Supporting Information

SYNTHESIS OF LACTONE-FUSED CYCLOPROPANES BY RING CONTRACTIVE α-KETOL REARRANGEMENT OF KETAL-FUSED CYCLOBUTANONES

Kiyosei Takasu,* Koichi Shigenaga, Kazuma Shimoda, Hiroshi Takikawa, and Yousuke Yamaoka

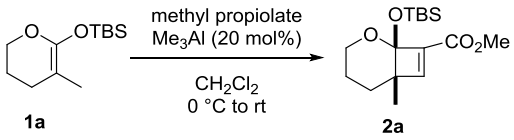
1. General Remarks

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware. Dehydrated solvents for the reactions were purchased and used without further desiccation. All reagents were purchased and used without further purification except for triethylamine, which was purified by distillation. Reactions were monitored by thin-layer chromatography (TLC) carried out on Wako TLC silica gel 70 F_{254}. Column chromatography was performed using Fuji Silysia BW-200 silica gel. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-LA (500 MHz for ^{1}H and 125 MHz for ^{13}C). The ^{1}H chemical shifts were calibrated with internal tetramethylsilane (TMS, 0 ppm) in $CDCl_3$. The ^{13}C chemical shifts are reported relative to $CDCl_3$ (77.0 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on a SHIMADZU LCMS-IT-TOF fitted with an ESI. IR experiments were recorded on a SHIMADZU IRAffinity-1 spectrometer. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. All melting points were determined using a Yamato MP-21 melting point apparatus and are uncorrected. X-ray diffraction data were recorded on a RIGAKU R-AXIS RAPID system.

2. Experimental Procedures

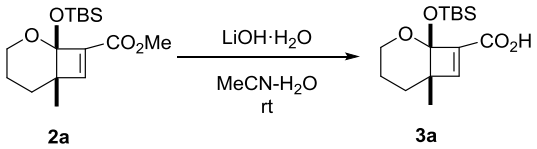
2–1. Synthesis of substrates

Methyl (1*R,6*S**)-1-(*tert*-Butyldimethylsilyloxy)-6-methyl-2-oxabicyclo[4.2.0]oct-7-ene-8-carboxylate (2a).**



To a solution of **1a** (16.0 g, 70.0 mmol) and methyl propiolate (7.0 mL, 84.0 mmol) in CH_2Cl_2 (100 mL) was added a mixture of Me_3Al (2.0 M solution in toluene, 7.0 mL, 14 mmol) and CH_2Cl_2 (100 mL) at 0 °C. After stirred for 1 h at room temperature, the mixture was quenched with saturated aq. Rochelle salt and stirred vigorously for additional 30 min. The whole was extracted three times with hexane and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo to afford pale yellow oil. The residue was purified with silica gel column chromatography (hexane/AcOEt 20 : 1) to give **2a** (22.0 g, quant) as colorless oil. R_f = 0.44 (hexane/AcOEt 10 : 1; UV, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 1H), 3.80 (t, *J* = 5.5 Hz, 2H), 3.75 (s, 3H), 1.77–1.53 (m, 4H), 1.14 (s, 3H), 0.89 (s, 9H), 0.20 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.7, 155.1, 140.6, 99.1, 61.4, 51.7, 51.1, 30.2, 25.8, 20.7, 20.0, 18.3, –3.4, –3.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{28}NaO_4Si^+$, 335.1649; found, 335.1649; IR ($CHCl_3$): ν 2951, 2886, 1728, 1616, 1462, 1250, 1099, 1061, 779 cm^{-1}.

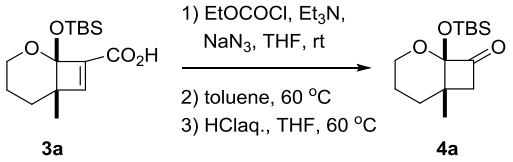
(1*R,6*S**)-1-(*tert*-Butyldimethylsilyloxy)-6-methyl-2-oxabicyclo[4.2.0]oct-7-ene-8-carboxylic Acid (3a).**



2a **3a**

To a solution of **2a** (200 mg, 0.640 mmol) in MeCN (2.0 mL) and H_2O (1.0 mL) was added LiOH•H_2O (54 mg, 1.3 mmol) at room temperature. After stirred for 15 h, the reaction mixture was quenched with aq. NH_4Cl and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford white solids. The residue was purified with silica gel column chromatography (hexane/AcOEt 1 : 1) to give **3a** (145 mg, 76%) as white solids. R_f = 0.14 (hexane/AcOEt 3:1; UV, *p*-anisaldehyde); Mp 86–88 °C (from hexane-Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H), 3.82 (t, *J* = 6.5 Hz, 2H), 1.78–1.55 (m, 4H), 1.16 (s, 3H), 0.89 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.2, 157.6, 140.3, 99.0, 61.5, 52.0, 30.1, 25.8, 20.6, 20.0, 18.3, –3.4, –3.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{26}NaO_4Si^+$, 321.1493; found, 321.1490; IR ($CHCl_3$): ν 3055, 2928, 2886, 1694, 1462, 1296, 1250, 1099, 883 cm^{-1}.

(1*R,6*S**)-1-(*tert*-Butyldimethylsilyloxy)-6-methyl-2-oxabicyclo[4.2.0]octan-8-one (4a).**

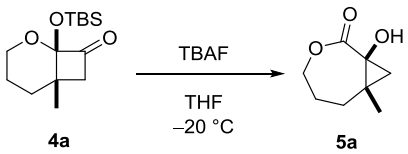


3a **4a**

To a solution of **3a** (5.12 g, 17.2 mmol) in THF (150 mL) were added triethylamine (2.9 mL, 21 mmol) and EtOCOCl (2.0 mL, 21 mmol) at room temperature, and the mixture was stirred for 20 min. To the mixture was added a solution of NaN_3 (1.17 g, 18.0 mmol) in H_2O (100 mL) and the mixture was stirred for additional 45 min. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding acyl azide (5.38 g) was obtained as colorless oil, which was used in the next step without further purification. A solution of the crude acyl azide in toluene (15 mL) was stirred for 2 h at 60 °C. The resulting mixture was concentrated in vacuo to give the corresponding isocyanate as colorless oil, which was used in the next step without further purification. A solution of the crude isocyanate in THF (150 mL) and 1% aq. HCl (150 mL) was stirred for 30 min at 60 °C. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt 20 : 1) to afford **4a** (3.32 g, 72% from **3a**) as colorless oil. R_f = 0.46 (hexane/AcOEt 10 : 1; *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 3.77 (ddd, *J* = 11.0, 4.0, 2.0 Hz, 1H), 3.53 (ddd, *J* = 12.0, 12.0, 2.0 Hz, 1H), 3.14 (d, *J* = 16.0 Hz, 1H), 2.13 (d, *J* = 16.0 Hz, 1H), 1.88–1.75 (m, 2H), 1.54–1.64 (m, 2H), 1.07 (s, 3H), 0.90 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.5, 106.1, 61.4, 49.0, 35.4, 28.5, 25.7, 24.0, 21.2, 18.1, –3.7, –4.1; HRMS (ESI) *m/z*: $[M+Na]^+$

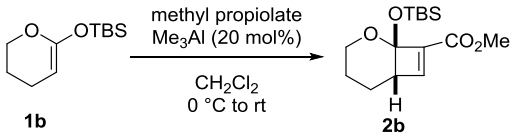
calcd for $C_{14}H_{26}NaO_3Si^+$, 293.1543; found, 293.1540; IR ($CHCl_3$): ν 2859, 1790, 1462, 1404, 1223, 1161, 1134, 1103, 783 cm^{-1}.

(1*S,7*S**)-1-Hydroxy-7-methyl-3-oxabicyclo[5.1.0]octan-2-one (5a).**



To a solution of **4a** (60 mg, 0.22 mmol) in THF (2.0 mL) was added TBAF (1.0 M in THF, 0.22 mL, 0.22 mmol) at –20 °C. After stirred for 10 min, the mixture was quenched with saturated aq. NH_4Cl and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford **5a** (27 mg, 78%) as colorless crystals. R_f = 0.38 (hexane/AcOEt 1:1, *p*-anisaldehyde); Mp 104−106 °C (from hexane-Et_2O); ^1H NMR ($CDCl_3$) δ 4.53 (ddd, *J* = 12.5, 12.5, 4.0 Hz, 1H), 4.26 (ddd, *J* = 12.5, 6.0, 0.5 Hz, 1H), 4.05 (br, 1H), 2.06 (ddd, *J* = 15.0, 6.0, 1.0 Hz, 1H), 1.91 (ddddd, *J* = 15.0, 12.5, 7.0, 6.0, 1.0 Hz, 1H), 1.77 (ddddd, *J* = 14.5, 12.5, 6.0, 4.0, 0.5 Hz, 1H), 1.20 (s, 3H), 0.89 (d, *J* = 6.5 Hz, 1H), 0.83 (ddd, *J* = 15.0, 12.5, 7.0 Hz, 1H), 0.80 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 173.9, 65.5, 60.4, 30.6, 25.2, 23.5, 21.5, 14.4; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_8H_{13}O_3^+$, 157.0859, found 157.0858; IR ($CHCl_3$): ν 3360, 2932, 1724, 1258, 1192, 910, 737 cm^{-1}. X-ray: Recrystallization from hexane/Et_2O gave colorless plates suitable for X-ray crystal structural analysis: *triclinic*, P–1; a = 6.3587(3), b = 7.4781(4), c = 8.4653(3); α = 90.605(4), β = 97.016(3), γ = 99.753(4); V = 393.54 (3), Z = 2, D_{calc} = 1.318, R = 0.0512, R_w = 0.1545, GOF = 1.145.

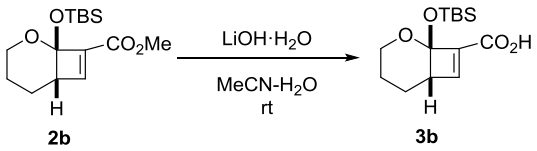
Methyl (1*R,6*S**)-1-(*tert*-Butyldimethylsilyloxy)- 2-oxabicyclo[4.2.0]oct-7-ene-8-carboxylate (2b).**



To a solution of **1b** (1.17 g, 5.45 mmol) and methyl propiolate (0.54 mL, 6.5 mmol) in CH_2Cl_2 (30 mL) was added a mixture of Me_3Al (2.0 M solution in toluene, 1.37 mL, 1.09 mmol) and CH_2Cl_2 (20 mL) at 0 °C. After stirred for 2 h at room temperature, the mixture was quenched with saturated aq. Rochelle salt and stirred vigorously for additional 30 min. The whole was extracted three times with hexane and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo to afford pale yellow oil. The residue was purified with silica gel column chromatography (hexane/AcOEt 20 : 1) to give **2b** (946 mg, 58%) as pale yellow oil. R_f = 0.36 (hexane/AcOEt 10 : 1; UV, *p*-anisaldehyde); ^1H NMR ($CDCl_3$) δ 7.02 (d, *J* = 1.0 Hz, 1H), 3.90 (ddd, *J* = 5.0, 6.5, 6.5 Hz, 1H), 3.82 (ddd, *J* = 5.0, 6.0, 6.5 Hz, 1H), 3.76 (s, 3H), 2.83 (ddd, *J* = 1.0, 6.5, 6.5 Hz, 1H), 1.92–1.86 (m, 1H), 1.73–1.58 (m, 3H), 0.89 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.3, 150.1, 142.5, 97.2, 62.1, 51.3, 50.3, 25.7, 22.9, 20.5, 18.0, –3.54, –3.57; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for

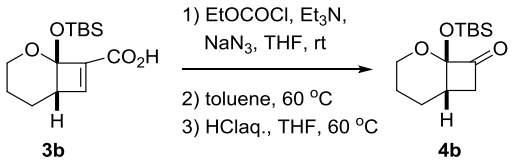
$C_{15}H_{26}NaO_4Si^+$, 321.1493; found, 321.1494; IR ($CHCl_3$): ν 2951, 2931, 2858, 1728, 1258, 1049, 837, 783 cm^{-1}.

(1*R,6*S**)-1-(*tert*-Butyldimethylsilyloxy)- 2-oxabicyclo[4.2.0]oct-7-ene-8-carboxylic Acid (3b).**



To a solution of **2b** (47 mg, 0.16 mmol) in MeCN (10 mL) and H_2O (5.0 mL) was added LiOH•H_2O (14 mg, 0.32 mmol) at room temperature. After stirred for 24 h, the reaction mixture was quenched with aq. NH_4Cl and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford yellow oil. The residue was purified with silica gel column chromatography (hexane/AcOEt 1 : 1) to give **3b** (32 mg, 71%) as pale yellow oil. R_f = 0.15 (hexane/ AcOEt 1:1; UV, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 7.10 (d, *J* = 1.0 Hz, 1H), 3.88 (ddd, *J* = 6.0, 11.5. 11.5 Hz, 1H), 3.81 (ddd, *J* = 6.0, 11.0. 11.0 Hz, 1H), 2.86 (ddd, *J* = 1.0, 6.0, 6.0 Hz, 1H), 1.94–1.87 (m, 1H), 1.73–1.56 (m, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.0, 152.4, 142.0, 97.1, 62.2, 50.5, 25.7, 22.8, 20.4, 18.0, 14.2, –3.5, –3.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{24}NaO_4Si^+$, 307.1336; found, 307.1336; IR ($CHCl_3$): ν 2951, 2931, 2859, 1697, 1254, 1045, 837, 779 cm^{-1}.

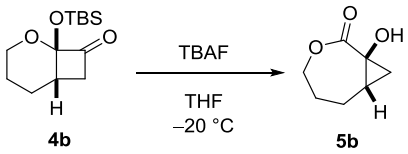
(1*R,6*S**)-1-(*tert*-Butyldimethylsilyloxy)-2-oxabicyclo[4.2.0]octan-8-one (4b).**



To a solution of **3b** (555 mg, 1.95 mmol) in THF (20 mL) were added triethylamine (0.33 mL, 2.3 mmol) and EtOCOCl (0.22 mL, 2.3 mmol) at room temperature, and the mixture was stirred for 10 min. To the mixture was added a solution of NaN_3 (133 mg, 2.05 mmol) in H_2O (15 mL) and the mixture was stirred for additional 20 min. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding acyl azide (410 mg) was obtained as colorless oil, which was used in the next step without further purification. A solution of the crude acyl azide in toluene (5 mL) was stirred for 2 h at 60 °C. The resulting mixture was concentrated in vacuo to give the corresponding isocyanate as colorless oil, which was used in the next step without further purification. A solution of the crude isocyanate in THF (20 mL) and 1% aq. HCl (20 mL) was stirred for 30 min at 60 °C. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt 20 : 1) to afford **4b** (186 mg, 42% from **3b**) as colorless oil. R_f = 0.75 (hexane/AcOEt 3 : 1; *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 3.76 (m, 1H), 3.63 (ddd, *J* = 11.5, 11.5, 2.0 Hz, 1H), 2.92 (dd, *J* = 16.0, 10.5 Hz, 1H), 2.59 (dd, *J* = 16.0, 10.0Hz,

1H), 2.42–2.37 (m, 1H), 1.98–1.90 (m, 1H), 1.81–1.72 (m, 2H), 1.54–1.50 (m, 1H), 0.89 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.1, 105.7, 61.5, 41.8, 33.6, 25.7, 20.4, 19.2, 17.9, –3.6, –3.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{24}NaO_3Si^+$, 279.1387; found, 279.1386; IR ($CHCl_3$): ν 2931, 2859, 1794, 1223, 1092, 1022, 833, 783 cm^{-1}.

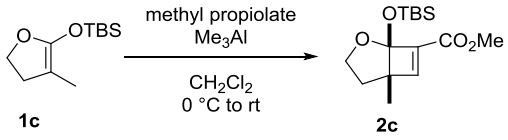
(1*S,7*S**)-1-Hydroxy-3-oxabicyclo[5.1.0]octan-2-one (5b).**



4b **5b**

To a solution of **4b** (51 mg, 0.20 mmol) in THF (2.0 mL) was added TBAF (1.0 M in THF, 0.20 mL, 0.20 mmol) at –20 °C. After stirred for 10min, the mixture was quenched with saturated aq. NH_4Cl and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford **5b** (13 mg, 46%) as pale yellow oil. R_f = 0.30 (hexane/AcOEt 1 : 1; *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 4.52 (ddd, *J* = 12.0, 12.0, 3.5 Hz, 1H), 4.27 (ddd, *J* = 12.0, 5.0, 2.0 Hz, 1H), 3.49 (br, 1H), 2.26–2.20 (m, 1H), 1.98–1.90 (m, 1H), 1.80–1.73 (m, 1H), 1.54–1.47 (m, 1H), 1.19 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.14–1.06 (m, 1H), 0.92 (dd, *J* = 6.5, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 174.4, 66.9, 58.6, 25.4, 24.8, 21.6, 19.8; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_7H_{10}NaO_3^+$, 165.0522; found, 165.0523; IR ($CHCl_3$): ν 3383, 2924, 1724, 1315, 1141, 1034, 910, 737 cm^{-1}.

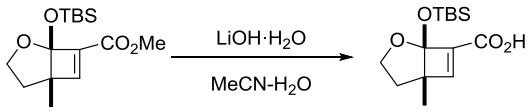
Methyl (1*R,5*S**)-1-(*tert*-Butyldimethylsilyloxy)-5-methyl-2-oxabicyclo[3.2.0]hept-6-ene-7-carboxylate (2c).**



1c **2c**

To a solution of **1c** (3.29 g, 15.3 mmol) and methyl propiolate (1.5 mL, 18 mmol) in CH_2Cl_2 (100 mL) was added a mixture of Me_3Al (2.0 M solution in toluene, 2.2 mL, 3.1 mmol) and CH_2Cl_2 (60 mL) at 0 °C. After stirred for 2 h at room temperature, the mixture was quenched with saturated aq. Rochelle salt and stirred vigorously for additional 30 min. The whole was extracted three times with hexane and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo to afford yellow oil. The residue was purified with silica gel column chromatography (hexane/AcOEt 20 : 1) to give **2c** (2.87 g, 63%) as pale yellow oil. R_f = 0.60 (hexane/AcOEt 3 : 1; UV, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1H), 4.10 (dd, *J* = 9.5, 8.0 Hz, 1H), 3.74 (s, 3H), 3.52 (ddd, *J* = 12.0, 9.5, 5.5 Hz, 1H), 1.73 (dd, *J* = 13.0, 5.5, Hz, 1H), 1.52 (ddd, *J* = 13.0, 12.0, 8.0 Hz, 1H), 1.18 (s, 3H), 0.91 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.6, 150.6, 136.9, 107.7, 65.2, 57.6, 51.2, 33.1, 25.8, 18.4, 18.0, –3.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{26}NaO_4Si^+$, 321.1493; found, 321.1494; IR ($CHCl_3$): ν 2955, 2928, 2858, 1728, 1292, 1253, 1049, 895 cm^{-1}.

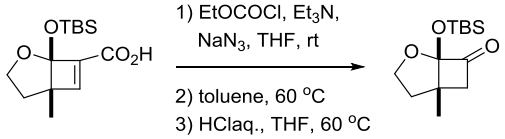
(1*R,5*S**)-1-(*tert*-Butyldimethylsilyloxy)-5-methyl-2-oxabicyclo[3.2.0]hept-6-ene-7-carboxylic Acid (3c).**



2c **3c**

To a solution of **2c** (2.36 g, 7.92 mmol) in MeCN (80 mL) and H_2O (80 mL) was added LiOH•H_2O (664 mg, 15.8 mmol) at room temperature. After stirred for 22 h, the reaction mixture was quenched with aq. NH_4Cl and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford white solids. The residue was purified with silica gel column chromatography (hexane/AcOEt 1 : 1) to give **3c** (1.93 g, 86%) as pale yellow solids. R_f = 0.40 (hexane/ AcOEt 1:3; UV, *p*-anisaldehyde); Mp 54–56 °C (from hexane-Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 1H), 4.12 (dd, *J* = 9.0, 8.0 Hz, 1H), 3.54 (ddd, *J* = 12.0, 9.0, 5.5 Hz, 1H), 1.75 (dd, *J* =13.0, 5.5 Hz, 1H), 1.54 (ddd, *J* = 13.0, 12.0, 8.0 Hz, 1H), 1.19 (s, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.9, 152.9, 136.6, 107.7, 65.2, 57.8, 33.1, 25.8, 18.2, 18.0, −3.2, −3.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{24}NaO_4Si^+$, 307.1336; found, 307.1338; IR ($CHCl_3$): ν 2955, 2928, 2859, 1694, 1292, 1049, 891 cm^{-1}.

(1*R,5*S**)-1-(*tert*-Butyldimethylsilyloxy)-5-methyl-2-oxabicyclo[3.2.0]heptan-7-one (4c).**

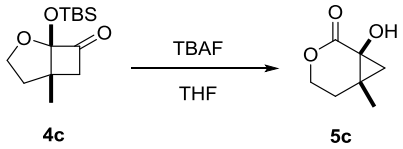


3c **4c**

To a solution of **3c** (47 mg, 0.17 mmol) in THF (3.0 mL) were added triethylamine (28 μL, 0.20 mmol) and EtOCOCl (19 μL, 0.20 mmol) at room temperature, and the mixture was stirred for 10 min. To the mixture was added a solution of NaN_3 (11 mg, 0.17 mmol) in H_2O (3.0 mL) and the mixture was stirred for additional 20 min. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding acyl azide (45 mg) was obtained, which was used in the next step without further purification. A solution of the crude acyl azide in toluene (5.0 mL) was stirred for 2 h at 60 °C. The resulting mixture was concentrated in vacuo to give the corresponding isocyanate as colorless oil, which was used in the next step without further purification. A solution of the crude isocyanate in THF (5.0 mL) and 1% aq. HCl (5.0 mL) was stirred for 30 min at 60 °C. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt 30 : 1) to afford **4c** (11 mg, 26% from **3c**) as colorless oil. R_f = 0.37 (hexane/AcOEt 10 : 1; *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 4.32 (ddd, *J* = 9.5, 8.5, 2.5 Hz, 1H), 3.92 (ddd, *J* = 10.0, 9.5, 6.5 Hz, 1H), 2.62 (d, *J* = 17.5 Hz, 1H), 2.50 (d, *J* = 17.5 Hz, 1H), 2.11 (ddd, *J* = 12.5, 6.5, 2.5 Hz, 1H), 1.94 (ddd, *J* = 12.5, 10.0, 8.5 Hz, 1H), 1.23 (s, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.6, 117.0, 68.3, 51.3, 44.9, 37.7, 25.7, 19.0, 18.0, −3.5, −3.9; HRMS (ESI) *m/z*: $[M+H]^+$ calcd

for $C_{13}H_{25}O_3Si^+$, 257.1567; found, 257.1567; IR ($CHCl_3$): ν 2959, 2932, 2859, 1790, 1296, 1115, 895, 837 cm^{-1}.

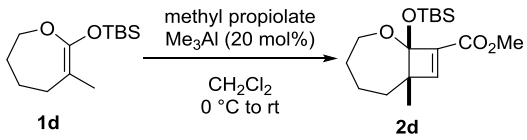
(1*S,6*S**)-1-Hydroxy-6-methyl-3-oxabicyclo[4.1.0]heptan-2-one (5c).**



4c **5c**

To a solution of **4c** (58 mg, 0.23 mmol) in THF (2.0 mL) was added TBAF (1.0 M in THF, 0.23 mL, 0.23 mmol) at –20 °C. After stirred for 5 min, the mixture was quenched with saturated aq. NH_4Cl and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1:1) to afford **5c** (20 mg, 62%) as colorless oil. R_f = 0.25 (hexane/ AcOEt 1 : 1; *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 4.26 (dd, *J* = 12.5, 6.0 Hz, 1H), 4.03 (ddd, *J* = 13.5, 12.5, 3.5 Hz, 1H), 3.47 (br, 1H, OH), 2.09 (ddd, *J* = 14.0, 13.5, 6.0 Hz, 1H), 1.90 (dd, *J* = 14.0, 3.5 Hz, 1H), 1.79 (d, *J* = 6.5 Hz, 1H), 1.40 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 174.3, 65.7, 58.6, 28.1, 26.6, 21.2, 17.3; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_7H_{11}O_3^+$, 143.0703; found, 143.0705; IR ($CHCl_3$): ν 3391, 2924, 1709, 1165, 1115, 1061 cm^{-1}.

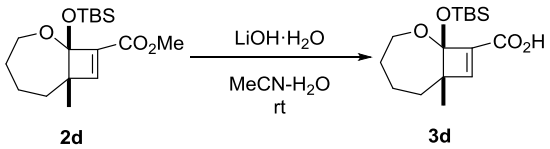
Methyl (1*R,7*S**)-1-(*tert*-Butyldimethylsilyloxy)-7-methyl-2-oxabicyclo[5.2.0]non-8-ene-9-carboxylate (2d).**



1d **2d**

To a solution of **1d** (5.78 g, 23.4 mmol) and methyl propiolate (2.34 mL, 28.1 mmol) in CH_2Cl_2 (200 mL) was added a mixture of Me_3Al (1.4 M solution in toluene, 3.3 mL, 4.7 mmol) and CH_2Cl_2 (40 mL) at 0 °C. After stirred for 2 h at room temperature, the mixture was quenched with saturated aq. Rochelle salt and stirred vigorously for additional 30 min. The whole was extracted three times with hexane and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo to afford pale yellow oil. The residue was purified with silica gel column chromatography (hexane/AcOEt 20 : 1) to give **2d** (2.75 g, 36%) as pale yellow oil. R_f = 0.30 (hexane/AcOEt 10 : 1; UV, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 7.07 (s, 1H), 3.89 (ddd, *J* = 12.5, 9.0, 3.5 Hz, 1H), 3.75 (s, 3H), 3.66 (ddd, *J* = 12.5, 3.5, 3.5 Hz, 1H), 1.70–1.61 (m, 5H), 1.55–1.46 (m, 1H), 1.17 (s, 3H), 0.92 (s, 9H), 0.24 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.0, 157.8, 137.6, 103.2, 64.4, 58.6, 51.2, 35.8, 31.5, 25.9, 22.9, 19.4, 18.5, –3.9, –4.0; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{30}NaO_4Si^+$, 349.1806; found, 349.1809; IR ($CHCl_3$): ν 2927, 2859, 1728, 1238, 1080, 1053, 837, 779 cm^{-1}.

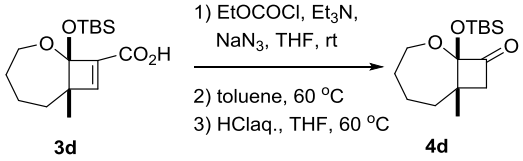
(1*R,7*S**)-1-(*tert*-Butyldimethylsilyloxy)-7-methyl-2-oxabicyclo[5.2.0]non-8-ene-9-carboxylic Acid (3d).**



2d **3d**

To a solution of **2d** (2.75 g, 8.42 mmol) in MeCN (80 mL) and H_2O (80 mL) was added LiOH•H_2O (707 mg, 16.9 mmol) at 60 °C. After stirred for 19 h, the reaction mixture was quenched with aq. NH_4Cl and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford white solids. The residue was purified with silica gel column chromatography (hexane/AcOEt 1 : 1) to give **3d** (1.73 g, 66%) as white solids. R_f = 0.41 (hexane/ AcOEt 1:1; UV, *p*-anisaldehyde); Mp 115–118 °C (from hexane-Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 1H), 3.89 (ddd, *J* = 12.5, 8.5, 4.5 Hz, 1H), 3.68 (ddd, *J* = 12.5, 3.5, 3.5 Hz, 1H), 1.72–1.62 (m, 5H), 1.56–1.47 (m, 1H), 1.18 (s, 3H), 0.92 (s, 9H), 0.23 (s, 3H), 0.06 (s, 3H);^{13}C NMR ($CDCl_3$) δ 166.1, 160.0, 137.3, 103.1, 64.5, 58.9, 35.7, 31.4, 25.9, 22.9, 19.3, 18.5, –3.8, –4.0; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{28}NaO_4Si^+$, 335.1649; found, 335.1646; IR ($CHCl_3$): ν 2928, 2855, 1694, 1250, 1080, 1049, 837, 779 cm^{-1}

(1*R,7*S**)-1-(*tert*-Butyldimethylsilyloxy)-7-methyl-2-oxabicyclo[5.2.0]heptan-9-one (4d).**

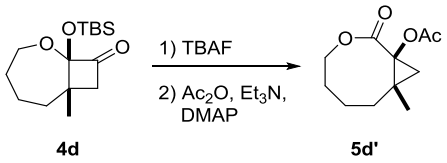


3d **4d**

To a solution of **3d** (977 mg, 3.13 mmol) in THF (30 mL) were added triethylamine (0.65 mL, 4.7 mmol) and EtOCOCl (0.36 mL, 3.8 mmol) at room temperature, and the mixture was stirred for 10 min. To the mixture was added a solution of NaN_3 (224 mg, 3.44 mmol) in H_2O (100 mL) and the mixture was stirred for additional 30 min. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding acyl azide was obtained as colorless oil, which was used in the next step without further purification. A solution of the crude acyl azide in toluene (20 mL) was stirred for 2 h at 60 °C. The resulting mixture was concentrated in vacuo to give the corresponding isocyanate as colorless oil, which was used in the next step without further purification. A solution of the crude isocyanate in THF (15 mL) and 1% aq. HCl (15 mL) was stirred for 2 h at 60 °C. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt 30 : 1) to afford **4d** (456 mg, 52% from **3d**) as colorless oil. R_f = 0.50 (hexane/AcOEt 10 : 1; *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 3.76 (ddd, *J* = 12.5, 11.5, 1.0 Hz, 1H), 3.68 (ddd, *J* = 12.5, 5.0, 3.0 Hz, 1H), 2.70 (d, *J* = 17.0 Hz, 1H), 2.47 (d, *J* = 17.0 Hz, 1H), 1.81–1.61 (m, 6H), 1.38 (s, 3H), 0.91 (s, 9H), 0.17 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.5, 110.0, 65.2, 55.2, 44.1, 37.5, 31.2, 25.7, 23.7, 20.4, 18.2, –3.9, –4.5; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{29}O_3Si^+$,

285.1880; found, 285.1879; IR ($CHCl_3$): ν 2928, 2859, 1794, 1096, 1049, 841, 783 cm^{-1}.

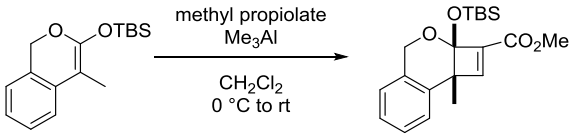
(1*S,8*S**)-1-Acetoxy-8-methyl-3-oxabicyclo[6.1.0]heptan-2-one (5d').**



4d **5d'**

To a solution of **4d** (104 mg, 0.366 mmol) in THF (5.0 mL) was added TBAF (1.0 M in THF, 0.37 mL, 0.37 mmol) at –20 °C. After stirred for 30 min, the mixture was quenched with saturated aq. NH_4Cl and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding cyclopropanol was obtained as pale yellow oil, which was used in the next step without further purification. To a solution of the crude cyclopropanol **5d** in CH_2Cl_2 (5.0 mL) were added acetic anhydride (33 μL, 0.34 mmol), triethylamine (48 μL, 0.34 mmol) and DMAP (2.0 mg, 17 μmol) at room temperature. After stirred for 20 h, the mixture was quenched with saturated aq. NH_4Cl and extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt 7 : 1) to afford **5d'** (26 mg, 33% from **4d**) as colorless oil. R_f = 0.33 (hexane/ AcOEt 3 : 1; *p*-anisaldehyde); ^1H NMR ($CDCl_3$) δ 4.76 (ddd, *J* = 11.5, 8.5, 4.0 Hz, 1H), 4.10 (ddd, *J* = 11.5, 5.0, 5.0 Hz, 1H), 2.13 (s, 3H), 2.12–2.09 (m, 1H), 1.95–1.89 (m, 1H), 1.84 (d, *J* = 6.5 Hz, 1H), 1.80–1.71 (m, 1H), 1.67–1.57 (m, 3H), 1.02 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 173.9, 170.3, 68.7, 63.1, 37.1, 32.2, 30.7, 28.0, 21.7, 20.7, 20.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{16}NaO_4^+$, 235.0941; found, 235.0941; IR ($CHCl_3$): ν 2931, 1740, 1369, 1227, 1134 cm^{-1}.

Methyl (2a*R,8b*R**)-2a-(*tert*-Butyldimethylsilyloxy)-8b-methyl-2a,8b-dihydro-4H-cyclobuta[*c*]isochromene-2-carboxylate (2e).**

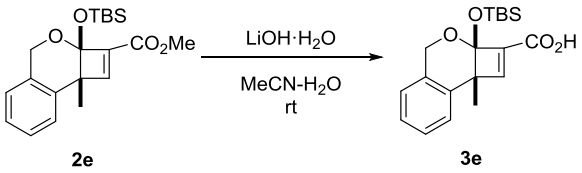


1e **2e**

To a solution of **1e** (7.63 g, 27.6 mmol) and methyl propiolate (2.8 mL, 33 mmol) in CH_2Cl_2 (100 mL) was added a mixture of Me_3Al (2.0 M solution in toluene, 14 mL, 28 mmol) and CH_2Cl_2 (100 mL) at 0 °C. After stirred for 2 h at room temperature, the mixture was quenched with saturated aq. Rochelle salt and stirred vigorously for additional 30 min. The whole was extracted three times with hexane and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo to afford pale yellow oil. The residue was purified with silica gel column chromatography (hexane/AcOEt 20 : 1) to give **2e** (7.16 g, 72%) as colorless oil. R_f = 0.33 (hexane/AcOEt 10 : 1; UV, *p*-anisaldehyde); ^1H NMR ($CDCl_3$) δ 7.32 (d, *J* = 7.5 Hz, 1H), 7.29 (dd, *J* = 7.5, 7.5 Hz,

1H), 7.19 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.95 (s, 1H), 4.82 (d, *J* = 14.0 Hz, 1H), 4.55 (d, *J* = 14.0 Hz, 1H), 3.76 (s, 3H), 1.52 (s, 3H), 0.92 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.5, 152.0, 138.8, 138.7, 134.5, 127.8, 126.2, 125.9, 125.0, 101.4, 64.1, 54.0, 51.3, 25.8, 20.7, 18.3, –3.2, –3.4; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{28}NaO_4Si^+$, 383.1629; found, 383.1647; IR ($CHCl_3$): ν 2955, 2932, 2855, 1728, 1250, 1061, 841 cm^{-1}.

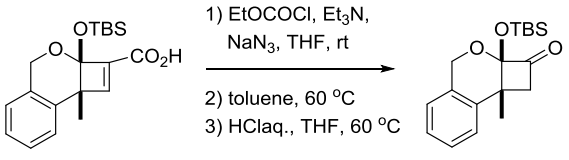
(2a*R,8b*R**)-2a-(*tert*-Butyldimethylsilyloxy)-8b-methyl-2a,8b-dihydro-4H-cyclobuta[*c*]isochromene-2-carboxylic Acid (3e).**



2e **3e**

To a solution of **2e** (4.17 g, 11.6 mmol) in MeCN (150 mL) and H_2O (150 mL) was added LiOH•H_2O (970 mg, 23.1 mmol) at 60 °C. After stirred for 3 h, the reaction mixture was quenched with aq. NH_4Cl and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford white solids. The residue was purified with silica gel column chromatography (hexane/AcOEt 1 : 1) to give **3e** (2.27 g, 57%) as white solids. R_f = 0.40 (hexane/ AcOEt 1:3; UV, *p*-anisaldehyde); Mp 158-161 ºC (from hexane-Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.33 (d, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.20 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.05 (s, 1H), 4.83 (d, *J* = 14.0 Hz, 1H), 4.57 (d, *J* = 14.0 Hz, 1H), 1.53 (s, 3H), 0.91 (s, 9H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.8, 154.5, 138.33, 138.30, 134.5, 127.9, 126.4, 125.9, 125.0, 101.4, 64.1, 54.2, 25.9, 20.5, 18.3, –3.2, –3.4; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{26}NaO_4Si^+$, 369.1493; found, 369.1494; IR ($CHCl_3$): ν 2959, 2928, 2859, 1794, 1250, 1096, 914, 841 cm^{-1}.

(2a*R,8b*R**)-2a-(*tert*-Butyldimethylsilyloxy)-4,8b-dihydro-1H-cyclobuta[*c*]isochromen-2(2aH)-one (4e).**

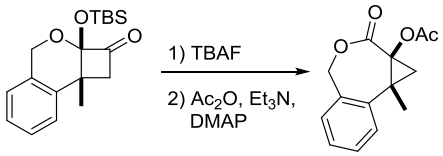


3e **4e**

To a solution of **3e** (204 mg, 0.589 mmol) in THF (6.0 mL) were added triethylamine (99 μL, 0.71 mmol) and EtOCOCl (67 μL, 0.71 mmol) at room temperature, and the mixture was stirred for 15 min. To the mixture was added a solution of NaN_3 (41 mg, 0.62 mmol) in H_2O (4.0 mL) and the mixture was stirred for additional 20 min. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding acyl azide (200 mg) was obtained as colorless oil, which was used in the next step without further purification. A solution of the crude acyl azide in toluene (10 mL) was stirred for 2 h at 60 °C. The resulting mixture was concentrated in vacuo to give the

corresponding isocyanate as colorless oil, which was used in the next step without further purification. A solution of the crude isocyanate in THF (5.0 mL) and 1% aq. HCl (5.0 mL) was stirred for 30 min at 60 °C. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt 30 : 1) to afford **4e** (95 mg, 51% from **3e**) as colorless oil. R_f = 0.50 (hexane/AcOEt 10 : 1; UV, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 7.34 (d, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 7.0, 7.5 Hz, 1H), 7.20 (dd, *J* = 7.0, 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 4.90 (d, *J* = 14.0 Hz, 1H), 4.52 (d, *J* = 14.0 Hz, 1H), 3.07 (d, *J* = 17.0 Hz, 1H), 2.81 (d, *J* = 17.0 Hz, 1H), 1.55 (s, 3H), 0.92 (s, 9H), 0.27 (s, 3H), 0.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.7, 139.6, 132.8, 128.2, 126.6, 126.2, 124.7, 107.9, 61.6, 55.3, 25.7, 22.6, 18.3, –3.6, –4.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{26}NaO_3Si^+$, 341.1543; found, 341.1544; IR ($CHCl_3$): ν 2959, 2928, 1794, 1250, 1092, 910, 841 cm^{-1}.

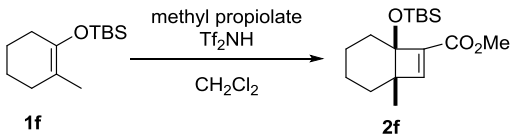
(1a*S,8b*R**)-1a-Acetoxy-8b-methyl-1,1a,4,8b-tetrahydro-2H-benzo[*c*]cyclopropa[*e*]oxepin-2-one (5e').**



4e **5e'**

To a solution of **4e** (67 mg, 0.21 mmol) in THF (3.0 mL) was added TBAF (1.0 M in THF, 0.21 mL, 0.21 mmol) at –20 °C. After stirred for 40 min, the mixture was quenched with saturated aq. NH_4Cl and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding cyclopropanol (42 mg) was obtained as colorless oil, which was used in the next step without further purification. To a solution of the crude cyclopropanol in CH_2Cl_2 (10 mL) were added acetic anhydride (39 μL, 0.41 mmol), triethylamine (58 μL, 0.41 mmol) and DMAP (3.0 mg, 21 μmol) at room temperature. After stirred for 22 h, the mixture was quenched with saturated aq. NH_4Cl and extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt 5 : 1) to afford **5e'** (36 mg, 70% from **4e**) as white solids. R_f = 0.35 (hexane/AcOEt 3 : 1; UV, *p*-anisaldehyde); Mp 88–91 °C (from hexane-Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.42–7.39 (m, 1H), 7.26–7.24 (m, 2H), 6.42 (d, *J* = 12.5 Hz, 1H), 4.76 (d, *J* = 12.5 Hz, 1H), 2.20 (s, 3H), 1.60 (d, *J* = 6.5 Hz, 1H), 1.52 (s, 3H), 1.18 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.8, 170.1, 141.7, 134.1, 130.4, 130.1, 129.1, 127.5, 69.6, 62.8, 32.0, 25.3, 20.9, 20.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{14}NaO_4^+$, 269.0784; found, 269.0780; IR ($CHCl_3$): ν 1732, 1238, 1219, 1123, 768, 733 cm^{-1}.

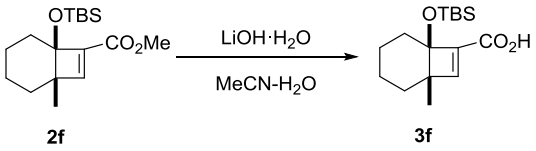
Methyl (1*S,6*R**)-1-(*tert*-Butyldimethylsilyloxy)-6-methyl-2-bicyclo[4.2.0]oct-7-ene-8-carboxylate (2f).**



1f **2f**

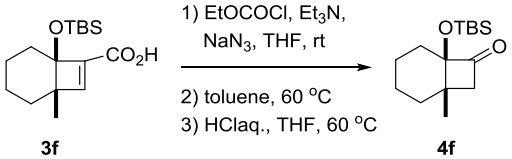
To a solution of **1f** (1.01 g, 4.46 mmol) and methyl propiolate (0.34 mL, 4.1 mmol) in CH_2Cl_2 (25 mL) was added a solution of Tf_2NH (0.080 M in toluene, 1.1 mL, 0.089 mmol) at room temperature. After stirred for 1 h, the mixture was quenched with saturated aq. $NaHCO_3$. The whole was extracted three times with hexane and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo to afford pale yellow oil. The residue was purified with silica gel column chromatography (hexane/diethyl ether 80 : 1) to give **2f** (473 mg, 38%) as colorless oil. R_f = 0.53 (hexane/diethyl ether 4 : 1; UV, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 6.95 (s, 1H), 3.74 (s, 3H), 2.03 (td, *J* = 4.5, 13.5 Hz, 1H), 1.82–1.76 (m, 1H), 1.62–1.53 (m, 1H), 1.53–1.44 (m, 2H), 1.43–1.33 (m, 2H), 1.09 (s, 3H), 0.86 (s, 9H), 0.13 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.7, 155.1, 141.0, 80.1, 51.2, 51.0, 31.1, 30.4, 25.9, 21.3, 18.4, 17.0, 16.9, –2.8, –3.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{17}H_{30}NaO_3Si^+$, 333.1856; found, 335.1857; IR ($CHCl_3$): ν 2932, 2855, 1724, 1246, 1146, 1119, 837, 775 cm^{-1}.

(1*S,6*R**)-1-(*tert*-Butyldimethylsilyloxy)-6-methyl-2-bicyclo[4.2.0]oct-7-ene-8-carboxylic Acid (3f).**



To a solution of **2f** (1.22 g, 3.93 mmol) in MeCN (35 mL) and H_2O (35 mL) was added LiOH•H_2O (330 mg, 7.85 mmol) at 80 °C. After stirred for 5 h, the reaction mixture was quenched with aq. NH_4Cl and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford white solids. The residue was purified with silica gel column chromatography (hexane/AcOEt 3 : 1) to give **3f** (884 mg, 74%) as white solids. R_f = 0.25 (hexane/AcOEt 3:1; UV, *p*-anisaldehyde); Mp 110-113 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (s, 1H), 2.04 (td, *J* = 4.5, 13.0 Hz, 1H), 1.78 (ddd, *J* = 13.0, 12.0, 5.5 Hz, 1H) 1.65–1.35 (m, 6H), 1.11 (s, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.6, 157.7, 140.5, 80.1, 51.5, 31.0, 30.3, 25.9, 21.2, 18.4, 17.1, 16.9, –2.7, –3.0; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{28}NaO_3Si^+$, 319.1700; found, 319.1697; IR ($CHCl_3$): ν 2932, 2855, 1686, 1254, 1150, 1119, 837, 775 cm^{-1}.

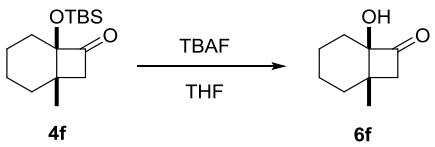
(1*S,6*R**)-1-(*tert*-Butyldimethylsilyloxy)-6-methyl-2-bicyclo[4.2.0]octan-8-one (4f).**



To a solution of **3f** (1.01 g, 3.41 mmol) in THF (35 mL) were added triethylamine (0.57 mL, 4.1 mmol) and EtOCOCl (0.39 mL, 4.1 mmol) at room temperature, and the mixture was stirred for 5 min. To the mixture was added a solution of NaN_3 (233 mg, 3.58 mmol) in H_2O (25 mL) and the mixture was stirred for additional 10 min. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding acyl azide (991 mg) was obtained as

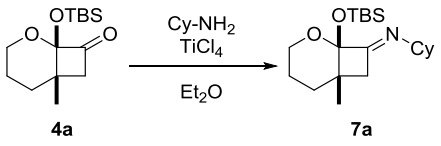
colorless oil, which was used in the next step without further purification. A solution of the crude acyl azide in toluene (30 mL) was stirred for 2 h at 60 °C. The resulting mixture was concentrated in vacuo to give the corresponding isocyanate as colorless oil, which was used in the next step without further purification. A solution of the crude isocyanate in THF (35 mL) and 1% aq. HCl (35 mL) was stirred for 30 min at 60 °C. The whole was extracted three times with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt 30 : 1) to afford **4f** (670 mg, 75% from **3f**) as colorless oil. R_f = 0.75 (hexane/AcOEt 3 : 1; *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 2.90 (d, *J* = 16.0 Hz, 1H), 2.09 (d, *J* = 16.0 Hz, 1H), 1.76–1.65 (m, 4H), 1.61–1.53 (m, 1H), 1.52–1.46 (m, 1H), 1.41–1.32 (m, 2H), 1.04 (s, 3H), 0.88 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.3, 87.0, 48.4, 33.9, 31.4, 30.7, 25.7, 24.3, 21.7, 20.0, 18.2, –3.48, –3.51; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{29}O_2Si^+$, 269.1931; found, 269.1928; IR ($CHCl_3$): ν 2928, 2858, 1778, 1118, 837, 779 cm^{-1}.

(1*S,6*R**)-1-Hydroxy-6-methyl-2-bicyclo[4.2.0]octan-8-one (6f).**



To a solution of **4f** (67 mg, 0.25 mmol) in THF (3.0 mL) was added TBAF (1.0 M in THF, 0.50 mL, 0.50 mmol) at rt. After stirred for 5 h, the mixture was quenched with H_2O and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford **6f** (30 mg, 79%) as pale yellow oil, contaminated with a small amount of impurities (assessed by ^{1}H NMR). A small portion was chromatographed to give analytically sample. R_f = 0.33 (hexane/ AcOEt 3 : 1; *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 3.07 (d, *J* = 13.2 Hz, 1H), 2.19 (d, *J* = 13.2 Hz, 1H), 1.85–1.33 (m, 8H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 209.5, 86.1, 48.8, 33.8, 30.3, 30.1, 22.9, 21.3, 19.8; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_9H_{14}NaO_2^+$, 177.0886; found, 177.0887; IR ($CHCl_3$): ν 3426, 2932, 1771, 1702, 910, 737 cm^{-1}.

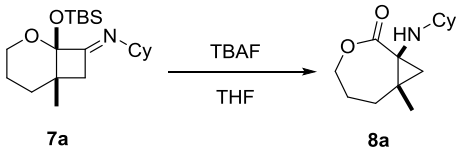
(1*R,6*S**)-1-(*tert*-Butyldimethylsilyloxy)-*N*-cyclohexyl-6-methyl-2-oxabicyclo[4.2.0]octan-8-imine (7a).**



To a solution of **4a** (114 mg, 0.422 mmol) in Et_2O (8.0 mL) were successively added cyclohexylamine (0.48 mL, 4.2 mmol) and a solution of $TiCl_4$ (1.0 M solution in CH_2Cl_2, 0.25 mL, 0.25 mmol) in Et_2O (8.0 mL) at 0 °C. After stirred for 1 h at 0 °C, the reaction mixture was warmed up to room temperature and stirred for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by gel permeation chromatography to afford **7a** (143 mg, 96%) as colorless oil. R_f = 0.46 (hexane/AcOEt 10:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 3.72–3.69 (m, 1H), 3.55 (ddd, *J* = 11.0, 11.0, 2.0 Hz, 1H), 3.09 (tt, *J* = 9.5, 4.0

Hz, 1H), 2.60 (d, *J* = 14.5 Hz, 1H), 2.08 (d, *J* = 14.5 Hz, 1H), 1.75–1.36 (m, 11H), 1.33–1.23 (m, 3H), 1.02 (s, 3H), 0.89 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.8, 102.2, 61.0, 60.0, 38.2, 38.1, 33.6, 33.5, 29.5, 25.9, 25.8, 24.4, 24.3, 24.2, 21.6, 18.3, –3.4, –3.5; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{38}NO_2Si^+$, 352.2666, found, 352.2670; IR ($CHCl_3$): ν 2928, 2855, 1724, 1250, 1111, 841 cm^{-1}.

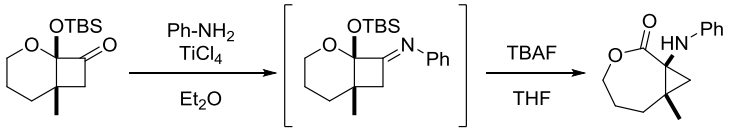
(1*S,7*S**)-1-(Cyclohexylamino)-7-methyl-3-oxabicyclo[5.1.0]octan-2-one (8a).**



7a **8a**

To a solution of **7a** (89 mg, 0.25 mmol) in THF (4.0 mL) was added TBAF (1.0 M in THF, 0.25 mL, 0.25 mmol) at room temperature. After stirred for 10 min, the mixture was quenched with saturated aq. NH_4Cl and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford **8a** (41 mg, 68%) as colorless oil. R_f = 0.50 (hexane/AcOEt 3:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$) δ 4.28 (ddd, *J* = 12.5, 12.5, 4.0 Hz, 1H), 4.20 (ddd, *J* = 12.5, 6.5, 0.5 Hz, 1H), 2.74 (tt, *J* = 10.5, 4.0 Hz, 1H), 2.09 (ddd, *J* = 15.0, 6.5, 0.5 Hz, 1H), 2.03 (br, 1H), 1.96–1.88 (m, 1H), 1.82–1.66 (m, 4H), 1.59–1.55 (m, 2H), 1.33–1.21 (m, 3H), 1.17–1.08 (m, 1H), 1.13 (s, 3H), 1.05–0.99 (m, 1H), 0.92 (ddd, *J* = 12.5, 12.5, 6.5 Hz, 1H), 0.90 (d, *J* = 5.5 Hz, 1H), 0.73 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.7, 64.3, 54.7, 45.3, 34.3, 33.4, 31.3, 25.8, 25.7, 24.6, 24.4, 23.1, 20.3, 14.7; HRMS (ESI) *m/z*: $[M+ Na]^+$ calcd for $C_{14}H_{23}NNaO_2^+$, 260.1621, found 260.1620; IR ($CHCl_3$): ν 2924, 2855, 1728, 1246, 1153, 1083 cm^{-1}.

(1*S,7*S**)-7-Methyl-1-(phenylamino)-3-oxabicyclo[5.1.0]octan-2-one (8b).**



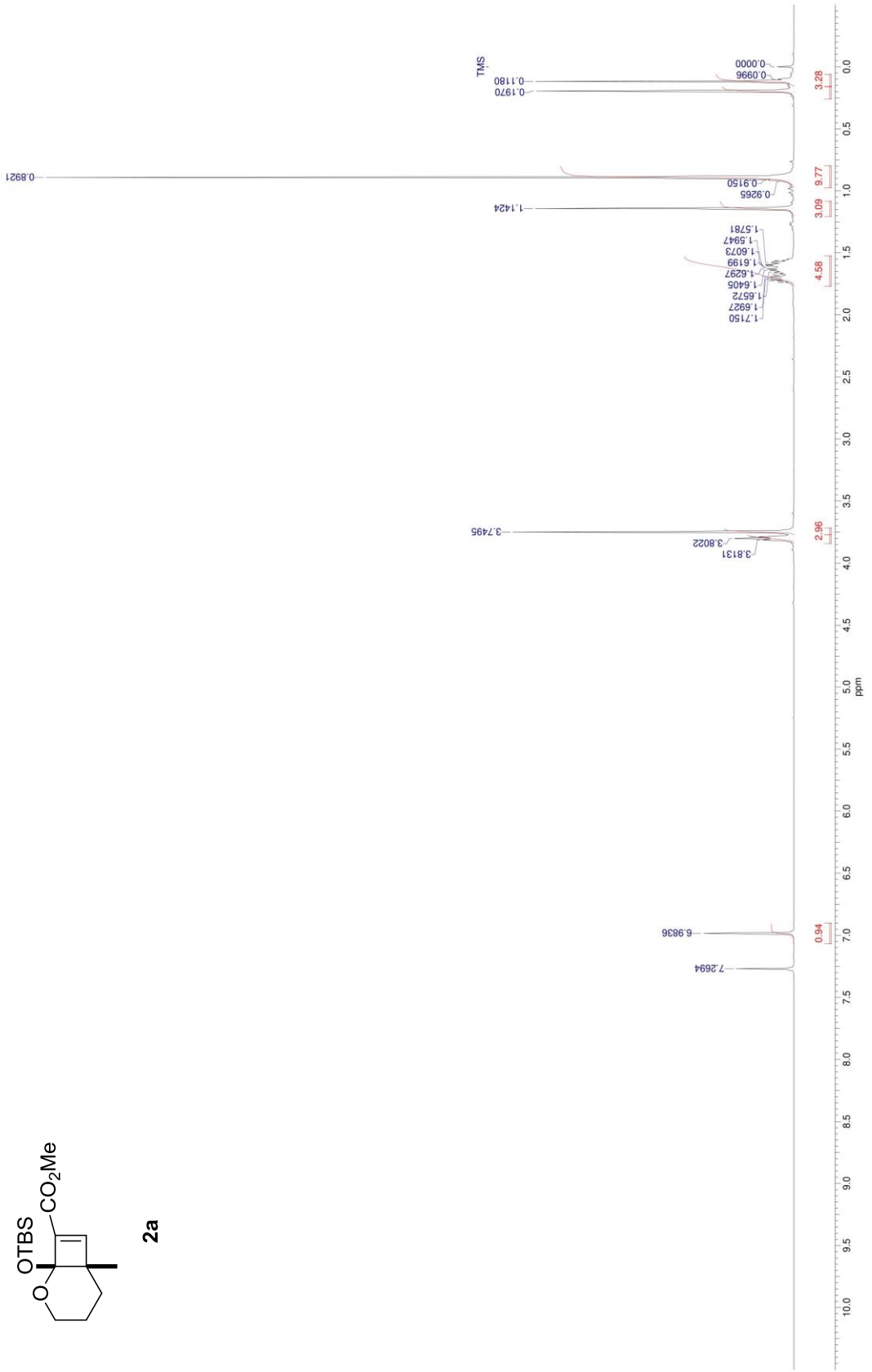
4a **7b** **8b**

To a solution of **4a** (54 mg, 0.20 mmol) in Et_2O (5.0 mL) were added aniline (0.18 mL, 2.0 mmol) and a mixture of $TiCl_4$ (1.0 M solution in CH_2Cl_2, 0.12 mL, 0.12 mmol) and Et_2O (5.0 mL) at 0 °C. After stirred for 1 h, the mixture was stirred for 24 h at room temperature. Then, the reaction mixture was quenched with saturated aq. NH_4Cl. The whole was extracted three times with Et_2O and the combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The crude mixture of the corresponding imine was obtained as yellow oil, which was used in the next step without further purification. To a solution of the crude imine in THF (3.0 mL) was added TBAF (1.0 M in THF, 0.20 mL, 0.20 mmol) at room temperature. After stirred for 10 min, the mixture was quenched with saturated aq. NH_4Cl and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to afford **8b** (16 mg, 34% from **4a**) as pale yellow solids. R_f = 0.50 (hexane/AcOEt 1 : 1; *p*-anisaldehyde); Mp 135-140 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (dd, *J* = 8.0, 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.78

(dd, *J* = 8.0, 8.0 Hz, 1H), 4.35 (ddd, *J* = 12.0, 12.0, 4.0 Hz, 1H), 4.29 (dd, *J* = 12.0, 6.5 Hz, 1H), 4.01 (brs, 1H), 2.19 (ddd, *J* = 15.0, 5.5, 0.5 Hz, 1H), 2.04–1.97 (m, 1H), 1.88–1.81 (m, 1H), 1.29 (d, *J* = 5.5 Hz, 1H), 1.23 (s, 3H), 1.05 (ddd, *J* = 15.0, 12.5, 6.5 Hz, 1H), 0.88 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.9, 145.6, 129.1, 118.8, 114.2, 64.5, 42.3, 31.1, 26.2, 23.4, 23.1, 15.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{17}NNaO_2^+$, 254.1151; found, 254.1149; IR ($CHCl_3$): ν 3360, 2931, 1717, 1601, 1501, 1250, 737 cm^{-1}.

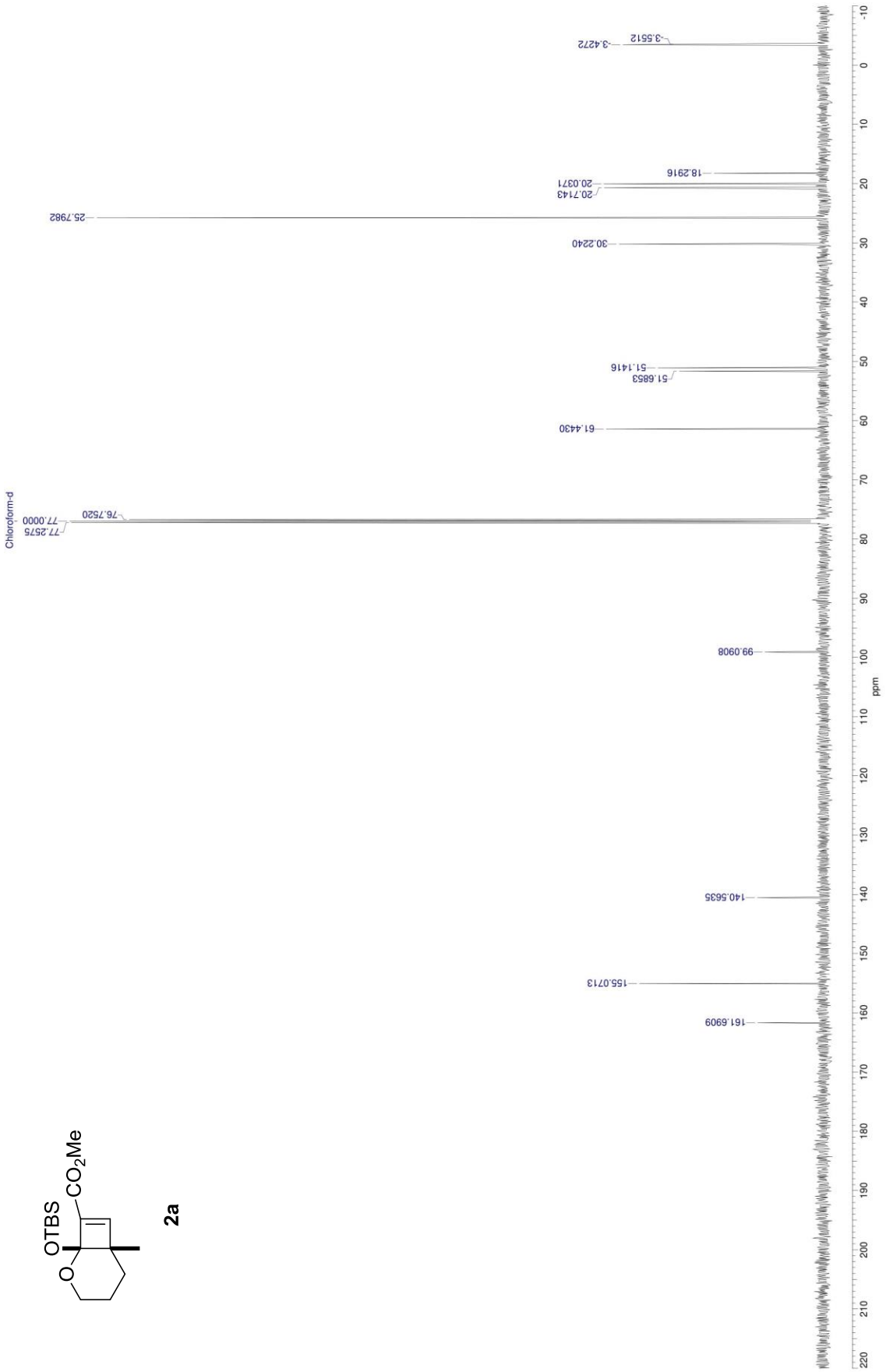
3. NMR Spectra

Compound **2a** (^{1}H NMR, $CDCl_3$)

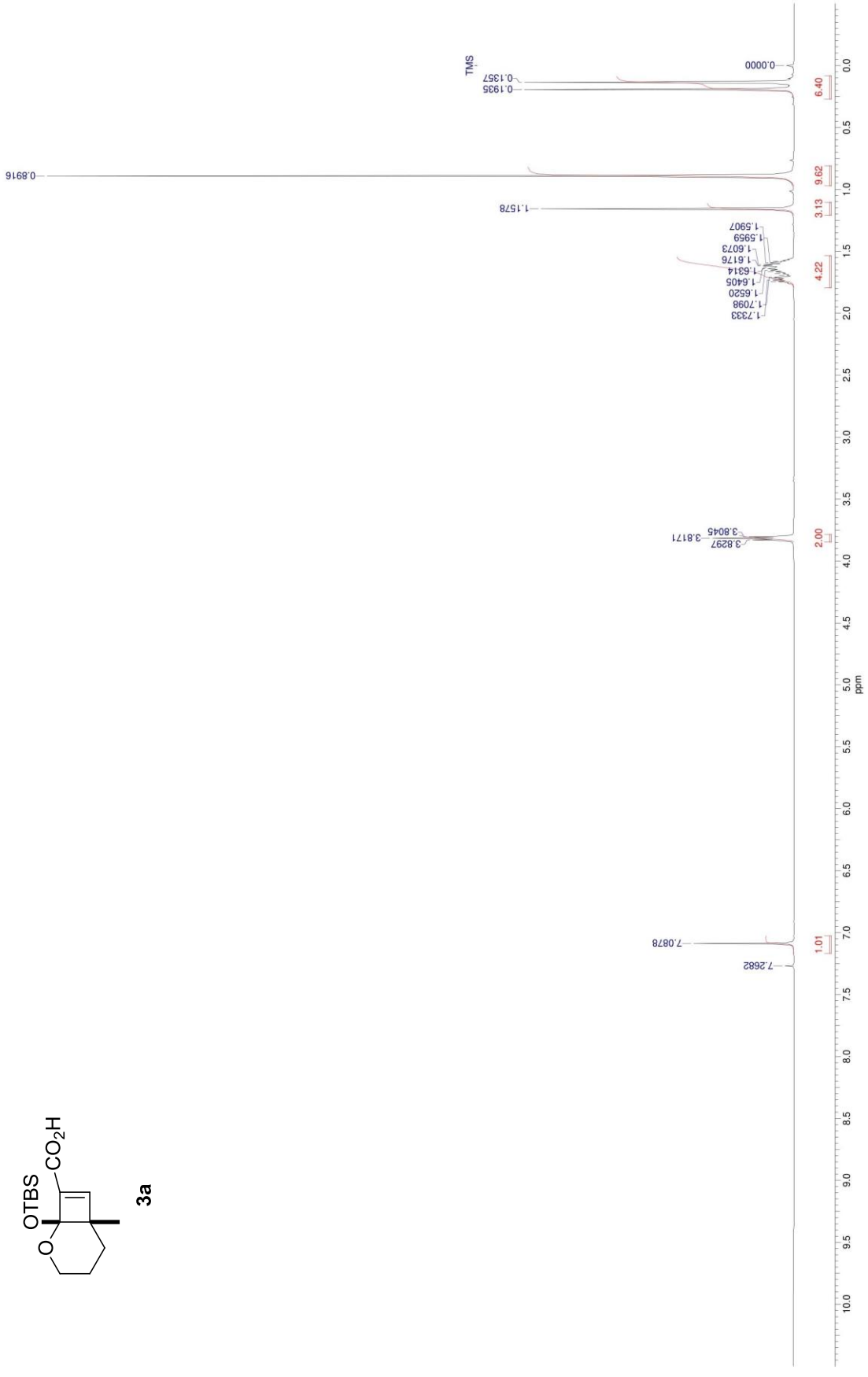


2a

Compound **2a** (^{13}C NMR, $CDCl_3$)

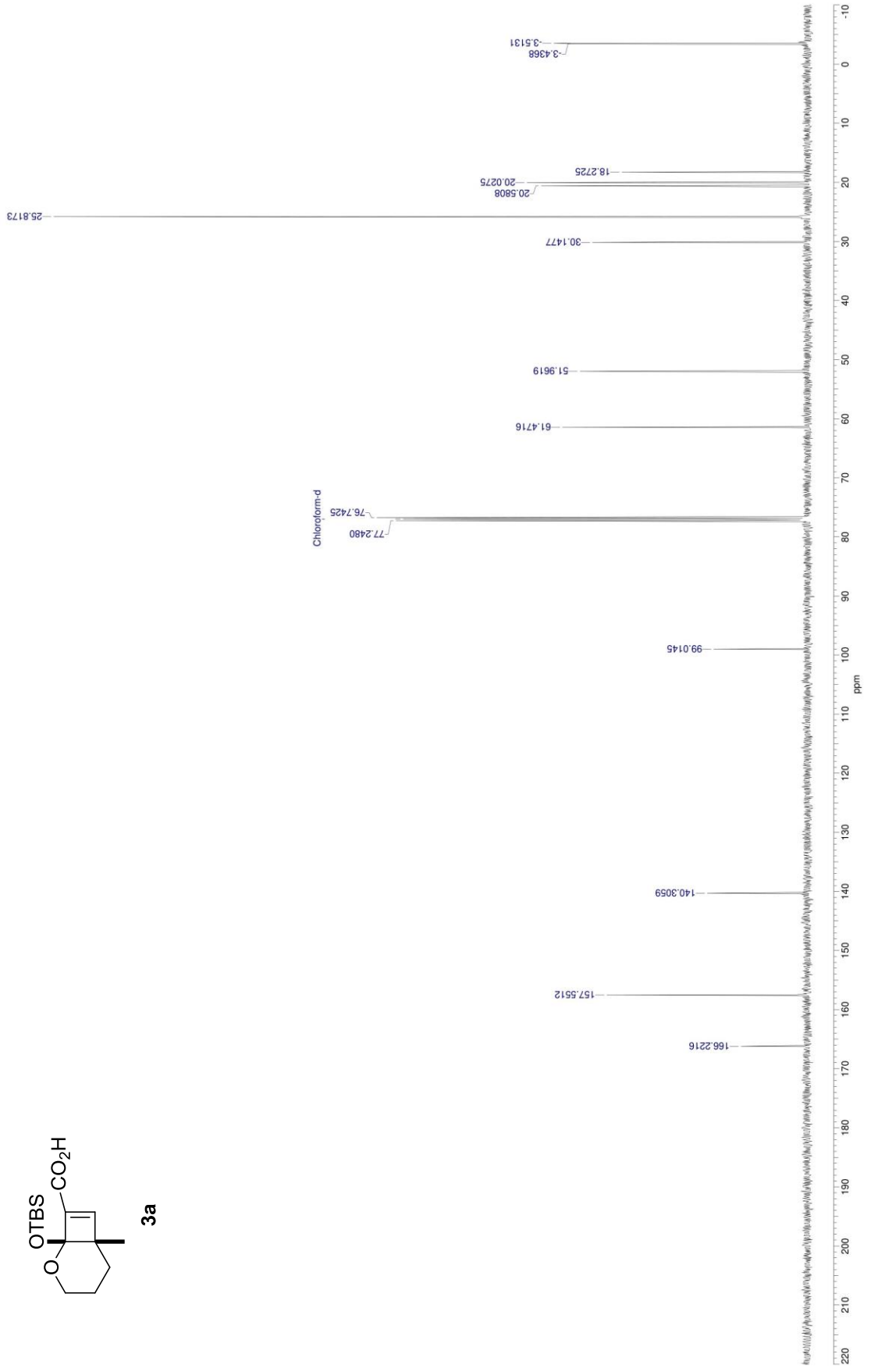


Compound **3a** (^{1}H NMR, $CDCl_3$)

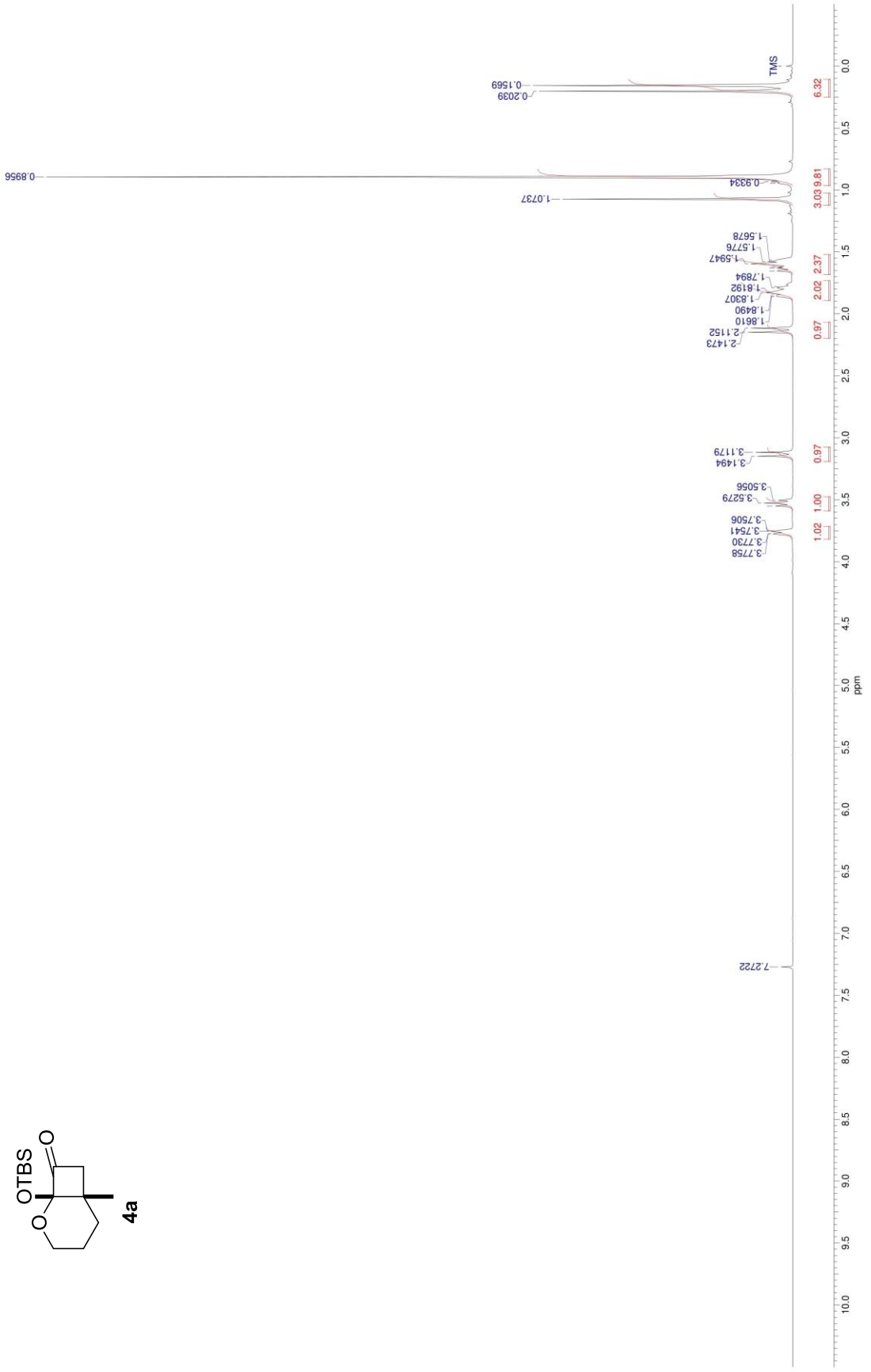


3a

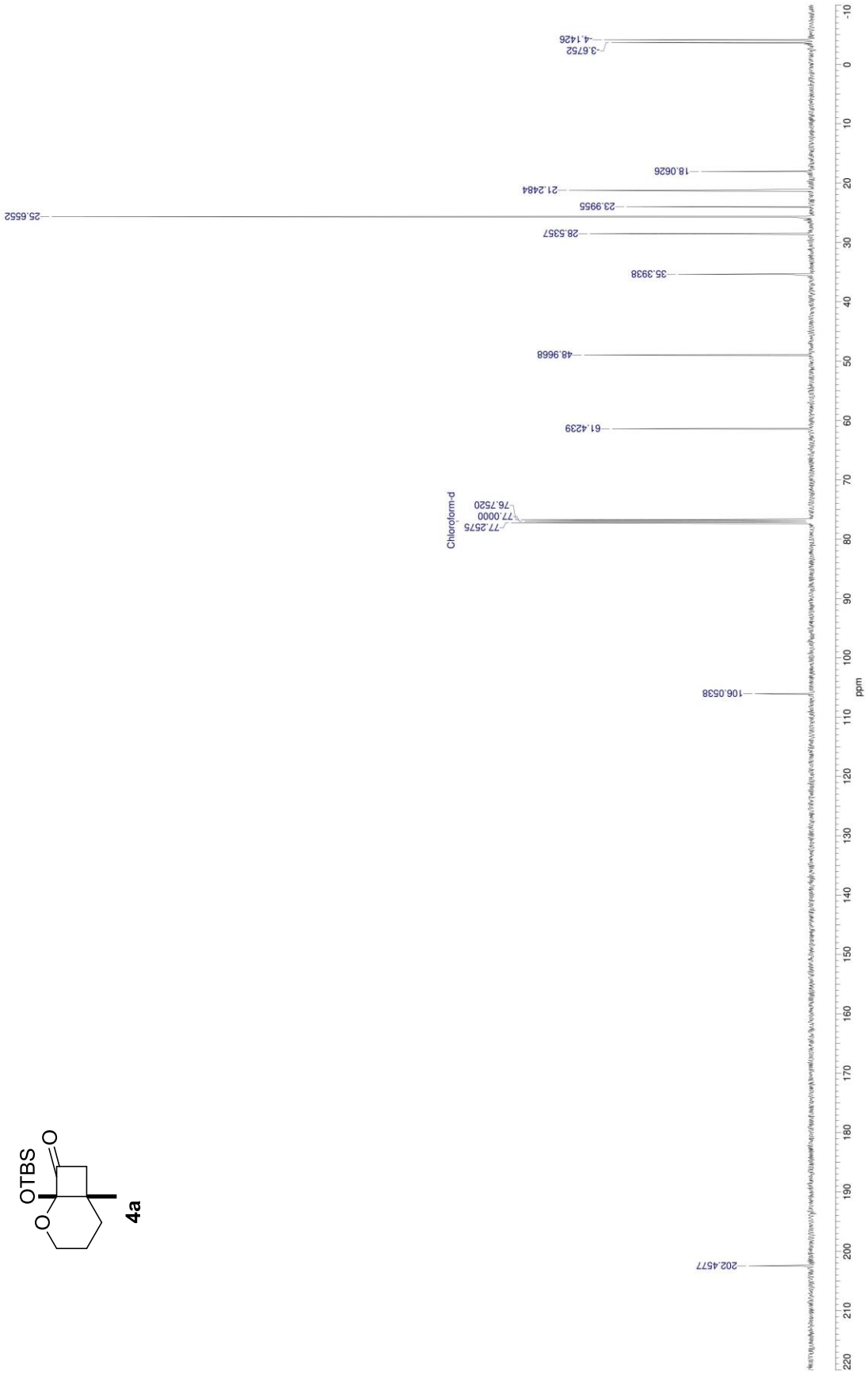
Compound **3a** (^{13}C NMR, $CDCl_3$)



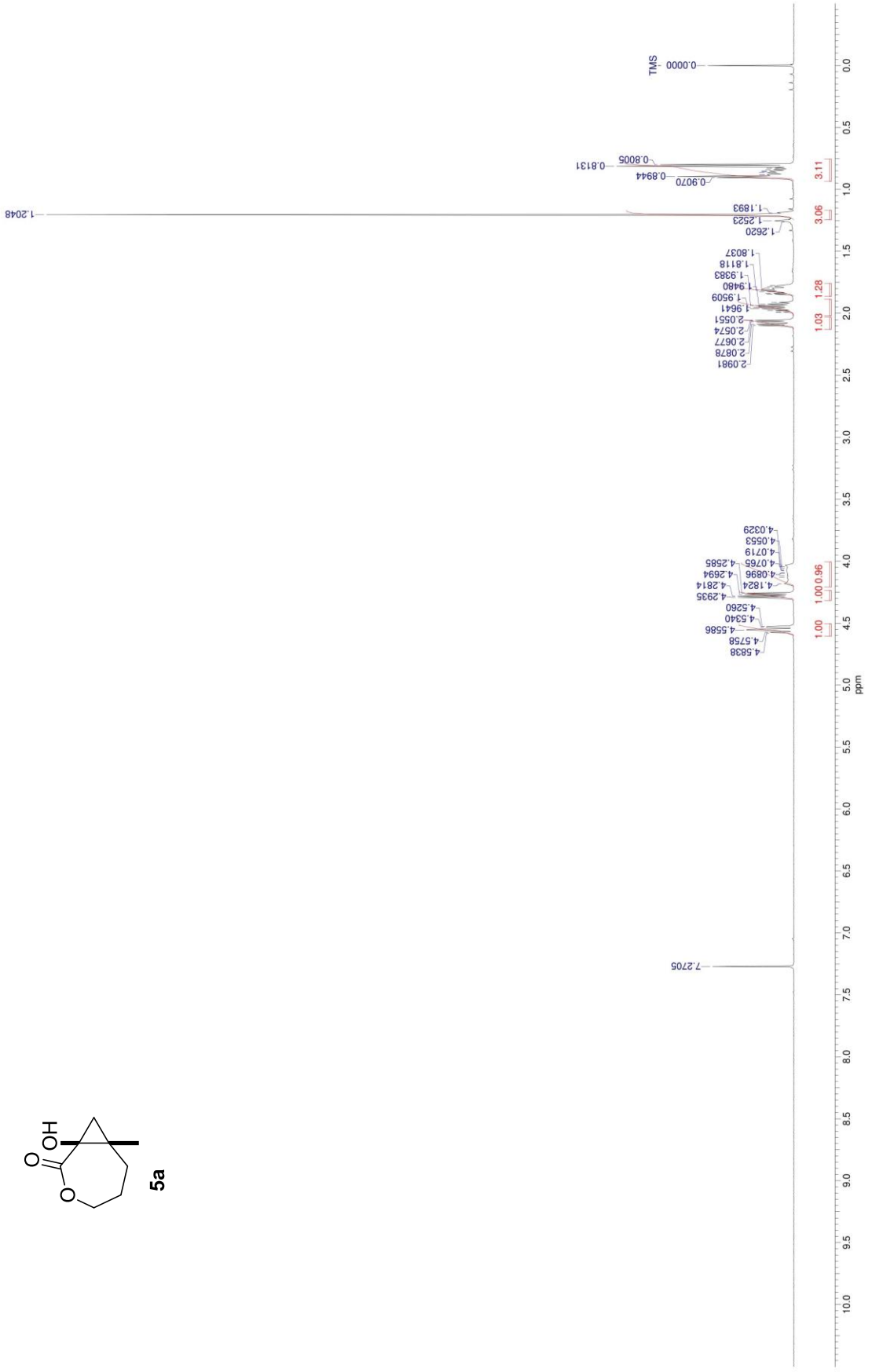
Compound **4a** (^{1}H NMR, $CDCl_3$)



Compound **4a** (^{13}C NMR, $CDCl_3$)

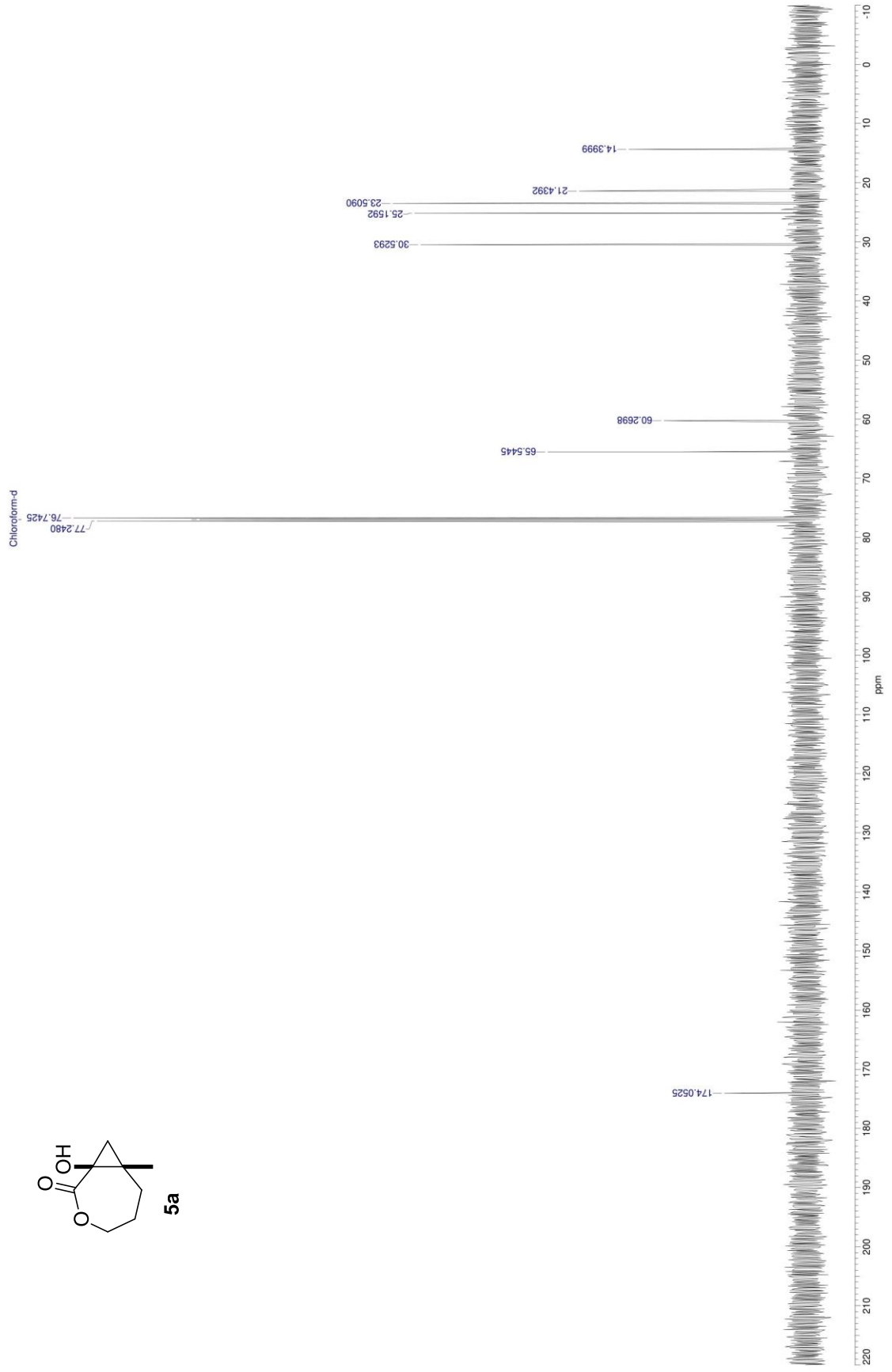


Compound **5a** (^{1}H NMR, $CDCl_3$)



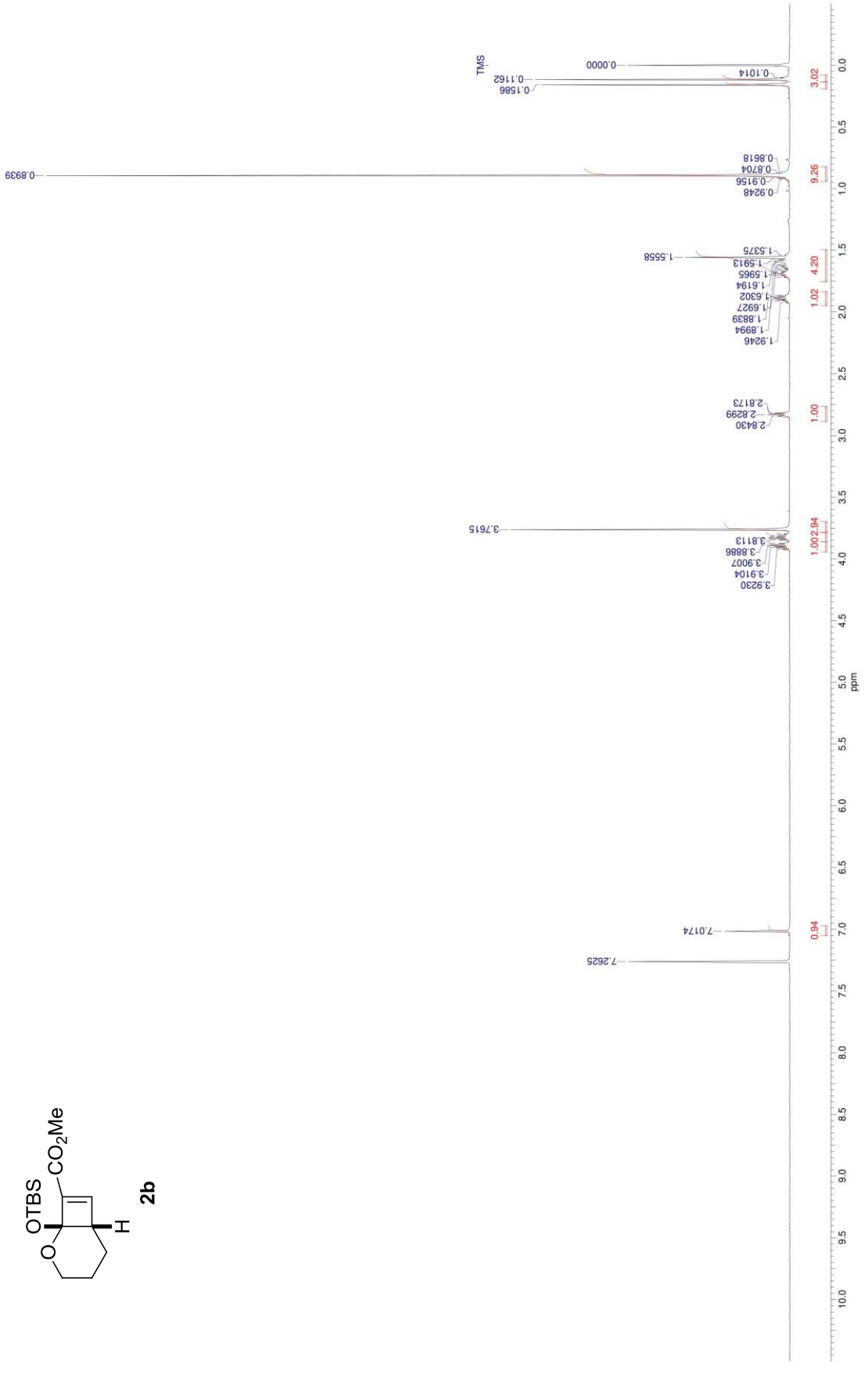
5a

Compound **5a** (^{13}C NMR, $CDCl_3$)

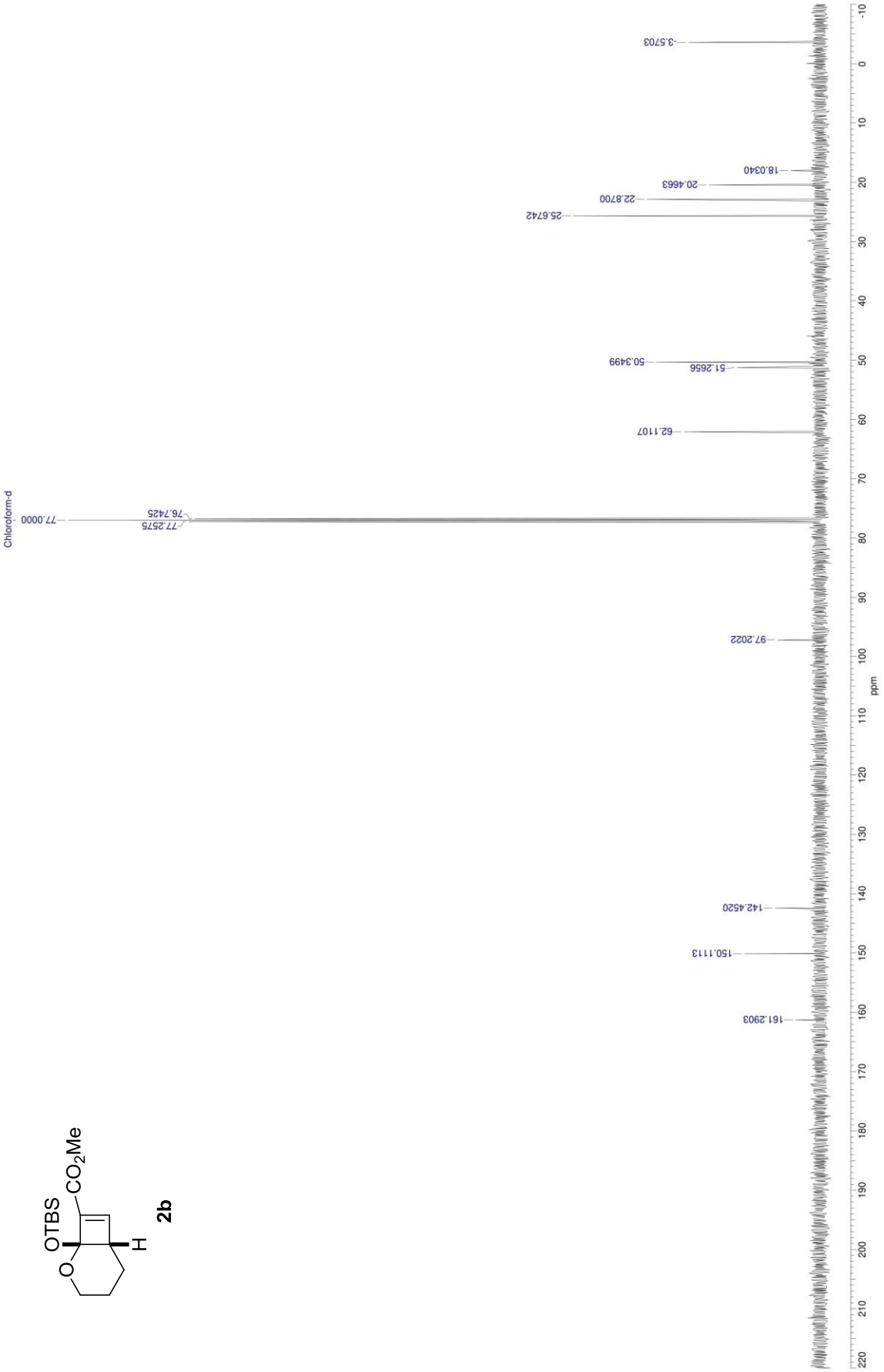


5a

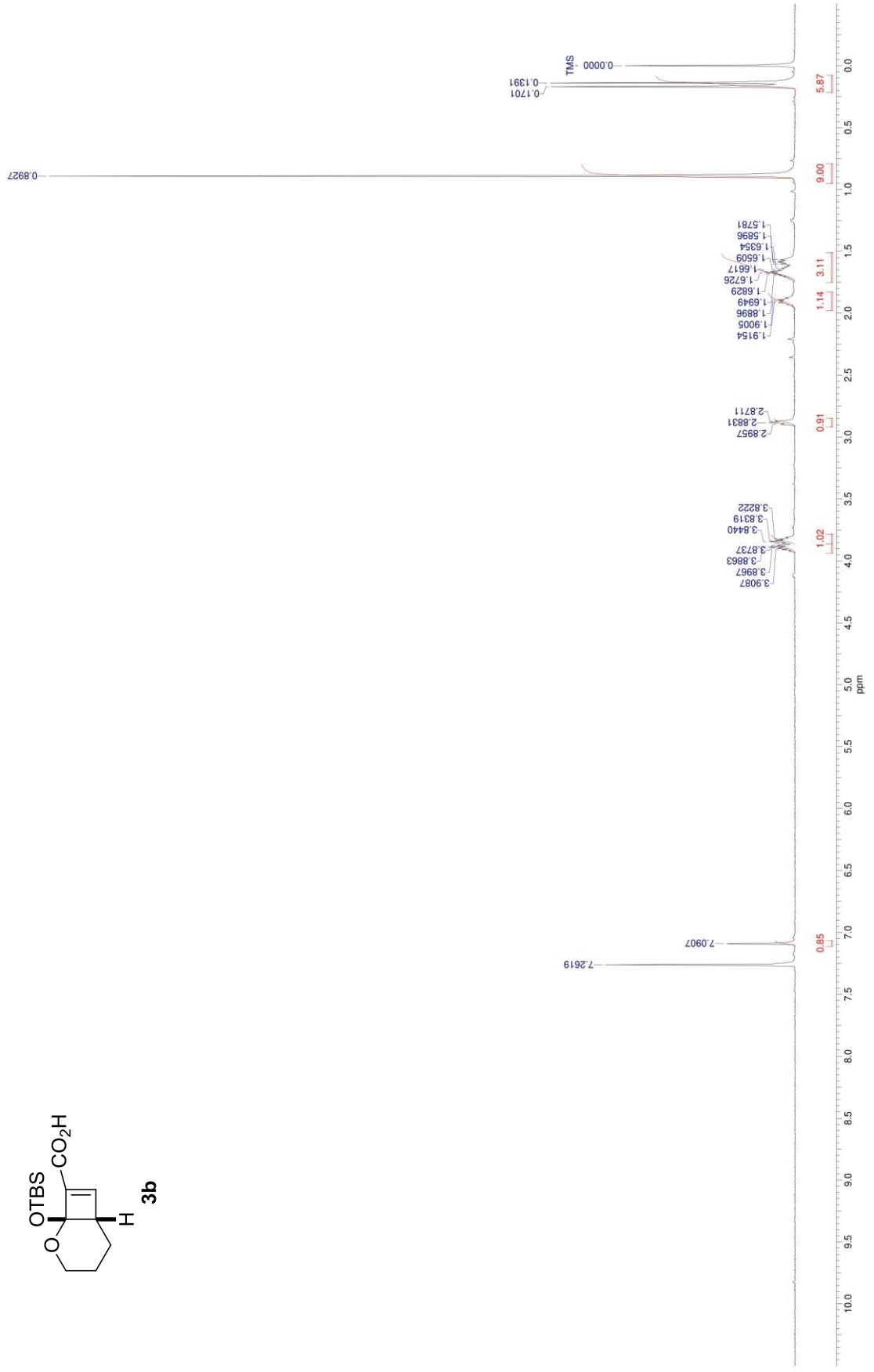
Compound **2b** (^{1}H NMR, $CDCl_3$)



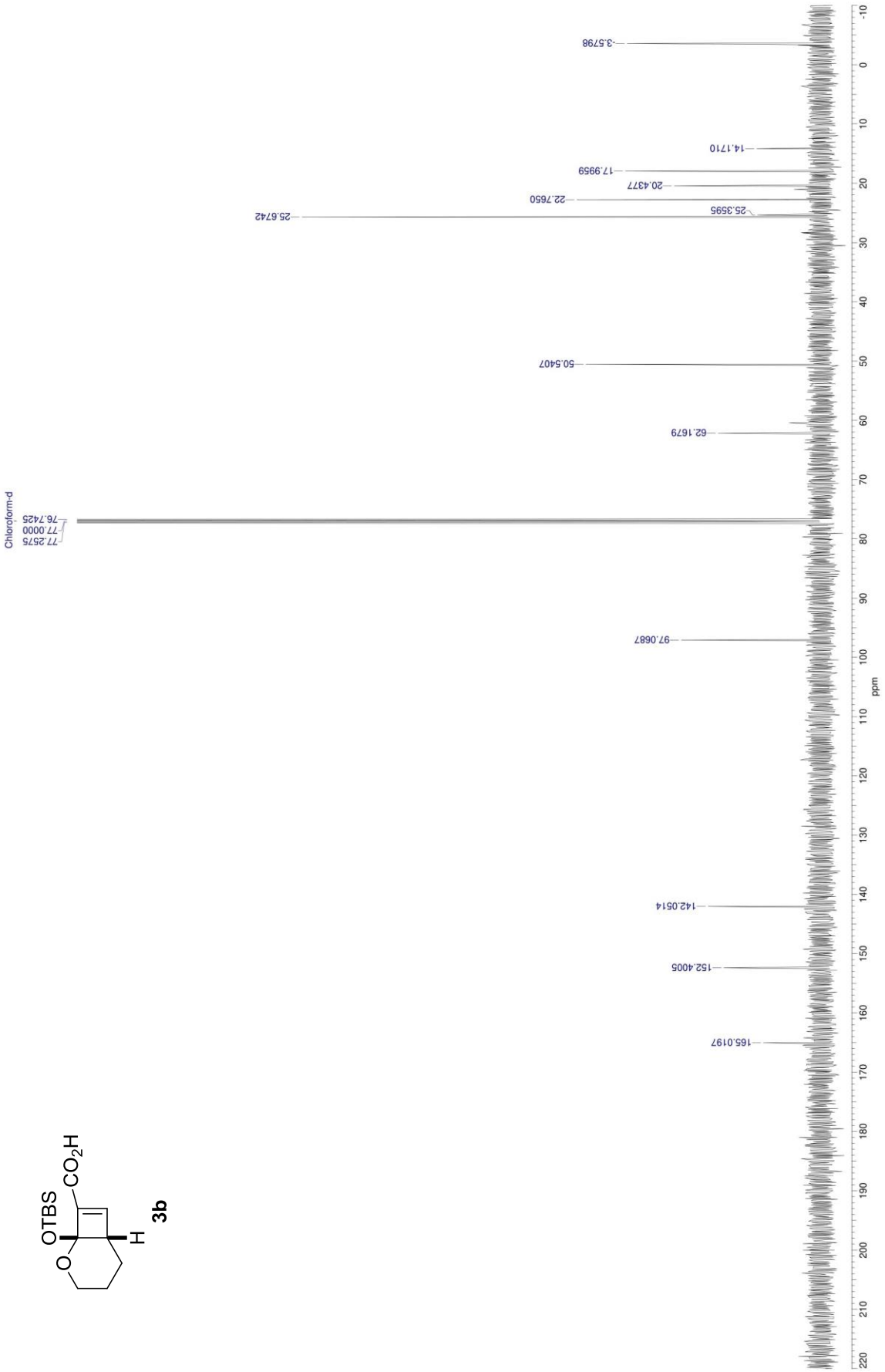
Compound **2b** (^{13}C NMR, $CDCl_3$)



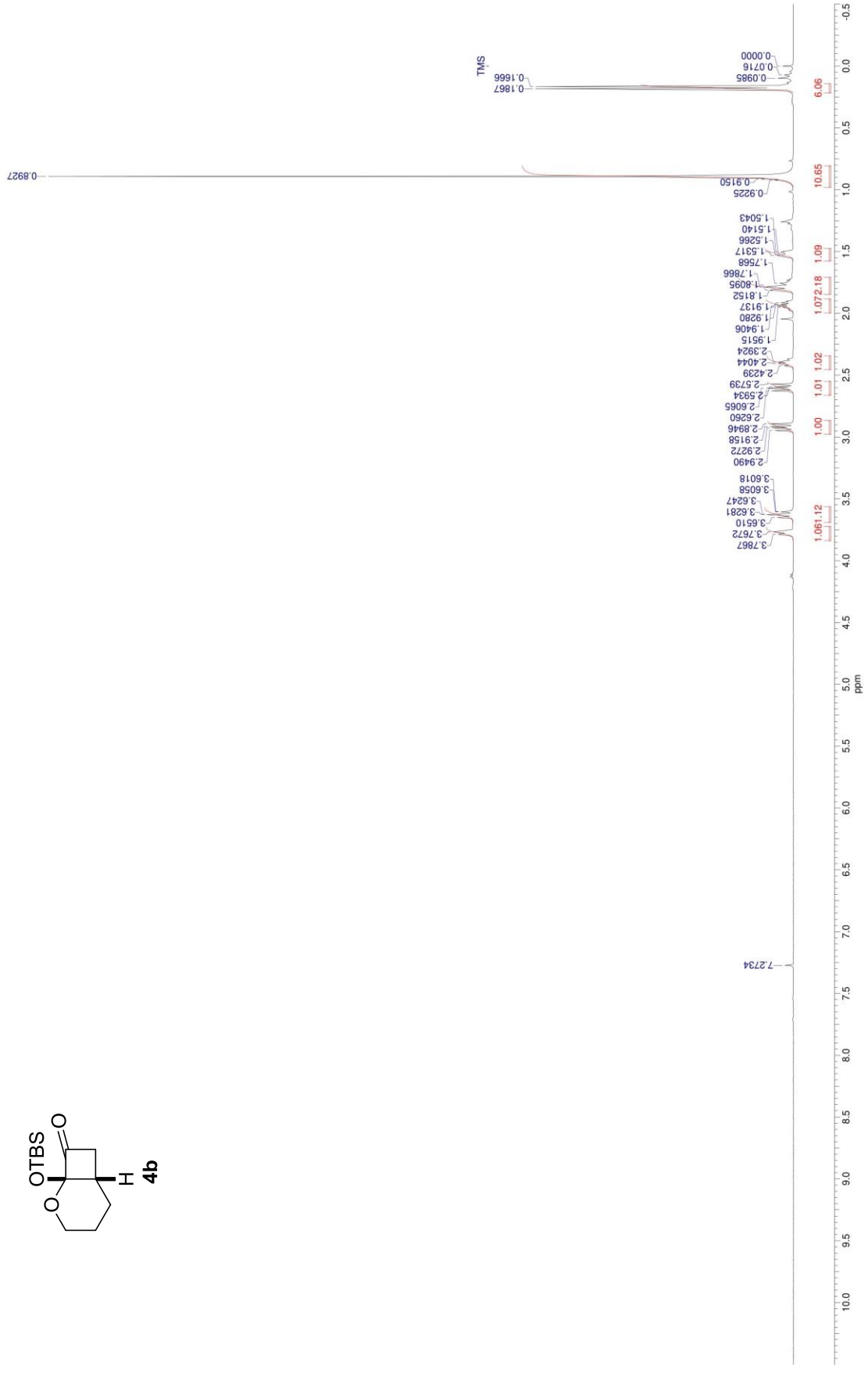
Compound **3b** (^{1}H NMR, $CDCl_3$)



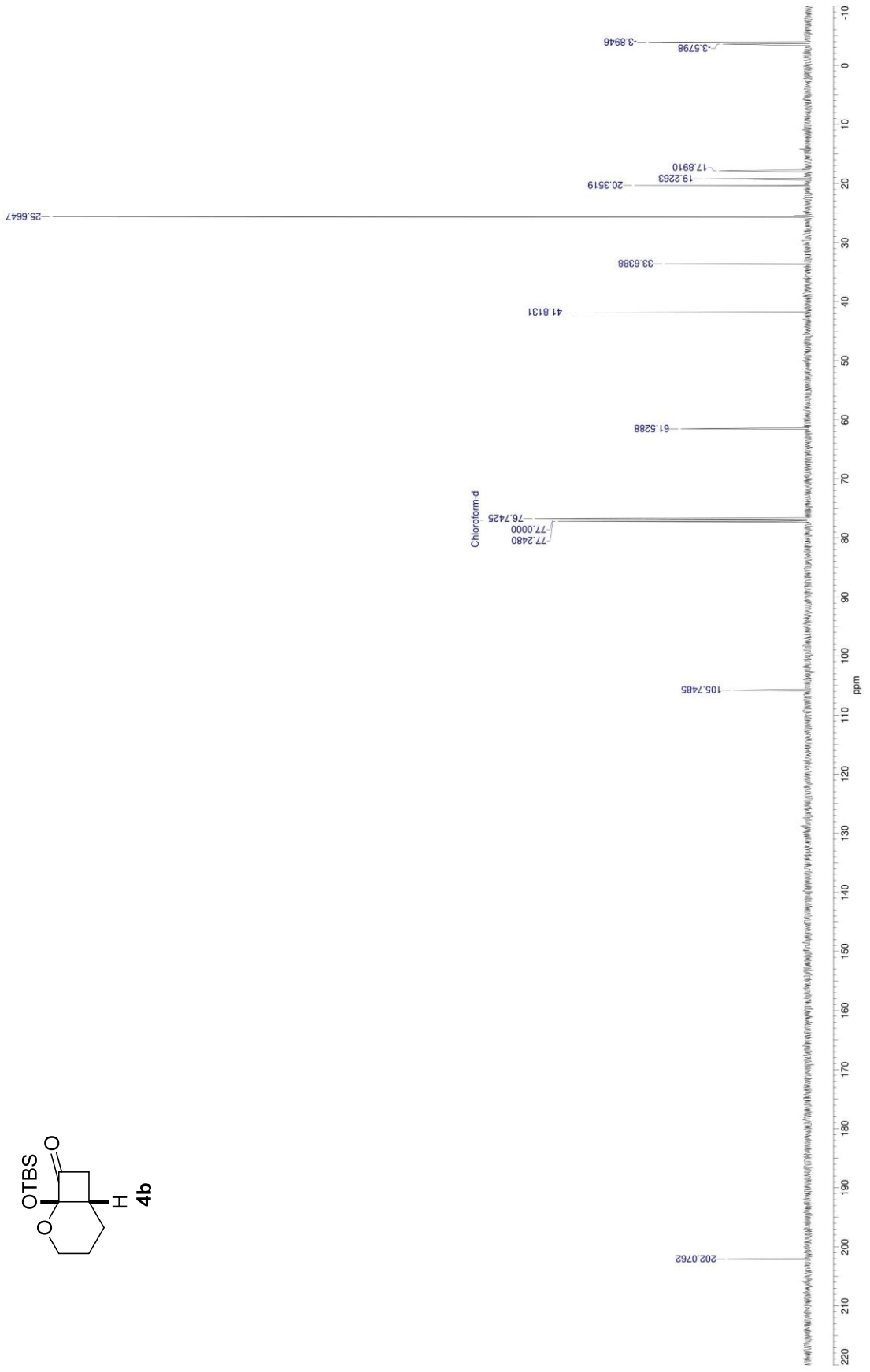
Compound **3b** (^{13}C NMR, $CDCl_3$)



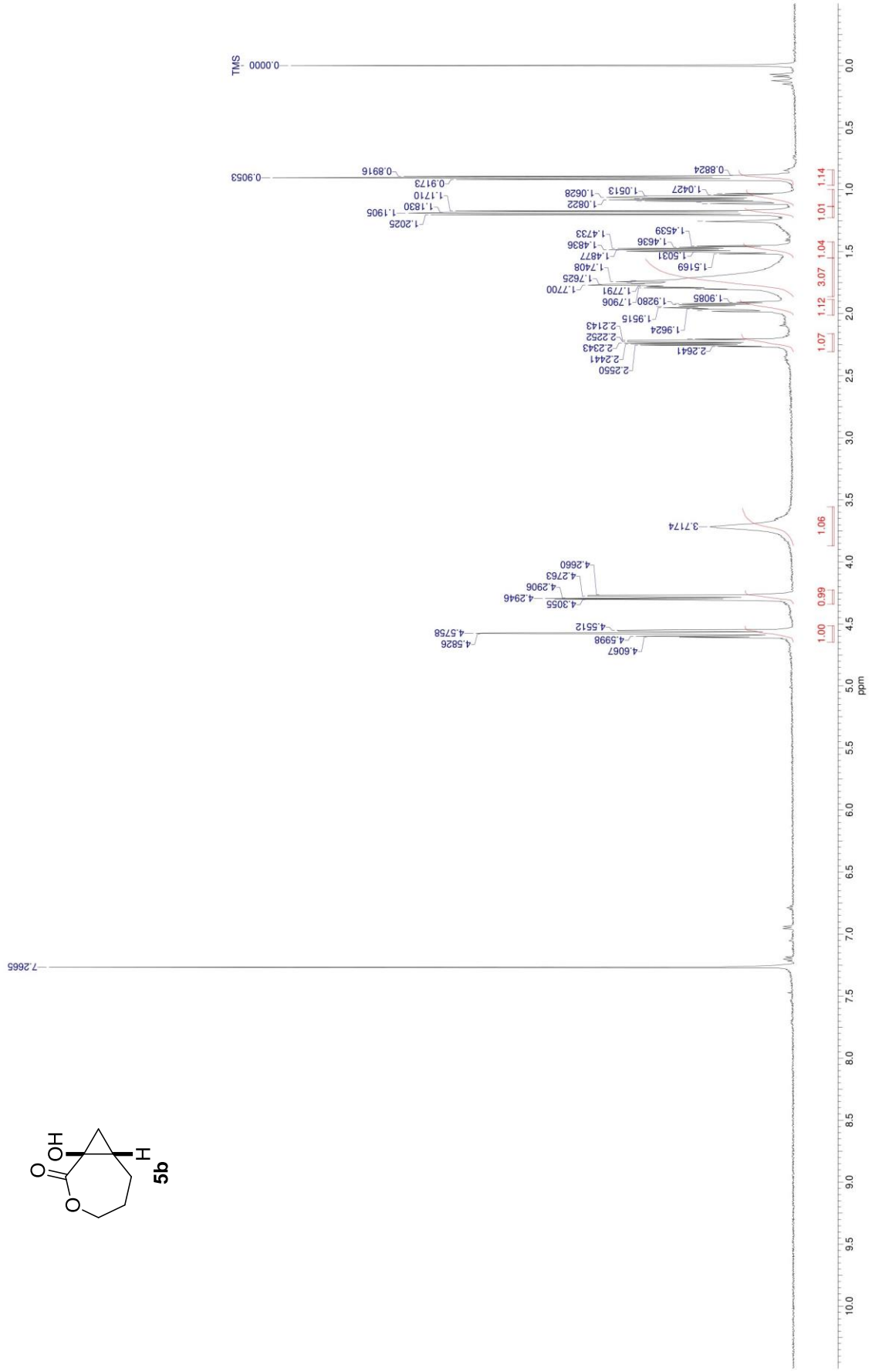
Compound **4b** (^{1}H NMR, $CDCl_3$)



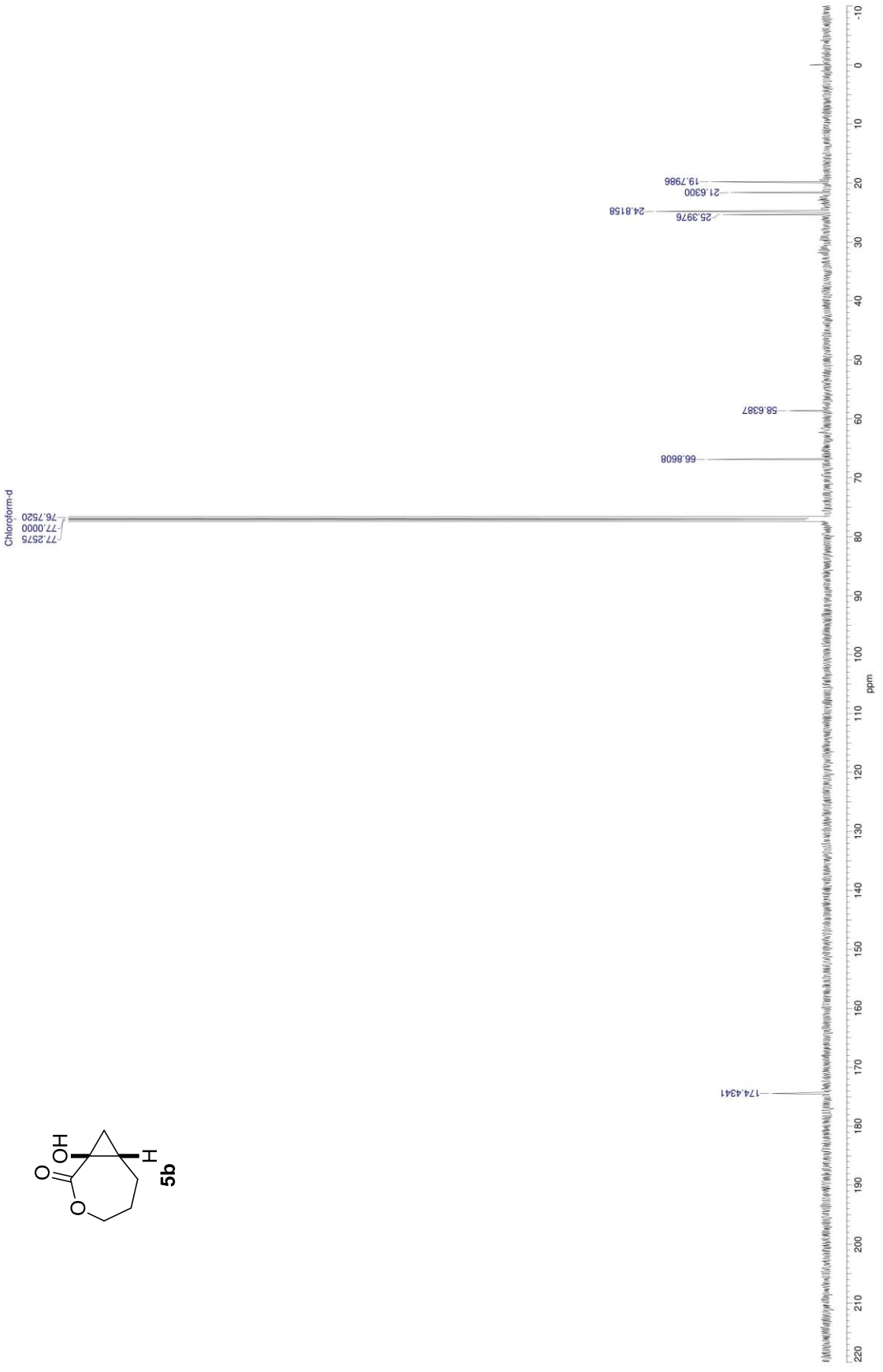
Compound **4b** (^{13}C NMR, $CDCl_3$)



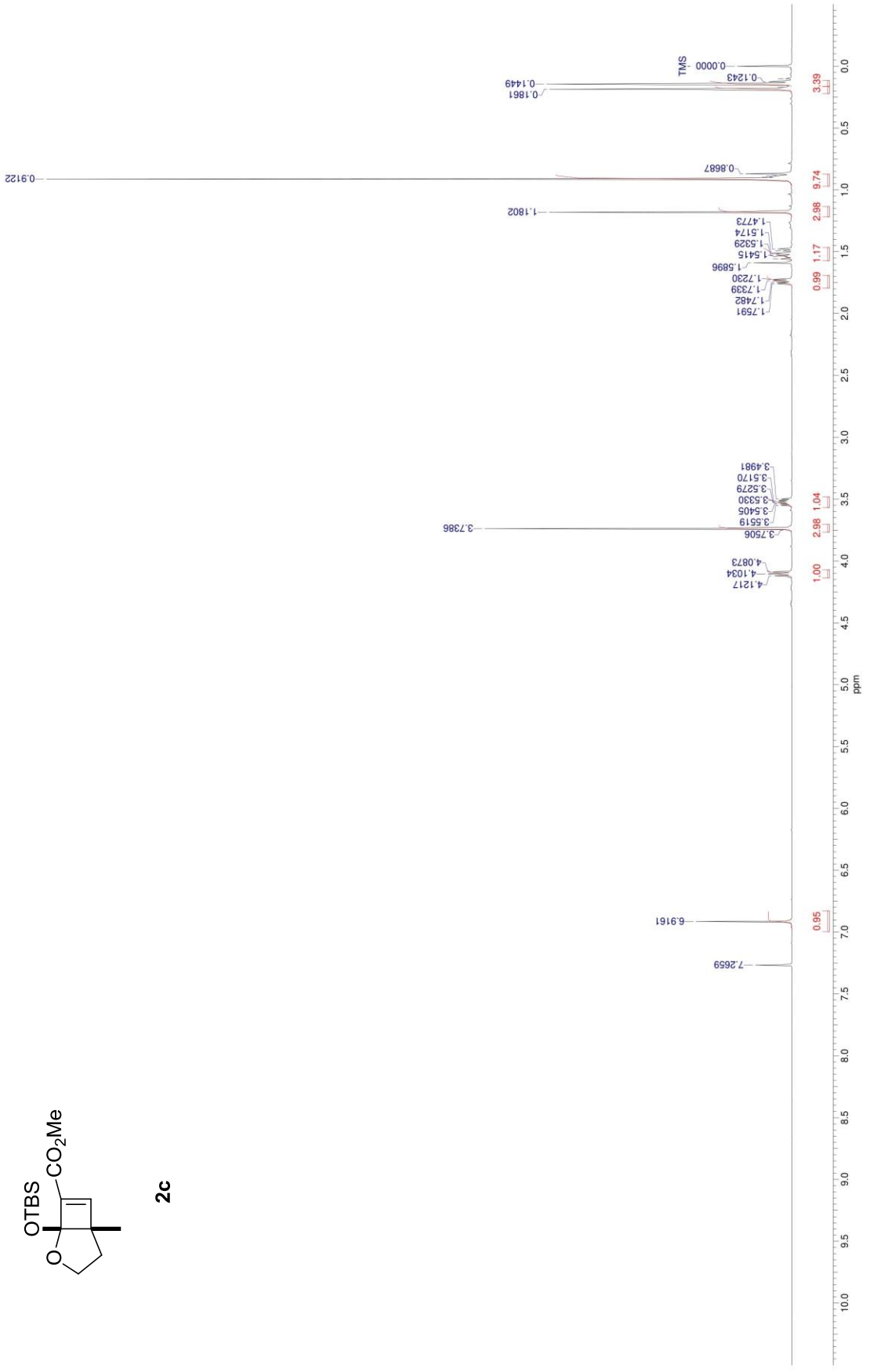
Compound **5b** (^{1}H NMR, $CDCl_3$)



Compound **5b** (^{13}C NMR, $CDCl_3$)

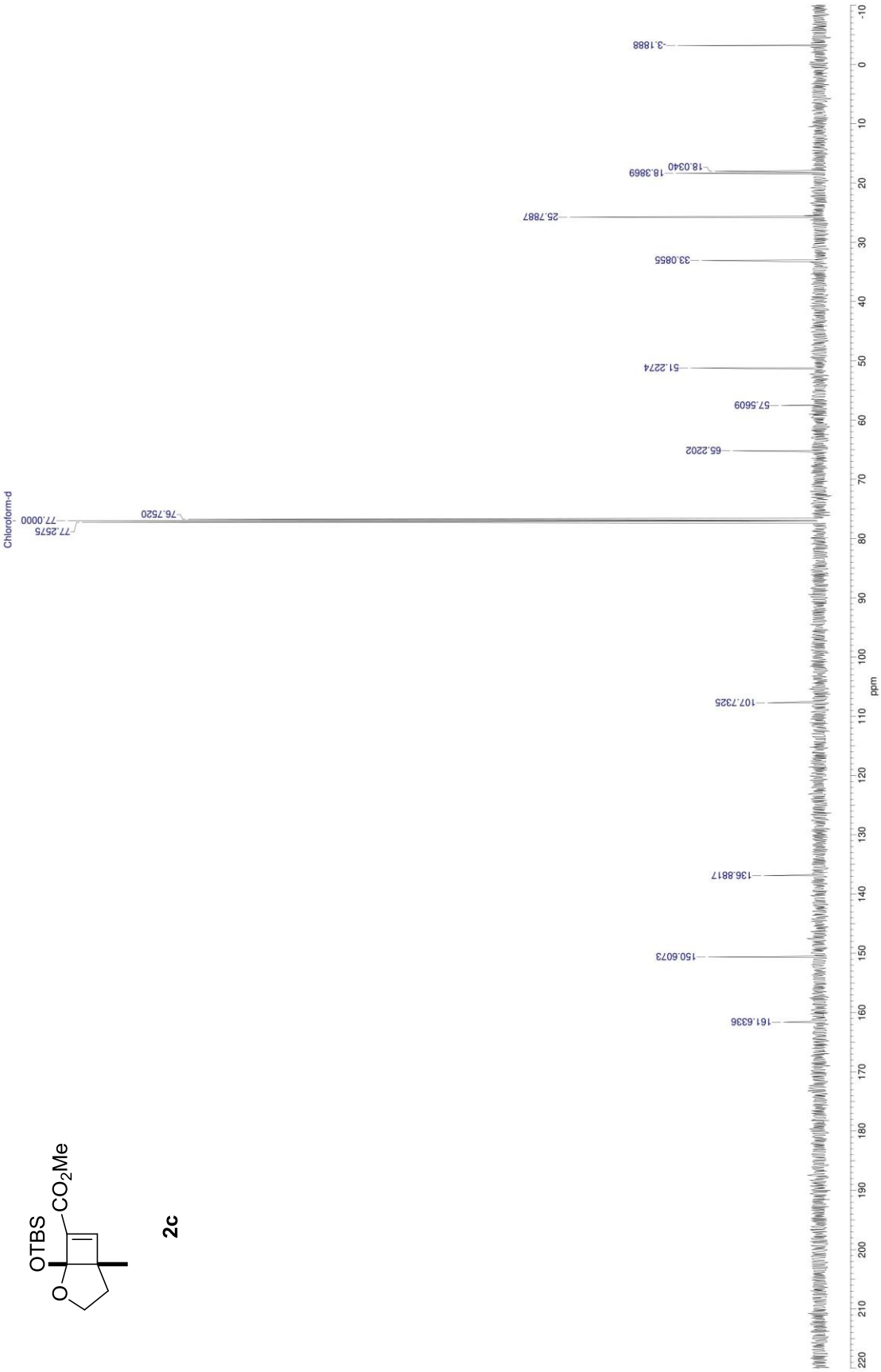


Compound **2c** (^{1}H NMR, $CDCl_3$)



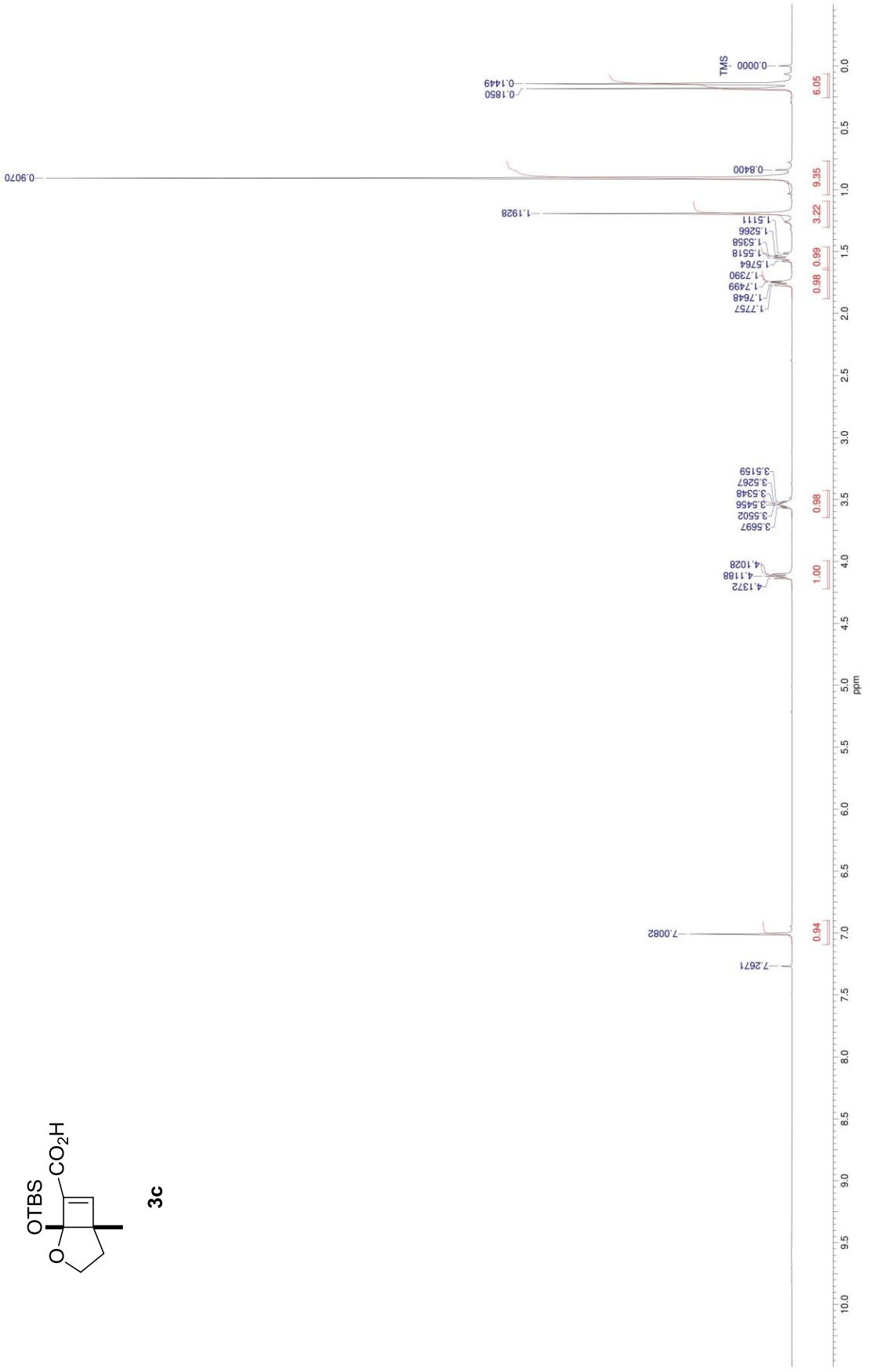
2c

Compound **2c** (^{13}C NMR, $CDCl_3$)



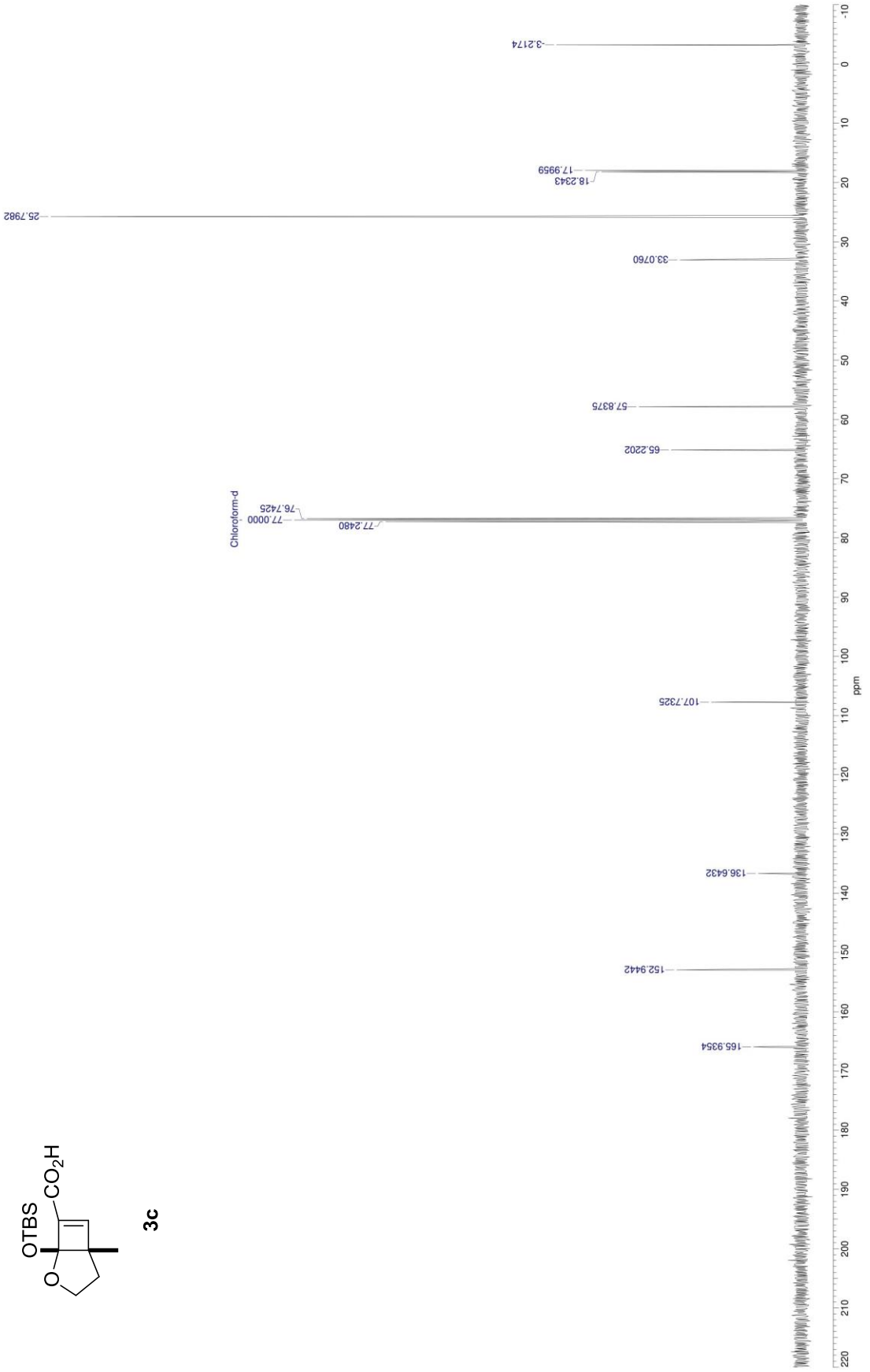
2c

Compound **3c** (^{1}H NMR, $CDCl_3$)



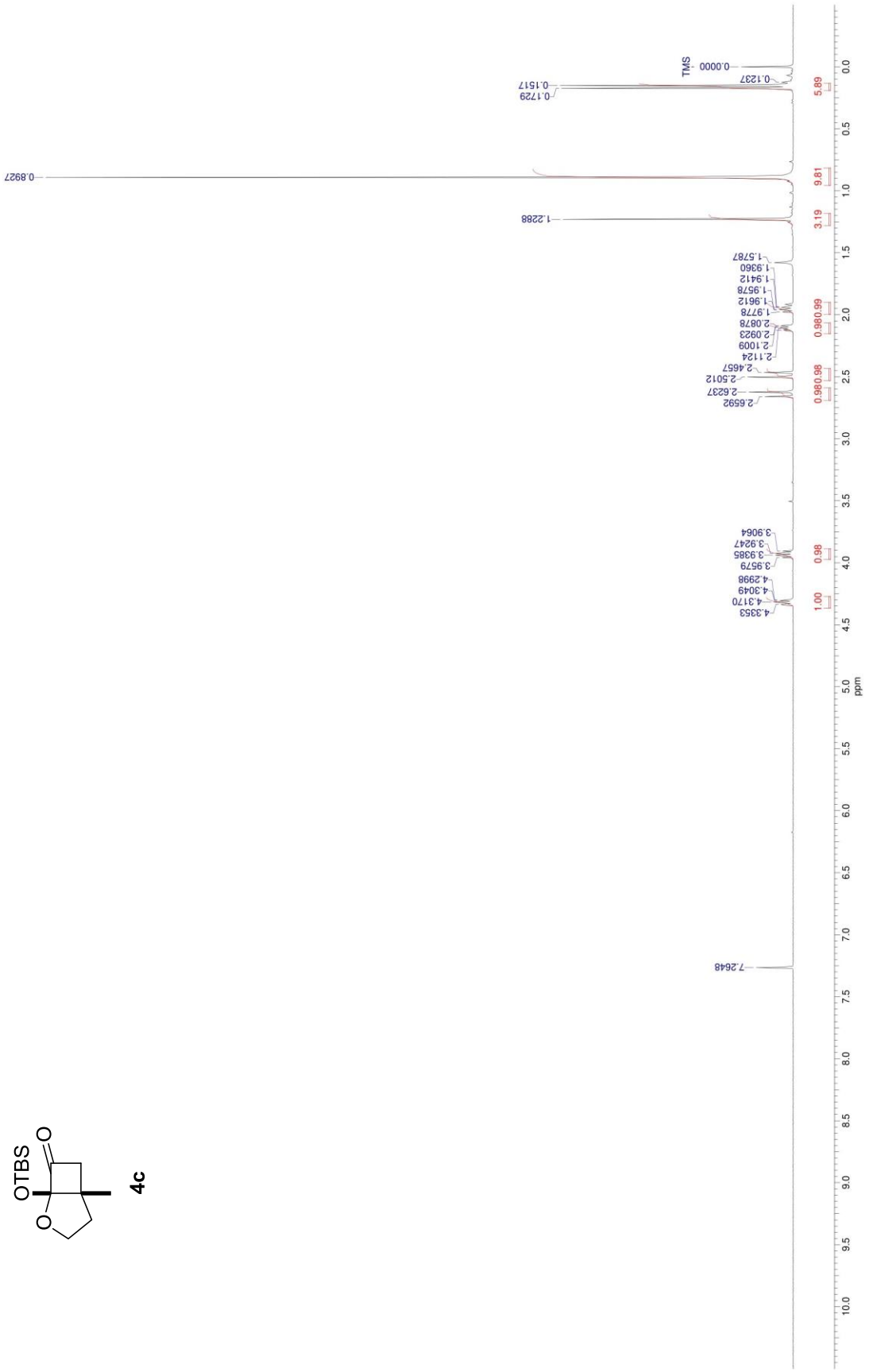
3c

Compound **3c** (^{13}C NMR, $CDCl_3$)



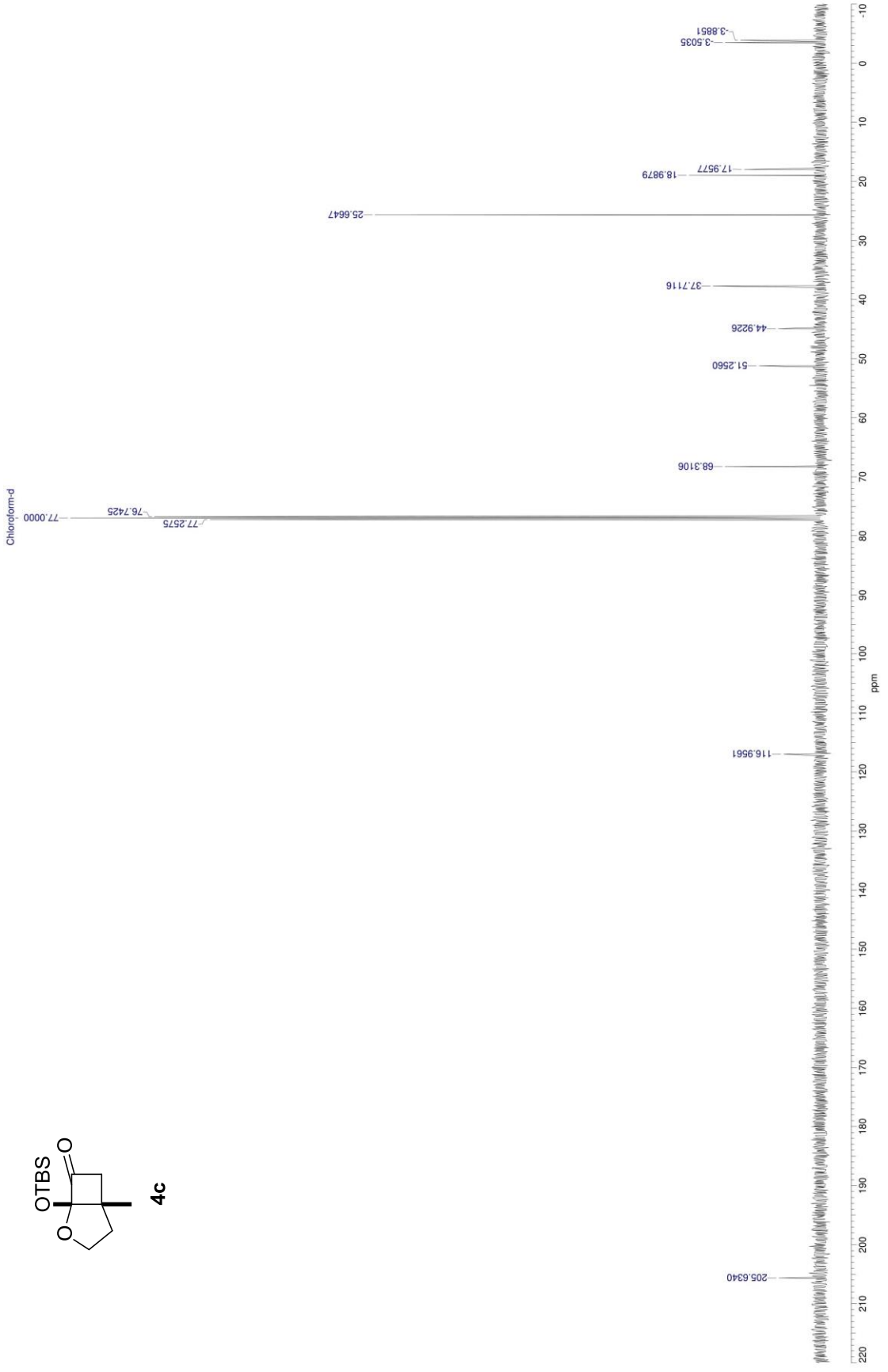
3c

Compound **4c** (^{1}H NMR, $CDCl_3$)

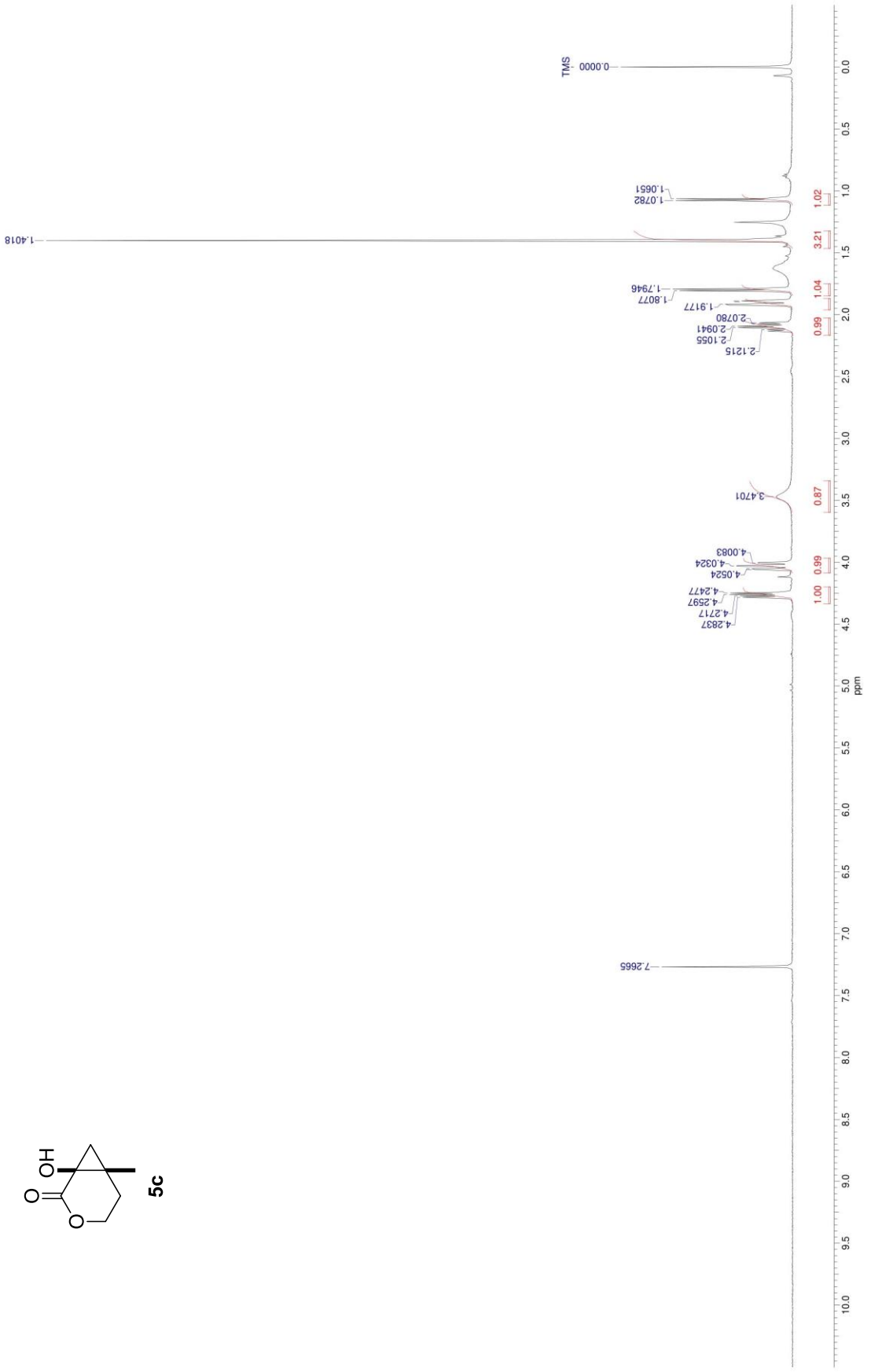


4c

Compound **4c** (^{13}C NMR, $CDCl_3$)

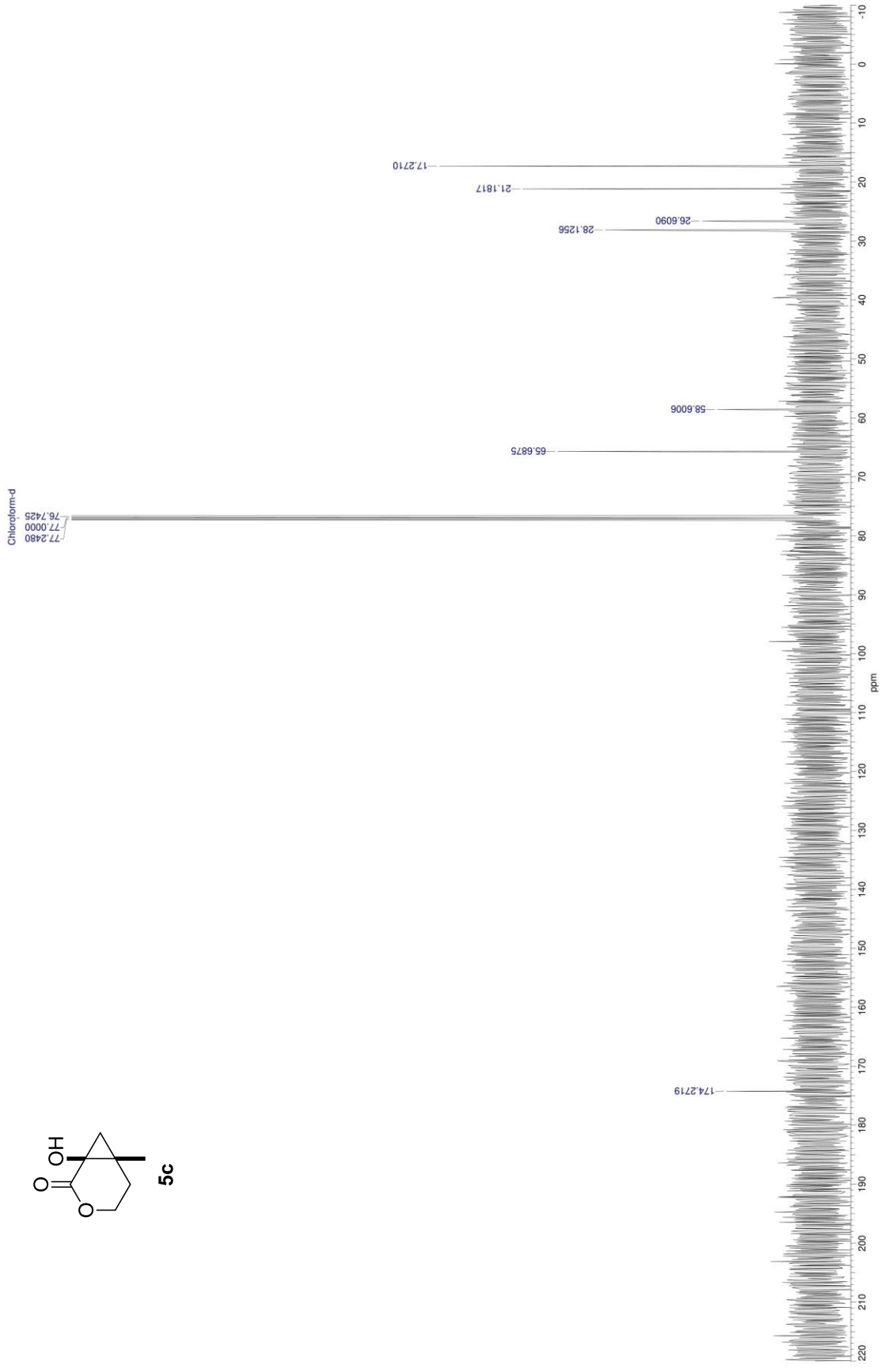


Compound **5c** (^{1}H NMR, $CDCl_3$)



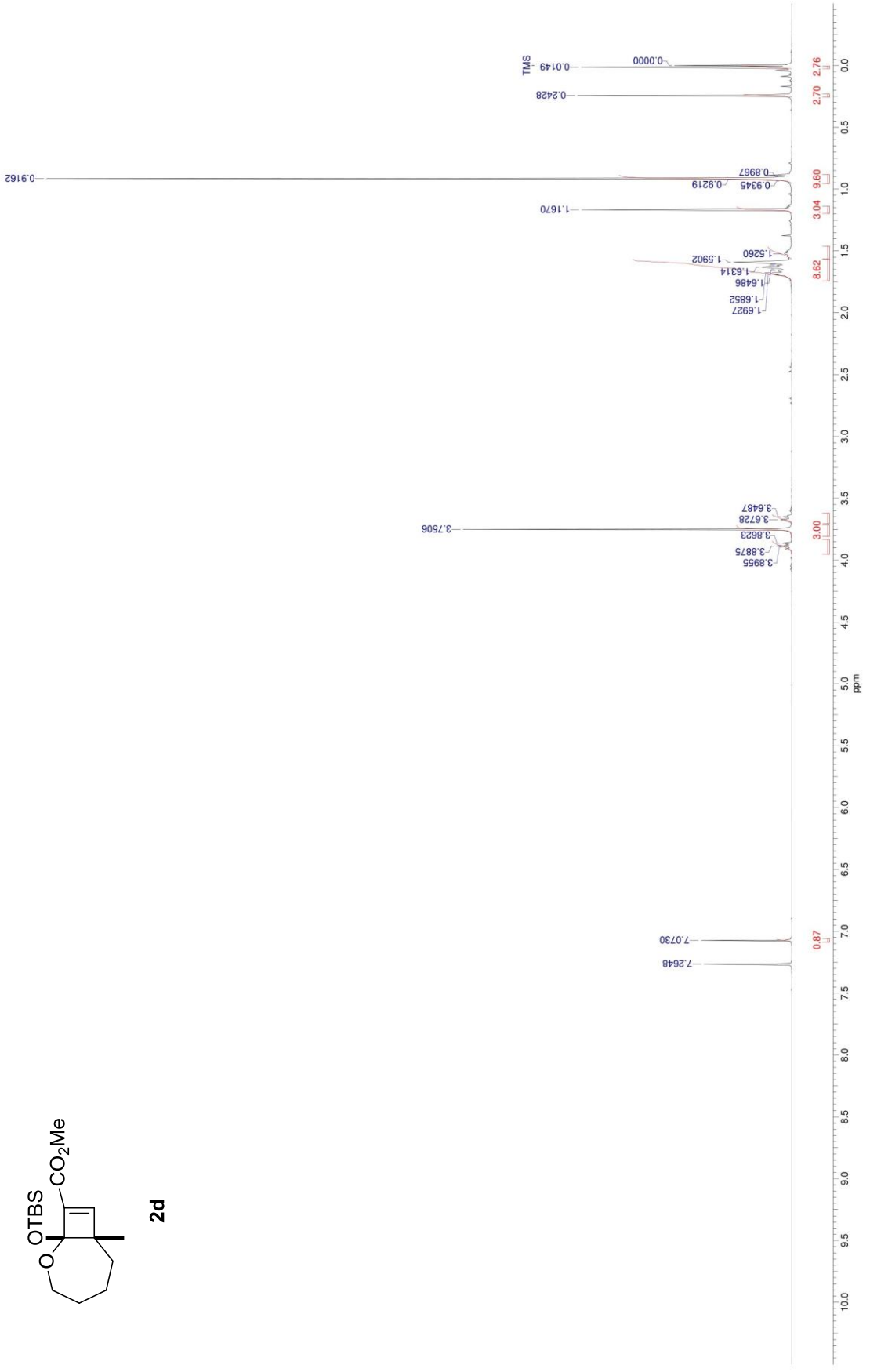
5c

Compound **5c** (^{13}C NMR, $CDCl_3$)



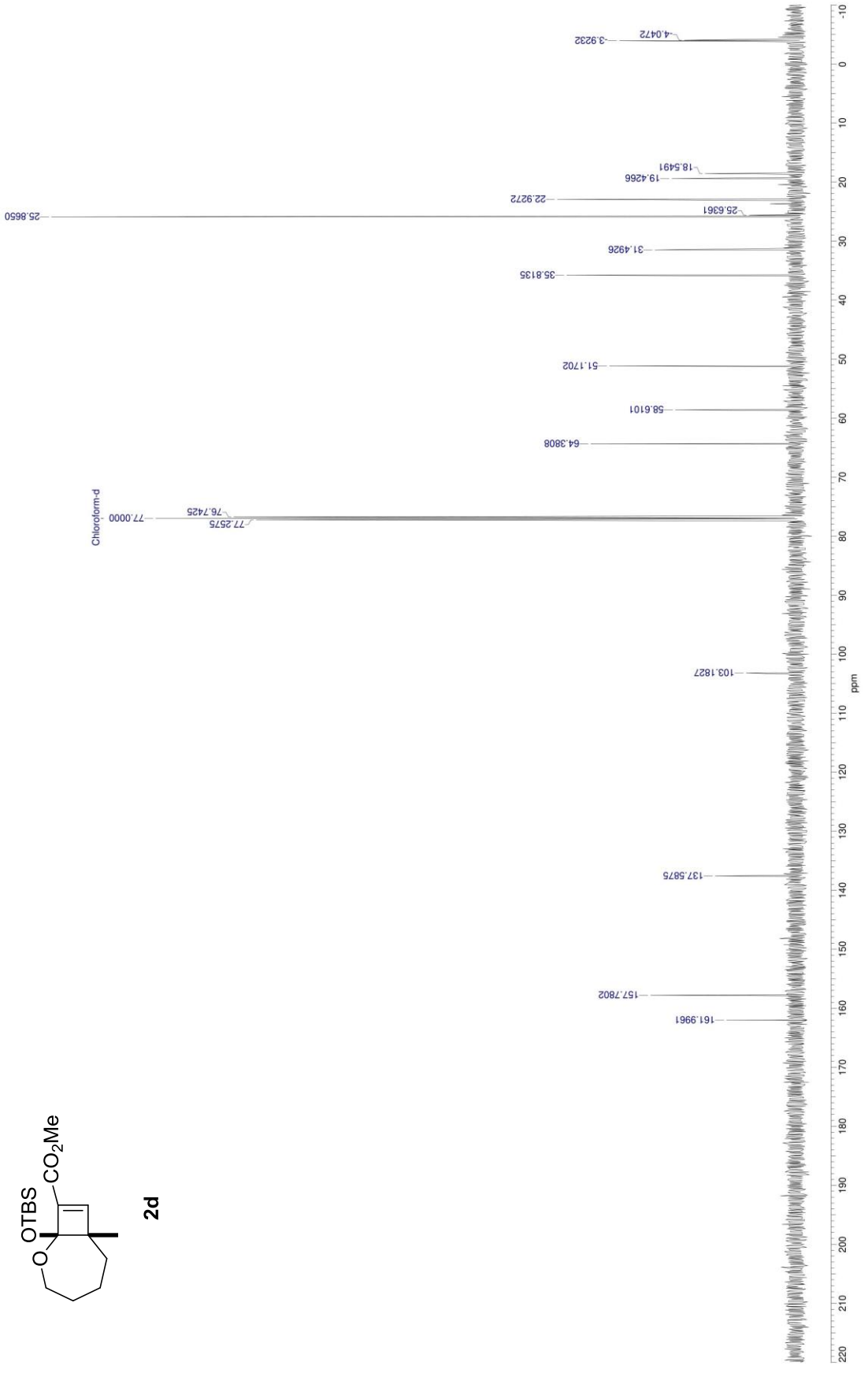
5c

Compound **2d** (^{1}H NMR, $CDCl_3$)

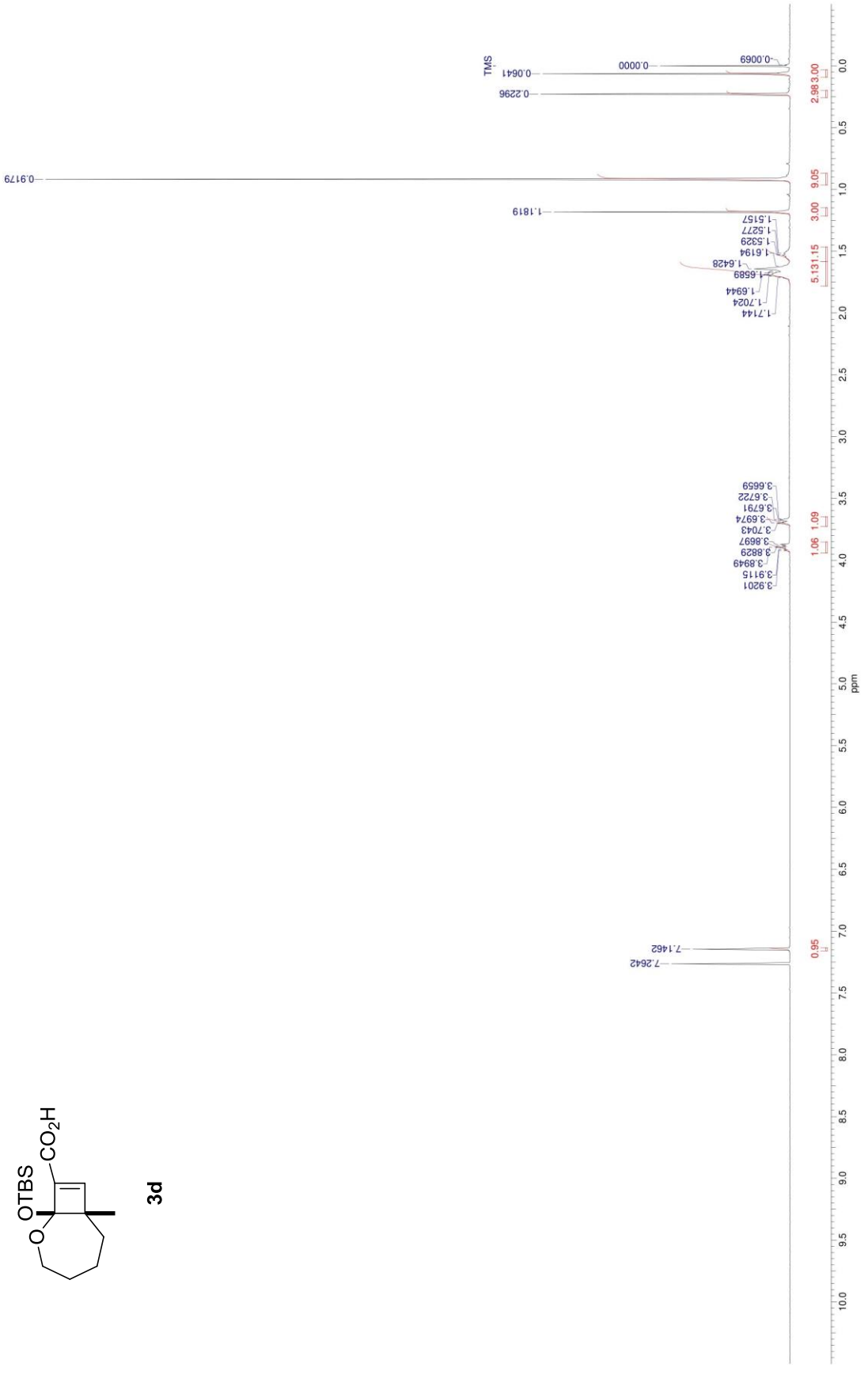


2d

Compound **2d** (^{13}C NMR, $CDCl_3$)

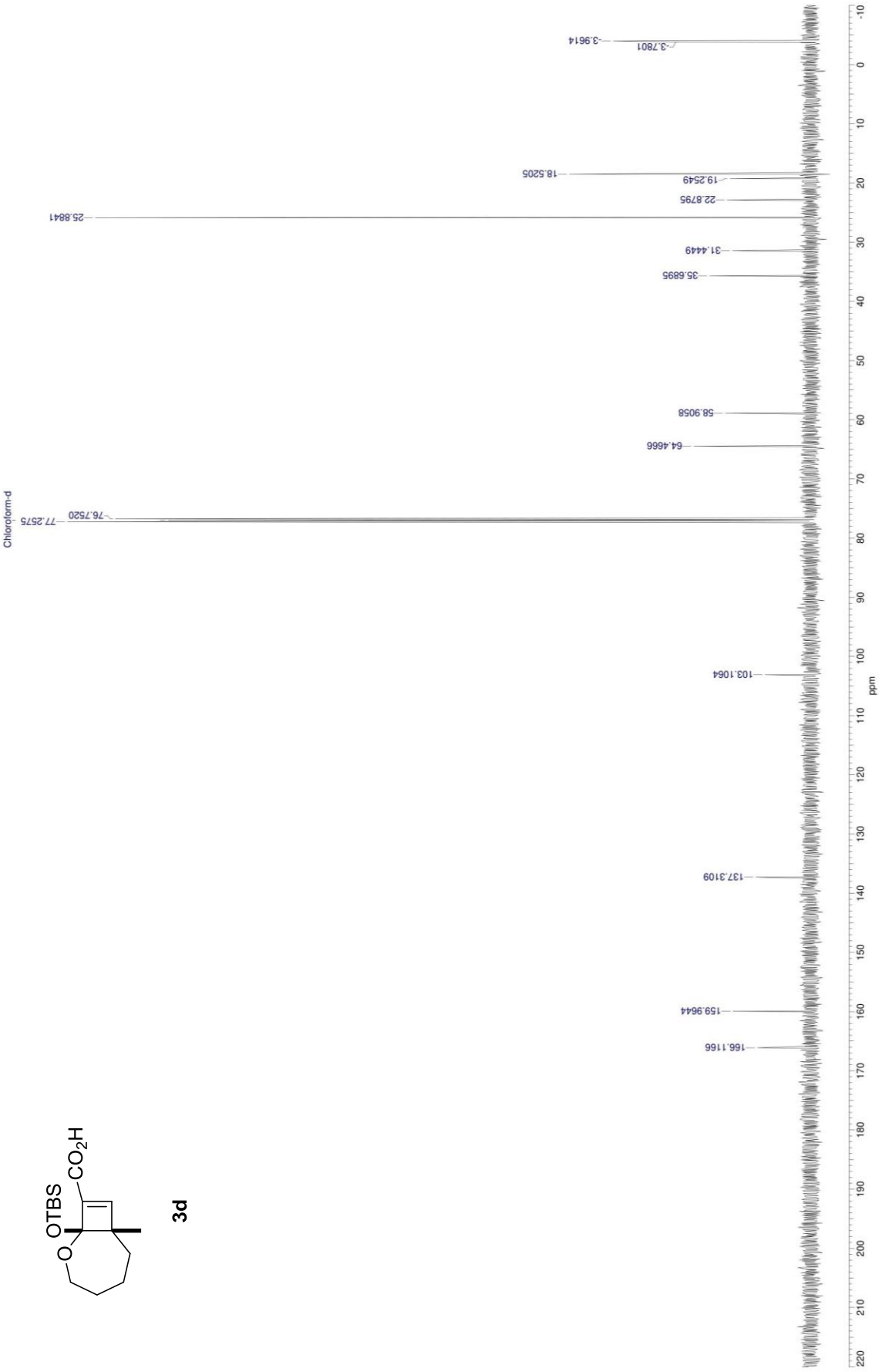


Compound **3d** (^{1}H NMR, $CDCl_3$)



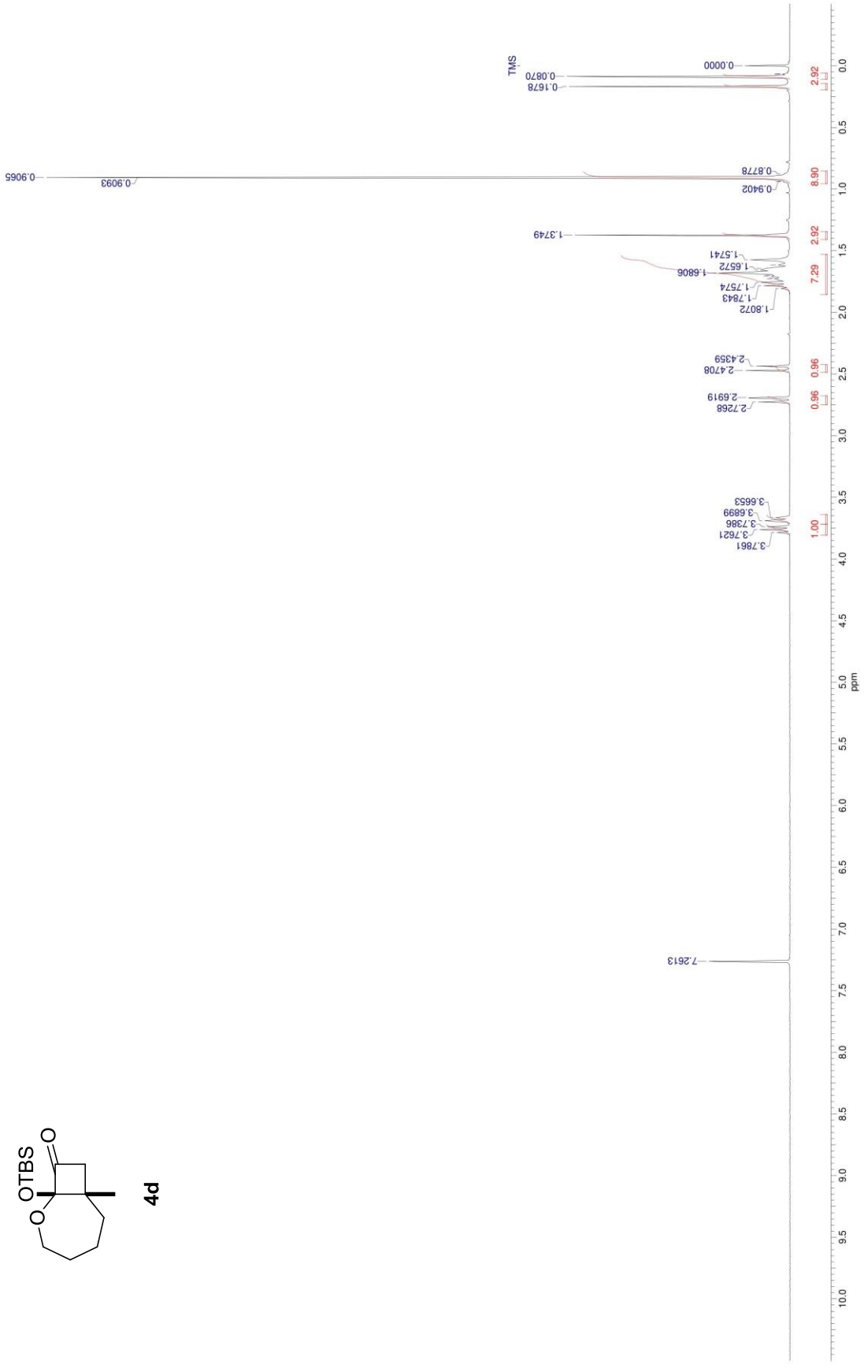
3d

Compound **3d** (^{13}C NMR, $CDCl_3$)



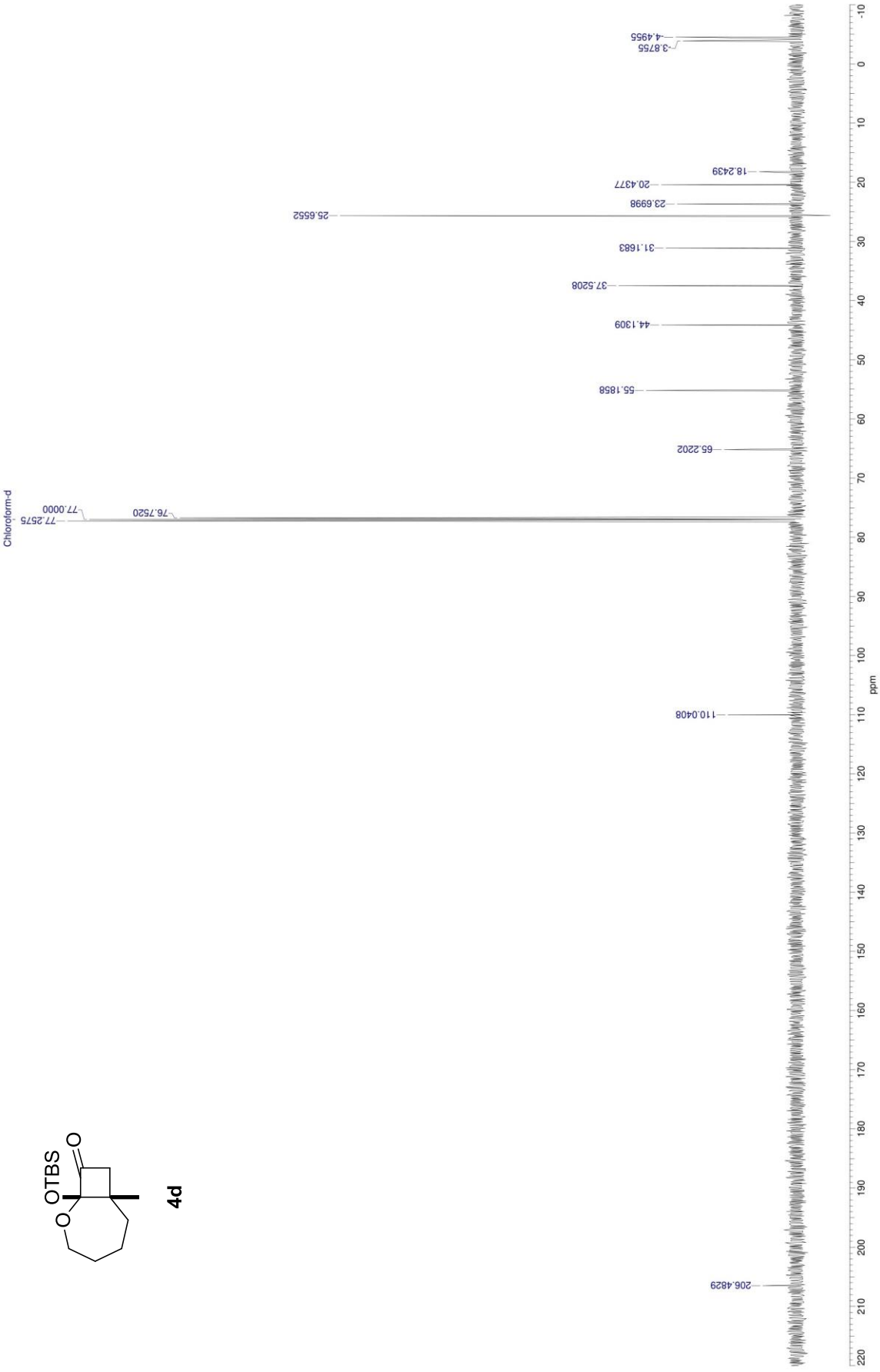
3d

Compound **4d** (^{1}H NMR, $CDCl_3$)

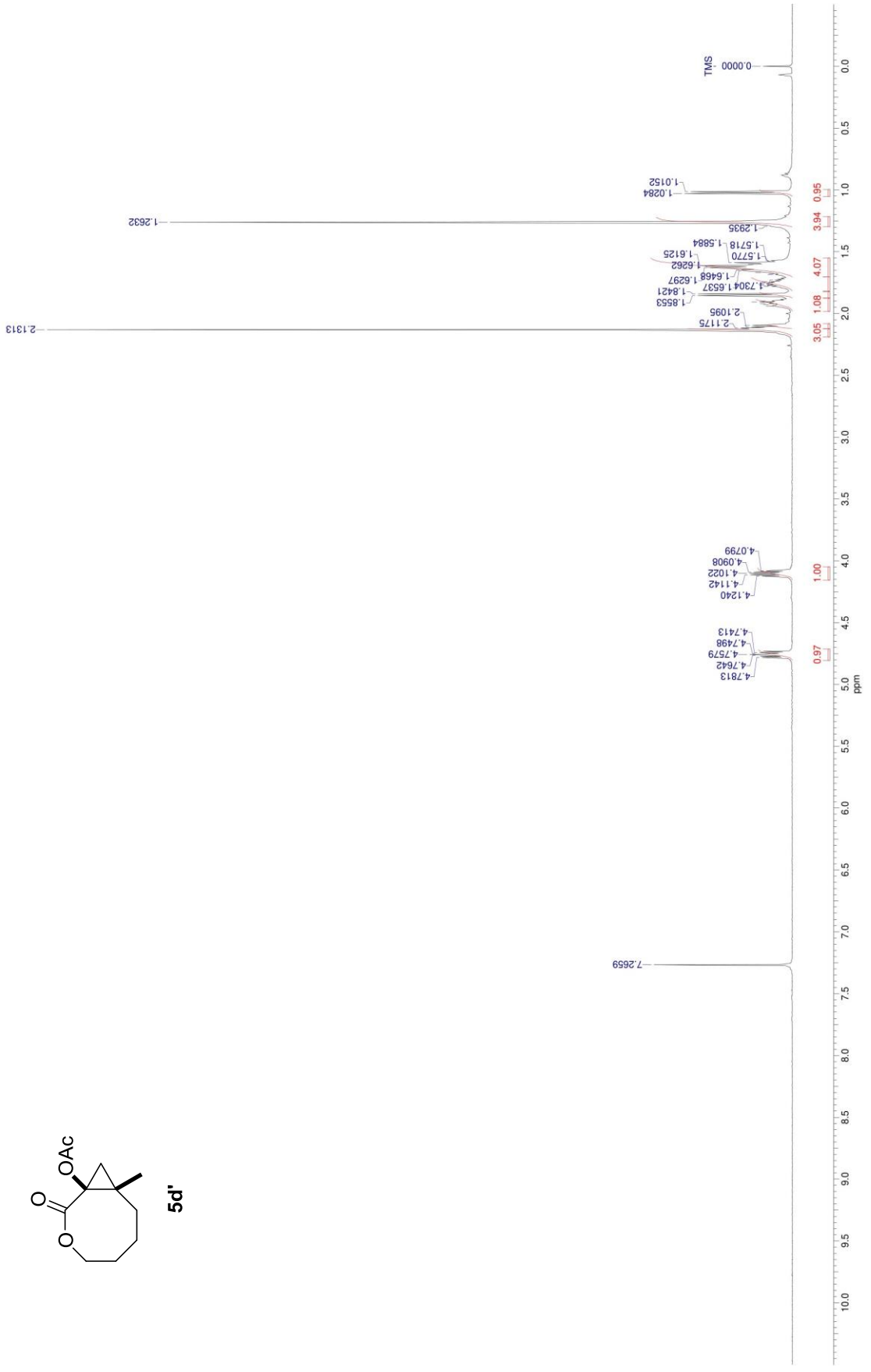


4d

Compound **4d** (^{13}C NMR, $CDCl_3$)

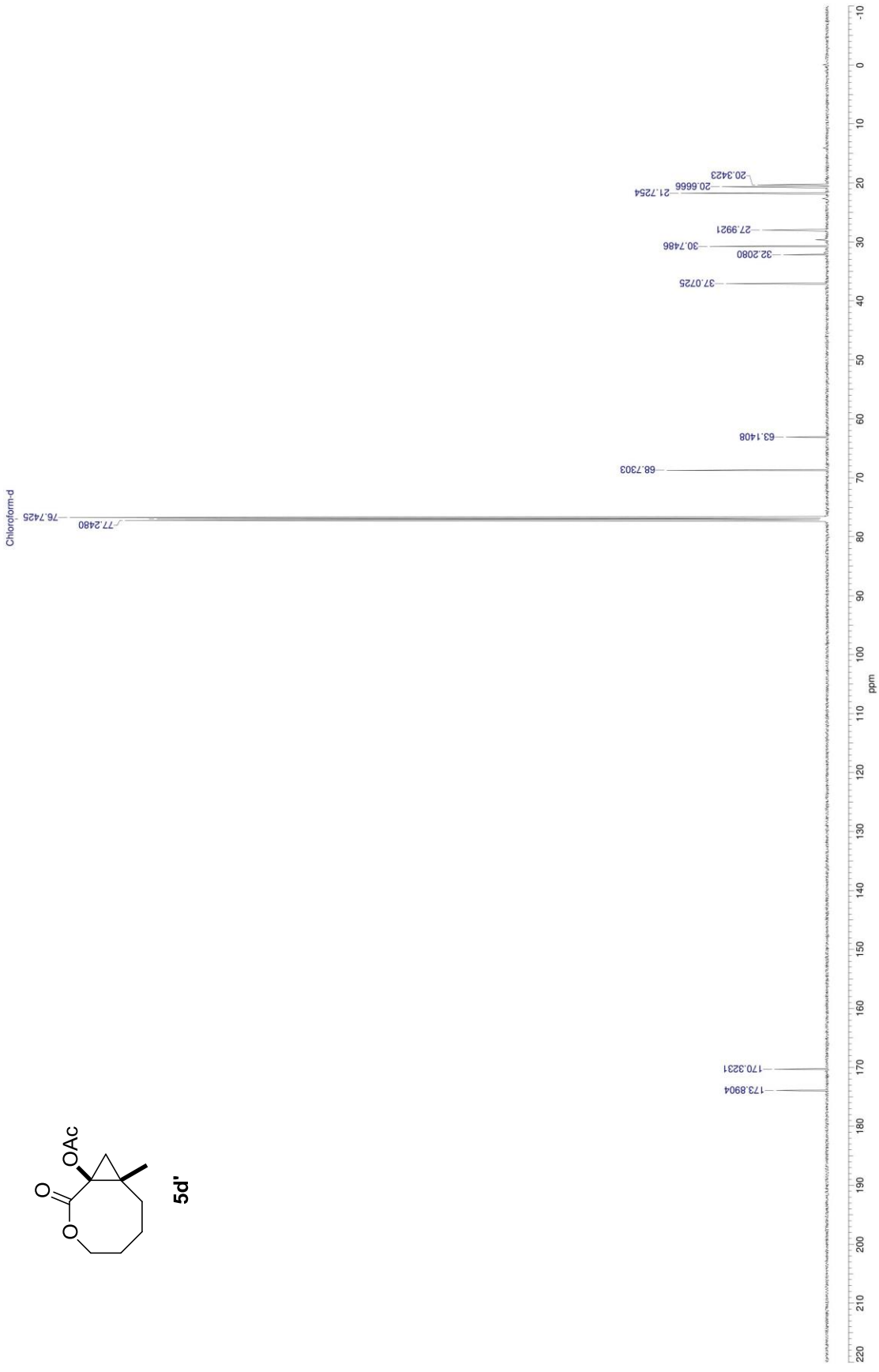


Compound **5d'** (^{1}H NMR, $CDCl_3$)



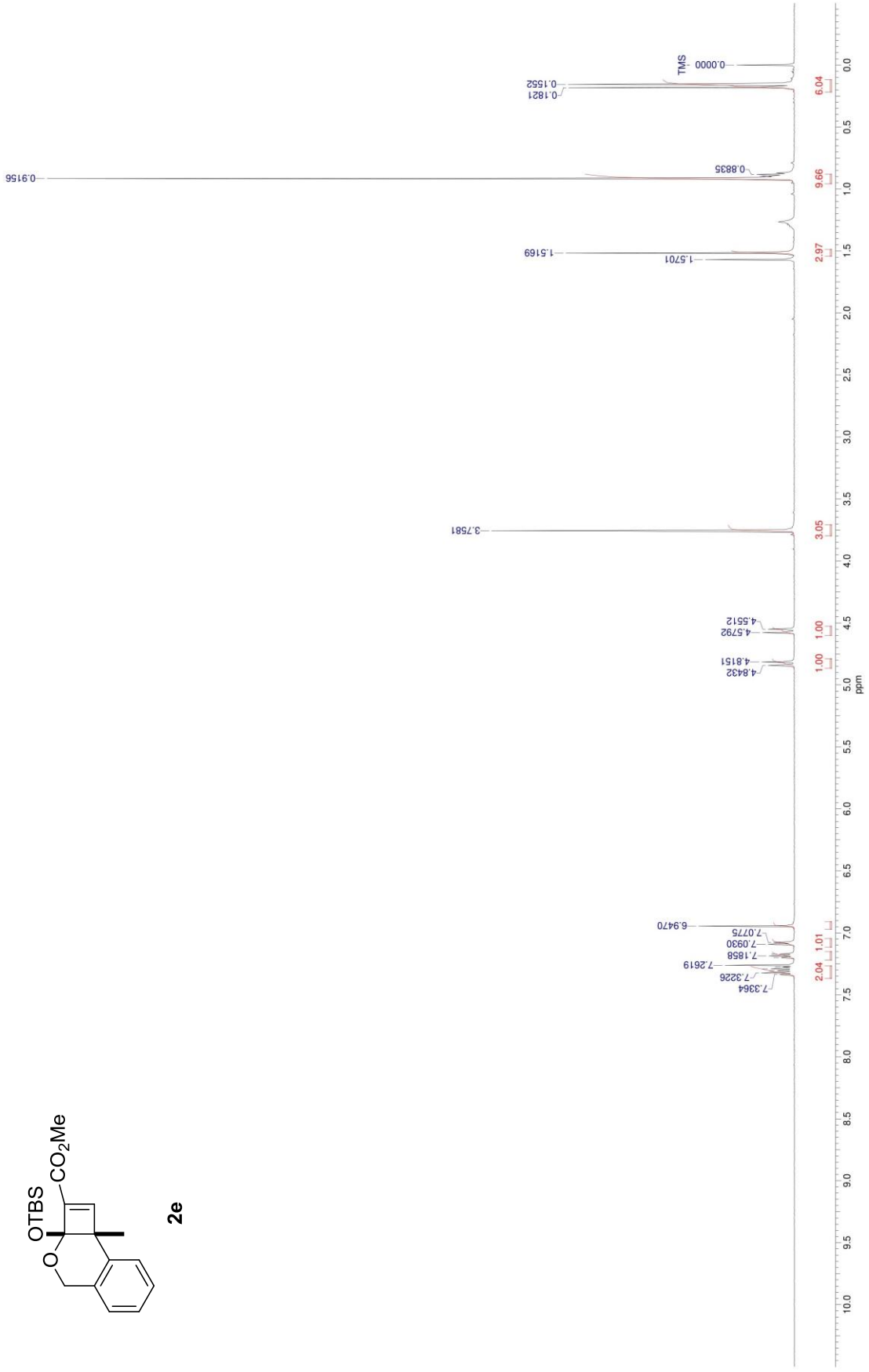
5d'

Compound **5d'** (^{13}C NMR, $CDCl_3$)



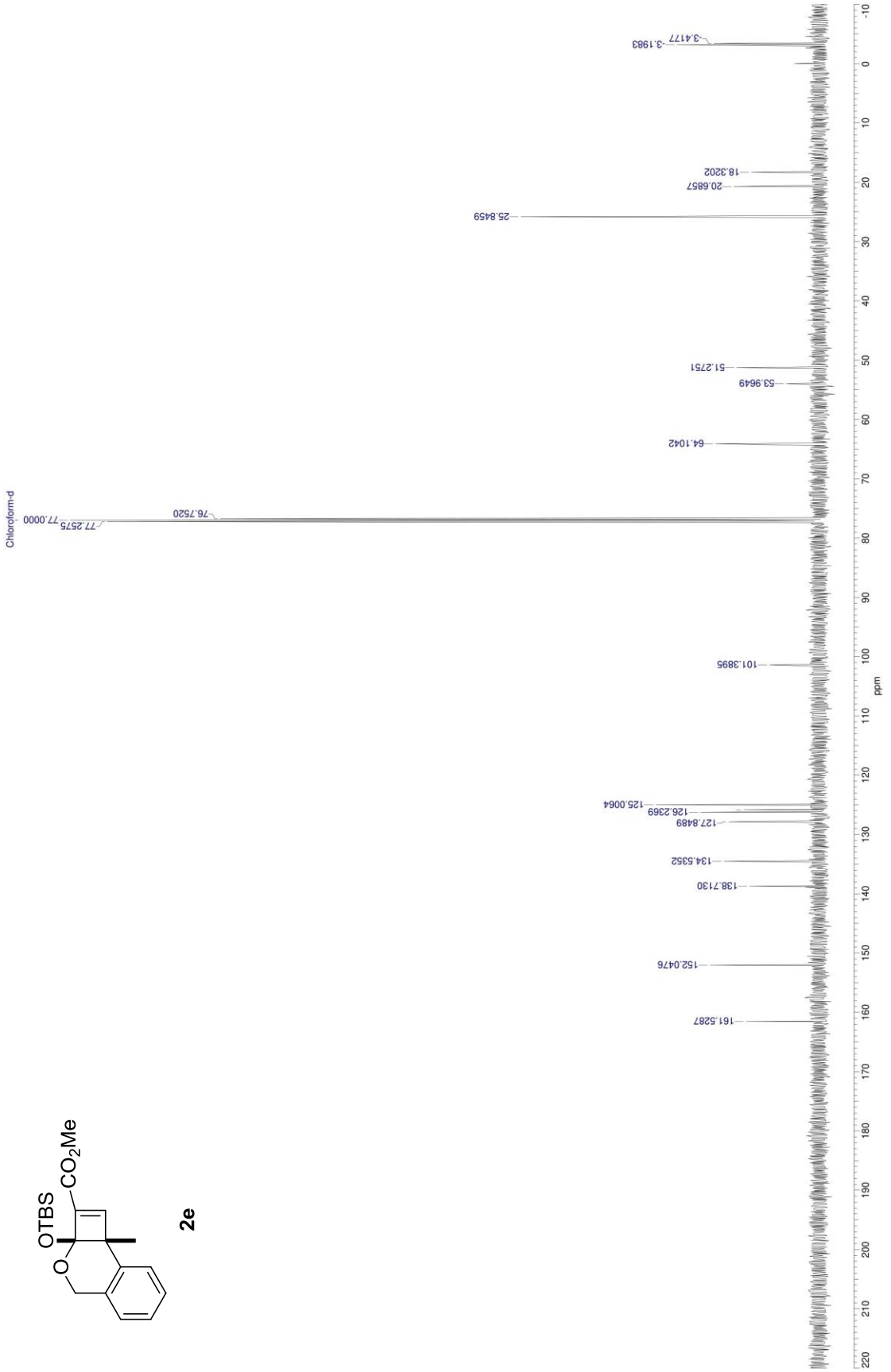
5d'

Compound **2e** (^{1}H NMR, $CDCl_3$)



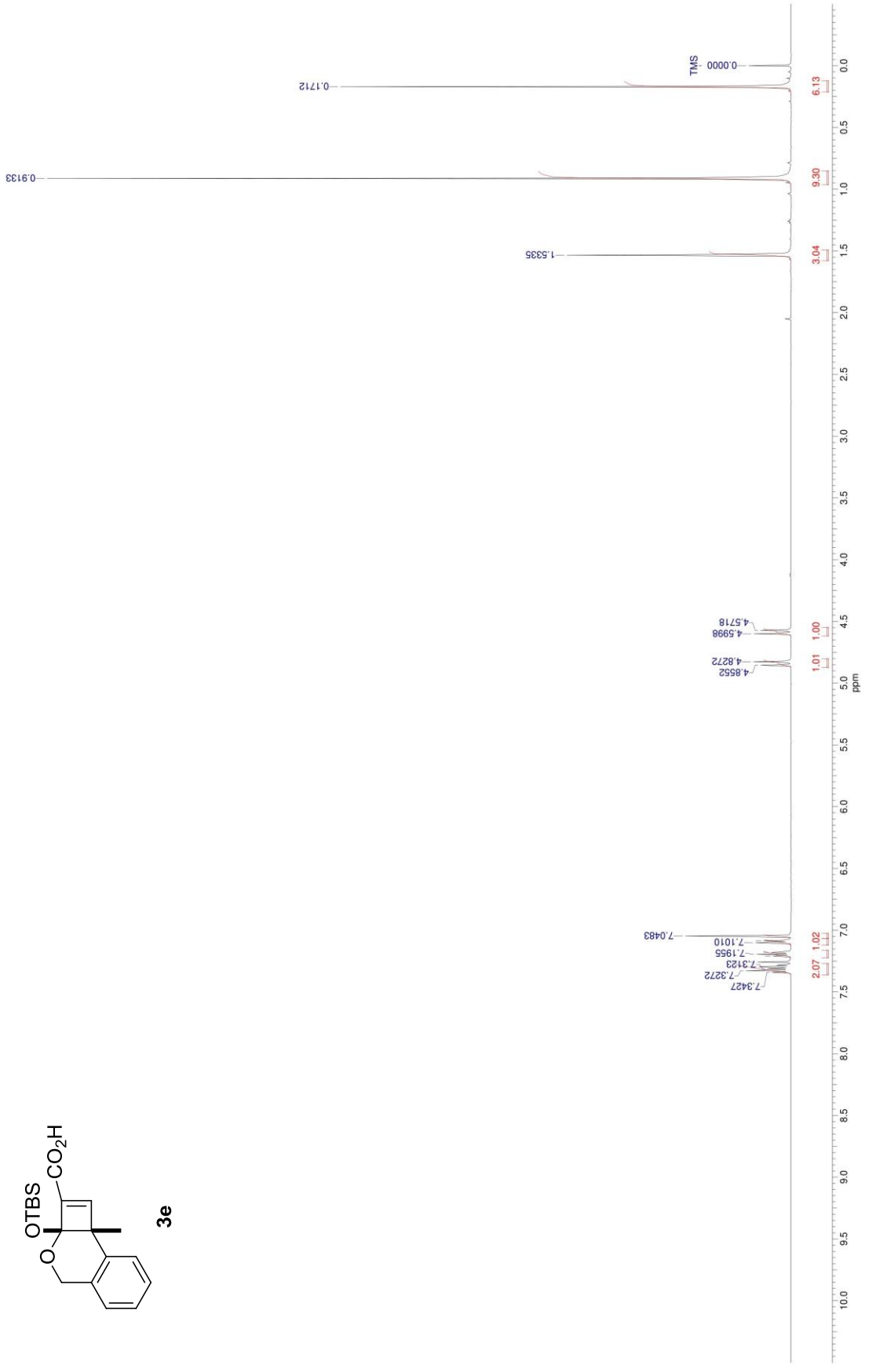
2e

Compound **2e** (^{13}C NMR, $CDCl_3$)



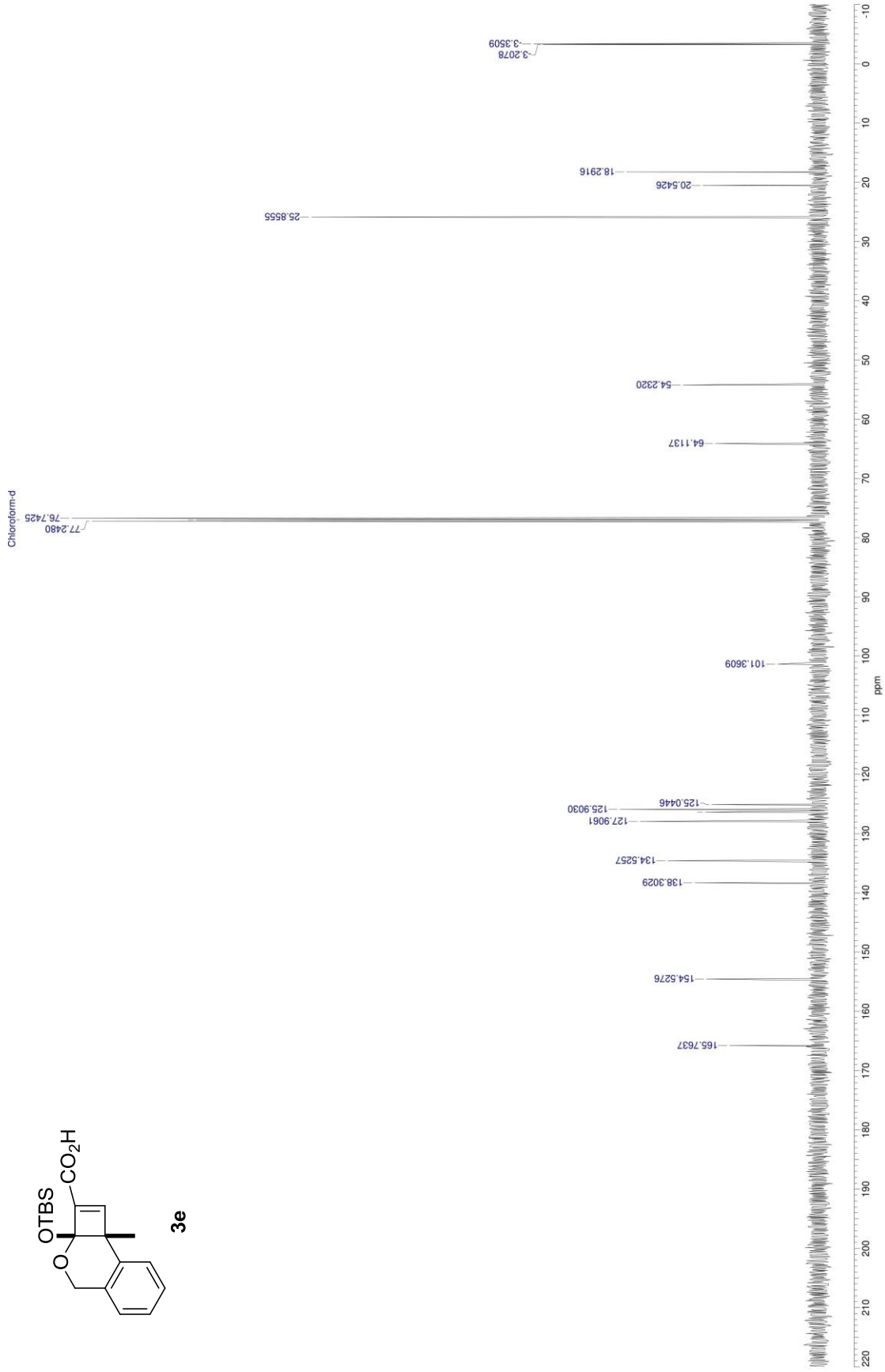
2e

Compound **3e** (^{1}H NMR, $CDCl_3$)

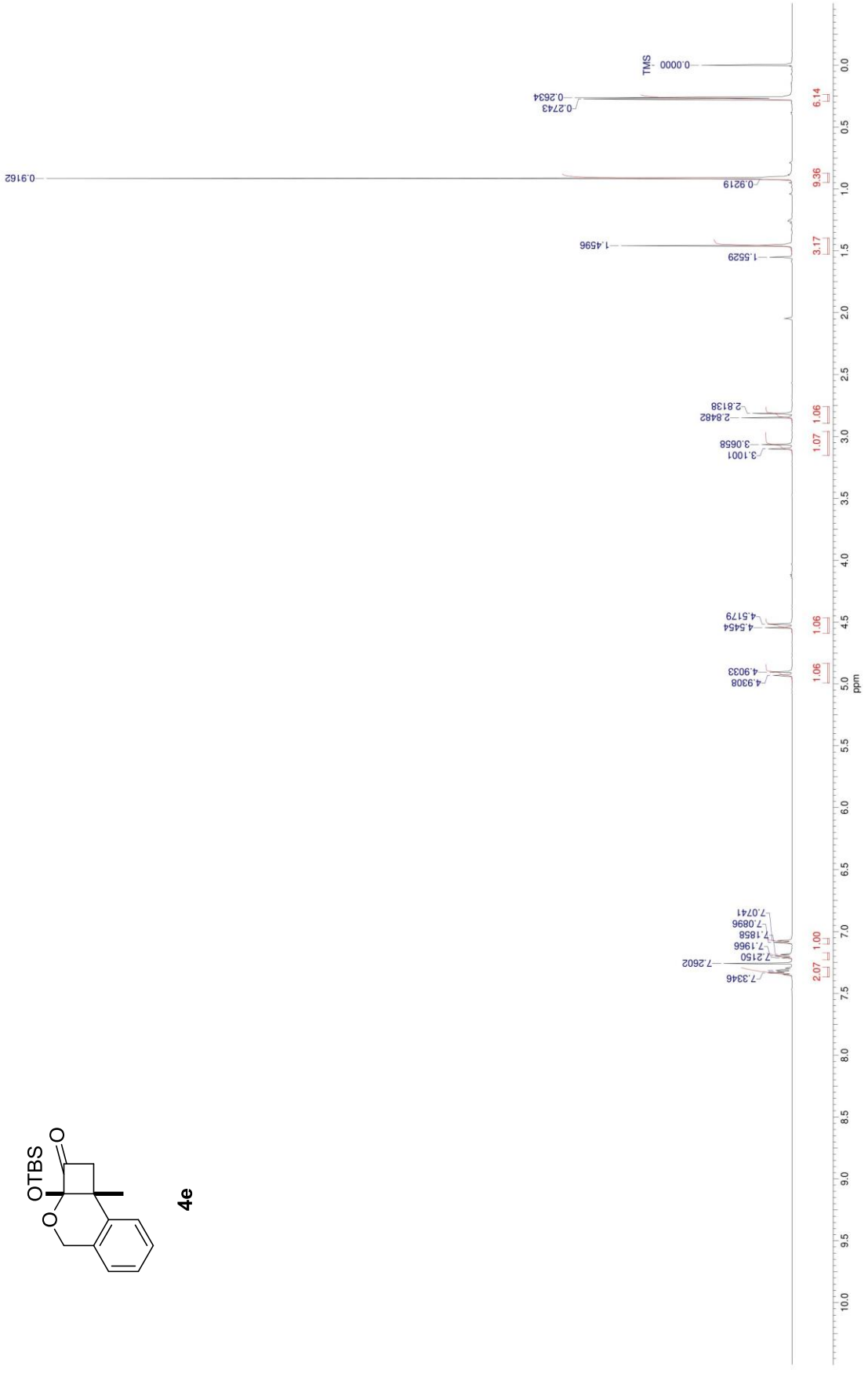


3e

Compound **3e** (^{13}C NMR, $CDCl_3$)

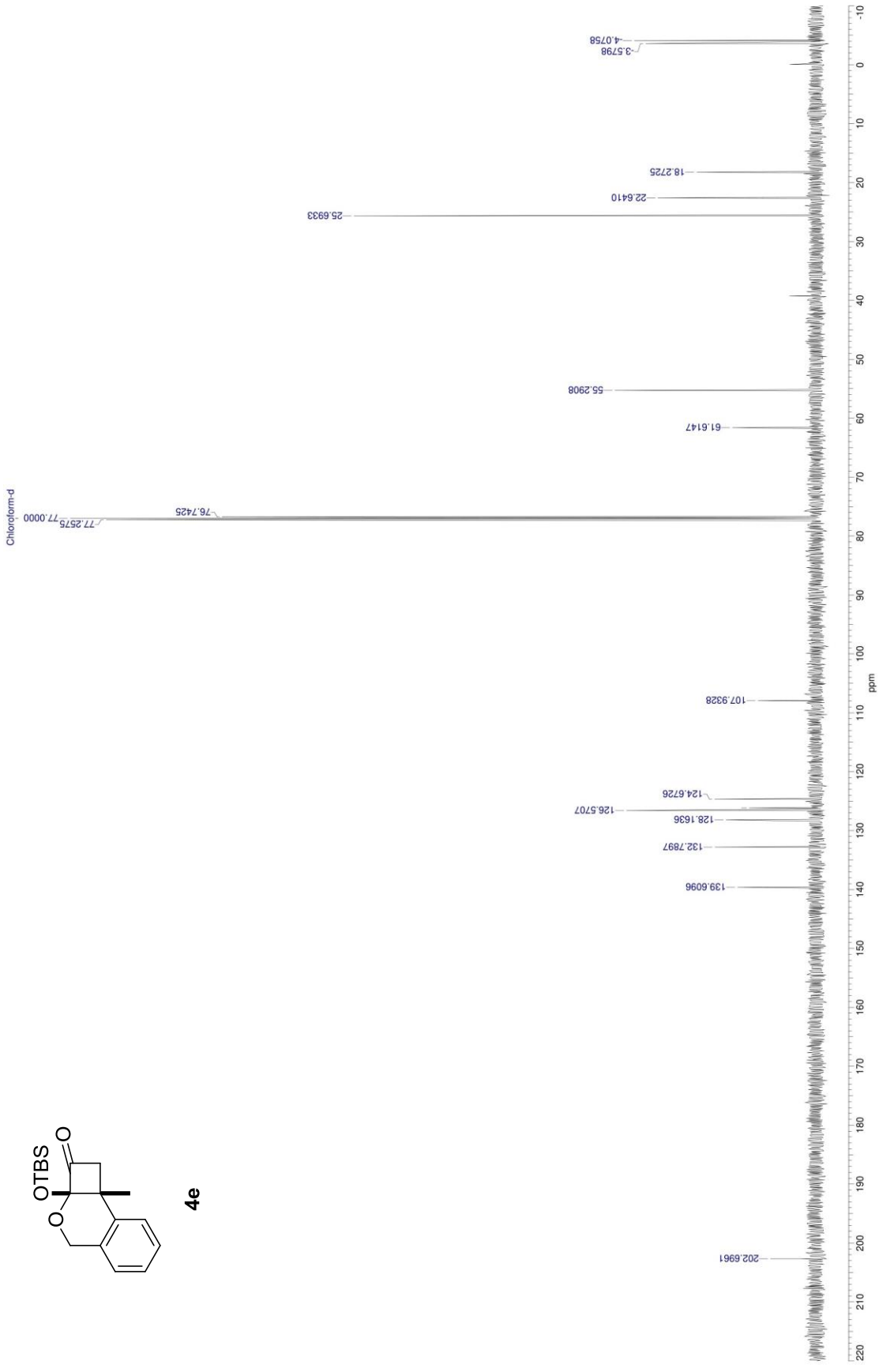


Compound **4e** (^{1}H NMR, $CDCl_3$)



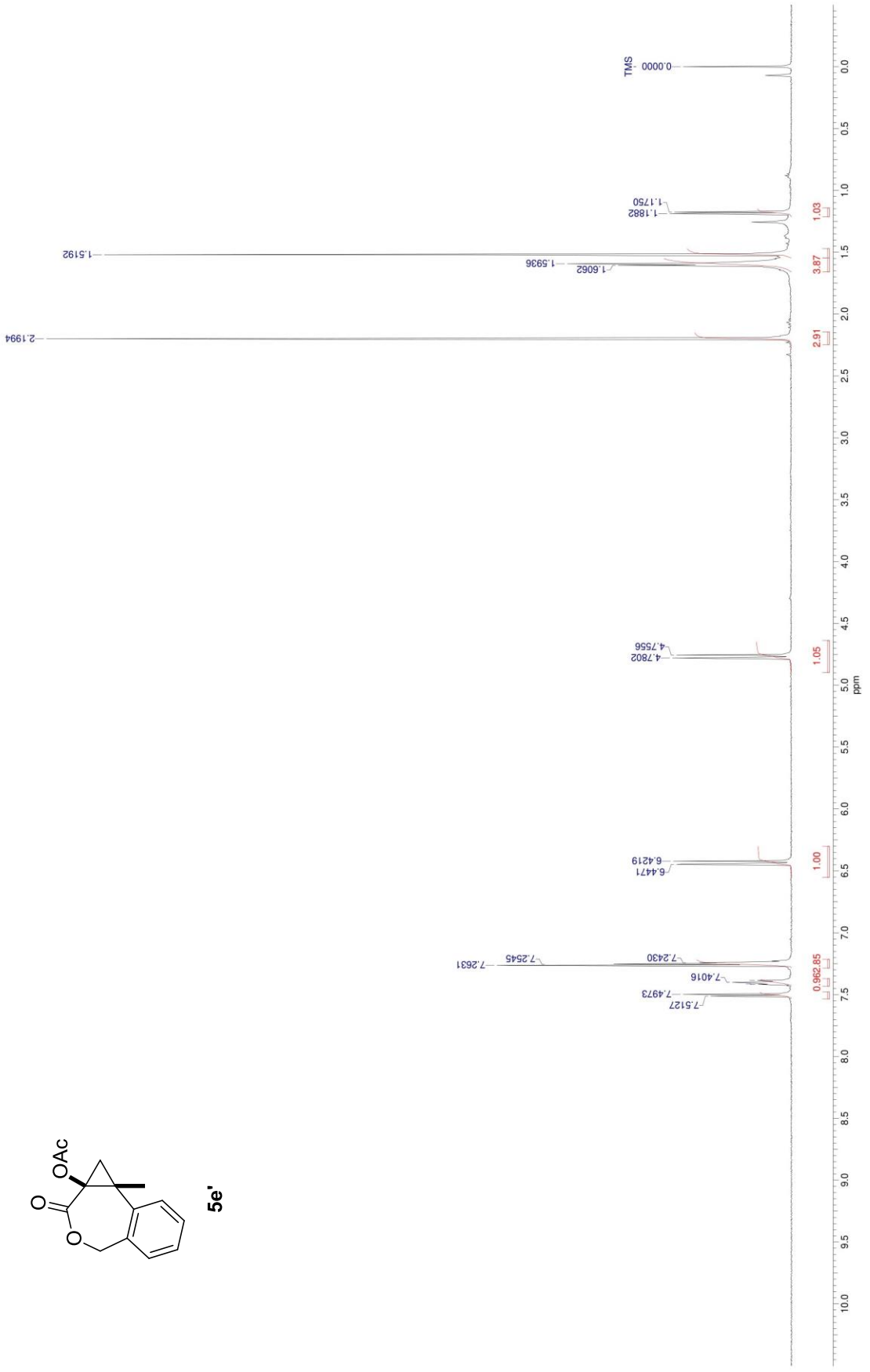
4e

Compound **4e** (^{13}C NMR, $CDCl_3$)



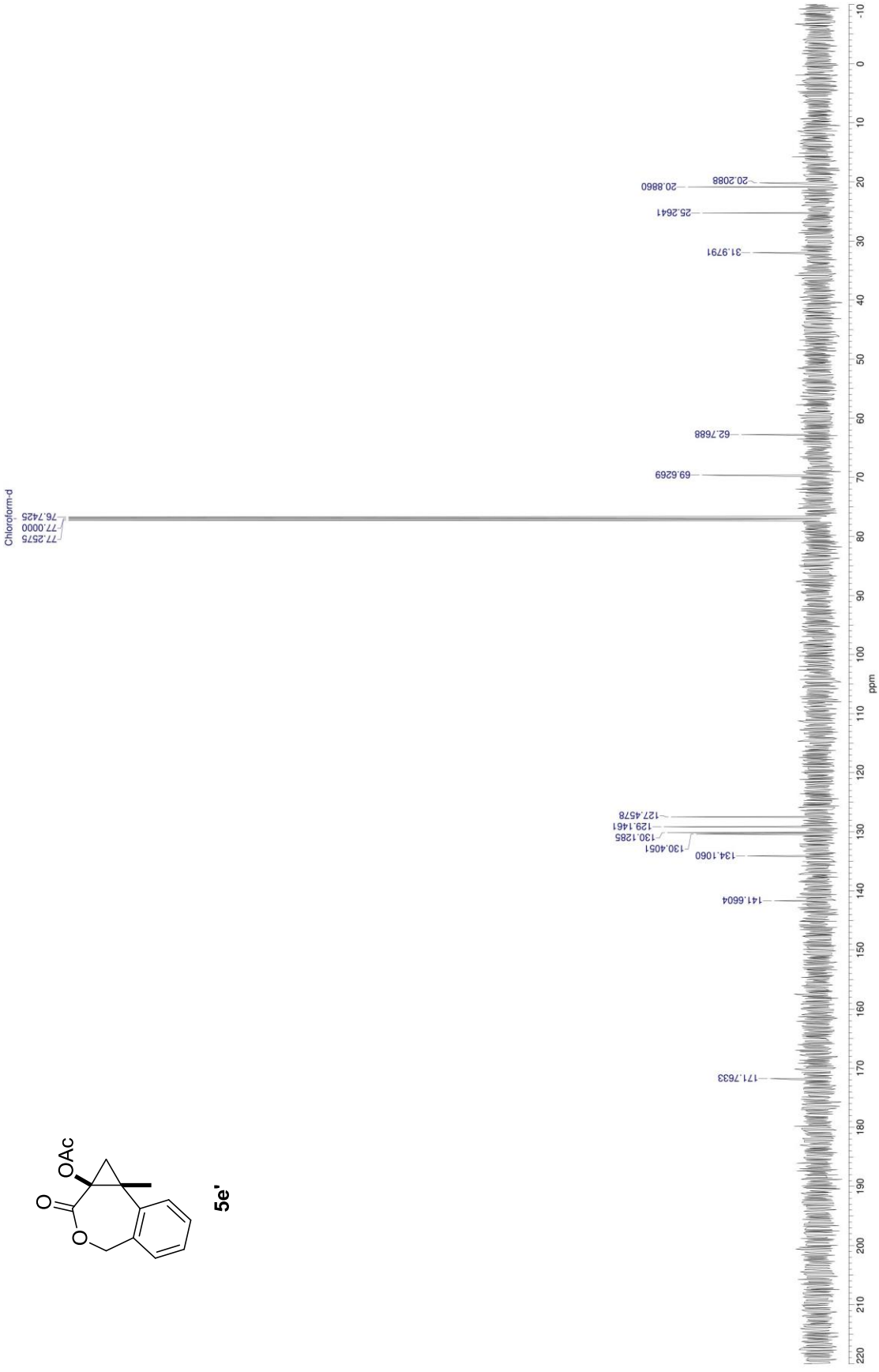
4e

Compound **5e'** (^{1}H NMR, $CDCl_3$)



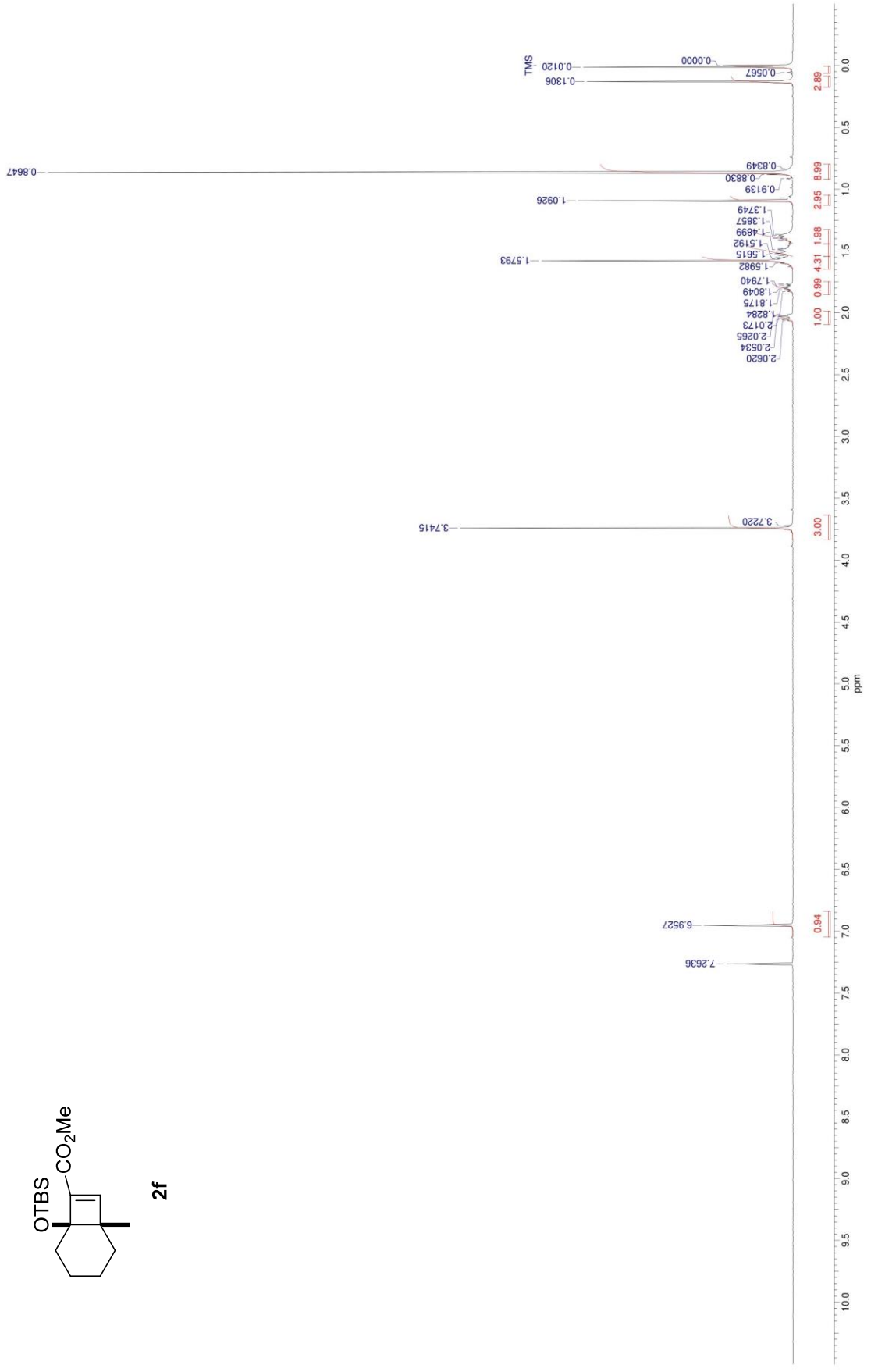
5e'

Compound **5e'** (^{13}C NMR, $CDCl_3$)



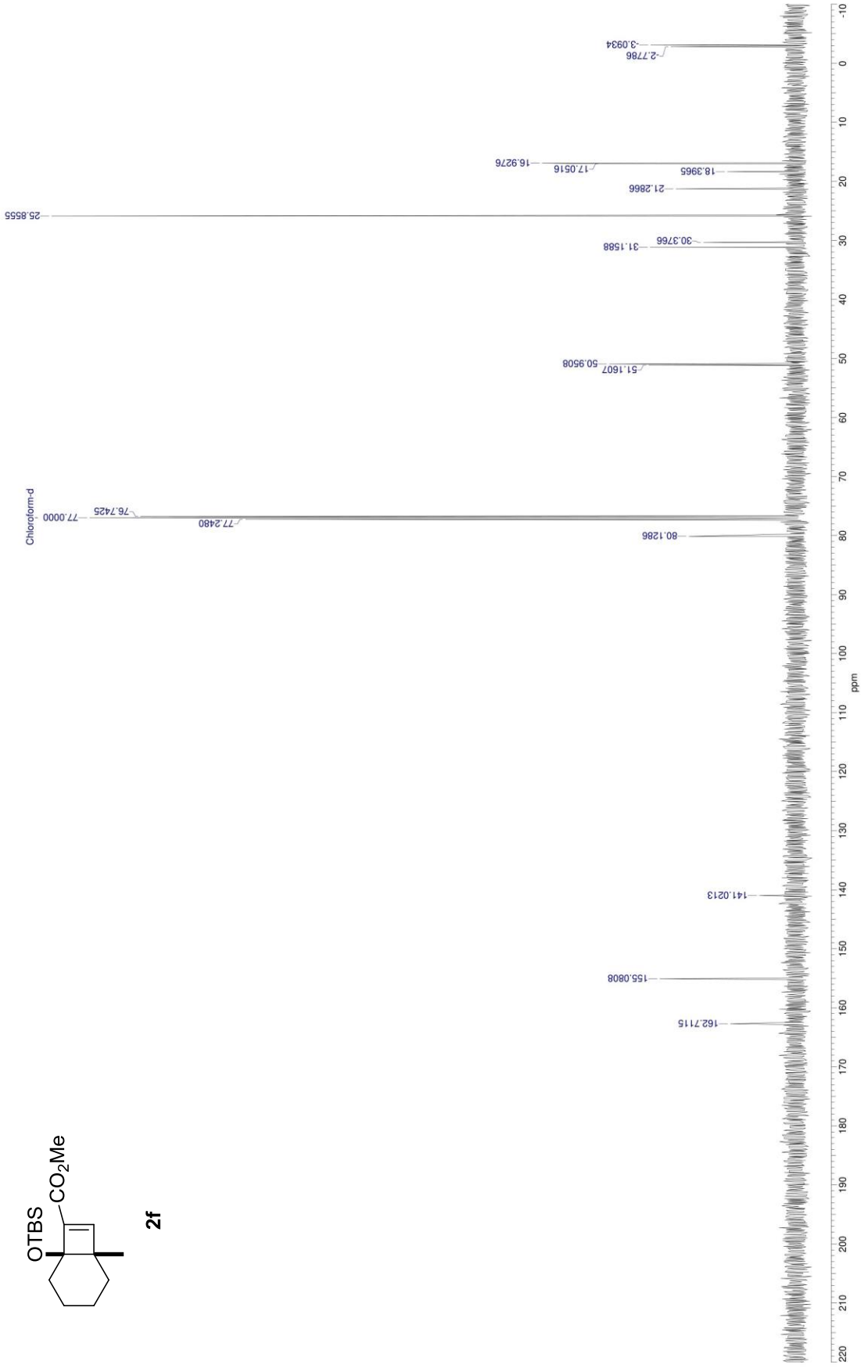
5e'

Compound **2f** (^{1}H NMR, $CDCl_3$)

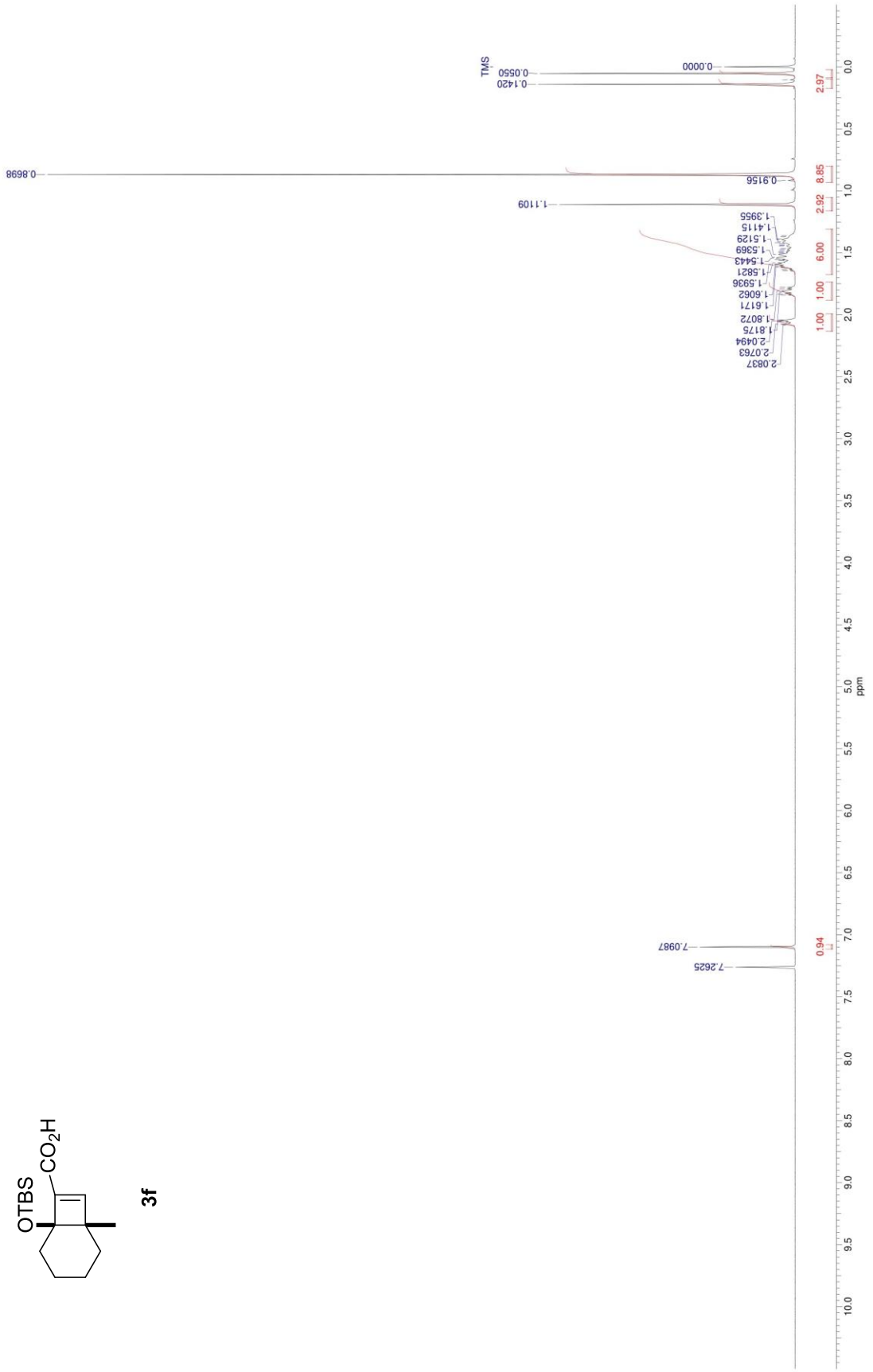


2f

Compound **2f** (^{13}C NMR, $CDCl_3$)

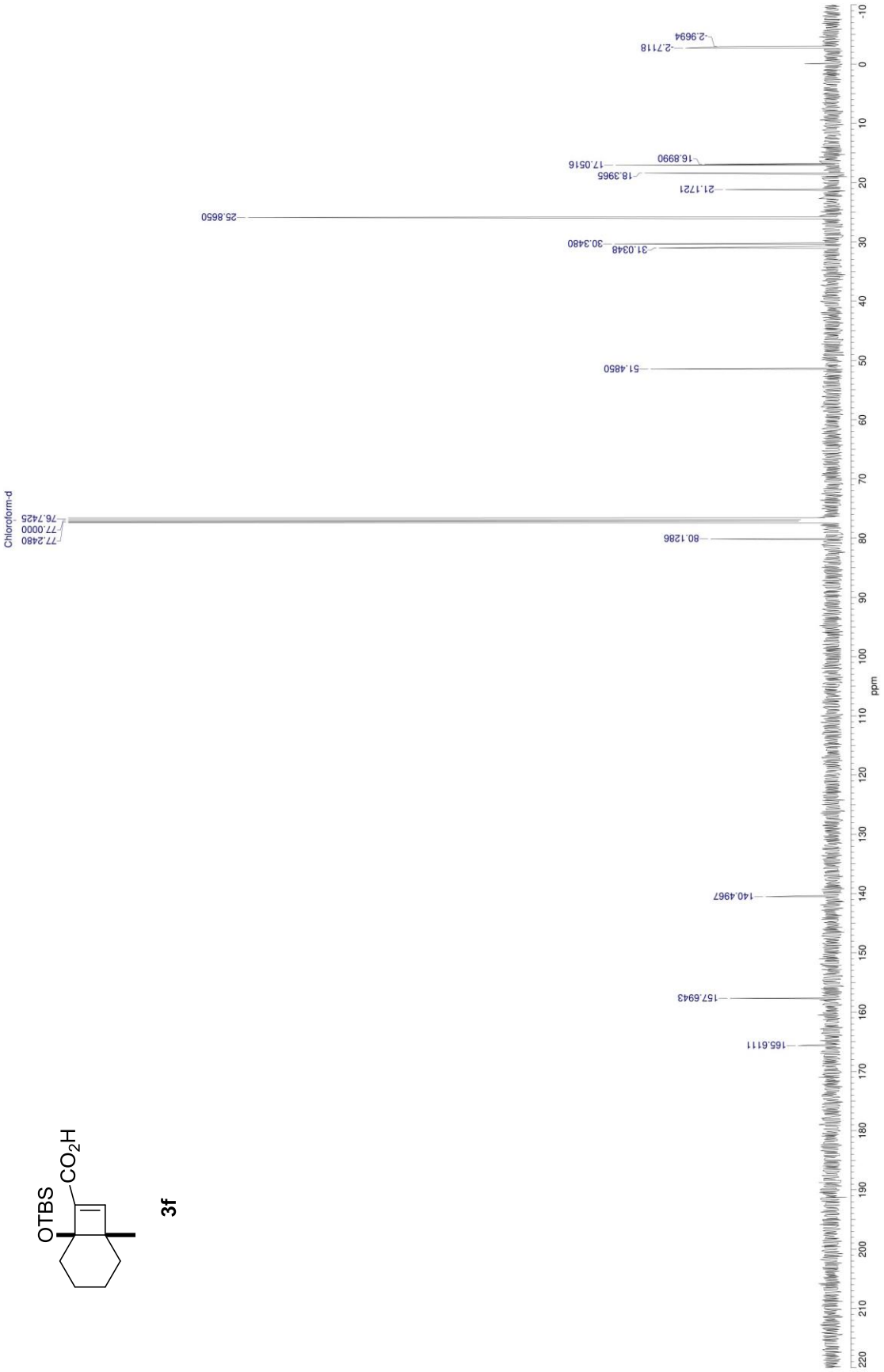


Compound **3f** (^{1}H NMR, $CDCl_3$)



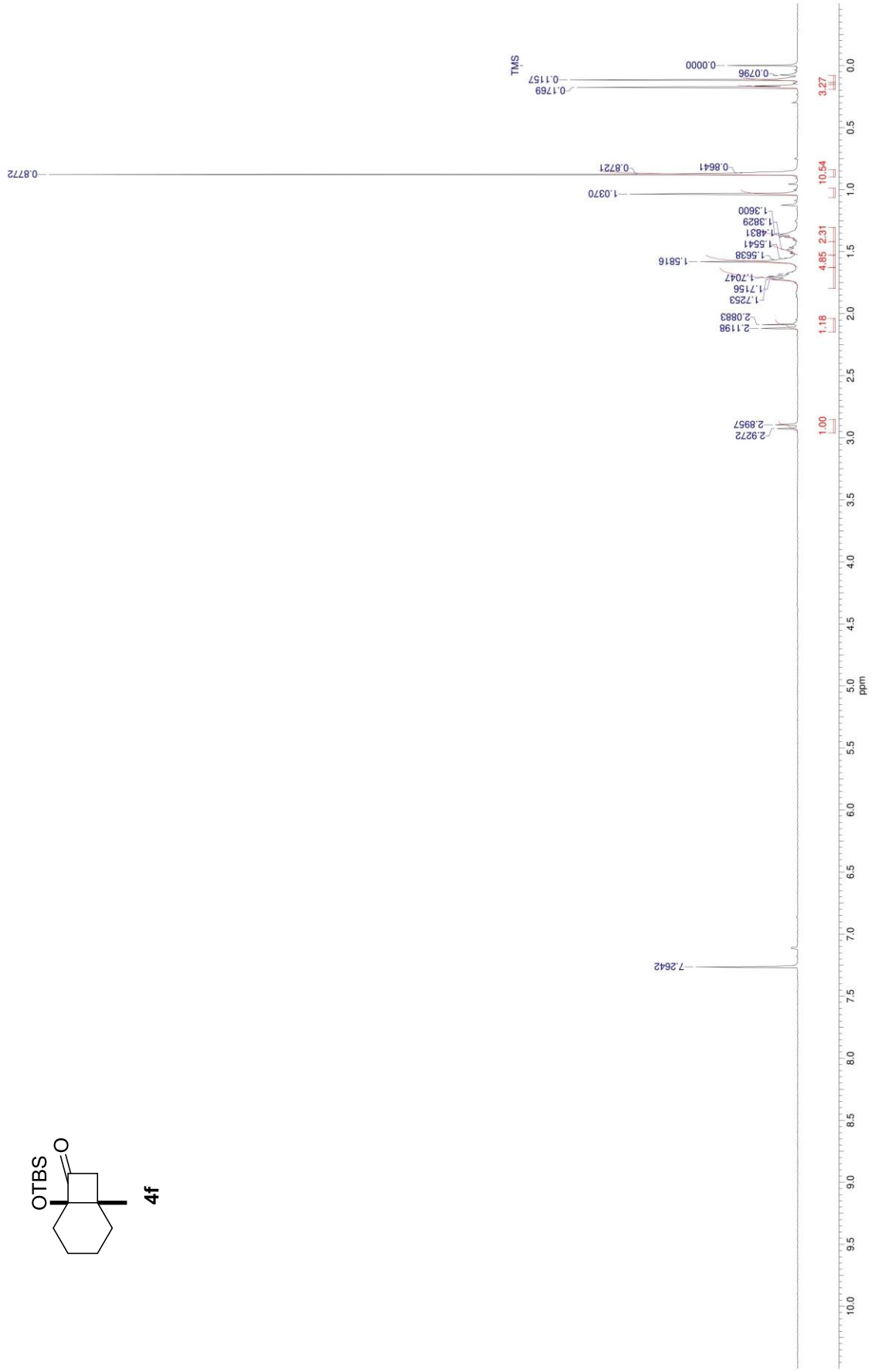
3f

Compound **3f** (^{13}C NMR, $CDCl_3$)

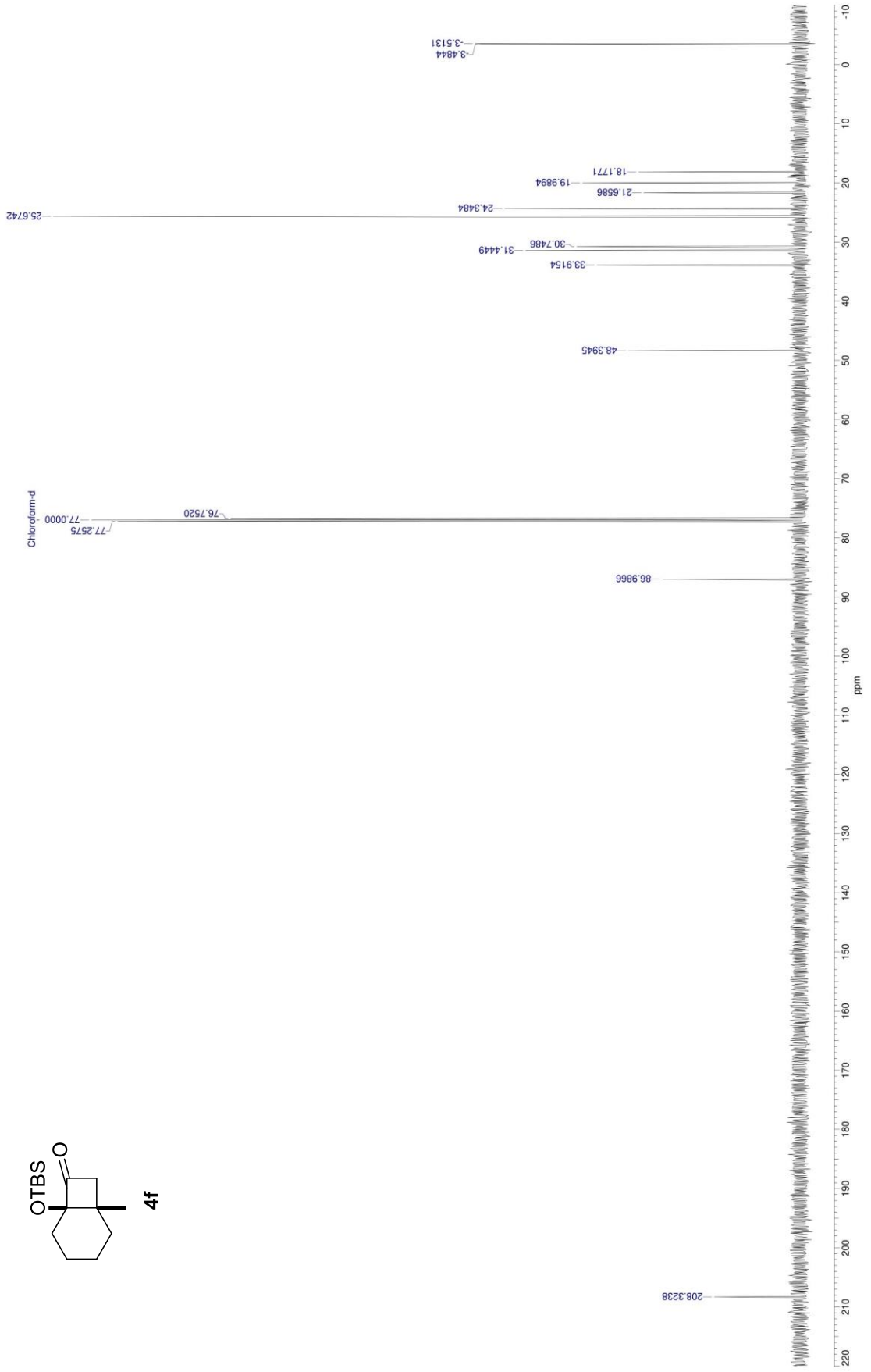


3f

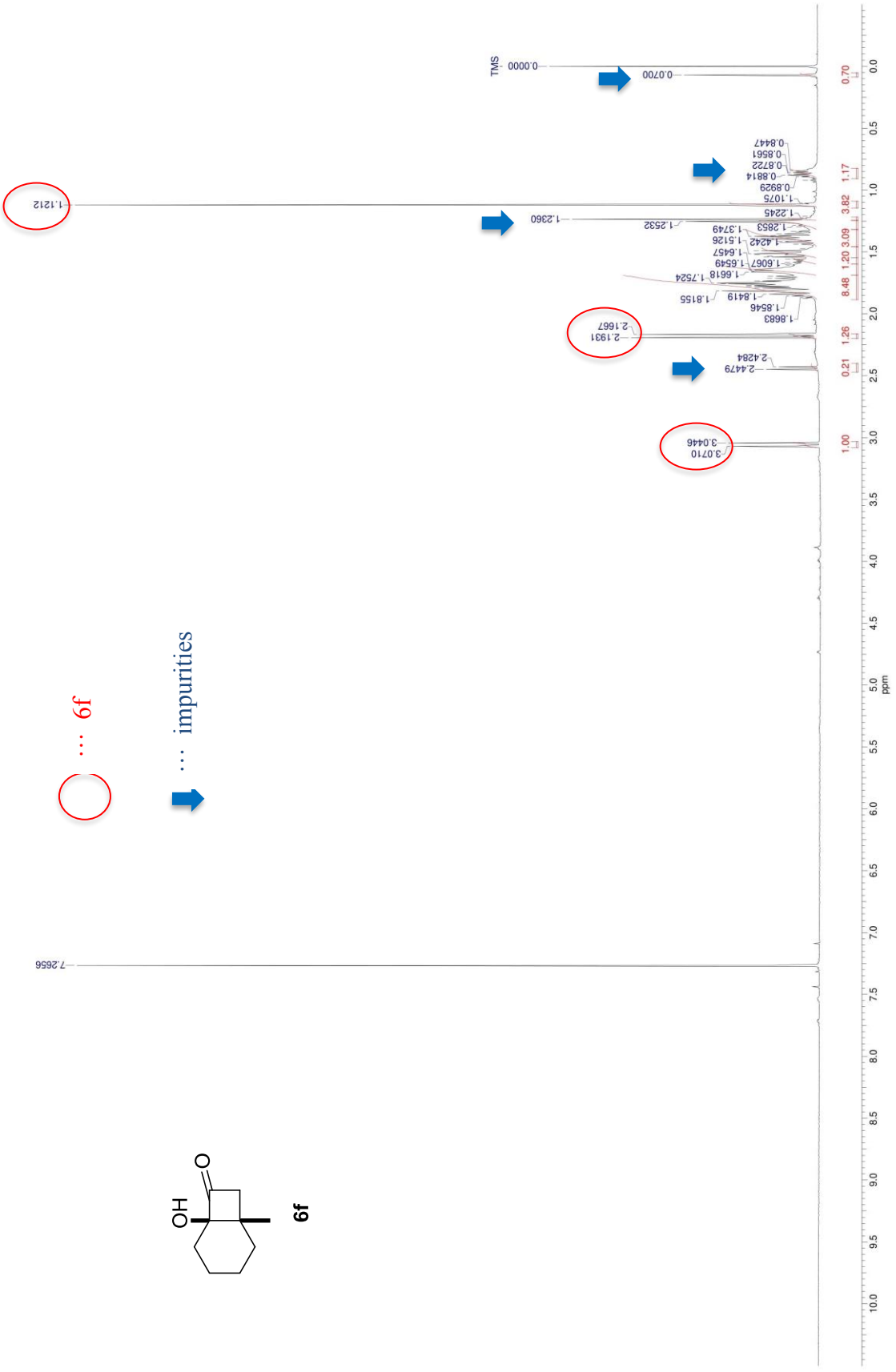
Compound **4f** (^{1}H NMR, $CDCl_3$)



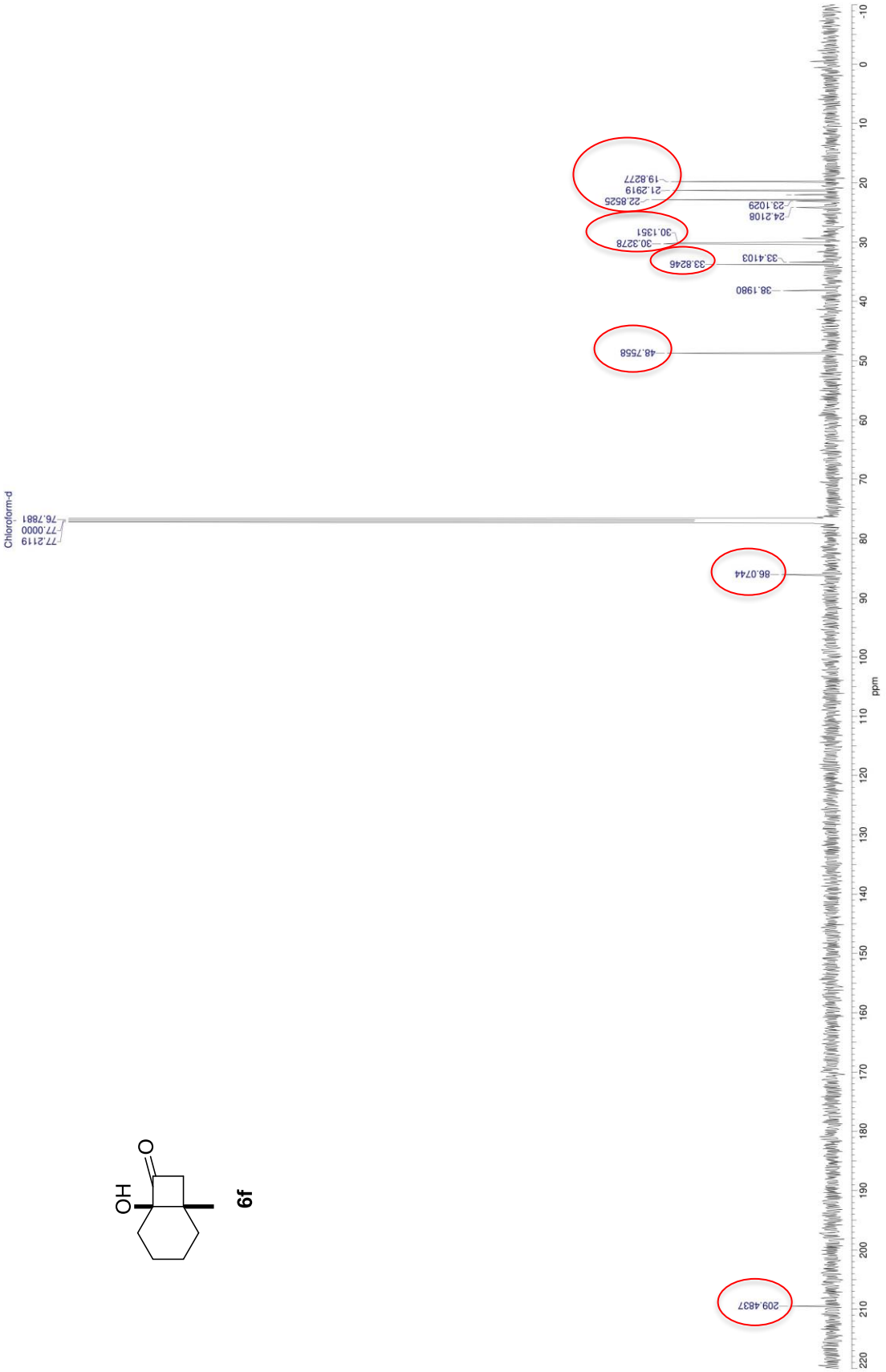
Compound **4f** (^{13}C NMR, $CDCl_3$)



Compound **6f** (^{1}H NMR, $CDCl_3$)

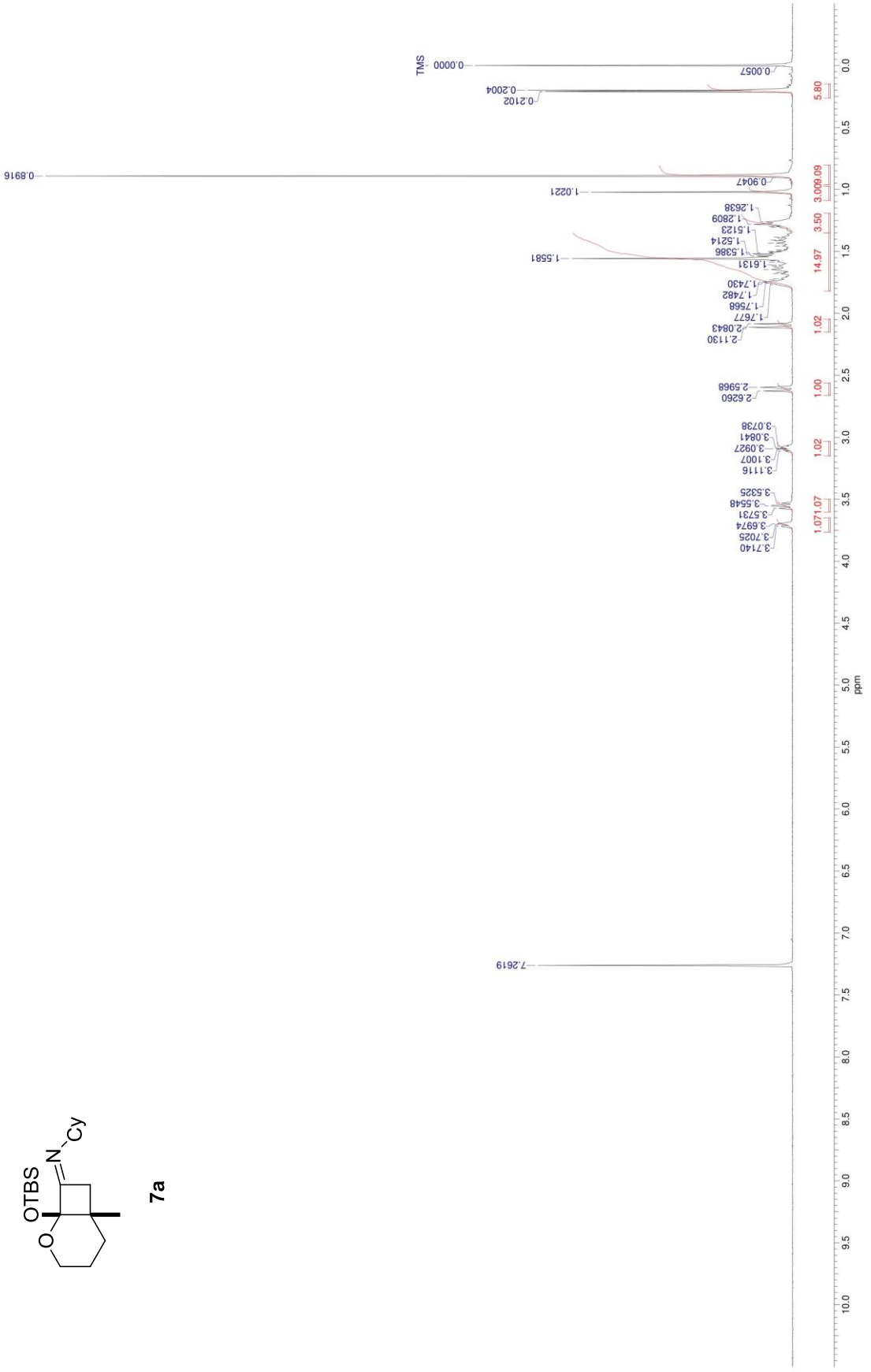


Compound **6f** (^{13}C NMR, $CDCl_3$)



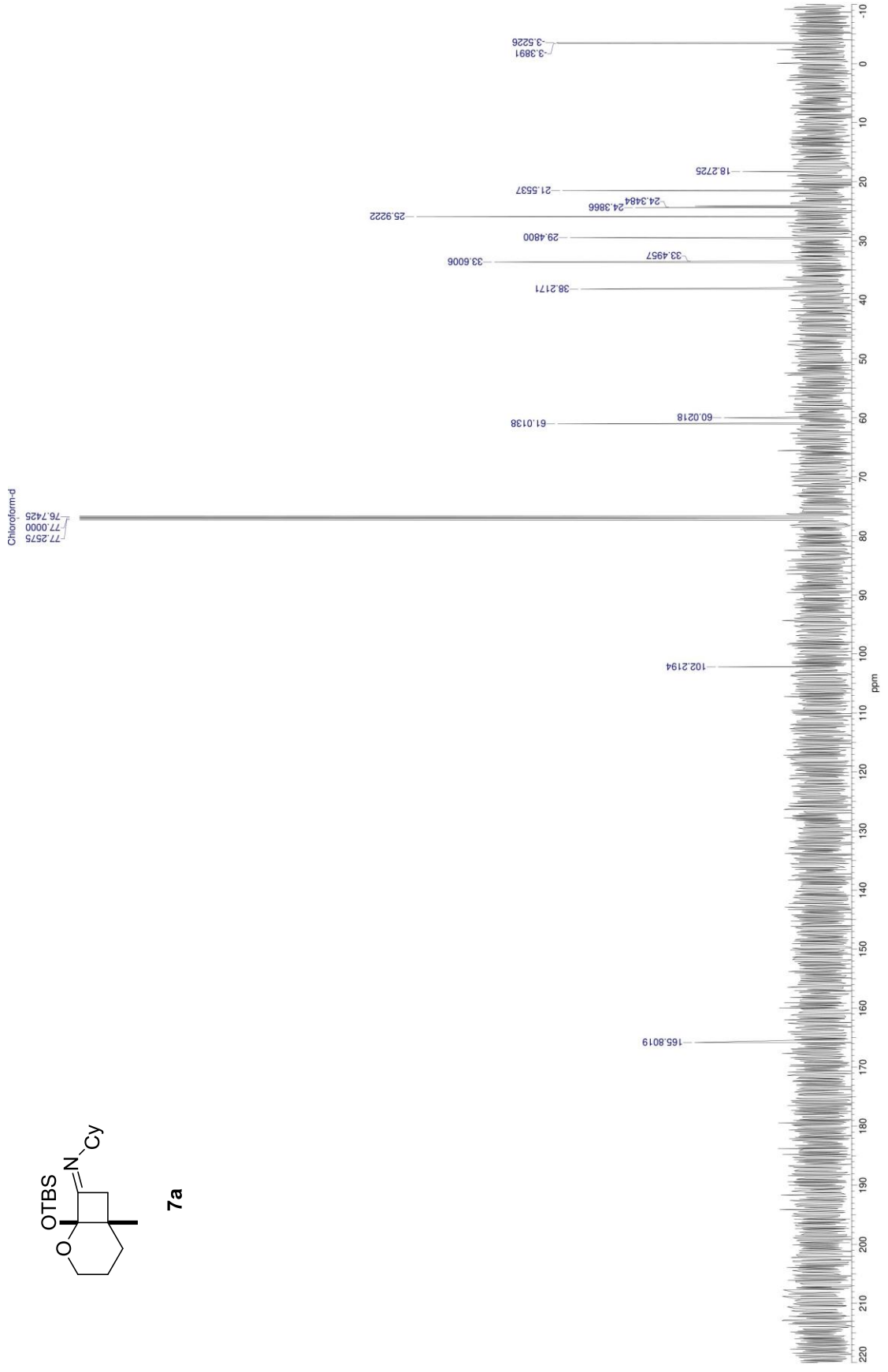
6f

Compound **7a** (^{1}H NMR, $CDCl_3$)

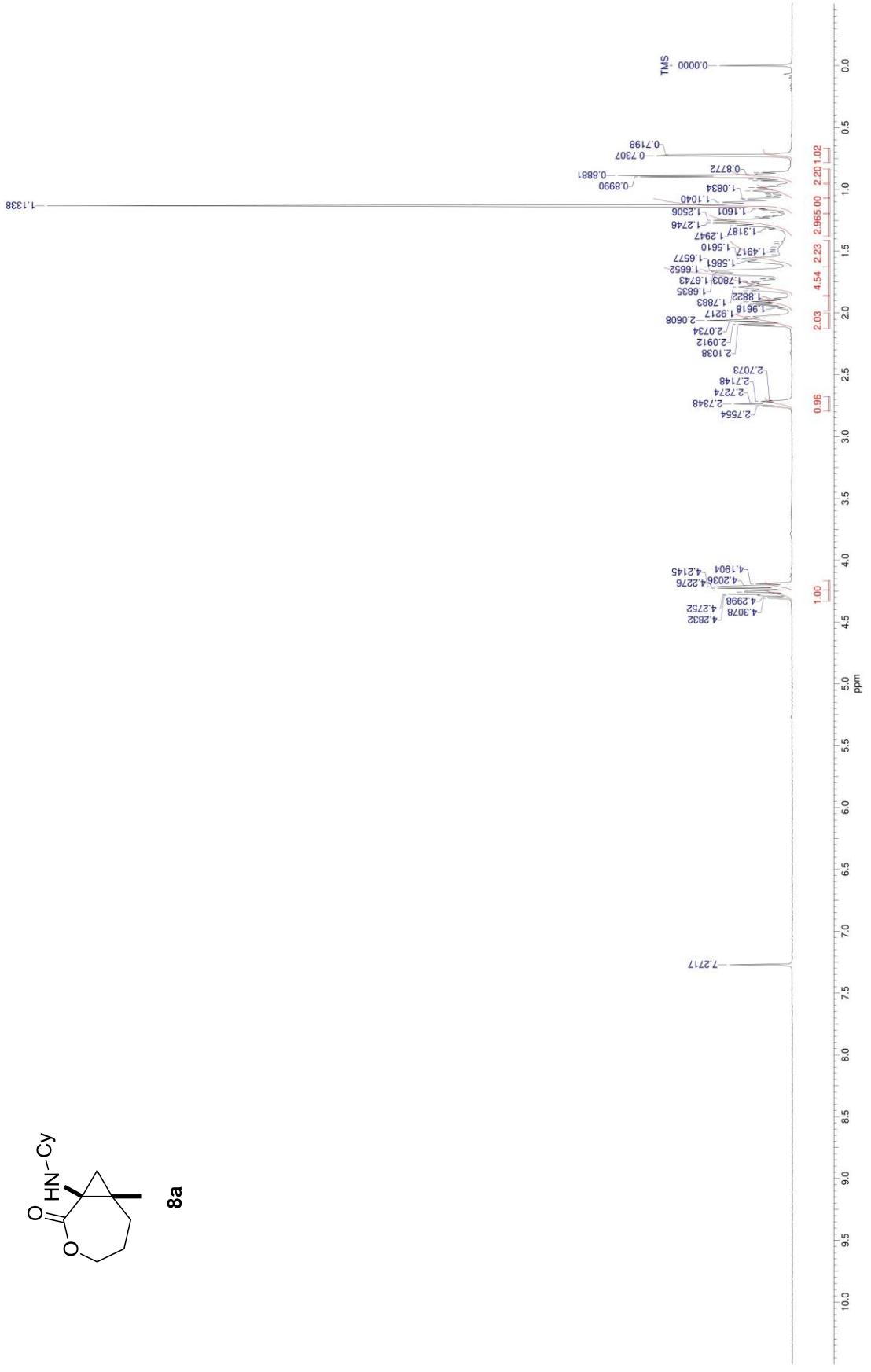


7a

Compound **7a** (^{13}C NMR, $CDCl_3$)

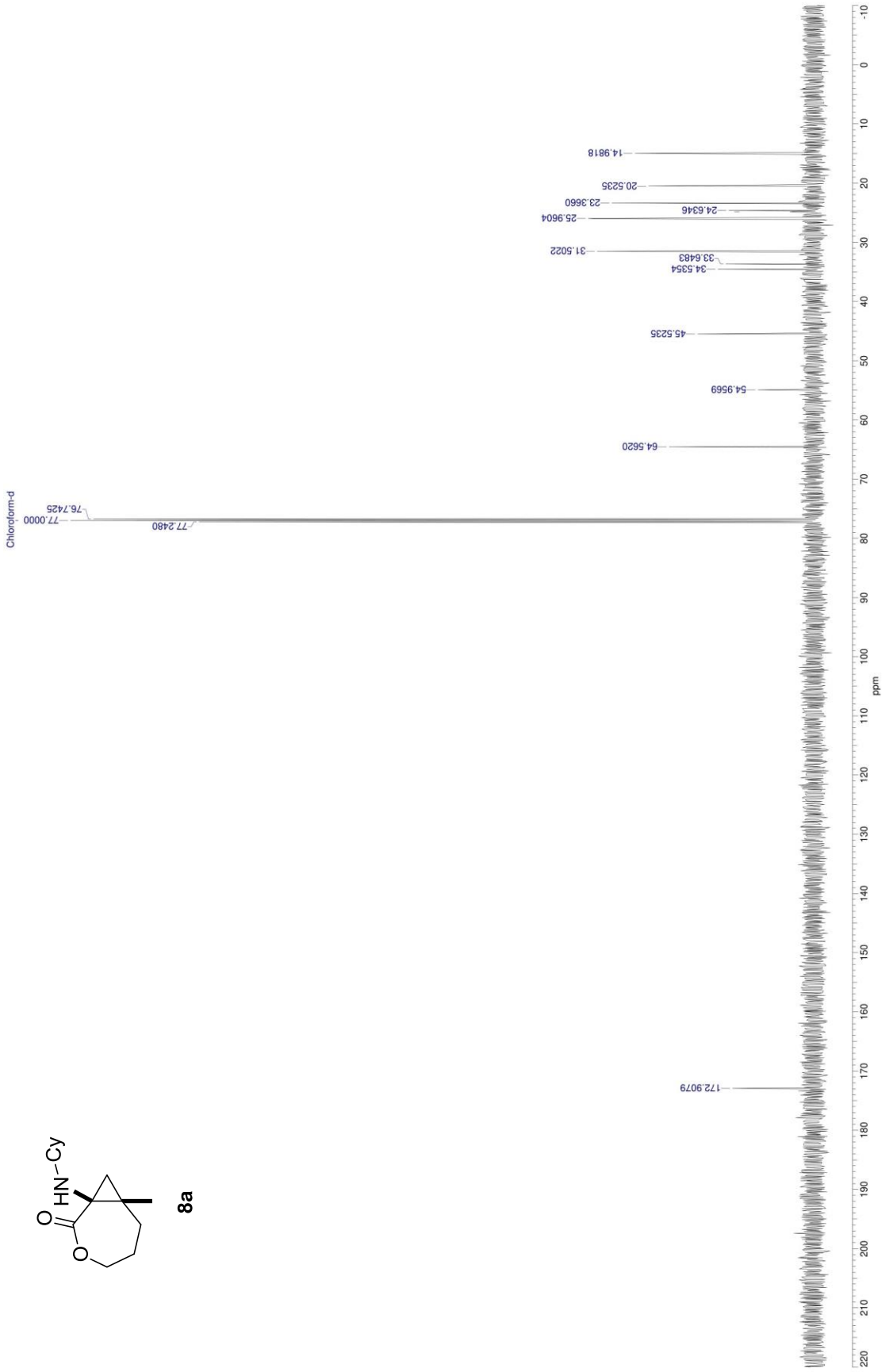


Compound **8a** (^{1}H NMR, $CDCl_3$)

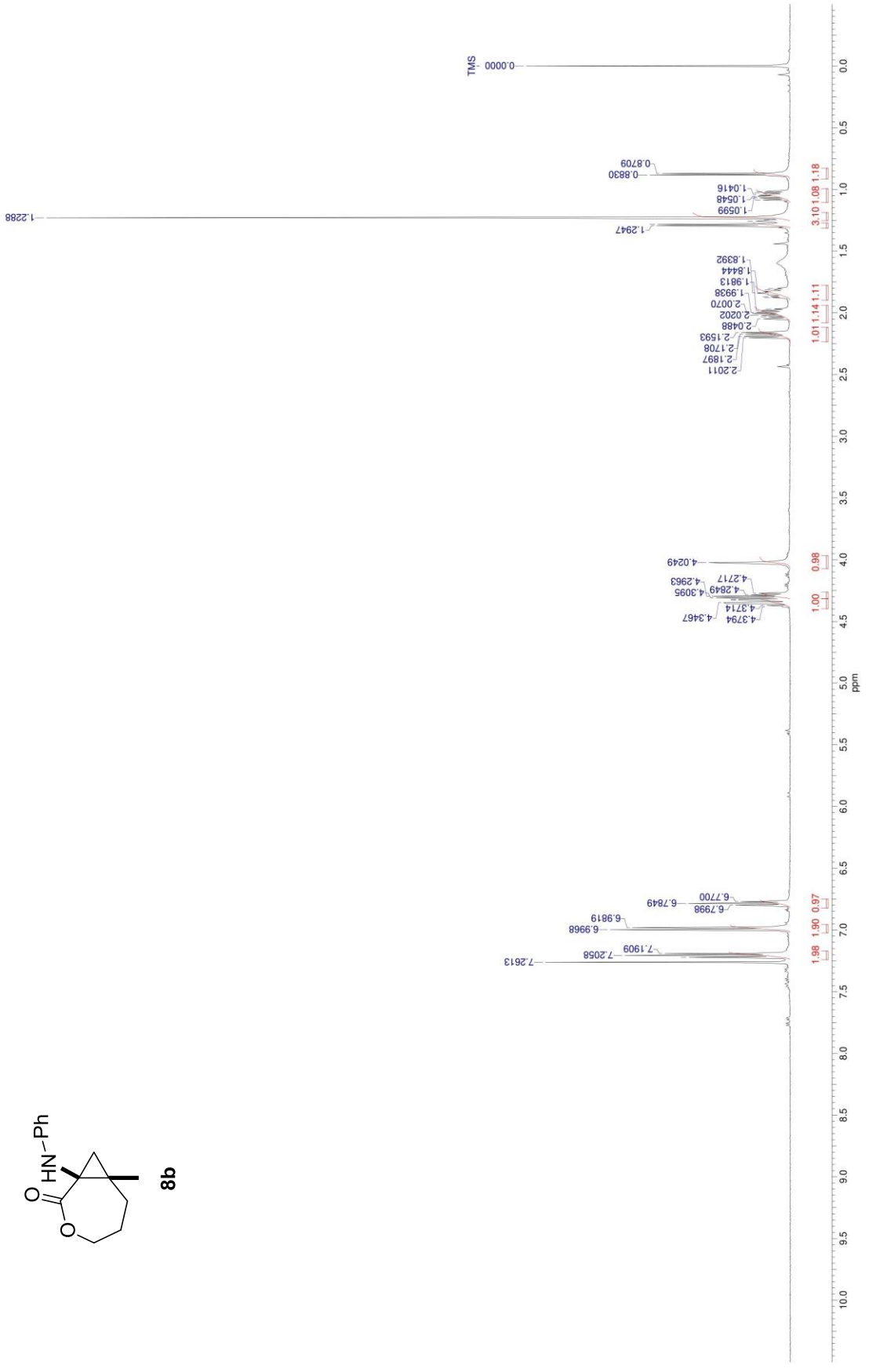


8a

Compound **8a** (^{13}C NMR, $CDCl_3$)



Compound **8b** (^{1}H NMR, $CDCl_3$)



8b

Compound **8b** (^{13}C NMR, $CDCl_3$)