

Supporting Information

**Concise Total Synthesis of (–)-Berkelic Acid
via Regioselective Spiroacetal/Pyran Formation**

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Experimental Section

I. Basic procedure

- a) All moisture-sensitive reactions were performed under an atmosphere of argon using heat-dried flasks, syringes, etc., and the starting materials were azeotropically dried with toluene before use.
- b) The reaction system was cooled in an ice-water bath (0 °C), a dry ice-methanol bath (-78 °C), and a liquid nitrogen-methanol bath (-97 °C). A heat block was used to heat the reaction system.
- c) The organic layer after extraction was dried by MgSO₄ with vigorously stirring, and the solid was removed by filtration.
- d) Concentration on a rotary evaporator was carried out under reduced pressure (10~100 mmHg) using a diaphragm pump. The residual solvent in an oily material was removed using a vacuum pump (approx. 1 mmHg) fitted with a trap cooled by liquid nitrogen.
- e) Celite® No. 535 purchased from Wako Pure Chemicals Co. was used for Celite filtration.
- f) The ratio of mixed solvents is expressed as a volume ratio.

II. Chromatography

a) Analytical thin layer chromatography

E. Merck TLC plates, TLC Silica gel 60 F₂₅₄, were used; detection of compounds on the TLC plates was performed by UV lamp (254 nm) irradiation and the use of the following coloration.

(Coloration)

Phosphomolybdic acid solution

12 Molybdo(IV) phosphoric acid (50 g) was dissolved in ethanol (450 mL).

The TLC plate was immersed in this solution and then heated on a hot plate (300 °C).

b) Analytical HPLC

Reaction was analyzed using reverse-phase HPLC in the below conditions.

Equipment	Shimadzu LC-2030
Column	YMC Triart C-18 (4.6 mm × 150 mm, 3 μm)
Mobile Phase	A: 10 mM H ₃ PO ₄ aq (pH 2) + 5% MeCN B: MeCN
Separation Modes	Gradient elution

	0 to 9 min: A/B = 100/0 to 0/100
	9 to 16 min: A/B = 0/100
Column Temp.	40 °C
Flow Rate	1.5 mL/min
Detector	UV: 210nm, 254 nm
Injection	5 µL

c) Analytical chiral HPLC

Enantiomeric ratio was analyzed using HPLC with chiral column in the below conditions.

Equipment	Shimadzu LC-2030
Column	DAICEL CHIRALPAK IA-3 (4.6 mm × 250 mm, 3 µm)
Mobile Phase	Hexane/THF = 85/15
Separation Modes	Isocratic Elution
Column temp	40 °C
Flow Rate	1.5 mL/min
Detector	UV: 210nm, 254 nm
Injection	10 µL

d) Column chromatography

Yamazen Smart Flash (W-Prep 2XY) and pre-packed Universal Column Premium were used. The weights of the packed silica gel of column sides M, L, and 3L are 16, 40, and 135 g, respectively. UV (210 nm, 254 nm) and MS were used as detectors. Solvents and gradients are described in each experimental section.

e) Preparative thin layer chromatography was performed on 0.5 mm or 1 mm Merck Millipore PLC silica gel 60 F₂₅₄ plates.

III. Instrumental analysis

a) Specific rotation ($[\alpha]_D^t$)

The instrument used was a digital optical rotation meter (DIP-1000) manufactured by JASCO Co. Chloroform through alumina [E. Merck Aluminium oxide 90 active neutral (activity stage I) for column chromatography], methanol for HPLC, or acetonitrile for HPLC was used as a measuring solvent. The measured values are listed as below, where t is the measurement temperature (°C) and the unit of concentration of the solution is given as g / dL.

$$[\alpha]_D^t \text{ specific rotation (} c \text{ concentration, solvent)}$$

b) Infrared absorption spectrum (IR)

The instrument used was a spectrophotometer (FT/IR-4100) manufactured by JASCO Co. Chloroform through alumina [E. Merck Aluminium oxide 90 active neutral (activity stage I) for column

chromatography] was used as the measurement solvent. The chloroform solution of the sample was placed in a dedicated NaCl cell and the measured values are listed as below.

IR (CHCl₃) absorption wavelength (cm⁻¹)

c) ¹H nuclear magnetic resonance spectrum (¹H NMR spectrum)

The instrument used was a spectrometer (Avance III HD 500, 500 MHz) manufactured by Bruker Co. Heavy chloroform (CDCl₃) was used as the measurement solvents. The measured values are listed as below.

¹H NMR (Measuring frequency, solvent) δ Chemical shift value (multiplicity, spin coupling value, a number of hydrogen)

Chemical shift values are listed as δ values (ppm), and residual protons of the measuring solvent [CHCl₃ (δ 7.26), CHD₂OD (δ 3.31)] were used as internal standards. Multiplicities were abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet, or overlap of multiple signals), and the broad signals were represented by the remark “br”. The spin coupling constant *J* is listed in Hz.

d) ¹³C nuclear magnetic resonance spectrum (¹³C NMR spectrum)

The instrument used was a spectrometer (Avance III HD 500, 125 MHz) manufactured by Bruker Co. Heavy chloroform (CDCl₃) was used as the measurement solvents. The measured values are listed as below.

¹³C NMR (Measuring frequency, solvent) δ Chemical shift value

Chemical shift values are listed as δ values (ppm), and the carbon signal of the measuring solvent [CDCl₃ (δ 77.00)] was used as an internal standard.

e) High resolution mass spectrometry (HRMS)

The instrument used was Thermo Scientific EXACTIVE Plus, and measurements were performed by electron spray ionization (ESI).

HRMS [ESI] calcd for molecular formula [ion] calculated value, found measured value.

IV. Preparation of solvents

Dehydrated Solvents

Dry Et₂O, THF, DMF and CH₂Cl₂ were purchased and used without further drying.

(3*S*)-4,4-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methyl-1-butyne (6**)**



Following the experimental procedure reported by Fañanás and Rodríguez¹⁾, diol **S1** was prepared through a sequence of three conversion reactions from (*S*)-3-butyne-2-ol. The spectral data of **S1** were in good agreement with those of the reported ones.

To a stirred solution of diol **S1** (8.00 g, 62.4 mmol) in DMF (160 mL) were added TBSCl (24.5 g, 162 mmol, 2.60 eq) and imidazole (17.0 g, 250 mmol, 4.00 eq) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature over 1 h. After being stirred for additional 5 h at the same temperature, the reaction mixture was quenched with H₂O (160 mL). The immiscible mixture was extracted with MTBE (2 × 80 mL). The combined organic layers were washed with brine (2 × 80 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (column size: 3 L, heptane/toluene = 100/0 to 95/5) to give **6** (22.00 g, 99%) as a colorless oil.

$[\alpha]_D^{25.4} +25.7$ (*c* 1.00, CHCl₃)

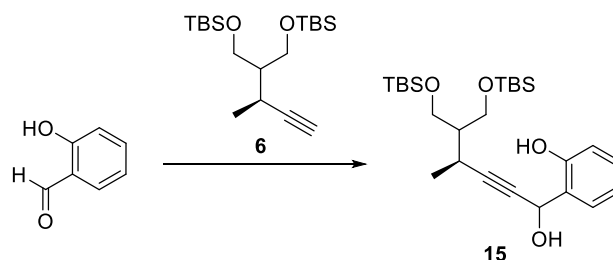
IR (CHCl₃) 3307, 2958, 2930, 2857, 2109, 1471, 1256, 1094, 838, 637, 435, 421 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 3.80 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.72–3.57 (m, 2H), 3.64 (dd, *J* = 10.0, 7.5 Hz, 1H), 2.76–2.69 (m, 1H), 2.01 (d, *J* = 3.0 Hz, 1H), 1.69–1.63 (m, 1H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.05 (s, 12H).

¹³C NMR (125 MHz, CDCl₃): δ 87.6, 69.0, 61.0, 60.7, 48.0, 25.9, 23.8, 18.4, -5.4.

HRMS [ESI]: calcd for C₁₉H₄₁O₂Si₂ [M+H]⁺ 357.2640, found 357.2636.

2-((4*S*)-5,5-Bis(((tert-butyl)dimethylsilyl)oxy)methyl)-1-hydroxy-4-methylpent-2-yn-1-yl)phenol (**15**)



To a stirred solution of alkyne **6** (392 mg, 1.10 mmol, 1.10 eq) in anhydrous THF (3.7 mL) was slowly added a solution of LHMDS in THF (1.3 M, 1.54 mL, 2.00 mmol, 2.00 eq) at 0 °C under argon. The resulting mixture was stirred at the same temperature for 30 min, and then a solution of salicylaldehyde (122 mg, 1.0 mmol) in THF (1.2 mL) was slowly added to the reaction mixture at 0 °C. After being stirred at the same temperature over 2 h, the reaction mixture was treated with saturated aqueous NH₄Cl (7.4 mL). The immiscible mixture was extracted with MTBE (2 × 3.7 mL). The combined organic layers were washed with brine (3.7 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (column size: M, heptane/EtOAc = 100/0 to 85/15) to give **15** (407 mg, 85%, mixture of diastereomers) as a brownish oil.

$[\alpha]_D^{25.4} +27.0$ (*c* 1.00, CHCl₃)

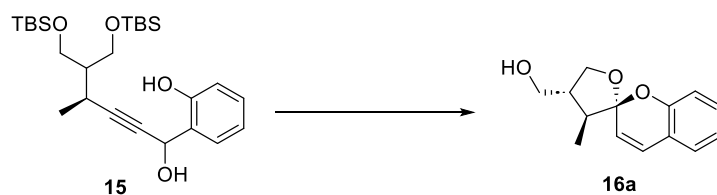
IR (CHCl₃) 3366, 2955, 2930, 2857, 2232, 2212, 1588, 1486, 1471, 1255, 1092, 838, 451, 444, 415, 403 cm⁻¹

¹H NMR (500 MHz, CDCl₃, major isomer): δ 7.34 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31 (brs, 1H), 7.23 (td, *J* = 7.5, 1.5 Hz, 1H), 6.90 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.88 (td, *J* = 7.5, 1.5 Hz, 1H), 5.67 (d, *J* = 5.0 Hz, 1H), 3.82–3.78 (m, 1H), 3.70–3.68 (m, 2H), 3.66–3.62 (m, 1H), 2.88–2.82 (m, 1H), 2.66 (d, *J* = 5.0 Hz, 1H), 1.74–1.68 (m, 1H), 1.25 (dd, *J* = 7.5, 1.5 Hz, 3H) 0.89–0.88 (m, 18H), 0.05–0.03 (m, 12H).

¹³C NMR (125 MHz, CDCl₃): δ 155.4, 130.0, 127.6, 125.0, 120.1, 117.1, 92.6, 78.8, 64.3, 61.2, 60.7, 48.1, 25.9, 24.2, 18.3, 18.2, -5.4.

HRMS [ESI]: calcd for C₂₆H₄₅O₄Si₂ [M-H]⁻ 477.2851, found 477.2856.

((2*S*,3'*S*,4'*R*)-3'-Methyl-4',5'-dihydro-3'H-spiro[chromene-2,2'-furan]-4'-yl)methanol (16a**)**



To a stirred solution of benzyl alcohol **15** (47.8 mg, 0.100 mmol) in THF (1 mL) was added *p*-TsOH·H₂O (95.1 mg, 0.500 mmol, 5.00 eq) at room temperature under argon. After being stirred for another 5 h at the same temperature, the reaction mixture was quenched with H₂O (4 mL). The immiscible mixture was extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (Heptane/EtOAc = 1/3) to give **16a** (16.8 mg, 67%) as a colorless oil.

$[\alpha]_D^{23.2} -15$ (*c* 0.57, CHCl₃)

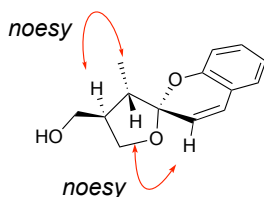
IR (CHCl₃) 3629, 3013, 2965, 2934, 1644, 1487, 1457, 1249, 1194, 991, 952 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 7.18 (td, *J* = 8.0, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.92 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.91 (td, *J* = 8.0, 1.5 Hz, 1H), 6.76 (d, *J* = 9.5 Hz 1H), 5.64 (d, *J* = 9.5 Hz, 1H), 4.26 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.85 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.78 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.69 (dd, *J* = 10.5, 6.5 Hz, 1H), 2.66–2.58 (m, 1H), 2.02–1.94 (m, 1H), 1.10 (d, *J* = 6.5 Hz, 3H).

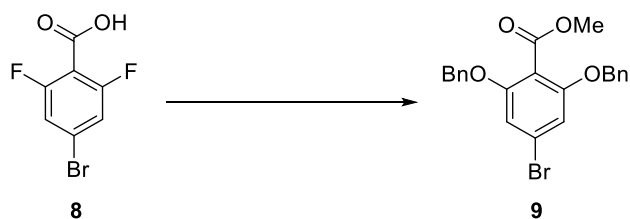
¹³C NMR (125 MHz, CDCl₃): δ 152.0, 129.3, 128.4, 126.9, 121.6, 121.0, 120.0, 116.3, 106.9, 70.1, 63.7, 46.7, 46.2, 12.6.

HRMS [ESI]: calcd for C₁₄H₁₇O₃ [M+H]⁺ 233.1172, found 233.1170.

The NOESY correlation of **16a**



Methyl 2,6-bis(benzyloxy)-4-bromobenzoate (**9**)



To a stirred DMF (540 mL) were added NaH (20.3 g, 508 mmol, 4.00 eq, used as 60% purity in mineral oil without washing) portionwisely and BnOH (39.3 mL, 381 mmol, 3.00 eq) dropwisely at 0 °C under argon. After the reaction mixture was stirred for 30 min at the same temperature, a solution of aryl bromide **8** (30.0 g, 127 mmol) in DMF (60 mL) was added dropwisely to the mixture at 0 °C. The reaction mixture was warmed to 40 °C over 1 h. After being stirred for another 2 h at the same temperature, the reaction mixture was cooled to 0 °C, and MeI (39.6 mL, 636 mmol, 5.00 eq) was added dropwisely at the same temperature. The reaction mixture was allowed to warm to room temperature over 1 h. After being stirred for additional 2 h at the same temperature, H₂O (1500 mL) was added to the reaction mixture over 1 h and stirred for another 1 h. The slurry was filtered, and the residue was washed with H₂O (300 mL) and dried at 40 °C in vacuo over 12 h to give **9** (51.4 g, 95%) as white crystals.

mp: 120–121 °C

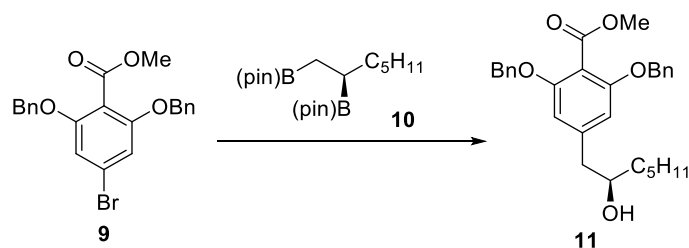
IR (CHCl₃) 3031, 3014, 2953, 2927, 1730, 1584, 1420, 1308, 1268, 1119, 1085, 697, 443, 410 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 7.43–7.34 (m, 8H), 7.34–7.26 (m, 2H), 6.77 (s, 2H), 5.08 (s, 4H), 3.86 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 166.0, 156.9, 136.0, 128.6, 128.0, 126.9, 124.4, 113.4, 109.7, 70.8, 52.4.

HRMS [ESI]: calcd for C₂₂H₂₀O₄Br [M+H]⁺ 427.0539, found 427.0537.

Methyl (*R*)-2,6-bis(benzyloxy)-4-(2-hydroxyheptyl)benzoate (**11**)



Referring to the experimental procedure reported by Morken ²⁾, asymmetric diboration/Suzuki-Miyaura coupling /oxidation cascade reaction were performed.

A solution of B₂(pin)₂ (18.0 g, 70.9 mmol, 1.00 eq), Pt(dba)₃ (637 mg, 0.709 mmol, 1.00 mol%) and (*S,S*)-3,5-di-*iso*-propylphenyl-TADDOLPPH (773 mg, 0.851 mmol, 1.20 mol%) in anhydrous THF (180 mL) was warmed to 70 °C and stirred for 30 min under argon. 1-Heptene (9.94 mL, 70.9 mmol, 1.00 eq) was added to the reaction mixture, and the reaction mixture was stirred 3 h at the same temperature. The reaction mixture was cooled to room temperature and the crude **10** was used for next reaction without further purification.

Aryl bromide **9** (27.3 g, 63.8 mmol, 0.900 eq), Pd(OAc)₂ (796 mg, 3.54 mmol, 5.00 mol%), RuPhos (1.65 g, 3.54 mmol, 5.00 mol%), KOH (11.9 g, 213 mmol, 3.00 eq) and H₂O (18 mL) were added to the reaction mixture containing **10**. The reaction mixture was warmed to 70 °C and stirred for 3 h to consume aryl bromide. The reaction mixture was cooled to 0 °C, and H₂O (72 mL) and NaBO₃ (43.6 g, 284 mmol, 4.00 eq) were added portionwisely to the reaction mixture. After being stirred at 0 °C to room temperature for 3 h, the reaction mixture was diluted with MTBE (360 mL) and quenched with saturated aqueous Na₂S₂O₃ (180 mL) at the same temperature. After all the oxidants were quenched, the immiscible mixture was separated. The aqueous layer was extracted with MTBE (180 mL). The combined organic layers were washed with brine (90 mL), dried over MgSO₄, filtered, and concentrated. The residue was divided into two portions, and each was purified by silica gel column chromatography (column size: 3 L, heptane/EtOAc = 85/15 to 70/30). The both fractions containing the desired product were combined and re-purified by same procedure (column size: L) to give **11** (23.7 g, 80% based on **9**) as a brownish amorphous.

$[\alpha]_D^{23.3} -12.2$ (*c* 0.600, CHCl₃)

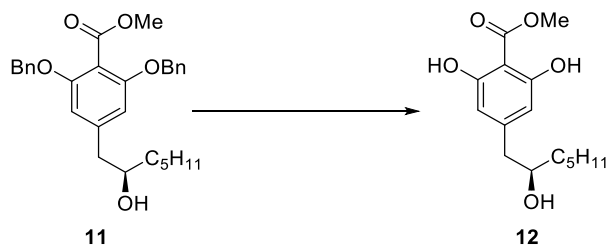
IR (CHCl₃) 3588, 3013, 2932, 1730, 1608, 1584, 1271, 1250, 1121, 1093, 780, 756, 741, 425, 405 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 7.40–7.34 (m, 8H), 7.31–7.27 (m, 2H), 6.45 (s, 2H), 5.11 (s, 4H), 3.88 (s, 3H), 3.74–3.66 (m, 1H), 2.72 (dd, *J* = 13.5, 4.1 Hz, 1H), 2.56 (dd, *J* = 13.5, 8.3 Hz, 1H), 1.48–1.37 (m, 4H), 1.35–1.22 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 166.8, 156.5, 142.4, 136.7, 128.5, 127.8, 126.9, 112.6, 107.1, 72.5, 70.5, 52.3, 44.7, 36.7, 31.8, 25.4, 22.7, 14.1.

HRMS [ESI]: calcd for C₂₉H₃₅O₅ [M+H]⁺ 463.2479, found 463.2479.

Methyl (*R*)-2,6-dihydroxy-4-(2-hydroxyheptyl)benzoate (**12**)



To a stirred solution of bis-benzyl ether **11** (23.0 g, 49.7 mmol) in EtOH (460 mL) was added Pd(OH)₂ (2.3 g, 10 wt%, wetted with ca. 50% water). The reaction mixture was stirred at room temperature under hydrogen atmosphere for 3 h and filtered through a pad of Celite. The residue was washed with EtOH (230 mL), and the filtrate and washings were concentrated. The residue was purified by silica gel column chromatography (column size: 3 L, heptane/EtOAc = 60/40 to 30/70) to give **12** (13.2 g, 94%) as white crystals. The spectroscopic data of **12** were in good agreement with those reported in the literature³⁾.

mp: 55–57 °C

$[\alpha]_{\text{D}}^{25.4} -15.0$ (*c* 1.00, CHCl₃, *ee* = 92%) {lit.³⁾ $[\alpha]_{\text{D}}^{23} -16.8$ (*c* 1.03, CHCl₃, *ee* = 95%)}

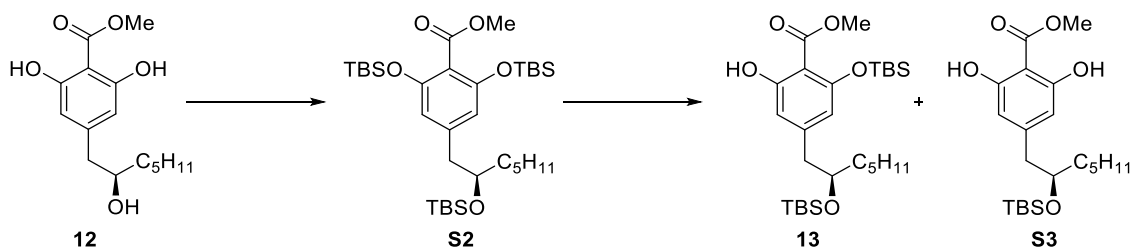
IR (CHCl₃) 3597, 3455, 3174, 3012, 2360, 1679, 1644, 1571, 1469, 1240, 1211, 1195, 1095, 758, 408 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 9.62 (brs, 2H), 6.37 (s, 2H), 4.07 (s, 3H), 3.87–3.80 (m, 1H), 2.71 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.56 (dd, *J* = 13.5, 8.4 Hz, 1H), 1.53–1.43 (m, 3H), 1.43–1.23 (m, 3H), 0.89 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 169.8, 160.8, 149.1, 109.2, 98.3, 72.1, 52.8, 44.4, 37.0, 31.8, 25.4, 22.6, 14.0.

HRMS [ESI]: calcd for C₁₅H₂₃O₅ [M+H]⁺ 283.1540, found 283.1540.

Methyl (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(2-((*tert*-butyldimethylsilyl)oxy)heptyl)-6-hydroxybenzoate (13**)**



Following the experimental procedure reported by Fürstner⁴, triol **12** was protected with TBS group, and then tris-TBS compound **S2** was chemoselectively deprotected to give phenol **13**.

To a stirred solution of triol **12** (12.0 g, 42.5 mmol) in DMF (240 mL) were added TBSCl (43.2 g 170 mmol, 4.00 eq) and imidazole (21.4 g, 255 mmol, 6.00 eq) at room temperature under argon. After being stirred for 2 h at the same temperature, the reaction mixture was diluted with MTBE (240 mL) and quenched with H₂O (240 mL) at 0 °C. The immiscible mixture was separated, and the aqueous layer was extracted with MTBE (240 mL). The combined organic layers were washed with H₂O (240 mL) and brine (120 mL), dried over MgSO₄, filtered, and concentrated. The residue was azeotroped with toluene (3 × 120 mL) to remove TBSOH and used for the subsequent reaction without further purification.

To a stirred solution of crude **S2** (42.5 mmol) in MeOH (530 mL) was added K₂CO₃ (6.46 g, 46.8 mmol, 1.10 eq) at room temperature. After being stirred for 2 h at the same temperature, the reaction mixture was diluted with MTBE (265 mL) and quenched with saturated aqueous NH₄Cl (265 mL). The immiscible mixture was separated, and the aqueous layer was extracted with MTBE (265 mL). The combined organic layers were washed with brine (132 mL), dried over MgSO₄, filtered, and concentrated. The residue was divided into two portions, and each was purified by silica gel column chromatography (column size: 3 L, heptane/toluene = 90/10 to 50/50) to give **13** (16.9 g, 78%) as a colorless oil and over-reacted **S3** (2.11 g, 13%) as a colorless oil.

13

$[\alpha]_D^{25.4} -9.71$ (*c* 1.00, CHCl₃)

IR (CHCl₃) 3732, 3565, 2955, 2931, 2859, 1656, 1618, 1441, 1428, 1256, 1204, 1092, 838, 420, 412 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 11.3 (s, 1H), 6.43 (d, *J* = 1.5 Hz, 1H), 6.18 (d, *J* = 1.5 Hz, 1H), 3.90 (s, 3H), 3.85–3.80 (m, 1H), 2.63 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.58 (dd, *J* = 13.0, 6.5 Hz, 1H), 1.42–1.35 (m, 3H), 1.32–1.19 (m, 5H), 1.01 (s, 9H), 0.87 (s, 9H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.01 (s, 3H), –0.07 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 171.6, 163.0, 156.6, 147.5, 113.1, 111.4, 103.8, 73.3, 51.9, 44.4, 36.8, 31.9, 25.9, 25.7, 25.0, 22.6, 18.3, 18.1, 14.0, –4.2, –4.3, –4.7, –4.7.

HRMS [ESI]: calcd for C₂₇H₅₁O₅Si₂ [M+H]⁺ 511.3270, found 511.3274.

S3

$[\alpha]_{\text{D}}^{25.4} -11.6$ (*c* 1.00, CHCl₃)

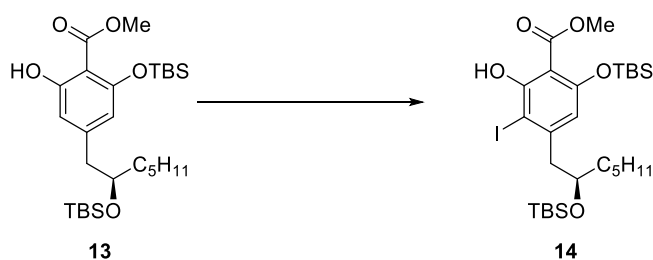
IR (CHCl₃) 3457, 2958, 2931, 2858, 1676, 1645, 1571, 1470, 1252, 1219, 1193, 1095, 837, 710, 472, 407 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 9.59 (brs, 2H), 6.34 (s, 2H), 4.06 (s, 3H), 3.85–3.81 (m, 1H), 2.61 (d, *J* = 6.5 Hz, 2H), 1.45–1.35 (m, 3H), 1.33–1.20 (m, 5H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.86 (s, 9H), -0.02 (s, 3H), -0.12 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 169.9, 160.4, 149.9, 109.7, 97.9, 73.1, 52.7, 44.4, 37.1, 31.9, 25.9, 24.9, 22.6, 18.1, 14.0, -4.7, -4.8.

HRMS [ESI]: calcd for C₂₁H₃₇O₅Si [M+H]⁺ 397.2405, found 397.2406.

Methyl (*R*)-6-((-butyldimethylsilyl)oxy)-4-(2-((*tert*-butyldimethylsilyl)oxy)heptyl)-2-hydroxy-3-iodobenzoate (14**)**



Following the experimental procedure reported by Fürstner ⁴⁾, the ortho position of phenol was iodinated.

To a stirred solution of phenol **13** (15.0 g, 29.4 mmol) in CH₂Cl₂ (150 mL) was added NIS (9.91 g, 44.0 mmol, 1.50 eq) at 0 °C under argon. The reaction mixture was warmed to 40 °C over 1 h. After being stirred for additional 4 h at the same temperature, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous Na₂S₂O₃ (150 mL). The immiscible mixture was extracted with MTBE (2 × 150 mL). The combined organic layers were washed with brine (75 mL), dried over MgSO₄, filtered, and concentrated. The residue was divided into two portions, and each was purified by silica gel column chromatography (column size: 3 L, heptane/EtOAc = 100/0 to 90/10) to give **14** (15.6 g, 83%) as a colorless oil.

$[\alpha]_D^{25.4} -22.6$ (*c* 1.00, CHCl₃)

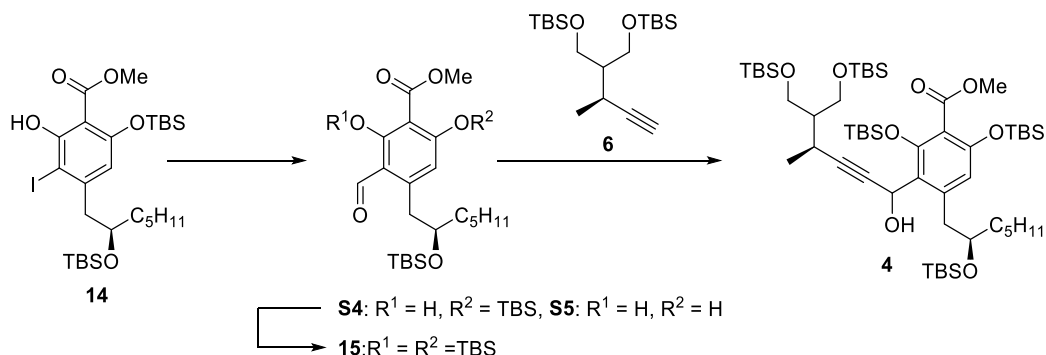
IR (CHCl₃) 3731, 3585, 2956, 2931, 2859, 1655, 1599, 1440, 1396, 1254, 1200, 1100, 840, 768, 757, 445, 421, 409 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 12.4 (s, 1H), 6.35 (s, 1H), 4.09–4.04 (m, 1H) 3.92 (s, 3H), 2.89 (dd, *J* = 13.0, 6.0 Hz, 1H), 2.84 (dd, *J* = 13.0, 7.0 Hz, 1H), 1.51–1.40 (m, 3H), 1.37– 1.23 (m, 5H), 1.00 (s, 9H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), -0.02 (s, 3H), -0.14 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 171.3, 161.5, 156.6, 149.9, 115.3, 103.9, 82.5, 71.3, 52.3, 48.9, 37.4, 32.0, 26.0, 25.6, 24.9, 22.6, 18.3, 18.0, 14.0, -4.1, -4.4, -4.4, -4.7.

HRMS [ESI]: calcd for C₂₇H₅₀O₅ISi₂ [M+H]⁺ 637.2236, found 637.2238.

Methyl 2,6-bis((*tert*-butyldimethylsilyl)oxy)-3-((4*S*)-6-((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-hydroxy-4-methylhex-2-yn-1-yl)-4-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)heptyl)benzoate (4**)**



To a stirred solution of iodephenol **14** (15.0 g, 23.6 mmol) in anhydrous Et₂O (225 mL) were carefully added a solution of MeLi in Et₂O (1.15 M, 24.6 mL, 28.3 mmol, 1.20 eq) and a solution of *t*-BuLi in pentane (1.56 M, 37.8 mL, 58.9 mmol, 2.50 eq) at $-97\text{ }^{\circ}\text{C}$ under argon. After the reaction mixture was stirred for 30 min at the same temperature, anhydrous DMF (18.2 mL, 236 mmol, 10.0 eq) was added to the reaction mixture, and the reaction mixture was allowed to warm to $-30\text{ }^{\circ}\text{C}$ over 2 h. After being stirred for 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH₄Cl (150 mL). The immiscible mixture was extracted with MTBE (2 \times 150 mL). The combined organic layers were washed with brine (75 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (column size: 3L, toluene/EtOAc = 100/0 to 90/10) to give a mixture of compounds **S4** and **S5**. This mixture was used for the subsequent reaction without further purification.

To a stirred solution of the mixture of **S4** and **S5** in DMF (100 mL) were added TBSCl (8.98 g, 35.4 mmol, 1.50 eq) and imidazole (5.95 g, 70.8 mmol, 3.00 eq) at room temperature under argon. After being stirred for 2 h at the same temperature, the reaction mixture was diluted with MTBE (200 mL) and quenched with H₂O (200 mL) at $0\text{ }^{\circ}\text{C}$. The immiscible mixture was separated, and the aqueous layer was extracted with MTBE (200 mL). The combined organic layers were washed with H₂O (200 mL) and brine (100 mL), dried over MgSO₄, filtered, and concentrated. The residue was azeotroped with toluene (3 \times 100 mL) to remove TBSOH, giving tris-TBS protected benzaldehyde **15** containing some impurities (12.0 g, ca. 18.4 mmol). Due to instability of the TBS group, semi-pure **15** was used for the subsequent reaction without further purification.

To a stirred solution of alkyne **6** (7.22 g, 20.2 mmol, 1.10 eq) in anhydrous THF (300 mL) was slowly added a solution of LHMDS in THF (1.3 M, 14.2 mL, 18.4 mmol, 1.00 eq) at $-20\text{ }^{\circ}\text{C}$ under argon. After the reaction mixture was stirred for 30 min at the same temperature, the crude benzaldehyde **15** (12.0 g, ca. 18.4 mmol) in anhydrous THF (60 mL) was added to the reaction mixture at $-20\text{ }^{\circ}\text{C}$. After being stirred for another 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH₄Cl (120 mL). The immiscible mixture was extracted with MTBE (2 \times 120 mL). The combined organic layers were washed with brine (60 mL), dried over MgSO₄, filtered, and concentrated. The residue was divided into two portions, and each was purified by silica gel column chromatography (column size: 3 L, heptane/toluene = 95/5 to 80/20) to give **4** (14.0 g, 59% from iodephenol **14**) as a colorless oil.

$[\alpha]_D^{25.4} -4.98$ (*c* 1.00, CHCl₃)

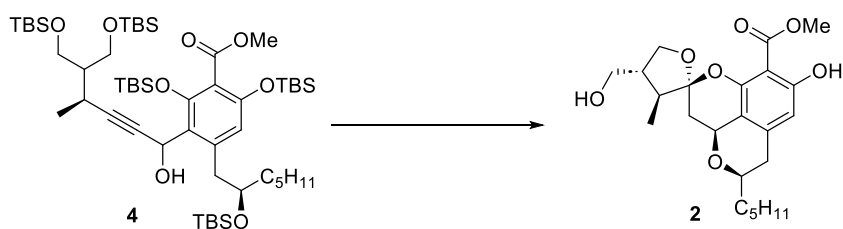
IR (CHCl₃) 2955, 2930, 2858, 2226, 1651, 1613, 1471, 1410, 1254, 1099, 837, 431, 411 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 6.34 (s, 1H), 6.18 (brs, 1H), 4.08 (brs, 1H) 3.89 (s, 3H), 3.76–3.73 (m, 1H), 3.68–3.64 (m, 2H), 3.59–3.56 (m, 1H), 3.47 (brs, 1H), 2.77–2.70 (m, 2H), 1.64–1.60 (m, 1H), 1.53–1.43 (m, 3H), 1.36–1.25 (m, 5H), 1.18 (d, *J* = 7.0 Hz, 3H) 1.01 (s, 9H), 0.93 (s, 9H), 0.89 (s, 9H), 0.89 (t, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 0.24 (s, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.11 (s, 3H) 0.01 (s, 6H), 0.01 (s, 6H), -0.04 (s, 3H), -0.15 (s, 3H), one proton (OH) was not observed.

¹³C NMR: Although the measurements with more than 40,000 scans were performed using more than 200 mg of pure sample, some signals could not be obtained. In addition, DEPT90, DEPT135, HSQC, and HMBC were measured, but all carbon chemical shifts supporting the desired structure could not be established.

HRMS [ESI]: calcd for C₅₃H₁₀₄O₈Si₅Na [M+Na]⁺ 1031.6475, found 1031.6490.

Methyl (2*S*,3*S*,3*a'S*,4*R*,5'*R*)-8'-hydroxy-4-(hydroxymethyl)-3-methyl-5'-pentyl-3',3*a'*,4,5,5',6'-hexahydro-3*H*-spiro[furan-2,2'-pyrano[2,3,4-*de*]chromene]-9'-carboxylate (**2**)**



To a stirred solution of alkyne **4** (4.00 g, 3.96 mmol) in MeOH (80 mL) was added conc. H₂SO₄ (4.22 mL, 20.0 eq) at room temperature under argon. After being stirred for 8 h at the same temperature, the reaction mixture was diluted with MTBE (160 mL) and washed with H₂O (40 mL) and brine (40 mL), successively. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (column size: L, heptane/EtOAc = 70/30 to 40/60) to give **2** (1.35 g, 81%, *dr* = 93:7) as a white amorphous mass. The spectroscopic data of **2** were in good agreement with those reported in the literature^{1, 4-6}.

$[\alpha]_D^{23.2} -121$ (*c* 1.00, CHCl₃)

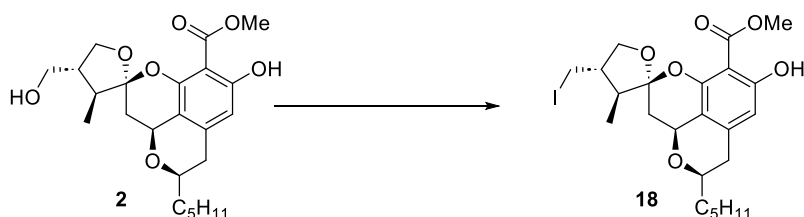
IR (CHCl₃) 3626, 3447, 3010, 2956, 2933, 1731, 1658, 1611, 1584, 1441, 1376, 1251, 1092, 1046, 738, 504, 417 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 11.4 (s, 1H), 6.32 (s, 1H), 4.76 (dd, *J* = 12.0, 5.5 Hz, 1H) 4.22 (t, *J* = 8.5 Hz 1H), 3.92 (s, 3H), 3.87–3.78 (m, 3H), 3.71–3.68 (m, 1H), 2.77 (dd, *J* = 17.5, 4.0 Hz, 1H), 2.61 (dd, *J* = 17.5, 11.0 Hz, 1H), 2.53–2.45 (m, 1H), 2.20 (dd, *J* = 12.0, 5.5 Hz, 1H), 1.97 (t, *J* = 12.0 Hz, 1H), 1.94–1.89 (m, 1H), 1.67–1.29 (m, 9H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 171.6, 162.1, 152.0, 141.4, 112.7, 109.5, 108.5, 100.0, 75.1, 70.1, 68.2, 63.7, 52.1, 46.3, 45.3, 36.4, 34.6, 33.7, 31.8, 25.1, 22.6, 14.1, 12.3.

HRMS [ESI]: calcd for C₂₃H₃₂O₇Na [M+Na]⁺ 443.2040, found 443.2040.

Methyl (2*S*,3*S*,3*a'S*,4*S*,5'*R*)-8'-hydroxy-4-(iodomethyl)-3-methyl-5'-pentyl-3',3*a'*,4,5,5',6'-hexahydro-3*H*-spiro[furan-2,2'-pyrano[2,3,4-*de*]chromene]-9'-carboxylate (**18**)**



Following the experimental procedure reported by Rodríguez¹⁾ and Wang⁵⁾, primary alcohol **2** was iodinated via Appel reaction.

To a stirred solution of alcohol **2** (1.30 g, 3.09 mmol) in anhydrous CH₂Cl₂ (18 mL) were added imidazole (631 mg, 9.27 mmol, 3.00 eq) and PPh₃ (1.62 g, 6.18 mmol, 2.00 eq) at 0 °C under argon. Then I₂ (1.57 g, 6.18 mmol, 2.00 eq) in anhydrous CH₂Cl₂ (8 mL) was added dropwisely to the reaction mixture, and the reaction mixture was allowed to warm to rt over 1 h. After being stirred for another 2 h at the same temperature, the reaction mixture was diluted with MTBE (26 mL) and quenched with saturated aqueous Na₂S₂O₃ (13 mL). The immiscible mixture was separated, and the aqueous layer was extracted with MTBE (26 mL). The combined organic layers were washed with brine (13 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (column size: L, heptane/EtOAc = 100/0 to 80/20) to give **18** (1.36 g, 83%) as white crystals. The spectroscopic data of **18** were in good agreement with those reported in the literature^{1, 4-6)}.

mp: 106–107 °C

[α]_D^{23.3} –83.7 (*c* 1.00, CHCl₃)

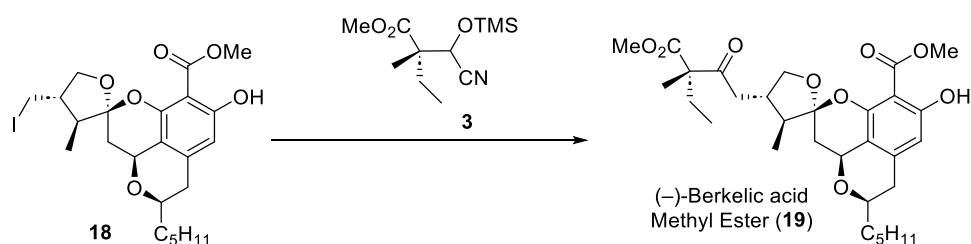
IR (CHCl₃) 3007, 2956, 2934, 2861, 1732, 1658, 1611, 1584, 1441, 1377, 1309, 1252, 1173, 1093, 847, 763, 749, 418, 408 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 11.3 (s, 1H), 6.33 (s, 1H), 4.75 (dd, *J* = 12.0, 5.5 Hz, 1H), 4.22 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.93 (s, 3H), 3.87–3.78 (m, 1H), 3.69 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.43 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.18 (dd, *J* = 10.0, 8.5 Hz, 1H), 2.76 (dd, *J* = 17.5, 4.0 Hz, 1H), 2.60 (dd, *J* = 17.5, 11.0 Hz, 1H), 2.56–2.49 (m, 1H), 2.22 (dd, *J* = 12.0, 5.5 Hz, 1H), 1.93 (dd, *J* = 12.0, 12.0 Hz, 1H), 1.85–1.79 (m, 1H), 1.68–1.29 (m, 8H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 171.5, 162.1, 151.8, 141.4, 112.6, 110.0, 108.7, 99.9, 75.1, 73.6, 68.0, 52.2, 49.6, 46.1, 36.4, 34.5, 33.8, 31.8, 25.1, 22.6, 14.0, 11.7, 7.5.

HRMS [ESI]: calcd for C₂₃H₃₁O₆INa [M+Na]⁺ 553.1058, found 553.1060.

Methyl (2*S*,3*S*,3*a'S*,4*S*,5'*R*)-8'-hydroxy-4-((*S*)-3-(methoxycarbonyl)-3-methyl-2-oxopentyl)-3-methyl-5'-pentyl-3',3*a'*,4,5,5',6'-hexahydro-3*H*-spiro[furan-2,2'-pyrano[2,3,4-*de*]chromene]-9'-carboxylate (**19**)**



Following the experimental procedure reported by Rodríguez¹⁾ and Wang⁵⁾, side-chain was installed via substitution reaction between cyanohydrin **3** and iodide **18**.

To a stirred solution of diisopropylamine (1.62 mL, 11.5 mmol, 4.50 eq) in anhydrous THF (40 mL) was added a solution of *n*-BuLi in THF (1.6 M, 6.36 mL, 10.2 mmol, 4.00 eq) at $-78\text{ }^{\circ}\text{C}$ under argon. After being stirred for 30 min, cyanohydrin **3** (1.24 g, 5.09 mmol, 2.00 eq) in anhydrous THF (10 mL) was added dropwisely to the reaction mixture and stirred for additional 30 min at the same temperature. Then DMPU (1.22 mL, 10.2 mmol, 4.00 eq) and iodide **18** (1.35 g, 2.55 mmol) in THF (10 mL) were added dropwisely, and the reaction mixture was allowed to warm to $-60\text{ }^{\circ}\text{C}$ over 1 h. After being stirred for another 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (27 mL). The mixture was allowed to warm to rt and extracted with MTBE ($2 \times 27\text{ mL}$). The combined organic layers were washed with brine (14 mL), dried over MgSO_4 , filtered, and concentrated.

The residue was dissolved into MeOH (27 mL), and tetrabutylammonium fluoride in THF (1 M, 7.64 mL, 7.64 mmol, 3.00 eq) was added at $0\text{ }^{\circ}\text{C}$ under argon. After being stirred for 3 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (27 mL). The mixture was allowed to warm to rt and extracted with MTBE ($2 \times 27\text{ mL}$). The combined organic layers were washed with brine (14 mL), dried over MgSO_4 , filtered, and concentrated. The residue was purified by silica gel column chromatography (column size: L, heptane/EtOAc = 100/0 to 80/20) to give **19** (1.13 g, 81%) as a colorless amorphous mass. The spectroscopic data of **19** were in good agreement with those reported in the literature^{1, 4-6)}.

$[\alpha]_{\text{D}}^{23.2} -48.3$ (*c* 1.18, CHCl_3)

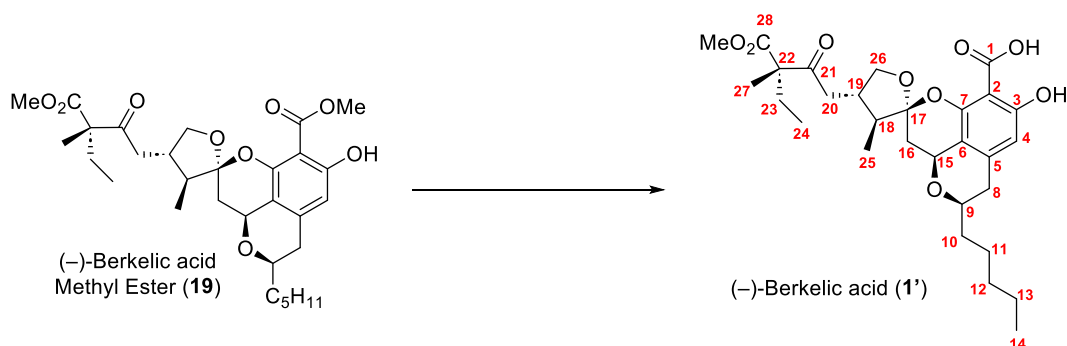
IR (CHCl_3) 3028, 2955, 2935, 2861, 1731, 1712, 1658, 1611, 1441, 1376, 1309, 1251, 1173, 1092, 1003, 773, 764, 740, 456, 435, 411 cm^{-1}

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 11.4 (s, 1H), 6.31 (s, 1H), 4.75 (dd, $J = 12.5, 5.5\text{ Hz}$, 1H), 4.34 (dd, $J = 8.5, 8.5\text{ Hz}$, 1H), 3.95 (s, 3H), 3.83–3.77 (m, 1H), 3.75 (s, 3H), 3.46 (dd, $J = 8.5, 8.5\text{ Hz}$, 1H), 2.81–2.74 (m, 3H), 2.60 (dd, $J = 17.5, 11.0\text{ Hz}$, 1H), 2.46 (dd, $J = 18.5, 10.0\text{ Hz}$, 1H), 2.16 (dd, $J = 12.0, 5.5\text{ Hz}$, 1H), 2.03–1.98 (m, 1H), 1.97–1.93 (m, 1H), 1.88–1.80 (m, 1H), 1.74–1.68 (m, 1H), 1.67–1.62 (m, 1H), 1.56–1.47 (m, 2H), 1.41–1.26 (m, 5H), 1.35 (s, 3H), 1.04 (d, $J = 7.0\text{ Hz}$, 3H), 0.90–0.89 (m, 3H), 0.86 (t, $J = 7.0\text{ Hz}$, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 206.8, 173.5, 171.6, 162.1, 152.0, 141.2, 112.6, 108.7, 108.4, 100.0, 75.1, 72.9, 68.2, 59.9, 52.4, 52.2, 48.3, 41.7, 39.0, 36.4, 34.5, 33.7, 31.8, 27.9, 25.1, 22.6, 18.4, 14.0, 11.6, 8.7.

HRMS [ESI]: calcd for $\text{C}_{30}\text{H}_{43}\text{O}_9$ $[\text{M}+\text{H}]^+$ 547.2900, found 547.2902.

(2*S*,3*S*,3*a'S*,4*S*,5'*R*)-8'-hydroxy-4-((*S*)-3-(methoxycarbonyl)-3-methyl-2-oxopentyl)-3-methyl-5'-pentyl-3',3*a'*,4,5,5',6'-hexahydro-3*H*-spiro[furan-2,2'-pyrano[2,3,4-*de*]chromene]-9'-carboxylic acid ((-)-Berkelic Acid, **1'**)**



To a stirred solution of berkelic acid methyl ester (**19**) (5.00 mg, 9.15 μmol) in toluene (150 μL) was added Bu_2SnO (2.28 mg, 9.15 μmol , 1.00 eq) at room temperature, and the reaction mixture was warmed to 100 $^\circ\text{C}$ under argon. After being stirred for 2 h at 100 $^\circ\text{C}$, the reaction mixture was diluted with MTBE (1 mL) and 1 M HCl (1 mL) and vigorously stirred for 15 min. Then, the immiscible mixture was separated, and the aqueous layer was extracted with MTBE (1 mL). The combined organic layers were washed with brine (1 mL), dried over MgSO_4 , filtered, and concentrated. The residue was purified by preparative thin layer chromatography (heptane/EtOAc/ HCO_2H = 100/30/2) to afford **1'** (3.81 mg, 78%) as a white amorphous mass. The spectroscopic data of **1'** were in good agreement with those reported in the literature^{1, 3-8}.

$[\alpha]_{\text{D}}^{23.3} -99.9$ (*c* 0.402, CHCl_3)

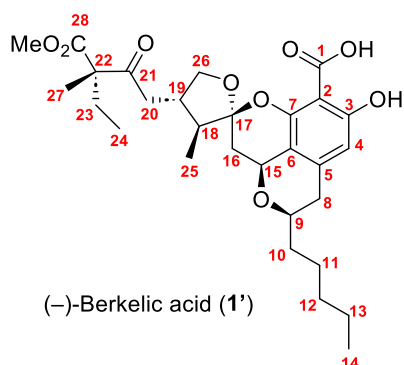
IR (CHCl_3) 3245, 3028, 2931, 2859, 1712, 1693, 1584, 1458, 1436, 1248, 1175, 1072, 1002, 886, 809, 651, 560 cm^{-1}

^1H NMR (500 MHz, CDCl_3): δ 11.84 (s, 1H, OH), 10.97 (brs, 1H, CO_2H), 6.44 (s, 1H, H_4), 4.79 (dd, $J = 12.0, 5.5$ Hz, 1H, H_{15}), 4.46 (t, $J = 8.5$ Hz 1H, H_{26a}), 3.85–3.80 (m, 1H, H_9), 3.76 (s, 3H, CO_2Me), 3.61 (dd, $J = 8.5, 8.5$ Hz, 1H, H_{26b}), 2.87 (dd, $J = 17.5, 3.0$ Hz, 1H, H_{20}), 2.81 (dd, $J = 17.0, 4.0$ Hz, 1H, H_{8a}), 2.62 (dd, $J = 17.0, 11.0$ Hz, 1H, H_{8b}), 2.56–2.49 (m, 1H, H_{19}), 2.45 (dd, $J = 17.5, 11.0$ Hz, 1H, H_{20}), 2.23 (dd, $J = 12.5, 5.5$ Hz, 1H, H_{16a}), 2.08 (dd, $J = 12.5, 12.5$ Hz, 1H, H_{20b}), 2.01–1.94 (m, 1H, H_{23a}), 1.92–1.86 (m, 1H, H_{18}), 1.85–1.79 (m, 1H, H_{23b}), 1.69–1.63 (m, 1H, H_{10a}), 1.56–1.51 (m, 3H, $\text{H}_{10b}, \text{H}_{11}$), 1.41–1.26 (m, 4H, $\text{H}_{12}, \text{H}_{13}$), 1.34 (s, 3H, H_{27}), 1.11 (d, $J = 6.5$ Hz, 3H, H_{25}), 0.91 (t, $J = 7.0$ Hz, 3H, H_{14}), 0.85 (t, $J = 7.5$ Hz, 3H, H_{24}).

^{13}C NMR (125 MHz, CDCl_3): δ 206.0 (C_{21}), 173.4 (C_{28}), 170.5 (C_1), 162.6 (C_3), 149.8 (C_7), 142.2 (C_5), 112.2 (C_6), 112.2 (C_{17}), 110.5 (C_4), 98.7 (C_2), 75.2 (C_9), 73.6 (C_{26}), 67.3 (C_{15}), 59.8 (C_{22}), 52.5 (OMe), 48.3 (C_{18}), 41.6 (C_{20}), 39.4 (C_{19}), 36.3 (C_{10}), 34.4 (C_8), 34.4 (C_{16}), 31.8 (C_{12}), 28.0 (C_{23}), 25.0 (C_{11}), 22.6 (C_{13}), 18.5 (C_{27}), 14.0 (C_{14}), 12.0 (C_{25}), 8.7 (C_{24}).

HRMS [ESI]: calcd for $\text{C}_{29}\text{H}_{41}\text{O}_9$ $[\text{M}+\text{H}]^+$ 533.2745, found 533.2752.

Table S1: Comparison of ^1H NMR spectral data reported by Stierle and co-workers for (-)-berkelic acid in CDCl_3 with compound **1'**.



Position	Natural (-)-berkelic acid ⁷⁾ (500 MHz, Stierle and co-workers)	Synthetic compound 1' (500 MHz)
OH	11.82 (s, 1H)	11.84 (s, 1H)
CO ₂ H	-	10.97 (brs, 1H)
H ₄	6.41 (brs, 1H)	6.44 (s, 1H)
H ₁₅	4.76 (dd, $J = 12.2, 5.7$ Hz, 1H)	4.79 (dd, $J = 12.0, 5.5$ Hz, 1H)
H _{26a}	4.43 (t, $J = 8.8$ Hz, 1H)	4.46 (t, $J = 8.5$ Hz, 1H)
H ₉	3.80 (m, 1H)	3.85–3.80 (m, 1H)
CO ₂ Me	3.73 (s, 3H)	3.76 (s, 3H)
H _{26b}	3.58 (t, $J = 8.8$ Hz, 1H)	3.61 (dd, $J = 8.5, 8.5$ Hz, 1H)
H _{20a}	2.84 (dd, $J = 17.0, 2.5$ Hz, 1H)	2.87 (dd, $J = 17.5, 3.0$ Hz, 1H)
H _{8a}	2.77 (dd, $J = 17.6, 4.0$ Hz, 1H)	2.81 (dd, $J = 17.0, 4.0$ Hz, 1H)
H _{8b}	2.59 (dd, $J = 17.6, 11.0$ Hz, 1H)	2.62 (dd, $J = 17.0, 11.0$ Hz, 1H)
H ₁₉	2.50 (m, 1H)	2.56–2.49 (m, 1H)
H _{20b}	2.42 (dd, $J = 17.0, 10.3$ Hz, 1H)	2.45 (dd, $J = 17.5, 11.0$ Hz, 1H)
H _{16a}	2.20 (dd, $J = 12.2, 5.7$ Hz, 1H)	2.23 (dd, $J = 12.5, 5.5$ Hz, 1H)
H _{16b}	2.05 (t, $J = 12.2$ Hz, 1H)	2.08 (dd, $J = 12.5, 12.5$ Hz, 1H)
H _{23a}	1.93 (m, 1H)	2.01–1.94 (m, 1H)
H ₁₈	1.87 (m, 1H)	1.92–1.86 (m, 1H)
H _{23b}	1.84 (m, 1H)	1.85–1.79 (m, 1H)
H _{10a}	1.61 (m, 1H)	1.69–1.63 (m, 1H)
H _{10b}	1.50 (m, 1H)	1.56–1.51 (m, 3H)
H ₁₁	1.50 (m, 2H)	
H ₁₂	1.30 (m, 4H)	1.41–1.26 (m, 4H)
H ₁₃		
H ₂₇	1.32 (s, 3H)	1.34 (s, 3H)
H ₂₅	1.07 (d, $J = 6.7$ Hz, 3H)	1.11 (d, $J = 6.5$ Hz, 3H)
H ₁₄	0.88 (t, 3H)	0.91 (t, $J = 7.0$ Hz, 3H)
H ₂₄	0.83 (t, $J = 7.7$ Hz, 3H)	0.85 (t, $J = 7.5$ Hz, 3H)

Table S2: Comparison of ^{13}C NMR spectral data reported by Stierle and co-workers for (–)-berkelic acid in CDCl_3 with compound **1'**.

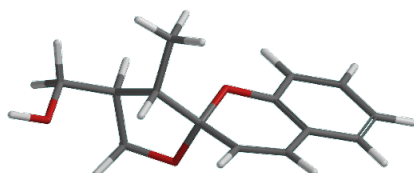
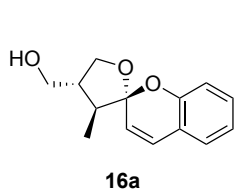
Position	Natural (–)-berkelic acid ⁷⁾ (125 MHz, Stierle and co-workers)	Synthetic compound 1' (125 MHz)
C ₂₁	206.1	206.0
C ₂₈	173.4	173.4
C ₁	170.5	170.5
C ₃	162.5	162.6
C ₇	149.8	149.8
C ₅	142.2	142.2
C ₁₇	112.2	112.2
C ₆	112.1	112.2
C ₄	110.5	110.5
C ₂	98.6	98.7
C ₉	75.2	75.2
C ₂₆	73.5	73.6
C ₁₅	67.2	67.3
C ₂₂	59.7	59.8
OMe	52.5	52.5
C ₁₈	48.2	48.3
C ₂₀	41.6	41.6
C ₁₉	39.3	39.4
C ₁₀	36.2	36.3
C ₈	34.3	34.4
C ₁₆	34.3	34.4
C ₁₂	31.7	31.8
C ₂₃	27.9	28.0
C ₁₁	25.0	25.0
C ₁₃	22.6	22.6
C ₂₇	18.4	18.5
C ₁₄	14.0	14.0
C ₂₅	12.0	12.0
C ₂₄	8.7	8.7

Calculation of the stable conformers

Models were built on Spartan'20. Conformational search with MMFF force field was performed with default settings, and the conformers within 20 kJ/mol from the global minimum conformer were kept. Against these conformers, the following calculation steps were conducted: (i) structural optimizations at the HF/3-21G level in which the conformers were kept within 20 kJ/mol of the global minimum, (ii) energy estimation at the ω B97X-D/6-31G* level in which the conformers were kept within 10 kJ/mol of the global minimum, (iii) structural optimization at ω B97X-D/6-31G* in which the conformers were kept within 5 kJ/mol of the global minimum, and (iv) energy estimation at the ω B97X-V/6-311+G(2df,2p)[6-311G*] level and the calculation of Boltzmann distribution of each isomer based on the obtained energy. The geometry and the energy of these stable conformers are provided as follows.

Results of the Calculation

Cartesian geometries and energy of the most stable conformer of **16a**

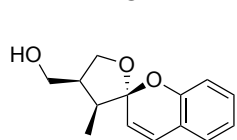


Energy (ω B97X-V/6-311+G(2df,2p)[6-311G*]) = -768.310906 au

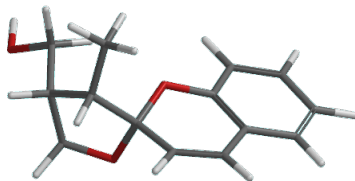
H	0.463481	-2.944050	-4.966239
C	0.354187	-2.476814	-3.992844
C	0.084027	-1.279972	-1.494954
C	0.490594	-3.234950	-2.829337
C	0.074913	-1.120174	-3.897513
C	-0.064019	-0.502935	-2.651817
C	0.356109	-2.642255	-1.579975
H	0.707117	-4.297040	-2.895307
H	-0.038637	-0.519423	-4.796626
H	0.458160	-3.214831	-0.664014
C	-0.376093	0.907950	-2.475989
H	-0.636891	1.496553	-3.352028
C	-0.337087	1.458797	-1.260870
H	-0.546917	2.510646	-1.094561
C	0.084401	0.662807	-0.062048
O	-0.098311	-0.744055	-0.262075
O	1.437641	0.929897	0.191794
C	1.716673	0.774731	1.585121
H	2.437204	-0.038680	1.721436
H	2.159456	1.708708	1.944705
C	-0.636457	1.004117	1.247636
H	-0.655650	2.098674	1.312960

C	0.375695	0.491679	2.280443
H	0.239548	-0.590534	2.396682
C	-2.049083	0.457110	1.375184
H	-2.050795	-0.635556	1.335588
H	-2.683407	0.825332	0.561947
H	-2.500766	0.774261	2.321192
C	0.249977	1.124411	3.657011
H	-0.718642	0.840865	4.097459
H	1.039294	0.726526	4.314665
O	0.357824	2.528846	3.526890
H	0.306453	2.919360	4.405484

Cartesian geometries and energy of the most stable conformer of **16b**



16b

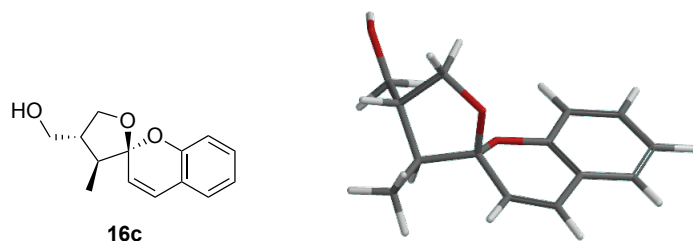


Energy (ω B97X-V/6-311+G(2df,2p)[6-311G*]) = -768.308498 au

H	1.268184	-2.086293	-4.947931
C	0.979678	-1.715342	-3.970218
C	0.252915	-0.765703	-1.458827
C	0.853910	-2.594324	-2.894068
C	0.731722	-0.362264	-3.782837
C	0.365033	0.131805	-2.528686
C	0.489975	-2.124925	-1.638078
H	1.044141	-3.654401	-3.033295
H	0.821415	0.331952	-4.614677
H	0.387192	-2.793487	-0.789696
C	0.067467	1.531545	-2.261550
H	-0.003369	2.218615	-3.100975
C	-0.110137	1.952158	-1.007429
H	-0.316156	2.991443	-0.771345
C	0.061983	1.016895	0.154581
O	-0.156832	-0.345051	-0.234239
O	1.358566	1.170333	0.654135
C	1.393877	0.914316	2.062755
H	2.019655	0.039172	2.262988
H	1.854263	1.784609	2.542713
C	-0.056489	0.697974	2.531039
H	-0.250009	1.265920	3.447155

C	-0.860346	1.283970	1.354297
H	-0.858568	2.374367	1.480738
C	-2.299237	0.819461	1.175925
H	-2.353036	-0.253735	0.979195
H	-2.760913	1.334254	0.326709
H	-2.891109	1.042187	2.069725
C	-0.346433	-0.763824	2.850281
H	-0.123232	-1.389540	1.977007
H	-1.411705	-0.887017	3.096357
O	0.468103	-1.108955	3.958646
H	0.379492	-2.056117	4.109606

Cartesian geometries and energy of the most stable conformer of **16c**

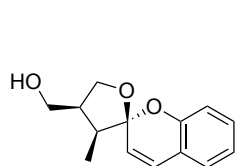


Energy (ω B97X-V/6-311+G(2df,2p)[6-311G*]) = -768.307539au

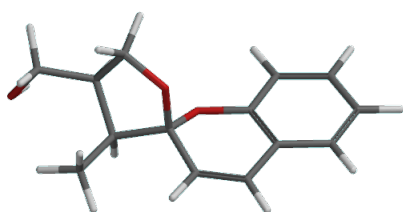
H	-0.910107	1.059068	-5.412352
C	-0.816357	0.804697	-4.361677
C	-0.575557	0.162654	-1.666913
C	-1.863463	1.068975	-3.478477
C	0.346618	0.211033	-3.889203
C	0.483936	-0.118189	-2.538819
C	-1.748496	0.749367	-2.131222
H	-2.776473	1.531821	-3.841499
H	1.167236	-0.004985	-4.569247
H	-2.552259	0.946589	-1.429196
C	1.660093	-0.761778	-1.973476
H	2.426653	-1.130035	-2.650918
C	1.791294	-0.893631	-0.651294
H	2.673996	-1.342517	-0.210910
C	0.767648	-0.309685	0.279988
O	-0.513493	-0.198933	-0.359511
O	1.220338	0.953945	0.668829
C	0.489980	1.370793	1.823641
H	-0.318019	2.051763	1.533822
H	1.186176	1.915418	2.464655

C	0.474380	-1.048606	1.602905
H	-0.285415	-1.815391	1.422687
C	-0.068615	0.093639	2.490337
H	0.320589	-0.001580	3.510141
C	1.716276	1.693826	2.215905
H	1.483749	-2.071269	3.215859
H	2.527500	-0.963954	2.310985
H	2.077072	-2.536810	1.618760
C	-1.586857	0.110686	2.588519
H	-1.938246	-0.849218	2.999752
H	-2.015765	0.226342	1.583454
O	-1.943938	1.188538	3.434873
H	-2.900472	1.295080	3.399604

Cartesian geometries and energy of the most stable conformer of **16d**



16d

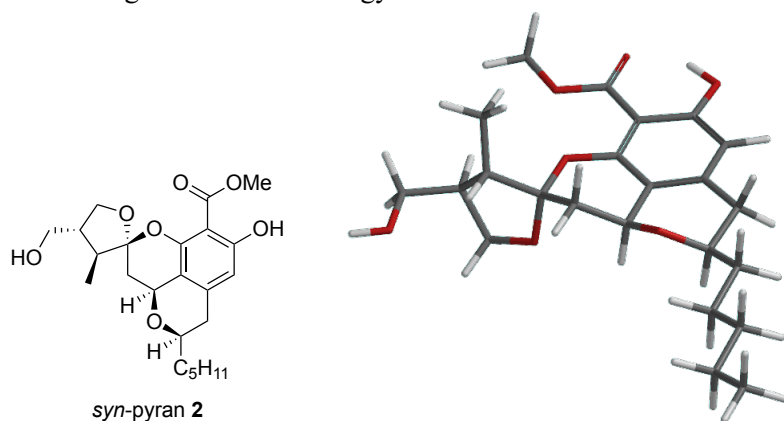


Energy (ω B97X-V/6-311+G(2df,2p)[6-311G*]) = -768.306631au

H	1.330831	-0.013831	-5.667441
C	1.037169	0.102757	-4.629428
C	0.294727	0.402068	-1.966059
C	1.228118	1.321752	-3.977431
C	0.465417	-0.960157	-3.943328
C	0.087189	-0.827250	-2.605245
C	0.857831	1.476631	-2.647090
H	1.673494	2.157703	-4.507967
H	0.306265	-1.912936	-4.442350
H	0.997422	2.416458	-2.122749
C	-0.534762	-1.887575	-1.825200
H	-0.847549	-2.794132	-2.336967
C	-0.709394	-1.745945	-0.508918
H	-1.139689	-2.535015	0.096201
C	-0.199121	-0.526427	0.200869
O	-0.110581	0.597837	-0.684426
O	1.078823	-0.834815	0.703494
C	1.388887	0.028270	1.794149
H	2.239578	0.664905	1.527489

H	1.682971	-0.599873	2.646014
C	-0.986507	0.001609	1.416290
H	-1.805507	0.635302	1.069567
C	0.118075	0.842636	2.093084
H	0.181413	1.796296	1.554132
C	-1.546611	-1.107605	2.303667
H	-1.998700	-0.671541	3.197262
H	-0.766857	-1.812386	2.612577
H	-2.327033	-1.670591	1.783803
C	-0.071341	1.137149	3.574958
H	0.783503	1.725625	3.944119
H	-0.090100	0.206952	4.150361
O	-1.295858	1.784736	3.854956
H	-1.322103	2.601392	3.341606

Cartesian geometries and energy of the most stable conformer of **2**



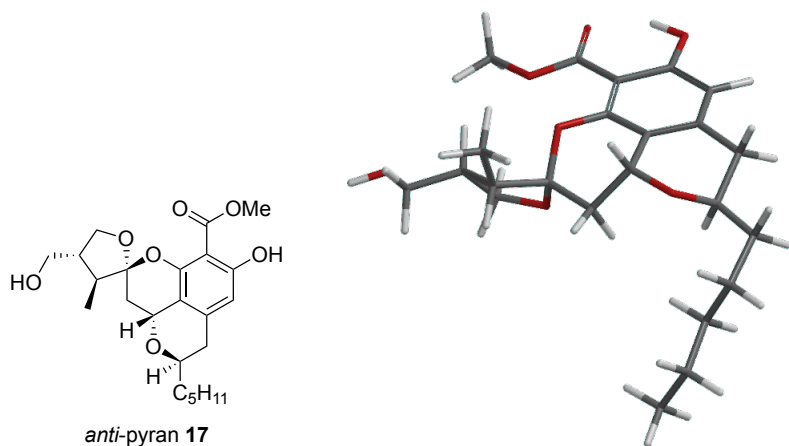
Energy (ω B97X-V/6-311+G(2df,2p)[6-311G*]) = -1421.443543au

C	-3.304906	1.000510	-0.854234
C	-0.800875	1.553732	-2.030006
C	-3.194402	1.861363	-1.982154
C	-2.112054	0.415174	-0.356417
C	-0.880637	0.662097	-0.957367
C	-1.947219	2.136286	-2.543398
H	-1.904921	2.827471	-3.378890
C	-4.642580	0.797727	-0.277898
O	-5.661814	1.302861	-0.748021
O	-4.714588	0.026753	0.808446
O	-4.249101	2.457909	-2.545183
H	-5.048460	2.183834	-2.039746
C	-6.021831	-0.145389	1.351816
H	-6.447302	0.815493	1.650529

H	-5.886322	-0.788807	2.221113
H	-6.685978	-0.617298	0.624211
O	-2.213729	-0.355599	0.744055
C	-1.067957	-1.032570	1.284949
C	0.201232	-0.227668	1.071182
H	1.050346	-0.782231	1.476960
H	0.123963	0.734146	1.589280
C	0.367737	0.006862	-0.417843
H	0.510583	-0.970605	-0.906449
O	1.507804	0.801692	-0.653630
C	1.682657	1.036761	-2.042302
H	1.640144	0.066600	-2.568464
C	0.559957	1.935737	-2.566412
H	0.553674	1.923677	-3.662484
C	-1.448292	-1.368151	2.728307
H	-0.540284	-1.750932	3.208450
O	-0.925723	-2.268387	0.650736
C	-1.812379	-3.218606	1.246475
H	-1.222618	-4.102812	1.503789
H	-2.585281	-3.497014	0.522774
C	-2.404100	-2.549525	2.498948
H	-3.397311	-2.148309	2.264962
C	-2.026914	-0.220773	3.541997
H	-1.308283	0.600541	3.635805
H	-2.273683	-0.555893	4.555523
H	-2.932567	0.169852	3.069447
C	-2.545134	-3.488206	3.685747
H	-3.219402	-4.316845	3.416178
H	-3.011232	-2.944887	4.522830
O	-1.264581	-3.970796	4.042132
H	-1.365738	-4.587319	4.775137
H	0.764941	2.971214	-2.263222
C	3.059295	1.652123	-2.238159
H	3.102540	2.582152	-1.655552
H	3.167272	1.933252	-3.294452
C	4.202039	0.727467	-1.823196
H	4.161697	-0.192334	-2.424127
H	4.050747	0.424787	-0.780659
C	5.576529	1.375913	-1.981122
H	5.614978	2.295243	-1.379290

H	5.717406	1.688942	-3.025852
C	6.728062	0.457833	-1.570947
H	6.691588	-0.459044	-2.174383
H	6.584815	0.144347	-0.528545
C	8.097526	1.117129	-1.724704
H	8.904443	0.440003	-1.426150
H	8.169963	2.018865	-1.105933
H	8.276260	1.413654	-2.764588

Cartesian geometries and energy of the most stable conformer of **2**



Energy (ω B97X-V/6-311+G(2df,2p)[6-311G*]) = -1421.438975au

C	3.207579	0.376053	-0.782367
C	2.330749	0.552214	1.905224
C	4.100114	0.150926	0.303316
C	1.881341	0.723301	-0.456795
C	1.461615	0.844736	0.856660
C	3.646316	0.218099	1.624656
H	4.351413	-0.012899	2.416358
C	3.710455	0.175783	-2.152162
O	4.884845	-0.080781	-2.406663
O	2.801548	0.266534	-3.120201
O	5.386800	-0.163803	0.124277
H	5.551056	-0.196742	-0.844974
C	3.263993	0.014813	-4.447719
H	3.754683	-0.958689	-4.505948
H	3.967451	0.788779	-4.761156
H	2.368470	0.031264	-5.070201
O	0.959607	0.996068	-1.413950
C	-0.306948	0.306180	-1.285249
C	-0.846806	0.356467	0.151833

H	-0.846192	-0.663761	0.546491
H	-1.879150	0.720019	0.159022
C	0.025369	1.241153	1.053770
H	-0.102562	2.286455	0.743097
O	-0.393703	1.200232	2.401351
C	0.256876	0.228839	3.209782
H	0.153380	-0.765886	2.746866
C	1.749583	0.557269	3.295741
H	2.268514	-0.170801	3.928908
C	-1.176301	0.913482	-2.391410
H	-2.181235	0.489587	-2.252125
O	-0.139934	-1.025726	-1.657121
C	-0.125368	-1.118269	-3.086614
H	-0.847569	-1.891175	-3.374161
H	0.867468	-1.423760	-3.422133
C	-0.525095	0.266969	-3.621691
H	0.379660	0.833464	-3.864990
C	-1.257145	2.432638	-2.398132
H	-1.661811	2.808228	-1.451097
H	-1.914393	2.785018	-3.200234
H	-0.266344	2.871707	-2.542889
C	-1.389228	0.202739	-4.862341
H	-1.696138	1.216853	-5.161751
H	-2.303739	-0.376190	-4.651487
O	-0.613299	-0.415034	-5.875001
H	-1.151863	-0.487057	-6.670715
H	1.865947	1.544302	3.761783
C	-0.444318	0.227026	4.560110
H	-0.242710	1.181577	5.062524
H	0.012223	-0.561394	5.173214
C	-1.958565	0.010223	4.470790
H	-2.365936	-0.020685	5.490527
H	-2.412810	0.876352	3.975340
C	-2.367370	-1.260478	3.724529
H	-1.835094	-2.127661	4.143605
H	-2.056398	-1.183469	2.673871
C	-3.873096	-1.520843	3.768607
H	-4.400996	-0.640859	3.377274
H	-4.192922	-1.631092	4.813344
C	-4.281606	-2.758867	2.972520

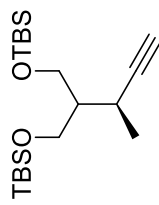
H	-5.362536	-2.926229	3.016714
H	-3.787295	-3.656298	3.360820
H	-4.000580	-2.656901	1.918352

Evaluation of cytotoxicity

Stock cultures of cancer cells (HeLa S3: ATCC CCL-2.2, HCT-116: ATCC CCL-247, MCF-7: ATCC HTB-22) were maintained in Dulbecco's Modified Eagle Medium (nacalai tesque) containing 10% fetal bovine serum (gibco) and 1% antibiotic (penicillin-streptomycin mixed solution, nacalai tesque) at 37 °C under 5% CO₂. For the purpose of the experiment, 2 x 10³ cells suspended in 100 μL of medium per well were plated in 96-well plate and incubated at 37 °C under 5% CO₂. After incubation for 24 h, a solution of compound in DMSO (1 μL, concentration: 0.001, 0.01, 0.1, 1, 10 mM, respectively) was added to the above-mentioned well, resulting in final concentrations of the compound (0.01, 0.1, 1, 10, 100 μM) or solvent control (1% DMSO). After additional incubation for 72 h under the same conditions, 1.4 mg/mL MTT solution in phosphate buffer saline (100 μL) was added to the cell culture. After 4 h, the culture medium was removed, and the precipitated formazan product was dissolved in DMSO (150 μL). Optical density at 570 nm was measured with a TECAN microplate reader (Infinite 200 Pro). All assays were performed in triplicate to confirm reproducibility.

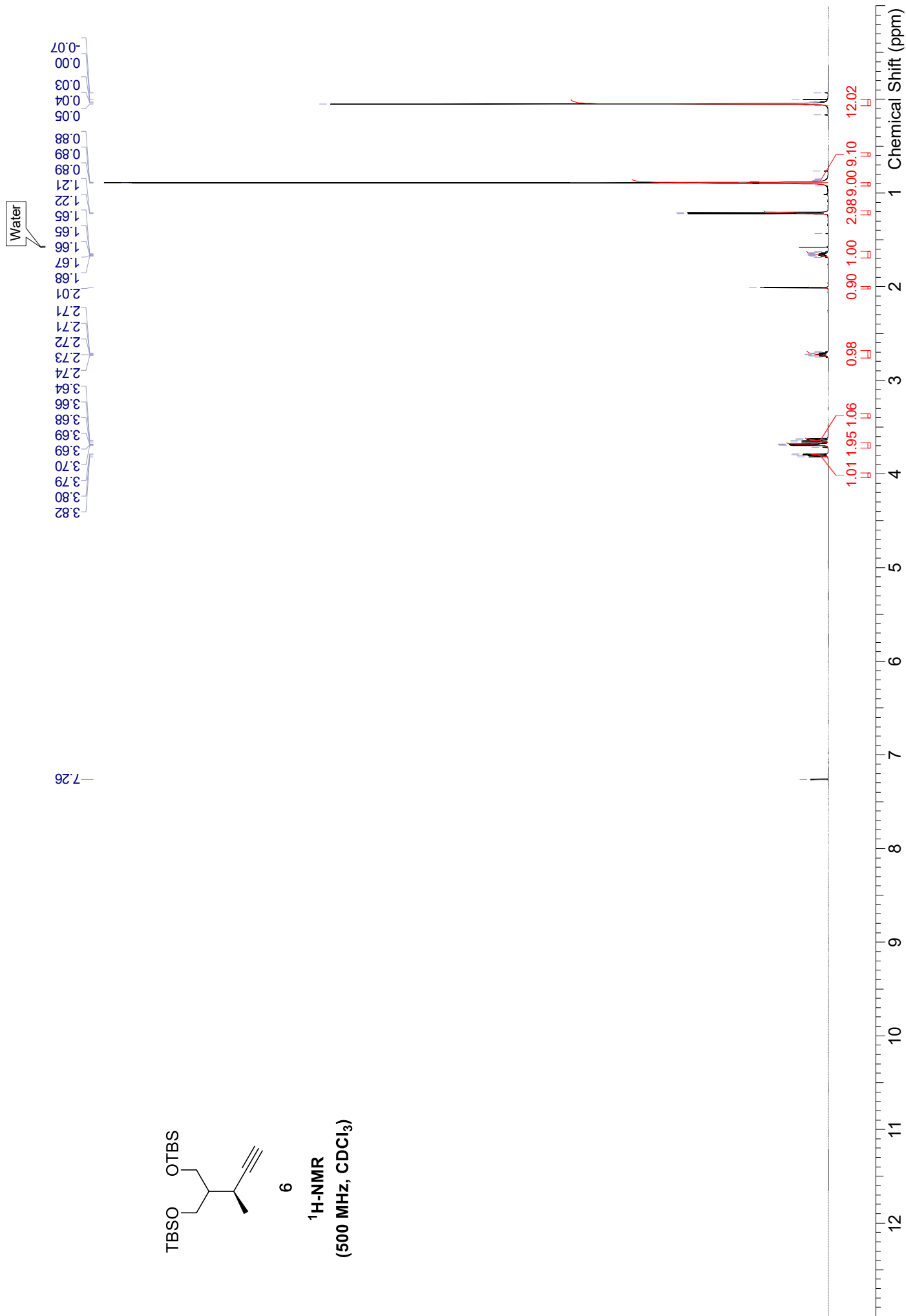
Table S3: Cytotoxicity (IC₅₀: μM) of synthetic **1'** and **19**

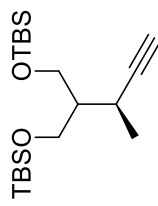
Cell line	1'	19
HeLa S3	46 ± 7.4	32 ± 1.4
MCF-7	41 ± 0.83	> 100
HCT-116	> 100	> 100



6

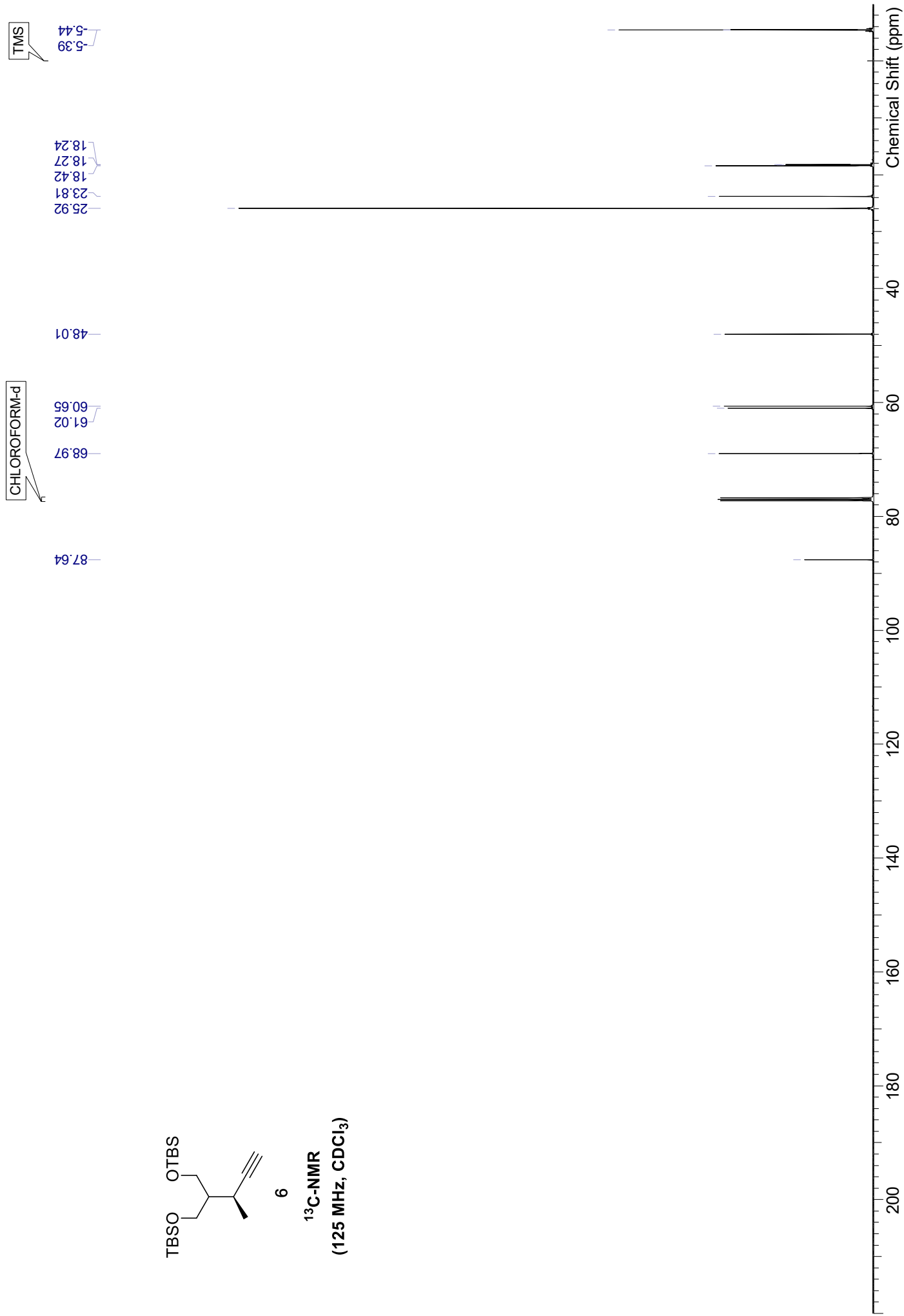
¹H-NMR
(500 MHz, CDCl₃)

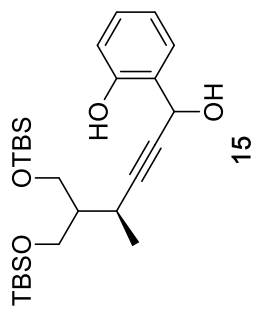




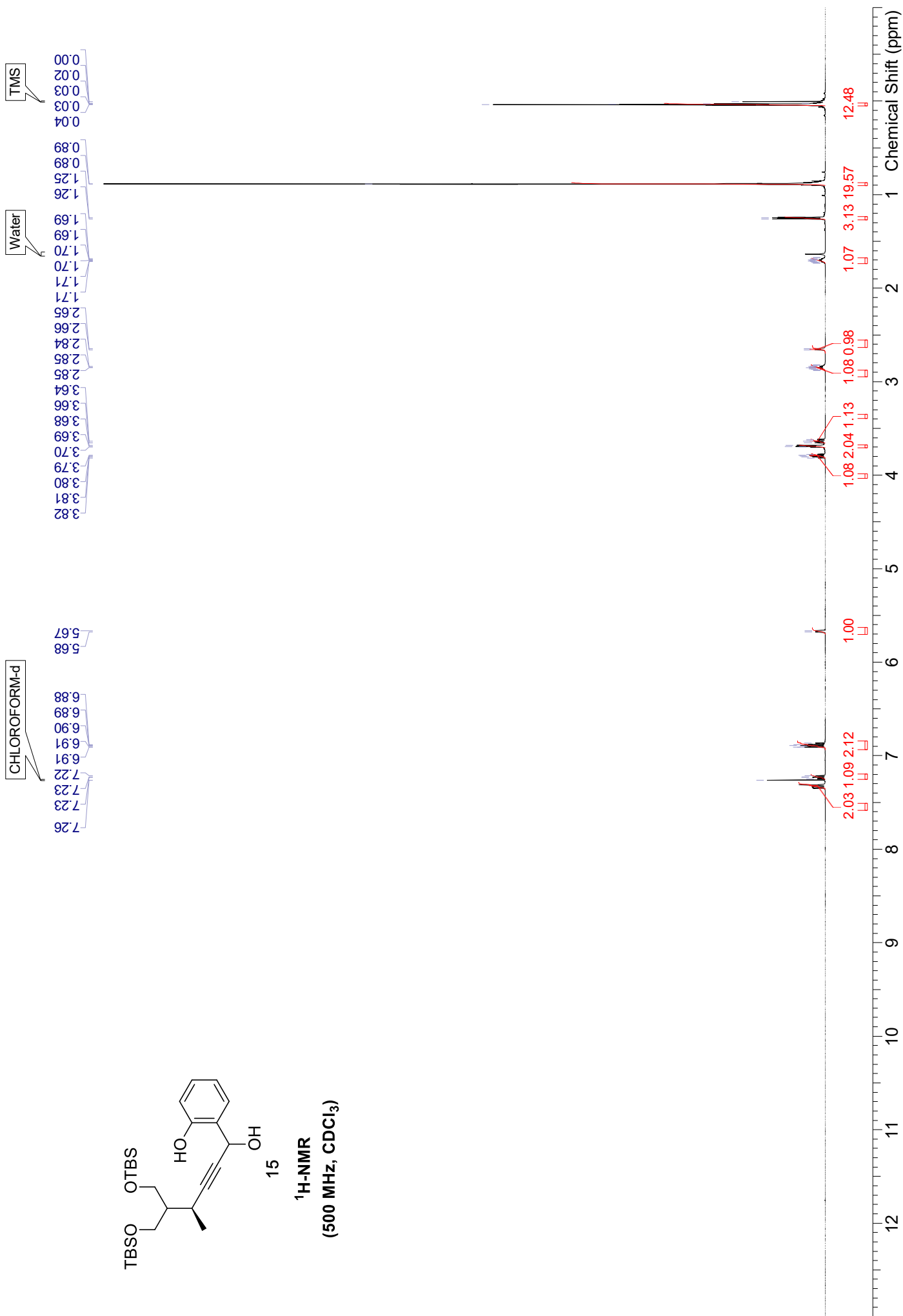
6

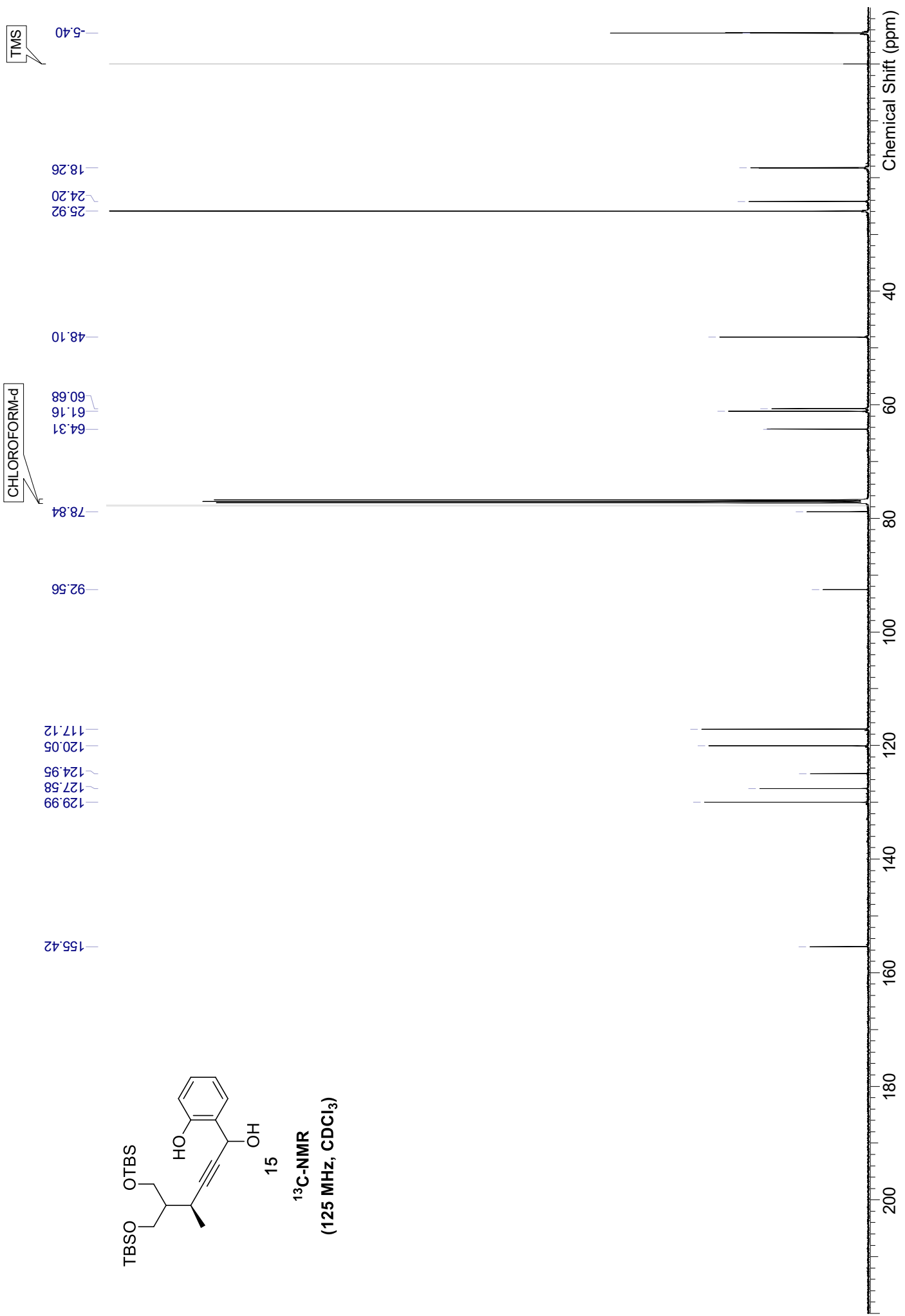
¹³C-NMR
(125 MHz, CDCl₃)

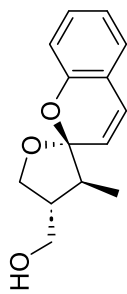




¹H-NMR
(500 MHz, CDCl₃)

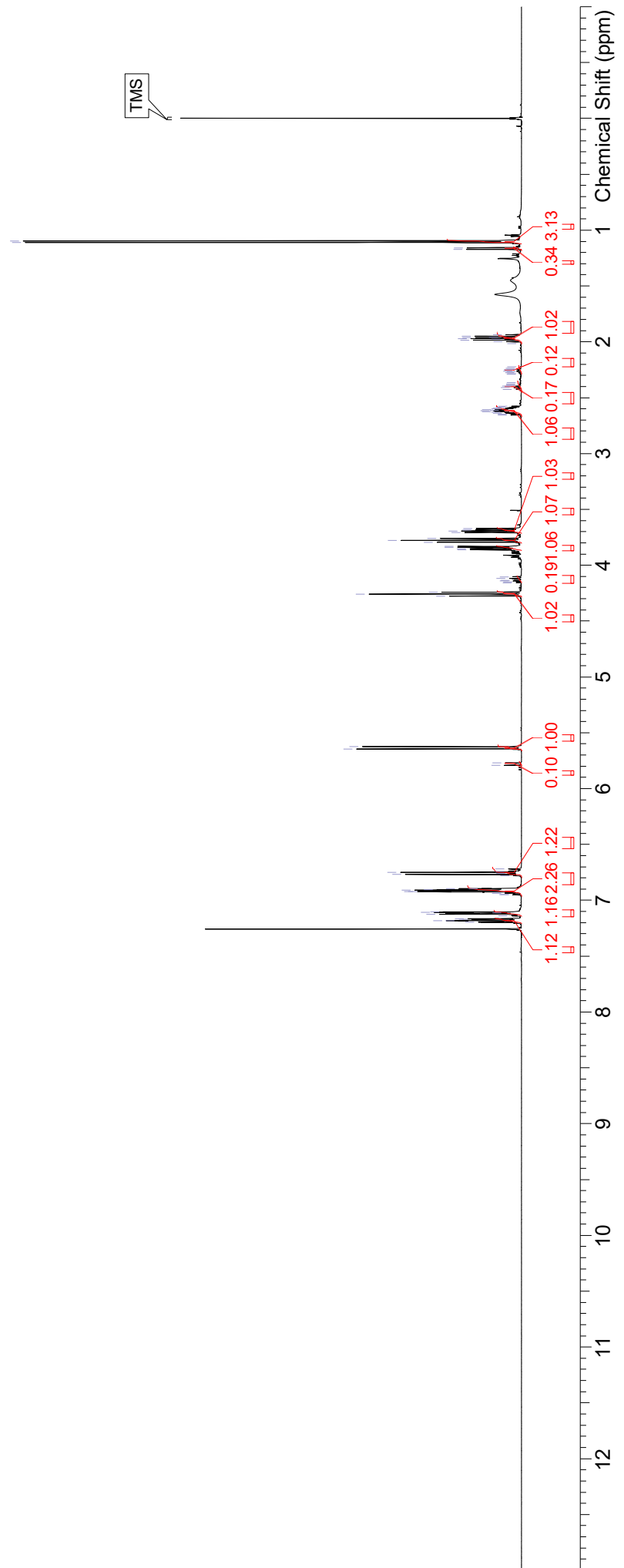
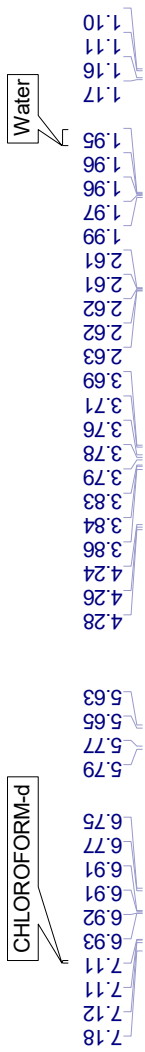


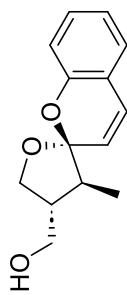




16a

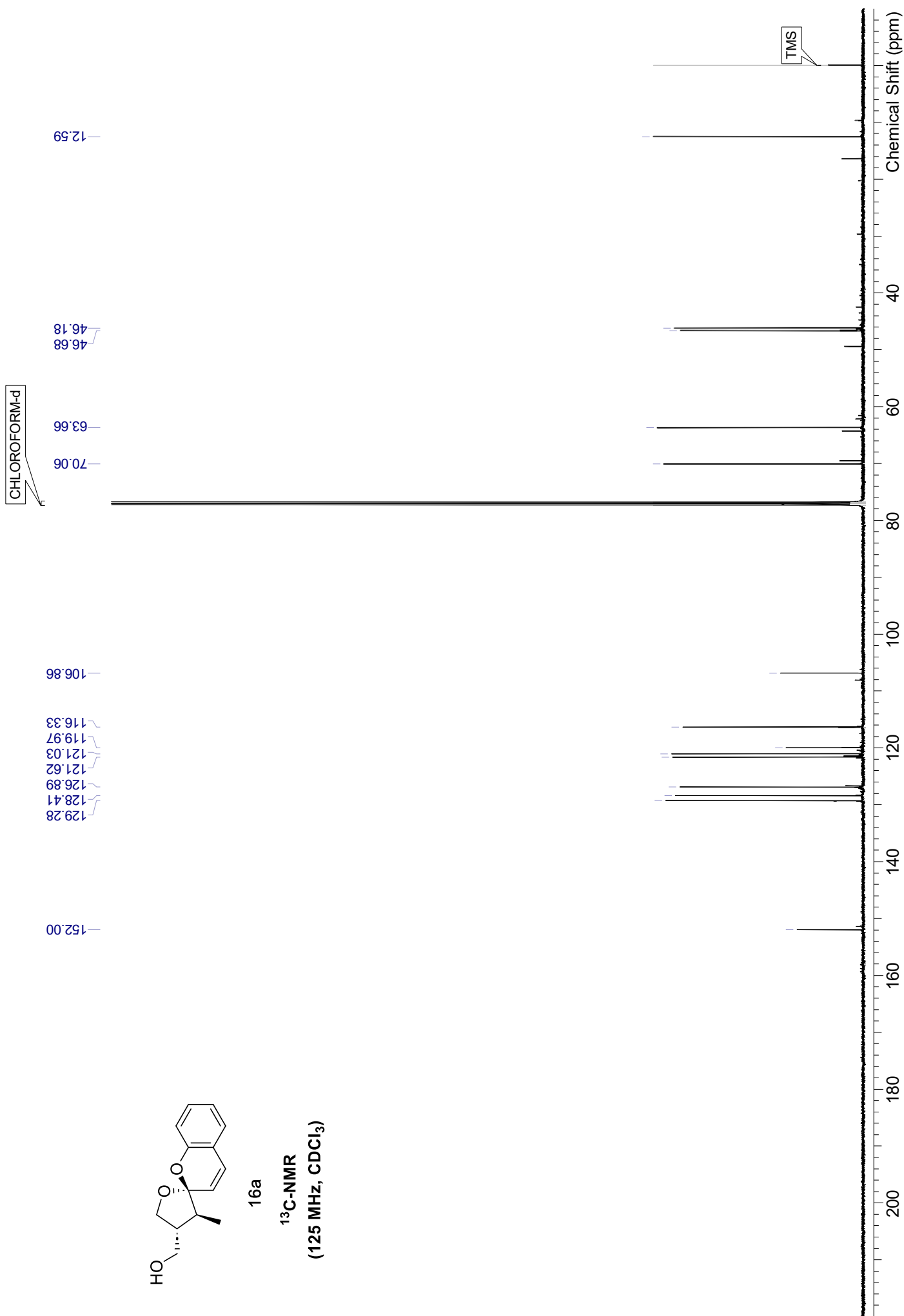
¹H-NMR
(500 MHz, CDCl₃)

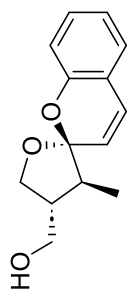




16a

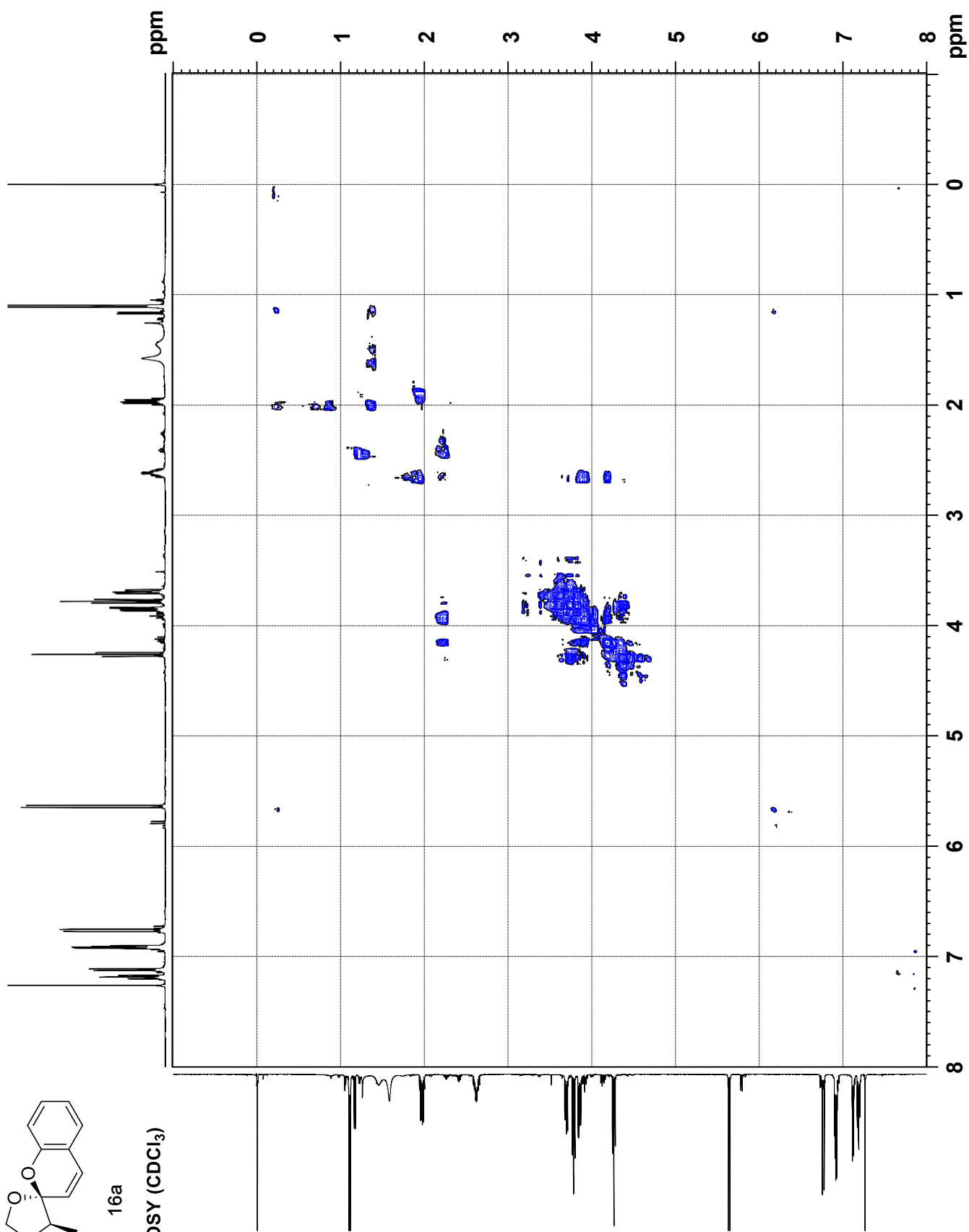
¹³C-NMR
(125 MHz, CDCl₃)

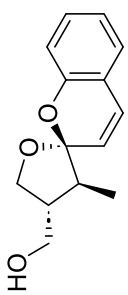




16a

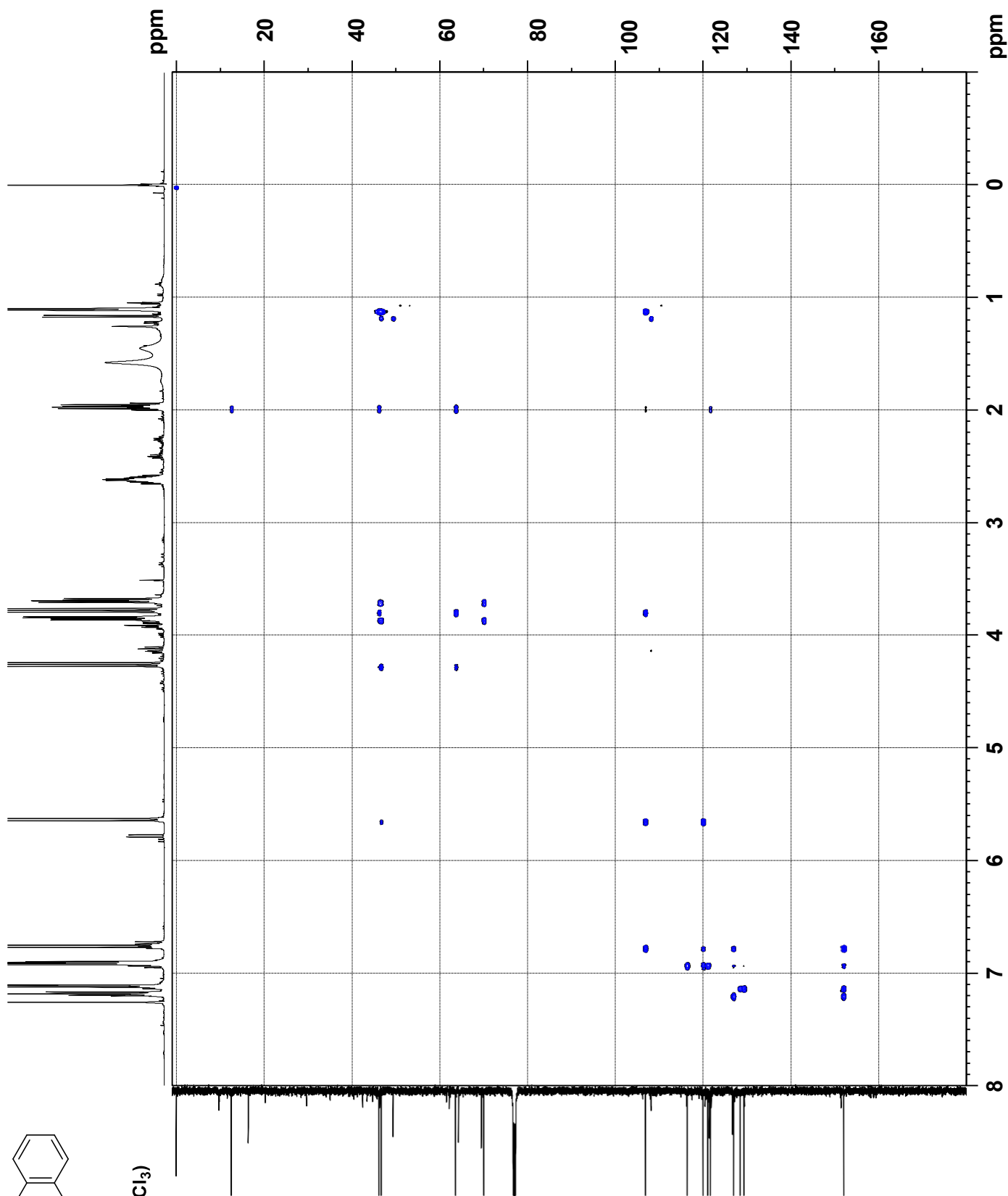
gCOSY (CDCl₃)

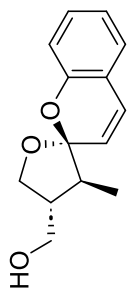




16a

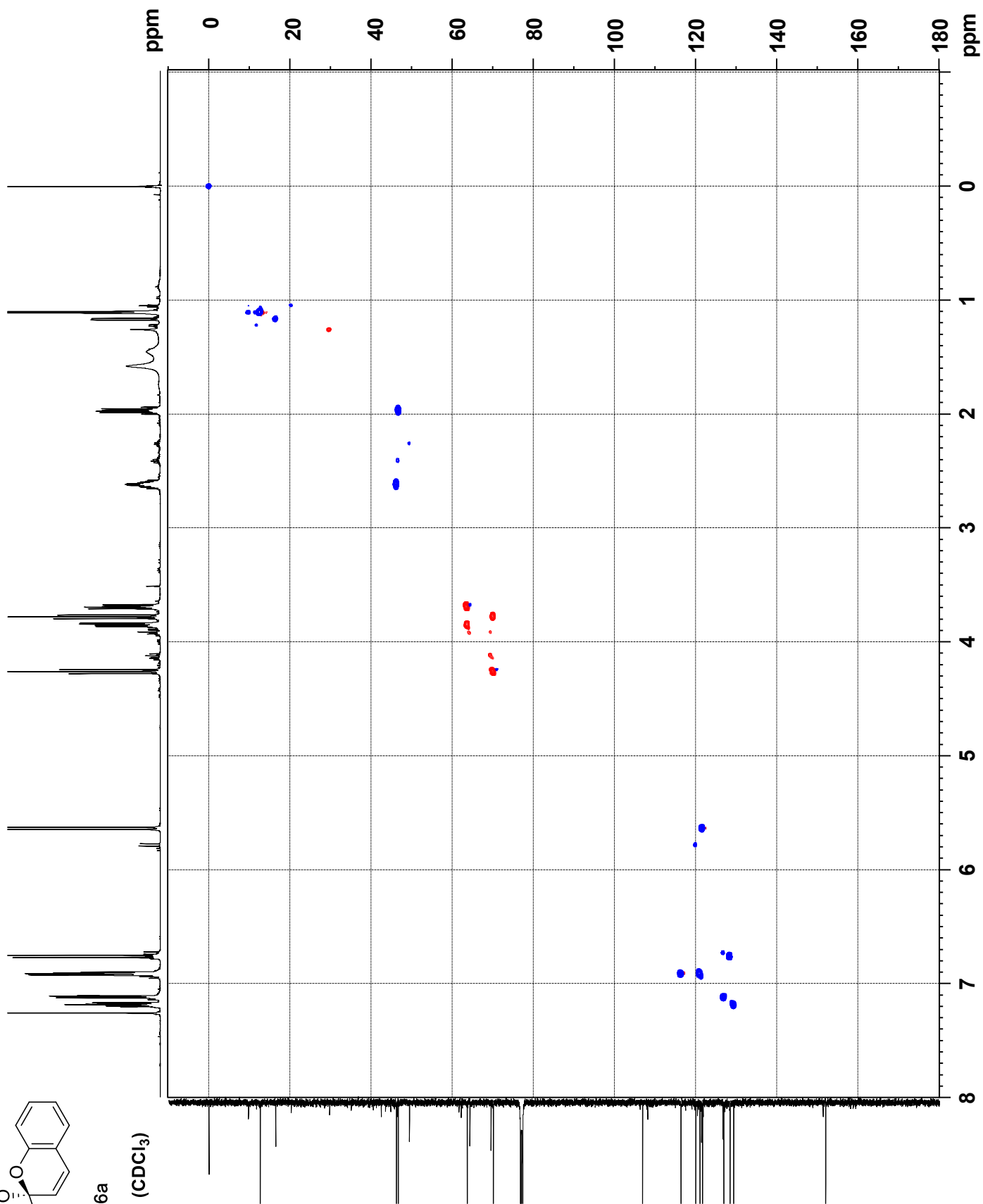
HMBC (CDCl₃)

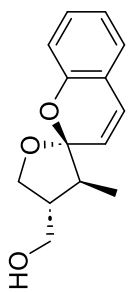




16a

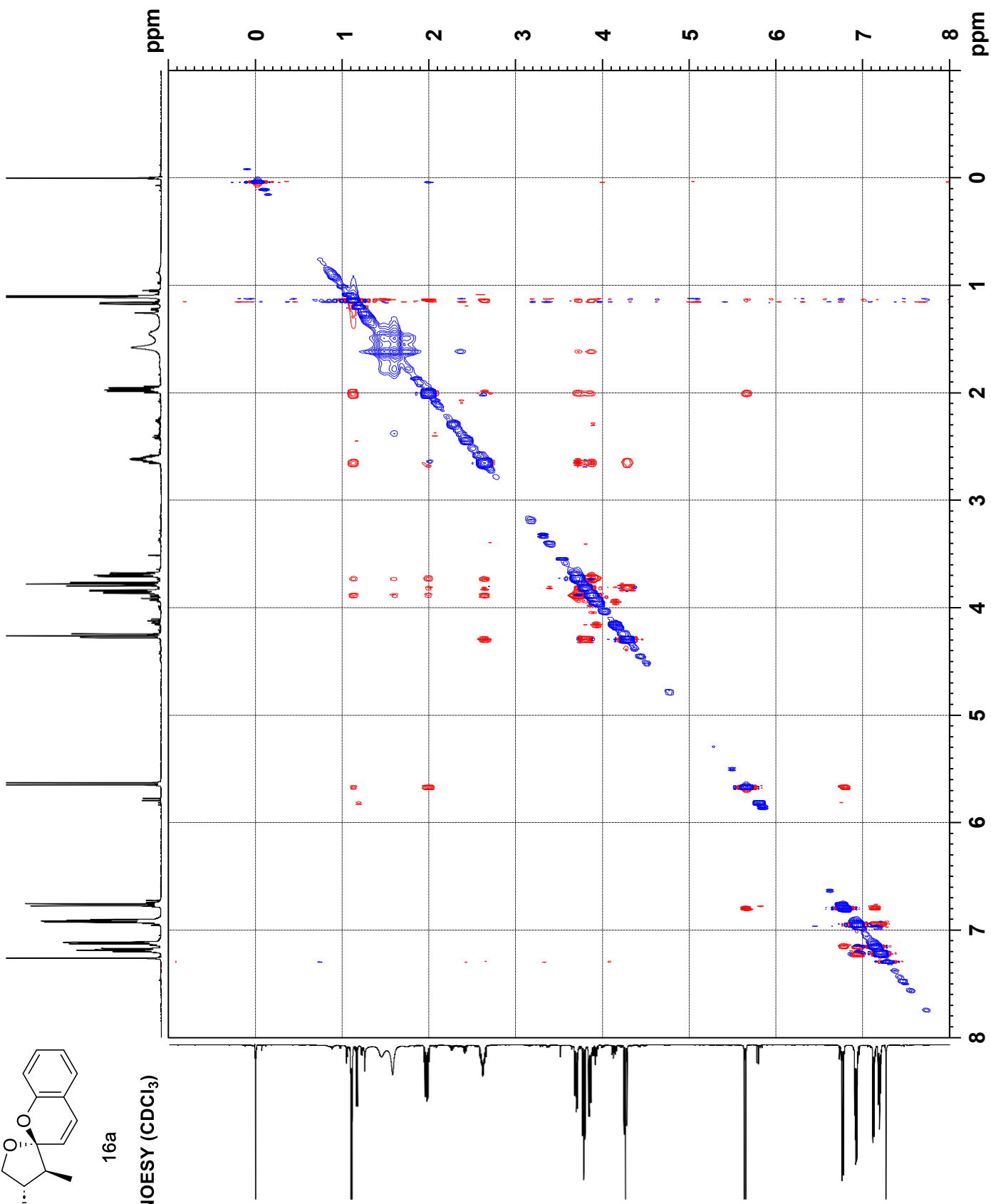
HSQC (CDCl₃)

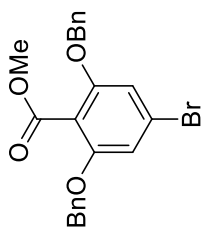




16a

NOESY (CDCl₃)





9

¹H-NMR
(500 MHz, CDCl₃)

CHLOROFORM-d

7.38
7.37
7.36
7.35
7.32
7.31
7.31
7.30
6.77

3.86

5.08

8.28
2.05

2.01

4.04

3.00

TMS

Water

1 Chemical Shift (ppm)

1

2

3

4

5

6

7

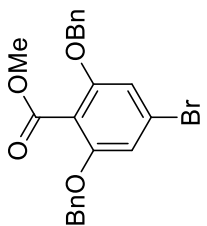
8

9

10

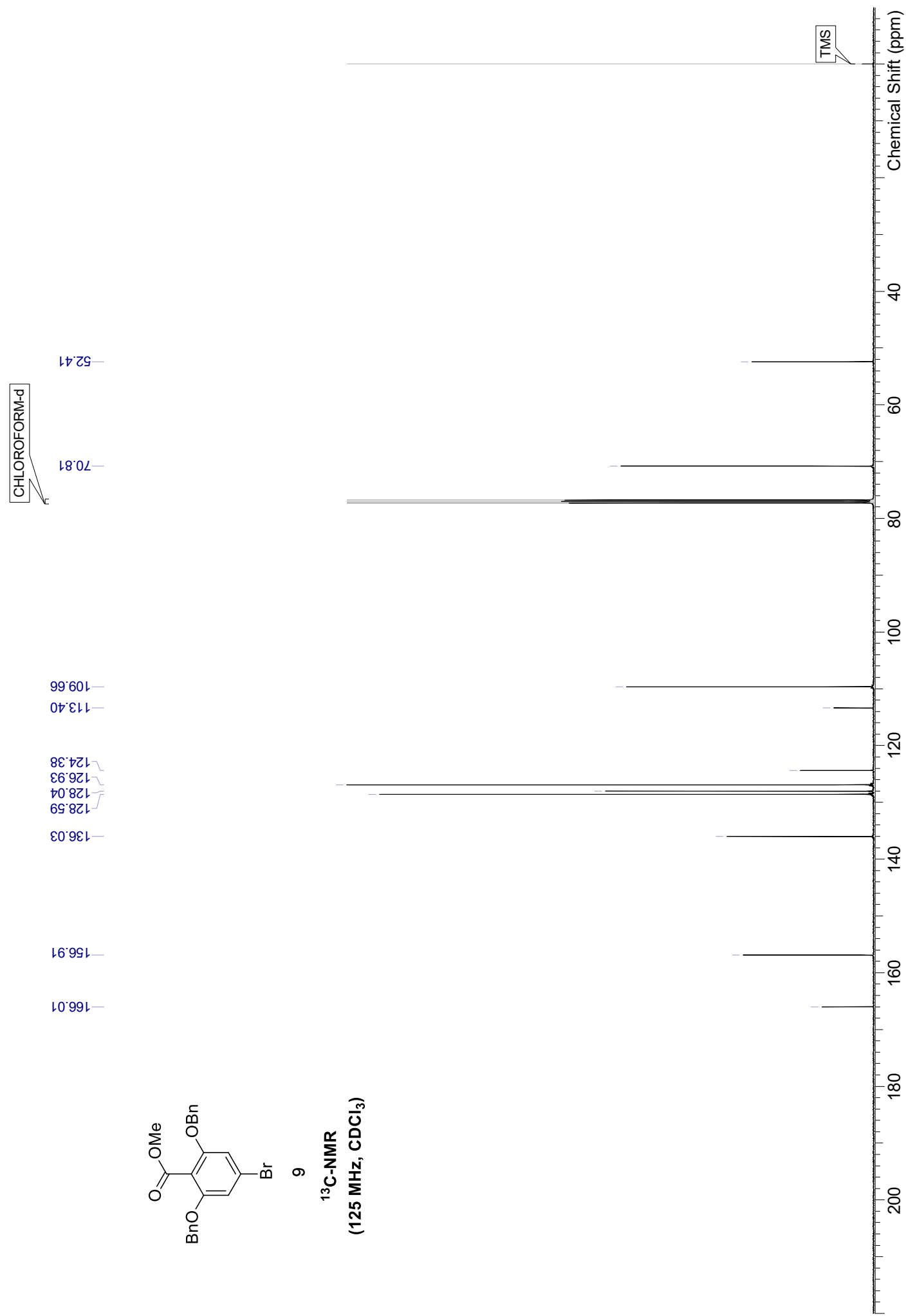
11

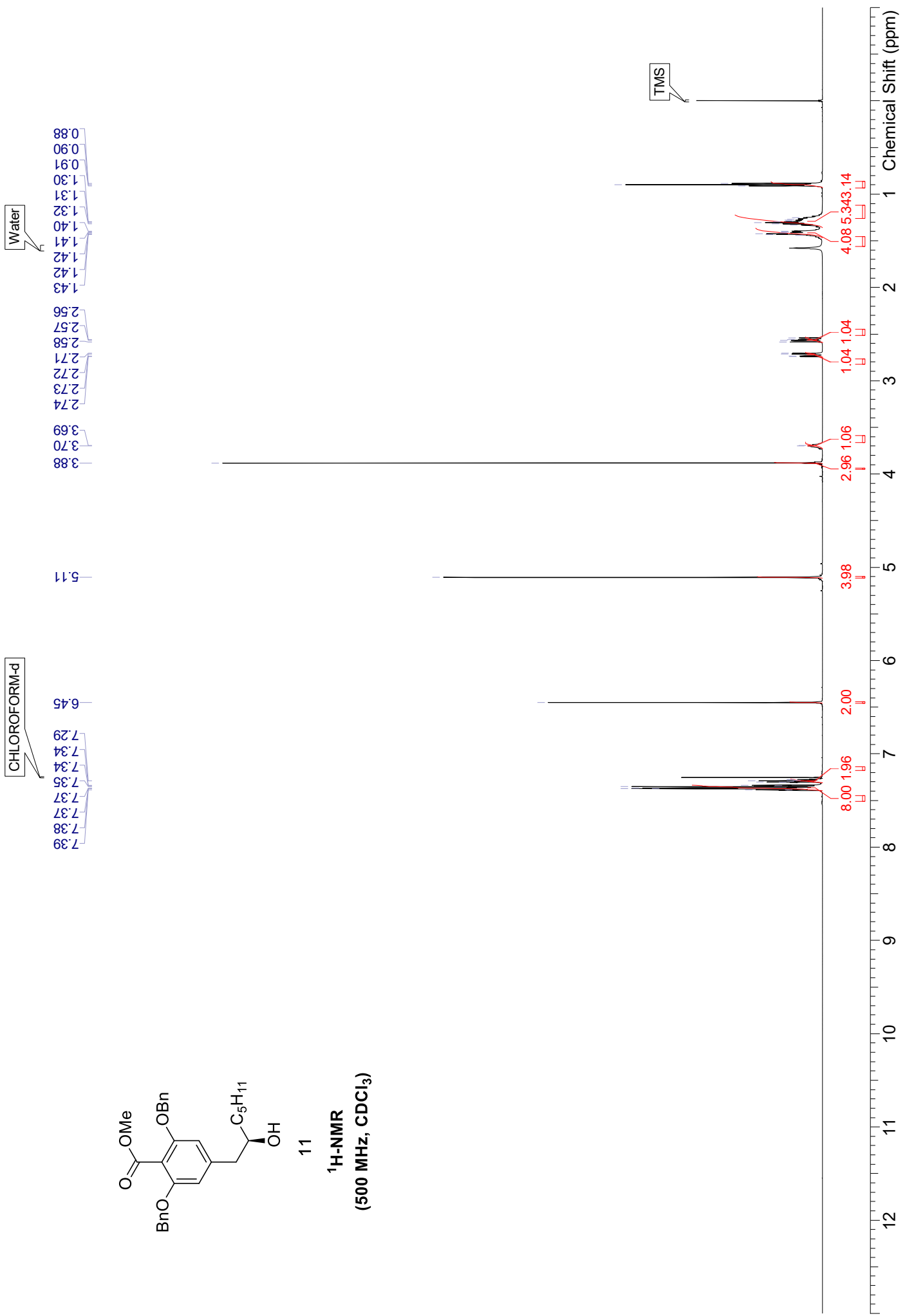
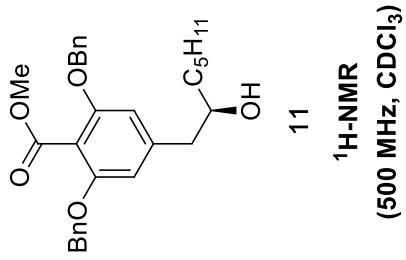
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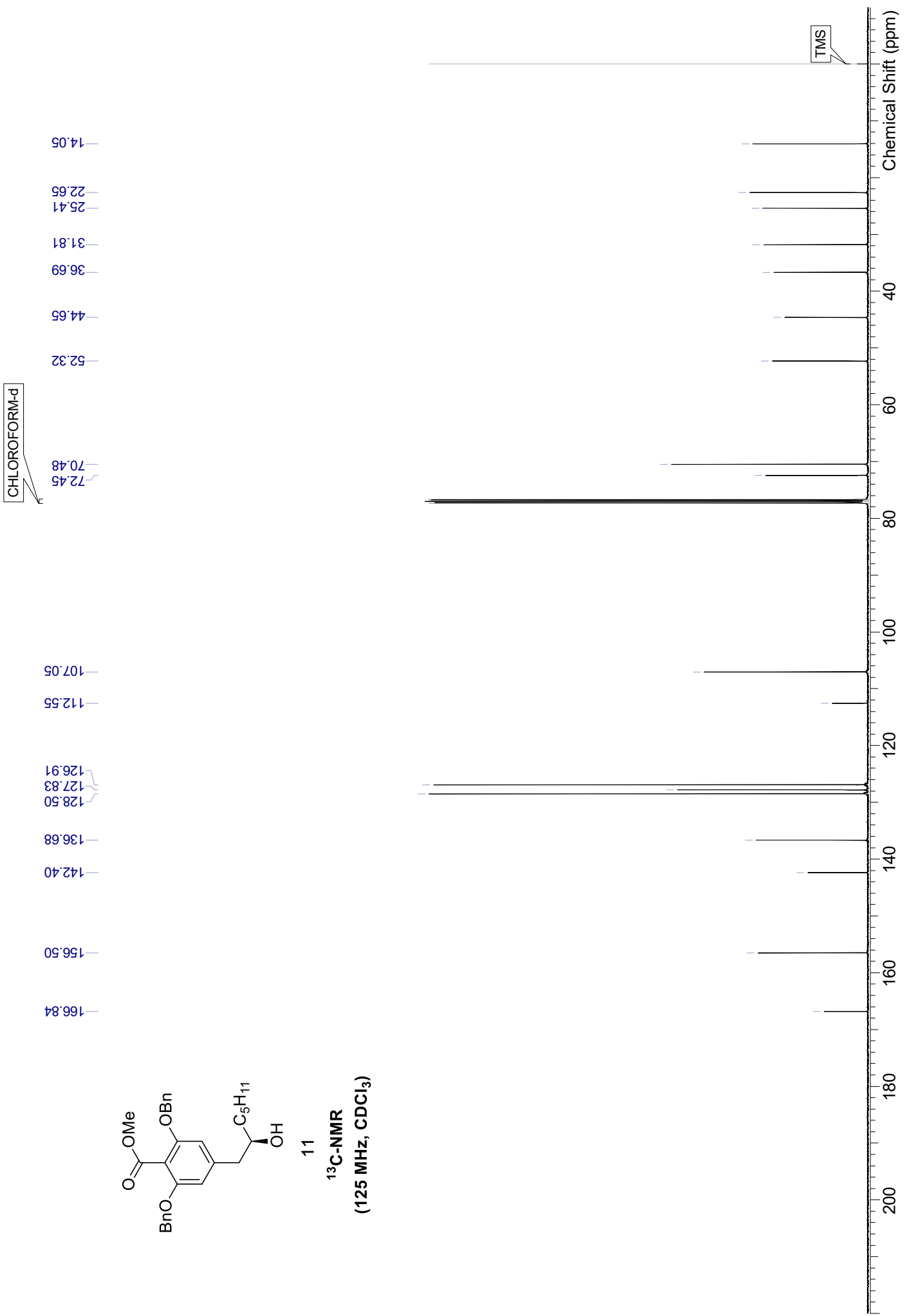
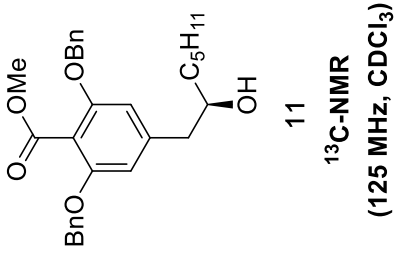


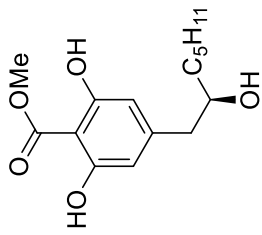
9

¹³C-NMR
(125 MHz, CDCl₃)



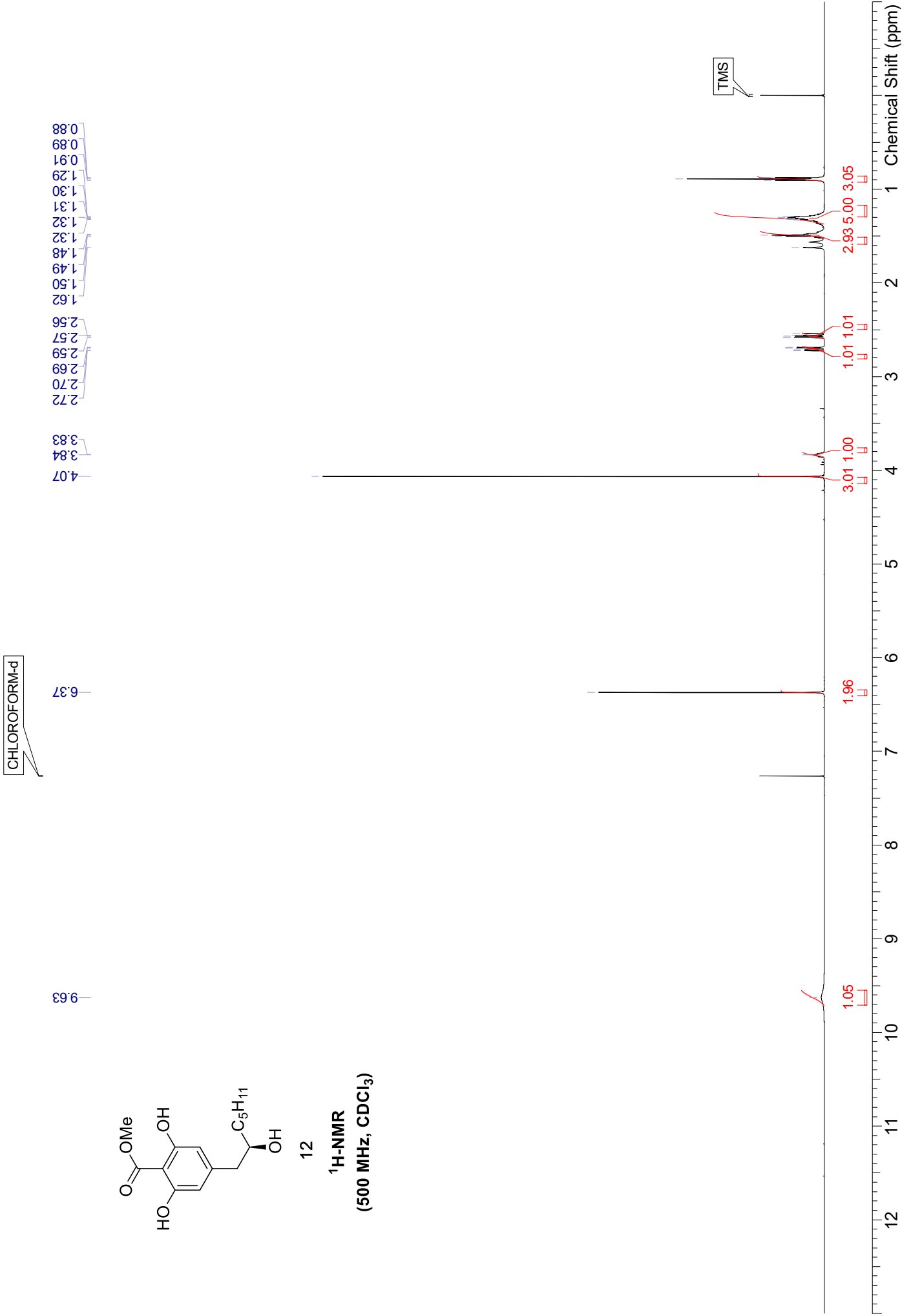


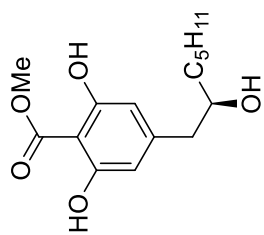




12

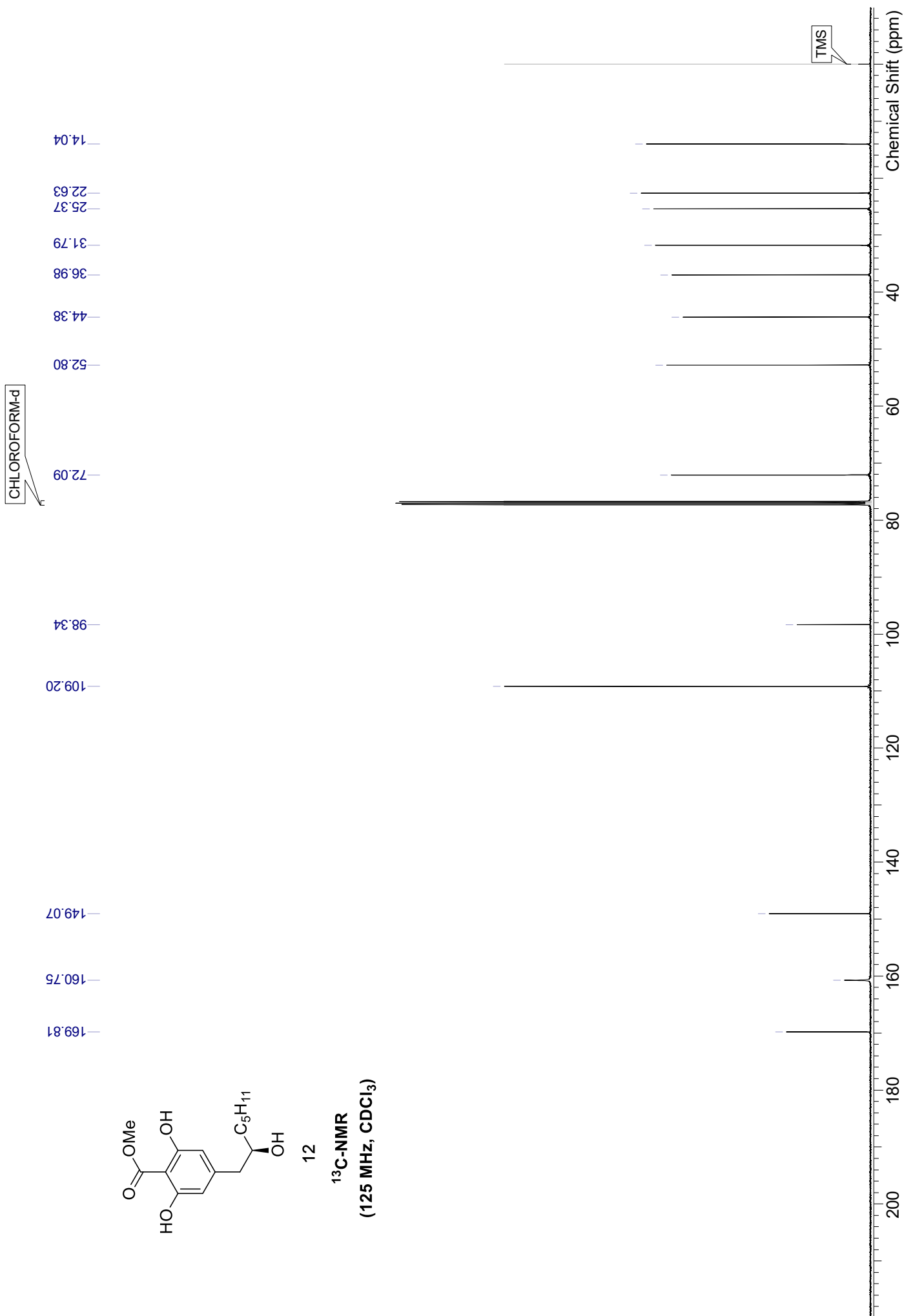
¹H-NMR
(500 MHz, CDCl₃)



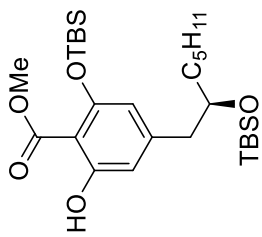


12

¹³C-NMR
(125 MHz, CDCl₃)

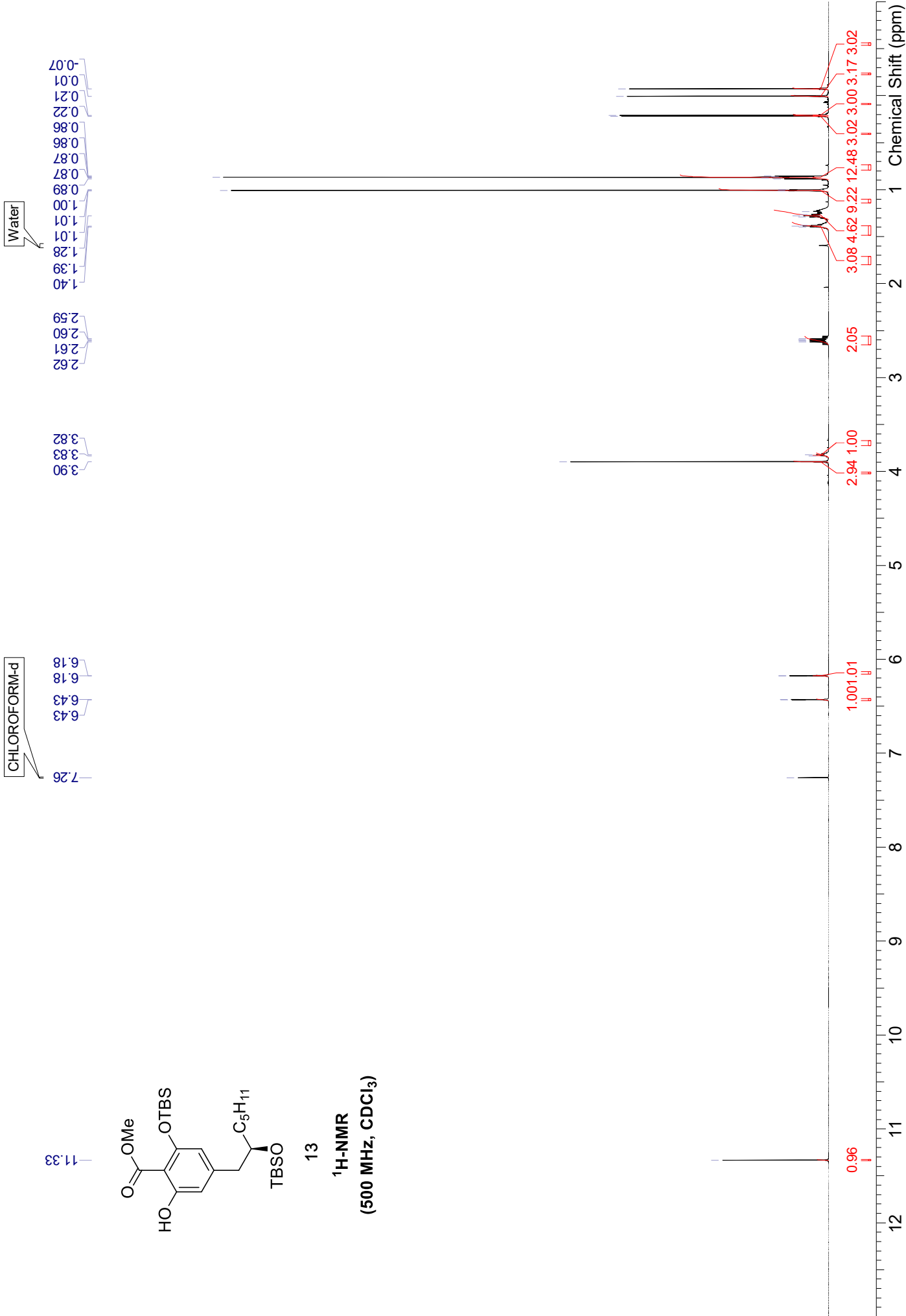


11.33



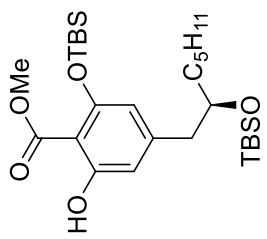
13

¹H-NMR
(500 MHz, CDCl₃)



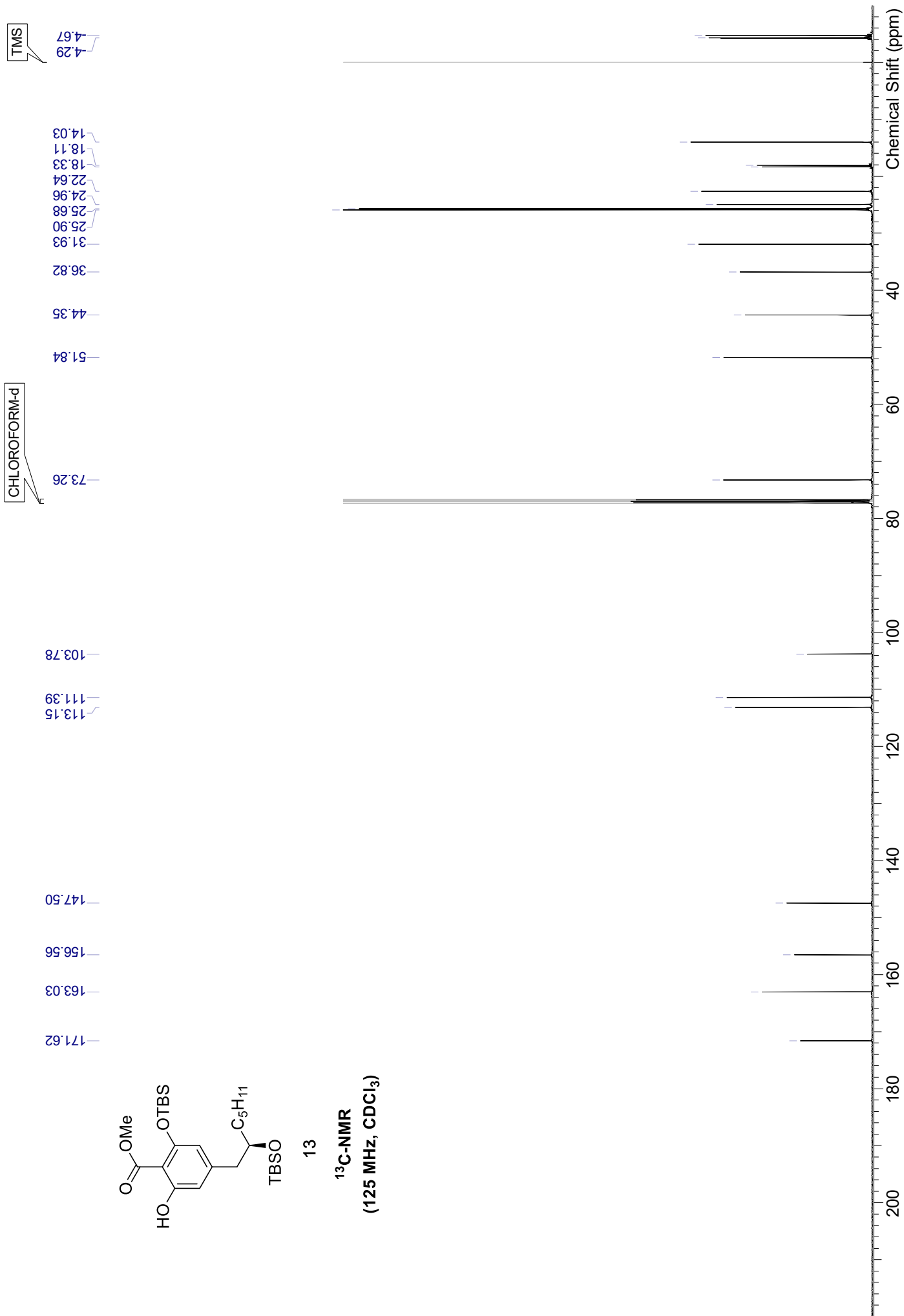
Water

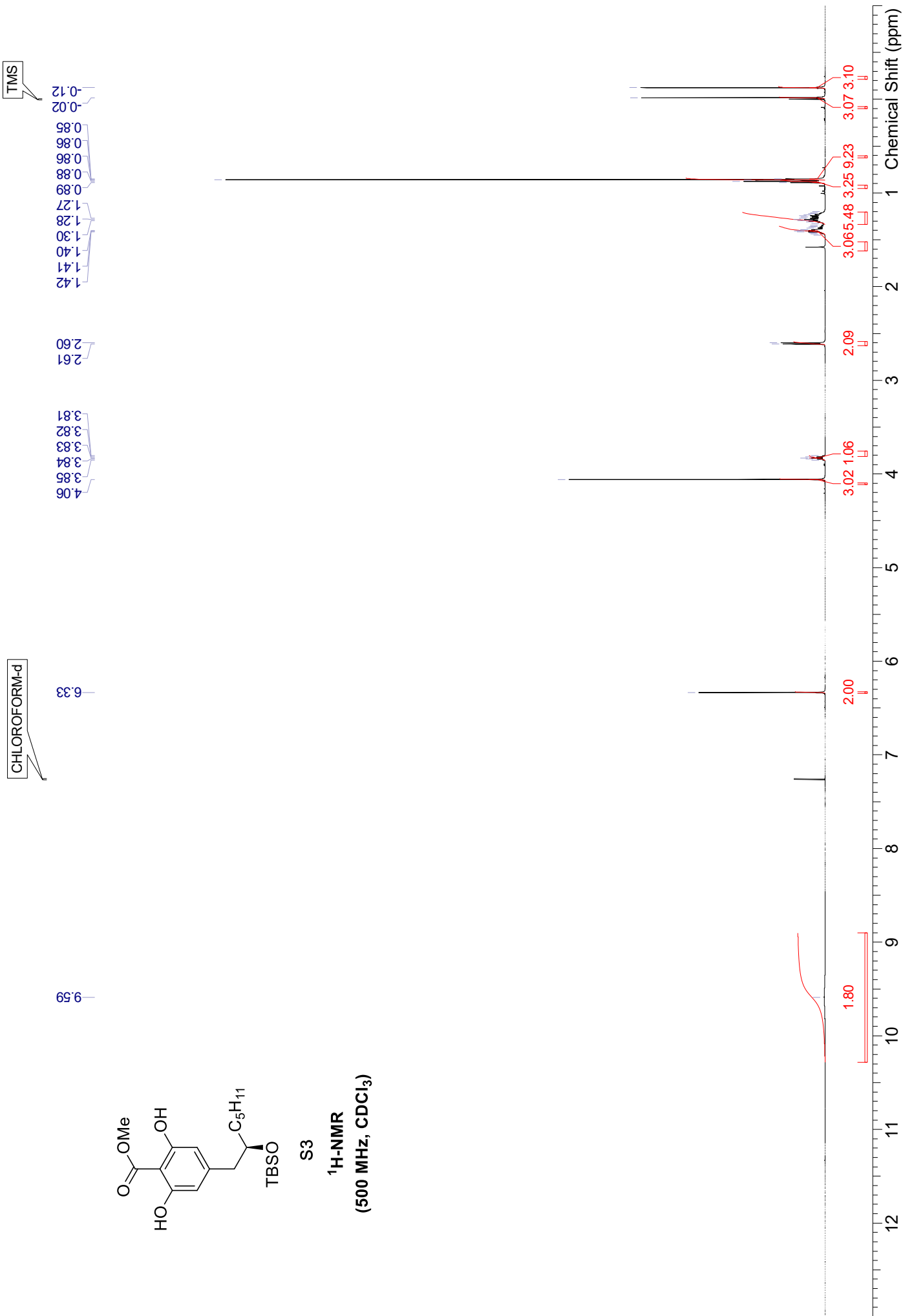
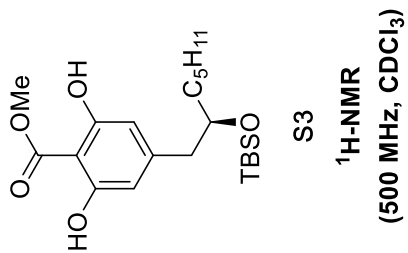
CHLOROFORM-d

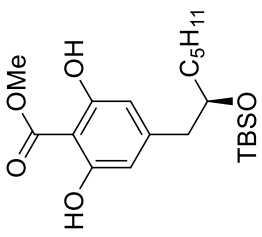


13

¹³C-NMR
(125 MHz, CDCl₃)

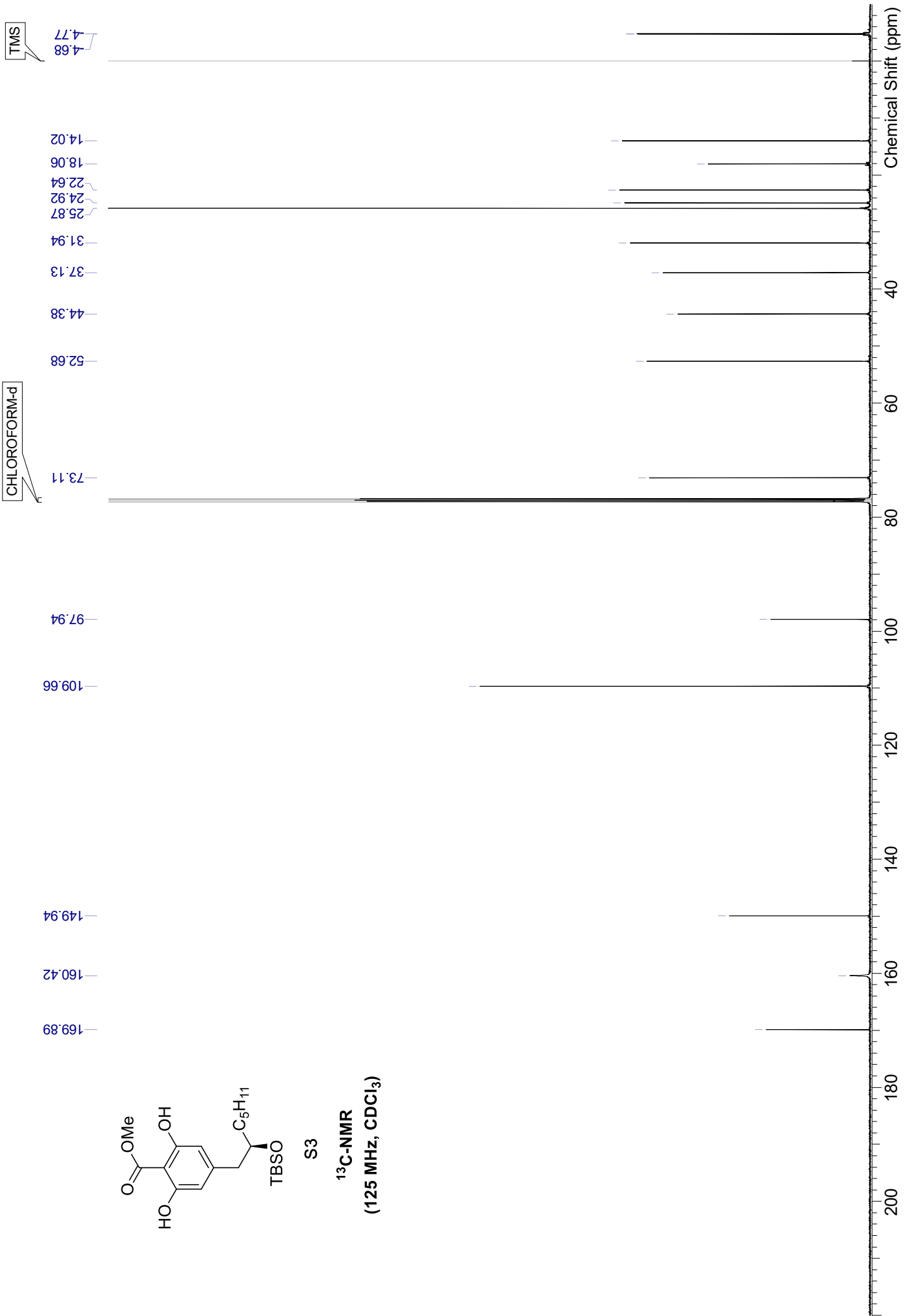


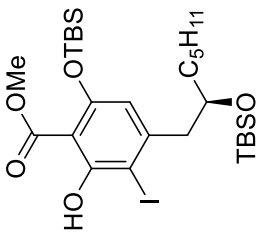




S3

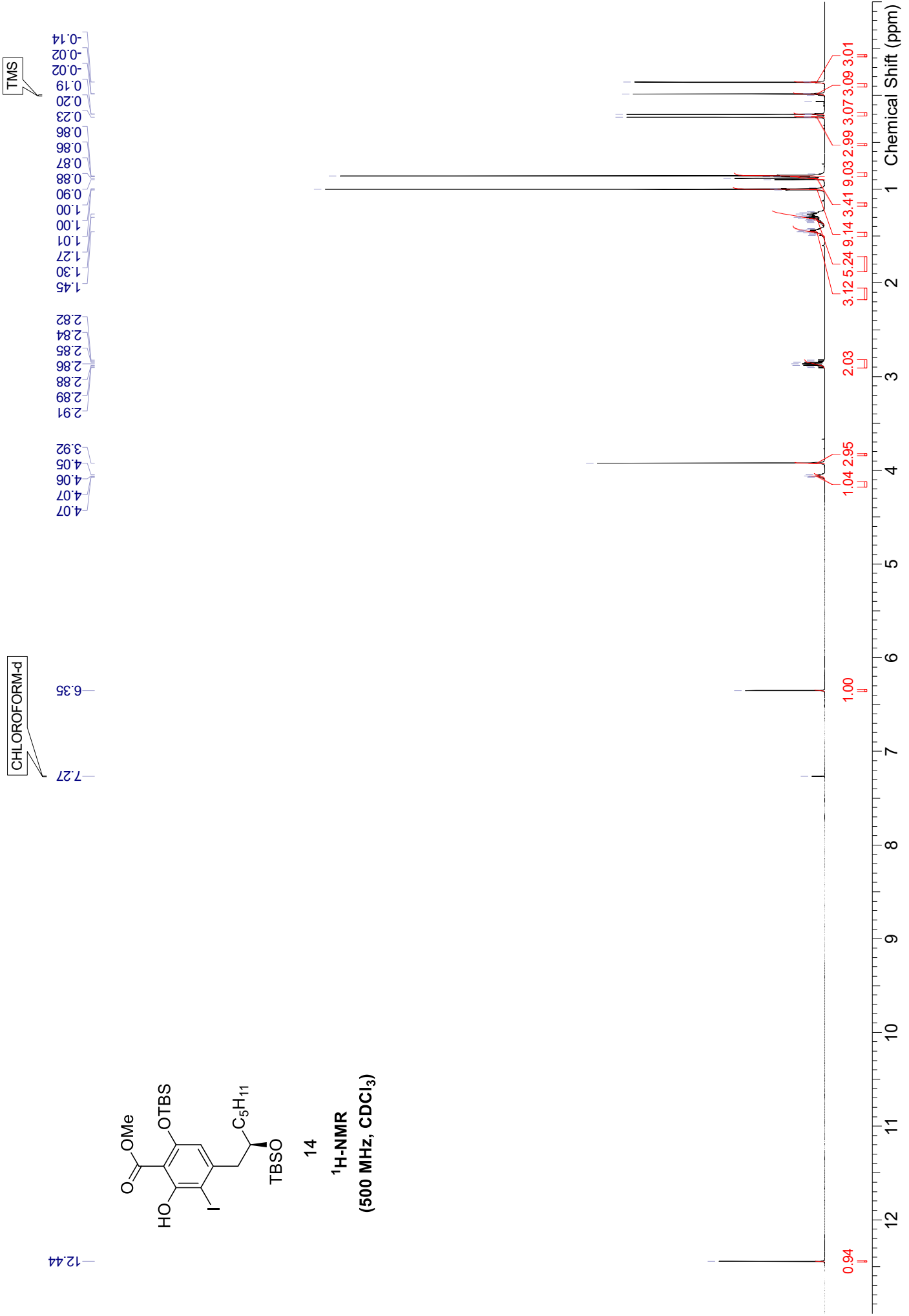
¹³C-NMR
(125 MHz, CDCl₃)

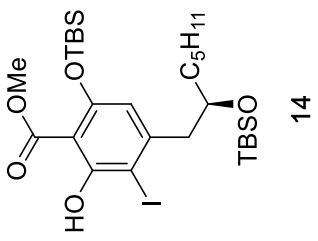




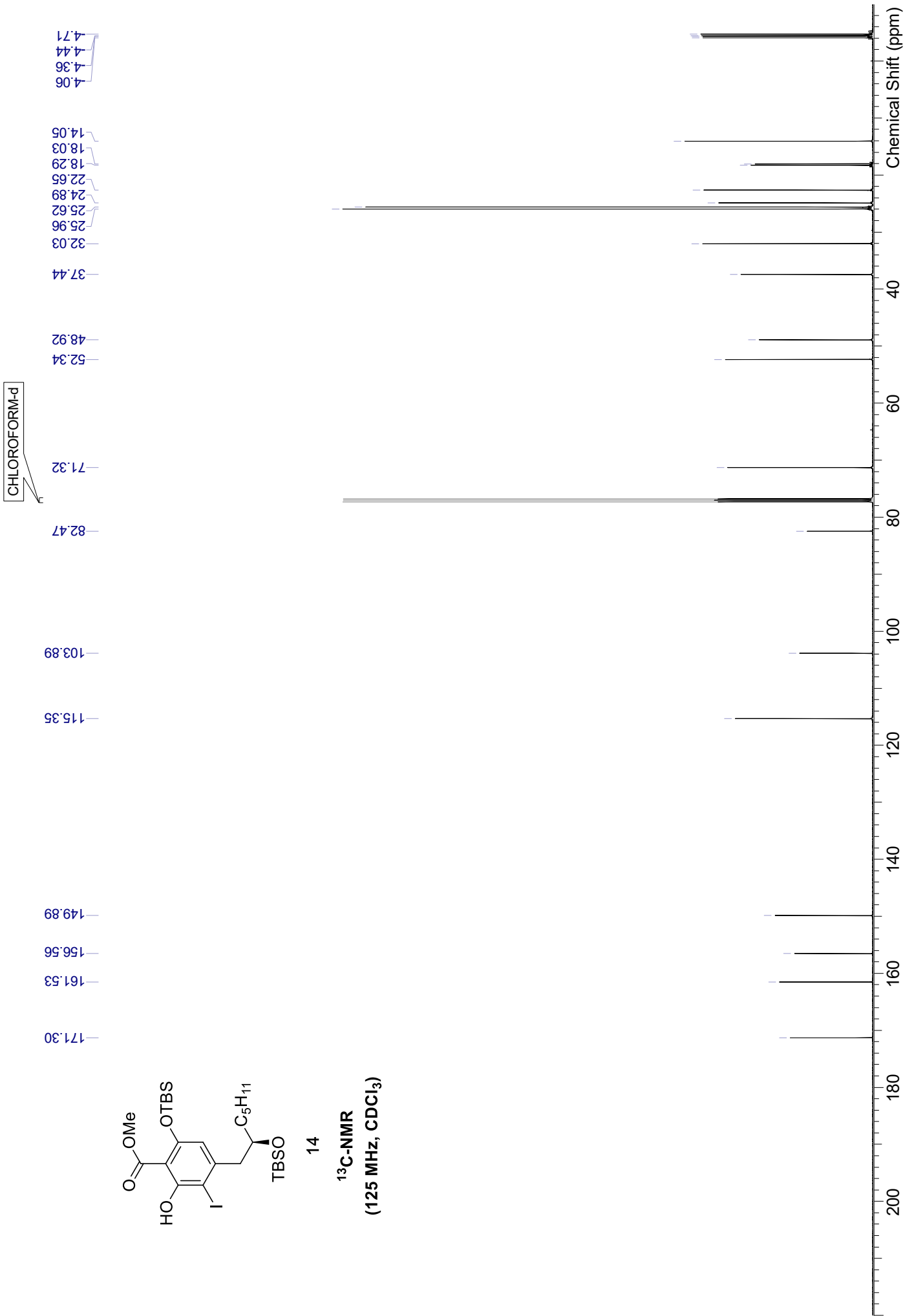
14

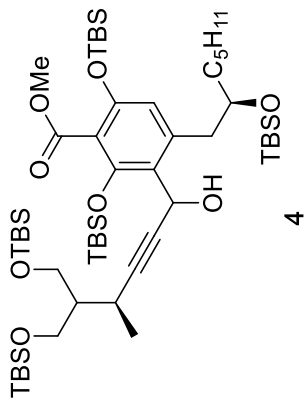
¹H-NMR
(500 MHz, CDCl₃)



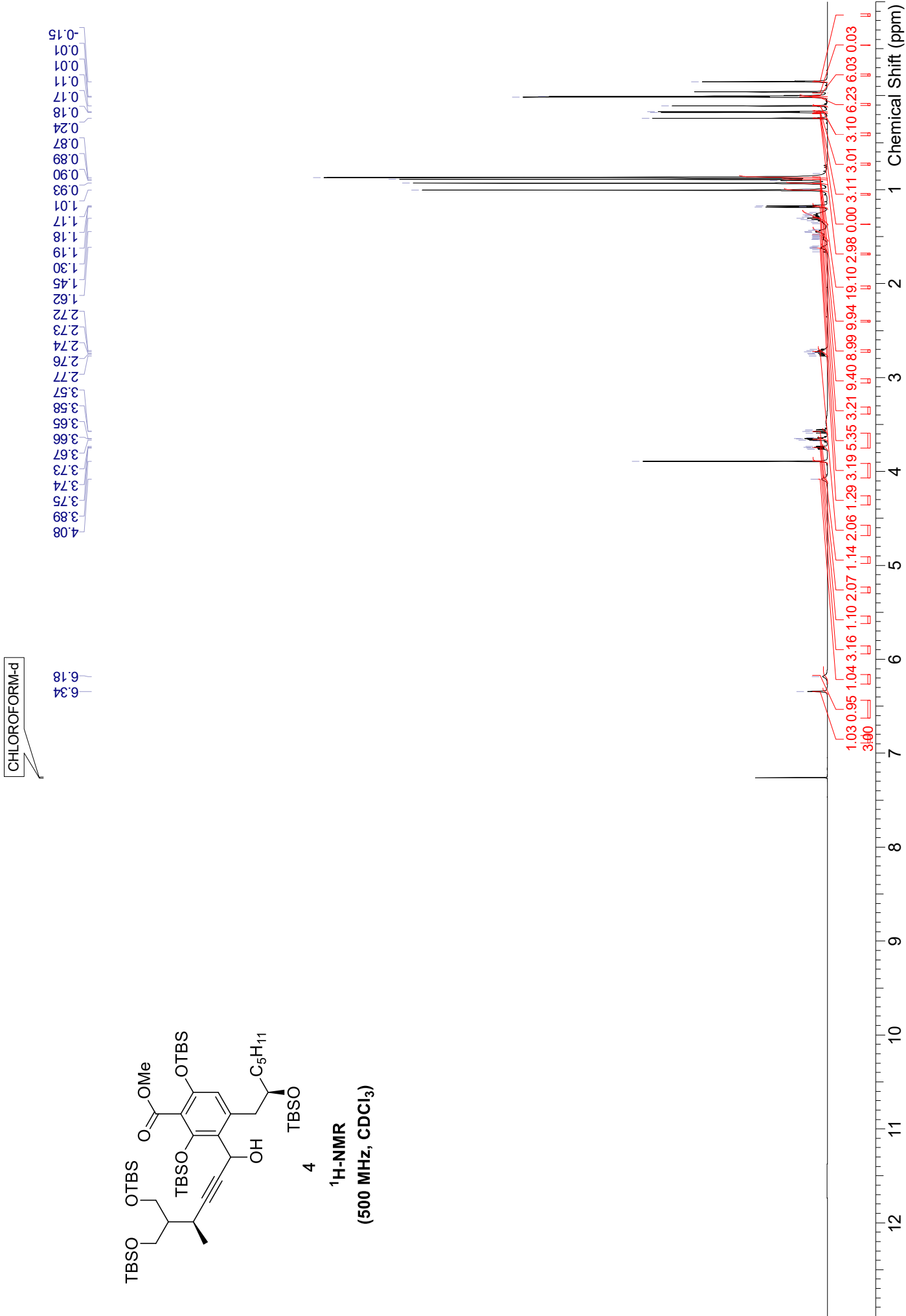


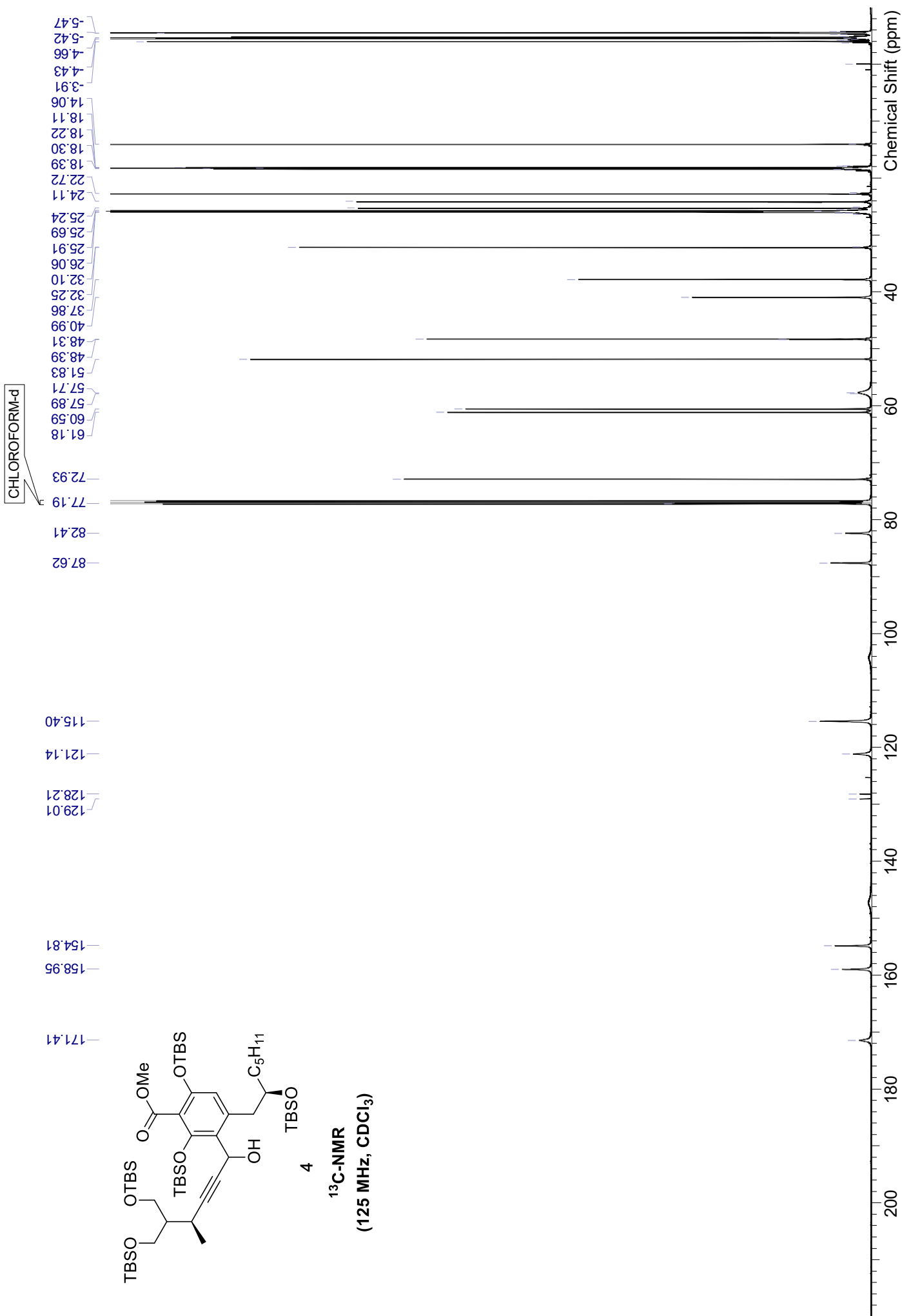
¹³C-NMR
(125 MHz, CDCl₃)

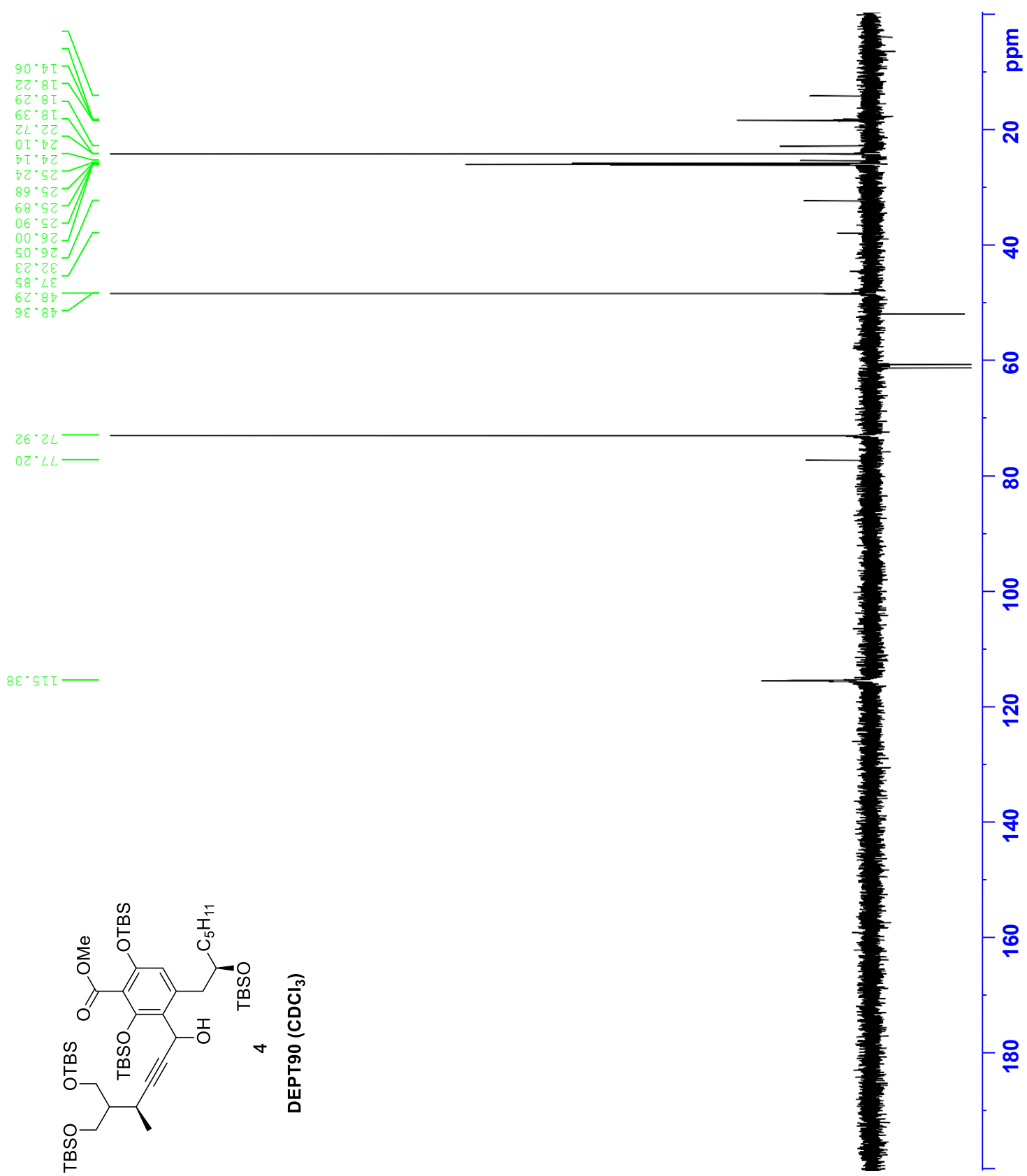


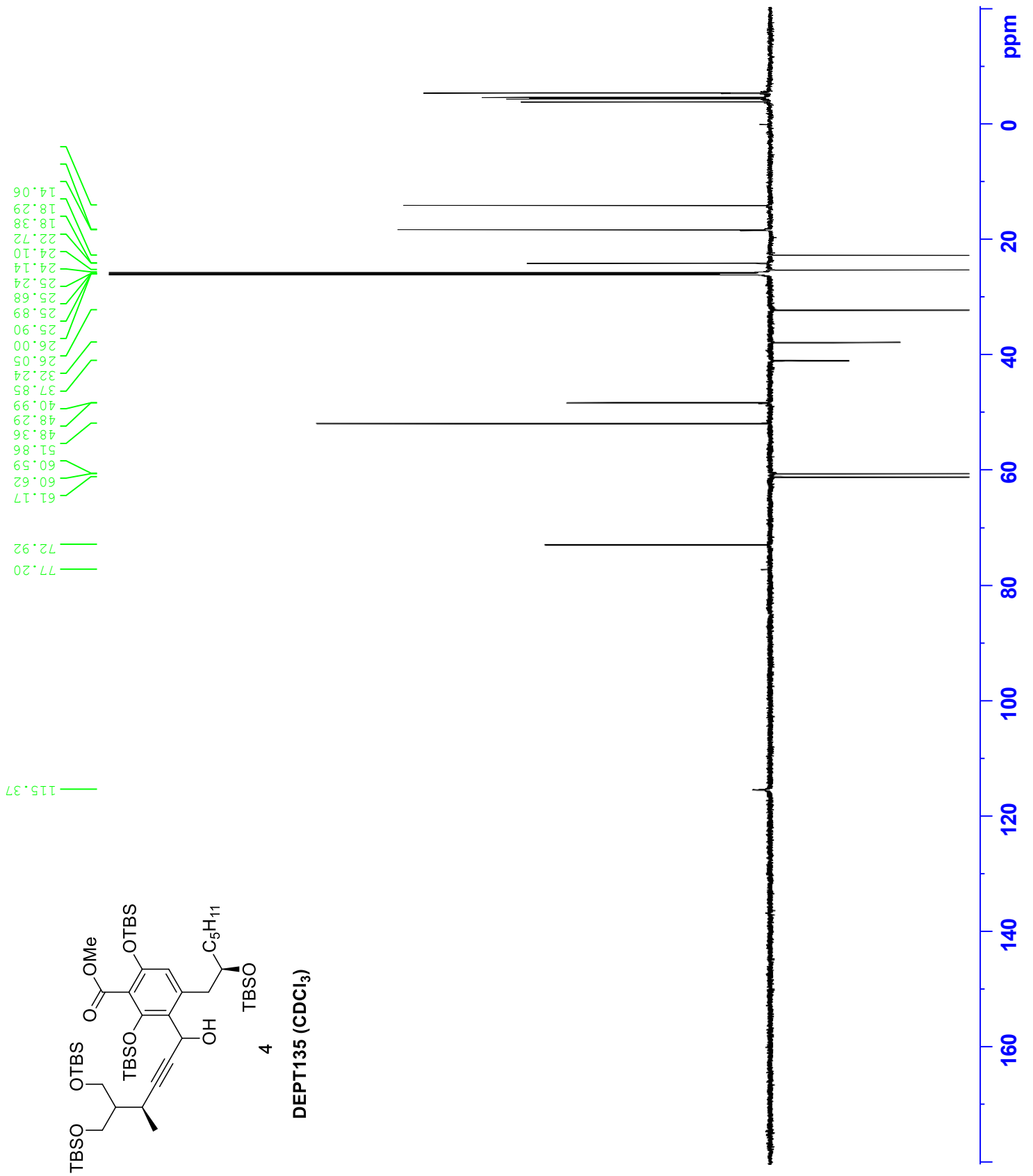


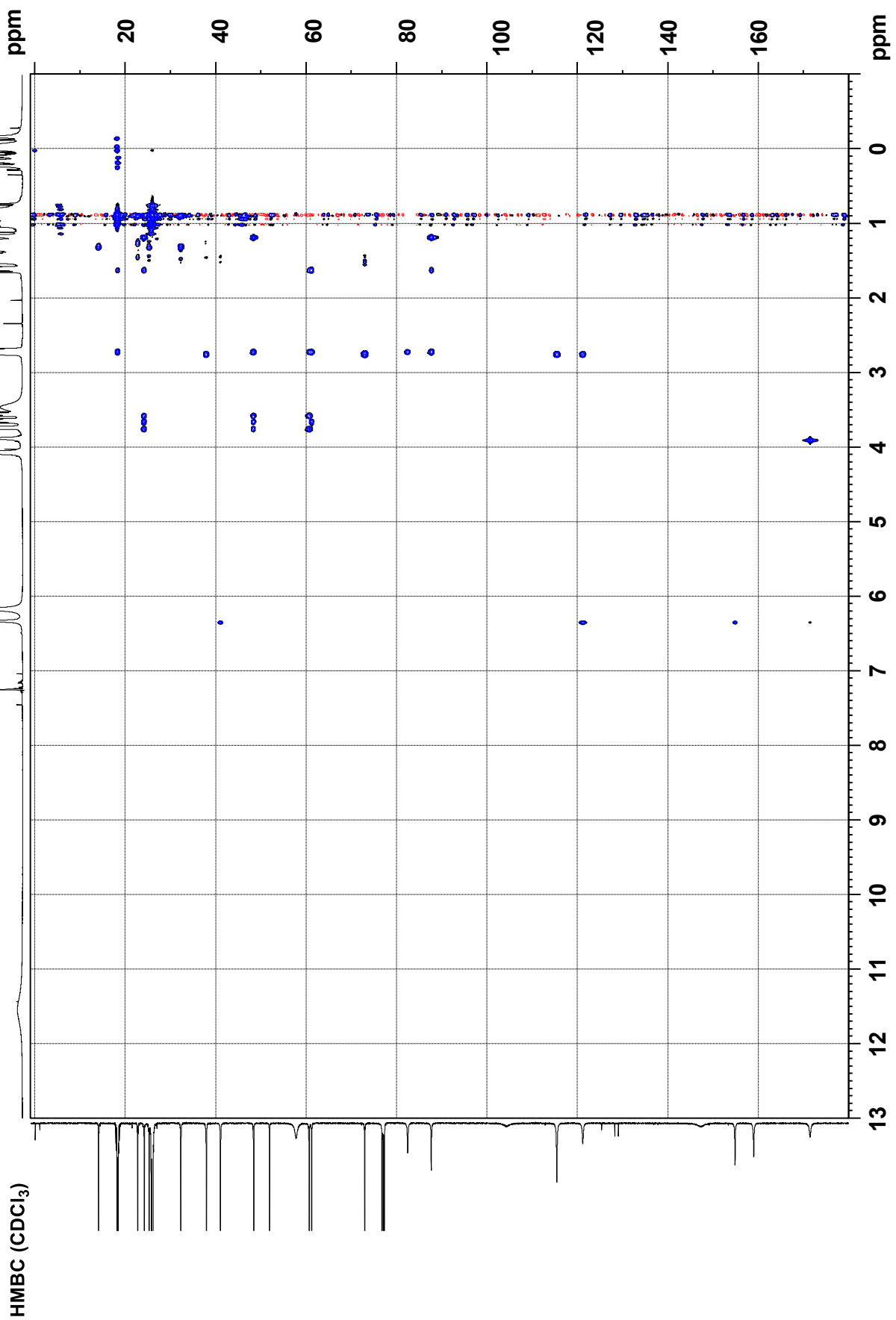
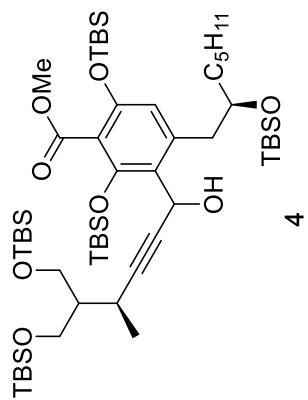
¹H-NMR
(500 MHz, CDCl₃)

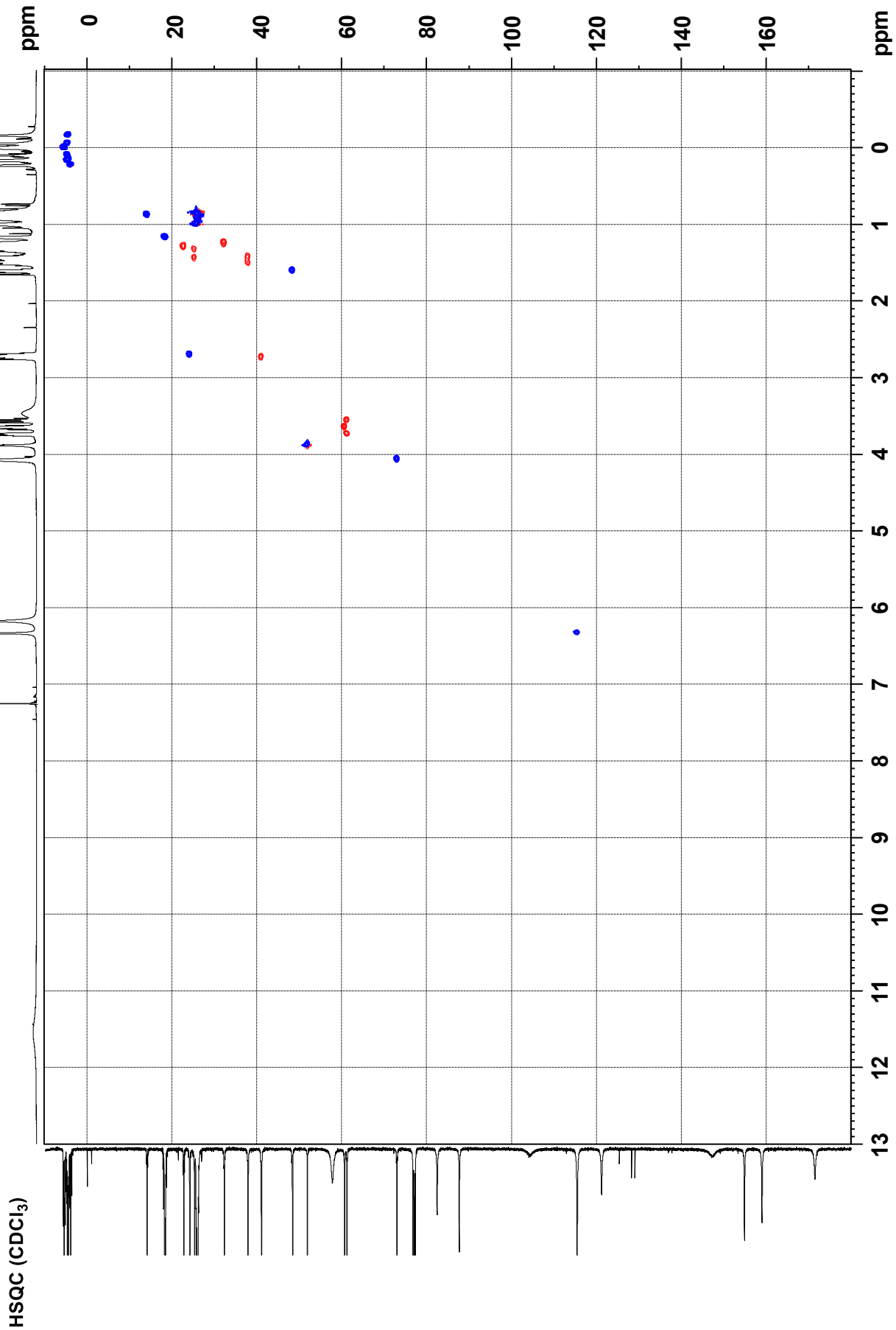
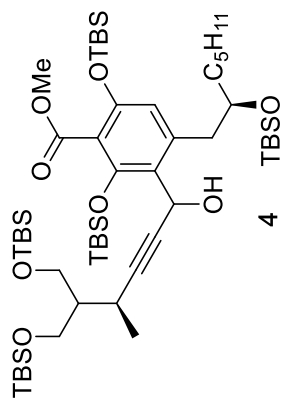




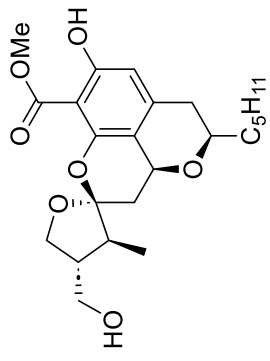








11.36



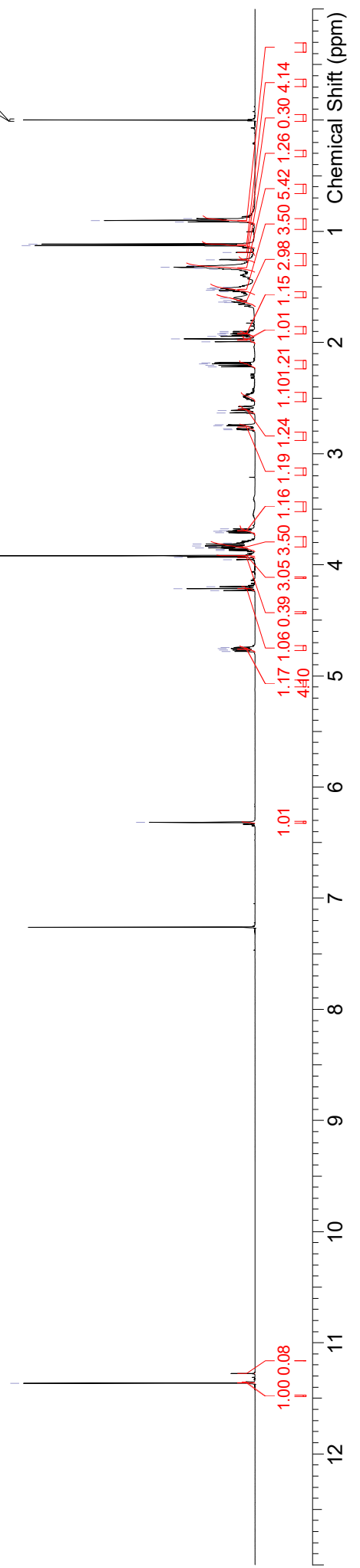
¹H-NMR
(500 MHz, CDCl₃)

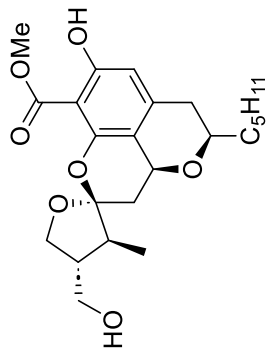
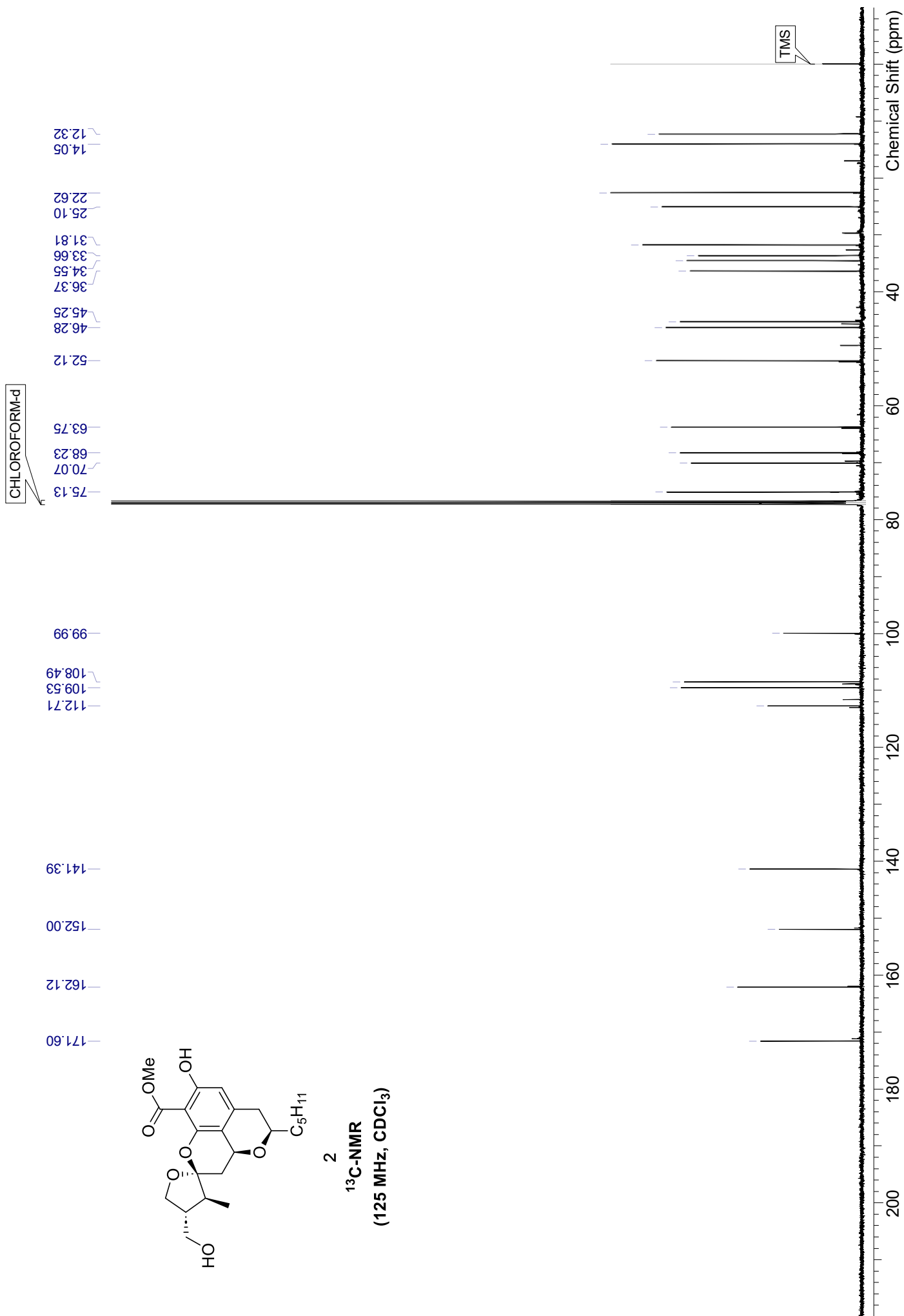
CHLOROFORM-d

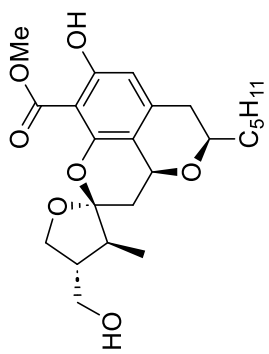
6.32

4.78
4.77
4.75
4.74
4.23
4.22
4.20
3.93
3.92
3.85
3.84
3.83
3.82
3.70
2.75
2.74
2.21
2.19
2.18
1.99
1.97
1.52
1.33
1.33
1.32
1.31
1.13
1.11
0.92
0.90
0.89

TMS

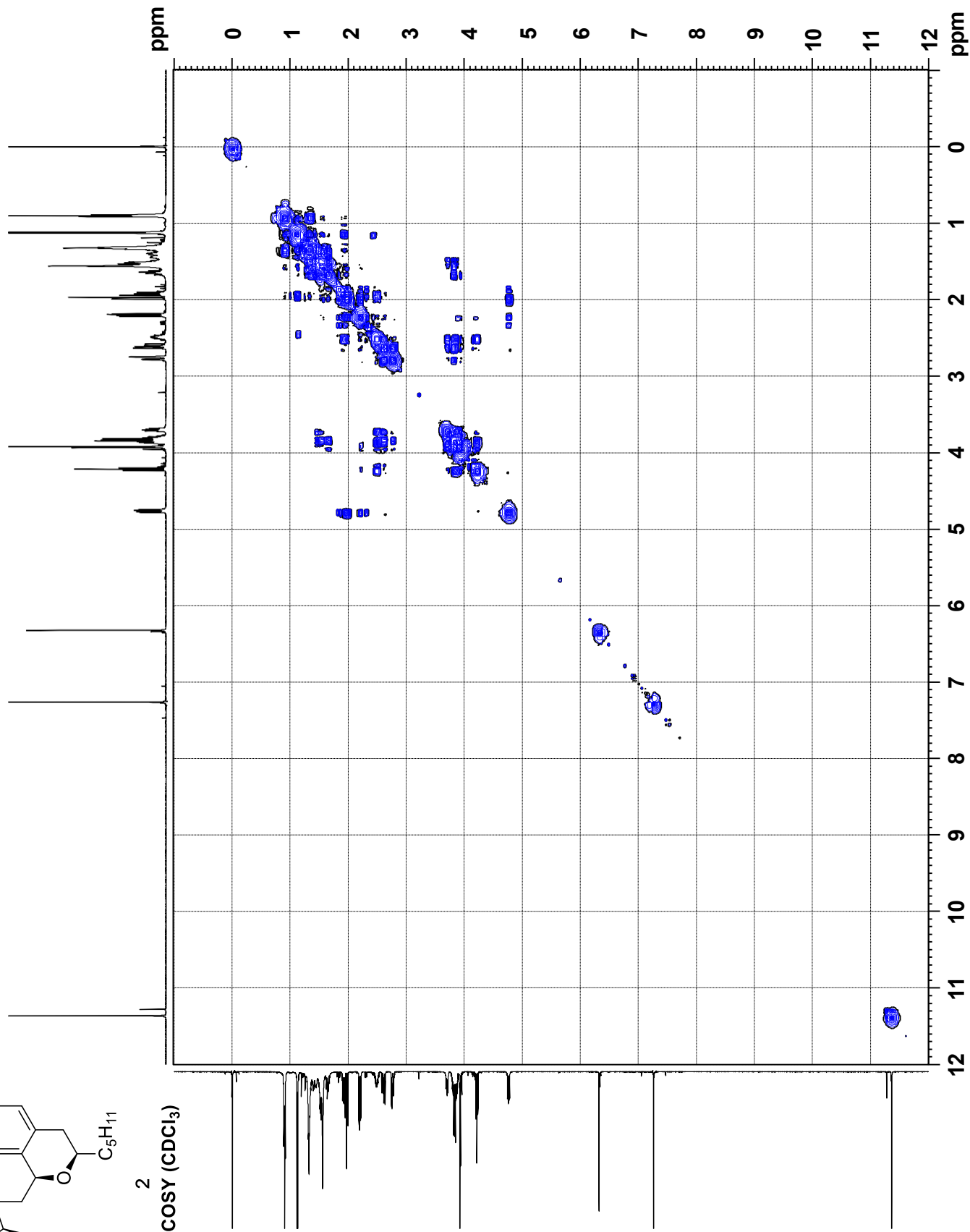


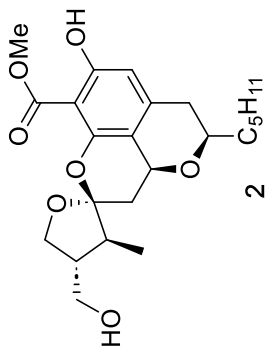




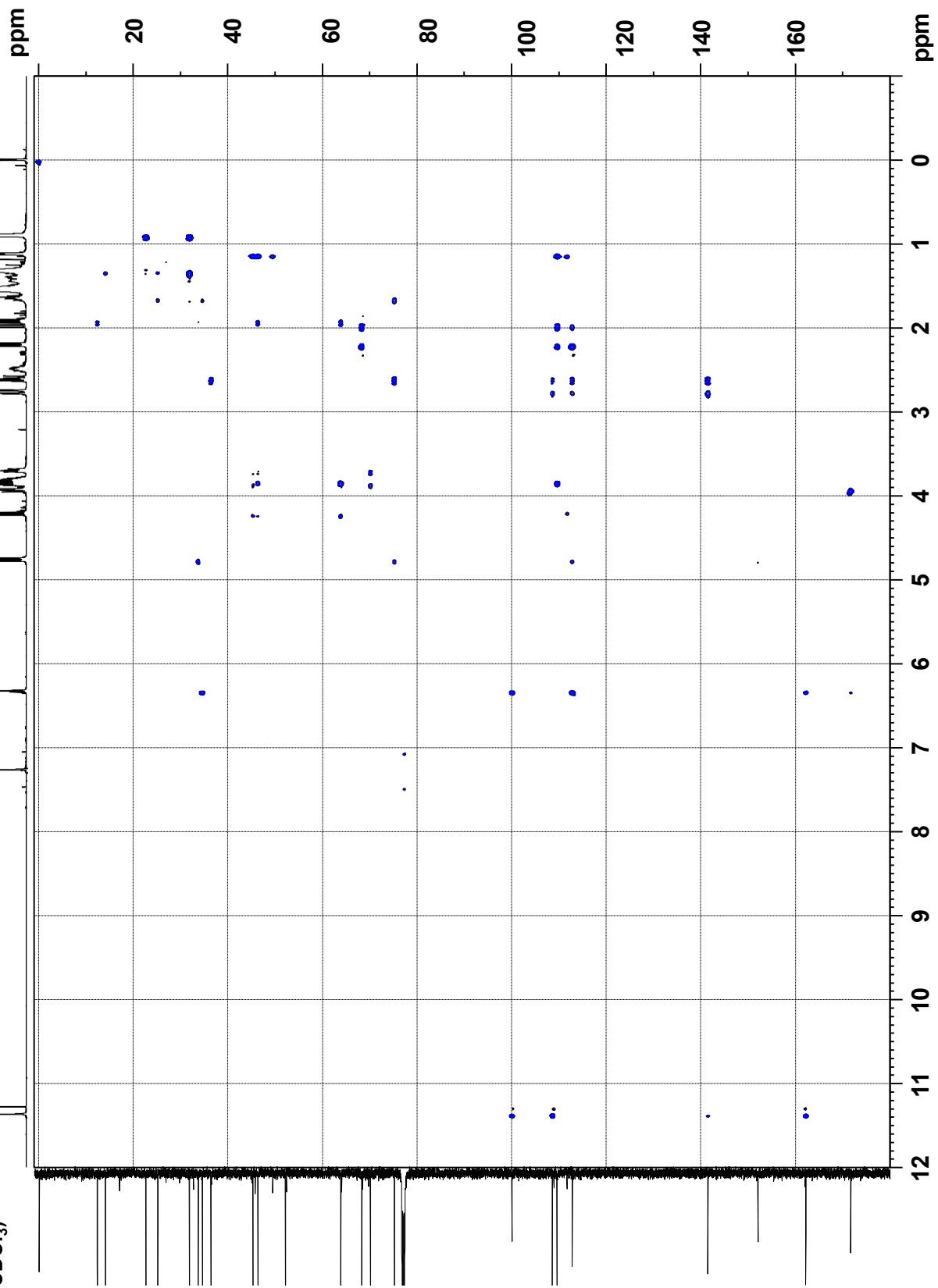
2

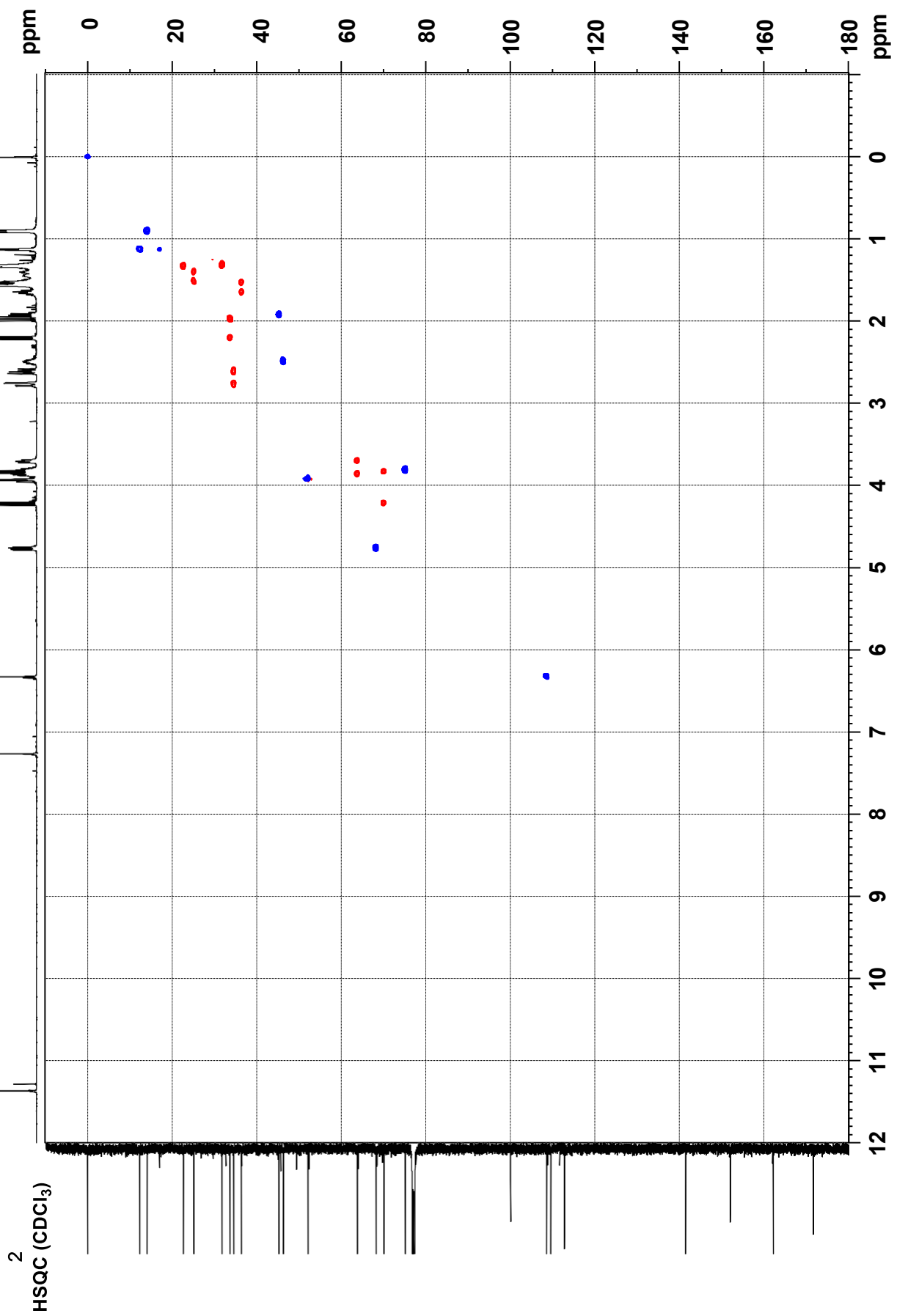
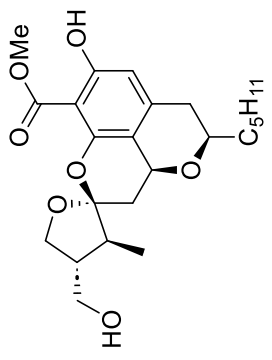
gCOSY (CDCl₃)

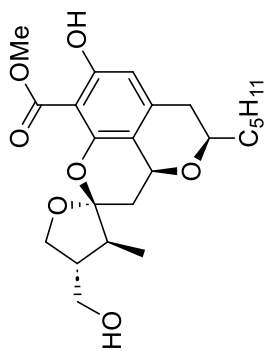




2 C₅H₁₁
HMBC (CDCl₃)

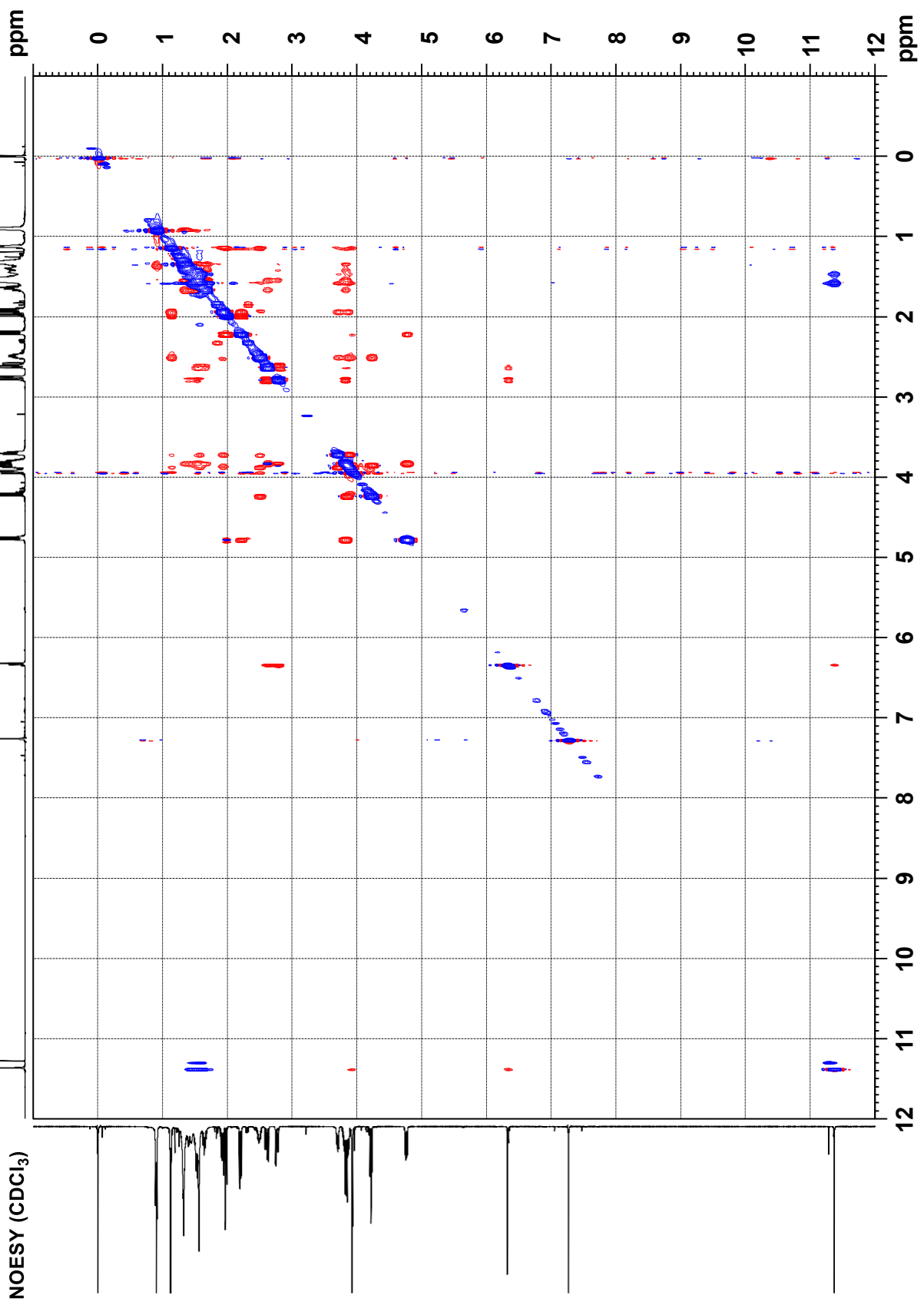




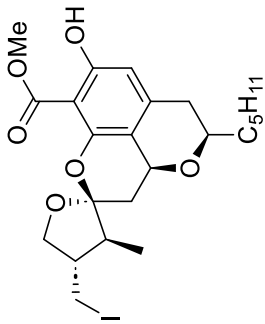


2

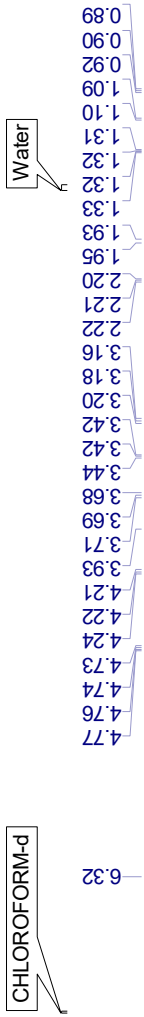
NOESY (CDCl₃)



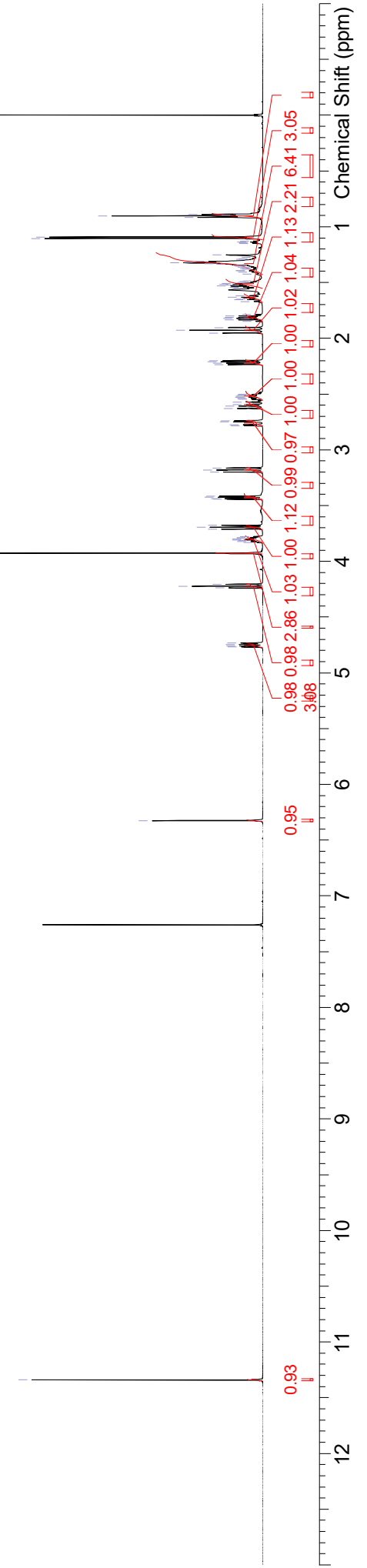
11.34

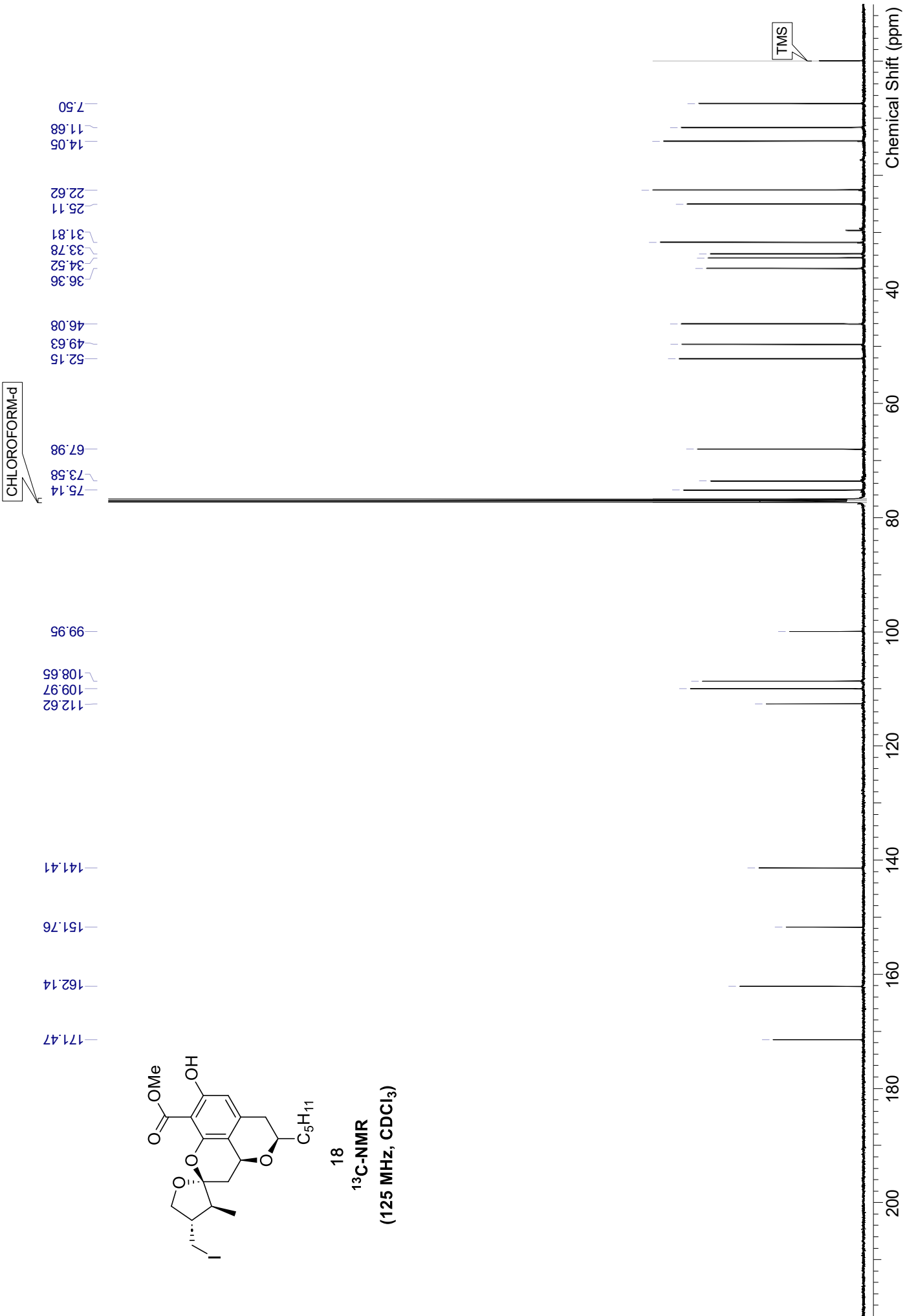


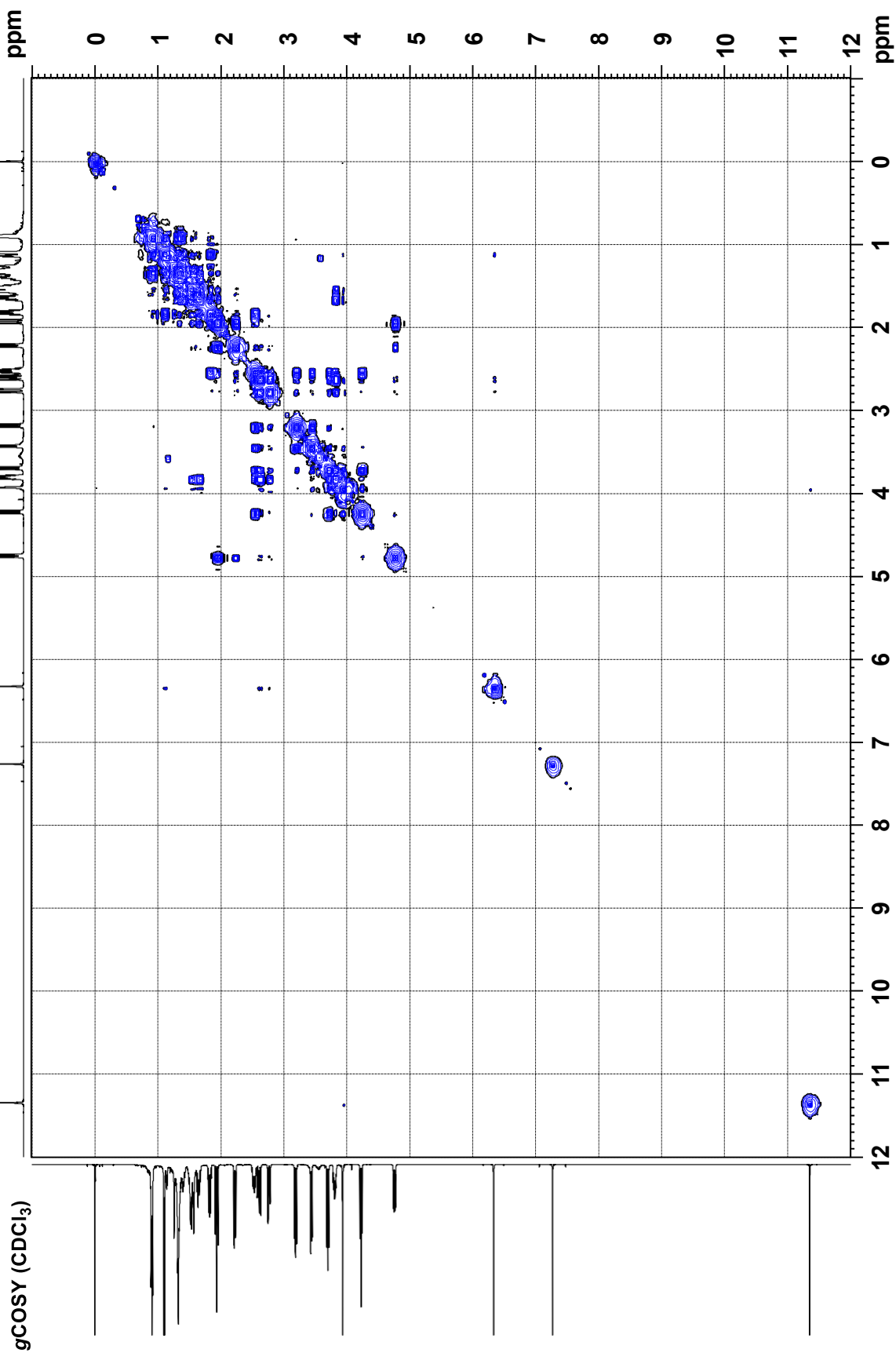
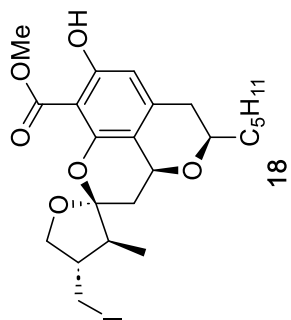
¹H-NMR
(500 MHz, CDCl₃)

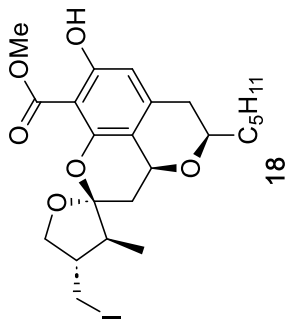


TMS

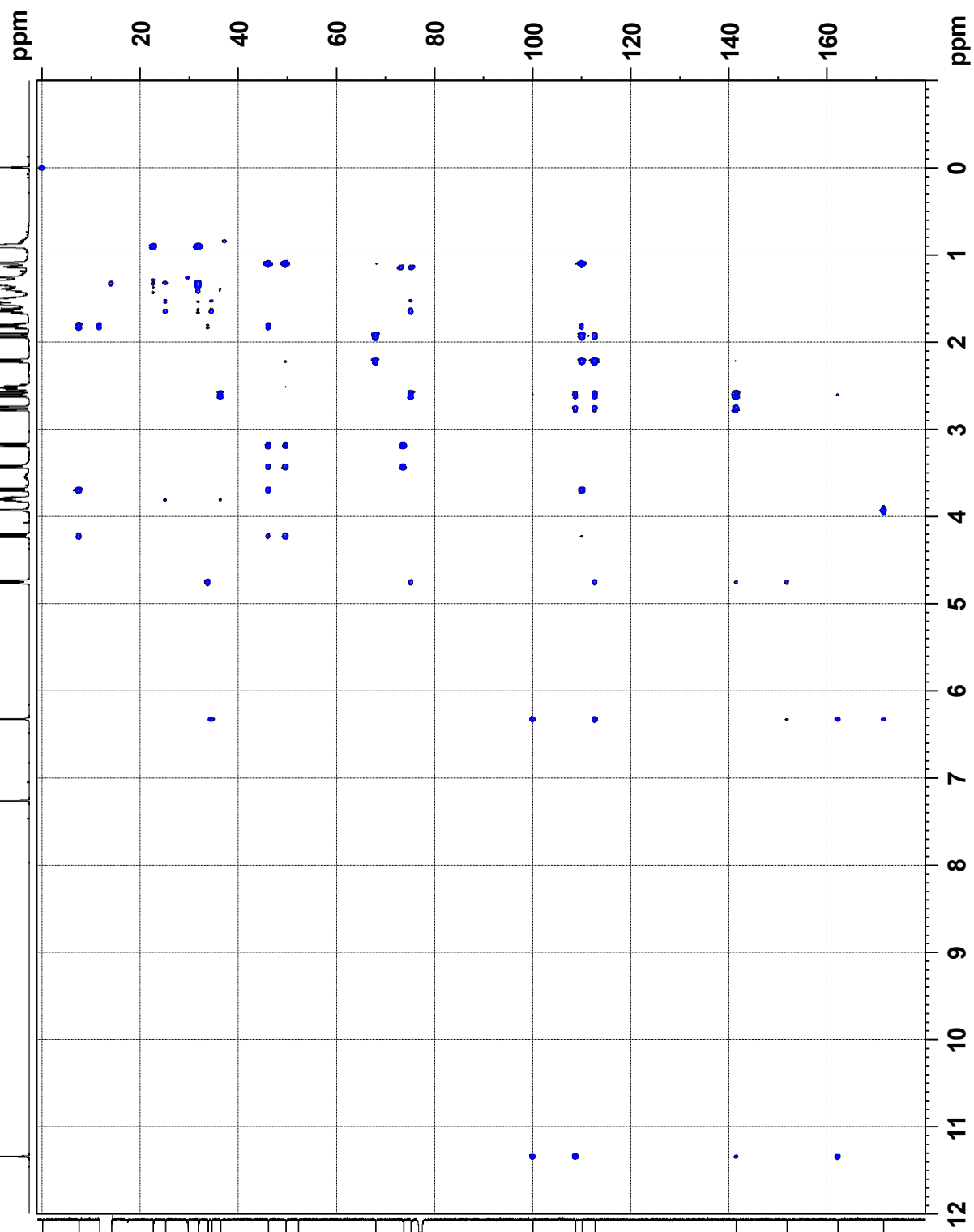


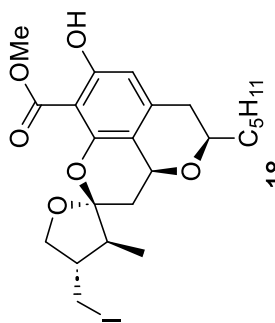




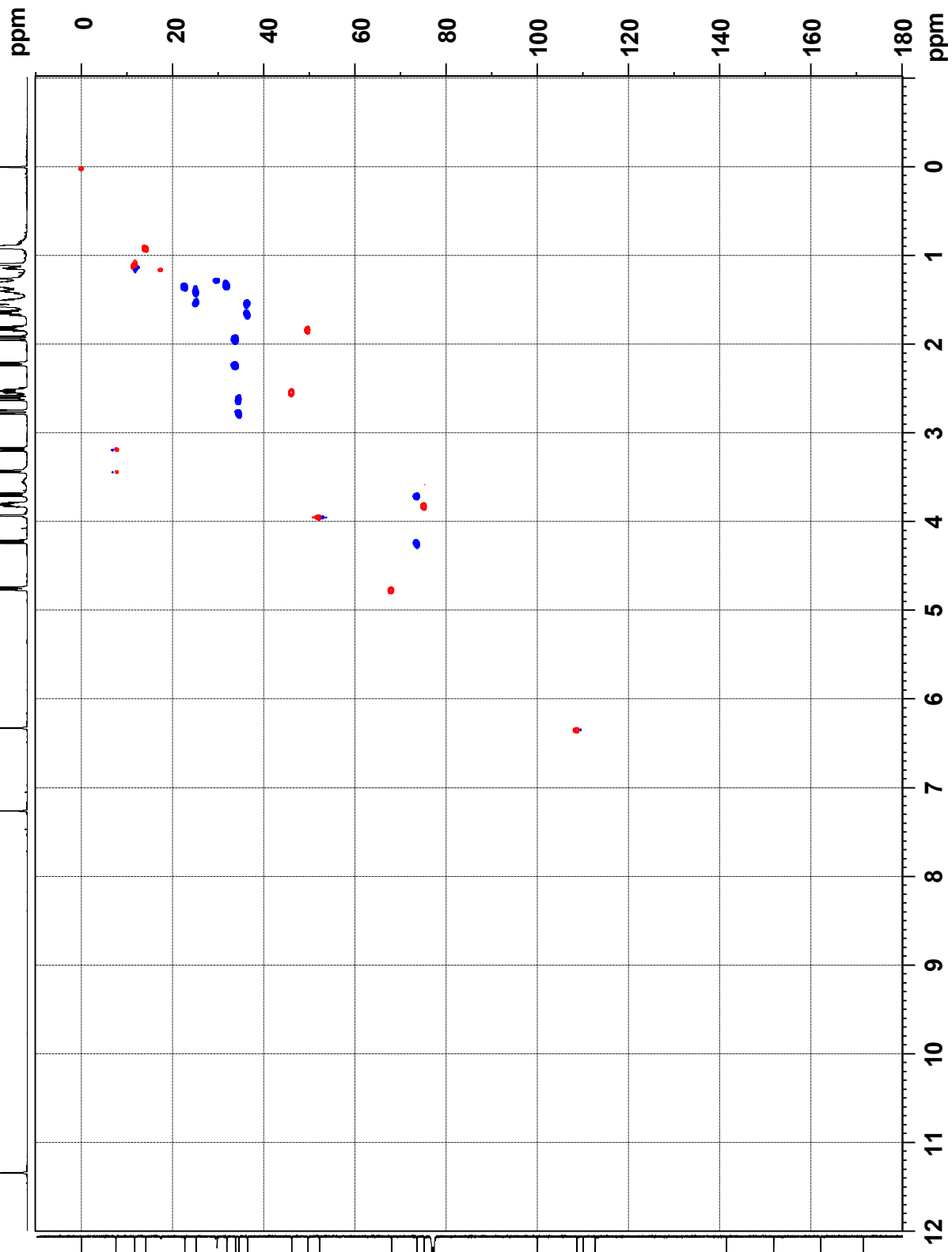


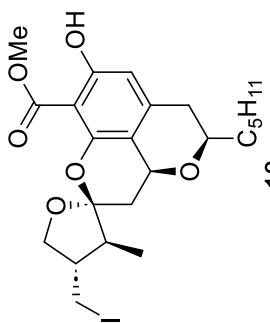
HMBC (CDCl₃)



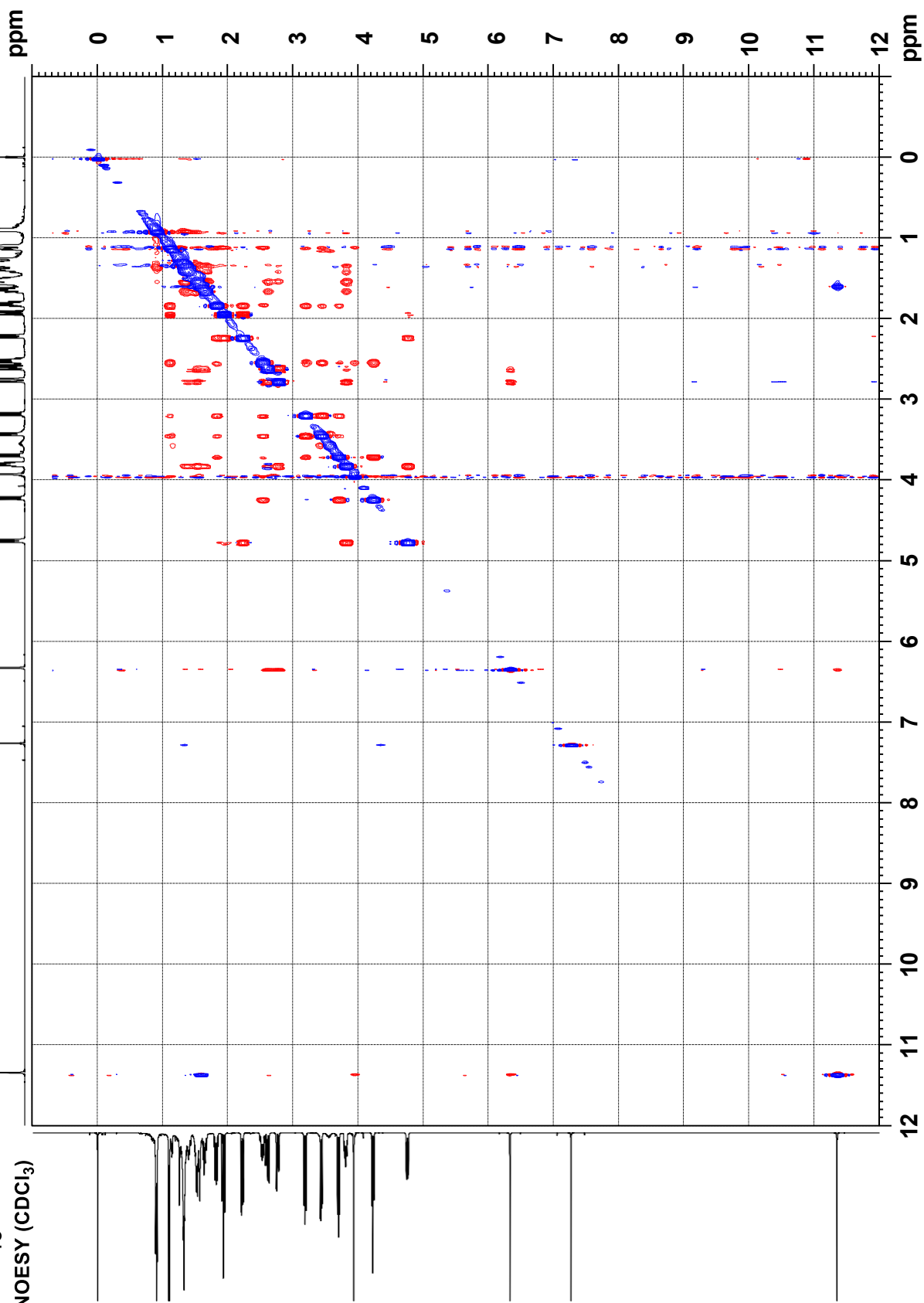


HSQC (CDCl₃)

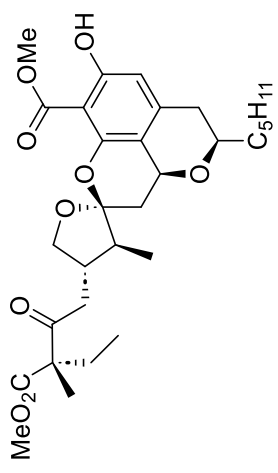




NOESY (CDCl₃)



11.37



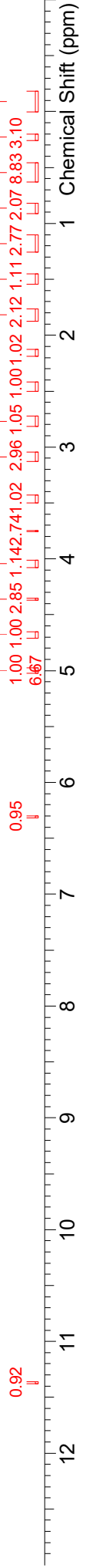
(-)-Berkelic acid
Methyl Ester (19)
¹H-NMR
(500 MHz, CDCl₃)

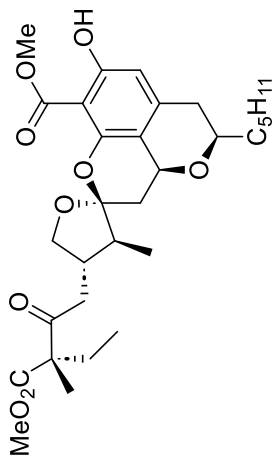
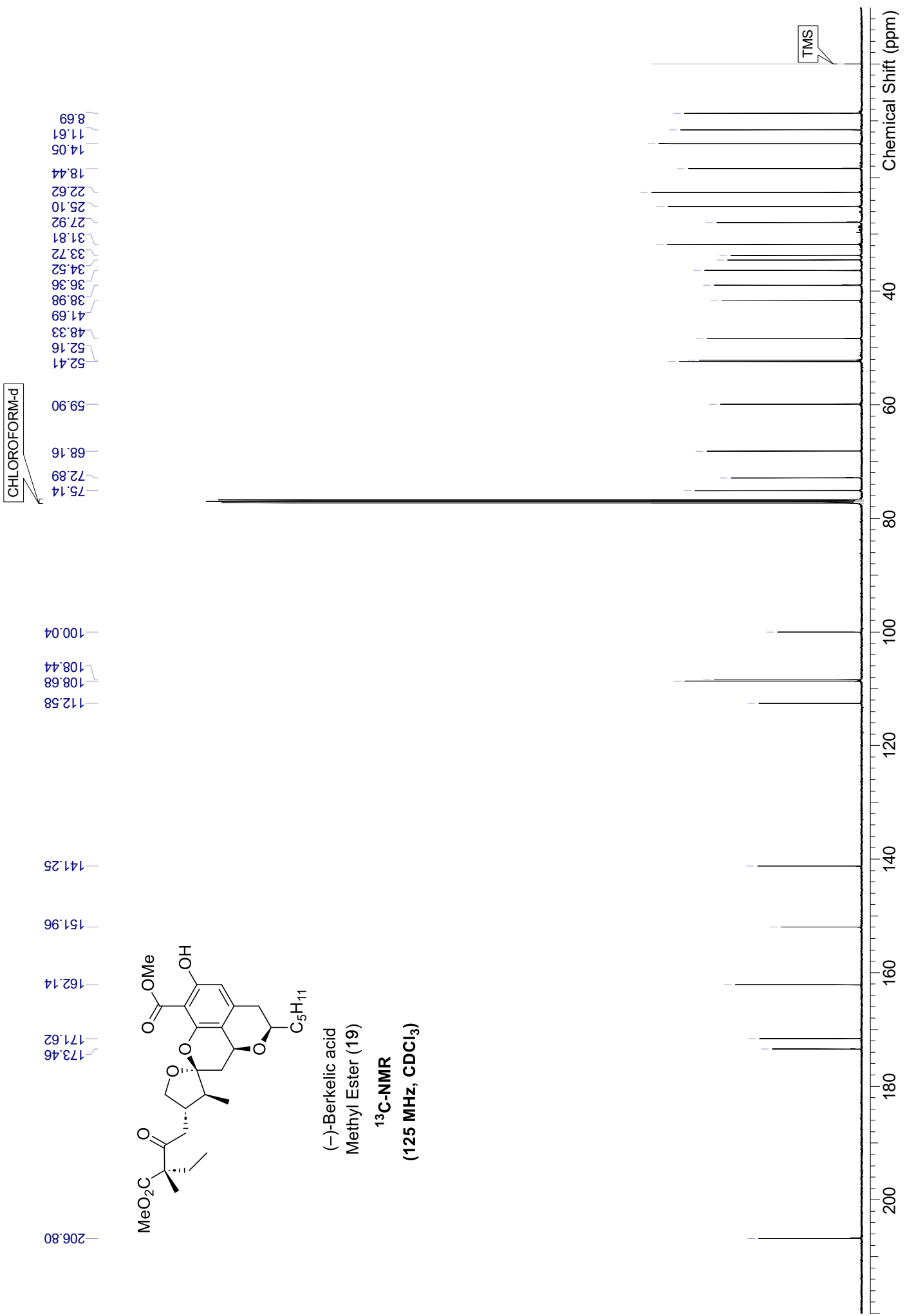
CHLOROFORM-d

6.31

4.77
4.76
4.74
4.73
4.35
4.34
4.32
3.95
3.80
3.75
3.46
3.45
2.79
2.77
2.76
2.76
2.15
2.14
1.98
1.96
1.62
1.36
1.36
1.35
1.32
1.05
1.04
0.91
0.90
0.87
0.86
0.84

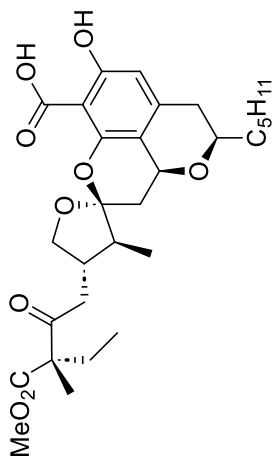
TMS





(-)-Berkeley acid
Methyl Ester (19)
¹³C-NMR
(125 MHz, CDCl₃)

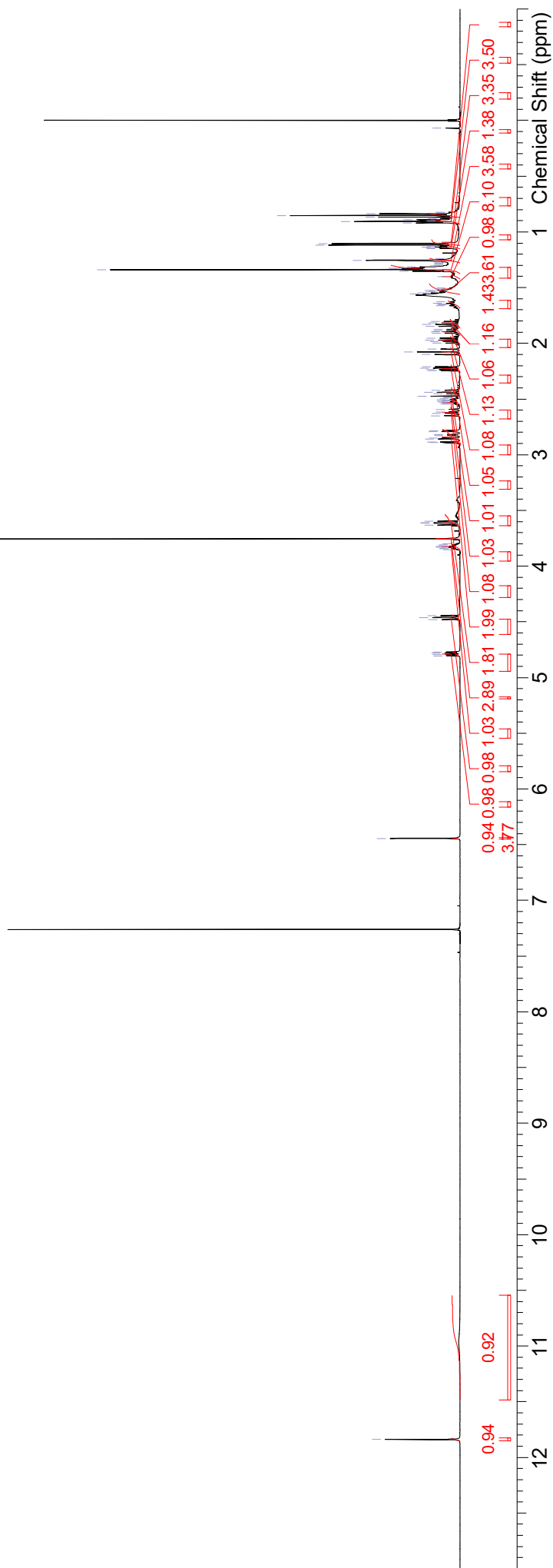
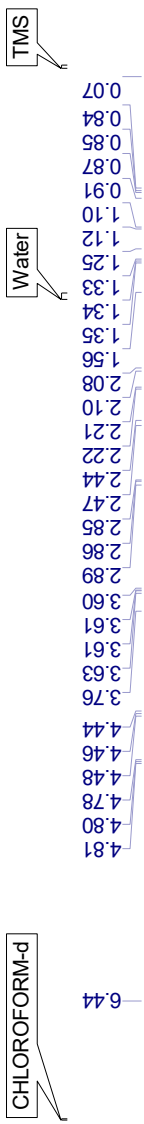
11.84

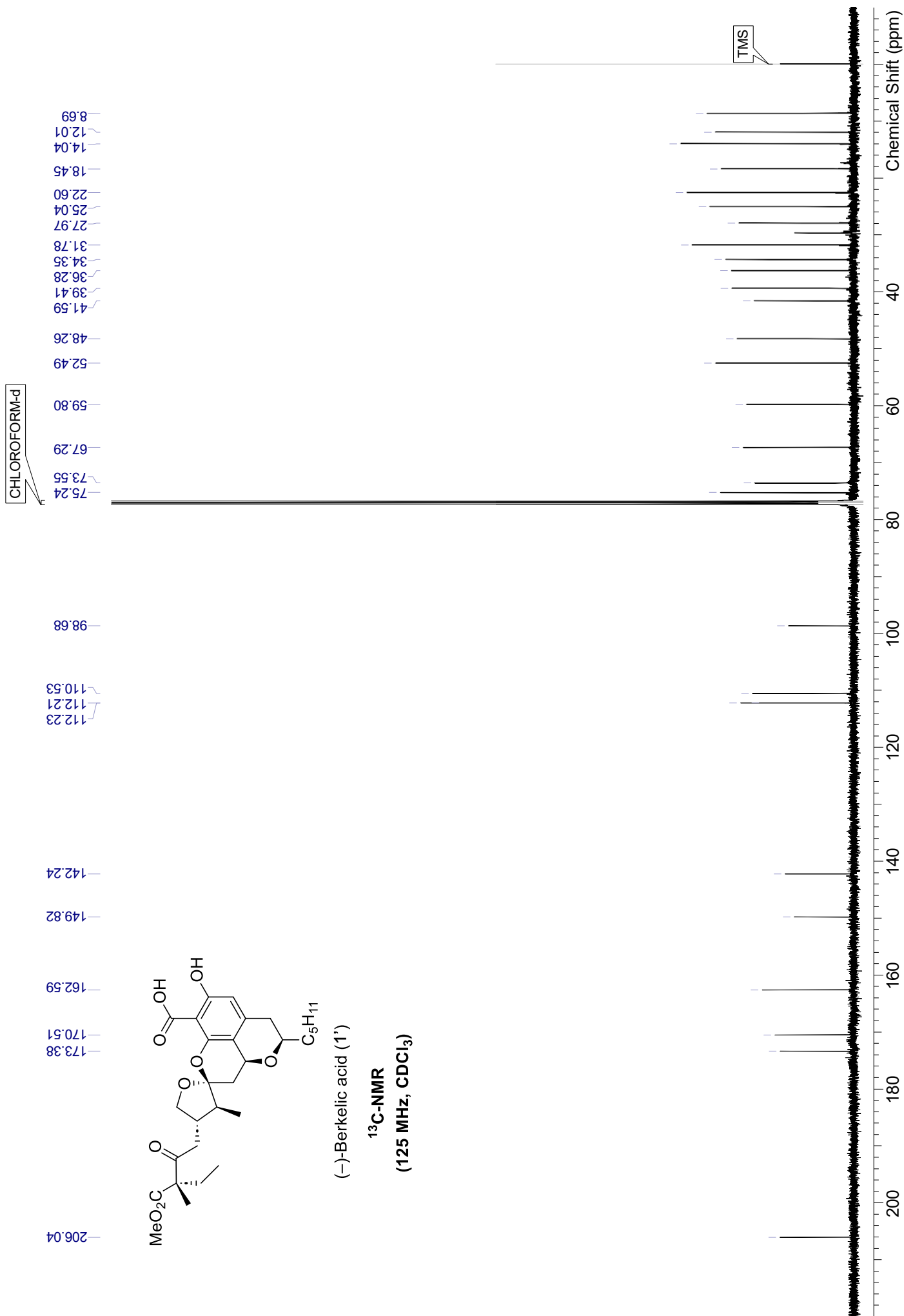


(-)-Berkeley acid (1')

¹H-NMR

(500 MHz, CDCl₃)





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