Intramolecular Ester Enolate-Imine Cyclization Reactions for the Asymmetric Synthesis of Polycyclic β-Lactams and Cyclic β-Amino Acid Derivatives

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General Experimental Details

All reactions were performed under a nitrogen atmosphere in oven-dried apparatus, unless otherwise stated. Anhydrous acetonitrile, dichloromethane and tetrahydrofuran were obtained from an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to the fraction of petroleum ether boiling at 40-60 °C. All other commercially available compounds were used as obtained from the chemical suppliers. Analytical thin layer chromatography was performed using commercially available aluminium backed plates coated with Merck G/UV254 neutral silica. Plates were visualised under UV light (at 254 nm) or by staining with phosphomolybdic acid followed by heating. Flash chromatography was performed using chromatography grade, silica 60 Å particle size 35-70 microns from Fisher Scientific. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C{^{1}H} spectra were recorded at 75 MHz on a Brüker Avance 300 spectrometer. Chemical shifts, δ, are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; app., apparent and br., broad.. Coupling constants, *J*, are quoted to the nearest 0.5 Hz. High resolution mass spectra were recorded on a Brüker Daltonics microTOF spectrometer with an electrospray source and external calibration. Masses were recorded in positive electrospray ionisation mode and were introduced by flow injection. Masses are accurate to 5 ppm and data was processed using DataAnalysis software from

Brüker Daltonics. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with only selected absorbances quoted as *v* in cm^{-1}.

General Procedures

General Procedure 1: Acetal Formation[1]

To a stirred substituted 2-bromobenzadehyde (1.0 equiv.) in toluene (50 mL), 1,3-propanediol (1.5 equiv.) and *p*-toluene sulphonic acid (PTSA) (0.1 equiv.) were added and the solution was heated at reflux under Dean-Stark conditions for 3 hours. After cooling to room temperature, the reaction mixture was washed with water, the organic extract dried using $MgSO_4$ and the solvent evaporated under reduced pressure. The crude compounds were purified by recrystallisation using a suitable solvent system.

General Procedure 2: Heck Reaction on Protected 2-Bromobenzaldehydes[2]

To a solution of substituted 2-(2-bromophenyl)-1,3-dioxolan (1.0 equiv.) in acetonitrile, palladium(II) acetate (0.05 equiv.) and tri(*o*-tolyl)phosphine (0.10 equiv.) were added. Diisopropylethylamine (3.0 equiv.) and the appropriate acrylate (1.0 equiv.) were added and the mixture was heated at reflux for 24 hours. After cooling to room temperature, the reaction was diluted with water (50 mL) and the aqueous layer extracted with toluene (2 x 50 mL). The combined organic extracts were combined and washed with water (2 x 50 mL) and brine (30 mL) then dried over $MgSO_4$. The mixture was filtered through a plug of Celite® and then the solvent removed under reduced pressure. Crude compounds were purified by flash column chromatography.

General Procedure 3: Chemoselective Conjugate Reduction of Esters[3]

Substituted ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoates (2.0 equiv.) were stirred in ethanol (10 mL) for 30 minutes prior to the addition of cobalt(II) chloride hexahydrate (0.02 equiv.). The solution was then cooled to 0 °C and sodium borohydride (4.0 equiv.) was added. The solution was then allowed to warm to room temperature and stirred for up to 48 hours. The reaction was then quenched with water (50 mL) and diluted with ethyl acetate (30 mL). The organic layer was separated, washed with brine (50 mL), dried with

$MgSO_4$ and the solvent evaporated under reduced pressure. Crude compounds were purified by flash column chromatography.

General Procedure 4: Acetal Deprotection

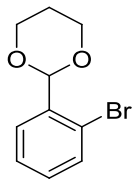
Substituted ethyl-3-(2-formylphenyl)propanoates were added to a solution of acetic acid: water (7 mL : 3 mL) and left to stir open to the air overnight. The residue was partioned between water (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) and brine (30 mL). The organics are then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure to yield pure products.

General Procedure 5: Imine-Enolate Cyclisation Reaction for 1a-g

Substituted (*S,E*)-ethyl-3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoates (1.0 equiv.) were dissolved in THF. 15-Crown-5 (1.1 equiv.) and NaHMDS (1.1 equiv.) were added and the mixture was left stirring for 8 hours at -40 ^{0}C. The reaction was quenched with a saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the organic layers were combined and washed with water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. Crude compounds were purified by flash column chromatography.

Acetals

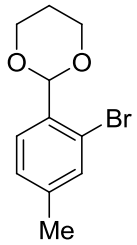
2-(2-Bromophenyl)-1,3-dioxane



The title compound was prepared according to General Procedure **1** from 2-bromobenzadehyde (10.0 g, 54 mmol), 1,3-propanediol (6.16 g, 81 mmol) and PTSA (0.86 g, 5 mmol). The crude was purified by recrystallisation from diethyl ether, yielding a white solid (10.47 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.59 (1H, dd, J = 8.0 and 1.5 Hz, CBrC*H*), 7.40 (1H, d, J = 8.0 Hz, Ar), 7.20 (1H, t, J = 7.5 Hz, Ar), 7.04 (1H, t of d, J = 8.0 and 1.5 Hz, Ar), 5.63 (1H, s, ArC*H*), 4.10 (2H, dd, J = 11.0 and 5.0 Hz, OCH_2), 3.85 (2H, t of d, J = 12.5 and 2.0 Hz, OCH_2), 2.16-1.98 (1H, m, OCH_2CH_2), 1.24 (1H, broad d, J = 13.5 Hz, OCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C =137.6, 132.6, 130.4, 128.2, 127.6, 122.4, 100.9, 67.6, 25.7; IR (film / cm^{-1}) v = 2846 (O-CH-O); HRMS: m/z (ES) 243.0018, $C_{10}H_{11}O_2Br$ $[M+H]^+$ requires 243.0021; mp 53-55 ^{0}C.

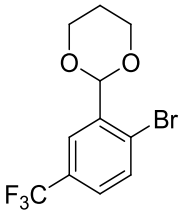
2-(2-Bromo-4-methylphenyl)-1,3-dioxane



The title compound was prepared according to General Procedure **1** from 2-bromo-4-methylbenzaldehyde 0.56 g, 2.8 mmol), 1,3-propanediol (0.30 mL, 4.2 mmol) and PTSA (0.05 g, 0.2 mmol). The crude was purified by recrystallisation from diethyl ether, yielding a pale yellow oil (0.61 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.47 (1H, d, J = 8.0 Hz, CBrC*H*), 7.26 (1H, d, J = 1.0 Hz, Ar), 7.04 (1H, d, J = 8.0 Hz, Ar), 5.63 (1H, s, ArC*H*), 4.18-4.10 (2H, app. ddd, J = 12.0, 5.0 and 1.0 Hz, OCH_2), 3.95-3.85 (2H, m, OCH_2), 2.21 (3H, s, ArCH_3), 2.18-2.04 (1H, m, OCH_2CH_2), 1.32 (1H, app. d of septet, J = 13.5 and 1.5, OCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 140.6, 134.7, 133.0, 128.3, 127.8, 122.1, 101.0, 67.6, 25.7, 20.9; IR (film / cm^{-1}) v = 2851 (O-CH-O); HRMS: m/z (ES) 279.0002, $C_{11}H_{13}O_2Br$ $[M+Na]^+$ requires 278.9997;

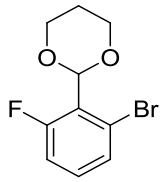
2-(2-Bromo-5-(trifluoromethyl)phenyl)-1,3-dioxane



The title compound was prepared according to General Procedure **1** from 2-bromo-5-(trifluoromethyl)benzaldehyde (3.59 g, 14.2 mmol), 1,3-propanediol (1.5 mL, 21.3 mmol) and PTSA (0.24 g, 1.4 mmol) . The crude product was purified by column chromatography [Petrol : EtOAc (80:20), R_f 0.88] to afford the title compound as a pale yellow oil (3.50 g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.89 (1H, d, J = 2.3Hz, Ar), 7.56 (1H, d, J = 8.2Hz, Ar), 7.37-7.32 (1H, dd, J = 8.5 and 2.4Hz, Ar), 5.66 (1H, s, ArC*H*), 4.23-4.14 (2H, ddd, J = 11.8, 5.0 and 1.2Hz, OCH_2), 3.98-3.88 (2H, m, OCH_2), 2.25-2.06 (1H, m, OCH_2CH_2), 1.37 (1H, m, OCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 138.6, 133.2, 130.3-129.8 (d, J = 33.3Hz, *C*CF_3), 126.9-126.8 (q, J = 3.56Hz, *C*HCCF_3), 126.18 (d, J = 1.65Hz, *C*HCCF_3), 125.6-125.3 (q, J = 3.82 Hz, *C*Br), 125.6-122.0 (d, J = 272.0 Hz, *C*F_3), 100.0, 67.6, 25.6; IR (film / cm^{-1}) v = 2855 (O-CH-O).

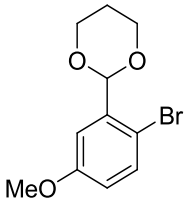
2-(2-Bromo-6-fluorophenyl)-1,3-dioxane



The title compound was prepared according to General Procedure **1** from 2-(2-bromo-6-fluorophenyl)-1,3-dioxane 0.93 g, 4.6 mmol), 1,3-propanediol (0.49 mL, 6.8 mmol) and PTSA (0.09 g, 0.5 mmol). The crude product was purified by recrystallisation from diethyl ether, to afford the title compound as a white solid (0.60 g, 50%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.29 (1H, d, J = 8.0Hz, CFC*H*), 7.13-7.04 (1H, app. t of d, J = 8.2 and 5.7Hz, CBrC*H*), 7.02-6.93 (1H, m, CHC*H*), 5.96 (1H, s, ArC*H*), 4.25-4.18 (2H, app. dd, J = 12.2 and 4.9Hz, OCH_2), 3.96-3.86 (2H, t, J = 12.4Hz, OCH_2), 2.35-2.18 (1H, m, OCH_2CH_2), 1.37 (1H, d of app. septets, J = 13.6 and 1.2Hz, OCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 159.8, 131.1 (d, J = 9.64Hz, CH*C*H), 129.0 (d, J = 3.75, CBr*C*H), 123.0, 116.2, 115.9, 100.7, 67.8, 25.6; IR (film / cm^{-1}) v = 2851 (O-CH-O); HRMS: m/z (ES) 282.9738, $C_{10}H_{10}O_2BrF$ $[M+Na]^+$ requires 282.9746; mp 59-60^{0}C.

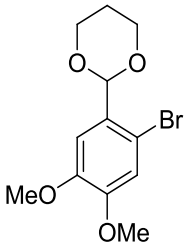
2-(2-Bromo-5-methoxyphenyl)-1,3-dioxane



The title compound was prepared according to General Procedure **1** from 2-bromo-5-methoxybenzaldehyde (0.47 g, 2.2 mmol), propan-1,3,diol (0.24 mL, 3.3 mmol) and PTSA (0.04 g, 0.2 mmol) . The crude was purified by recrystallisation from diethyl ether, yielding a white solid (0.58 g, 96%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.32 (1H, broad d, J = 8.8 Hz, Ar), 7.17 (1H, d, J = 3.2 Hz, Ar), 6.69 (1H, dd, J = 8.7 and 3.2, Ar), 5.64 (1H, s, C*H*O), 4.19 (2H, ddd, J = 11.8, 5.1 and 1.2 Hz, OC*H*$_2$CH$_2$), 3.95 (2H, app. broad t, OC*H*$_2$CH$_2$), 3.73 (3H, s, OMe), 2.30-2.08 (1H, m, OCH$_2$C*H*$_2$), 1.37 (1H, app. d of sept, J = 13.7 and 1.3 Hz, OC*H*$_2$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 159.5, 138.7, 133.6, 117.5, 113.1, 113.0, 101.2, 68.0, 55.9, 26.1; IR (film / cm^{-1}) v = 2853 (O-CH-O); HRMS: m/z (ES) 273.0129, $C_{11}H_{13}O_3Br$ $[M+H]^+$ requires 273.0126, mp 79-81 ^{o}C.

2-(6-Bromo-2,3-dimethoxyphenyl)-1,3-dioxane



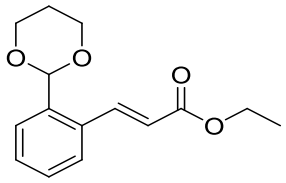
The title compound was prepared according to General Procedure **1** from 6-bromoveratraldehyde (2.03 g, 8.3 mmol), 1,3-propanediol (0.9 mL, 12.4 mmol) and PTSA (0.14 g, 0.8 mmol). The crude was purified by recrystallisation from diethyl ether, yielding a white solid (2.11 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.21 (1H, s, Ar), 6.99 (1H, s Ar), 5.70 (1H, s, C*H*O), 4.27 (2H, ddd, J = 11.9, 6.4 and 1.3 Hz, OC*H*$_2$CH$_2$), 4.08-3.97 (2H, m, OC*H*$_2$CH$_2$), 3.91 (3H, s, OMe), 3.87 (3H, s, OMe), 2.35-2.16 (1H, m, OCH$_2$C*H*$_2$), 1.46 (1H, app. d of sept, J = 13.6 and 1.4 Hz, OCH$_2$C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 150.2, 149.0, 130.2, 115.5, 112.9, 110.7, 101.4,

68.0, 56.6, 56.4, 26.0; IR (film / cm^{-1}) v = 2855 (O-CH-O); HRMS: m/z (ES) 303.0232, $C_{12}H_{15}O_4Br$ $[M+H]^+$ requires 303.0232; mp 98-99 ^0C.

Heck Products

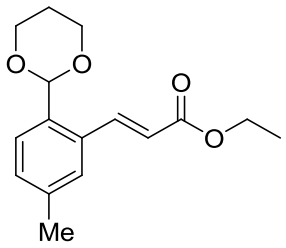
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate



The title compound was prepared according to General Procedure **2** from 2-(2-bromophenyl)-1,3-dioxane (10.8 g, 44.4 mmol), ethyl acrylate (4.82 mL, 44.4 mmol), palladium (II) acetate (0.49 g, 2.2 mmol), tri(*o*-tolyl)phosphine (1.35 g, 4.5 mmol) and diisopropylethyl amine (23.2 mL, 133.4 mmol) in acetonitrile (120 mL). The crude product was purified by column chromatography [Petrol : EtOAc (80:20), R_f 0.39] yielding a yellow oil (11.2 g, 96%).

^1H NMR (300 MHz, $CDCl_3$): δ_H = 8.16 (1H, d, J = 16.0Hz, ArC*H*CH), 7.53 (2H, app. t of d, J = 2.0Hz, Ar), 7.35-7.24 (2H, m, Ar), 6.28 (1H, d, J = 16.0Hz, ArCHC*H*), 5.63 (1H, s, C*H*O), 4.25-4.16 (4H, m, OCH_2CH_2 and OCH_2CH_3), 4.00-3.89 (2H, m, OCH_2CH_2), 2.30-2.13 (1H, diastereotopic multiplet, OCH_2CH_2), 1.40 (1H, app. d of sept, J = 1.5Hz, OCH_2CH_2), 1.27 (3H, t, J = 7.0Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 167.0, 142.2, 137.1, 132.9, 129.8, 129.1, 127.0, 126.7, 119.9, 100.3, 67.6, 60.5, 25.7, 14.3; IR (film / cm^{-1}) v = 2851 (O-CH-O), 1728 (C=O), 1608 (C=C); HRMS: m/z (ES) 287.1259, $C_{15}H_{20}O_4$ $[M+Na]^+$ requires 287.1259.

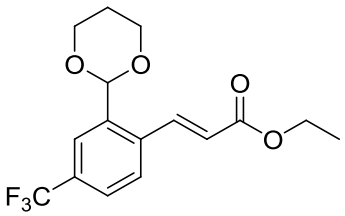
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)acrylate



The title compound was prepared according to General Procedure **2** from 2-(2-bromo-4-methylphenyl)-1,3-dioxane (0.96 g, 3.7 mmol), ethyl acrylate (0.40 mL, 3.7 mmol), palladium (II) acetate (0.04 g, 0.19 mmol), tri(*o*-tolyl)phosphine (0.11 g, 0.37 mmol) and diisopropylethyl amine (1.95 mL, 11.2 mmol) in acetonitrile (30 mL). The crude product was purified by column chromatography [Petrol : EtOAc (90:10), R_f 0.20] yielding a yellow oil (0.74 g, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.14 (1H, d, J = 16.0Hz, C*H*CHCO$_2$), 7.42 (1H, d, J = 7.8Hz, Ar), 7.33 (1H, s, Ar), 7.12 (1H, d, J = 7.8Hz, Ar), 6.28 (1H, d, J = 16.0Hz, CHC*H*CO$_2$), 5.60 (1H, s, ArC*H*), 4.23-4.16 (4H, m, OC*H*$_2$CH$_3$ and OC*H*$_2$CH$_3$), 3.98-3.89 (2H, m, OC*H*$_2$), 2.28 (3H, s, CC*H*$_3$), 2.25-2.13 (1H, m, OCH$_2$C*H*), 1.39 (1H, app. d, J = 13.5Hz, OCH$_2$C*H*$_2$), 1.27 (3H, t, J = 7.1Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 167.0, 142.4, 138.3, 134.5, 132.6, 130.6, 127.3, 127.0, 119.6, 100.4, 67.5, 60.4, 25.7, 21.2, 14.3; IR (film / cm^{-1}) v = 2852 (O-CH-O), 1709 (C=O), 1636 (C=C), 1612 (C-O); HRMS: m/z (ES) 277.1444, $C_{16}H_{20}O_4$ $[M+H]^+$ requires 277.1440.

(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)acrylate

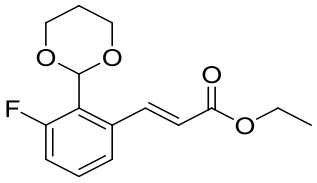


The title compound was prepared according to General Procedure **2** from 2-(2-bromo-5-(trifluoromethyl)phenyl)-1,3-dioxane (0.80 g, 2.6 mmol), ethyl acrylate (0.28 mL, 2.6 mmol), palladium (II) acetate (0.03 g, 0.13 mmol), tri(*o*-tolyl)phosphine (0.08 g, 0.26 mmol) and diisopropylethyl amine (1.34 mL, 7.7 mmol) in acetonitrile (25 mL). The crude product was purified by column chromatography [Petrol : EtOAc (80:20), R_f 0.48] yielding a yellow oil (0.57 g, 68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.05 (1H, d, J = 16.0Hz, C*H*CHCO$_2$), 7.83 (1H, app. s, Ar), 7.57-7.47 (2H, m, Ar), 6.30 (1H, d, J = 16.0 Hz, CHC*H*CO$_2$), 5.62 (1H, s, ArC*H*), 4.23-4.16 (4H, m, OC*H*$_2$CH$_2$ and OC*H*$_2$CH$_3$), 3.98-3.87 (2H, app. dd, J = 12.4 and 2.5, OC*H*$_2$CH$_2$), 2.27-2.09 (1H, m, OCH$_2$C*H*$_2$), 1.39 (1H, app. d of sept, J = 13.7 and 1.3 Hz, OCH$_2$C*H*$_2$), 1.26 (3H, t, J = 7.3

Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 166.4, 140.5-137.8 (d, J = 207.27Hz, Ar*C*HCH), 136.4 (d, J = 1.27Hz, *C*CHCH), 132.0-130.7 (q, J = 32.66Hz, *C*CF_3), 127.2, 125.8-125.7 (q, J = 3.66Hz, *C*HCCF_3), 124.2-124.0 (q, J = 3.87Hz, *C*F_3), 122.2, 118.4, 100.4, 99.09, 67.5, 60.7, 25.5, 14.2; IR (film / cm^{-1}) v = 2872 (O-CH-O), 1716 (C=O), 1630 (C=C), 1580 (C-O); HRMS: m/z (ES) 331.1147, $C_{16}H_{17}O_4F_3$ $[M+H]^+$ requires 331.1157.

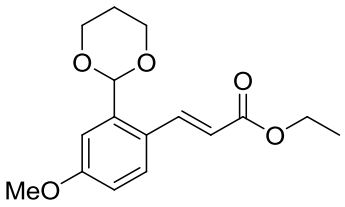
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)acrylate



The title compound was prepared according to General Procedure **2** from 2-(2-bromo-6-fluorophenyl)-1,3-dioxane (0.46 g, 1.8 mmol), ethyl acrylate (0.19 mL, 1.8 mmol), palladium (II) acetate (0.02 g, 0.09 mmol), tri(*o*-tolyl)phosphine (0.05 g, 0.18 mmol) and diisopropylethyl amine (0.92 mL, 5.3 mmol) in acetonitrile (15 mL). The crude product was purified by column chromatography [Petrol : EtOAc (80:20), R_f 0.48] yielding a yellow oil (0.40 g, 81%).

^1H NMR (300 MHz, $CDCl_3$): δ_H = 8.68 (1H, d, J = 16.1Hz, ArC*H*CH), 7.35 (1H, d, J = 7.8Hz, Ar), 7.26-7.19 (1H, m, Ar), 7.01-6.93 (1H, m, Ar), 6.24 (1H, d, J = 16.1Hz, ArCHC*H*), 5.98 (1H, s, Ar*CH*CO_2), 4.25-4.16 (4H, m, O*CH*$_2$$CH_2$ and O*CH*$_2$$CH_3$), 3.95-3.84 (2H, m, O*CH*$_2$$CH_2$), 2.40-2.23 (1H, m, OCH_2CH_2), 1.40 (1H, app. d of sept, J = 13.6 and 1.2Hz, OCH_2CH_2), 1.28 (3H, t, J = 7.2Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 166.9, 161.9-158.6 (d, J = 248.49Hz, *C*F), 143.3 (d, J = 2.78Hz, Ar*C*HCH), 136.3 (d, J = 2.78Hz, *C*CHCH), 130.4 (d, J = 9.48Hz, CFCH*C*H), 124.3 (d, J = 11.25Hz, ArCH*C*H), 123.3 (d, J = 3.41, CF*C*C), 119.6, 116.5 (d, J = 23.51Hz, CF*C*H), 96.3 (d, J = 10.11Hz, Ar*C*HO_2), 68.0, 60.4, 25.9, 14.3; IR (film / cm^{-1}) v = 2856 (O-CH-O), 1710 (C=O), 1639 (C=C), 1577 (C-O); HRMS: m/z (ES) 281.1179, $C_{15}H_{17}O_4F$ $[M+H]^+$ requires 281.1189.

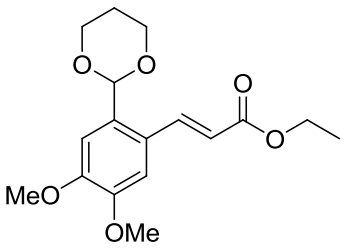
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)acrylate



The title compound was prepared according to General Procedure **2** from 2-(2-bromo-5-methoxyphenyl)-1,3-dioxane (0.58 g, 2.1 mmol), ethyl acrylate (0.23 mL, 2.1 mmol), palladium (II) acetate (0.02 g, 0.11 mmol), tri(*o*-tolyl)phosphine (0.06 g, 0.21 mmol) and diisopropylethyl amine (1.10 mL, 6.4 mmol) in acetonitrile (15 mL). The crude product was purified by column chromatography [Petrol : EtOAc (85:15), R_f 0.25] yielding a yellow crystalline solid (0.36 g, 58%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.04 (1H, broad d, J =15.9 Hz, ArC*H*CH), 7.49 (1H, d, J = 8.7 Hz, Ar), 7.11 (1H, d, J = 2.7, Ar), 6.81 (1H, dd, J = 8.6 and 2.7 Hz, Ar), 6.20 (1H, broad d, J = 15.9, ArCHC*H*), 5.64 (1H, s, C*H*O), 4.26-4.14 (4H, m, OCH_2CH$_2$ and OCH_2CH$_3$), 4.01-3.90 (2H, m, OCH_2CH$_2$), 3.77 (3H, s, OMe), 2.31-2.12 (1H, m, OCH$_2$CH_2), 1.40 (1H, app. d of sept, J = 1.3 Hz, OCH$_2$CH_2) 1.26 (3H, t, J = 7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 167.7, 161.4, 141.9, 139.3, 128.6, 125.5, 117.9, 115.8, 111.9, 100.0, 67.9, 60.7, 55.8, 26.0, 14.7; IR (film / cm^{-1}) v = 2855 (O-CH-O), 1702 (C=O), 1605 (C=C); HRMS: m/z (ES) 315.1195, $C_{16}H_{20}O_5$ $[M+Na]^+$ requires 315.1208; mp 43-44 ^{0}C.

(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-3,4-dimethoxyphenyl)acrylate



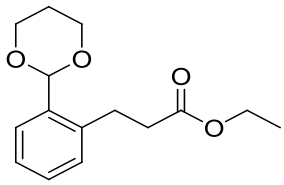
The title compound was prepared according to General Procedure **2** from 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxane (1.02 g, 3.4 mmol), ethyl acrylate (0.36 mL, 3.4 mmol), palladium (II) acetate (0.04 g, 0.17 mmol), tri(*o*-tolyl)phosphine (0.10 g, 0.34 mmol) and diisopropylethyl amine (1.75 mL, 10.0 mmol) in acetonitrile (40 mL). The crude product was

purified by column chromatography [Petrol : EtOAc (70:30), R_f 0.49] yielding a yellow oil (0.82 g, 76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.03 (1H, broad d, J = 15.8 Hz, ArC*H*CH), 7.11 (1H, s, Ar), 7.00 (1H, s, Ar), 6.22 (1H, broad d, J = 15.8 Hz, ArCHC*H*), 5.66 (1H, s, C*H*O), 4.26-4.15 (4H, m, OCH_2CH_2 and CH_2CH_3), 4.02-3.90 (2H, m, OCH_2CH_2), 3.87 (3H, s, OMe), 3.83 (3H, s, OMe), 2.33-2.10 (1H, m, OCH_2CH_2), 1.41 (1H, broad d, J = 13.5 Hz, OCH_2CH_2), 1.28 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 167.6, 151.0, 149.5, 141.7, 131.6, 125.5, 118.1, 109.7, 109.0, 99.7, 67.9, 60.8, 56.4, 26.0, 14.8; IR (film / cm^{-1}) v = 2853 (O-CH-O), 1703 (C=O), 1602 (C=C); HRMS: m/z (ES) 323.1495, $C_{17}H_{22}O_6$ $[M+H]^+$ requires 323.1495.

Chemoselective Reduction Products

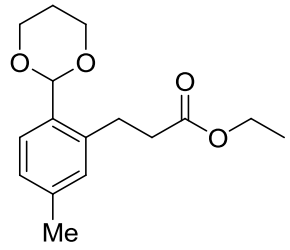
Ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoate



The title compound was prepared according to General Procedure **3** from ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate (1.91 g, 7.7 mmol), cobalt (II) chloride hexahydrate (0.02 g, 0.08 mmol) in ethanol (30 mL) with the addition of sodium borohydride (0.58 g, 15.4 mmol). The crude was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f 0.74] yielding a yellow oil (1.65 g, 81%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.62-7.57 (1H, m, Ar), 7.31-7.16 (3H, m, Ar), 5.67 (1H, s, ArC*H*O), 4.27 (2H, ddd, J = 10.6, 5.2 and 1.2 Hz, OCH_2CH_2), 4.16 (2H, q, OCH_2CH_3), 4.01 (2H, t of d, OCH_2CH_2), 3.12-3.03 (2H, m, $ArCH_2CH_2$), 2.69-2.59 (2H, m, $ArCH_2CH_2$), 2.35-2.17 (1H, m, OCH_2CH_2), 1.50-1.41 (1H, m, OCH_2CH_2), 1.27 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.6, 138.9, 136.8, 129.9, 129.3, 127.0, 126.8, 100.6, 67.7, 60.7, 36.5, 28.3, 26.1, 14.6; IR (film / cm^{-1}) v = 1729 (C=O); HRMS: m/z (ES) 287.1247, $C_{15}H_{20}O_4$ $[M+Na]^+$ requires 287.1259.

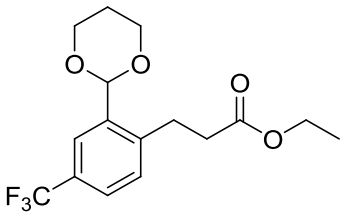
Ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)propanoate



The title compound was prepared according to General Procedure **3** from (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)acrylate (0.64 g, 2.3 mmol), cobalt (II) chloride hexahydrate (0.05 g, 0.02 mmol) in ethanol (20 mL) with the addition of sodium borohydride (0.17 g, 4.6 mmol). The crude was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f 0.54] yielding a colourless oil (0.44 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.38 (1H, d, J = 8.0Hz, CH_3CCHCH), 6.96 (1H, d, J = 8.0Hz, CH_3CCHCH), 6.91 (1H, s, CH_2CCH), 5.54 (1H, s, $ArCHO_2$), 4.21-4.13 (2H, m, OCH_2CH_2), 4.07 (2H, q, J = 7.0Hz, OCH_2CH_3), 3.95-3.84 (2H, m, OCH_2CH_2), 2.99-2.91 (2H, diastereotopic multiplet, $ArCH_2CH_2$), 2.58-2.50 (2H, diastereotopic multiplet, $ArCH_2CH_2$), 2.20 (3H, s, $ArCH_3$), 2.20-2.07 (1H, m, OCH_2CH_2), 1.35 (1H, app. d of sept, J = 1.0Hz, OCH_2CH_2), 1.18 (3H, t, J = 7.0Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.3, 138.6, 138.3, 133.6, 130.2, 127.2, 126.5, 100.3, 67.5, 60.3, 36.2, 27.7, 25.8, 21.2, 14.3; IR (film / cm^{-1}) v = 2854 (O-CH-O), 1730 (C=O), 1617 (C-O); HRMS: m/z (ES) 279.1587, $C_{16}H_{22}O_4$ $[M+H]^+$ requires 279.1596.

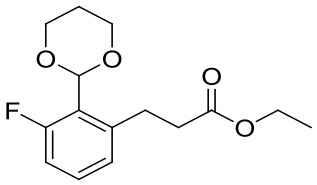
Ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)propanoate



The title compound was prepared according to General Procedure **3** from (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)acrylate 0.32 g, 1.0 mmol), cobalt (II) chloride hexahydrate (0.002 g, 0.01 mmol) in ethanol (10 mL) with the addition of sodium borohydride (0.07 g, 1.9 mmol). The crude was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f0.49] yielding a colourless oil (0.17 g, 54%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.25 (1H, app. dd, J = 10.0 and 2.5Hz, Ar), 7.07 (1H, app. dd, J = 5.5 and 8.5Hz, Ar), 6.88 (1H, app. t of d, J = 8.5 and 3.0Hz, Ar), 5.54 (1H, s, C*H*O_2), 4.22-4.14 (2H, m, OC*H*$_2$$CH_2$), 4.07 (2H, q, J = 7.0Hz, OC*H*$_2$$CH_3$), 3.97-3.89 (2H, m, OC*H*$_2$$CH_2$), 2.93 (2H, app. t, J = 8.0Hz, OC*H*$_2$$CH_2$), 2.55-2.48 (2H, diastereotopic multiplet, ArCH_2C*H*$_2$), 2.24-2.06 (1H, diastereotopic multiplet, OCH_2C*H*$_2$), 1.37 (1H, app. d of sept, J = 1.5Hz, OCH_2C*H*$_2$), 1.17 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 172.8, 142.6, 137.3, 129.9, 128.7 (d, J = 33.0Hz, *C*CF_3), 126.0 and 122.4 (d, J = 271.5Hz, *C*F_3), 125.6 (q, J = 4.0Hz, *C*HCCF_3), 123.8 (q, J = 4.0Hz, *C*HCCF_3), 99.1, 67.4, 60.5, 53.4, 35.5, 27.5, 25.6, 14.2; IR (film / cm^{-1}) v = 2856 (O-CH-O), 1731 (C=O), 1624 (C-O); HRMS: m/z (ES) 333.1300, $C_{16}H_{19}O_4F_3$ $[M+H]^+$ requires 333.1314.

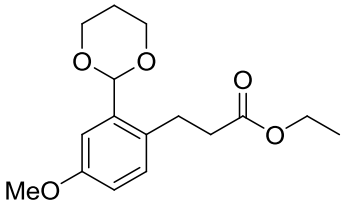
Ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)propanoate



The title compound was prepared according to General Procedure **3** from (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)acrylate (0.38 g, 1.4 mmol), cobalt (II) chloride hexahydrate (0.003 g, 0.01 mmol) in ethanol (10 mL) with the addition of sodium borohydride (0.10 g, 2.7 mmol) for 72 hours. The crude was purified using flash column chromatography [Petrol: EtOAc (75:25), R_f 0.69] yielding a colourless oil (0.19 g, 49%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.19-7.08 (1H, m, Ar), 6.93 (1H, app. d, J = 7.5Hz, Ar), 6.87-6.76 (1H, m, Ar), 5.92 (1H, s, C*H*O_2), 4.23-4.14 (2H, m, OC*H*$_2$$CH_2$), 4.08 (2H, q, J = 7.0Hz, OC*H*$_2$$CH_3$), 3.89 (2H, app. t of d, J = 12.0 and 2.0Hz, OC*H*$_2$$CH_2$), 3.33-3.28 (2H, diastereotopic multiplet, ArC*H*$_2$$CH_2$), 2.64-2.54 (2H, diastereotopic multiplet, ArCH_2C*H*$_2$), 2.31-2.10 (1H, diastereotopic multiplet, OCH_2C*H*$_2$), 1.37 (1H, app. d of sept, J = 1.5Hz, OCH_2C*H*$_2$), 1.20 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.4, 162.1-158.3 (d, J = 247.5Hz, *C*F), 143.0 (d, J = 2.0Hz, *C*CH_2), 130.2 (d, J = 9.5 Hz, CFCH*C*H), 126.5 (d, J = 3.5 Hz, CFCHCH*C*H), 123.8 (d, J = 10.5 Hz, CF*C*CHO_2), 113.4 (d, J = 23.55 Hz, *C*HCF), 97.0 (d, J = 10.01 Hz, *C*HO_2), 67.7, 60.3, 36.6, 28.6 (d, J = 1.85 Hz, Ar*C*H_2), 25.8, 14.3; IR (film / cm^{-1}) v = 2856 (O-CH-O), 1729 (C=O), 1619 (C-O); HRMS: m/z (ES) 283.1351, $C_{15}H_{19}O_4F$ $[M+H]^+$ requires 283.1346.

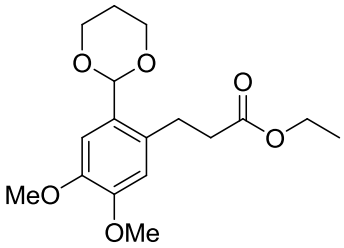
Ethyl 3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)propanoate



The title compound was prepared according to General Procedure **3** from ethyl 3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)acrylate (0.36 g, 1.2 mmol), cobalt (II) chloride hexahydrate (0.003 g, 0.01 mmol) in ethanol (10 mL) with the addition of sodium borohydride (0.09 g, 2.4 mmol) and left stirring at room temperature for 48 hours. The crude was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f 0.44] yielding a colorless oil (0.26 g, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.08 (1H, d, J = 2.8 Hz, Ar), 7.01 (1H, broad d, J = 8.4 Hz, Ar), 6.73 (1H, dd, J = 8.5 and 2.9 Hz), 5.55 (1H, s, Ar*C*HO_2), 4.18 (2H, dd, J = 11.2 and 5.0 Hz, O*C*H_2CH_2), 4.06 (2H, q, J = 7.4 Hz, O*C*H_2CH_3), 3.91 (2H, t of d, J = 12.6 and 2.2 Hz, O*C*H_2CH_2), 3.71 (3H, s, OMe), 2.91 (2H, t, J = 7.8 Hz, ArCH_2*C*H_2), 2.50 (2H, t, J = 7.6 Hz, Ar*C*H_2CH_2), 2.16 (1H, m, OCH_2*C*H_2), 1.36 (1H, m, OCH_2*C*H_2), 1.17 (3H, t, J = 7.2 Hz, OCH_2*C*H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C =173.7, 158.6, 137.8, 131.0, 130.8, 115.6, 111.6, 100.2, 67.8, 60.7, 55.7, 36.7, 27.4, 26.1, 14.6; IR (film / cm^{-1}) v = 2852 (O-CH-O), 1729 (C=O); HRMS: m/z (ES) 295.1551, $C_{16}H_{22}O_5$ $[M+H]^+$ requires 295.1545.

Ethyl 3-(2-(1,3-dioxan-2-yl)-3,4-dimethoxyphenyl)propanoate



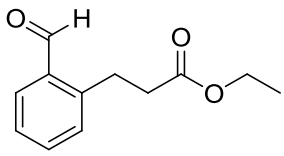
The title compound was prepared according to General Procedure **3** from ethyl 3-(2-(1,3-dioxan-2-yl)-4,5-dimethoxyphenyl)acrylate 0.82 g, 2.6 mmol), cobalt (II) chloride hexahydrate (0.01 g, 0.03 mmol) in ethanol (20 mL) with the addition of sodium borohydride (0.19 g, 5.1 mmol) and left stirring at room temperature for 48 hours. The crude was

purified using flash column chromatography [Petrol: EtOAc (80:20), R_f 0.11] yielding a pale yellow crystalline solid (0.73 g, 87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.07 (1H, s, Ar), 6.61 (1H, s, Ar), 5.54 (1H, s, C*H*O_2), 4.19 (2H, dd, J = 12.0 and 5.1 Hz, OC*H*$_2$$CH_2$), 4.08 (2H, q, J = 7.0 Hz, OC*H*$_2$$CH_3$), 3.92 (2H, t of d, J = 12.4 and 2.4 Hz, OC*H*$_2$$CH_2$), 3.82 (3H, s, OMe), 3.78 (3H, s, OMe), 2.95-2.87 (2H, m, ArC*H*$_2$$CH_2$), 2.56-2.49 (2H, m, Ar$CH_2$C*H*$_2$), 2.26-2.09 (1H, m, OCH_2C*H*$_2$), 1.37 (1H, app. d of sept, J = 1.3 Hz, OCH_2C*H*$_2$), 1.19 (3H, t, J = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.6, 149.4, 147.8, 131.3, 129.2, 112.8, 109.8, 100.1, 67.9, 60.8, 56.3, 36.8, 27.8, 26.1, 14.6; IR (film / cm^{-1}) v = 2858 (O-CH-O), 1729 (C=O); HRMS: m/z (ES) 325.1667, $C_{17}H_{25}O_6$ $[M+H]^+$ requires 325.1651; mp 58-60 ^{0}C.

Aldehydes

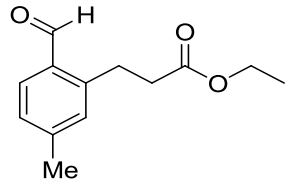
Ethyl 3-(2-formylphenyl)propanoate



The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoate (0.55 g, 2.2 mmol) which was added to a solution of acetic acid: water (7 mL : 3 mL) and left to stir open to the air overnight. The product was obtained as a yellow colourless oil (0.32 g, 75%).

^{1}H NMR (250 MHz, $CDCl_3$): δ_H = 10.25 (1H, s, ArC*H*O), 7.89-.7.80 (1H, m, Ar), 7.60-7.27 (3H, m, Ar), 4.14 (2H, q, J =7.2 Hz, OC*H*$_2$$CH_3$), 3.89 (2H, t, J = 7.5 Hz, ArC*H*$_2$$CH_2$), 2.67 (2H, t, J = 7.7 Hz, ArC*H*$_2$$CH_2$), 1.25 (3H, t, J = 7.1 Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 192.7, 172.6, 142.9, 133.8, 133.8, 133.4, 131.2, 127.0, 60.5, 35.6, 28.0, 14.2; IR (film / cm^{-1}) v = 1728 (C=O), 1694 (C=O) HRMS: m/z (ES) 207.1009, $C_{12}H_{14}O_3$ $[M+H]^+$ requires 207.1021.

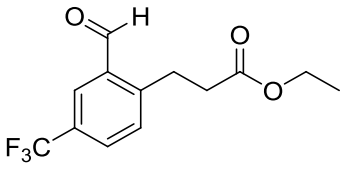
Ethyl 3-(2-formyl-5-methylphenyl)propanoate



The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)propanoate (0.26 g, 1.0 mmol) which was added to a solution of acetic acid: water (14 mL : 6 mL) and left to stir open to the air overnight. The product was obtained as a white crystalline solid (0.16 g, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.07 (1H, s, C*H*O), 7.63 (1H, d, J = 8.0Hz, C*H*CCOH), 7.14 (1H, broad d, J = 8.0Hz, C*H*CCH_3), 7.06 (1H, broad s, C*H*CCH_3), 4.04 (2H, q, J = 7.0Hz, OC*H*$_2$CH_3), 3.24 (2H, app. t, J =8.0Hz, ArC*H*$_2$CH_2), 2.55 (2H, app. t, J = 8.0Hz, ArCH_2C*H*$_2$), 2.32 (3H, s, ArC*H*$_3$), 1.15 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 192.3, 172.8, 144.9, 142.9, 133.9, 132.0, 131.5, 127.8, 60.5, 35.6, 28.1, 21.8, 14.2; IR (film / cm^{-1}) v = 1729 (C=O), 1690 (C=O), 1610 (C-O); HRMS: m/z (ES) 243.0989, $C_{13}H_{16}O_3$ $[M+Na]^+$ requires 243.0997, mp 37-39 ^{o}C.

Ethyl 3-(2-formyl-4-(trifluoromethyl)phenyl)propanoate

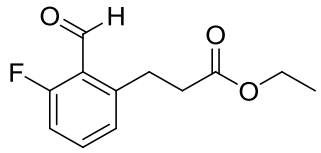


The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)propanoate (0.15 g, 0.46 mmol) which was added to a solution of acetic acid: water (14 mL : 6 mL) and left to stir open to the air for 36 hours. The product was obtained as a colourless oil (0.09 g, 69%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.21 (1H, s, C*H*O), 8.01 (1H, broad s, C*H*CCHO), 7.69 (1H, dd, J = 8.0 and 1.5Hz, CC*H*CH), 7.43 (1H, d, J = 8.0Hz, C*H*CCH_2), 4.05 (2H, q, J = 7.0Hz, OC*H*$_2$CH_3), 3.34 (2H, t, J = 7.5 Hz, ArC*H*$_2$CH_2), 2.60 (2H, t, J = 7.5Hz, ArCH_2C*H*$_2$), 1.15 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 191.1, 172.2, 146.8, 134.1, 132.0, 130.1,

130.0, 129.7, 60.7, 35.2, 27.8, 14.2; IR (film / cm^{-1}) v = 1731 (C=O), 1704 (C=O), 1618 (C-O); HRMS: m/z (ES) 275.0868, $C_{13}H_{13}O_3F_3$ $[M+H]^+$ requires 275.0895.

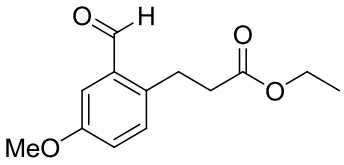
Ethyl 3-(3-fluoro-2-formylphenyl)propanoate



The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)propanoate (0.19 g, 0.68 mmol) which was added to a solution of acetic acid: water (7 mL : 3 mL) and left to stir open to the air overnight. The product was obtained as a colourless oil (0.12 g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.46 (1H, s, C*H*O), 7.41 (1H, td, J = 8.0 and 6.0Hz, Ar), 7.07-6.94 (2H, m, Ar), 4.04 (2H, q, J = 7.0Hz, OC*H*$_2$CH$_3$), 3.23 (2H, t, J = 7.5Hz, ArC*H*$_2$), 2.55 (2H, t, J = 7.5Hz, ArCH$_2$C*H*$_2$), 1.15 (3H, t, J = 7.0Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 189.0 (d, J = 11.8, *C*HO), 172.8, 166.64 (d, J = 257.7, *C*F), 144.7, 135.40 (d, J = 10.54, CFCH*C*H), 127.2 (d, J = 3.43, CH$_2$C*C*H), 122.19 (d, J = 5.29, CF*C*), 114.6 (d, J = 21.87, CF*C*H), 60.5, 35.0, 29.03 (d, J = 2.22, Ar*C*H$_2$), 14.2; IR (film / cm^{-1}) v = 1730 (C=O), 1695 (C=O), 1610 (C-O).

Ethyl 3-(2-formyl-4-methoxyphenyl)propanoate

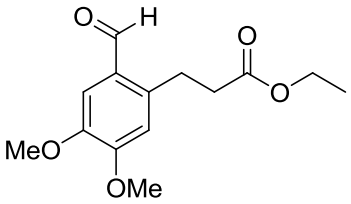


The title compound was prepared according to General Procedure **4** from ethyl-3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)propanoate (0.15 g, 0.5 mmol) which was added to a solution of acetic acid: water (14 mL : 6 mL) and left to stir open to the air overnight. The product was obtained as an orange oil (0.12 g, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.16 (1H, s, C*H*O), 7.27 (1H, d, J = 2.8 Hz, Ar), 7.19 (1H, d, J = 4.9 Hz, Ar), 6.99 (1H, dd, J = 8.4 and 2.9 Hz, Ar), 4.04 (2H, q, J = 7.1 Hz, OC*H*$_2$CH$_3$), 3.78 (3H, s, OMe), 3.21 (2H, t, J = 7.6 Hz, ArC*H*$_2$CH$_2$), 2.51 (2H, t, J = 7.6 Hz, ArCH$_2$C*H*$_2$) 1.15 (3H, t, J = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 192.3, 173.0, 158.9, 135.7, 134.9, 132.7, 120.9,

116.2, 60.9, 55.9, 36.5, 27.2, 14.6; IR (film / cm^{-1}) v = 1728 (C=O), 1686 (C=O); HRMS: m/z (ES) 259.0941, $C_{13}H_{16}O_4$ $[M+Na]^+$ requires 259.0946.

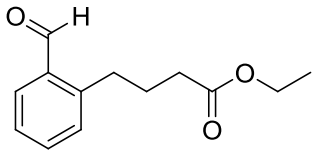
Ethyl 3-(2-formyl-3,4-dimethoxyphenyl)propanoate



The title compound was prepared according to General Procedure **4** from ethyl-3-(2-(1,3-dioxan-2-yl)-4,5-dimethoxyphenyl)propanoate (0.47 g, 1.5 mmol) which was added to a solution of acetic acid: water (14 mL : 6 mL) and left to stir open to the air overnight. The product was obtained as a white solid (0.30 g, 77%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.10 (1H, s, C*H*O), 7.28 (1H, s, Ar), 6.71 (1H,s, Ar), 4.05 (2H, q, J = 7.2 Hz, OC*H*$_2$CH$_3$), 3.88 (3H, s, OMe), 3.85 (3H, s, OMe), 3.24 (2H, t, J = 7.6 Hz, ArC*H*$_2$CH$_2$), 2.57 (2H, t, J = 7.6 Hz, ArCH$_2$C*H*$_2$), 1.16 (3H, t, J = 7.3 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 190.4, 172.9, 154.1, 148.3, 138.7, 127.1, 113.5, 112.9, 61.0, 56.5, 56.4, 36.8, 27.4, 14.6 IR (film / cm^{-1}) v = 1727 (C=O), 1673 (C=O); HRMS: m/z (ES) 289.1035, $C_{14}H_{18}O_5$ $[M+Na]^+$ requires 289.1052, mp 121-123 ^{o}C

Ethyl 4-(2-formylphenyl)butanoate



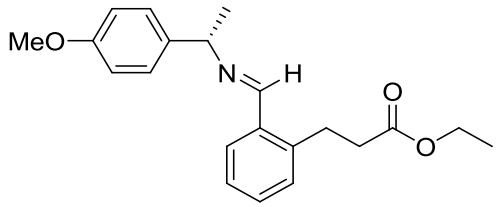
To a Schlenk flask flushed with nitrogen, anhydrous LiCl (0.75 g, 17.6 mmol) was added dried under vacuum. Zinc dust (1.15 g, 17.6 mmol) was added and the resultant mixture was further dried under high vacuum. THF (10 mL) was added and left to stir for 10 mins. To the suspension, dibromoethane (0.076 mL, 0.58 mmol), Me_3SiCl (0.015 mL, 0.12 mmol), iodine (0.09 g, 0.35 mmol) and ethyl 4-bromobutyrate (1.68 mL, 11.8 mmol) were added and the solution was stirred for 12 hrs at 50 ^{o}C. The resultant grey suspension was cooled to room temperature and 2-bromobenzaldehyde (1.10 mL, 9.4 mmol), PEPPSI (0.04 g, 0.06 mmol) and DMI (5 mL) were added to the solution which was left to stir at room temperature for

12 hrs. The reaction was quenched with a saturated solution of NH_4Cl (20 mL) and then filtered through cotton wool. The aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organics were collected, washed with brine (2 x 10 mL) and dried over $MgSO_4$. The solution was then filtered and the solvent evaporated under reduced pressure.[4] The crude compound was purified using flash column chromatography [Petrol : EtOAc, 90:10, R_f – 0.50] yielding a yellow oil (0.90 g, 51%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.19 (1H, s, C*H*O), 7.77 (1H, app. dd, J = 7.5 and 1.5Hz, Ar), 7.45 (1H, t of d, J = 7.5 and 1.5Hz, Ar), 7.32 (1H, t of d, J = 7.5 and 1.5Hz, Ar), 7.28-7.20 (1H, m, Ar), 4.06 (2H, q, J = 7.0Hz, OC*H*$_2$CH$_3$), 3.01 (2H, t, J = 7.5Hz, ArC*H*$_2$CH$_2$), 2.31 (2H, t, J = 7.5Hz, CH$_2$CH$_2$C*H*$_2$), 1.93-1.82 (2H, p, J = 7.5Hz, ArCH$_2$C*H*$_2$), 1.19 (3H, t, J = 7.0Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 192.5, 173.3, 144.3, 133.8, 133.7, 132.5, 131.2, 126.8, 60.4, 33.8, 31.8, 27.0, 14.3; IR (film / cm^{-1}) v = 1728 (C=O), 1695 (C=O), 1600 (C-O); HRMS: m/z (ES) 243.0984, $C_{13}H_{16}O_3$ $[M+Na]^+$ requires 243.0997.

Imines

(*S,E*)-Ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate, 1a

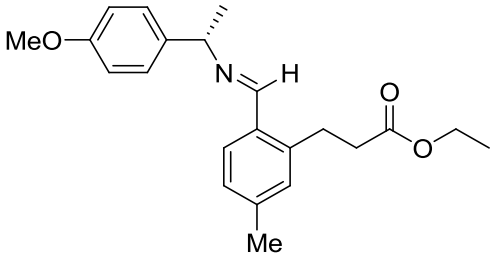


Ethyl 3-(2-formylphenyl)propanoate (4.07 g, 19.8 mmol) was dissolved in dry CH_2Cl_2 (150 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes (*S*)-(-)-4-methoxy-α-methylbenzylamine (2.92 mL, 19.8 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a yellow oil (6.34 g, 95 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.67 (1H, s, ArC*H*N), 7.86 (1H, dd, J = 7.5 and 1.5Hz, Ar), 7.44-7.24 (5H, m, Ar), 6.96-6.92 (2H, m, Ar), 4.55 (1H, q, J =6.5Hz, CHC*H*$_3$), 4.19 (2H, q, J = 7.0Hz, OC*H*$_2$CH$_3$), 3.85 (3H, s, OC*H*$_3$), 3.30 (2H, t, J = 8.0Hz, ArC*H*$_2$CH$_2$), 2.66 (2H, t, J = 8.0Hz, ArCH$_2$C*H*$_2$), 1.62 (3H, d, J = 6.5Hz, C*H*CH$_3$), 1.29 (3H, t, J = 7.0Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.0, 158.5, 157.9, 140.3, 137.5, 134.1, 130.2, 130.1, 129.5, 127.6, 127.4,

126.7, 114.1, 113.8, 70.1, 60.4, 55.3, 35.9, 28.4, 25.2, 14.2; IR (film / cm^{-1}) v = 1730 (C=O), 1639 (C=N), 1611 (C-O); HRMS: m/z (ES) 340.1912, $C_{21}H_{25}O_3N$ $[M+H]^+$ requires 340.1913; $[\alpha]_D^{25}$ = +15.2 (c 1.45, $CHCl_3$).

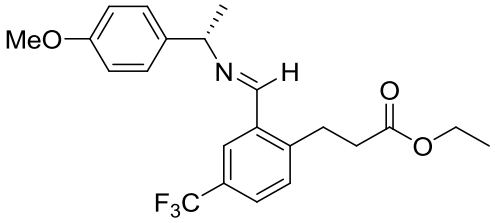
(*S,E*)-Ethyl3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)-5-methylphenyl)propanoate, 1b



Ethyl 3-(2-formyl-5-methylphenyl)propanoate (0.07 g, 0.30 mmol) was dissolved in dry CH_2Cl_2 (15 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.04 mL, 0.30 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a hygroscopic white solid (0.10 g, 82 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.45 (1H, s, ArC*H*N), 7.61 (1H, d, J = 8.0Hz, Ar), 7.31-7.24 (2H, m, Ar), 7.02-6.93 (2H, m, Ar), 6.84 -6.77 (2H, m, Ar), 4.39 (1H, q, J = 4.5Hz, C*H*CH_3), 4.06 (2H, q, J = 7.0Hz, O*CH*$_2$$CH_3$), 3.72 (3H, s, O*CH*$_3$), 3.14 (2H, t, J = 8.5Hz, ArC*H*$_2$$CH_2$), 2.51 (2H, t, J = 8.0Hz, ArCH_2C*H*$_2$), 2.26 (3H, s, ArC*H*$_3$), 1.48 (3H, d, J = 6.5Hz, CHC*H*$_3$), 1.17 (3H, t, J =7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.0, 158.4, 157.9, 140.3, 140.2, 137.7, 131.4, 131.0, 129.7, 127.6, 127.5, 126.9, 113.9, 113.8, 70.1, 60.4, 55.3, 36.0, 28.5, 25.3, 21.4, 14.3; HRMS: m/z (ES) 354.2071, $C_{22}H_{27}O_3N$ $[M+H]^+$ requires 354.2069.

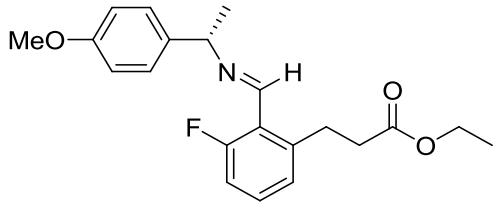
(*S,E*)-Ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)-4-(trifluoromethyl)phenyl) propanoate, 1c



Ethyl 3-(2-formyl-4-(trifluoromethyl)phenyl)propanoate (0.11 g, 0.39 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.06 mL, 0.39 mmol) was added and left stirring for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a yellow oil (0.14 g, 85 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.55 (1H, s, ArC*H*N), 8.01 (1H, s, C*H*CCHN), 7.48 (1H, app. dd, J = 8.0 and 1.5Hz, Ar), 7.30-7.23 (3H, m, Ar), 6.85-6.78 (2H, m, Ar), 4.46 (1H, q, J = 6.5Hz, C*H*CH_3), 4.06 (2H, q, J = 7.0Hz), 3.73 (3H, s, OC*H*$_3$), 3.20 (2H, t, J = 8.0Hz, ArC*H*$_2$$CH_2$), 2.57-2.50 (2H, diastereotopic multiplet, ArCH_2C*H*$_2$), 1.51 (3H, d, J = 6.5Hz, CHC*H*$_3$), 1.16 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); HRMS: m/z (ES) 408.1802, $C_{22}H_{24}O_3NF_3$ $[M+H]^+$ requires 408.1787.

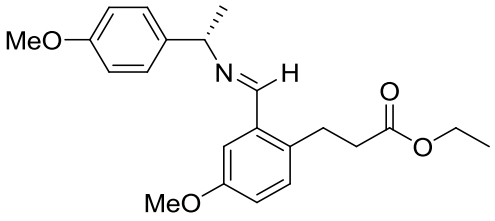
(*S,E*)-Ethyl 3-(3-fluoro-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate, 1d



Ethyl 3-(3-fluoro-2-formylphenyl)propanoate (0.06 g, 0.27 mmol) was dissolved in dry CH_2Cl_2 (15 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.04 mL, 0.27 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a yellow oil (0.08 g, 82 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.65 (1H, s, ArC*H*N), 7.35-7.15 (2H, m, Ar), 7.02-6.72 (5H, m, Ar), 4.38 (1H, q, J = 6.5Hz, C*H*CH_3), 4.06 (2H, q, J = 7.0Hz, OC*H*$_2$$CH_3$), 3.72 (3H, s, OC*H*$_3$), 3.26 (2H, t, J = 8.0Hz, ArC*H*$_2$$CH_2$), 2.55 (2H, t, J = 8.0Hz, ArCH_2C*H*$_2$), 1.49 (3H, d, J = 6.5Hz, CHC*H*$_3$), 1.17 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.3, 158.5, 153.4, 143.2, 137.4, 130.9, 130.8, 127.6, 127.3, 126.7, 122.5, 113.8, 113.5, 71.4, 60.3, 55.3, 35.6, 29.7, 25.6, 14.3; HRMS: m/z (ES) 258.1815, $C_{21}H_{24}O_3NF$ $[M+H]^+$ requires 358.1818.

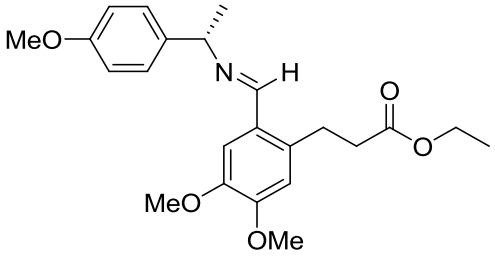
(*S,E*)-Ethyl 3-(4-methoxy-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate, 1e



Ethyl-3-(2-formyl-4-methoxyphenyl)propanoate (0.18 g, 0.75 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.11 mL, 0.75 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a yellow oil (0.23 g, 85 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.50 (1H, s, ArC*H*N), 7.34-7.24 (3H, m, Ar), 7.04 (1H, d, J = 8.5Hz, Ar), 6.82-6.76 (3H, m, Ar), 4.42 (1H, q, J = 6.5Hz, C*H*CH_3), 4.03 (2H, q, J = 7.0Hz, OC*H*$_2CH_3$), 3.72 (3H, s, OC*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 3.07 (2H, broad t, J = 7.5Hz, ArC*H*$_2CH_2$), 2.47 (2H, t, J = 7.5Hz, ArCH_2C*H*$_2$), 1.48 (3H, d, J = 6.5Hz, CHC*H*$_3$), 1.15 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 172.9, 158.5, 158.3, 157.5, 137.4, 135.0, 132.7, 131.3, 127.7, 116.7, 114.1, 113.8, 113.2, 69.9, 60.4, 55.4, 55.3, 36.3, 29.7, 27.5, 25.2, 14.3; HRMS: m/z (ES) 370.2021, $C_{22}H_{27}O_4N$ $[M+H]^+$ requires 370.2018.

(*S,E*)-Ethyl 3-(3,4-dimethoxy-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl) propanoate, 1f

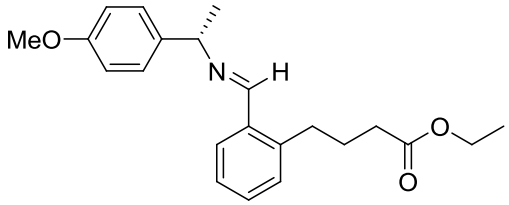


Ethyl 3-(2-formyl-3,4-dimethoxyphenyl)propanoate (0.49 g, 1.9 mmol) was dissolved in dry CH_2Cl_2 (35 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.28 mL, 1.9 mmol) was added and the solution

was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a yellow oil (0.68 g, 93 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.60 (1H, s, ArC*H*N), 7.53 (1H, broad s, Ar), 7.42-7.38 (2H, m, Ar), 6.96-6.91 (2H, m, Ar), 6.74 (1H, s, Ar), 4.55 (1H, q, J = 6.5Hz, C*H*CH_3), 4.18 (2H, q, J = 7.0Hz, C*H*$_2$$CH_3$), 3.97 (3H, s, OC*H*$_3$), 3.94 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.19 (2H, t, J = 8.0Hz, ArC*H*$_2$$CH_2$), 2.64-2.59 (2H, diastereotopic multiplet, $ArCH_2$C*H*$_2$), 1.62 (3H, d, J = 6.5Hz, CHC*H*$_3$), 1.29 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 172.8, 158.5, 156.7, 150.7, 147.7, 137.6, 133.9, 127.7, 126.5, 113.8, 112.6, 110.7, 69.6, 60.5, 56.0, 55.9, 55.3, 36.5, 27.6, 25.1, 14.3; HRMS: m/z (ES) 400.2143, $C_{23}H_{30}O_5N$ $[M+H]^+$ requires 400.2124.

(*S,E*)-Ethyl 4-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)butanoate, 1g

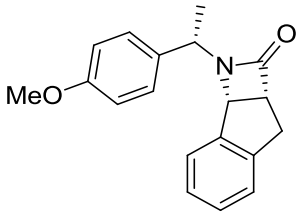


Ethyl 4-(2-formylphenyl)butanoate (0.84 g, 3.8 mmol) was dissolved in dry CH_2Cl_2 (50 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.56 mL, 3.8 mmol) was added and stirring was continued for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a colourless oil (1.10 g, 82 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.57 (1H, s, ArC*H*N), 7.82 (1H, app. dd, J = 7.5 and 1.5Hz, C*H*CCHN), 7.28 (2H, d, J = 8.5Hz, Ar), 7.24-7.13 (2H, m, Ar), 7.09 (1H, d, J = 7.0Hz, $CH_3OCCHCH$), 6.81 (2H, d, J = 8.5Hz, CH_3OCCH), 4.44 (1H, q, J = 6.5Hz, C*H*CH_3), 4.06 (2H, q, J = 7.0Hz, OC*H*$_2$$CH_3$), 3.71 (3H, s, OC*H*$_3$), 2.82 (2H, t, J = 7.5Hz, ArC*H*$_2$$CH_2$), 2.25 (2H, t, J = 7.5Hz, $ArCH_2CH_2$C*H*$_2$), 1.82 (2H, p, J = 7.5Hz, $ArCH_2$C*H*$_2$), 1.50 (3H, d, J = 6.5Hz, CHC*H*$_3$), 1.18 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.4, 158.5, 157.8, 141.2, 137.5, 134.1, 130.2, 130.1, 128.6, 127.7, 126.5, 113.8, 69.7, 60.3, 55.3, 33.8, 32.2, 26.9, 25.0, 14.3; HRMS: m/z (ES) 354.2074, $C_{22}H_{27}O_3N$ $[M+H]^+$ requires 354.2069.

Cyclised Products

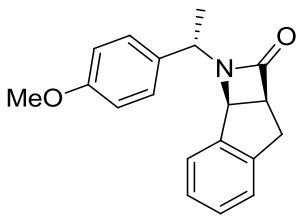
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 2a



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **1a** (0.144 g, 0.42 mmol) which was dissolved in THF (10 mL) under a nitrogen atmosphere. 15-Crown-5 (0.09 mL, 0.46 mmol) and NaHMDS (1M in THF, 0.46 mL, 0.46 mmol) was added and the mixture was left stirring for 8 hours at -40 ^{0}C and allowed to warm to room temperature. The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f- 0.47] yielding a white crystalline solid (0.088 g, 73 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.34-7.28 (4H, m, Ar), 7.22-7.14 (2H, m, CH_3OCHCH), 6.98-6.94 (2H, m, CH_3OCH), 5.00 (1H, q, J = 7.0Hz, $CHCH_3$), 4.83 (1H, d, J = 4.5Hz, CHCHN), 3.92-3.89 (1H, m, $CHCH_2$), 3.88 (3H, s, OCH_3), 3.41 (1H, dd, J = 17.5 and 2.0Hz, CH_2CH), 3.03 (1H, dd, J = 17.5 and 10.5Hz, CH_2CH), 1.44 (3H, d, J = 7.0Hz, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 169.8, 159.1, 145.1, 139.7, 132.0, 128.8, 128.4, 126.5, 126.4, 126.2, 114.0, 61.4, 55.4, 51.7, 51.2, 30.1, 18.9; IR (film / cm^{-1}) v = 1731 (C=O) HRMS: m/z (ES) 316.1308, $C_{19}H_{19}O_2N$ $[M+Na]^+$ requires 316.1313; mp 90-92 ^{0}C; $[\alpha]_D^{25}$ = -52 (*c* 1.15, $CHCl_3$).

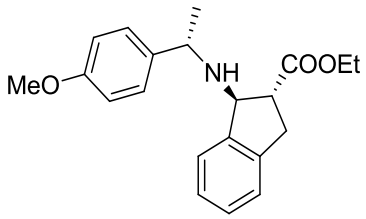
(2aS,7bS)-1-((S)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)one, 3a



(*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **1a** (0.24 g, 0.7 mmol) was dissolved in THF (23 mL). KHMDS (0.5M in Toluene, 1.5 mL, 0.78 mmol) was added and the mixture was left stirring for 8 hours at room temperature. The reaction was quenched with a saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the organic layers were combined and washed with NH_4Cl (50 mL) and water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Hexane: Et_2O (1:1), R_f 0.15] yielding a white crystalline solid (0.031 g, 15 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.33-7.28 (2H, m, Ar), 7.24-7.19 (2H, m, Ar), 7.15-7.10 (1H, m, Ar), 6.93-6.86 (3H, m, Ar), 4.82 (1H, d, J = 4.5Hz, CHC*H*N), 4.48 (1H, q, J = 7.0Hz, C*H*CH_3), 3.92-3.89 (1H, m, C*H*CH_2), 3.86 (3H, s, OC*H*$_3$), 3.40 (1H, dd, J = 17.5 and 2.0Hz, C*H*$_2$CH), 3.07 (1H, dd, J = 17.5 and 10.5Hz, C*H*$_2$CH), 1.71 (3H, d, J = 7.0Hz, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 170.3, 159.0, 144.9, 138.9, 133.4, 128.8, 128.1, 126.5, 126.4, 125.8, 114.1, 61.1, 55.4, 53.9, 51.5, 30.3, 20.8; IR (film / cm^{-1}) v = 1737 (C=O); HRMS: m/z (ES) 294.1502, $C_{19}H_{19}O_2N$ $[M+H]^+$ requires 294.1494; mp 93-95 ^{0}C; $[\alpha]_D^{17}$ = +37.3 (*c* 0.375, $CHCl_3$).

(1S,2R)-Ethyl 1-((S)-1-(4-ethoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate, 4

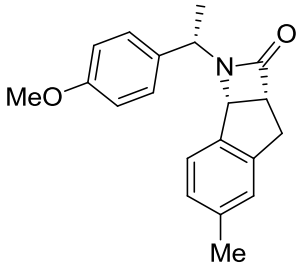


(*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **1a** (0.060 g, 0.18 mmol) was dissolved in THF (6 mL). KHMDS (0.5M in toluene, 0.39 mL, 0.19 mmol) was added and the mixture was left stirring for 8 hours at room temperature. The reaction was quenched with a saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the organic layers were combined and washed with NH_4Cl (50 mL) and water (50 mL), dried over $MgSO_4$ and the evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol: EtOAc (70:30), R_f 0.74] yielding a yellow oil (0.011 g, 18 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.40 (3H, d, J = 7.5Hz, Ar), 7.25-7.19 (2H, m, Ar), 7.19-7.16 (1H, m, Ar), 6.91 (2H, d, J = 8.5Hz), 4.45 (1H, broad d, J = 3.5Hz, NHC*H*CH), 4.19-4.06 (3H, m, C*H*CH_3 and OC*H*$_2$$CH_3$), 3.82 (3H, s, OC*H*$_3$), 3.36-3.25 (1H, broad s, C*H*$_2$CH), 3.18-3.06 (2H, m, C*H*$_2$C*H*), 1.35 (3H, d, J = 6.5Hz, C*H*CH_3), 1.24 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 175.3, 158.7, 143.8, 140.7, 137.2, 130.6, 127.9, 126.9, 124.6, 124.3, 113.8, 64.8, 60.7, 55.3, 53.3, 35.0, 26.4, 25.5, 14.2; IR (film / cm^{-1}) v = 1726 (C=O); HRMS: m/z (ES) 340.1899, $C_{21}H_{25}O_3N$ $[M+H]^+$ requires 340.1913; $[\alpha]_D^{25}$ = +21 (*c* 0.99, $CHCl_3$).

The stereochemistry was confirmed using experimental data described on page S36.

(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-5-methyl-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 2b

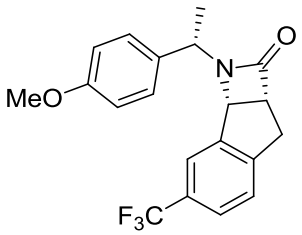


The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)-5-methylphenyl)propanoate **1b** (0.087 g, 0.25 mmol) which was dissolved in THF (7 mL) under a nitrogen atmosphere. 15-Crown-5 (0.05 mL, 0.27 mmol) and NaHMDS (1M in THF, 0.27 mL, 0.27 mmol) was added and the mixture was left stirring for 8 hours at -40 ^{0}C and allowed to warm to room temperature. The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f 0.35] yielding a white crystalline solid (0.045 g, 60 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.34-7.29 (2H, m, Ar), 7.11 (1H, s, Ar), 7.06 (1H, d, J = 8.0Hz, Ar), 7.02-6.98 (1H, m, Ar), 6.98-6.95 (2H, m, Ar), 5.00 (1H, q, J = 7.0Hz, C*H*CH_3), 4.86 (1H, d, J = 4.5Hz, CHC*H*N), 3.91-3.86 (4H, m, C*H*CH_2 and OC*H*$_3$), 3.36 (1H, d, J = 17.5Hz, CHC*H*$_2$), 2.99 (1H, dd, J = 17.5 and 10.5Hz, CHC*H*$_2$), 2.38 (3H, s, ArC*H*$_3$), 1.44 (3H, d, J = 7.0Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 169.9, 159.0, 145.4, 138.8, 136.9, 132.1, 128.4, 127.4, 126.9, 125.9, 114.0, 61.1, 55.4, 51.9, 50.9, 29.9, 21.4, 18.9; IR (film / cm^{-1}) v = 1738 (C=O); HRMS:

m/z (ES) 208.1642, $C_{20}H_{21}O_2N$ $[M+H]^+$ requires 308.1651; mp 71-73 ^oC; $[\alpha]_D^{25}$ = -18 (*c* 0.895, $CHCl_3$).

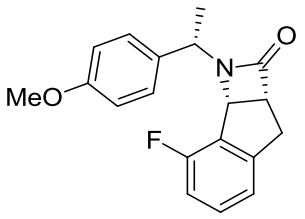
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-(trifluoromethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 2c



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)-4-(trifluoromethyl)phenyl)propanoate **1c** (0.086 g, 0.21 mmol) which was dissolved in THF (6 mL) under a nitrogen atmosphere. 15-Crown-5 (0.05 mL, 0.23 mmol) and NaHMDS (1M in THF, 0.23 mL, 0.23 mmol) was added and the mixture was left stirring for 8 hours at -40 ^0C and allowed to warm to room temperature. The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f 0.24] yielding a white crystalline solid (0.053 g, 69 %).

^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.53 (1H, d, J = 7.5Hz, Ar), 7.39 (1H, d, J = 8.0Hz, Ar), 7.24 (2H, d, J = 8.5Hz, Ar), 7.14 (1H, s, Ar), 6.92 (2H, d, J = 8.5Hz, Ar), 4.89 (1H, q, J = 7.0Hz, C*H*CH_3), 4.84 (1H, d, J = 4.0Hz, NC*H*CH), 3.96 (1H, dq, J = 10.5 and 2.0Hz, C*H*CH_2), 3.87 (3H, s, OC*H*$_3$), 3.45 (1H, d, J = 18.0Hz, CHC*H*$_2$), 3.08 (1H, dd, J = 17.5 and 10.5Hz, CHC*H*$_2$), 1.51 (3H, d, J = 7.0Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 169.3, 159.3, 149.1, 140.4, 131.7, 128.7 (q, J = 31.0Hz, CF_3*C*), 128.4, 126.7, 125.8 (q, J = 4.0 Hz, CHC*C*H), 124.1 (q, J = 273.0Hz, *C*F_3), 123.2 (q, J = 4.0 Hz, *C*F_3CCH), 122.7, 114.1, 61.2, 55.3, 52.8, 51.7, 30.2, 19.3; IR (film / cm^{-1}) v = 1742 (C=O); HRMS: m/z (ES) 362.1358, $C_{20}H_{18}O_2NF_3$ $[M+H]^+$ requires 362.1368; mp 108-110 ^0C; $[\alpha]_D^{25}$ = -14 (*c* 0.5825, $CHCl_3$).

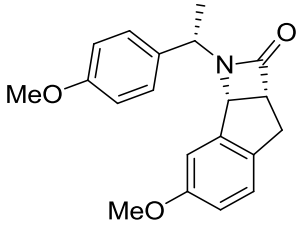
(2a*R*,7b*R*)-7-Fluoro-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 2d



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(3-fluoro-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **1d** (0.070 g, 0.20 mmol) which was dissolved in THF (6 mL) under a nitrogen atmosphere. 15-Crown-5 (0.04 mL, 0.22 mmol) and NaHMDS (1M in THF, 0.22 mL, 0.22 mmol) was added and the mixture was left stirring for 8 hours at -40 ^{0}C and allowed to warm to room temperature. The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f 0.30] yielding a white crystalline solid (0.048 g, 79 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.37-7.26 (3H, m, Ar), 7.08 (1H, s, Ar), 6.94-6.86 (3H, m, Ar), 5.02-4.95 (2H, m, NC*H*CH and C*H*CH_3), 3.98-3.92 (1H, m, C*H*CH_2), 3.85 (3H, s, OC*H*$_3$), 3.44 (1H, d, J = 17.5Hz, CHC*H*$_2$), 3.05 (1H, dd, J = 18.0 and 11.0Hz, CHC*H*$_2$), 1.51 (3H, d, J = 7.0Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 169.2, 161.5-158.2 (d, J = 247.81Hz, *C*F), 158.9, 148.7 (d, J = 4.54Hz, CH_2*C*), 132.6, 131.1 (d, J = 7.5Hz, CF*C*CH), 128.2 (d, J = 1.0Hz, CFCH*C*H), 127.2, 127.0, 122.0 (d, J = 3.5Hz, CFCHCH*C*H), 113.9, 113.2 (d, J = 20.5Hz, CF*C*H), 57.7, 55.3, 52.5, 51.4, 30.2, 18.2 (d, J = 3.5Hz, who); IR (film / cm^{-1}) v = 1743 (C=O); HRMS: m/z (ES) 334.1225, $C_{19}H_{18}O_2NF$ $[M+Na]^+$ requires 334.1219; mp 75-77 ^{o}C; $[\alpha]_D^{25}$ = -46 (*c* 0.5475, $CHCl_3$).

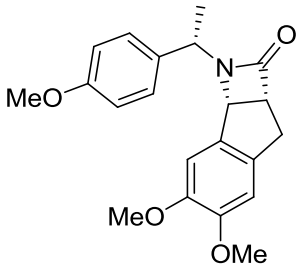
(2a*R*,7b*R*)-6-Methoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 2e



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(4-methoxy-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **1e** (0.105 g, 0.28 mmol) which was dissolved in THF (7 mL) under a nitrogen atmosphere. 15-Crown-5 (0.06 mL, 0.31 mmol) and NaHMDS (1M in THF, 0.31 mL, 0.31 mmol) was added and the mixture was left stirring for 8 hours at -40 ^{0}C and allowed to warm to room temperature. The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f 0.25] yielding a white crystalline solid (0.057 g, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.30 (2H, d, J = 8.0Hz, Ar), 7.19 (1H, d, J = 8.5Hz, Ar), 6.98-6.94 (2H, m, Ar), 6.86 (1H, dd, J = 8.0 and 2.5Hz, Ar), 6.60 (1H, d, J = 2.5Hz, Ar), 4.98 (1H, q, J = 7.0Hz, C*H*CH_3), 4.77 (1H, d, J = 4.5Hz, NC*H*CH), 3.91 (1H, dq, J = 10.5 and 2.5Hz, C*H*CH_2), 3.88 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.33 (1H, d, J = 17.0Hz, CHC*H*$_2$), 2.96 (1H, dd, J = 17.0 and 10.5Hz, CHC*H*$_2$), 1.48 (3H, d, J = 7.0Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 170.0, 159.1, 158.5, 140.9, 136.9, 132.0, 128.5, 126.9, 114.9, 114.0, 111.4, 61.5, 55.5, 55.3, 52.4, 51.5, 29.3, 19.1; IR (film / cm^{-1}) v = 1730 (C=O); HRMS: m/z (ES) 324.1601, $C_{20}H_{21}O_3N$ $[M+H]^+$ requires 324.1600; mp 128-130 ^{0}C; $[\alpha]_D^{25}$ = -55 (*c* 0.60, $CHCl_3$).

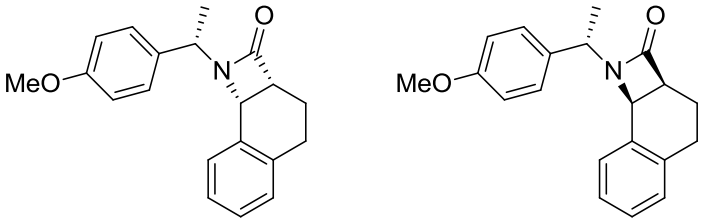
(2a*R*,7b*R*)-6,7-Dimethoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 2f



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(3,4-dimethoxy-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **1f** (0.054 g, 0.14 mmol) which was dissolved in THF (5 mL) under a nitrogen atmosphere. 15-Crown-5 (0.03 mL, 0.15 mmol) and NaHMDS (1M in THF, 0.15 mL, 0.15 mmol) was added and the mixture was left stirring for 8 hours at -40 ^{0}C and allowed to warm to room temperature. The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f 0.15] yielding a white crystalline solid (0.029 g, 60 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.32-7.27 (2H, m, Ar), 6.95 (2H, d, J = 8.5Hz, Ar), 6.77 (1H, s, C*H*$COCH_3$), 6.47 (1H, s, C*H*$COCH_3$), 4.95 (1H, q, J = 7.0Hz, C*H*CH_3), 4.76 (1H, d, J = 4.0Hz, CHC*H*N), 3.92-3.95 (1H, m, C*H*CH_2), 3.90 (3H, s, ArOC*H*$_3$), 3.87 (3H, s, ArOC*H*$_3$), 3.82 (3H, s, ArOC*H*$_3$), 3.34 (1H, d, J = 17.0Hz, CHC*H*$_2$), 2.97 (1H, dd, J = 17.0 and 10.5Hz, CHC*H*$_2$), 1.49 (3H, d, J = 7.0Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 170.2, 159.1, 149.9, 147.9, 137.2, 132.1, 131.4, 128.5, 114.0, 108.8, 108.5, 61.9, 56.0, 55.9, 55.3, 52.4, 51.6, 30.0, 19.2; IR (film / cm^{-1}) v = 1720 (C=O); HRMS: m/z (ES) 354.1692, $C_{21}H_{23}O_4N$ $[M+H]^+$ requires 354.1701; mp 142-144^{0}C; $[\alpha]_D^{25}$ = -3.5 (*c* 0.565, $CHCl_3$).

(2a*R*,8b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-1,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(2aH)-one, 2g



Major Minor

The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 4-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)butanoate **1g** (0.064 g, 0.18 mmol) which was dissolved in THF (6 mL) under a nitrogen atmosphere. 15-Crown-5 (0.07 mL, 0.36 mmol) and NaHMDS (1M in THF, 0.36 mL, 0.36 mmol) was added and the mixture was left stirring for 8 hours at -40 ^{0}C and allowed to warm to room temperature. The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f 0.36] yielding a colorless oil (0.032 g, 57 %).

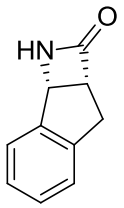
Major Diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31-7.25 (1H, m, Ar), 7.22-7.17 (4H, m, Ar), 6.97-6.89 (3H, m, Ar), 4.99 (1H, q, J = 7.0Hz, C*H*CH_3), 4.42 (1H, d, J = 5.0Hz, NC*H*CH), 3.87 (3H, s, OC*H*$_3$), 3.59-3.55 (1H, m, NCHC*H*), 2.85-2.70 (2H, m, ArC*H*$_2$), 2.40 (1H, app. d of sep, J = 13.5 and 1.5Hz, CHC*H*$_2$CH$_2$), 1.61-1.50 (1H, m, CHC*H*$_2$CH$_2$), 1.18 (3H, d, J = 7.0Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 169.1, 158.9, 139.9, 133.7, 131.6, 130.1, 128.8, 128.7, 128.3, 126.2, 113.8, 55.3, 52.8, 50.6, 49.4, 26.8, 23.1, 18.2;

Minor Diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31-7.25 (1H, m, Ar), 7.22-7.17 (2H, m, Ar), 7.10-7.07 (2H, m, Ar), 7.03 (1H, d, J = 7.5Hz, Ar), 6.82-6.78 (2H, m, Ar), 4.50 (1H, d, J = 5.0Hz, NC*H*CH), 4.32 (1H, q, J = 7.0Hz, C*H*CH_3), 3.82 (3H, s, OC*H*$_3$), 3.59-3.55 (1H, m, NCHC*H*), 2.85-2.70 (2H, m, ArC*H*$_2$), 2.40 (1H, app. d of sep, J = 13.5 and 1.5Hz, CHC*H*$_2$CH$_2$), 1.67 (3H, d, J = 7.0Hz, CHC*H*$_3$), 1.47-1.40 (1H, m, CHC*H*$_2$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 169.4, 158.7, 139.9, 132.7, 131.6, 130.3, 128.8, 128.6, 128.3, 127.8, 114.0, 55.3, 52.8, 50.6, 49.2, 26.8, 22.9, 19.9;

IR (film / cm^{-1}) v = 1727 (C=O); HRMS: m/z (ES) 308.1644, $C_{20}H_{21}O_2N$ $[M+H]^+$ requires 308.1650.

Deprotection, Esters and Amino Acids

(2a*R*,7b*R*)-2a,3-Dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 5a

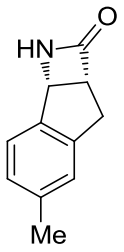


(2a*R*,7b*R*)-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one (0.035 g, 0.12 mmol) **2a** was added to a solution of acetonitrile : water (7.5 mL : 1.5 mL). Ammonium cerium(IV) nitrate (0.19 g, 0.35 mmol) was added portion-wise and the solution was left to stir for 16 hrs. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified by recrystallisation from dichloromethane and hexane yielding a white crystalline solid (0.14 g, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.35-7.21 (4H, m, Ar), 6.25 (1H, broad s, N*H*), 5.03 (1H, d, J = 4.5Hz, NC*H*CH), 4.06-4.00 (1H, m, C*H*CH_2), 3.35 (1H, d, J = 17.5, CHC*H*$_2$), 3.07 (1H, dd, J = 17.5 and 10.5Hz, CHC*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 170.5, 143.2, 139.5, 128.1, 126.1, 125.3,

124.1, 57.5, 53.2, 29.3; IR (film / cm^{-1}) v = 3164 (N-H), 1695 (C=O); HRMS: m/z (ES) 182.0581, $C_{10}H_9ON[M+Na]^+$ requires 181.0582; mp 191-192^{0}C; $[\alpha]_D^{21}$ = -214 (*c* 0.69, $CHCl_3$).

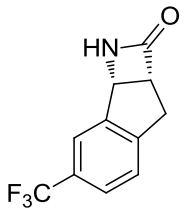
(2aR,7bR)-5-methyl-2a,3-Dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 5b



(2a*R*,7b*R*)-1-((*S*)-1-(4-methoxyphenyl)ethyl)-5-methyl-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one (0.019 g, 0.06 mmol) **2b** was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium(IV) nitrate (0.10 g, 0.18 mmol) was added portion-wise and the solution was left to stir for 16 hrs. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol: EtOAc (65:45), R_f 0.17] yielding a white crystalline solid (0.007 g, 66 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.23 (1H, d, J = 7.5Hz, CH_3CCHCH), 7.12 (1H, s, CH_3CCHC), 7.06 (1H, d, J = 7.5Hz, CH_3CCHCH), 6.19 (1H, broad s, N*H*), 5.01 (1H, d, J = 4.0, C*H*NH), 4.04 (1H, d, J = 10.5Hz, C*H*CH_2), 3.33 (1H, dd, J = 17.5Hz, CHCH_2), 3.05 (1H, dd, J = 17.5 and 10.5Hz, CHCH_2), 2.37 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 171.5, 144.5, 139.1, 137.7, 128.0, 126.9, 124.8, 58.3, 54.5, 30.3, 21.4; IR (film / cm^{-1}) v = 3194 (N-H), 1701 (C=O); HRMS: m/z (ES) 174.0903, $C_{11}H_{11}ON$ $[M+H]^+$ requires 174.0910; mp 97-100 ^{o}C; $[\alpha]_D^{21}$ = -140 (*c* 0.22, $CHCl_3$).

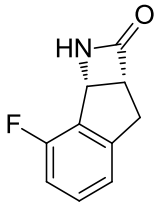
(2aR,7bR)-6-(Trifluoromethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 5c



(2a*R,*7b*R*)-1-((*S*)-1-(4-methoxyphenyl)ethyl)-6-(trifluoromethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one (0.024 g, 0.07 mmol) **2c** was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium(IV) nitrate (0.11 g, 0.20 mmol) was added portion-wise and the solution was left to stir for 16 hrs. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol: EtOAc (70:30), R_f 0.15] yielding a white crystalline solid (0.009 g, 61 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.62 (1H, s, CF_3CHC), 7.59 (1H, d, J = 8.0Hz, CF_3CHCH), 7.42 (1H, d, J = 18.0Hz CF_3CHCH), 6.35 (1H, broad s, N*H*), 5.09 (1H, d, J = 4.5Hz, NC*H*CH), 4.12 (1H, m, C*H*CH_2), 3.42 (1H, d, J = 18.0 Hz, CHCH_2), 3.14 (1H, dd, J = 17.5 and 10.5Hz, CHCH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 170.5, 148.4, 141.3, 129.9 (q, J = 33.0Hz, CF_3C) 126.8, 126.2 (q, J = 4.0Hz, CHC*C*H), 124.0 (q, J = 272.0Hz, *C*F_3), 122.3 (q, J = 4.0Hz, CCH*C*H), 58.0, 54.6, 30.4; IR (film / cm^{-1}) v = 3201 (N-H), 1755 (C=O); HRMS: m/z (ES) 228.0639, $C_{11}H_8ONF_3$ $[M+H]^+$ requires 228.0636; mp 138-139 ^{0}C; $[\alpha]_D^{21}$ = -221 (*c* 0.24, $CHCl_3$).

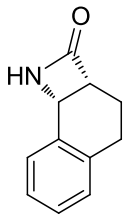
(2aR,7bR)-7-Fluoro-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one, 5d



(2a*R*,7b*R*)-7-fluoro-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one (0.024 g, 0.08 mmol) **2d** was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium(IV) nitrate (0.13 g, 0.23 mmol) was added portion-wise and the solution was left to stir for 16 hrs. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol: EtOAc (70:30), R_f 0.25] yielding a white crystalline solid (0.0085 g, 62 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.33-7.28 (1H, m, CFCHC*H*), 7.07 (1H, d, J = 7.5Hz, CFCHCHC*H*), 6.92 (1H, app. t, J = 9.0Hz, CFC*H*), 6.30 (1H, broad s, N*H*), 5.18 (1H, d, J = 4.5Hz, NC*H*CH), 4.14-4.10 (1H, m, C*H*CH_2), 3.40 (1H, d, J = 17.5, CHC*H*$_2$), 3.10 (1H, dd, J = 17.5 and 10.5Hz, CHC*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 170.7, 160.1 (d, J = 248.0Hz, *C*F), 147.8 (d, J = 4.5Hz, CFC*C*CH), 131.4 (d, J = 7.0Hz, CFCH*C*H), 127.6 (d, J = 19.0Hz, CF*C*CCH), 121.9 (d, J = 19.0Hz, CFCC*C*H), 113.5 (d, J = 19.0Hz, CF*C*H), 55.2, 55.1, 30.6; IR (film / cm^{-1}) v = 3225 (N-H), 1786 (C=O); HRMS: m/z (ES) 200.0472, $C_{10}H_8ONF[M+Na]^+$ requires 200.0488; mp 151-153 ^{0}C; $[\alpha]_D^{21}$ = -182 (*c* 0.28, $CHCl_3$).

(2aR,8bR)-1,3,4,8b-Tetrahydronaphtho[1,2-b]azet-2(2aH)-one, 5g

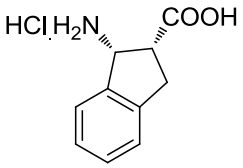


(2a*R*,8b*R*)-1-((*S*)-1-(4-methoxyphenyl)ethyl)-1,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(2aH)-one **2g** (0.027 g, 0.09 mmol) was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium(IV) nitrate (0.15 g, 0.27 mmol) was added portion-wise and the solution was left to stir for 16 hrs. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered

before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol: EtOAc (70:30), R_f 0.29] yielding a white crystalline solid (0.011 g, 72 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.32-7.20 (4H, m, Ar), 6.06 (1H, broad s, N*H*), 4.70 (1H, d, J = 5.0Hz, NC*H*CH), 3.74 (1H, s, C*H*CH_2CH_2), 2.88-2.73 (2H, m, $CHCH_2CH_2$), 2.35 (1H, d, J = 13.5, $CHCH_2CH_2$), 1.68-1.59 (1H, m, $CHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 170.6, 139.3, 134.0, 129.6, 129.0, 128.5, 126.6, 51.5, 50.2, 26.9, 22.9; IR (film / cm^{-1}) v = 3235 (N-H), 1737 (C=O); HRMS: m/z (ES) 196.0721, $C_{11}H_{11}ON[M+Na]^+$ requires 196.0738; mp 103-105 ^oC.

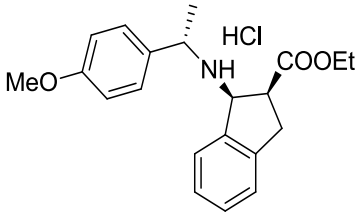
(1*R*,2*R*)-1-Amino-2,3-dihydro-1H-indene-2-carboxylic acid hydrochloride, 6



(2a*R*,7b*R*)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one **5a** (0.020 g, 0.13 mmol) was refluxed in 18% HCl solution for 3 hours. The solvent was then evaporated under reduced pressure. The crude was purified by recrystallisation from ethanol and diethyl ether yielding a white crystalline solid (0.022 g, 83%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.45 (1H, d, J = 8.0Hz, Ar), 7.40-7.34 (2H, m, Ar), 7.31 (1H, t, J = 7.0Hz, Ar), 4.94 (1H, d, J = 6.5Hz, NC*H*), 3.69 (1H, q, J = 8.0Hz, NCHC*H*), 3.30 (2H, d, J = 8.5Hz, $CHCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 175.4, 142.1, 136.6, 130.3, 127.7, 125.4, 125.3, 55.3, 45.5, 33.3; IR (film / cm^{-1}) v = 3384 (O-H), 1715 (C=O); HRMS: m/z (ES) 200.0680, $C_{10}H_{11}O_2N$ [M+Na]$^+$ requires 200.0687; mp 210-214 ^{0}C; $[\alpha]_D^{25}$ = -2.5 (*c* 0.4, MeOH).

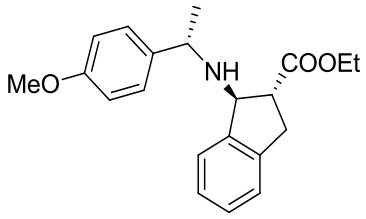
(1S,2S)-Ethyl-1-(((S)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate hydrochloride



(2aS,7bS)-1-((S)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet 2(7bH)one **3a** (0.011 g, 0.037 mmol) was refluxed in ethanol (2.1 ml) with dry hydrogen chloride (1M in diethyl ether, 0.9 mL) for 5 hours. The solvent was then evaporated under reduced pressure yielding a yellow oil (0.0136 g, 96%).

^{1}H NMR (500 MHz, MeOD): δ_H = 7.60 (1H, d, J = 7.5Hz, Ar), 7.54 (2H, d, J = 8.5Hz, Ar), 7.46-7.35 (3H, m, Ar), 7.07 (2H, d, J = 8.5Hz, Ar), 4.75 (1H, d, J = 6.5Hz, NHC*H*CH), 4.66 (1H, q, J = 6.5 Hz C*H*CH_3), 4.33-4.24 (2H, m, OC*H*$_2CH_3$), 3.84 (3H, s, OC*H*$_3$), 3.69-3.62 (1H, m, CH_2C*H*), 3.42-3.32 (2H, m, C*H*$_2$CH), 1.72 (3H, d, J = 6.5Hz, C*H*CH_3), 1.32 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 173.9, 160.3, 143.6, 134.3, 130.7, 128.7, 128.4, 127.5, 126.2, 125.9, 115.3, 62.7, 59.3, 56.6, 55.6, 45.6, 34.5, 22.4, 14.1; IR (film / cm^{-1}) v = 1727 (C=O); HRMS: m/z (ES) 340.1968, $C_{21}H_{25}NO_3$ $[M+H]^+$ requires 340.1913.

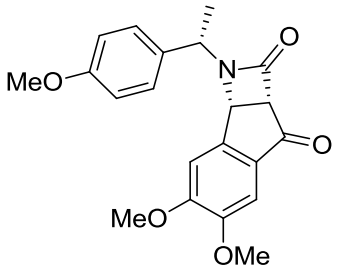
(1S,2R)-Ethyl 1-((S)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate, 4



(1S,2S)-ethyl-1-(((S)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate hydrochloride (0.015 g, 0.039 mmol) was dissolved in dry ethanol (3 ml) under a nitrogen atmosphere. Sodium ethoxide (0.007 g, 0.10 mmol) was added and the reaction was heated at reflux for 48 hours. After cooling, the reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the aqueous layer extracted with dichloromethane (2 x 20 mL). The combined organics were collected and washed with water (2 x 20 mL) and then dried over $MgSO_4$. The solvent was then evaporated under reduced pressure.[5] The crude was purified using flash column chromatography [Petrol: EtOAc (70:30), R_f 0.74] yielding a yellow oil (0.011 g, 81 %).

Data for this compound identical to that reported on page S25

(2aS,7bR)-5,6-Dimethoxy-1-((S)-1-(4-methoxyphenyl)ethyl)-1H-indeno[1,2-b]azete-2,3(2aH,7bH)-dione, 12

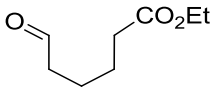


(2a*R*,7b*R*)-6,7-dimethoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one **2f** (0.020 g, 0.06 mmol) was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium(IV) nitrate (0.093 g, 0.17 mmol) was added portion-wise and the solution was left to stir for 16 hrs. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure yielding a yellow oil (0.004 g, 19%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.18-7.12 (3H, m, Ar), 6.86-6.80 (2H, d, J = 8.5Hz, Ar), 6.25 (1H, s, Ar), 4.82 (1H, q, J = 7.0Hz, CH_3CH), 4.65 (1H, d, J = 3.5Hz, COC*H*), 4.15 (1H, d, J = 3.5Hz, NHC*H*CH), 3.84 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 1.44 (3H, d, J = 7.0Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 193.6, 161.7, 159.4, 155.0, 150.9, 144.3, 131.4, 131.3, 128.6, 114.2, 108.2, 105.4, 63.1, 56.3, 56.2, 55.4, 53.5, 53.3, 19.4; IR (film / cm^{-1}) v = 1729 (C=O); HRMS: m/z (ES) 370.1651, $C_{21}H_{23}O_5N[M+H]^+$ requires 370.1654.

Acyclic Substrates

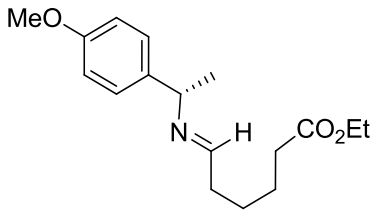
Ethyl 6-oxohexanoate



Ethyl-6-hydrohexanoate (0.50 mL, 3.1 mmol) was added to pyridinium chlorochromate (1.00 g, 3.1 mmol) in CH_2Cl_2 (14 mL) and allowed to stir at room temperature for 2 hours. The reaction mixture was filtered through a pad of Celite® and Fluorosil® and then evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f- 0.51] yielding a colourless liquid (0.44 g, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 9.76 (1H, br s, C*H*O), 4.13 (2H, q, J = 7.0Hz, OC*H*$_2$CH$_3$), 2.46 (2H, app q, C*H*$_2$CHO), 2.32 (2H, m, C*H*$_2$CO$_2$Et), 1.67 (4H, m, J = 3.0Hz, C*H*$_2$C*H*$_2$CH$_2$), 1.25 (3H, t, J = 7.0Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 201.9, 173.1, 60.1, 43.3, 33.8, 24.3, 21.4, 14.1; IR (film / cm^{-1}) v = 1721 (C=O); HRMS: m/z (ES) 159.1013, $C_8H_{14}O_3$[M+H]$^+$ requires 159.1021.

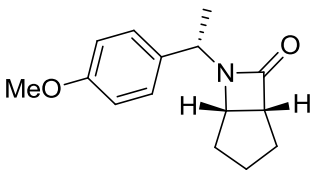
(*S*,*E*)-Ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)hexanoate, 1h



Ethyl-6-oxohexanoate (0.193 g, 1.22 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$. After 5 minutes (*S*)-(−)-4-Methoxy-α-methylbenzylamine (0.180 mL, 1.22 mmol) was added and the reaction was left to stir for 3 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a pale yellow oil (0.318 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.71 (1H, t, J = 5.0Hz, CNH), 7.29-7.20 (2H, m, Ar), 6.85 (2H, d, J = 8.5Hz, Ar), 4.24 (1H, q, J = 6.5Hz, CH_3CH), 4.11 (2H, q, J = 7.0Hz, CH_2CH_3), 3.78 (3H, s, OCH_3), 2.34-2.22 (4H, m, $CH_2CH_2CH_2CH_2$), 1.71-1.52 (4H, m, $CH_2CH_2CH_2$), 1.46 (3H, d, J = 6.5Hz, CH_3CH), 1.24 (3H, t, J = 7.0Hz, CH_2CH_3); HRMS: m/z (ES) 292.1911, $C_{17}H_{25}O_3N$[M+H]$^+$ requires 292.1913.

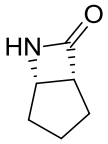
(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one, 2h



(*S*,*E*)-ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)hexanoate **1h** (0.966 g, 3.31 mmol) was dissolved in THF (50 mL). 15-Crown-5 (1.31 mL, 6.62 mmol) and NaHMDS (1M in THF, 6.62 mL, 6.62 mmol) were added and the mixture was left stirring for 8 hours at room temperature. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the THF was removed under reduced pressure. The resulting solution was further diluted with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic layers were combined and washed with water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. . The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f- 0.41] yielding a yellow oil (0.357 g, 44 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.26 (2H , m, Ar), 6.88 (2H, d, J = 8.5Hz, Ar), 4.81 (1H, q, J = 7.0Hz, CH_3CH), 3.83 (4H, m, OCH_3 & CHNH), 3.32 (1H, dd, J = 3.5Hz & 8.0Hz, CHCHNH), 2.07-1.99 (1H, m, CH_2CH_2), 1.87-1.62 (3H, m, $CH_2CH_2CH_2$), 1.58 (3H, d, J = 7.0Hz, CH_3CH), 1.38-1.13 (2H, m, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.9, 159.0, 132.9, 128.2, 114.0, 57.2, 55.3, 53.8, 51.5, 29.2, 24.8, 22.7, 19.6; IR (film / cm^{-1}) v = 1731 (C=O); HRMS: m/z (ES) 246.1489, $C_{15}H_{19}O_2N[M+H]^+$ requires 246.1494. $[\alpha]_D^{21}$ = -14 (*c* 1.09, $CHCl_3$).

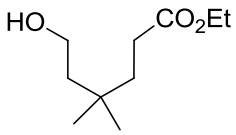
(1*R*,5*S*)-6-Azabicyclo[3.2.0]heptan-7-one, 5h



(1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one **2h** (0.297 g, 1.2 mmol) was added to a solution of acetonitrile : water (15 mL : 15 mL). Ammonium cerium(IV) nitrate (2.63 g, 4.8 mmol) was added portion-wise and the solution was left to stir for 4 hrs. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with CH_2Cl_2 (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified by recrystallisation from dichloromethane and hexane yielding a white solid (0.095 g, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 6.17 (1H, br s, N*H*), 4.01 (1H, t, J = 4.0Hz, CHC*H*NH), 3.47-3.43 (1H, m, C*H*CHNH), 1.99 (1H, dd, J = 13.5 & 6.0Hz, CH_2CH_2CH_2), 1.85-1.69 (3H, m, CH_2CH_2CH_2), 1.44-1.28 (2H, m, CH_2CH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 171.0, 55.9, 54.0, 30.0, 25.2, 22.4; IR (film / cm^{-1}) v = 3250 (N-H), 1716 (C=O); HRMS: m/z (ES) 112.0778, $C_6H_9ON[M+H]^+$ requires 112.0762; mp 49-50 ^{o}C; $[\alpha]_D^{17}$ = -33 (*c* 0.87, $CHCl_3$).

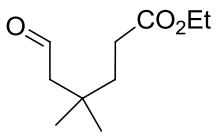
Ethyl 6-hydroxy-4,4-dimethylhexanoate



Potassium persulfate (2.40 g, 8.87 mmol) is added to a solution of H_2SO_4 (5 mL), ethanol (10 mL) and water (2 mL) which has been cooled to 15 ^{0}C. A solution of 4,4'-dimethylcyclohexanone (0.373 g, 2.96 mmol) in ethanol (3 mL) was added dropwise and the reaction was left to stir overnight. The reaction was diluted with water (30 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organics were collected, dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f- 0.23] yielding a colourless oil (0.445 g, 80 %).[6]

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.05 (2H, q, J = 7.0Hz, OCH_2), 3.61 (2H, t, J = 7.0Hz, CH_2OH), 2.68 (1H, br s, O*H*), 2.25-2.17 (2H, m, CH_2CO_2Et), 1.54-1.40 (4H, m, CH_2C$(CH_3)_2$CH_2), 1.19 (3H, t, J = 7.0Hz, OCH_2CH_3), 0.83 (6H, s, C (CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 174.4, 60.4, 59.5, 44.0, 36.9, 31.9, 29.6, 27.1, 14.2; IR (film / cm^{-1}) v = 3413 (O-H), 1733 (C=O); HRMS: m/z (ES) 189.1486, $C_{10}H_{20}O_3[M+H]^+$ requires 189.1490.

Ethyl 4,4-dimethyl-6-oxohexanoate

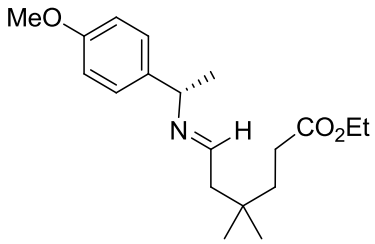


Pyridinium chlorochromate (0.589 g, 2.73 mmol) was added to Ethyl 6-hydroxy-4,4-dimethylhexanoate (0.343 mL, 1.82 mmol) in CH_2Cl_2 (15 mL) and allowed to stir at room temperature for 2 hours. The reaction mixture was filtered through a pad of Celite® and

Fluorosil® and then evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f- 0.79] yielding a colourless oil (0.295 g, 87 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 9.80 (1H, s, C*H*O), 4.15-4.01 (2H, br s, OC*H*$_2$CH$_3$), 2.34-2.18 (4H, br s, C*H*$_2$CHO & C*H*$_2$CO$_2$), 1.75-1.59 (2H, br s, C*H*$_2$C(CH$_3$)$_2$), 1.30-1.15 (3H, br s, OCH$_2$C*H*$_3$), 1.10-0.95 (6H, s, C(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 202.9, 173.6, 60.5, 54.5, 37.1, 33.1, 29.4, 27.0, 14.2; IR (film / cm^{-1}) v = 1732 (C=O); HRMS: m/z (ES) 187.1340, $C_{10}H_{18}O_3[M+H]^+$ requires 187.1334.

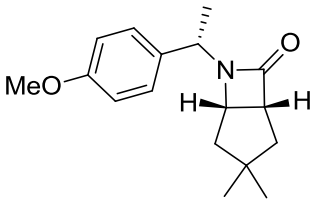
(*S*,*E*)-Ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)-4,4-dimethylhexanoate, 1i



Ethyl 4,4-dimethyl-6-oxohexanoate (0.183 g, 0.98 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$. After 5 minutes (*S*)-(−)-4-Methoxy-α-methylbenzylamine (0.145 mL, 0.98 mmol) was added and the reaction was left to stir for 3 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a pale yellow oil (0.272 g, 87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.72 (1H, t, J = 5.5Hz, CN*H*), 7.17 (2H, d, J = 8.5Hz, Ar), 6.78 (2H, d, J = 8.5 Hz, Ar), 4.20 (1H, q, J = 6.5Hz, C*H*CH$_3$), 4.04 (2H, q, J = 7.0Hz, OC*H*$_2$CH$_3$), 3.71 (3H, s, OC*H*$_3$), 2.26-2.19 (2H, m, C*H*$_2$CO), 2.11 (2H, d, J = 5.5Hz, C*H*$_2$C(CH$_3$)$_2$), 1.57-1.50 (2H, m, C*H*$_2$CHN), 1.41 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.17 (3H, t, J = 7.0Hz, OCH$_2$C*H*$_3$), 0.87 (6H, s, C(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 174.0, 161.5, 158.4, 137.0, 127.6, 114.1, 113.8, 69.3, 60.3, 55.3, 47.0, 37.0, 33.3, 29.5, 27.0, 24.3, 14.2; IR (film / cm^{-1}) v = 1731 (C=O), 1661 (C=N), 1611 (C-O);

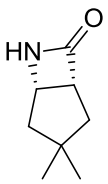
(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one, 2i



(*S*,*E*)-Ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)-4,4-dimethylhexanoate **1i** (0.378 g, 1.18 mmol) was dissolved in THF (40 mL). 15-Crown-5 (0.47 mL, 2.36 mmol) and NaHMDS (1M in THF, 2.36 mL, 2.36 mmol) were added and the mixture was left stirring for 8 hours at room temperature. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the THF was removed under reduced pressure. The resulting solution was further diluted with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic layers were combined and washed with water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. . The crude was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f- 0.57] yielding a pale yellow oil (0.252 g, 78 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.19-7.14 (2H, m, Ar), 6.84-6.78 (2H, m, Ar), 4.85 (1H, q, J = 7.0Hz, C*H*CH_3), 3.80-3.75 (1H, m, CHC*H*N), 3.74 (3H, s, OC*H*$_3$), 3.36 (1H, ddd, J = 9.0, 4.5 & 2.0Hz, C*H*CHN), 1.81 (1H, dd, J = 14.0 & 2.0 Hz, C*H*$_2$C(CH_3)CH_2), 1.67 (1H, d, J = 14.5Hz, CH_2C(CH_3)C*H*$_2$), 1.49 (3H, d, J = 7.0Hz, CHC*H*$_3$), 1.39-1.27 (2H, m, C*H*$_2$C(CH_3)C*H*$_2$), 1.08 (3H, s, C(C*H*$_3$)$_2$), 0.94 (3H, s, C(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 170.3, 158.9, 132.7, 128.3, 113.9, 57.9, 55.3, 55.2, 50.6, 43.2, 42.0, 38.3, 31.2, 30.1, 18.8; IR (film / cm^{-1}) v = 1737 (C=O); HRMS: m/z (ES) 296.1644, $C_{17}H_{23}O_2N$[M+Na]$^+$ requires 296.1626; $[\alpha]_D^{21}$ = -18 (*c* 0.55, $CHCl_3$)

(1*R*,5*S*)-3,3-Dimethyl-6-azabicyclo[3.2.0]heptan-7-one, 5i

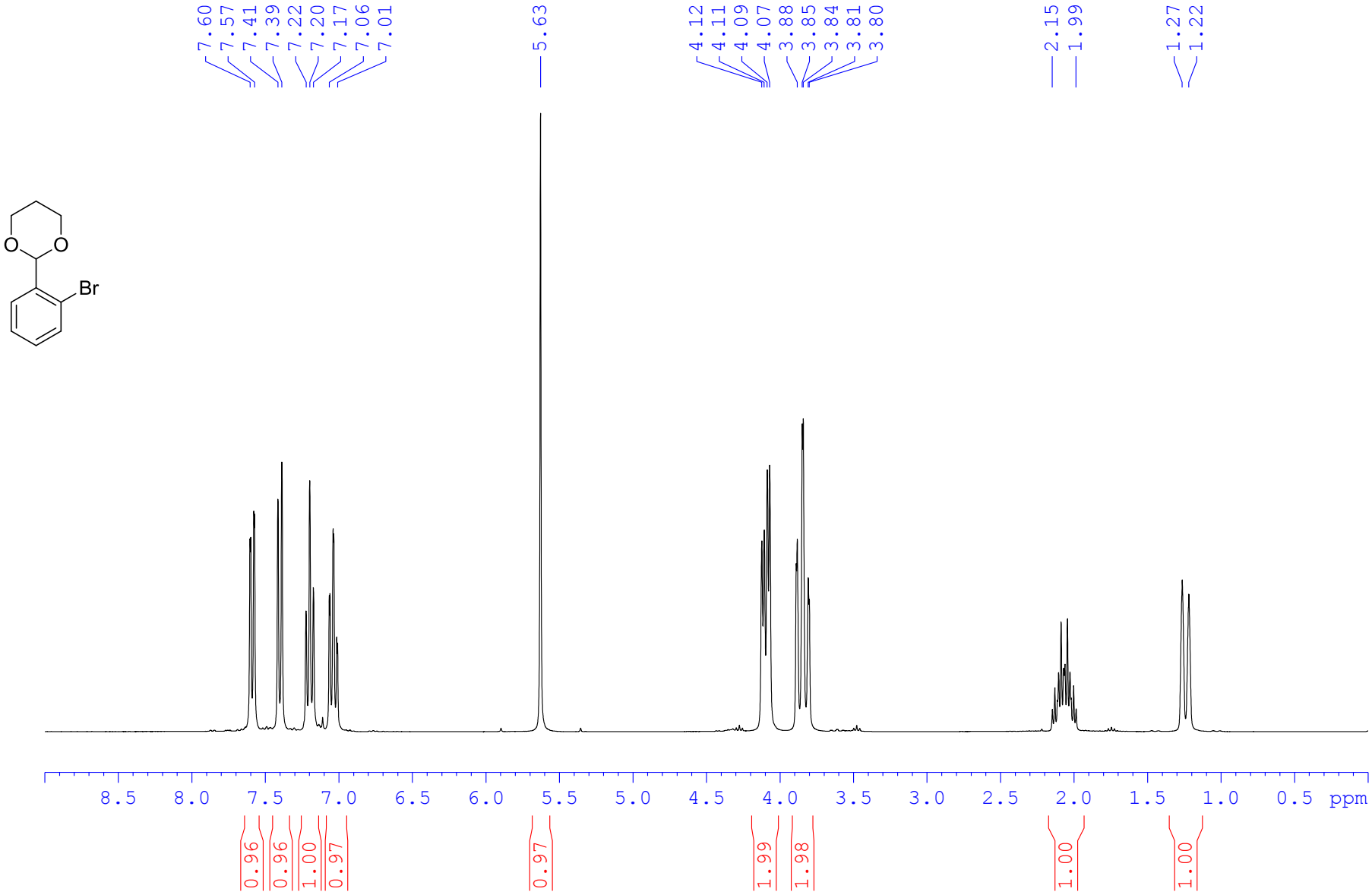


(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **2i** (0.227 g, 0.83 mmol) was added to a solution of acetonitrile : water (20 mL : 20 mL). Ammonium cerium(IV) nitrate (1.82 g, 3.32 mmol) was added portion-wise and the solution

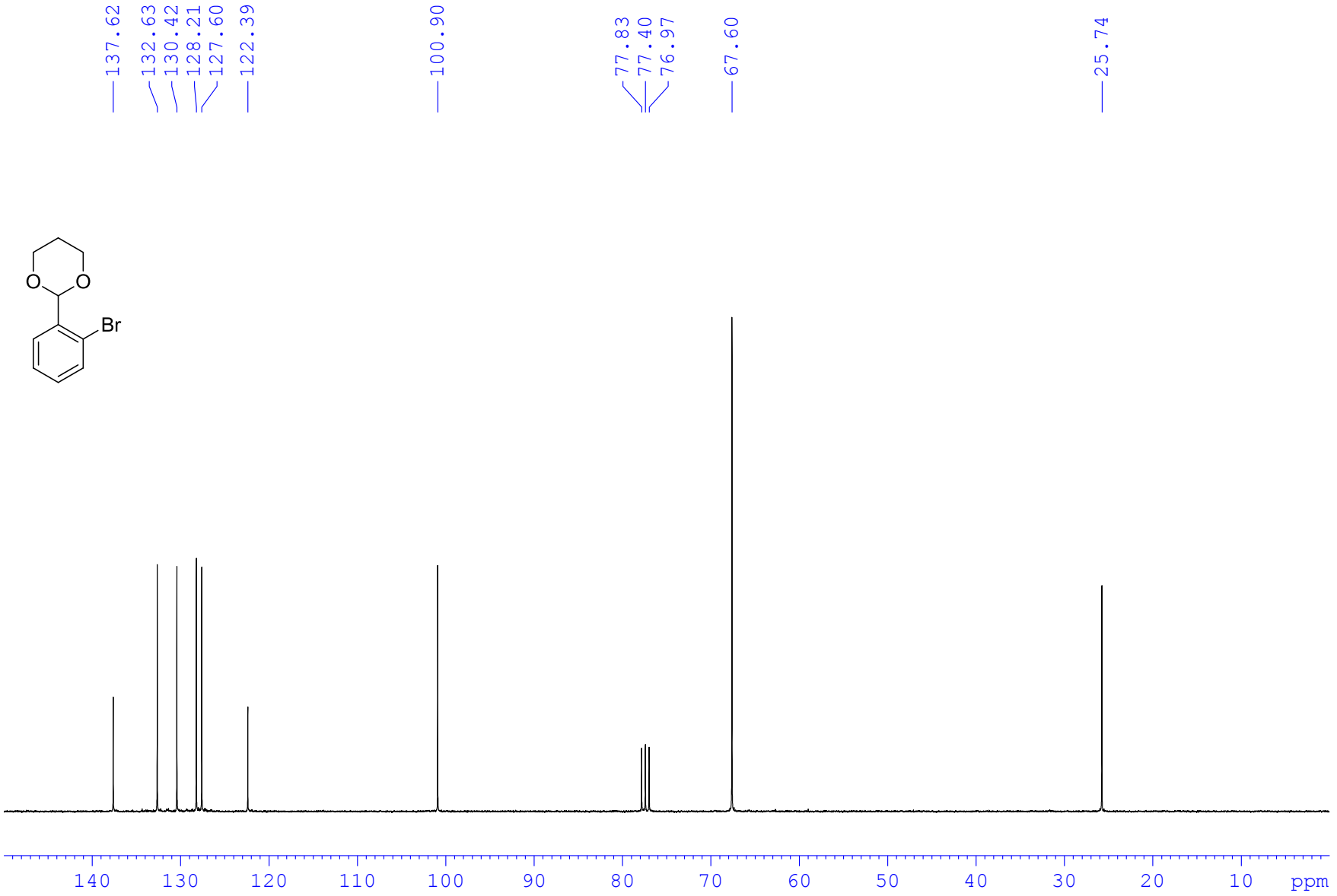
was left to stir for 4 hrs. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified by recrystallisation from Et_2O and petroleum ether yielding a white crystalline solid (0.100 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 5.99 (1H, br s, N*H*), 4.17 (1H, t, J = 5.0Hz, C*H*NH), 3.64-3.59 (1H, m, CHC*H*), 1.99 (1H, dd, J = 14.0 & 5.0Hz, CH_2C(CH_3)CH_2), 1.76 (1H, d, J = 14.5Hz, CH_2C(CH_3)CH_2), 1.61-1.53 (2H, m, CH_2C(CH_3)CH_2), 1.25 (3H, s, C(CH_3)$_2$), 1.10 (3H, s, C(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 172.3, 57.4, 55.9, 44.1, 41.9, 39.5, 31.5, 30.1; IR (film / cm^{-1}) v = 3218 (N-H), 1735 (C=O); HRMS: m/z (ES) 140.1056, $C_8H_{13}ON[M+H]^+$ requires 140.1075; mp 95-97 ^{0}C; $[\alpha]_D^{17}$ = -2 (*c* 1.01, $CHCl_3$)

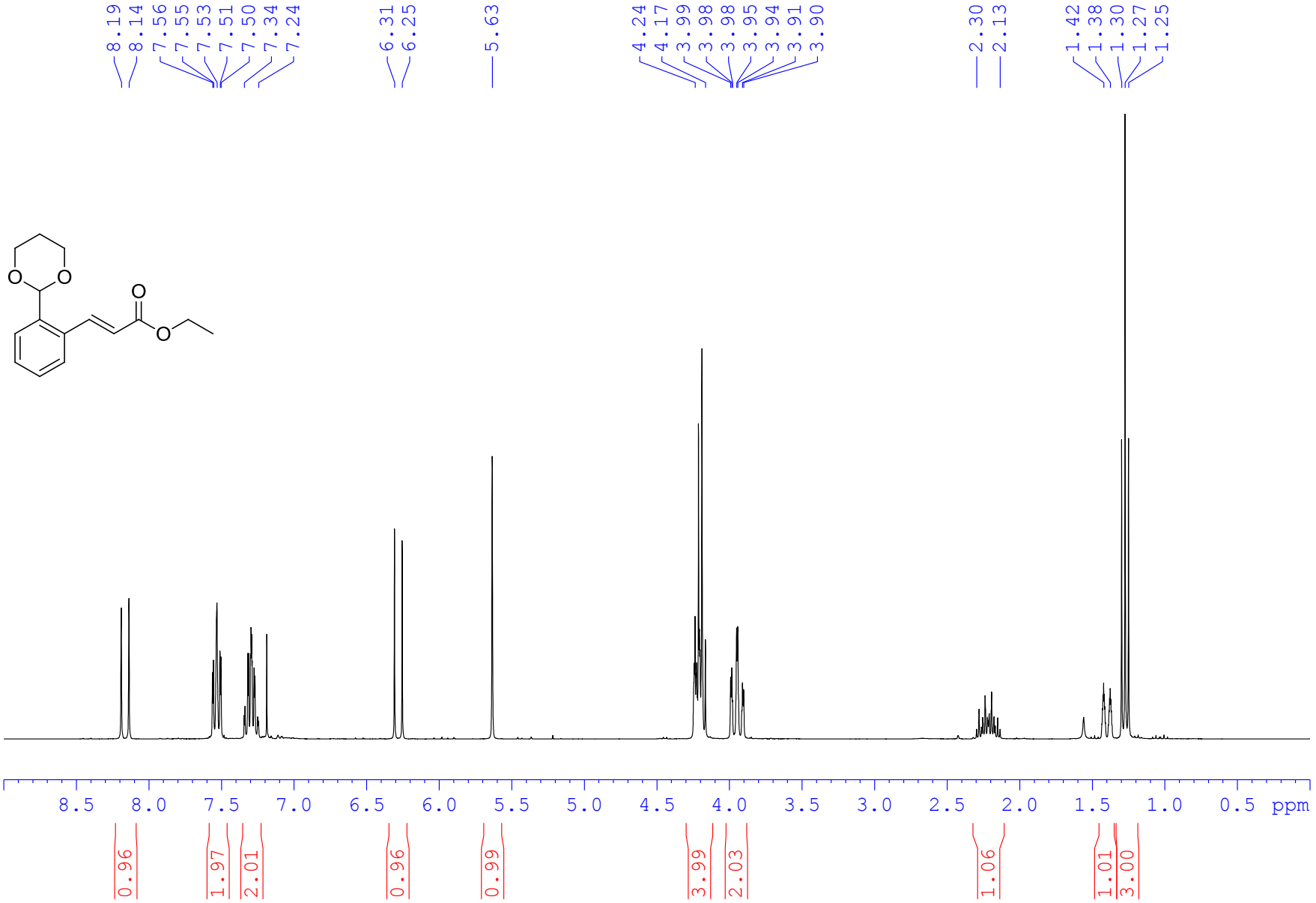
2-(2-Bromophenyl)-1,3-dioxane, 300 MHz, $CDCl_3$



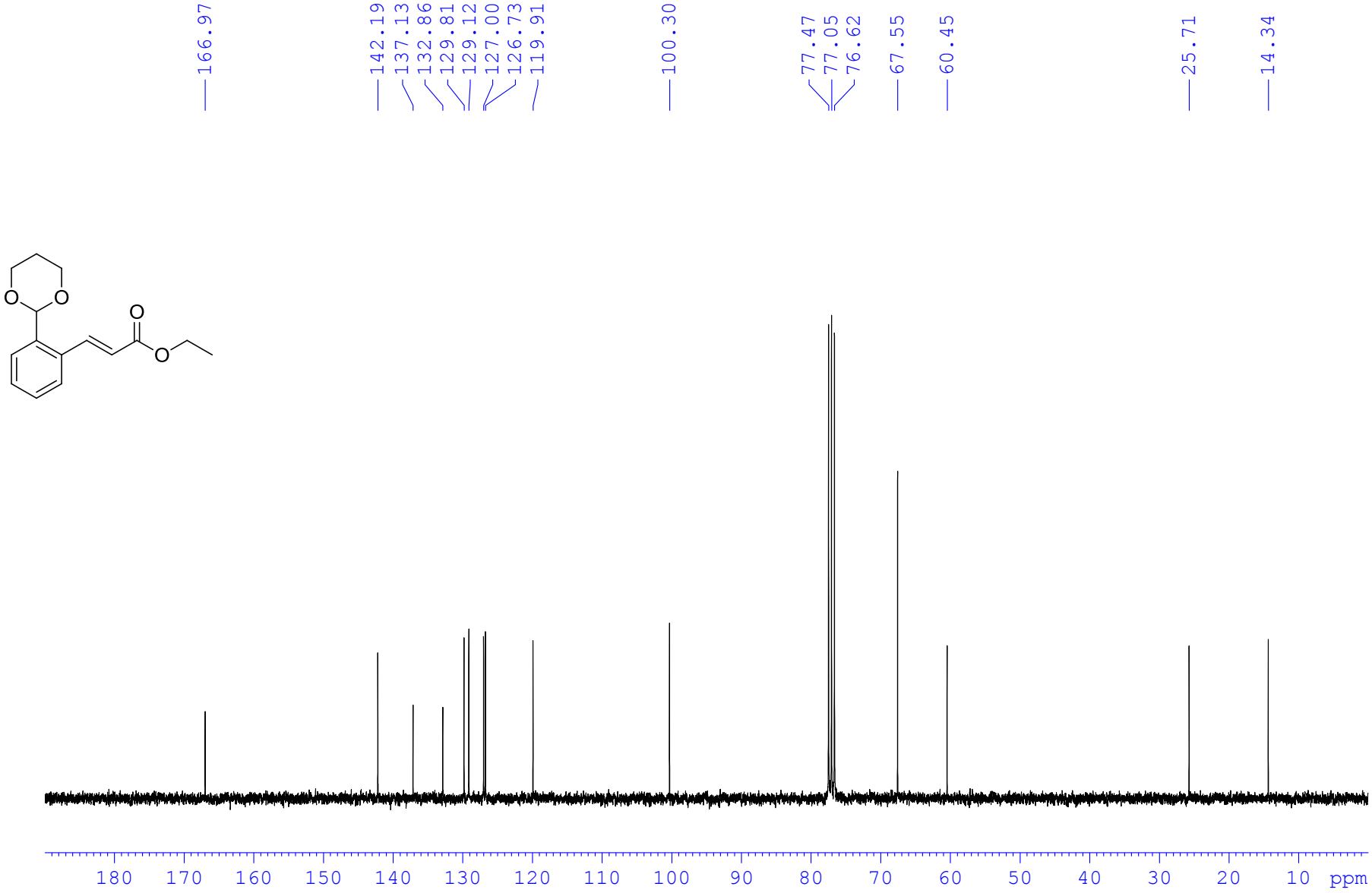
2-(2-Bromophenyl)-1,3-dioxane, 75 MHz, $CDCl_3$



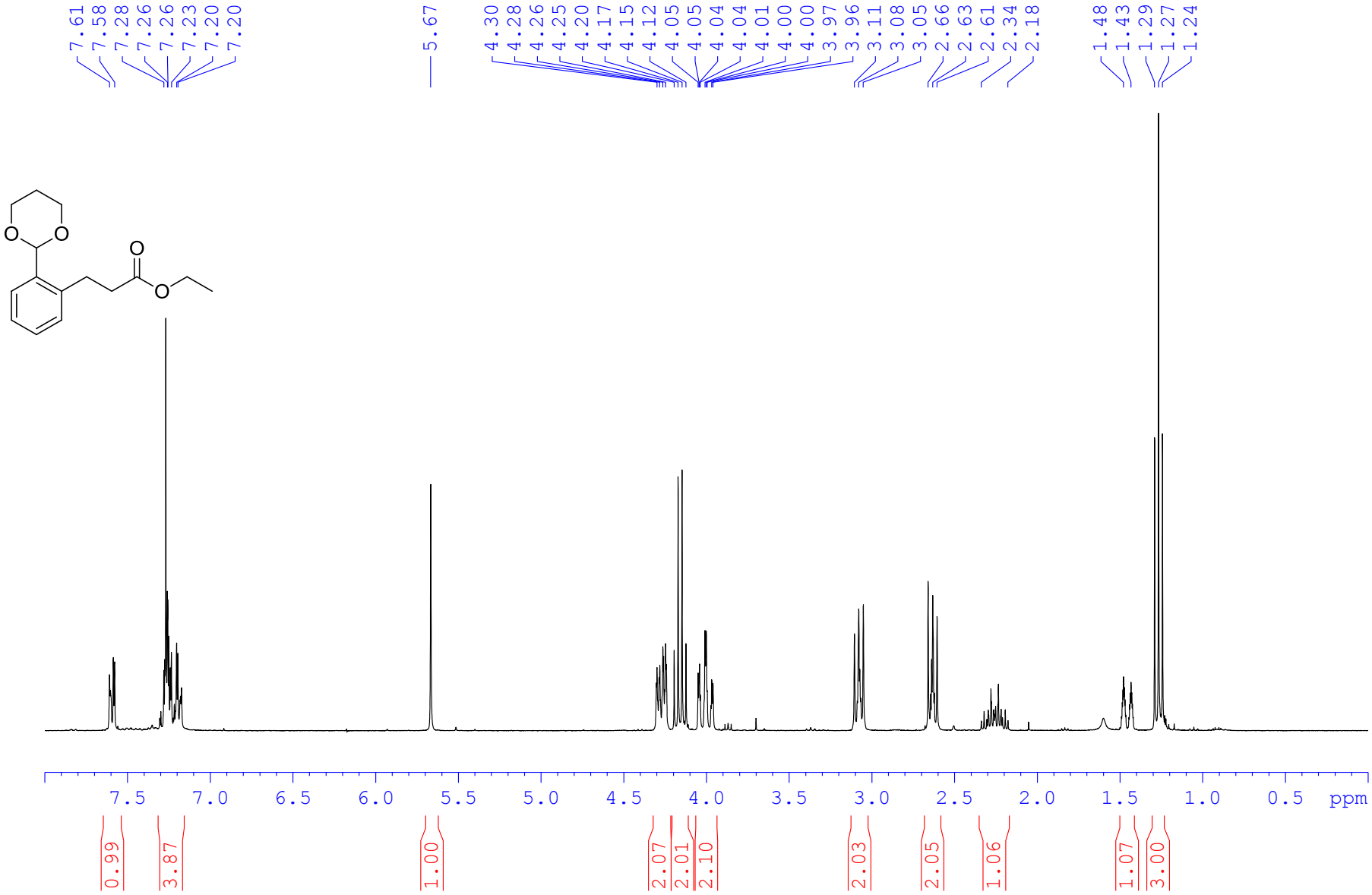
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate, 300 MHz, $CDCl_3$



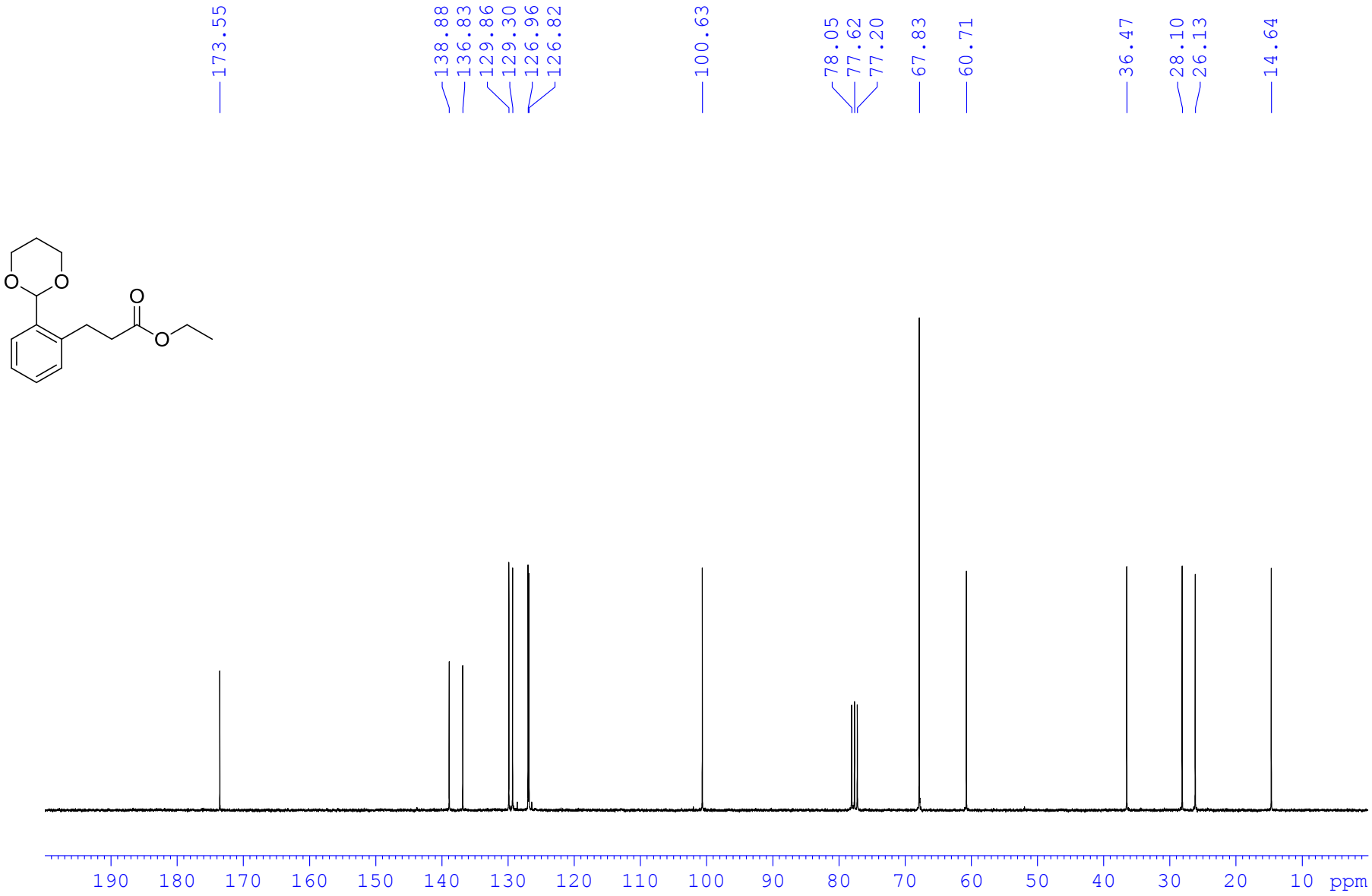
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate, 75 MHz, $CDCl_3$



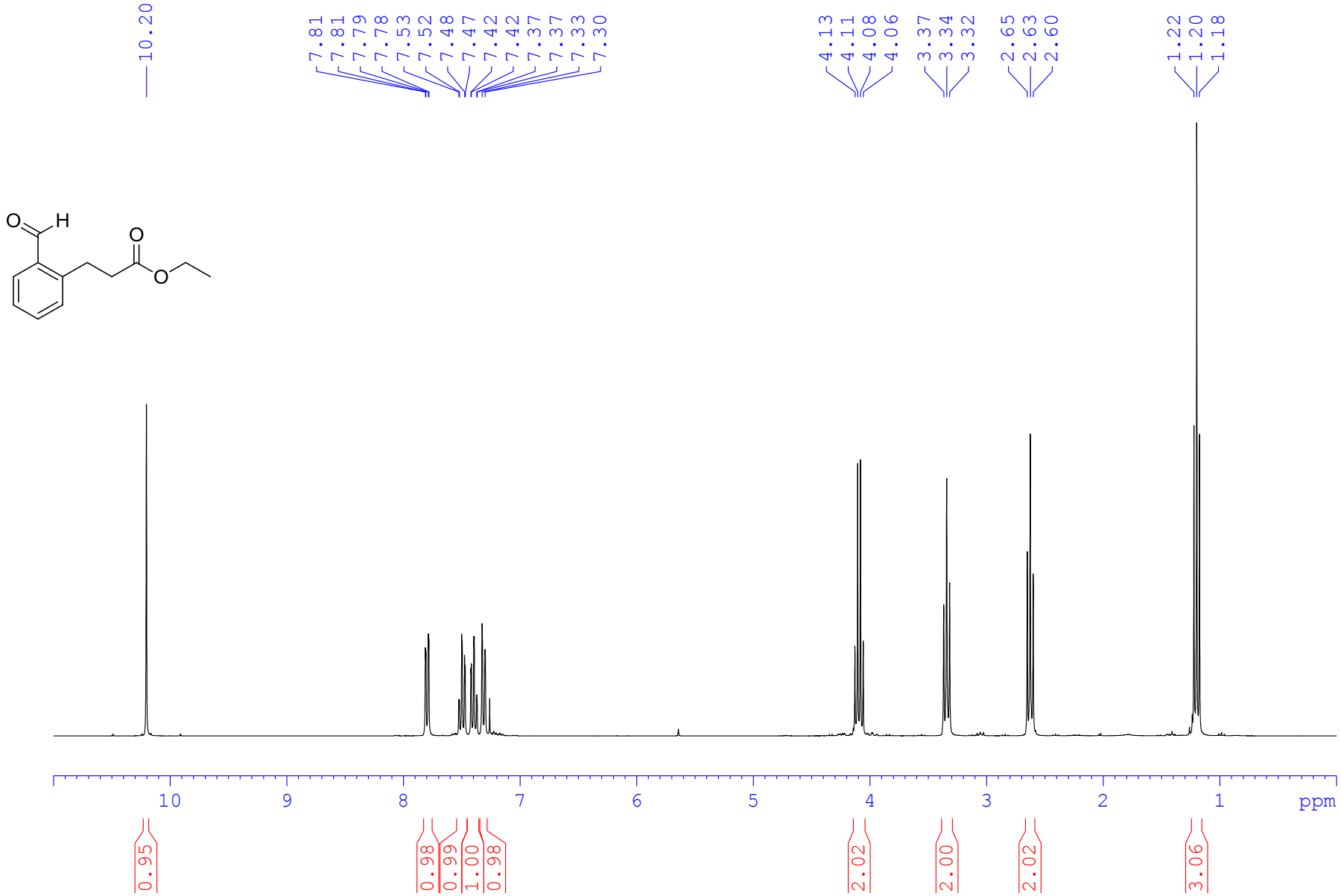
Ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoate, 300 MHz, $CDCl_3$



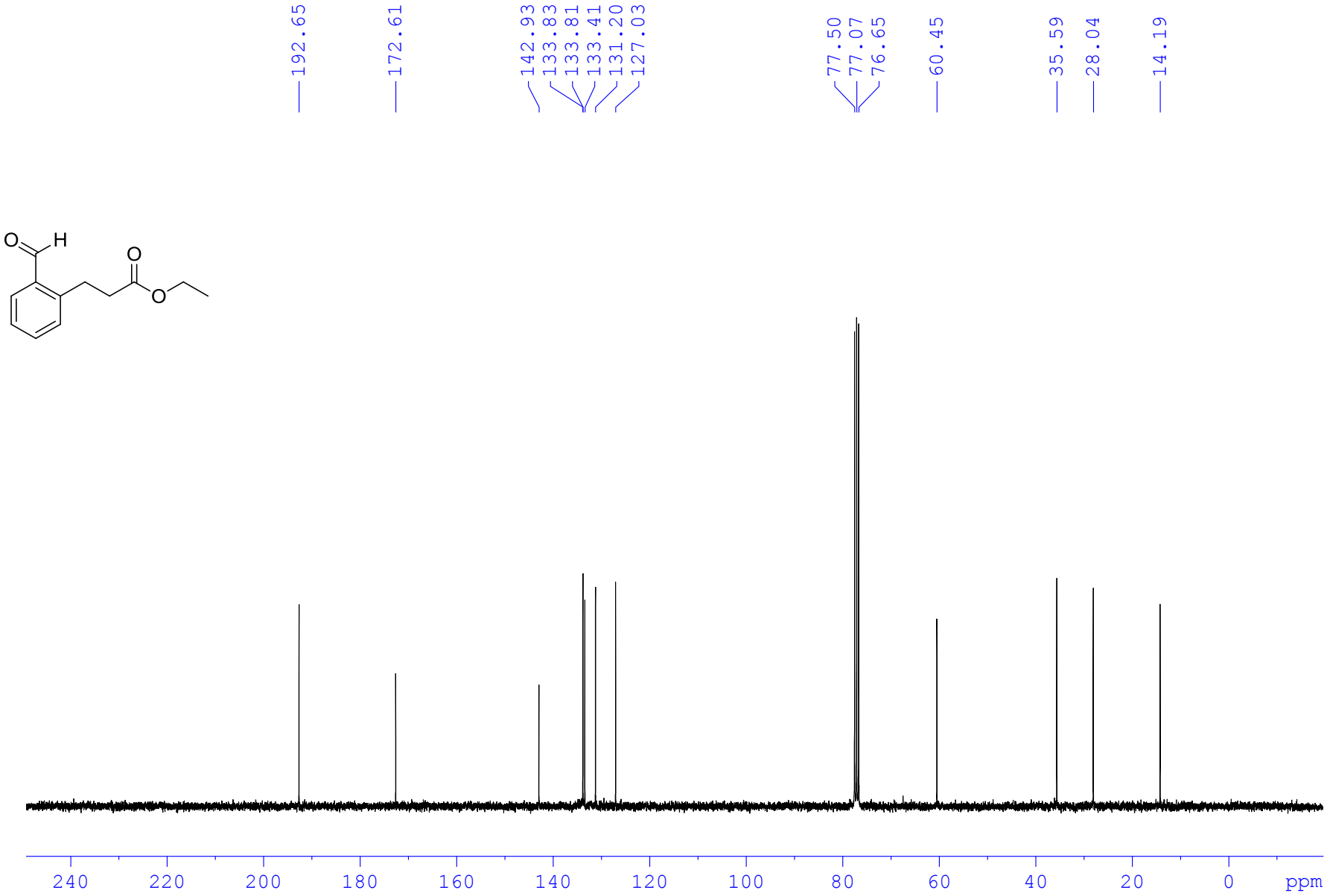
Ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoate, 75 MHz, $CDCl_3$



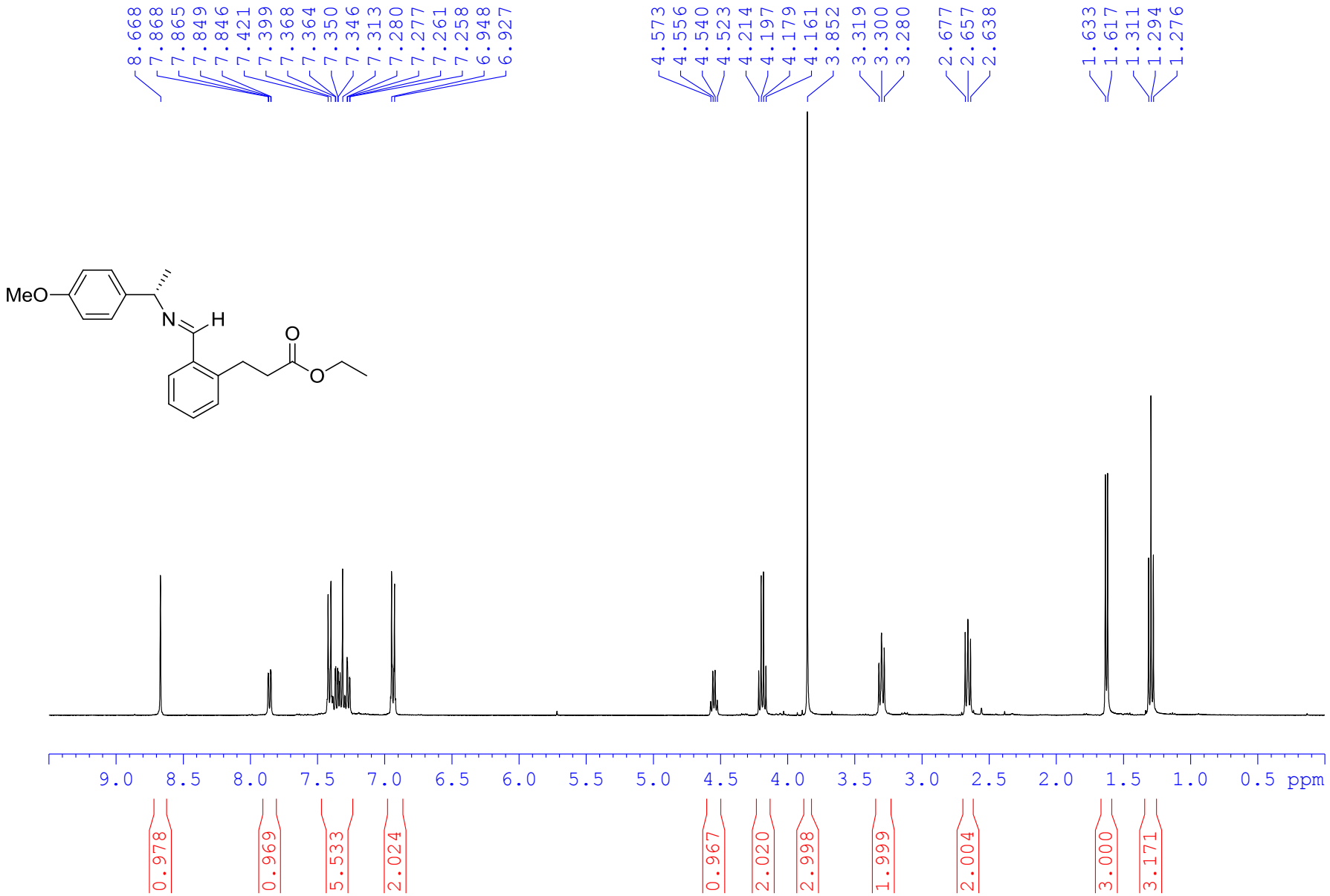
Ethyl 3-(2-formylphenyl)propanoate, 300 MHz, $CDCl_3$



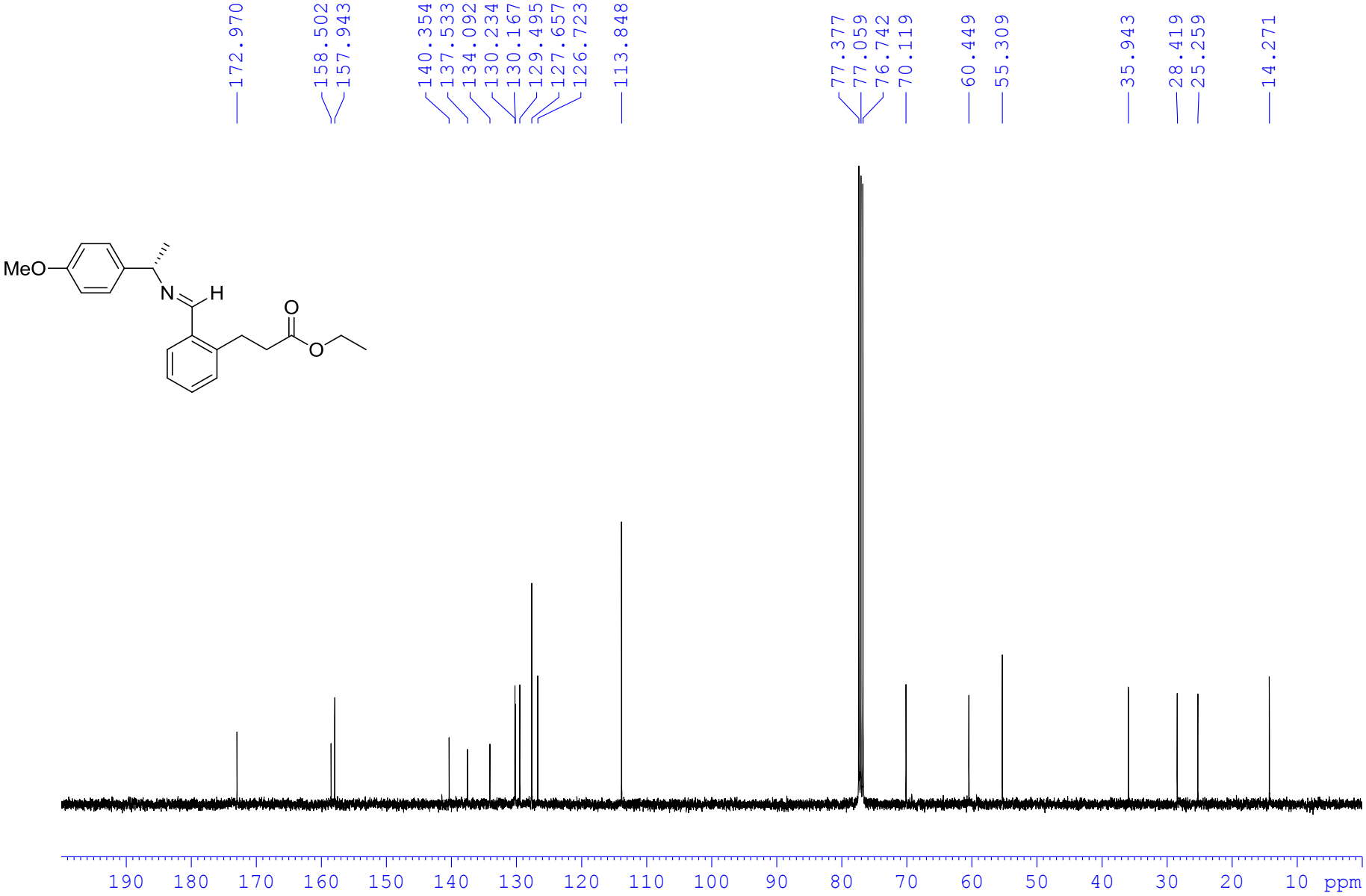
Ethyl 3-(2-formylphenyl)propanoate, 75 MHz, $CDCl_3$



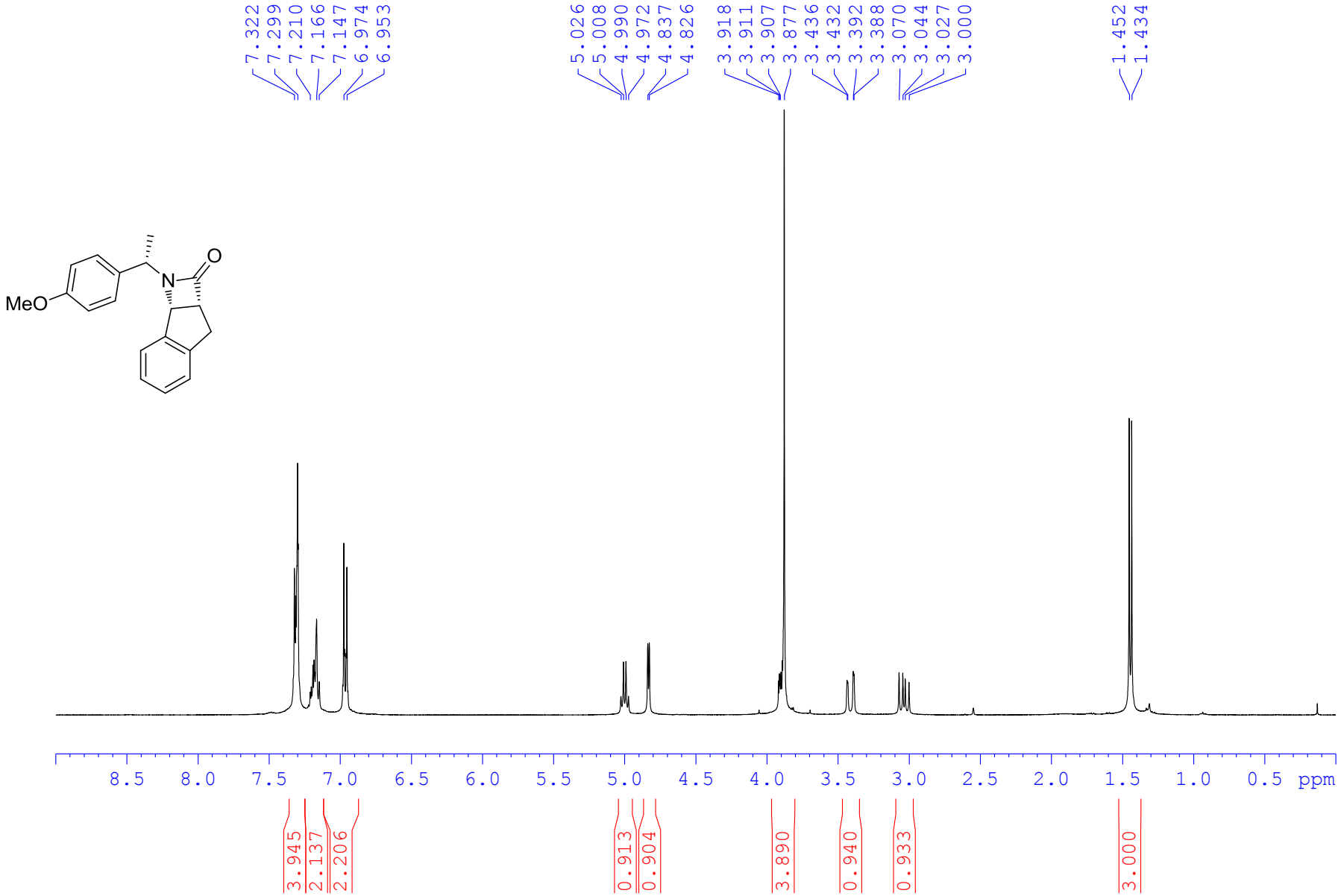
(*S*,*E*)-Ethyl 3-(2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenyl)propanoate **(1a)**, 400 MHz, $CDCl_3$



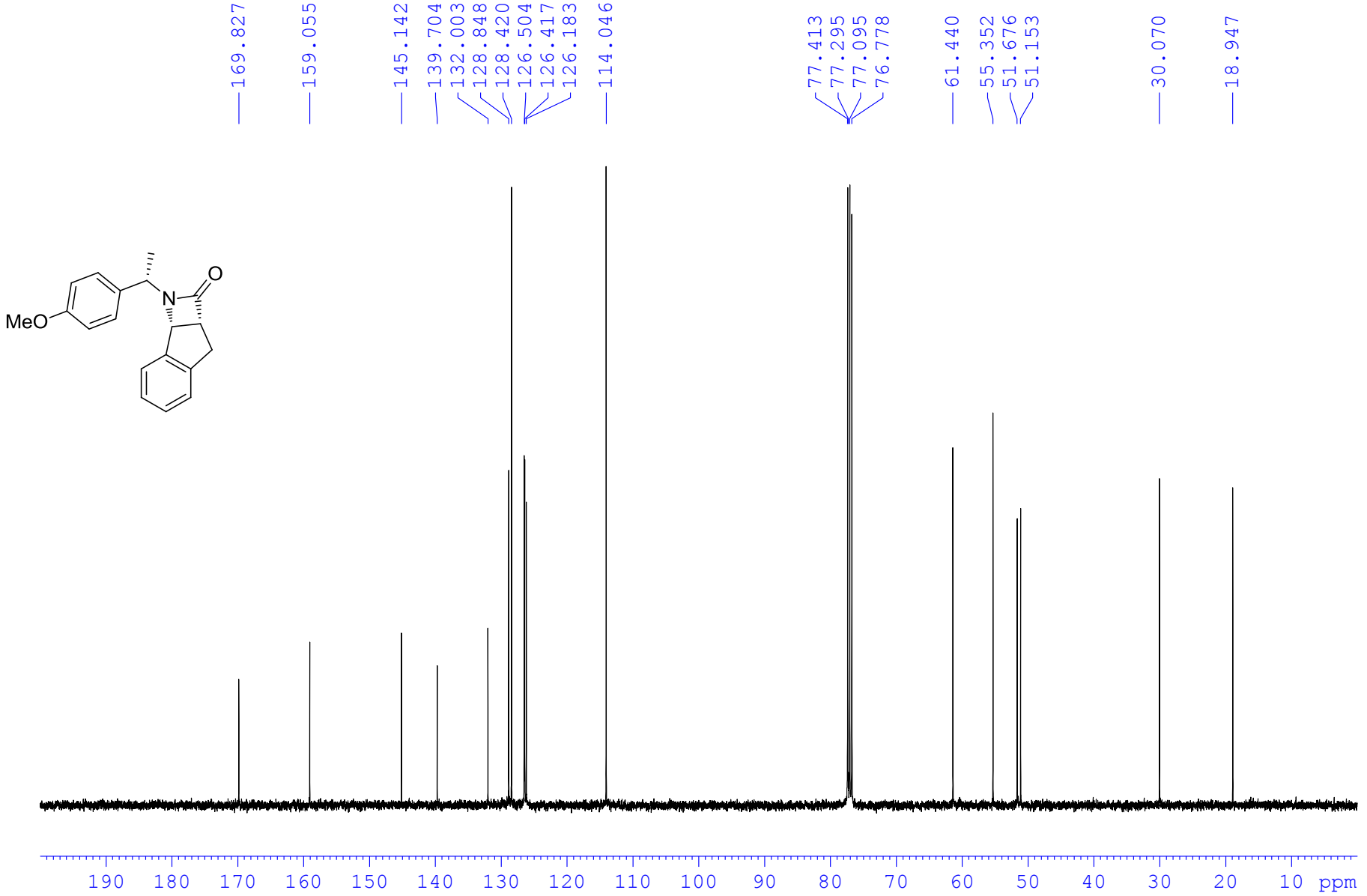
(*S*,*E*)-Ethyl 3-(2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenyl)propanoate **(1a)**, 100 MHz, $CDCl_3$



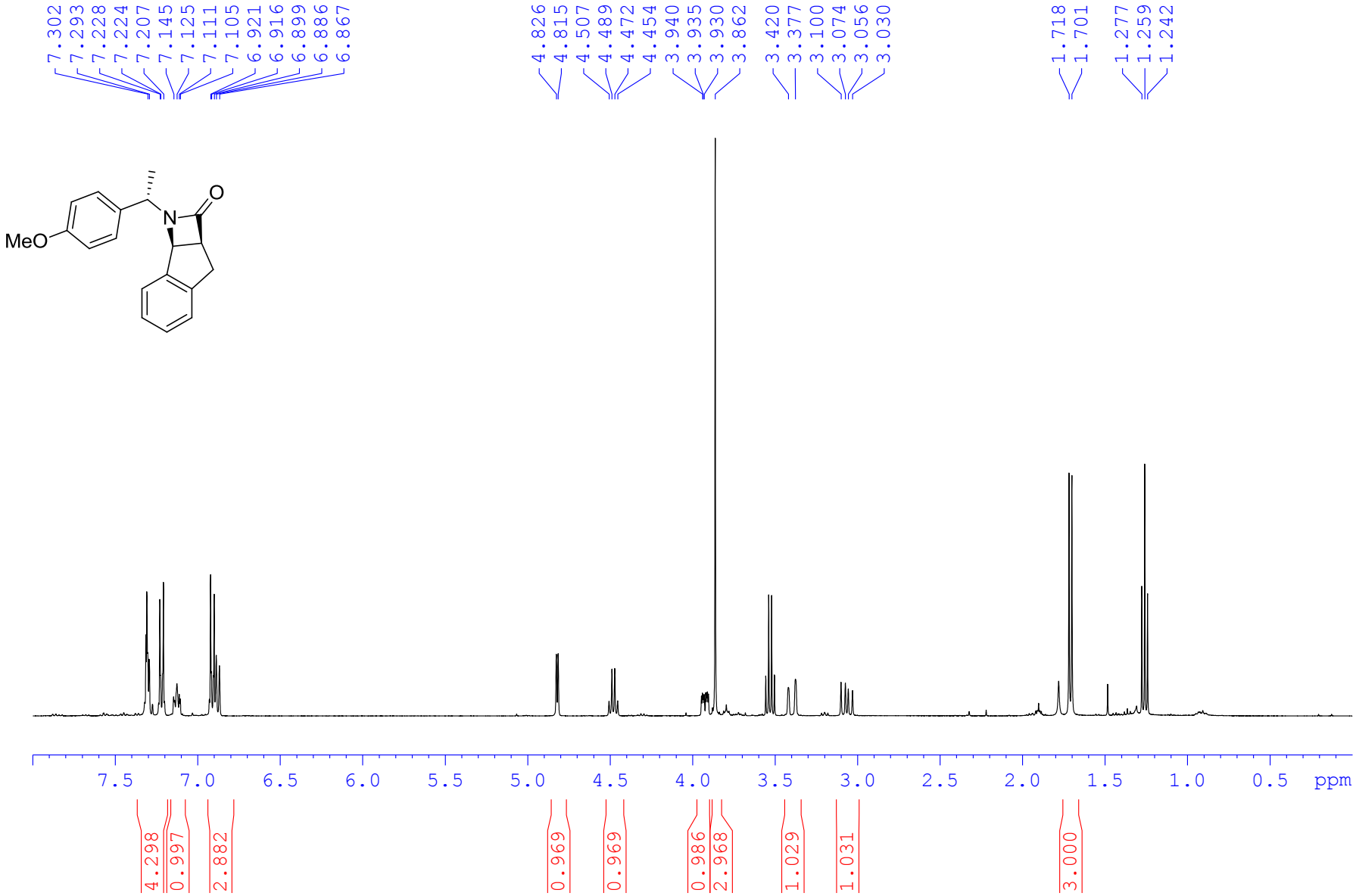
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2a)**, 300 MHz, $CDCl_3$



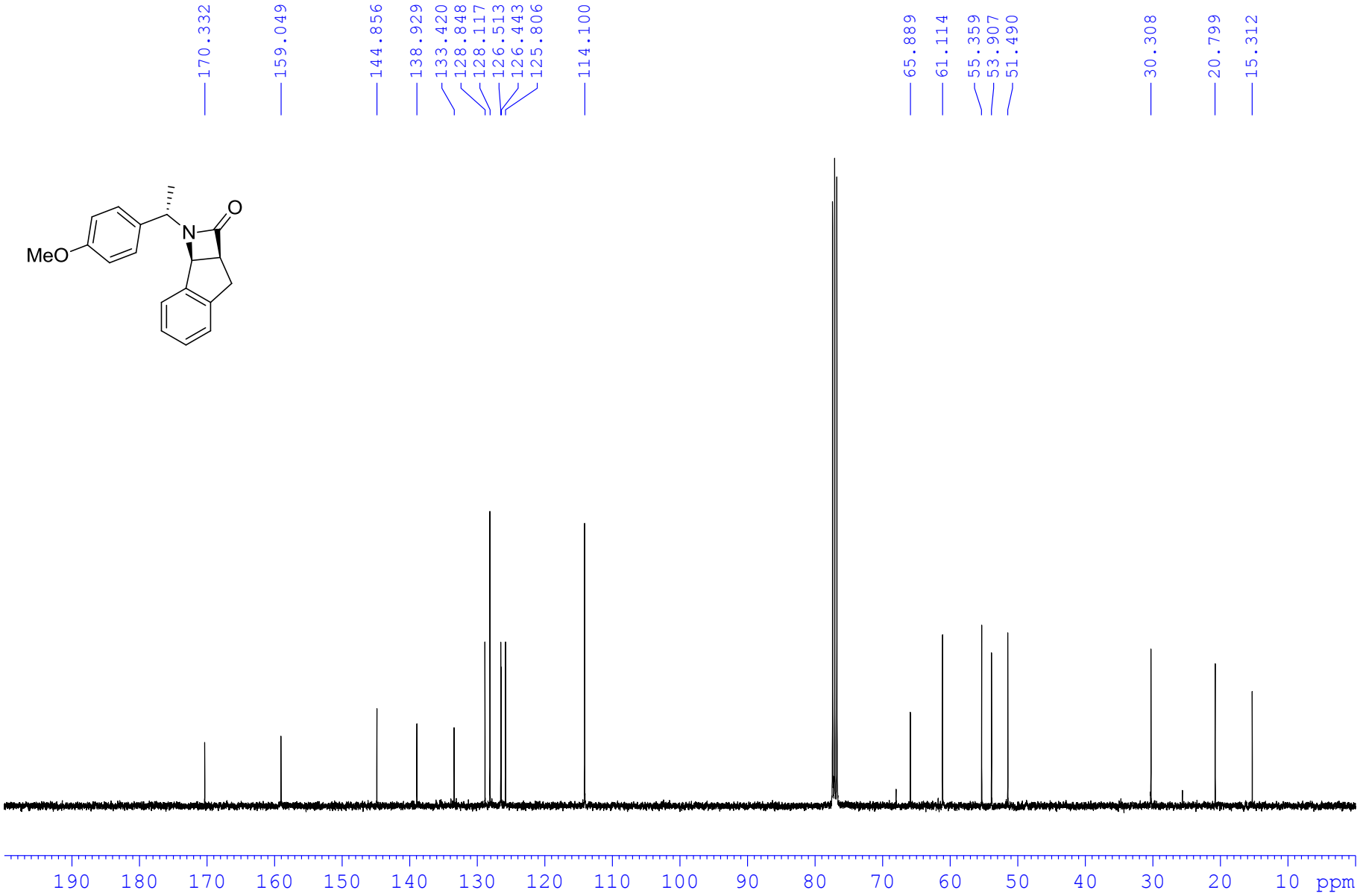
(2a*S*,7b*S*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2a)**, 400 MHz, $CDCl_3$



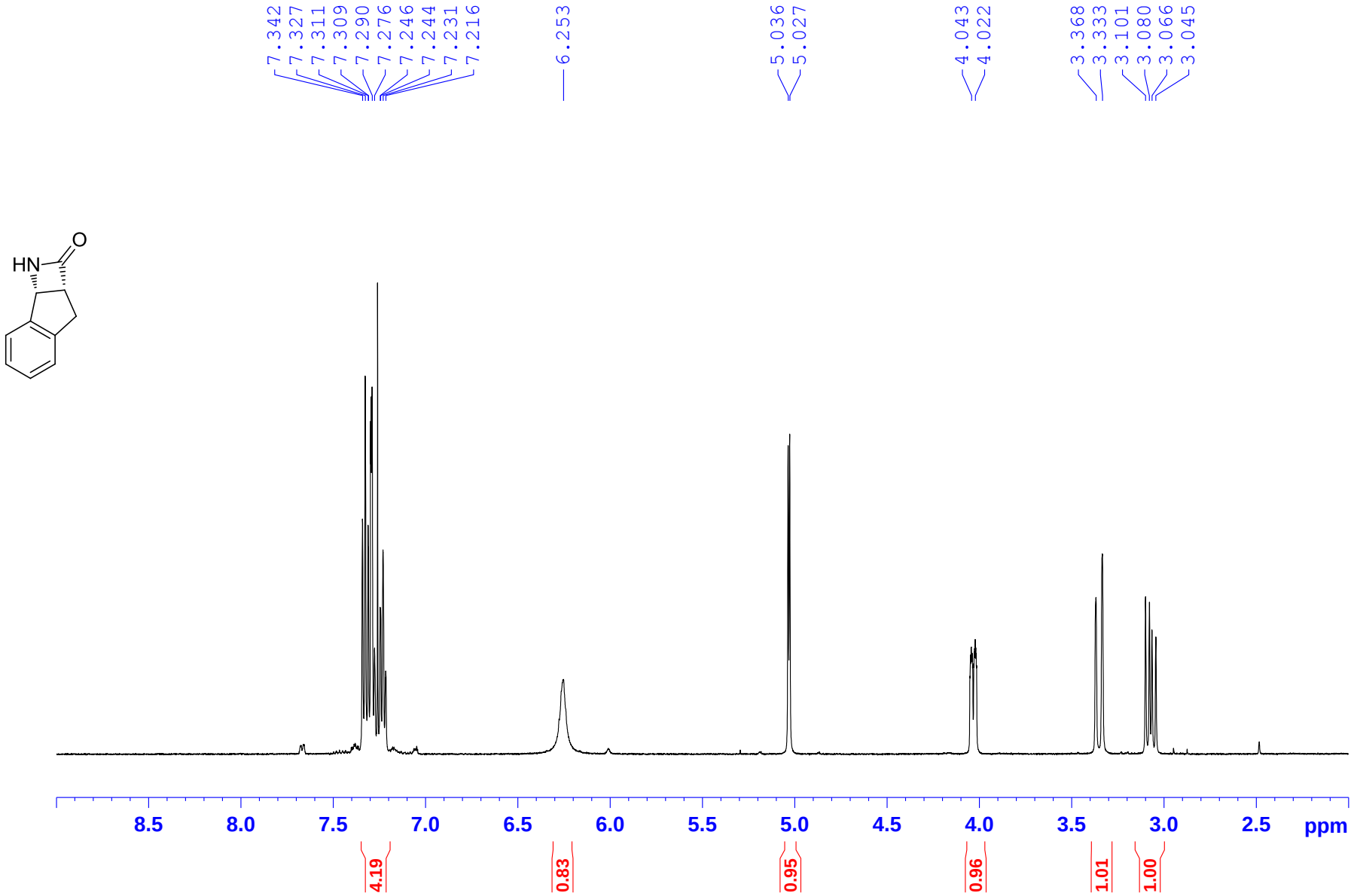
(2a*S*,7b*S*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(3a)**, 400 MHz, $CDCl_3$



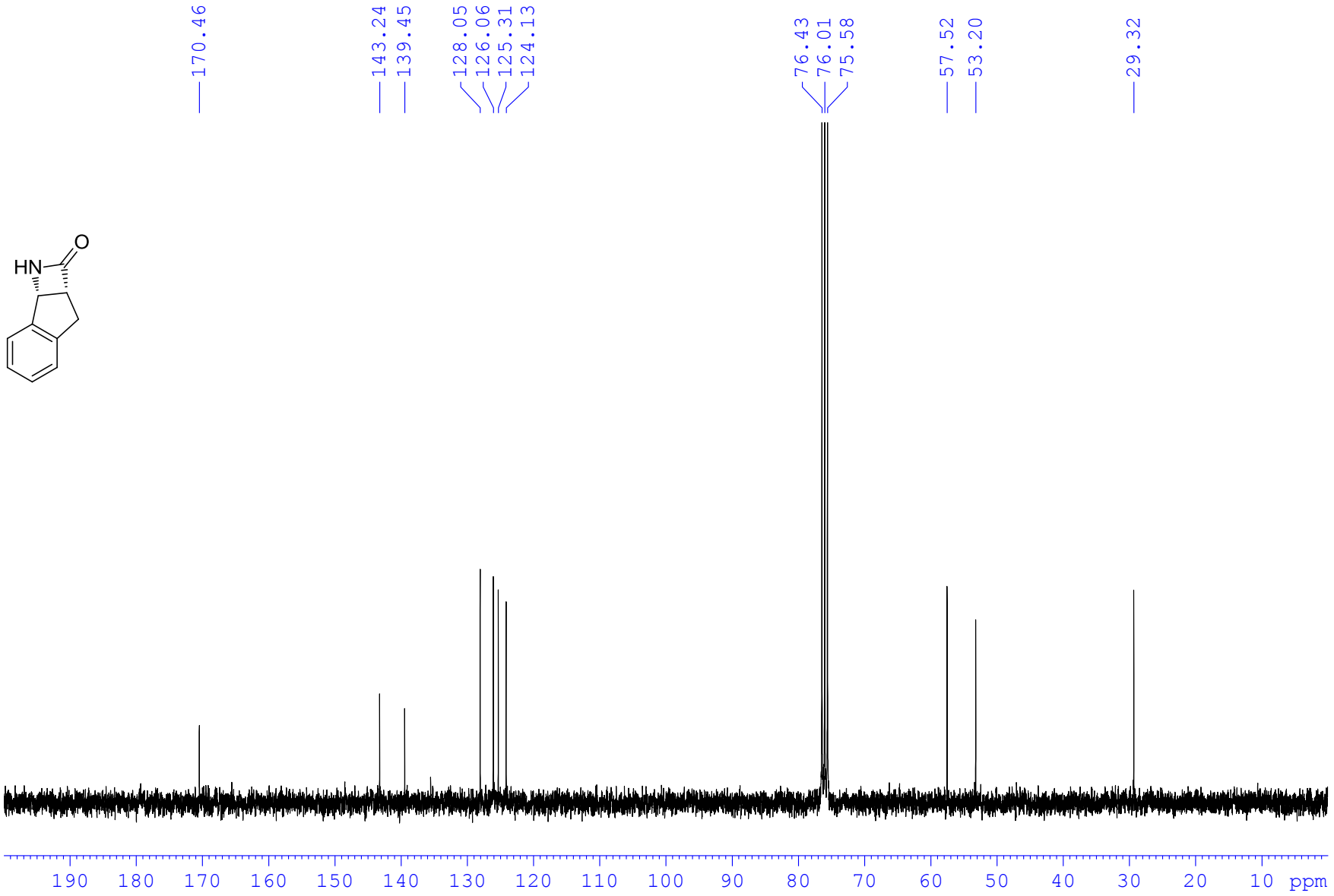
(2a*S*,7b*S*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(3a)**, 100 MHz, $CDCl_3$



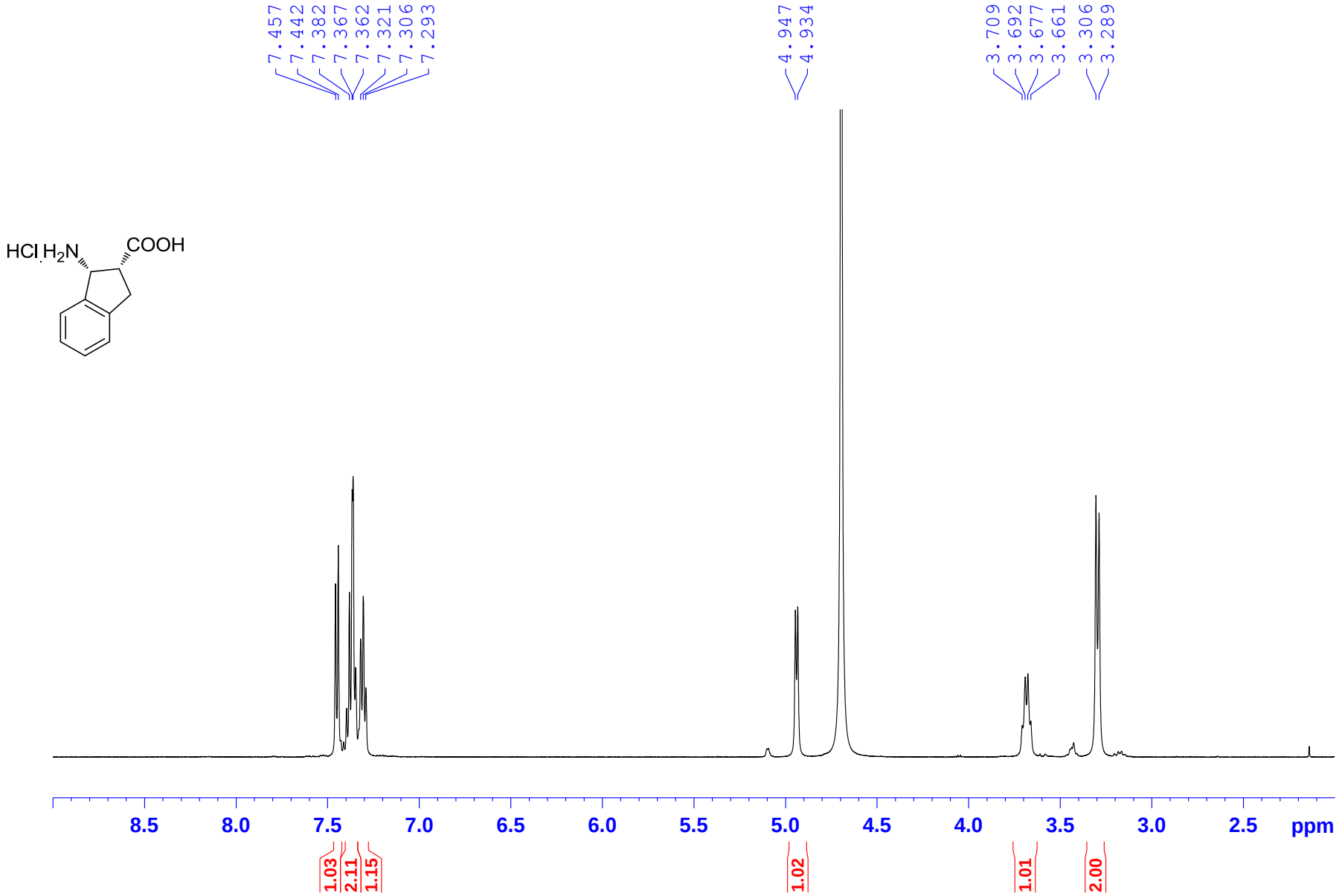
(2a*R*,7b*R*)-2a,3-Dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(5a)**, 500 MHz, $CDCl_3$



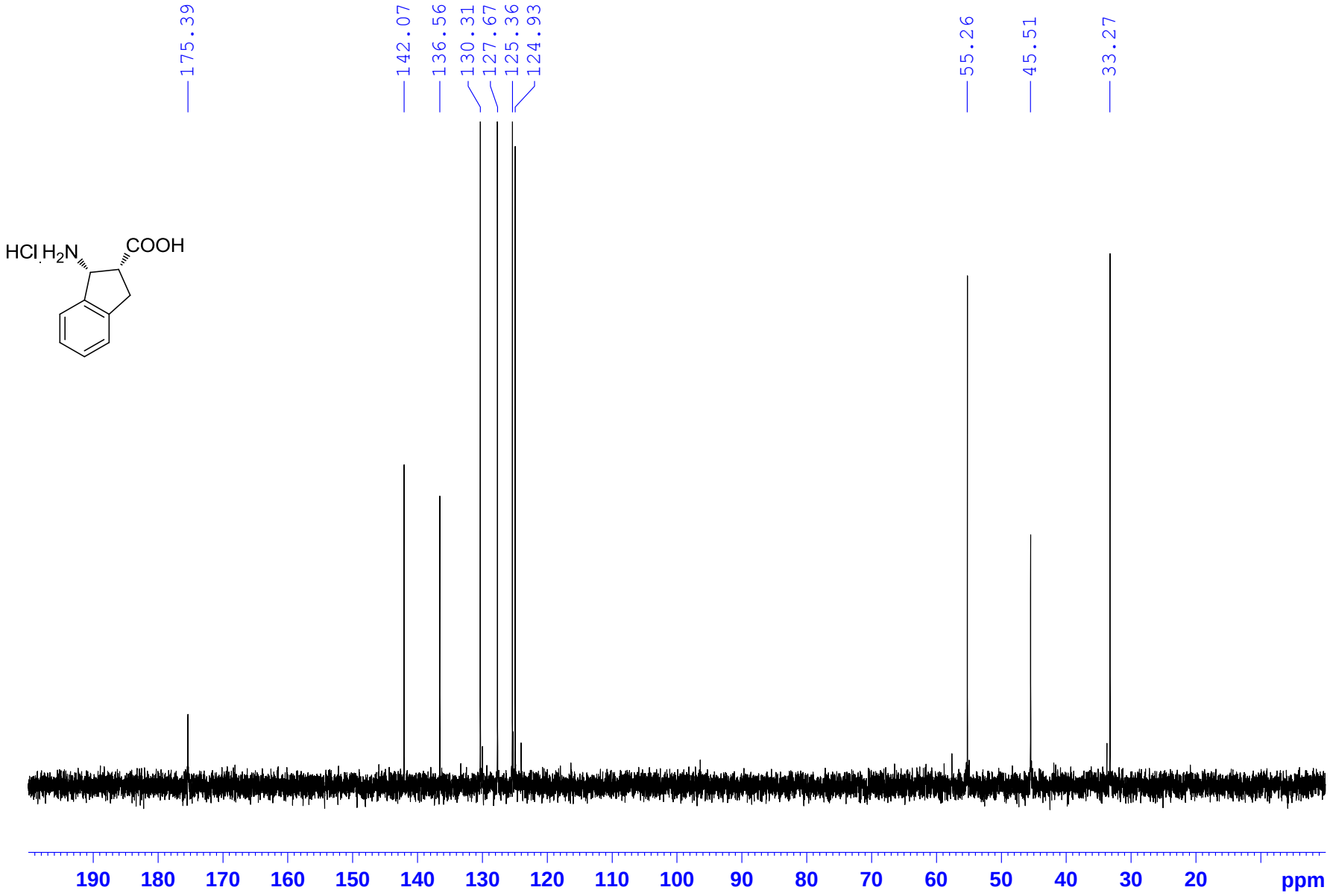
(2a*R*,7b*R*)-2a,3-Dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(5a)**, 75 MHz, $CDCl_3$



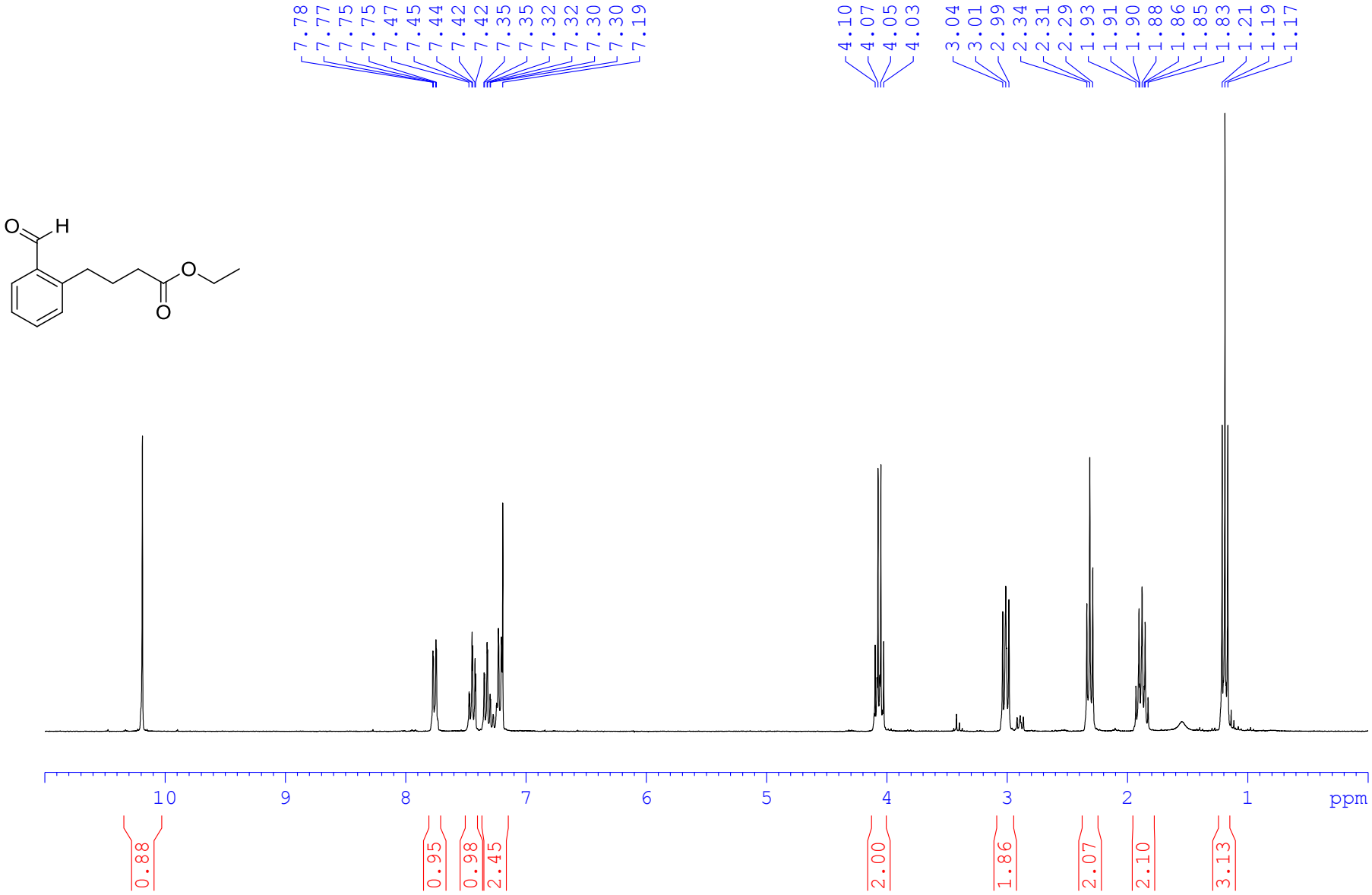
(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-indene-2-carboxylic acid hydrochloride **(6)**, 500 MHz, D_2O



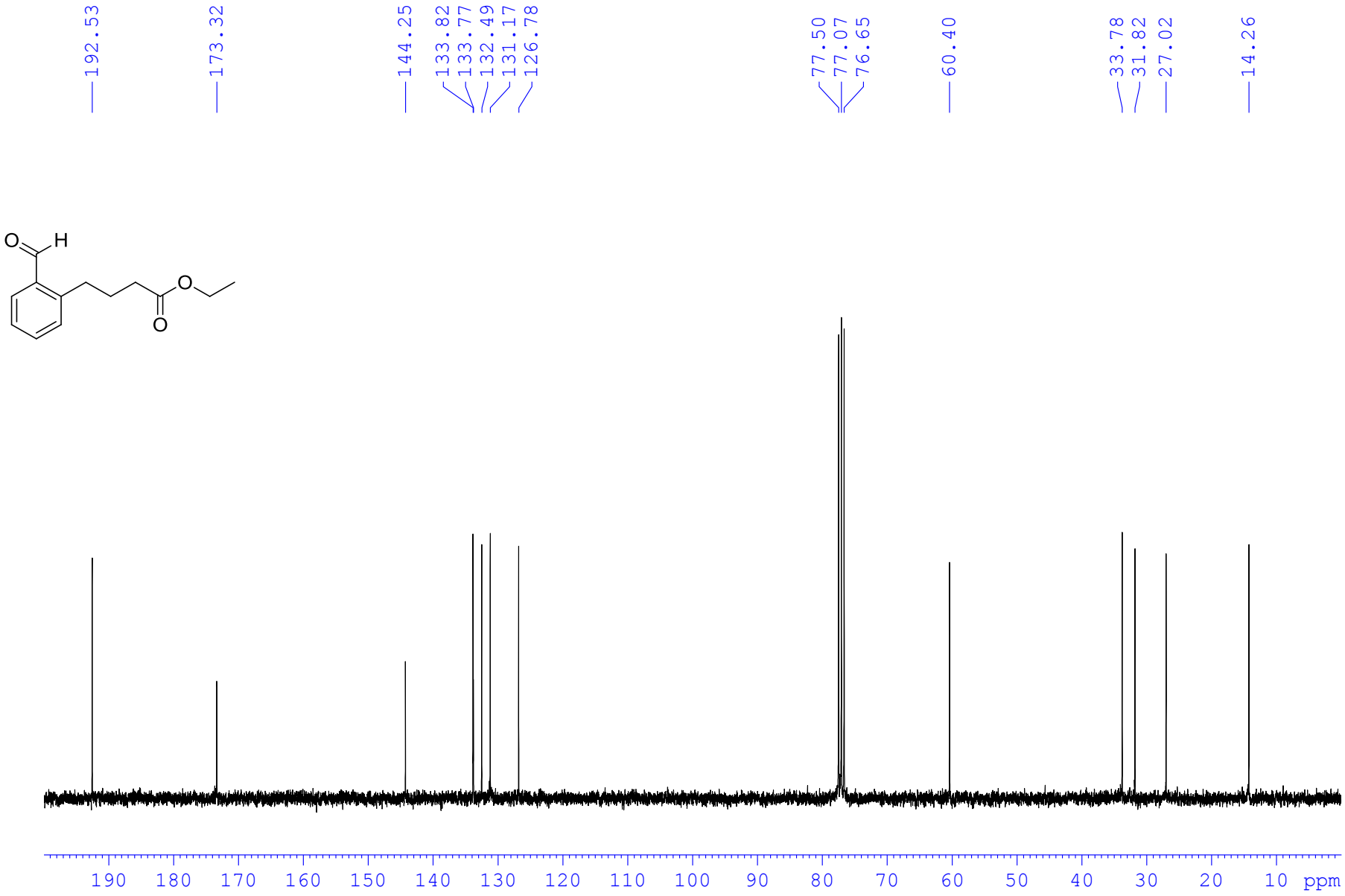
(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-indene-2-carboxylic acid hydrochloride **(6)**, 125 MHz, D_2O



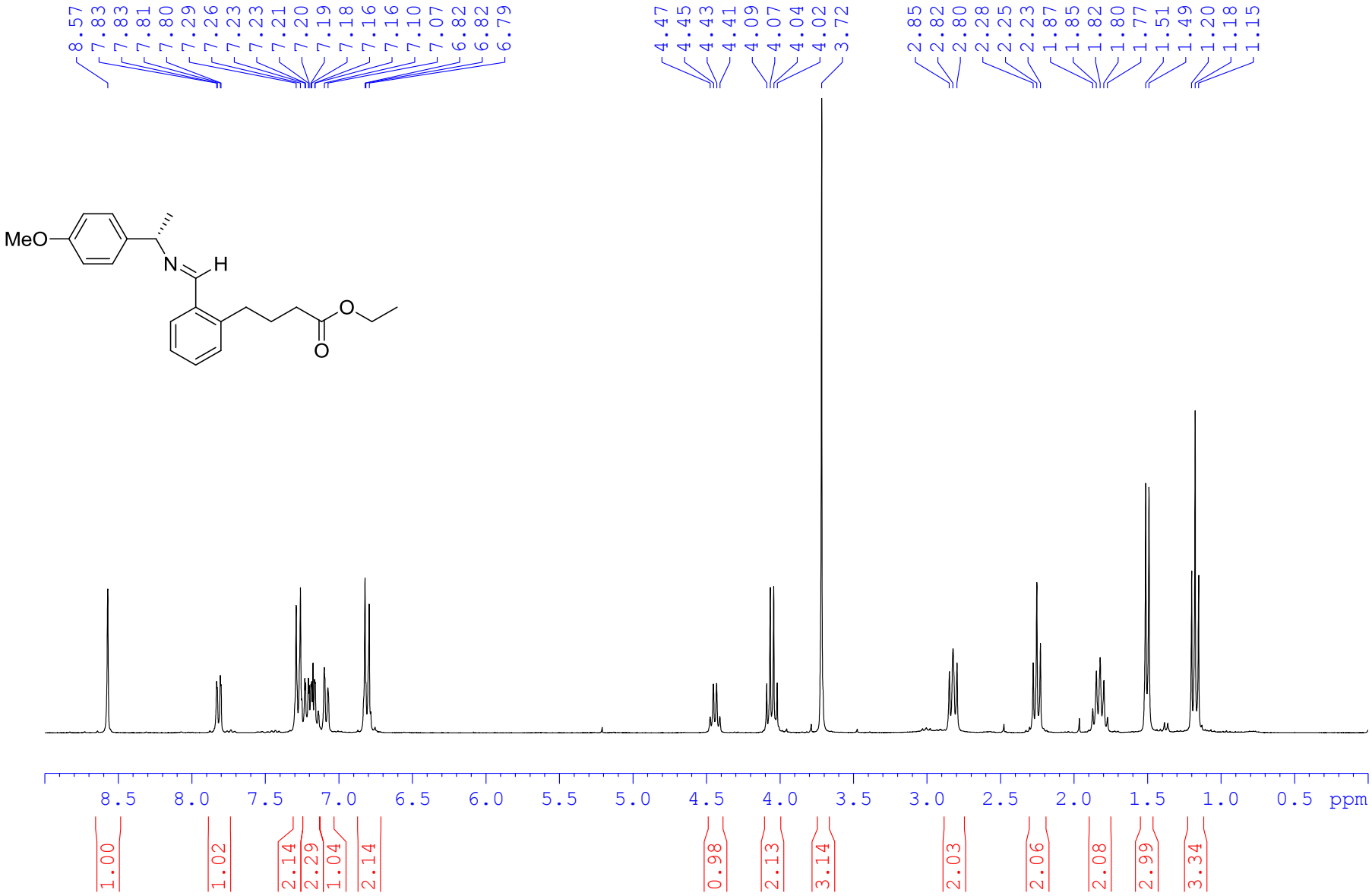
Ethyl 4-(2-formylphenyl)butanoate, 300 MHz, $CDCl_3$



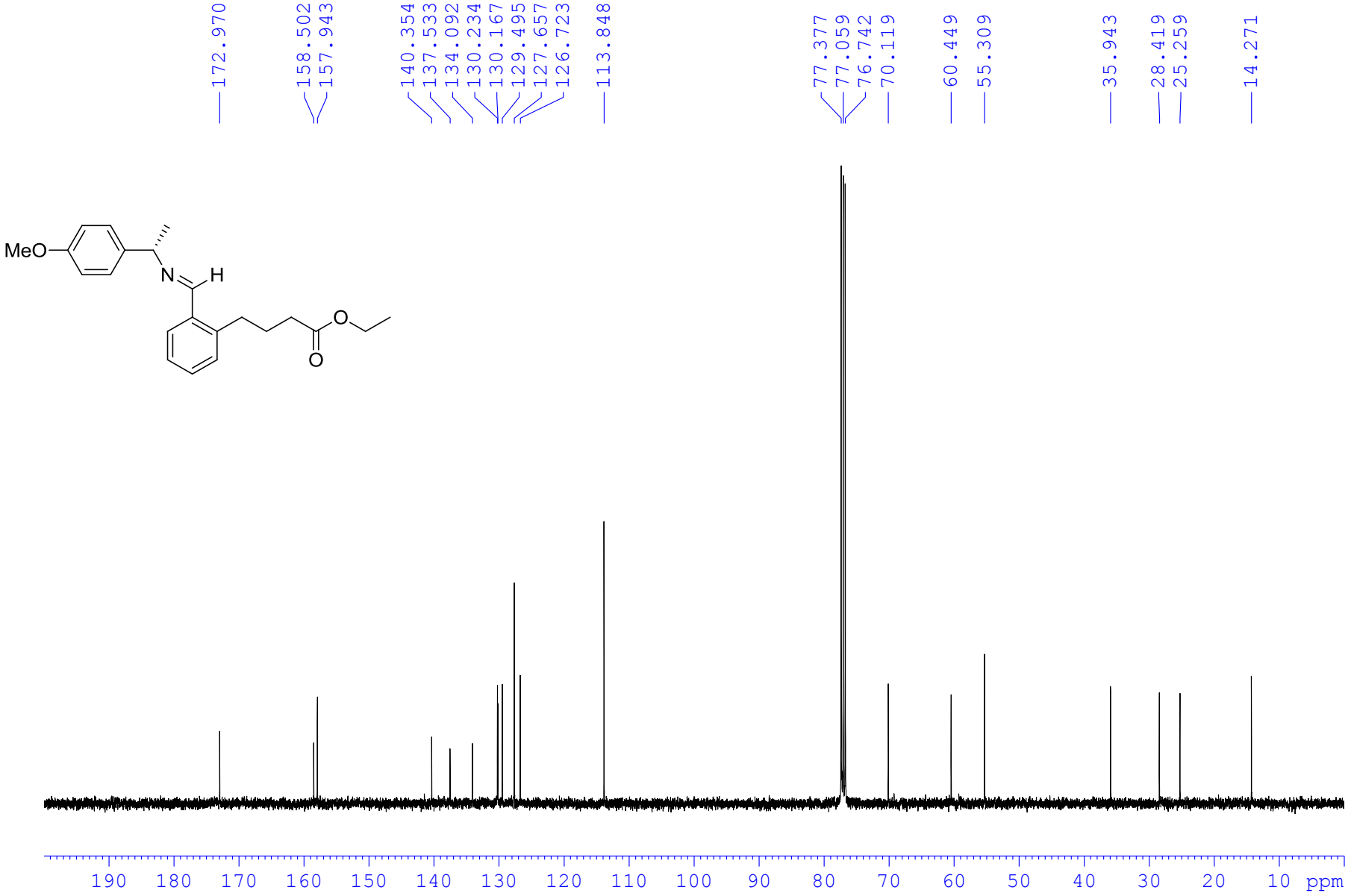
Ethyl 4-(2-formylphenyl)butanoate, 75 MHz, $CDCl_3$



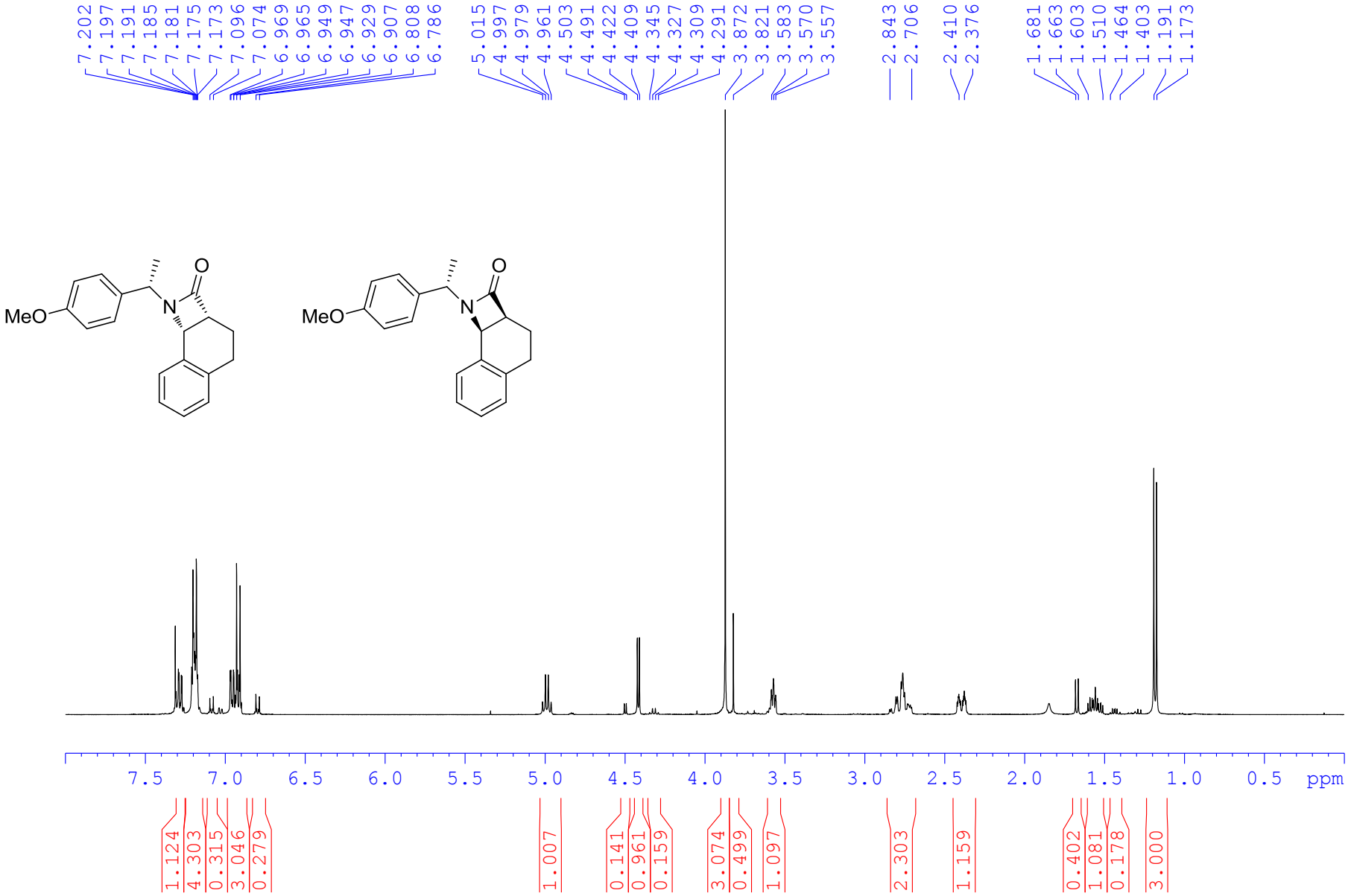
(*S*,*E*)-Ethyl 4-(2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenyl)butanoate **(1g)**, 300 MHz, $CDCl_3$



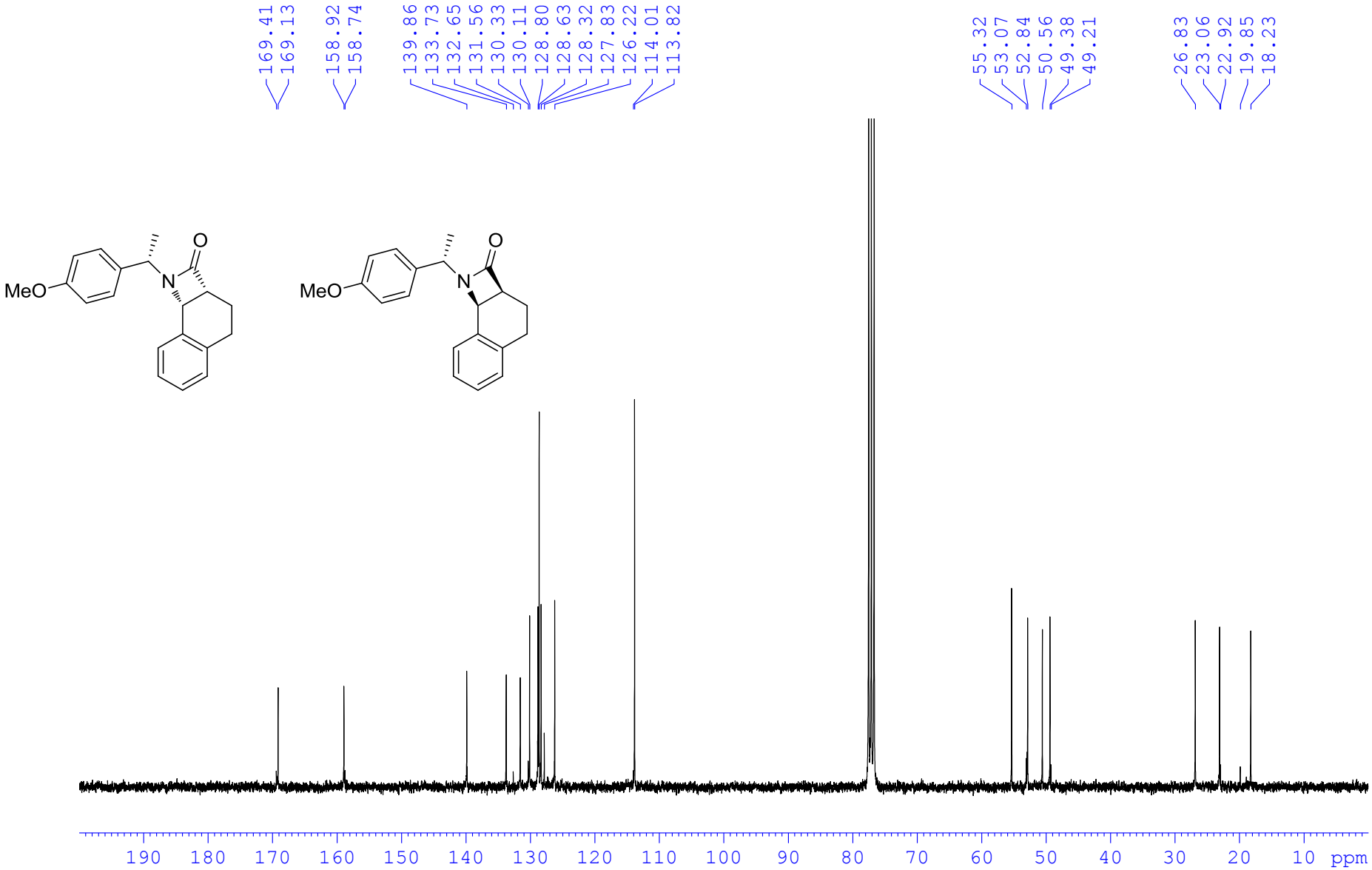
(*S*,*E*)-Ethyl 4-(2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenyl)butanoate **(1g)**, 75 MHz, $CDCl_3$



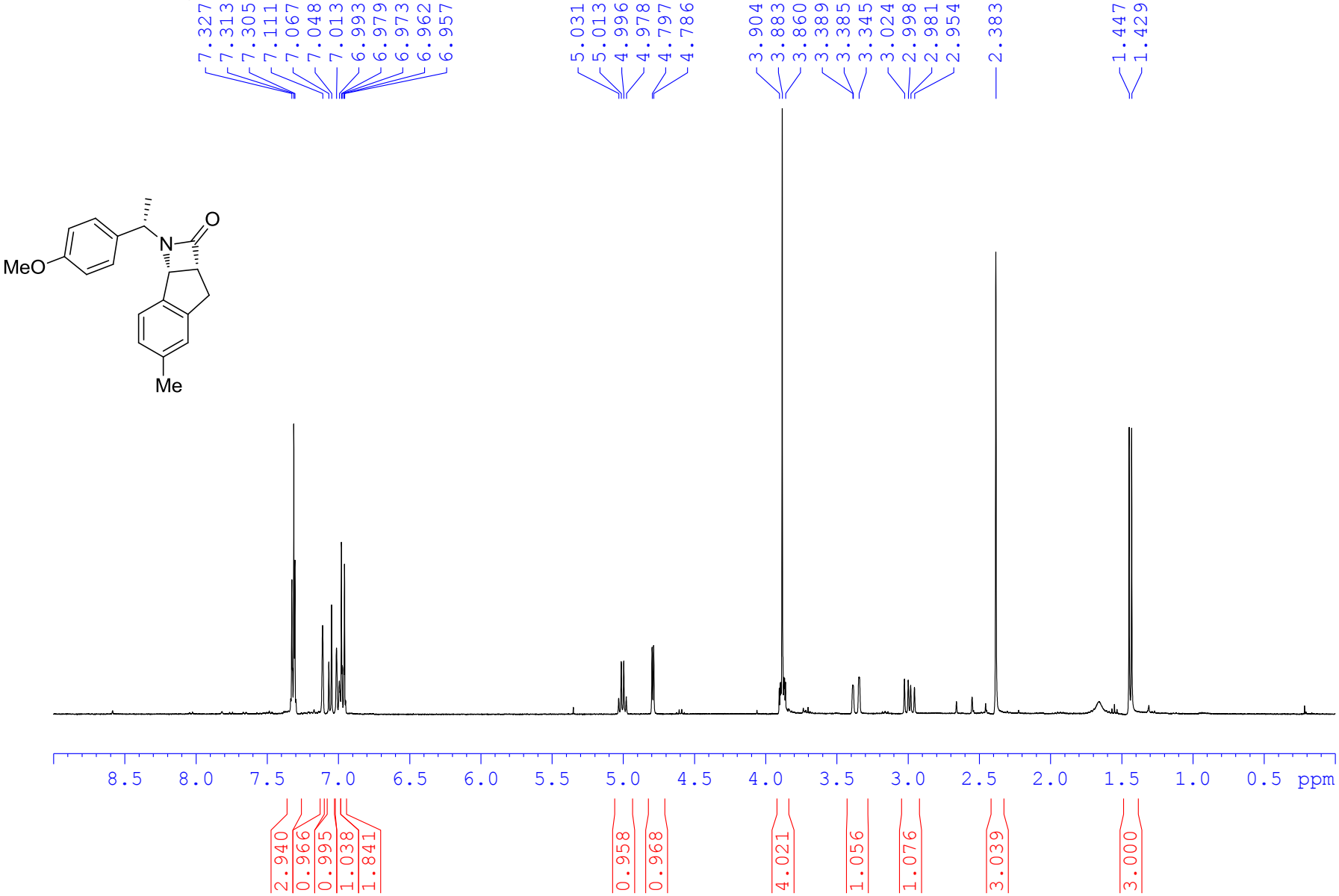
(2a*S*,8b*S*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-1,3,4,8b-tetrahydronaphtho[1,2-*b*]azet-2(2a*H*)-one **(2g)**, 400MHz, $CDCl_3$



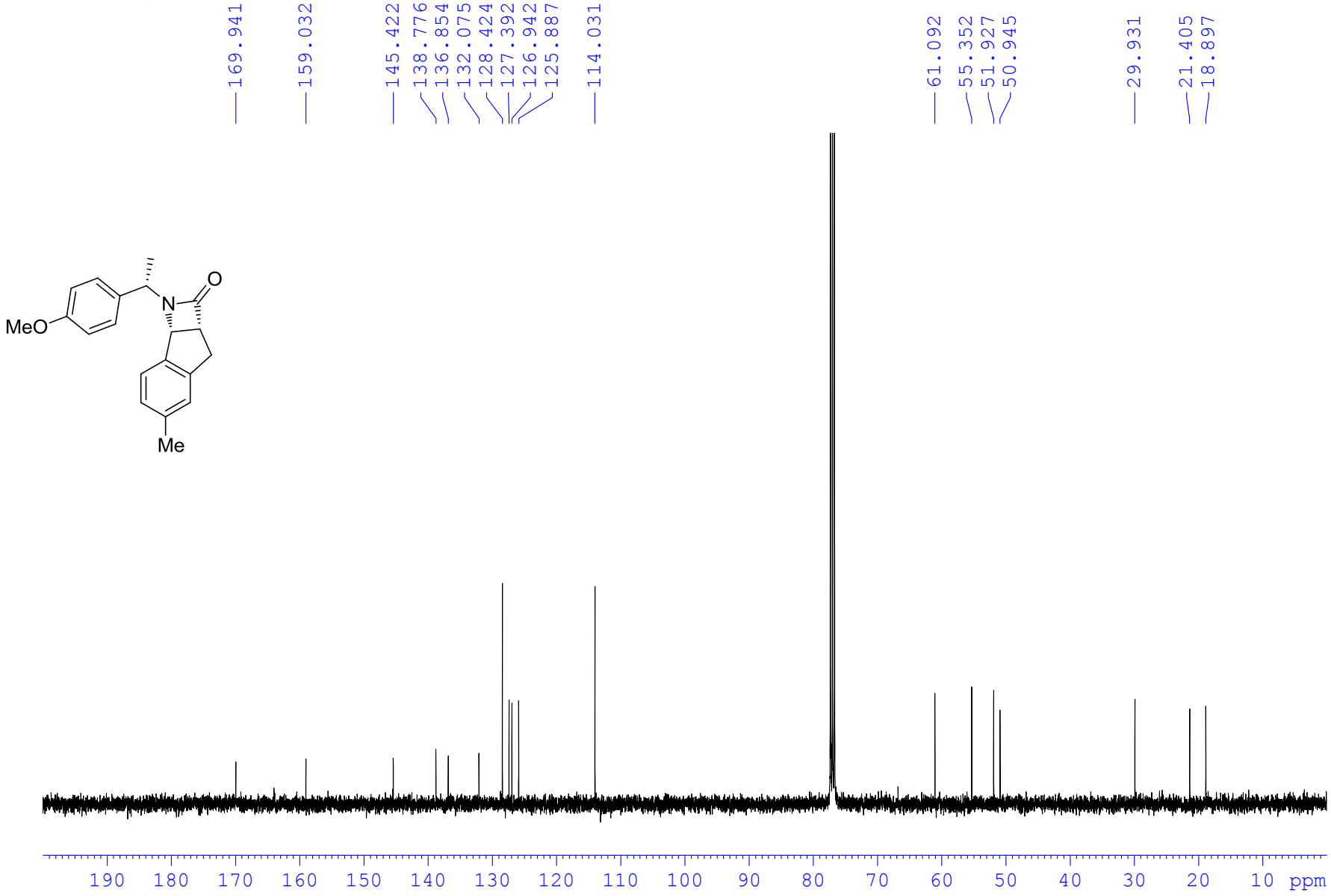
(2a*S*,8b*S*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-1,3,4,8b-tetrahydronaphtho[1,2-*b*]azet-2(2a*H*)-one **(2g)**, 75 MHz, $CDCl_3$



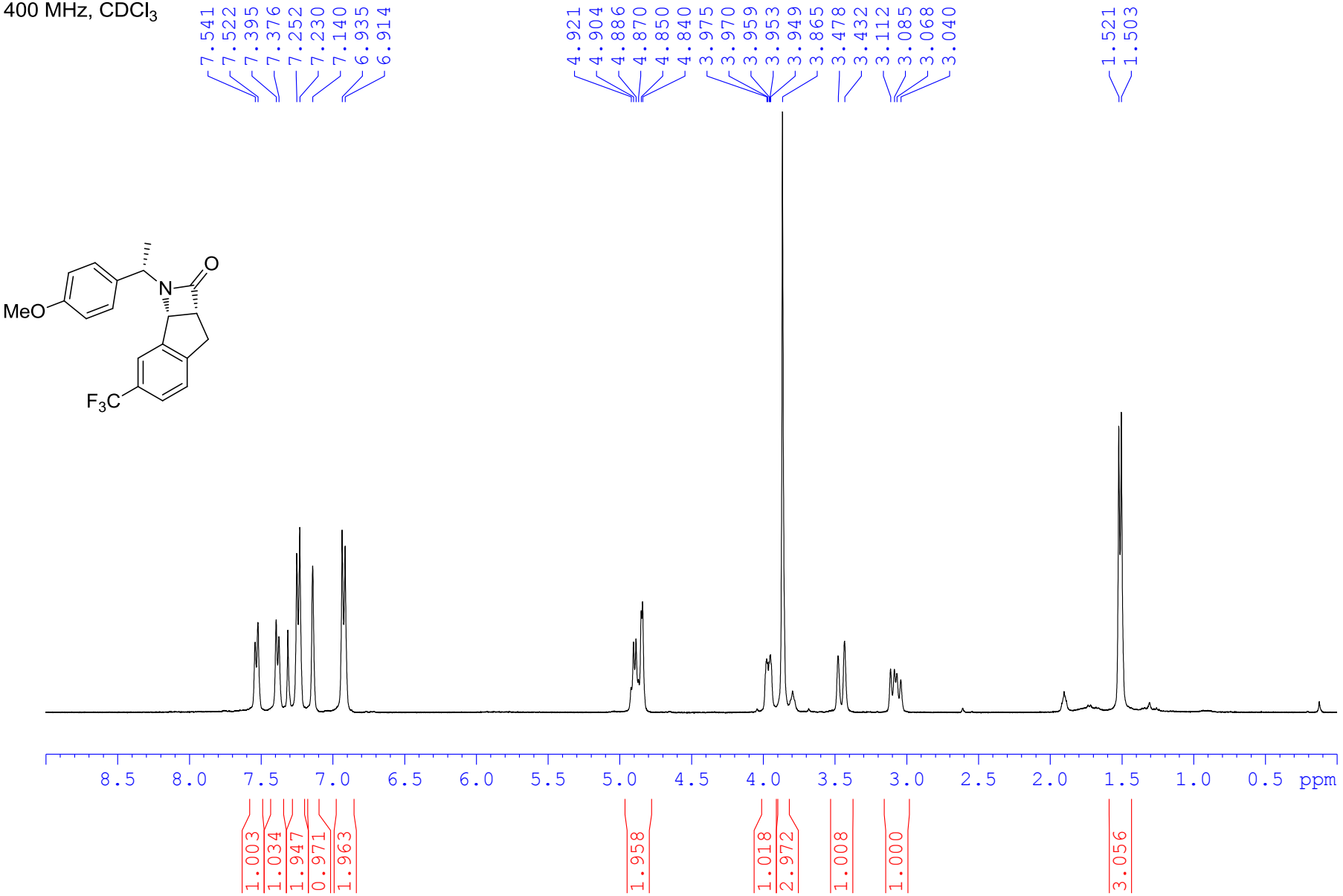
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-5-methyl-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2b)**,
400 MHz, $CDCl_3$



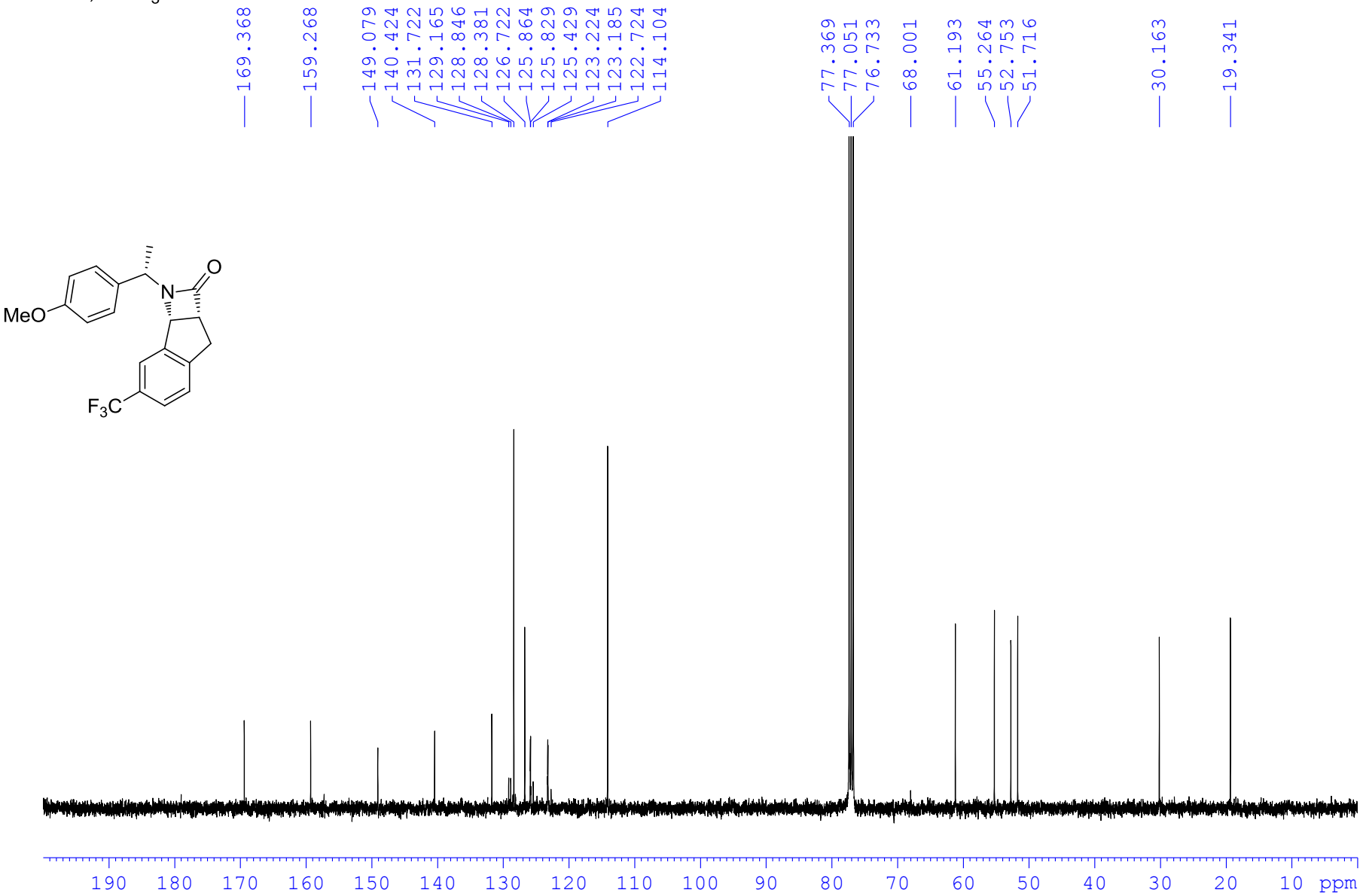
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-5-methyl-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2b)**,
100 MHz, $CDCl_3$



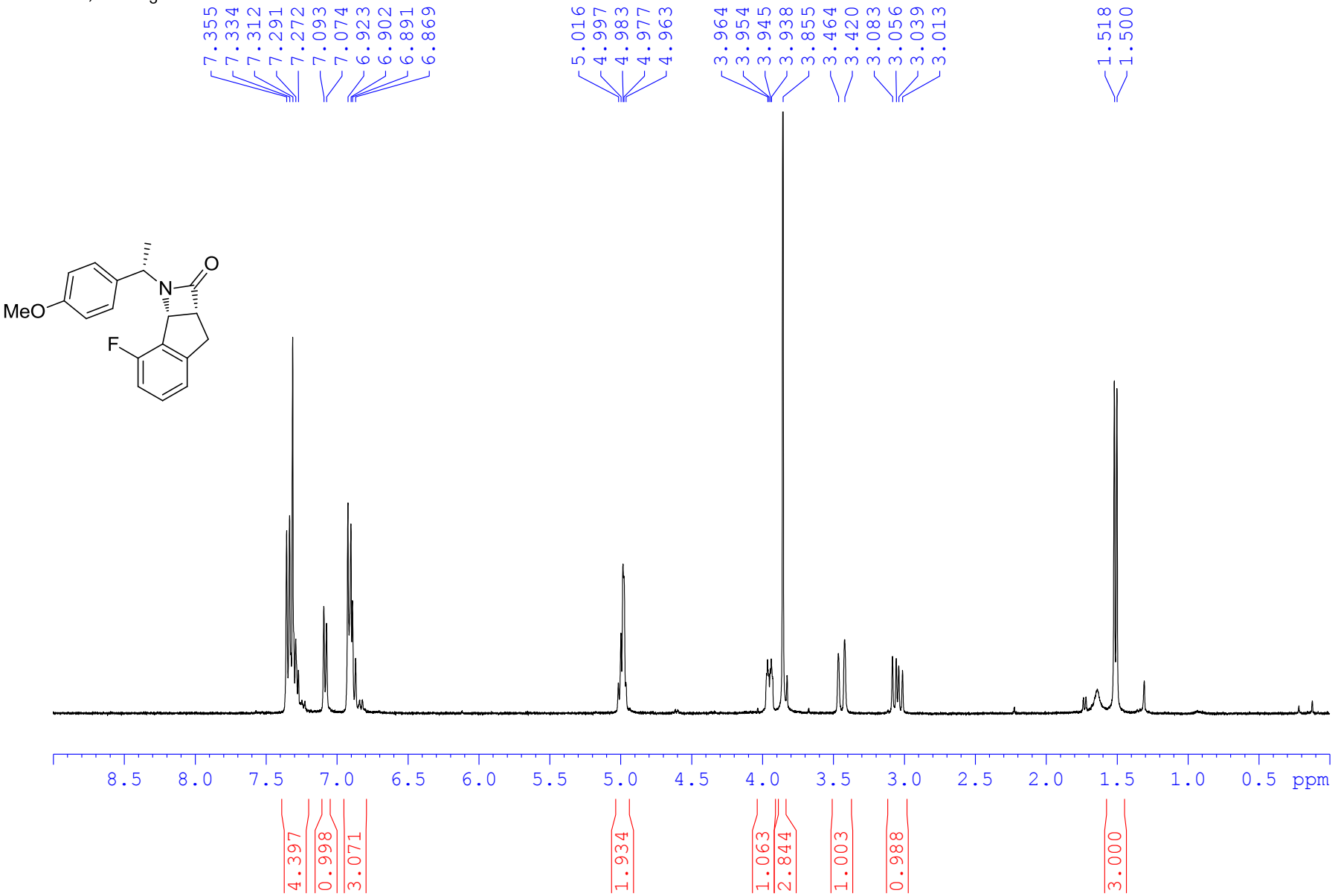
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-(trifluoromethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2c)**,
400 MHz, $CDCl_3$



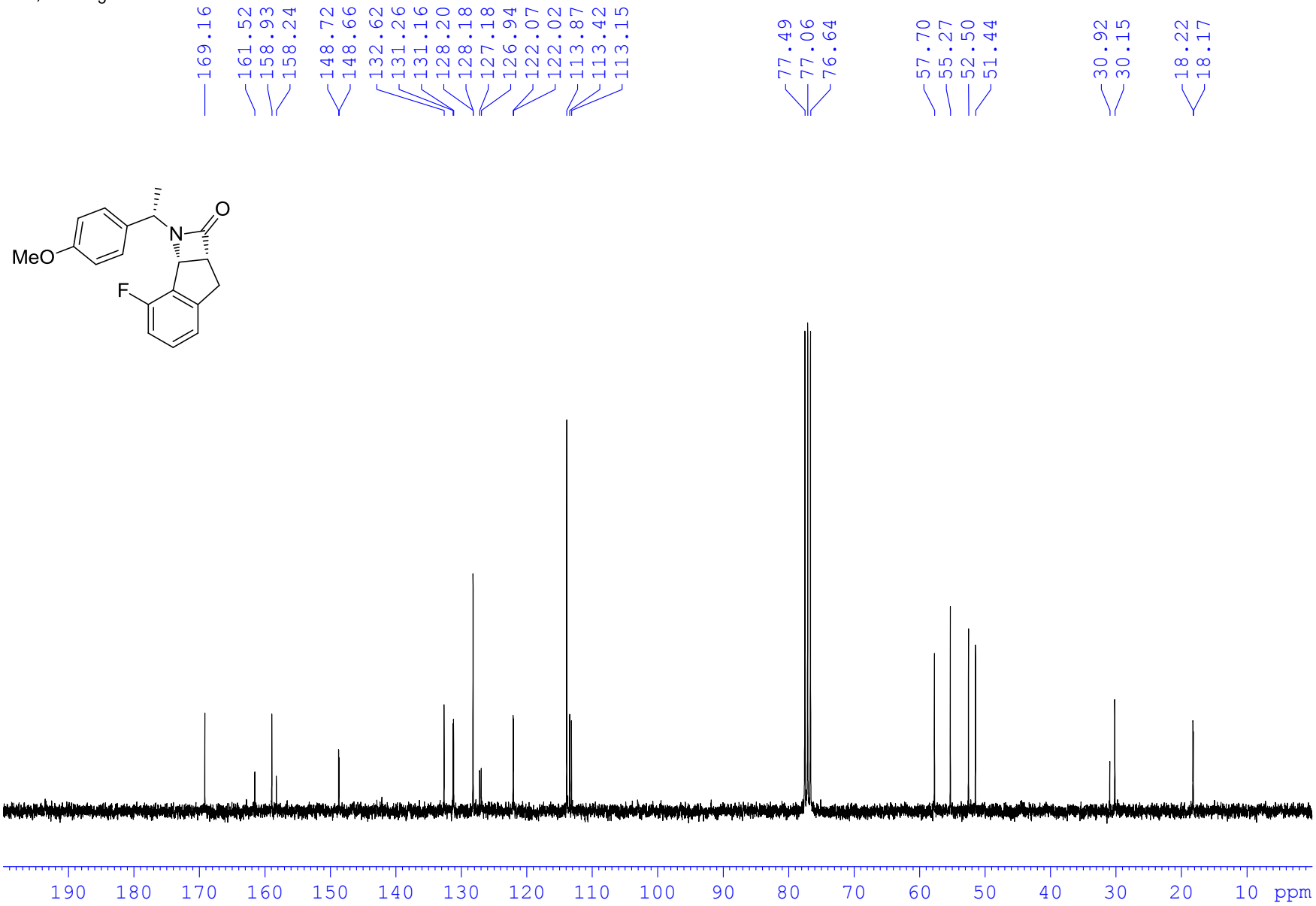
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-(trifluoromethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2c)**,
100 MHz, $CDCl_3$



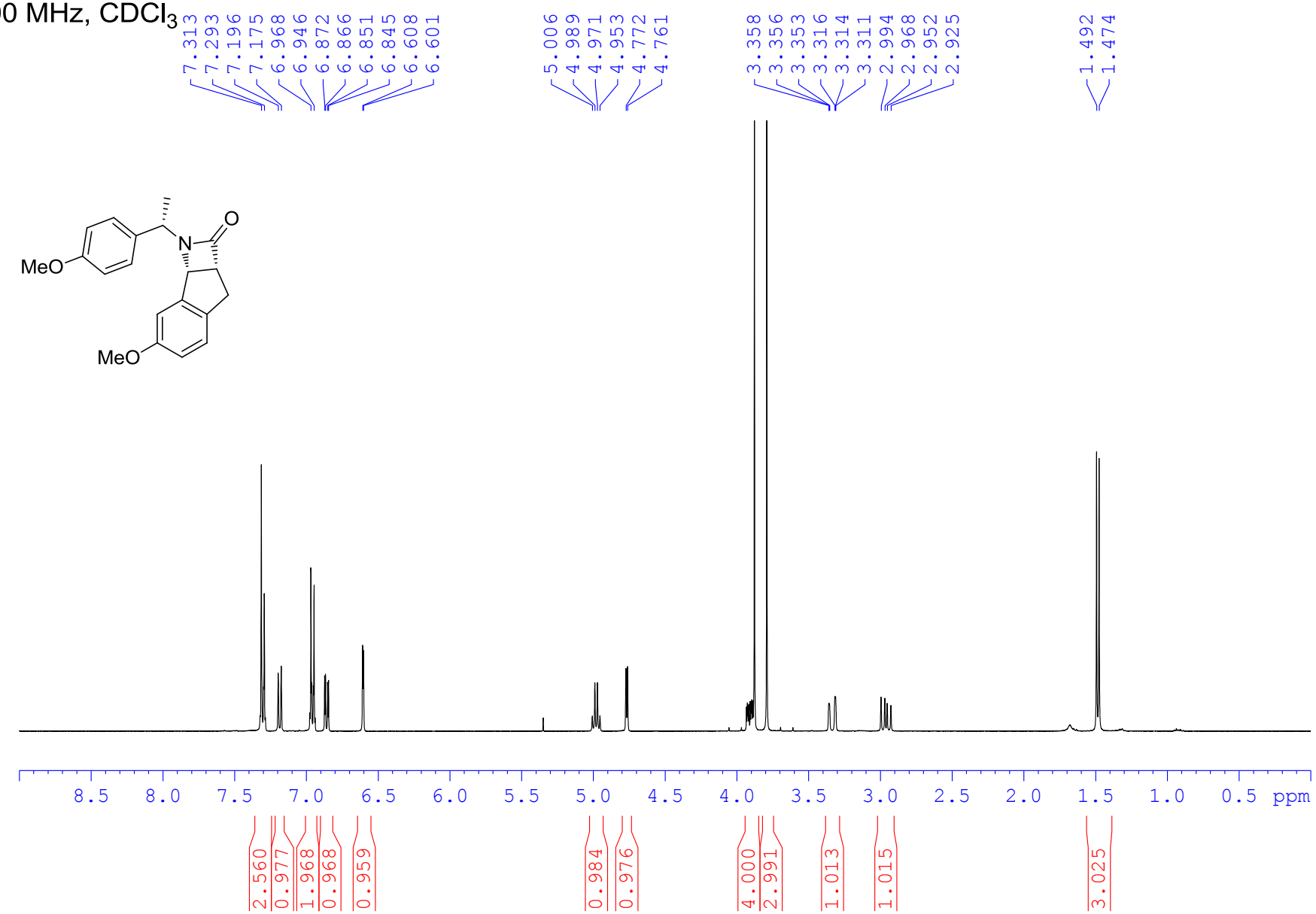
(2a*R*,7b*R*)-7-Fluoro-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2d)**, 400 MHz, $CDCl_3$



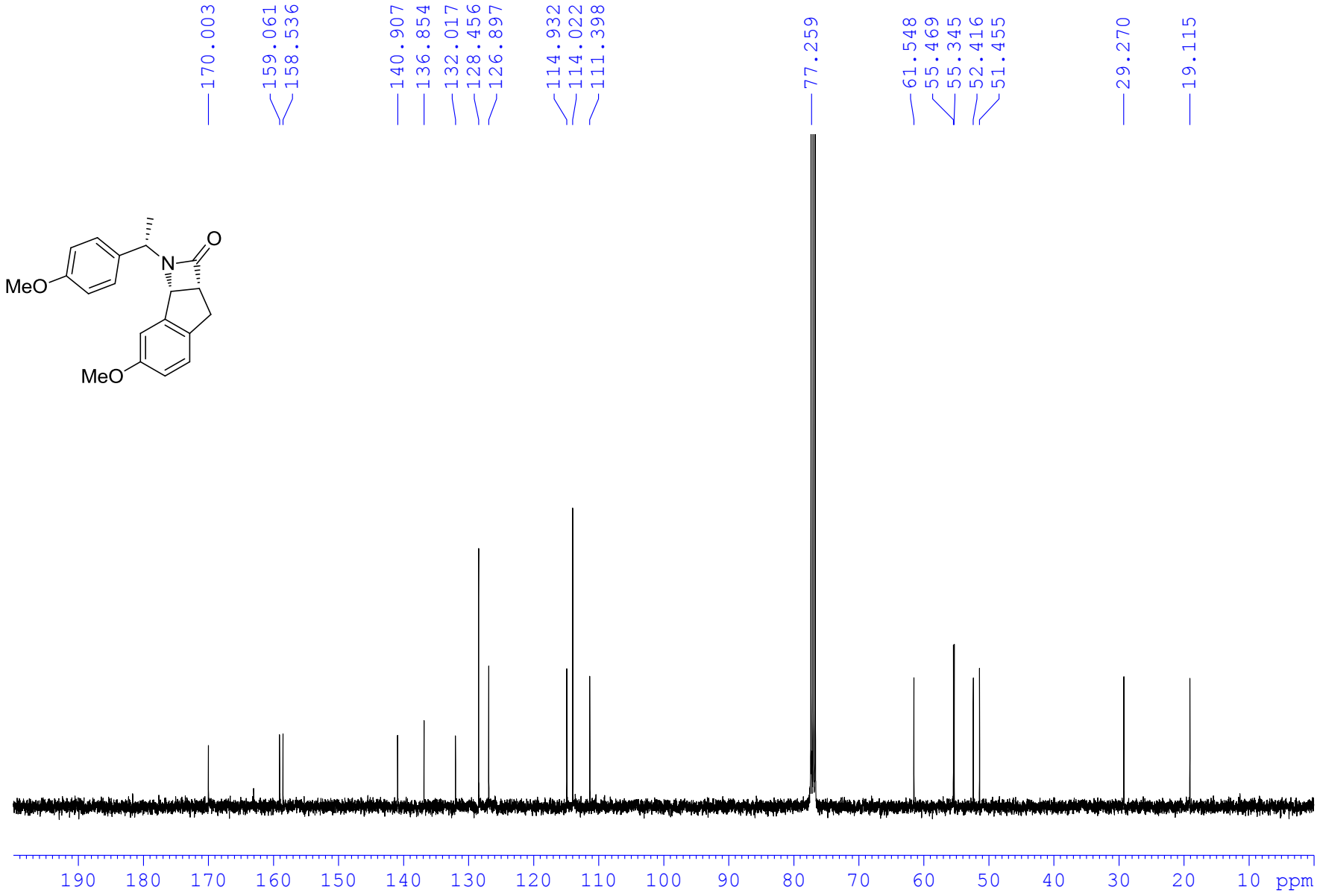
(2a*R*,7b*R*)-7-Fluoro-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2d)**,
75 MHz, $CDCl_3$



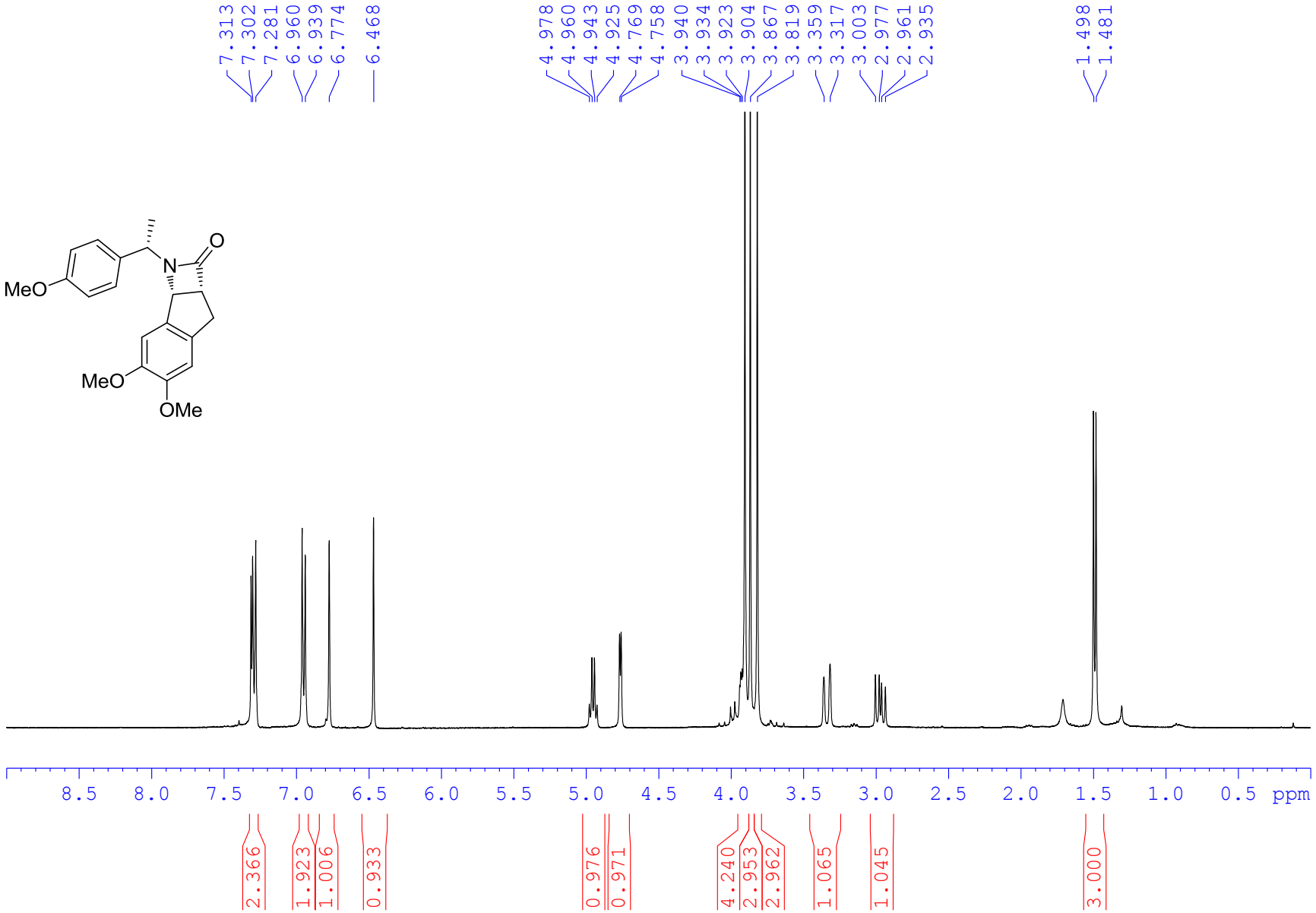
(2a*R*,7b*R*)-6-Methoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2e)**, 400 MHz, $CDCl_3$



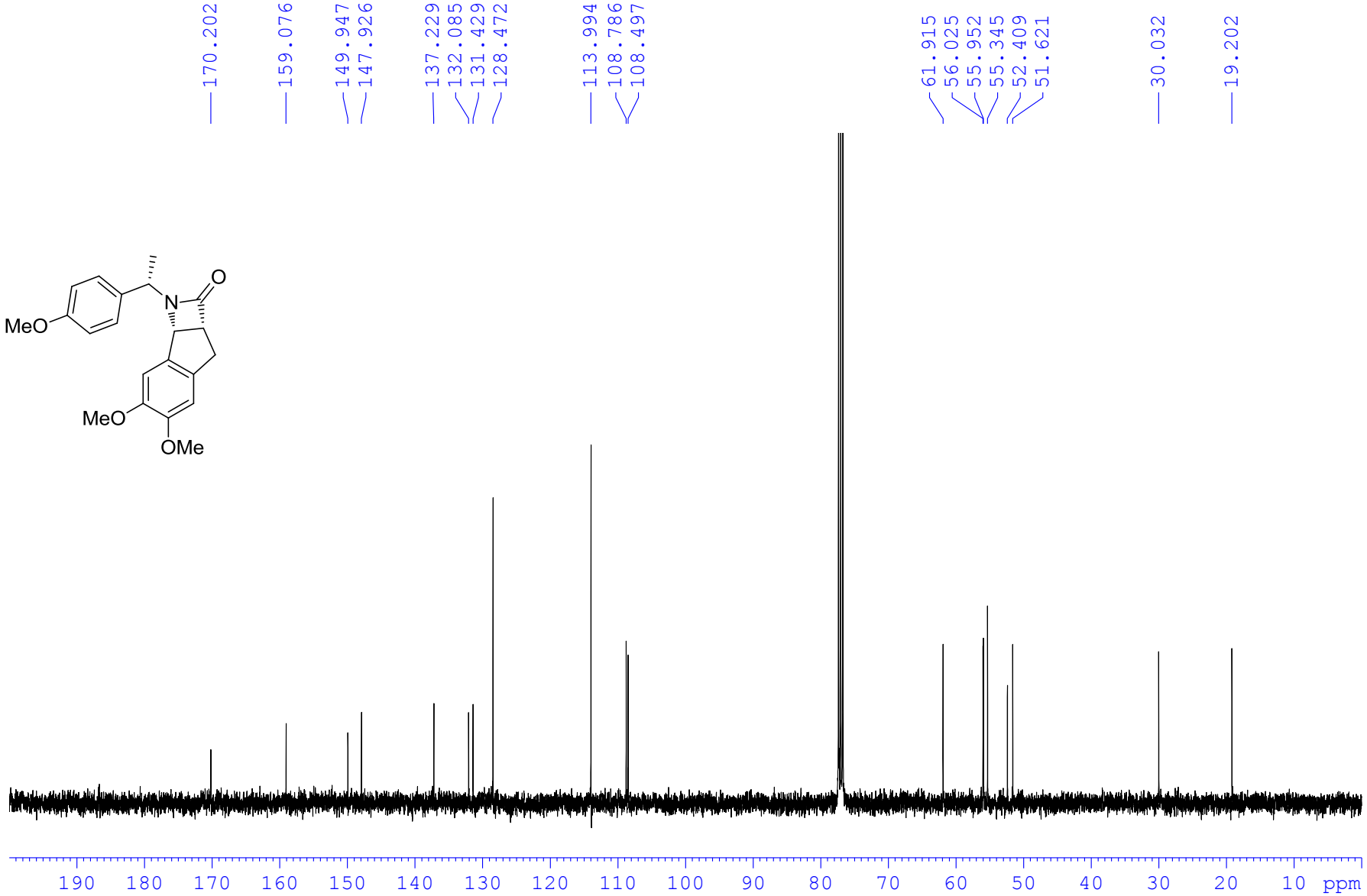
(2a*R*,7b*R*)-6-Methoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2e)**,
100 MHz, $CDCl_3$



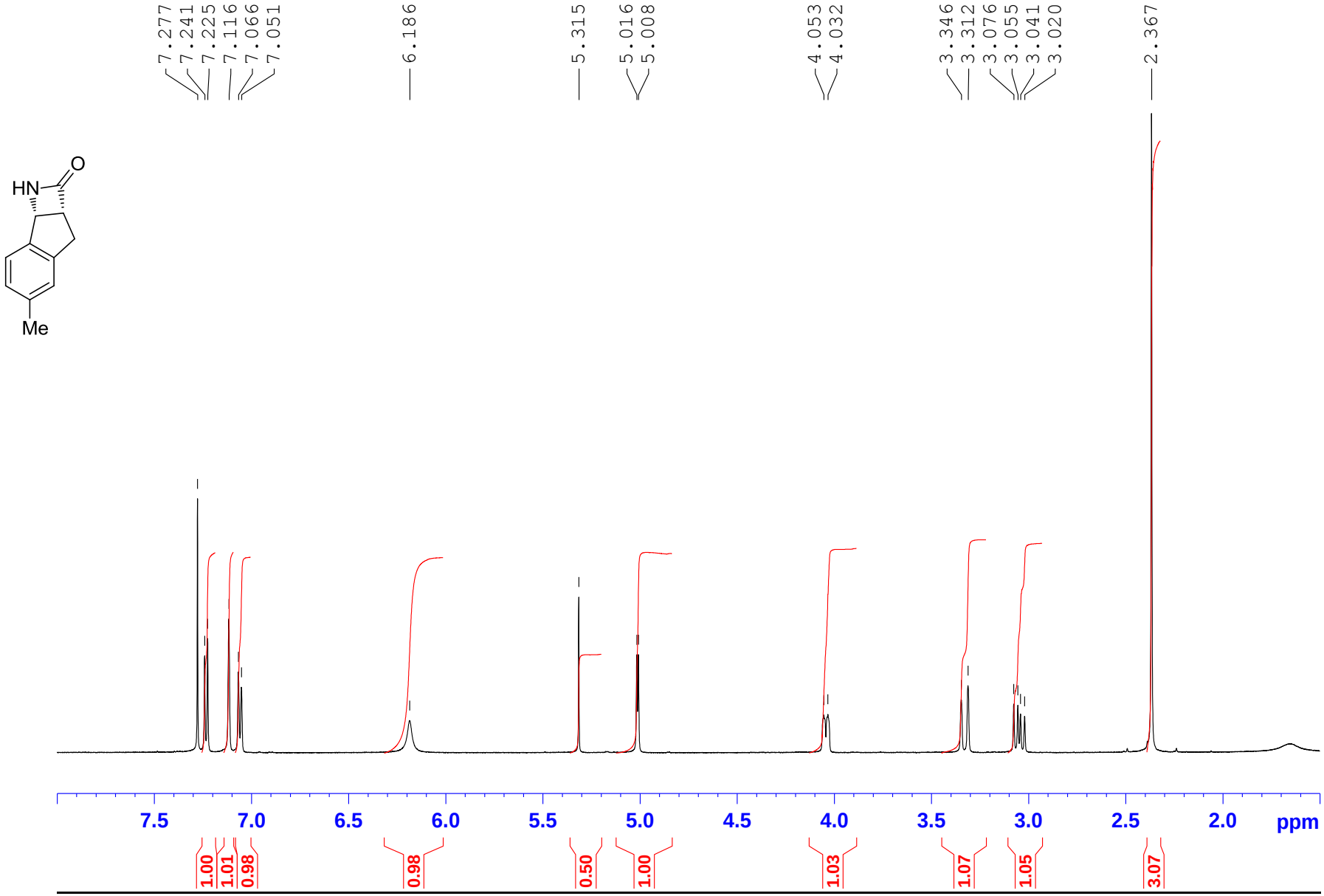
(2a*R*,7b*R*)-5,6-Dimethoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2f)**, 400 MHz, $CDCl_3$



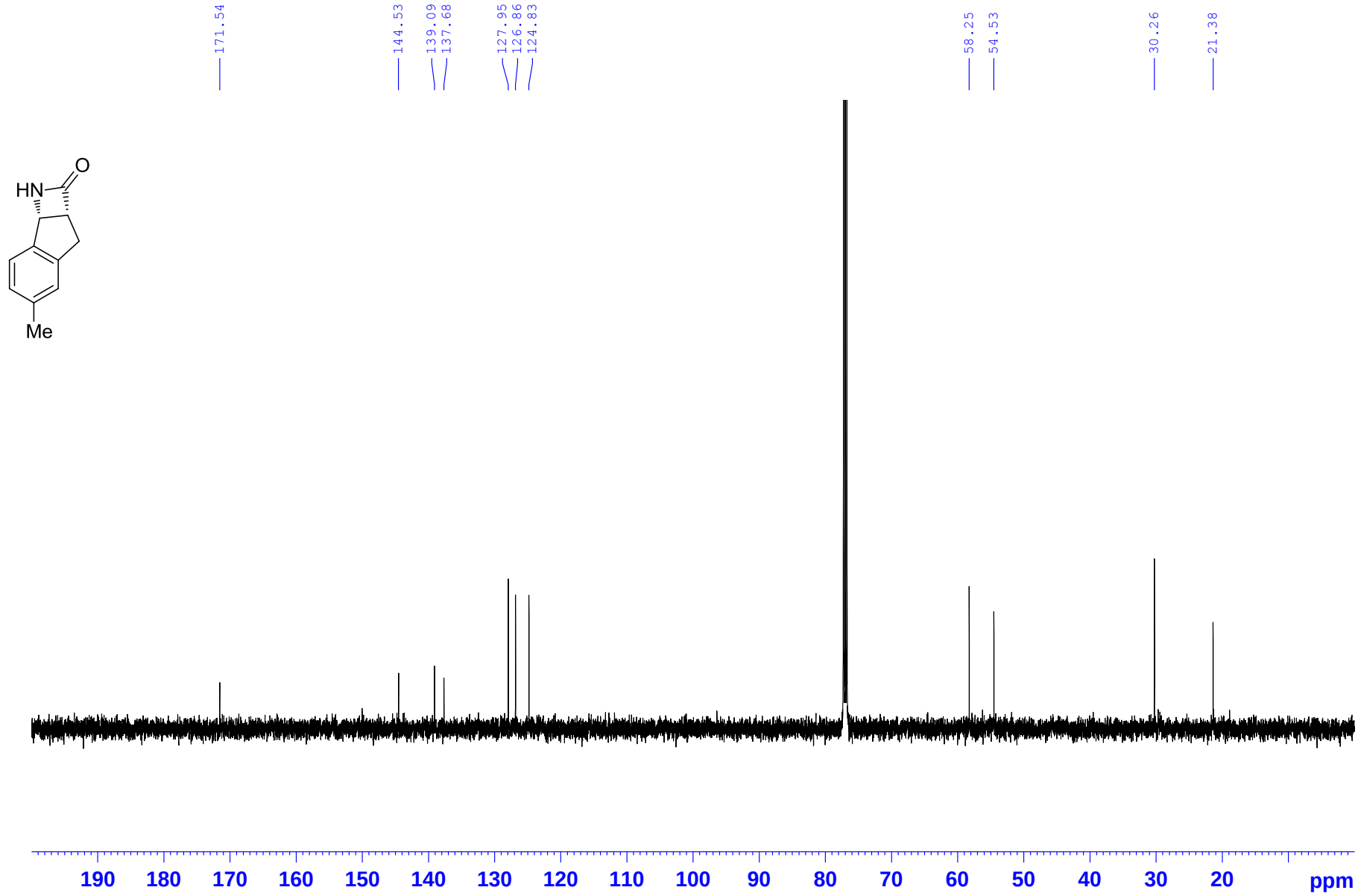
(2a*R*,7b*R*)-5,6-Dimethoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(2f)**, 100 MHz, $CDCl_3$



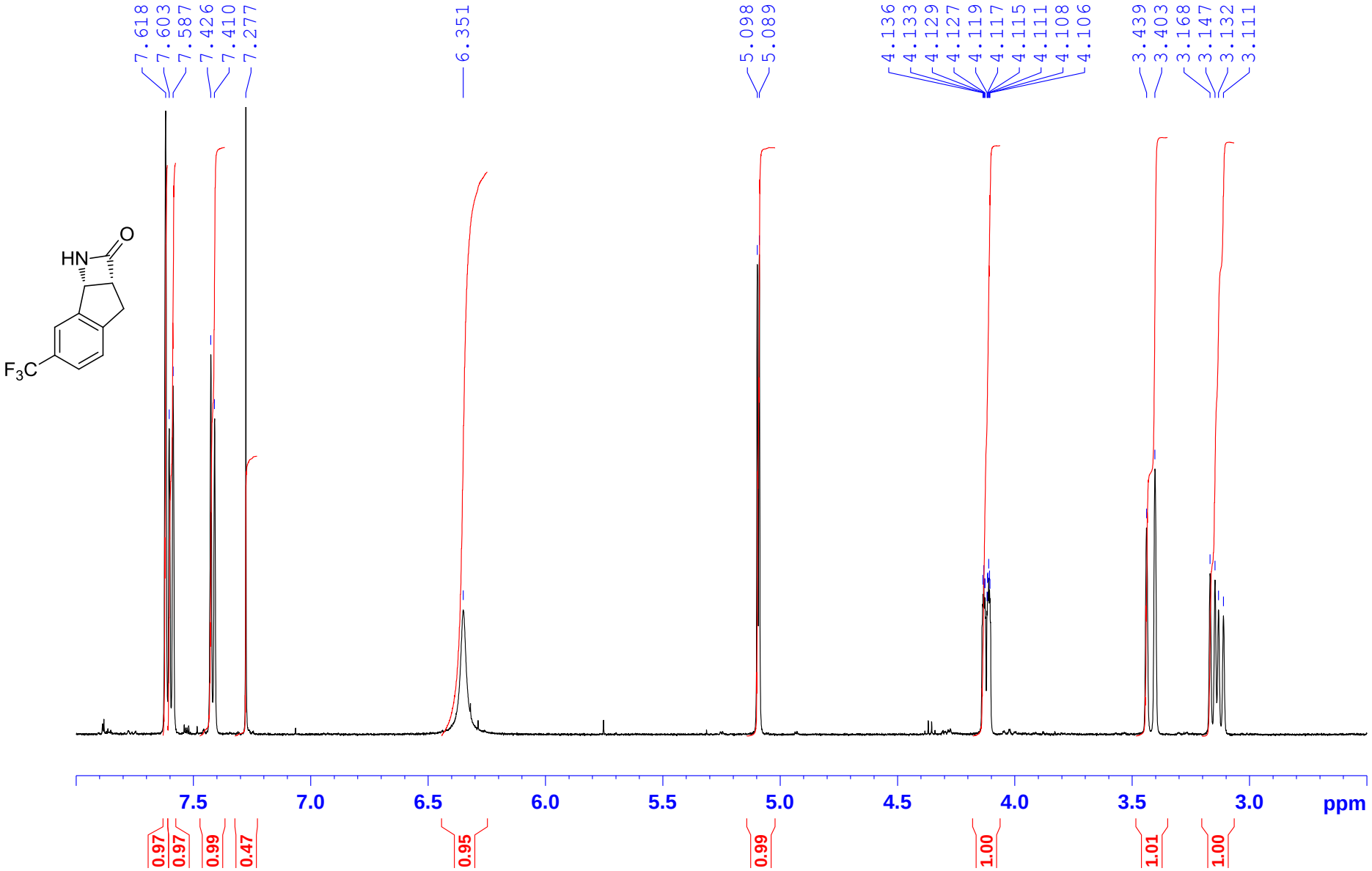
(2a*R*,7b*R*)-5-Methyl-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(5b)**, 400 MHz, $CDCl_3$



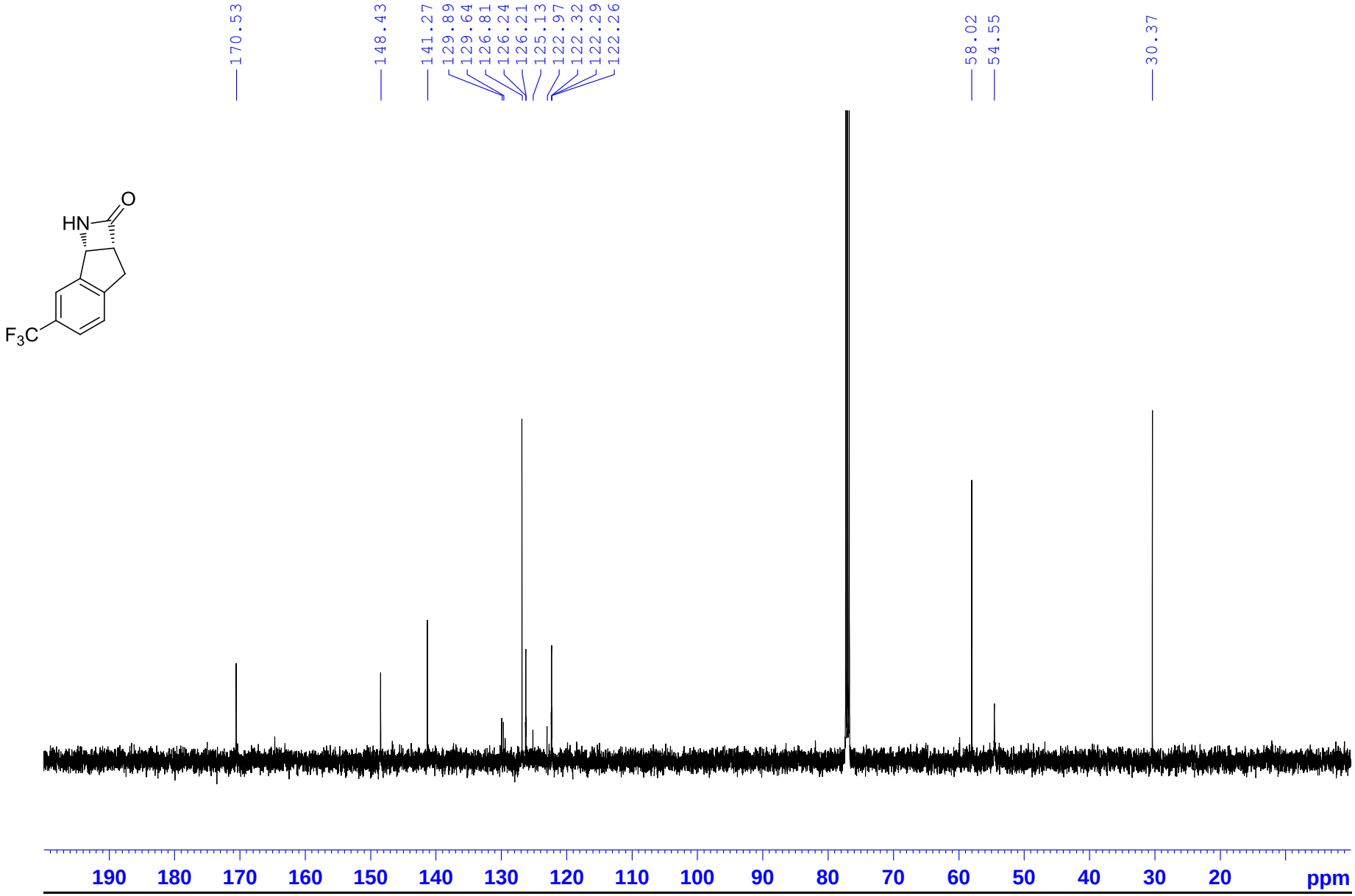
(2a*R*,7b*R*)-5-Methyl-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(5b)**, 100 MHz, $CDCl_3$



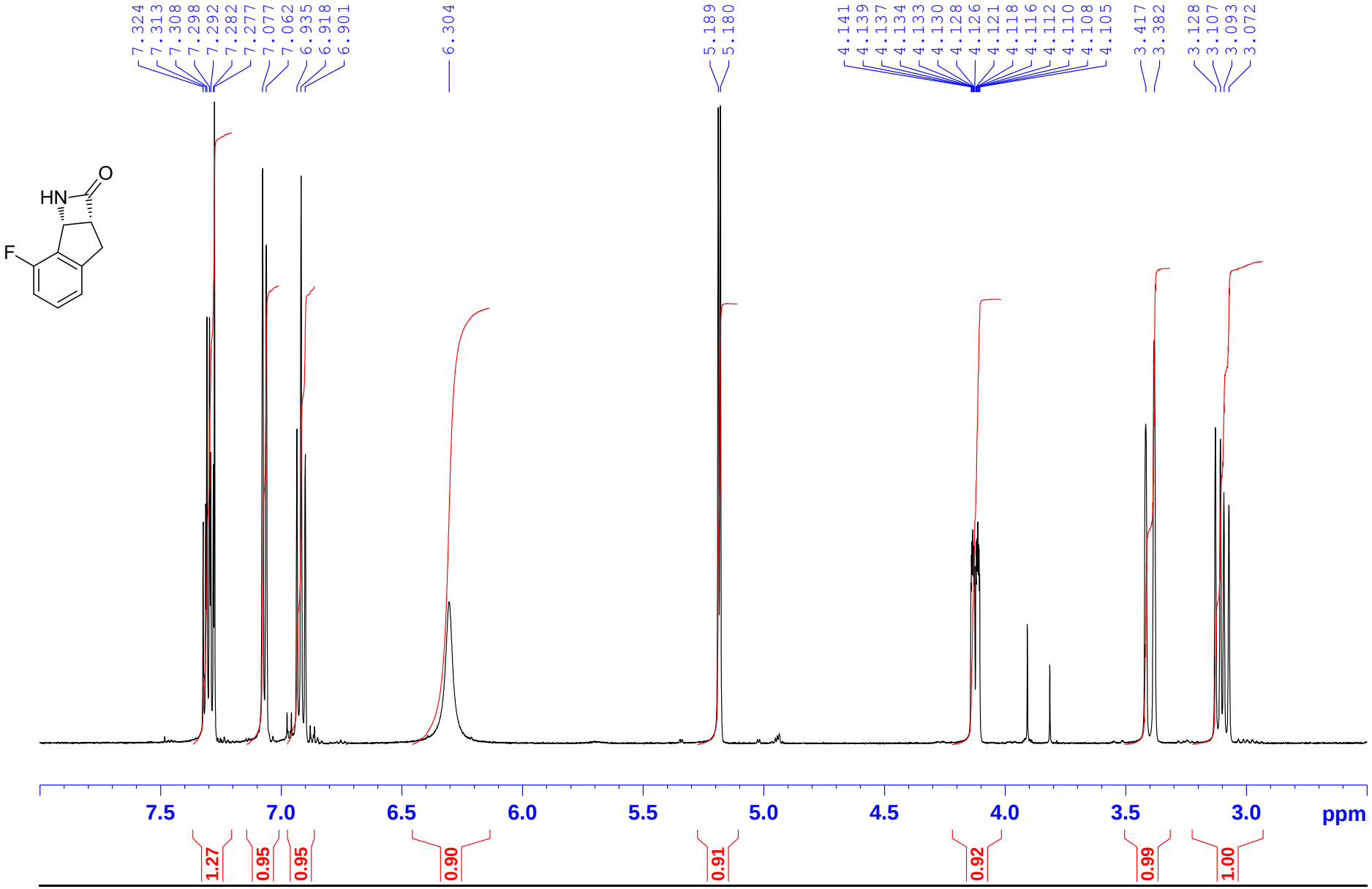
(2a*R*,7b*R*)-6-(Trifluoromethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(5c)**, 500 MHz, $CDCl_3$



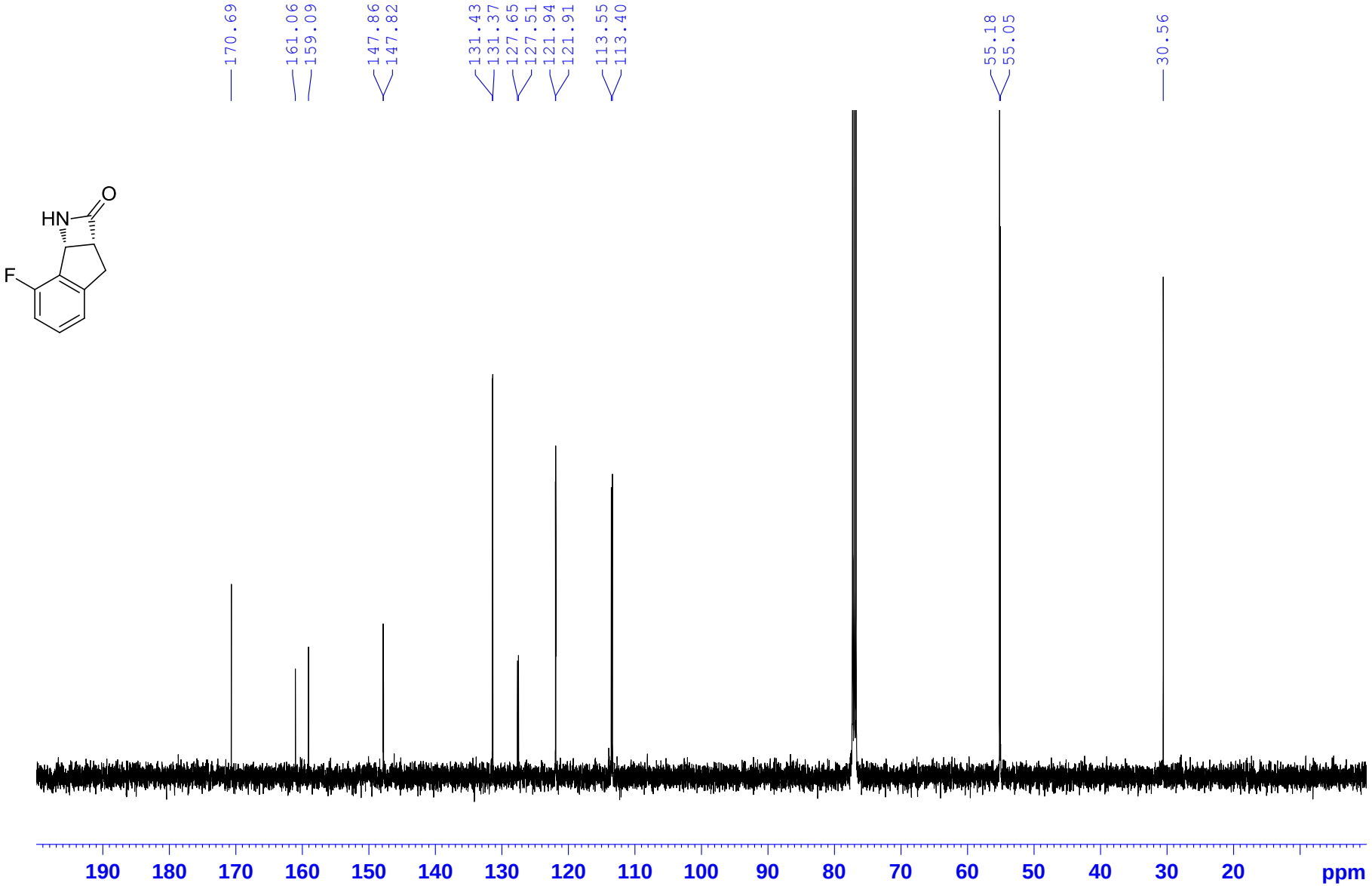
(2a*R*,7b*R*)-6-(Trifluoromethyl)-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(5c)**, 125 MHz, $CDCl_3$



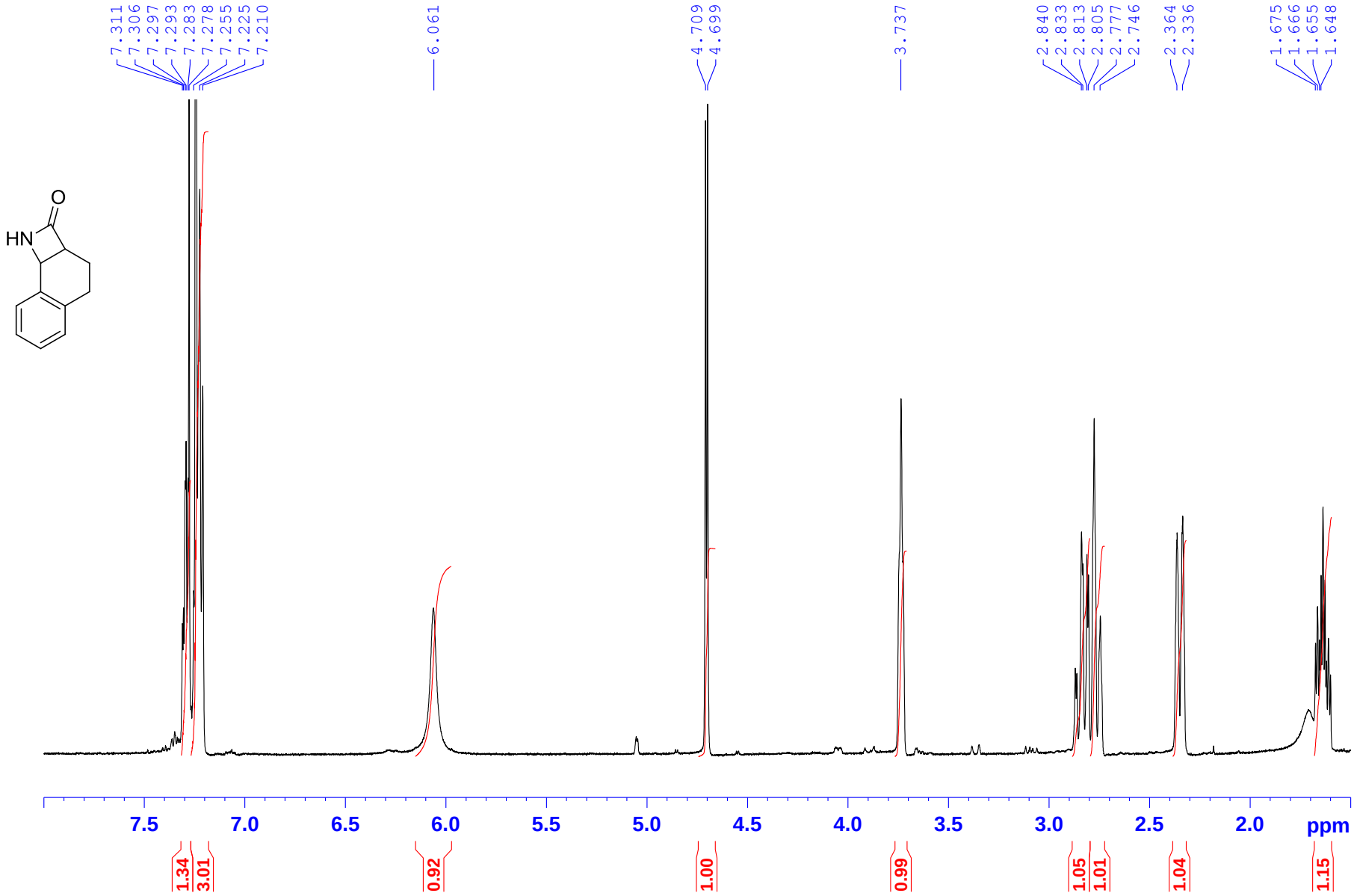
(2a*R*,7b*R*)-7-Fluoro-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(5d)**, 500 MHz, $CDCl_3$



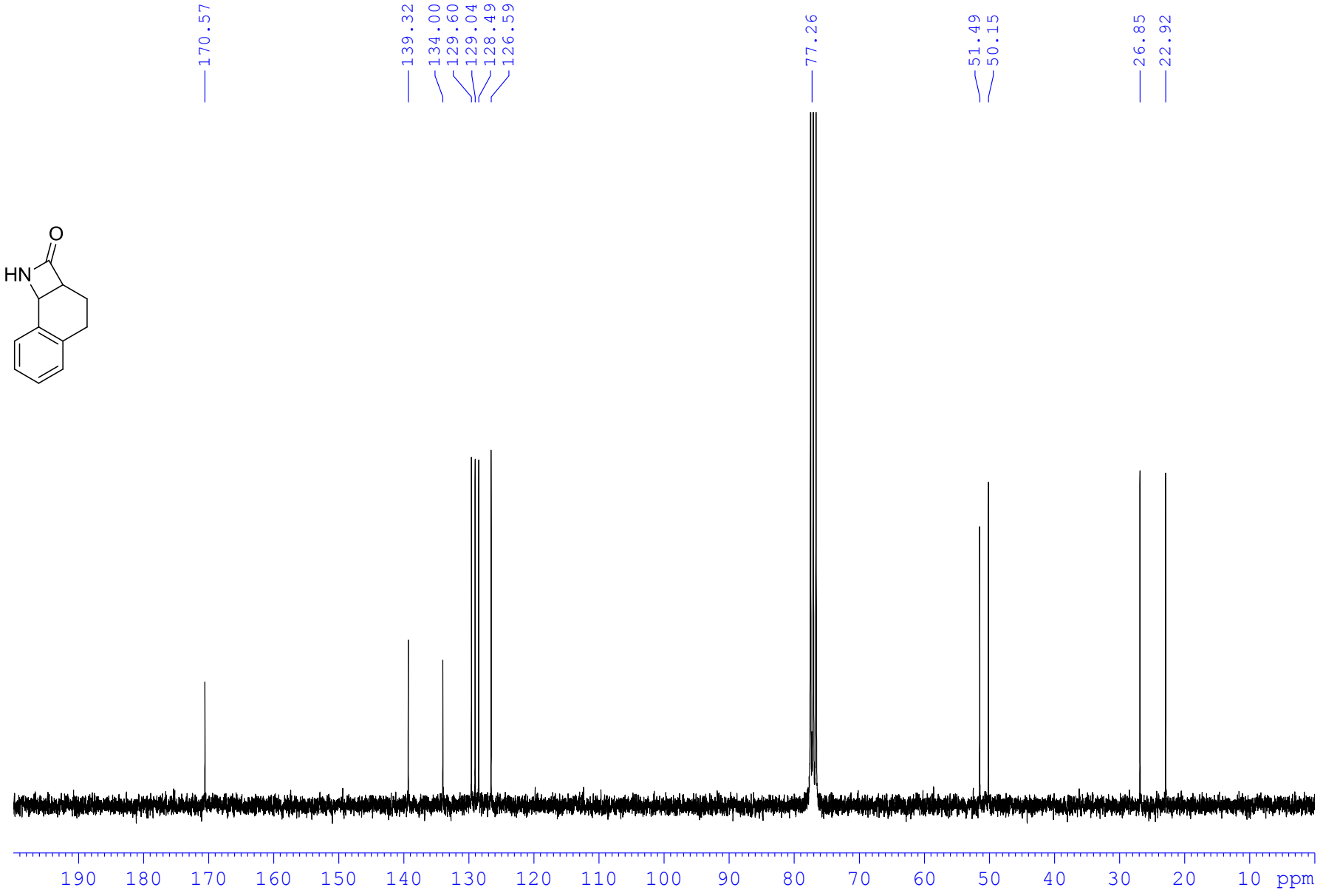
(2a*R*,7b*R*)-7-Fluoro-2a,3-dihydro-1*H*-indeno[1,2-*b*]azet-2(7b*H*)-one **(5d)**, 125 MHz, $CDCl_3$



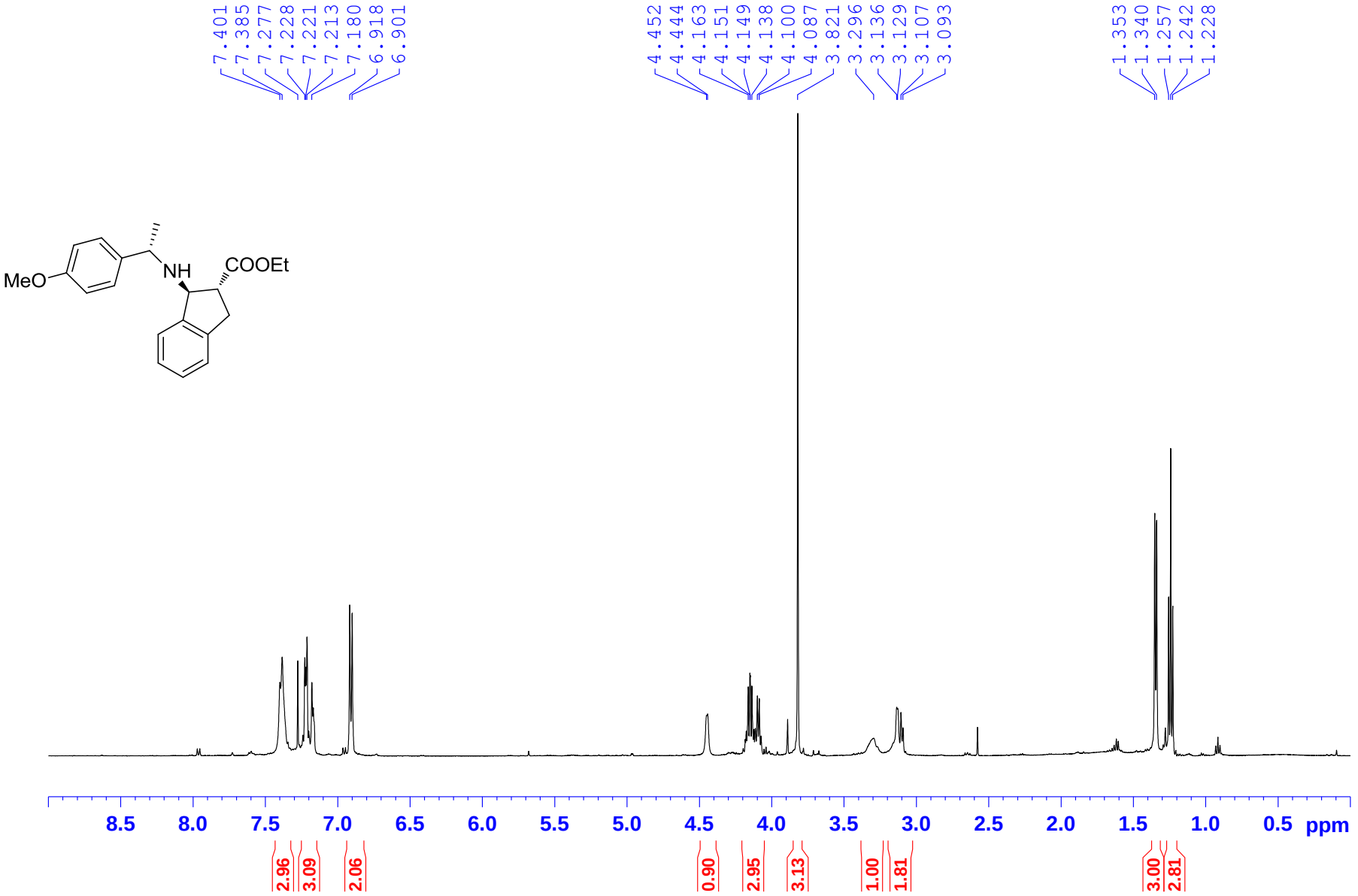
1,3,4,8b-Tetrahydronaphtho[1,2-*b*]azet-2(2a*H*)-one **(5g)**, 500 MHz, $CDCl_3$



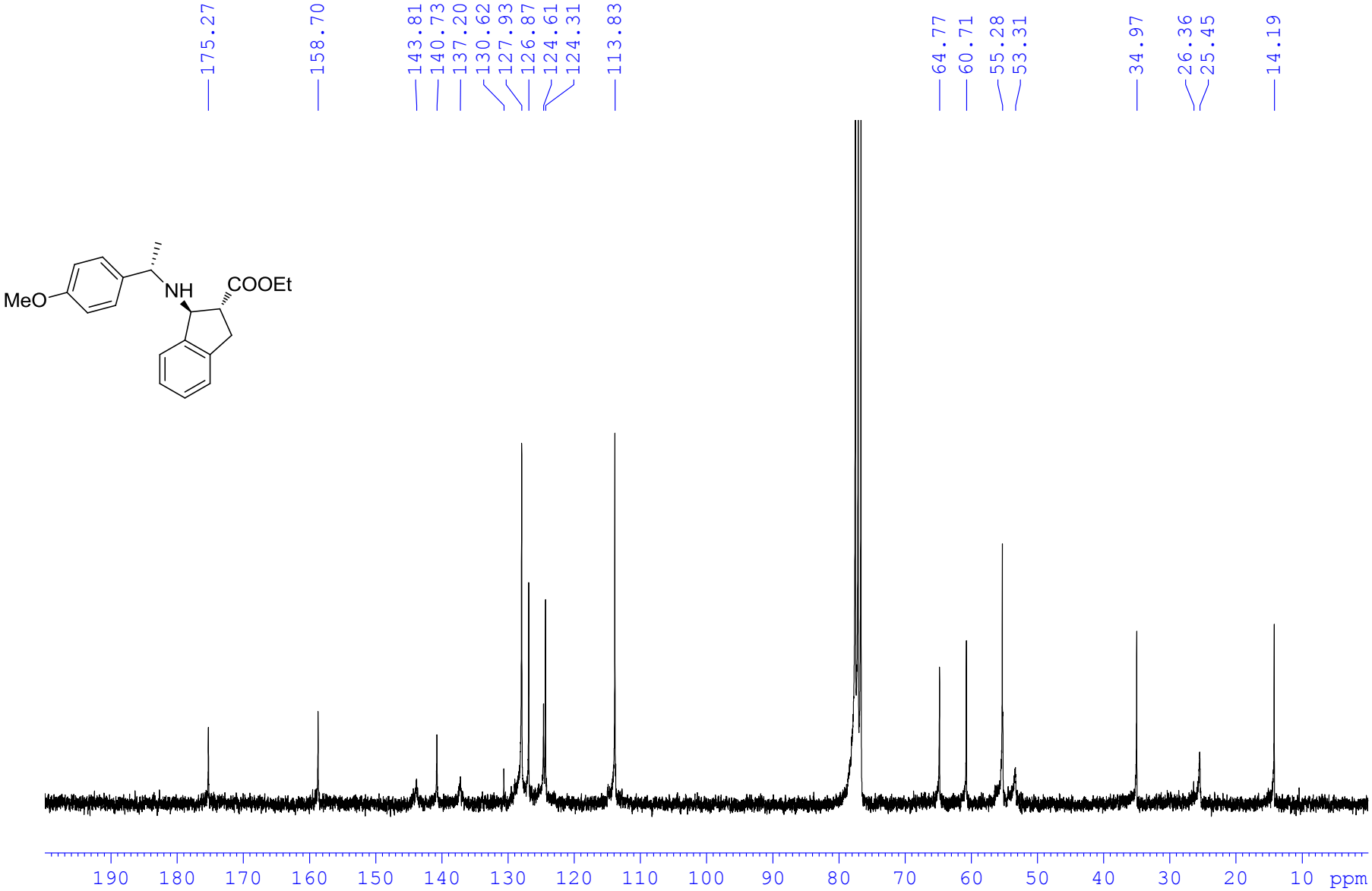
1,3,4,8b-Tetrahydronaphtho[1,2-*b*]azet-2(2a*H*)-one **(5g)**, 75 MHz, $CDCl_3$



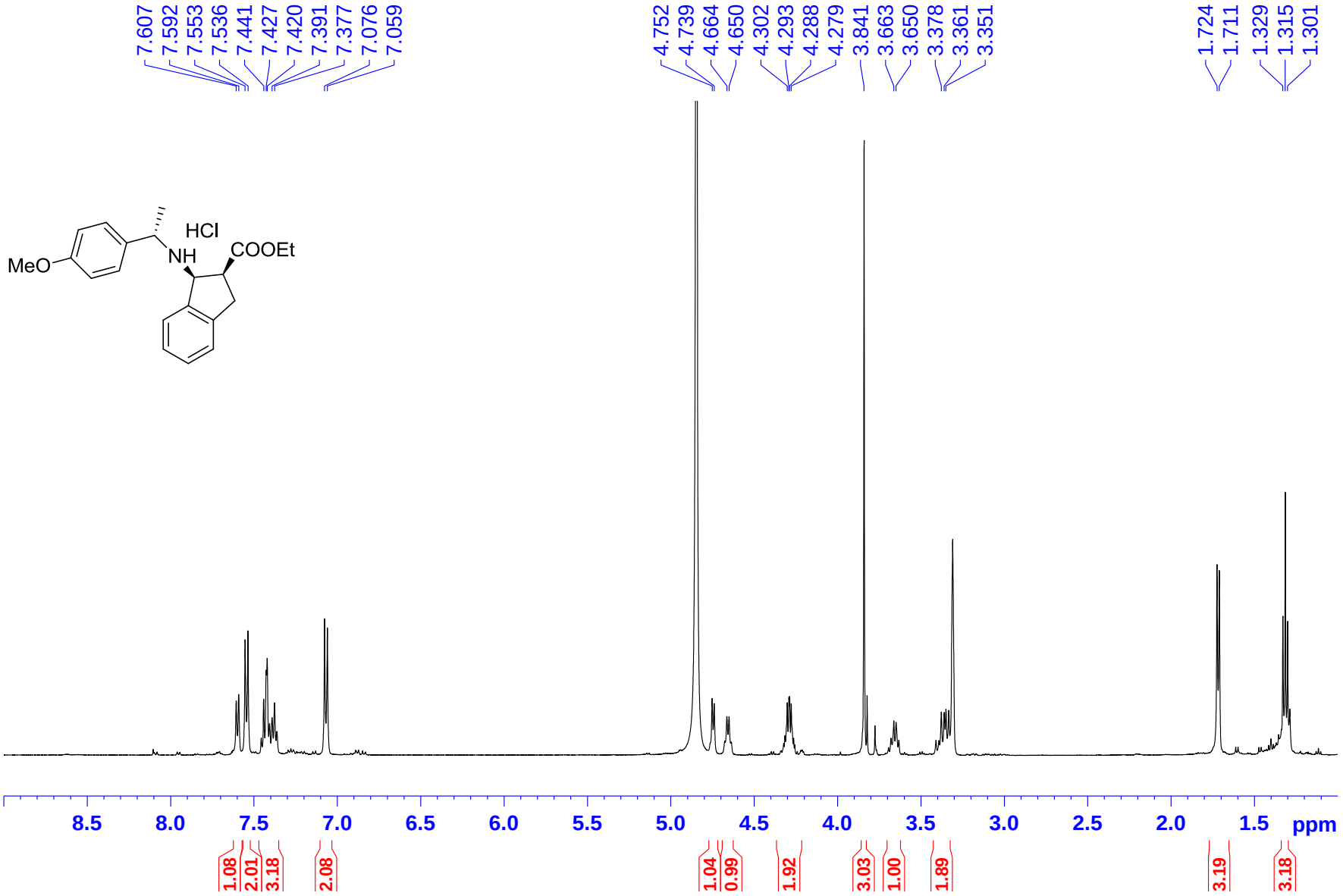
(1*S*,2*R*)-Ethyl 1-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate **(4)**, 500 MHz, $CDCl_3$



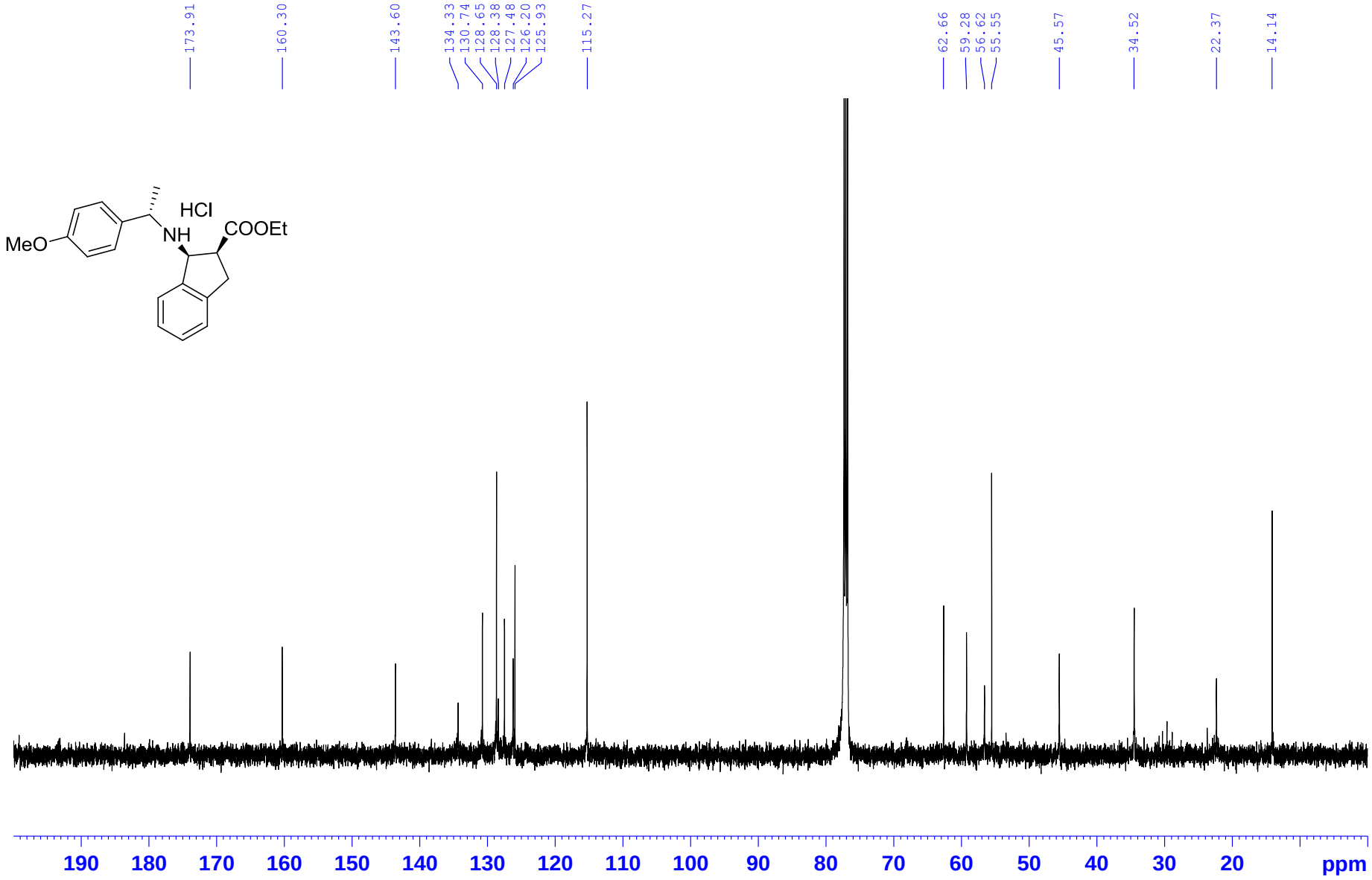
(1*S*,2*R*)-Ethyl 1-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate **(4)**, 75 MHz, $CDCl_3$



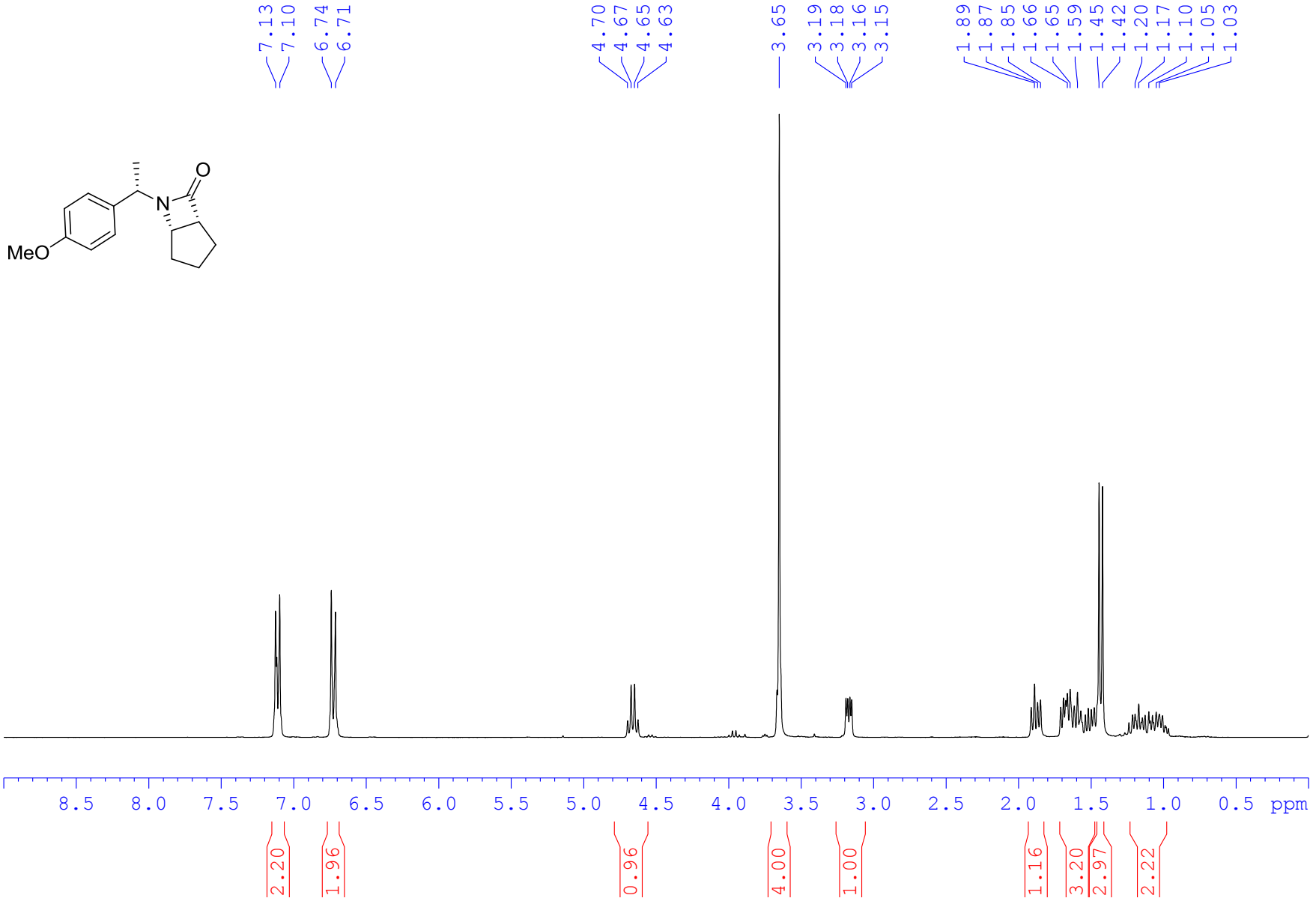
(1*S*,2*S*)-Ethyl 1-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate, 500 MHz, MeOD



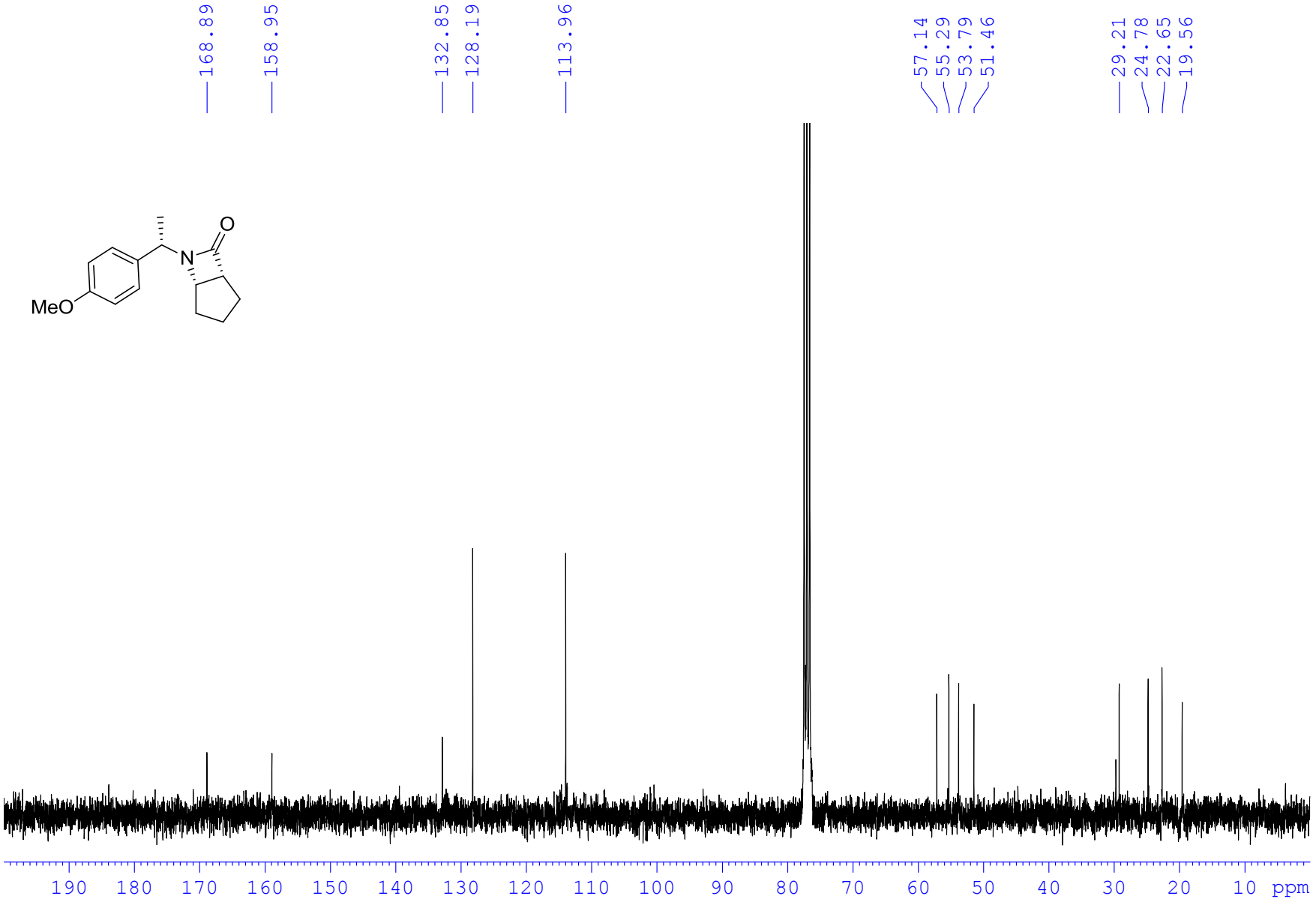
(1*S*,2*S*)-Ethyl 1-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate, 125 MHz, $CDCl_3$



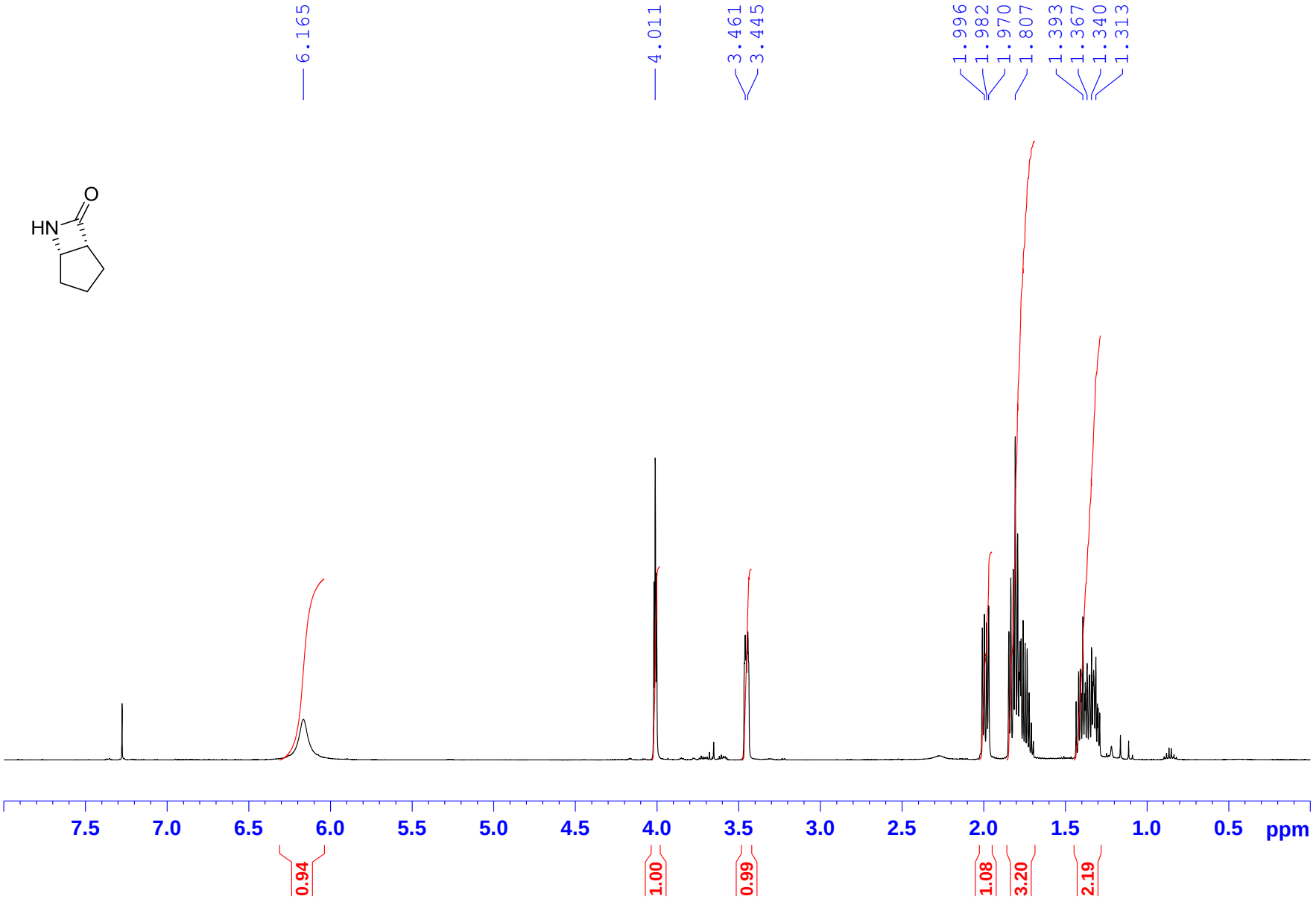
(1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one **(2h)** 300MHz, $CDCl_3$



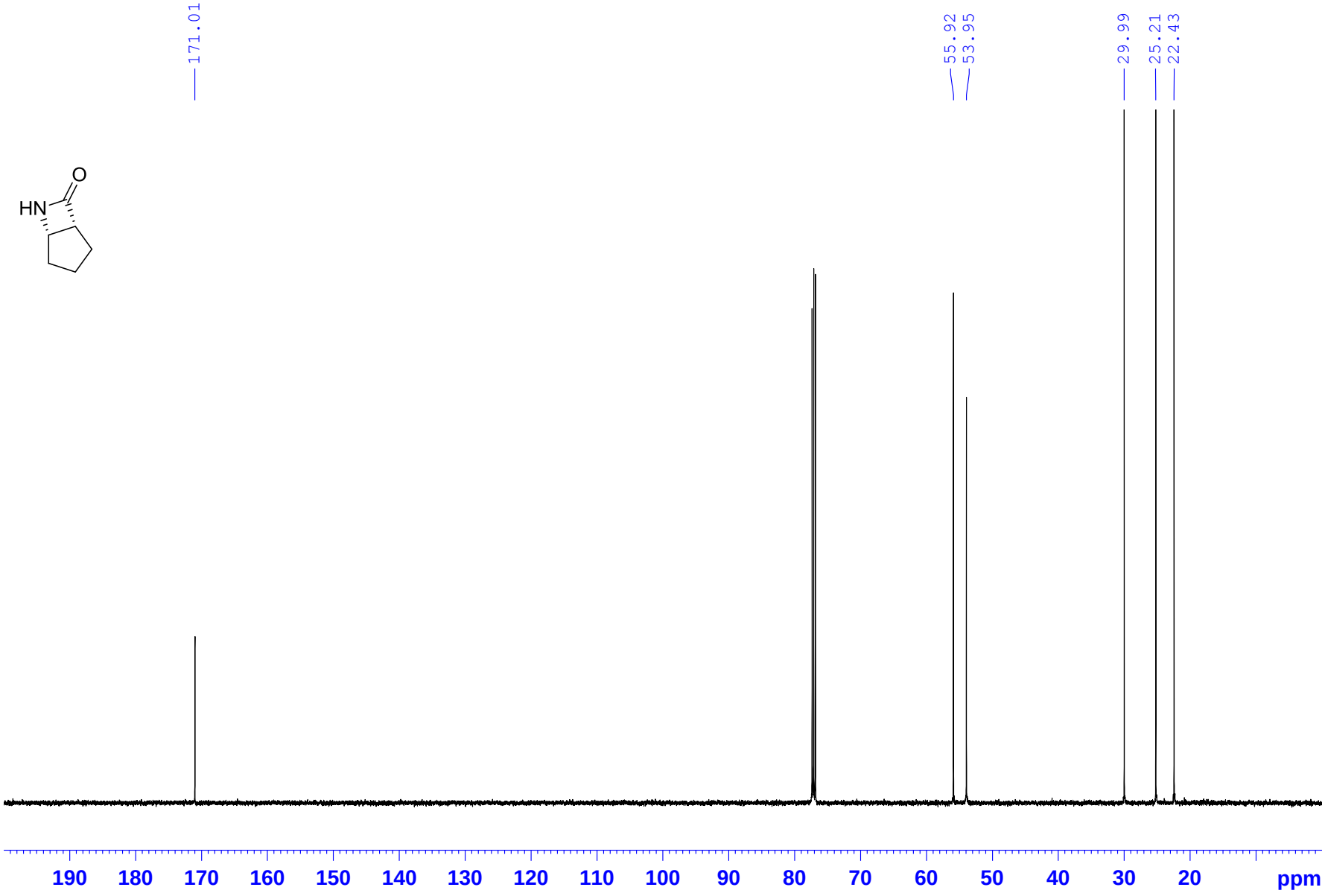
(1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one **(2h)** 75MHz, $CDCl_3$



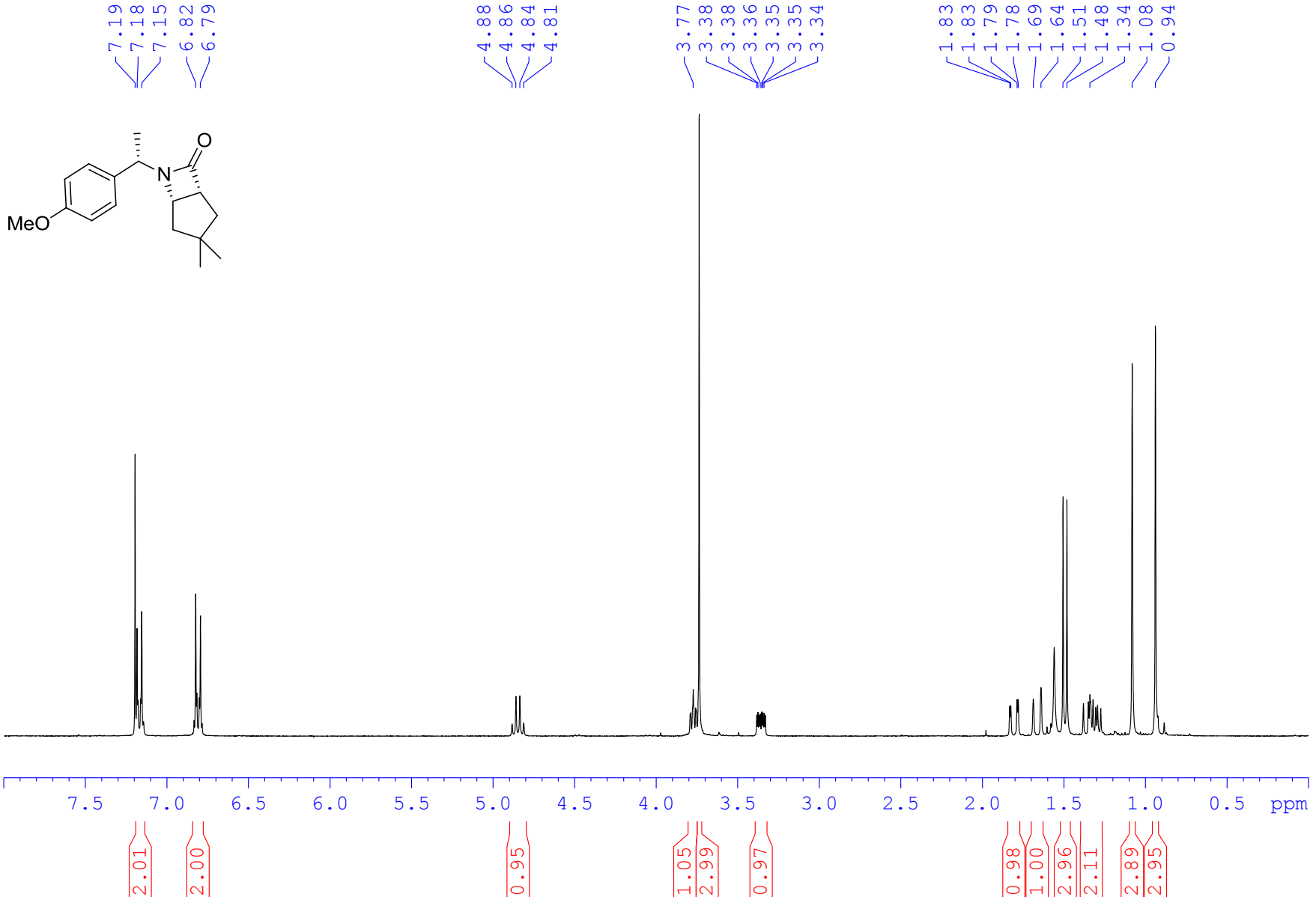
(1*R*,5*S*)-6-azabicyclo[3.2.0]heptan-7-one **(5h)**, 500MHz, $CDCl_3$



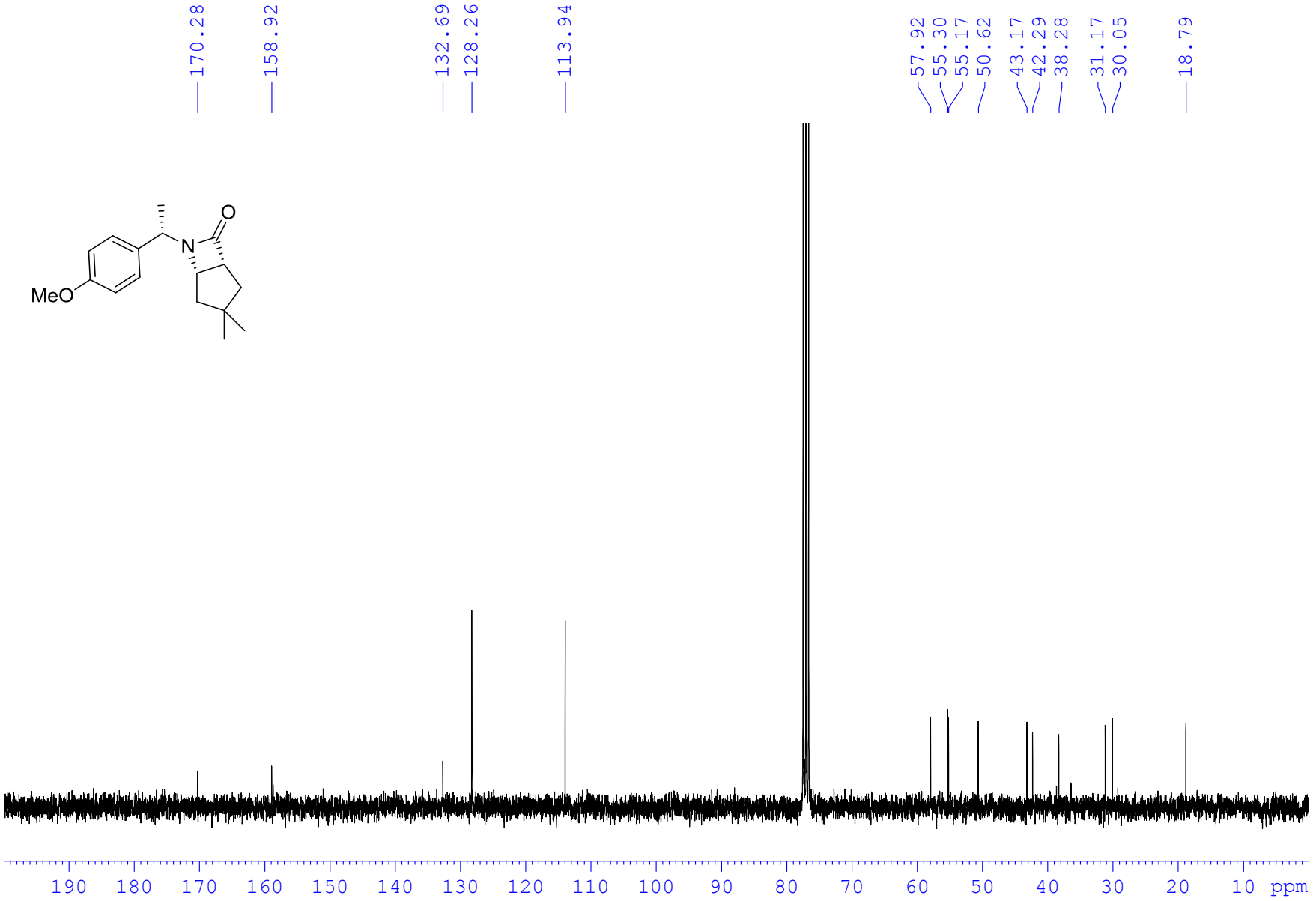
(1*R*,5*S*)-6-azabicyclo[3.2.0]heptan-7-one **(5h)**, 125MHz, $CDCl_3$



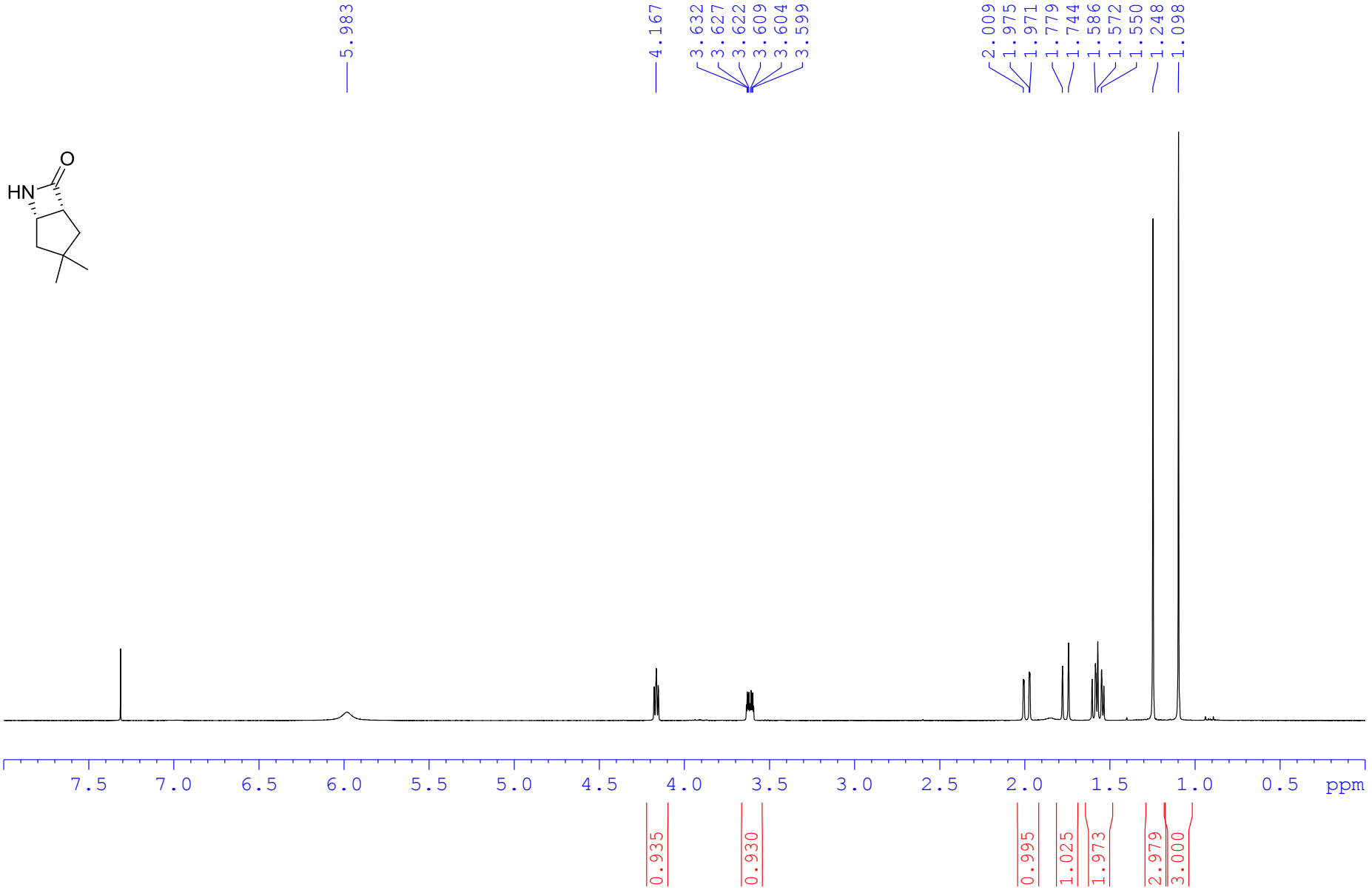
(1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **(2i)**, 300MHz, $CDCl_3$



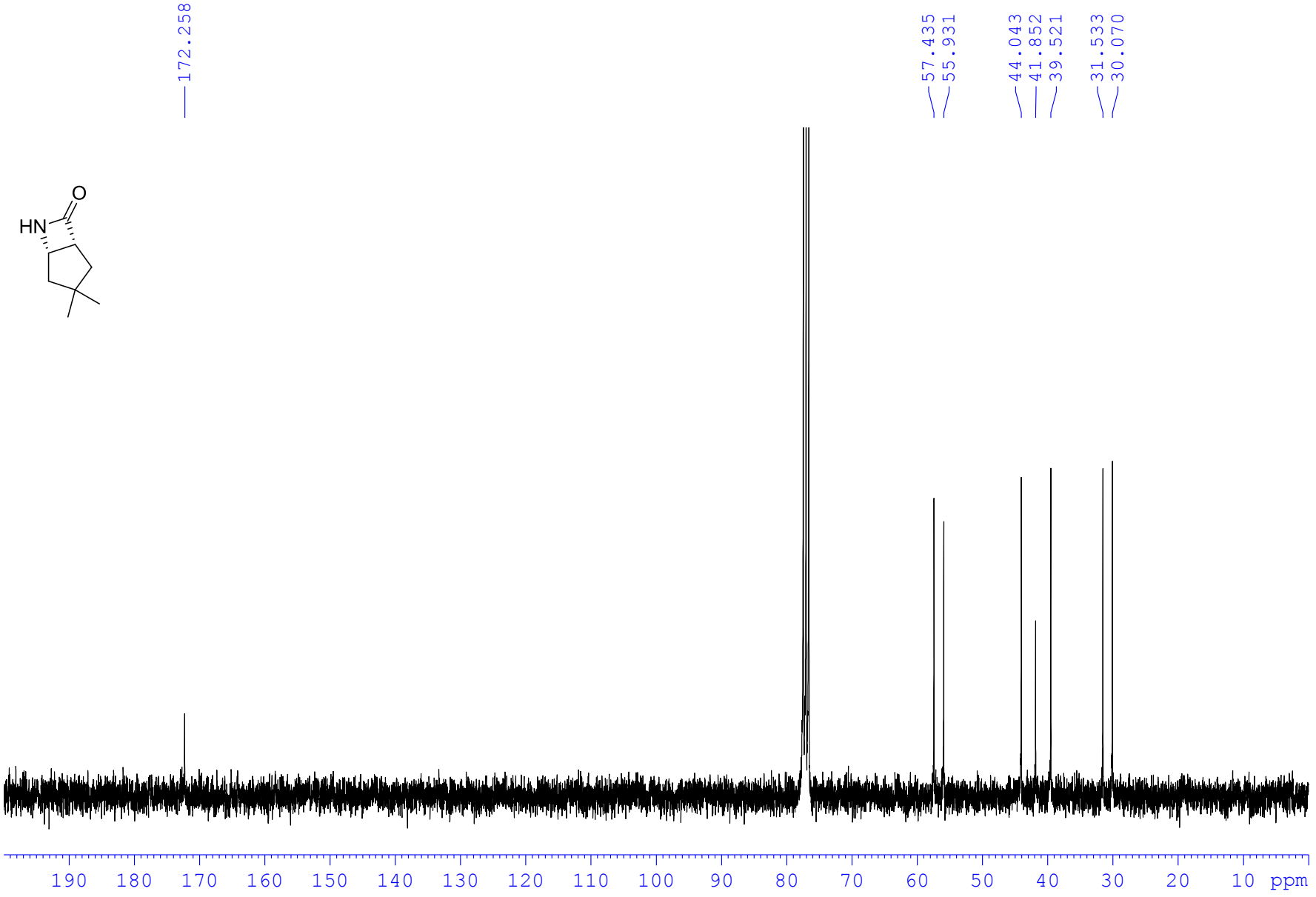
(1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **(2i)**, 75MHz, $CDCl_3$



3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **(5i)**, 400MHz, $CDCl_3$



3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **(5i)**, 75MHz, $CDCl_3$



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