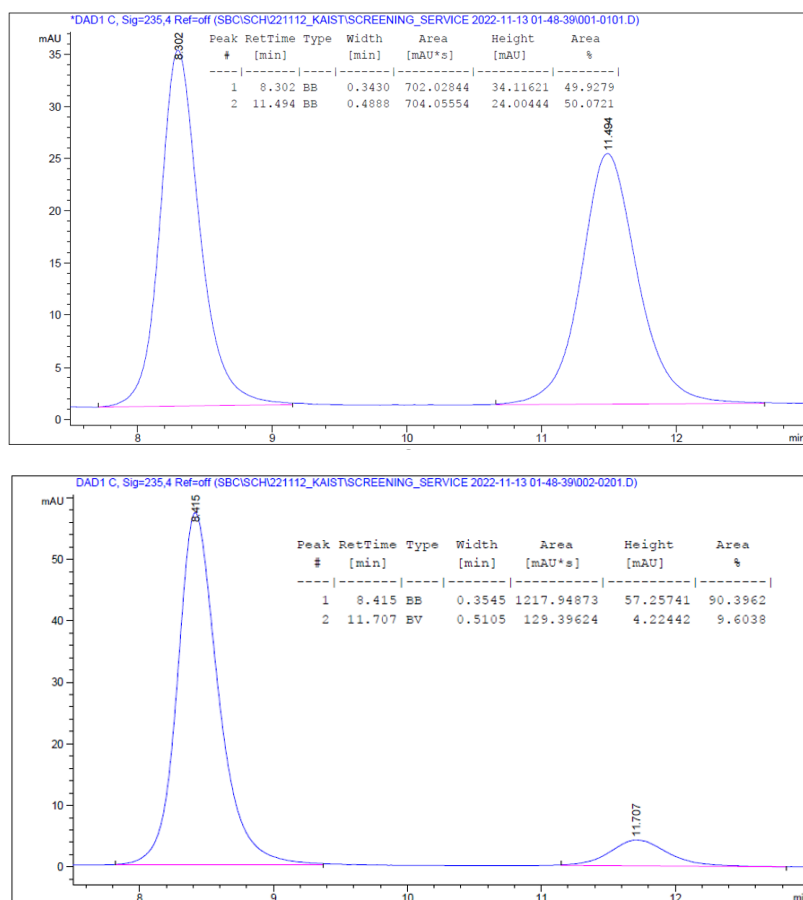
General Procedure B, in 0.05 mmol scale; White solid (11.0 mg, 65%, 92:8 d.r. determined by ^1H NMR of the crude mixture); **m.p.** = 161 – 163 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.25 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.91 (s, 1H), 5.82 (br. s, 1H), 3.84 (dtd, J = 8.0, 5.0, 2.0 Hz, 1H), 3.08 (dd, J = 15.0, 4.0 Hz, 1H), 2.96 – 2.87 (m, 3H), 2.77 (dd, J = 13.5, 8.0 Hz, 1H), 2.69 (d, J = 15.0 Hz, 1H), 2.51 (dd, J = 19.0, 8.5 Hz, 1H), 2.42 (dt, J = 13.5, 4.0 Hz, 1H), 2.29 (td, J = 10.5, 4.0 Hz, 1H), 2.20 – 2.00 (m, 3H), 1.99 – 1.94 (m, 1H), 1.69 – 1.39 (m, 6H), 0.91 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 220.9, 167.6, 138.6, 137.1, 135.1, 129.5, 126.3, 126.0, 50.6, 49.0, 48.1, 44.4, 43.5, 41.5, 38.3, 36.0, 31.7, 29.5, 26.6, 25.9, 21.7, 14.0; **IR** (cm^{-1}) 3266, 2920, 2854, 1702, 1359, 1005, 825; **High Resolution MS** (EI): Calculated for $\text{C}_{22}\text{H}_{27}\text{NO}_2$ $[\text{M}]^+$: 337.2042, Found: 337.2039; **Specific Rotation** $[\alpha]_D^{21} +161.2^\circ$ (c = 0.14, CH_2Cl_2);

(2R,3R,4S,5R,6S)-2-(Acetoxymethyl)-6-{2-methoxy-4-[(*R*)-4-oxoazetidin-2-yl)methyl]phenoxy}-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, **71**



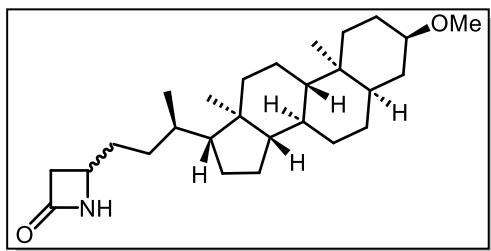
General Procedure A, in 0.05 mmol scale; Pale yellow solid (11.8 mg, 44%); **General Procedure B**, in 0.1 mmol scale; (20.3 mg, 38%, 90:10 d.r. determined by chiral HPLC); **m.p.** = 56 – 57 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.06 (d, *J* = 8.0 Hz, 1H), 6.72 – 6.64 (m, 2H), 5.92 (br. s, 1H), 5.32 – 5.21 (m, 2H), 5.21 – 5.11 (m, 1H), 4.99 – 4.89 (m, 1H), 4.27 (dd, *J* = 12.0, 5.0 Hz, 1H), 4.16 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.85 – 3.80 (m, 4H), 3.76 (ddd, *J* = 10.0, 5.0, 2.5 Hz, 1H), 3.07 (ddd, *J* = 15.0, 5.0, 2.0 Hz, 1H), 2.93 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.82 – 2.72 (m, 1H), 2.67 (ddd, *J* = 15.0, 2.5, 1.0 Hz, 1H), 2.07 (s, 6H), 2.031 (s, 3H), 2.027 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 170.7, 170.4, 169.6, 169.5, 167.5, 151.0, 145.0, 134.4, 120.9, 120.7, 113.4, 100.9, 72.7, 72.1, 71.3, 68.5, 62.0, 56.2, 49.0, 43.4, 41.7, 20.9, 20.80, 20.77, 20.7; **IR** (cm⁻¹) 3354, 2926, 2854, 1747, 1513, 1368, 1221, 1036; **High Resolution MS** (FAB): Calculated for C₂₅H₃₂NO₁₂ [M+H]⁺: 538.1919, Found: 538.1928.

Specific Rotation [α]_D²¹ +16.9 (*c* = 1.06, CH₂Cl₂); **HPLC Analysis** CHIRALPAK IA, 32 °C, EtOH/*n*-hexane = 50/50, 1.0 mL/min, UV 214 nm, *t*_{major} = 8.4 min, *t*_{minor} = 11.7 min, 90:10 d.r.



HPLC traces of compound **71** obtained by standard and asymmetric conditions

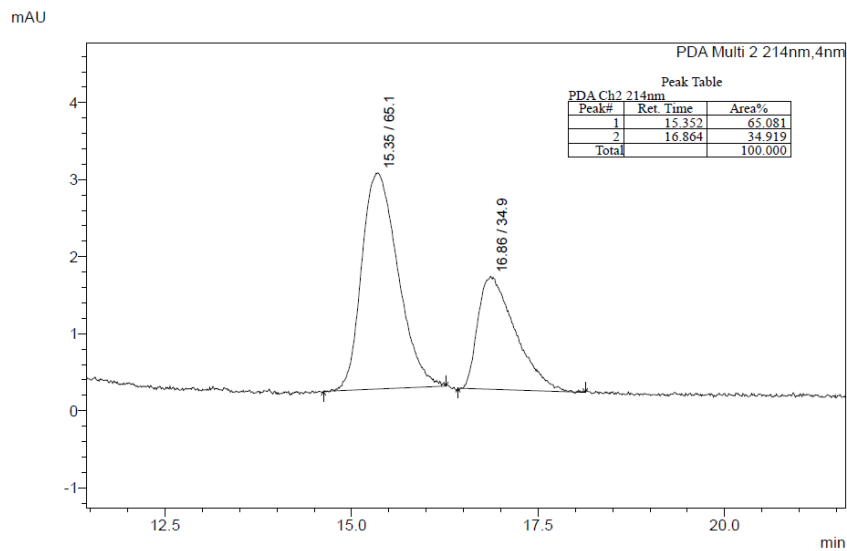
4-[(*R*)-3-[(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Methoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]butyl]azetidin-2-one, 72



General Procedure A, in 0.1 mmol scale; White solid (27.5 mg, 66%, 65:35 d.r. determined by chiral HPLC); **m.p.** = 145 – 147 °C; ¹H NMR (400 MHz, CDCl₃) δ 6.06 (br. s, 1H), 3.54 (dt, *J* = 7.0, 4.5, 2.5 Hz, 1H), 3.34 (s, 3H), 3.15 (td, *J* = 10.5, 5.5 Hz, 1H), 3.03 (ddt, *J* = 15.0, 4.5, 2.5 Hz, 1H), 2.58 – 2.47 (m, 1H), 1.93 (dt, *J* = 12.5, 3.0 Hz,

1H), 1.89 – 1.70 (m, 4H), 1.70 – 1.44 (m, 5H), 1.43 – 1.30 (m, 7H), 1.30 – 1.15 (m, 5H), 1.15 – 0.98 (m, 6H), 0.91 – 0.90 (m, 6H), 0.62 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 168.3, 80.5, 56.6, 56.0, 55.7, 48.74, 48.67 (minor diastereomer), 43.7 (minor diastereomer), 43.6, 42.8, 42.1, 40.4, 40.3, 35.9, 35.62, 35.59 (minor diastereomer), 35.4, 35.0, 32.9, 32.45, 32.42 (minor diastereomer), 32.09, 32.06 (minor diastereomer), 28.4, 27.4, 26.9, 26.5, 24.3, 23.5, 20.9, 18.8, 12.2 (*all other peaks for minor diastereoisomer overlap with those of major diastereomer*); **IR** (cm⁻¹) 2977, 2860, 1756, 1453, 1376, 1175, 1098, 687; **High Resolution MS** (EI): Calculated for C₂₇H₄₅NO₂ [M]⁺: 415.3450, Found: 415.3447.

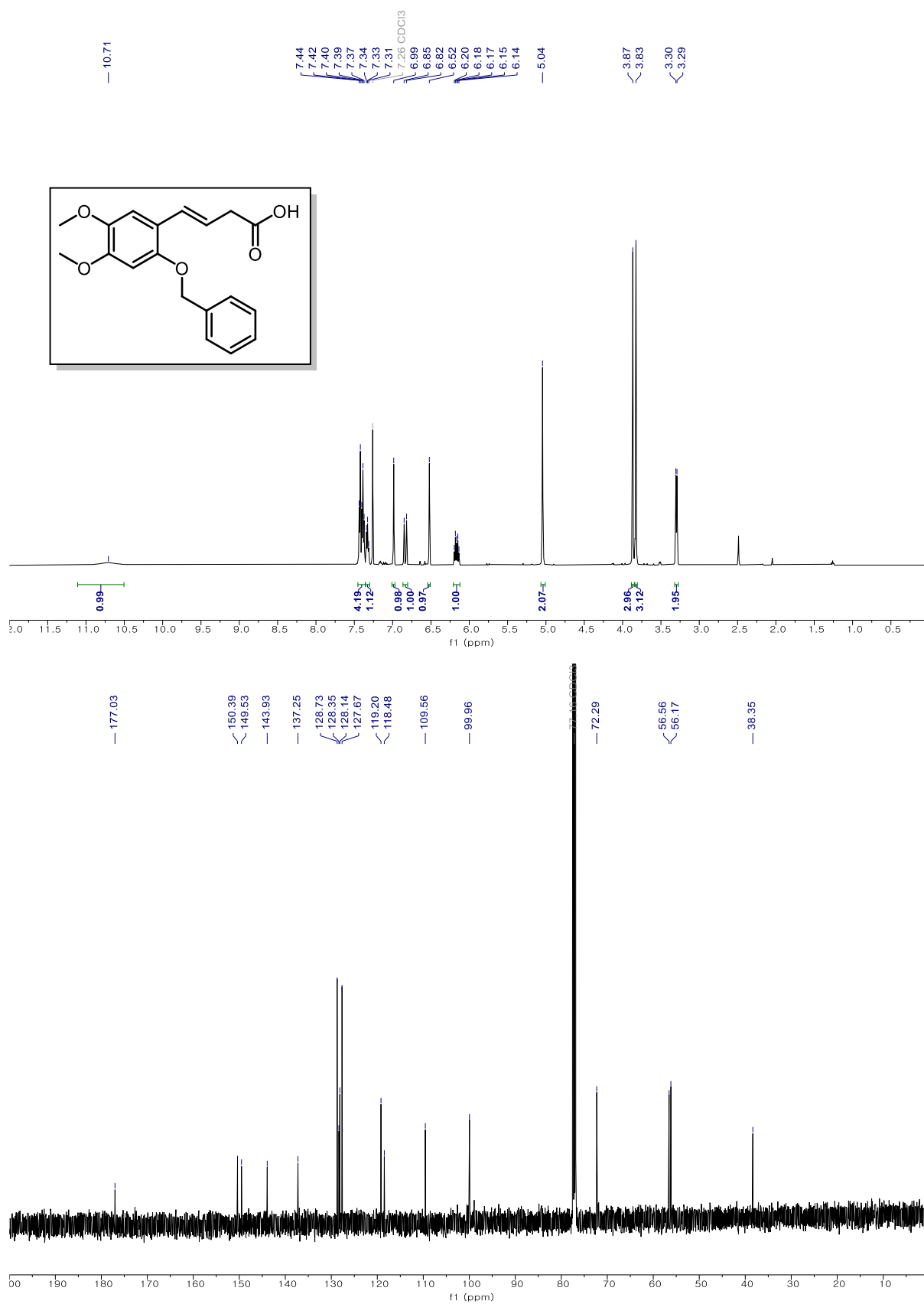
HPLC Analysis CHIRALPAK IA, 32 °C, *i*-PrOH/*n*-hexane = 10/90, 0.5 mL/min, UV 214 nm, *t*_{major} = 15.4 min, *t*_{minor} = 16.9 min, 65:35 d.r.



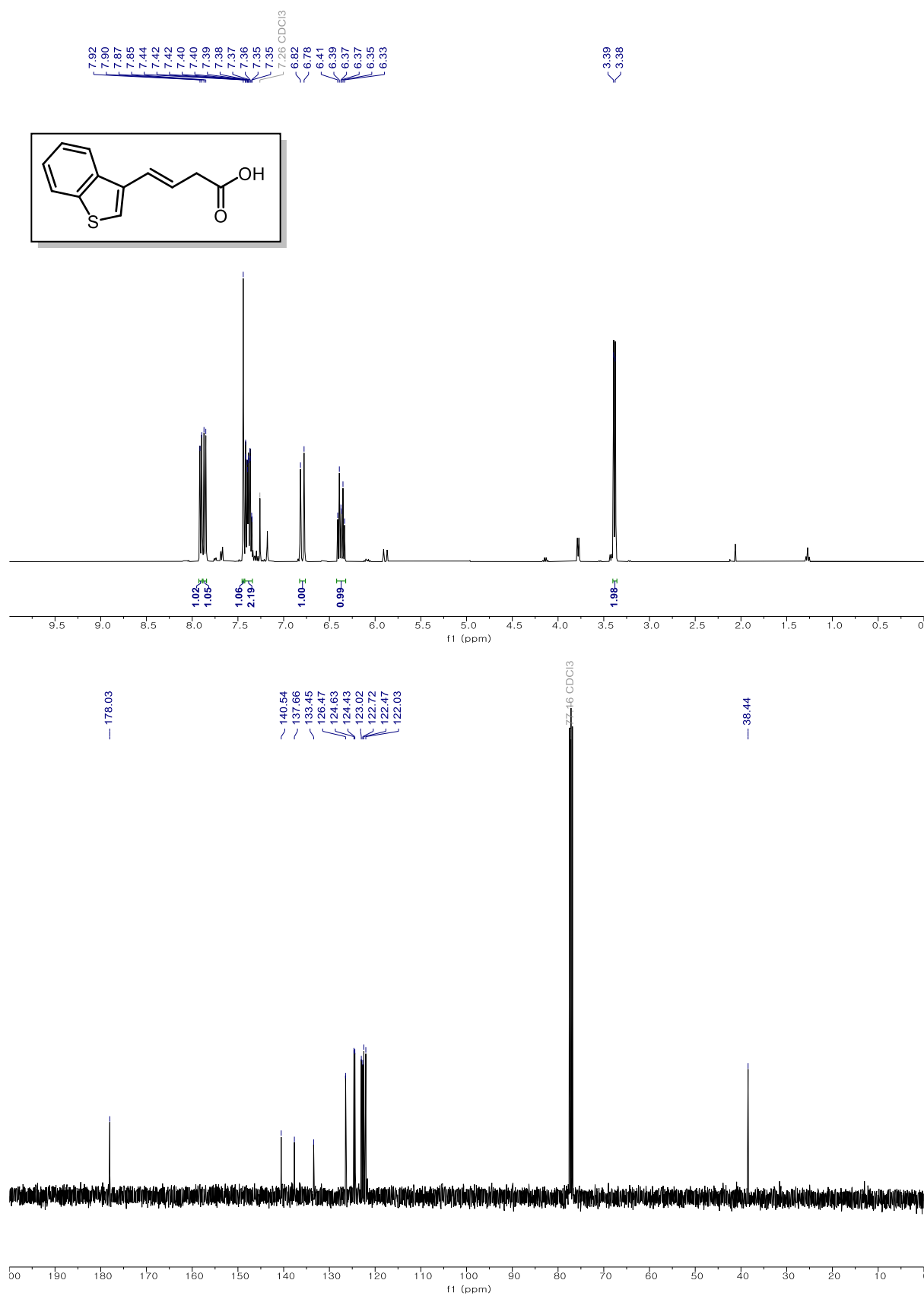
HPLC traces of compound 72

Spectral Copies of ^1H , ^{13}C , and ^{19}F NMR of Novel Compounds Obtained in This Study

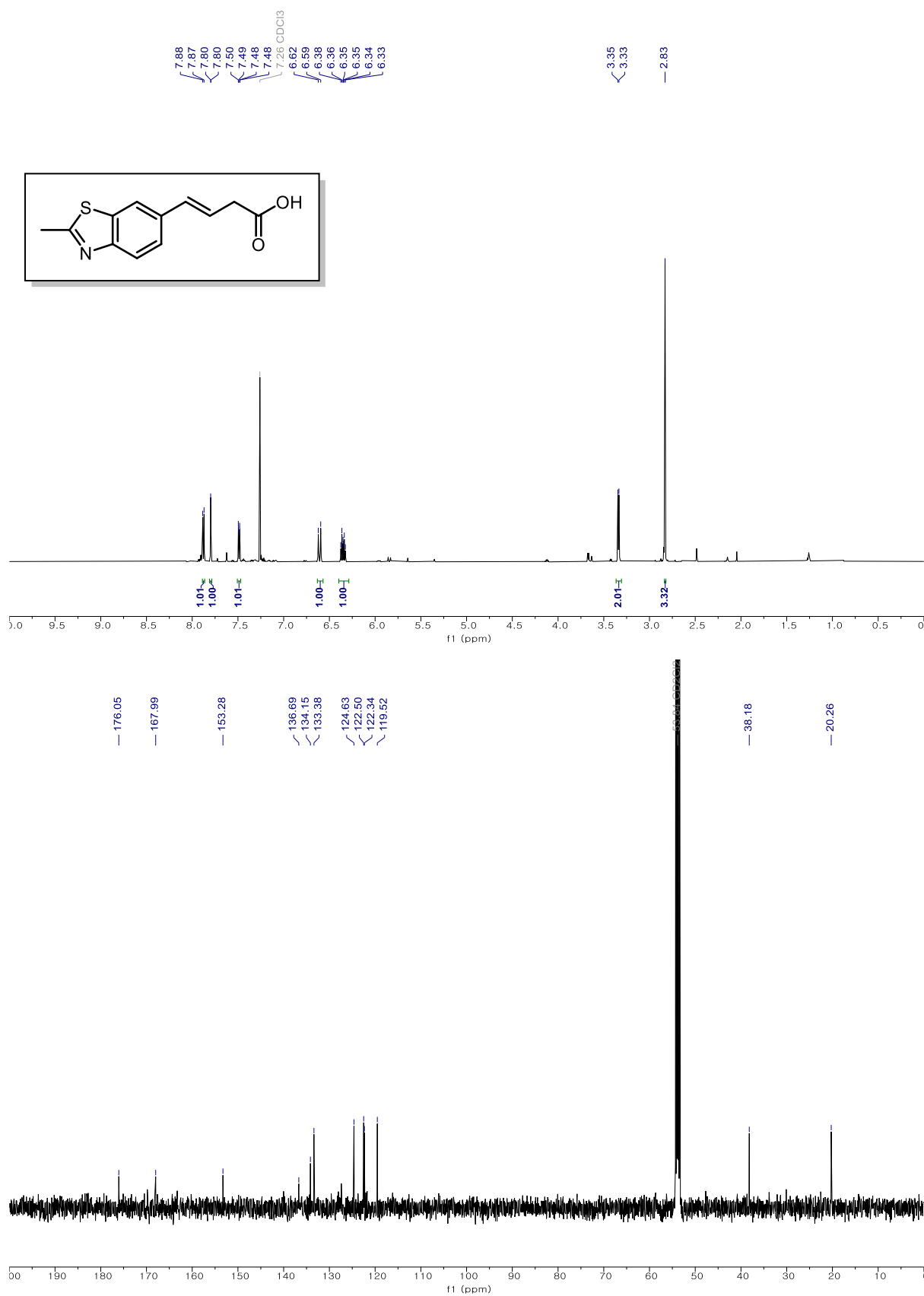
(E)-4-[2-(Benzyloxy)-4,5-dimethoxyphenyl]but-3-enoic acid



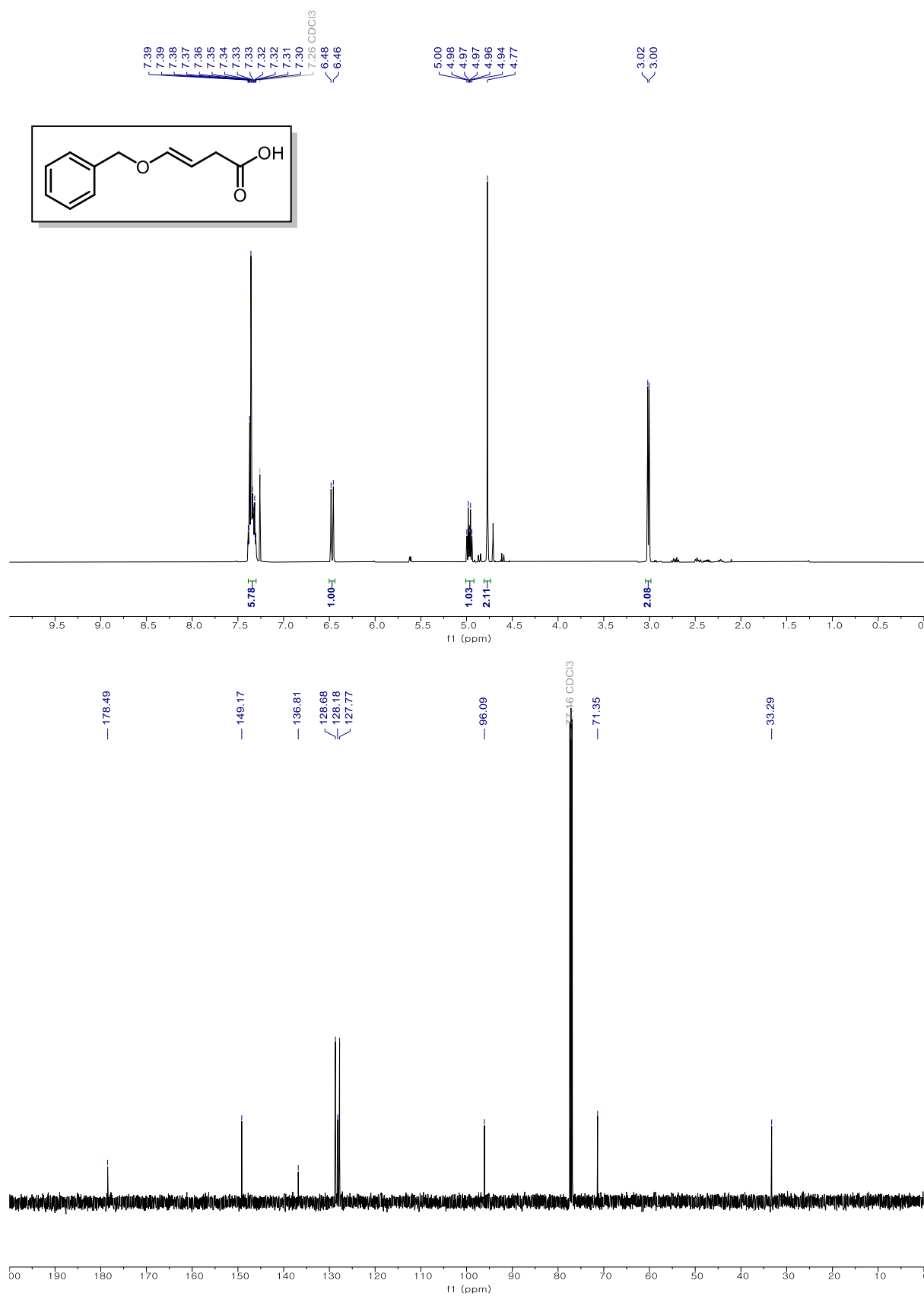
(E)-4-(Benzo[*b*]thiophen-3-yl)but-3-enoic acid



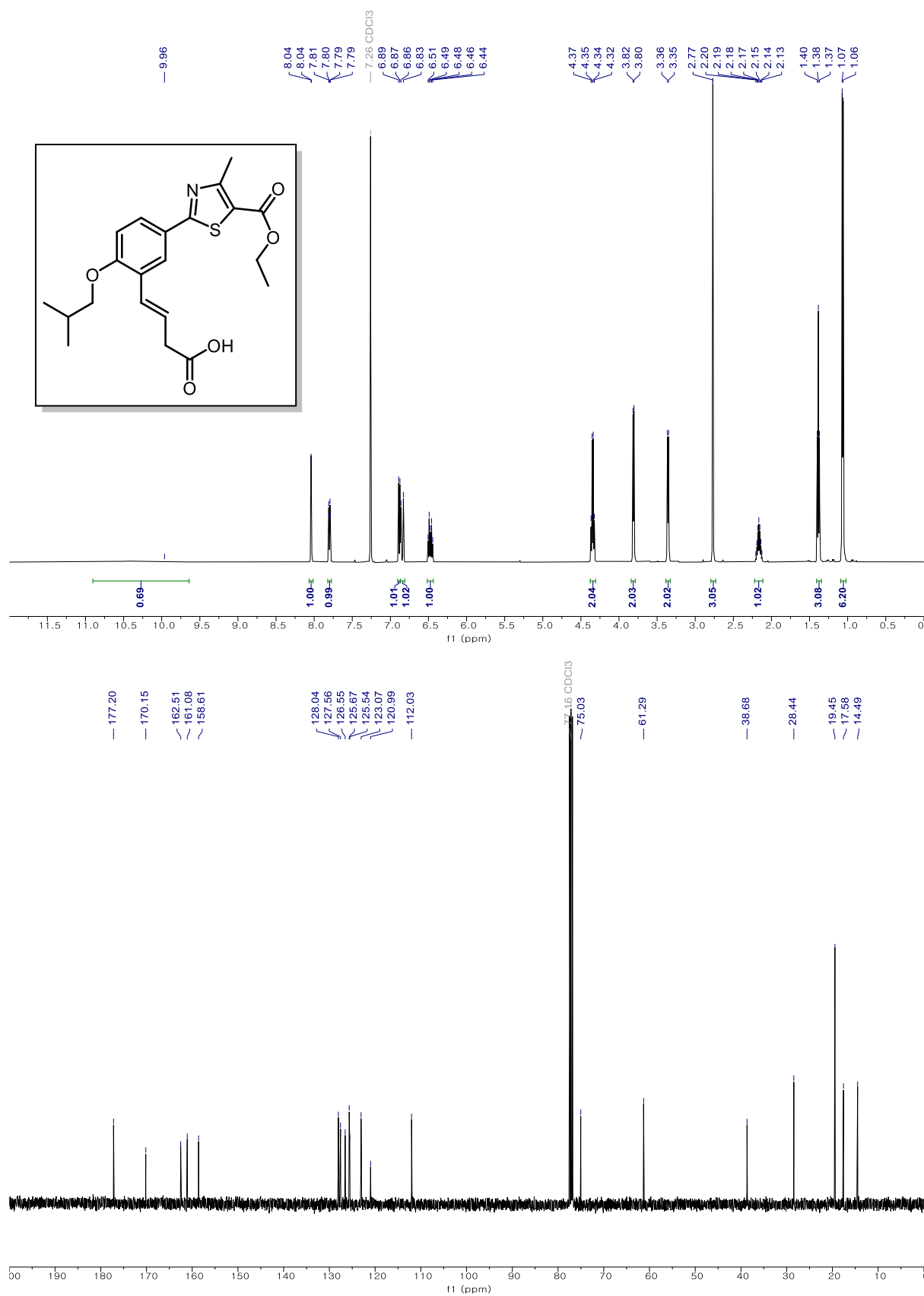
(E)-4-(2-methylbenzo[d]thiazol-6-yl)but-3-enoic acid



(E)-4-(Benzyloxy)but-3-enoic acid



(E)-4-{5-[5-(Ethoxycarbonyl)-4-methylthiazol-2-yl]-2-isobutoxyphenyl}but-3-enoic acid



Chemical structure of compound 10: CC(=O)O[C@H]1O[C@@H](COc2ccc(cc2)/C=C/C(=O)O)[C@H](OC(=O)C)[C@@H](OC(=O)C)[C@H](OC(=O)C)[C@H]1OC(=O)C

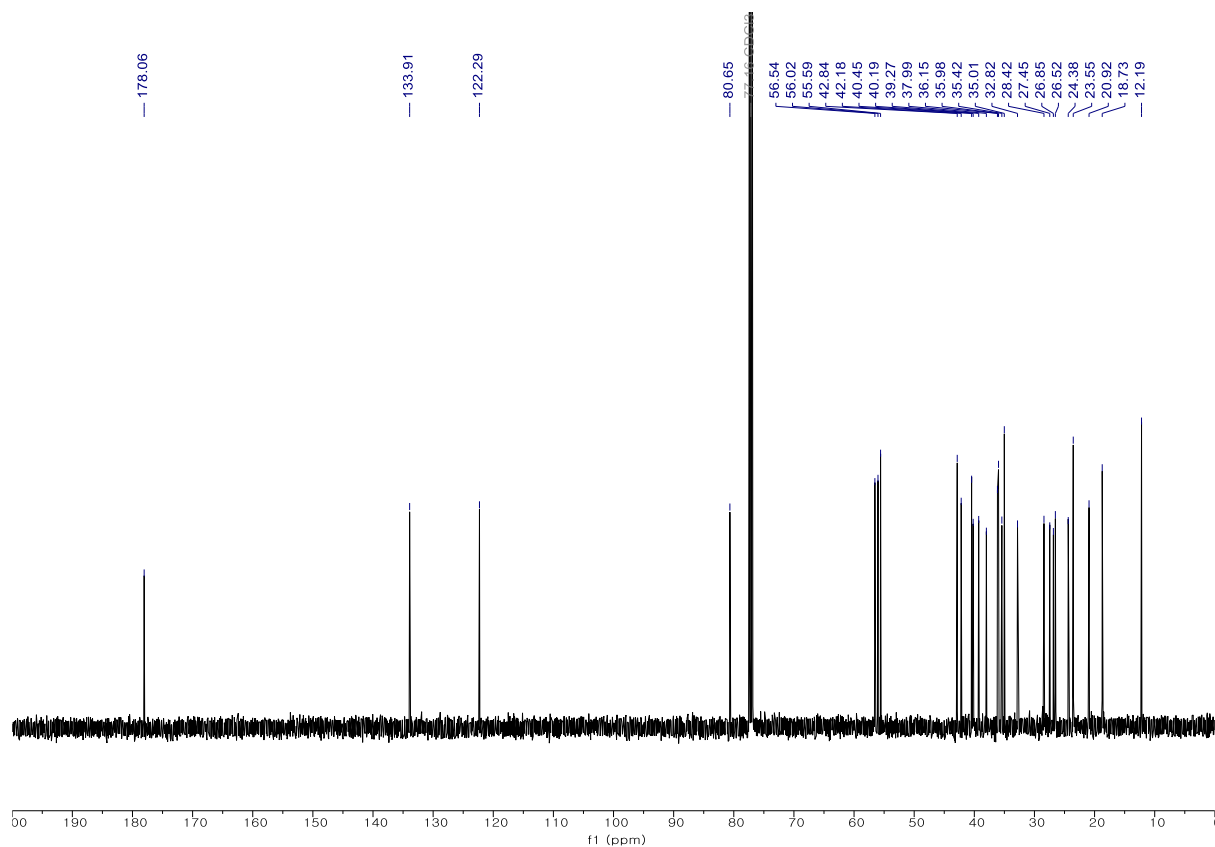
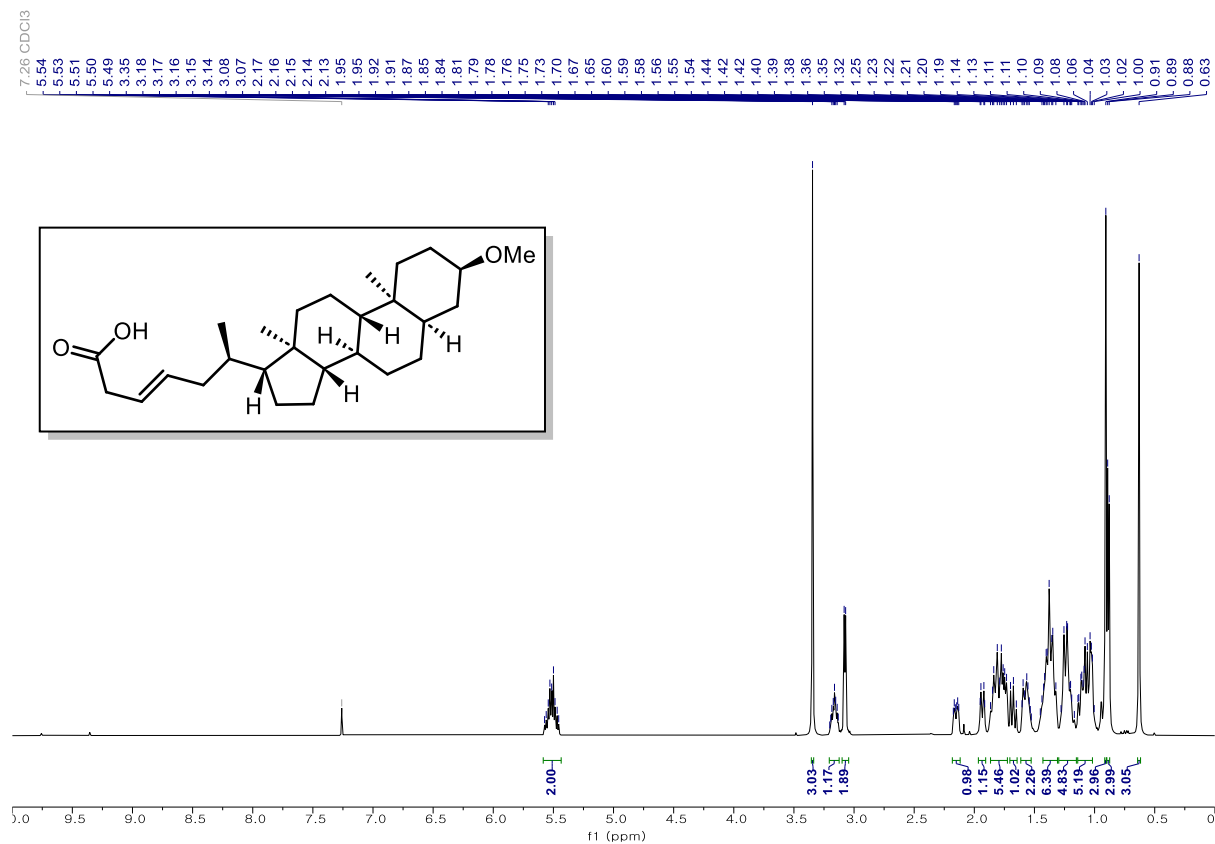
¹H NMR spectrum (CDCl₃) of compound 10. The x-axis represents the chemical shift in ppm (f1), ranging from 0.5 to 10.0. The spectrum shows several peaks, with integration values provided below the baseline and a list of chemical shifts (δ) on the right.

Integration values (from left to right): 0.56, 1.12, 1.01, 1.01, 1.00, 2.24, 1.12, 1.14, 1.15, 1.14, 3.01, 1.13, 2.01, 6.12, 6.36.

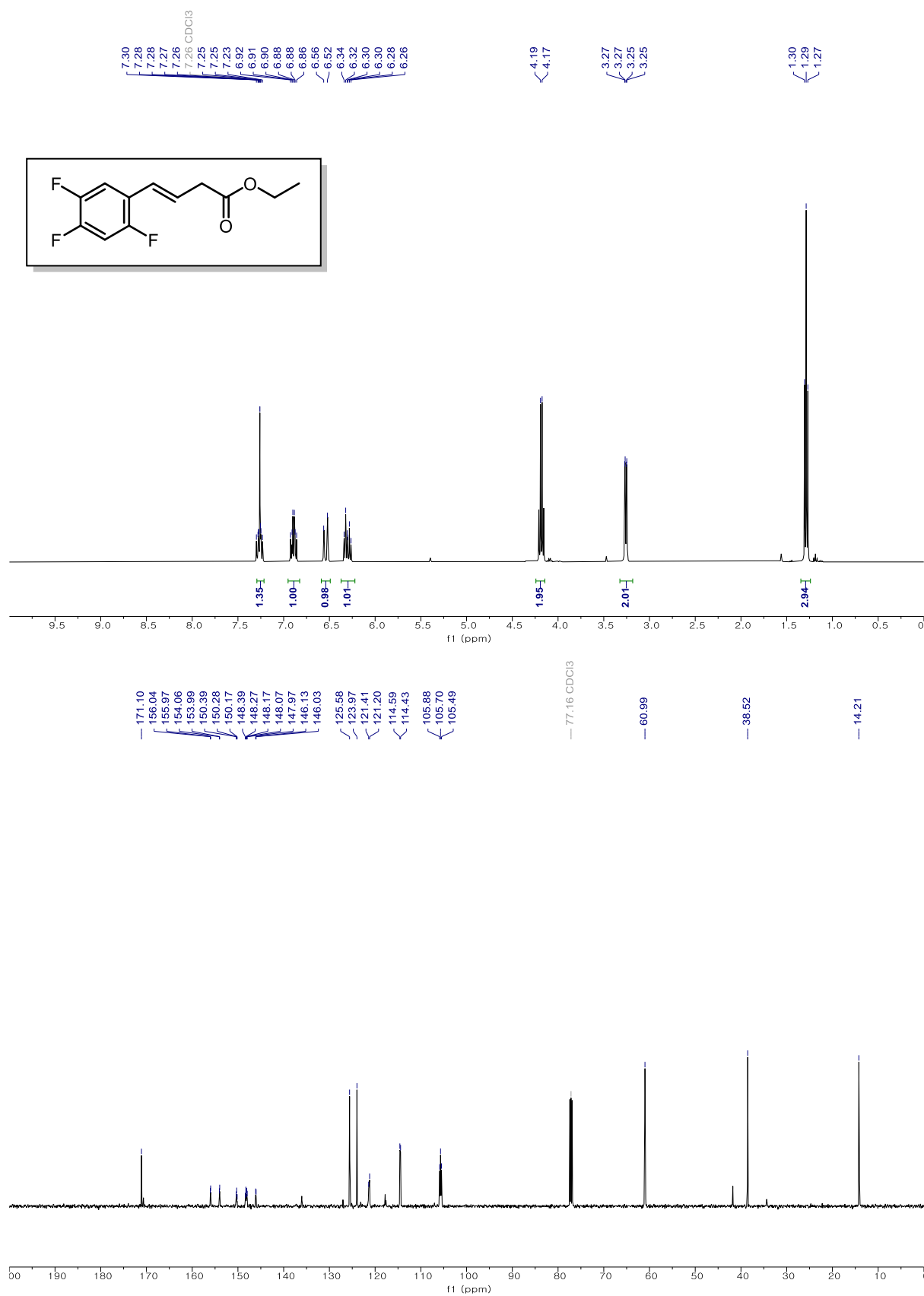
Chemical shifts (δ) (from left to right): 9.88, 7.26, 7.05, 7.04, 6.92, 6.91, 6.87, 6.86, 6.85, 6.85, 6.46, 6.43, 6.21, 6.20, 6.18, 6.16, 6.17, 6.15, 5.30, 5.28, 5.28, 5.27, 5.26, 5.25, 5.17, 5.17, 5.16, 5.14, 5.14, 4.94, 4.94, 4.93, 4.29, 4.28, 4.26, 4.25, 4.17, 4.16, 4.14, 4.14, 3.78, 3.77, 3.77, 3.76, 3.76, 3.75, 3.74, 3.74, 3.29, 3.27, 2.07, 2.03.

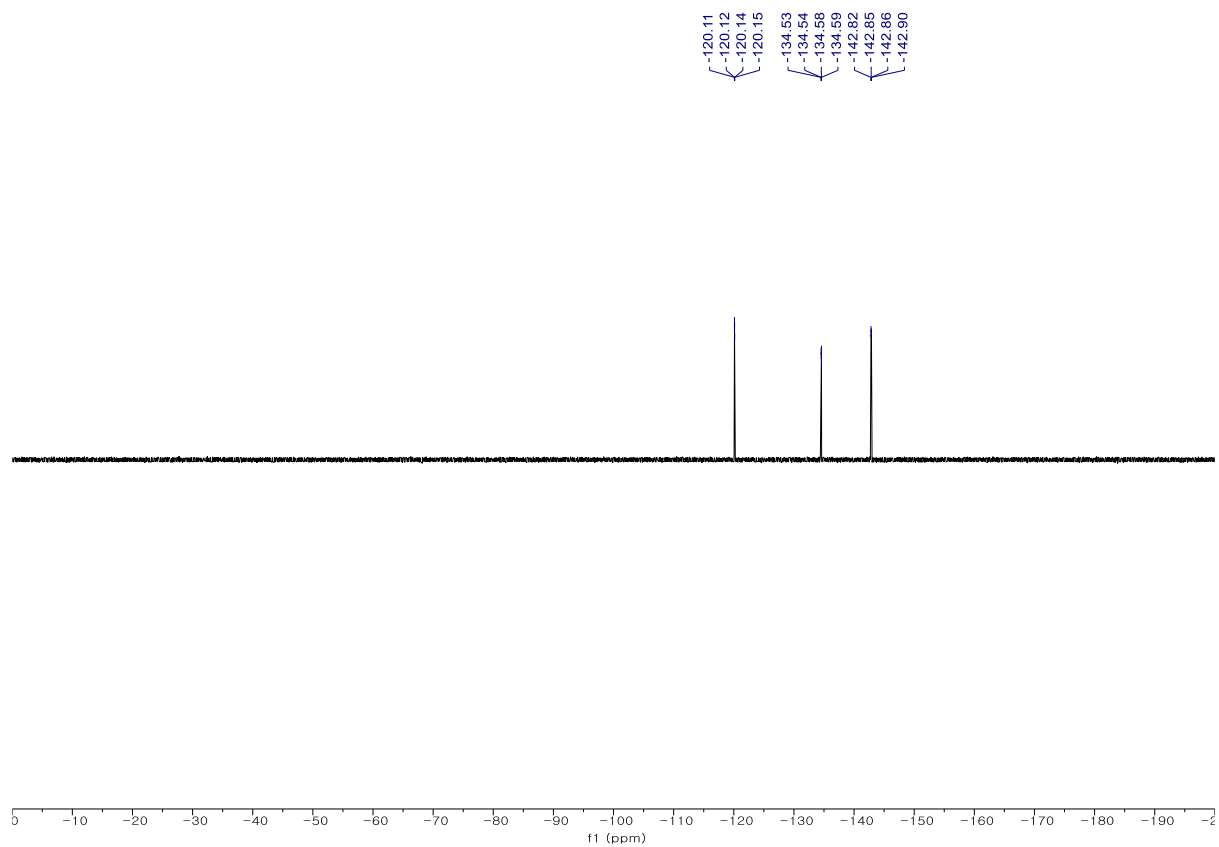


(*R,E*)-6-[(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Methoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]hept-3-enoic acid

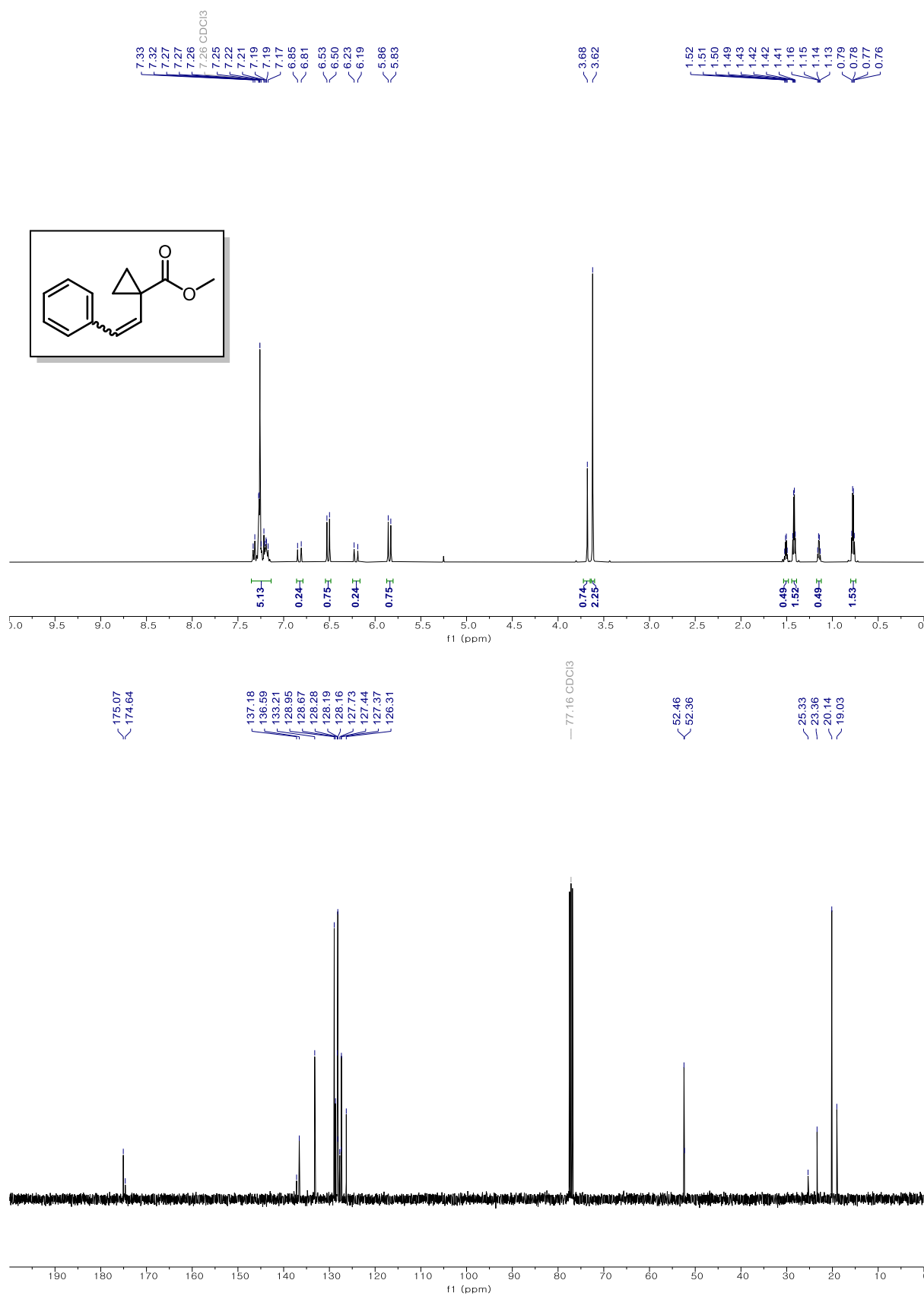


Ethyl (E)-4-(2,4,5-trifluorophenyl)but-3-enoate

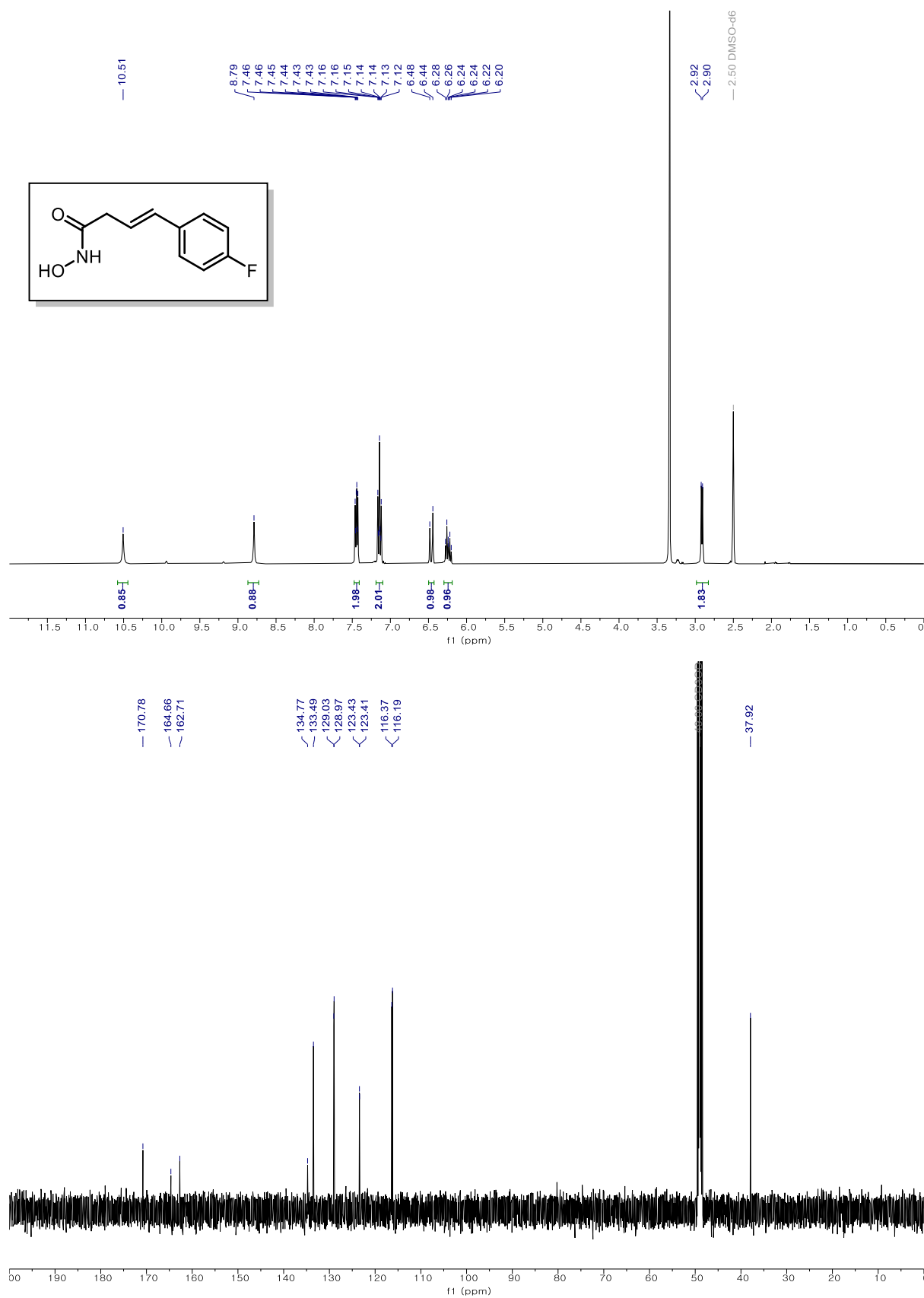


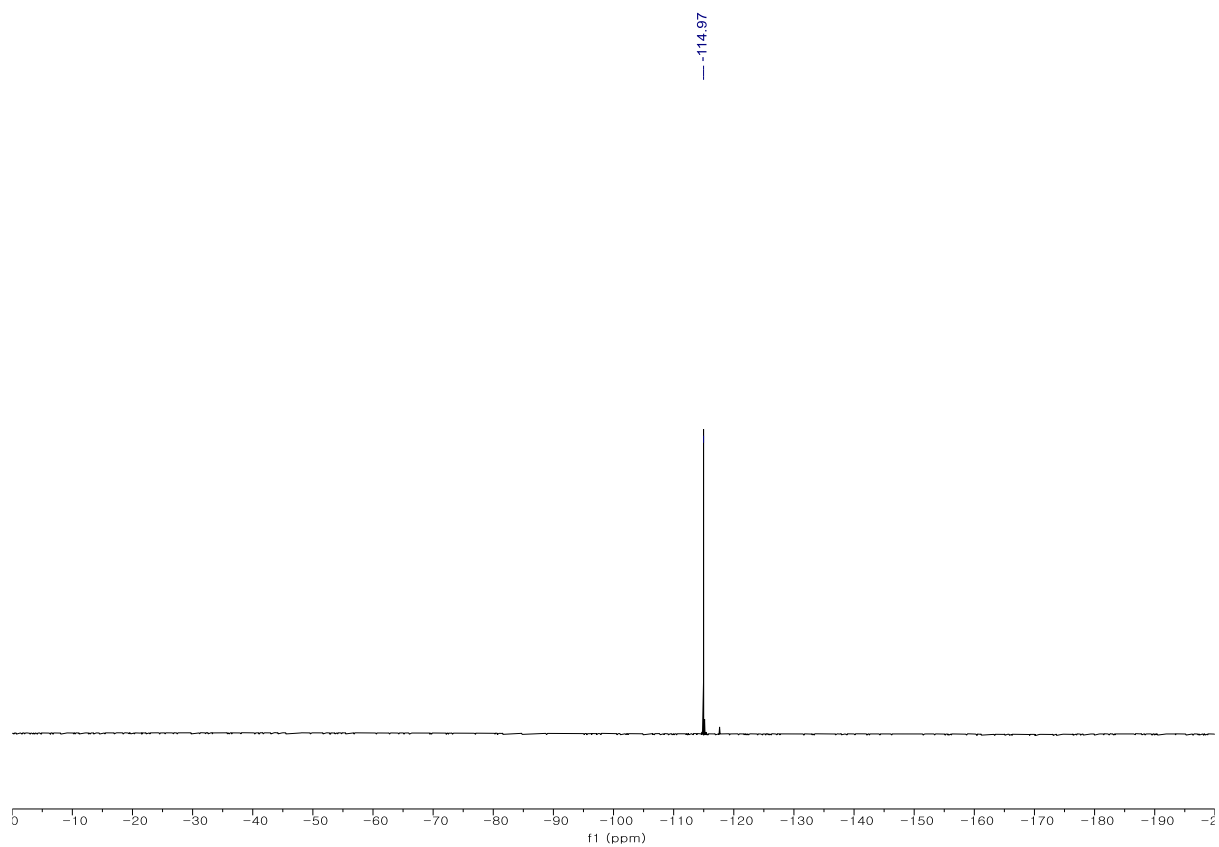


Methyl 1-styrylcyclopropane-1-carboxylate (*Z/E* = 3:1 mixture)



(E)-4-(4-Fluorophenyl)-N-hydroxybut-3-enamide





Chemical structure: NC(=O)C=Cc1ccccc1Br

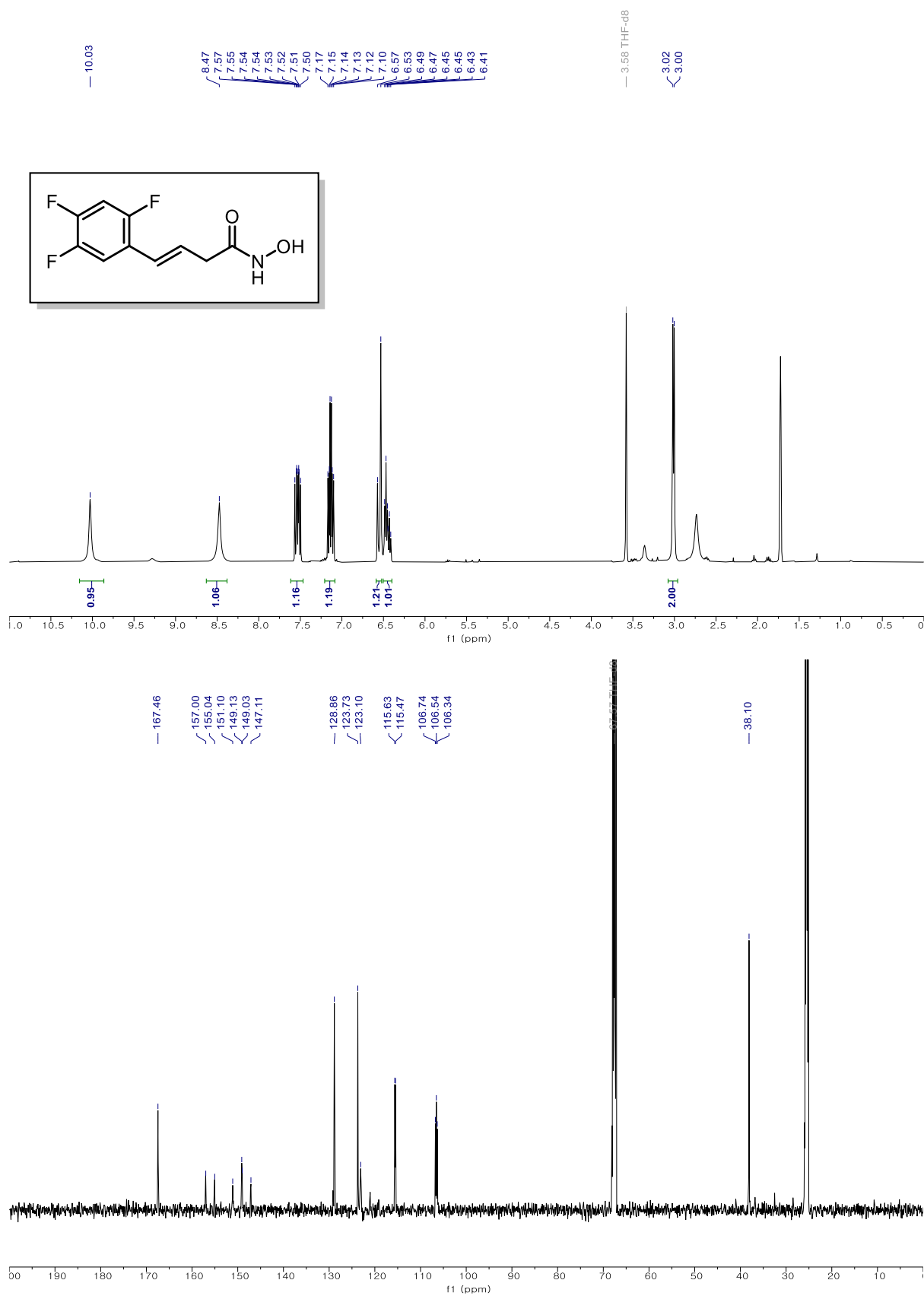
¹H NMR spectrum (CD₃OD) showing peaks at the following chemical shifts (ppm):

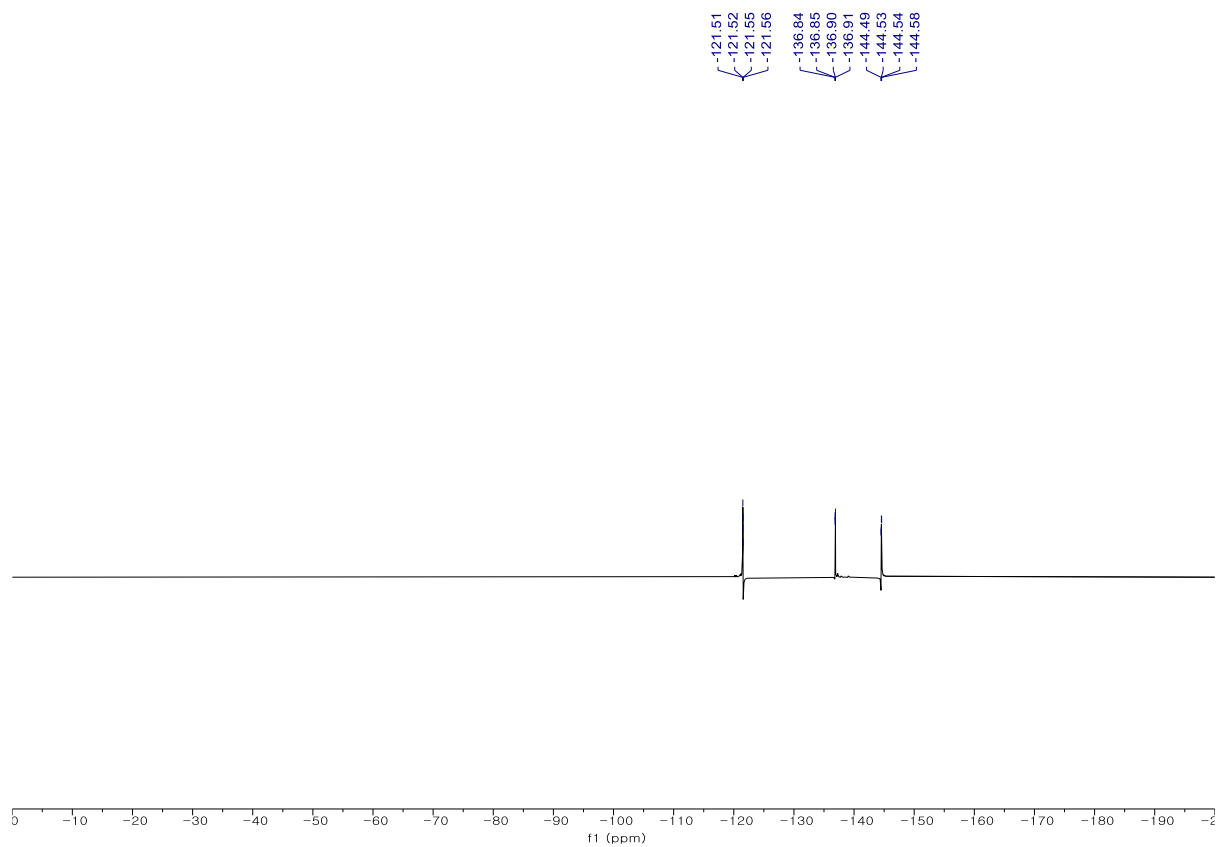
- 7.58, 7.57, 7.56, 7.55, 7.53, 7.31, 7.29, 7.28, 7.14, 7.14, 7.13, 7.11, 7.11, 6.89, 6.86, 6.32, 6.31, 6.29, 6.28, 6.26
- 3.31 (CD₃OD)
- 3.09
- 3.08

Integration values: 0.99, 0.98, 1.17, 1.03, 0.98, 1.00, 1.94, 3.31, 3.09, 3.08.



(E)-N-Hydroxy-4-(2,4,5-trifluorophenyl)but-3-enamide





The figure displays the chemical structure of compound 10 and its corresponding ¹H and ¹³C NMR spectra.

Chemical Structure of Compound 10:

COc1cc(OC)c(C=C/C(=O)NO)c(OCc2ccccc2)c1

¹H NMR Spectrum (CDCl₃):

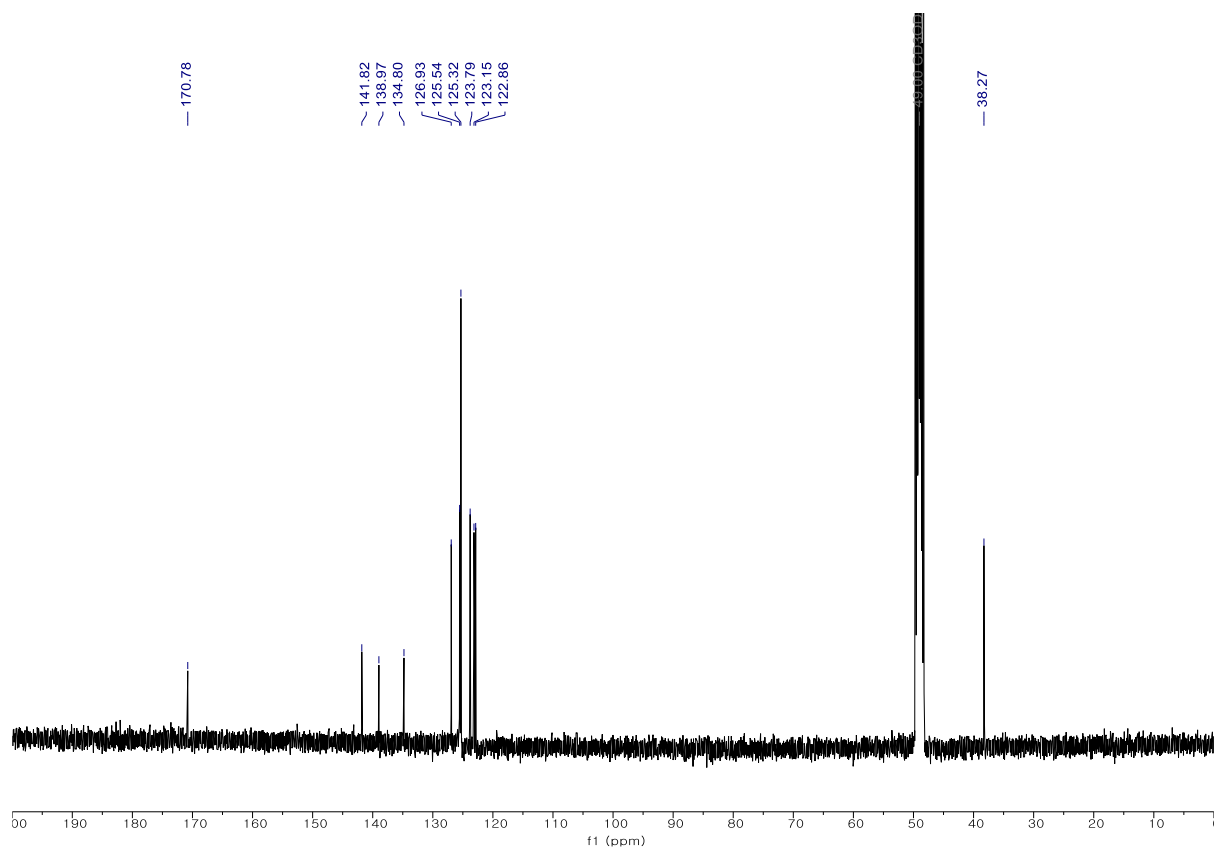
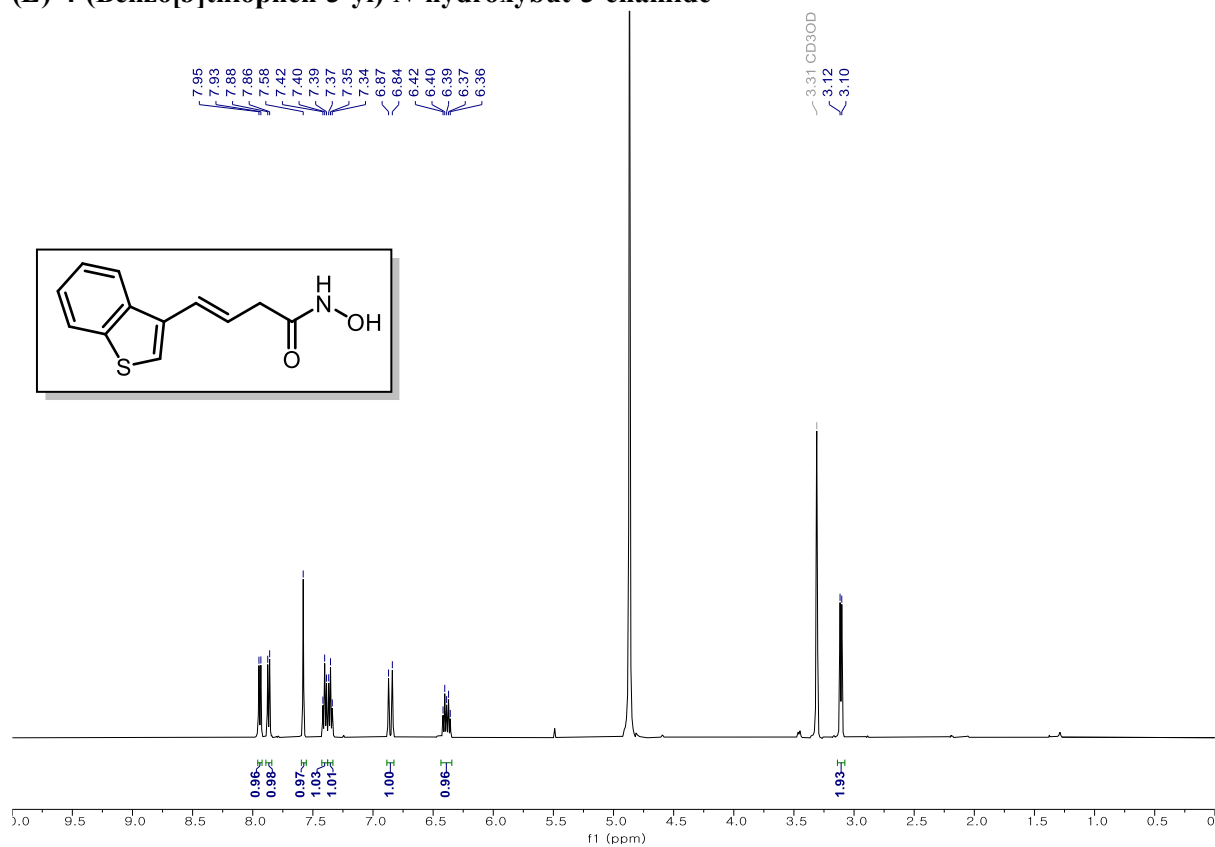
Chemical shift (ppm): 7.46, 7.44, 7.39, 7.38, 7.36, 7.33, 7.31, 7.30, 7.05, 6.83, 6.80, 6.67, 6.20, 6.19, 6.17, 6.16, 6.14, 5.07, 3.80, 3.79, 3.24, 3.01, 3.00.

Integration values: 1.93, 1.95, 0.98, 0.90, 0.98, 0.98, 1.00, 1.95, 2.95, 2.91, 1.85.

¹³C NMR Spectrum (CDCl₃):

Chemical shift (ppm): 171.15, 151.80, 150.97, 145.04, 138.82, 129.54, 129.02, 128.93, 128.79, 121.67, 119.87, 111.59, 101.24, 72.80, 57.20, 56.54, 55.54, 55.44, 55.34, 55.24, 55.14, 55.04, 54.94, 54.84, 54.74, 54.64, 54.54, 54.44, 54.34, 54.24, 54.14, 54.04, 53.94, 53.84, 53.74, 53.64, 53.54, 53.44, 53.34, 53.24, 53.14, 53.04, 52.94, 52.84, 52.74, 52.64, 52.54, 52.44, 52.34, 52.24, 52.14, 52.04, 51.94, 51.84, 51.74, 51.64, 51.54, 51.44, 51.34, 51.24, 51.14, 51.04, 50.94, 50.84, 50.74, 50.64, 50.54, 50.44, 50.34, 50.24, 50.14, 50.04, 49.94, 49.84, 49.74, 49.64, 49.54, 49.44, 49.34, 49.24, 49.14, 49.04, 48.94, 48.84, 48.74, 48.64, 48.54, 48.44, 48.34, 48.24, 48.14, 48.04, 47.94, 47.84, 47.74, 47.64, 47.54, 47.44, 47.34, 47.24, 47.14, 47.04, 46.94, 46.84, 46.74, 46.64, 46.54, 46.44, 46.34, 46.24, 46.14, 46.04, 45.94, 45.84, 45.74, 45.64, 45.54, 45.44, 45.34, 45.24, 45.14, 45.04, 44.94, 44.84, 44.74, 44.64, 44.54, 44.44, 44.34, 44.24, 44.14, 44.04, 43.94, 43.84, 43.74, 43.64, 43.54, 43.44, 43.34, 43.24, 43.14, 43.04, 42.94, 42.84, 42.74, 42.64, 42.54, 42.44, 42.34, 42.24, 42.14, 42.04, 41.94, 41.84, 41.74, 41.64, 41.54, 41.44, 41.34, 41.24, 41.14, 41.04, 40.94, 40.84, 40.74, 40.64, 40.54, 40.44, 40.34, 40.24, 40.14, 40.04, 39.94, 39.84, 39.74, 39.64, 39.54, 39.44, 39.34, 39.24, 39.14, 39.04, 38.94, 38.84, 38.74, 38.64, 38.54, 38.44, 38.34, 38.24, 38.14, 38.04, 37.94, 37.84, 37.74, 37.64, 37.54, 37.44, 37.34, 37.24, 37.14, 37.04, 36.94, 36.84, 36.74, 36.64, 36.54, 36.44, 36.34, 36.24, 36.14, 36.04, 35.94, 35.84, 35.74, 35.64, 35.54, 35.44, 35.34, 35.24, 35.14, 35.04, 34.94, 34.84, 34.74, 34.64, 34.54, 34.44, 34.34, 34.24, 34.14, 34.04, 33.94, 33.84, 33.74, 33.64, 33.54, 33.44, 33.34, 33.24, 33.14, 33.04, 32.94, 32.84, 32.74, 32.64, 32.54, 32.44, 32.34, 32.24, 32.14, 32.04, 31.94, 31.84, 31.74, 31.64, 31.54, 31.44, 31.34, 31.24, 31.14, 31.04, 30.94, 30.84, 30.74, 30.64, 30.54, 30.44, 30.34, 30.24, 30.14, 30.04, 29.94, 29.84, 29.74, 29.64, 29.54, 29.44, 29.34, 29.24, 29.14, 29.04, 28.94, 28.84, 28.74, 28.64, 28.54, 28.44, 28.34, 28.24, 28.14, 28.04, 27.94, 27.84, 27.74, 27.64, 27.54, 27.44, 27.34, 27.24, 27.14, 27.04, 26.94, 26.84, 26.74, 26.64, 26.54, 26.44, 26.34, 26.24, 26.14, 26.04, 25.94, 25.84, 25.74, 25.64, 25.54, 25.44, 25.34, 25.24, 25.14, 25.04, 24.94, 24.84, 24.74, 24.64, 24.54, 24.44, 24.34, 24.24, 24.14, 24.04, 23.94, 23.84, 23.74, 23.64, 23.54, 23.44, 23.34, 23.24, 23.14, 23.04, 22.94, 22.84, 22.74, 22.64, 22.54, 22.44, 22.34, 22.24, 22.14, 22.04, 21.94, 21.84, 21.74, 21.64, 21.54, 21.44, 21.34, 21.24, 21.14, 21.04, 20.94, 20.84, 20.74, 20.64, 20.54, 20.44, 20.34, 20.24, 20.14, 20.04, 19.94, 19.84, 19.74, 19.64, 19.54, 19.44, 19.34, 19.24, 19.14, 19.04, 18.94, 18.84, 18.74, 18.64, 18.54, 18.44, 18.34, 18.24, 18.14, 18.04, 17.94, 17.84, 17.74, 17.64, 17.54, 17.44, 17.34, 17.24, 17.14, 17.04, 16.94, 16.84, 16.74, 16.64, 16.54, 16.44, 16.34, 16.24, 16.14, 16.04, 15.94, 15.84, 15.74, 15.64, 15.54, 15.44, 15.34, 15.24, 15.14, 15.04, 14.94, 14.84, 14.74, 14.64, 14.54, 14.44, 14.34, 14.24, 14.14, 14.04, 13.94, 13.84, 13.74, 13.64, 13.54, 13.44, 13.34, 13.24, 13.14, 13.04, 12.94, 12.84, 12.74, 12.64, 12.54, 12.44, 12.34, 12.24, 12.14, 12.04, 11.94, 11.84, 11.74, 11.64, 11.54, 11.44, 11.34, 11.24, 11.14, 11.04, 10.94, 10.84, 10.74, 10.64, 10.54, 10.44, 10.34, 10.24, 10.14, 10.04, 9.94, 9.84, 9.74, 9.64, 9.54, 9.44, 9.34, 9.24, 9.14, 9.04, 8.94, 8.84, 8.74, 8.64, 8.54, 8.44, 8.34, 8.24, 8.14, 8.04, 7.94, 7.84, 7.74, 7.64, 7.54, 7.44, 7.34, 7.24, 7.14, 7.04, 6.94, 6.84, 6.74, 6.64, 6.54, 6.44, 6.34, 6.24, 6.14, 6.04, 5.94, 5.84, 5.74, 5.64, 5.54, 5.44, 5.34, 5.24, 5.14, 5.04, 4.94, 4.84, 4.74, 4.64, 4.54, 4.44, 4.34, 4.24, 4.14, 4.04, 3.94, 3.84, 3.74, 3.64,

(E)-4-(Benzo[*b*]thiophen-3-yl)-*N*-hydroxybut-3-enamide



O=C(O)C/C=C/Cc1ccccc1

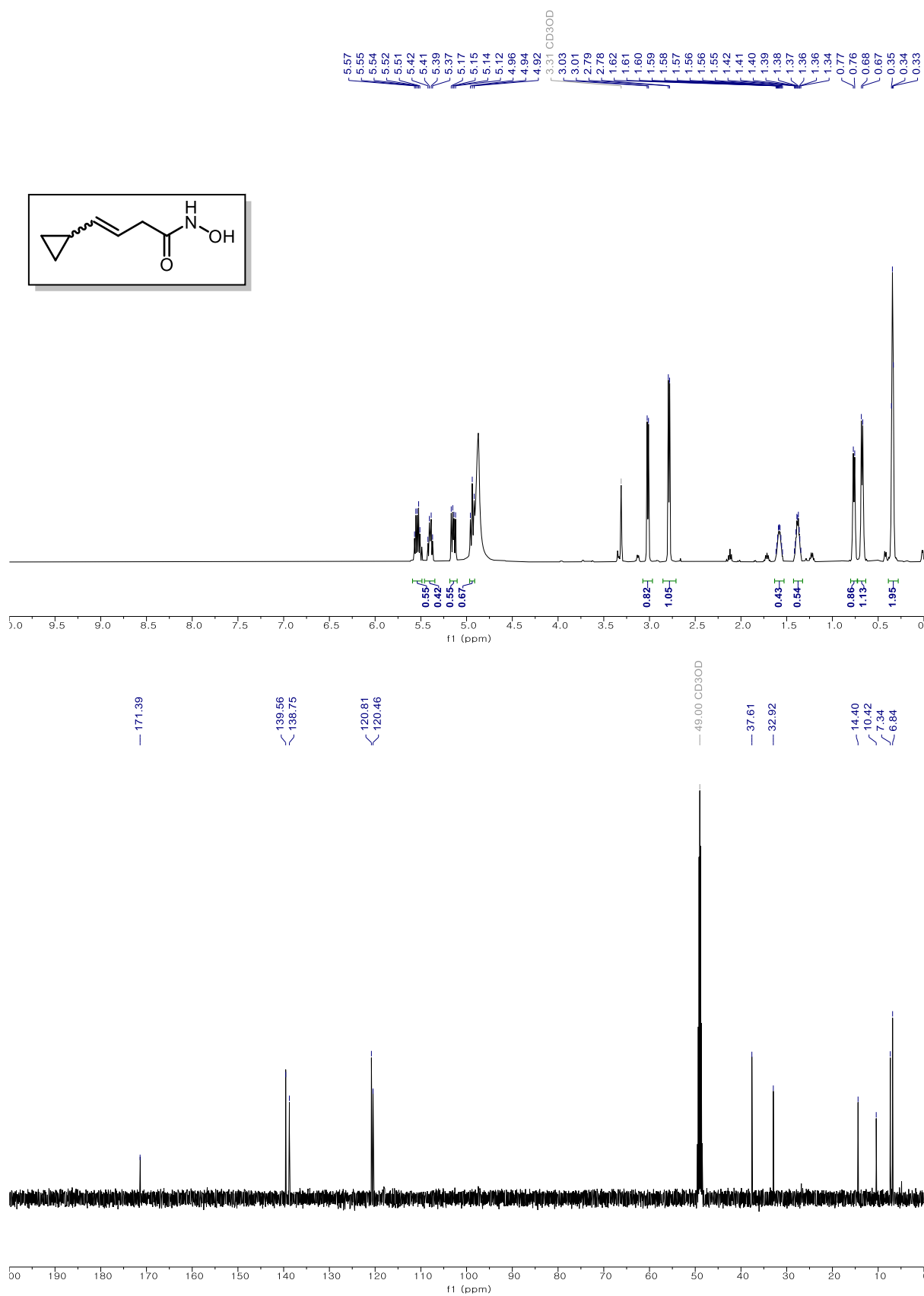
¹H NMR Spectrum (400 MHz, CDCl₃)

Chemical Shift (ppm)	Integration
7.27, 7.25, 7.23, 7.17, 7.15, 7.13	2.08, 3.09
5.80, 5.78, 5.76, 5.74, 5.73, 5.61, 5.60, 5.58, 5.56, 5.54	1.04, 1.00
3.36, 3.34, 3.31, 2.85, 2.83	2.07, 1.96

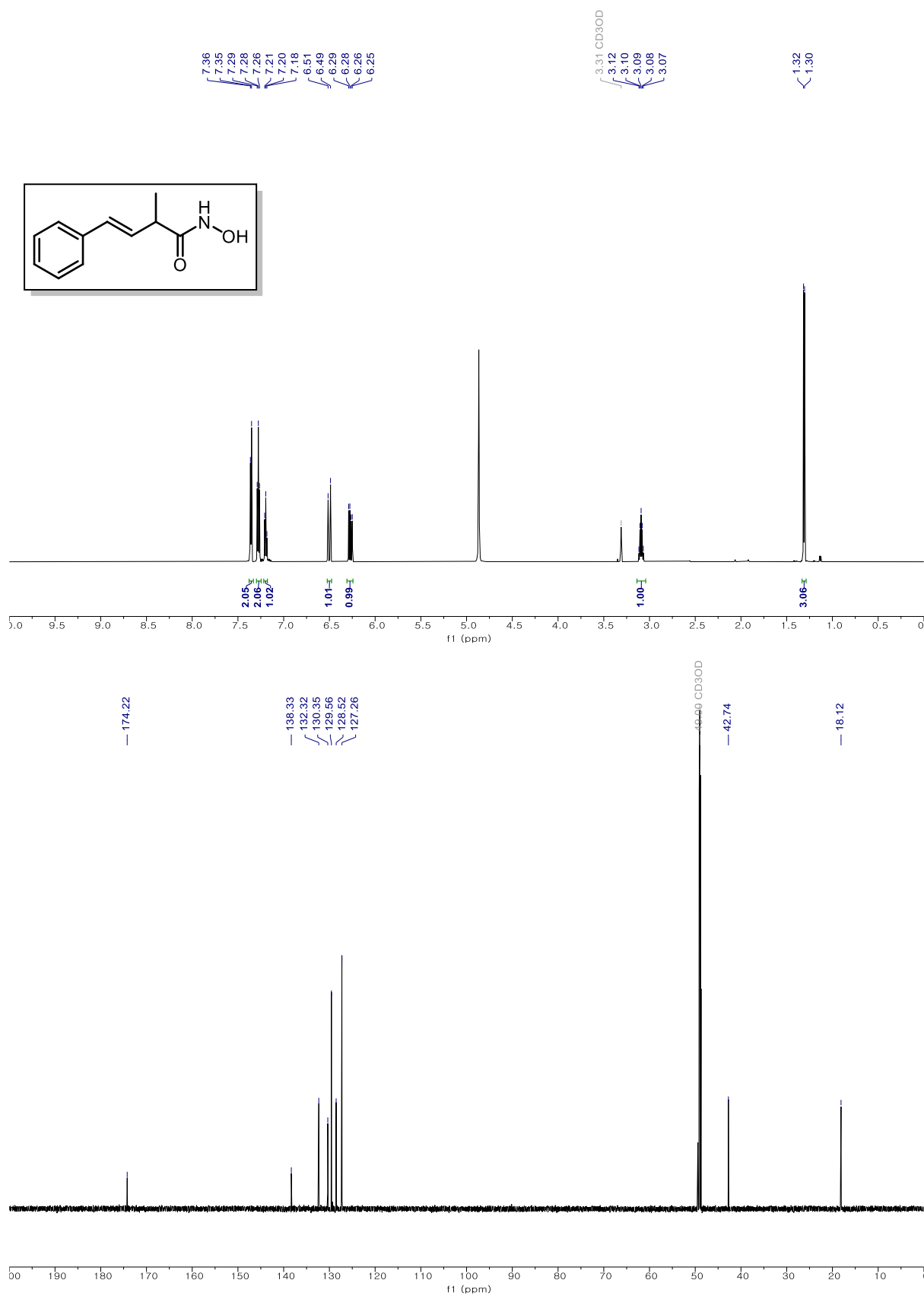
¹³C NMR Spectrum (100 MHz, CDCl₃)

Chemical Shift (ppm)
171.11
141.42, 134.70, 129.55, 129.40, 127.05, 124.86
39.78, 37.63

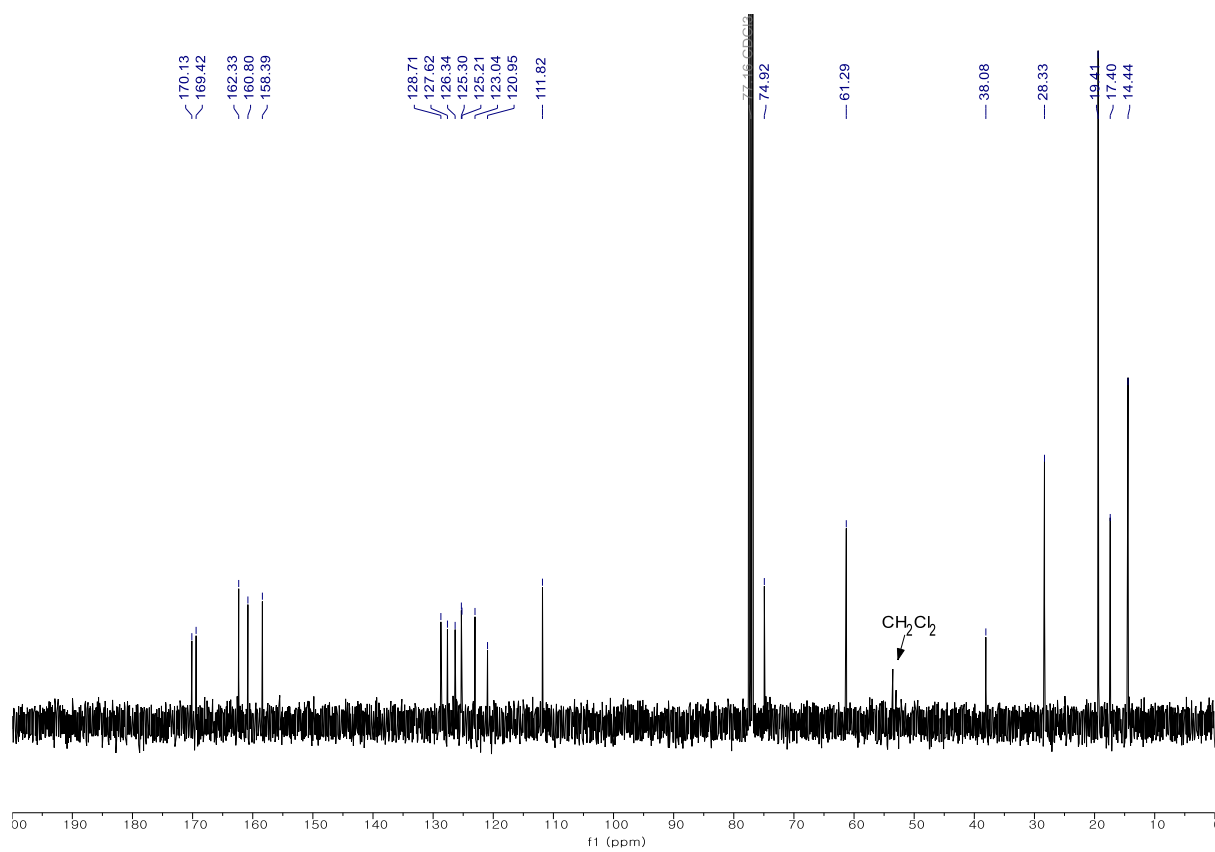
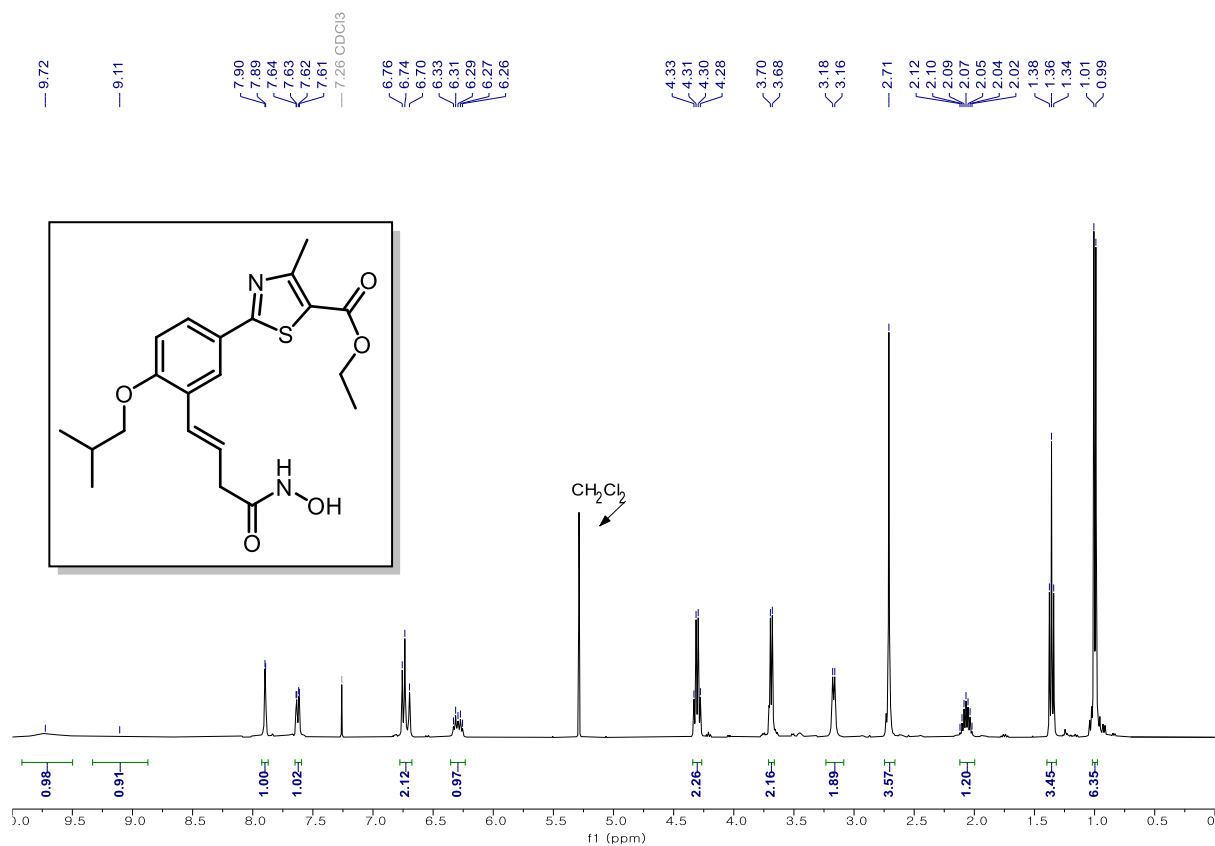
4-Cyclopropyl-N-hydroxybut-3-enamide (*E/Z*=1.1:1 mixture)



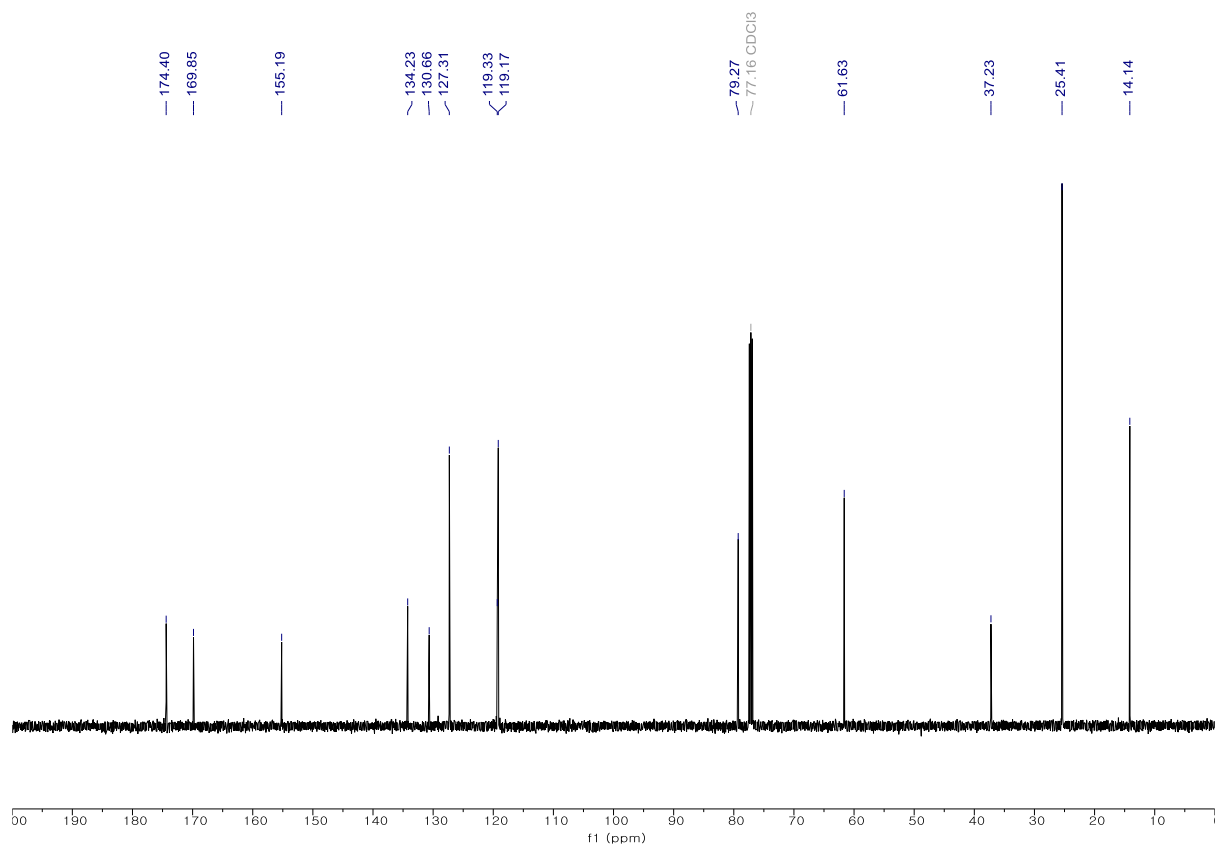
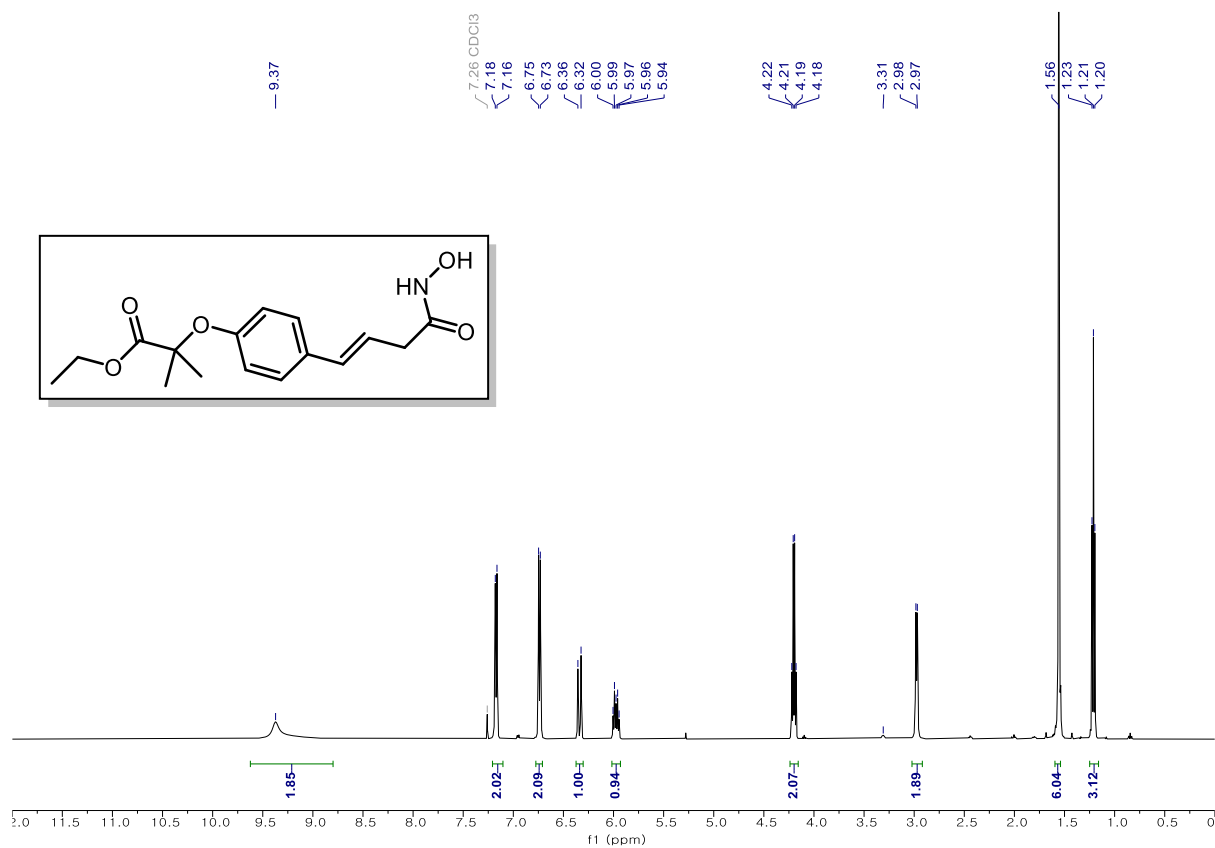
(E)-N-Hydroxy-2-methyl-4-phenylbut-3-enamide



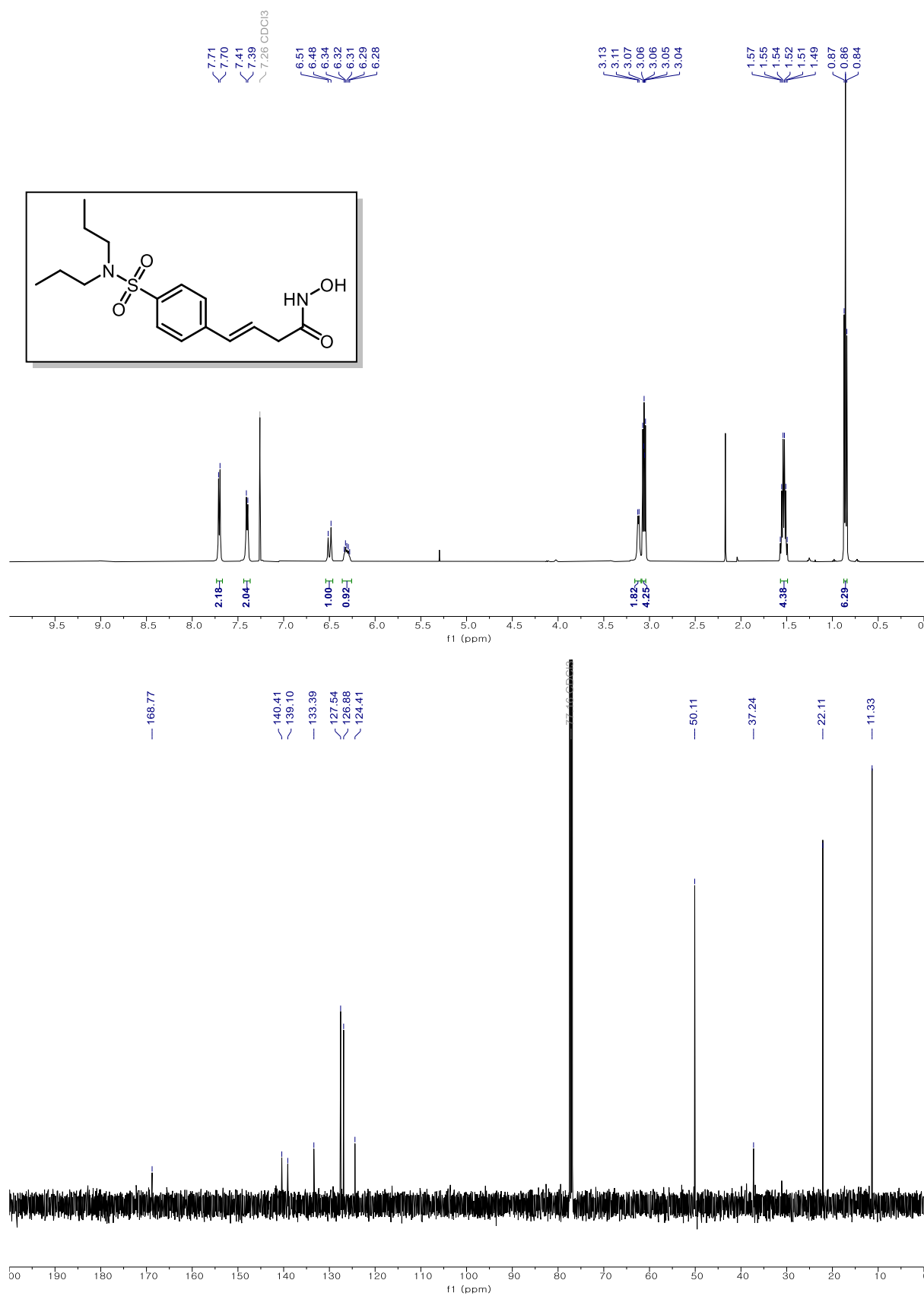
Ethyl (E)-2-{3-[4-(hydroxyamino)-4-oxobut-1-en-1-yl]-4-isobutoxyphenyl}-4-methylthiazole-5-carboxylate



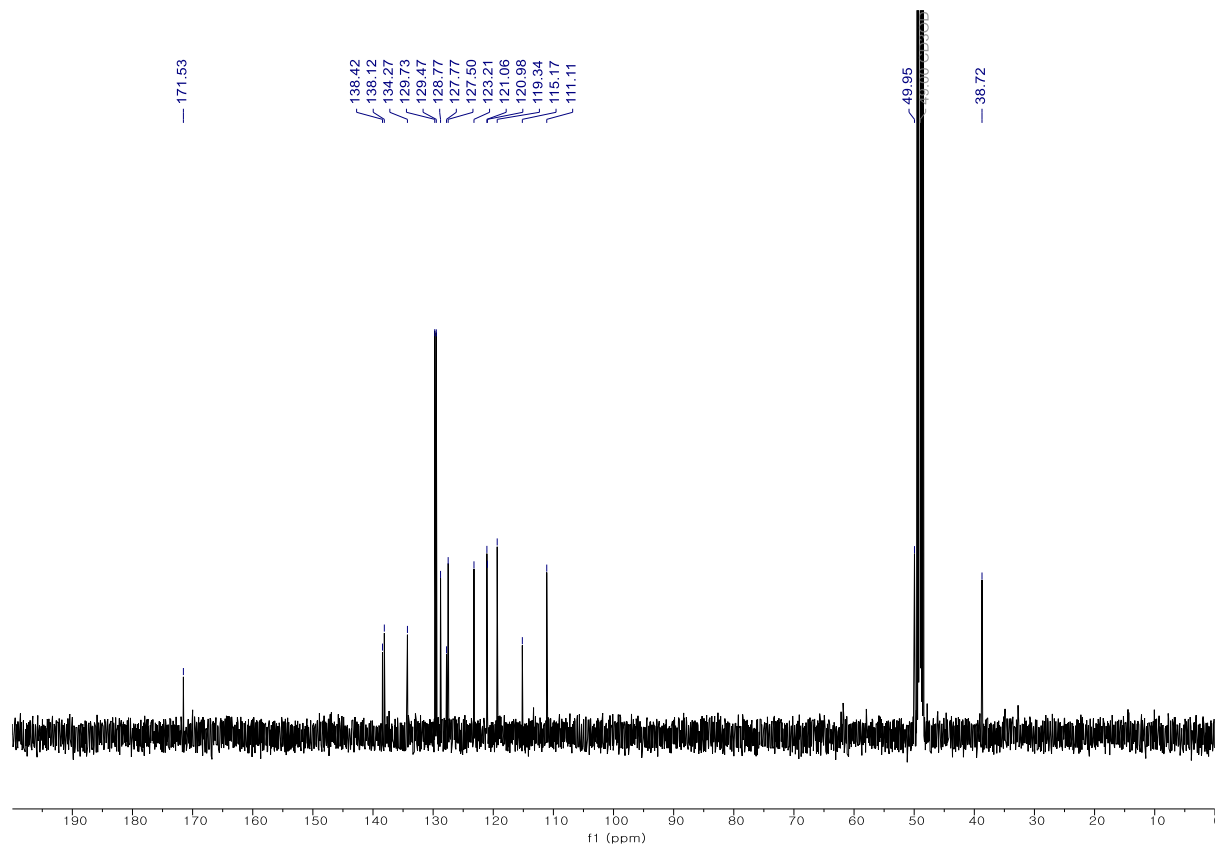
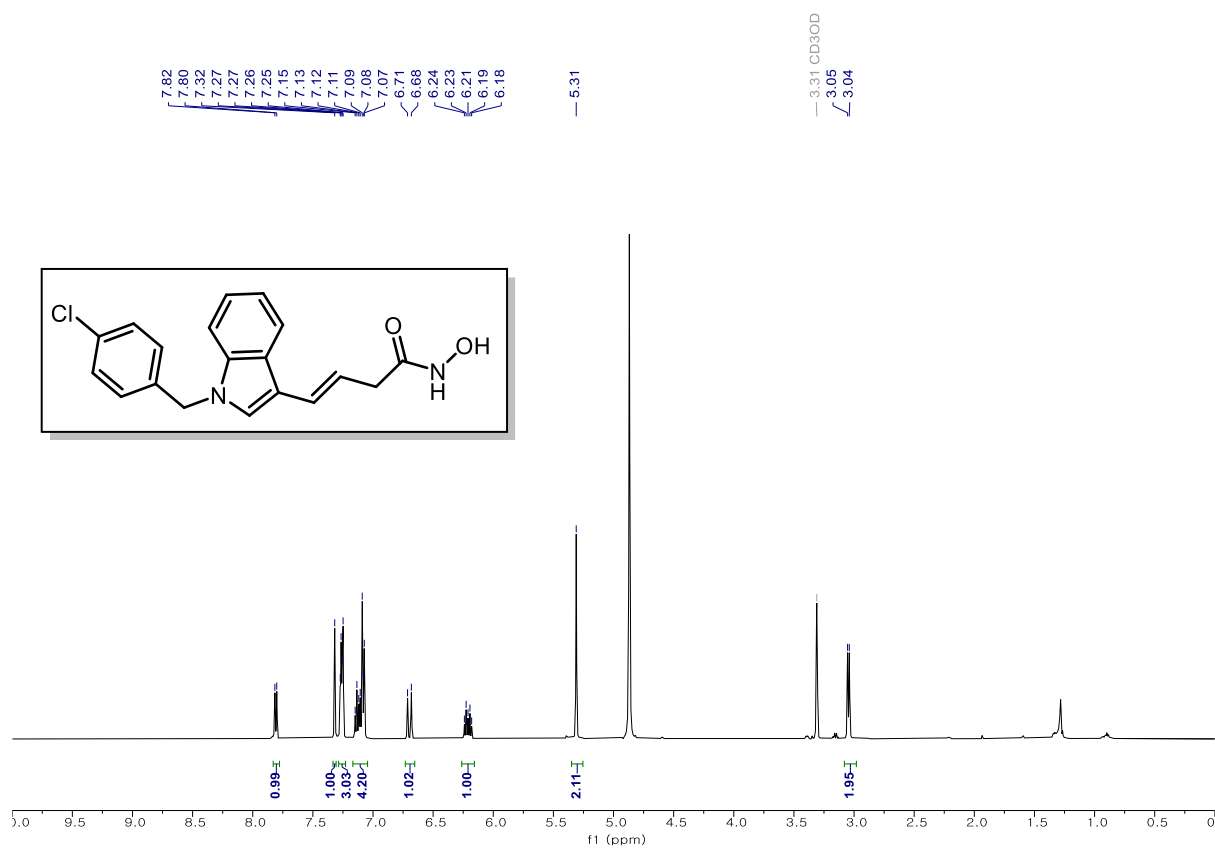
Ethyl (E)-2-{4-[4-(hydroxyamino)-4-oxobut-1-en-1-yl]phenoxy}-2-methylpropanoate



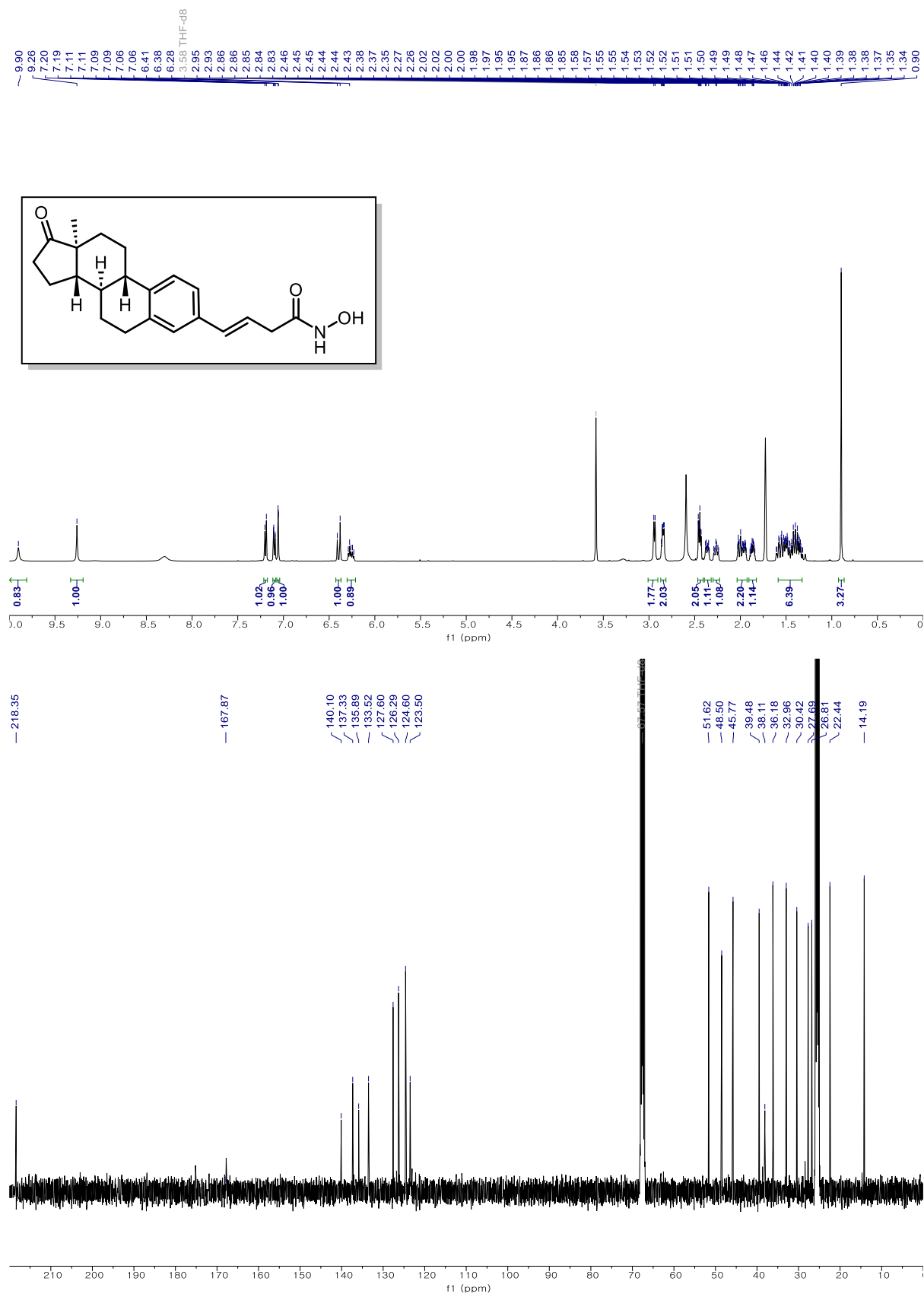
(E)-4-[4-(*N,N*-Dipropylsulfamoyl)phenyl]-*N*-hydroxybut-3-enamide



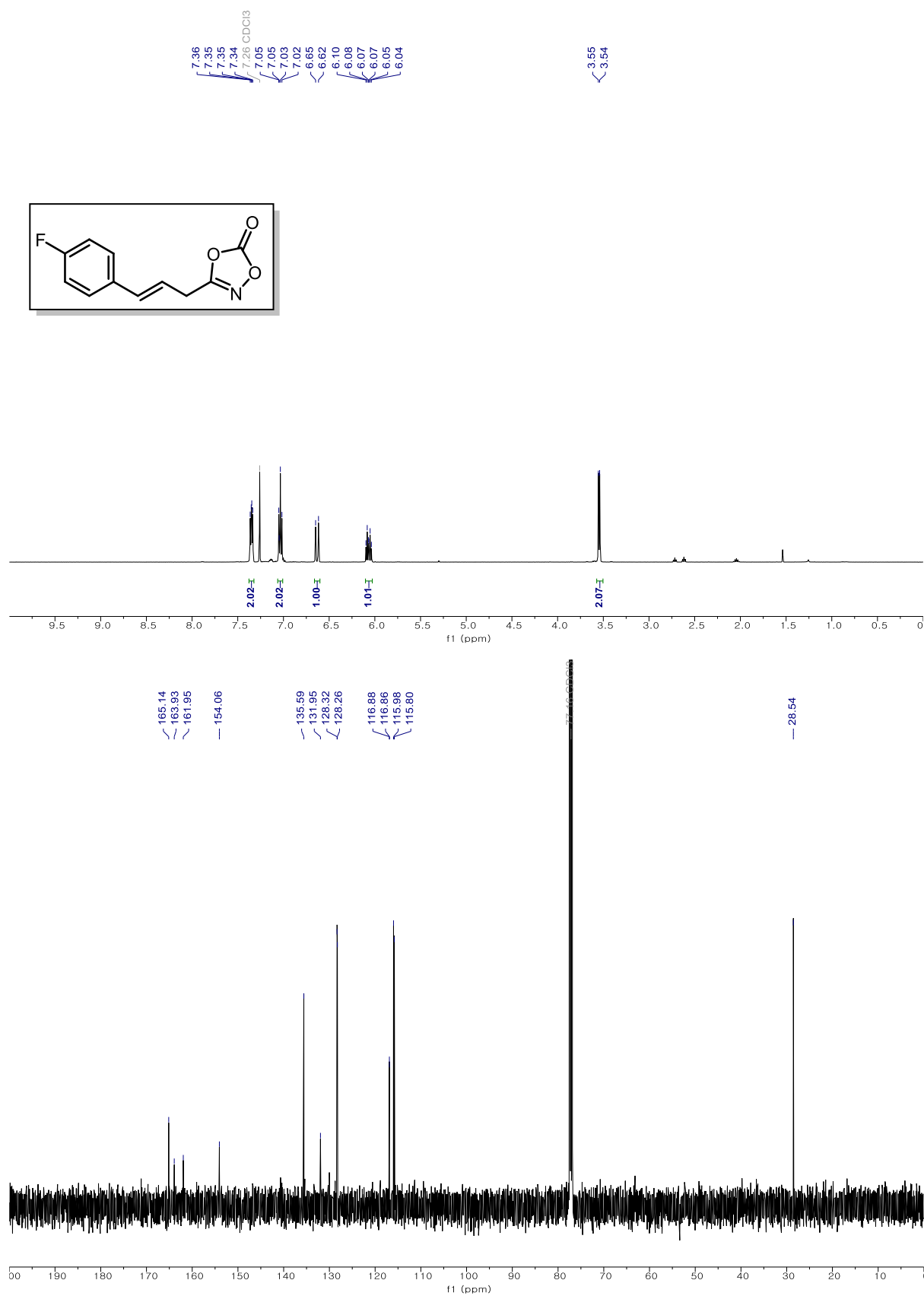
(E)-4-[1-(4-Chlorobenzyl)-1H-indol-3-yl]-N-hydroxybut-3-enamide

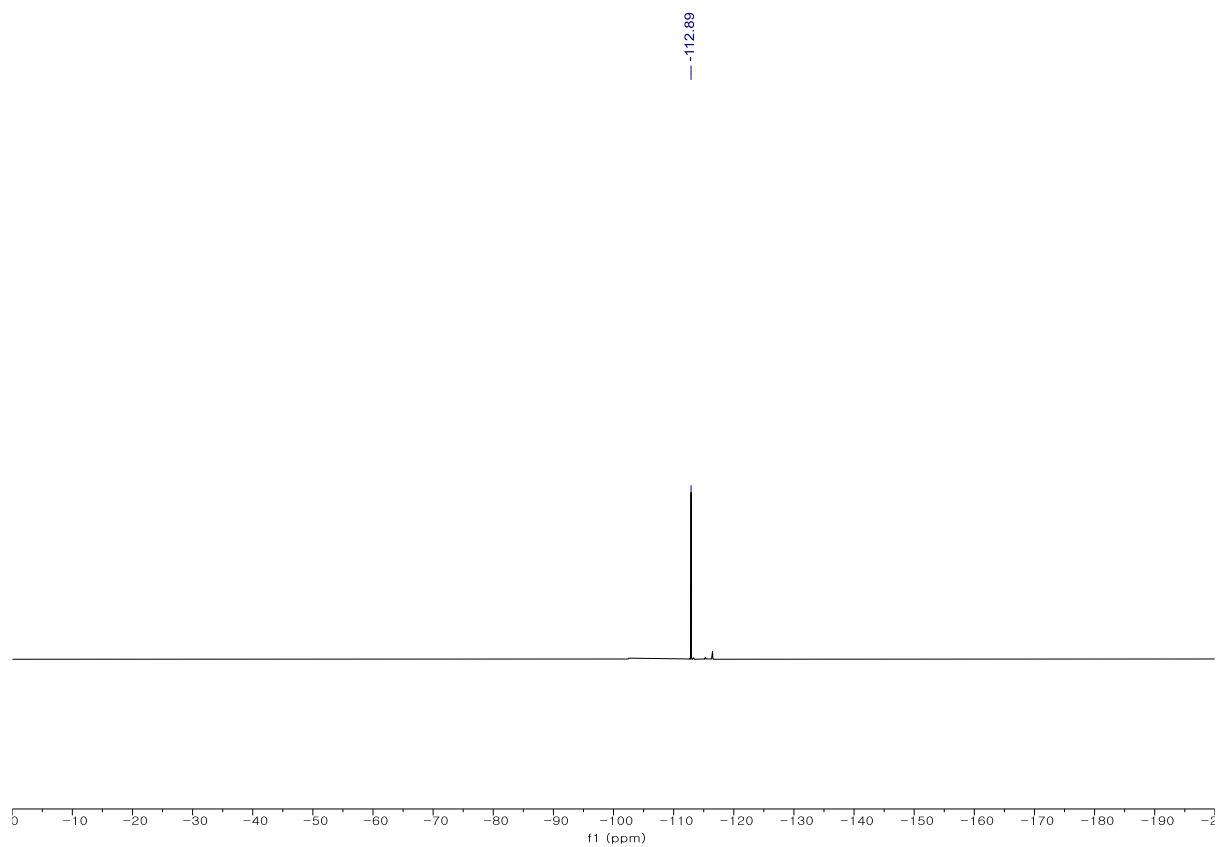


(E)-N-Hydroxy-4-[(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-3-yl]but-3-enamide

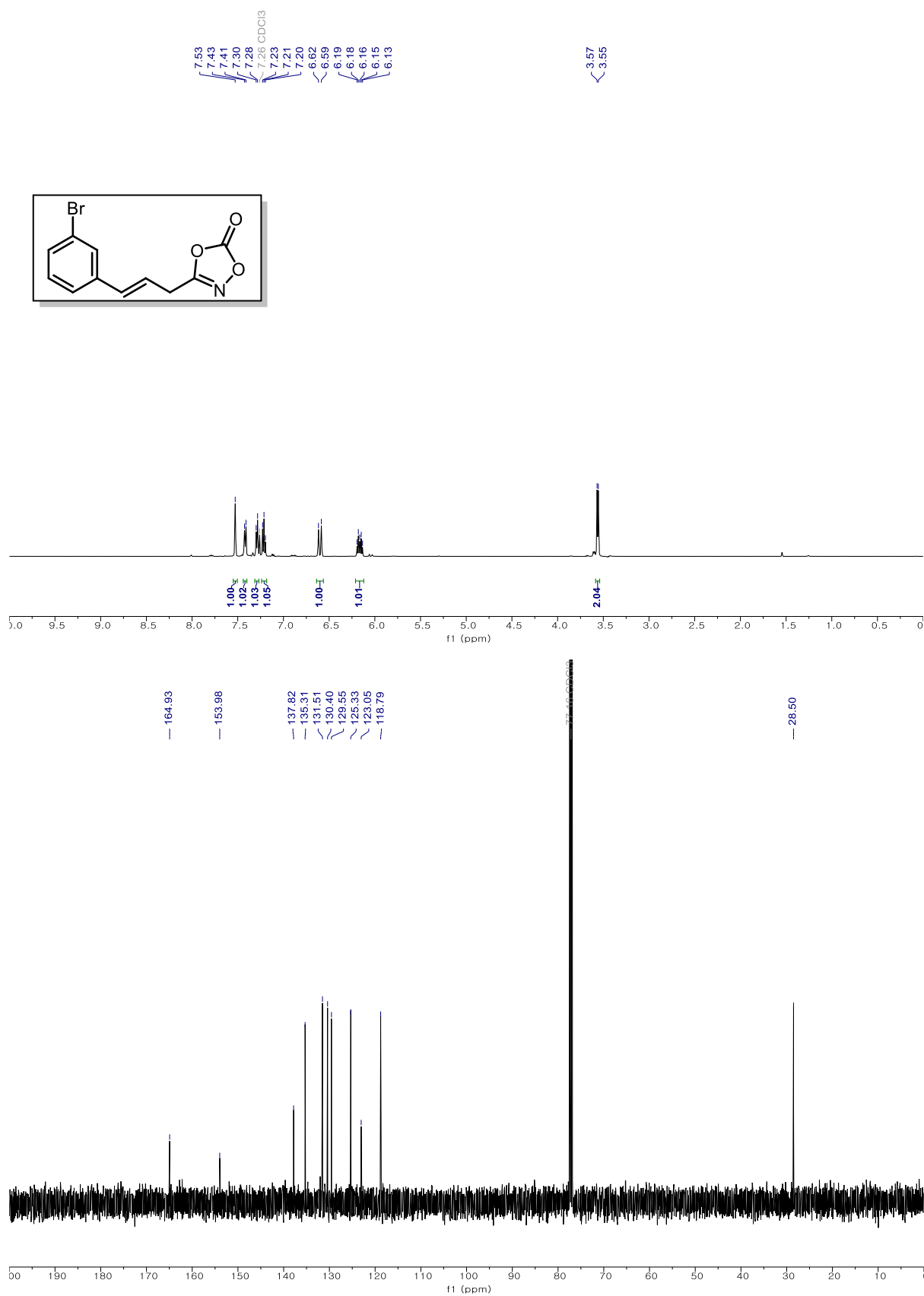


(E)-3-[3-(4-Fluorophenyl)allyl]-1,4,2-dioxazol-5-one

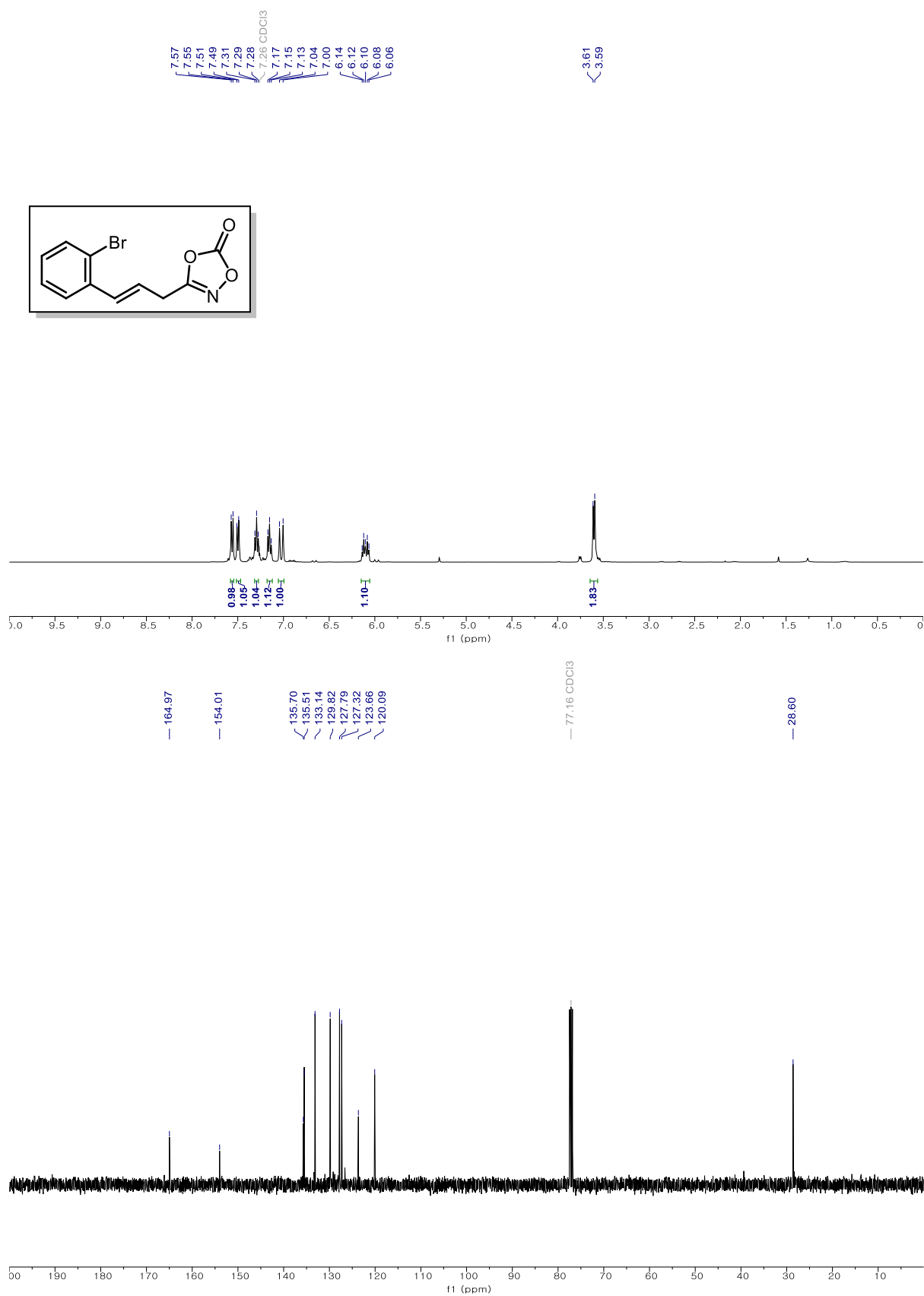




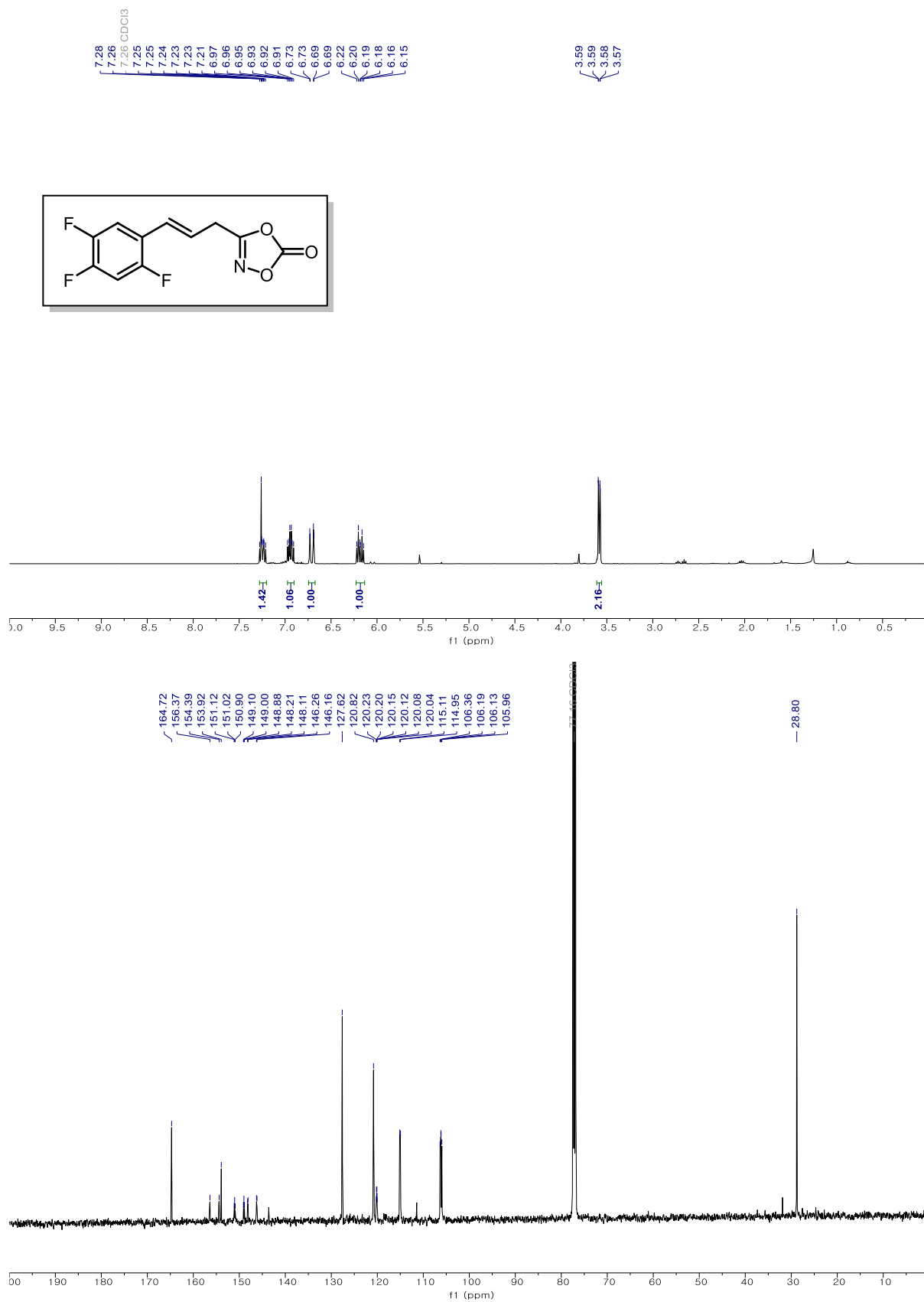
(E)-3-[3-(3-Bromophenyl)allyl]-1,4,2-dioxazol-5-one

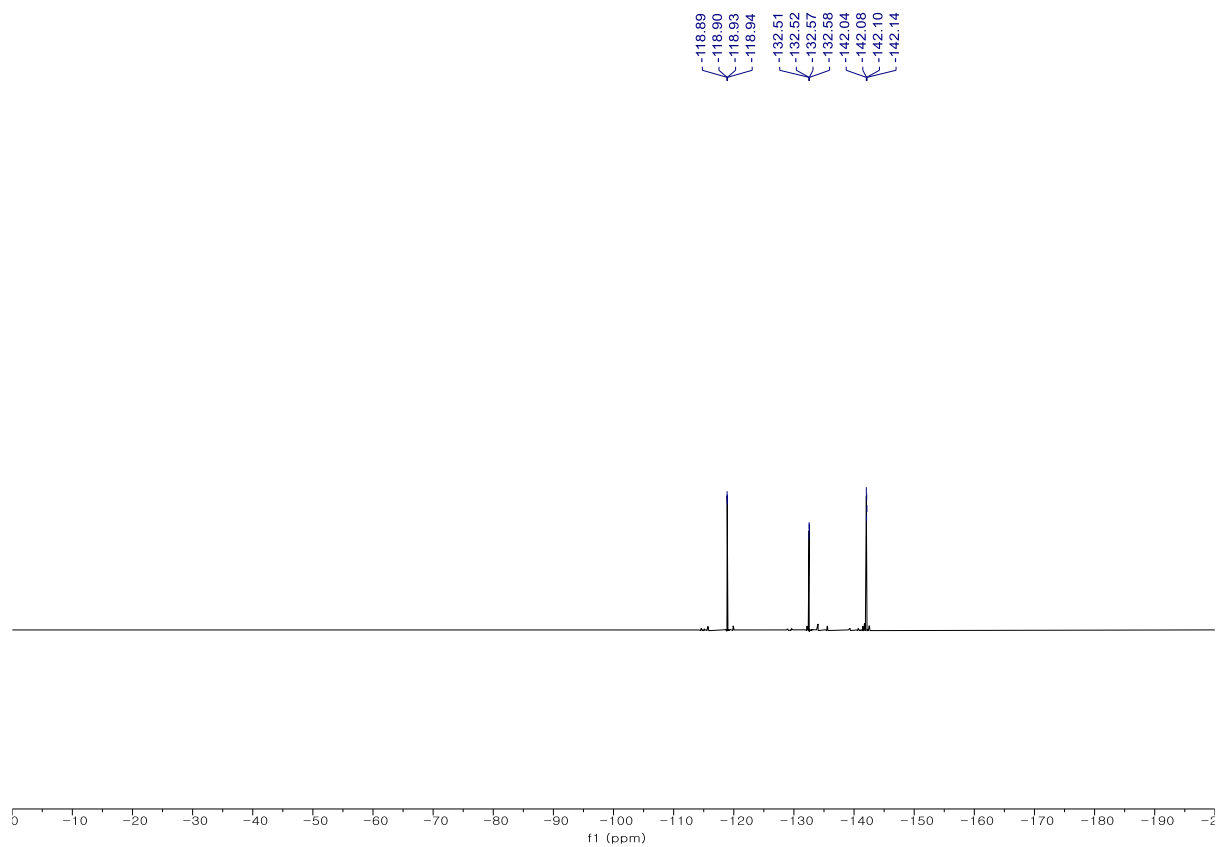


(E)-3-[3-(2-Bromophenyl)allyl]-1,4,2-dioxazol-5-one

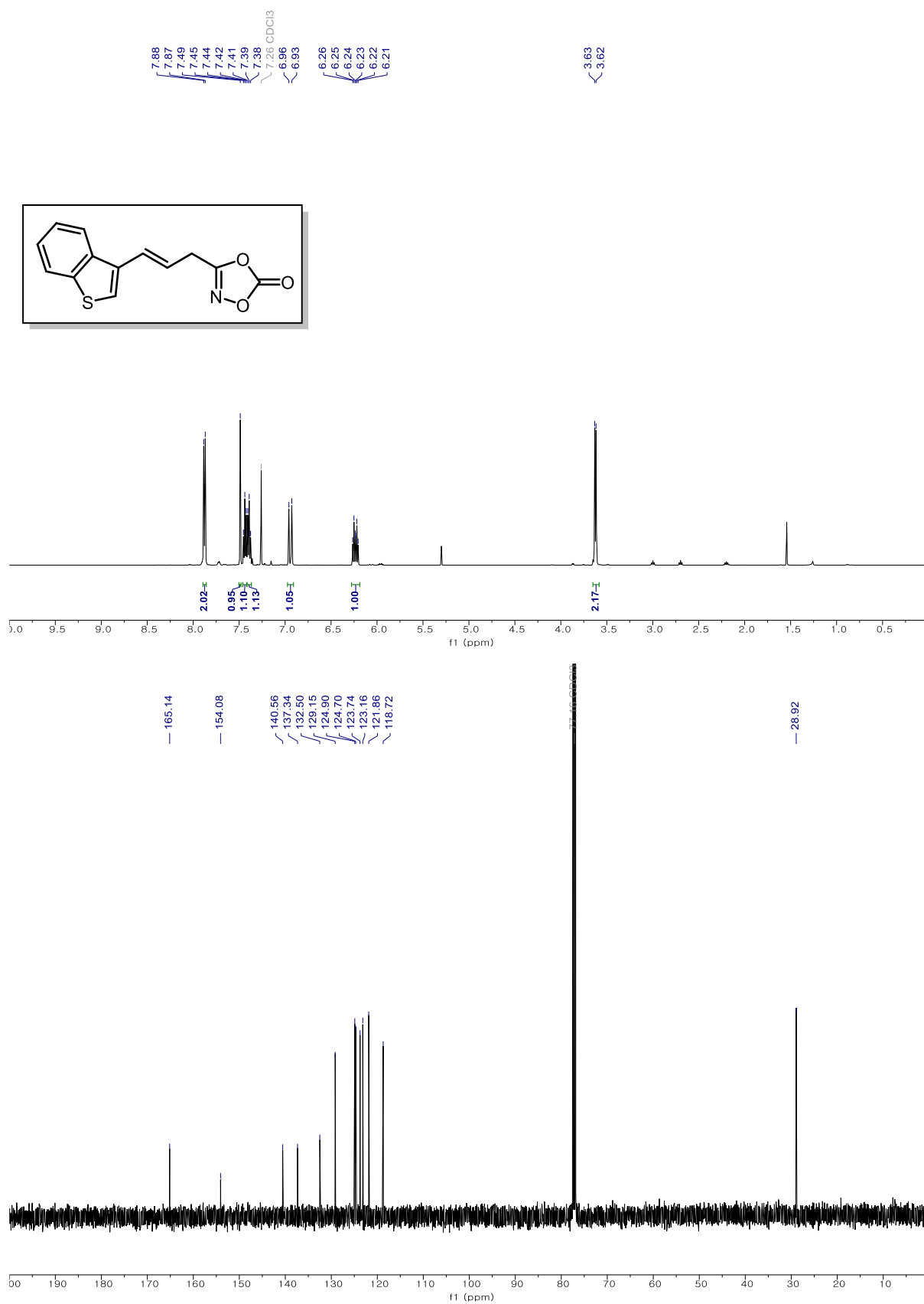


(E)-3-[3-(2,4,5-Trifluorophenyl)allyl]-1,4,2-dioxazol-5-one

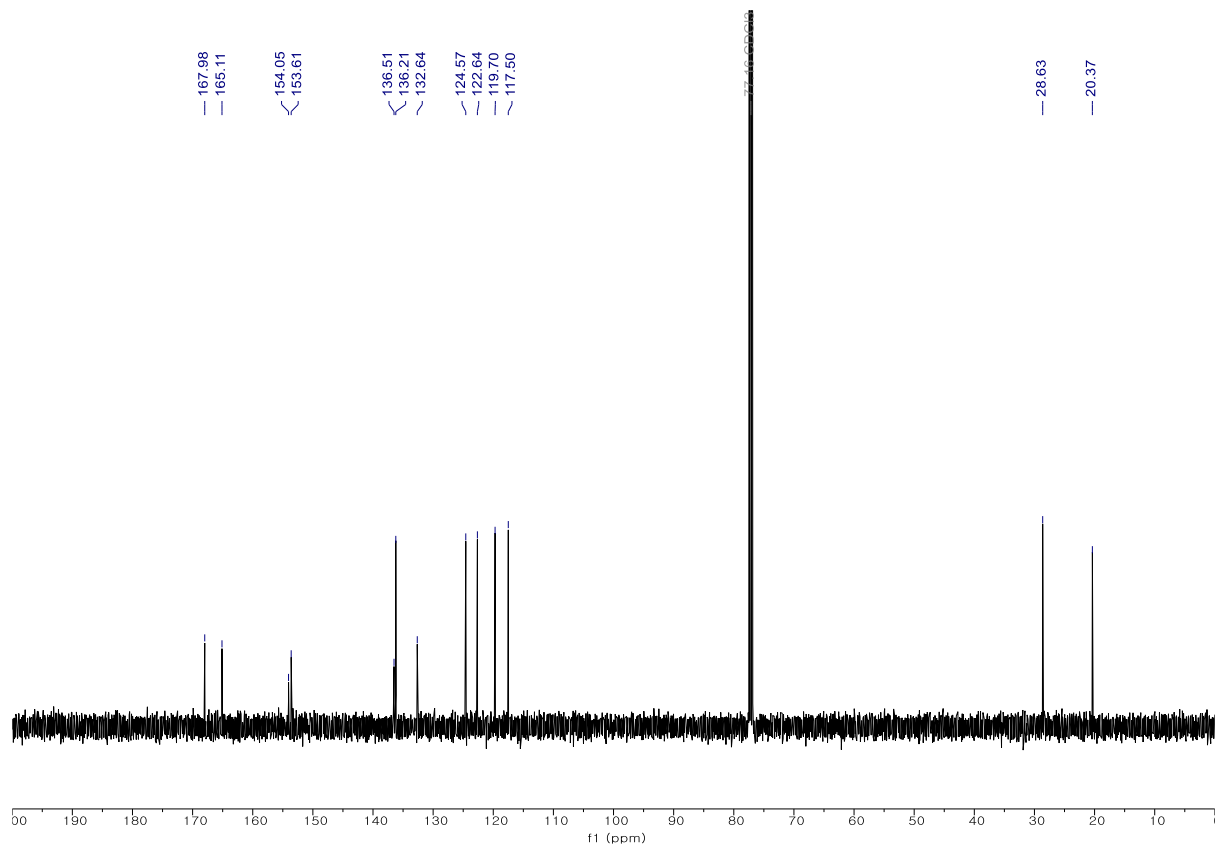
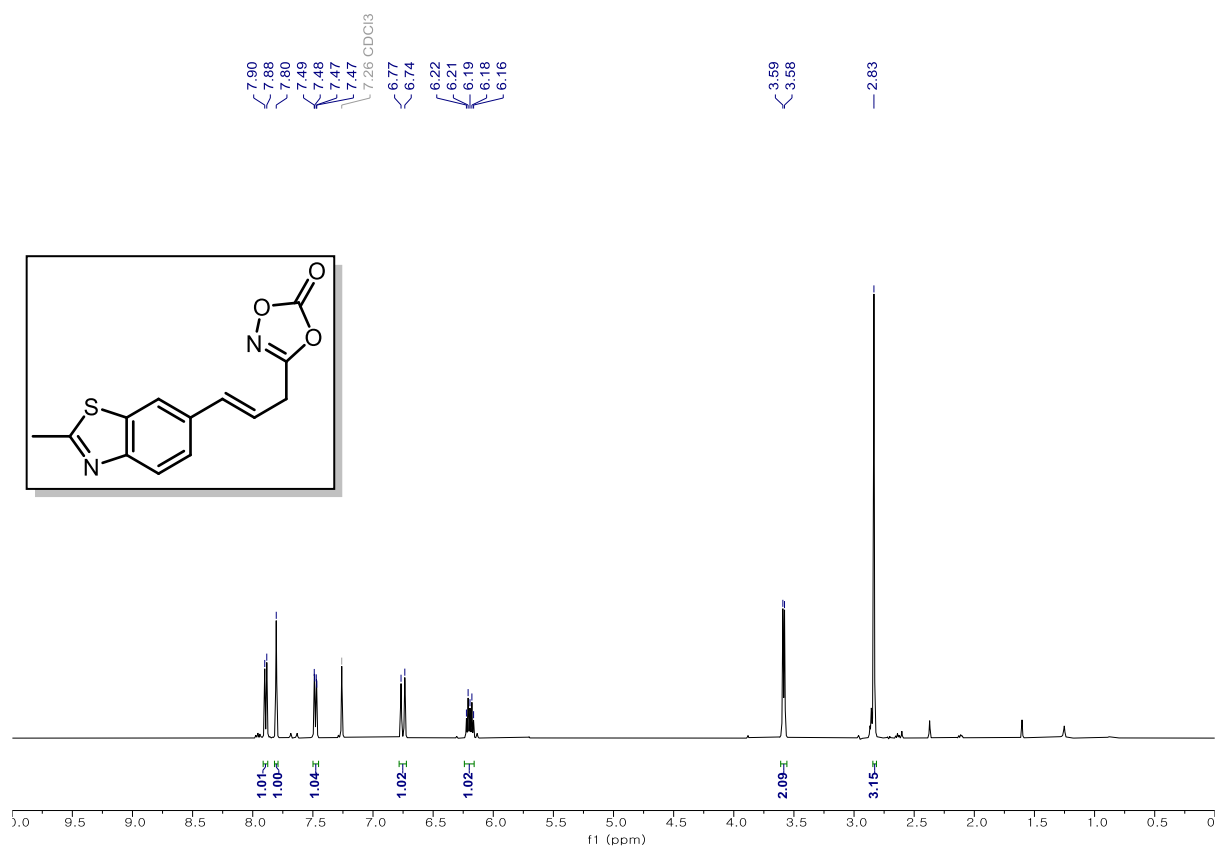




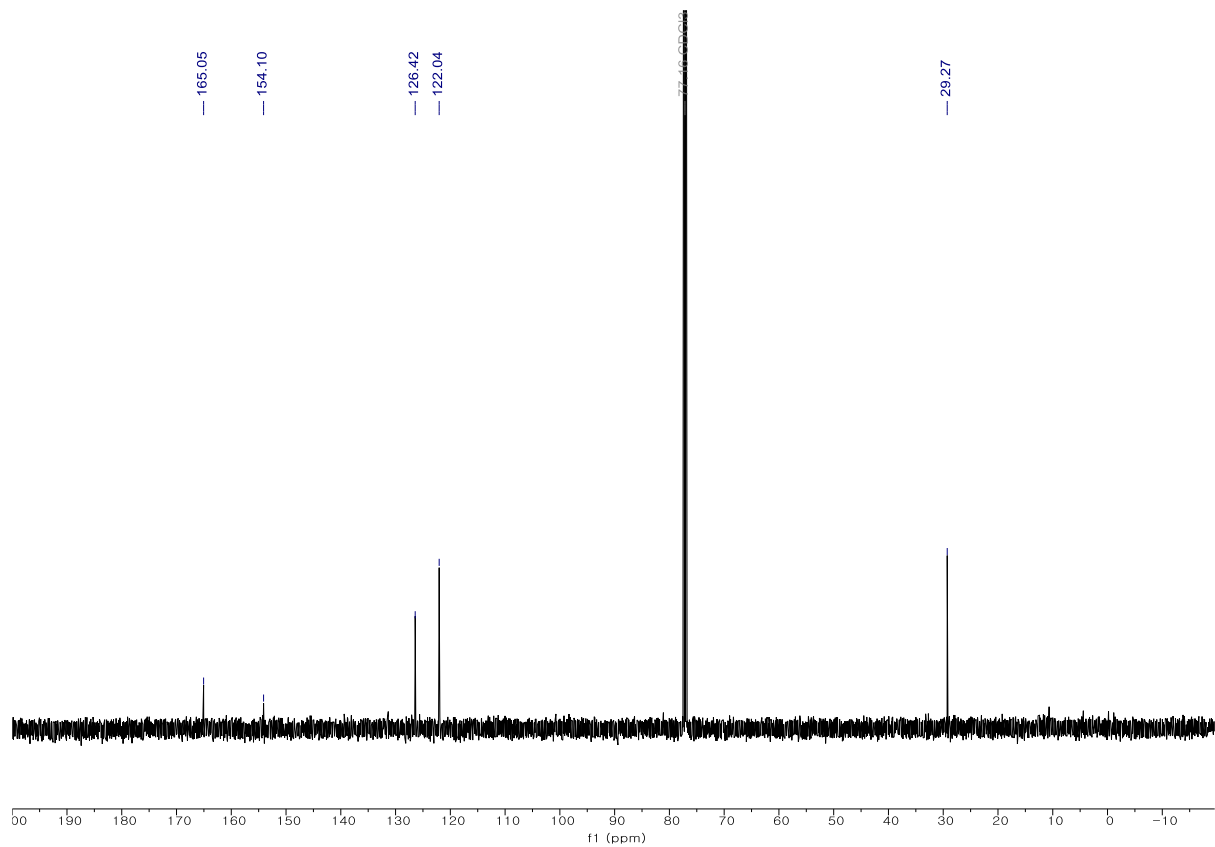
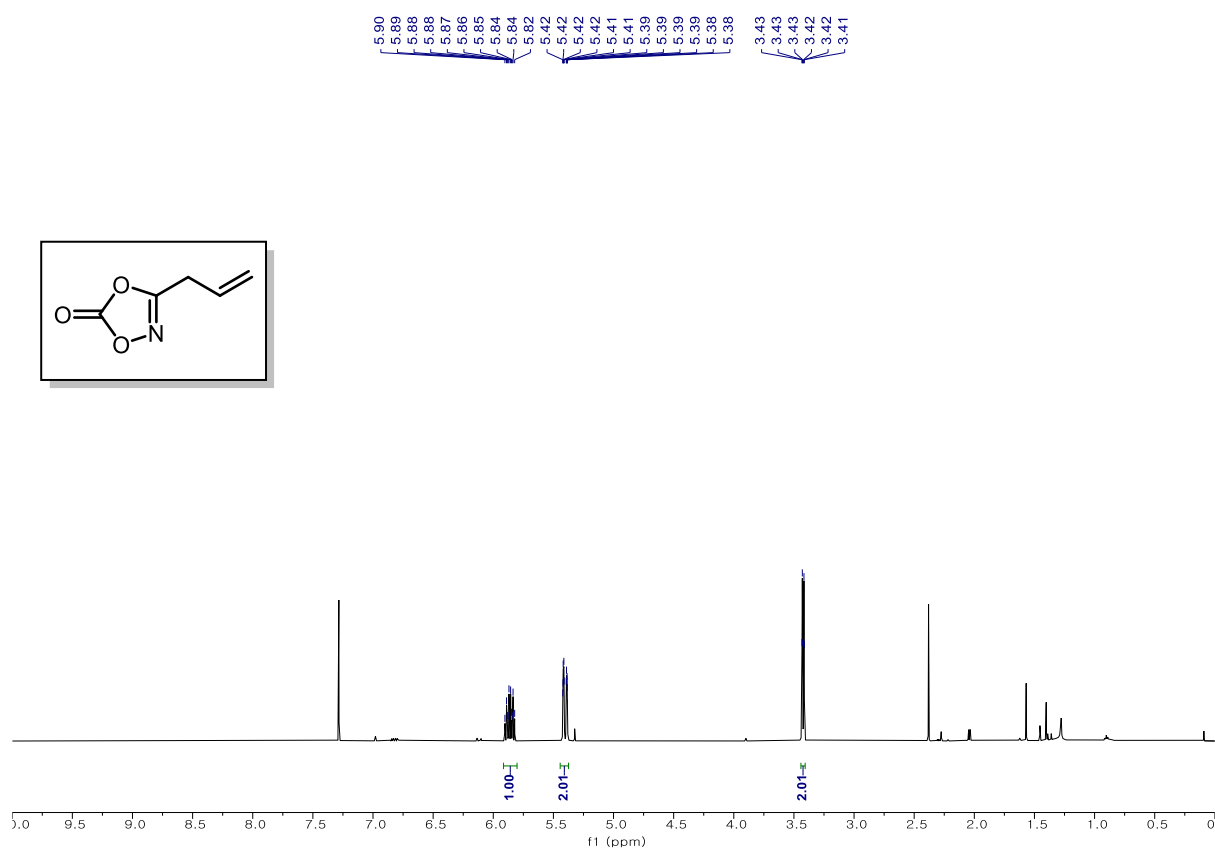
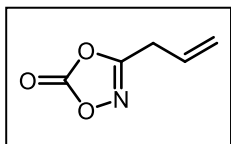
(E)-3-[3-(Benzo[b]thiophen-3-yl)allyl]-1,4,2-dioxazol-5-one



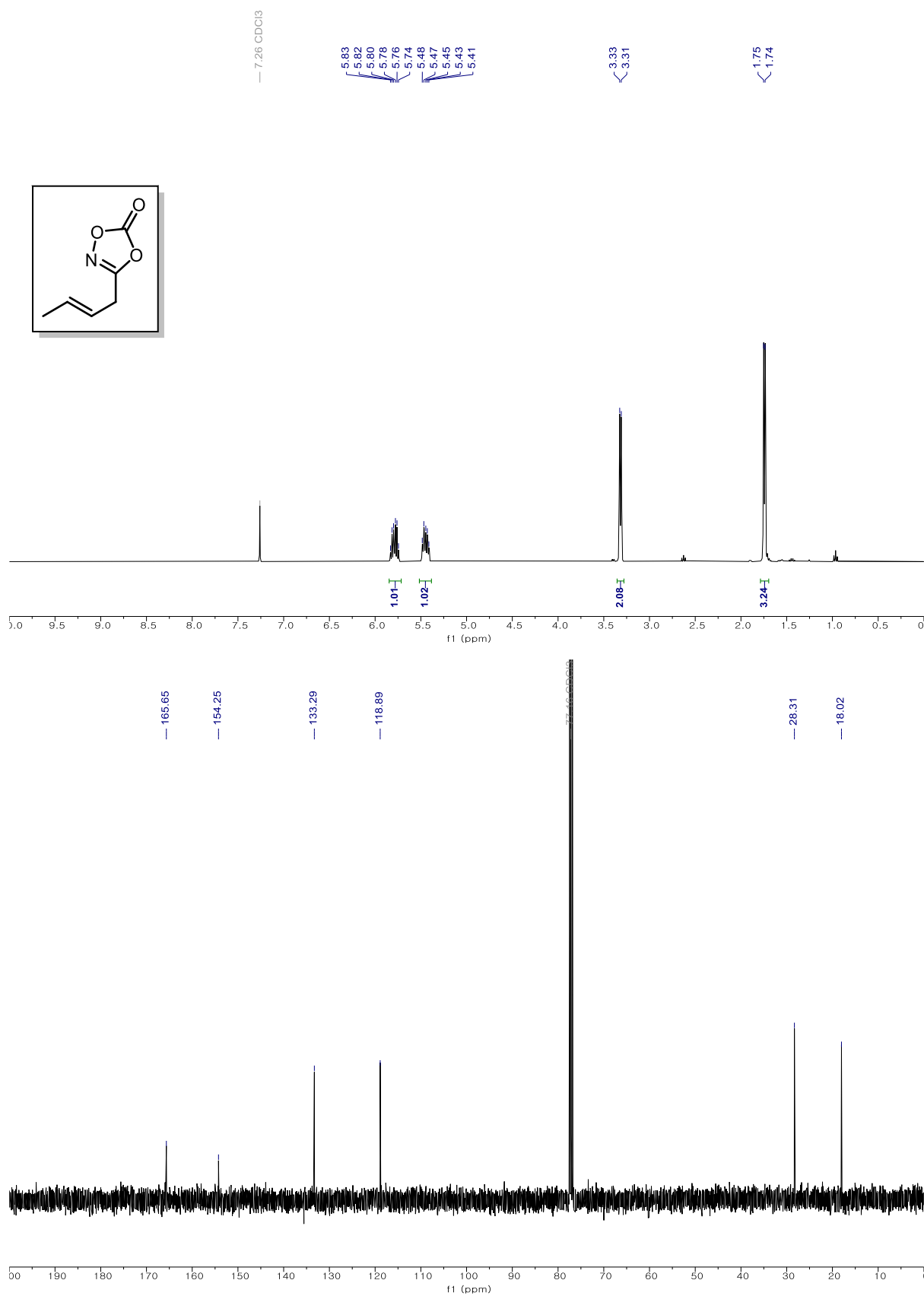
(E)-3-[3-(2-Methylbenzo[d]thiazol-6-yl)allyl]-1,4,2-dioxazol-5-one



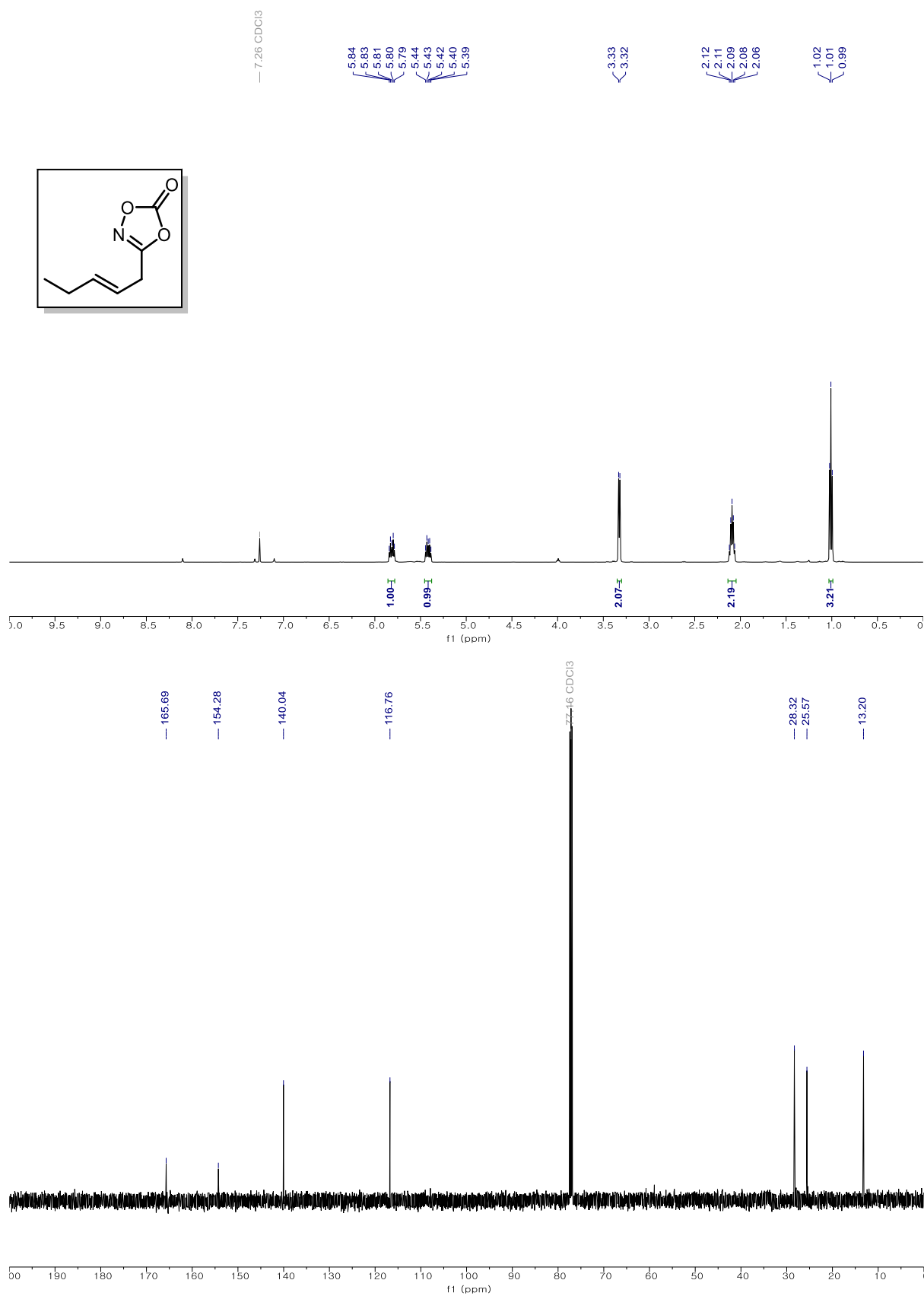
3-Allyl-1,4,2-dioxazol-5-one



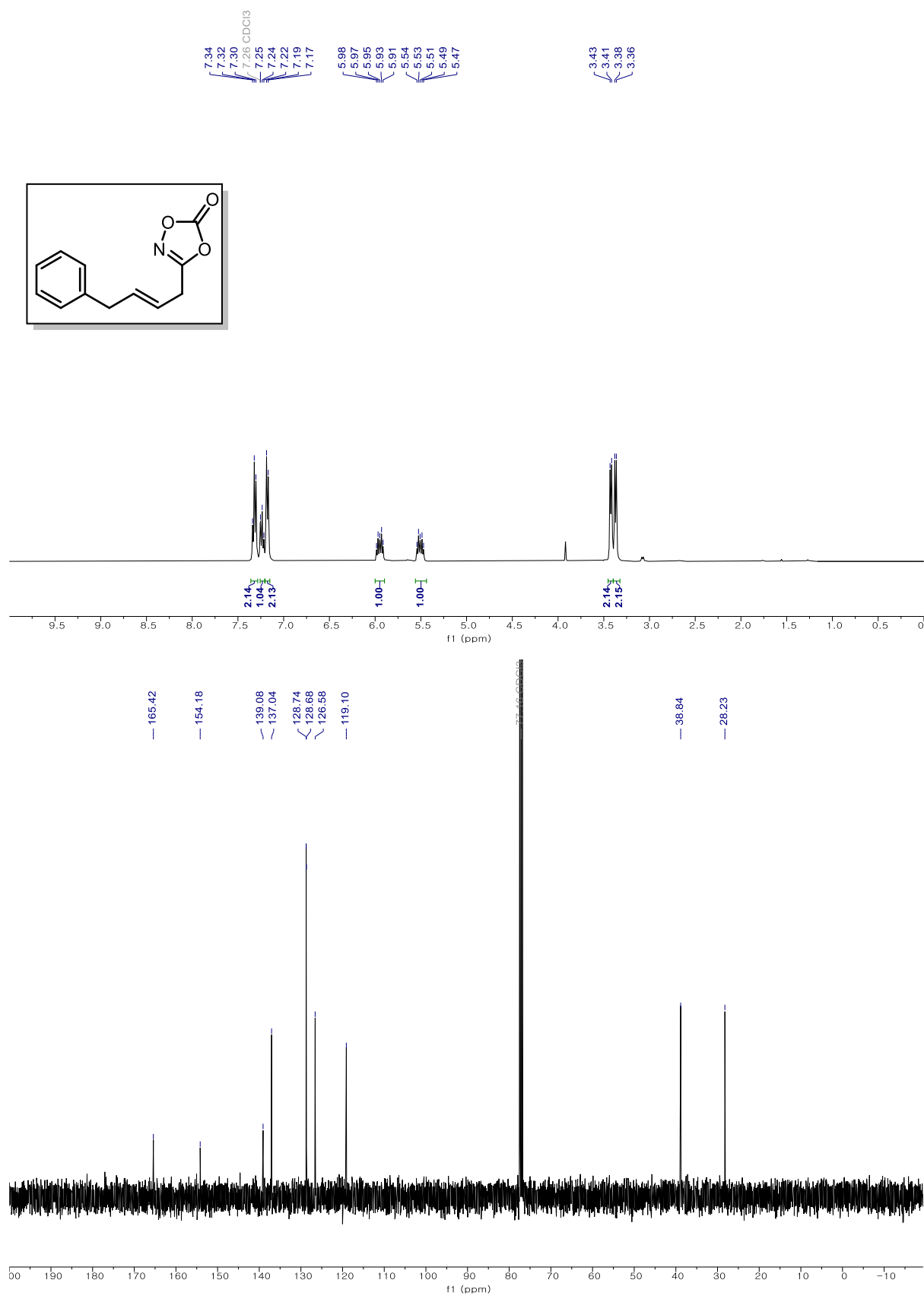
(E)-3-(But-2-en-1-yl)-1,4,2-dioxazol-5-one



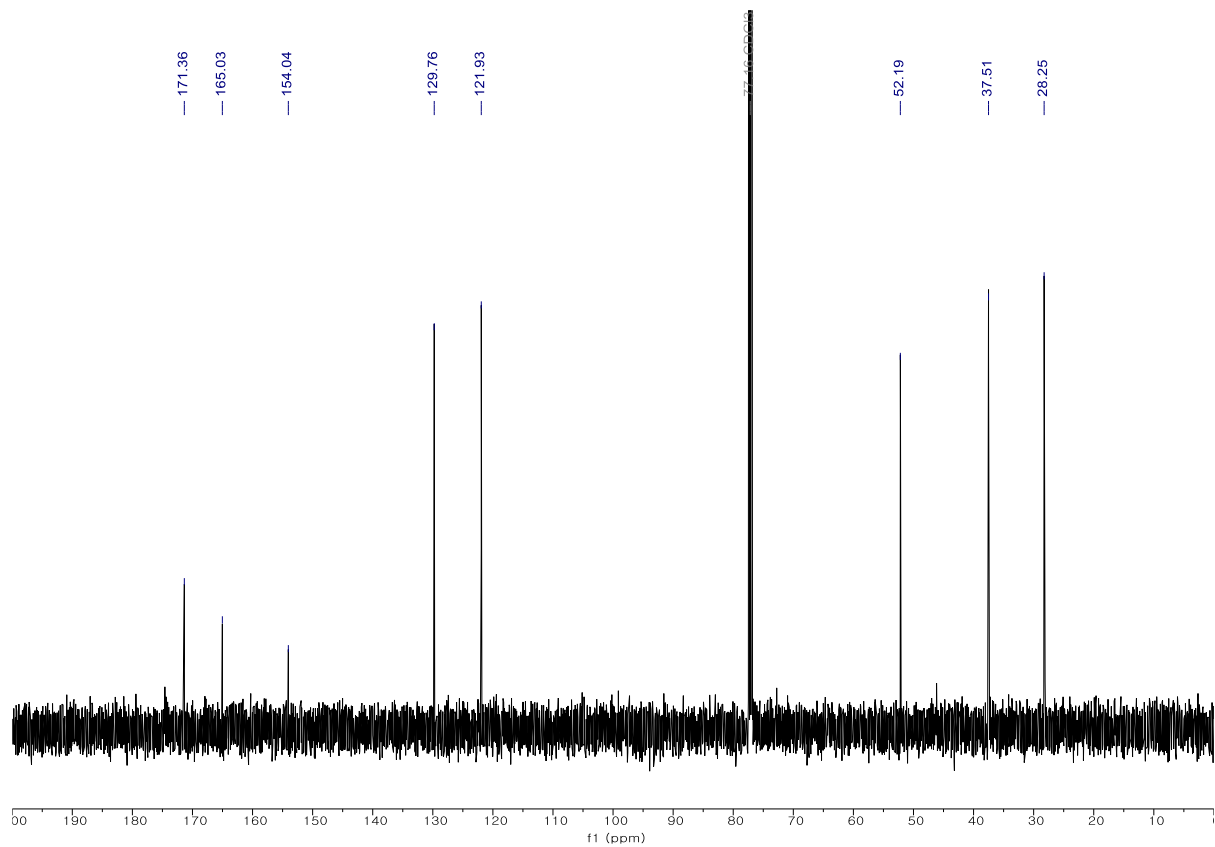
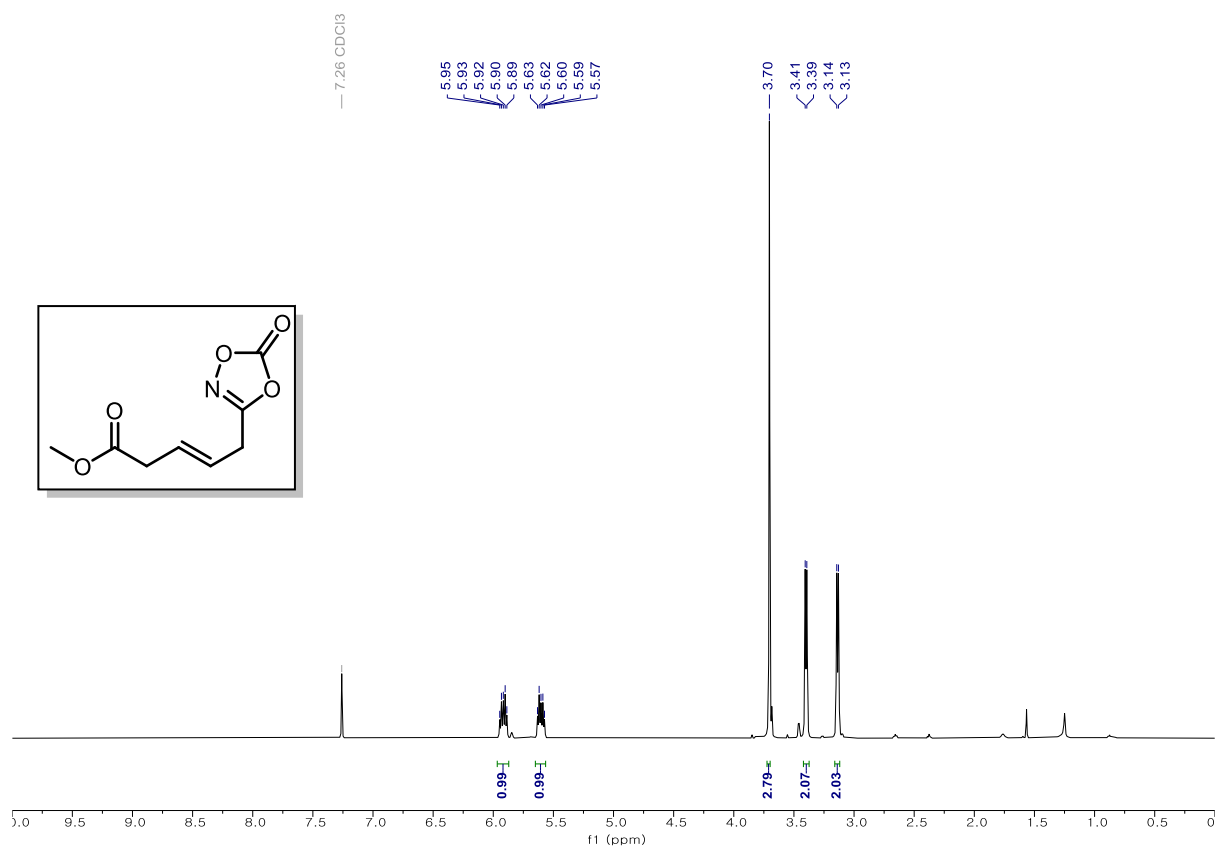
(E)-3-(Pent-2-en-1-yl)-1,4,2-dioxazol-5-one



(E)-3-(4-Phenylbut-2-en-1-yl)-1,4,2-dioxazol-5-one



Methyl (E)-5-(5-oxo-1,4,2-dioxazol-3-yl)pent-3-enoate



Chemical structure of compound 10: CC(C)(C)SiC/C=C/C1=CN2C(=O)OC2=O1

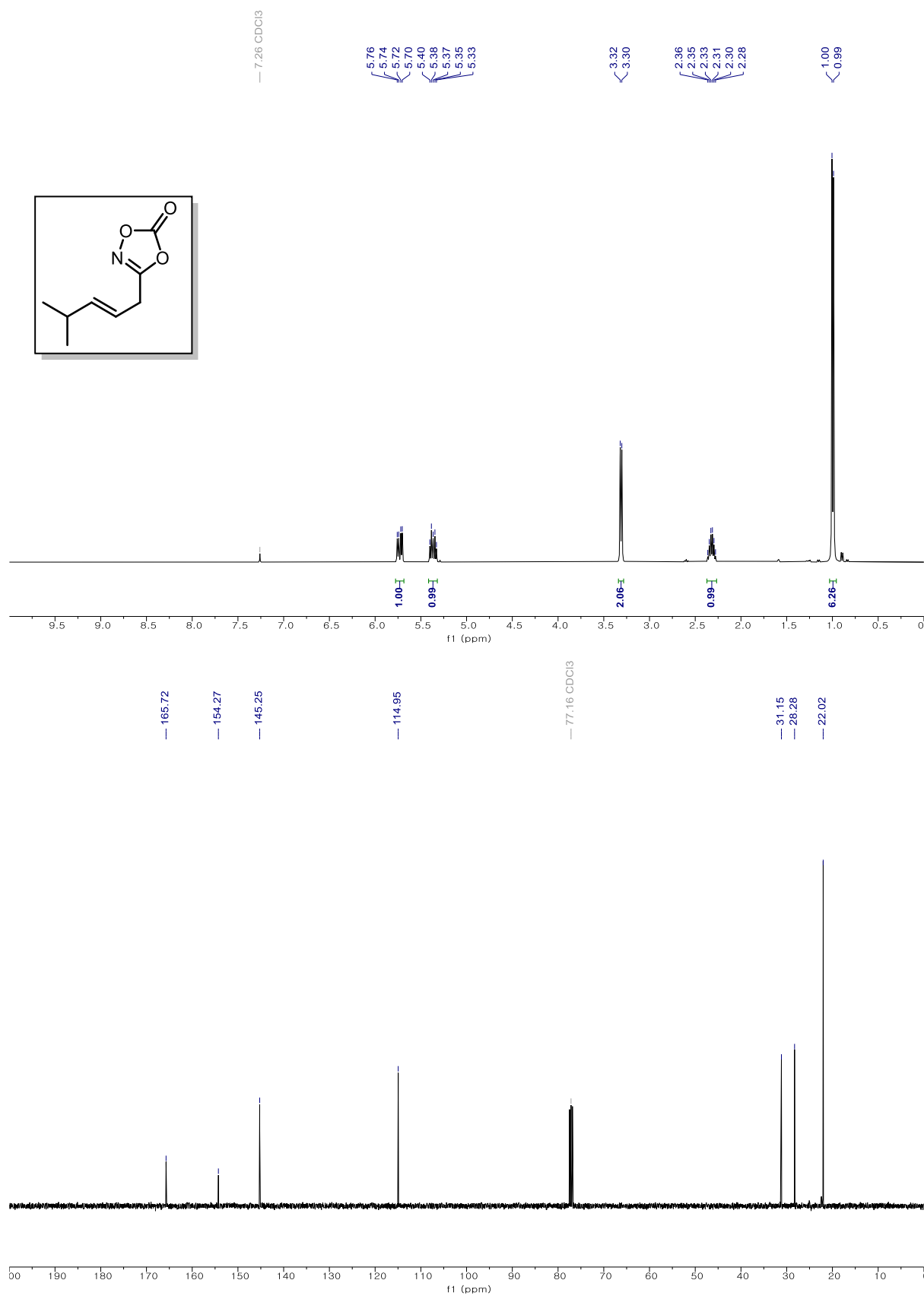
¹H NMR (400 MHz, CDCl₃) spectrum (top):

- Chemical shift range: 0.01 to 5.83 ppm.
- Integration values: 1.00, 0.51, 0.49, 1.02, 1.00, 1.04, 1.04, 4.44, 4.54.

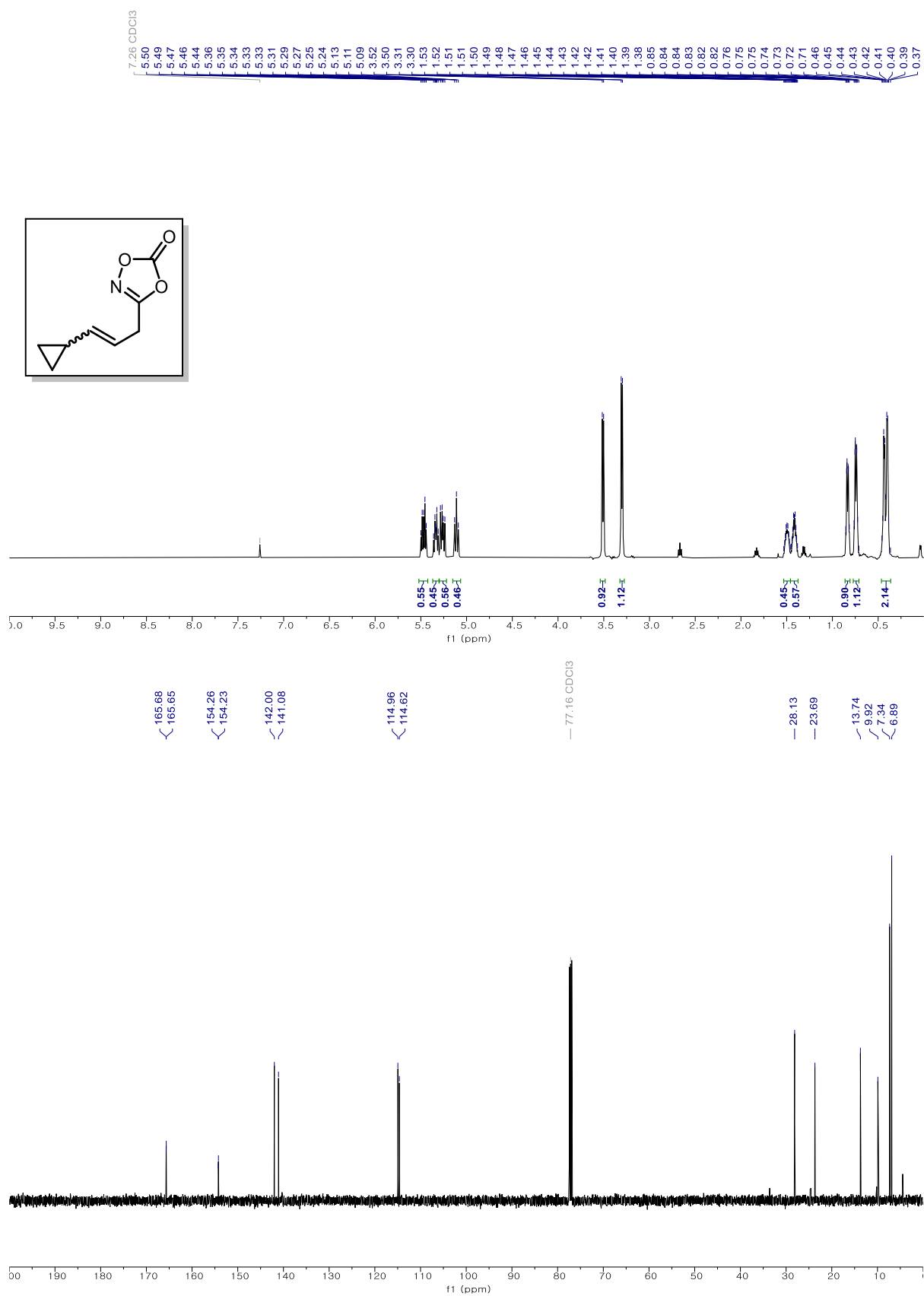
¹³C NMR (100 MHz, CDCl₃) spectrum (bottom):

- Chemical shift range: -1.88 to 165.96 ppm.

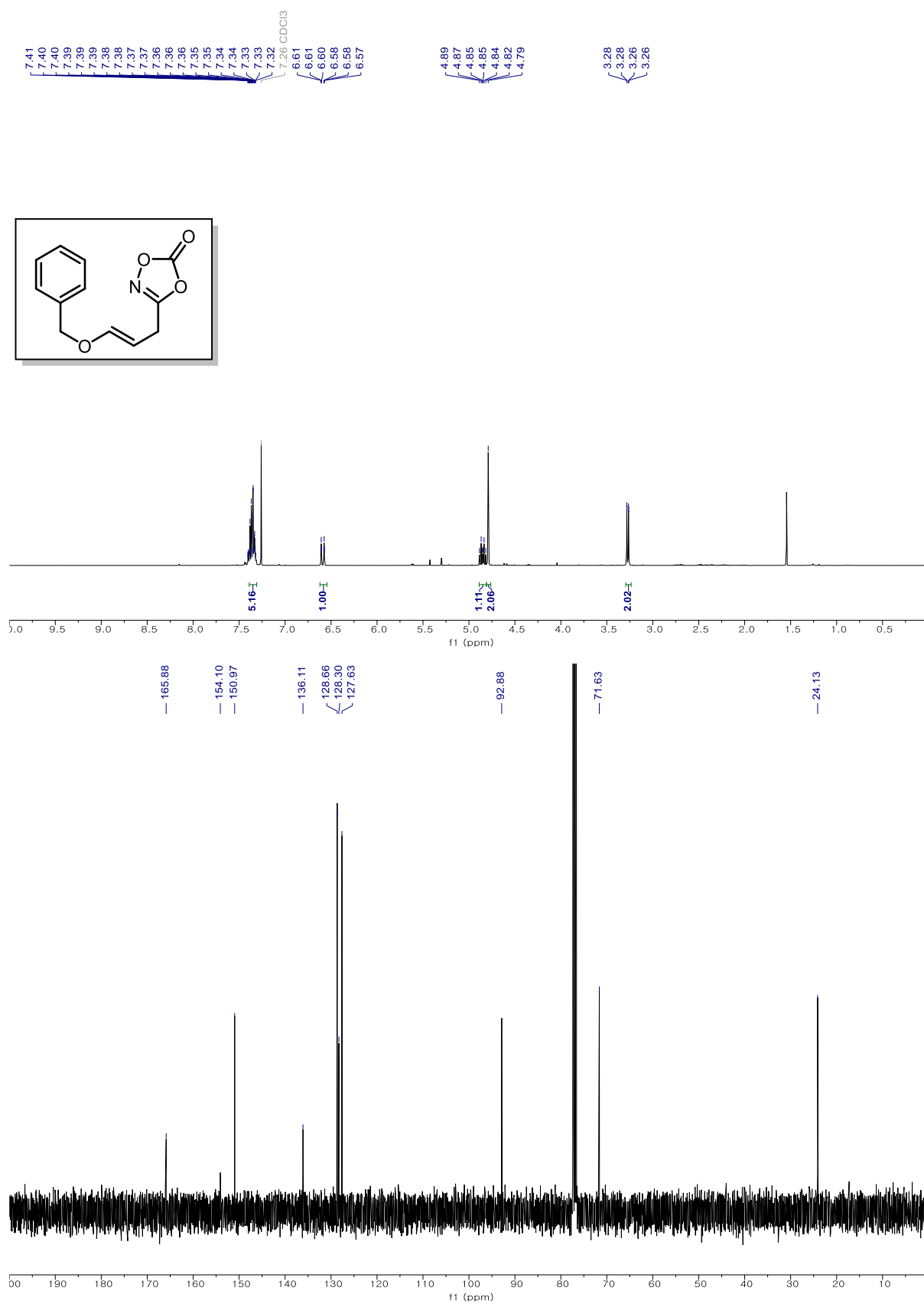
(E)-3-(4-Methylpent-2-en-1-yl)-1,4,2-dioxazol-5-one



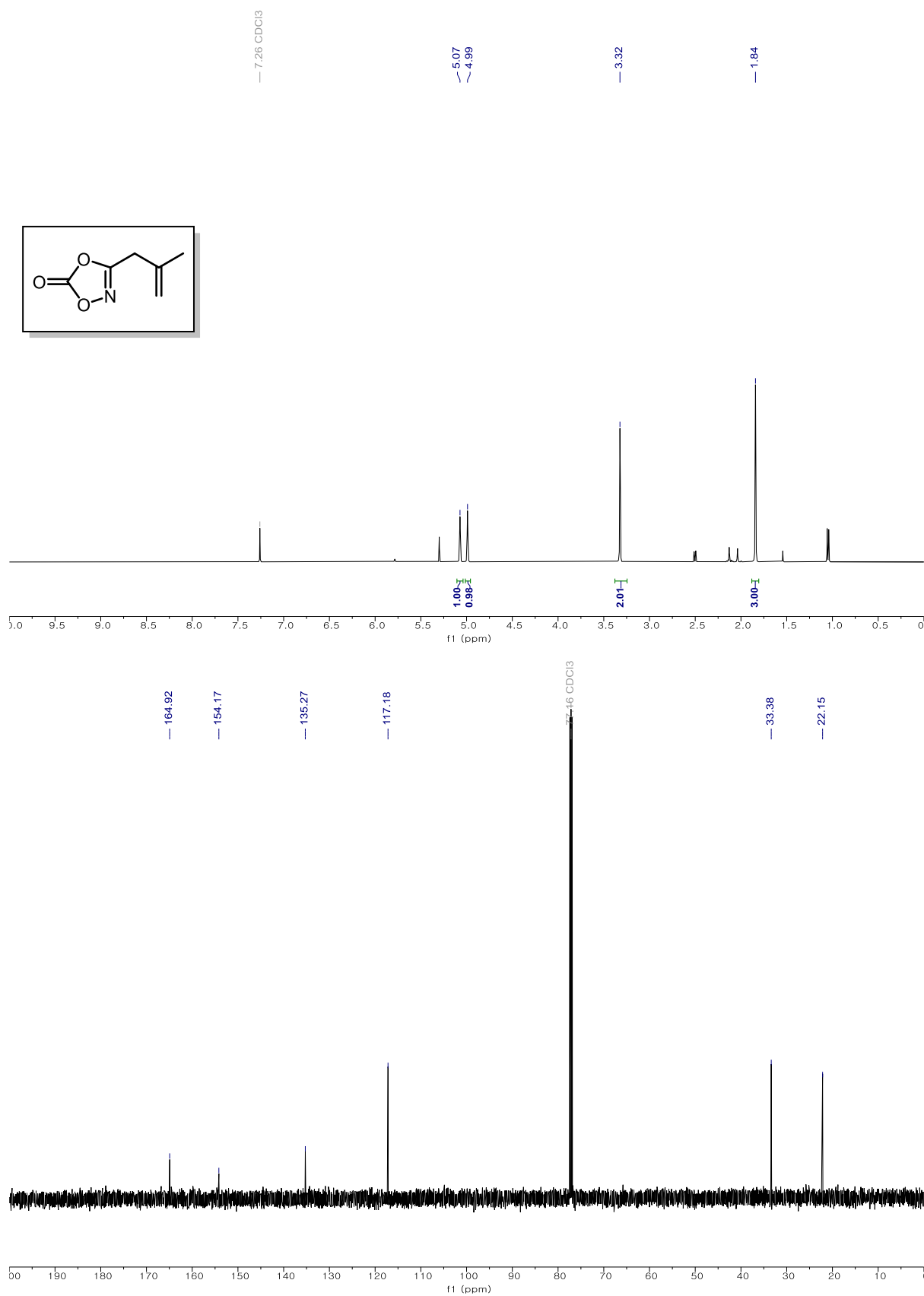
3-(3-Cyclopropylallyl)-1,4,2-dioxazol-5-one (E/Z = 1.2:1 mixture)



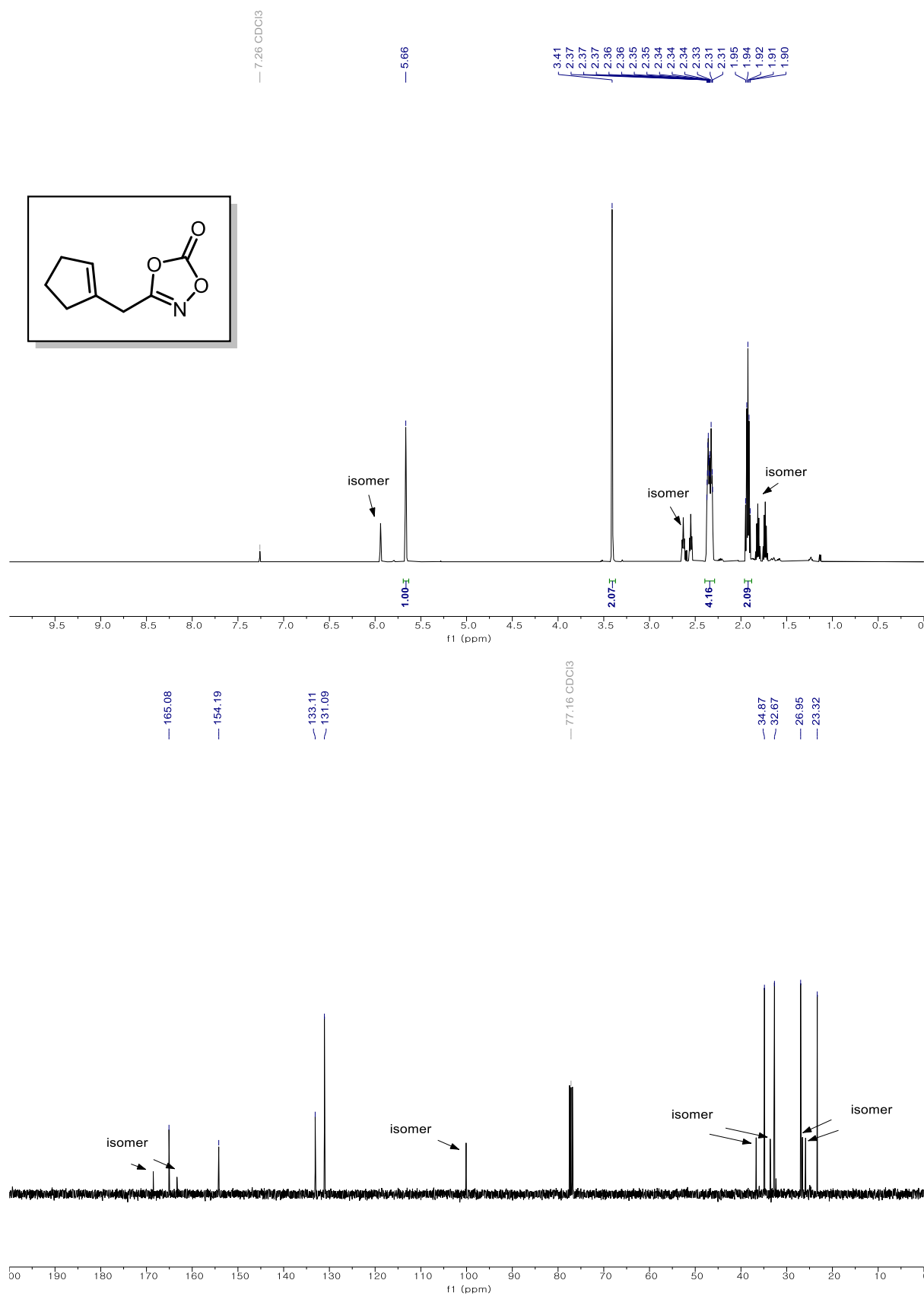
(E)-3-[3-(Benzyloxy)allyl]-1,4,2-dioxazol-5-one



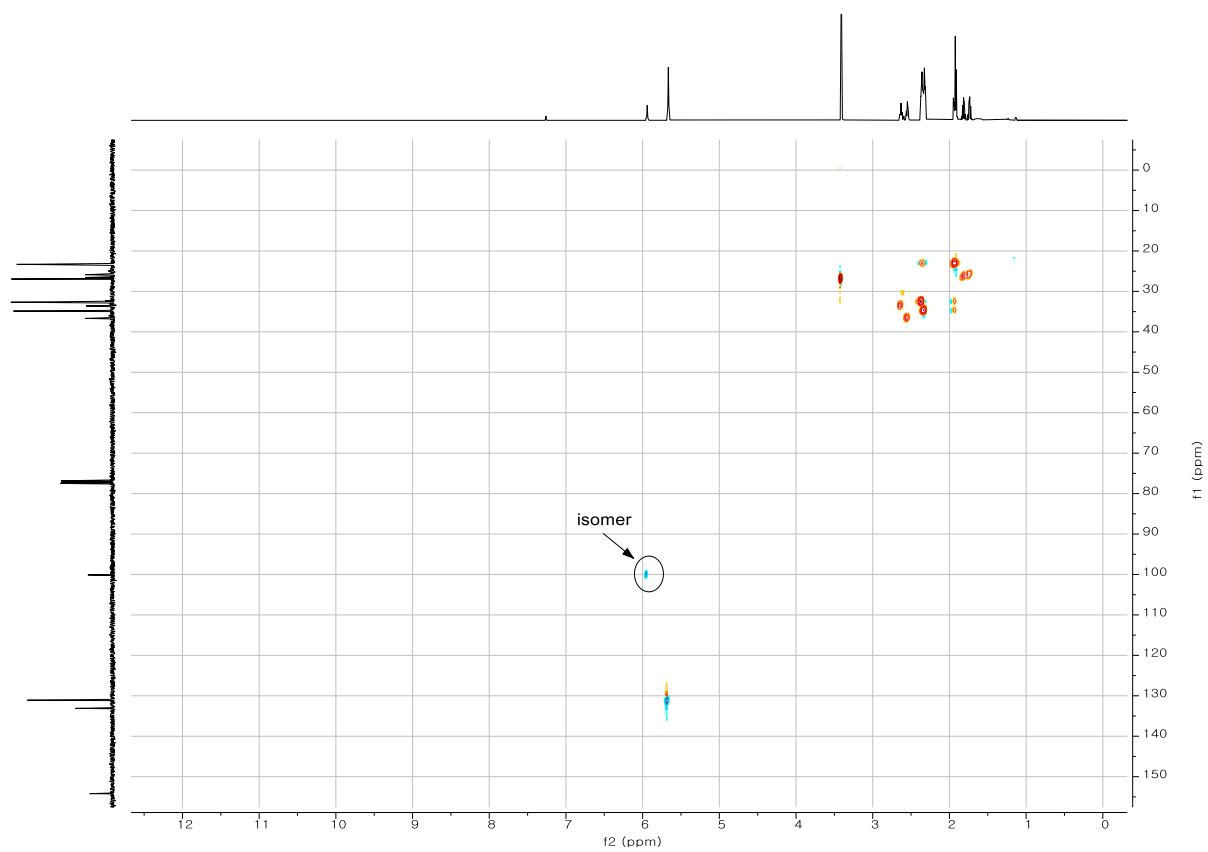
3-(2-Methylallyl)-1,4,2-dioxazol-5-one



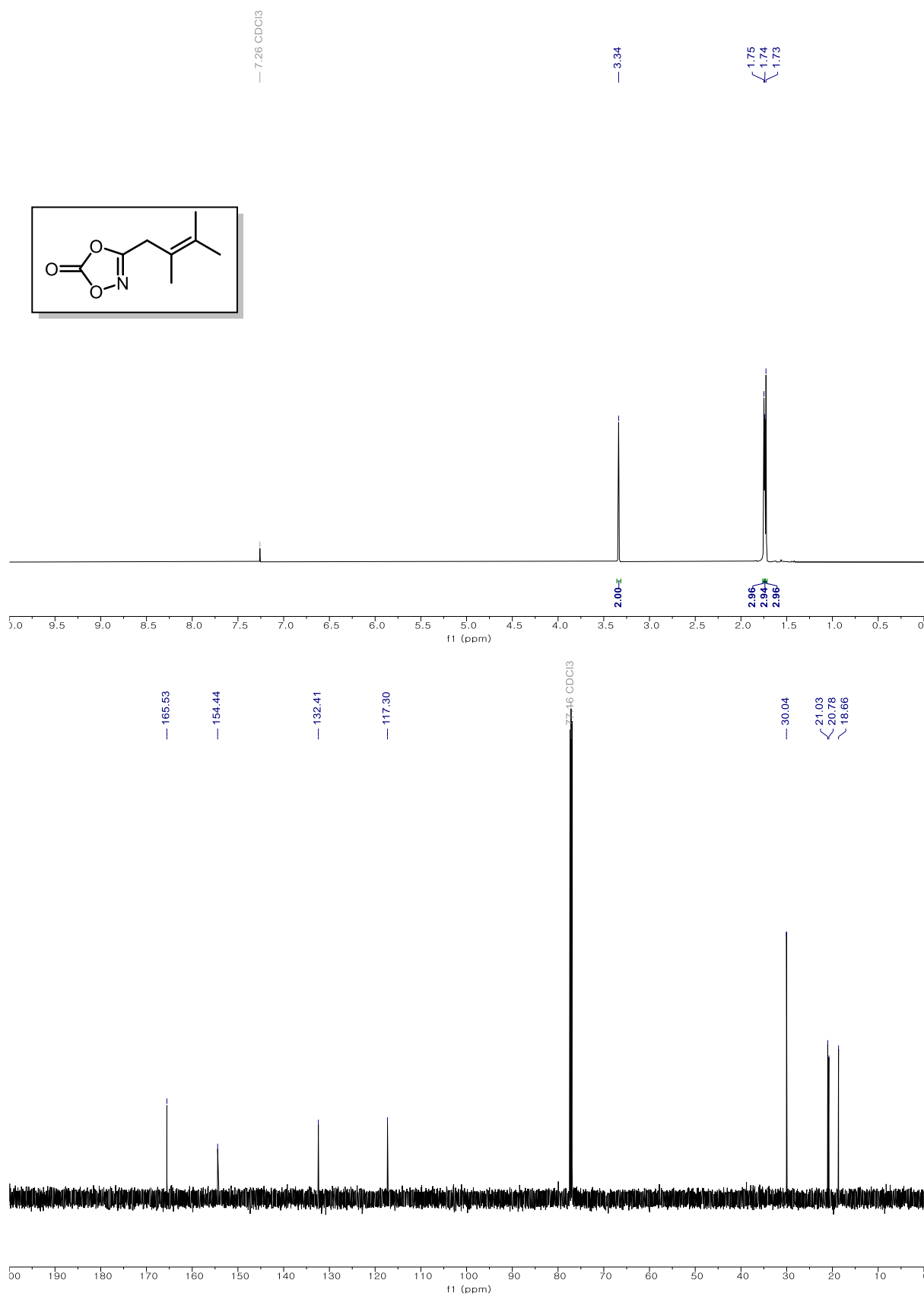
3-(Cyclopent-1-en-1-ylmethyl)-1,4,2-dioxazol-5-one



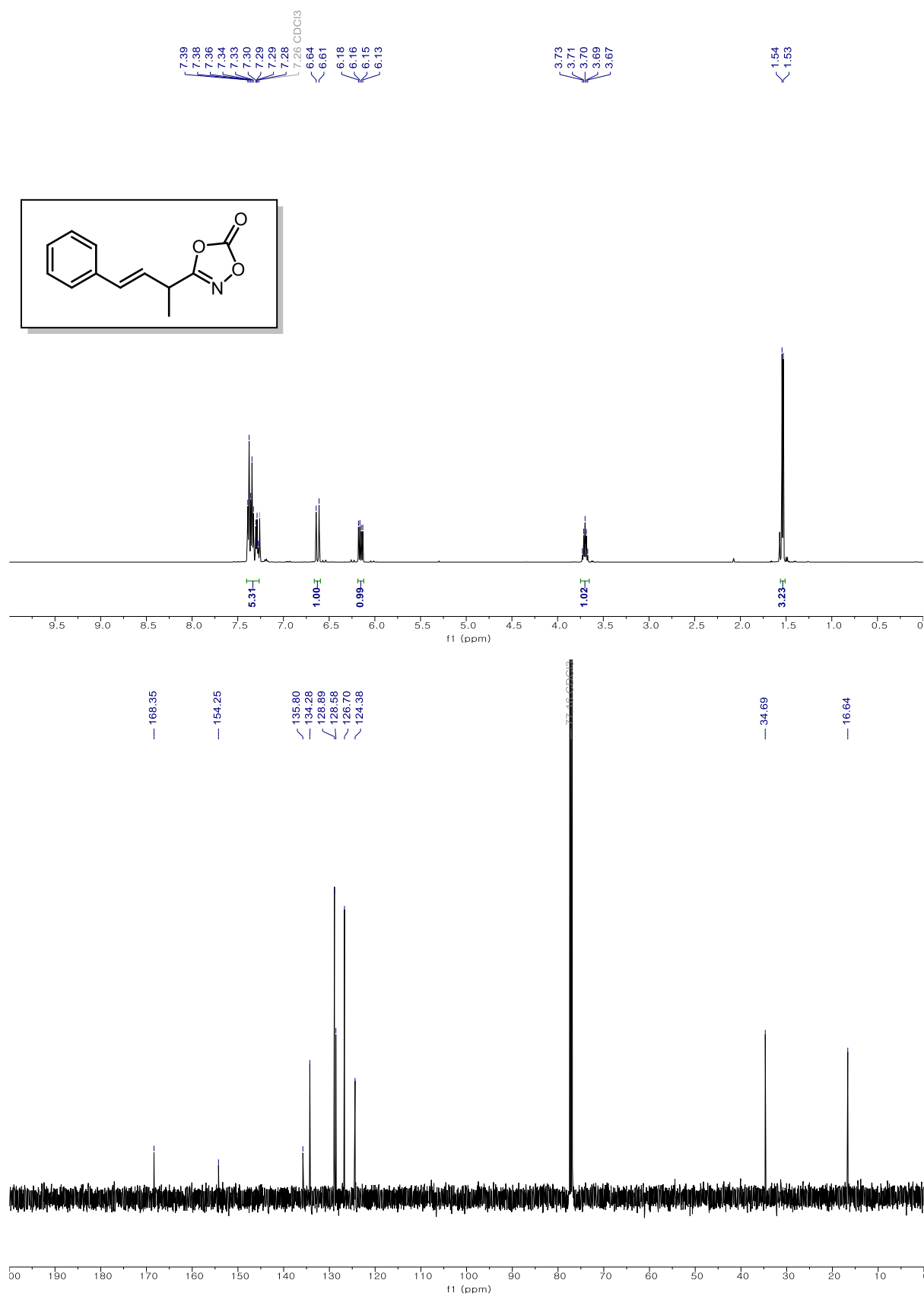
HSQC of 3-(Cyclopent-1-en-1-ylmethyl)-1,4,2-dioxazol-5-one



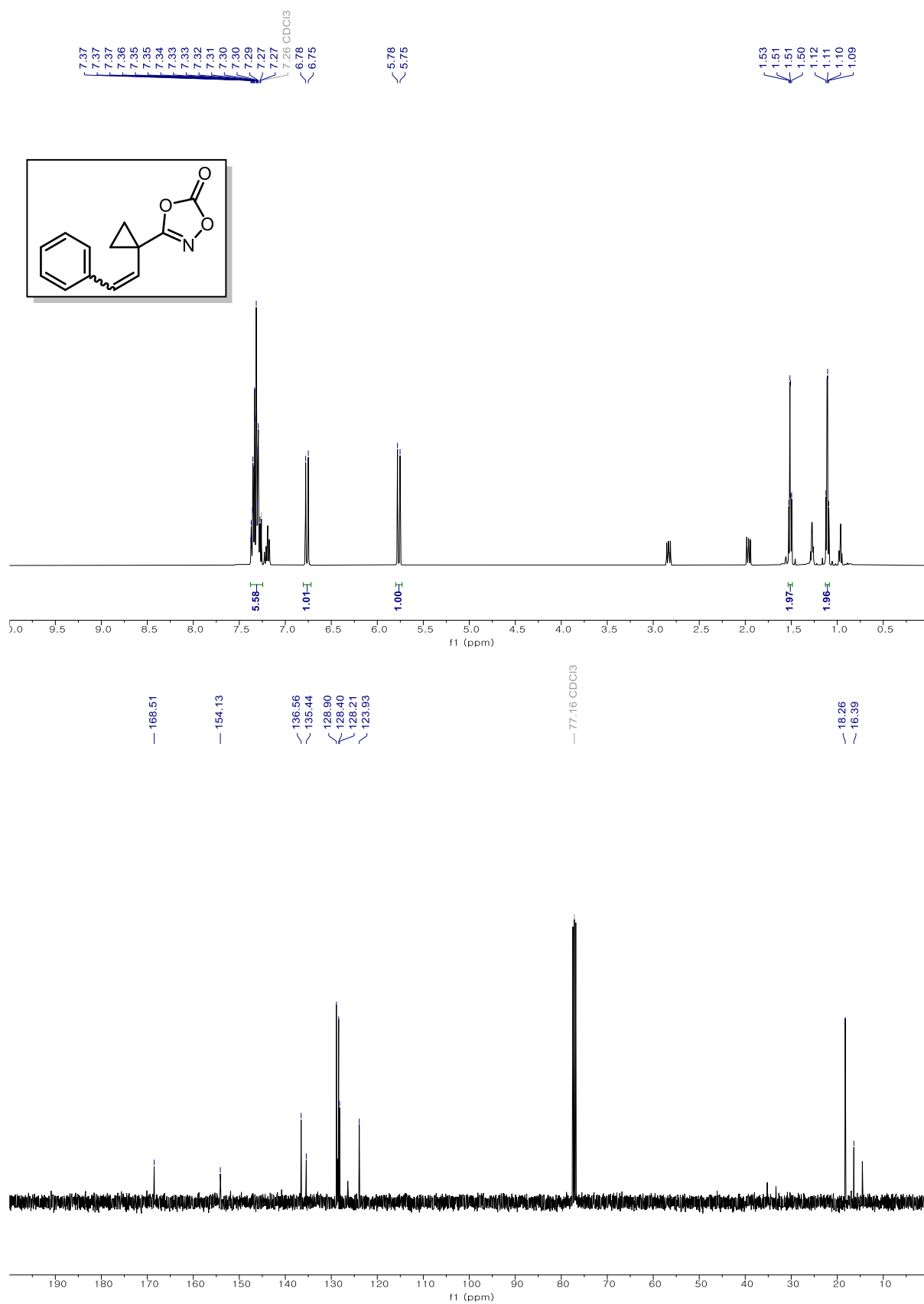
3-(2,3-Dimethylbut-2-en-1-yl)-1,4,2-dioxazol-5-one



(E)-3-(4-Phenylbut-3-en-2-yl)-1,4,2-dioxazol-5-one



3-(1-Styrylcyclopropyl)-1,4,2-dioxazol-5-one



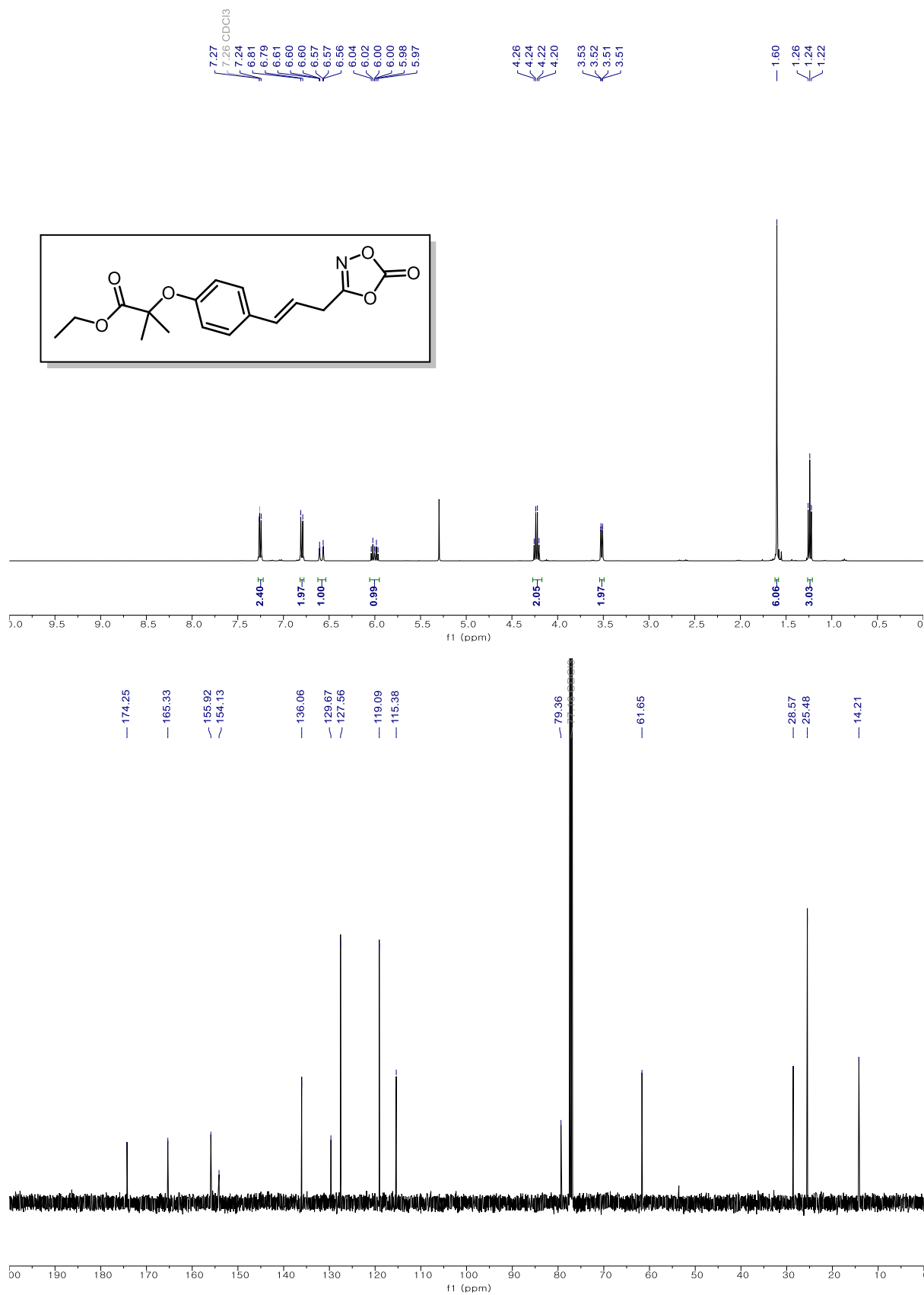
Chemical Structure of 10: CCOC(=O)c1c(C)nc(C2=CC=C(C=C2)C(=C/C3=CC(=C(C=C3)COC(C)C)C=C/C4=CC=CC=C4C5=CC=CC=C5)C6=CC=CC=C6)cs1

¹H NMR Spectrum (CDCl₃):

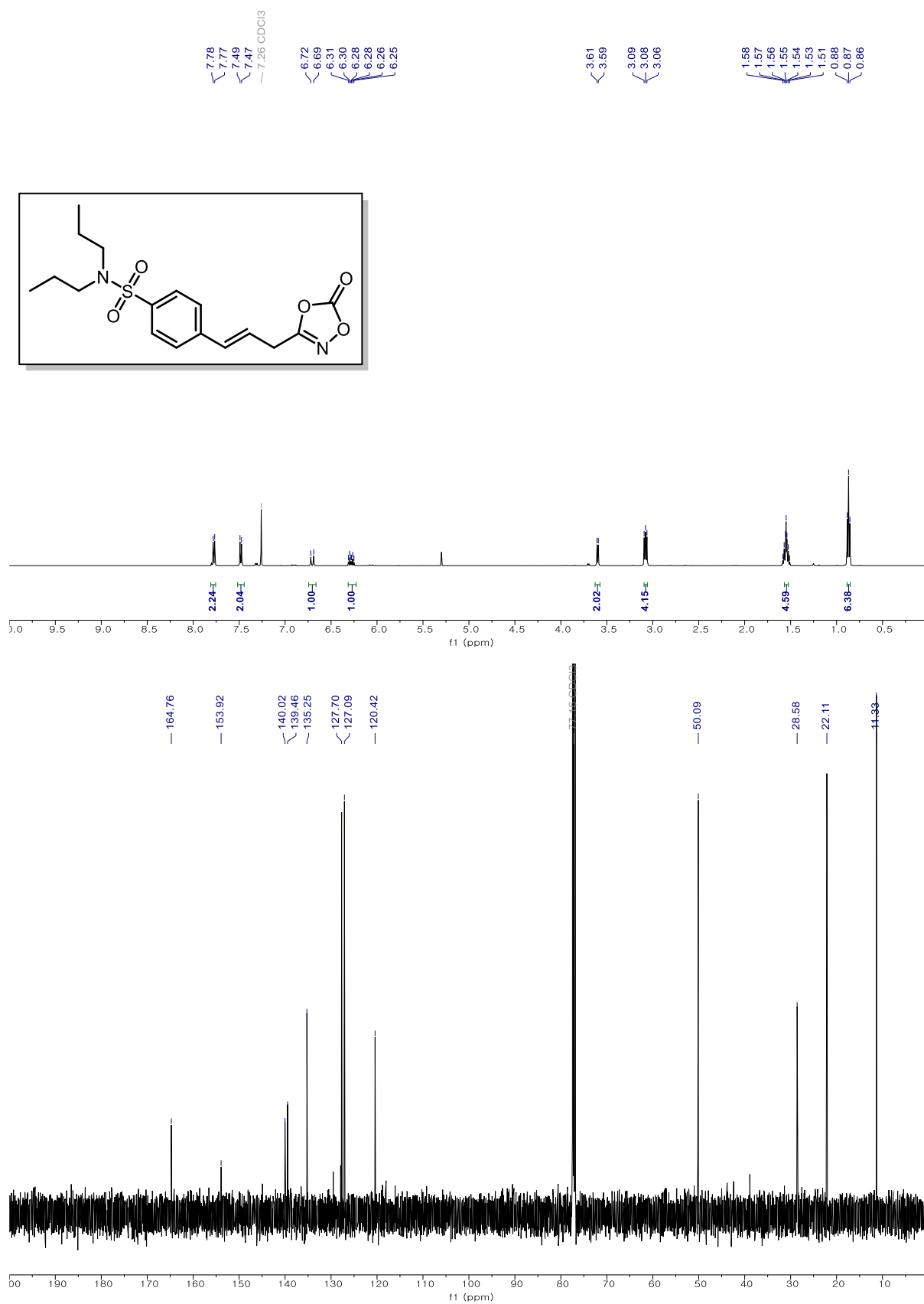
Chemical Shift (ppm)	Integration
8.00, 7.99, 7.83, 7.82, 7.81, 7.80	1.00, 1.01
6.98, 6.98, 6.98, 6.94, 6.94, 6.94, 6.94, 6.91, 6.88, 6.37, 6.35, 6.33, 6.33, 6.31, 6.29	1.06, 1.08, 1.02
4.36, 4.35, 4.33, 4.31, 3.82, 3.81, 3.60, 3.59, 3.58, 3.58	2.13, 2.16, 2.09
2.76	3.29
2.21, 2.19, 2.17, 2.16, 2.14, 2.12, 2.11	1.14
1.40, 1.38, 1.36, 1.07, 1.05	3.22, 6.06



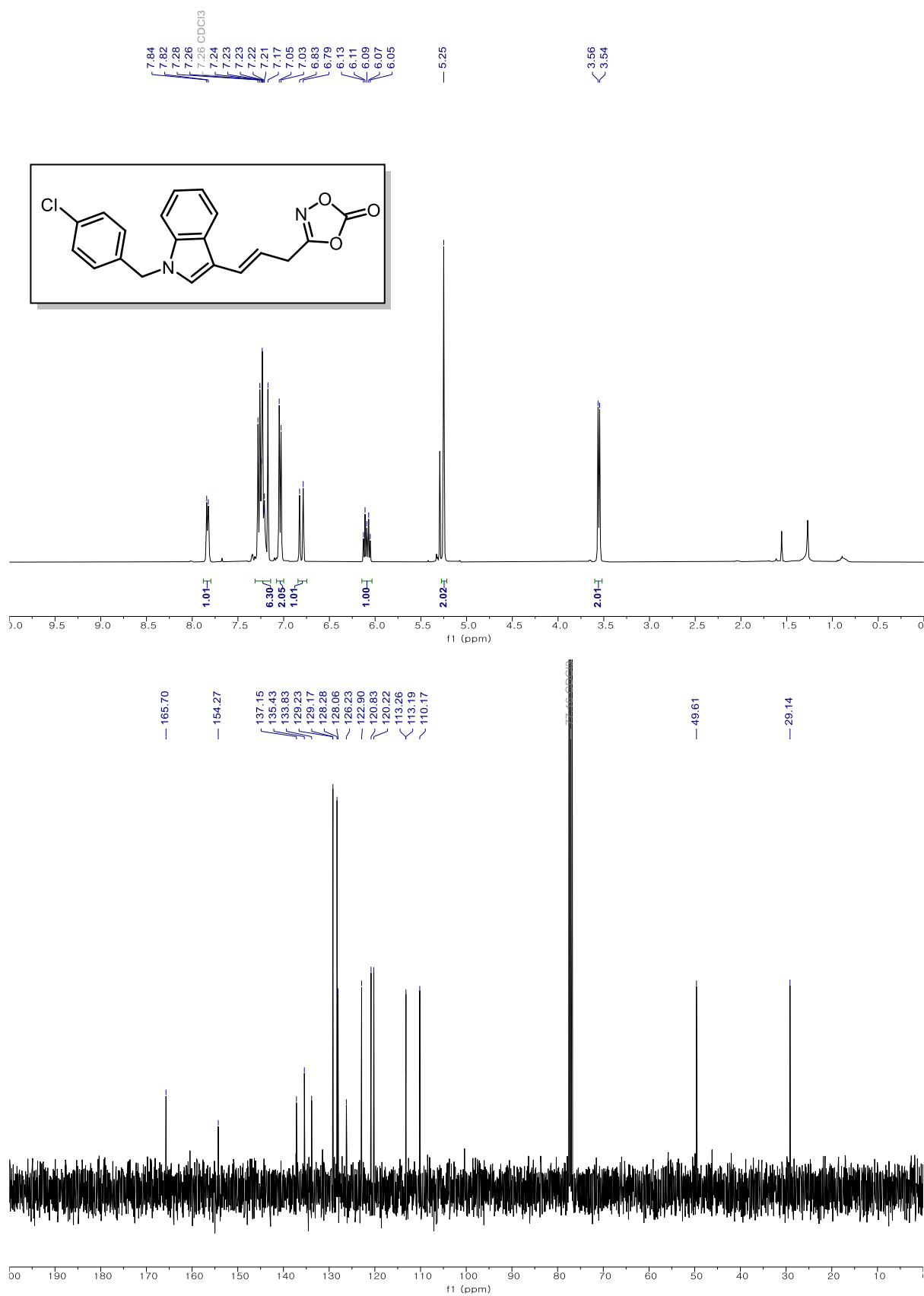
Ethyl (E)-2-methyl-2-{4-[3-(5-oxo-1,4,2-dioxazol-3-yl)prop-1-en-1-yl]phenoxy}propanoate



(E)-4-[3-(5-Oxo-1,4,2-dioxazol-3-yl)prop-1-en-1-yl]-N,N-dipropylbenzenesulfonamide



(E)-3-{3-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]allyl}-1,4,2-dioxazol-5-one

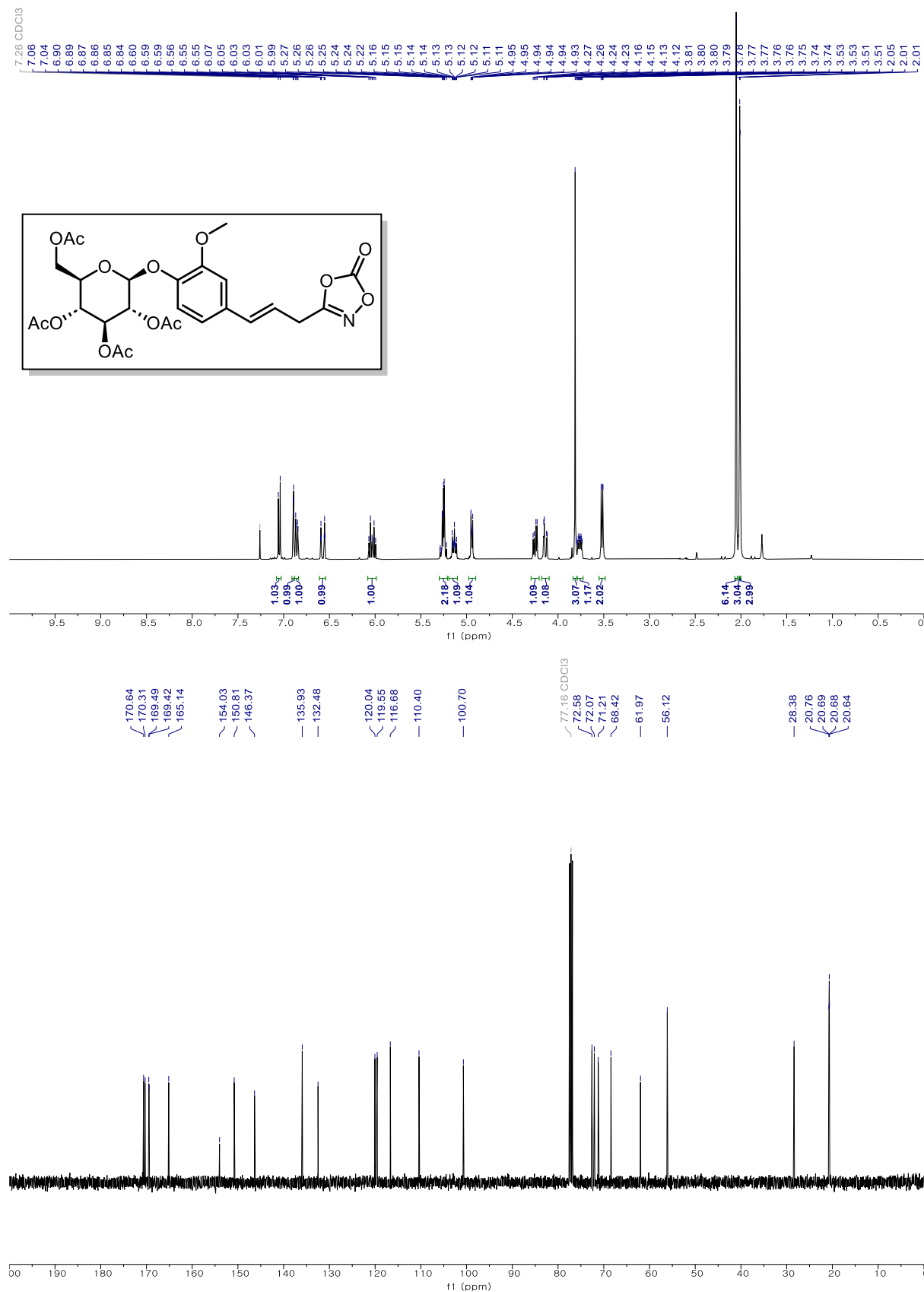


Chemical structure of compound 10 is shown in the inset. The ^1H NMR spectrum (400 MHz, CDCl_3) displays the following peaks (ppm) and integrations:

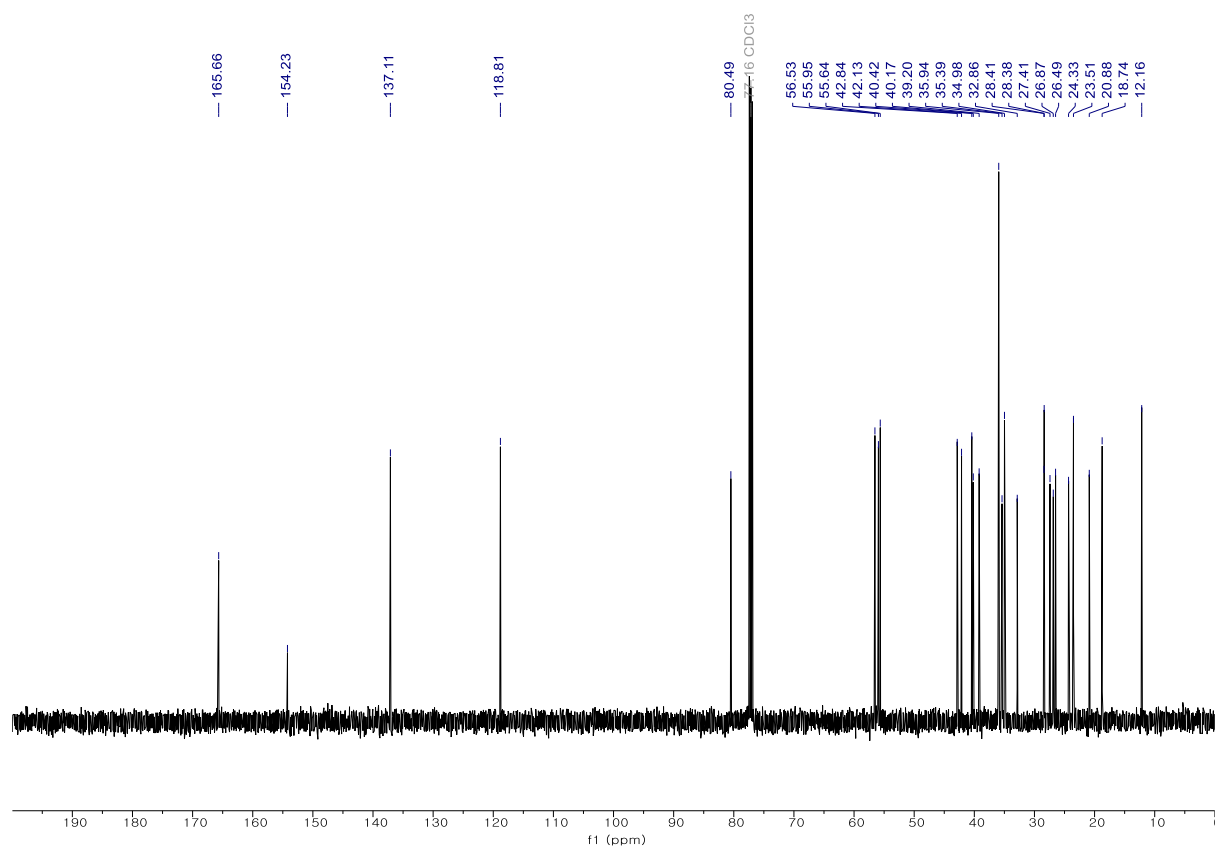
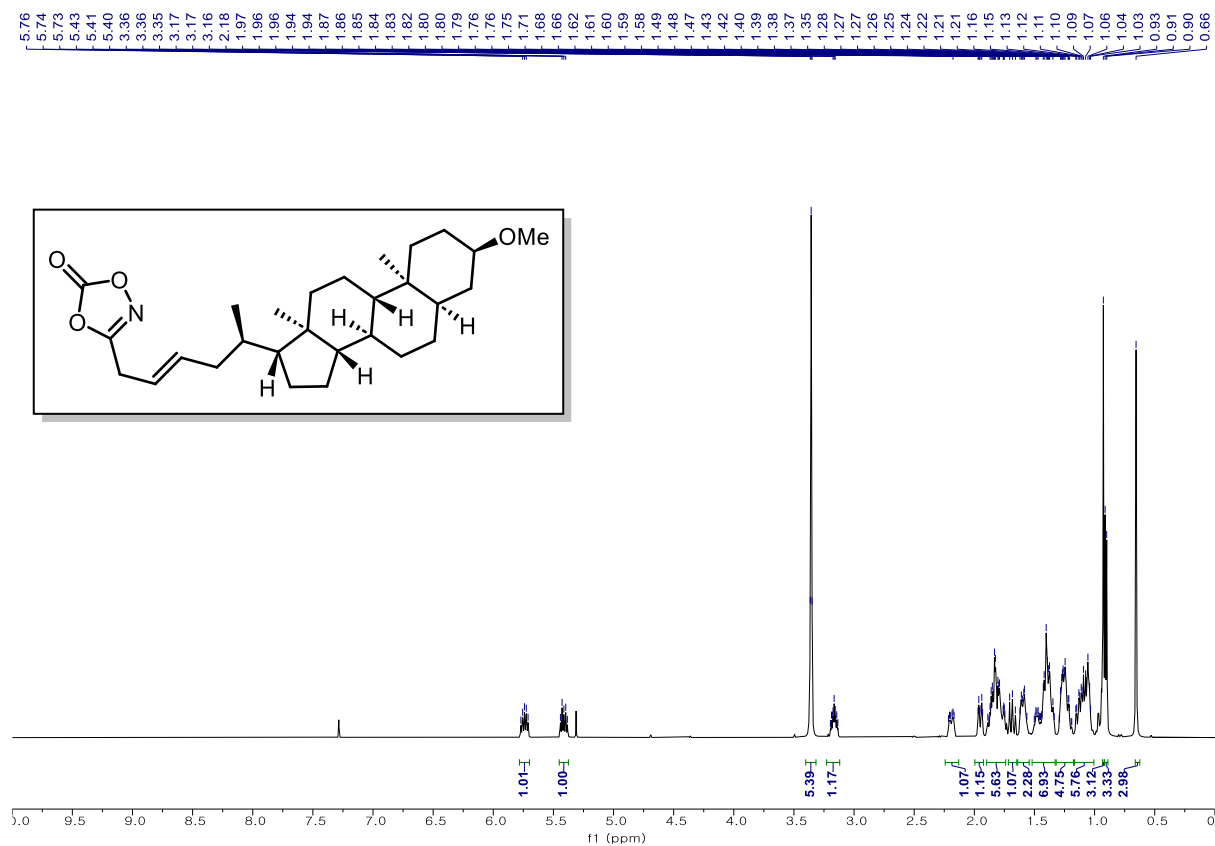
Chemical Shift (ppm)	Integration
7.26, 7.28	1.13
7.18, 7.16, 7.11	0.98
6.62, 6.59, 6.13, 6.11, 6.10	0.97
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3.13	1.98
2.04	2.04
1.55, 1.53, 1.51, 1.49, 1.48, 1.47, 1.46, 1.45, 1.43, 1.41, 1.39, 1.37, 1.35, 1.33, 1.31, 1.29, 1.27, 1.25, 1.23, 1.21, 1.19, 1.17, 1.15, 1.13, 1.11, 1.09	1.05, 1.02, 1.05, 1.02, 4.25, 6.48
0.91	3.13



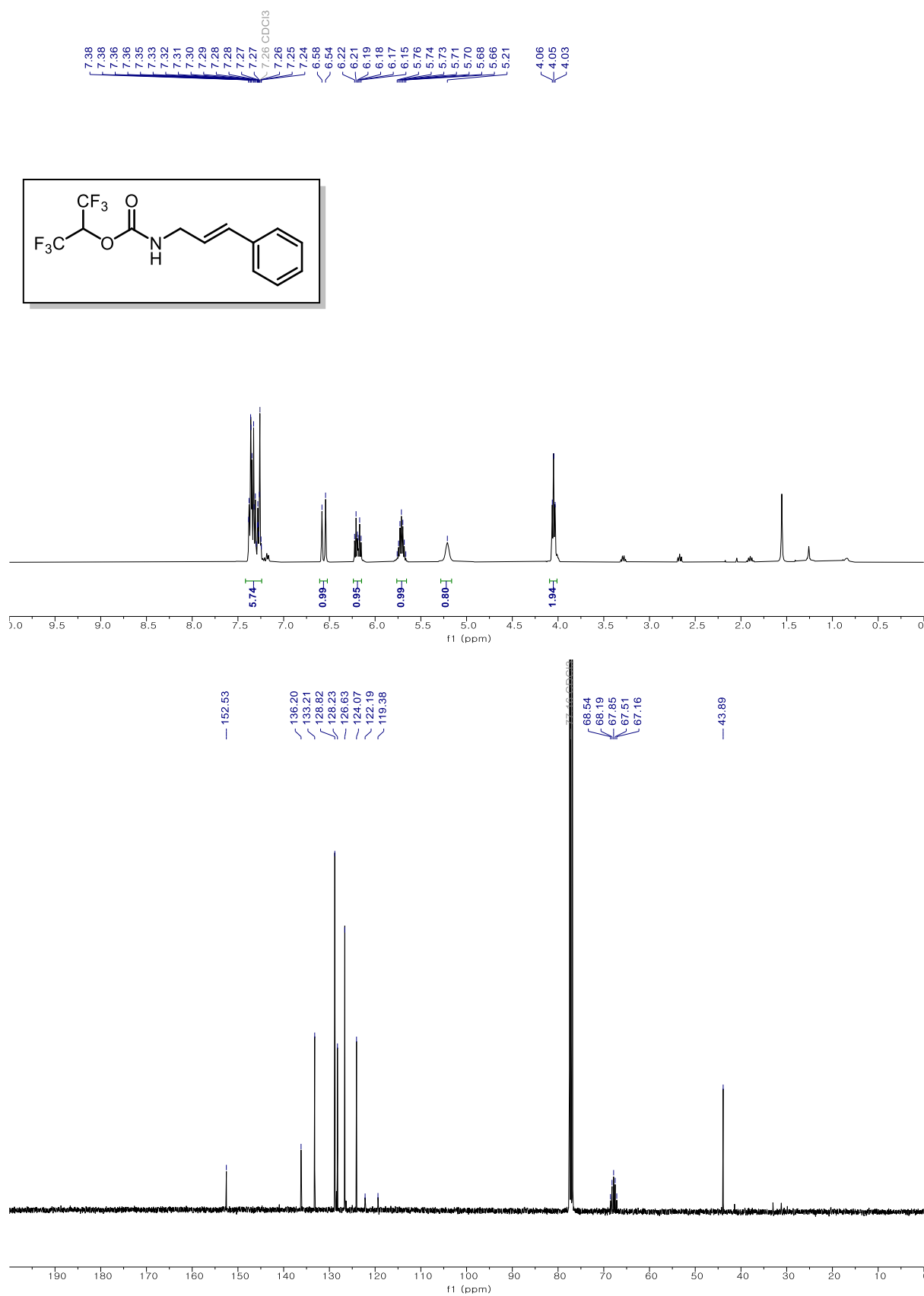
(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-{2-methoxy-4-[(*E*)-3-(5-oxo-1,4,2-dioxazol-3-yl)prop-1-en-1-yl]phenoxy}tetrahydro-2*H*-pyran-3,4,5-triyl triacetate

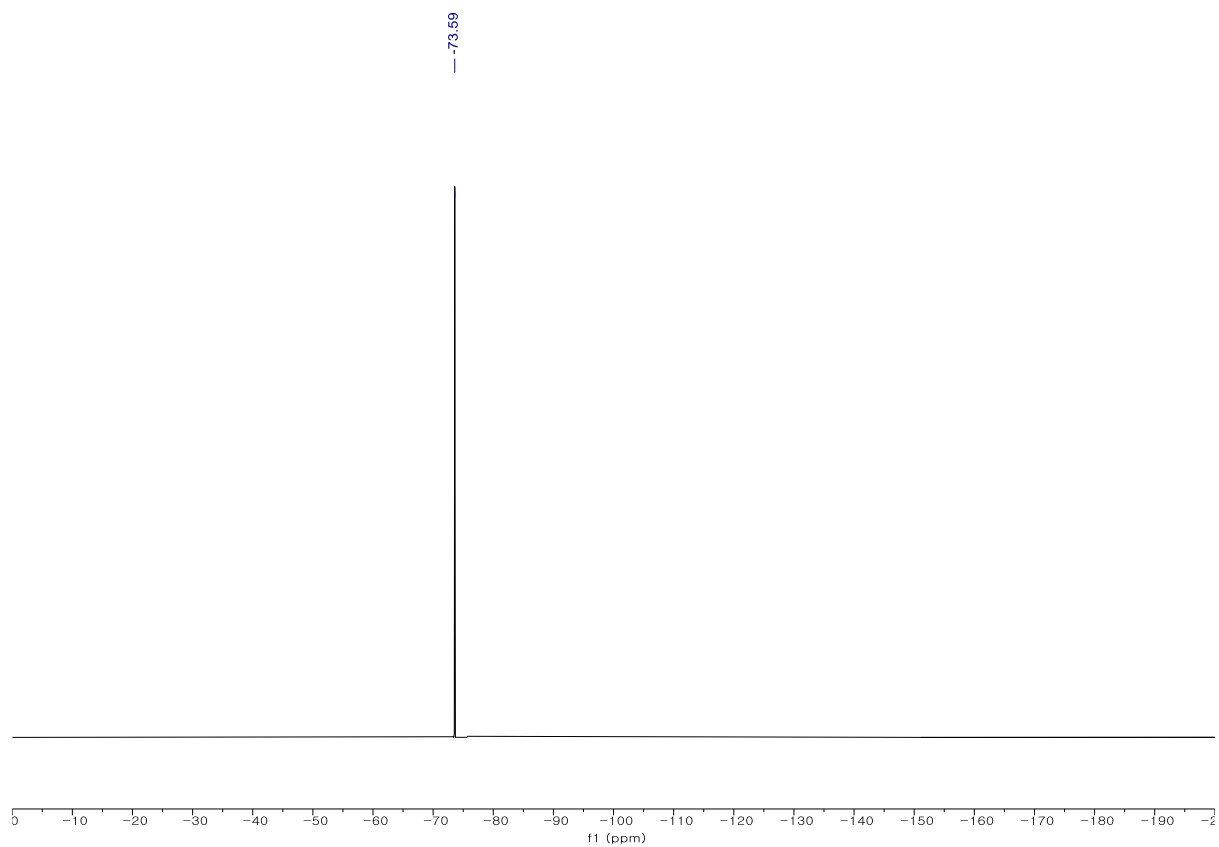


3-[(*R,E*)-5-[(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Methoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]hex-2-en-1-yl]-1,4,2-dioxazol-5-one

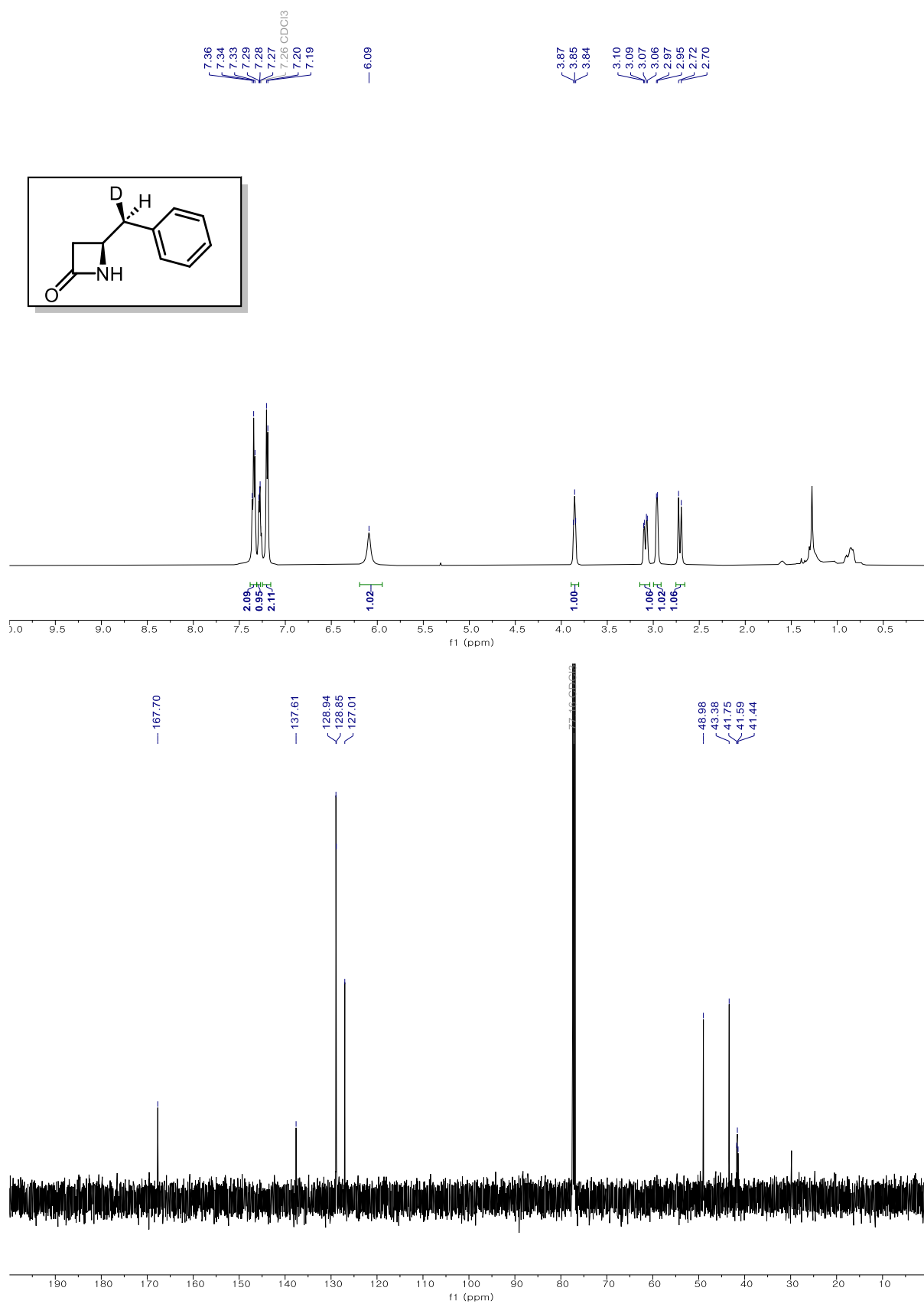


1,1,1,3,3,3-Hexafluoropropan-2-yl cinnamylcarbamate

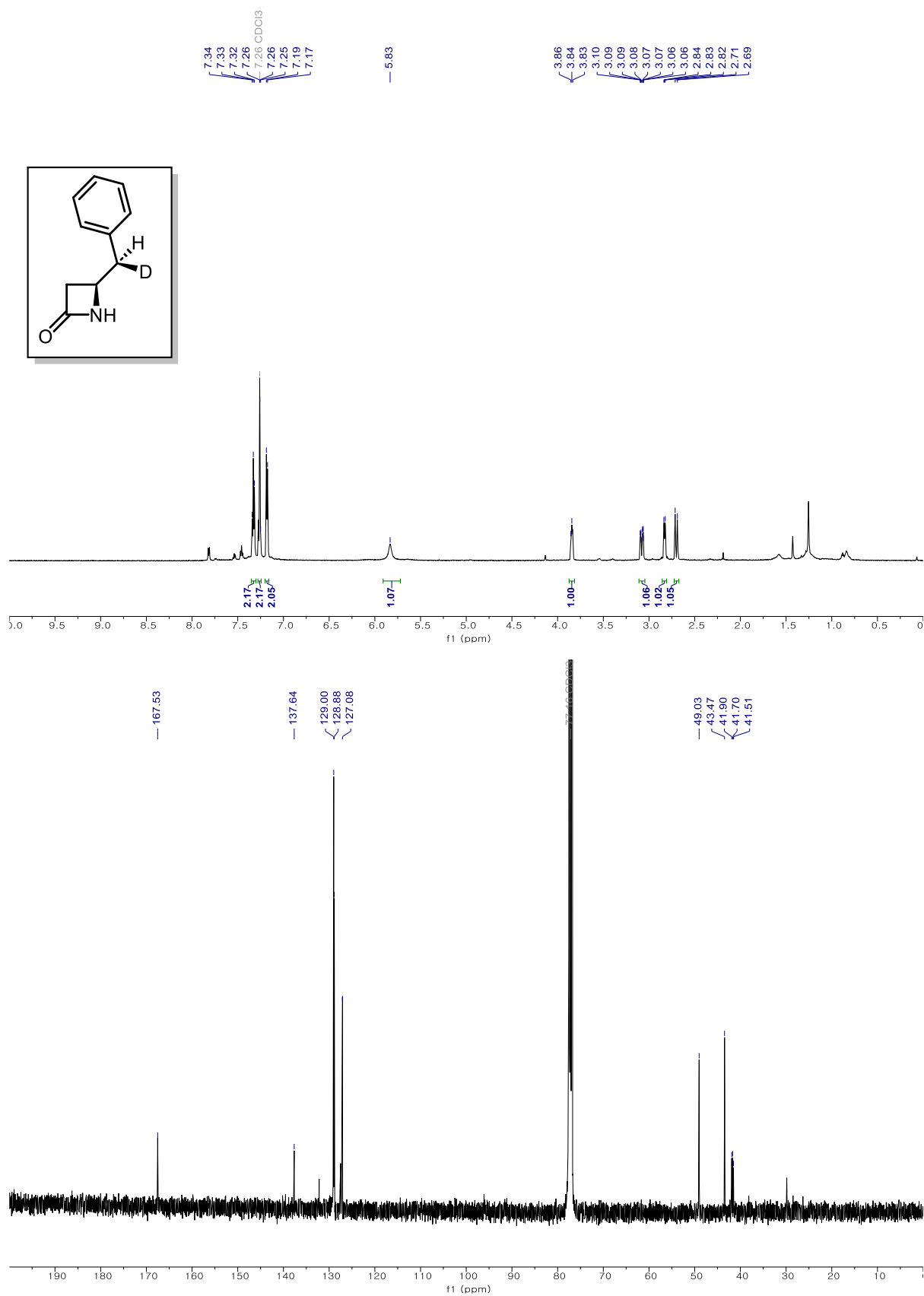




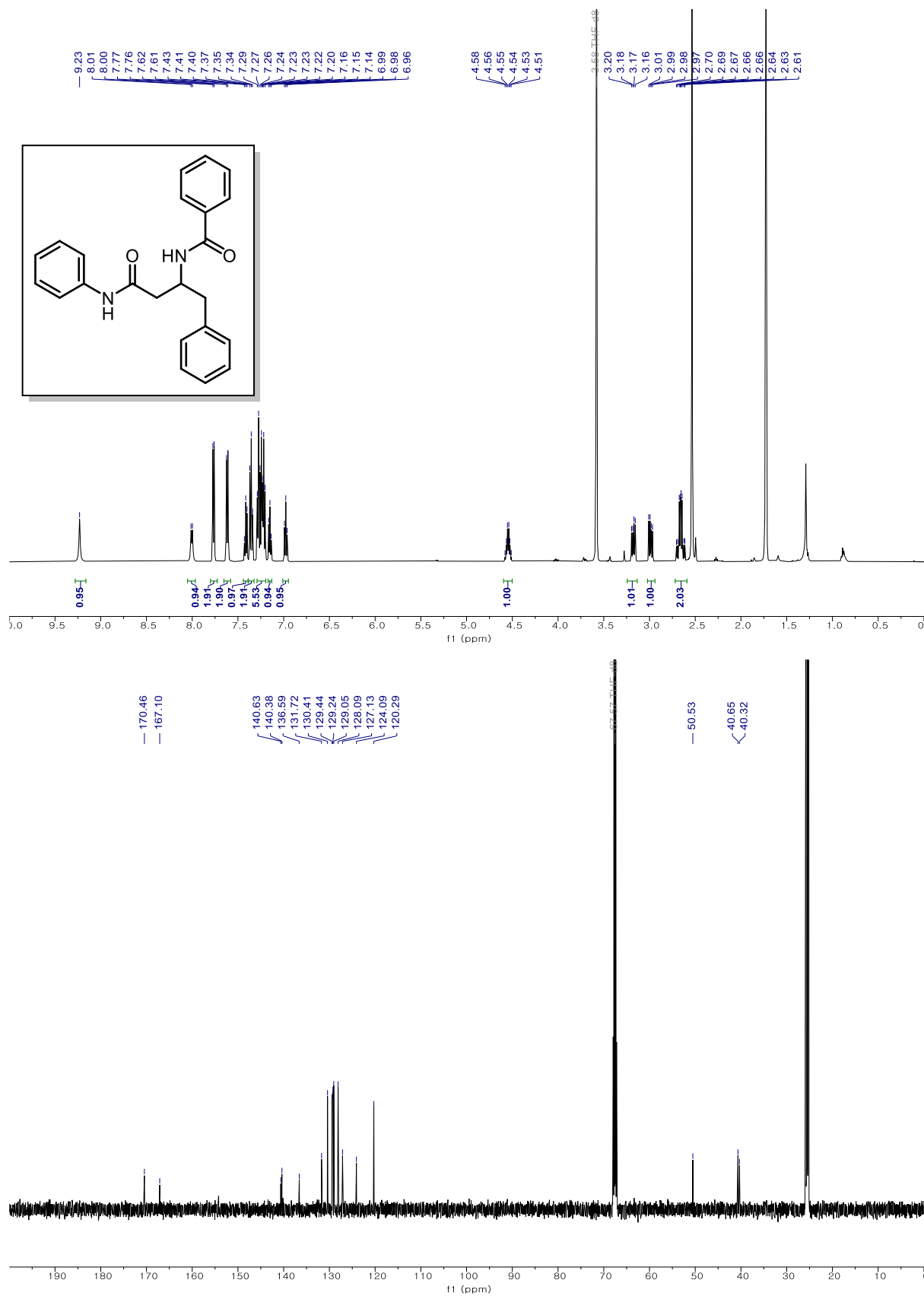
4-(Phenylmethyl-*d*)azetidin-2-one, *rac*-2-*d*1



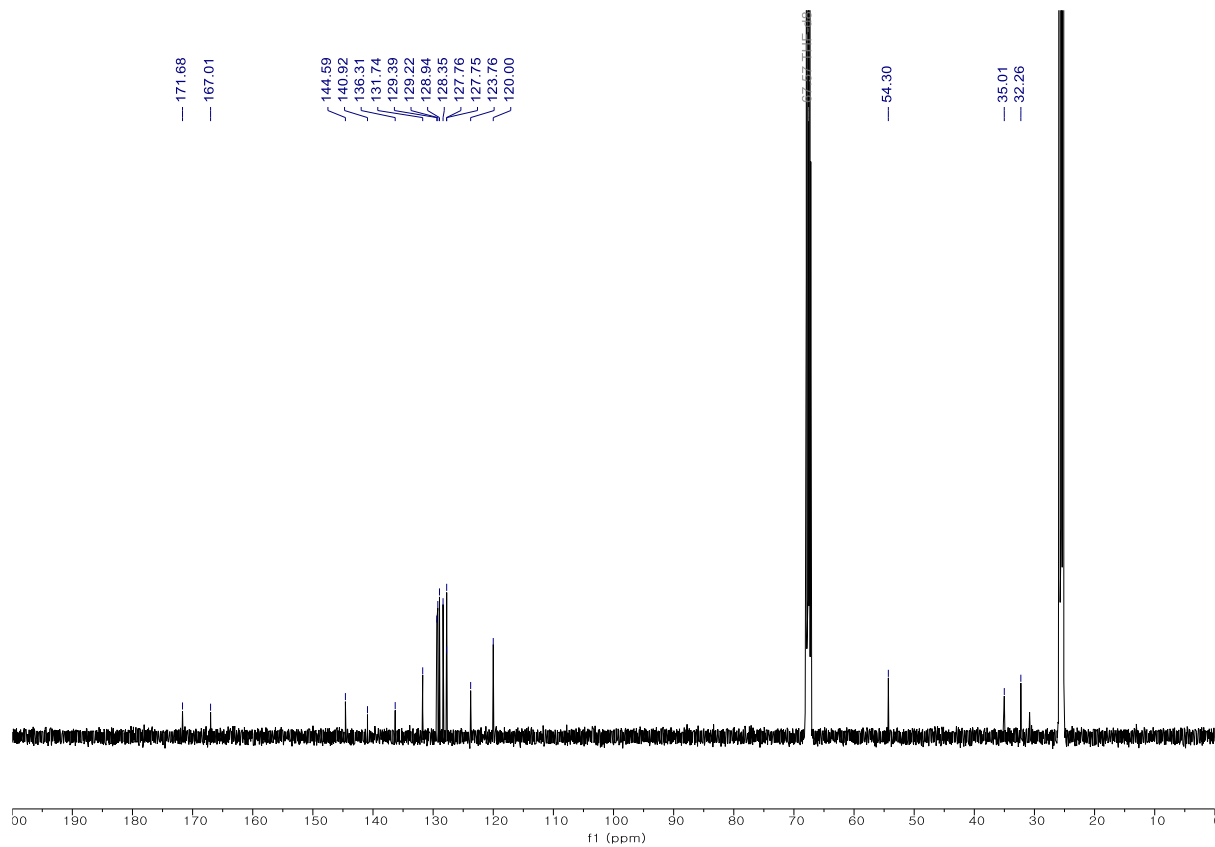
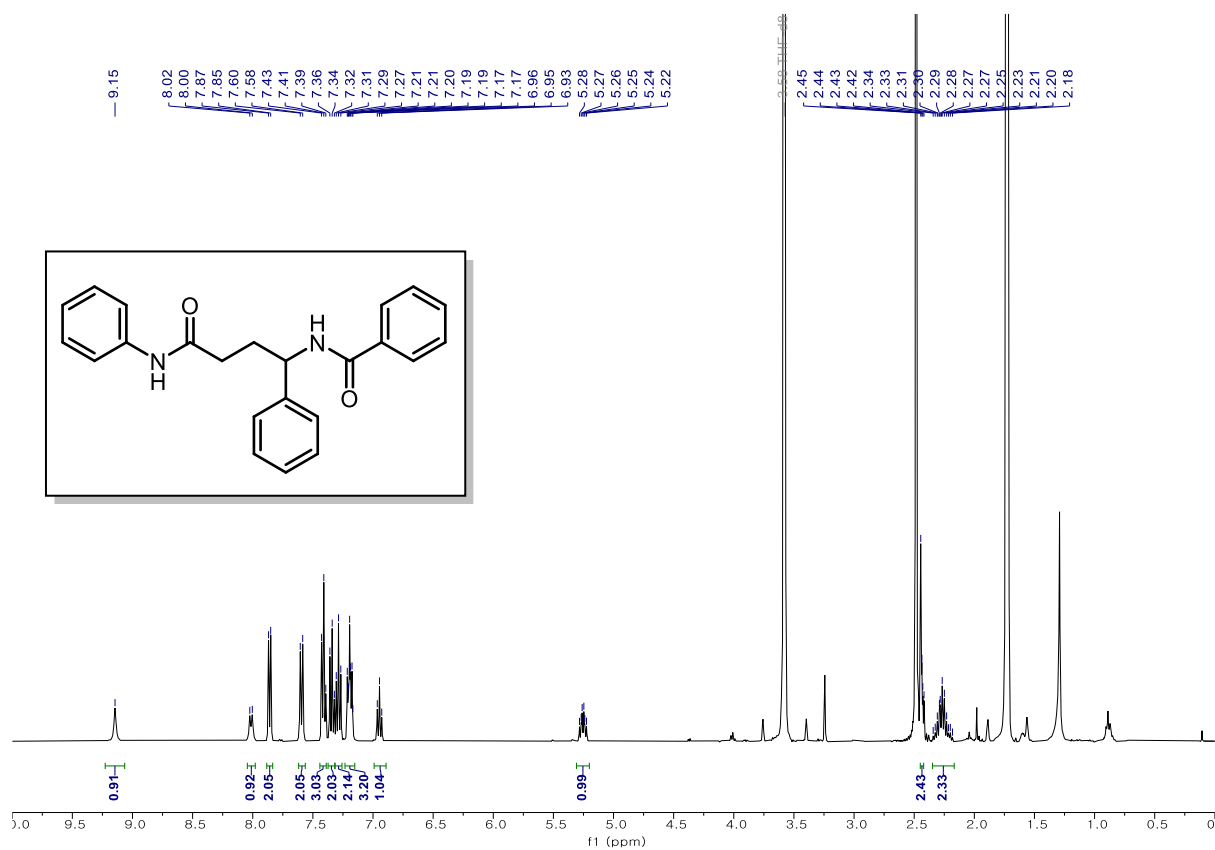
4-(Phenylmethyl-*d*)azetidin-2-one, *rac*-2-*d*2



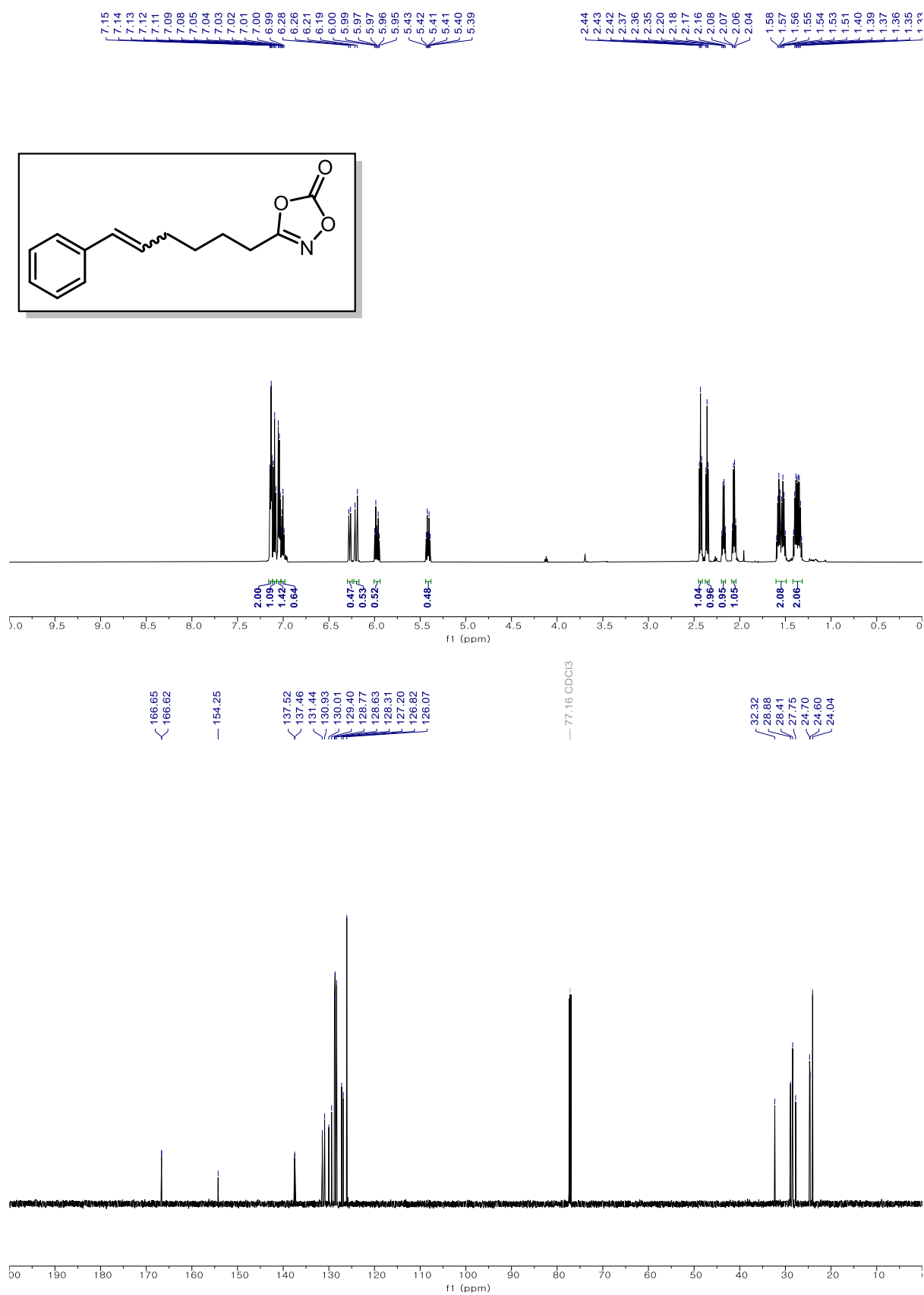
***N*-[4-Oxo-1-phenyl-4-(phenylamino)butan-2-yl]benzamide, 11**



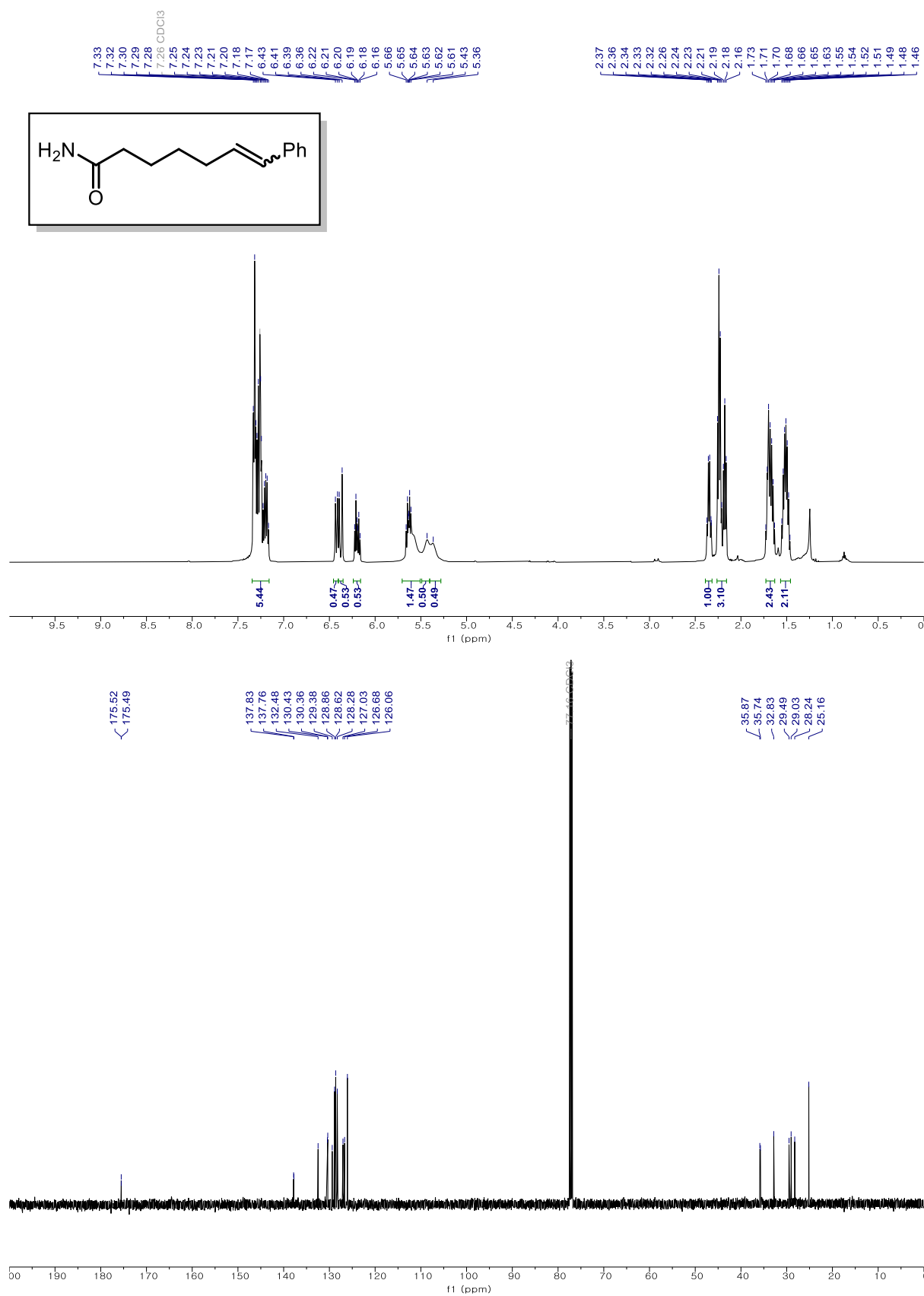
***N*-[4-Oxo-1-phenyl-4-(phenylamino)butyl]benzamide, 11'**



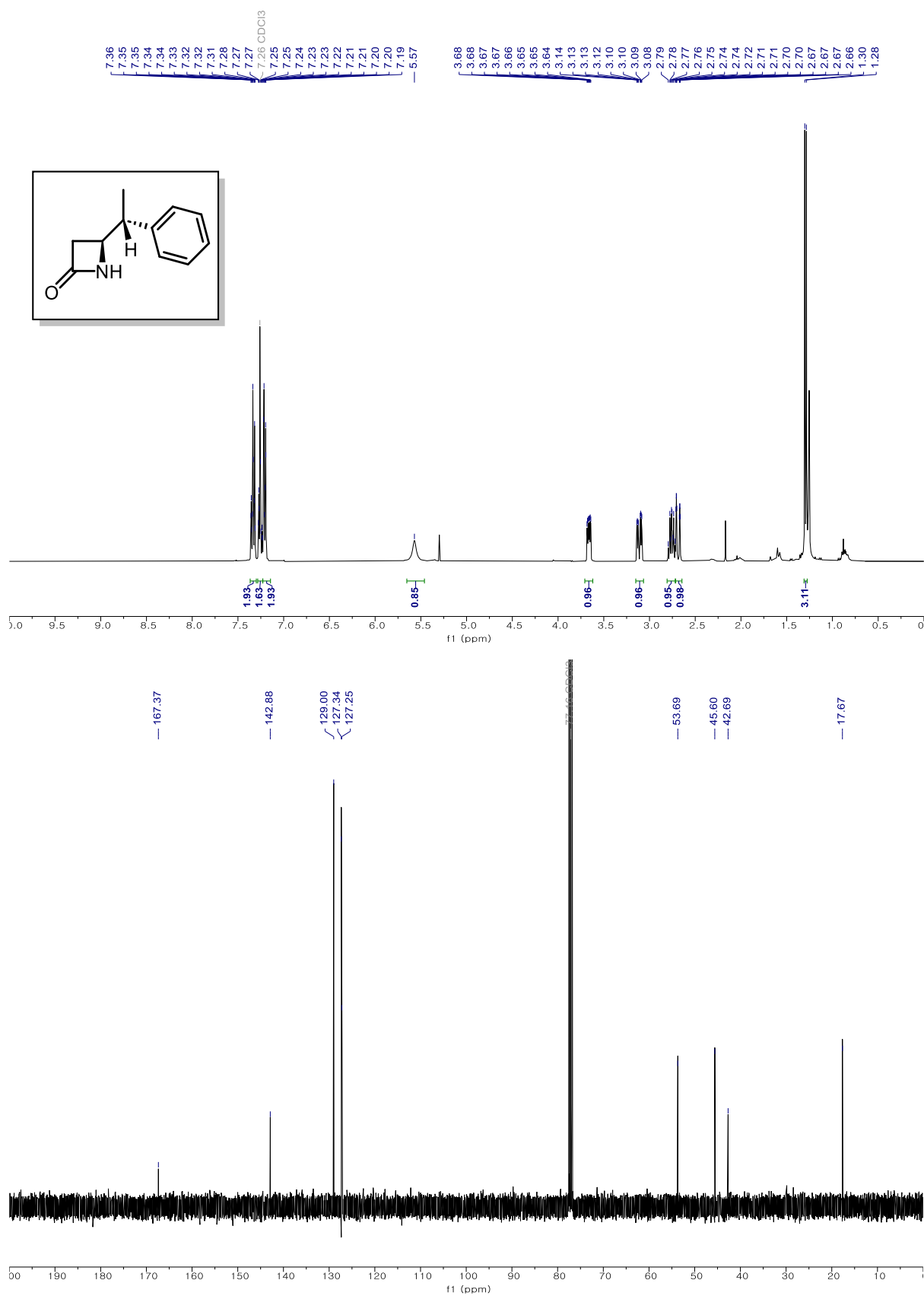
3-(6-Phenylhex-5-en-1-yl)-1,4,2-dioxazol-5-one, 12 (*E/Z* = 1.1:1 mixture)



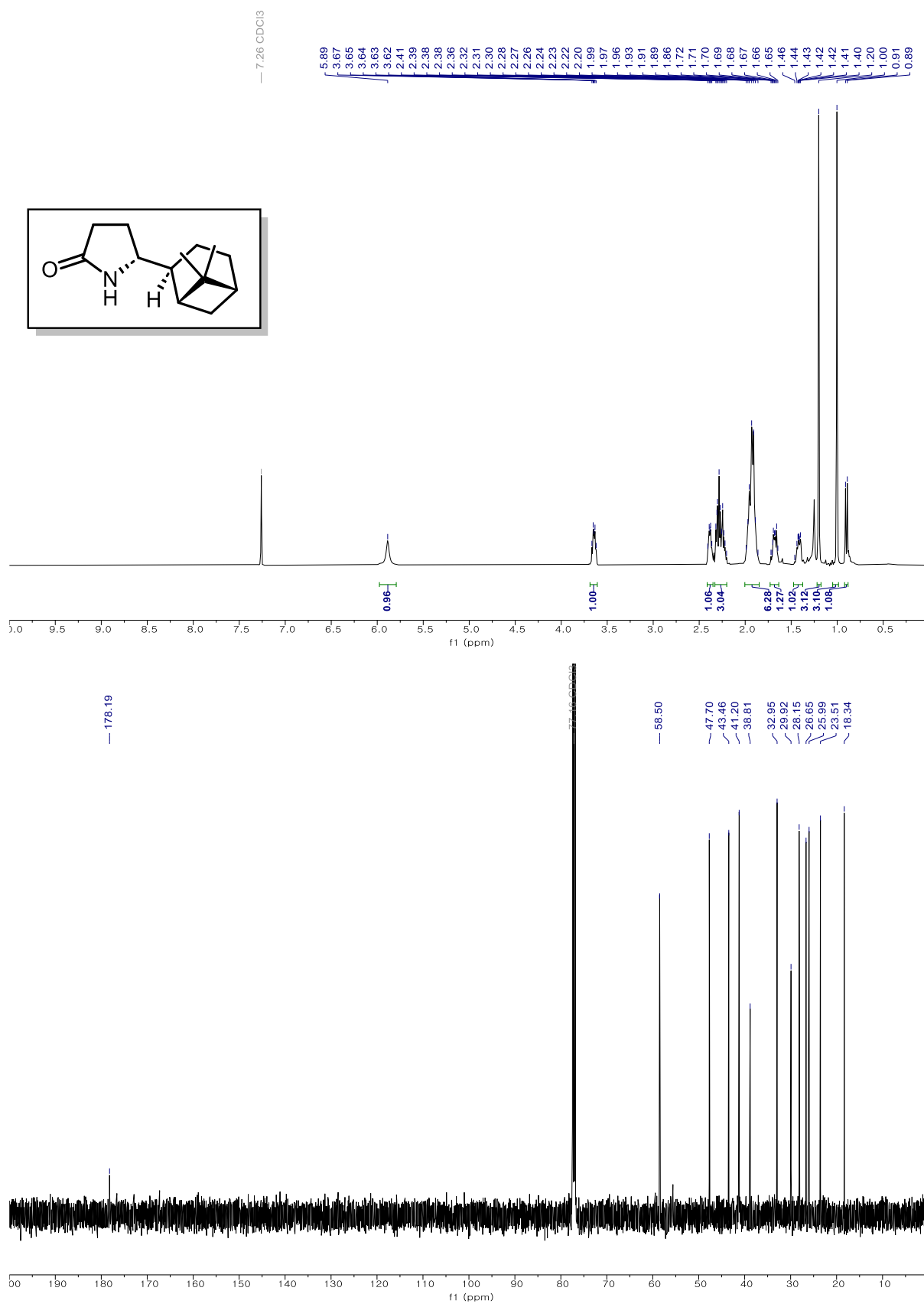
7-Phenylhept-6-enamide, **13** (*E/Z* = 1.1:1 mixture)



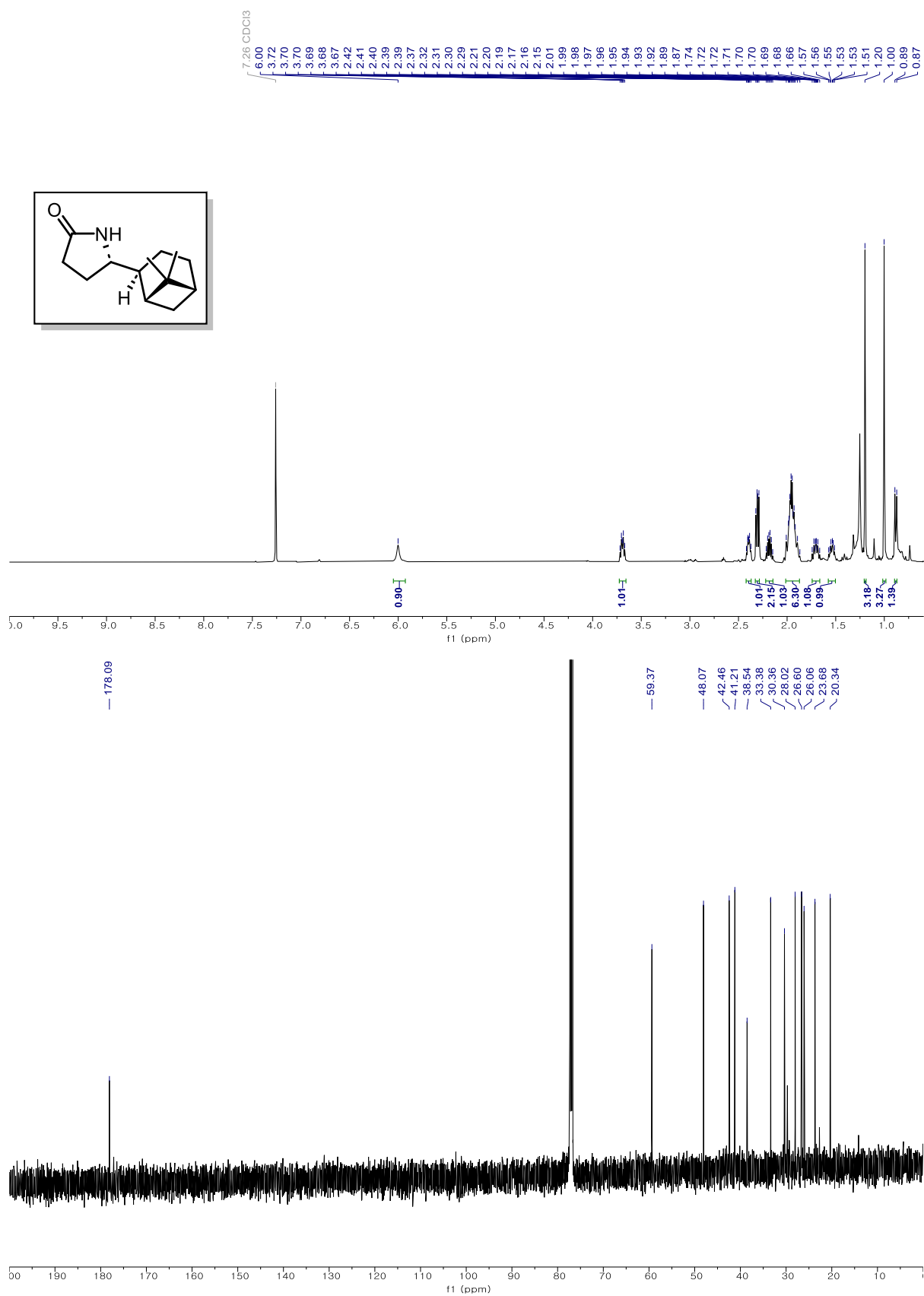
4-(1-Phenylethyl)azetidin-2-one, *rac*-15



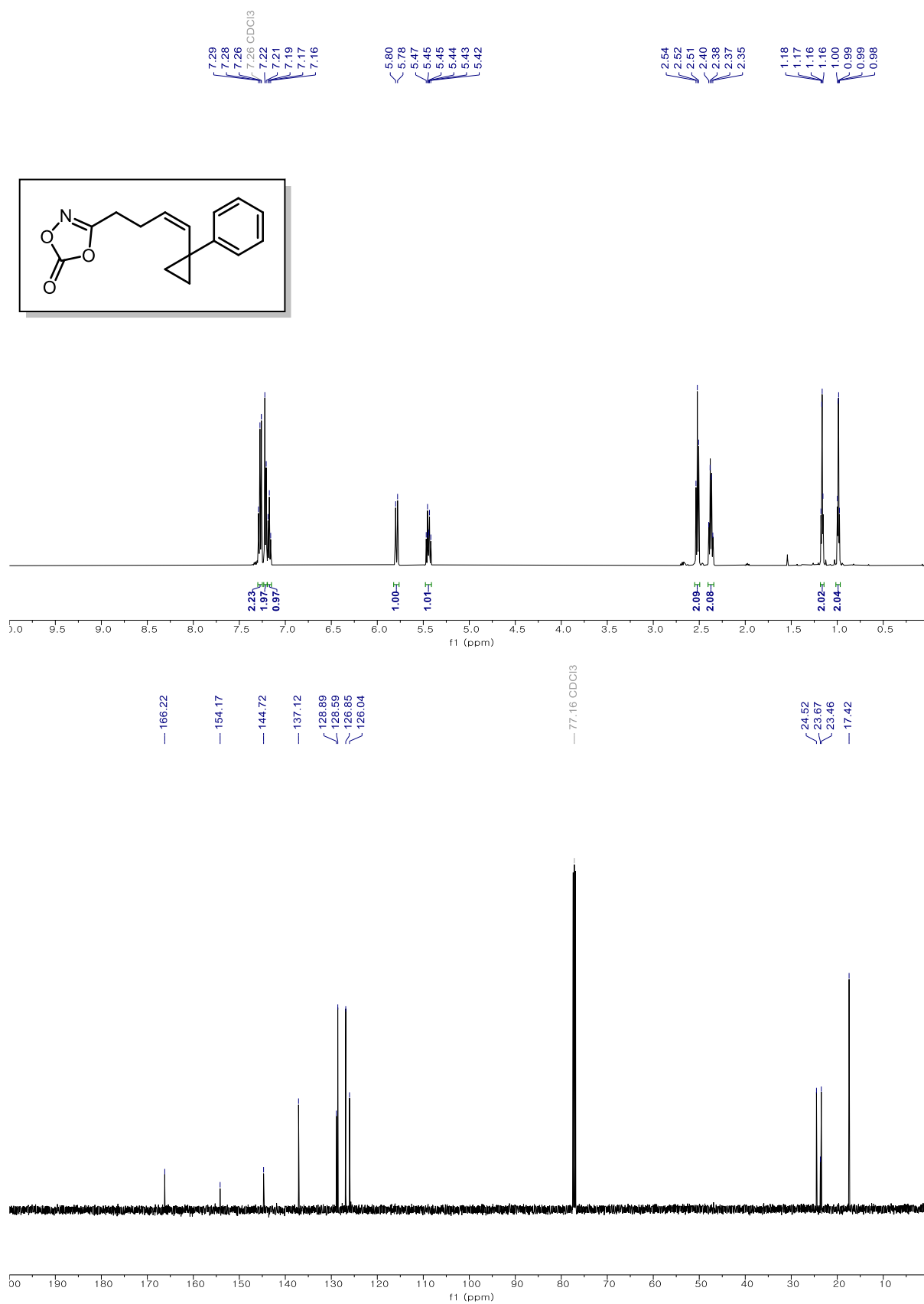
5-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)pyrrolidin-2-one, *rac*-17 (major)



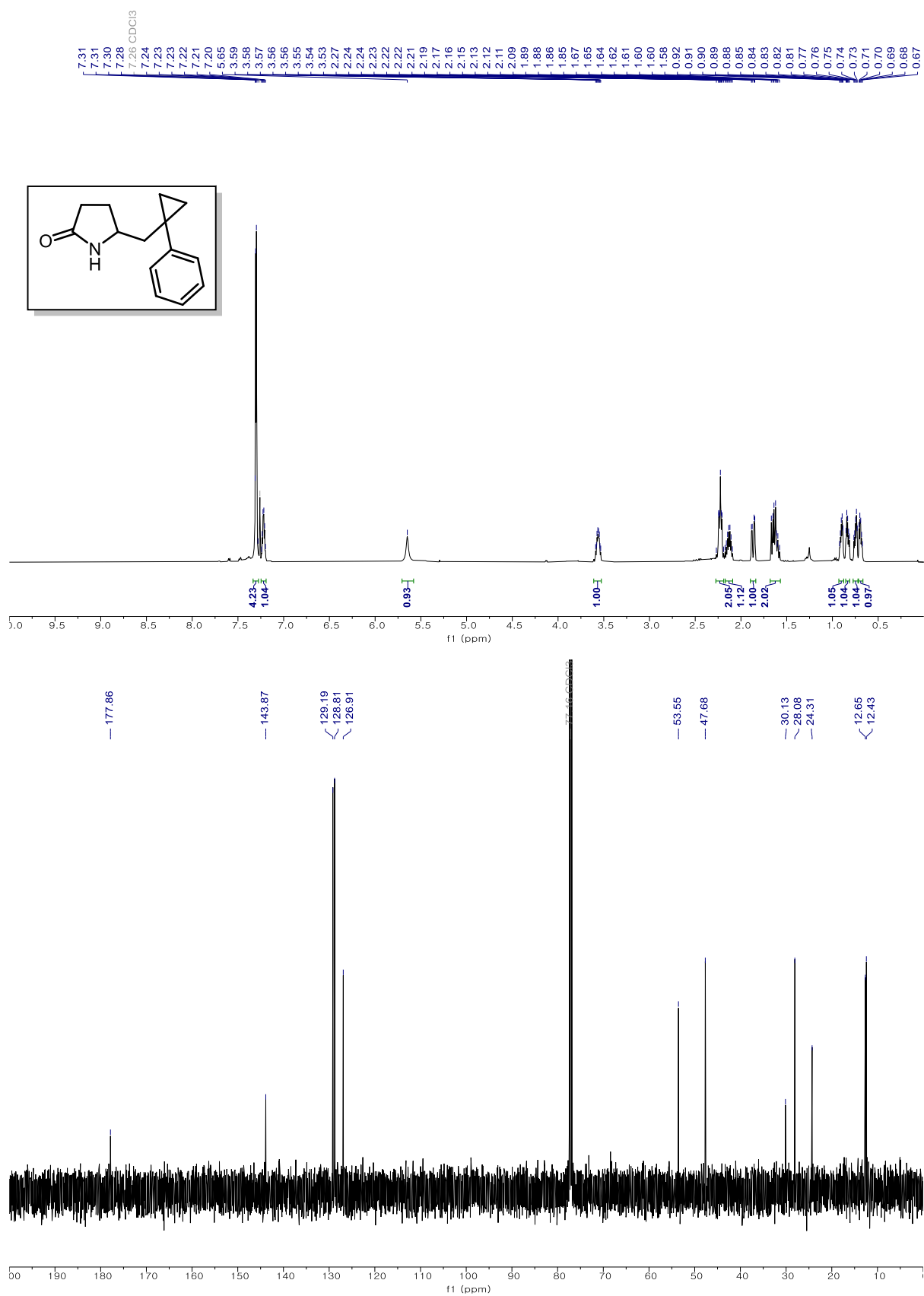
5-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)pyrrolidin-2-one, *rac*-17 (minor)



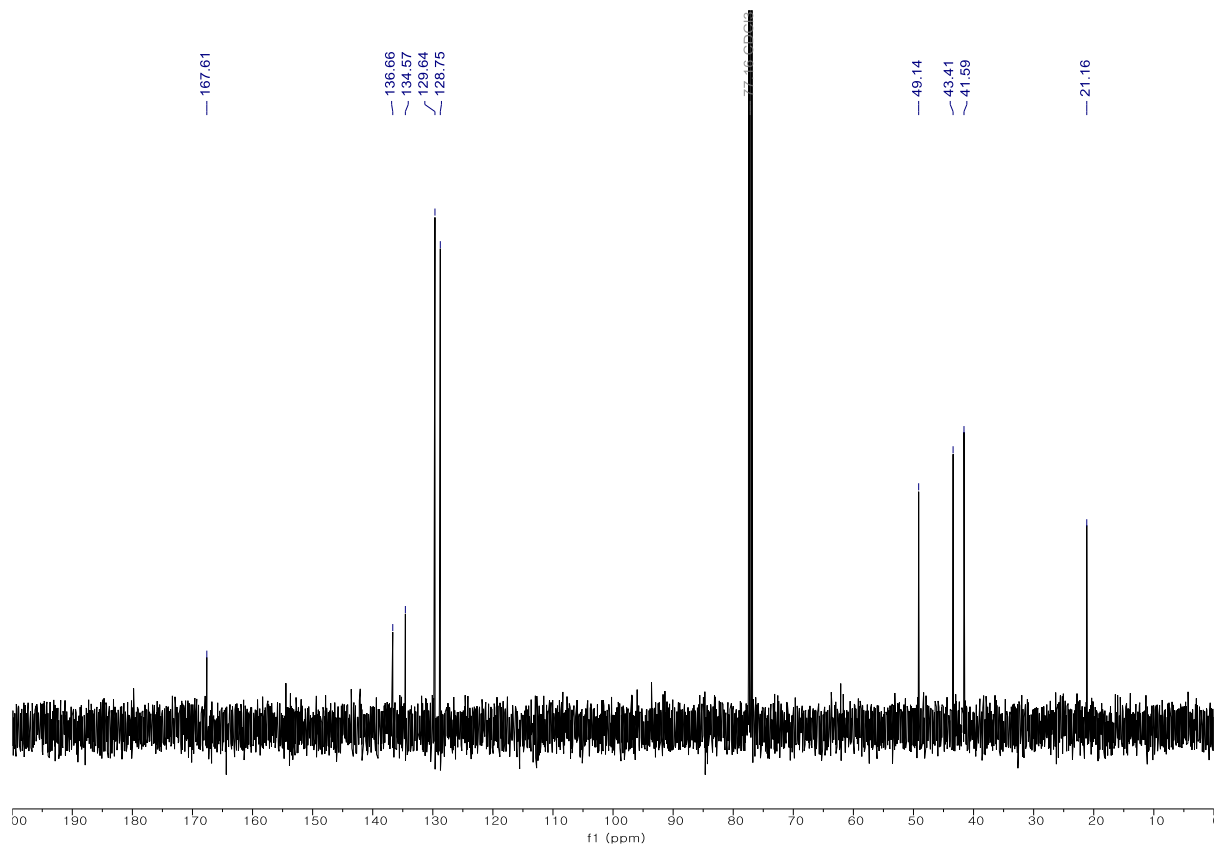
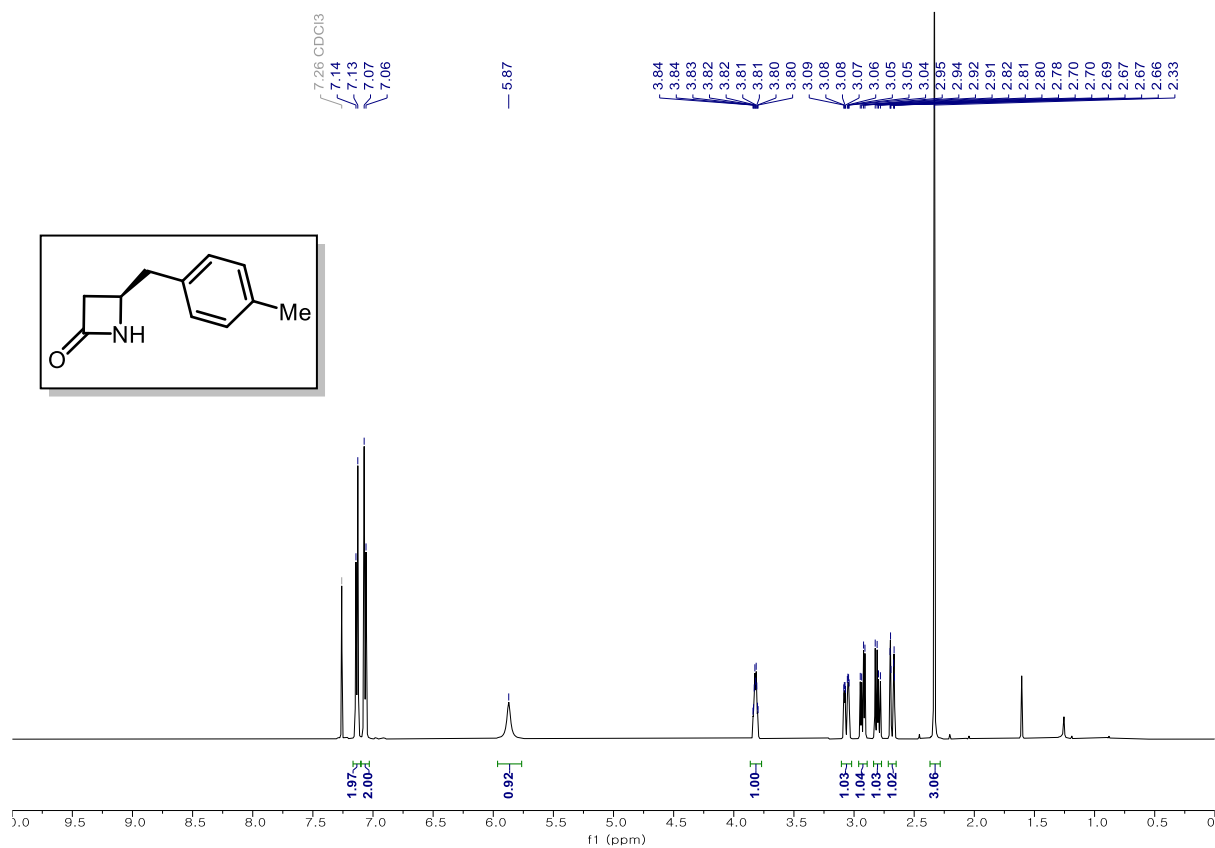
(Z)-3-[4-(1-phenylcyclopropyl)but-3-en-1-yl]-1,4,2-dioxazol-5-one, 18



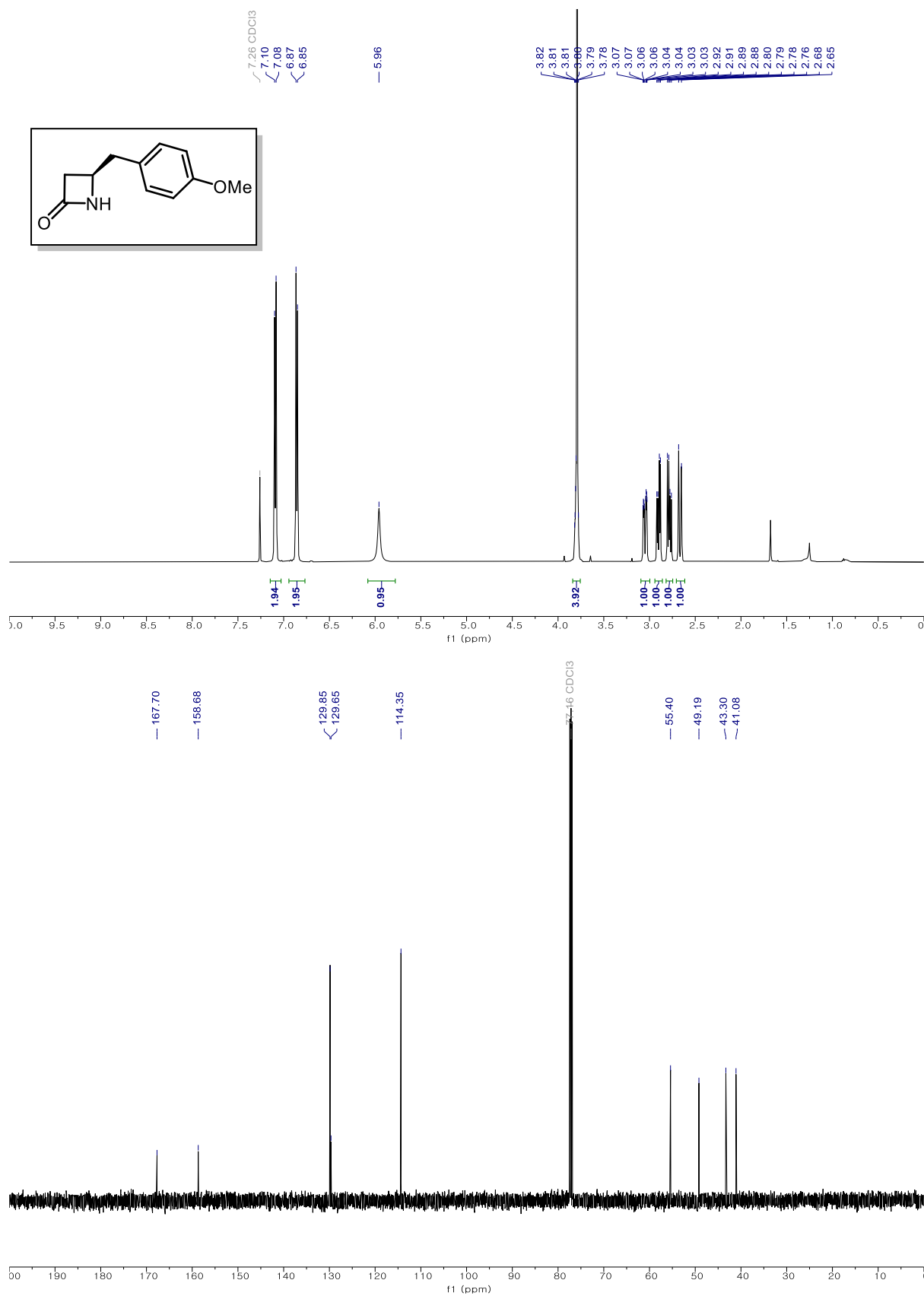
5-[(1-Phenylcyclopropyl)methyl]pyrrolidin-2-one, 19



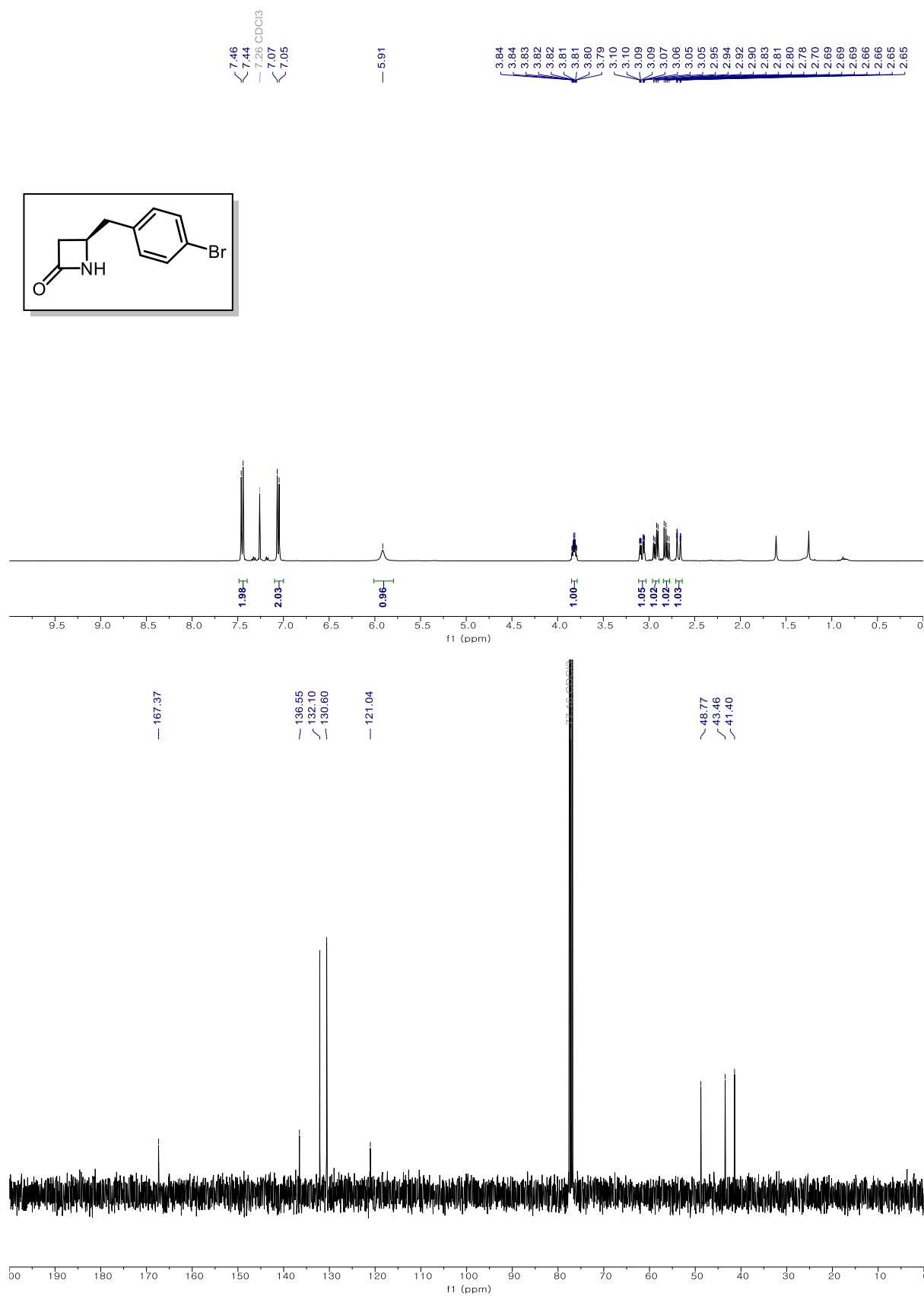
(R)-4-(4-Methylbenzyl)azetidin-2-one, (R)-20



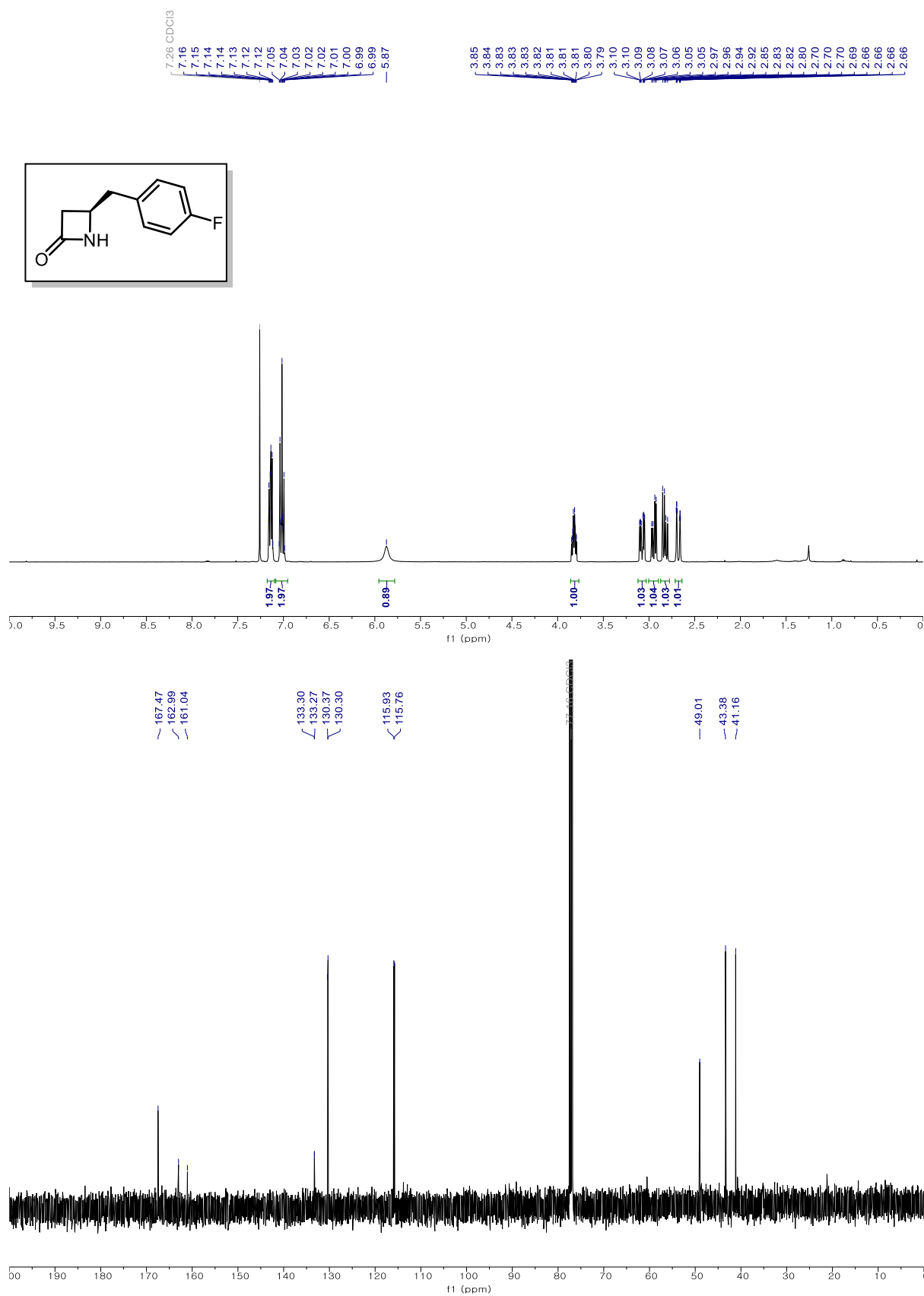
(R)-4-(4-Methoxybenzyl)azetidin-2-one, (R)-21

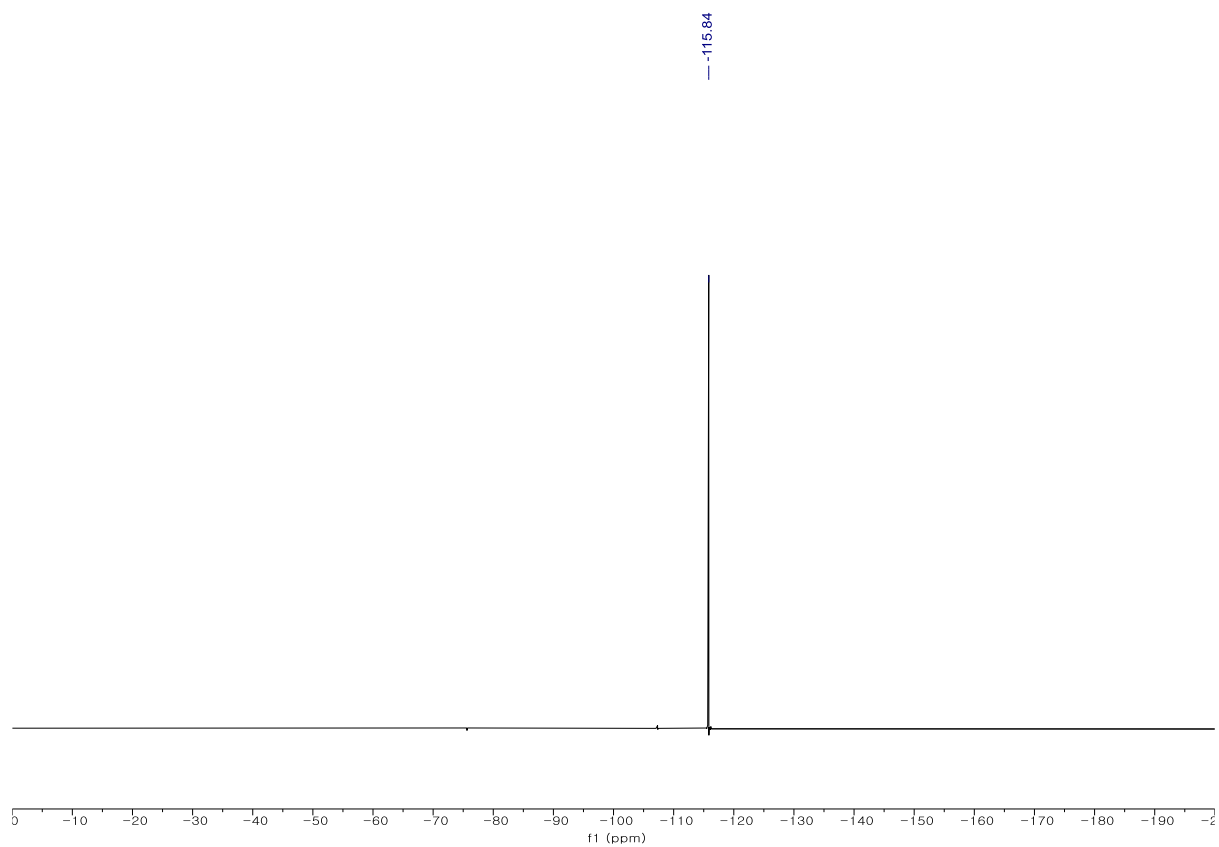


(R)-4-(4-Bromobenzyl)azetidin-2-one, (R)-22

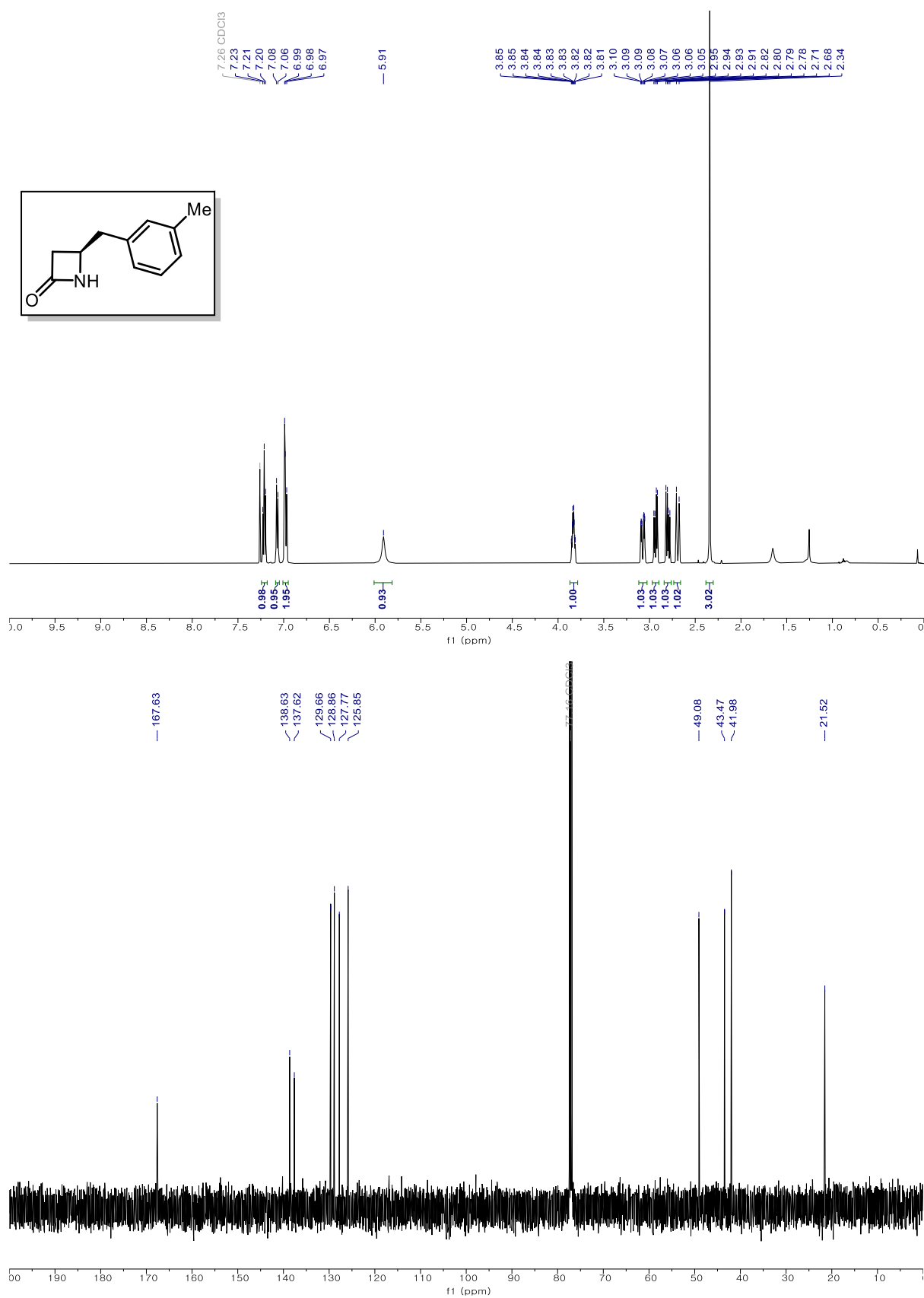


(R)-4-(4-Fluorobenzyl)azetidin-2-one, (R)-23

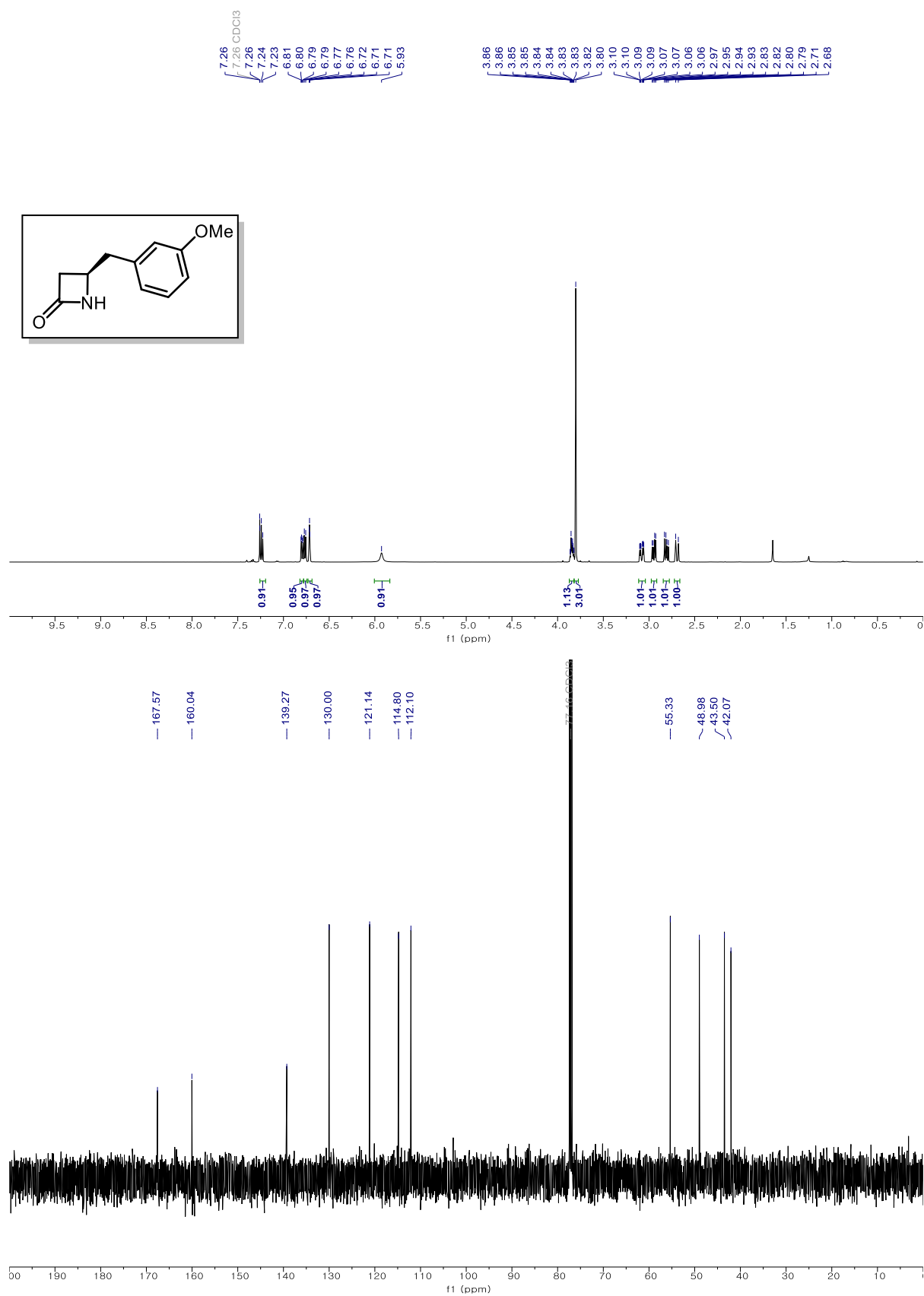




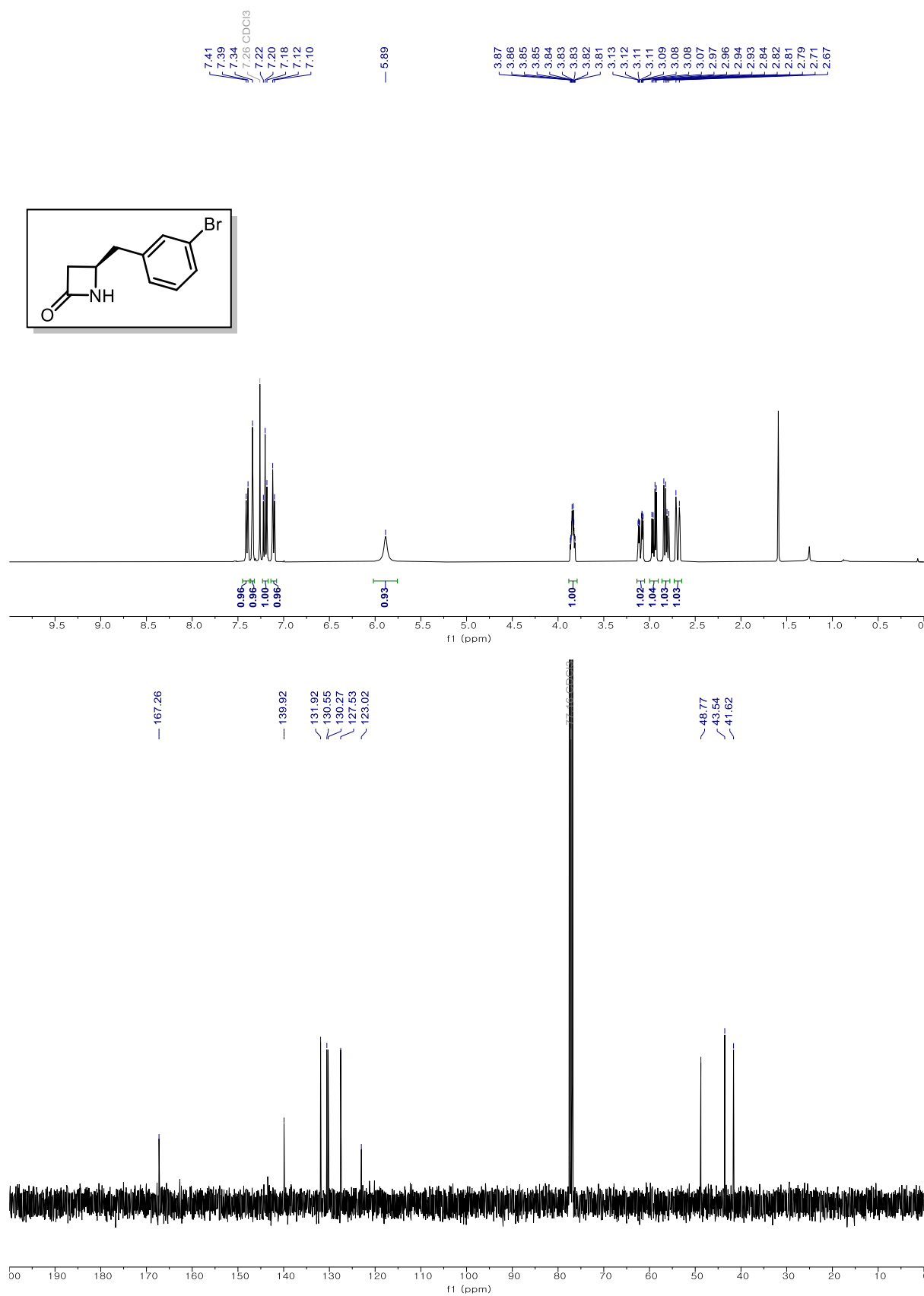
(R)-4-(3-Methylbenzyl)azetidin-2-one, (R)-24



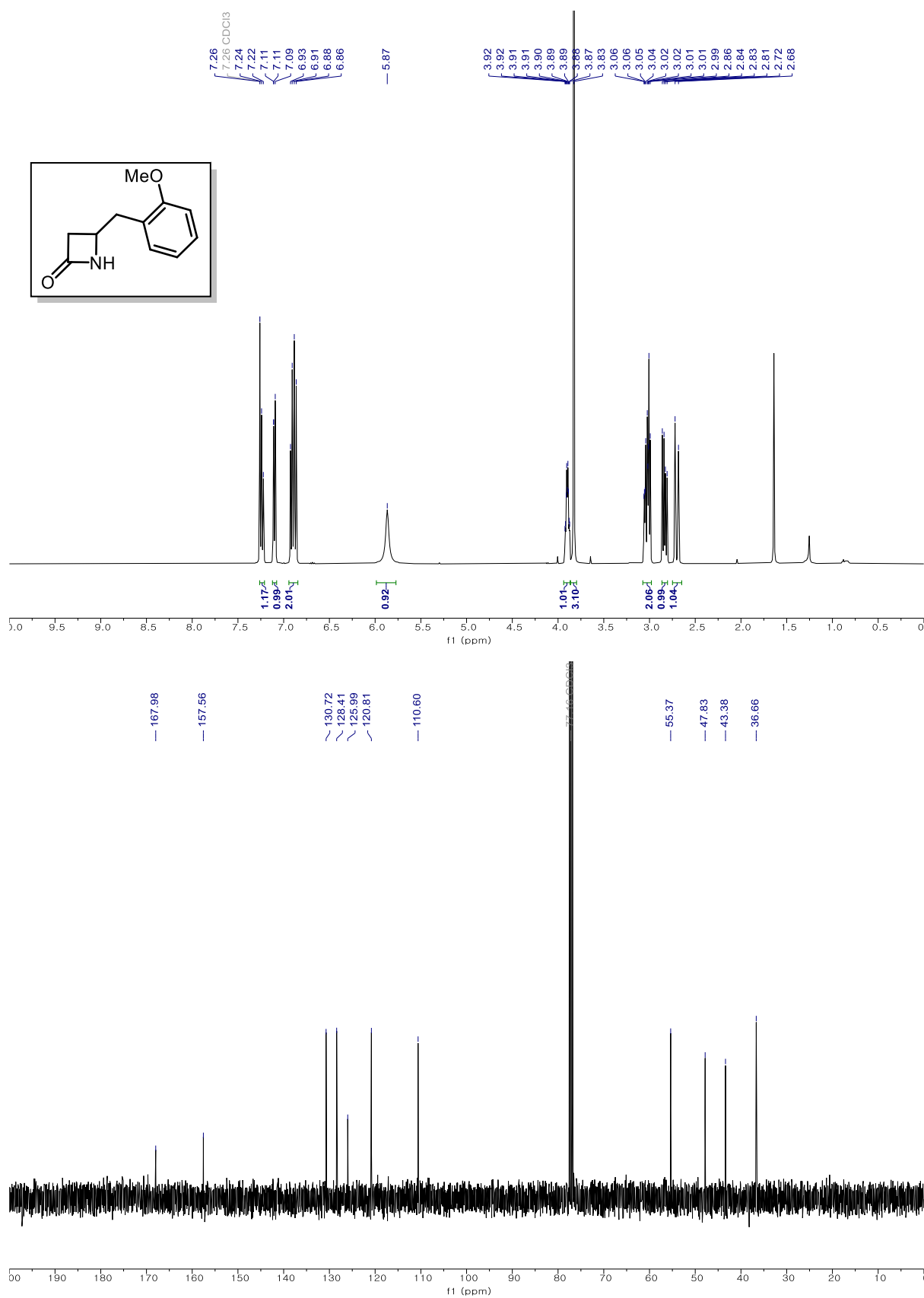
(R)-4-(3-Methoxybenzyl)azetidin-2-one, (R)-25



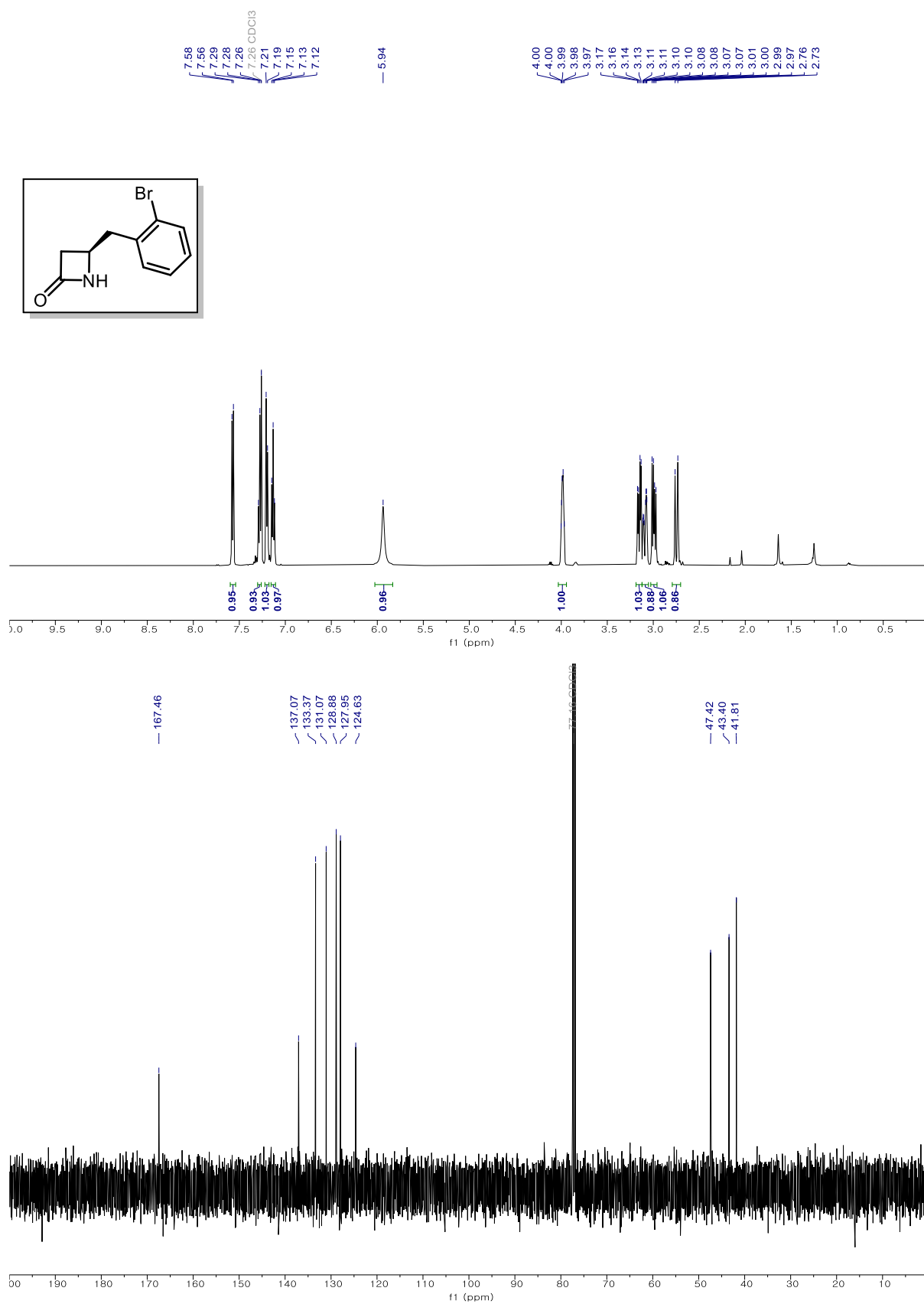
(R)-4-(3-Bromobenzyl)azetidin-2-one, (R)-26



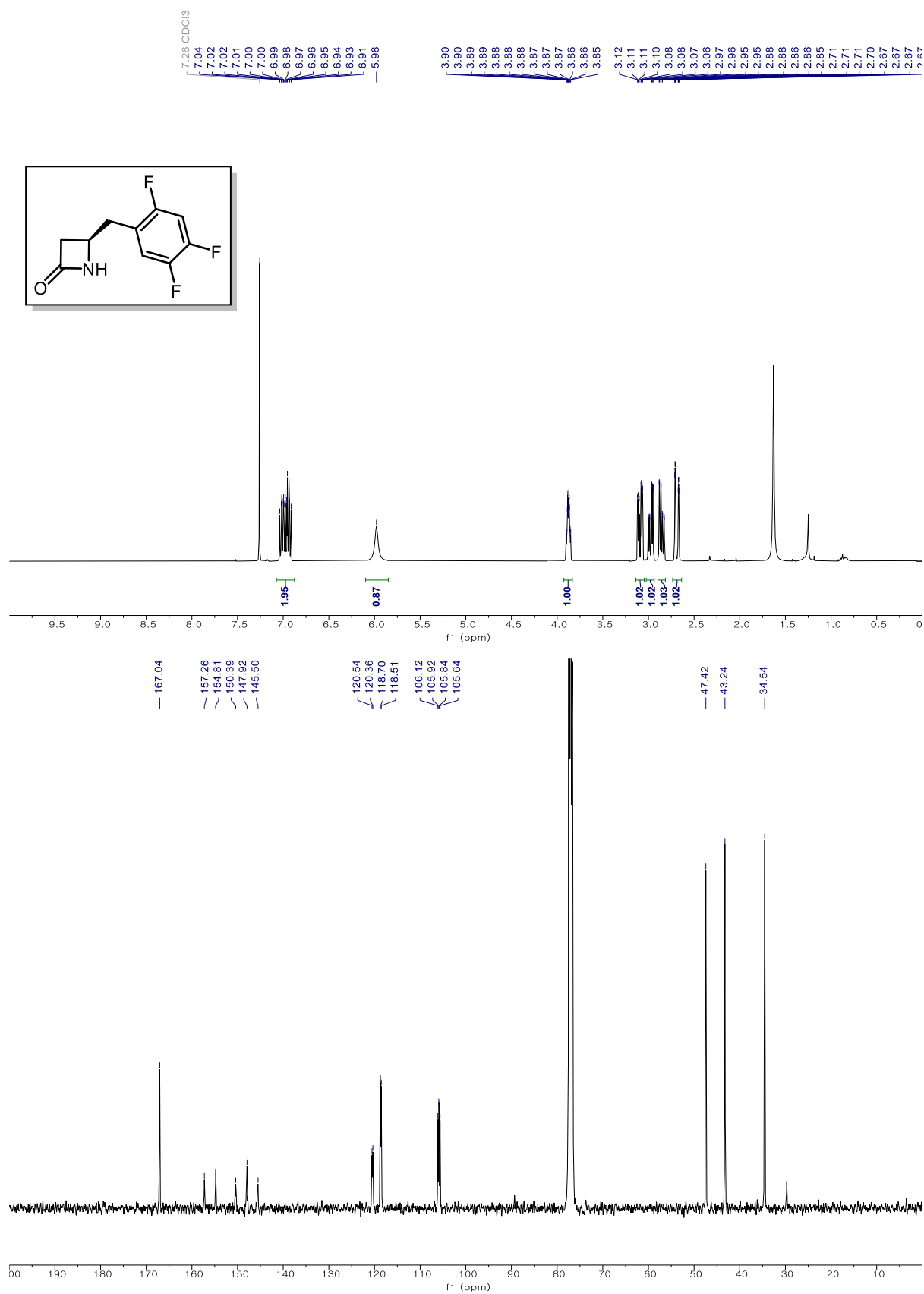
4-(2-Methoxybenzyl)azetidin-2-one, 27

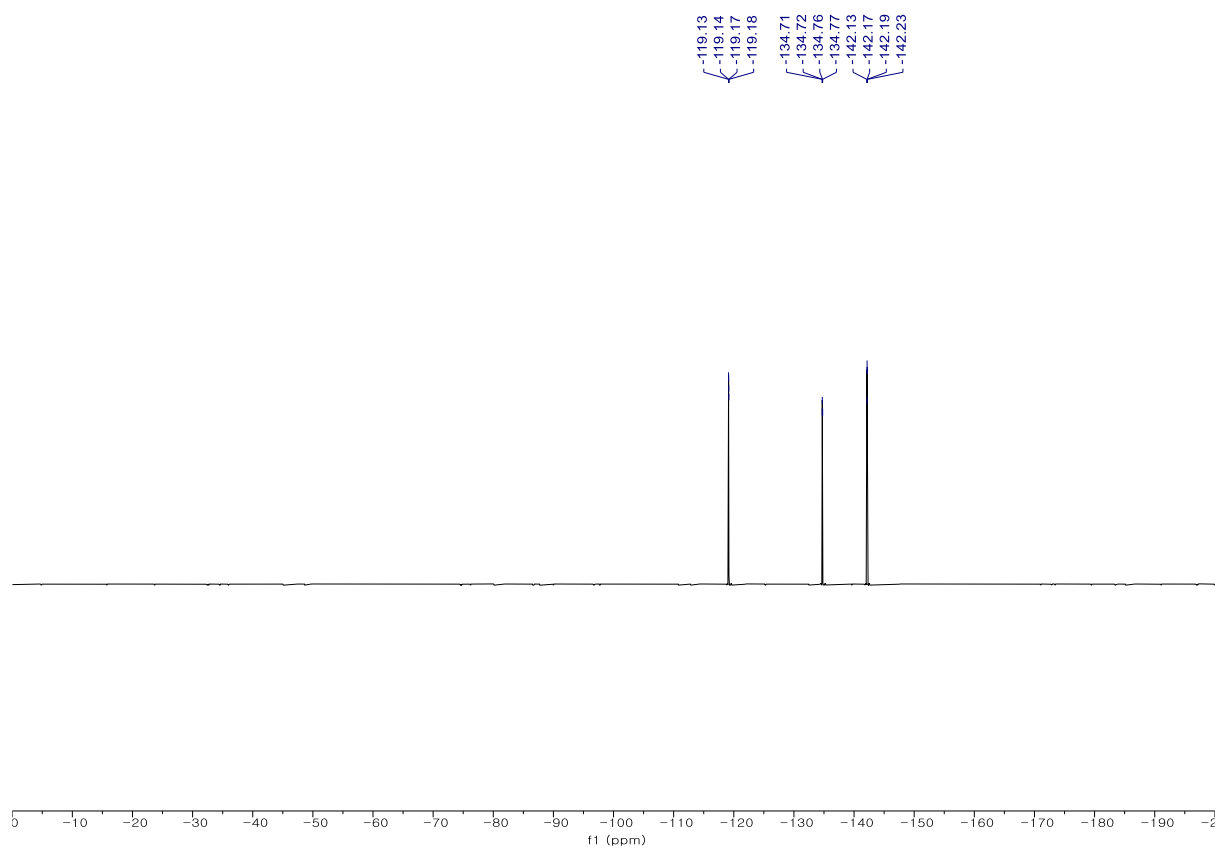


(R)-4-(2-Bromobenzyl)azetidin-2-one, (R)-28

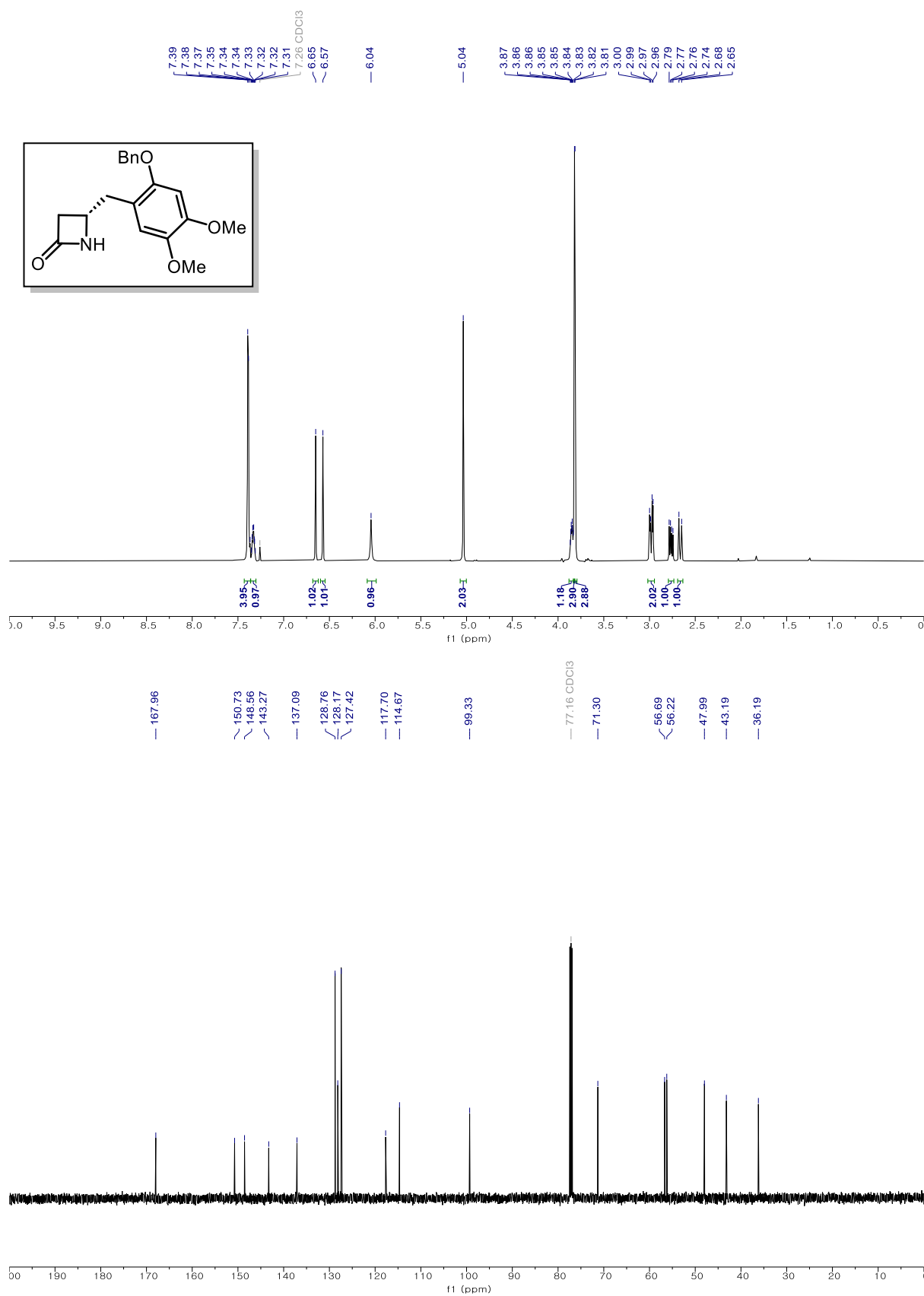


(R)-4-(2,4,5-Trifluorobenzyl)azetidin-2-one, (R)-29

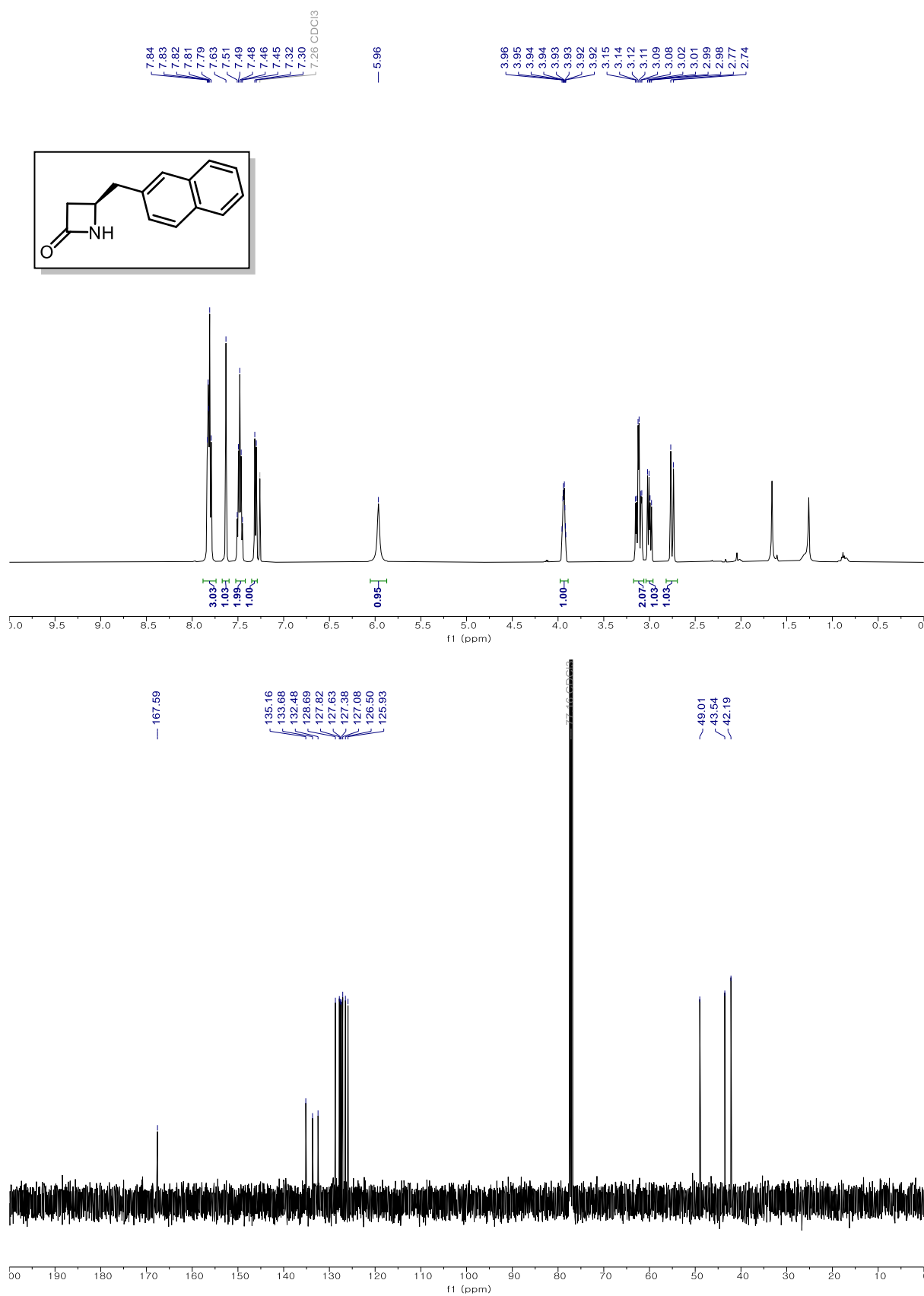




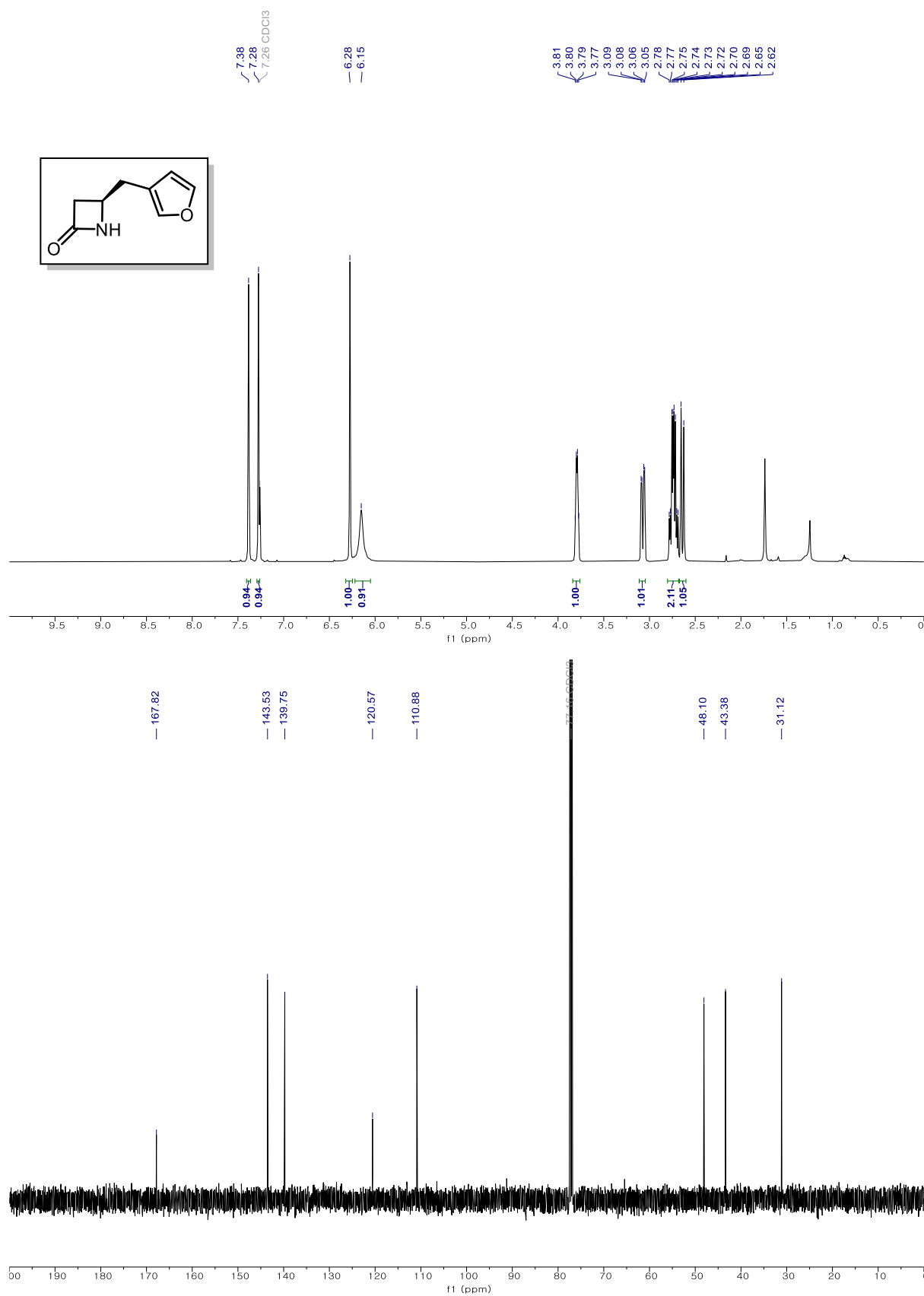
(S)-4-[2-(Benzyloxy)-4,5-dimethoxybenzyl]azetidin-2-one, (S)-30



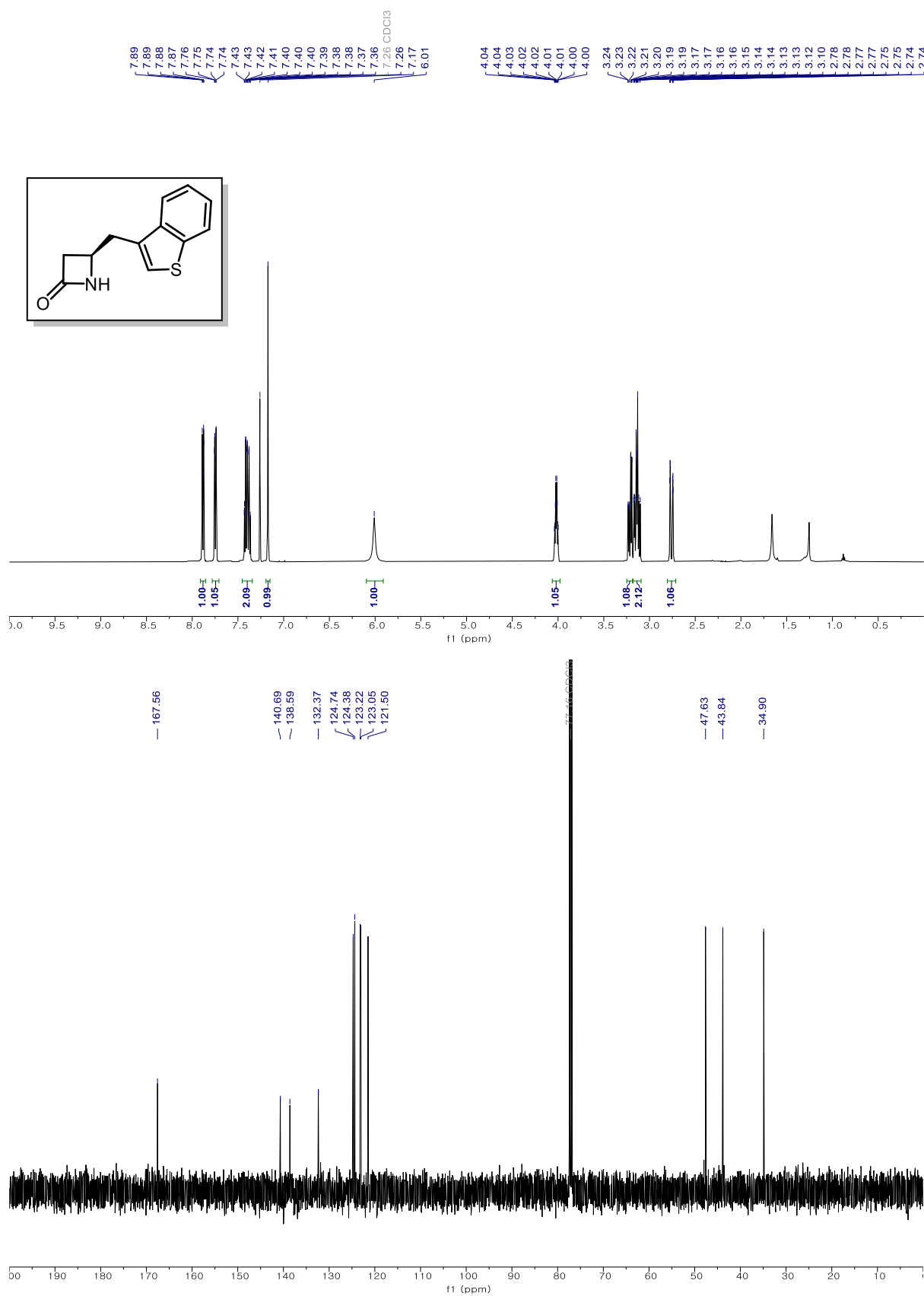
(R)-4-(Naphthalen-2-ylmethyl)azetidin-2-one, (R)-31



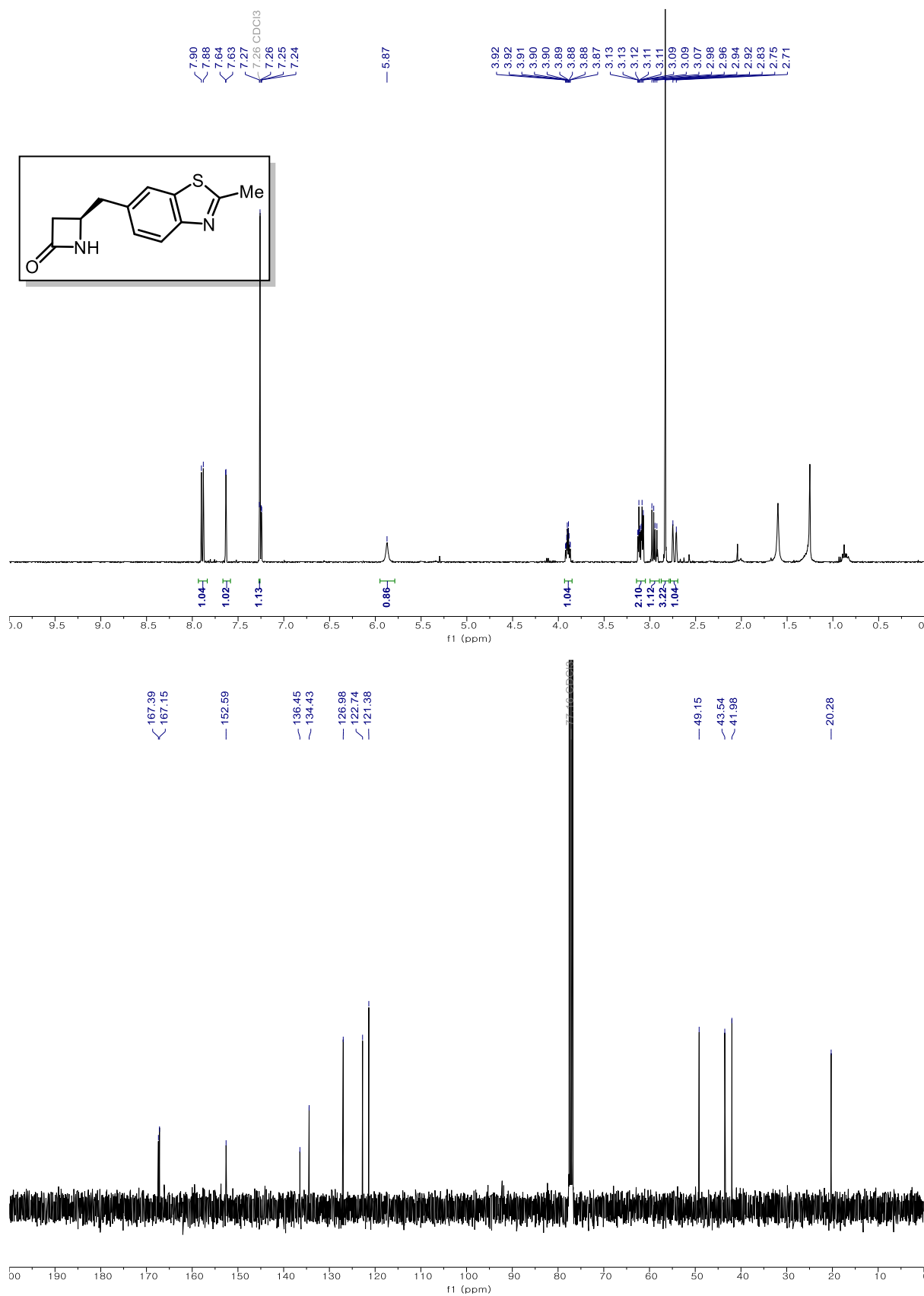
(R)-4-(Furan-3-ylmethyl)azetidin-2-one, (R)-32



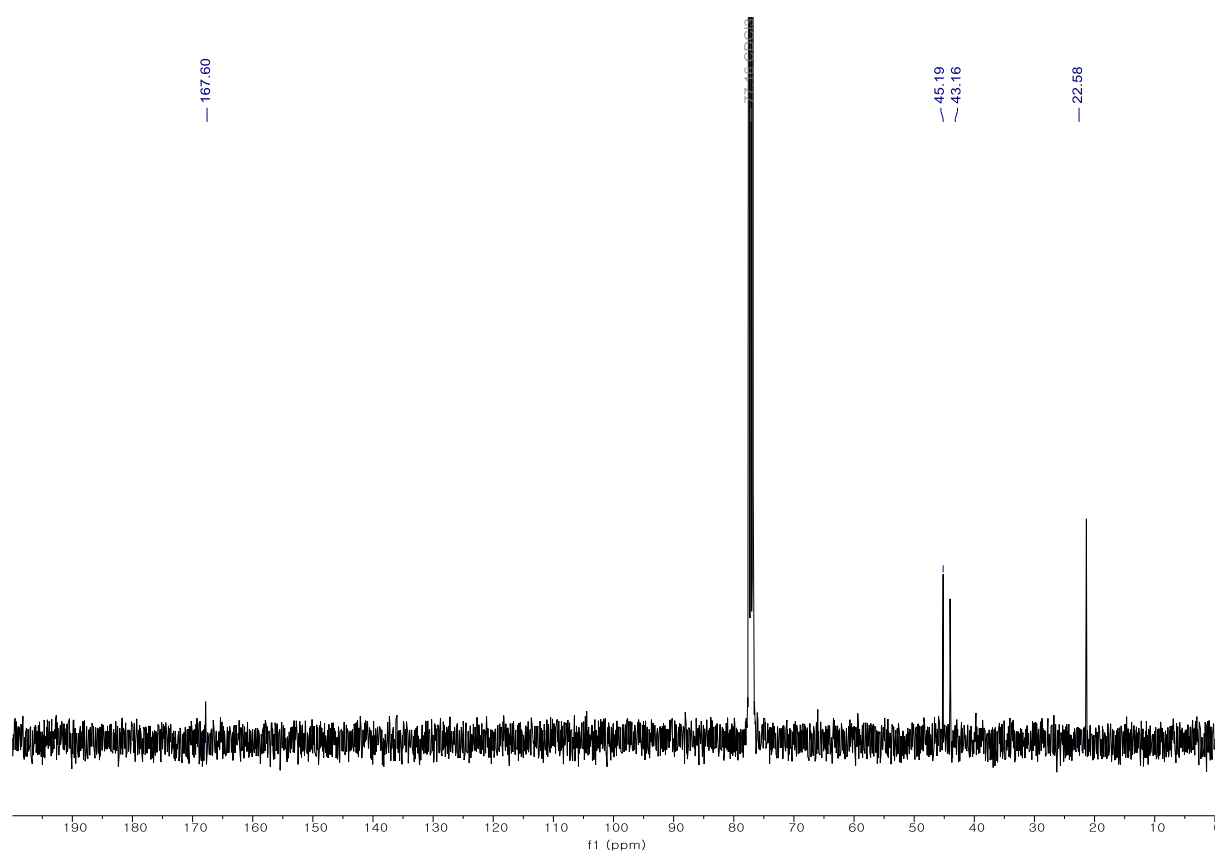
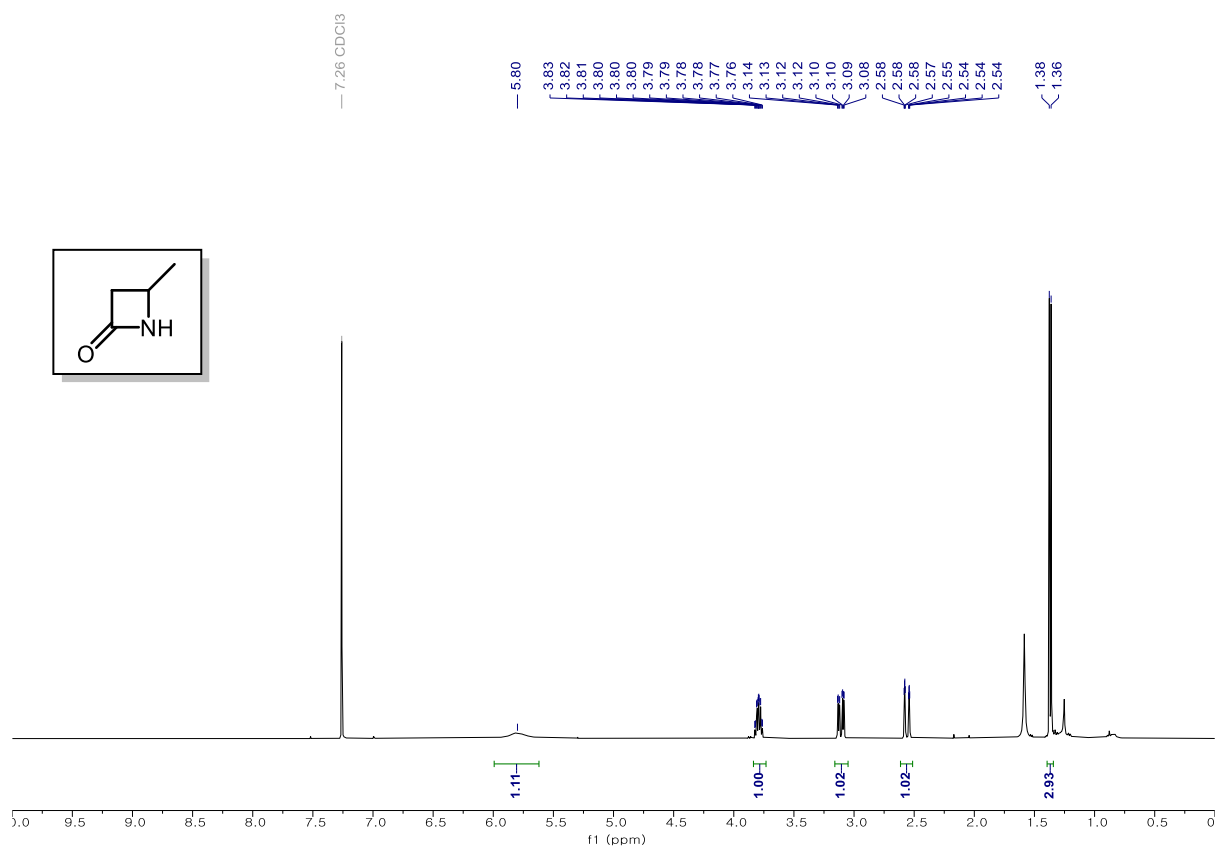
(R)-4-(Benzo[b]thiophen-3-ylmethyl)azetidin-2-one, (R)-33



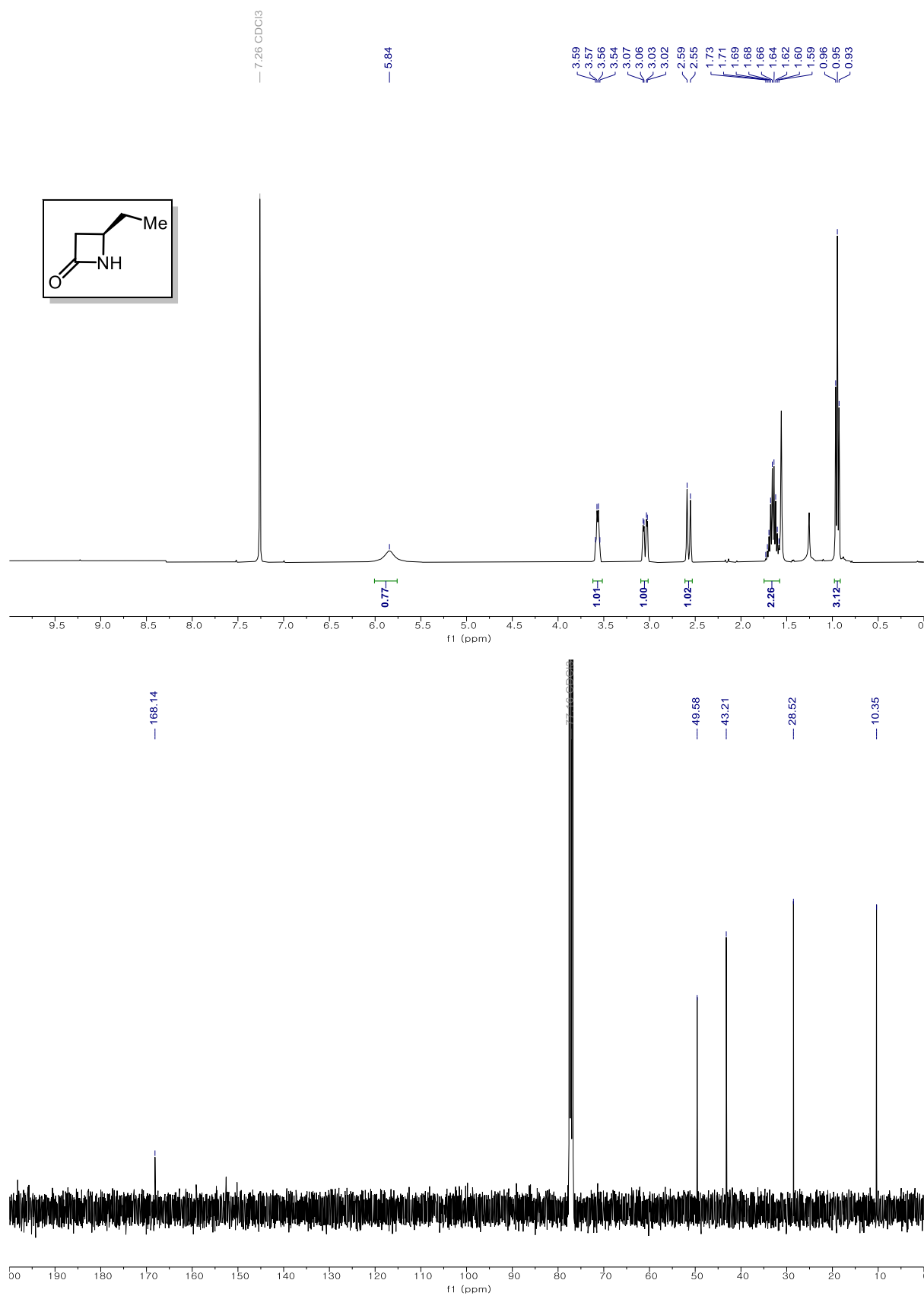
(R)-4-[(2-Methylbenzo[d]thiazol-6-yl)methyl]azetidin-2-one, (R)-34



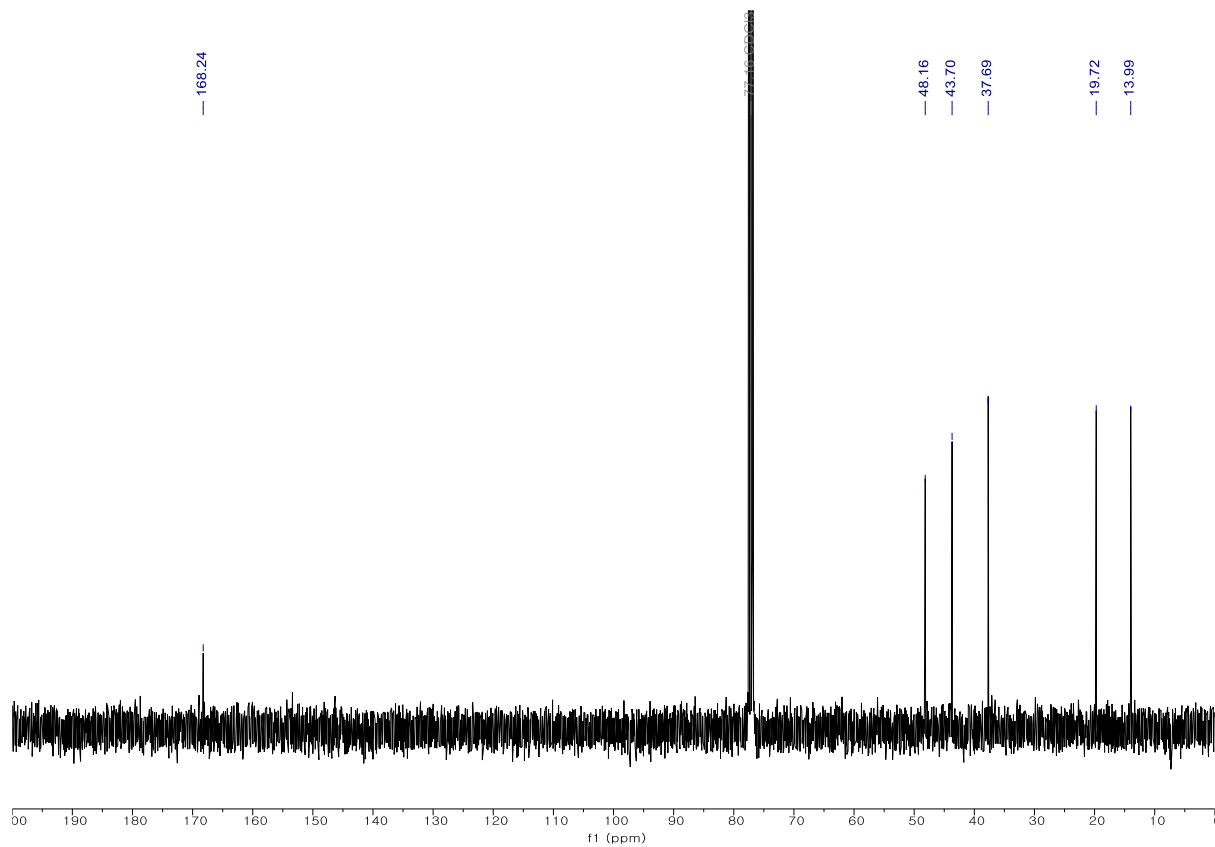
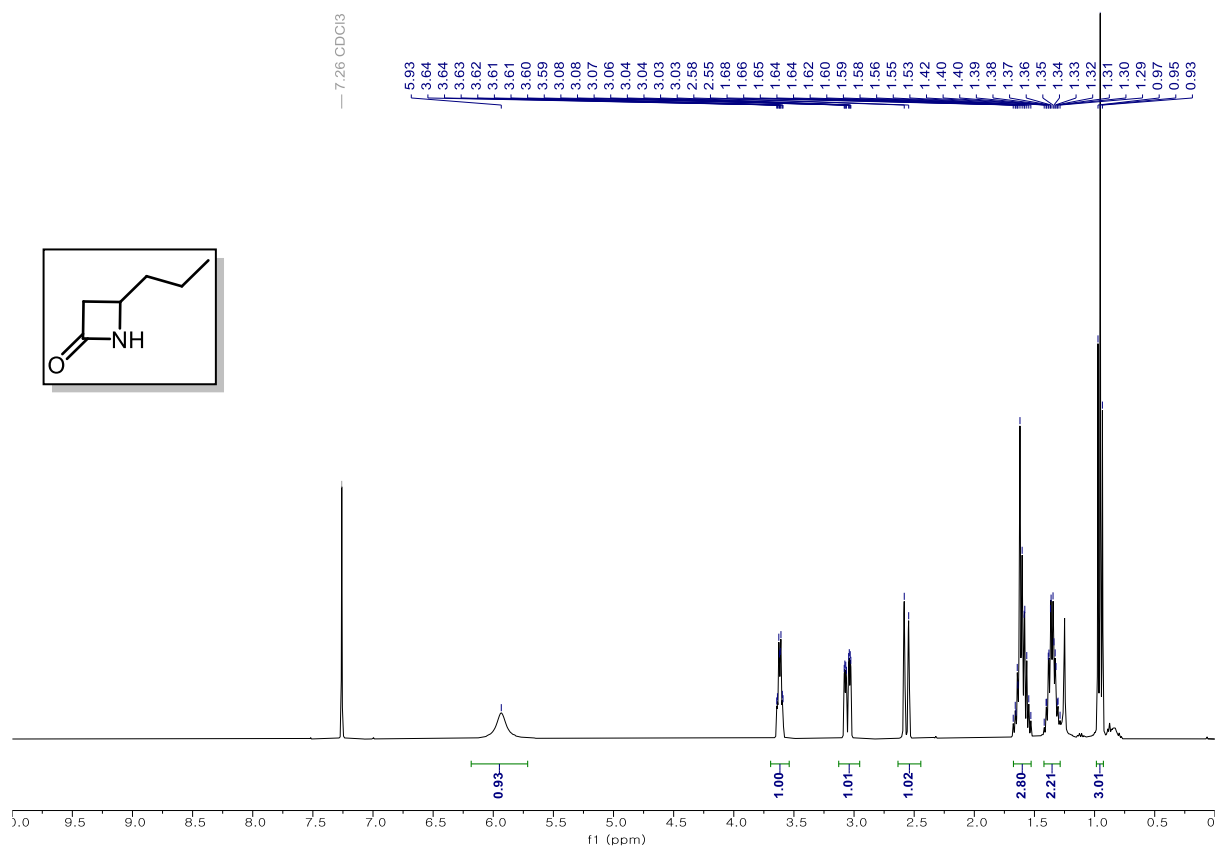
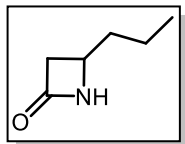
4-Methylazetidin-2-one, 35



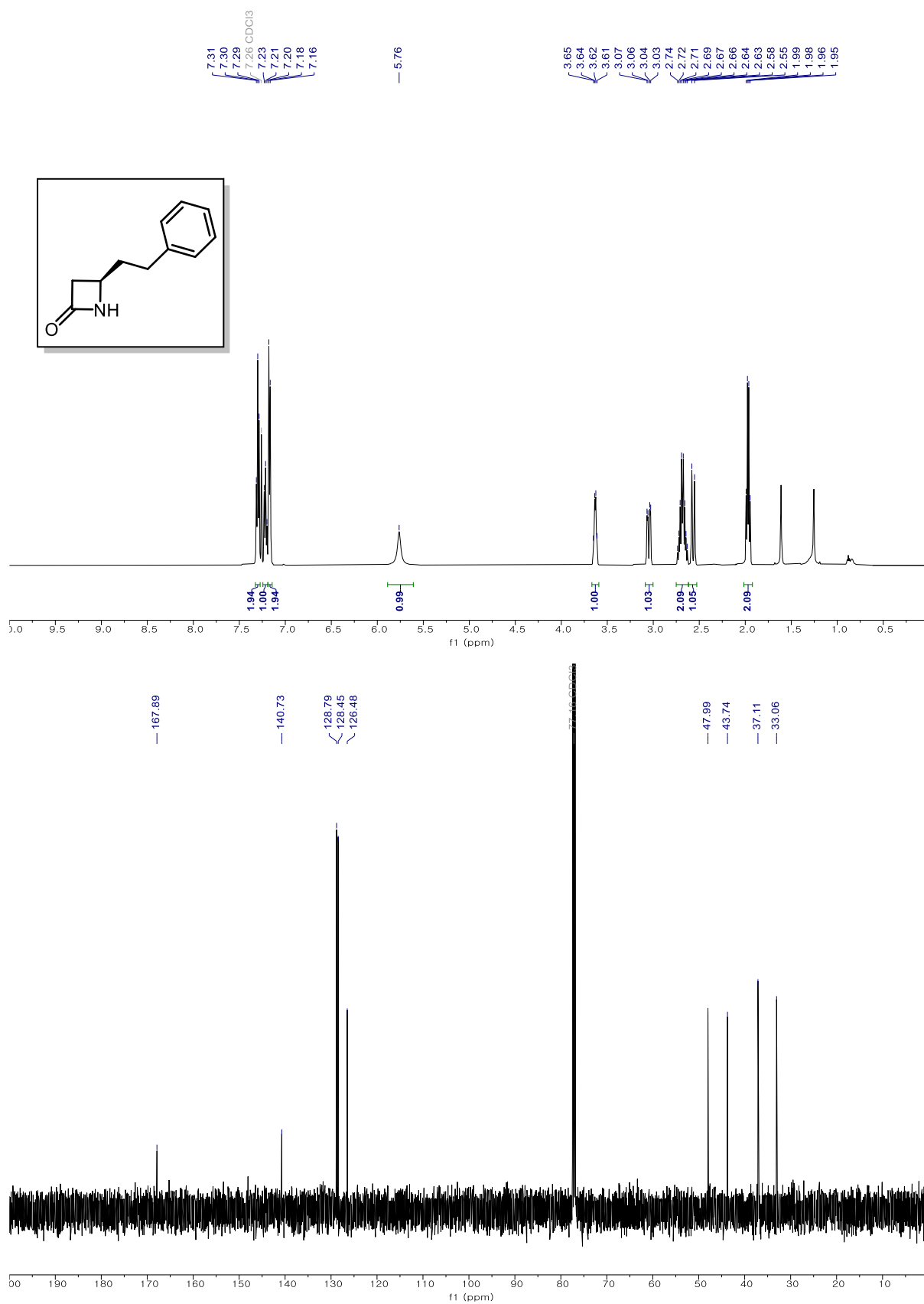
4-Ethylazetidin-2-one, (R)-36



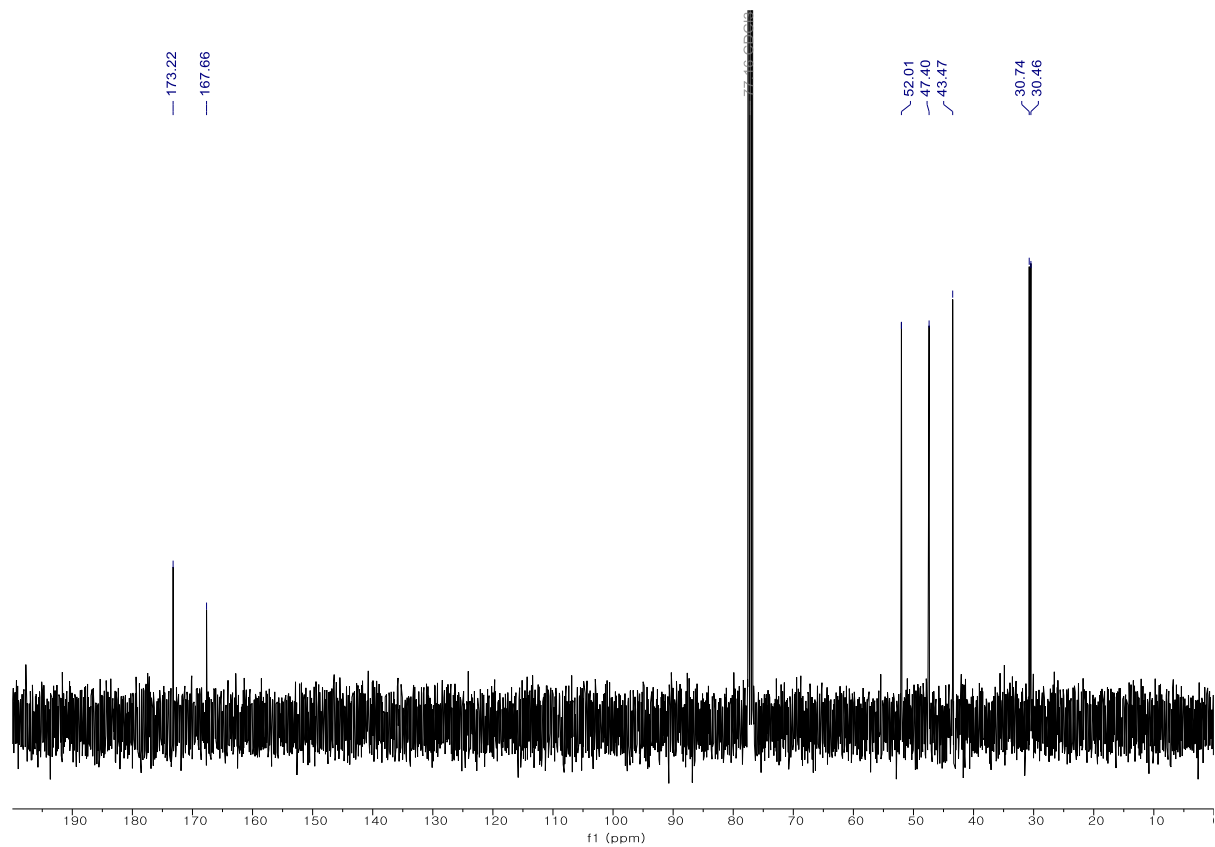
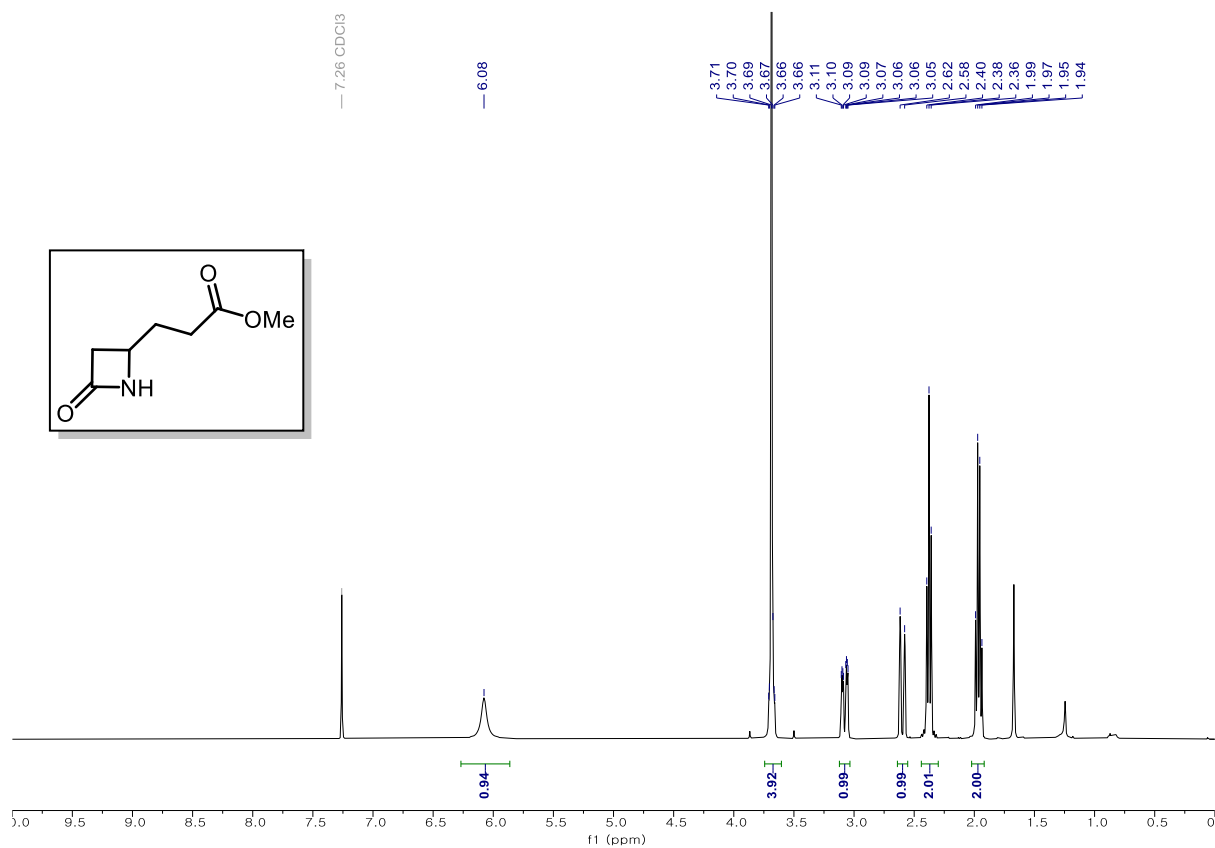
4-Propylazetidin-2-one, 37



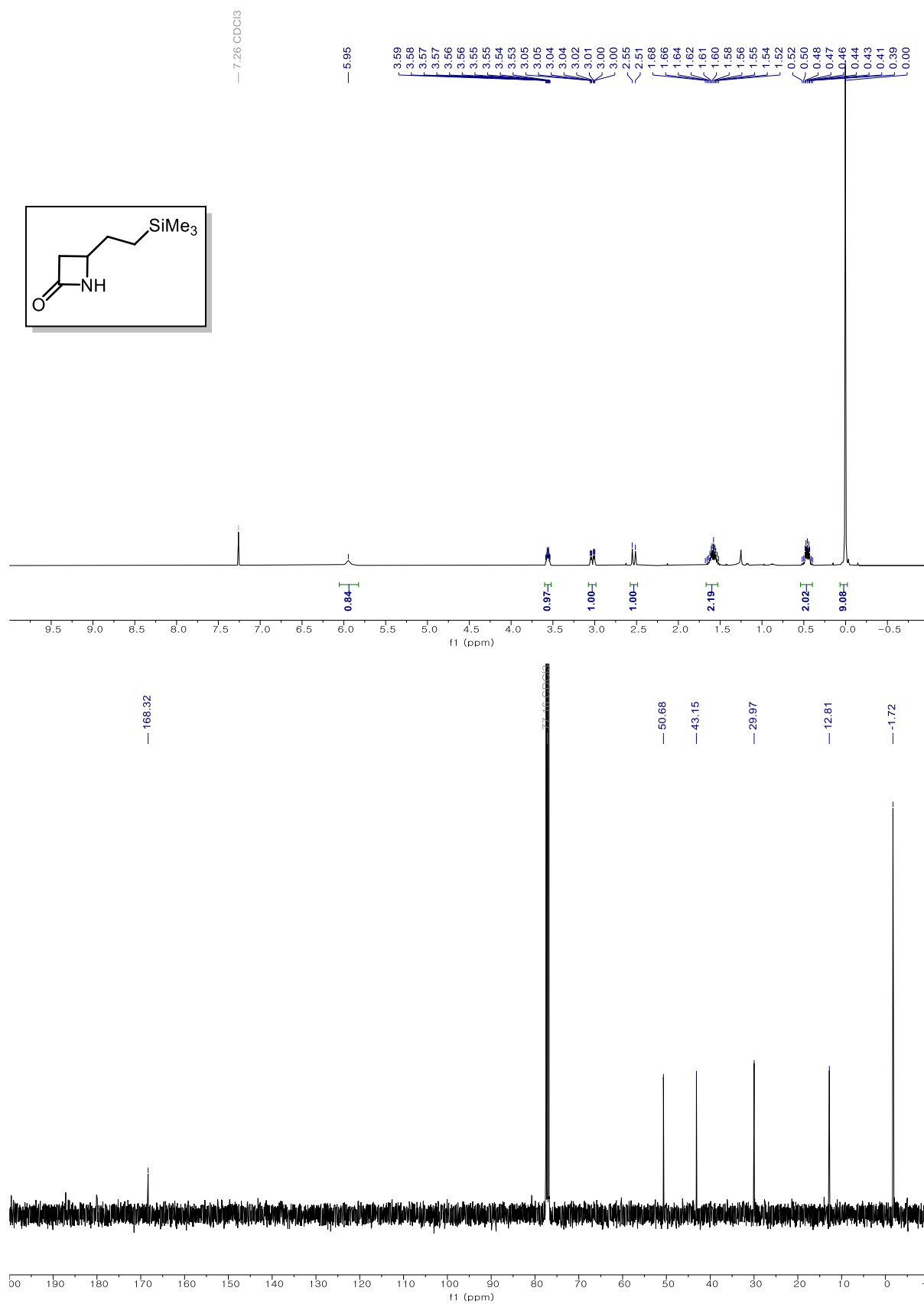
(R)-4-Phenethylazetidin-2-one, (R)-38



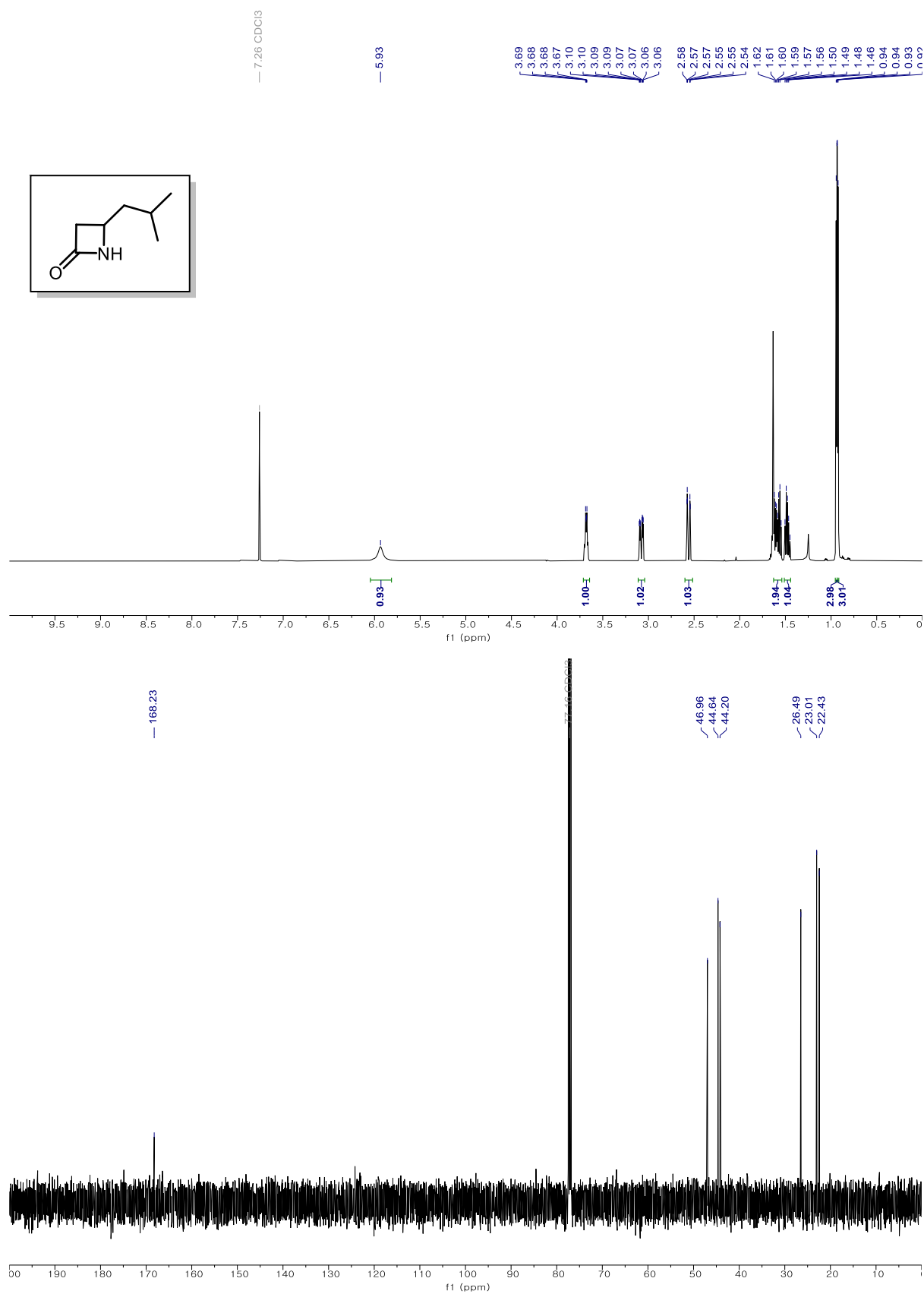
Methyl 3-(4-oxoazetidin-2-yl)propanoate, 39



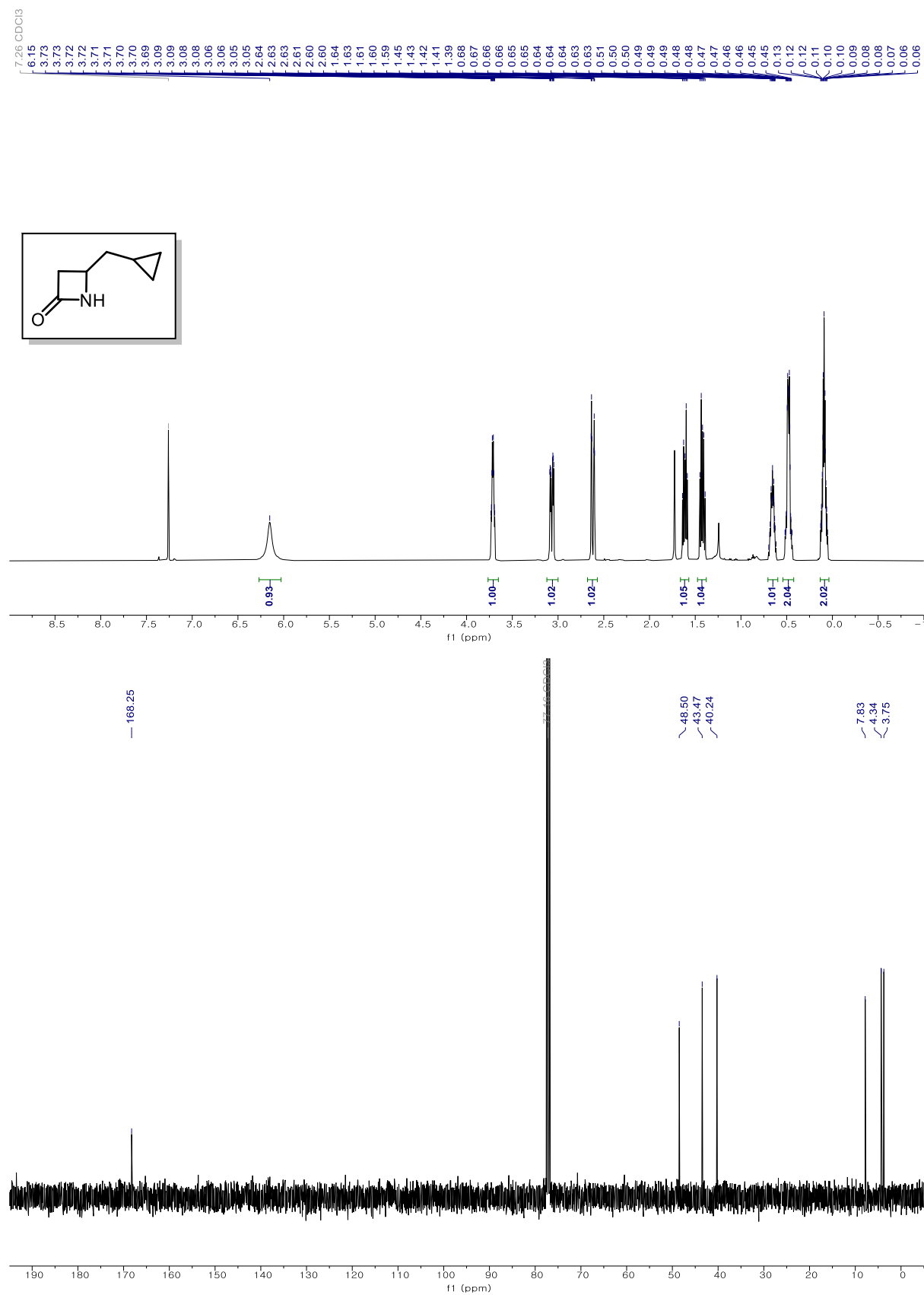
4-[2-(Trimethylsilyl)ethyl]azetidin-2-one, 40



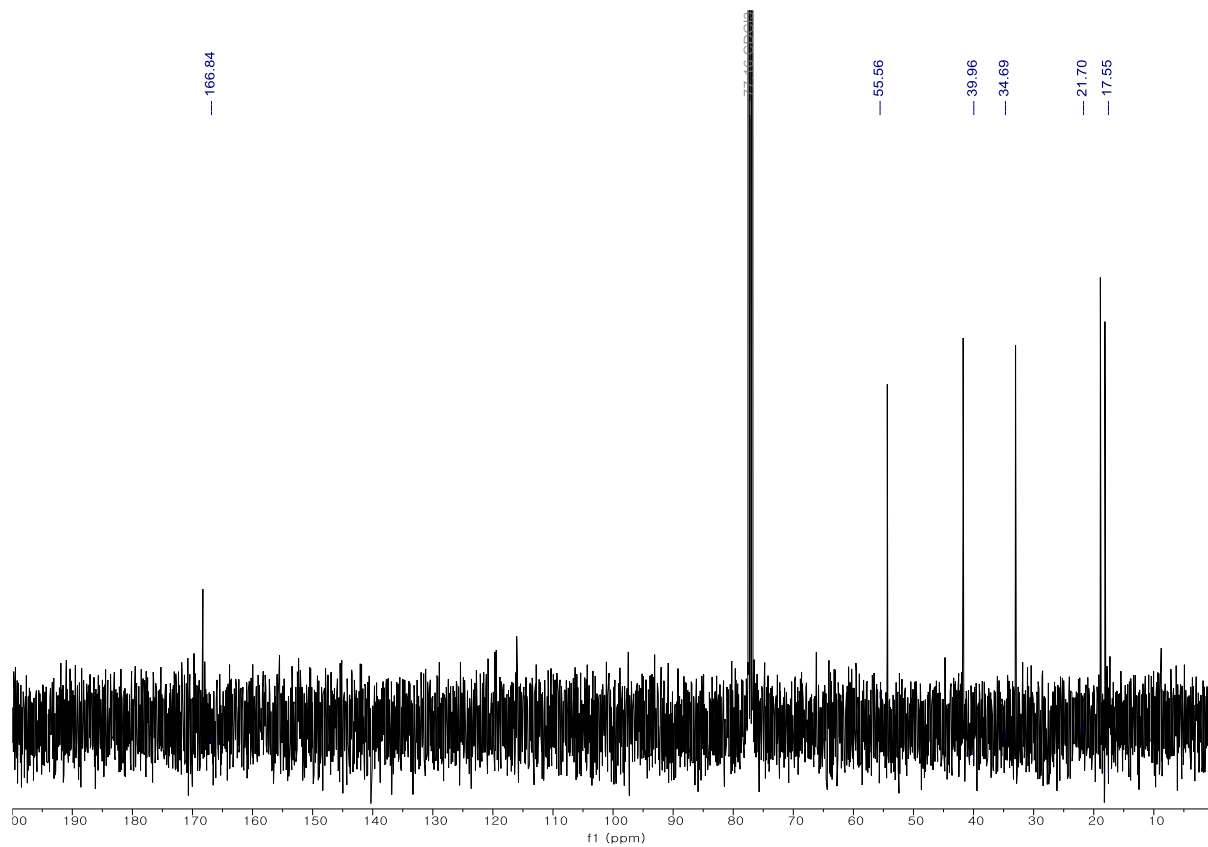
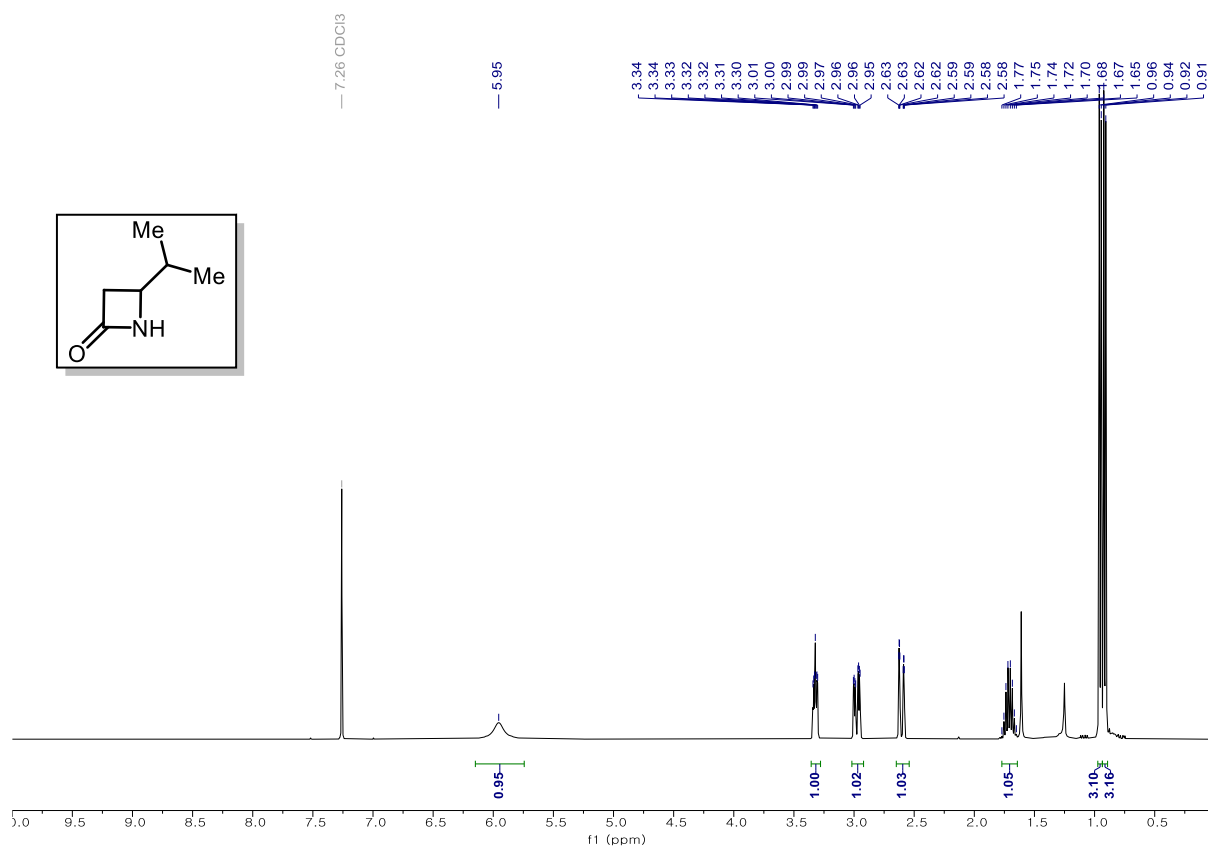
4-Isobutylazetidin-2-one, 41



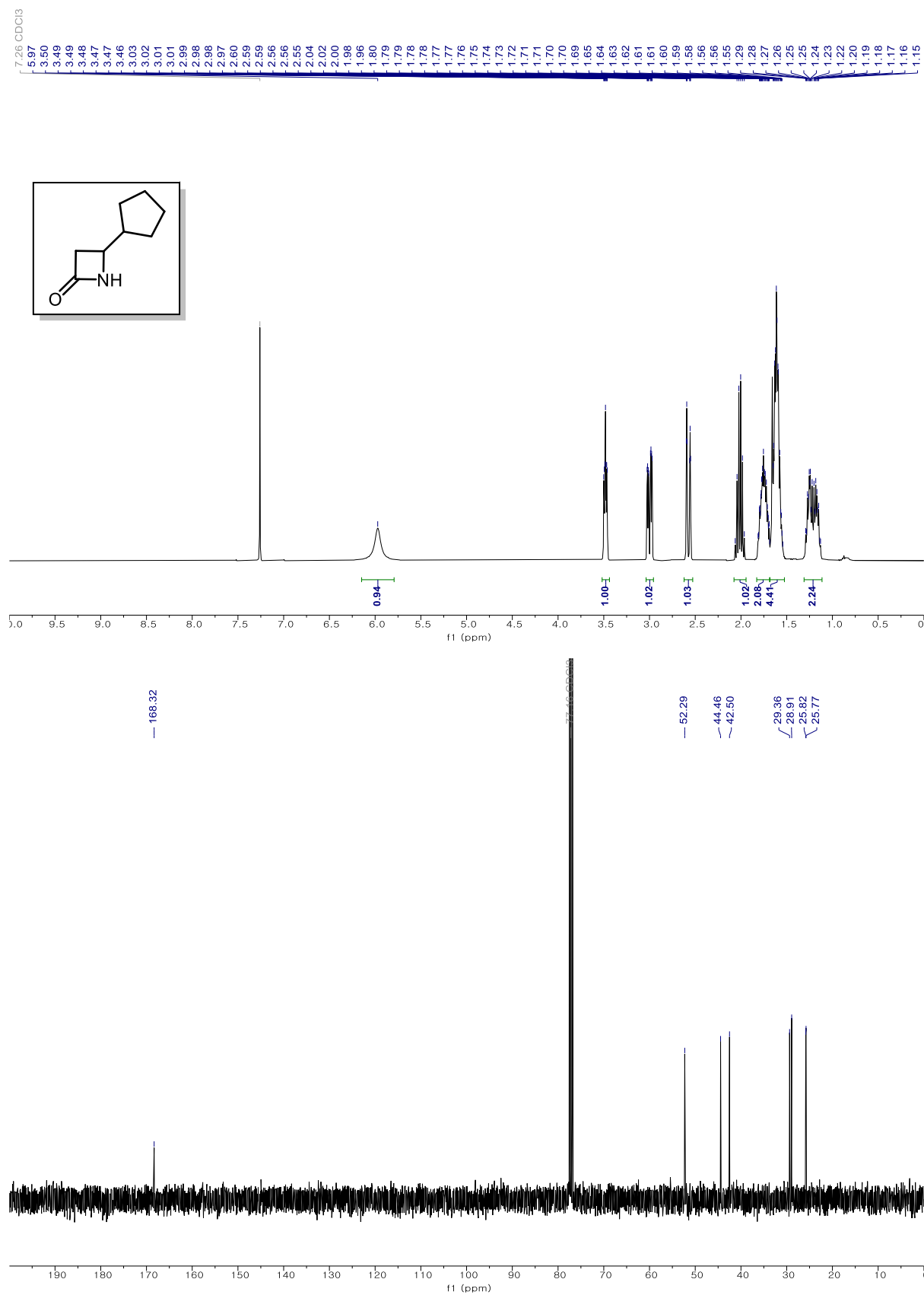
4-(Cyclopropylmethyl)azetidin-2-one, 42



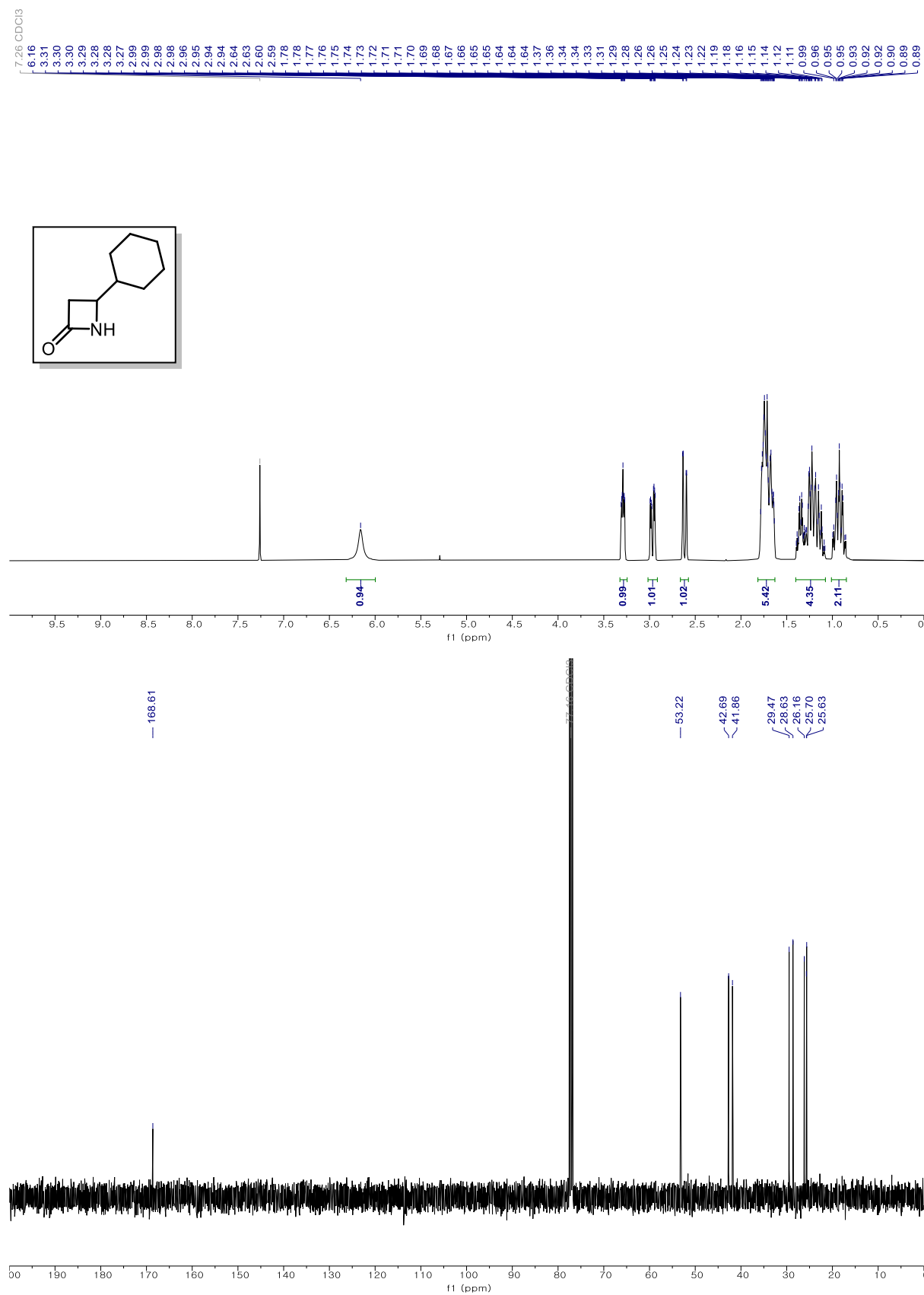
4-Isopropylazetidin-2-one, 43



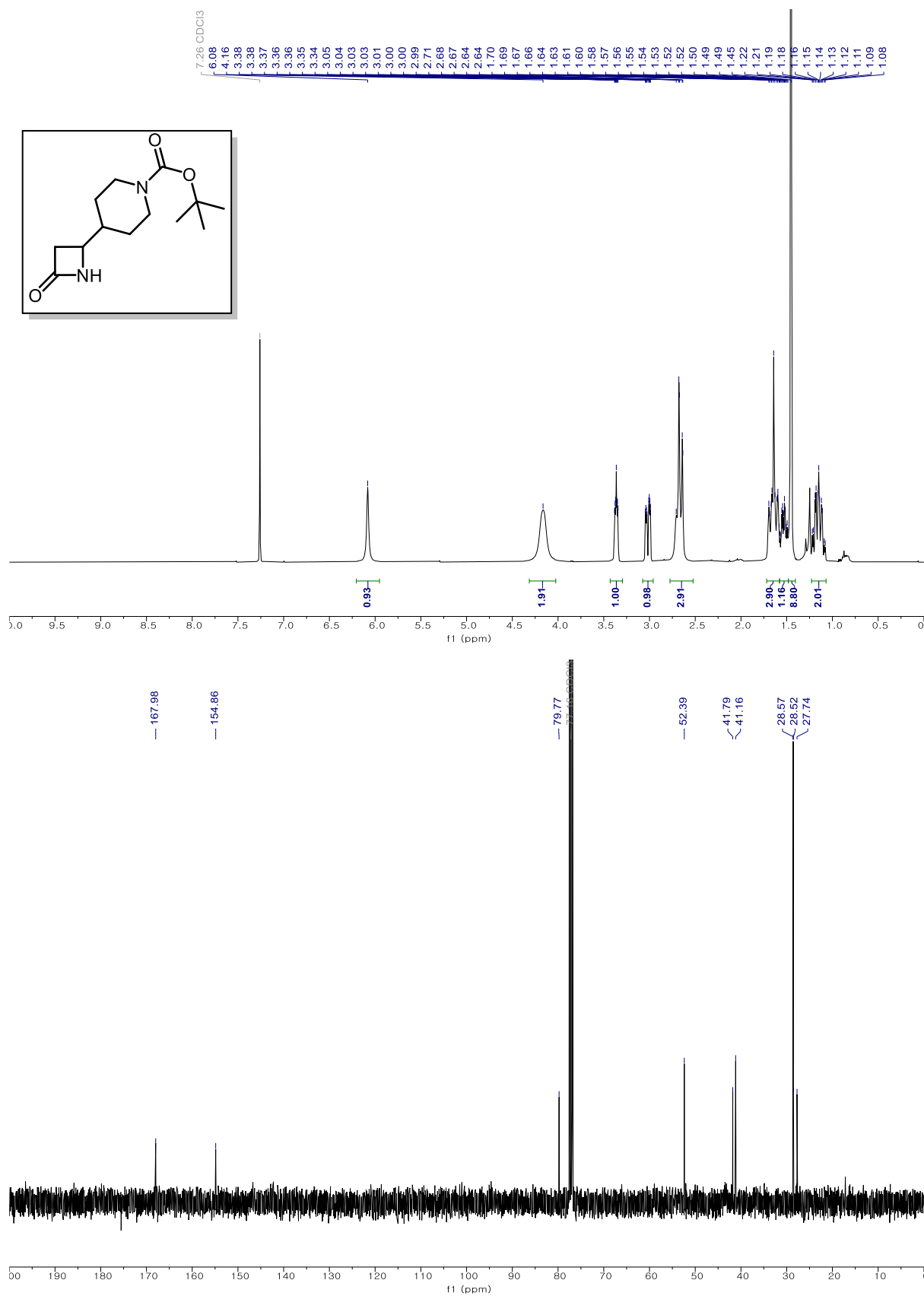
4-Cyclopentylazetidin-2-one, 44



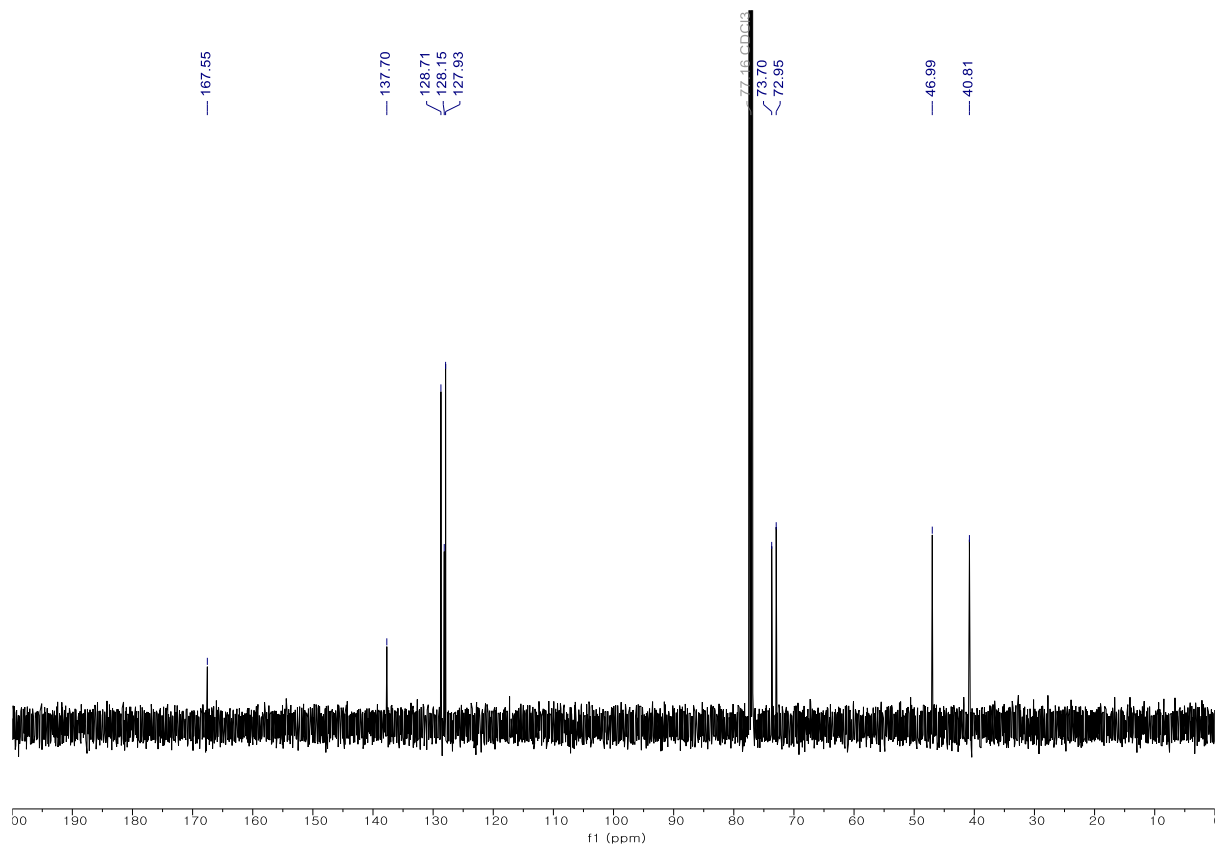
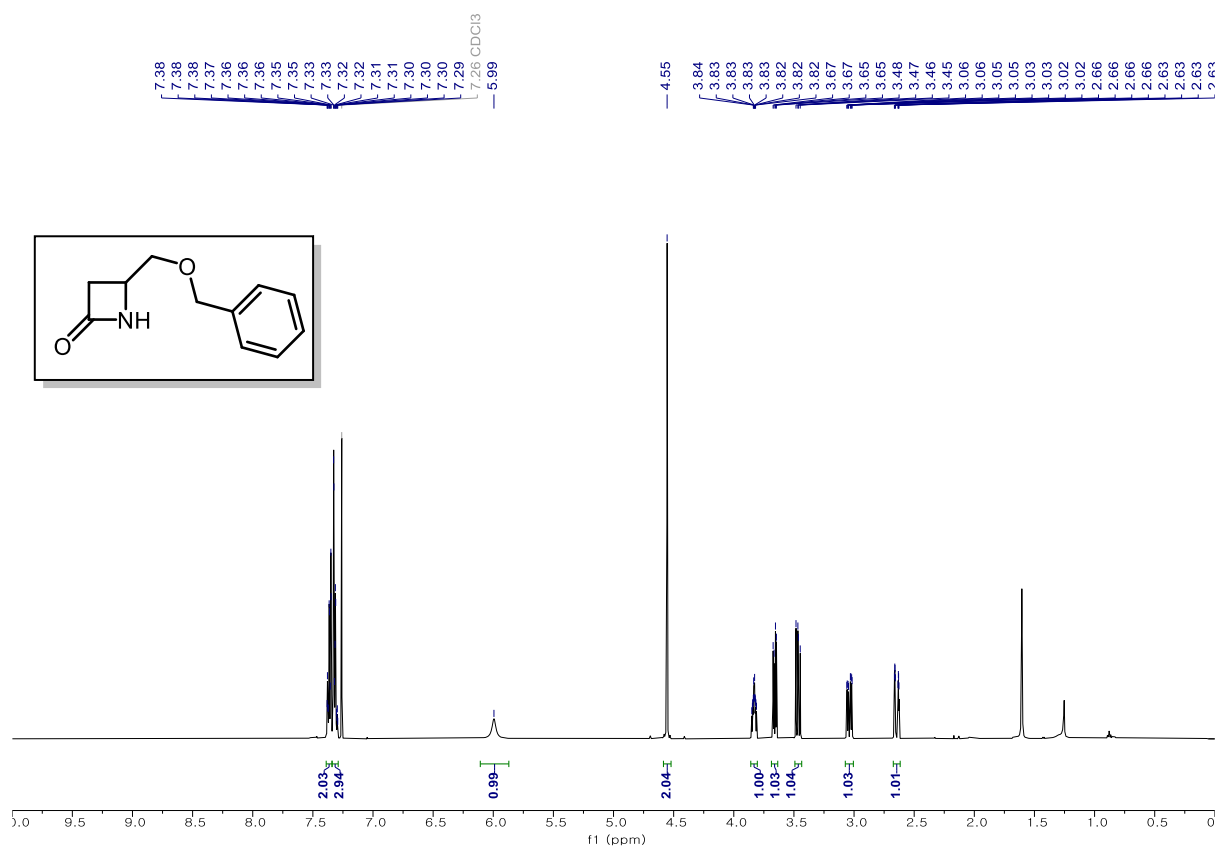
4-Cyclohexylazetidin-2-one, 45



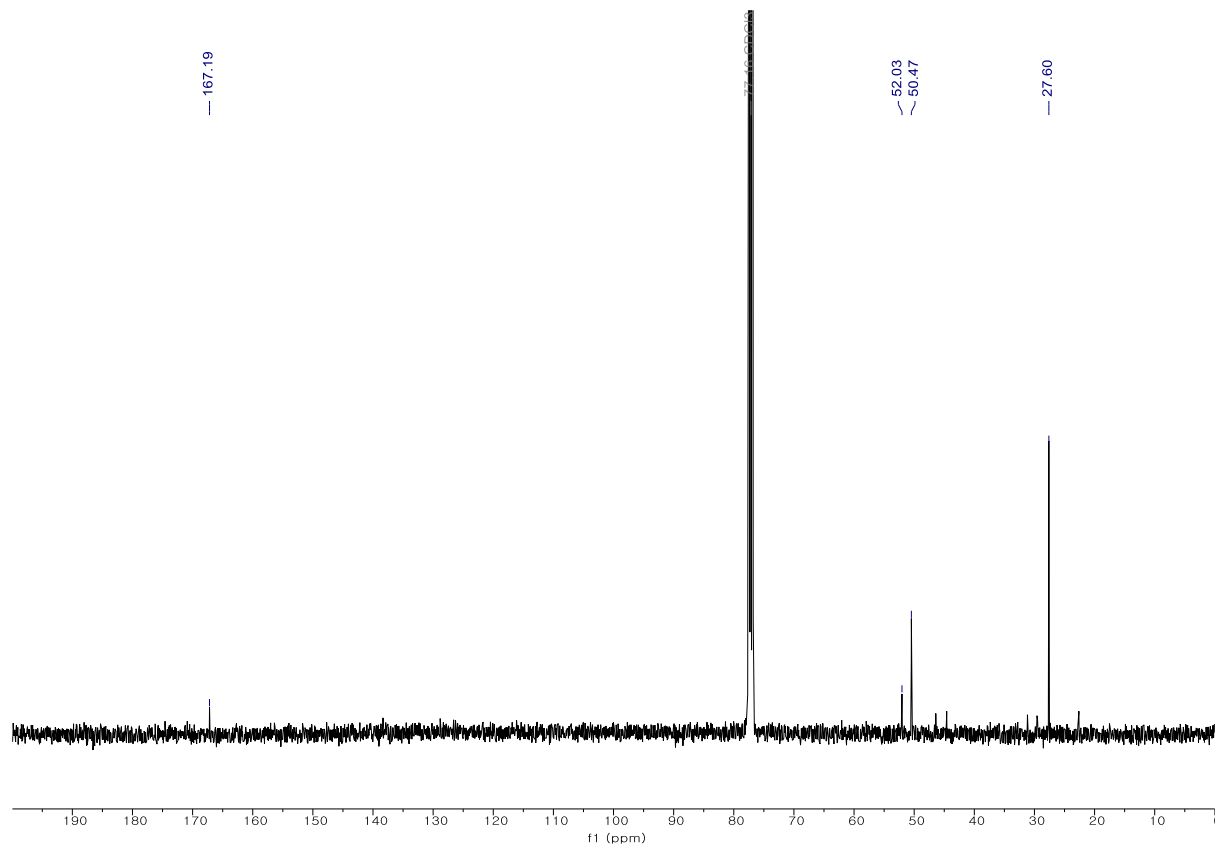
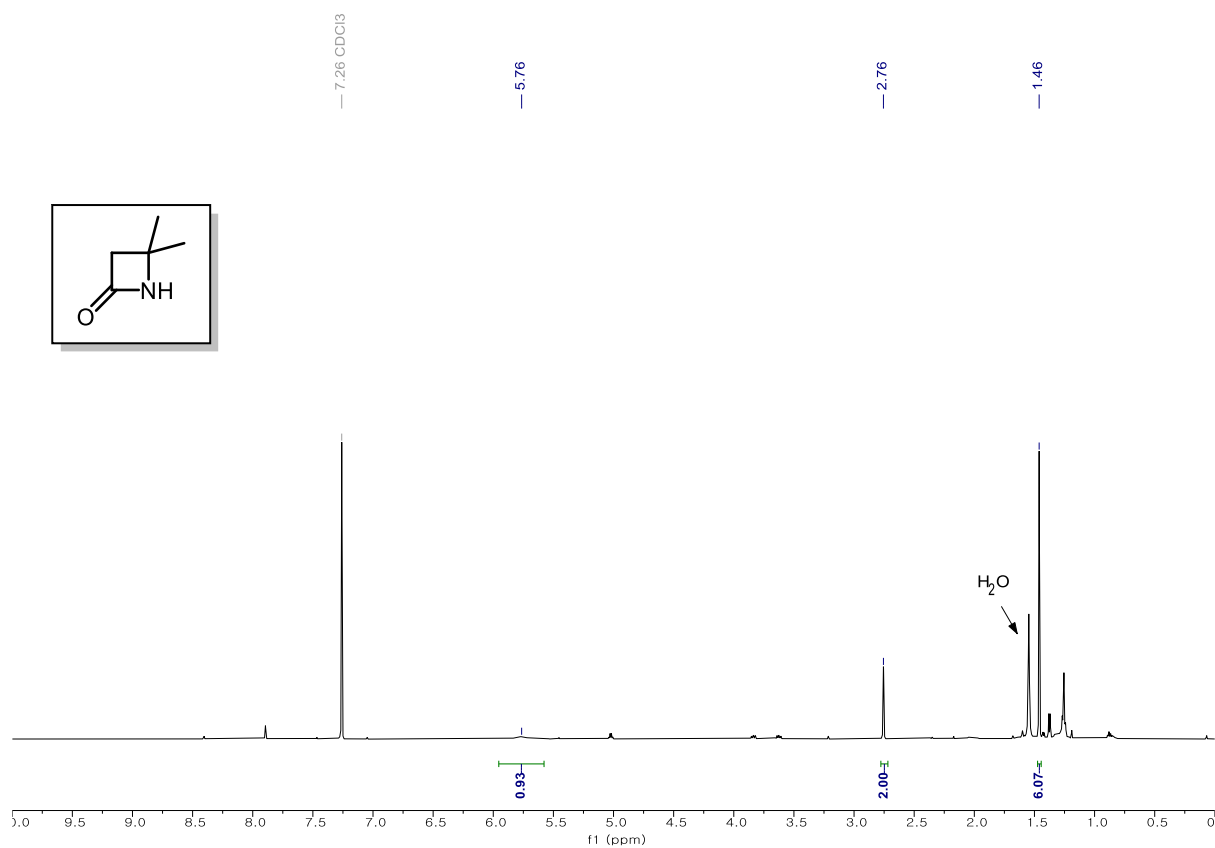
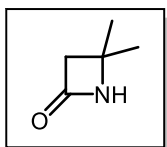
***tert*-Butyl 4-(4-oxoazetidin-2-yl)piperidine-1-carboxylate, 46**



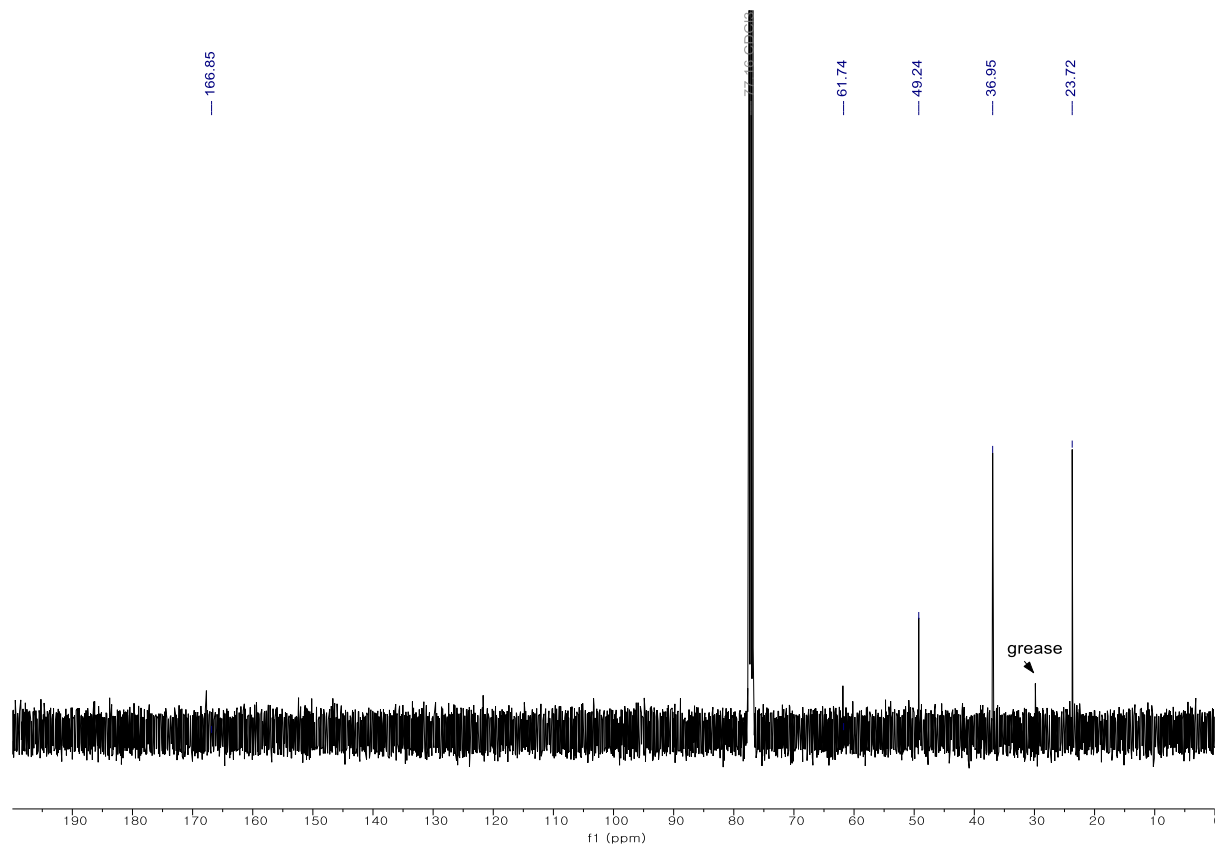
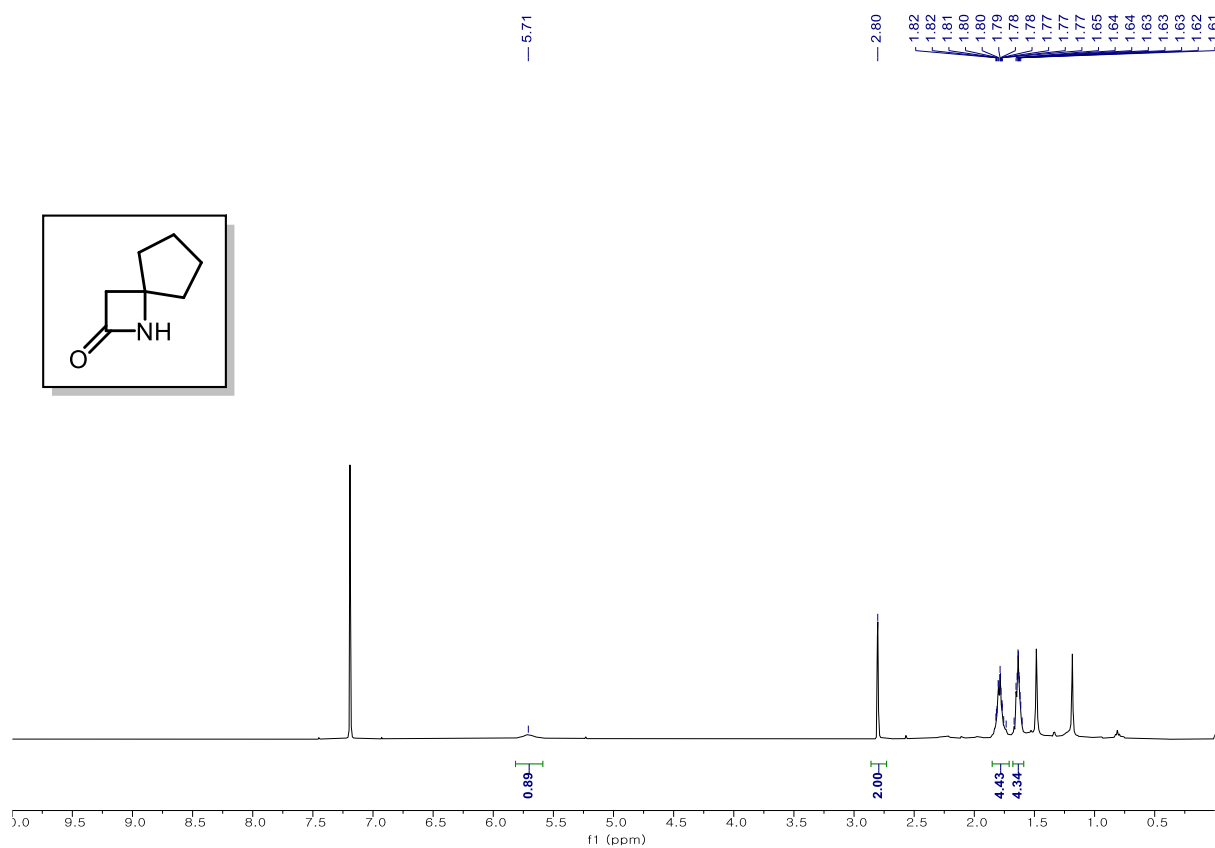
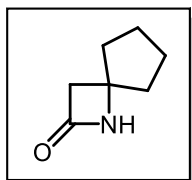
4-[(Benzyloxy)methyl]azetidin-2-one, 47



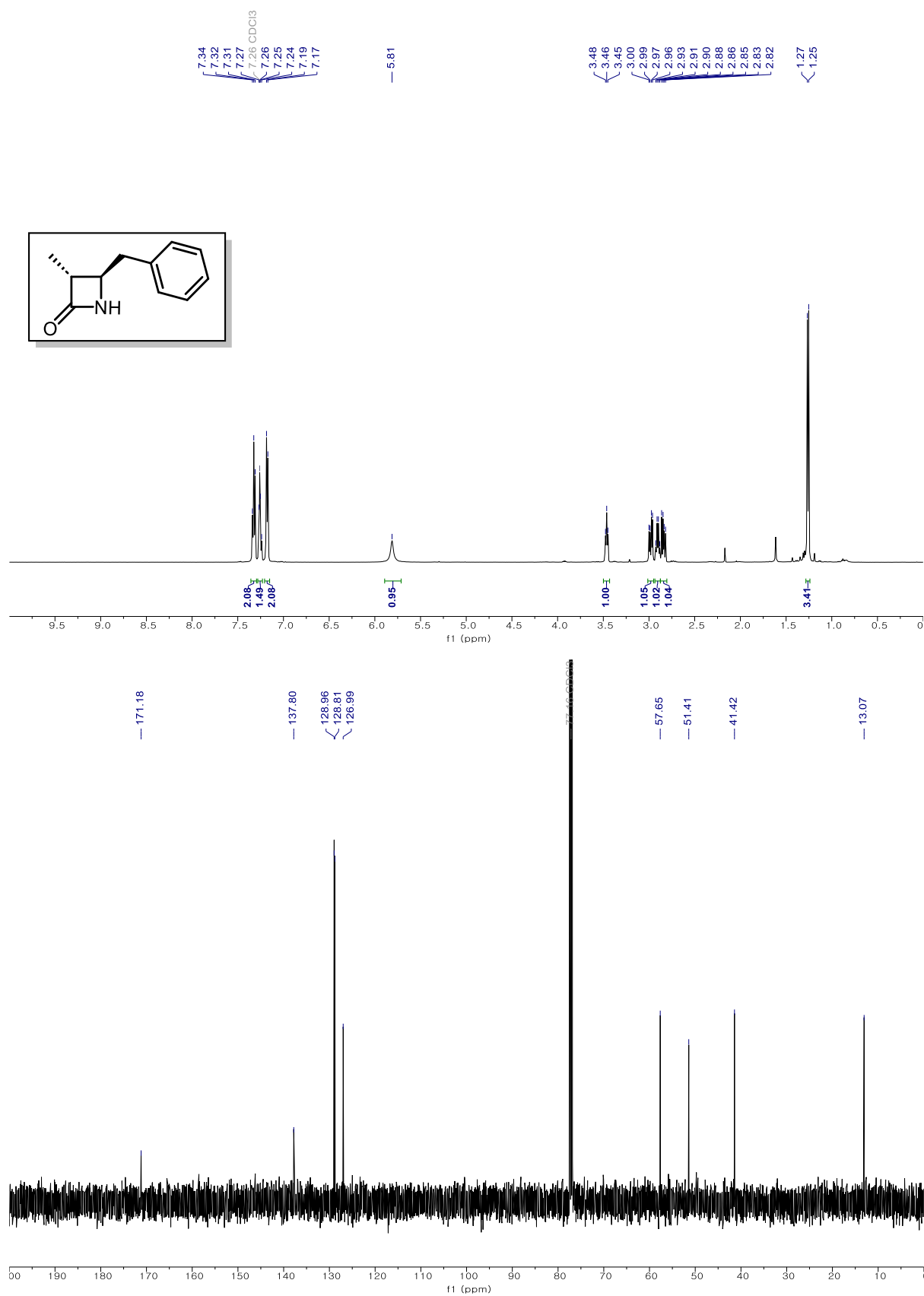
4,4-Dimethylazetidin-2-one, 48



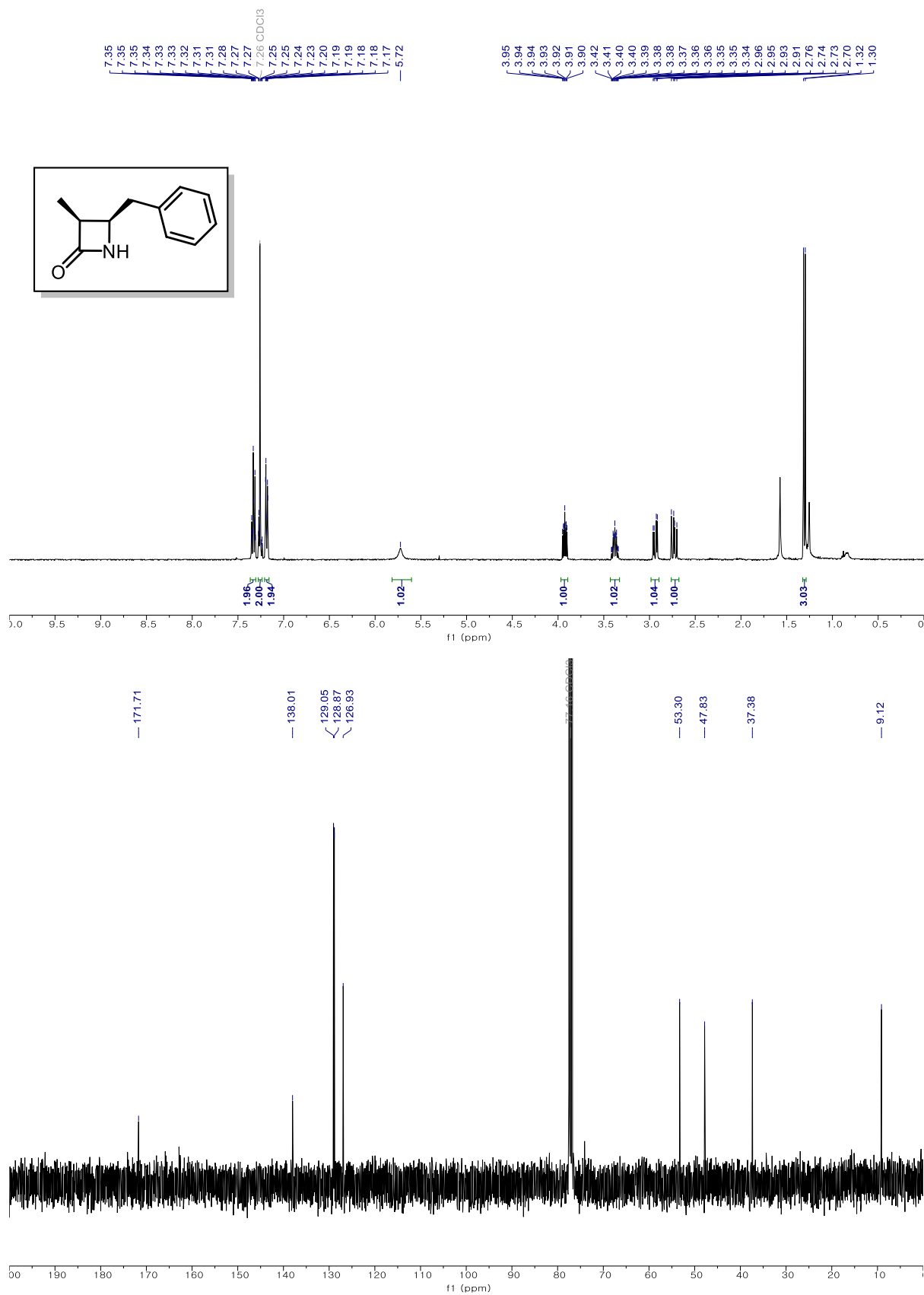
1-Azaspiro[3.4]octan-2-one, 49



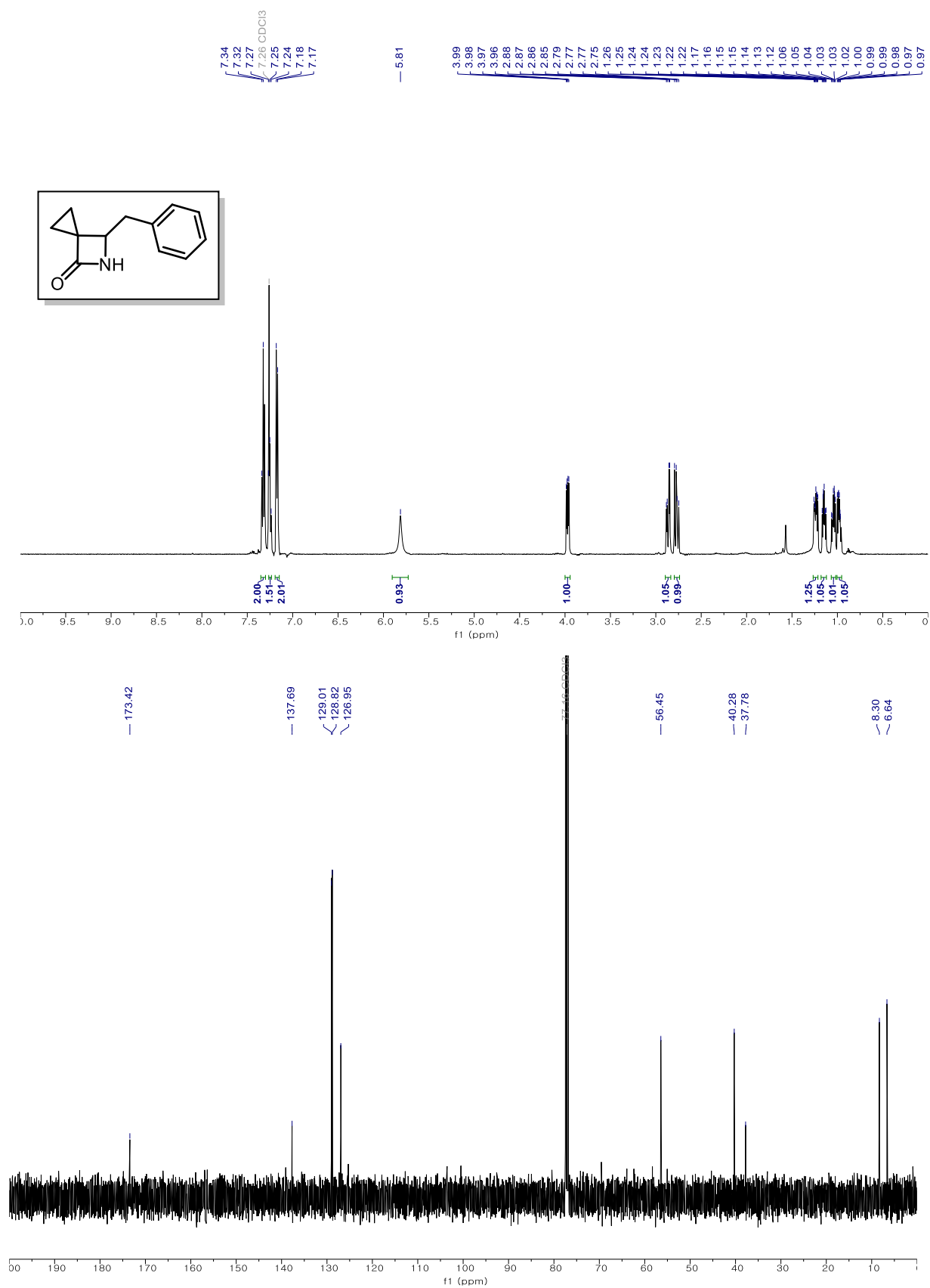
4-Benzyl-3-methylazetidin-2-one, (*R,R*)-51 (major)



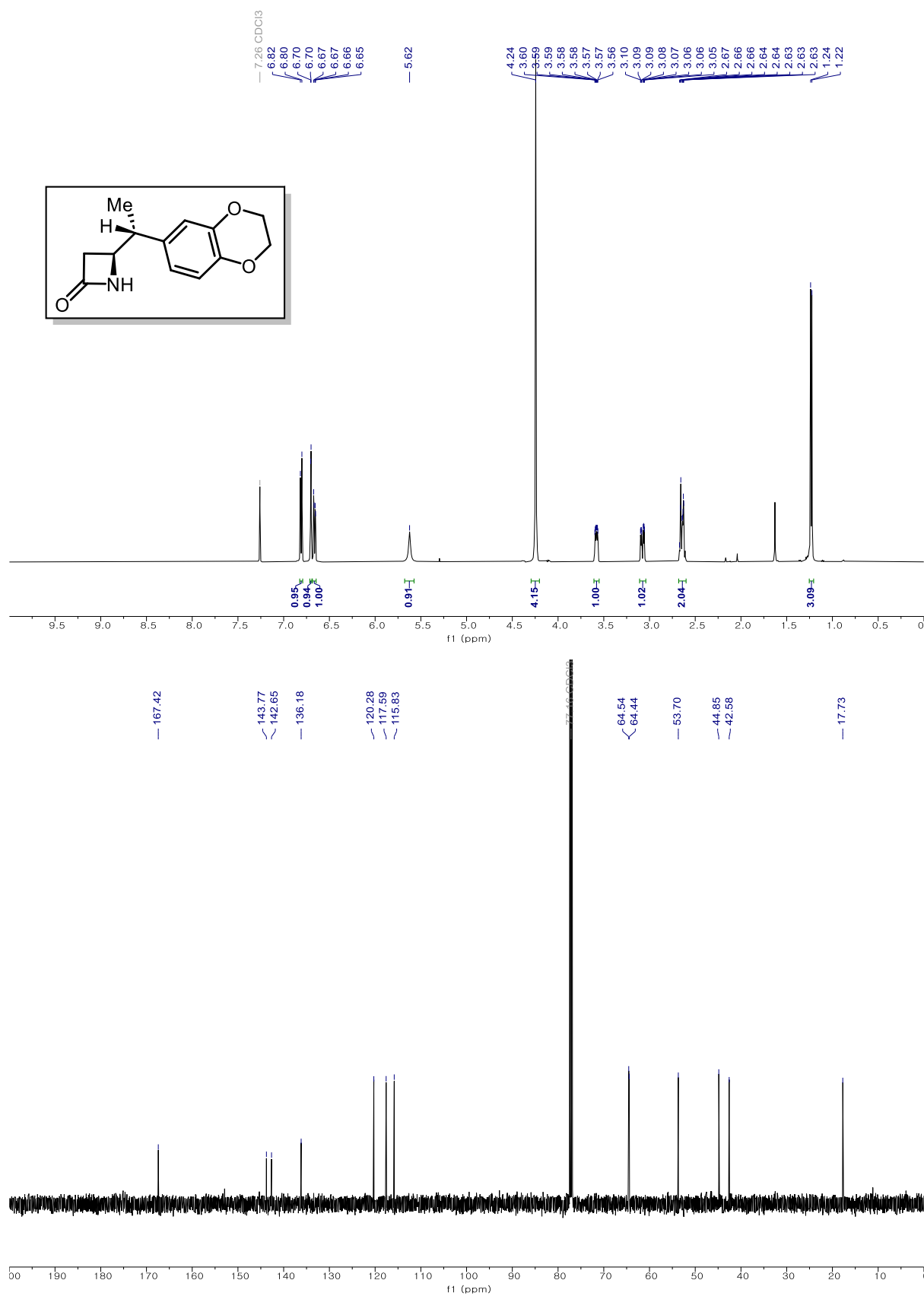
4-Benzyl-3-methylazetidin-2-one, *rac*-51 (minor)



6-Benzyl-5-azaspiro[2.3]hexan-4-one, 52



4-[1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl]azetidin-2-one, *rac*-53



¹H NMR (CD₃OD)

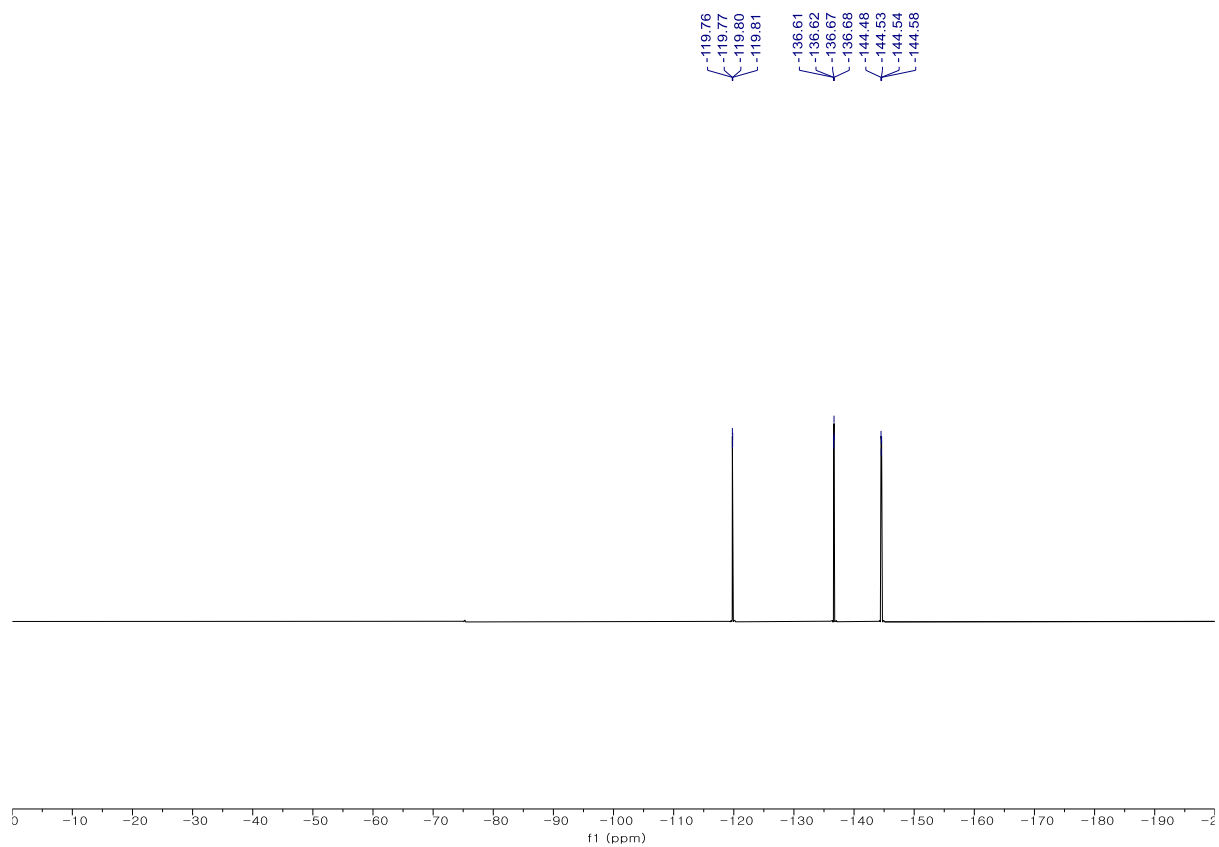
Chemical structure: (S)-2-amino-3-(2,4,6-trifluorophenyl)propanoic acid hydrochloride

Peak list (ppm): 7.39, 7.37, 7.36, 7.35, 7.34, 7.32, 7.26, 7.24, 7.23, 7.22, 7.21, 7.19, 3.85, 3.83, 3.82, 3.80, 3.79, 3.31, 3.11, 3.10, 3.08, 3.06, 3.04, 3.02, 3.00, 2.74, 2.72, 2.69, 2.68, 2.66, 2.65, 2.62, 2.60

Integration values: 1.00, 1.00, 0.98, 2.01, 2.02

¹³C NMR (CD₃OD)

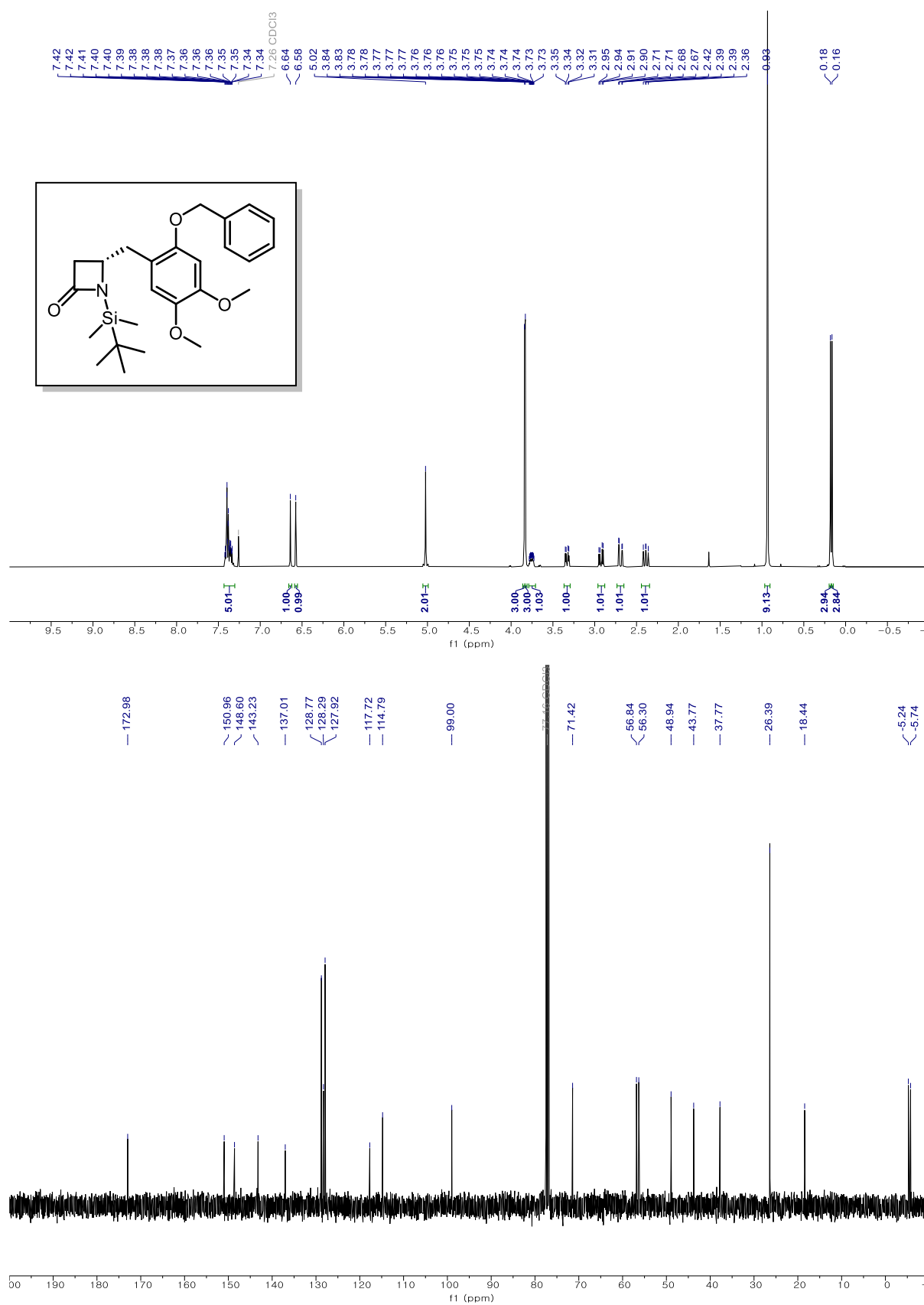
Peak list (ppm): 173.24, 158.99, 158.92, 157.04, 156.98, 152.09, 151.98, 151.87, 150.10, 150.00, 149.99, 149.22, 149.13, 147.31, 147.21, 120.71, 120.67, 120.56, 120.51, 120.43, 120.28, 107.20, 107.03, 106.97, 106.80, 36.32, 32.27



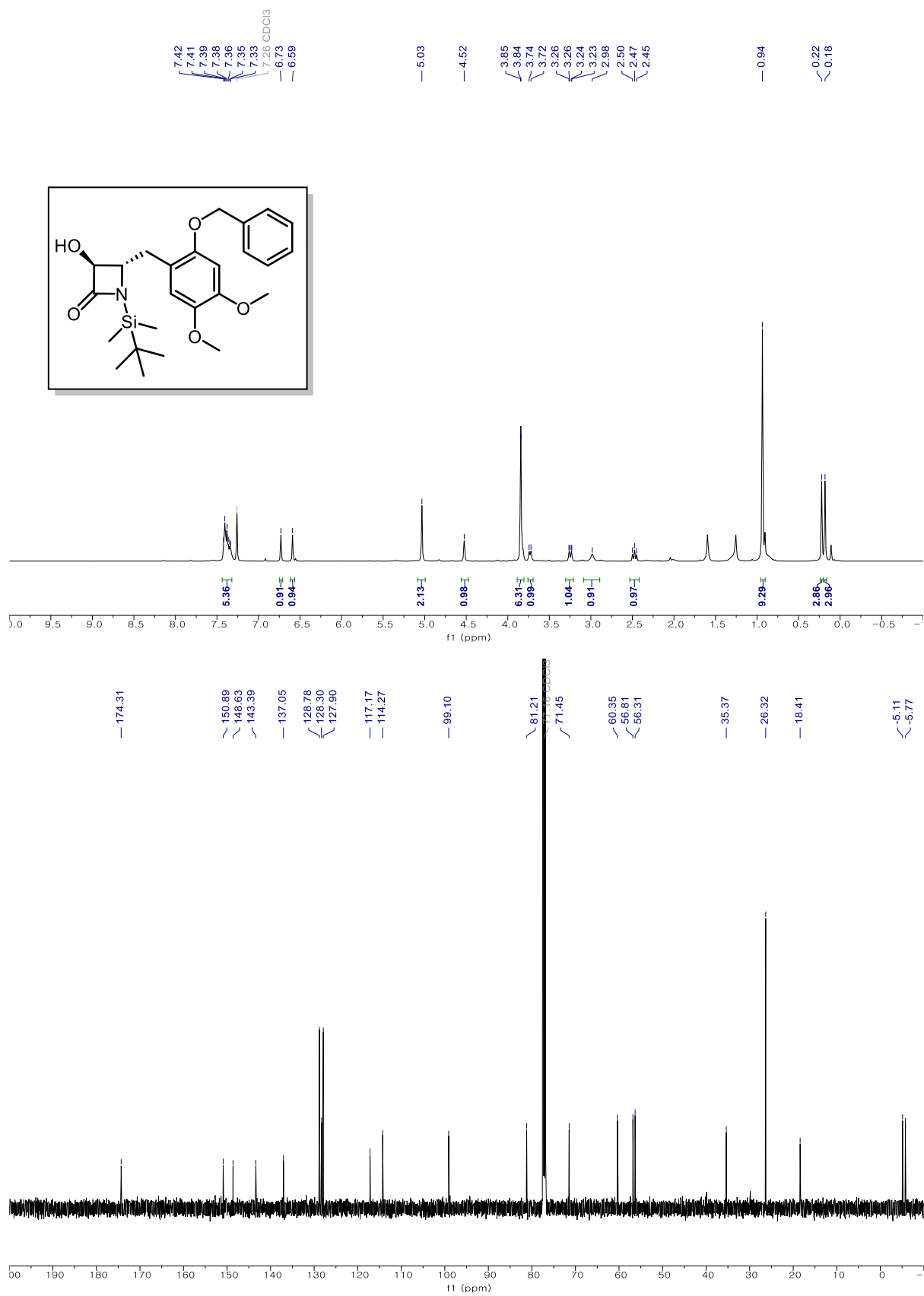
(E)-3-{3-[2-(Benzyloxy)-4,5-dimethoxyphenyl]allyl}-1,4,2-dioxazol-5-one, 55



(S)-4-[2-(Benzyloxy)-4,5-dimethoxybenzyl]-1-(*tert*-butyldimethylsilyl)azetidin-2-one, 56



(3*S*,4*S*)-4-[2-(Benzyloxy)-4,5-dimethoxybenzyl]-1-(*tert*-butyldimethylsilyl)-3-hydroxyazetidin-2-one, 57



The figure displays the chemical structure of compound 10 and its corresponding ¹H and ¹³C NMR spectra. The chemical structure is a substituted pyrrolidine-2-one derivative, featuring a 4-methoxyphenyl group, a 3,5-bis(methoxy)phenyl group, and a 4-methoxybenzyl group, all attached to a pyrrolidine ring. The pyrrolidine ring is also substituted with a tert-butyldimethylsilyl group and a hydroxyl group.

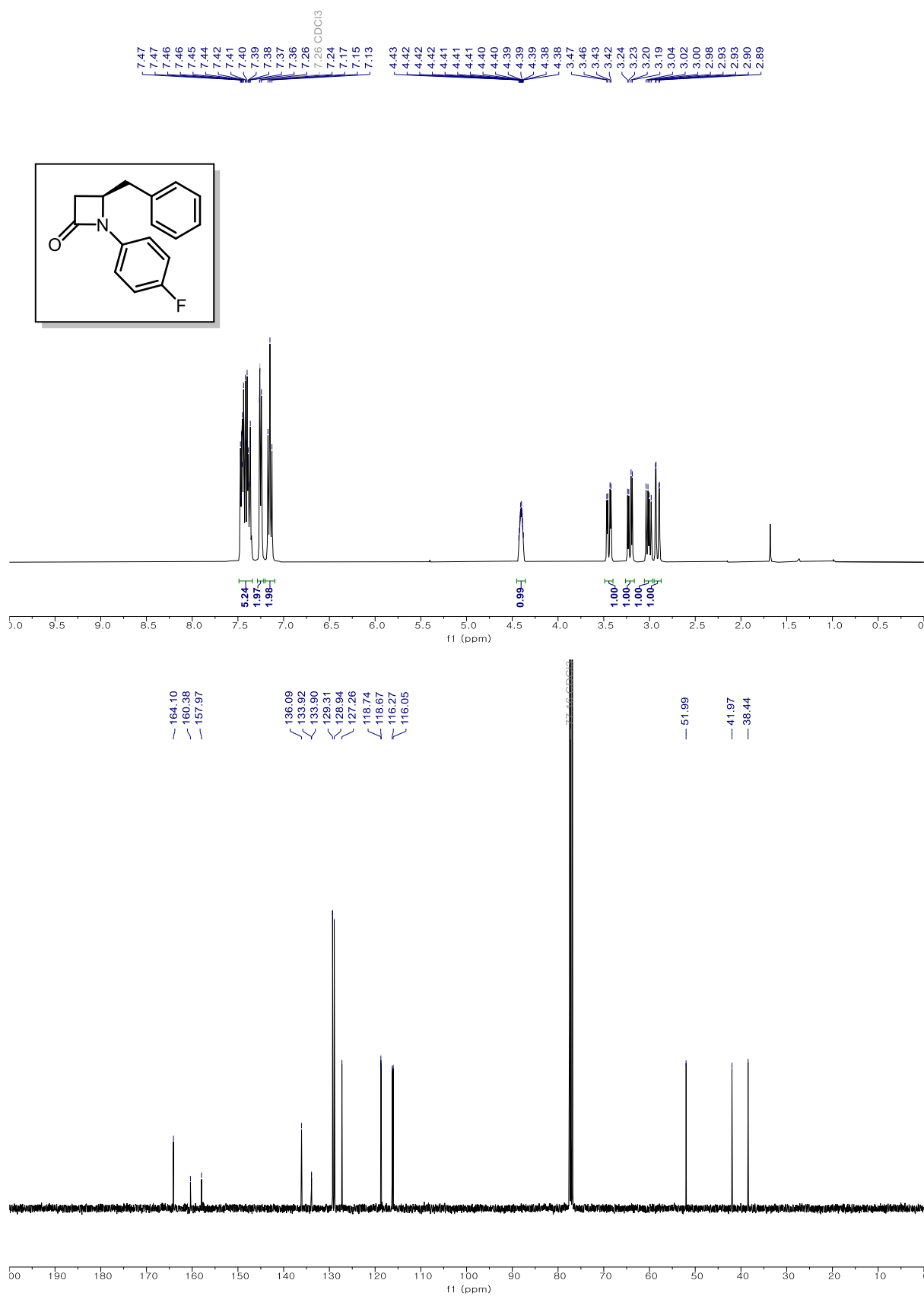
The ¹H NMR spectrum (top) shows peaks in the aromatic region (6.5-7.4 ppm), a methine proton (5.0 ppm), a methoxy singlet (3.8 ppm), and aliphatic protons (3.0-3.7 ppm). Integration values are provided below the peaks.

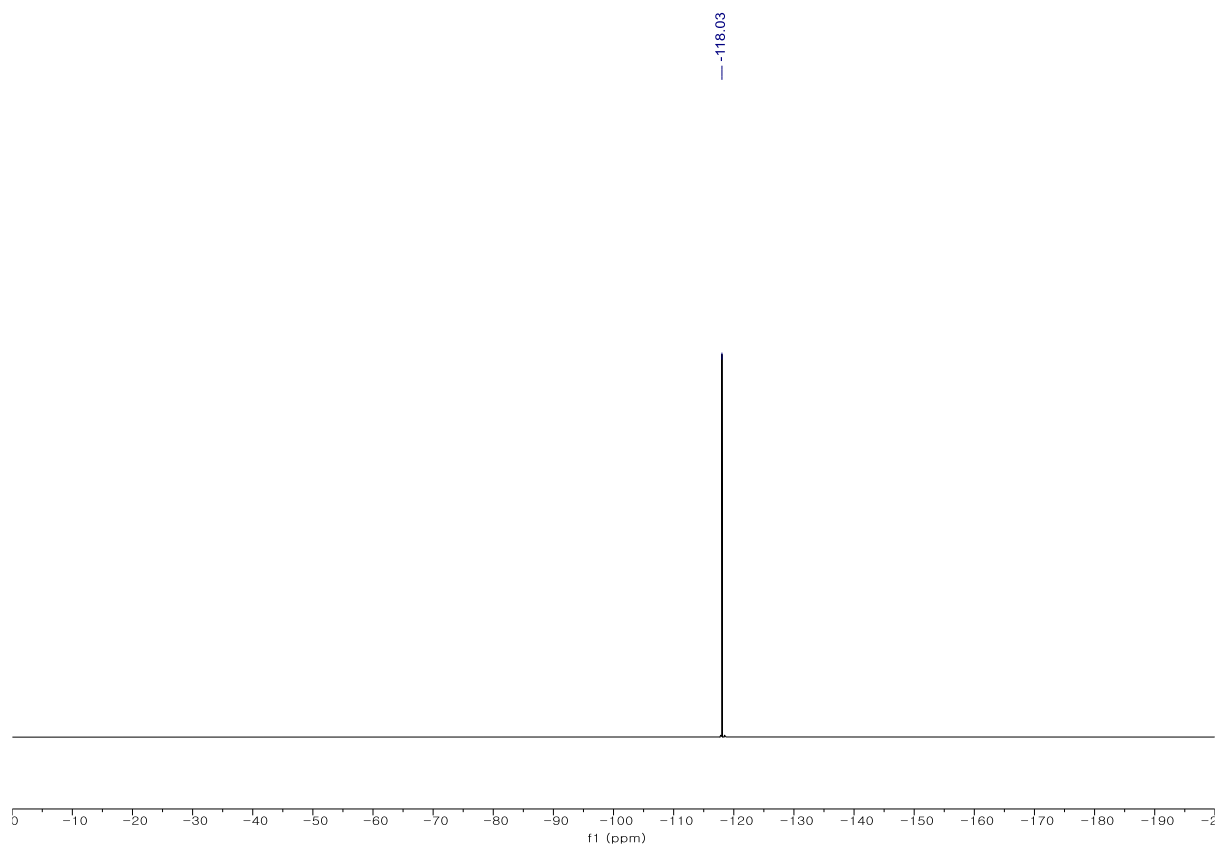
The ¹³C NMR spectrum (bottom) shows peaks in the aromatic region (110-150 ppm), a carbonyl carbon (174 ppm), and aliphatic carbons (18-64 ppm). The solvent peak for CDCl₃ is visible at 77.26 ppm.

¹H NMR (CDCl₃) peaks (ppm): 7.34, 7.31, 7.30, 7.26 (CDCl₃), 7.17, 7.15, 7.14, 7.04, 6.81, 6.79, 6.78, 6.77, 6.61, 6.53, 5.03, 5.00, 4.99, 4.97, 3.97, 3.96, 3.95, 3.94, 3.81, 3.79, 3.59, 3.25, 3.23, 3.21, 3.20, 3.07, 3.05, 3.02, -0.92, -0.17, -0.13.

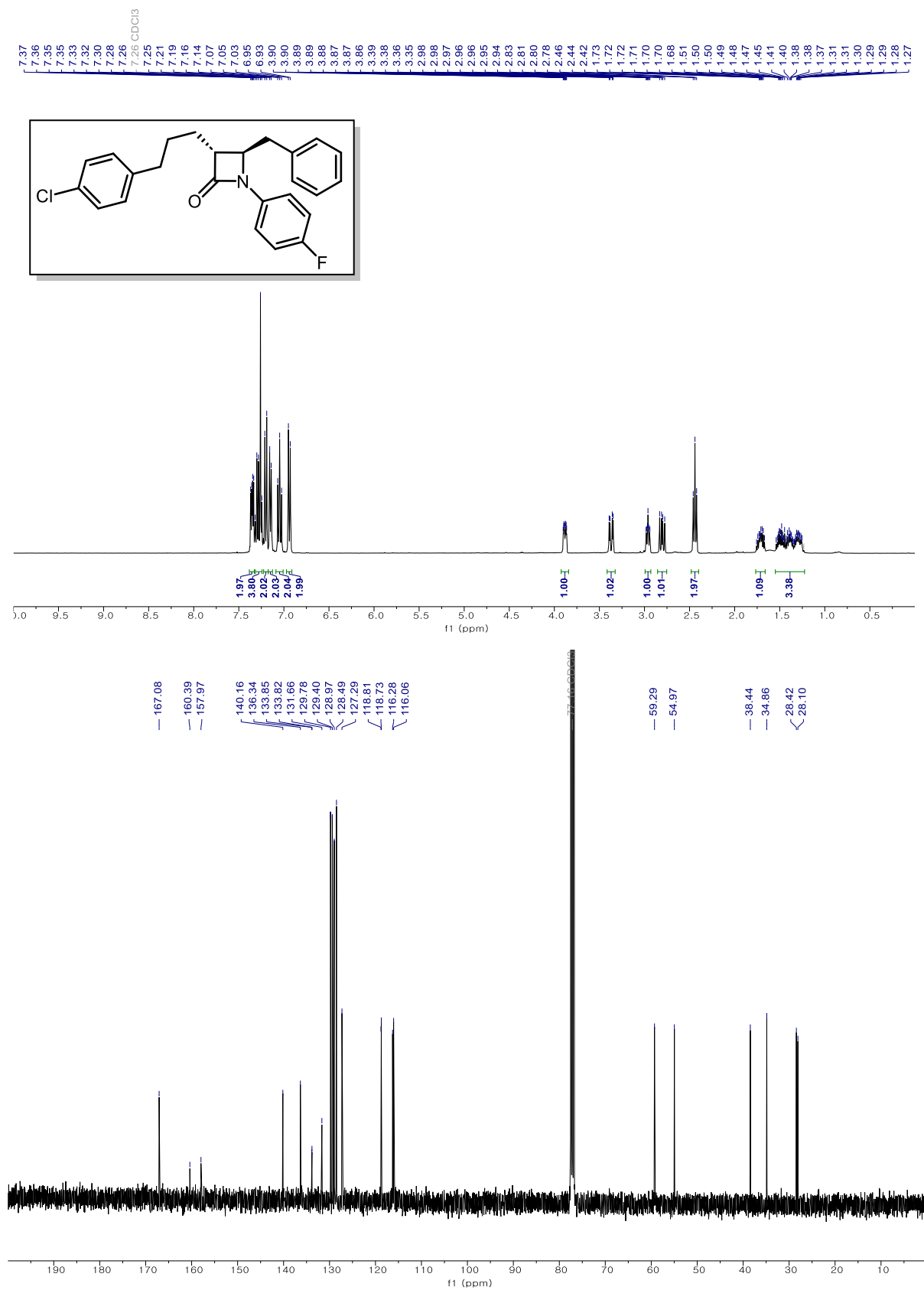
¹³C NMR (CDCl₃) peaks (ppm): 174.64, 159.86, 150.79, 148.26, 143.08, 141.83, 136.87, 129.75, 128.75, 128.32, 128.20, 118.05, 117.80, 115.88, 114.93, 110.75, 98.74, 86.64, 71.58, 64.37, 56.62, 56.27, 55.10, 31.67, 26.36, 18.40, -5.22, -5.72.

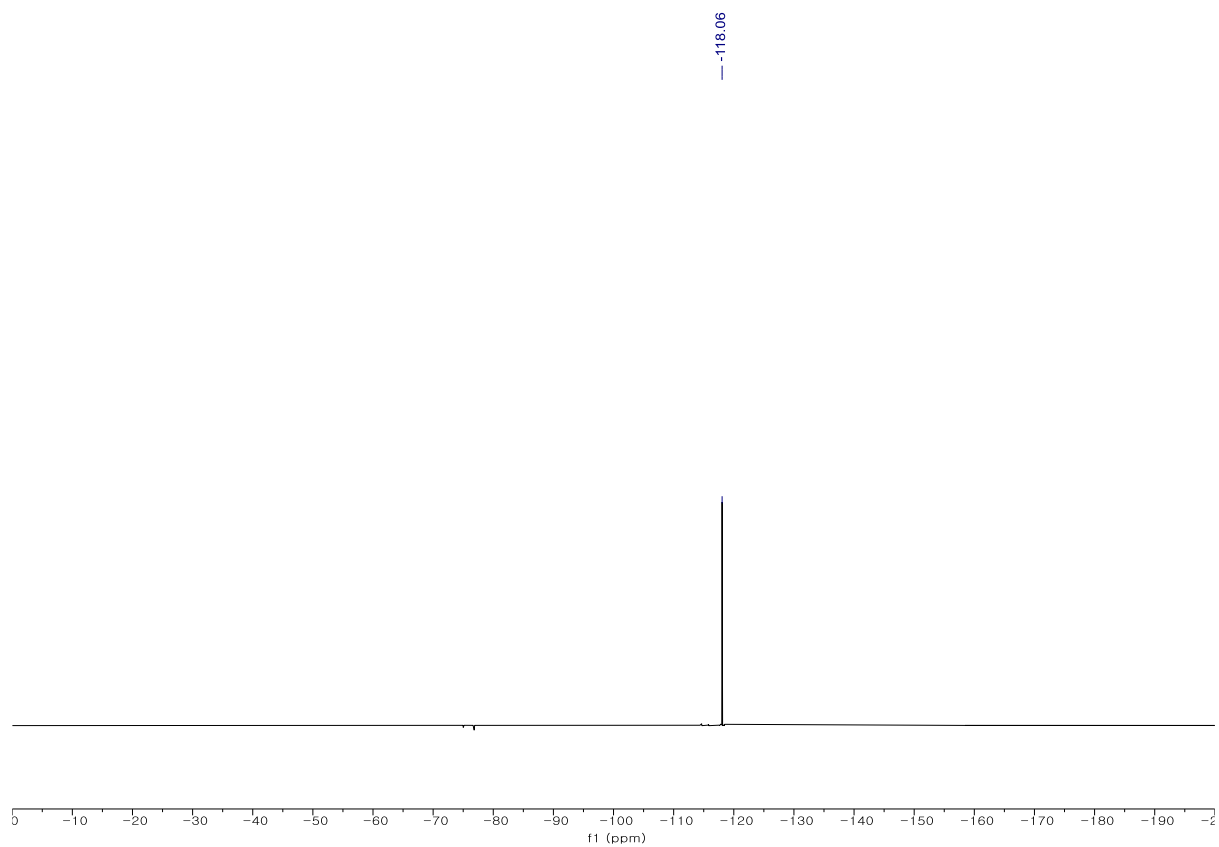
(R)-4-Benzyl-1-(4-fluorophenyl)azetidin-2-one, 59



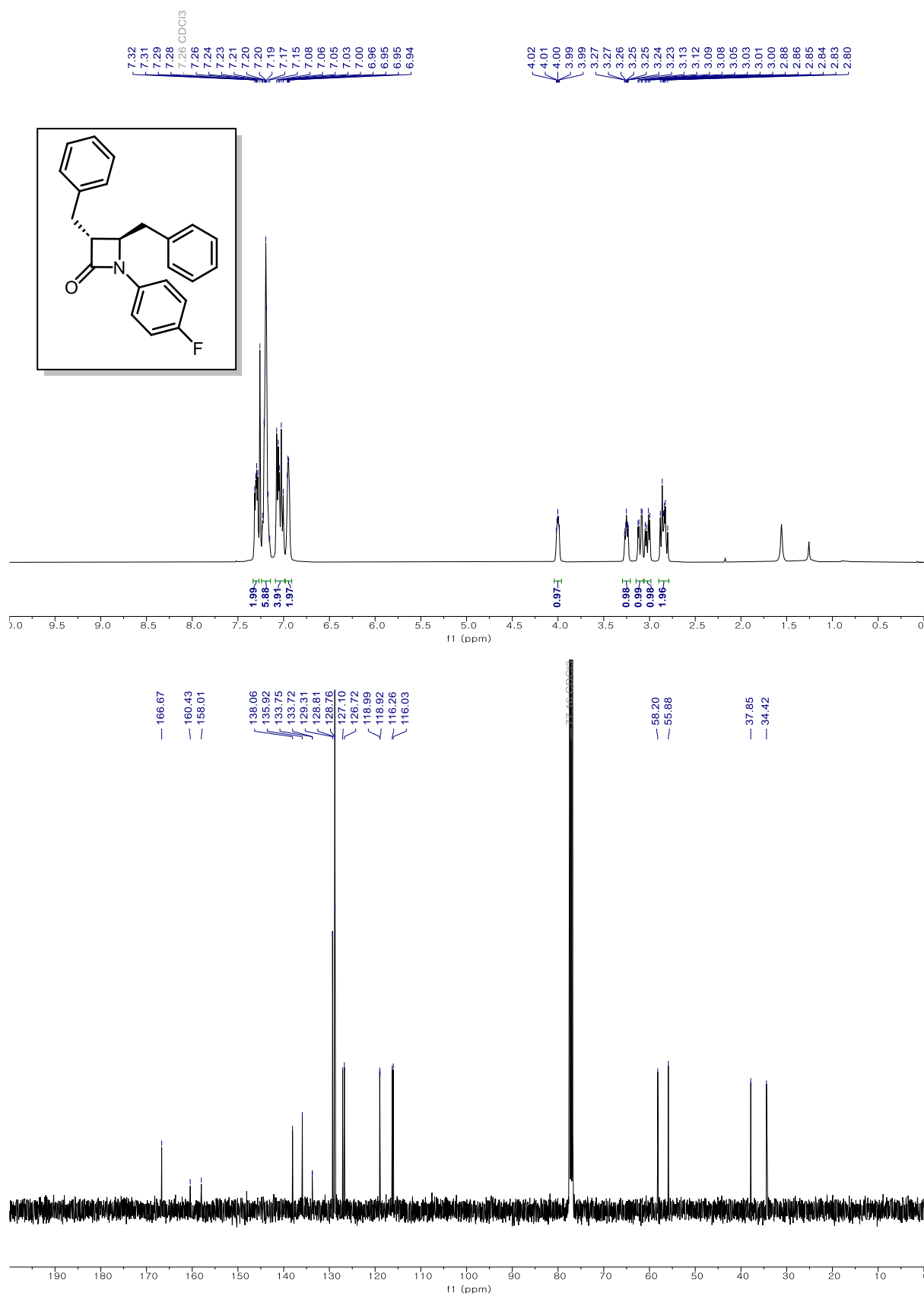


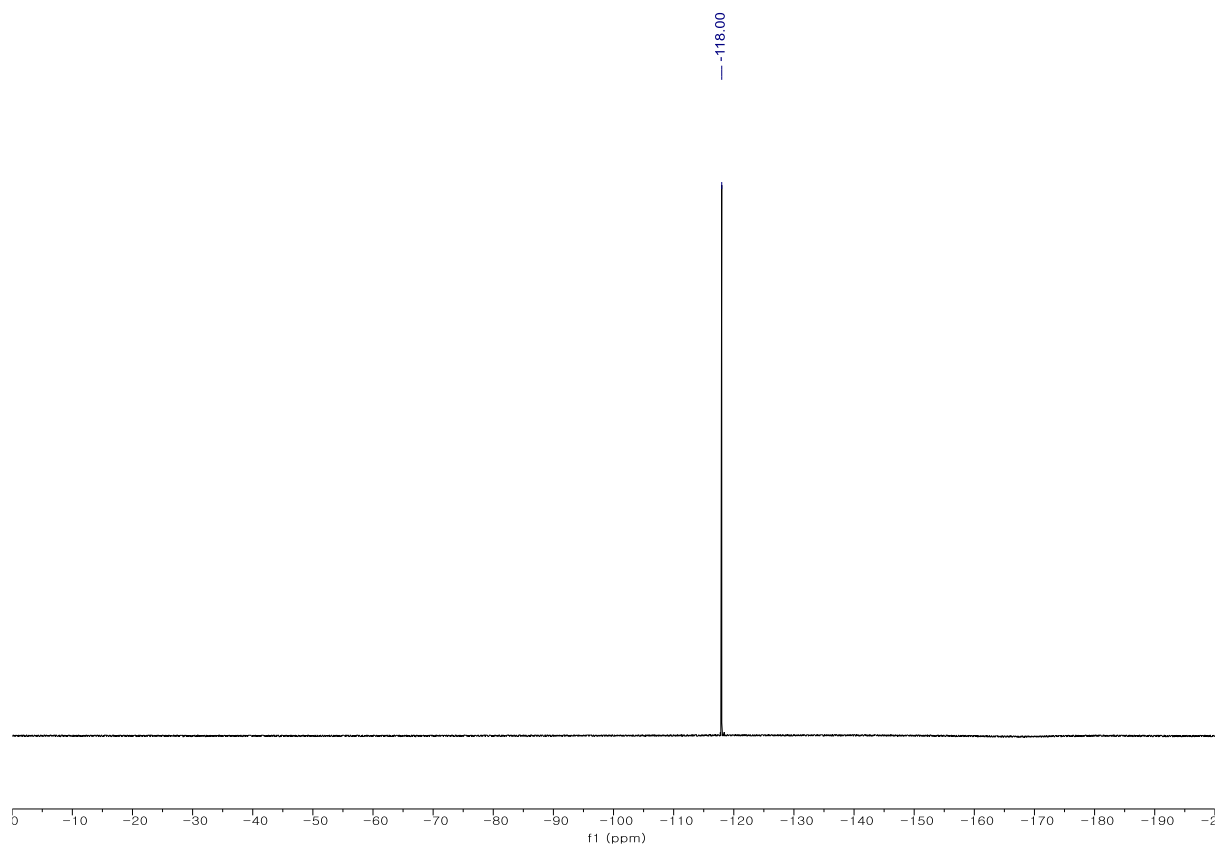
(3*R*,4*R*)-4-Benzyl-3-[3-(4-chlorophenyl)propyl]-1-(4-fluorophenyl)azetidin-2-one, 60



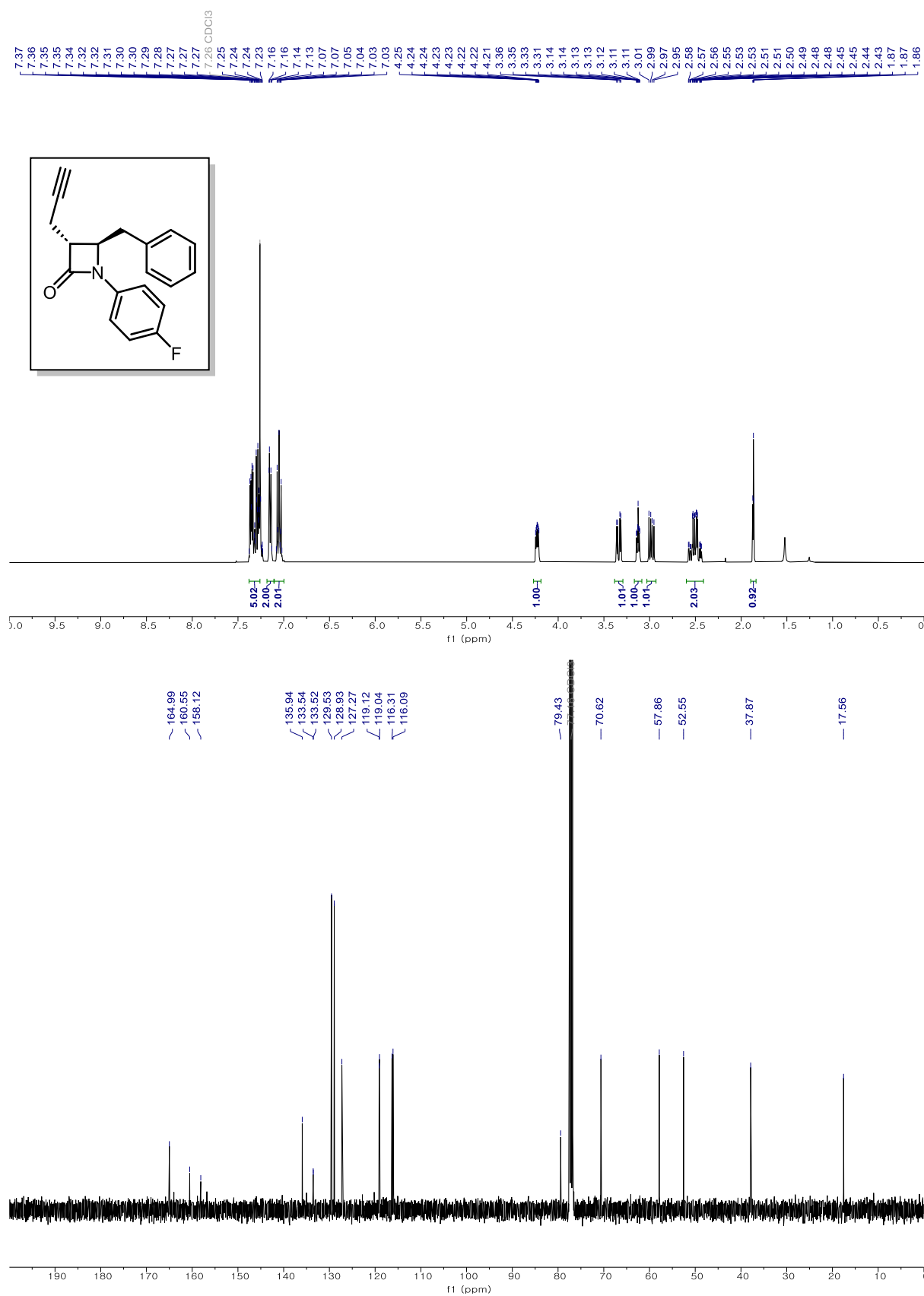


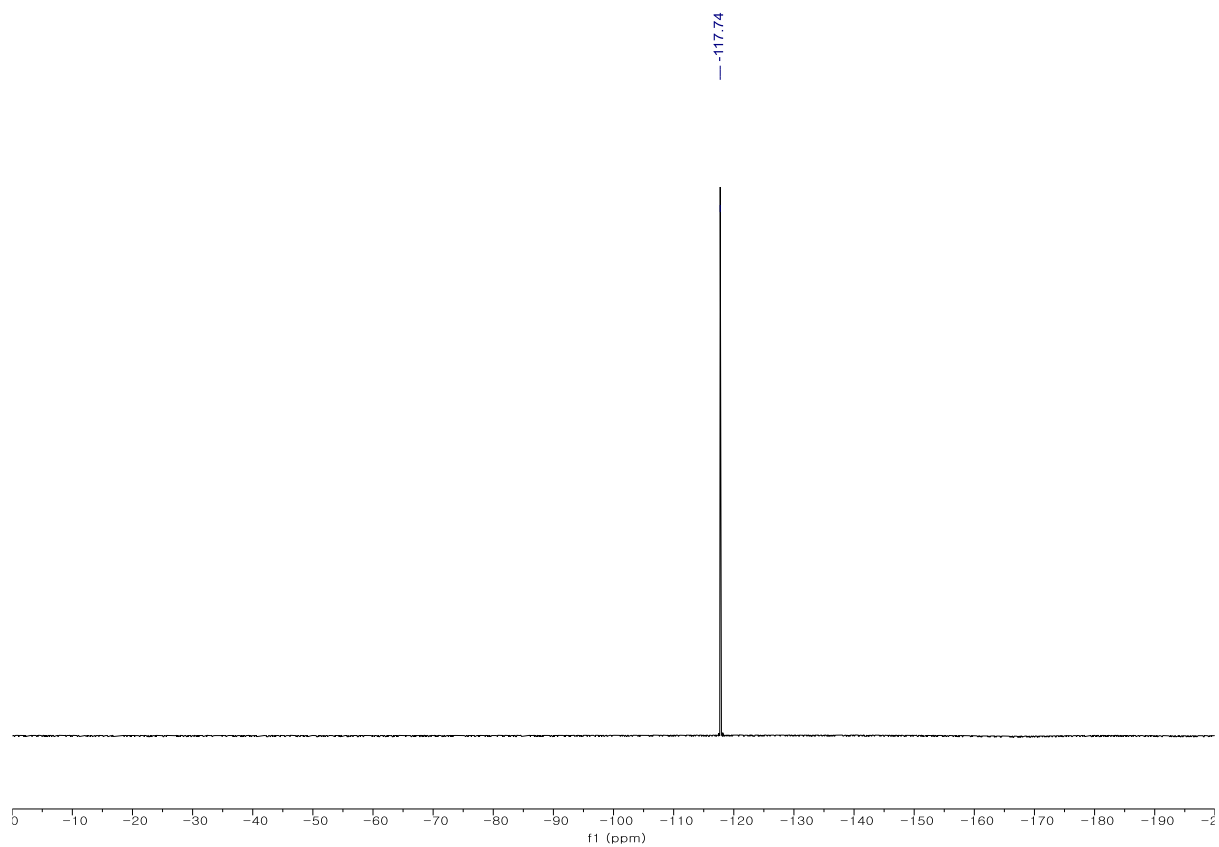
(3*R*,4*R*)-3,4-Dibenzyl-1-(4-fluorophenyl)azetidin-2-one, 61



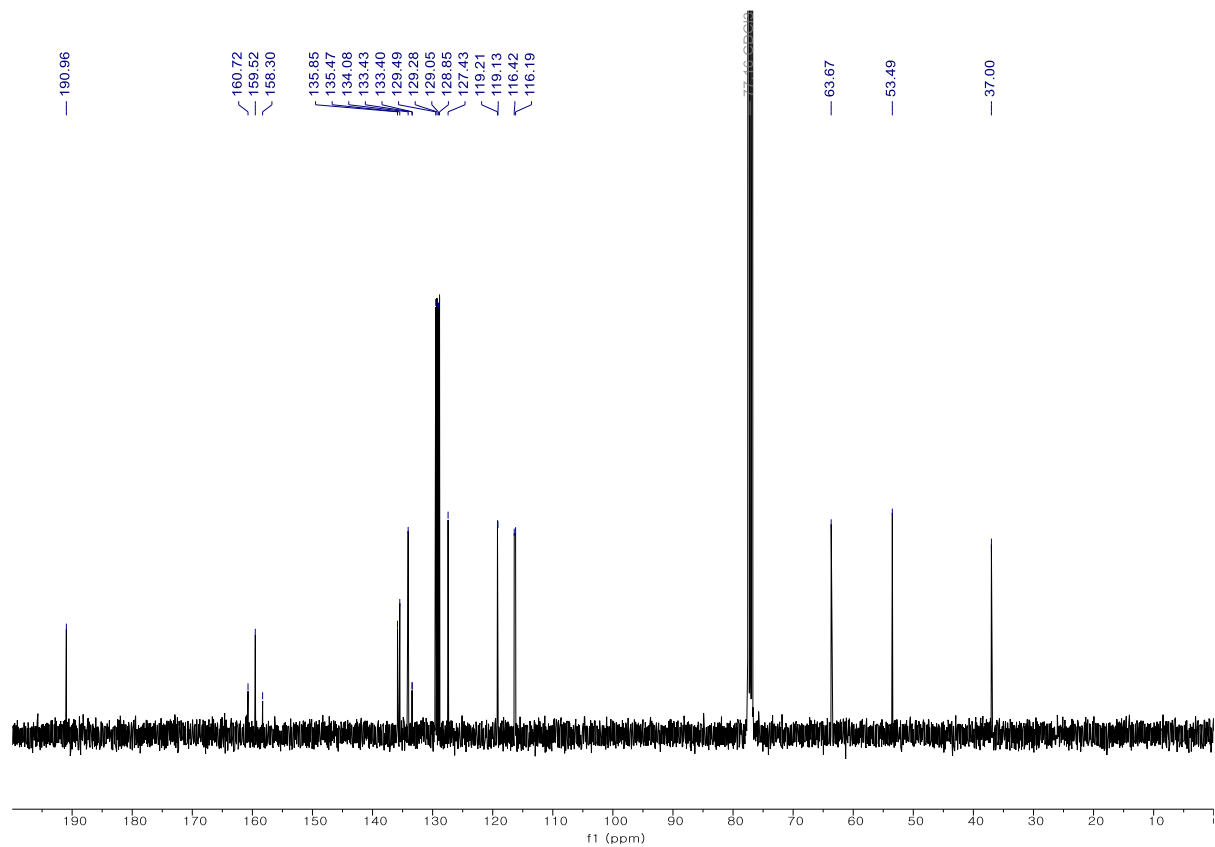
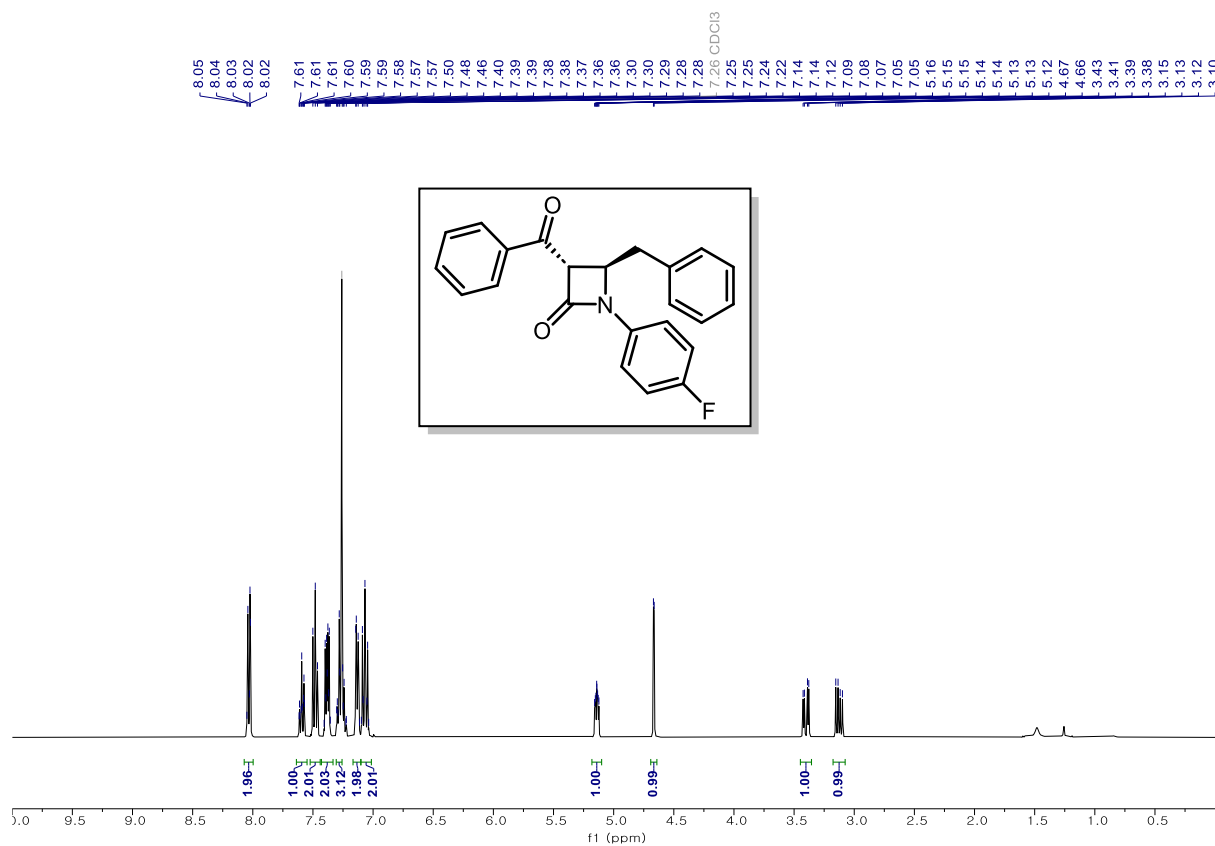


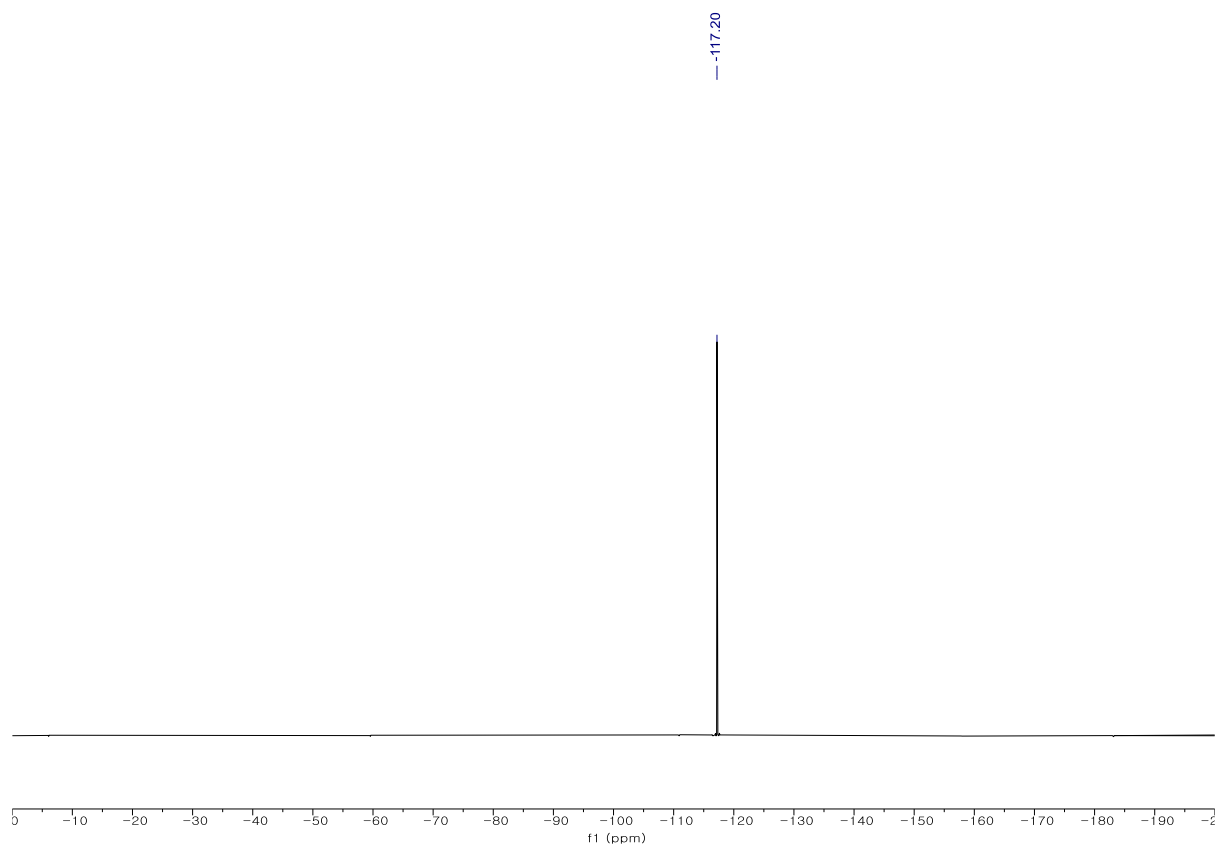
(3R,4R)-4-Benzyl-1-(4-fluorophenyl)-3-(prop-2-yn-1-yl)azetidin-2-one, 62



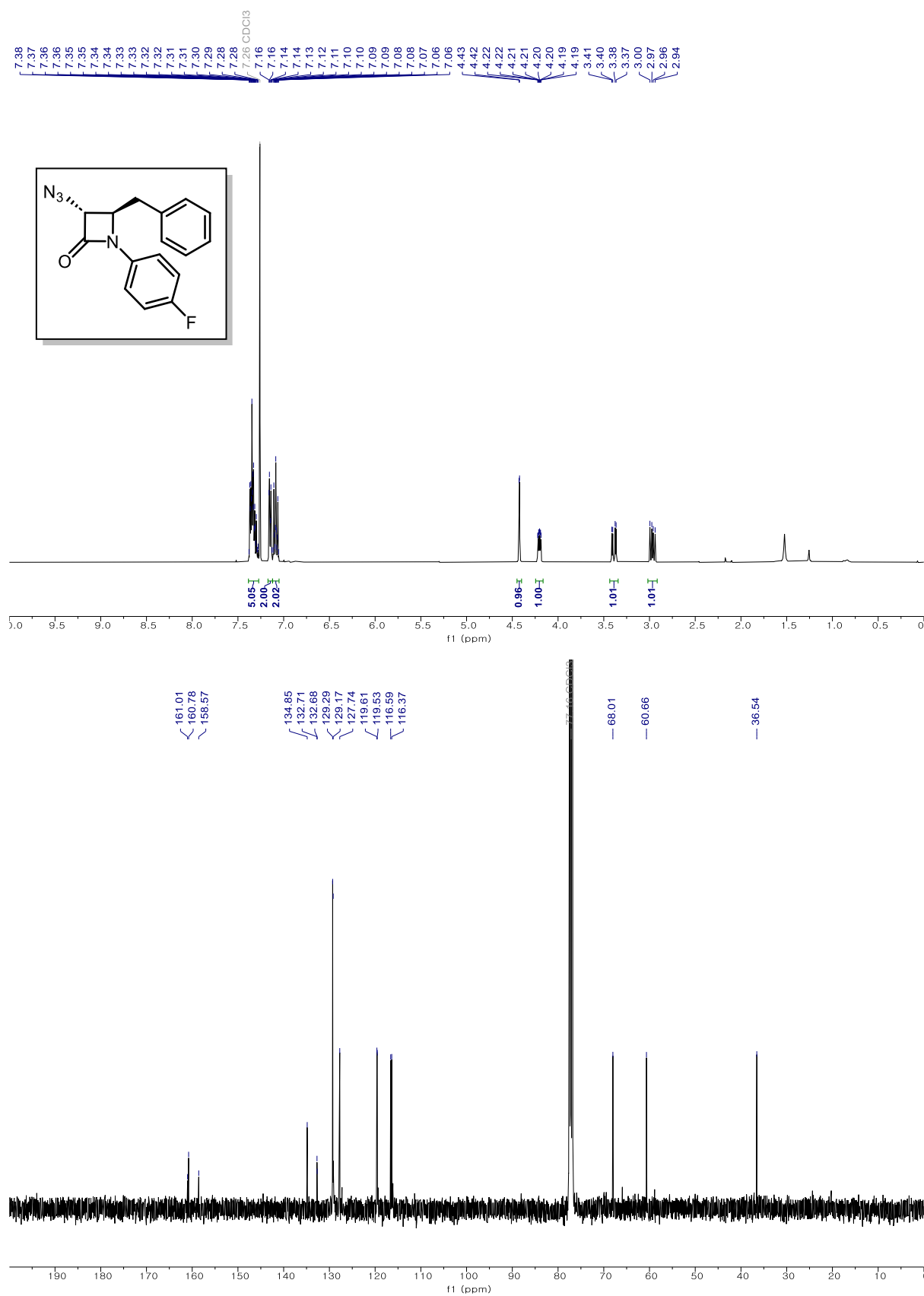


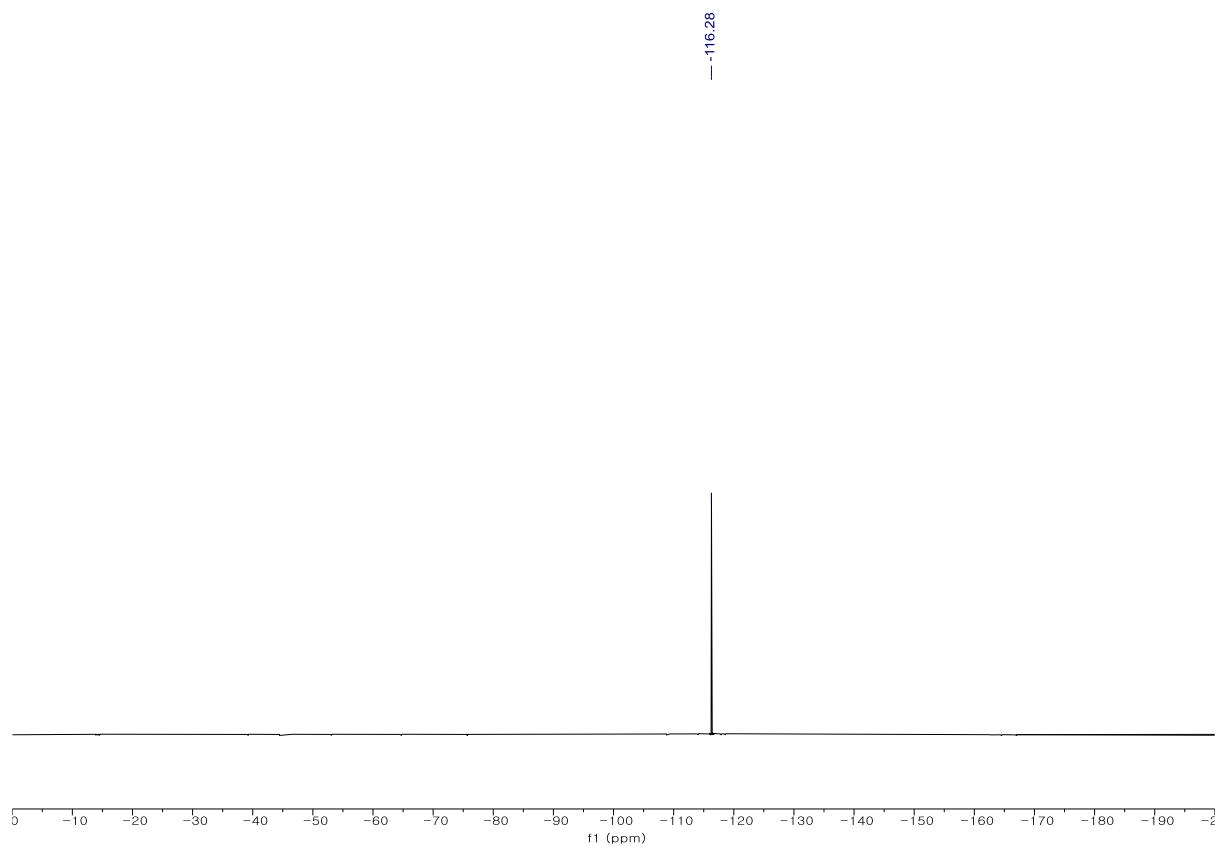
(3*S*,4*R*)-3-Benzoyl-4-benzyl-1-(4-fluorophenyl)azetidin-2-one, 63



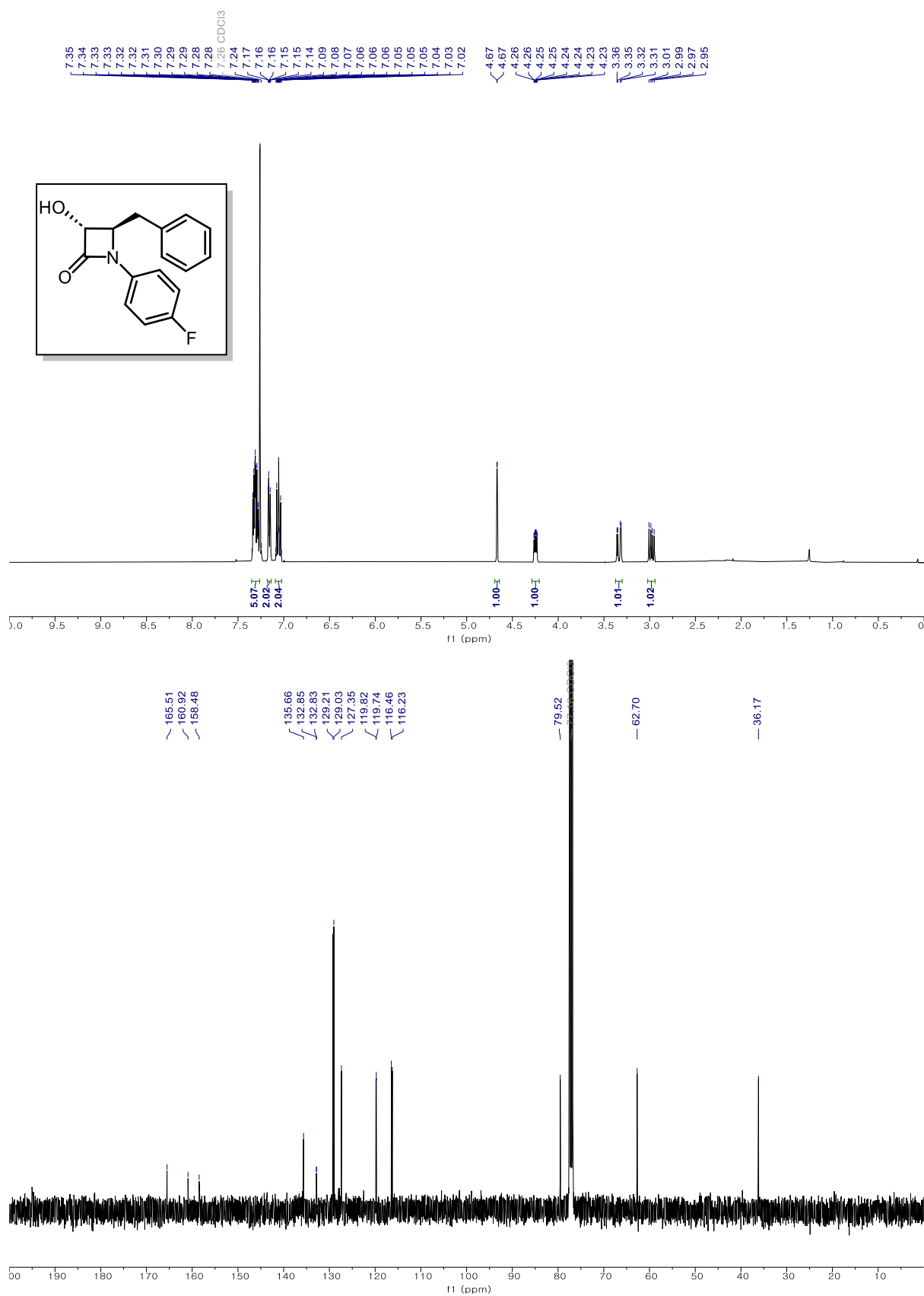


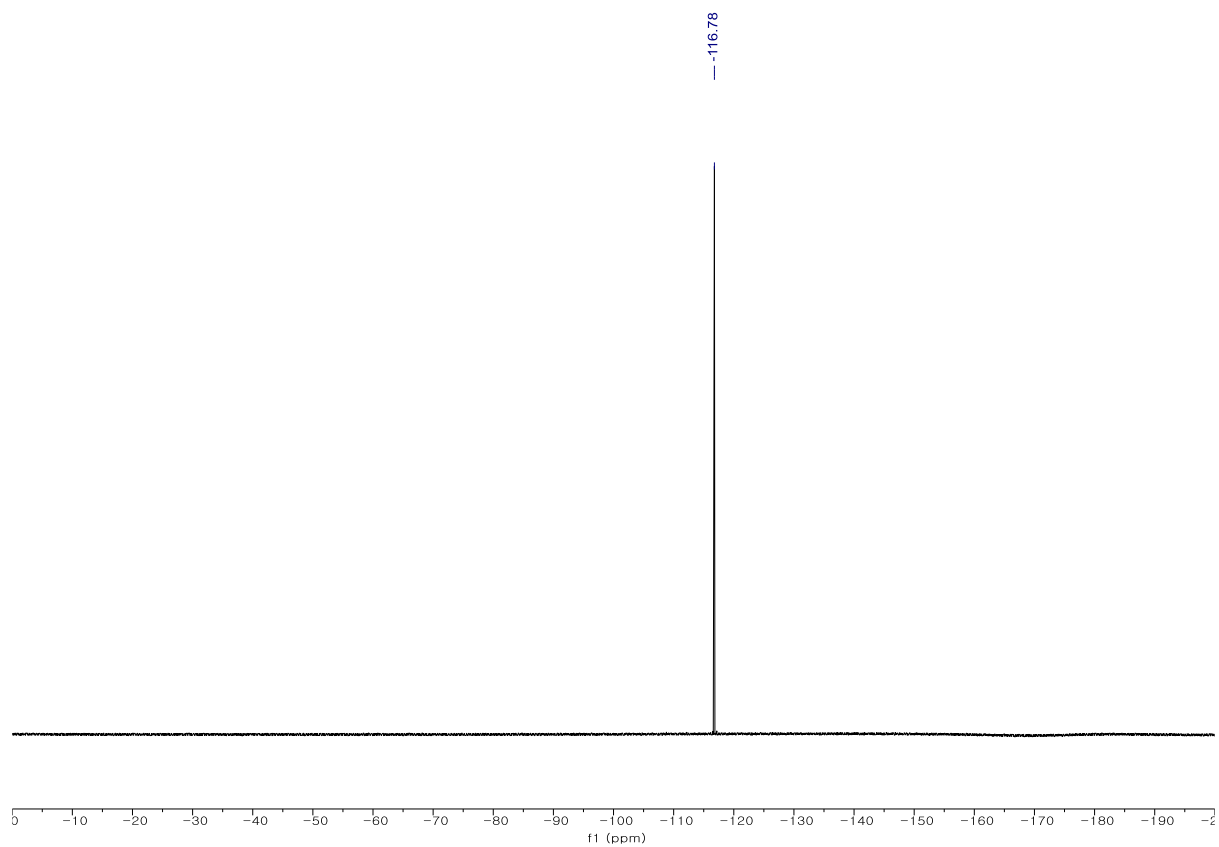
(3*R*,4*R*)-3-Azido-4-benzyl-1-(4-fluorophenyl)azetidin-2-one, 64





(3R,4R)-4-Benzyl-1-(4-fluorophenyl)-3-hydroxyazetidin-2-one, 65

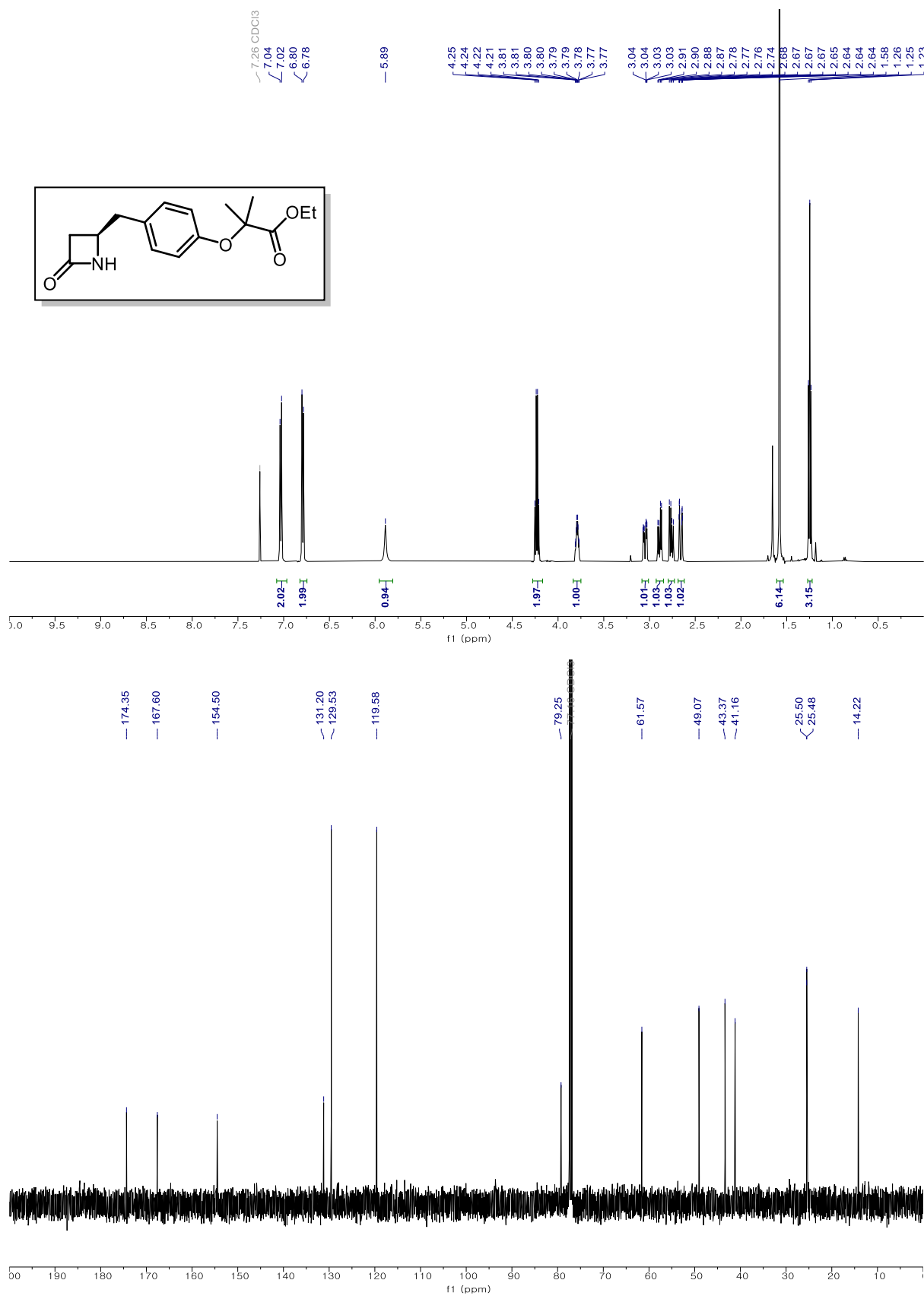




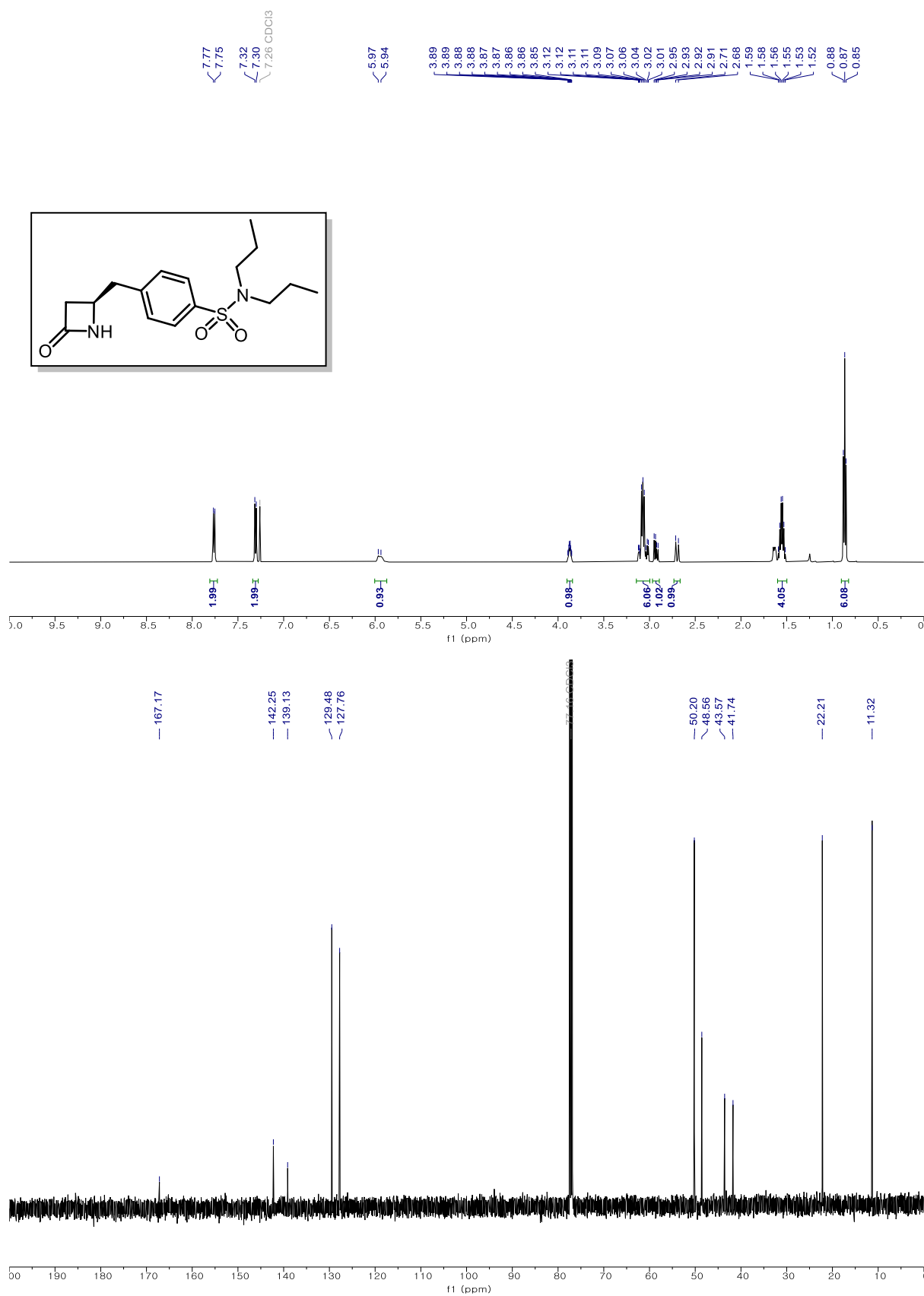
66



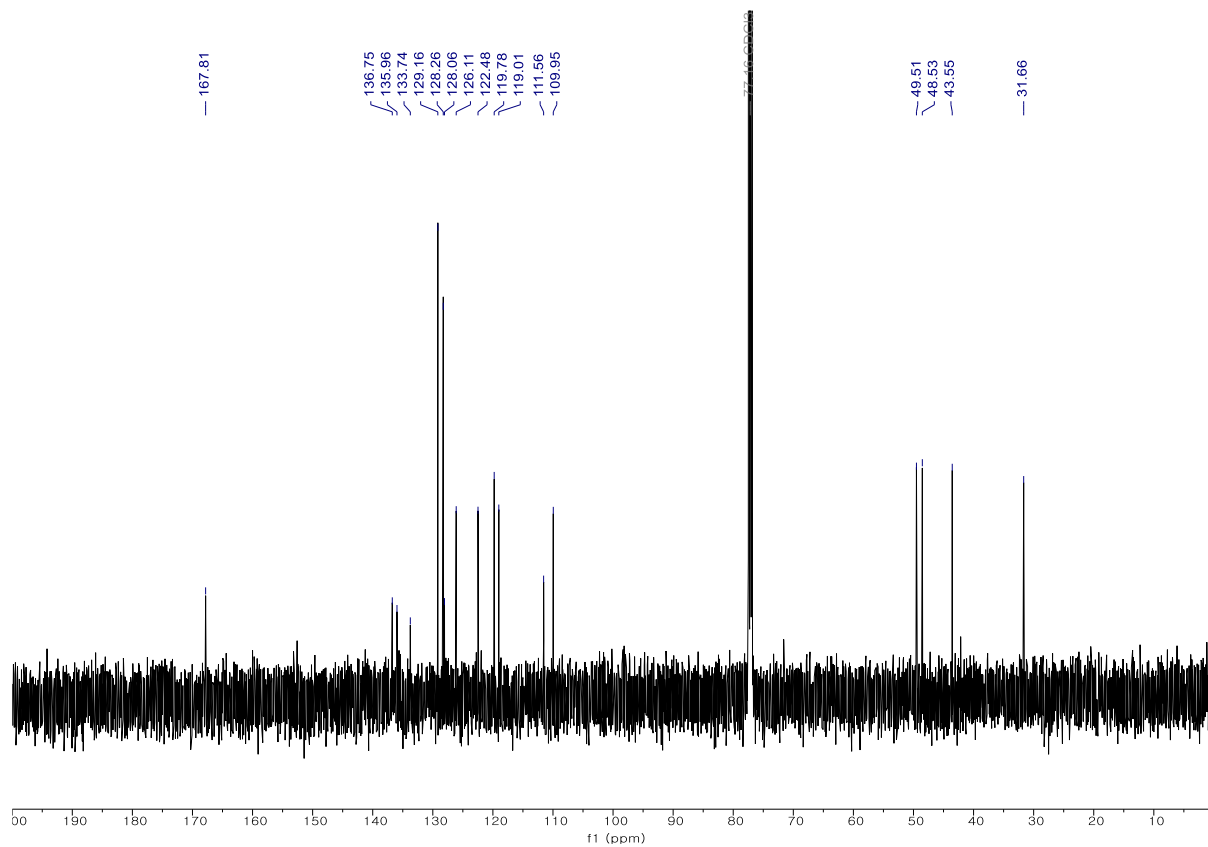
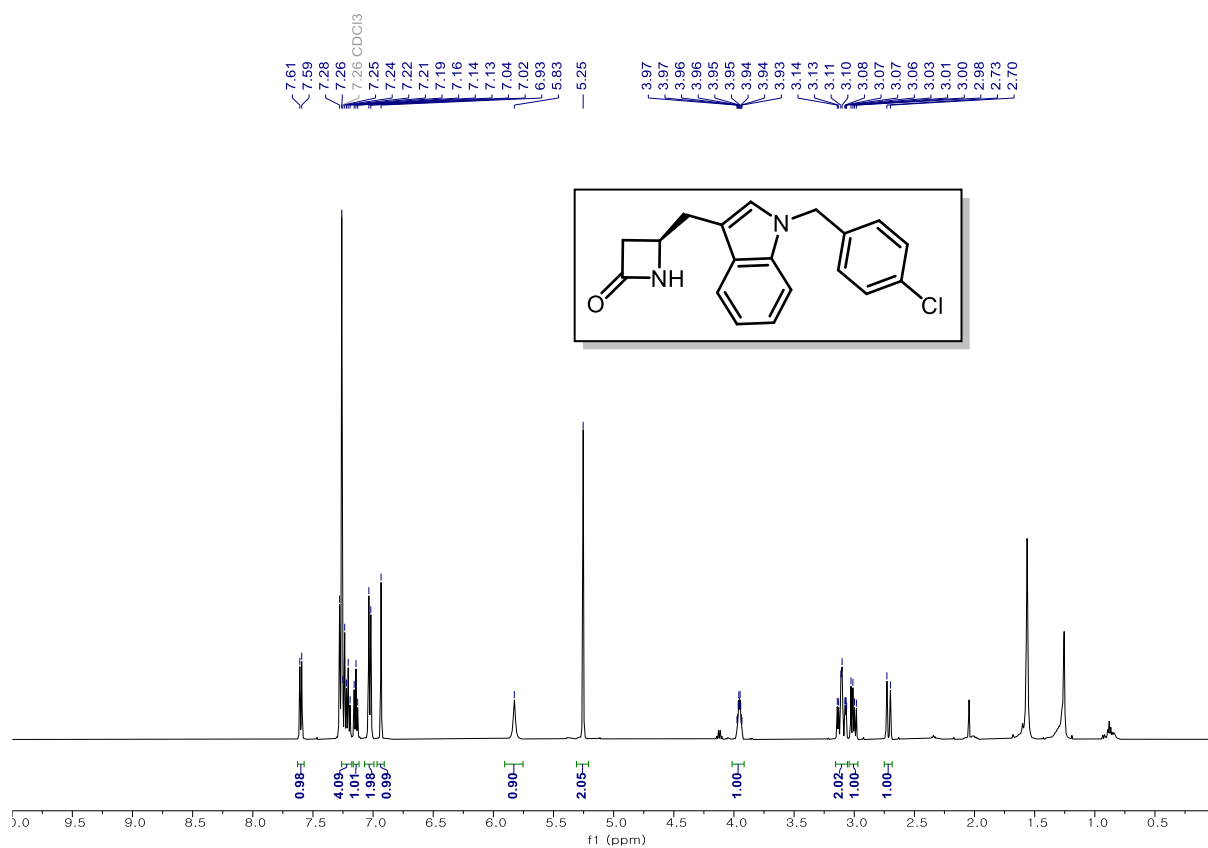
Ethyl (R)-2-methyl-2-{4-[(4-oxazetidin-2-yl)methyl]phenoxy}propanoate, 67



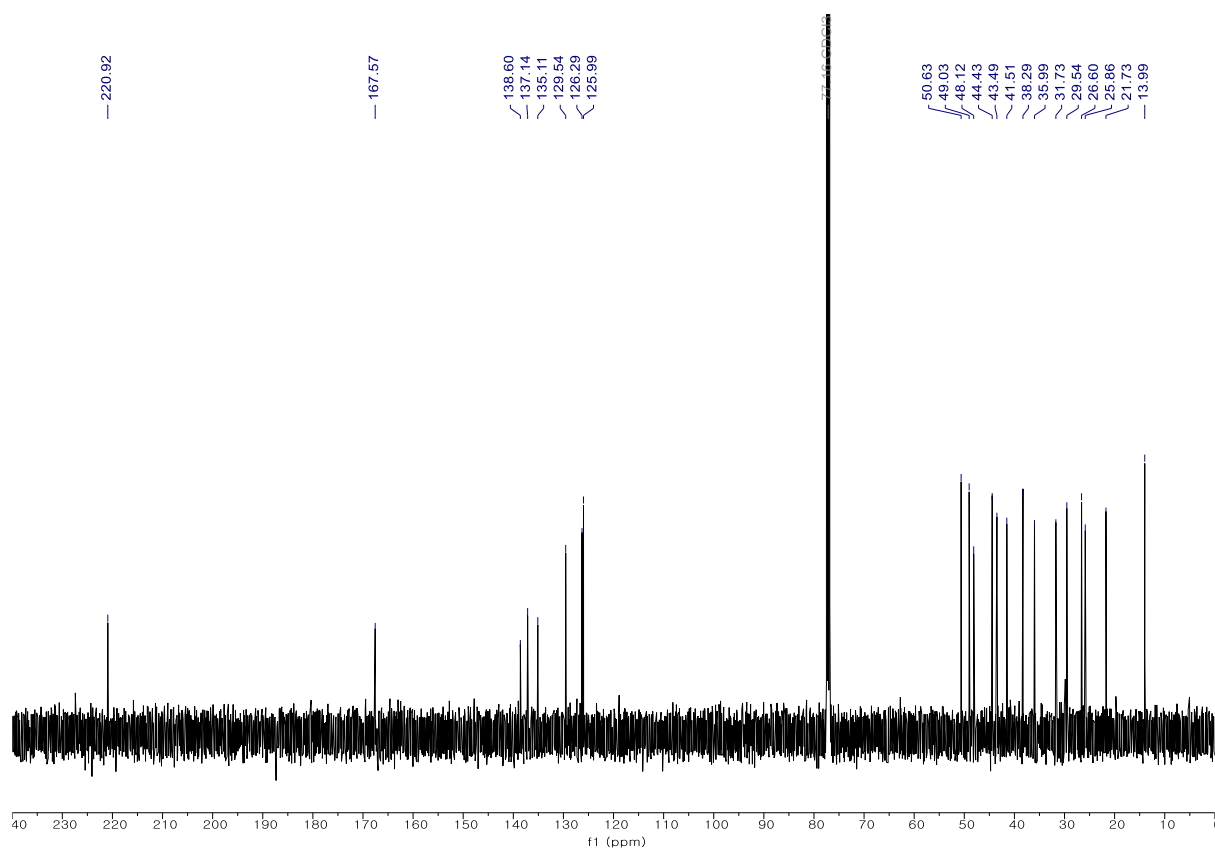
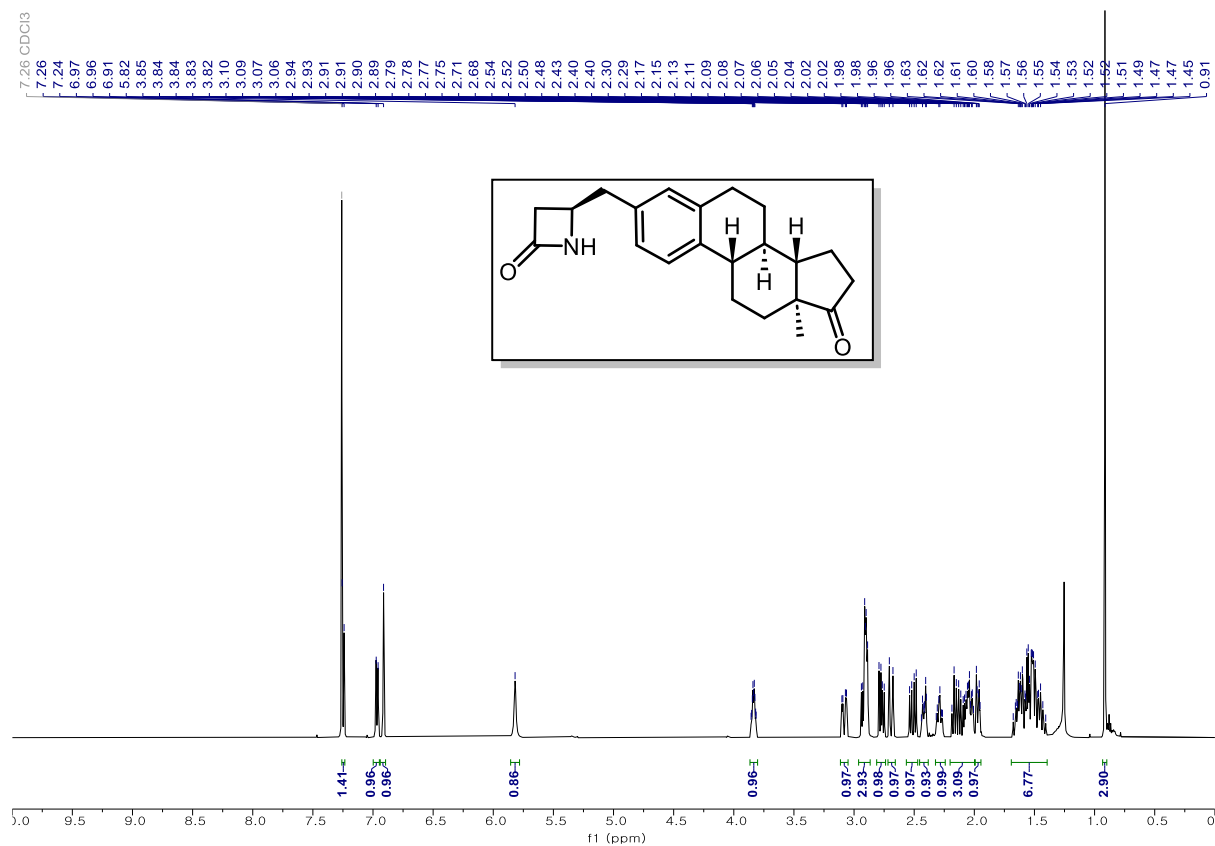
(R)-4-[(4-Oxoazetidin-2-yl)methyl]-N,N-dipropylbenzenesulfonamide, 68



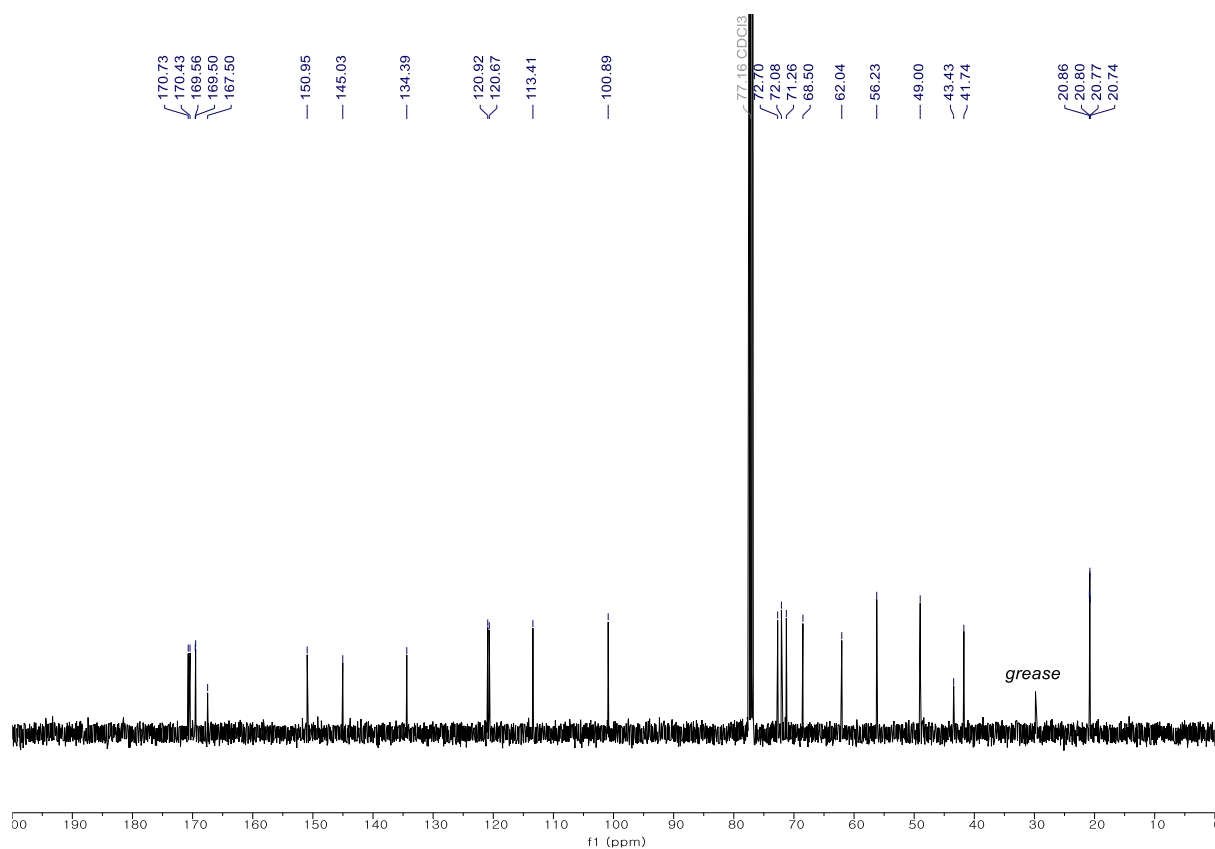
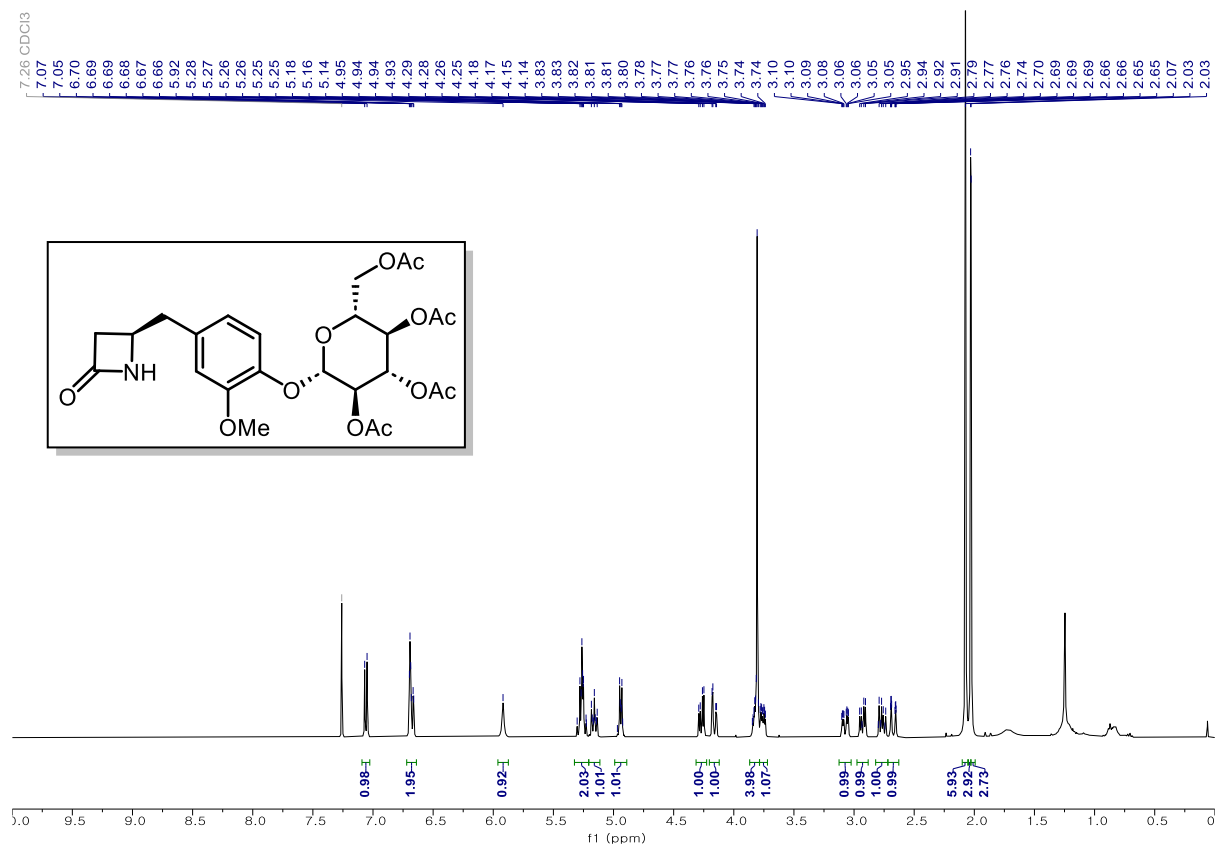
(R)-4-{[1-(4-Chlorobenzyl)-1H-indol-3-yl]methyl}azetidin-2-one, 69



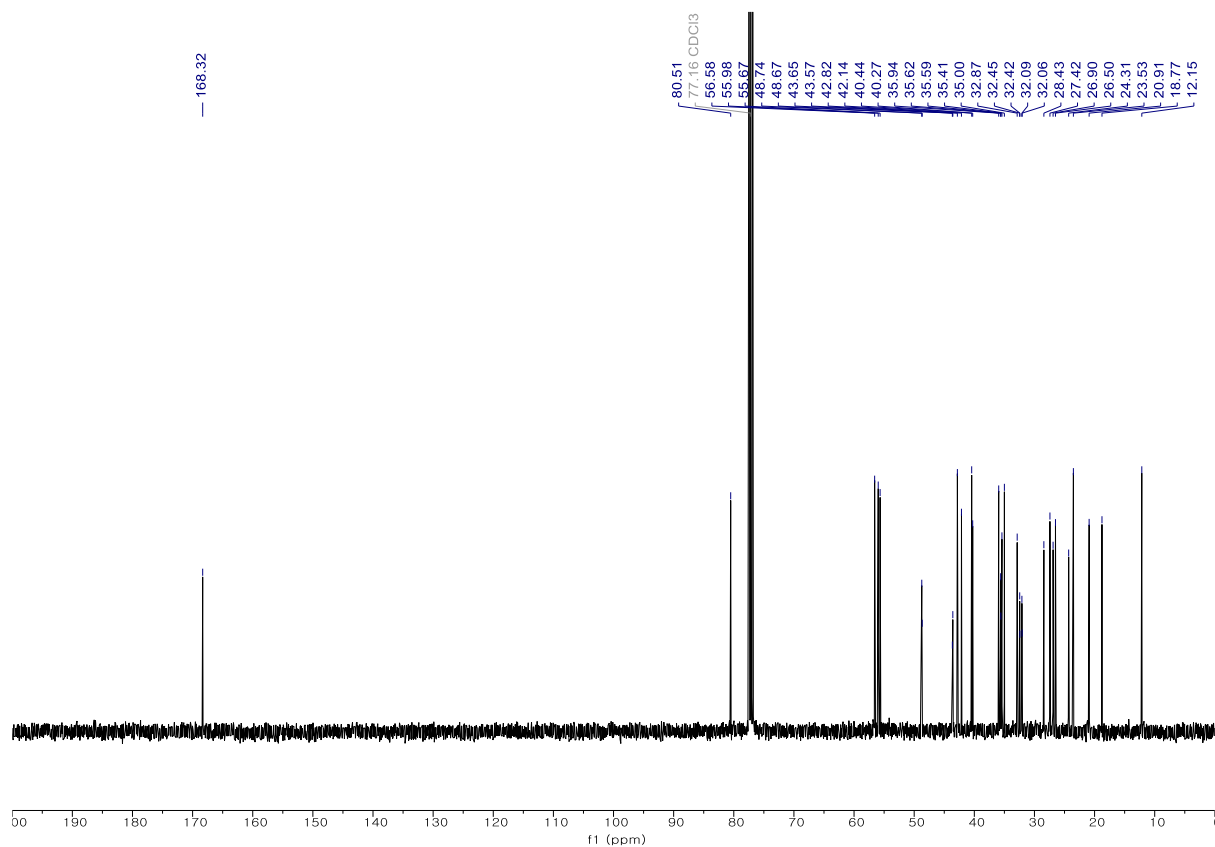
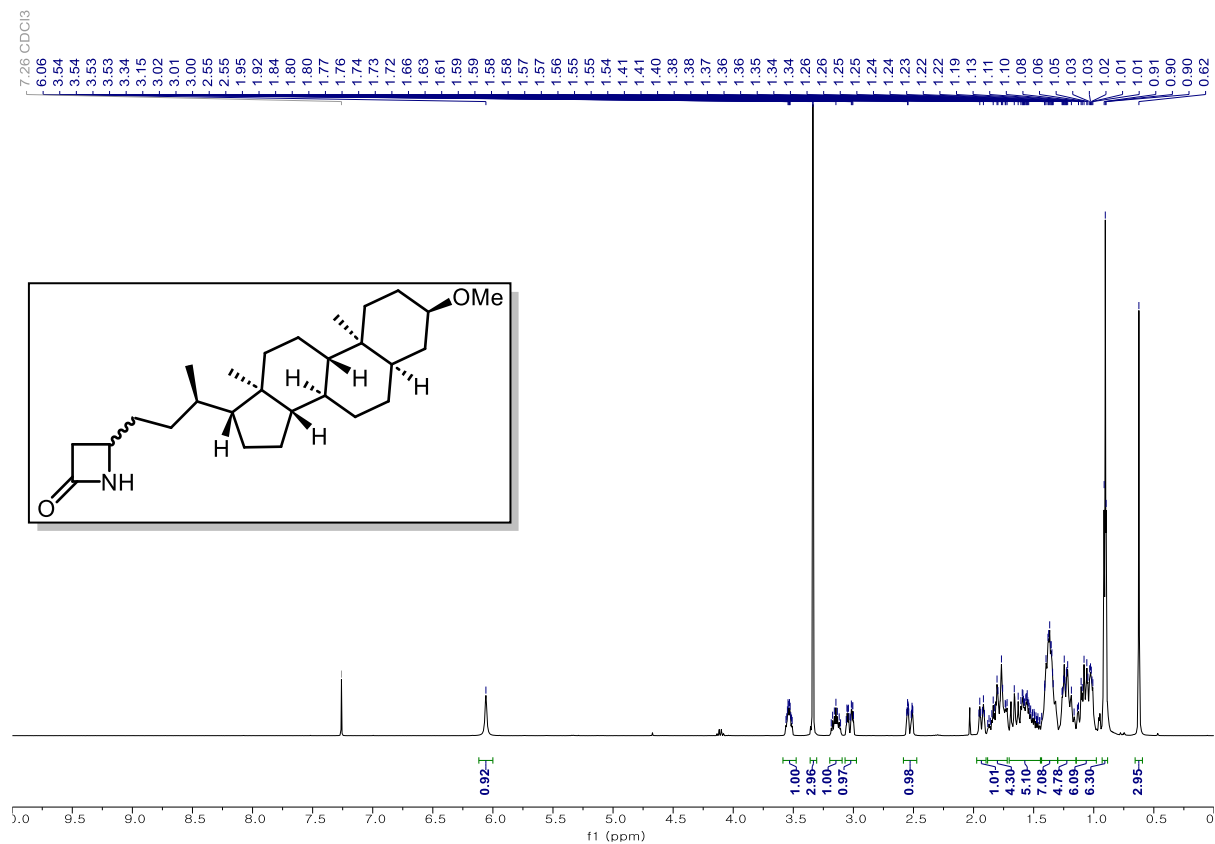
(R)-4-{[(8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-3-yl]methyl}azetidin-2-one, 70



(2R,3R,4S,5R,6S)-2-(Acetoxymethyl)-6-{2-methoxy-4-[(R)-4-oxoazetidin-2-yl)methyl]phenoxy}-tetrahydro-2H-pyran-3,4,5-triyl triacetate, 71

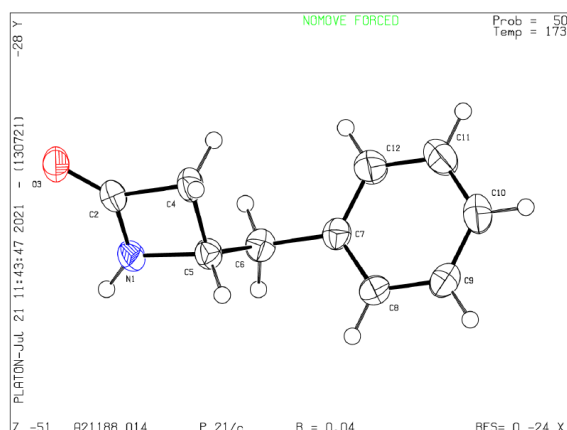


4-[(*R*)-3-[(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Methoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]butyl}azetidin-2-one, 72



Crystallographic Data

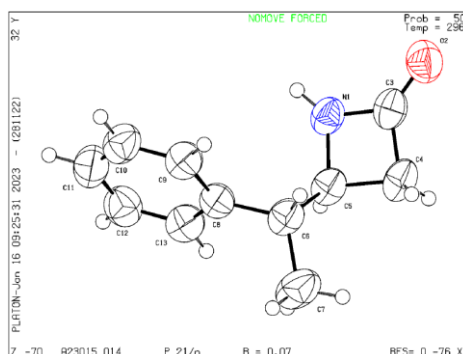
Crystallographic Data of Compound 2 (CCDC 2236294)



Supplementary Table 12. Crystal data and structure refinement for **Compound 2**.

Identification Code	Compound 2	
Empirical formula	$C_{10}H_{11}NO$	
Formula weight	161.20	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	$a = 14.2584(17)$ Å	$\alpha = 90^\circ$
	$b = 6.8590(7)$ Å	$\beta = 102.067(4)^\circ$
	$c = 9.4690(10)$ Å	$\gamma = 90^\circ$
Volume	$905.59(17)$ Å ³	
Z	4	
Density (calculated)	1.182 Mg/m ³	
Absorption coefficient	0.077 mm ⁻¹	
F(000)	344	
Crystal size	0.142 x 0.087 x 0.052 mm ³	
Theta range for data collection	3.310 to 27.441°.	
Index ranges	$-18 \leq h \leq 18$, $-8 \leq k \leq 8$, $-12 \leq l \leq 12$	
Reflections collected	14949	
Independent reflections	2042 [R(int) = 0.0508]	
Completeness to theta = 25.242°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.6243	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2042 / 0 / 112	
Goodness-of-fit on F ²	1.048	
Final R indices [I > 2sigma(I)]	R1 = 0.0403, wR2 = 0.0966	
R indices (all data)	R1 = 0.0522, wR2 = 0.1066	
Largest diff. peak and hole	0.203 and -0.143 e·Å ⁻³	

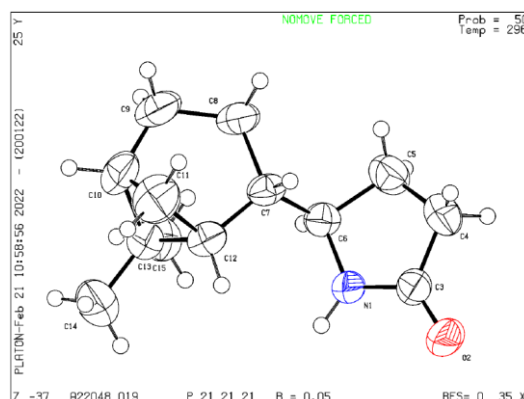
Crystallographic Data of Compound 15 (CCDC 2236394)



Supplementary Table 13. Crystal data and structure refinement for **Compound 15**.

Identification Code	Compound 15	
Empirical formula	$C_{11}H_{13}NO$	
Formula weight	175.22	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	$a = 5.728(2)$ Å	$\alpha = 90^\circ$
	$b = 20.161(7)$ Å	$\beta = 105.583(14)^\circ$
	$c = 8.785(3)$ Å	$\gamma = 90^\circ$
	$V = 977.2(6)$ Å ³	
Volume	977.2(6) Å ³	
Z	4	
Density (calculated)	1.191 Mg/m ³	
Absorption coefficient	0.076 mm ⁻¹	
F(000)	376	
Crystal size	0.121 x 0.081 x 0.028 mm ³	
Theta range for data collection	2.610 to 27.047°.	
Index ranges	$-7 \leq h \leq 7$, $-25 \leq k \leq 25$, $-11 \leq l \leq 11$	
Reflections collected	10933	
Independent reflections	2124 [R(int) = 0.1155]	
Completeness to theta = 25.242°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7455 and 0.5139	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2124 / 0 / 128	
Goodness-of-fit on F ²	1.011	
Final R indices [I > 2sigma(I)]	R1 = 0.0687, wR2 = 0.1174	
R indices (all data)	R1 = 0.1539, wR2 = 0.1429	
Largest diff. peak and hole	0.145 and -0.133 e·Å ⁻³	

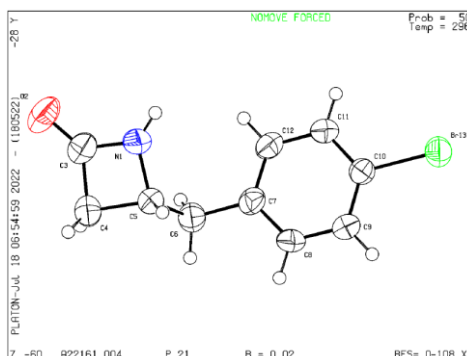
Crystallographic Data of Compound 17 (CCDC 2236312)



Supplementary Table 14. Crystal data and structure refinement for **Compound 17**.

Identification Code	Compound 17 (CCDC 2236312)	
Empirical formula	$C_{13}H_{21}NO$	
Formula weight	207.31	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	$a = 7.8775(6)$ Å	$\alpha = 90^\circ$
	$b = 10.9078(8)$ Å	$\beta = 90^\circ$
	$c = 14.1529(12)$ Å	$\gamma = 90^\circ$
Volume	$1216.10(16)$ Å ³	
Z	4	
Density (calculated)	1.132 Mg/m ³	
Absorption coefficient	0.071 mm ⁻¹	
F(000)	456	
Crystal size	0.151 x 0.138 x 0.095 mm ³	
Theta range for data collection	2.878 to 28.294°.	
Index ranges	$-10 \leq h \leq 9$, $-13 \leq k \leq 14$, $-18 \leq l \leq 18$	
Reflections collected	15378	
Independent reflections	2986 [R(int) = 0.0659]	
Completeness to theta = 25.242°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.6934	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2986 / 0 / 147	
Goodness-of-fit on F ²	1.039	
Final R indices [I > 2sigma(I)]	R1 = 0.0525, wR2 = 0.0980	
R indices (all data)	R1 = 0.0993, wR2 = 0.1146	
Absolute structure parameter	-0.1(9)	
Largest diff. peak and hole	0.131 and -0.112 e·Å ⁻³	

Crystallographic Data of Compound (R)-22 (CCDC 2236313)



Supplementary Table 15. Crystal data and structure refinement for **Compound (R)-22**.

Identification Code	Compound (R)-22 (CCDC 2236313)	
Empirical formula	C ₁₀ H ₁₀ Br N O	
Formula weight	240.10	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2 ₁	
Unit cell dimensions	a = 6.1255(4) Å	α = 90°
	b = 5.0950(4) Å	β = 93.841(2)°
	c = 15.8554(12) Å	γ = 90°
Volume	493.73(6) Å ³	
Z	2	
Density (calculated)	1.615 Mg/m ³	
Absorption coefficient	4.121 mm ⁻¹	
F(000)	240	
Crystal size	0.161 x 0.062 x 0.019 mm ³	
Theta range for data collection	2.575 to 27.990°.	
Index ranges	-7 ≤ h ≤ 8, -6 ≤ k ≤ 6, -20 ≤ l ≤ 20	
Reflections collected	10476	
Independent reflections	2353 [R(int) = 0.0406]	
Completeness to theta = 25.242°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.5393	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2353 / 1 / 125	
Goodness-of-fit on F ²	1.008	
Final R indices [I > 2σ(I)]	R1 = 0.0238, wR2 = 0.0505	
R indices (all data)	R1 = 0.0292, wR2 = 0.0521	
Absolute structure parameter	0.028(13)	
Largest diff. peak and hole	0.237 and -0.175 e·Å ⁻³	

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