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C(sp^3)-H Arylation to Construct All-*Syn* Cyclobutane-Based Heterobicyclic Systems: A Novel Fragment Collection

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SUPPLEMENTARY INFORMATION

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1. SUPPLEMENTARY FIGURES

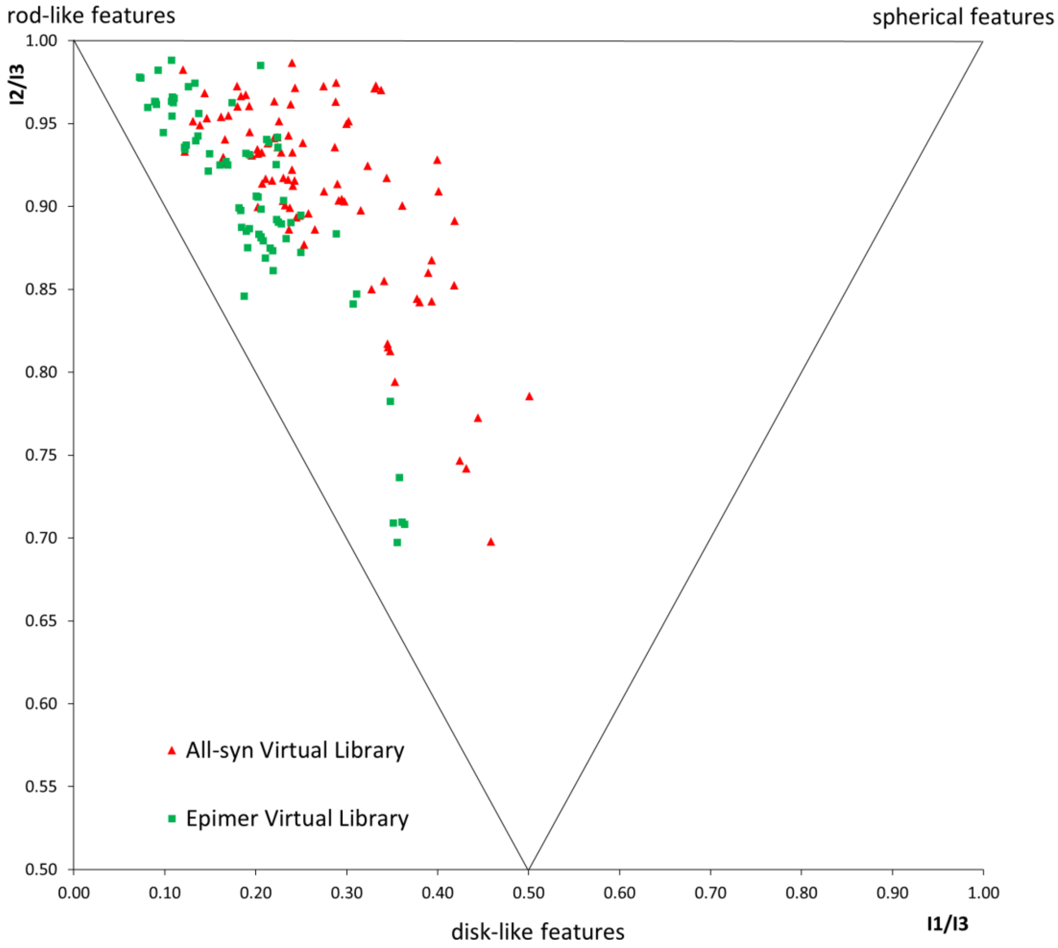


Figure S1. Comparative shape comparison using a PMI plot of all-*syn* library described (red triangles) compared to the *anti*-epimer library (green squares). This revealed significantly higher 3D character of the syn fragments. See Section Four for details.

2. GENERAL REMARKS

All non-aqueous reactions were performed in dry glassware under a stream of Argon using anhydrous solvents. Tetrahydrofuran was dried over sodium wire and distilled from a mixture of lithium aluminium hydride and calcium hydride with triphenylmethane as the indicator. Dichloromethane, toluene and methanol were all distilled from calcium hydride. Petroleum ether was distilled before use and refers to the fraction between 40-60 ºC; anhydrous DMF was purchased from Aldrich and used as received. All reagents were obtained from commercial suppliers and used without further purification. Reactions were carried out at ambient temperature unless otherwise stated. All temperatures below 0 ºC are achieved with an external bath: those of 0 ºC were maintained using an ice/water bath, those of lower temperatures using a dry ice/acetone bath.

Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on commercially available glass pre-coated Merck Kiesel gel 60 F254 plates. Visualisation was by quenching of UV fluorescence (λ max = 254 nm) or by staining with potassium permanganate. R_f values are quoted to the nearest 0.01. Where possible, reactions were monitored using TLC. Flash column chromatography was performed using slurry-packed SiO_2 (Merck Grade 9385, 230-400 mesh) under a positive pressure of N_2. Melting points were obtained on a Buchi B-545 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded using an internal deuterium lock at ambient probe temperatures (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz), Bruker BB 500 (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts (δH) are referenced to the residual non-deuterated solvent peak and quoted in parts per million (ppm) to the nearest 0.01 ppm. Coupling constants are quoted in Hertz to the nearest 0.1 Hz. Data are reported in the format: chemical shift, multiplicity [app = apparent; br = broad; s =s singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet; or as a combination of these, e.g. dd], coupling constant(s), integration. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded by broadband proton spin decoupling at ambient probe temperatures (unless otherwise stated) using an internal deuterium lock on the following instruments: Bruker DPX-400 (100 MHz), Bruker Avance 400 QNP (100 MHz), Bruker BB 500 (125 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz). Chemical shifts (δC) are referenced to the residual non-deuterated solvent peak and quoted in parts per million (ppm) to the nearest 0.1 ppm. High resolution mass spectrometry (HRMS), measurements were carried out on a Micromass LCT Premier spectrometer using electron spray ionisation (ESI) techniques. Masses are quoted within the error limits of ±5ppm mass units.

3. SYNTHETIC SCHEMES

Synthesis of Substrate 3

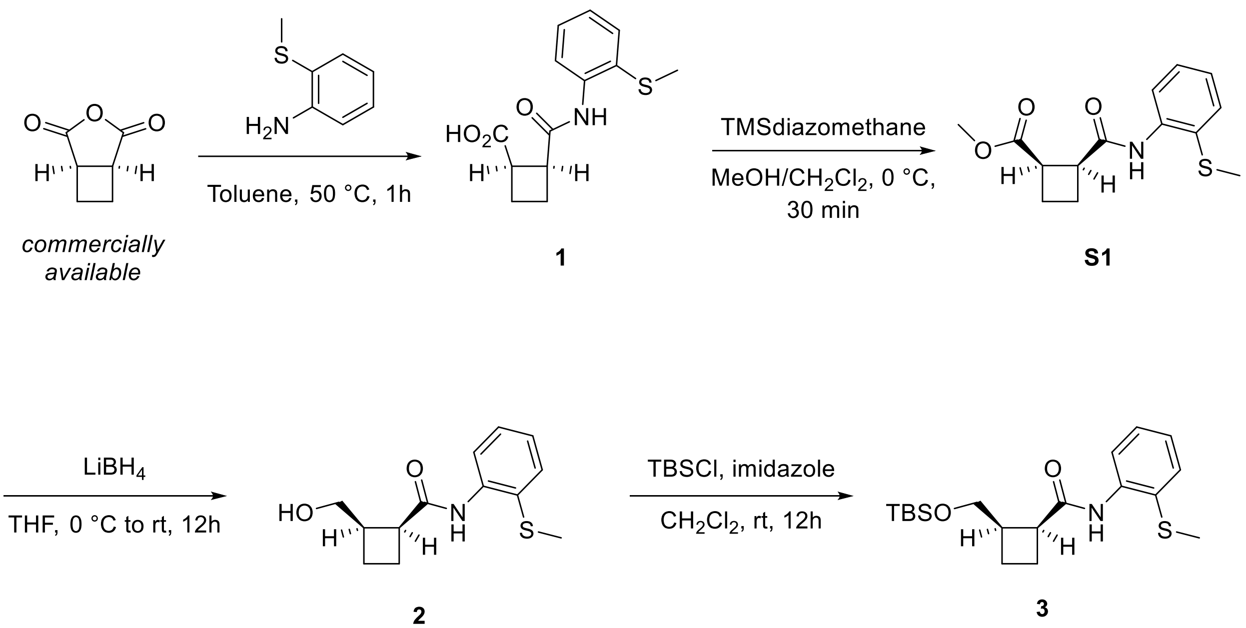
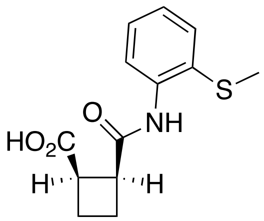


Figure S2. Full synthetic route to substrate **3** used in C-H arylation.

4. SYNTHETIC PROCEDURES

Synthesis of (±)-(1*R*,2*S*)-2-((2-(methylthio)phenyl)carbamoyl)cyclobutane-1-carboxylic acid (1)



Syn-1,2-cyclobutanedicarboxylic anhydride, (1.00 g, 7.93 mmol, 1.0 equiv.) was dissolved in toluene (5 mL) and 2-(methylthio)-aniline (1.10 g, 7.93 mmol, 1.0 equiv.) was added. The mixture was stirred at 50 °C for 1 hour and then allowed to cool to room temperature. (A precipitate usually forms within 5 minutes, but the reaction is stirred longer to ensure full conversion). The precipitate was collected via suction filtration and washed with ice-cold toluene (70 mL). The product, **1** was obtained as a white (sometimes very light pink), amorphous solid (2.06 g, 98%).

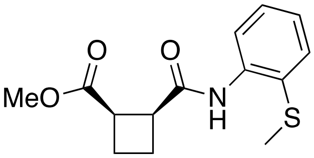
R$_f$: 0.28 in 5% MeOH/CH_2Cl_2;

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 8.28 (d, 1H, *J* = 8.0 Hz), 7.46 (d, 1H, *J* = 7.5 Hz), 7.26 (t, 1H, *J* = 7.8 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 3.50 (m, 2H), 2.48 (m, 2H), 2.29-2.24 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 171.4, 138.2, 133.3, 129.1, 125.5, 124.6, 121.0, 43.6, 40.9, 22.6, 22.0, 19.1;

HRMS (ESI+)**:** *m/z* calc'd for $C_{13}H_{15}NNaO_3S^+$ $[M+Na]^+$: 288.0665, found: 288.0655.

Synthesis of (±)-(1*R*,2*S*)-methyl 2-((2-(methylthio)phenyl)carbamoyl)cyclobutanecarboxylate (S1)



Carboxylic acid **1** (2.06 g, 7.75 mmol, 1.0 equiv.) was dissolved in a 1:2 mixture of methanol and CH_2Cl_2 (30 mL). The solution was cooled to 0 °C and TMS-diazomethane (2 M in ether, 5.90 mL, 11.8 mmol, 1.5 equiv.) was added dropwise over 30 minutes via dropping funnel to maintain slow and steady bubbling of the reaction. After the addition bubbling ceased and the solution persisted yellow indicating the presence of unreacted TMS-diazomethane. When TLC analysis confirmed full conversion of the starting material, the reaction was quenched by dropwise addition of acetic acid, until the yellow colour disappeared and bubbling ceased. The solvent was removed under reduced pressure and crude **S1** was obtained as a white, amorphous solid. The crude material is usually taken on without further purification, but can be purified via flash chromatography (silica gel; 50% EtOAc/ Hexanes), giving the spectral information provided below.

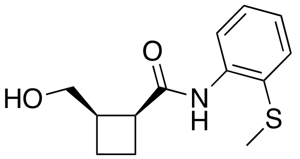
R$_f$: 0.42 in 50% EtOAc/ Hexanes;

^{1}H NMR (400 MHz, $CDCl_3$) 8.32 (m, 2H), 7.47 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.28 (td, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 7.05 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 3.64 (s, 3H), 3.50 (m, 2H), 2.51 (m, 2H), 2.38 (s, 3H), 2.27 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) 173.9, 171.0, 138.5, 133.2, 129.2, 125.1, 124.4, 120.6, 52.0, 43.8, 40.9, 22.5, 21.9, 19.1;

HRMS (ESI+)**:** *m/z* calc'd for $C_{14}H_{17}NO_3SNa^+$ $[M+Na]^+$: 302.0821, found 302.0811.

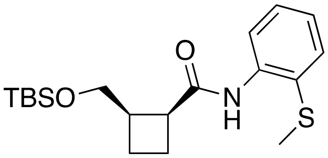
Synthesis of (±)-(1*S*,2*R*)-2-(hydroxymethyl)-*N*-(2-(methylthio)phenyl)cyclobutanecarboxamide (2)



A solution of crude ester **S1** in anhydrous THF (20 mL) was cooled to 0 °C. Lithium borohydride solution (2 M in THF, 5.80 mL, 11.6 mmol, 1.5 equiv.) was added dropwise over 30 minutes via syringe pump. The mixture was allowed to warm slowly to room temperature and was stirred overnight. The reaction mixture was cooled to 0 °C and quenched with methanol (10 mL), then acidified with HCl (3 M, 10 mL) and diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride (20 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. After purification by flash chromatography (silica gel; gradient 40-75% EtOAc/Hexanes), product **2** was obtained as an oil (1.40 g, 70%).

R_f: 0.45 in 50% EtOAc/ Hexanes;
^{1}H NMR (400 MHz, $CDCl_3$) 8.37 (br s, 1H), 8.28 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 7.6 Hz), 7.30 (td, 1H, J_1 = 7.2 Hz, J_2 = 0.8 Hz), 7.09 (t, 1H, J = 7.2 Hz), 3.90 (m, 1H), 3.71 (m, 2H), 3.50 (q, 1H, J = 8.8 Hz), 2.90 (br s, 1H), 2.46 (m, 1H), 2.38 (s, 3H), 2.30 (m, 1H), 2.16 (m, 1H), 1.77 (m, 1H);
^{13}C NMR (100 MHz, $CDCl_3$) 173.3, 137.8, 132.8, 128.9, 125.9, 124.9, 121.1, 63.9, 43.2, 40.5, 23.2, 20.6, 18.9;
HRMS (ESI+)**:** *m/z* calc'd for $C_{13}H_{17}NNaO_2S^+$ [M+Na]$^+$: 274.0878, found 274.0888.

Synthesis of (±)-(1*S*,2*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(2-(methylthio)phenyl) cyclobutanecarboxamide (3)



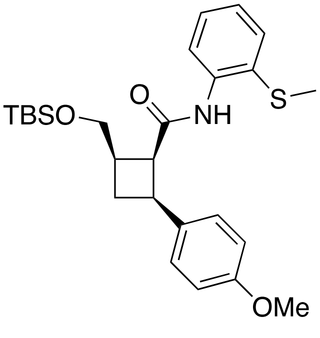
To a solution of alcohol **2** (1.40 g, 5.57 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at room temperature was added tert-butyldimethylsilyl chloride (4.20 g, 27.8 mmol, 5.0 equiv.), followed by DMAP (60.0 mg, 0.491 mmol, 0.1 equiv.) and imidazole (2.30 g, 33.8 mmol, 6.0 equiv.). A white precipitate formed within a few minutes and the mixture was stirred overnight. The mixture was diluted with MeOH, the flask fitted with a water-cooled reflux condenser, and heated to gentle reflux (40°C) for 30 minutes. The solvent and volatiles were removed under reduced pressure (heating on the rotary evaporator to 40 °C at approx. 20 mbar for 1.5 hours). The remaining white solid crude residue was adsorbed onto silica gel for purification by passing through a silica gel plug (75 mL dry silica), eluting first with hexanes (200 mL) and then 20% EtOAc/Hexanes until the product had finished eluting by TLC. This procedure yielded silyl ether product **3** (1.61 g, 78%).

R*f*: 0.48 in 20% EtOAc/ Hexanes;
^{1}H NMR (500 MHz, $CDCl_3$) 8.40-8.34 (m, 2H), 7.44 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 7.27 (td, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.04 (td, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 3.83 (dd, 1H, J_1 = 10.5 Hz, J_2 = 7.0 Hz), 3.77 (dd, 1H, J_1 = 10.5 Hz, J_2 = 6.0 Hz), 3.35 (q, 1H, J = 8.5 Hz), 2.86 (m, 1H), 2.49 (m, 1H), 2.36 (s, 3H), 2.11 (m, 2H), 1.84 (m, 1H), 0.78 (s, 9H), -0.05 (s, 3H), -0.07 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$) 171.7, 138.6, 132.7, 128.8, 125.2, 124.1, 120.6, 63.5, 42.4, 40.2, 26.0, 21.6, 21.2, 18.9, 18.4, -5.4;
HRMS (ESI+)**:** *m/z* calc'd for $C_{19}H_{31}NNaO_2SSi^+$ [M+Na]$^+$: 388.1737, found 388.1728.

Standard Procedure for C-H Arylation of 3.

A reaction tube was charged with $Pd(OAc)_2$ (0.1 equiv.), aryl iodide (2.0 equiv.), pivalic acid (1.0 equiv.), and silver carbonate (1.0 equiv.). A solution of substrate **3** (1.0 equiv.) in hexafluoroisopropanol (0.2 M) was added to the tube, then the tube was sealed and stirred in a 75 °C oil bath for 24 hours. The reaction was cooled to RT, diluted with DCM and passed through a Celite plug, washing with CH_2Cl_2 until the washes ran colorless. The solution was concentrated under reduced pressure, (then high vacuum for 15 min prior to crude 1H NMR spectroscopy, if desired), and concentrated onto silica gel for purification via flash chromatography to yield arylated product.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(4-methoxyphenyl)-*N*-(2-(methylthio)phenyl)cyclobutane-1-carboxamide (4)



Run 1: According to the Standard Procedure, substrate **3** (500 mg, 1.37 mmol, 1.0 equiv.) was reacted with 4-iodoanisole (641 mg, 2.74 mmol, 2.0 equiv.). $Pd(OAc)_2$ (31.4 mg, 0.140 mmol, 0.1 equiv.), silver carbonate (378 mg, 1.37 mmol, 1.0 equiv.), and pivalic acid (140 mg, 1.37 mmol,

1.0 equiv.) in hexafluoroisopropanol (6.8 mL). Flash chromatography (silica gel; 5% EtOAc /Petroleum ether) afforded product **4** (497 mg, 77% yield).

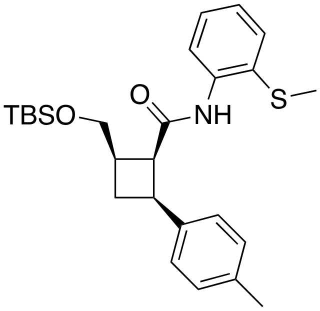
R*f*: 0.20 in 10% Acetone/ Petroleum ether;

^{1}H NMR (400 MHz $CDCl_3$) δ 8.04-8.02 (m, 2H), 7.37 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.17-7.13 (m, 3H), 6.98-6.94 (m, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 3.98 (dd, *J* = 8.5, 10.1 Hz, 1H), 3.84-3.77 (m, 2H), 3.71 (s, 3H), 2.48 (td, *J* = 2.6, 8.2 Hz, 1H), 2.90-2.79 (m, 1H), 2.67 (app q, *J* = 10.8 Hz, 1H), 2.37-2.27 (m, 1H), 2.23 (s, 3H), 0.82 (s, 9H), 0.00 (s, 3H), -0.05 (s, 3H);

^{13}C NMR (101 MHz $CDCl_3$) δ 169.8, 158.0, 138.3, 132.7, 132.5, 128.6, 128.2, 124.6, 123.9, 120.6, 113.5, 63.3, 55.2, 50.3, 39.0, 36.7, 28.9, 25.9, 18.3, -5.35, -5.37;

HRMS (ESI): *m/z* calc'd for $C_{26}H_{38}NO_3SSi^+$ $[M+H]^+$: 472.2336, found: 472.2334.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(2-(methylthio)phenyl)-4-(*p*-tolyl)cyclobutane-1-carboxamide (5)



Run 1: According to the Standard Procedure, substrate **3** (80.4 mg, 0.220 mmol, 1.0 equiv.) was reacted with 4-iodotoluene (95.9 mg, 0.440 mmol, 2.0 equiv.). $Pd(OAc)_2$ (4.90 mg, 0.0220 mmol, 0.1 equiv.), silver carbonate (60.6 mg, 0.220 mmol, 1.0 equiv.), and pivalic acid (22.5 mg, 0.220 mmol, 1.0 equiv.) in hexafluoroisopropanol (1.1 mL). Flash chromatography (silica gel; 5% EtOAc/ Petroleum ether) afforded product **5** (72.7 mg, 72% yield).

Run 2: According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 4-iodotoluene (71.0 mg, 0.320 mmol, 2.0 equiv.), $Pd(OAc)_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; 5% EtOAc/ Petroleum ether) afforded product **5** (44.3 mg, 59% yield).

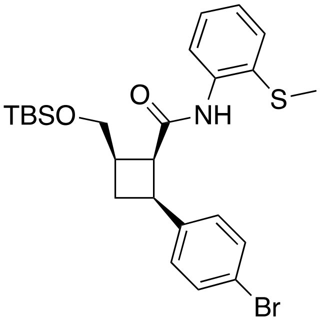
R*f*: 0.34 in 5% EtOAc/Petroleum ether;

^{1}H NMR (400 MHz CDCl$_3$) δ 8.15-8.03 (m, 2H), 7.38 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.17-7.10 (m, 3H), 7.06--6.95 (m, 2H), 3.97 (dd, *J* = 8.5, 10.1 Hz, 1H), 3.86-3.79 (m, 2H), 3.55 (td, *J* = 2.6, 10.7 Hz, 1H), 2.92-2.80 (m, 1H), 2.69 (app q, *J* = 10.8 Hz, 1H), 2.37-2.28 (m, 2H), 2.24 (s, 6H), 0.82 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H);

^{13}C NMR (101 MHz CDCl$_3$) δ 169.7, 137.6, 135.6, 132.9, 128.8, 128.6, 126.8, 123.8, 63.3, 50.2, 39.2, 36.8, 28.7, 25.9, 21.0, 18.8, 18.3, -5.4, -5.4;

HRMS (ESI): *m/z* calc'd for $C_{26}H_{38}NO_2SSi^+$ $[M+H]^+$: 456.2387, found: 456.2387.

Synthesis of (±)-(1*S*,2*S*,4*R*)-2-(4-bromophenyl)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(2-(methylthio)phenyl)cyclobutanecarboxamide (6)



According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 4-iodo-1-bromobenzene (90.5 mg, 0.320 mmol, 2.0 equiv.), Pd(OAc)$_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 5% to 10% Acetone/ Hexanes) afforded product **6** (59.0 mg, 71% yield). Recrystallisation from 10% acetone in hexanes afforded a white, feathery, crystalline solid.

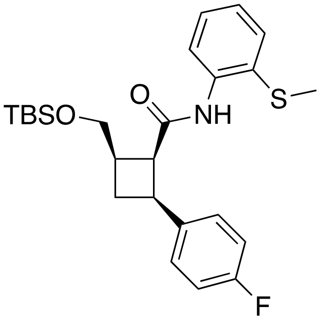
R$_f$: 0.33 in 10% Acetone/ Hexanes;

^{1}H NMR (500 MHz, CDCl$_3$) 8.10 (br s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.17 (td, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 3.94 (dd, J_1 = 10 Hz, J_2 = 9.0 Hz, 1H), 3.79 (m, 2H), 3.56 (td, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 2.88 (m, 1H), 2.66 (q, *J* = 10.5 Hz, 1H), 2.33 (qd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 2.27 (s, 3H), 0.81 (s, 9H), 0.00 (s, 3H), -0.06 (s, 3H);

^{13}C NMR (125 MHz, CDCl$_3$) 169.5, 139.9, 138.2, 132.7, 131.3, 128.8, 128.7, 125.4, 124.3, 120.8, 120.1, 63.3, 50.1, 38.9, 36.9, 28.6, 26.0, 18.9, 18.4, -5.2, -5.3;

HRMS (ESI+)**:** *m/z* calc'd for $C_{25}H_{35}BrNO_2SSi^+$ $[M+H]^+$: 520.1341, found 520.1361.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(4-fluorophenyl)-*N*-(2-(methylthio)phenyl)cyclobutane-1-carboxamide (7)



According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 4-fluoroiodobenzene (73.3 mg, 0.320 mmol, 2.0 equiv.), Pd(OAc)$_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; 6% EtOAc/ Petroleum ether) afforded product **7** (38.5 mg, 53% yield).

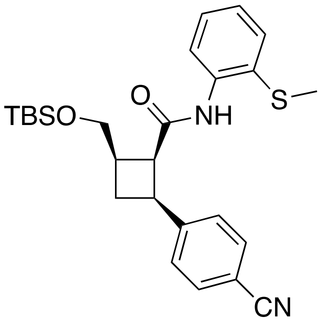
R$_f$: 0.33 in 10% EtOAc/ Petroleum ether;

^{1}H NMR (400 MHz CDCl$_3$) δ 8.07 (br s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.21-7.16 (m, 3H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.91 (t, *J* = 8.7 Hz, 2H), 3.96 (t, *J* = 9.4 Hz, 1H), 3.83-3.79 (m, 2H), 3.54 (td, *J* = 2.3, 8.2 Hz, 1H), 2.92-2.81 (m, 1H), 2.68 (app q, *J* = 10.8 Hz, 1H), 2.36-2.29 (m, 1H), 2.26 (s, 3H), 0.82 (s, 9H), 0.02 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (101 MHz CDCl$_3$) δ 169.7, 161.6 (d, *J* = 244 Hz), 138.2, 136.3 (d, *J* = 3.2 Hz), 132.7, 128.6 (d, *J* = 7.9 Hz), 124.2, 120.7, 115.0 (d, *J* = 21.2 Hz), 63.3, 50.4, 38.9, 36.8, 28.9, 26.0, 26.0, 18.9, 18.4, -5.2, -5.2.

HRMS (ESI): *m/z* calc'd for $C_{250}H_{34}FNO_2SSi^+$ [M+H]$^+$: 460.2136, found: 460.2126.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(4-cyanophenyl)-*N*-(2-(methylthio)phenyl)cyclobutane-1-carboxamide (8)



Run 1: According to the Standard Procedure, substrate **3** (82.0 mg, 0.220 mmol, 1.0 equiv.) was reacted with 4-iodobenzonitrile (101 mg, 0.440 mmol, 2.0 equiv.), $Pd(OAc)_2$ (4.90 mg, 0.0220 mmol, 0.1 equiv.), silver carbonate (60.6 mg, 0.220 mmol, 1.0 equiv.), and pivalic acid (22.5 mg, 0.220 mmol, 1.0 equiv.) in hexafluoroisopropanol (1.1 mL). Flash chromatography (silica gel; gradient 5% to 10% Acetone / Hexanes) afforded product **8** (69.6 mg, 68% yield).

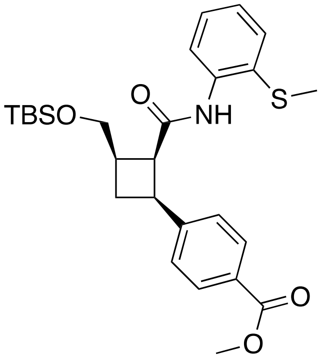
R_f: 0.24 in 10% Acetone/ Hexanes;

^{1}H NMR (400 MHz $CDCl_3$) δ 8.14 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.17-7.13 (m, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 3.92-3.84 (m, 2H), 3.76 (dd, *J* = 6.0, 10.2 Hz, 1H), 3.65-3.62 (m, 1H), 2.98-2.88 (m, 1H), 2.68 (app q, *J* = 10.7 Hz, 1H), 2.40-2.34 (m, 1H), 2.32 (s, 3H), 0.80 (s, 9H), -0.01 (s, 3H), -0.07 (s, 3H);

^{13}C NMR(101 MHz $CDCl_3$) δ 169.2, 146.9, 137.8, 132.4, 132.0, 128.6, 127.6, 125.3, 124.5, 120.7, 119.2, 109.9, 63.2, 50.1, 39.0, 36.8, 28.2, 26.0, 18.8, 18.4, -5.3, -5.3;

HRMS (ESI): *m/z* calcd for $C_{26}H_{35}N_2O_2SSi^+$ $[M+H]^+$: 467.2183, found: 467.1634.

Synthesis of (±)-methyl 4-((1*S*,2*S*,3*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-((2-(methylthio)phenyl)carbamoyl)cyclobutyl)benzoate (9)



According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with methyl-4-iodobenzoate (86.0 mg, 0.320 mmol, 2.0 equiv.). Pd(OAc)$_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 4% to 12% Acetone/ Petroleum ether) afforded product **9** (53 mg, 66% yield).

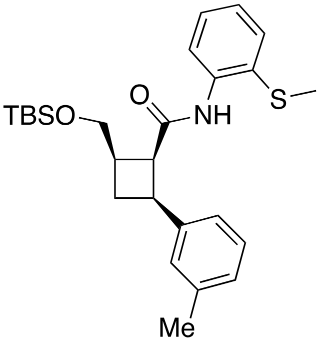
R$_f$: 0.14 in 10% Acetone/ Petroleum ether;

^{1}H NMR (400 MHz CDCl$_3$) δ 8.15 (br s, 1H), 8.04-7.98 (m, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 2H), 7.16-7.11 (m, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 3.95-3.87 (m, 2H), 3.85 (s, 3H), 3.78 (dd, *J* = 6.1, 10.4 Hz, 1H), 3.62 (td, *J* = 2.3, 8.2 Hz, 1H), 2.97-2.87 (m, 1H), 2.72 (app q, *J* = 10.7 Hz, 1H), 2.40-2.33 (m, 1H), 2.28 (s, 3H), 0.81 (s, 9H), 0.01 (s, 3H), -0.06 (s, 3H);

^{13}C NMR (101 MHz CDCl$_3$) δ 169.4, 167.2, 146.6, 138.2, 132.7, 129.6, 128.7, 128.0, 126.9, 124.3, 120.7, 63.3, 52.0, 50.3, 39.3, 37.0, 28.5, 26.0, 19.0, 18.4, -5.2, -5.3;

HRMS (ESI): *m/z* calcd for $C_{27}H_{38}NO_4SSi^+$ [M+H]$^+$: 500.2291; found: 500.2286.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(2-(methylthio)phenyl)-4-(*m*-tolyl)cyclobutane-1-carboxamide (10)



Run 1: According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 3-iodotoluene (42.0 μL, 0.32 mmol, 2.0 equiv.), Pd(OAc)$_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 5% to 12% Acetone/ Hexanes) afforded product **10** (45.7 mg, 61%).

Run 2: According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 3-iodotoluene (42.0 μL, 0.320 mmol, 2.0 equiv.), Pd(OAc)$_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 5% to 12% Acetone/ Hexanes) afforded product afforded **10** (49.6 mg, 66% yield).

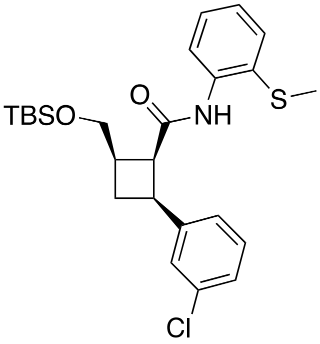
R*f*: 0.32 in 10% Acetone/ Petroleum ether;

^{1}H NMR (400 MHz $CDCl_3$) δ 8.07-8.02 (m, 2H), 7.37 (dd, *J* = 1.4, 7.7 Hz, 1H), 7.17-7.08 (m, 2H), 7.03-6.90 (m, 4H), 3.97 (dd, *J* = 8.4, 10.1 Hz, 1H), 3.82 (dd, *J* = 6.4, 10.1 Hz, 1H), 3.57 (td, *J* = 2.5, 8.4 Hz, 1H), 2.94-2.82 (m, 1H), 2.70 (app q, *J* = 10.8 Hz, 1H), 2.40-2.29 (m, 1H), 2.25 (s, 6H), 0.82 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H);

^{13}C NMR (101 MHz $CDCl_3$) δ 169.9, 140.6, 138.5, 137.7, 132.8, 128.7, 128.1, 127.8, 127.1, 124.1, 120.8, 63.4, 50.3, 39.5, 37.0, 28.8, 26.0, 21.6, 18.9, 18.4, -5.2, -5.2;

HRMS (ESI): *m/z* calcd for $C_{26}H_{38}NO_2SSi^+$ $[M+H]^+$: 456.2393, found: 456.2397.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(3-chlorophenyl)-*N*-(2-(methylthio)phenyl)cyclobutanecarboxamide (11)



According to the Standard Procedure, substrate **3** (548 mg, 1.50 mmol, 1.0 equiv.) was reacted with 3-chloroiodobenzene (715 mg, 3.00 mmol, 2.0 equiv.), $Pd(OAc)_2$ (33.7 mg, 0.150 mmol, 0.1 equiv.), silver carbonate (414 mg, 1.50 mmol, 1.0 equiv.), and pivalic acid (152 mg, 1.50 mmol, 1.0 equiv.) in hexafluoroisopropanol (7.5 mL). Flash chromatography (silica gel; gradient 5% to 10% Acetone / Hexanes) afforded product **11** (471 mg, 66% yield) as a yellow amorphous solid.

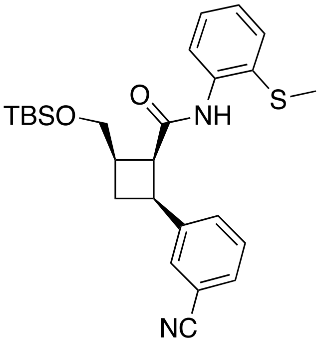
R*f*: 0.32 in 10% Acetone/ Hexanes;

^{1}H NMR (400 MHz, $CDCl_3$) 8.12 (br s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.13 (m, 5H), 6.99 (t, *J* = 7.6 Hz, 1H), 3.95 (t, *J* = 9.2 Hz, 1H), 3.80 (m, 2H), 3.57 (td, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 2.89 (m, 1H), 2.68 (q, *J* = 10.8 Hz, 1H), 2.36 (m, 1H), 2.29 (s, 1H), 0.82 (s, 9H), 0.00 (s, 3H), -0.05 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) 169.3, 142.8, 138.1, 134.0, 132.6, 129.3, 128.6, 127.1, 126.3, 125.0, 124.1, 120.7, 63.1, 50.0, 38.9, 36.8, 28.4, 25.9, 18.8, 18.2, -5.4;

HRMS (ESI+)**:** m/z calc'd for $C_{25}H_{34}ClNNaO_2SSi^+$ [M+Na]+: 498.1666, found: 498.1687.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(3-cyanophenyl)-*N*-(2-(methylthio)phenyl)cyclobutane-1-carboxamide (12)



According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 3-iodobenzonitrile (73.3 mg, 0.320 mmol, 2.0 equiv.). $Pd(OAc)_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 7% to 15% Acetone/ Hexanes) afforded product **12** (47.6 mg, 62% yield).

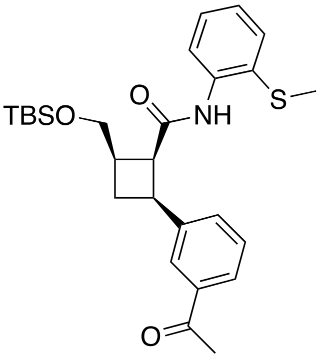
R_f: 0.11 in 10% Acetone/ Petroleum ether;

^{1}H NMR (400 MHz $CDCl_3$) δ 8.12 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.49 (s, 1H), 7.46-7.30 (m, 4H), 7.17-7.13 (m, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 3.94-3.81 (m, 2H), 3.78 (dd, *J* = 6.0, 10.3 Hz, 1H), 3.64-3.59 (m, 1H), 2.98-2.87 (m, 1H), 2.69 (app q, *J* = 10.7 Hz, 1H), 2.39-2.32 (m, 4H), 0.81 (s, 9H), 0.00 (s, 3H), -0.06 (s, 3H);

^{13}C NMR (101 MHz $CDCl_3$) δ 169.1, 142.4, 137.7, 132.2, 131.4, 130.6, 129.9, 128.8, 128.4, 124.4, 120.7, 119.1, 112.1, 63.1, 49.9, 38.5, 36.8, 28.0, 25.9, 18.3, -5.3, -5.4;

HRMS (ESI): *m/z* calcd for $C_{26}H_{34}N_2NaO_2SSi^+$ $[M+Na]^+$: 489.2002, found: 489.1990.

Synthesis of (±)-(1*S*,2*S*,4*R*)-2-(3-acetylphenyl)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(2-(methylthio)phenyl)cyclobutane-1-carboxamide (13)



Run 1: According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 3-iodoacetophenone (78.7 mg, 0.320 mmol, 2.0 equiv.). $Pd(OAc)_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 10% to 35% EtOAc/ Petroleum ether) afforded product **13** (40.7 mg, 53% yield).

Run 2: According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 3-iodoacetophenone (78.7 mg, 0.320 mmol, 2.0 equiv.). $Pd(OAc)_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 10% to 35% EtOAc/ Petroleum ether) afforded product **13** (39.4 mg, 50% yield).

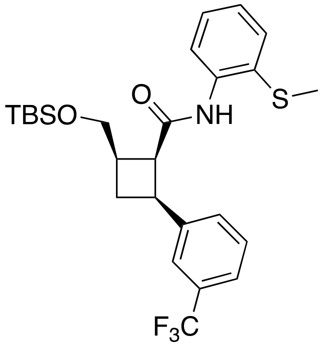
R*f*: 0.17 in 10% EtOAc/ Petroleum ether;

^{1}H NMR (400 MHz $CDCl_3$) δ 8.18 (s, 1H), 8.00 (d *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.38-7.31 (m, 2H), 7. 15-7.11 (m, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 3.97-3.86 (m, 2H), 3.80 (dd, *J* = 6.3, 10.3 Hz, 1H), 3. 62 (td, *J* = 2.4, 8.3 Hz, 1H), 2.97-2.87 (m, 1H), 2.81-2.67 (m, 1H), 2.51 (s, 3H), 2.42-2.34 (m, 1H), 2.27 (s, 3H), 0.81 (s, 9H), 0.00 (s, 3H), -0.06 (s, 3H);

^{13}C NMR (101 MHz $CDCl_3$) δ 198.5, 169.6, 141.6, 138.2, 137.0, 132.7, 131.8, 128.7, 128.4, 126.8, 126.4, 124.2, 120.6, 63.3, 50.2, 39.2, 37.0 28.6, 26.8, 26.0, 18.9, 18.4, -5.2, -5.3;

HRMS (ESI): *m/z* calcd for $C_{27}H_{37}NNaO_3SSi^+$ $[M+Na]^+$: 506.2156, found: 506.2146.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(2-(methylthio)phenyl)-4-(3-(trifluoromethyl)phenyl)cyclobutane-1-carboxamide (14)



According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 1-iodo-3-(trifluoromethyl)benzene (89.0 mg, 0.320 mmol, 2.0 equiv.), $Pd(OAc)_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 7% to 15% Acetone/ Hexanes) afforded product **14** (42.4 mg, 51% yield).

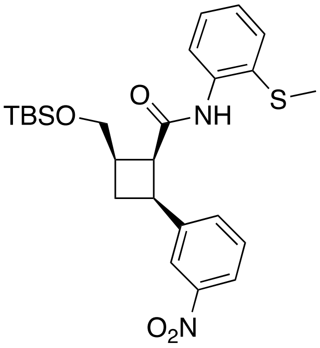
R_f : 0.23 in 10% Acetone/ Petroleum ether;

^{1}H NMR (400 MHz $CDCl_3$) δ 8.13 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.45-7.32 (m, 5H), 7.17-7.13 (m, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 3.95 (dd, *J* = 8.9, 10.3 Hz, 1H), 3.92-3.85 (m, 1H), 3.80 (dd, *J* = 6.0, 10.3 Hz, 1H), 3.61 (td, *J* = 2.4, 8.3 Hz, 1H), 2.97-2.87 (m, 1H), 2.42-2.33 (m, 1H), 2.26 (s, 3H), 0.81 (s, 9H), 0.00 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (101 MHz $CDCl_3$) δ 170.2, 141.7, 132.5, 130.3, 128.5, 124.2, 122.9 (q, *J* = 4.2 Hz), 122.8, 123.0 (q, *J* = 3.9 Hz), 120.6, 63.1, 50.1, 39.0, 36.8, 28.4, 25.9, 25.9, 18.7, 18.2, -5.4. The region between 136 and 120 ppm appears as complex overlapping quartets due to the presence of the CF_3 group. As a result, the peaks in this region are reported as observed.

HRMS (ESI): *m/z* calcd for $C_{26}H_{34}F_3NNaO_2SSi^+$ $[M+Na]^+$: 532.1924, found: 532.1902.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(2-(methylthio)phenyl)-4-(3-nitrophenyl)cyclobutane-1-carboxamide (15)



According to the Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 1-iodo-3-nitrobenzene (81.0 mg, 0.320 mmol, 2.0 equiv.), $Pd(OAc)_2$ (3.60 mg, 0.0160 mmol, 0.1 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; gradient 7% to 20% Acetone/ Hexanes) afforded product **15** (57.5 mg, 72% yield).

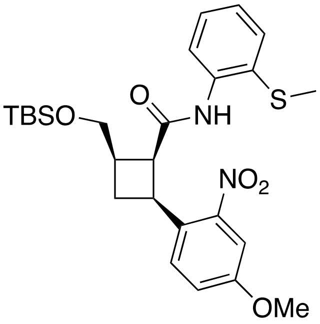
R*f*: 0.16 in 10% Acetone/ Petroleum ether;

^{1}H NMR (400 MHz $CDCl_3$) δ 8.18 (br s, 1H,), 8.05 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.39 (m, 2H), 7.13 (m, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 3.91 (m, 2H), 3.78 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.66 (td, *J* = 8.1, 2.3 Hz, 1H), 2.96 (m, 1H), 2.74 (q, *J* = 8 Hz, 1H), 2.40 (m, 1H), 2.31 (s, 3H), 0.81 (s, 9H), 0.00 (s, 3H), -0.06 (s, 3H);

^{13}C NMR (101 MHz $CDCl_3$) δ 169.2, 150.4, 148.2, 145.8, 143.3, 137.9, 133.1, 132.5, 129.0, 128.6, 124.5, 122.0, 121.3, 120.7, 63.2, 50.0, 38.7, 36.9, 28.3, 26.0, 18.8, 18.4, -5.3;

HRMS (ESI): *m/z* calcd for $C_{25}H_{35}N_2O_4SSi$ $[M+H]^+$: 486.2087; found: 486.2086.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(4-methoxy-2-nitrophenyl)-*N*-(2-(methylthio)phenyl)cyclobutane-1-carboxamide (16)



According to the Standard Procedure, substrate **3** (157 mg, 0.430 mmol, 1.0 equiv.) was reacted with 1-iodo-2-nitro-4-methoxybenzene (239 mg, 0.860 mmol, 2.0 equiv.), $Pd(OAc)_2$ (9.60 mg, 0.0430 mmol, 0.1 equiv.), silver carbonate (118 mg, 0.430 mmol, 1.0 equiv.), and pivalic acid (43.8 mg, 0.430 mmol, 1.0 equiv.) in hexafluoroisopropanol (2.1 mL). Flash chromatography (silica gel; 6% EtOAc / Petroleum ether) afforded product **16** (111 mg, 50% yield).

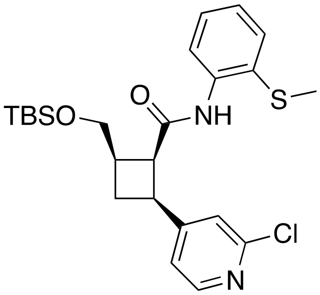
R*f*: 0.25 (6% Acetone in Hexane);

^{1}H NMR (400 MHz $CDCl_3$) δ 8.18 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.39-7.37 (m, 2H), 7.15-7.09 (m, 2H), 6.96 (td, *J* = 1.4, 7.6 Hz, 1H), 4.12-4.05 (m, 1H), 3.97-3.79 (m, 6H), 2.95-2.84 (m, 1H), 2.74 (app q, *J* = 10.6 Hz, 1H), 2.32-2.25 (m, 4H), 0.80 (s, 9H), 0.00 (s, 3H), -0.07 (s, 3H);

^{13}C NMR (101 MHz $CDCl_3$) δ 169.8, 158.4, 149.0, 138.4, 133.0, 131.4, 128.6, 127.9, 125.4, 124.1, 120.5, 119.7, 109.4, 63.4, 55.9, 50.8, 36.7, 36.5, 27.8, 26.0, 19.0, 18.4, -5.3, -5.3;

HRMS (ESI): *m/z* calcd for $C_{26}H_{37}N_2O_5SSi^+$ $[M+H]^+$: 517.2192; found: 517.2192.

Synthesis of (±)-(1*S*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(2-chloropyridin-4-yl)-*N*-(2-(methylthio)phenyl)cyclobutane-1-carboxamide (17)



Run 1: According to the Standard Procedure, substrate **3** (75.0 mg, 0.210 mmol, 1.0 equiv.) was reacted with 2-chloro-4-iodopyridine (101 mg, 0.420 mmol, 2.0 equiv.). $Pd(OAc)_2$ (4.70 mg, 0.0210 mmol, 0.1 equiv.), silver carbonate (57.9 mg, 0.210 mmol, 1.0 equiv.), and pivalic acid (21.5 mg, 0.210 mmol, 1.0 equiv.) in hexafluoroisopropanol (1 mL). Flash chromatography (silica gel; gradient 20% to 75% EtOAc/ Petroleum ether) afforded product **17** (58.5 mg, 58% yield).

Run 2: According to the Standard Procedure, substrate **3** (200 mg, 0.550 mmol, 1.0 equiv.) was reacted with 2-chloro-4-iodopyridine (263 mg, 1.10 mmol, 2.0 equiv.). $Pd(OAc)_2$ (12.3 mg, 0.0550 mmol, 0.1 equiv.), silver carbonate (152 mg, 0.550 mmol, 1.0 equiv.), and pivalic acid (56.2 mg, 0.550 mmol, 1.0 equiv.) in hexafluoroisopropanol (2.8 mL). Flash chromatography afforded **17** (154 mg, 58% yield).

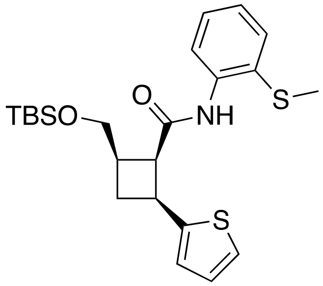
R*f*: 0.05 in 10% EtOAc/ Hexanes;

^{1}H NMR (400 MHz $CDCl_3$) δ 8.21 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.22-7.14 (m, 2H), 7.03 (d, *J* = 5.4 Hz, 2H), 3.87 (app t, *J* = 9.6 Hz, 1H), 3.80-3.72 (m, 2H), 3.66-3.62 (m, 1H), 2.99-2.89 (m, 1H), 2.64 (app q, *J* = 10.7 Hz, 1H), 2.34 (s, 3H), 0.80 (s, 9H), -0.01 (s, 3H), -0.07 (s, 3H);

^{13}C NMR (101 MHz $CDCl_3$) δ 168.8, 153.9, 151.5, 149.2, 137.6, 132.3, 128.5, 124.5, 122.5, 120.8, 120.7, 63.0, 49.7, 37.8, 36.9, 27.7, 25.8, 18.7, 18.2, -5.4, -5.3;

HRMS (ESI): *m/z* calc'd for $C_{24}H_{34}ClN_2O_2SSi^+$ $[M+H]^+$: 477.1793, found: 477.1790.

Synthesis of (±)-(1*R*,2*R*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(2-(methylthio)phenyl)-4-(thiophen-2-yl)cyclobutane-1-carboxamide (18)



According to a modified Standard Procedure, substrate **3** (60.0 mg, 0.160 mmol, 1.0 equiv.) was reacted with 2-iodothiophene (177 μL, 1.6 mmol, 10.0 equiv.), $Pd(OAc)_2$ (5.40 mg, 0.0240 mmol, 0.15 equiv.), silver carbonate (44.1 mg, 0.160 mmol, 1.0 equiv.), and pivalic acid (16.4 mg, 0.160 mmol, 1.0 equiv.) in hexafluoroisopropanol (0.8 mL). Flash chromatography (silica gel; 5% EtOAc/ Petroleum ether) afforded product **18** (19.4 mg, 27% yield).

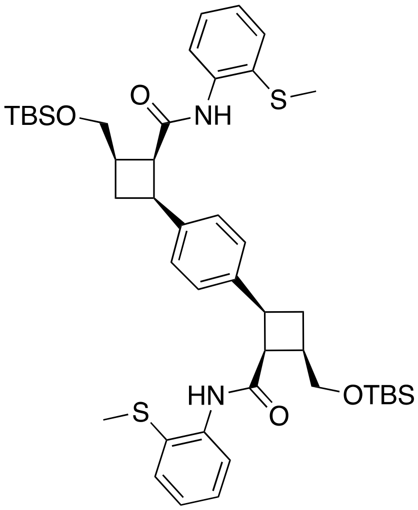
R$_f$: 0.35 in 10% EtOAc/ Petroleum ether;

^{1}H NMR (400 MHz CDCl$_3$) δ 8.21-8.05 (m, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.21-7.17 (m, 1H), 7.06 (d, *J* = 5.1 Hz, 1H), 6.98 (app t, *J* = 7.6 Hz, 1H), 6.92-6.91 (m, 1H), 6.86 (dd, *J* = 3.6, 4.9 Hz, 1H), 4.06-3.98 (m, 2H), 3.84 (dd, *J* = 6.3, 10.4 Hz, 1H), 3.51 (td, *J* = 2.4, 8.2 Hz, 1H), 2.89-2.79 (m, 1H), 2.69 (app q, *J* = 10.7 Hz, 1H), 2.49-2.41 (m, 1H), 2.24 (s, 3H), 0.82 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H);

^{13}C NMR(101 MHz CDCl$_3$) δ 169.4, 143.8, 138.5, 133.0, 128.8, 126.9, 125.1, 124.1, 123.9, 120.8, 63.2, 51.1, 37.2, 35.6, 31.8, 26.0, 19.0, 18.4, -5.2, -5.2;

HRMS (ESI): *m/z* calc'd for $C_{23}H_{34}NO_2S_2Si^+$ $[M+H]^+$: 448.1795, found: 448.1786.

Synthesis of (±)-(1*S*,1'*S*,2*R*,2'*R*,4*S*,4'*S*)-4,4'-(1,4-phenylene)bis(2-(((*tert*-butyldimethylsilyl)oxy) methyl)-*N*-(2-(methylthio)phenyl)cyclobutanecarboxamide) (19)



According to the Standard Procedure, substrate **3** (100 mg, 0.270 mmol, 1.0 equiv.) was reacted with 1,4-diiodobenzene (183 mg, 0.550 mmol, 2.0 equiv.), Pd(OAc)$_2$ (6.00 mg, 0.0270 mmol, 0.1 equiv.), silver carbonate (77.5 mg, 0.280 mmol, 1.0 equiv.), and pivalic acid (28.2 mg, 0.280 mmol, 1.0 equiv.) in hexafluoroisopropanol (1.4 mL). Flash chromatography (silica gel; gradient 5% to 15% Acetone/ Hexanes) afforded product **19** (32.8 mg, 33% yield) as a yellow amorphous solid.

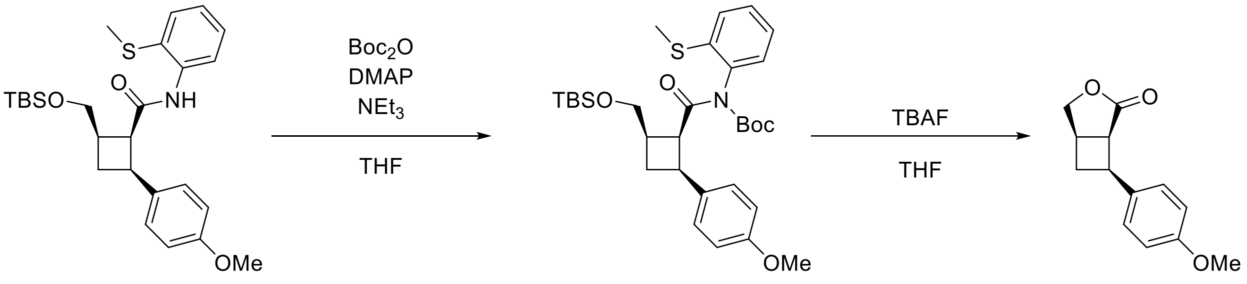
R$_f$: 0.24 in 10% Acetone/ Hexanes;

^{1}H NMR (500 MHz, CDCl$_3$) 8.12-7.92 (m, 4H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.11 - 7.07 (m, 6H), 6.94 (t, *J* = 7.0 Hz, 2H), 3.93 (t, *J* = 8.5 Hz, 2H), 3.75 (m, 4H), 3.50 (app. sept, *J* = 4.0 Hz, 2H), 2.82 (m, 2H), 2.63 (m, 2H), 2.25 (m, 2H), 2.19 (s, 6H), 0.80 (br s, 18H), -0.02 (s, 6H), -0.07 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) 169.9, 138.5, 138.4, 132.9, 128.8, 126.9, 124.9, 123.9, 120.8, 63.4, 50.3, 39.3, 37.0, 28.9, 26.0, 19.0, 18.4, -5.2, -5.3;

HRMS (ESI+)**:** m/z calc'd for $C_{44}H_{65}N_2O_4S_2Si_2^+$ $[M+H]^+$: 805.3924, found: 805.3952.

Synthesis of (±)-(1*S*,5*R*,7*S*)-7-(4-methoxyphenyl)-3-oxabicyclo[3.2.0]heptan-2-one (20)



4 **S2** **20**

A reaction tube was charged with **4** (226 mg, 0.480 mmol, 1.0 equiv.) in THF (5 mL) and to this was added Boc_2O (210 mg, 0.960 mmol, 2.0 equiv.), DMAP (5.8 mg, 0.0480 mmol, 0.1 equiv.) and triethylamine (133 µL, 0.960 mmol, 2.0 equiv.). The reaction tube was sealed and heated to 70 °C overnight, then the tube was cooled to room temperature and concentrated *in vacuo*. Flash chromatography (silica gel; 5% EtOAc/ Hexanes) afforded Boc-protected intermediate **S2** (268 mg).

To a solution of **S2** (268 mg, 0.470 mmol, 1.0 equiv.) in THF (25 mL) at 0 °C was added tetrabutylammonium fluoride solution (0.510 mL of 1M solution in THF, 0.510 mmol, 1.1 equiv.). The reaction was allowed to warm to room temperature and stirred for 48 hours. The reaction mixture was concentrated and purified via flash chromatography (silica gel; 10% Acetone/ Hexane) to afford **22** (115 mg, 95% yield).

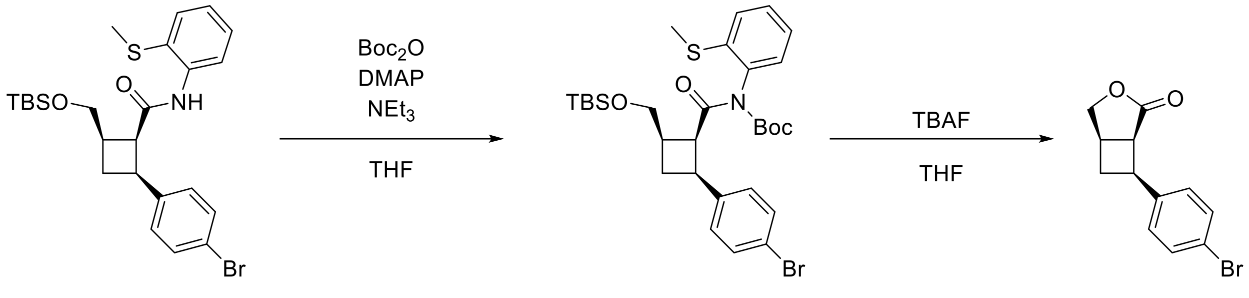
R_f: 0.11 in 10% Acetone/ Hexanes;

^{1}H NMR (400 MHz $CDCl_3$) δ 7.15 (d, *J* = 11.0 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.35-4.27 (m, 2H), 3.97 (s, 3H), 3.43 (dddd, *J* = 0.9, 5.5, 7.0, 9.6 Hz, 1H), 3.19-3.12 (m, 1H), 2.79-2.71 (m, 1H), 2.45-2.38 (m, 1H);

^{13}C NMR (101 MHz $CDCl_3$) δ 177.0, 158.8, 130.9, 128.6, 113.9, 73.9, 55.3, 44.5, 38.8, 31.4, 31.0;

HRMS (ESI): *m/z* calc'd for $C_{13}H_{15}O_3^+$ $[M+H]^+$: 219.1016, found: 219.1025.

Synthesis of (±)-(±)-(1S,5R,7S)-7-(4-bromophenyl)-3-oxabicyclo[3.2.0]heptan-2-one (21)



6 **S3** **21**

To a 0.1 M solution of **6** (0.201 g, 0.380 mmol, 1.0 equiv.) in acetonitrile (4 mL) was added DMAP (0.0199 g, 0.0163 mmol, 0.05 equiv.), Boc$_2$O (0.253 g, 1.16 mmol, 3.0 equiv.) and triethylamine (0.0466 g, 0.460 mmol, 1.2 equiv.). The mixture was stirred for 70 hours before being diluted with ethyl acetate (15 mL), acidified with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (10 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Flash chromatography (silica gel; gradient 5% to 10% EtOAc/ Hexanes) afforded intermediate **S3** (0.187 g) as a complex mixture of rotamers.

In an oven-dried flask, **S3** (0.0830 g, 0.130 mmol) was dissolved in THF (3 mL) and was stirred under nitrogen. The mixture was cooled to 0 °C and tetra-butyl ammonium fluoride (130 µL, 0.130 mmol) was added dropwise over 1 minute. The mixture was stirred at 0 °C for 1 hour and then allowed to warm to room temperature with stirring for a further 70 hours. The mixture purified by flash chromatography (silica gel; 10% EtOAc/ Hexanes followed by 5% EtOAc/ CH_2Cl_2 with 1% acetic acid) to yield the product, **21** (0.0269 g, 0.100 mmol, 77%), as a white, amorphous solid.

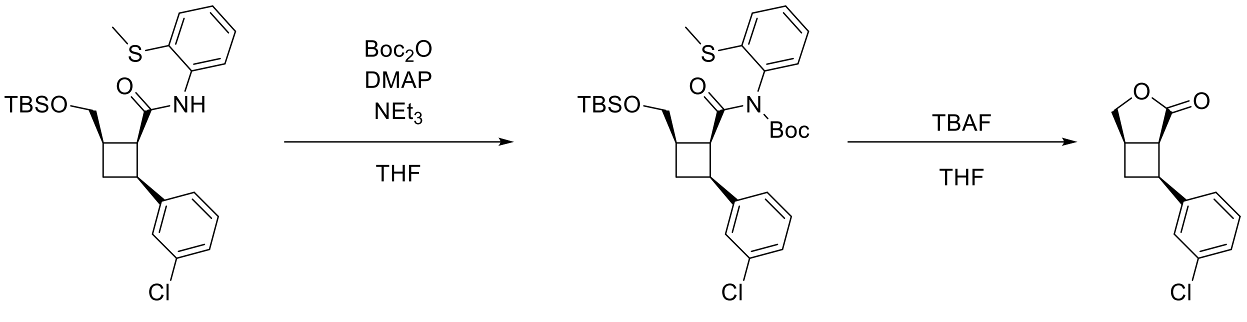
R*f*: 0.26 in 50% EtOAc/ Hexanes;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.33 (dd, J_1 = 9.2 Hz, J_2 = 5.6 Hz, 1H), 4.27 (d, *J* = 9.2 Hz, 1H), 3.98 (q, *J* = 9.6 Hz, 1H), 3.46 (app. td, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1H), 3.19 (quin, *J* = 6.8 Hz, 1H), 2.77 (m, 1H), 2.40 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 137.6, 131.4, 129.1, 121.1, 73.6, 43.9, 38.6, 31.0, 30.7;

HRMS (ESI+)**:** *m/z* calc'd for $C_{12}H_{11}BrO_2Na^+$ $[M+Na]^+$: 288.9840, found: 288.9850.

Synthesis of (1S,5R,7S)-7-(3-chlorophenyl)-3-oxabicyclo[3.2.0]heptan-2-one (22)



11 **S4** **22**

To a 0.1 M solution of **11** (0.200 g, 0.420 mmol, 1.0 equiv.) in acetonitrile (4 mL) was added DMAP (0.0219 g, 0.180 mmol, 0.4 equiv.), Boc_2O (0.348 g, 1.59 mmol, 3.8 equiv.) and triethylamine (0.0542 g, 0.540 mmol, 1.3 equiv.). The mixture was stirred for 45 hours before being diluted with ethyl acetate (15 mL), acidified with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (40 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Flash chromatography (silica gel; 5% EtOAc/ Hexanes) afforded the intermediate **S4** (206 mg) as a complex mixture of rotamers.

In an oven-dried flask, **S4** (0.102 g, 0.180 mmol) was dissolved in THF (3 mL) and was stirred under nitrogen. The mixture was cooled to 0 °C and tetra-butyl ammonium fluoride (180 µL, 0.180 mmol) was added dropwise over 1 minute. The mixture was stirred at 0 °C for 1 hour and then allowed to warm to room temperature with stirring for a further 72 hours. The mixture was purified by flash chromatography (silica gel; 10% EtOAc/ Hexanes followed by 5% EtOAc/ CH_2Cl_2 with 1% acetic acid) to yield the product, **22** (281 mg, 0.130 mmol, 70%), as a colourless oil.

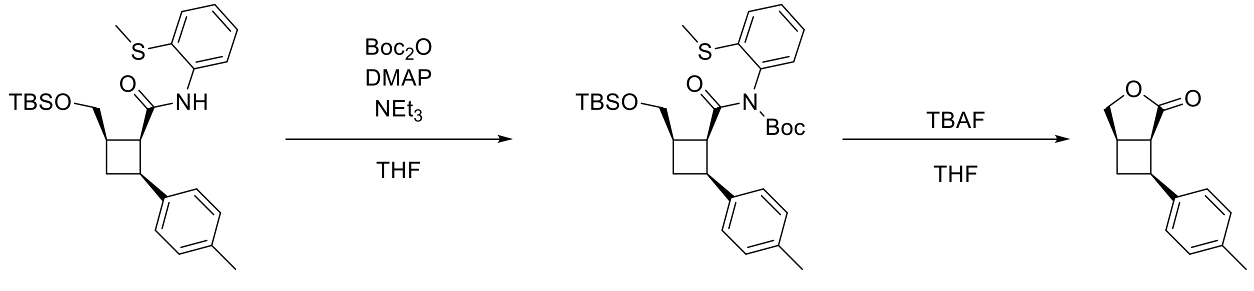
R*f*: 0.31 in 50% EtOAc/ Hexanes;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.14 (m, 4H), 4.37-4.28 (m, 2H), 3.97 (q, *J* = 9.6 Hz, 1H), 3.45 (m, 1H), 3.17 (quin.d, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 1H), 2.73 (m, 1H), 2.40 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 140.7, 134.2, 129.5, 127.5, 127.2, 125.6, 73.6, 44.0, 38.6, 31.1, 30.5;

HRMS (ESI+)**:** *m/z* calc'd for $C_{12}H_{11}ClO_2Na^+$ $[M+Na]^+$:245.0345, found: 245.0345.

Synthesis of (±)-(1*S*,5*R*,7*S*)-7-(*p*-tolyl)-3-oxabicyclo[3.2.0]heptan-2-one (23)



5 **S5** **23**

A reaction tube was charged with **5** (72.0 mg, 0.160 mmol, 1.0 equiv.) in THF (4 mL) and to this was added Boc_2O (70.0 mg, 0.320 mmol, 2.0 equiv.), DMAP (4.00 mg, 0.0320 mmol, 0.1 equiv.) and triethylamine (46.0 μL, 0.320 mmol, 2.0 equiv.). The reaction tube was sealed and heated to 70 °C overnight, then the tube was cooled and recharged with more Boc_2O (150 mg, 0.687 mmol, 4.3 equiv.) and DMAP (10 mg, 0.0818 mmol, 2.5 equiv.), sealed and heated to 70 °C overnight. The mixture was cooled to room temperature and concentrated *in vacuo*. Flash chromatography (silica gel; 5% EtOAc/ Hexanes) afforded Boc-protected intermediate **S5** (45.2 mg) as a complex mixture of rotamers. Intermediate **S5** was dissolved in THF (3 mL), and TBAF (82.0 μL, 0.0820 mmol, 1.0 equiv.) was added and the reaction stirred at room temperature for 48 hours. The crude reaction was concentrated *in vacuo*. Flash chromatography (silica gel; gradient 20% to 100% EtOAc/ Hexanes) afforded lactone **23** (12.8 mg, 77% yield).

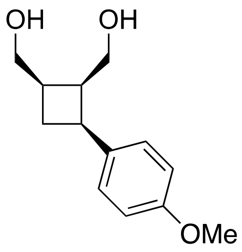
R_f: 0.66 in 50% EtOAc/ Hexanes;

^{1}H NMR (400 MHz $CDCl_3$) δ 7.15-7.10 (m, 4H), 4.35-4.27 (m, 2H), 3.99 (app q, *J* = 9.7 Hz, 1H), 3.47-3.43 (m, 1H), 3.20-3.13 (m, 1H), 2.79-2.70 (m, 1H), 2.48-2.41 (m, 1H), 2.31 (s, 3H);

^{13}C NMR (101 MHz $CDCl_3$) δ 176.9, 136.8, 135.7, 129.2, 127.3, 73.9, 44.3, 39.1, 31.1, 31.0, 21.2;

HRMS (ESI): *m/z* calc'd for $C_{13}H_{14}O_2Na^+$ $[M+Na]^+$: 225.0886, found: 225.0892.

Synthesis of (±)- ((1*R*,2*S*,3*S*)-3-(4-methoxyphenyl)cyclobutane-1,2-diyl)dimethanol (24)



Lactone **20** (100 mg, 0.460 mmol, 1.0 equiv.) was dissolved in THF (5.5 mL) and cooled to 0 °C. To this solution was added $LiAlH_4$ (20.9 mg, 0.550 mmol, 1.2 equiv.). The reaction was stirred for 10 minutes at 0 °C then warmed to room temperature and stirred for 1 hour. The mixture was diluted with Et_2O (5 mL) and cooled to 0 °C. Then, 50 μL of H_2O was added, followed by 50 μL of 3M NaOH, and 100 μL of H_2O and stirred for 15 minutes. A small amount of $MgSO_4$ was added to this slurry, which was then filtered through a pad of Celite, washing with Et_2O, and concentrated to afford **24** (102 mg, quant), which was used without further purification.

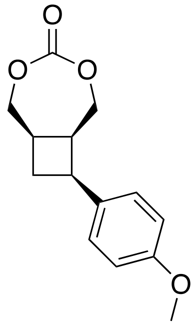
R*f*: 0.20 in 50% EtOAc/ Hexanes;

^{1}H NMR (400 MHz $CDCl_3$) δ 7.05 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 3.76-3.63 (m, 4H), 3.32 (dd, *J* = 4.4, 11.1 Hz, 1H), 3.00-2.91 (m, 3H), 2.83-2.73 (m, 1H), 2.27-2.09 (m, 2H);

^{13}C NMR (101 MHz $CDCl_3$) δ 158.1, 132.2, 128.3, 113.8, 63.3, 60.8, 55.4, 42.9, 36.7, 35.2, 25.8;

HRMS (ESI): *m/z* calc'd for $C_{13}H_{19}O_3^+$ $[M+H]^+$: 2223.1334, found: 223.1336.

Synthesis of (±)-(1*R*,7*S*,8*S*)-8-(4-methoxyphenyl)-3,5-dioxabicyclo[5.2.0]nonan-4-one (25)



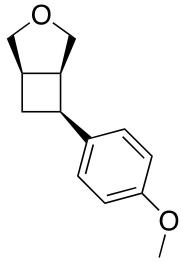
A round bottom flask under N_2 was charged with diol **24** (20.0 mg, 0.0900 mmol, 1.0 equiv.), pyridine (23.4 μL, 0.290 mmol, 3.2 equiv.), and THF (1 mL) and cooled to 0 °C. A solution of triphosgene (13.3 mg, 0.0450 mmol, 0.5 equiv.) in THF (1 mL) was added dropwise over 10 minutes. White precipitate formed during the addition of triphosgene, and the resulting mixture was allowed to warm to room temperature and stirred overnight. The crude reaction mixture was concentrated and purified by flash chromatography (silica gel; gradient 30% to 50% EtOAc/ Hexanes) to afford **25** (14.8 mg, 66% yield).

R*f*: 0.67 in 50% EtOAc/ Hexanes;

^{1}H NMR (400 MHz $CDCl_3$) δ 7.04 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.31-4.22 (m, 3H), 3.81-3.73 (m, 5H), 3.19-3.10 (m, 1H), 2.83-2.74 (m, 1H), 2.64 (app q, *J* = 10.8 Hz, 1H), 2.40-2.33 (m, 1H);

^{13}C NMR (101 MHz $CDCl_3$) δ 158.5, 155.0, 130.5, 127.9, 114.0, 70.9, 69.2, 55.4, 39.6, 36.7, 32.3, 25.4;

Synthesis of (±)- (1*R*,5*S*,6*S*)-6-(4-methoxyphenyl)-3-oxabicyclo[3.2.0]heptane (26)



To a solution of diol **24** (20.0 mg, 0.0900 mmol, 1.0 equiv.) in CH_2Cl_2 (0.45 mL) at 0 °C was added pyridine (36.0 μL, 0.45 mmol, 5.0 equiv.), followed by dropwise addition of trifluoromethanesulfonic anhydride (30.3 μL, 0.180 mmol, 2.0 equiv.). The resulting mixture was stirred for 5 minutes at 0 °C then warmed to room temperature and stirred overnight. The mixture was concentrated and purified by flash chromatography (silica gel; 50% EtOAc/ Hexanes) to afford **26** (15.6 mg, 85 % yield).

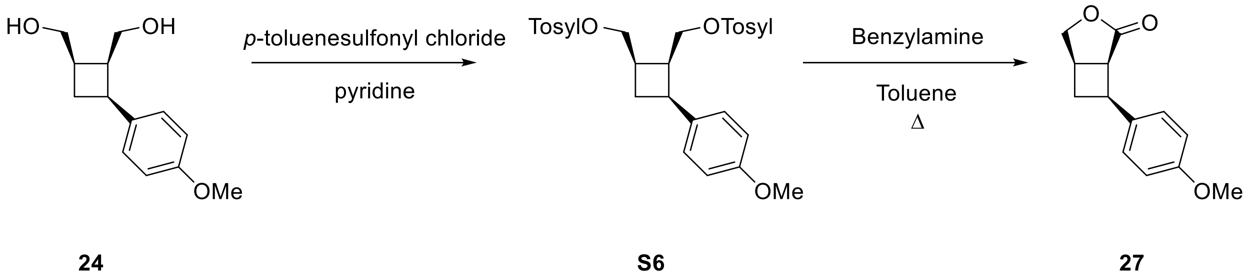
R*f*: 0.62 in 50% EtOAc/ Hexanes;

^{1}H NMR (400 MHz $CDCl_3$) δ 7.14 (d, *J* = 8.55 Hz, 2H), 6.86 (d, *J* = 8.55 Hz, 2H), 3.83 (d, *J* = 8.9 Hz, 1H), 3.79 (s, 3H), 3.73- 3.63 (m, 2H),, 3.42 (dd, *J* = 4.5, 8.9 Hz, 1H), 3.35 (dd, *J* = 6.8, 9.8 Hz, 1H), 3.15 (app q, *J* = 7.3 Hz, 1H), 3.03-2.96 (m, 1H), 2.47-2.38 (m, 1H), 2.10 (ddd, *J* = 6.8, 9.7, 11.9 Hz, 1H);

^{13}C NMR (101 MHz $CDCl_3$) δ 158.0, 133.4, 129.0, 113.8, 73.8, 68.9, 55.4, 44.1, 37.0, 35.7, 29.3;

HRMS (ESI): *m/z* calc'd for $C_{13}H_{17}O_2^+$ $[M+H]^+$: 205.1223, found: 205.1224.

Synthesis of (±)-((1*R*,2*S*,3*S*)-3-(4-methoxyphenyl)cyclobutane-1,2-diyl)bis(methylene) bis(4-methylbenzenesulfonate) (27)



To a solution of diol **24** (35.5 mg, 0.160 mmol, 1.0 equiv.) in pyridine (0.65 mL) at room temperature was added *p*-toluenesulfonyl chloride (200 mg, 1.04 mmol, 6.5 equiv.). The resulting slurry was stirred at room temperature for 24 hours, then partitioned between Et_2O and 3N HCl in a separatory funnel. The aqueous layer was extracted with EtOAc (3 x 10 mL), and combined organic layers were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (silica gel; gradient 20% to 67% EtOAc/ Hexanes) afforded di-tosylate **S6** (43.1 mg, 50% yield).

Benzylamine (70 μL) was added to a microwave reaction tube containing **S6** (20.0 mg, 0.0380 mmol, 1.0 equiv.) in toluene (25 μL) and heated to 185 °C for 1 hour in a Biotage microwave reactor. The mixture was then purified by Prep-TLC (30% EtOAc / Petroleum ether) to yield compound **27** (6.10 mg, 51% yield).

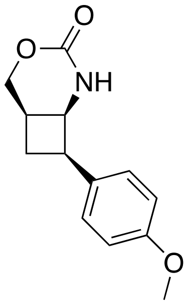
R_f: 0.37 in 20% EtOAc/ Petroleum ether;

^{1}H NMR (400 MHz $CDCl_3$) δ 7.31-7.21 (m, 7H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.67-3.48 (m, 3H), 3.03 (m, 1H), 2.82 (m, 2H), 2.61 (d, *J* = 10.3 Hz, 1H), 2.44-2.36 (m, 1H), 2.32-2.25 (m, 1H), 2.17-2.07 (m, 1H), 1.93-1.89 (m, 1H);

^{13}C NMR (101 MHz $CDCl_3$) δ 157.6, 129.2, 128.5, 128.0, 126.5, 113.3, 60.5, 59.9, 55.2, 54.8, 43.0, 37.7, 34.1, 30.9, 29.7;

HRMS (ESI): *m/z* calcd for $C_{20}H_{24}NO^+$ $[M+H]^+$: 294.1852, found: 294.1853.

Synthesis of (±)-(1*S*,6*R*,8*R*)-8-(4-methoxyphenyl)-4-oxa-2-azabicyclo[4.2.0]octan-3-one (28)



To a suspension of lactone **20** (20.0 mg, 0.0900 mmol, 1.0 equiv.) in MeOH (0.3 mL) was added hydrazine monohydrate (32.0 μL, 0.550 mmol, 6.0 equiv.). The reaction was stirred at room temperature overnight, then concentrated. The crude residue was redissolved 1:1 Et_2O : H_2O (0.5 mL) and cooled to 0 °C. To this solution was added sodium nitrite (9.30 mg, 0.135 mmol, 1.5

equiv.), followed by dropwise addition of 6M HCl (22.0 μL, 0.135 mmol, 1.5 equiv.). The clear, colourless mixture turned opaque and light yellow, and was stirred for 30 minutes. The mixture was diluted with $CHCl_3$, the layers separated, and the aqueous layer extracted with $CHCl_3$ (2 x 10 mL). Combined organics were washed with sat. $NaHCO_3$ (10 mL), then dried over Na_2SO_4. The dry solution in $CHCl_3$ was concentrated to half volume on a rotary evaporator, then diluted with toluene (5 mL), and reduced in volume again until most of the $CHCl_3$ had been evaporated, leaving only a toluene solution containing crude acyl azide. This solution was heated to 80 °C overnight, then concentrated *in vacuo*. Flash chromatography (silica gel; gradient 20% to 50% Acetone/ Hexanes) afforded **28** (10.8 mg, 51 % yield).

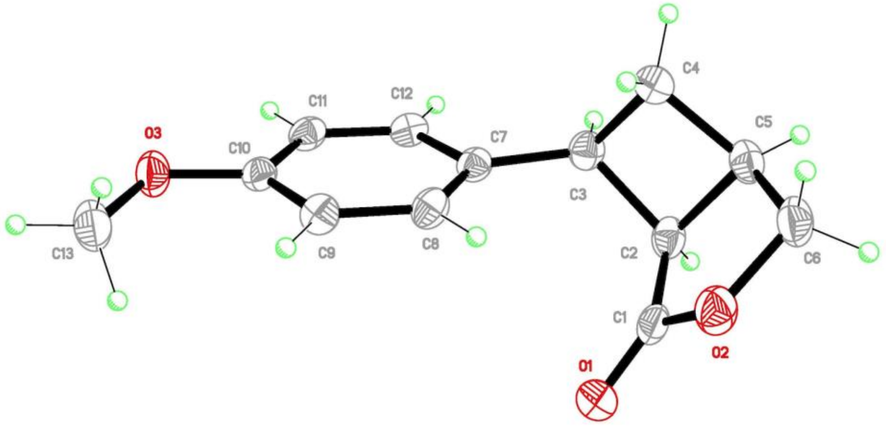
R_f: 0.35 in 50% Acetone/ Hexanes;

^{1}H NMR (400 MHz $CDCl_3$) δ 7.07 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.65 (br s, 1H), 4.26 (dd, *J* = 2.7, 11.7 Hz, 1H), 4.17 (dd, *J* = 1.2, 11.8 Hz, 1H), 4.11-4.08 (m, 1H), 3.79 (s, 3H), 3.73-3.66 (m, 1H), 2.92 (app q, *J* = 8.4 Hz, 1H), 2.63 (app q, *J* = 10.8 Hz, 1H), 2.43-2.35 (m, 1H);

^{13}C NMR (101 MHz $CDCl_3$) δ 178.1, 158.9, 154.6, 129.1, 114.4, 67.1, 55.4, 54.4, 42.7, 27.6, 25.1;

HRMS calc'd for $C_{13}H_{16}NO_3^+$ $[M+H]^+$: 234.1125, found: 234.1127.

5. CRYSTALLOGRAPHIC DATA for compound 20



Identification code	DS_B1_0032	**CCDC**	1986749
Empirical formula	$C_{14}H_{13}O_3$	**Formula weight (Da)**	218.24
Temperature (K)	180	**Wavelength (Å)**	1.54178
Crystal System	monoclinic	**Space group**	C 2/c
Unit cell lengths (Å)	a 17.1906(5) b 6.2367(2) c 21.3876(7)	**Unit cell angles (°)**	α 90 β 112.3105(14) γ 90
Volume (Å^3)	2121.36(12)	**Z**	8
Density calculated (gcm^{-3})	1.367	**Absorption coefficient (mm^{-1})**	0.788
F(000)	928	**Crystal size (mm^3)**	0.350 × 0.100 × 0.040
θ Range for data coll. (°)	5.56 to 66.69	**Completeness to θ = 66.699**	99.8%
Reflections collected	11799	**Independent reflections**	1872
Index ranges	$-20<h<19$, $-6<k<7$, $-25<l<25$	**Refinement method**	Full-matrix least-squares on F^2
Absorption correction	multi-scan	**Max./min. transmission**	0.969/0.770
Data/restraints/parameters	1872/0/146	**Largest diff. peak/hole (eÅ^{-3})**	0.154/-0.256
Goodness of fit F^2	1.072	**R indices (all data)**	R = 0.0461, wR = 0.0946
Final R indices [I > 2σ(I)]	R = 0.0366, wR = 0.0883		

6. COMPUTATIONAL ANALYSIS

General Details

Principal Moment of Inertia (PMI) analysis and physicochemical property predictions were performed using LLAMA (Lead-Likeness and Molecular Analysis; llama.leeds.ac.uk). This is open-access computational tool developed by Colomer *et al.*[1] Remaining properties were calculated with Molecular Operating Environment (MOE) software package version 2012.10 from the Chemical Computing Group. Merck molecular force field 94X (MMFF94x), an all-atom force field parameterised for small organic molecules with the Generalised Born solvation model, was used to minimise the energy potential of the library members. A LowModeMD search was employed for the conformation generation. Detailed settings for conformational search are listed below.

Rejection Limit	100
RMS Gradient	0.005
Iteration Limit	10000
MM Iteration Limit	500
RMSD Limit	0.15
Energy window	3
Conformation Limit	100

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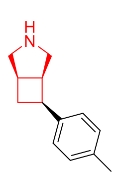
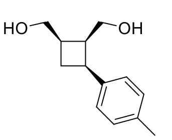
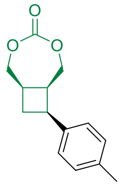
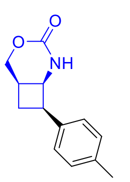
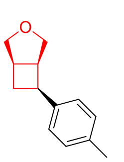
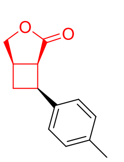
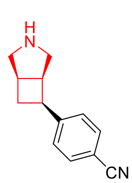
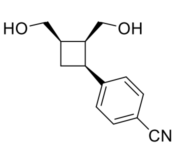
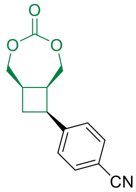
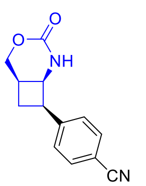
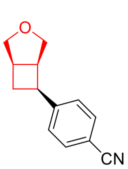
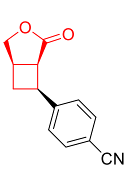
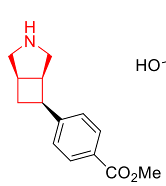
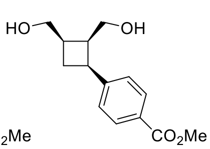
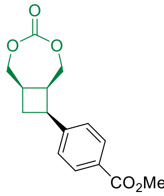
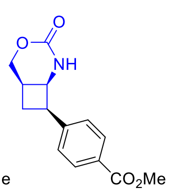
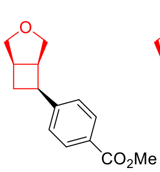
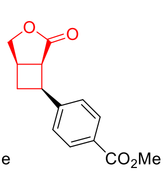
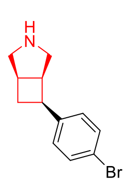
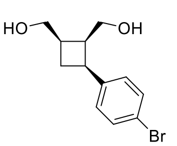
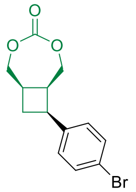
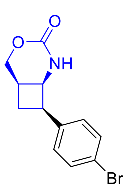
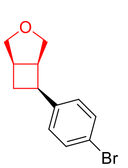
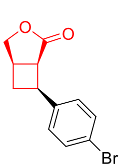
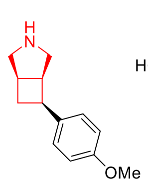
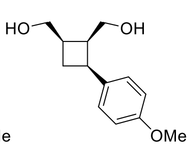
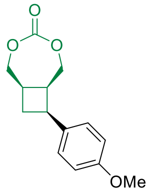
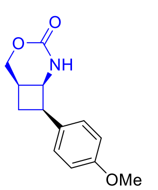
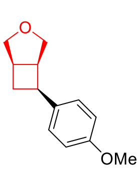
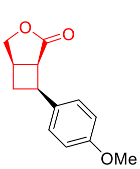
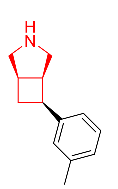
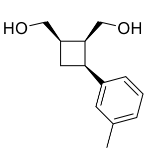
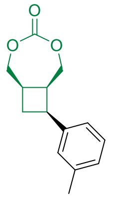
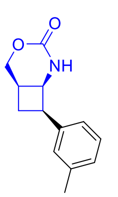
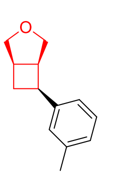
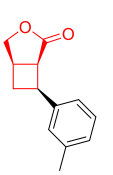
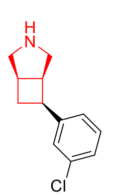
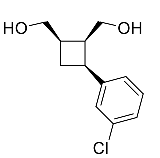
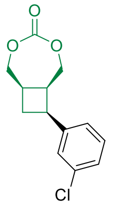
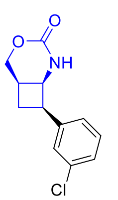
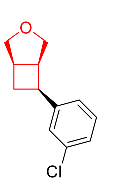
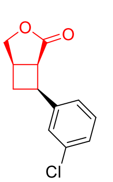
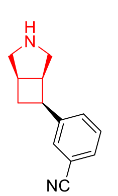
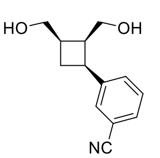
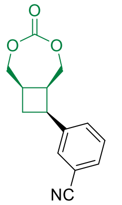
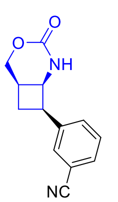
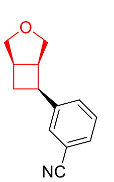
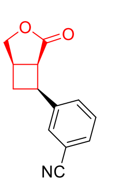
[1] I. Colomer, C.J. Empson, P. Craven, *et al.* Chem Commun, 52 (2016), pp. 7209-7212

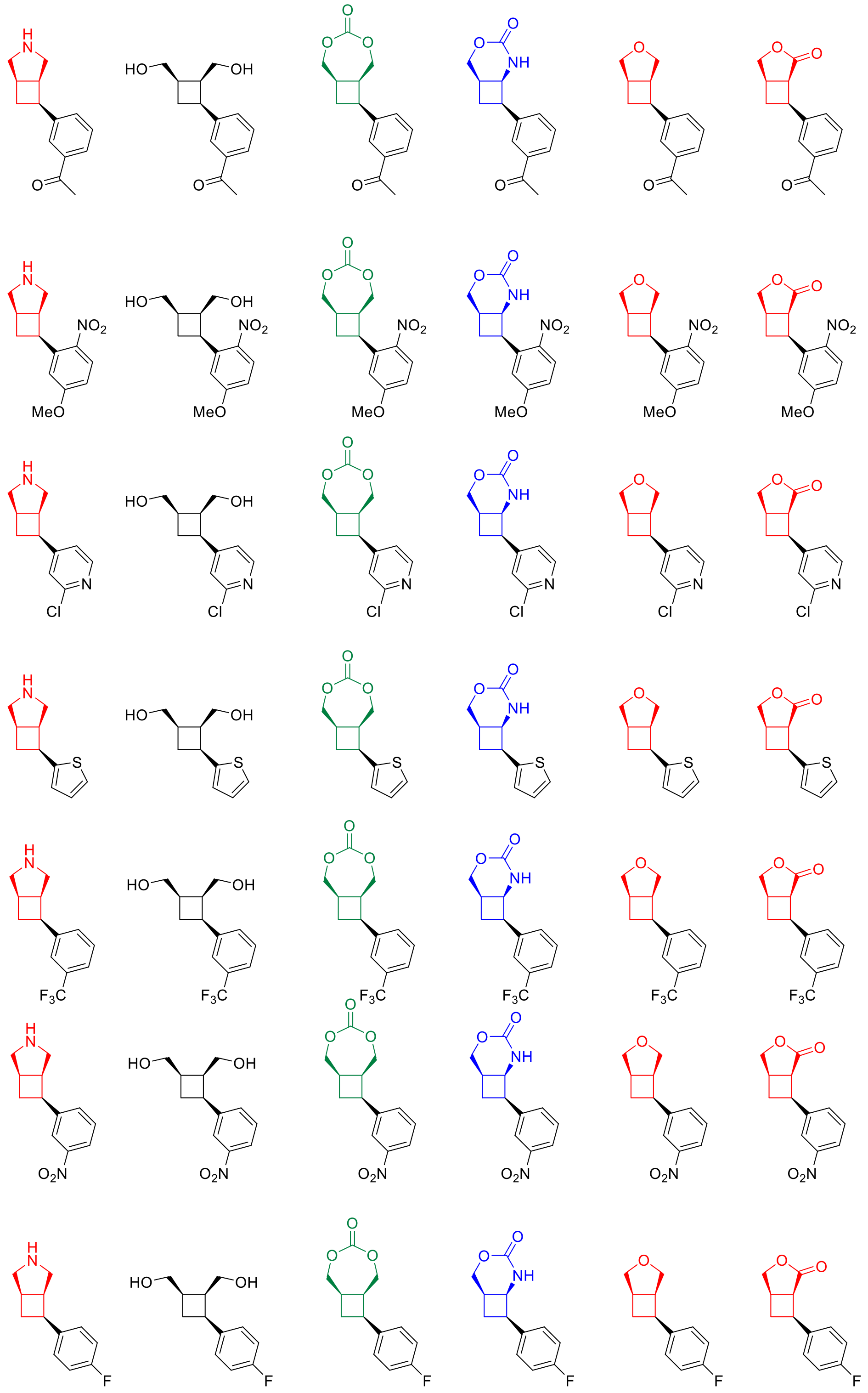


Figure S3. Full all-*syn* virtual library generated by enumerating the 15 products from the substrate scope (**4**-**19**) explorations and the six divergent modifications (**20**, **24**-**28**).

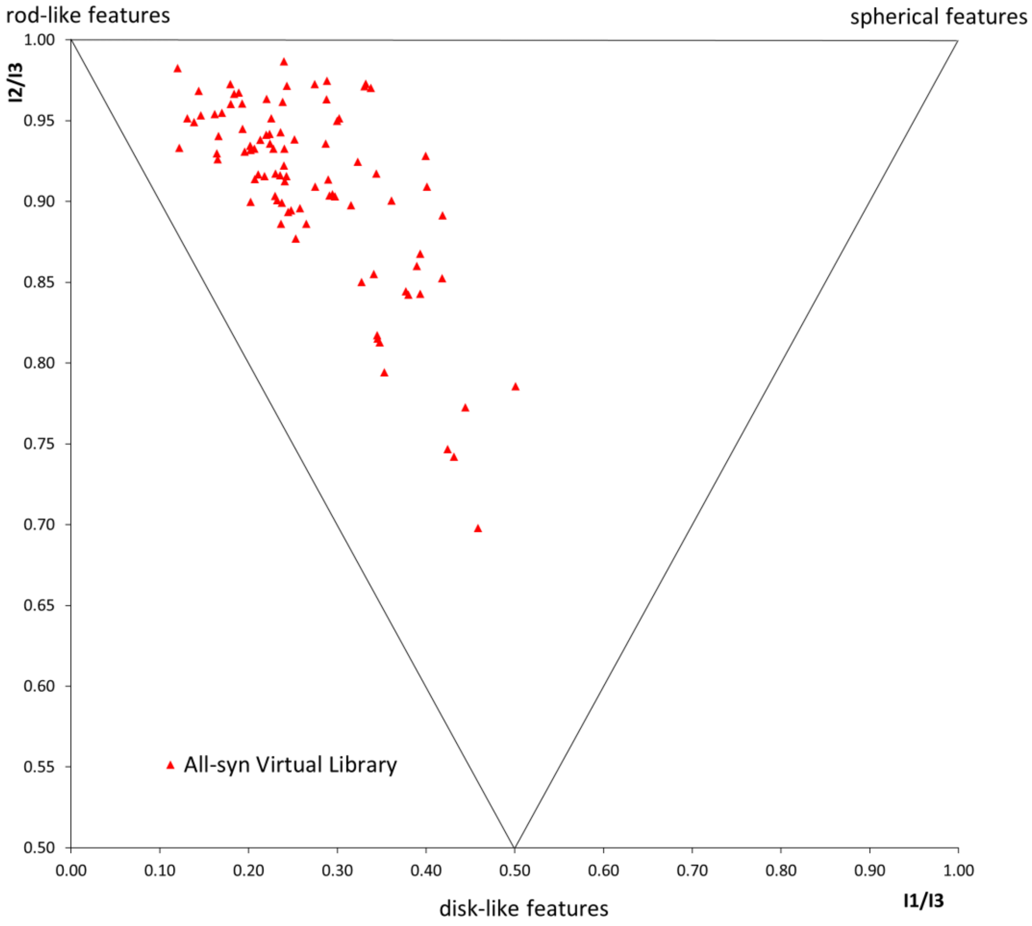
Table S1. Calculated npr1 and npr2 and summed values for the all-*syn* virtual library shown in Figure S2.

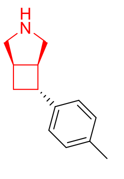
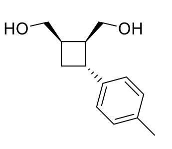
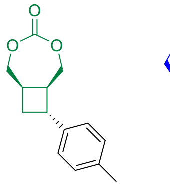
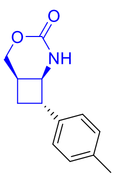
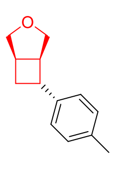
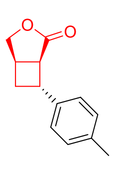
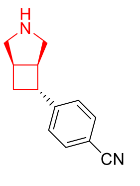
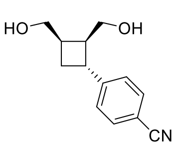
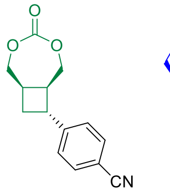
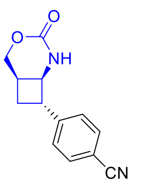
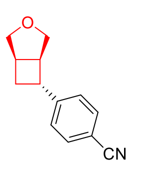
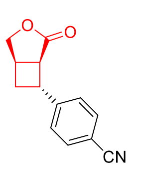
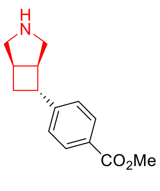
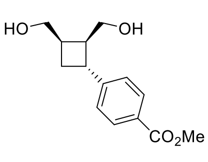
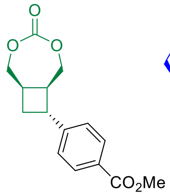
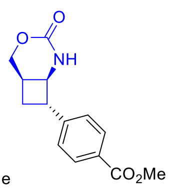
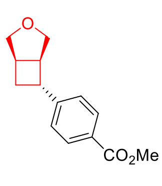
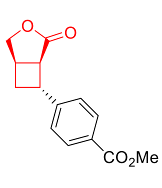
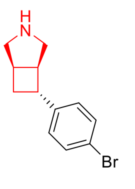
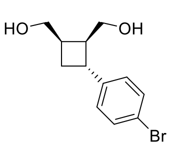
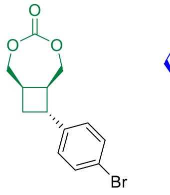
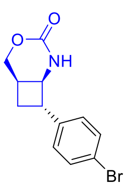
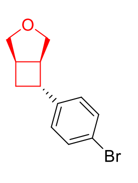
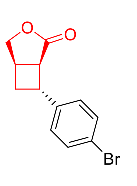
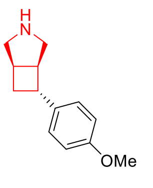
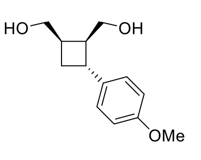
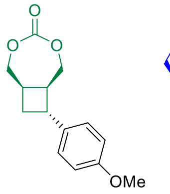
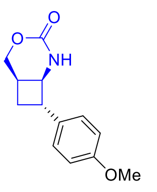
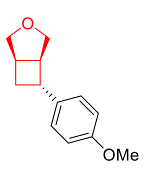
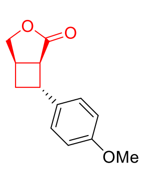
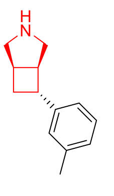
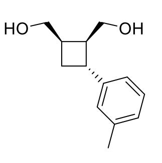
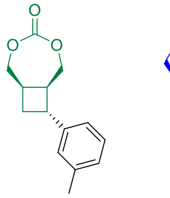
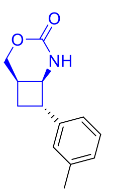
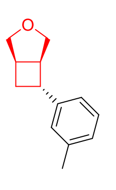
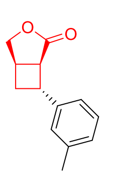
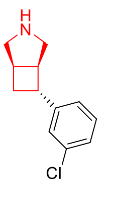
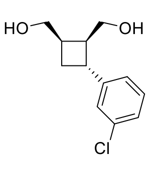
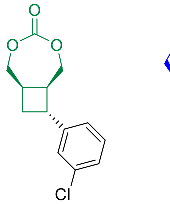
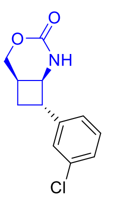
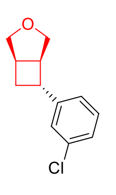
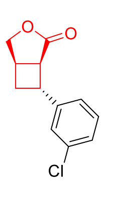
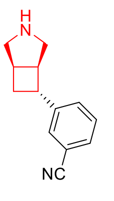
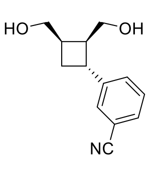
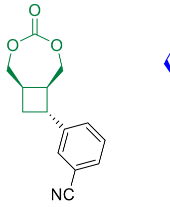
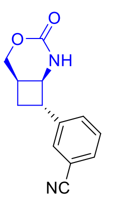
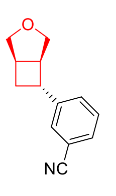
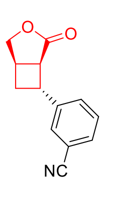
SMILES	npr1	npr2	npr1 + npr2
O=C1OC[C@H]2[C@@H]1[C@@H](c1ccc(C)cc1)C2	0.287	0.936	1.22
O=C1OC[C@H]2[C@H]([C@@H](c3ccc(C)cc3)C2)N1	0.291	0.904	1.19
O=C1OC[C@H]2[C@@H](c3ccc(C)cc3)C[C@H]2CO1	0.224	0.936	1.16
Cc1ccc([C@@H]2[C@H]3[C@@H](C2)COC3)cc1	0.240	0.922	1.16
Cc1ccc([C@@H]2[C@H]3[C@@H](C2)CNC3)cc1	0.220	0.964	1.18
OC[C@@H]1[C@H](CO)C[C@@H]1c1ccc(C)cc1	0.290	0.914	1.20
O=C1OC[C@H]2[C@@H]1[C@@H](c1ccc(C#N)cc1)C2	0.236	0.943	1.18
O=C1OC[C@H]2[C@H]([C@@H](c3ccc(C#N)cc3)C2)N1	0.243	0.916	1.16
O=C1OC[C@H]2[C@@H](c3ccc(C#N)cc3)C[C@H]2CO1	0.202	0.934	1.14
N#Cc1ccc([C@@H]2[C@H]3[C@@H](C2)COC3)cc1	0.196	0.931	1.13
N#Cc1ccc([C@@H]2[C@H]3[C@@H](C2)CNC3)cc1	0.180	0.973	1.15
OC[C@@H]1[C@H](CO)C[C@@H]1c1ccc(C#N)cc1	0.240	0.987	1.23
O=C(OC)c1ccc([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)cc1	0.193	0.945	1.14
O=C(OC)c1ccc([C@@H]2[C@@H]3NC(=O)OC[C@@H]3C2)cc1	0.193	0.961	1.15
O=C(OC)c1ccc([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)cc1	0.162	0.954	1.12
O=C(OC)c1ccc([C@@H]2[C@H]3[C@@H](C2)COC3)cc1	0.165	0.926	1.09
O=C(OC)c1ccc([C@@H]2[C@H]3[C@@H](C2)CNC3)cc1	0.144	0.969	1.11
O=C(OC)c1ccc([C@@H]2[C@H](CO)[C@H](CO)C2)cc1	0.207	0.933	1.14
Brc1ccc([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)cc1	0.146	0.953	1.10
Brc1ccc([C@@H]2[C@@H]3NC(=O)OC[C@@H]3C2)cc1	0.166	0.941	1.11
Brc1ccc([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)cc1	0.139	0.949	1.09
Brc1ccc([C@@H]2[C@H]3[C@@H](C2)COC3)cc1	0.131	0.951	1.08
Brc1ccc([C@@H]2[C@H]3[C@@H](C2)CNC3)cc1	0.120	0.982	1.10
Brc1ccc([C@@H]2[C@H](CO)[C@H](CO)C2)cc1	0.170	0.955	1.12
O=C1OC[C@H]2[C@@H]1[C@@H](c1cc(C)ccc1)C2	0.401	0.909	1.31
O=C1OC[C@H]2[C@H]([C@@H](c3cc(C)ccc3)C2)N1	0.344	0.917	1.26
O=C1OC[C@H]2[C@@H](c3cc(C)ccc3)C[C@H]2CO1	0.288	0.963	1.25
Cc1cc([C@@H]2[C@H]3[C@@H](C2)COC3)ccc1	0.341	0.855	1.20
Cc1cc([C@@H]2[C@H]3[C@@H](C2)CNC3)ccc1	0.275	0.909	1.18
OC[C@@H]1[C@H](CO)C[C@@H]1c1cc(C)ccc1	0.393	0.868	1.26
O(C)c1ccc([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)cc1	0.252	0.938	1.19
O(C)c1ccc([C@@H]2[C@H]3NC(=O)OC[C@H]3C2)cc1	0.122	0.933	1.05
O(C)c1ccc([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)cc1	0.213	0.938	1.15
O(C)c1ccc([C@@H]2[C@H]3[C@@H](C2)COC3)cc1	0.211	0.917	1.13
O(C)c1ccc([C@@H]2[C@H]3[C@@H](C2)CNC3)cc1	0.180	0.960	1.14

O(C)c1ccc([C@@H]2[C@H](CO)[C@H](CO)C2)cc1	0.228	0.933	1.16
Clc1cc([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)ccc1	0.380	0.842	1.22
Clc1cc([C@@H]2[C@@H]3NC(=O)OC[C@@H]3C2)ccc1	0.302	0.951	1.25
Clc1cc([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)ccc1	0.297	0.903	1.20
Clc1cc([C@@H]2[C@H]3[C@@H](C2)COC3)ccc1	0.348	0.813	1.16
Clc1cc([C@@H]2[C@H]3[C@@H](C2)CNC3)ccc1	0.345	0.817	1.16
Clc1cc([C@@H]2[C@@H](CO)[C@H](CO)C2)ccc1	0.236	0.886	1.12
O=C1OC[C@H]2[C@@H]1[C@@H](c1cc(C#N)ccc1)C2	0.418	0.853	1.27
O=C1OC[C@H]2[C@H]([C@@H](c3cc(C#N)ccc3)C2)N1	0.323	0.924	1.25
O=C1OC[C@@H]2[C@@H](c3cc(C#N)ccc3)C[C@@H]2CO1	0.224	0.942	1.17
N#Cc1cc([C@@H]2[C@H]3[C@@H](C2)COC3)ccc1	0.220	0.941	1.16
N#Cc1cc([C@@H]2[C@H]3[C@@H](C2)CNC3)ccc1	0.265	0.886	1.15
OC[C@@H]1[C@H](CO)C[C@@H]1c1cc(C#N)ccc1	0.240	0.933	1.17
O=C1OC[C@H]2[C@@H]1[C@@H](c1cc([C@H](O)C)ccc1)C2	0.393	0.843	1.24
O=C1OC[C@H]2[C@H]([C@@H](c3cc([C@H](O)C)ccc3)C2)N1	0.331	0.971	1.30
O=C1OC[C@H]2[C@@H](c3cc([C@@H](O)C)ccc3)C[C@H]2CO1	0.315	0.898	1.21
O[C@@H](C)c1cc([C@@H]2[C@H]3[C@@H](C2)COC3)ccc1	0.353	0.794	1.15
O[C@H](C)c1cc([C@@H]2[C@H]3[C@@H](C2)CNC3)ccc1	0.258	0.896	1.15
O[C@@H](C)c1cc([C@@H]2[C@H](CO)[C@H](CO)C2)ccc1	0.390	0.860	1.25
O=[N+]([O-])c1c([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)cc(OC)cc1	0.444	0.773	1.22
O=[N+]([O-])c1c([C@@H]2[C@@H]3NC(=O)OC[C@@H]3C2)cc(OC)cc1	0.501	0.786	1.29
O=[N+]([O-])c1c([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)cc(OC)cc1	0.327	0.850	1.18
O=[N+]([O-])c1c([C@@H]2[C@H]3[C@@H](C2)COC3)cc(OC)cc1	0.424	0.747	1.17
O=[N+]([O-])c1c([C@@H]2[C@H]3[C@@H](C2)CNC3)cc(OC)cc1	0.432	0.742	1.17
O=[N+]([O-])c1c([C@@H]2[C@H](CO)[C@H](CO)C2)cc(OC)cc1	0.458	0.698	1.16
Clc1nccc([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)c1	0.377	0.844	1.22
Clc1nccc([C@@H]2[C@@H]3NC(=O)OC[C@@H]3C2)c1	0.300	0.950	1.25
Clc1nccc([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)c1	0.295	0.905	1.20
Clc1nccc([C@@H]2[C@H]3[C@@H](C2)COC3)c1	0.345	0.815	1.16
Clc1nccc([C@@H]2[C@H]3[C@@H](C2)CNC3)c1	0.248	0.895	1.14
Clc1nccc([C@@H]2[C@H](CO)[C@H](CO)C2)c1	0.226	0.951	1.18
O=C1OC[C@H]2[C@@H]1[C@@H](c1sccc1)C2	0.361	0.901	1.26
O=C1OC[C@H]2[C@H]([C@@H](c3sccc3)C2)N1	0.419	0.891	1.31
O=C1OC[C@H]2[C@@H](c3sccc3)C[C@H]2CO1	0.230	0.903	1.13
[C@@H]1(c2sccc2)[C@H]2[C@@H](C1)COC2	0.332	0.973	1.31
[C@@H]1(c2sccc2)[C@H]2[C@@H](C1)CNC2	0.338	0.970	1.31
OC[C@@H]1[C@H](CO)C[C@@H]1c1sccc1	0.400	0.928	1.33
FC(F)(F)c1cc([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)ccc1	0.245	0.894	1.14

FC(F)(F)c1cc([C@@H]2[C@@H]3NC(=O)OC[C@@H]3C2)ccc1	0.275	0.973	1.25
FC(F)(F)c1cc([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)ccc1	0.238	0.962	1.20
FC(F)(F)c1cc([C@@H]2[C@H]3[C@@H](C2)COC3)ccc1	0.230	0.917	1.15
FC(F)(F)c1cc([C@@H]2[C@H]3[C@@H](C2)CNC3)ccc1	0.235	0.916	1.15
FC(F)(F)c1cc([C@@H]2[C@H](CO)[C@H](CO)C2)ccc1	0.202	0.900	1.10
O=[N+]([O-])c1cc([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)ccc1	0.253	0.877	1.13
O=[N+]([O-])c1cc([C@@H]2[C@@H]3NC(=O)OC[C@@H]3C2)ccc1	0.288	0.975	1.26
O=[N+]([O-])c1cc([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)ccc1	0.243	0.972	1.21
O=[N+]([O-])c1cc([C@@H]2[C@H]3[C@@H](C2)COC3)ccc1	0.232	0.901	1.13
O=[N+]([O-])c1cc([C@@H]2[C@H]3[C@@H](C2)CNC3)ccc1	0.237	0.899	1.14
O=[N+]([O-])c1cc([C@@H]2[C@H](CO)[C@H](CO)C2)ccc1	0.207	0.914	1.12
Fc1ccc([C@@H]2[C@@H]3C(=O)OC[C@@H]3C2)cc1	0.218	0.916	1.13
Fc1ccc([C@@H]2[C@@H]3NC(=O)OC[C@@H]3C2)cc1	0.241	0.913	1.15
Fc1ccc([C@@H]2[C@H]3[C@@H](C2)COC(=O)OC3)cc1	0.202	0.932	1.13
Fc1ccc([C@@H]2[C@H]3[C@@H](C2)COC3)cc1	0.184	0.967	1.15
Fc1ccc([C@@H]2[C@H]3[C@@H](C2)CNC3)cc1	0.189	0.968	1.16
Fc1ccc([C@@H]2[C@H](CO)[C@H](CO)C2)cc1	0.164	0.930	1.09

Figure S4. PMI plot of all-*syn* virtual library (blue triangles).



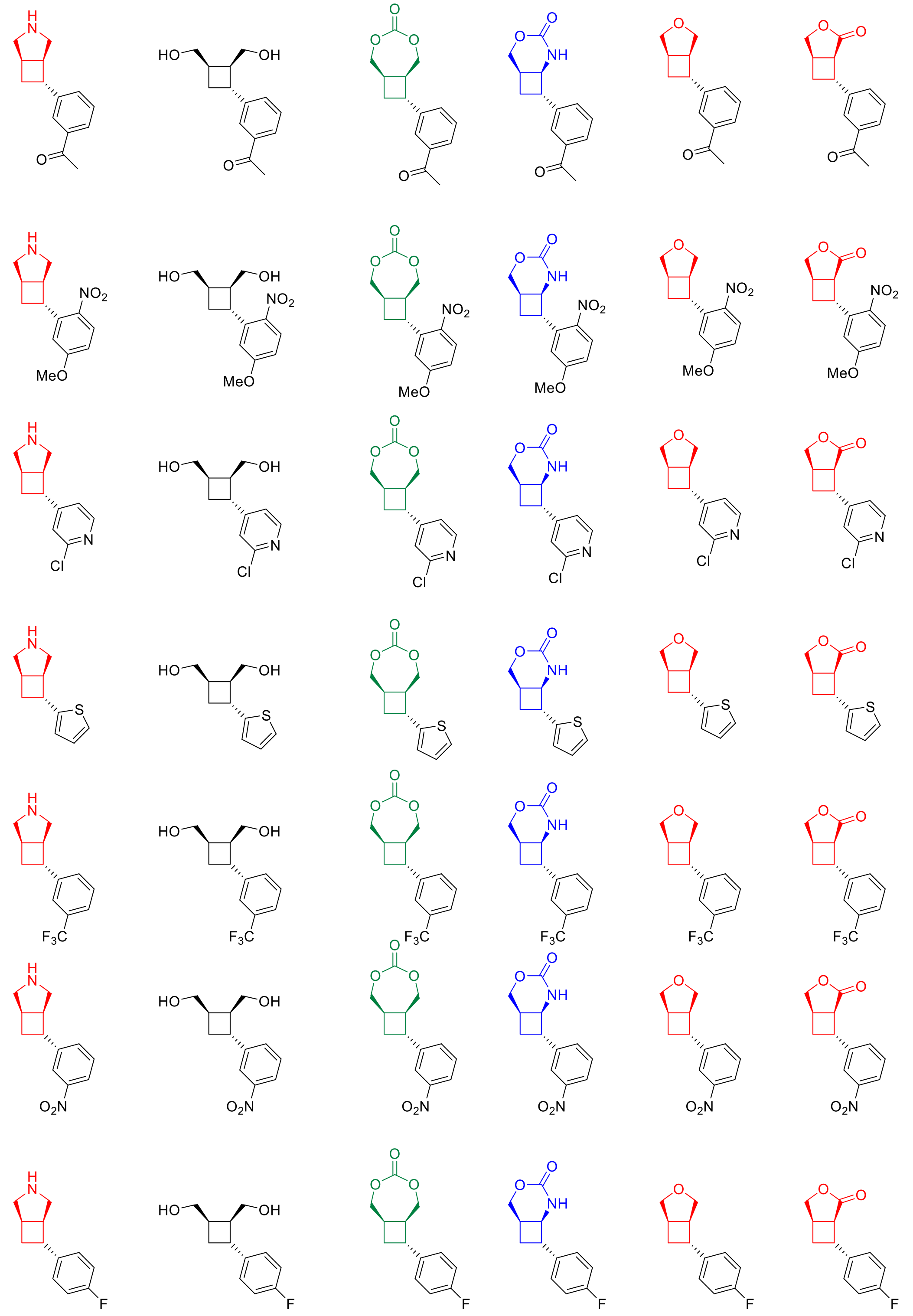


Figure S5. Full *anti*-epimer virtual library generated by enumerating the epimer variants of the 15 products from the substrate scope (**4**-**19**) explorations and the six divergent modifications (**20**, **24**-**28**).

Table S2. Calculated npr1 and npr2 and summed values for the *anti*-epimer virtual library shown in Figure S4.

SMILES	**npr1**	**npr2**	**npr1+npr2**
Cc1ccc(cc1)[C@@H]1C[C@H]2COC(=O)N[C@H]21	0.148	0.921	1.07
Cc1ccc(cc1)[C@@H]1C[C@H]2COC(=O)[C@H]21	0.167	0.927	1.09
Cc1ccc(cc1)[C@H]1C[C@H]2COC(=O)OC[C@H]21	0.224	0.936	1.16
Cc1ccc(cc1)[C@@H]1C[C@H]2CNC[C@H]21	0.137	0.956	1.09
N#Cc1ccc(cc1)[C@@H]1C[C@H]2COC(=O)[C@H]21	0.136	0.943	1.08
Cc1ccc(cc1)[C@@H]1C[C@@H](CO)[C@H]1CO	0.187	0.846	1.03
N#Cc1ccc(cc1)[C@@H]1C[C@H]2COC(=O)N[C@H]21	0.121	0.936	1.06
N#Cc1ccc(cc1)[C@@H]1C[C@H]2COC(=O)OC[C@H]21	0.133	0.974	1.11
N#Cc1ccc(cc1)[C@@H]1C[C@H]2COC[C@H]21	0.108	0.966	1.07
N#Cc1ccc(cc1)[C@@H]1C[C@H]2CNC[C@H]21	0.110	0.965	1.08
N#Cc1ccc(cc1)[C@@H]1C[C@@H](CO)[C@H]1CO	0.169	0.925	1.09
COC(=O)c1ccc(cc1)[C@@H]1C[C@H]2COC(=O)[C@@H]12	0.108	0.955	1.06
COC(=O)c1ccc(cc1)[C@@H]1C[C@H]2COC(=O)N[C@@H]12	0.098	0.945	1.04
COC(=O)c1ccc(cc1)[C@@H]1C[C@H]2COC(=O)OC[C@H]21	0.107	0.988	1.10
COC(=O)c1ccc(cc1)[C@@H]1C[C@H]2COC[C@@H]12	0.089	0.964	1.05
COC(=O)c1ccc(cc1)[C@@H]1C[C@H]2CNC[C@H]21	0.090	0.963	1.05
COC(=O)c1ccc(cc1)[C@@H]1C[C@@H](CO)[C@H]1CO	0.149	0.932	1.08
O=C1OC[C@@H]2C[C@H]([C@H]12)c1ccc(Br)cc1	0.091	0.962	1.05
O=C1N[C@H]2[C@@H](C[C@H]2CO1)c1ccc(Br)cc1	0.081	0.960	1.04
O=C1OC[C@H]2[C@@H](C[C@H]2CO1)c1ccc(Br)cc1	0.092	0.982	1.07
Brc1ccc(cc1)[C@@H]1C[C@H]2COC[C@H]21	0.072	0.978	1.05
Brc1ccc(cc1)[C@@H]1C[C@H]2CNC[C@H]21	0.073	0.978	1.05
OC[C@@H]1C[C@H]([C@@H]1CO)c1ccc(Br)cc1	0.122	0.934	1.06
Cc1cc(ccc1)[C@@H]1C[C@H]2COC(=O)[C@H]21	0.230	0.904	1.13
Cc1cc(ccc1)[C@@H]1C[C@H]2COC(=O)N[C@H]21	0.190	0.885	1.08
Cc1cc(ccc1)[C@@H]1C[C@H]2COC(=O)OC[C@H]21	0.205	0.985	1.19
Cc1cc(ccc1)[C@@H]1C[C@H]2COC[C@H]21	0.200	0.906	1.11
Cc1cc(ccc1)[C@@H]1C[C@H]2CNC[C@H]21	0.202	0.906	1.11
Cc1cc(ccc1)[C@@H]1C[C@@H](CO)[C@H]1CO	0.249	0.872	1.12
COc1ccc(cc1)[C@@H]1C[C@H]2COC(=O)[C@@H]12	0.134	0.940	1.07
COc1ccc(cc1)[C@@H]1C[C@H]2COC(=O)N[C@@H]12	0.123	0.937	1.06
COc1ccc(cc1)[C@@H]1C[C@H]2COC(=O)OC[C@H]21	0.126	0.972	1.10
COc1ccc(cc1)[C@@H]1C[C@H]2COC[C@@H]12	0.107	0.963	1.07
COc1ccc(cc1)[C@@H]1C[C@H]2CNC[C@H]21	0.109	0.963	1.07
COc1ccc(cc1)[C@@H]1C[C@@H](CO)[C@H]1CO	0.161	0.925	1.09

O=C1OC[C@@H]2C[C@H]([C@H]12)c1cc(Cl)ccc1	0.225	0.891	1.12
O=C1N[C@H]2[C@@H](C[C@H]2CO1)c1cc(Cl)ccc1	0.183	0.898	1.08
O=C1OC[C@H]2[C@@H](C[C@H]2CO1)c1cccc(Cl)c1	0.214	0.939	1.15
Clc1cc(ccc1)[C@@H]1C[C@H]2COC[C@H]21	0.205	0.881	1.09
Clc1cc(ccc1)[C@@H]1C[C@H]2CNC[C@H]21	0.208	0.880	1.09
OC[C@@H]1C[C@H]([C@@H]1CO)c1cccc(Cl)c1	0.288	0.884	1.17
N#Cc1cccc(c1)[C@@H]1C[C@H]2COC(=O)[C@H]21	0.238	0.890	1.13
N#Cc1cccc(c1)[C@@H]1C[C@H]2COC(=O)N[C@H]21	0.193	0.887	1.08
N#Cc1cc(ccc1)[C@@H]1C[C@H]2COC(=O)OC[C@H]21	0.224	0.942	1.17
N#Cc1cccc(c1)[C@@H]1C[C@H]2COC[C@H]21	0.216	0.875	1.09
N#Cc1cccc(c1)[C@@H]1C[C@H]2CNC[C@H]21	0.219	0.873	1.09
N#Cc1cccc(c1)[C@@H]1C[C@@H](CO)[C@H]1CO	0.205	0.899	1.10
CC(=O)c1cc(ccc1)[C@@H]1C[C@H]2COC(=O)[C@H]21	0.233	0.881	1.11
CC(=O)c1cc(ccc1)[C@@H]1C[C@H]2COC(=O)N[C@H]21	0.184	0.887	1.07
CC(=O)c1cc(ccc1)[C@@H]1C[C@H]2COC(=O)OC[C@H]21	0.222	0.925	1.15
CC(=O)c1cccc(c1)[C@@H]1C[C@H]2COC[C@H]21	0.211	0.869	1.08
CC(=O)c1cccc(c1)[C@@H]1C[C@H]2CNC[C@H]21	0.219	0.861	1.08
CC(=O)c1cccc(c1)[C@@H]1C[C@@H](CO)[C@H]1CO	0.307	0.841	1.15
COc1cc([C@@H]2C[C@H]3COC(=O)[C@@H]23)c(cc1)[N+]([O-])=O	0.358	0.737	1.10
COc1cc([C@@H]2C[C@H]3COC(=O)N[C@@H]23)c(cc1)[N+]([O-])=O	0.351	0.709	1.06
COc1cc([C@@H]2C[C@H]3COC(=O)OC[C@H]32)c(cc1)[N+]([O-])=O	0.348	0.783	1.13
COc1cc([C@@H]2C[C@H]3COC[C@@H]23)c(cc1)[N+]([O-])=O	0.360	0.710	1.07
COc1cc([C@@H]2C[C@H]3CNC[C@H]32)c(cc1)[N+]([O-])=O	0.363	0.708	1.07
COc1cc([C@@H]2C[C@@H](CO)[C@H]2CO)c(cc1)[N+]([O-])=O	0.356	0.697	1.05
O=C1OC[C@@H]2C[C@H]([C@H]12)c1cc[n]c(Cl)c1	0.223	0.892	1.12
O=C1N[C@H]2[C@@H](C[C@H]2CO1)c1cc[n]c(Cl)c1	0.181	0.899	1.08
O=C1OC[C@H]2[C@@H](C[C@H]2CO1)c1cc[n]c(Cl)c1	0.212	0.940	1.15
Clc1cc(cc[n]1)[C@@H]1C[C@H]2COC[C@H]21	0.203	0.883	1.09
Clc1cc(cc[n]1)[C@@H]1C[C@H]2CNC[C@H]21	0.206	0.882	1.09
OC[C@H]1[C@@H](C[C@H]1CO)c1cc[n]c(Cl)c1	0.311	0.847	1.16
O=C1OC[C@@H]2C[C@H]([C@H]12)c1ccc[s]1	0.228	0.890	1.12
O=C1OC[C@H]2[C@@H](C[C@H]2CO1)c1ccc[s]1	0.174	0.963	1.14
O=C1N[C@H]2[C@@H](C[C@H]2CO1)c1ccc[s]1	0.191	0.875	1.07
C1[C@H]([C@@H]2COC[C@@H]21)c1ccc[s]1	0.189	0.932	1.12
C1[C@H]([C@@H]2CNC[C@@H]21)c1ccc[s]1	0.193	0.931	1.12
OC[C@@H]1C[C@H]([C@@H]1CO)c1ccc[s]1	0.249	0.895	1.14
FC(F)(F)c1cc([C@H]2[C@@H]3C(=O)OC[C@@H]3C2)ccc1	0.161	0.890	1.05
FC(F)(F)c1cc([C@H]2[C@@H]3NC(=O)OC[C@@H]3C2)ccc1	0.225	0.828	1.05

FC(F)(F)c1cc([C@H]2[C@H]3[C@@H](C2)COC(=O)OC3)ccc1	0.136	0.938	1.07
FC(F)(F)c1cc([C@H]2[C@H]3[C@@H](C2)COC3)ccc1	0.161	0.902	1.06
FC(F)(F)c1cc([C@H]2[C@H]3[C@@H](C2)CNC3)ccc1	0.161	0.902	1.06
FC(F)(F)c1cc(C2[C@H](CO)[C@H](CO)C2)ccc1	0.154	0.895	1.05
O=[N+]([O-])c1cc([C@H]2[C@@H]3C(=O)OC[C@@H]3C2)ccc1	0.164	0.862	1.03
O=[N+]([O-])c1cc([C@H]2[C@@H]3NC(=O)OC[C@@H]3C2)ccc1	0.218	0.812	1.03
O=[N+]([O-])c1cc([C@H]2[C@H]3[C@@H](C2)COC(=O)OC3)ccc1	0.138	0.923	1.06
O=[N+]([O-])c1cc([C@H]2[C@H]3[C@@H](C2)COC3)ccc1	0.157	0.879	1.04
O=[N+]([O-])c1cc(C2[C@H]3[C@@H](C2)CNC3)ccc1	0.158	0.878	1.04
O=[N+]([O-])c1cc([C@H]2[C@H](CO)[C@H](CO)C2)ccc1	0.155	0.871	1.03
Fc1ccc(C2[C@@H]3C(=O)OC[C@@H]3C2)cc1	0.164	0.867	1.03
Fc1ccc(C2[C@@H]3NC(=O)OC[C@@H]3C2)cc1	0.241	0.913	1.15
Fc1ccc([C@H]2[C@H]3[C@@H](C2)COC(=O)OC3)cc1	0.134	0.921	1.05
Fc1ccc([C@H]2[C@H]3[C@@H](C2)COC3)cc1	0.129	0.916	1.04
Fc1ccc(C2[C@H]3[C@@H](C2)CNC3)cc1	0.129	0.917	1.05
Fc1ccc(C2[C@H](CO)[C@H](CO)C2)cc1	0.142	0.889	1.03
CC(C=C1)=CC=C1[C@@H]2C[C@@H]3[C@H]2COC3	0.134	0.914	1.05

Figure S6. PMI Plot of the *anti*-epimer virtual library (green squares).

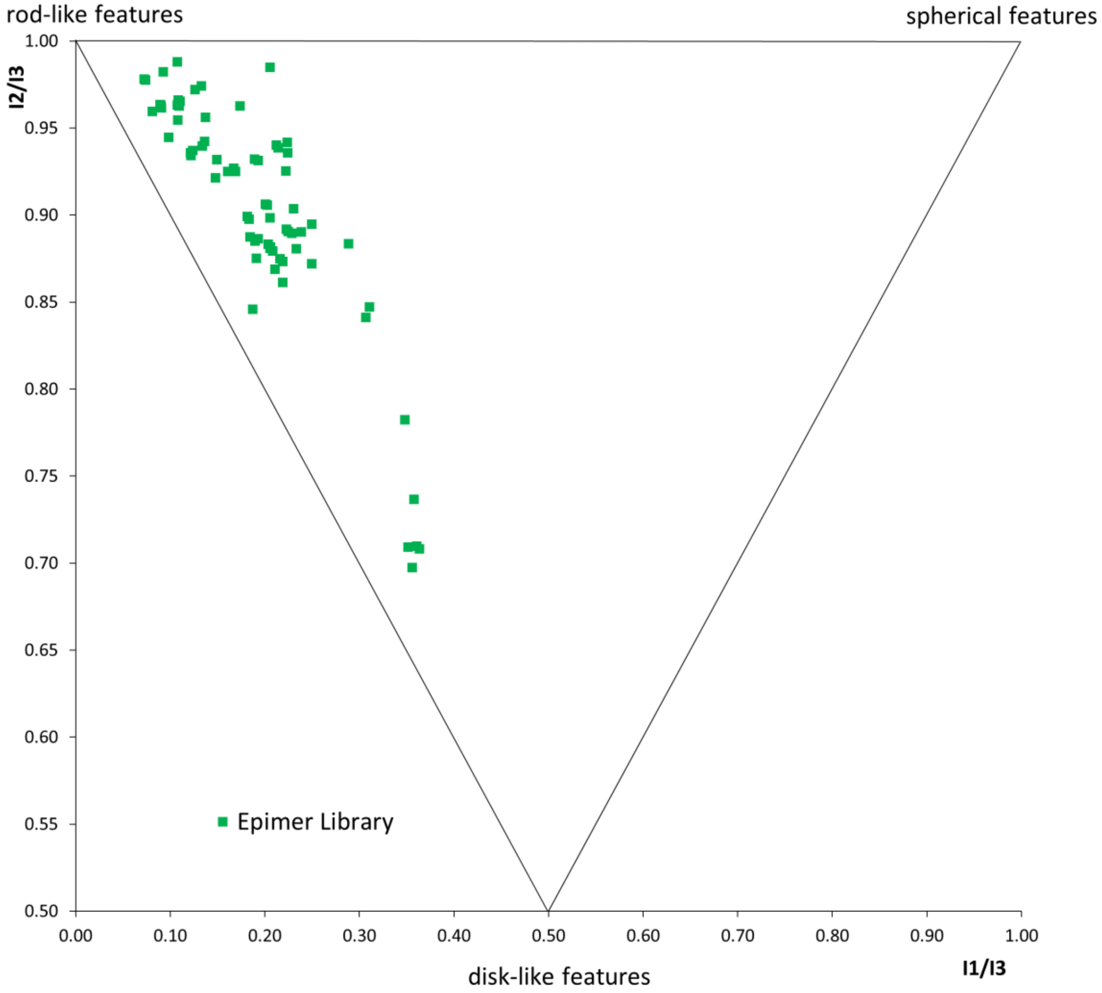


Table S3. The 91 ChEMBL structures used for comparative analysis with their respective npr1, npr2 and summed values. ChEMBL structures represent biologically active molecules containing an aryl substituted cyclobutane substructure with less than 300 Da MW from the ChemBL database.

SMILES	npr1	npr2	npr1 + npr2
COc1cc2c(cc1OC)N=C(N)C12CCC1	0.305	0.735	1.04
Oc1c(F)c(ccc1C1CCC1)-c1cc2CCNc2[n]c1	0.130	0.925	1.05
CCCCCN1C(=O)C2CC(C2)(c2ccc(N)cc2)C1=O	0.297	0.836	1.13
C1NCCN2C1CCc1c(cccc21)C1CCC1	0.213	0.850	1.06
CC1(C)CCC[C@@]2(C)[C@H]3[C@@H](C(=O)[C@H]3C=C12)c1ccccc1C	0.252	0.873	1.13
Nc1ccc(cc1)C12CC(C1)C(=O)N(C1CCCCC1)C2=O	0.260	0.864	1.12
COCC(=O)NC1(CCC1)c1cccc(c1)C(F)(F)F	0.446	0.813	1.26
COc1c(F)c(ccc1C1CCC1)-c1ccc(N)[n][n]1	0.186	0.850	1.04
COc1cc2c(cc1)N=C(N)C12CCC1	0.304	0.750	1.05

C[C@H]1[C@@H]2C(=O)C=C(OC)C(=O)[C@]2(C)[C@@H]1c1ccccc1	0.592	0.755	1.35
COc1c(F)c(ccc1C1CCC1)-c1c[n]c(N)cc1	0.190	0.857	1.05
COc1c(F)c(ccc1C1CCC1)-c1c[n]c(N)c(C#N)[n]1	0.189	0.861	1.05
COC1=CC(=O)C2[C@H]3Cc4ccccc4[C@H]3[C@@]2(C)C1=O	0.242	0.841	1.08
COc1c(F)c(ccc1C1CCC1)-c1cc2CCNc2[n]c1	0.167	0.889	1.06
Fc1ccc(cc1)C1(CNC2NCCCN=2)CCC1	0.485	0.709	1.19
Nc1[n]cc([n]c1C#N)-c1ccc(C2CCC2)c(O)c1F	0.151	0.892	1.04
OC(=O)C1=CN(CC2(CCC2)c2ccccc2)C=C(O)C1=O	0.401	0.758	1.16
CC(=O)c1c[n](C)c(c1)C(=O)NC1(CCC1)c1ccccc1	0.325	0.990	1.32
CN1CCOC(C1)CNC(=O)C1(CCC1)c1ccccc1	0.389	0.815	1.20
CN1C=C(C=CC1=O)NC(=O)C1CC(C1)c1ccccc1	0.106	0.977	1.08
CNC1CC(C1)(c1ccccc1)c1ccccc1	0.574	0.648	1.22
Cc1cc(ccc1)C1(CCC1)c1[n][n]c2CCCCCC[n]21	0.543	0.776	1.32
NC(=O)NC(=O)CNC1(CCC1)c1ccc(Cl)cc1	0.282	0.819	1.10
CN1N=C(C=CC1=O)C(=O)NC1(CCC1)c1ccccc1	0.272	0.927	1.20
Nc1c[n]c(c(C#N)[n]1)-c1ccc(C2CCC2)c(O)c1F	0.201	0.881	1.08
COc1c(F)c(ccc1C1CCC1)-c1c[n]c(N)c[n]1	0.186	0.850	1.04
O=C1Nc2ccc(cc2C21CCC2)-c1cc(Cl)ccc1	0.211	0.844	1.05
CC1(CC(C)(C1)c1ccc(O)cc1)c1ccc(O)cc1	0.290	0.841	1.13
N[C@@H]1CC[C@]1(O)c1ccccc1	0.339	0.943	1.28
Fc1ccc(cc1)C1(CCC1)c1[n][n]c2CCCCCC[n]21	0.463	0.725	1.19
Cc1ccc(cc1)C1(CCC1)c1[n][n]c2CCCCCC[n]21	0.505	0.717	1.22
COc1c(F)c(ccc1C1CCC1)-c1cc2cc[nH]c2[n][n]1	0.173	0.862	1.04
Cc1ccccc1C1(CCC1)c1[n][n]c2CCCCCC[n]21	0.504	0.776	1.28
COc1c(F)c(ccc1C1CCC1)-c1c[n]c2[nH]c[n]c2c1	0.152	0.897	1.05
CC(C)CC(N(C)C)C1(CCC1)c1ccc(Cl)cc1	0.377	0.901	1.28
Nc1ccc(c[n]1)-c1ccc(C2CCC2)c(O)c1F	0.144	0.902	1.05
COCc1[n]oc([n]1)C1(CCC1)c1ccc(F)cc1	0.402	0.766	1.17
OC(=O)C1(CCC1)c1ccc(Cl)cc1	0.236	0.966	1.20
CCN(C)C(=O)C1(CCC1)c1ccc(F)cc1F	0.502	0.866	1.37
CCCN1C(=O)C2CC(C2)(c2ccc(N)cc2)C1=O	0.228	0.913	1.14
Nc1c[n]c(c[n]1)-c1ccc(C2CCC2)c(O)c1F	0.140	0.895	1.04
ONC(=O)c1c[n]c(NC2(CCC2)c2ccccc2)[n]c1	0.242	0.880	1.12
Cc1cc([n]c2c1cccc2C1CCC1)C1CCC1	0.459	0.606	1.06
COc1cc(C2CC[C@H]2N)c(cc1OC)OC	0.381	0.658	1.04
OC(=O)C1(CCC1)c1cccc(Cl)c1	0.355	0.954	1.31
Oc1c(F)c(ccc1C1CCC1)-c1c[n]c2[nH]ccc2[n]1	0.127	0.910	1.04
C1C(CNC2(CCC2)c2ccccc2)CNc2cc[n][n]21	0.189	0.880	1.07
O=C1CCC(=NN1)c1ccc2NC(=O)C3(CCC3)c2c1	0.162	0.871	1.03
C1CCCCC[n]2c([n][n]c21)C1(CCC1)c1ccccc1	0.471	0.739	1.21
CN(C)C1CC(C1)(c1ccccc1)c1ccccc1	0.528	0.698	1.23
CN(C(=O)C1(CCC1)c1ccc(Cl)cc1)c1ccccc1	0.469	0.747	1.22
COc1c(F)c(ccc1C1CCC1)-c1cc2cc[nH]c2[n]c1	0.168	0.886	1.05

Nc1ccc([n][n]1)-c1ccc(C2CCC2)c(O)c1F	0.140	0.895	1.04
COc1c(F)c(ccc1C1CCC1)-c1[n]cc(N)[n]c1C#N	0.220	0.846	1.07
Cc1[n][n]c(NC(=O)C2(CCC2)c2ccc(F)cc2)[s]1	0.303	0.841	1.14
COc1c(F)c(ccc1C1CCC1)-c1c[n]c2[nH]ccc2[n]1	0.166	0.874	1.04
COc1cc(C2CC[C@@H]2N)c(cc1OC)OC	0.392	0.684	1.08
OC(=O)C1C(C(C1c1ccccc1)C(O)=O)c1ccccc1	0.472	0.988	1.46
Nc1ccc(cc1)C12CC(C1)C(=O)NC2=O	0.172	0.965	1.14
NC1=N[C@H](CO1)CCC1(CCC1)c1ccc(Cl)cc1	0.385	0.735	1.12
COc1c(F)c(ccc1C1CCC1)-c1c[n]c2[nH]c[n]c2[n]1	0.166	0.875	1.04
C[C@H]1[C@@H]([C@H]2C(=O)C(=CC(=O)[C@@]12C)OC)c1ccccc1	0.325	0.829	1.15
CC(C)CC(N)C1(CCC1)c1ccc(Cl)cc1	0.333	0.821	1.15
NCC12C3C4C1C1C2C3C14c1ccccc1	0.149	0.951	1.10
CC1(C)CCC[C@@]2(C)[C@H]3[C@@H](C(=O)[C@H]3C=C12)c1ccccc1F	0.297	0.923	1.22
OC(=O)CC1(CC2(C1)CCCCC2)c1ccc(F)cc1	0.317	0.822	1.14
CC1(C)[C@H]2C[C@@H]1Cc1cc3[n]c4cccc[n]4c3cc12	0.167	0.919	1.09
COc1c(F)c(ccc1C1CCC1)-c1c[n]c(N)[n]c1	0.189	0.857	1.05
Fc1ccccc1C1(CCC1)c1[n][n]c2CCCCCC[n]21	0.503	0.793	1.30
Fc1ccc(cc1)C1(CCC1)NCc1[n]c(o[n]1)C1CC1	0.196	0.879	1.08
CCCc1cc([n]c(C#N)[n]1)-c1cc(ccc1)C1CCC1	0.271	0.787	1.06
Fc1cc(ccc1)C1(CCC1)c1[n][n]c2CCCCCC[n]21	0.391	0.936	1.33
Nc1c[n]c(c[n]1)-c1ccc(C2CCC2)c(OCC#N)c1F	0.265	0.764	1.03
Oc1cc2CCC3C(C4CCc5cc(O)ccc5C34)c2cc1	0.138	0.903	1.04
C(c1ccccc1)c1ccc(cc1)[C@@H]1C[C@@H](C1)N1CCCC1	0.146	0.950	1.10
Cc1[n][n]c(NCC2(CCC2)c2ccccc2)c(C#N)c1C	0.434	0.875	1.31
C1CCCCN1C1(CCC1)c1ccccc1	0.471	0.836	1.31
Oc1c(F)c(ccc1C1CCC1)-c1c[n]c2[nH]ccc2c1	0.130	0.923	1.05
N[C@@H]1CC[C@@]1(O)c1ccccc1	0.286	0.893	1.18
O=C(CCC[n]1c[n]c[n]1)NC1(CCC1)c1ccccc1	0.246	0.896	1.14
C[C@H]1[C@@H](c2ccccc2)[C@@]2(C)[C@@H]1C(=O)C(=CC2=O)OC	0.221	0.890	1.11
SC1=Nc2ccc(cc2C21CCC2)-c1cc(Cl)ccc1	0.179	0.868	1.05
Cc1cc(OC)c(cc1OC)C1CC[C@@H]1N	0.426	0.618	1.04
CN(C)CC1(CCC1)c1cc(Cl)c(Cl)cc1	0.352	0.919	1.27
Nc1[n]cc(c[n]1)-c1ccc(C2CCC2)c(O)c1F	0.143	0.902	1.05
OC1(CCC1)c1ccc(cc1)OCCCN1CCCCC1	0.049	0.988	1.04
NC1CC(C1)(c1ccccc1)c1ccccc1	0.507	0.754	1.26
CC(C)CN1C(=O)C2(CC(C2)C1=O)c1ccc(N)cc1	0.245	0.881	1.13
NCC1(CCC1)c1cccc(c1)C(F)(F)F	0.319	0.945	1.26
Oc1c(F)c(ccc1C1CCC1)-c1cc2cc[nH]c2[n][n]1	0.137	0.896	1.03
O=C1Nc2c(Br)cccc2C2(CCC2)N1	0.281	0.755	1.04

Figure S7. PMI plot for the 91 ChEMBL structures used for comparison.

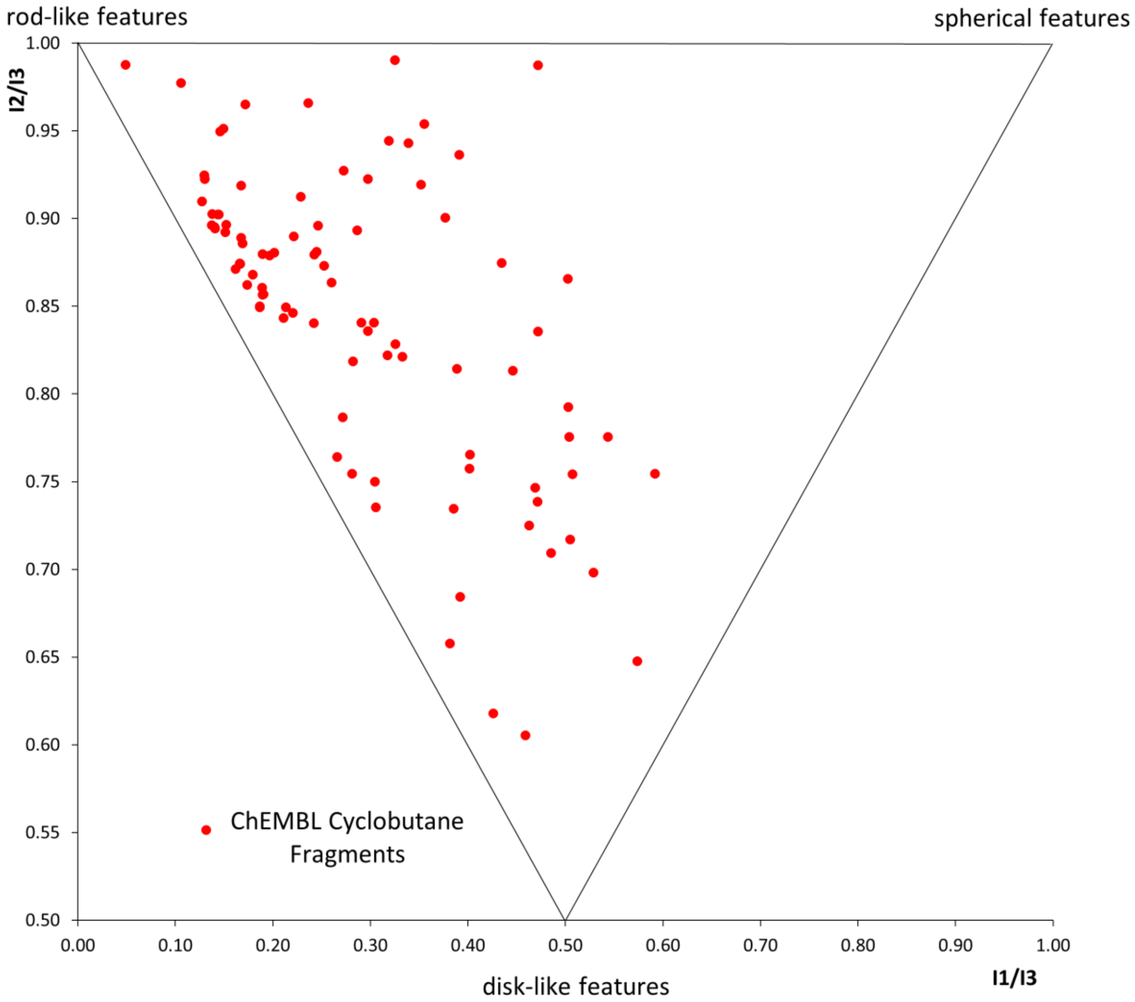
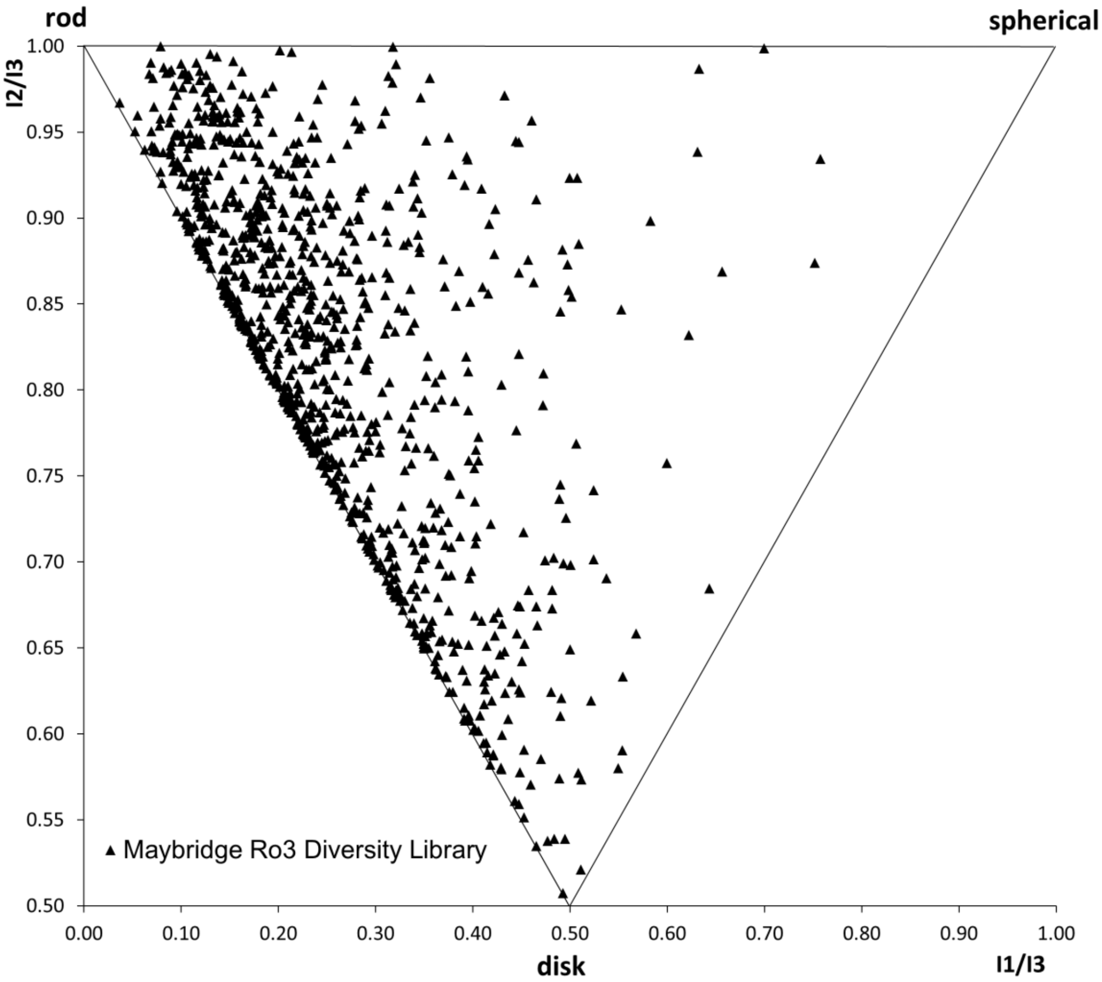
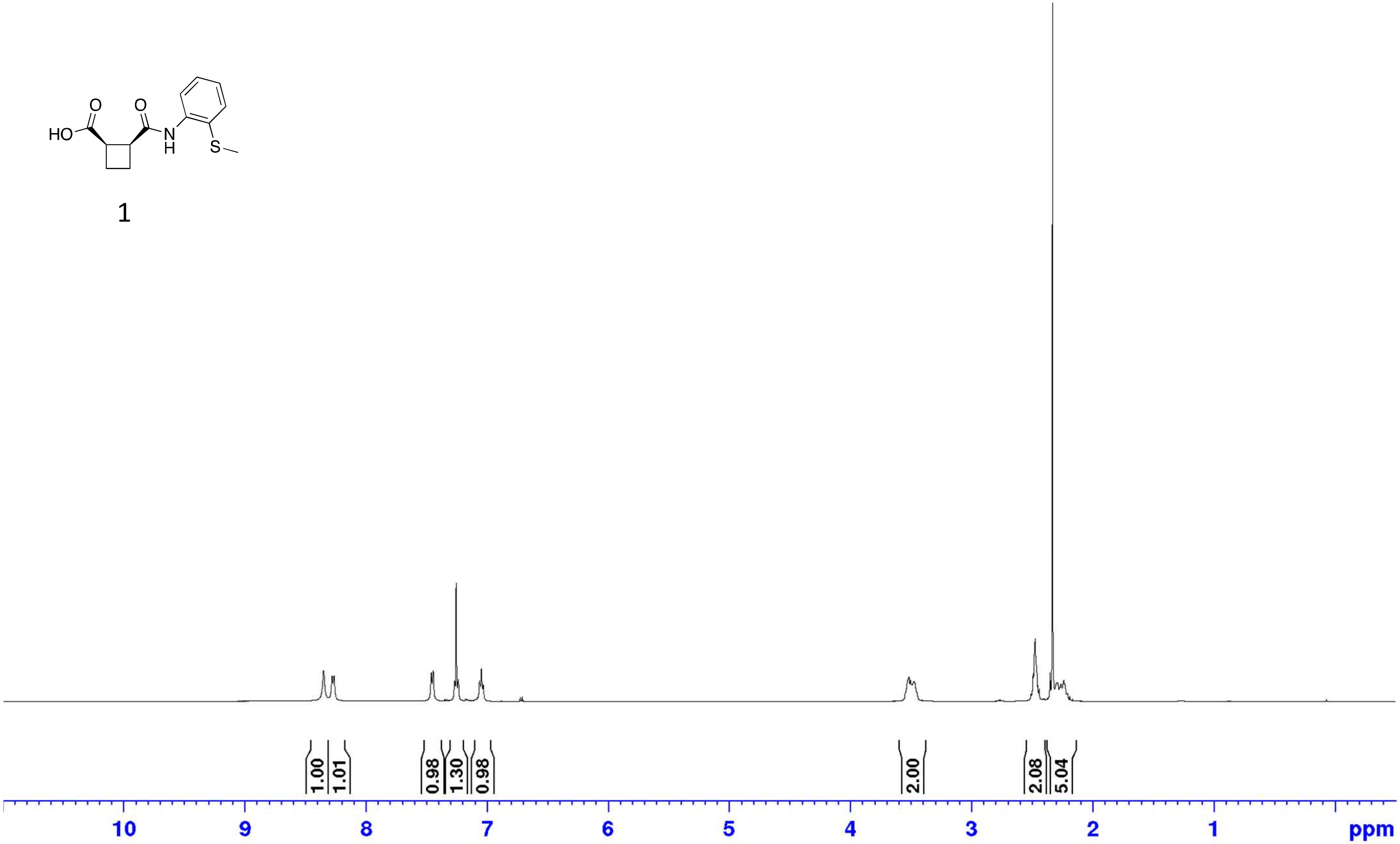


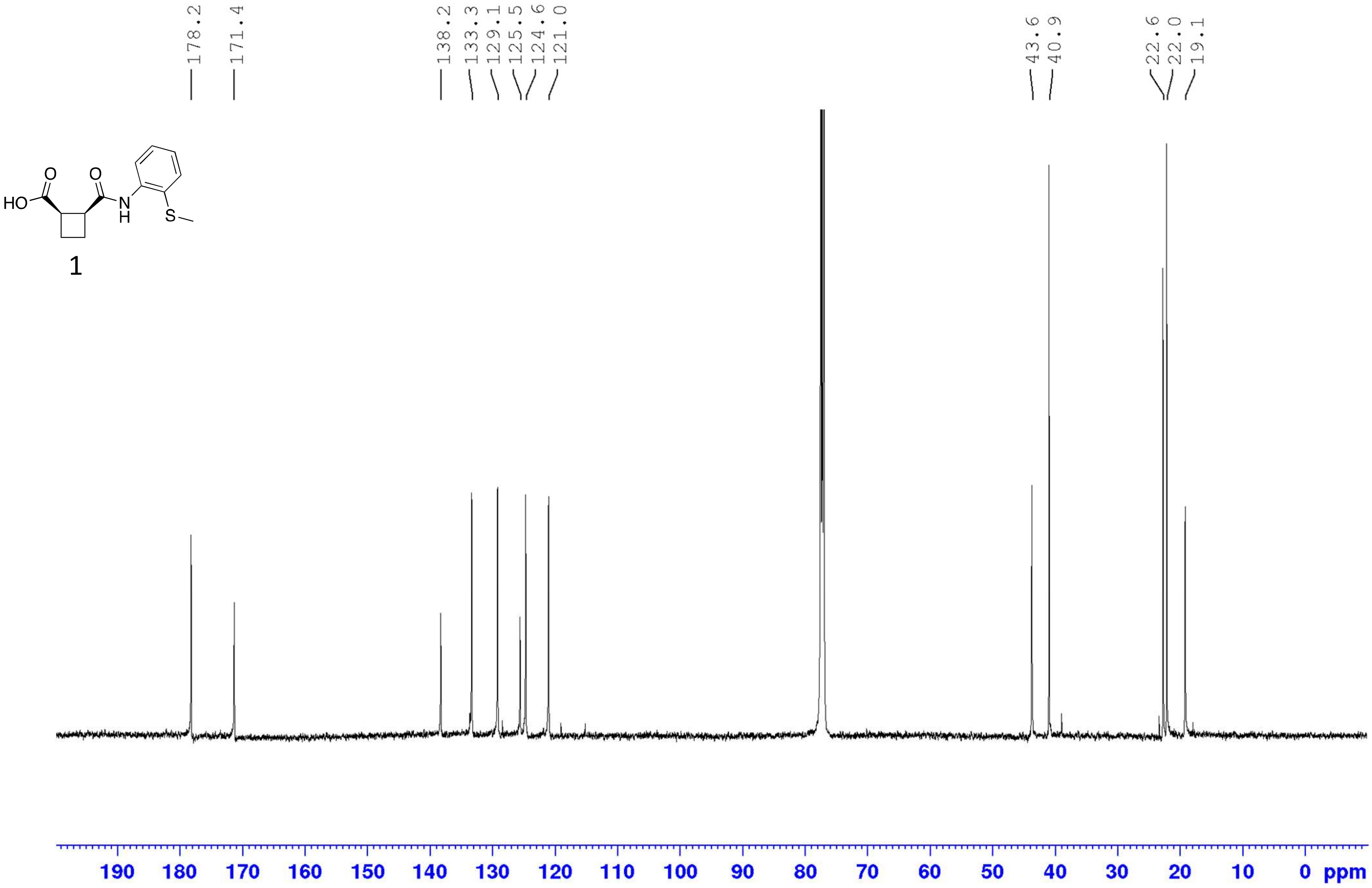
Figure S8. PMI plot of the 1000-member Maybridge Ro3 Diversity set used for comparison**.**

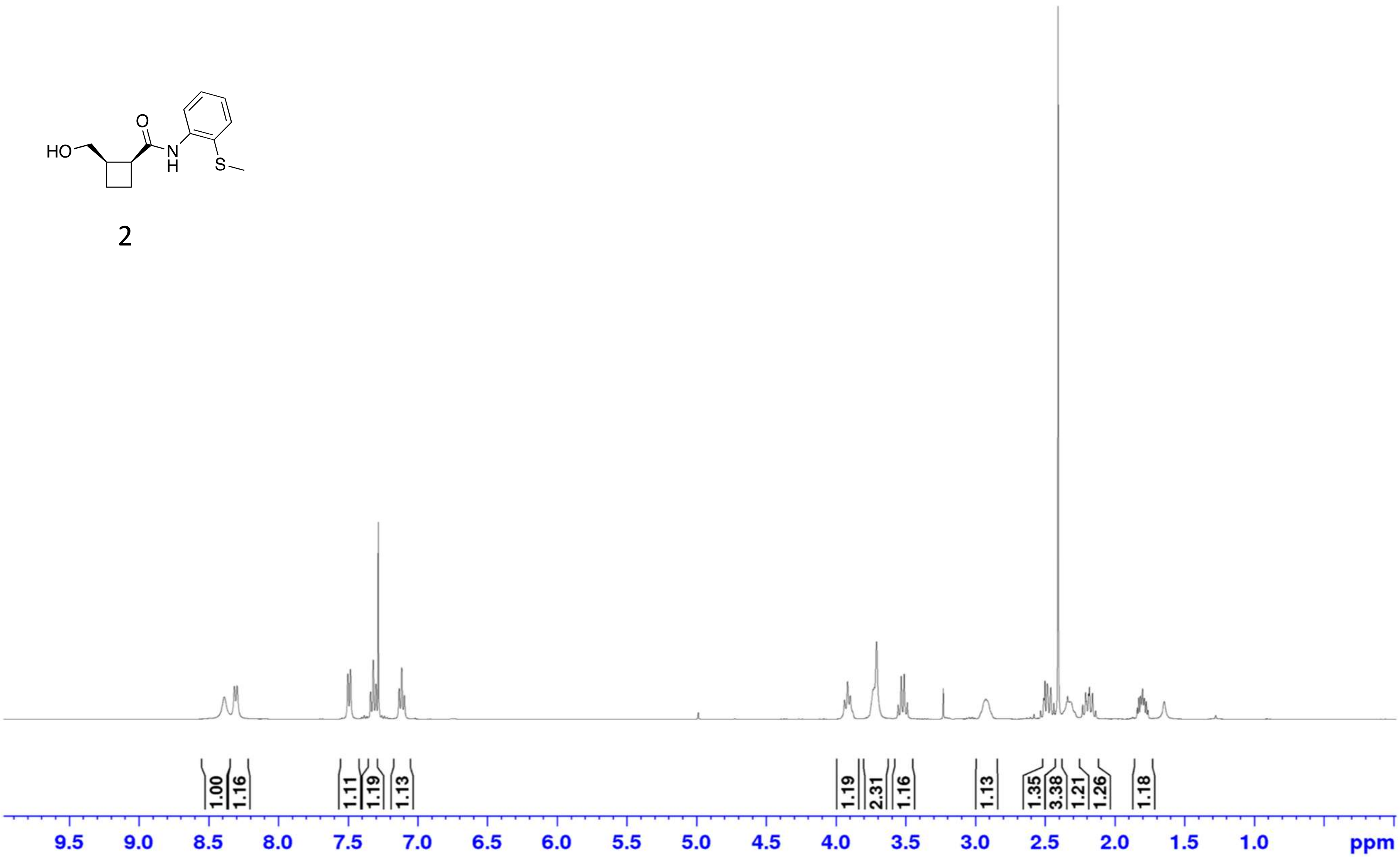


7. NMR SPECTRA

1

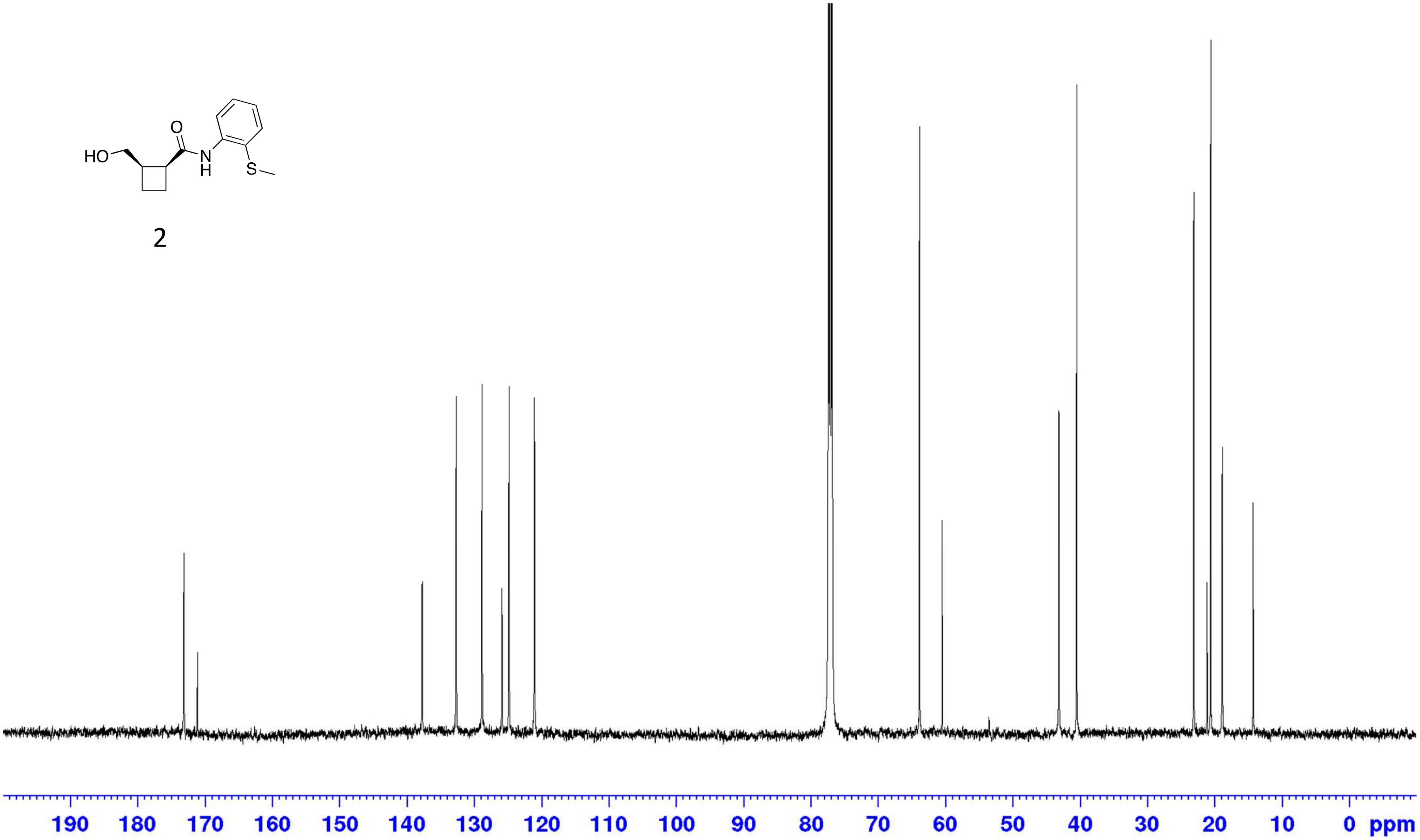



178.2
171.4
138.2
133.3
129.1
125.5
124.6
121.0
43.6
40.9
22.6
22.0
19.1
HO
O
O
N
H
S
1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

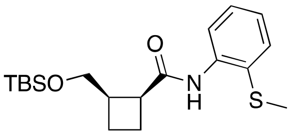

HO
O
N
H
S

2

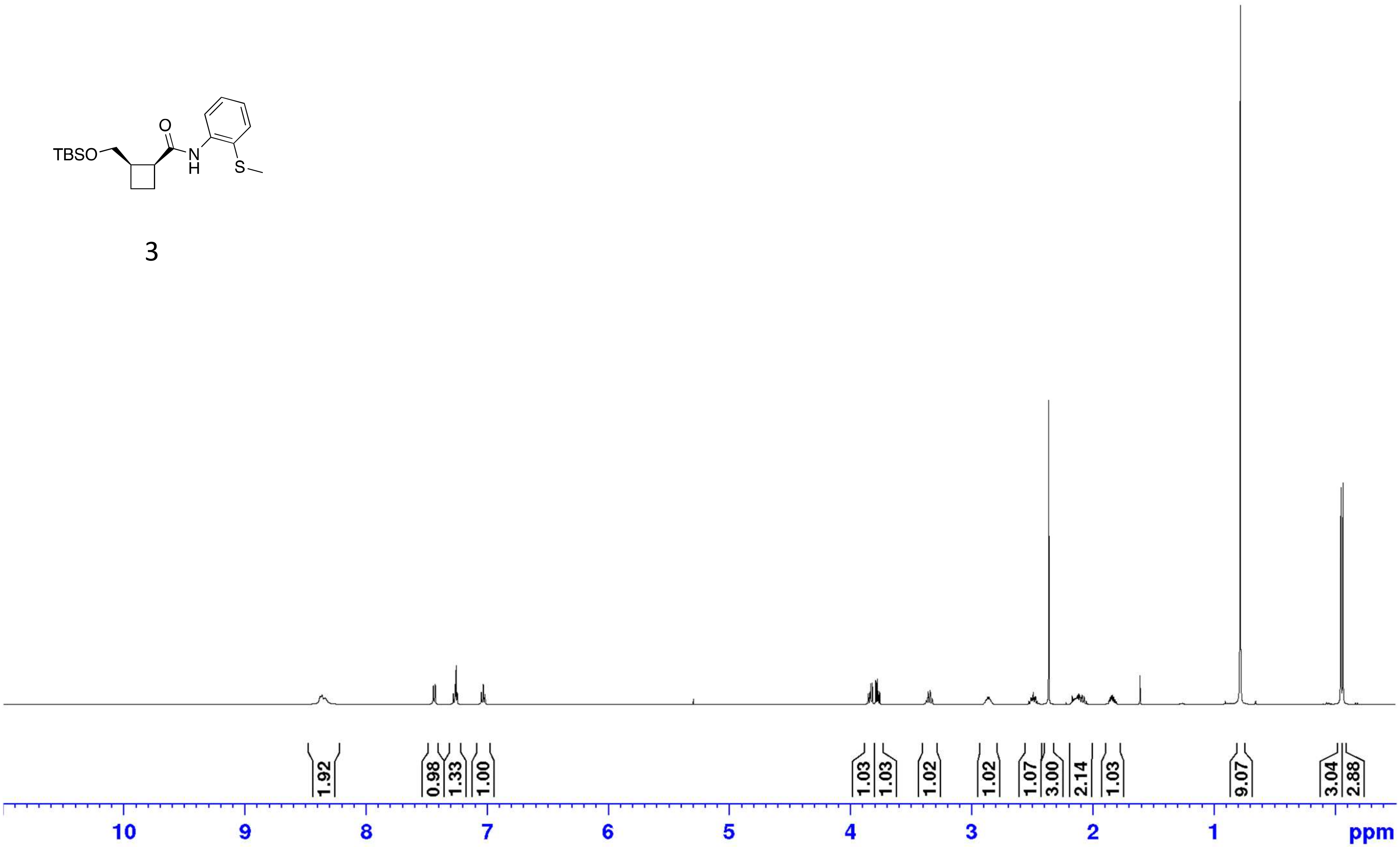
1.00
1.16
1.11
1.19
1.13
1.19
2.31
1.16
1.13
1.35
3.38
1.21
1.26
1.18
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

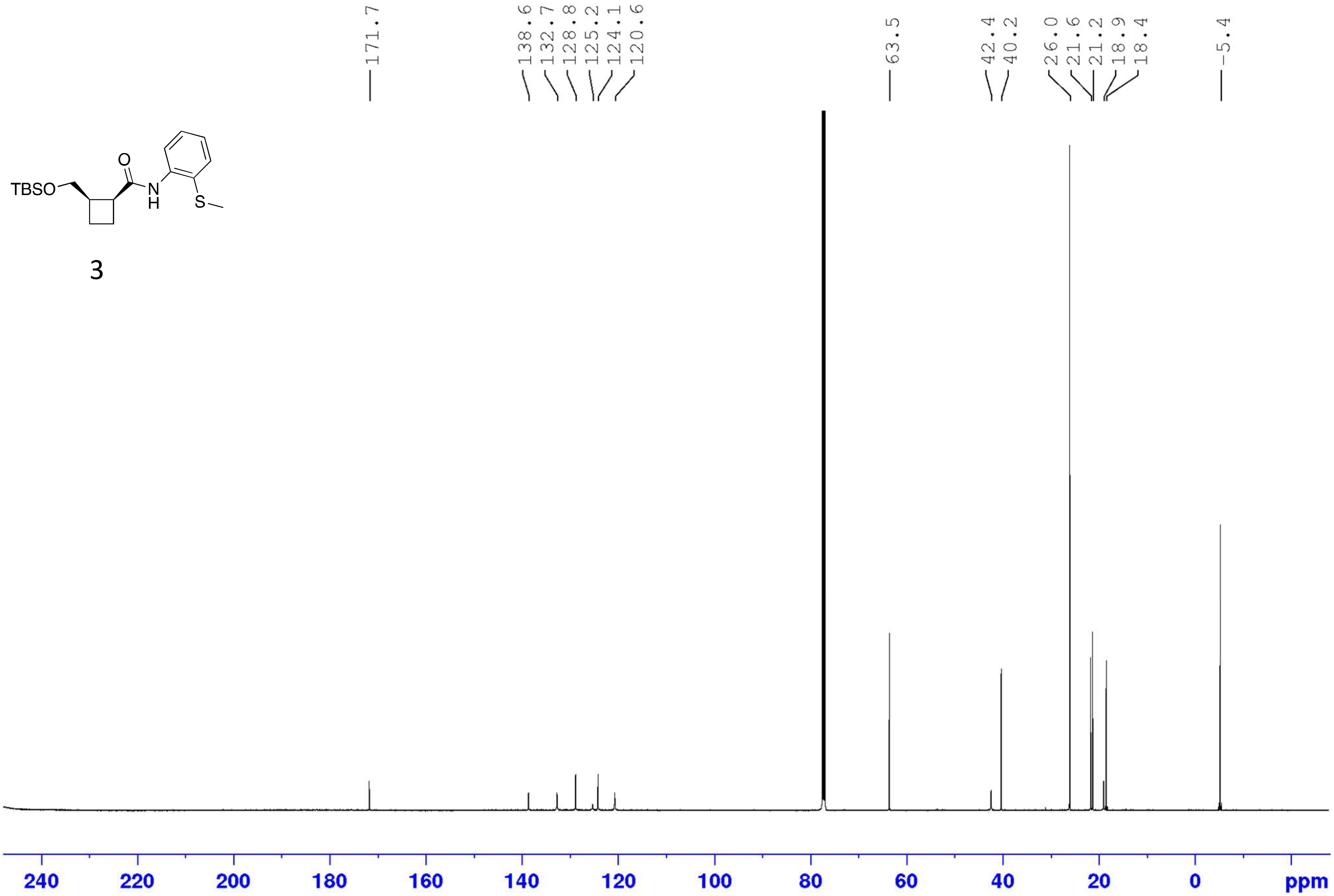

HO
O
N
H
S
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

2

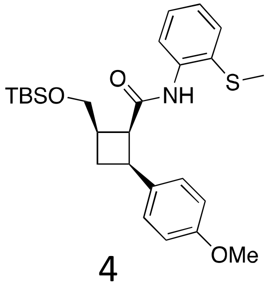

TBSO
O
N
H
S

3

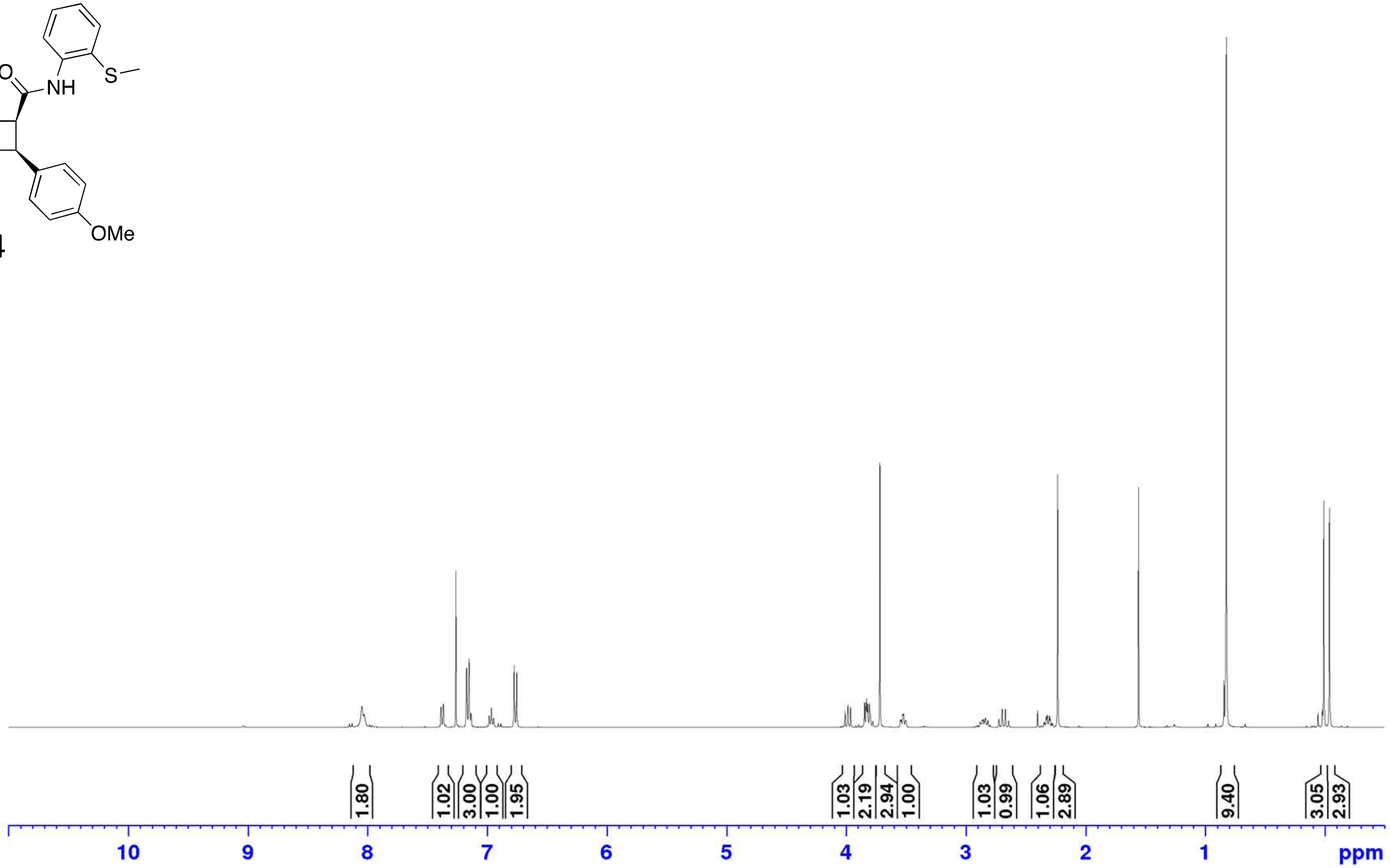

1.92
0.98
1.33
1.00
1.03
1.03
1.02
1.02
1.07
3.00
2.14
1.03
9.07
3.04
2.88
10
9
8
7
6
5
4
3
2
1
ppm


171.7
138.6
132.7
128.8
125.2
124.1
120.6
63.5
42.4
40.2
26.0
21.6
21.2
18.9
18.4
-5.4
TBSO
O
N
H
S
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

3


TBSO
O
NH
S
OMe

4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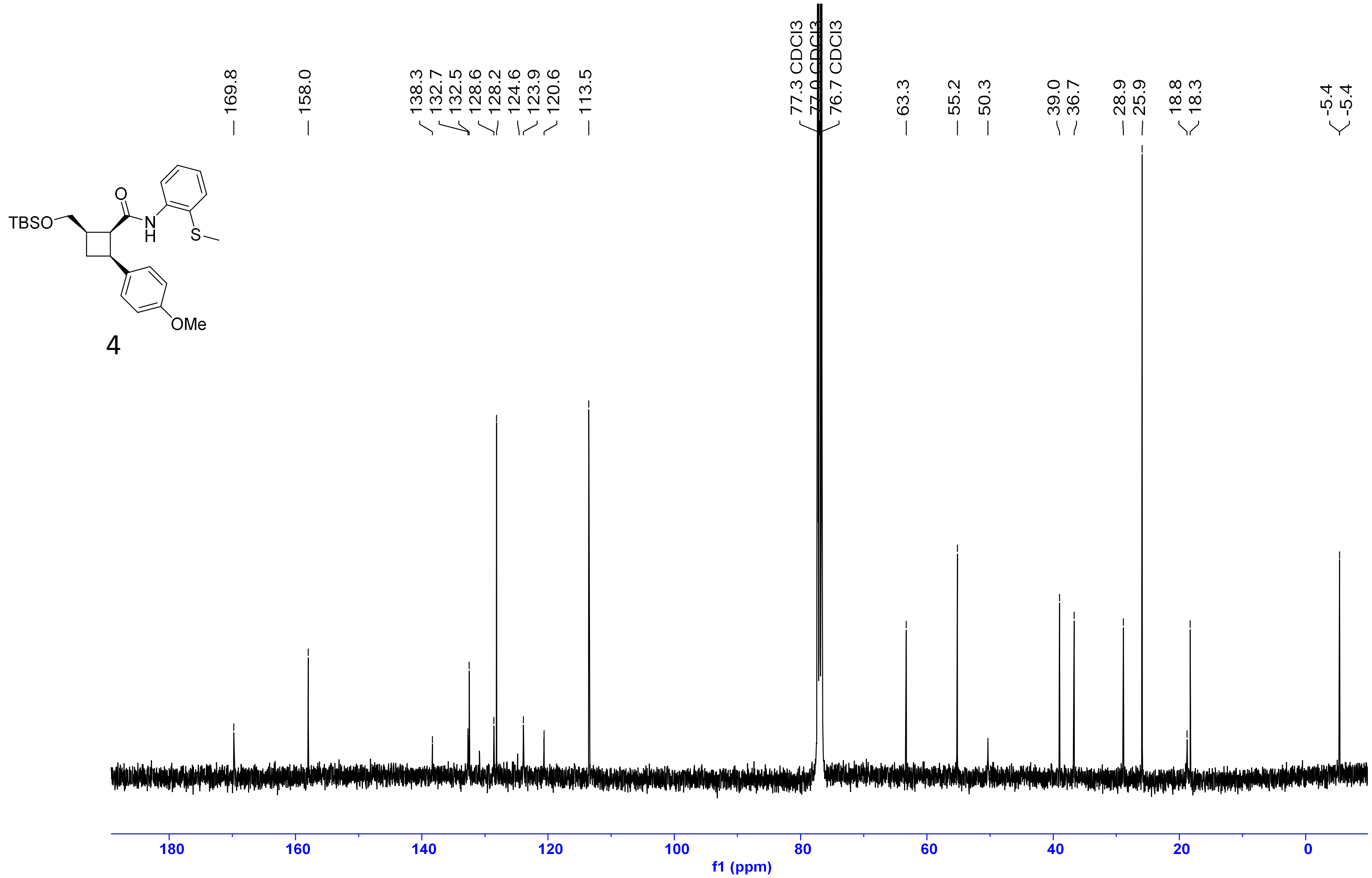
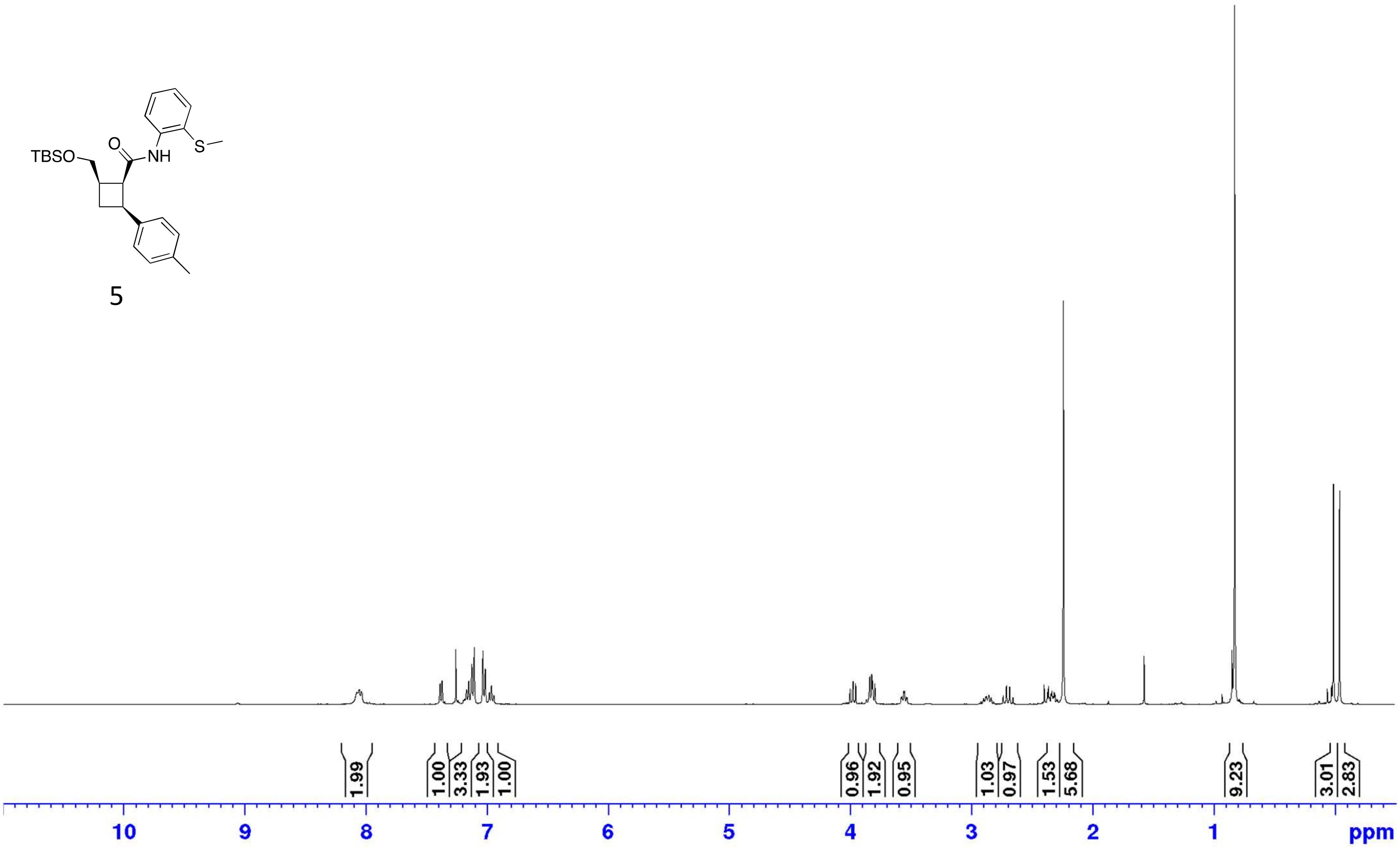
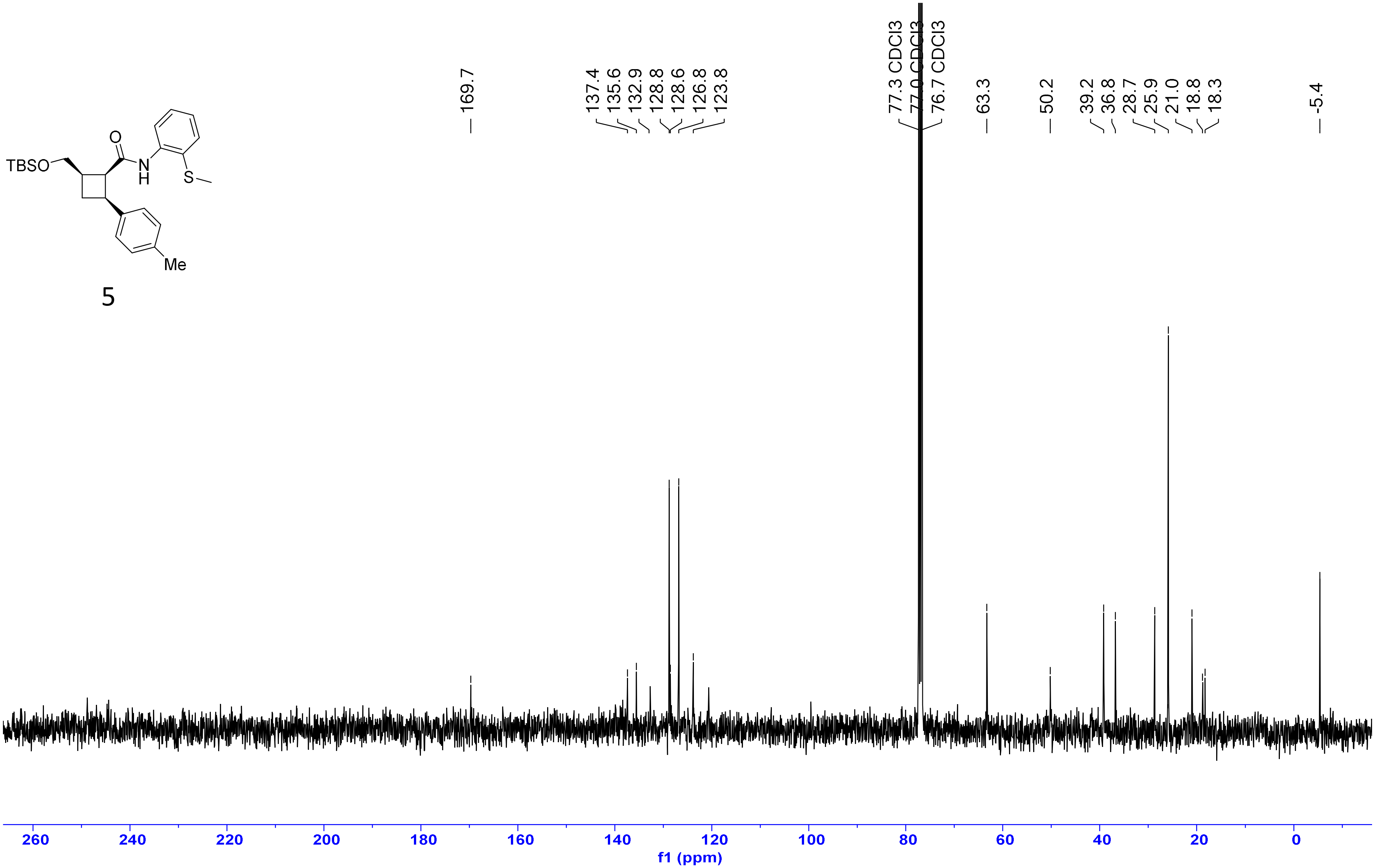
1.02
3.00
1.00
1.95
1.03
2.19
2.94
1.00
1.03
0.99
1.06
2.89
9.40
3.05
2.93
10
9
8
7
6
5
4
3
2
1
ppm


169.8
158.0
138.3
132.7
132.5
128.6
128.2
124.6
123.9
120.6
113.5
77.3 CDCl3
77.0 CDCl3
76.7 CDCl3
63.3
55.2
50.3
39.0
36.7
28.9
25.9
18.8
18.3
-5.4
-5.4
TBSO
O
N
H
S
OMe
4
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

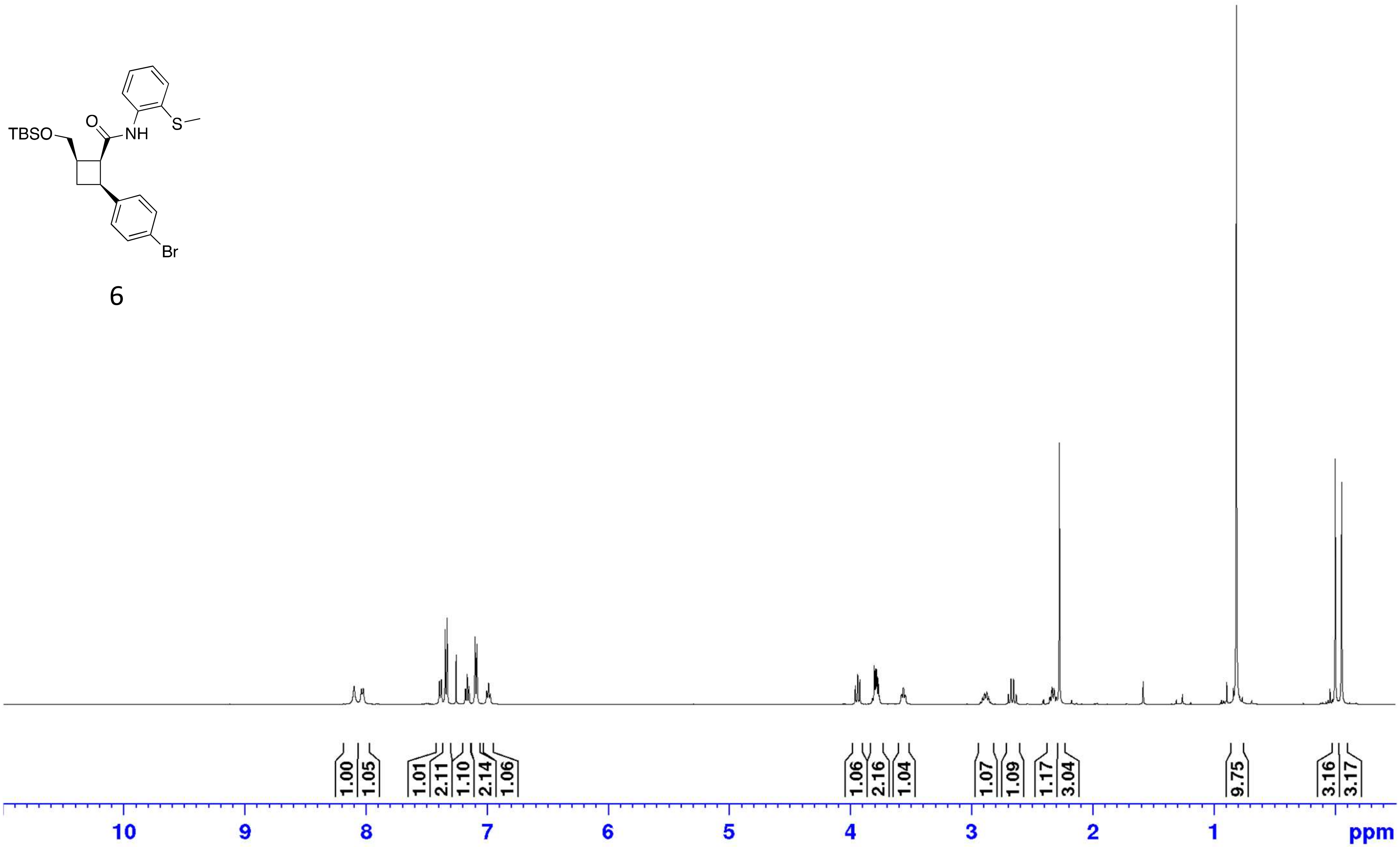

TBSO
O
NH
S
1.99
1.00
3.33
1.93
1.00
0.96
1.92
0.95
1.03
0.97
1.53
5.68
9.23
3.01
2.83
10
9
8
7
6
5
4
3
2
1
ppm

5


TBSO
O
N
H
S
Me

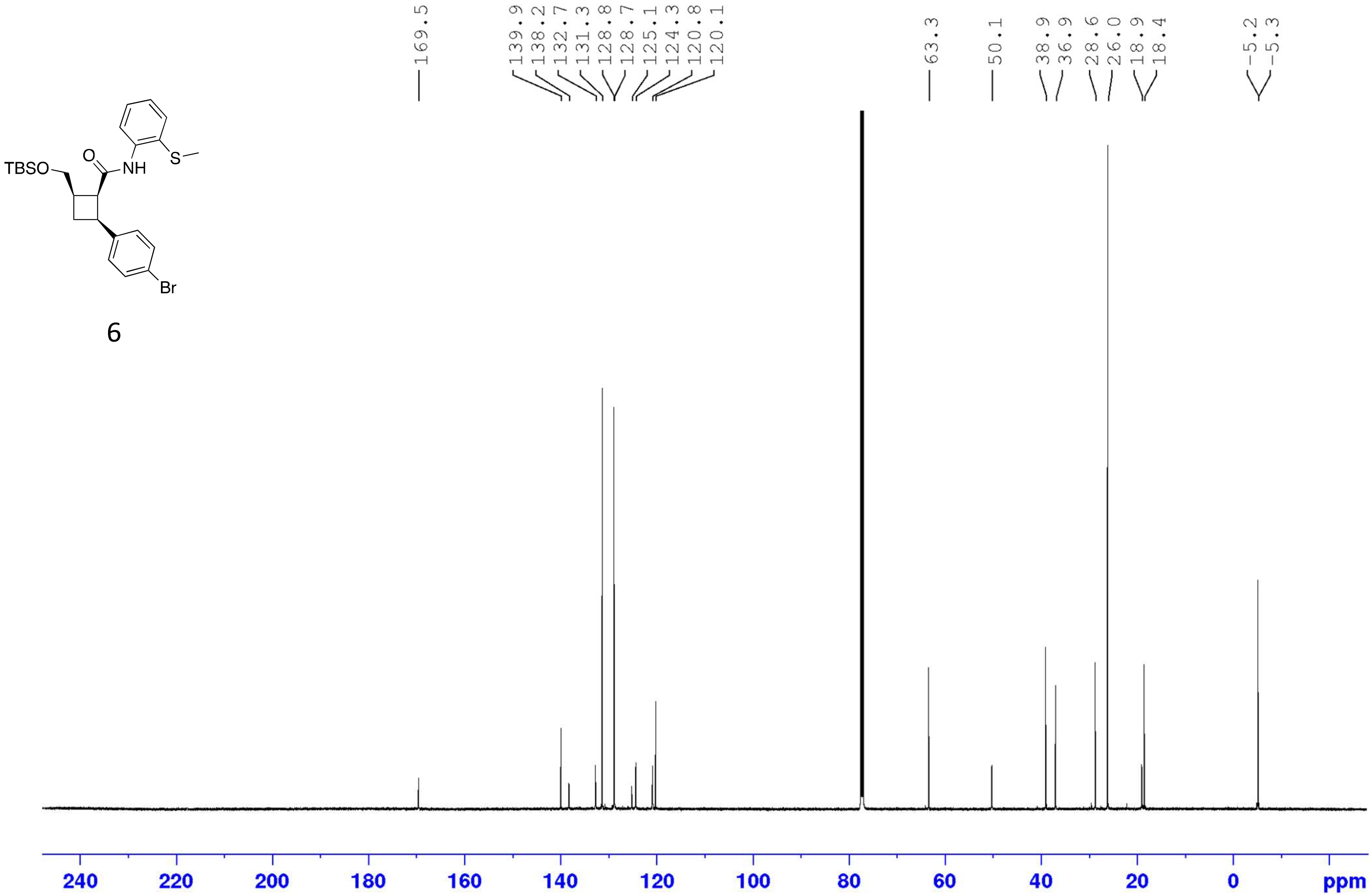
5

169.7
137.4
135.6
132.9
128.8
128.6
126.8
123.8
77.3 CDCl3
77.0 CDCl3
76.7 CDCl3
63.3
50.2
39.2
36.8
28.7
25.9
21.0
18.8
18.3
-5.4
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


TBSO
O
NH
S
Br

6

1.00
1.05
1.01
2.11
1.10
2.14
1.06
1.06
2.16
1.04
1.07
1.09
1.17
3.04
9.75
3.16
3.17
10
9
8
7
6
5
4
3
2
1
ppm

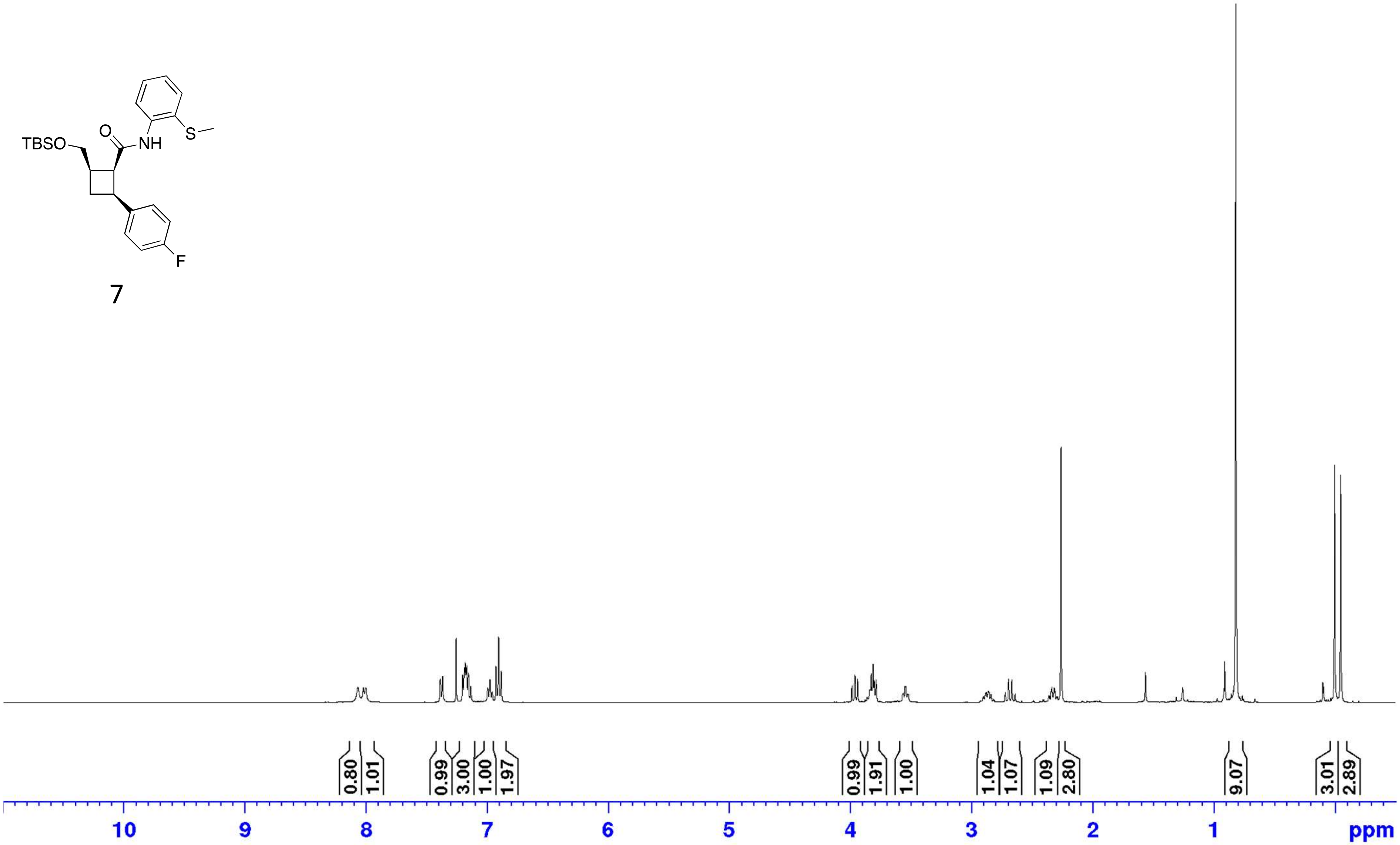

TBSO
O
NH
S
Br

6

169.5
139.9
138.2
132.7
131.3
128.8
128.7
125.1
124.3
120.8
120.1
63.3
50.1
38.9
36.9
28.6
26.0
18.9
18.4
-5.2
-5.3
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

TBSO
O
NH
S
F

7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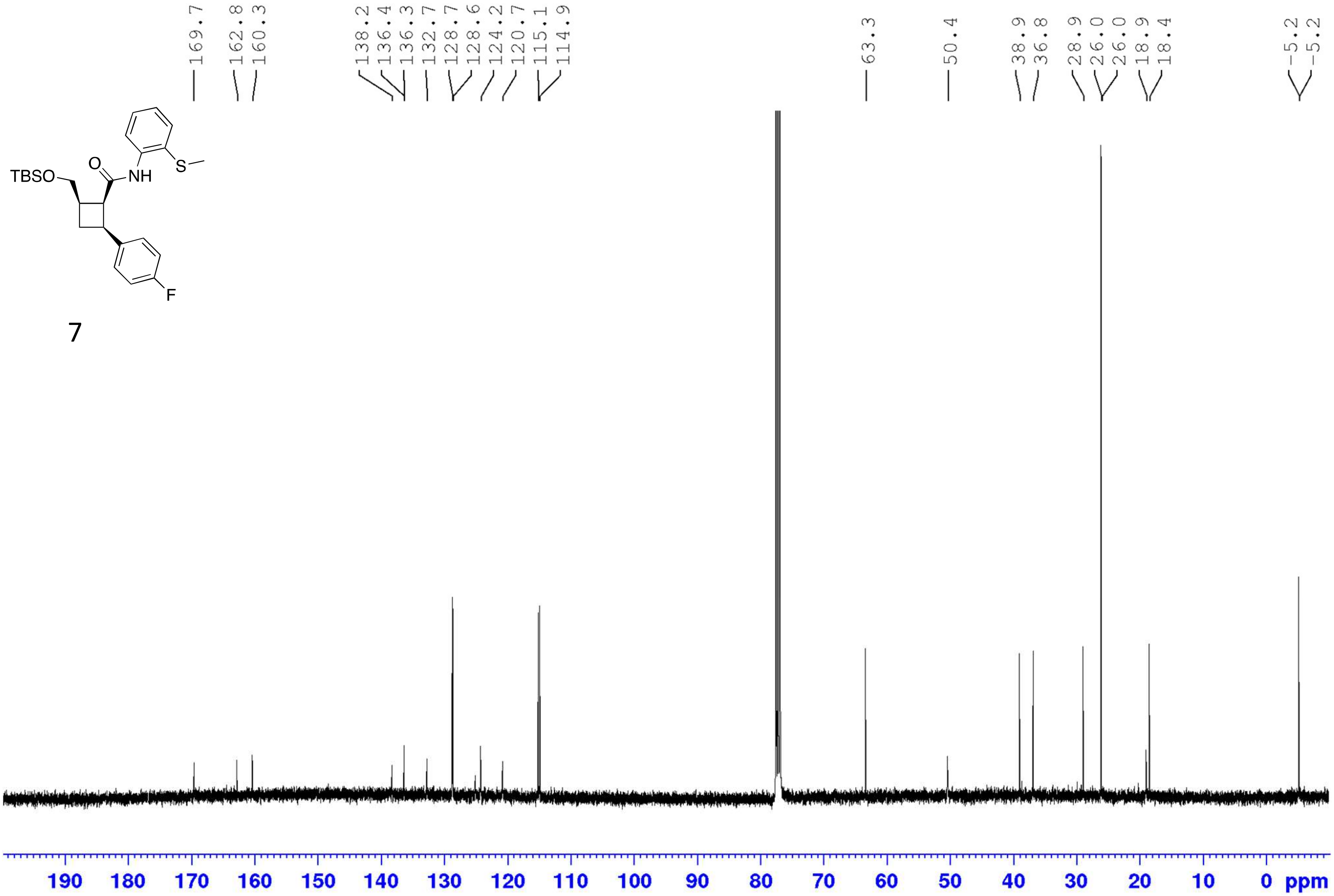
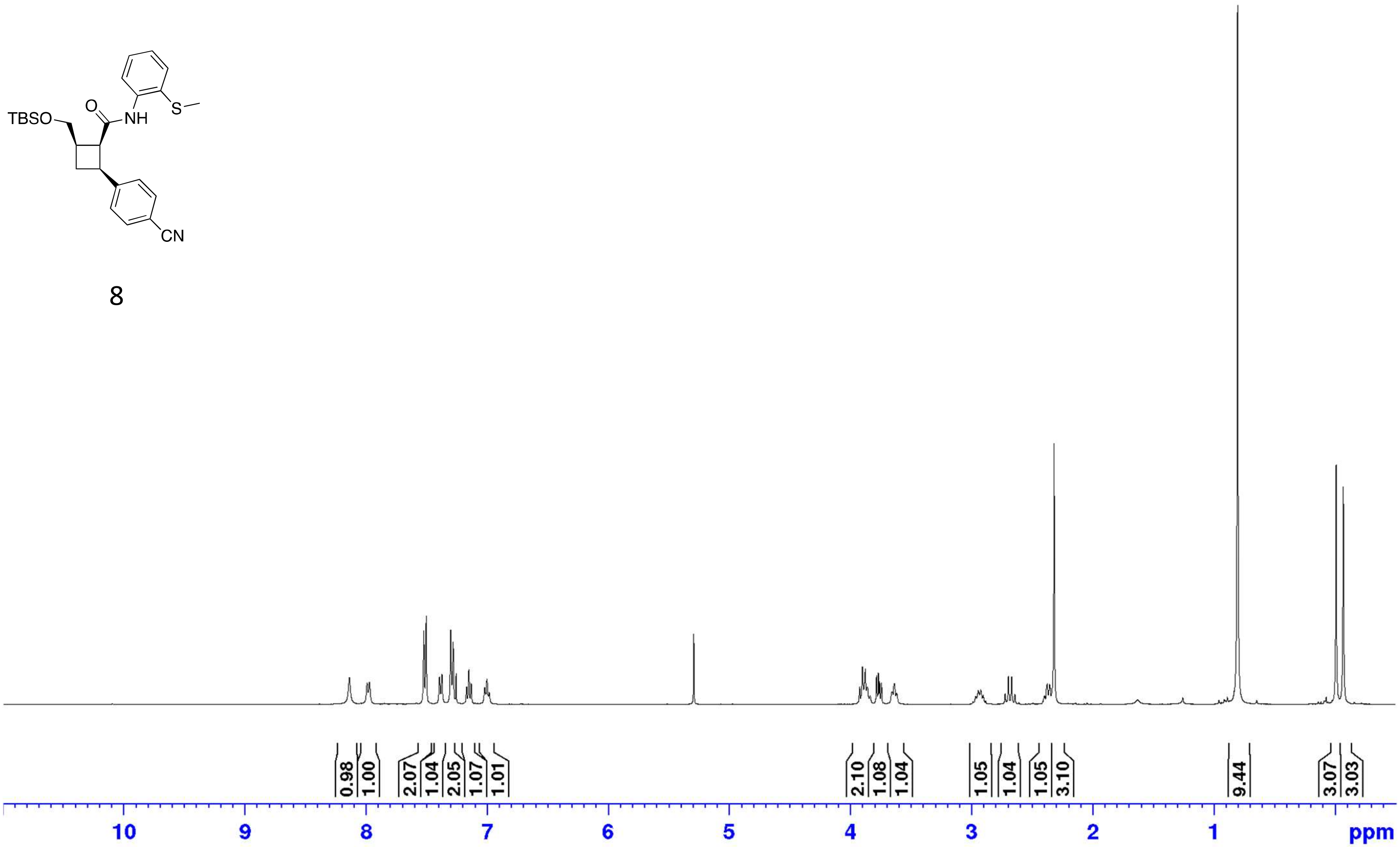
0.99
3.00
1.00
1.97
0.99
1.91
1.00
1.04
1.07
1.09
2.80
9.07
3.01
2.89
10
9
8
7
6
5
4
3
2
1
ppm


7

169.7
162.8
160.3
138.2
136.4
136.3
132.7
128.7
128.6
124.2
120.7
115.1
114.9
63.3
50.4
38.9
36.8
28.9
26.0
26.0
18.9
18.4
-5.2
-5.2
TBSO
O
NH
S
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

TBSO
O
NH
S
CN

8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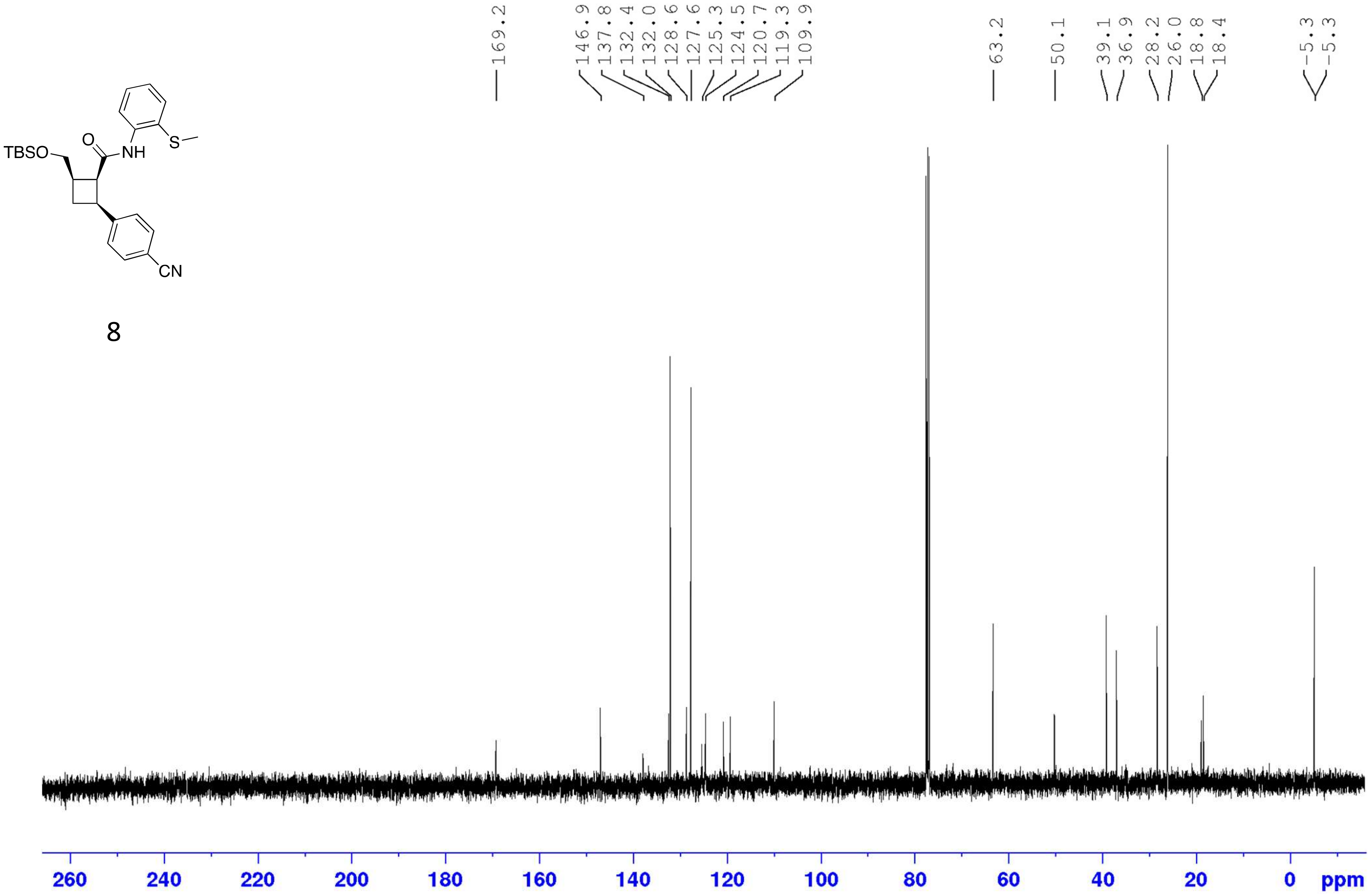
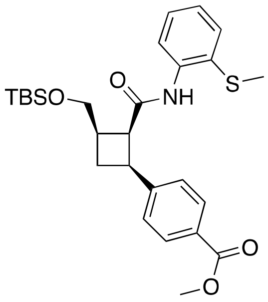
1.00
2.07
1.04
2.05
1.07
1.01
2.10
1.08
1.04
1.05
1.04
1.05
3.10
9.44
3.07
3.03
10
9
8
7
6
5
4
3
2
1
ppm

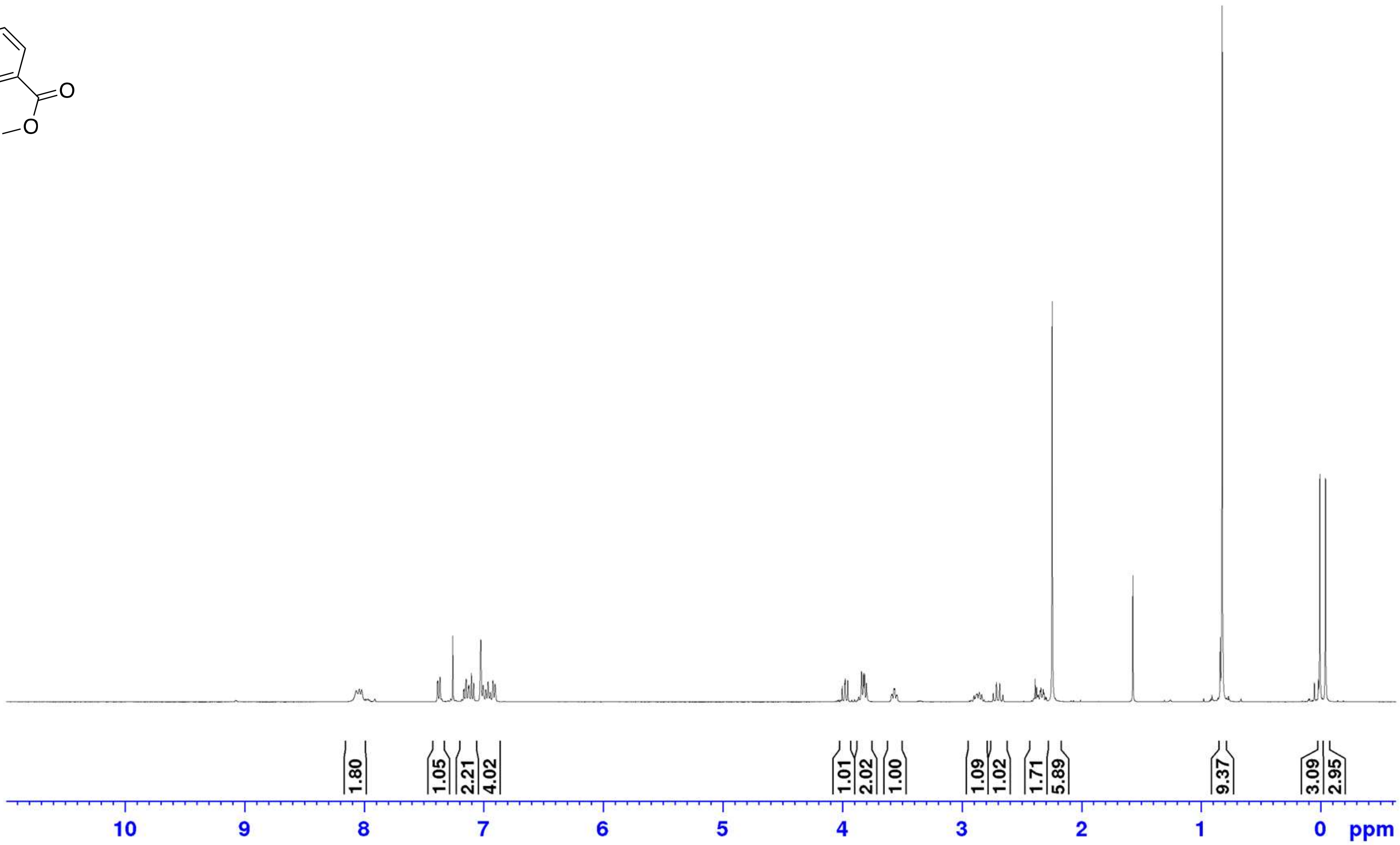

TBSO
O
NH
S
CN

8

169.2
146.9
137.8
132.4
132.0
128.6
127.6
125.3
124.5
120.7
119.3
109.9
63.2
50.1
39.1
36.9
28.2
26.0
18.8
18.4
-5.3
-5.3
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
O
NH
S
O
O

9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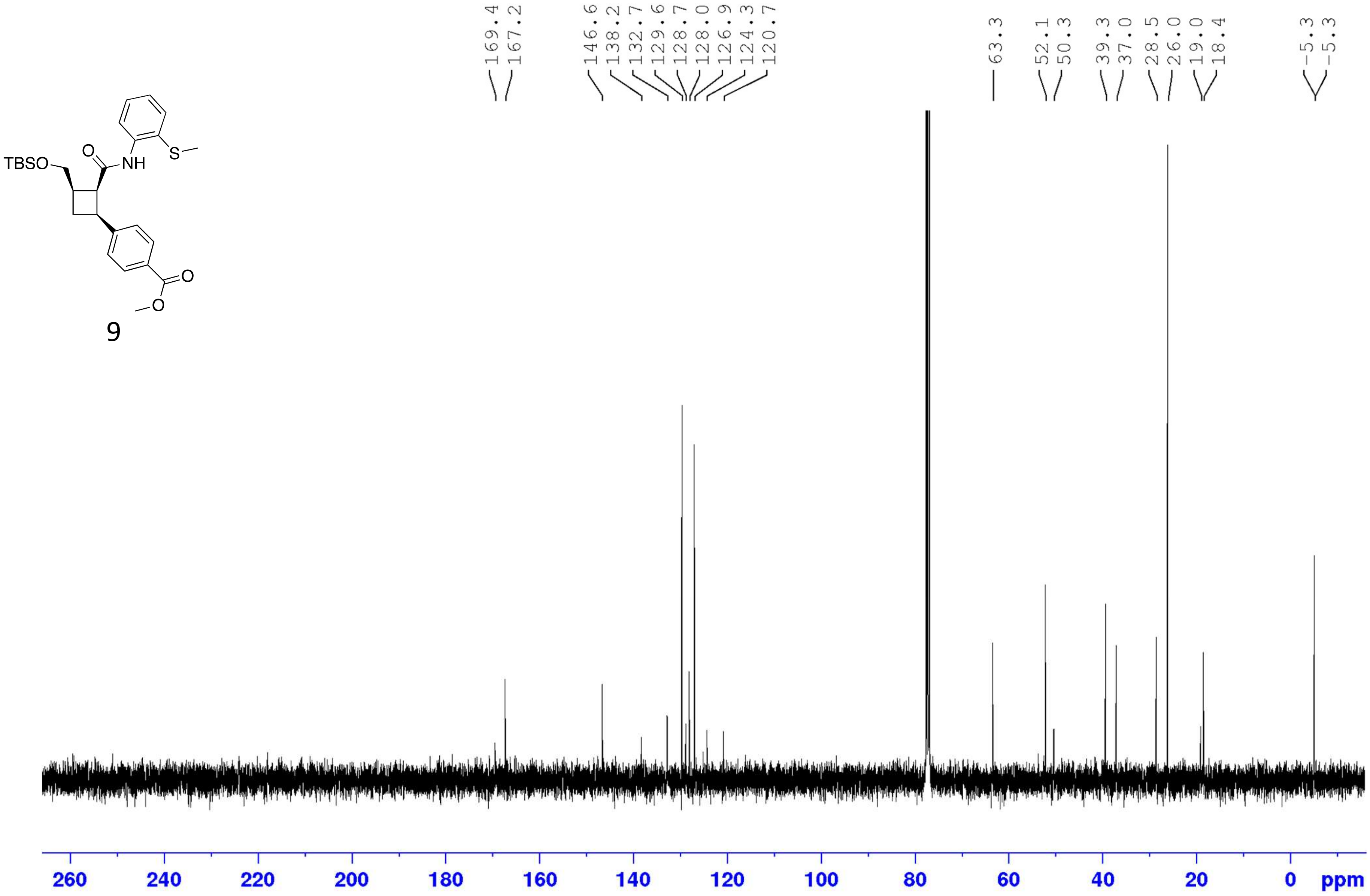
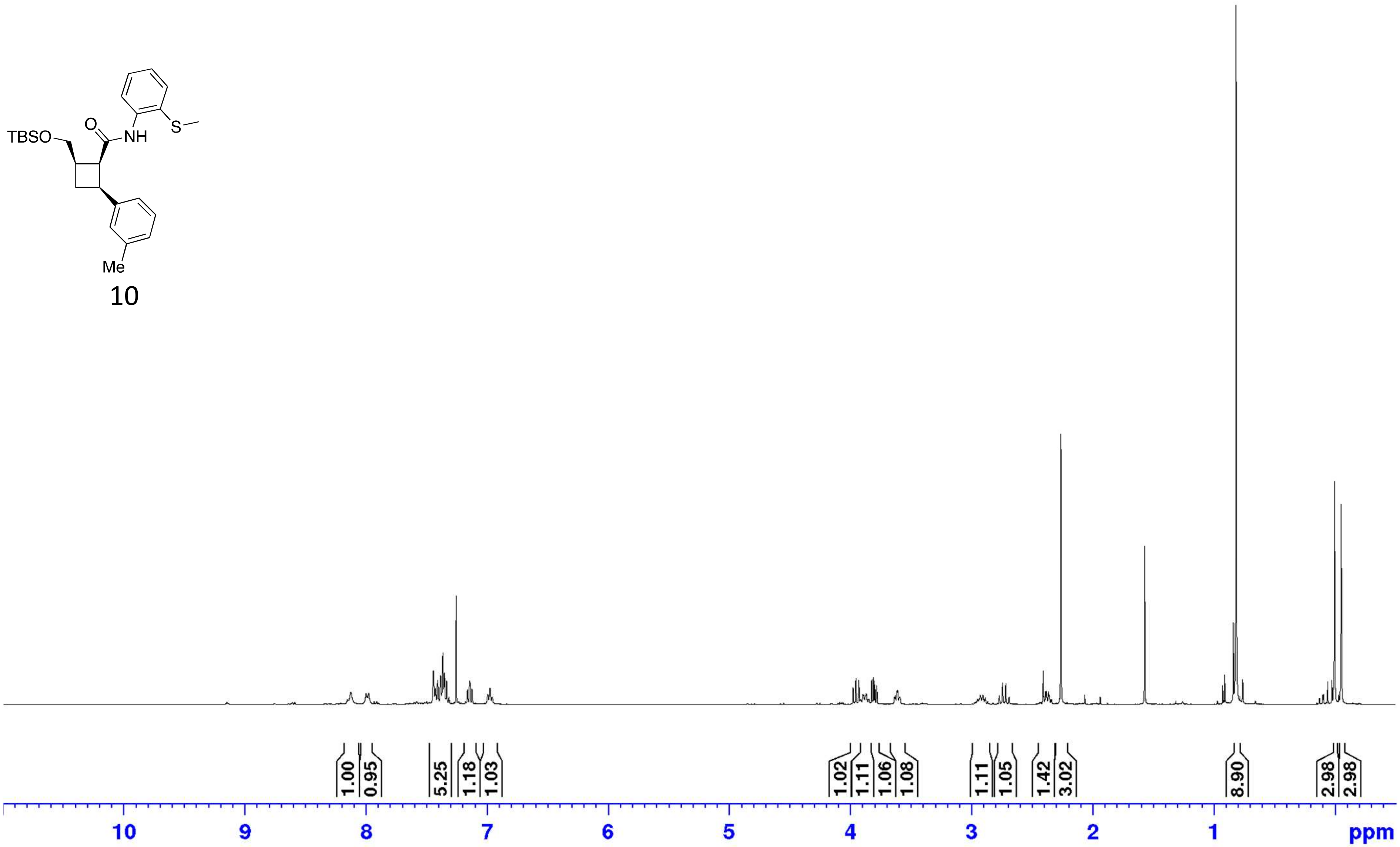
1.05
2.21
4.02
1.01
2.02
1.00
1.09
1.02
1.71
5.89
9.37
3.09
2.95
10
9
8
7
6
5
4
3
2
1
0
ppm



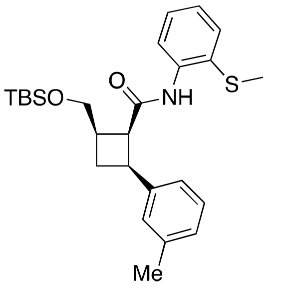
9

169.4
167.2
146.6
138.2
132.7
129.6
128.7
128.0
126.9
124.3
120.7
63.3
52.1
50.3
39.3
37.0
28.5
26.0
19.0
18.4
-5.3
-5.3
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

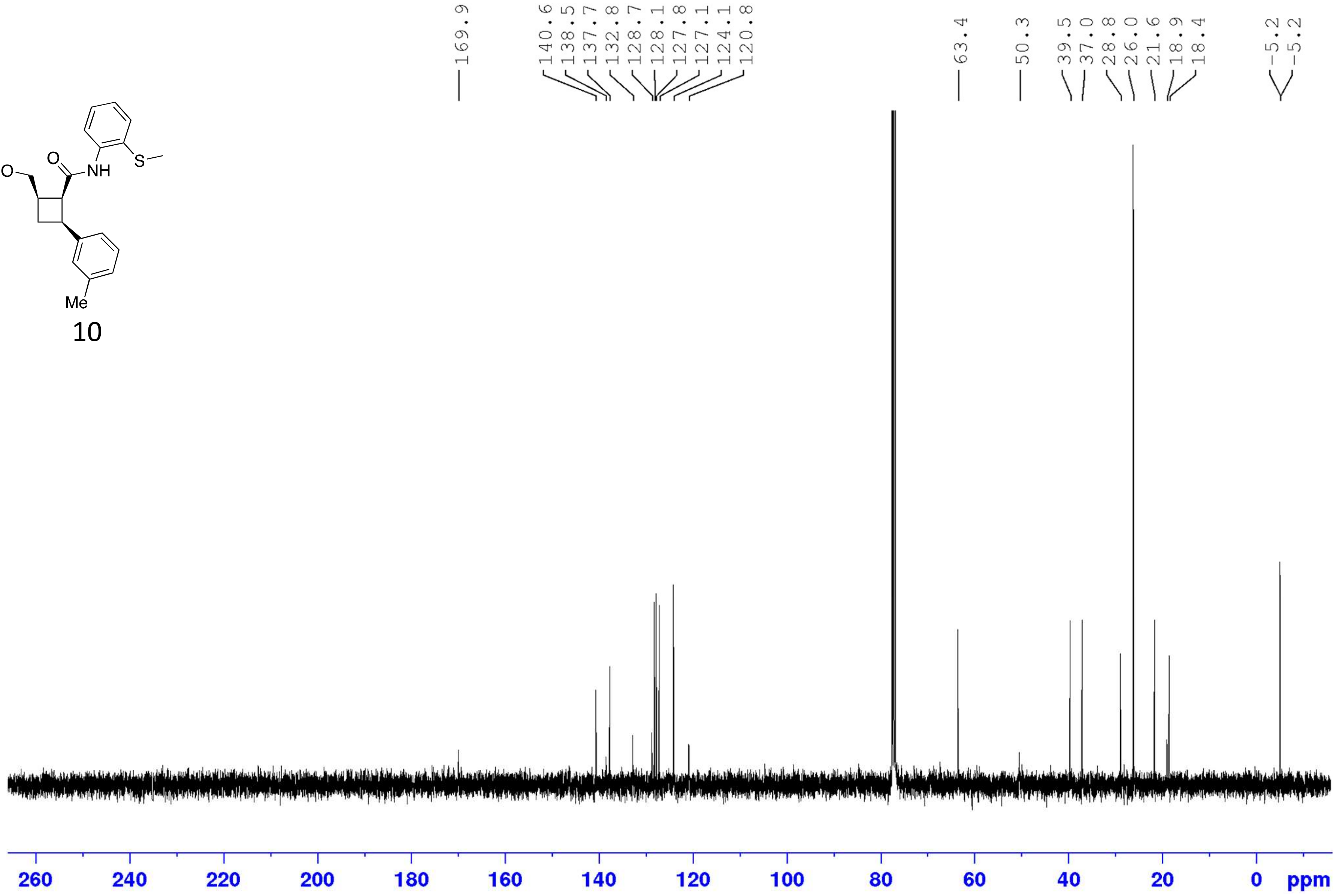


10

TBSO
O
NH
S
Me
1.00
0.95
5.25
1.18
1.03
1.02
1.11
1.06
1.08
1.11
1.05
1.42
3.02
8.90
2.98
2.98
10
9
8
7
6
5
4
3
2
1
ppm


TBSO
O
NH
S
Me

10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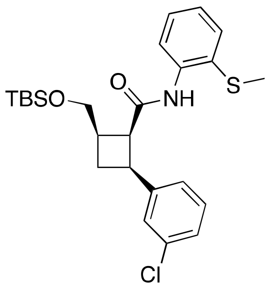
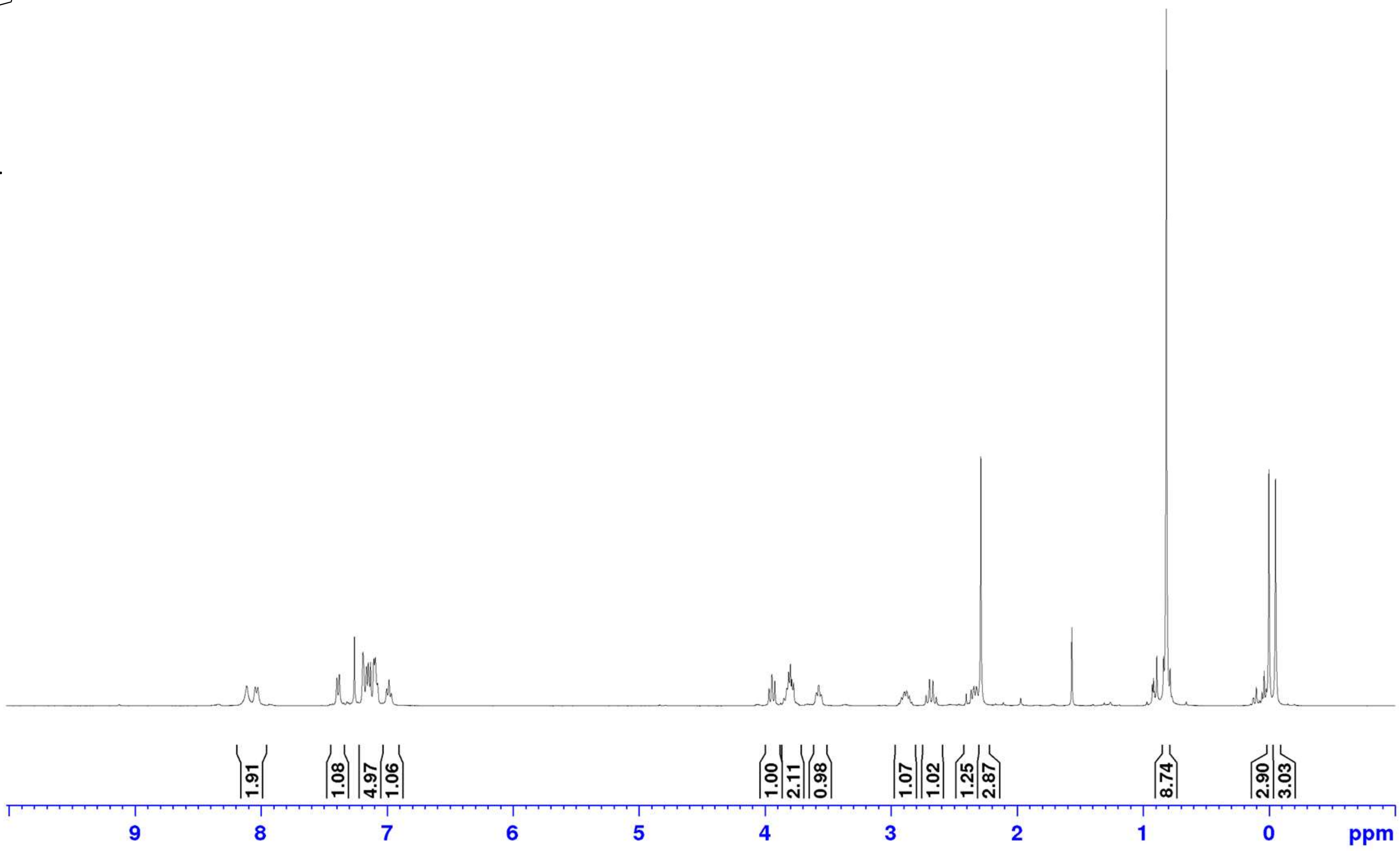
138.5
137.7
132.8
128.7
128.1
127.8
127.1
124.1
120.8
63.4
50.3
39.5
37.0
28.8
26.0
21.6
18.9
18.4
-5.2
-5.2
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
O
NH
S
Cl

11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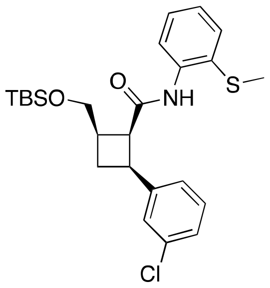
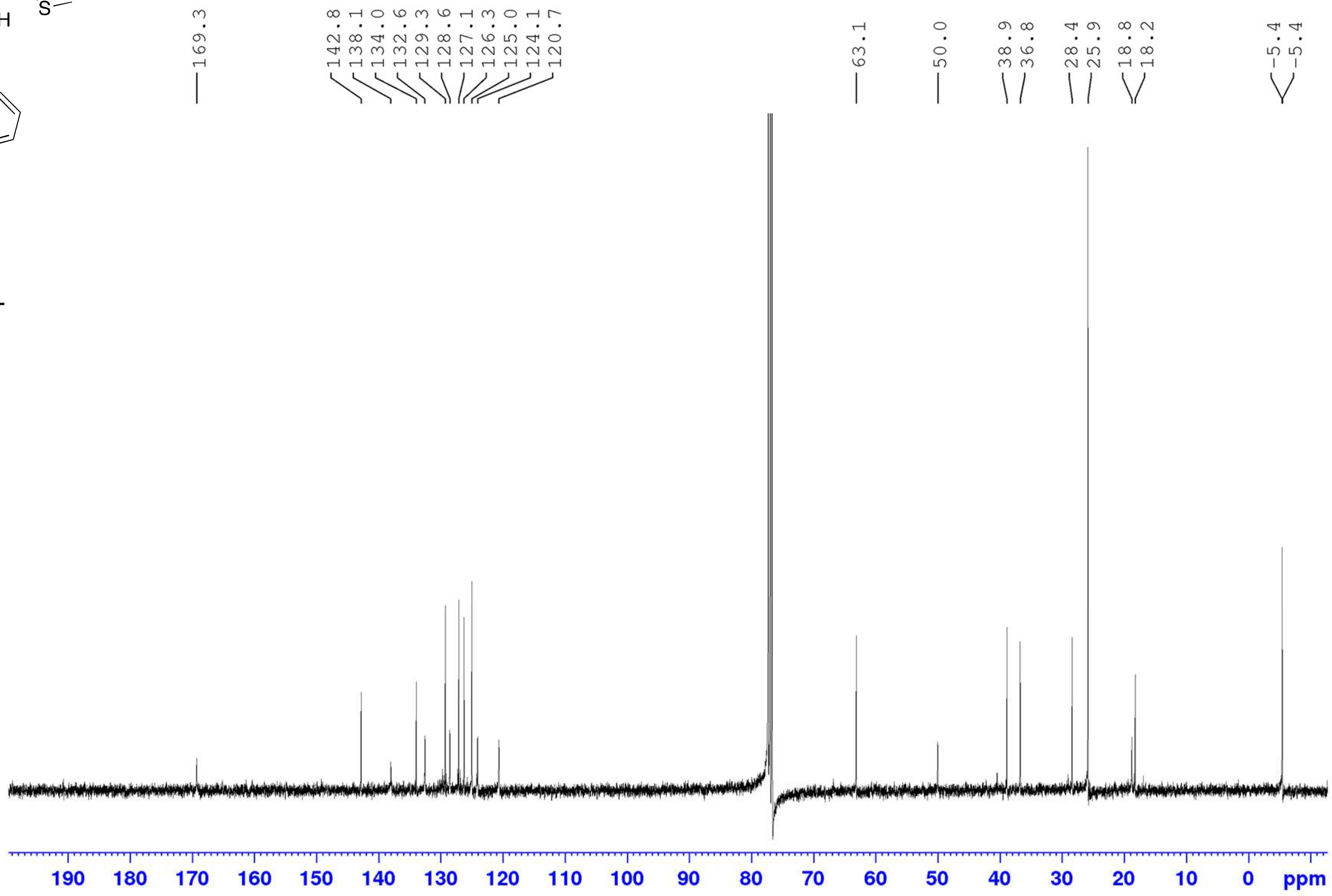
1.08
4.97
1.06
1.00
2.11
0.98
1.07
1.02
1.25
2.87
8.74
2.90
3.03
9
8
7
6
5
4
3
2
1
0
ppm

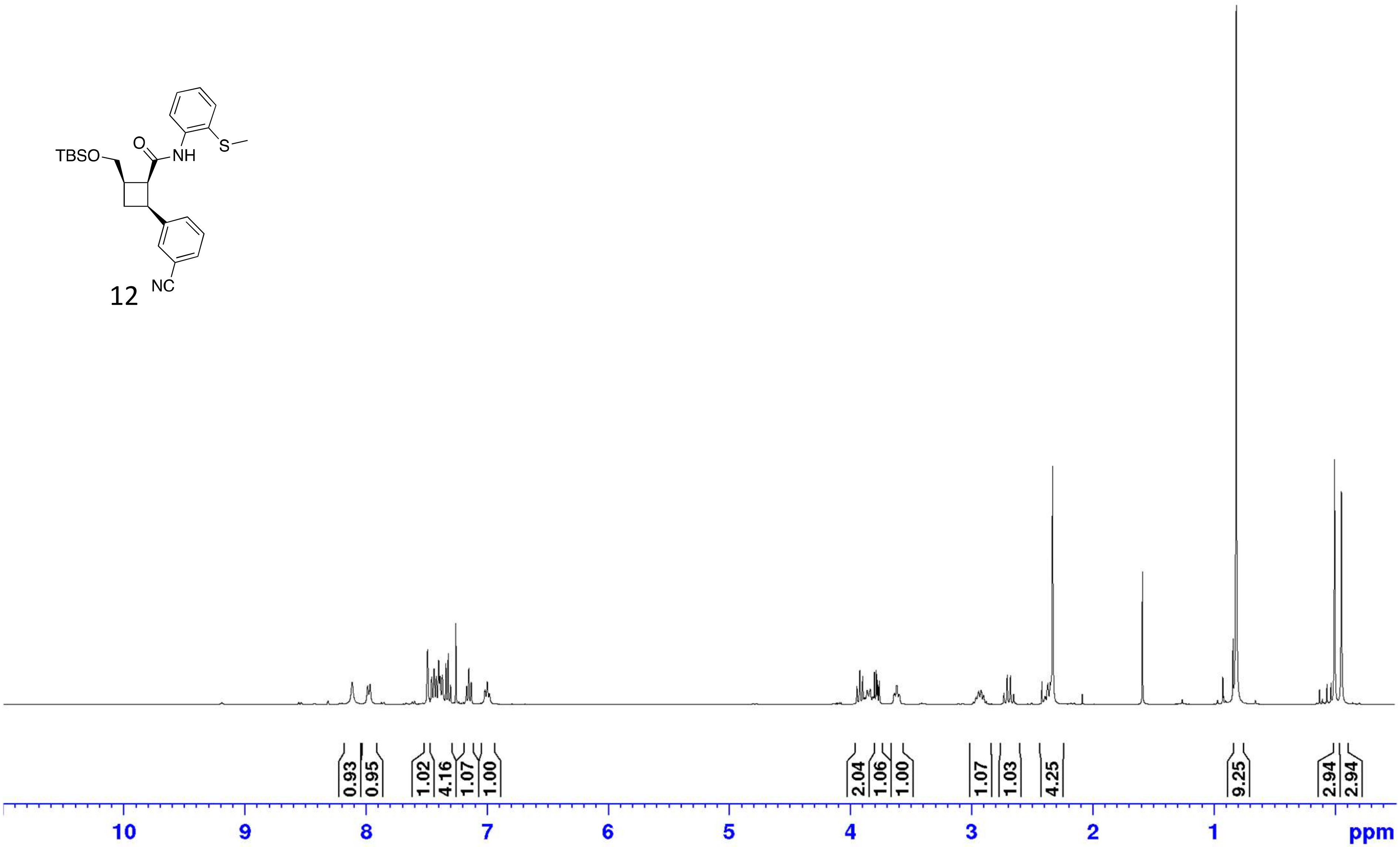

TBSO
O
NH
S
Cl

11


169.3
142.8
138.1
134.0
132.6
129.3
128.6
127.1
126.3
125.0
124.1
120.7
63.1
50.0
38.9
36.8
28.4
25.9
18.8
18.2
-5.4
-5.4
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

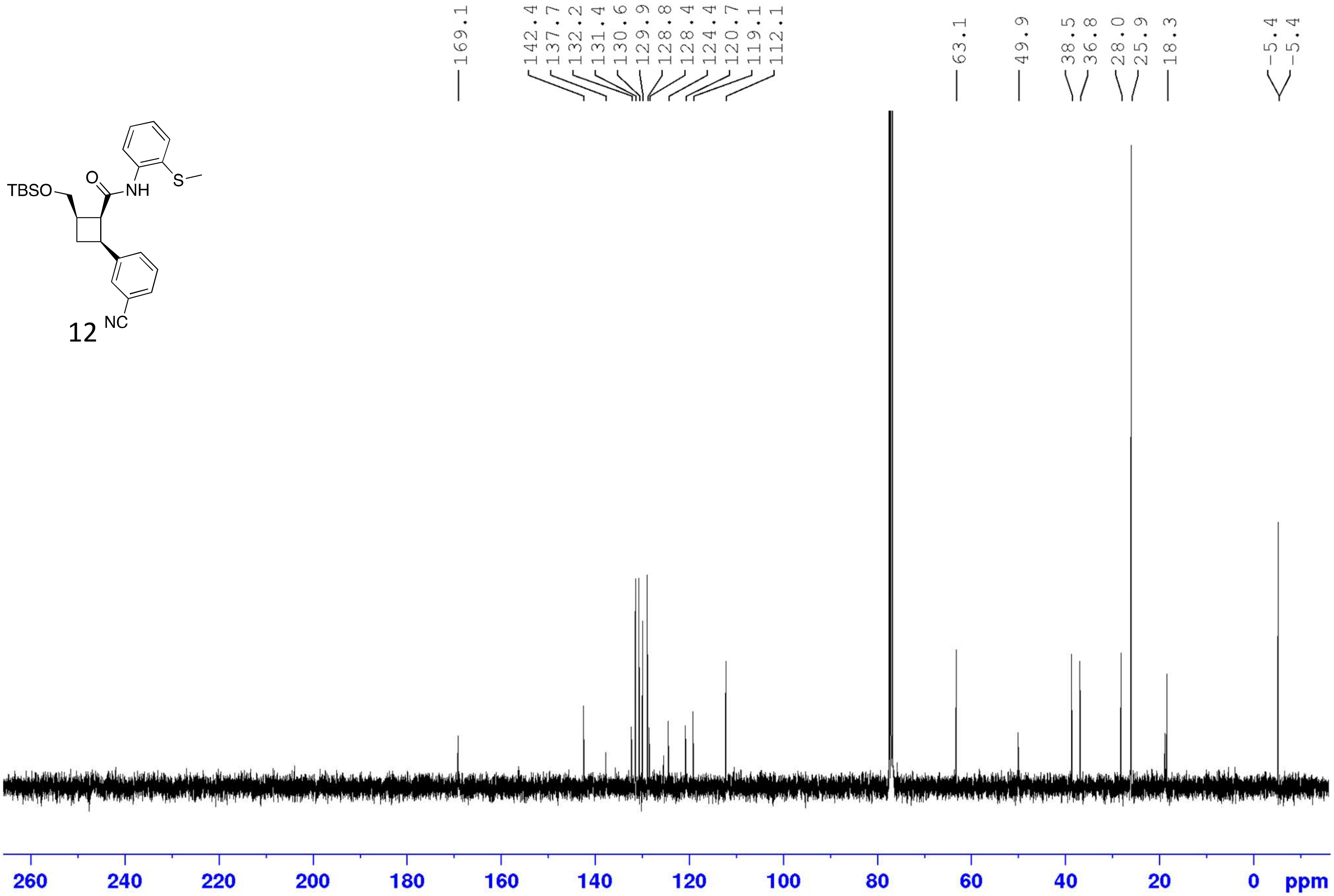
TBSO
O
NH
S
NC

12


0.93
0.95
1.02
4.16
1.07
1.00
2.04
1.06
1.00
1.07
1.03
4.25
9.25
2.94
2.94
10
9
8
7
6
5
4
3
2
1
ppm

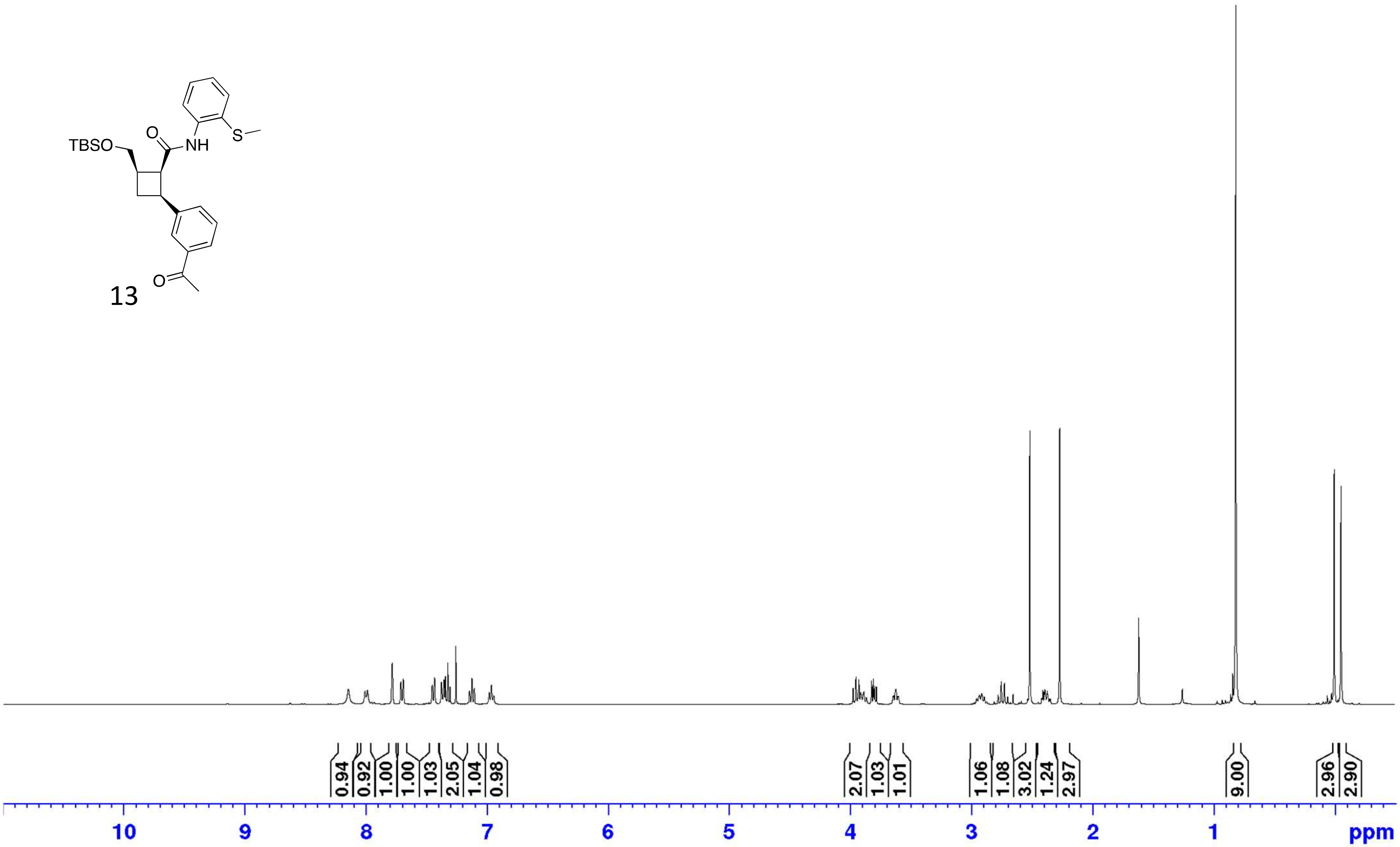
TBSO
O
NH
S
NC

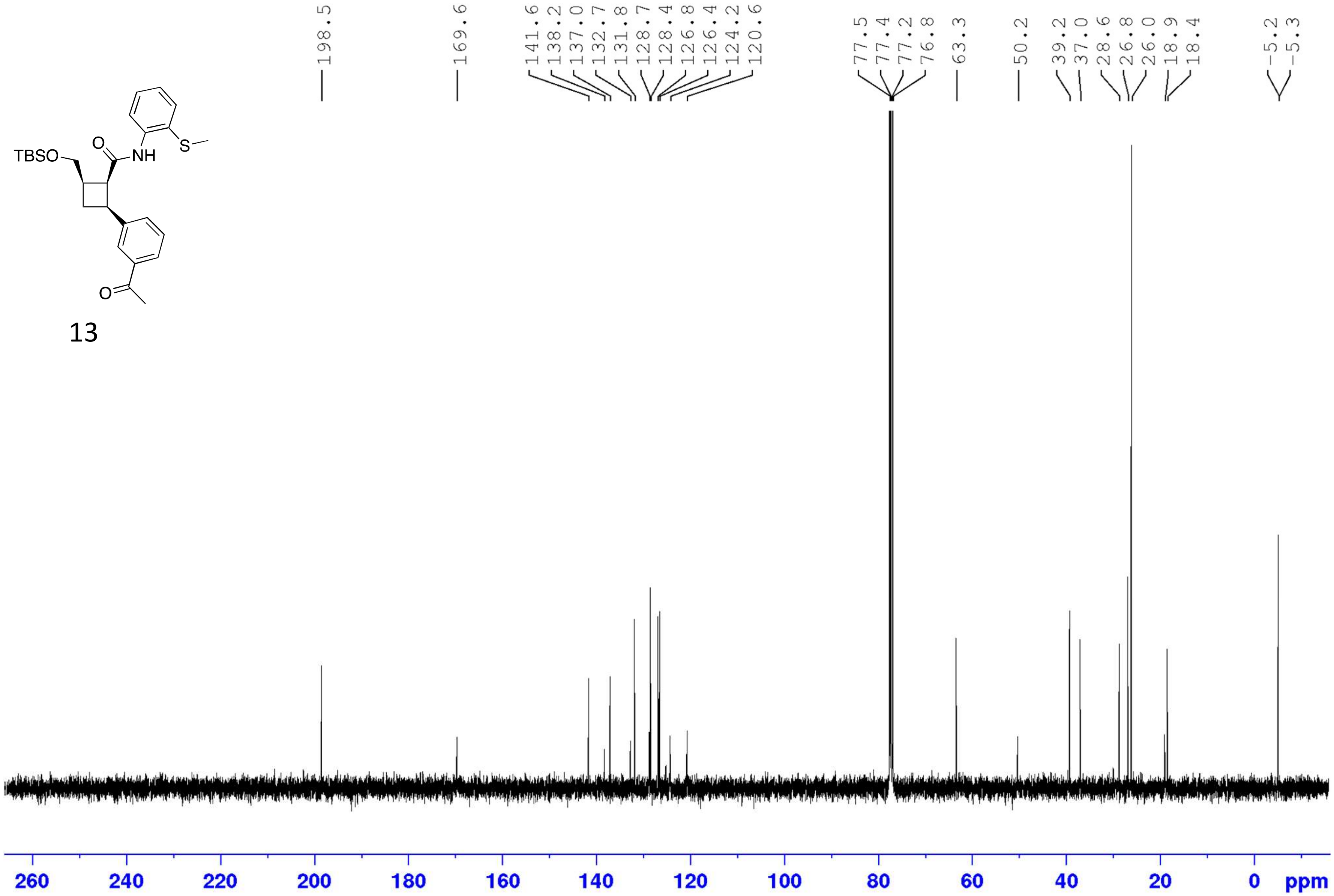
12


169.1
142.4
137.7
132.2
131.4
130.6
129.9
128.8
128.4
124.4
120.7
119.1
112.1
63.1
49.9
38.5
36.8
28.0
25.9
18.3
-5.4
-5.4
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

TBSO
O
NH
S
O

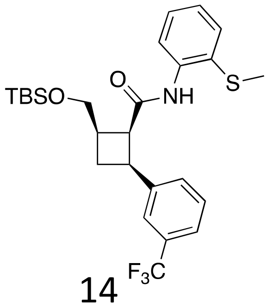
13


0.94
0.92
1.00
1.00
1.03
2.05
1.04
0.98
2.07
1.03
1.01
1.06
1.08
3.02
1.24
2.97
9.00
2.96
2.90
10
9
8
7
6
5
4
3
2
1
ppm

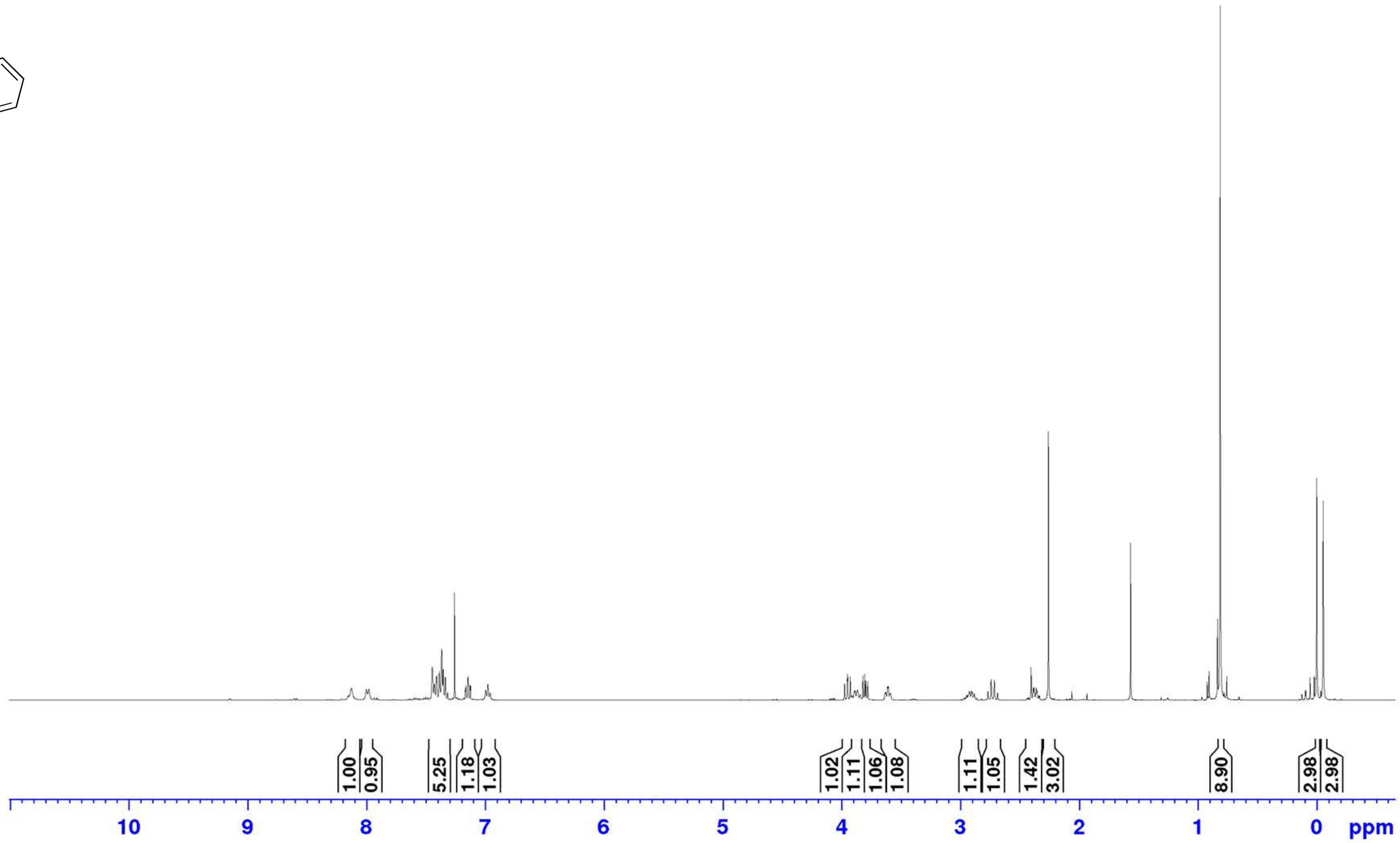

TBSO
O
NH
S
O

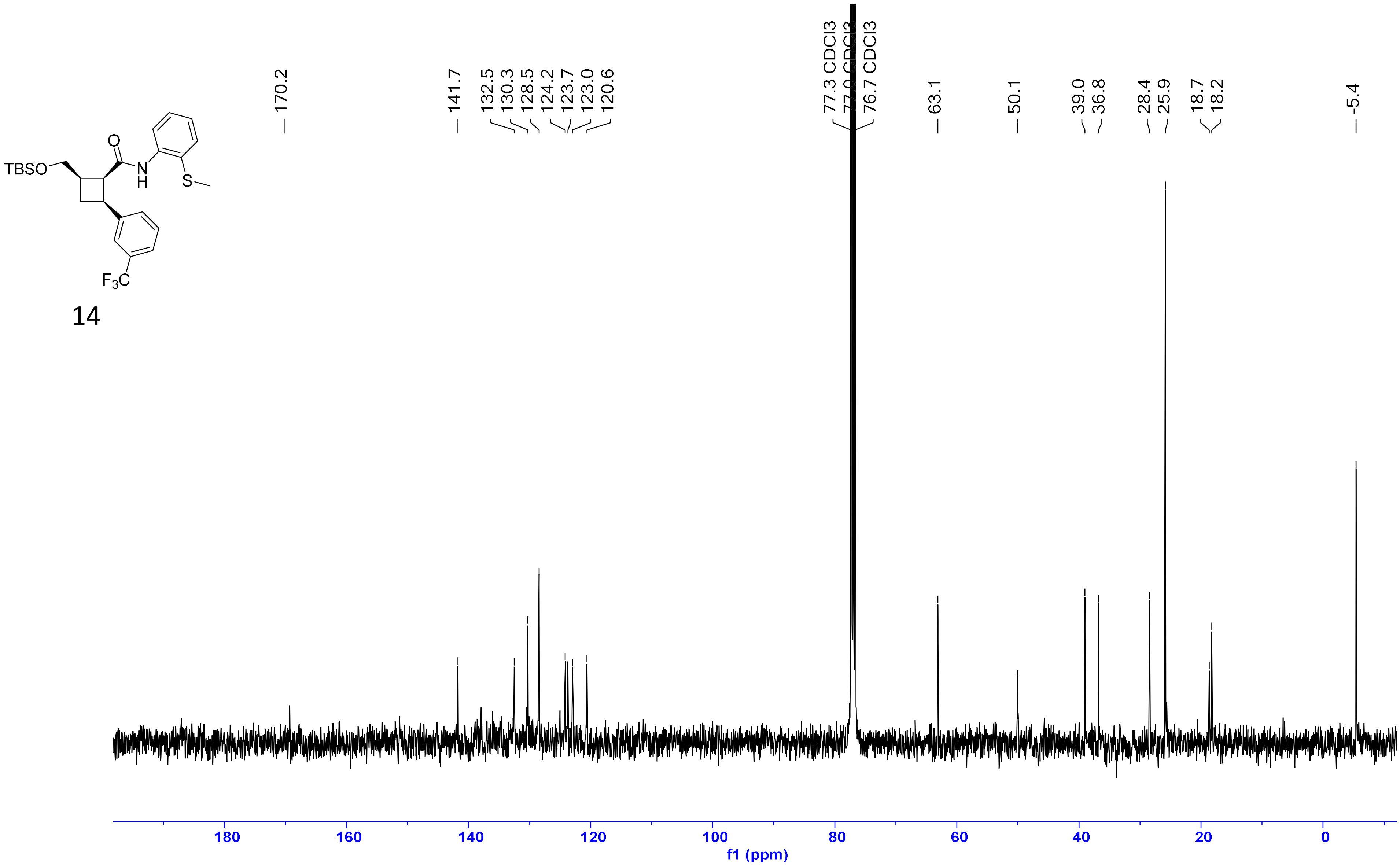
13

198.5
169.6
141.6
138.2
137.0
132.7
131.8
128.7
128.4
126.8
126.4
124.2
120.6
77.5
77.4
77.2
76.8
63.3
50.2
39.2
37.0
28.6
26.8
26.0
18.9
18.4
-5.2
-5.3
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
O
NH
S
F3C

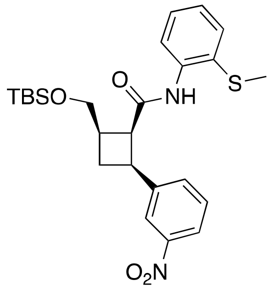
14


1.00
0.95
5.25
1.18
1.03
1.02
1.11
1.06
1.08
1.11
1.05
1.42
3.02
8.90
2.98
2.98
10
9
8
7
6
5
4
3
2
1
0
ppm

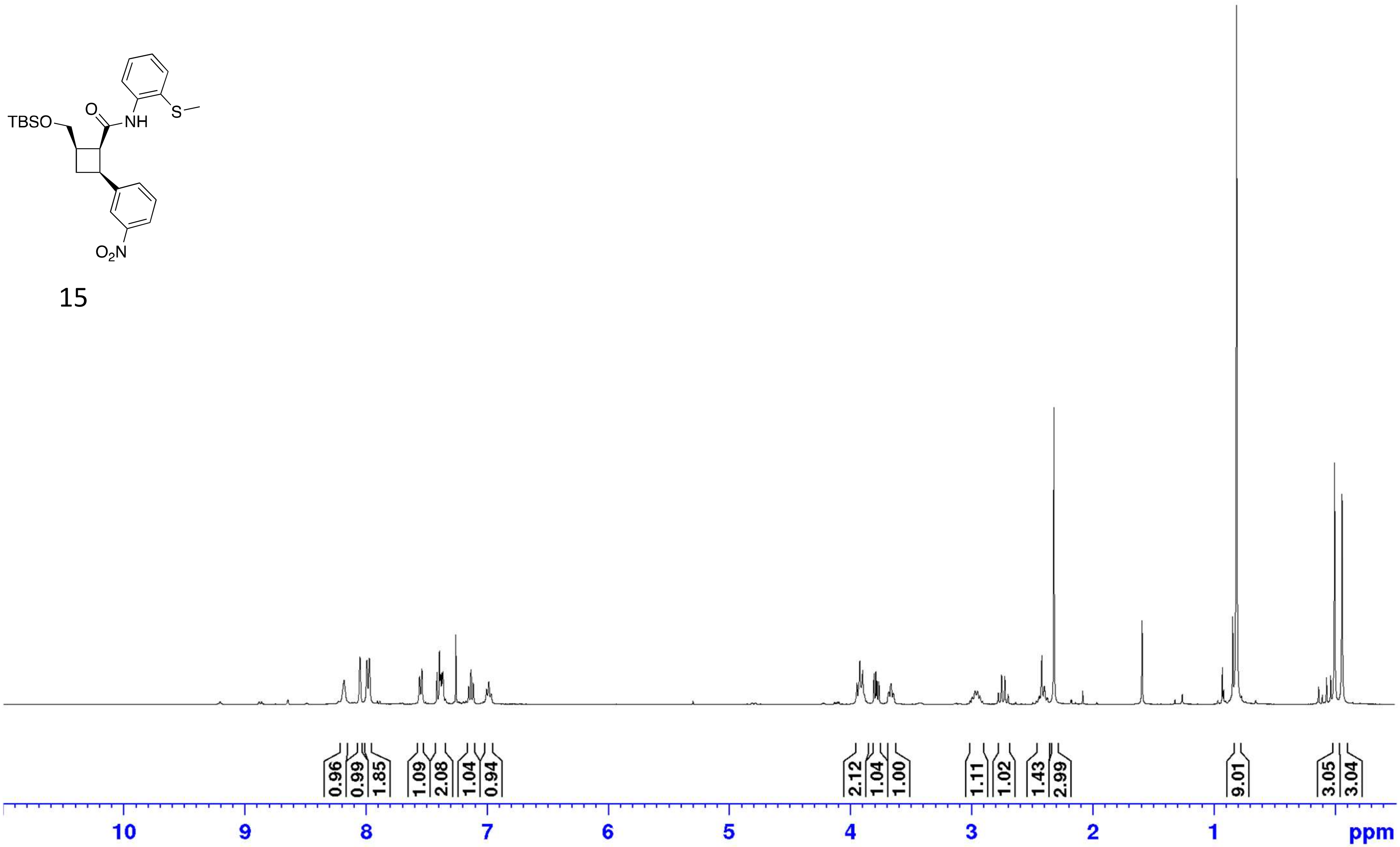


14

170.2
141.7
132.5
130.3
128.5
124.2
123.7
123.0
120.6
77.3 CDCl3
77.0 CDCl3
76.7 CDCl3
63.1
50.1
39.0
36.8
28.4
25.9
18.7
18.2
-5.4
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


TBSO
O
NH
S
O2N

15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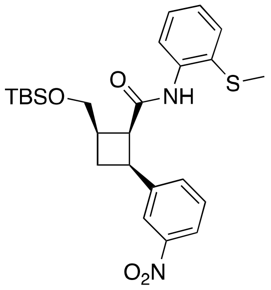
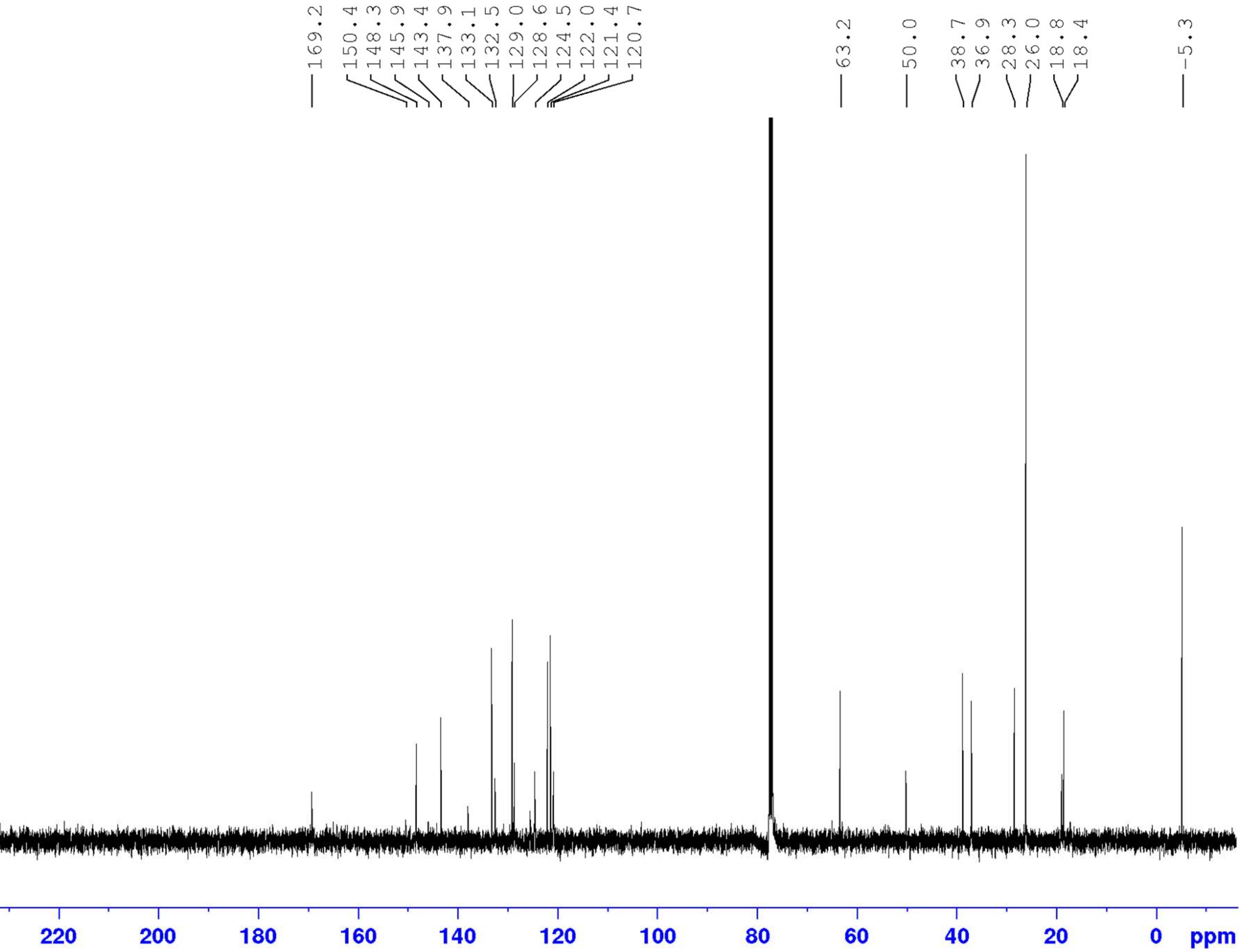
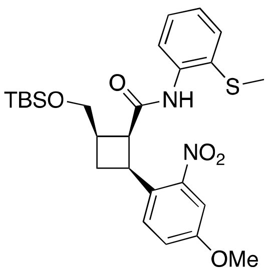
0.99
1.85
1.09
2.08
1.04
0.94
2.12
1.04
1.00
1.11
1.02
1.43
2.99
9.01
3.05
3.04
10
9
8
7
6
5
4
3
2
1
ppm

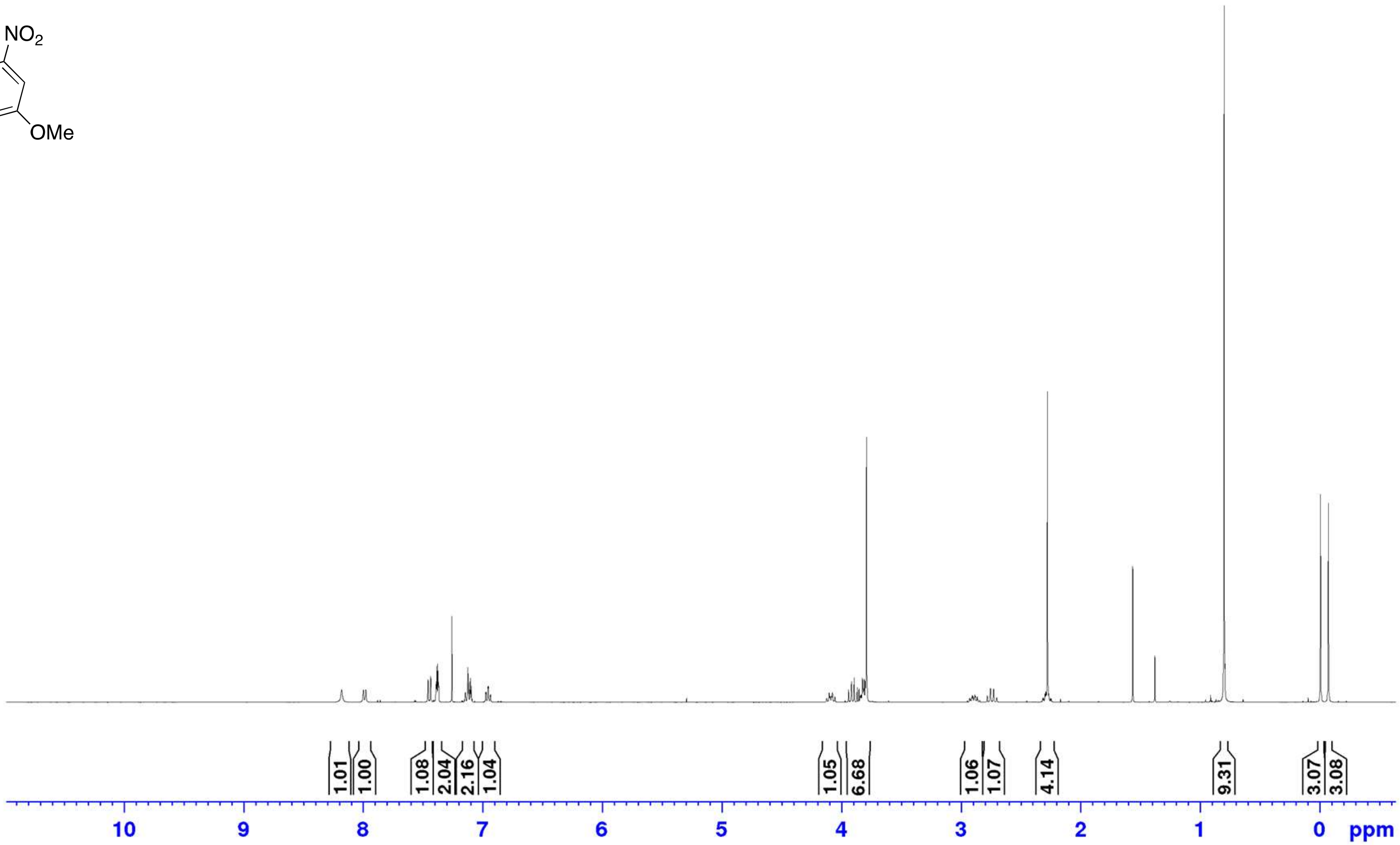

TBSO
O
NH
S
O_2N

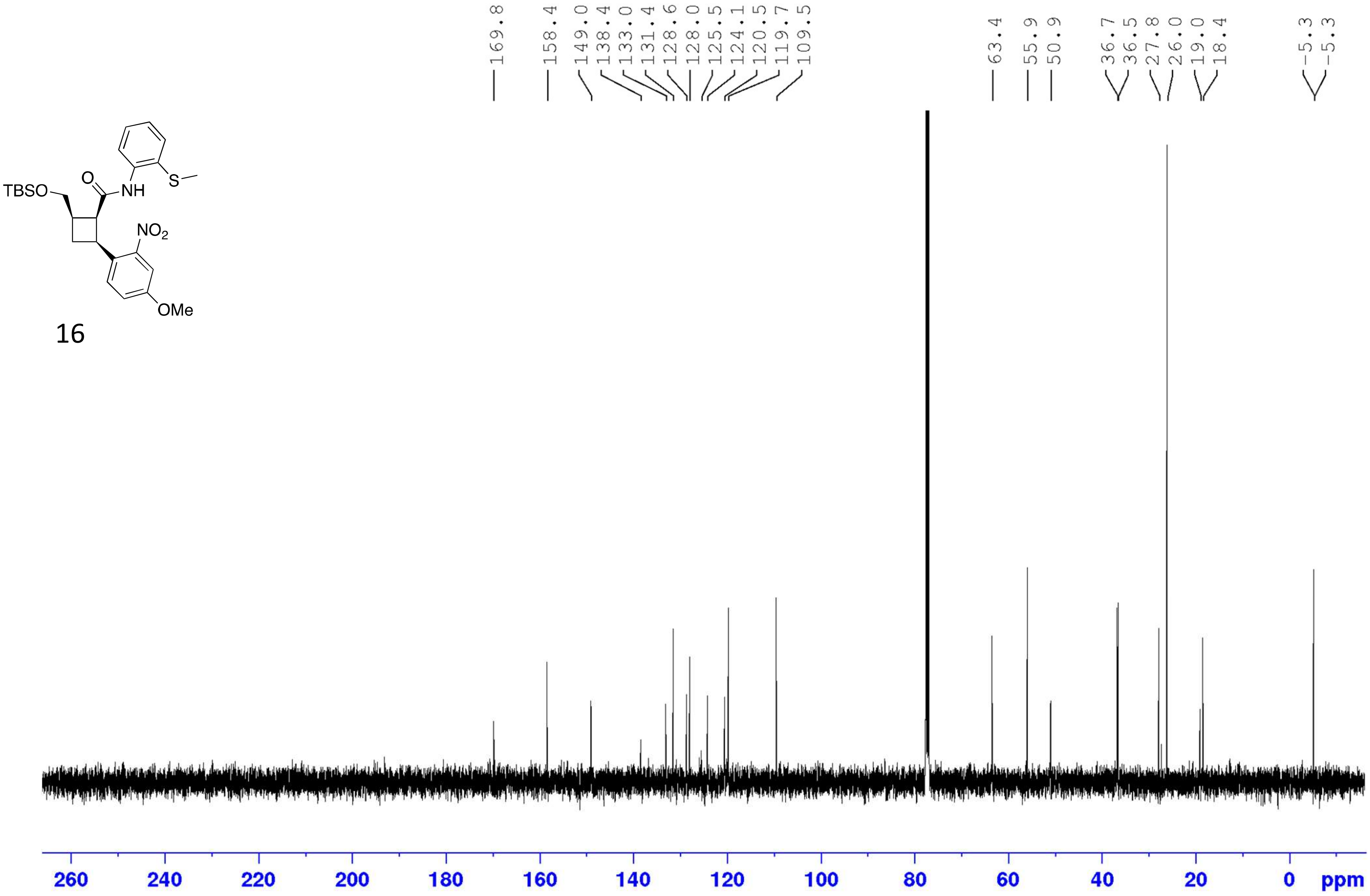
15


169.2
150.4
148.3
145.9
143.4
137.9
133.1
132.5
129.0
128.6
124.5
122.0
121.4
120.7
63.2
50.0
38.7
36.9
28.3
26.0
18.8
18.4
-5.3
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
O
NH
S
NO2
OMe

16


1.01
1.00
1.08
2.04
2.16
1.04
1.05
6.68
1.06
1.07
4.14
9.31
3.07
3.08
10
9
8
7
6
5
4
3
2
1
0
ppm

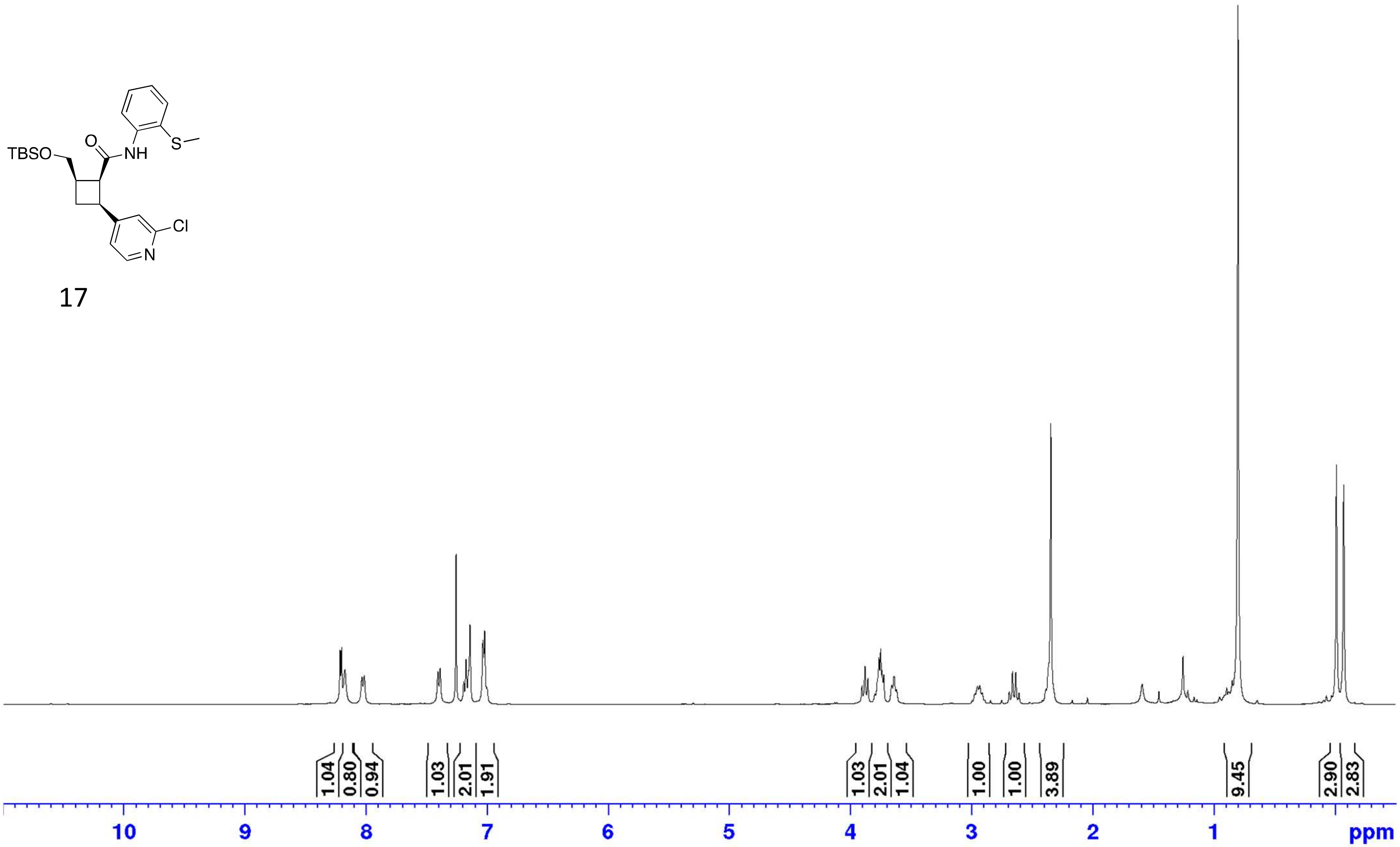

TBSO
O
NH
S
NO_2
OMe

16

169.8
158.4
149.0
138.4
133.0
131.4
128.6
128.0
125.5
124.1
120.5
119.7
109.5
63.4
55.9
50.9
36.7
36.5
27.8
26.0
19.0
18.4
-5.3
-5.3
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

TBSO
O
NH
S
Cl
N

17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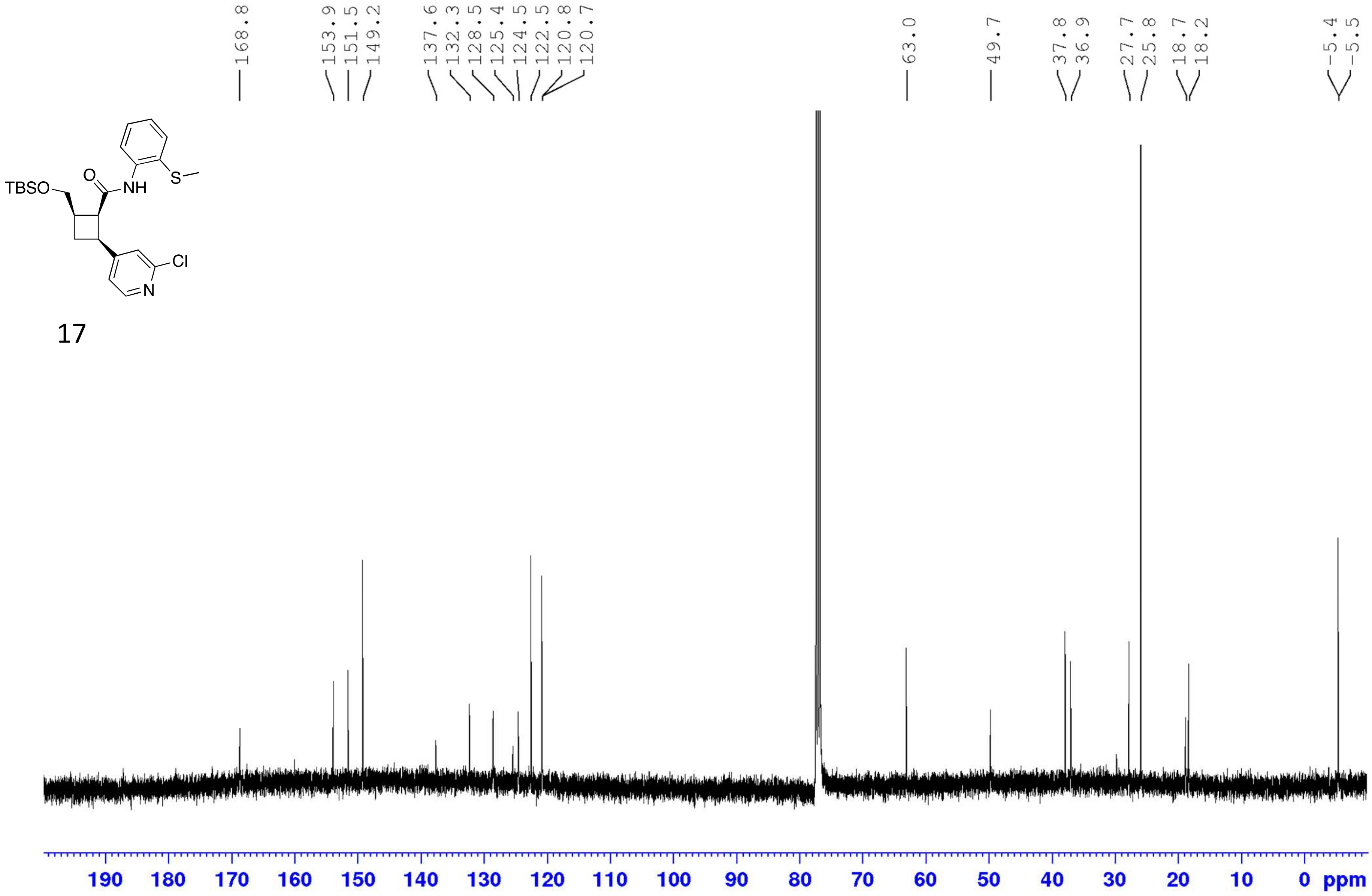
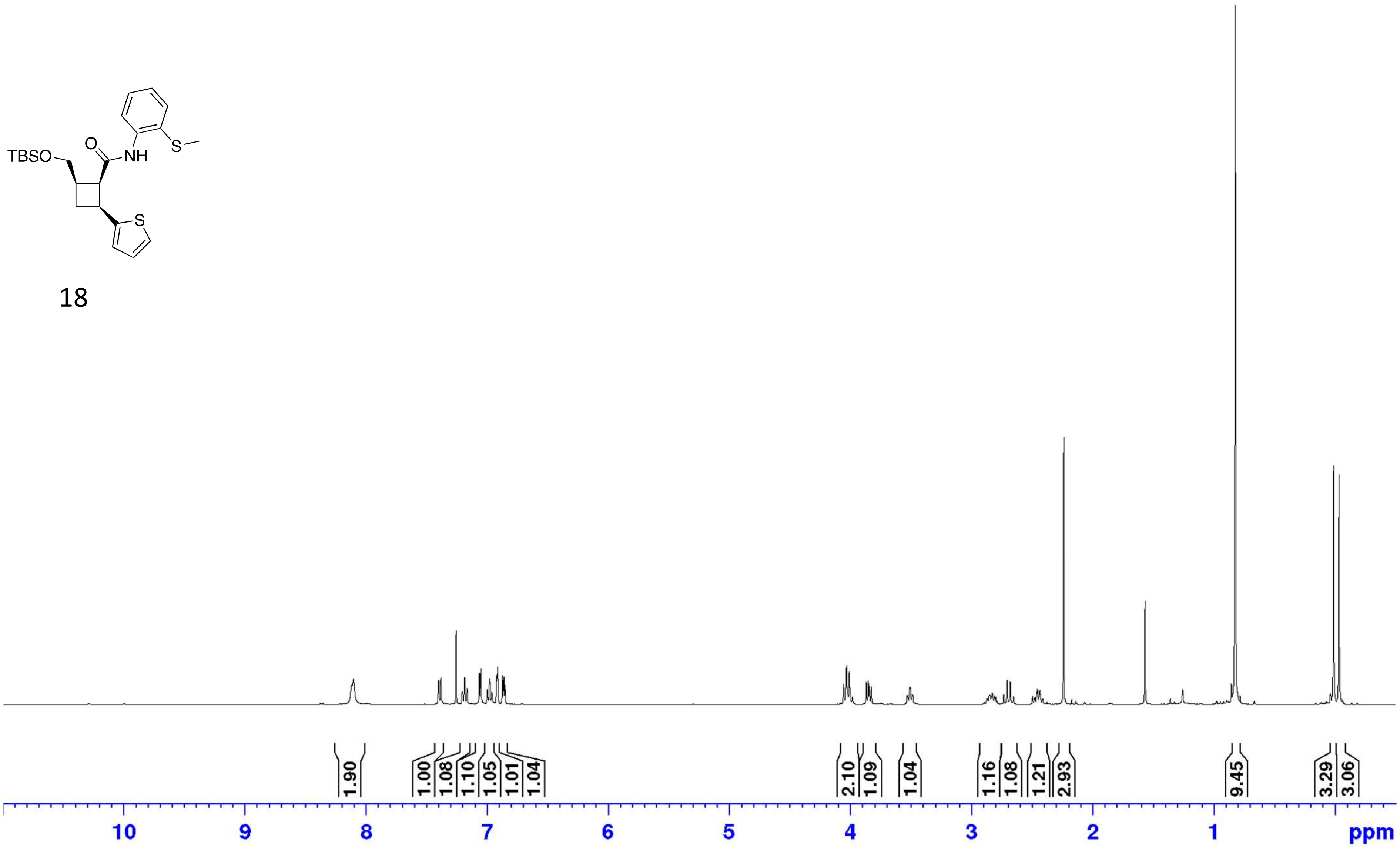
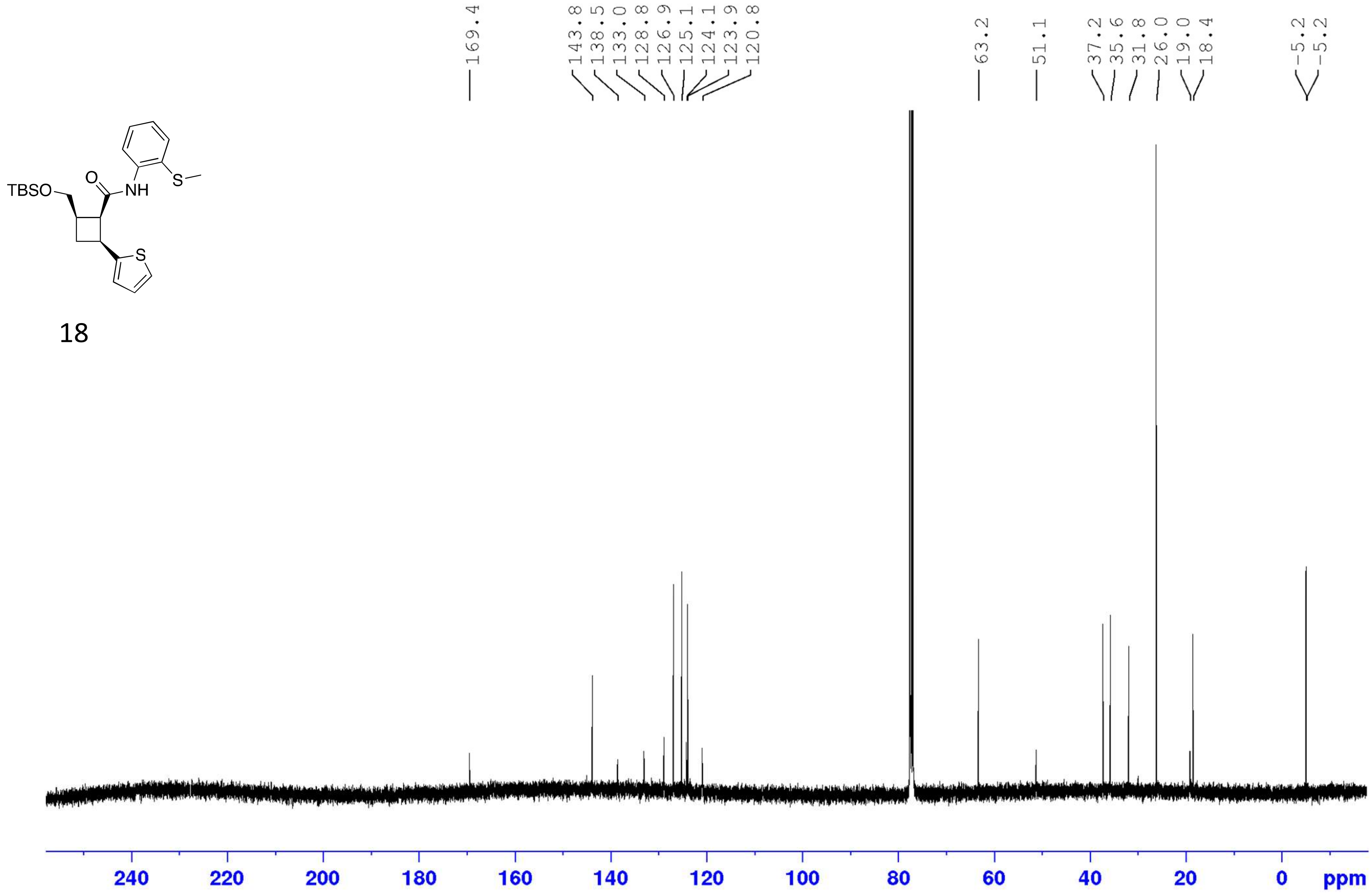
0.80
0.94
1.03
2.01
1.91
1.03
2.01
1.04
1.00
1.00
3.89
9.45
2.90
2.83
10
9
8
7
6
5
4
3
2
1
ppm


168.8
153.9
151.5
149.2
137.6
132.3
128.5
125.4
124.5
122.5
120.8
120.7
63.0
49.7
37.8
36.9
27.7
25.8
18.7
18.2
-5.4
-5.5
TBSO
O
NH
S
Cl
N
17
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

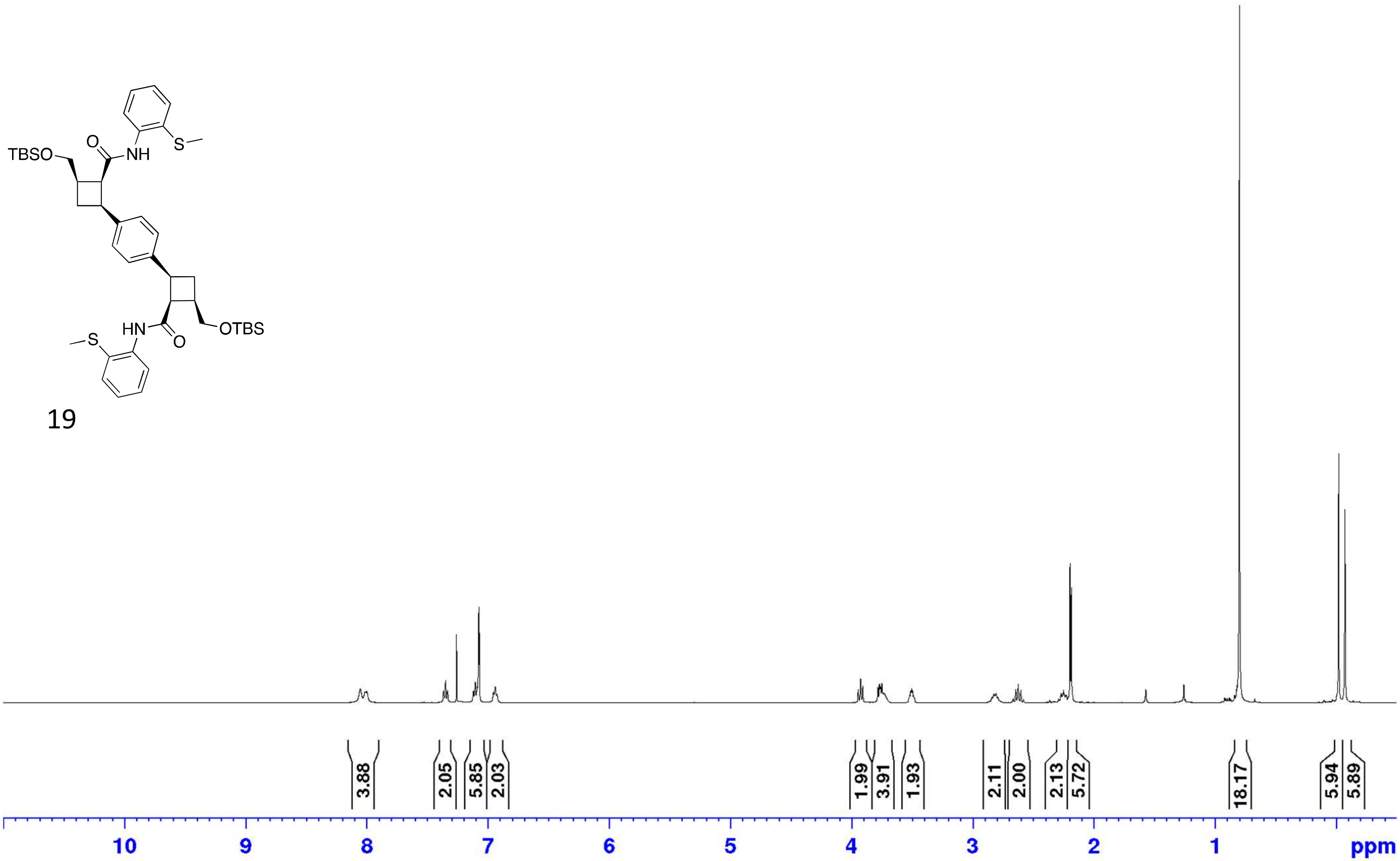

TBSO
O
NH
S
S

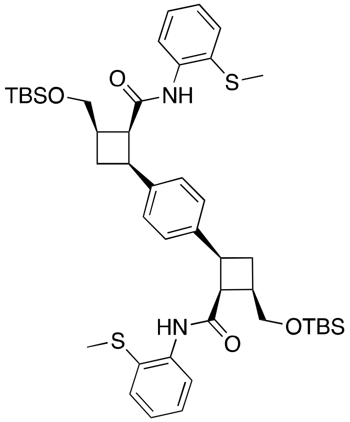
18

1.90
1.00
1.08
1.10
1.05
1.01
1.04
2.10
1.09
1.04
1.16
1.08
1.21
2.93
9.45
3.29
3.06
10
9
8
7
6
5
4
3
2
1
ppm

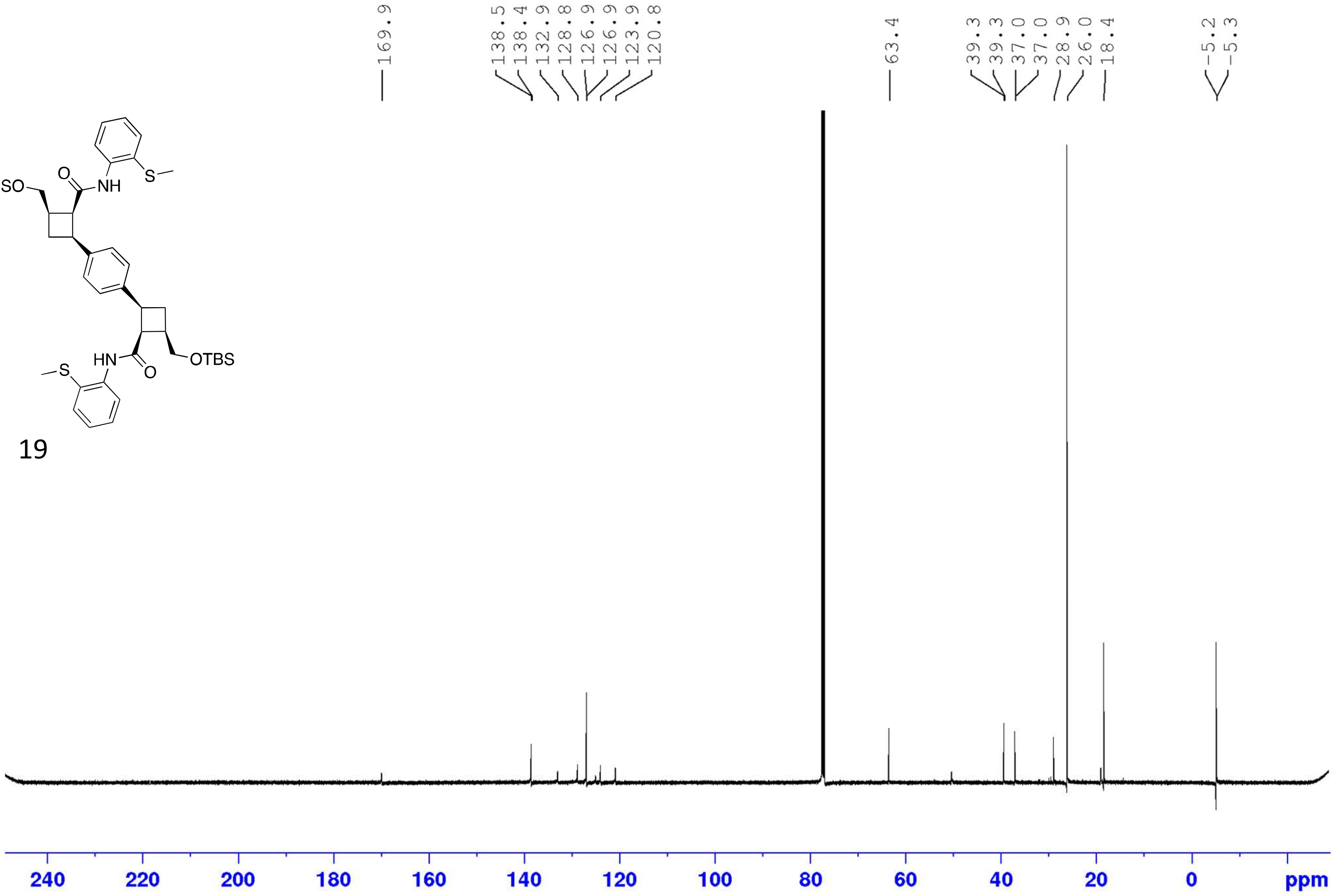

TBSO
O
NH
S
S
169.4
143.8
138.5
133.0
128.8
126.9
125.1
124.1
123.9
120.8
63.2
51.1
37.2
35.6
31.8
26.0
19.0
18.4
-5.2
-5.2
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

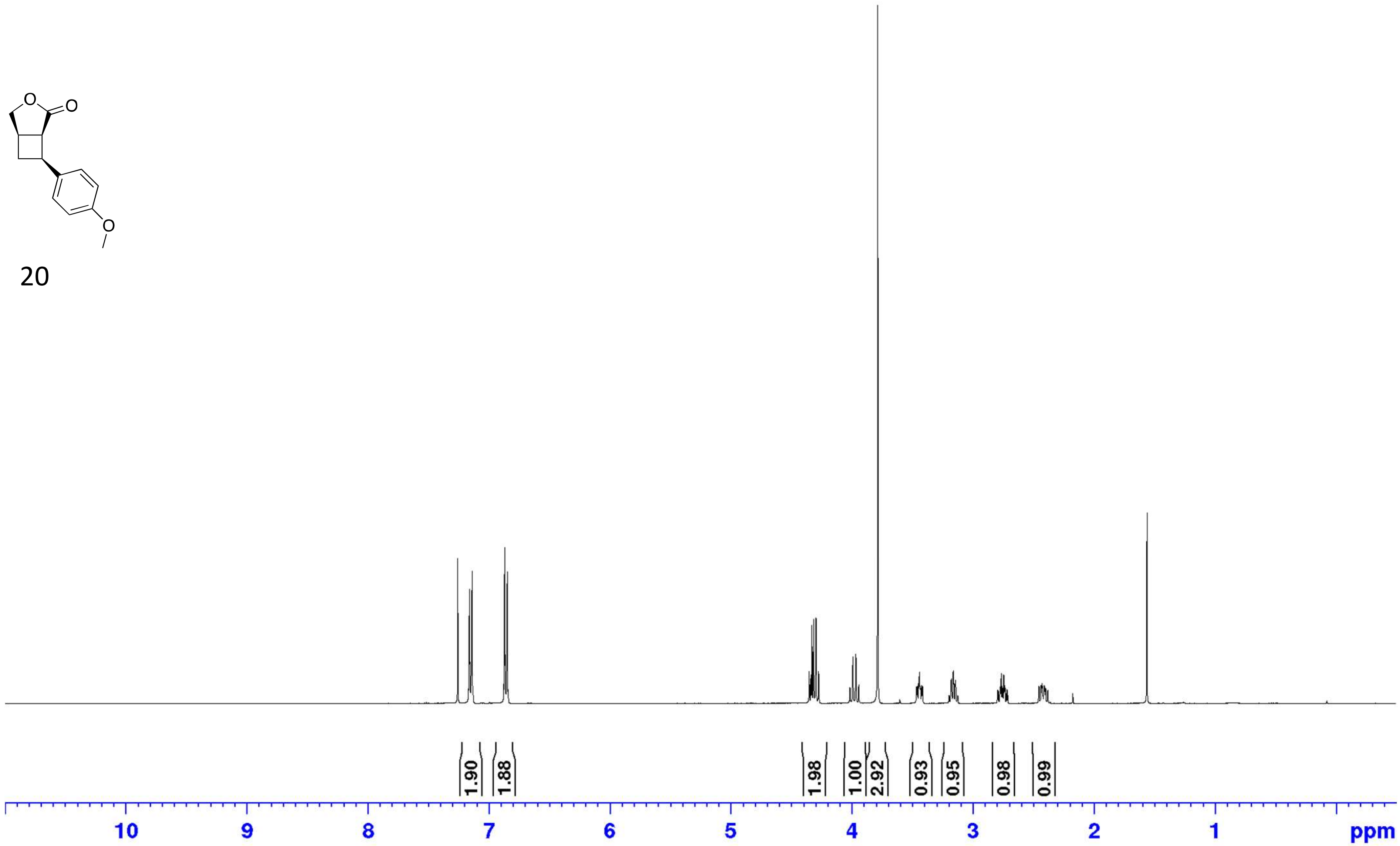
18


TBSO
O
NH
S
HN
O
OTBS
S
19
3.88
2.05
5.85
2.03
1.99
3.91
1.93
2.11
2.00
2.13
5.72
18.17
5.94
5.89
10
9
8
7
6
5
4
3
2
1
ppm

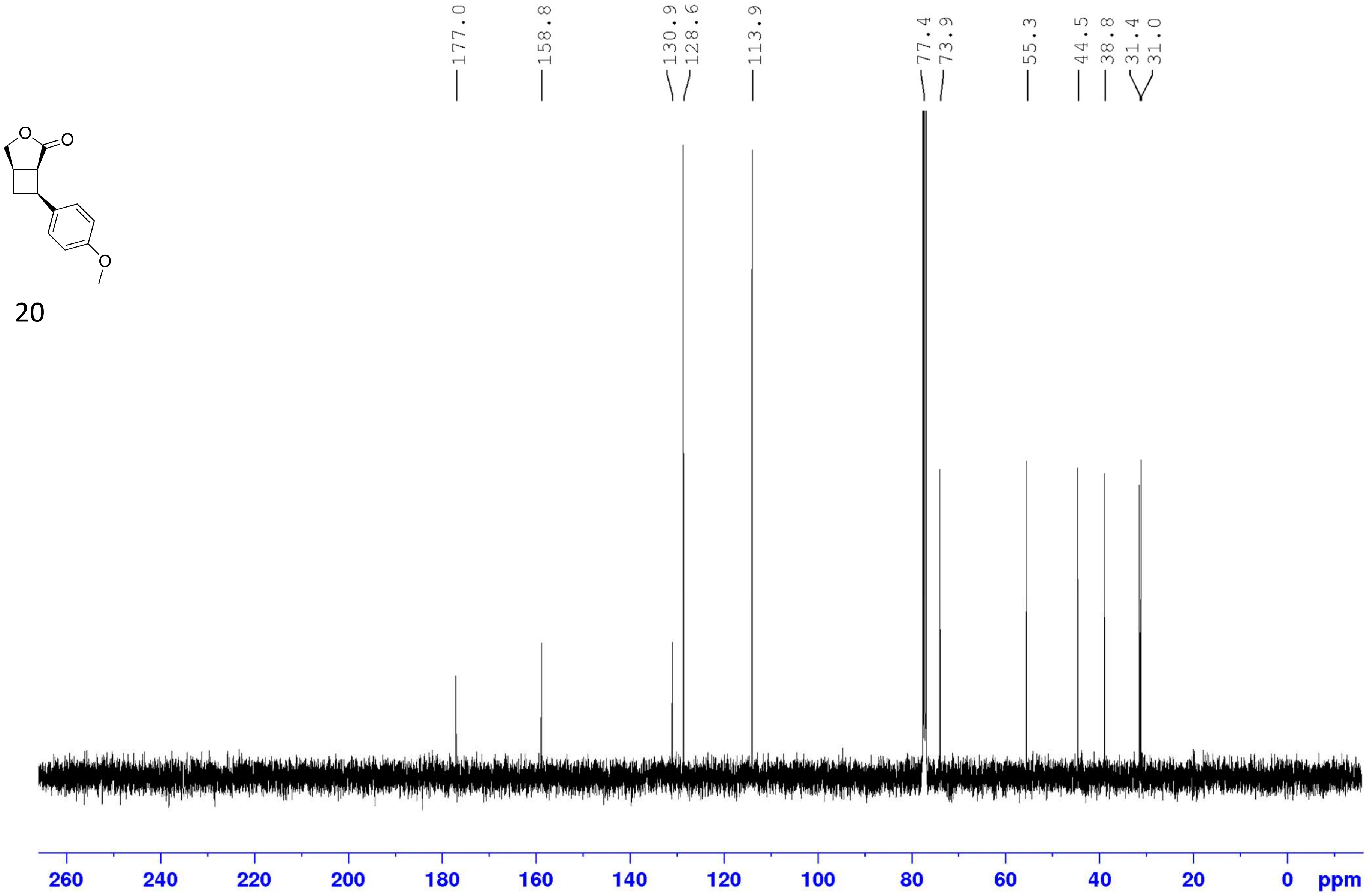

TBSO
O
NH
S
HN
O
OTBS
S

19


169.9
138.5
138.4
132.9
128.8
126.9
126.9
123.9
120.8
63.4
39.3
39.3
37.0
37.0
28.9
26.0
18.4
-5.2
-5.3
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

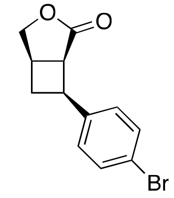


20

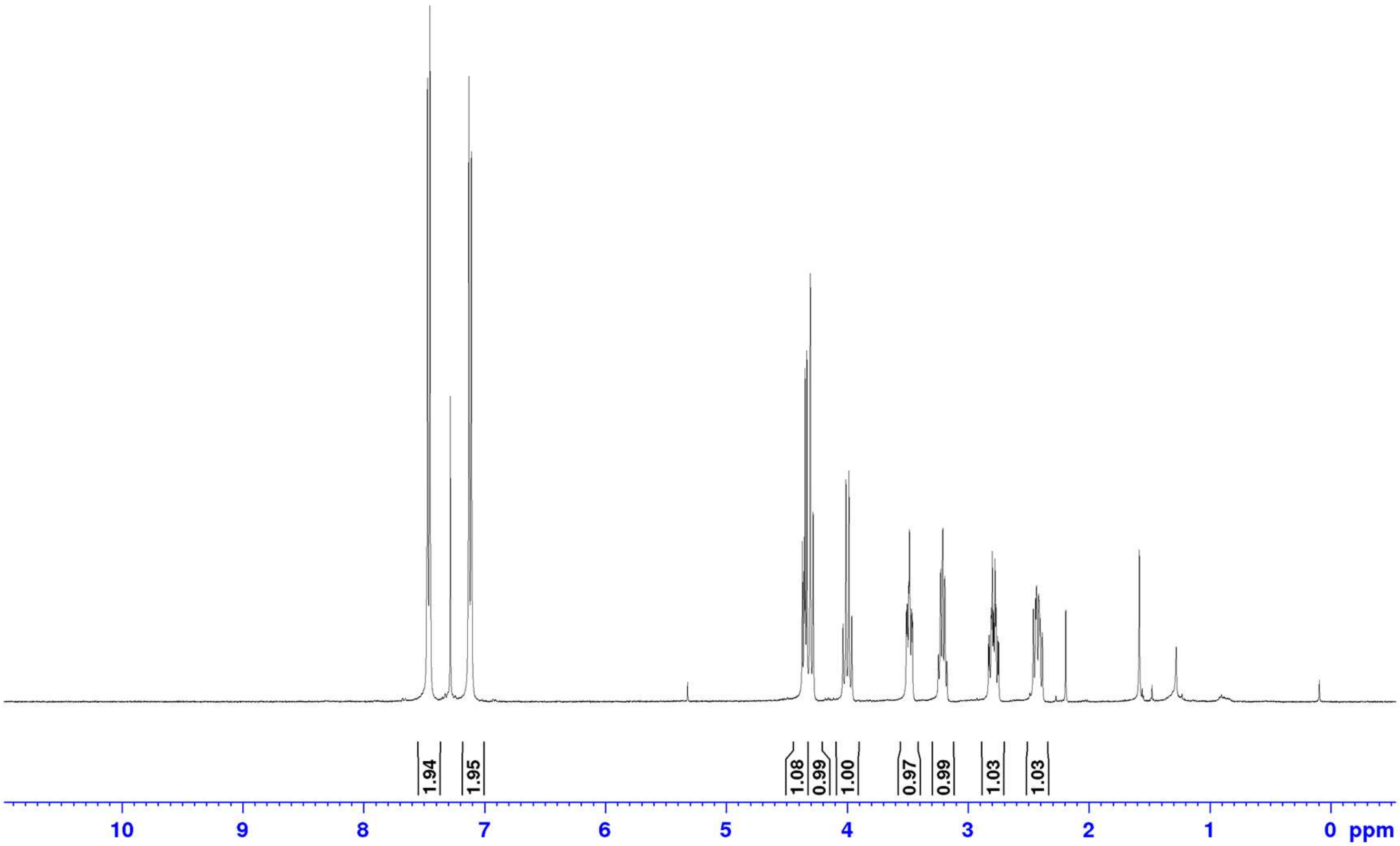


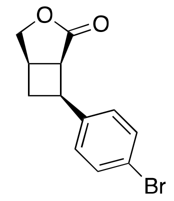
20

177.0
158.8
130.9
128.6
113.9
77.4
73.9
55.3
44.5
38.8
31.4
31.0
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

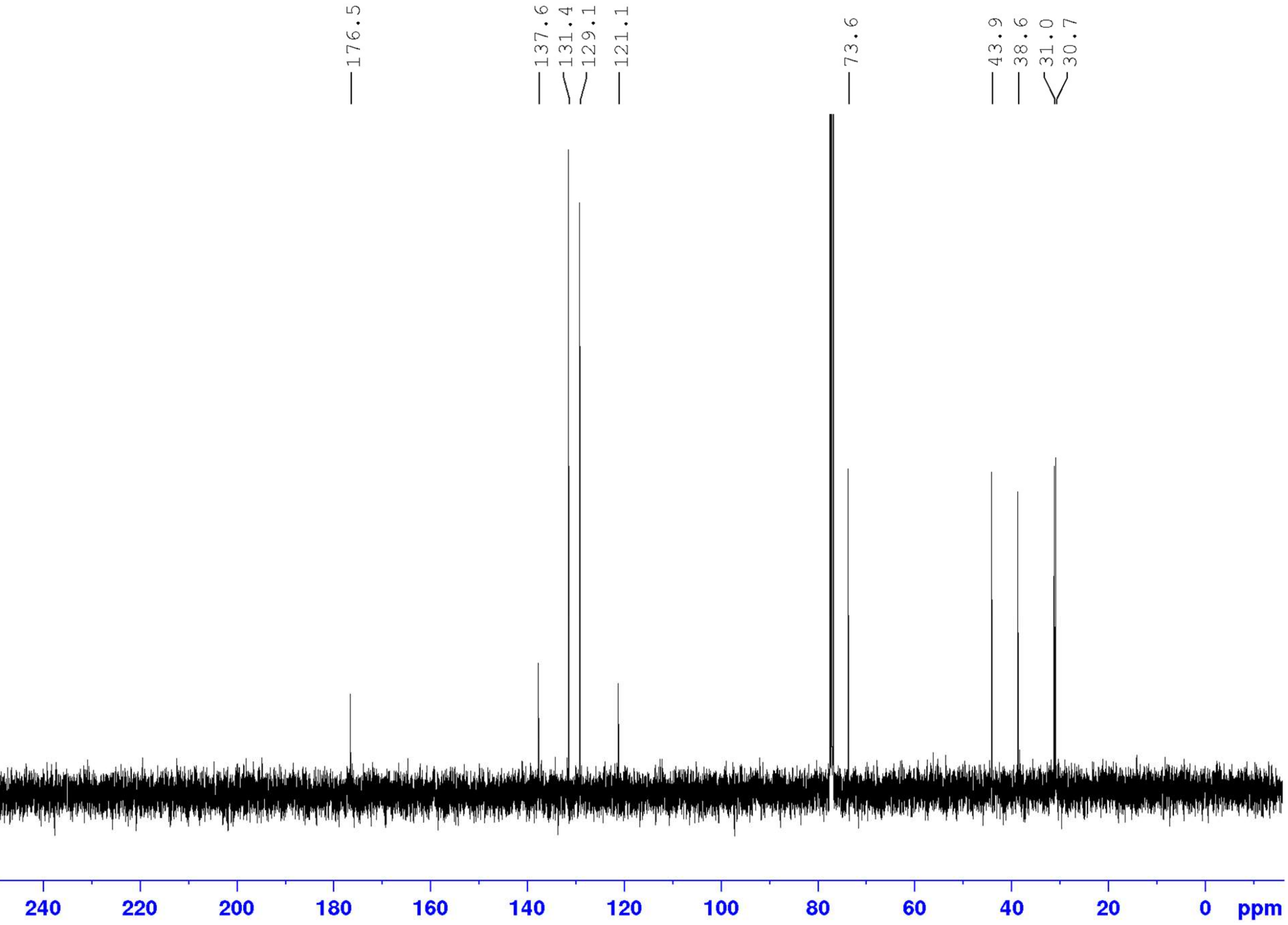


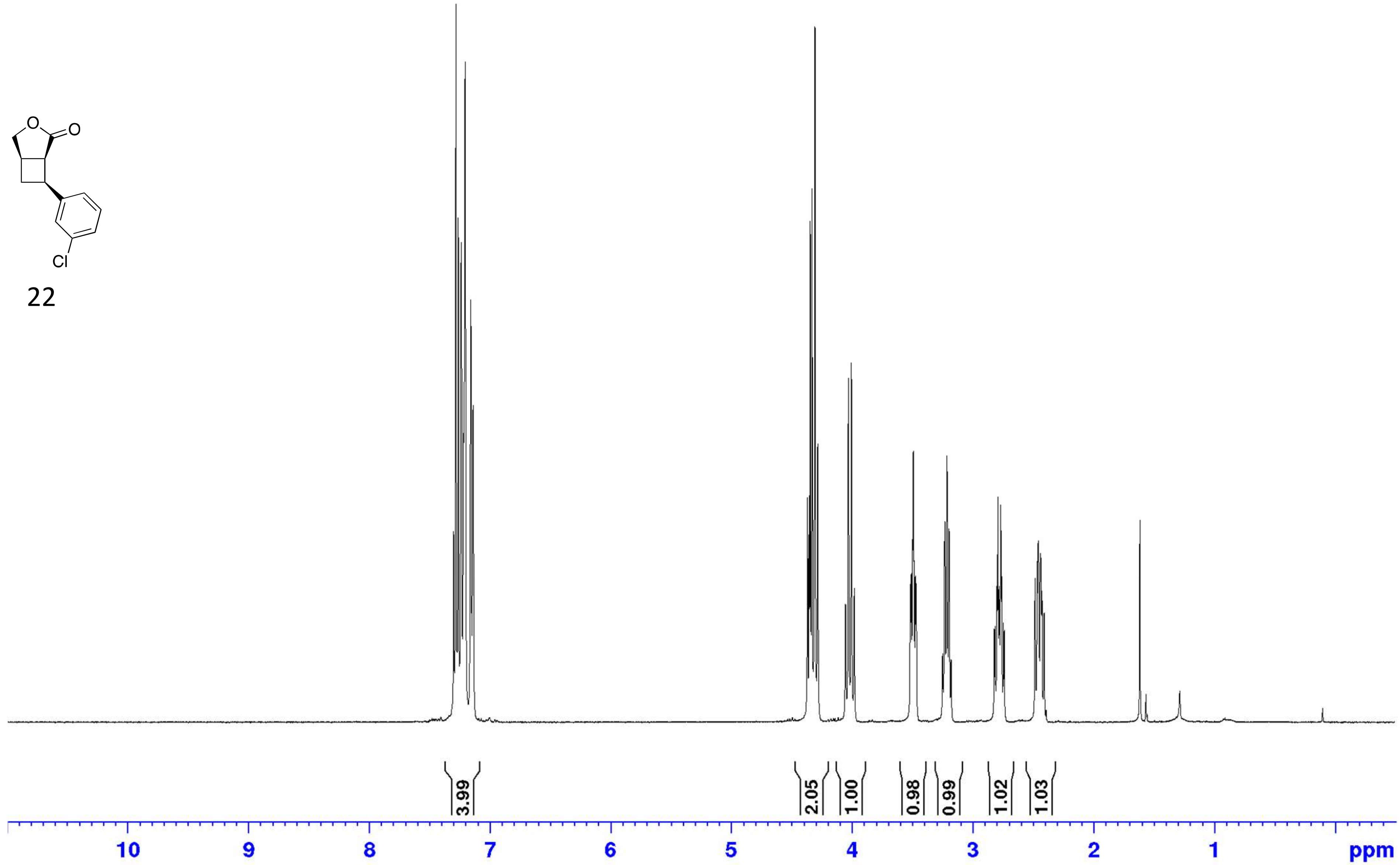
21



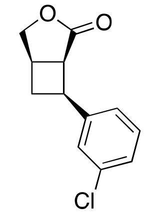

O
O
Br

21

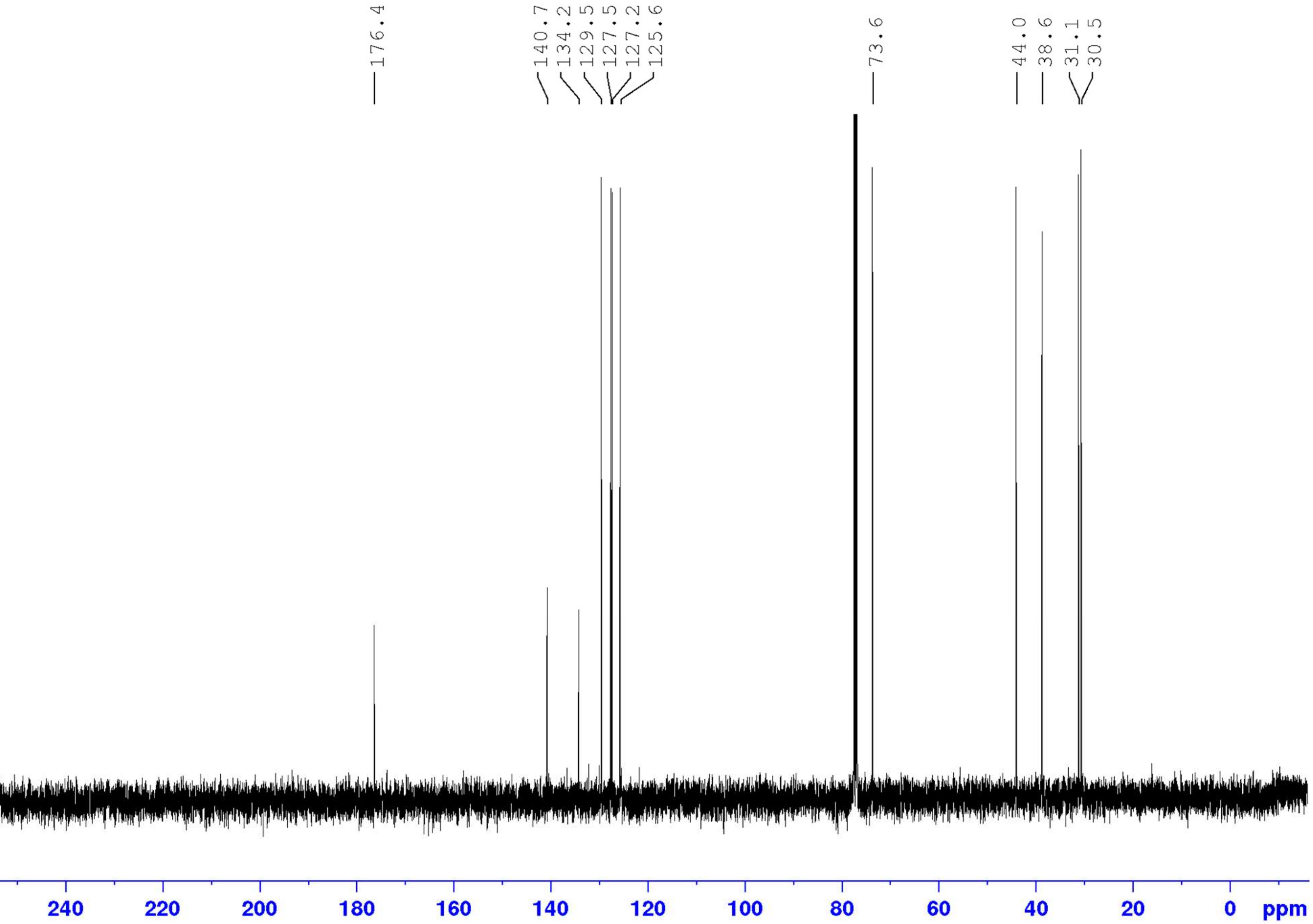

176.5
137.6
131.4
129.1
121.1
73.6
43.9
38.6
31.0
30.7
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

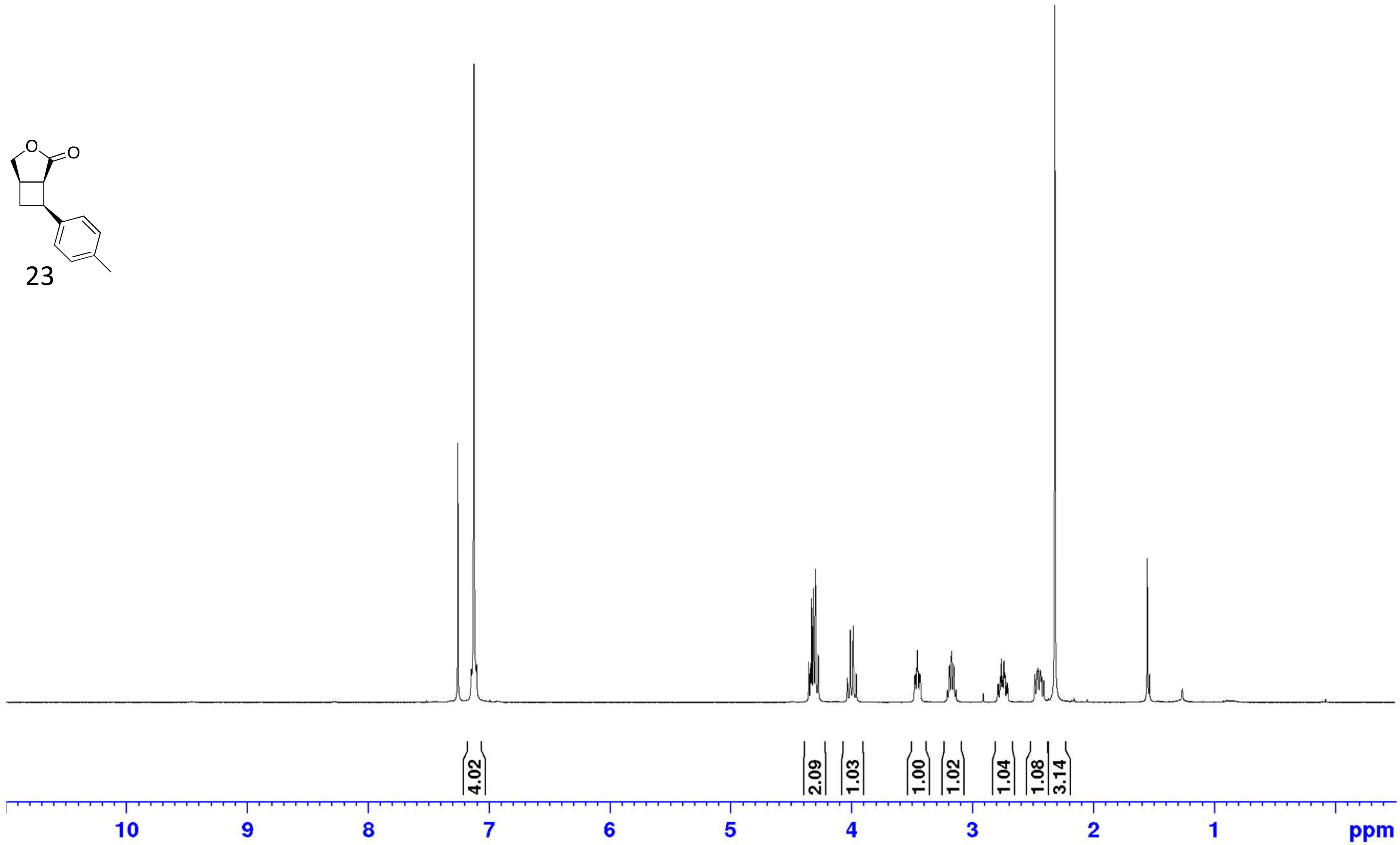


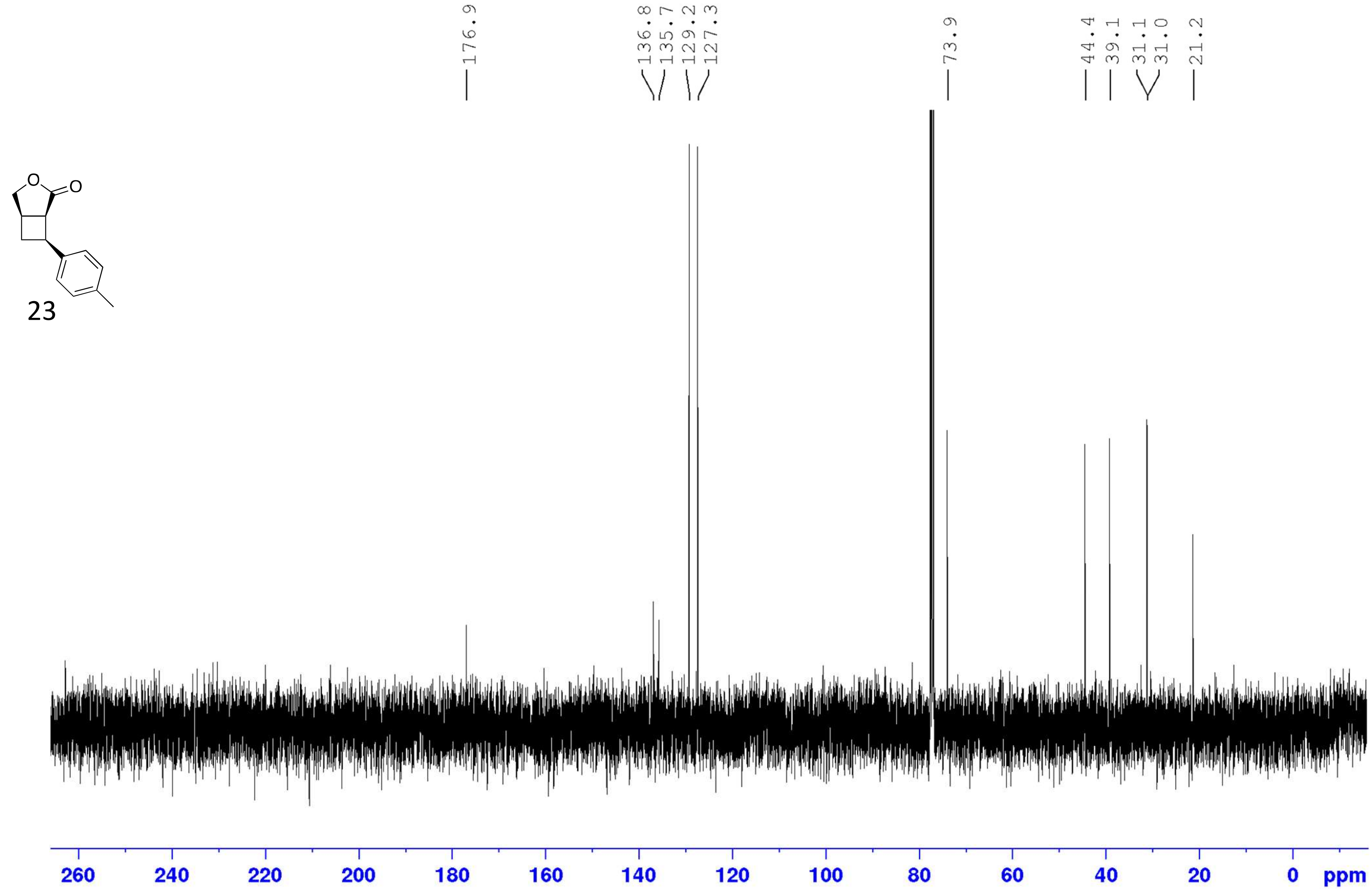
22



22

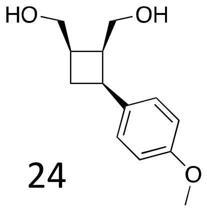

176.4
140.7
134.2
129.5
127.5
127.2
125.6
73.6
44.0
38.6
31.1
30.5
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


23

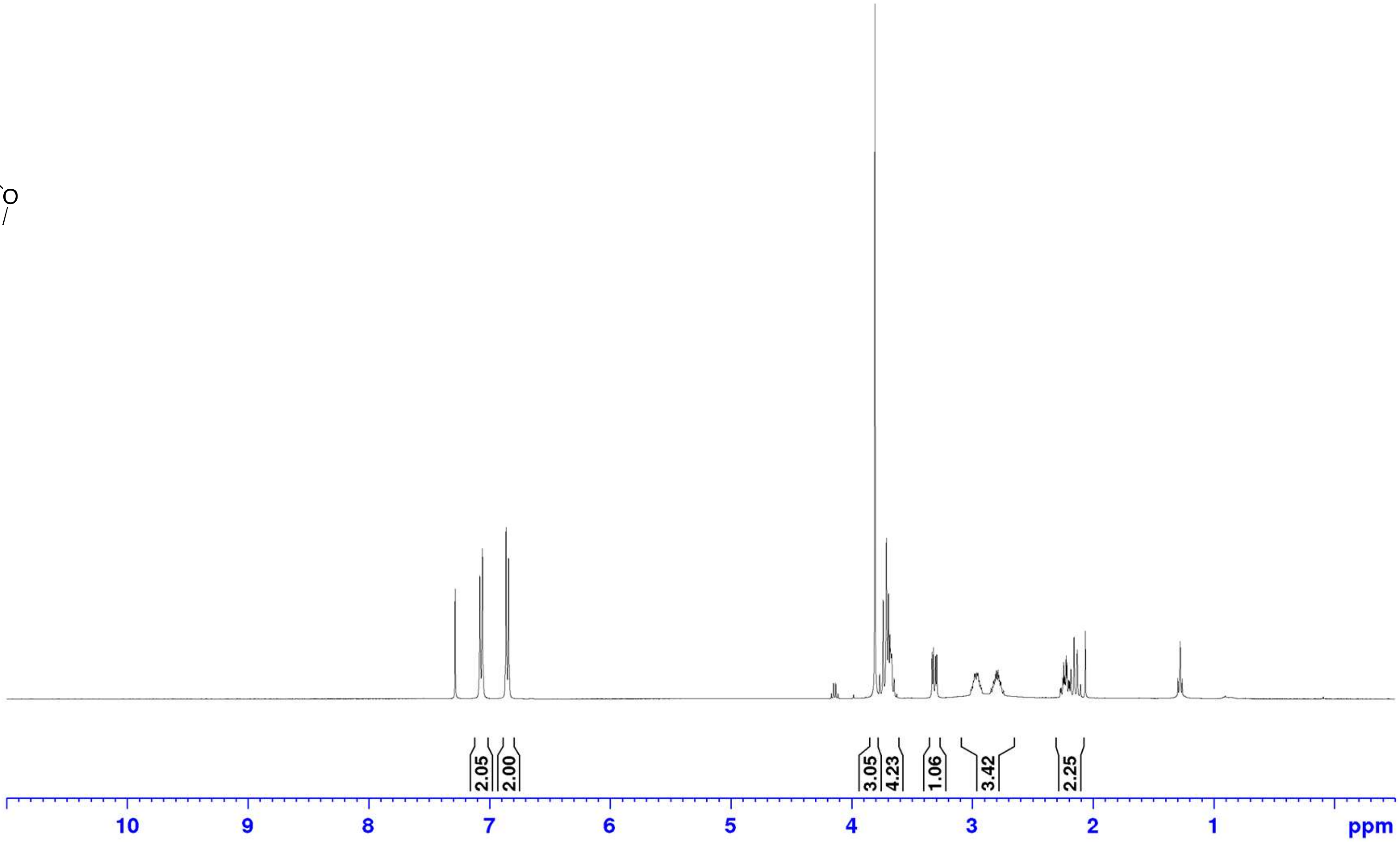


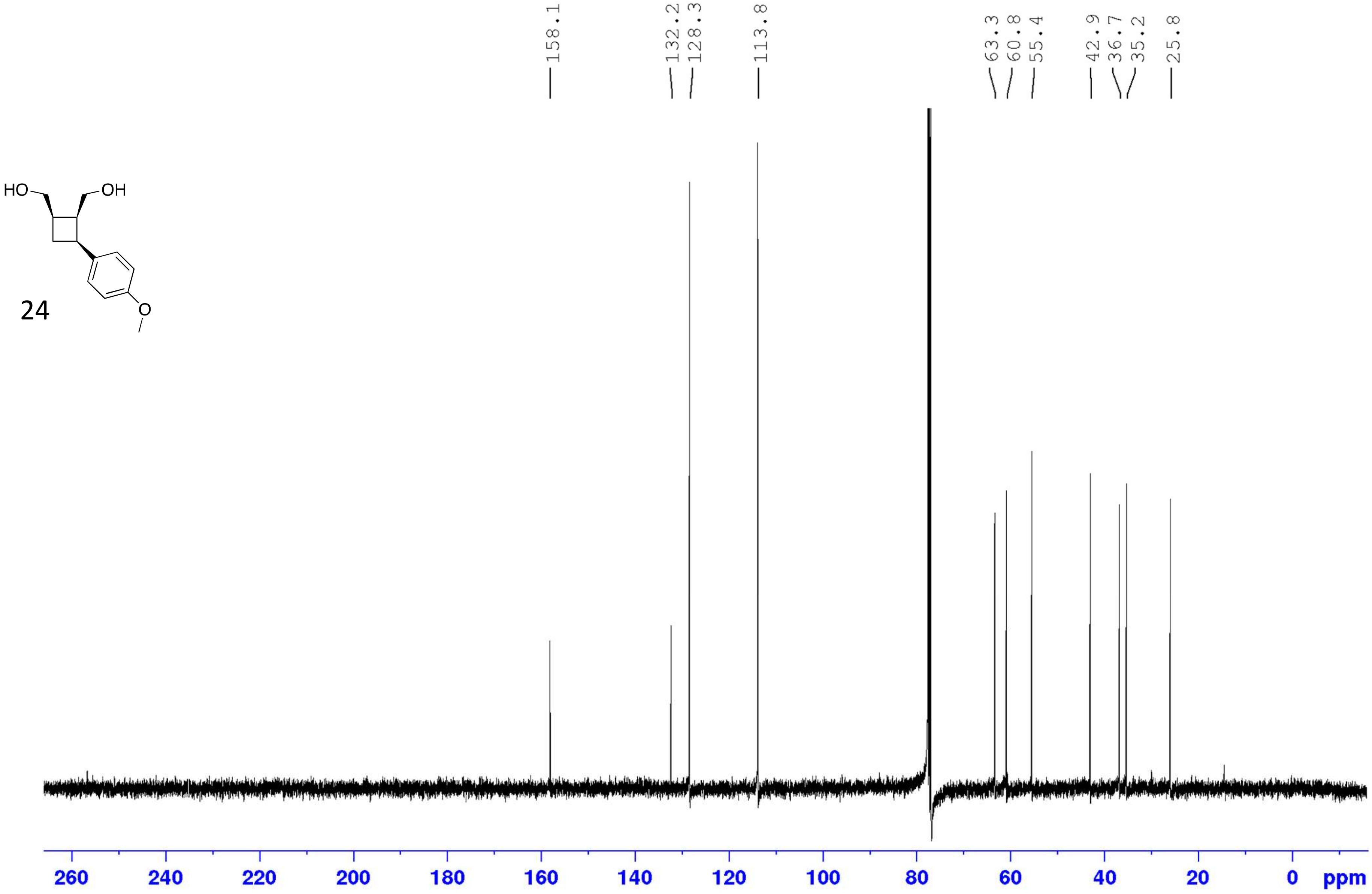
23

176.9
136.8
135.7
129.2
127.3
73.9
44.4
39.1
31.1
31.0
21.2
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm



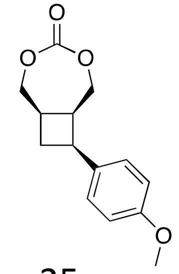
24



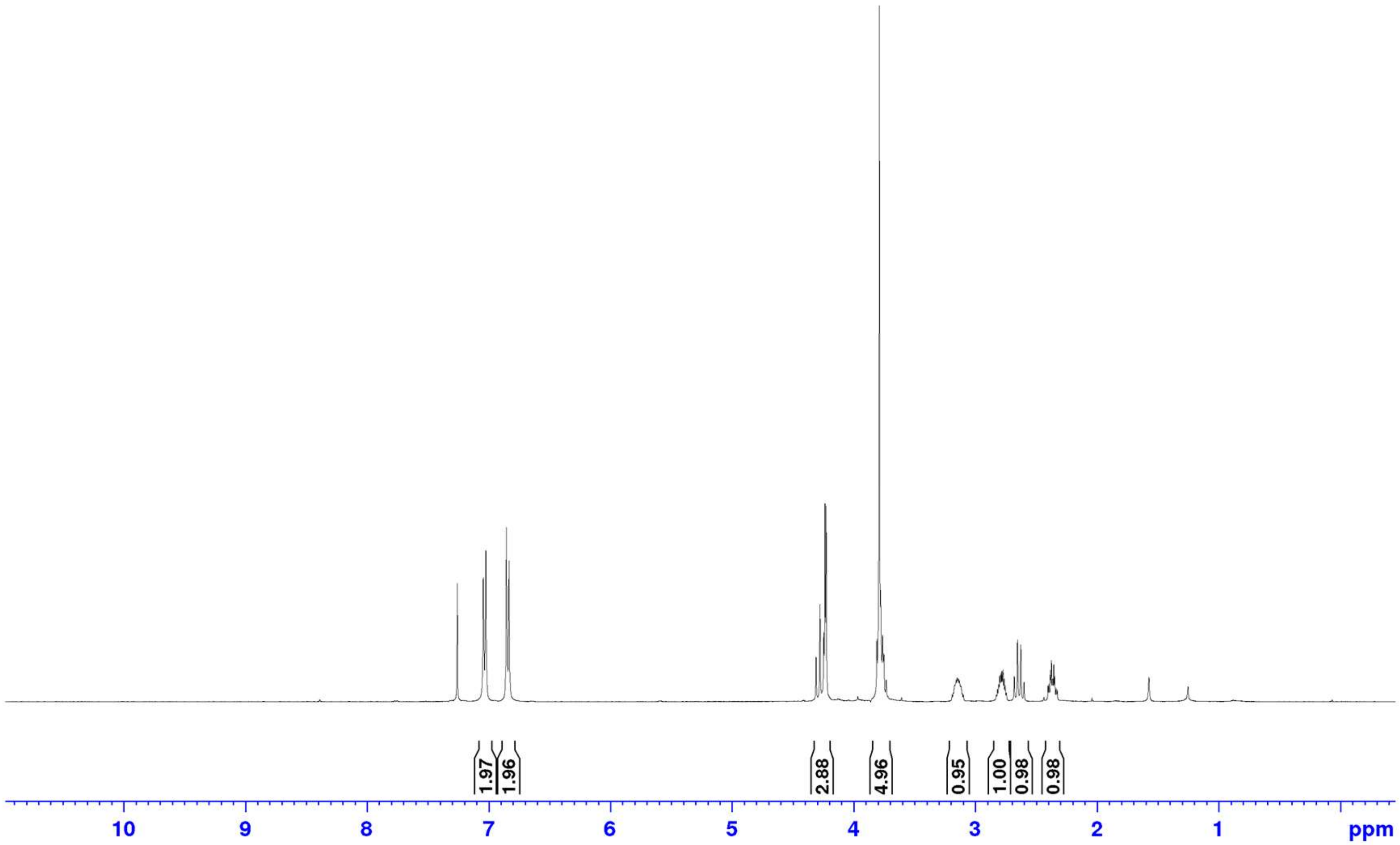

HO
OH
O

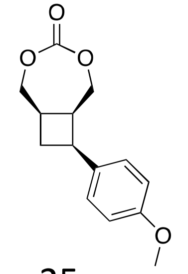
24

158.1
132.2
128.3
113.8
63.3
60.8
55.4
42.9
36.7
35.2
25.8
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

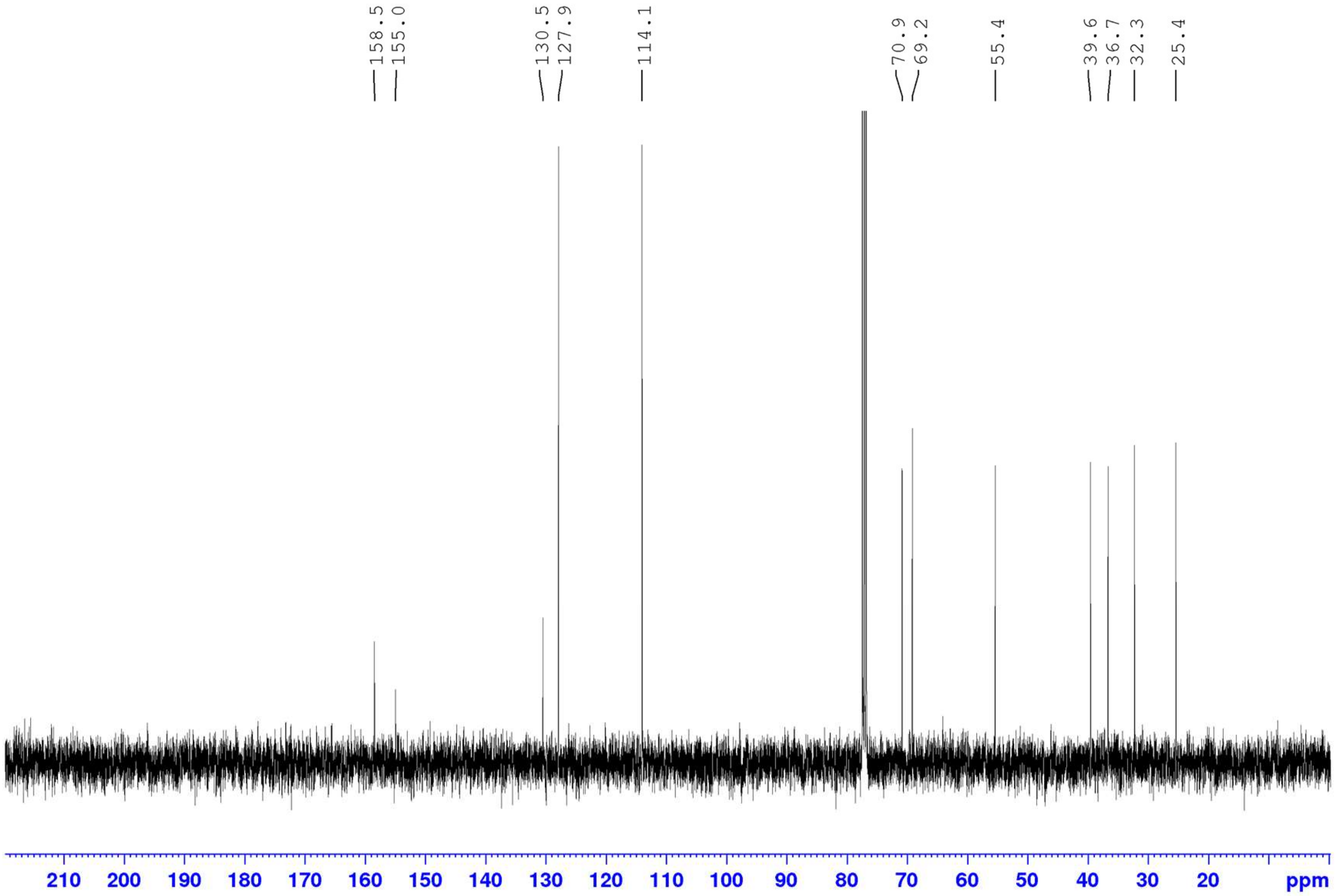


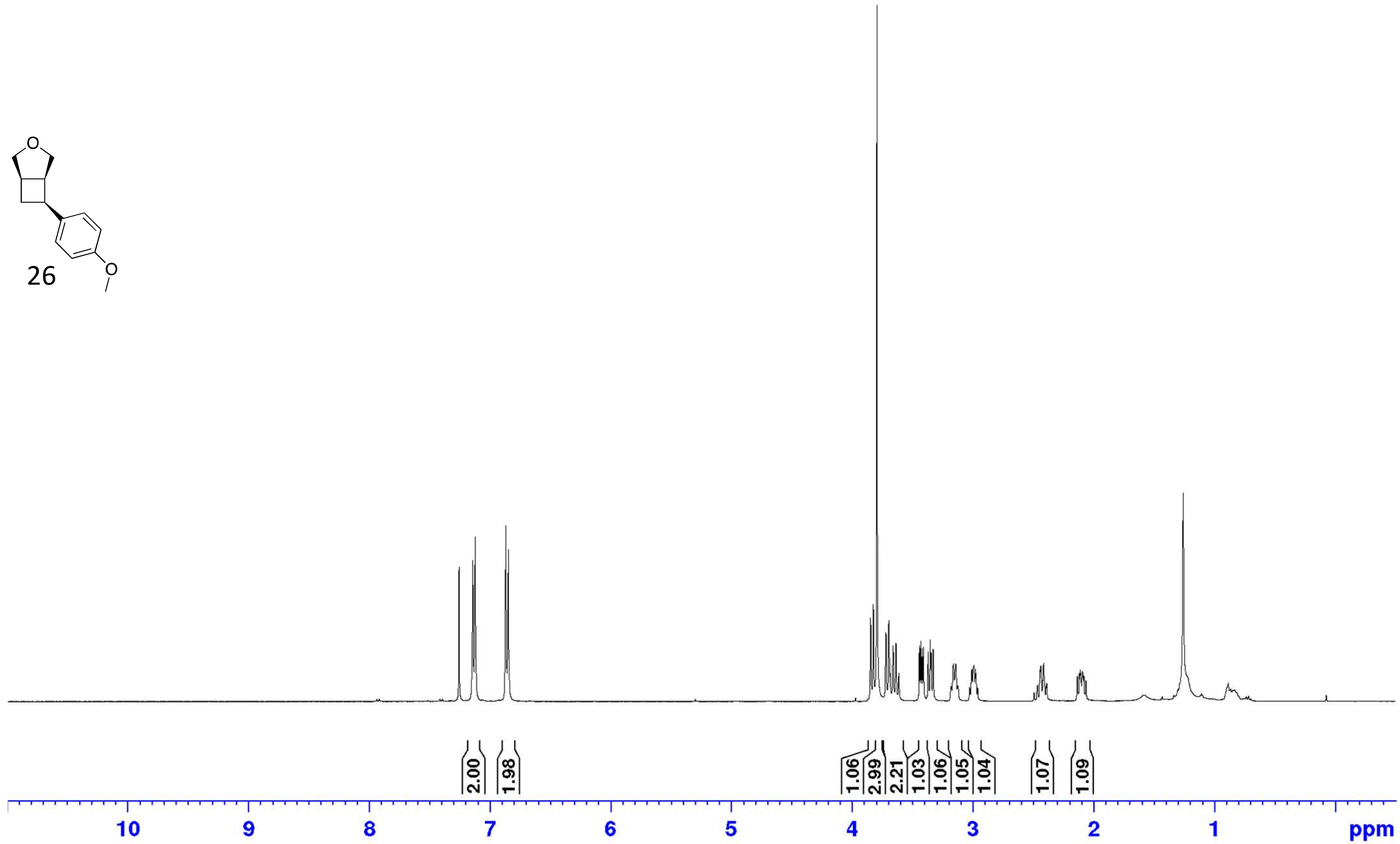
25



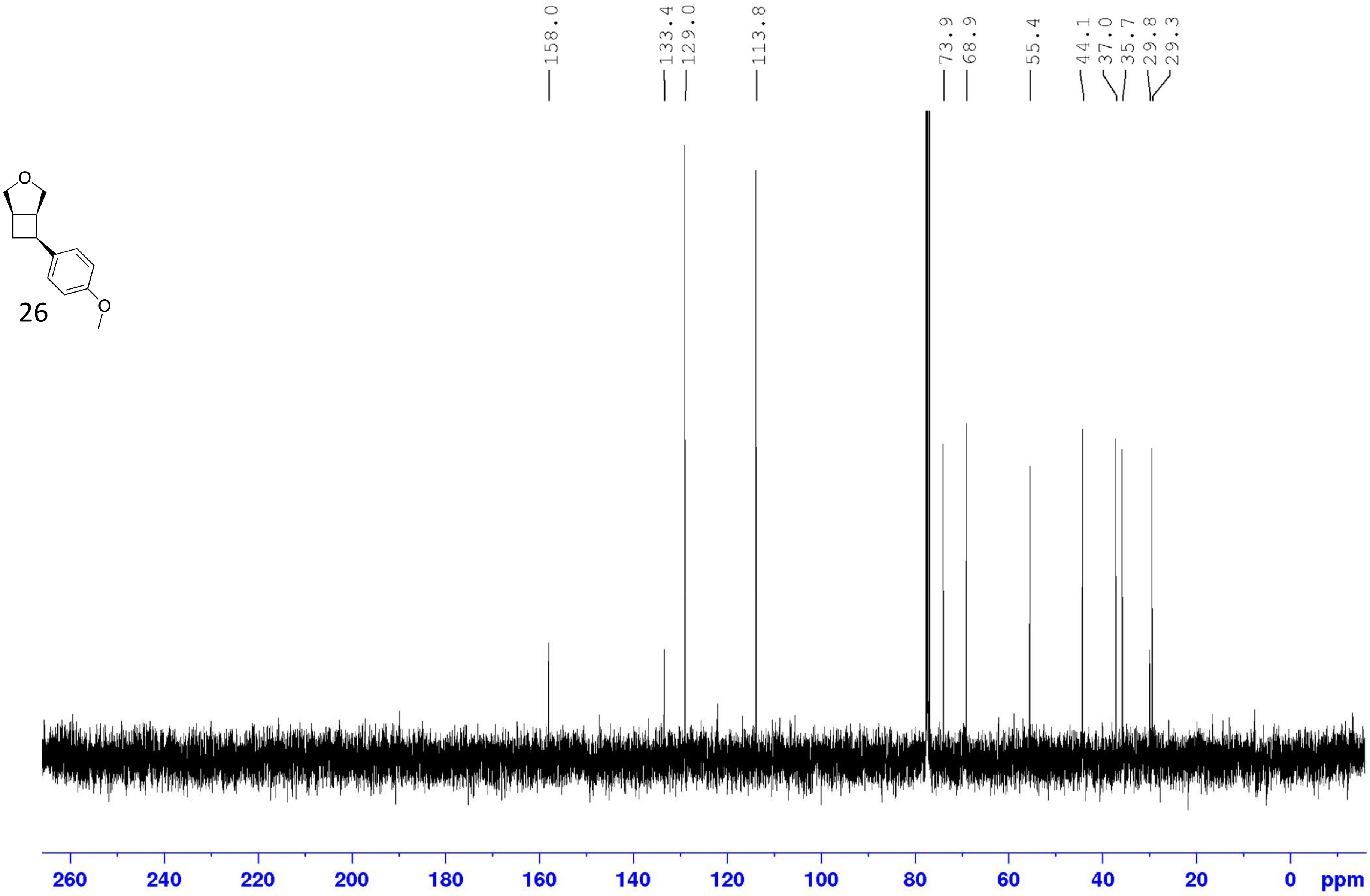


25


158.5
155.0
130.5
127.9
114.1
70.9
69.2
55.4
39.6
36.7
32.3
25.4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

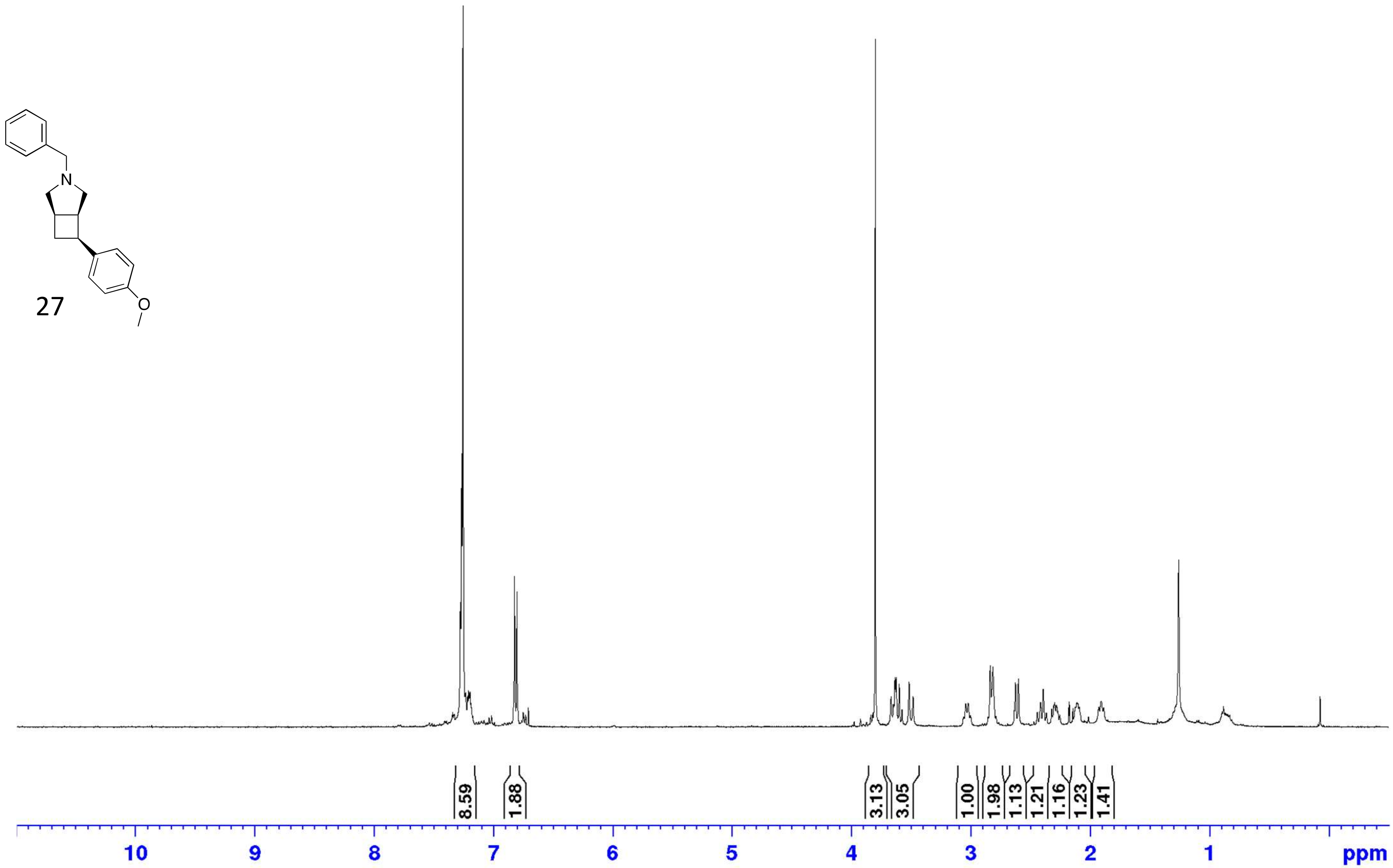


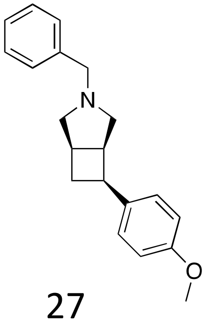
26



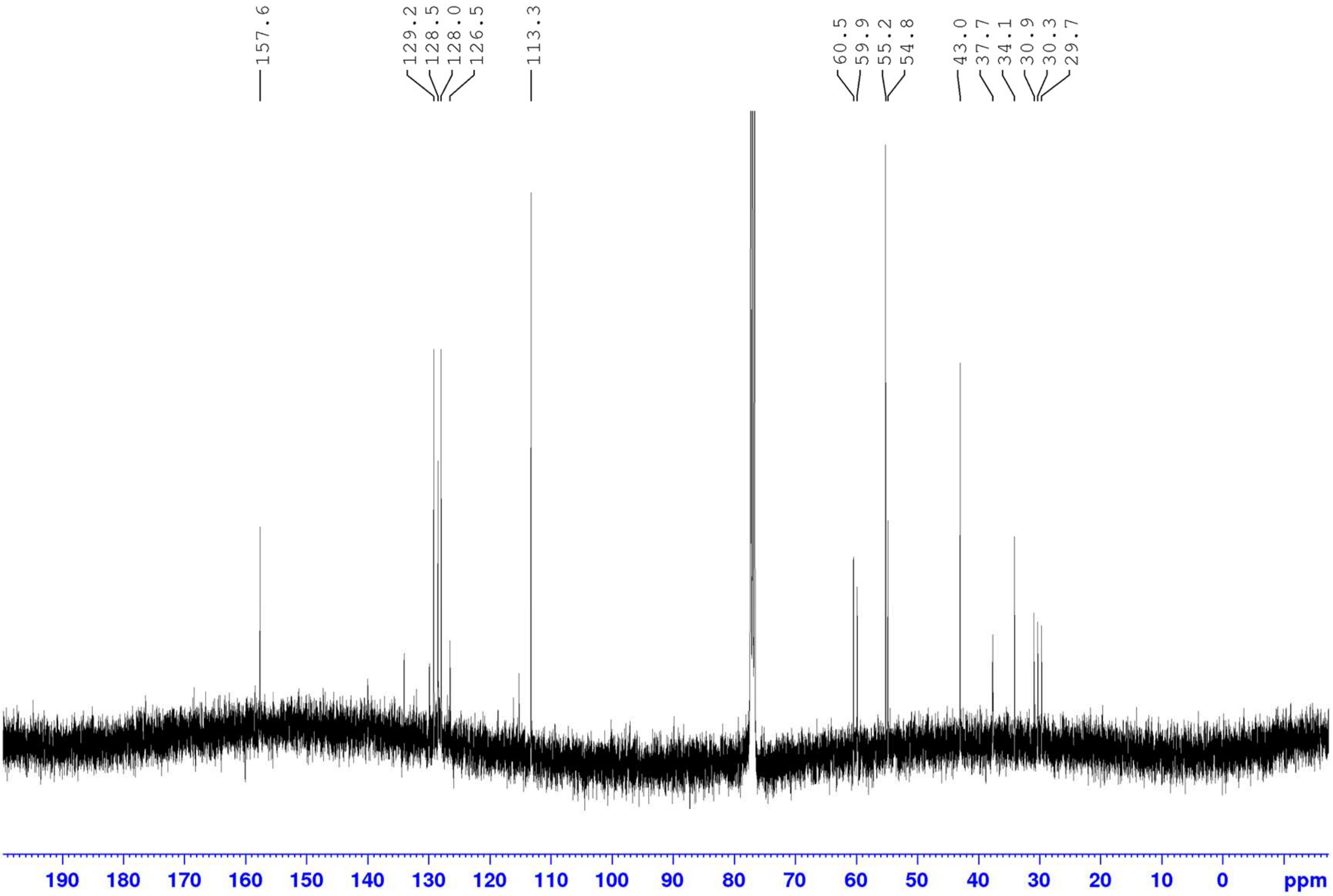
26

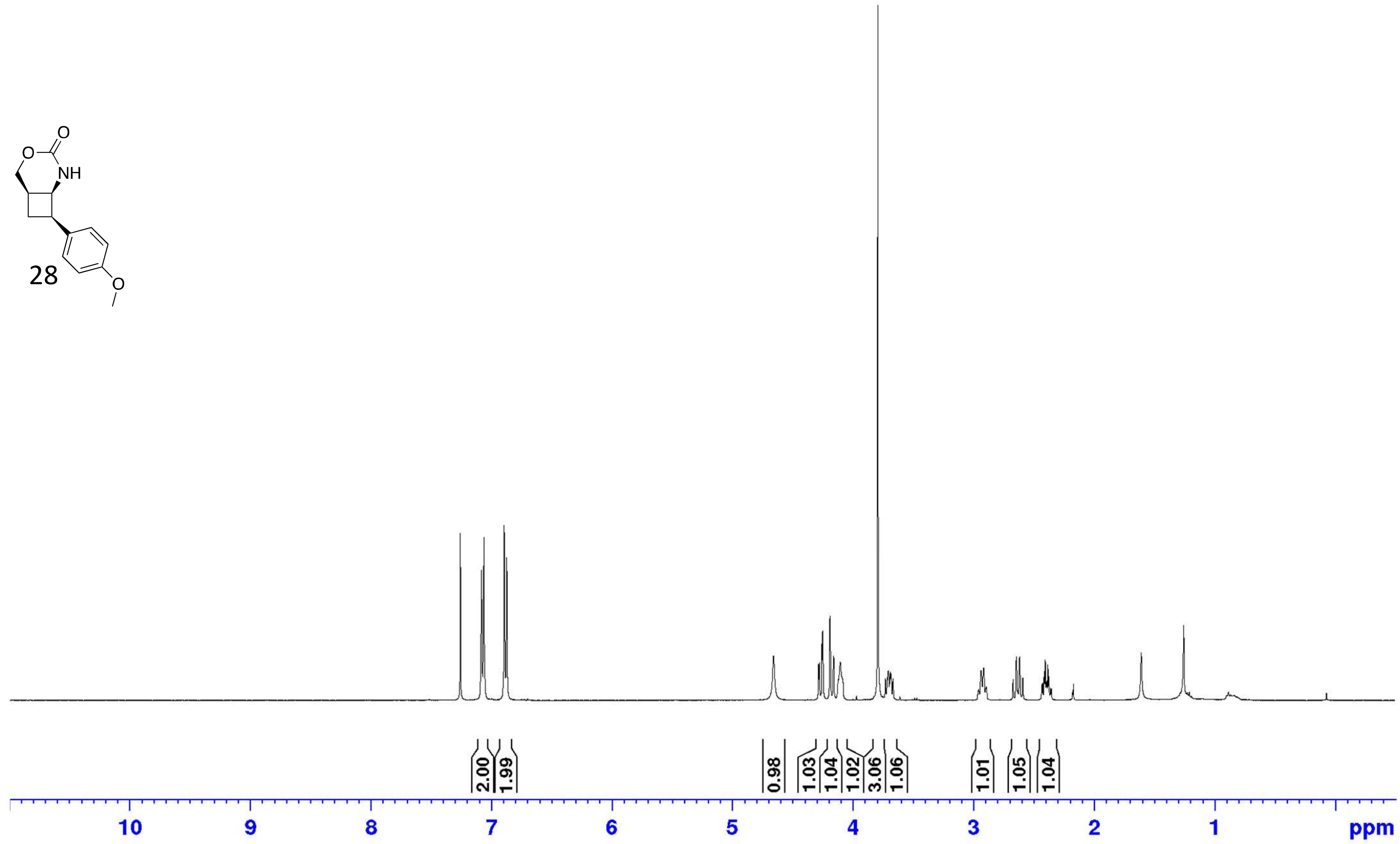
158.0
133.4
129.0
113.8
73.9
68.9
55.4
44.1
37.0
35.7
29.8
29.3
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


27

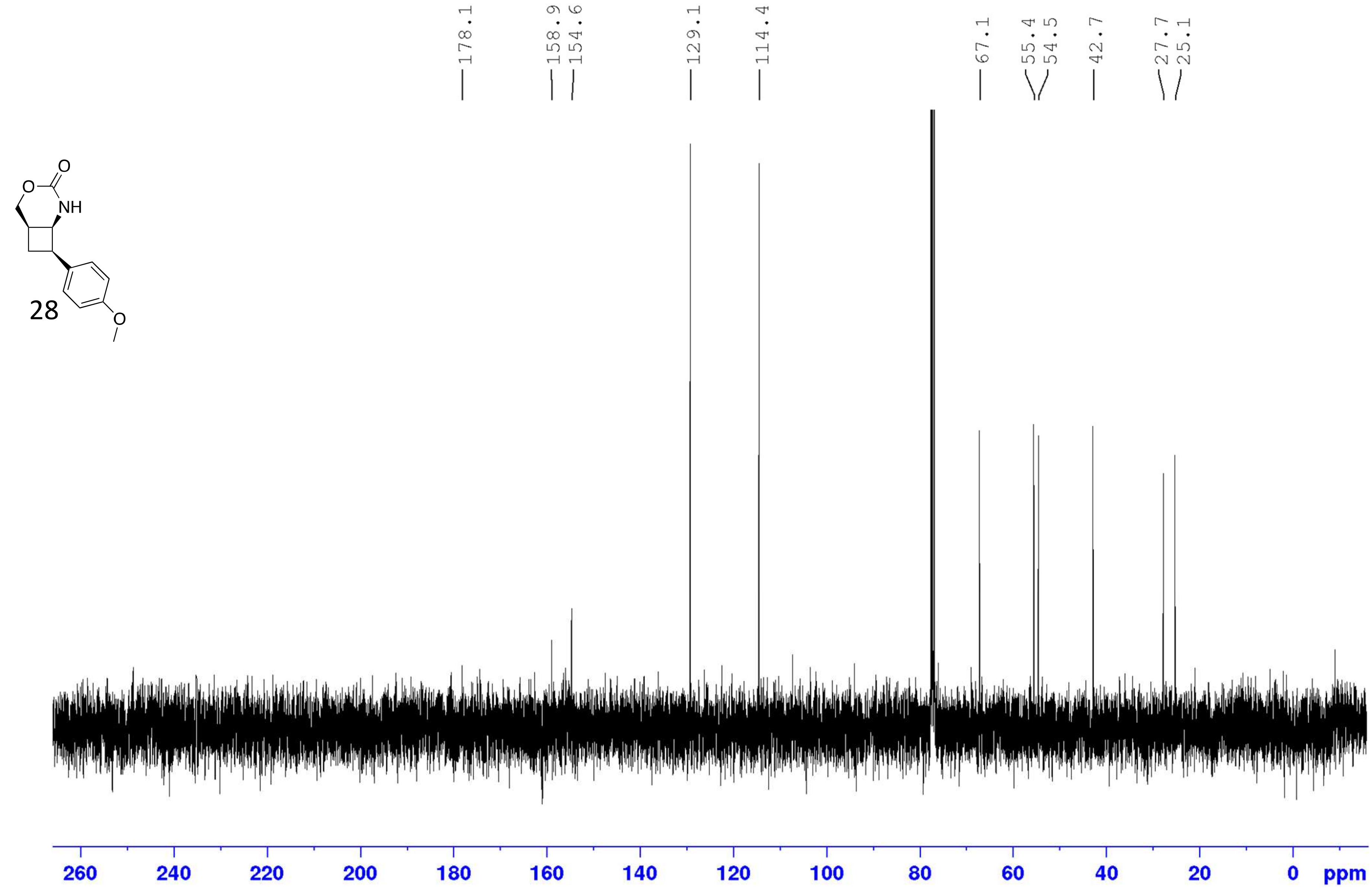


27


157.6
129.2
128.5
128.0
126.5
113.3
60.5
59.9
55.2
54.8
43.0
37.7
34.1
30.9
30.3
29.7
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


28

O
O
NH
O
2.00
1.99
0.98
1.03
1.04
1.02
3.06
1.06
1.01
1.05
1.04
10
9
8
7
6
5
4
3
2
1
ppm


28
178.1
158.9
154.6
129.1
114.4
67.1
55.4
54.5
42.7
27.7
25.1
O
O
NH
O
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm